UNIVERSITÉ DU QUÉBEC À MONTRÉAL

RÉACTIONS IPSO-OXYDATIVES, CYCLOADDITIONS DÉSAROMATISANTES ET SYNTHÈSE FORMELLE DE LA STRYCHNINE

THÈSE

PRÉSENTÉE

COMME ÉXIGENCE PARTIELLE

DU DOCTORAT EN CHIMIE

PAR

GUILLAUME JACQUEMOT

MARS 2014

UNIVERSITÉ DU QUÉBEC À MONTRÉAL
Service des bibliothèques

Avertissement

La diffusion de cette thèse se fait dans le respect des droits de son auteur, qui a signé le formulaire *Autorisation de reproduire et de diffuser un travail de recherche de cycles supérieurs* (SDU-522 – Rév.01-2006). Cette autorisation stipule que «conformément à l'article 11 du Règlement no 8 des études de cycles supérieurs, [l'auteur] concède à l'Université du Québec à Montréal une licence non exclusive d'utilisation et de publication de la totalité ou d'une partie importante de [son] travail de recherche pour des fins pédagogiques et non commerciales. Plus précisément, [l'auteur] autorise l'Université du Québec à Montréal à reproduire, diffuser, prêter, distribuer ou vendre des copies de [son] travail de recherche à des fins non commerciales sur quelque support que ce soit, y compris l'Internet. Cette licence et cette autorisation n'entraînent pas une renonciation de [la] part [de l'auteur] à [ses] droits moraux ni à [ses] droits de propriété intellectuelle. Sauf entente contraire, [l'auteur] conserve la liberté de diffuser et de commercialiser ou non ce travail dont [il] possède un exemplaire.»

REMERCIEMENTS

Je souhaiterais tout d'abord remercier chaleureusement le Pr. Sylvain Canesi de m'avoir donné l'opportunité de faire mon doctorat dans son laboratoire. Ces trois années ont été très enrichissantes et il a toujours été présent lorsque j'en avais besoin. Sa créativité sans limites, ses conseils avisés et son expérience ont été essentiels à la réussite de mon doctorat.

Je voudrais également remercier le Pr. Livain Breau, directeur du département, ainsi que le Pr. Huu Van Tra, directeur du progamme de doctorat, pour leur travail au sein du département durant ces trois années.

J'aimerais aussi remercier mes collègues du laboratoire sans qui ces années de recherches scientifiques n'auraient pas été aussi agréables. Marc-André, Gaëtan, Chantal, Sam, Marco, Chloé, Amandine, votre soutien ainsi que les moments agréables passés au laboratoire ou en dehors resteront des souvenirs inoubliables. Je remercie tout particulièrement Marco et Chloé pour leur fantastique travail afin de developper les réactions de cycloaddition et de couplage.

Je tiens également à exprimer toute ma gratitude à Alexandre Arnold pour son expertise RMN, ainsi que Leanne Ohlund et Vladimir Kriuchkov pour leurs analyses HRMS.

Je voudrais aussi remercier tous les amis et membres des laboratoires du département de chimie de l'UQAM pour leur sympathie.

Je tiens également à remercier particulièrement ma famille pour tout ce qu'elle a fait pour moi tout au long de mon parcours académique. Son soutien, aussi bien moral que financier m'a permis d'aller au bout de mes études et d'avancer dans la vie.

Enfin, je voudrais remercier de tout mon cœur Pauline pour son soutien, sa capacité à me supporter ainsi que tout ce qu'elle m'apporte au quotidien.

TABLE DES MATIÈRES

LISTE DES FIGURES vii

LISTE DES ABRÉVIATIONS, SIGLES ET ACRONYMES ix

RÉSUMÉ xiii

ABSTRACT xv

INTRODUCTION 1

0. 1. Iode hypervalent 1

0. 2. *Umpolung* et Oxydation à l'iode hypervalent 4

0. 3. Réactions ipso 8

0. 4. Cycloadditions 12

0. 5. Synthèse de Strychnine 16

CHAPITRE I

RÉACTIONS IPSO-OXYDATIVES ET SYNTHÈSE DE LA SCELÉTÉNONE 21

1. 1. Introduction 21

1. 2. Informations supplémentaires 21

1. 3. Conclusion 22

CHAPITRE II

RÉACTIONS DE CYCLOADDITIONS OXYDATIVES ET DE COUPLAGES SUR DES DÉRIVÉS AROMATIQUES NON-ACTIVÉS 23

2. 1. Introduction 23

2. 2. Informations supplémentaires 24

2. 3. Conclusion 24

CHAPITRE III

SYNTHÈSE FORMELLE DE LA STRYCHNINE 25

3. 1. Introduction 25

3. 2. Informations supplémentaires 25

3. 3. Perspectives et travaux futurs 26

3. 4. Conclusion 27

CONCLUSION 29

ANNEXE A : 31

"OXYDATIVE *IPSO*-REARRANGEMENT PERFORMED BY A HYPERVALENT IODINE REAGENT AND ITS APPLICATION" ARTICLE 31

ANNEXE B : 39

"OXYDATIVE *IPSO*-REARRANGEMENT PERFORMED BY A HYPERVALENT IODINE REAGENT AND ITS APPLICATION" SUPPORTING INFORMATION 39

ANNEXE C : 85

"OXIDATIVE CYCLOADDITION AND CROSS-COUPLING PROCESSES ON UNACTIVATED BENZENE DERIVATIVES" ARTICLE 85

ANNEXE D : 93

"OXIDATIVE CYCLOADDITION AND CROSS-COUPLING PROCESSES ON UNACTIVATED BENZENE DERIVATIVES" SUPPORTING INFORMATION 93

ANNEXE E : 215

"A CONCISE FORMAL SYNTHESIS OF STRYCHNINE" ARTICLE 215

ANNEXE F : 219

"A CONCISE FORMAL SYNTHESIS OF STRYCHNINE" SUPPORTING INFORMATION 219

RÉFÉRENCES 243

LISTE DES FIGURES

Figure		Page
0.1	Réactifs à base d'iode hypervalent	1
0.2	Structures des réactifs à l'iode hypervalent	2
0.3	Réactions de fonctionnalisation à l'iode hypervalent	2
0.4	Mécanismes possibles d'oxydation de phénols	3
0.5	Oxydation de phénols par IBX	4
0.6	Désaromatisations énantionsélectives catalytiques en iode hypervalent	4
0.7	Réactions d'*Umpolung* Seebach et Corey	4
0.8	Réaction de condensation benzoïne	5
0.9	Réaction de Stetter	5
0.10	Addition asymétrique d'énals sur des nitro-alcènes catalysée par des carbènes N-hétérocycliques	5
0.11	Addition asymétrique d'homoénolates sur des acyl phosphonates catalysée par des carbènes N-hétérocycliques	6
0.12	Mécanisme radicalaire d'oxydation à l'iode hypervalent	7
0.13	Addition nucléophile sur un phénol ou une sulfonamide	8
0.14	Réaction de substitution *Ipso*	8
0.15	Applicabilité des substitutions Ipso aux oxydations à l'iode hypervalent	9
0.16	Réactions de Friedel et Crafts oxydatives	9
0.17	Application à la synthèse de la Mésembrine	9
0.18	Transposition 1,2 de type Wagner-Meerwein	10
0.19	Transposition 1,3 et application à la synthèse de l'Acétylaspidoalbidine	10
0.20	Mécanisme des réactions *ipso*-oxydatives	11
0.21	Application à la synthèse de la Sceléténone	12
0.22	Réaction de cycloaddition 1,3 dipôlaire	12
0.23	Orbitales moléculaires et intérations HO/BV	12
0.24	Exemples de Dipôles 1,3	13
0.25	Cycloaddition [2+3] de phénol et de furane en présence d'iode hypervalent	13
0.26	Application aux synthèses du (±)-panacène et du (±)-desbromopanacène	13

0.27	Cycloaddition [2+3] asymétrique et synthèse de l'Aflatoxin B2	14
0.28	Réactions de couplage de N-aryl méthanesulfonamides et de thiophènes	14
0.29	Réactions de Cycloadditions et de Couplages	15
0.30	Mécanisme des cycloadditions désaromatisantes	15
0.31	Alcaloïdes du genre *Strychnos*	16
0.32	Biosynthèsede la Strychnine	17
0.33	Rétrosynthèse de Woodward	18
0.34	Rétrosynthèse de Rawal	19
0.35	Schéma rétrosynthétique	20
3.1	Réaction de désymétrisation de diénone	26

LISTE DES ABRÉVIATIONS, SIGLES ET ACRONYMES

Å	Angström
Ac	Acétyle
AcOH	Acide acétique
AcOEt	Acétate d'éthyle
All	Allyle
aq.	Aqueux
Ar	Aryle
Bn	Benzyle
BBr_3	Tribromure de bore
Br	Brome
BuLi	Butyl lithium
BV	Basse vacante
CCM	Chromatographie sur couche mince
$CHCl_3$	Chloroforme
Cl	Chlore
DCM	Dichlorométhane
DEAD	Diéthylazodicarboxylate
DIB	(Diacétoxy)iodobenzène
DIBAL-H	Hydrure de Diisobutylaluminium
DMAP	Diméthylaminopyridine
DMF	Diméthylformamide
DMP	Dess-Martin périodinane
E	Électrophile
E1	Élimination E1
Et	Éthyle
Et_3N	Triéthylamine
EtOH	Éthanol
EtOAc	Acétate d'éthyle

Et_2O	Diéthyl éther
Glc	Glucose
H	Hydrogène
H_2	Di-Hydrogène
HFIP	Héxafluoroisopropanol
HO	Haute occupée
HRMS	Sprectroscopie de Masse Haute Résolution
IBX	acide 2-iodoxybenzoïque
K_2CO_3	Carbonate de potassium
KHMDS	Héxaméthyldisilazane de potassium
$LiAlH_4$	Hydrure de lithium alumium
Me	Méthyle
MeOH	Méthanol
NaH	Hydrure de sodium
$NaBH_4$	Borohydrure de sodium
NaCN	Cyanure de sodium
Na_2CO_3	Carbonate de sodium
$NaHCO_3$	Hydrogénocarbonate de sodium
Na_2SO_4	Sulfate de sodium
$Na_2S_2O_3$	Thiosulfate de sodium
NH_2Me	Méthylamine
NH_4Cl	Chlorure d'ammonium
NMO	Oxyde de N-méthylmorpholine
NsCl	Chlorure de nosyle
Nu	Nucléophile
o	*Ortho*
[O]	Oxydation
O_3	Ozone
OsO_4	Tetroxyde d'osmium
p	*Para*
Pd	Palladium

Pd/C	Palladium sur charbon
Ph	Phényle
PhI^{2+}	Iode hypervalent
PhI(OAc)2	(Diacétoxy)iodobenzène
PIB	Bis(pivalate)iodobenzène
PIFA	bis(trifluoracétoxy)iodobenzène
PPh_3	Triphénylphosphine
i-Pr	*iso*-propyle
RMN	Résonance Magnétique Nucléaire
RT	''Room temperature'' (température pièce)
sat.	Saturée
SET	Transfert d'électron célibataire
S_N2	Substitution nucléophile d'ordre 2
$SOCl_2$	Chlorure de thionyle
sp^2	Hybridation sp^2
TBAF	Fluorure de tetrabutylammonium
t-Bu	*tert*-butyle
t-$BuSiCl_3$	*tert*-butyltrichlorosilane
TBDPS	*tert*-butyldiphénylsilyle
TBDPS-Cl	Chlorure de *tert*-butyldiphénylsilyle
TBS	*tert*-butyldiméthylsilyle
TBS-Cl	Chlorure de *tert*-butyldiméthylsilyle
TFA	Acide trifluoroacétique
TFE	Trifluoroéthanol
THF	Tétrahydrofurane
TLC	"Thin Layer Chromatography" (Chromatographie sur couche mince)
TMS	Triméthylsilyle
Tol	Tolyle
Tp	Température pièce
TPAP	Pérruthénate de tetrapropylammonium
Zn	Zinc

RÉSUMÉ

De nouvelles réactions d'oxydation de phénols et d'aryl-sulfonamides par des réactifs d'iode hypervalent ont été développées, ainsi que des applications en synthèse totale de produits naturels.

Les réactions *Ipso*-oxydatives à l'iode hypervalent permettent la génération rapide d'une diénone fonctionnalisée contenant un carbone quaternaire connecté à plusieurs centres sp^2. Ce procédé a lieu par le transfert d'un groupement aryle porté par un silicium présent sur la chaine latérale. Pour illustrer le potentiel de cette transformation, la synthèse totale de la Sceléténone, un alcaloïde de la famille des *Amaryllidaceae*, a été réalisée.

Des réactions de cycloadditions [2+3] désaromatisantes de phénols et d'aryl-sulfonamides sur des dérivés de benzènes et de naphtalènes non-activés ont été développées grâce à l'utilisation de réactifs à l'iode hypervalent. Cette réaction passe par une addition nucléophile intramoléculaire sur un intermédiaire de type Wheland généré durant l'oxydation. Des réactions de couplage bi-arylique ont également été mises au point de manière indirecte, par traitement en conditions acides des composés de cycloadditions, mais aussi de manière directe par l'utilisation d'aryl-sulfamides.

Enfin, la synthèse formelle de la Strychnine, un alcaloïde connu pour ses propriétés biologiques, a été réalisée à partir du 3-(4-hydroxyphényl)propionate de méthyle en 9 étapes. Cette synthèse implique une oxydation désaromatisante à l'iode hypervalent, un nouveau procédé tandem aza Michael-éther d'énol ainsi qu'une cyclisation par un couplage de Heck et une isomérisation réductrice.

ABSTRACT

New oxidation reactions of phenols and aryl-sulfonamides mediated by hypervalent iodine reagents have been developed as well as their applications in total synthesis of natural products.

The oxidative ipso-rearrangement mediated by a hypervalent iodine reagent enables rapid generation of a functionalized dienone system containing a quaternary carbon center connected to several sp^2 centers. The process occurs through the transfer of an aryl group from a silyl segment present on the lateral chain. As an illustration of the potential of this transformation, the total synthesis of Sceletenone, a small *Amaryllidaceae* alkaloid, is described.

New dearomatizing [2+3] cycloaddition reactions of phenols or aryl-sulfonamides and benzene or naphthalene derivatives have been developed through the use of a hypervalent iodine reagent. This process occurs via an intramolecular nucleophilic addition to the Wheland species generated during the oxidative activation. Subsequent treatment under acidic conditions readily transforms the tricyclic system into a biaryl via a formal cross-coupling process. A direct cross-coupling methodology has also been developed using aryl-sulfamides.

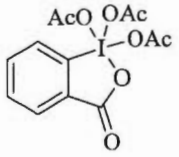
Finally, a concise formal synthesis of Strychnine has been achieved from available 3-(4-Hydroxyphenyl)propionic acid methyl ester in 9 steps. The synthesis involves an oxidative dearomatization mediated by a hypervalent iodine reagent, a novel aza Michael-ether-enol tandem process, a heck type cyclization and a reductive isomerization.

INTRODUCTION

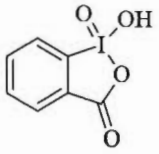
0. 1. Iode hypervalent

La synthèse totale de produits naturels bioactifs occupe une place importante en science, aussi bien pour les applications pharmaceutiques que pour le développement de nouvelles méthodologies qu'elle inspire. Dans un contexte d'économie des ressources et d'écologie, il est essentiel de développer de nouvelles synthèses plus rapides et plus efficaces tout en évitant les rejets toxiques. Du fait qu'ils permettent de remplacer l'utilisation de métaux lourds, chers et toxiques tels que le Thallium (III), le Mercure (II) ou encore le Plomb (IV), les réactifs à base d'iode hypervalent jouent un rôle important en synthèse[1-3].

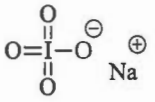
Généralement monovalent et de degré d'oxydation -1, l'iode présente des degrés d'oxydation supérieurs (III, V, et VII) connus sous le nom d'iodes hypervalents (Schéma 1).



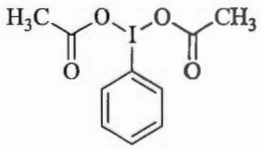
DMP **(V)**



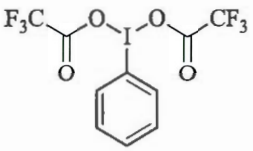
IBX **(V)**



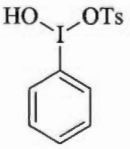
$NaIO_4$ **(VII)**



DIB **(III)**



PIFA **(III)**



Réactif de Koser **(III)**

Schéma 1: Réactifs à base d'iode hypervalent

Parmi les plus utilisés, les réactifs à base d'iode (V) permettent notamment des oxydations d'alcools en aldéhydes ou cétones en conditions douces. On retrouve parmi ces composés, le périodinane de Dess-Martin (DMP) et l'acide 2-iodoxybenzoïque (IBX). Le périodate de sodium, réactif à base d'iode (VII) permet quant à lui de réaliser des coupures oxydantes de diols vicinaux.

Enfin, les réactifs à base d'iode hypervalents (III) réagissent avec de nombreux composés dans des réactions d'oxydations et sont égalements utilisés dans des réactions de fonctionnalisation de carbonyle et de réarrangements. Parmi les plus connus, on peut citer le diacétoxyiodobenzène (DIB), le PIFA ou encore le réactif de Koser (Schéma 1).

Les composés à base d'iode (III) sont caractérisés par une structure bipyramide trigonale, où le groupement aryl et les deux paires d'électrons libres sont en positions équatoriales. Les deux ligands sont eux en positions apicales et partagent une liaison hypervalente avec l'iode. En revanche, ceux à base d'iode (V) possédent 4 ligands et 2 liens hypervalents orthogonaux (Schéma 2).

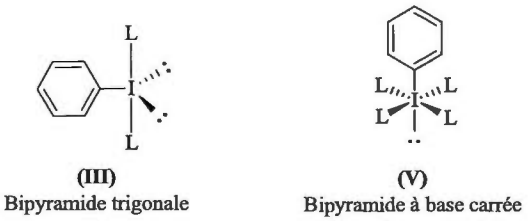


Schéma 2 : Structures des réactifs à l'iode hypervalent

Du fait de leur forte déficience en électrons, les réactifs à base d'iode hypervalent sont très réactifs et peuvent être impliqués dans des réactions d'échanges de ligands par l'attaque d'un nucléophile ainsi que dans des réactions de transfert d'électrons.

Ils permettent notamment de nombreuses fonctionnalisations, telles que les fonctionnalisations des cétones en position α, des réactions d'aziridination et d'amination, ou encore la création de liaisons C-C[4].

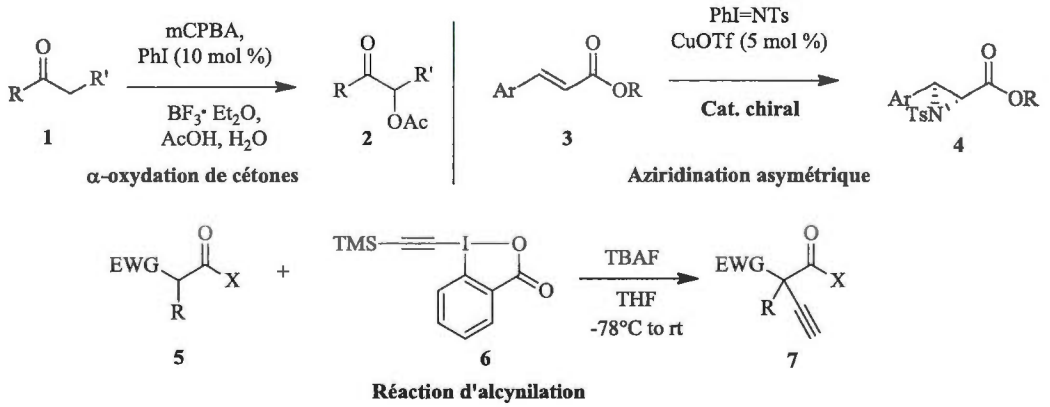


Schéma 3 : Réactions de fonctionnalisation à l'iode hypervalent

Les réactifs à base d'iode hypervalent réagissent également avec des phénols dans des réactions d'oxydations (Schéma 4). Divers mécanismes sont proposés pour ces désaromatisations : des mécanismes dissociatif et associatif, ainsi qu'un mécanisme par échange de ligands[5].

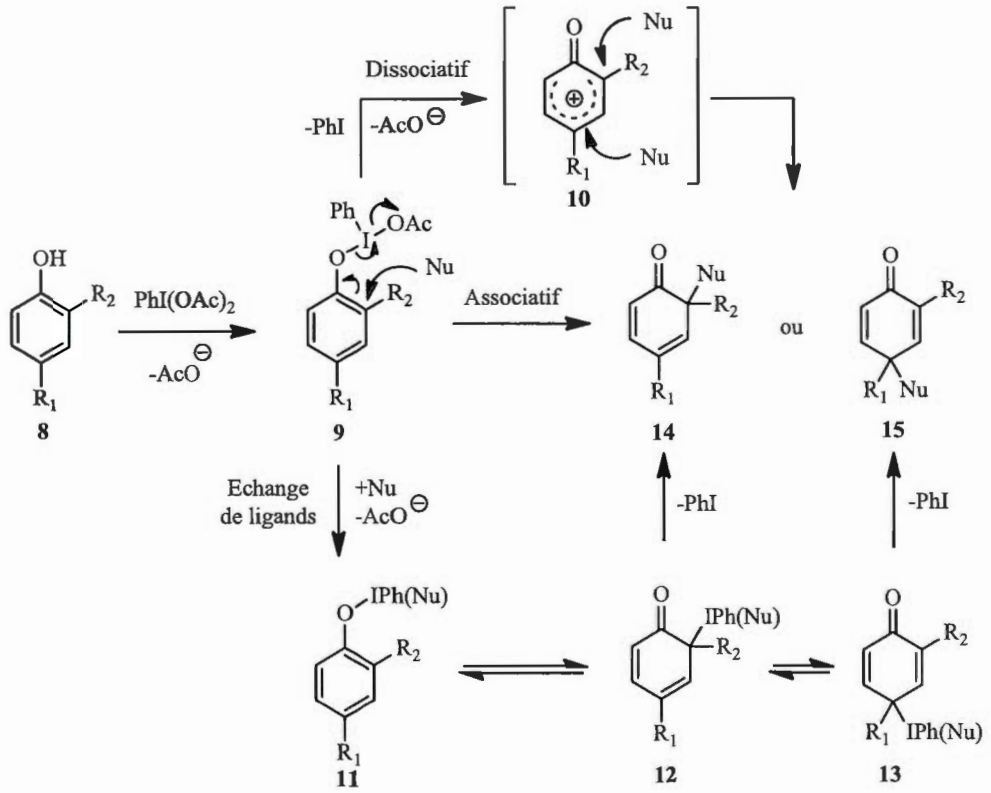


Schéma 4 : Mécanimes possibles d'oxydation de phénols

Des experiences de solvolyse ont demontré que le groupement $PhI(BF_4)_2$ est de très loin un meilleur groupement partant qu'un triflate[6]. Ce caractère « hypernucléofuge » est un argument de poids en faveur du mécanisme par transfert d'électrons, notamment en présence de solvants protiques. De plus, la formation de composés aromatiques radicalaires lors d'oxydation à l'iode hypervalent a été mise en évidence par le Pr. Kita par résonnance de spin électronique.[7]

L'IBX permet également l'oxydation de phénols riches en électrons afin de former des *o*-quinone de manière régiosélective, donnant ainsi accès à de nombreux catechols (Schéma 5)[8].

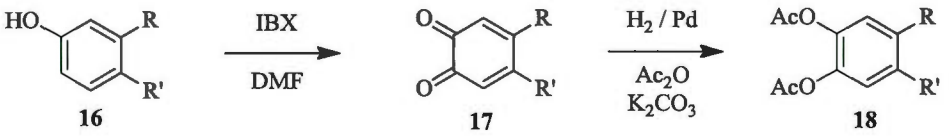


Schéma 5 : Oxydation de phénols par IBX

Ces différences de réactivités s'expliquent par les différences structurales entre les réactifs à l'iode hypervalent (III) et (V).

Enfin, notons que les réactifs a l'iode hypervalent peuvent aussi être utilisés en quantité catalytique, par l'utilisation d'un co-oxydant. C'est le cas notamment des désaromatisations énantiosélectives développées par Kita en utilisant du mCPBA comme co-oxydant (Schéma 6)[9].

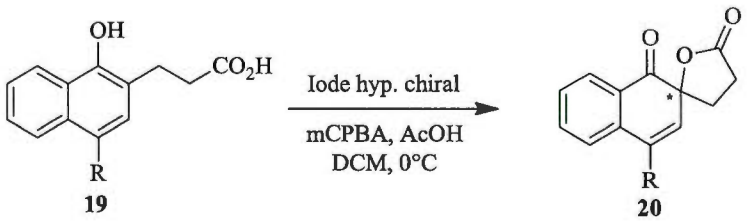
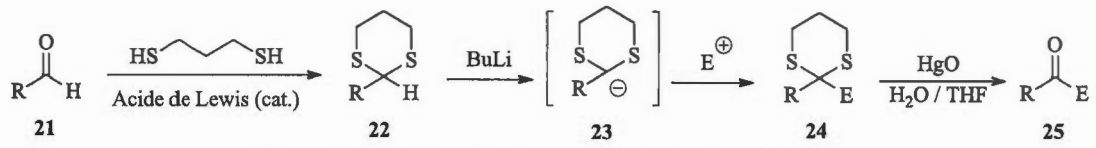


Schéma 6 : Désaromatisations énantiosélectives catalytiques en iode hypervalent

Ces réactions *Umpolung* de désaromatisations oxydantes de phénols sont un outil puissant permettant le développement de nombreuses stratégies en synthèse totale.

0. 2. *Umpolung* et Oxydation à l'iode hypervalent

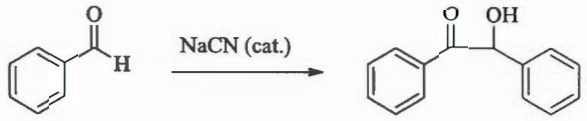
Introduit dans les années 70 par Seebach et Corey[10], le concept d'*Umpolung* consiste en une modification permettant d'inverser la polarité d'un groupe fonctionnel et ainsi modifier sa réactivité. Dans le cas de la méthode développée par Seebach et Corey sur des aldehydes, le carbonyle électrophile **21** est protégé sous forme de thiocétal **22** par traitment avec du 1,3-propanedithiol en milieu acide (Schéma 7). Le proton acide de la molécule peut maintenant être arraché par une base forte et l'anion acylure **23** ainsi formé peut réagir en tant que nucléophile sur de nombreux électrophiles.



21 22 23 24 25

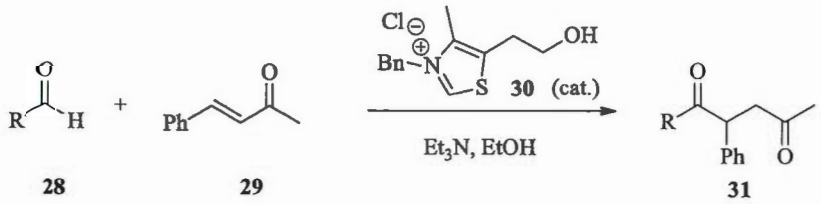
Schéma 7: Réaction d'*Umpolung* de Seebach et Corey

De nombreuses réactions utilisant ce principe ont été développées par la suite, parmi lesquelles se trouvent la condensation benzoïne (Schéma 8), ou encore la réaction de Stetter[11] (Schéma 9). Ce concept permet alors d'étendre la réactivité d'un groupe fonctionnel et donne de nouvelles alternatives, notamment en synthèse totale.



26 27

Schéma 8: Réaction de condensation benzoïne



28 29 31

Schéma 9: Réaction de Stetter

Plus récemment, des réactions d'*Umpolung* catalysées par des carbènes N-hétérocycliques ont également été mises au point, de même que leurs versions asymétriques. Rovis a notamment developpé des réactions d'additions 1,4 asymétriques d'énals sur des nitro-alcénes avec d'excellentes sélectivités (Schéma 10)[12].

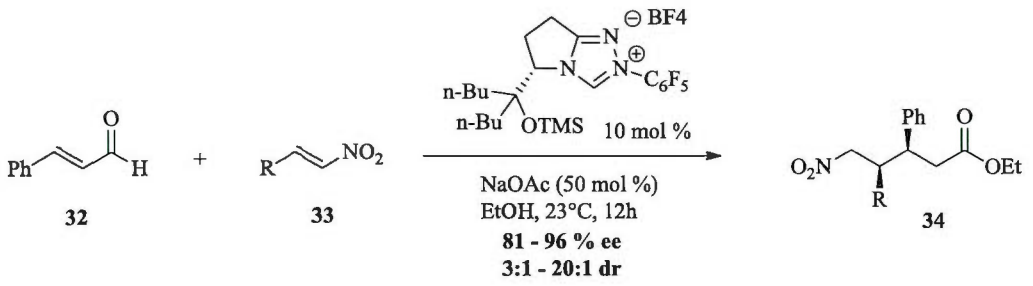


Schéma 10 : Addition asymétrique d'énals sur des nitro-alcènes catalysée par des carbènes N-hétérocycliques

Scheidt a quant à lui développé des réactions d'additions asymétriques d'homoénolates sur des acyl phosphonates via l'utilisation de carbènes N-hétérocycliques, aboutissant a la synthèse de lactone de manière stéréosélective (Schéma 11)[13].

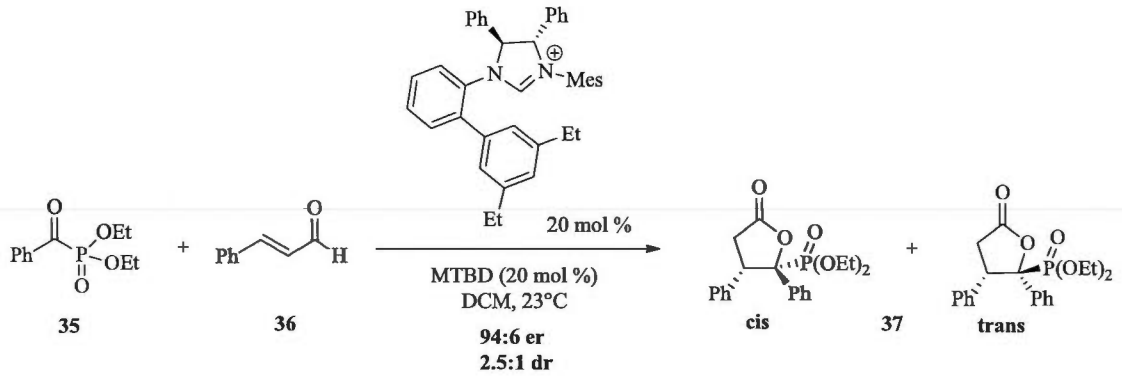


Schéma 11 : Addition asymétrique d'énals sur des nitro-alcènes catalysée par des carbènes N-hétérocycliques

Développé en série aliphatique, ce concept d'*Umpolung* peut également être appliqué en série aromatique[14], par l'intermédiaire de réactifs à base d'iode hypervalent[14-26], sur des aromatiques riches en électrons tels que les phénols[23-24] ou les aryl-sulfonamides[25]. Le mécanisme considéré ici est une oxydation par transfert d'électrons (Schéma 12). Le phénol **38** réagit avec le diacétoxyiodobenzène **39** afin de former le radical cation **40**, qui va être deprotonné par une molécule d'acétate relachée dans le milieu afin d'obtenir le radical **42**.

Celui-ci réagit ensuite avec le radical iodé **41** pour former l'iodobenzène **43** ainsi que l'ion phénoxonium **44** possédant trois formes de résonnance.

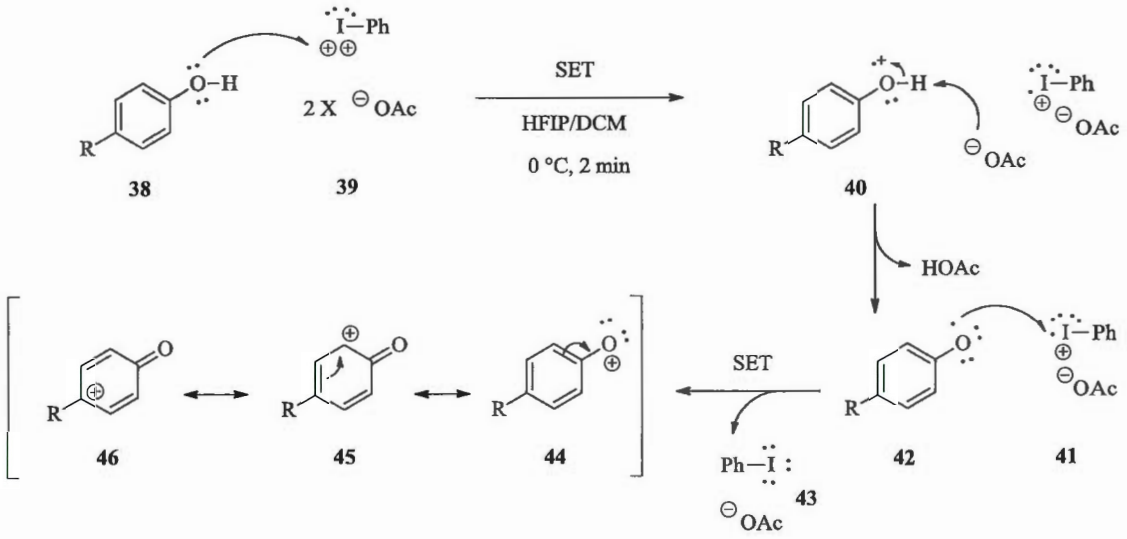


Schéma 12: Mécanisme radicalaire d'oxydation à l'iode hypervalent

En oxydant des phénols **47** (ou aryl-sulfonamides) habituellement nucléophiles, ces réactifs permettent la formation d'un ion phénoxonium **48** (ou phénoximinium). L'intérmédiaire électrophile formé peut alors réagir avec de nombreux nucléophiles en position *ortho* ou *para*, dépendamment du nucléophile utilisé. Dans le cas d'un nucléophile faiblement encombré, l'attaque se fait sous contrôle stéréoélectronique en position *para*, du fait de la stabilité de la forme de résonnance formée (carbocation tertiaire). Ces oxydations permettent l'obtention d'un squelette hautement fonctionnalisé, contenant un carbone tertiaire ou quaternaire (si l'attaque est réalisée par un nucléophile carboné) connecté à plusieurs centres sp^2 ainsi qu'une diénone **50** prochirale permettant de nombreuses fonctionnalisations subséquentes. En revanche, lors de l'utilisation d'un nucléophile encombré, l'attaque se fait sous contrôle stérique en position *ortho*. Le produit **49** obtenu est dans ce cas un aromatique substitué, du même type que ceux obtenus dans les réactions de Friedel et Crafts.

Pionnier dans ce domaine, le Pr. Kita a notamment démontré la faisabilité des réactions d'oxydations désaromatisantes utilisant des réactifs à base d'iode hypervalent, en réalisant des additions oxydantes de méthanol sur des phénols. Il a également démontré que

l'utilisation d'héxafluoroisopropanol (HFIP) permet la stabilisation de l'ion phénoxonium formé[15-16,24]. En effet, cet intermédiaire est instable et réagit avec les nucléophiles présents dans le milieu. Si le solvant utilisé est nucléophile (eau, methanol, ...), la réaction a lieu avec le solvant. L'héxafluoroisopropanol étant un solvant protique non nucléophile, il permet une stabilisation de l'ion phénoxonium tout en ne réalisant pas d'addition nucléophile. Il donne ainsi un temps de vie plus long à l'intermédiaire, lui permettant de réagir avec le nucléophile désiré.

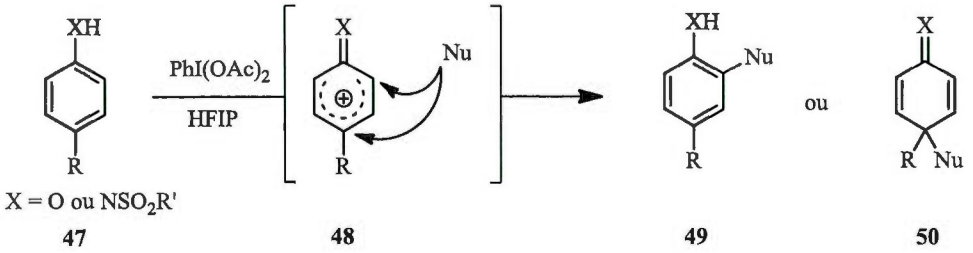


Schéma 13: Addition nucléophile sur un phénol ou un aryl-sulfonamide

0. 3. Réactions ipso

Venant du latin signifiant « lui-même », la position *Ipso* d'un composé aromatique **51** est celle où se trouve déjà le groupement fonctionnel[27-28]. On parle alors de « substitution *Ipso* » lorsque la substitution a lieu sur cette position, entrainant ainsi un changement de fonction sur la molécule aromatique **53** (Scéma 14).

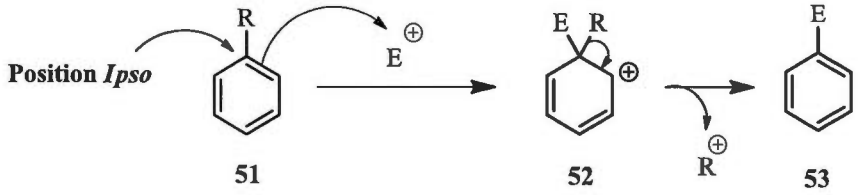


Schéma 14: Réaction de substitution *Ipso*

Appliquées dans le contexte des oxydations à l'iode hypervalent, ces réactions *Ipso* permettraient l'introduction de groupements aryls sur des phénols **54** en position *para*, l'ion phénoxonium **55** jouant le rôle d'électrophile lors de la substitution *Ipso* (Schéma 15).

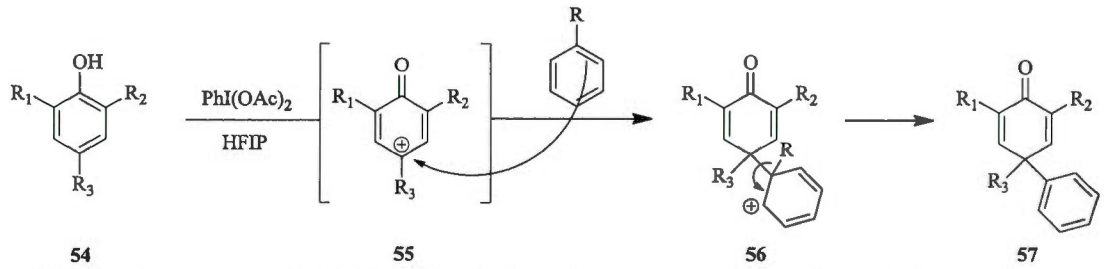


Schéma 15 : Applicabilité des substitutions Ipso aux oxydations à l'iode hypervalent

Antérieurement aux réactions *Ipso*-oxydatives, notre laboratoire avait développé des réactions de Friedel et Craft oxydatives à base d'iode hypervalent, sur des phénols polysubstitués **58**, permettant d'obtenir des motifs similaires avec introduction d'aryls et formation d'un carbone quaternaire (Schéma 16).[14e]

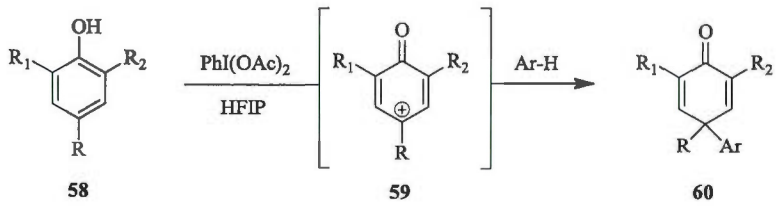


Schéma 16 : Réactions de Friedel et Crafts oxydatives

Tout comme les réactions *Ipso*-oxydatives, ces transformations intermoléculaires permettent un accès rapide à un squelette hautement fonctionnalisé, contenant une diénone ainsi qu'un cycle aromatique lié a un carbone quaternaire. Cette méthodologie a également été appliquée à la synthèse de la Mésembrine, un alcaloïde de la famille des *Amaryllidaceae* (Schéma 17).

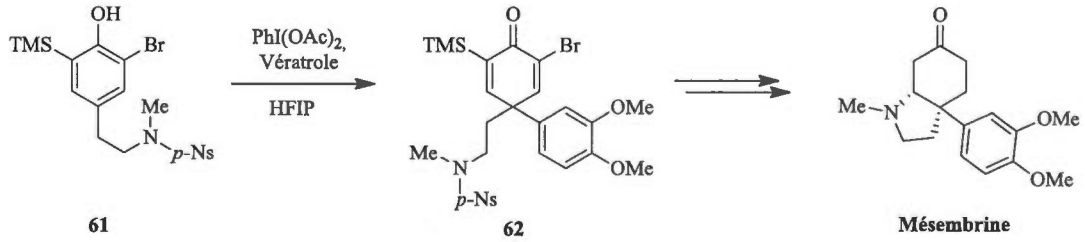


Schéma 17 : Application à la synthèse de la Mésembrine

Bien que très efficaces, ces réactions présentent l'inconvénient de n'être compatibles uniquement avec les phénols di-substitués en position *ortho*, évitant ainsi l'obtention de produits secondaires d'additions nucléophiles sur ces positions.

Des migrations de groupements aryls ont également été démontrées possibles de manière intramoléculaire par notre laboratoire, lors de transpositions 1,2 et 1,3 de type Wagner-Meerwein par oxydation à l'iode hypervalent (Schéma 18).[14g,14k]

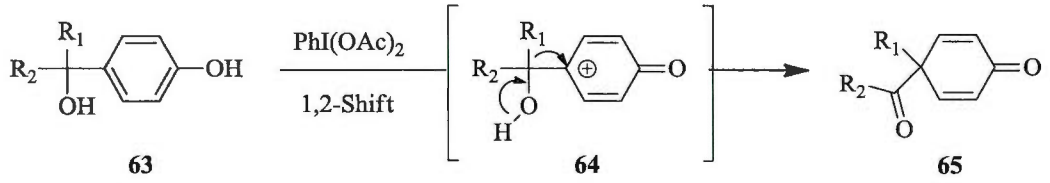


Schéma 18 : Transposition 1,2 de type Wagner-Meerwein

Ces transpositions 1,2 et 1,3 oxydatives à l'iode hypervalent permettent l'obtention rapide de diénone prochirale, un carbone quaternaire lié à plusieurs centres Sp^2 ainsi qu'une fonction carbonyle ou un précurseur. Une version énantiosélective de ce procédé a également été développée par l'utilisation d'un composé énantio-enrichi. Les produits formés représentent le squelette principal de nombreux produits naturels biologiquement actifs. Pour illustrer la portée de ces transpositions, la synthèse rapide de plusieurs systèmes polycycliques a été réalisée, ainsi que la synthèse formelle de l'acétylaspidoalbidine, un alcaloïde héxacyclique de la famille des *Aspidosperma* (Schéma 19).

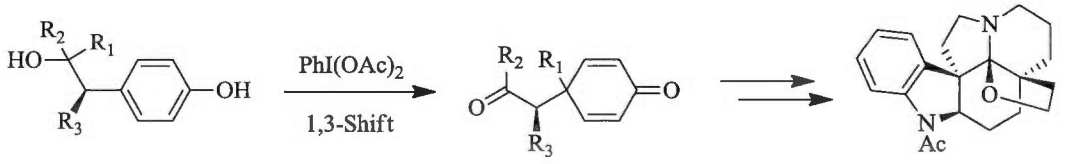


Schéma 19 : Transposition 1,3 et application à la synthèse de l'Acétylaspidoalbidine

Réalisées sur des phénols, ces réactions s'avèrent efficaces avec de nombreux groupements allyles mais restent limitées dans le cas de migration de groupements vinyles ou phényles.

Dans le cas de notre méthodologie, les réactions *Ipso*-oxydatives développées présentent l'avantage d'être compatibles avec des phénols non-substitués en position *ortho* et permettent la migration de groupements aromatiques substitués riches en électrons. Ces réarrangements *Ipso*-oxydatifs ont également été réalisés sur des N-aryl sulfonamides, élargissant ainsi l'étendue de ces réactions.

Au cours de cette transformation, une oxydation de phénol **68** par du DIB conduit à la formation d'un ion phénoxonium dans un état de transition de type chaise. L'intermédiaire **69** formé est ensuite piégé de manière intra-moléculaire par un groupement aromatique présent sur la chaine latérale, grace à un groupement protecteur de type TBDPS. Cet aromatique réalise alors la substitution *Ipso*, conduisant à la formation de la diénone prochirale **70**. L'expulsion du groupement silicium se fait par attaque nucléophile de l'héxafluoroisopropanol (HFIP), entrainant la réaromatisation de l'aryl ayant migré (Schéma 20).

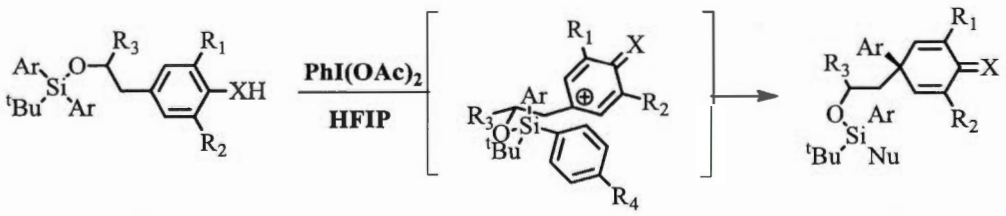
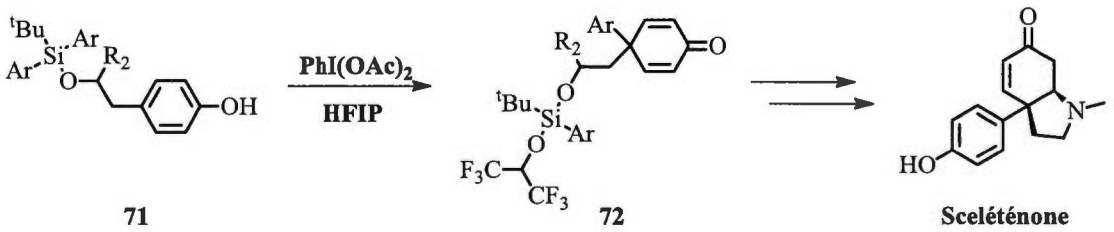


Schéma 20: Mécanisme des réactions *ipso*-oxydatives

En application à ces nouvelles réactions *ipso*-oxydatives, la synthèse de la Sceléténone, un autre alcaloïde de la famille des *Amaryllidaceae*, a été réalisée (Schéma 21). Isolée de *Aptenia Cordifolia* en Afrique du Sud, la Sceléténone possède notamment des propriétés anti-depressives[29].

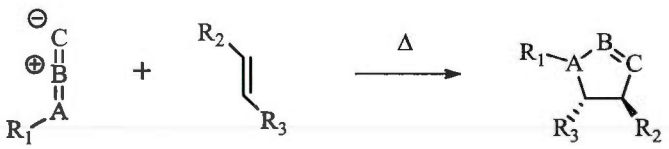


71 **72** **Sceléténone**

Schéma 21: Application à la synthèse de la Sceléténone

0. 4. Cycloadditions

Développée dans les années 1960 par Huisgen[30], les cycloadditions 1,3 dipolaires, ou cycloadditions [2+3], appartiennent à la famille des cycloadditions péricycliques concertées[31]. Rapide et efficace dans la synthèse d'hétérocycles à 5 membres, cette réaction a lieu entre un dipôle 1,3 **73** et un dipôlarophile **74** (Schéma 22).



73 **74** **75**

Schéma 22: Réaction de cycloaddition 1,3 dipôlaire

Durant la cycloaddition, 4 électrons π du dipôle 1,3 réagissent avec 2 électrons π du dipôlarophile. La réactivité et la régiosélectivité sont régies par la théorie HO/BV et il existe deux types d'intéractions (Schéma 23).

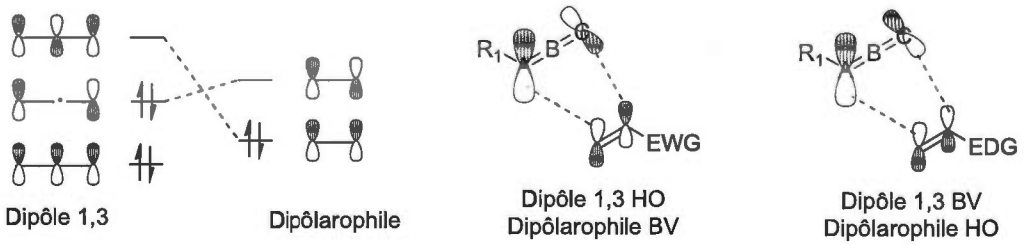


Schéma 23: Orbitales moléculaires et intéractions HO/BV

Parmi les dipôles 1,3 les plus connus et les plus utilisés, on peut citer les oxydes de nitriles, les nitrones, les azotures ou encore les diazoalcanes et l'ozone (Schéma 24).

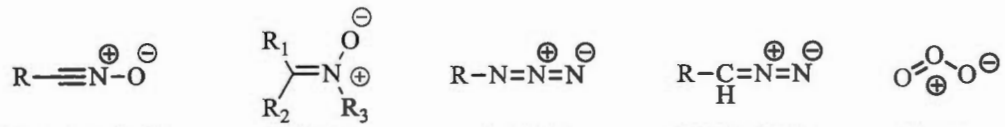


Schéma 24: Exemples de Dipôles 1,3

L'utilisation de l'ion phénoxonium comme dipôle 1,3 dans des réactions de cycloaddition [2+3] à l'iode hypervalent a déjà été démontré possible par notre laboratoire plusieurs années auparavant. En effet, le traitement de divers phénols substitués **76** en présence de diacétoxyiodobenzène et de furane dans le trifluoroéthanol a permis la réalisation de réactions de cycloaddition [2+3] oxydatives formelles de manière efficace (Schéma 25).[14a]

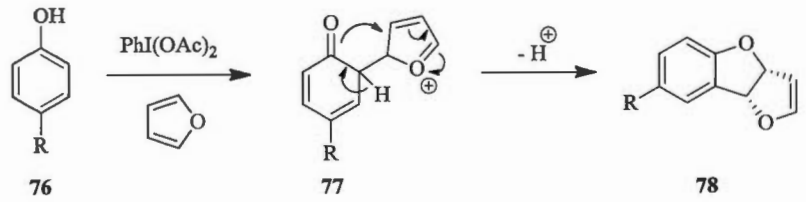


Schéma 25 : Cycloaddition [2+3] de phénol et de furane en présence d'iode hypervalent

En application de cette méthode basée sur le concept d'*Umpolung* aromatique, les synthèses diastéréosélectives et rapides du (±)-panacène et du (±)-desbromopanacène ont été réalisées (Schéma 26).[14c]

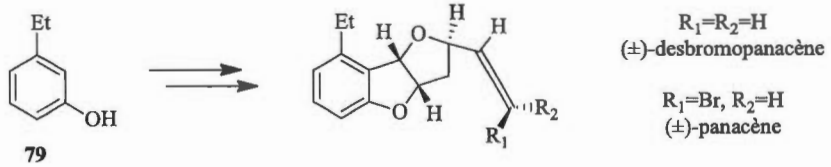


Schéma 26 : Application aux synthèses du (±)-panacène et du (±)-desbromopanacène

Corey a également développé des réactions de cycloadditions [2+3] formelles asymétriques entre des benzoquinones et des éthers vinyliques catalysées par un ion oxazaborolidinium chiral[32]. Cette réaction procède avec d'excellents excès énantionmeriques et a été applique à la synthèse énantioselective de l'Aflatoxin B2 (Schéma 27).

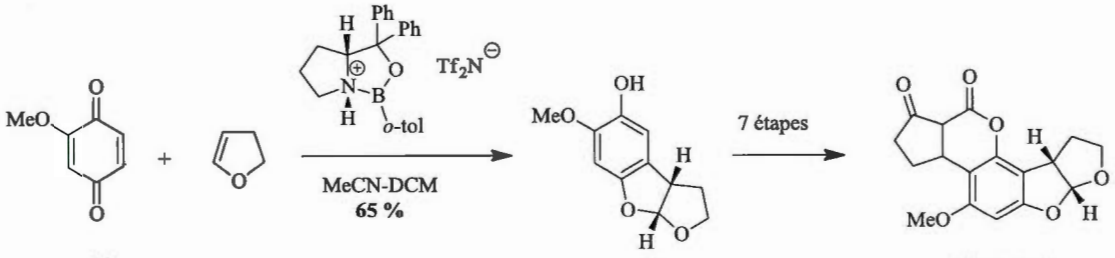


Schéma 27: Cycloaddition [2+3] asymétrique et synthèse de l'Aflatoxin B_2

Des réactions de couplage ont également été développées par oxydation de N-aryl méthanesulfonamides **82** à l'iode hypervalent en présence de thiophènes substitués (Schéma 28).[14b]

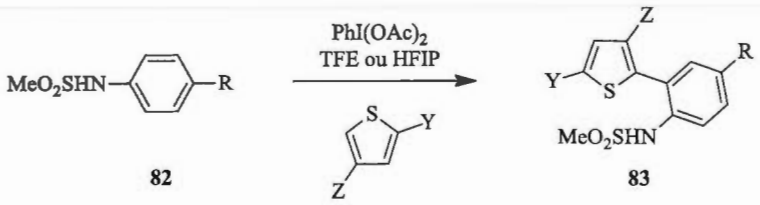


Schéma 28 : Réactions de couplage de N-aryl méthanesulfonamides et de thiophènes

Fonctionnant de manière efficace, les réactions précédentes sont cependant limitées à l'utilisation de furanes ou de thiophènes en tant que dipôlarophiles ou partenaires de couplages. Dans notre cas, l'applicabilité de ces réactions de cycloadditions [2+3] et de couplages a été étendue à l'utilisation de dérivés benzèniques et naphtaléniques non activés, en temps normal peu réactifs.

Comme évoqué précédemment, la réaction de cycloaddition [2+3] développée est formelle. Elle a lieu entre un ion phénoxonium (ou phénoximinium) résultant de l'oxydation d'un phénol **84** (ou aryl-sulfonamide) par un réactif d'iode hypervalent, et un dérivé benzénique

non activé **85** (Schéma 29). Le produit **86** obtenu est alors une molécule polycyclique où le dérivé benzénique a subit une désaromatisation, permettant de nombreuses fonctionnalisations subséquentes. Le produit de couplage bi-arylique **87** peut également être synthétisé par traitement en milieu acide du produit de cycloaddtion, ou bien directement en réalisant l'oxydation avec un aryl-sulfamide.

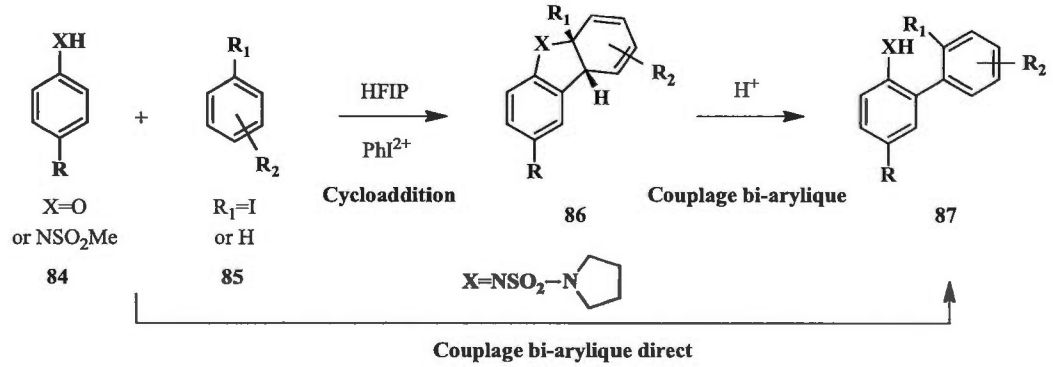


Schéma 29: Réactions de Cycloadditions et de Couplages

Mécanistiquement, l'oxydation du phénol **88** par de l'iode hypervalent conduit à la formation de l'ion phénoxonium **90**, qui pour des raisons stériques, est piégé en position *ortho* par le dérivé benzénique **91** utilisé, conduisant à la formation de l'intermédiaire de type Wheland **92** (Schéma 30). Cet intermédiaire est ensuite piégé de manière intramoléculaire par le doublet de l'oxygène permettant l'obtention du composé **93**. La présence d'une sulfone sur la chaine latérale se revèle être essentielle car elle permet, à l'instar de l'HFIP, une stabilisation du cation formé, lui donnant ainsi un temps de vie suffisamment long pour que la réaction se produise.

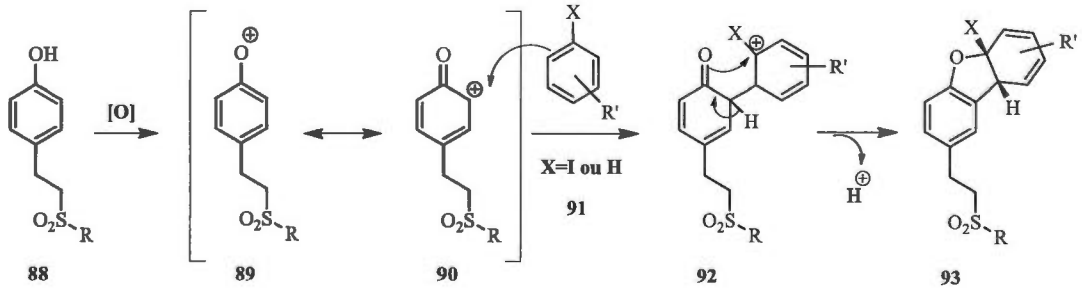


Schéma 30: Mécanisme des cycloadditions désaromatisantes

0. 5. Synthèse de Strychnine

Isolée des graines de *Strychnos ignatii Bergius* et *Strychnos nux-vomica*[33], la Strychnine appartient au genre *Strychnos*, tout comme l'icajine et l'akuammicine (Schéma 31). C'est l'un des alcaloïdes les plus connus au monde, autant par les chimistes que par le grand public du fait de ces propriétés biologiques. En effet, en plus d'être un poison ayant été utilisé dans de nombreux meurtres[34], la Strychnine est considérée comme la première synthèse totale complexe, réalisée en 1954 par Woodward[35]. Cette synthèse conclut ainsi un processus d'isolation et d'élucidation structurale entamé en 1818 par Pelletier et Caventou[36], et auquel a notamment contribué Robinson, prix Nobel en 1947 pour ses travaux sur les alcaloïdes.

Schéma 31: Alcaloïdes du genre *Strychnos*

Dans la nature, la biosynthèse[37] de la Strychnine débute par une condensation de Pictet-Spengler entre la tryptamine et la sécologanine afin de former la strictosidine, permettant d'obtenir la geissoschizine après déglycosilation (Schéma 32). Un réarrangement oxydatif de l'indole permet l'obtention du spiroxindole **94**, qui après condensation avec le motif 1,3-dicarbonyle masqué donne la déhydropréakuammicine. Une décarboxylation aboutit à la norfluorocurarine. Ensuite, une oxydation de la position allylique terminale, suivi d'une réduction du formamide vinylque donne l'aldéhyde de Wieland-Gumlich[38], un produit naturel également connu sous le nom de curacurine VII. Enfin, la Strychnine est obtenue par condensation avec de l'acide malonique[39].

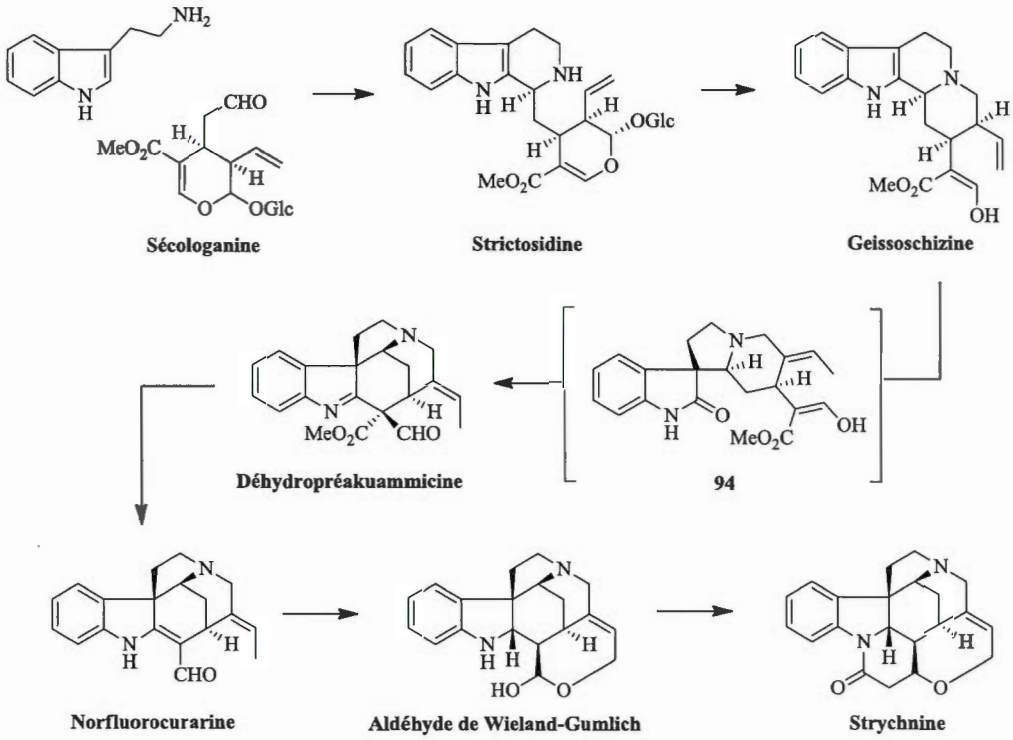


Schéma 32: Biosynthèse de la Strychnine

Dès lors, de nombreuses synthèses totales, racémiques et asymétriques, ont été réalisées au fil des années[40-41].

