UNIVERSITÉ DU QUÉBEC À MONTRÉAL

POLYCYCLISATION OXYDATIVE ET SON APPLICATION EN SYNTHÈSE ASYMÉTRIQUE

MÉMOIRE

PRÉSENTÉ

COMME EXIGENCE PARTIELLE

DE LA MAÎTRISE EN CHIMIE

PAR

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LISTE DES ABRÉVIATIONS, SIGLES ET ACRONYMES

Ac	Acétyle
AcOEt	Acétate d'éthyle
AgOTf	Triméthylsulfonate d'argent
All	Allyle
aq.	Aqueux
ATP	Adénosine triphosphate
BINAP	2,2'-bis(diphénylphosphino)-1,1'-binaphthyle
BuLi	Butyl lithium
CBr_4	Tétrabromométhane
CCM	Chromatographie sur couche mince
$CHCl_3$	Chloroforme
CoA	Coenzyme A
DCM	Dichlorométhane
DIB	(Diacétoxy)iodobenzène
DIBAL-H	Hydrure de Diisobutylaluminium
DIPEA	*N,N*-Diisopropyléthylamine
DMF	Diméthylformamide
DMP	Dess-Martin périodinane
DMPU	1,3-diméthyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
ed	Excès diastéréomérique
ee	Excès énantiomérique
Et	Éthyle
Et_3N	Triéthylamine
EtOAc	Acétate d'éthyle
H_2	Hydrogène
HFIP	Hexafluoroisopropanol
i-PrOH	Isopropanol
K-10 clay	Argile montmorillonite K-10
K_2CO_3	Carbonate de potassium

KHMDS	Hexaméthyldisilazane de potassium
LAH	Hydrure de lithium alumium
m-CPBA	Acide *méta*-chloroperbenzoïque
Me	Méthyle
MeOH	Méthanol
MOM-Cl	Méthyl de chlorométhyl éther
$Na_2S_2O_3$	Thiosulfate de sodium
$NABH_4$	Borohydrure de sodium
NADH	Nicotinamide adénine dinucléotide déshydrogénase
$NAHCO_3$	Carbonate de sodium
NBS	*N*-bromosuccinimide
n-Bu	*n*-Butyle
n-Buli	*n*-Butyllithium
Na_2SO_4	Sulfate de sodium
NOE	Nuclear Overhauser Effect
n-Pr	*n*-Propyle
NH_4Cl	Chlorure d'ammonium
Nu	Nucléophile
O_3	Ozone
PCC	Chlorochromate de pyridinium
Pd	Palladium
Pd/C	Palladium sur charbon
Ph	Phényle
PIFA	bis(trifluoracétoxy)iodobenzène
PPh_3	Triphénylphosphine
RMN	Résonance Magnétique Nucléaire
RT	''Room temperature'' (température pièce)
Ru	Ruthénium
sat.	Saturée
S_N2	Substitution nucléophile d'ordre 2
$SOCl_2$	Chlorure de thionyl

sp	Hybridation *sp*
TBS	*tert*-Butyldiméthylsilyle
TBS-Cl	Chlorure de *tert*-Butyldiméthylsilyle
TEMPO	(2,2,6,6-Tétramethyl-pipéridin-1-yl)oxyl
THF	Tétrahydrofurane
TFAA	Acide trifluoroacétique
TIPS	Triisopropylsilyle
TIPSOTf	Trifluorométhanesulfonate de triisopropylsilyle
TMS-CN	Cyanure de triméthylsilyle
Tp	Température pièce
TsOH	Acide paratoluènesulfonique

RÉSUMÉ

L'activation par voie oxydative de dérivés phénoliques contenant une chaine latérale insaturée avec un réactif d'iode hypervalent permet la formation de produits bicycliques et tricycliques via l'intermédiaire d'un processus de cyclisation cationique en cascade. Il s'agit d'un procédé efficace permettant, en une seule étape de synthèse, de construire le squelette principal de plusieurs produits naturels avec un stéréocontrole total, régi par les interactions de contrainte 1,3 allyliques et par la configuration des doubles liaisons des chaînes latérales. Une application de cette nouvelle méthodologie pour la synthèse du squelette de la famille des kauranes a été réalisée énantiosélectivement, en une seule étape, via la déaromatisation d'un phénol élaboré. De plus, une version oxydative de la réaction de Polonovski classique permet avec l'aide d'un iode hypervalent, de transformer une amine benzylique en aldéhyde chimiosélectivement.

Mot-clés : Déaromatisation / Iode hypervalent / Phénol / Prins / Polonovski / Produit naturel / Polycyclisation / Umpolung /

ABSTRACT

Oxidative activation of phenol derivatives containing an unsaturated lateral chain in the presence of a hypervalent iodine reagent promotes the formation of bicyclic and tricyclic products via a cationic cascade process. The method allows efficient one-step synthesis of scaffolds present in several natural products and occurs with total stereocontrol, governed by 1,3 allylic strain interactions and by the configuration of the side chain double bonds. An application of this new methodology, of the main tetracyclic core of a large class of compounds belonging to the kaurane family has been enantioselectively synthesized in one step from an elaborated phenol derivative involving an oxidative polycyclization-pinacol tandem process. In addition, a chemoselective and environmentally benign oxidation of benzylic amines into aldehydes mediated by a hypervalent iodine reagent has also been developed.

Keywords : Dearomatization / hypervalent iodine / Natural product / Phenol / Polonovski / Prins / Polycyclization / Umpolung /

INTRODUCTION

Biosynthèse des terpènes

Un très grand nombre de produits naturels possèdent une structure polycyclique, tels que les terpènes, largement représentés dans le milieu végétal. Ces structures représentent un défi synthétique de taille, compte tenu de leur assemblage compact, comportant plusieurs centres quaternaires stéréogéniques. Dans la nature, la biosynthèse des terpènes a lieu dans les cellules.[1] Plus particulièrement dans le cytosol pour les sesquiterpènes et dans les plastides pour les mono et diterpènes (voir Schéma 1).[1]

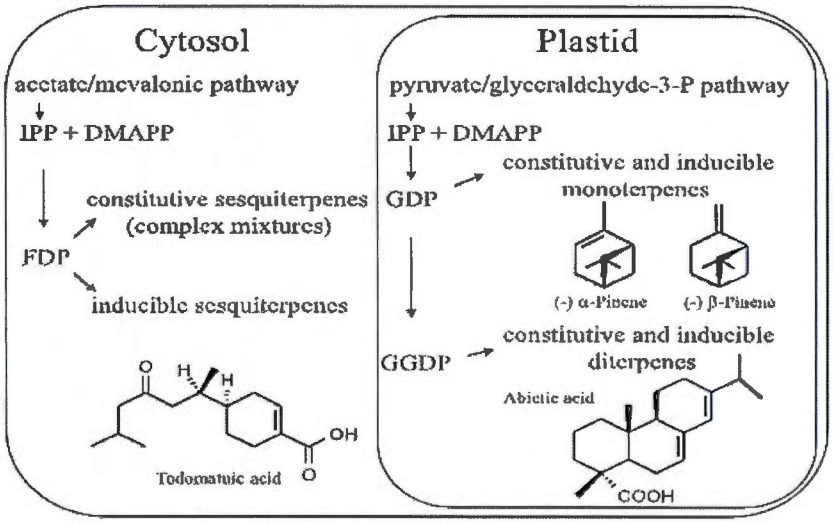


Schéma 0.1 Compartimentation de la biosynthèse de différents terpènes composant l'oléorésine[1]

La biosynthèse des terpènes débute par la formation de l'acide mévalonique, précurseurs des isoprènes qui sont à la base du squelette terpénique. L'acide mévalonique est obtenu par une condensation de type Claisen de deux unités d'acétyle CoA, suivi d'une condensation cétolique d'une autre unité d'acétyle CoA sur l'acétoacétyle CoA, pour finalement subir une réduction avec NADH et une hydratation.[1] Une fois l'acide mévalonique obtenu, il subit une phosphorylation par l'action de trois molécules d'ATP et une décarboxylation. Les précurseurs engendrés soient le 3-3, diméthylallyle pyrophosphate (DMAPP) et le 3-

isopenténylе pyrophosphate (IPP) (voir Schéma 2) sont à la base de presque tous les terpènes connus.[1]

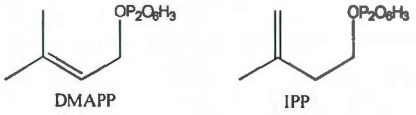


Schéma 0.2 Précurseurs biosynthétiques; l'IPP et le DMAPP

Ces précurseurs biosynthétiques offrent par la suite plusieurs options, dont le couplage d'une molécule de DMAPP et une d'IPP qui forme le géranyle pyrophosphate.[1] Cet intermédiaire permet de produire une multitude de dérivés terpéniques, tels que le géranylgéranyl pyrophosphate (GGPP) (voir Schéma 3) qui permet la biosynthèse de nombreux diterpènes, dont les dérivés de kauranes.[24]

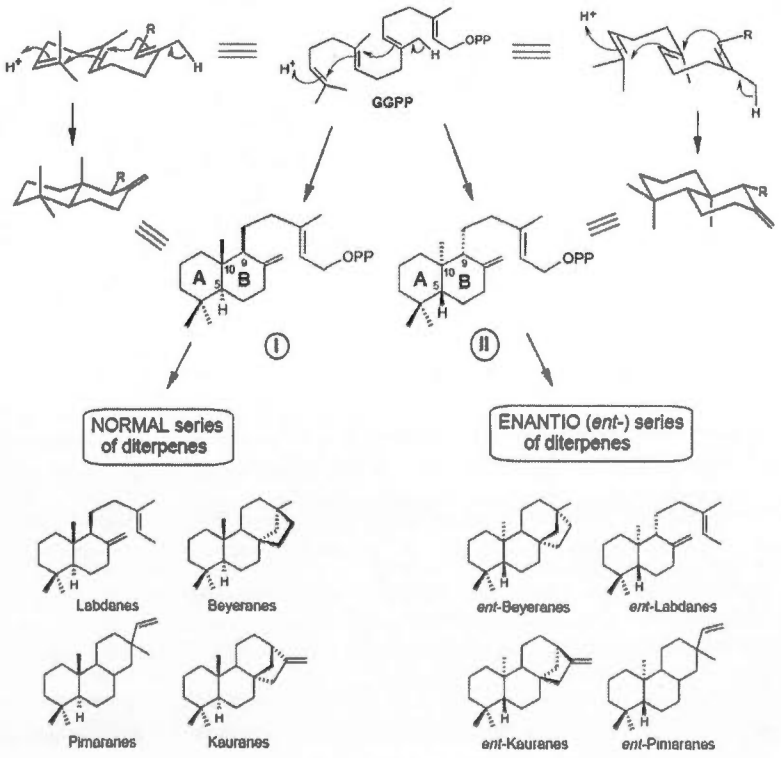


Schéma 0.3 Polycyclisation enzymatique pour la formation des kauranes[24]

Synthèses biomimétiques

Les synthèses biomimétiques tentent de reproduire artificiellement en laboratoire ce qui se produit dans les systèmes biologiques. Un exemple flagrant est la polycyclisation cationique qui trouve ses sources dans les cascades enzymatiques, lors de la formation des terpènes. Un exemple intéressant est celui de Johnson et *al.*[2] pour la synthèse du 11 α-méthylprogestérone **2** (voir Schéma 4).

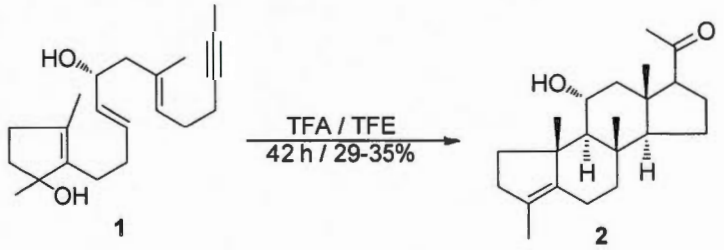


Schéma 0.4 **Polycyclisation cationique**[2]

Cette classe de polycyclisation cationique permettant de former rapidement et diastéréosélectivement des squelettes polycondensés, suscite toujours la curiosité de la communauté scientifique. L'intérêt du laboratoire Canesi à la déaromatisation par voie oxydative de composés aromatiques riches en électrons, via l'addition de nucléophiles carbonés,[3] permet de se questionner sur la possibilité d'étendre ce principe à une polycyclisation oxydative cationique, déclenchée par une activation oxydante de type umpolung.

Umpolung classique

Le principe d'umpolung a d'abord été répertorié par Corey et Seebach[4] au courant des années 70. Il repose sur l'inversion de la polarité naturelle d'une fonction et modifie sa réactivité (un nucléophile est transformé en électrophile et vice et versa). Le carbonyle **3** (voir Schéma 5) normalement électrophile subit une réaction de protection avec le 1,3-dithiol **4** suivi d'un traitement basique pour déprotoner l'hydrogène devenu « acide » dans **5** et former ainsi un

anion acylium **6**, qui réagit désormais comme nucléophile, une déprotection subséquente de l'activant umpolung (groupement dithiane) conduit à la cétone **8**.

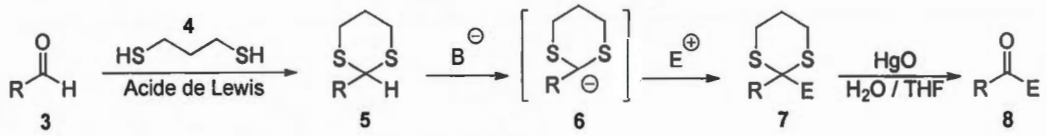


Schéma 0.5 **Principe d'umpolung de Corey et Seebach**

Umpolung aromatique

Une extension de cette méthodologie aux composés aromatiques riches en électrons, tels que les phénols[18-19] et les dérivés d'anilines-sulfonamides,[20] est aussi possible. En réactivité classique, ces composés réagissent en tant que nucléophiles. Cependant une activation oxydante[5-17] permet de transformer ces espèces en électrophiles par l'emploi d'un réactif à base d'iode hypervalent **10** (voir Schéma 6), selon un mécanisme de transfert d'électrons. Le phénol **9** réagit avec le diacétoxyiodobenzène **10** pour former un radical phénol **11**, l'espèce **12** et une molécule d'acide acétique. Le second échange d'électron permet de générer de l'iodobenzène **14**, une seconde molécule d'acide acétique ainsi que l'ion phénoxonium **15** dont la forme de résonnance la plus stable est **16**.

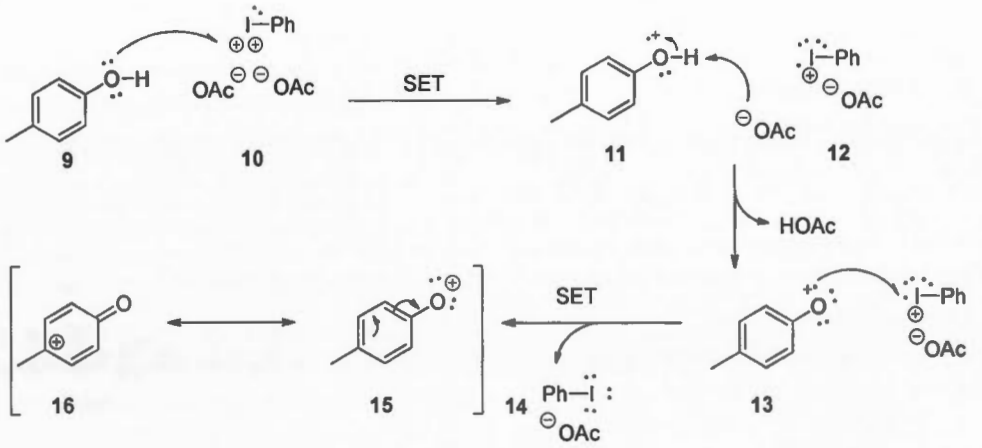
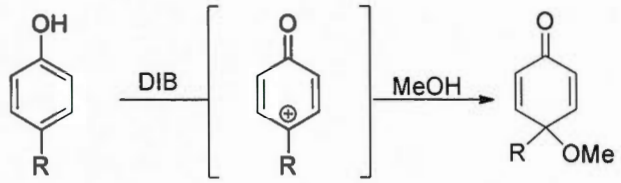


Schéma 0.6 **Mécanisme radicalaire de l'umpolung aromatique**

Le professeur Kita est un des pionniers qui a démontré la faisabilité de telles réactions de déaromatisation de phénols par addition oxydante de méthanol par l'emploi d'iode hypervalents,[18-19] ouvrant ainsi de nombreuses possibilités synthétiques (voir Schéma 7).



17 18 19

Schéma 0.7 Addition de méthanol sur un phénol riche en électrons

L'ion phénoxonium **18** a besoin d'être stabilisé lors de la réaction pour lui permettre de réagir avec le nucléophile désiré. Pour ce faire, l'utilisation d'un solvant protique est nécessaire. Puisque ces solvants sont généralement eux-mêmes nucléophiles, tel que le méthanol, il est nécessaire d'utiliser un autre type de solvant lorsque la réaction avec le solvant n'est pas désirée. Il a aussi été démontré par Kita[6-8,15,17,21] que l'hexafluoroisopropanol (HFIP)[6-8,15] agit en tant que solvant protique non nucléophile et permet une stabilisation adéquate de l'ion phénoxonium **18**.

Réaction de Prins

Les travaux précédents du laboratoire[3] ont démontré la possibilité de capter l'ion phénoxonium par un nucléophile carboné, un dérivé de la réaction de Prins classique étendue aux ions phénoxonium plutôt qu'oxoniums.[22] Dans sa version originale, la réaction de Prins[22] est induite en milieu acide et comporte l'addition d'un alcène **22** (voir Schéma 8) ou d'un alcyne sur un ion oxonium **21**, suivi d'une capture nucléophilique ou d'une élimination d'un proton. Dans sa version oxydative,[3] l'ion phénoxonium **25** est généré par une activation du phénol par un iode hypervalent, suivie par l'addition d'un alcène ou d'un alcyne intramoléculaire **25**, formant ainsi un mélange de produits par élimination d'un proton ou par l'addition d'un nucléophile externe **26**.

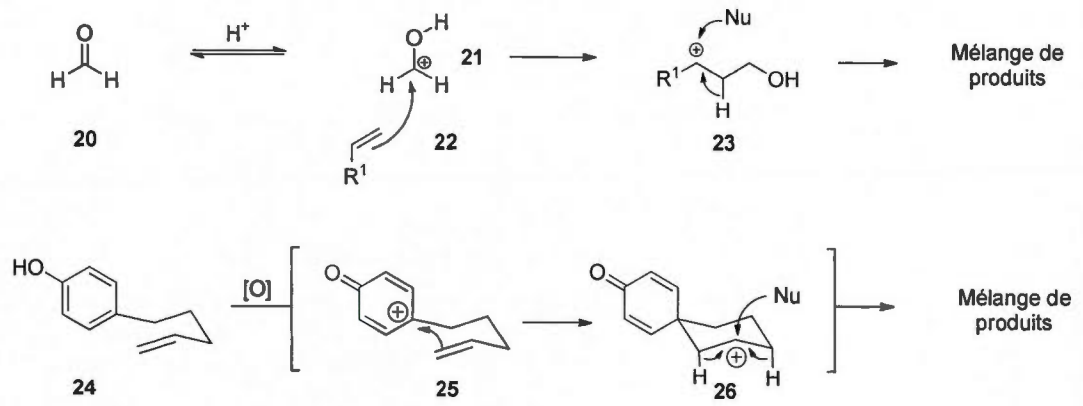


Schéma 0.8 **Réaction de Prins classique versus Prins oxydative**

Pour éviter d'obtenir un mélange de produits, Overman et *al.*[23] ont proposé un processus tandem de Prins-Pinacol (voir Schéma 9) qui permet, suite à la Prins, d'effectuer un réarrangement pinacolique successif, évitant ainsi l'élimination d'un hydrogène ou la capture du carbocation par un nucléophile externe.

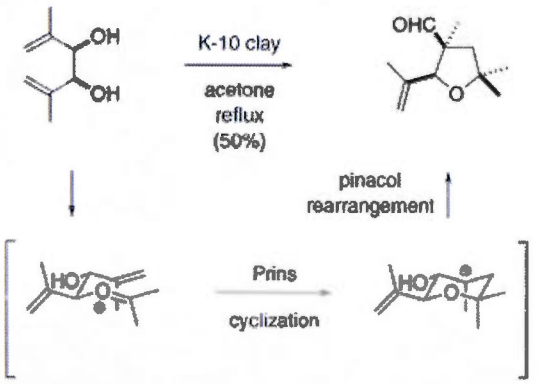


Schéma 0.9 **Réaction de Prins-Pinacol**

Toutefois, une méthode simple suggère l'utilisation d'un alcyne[3] **27** (voir Schéma 10) pour la capture de l'espèce électrophile **28.** Lors de l'addition de Prins intramoléculaire, l'espèce életrophilique générée possède une géométrie *sp* dans un état de transition demi-chaise excessivement tendu. La tension de cycle du carbocation **28** ne permet alors aucune

élimination d'hydrogène. Ainsi uniquement l'addition d'un nucléophile externe est permise pour générer le composé spirocyclique **29**.

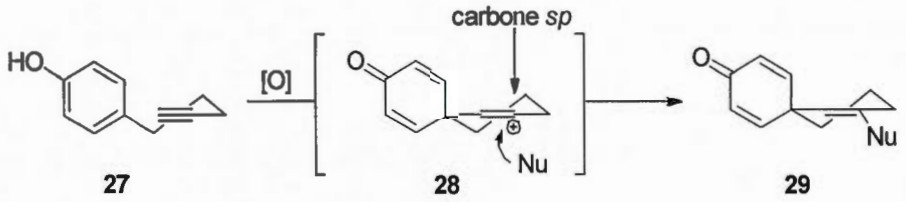


Schéma 0.10 **Prins oxydative avec un alcyne terminal[3] (Figure 3)**

Polonovski et Polonovski-Poitier

La réaction de Polonovski[26-27] permet de transformer un groupement *N*-Oxyde tertiaire **30** (voir Schéma 11) en aldéhyde à partir de l'addition de ce dernier sur l'anhydride acétique **31**. Il y a alors formation d'un iminium qui est suivie d'une addition de l'acétate **33**, libéré à partir de l'anhydride acétique. Un réarrangement intramoléculaire (ou intermoléculaire) produit alors l'acétamide **35** et l'aldéhyde **34** correspondant. Une modification à la réaction de Polonovski[26] faite par Potier,[27-29] consiste à remplacer l'anhydride acétique par l'anhydrique trifluoroacétique **37** pour obtenir des conditions réactionnelles ne nécessitant pas de chauffage du fait de la réactivité accrue de l'anhydride **37** utilisé. De plus, le manque de réactivité de l'ion trifluoro-acétate libéré conduit plutôt à une énamine apte de réagir à nouveau avec un second équivalent de TFAA produisant **41**.

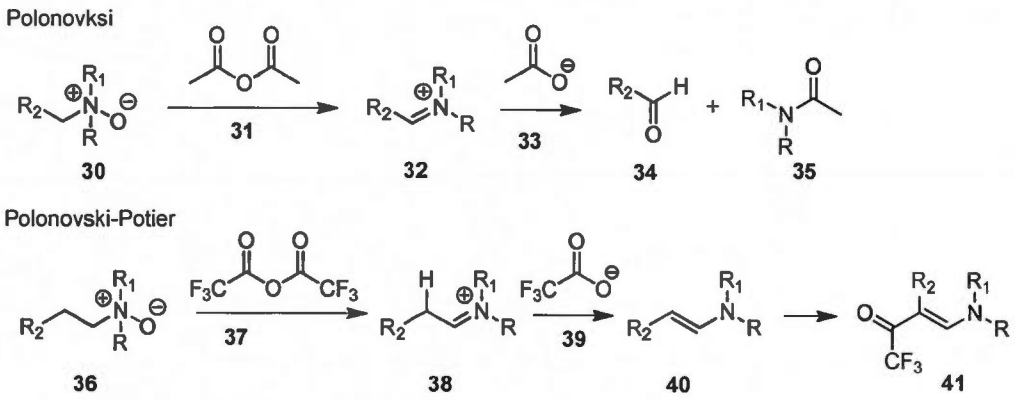


Schéma 0.11 Réaction de Polonovski et Polonovski-Potier

L'intérêt du laboratoire Canesi dans l'utilisation de l'iode hypervalent permet de suggérer qu'un intermédiaire de type Polonovksi pourrait être généré *in situ*, sans l'utilisation d'une amine activée de type *N*-oxyde, pour générer l'aldéhyde correspondant.

Iodes hypervalents

L'iode est généralement monovalent et présente un degré d'oxydation de -1. Toutefois, des dérivés d'iodes à degré d'oxydation supérieur (III, IV et VII) sont connus et portent le nom d'iodes hypervalents ou iodanes. Leurs utilisations sont en plein essor avec le développement de la chimie verte, puisque les réactifs organiques à base d'iode hypervalents présentent l'avantage d'être inodores, facile à manipuler (solides), non toxiques et peu coûteux par comparaison avec les métaux lourds ayant des propriétés chimiques similaires. Parmi les plus connus des iodes (III) pour la déaromatisation des phénols, notons le DIB, le PIDA et le réactif de Koser (voir Schéma 12).

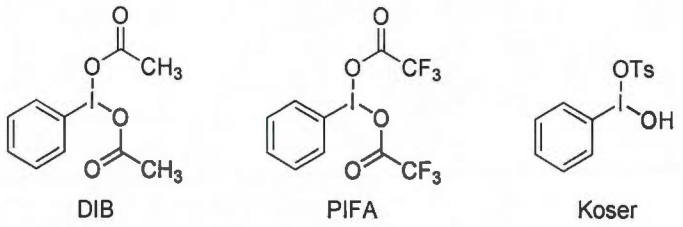


Schéma 0.12 Iodes hypervalents (III)

Le contre ion associé à l'iode hypervalent (III) influence sur son choix, puisque l'acide trifluoroacétique relâché par le PIFA n'est pas compatible avec les produits sensibles, comparativement à l'acide acétique beaucoup moins acide relâché par le DIB. Ce dernier est donc moins réactif, mais plus doux comparativement au PIFA et au réactif de Koser.

Objectifs

La structure polycyclique des terpènes représente un défi synthétique de taille compte tenu du squelette polycondensé et des nombreux centres stéréogéniques. Les travaux précédents du laboratoire[3] de la réaction de type Prins oxydative (Schéma 12), représentent une suite logique pour le développement d'une nouvelle réaction de polycyclisation oxydative. Le concept d'umpolung aromatique permettrait la formation, en une seule étape, de squelettes complexes avec la stéréochimie désirée y étant rattachée.

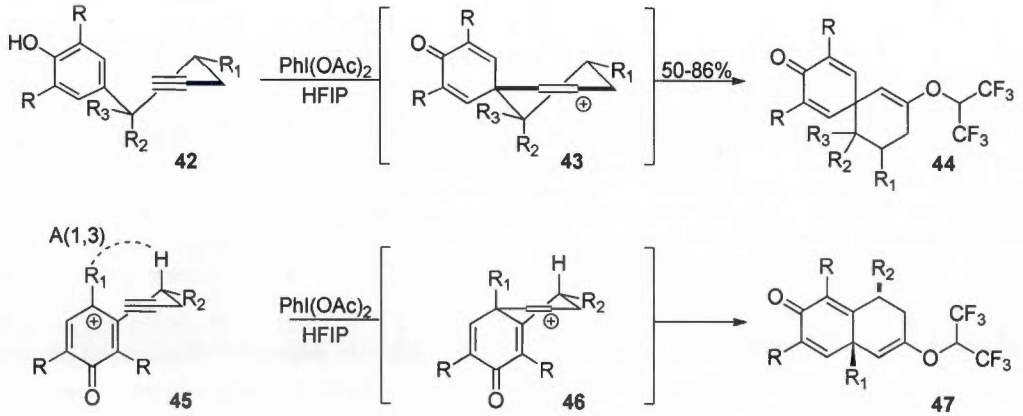


Schéma 0.13 Formation de systèmes spirocycliques ou de type décalines

Un intérêt supplémentaire porte sur le développement d'une réaction de type Polonovski, généré avec un réactif d'iode hypervalent, sans l'utilisation d'une amine activée de type *N*-oxyde.

CHAPITRE I.
POLYCYSLISATION OXYDATIVE ET STÉRÉOSÉLECTIVE PAR UN RÉACTIF D'IODE HYPERVALENT

1.1 INFORMATIONS SUPPLÉMENTAIRES

L'article[30] issu de ces résultats est présenté à l'Annexe 1 et les informations supplémentaires de cet article, incluant les procédures expérimentales et les caractérisations de chaque nouveau produit, sont présentées à l'Annexe 2.

CHAPITRE II.
SYNTHÈSE ASYMÉTRIQUE DU SQUELETTE PRINCIPAL DE LA FAMILLE DES KAURANES RÉALISÉE PAR UN PROCESSUS OXYDATIF TANDEM DE POLYCYLISATION-PINACOL

2.1 INFORMATIONS SUPPLÉMENTAIRES

L'article issu de ces résultats est présenté à l'Annexe 3 et les informations supplémentaires de cet article, incluant les procédures expérimentales et les caractérisations de chaque nouveau produit, sont présentées à l'Annexe 4.

2.2 PERSPECTIVE ET TRAVAUX FUTURS

Afin d'être en mesure de finaliser une synthèse totale d'un dérivé des kauranes, l'intermédiaire polycyclique **48** (voir Schéma 14) obtenu, pourrait subir des déshydrogénations sélectives avec du palladium sur charbon pour conduire au produit **49**. Dans cette stratégie, le brome le plus encombré et la double liaison tétrasubstituée devraient être les plus difficiles à réduire. Par la suite, l'ajout d'un hydrure encombré[32] permettrait de réduire sélectivement la fonction aldéhyde en l'alcool correspondant **50**, sans toucher à la fonction cétone, puis une méthylation de Stille[33] pourrait mener à **51.** Une élimination subséquente de la fonction alcool via le réactif de Burgess pourrait conduire à l'alcène exocyclique[34] **52**. La synthèse serait finalement conclue par une méthylation réductrice de Birch,[35] pour obtenir un produit naturel de la famille des kauranes, le kaur-16-en-3-one **53**.

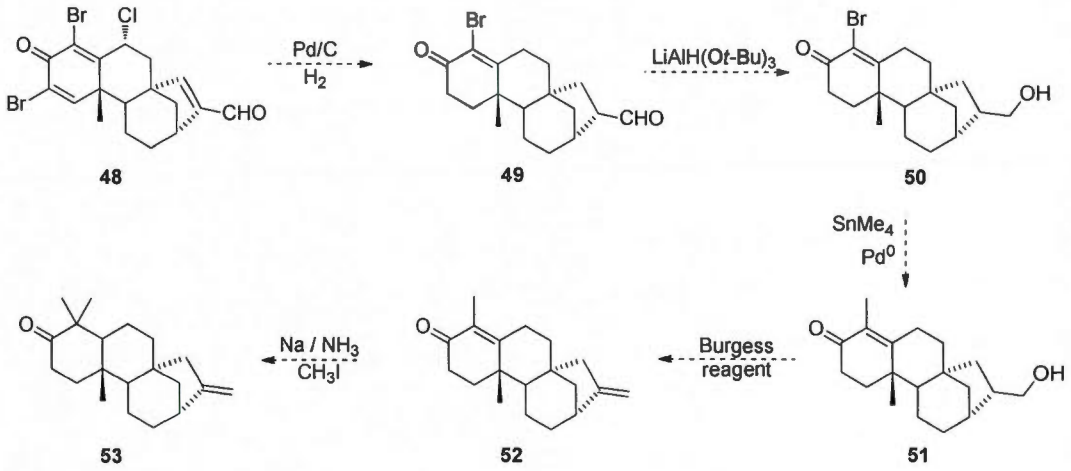


Schéma 2.1 **Perspective de synthèse totale pour le kaur-16-en-3-one**

CHAPITRE III.
OXYDATION DOUCE D'AMINES BENZILIQUES EN ALDÉHYDES PAR UN PROCÉDÉ OXYDATIF DE TYPE POLONOVSKI

3.1 INFORMATIONS SUPPLÉMENTAIRES

L'article[31] issu de ces résultats est présenté à l'Annexe 5 et les informations supplémentaires de cet article, incluant les procédures expérimentales et les caractérisations de chaque nouveau produit, sont présentées à l'Annexe 6.

CONCLUSION

En conclusion, une nouvelle réaction de polycyclisation oxydative, sans utiliser de métaux, a été développée avec succès. Ce nouveau processus permet d'obtenir pour l'instant jusqu'à quatre cycles condensés avec un stéréocontrôle total. Cette méthode introduit diastéréosélectivement plusieurs centres stéréogéniques en une seule étape, gouvernés par les interactions de contraintes 1,3 allyliques créées par la position *méta* benzylique (vis-à-vis de l'hydroxyle) ainsi que suivant la configuration de la double liaison contenue dans la chaîne latérale. Une application de la méthodologie en synthèse a permis de générer le squelette tétracyclique d'une grande classe de composé appartenant à la famille des kauranes. L'étape clé est basée sur un processus tandem de polycyclisation-pinacol induit par un réactif d'iode hypervalent, peu coûteux et respectueux de l'environnement. Cette première application démontre l'utilité du concept ''d'umpolung aromatique''. Toutefois, une application plus avancée en synthèse totale pourra être réalisée à partir du squelette asymétrique développé pour obtenir un produit naturel, le kaur-16-en-3-one.

Une application supplémentaire de l'iode hypervalent à une réaction connue de Polonovski a permis d'obtenir un aldéhyde à partir d'une amine tertiaire, sans l'utilisation d'amine activée de type *N*-oxyde, comme proposé en réactivité classique.

ANNEXE A

« A STEREOSELECTIVE OXIDATIVE POLYCYCLIZATION PROCESS MEDIATED BY A HYPERVALENT IODINE REAGENT » ARTICLE[30]

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Titre : A Stereoselective Oxidative Polycyclisation Process Mediated by a Hypervalent Iodine Reagent

Auteurs : Samuel Desjardins, Jean-Christophe Andrez, Sylvain Canesi*

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A Stereoselective Oxidative Polycyclization Process Mediated by a Hypervalent Iodine Reagent

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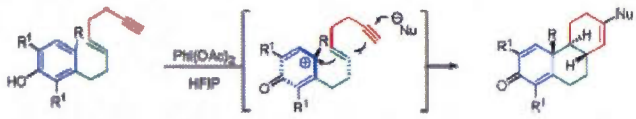
ABSTRACT



Activation of phenol derivatives with a hypervalent iodine reagent promotes the formation of bicyclic and tricyclic products via a cationic cyclization process. The method allows efficient one-step syntheses of scaffolds present in several natural products and occurs with total stereocontrol, governed by 1,3 allylic strain interactions and by the configuration of the side chain double bonds.

The use of cationic polycyclizations of polyunsaturated compounds in biomimetic syntheses allows rapid access to complex architectures with excellent diastereoselectivity. The first remarkable examples can be attributed to Johnson et al. for the syntheses of steroids in 1976;[1] however such strategies are still under intensive investigation.[2] Our own interest in oxidative dearomatization of electron-rich aromatics involving carbon-based nucleophiles[3] led us to question whether an oxidative cationic polycyclization could be triggered by activation of a phenol. Although electron-rich aromatic compounds such as phenols and their derivatives normally react as nucleophiles, oxidative activation[4,5] can transform these compounds into highly reactive electrophilic species such as **2**. This phenoxonium ion[6] **2** could be intercepted in an intramolecular fashion by appropriate carbon-based nucleophiles such as π bonds, thus initiating a diastereoselective polycyclization leading to tricyclic core **3**. This phenol reversal of reactivity may be thought of as involving an "aromatic ring umpolung". The oxidative process could rapidly generate the core of several natural products such as the human

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10.1021/ol201145u
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steroidal hormone skeleton 4,[1] or cassaic acid 5 and its derivatives,[7] Figure 1.

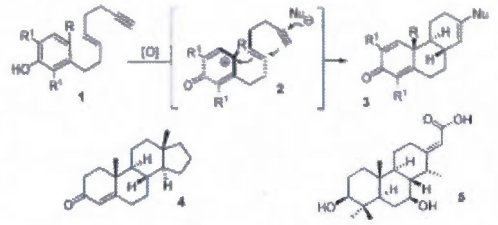
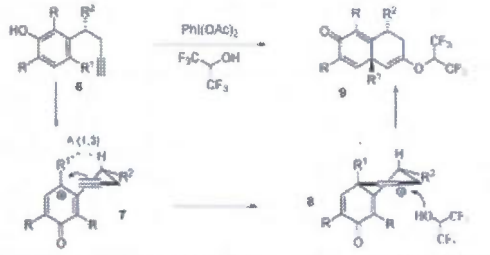


Figure 1. Oxidative cationic polycyclization cascade.

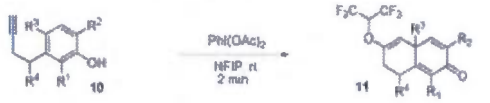
An indication of how the necessary phenol activation can be efficiently achieved is apparent in the work of Kita,[8] who demonstrated that phenols react under the influence of hypervalent iodine reagents[9] such as (diacetoxyiodo)benzene (DIB), an environmentally benign and inexpensive reagent. This reaction is best performed in solvents such as hexafluoroisopropanol (HFIP).[8f] In our first study, an oxidative vicinal fused carbocycle formation was performed with a terminal alkyne on a lateral chain at the *meta*-position relative to the phenol group **6**. During the umpolung activation, we speculate that a strained half-chair intermediate **8** was generated which strongly favored nucleophile capture, leading to the unsaturated decalin system **9**, Scheme 1.

Scheme 1. Formation of Functionalized Decalin Cores



The strain created by the transient *sp*-hybridized carbonium ion in species **8** resulted in the intermediate being highly electrophilic and enabled it to react with the weakly reactive nucleophile HFIP,[8f] normally used as an inert solvent. This reaction produced the highly functionalized bicyclic system **9** containing a quaternary carbon center, a dienone functionality, and an enol-ether as a masked carbonyl. In order to determine the scope and limitations of this new transformation, substituents were introduced on the lateral chain, on the aromatic ring, and at the *para* position to produce the elaborated bicyclic cores **11**. In addition, the new process can efficiently afford the tricyclic core **11h** in excellent yield from a simple tetralone derivative **10h**, Table 1.

Table 1. Oxidative Bicyclization Process



entry	R^1	R^2	R^3	R^4	R^3/R^4	yield (%)
a	H	H	Me	H		43
b	Br	Br	Me	H		86
c	H	H	Me	Me	*trans*	50
d	H	Br	Me	Me	*trans*	70
e	Br	Br	Et	H		91
f	Br	Br	Bn	H		85
g	Br	Br	*n*-Pr	H		79
h	Br	Br	$H_2C-CH_2-CH_2$		*cis*	90

This bicyclization reaction produced vicinal fused carbocycles in very good yields. However, the oxidation of compounds containing open *ortho*-positions (entries **10a** and **10c**) occurred in lower yields compared to the dibromo analogs. This may be explained by considering that the first intermediate is a highly delocalized carbonium ion, which can be represented by **7** (Scheme 1, R = Br) as one of its resonance structures. We believe that because of the presence of the electron-withdrawing bromine atoms, **7** is the more dominant resonance form rather than the *ortho* mesomer. Consequently the cyclization occurs mainly at

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the desired *para*-position when bromines are protecting the *ortho*-positions. An added advantage is that the bromine atoms could be used subsequently to introduce others substitutents, using transition metal chemistry. Furthermore, entries 10c and 10d (R^4 = Me) led exclusively to the *trans* diastereoisomer.[10] This stereoselectivity could be explained by the required minimal 1,3 allylic strain interactions between the two methyl groups during the transition state 7 (Scheme 1, R^2 = Me). These observations demonstrate the high diastereoselectivity of this new process and could have applications in asymmetric synthesis governed by the *meta* first stereogenic benzilic center. Such scaffolds are present in numeral natural products such as anominine[11] 12, andrographolide[12] 13, or the decalin core of azadirachtin[13] 14, Figure 2.

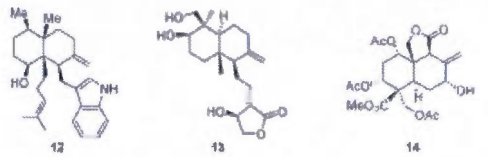
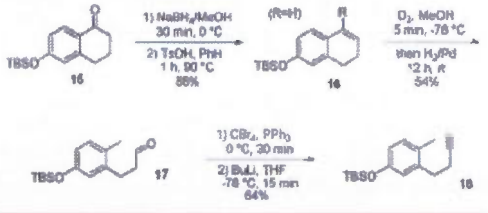


Figure 2. Natural products containing a decalin core.

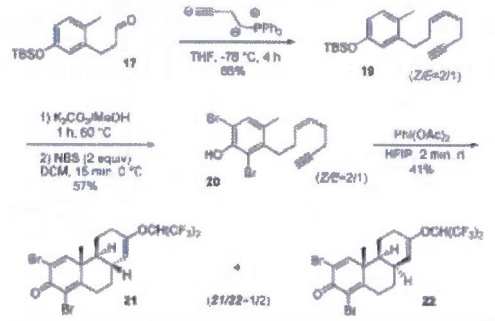
The required starting materials were obtained from tetralone 15, via a reduction/elimination sequence[14] leading to 16 followed by ozonolysis and reductive treatment with H_2/Pd to provide aldehyde 17 in 54% overall yield. This substrate was further easily transformed into product 18 using a Corey–Fuchs strategy,[15] Scheme 2.

Scheme 2. Formation of Starting Materials



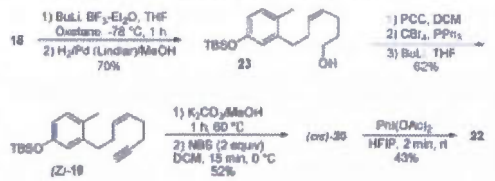
We were also interested in the possible extension of this process to the formation of tricyclic systems as well as in the diastereoselectivity of the cyclization with respect to the configuration of the central double bond in compound 20. A Wittig reaction transformed aldehyde 17 into an inseparable mixture of *cis* and *trans* alkenes 19 in a 2:1 ratio in favor of the (*Z*)-isomer. The mixture was further transformed in two steps into a diastereoisomeric mixture of phenols 20. The same umpolung activation led to the desired tricyclic systems 21 and 22 in 41% yield.[16] The cyclization reaction occurred with total stereocontrol in agreement with the configuration of the starting olefin (*Z* or *E*), since a 2:1 mixture of diastereomers[10] was obtained. It should be stressed that compound 21 represents the main core of cassaic acid 5, Scheme 3.

Scheme 3. Oxidative Tricyclization Process



To verify the high diastereoselectivity of this process, *cis*-20 was efficiently synthesized by a Lindlar reduction of an internal triple bond. The requisite alkyne was prepared via oxetane ring opening by the lithium salt of 18 (made directly from the dibromoalkene precursor) and then further transformed into the *cis* compound 19 via a Corey–Fuchs reaction in 62% overall yield from compound 23. The oxidation of *cis*-20 led exclusively to the tricyclic core 22 in 43% yield,[10] Scheme 4.

Scheme 4. Diastereoselective Tricyclization Process



In summary, an unprecedented oxidative polycyclization process has been developed that enables rapid access to bicyclic and tricyclic systems present in several natural

(10) The stereoselectivity was verified and attributed by ^{1}H NMR and ^{1}H NMR NOE.

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(13) Nicolaou, K. C.; Roecker, A. J.; Follmann, M.; Baati, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2107.

(14) Grignard reagents were used to produce more elaborate phenols: Beaubien, S.; Deslongchamps, P. *Can. J. Chem.* **2006**, *84*, 29.

(15) Synthetic details are provided as Supporting Information.

(16) The two diastereomers were separated by chromatography at this point.

products, from inexpensive phenol derivatives. This method is an efficient means of diastereoselectively introducing several stereogenic centers in one step, with total stereocontrol, governed by 1,3 allylic strain interactions and by the configuration of the side chain double bonds. Ongoing investigations of this process and potential applications will be disclosed in due course.

Acknowledgment. We are very grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada Foundation for Innovation (CFI), the provincial government of Quebec (FQRNT and CCVC), and Boehringer Ingelheim (Canada) Ltd. for their precious financial support in this research.

Supporting Information Available. Experimental procedures and spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

ANNEXE B

« A STEREOSELECTIVE OXIDATIVE POLYCYCLIZATION PROCESS MEDIATED BY A HYPERVALENT IODINE REAGENT » SUPPORTING INFORMATION[30]

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Titre : A Stereoselective Oxidative Polycyclisation Process Mediated by a Hypervalent Iodine Reagent

Auteurs : Samuel Desjardins, Jean-Christophe Andrez, Sylvain Canesi*

A Stereoselective Oxidative Polycyclisation Process Mediated by a Hypervalent Iodine Reagent

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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), 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.