Inspirée de la biosynthèse, la synthèse réalisée par Woodward en 1954 est un événement marquant dans le domaine de la synthèse totale (Schéma 33)[35]. La cible de ces travaux est l'isostrychnine permettant d'obtenir la Strychnine par traitement en milieu basique. L'isostrychnine a ainsi été obtenue à partir de l'α-cétolactame **95** notamment par une alkylation et un réarrangement allylique. L'héxacycle **95** a été synthétisé à partir du γ-amino acide **96** par une cyclisation oxydante avec du dioxide de Sélénium, lui-même obtenu par une condensation de Dieckmann du di-ester **97**. Le groupe du Pr. Woodward a ensuite utilisé un groupement vératryl comme précurseur d'ester, permettant la formation du lactame après une coupure oxydante du composé **98**. Enfin, cette immine a été synthétisé à partir de l'indole fonctionnalisé **99** par une réaction de Pictet-Spengler avec l'aldéhyde correspondant.

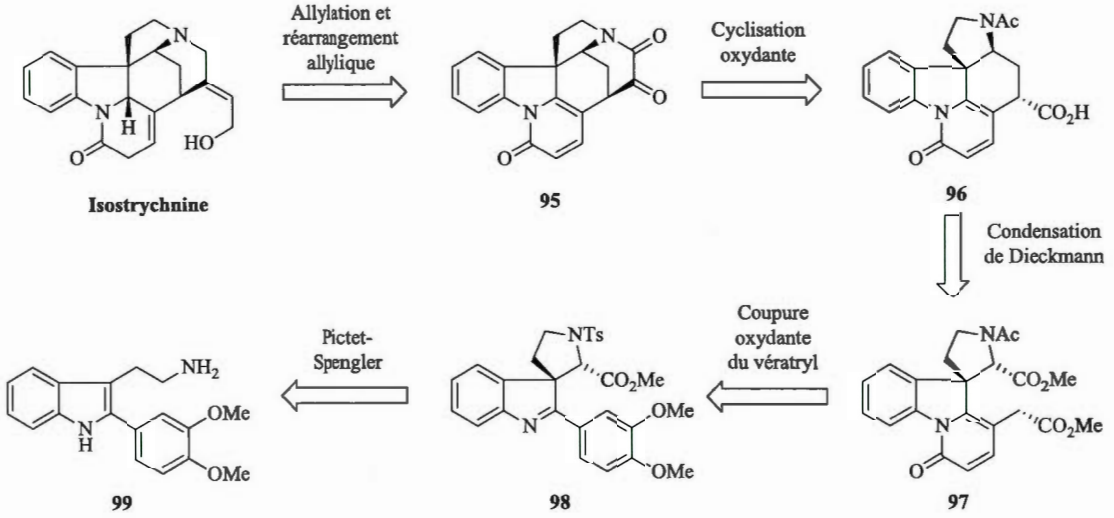


Schéma 33: Rétrosynthèse de Woodward

Ce challenge relevé par le groupe du Pr. Woodward a permis de mettre en avant des concepts importants en synthèse totale, comme l'utilisation de groupements précurseurs de fonctions réactives ainsi que l'importance des réactions intramoléculaires.

Rawal a également réalisé la synthèse racémique de la Strychnine en 1994 (Schéma 34)[40e]. Cette synthese est à l'heure actuelle l'une des plus efficaces, avec un rendement global de 10% sur 13 étapes. Elle comporte notamment une extension de cycle du cyclopropane permettant l'obtention de la pyrroline **101** à partir de la cyclopropyl imine **102**, ainsi qu'une réaction de Diels-Alder intramoléculaire et une alkylation de l'amine secondaire afin de former le pentacycle **100**. L'isostrychnine est ensuite obtenue par un couplage de Heck suivi d'une désillylation de l'alcool primaire en milieu acide.

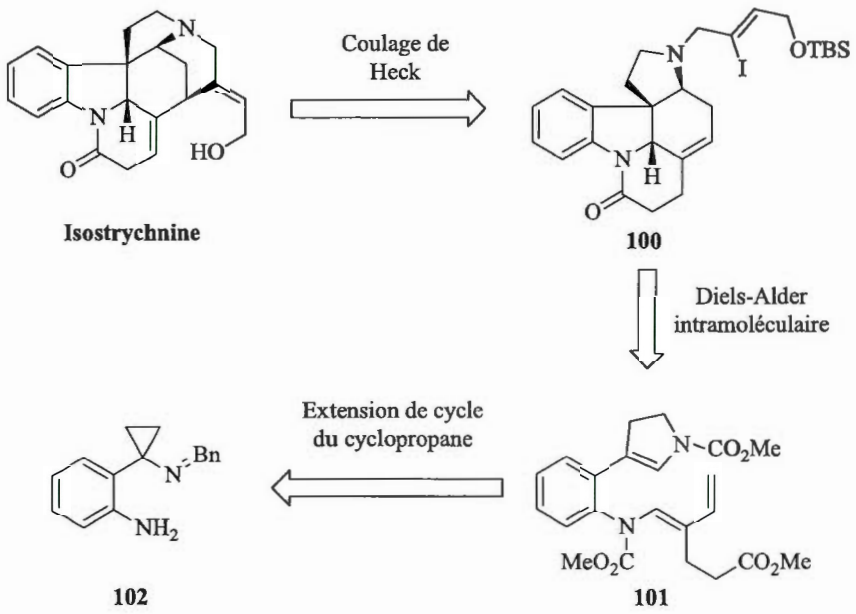


Schéma 34 : Rétrosynthèse de Rawal

La rétrosynthèse envisagée par notre laboratoire pour la synthèse formelle de la Strychnine est la suivante (Schéma 35). La Strychnine sera synthétisée à partir de l'intermédiaire de synthèse formelle **100**, par une réaction de Heck suivi d'une déprotection de l'alcool primaire en milieu acide et d'une cyclisation en milieu basique de l'isostrychnine obtenue[40e, 40p]. Cette amine cyclique sera préparée à partir du produit **103**, par une isomérisation réductrice et une double amination réductrice. Cet aldéhyde sera obtenu à partir du tétracycle **104** par une allylation en milieu basique suivie d'une coupure oxydante. Le tétracycle sera synthétisé à partir de la diénone **105** par une cyclisation par un procédé tandem aza-Michael-éther d'énol silylé suivi d'une réaction de Heck intramoléculaire. Cette diénone sera obtenue à partir du 3-(4-hydroxyphényl)propionate de méthyle **106** par une amidification de Weinreb suivie d'une oxydation à l'iode hypervalent dans le méthanol.

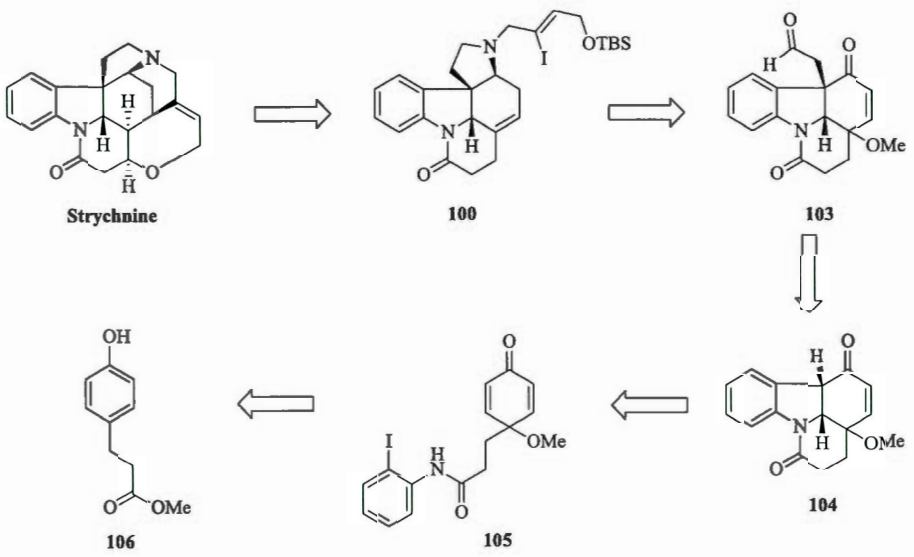


Schéma 35: Schéma rétrosynthètique

CHAPITRE I

RÉACTIONS IPSO-OXYDATIVES ET SYNTHÈSE DE LA SCELÉTÉNONE

1. 1. Introduction

Du fait quelles se retrouvent dans un nombre important de produits naturels biologiquement actifs, les structures contenant un carbone quaternaire connectée à un groupement aryle et possédant un motif de type cyclohéxanone suscitent un grand intérêt.

C'est le cas notamment des alcaloïdes de la famille des *Amaryllidaceae* tels que la sceléténone ainsi que son dérivé méthylé, la *O*-méthylsceléténone, possédants des propriétés anti-dépressives.

Pour générer ces structures, nous avons développé une approche impliquant un réarrangement *ipso*-oxydatif intramoléculaire via l'oxydation d'un phénol substitué possédant un groupement migrant de type aryle porté par un atome de silicium présent sur la chaine latérale.

1. 2. Informations supplémentaires

L'article issu de ces travaux est présentée à l'Annexe A. Les informations supplémentaires, contenant les protocoles expérimentaux ainsi que les caractérisations et spectres RMN, sont présentées à l'Annexe B.

1. 3. Conclusion

En conclusion, un nouveau réarrangement *ipso*-oxydatif intramoléculaire a été développé avec succès. Cette transformation fournit de nouvelles stratégies en synthèse totale en permettant, à partir d'un simple composé aromatique stable, l'obtention d'une diénone reactive possédant un carbone quaternaire polyfonctionnalisé, caractéristique de nombreux produits naturels.

L'utilité de cette méthodologie a également été illustrée par la synthèse de la O-méthylsceléténone et de la sceléténone, respectivement en 8 et 9 étapes, deux alcaloïdes de la famille des *Amaryllidaceae* possédant des propriétés anti-dépressives.

CHAPITRE II

RÉACTIONS DE CYCLOADDITIONS OXYDATIVES ET DE COUPLAGES SUR DES DÉRIVÉS AROMATIQUES NON-ACTIVÉS

2. 1. Introduction

Généralement réalisées sur des alcènes ou des alcynes, les réactions de cycloaddition présentent un grand intérêt en synthèse. Cependant, une transformation similaire permettant la désaromatisation d'un lien π d'un système aromatique normalement inerte fournirait un moyen efficace pour la préparation d'intermédiaires polyfonctionnalisés. De nombreuses réactions pourraient notamment être réalisées sur les doubles liaisons restantes pour générer rapidement des produits complexes à partir de dérivés aromatiques simples.

En revanche, les réactions de couplage bi-aryliques ont reçu une attention particulière ces dernières années de part le nombre important de produits naturels possédant ce type de structures, ainsi que par l'utilisation massive de composés bi-aryliques chiraux dans les réactions asymétriques. Impliquant généralement l'utilisation de métaux lourds, des réactions de couplage bi-aryliques réalisées sans métaux ont également été reportées. Celles-ci utilisent des réactifs à l'iode hypervalent et des thiophènes, polyméthylbenzènes ou dérivés d'anisole en tant que partenaires de couplage.

Pour réaliser ce type de transformations, nous avons développé de nouvelles réactions de cycloaddition [2+3] à l'iode hypervalent entre des dérivés benzèniques et des phénols ou anilines. L'utilisation de conditions légèrement modifiées ont également permit l'obtention du produit de couplage bi-arylique entre deux composés aromatiques non-activés.

2. 2. Informations supplémentaires

L'article issu de ces travaux est présentée à l'Annexe C. Les informations supplémentaires, contenant les protocoles expérimentaux ainsi que les caractérisations et spectres RMN, sont présentées à l'Annexe D.

2. 3. Conclusion

En conclusion, de nouvelles réactions de cycloadditions désaromatisantes entre des phénols ou anilines et des dérivés aromatiques ont été développées.

Permettant l'obtention rapide de composés fonctionnalisés et hautement fonctionnalisables, ces réactions sont rendues possibles par l'utilisation d'un groupement sulfonyle permettant la stabilisation de l'espèce électrophilique générée durant le processus d'oxydation à l'iode hypervalent. Un simple traitement en conditions acides a ensuite permit d'obtenir le produit de couplage bi-arylique avec d'excellents rendements.

Des conditions d'oxydation légèrement modifiées ont également été utilisés afin de réaliser directement le couplage bi-arylique entre deux composés aromatiques non activés, constituant ainsi une alternative efficace pour l'activation de lien C-H.

CHAPITRE III

SYNTHÈSE FORMELLE DE LA STRYCHNINE

3. 1. Introduction

Isolée des graines de *Strychnos ignatii Bergius* and *Strychnos nux-vomica,* la Strychnine est un des alcaloïdes les plus connus de par ces propriétés biologiques. Isolée par Pelletier et Caventou en 1818, cet alcaloïde du genre *Strychnos* fût synthètisé pour la première fois par Woodward en 1954. Cette synthèse totale est considérée comme la première synthèse complexe et conclut un processus d'isolation et d'élucidation structurale auquel a notamment contribué Robinson, prix Nobel en 1947 pour ses travaux sur les alcaloïdes. Véritable source d'inspiration ayant permit des avancées en synthèse organique, la strychinine est un alcaloïde heptacyclique dont de nombreuses synthèses racémiques et asymétriques ont été réalisées.

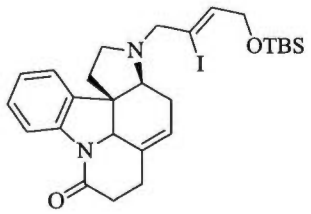
La synthèse formelle rapide développée par notre laboratoire est réalisée en 8 étapes et comporte notamment une déasromatisation de phénol à l'iode hypervalent, une cyclisation de type Heck, un procédé tandem aza-Michael-éther d'énol non reporté à ce jour ainsi qu'une isomerisation reductive et une double amination réductrice. L'intermédiaire de synthèse formelle obtenue permet ensuite l'obtention de la strychnine en 2-3 étapes, conformément aux travaux menés par Rawal en 1994.

3. 2. Informations supplémentaires

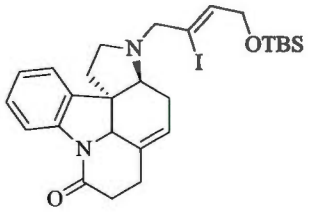
L'article issu de ces travaux est présentée à l'Annexe E. Les informations supplémentaires, contenant les protocoles expérimentaux ainsi que les caractérisations et spectres RMN, sont présentées à l'Annexe F.

3. 3. Perspectives et travaux futurs

Afin de finaliser ce travail portant sur la synthèse formelle de la Strychnine et publier l'article définitif, les conditions expérimentales de double amination réductrice seront améliorées et la version asymmétrique sera développée. A l'heure actuelle, le produit de synthèse formelle **100** a été isolé avec des rendements faibles (29%), dans un mélange 1 :1 avec son diastéréoisomère possédant le cycle a 5 *trans* **107**.

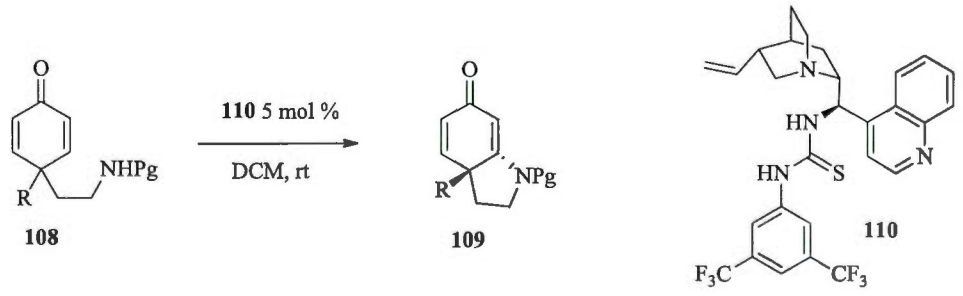


100



107

La version asymétrique de la synthèse est également à l'étude et pourrait être obtenue lors de l'étape de cyclisation tandem aza-Michael-éther d'énol par l'emploi d'un catalyseur chiral. Ce genre de désymetrisation de diénone a été démontré possible par You en 2011 par l'utilisation de dérivés de cinchonine (Schéma 36)[42].



108 **109** **110**

Schéma 1 : Réaction de désymétrisation de diénone

3. 4. Conclusion

En conclusion, une synthèse formelle de la strychnine a été réalisée en 9 étapes à partir d'un phénol simple et bon marché. Cette synthèse formelle comporte notamment une déasromatisation de phénol à l'iode hypervalent, une cyclisation de type Heck, un procédé tandem aza-Michael-éther d'énol non reporté à ce jour ainsi qu'une isomerisation reductive et une double amination réductrice.

Cette synthèse permet également de mettre en lumière l'utilisation de l'iode hypervalent en synthèse totale de produits naturels complexes. La version asymétrique de cette synthése et l'optimisation de certaines réactions présentées est présentement à l'étude au laboratoire.

CONCLUSION

En conclusion, de nouvelles méthodologies d'oxydations à l'iode hypervalent ainsi qu'une synthèse totale de la Strychnine ont été développées. Les réactions *Ipso*-oxydatives ont permis l'obtention de composés hautement fonctionnalisés possédant une diénone prochirale et un carbone quaternaire connecté à plusieurs carbone sp^2. Les insaturations "dormantes" du phénol révélées lors de l'oxydation permettent de nombreuses fonctionnalisations subséquentes et les applications possibles en synthèse de produits naturels sont nombreuses. L'applicabilité de cette méthode a été illustrée par la synthèse de la *O*-méthylsceléténone et de la Sceléténone, deux alcaloïdes naturels de la famille des *Amaryllidaceae*.

De nouvelles réactions de cycloadditions entre un phénol (ou aryl-sulfonamide) et un dérivé benzénique ont également été développées. Rendues possibles par la présence d'un groupement sulfonyle stabilisant l'électrophile formé, ces réactions permettent l'obtention de polycycles fonctionnalisés dont les potentielles applications en synthèse sont multiples. Cette méthodologie pernet également l'obtention de produit de couplage bi-arylique, sans utiliser de métaux, de manière directe et indirecte.

Enfin, une synthèse formelle et rapide de la Strychnine a été développée. Réalisée en 9 étapes à partir d'un phénol peu couteux et facilement accessible, cette synthèse met en jeu une réaction de désaromatisation oxydative de phénol à l'iode hypervalent, une nouvelle réaction tandem aza-Michael-éther d'énol silylé ainsi qu'une réaction de Heck.

Tous ces travaux mettent en lumière l'importance des réactifs à base d'iode hypervalent et leur exceptionnelle utilité en synthèse totale de produits naturels.

ANNEXE A :

"OXYDATIVE *IPSO*-REARRANGEMENT PERFORMED BY A HYPERVALENT IODINE REAGENT AND ITS APPLICATION" ARTICLE

Journal of Organic Chemistry, **2012**, *77*, page 7588–7594

DOI: 10.1021/jo301408j

Date de publication (Web) : 6 Août 2012

http://pubs.acs.org/doi/pdf/10.1021/jo301408j

Titre: Oxydative Ipso-Rearrangement Performed by a Hypervalent Iodine reagent and Its Application

Auteurs: Guillaume Jacquemot et Sylvain Canesi*

JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

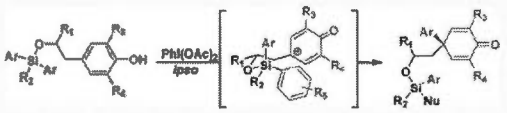
Oxidative *ipso*-Rearrangement Performed by a Hypervalent Iodine Reagent and Its Application

Guillaume Jacquemot and Sylvain Canesi*

Laboratoire de Méthodologie et Synthèse de Produits Naturels, Université du Québec à Montréal, C.P. 8888, Succ. Centre-Ville, Montréal, H3C 3P8 Québec, Canada

Supporting Information

ABSTRACT: An oxidative *ipso*-rearrangement mediated by a hypervalent iodine reagent that enables rapid generation of a functionalized dienone system containing a quaternary carbon center connected to several sp^2 centers has been developed. The process occurs through transfer of an aryl group from a silyl segment present on the lateral chain. As an illustration of the potential of this transformation, a total synthesis of sceletenone, a small alkaloid, is described.



INTRODUCTION

Structures containing a quaternary carbon center connected to an aryl group and including a cyclohexanone derivative have attracted substantial interest due to the large number of bioactive natural products containing a similar motif, including Amaryllidaceae alkaloids such as *O*-methylsceletenone **1a**, isolated from *Aptenia Cordifolia*[1] in South Africa, and its *O*-demethylated analogue sceletenone, isolated from the phenolic alkaloid fraction of *Sceletium strictum*.[1] Both of these compounds are potent serotonin reuptake inhibitors. Other examples include narwedine[2] **2** and vindoline **3**, which is an important moiety of vincristine, a mitotic inhibitor isolated from *catharanthus roseus*[3] and used in cancer chemotherapy (Figure 1).

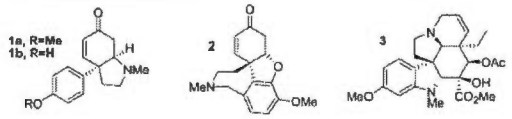


Figure 1. Natural alkaloids containing quaternary carbon centers.

To generate these structures, we have developed an approach involving a hypothetical intramolecular "oxidative *ipso*-rearrangement" promoted by subsequent oxidation of a substituted phenol containing a preactivated migrating group and connected to a silicon atom on the lateral chain. We assume that this process occurs via a chairlike transition state **5** leading to compound **6** (Figure 2).

In this paper, we describe an oxidative *ispo*-shift process occurring in electron-rich aromatic compounds and leading to the formation of a prochiral dienone system containing a quaternary carbon center connected to several sp^3 centers. The method is then applied to the total syntheses of *O*-methylsceletenone and sceletenone, two natural alkaloids.

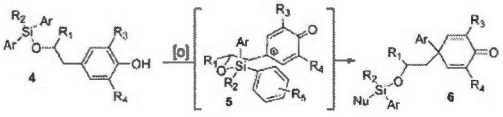


Figure 2. Oxidative *ipso*-rearrangement pathway.

RESULTS AND DISCUSSION

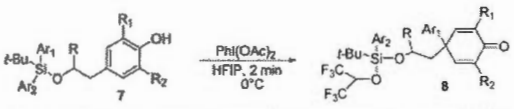
The approach requires activation to transform the electron-rich phenol into an electrophilic species susceptible to trapping by the silyl-aryl group. When the process involves an intermediate such as **5** it may be termed "aromatic ring umpolung".[4] Although electron-rich aromatic systems such as **4** normally react as nucleophiles, oxidative activation converts them into highly electrophilic species that may then be intercepted with appropriate nucleophiles. This umpolung activation is mediated by hypervalent iodine reagents such as iodobenzene diacetate (DIB) or equivalent mild oxidizing agents. The potential of this environmentally benign reagent was made evident in the pioneering work of Kita.[5] In particular, DIB promotes oxidative transformation of phenols[6,7] in a manner consistent with recent requirements for green chemical processes. As observed by Kita and co-workers,[8] DIB reactions generally occur best in non-nucleophilic highly polar solvents such as trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP). In this paper, we propose an unprecedented *ipso*-rearrangement initiated by a hypervalent iodine reagent to form a functionalized dienone system containing a quaternary carbon center connected to several sp^2 atoms including an aromatic moiety, a structural feature present in a large number of bioactive natural products. Our first attempts to verify the feasibility of this transformation were undertaken using a simple TBDPS (or a derivative)-

Received: July 5, 2012

 © XXXX American Chemical Society dx.doi.org/10.1021/jo301408j | J. Org. Chem. XXXX, XXX, XXX−XXX

protected alcohol functionality easily accessible on a large scale by protection of inexpensive starting materials **7** (Table 1).

Table 1. Oxidative *ipso*-shift process

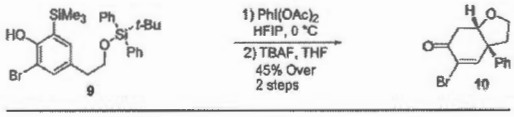


entry	Ar_1	Ar_2	R	R_1	R_2	yield (%)
a	Ph	Ph	H	H	H	40
b	*p*-anisole	*p*-anisole	H	H	H	74
c	*p*-toluene	*p*-toluene	H	H	H	51
d	Ph	OH	Me	H	H	37[a]
e	Ph	Ph	H	Br	*t*-Bu	62
f	Ph	Ph	H	*t*-Bu	*t*-Bu	85[a]
g	Ph	Ph	H	OMe	H	44[a]

[a]A minor amount of $OCH(CF_3)_2$ has been substituted by an acetate or an hydroxyl

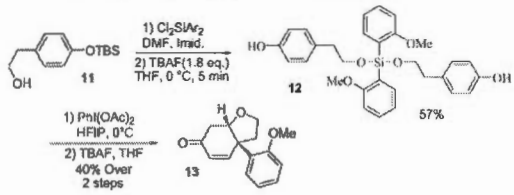
It should be stressed that the reaction occurs in moderate to good yield (37–85%) with a simple benzene derivative; however, the one-step transformation of the simple and easily accessible starting material **7** in a highly functionalized core **8** would provide even more favorable results in terms of global yield and number of steps than traditional methodologies. As expected with *p*-toluene and *p*-anisole derivatives (entries **7c** and **7b**), the reaction occurs in higher yield compared to entry **7a** due to the presence of an electron-donating methyl or methoxy group in the *para* position. As previously observed in similar transformations, the reaction occurs in greater yields (up to 85%, entries **7e** and **7f**) when the phenol moiety is substituted with a *tert*-butyl group.[4d] This can be rationalized by considering the *tert*-butyl group as an electron donor stabilizing the electrophilic species **5**, enabling the *ipso* rearrangement and limiting alternate reaction pathways such as elimination of a benzilic hydrogen. A surprising aspect of this process is the nucleophilic addition of HFIP to the nascent asymmetric silicon center, sometimes accompanied by a small amount of acetate (~10%) released from the hypervalent iodine reagent. HFIP is a weakly reactive nucleophile and is normally considered an inert solvent. Further treatment of the resulting dienone system with TBAF furnishes oxygenated versions of bicyclic systems similar to the natural products illustrated in Figure 1. For example, oxidation of compound **9** followed by direct treatment of the crude mixture with TBAF leads to the bicyclic system **10** in 45% yield over two steps (Scheme 1).

Scheme 1. Oxidative *ipso*-1,4-Conjugate Addition



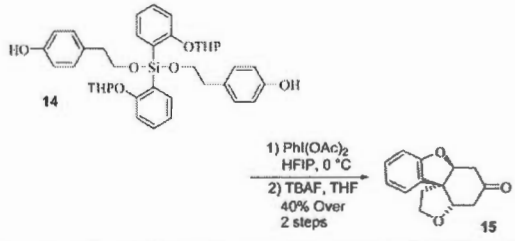
In order to develop a method with favorable atom economy, dimers such as **12** containing two phenol moieties and two aromatic segments have been prepared. In this case, only one silicon atom is used as a tether to generate two dienone subunits, and subsequent treatment with TBAF produces the tricyclic core **13**. In order to generate the more elaborate quaternary carbon-connected aromatic systems found in natural products, an *o*-anisole subunit was used as a migrating group. The corresponding dimer was obtained by treatment of dichloro-diarylsilane with an *O*-TBS-protected phenol followed by a selective phenol deprotection in 57% overall yield (Scheme 2).

Scheme 2. Application to Dimeric Substrates



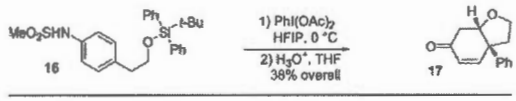
The potential utility of this new method is demonstrated in an expeditious two-step method to generate the tetracyclic system **15**, an oxygenated version of the main core of vindoline **3** (Figure 1). The oxidation occurs via *ipso*-rearrangement followed by a tetrahydropyran deprotection and subsequent 1,4-conjugate addition from the resulting phenol moiety, provoked by the acidity of the medium used (HFIP and acetic acid released). Further treatment with TBAF furnishes the elaborated tetracyclic core **15** in 40% overall yield from the simple dimer **14** (Scheme 3).

Scheme 3. Rapid Formation of Oxygenated Tetracyclic Core



The process is not restricted to phenol derivatives, as illustrated by the generation of **17** from the aniline derivative **16** under similar conditions. The reaction proceeds via formation of a sulfonyl dieniimine that is subsequently hydrolyzed under acidic conditions into dienone subunit **17** in similar yield (Scheme 4).

Scheme 4. *N*-(Sulfonyl)-aniline *ipso*-Transformation



As an initial application of the oxidative *ipso*-rearrangement, we describe the total syntheses of *O*-methylsceletenone **1a** and sceletenone **1b**.[1] These small molecules belonging to the Amaryllidaceae family are generally isolated in racemic form, most probably due to an aza-Michael/retro-Michael equilibrium. The compounds are known to have antidepressant properties and are bioprecursors to the natural analogue mesembrine.[1c,9] A retrosynthetic pathway is presented in Figure 3.

dx.doi.org/10.1021/jo301408j | J. Org. Chem. XXXX, XXX, XXX−XXX

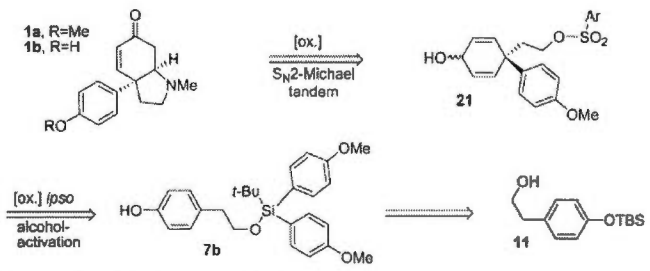
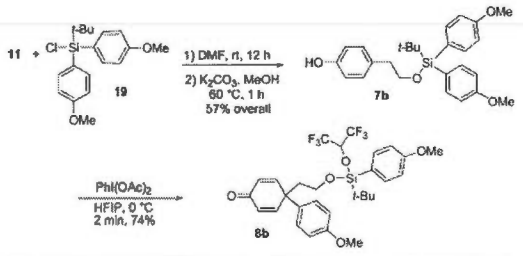


Figure 3. Retrosynthetic pathway to *O*-methylsceletenone and sceletenone.

Starting from compound **11**,[10] the primary alcohol functionality is protected with a modified *p*-methoxy-TBDPSCl segment **19** using classical conditions. The modified TBDPSCl reagent **19** is obtained by treatment of *tert*-butyltrichlorosilane with 2 equiv of the corresponding aryl-organolithium reagent **18**. Selective deprotection of the phenol group using potassium carbonate in methanol furnishes **7b** in 57% yield over two steps. At this stage, the key oxidative *ispo*-rearrangement promoted by a hypervalent iodine reagent produces the functionalized dienone system **8b** in 74% yield. It should be noted that the silicon moiety used during this transformation not only acts as a simple protecting group but also enables the formation of an important component of the target as a tether. In addition, the modified fluorinated protecting group emerging in compound **8b** remains available for further transformations (Scheme 5).

Scheme 5. Oxidative Key Step



A reduction of the ketone functionality in **8b** with DIBAL-H leads stereoselectively to the diastereoisomer **20** in a 9:1 ratio. Subsequent deprotection of the primary alcohol using TBAF produces the diol in 85% yield. A selective activation of the primary alcohol into a leaving group performed in the presence of a hindered sulfonyl moiety such as *o*-nosyl chloride furnishes compound **21** in 40% yield. Oxidation with TPAP/NMO regenerates the dienone system and further treatment of this core with methylamine via a S$_N$2-aza-Michael tandem process leads to the target *O*-methylsceletenone **1a** in 76% yield. Despite the fact that *O*-methylsceletenone **1a** are isolated in racemic form,[1] You and Gu[11] recently reported an asymmetric synthesis based on a sulfonamide derivative and employing a cinchonine-derived thiourea catalyst[11] to desymmetrize enantioselectively similar dienone systems. In addition, sceletenone **1b** can also be easily and quantitatively obtained from **1a** by treatment with BBr_3 (Scheme 6).

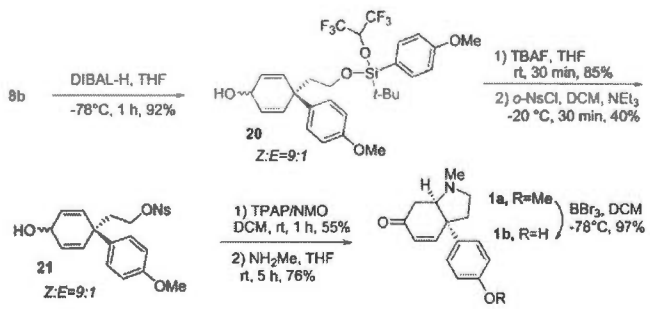
■ CONCLUSION

A practical new method for inducing intramolecular oxidative *ipso*-rearrangements is now available. The transformation provides new strategic opportunities by enabling one-step transformation of stable and simple aromatic compounds into more reactive dienone cores containing a polyfunctionalized quaternary carbon center, a prominent feature of several natural products. The utility of this method is illustrated through its application to total syntheses of *O*-methylsceletenone and sceletenone.

■ EXPERIMENTAL SECTION

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

Scheme 6. Syntheses of *O*-Methylsceletenone and Sceletenone



dx.doi.org/10.1021/jo301408j | J. Org. Chem. XXXX, XXX, XXX−XXX

recorded from thin films. HRMS were measured in the electrospray (ESI) mode on a LC-MSD TOF mass analyzer.

General Procedure for the Formation of Phenols 7. To a solution of **11** (2.52 mmol, 1.0 equiv) in DMF (3.0 mL) was added imidazole (7.56 mmol, 3.0 equiv), and the solution was stirred for 5 min. TBDPS-Cl (3.78 mmol, 1.5 equiv) was then added, and the reaction mixture was stirred at room temperature. The reaction was followed by TLC. After completion, ether was added, followed by water. The aqueous phase was extracted with ether, and the organic phases were then washed with water and brine and then dried with Na_2SO_4. The solution was filtered and concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford the protected alcohol. The substrate was then diluted in methanol (16.0 mL), K_2CO_3 (5.04 mmol, 2.0 equiv) was added, and the solution was stirred at 60 °C. The reaction was followed by TLC. After completion, aqueous NH_4Cl was added, and the aqueous phase was extracted with DCM. The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give the corresponding phenol for more details.

General Procedure for the Oxidative *ipso*-Rearrangement. A solution of $PhI(OAc)_2$ ("DIB", 78 mg, 0.24 mmol, 1.2 equiv) in $(CF_3)_2CHOH$ ("HFIP", 0.35 mL) was added dropwise over 30 s to a vigorously stirred solution of phenol (0.2 mmol, 1 equiv) in HFIP (0.6 mL) at 0 °C. The mixture was then stirred for 30 s and concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane.

1-(2-((*tert*-Butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(phenyl)silyl)oxy)ethyl)-[1,1′-biphenyl]-4(1*H*)-one (8a). Pale yellow oil: 0.059 mmol, 31.9 mg, 40% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.36 (m, 8H), 6.98 (d, 2H, J = 10.0 Hz), 6.36 (d, 2H, J = 10.7 Hz), 4.46 (hept, 1H, J = 5.8 Hz), 3.90 (m, 2H), 2.51 (t, 2H, J = 6.9 Hz), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.0, 153.7, 153.7, 139.5, 135.7, 135.2, 131.1, 129.3, 128.7, 128.6, 128.6, 128.3, 128.0, 127.8, 126.5, 70.6 (hept, J_2 = 33.6 Hz), 60.8, 47.6, 40.1, 27.0, 26.0, 19.4; HRMS (ESI) calcd for $C_{27}H_{28}F_6O_3Si$ (M + H)$^+$ 543.1785, found 543.1776.

1-(2-((*tert*-Butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(4-methoxyphenyl)silyl)oxy)ethyl)-4′-methoxy-[1,1′-biphenyl]-4(1*H*)-one (8b). Pale yellow oil: 0.033 mmol, 20.0 mg, 74% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 8.6 Hz, 2H), 7.23 (t, J = 6.0 Hz, 2H), 6.93 (dt, J = 14.3, 8.5 Hz, 6H), 6.34 (d, J = 9.9 Hz, 2H), 4.43 (hept, 1H, J = 5.8 Hz), 3.90 (m, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.46 (t, J = 6.9 Hz, 2H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.1, 161.9, 159.2, 154.1, 154.1, 137.3, 136.9, 131.1, 128.3, 128.2, 127.7, 119.3, 114.7, 114.1, 70.5 (hept, J_2 = 33.6 Hz), 60.7, 55.5, 55.19, 55.1, 47.0, 40.1, 25.9, 19.5, 19.3; HRMS (ESI) calcd for $C_{29}H_{33}F_6O_5Si$ (M + H)$^+$ 603.1996, found 603.1986.

1-(2-((*tert*-Butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(*p*-tolyl)silyl)oxy)ethyl)-4′-methyl-[1,1′-biphenyl]-4(1*H*)-one (8c). Pale yellow oil: 0.021 mmol, 12.2 mg, 51% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 7.8 Hz, 2H), 7.25–7.15 (m, 6H), 6.96 (d, J = 9.6 Hz, 2H), 6.34 (d, J = 9.8 Hz, 2H), 4.43 (hept, 1H, J = 5.8 Hz), 3.87 (m, 2H), 2.47 (t, J = 6.9 Hz, 2H), 2.38 (s, 3H), 2.34 (s, 3H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.1, 154.0, 154.0, 141.3, 137.8, 136.4, 135.3, 130.0, 129.1, 128.5, 128.4, 126.4, 125.0, 70.5 (hept, J_2 = 33.6 Hz), 60.7, 47.4, 40.1, 26.0, 25.9, 21.7, 21.1, 19.4; IR υ (cm^{-1}) 1667, 1626, 1218, 1106; HRMS (ESI) calcd for $C_{29}H_{32}F_6NaO_3Si$ (M + Na)$^+$ 593.1917, found 593.1910.

1-(2-((*tert*-Butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(phenyl)silyl)oxy)propyl)-[1,1′-biphenyl]-4(1*H*)-one (8d). Pale yellow oil: 0.012 mmol, 6.1 mg, 37% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.28 (m, 5H), 7.08–6.99 (m, 2H), 6.41 (dd, J = 10.1, 1.8 Hz, 1H), 6.30 (dd, J = 10.1, 1.8 Hz, 1H), 4.63 (h, J = 5.8 Hz, 1H), 4.10 (m, 1H), 2.48 (dd, J = 14.1, 5.6 Hz, 1H), 2.21 (dd, J = 14.1, 3.5 Hz, 1H), 1.25 (d, J = 6.1 Hz, 3H), 0.95 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.0, 155.5, 154.0, 139.9, 129.3, 128.9, 127.9, 127.5, 126.6, 70.2 (hept, J_2 = 33.6 Hz), 67.3, 48.2, 47.8, 25.8, 25.2, 17.4; IR υ (cm^{-1}) 3354, 1654, 1617, 1376, 1292, 1227, 1195, 1103; HRMS (ESI) calcd for $C_{22}H_{26}F_6NaO_3Si$ (M + Na)$^+$ 519.1397, found 519.1399.

3-Bromo-5-(*tert*-butyl)-1-(2-((*tert*-butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(phenyl)silyl)oxy)ethyl)-[1,1′-biphenyl]-4(1*H*)-one (8e). Pale yellow oil: 0.018 mmol, 12.0 mg, 62% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.39 (m, 8H), 7.29 (d, 1H, J = 1.7 Hz), 6.71 (dd, 1H, J = 4.6, 2.8 Hz), 4.46 (hept, 1H, J = 5.8 Hz), 3.84 (m, 2H), 2.49 (m, 2H), 1.24 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 152.1, 152.1, 147.0, 146.9, 145.3, 145.19, 139.3, 139.3, 135.3, 135.2, 131.2, 129.5, 128.5, 128.4, 128.3, 128.1, 126.4, 125.7, 125.5, 70.5 (hept, J_2 = 33.6 Hz), 60.6, 49.8, 49.8, 40.2, 35.5, 29.2, 26.0, 19.4; IR υ (cm^{-1}) 1659, 1232, 1229, 1197, 1106; HRMS (ESI) calcd for $C_{31}H_{35}BrF_6NaO_3Si$ (M + Na)$^+$ 701.1320, found 701.1314.

3,5-Di-*tert*-butyl-1-(2-((*tert*-butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(phenyl)silyl)oxy)ethyl)-[1,1′-biphenyl]-4(1*H*)-one (8f). Pale yellow oil: 0.02 mmol, 13.2 mg, 85% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.40 (m, 6H), 7.29 (m, 2H), 6.55 (m, 2H), 4.45 (hept, 1H, J = 5.8 Hz), 3.79 (ddd, 2H, J = 10.7, 5.5, 2.7 Hz), 2.48 (m, 2H), 1.21 (s, 9H), 1.19 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.2, 146.7, 146.7, 144.6, 144.5, 141.8, 135.3, 131.1, 129.1, 128.8, 128.2, 127.4, 126.3, 70.5 (hept, J_2 = 33.6 Hz), 61.1, 45.6, 39.9, 35.0, 35.0, 29.5, 29.4, 25.9, 19.4; IR υ (cm^{-1}) 1644, 1215; HRMS (ESI) calcd for $C_{35}H_{44}ClF_6O_3Si$ (M + Cl)$^-$ 689.2658, found 689.2674.

1-(2-((*tert*-Butyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)(phenyl)silyl)oxy)ethyl)-3-methoxy-[1,1′-biphenyl]-4(1*H*)-one (8g). Pale yellow oil: 0.012 mmol, 7.0 mg, 44% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 4H), 7.40 (m, 6H), 6.82 (dd, 1H, J = 9.9, 2.1 Hz), 6.12 (d, J = 2.1 Hz 1H), 6.01 (d, 1H, J = 9.9 Hz), 5.54 (hept, 1H, J = 5.8 Hz), 3.83 (t, 2H, J = 6.0 Hz), 3.35 (s, 3H), 2.48 (t, 2H, J = 5.8 Hz), 1.03 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.9, 137.6, 135.7, 135.7, 135.1, 133.3, 133.3, 129.9, 129.6, 129.3, 128.7, 128.3, 127.9, 125.1, 124.9, 67.5 (hept, J_2 = 33.6 Hz), 62.3, 52.2, 38.4, 29.9, 26.9, 25.8, 19.2; calcd for $C_{28}H_{30}F_6O_4SiNa$ (M + Na)$^+$ 595.1170, found 595.1171.

5-Bromo-3a-phenyl-3,3a,7,7a-tetrahydrobenzofuran-6(2*H*)-one (10). Pale yellow oil: 0.018 mmol, 5.2 mg, 45% yield over 2 steps; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 5H), 7.19 (d, 1H, J = 2.2 Hz), 4.35 (q, 1H, J = 2.8 Hz), 4.12 (td, 1H, J = 8.8, 3.1 Hz), 3.95 (ddd, 1H, J = 9.7, 8.6, 6.8 Hz), 3.01 (ddd, 1H, J = 17.2, 3.1, 0.7 Hz), 2.74 (m, 2H), 2.36 (ddd, 1H, J = 12.9, 6.8, 3.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 150.7, 138.6, 129.4, 128.1, 126.6, 124.0, 83.1, 67.1, 54.6, 40.2, 38.9; calcd for $C_{14}H_{14}O_2Br$ (M + H)$^+$ 293.0172, found 293.0171.

4,4′-(((Bis(2-methoxyphenyl)silanediyl)bis(oxy))bis(ethane-2,1-diyl))diphenol (12). To a solution of **18** (16.7 mg, 0.066 mmol, 1.0 equiv) in DMF (1.0 mL) was added imidazole (53.9 mg, 0.792 mmol, 12.0 equiv), and the solution was stirred during 5 min. The solution was then added to a solution of "dichlorosilane" (0.198 mmol, 3.0 equiv) in DMF (1.0 mL). The reaction mixture was stirred at room temperature, and the reaction was followed by TLC. After completion, ether was added, followed by water. The aqueous phase was extracted with ether, and the organic phases were then washed with water and brine and then dried with Na_2SO_4. The solution was filtered and concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford the protected dimer. To this dimer in THF (1.0 mL) was added TBAF (42 μL, 0.042 mmol, 1.8 equiv) at 0 °C under stirring, and the reaction was followed by TLC. After completion, aqueous NH_4Cl was added, and the aqueous phase was extracted with EtOAc. The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 9.7 mg (57% over 2 steps) of a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 7.1 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.00 (d, J = 8.2 Hz, 4H), 6.94 (t, J = 7.3 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 6.69 (d, J = 8.3 Hz, 4H), 3.90 (t, J = 7.3 Hz, 4H), 3.64 (s, 6H), 2.80 (t, J = 7.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 153.9, 137.4, 131.9, 130.3, 122.2, 120.6, 115.1, 109.9, 64.7, 55.3, 38.4; IR υ (cm^{-1}) 3389, 1615, 1455, 1240; HRMS (ESI) calcd for $C_{30}H_{33}O_6Si$ (M + H)$^+$ 517.2041, found 517.2034.

dx.doi.org/10.1021/jo301408j | J. Org. Chem. XXXX, XXX, XXX−XXX

After completion, the solution was directly purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 55.1 mg (85%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 2H), 6.85 (dd, J = 8.7, 3.1 Hz, 2H), 5.99 (d, J = 10.2 Hz, 2H), 5.87 (d, J = 9.7 Hz, 2H), 4.57 (s, 1H), 3.78 (s, 3H), 3.73 (t, J = 6.4 Hz, 2H), 2.16 (t, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 137.6, 136.8, 135.8, 127.6, 127.4, 126.9, 114.0, 61.9, 60.5, 60.2, 55.4, 43.2, 41.7, 41.0, 20.4, 13.7; HRMS (ESI) calcd for $C_{15}H_{18}NaO_3$ (M + Na)$^+$ 269.1148, found 269.1145.

2-(4-Hydroxy-4′-methoxy-1,4-dihydro-[1,1′-biphenyl]-1-yl)-ethyl 2-nitrobenzenesulfonate (21). To a solution of "diol" (33.9 mg, 0.14 mmol, 1.0 equiv) in DCM (2.0 mL) at −20 °C was added Et_3N (27.8 mg, 0.28 mmol, 2.0 equiv), followed by DMAP (8.4 mg, 0.07 mmol, 0.5 equiv) and NsCl (33.5 mg, 0.15 mmol, 1.1 equiv). The reaction was followed by TLC. After completion, the solution was directly purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 23.1 mg (40%) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 7.2 Hz, 1H), 7.85−7.72 (m, 4H), 7.16 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.9 Hz, 2H), 6.01 (dd, J = 10.2, 3.2 Hz, 2H), 5.78 (dd, J = 10.2, 1.6 Hz, 2H), 4.54 (s, 1H), 4.34 (t, J = 6.7 Hz, 2H), 3.77 (s, 3H), 2.34 (t, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 136.6, 135.0, 133.9, 132.4, 131.3, 129.5, 128.2, 127.3, 124.8, 114.2, 70.1, 61.9, 55.4, 42.8, 36.9; HRMS (ESI) calcd for $C_{21}H_{21}NNaO_5S$ (M + Na)$^+$ 454.0931, found 454.0930.

2-(4′-Methoxy-4-oxo-1,4-dihydro-[1,1′-biphenyl]-1-yl)ethyl 2-nitrobenzenesulfonate (21bis). To a solution of **21** (22.8 mg, 0.05 mmol, 1.0 equiv) and molecular sieves 4Å in DCM (2.0 mL) at 0 °C was added TPAP (1.8 mg, 0.005 mmol, 0.1 equiv) under stirring, followed by NMO (18.6 mg, 0.16 mmol, 3.0 equiv). The reaction was followed by TLC. After completion, the reaction mixture was diluted with ethyl acetate, filtered through a pad of Celite, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 12.4 mg (55%) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.6 Hz, 1H), 7.86−7.71 (m, 2H), 7.18 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 9.3 Hz, 4H), 6.27 (d, J = 10.1 Hz, 2H), 4.25 (t, J = 6.9 Hz, 2H), 3.79 (s, 3H), 2.62 (t, J = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.4, 159.4, 152.7, 135.2, 132.5, 131,3, 130.2, 129.3, 128.9, 127.5, 124.9, 114.8, 68.5, 55.5, 46.6, 36.3; IR υ (cm^{-1}) 1667, 1543, 1511, 1255, 1369, 1214; HRMS (ESI) calcd for $C_{21}H_{19}NNaO_5S$ (M + Na)$^+$ 452.0774, found 452.0772.

3a-(4-Methoxyphenyl)-1-methyl-3,3a,7,7a-tetrahydro-1*H*-indol-6(2*H*)-one, *O*-Methylsceletenone (1a). To a solution of "dienone" (11.5 mg, 0.027 mmol, 1.0 equiv) in THF (1.0 mL) at room temperature was added aqueous $MeNH_2$ (8.3 mg, 0.27 mmol, 10.0 equiv) under stirring. The reaction was followed by TLC. After completion, water was added to the solution. The phases were separated and the aqueous phase was extracted with EtOAc. The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of ethyl acetate/methanol to afford *O*-methylsceletenone **1** in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.72 (dd, J = 10.1, 1.7 Hz, 1H), 6.10 (d, J = 10.1 Hz, 1H), 3.81 (s, 3H), 3.31 (t, J = 7.9 Hz, 1H), 2.68−2.37 (m, 5H), 2.32 (s, 3H), 2.26−2.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 158.7, 153.9, 135.3, 127.9, 126.6, 114.3, 73.9, 56.2, 55.5, 50.8, 40.2, 38.8, 36.3; IR υ (cm^{-1}) 1649, 1216; HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ (M + H)$^+$ 258.1489, found 258.1488.

Sceletenone (1b). To a solution of **1a** (4.2 mg, 0.016 mmol, 1.0 equiv) in DCM (1.0 mL) at 0 °C under argon was added BBr_3 (12.3 mg, 0.049 mmol, 3.0 equiv) under stirring. The reaction was followed by TLC. After completion, $NaHCO_3$ was added to the solution. The phases were separated, and the aqueous phase was extracted with DCM. The organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by silica gel chromatography with a mixture of DCM/methanol to afford **1b** in quantitative yield. ^{1}H NMR (300 MHz, CDCl3) δ 7.22 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 10.1 Hz, 1H), 6.10 (d, J = 10.1 Hz, 1H), 3.31 (t, J = 7.9 Hz, 1H), 2.63 (d, J = 7.6 Hz, 1H), 2.47 (ddd, J = 21.7, 14.2, 10.1 Hz, 4H), 2.32 (s, 3H), 2.26−2.13 (m,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 154.9, 154.1, 135.2, 128.1, 126.7, 115.8, 73.9, 56.2, 50.8, 40.2, 38.7, 36.2; IR υ (cm^{-1}) 3403, 1648, 1215; HRMS (ESI) calcd for $C_{15}H_{17}NO_2Na$ (M + Na)$^+$ 266.1151, found 266.1147.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: canesi.sylvain@uqam.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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.

■ REFERENCES

(1) (a) Jeffs, W.; Capps, T. M.; Johnson, D. B.; Karle, J. M.; Martin, N. H.; Rauckman, B. *J. Org. Chem.* **1974**, *39*, 2703. (b) Sanchez, I. H.; Larraza, M. I.; Flores, H. J.; Rojas, I.; Alcala, R. *Synth. Commun.* **1983**, *13*, 35. (c) Jeffs, P. W.; Karle, J. M.; Martin, N. H. *Phytochemistry* **1978**, *17*, 719. (d) Gaffney, C. D. Dissertation, University of Johannesburg, 2008.

(2) (a) Bazhenova, E. D.; Aliev, Kh. U.; Zakirov, U. B. *Farmakol. Alkaloidov Ikh. Proizvod.* **1972**, 74. (b) Shieh, W. C.; Carlson, J. A. *J. Org. Chem.* **1994**, *59*, 5463.

(3) Gorman, M.; Neuss, N.; Biemann, K. *J. Am. Chem. Soc.* **1962**, *84*, 1058.

(4) (a) Guérard, K. C.; Sabot, C.; Racicot, L.; Canesi, S. *J. Org. Chem.* **2009**, *74*, 2039. (b) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941. (c) Guérard, K. C.; Chapelle, C.; Giroux, M. A.; Sabot, C.; Beaulieu, M. A.; Achache, N.; Canesi, S. *Org. Lett.* **2009**, *11*, 4756. (d) Guérard, K. C.; Sabot, C.; Beaulieu, M. A.; Giroux, M. A.; Canesi, S. *Tetrahedron* **2010**, *66*, 5893. (e) Andrez, J. A.; Giroux, M. A.; Lucien, J.; Canesi, S. *Org. Lett.* **2010**, *12*, 4368. (f) Beaulieu, M. A.; Sabot, C.; Achache, N.; Guérard, K. C.; Canesi, S. *Chem.—Eur. J.* **2010**, *16*, 11224. (g) Desjardins, S.; Andrez, J. A.; Canesi, S. *Org. Lett.* **2011**, *13*, 3406. (h) Beaulieu, M. A.; Guérard, K. C.; Maertens, G.; Sabot, C.; Canesi, S. *J. Org. Chem.* **2011**, *76*, 9460. (i) Guérard, K. C.; Guerinot, A.; Bouchard-Aubin, C.; Ménard, M. A.; Lepage, M.; Beaulieu, M. A.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 2121.

(5) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (c) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5854. (d) Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T. *Chem. Commun.* 1996, 1481. (e) Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698. (f) Arisawa, M.; Utsumi, S.; Nakajima, M.; Ramesh, N. G.; Tohma, H.; Kita, Y. *Chem. Commun.* **1999**, 469. (g) Akai, S.; Kawashita, N.; Morita, N.; Nakamura, Y.; Iio, K.; Kita, Y. *Heterocycles* **2002**, *58*, 75. (h) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787. (i) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (j) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797.

(k) Fujioka, H.; Komatsu, H.; Nakamura, T.; Miyoshi, A.; Hata, K.; Ganesh, J.; Murai, K.; Kita, Y. *Chem. Commun.* **2010**, *46*, 4133. (l) Dohi, T.; Kato, D.; Hyodo, R.; Yamashita, D.; Shiro, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 3784.

(6) (a) Vanderlaan, D. G.; Schwartz, M. A. *J. Org. Chem.* **1985**, *50*, 743. (b) Lewis, N.; Wallbank, P. *Synthesis* **1987**, 1103. (c) *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis*; Wirth, T., Ed.; Springer: New York, 2003; Topics in Current Chemistry Vol. 224. (d) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135. (e) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, *24*, 3759. (f) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (g) Quideau, S.; Looney, M. A.; Pouységu, L. *Org. Lett.* **1999**, *1*, 1651. (h) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (i) Liang, H.; Ciufolini, M. A. *Chem.—Eur. J.* **2010**, *16*, 13262. (j) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534. (k) Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M. A. *Tetrahedron* **2001**, *57*, 319. (l) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336. (m) Quideau, S.; Pouységu, L.; Deffieux, D. *Curr. Org. Chem.* **2004**, *8*, 113. (n) Silva, L. F., Jr.; Siqueira, F. A.; Pedrozo, E. C.; Vieira, F. Y. M.; Doriguetto, A. C. *Org. Lett.* **2007**, *9*, 1433. (o) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, 467. (p) Liang, H.; Ciufolini, M. A. *J. Org. Chem.* **2008**, *73*, 4299. (q) Giroux, M. A.; Guérard, K. C.; Beaulieu, M. A.; Sabot, C.; Canesi, S. *Eur. J. Org. Chem.* **2009**, 3871. (r) Peuchmaur, M.; Saidani, N.; Botté, C.; Maréchal, E.; Vial, H.; Wong, Y. S. *J. Med. Chem.* **2008**, *51*, 4870. (s) Mendelsohn, B. A.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 4736. (t) Jen, T.; Mendelsohn, B. A.; Ciufolini, M. A. *J. Org. Chem.* **2011**, *76*, 728. (u) Traoré, M.; Ahmed-Ali, S.; Peuchmaur, M.; Wong, Y. S. *J. Org. Chem.* **2011**, *76*, 1409.

(7) (a) Pelter, A.; Drake, R. A. *Tetrahedron Lett.* **1988**, *29*, 4181. (b) Quideau, S.; Looney, M. A.; Pouységu, L. *J. Org. Chem.* **1998**, *63*, 9597. (c) Ozanne-Beaudenon, A.; Quideau, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7065. (d) Ciufolini, M. A.; Canesi, S.; Ousmer, M.; Braun, N. A. *Tetrahedron* **2006**, *62*, 5318. (e) Bérard, D.; Jean, A.; Canesi, S. *Tetrahedron Lett.* **2007**, *48*, 8238. (f) Jean, A.; Cantat, J.; Bérard, D.; Bouchu, D.; Canesi, S. *Org. Lett.* **2007**, *9*, 2553. (g) Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A. M.; Miqueu, K.; Sotiropoulos, J. M.; Quideau, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3552. (h) Bérard, D.; Racicot, L.; Sabot, C.; Canesi, S. *Synlett* **2008**, 1076. (i) Pouységu, L.; Marguerit, M.; Gagnepain, J.; Lyvinec, G.; Eatherton, A. J.; Quideau, S. *Org. Lett.* **2008**, *10*, 5211. (j) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539. (k) Quideau, S.; Lyvinec, G.; Marguerit, Bathany, K.; Ozanne-Beaudenon, A.; Bufeteau, T.; Cavagnat, D.; Chenede, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605. (l) Liang, H.; Ciufolini, M. A. *Org. Lett.* **2010**, *12*, 1760. (m) Traoré, M.; Ahmed-Ali, S.; Peuchmaur, M.; Wong, Y. S. *Tetrahedron* **2010**, *66*, 5863. (n) Liang, H.; Ciufolini, M. A. *Tetrahedron* **2010**, *66*, 5884. (o) Pouységu, L.; Sylla, T.; Garnier, T.; L. B. Rojas, L. B.; Charris, J.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 5908. (p) Dylan Turner, C.; Ciufolini, M. A. *ARKIVOC* **2011**, *1*, 410. (q) Chau, J.; Ciufolini, M. A. *Mar. Drugs* **2011**, *9*, 2016. (r) Liang, H; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11849.

(8) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775.

(9) (a) Popelak, A.; Haack, E.; Lettenbauer, G.; Spingler, H. *Naturwissenschaften* **1960**, *47*, 156. (b) Smith, E.; Hosansky, N.; Shamma, M.; Moss, J. B. *Chem. Ind* **1961**, 402. (c) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711. (d) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143.

(10) Nakajima, R.; Ono, M.; Aiso, S.; Akita, H. *Chem. Pharm. Bull* **2005**, *53*, 684.

(11) Gu, Q.; You, S. L. *Chem. Sci.* **2011**, *2*, 1519.

dx.doi.org/10.1021/jo301408j | *J. Org. Chem.* XXXX, XXX, XXX−XXX

ANNEXE B :

"OXYDATIVE *IPSO*-REARRANGEMENT PERFORMED BY A HYPERVALENT IODINE REAGENT AND ITS APPLICATION" SUPPORTING INFORMATION

Journal of Organic Chemistry, **2012**, *77*, page 7588–7594

DOI: 10.1021/jo301408j

Date de publication (Web) : 6 Août 2012

http://pubs.acs.org/doi/suppl/10.1021/jo301408j/suppl_file/jo301408j_si_001.pdf

Titre: Oxydative Ipso-Rearrangement Performed by a Hypervalent Iodine reagent and Its Application.

Auteurs: Guillaume Jacquemot et Sylvain Canesi*

Oxidative *Ipso*-Rearrangement Performed by a Hypervalent Iodine Reagent and Its Application

Guillaume Jacquemot and Sylvain Canesi*

Laboratoire de Méthodologie et Synthèse de Produit Naturels.
Université du Québec à Montréal, C.P.8888, Succ. Centre-Ville, Montréal. H3C 3P8,
Québec, Canada.

Supporting Information

Table of Contents

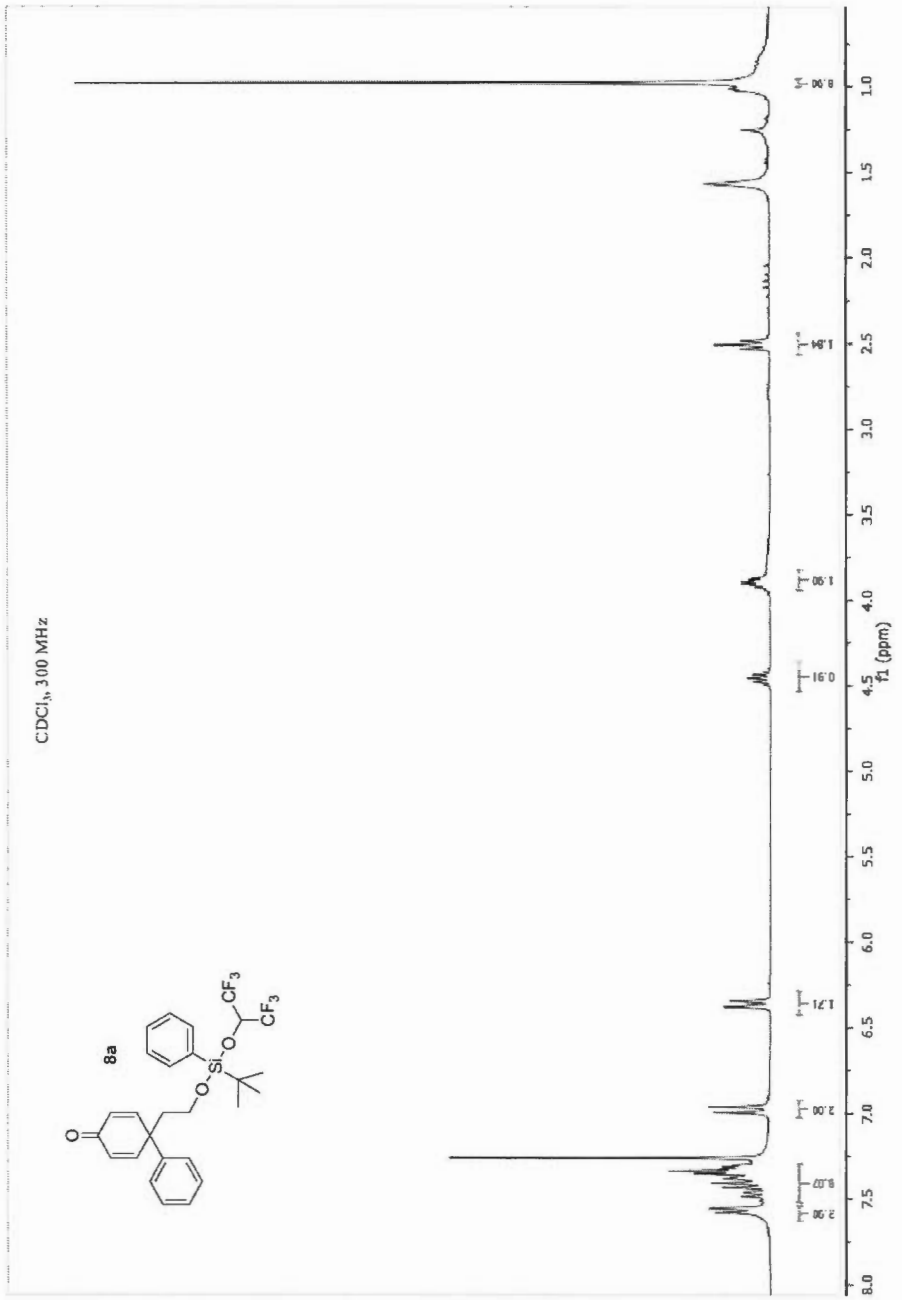
1. General information -S1-

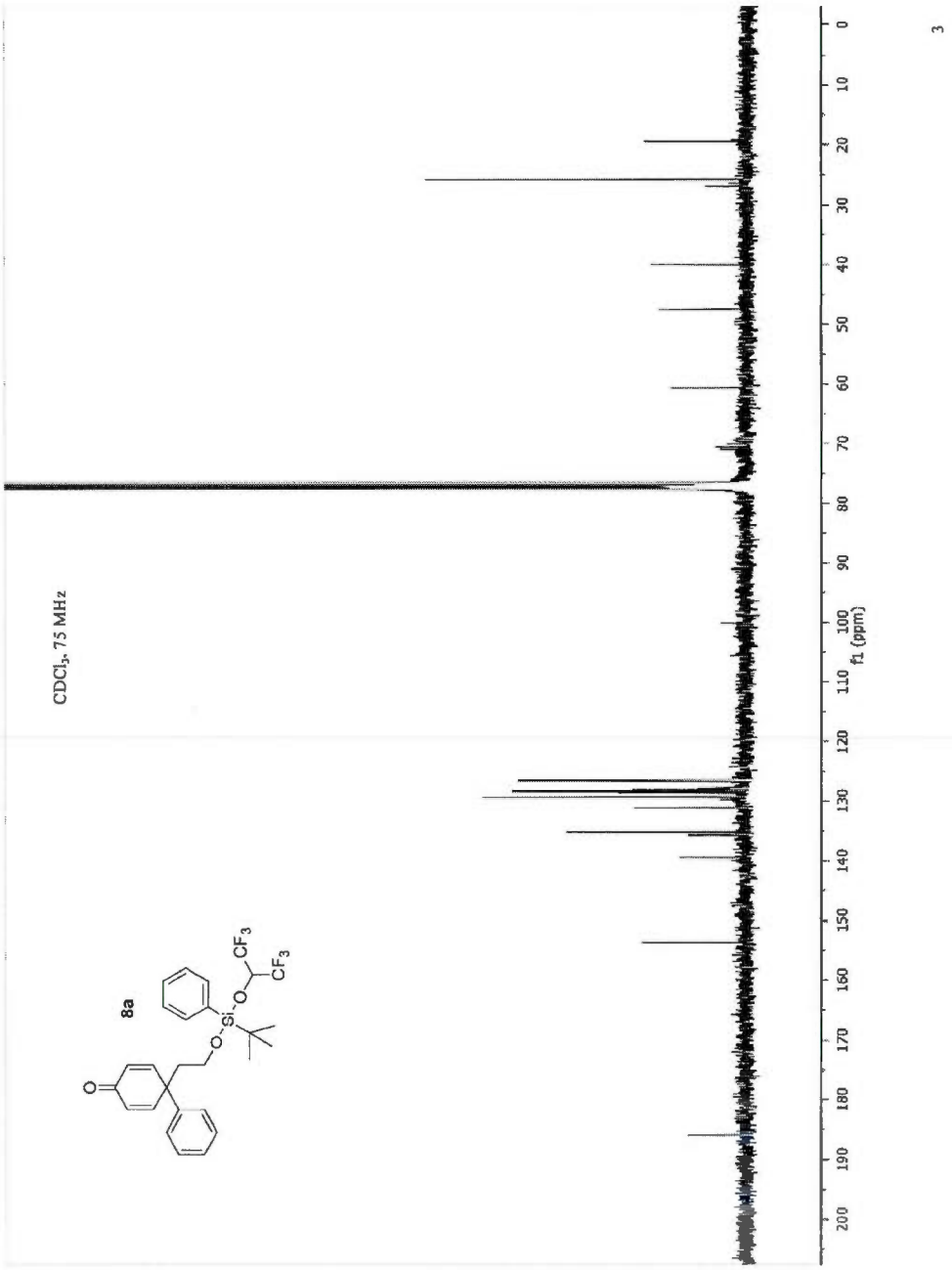
2. Copies of ^{1}H and ^{13}C NMR spectra for all compounds -S2-S-35

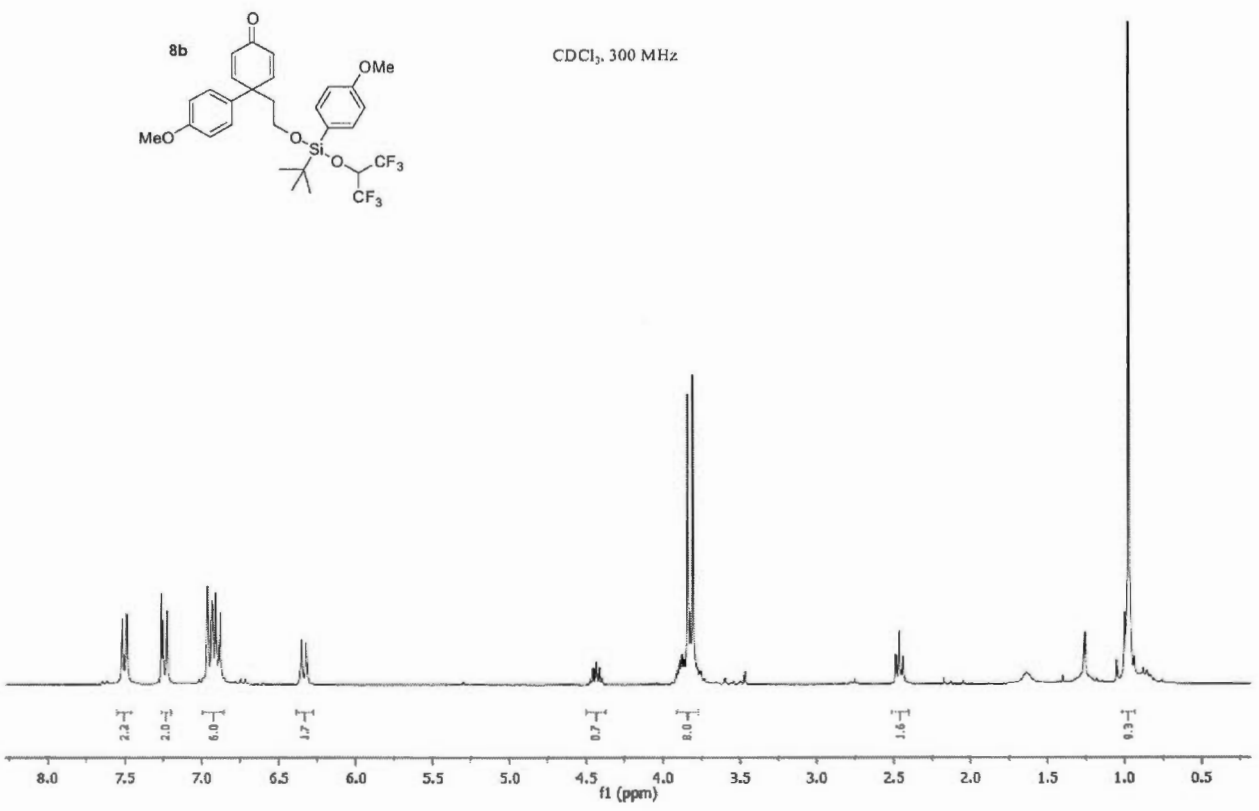
I. General information and materials

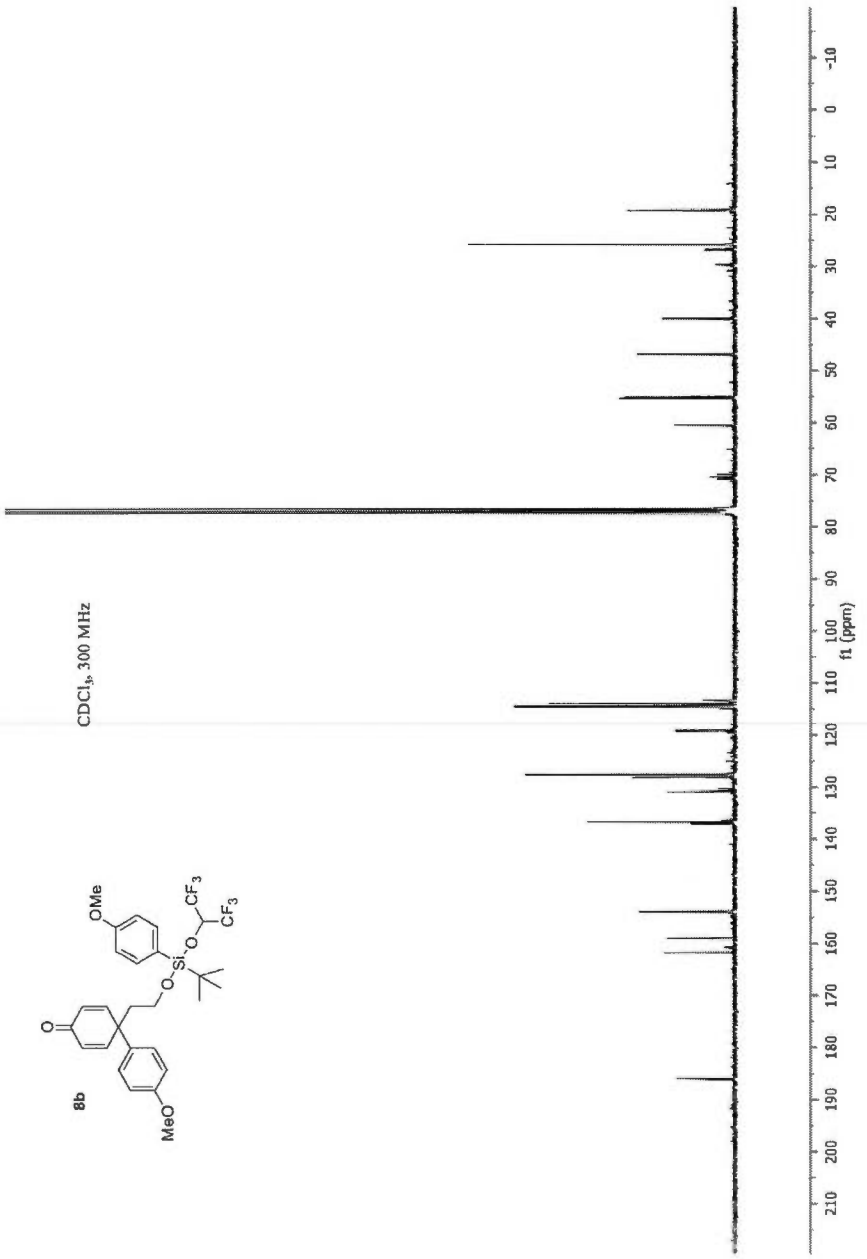
Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets,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

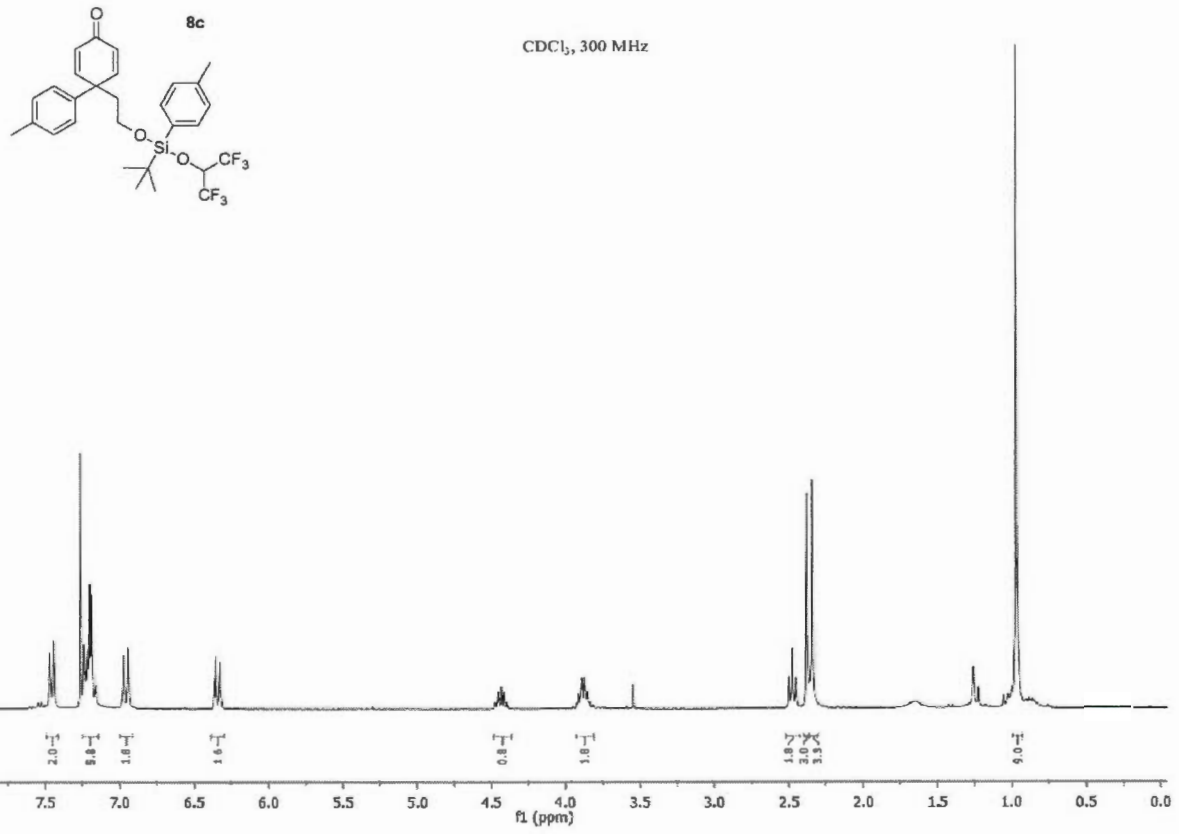
II. Copies of ^{1}H and ^{13}C NMR spectra

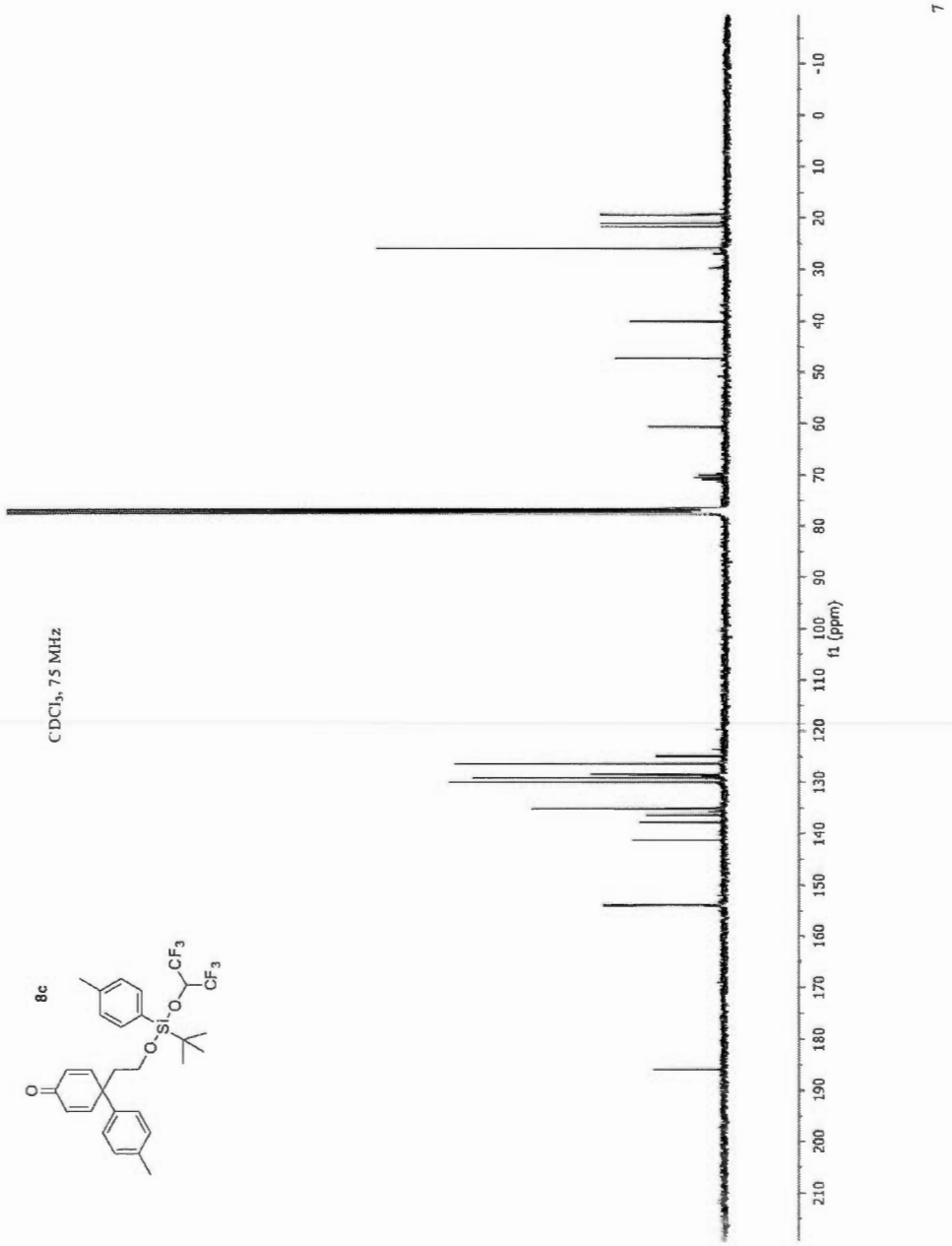

CDCl3, 300 MHz
8a
O
O
Si
O
CF3
CF3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

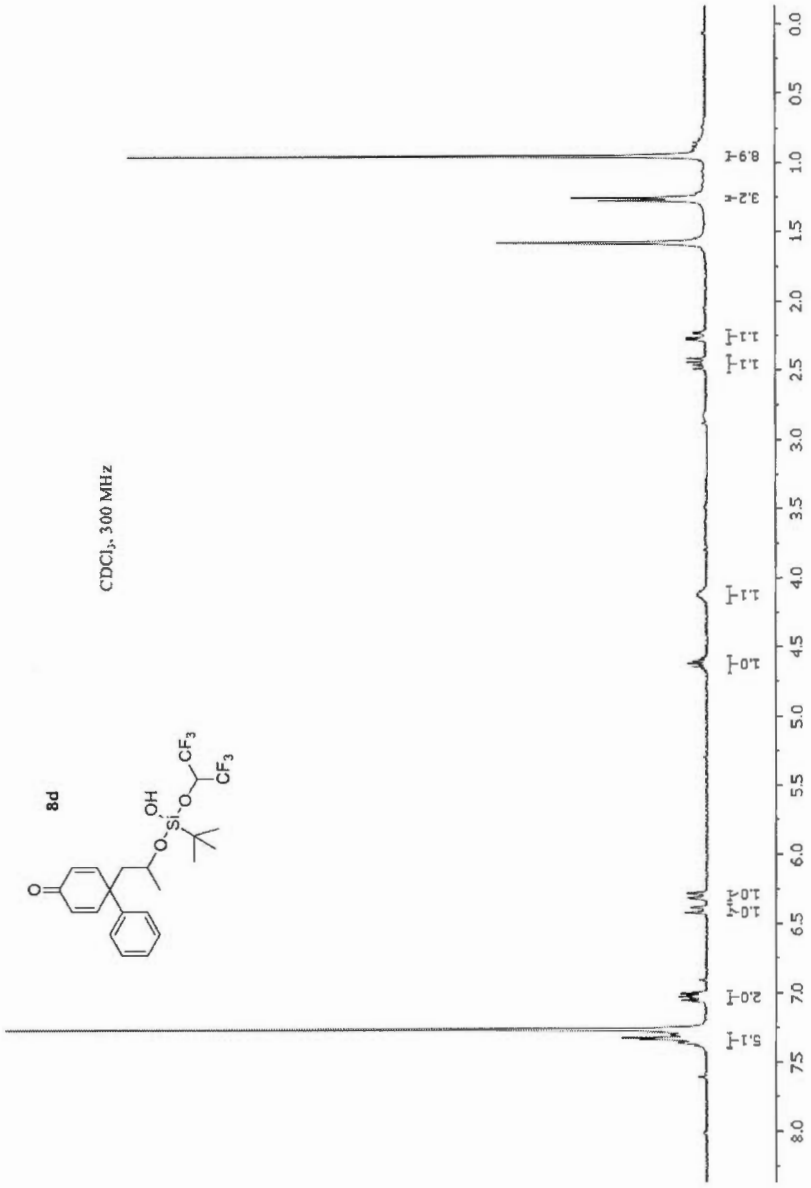

CDCl3, 75 MHz
8a
O
O
Si
O
CF3
CF3
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

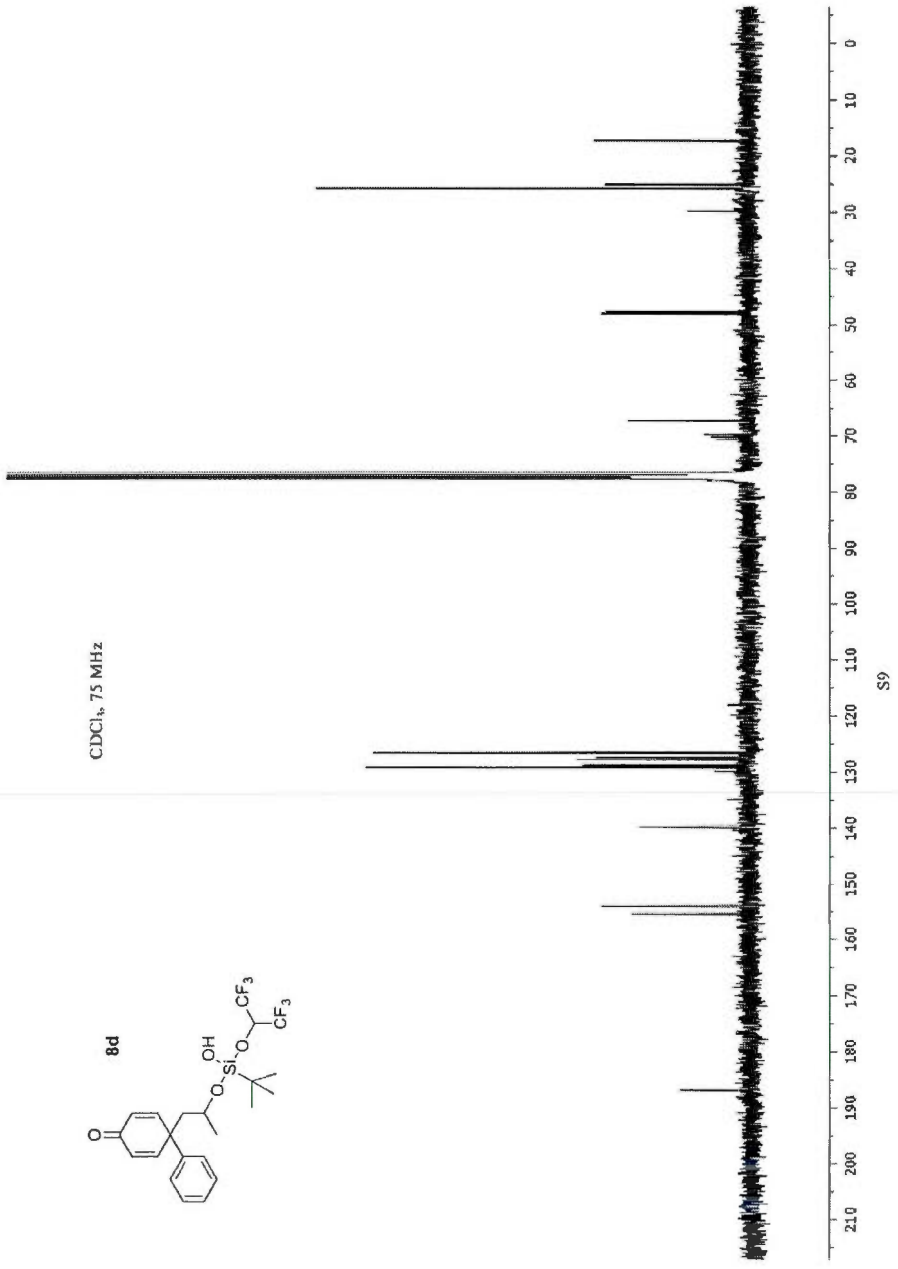

8b
O
OMe
MeO
O
Si
O
CF3
CF3
CDCl3, 300 MHz
2.2
2.0
6.0
1.7
0.7
8.0
1.6
9.3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

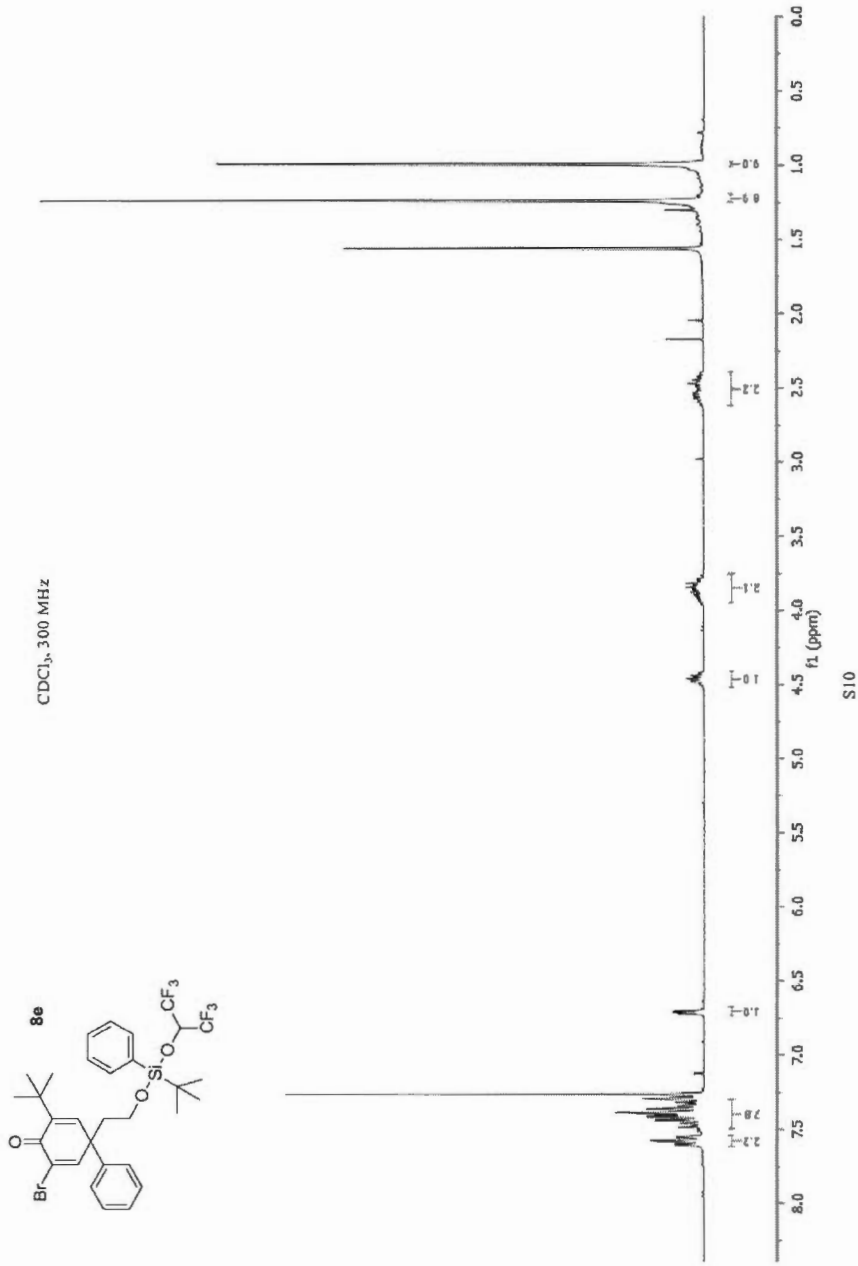

CDCl3, 300 MHz
f1 (ppm)
8b
OMe
MeO
O
Si
O
CF3
CF3

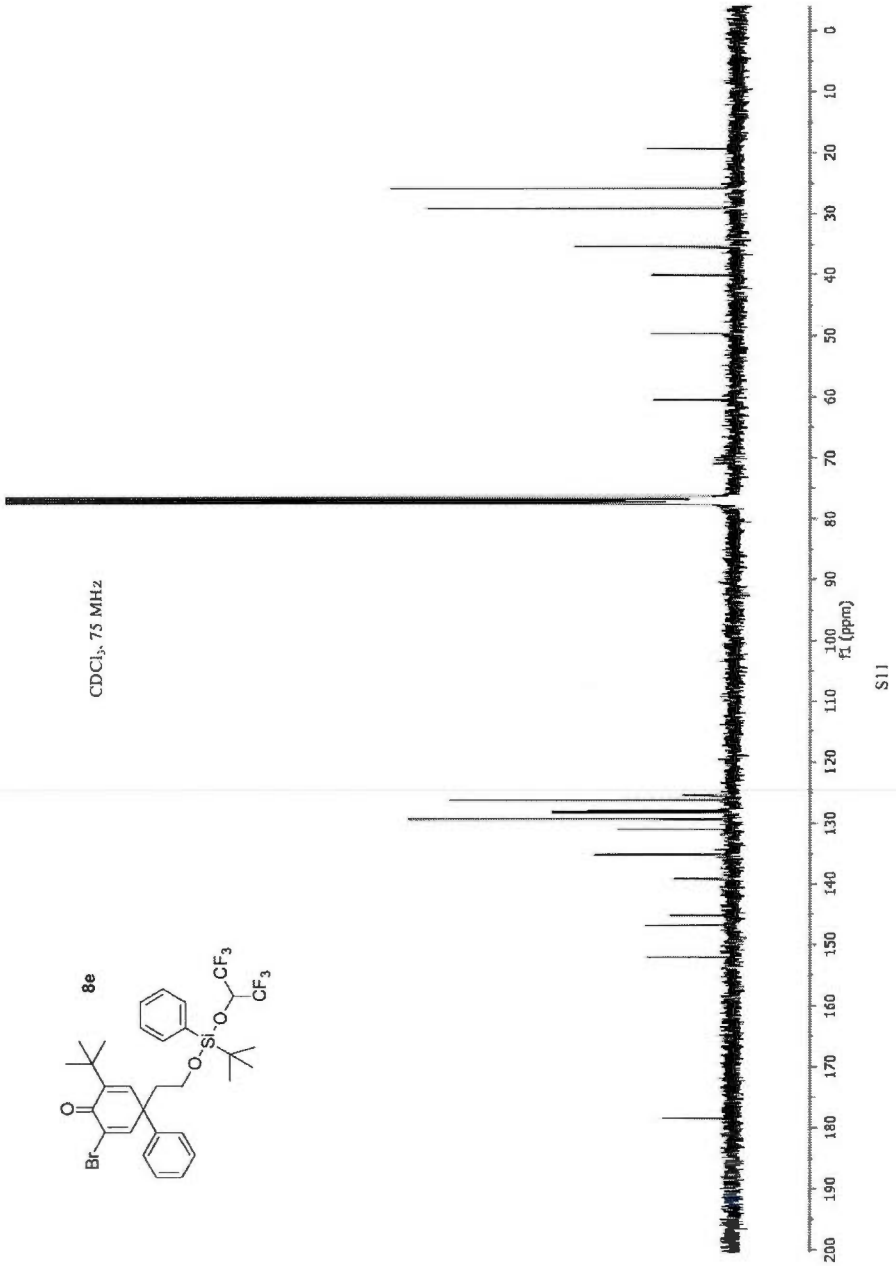

8c
CDCl3, 300 MHz
f1 (ppm)

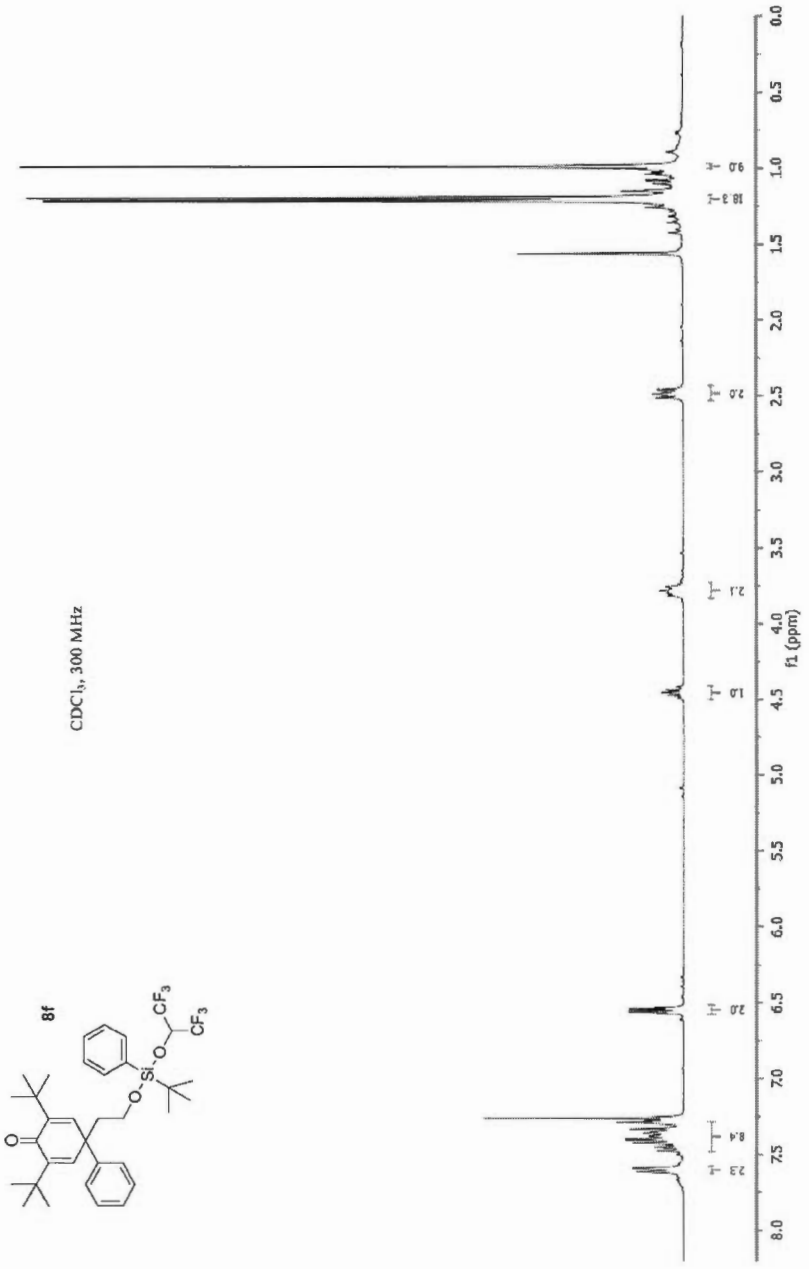

8c
CDCl3, 75 MHz
f1 (ppm)

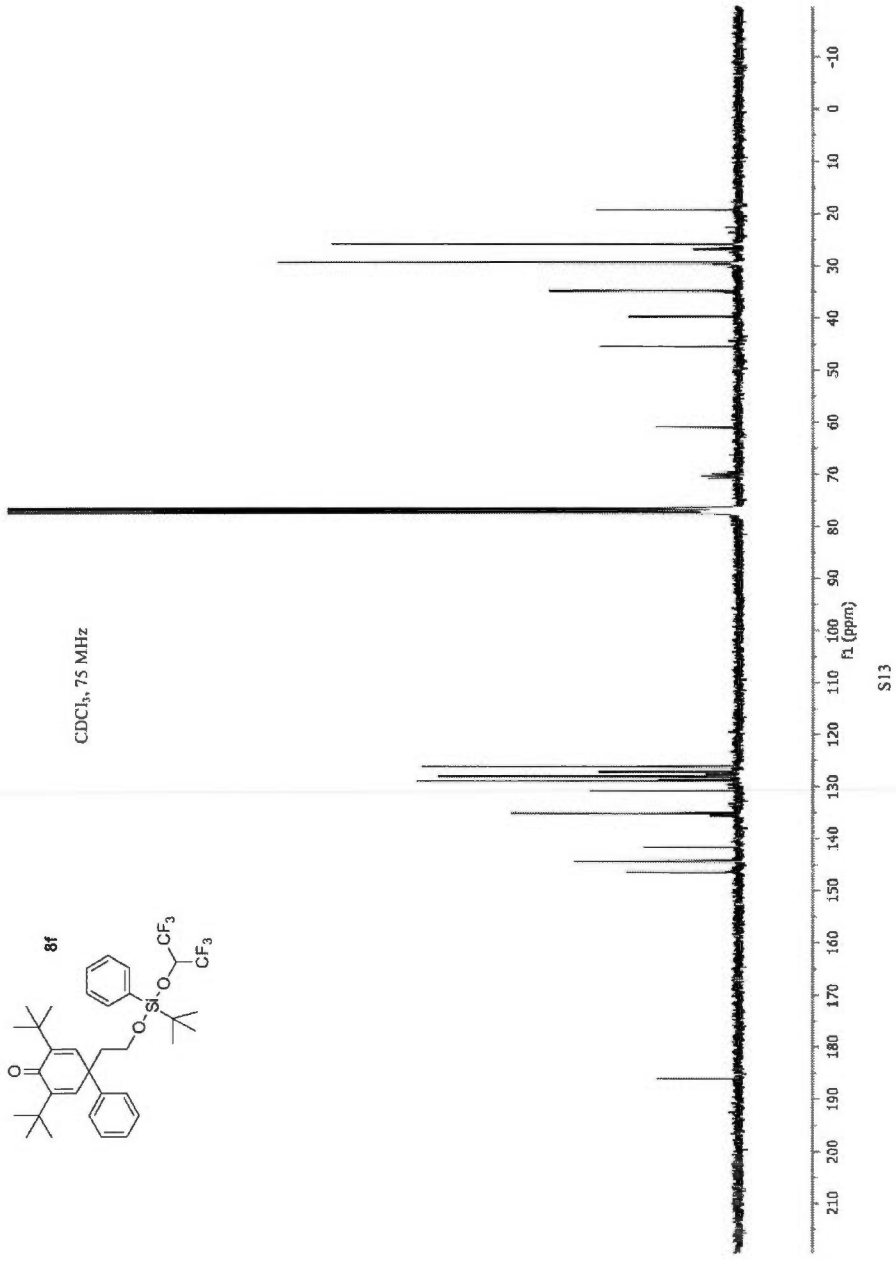

8d
CDCl3, 300 MHz
OH
Si
O
CF3
CF3
O
8.9
3.2
1.1
1.1
1.0
1.1
1.0
1.0
2.0
5.1
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0

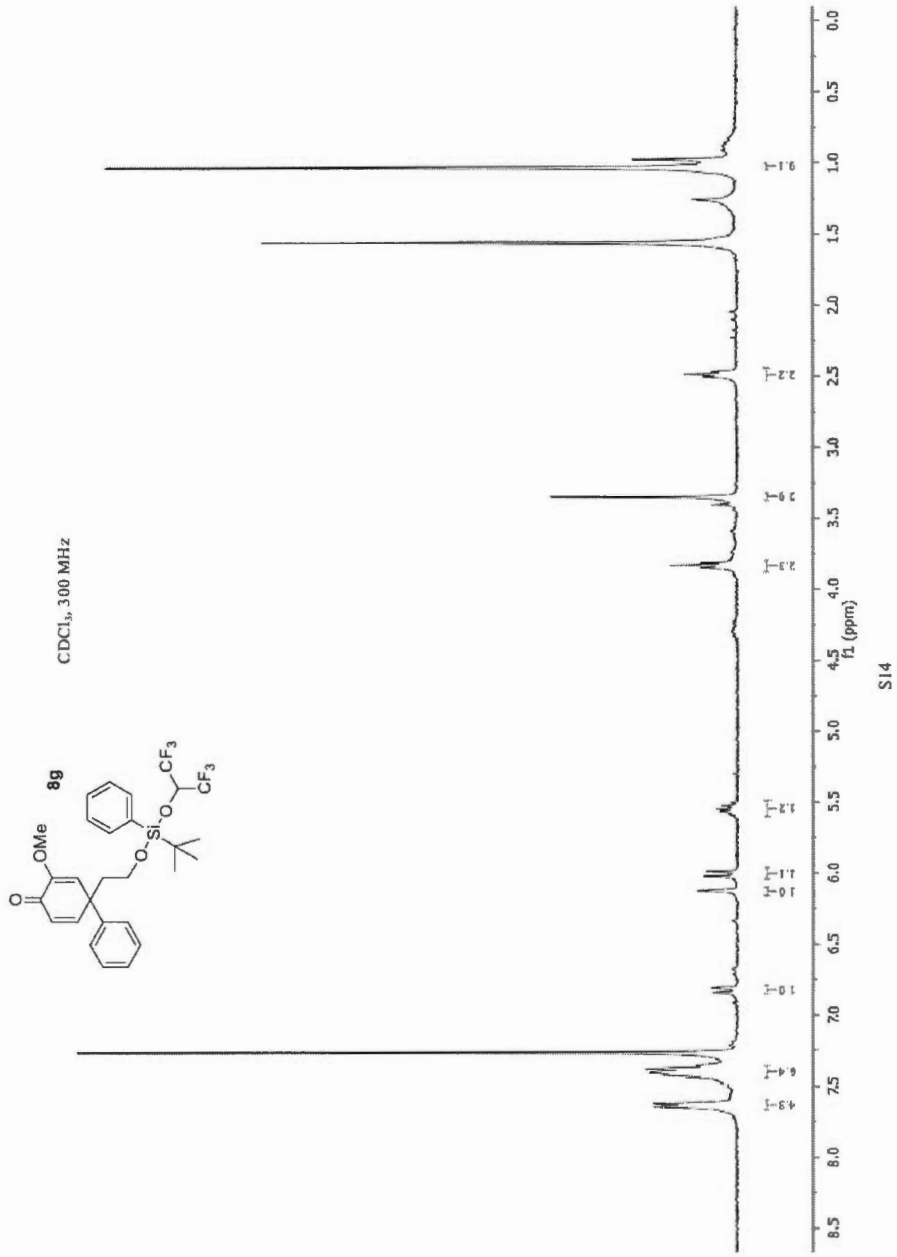

8d
OH
Si
O
CF3
CF3
CDCl3, 75 MHz
S9

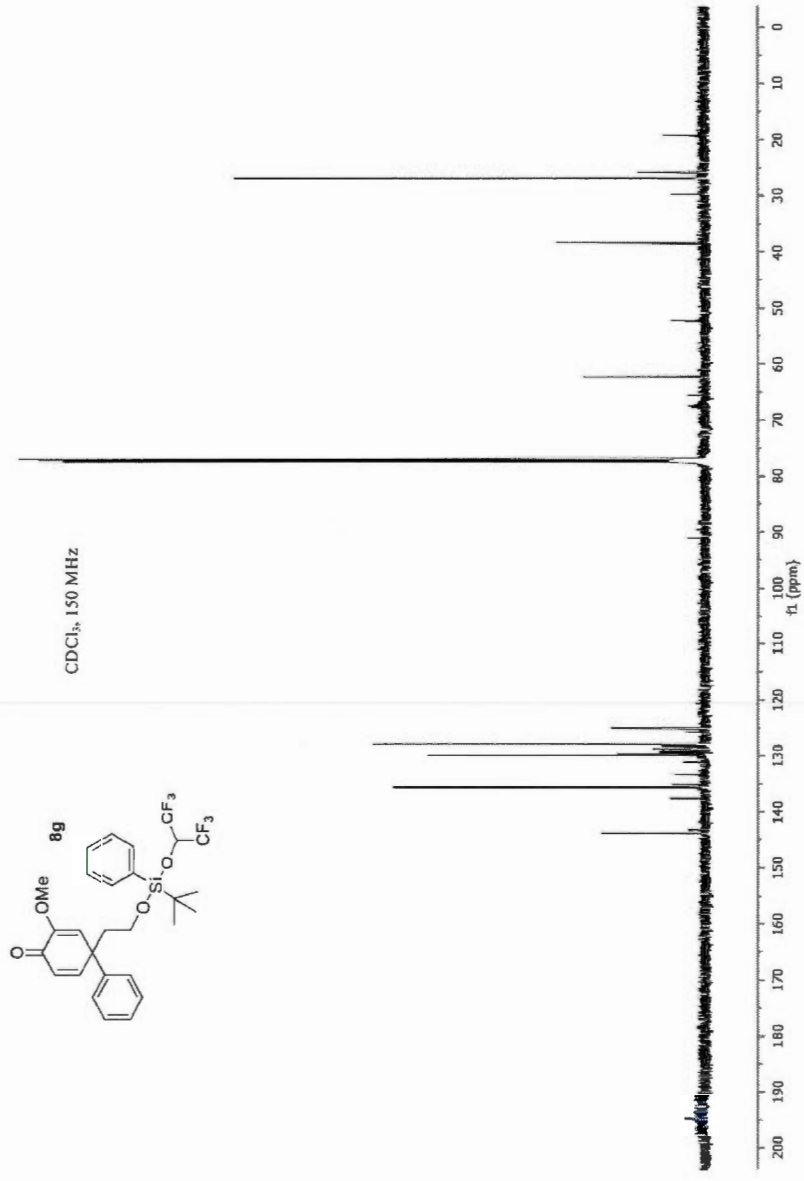

8e
CDCl3, 300 MHz
f1 (ppm)
S10

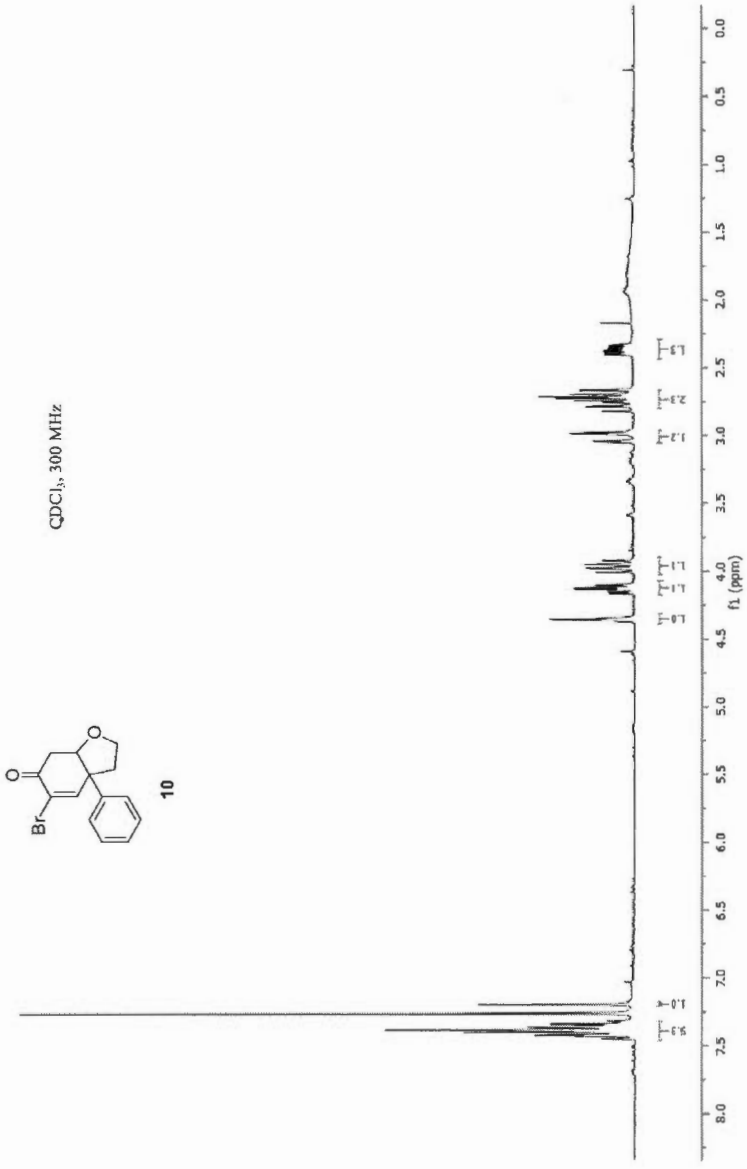

8e
Br
O
Si
O
CF3
CF3
CDCl3, 75 MHz
f1 (ppm)
S11

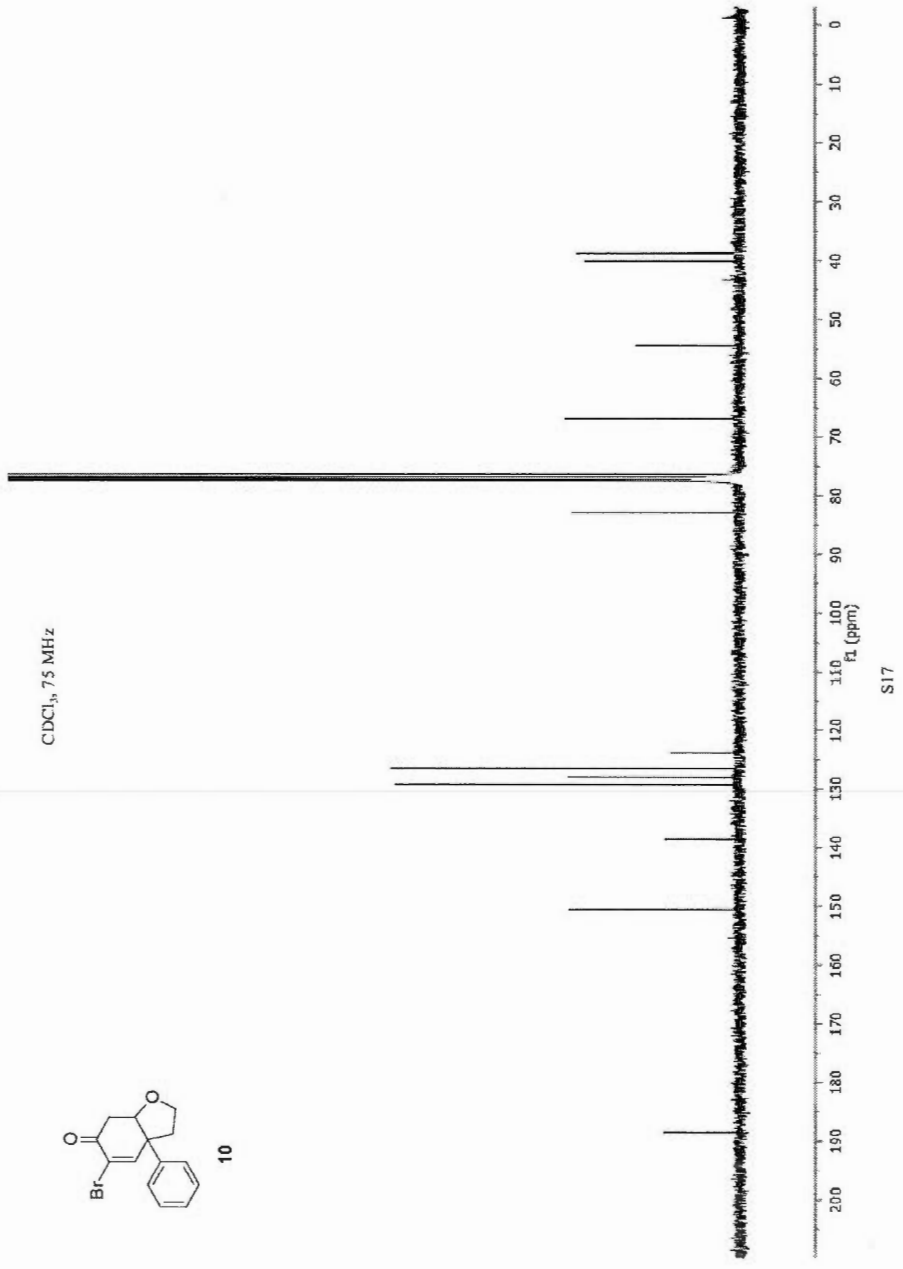

8f
CDCl3, 300 MHz
f1 (ppm)
S12

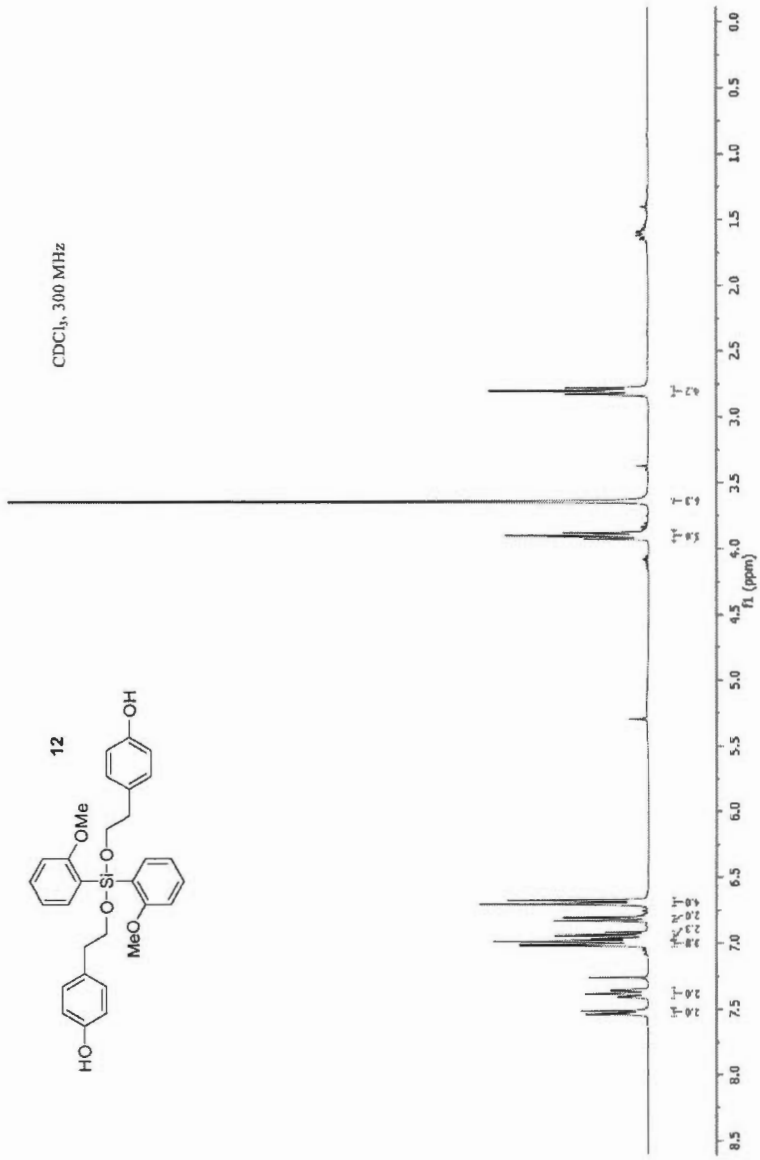

8f
CDCl3, 75 MHz
F1 (ppm)
S13

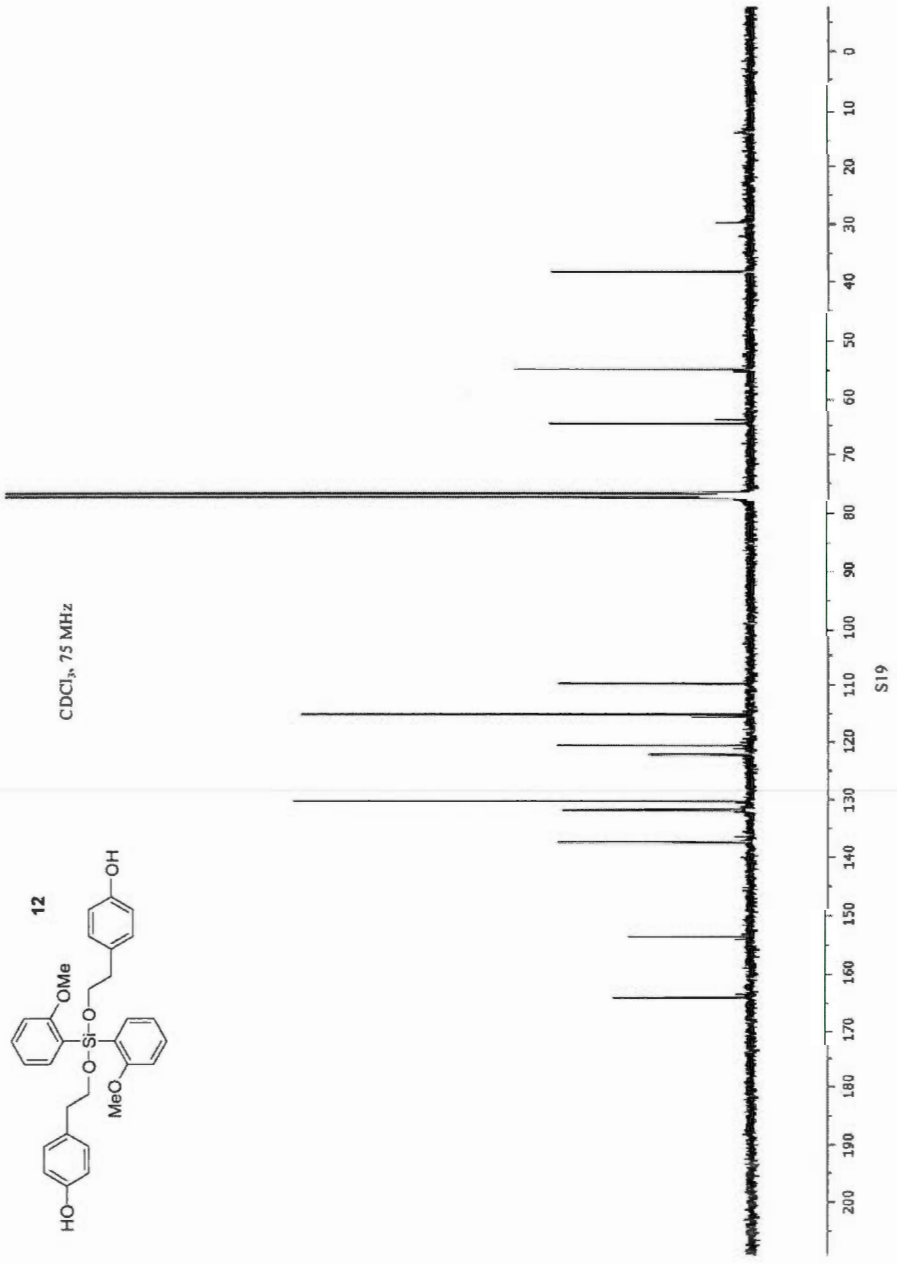

8g
CDCl3, 300 MHz
OMe
O
O
Si
O
CF3
CF3
f1 (ppm)
S14

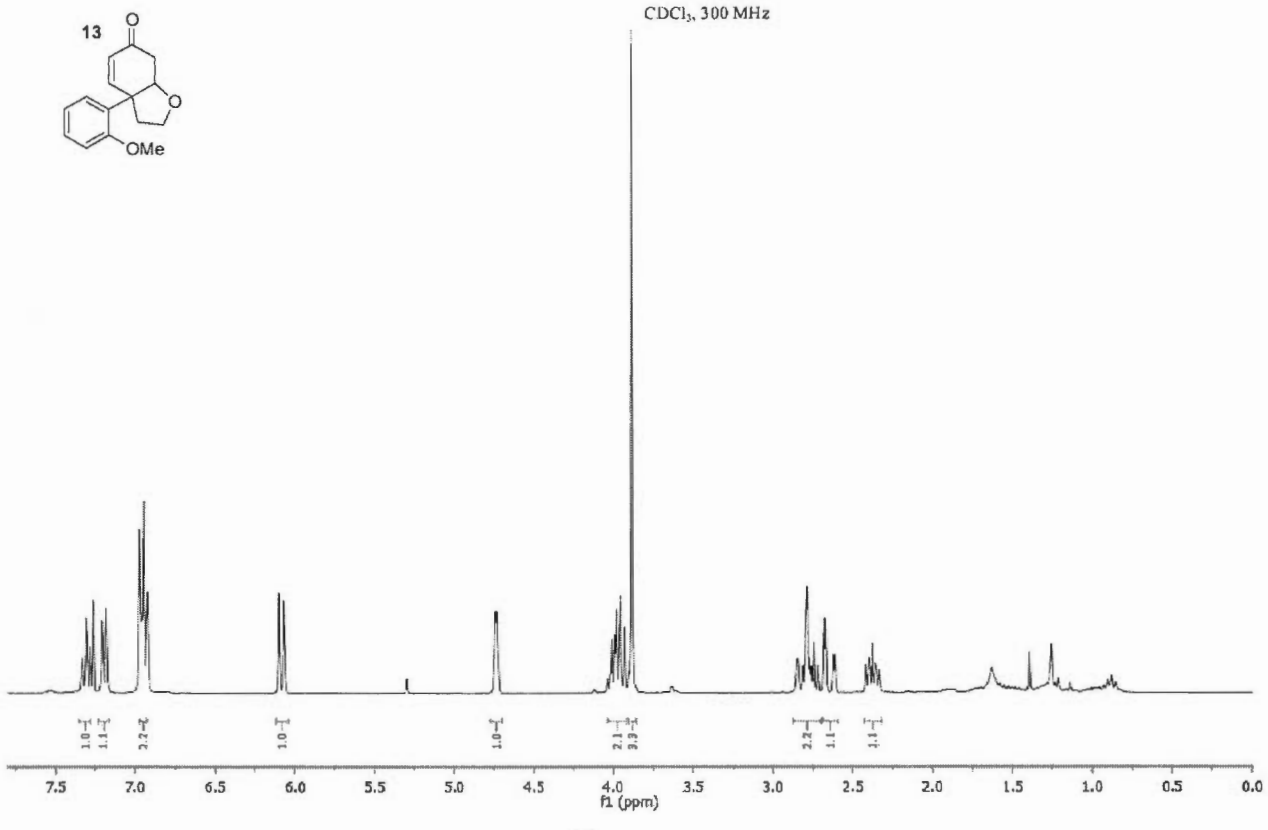

8g
CDCl3, 150 MHz
f1 (ppm)