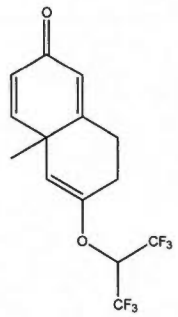
II. Experimental procedures

II.1. General procedure for the oxidative cyclisation process:

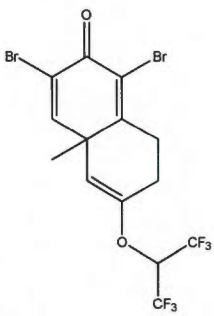
A solution of $PhI(OAc)_2$ ("DIB", 38 mg, 0.11 mmol, 1.1 equiv.) in $(CF_3)_2CHOH$ ("HFIP", 1 mL) was added over 5 seconds to a vigorously stirred solution of phenol (0.1 mmol, 1 equiv.) in 3 mL of HFIP at room temperature. After addition of DIB, the solution was stirred for 2 min, quenched with 0.3 mL of acetone, filtered directly over silicagel (EtOAc) and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford the corresponding dienone. *NB: A further treatment of the resulting enol-ether with mCPBA generates a hydroxy-ketone functionality in good yield. This reaction is less efficient in presence of Trifluoroethanol (TFE); indeed a direct attack on the phenoxonium ion has been observed in such conditions.*

II.2. Analytical data:

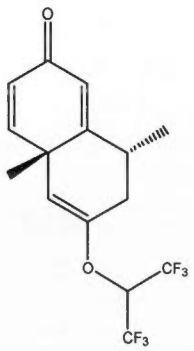
Compound 11a : 0.076mmol, 24.8 mg, 43% yield. **IR** υ (cm^{-1}) 2935, 1661, 1615, 1404; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.79 (d, J = 9.8 Hz, 1H), 6.22 (d, J = 9.9 Hz, 1H), 6.14 (s, 1H), 4.92 (s, 1H), 4.66 (hept., J = 5.7 Hz, 1H), 2.98-2.79 (m, 1H), 2.63-2.41 (c, 3H), 1.38 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.2, 162.2, 154.5, 154.0, 127.6, 124.9, 105.6, 73.4, 40.5, 30.4, 29.4, 29.0, 28.5; **HRMS** (ESI): Calc. for $C_{14}H_{13}F_6O_2$ $(M+H)^+$: 327.0814, found: 327.0800.



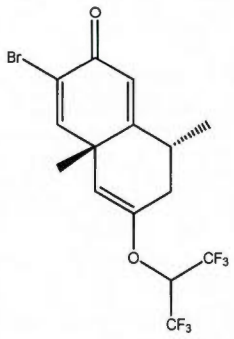
Compound 11b : 0.087 mmol, 45.2 mg, 86% yield. **IR** υ (cm^{-1}) 2935, 1661, 1617, 1409; **^{1}H NMR** (300 MHz, $CDCl_3$), δ 7.27 (s, 1H), 4.95 (s, 1H), 4.69 (hept., J = 5.5 Hz, 1H), 3.40 (ddd, J = 13.2; 7.7; 2.2 Hz, 1H), 2.84-2.70 (m, 1H), 2.66-2.38 (c, 3H), 1.49 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4, 160.0, 155.1, 153.2, 121.1, 120.7, 103.9, 73.3, 46.1, 30.34, 29.4, 28.4; **HRMS** (ESI): Calc. for $C_{14}H_{11}Br_2F_6O_2$ $(M+H)^+$: 484,9005, found: 484,8996.



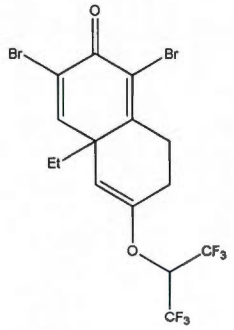
Compound 11c : 0.069 mmol, 23.4 mg, 50% yield. **IR** υ (cm^{-1}) 2935, 1661, 1615, 1404; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 (d, J = 9.81 Hz, 1H), 6.21 (d, J = 9.8 Hz 1H), 6.17 (s, 1H), 4.90 (s, 1H), 4.65 (hept., J = 5.7 Hz, 1H), 2.99 (hept., J = 6.1 Hz, 1H), 2.55 (dd, J = 17.0; 6.3 Hz, 1H), 2.07 (ddd, J =17.0; 11.22; 2.2 Hz, 1H), 1.38 (s, 3H), 1.25 (d, J = 6.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.4, 166.5, 154.3, 154.0, 127.3, 121.8, 105.5, 73.7, 41.3, 37.9, 31.4, 30.9, 16.3; **HRMS** (ESI): Calc. for $C_{15}H_{15}F_6O_2$ $(M+H)^+$: 341.0976, found: 341.0971.



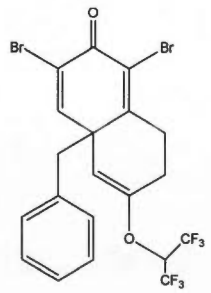
Compound 11d : 0.033mmol, 13.9 mg, 70% yield. **IR** υ (cm^{-1}) 2941, 1661, 1618, 1404; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24 (s, 1H), 6.27 (s, 1H), 4.87 (s, 1H), 4.65 (hept., J = 5.6 Hz, 1H), 3.00 (sext., J = 9.6 Hz 1H), 2.59 (dd, J = 17.0; 6.4 Hz, 1H), 2.09 (ddd, J = 17.0; 11.3; 1.9 Hz, 1H), 1.44 (s, 3H), 1.27 (d, J = 6.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 179.2, 167.0, 154.4, 154.0, 123.8, 120.4, 104.5, 73.4, 44.6, 38.1, 31.5, 30.8, 16.3; **HRMS** (ESI): Calc. for $C_{15}H_{14}BrF_6O_2$ $(M+H)^+$: 419.0074, found: 419.0076.



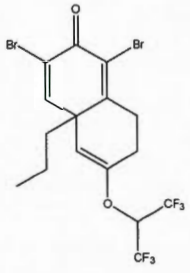
Compound 11e : 0.044 mmol, 21.3 mg, 91% yield. **IR** υ (cm^{-1}) 2957, 1707, 1640, 1623; **^{1}H NMR** (600 MHz, $CDCl_3$), δ 7.13 (s, 1H), 4.97 (s, 1H), 4.69 (hept., J = 5.9 Hz, 1H), 3.38-3.35 (dd, J = 17.0; 6.4 Hz, 1H), 2.68-2.63 (m, 1H), 2.57-2.46 (c, 2H), 1.87 (m, 2H), 0.68 (t, J = 7.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4, 155.1, 151.2, 151.2, 127.4, 121.7, 103.8, 73.3, 50.3, 36.2, 29.1, 28.2, 8.3; **HRMS** (ESI): Calc. for $C_{15}H_{13}Br_2F_6O_2$ $(M+H)^+$: 498.9161, found: 498.9153.



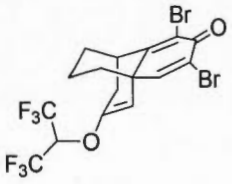
Compound 11f : 0.011 mmol, 6.6 mg, 85% yield. **IR** υ (cm^{-1}) 3150, 2928, 1650, 1615, 1404, 763; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29-7.23 (c, 3H), 7.15 (s, 1H), 6.93 (dd, J = 5.4; 2.1 Hz, 2H), 4.89 (s, 1H), 4.67 (hept., J = 5.7 Hz, 1H), 3.46 (ddd, J = 13.8; 5.8; 1.9 Hz 1H), 3.11 (d, J = 18.3 Hz, 1H), 3.01 (d, J = 18.3 Hz, 1H), 2.90 (m, 1H), 2.68-2.46 (c, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.6, 155.5, 151.5, 133.4, 130.2, 128.3, 128.0, 122.3, 122.1, 102.4, 76.6, 73.29, 51.1, 50.36, 29.6, 28.4; **HRMS** (ESI): Calc. for $C_{20}H_{15}Br_2F_6O_2$ $(M+H)^+$: 560.9318, found: 560.9304.



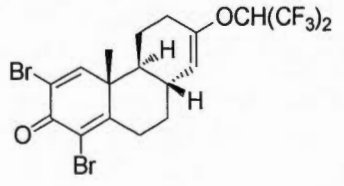
Compound 11g : 0.021 mmol, 10.8 mg, 79% yield. **IR** υ (cm^{-1}) 2941, 1660, 1617, 1415; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 4.95 (s, 1H), 4.66 (hept., J = 5.6 Hz, 1H), 3.37 (ddd, J = 13.3; 5.6; 2.1 Hz, 1H), 2.76-2.46 (c, 3H), 1.80 (m, 2H), 1.0 (c, 2H), 0.85 (t, 7.6 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.6, 158.7, 155.0, 152.0, 122.2, 104.0, 73.3, 50.0, 45.2, 29.2, 28.3, 17.2, 13.7; **HRMS** (ESI): Calc. for $C_{16}H_{15}Br_2F_6O_2$ $(M+H)^+$: 512.9318, found: 512.9327.



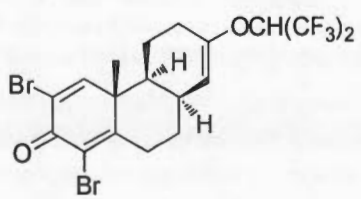
Compound 11h : 0.021 mmol, 10.8 mg, 90% yield. **IR** υ (cm^{-1}) 1740, 1372, 1243, 1046; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25(s, 1H), 4.72 (s, 1H), 4.69 (hept., J = 5.7 Hz, 1H), 3.77 (m, 1H), 2.73 (dd, J = 18.2; 7.3 Hz, 1H), 2.38 (d, J = 18.1 Hz, 1H), 2.00-1.89 (m, 2H), 1.87-160 (c, 3H), 1.44 (td, J = 12.2; 4.2 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.6, 161.8, 157.8, 152.7, 122.9, 117.8, 100.0, 73.3, 47.5, 40.2, 38.1, 34.4, 34.1, 17.6; **HRMS** (ESI): Calc. for $C_{16}H_{13}Br_2F_6O_2$ $(M+H)^+$: 510.9161, found: 510.9165.



Compound 21 : 0.021 mmol, 5.1 mg, 41% yield. **IR** υ (cm^{-1}) 2923, 1732, 1751, 1668, 1540, 1456, 1373, 1288; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.54 (s, 1H), 4.77 (s, 1H), 4.64 (hept., J = 5.9 Hz, 1H), 3.36 (dt, J = 14.1; 3.5 Hz, 1H), 2.53 (tm, 12.3 Hz, 1H), 2.46 (td, J = 14.1; 4.7 Hz); 2.31 (s, 3H), 2.10-2.00 (m, 3H), 1.70 (c, 1H), 1.67 (dt, 10.0; 2.3 Hz, 1H), 1.56 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 172.3, 167.0, 164.7, 154.2, 154.1, 122.0, 121.3, 103.6, 73.3, 49.3, 48.6, 34.5, 34.0, 33.2, 27.7, 23.5, 19.2; **HRMS** (ESI): Calc. for $C_{18}H_{17}Br_2F_6O_2$ $(M+H)^+$: 538.9475, found: 538.9489.

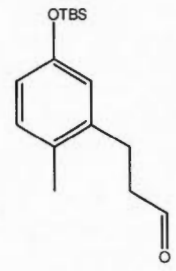


Compound 22 : 0.018 mmol, 9.9 mg, 41% yield. **IR** υ (cm^{-1}) 2928, 1732, 1755, 1668, 1536, 1451, 1373, 1281; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.21 (s, 1H), 5.03 (d, J = 5.9 Hz, 1H), 4.64 (hept., J = 5.9 Hz, 1H), 3.22 (dq, J = 14.6; 2.3 Hz 1H), 2.81 (m, 1H), 2.46 (td, J = 14.7; 5.3 Hz, 2H), 2.27-2.19 (m, 1H), 2.14 (dd, J = 17,6; 5.9 Hz, 1H), 2.06-1.97 (c, 3H), 1.50-1.37 (c, 6H); **^{13}C NMR**



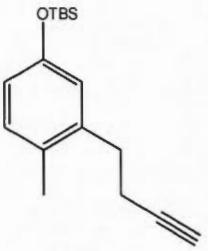
(150 MHz, $CDCl_3$) δ 173.1, 167.4, 156.3, 156.2, 154.4, 121.5, 121.2, 103.5, 73.3, 50.5, 46.5, 32.2, 30.6, 30.0, 27.4, 25.8, 20.1; **HRMS** (ESI): Calc. for $C_{18}H_{17}Br_2F_6O_2$ $(M+H)^+$: 538.9475, found: 538.9477.

Compound 17: To a solution of compound **16** (520 mg, 2 mmol) in MeOH (50 mL) at -78°C



was performed an ozonolysis. To the resulting solution was added 60 mg of Pd/C-(10%) and was saturated under hydrogen atmosphere overnight then filtrated and purified by chromatography on silica gel (*n*-hexane:EtOAc, 93:7) to afford 300 mg, (54%) of compound **17**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.00 (d, J = 7.0 Hz, 1H), 6.64 (s, 1H), 6.61 (s, J = 6.6 Hz, 1H), 2.88 (t, J = 2.9 Hz, 2H), 2.71 (t, J = 2.7 Hz, 2H), 2.23 (s, 3H), 1.00 (s, 9H), 0.20 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.6, 153.9, 139.6, 131.2, 128.5, 120.3, 118.0, 44.1, 34.4, 25.8, 25.7, 18.5, 18.2, -4.3. **HRMS** (ESI): Calc. for $C_{16}H_{27}O_2Si$ $(M+H)^+$: 279.1775, found: 279.1770.

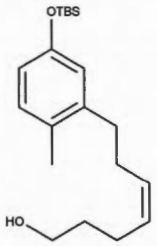
Compound 18: To a solution of CBr_4 (650 mg, 2 eq.) in dry CH_2Cl_2 (0.75 mL) at 0°C, was



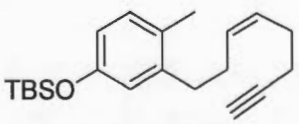
added PPh_3 (1050 mg, 4 eq.), the solution was stirred during 20 minutes and compound **17** (280 mg, 1 mmol, 1 eq.) diluted in CH_2Cl_2 (0.25 mL) was added dropwise. The solution was stirred for 1 h at room temperature and was firstly filtrated on a plug of silica gel (*n*-hexane:EtOAc, 85:15) and concentrated under reduced pressure. The crude dibromo alkene (296 mg, 0.68 mmol) was subsequently diluted in dry THF (3 mL) at -78°C and *n*-BuLi (0.6 mL at 2.5 M., 1.5 mmol, 2.2 eq.) was added and the solution was stirred for 15 minutes and then a solution of 5 mL of sat. aq. NH_4Cl was added. The aqueous phase was extracted with EtOAc (3 *5 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by chromatography (*n*-hexane:EtOAc, 97:3) to afford 0.176 g (64%) of the desired compound **18** as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.1 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.70 (dd, J = 6.7; 6.7 Hz, 1H), 2.84 (t, J = 7.7 Hz, 2H), 2.48 (td, J = 7.7; 2.6 Hz, 2H), 2.29 (s, 3H), 2.03 (t, J = 2.6 Hz, 1H), 1.03 (s, 9H), 0.24 (s, 6H);**^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.8, 139.7,

131.1, 128.59, 120.7, 118.1, 84.1, , 68.9, 32.4, 25.9, 19.3, 18.5, 18.4, -4.3. **HRMS** (ESI): Calc. for $C_{17}H_{27}OSi$ $(M+H)^+$: 275.1826, found: 275.1832.

Compound 23 : To a solution of compound **18** (244 mg, 0.9 mmol.) in dry THF (2 mL) at -78°C, was added *n*-BuLi (0.4 mL at 2.5M., 1 mmol, 1.1 eq), the solution was stirred for 10 minutes and was subsequently added in the following order BF_3-OEt_2 (0.16 mL) and oxetane (0.09 mL). The reaction was stirred overnight and then a solution of 5 mL of sat. aq. NH_4Cl was added. The aqueous phase was extracted with EtOAc (3 *5 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by chromatography (*n*-hexane:EtOAc, 75:25) to afford 228 mg (80%) of the desired alcohol. This compound was diluted in MeOH (5 mL) and Lindlar catalyst (0.1mmol, 15%) was added and the solution was saturated under hydrogen atmosphere during 1 hour. The reaction was filtrated and purified by chromatography on silica gel (*n*-hexane:EtOAc, 75:25) to afford 213 mg (70%) of compound **23**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.97 (d, J = 8.0 Hz, 1H), 6.68 – 6.51 (m, 2H), 5.55 – 5.32 (m, 2H), 3.60 (dd, J = 11.2; 5.7 Hz, 2H), 2.58 (t, J = 7.7 Hz, 2H), 2.31 (q, J = 7.5 Hz, 2H), 2.23 (s, 3H), 2.08 (q, J = 7.5 Hz, 2H), 1.56 (p, J = 7.0 Hz, 2H), 0.98 (s, 9H), 0.18 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.5, 141.2, 130.7, 129.6, 129.5, 128.4, 120.6, 117.3, 77.4, 77.0, 76.5, 62.4, 33.2, 32.5, 27.7, 25.7, 23.5, 18.4, 18.1, -4.5. **HRMS** (ESI): Calc. for $C_{20}H_{35}O_2Si$ $(M+H)^+$: 335.2401, found: 335.2404.

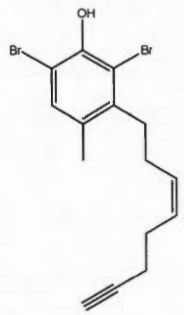


Compound 19 : To a solution of compound **23** (142.2 mg, 0.4 mmol) in dry CH_2Cl_2 (4.3 mL) was added molecular sieve and PCC (230 mg, 2.5 eq.). The solution was stirred for 1 hour at room temperature and directly filtrated on silica gel (*n*-hexane:EtOAc, 85:15) to afford 93 mg of the desired aldehyde. This aldehyde was treated in the same conditions than compound **18** to produce 82 mg of compound **19** in 62% overall yield from compound **23**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.98 (d, J = 8.1 Hz, 1H), 6.65 (d, J = 2.5 Hz, 1H), 6.60 (dd, J = 8.1; 2.6 Hz, 1H), 5.61-5.39 (m, 2H), 2.60 (m, 2H), 2.38 – 2.13 (m, 9H), 1.95 (t, J = 2.5 Hz, 1H), 1.00 (s, 9H), 0.20 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.8, 141.3, 130.9, 130.6, 128.6, 128.3,



120.7, 117.5, 84.3, 77.6, 77.16, 76.7, 68.5, 33.5, 28.0, 26.5, 25.9, 18.9, 18.6, 18.4, -4.3. **HRMS** (ESI): Calc. for $C_{21}H_{33}OSi$ $(M+H)^+$: 329.2295, found: 329.2298.

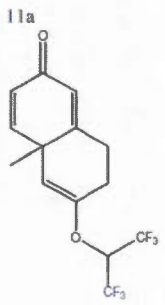
Compound 20 : To a solution of compound **19** (67 mg, 0.2 mmol) in MeOH (4 mL) was



added K_2CO_3 (68 mg, 2.5 eq.). The solution was heated at 60°C for 1 hour and then a solution of 5 mL of sat. aq. NH_4Cl was added. The aqueous phase was extracted with EtOAc (3 *5 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was used without further purification and diluted in CH_2Cl_2 (3 mL) at 0°C and a solution of NBS (35 mg) in CH_2Cl_2 (1 mL) was added dropwise. The solution was stirred for 15 minutes and diluted with a saturated solution of $Na_2S_2O_3$ (4 mL), the aqueous phase was extracted with CH_2Cl_2 (3 *5 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude mixture was purified by chromatography (*n*-hexane:EtOAc, 93:7) to afford 38 mg (52%) of compound **20**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 (s, 1H), 5.81 (s, 1H), 5.67 – 5.36 (m, 2H), 2.89 – 2.72 (m, 2H), 2.38 – 2.13 (m, 9H), 1.95 (t, J = 2.4 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.6, 140.2, 132.8, 130.4, 129.7, 129.0, 113.3, 106.4, 84.1, 68.6, 33.6, 26.4, 26.3, 19.8, 18.9. **HRMS** (ESI): Calc. For $C_{15}H_{17}Br_2O$ $(M+H)^+$: 372.9621, found: 372.9629.

III. Copies of 1H and 13C NMR spectra

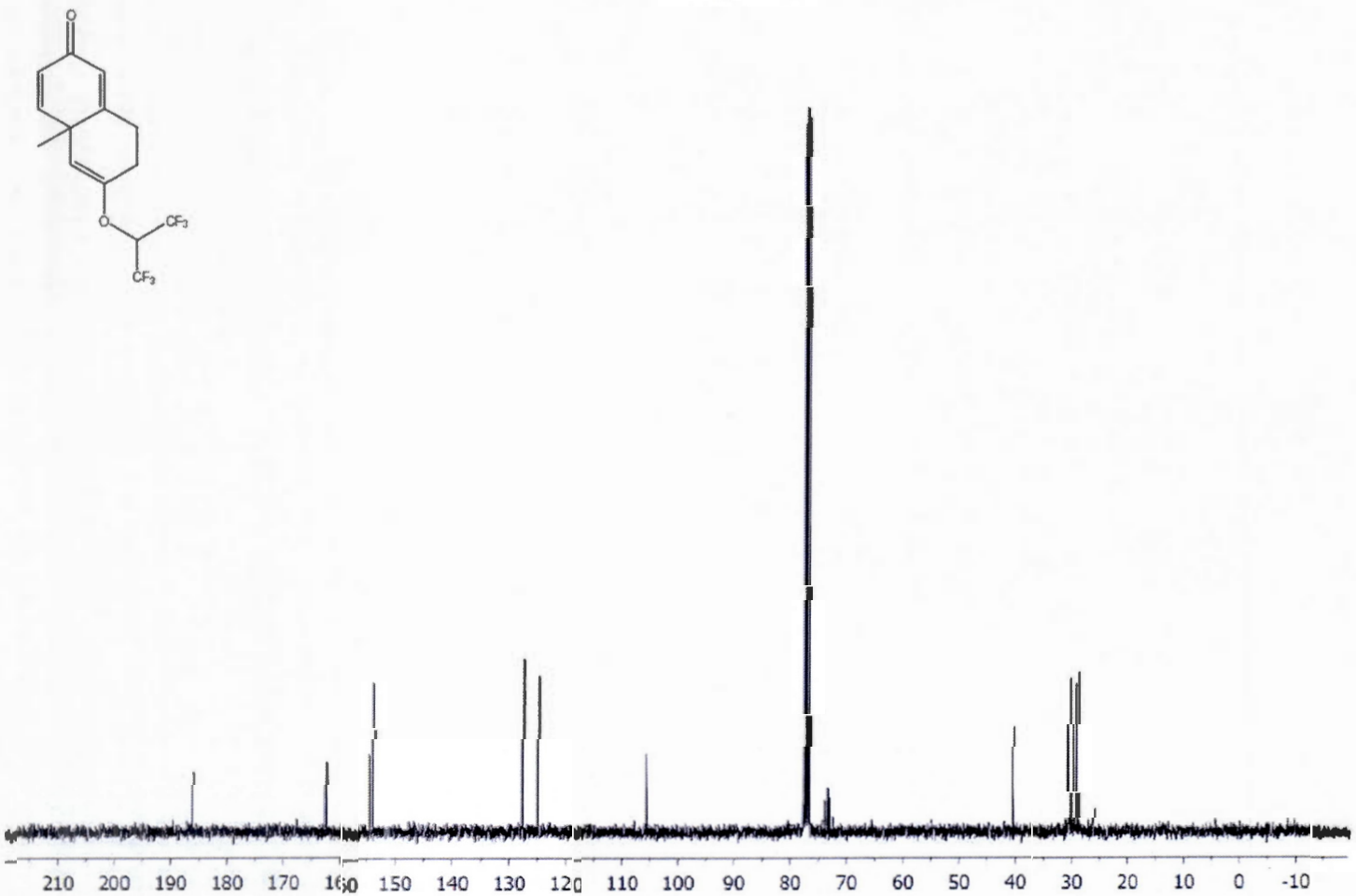
11a



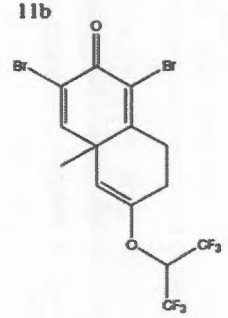
$CDCl_3$, 300 MHz

11a

$CDCl_3$, 75 MHz



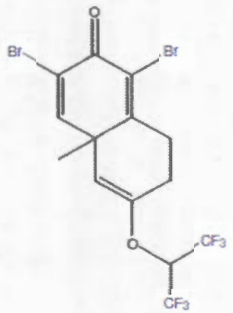
11b



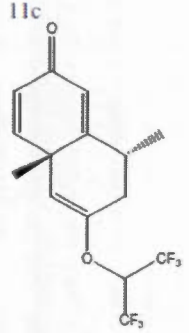
$CDCl_3$, 300 MHz

11b

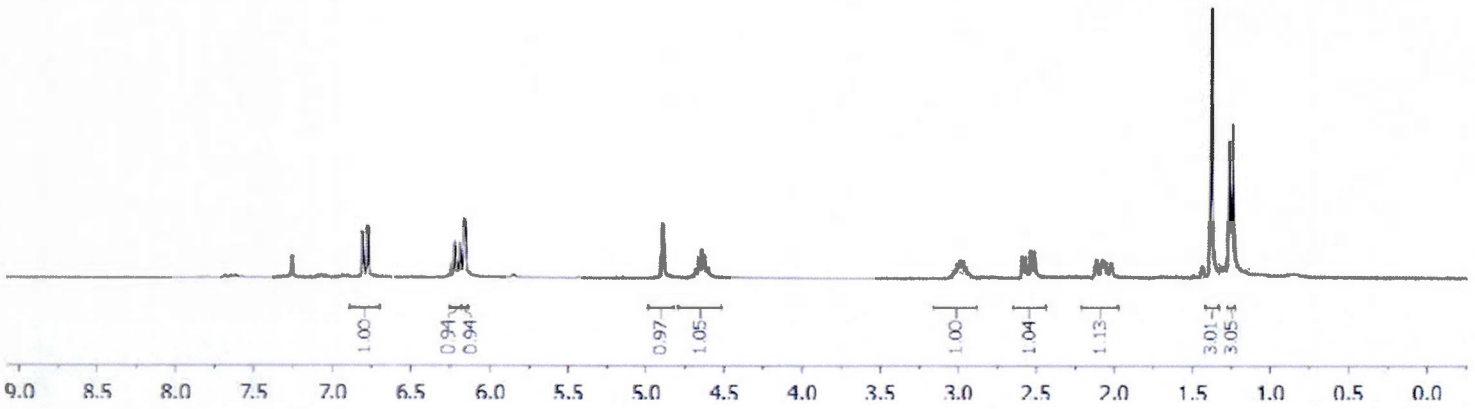
$CDCl_3$, 75 MHz



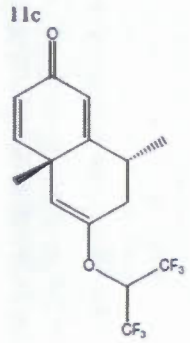
11c



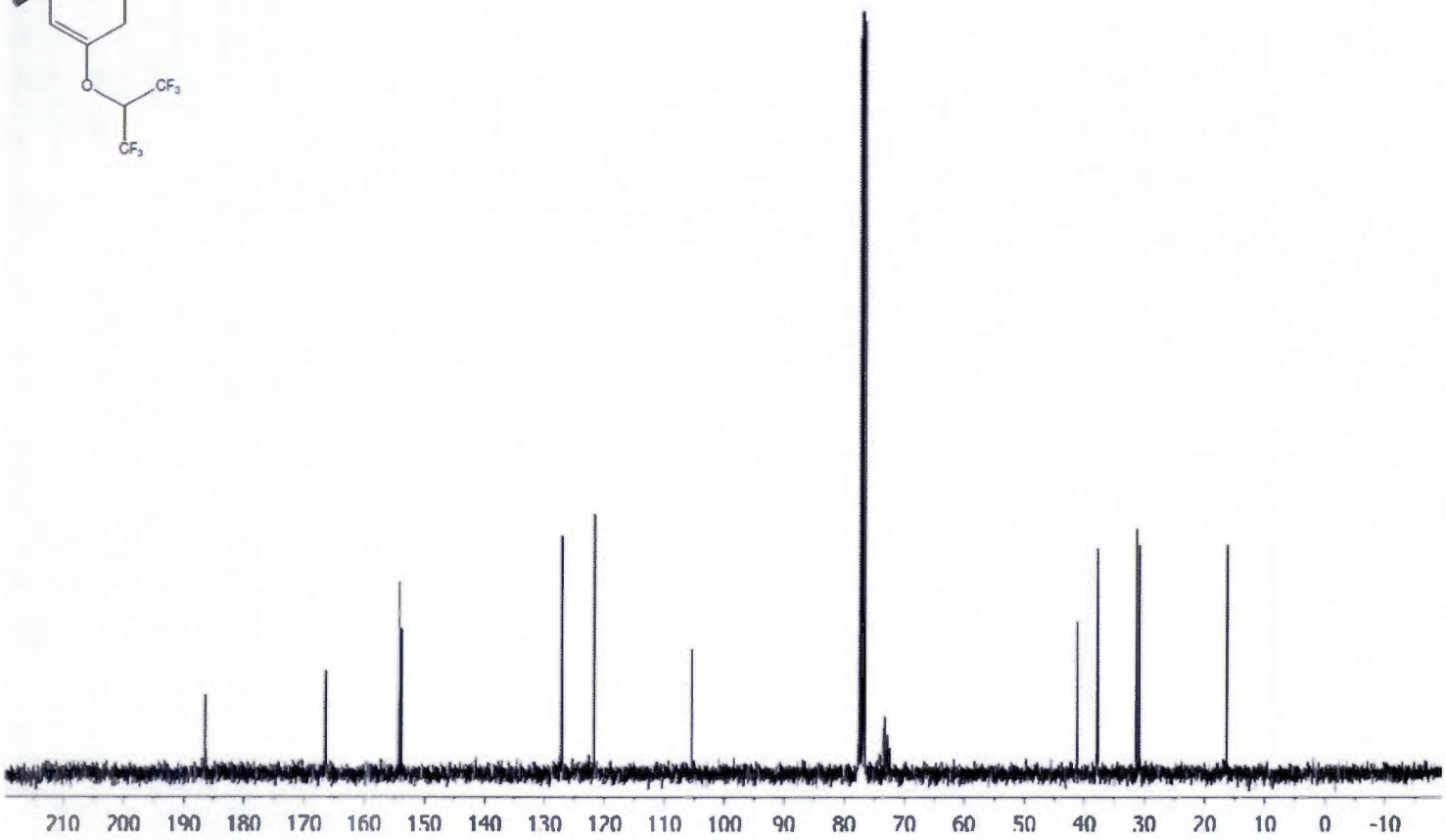
$CDCl_3$, 300 MHz



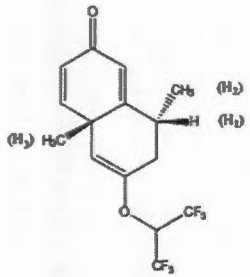
11c



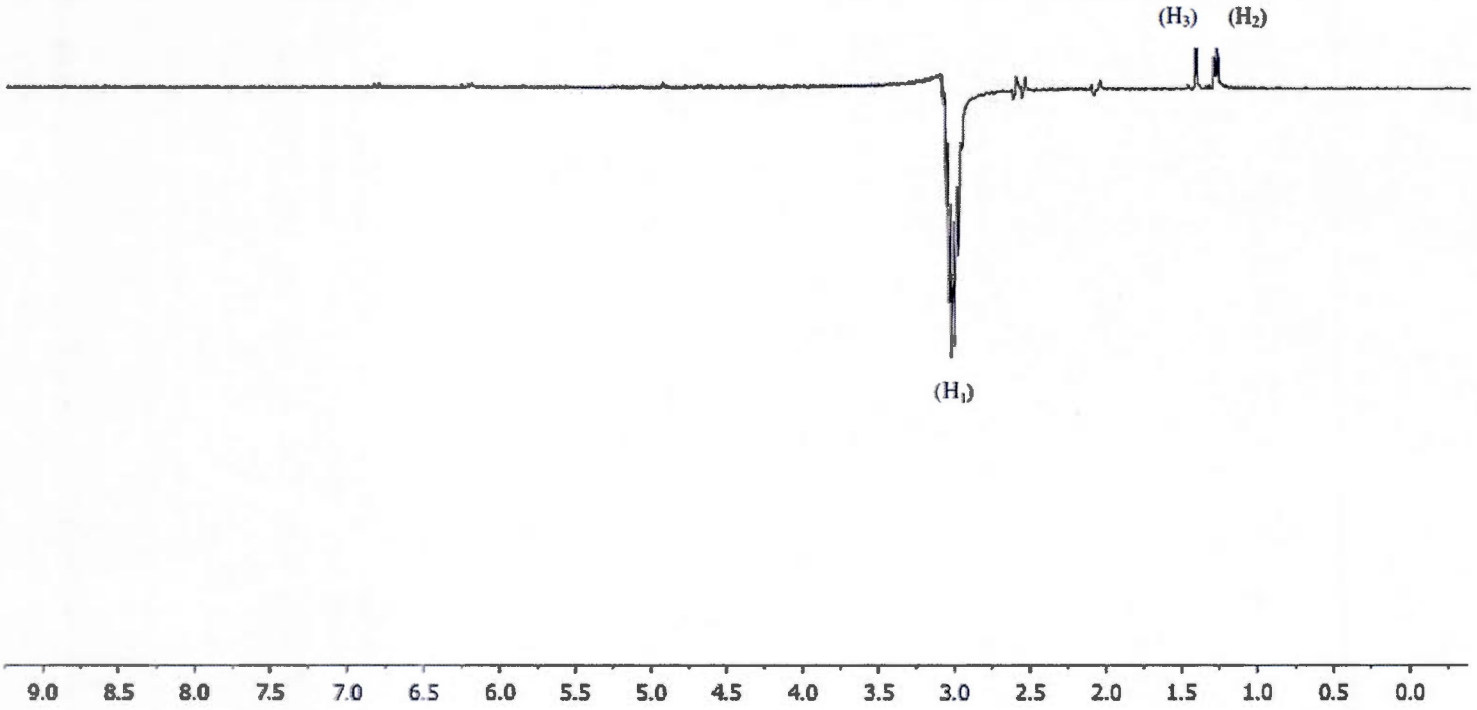
$CDCl_3$, 75 MHz



11c



$CDCl_3$, 300 MHz



11d

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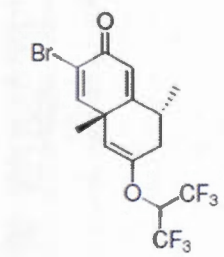
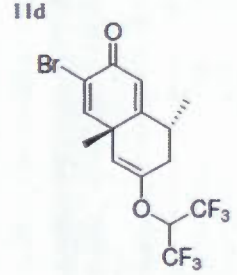
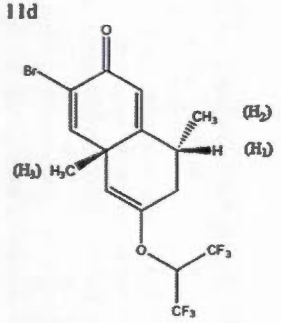


11d



$CDCl_3$, 75 MHz

11d



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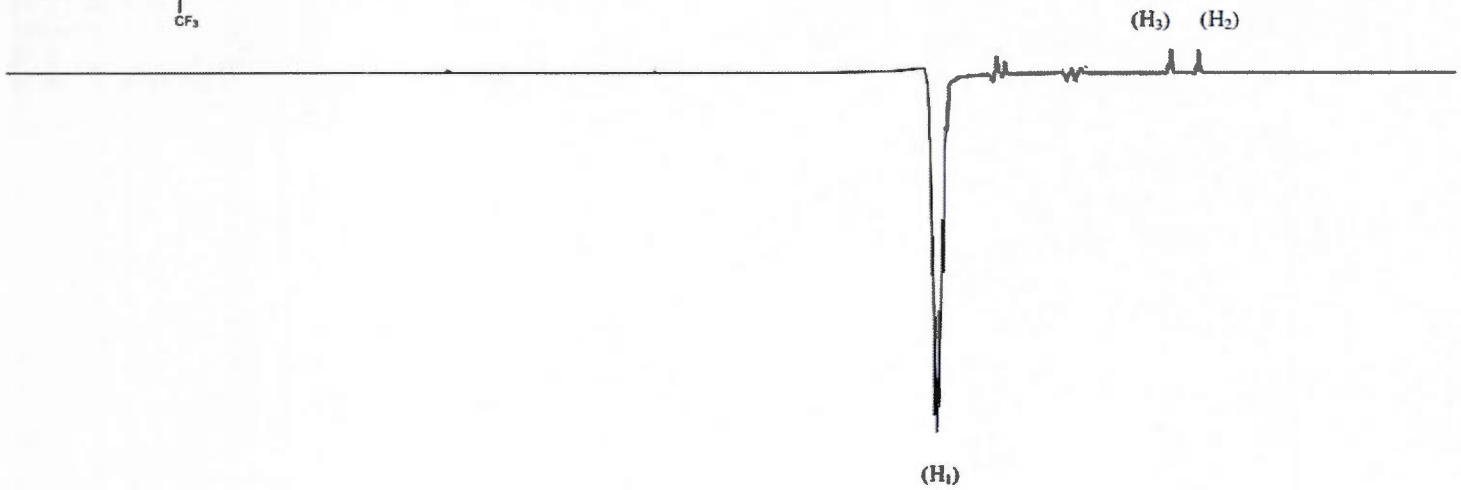
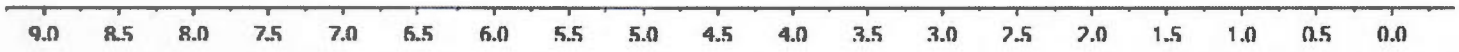
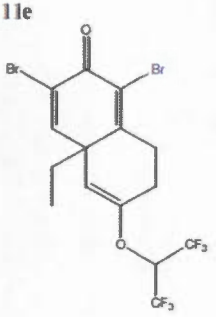
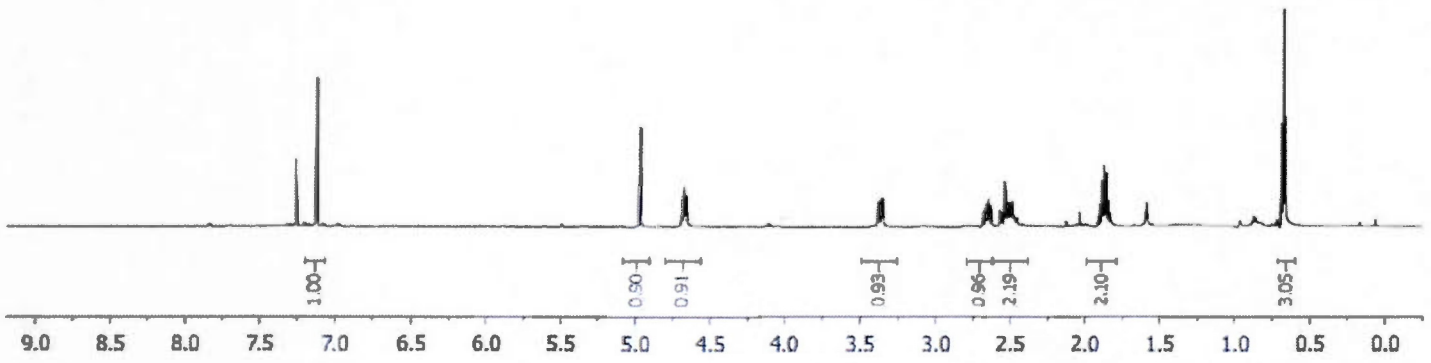




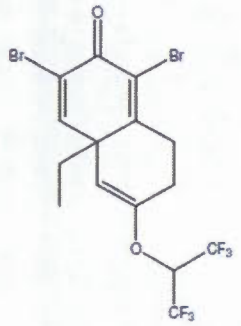
11e



$CDCl_3$, 600 MHz

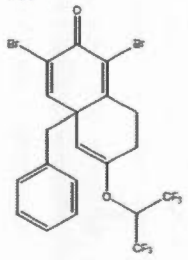


11e



$CDCl_3$, 75 MHz

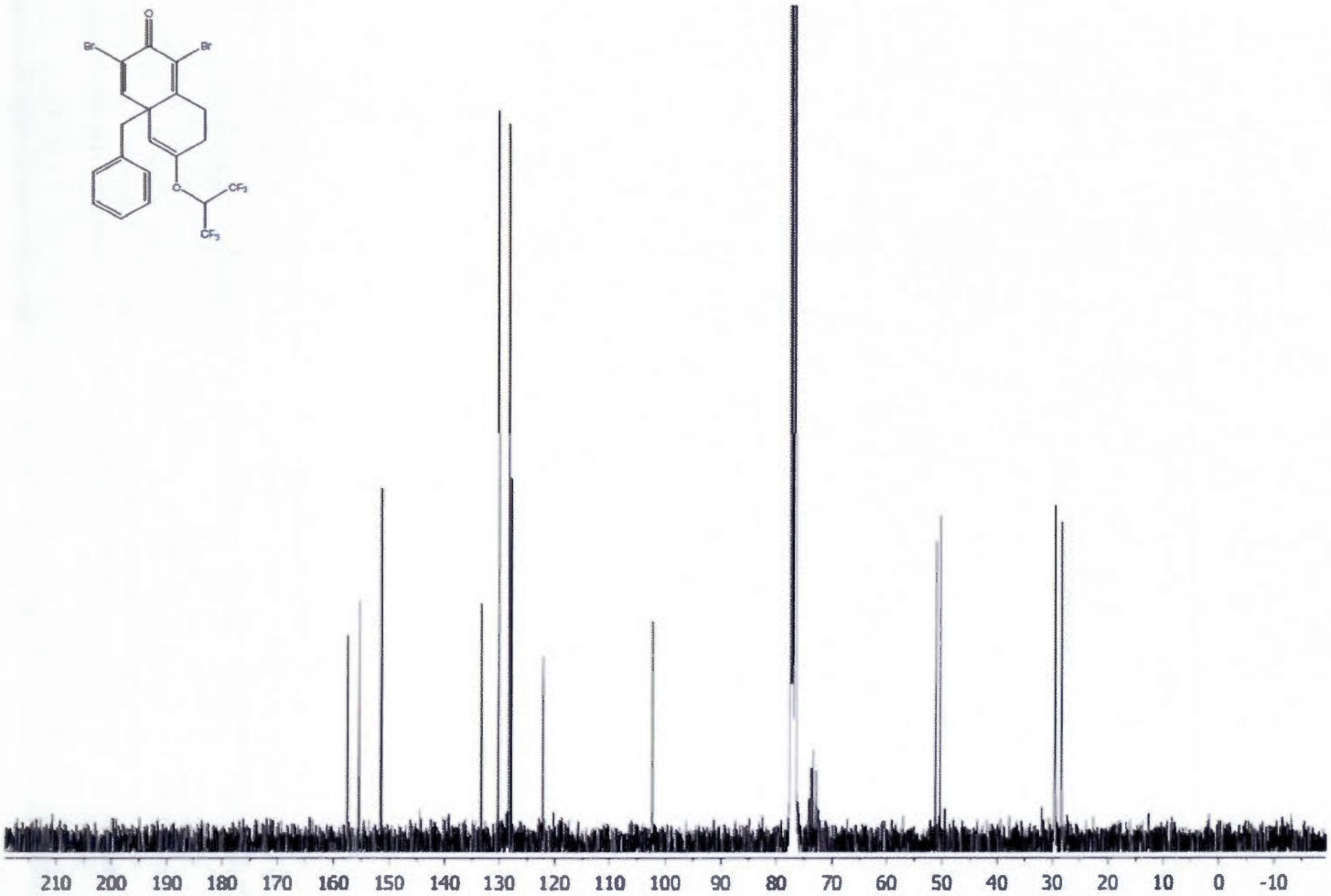
11f



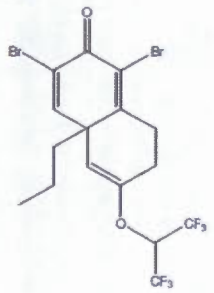
$CDCl_3$, 300 MHz

11f

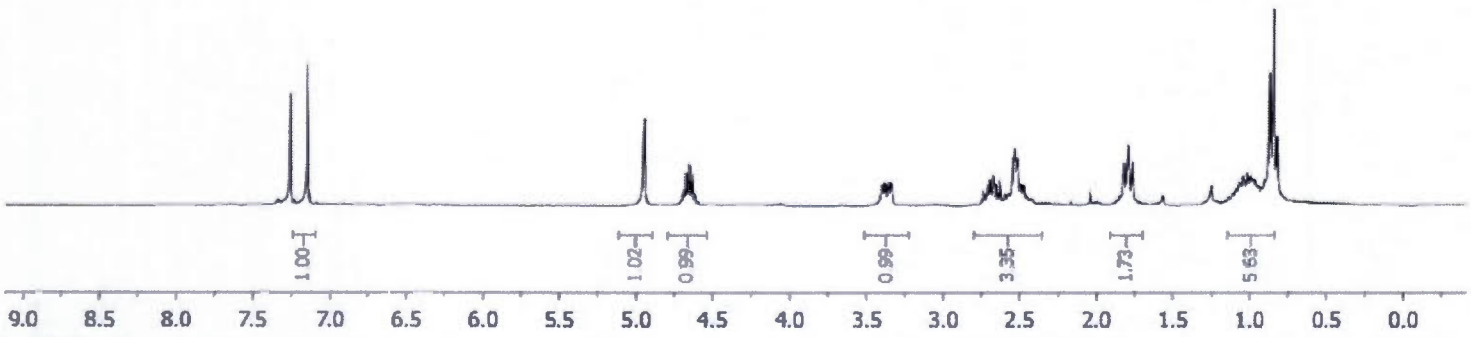
$CDCl_3$, 300 MHz



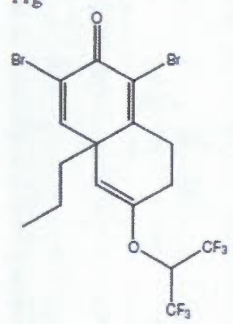
11g



$CDCl_3$, 300 MHz

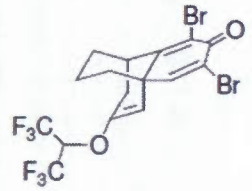


11g

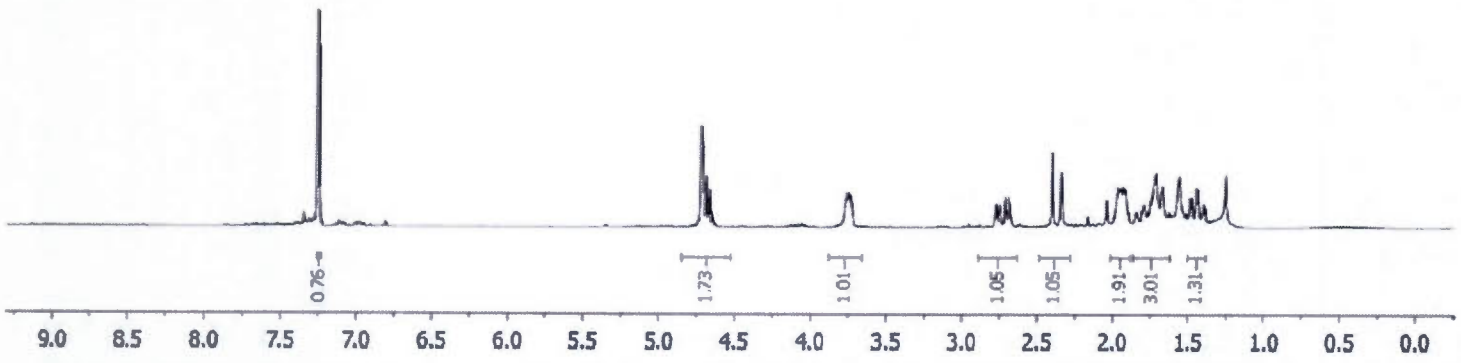


$CDCl_3$, 300 MHz

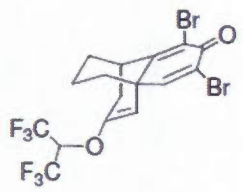
11h



CDCl3, 300 MHz

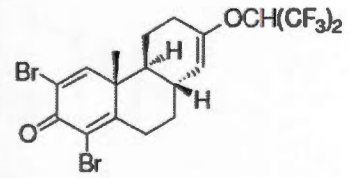


11h



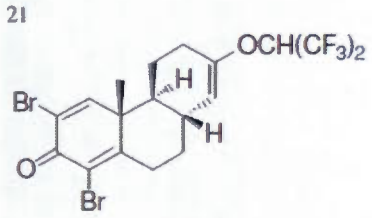
$CDCl_3$, 75 MHz

21



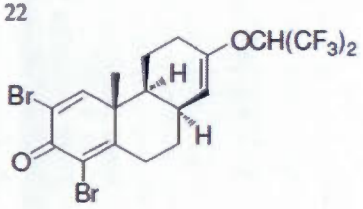
$CDCl_3$, 600 MHz

21

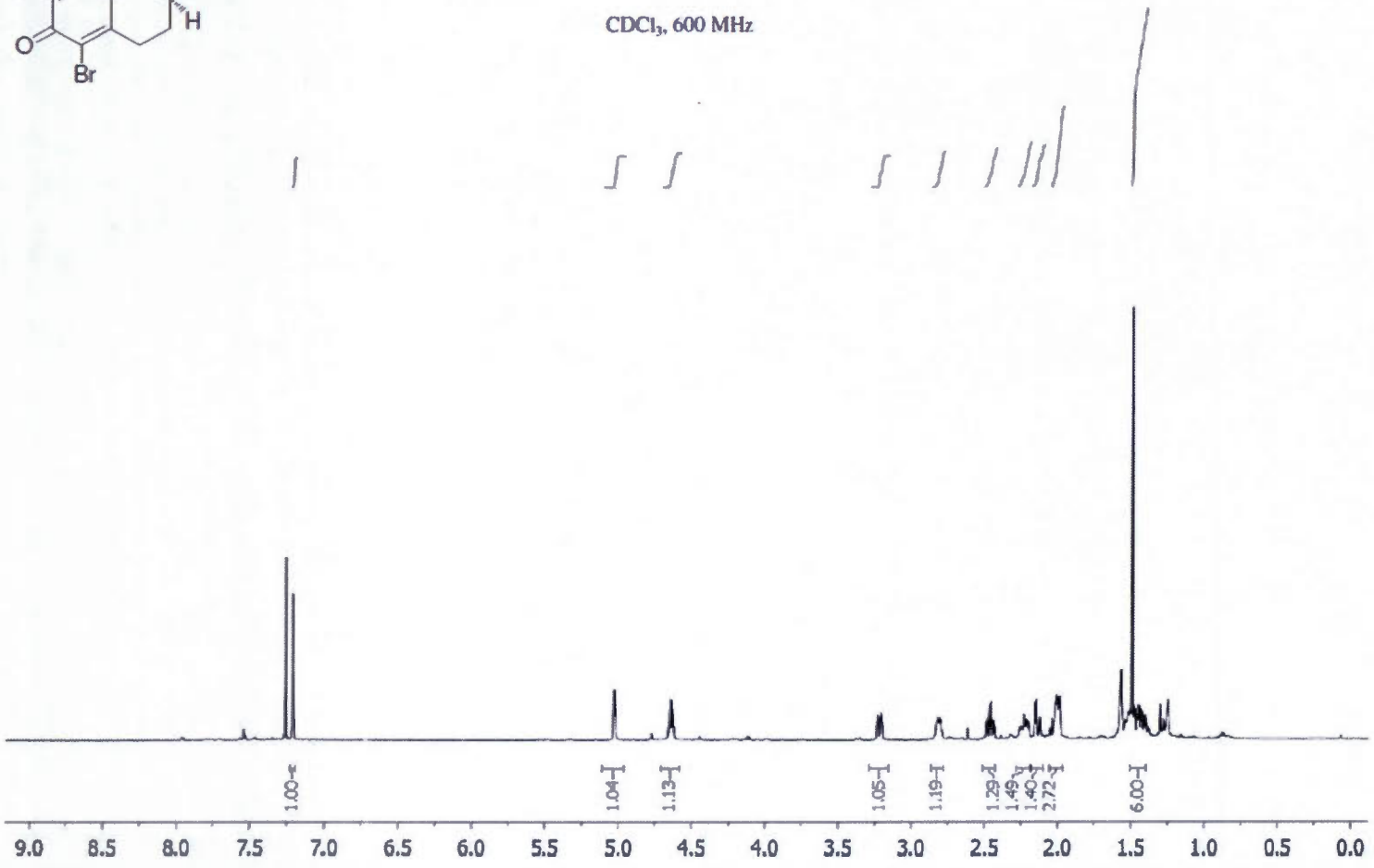


CDCl$_3$, 150 MHz

22



$CDCl_3$, 600 MHz



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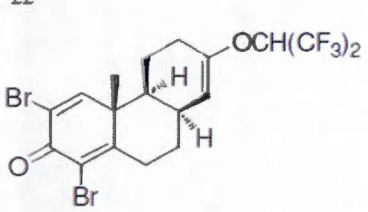
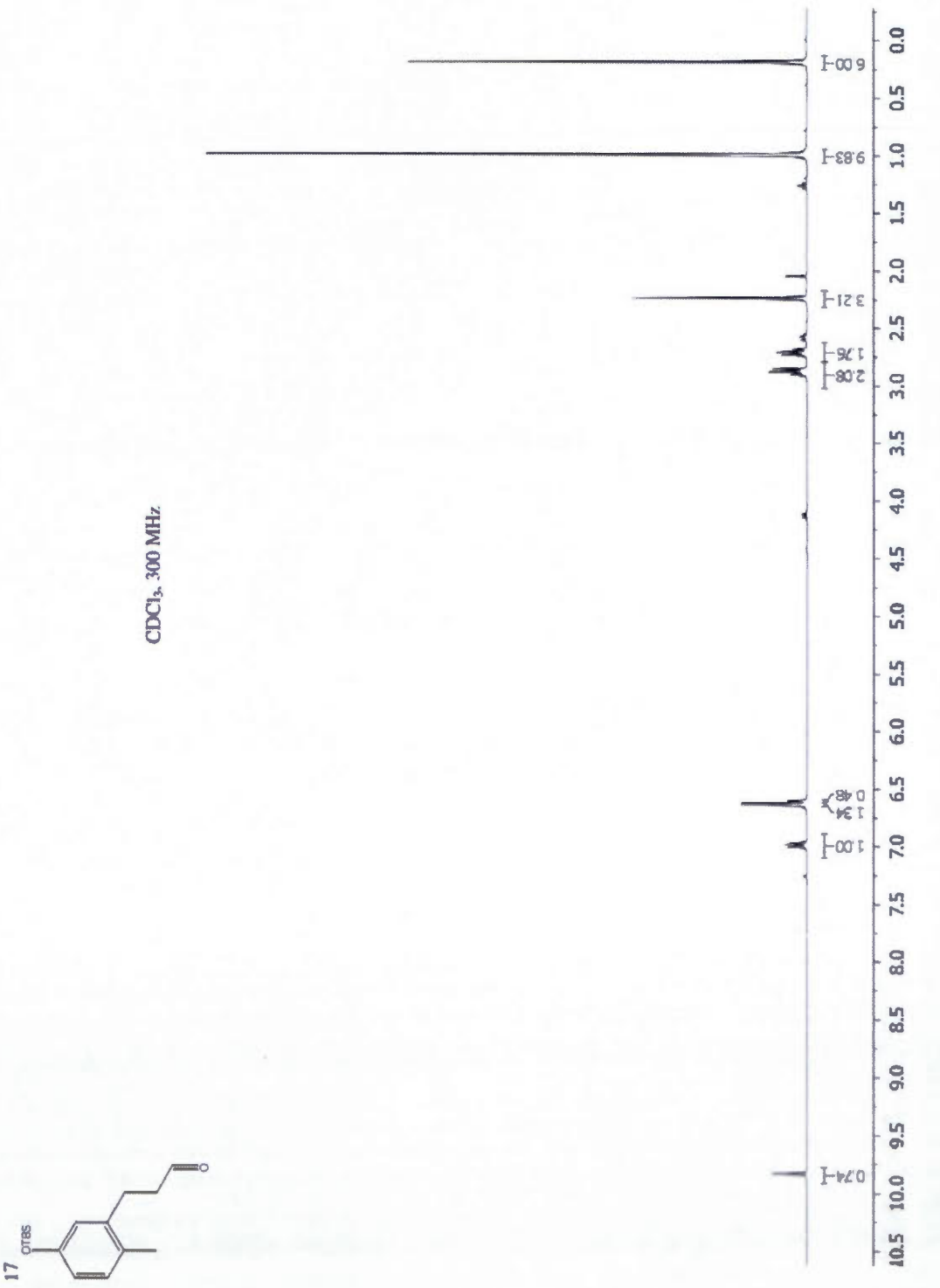
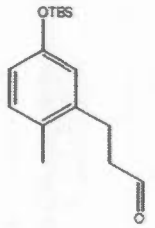
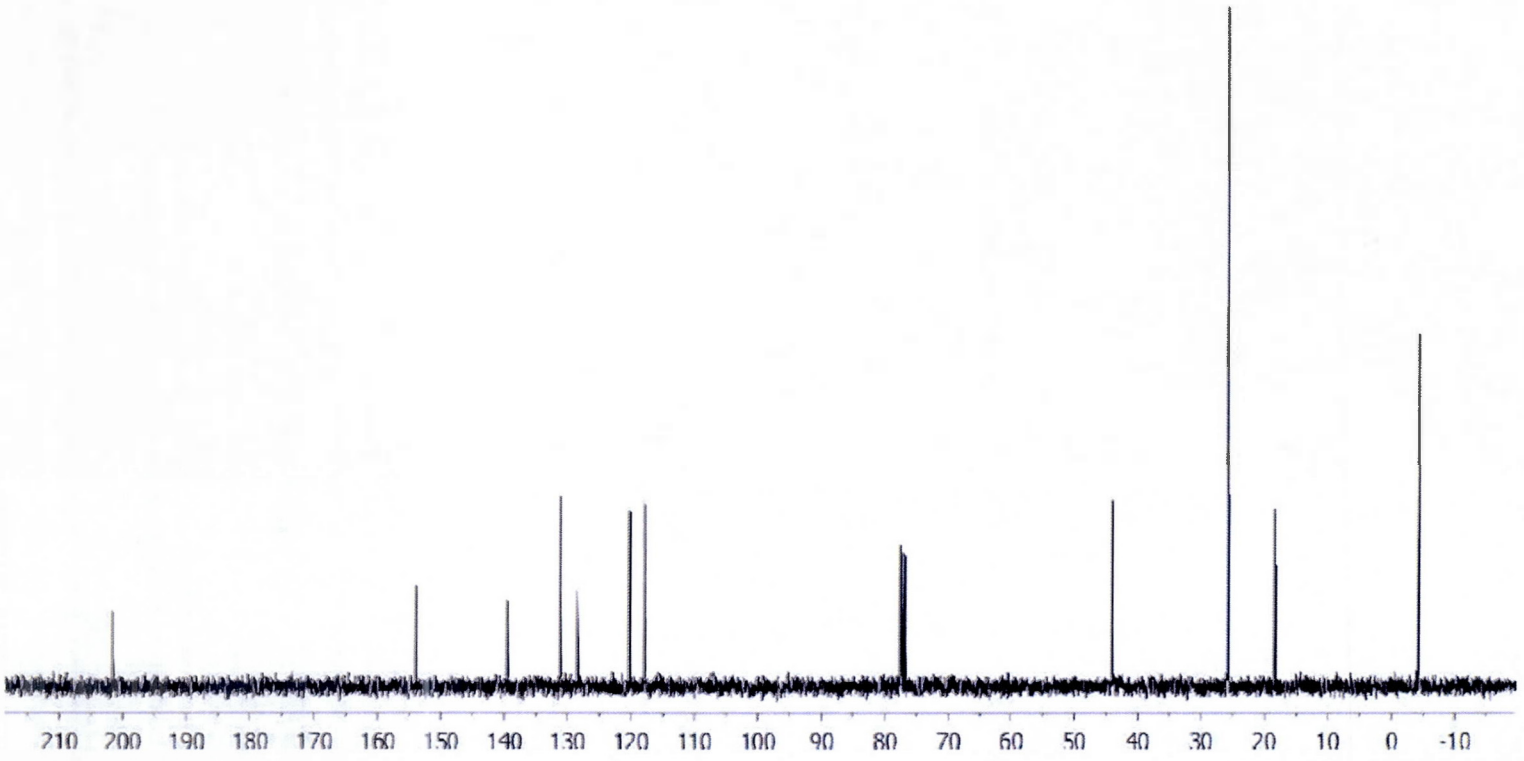


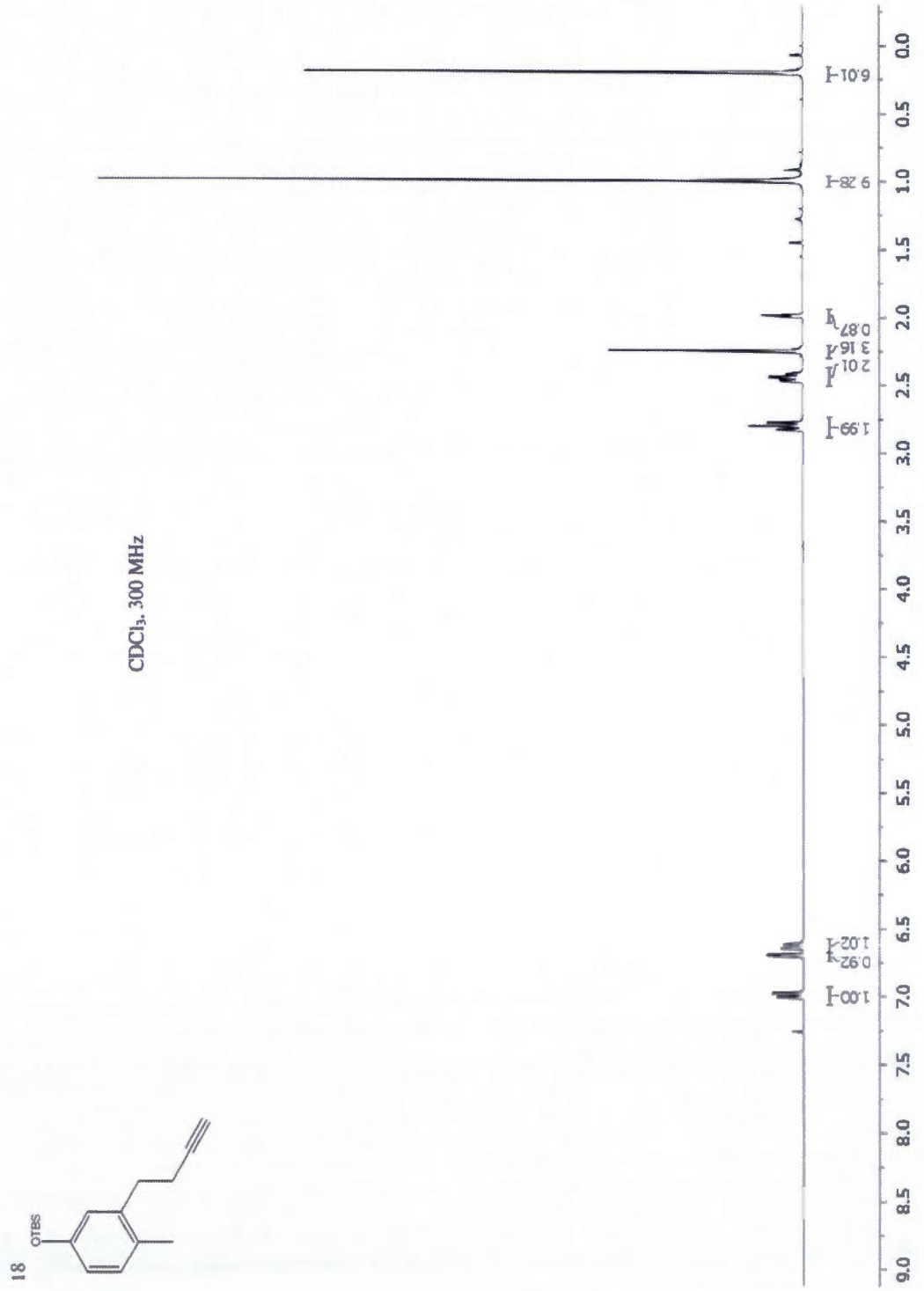
$CDCl_3$, 150 MHz


17
OTBS
CDCl3, 300 MHz
0.74
1.00
1.34
0.48
3.21
2.08
1.36
9.83
6.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

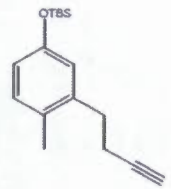

OTBS
O

$CDCl_3$, 75 MHz

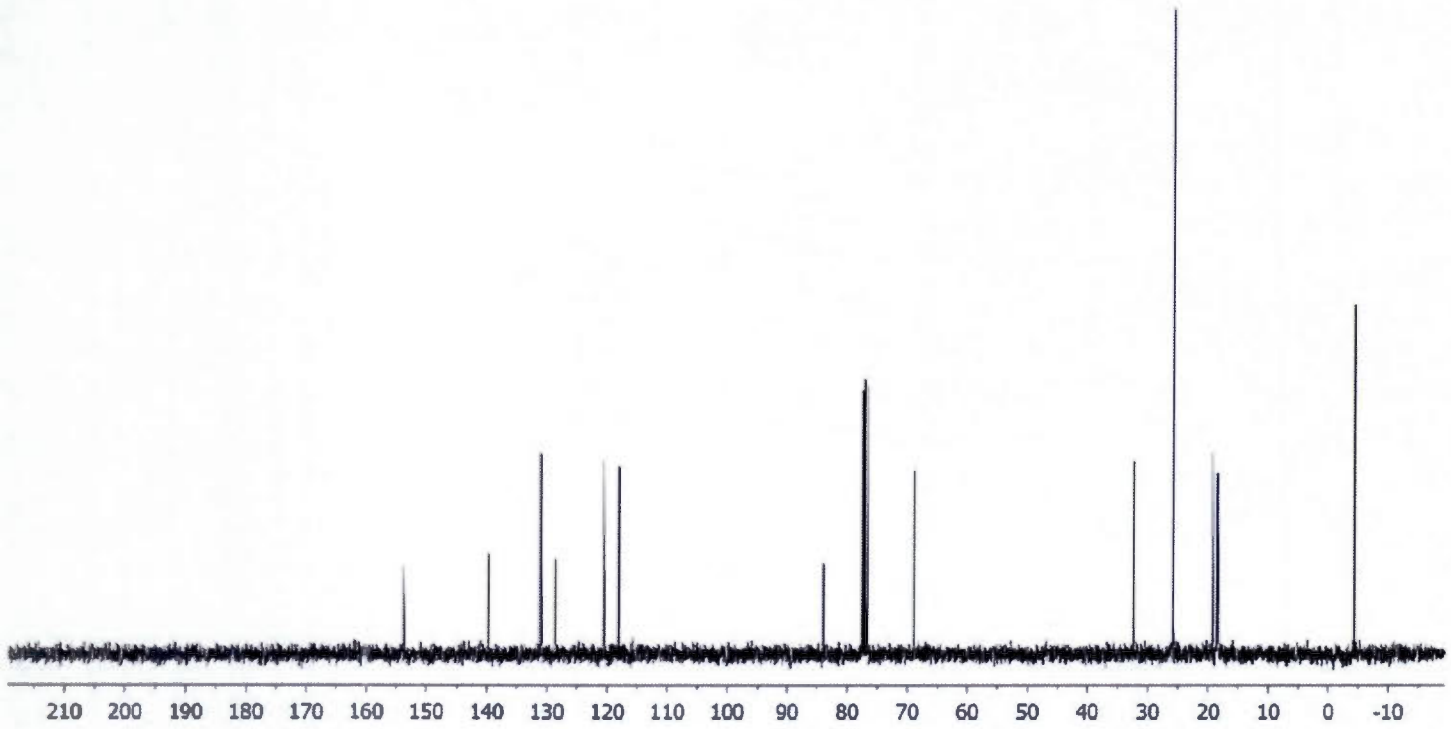

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


18
OTBS
CDCl3, 300 MHz
6.01
9.28
2.01
3.16
0.87
1.99
0.92
1.02
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

18



$CDCl_3$, 75 MHz



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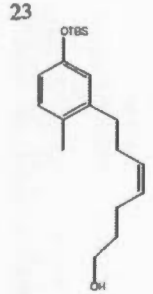
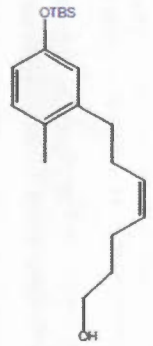


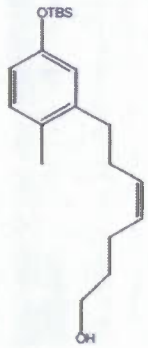
$CDCl_3$, 300 MHz

23



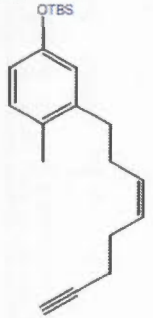
$CDCl_3$, 75 MHz

23



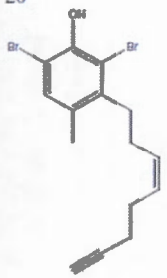
$CDCl_3$, 75 MHz

19

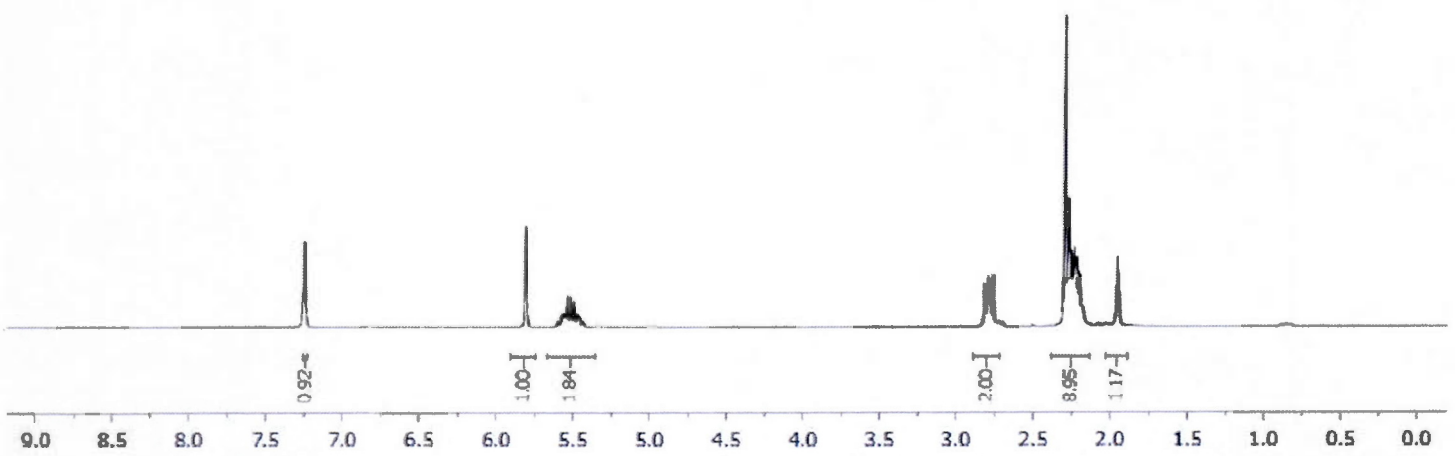


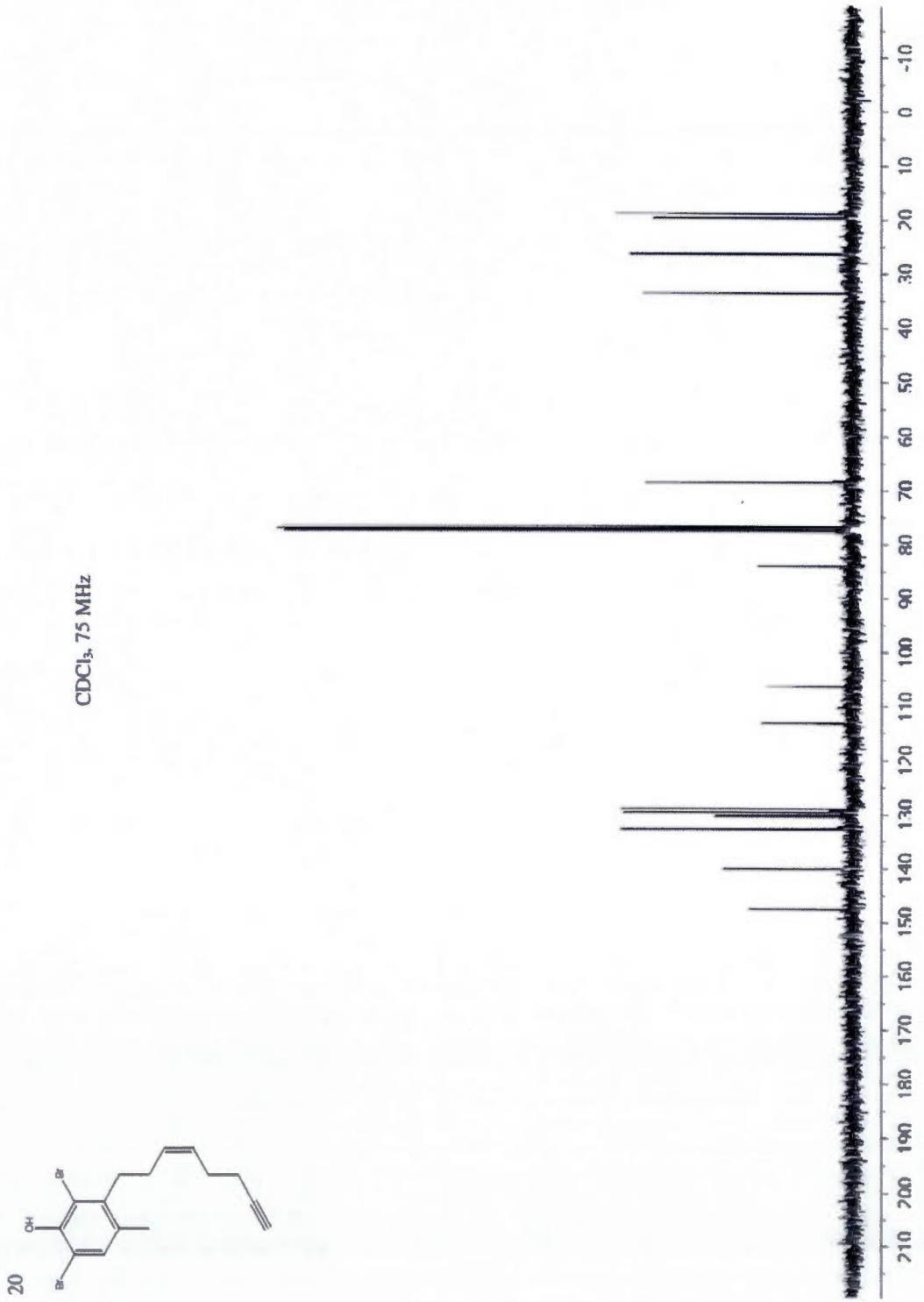
$CDCl_3$, 75 MHz

20



$CDCl_3$, 300 MHz




CDCl3, 75 MHz
20
OH
Br
Br
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

ANNEXE C

« ASYMMETRIC SYNTHESIS OF THE MAIN CORE OF KAURANE FAMILY MEMBERS TRIGGERED BY AN OXIDATIVE POLYCYCLIZATION-PINACOL TANDEM PROCESS » ARTICLE

L'article sera soumis sous peu

Titre : Asymmetric Synthesis of the Main Core of Kaurane Family Members Triggered by an Oxidative Polycyclization-Pinacol Tandem Process

Auteurs : Samuel Desjardins, Sylvain Canesi*

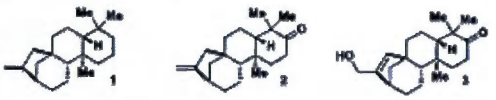
Oxidative Polycyclization

DOI: 10.1002/anie.200((will be filled in by the editorial staff))

Asymmetric Synthesis of the Main Core of Kaurane Family Members Triggered by an Oxidative Polycyclization-Pinacol Tandem Process**

Samuel Desjardins and Sylvain Canesi*

Cationic polycyclizations of poly-unsaturated compounds in biomimetic syntheses have been used to access to complex architectures with excellent diastereoselectivity.[1] One remarkable example has been developed by Johnson *et al.* for the syntheses of steroids;[1a] Due to their elegance and efficiency such strategies are still under intensive investigation as an expeditious access to complex natural products. Such methods are generally triggered by an electrophilic species selectively generated which is rapidly trapped by several π-bonds in a stereoselective avenue and the cascade is concluded by a nucleophilic capture from an external nucleophile. Moreover, others important transformations that can be performed in similar conditions are the cationic molecular transpositions.[2] Despite being first described more than a century ago, these cationic molecular transpositions still represent an appealing and efficient route to elaborated structures via 1,2-substituent shifts such as the Wagner-Meerwein, pinacolic, and the Prins-pinacol processes. As an illustration, the Prins-pinacol tandem process has often been used as a key strategy in syntheses of natural products, as well demonstrated by Overman and coworkers.[3] We were wondering, if a combination of these powerful synthetic tools could lead to a rapid stereoselective avenue of complex skeletons present in a large family of diterpens named kaurane.[4] These polycyclic natural products have been isolated from numerous natural sources and have a plethora of biological properties.[4a] Until now, if some hemi-syntheses have been reported from an elaborated natural starting material, none total synthesis of these compounds has been reported in the literature. However the architecture of these compounds appears an interesting synthetic challenge; indeed, the tetracyclic system contains several quaternary carbon centers as well as contiguous asymmetric centres. The main carbon-skeleton of an ent-kaurane diterpene **1** as well as two members belonging to this family, kaur-16-en-3-one **2** and 3-oxo-kaur-15-en-17-al **3** are described in Figure 1.



[*] S. Desjardins and Prof. Dr. S. Canesi
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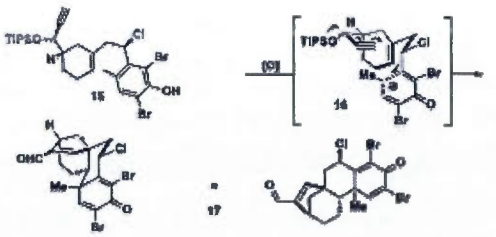
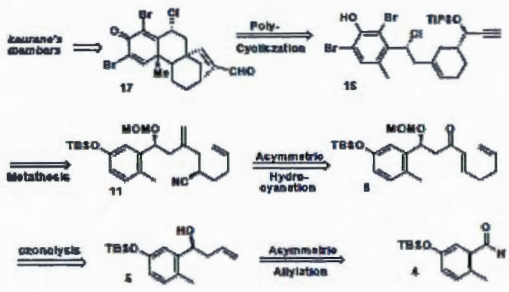
One important key aspect enabling a successful polycyclization process is the capacity to induce selectively an electrophilic species enabling to trigger the cascade. In addition, the cyclohexanone core of compound **3** could hypothetically derive from a phenol derivative **15** which would be dearomatized by chimioselective activation. Our interest in oxidative dearomatization of electron-rich aromatics involving carbon-based nucleophiles[5] led us to question whether the oxidative cationic polycylisation could be triggered by activation of a phenol. Although electron-rich aromatic compounds such as phenols and their derivatives normally react as nucleophiles, oxidative activation can transform these compounds into highly reactive electrophilic species such as **16**. This phenoxonium ion **16** could be intercepted in an intramolecular fashion by appropriate carbon-based nucleophiles such as π bonds, thus initiating a polycyclization via a cationic cascade that would be concluded in this case by a stereoselective ring contraction mediated by a pinacol process. A combination of these methods allows knitting the lateral chain into the tetracyclic core of kaurane **17** with the correct configuration for each stereocenter. An unprecedented enantiospecific avenue is controlled by the benzilic stereocenter enabling the selective formation of the first quaternary carbon via a chair transition state **16**, in minimizing steric and electronic interactions. This phenol reversal of reactivity may be thought of as involving "aromatic ring umpolung"[6], Figure 2.

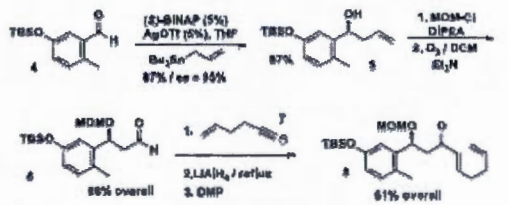


An indication of how the formation of the corresponding phenoxonium ion **16** can be generated is apparent in the work of Kita,[7] who has shown that phenols may be activated under the influence of hypervalent iodine reagents[8,9] such as iodobenzene diacetate (DIB) or phenyliodine bis(trifluoroacetate (PIFA), environmentally benign reagents. This reaction is generally best performed in solvents such as hexafluoroisopropanol (HFIP).[10] This aromatic ring umpolung concept provides new strategic

opportunities in synthetic chemistry, by extension of several well-known reactions in aliphatic chemistry to the aromatic chemistry. In this paper, we present a rapid asymmetric synthesis of the main tetracyclic core of kaurane derivative 17 mediated by an oxidative polycyclization-pinacol tandem process; a retrosynthesis pathway from a basic phenol derivative 4 is described in Figure 3.

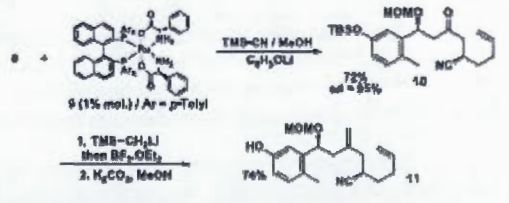


Starting from known compound 4,[11] the first asymmetric center is installed using a Yamamoto allylation process[12] leading to alcohol 5 in 87% yield and 95% ee. This compound is protected with MOMCl and a subsequent ozonolysis leads to aldehyde 6 in 88% yield overall. A nucleophilic capture of 6 with the anion of alkyne 7[13] produces an epimeric mixture of propargylic alcohol, a further treatment with LAH reduces stereoselectively the alkyne moiety into a trans alkene by assistance with the hydroxyl group and the alcohol mixture is oxidized with Dess–Martin periodinane leading to ketone 8 in 61% yield over three steps, Scheme 1.



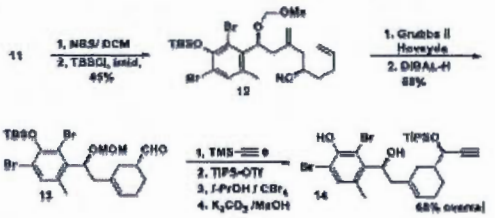
Scheme 1.

An asymmetric hydrocyanation mediated by a ruthenium catalyst developed by Ohkuma et al.[14] controls the formation of the new stereocenter required in 72% yield and 95% ed. A Peterson olefination on ketone 10 followed by a TBS deprotection in basic conditions afford phenol 11 in 74% yield overall, Scheme 2.



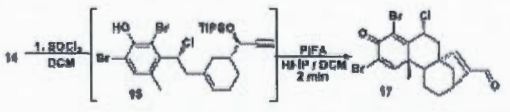
Scheme 2.

At this stage, bromines have been introduced on the aromatic moiety; these halides have a double utility. Firstly, they are used as a protecting atom of *ortho*-positions of the phenol moiety, forcing the polycyclization during the umpolung activation to occur at the *para* position which is assumed to be the most stable resonance form of the phenoxonium species 16 (Figure 2). Indeed, due to their electron-withdrawing effect, bromines destabilize the resonance positive charge in *ortho* and less hinder position. Secondly, bromine could be used subsequently to introduce one of the methyl group required at this position for the synthesis of a kaurane derivative, using transition metal chemistry. It appeared during the synthesis that compound 11 was the best precursor to introduce halides; others attempts accomplished on further intermediates were unsuccessful probably for steric reasons. It has been observed that it was more convenient to protect with a TBS the phenol moiety and a metathesis reaction on compound 12 with Hoveyda-Grubbs second generation leads to the desired cyclohexene core, a subsequent treatment with DIBAL-H produces the aldehyde 13 in 68% yield overall. In presence of the anion of TMS-acetylene, a mixture of secondary propargylic alcohol is obtained in a ratio (1:1), both of them leads to the same aldehyde 17 after the key oxidative polycyclization-pinacol tandem process (Figure 1). The alcohol moiety is protected with a hinder TIPS group to avoid that the propargylic alcohol moiety traps an electrophilic species generated during the cationic cascade instead of the alkyne segment, the MOM group is selectively cleaved in mild acidic conditions and the TBS and alkyne TMS groups are selectively removed in basic condition, producing 14 in 68% yield over four steps, Scheme 3.



Scheme 3.

At this stage, the secondary alcohol functionality emerging is substituted by chlorine with inversion of configuration. It should be noted that the configuration of this benzilic stereocenter is very important and allows controlling all the emerging stereocenters generated during the umpolung activation in favouring the chair like transition state 16, Figure 1. The elaborated lateral chain 15 represents the key intermediate enabling one step stereoselective formation of the tetracyclic system 17 belonging to the kaurane's family triggered by PIFA in 25% yield over two steps, Scheme 4.



Scheme 4.

ANNEXE D

« ASYMMETRIC SYNTHESIS OF THE MAIN CORE OF KAURANE FAMILY MEMBERS TRIGGERED BY AN OXIDATIVE POLYCYCLIZATION-PINACOL TANDEM PROCESS » SUPPORTING INFORMATION

L'article sera soumis sous peu

Titre : Asymmetric Synthesis of the Main Core of Kaurane Family Members Triggered by an Oxidative Polycyclization-Pinacol Tandem Process

Auteurs : Samuel Desjardins, Sylvain Canesi*

Asymmetric Synthesis of the Main Core of Kaurane Family Members triggered by an Oxidative Polycyclization-Pinacol Tandem Process

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Supporting Information

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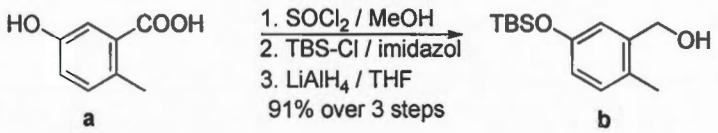
1. General information and materials

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), td (triplet of doublets), q (quartet), p (pentuplet), m (multiplet), and further qualified as app (apparent), br (broad), c (complex). Coupling constants, J, are reported in Hz. Mass spectra (m/e) were measured in the electrospray (ESI) mode.

2. Experimental procedures and analytical data



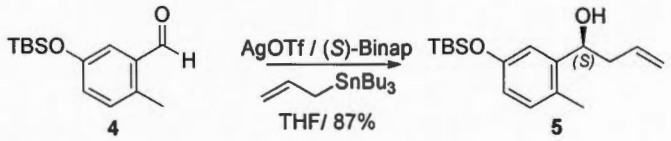
a b

(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)methanol : To a solution of commercially available carboxylic acid **a** (5000 mg, 1.0 eq, 32.9 mmol) in methanol (150 mL) was added $SOCl_2$ (6.0 ml , 2.5 eq, 82.2 mmol) in a dropwise manner. The solution was heated to reflux for 12 hours. The resulting solution was concentrated under reduced pressure and the resulting product was used without further purification. To a solution of crude product in dry DMF (30 mL) at 0°C, was added imidazole (5821 mg, 2.6 eq, 85.5 mmol) and TDMS-Cl (6443 mg, 1.3 eq, 42.7 mmol) and the solution was stirred during 2 hours at room temperature. The reaction was diluted with brine (1000 mL). The aqueous phase was extracted with ether (3 *100 mL) and the combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. The crude mixture was filtrated on silica (*n*-hexane:EtOAc, 80:20), concentrated under reduced pressure and the resulting product was used without further purification. To a solution of crude product in dry THF (250 mL) was added potionwise lithium aluminum hydride (1748 mg, 1.4 eq, 46.1 mmol). The solution was stirred for 1 hour at 0°C. To the resulting solution was added sat. aq NH_4Cl (8 mL) and the slurry solution was filtered directly over celite (EtOAc) and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography (*n*-hexane:EtOAc, 90:10 to afford 7562 mg (91% over 3 stepg) of the desired alcohol **b**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.05 (d, *J*=8.2, 1H), 6.91 (d, *J*=2.6, 1H), 6.72 (dd, *J*=8.1, 2.6, 1H), 4.67 (s, 2H), 2.30 (s, 3H), 1.02 (s, 9H), 0.23 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 153.94, 140.00, 131.11, 128.35, 119.15, 118.89, 63.29, 25.82, 18.28, 17.83, -4.31.

b 4

5-((tert-butyldimethylsilyl)oxy)-2-methylbenzaldehyde : To a solution of benzylic alcohol (7562 mg, 1.0 eq, 30.0 mmol) in dry DCM (150 mL) was added DIB (15.5g , 1.6 eq, 48.0 mmol) and TEMPO (703 mg, 0.15 eq, 4.5 mmol). The solution was stirred at room temperature for 8 hours. To the resulting solution was added sat. aq $Na_2S_2O_3$ (100 mL) and sat. aq $NaHCO_3$ (500 mL). The aqueous phase was extracted with DCM (3 * 150 mL) and the combined organic layers were washed dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography (hexane to *n*-hexane:EtOAc, 97:3) to afford 6377 mg (85%) of the desired aldehyde **4**. **^{1}H NMR** (300 MHz, $CDCl_3$)

δ = 10.18 (s, 1H), 7.24 (d, *J*=2.7, 1H), 7.07 (d, *J*=8.2, 1H), 6.93 (dd, *J*=8.2, 2.7, 1H), 2.54 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 192.03, 154.17, 134.95, 133.32, 132.80, 132.59, 125.74, 121.92, 25.67, 18.39, 18.19, -4.45; **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 153.94, 140.00, 131.11, 128.35, 119.15, 118.89, 63.29, 25.82, 18.28, 17.83, -4.31.



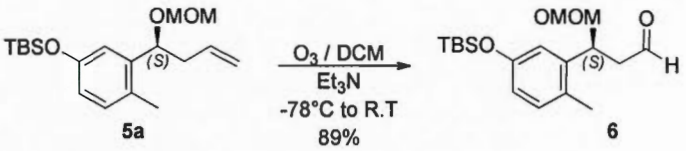
4 5

(S)-1-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)but-3-en-1-ol (96% ee) : A mixture of AgOTf (150 mg, 0.05 eq, 0.58 mmol) and (*S*)-Binap (364 mg, 0.05 eq, 0.58 mmol) was dissolved in dry THF (18 mL) under argon atmosphere and exclusion of direct light, and stirred at 20°C for 10 min. To the resulting solution was added a THF solution (18 mL) of aldehyde **4** (2928 mg, 1.0 eq, 11.69 mmol) and the allyltributyltin (3.81 mL, 1.05 eq, 12.28mmol) was added dropwise at -20°C. The mixture was stirred for 12 hours at this temperature and then a solution of 40 mL of sat. aq. NH_4Cl was added. The aqueous phase was extracted with EtOAc (3 * 25 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by chromatography (hexane to *n*-hexane:EtOAc, 95:5) to afford 2979 mg (87%) of the desired compound **5** as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.05 – 6.92 (m, 2H), 6.66 (dd, *J*=8.2, 2.6, 1H), 5.85 (ddt, *J*=17.1, 10.1, 7.1, 1H), 5.17 (m, 2H), 4.91 (dd, *J*=8.0, 4.5, 1H), 2.55 – 2.32 (m, 2H), 2.25 (s, 3), 0.99 (s, 9H), 0.19 (s, 6H) ; **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 154.13, 143.20, 134.76, 131.21, 126.90, 118.81, 118.31, 117.03, 69.71, 42.62, 25.80, 18.30, -4.33, -4.36; **HRMS** (ESI): Calc. for $C_{17}H_{28}O_2Si$ $(M+H - [H_2O])^+$: 275.1826, found : 275.1821; **$[\alpha]_D$** (25°C, c = (12.2 mg/ 2mL), CH_2Cl_2) = -33.2°.