CDCl3, 300 MHz
Br
O
O
10
f1 (ppm)
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


CDCl3, 75 MHz
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
O
Br
10
S17


12
CDCl3, 300 MHz
OMe
MeO
HO
OH
Si
O
f1 (ppm)

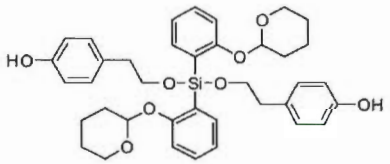

12
OMe
OH
Si
O
MeO
HO
CDCl3, 75 MHz
S19


13
O
O
OMe
CDCl3, 300 MHz
1.0
1.1
2.2
1.0
1.0
2.1
3.3
2.2
1.1
1.1
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)

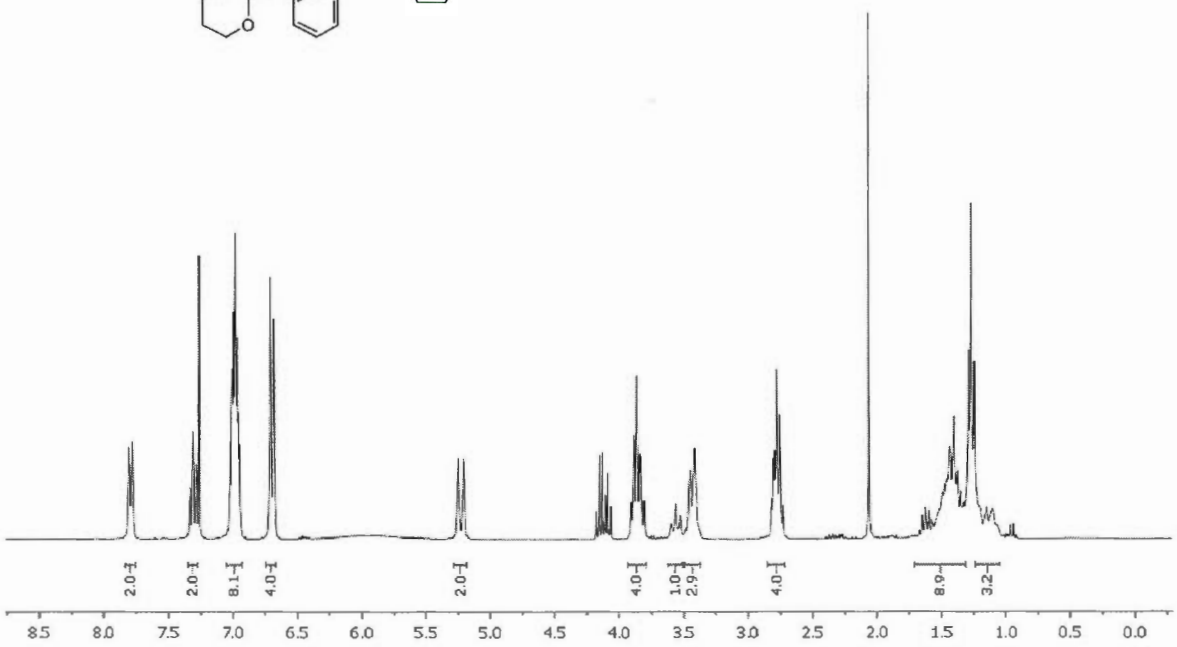
S20

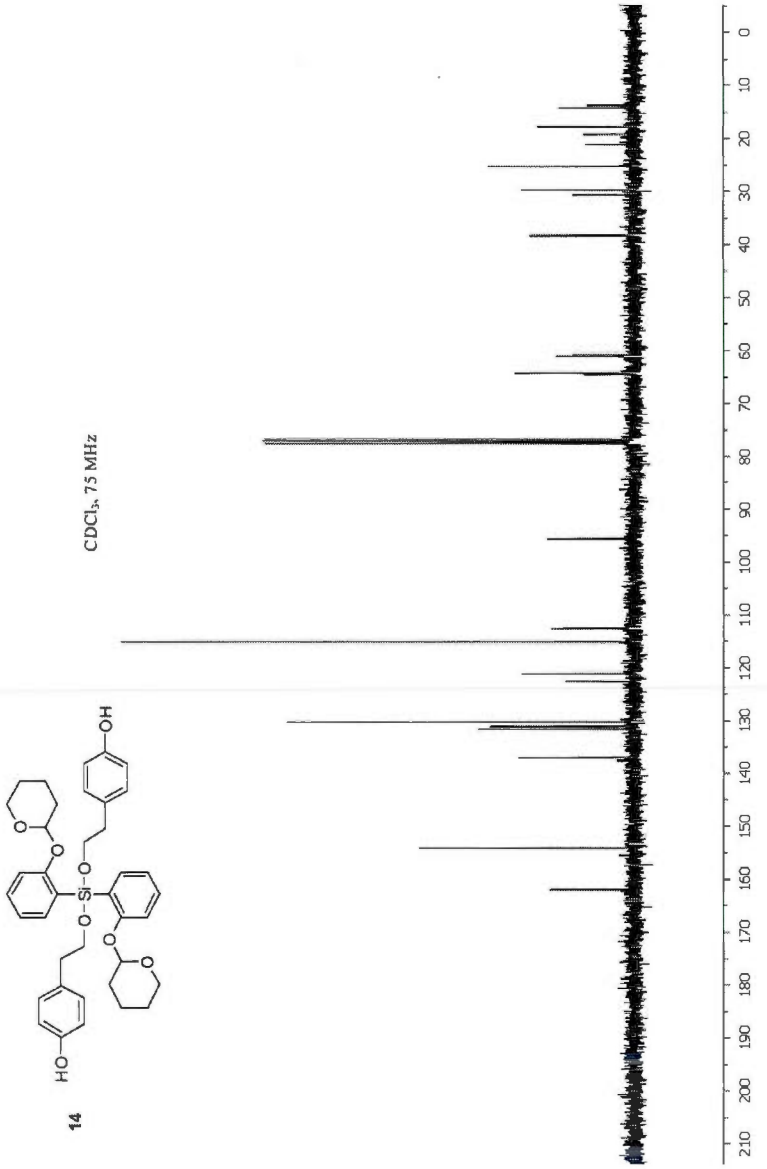
13
OMe
O
CDCl3, 75 MHz
f1 (ppm)
S21

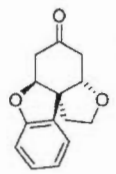
14



$CDCl_3$, 300 MHz

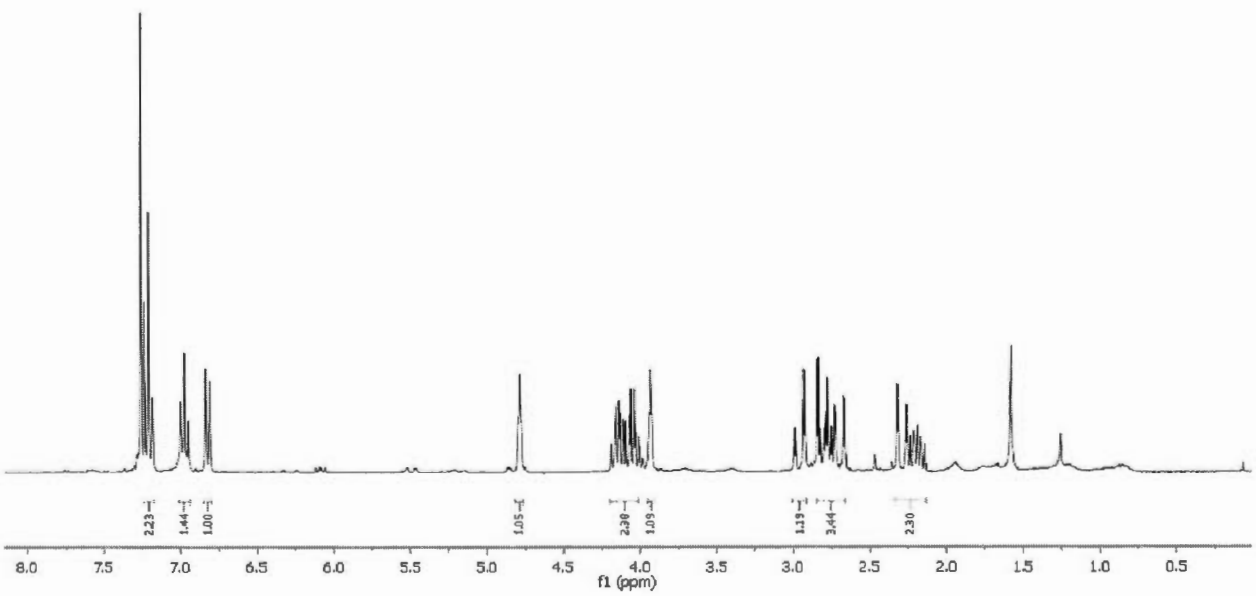


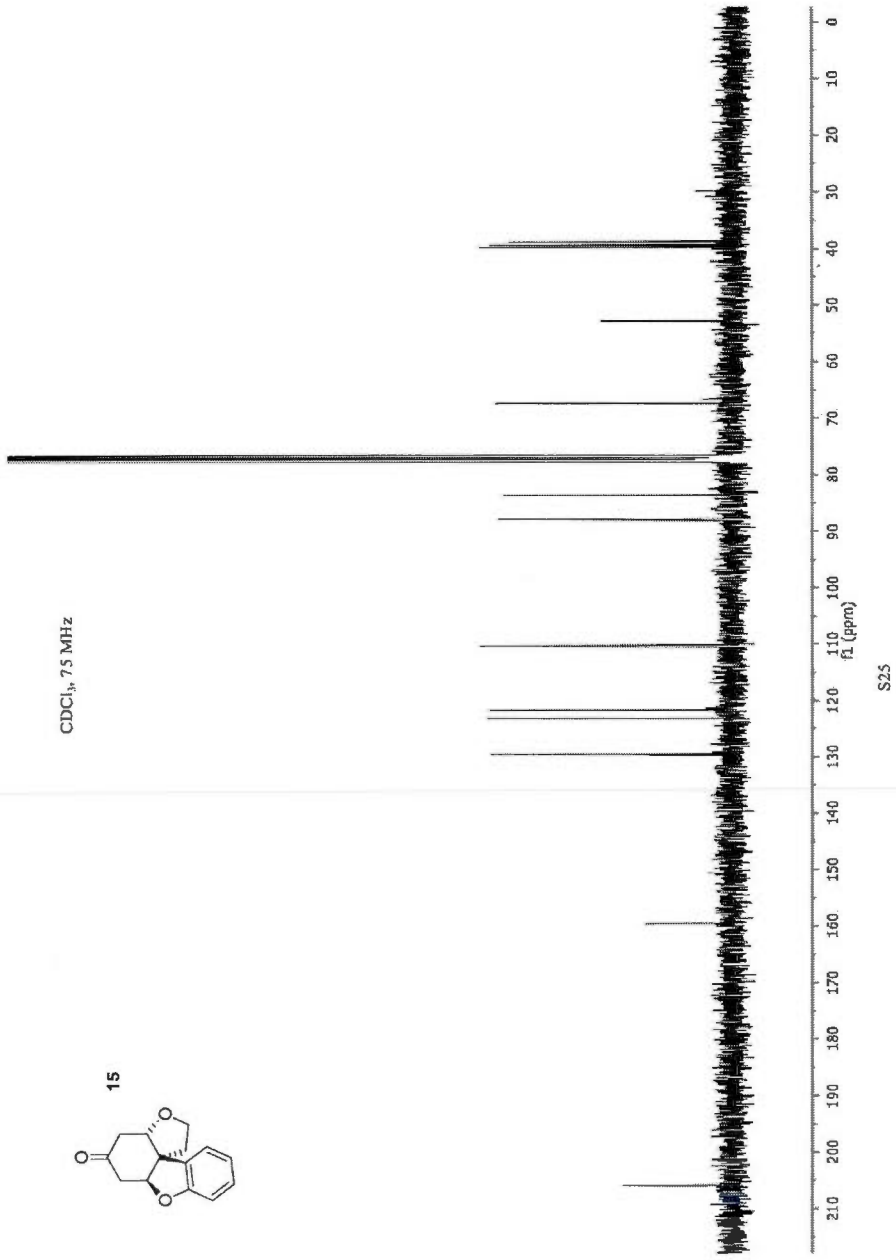

CDCl3, 75 MHz
14
S23

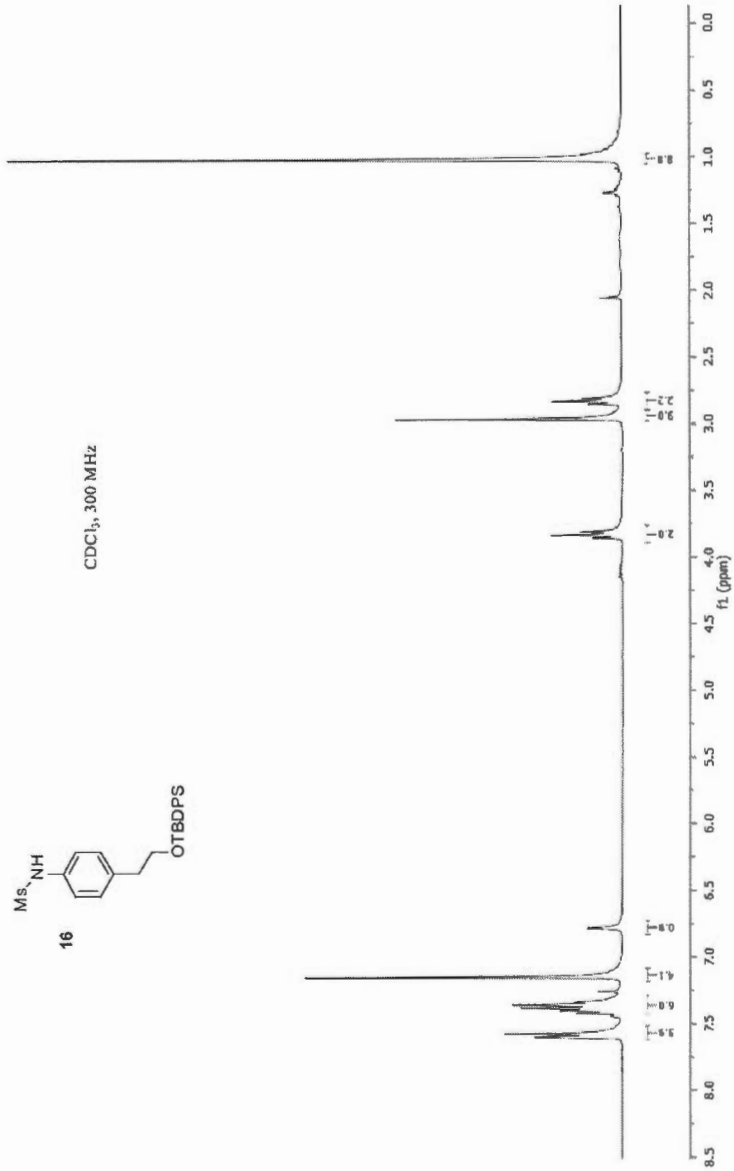


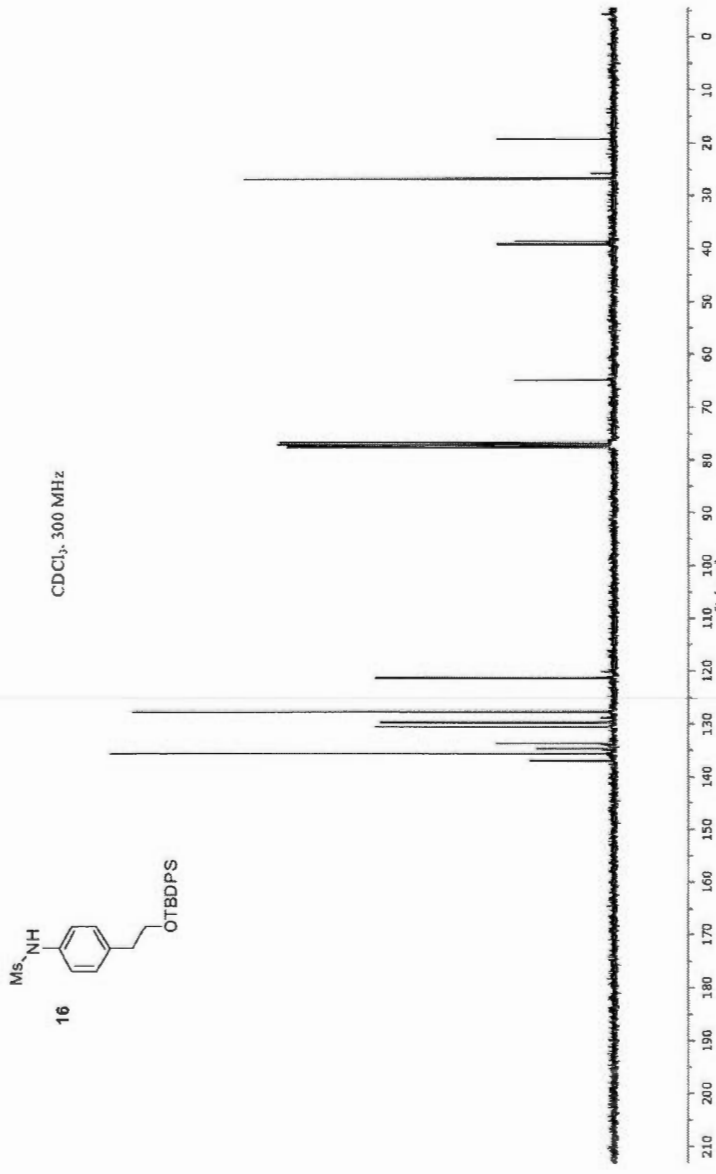
15

$CDCl_3$, 300 MHz

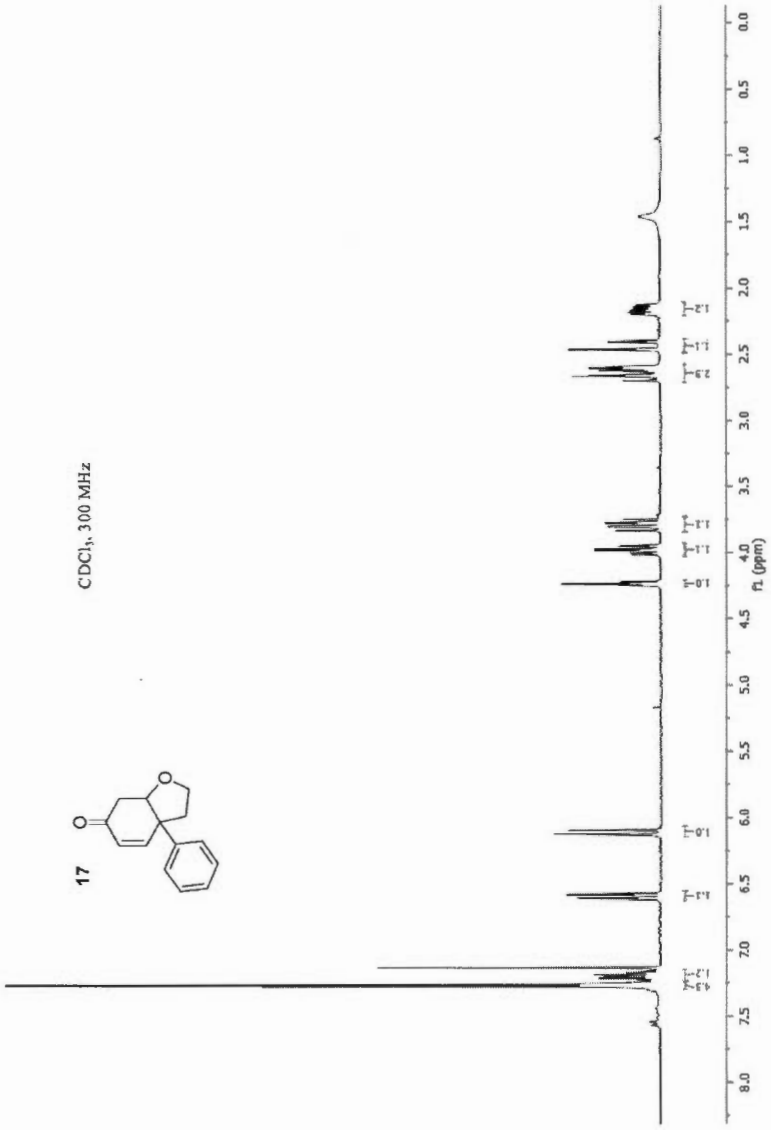


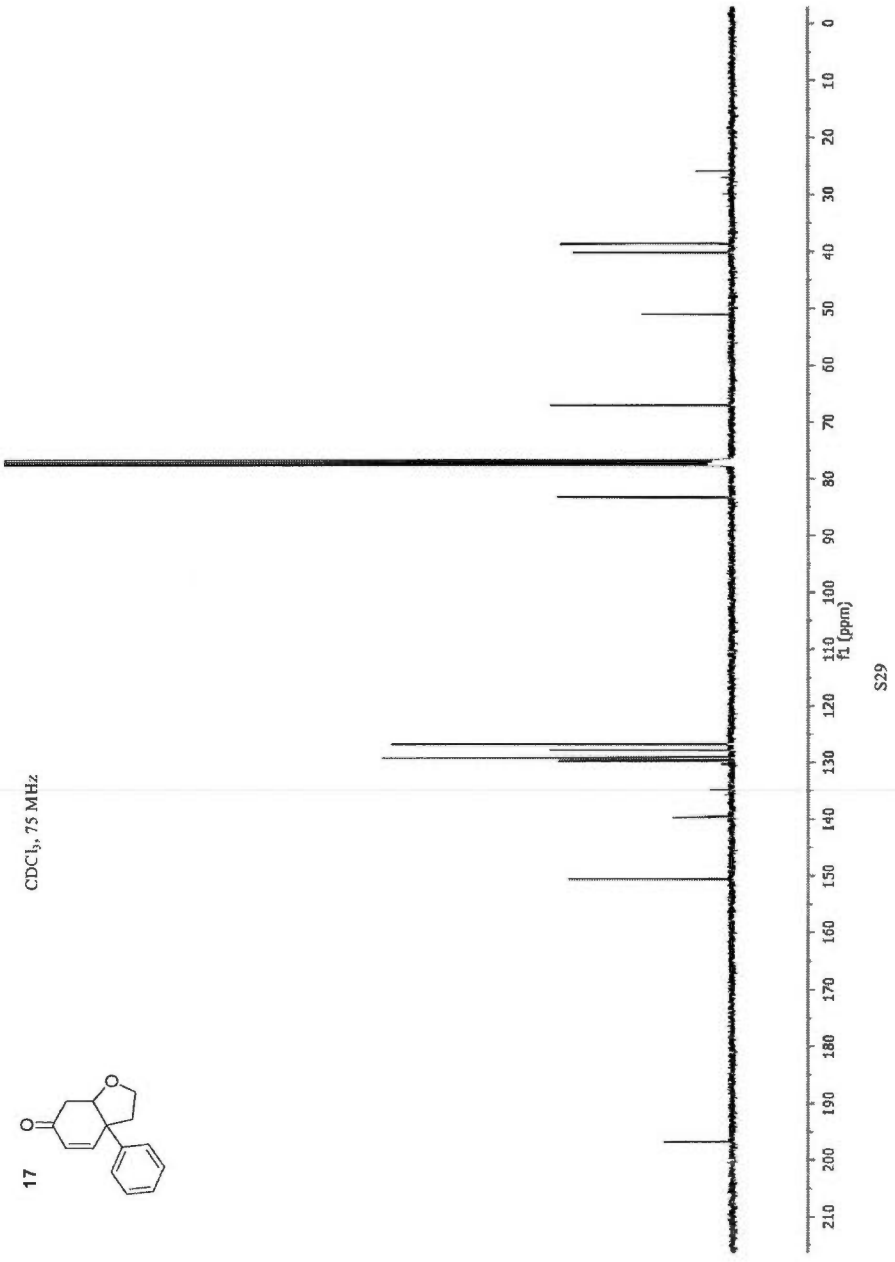

15
CDCl3, 75 MHz
f1 (ppm)
S25

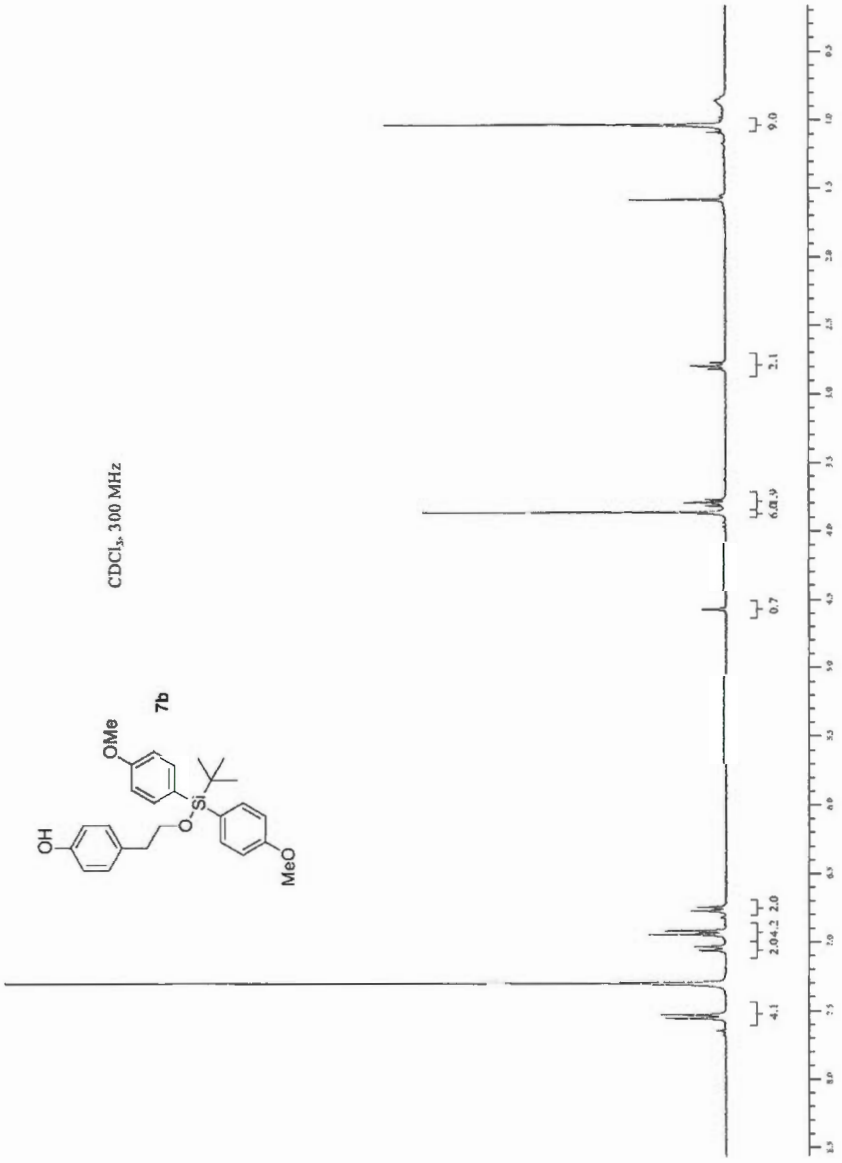

Ms
NH
OTBDPS
16
CDCl3, 300 MHz
f1 (ppm)



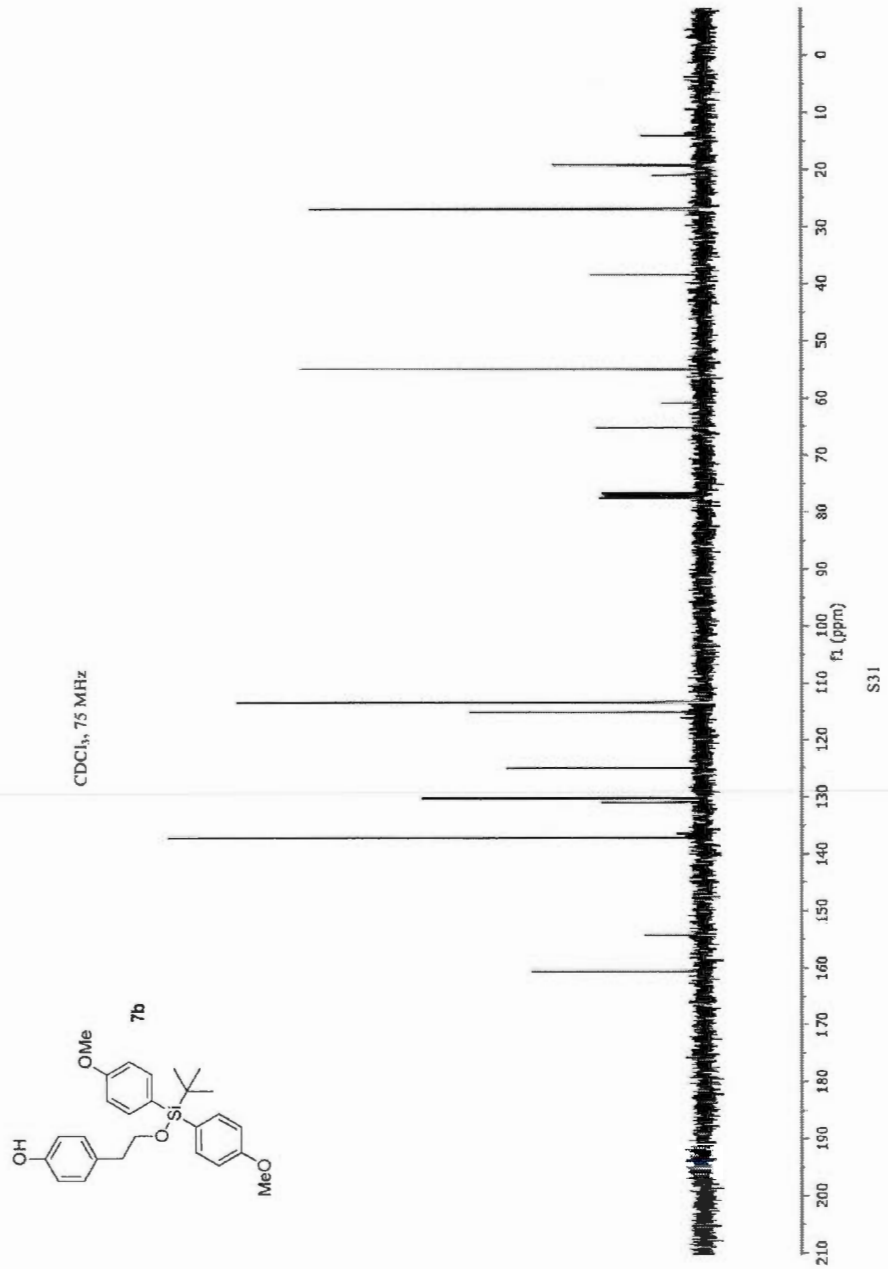
S27

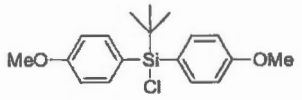

17
CDCl3, 300 MHz
f1 (ppm)


17
CDCl3, 75 MHz
f1 (ppm)
S29



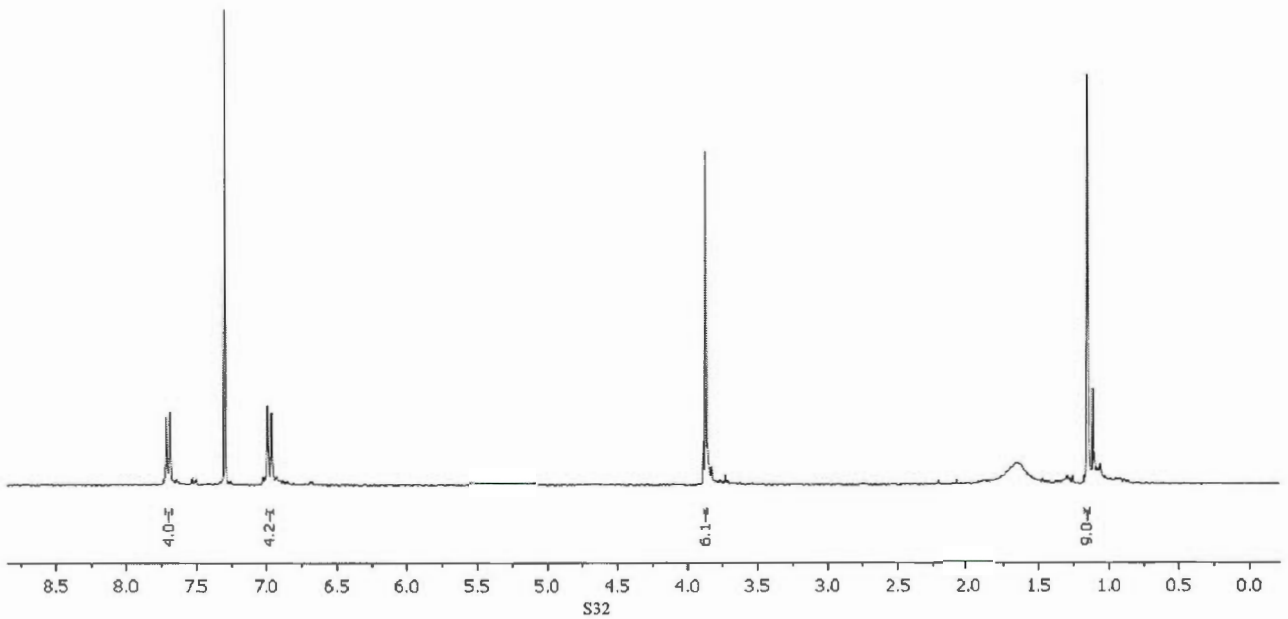
S30

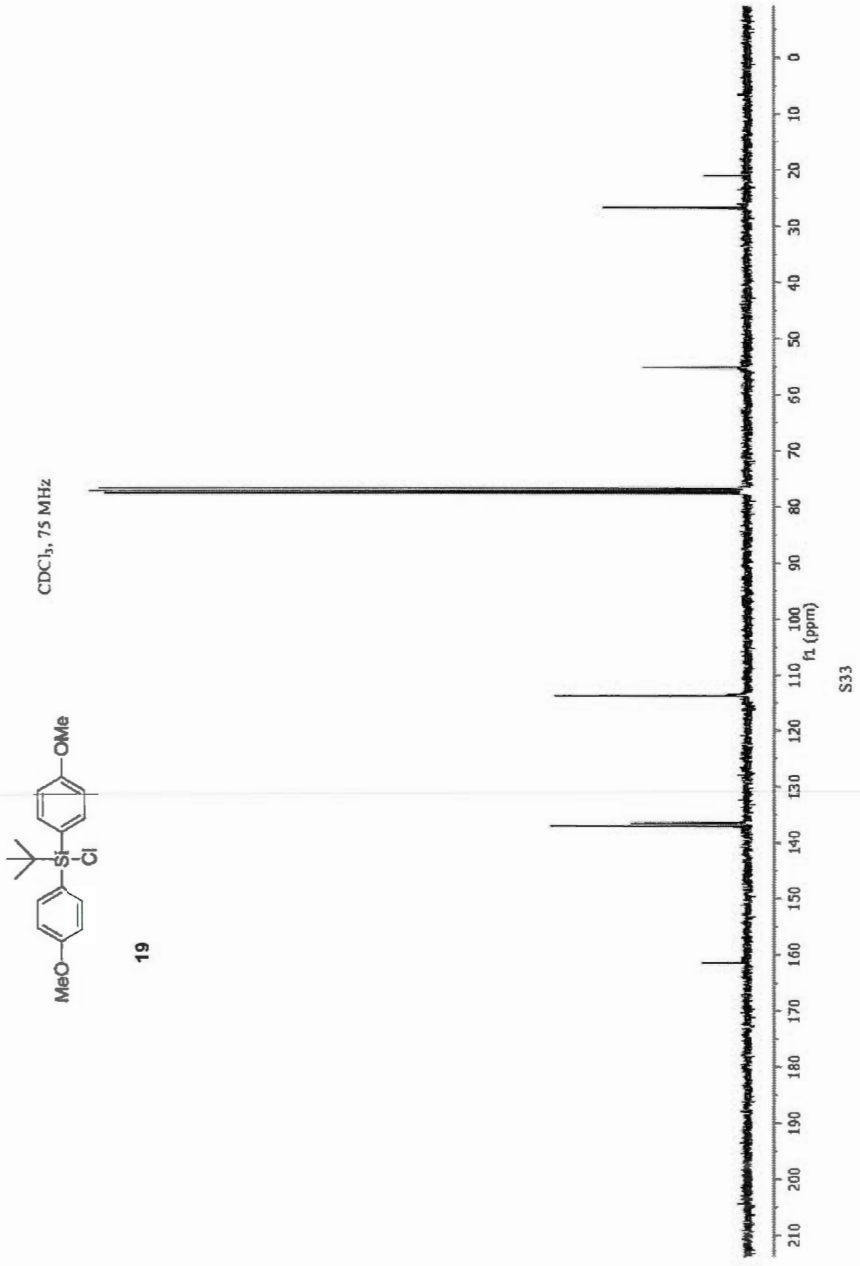

CDCl3, 75 MHz
7b
OMe
OH
Si
O
MeO
f1 (ppm)
S31

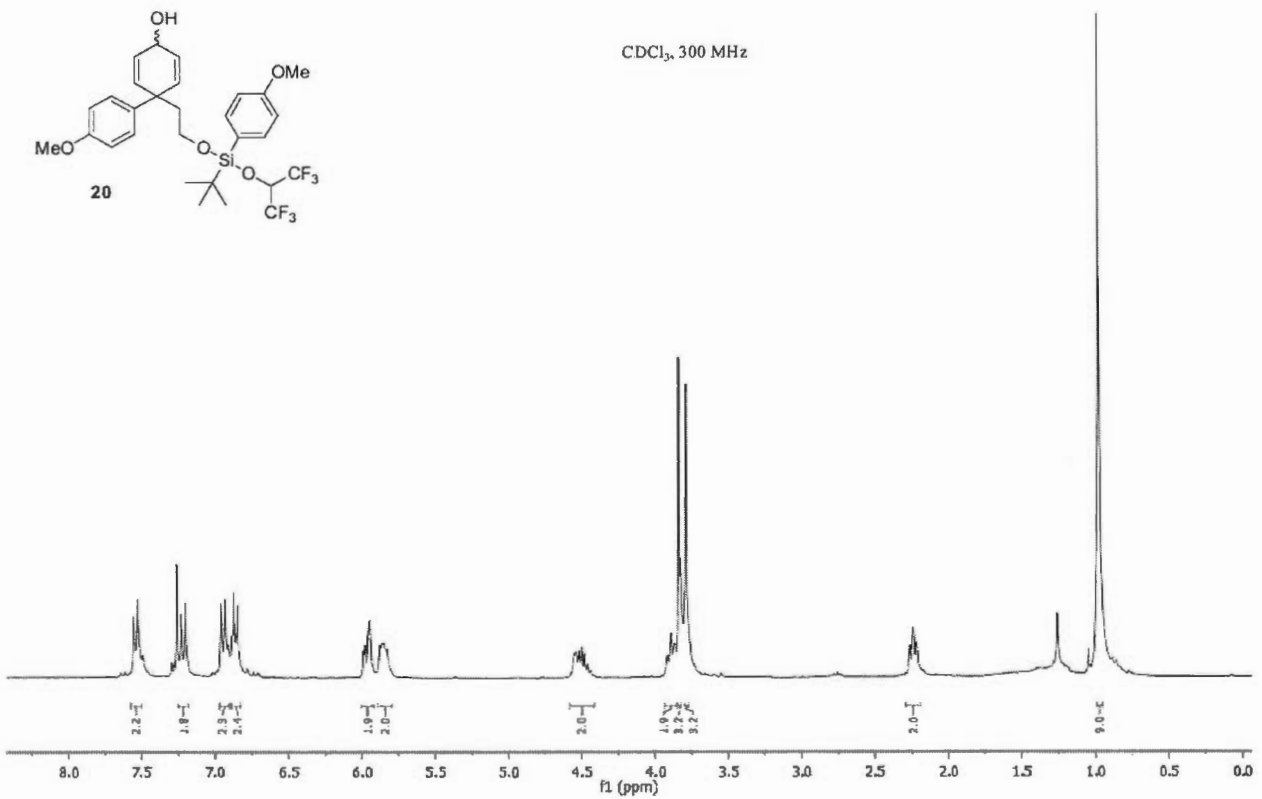


19

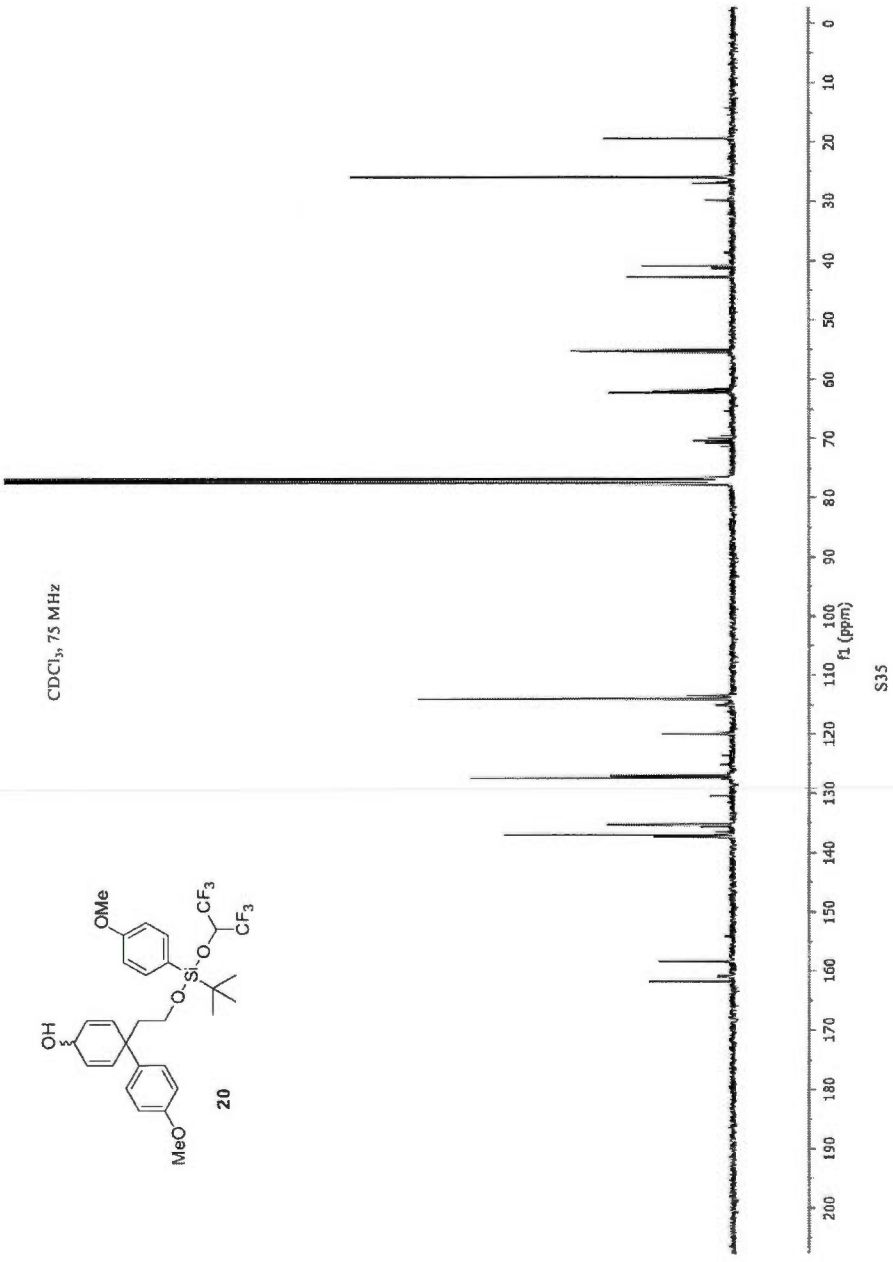
$CDCl_3$, 300 MHz

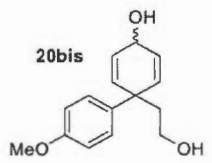



CDCl3, 75 MHz
MeO
OMe
Si
Cl
19
f1 (ppm)
S33

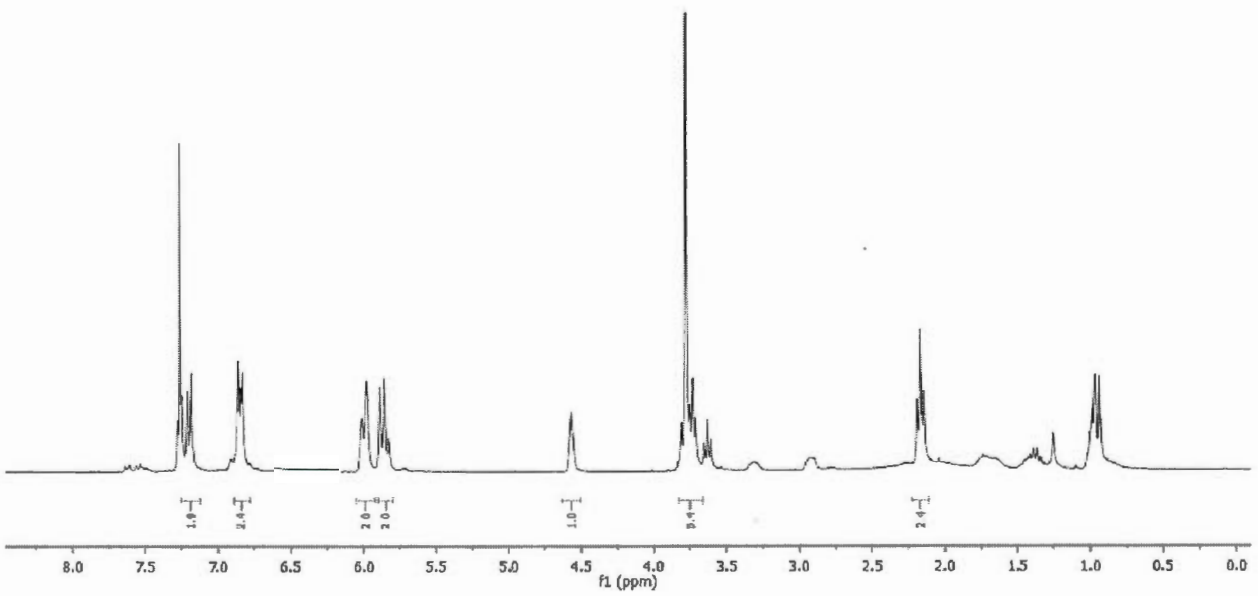

OH
OMe
MeO
O
Si
O
CF3
CF3
20
CDCl3, 300 MHz
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

S34

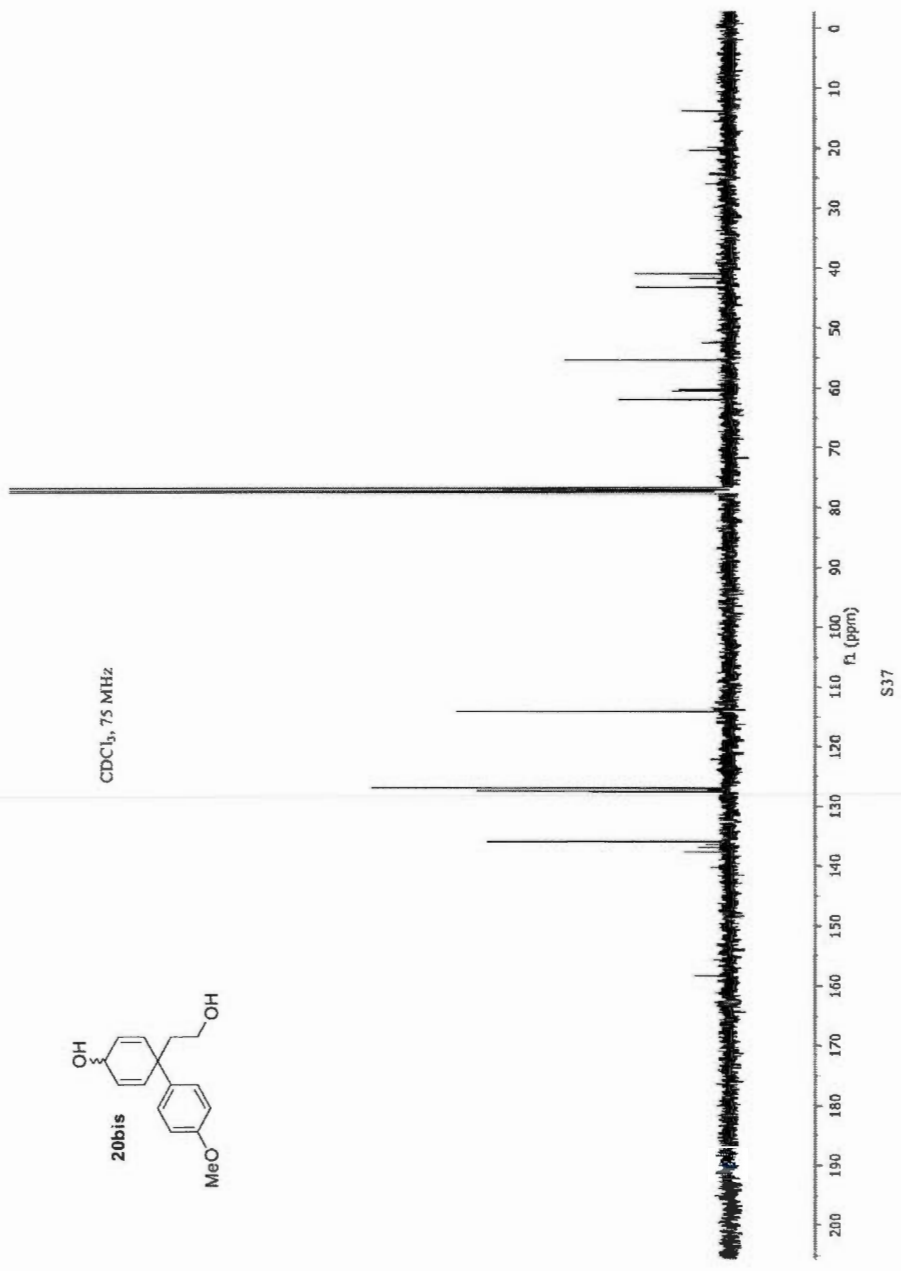

CDCl3, 75 MHz
f1 (ppm)
OMe
OH
MeO
Si
O
CF3
CF3
20

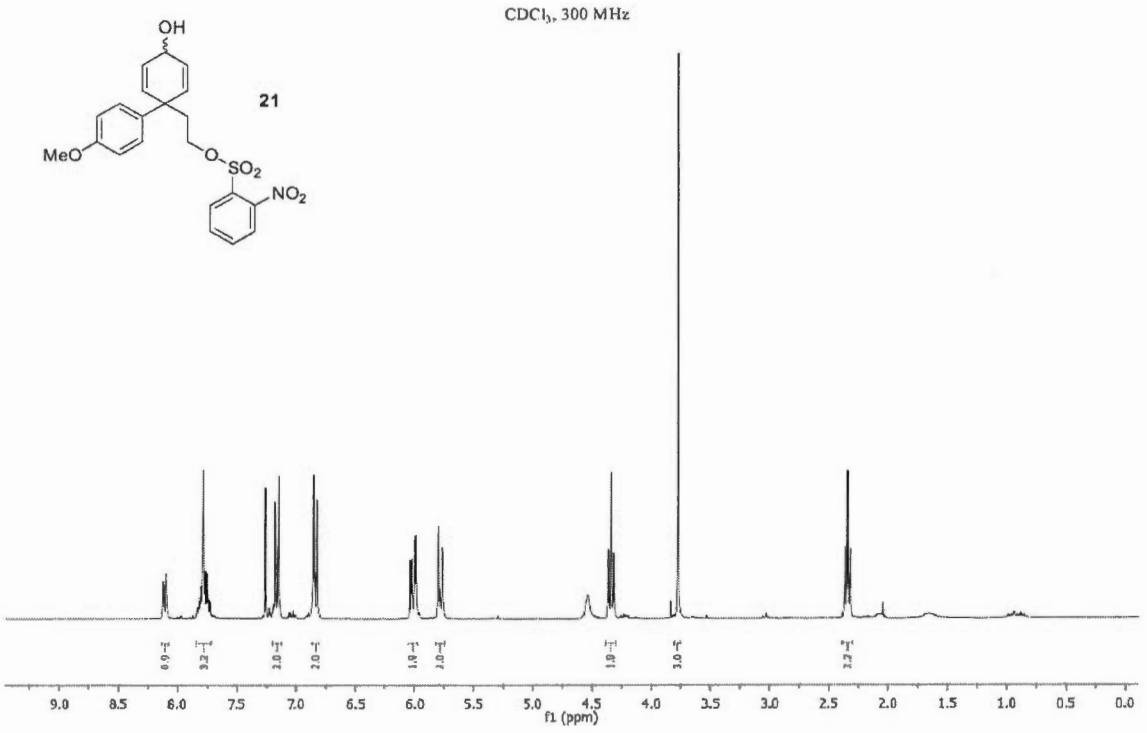


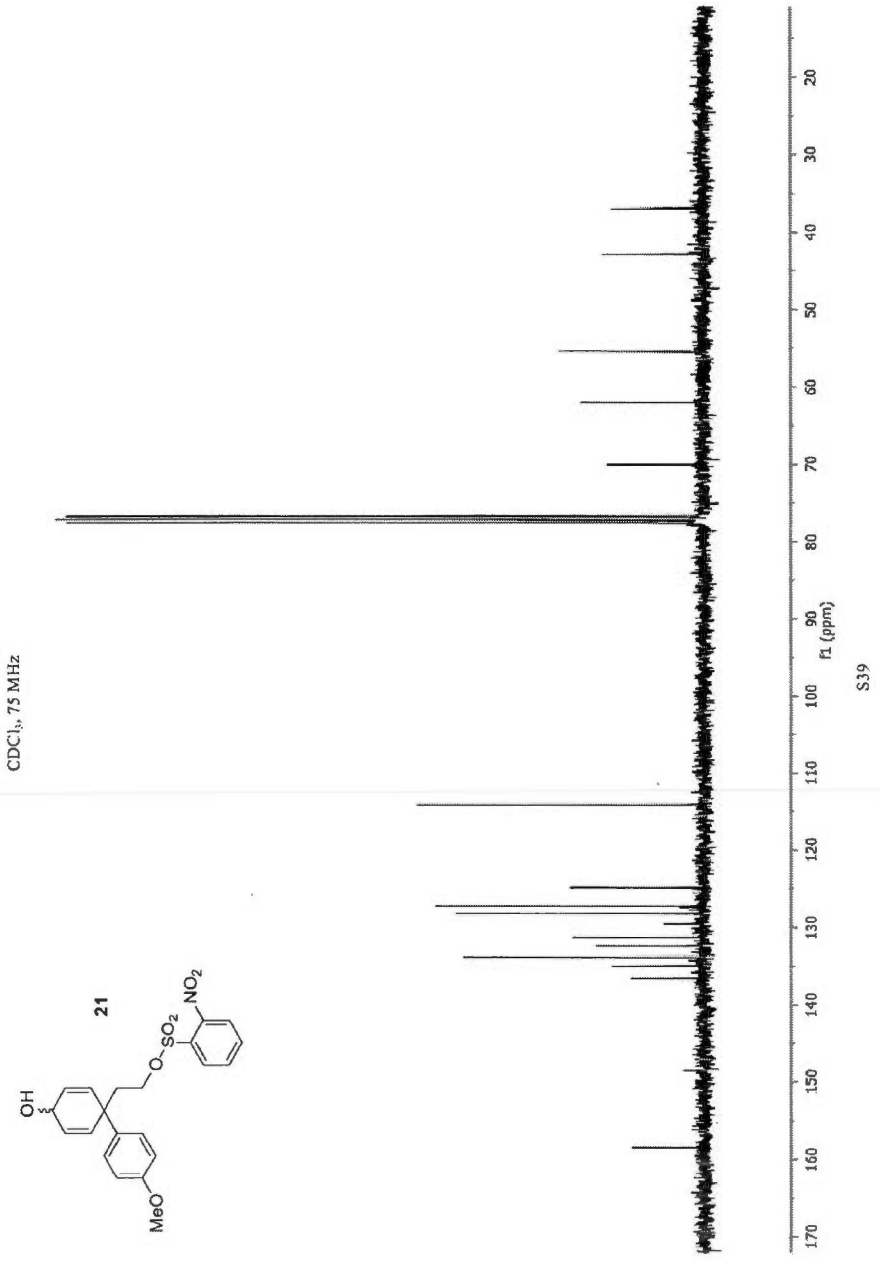
$CDCl_3$, 300 MHz

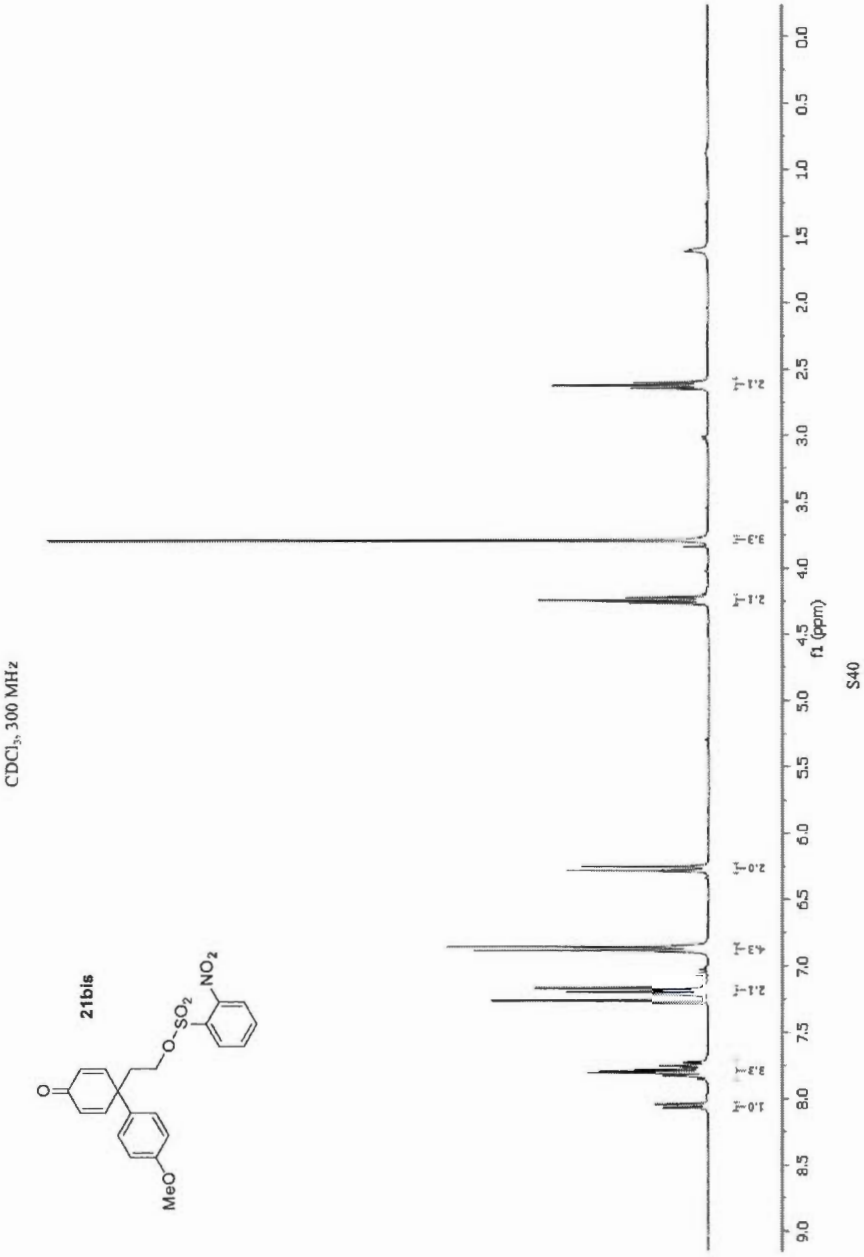


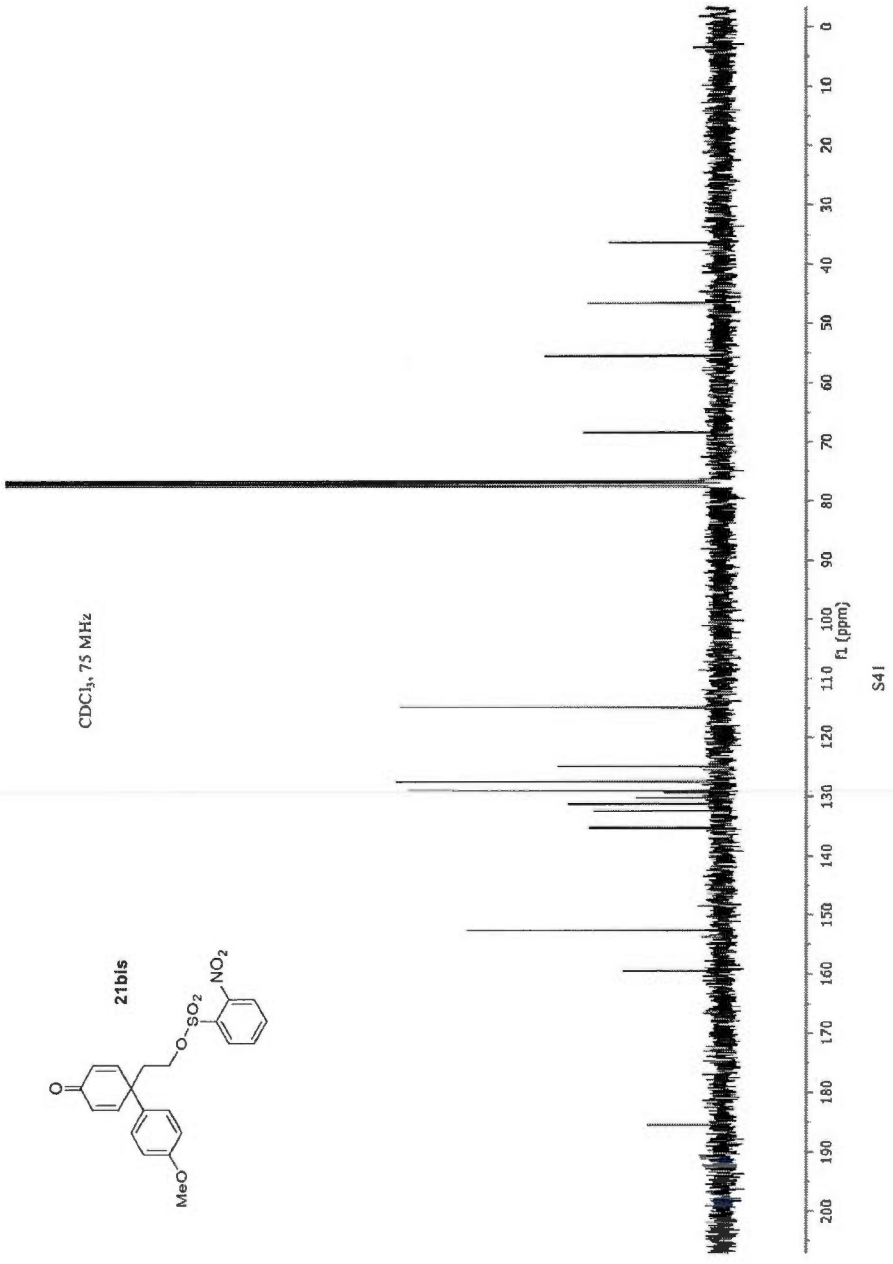
S36

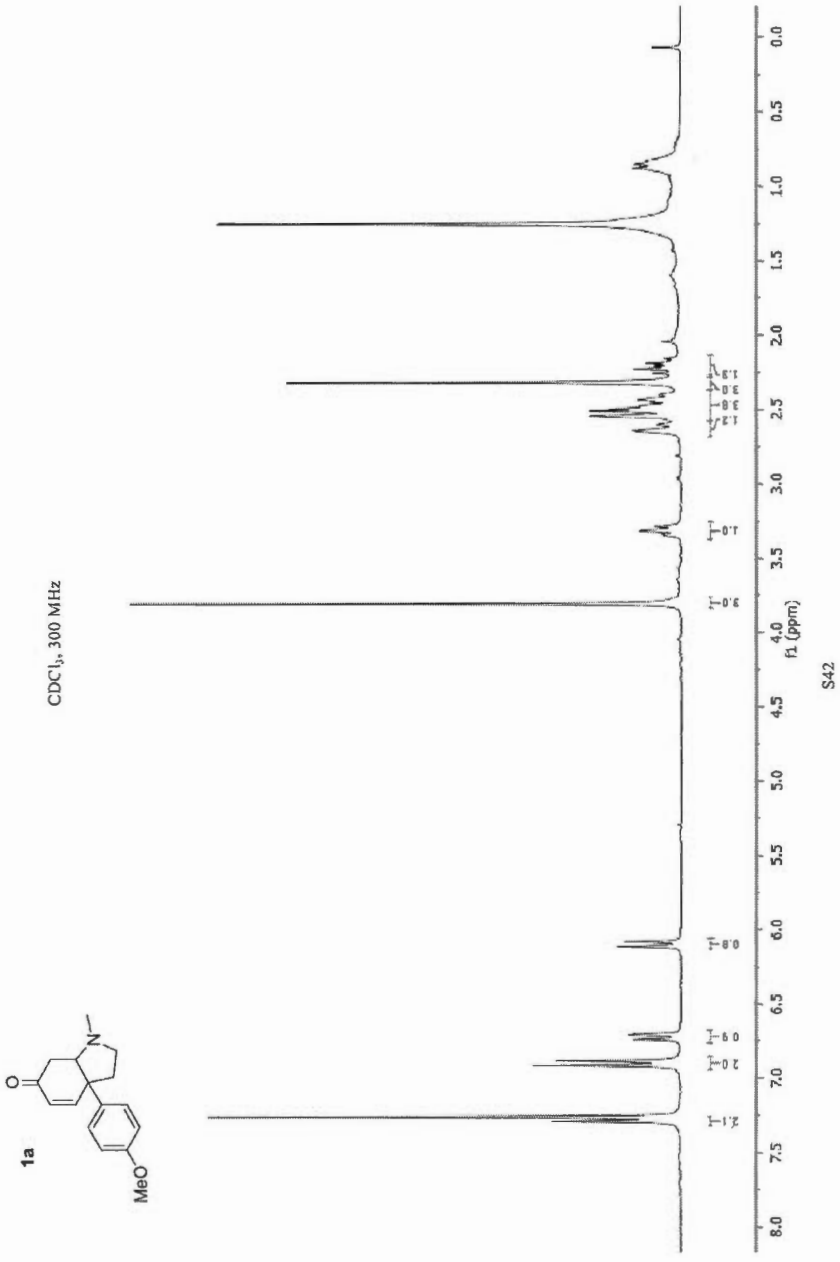

CDCl3, 75 MHz
f1 (ppm)
S37
20bis
OH
OH
MeO

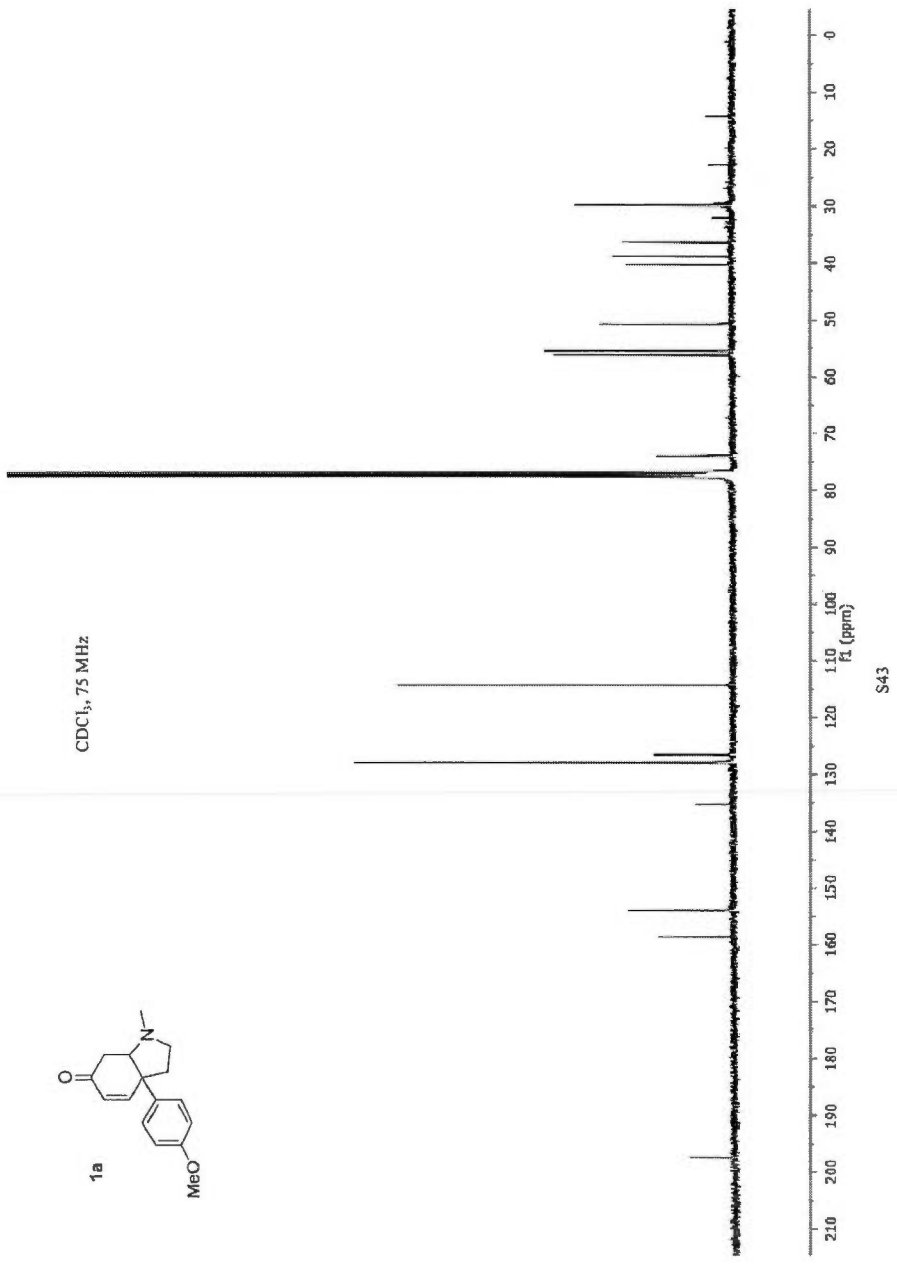

CDCl3, 300 MHz
OH
21
MeO
O
SO2
NO2
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