5 5a

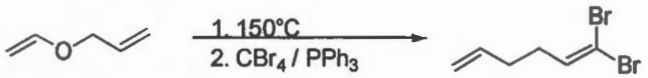
(S)-tert-butyl(3-(1-(methoxymethoxy)but-3-en-1-yl)-4-methylphenoxy)dimethylsilane : To a solution of compound **5** (5996 mg, 1 eq, 20.50 mmol) in dry CH_2Cl_2 (80 mL) at 0°C was added Hunig's base (10.71 mL, 3.0 eq, 61.50 mmol) then chloromethyl methyl ether (9.34 mL, 6.0 eq, 123 mmol). The mixture was stirred at room temperature for 4 hours and then a solution of sat. aq. $NaHCO_3$ (50 mL) was added. The aqueous phase was extracted with DCM (3 * 60 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by chromatography (hexane to *n*-hexane:EtOAc, 95:5) to afford 6900 mg (99%) of the desired protected compound as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 6.95 - 6.67 (m, 2H), 5.86 (ddt,

J=17.1, 10.1, 7.0, 1H), 5.10 (m, 1H), 4.87 (dd, *J*=8.0, 5.1, 1H), 4.52 (m, 2H), 3.37 (s, 3H), 2.60 – 2.35 (m, 2H), 2.25 (s, 3H), 1.00 (s, 9H), 0.20 (s, 6H) ; **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 154.06, 140.94, 134.97, 131.15, 128.10, 119.11, 117.85, 117.08, 94.05, 73.62, 55.54, 41.60, 25.81, 18.37, 18.31, -4.38; **HRMS** (ESI): Calc. for $C_{19}H_{32}O_3Si$ $(M+H - [H_2O])^+$: 319.2088, found : 319.2094 ; **[α]$_D$** (25°C, c = (27.2 mg/ 2mL), CH_2Cl_2) = -116.9°.



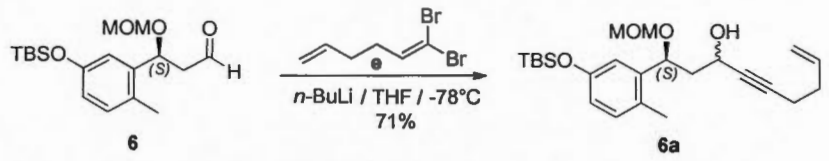
5a 6

(S)-3-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)-3-(methoxymethoxy)propanal : To a solution of **5a** (6900 mg, 1eq, 20.50 mmol) in DCM (600 mL) at -78°C was performed an ozonolysis. The resulting solution was degazed with N_2 then was added triethylamine (14.3 mL, 5 eq, 102.5 mmol) and the mixture was stirred at room temperature for 2 hours and then a solution of sat. aq. NH_4Cl (200mL) was added. The aqueous phase was extracted with DCM (3 *75 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was filtrated on a plug of silica gel (*n*-hexane:EtOAc, 80:20) and concentrated under reduced pressure to afford 6158 mg (89%) of the desired compound **6** as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 9.80 (dd, *J*=2.6, 1.3, 1H), 6.96 (d, *J*=8.2, 1H), 6.88 (d, *J*=2.6, 1H), 6.64 (dt, *J*=6.5, 3.2, 1H), 5.35 (dd, *J*=9.5, 3.6, 1H), 4.48 (s, 2H), 3.32 (s, 3H), 2.80-2.78 (m, 1H), 2.57 (ddd, *J*=16.5, 3.5, 1.2, 1H), 2.24 (s, 3H), 0.95 (s, 9H), 0.15 (s, 6H) ; **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 200.30, 154.22, 139.36, 131.55, 127.80, 119.55, 117.69, 94.01, 68.97, 55.80, 50.21, 25.72, 18.23, 18.12, -4.44; **HRMS** (ESI): Calc. for $C_{18}H_{30}O_4Si$ $(M+NH_4)^+$: 356.2252, found : 356.2238 ; **[α]$_D$** (25°C, c = (16.4 mg/ 2mL), CH_2Cl_2) = -132.2°.



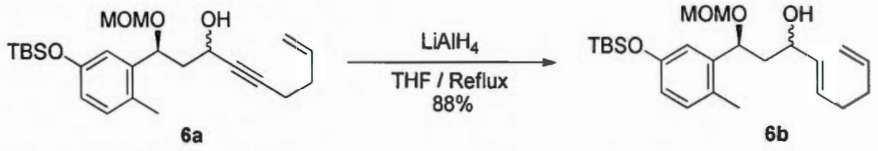
d e

1,1-dibromohexa-1,5-diene : In a seal tube was added allyl vinyl ether (956.6 mg, 1eq, 11.4 mmol) and was stirred at 150°C for 24 hours. The resulting product was used without further purification. To a solution of anhydrous carbon tetrabromide (7543mg, 2eq, 22.8 mmol) in anhydrous DCM (11 mL) at 0°C was added portion wise triphenylphosphine (11929 mg, 45.5 mmol, 4eq). After 30 minutes, the above crude aldehyde was added to the mixture. After stirring for 2 hours at room temperature, the resulting mixture was quenched by a slow addition of sat. aq. NH_4Cl (15mL). The mixture was filtrated directly over silica gel (*n*-hexane:EtOAc, 93:7) and concentrated under reduced pressure to afford 2150 mg (79%) of the desired compound. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 6.45 – 6.34 (m, 1H), 5.89 – 5.70 (m, 1H), 5.11 – 4.99 (m, 2H), 2.28 – 2.12 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 138.03, 137.01, 115.93, 89.20, 32.42, 31.89.



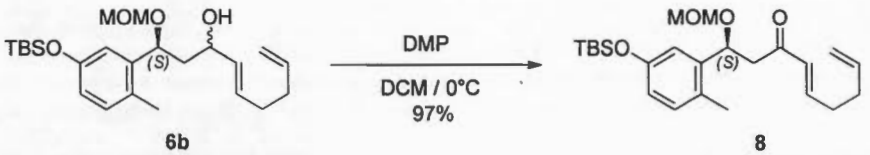
6 6a

(1S)-1-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)-1-(methoxymethoxy)non-8-en-4-yn-3-ol : To a solution of 1,1-dibromohexa-1,5-diene **e** (2201 mg, 2.5 eq, 9.17 mmol) in dry THF (19 mL) at -78°C was added *n*-BuLi (3.60 mL at 2.5 M., 8.99 mmol, 2.45 eq.), the solution was stirred for 30 minutes. To the resulting solution was added dropwise a THF solution (5 mL) of aldehyde **6** (1242 mg, 1.0 eq, 3.67 mmol) at -78°C. The mixture was stirred for 8 hours at this same temperature and then a solution of 15 mL of sat. aq. NH_4Cl was added. The aqueous phase was extracted with EtOAc (3 * 15 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by chromatography (*n*-hexane:EtOAc, 90:10 to 85 : 15) to afford 1093 mg (71%) of the desired propargylic alcohol **6a** as a yellow oil as a diastereoisomeric mixture (2/3). **HRMS** (ESI): Calc. for $C_{24}H_{38}O_4Si$ $(M+Na)^+$: 441.2437, found : 441.2431.



6a 6b

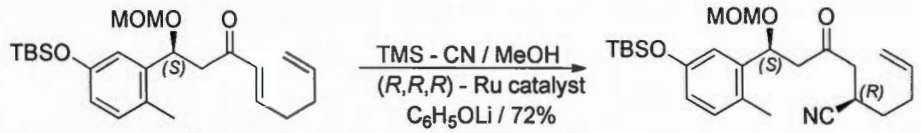
(1S,E)-1-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)-1-(methoxymethoxy)nona-4,8-dien-3-ol : To a solution of **6a** (1888 mg, 1eq, 4.51 mmol) in anhydrous THF (45 mL) was added potionwise lithium aluminum hydride (428 mg, 2.5 eq, 11.27 mmol). The solution was heated to reflux for 1 hour. To the resulting solution was added sat. aq NH_4Cl (5 mL) and the slurry solution was filtered directly over celite (EtOAc) and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography (*n*-hexane:EtOAc, 85 : 15) to afford 1670 mg (88%) of the desired trans alkene **6b** as a yellow oil as a diastereoisomeric mixture (2/3). **HRMS** (ESI): Calc. for $C_{24}H_{40}O_4Si$ $(M+Na)^+$: 443.2594, found : 443.2587.



6b 8

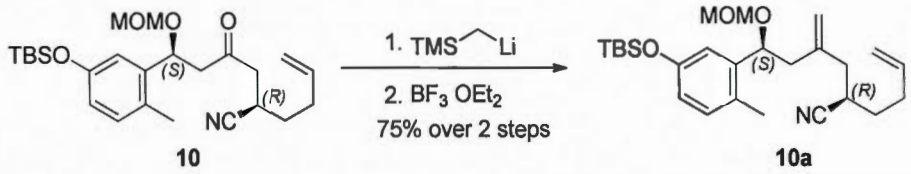
(S,E)-1-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)-1-(methoxymethoxy)nona-4,8-dien-3-one : To a solution of alcohol mixture **6b** (4207 mg, 1 eq, 10.00 mmol) in dry CH_2Cl_2 (100 mL) at 0°C was added Dess-Martin periodinane (10.60g, 2.5 eq, 25 mmol). The mixture

was stirred at room temperature for 1 hour and then a solution of sat. aq. $NaHCO_3$ (50 mL) and sat. aq. $Na_2S_2O_3$ (50 mL) was added subsequently. The aqueous phase was extracted with CH_2Cl_2 (3 *50 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude mixture was purified by chromatography (*n*-hexane:EtOAc, 93:7 to 90:10) to afford 4069 mg (97%) of compound **8** as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 6.96 (d, *J*=8.2, 1H), 6.92 (d, *J*=2.6, 1H), 6.83 (dt, *J*=15.9, 6.6, 1H), 6.65 (dd, *J*=8.2, 2.6, 1H), 6.15 (dt, *J*=15.8, 1.3, 1H), 5.78 (ddt, *J*=16.6, 10.2, 6.4, 1H), 5.35 (dd, *J*=9.4, 3.4, 1H), 5.09 – 4.97 (m, 2H), 4.53 – 4.42 (m, 2H), 3.29 (s, 3H), 3.07 (dd, *J*=15.8, 9.4, 1H), 2.62 (dd, *J*=15.8, 3.4, 1H), 2.37 – 2.15 (m, 7H), 0.97 (s, 9H), 0.17 (s, 6H) ; **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 197.63, 154.15, 147.21, 140.52, 137.04, 131.44, 131.13, 128.08, 119.30, 117.75, 115.75, 94.27, 70.42, 55.82, 47.26, 32.18, 31.83, 25.81, 18.32, 18.29, -4.34; **HRMS** (ESI): Calc. for $C_{24}H_{38}O_4Si$ $(M+Na)^+$: 441.2432, found : 441.2435; **[α]$_D$** (25°C, c = (27.7 mg/ 2mL), CH_2Cl_2) = **-88.8°**.



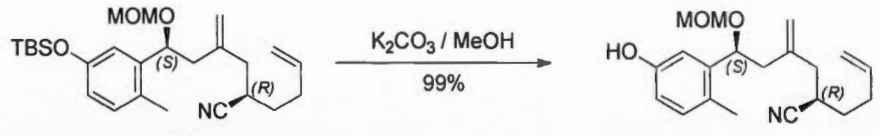
8 **10**

(R)-2-((S)-4-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)-4-(methoxymethoxy)-2-oxobutyl)hex-5-enenitrile : Ruthenium complexe **9 (See Ref 14 for synthesis)** (105 mg, 1.0 mol%, 0.097 mmol) was placed in 100 mL round-bottom flask, and purged by argon. Anhydrous methanol (0.59 mL, 1.50 eq, 14.57 mmol) was added to this flask *(CAUTION : formation of HCN)*, and the mixture was cooled at 0°C. Then trimethylsilyl cyanide (1.80 mL, 1.48 eq, 14.38 mmol) was added in a dropwise manner, and the mixture was stirred for 15 min. To this solution, anhydrous *tert*-butyl methyl ether (50 mL) and lithium phenoxyde (1.46 mL at 60 mM in THF, 0.9 mol%, 0.087 mmol) were added at 0°C, and the mixture was stirred for 30 min. Then compound **8** (4069 mg, 1eq, 9.72 mmol), was added to this solution in a dropwise manner over 5 min, and the reaction mixture was stirred for 12 hours at this same temperature. Then a solution of sat. aq. $NaHCO_3$ (50 mL) was added. The aqueous phase was extracted with AcOEt (3 *50 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude mixture was purified by chromatography (*n*-hexane:EtOAc, 87:13 to afford 3122 mg (72%) of compound **10** as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 6.98 (d, *J*=8.2, 1H), 6.86 (d, *J*=2.6, 1H), 6.67 (dd, *J*=8.2, 2.6, 1H), 5.77 (ddt, *J*=17.0, 10.2, 6.7, 1H), 5.31 (dd, *J*=9.8, 3.3, 1H), 5.17 – 5.01 (m, 2H), 4.46 (q, *J*=6.7, 2H), 3.30 (s, 3H), 3.10 (dq, *J*=13.1, 6.6, 1H), 2.98 – 2.71 (m, 3H), 2.54 (dd, *J*=15.7, 3.3, 1H), 2.40 – 2.13 (m, 5H), 1.76 – 1.55 (m, 9H), 0.97 (s, 8H), 0.17 (s, 6H) ; **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 203.80, 154.31, 139.54, 136.18, 131.70, 128.09, 121.40, 119.65, 117.63, 116.64, 94.33, 70.43, 56.05, 49.73, 45.92, 31.18, 31.02, 25.83, 25.37, 18.35, 18.22, -4.29; **HRMS** (ESI) Calc. for $C_{25}H_{39}NO_4Si$ $(M+ NH_4)^+$: 463.2987, found : 463.2986; **[α]$_D$** (25°C, c = (38.6 mg/ 2mL), CH_2Cl_2) = **-92.1°**.



10 **10a**

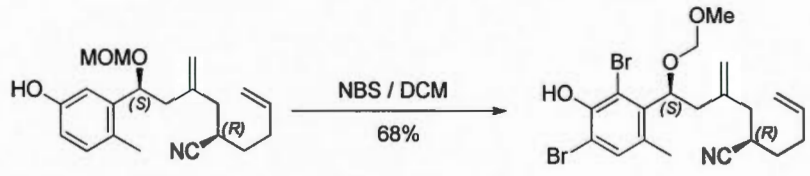
(R)-2-((S)-4-(5-((tert-butyldimethylsilyl)oxy)-2-methylphenyl)-4-(methoxymethoxy)-2-methylenebutyl)hex-5-enenitrile : To a solution of compound **10** (483 mg, 1eq, 1.08 mmol) in dry THF (3mL) at -78°C was added (Trimethylsilyl)methyl lithium (1.2 mL at C = 1.0M , 1.1 eq, 1.2 mmol) dropwise, to avoid a not wished pink coloration, over a period of 3 hours . Then a solution of 15 mL of sat. aq. NH_4Cl was added. The aqueous phase was extracted with EtOAc (3 *15 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was used without further purification and diluted in CH_2Cl_2 (10 mL) at 0°C and boron trifluoride diethyl etherate (0.21 mL, 1.5 eq, 1.64 mmol) was added dropwise. The solution was stirred for 15 minutes and diluted with a saturated solution of $NaHCO_3$ (10 mL), the aqueous phase was extracted with CH_2Cl_2 (3 *10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude mixture was purified by chromatography (*n*-hexane:EtOAc, 90:10) to afford 360 mg (75 %) of external alkene **10a**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 6.97 (d, *J*=8.2, 1H), 6.87 (d, *J*=2.6, 1H), 6.66 (dd, *J*=8.2, 2.6, 1H), 5.84 – 5.68 (m, 4H), 4.46 (q, *J*=6.7, 2H), 3.33 (s, 3H), 2.80 – 2.66 (m, 1H), 2.50 – 2.13 (m, 9H), 1.75 – 1.65 (m, 2H), 0.97 (s, 9H), 0.17 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 154.12, 141.63, 140.83, 136.31, 131.29, 127.80, 121.63, 119.18, 117.66, 116.42, 115.88, 94.13, 73.35, 55.79, 42.88, 39.06, 31.28, 31.06, 29.45, 25.74, 18.30, 18.23, -4.41; **HRMS** (ESI) Calc. for $C_{26}H_{41}NO_3Si$ $(M+NH_4)^+$: 461.3194, found : 463.3195; **$[\alpha]_D$** (25°C, c = (44.8 mg/ 2mL), CH_2Cl_2) = -68.0°.



10a **11**

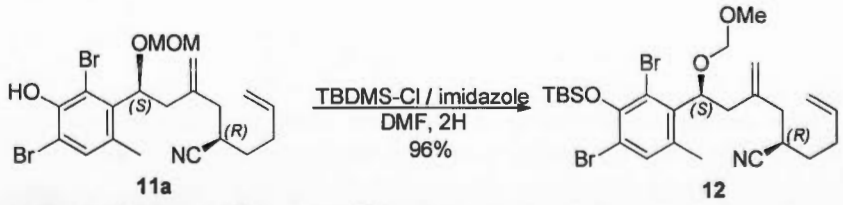
***(R)*-2-((*S*)-4-(5-hydroxy-2-methylphenyl)-4-(methoxymethoxy)-2-methylenebutyl)hex-5-enenitrile** : To a solution of **10a** (1643 mg, 1 eq, 3.70 mmol) in MeOH (37 mL) was added K_2CO_3 (1.2g, 2.5 eq, 9.25 mmol). The solution was heated at 60°C for 1 hour and then a solution of 50 mL of sat. aq. NH_4Cl was added. The aqueous phase was extracted with DCM (3 *50 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was filtrated on a plug of silica gel (*n*-hexane:EtOAc, 70:30) and concentrated under reduced pressure to afford 1240 mg (99%) of the desired compound **11** as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 6.97 – 6.87 (m, 2H), 6.75 (s, 1H), 6.63 (dd, *J*=8.2, 2.6, 1H), 5.74 (ddt, *J*=17.0, 10.1, 6.7, 1H), 5.14 – 4.98 (m,

4H), 4.92 (dd, *J*=8.6, 4.4, 1H), 4.47 (s, 2H), 3.34 (s, 3H), 2.75 (tt, *J*=9.1, 5.7, 1H), 2.50 – 2.09 (m, 9H), 1.77 – 1.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.63, 141.41, 140.69, 136.20, 131.40, 126.49, 121.66, 116.36, 115.80, 114.53, 112.83, 94.01, 73.45, 55.73, 42.66, 38.80, 31.12, 30.94, 29.34, 18.10; **HRMS** (ESI) Calc. for $C_{20}H_{27}NO_3$ $(M+NH_4)^+$: 347.2329, found : 347.2330; $[\alpha]_D$ (25°C, c = (12.4 mg/ 2mL), CH_2Cl_2) = -88.3°.



11 11a

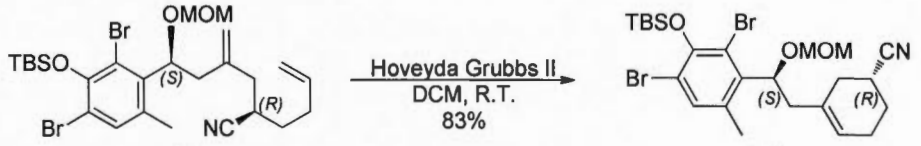
(R)-2-((S)-4-(2,4-dibromo-3-hydroxy-6-methylphenyl)-4-(methoxymethoxy)-2-methylenebutyl) hex-5-enenitrile : The compound **11** (1240 mg, 1 eq, 3.70 mmol was diluted in CH_2Cl_2 (30 mL) at 0°C and a solution of NBS freshly recristallized in water (1383 mg, 2.1 eq, 7.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The solution was stirred for 25 minutes and diluted with a saturated solution of $Na_2S_2O_3$ (5 mL), the aqueous phase was extracted with CH_2Cl_2 (3 *30 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude mixture was purified by chromatography (*n*-hexane:EtOAc, 80:20) to afford 1220 mg (68 %) of compound **11a** as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.25 (s, 1H), 6.03 (br, 1H), 5.75 (ddt, *J*=17.1, 10.2, 6.7, 1H), 5.41 (dd, *J*=9.8, 4.1, 1H), 5.16 – 4.96 (m, 4H), 4.51 – 4.40 (m, 1H), 3.28 (s, 3H), 2.84 – 2.72 (m, 1H), 2.67 – 2.13 (m, 10H), 1.75 – 1.65 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 147.16, 140.82, 137.38, 136.00, 134.32, 130.55, 121.08, 115.89, 115.72, 112.91, 108.01, 94.25, 77.42, 55.44, 39.28, 38.09, 30.96, 30.63, 29.17, 19.27; **HRMS** (ESI) Calc. For $C_{20}H_{25}Br_2NO_3$ $(M+NH_4)^+$: 503.0539, found : 503.0538; $[\alpha]_D$ (25°C, c = (15.7 mg/ 2mL), CH_2Cl_2) = -58.7°.



11a 12

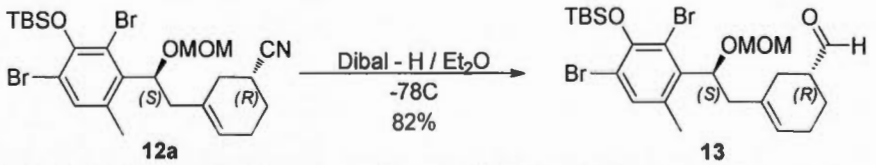
(R)-2-((S)-4-(2,4-dibromo-3-((tert-butyldimethylsilyl)oxy)-6-methylphenyl)-4-(methoxymethoxy) -2-methylenebutyl)hex-5-enenitrile : To a solution of **11a** (1220 mg, 1 eq, 2.50 mmol) in dry DMF (5 mL) at 0°C, was added imidazole (477 mg, 2.8 eq, 7 mmol) and TDMS-Cl (528 mg, 1.4 eq, 3.5 mmol) and the solution was stirred during 2 hours at room temperature. The reaction was diluated with brine (600 mL). The aqueous phase was extracted with ether (3 *30 mL) and the combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. The crude mixture was purified by chromatography (*n*-hexane:EtOAc, 90:10) to afford 1448 mg (96 %) of compound **12**. **^{1}H NMR** (300 MHz,

$CDCl_3$) δ = 7.26 (s, 1H), 5.73 (ddt, *J*=17.0, 10.1, 6.7, 1H), 5.47 (dd, *J*=9.9, 4.1, 1H), 5.14 – 4.96 (m, 4H), 4.44 (dd, *J*=19.9, 6.7, 2H), 3.25 (s, 3H), 2.79 (tt, *J*=9.2, 5.8, 1H), 2.69 – 2.08 (m, 9H), 1.80 – 1.56 (m, 2H), 1.01 (s, 9H), 0.32 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 148.00, 141.11, 138.31, 136.26, 135.55, 132.20, 121.43, 119.14, 116.45, 113.76, 94.89, 78.05, 55.83, 39.73, 38.55, 31.46, 31.05, 29.63, 26.25, 25.67, 19.77, 18.98, -1.88, -1.95; **HRMS** (ESI) Calc. For $C_{26}H_{39}Br_2NO_3Si$ $(M+Na)^+$: 624.0940, found : 624.0931; **[α]$_D$** (25°C, c = (18.6 mg/ 2mL), CH_2Cl_2) = -50.9°.



12 12a

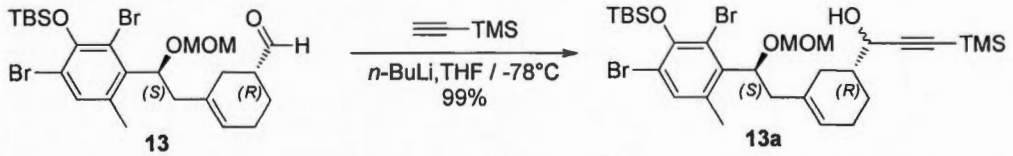
(R)-3-((S)-2-(2,4-dibromo-3-((tert-butyldimethylsilyl)oxy)-6-methylphenyl)-2-(methoxymethoxy) ethyl)cyclohex-3-enecarbonitrile : To a solution of compound **12** (1448 mg, 1 eq, 2.41 mmol) in DCM (200 mL) was added Hoveyda Grubbs II catalyst (45 mg, 3 mol%, 0.07 mmol). The reaction was stirred for 12 hours then then filtrated and purified by chromatography on silica gel (*n*-hexane:EtOAc, 90:10) to afford 1140 mg, (83%) of **12a**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.22 (s, 1H), 5.56 (s, 1H), 5.41 (dd, *J*=9.6, 4.3, 1H), 4.40 (dd, *J*=19.3, 6.6, 2H), 3.22 (s, 3H), 2.93 – 2.70 (m, 1H), 2.54 – 2.00 (m, 9H), 1.91 – 1.70 (m, 2H), 0.98 (s, 9H), 0.29 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 147.82, 138.48, 135.31, 132.07, 131.00, 123.84, 122.02, 119.05, 113.49, 94.70, 78.04, 55.53, 41.66, 31.44, 26.14, 24.93, 22.99, 19.65, 18.83, -2.02, -2.08; **HRMS** (ESI) Calc. for $C_{24}H_{35}Br_2NO_3Si$ $(M+Na)^+$: 596.0627, found : 596.0622 ; **[α]$_D$** (25°C, c = (14.1 mg/ 2mL), CH_2Cl_2) = -40.8°.



12a 13

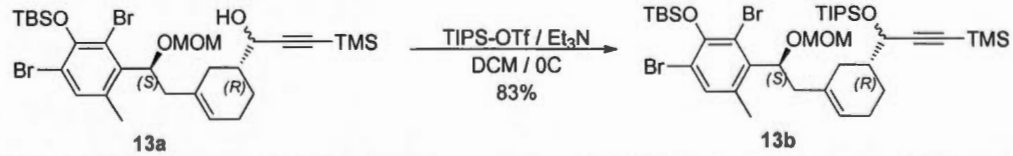
(R)-3-((S)-2-(2,4-dibromo-3-((tert-butyldimethylsilyl)oxy)-6-methylphenyl)-2-(methoxymethoxy) ethyl)cyclohex-3-enecarbaldehyde : To a solution of cyanide compound **12a** (1140 mg, 1eq, 1.99 mmol) in dry ether (20 mL) at -78°C, was added DIBAL-H (4.98 mL at 1.0M., 2.5eq, 4.98 mmol) in a dropwise manner, the solution was stirred for 2 hours and was subsequently added in the following order methanol (10 mL) and sat. aq. NH_4Cl (50 mL). This solution was transferred in a sat aq. Rochelle's Salt and the mixture was stirred for 60 min at room temperature. The resulting solution was extracted with EtOAc (3 *40 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was filtrated on a plug of silica gel (*n*-hexane:EtOAc, 80:20) to afford 939 mg (82%) of the compound **13**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 9.71 (s, 1H), 7.27 (s, 1H), 5.56 (s, 1H), 5.51 (dd, *J*=9.4, 4.5, 1H), 4.46 (dd,

J=18.1, 6.6, 3H), 3.28 (s, 3H), 2.62 – 2.20 (m, 9H), 1.99 – 1.90 (m, 1H), 1.70 – 1.50 (m, 2H), 1.03 (s, 9H), 0.33 (d, *J*=2.1, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 203.75, 147.87, 138.82, 135.35, 132.22, 132.16, 124.27, 119.26, 113.47, 94.69, 78.00, 55.53, 46.50, 42.06, 27.58, 26.23, 23.88, 21.80, 19.76, 18.93, -1.95, -2.01; **HRMS** (ESI) Calc. for $C_{24}H_{36}Br_2O_4Si$ $(M+Na)^+$: 599.0623, found : 599.0625 ; **$[\alpha]_D$** (25°C, c = (24.8 mg/ 2mL), CH_2Cl_2) = -27.1°.



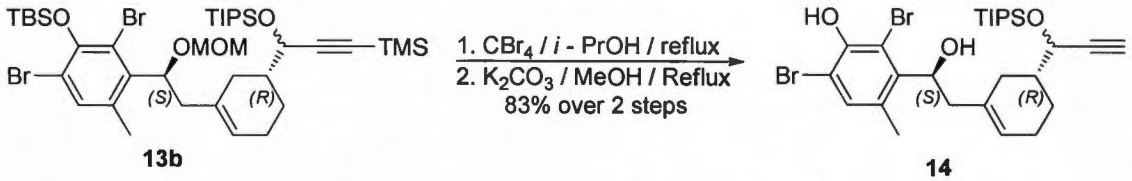
13 13a

1-((R)-3-((S)-2-(2,4-dibromo-3-((tert-butyldimethylsilyl)oxy)-6-methylphenyl)-2-(methoxy methoxy)ethyl)cyclohex-3-en-1-yl)-3-(trimethylsilyl)prop-2-yn-1-ol: To a solution of Trimethylsilylacetylene (1.04 mL, 4.5eq, 7.34 mmol) in dry THF (8 mL) at -78°C was added *n*-BuLi (4.3 mL at 2.5 M., 4.3 eq, 2.80 mmol), the solution was stirred for 30 minutes. To the resulting solution was added dropwise a THF solution (3 mL) of aldehyde **13** (1.63 mmol) at -78C. The mixture was stirred for 2H at this same temperature and then a solution of 20 mL of sat. aq. NH_4Cl was added. The aqueous phase was extracted with EtOAc (3 * 15 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by chromatography (*n*-hexane:EtOAc, 85:15) to afford 1100 mg (99%) of the desired propargylic alcohol **13a** as a brown oil as a diastereoisomeric mixture (1:1). **HRMS** (ESI) Calc. For $C_{29}H_{46}Br_2O_4Si_2$ $(M+Na)^+$: 697.1176, found : 697.1170.



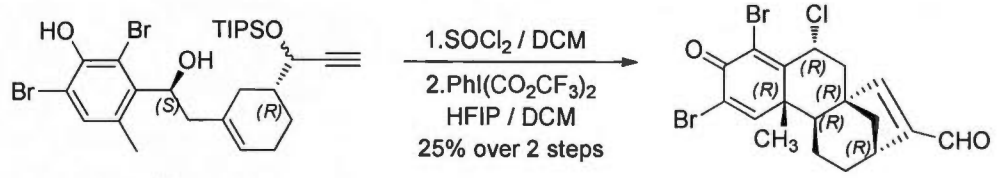
13a 13b

tert-butyl(2,6-dibromo-3-((S)-1-(methoxymethoxy)-2-((R)-5-(1-((triisopropylsilyl)oxy)-3-(trimethylsilyl)prop-2-yn-1-yl)cyclohex-1-en-1-yl)ethyl)-4-methylphenoxy)dimethylsilane : To a solution of propargylic alcohol **13a** (1100 mg, 1eq, 1.63 mmol.) in DCM (16 mL) at 0°C, was added in the following order Et_3N (0.55 mL, 2.4 eq, 3.91 mmol) and TIPS-OTf (0.53 mL, 1.2 eq, 1.96 mmol) in a dropwise manner. The solution was stirred for 3 hours at this same temperature. Then a solution of 10 mL of water was added. The aqueous phase was extracted with DCM (3 * 15 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by chromatography (*n*-hexane:EtOAc, 97:3) to afford 1.1246g (83%) of the desired protected propargylic alcohol **13b** as a brownish oil as a diastereoisomers mixture (1:1). **HRMS** (ESI) Calc. For $C_{38}H_{66}Br_2O_4Si_3$ $(M+Na)^+$: 851.2528, found : 851.2681.



13b **14**

2,6-dibromo-3-((S)-1-hydroxy-2-((R)-5-(1-((triisopropylsilyl)oxy)prop-2-yn-1-yl)cyclohex-1-en-1-yl)ethyl)-4-methylphenol : To a solution of **13b** (1125 mg, 1 eq, 1.35 mmol) in anhydrous *i*-PrOH (14 mL) was added dry CBr_4 (90 mg ,0.2 eq, 0.3 mmol). The solution was heated at 84°C for 5 hours and then a solution of 10 mL of sat. aq. $NaHCO_3$ was added. The aqueous phase was extracted with DCM (3 *10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The product was used without further purification and diluted in methanol (15 mL) was added K_2CO_3 (559 mg, 3.0 eq, 4.1 mmol). The solution was heated at 60°C for 1 hour and then a solution of 30 mL of sat. aq. NH_4Cl was added. The aqueous phase was extracted with DCM (3 *20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by chromatography (*n*-hexane:EtOAc, 90:10) to afford 670 mg (83%) of the desired compound **14** as a yellow oil as a diastereoisomer mixture (1:1). **HRMS** (ESI) Calc. For $C_{27}H_{40}Br_2O_3Si$ $(M+Na - [H_2O])^+$: 583.1062, found : 583.1062.



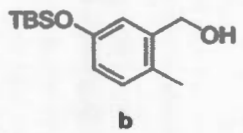
14 **17**

(5R,6aR,9R,11aR,11bR)-2,4-dibromo-5-chloro-11b-methyl-3-oxo-3,5,6,9,10,11,11a,11b-octahydro-6a,9-methanocyclohepta[a]naphthalene-8-carbaldehyde : To a solution of compound **14** (105 mg, 1 eq, 0.175mmol) in anhydrous DCM (3 mL) was added $SOCl_2$ (38µL, 3.0 eq, 0.525 mmol). The solution was heated at 46°C for 8 hours and then a solution of 10 mL of sat. aq. $NaHCO_3$ was added. The aqueous phase was extracted with DCM (3 *10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was filtrated on a plug of silica gel (*n*-hexane:EtOAc, 90:10) and was used without further purification. To a solution of $PhI(CO_2CF_3)_2$ (83 mg, 1.1 eq, 0.192 mmol) in a mixture of HFIP/DCM (5:3 ; 0.6 mL) was added over 5 seconds to a vigorously stirred solution of crude phenol in a mixture of HFIP/DCM (5:3 ; 1 mL) at room temperature. After addition of PIFA, the solution was stirred for 2 min, quenched with 1 mL of acetone, filtered directly over silica gel (EtOAc) and the filtrate was concentrated under reduced pressure. The residue was purified by silica

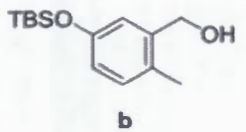
gel chromatography with hexane/ethyl acetate (75:25) to afford 20.3 mg of tetracyclic core **17** in 25 % yield over 2 steps. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 9.67 (s, 1H), 7.31 (s, 1H), 6.13 (s, 1H), 5.42 (t, *J*=9.5, 1H), 3.05 – 3.00 (m, 1H), 2.46 (d, *J*=9.6, 2H), 2.18 (dd, *J*=12.9, 5.0, 1H), 2.05 – 1.98 (m, 1H), 1.90 – 1.82 (m, 1H), 1.72 (s, 3H), 1.46 – 1.40 (m, 2H), 0.96 – 0.85 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 188.86, 172.36, 158.58, 155.18, 150.01, 147.49, 127.54, 119.28, 56.42, 52.49, 51.07, 50.83, 49.63, 40.01, 36.89, 31.08, 25.16, 23.03; **HRMS** (ESI) Calc. For $C_{18}H_{17}Br_2ClO_2$ $(M+Na)^+$: 482.9155, found : 482.9159; **$[\alpha]_D$** (25°C, c = (11.6 mg/ 2mL), AcOEt) = -4.3°.