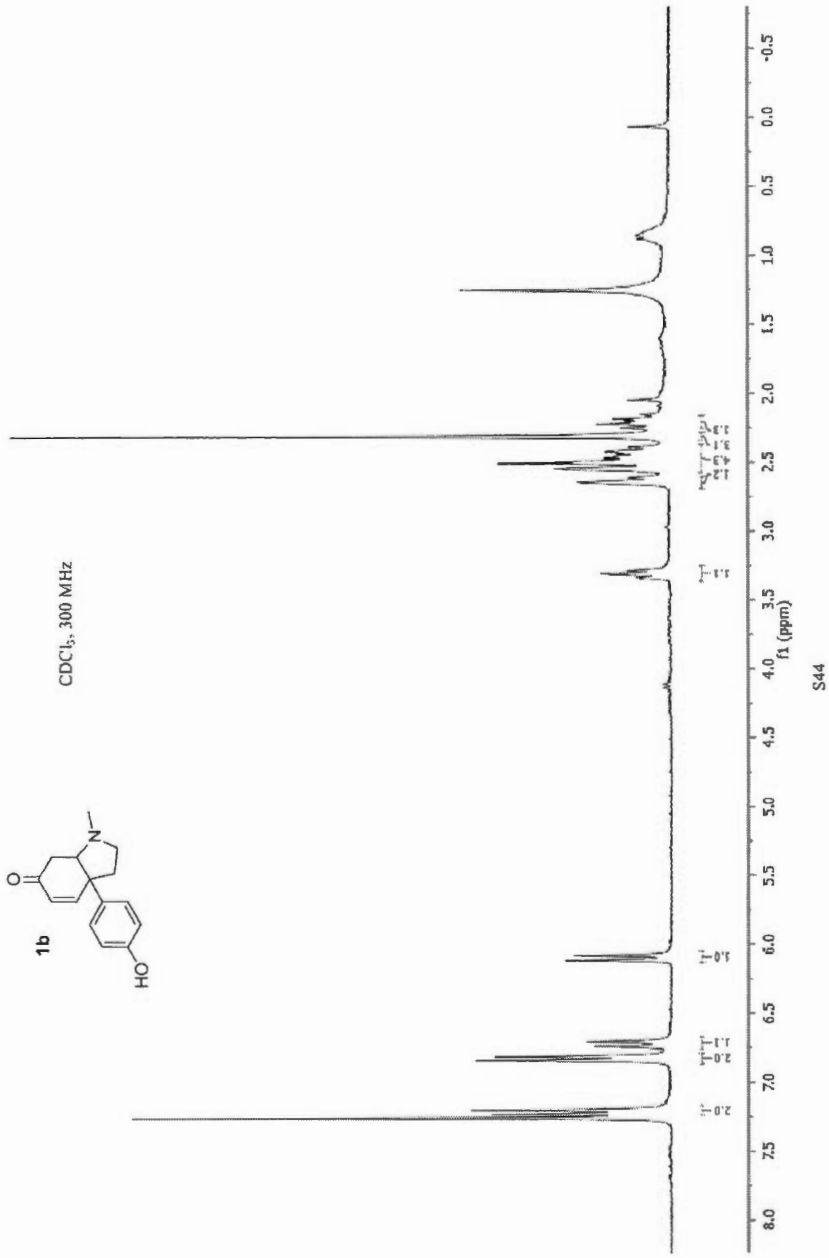

CDCl3, 75 MHz
21
OH
MeO
O
SO2
NO2
f1 (ppm)
S39

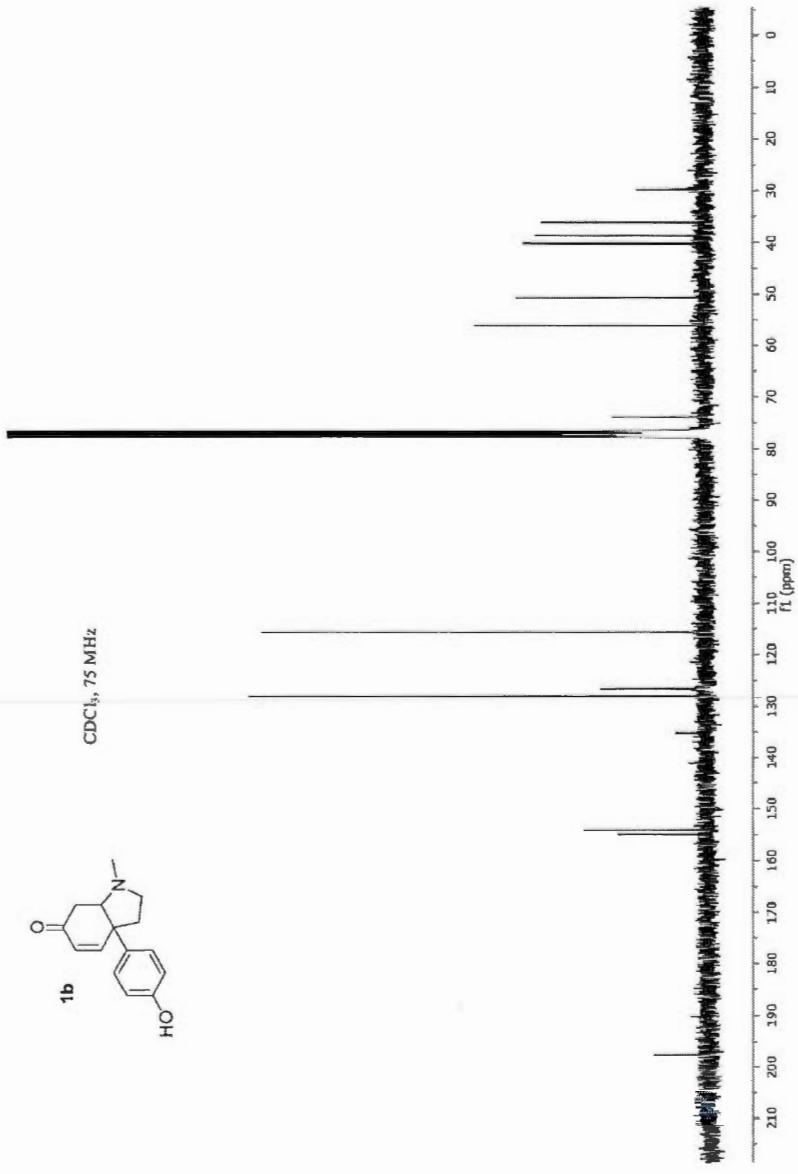

CDCl3, 300 MHz
21bis
O
O~SO2
NO2
MeO
f1 (ppm)
S40


21bis
CDCl3, 75 MHz
f1 (ppm)
S41


1a
MeO
CDCl3, 300 MHz
f1 (ppm)
S42


CDCl3, 75 MHz
1a
MeO
O
N
f1 (ppm)
S43


1b
CDCl3, 300 MHz
HO
f1 (ppm)
S44



S45

ANNEXE C :

"OXIDATIVE CYCLOADDITION AND CROSS-COUPLING PROCESSES ON UNACTIVATED BENZENE DERIVATIVES" ARTICLE

Chemical Science, **2013**, *4*, page 1287-1292

DOI: 10.1039/c2sc22318j

Date de publication (Web) : 2 Janvier 2013

http://pubs.rsc.org/en/content/articlepdf/2013/sc/c2sc22318j

Titre: Oxidative cycloaddition and cross-coupling processes on unactivated benzene derivatives

Auteurs: Guillaume Jacquemot, Marc-André Ménard, Chloé L'Homme et Sylvain Canesi*

Chemical Science

RSCPublishing

EDGE ARTICLE

View Article Online

Oxidative cycloaddition and cross-coupling processes on unactivated benzene derivatives†

Cite this: *Chem. Sci.*, 2013, **4**, 1287

Guillaume Jacquemot, Marc-André Ménard, Chloé L'Homme and Sylvain Canesi*

Received 29th September 2012
Accepted 2nd January 2013

DOI: 10.1039/c2sc22318j

www.rsc.org/chemicalscience

Treatment of phenols or anilines containing a sulfonyl group in the presence of a hypervalent iodine reagent promotes a formal dearomatizing [2 + 3] cycloaddition reaction on unactivated benzene and naphthalene derivatives. This process occurs *via* an intramolecular nucleophilic addition to the Wheland species generated during the oxidative activation. Subsequent treatment under acidic conditions readily transforms the tricyclic system into a biaryl *via* a formal cross-coupling process.

Introduction

Cycloaddition[1] and cross-coupling[2] transformations are extensively used in organic synthesis. Cycloadditions are generally performed on alkenes and alkynes; however, a similar transformation involving dearomatization of the normally inert π-bonds of an aromatic core would provide a means of preparing key polyfunctional intermediates. Only a few examples of such cycloaddition methods have been reported in the literature.[3] Although the reported reactions have been exclusively intramolecular, a bimolecular approach would provide a greater variety of potential synthetic avenues. In particular, the remaining double bonds could be readily involved in further transformations to rapidly generate elaborate products from inexpensive aromatic derivatives. From a chemical standpoint, such a transformation has been regarded as difficult to achieve. However, biaryl syntheses involving cross-coupling of two unactivated aromatic systems have received attention due to the large number of natural targets incorporating these cores[4] and the potential for using axially chiral bi-aromatics as ligands in asymmetric reactions.[5] Previous methods of achieving this type of transformation have generally involved heavy metals, but a recent report in the literature suggested that similar cross-coupling methodologies may be accomplished under metal-free conditions using hypervalent iodine reagents[6] and thiophenes,[6a] polymethylbenzenes,[6b] or anisole derivatives[6f] as coupling partners. Other noteworthy cross-coupling processes involving hypervalent iodine reagents in combination with copper triflate have been efficiently developed by Gaunt and co-workers. In these reactions the copper salt remains crucial.[7] The few reported metal-free cycloaddition reactions involving phenols have been limited to electron-rich alkenes[8] and furan[9] and have not been successfully extended to include "dipolarophiles" similar to the aryl system **2**, Fig. 1.

In this paper, we present a versatile methodology facilitating [2 + 3] cycloaddition processes between benzene derivatives and phenols or anilines. Slightly modified conditions may be used to produce the cross-coupling adduct from these two unactivated aromatic subunits. The processes are reminiscent of Friedel–Crafts chemistry in their approach to the connection of two aromatic units under metal-free conditions.

Results and discussion

For the reactions to proceed, one of the systems must be converted into an electrophilic species for trapping by the remaining aryl acting as a nucleophile. This reversal of reactivity may be thought of as involving "aromatic ring umpolung".[10] An indication of how such selective aromatic activations may be accomplished is provided in the work of Kita,[11] who demonstrated the reactivity of electron-rich systems such as phenols in the presence of hypervalent iodine reagents,[12] for example (diacetoxyiodo)benzene (DIB) or phenyliodine bis(trifluoroacetate) (PIFA).[13] The activation is best performed in solvents such as trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP)[10f] and involves electron transfer to produce a phenoxonium ion **3**. This ion is readily trapped by an aryl partner **2**, leading to a Wheland species **4**. At this stage one of two pathways may occur, a classical elimination

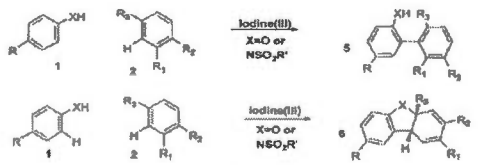


Fig. 1 Cross-coupling and aromatic cycloaddition.

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

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2sc22318j

(*pathway a*) affording the biaryl core **5** or an intramolecular nucleophilic attack on arenium ion **4** (*pathway b*) leading to the polycycle **6**, Fig. 2.

A key aspect of this transformation is the relative stability of the electrophilic species generated. Indeed, the phenoxonium **3** and arenium **4** ions produced during the umpolung activation must be sufficiently stable to react with their respective nucleophile partners in order to avoid competitive elimination pathways such as benzylic hydrogen elimination from **3**, which generates an unstable polymerizable quinone methide (Fig. 3).

Because of its polar and non-nucleophilic properties, HFIP is a valuable solvent that provides sufficient stabilization of electrophilic species **3** and **4** in the presence of fairly reactive and electron-rich partners such as enol ethers or furans.[8c] However, the reaction is inefficient with simple benzene derivatives such as iodo-aryls, naphthalene or benzene. To promote reactions with these important compounds other issues must be resolved. For instance, we have observed that a sulfonyl moiety on the lateral chain behaves similarly to HFIP, enabling nucleophilic attack even with poor electron systems such as iodobenzene. We assume that in an intramolecular pathway the poor nucleophilicity of the lone pairs on the sulfonyl oxygen atoms stabilize the transition state **10** by overlapping phenoxonium ion **3** (n–π^* interaction) without producing a carbon–oxygen bond, Fig. 4.

Direct formation of compound **5** would be an interesting example of cross-coupling; however, the nascent relatively electron-rich system **5** would be reoxidized more quickly by the unreacted hypervalent iodine reagent than the remaining starting material **1**. It appears that formation of the cycloadduct **6** is essential during the process. In a sense, compound **6** serves as a protecting group for the phenol or aniline functionality and minimizes undesirable overoxidation of the latter. Moreover, further treatment of **6** in a second step under acidic conditions and in the absence of hypervalent iodine regenerates the arenium species **4** and displaces the equilibrium in favor of the irreversible pathway a, leading to biaryl **5**. For this reason, it is important to control the acidity of the medium during the reaction to avoid reopening the cycloadduct **6**, leading to compound **5** that could be subsequently overoxidized due to the presence of NH or OH bonds. Several conditions and hypervalent iodine reagents were investigated. Iodobenzene was the first "dipolarophile" tried because it is released during the process following reduction of the hypervalent iodine reagent. Bis(pivalate)iodobenzene (PIB, entry d) was the oxidizing agent

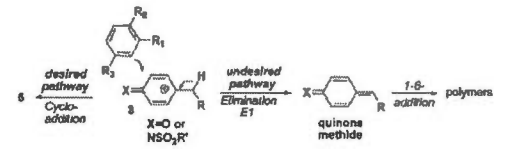


Fig. 3 Competitive transformations of phenoxonium species **3**.

of choice, and the reaction was optimized at −4 °C in a mixture of HFIP–DCM (2 : 1). Pivalic acid, a weak carboxylic acid, was released during the reaction. Similar results were observed using DIB combined with Na_2CO_3 to neutralize the acetic acid released, as the pH of the solution seems to be an important aspect of this transformation. As expected, compound **11** was not produced under harsher conditions employing PIFA. Since this process occurred in an intermolecular manner and due to the instability of species **3** (Fig. 3), ten equivalents of inexpensive iodobenzene were used to favor formation of compound **11** over the polymeric by-products. If desired, the excess aromatic partner could be chromatographically separated and reused. In no case was it necessary to add more than ten equivalents of iodobenzene (see Table 1, entries d, f and g). The nature of the sulfonyl group does not really influence the transformation, although a slight diminution of yield was observed in the presence of a withdrawing group (entry j). The reaction occurred in the presence of a Julia–Kocienski auxiliary[44] that could be useful for further elaboration of the lateral chain, Table 1.

With the optimized conditions in hand, we investigated the use of other aromatic systems as dipolarophiles. Iodo-aryl compounds were competent substrates for this transformation. The regioselectivity observed with *para*-substituted iodo-aryl compounds appears to be controlled by steric factors, and a protecting group was tolerated (entry e). In addition, the crucial sulfone moiety may be successfully incorporated in a six-membered-ring transition state with a lower overall yield as expected (entry f). We were pleased to observe that the new process even occurred using benzene and was efficient when naphthalene was used (72%), most probably due to the fact that one aromatic core remains intact during the formation of **12h**, Table 2.

In some cases when iodobenzene was not used as a dipolarophile, a small amount of compound **11** (~5%) was observed, originating from a competition with iodobenzene released during the umpolung activation. The successful extension of

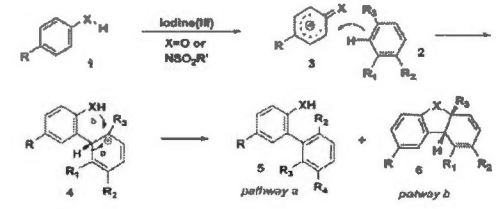


Fig. 2 Oxidative cross-coupling *vs.* cycloaddition.

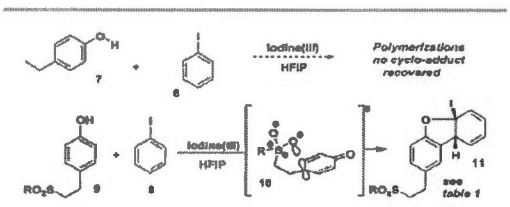


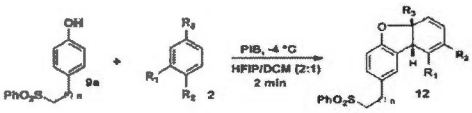
Fig. 4 Oxidative dearomatizing "2 + 3" cycloaddition.

This journal is © The Royal Society of Chemistry 2013

Table 1 Cycloaddition optimization conditions

Entry	R	Iodine(III)	PhI equiv.	Yield (%)
a	Ph	PIFA	10	—
b	Ph	DIB	10	34
c	Ph	DIB + Na_2CO_3	10	47
d	**Ph**	**PIB**	**10**	**51**
e	Ph	PIB + Na_2CO_3	10	50
f	Ph	PIB	20	53
g	Ph	PIB	5	37
h	***n*-Propyl**	**PIB**	**10**	**55**
i	*p*-PhOMe	PIB	10	48
j	*p*-$PhNO_2$	PIB	10	41
k	**Benzothiazol**	**PIB**	**10**	**45**

Table 2 Cycloadditions with benzene derivatives



Entry	*n*	2 (equiv.)	R_1	R_2	R_3	Yield (%)
a	1	10	H	H	I	51
b	1	10	H	Me	I	54
c	1	10	H	Et	I	47
d	1	10	H	*i*Pr	I	40
e	1	8	H	CH_2OTBS	I	35
f	2	10	H	H	I	31
g	**1**	**20**	**H**	**H**	**H**	**40**
h	**1**	**10**	**CH=CHCH=CH**		**H**	**72**

this process to systems other than iodobenzene provides support for the mechanism proposed in Fig. 2 and rules out an intramolecular process involving the hypervalent iodine reagent. This method could be employed in total syntheses of natural products containing hydrodibenzofuran cores such as linderol A,[15a] a potent inhibitor of melanin biosynthesis in cultured B-16 melanoma cells, or rubiyunnanin A[15b] (Fig. 5).

Other systems have been tested including anthracene, in which a formal "4 + 3" cycloaddition occurred to produce **13**.

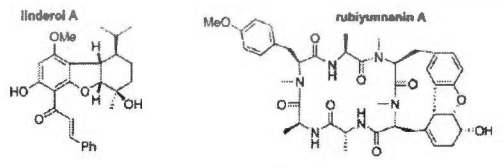
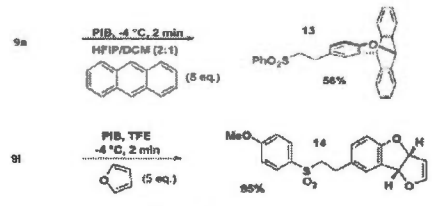


Fig. 5 Natural products containing hydrodibenzofuran cores.

Compound **9i** reacted in the presence of furan to afford **14** in 95% yield. It should be stressed that in the presence of PIB and with a sulfone on the lateral chain, the overall yield observed was double that of the same transformation employing ethylphenol[9e] and furan, a fairly reactive and electron-rich partner (~45% yield), demonstrating the importance of the sulfonyl moiety as a stabilizing and anchimeric assisting group for the phenoxonium species generated in the reaction, Scheme 1.

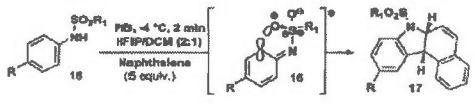
Although the sulfone moiety present on the lateral chain could be further transformed using Julia–Kocienski chemistry (compound **11k**), it would be more convenient to introduce a removable auxiliary to enable the cycloaddition by stabilizing the electrophilic species **16**. In addition, the valence of the oxygen atom makes development of an asymmetric pathway difficult. Toward this goal a similar reaction involving a sulfonamide group has been envisaged; in this case the required stabilizing sulfonyl group is directly connected to the aniline and may stabilize the *ortho* positions of the electrophilic species **16** in a manner similar to **10**. This option could lead to a further asymmetric pathway through the introduction of a chiral sulfonamide. This alternative tolerated a variety of spectator functionalities and several sulfonamides. However, lower yields were observed with substituted sulfonamides (Table 3, entries **17c** and **17d**). Naphthalene underwent efficient reaction with sulfonamides **15**, most probably because the second aromatic ring stabilized the resulting areniun ion **4** (Table 3).

Only five equivalents of naphthalene were required when a sulfonamide was used as the polarophile. This process represents an expeditious route to indoline cores, an important functionality present in a large number of bioactive products. The synthesis of scaffolds such as **12** or **17** has not been documented in the literature, and only a few examples of isomers having modified connectivity have been prepared from benzofuran, oxabicycle and styrene derivatives.[16] Most of these methods have involved transition metals. Reactions have been attempted using other aromatic partners in combination with sulfonamide **15**, including a substituted naphthalene, to generate tetracycle **18**. Highly electron-rich methoxynaphthalene derivatives were unsatisfactory substrates for the cycloaddition pathway and led to several cross-coupling adducts. However, when using a moderate electron-donor group such as a mesylate, cycloadduct **18** was obtained as well as the C–N cross-coupling compound **19** resulting from direct attack of the naphthalene derivative on the nascent electrophilic nitrogen generated during the umpolung activation. A



Scheme 1 Anthracene and furan cycloadditions.

Table 3 Cycloaddition with sulfonamides

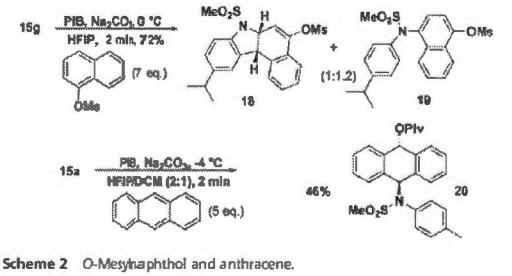


Entry	R_1	R	Yield (%)
a	Me	Me	61
b	Et	Me	59
c	Tol	Me	32
d	*i*Pr	Me	38
e	Bn	Me	45
f	Me	Cl	51
g	Me	*i*Pr	52
h	Me	*n*Pr	51
i	Me	$CH_2CH_2SO_2Ph$	54
j	Me	CH_2OH	53
k	Me	CH_2CH_2OH	62
l	Me	CH_2CH_2OTBS	52
m	Me	TMS	43

similar transformation was observed in the presence of anthracene, and we assumed that the quite stable dibenzylic arenium ion **4** generated from the anthracene attack was trapped by pivalic acid released in the medium, leading to compound **20** in 46% yield, Scheme 2.

Interestingly, in a second step under acidic conditions mediated by trifluoroacetic acid, the conversion of cycloadduct **21** to biaryl **5** was quantitatively observed, probably *via* regeneration of species **4** and displacement of the equilibrium in favor of pathway a as discussed in Fig. 2. This suggests that further acid treatment of compounds **12** or **17** leads to a formal cross-coupling process involving unactivated aromatic subunits as a route to C–H activation, Table 4.

A direct cross-coupling process may also be undertaken from the sulfamide derivative **22**. In this case biaryl systems were directly obtained and only a small amount of cycloadduct product was occasionally detected. This compound was rapidly transformed into the biaryl **23** in the presence of slightly acidified $CDCl_3$. This result may be rationalized if we consider that the new cycloadduct derivative is rapidly transformed into **23** due to the presence of the additional basic pyrrolidine moiety. The sulfamide segment appears to be a direct C–H



Scheme 2 *O*-Mesylnaphthol and anthracene.

Table 4 Formal cross-coupling process

Entry	X	R	R_3	R_2	R_1	Yield (%)
a	O	$CH_2CH_2SO_2Ph$	H	H	I	97
b	O	$CH_2CH_2SO_2Ph$	H	Me	I	91
c	O	$CH_2CH_2SO_2Ph$	H	Et	I	98
d	O	$CH_2CH_2SO_2Ph$	H	*i*Pr	I	90
e	O	$CH_2CH_2SO_2Ph$	H	H	H	97
f	O	$CH_2CH_2SO_2C_6H_4OMe$	H	H	I	87
g	O	$CH_2CH_2SO_2Ph$	$-C_4H_4-^a$		H	98
h	NSO_2Et	Me	$-C_4H_4-$		H	97
i	NSO_2Me	*n*Pr	$-C_4H_4-$		H	83
j	NSO_2Me	*i*Pr	$-C_4H_4-$		H	97
k	NSO_2Me	CH_2CH_2OH	$-C_4H_4-$		H	76
l	NSO_2Me	CH_2CH_2OTBS	$-C_4H_4-$		H	79[b]
m	NSO_2Me	$CH_2CH_2SO_2Ph$	$-C_4H_4-$		H	94

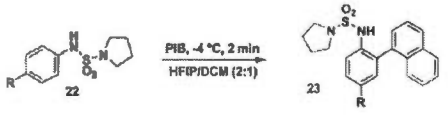
[a] $-C_4H_4-$ = $-CH{=}CHCH{=}CH-$. [b] The trifluoro ester derivative is isolated.

inductor, enabling cross-coupling with naphthalene derivatives, Table 5.

Guziec and Wang have described reductive removal of the sulfonamido group[17] in the presence of NH_4Cl and NaH to produce biaryls **25** from compound **24** through an overall sequence that neatly complements established methods, Fig. 6.

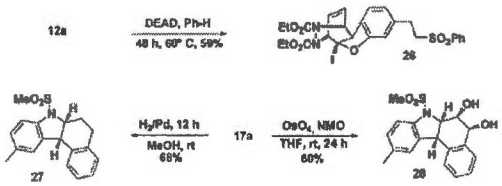
An interesting aspect of this transformation is its ability to dearomatize a benzene derivative into a functionalized system ready for further transformations. As an illustration of some possibilities provided by this method, several conventional reactions enabling quick transformation of the key cycloaddition product into further functionalized cores are presented in Scheme 3. For example, Diels–Alder reaction of **12a** led to compound **26** in 59% yield. Hydrogenation of **17a** provided the tetracyclic indoline **27** in 66% yield, and treatment of **17a** with OsO_4 and NMO produced diol **28** in 60% yield.

Table 5 Direct cross-coupling process



Entry	R	Yield (%)
a	Me	55
b	Et	64
c	*i*Pr	54
d	Cl	81
e	CH_2CO_2Me	36
f	TMS	52

Fig. 6 Guziec and Wang desulfonamidation.



Scheme 3 Functionalization of cycloadducts **12** and **17**.

Conclusions

In summary, a new oxidative dearomatizing cycloaddition process between phenols or anilines and aromatic derivatives has been developed. This process is made possible by the introduction of a key sulfonyl group to stabilize the electrophilic species generated during the hypervalent iodine-mediated umpolung activation. Slightly modified conditions may be used to obtain a cross-coupling adduct from these two unactivated aromatic subunits as an alternative C–H activation transformation. Ongoing investigations of these processes, including an asymmetric version with a chiral sulfonamide moiety, and potential applications will be disclosed in due course.

Acknowledgements

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.

Notes and references

1 (*a*) F. Caramella and P. Grunanger, *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley-Interscience, New York, NY, 1984, p. 291; (*b*) V. Jager and P. A. Colinas, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, ed. A. Padwa and W. H. Pearson, John Wiley and Sons, New Jersey, NJ, 2003, p. 361.

2 (*a*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*b*) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (*c*) R. Li, L. Jiang and W. Lu, *Organometallics*, 2006, **25**, 5973; (*d*) Y. Rong, R. Li and W. Lu, *Organometallics*, 2007, **26**, 4376; (*e*) Y. Wei and W. Su, *J. Am. Chem. Soc.*, 2010, **132**, 16377; (*f*) M. J. Tredwell, M. Gulias, N. Gaunt Bremeyer, C. C. C. Johansson, B. S. L. Collins and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 1076.

3 (*a*) G. Himbert and L. Henn, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 620; (*b*) Y. Soro, F. Bamba, S. Siaka and J. M. Coustard, *Tetrahedron Lett.*, 2006, **47**, 3315; (*c*) M. Yonewaka, Y. Koyama, S. Kuwata and T. Takata, *Org. Lett.*, 2012, **14**, 1164; (*d*) T. R. Hoyel, B. Baire, D. Niu, P. H. Willoughby and B. P. Woods, *Nature*, 2012, **490**, 208; (*e*) J. K. Lam, Y. Schmidt and C. D. Vanderwal, *Org. Lett.*, 2012, **14**, 5566.

4 G. Bringmann, R. Walter and R. Weirich, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 977.

5 (*a*) R. Noyori, *Chem. Soc. Rev.*, 1989, **18**, 187; (*b*) K. Narasaka, *Synthesis*, 1991, 1.

6 (*a*) A. Jean, J. Cantat, D. Bérard, D. Bouchu and S. Canesi, *Org. Lett.*, 2007, **9**, 2553; (*b*) T. Dohi, M. Ito, K. Morimoto, M. Iwata and Y. Kita, *Angew. Chem., Int. Ed.*, 2008, **47**, 1301; (*c*) M. A. Giroux, K. C. Guérard, M. A. Beaulieu, C. Sabot and S. Canesi, *Eur. J. Org. Chem.*, 2009, 3871; (*d*) Y. Kita, K. Morimoto, M. Ito, C. Ogawa, A. Goto and T. Dohi, *J. Am. Chem. Soc.*, 2009, **131**, 1668; (*e*) K. Morimoto, N. Yamaoka, C. Ogawa, T. Nakae, H. Fujioka, T. Dohi and Y. Kita, *Org. Lett.*, 2010, **12**, 3804; (*f*) T. Dohi, M. Ito, I. Itani, N. Yamaoka, K. Morimoto, H. Fujioka and Y. Kita, *Org. Lett.*, 2011, **13**, 6208; (*g*) R. Samanta, J. Lategahn and A. P. Antonchick, *Chem. Commun.*, 2012, **48**, 3194; (*h*) J. Wen, R. Y. Zhang, S. Y. Chen, J. Zhang and X. Q. Yu, *J. Org. Chem.*, 2012, **77**, 766.

7 (*a*) R. J. Phipps, N. P. Grimster and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 8172; (*b*) R. J. Phipps and M. J. Gaunt, *Science*, 2009, **323**, 1593; (*c*) C. L. Ciana, R. J. Phipps, J. R. Brandt, F. M. Meyer and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2010, **50**, 457; (*d*) C. L. Ciana, R. J. Phipps, J. R. Brandt, F. M. Meyer and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 458; (*e*) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 463.

8 (*a*) B. D. Gates, P. Dalidowicz, A. Tebben, S. Wang and J. S. Swenton, *J. Org. Chem.*, 1992, **57**, 2135; (*b*) D. Bérard, L. Racicot, C. Sabot and S. Canesi, *Synlett*, 2008, 1076; (*c*) D. Bérard, M. A. Giroux, L. Racicot, C. Sabot and S. Canesi, *Tetrahedron*, 2008, **64**, 7537; (*d*) T. Dohi, Y. Hu, T. kamitanaka, N. Washimi and Y. Kita, *Org. Lett.*, 2011, **13**, 4814.

9 (*a*) D. Bérard, A. Jean and S. Canesi, *Tetrahedron Lett.*, 2007, **48**, 8238; (*b*) C. Sabot, D. Bérard and S. Canesi, *Org. Lett.*, 2008, **10**, 4629; (*c*) K. C. Guérard, C. Sabot, M. A. Beaulieu, M. A. Giroux and S. Canesi, *Tetrahedron*, 2010, **66**, 5893.

10 (*a*) C. Sabot, B. Commare, S. Nahi, M. A. Duceppe, K. C. Guérard and S. Canesi, *Synlett*, 2008, 3226; (*b*) K. C. Guérard, C. Sabot, L. Racicot and S. Canesi, *J. Org. Chem.*, 2009, **74**, 2039; (*c*) C. Sabot, K. C. Guérard and S. Canesi, *Chem. Commun.*, 2009, 2941; (*d*) K. C. Guérard, C. Chapelle, M. A. Giroux, C. Sabot, M. A. Beaulieu, N. Achache and S. Canesi, *Org. Lett.*, 2009, **11**, 4756; (*e*) J. A. Andrez, M. A. Giroux, J. Lucien and S. Canesi, *Org. Lett.*, 2010, **12**, 4368; (*f*) M. A. Beaulieu, C. Sabot, N. Achache, K. C. Guérard and S. Canesi, *Chem.–Eur. J.*, 2010, **16**, 11224; (*g*) M. A. Beaulieu, K. C. Guérard, G. Maertens, C. Sabot and S. Canesi, *J. Org. Chem.*, 2011, **76**, 9460; (*h*) K. C. Guérard, A. Guerinot, C. Bouchard-Aubin, M. A. Ménard, M. Lepage, M. A. Beaulieu and S. Canesi, *J. Org. Chem.*, 2012, **77**, 2121.

View Article Online

11 (*a*) Y. Tamura, T. Yakura, J. Haruta and Y. Kita, *J. Org. Chem.*, 1987, 52, 3927; (*b*) Y. Kita, H. Tohma, K. Hatanaka, T. Takada, S. Fujita, S. Mitoh, H. Sakurai and S. Oka, *J. Am. Chem. Soc.*, 1994, **116**, 3684; (*c*) T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer and Y. Kita, *Angew. Chem., Int. Ed.*, 2008, **47**, 3787; (*d*) T. Dohi and Y. Kita, *Chem. Commun.*, 2009, 2073; (*e*) T. Dohi, M. Itob, N. Yamaokaa, K. Morimotoa, H. Fujiokab and Y. Kita, *Tetrahedron*, 2009, **65**, 10797; (*f*) T. Dohi, N. Yamaoka and Y. Kita, *Tetrahedron*, 2010, **66**, 5775.

12 (*a*) A. Pelter and R. A. Drake, *Tetrahedron Lett.*, 1988, **29**, 4181; (*b*) A. Ozanne-Beaudenon and S. Quideau, *Angew. Chem., Int. Ed.*, 2005, **44**, 7065; (*c*) M. A. Ciufolini, S. Canesi, M. Ousmer and N. A. Braun, *Tetrahedron*, 2006, **62**, 5318; (*d*) L. Pouységu, S. Chassaing, D. Dejugnac, A. M. Lamidey, K. Miqueu, J. M. Sotiropoulos and S. Quideau, *Angew. Chem., Int. Ed.*, 2008, **47**, 3552; (*e*) L. Pouységu, M. Marguerit, J. Gagnepain, G. Lyvinec, A. J. Eatherton and S. Quideau, *Org. Lett.*, 2008, **10**, 5211; (*f*) B. A. Mendelsohn, S. Lee, S. Kim, F. Teyssier, V. S. Aulakh and M. A. Ciufolini, *Org. Lett.*, 2009, **11**, 1539; (*g*) S. Quideau, G. Lyvinec, K. Marguerit, Bathany, A. Ozanne-Beaudenon, T. Bufeteau, D. Cavagnat and A. Chenede, *Angew. Chem., Int. Ed.*, 2009, **48**, 4605; (*h*) H. Liang and M. A. Ciufolini, *Org. Lett.*, 2010, **12**, 1760; (*i*) M. Traoré, S. Ahmed-Ali, M. Peuchmaur and Y. S. Wong, *Tetrahedron*, 2010, **66**, 5863; (*j*) H. Liang and M. A. Ciufolini, *Tetrahedron*, 2010, **66**, 5884; (*k*) L. Pouységu, T. Sylla, T. L. B. Garnier, L. B. Rojas, J. Charris, D. Deffieux and S. Quideau, *Tetrahedron*, 2010, **66**, 5908; (*l*) H. Liang and M. A. Ciufolini, *Angew. Chem., Int. Ed.*, 2011, **50**, 11849; (*m*) T. Jen, B. A. Mendelsohn and M. A. Ciufolini, *J. Org. Chem.*, 2011, **76**, 728; (*n*) M. Traoré, S. Ahmed-Ali, M. Peuchmaur and Y. S. Wong, *J. Org. Chem.*, 2011, **76**, 1409; (*o*) S. Desjardins, G. Jacquemot and S. Canesi, *Synlett*, 2012, 1497; (*p*) T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka and Y. Kita, *Angew. Chem., Int. Ed.*, 2010, **49**, 3334; (*q*) G. Jaquemot and S. Canesi, *J. Org. Chem.*, 2012, **77**, 7588.

13 (*a*) D. G. Vanderlaan and M. A. Schwartz, *J. Org. Chem.*, 1985, **50**, 743; (*b*) N. Lewis and P. Wallbank, *Synthesis*, 1987, 1103; (*c*) Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis, in *Topics in Current Chemistry*, ed. T. Wirth, 2003, p. 224; (*d*) M. A. Ciufolini, N. A. Braun, S. Canesi, M. Ousmer, J. Chang and D. Chai, *Synthesis*, 2007, 3759; (*e*) V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2008, **108**, 5299; (*f*) S. Quideau, M. A. Looney and L. Pouységu, *Org. Lett.*, 1999, **1**, 1651; (*g*) B. A. Mendelsohn and M. A. Ciufolini, *Org. Lett.*, 2009, **11**, 4736; (*h*) H. Liang and M. A. Ciufolini, *Chem.–Eur. J.*, 2010, **16**, 13262; (*i*) M. Ousmer, N. A. Braun, C. Bavoux, M. Perrin and M. A. Ciufolini, *J. Am. Chem. Soc.*, 2001, **123**, 7534; (*j*) S. Canesi, P. Belmont, D. Bouchu, L. Rousset and M. A. Ciufolini, *Tetrahedron Lett.*, 2002, **43**, 5193; (*k*) S. Canesi, D. Bouchu and M. A. Ciufolini, *Angew. Chem., Int. Ed.*, 2004, **43**, 4336; (*l*) S. Canesi, D. Bouchu and M. A. Ciufolini, *Org. Lett.*, 2005, **7**, 175; (*m*) L. F. Silva Jr, F. A. Siqueira, E. C. Pedrozo, F. Y. M. Vieira and A. C. Doriguetto, *Org. Lett.*, 2007, **9**, 1433; (*n*) L. Pouységu, D. Deffieux and S. Quideau, *Tetrahedron*, 2010, **66**, 2235; (*o*) M. Peuchmaur, N. Saïdani, C. Botté, E. Maréchal, H. Vial and Y. S. Wong, *J. Med. Chem.*, 2008, **51**, 4870.

14 P. J. Kocienski, *Phosphorus Sulfur Relat. Elem.*, 1985, **24**, 97.

15 (*a*) Y. Mimaki, A. Kameyama, Y. Sashida, Y. Miyata and A. Fujii, *Chem. Pharm. Bull.*, 1995, **43**, 893; (*b*) J.-T. Fan, Y.-S. Chen, W.-Y. Xu, L. Du, G.-Z. Zeng, Y.-M. Zhang, J. Su, Y. Li and N.-H. Tan, *Tetrahedron Lett.*, 2010, **51**, 6810.

16 (*a*) D. Pèréz, B. A. Siesel, M. J. Malaska, E. David and K. P. C. Vollhardt, *Synlett*, 2000, 306; (*b*) O. Meth-Cohn and G. van Vuuren, *J. Chem. Soc., Perkin Trans. 1*, 1986, 233; (*c*) C. D. Buarque, G. C. G. Milit, D. J. B. Lima, L. V. Costa-Lotufo, C. Pessoa, M. Odorico de Moraes, E. Ferreira Cunha-Junior, E. C. Torres-Santos, C. D. Netto and P. R. R. Costa, *Bioorg. Med. Chem.*, 2011, **19**, 6885; (*d*) G. C. Tsui, J. Tsoung, P. Dougan and M. Lautens, *Org. Lett.*, 2012, **14**, 5542.

17 Y. Wang and F. S. Guziec, *J. Org. Chem.*, 2001, **66**, 8293.

This journal is © The Royal Society of Chemistry 2013

ANNEXE D :

"OXIDATIVE CYCLOADDITION AND CROSS-COUPLING PROCESSES ON UNACTIVATED BENZENE DERIVATIVES" SUPPORTING INFORMATION

Chemical Science, **2013**, *4*, page 1287-1292

DOI: 10.1039/c2sc22318j

Date de publication (Web) : 2 Janvier 2013

http://www.rsc.org/suppdata/sc/c2/c2sc22318j/c2sc22318j.pdf

Titre: Oxidative cycloaddition and cross-coupling processes on unactivated benzene derivatives

Auteurs: Guillaume Jacquemot, Marc-André Ménard, Chloé L'Homme et Sylvain Canesi*

Oxidative Cycloaddition and Cross-Coupling Processes on Unactivated Benzene Derivatives

Guillaume Jacquemot, Marc-André Ménard, Chloé L'Homme and Sylvain Canesi*

Laboratoire de Méthodologie et Synthèse de Produit Naturels.
Université du Québec à Montréal, C.P.8888, Succ. Centre-Ville, Montréal. H3C 3P8,
Québec, Canada.

Supporting Information

Table of Contents

1. General information SI-2

2. Experimental procedures SI-2-SI-15

3. Copies of ^{1}H and ^{13}C NMR spectra for all compounds SI-15-SI-121

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

General procedure for the formation of cycloadduct 11:
A solution of hypevalent iodine (0.32 mmol, 1.6 equiv.) in $(CF_3)_2CHOH$ ("HFIP", 0.35 ml) was added dropwise on 30 second to a vigorously stirred solution of phenol **9** (0.20 mmol, 1 equiv.) and the corresponding aromatic compound (10 equiv.) in HFIP/DCM (2:1; ml) at -4 °C. The mixture was then stirred for 30 seconds and quenched with $NaHCO_3$. The phases were separated and the aqueous phase extracted with EtOAc. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give the corresponding cycloaddition product **11**.

4a-iodo-8-(2-(phenylsulfonyl)ethyl)-4a,9b-dihydrodibenzo[b,d]furan (11a-g or 12a): Pale yellow oil: 0.032 mmol, 14.8 mg, 34-51% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 2H), 7.69 – 7.54 (m, 4H), 7.49 (s, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.73 – 6.66 (m, 2H), 6.02 (dd, J = 9.6, 4.4 Hz, 1H), 5.82 (dd, J = 9.6, 6.1 Hz, 1H), 5.36 (dd, J = 11.3, 4.4 Hz, 1H), 4.35 (d, J = 11.3 Hz, 1H), 3.40 – 3.33 (m, 2H), 3.08 – 3.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 139.3, 133.9, 133.3, 129.5, 128.9, 128.2, 128.1, 126.9, 126.6, 121.9, 109.8, 101.15, 81.3, 58.0, 49.9, 28.5; HRMS (ESI): Calc. for $C_{20}H_{18}IO_3S$ $(M+H)^+$: 465.0016; found: 465.0011.

4a-iodo-8-(2-(propylsulfonyl)ethyl)-4a,9b-dihydrodibenzo[b,d]furan (11h): Pale yellow oil: 0.037 mmol, 16.2 mg, 55% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.04 (dd, J = 8.2, 1.7 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.70 (dd, J = 6.1, 1.7 Hz, 1H), 6.05 (dd, J = 9.6, 4.4 Hz, 1H), 5.84 (dd, J = 9.6, 6.1 Hz, 1H), 5.39 (dd, J = 11.2, 4.4 Hz, 1H), 4.40 (d, J = 11.2 Hz, 1H), 3.25 – 3.09 (m, 4H), 2.91 – 2.84 (m, 2H), 1.92 – 1.79 (sx, J = 7.6 Hz, 2H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 133.3, 129.7, 129.1, 128.3, 126.9, 126.8, 121.9, 110.0, 101.2, 81.4, 55.2, 54.7, 49.9, 27.9, 16.0, 13.3; HRMS (ESI): Calc. for $C_{17}H_{20}IO_3S$ $(M+H)^+$: 431.0172; found: 431.0171.

4a-iodo-8-(2-((4-methoxyphenyl)sulfonyl)ethyl)-4a,9b-dihydrodibenzo[b,d]furan (11i): Pale yellow oil: 0.048 mmol, 24.0 mg, 48% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.8 Hz, 2H), 7.48 (s, 1H), 7.01 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.67 (dd, J = 6.2, 1.7 Hz, 1H), 6.02 (dd, J = 9.6, 4.4 Hz, 1H), 5.82 (dd, J = 9.6, 6.1 Hz, 1H), 5.36 (dd, J = 11.2, 4.4 Hz, 1H), 4.34 (d, J = 11.1 Hz, 1H), 3.88 (s, 3H), 3.37 – 3.30 (m, 2H), 3.04 – 2.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 157.2, 133.2, 130.8, 130.4, 129.6, 128.9, 128.0, 126.8, 126.1, 121.9, 114.7, 109.8, 101.2, 81.3, 58.3, 55.8, 49.9, 28.7; HRMS (ESI): Calc. for $C_{21}H_{20}IO_4S$ $(M+H)^+$: 495.0121; found: 495.014.

4a-iodo-8-(2-((4-nitrophenyl)sulfonyl)ethyl)-4a,9b-dihydrodibenzo[b,d]furan (11j): Pale yellow oil: 0.071 mmol, 36.4 mg, 41% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 8.7 Hz, 2H), 8.07 (dd, J = 7.5, 5.7 Hz, 2H), 7.45 (s, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.66 (dd, J = 10.9, 4.9 Hz, 2H), 6.00 (dd, J = 9.6, 4.3 Hz, 1H), 5.81 (dd, J = 9.6, 6.1 Hz, 1H), 5.36 (dd, J = 11.4, 4.3 Hz, 1H), 4.33 (d, J = 11.3 Hz, 1H), 3.45 (dd, J = 9.4, 6.5 Hz, 2H), 3.07 (dd, J = 9.4, 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 150.9, 145.0, 133.3, 129.7, 129.1, 128.6, 128.2, 126.7, 126.4, 124.5, 122.0, 109.9, 100.7, 81.4, 57.9, 49.8, 28.5; HRMS (ESI): Calc. for $C_{20}H_{17}INO_5S$ $(M+H)^+$: 509.9867; found: 509.9878.

2-((2-(5a-iodo-5a,9a-dihydrodibenzo[b,d]furan-2-yl)ethyl)sulfonyl)benzo[d]thiazole (11k): Pale yellow oil: 0.019 mmol, 10.2 mg, 45% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 7.6 Hz, 1H), 8.02 (d, J = 7.4 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.52 (s, 1H), 6.98 (dd, J = 8.2, 1.7 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 6.66 (dd, J = 6.1, 1.8 Hz, 1H), 6.00 (dd, J = 9.6, 4.4 Hz, 1H), 5.81 (dd, J = 9.6, 6.1 Hz, 1H), 5.28 (dd, J = 11.3, 4.4 Hz, 1H), 4.26 (d, J = 11.4 Hz, 1H), 3.81 (td, J = 7.2, 3.2 Hz, 2H), 3.24 – 3.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 157.4, 152.8, 137.0, 133.2, 129.2, 128.9, 128.2, 128.1, 127.8, 126.8, 126.7, 125.7, 122.5,

121.9, 109.8, 101.1, 81.3, 56.4, 49.8, 28.4; HRMS (ESI): Calc. for $C_{21}H_{17}INO_3S_2$ $(M+H)^+$: 521.9689; found: 521.9692.

General procedure for the formation of cycloadduct 12:

A solution of bis(*tert*-butylcarbonyloxy)iodobenzene (0.32 mmol, 1.6 equiv.) in $(CF_3)_2CHOH$ ("HFIP", 0.35 ml) was added dropwise on 30 second to a vigorously stirred solution of phenol **9** (0.20 mmol, 1 equiv.) and the corresponding aromatic compound (2.00 mmol, 10.0 equiv.) in HFIP/DCM (2:1; ml) at -4 °C. The mixture was then stirred for 30 seconds and quenched with $NaHCO_3$. The phases were separated and the aqueous phase extracted with EtOAc. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give the corresponding cycloaddition product **12**.

4a-iodo-9b-methyl-8-(2-(phenylsulfonyl)ethyl)-4a,9b-dihydrodibenzo[b,d]furan (12b):

Pale yellow oil: 0.019 mmol, 9.2 mg, 54% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, J = 5.3, 3.3 Hz, 2H), 7.70 – 7.53 (m, 4H), 7.48 (s, 1H), 6.90 (dd, J = 8.1, 1.7 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 6.56 (dd, J = 6.3, 1.7 Hz, 1H), 5.57 (dd, J = 6.3, 1.5 Hz, 1H), 5.16 (d, J = 11.0 Hz, 1H), 4.34 (d, J = 10.9 Hz, 1H), 3.41 – 3.33 (m, 2H), 3.08 – 3.00 (m, 2H), 1.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 139.3, 133.9, 133.8, 131.3, 129.5, 129.4, 128.9, 128.7, 128.2, 126.5, 122.7, 109.7, 97.1, 85.3, 58.1, 50.3, 28.5, 20.6; HRMS (ESI): Calc. for $C_{21}H_{20}IO_3S$ $(M+H)^+$: 479.0172; found: 479.0165.

9b-ethyl-4a-iodo-8-(2-(phenylsulfonyl)ethyl)-4a,9b-dihydrodibenzo[b,d]furan (12c):

Pale yellow oil: 0.020 mmol, 9.9 mg, 47% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.4 Hz, 2H), 7.69 – 7.53 (m, 4H), 7.47 (s, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.61 (d, J = 6.4 Hz, 1H), 5.57 (d, J = 6.4 Hz, 1H), 5.18 (d, J = 10.9 Hz, 1H), 4.31 (d, J = 10.9 Hz, 1H), 3.41 – 3.32 (m, 2H), 3.08 – 3.00 (m, 2H), 2.41 – 2.19 (m, 2H), 1.12 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 139.3, 136.7, 133.9, 133.8, 129.5, 129.4, 128.8, 128.7, 128.2, 126.7, 121.0, 109.7, 97.7, 84.4, 58.1, 50.4, 28.5, 27.1, 11.7; HRMS (ESI): Calc. for $C_{22}H_{22}IO_3S$ $(M+H)^+$: 493.0329; found: 493.0319.

4a-iodo-9b-isopropyl-8-(2-(phenylsulfonyl)ethyl)-4a,9b-dihydrodibenzo[b,d]furan (12d):

Pale yellow oil: 0.015 mmol, 7.7 mg, 40% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, J = 7.3 Hz, 2H), 7.70 – 7.55 (m, 5H), 7.44 (s, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.69 (d, J = 8.1 Hz,

1H), 6.63 (dd, J = 6.5, 1.9 Hz, 1H), 5.62 (d, J = 6.2 Hz, 1H), 5.22 (d, J = 10.4 Hz, 1H), 4.24 (d, J = 10.1 Hz, 1H), 3.39 – 3.30 (m, 2H), 3.07 – 3.00 (m, 2H), 2.56 (h, J = 6.5 Hz, 1H), 1.14 (dd, J = 6.8, 2.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 140.7, 139.3, 134.0, 133.9, 129.5, 129.4, 128.8, 128.7, 128.3, 126.8, 120.5, 109.7, 98.3, 83.4, 58.1, 50.6, 32.1, 28.6, 21.9, 21.1; HRMS (ESI): Calc. for $C_{23}H_{24}IO_3S$ $(M+H)^+$: 507.0485; found: 507.0489.

tert-butyl((5a-iodo-2-(2-(phenylsulfonyl)ethyl)-5a,9a-dihydrodibenzo[b,d]furan-9a-yl)methoxy)dimethylsilane (12e): Pale yellow oil: 0.014 mmol, 8.8 mg, 35% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.2 Hz, 2H), 7.71 – 7.53 (m, 4H), 7.48 (s, 1H), 6.93 – 6.87 (m, 1H), 6.67 (dd, J = 9.3, 4.8 Hz, 2H), 5.81 (d, J = 6.4 Hz, 1H), 5.25 (d, J = 10.9 Hz, 1H), 4.31 (s, 2H), 3.41 – 3.32 (m, 2H), 3.09 – 2.99 (m, 2H), 0.91 (s, 9H), 0.09 (d, J = 2.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 139.3, 137.8, 134.0, 133.9, 133.5, 129.5, 129.5, 129.0, 128.9, 128.5, 128.2, 126.7, 121.2, 109.7, 99.3, 81.7, 63.9, 58.1, 50.3, 28.5, 26.0, 18.5, -5.2, -5.3; HRMS (ESI): Calc. for $C_{27}H_{34}IO_4SSi$ $(M+H)^+$: 609.0986; found: 609.0978.

4a-iodo-8-(3-(phenylsulfonyl)propyl)-4a,9b-dihydrodibenzo[b,d]furan (12f): Pale yellow oil: 0.013 mmol, 6.2 mg, 31% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.3 Hz, 2H), 7.69 – 7.52 (m, 4H), 7.47 (s, 1H), 6.90 (d, J = 8.1 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.69 (dd, J = 6.1, 1.9 Hz, 1H), 6.06 (dd, J = 9.7, 4.5 Hz, 1H), 5.85 (dd, J = 9.6, 6.1 Hz, 1H), 5.34 (dd, J = 11.1, 4.5 Hz, 1H), 4.34 (d, J = 10.9 Hz, 1H), 3.09 (dd, J = 8.7, 7.2 Hz, 2H), 2.69 (t, J = 7.3 Hz, 2H), 2.04 (dq, J = 11.3, 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 139.4, 133.8, 133.3, 132.0, 129.4, 129.0, 128.2, 127.8, 127.0, 126.8, 121.8, 109.6, 102.0, 81.1, 55.6, 49.8, 33.8, 24.7; HRMS (ESI): Calc. for $C_{21}H_{20}IO_3S$ $(M+H)^+$: 479.0172; found: 479.0182.

8-(2-(phenylsulfonyl)ethyl)-4a,9b-dihydrodibenzo[b,d]furan (12g): Pale yellow oil: 0.041 mmol, 14.2 mg, 40% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 7.2 Hz, 2H), 7.70 – 7.52 (m, 4H), 6.98 (s, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 6.12 (dd, J = 9.8, 5.5 Hz, 1H), 5.97 – 5.88 (m, 2H), 5.77 (dd, J = 9.7, 3.3 Hz, 1H), 5.42 (dd, J = 12.1, 4.6 Hz, 1H), 4.17 (d, J = 12.0 Hz, 1H), 3.33 (dd, J = 10.4, 6.2 Hz, 2H), 2.99 (dd, J = 10.4, 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 139.3, 133.9, 130.1, 129.8, 129.4, 128.2, 128.1, 127.6, 126.5, 124.6, 121.3, 121.2, 110.0, 78.7, 58.1, 40.8, 28.4; HRMS (ESI): Calc. for $C_{20}H_{18}O_3SNa$ $(M+Na)^+$: 361.0869; found: 361.0860.

10-(2-(phenylsulfonyl)ethyl)-6a,11b-dihydronaphtho[2,1-b]benzofuran (12h): Pale yellow oil: 0.095 mmol, 37.1 mg, 72% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.3 Hz, 2H), 7.68 – 7.49 (m, 5H), 7.38 – 7.19 (m, 4H), 7.07 (d, J = 7.2 Hz, 1H), 6.87 – 6.79 (m, 2H), 6.72 (d, J = 8.1 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 5.85 – 5.76 (m, 2H), 4.64 (d, J = 10.5 Hz, 1H), 3.33 – 3.23 (m, 2H), 2.98 – 2.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 139.2, 133.8, 132.7, 130.6, 130.5, 129.8, 129.6, 129.4, 128.6, 128.5, 128.4, 128.2, 128.0, 127.7, 124.6, 124.5, 110.0, 81.4, 58.0, 43.7, 28.3; HRMS (ESI): Calc. for $C_{24}H_{20}O_3SNa$ $(M+Na)^+$: 411.1025; found: 411.1028.

2-(2-(phenylsulfonyl)ethyl)-6,11-dihydro-6,11-[1,2]benzenodibenzo[b,e]oxepine (13): A solution of bis(*tert*-butylcarbonyloxy)iodobenzene (0.17 mmol, 1.6 equiv.) in $(CF_3)_2CHOH$ ("HFIP", 0.35 ml) was added dropwise on 30 second to a vigorously stirred solution of phenol **9** (0.11 mmol, 1 equiv.) and the anthracene (0.55 mmol, 5.0 equiv.) in HFIP/DCM (2:1; ml) at -4 °C. The mixture was then stirred for 30 seconds and quenched with $NaHCO_3$. The phases were separated and the aqueous phase extracted with EtOAc. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford **13** in 58% yield (0.034 mmol, 14.8 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.2 Hz, 2H), 7.62 – 7.54 (m, 2H), 7.53 – 7.42 (m, 5H), 7.38 – 7.32 (m, 2H), 7.25 – 7.22 (m, 2H), 6.93 (d, J = 2.2 Hz, 1H), 6.71 (dd, J = 8.4, 2.2 Hz, 1H), 6.44 (d, J = 8.3 Hz, 1H), 5.88 (s, J = 6.6 Hz, 1H), 4.51 (s, 1H), 3.33 – 3.24 (m, 2H), 2.95 – 2.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 144.8, 139.3, 134.8, 133.7, 129.3, 129.3, 128.8, 128.7, 128.4, 128.1, 127.5, 127.4, 124.5, 120.3, 78.8, 57.8, 52.3, 28.0; HRMS (ESI): Calc. for $C_{28}H_{23}O_3S$ $(M+H)^+$: 439.1362; found: 439.1353.

7-(2-((4-methoxyphenyl)sulfonyl)ethyl)-3a,8b-dihydrofuro[3,2-b]benzofuran (14): A solution of bis(*tert*-butylcarbonyloxy)iodobenzene (0.08 mmol, 1.6 equiv.) in $(CF_3)_2CHOH$ ("HFIP", 0.35 ml) was added dropwise on 30 second to a vigorously stirred solution of phenol **9i** (0.05 mmol, 1 equiv.) and the furan (0.75 mmol, 15.0 equiv.) in TFE at -25 °C. After completion the reaction was quenched with $NaHCO_3$. The phases were separated and the aqueous phase extracted with EtOAc. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford **14** in 95% yield (0.047 mmol, 16.8 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.9 Hz, 2H), 7.17 (d, J = 1.4 Hz, 1H), 7.01 (d, J = 8.8 Hz, 3H), 6.76 (d, J = 8.3 Hz, 1H), 6.61 (d, J = 2.5 Hz, 1H), 5.97 (s, 2H), 5.28 (t, J = 2.3 Hz, 1H),

3.89 (s, 3H), 3.35 – 3.27 (m, 2H), 3.02 – 2.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 158.5, 151.3, 131.7, 131.5, 130.6, 130.4, 130.1, 126.3, 125.4, 114.6, 111.2, 100.2, 89.4, 85.1, 58.2, 55.8, 28.5; HRMS (ESI): Calc. for $C_{19}H_{18}O_5SNa$ $(M+Na)^+$: 381.0767; found: 381.0779.

General procedure for the formation of cycloadduct 17: A solution of bis(*tert*-butylcarbonyloxy)iodobenzene (0.22 mmol, 1.6 equiv.) in $(CF_3)_2CHOH$ ("HFIP", 0.35 ml) was added dropwise on 30 second to a vigorously stirred solution of sulfonamide **15** (0.14 mmol, 1 equiv.) and the corresponding aromatic compound (0.70 mmol, 5.0 equiv.) in HFIP/DCM (2:1; ml) at -4 °C. The mixture was then stirred for 30 seconds and quenched with $NaHCO_3$. The phases were separated and the aqueous phase extracted with EtOAc. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give the corresponding cycloaddition product **17**.

10-methyl-7-(methylsulfonyl)-7,11b-dihydro-6aH-benzo[c]carbazole (17a): Pale yellow oil: 0.074 mmol, 23.3 mg, 61% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 4H), 7.05 (dd, J = 14.5, 7.5 Hz, 2H), 6.75 (s, 1H), 6.43 (dd, J = 9.9, 2.1 Hz, 1H), 5.83 (dd, J = 9.9, 2.5 Hz, 1H), 5.53 (dt, J = 9.8, 2.3 Hz, 1H), 4.64 (d, J = 9.8 Hz, 1H), 2.94 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 135.0, 135.0, 131.6, 130.7, 129.2, 128.8, 128.1, 128.1, 127.9, 126.5, 125.3, 116.2, 64.0, 43.9, 37.7, 21.1; HRMS (ESI): Calc. for $C_{18}H_{18}NO_2S$ $(M+H)^+$: 312.1058; found: 312.1051.

7-(ethylsulfonyl)-10-methyl-7,11b-dihydro-6aH-benzo[c]carbazole (17b): Pale yellow oil: 0.081 mmol, 26.4 mg, 59% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, J = 9.1, 6.7 Hz, 4H), 7.07 (d, J = 6.7 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.72 (s, 1H), 6.41 (dd, J = 9.9, 2.0 Hz, 1H), 5.84 (dd, J = 9.9, 2.4 Hz, 1H), 5.53 (dt, J = 9.8, 2.3 Hz, 1H), 4.62 (d, J = 9.7 Hz, 1H), 3.18 – 3.08 (m, 2H), 2.22 (s, 3H), 1.38 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 134.7, 134.4, 131.6, 130.7, 129.3, 129.2, 128.6, 128.1, 128.0, 127.9, 127.1, 125.2, 115.4, 64.0, 45.9, 44.0, 21.1, 8.2; HRMS (ESI): Calc. for $C_{19}H_{20}NO_2S$ $(M+H)^+$: 326.1209; found: 326.1207.

10-methyl-7-tosyl-7,11b-dihydro-6aH-benzo[c]carbazole (17c): Pale yellow oil: 0.030 mmol, 11.7 mg, 32% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 2H), 7.24 – 7.18

(m, 4H), 7.14 – 6.99 (m, 4H), 6.55 (s, 1H), 6.38 (d, J = 9.9 Hz, 1H), 5.86 (dd, J = 9.8, 2.3 Hz, 1H), 5.39 (d, J = 9.6 Hz, 1H), 3.80 (d, J = 9.7 Hz, 1H), 2.40 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 138.0, 135.9, 135.9, 135.3, 131.6, 130.8, 129.9, 129.2, 129.1, 128.5, 128.0, 127.8, 127.8, 127.2, 127.1, 124.8, 118.1, 63.8, 43.4, 21.7, 21.2; HRMS (ESI): Calc. for $C_{24}H_{22}NO_2S$ $(M+H)^+$: 388.1369; found: 388.1374.

7-(isopropylsulfonyl)-10-methyl-7,11b-dihydro-6aH-benzo[c]carbazole (17d): Pale yellow oil: 0.032 mmol, 11.0 mg, 38% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 7.06 (d, J = 6.8 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 6.70 (s, 1H), 6.41 (d, J = 9.9 Hz, 1H), 5.86 (dd, J = 9.9, 2.2 Hz, 1H), 5.51 (d, J = 9.7 Hz, 1H), 4.63 (d, J = 9.7 Hz, 1H), 3.40 (h, J = 6.8 Hz, 1H), 2.21 (s, 3H), 1.45 – 1.37 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 134.1, 133.7, 131.7, 129.3, 129.1, 128.5, 128.1, 128.0, 127.8, 127.5, 125.2, 114.7, 64.4, 54.0, 43.9, 21.1, 17.2, 16.8; HRMS (ESI): Calc. for $C_{20}H_{22}NO_2S$ $(M+H)^+$: 340.1366; found: 340.1358.

7-(benzylsulfonyl)-10-methyl-7,11b-dihydro-6aH-benzo[c]carbazole (17e): Pale yellow oil: 0.048 mmol, 18.5 mg, 45% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.26 – 7.23 (m, 3H), 7.19 (t, J = 6.1 Hz, 2H), 7.00 (dd, J = 9.8, 4.2 Hz, 2H), 6.70 (s, 1H), 6.30 (dd, J = 9.9, 1.9 Hz, 1H), 5.69 (dd, J = 9.9, 2.5 Hz, 1H), 4.96 (dt, J = 10.1, 2.2 Hz, 1H), 4.40 (d, J = 2.6 Hz, 2H), 3.92 (d, J = 10.1 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 134.9, 134.2, 131.8, 130.8, 130.7, 129.2, 129.2, 129.0, 128.6, 128.0, 127.9, 127.8, 127.7, 127.3, 125.2, 114.7, 64.7, 57.3, 43.2, 21.2; HRMS (ESI): Calc. for $C_{24}H_{22}NO_2S$ $(M+H)^+$: 388.1369; found: 388.1381.

10-chloro-7-(methylsulfonyl)-7,11b-dihydro-6aH-benzo[c]carbazole (17f): Pale yellow oil: 0.043 mmol, 14.3 mg, 51% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 4H), 7.18 (ddd, J = 8.5, 2.0, 0.9 Hz, 1H), 7.12 – 7.06 (m, 1H), 6.93 – 6.88 (m, 1H), 6.45 (dd, J = 9.9, 2.0 Hz, 1H), 5.83 (dd, J = 9.9, 2.5 Hz, 1H), 5.55 (dt, J = 9.8, 2.3 Hz, 1H), 4.65 (d, J = 9.8 Hz, 1H), 2.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 137.0, 130.7, 130.6, 130.3, 130.1, 129.8, 129.1, 128.8, 128.5, 128.4, 128.1, 127.4, 125.9, 125.1, 117.1, 64.1, 43.8, 38.3; HRMS (ESI): Calc. for $C_{17}H_{14}NO_2SClNa$ $(M+Na)^+$: 354.0326; found: 354.0320.

10-isopropyl-7-(methylsulfonyl)-7,11b-dihydro-6aH-benzo[c]carbazole (17g): Pale yellow oil: 0.023 mmol, 7.8 mg, 52% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 4H), 7.07

(d, J = 6.7 Hz, 2H), 6.78 (s, 1H), 6.43 (dd, J = 9.9, 2.0 Hz, 1H), 5.85 (dd, J = 9.9, 2.5 Hz, 1H), 5.53 (dt, J = 9.9, 2.3 Hz, 1H), 4.65 (d, J = 9.7 Hz, 1H), 2.95 (s, 3H), 2.79 (h, J = 6.9 Hz, 1H), 1.15 (dd, J = 6.9, 3.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 137.8, 134.8, 131.7, 130.8, 129.2, 128.9, 128.1, 128.1, 128.0, 127.7, 126.5, 122.8, 116.1, 63.9, 43.9, 37.9, 33.9, 24.4, 24.0; HRMS (ESI): Calc. for $C_{20}H_{22}NO_2S$ $(M+H)^+$: 340.1366; found: 340.1361.

7-(methylsulfonyl)-10-propyl-7,11b-dihydro-6aH-benzo[c]carbazole (17h): Pale yellow oil: 0.061 mmol, 20.7 mg, 51% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 4H), 7.05 (dd, J = 12.8, 7.5 Hz, 2H), 6.74 (s, 1H), 6.43 (dd, J = 9.9, 2.0 Hz, 1H), 5.84 (dd, J = 9.9, 2.5 Hz, 1H), 5.53 (dt, J = 9.8, 2.3 Hz, 1H), 4.64 (d, J = 9.8 Hz, 1H), 2.95 (s, 3H), 2.51 – 2.43 (m, 2H), 1.53 (sx, J = 7.4 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 137.8, 134.9, 131.6, 130.7, 129.2, 128.8, 128.7, 128.1, 128.1, 127.9, 126.5, 124.6, 116.1, 64.0, 43.9, 37.8, 37.8, 24.8, 14.0; HRMS (ESI): Calc. for $C_{20}H_{22}NO_2S$ $(M+H)^+$: 340.1366; found: 340.1368.

7-(methylsulfonyl)-10-(2-(phenylsulfonyl)ethyl)-7,11b-dihydro-6aH-benzo[c]carbazole (17i): Pale yellow oil: 0.016 mmol, 7.6 mg, 54% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.2 Hz, 2H), 7.68 – 7.49 (m, 5H), 7.39 – 7.28 (m, 5H), 7.08 (dd, J = 5.7, 2.4 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.71 (s, 1H), 6.42 (dd, J = 9.9, 2.0 Hz, 1H), 5.81 (dd, J = 9.9, 2.5 Hz, 1H), 5.52 (dt, J = 9.9, 2.3 Hz, 1H), 4.60 (d, J = 9.8 Hz, 1H), 3.29 – 3.20 (m, 3H), 2.99 – 2.91 (m, 2H), 2.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 139.0, 135.6, 134.3, 134.0, 131.2, 130.6, 129.5, 129.2, 129.0, 128.7, 128.4, 128.2, 128.0, 126.2, 124.7, 116.3, 64.0, 57.6, 43.8, 38.2, 28.4; HRMS (ESI): Calc. for $C_{25}H_{23}NO_4SNa$ $(M+Na)^+$: 488.0961; found: 488.0957.

(7-(methylsulfonyl)-7,11b-dihydro-6aH-benzo[c]carbazol-10-yl)methanol (17j): Pale yellow oil: 0.064 mmol, 21.0 mg, 53% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8.1 Hz, 1H), 7.37 – 7.29 (m, 3H), 7.21 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.98 (s, 1H), 6.43 (d, J = 9.9 Hz, 1H), 5.84 (dd, J = 9.9, 2.2 Hz, 1H), 5.56 (d, J = 9.9 Hz, 1H), 4.66 (d, J = 9.9 Hz, 1H), 4.56 (s, 2H), 2.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 139.5, 137.8, 135.4, 131.8, 131.3, 130.6, 129.3, 128.9, 128.3, 128.3, 128.0, 127.8, 126.2, 123.7, 118.4, 116.0, 65.0, 60.6, 43.8, 38.1; HRMS (ESI): Calc. for $C_{18}H_{17}NO_3SNa$ $(M+Na)^+$: 350.0821; found: 350.0811.

2-(7-(methylsulfonyl)-7,11b-dihydro-6aH-benzo[c]carbazol-10-yl)ethanol (17k): Pale yellow oil: 0.042 mmol, 14.2 mg, 62% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8.1 Hz, 1H), 7.39 – 7.31 (m, 3H), 7.12 (dd, J = 7.3, 3.0 Hz, 2H), 6.84 (s, 1H), 6.47 (dd, J = 9.9, 2.0 Hz, 1H), 5.88 (dd, J = 9.9, 2.5 Hz, 1H), 5.58 (dt, J = 9.9, 2.3 Hz, 1H), 4.69 (d, J = 9.9 Hz, 1H), 3.81 (t, J = 6.5 Hz, 2H), 3.01 (s, 3H), 2.79 (t, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 135.5, 135.3, 131.4, 130.7, 130.1, 129.3, 129.2, 128.9, 128.2, 128.2, 128.0, 126.3, 125.5, 125.3, 116.2, 64.0, 63.7, 43.8, 38.8, 38.1; HRMS (ESI): Calc. for $C_{19}H_{19}NO_3SNa$ $(M+Na)^+$: 364.0978; found: 364.0972.

10-(2-((tert-butyldimethylsilyl)oxy)ethyl)-7-(methylsulfonyl)-7,11b-dihydro-6aH-benzo[c]carbazole (17l): Pale yellow oil: 0.048 mmol, 21.8 mg, 52% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.1 Hz, 1H), 7.29 (dd, J = 9.0, 4.2 Hz, 3H), 7.09 – 7.03 (m, 2H), 6.80 (s, 1H), 6.42 (dd, J = 9.9, 1.9 Hz, 1H), 5.83 (dd, J = 9.9, 2.4 Hz, 1H), 5.53 (dt, J = 9.8, 2.2 Hz, 1H), 4.63 (d, J = 9.8 Hz, 1H), 3.71 (t, J = 6.6 Hz, 2H), 2.93 (s, 3H), 2.69 (t, J = 6.6 Hz, 2H), 0.81 (d, J = 6.6 Hz, 10H), -0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 136.7, 134.9, 131.5, 130.7, 129.4, 129.2, 128.8, 128.2, 128.1, 127.9, 126.5, 125.6, 121.2, 116.1, 64.4, 64.0, 43.9, 39.1, 37.7, 26.0, 18.4, -5.3, -5.4; HRMS (ESI): Calc. for $C_{25}H_{33}NO_3SNa$ $(M+Na)^+$: 478.1843; found: 478.1850.

7-(methylsulfonyl)-10-(trimethylsilyl)-7,11b-dihydro-6aH-benzo[c]carbazole (17m): Pale yellow oil: 0.038 mmol, 14.2 mg, 43% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 1H), 7.40 – 7.31 (m, 3H), 7.08 (d, J = 5.5 Hz, 2H), 6.44 (dd, J = 9.9, 2.0 Hz, 1H), 5.86 (dd, J = 9.9, 2.5 Hz, 1H), 5.54 (dt, J = 10.0, 2.3 Hz, 1H), 4.67 (d, J = 10.0 Hz, 1H), 2.98 (s, 3H), 0.19 – 0.15 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 136.6, 134.0, 133.9, 131.6, 130.7, 129.3, 129.2, 129.0, 128.1, 128.0, 126.1, 115.1, 63.7, 43.8, 38.4, -0.9; HRMS (ESI): Calc. for $C_{20}H_{24}NO_2SSi$ $(M+H)^+$: 370.1292; found: 370.1299.

10-isopropyl-7-(methylsulfonyl)-7,11b-dihydro-6aH-benzo[c]carbazol-5-yl methanesulfonate (18) and 4-(N-(4-isopropylphenyl)methylsulfonamido)naphthalen-1-yl methanesulfonate (19) :

A solution of bis(*tert*-butylcarbonyloxy)iodobenzene (0.08 mmol, 1.6 equiv.) in $(CF_3)_2CHOH$ ("HFIP", 0.2 ml) was added dropwise on 30 second to a vigorously stirred solution of sulfonamide **15a** (10.7 mg , 0.05 mmol, 1 equiv.) and the O-Mesyl-Naphthol (0.35 mmol, 7.0 equiv.) in HFIP/DCM (2:1; ml) at -4 °C. The mixture was then stirred for 30 seconds and

quenched with $NaHCO_3$. The phases were separated and the aqueous phase extracted with EtOAc. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford **18 and 19** in 72% yield (0.036 mmol, 15.6 mg) as a 1:1.2 ratio. **18:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 7.6 Hz, 1H), 7.48 – 7.33 (m, 5H), 7.11 (d, J = 8.2 Hz, 1H), 6.78 (s, 1H), 5.93 (d, J = 2.9 Hz, 1H), 5.70 (dd, J = 9.8, 3.0 Hz, 1H), 4.68 (d, J = 9.7 Hz, 1H), 3.09 (s, 3H), 2.99 (s, 3H), 2.80 (p, J = 6.9 Hz, 1H), 1.16 (d, J = 4.0 Hz, 3H), 1.14 (d, J = 4.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 145.9, 137.5, 133.7, 133.0, 129.8, 129.2, 128.3, 126.9, 123.4, 122.8, 115.8, 114.5, 63.3, 43.8, 38.3, 38.1, 33.9, 24.4, 24.0. HRMS (ESI): Calc. for $C_{21}H_{24}NO_5S_2$ $(M+H)^+$: 434.1090; found: 434.1083.

19: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (dd, J = 7.1, 2.4 Hz, 1H), 8.14 (dd, J = 7.0, 2.5 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.60 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 3.25 (s, 3H), 3.24 (s, 3H), 2.86 (p, J = 6.9 Hz, 1H), 1.19 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 145.6, 138.7, 136.3, 133.8, 128.6, 128.4, 128.1, 127.7, 127.4, 125.9, 124.4, 122.1, 118.2, 40.1, 38.4, 33.7, 24.0. HRMS (ESI): Calc. for $C_{21}H_{23}NO_5S_2Na$ $(M+Na)^+$: 456.0910; found: 456.0913.

(9s,10s)-10-(N-p-tolylmethylsulfonamido)-9,10-dihydroanthracen-9-yl pivalate (20) :
A solution of bis(*tert*-butylcarbonyloxy)iodobenzene (0.096 mmol, 1.6 equiv.) in $(CF_3)_2CHOH$ ("HFIP", 0.2 ml) was added dropwise on 30 second to a vigorously stirred solution of sulfonamide **15a** (11.1 mg, 0.060 mmol, 1 equiv.) and the anthracene (0.299 mmol, 5.0 equiv.) in HFIP/DCM (2:1; ml) and Na_2CO_3 at -4 °C. The mixture was then stirred for 30 seconds and quenched with $NaHCO_3$. The phases were separated and the aqueous phase extracted with EtOAc. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford **20** in 46% yield (0.027 mmol, 12.1 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 7.5 Hz, 2H), 7.46 (t, J = 7.4 Hz, 2H), 7.35 (t, J = 7.1 Hz, 2H), 7.02 (d, J = 7.8 Hz, 2H), 6.85 (d, J = 7.0 Hz, 2H), 6.84 (s, 1H), 6.16 (d, J = 8.2 Hz, 2H), 5.52 (s, 1H), 3.00 (s, 3H), 2.26 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 139.7, 138.4, 133.2, 131.9, 131.7, 129.7, 129.4, 128.5, 128.5, 125.2, 66.4, 60.3, 41.1, 39.1, 27.4, 21.3. HRMS (ESI): Calc. for $C_{27}H_{30}NO_4S$ $(M+H)^+$: 464.1890; found: 464.1882.

General procedure for the formation of coupling product 5:

Trifluoroacetic acid (0.55 mmol, 5.0 equiv.) was added to a solution of cycloaddition product **21** (0.11 mnol, 1.0 equiv.) in DCM at room temperature and the solution was heated at 40 °C. After completion, the solution was evaporated under reduced pressure and purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give the corresponding coupling product **5**.

2'-iodo-5-(2-(phenylsulfonyl)ethyl)-[1,1'-biphenyl]-2-ol (5a): Pale yellow oil: 0.032 mmol, 15.0 mg, 97% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.92 (m, 3H), 7.67 – 7.54 (m, 3H), 7.43 (dd, J = 7.4, 6.6 Hz, 1H), 7.24 (d, J = 1.6 Hz, 1H), 7.08 (ddd, J = 15.8, 8.0, 1.9 Hz, 2H), 6.88 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 2.1 Hz, 1H), 3.41 – 3.32 (m, 2H), 3.06 – 2.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 141.5, 139.9, 139.2, 133.9, 131.3, 131.0, 130.3, 130.1, 129.8, 129.5, 129.4, 128.9, 128.3, 116.4, 100.6, 57.9, 28.1; IR υ (cm−1) 3418, 1634, 1511, 1446, 1306, 1149; HRMS (ESI): Calc. for $C_{20}H_{18}IO_3S$ $(M+H)^+$: 465.0016; found: 465.0013.

2'-iodo-5'-methyl-5-(2-(phenylsulfonyl)ethyl)-[1,1'-biphenyl]-2-ol (5b): Pale yellow oil: 0.051 mmol, 24.5 mg, 91% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.1 Hz, 2H), 7.82 (d, J = 8.1 Hz, 1H), 7.67 – 7.53 (m, 3H), 7.07 (d, J = 1.9 Hz, 1H), 7.04 (dd, J = 8.3, 2.3 Hz, 1H), 6.92 (dd, J = 8.2, 2.1 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 2.2 Hz, 1H), 3.41 – 3.33 (m, 2H), 3.05 – 2.97 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 141.2, 139.6, 139.2, 139.1, 133.9, 131.8, 131.3, 131.2, 130.3, 129.7, 129.5, 129.4, 128.3, 116.3, 96.3, 57.9, 28.1, 21.0; HRMS (ESI): Calc. for $C_{21}H_{23}INO_3S$ $(M+NH_4)^+$: 496.0438; found: 496.0416.

5'-ethyl-2'-iodo-5-(2-(phenylsulfonyl)ethyl)-[1,1'-biphenyl]-2-ol (5c): Pale yellow oil: 0.041 mmol, 20.0 mg, 98% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.1 Hz, 2H), 7.85 (d, J = 8.1 Hz, 1H), 7.67 – 7.55 (m, 3H), 7.09 (d, J = 2.1 Hz, 1H), 7.05 (dd, J = 8.3, 2.2 Hz, 1H), 6.98 – 6.91 (m, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 2.1 Hz, 1H), 4.71 (s, 1H), 3.41 – 3.33 (m, 2H), 3.05 – 2.98 (m, 2H), 2.62 (q, J = 7.6 Hz, 2H), 1.23 (t, J = 7.5 Hz , 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 145.4, 141.2, 139.8, 139.2, 133.9, 131.4, 130.6, 130.3, 130.0, 129.7, 129.5, 129.4, 128.3, 116.3, 96.5, 57.9, 28.4, 28.1, 15.4; HRMS (ESI): Calc. for $C_{22}H_{22}IO_3S$ $(M+H)^+$: 493.0329; found: 493.0324.

2'-iodo-5'-isopropyl-5-(2-(phenylsulfonyl)ethyl)-[1,1'-biphenyl]-2-ol (5d): Pale yellow oil: 0.059 mmol, 29.7 mg, 90% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 7.2 Hz, 2H), 7.86 (d, J = 8.2 Hz, 1H), 7.67 – 7.57 (m, 4H), 7.12 (d, J = 2.2 Hz, 1H), 7.05 (dd, J = 8.3, 2.1 Hz, 1H), 6.98 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 3.42 – 3.34 (m, 2H), 3.06 – 2.97 (m, 2H), 2.94 – 2.83 (m, 1H), 1.23 (t, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 150.2, 141.2, 139.8, 139.1, 137.5, 134.0, 131.5, 130.3, 129.7, 129.5, 129.4, 129.3, 128.8, 128.6, 128.3, 116.3, 96.6, 57.9, 33.8, 28.1, 23.9, 23.9; IR υ (cm−1) 3426, 1509, 1446, 1306, 1149; HRMS (ESI): Calc. for $C_{23}H_{24}IO_3S$ $(M+H)^+$: 507,0485; found: 507,0493.

5-(2-(phenylsulfonyl)ethyl)-[1,1'-biphenyl]-2-ol (5e): Pale yellow oil: 0.082 mmol, 27.7 mg, 97% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 7.2 Hz, 2H), 7.67 – 7.55 (m, 3H), 7.50 – 7.37 (m, 5H), 7.02 – 6.96 (m, 2H), 6.87 (d, J = 8.1 Hz, 1H), 3.42 – 3.33 (m, 2H), 3.06 – 2.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 139.2, 136.8, 133.9, 130.2, 129.7, 129.5, 129.4, 129.1, 129.0, 128.6, 128.2, 128.2, 116.4, 57.9, 28.1; IR υ (cm−1) 3425, 1446, 1305, 1149; HRMS (ESI): Calc. for $C_{40}H_{36}NaO_6S_2$ $(2M+Na)^+$: 699.1846; found: 699.1823.

2'-iodo-5-(2-((4-methoxyphenyl)sulfonyl)ethyl)-[1,1'-biphenyl]-2-ol (5f): Pale yellow oil: 0.025 mmol, 12.3 mg, 87% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 – 7.95 (m, 1H), 7.85 (d, J = 8.9 Hz, 2H), 7.43 (dt, J = 7.5, 3.7 Hz, 1H), 7.08 (ddd, J = 15.7, 7.9, 1.9 Hz, 2H), 7.02 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 2.1 Hz, 1H), 3.88 (s, 3H), 3.38 – 3.30 (m, 2H), 3.05 – 2.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 151.2, 141.6, 139.9, 131.3, 131.0, 130.5, 130.3, 130.1, 129.8, 129.6, 128.9, 128.4, 116.4, 114.7, 100.6, 58.2, 55.9, 28.3; IR υ (cm−1) 3418, 1594, 1497, 1262, 1144; HRMS (ESI): Calc. for $C_{21}H_{20}IO_4S$ $(M+H)^+$: 495.0121; found: 495.0116.

2-(naphthalen-1-yl)-4-(2-(phenylsulfonyl)ethyl)phenol (5g): Pale yellow oil: 0.030 mmol, 11.5 mg, 98% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, J = 5.3, 3.2 Hz, 4H), 7.63 (d, J = 7.3 Hz, 1H), 7.55 (t, J = 7.8 Hz, 5H), 7.49 (dd, J = 8.5, 1.3 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.12 (dd, J = 8.3, 2.3 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 3.42 – 3.35 (m, 2H), 3.09 – 3.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 139.3, 134.1, 133.9, 133.7, 131.8, 131.0, 129.5, 129.5, 129.2, 128.7, 128.3, 128.2, 127.0, 126.8, 126.6, 125.9, 125.6, 116.2, 57.9, 28.1; HRMS (ESI): Calc. for $C_{24}H_{24}NO_3S$ $(M+NH_4)^+$: 406.1471; found: 406.1453.

N-(4-methyl-2-(naphthalen-1-yl)phenyl)ethanesulfonamide (5h): Pale yellow oil: 0.074 mmol, 24.0 mg, 97% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 2H), 7.62 – 7.46 (m, 5H), 7.41 (dd, J = 7.0, 1.1 Hz, 1H), 7.30 (dd, J = 8.3, 1.6 Hz, 1H), 7.22 (d, J = 1.9 Hz, 1H), 2.83 (q, J = 7.4 Hz, 2H), 2.41 (s, 3H), 0.80 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 134.8, 134.0, 132.6, 132.1, 131.8, 131.6, 130.0, 129.2, 128.9, 127.6, 127.2, 126.7, 125.8, 125.2, 120.8, 46.1, 20.9, 7.9; IR υ (cm−1) 3357, 1498, 1333, 1153; HRMS (ESI): Calc. for $C_{19}H_{20}NO_2S$ $(M+H)^+$: 326.1209; found: 326.1203.

N-(2-(naphthalen-1-yl)-4-propylphenyl)methanesulfonamide (5i): Pale yellow oil: 0.051 mmol, 17.2 mg, 83% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.3 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.46 (d, J = 3.2 Hz, 2H), 7.39 (d, J = 7.0 Hz, 1H), 7.30 (dd, J = 8.3, 1.9 Hz, 1H), 7.15 (d, J = 1.9 Hz, 1H), 2.69 (s, 3H), 2.67 – 2.59 (m, 2H), 1.68 (sx, J = 7.4 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 135.0, 134.1, 132.7, 131.8, 131.7, 131.5, 129.4, 129.2, 128.9, 127.7, 127.2, 126.7, 125.8, 125.1, 120.9, 39.4, 37.4, 24.6, 13.9; HRMS (ESI): Calc. for $C_{20}H_{22}NO_2S$ $(M+H)^+$: 340.1366; found: 340.1359.

N-(4-isopropyl-2-(naphthalen-1-yl)phenyl)methanesulfonamide (5j): Pale yellow oil: 0.105 mmol, 35.8 mg, 97% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.4 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.48 – 7.45 (m, 2H), 7.40 (dd, J = 7.0, 1.1 Hz, 1H), 7.35 (dd, J = 8.4, 2.2 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 2.95 (h, J = 6.9 Hz, 1H), 2.69 (s, 3H), 1.27 (d, J = 1.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 135.1, 134.1, 132.7, 131.8, 131.7, 129.6, 129.2, 128.9, 127.7, 127.4, 127.2, 126.7, 125.8, 125.1, 121.0, 39.5, 33.7, 24.1; HRMS (ESI): Calc. for $C_{20}H_{22}NO_2S$ $(M+H)^+$: 340.1366; found: 340.1352.

N-(4-(2-hydroxyethyl)-2-(naphthalen-1-yl)phenyl)methanesulfonamide (5k): Pale yellow oil: 0.016 mmol, 5.5 mg, 76% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.55 (ddd, J = 7.6, 6.5, 5.0 Hz, 2H), 7.45 (d, J = 3.7 Hz, 2H), 7.40 – 7.33 (m, 2H), 7.20 (d, J = 2.0 Hz, 1H), 6.01 (s, 1H), 3.91 (t, J = 6.5 Hz, 2H), 2.91 (t, J = 6.5 Hz, 2H), 2.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 134.6, 134.1, 133.5, 132.1, 131.9, 131.7, 130.0, 129.4, 129.0, 127.8, 127.3, 126.8, 125.8, 125.0, 120.9, 63.6, 39.6, 38.6; IR υ (cm−1) 3349, 1496, 1329, 1155; HRMS (ESI): Calc. for $C_{19}H_{19}NNaO_3S$ $(M+Na)^+$: 364.0978; found: 364.0968.

4-(methylsulfonamido)-3-(naphthalen-1-yl)phenethyl 2,2,2-trifluoroacetate (5l): Pale yellow oil: 0.038 mmol, 16.5 mg, 79% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.62 – 7.51 (m, 2H), 7.50 – 7.32 (m, 5H), 7.19 (d, J = 1.9 Hz, 1H), 4.59 (t, J = 6.8 Hz, 2H), 3.09 (t, J = 6.8 Hz, 2H), 2.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.2, 133.1, 132.1, 131.9, 131.7, 129.9, 129.6, 129.0, 127.7, 127.4, 126.9, 125.8, 124.9, 120.7, 68.2, 39.6, 34.1; HRMS (ESI): Calc. for $C_{21}H_{18}F_3NNaO_4S$ $(M+Na)^+$: 460.0801; found: 460.0795.

N-(2-(naphthalen-1-yl)-4-(2-(phenylsulfonyl)ethyl)phenyl)methanesulfonamide (5m): Pale yellow oil: 0.011 mmol, 5.0 mg, 94% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (t, J = 6.8 Hz, 4H), 7.72 – 7.63 (m, 2H), 7.62 – 7.51 (m, 4H), 7.44 (t, J = 7.5 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.08 (d, J = 1.6 Hz, 1H), 5.98 (s, 1H), 3.44 – 3.36 (m, 2H), 3.15 – 3.06 (m, 2H), 2.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 134.4, 134.0, 132.0, 131.6, 131.4, 129.6, 129.6, 129.4, 129.1, 128.3, 127.7, 127.4, 126.9, 125.8, 124.8, 120.8, 57.5, 39.7, 28.2; HRMS (ESI): Calc. for $C_{25}H_{24}NO_4S_2$ $(M+H)^+$: 466.1141; found: 466.1133.

General procedure for the formation of coupling product 23:

A solution of bis(*tert*-butylcarbonyloxy)iodobenzene (0.17 mmol, 1.6 equiv.) in $(CF_3)_2CHOH$ ("HFIP", 0.35 ml) was added dropwise on 30 second to a vigorously stirred solution of sulfamide **22** (0.11 mmol, 1 equiv.) and naphthalene (0.55 mmol, 5.0 equiv.) in HFIP/DCM (2:1; ml) at -4 °C. The mixture was then stirred for 30 seconds and quenched with $NaHCO_3$. The phases were separated and the aqueous phase extracted with EtOAc. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give the corresponding coupling product **23**.

N-(4-methyl-2-(naphthalen-1-yl)phenyl)pyrrolidine-1-sulfonamide (23a): Pale yellow oil: 0.035 mmol, 12.9 mg, 55% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.57 – 7.48 (m, 3H), 7.46 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 3.36 (t, J = 6.6 Hz, 4H), 2.28 (s, 3H), 1.72 – 1.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 138.2, 135.9, 135.1, 132.0, 129.7, 128.9, 128.4, 128.0, 127.1, 126.4, 125.6, 125.5, 123.8, 49.0, 25.8, 21.0; HRMS (ESI): Calc. for $C_{21}H_{23}N_2O_2S$ $(M+H)^+$: 367.1475; found: 367.1471.

N-(4-ethyl-2-(naphthalen-1-yl)phenyl)pyrrolidine-1-sulfonamide (23b): Pale yellow oil: 0.057 mmol, 21.6 mg, 64% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 7.4 Hz, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.58 – 7.45 (m, 5H), 7.11 (d, J = 8.5 Hz, 2H), 3.36 (t, J = 6.6 Hz, 4H), 2.58 (q, J = 7.6 Hz, 2H), 1.71 – 1.64 (m, 4H), 1.17 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 140.3, 138.2, 135.1, 132.1, 128.9, 128.5, 128.4, 128.1, 127.1, 126.4, 125.6, 125.5, 123.8, 49.0, 28.4, 25.8, 15.5; IR υ (cm−1) 1595, 1506, 1343, 1156; HRMS (ESI): Calc. for $C_{22}H_{24}N_2NaO_2S$ $(M+Na)^+$: 403.1451; found: 403.1431.

N-(4-isopropyl-2-(naphthalen-1-yl)phenyl)pyrrolidine-1-sulfonamide (23c): Pale yellow oil: 0.031 mmol, 12.4 mg, 54% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 7.4 Hz, 1H), 7.85 (d, J = 8.1 Hz, 2H), 7.59 – 7.45 (m, 5H), 7.13 (d, J = 8.5 Hz, 2H), 3.35 (t, J = 6.5 Hz, 4H), 2.92 – 2.76 (m, 1H), 1.71 – 1.63 (m, 4H), 1.18 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 140.3, 138.2, 135.1, 132.1, 128.9, 128.4, 128.0, 127.1, 126.4, 125.6, 125.5, 123.8, 49.0, 33.7, 25.8, 24.0. IR υ (cm−1) 1498, 1343, 1156; HRMS (ESI): Calc. for $C_{23}H_{27}N_2O_2S$ $(M+H)^+$: 395.1788; found: 395.1797.

N-(4-chloro-2-(naphthalen-1-yl)phenyl)pyrrolidine-1-sulfonamide (23d): Pale yellow oil: 0.054 mmol, 21.0 mg, 81% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 – 8.21 (m, 1H), 7.92 – 7.79 (m, 4H), 7.58 – 7.48 (m, 3H), 7.48 – 7.40 (m, 3H), 7.23 (d, J = 8.9 Hz, 2H), 3.33 (d, J = 6.4 Hz, 4H), 1.72 – 1.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 137.4, 135.1, 131.9, 131.1, 129.5, 129.4, 129.2, 128.6, 128.7, 127.4, 126.6, 125.8, 125.6, 123.5, 49.0, 25.8. HRMS (ESI): Calc. for $C_{20}H_{19}ClKN_2O_2S$ $(M+K)^+$: 425.0487; found: 425.0466.

N-(2-(naphthalen-1-yl)-4-(trimethylsilyl)phenyl)pyrrolidine-1-sulfonamide (23e): Pale yellow oil: 0.056 mmol, 23.7 mg, 52% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 8.0 Hz, 1H), 7.90 – 7.82 (m, 3H), 7.52 (q, J = 8.0 Hz, 4H), 7.43 (q, J = 8.6 Hz, 4H), 3.37 (s, 4H), 1.72 – 1.65 (m, 4H), 0.21 (s, J = 3.2 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 137.7, 137.3, 135.1, 134.2, 132.2, 129.1, 128.4, 128.4, 127.2, 126.5, 125.6, 123.8, 123.5, 49.0, 25.8, -1.0; IR υ (cm−1) 1592, 1499, 1347, 1157; HRMS (ESI): Calc. for $C_{46}H_{56}N_4NaO_4S_2Si$ $(2M+Na)^+$: 871.3174; found: 871.3148.

Diethyl 8-(2-(phenylsulfonyl)ethyl)-1,4,4a,9b-tetrahydro-1,4-pidiazanodibenzo[b,d]furan-10,11-dicarboxylate (26) :

To a solution of **12a** (36.7 mg, 0.079 mmol, 1.0 equiv.) in benzene (1.0 ml) was added DEAD (0.094 mmol, 1.2 equiv.). The reaction was heated at 60°C and the reaction was followed by TLC. After completion, the mixture was rapidly purified by silica gel chromatography with a mixture of ethyl acetate/hexane and the residue was treated with LiOH in THF/H_2O (1:1) at 40°C. After 24h, the reaction was quenched with NH_4Cl. The phases were separated and the aqueous phase extracted with EtOAc. The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford **26** in 59 % yield (0.047 mmol, 29.5 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 7.3 Hz, 2H), 7.72 – 7.64 (m, 1H), 7.63 – 7.50 (m, 3H), 6.91 (d, J = 7.7 Hz, 1H), 6.62 (s, 1H), 6.55 (d, J = 8.2 Hz, 1H), 6.35 (s, 1H), 5.20 – 5.00 (m, 2H), 4.89 (s, 1H), 4.34 – 4.10 (m, 4H), 3.39 – 3.29 (m, 2H), 3.07 – 2.96 (m, 2H), 1.35 – 1.22 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 157.2, 139.2, 133.9, 129.8, 129.5, 128.2, 125.4, 109.8, 80.7, 63.4, 63.2, 58.0, 54.4, 51.0, 28.4, 14.6, 14.5; HRMS (ESI): Calc. for $C_{26}H_{27}IN_2O_7S$ $(M+H)^+$: 638.0578; found: 638.0568.

10-methyl-7-(methylsulfonyl)-6,6a,7,11b-tetrahydro-5H-benzo[c]carbazole (27) :

To a solution of **17a** (23.2 mg, 0.075 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added Pd/C (0.0038mmol, 0.05 equiv.). The mixture was stirred at room temperature and the reaction was followed by Mass Spectroscopy. After completion the mixture was filtered through Celite and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford **28** in 66% yield (0.049 mmol, 15.4 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.3 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.21 (td, J = 7.4, 1.3 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.90 (s, 1H), 4.81 – 4.71 (m, 2H), 2.93 (d, J = 7.0 Hz, 3H), 2.69 (t, J = 6.0 Hz, 2H), 2.38 – 2.26 (m, 1H), 2.23 (s, 3H), 2.03 – 1.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 138.2, 135.0, 134.6, 134.4, 129.3, 129.0, 128.8, 127.0, 126.7, 125.9, 115.2, 63.1, 44.9, 36.4, 29.8, 26.2, 21.1. HRMS (ESI): Calc. for $C_{18}H_{20}NO_2S$ $(M+H)^+$: 314.1209; found: 314.1211.

10-methyl-7-(methylsulfonyl)-6,6a,7,11b-tetrahydro-5H-benzo[c]carbazole-5,6-diol (28) :

To a solution of **17a** (18.7 mg, 0.060 mmol, 1.0 equiv.) in THF (1.5 mL) was added OsO_4 (0.012 mmol, 0.2 equiv.) and NMO (0.120 mmol, 2.0 equiv.). The mixture was stirred at room temperature and the reaction was followed by TLC. After completion, $Na_2S_2O_3$ was

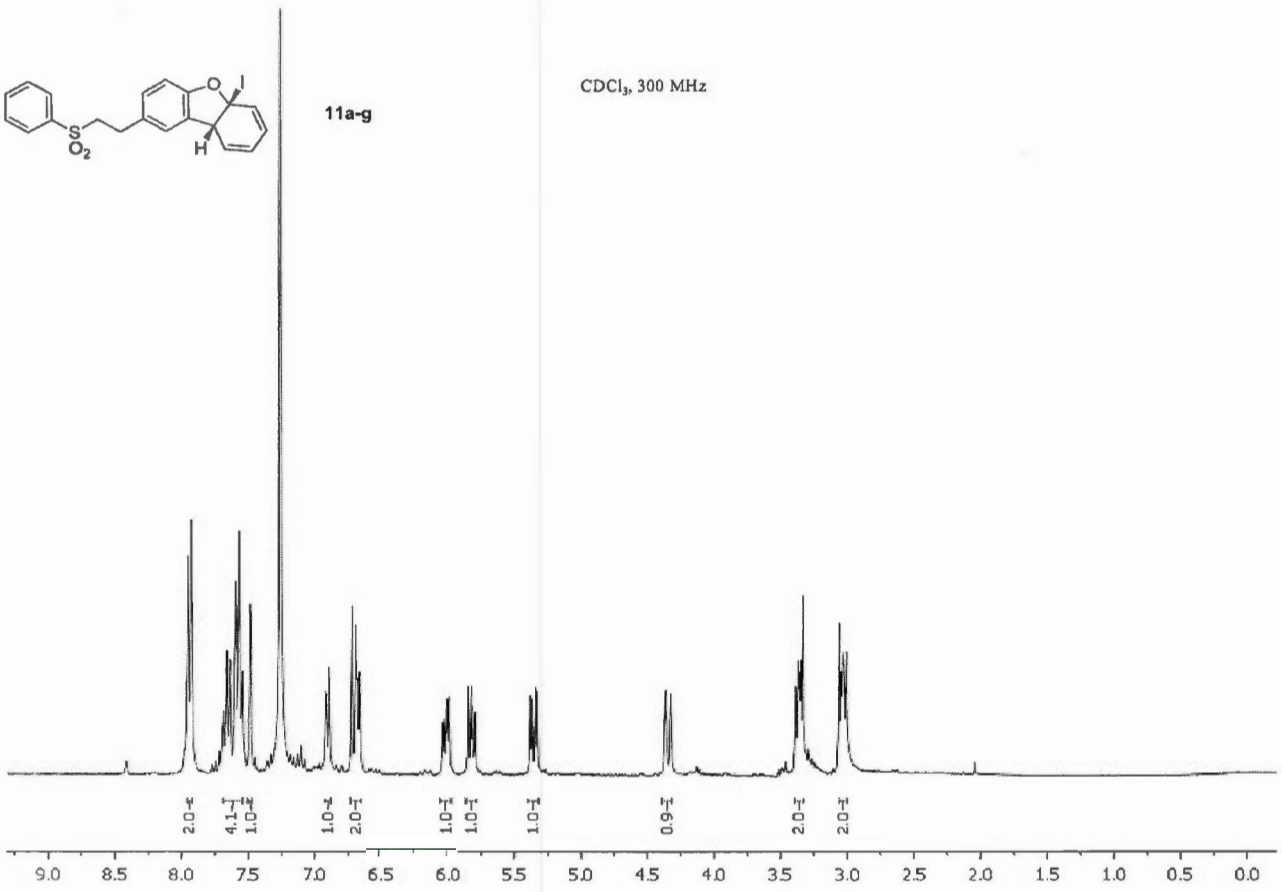
added, followed by Celite and EtOAc. The mixture was stirred during 30 minutes, filtered through Celite and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford **28** in 60% yield (0.036 mmol, 12.5 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 4.0 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.99 (s, 1H), 4.85 (t, J = 9.9 Hz, 1H), 4.81 – 4.74 (m, 2H), 4.01 (dd, J = 7.4, 2.8 Hz, 1H), 2.97 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 135.5, 135.0, 134.2, 133.1, 130.0, 129.4, 129.2, 129.0, 127.9, 125.3, 117.2, 70.9, 69.5, 65.3, 44.7, 37.0, 21.2. HRMS (ESI): Calc. for $C_{18}H_{20}NO_4S$ $(M+H)^+$: 346.1108; found: 346.1102.

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

This journal is © The Royal Society of Chemistry 2013

11a-g

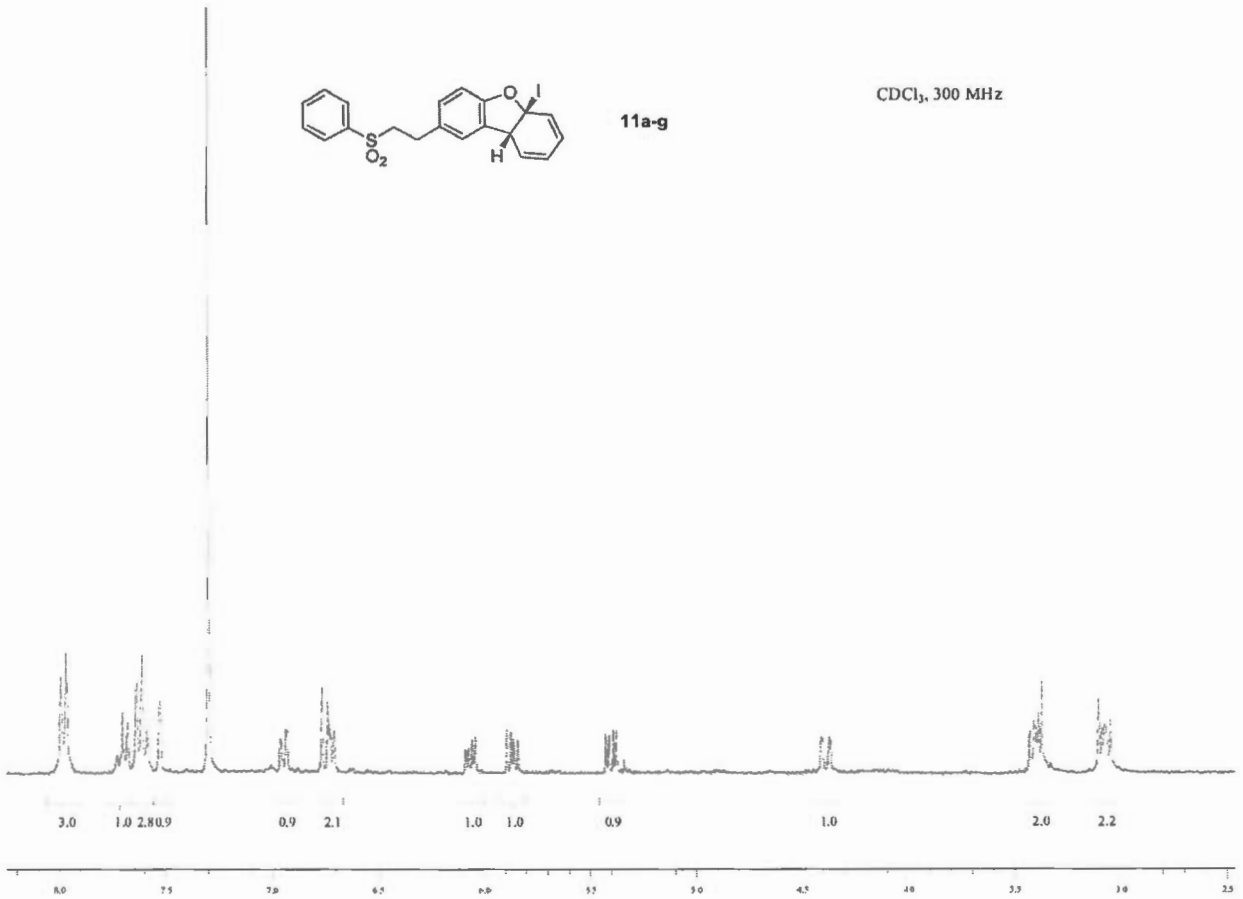
$CDCl_3$, 300 MHz



This journal is © The Royal Society of Chemistry 2013

11a-g

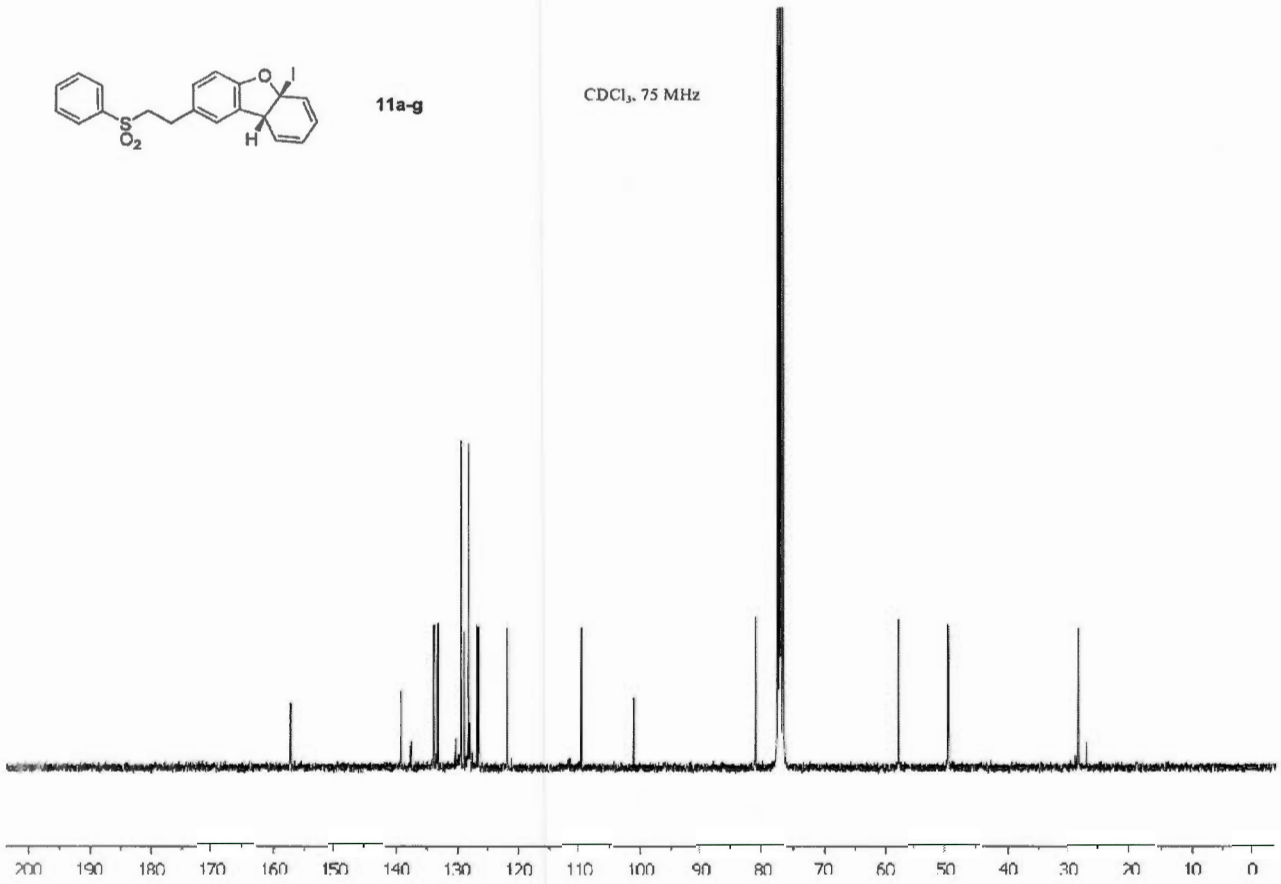
$CDCl_3$, 300 MHz



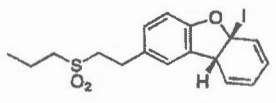
This journal is © The Royal Society of Chemistry 2013

11a-g

$CDCl_3$, 75 MHz

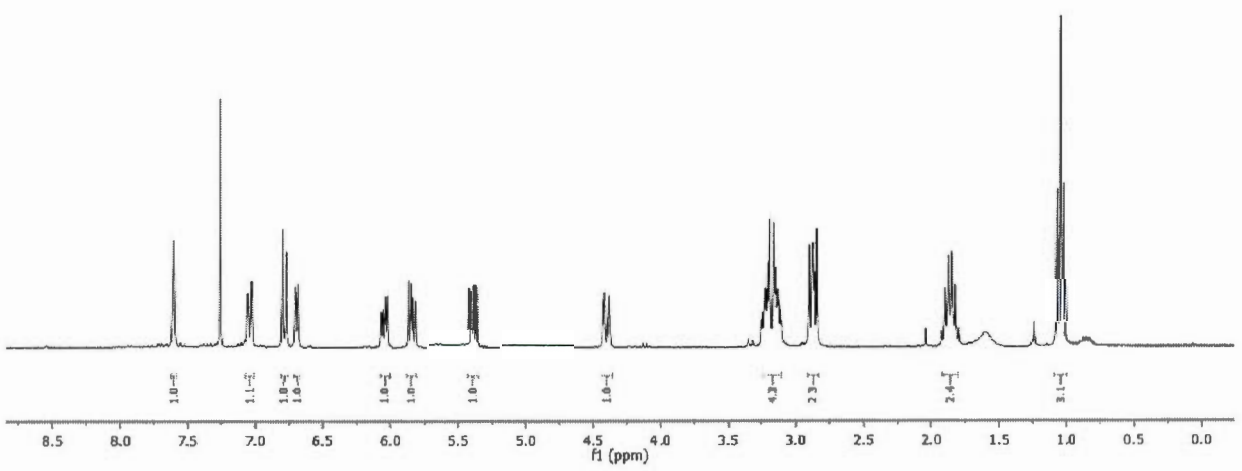


This journal is © The Royal Society of Chemistry 2013



11h

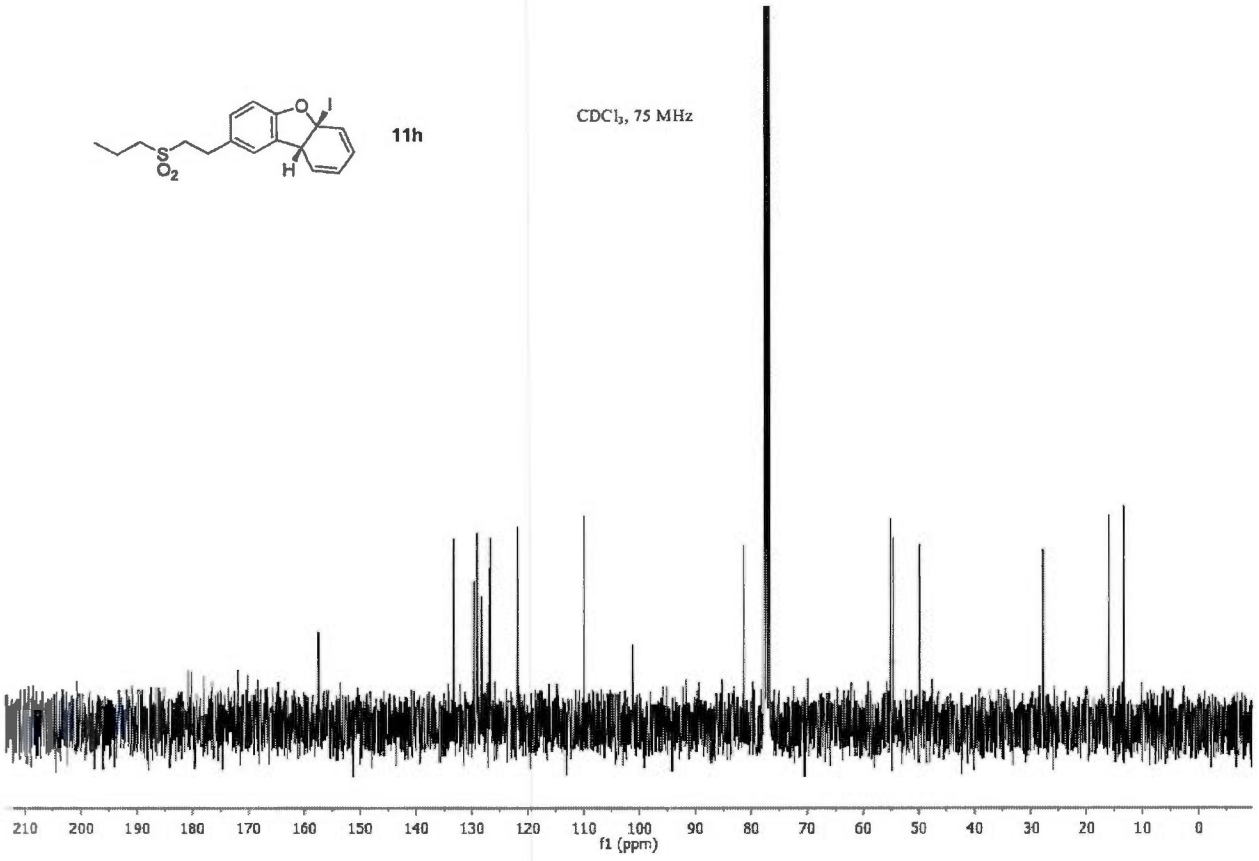
$CDCl_3$, 300 MHz



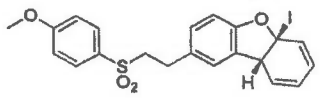
This journal is © The Royal Society of Chemistry 2013