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

$CDCl_3$, 300 MHz

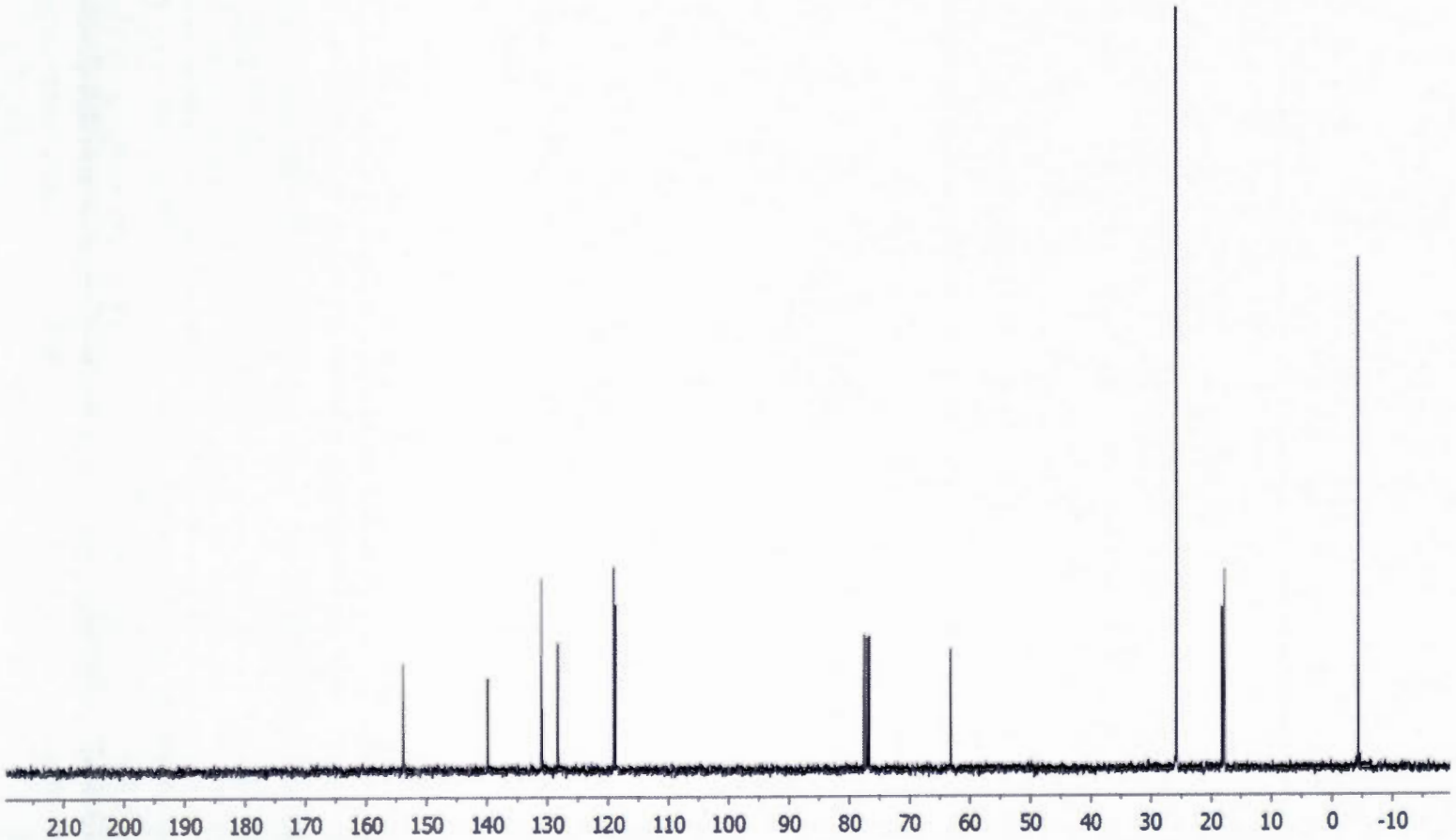


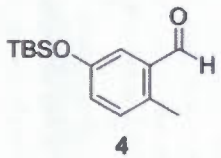
b



b

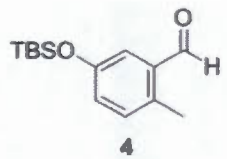
$CDCl_3$, 75 MHz





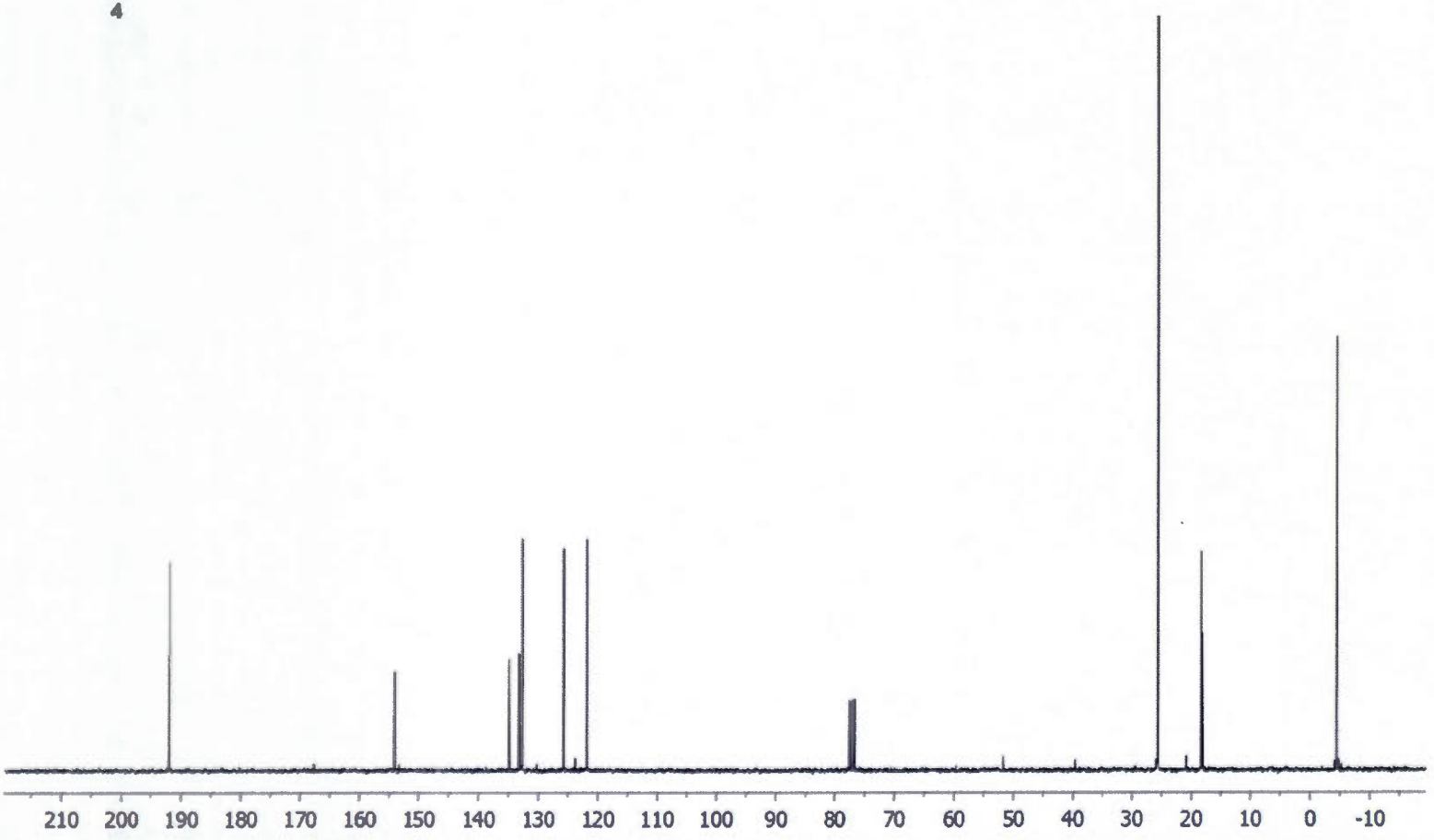
4

$CDCl_3$, 300 MHz

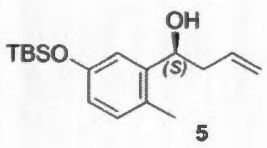


4

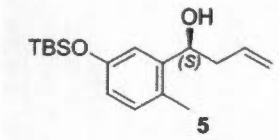
$CDCl_3$, 75 MHz



$CDCl_3$, 300 MHz

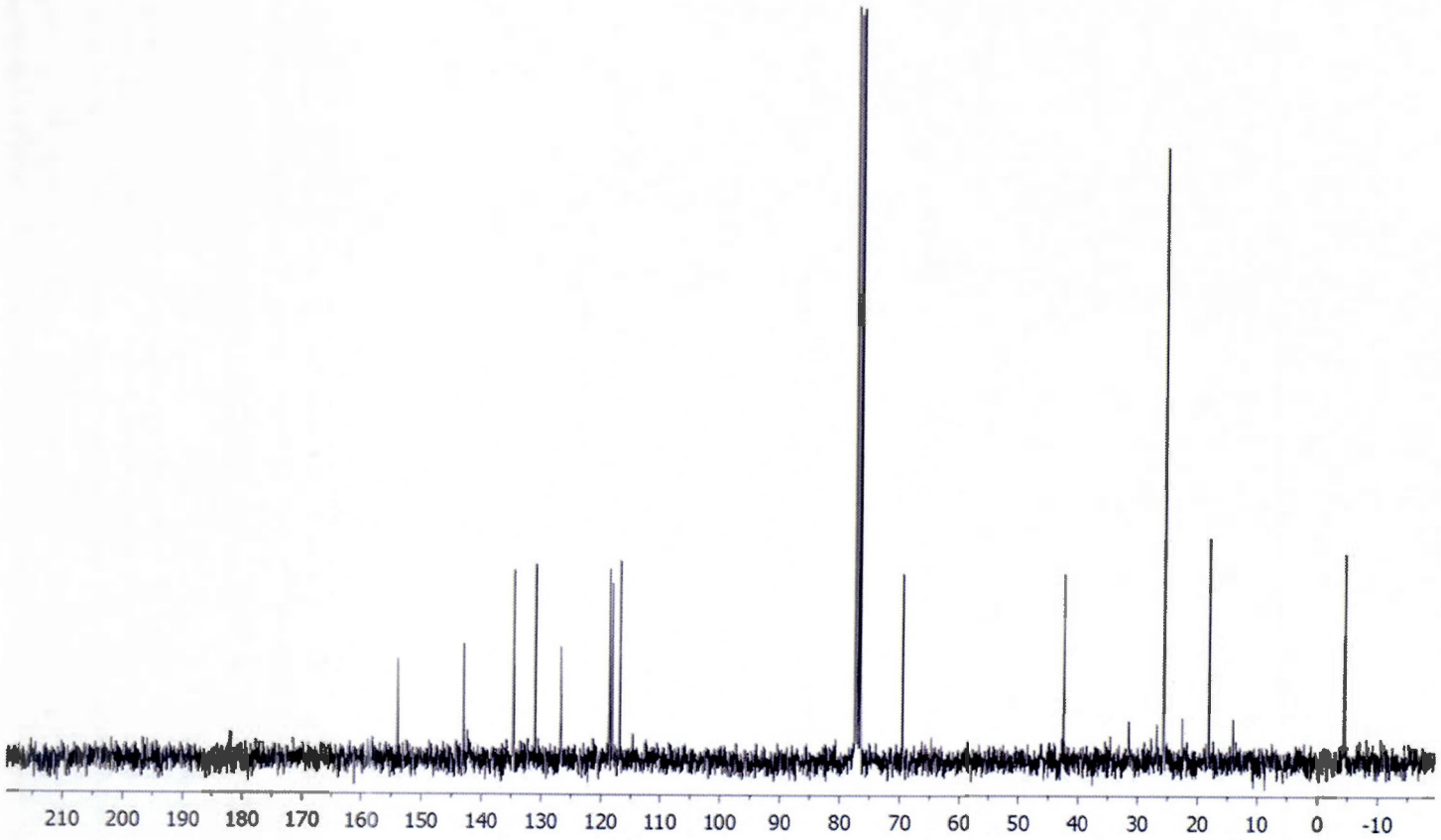


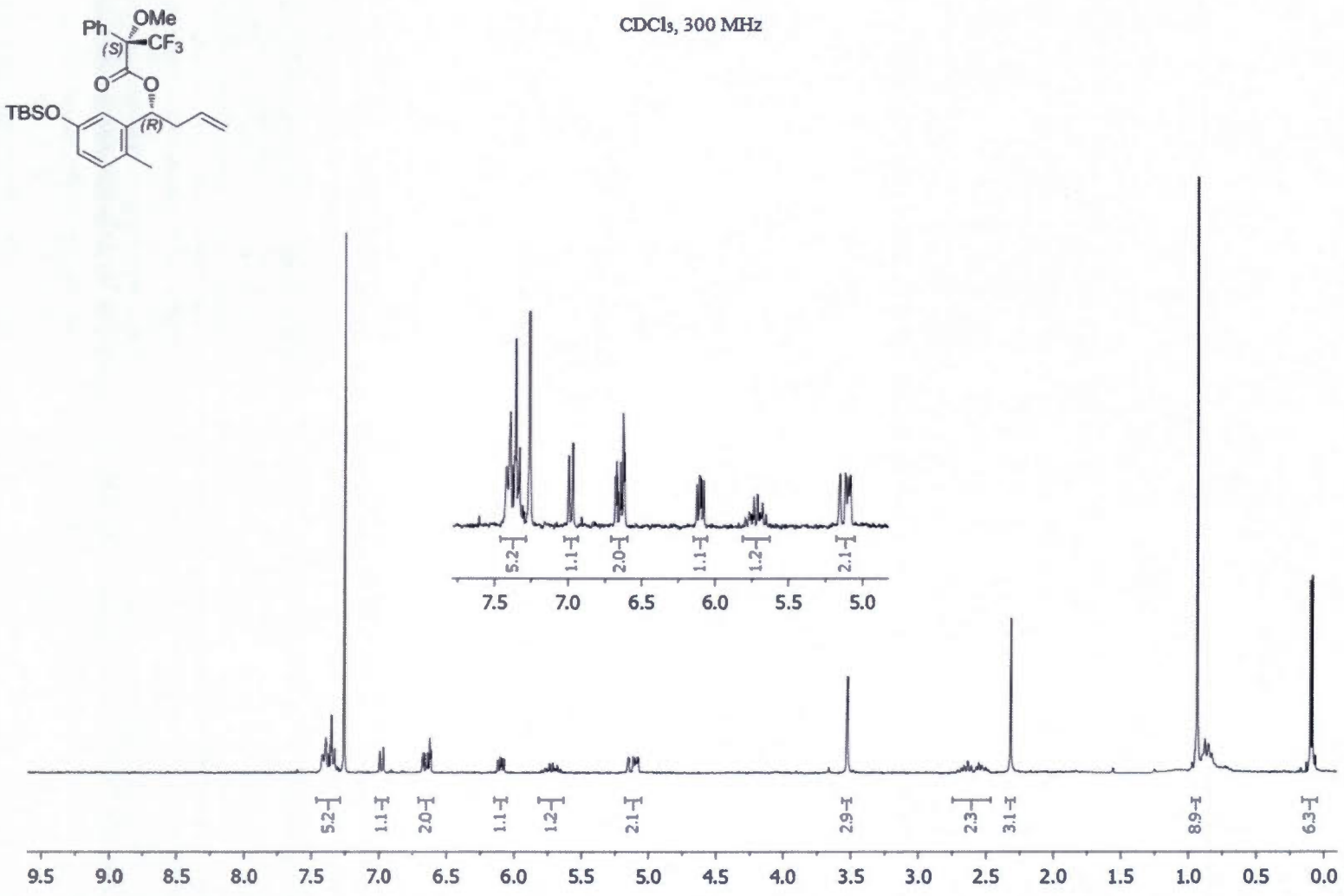
5

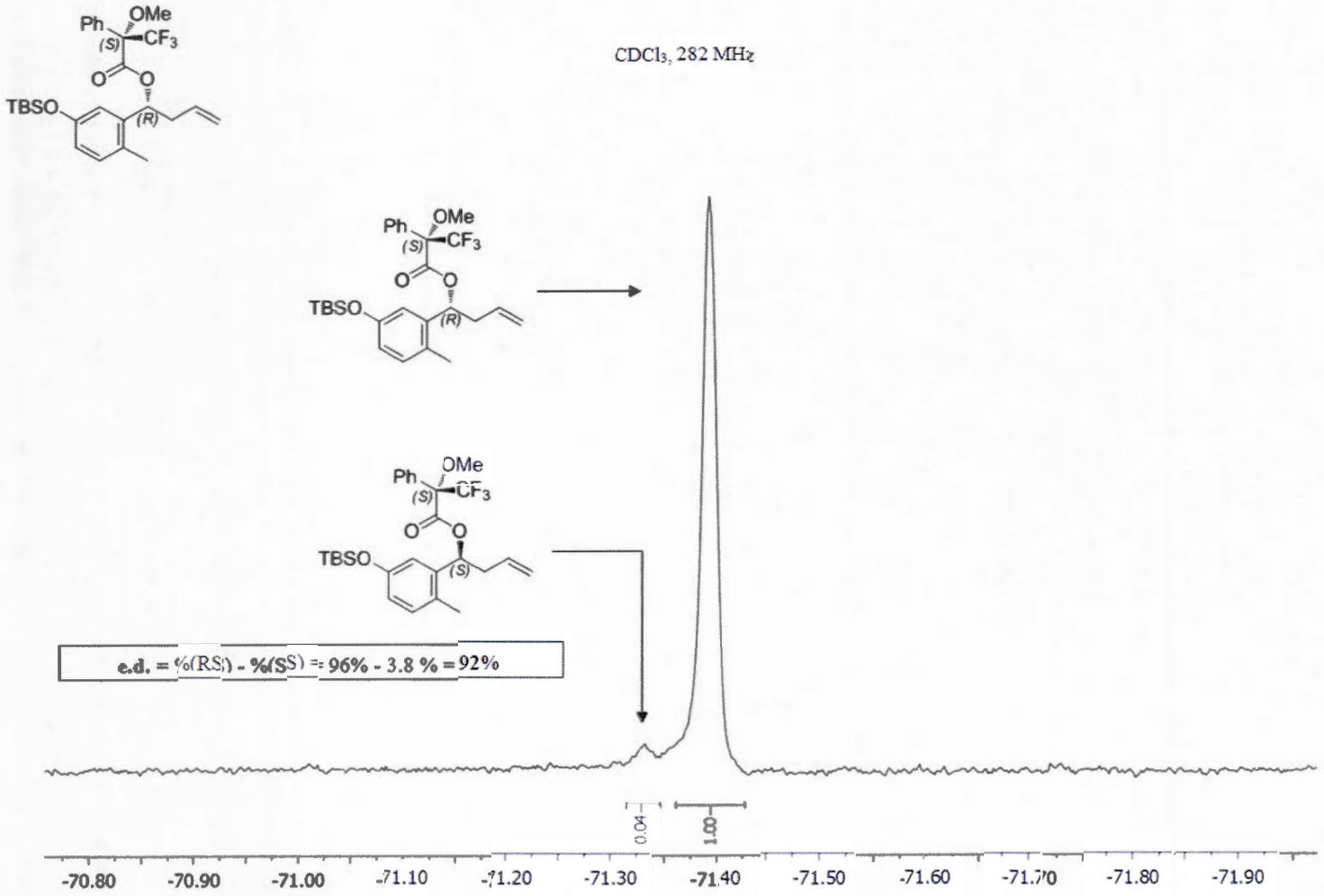


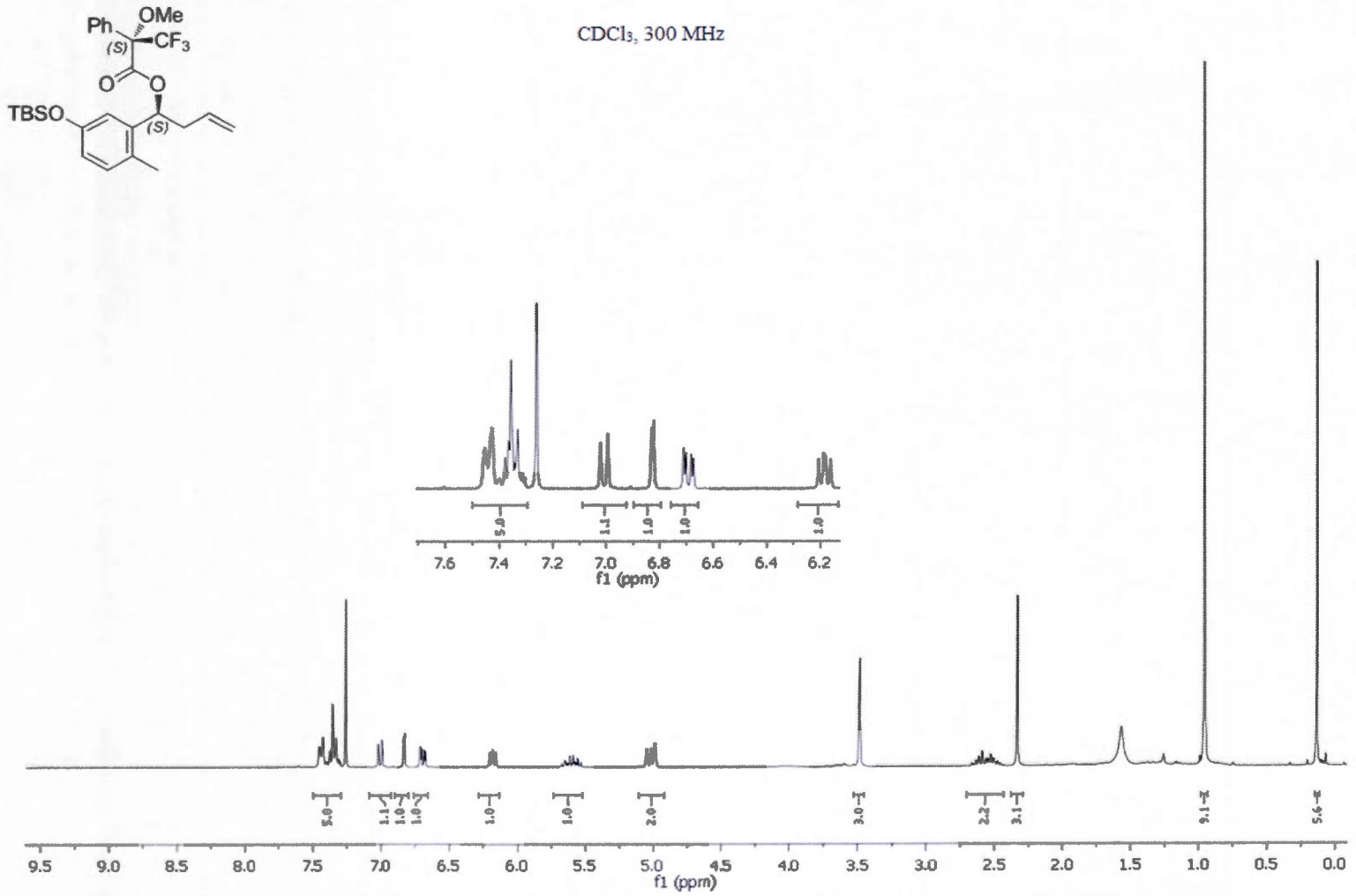
5

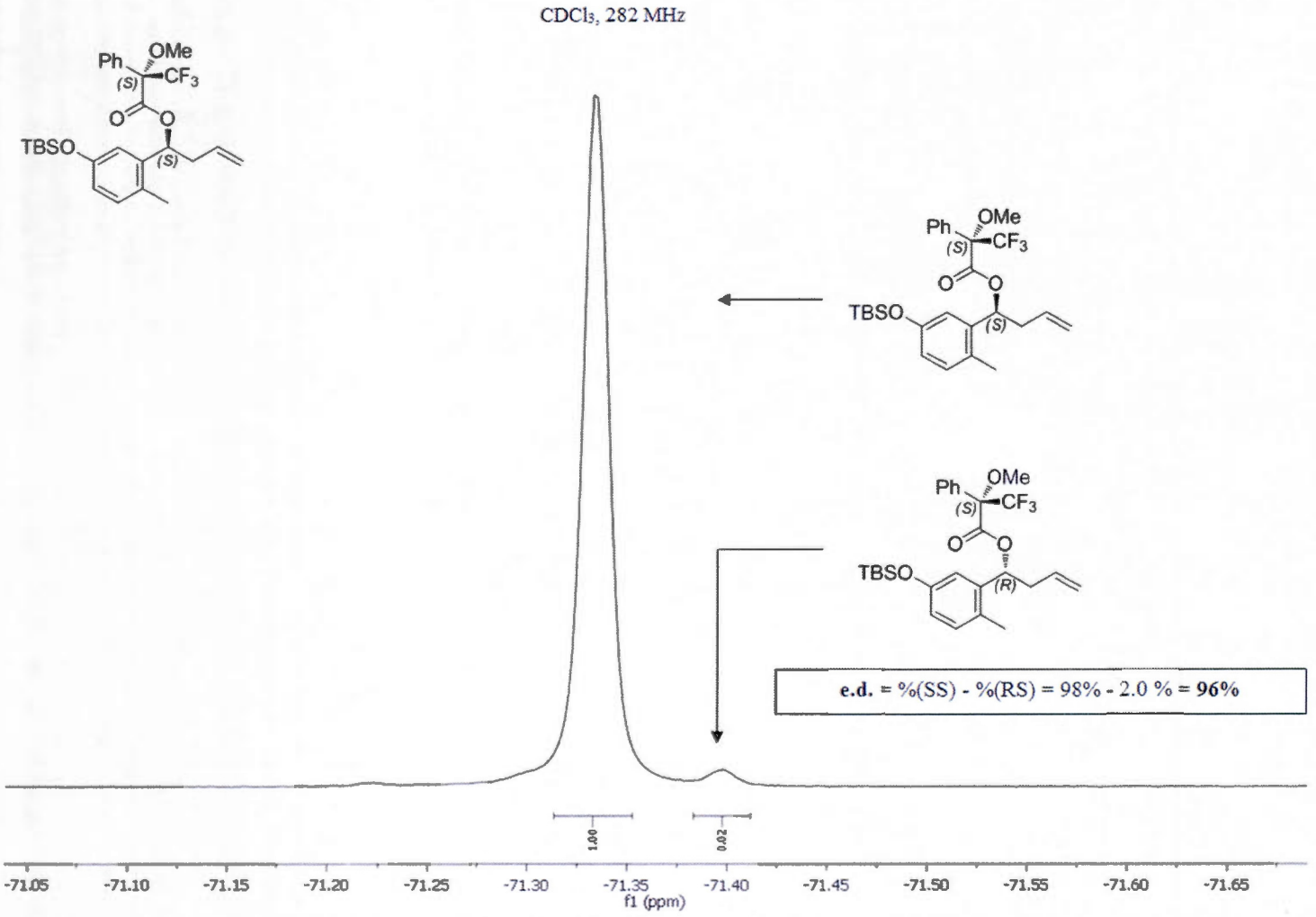
$CDCl_3$, 75 MHz

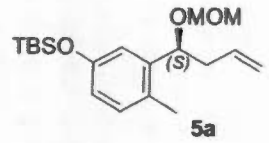



Ph
OMe
(S)
CF3
O
O
TBSO
(R)
CDCl3, 300 MHz
5.2
1.1
2.0
1.1
1.2
2.1
2.9
2.3
3.1
8.9
6.3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
7.5 7.0 6.5 6.0 5.5 5.0


Ph
OMe
(S)
CF3
O
O
TBSO
(R)
CDCl3, 282 MHz
(S)
(R)
e.d. = %(RS) - %(SS) = 96% - 3.8 % = 92%
0.04
1.00
-70.80
-70.90
-71.00
-71.10
-71.20
-71.30
-71.40
-71.50
-71.60
-71.70
-71.80
-71.90

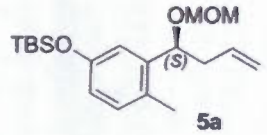

Ph
OMe
(S)
CF3
O
O
TBSO
(S)
CDCl3, 300 MHz
f1 (ppm)


CDCl3, 282 MHz
Ph
OMe
(S)
CF3
O
O
TBSO
(S)
Ph
OMe
(S)
CF3
O
O
TBSO
(S)
Ph
OMe
(S)
CF3
O
O
TBSO
(R)
e.d. = %(SS) - %(RS) = 98% - 2.0 % = 96%
1.00
0.02
-71.05
-71.10
-71.15
-71.20
-71.25
-71.30
-71.35
-71.40
-71.45
-71.50
-71.55
-71.60
-71.65
f1 (ppm)



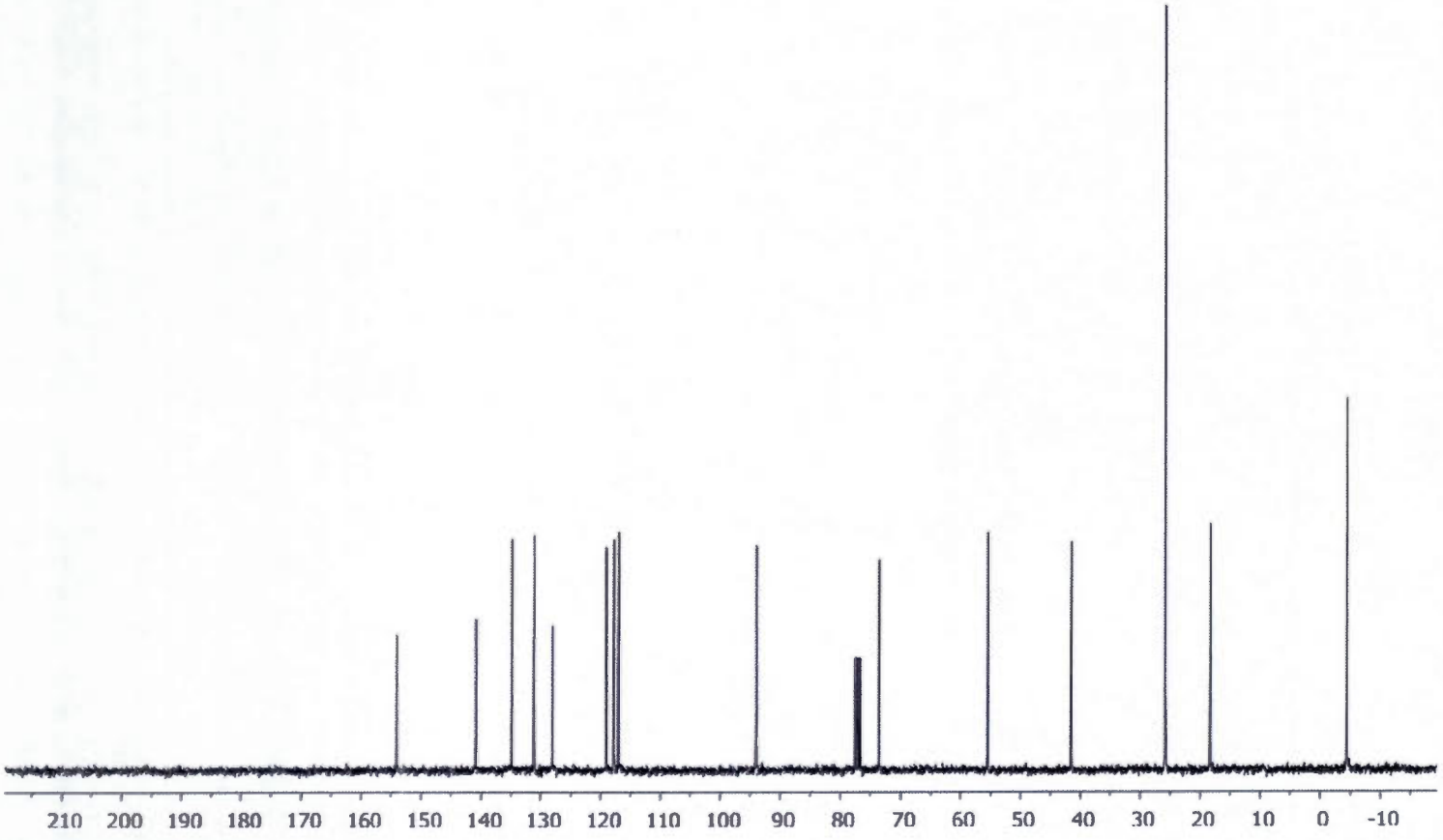
5a

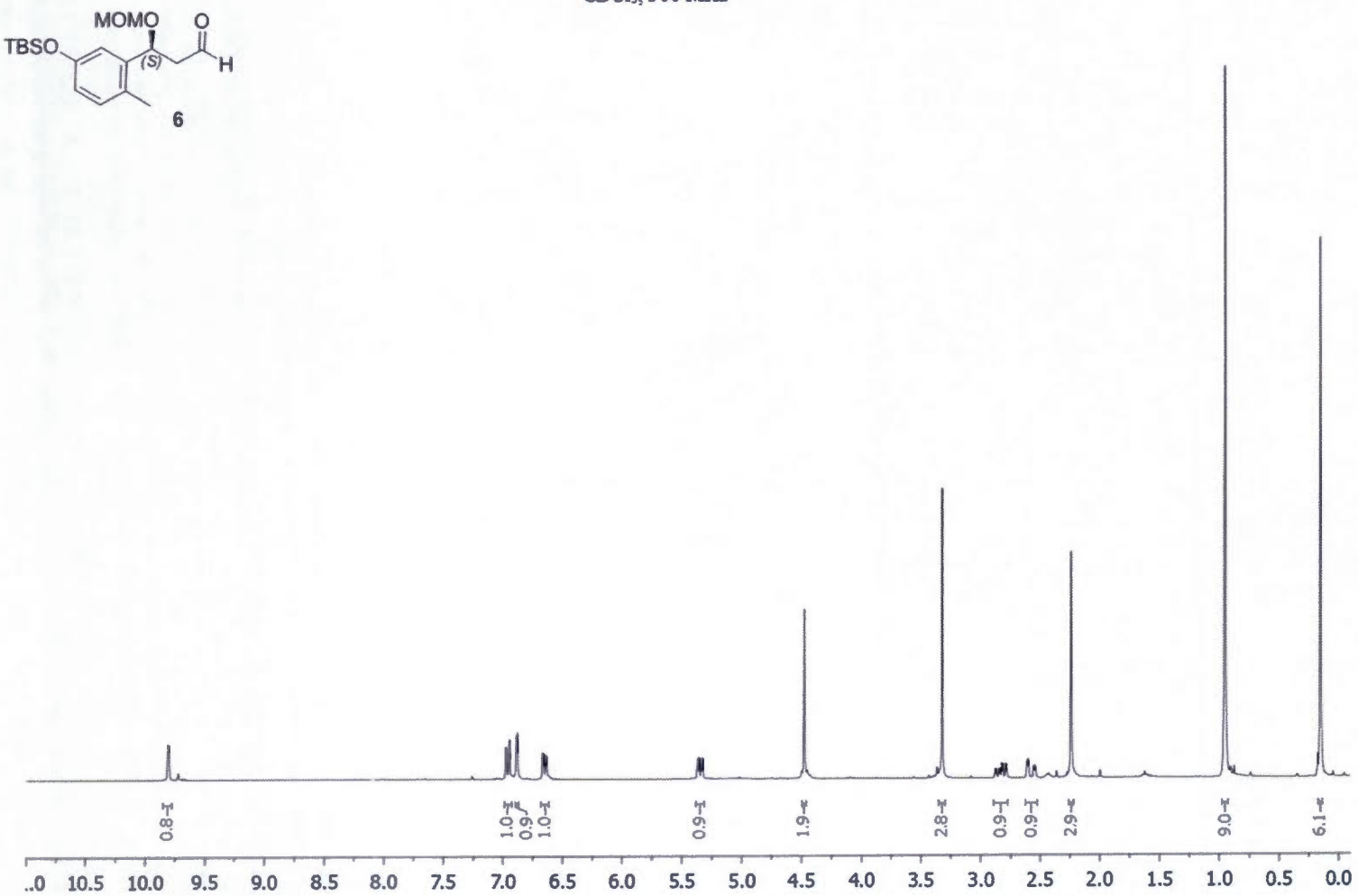
$CDCl_3$, 300 MHz

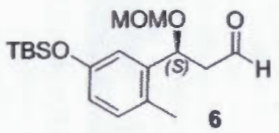


5a

CDCl3, 75 MHz

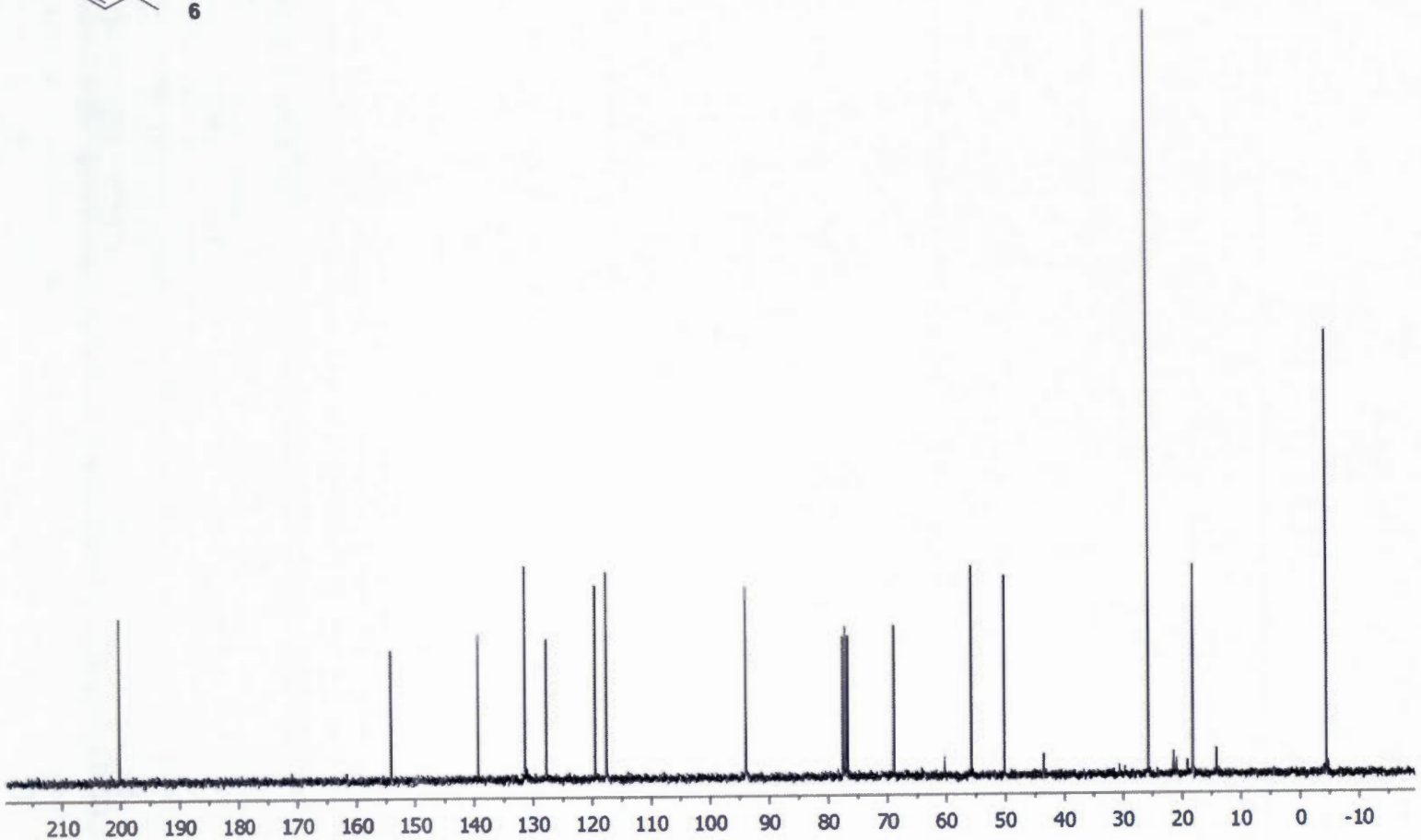


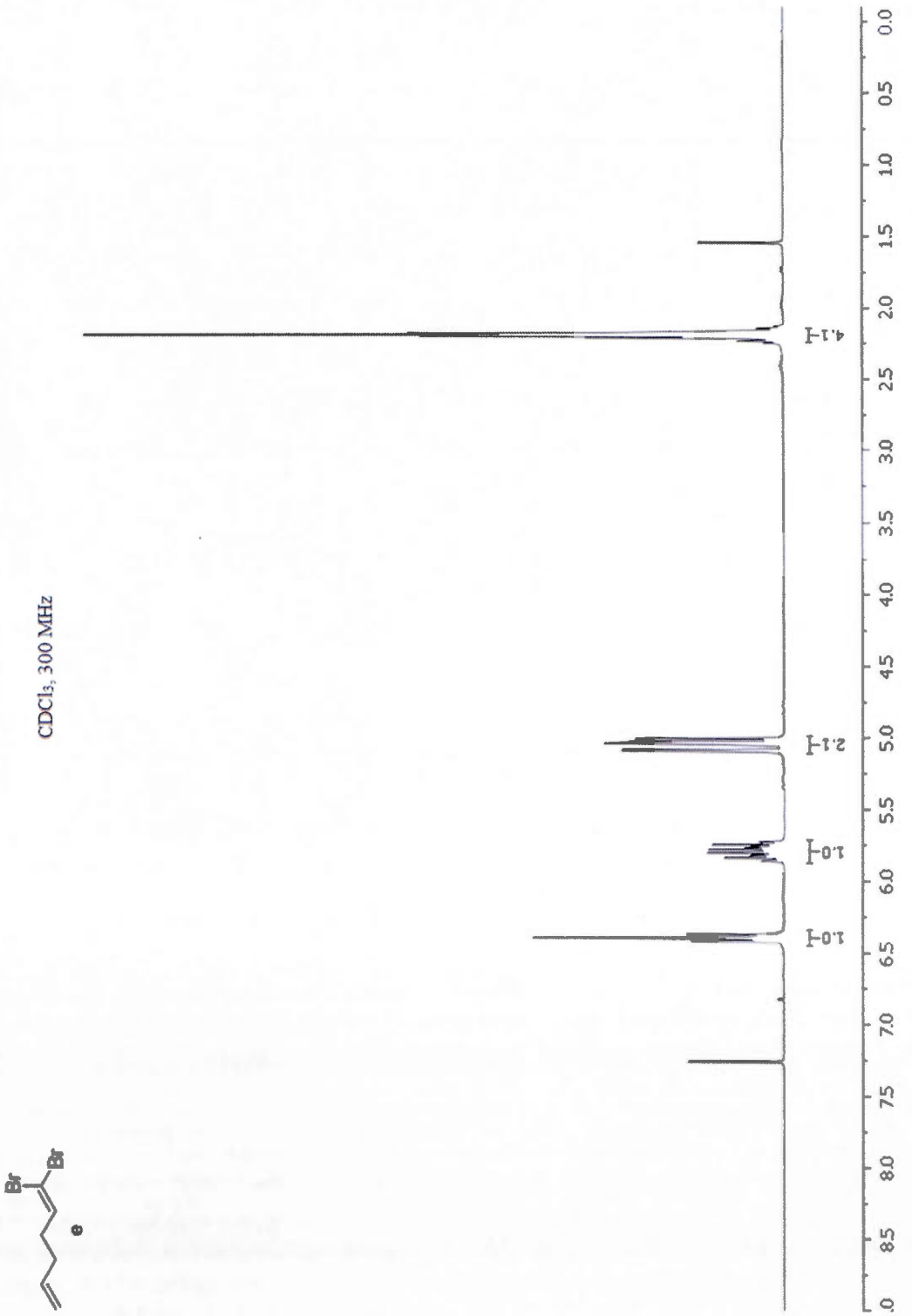

MOMO
O
TBSO
(S)
H
6
CDCl3, 300 MHz
0.8
1.0
0.9
1.0
0.9
1.9
2.8
0.9
0.9
2.9
9.0
6.1
..0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

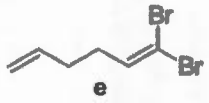


6

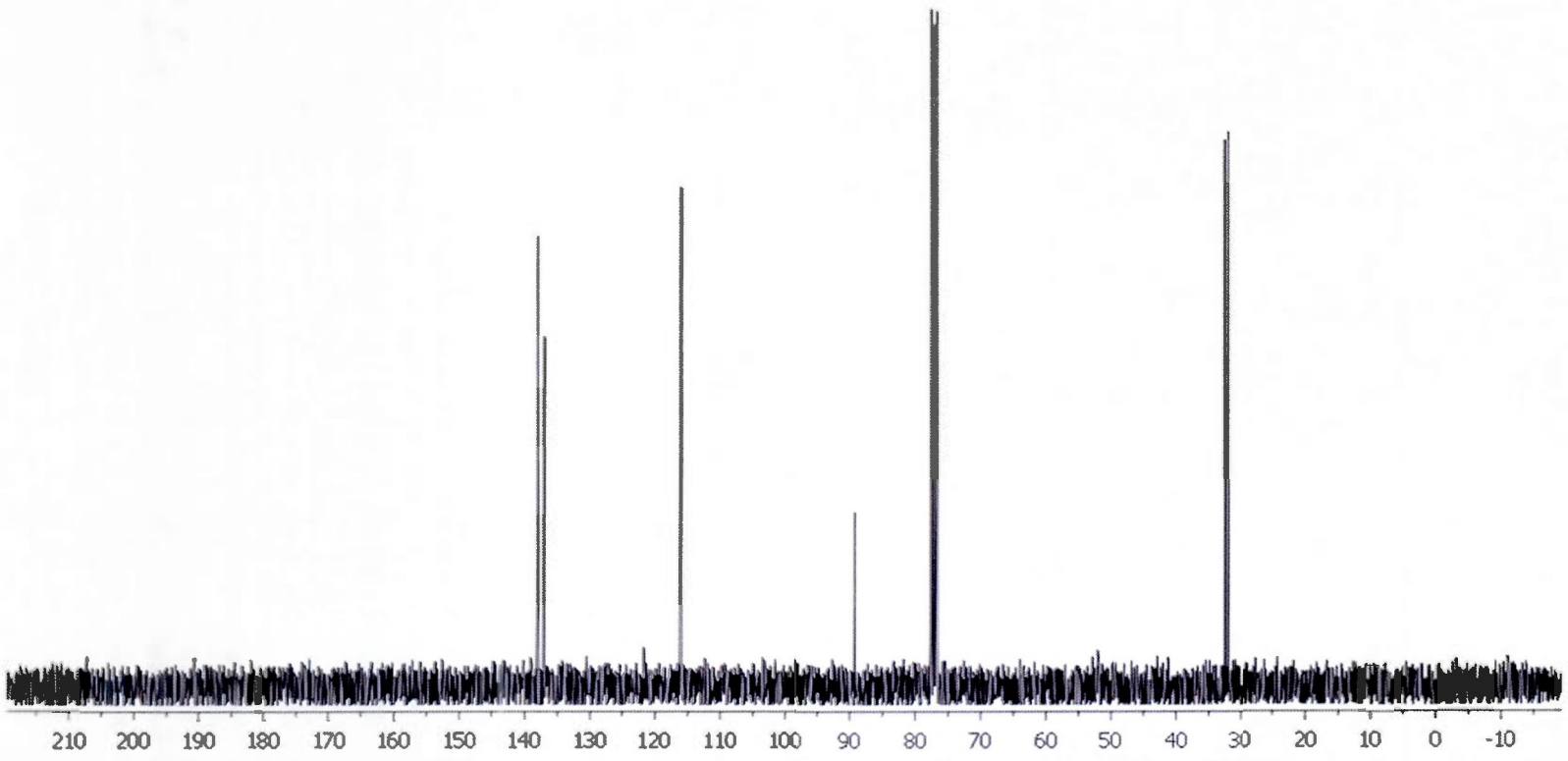
$CDCl_3$, 75 MHz

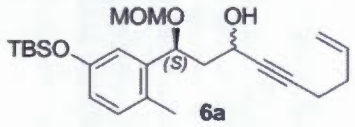



Br
Br
CDCl3, 300 MHz
4.1
2.1
1.0
1.0
1.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
.0