11h

$CDCl_3$, 75 MHz

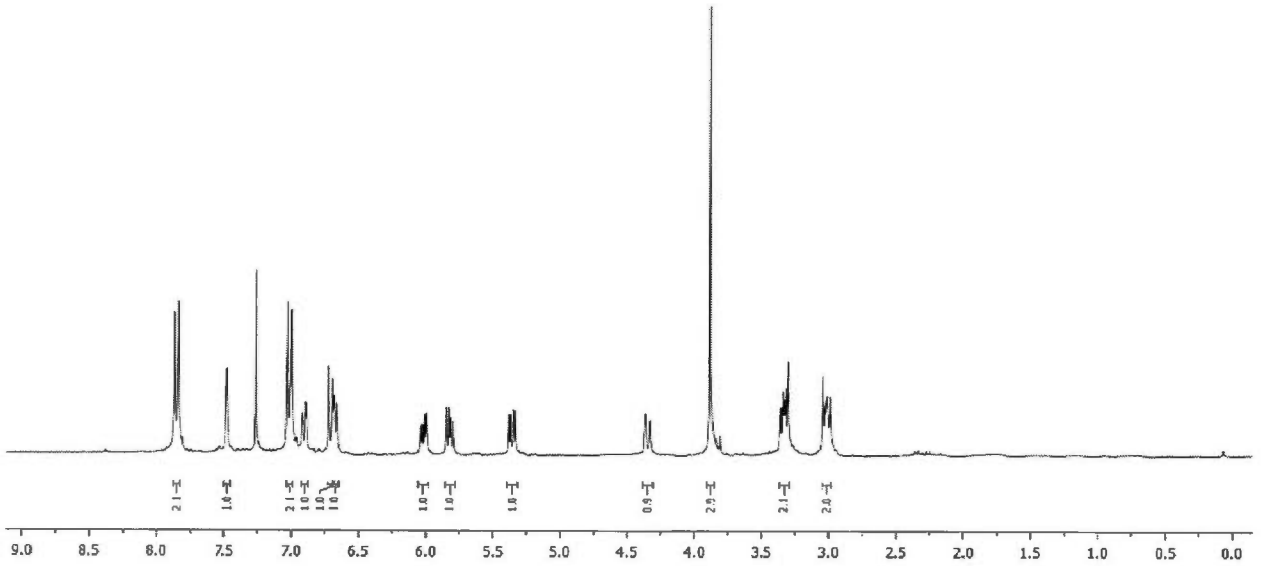


This journal is © The Royal Society of Chemistry 2013



11i

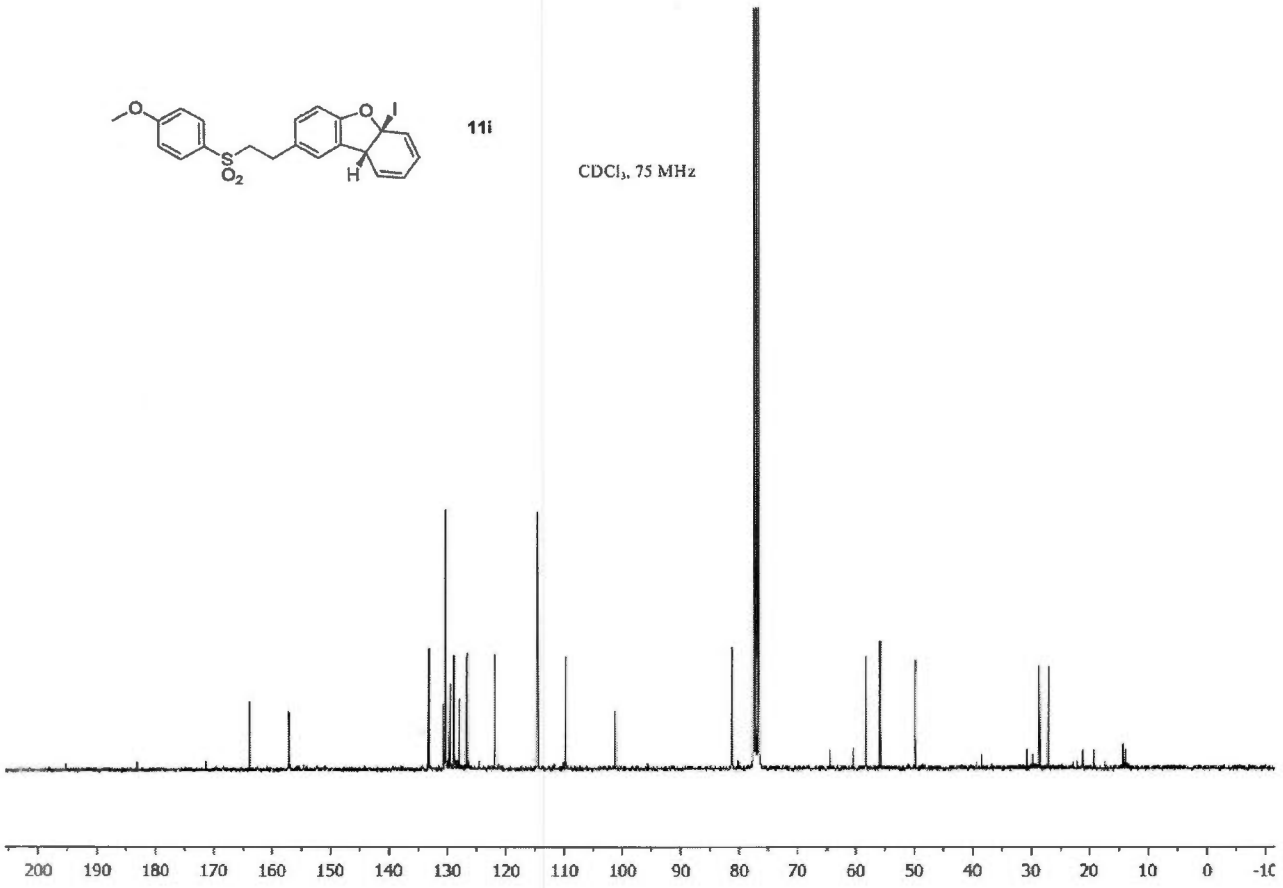
$CDCl_3$, 300 MHz



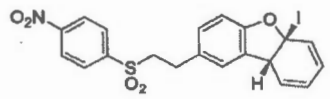
This journal is © The Royal Society of Chemistry 2013

11i

$CDCl_3$, 75 MHz

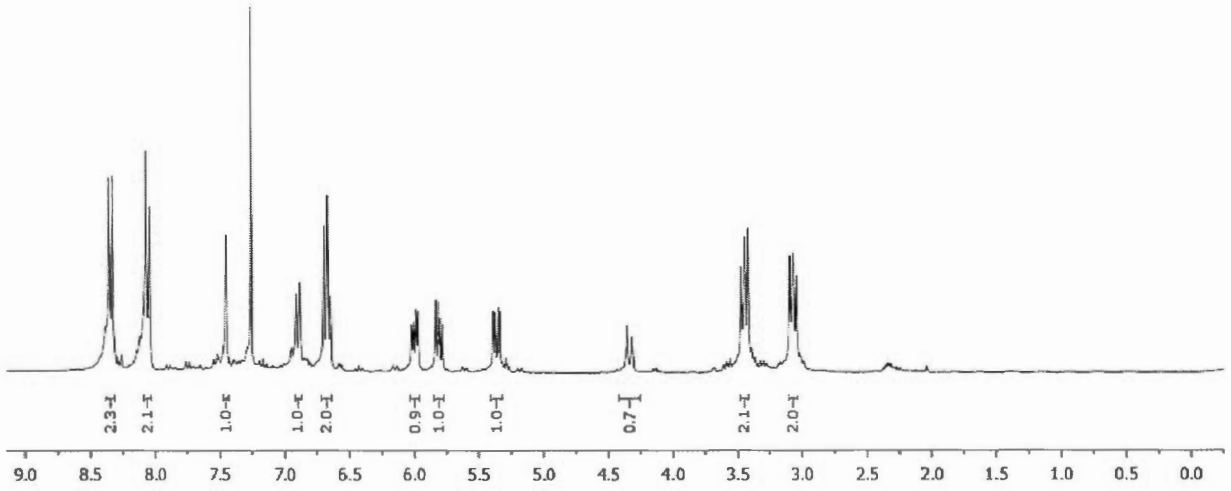


This journal is © The Royal Society of Chemistry 2013



11j

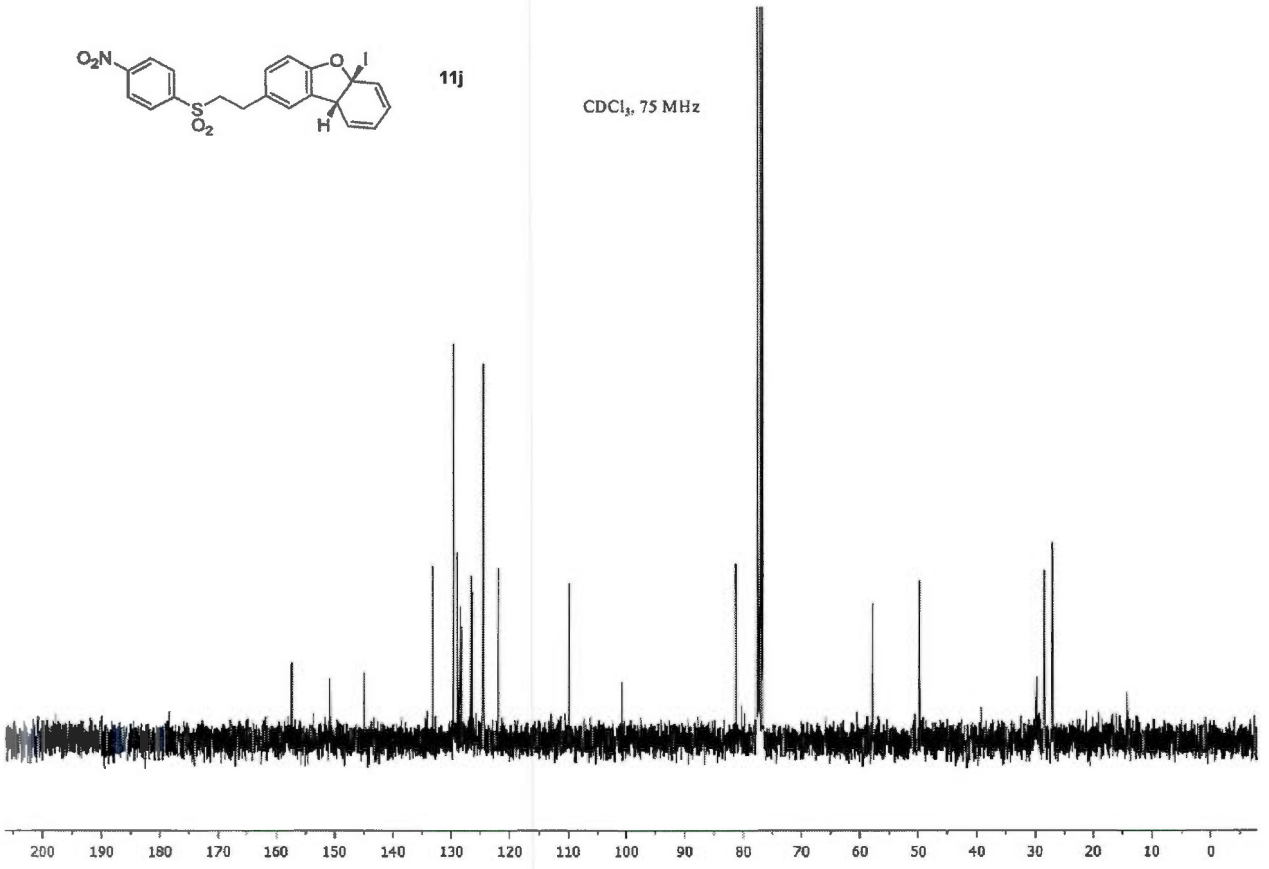
$CDCl_3$, 300 MHz



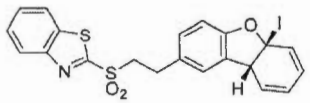
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

11j

$CDCl_3$, 75 MHz

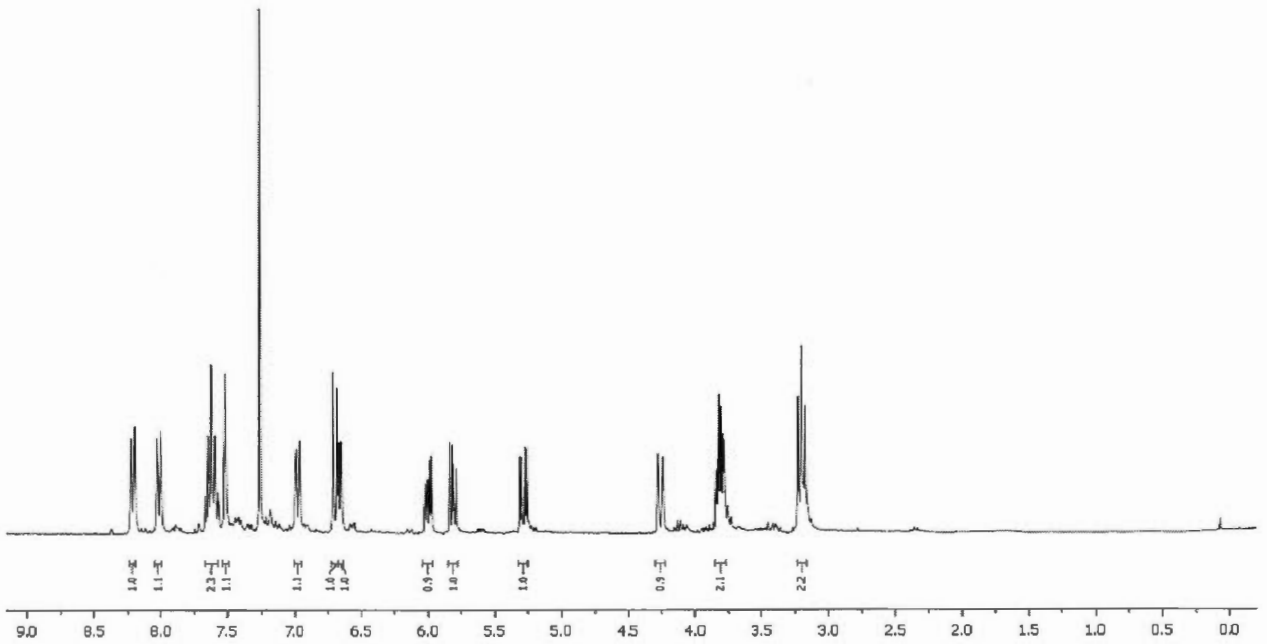


This journal is © The Royal Society of Chemistry 2013



11k

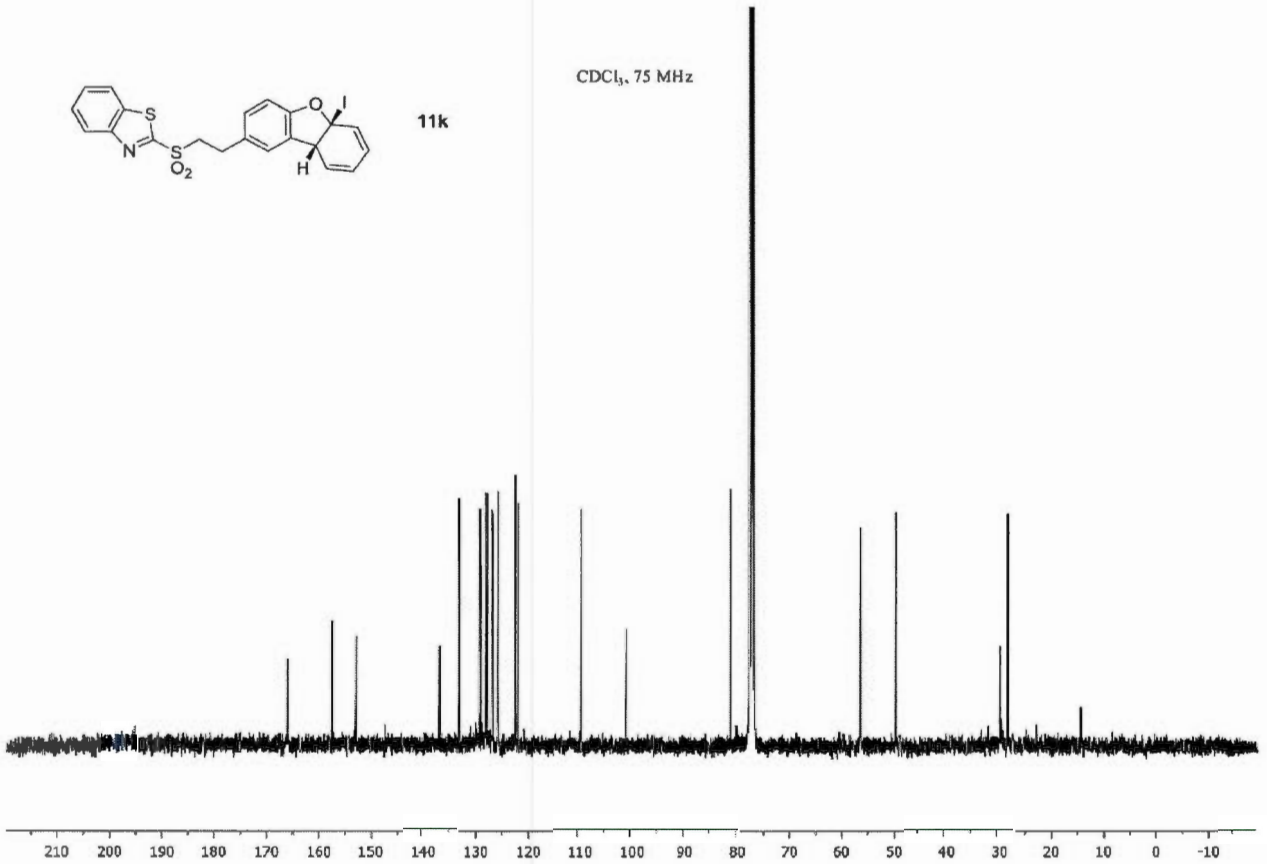
$CDCl_3$, 300 MHz



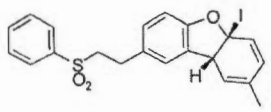
This journal is © The Royal Society of Chemistry 2013

11k

$CDCl_3$, 75 MHz

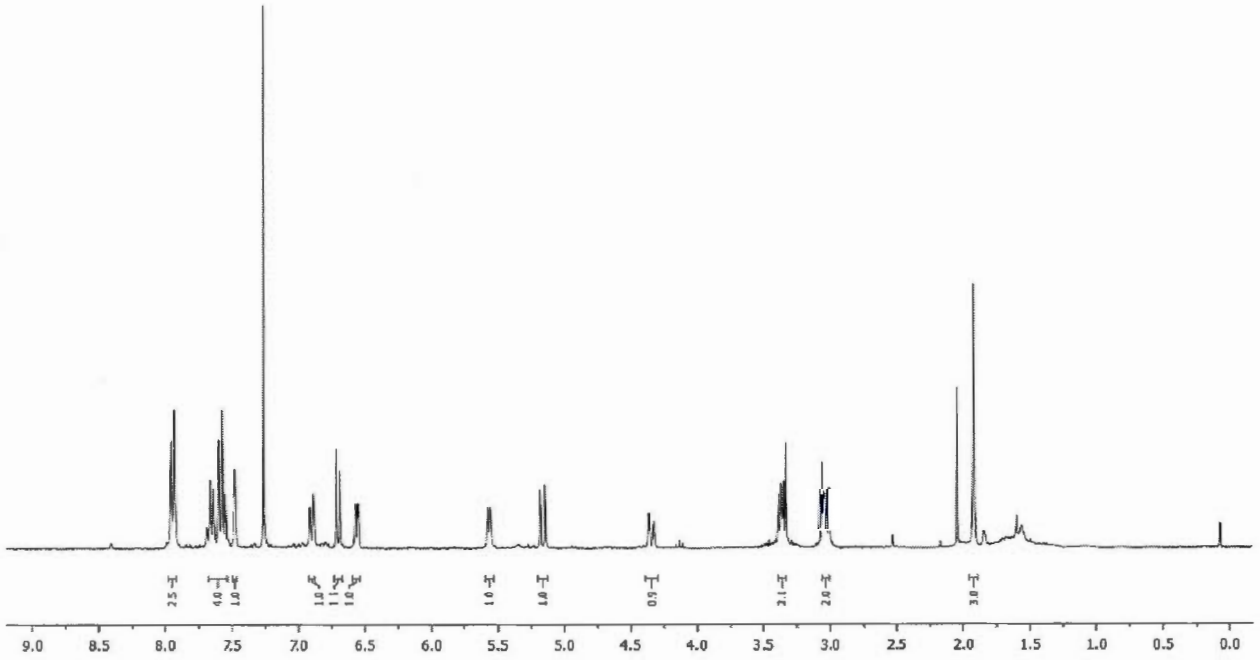


This journal is © The Royal Society of Chemistry 2013



12b

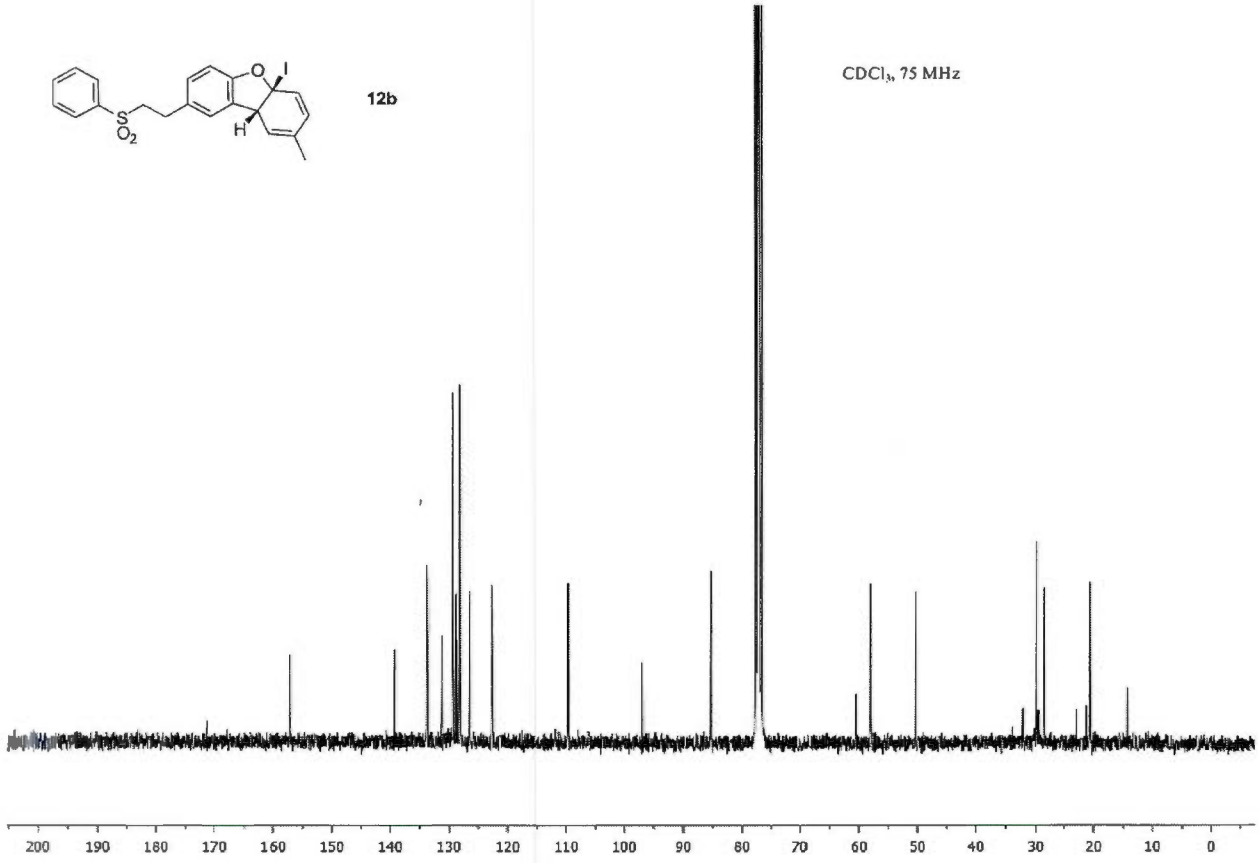
$CDCl_3$, 300 MHz



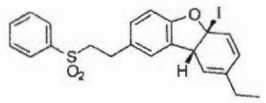
This journal is © The Royal Society of Chemistry 2013

12b

$CDCl_3$, 75 MHz

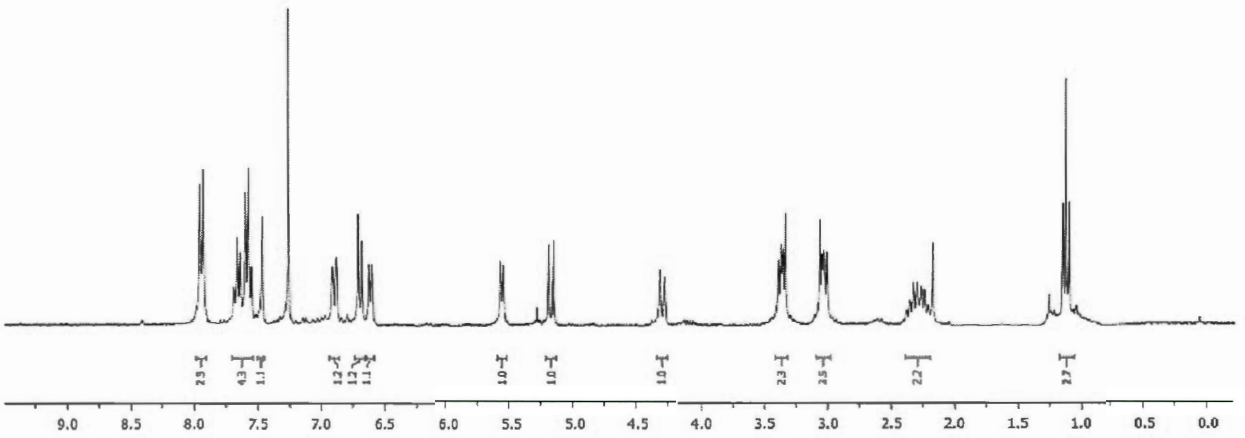


This journal is © The Royal Society of Chemistry 2013



12c

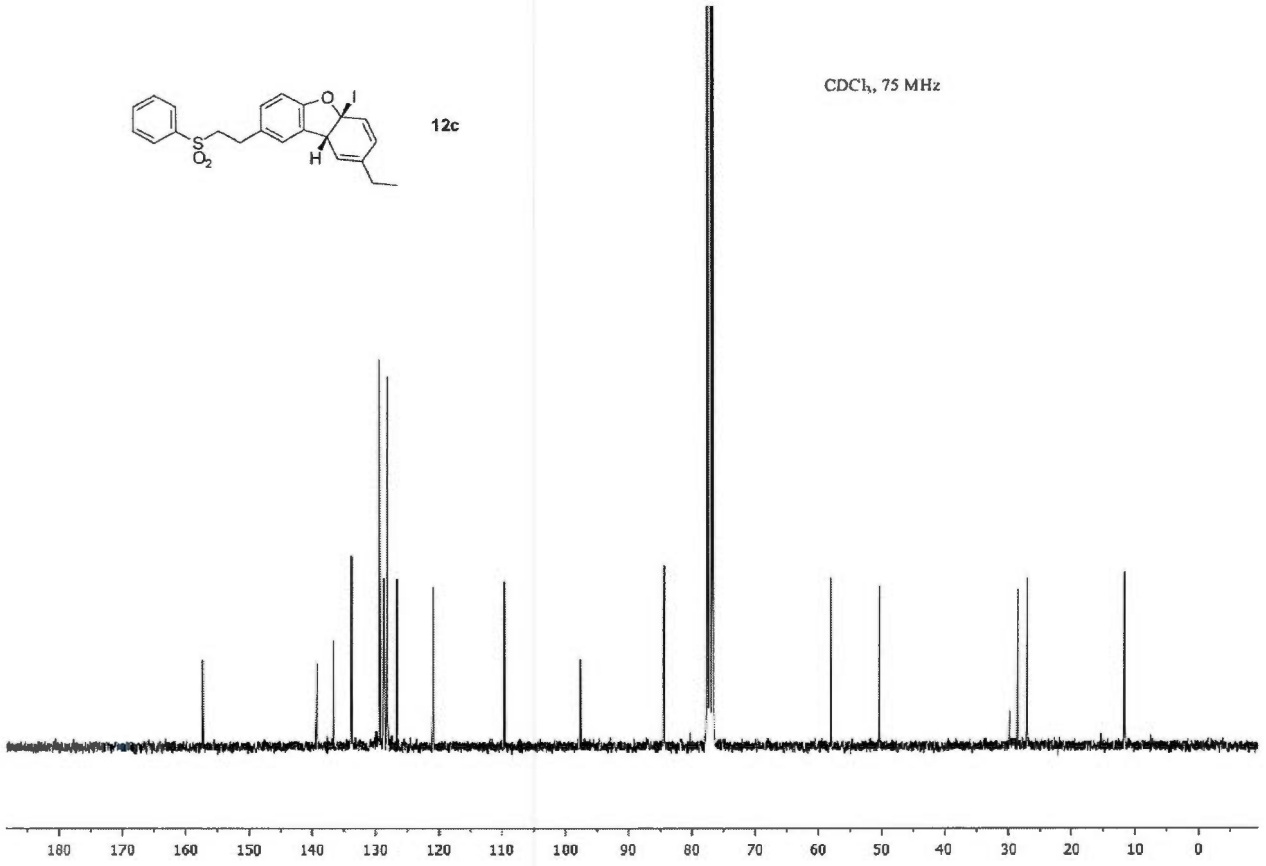
$CDCl_3$, 300 MHz



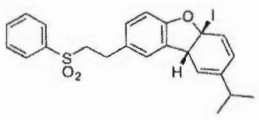
This journal is © The Royal Society of Chemistry 2013

12c

CDCl3, 75 MHz

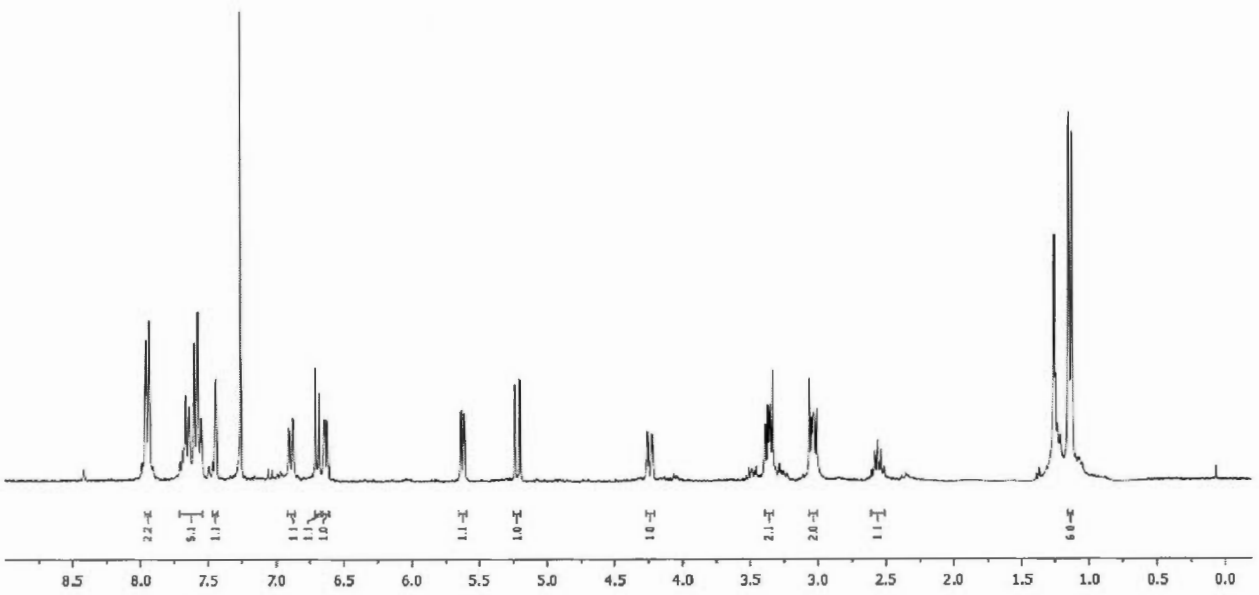


This journal is © The Royal Society of Chemistry 2013

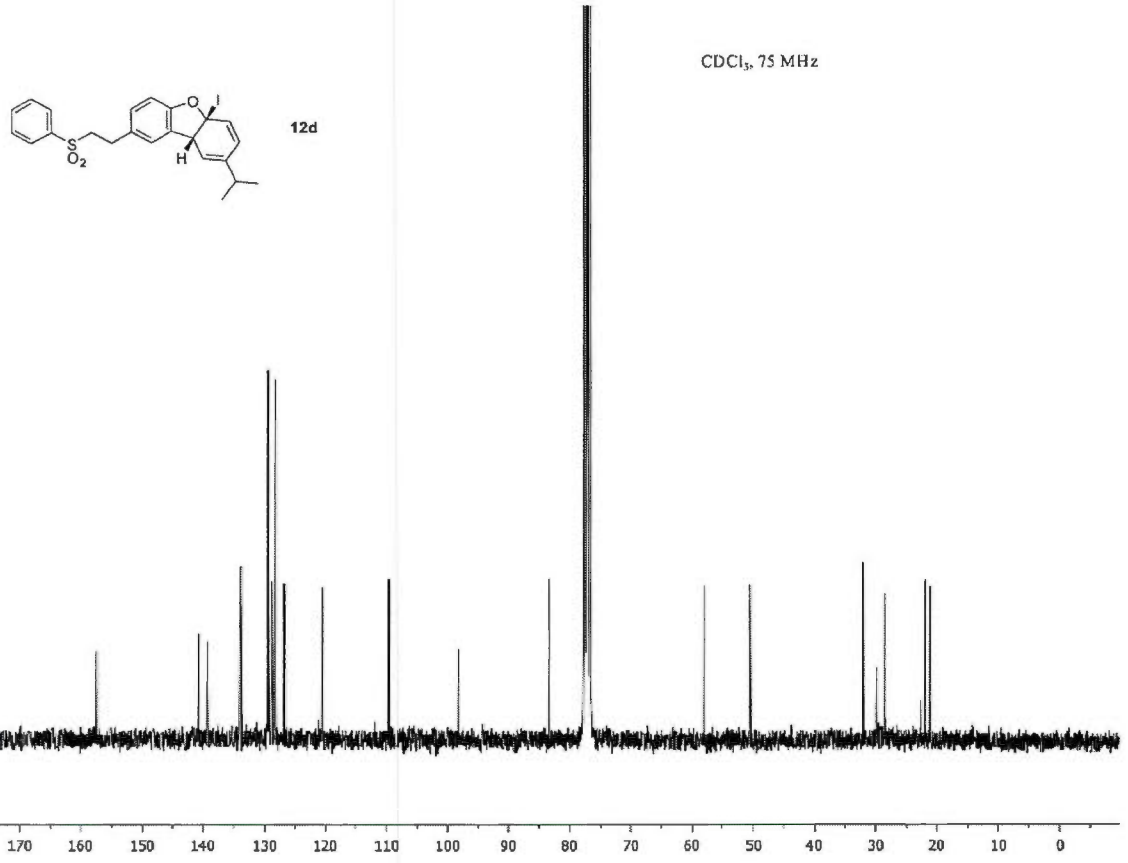


12d

$CDCl_3$, 300 MHz



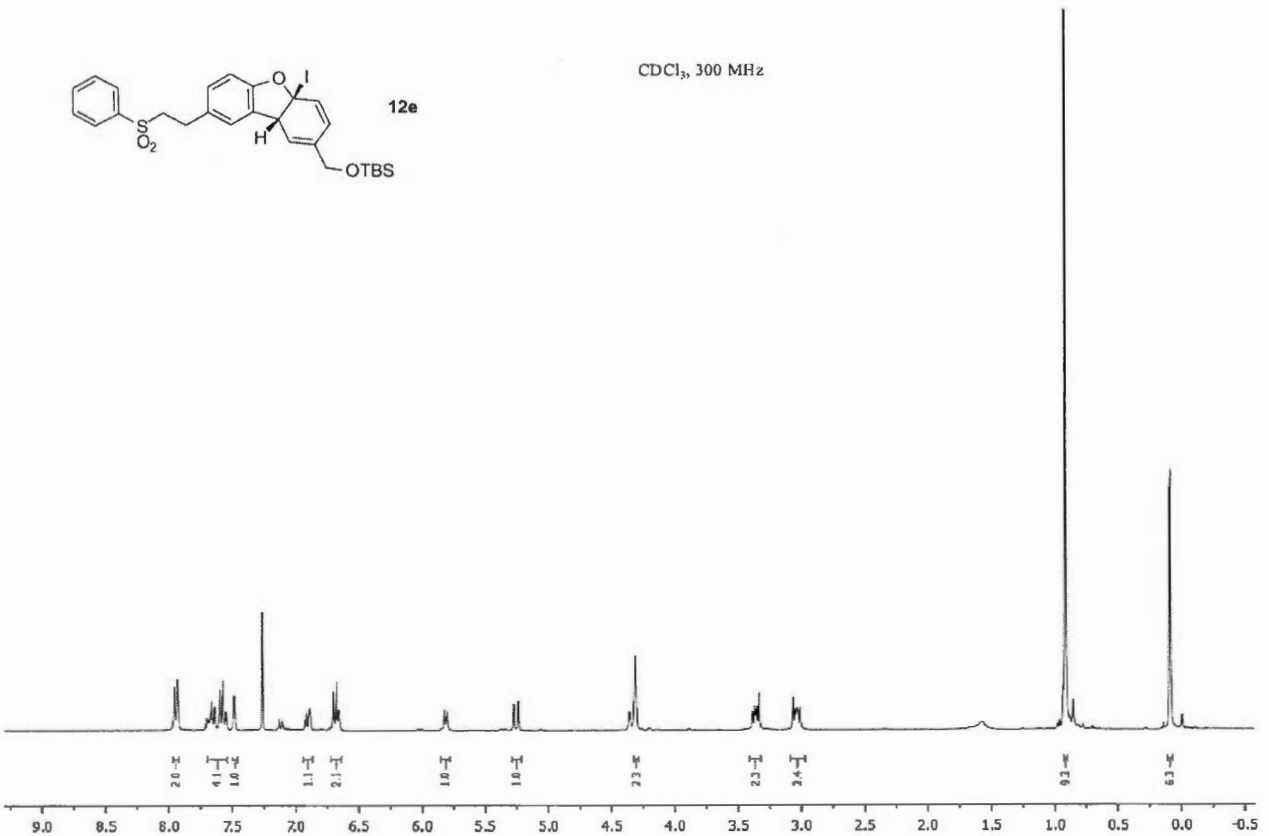
This journal is © The Royal Society of Chemistry 2013



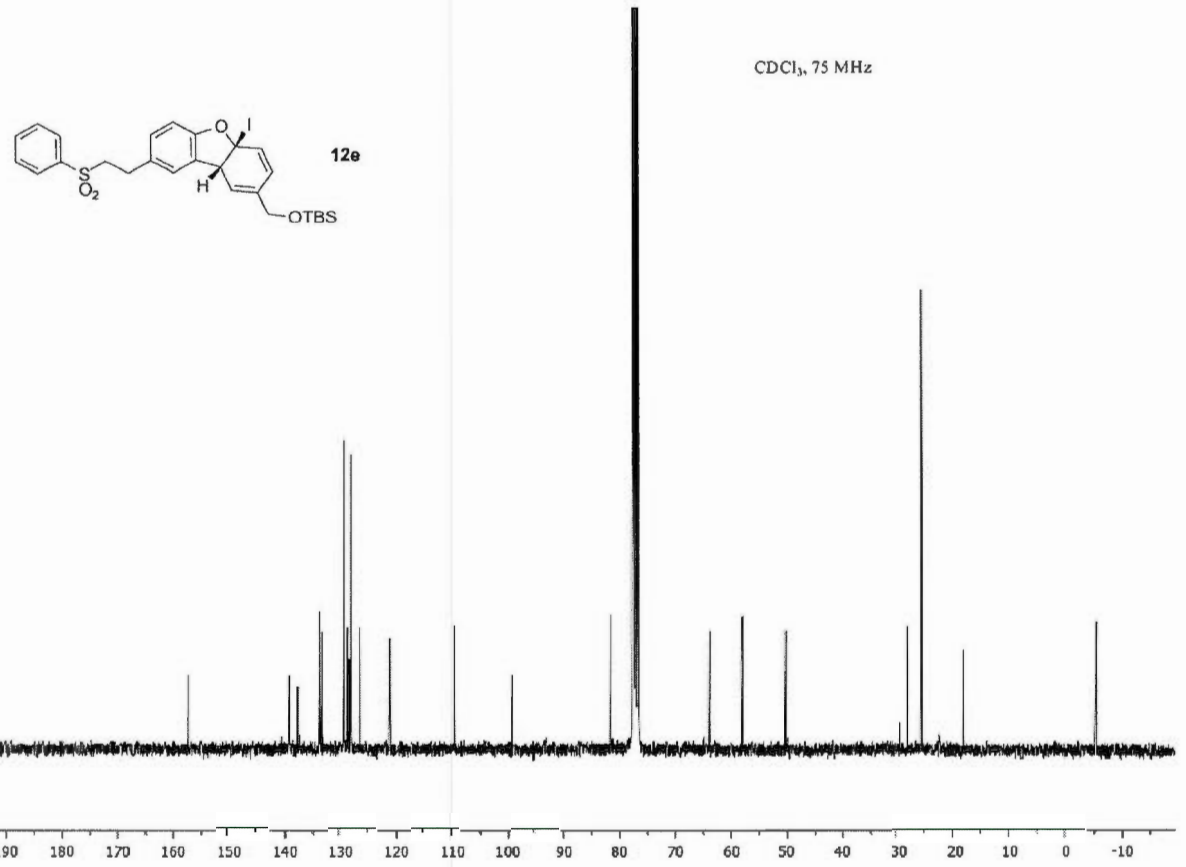
This journal is © The Royal Society of Chemistry 2013

12e

$CDCl_3$, 300 MHz



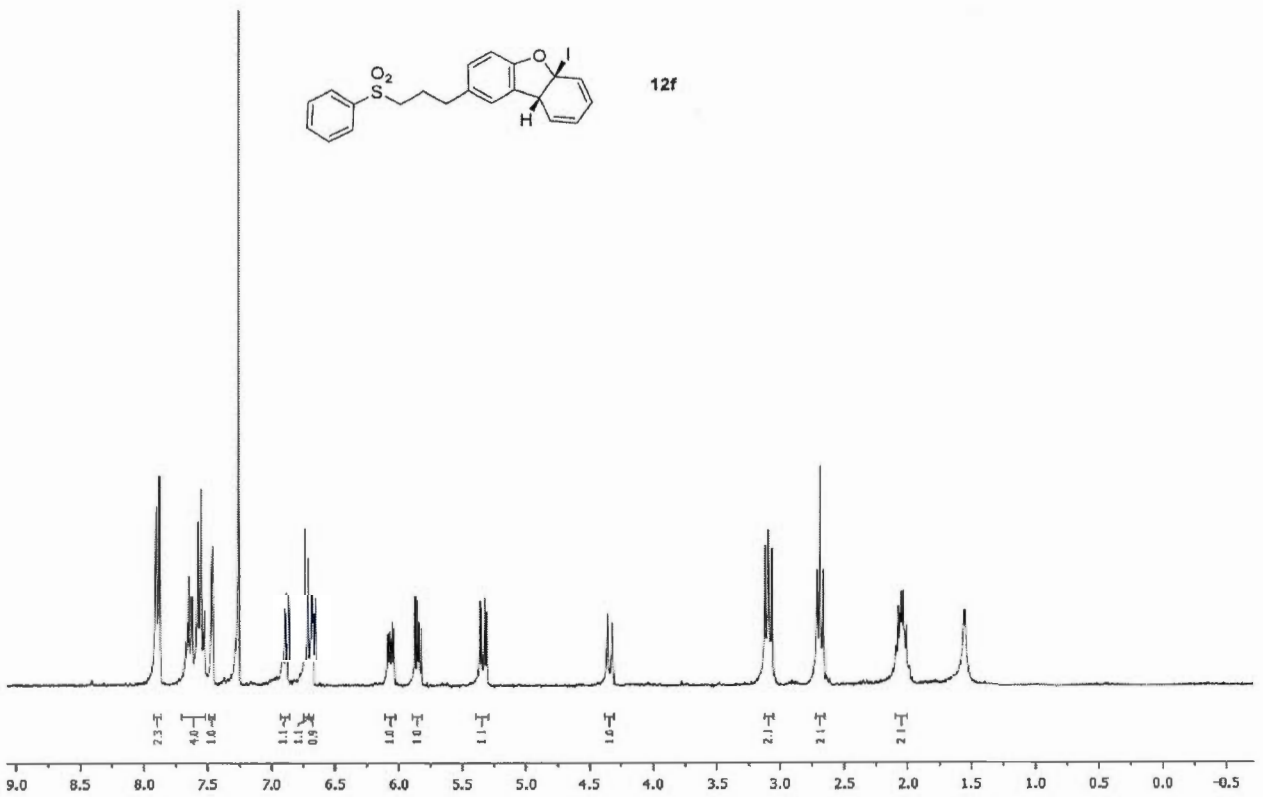
This journal is © The Royal Society of Chemistry 2013



This journal is © The Royal Society of Chemistry 2013

$CDCl_3$, 300 MHz

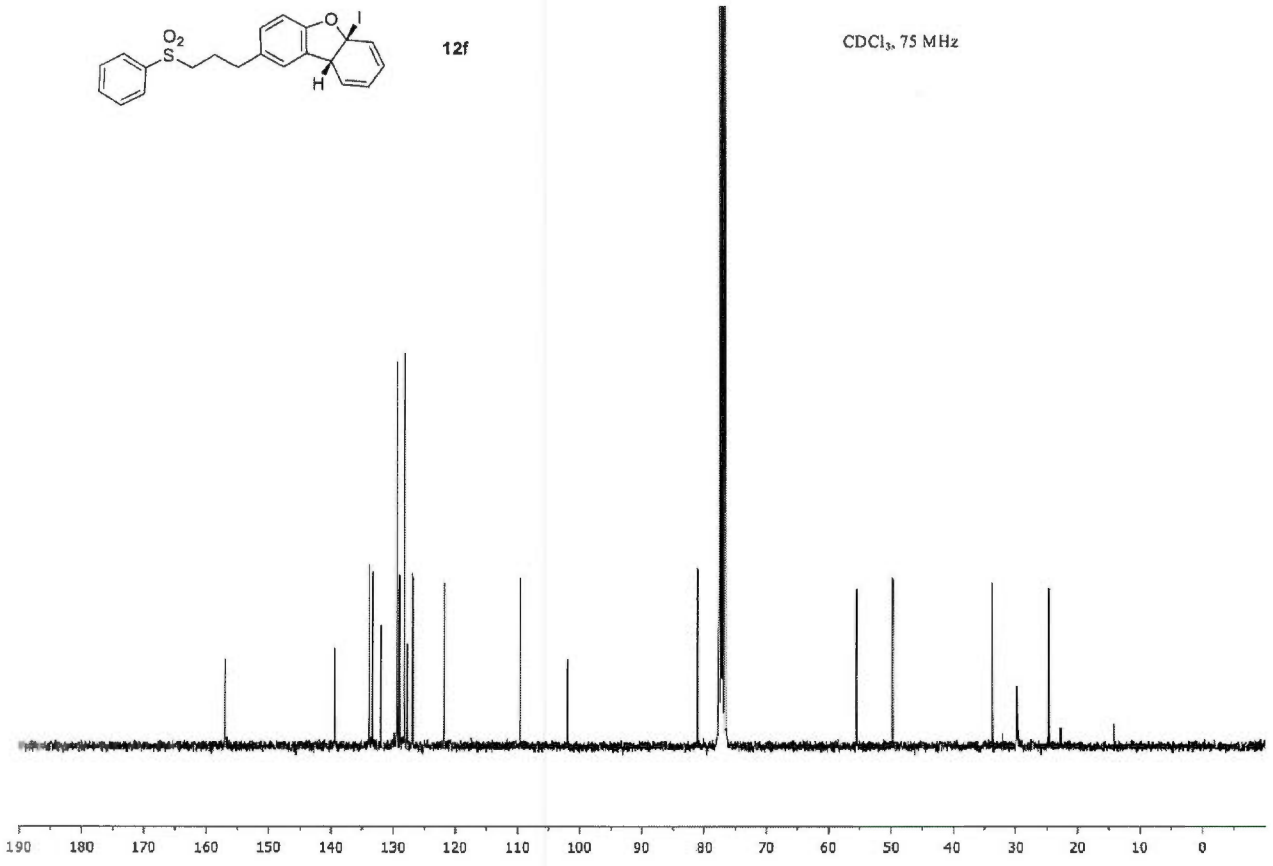
12f



This journal is © The Royal Society of Chemistry 2013

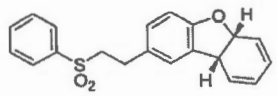
12f

$CDCl_3$, 75 MHz

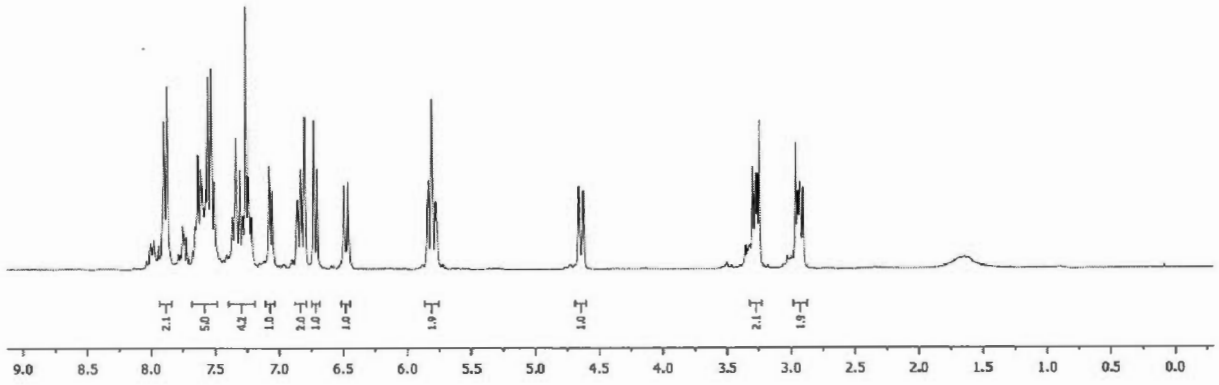


This journal is © The Royal Society of Chemistry 2013

$CDCl_3$, 300 MHz

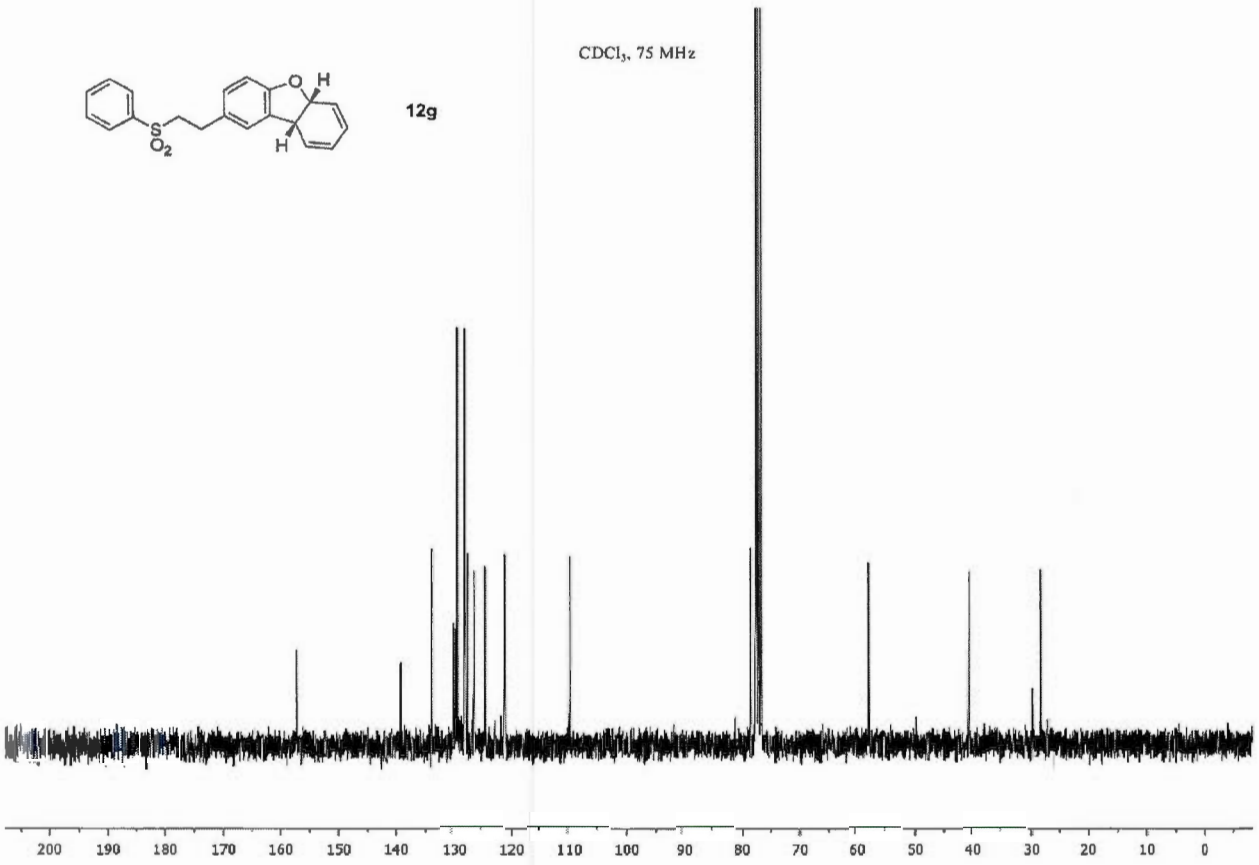


12g



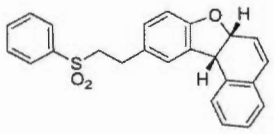
12g

$CDCl_3$, 75 MHz

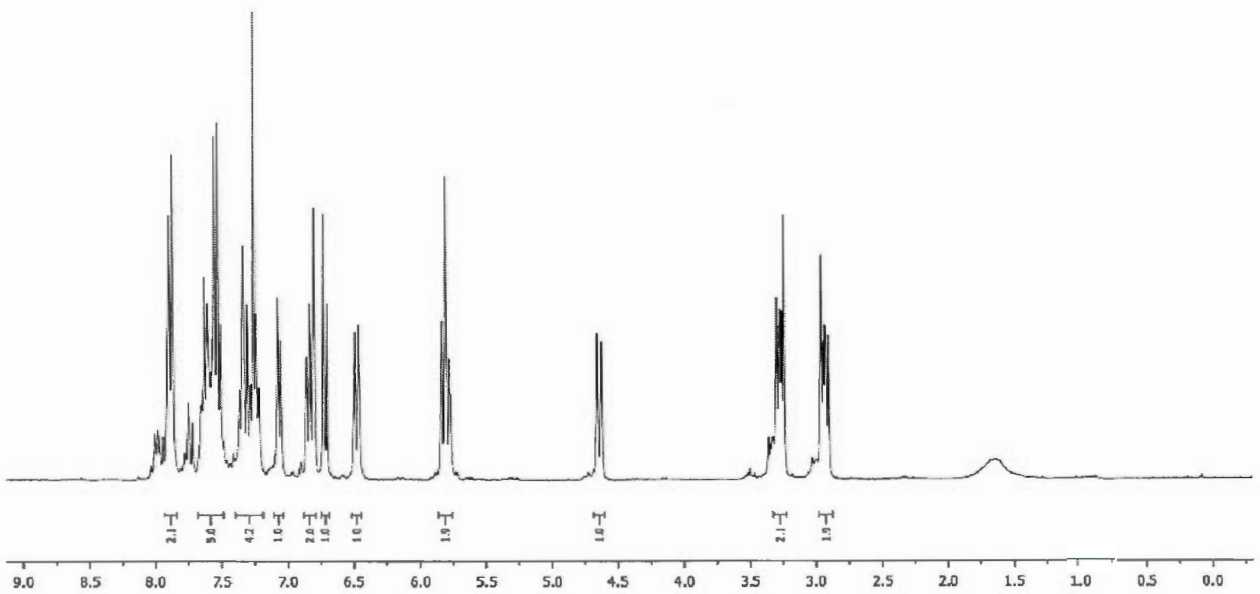


This journal is © The Royal Society of Chemistry 2013

$CDCl_3$, 300 MHz



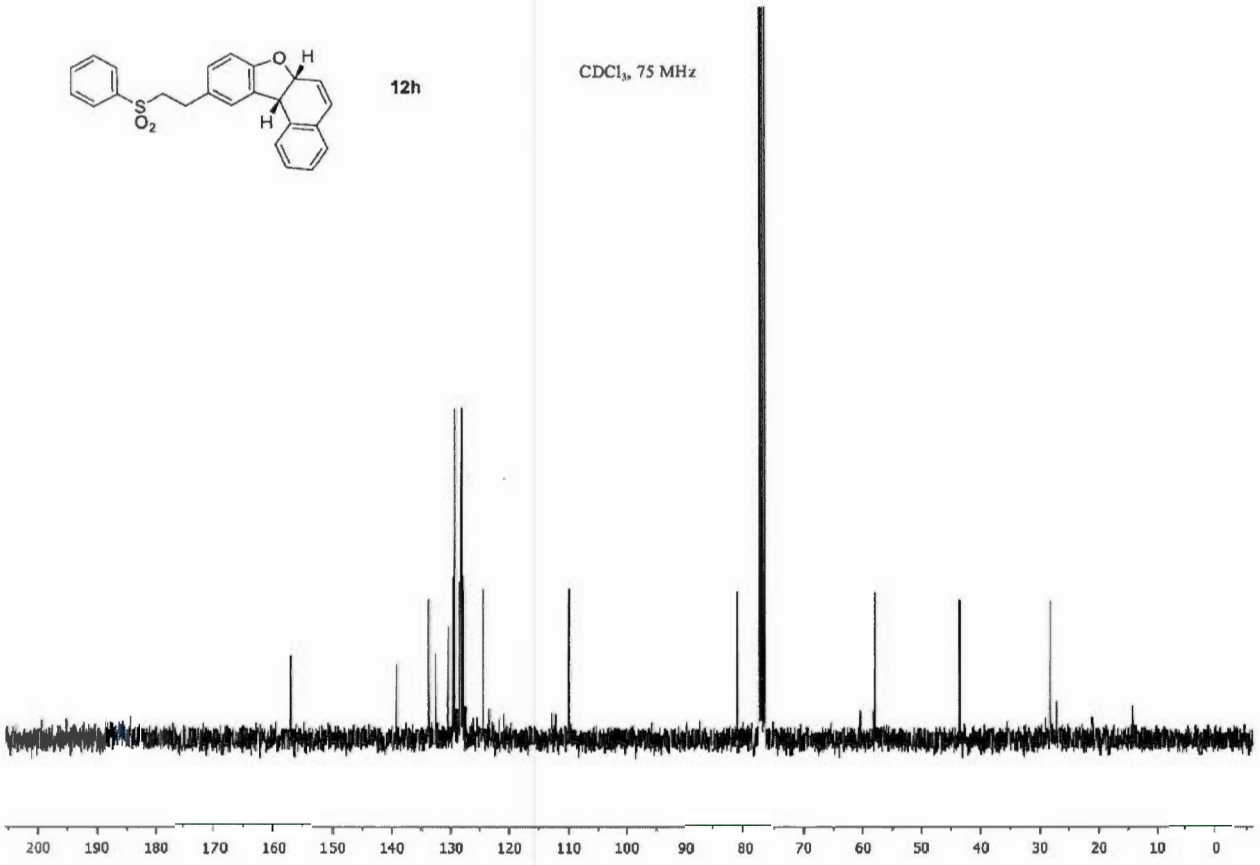
12h



This journal is © The Royal Society of Chemistry 2013

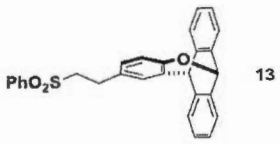
12h

$CDCl_3$, 75 MHz

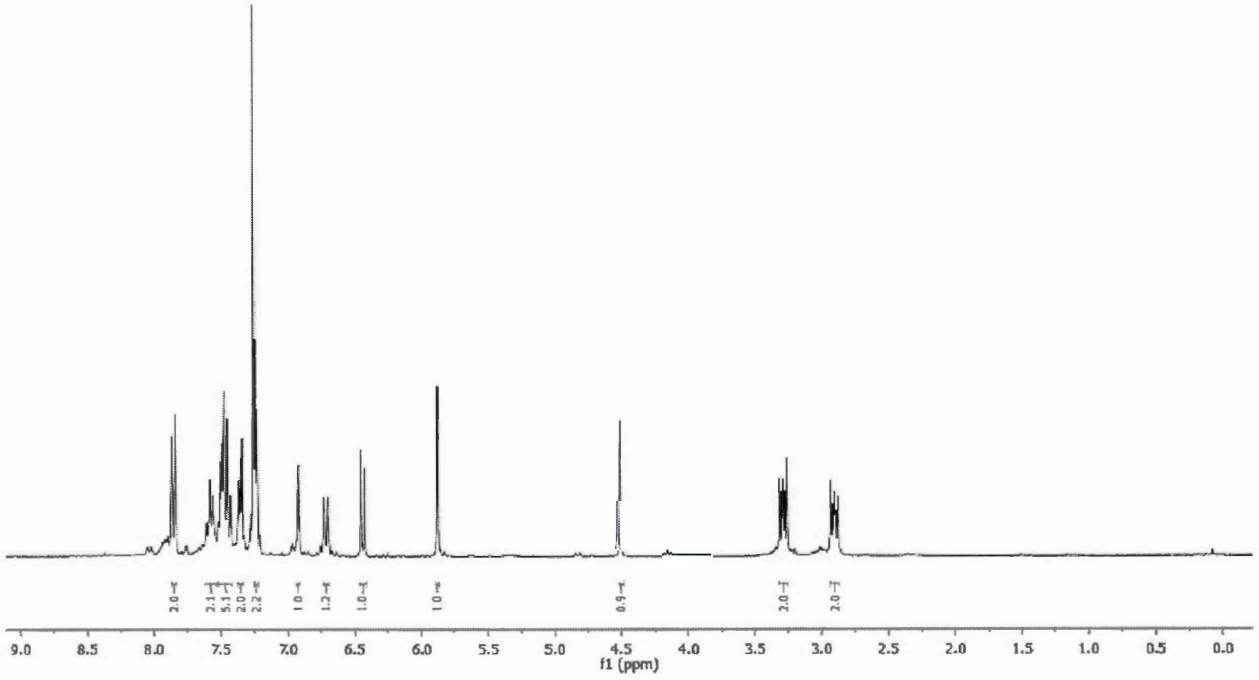


This journal is © The Royal Society of Chemistry 2013

$CDCl_3$, 300 MHz



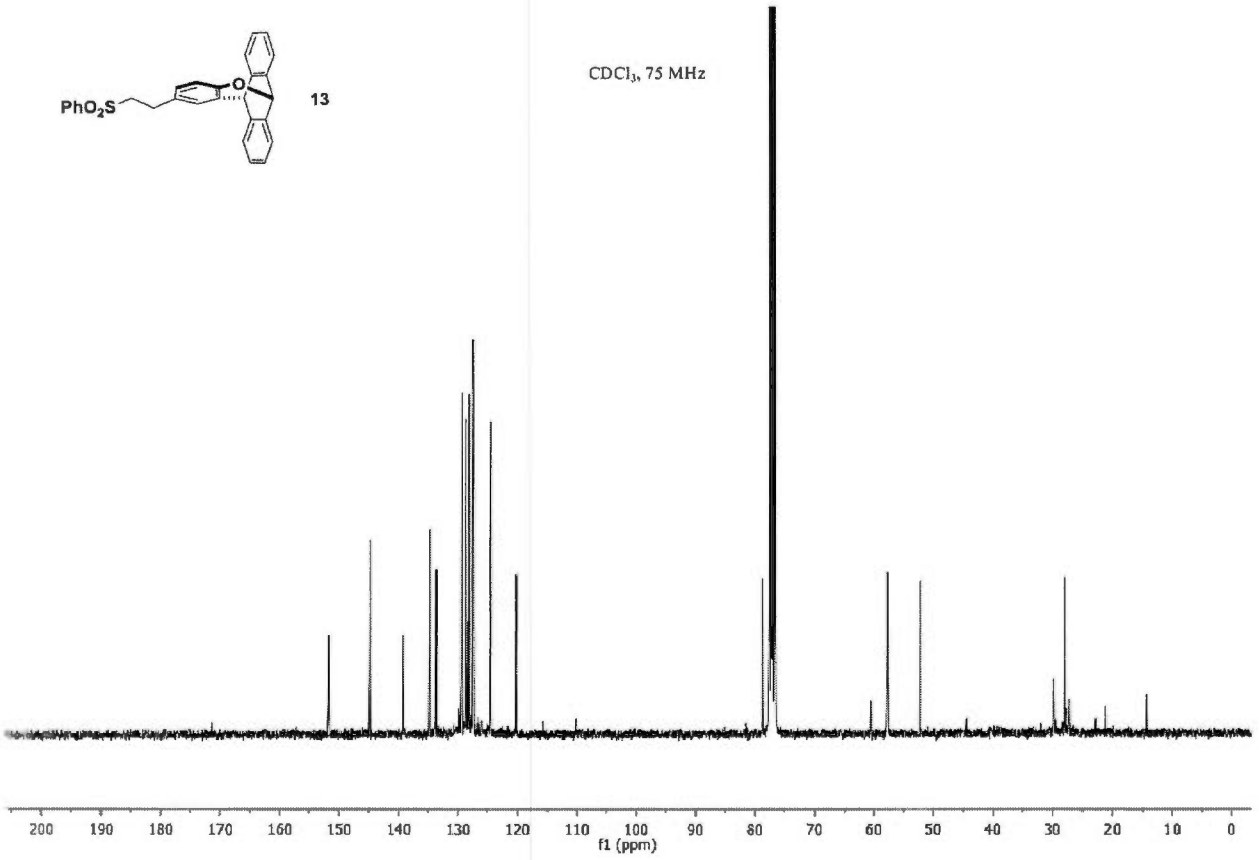
13



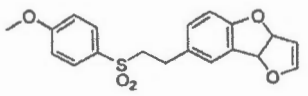
This journal is © The Royal Society of Chemistry 2013