Br
Br
e

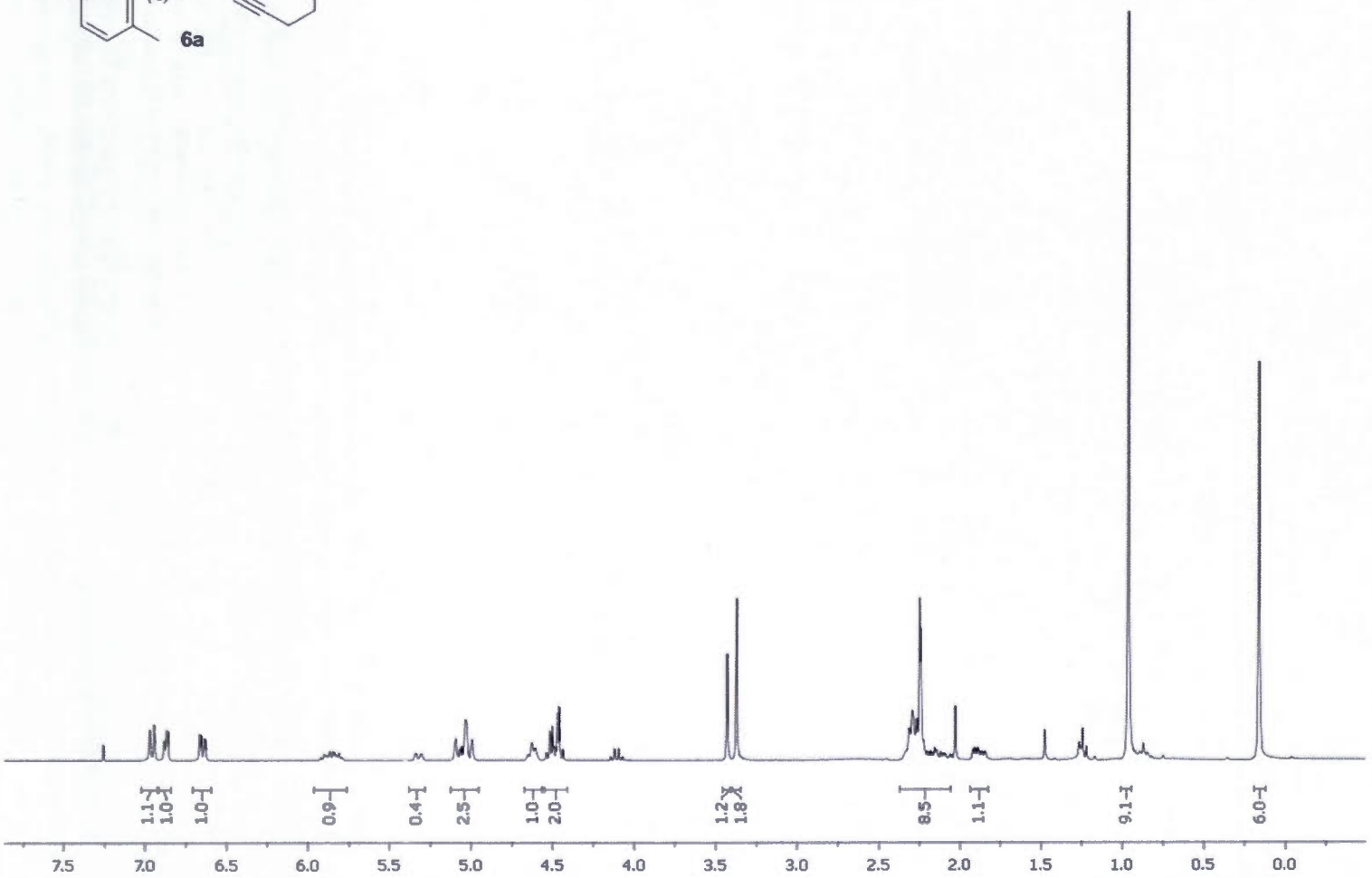
$CDCl_3$, 75 MHz

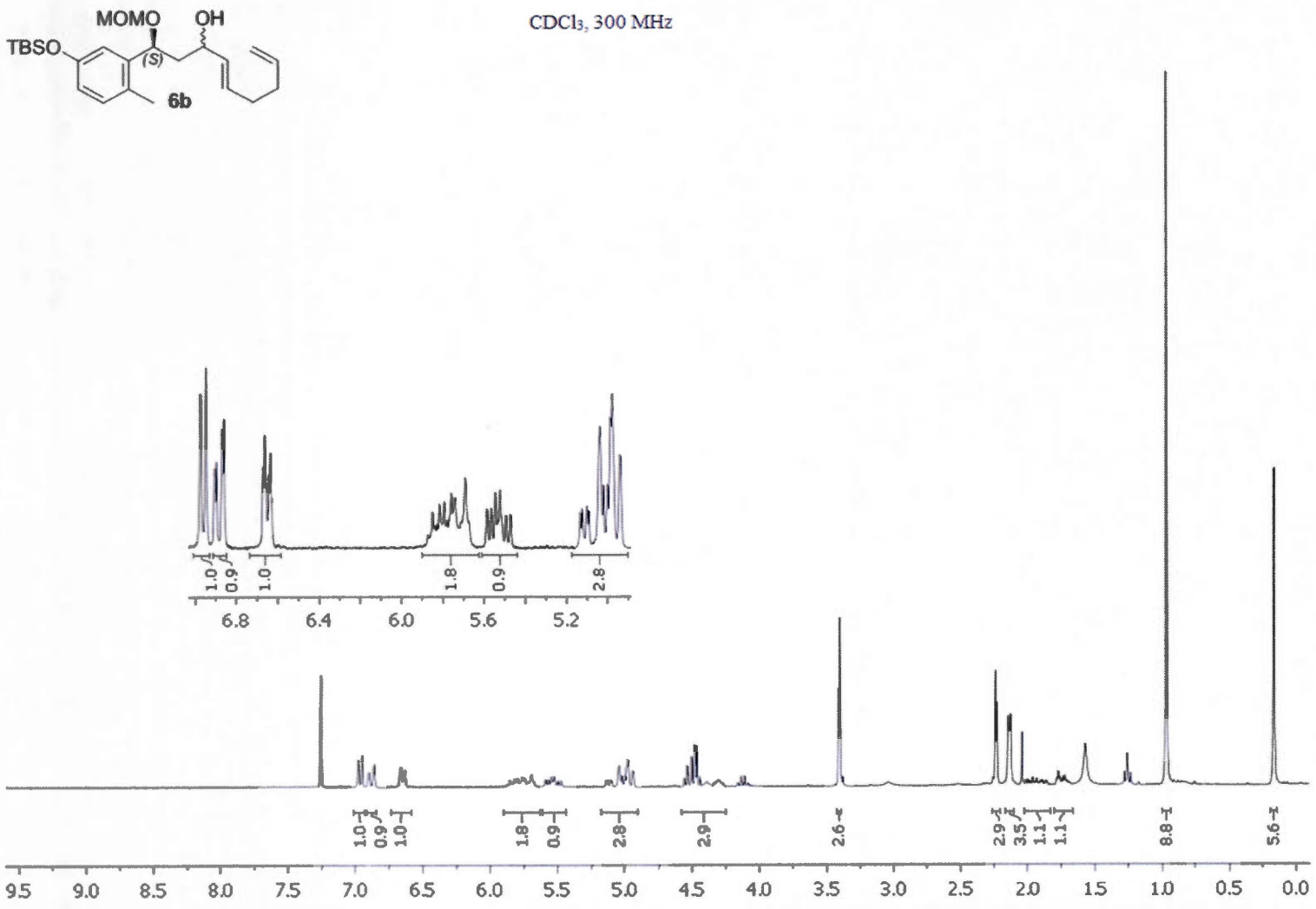

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

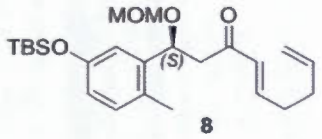


6a

$CDCl_3$, 300 MHz

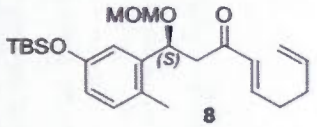



MOMO
OH
TBSO
(S)
6b
CDCl3, 300 MHz



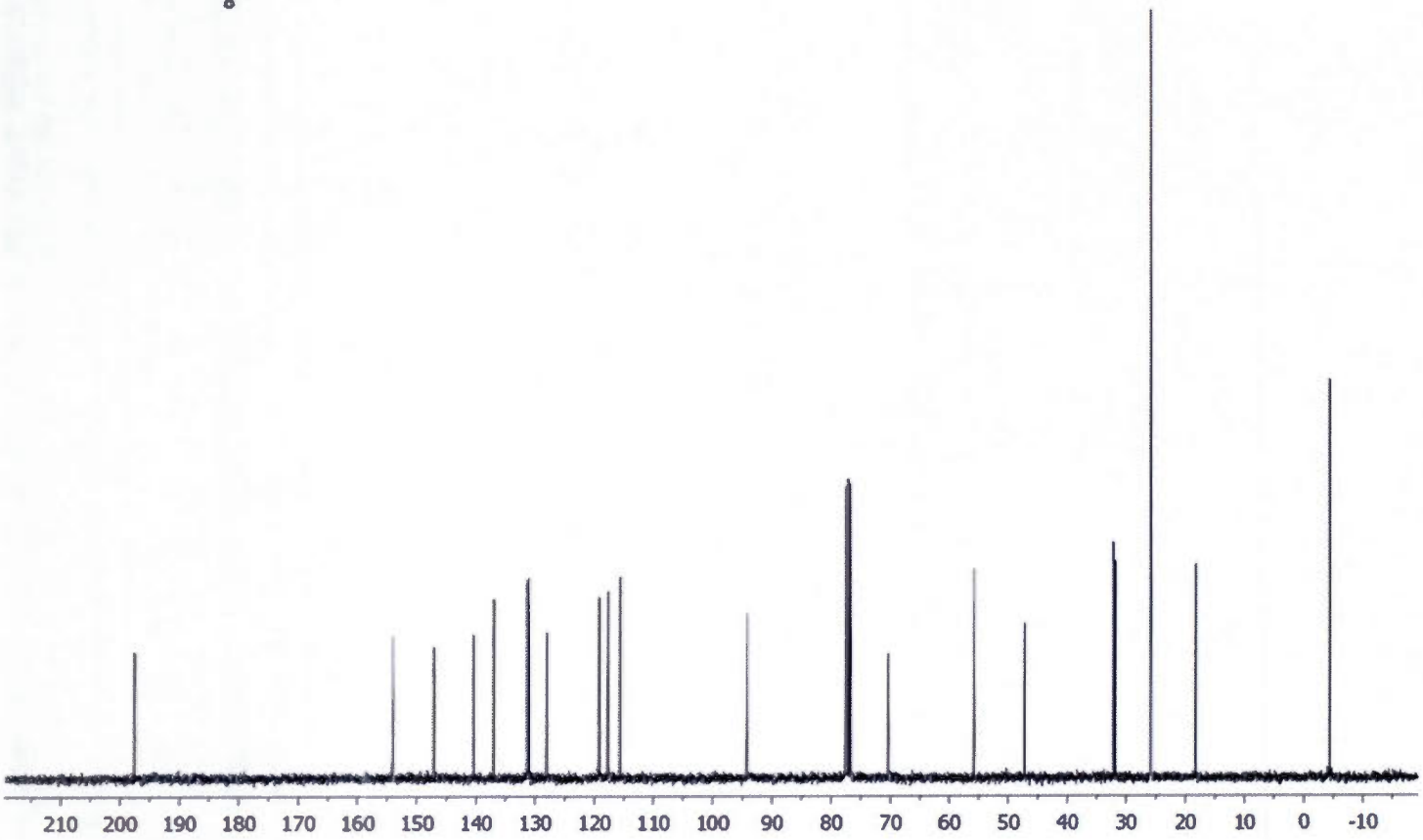
8

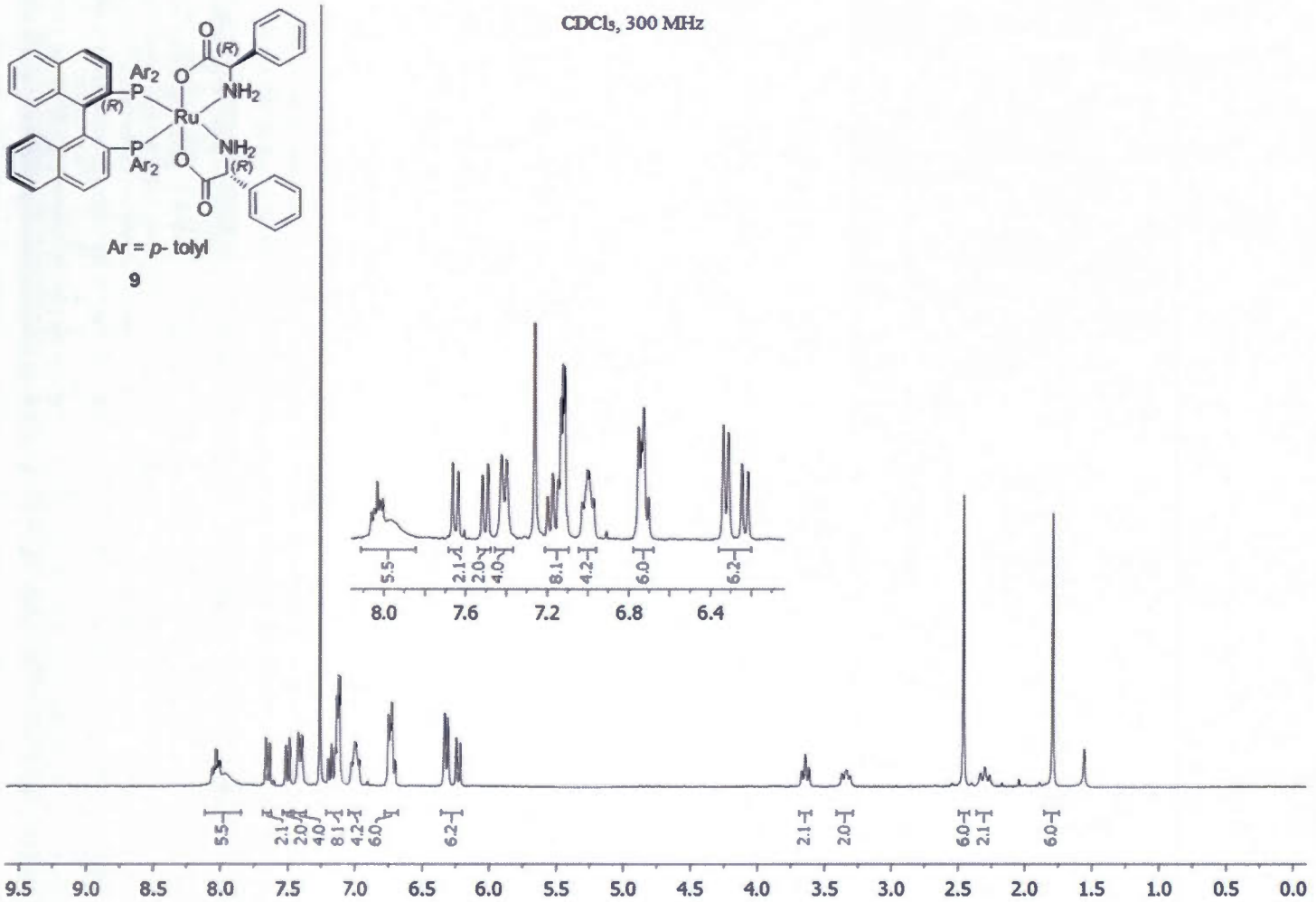
$CDCl_3$, 300 MHz

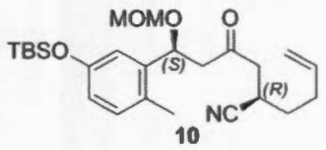


8

CDCl3, 75 MHz

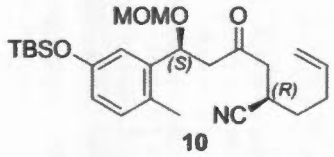



CDCl3, 300 MHz
Ar = p- tolyl
9



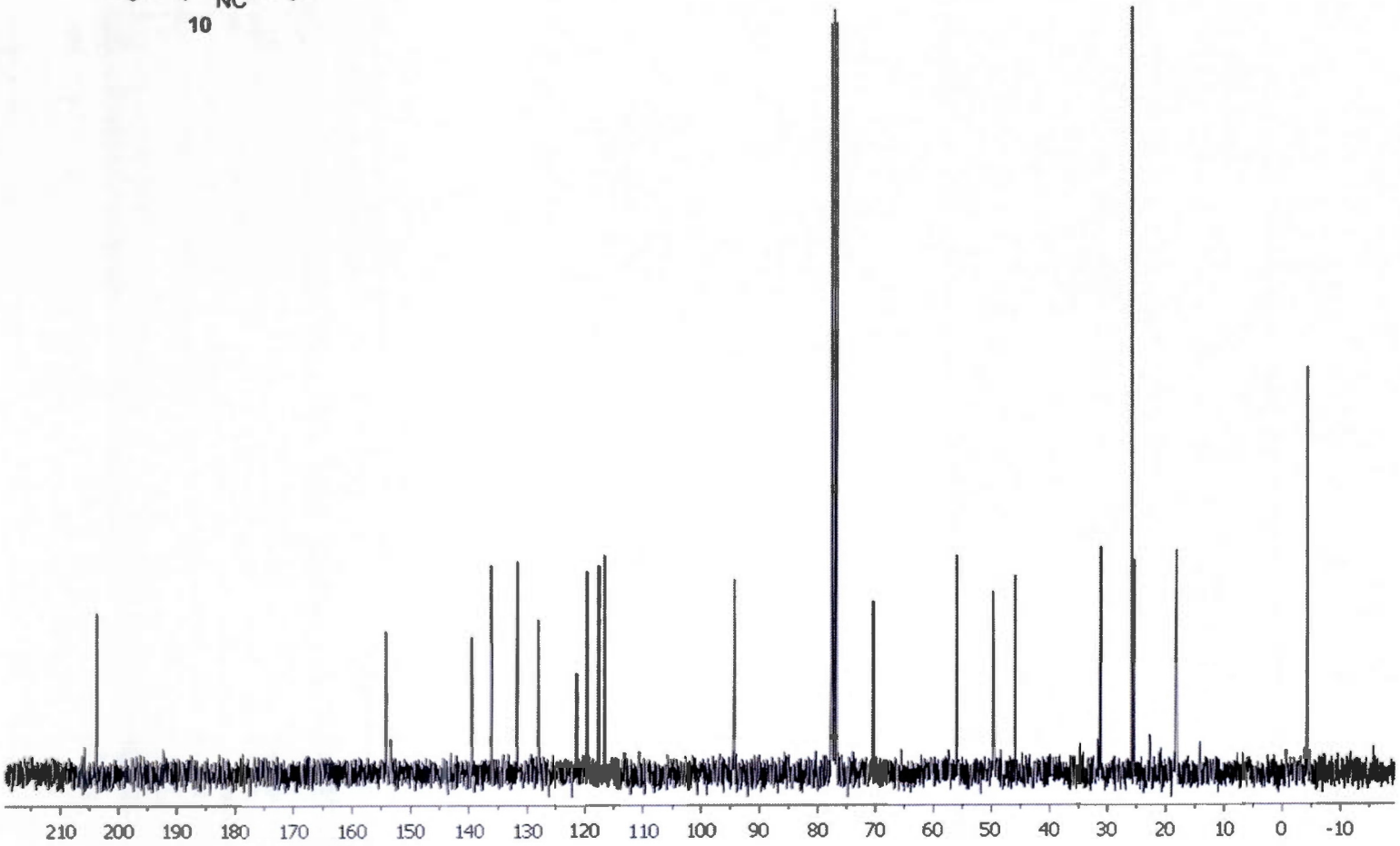
10

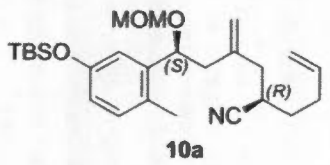
$CDCl_3$, 300 MHz



10

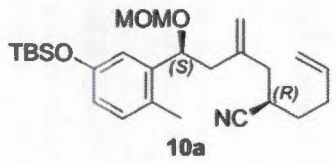
CDCl3, 75 MHz





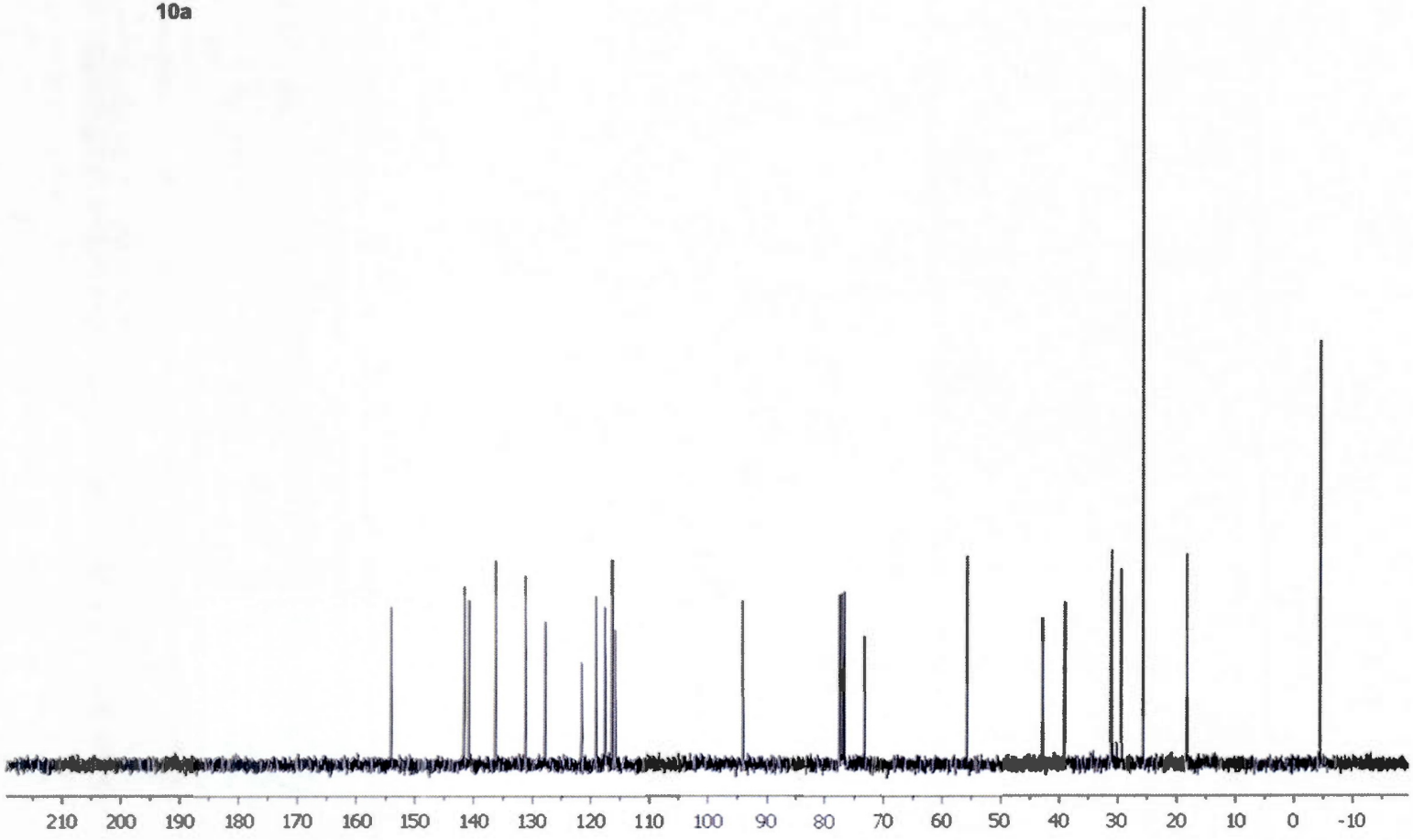
10a

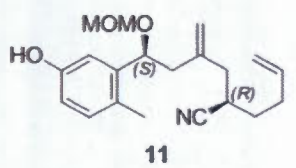
$CDCl_3$, 300 MHz



10a

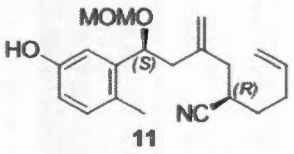
$CDCl_3$, 75 MHz





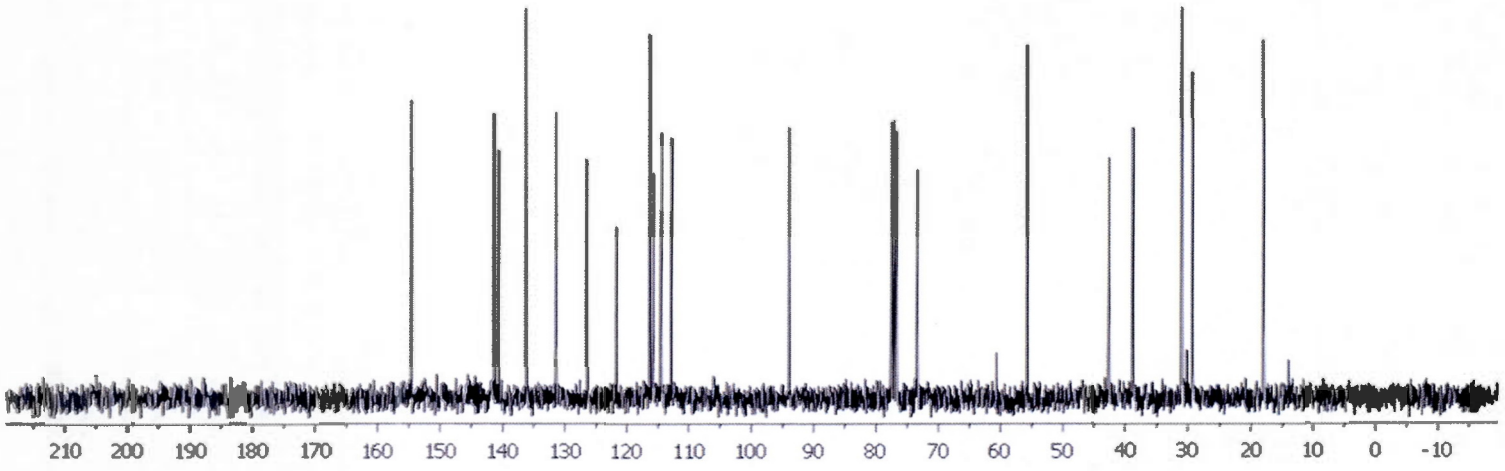
11

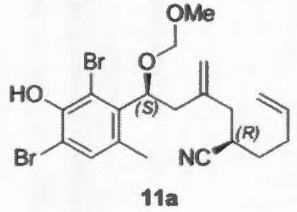
CDCl3, 300 MHz



11

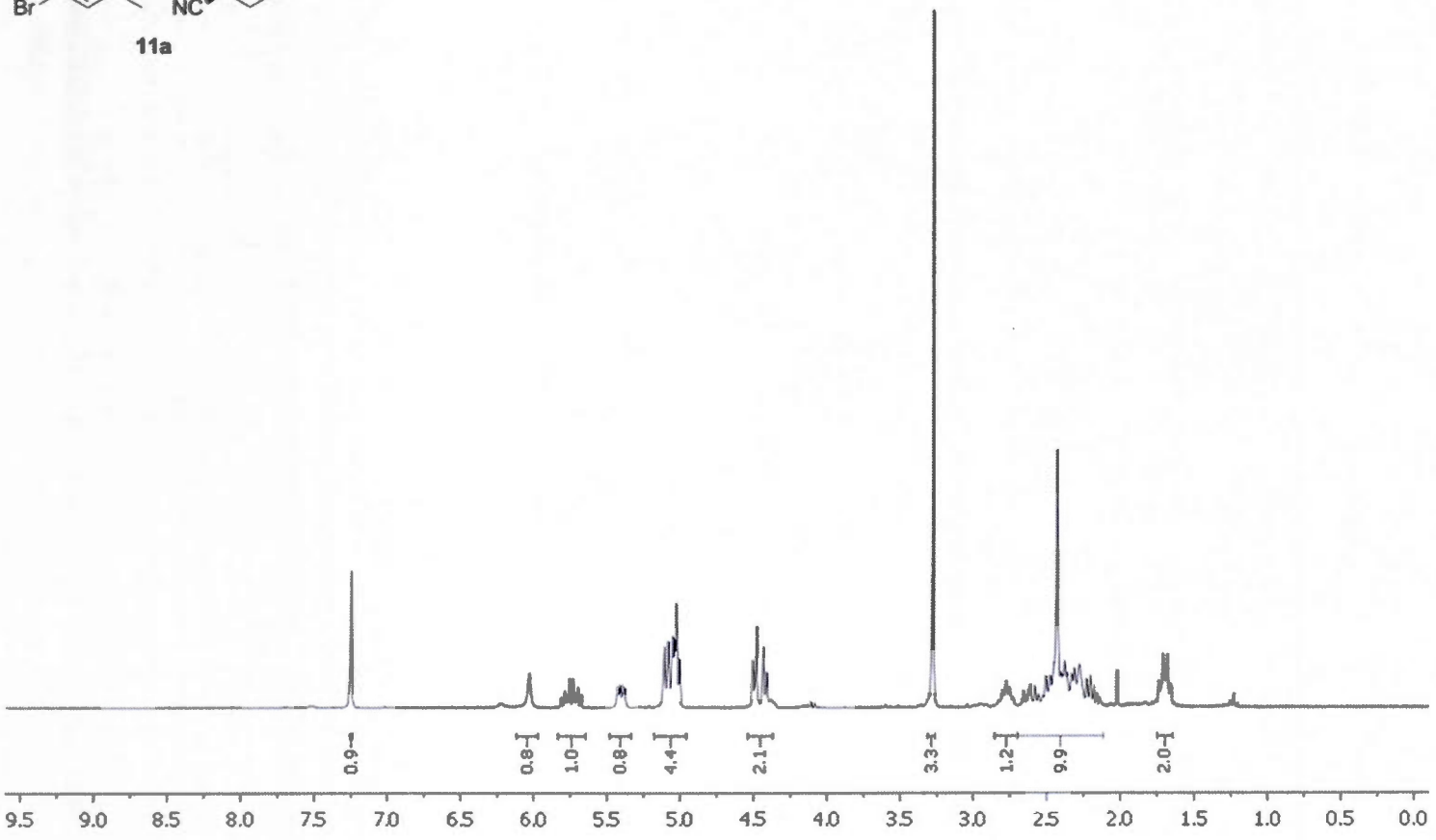
$CDCl_3$, 75 MHz

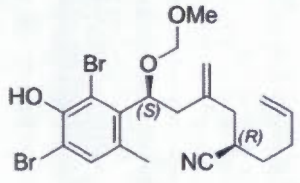




11a

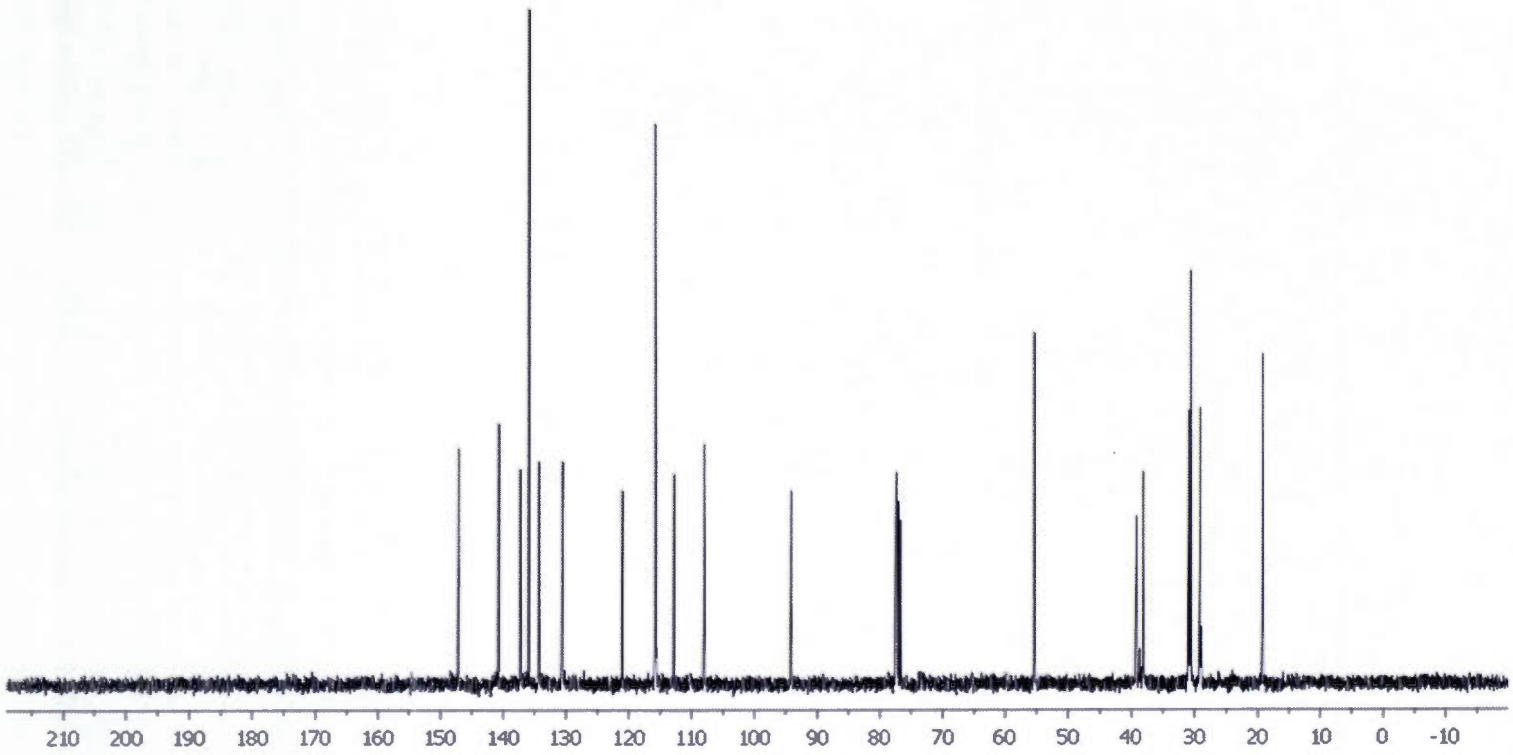
$CDCl_3$, 300 MHz

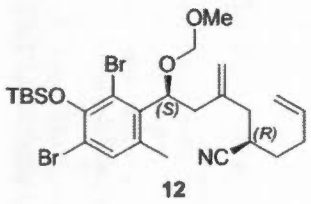




11a

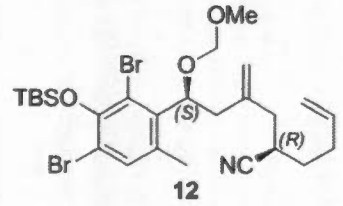
$CDCl_3$, 75 MHz





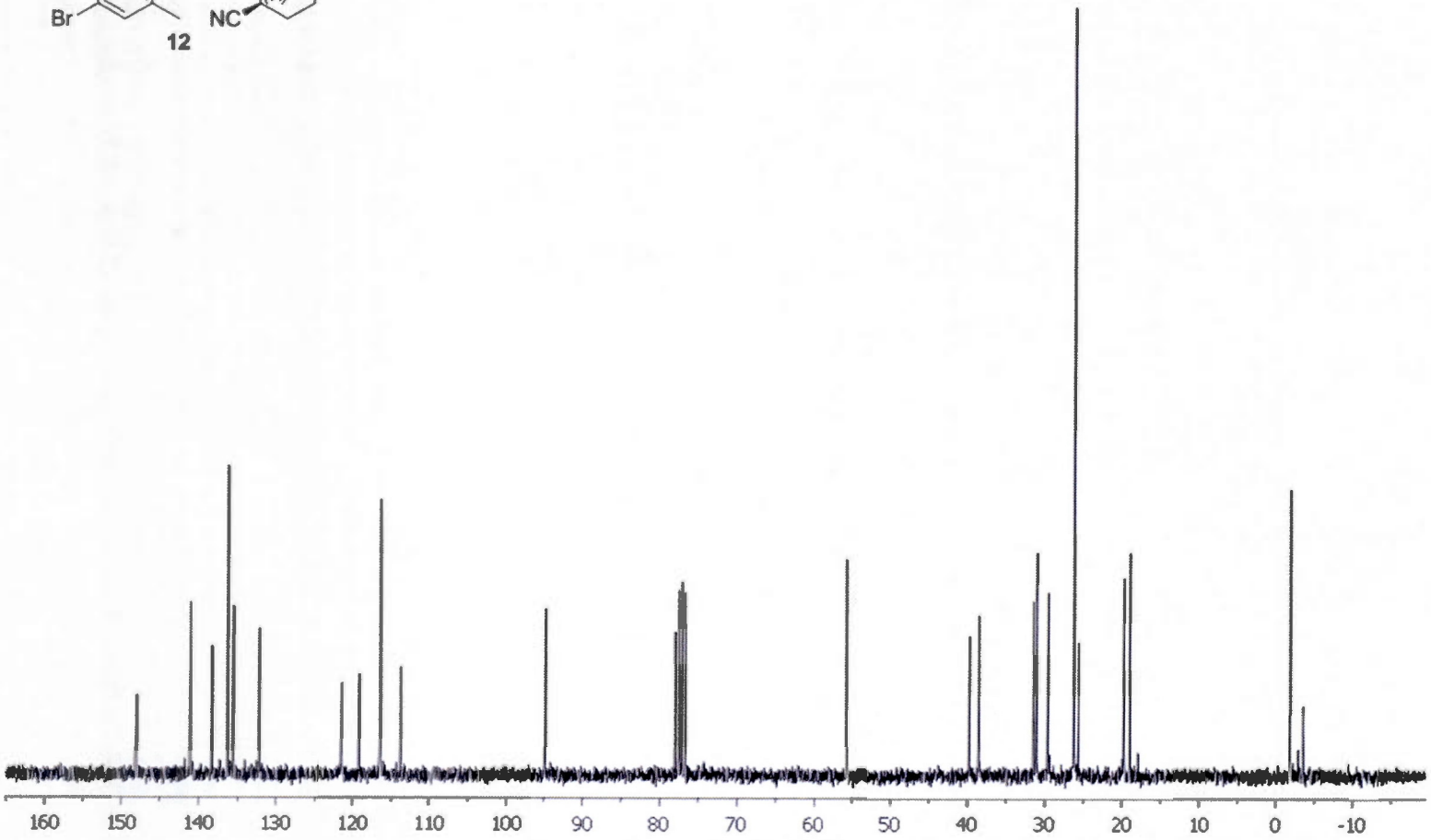
12

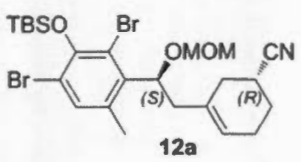
CDCl3, 300 MHz



12

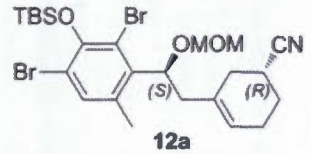
$CDCl_3$, 75 MHz





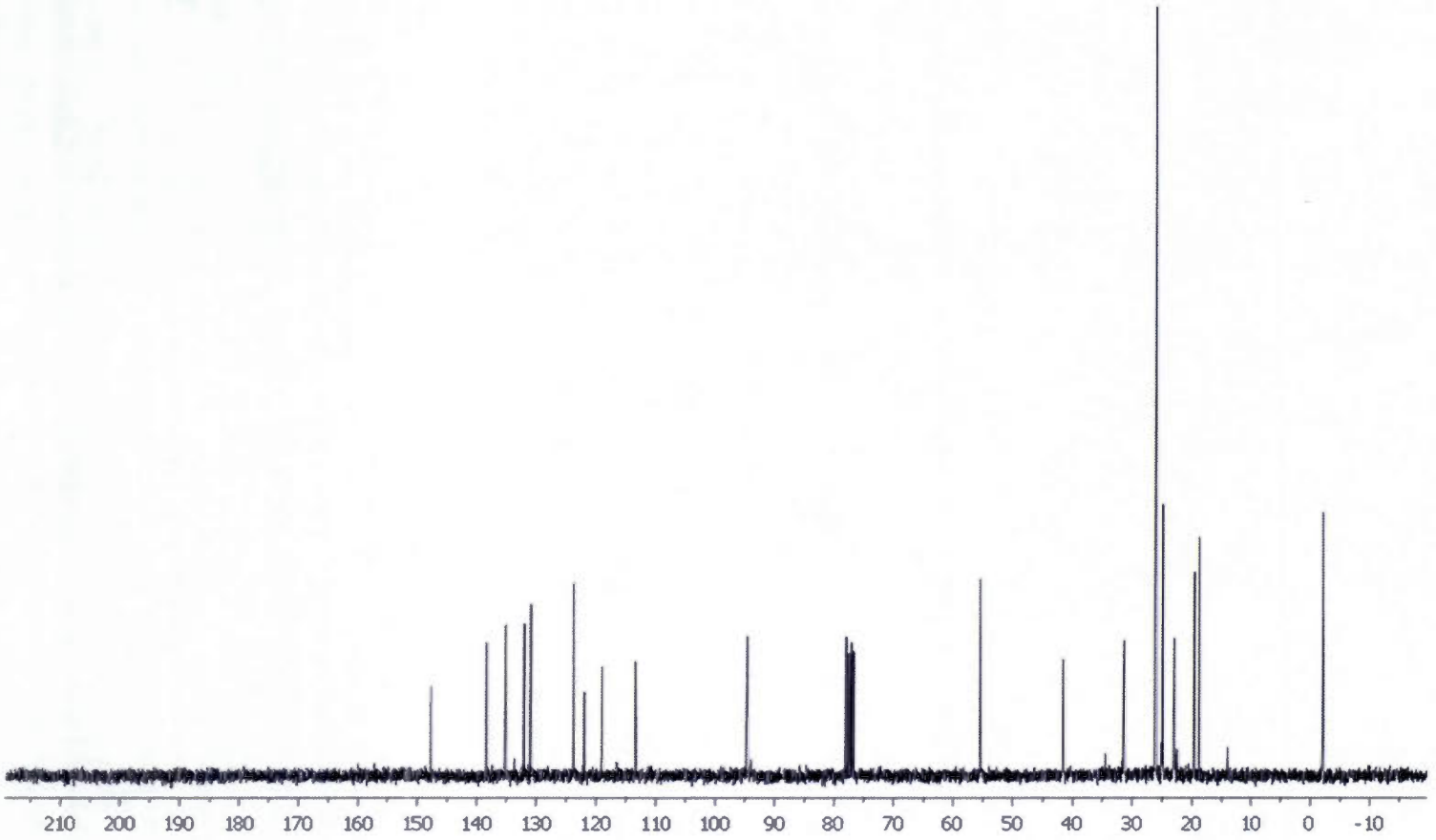
12a

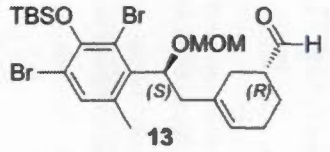
$CDCl_3$, 300 MHz



12a

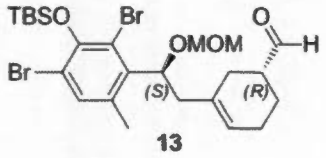
$CDCl_3$, 75 MHz





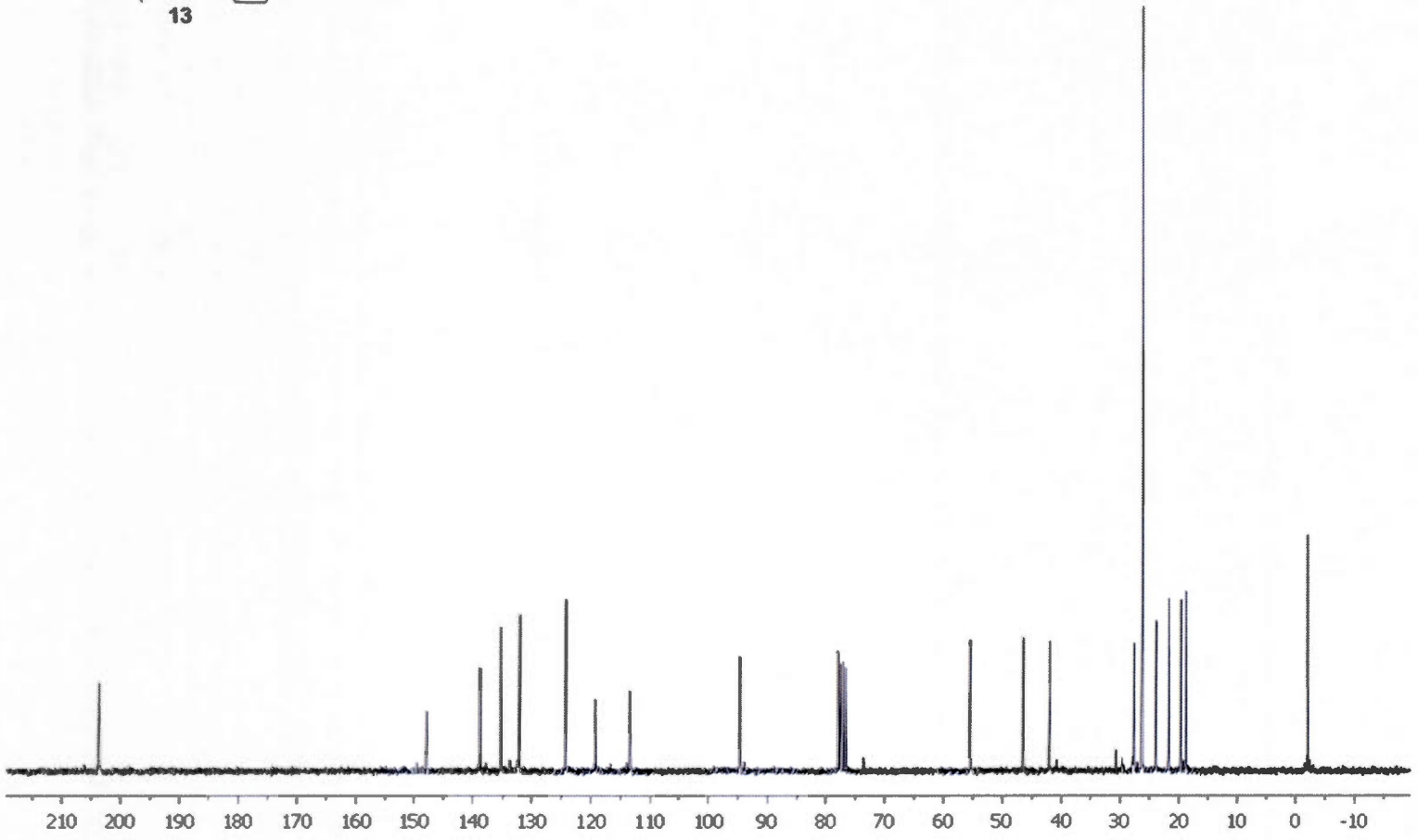
13

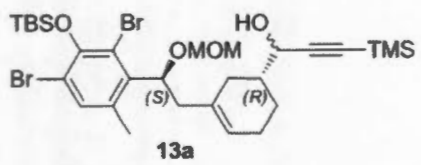
$CDCl_3$, 300 MHz



13

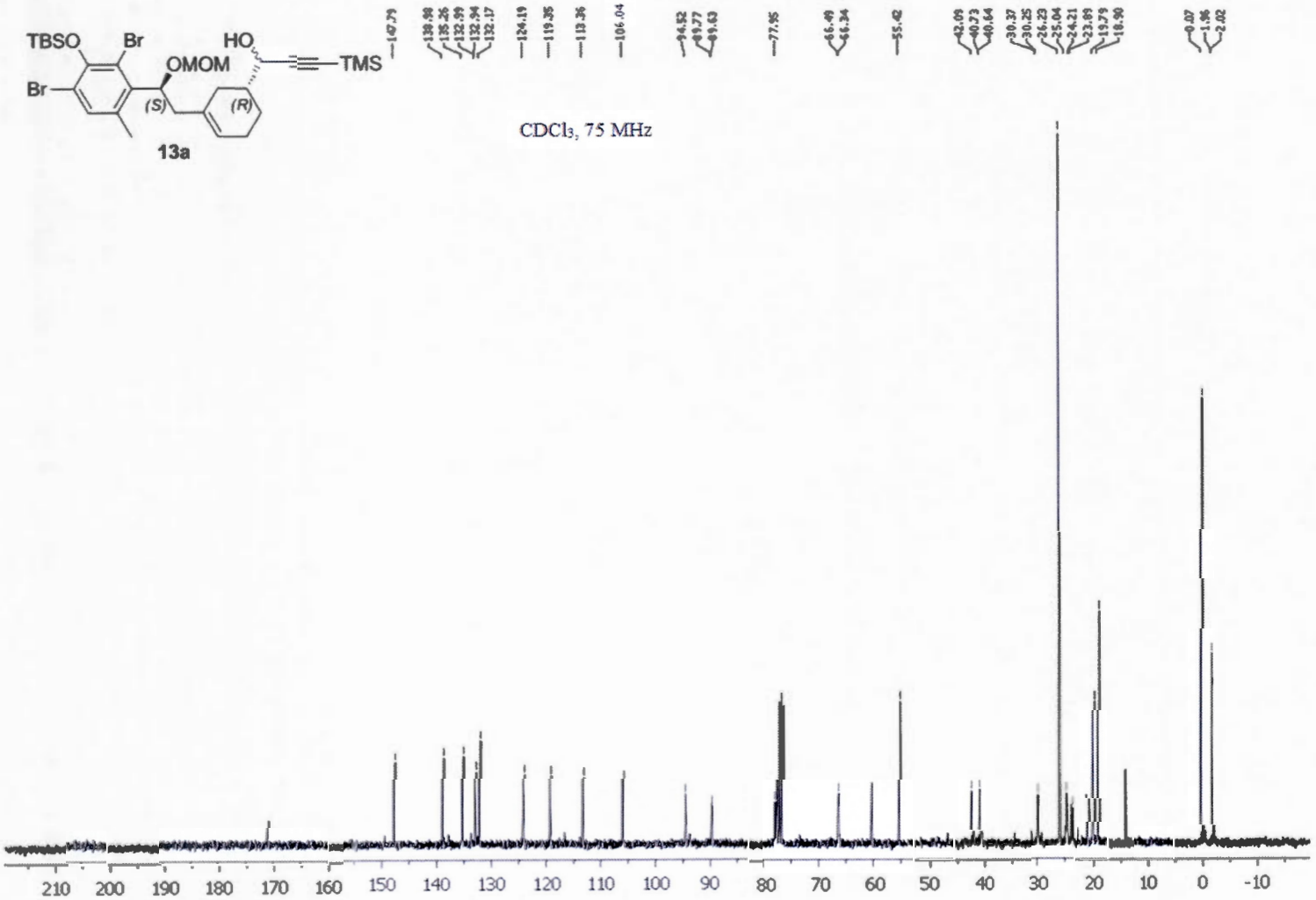
$CDCl_3$, 75 MHz

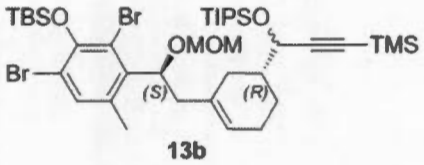




13a

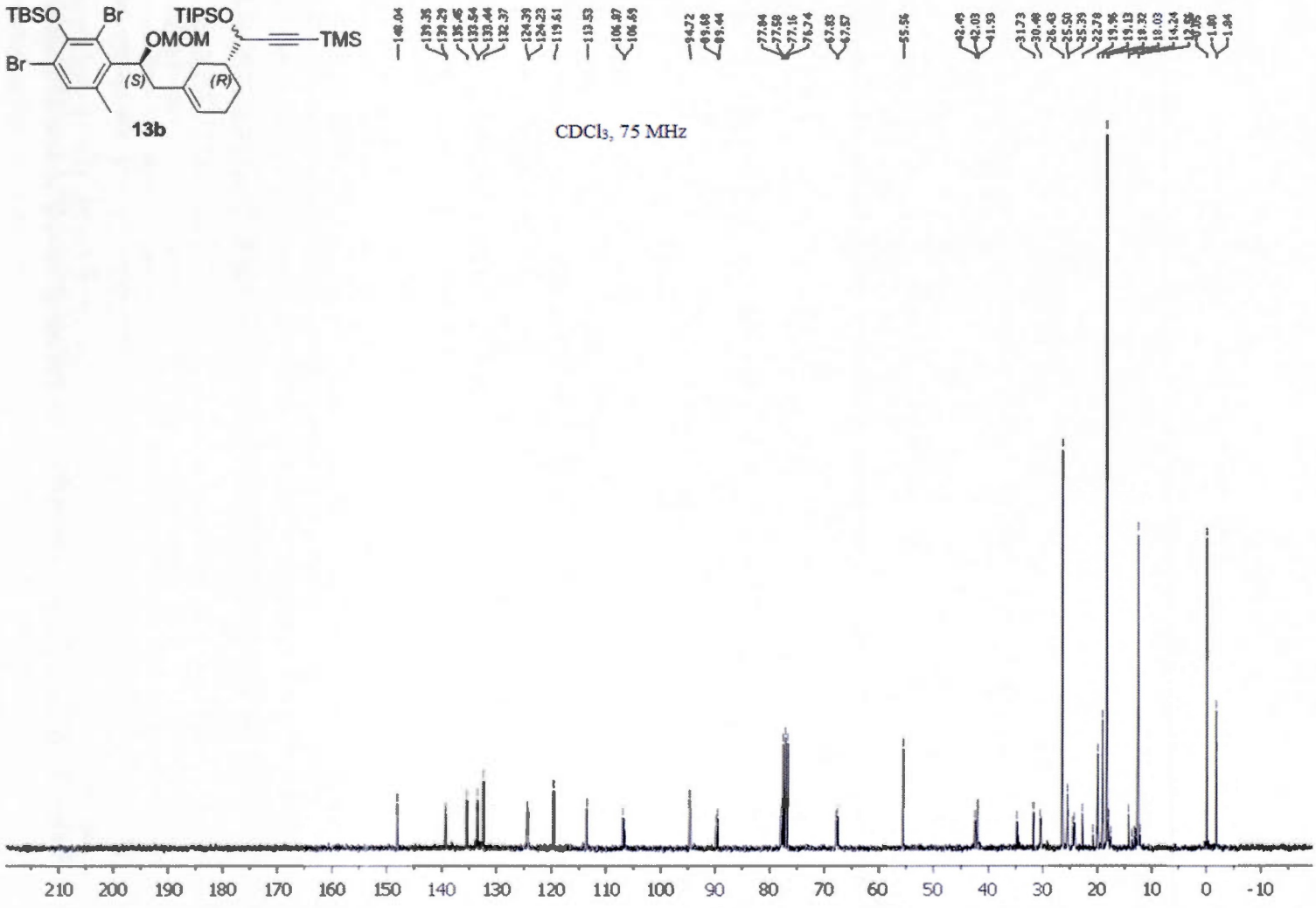
$CDCl_3$, 300 MHz

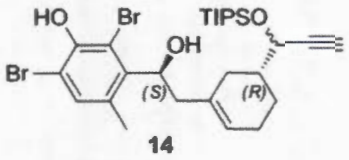

TBSO
Br
HO
OMOM
TMS
Br
(S)
(R)
13a
CDCl3, 75 MHz
147.79
130.98
128.26
122.59
122.54
122.17
124.19
119.35
113.36
106.04
94.52
89.77
89.63
77.95
66.49
66.34
55.42
42.09
40.73
40.64
30.37
30.25
26.23
25.04
24.21
23.89
19.79
18.90
0.07
-1.96
-2.02
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10



13b

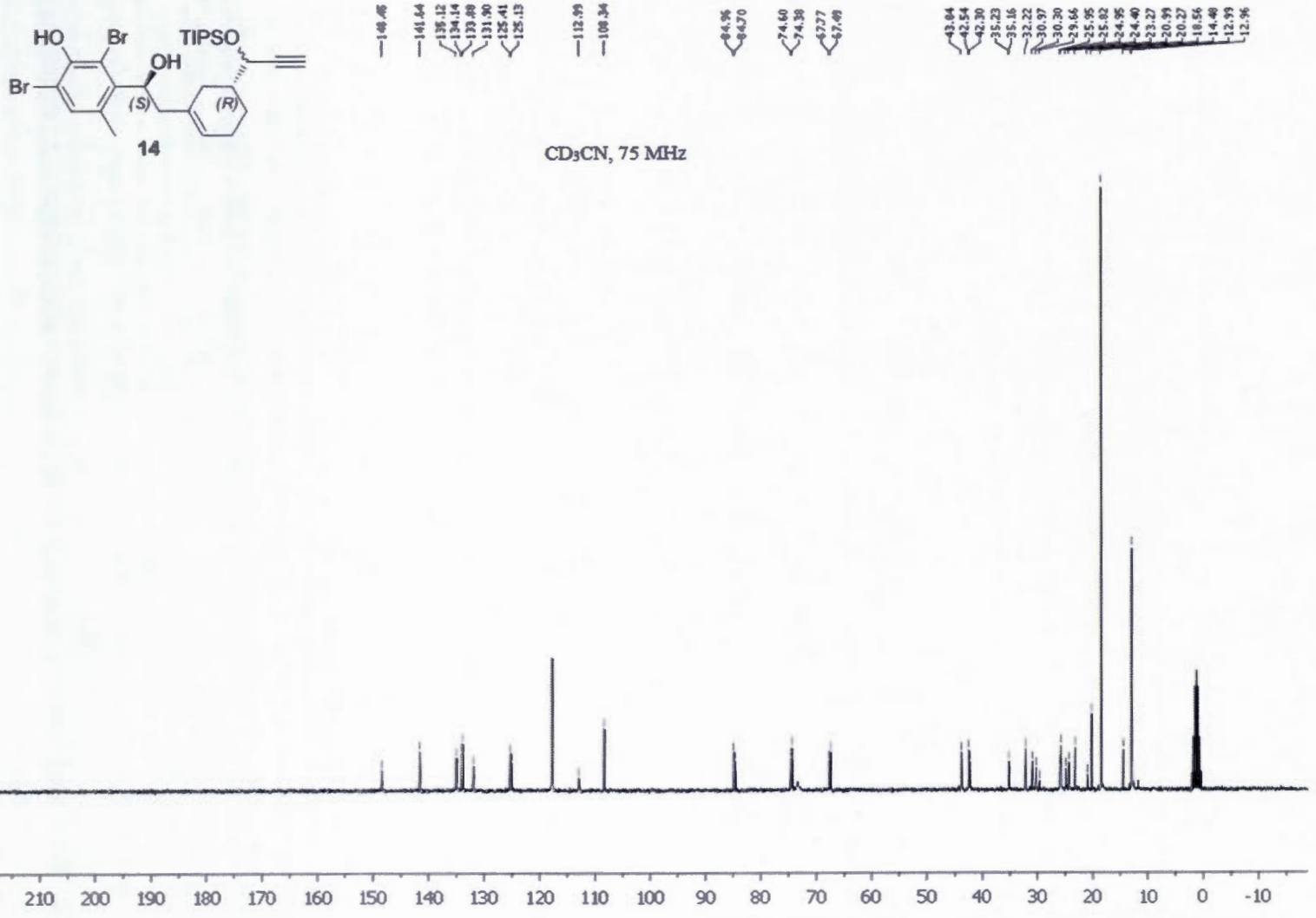
$CDCl_3$, 300 MHz

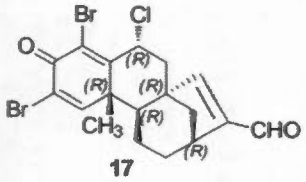

TBSO
Br
TIPSO
OMOM
TMS
Br
(S)
(R)
13b
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10



14

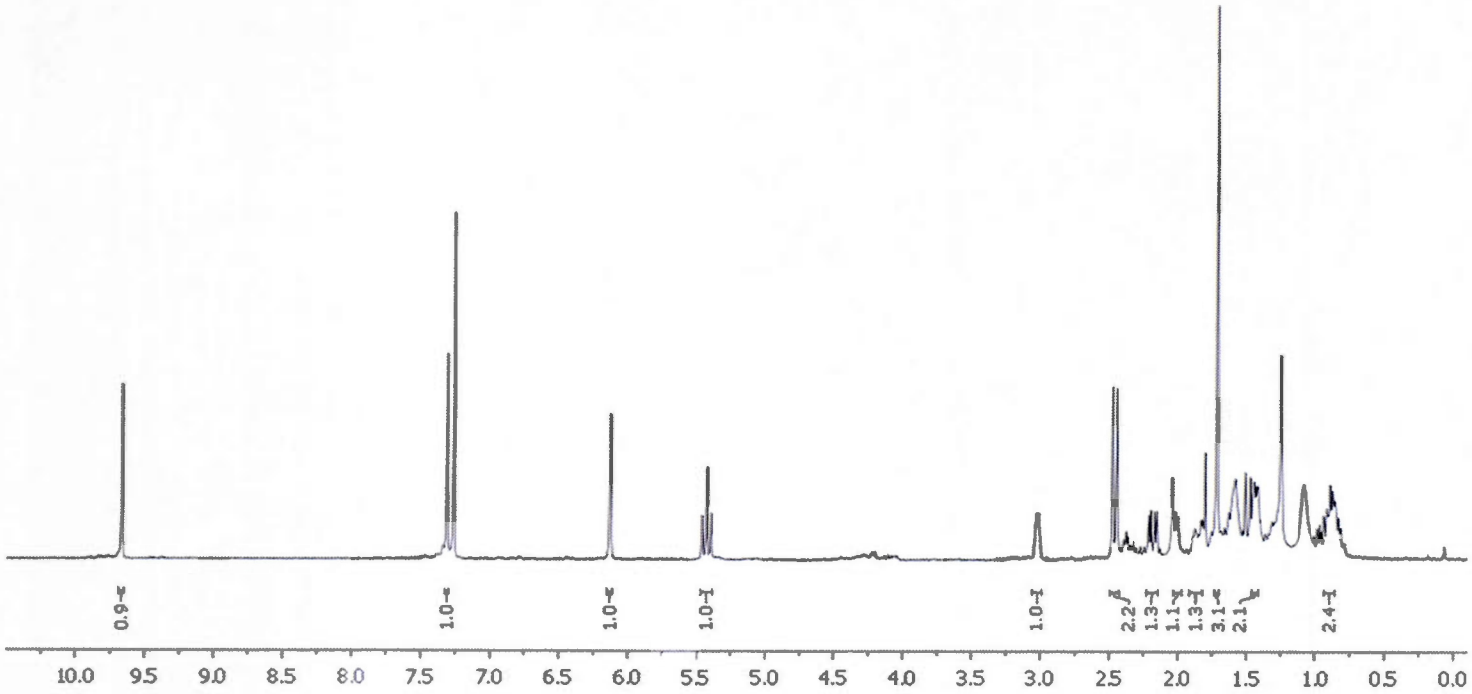
$CDCl_3$, 300 MHz

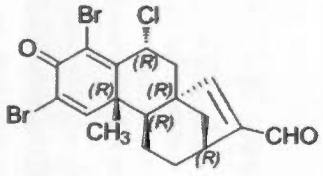

HO
Br
TIPSO
OH
Br
(S)
(R)
14
CD3CN, 75 MHz
148.46
141.64
135.12
134.14
133.88
131.90
125.41
125.13
112.99
108.34
84.96
84.70
74.60
74.38
67.77
67.49
43.84
42.54
42.30
35.23
35.16
32.22
30.97
30.30
29.66
25.95
25.82
24.95
24.40
23.27
20.99
20.27
18.56
14.40
12.99
12.96
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10



17

$CDCl_3$, 300 MHz





17

$CDCl_3$, 75 MHz

ANNEXE E
« MILD OXIDATION OF BENZILIC AMINES INTO ALDEHYDES USING AN OXIDATIVE POLONOVSKI-LIKE PROCESS » ARTICLE[31]

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Titre : Mild Oxidation of Benzilic Amines into Aldehydes Using an Oxidative Polonovski-Like Process

Auteurs : Samuel Desjardins, Guillaume Jacquemot, Sylvain Canesi*

Mild Oxidation of Benzylic Amines into Aldehydes Using an Oxidative Polonovski-Like Process

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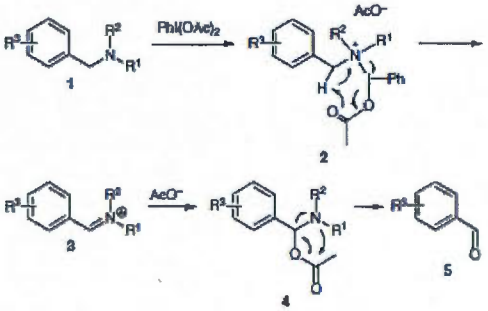
Abstract: A chemoselective and environmentally benign oxidation of benzylic amines into aldehydes mediated by a hypervalent iodine reagent has been developed. This mild oxidative version of the Polonovski process may be selectively carried out in the presence of several functionalities including a free alcohol and provides new synthetic opportunities as a masked aldehyde segment.

Key words: hypervalent iodine, oxidation, amines, Polonovski, aromatic aldehydes

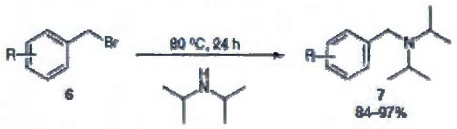
Aromatic aldehydes are important components of several natural products and are employed as valuable precursors in various synthetic processes. These common functionalities may be obtained using traditional transformations such as oxidation of an alcohol, but this may require the use of protecting groups to ensure selective oxidation if several alcohols are present in the molecule. In this paper, we describe a mild and chemoselective method for the selective transformation of a benzylic amine into an aldehyde even in the presence of a free alcohol. Similar reactions have been reported in the literature for oxidizing amines into carbonyl groups through imine or iminium species, but most of these have required toxic heavy metals or multistep processes.[1] This new method is promoted by hypervalent iodine reagents[2,3] such as iodobenzene diacetate (DIB), a mild and environmentally benign oxidizing reagent, avoiding the need for poisonous transition metals. Our method involves the formation of an iminium species **3** through a route similar to an oxidative Polonovski transformation[4,5] following the exposure of an amine to iodobenzene diacetate. A potential mechanism is described in Scheme 1.

The process was applied to several benzylic secondary and tertiary amines to determine the scope of the transformation, and a summary of representative investigations appears in Table 1.

It appears that the process occurs slowly and in moderate yields with unhindered amines. However, when a very bulky amino segment such as a diisopropylamine (entries 1a vs. 1f) was used, a clear improvement was observed in terms of yield and reaction rate (two hours instead of one day). We suppose that in the presence of bulky substituents, formation of the iminium species **3** mediated by acetate ion attack occurs mainly at the most accessible benzylic position without competition from the hindered tertiary positions neighboring the ammonium ion. It should be noted that the corresponding starting amines may be easily and efficiently obtained from their bromo derivatives **6** using a simple S_N2 transformation in the presence of inexpensive diisopropylamine.[6] In addition, bulky segments such as these may be safely used in syntheses as an inert functionality compatible with several traditionally used transformations (Scheme 2).



Scheme 1



Scheme 2

To verify this hypothesis, several hindered amines **7** were oxidized to produce the aldehydes **8**; a summary of representative experiments appears in Table 2.[7]

Under these conditions, aldehydes were obtained in useful to high yields (50–86%). An important aspect of this transformation is the chemoselectivity, which permits this reaction to occur in the presence of several spectator functionalities including a free alcohol (Table 2, entry 7). The method was also attempted using a secondary methyl-aryl amine derivative to produce a ketone but as expected with the Polonovsky or Pummerer[8] processes, the ketone adduct was not observed, demonstrating that this transfor-

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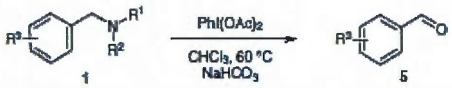
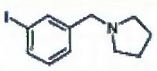
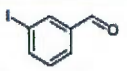
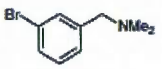
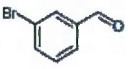
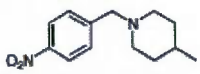
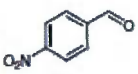
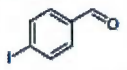
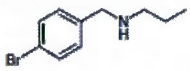
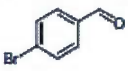
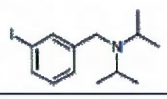
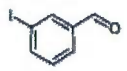
Advanced online publication: 25.05.2012
DOI: 10.1055/s-0031-1290676; Art ID: ST-2012-S0193-L

Table 1 Synthesis of Compounds 5

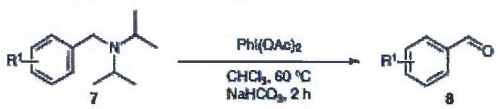


1 5

Entry			Time (h)		Yield (%)
1	a		24		55
2	b		12		42
3	c		24		50
4	d		24		5
5	e		24		50
6	f		2		75

mation occurs selectively on a primary center to enable almost exclusive formation of aldehyde moieties. This observation explains why the reaction is more effective with a hindered base such as diisopropylamine, which avoids competition at other positions during iminium ion formation (Scheme 1).

Table 2 Synthesis of Aldehydes 8



7 8

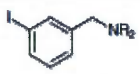
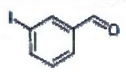
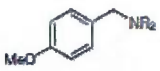
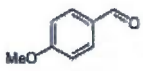
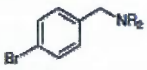
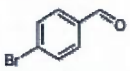
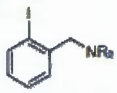
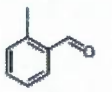
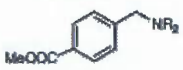
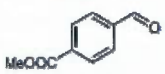
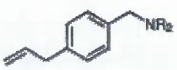
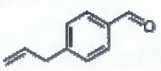
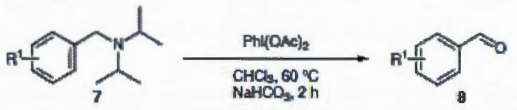
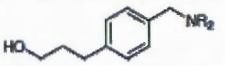
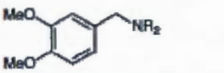
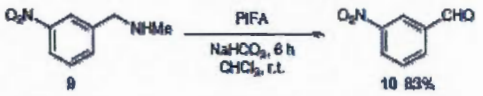
Entry				Yield (%)
1	a			75
2	b			69
3	c			83
4	d			75
5	e			65
6	f			50

Table 2 Synthesis of Aldehydes 8 (continued)



Entry			Yield (%)
7	g		65
8	h		86

The reaction was also undertaken using alternate hypervalent iodine reagents such as PIFA {[bis(trifluoroacetoxy)iodo]benzene} or Koser's reagent,[9] known to be more reactive oxidants. Yields were generally higher with DIB, most probably due to the less acidic environment generated by acetic acid versus the trifluoro homologue present in PIFA. However, if the desired product is compatible with the more rigorous conditions of PIFA, the desired aldehyde **10** may be obtained at room temperature in 83% yield from the secondary amine **9** (Scheme 3).



Scheme 3

In conclusion, a practical and mild method to oxidize selectively hindered benzylic amines into aldehydes has been developed. The transformation involves the use of a hypervalent iodine reagent as an environmentally benign oxidant to avoid the need for toxic heavy metals. The process occurs efficiently in the presence of several spectator functionalities including a free alcohol.

Experimental Procedure

To a stirred solution of amine **7** (1 mmol) in $CHCl_3$ (4 mL) was added $NaHCO_3$ (92 mg, 1.1 mmol, 1.1 equiv) and $PhI(OAc)_2$ (451 mg, 1.4 mmol, 1.4 equiv). The solution was stirred at reflux (60 °C) for 2 h, after which a solution of sat. aq NH_4Cl was added. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was chromatographically purified (*n*-hexane–EtOAc) to afford the corresponding aldehyde **8**.

Acknowledgment

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ANNEXE F

« MILD OXIDATION OF BENZILIC AMINES INTO ALDEHYDES USING AN OXIDATIVE POLONOVSKI-LIKE PROCESS » SUPPORTING INFORMATION[15]

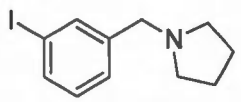
SYNLETT, 2012, Vol. 23, Pages 1497-1500

DOI : 10.10554/s-0031-1290676; Art ID : ST-2012-S0193-L

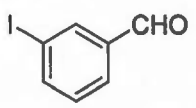
Date de publication (Web) : 25 Mai 2012

Titre : Mild Oxidation of Benzilic Amines into Aldehydes Using an Oxidative Polonovski-Like Process

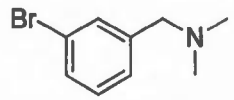
Auteurs : Samuel Desjardins, Guillaume Jacquemot, Sylvain Canesi*

1a 

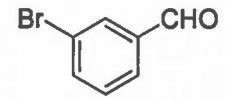
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.69 (s, 1H), 7.59 – 7.51 (m, 1H), 7.29 – 7.25 (m, 1H), 7.01 (t, *J*=7.7, 1H), 3.53 (s, 2H), 2.51 – 2.43 (m, 4H), 1.80 – 1.71 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 141.98, 137.61, 135.91, 129.95, 128.01, 94.44, 59.98, 54.16, 23.51.

5a 

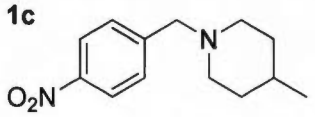
^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.21 (s, 1H), 7.50 (s, 1H), 7.25 (d, *J*=7.8, 1H), 7.13 (d, *J*=7.6, 1H), 6.64 – 6.52 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 190.80, 143.30, 138.56, 138.12, 130.85, 129.02, 94.77.

1b 

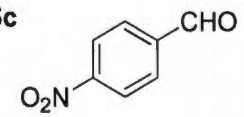
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.49 (s, 1H), 7.39 (d, *J*=7.7, 1H), 7.25 – 7.15 (m, 2H), 3.41 (s, 2H), 2.26 (s, 6H).

5b 

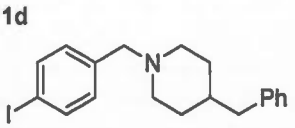
^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.97 (s, 1H), 8.02 (t, *J*=1.7, 1H), 7.81 (dt, *J*=7.6, 1.3, 1H), 7.76 (ddd, *J*=8.0, 2.0, 1.1, 1H), 7.43 (t, *J*=7.8, 1H).

1c 

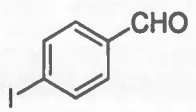
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.12 – 8.05 (m, 2H), 7.45 (d, *J*=8.7, 2H), 3.50 (s, 2H), 2.78 – 2.69 (m, 2H), 1.93 (td, *J*=11.6, 2.1, 2H), 1.60 – 1.49 (m, 2H), 1.39 – 1.10 (m, 3H), 0.86 (d, *J*=6.2, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 147.16, 146.92, 129.35, 123.31, 62.51, 54.02, 34.29, 30.58, 21.84.

5c 

^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.16 (s, 1H), 8.39 (d, *J*=8.4, 2H), 8.07 (d, *J*=8.6, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 190.42, 140.24, 130.62, 124.44.

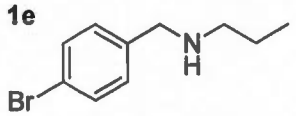
1d 

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.67 (d, *J*=8.2, 1H), 7.36 – 7.27 (m, 1H), 7.26 – 7.14 (m, 2H), 7.11 (d, *J*=8.2, 1H), 3.45 (s, 1H), 2.87 (d, *J*=11.6, 1H), 2.58 (d, *J*=6.8, 1H), 1.93 (td, *J*=11.7, 2.0, 1H), 1.71 – 1.47 (m, 2H), 1.34 (ddd, *J*=14.8, 11.8, 3.8, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 140.82, 138.48, 137.33, 131.23, 129.23, 128.27, 125.89, 92.31, 77.58, 77.16, 76.74, 62.86, 53.92, 43.32, 37.97, 32.27.

5d 

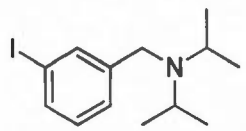
^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.96 (s, 1H), 7.92 (d, *J*=8.2, 2H), 7.59 (d, *J*=8.3, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 191.68, 138.58, 135.69, 130.95.

1e



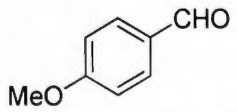
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.44 (d, *J*=8.3, 2H), 7.20 (d, *J*=8.2, 2H), 3.74 (s, 2H), 2.64 – 2.51 (m, 2H), 1.60 – 1.44 (m, 2H), 0.92 (t, *J*=7.4, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 131.56, 129.96, 53.41, 51.39, 23.28, 11.89.

1f



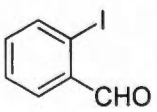
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.78 (s, *J*=8.8, 1H), 7.55 (d, *J*=7.8, 1H), 7.38 (d, *J*=7.7, 1H), 7.04 (t, *J*=7.7, 1H), 3.62 (s, *J*=8.1, 2H), 3.04 (hept, *J*=6.6, 2H), 1.05 (d, *J*=6.6, 12H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 146.10, 136.87, 135.28, 129.84, 127.09, 94.48, 77.58, 77.16, 76.74, 48.52, 48.06, 20.89.

8b



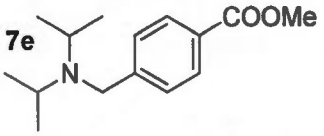
^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.88 (s, 1H), 7.83 (d, *J*=8.8, 2H), 6.99 (d, *J*=8.7, 2H), 3.88 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 190.94, 164.73, 132.10, 130.07, 114.43, 77.58, 77.16, 76.74, 55.70.

8d



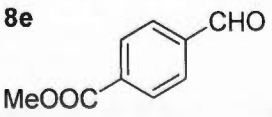
^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.08 (s, *J*=0.4, 1H), 7.96 (dd, *J*=7.9, 0.9, 1H), 7.88 (dd, *J*=7.7, 1.8, 1H), 7.47 (t, *J*=6.9, 1H), 7.30 (dd, *J*=7.7, 1.7, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 195.91, 140.80, 135.61, 130.42, 128.87.

7e



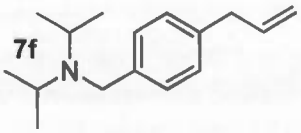
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.94 (d, *J*=8.3, 2H), 7.43 (d, *J*=8.3, 2H), 3.86 (s, 3H), 3.65 (s, 2H), 2.98 (hept, *J*=6.6, 2H), 0.99 (d, *J*=6.6, 12H) ; **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 167.13, 149.19, 129.37, 127.69, 51.80, 48.93, 48.20, 20.69.

8e

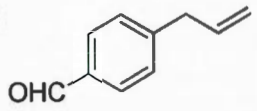


^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.09 (s, 1H), 8.18 (d, *J*=8.3, 2H), 7.94 (d, *J*=8.4, 2H), 3.95 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 191.60, 166.26, 139.18, 135.12, 130.20, 129.51, 77.48, 77.05, 76.63, 52.57.

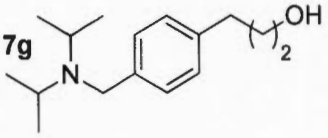
7f



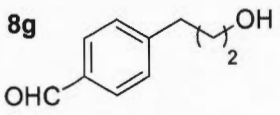
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32 (d, *J*=7.9, 2H), 7.12 (d, *J*=7.8, 2H), 5.99 (ddt, *J*=16.8, 10.0, 6.7, 1H), 5.14 – 5.04 (m, 1H), 3.63 (s, 2H), 3.38 (d, *J*=6.6, 2H), 3.04 (d, *J*=6.6, 2H), 1.03 (d, *J*=6.6, 12H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 140.93, 138.01, 137.91, 128.30, 128.11, 115.63, 48.71, 47.90, 40.07, 20.86.

8f 

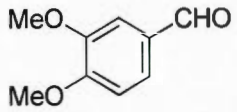
^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.88 (s, 1H), 7.72 (d, *J*=8.0, 2H), 7.26 (d, *J*=7.0, 2H), 5.86 (ddt, *J*=13.5, 10.5, 6.7, 1H), 5.09 – 4.93 (m, 2H), 3.37 (d, *J*=6.6, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 192.12, 147.62, 136.17, 130.13, 129.41, 117.05, 40.44.

7g 

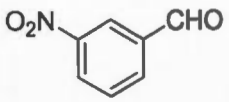
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36 (d, *J*=7.9, 2H), 7.17 (d, *J*=7.9, 2H), 3.74 – 3.58 (m, 4H), 3.16 – 2.93 (m, 2H), 2.78 – 2.67 (m, 2H), 1.99 – 1.87 (m, 2H), 1.09 (d, *J*=6.6, 12H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 139.67, 129.03, 128.00, 127.88, 61.95, 48.54, 47.63, 34.24, 31.71, 20.71.

8g 

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.96 (s, 1H), 7.80 (d, *J*=8.0, 2H), 7.36 (d, *J*=7.9, 2H), 3.68 (t, *J*=6.3, 2H), 2.83 – 2.76 (m, 2H), 1.98 – 1.86 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 192.08, 149.76, 134.64, 130.04, 129.17, 77.50, 77.07, 76.65, 61.92, 33.77, 32.34.

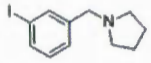
8h 

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.85 (s, 1H), 7.46 (dd, *J*=8.2, 1.9, 1H), 7.41 (d, *J*=1.8, 1H), 6.99 (d, *J*=8.2, 1H), 3.97 (s, 3H), 3.94 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 190.95, 154.53, 149.66, 130.18, 126.92, 110.44, 108.97, 56.22, 56.04.

10 

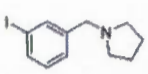
^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.13 (s, 1H), 8.73 (s, 1H), 8.50 (d, *J*=8.2, 1H), 8.24 (d, *J*=7.6, 1H), 7.77 (t, *J*=7.9, 1H).

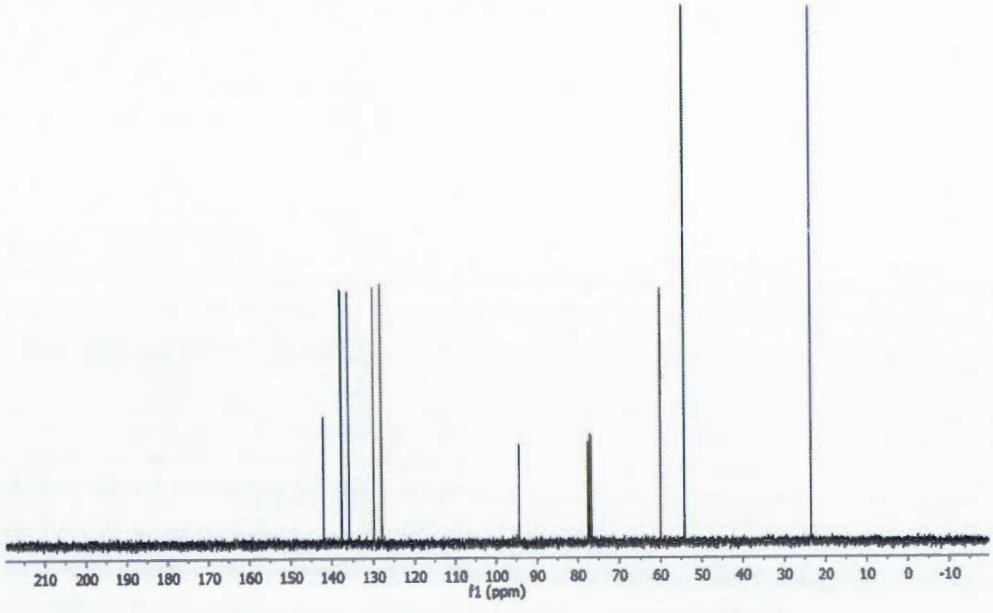
1a



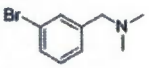
CDCl3, 300 MHz
1.0
1.0
1.0
1.0
2.0
4.2
4.2
11.5
10.5
9.5
8.5
7.5
7.0
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
f1 (ppm)

5a



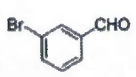

CDCl3, 75 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

1b


Br
N

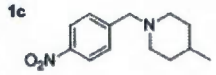
CDCl3, 300 MHz
1.0
1.0
1.9
2.1
6.0
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

5b

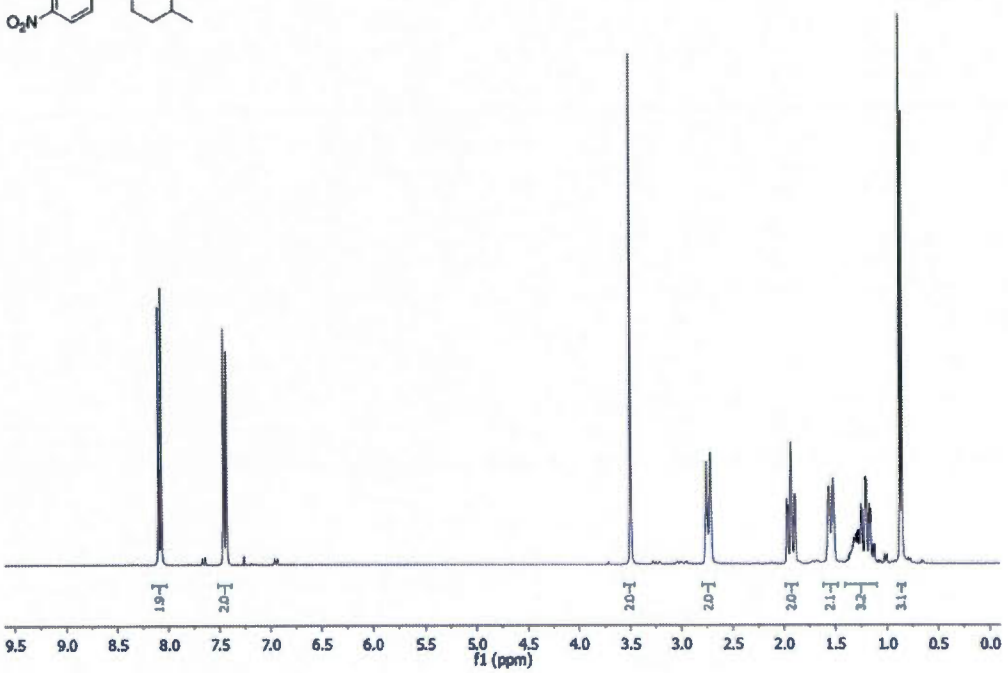

Br
CHO

CDCl3, 300 MHz
1.0
0.9
1.0
1.0
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

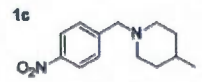
1c



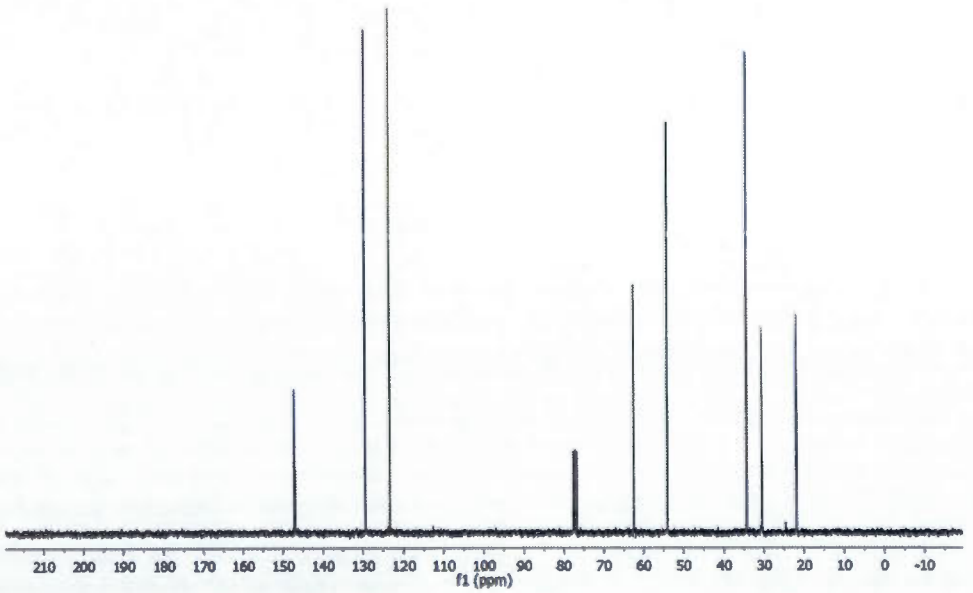
$CDCl_3$, 300 MHz



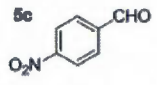
1c



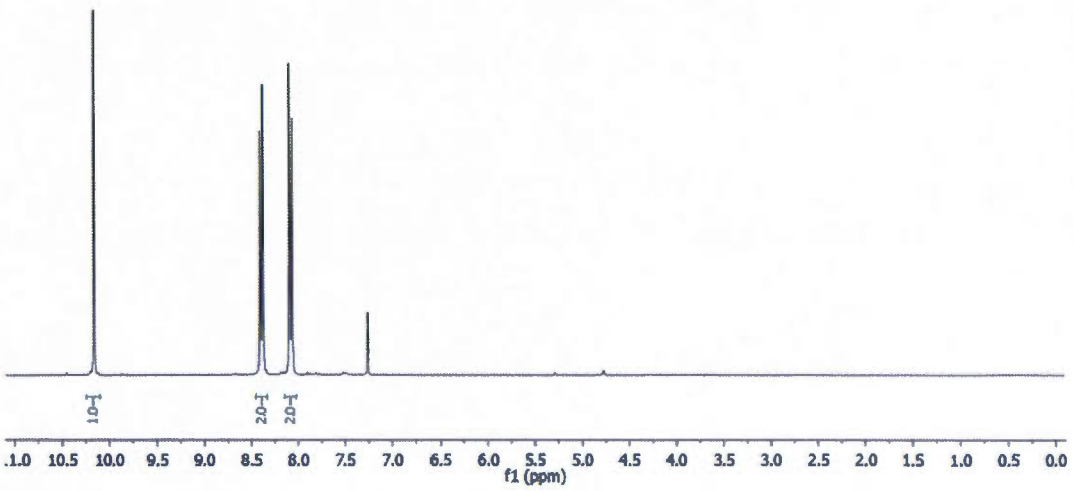
$CDCl_3$, 75 MHz



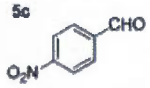
5c



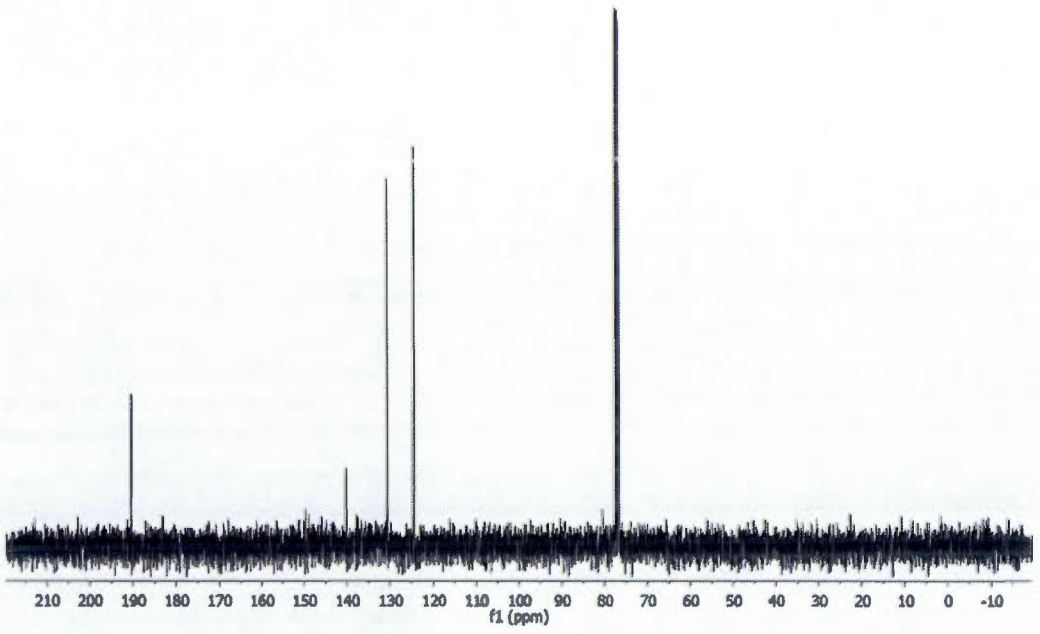
$CDCl_3$, 300 MHz

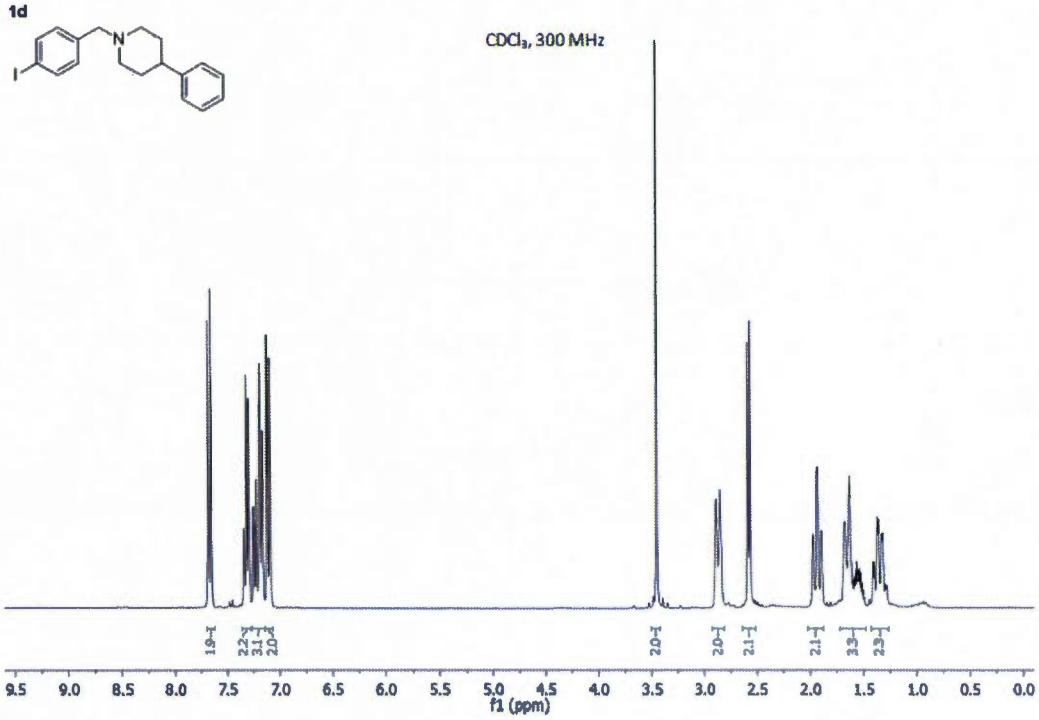


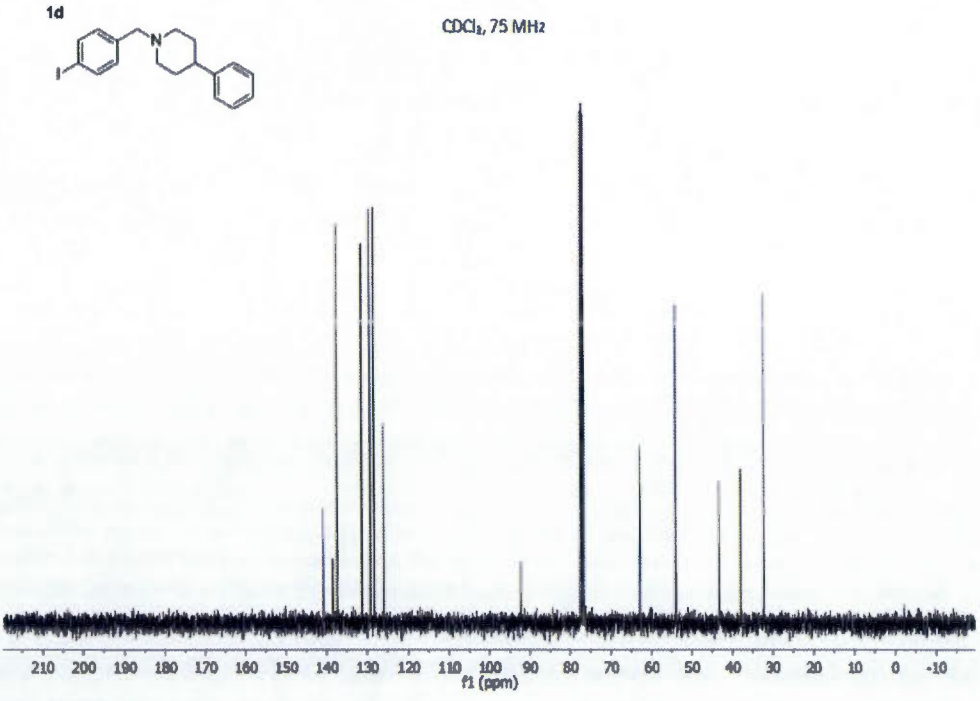
5c

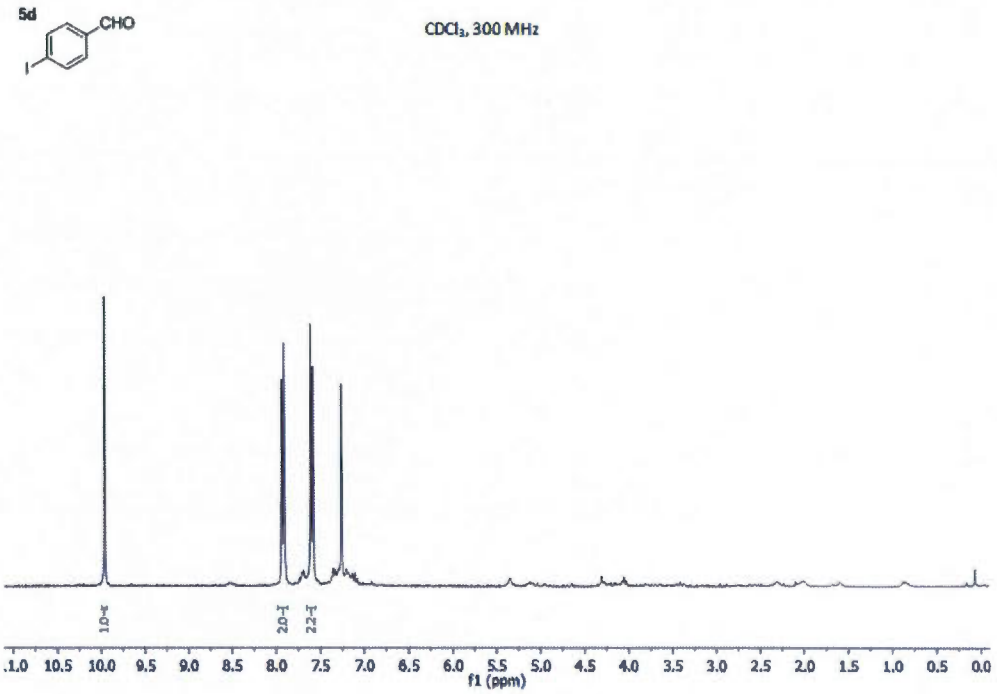


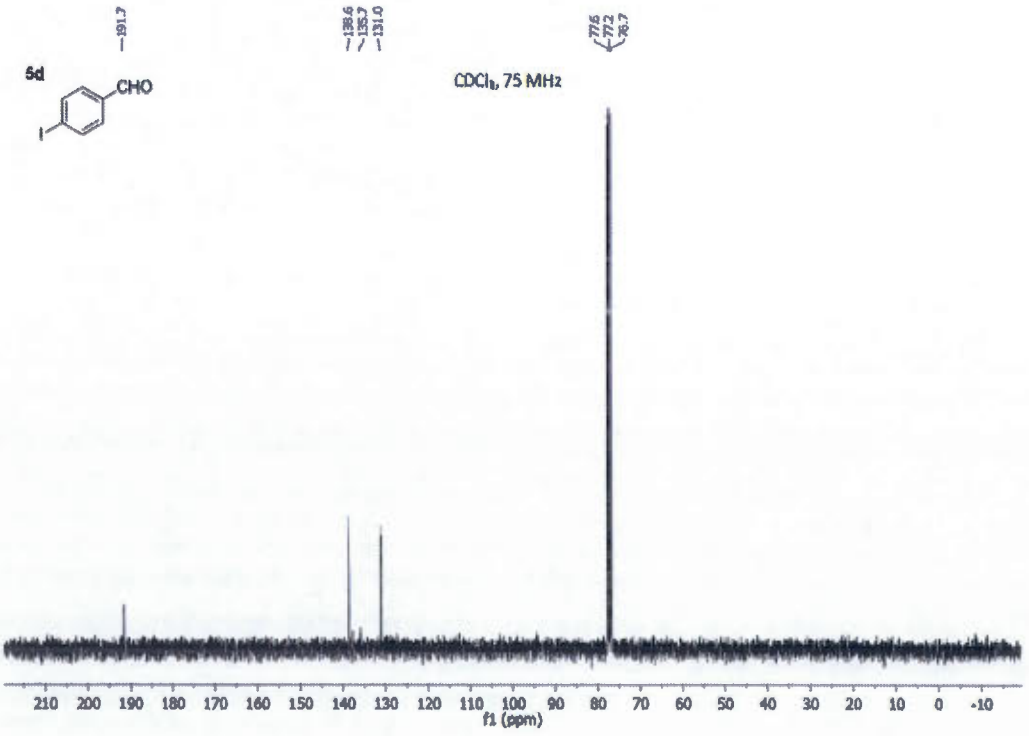
$CDCl_3$, 75 MHz



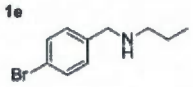

1d
CDCl3, 300 MHz
1.9
2.2
3.1
2.0
2.0
2.0
2.1
2.1
3.3
2.3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


1d
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

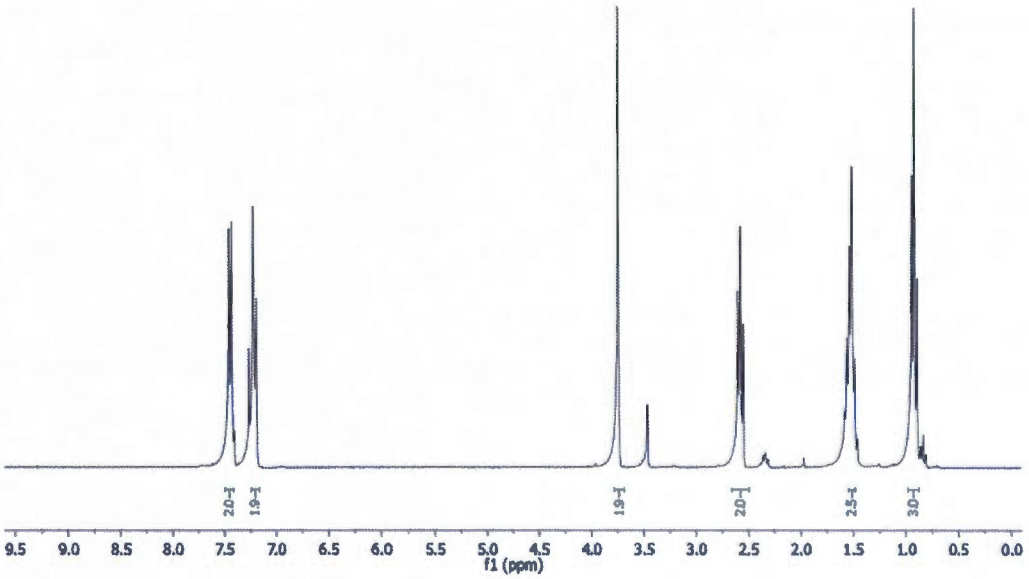

5d
CHO
I
CDCl3, 300 MHz
1.0-I
2.0-I
2.2-I
f1 (ppm)


191.7
138.6
135.7
131.0
77.6
77.2
76.7
5d
CHO
I
CDCl3, 75 MHz
f1 (ppm)

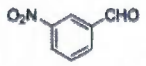
1e



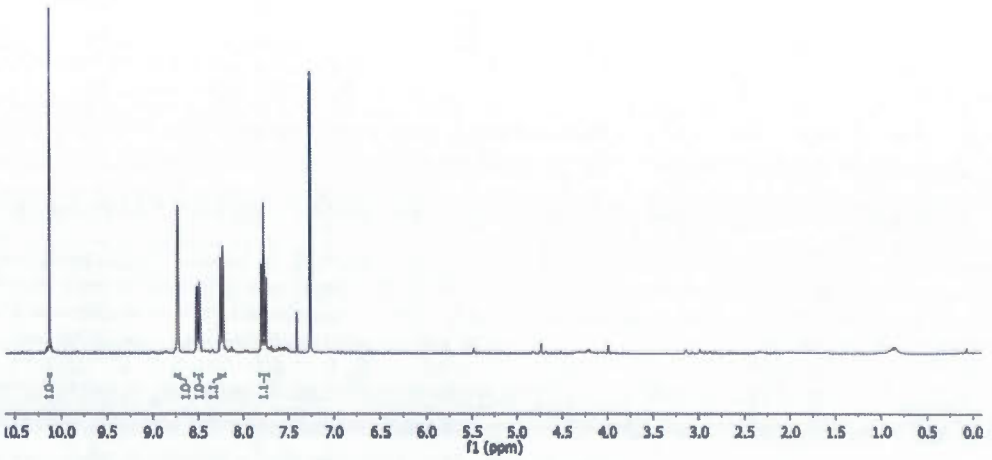
$CDCl_3$, 300 MHz



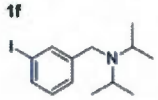
10



$CDCl_3$, 300 MHz

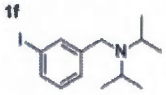


1f

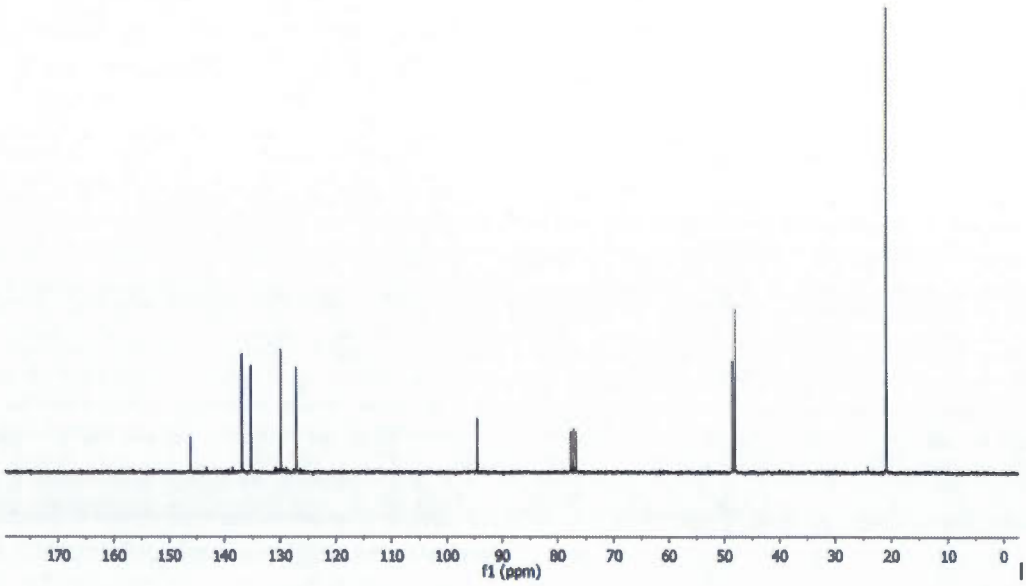


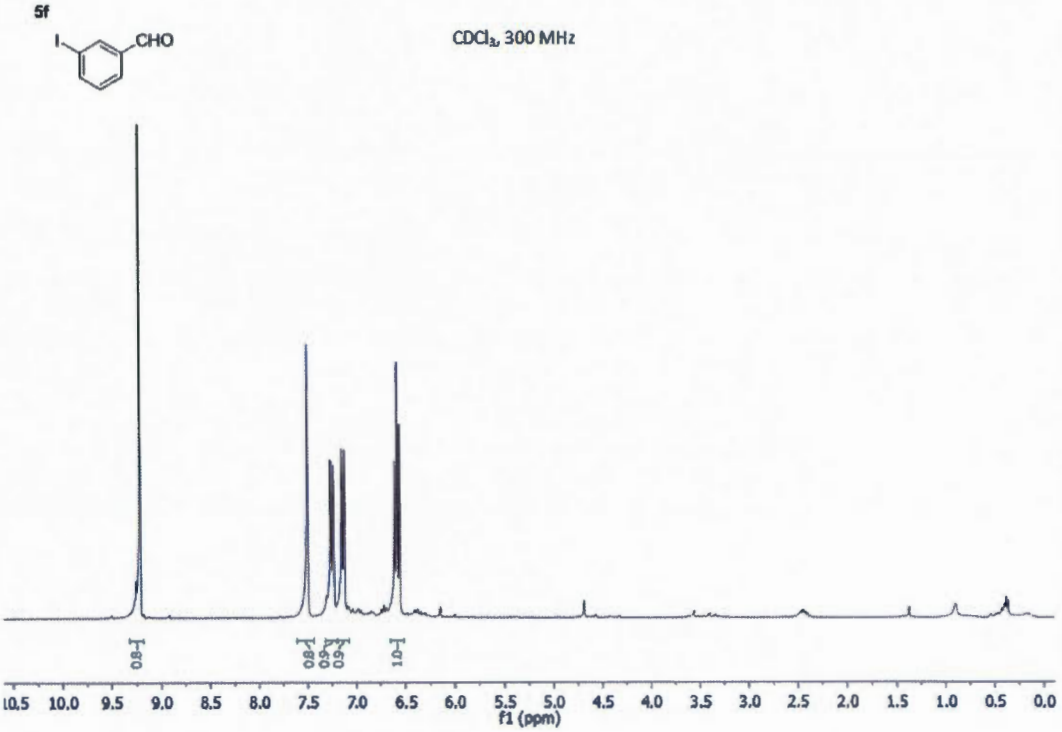
$CDCl_3$, 300 MHz

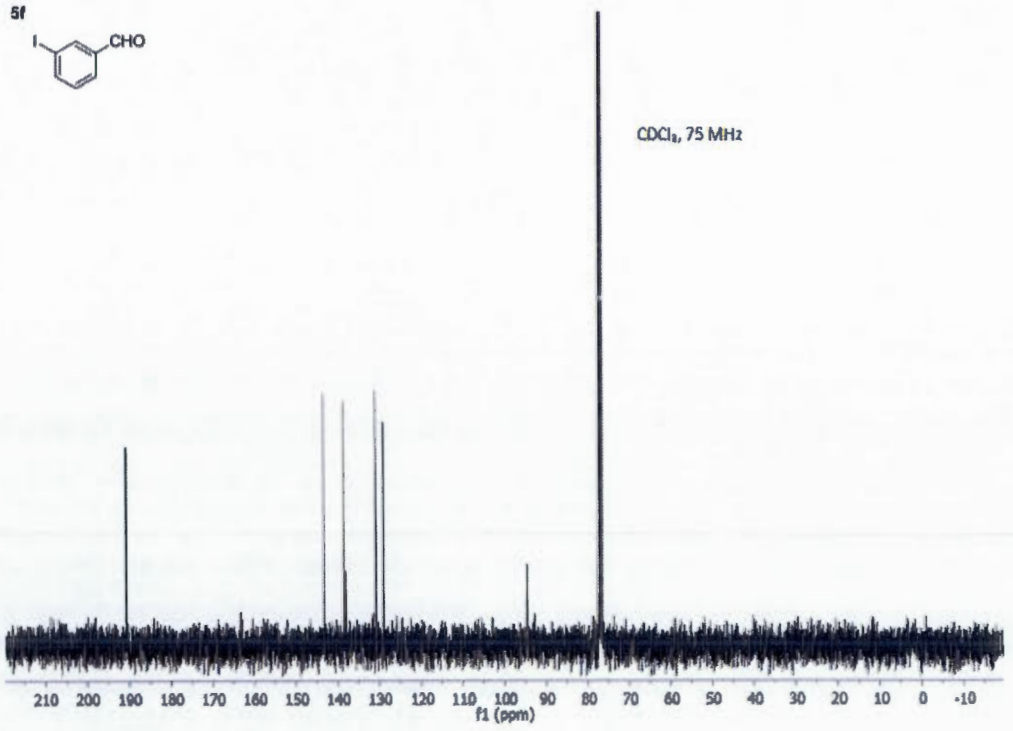
1f

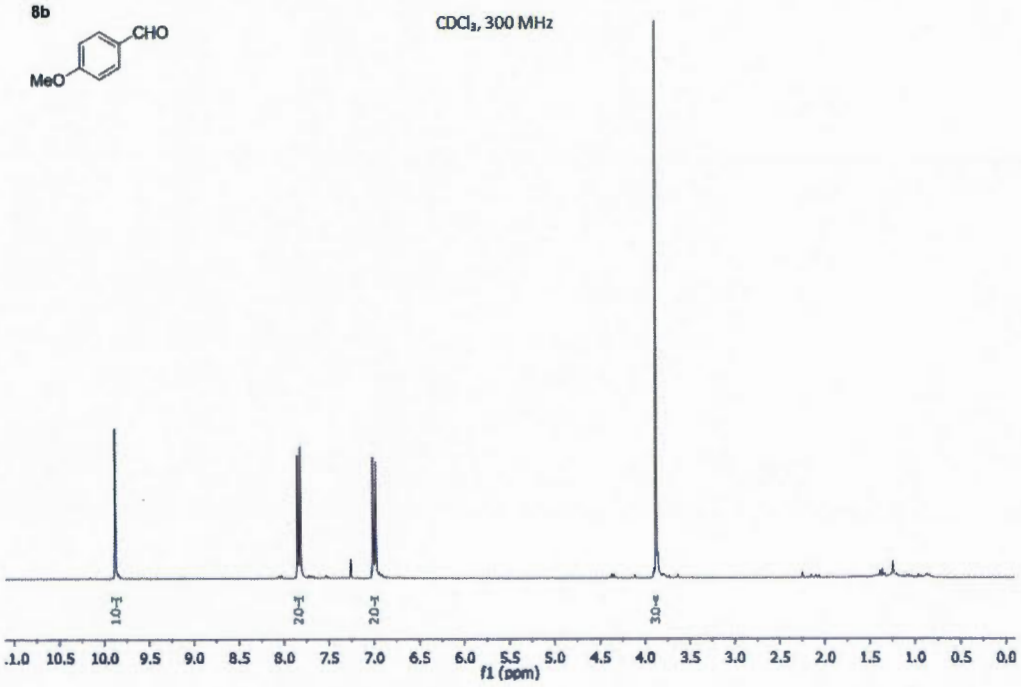


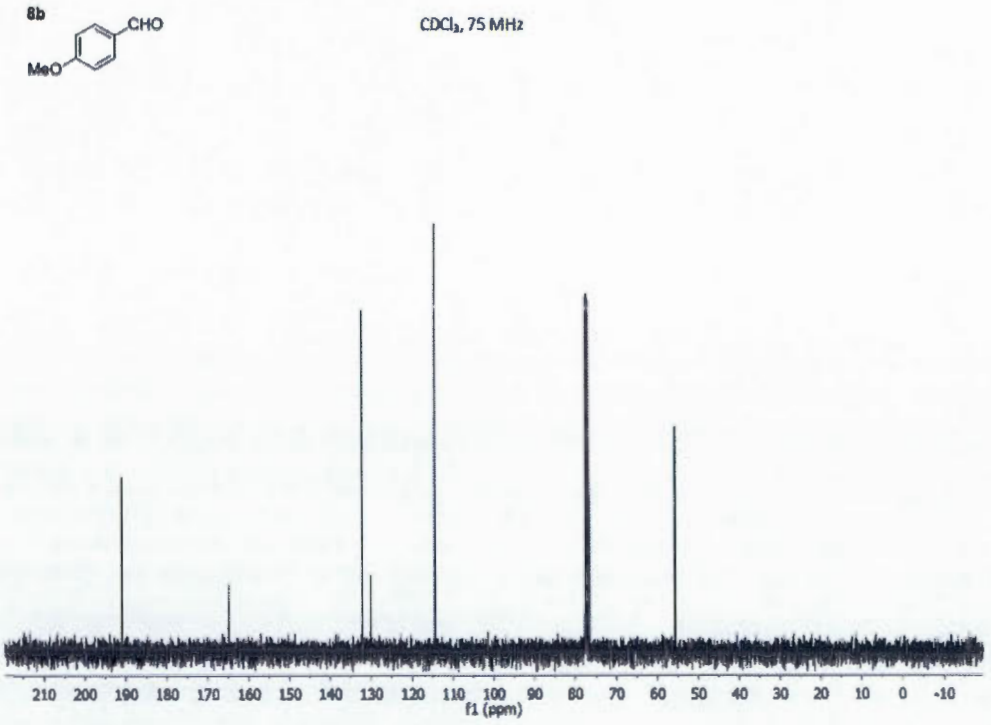
$CDCl_3$, 75 MHz

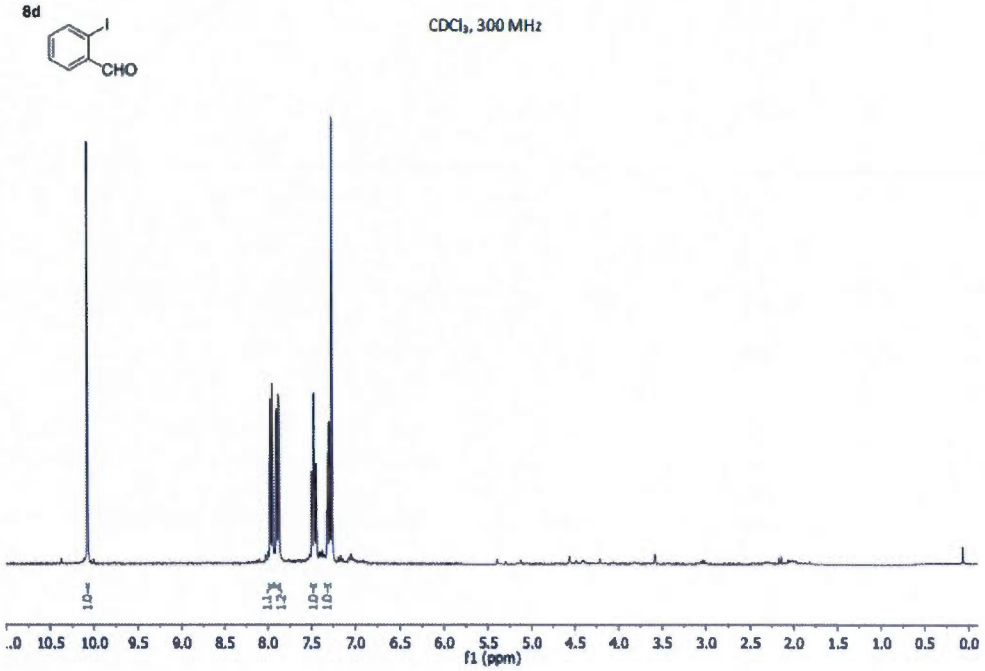


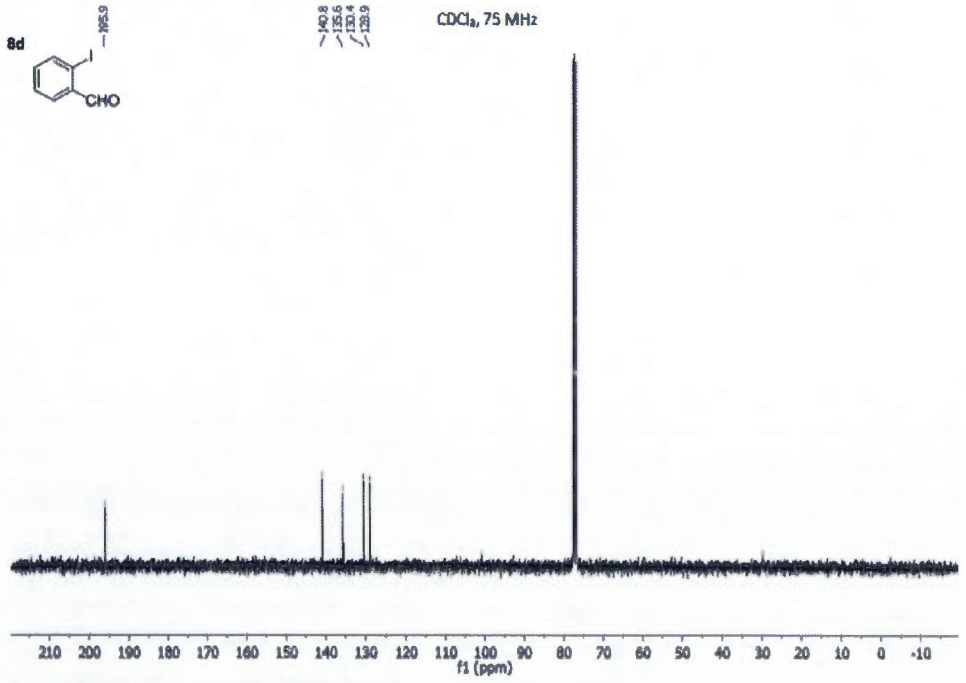

5f
I
CHO
CDCl3, 300 MHz
0.8
0.8
0.9
0.9
1.0
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


5f
I
CHO
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

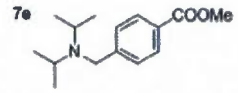

8b
CHO
MeO
CDCl3, 300 MHz
10-I
20-I
20-I
30-I
.1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


8b
CHO
MeO
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

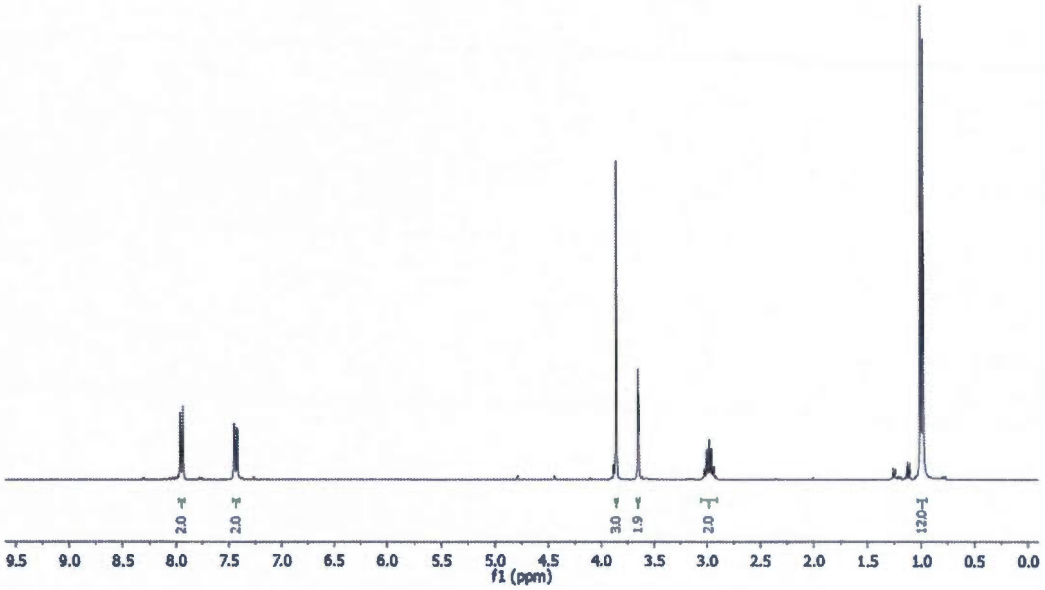

8d
I
CHO
CDCl3, 300 MHz
1.0
1.1
1.2
1.0
1.0
f1 (ppm)


8d
I
CHO
95.9
140.8
135.6
133.4
128.9
CDCl3, 75 MHz
f1 (ppm)

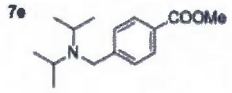
7e



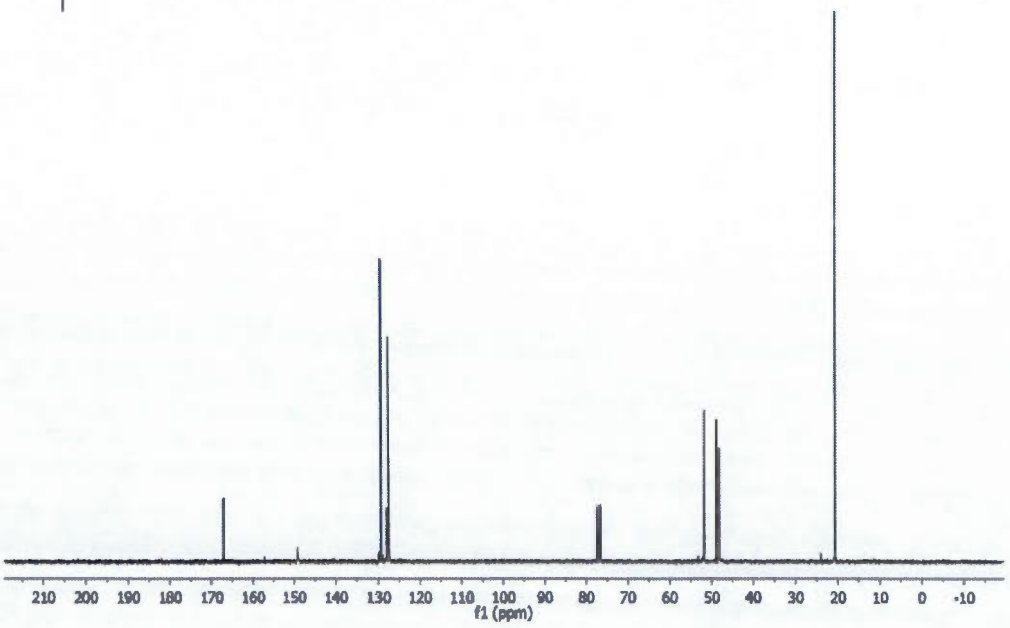
$CDCl_3$, 300 MHz

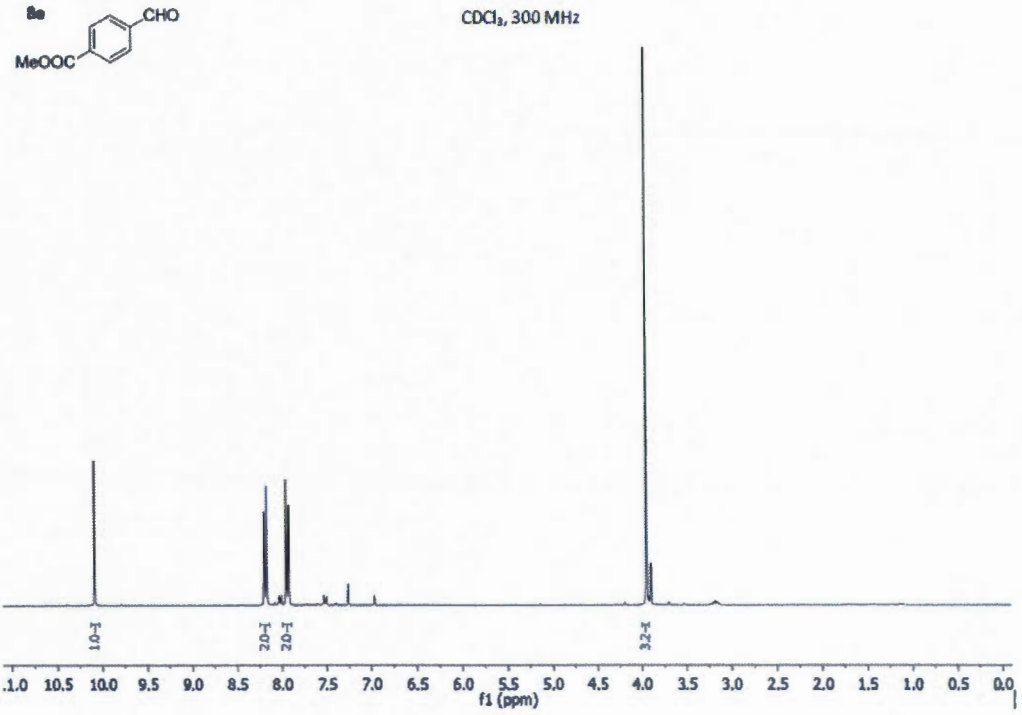


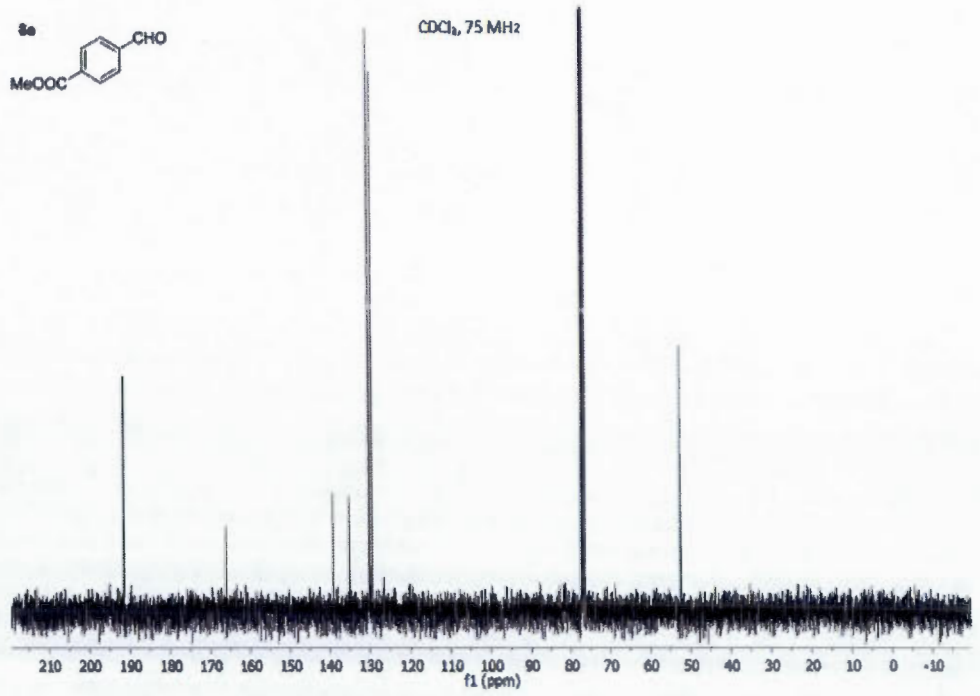
7e



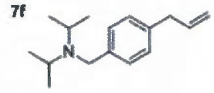
$CDCl_3$, 75 MHz



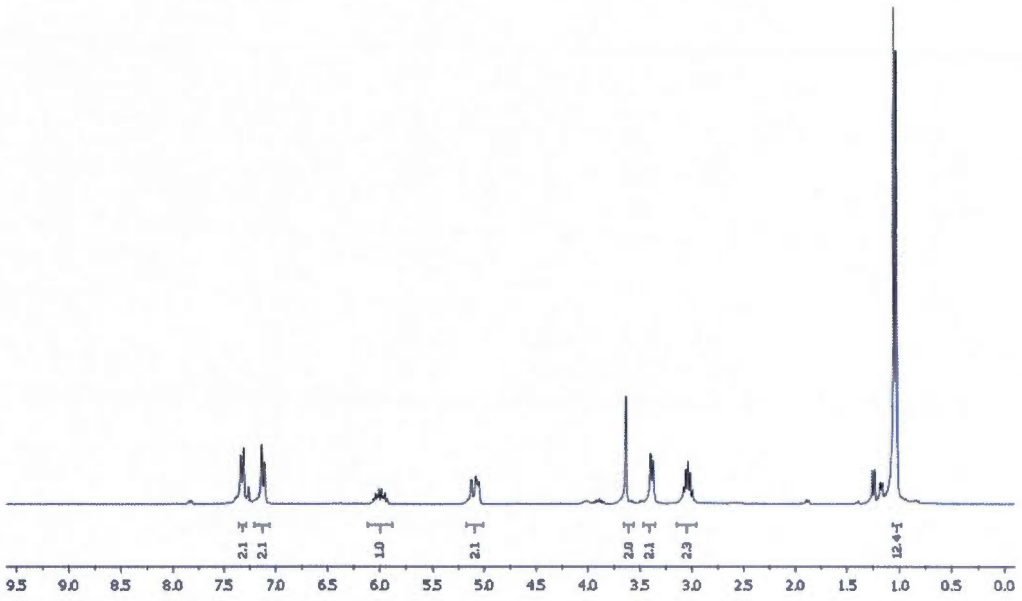

8e
CHO
MeOOC
CDCl3, 300 MHz
1.0
2.0
2.0
3.2
f1 (ppm)


8e
CHO
MeOOC
CDCl3, 75 MHz
f1 (ppm)

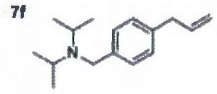
7f



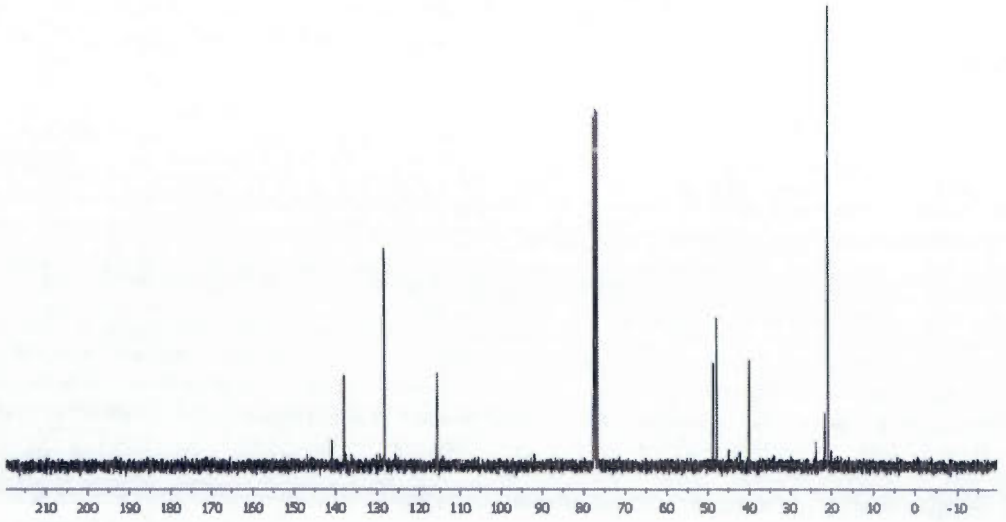
$CDCl_3$, 300 MHz

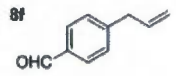


7f

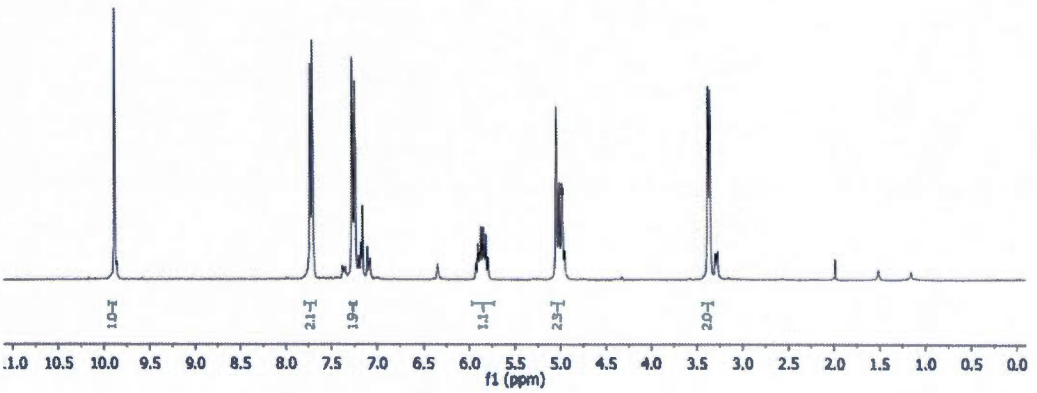


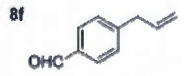
$CDCl_3$, 75 MHz



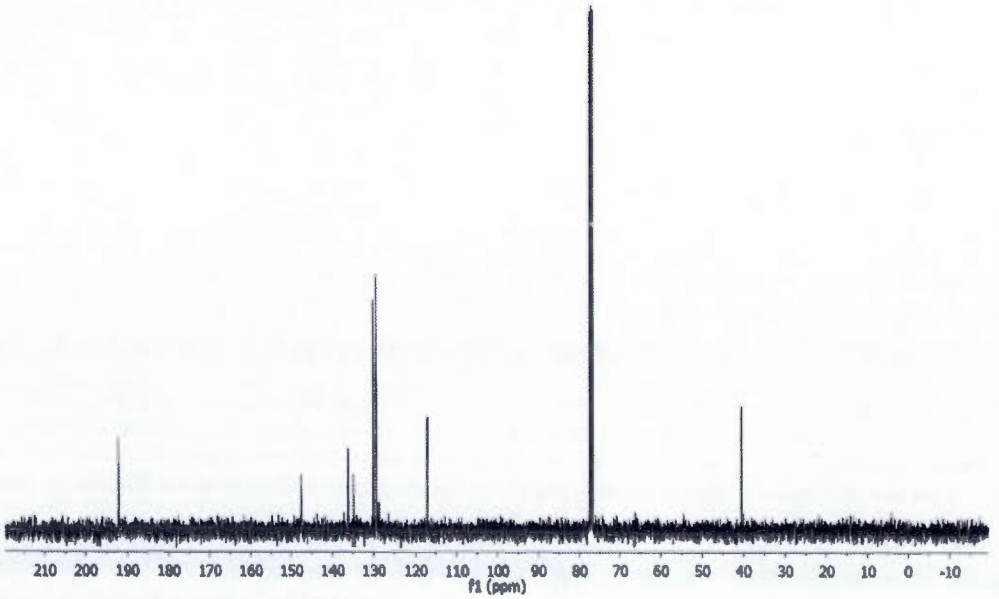


$CDCl_3$, 300 MHz

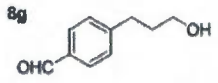




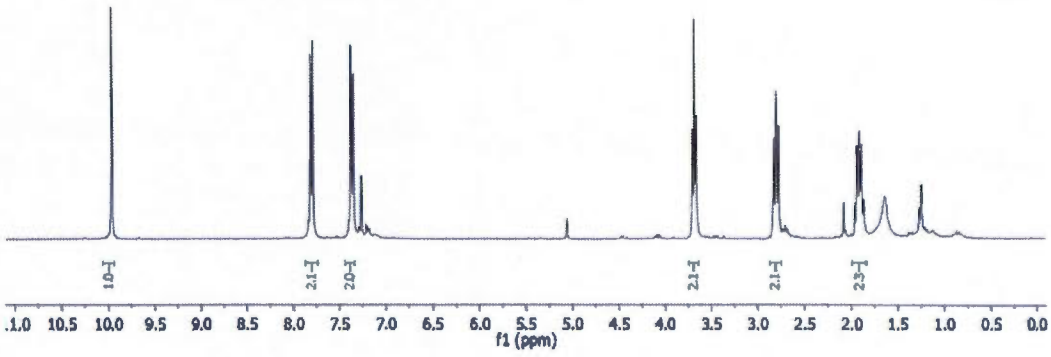
$CDCl_3$, 75 MHz



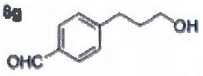
8g



$CDCl_3$, 300 MHz



8g



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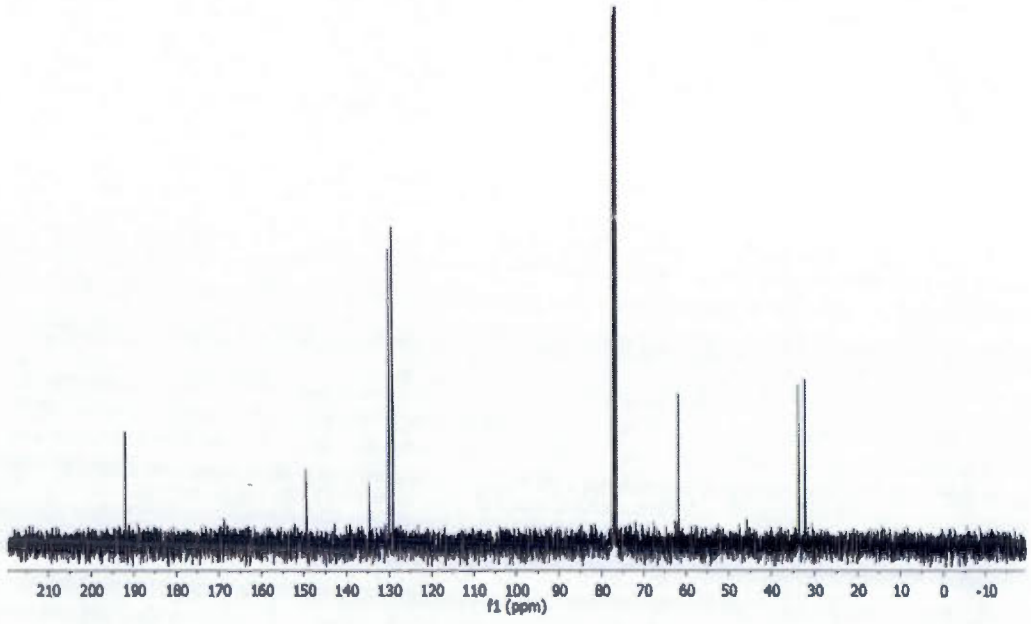
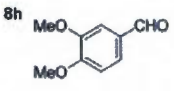
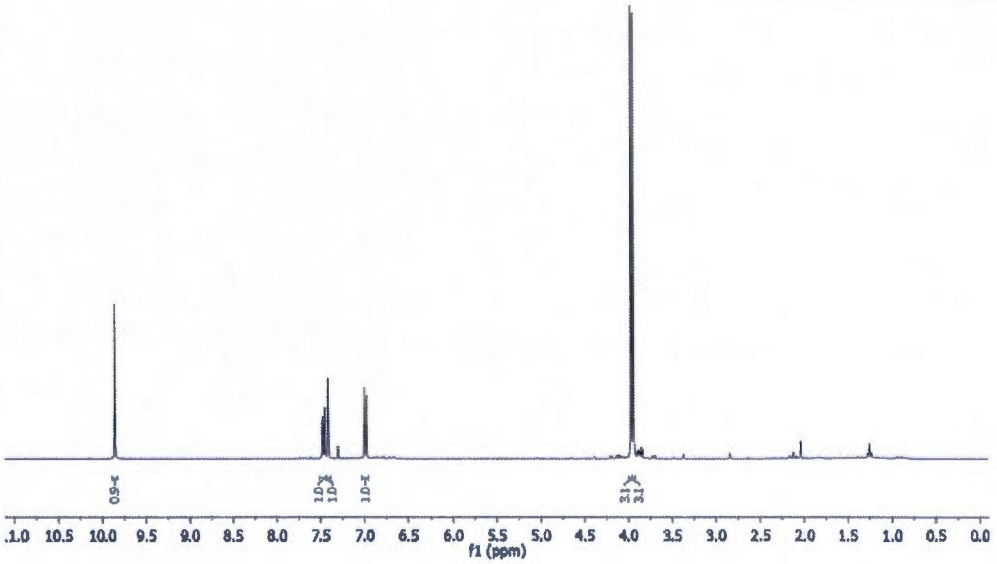


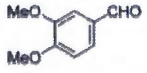
8h



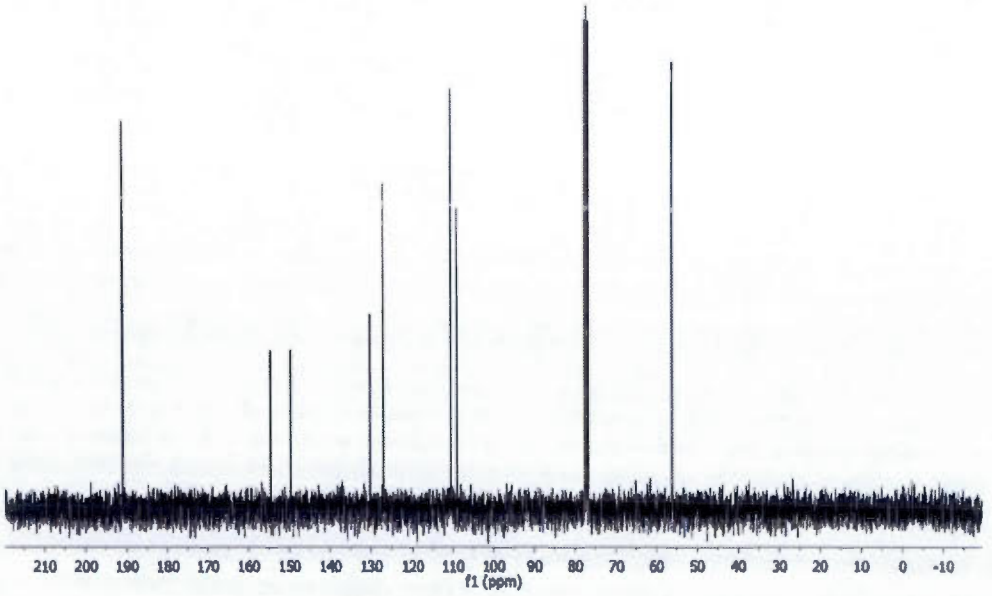
$CDCl_3$, 300 MHz



8h



$CDCl_3$, 75 MHz



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