13

$CDCl_3$, 75 MHz

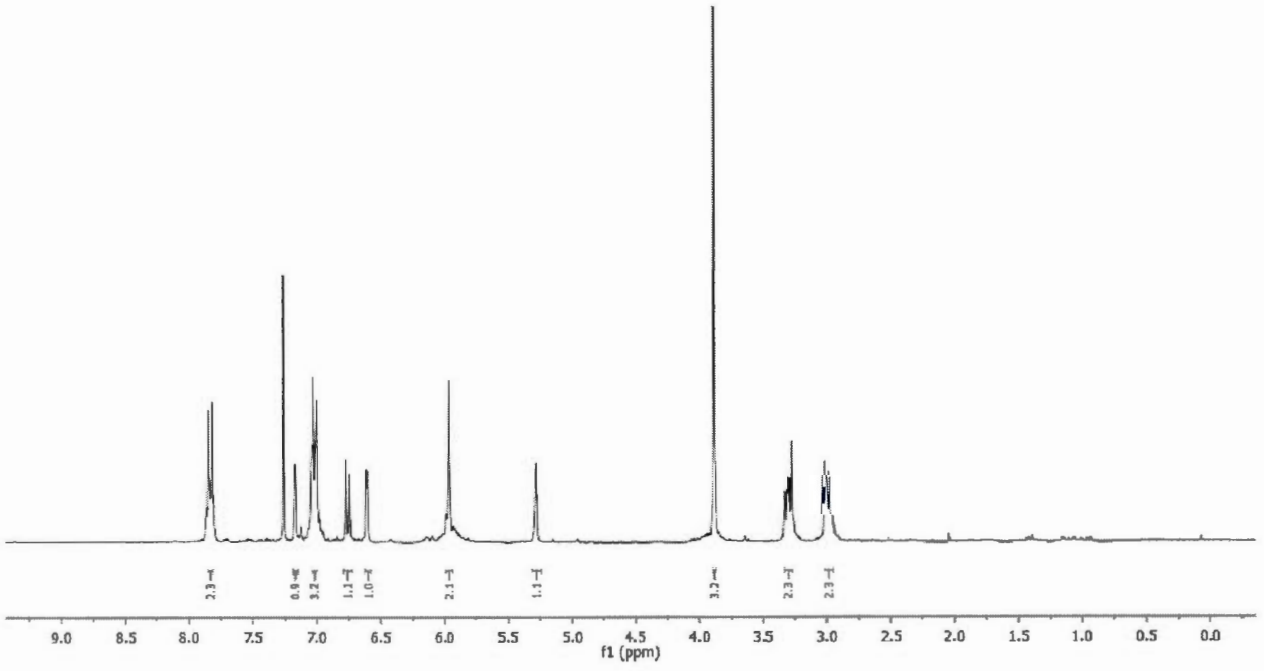


This journal is © The Royal Society of Chemistry 2013



14

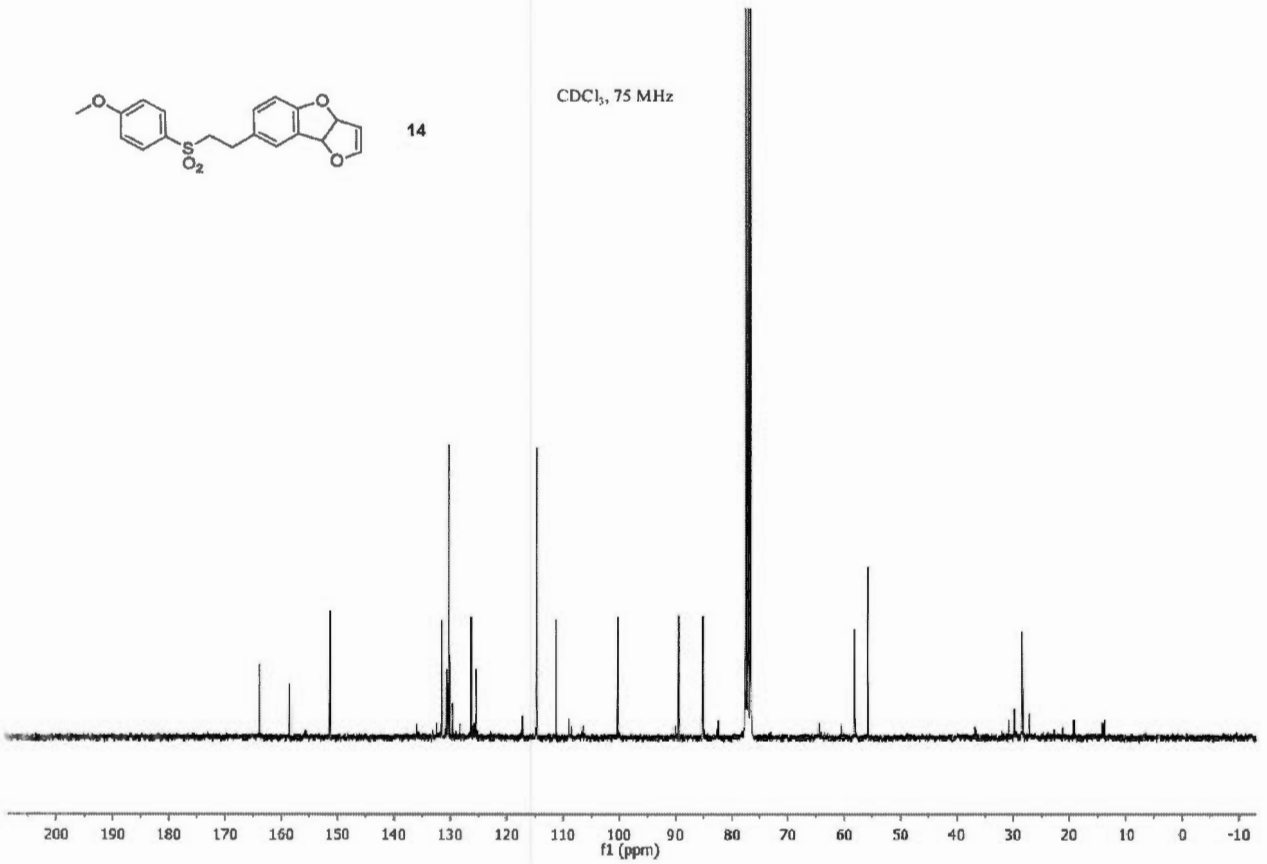
$CDCl_3$, 300 MHz



This journal is © The Royal Society of Chemistry 2013

14

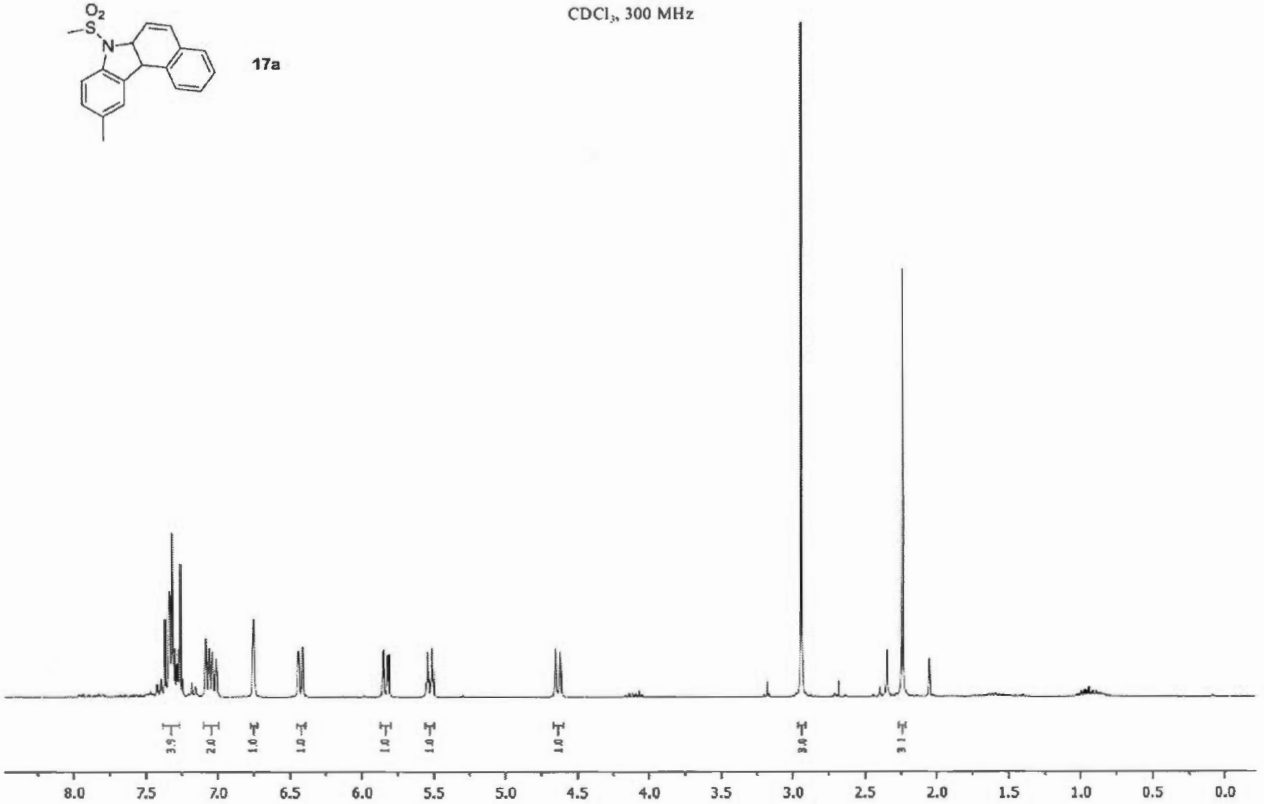
$CDCl_3$, 75 MHz



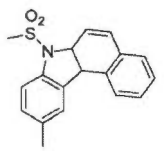
This journal is © The Royal Society of Chemistry 2013

17a

$CDCl_3$, 300 MHz

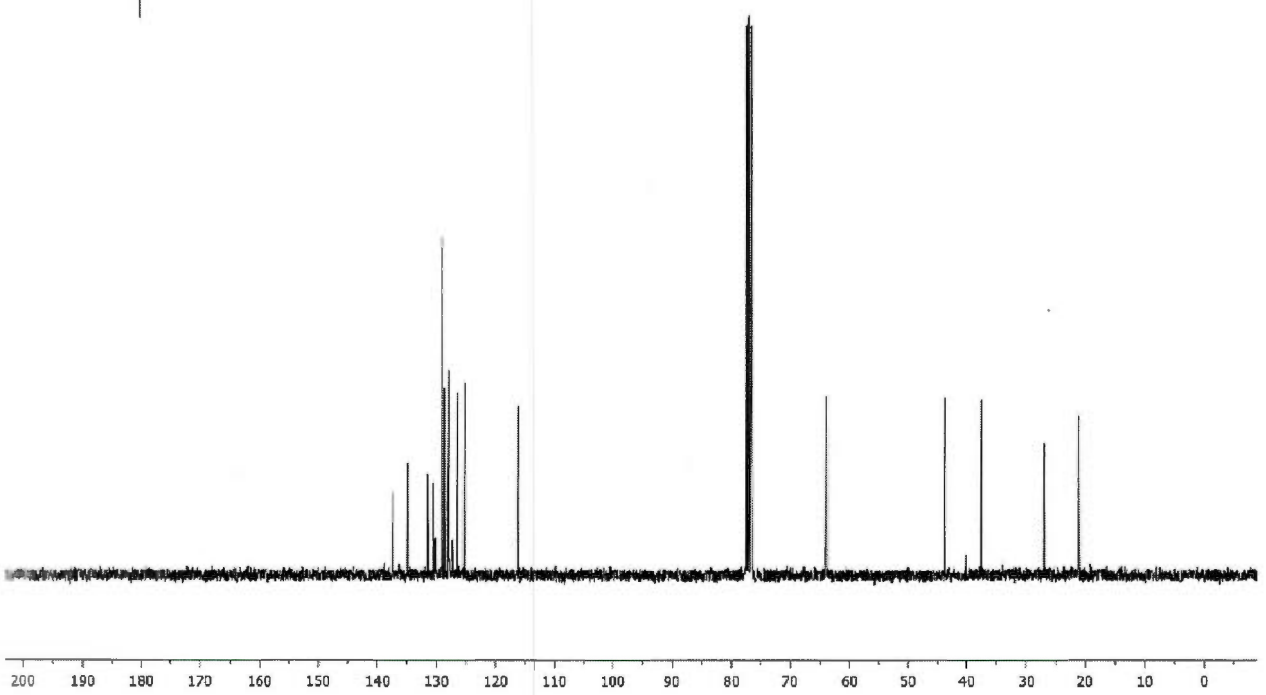


This journal is © The Royal Society of Chemistry 2013

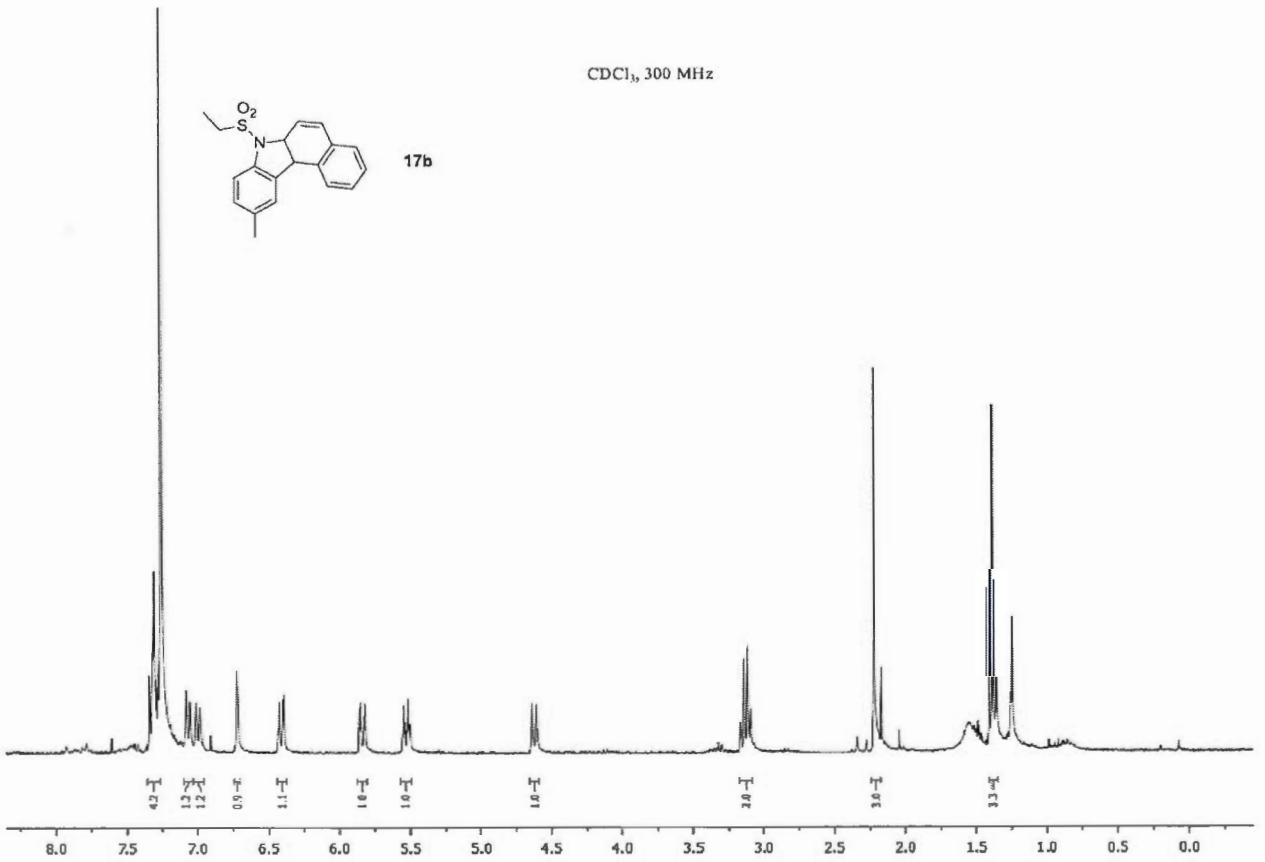


17a

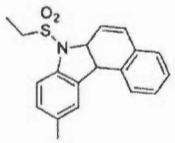
$CDCl_3$, 75 MHz



Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

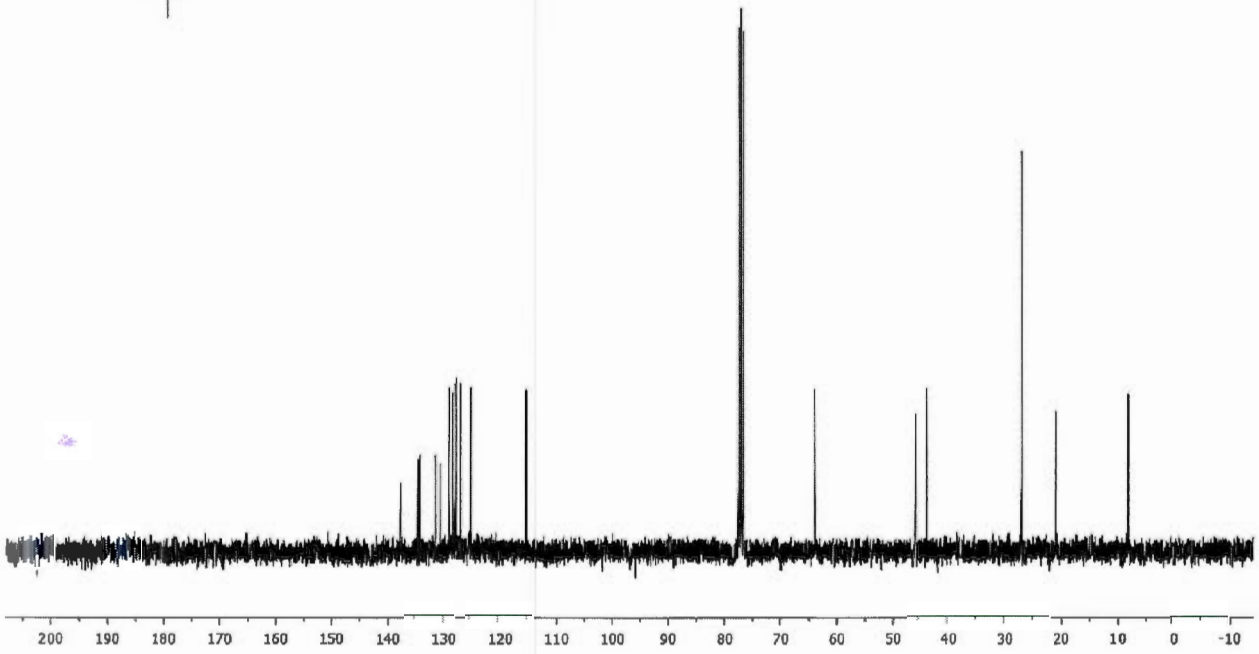


Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

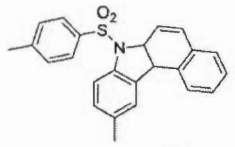


17b

$CDCl_3$, 75 MHz

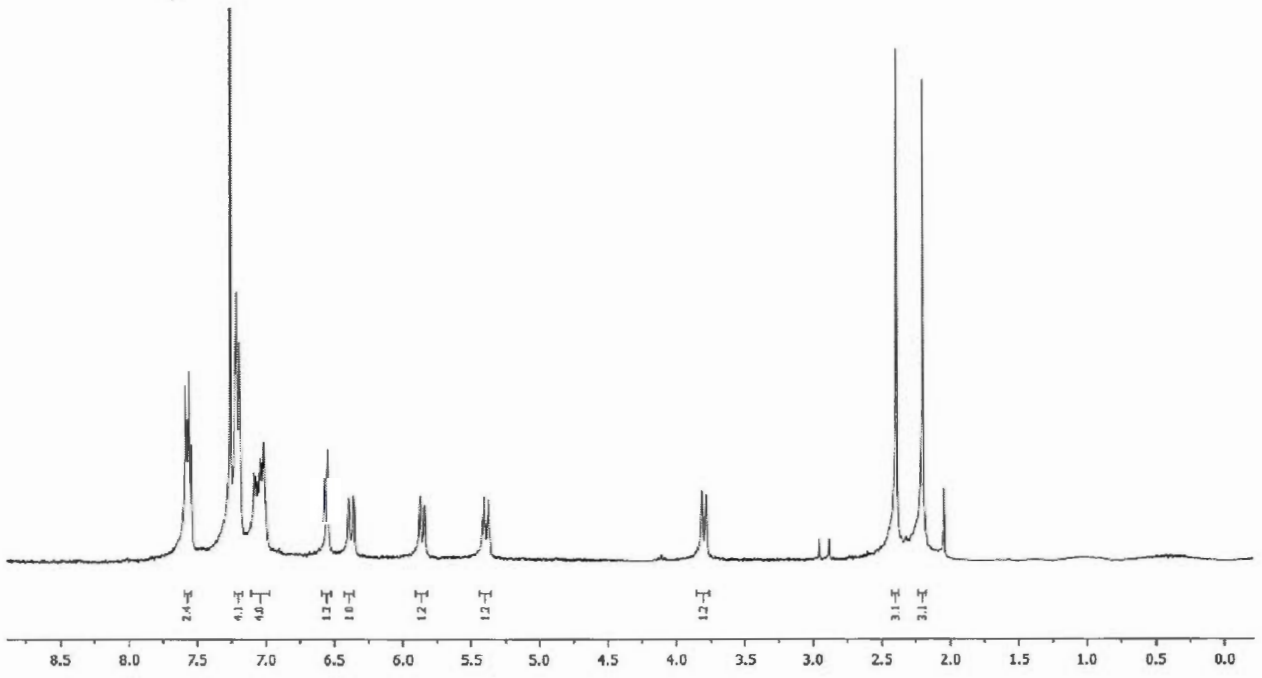


This journal is © The Royal Society of Chemistry 2013



17c

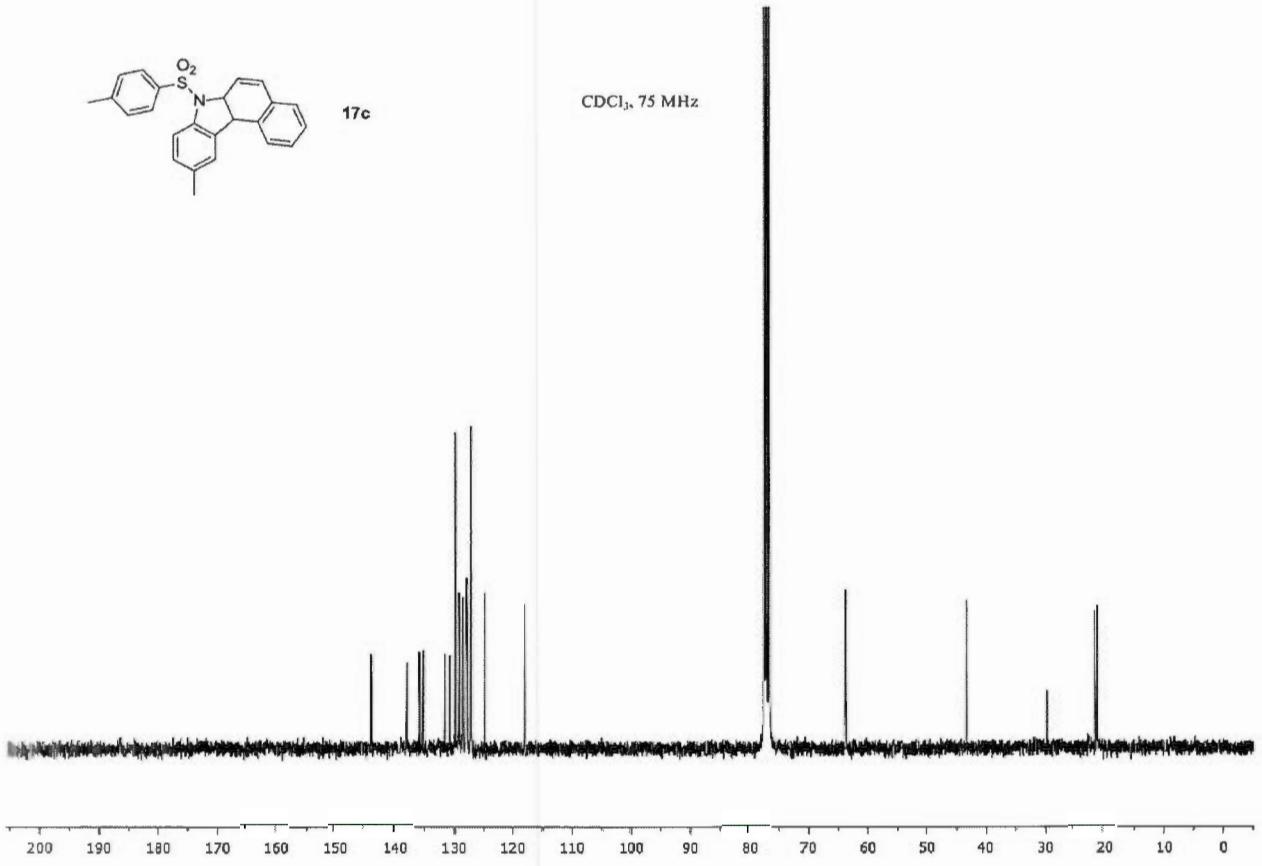
$CDCl_3$, 300 MHz



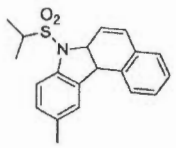
This journal is © The Royal Society of Chemistry 2013

17c

$CDCl_3$, 75 MHz

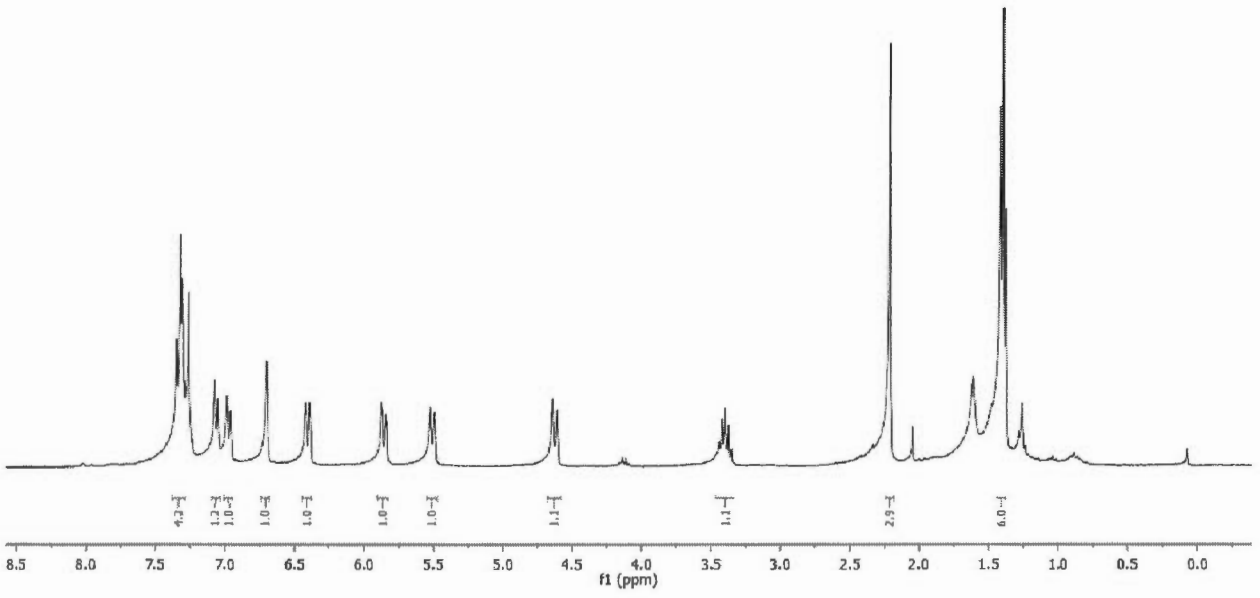


This journal is © The Royal Society of Chemistry 2013



17d

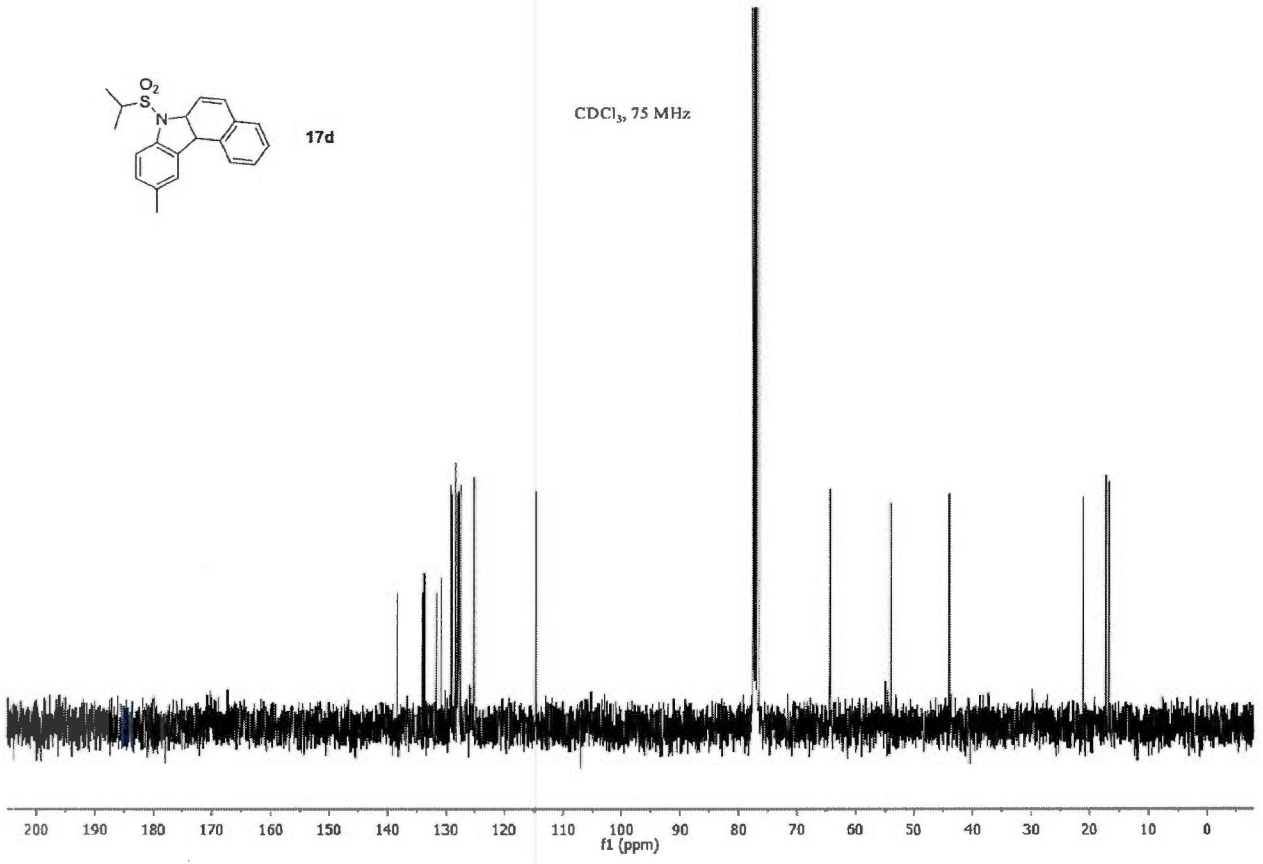
$CDCl_3$, 300 MHz



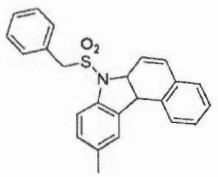
This journal is © The Royal Society of Chemistry 2013

17d

$CDCl_3$, 75 MHz

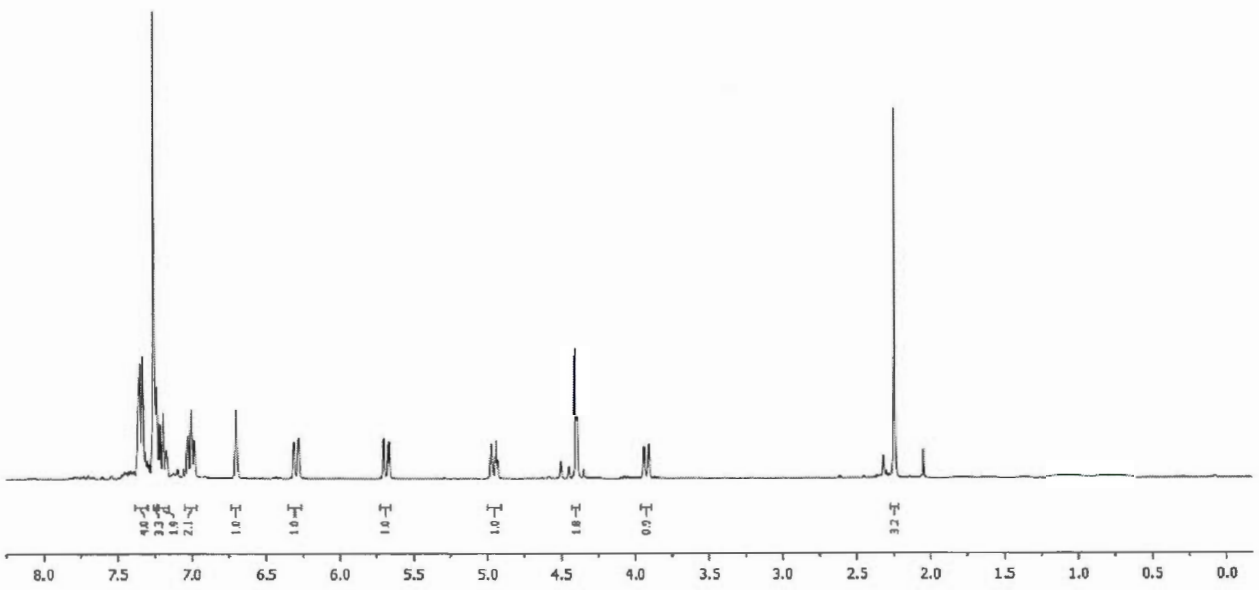


This journal is © The Royal Society of Chemistry 2013



17e

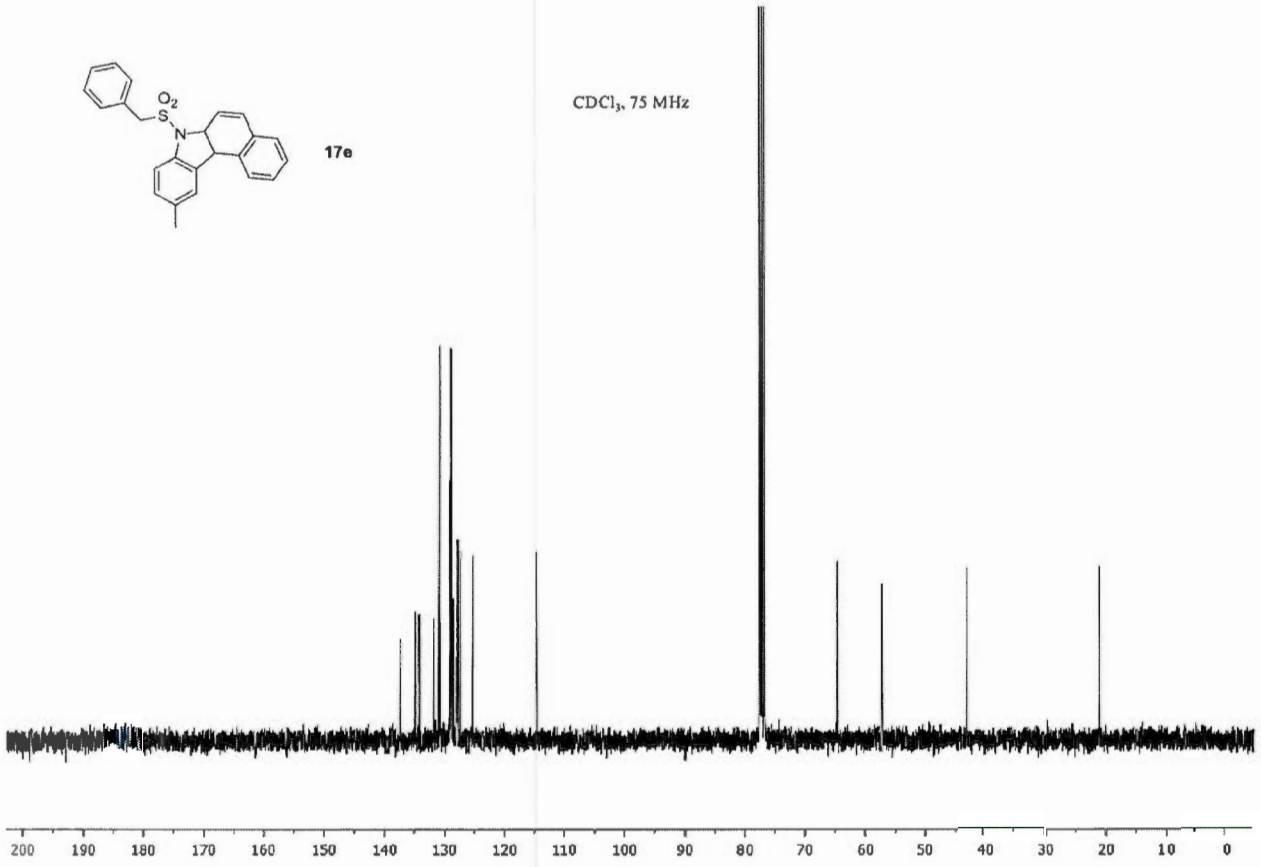
$CDCl_3$, 300 MHz



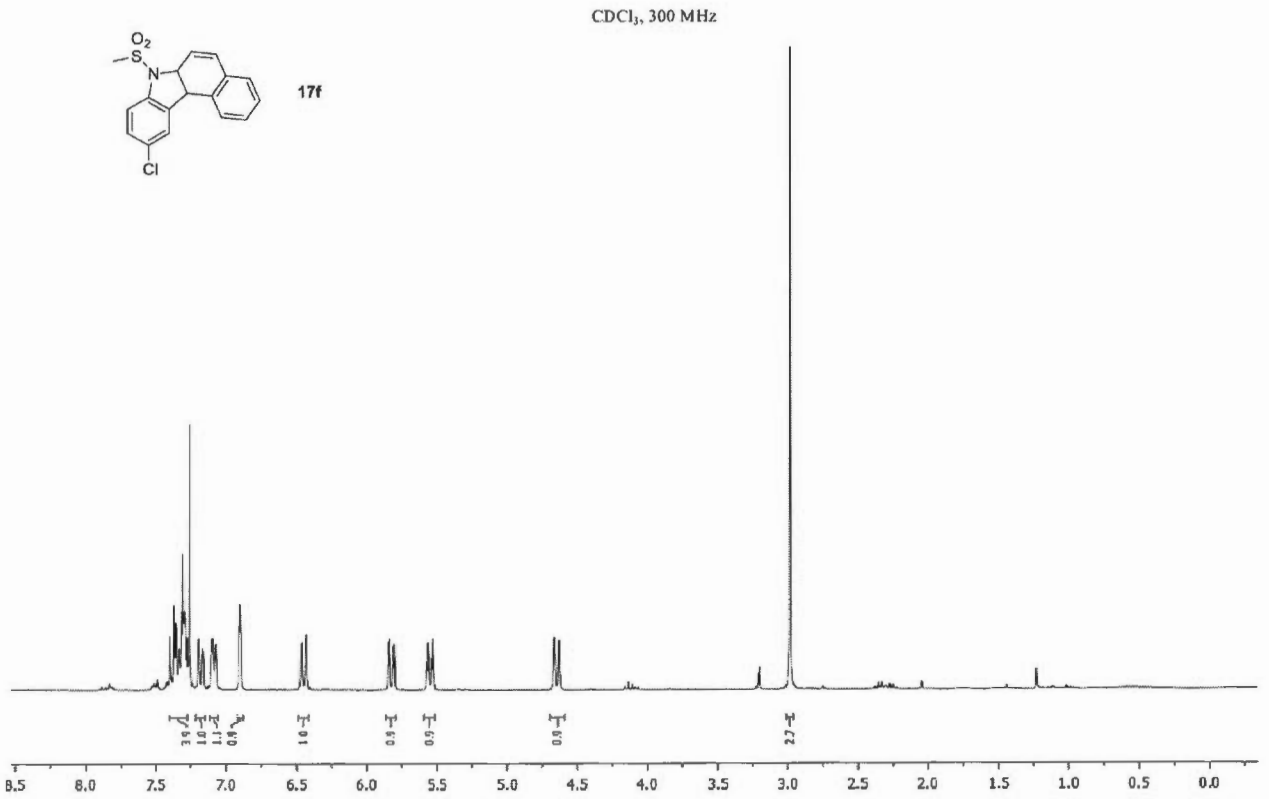
This journal is © The Royal Society of Chemistry 2013

17e

$CDCl_3$, 75 MHz



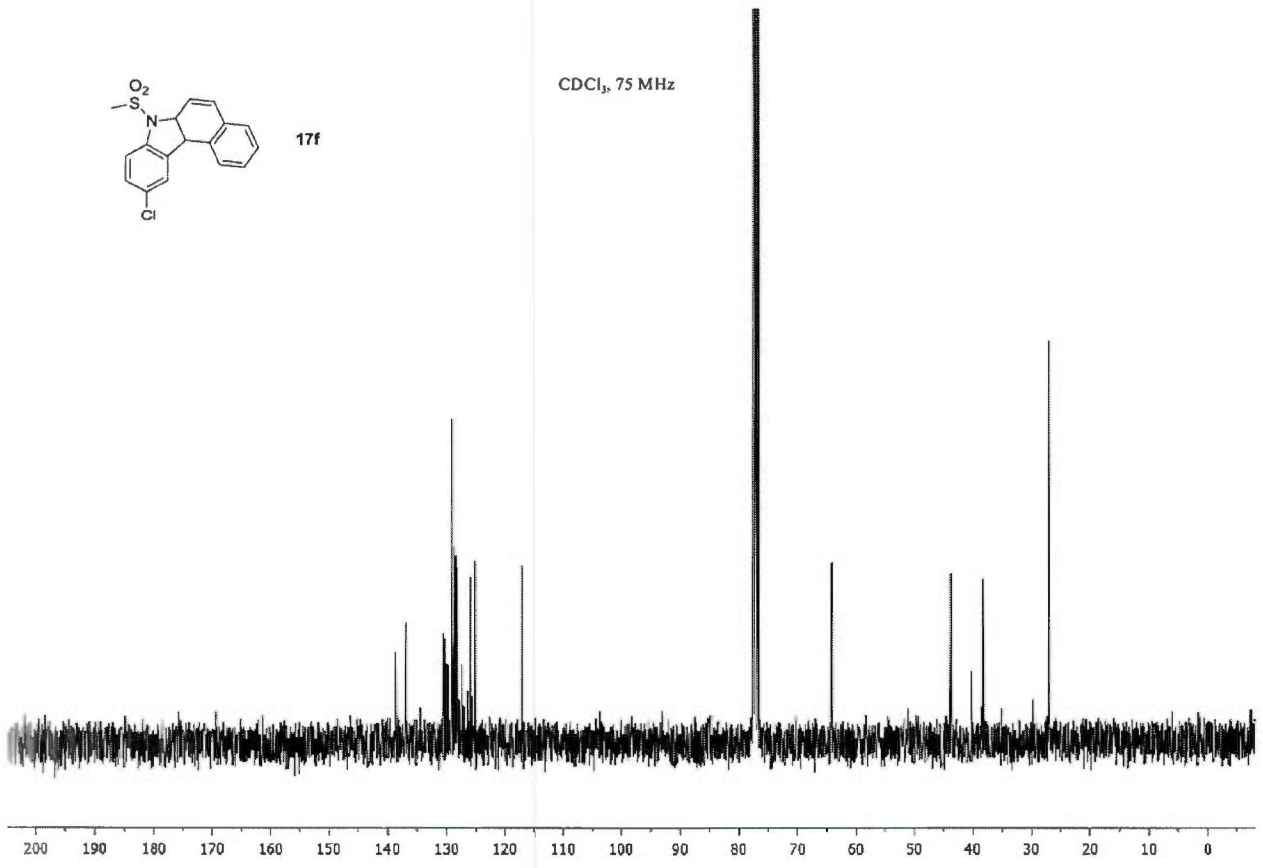
This journal is © The Royal Society of Chemistry 2013



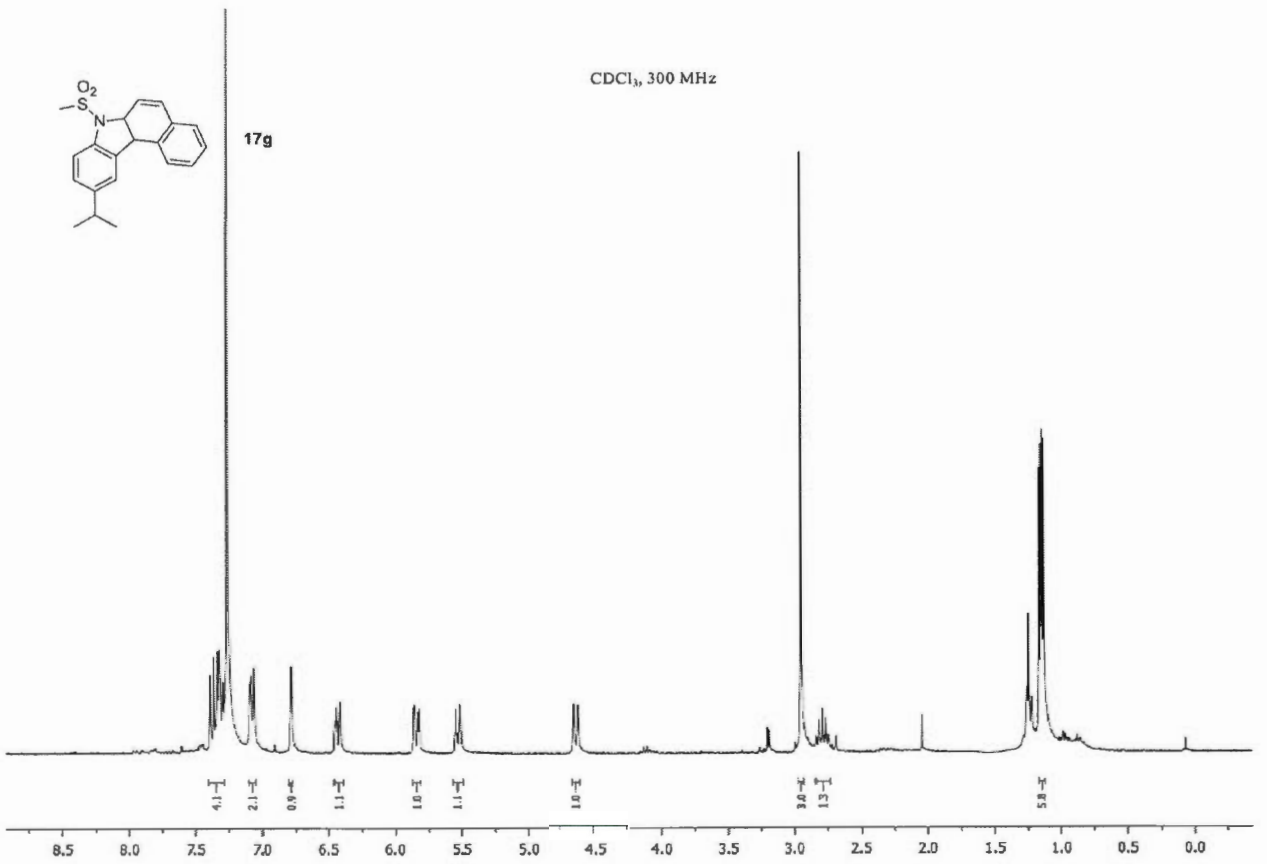
This journal is © The Royal Society of Chemistry 2013

17f

$CDCl_3$, 75 MHz



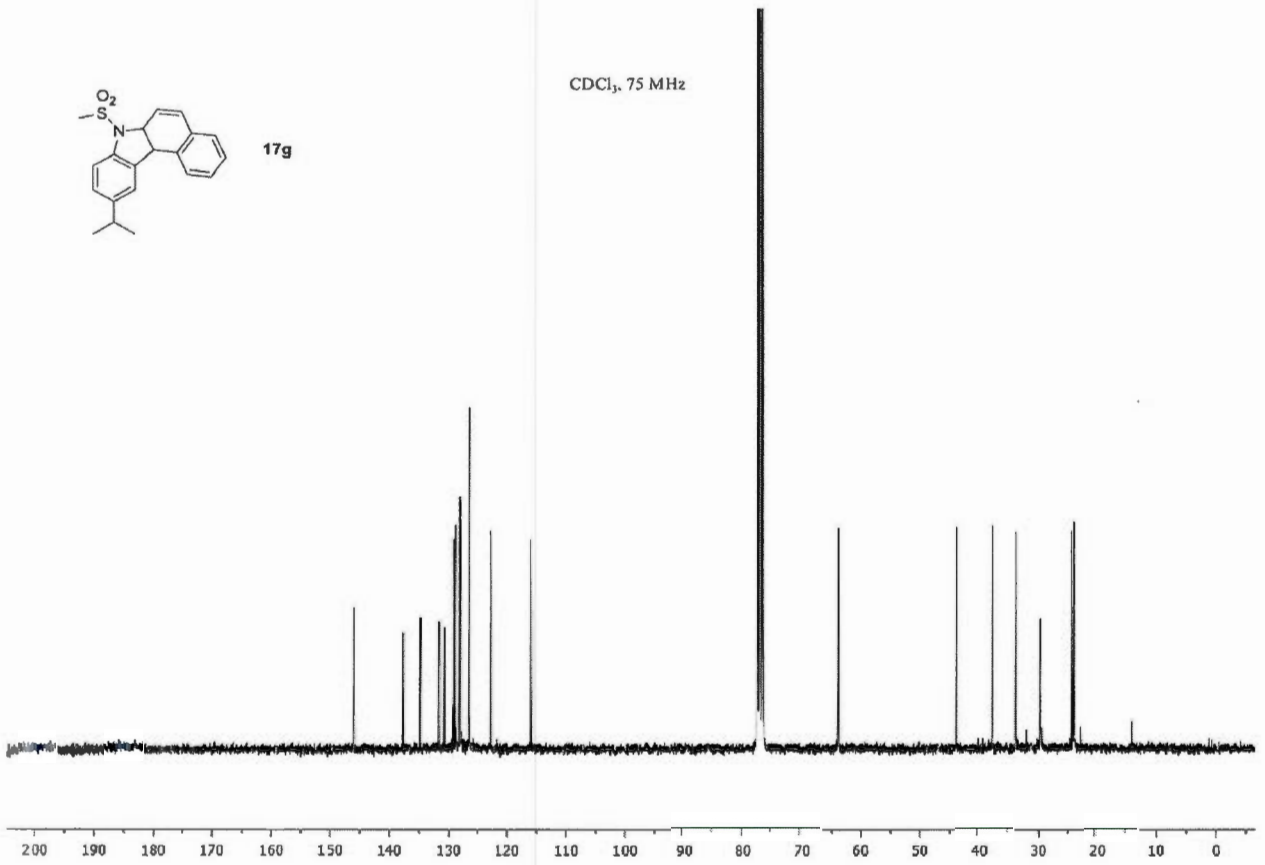
This journal is © The Royal Society of Chemistry 2013



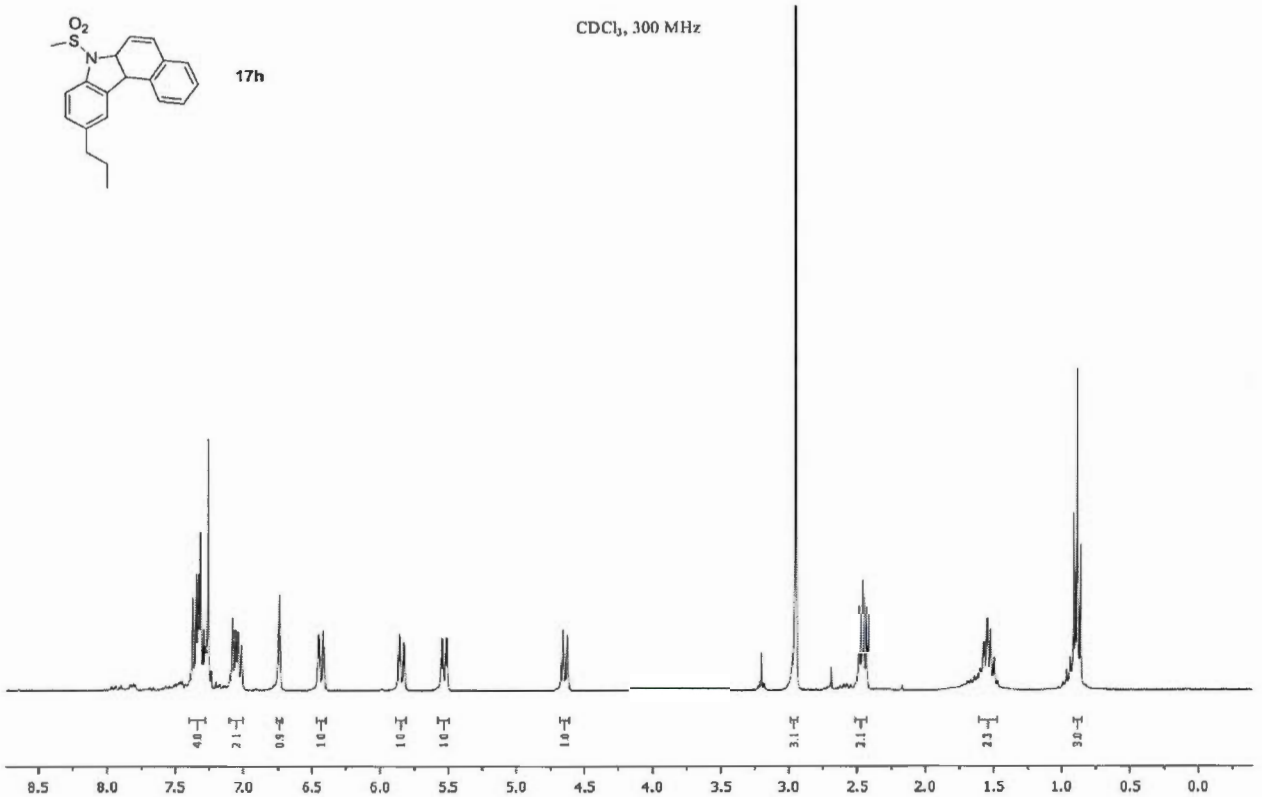
This journal is © The Royal Society of Chemistry 2013

17g

$CDCl_3$, 75 MHz



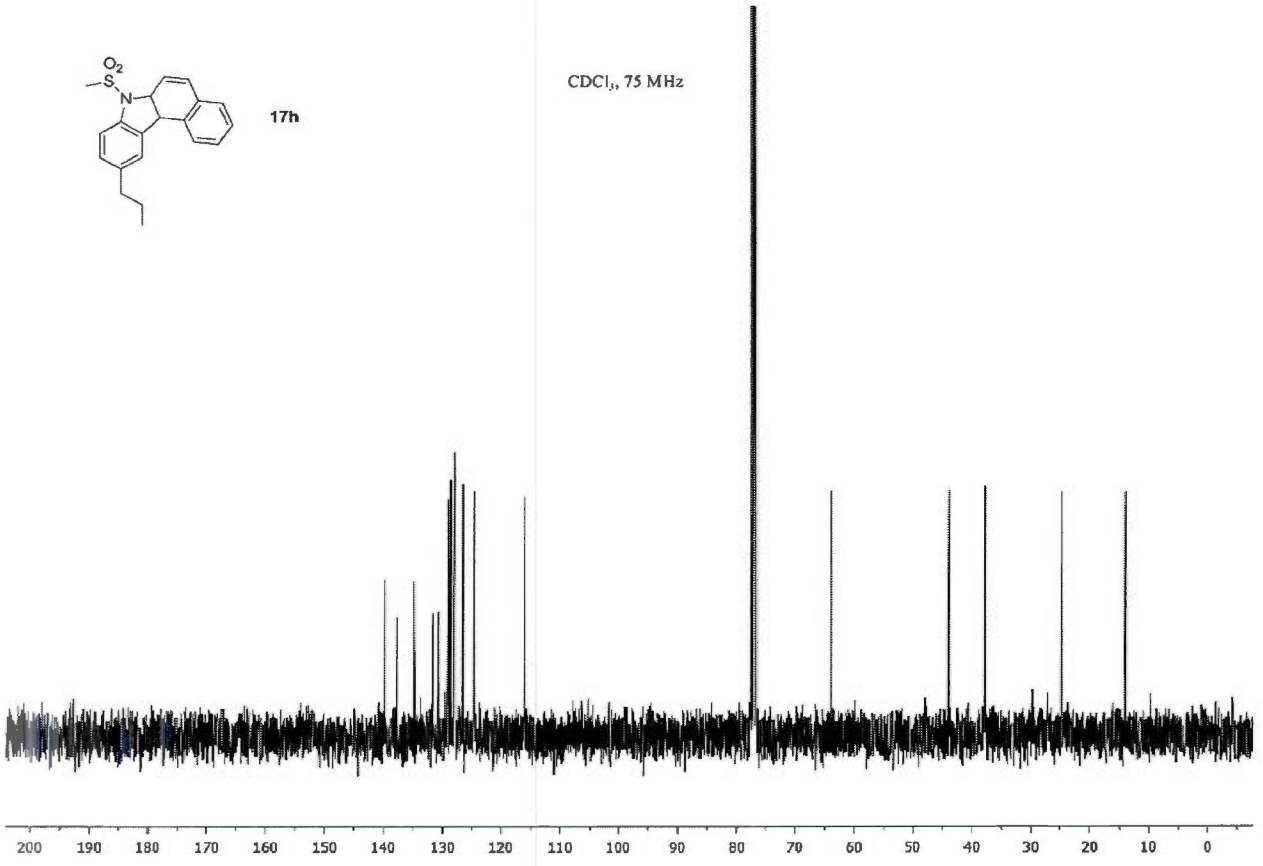
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013



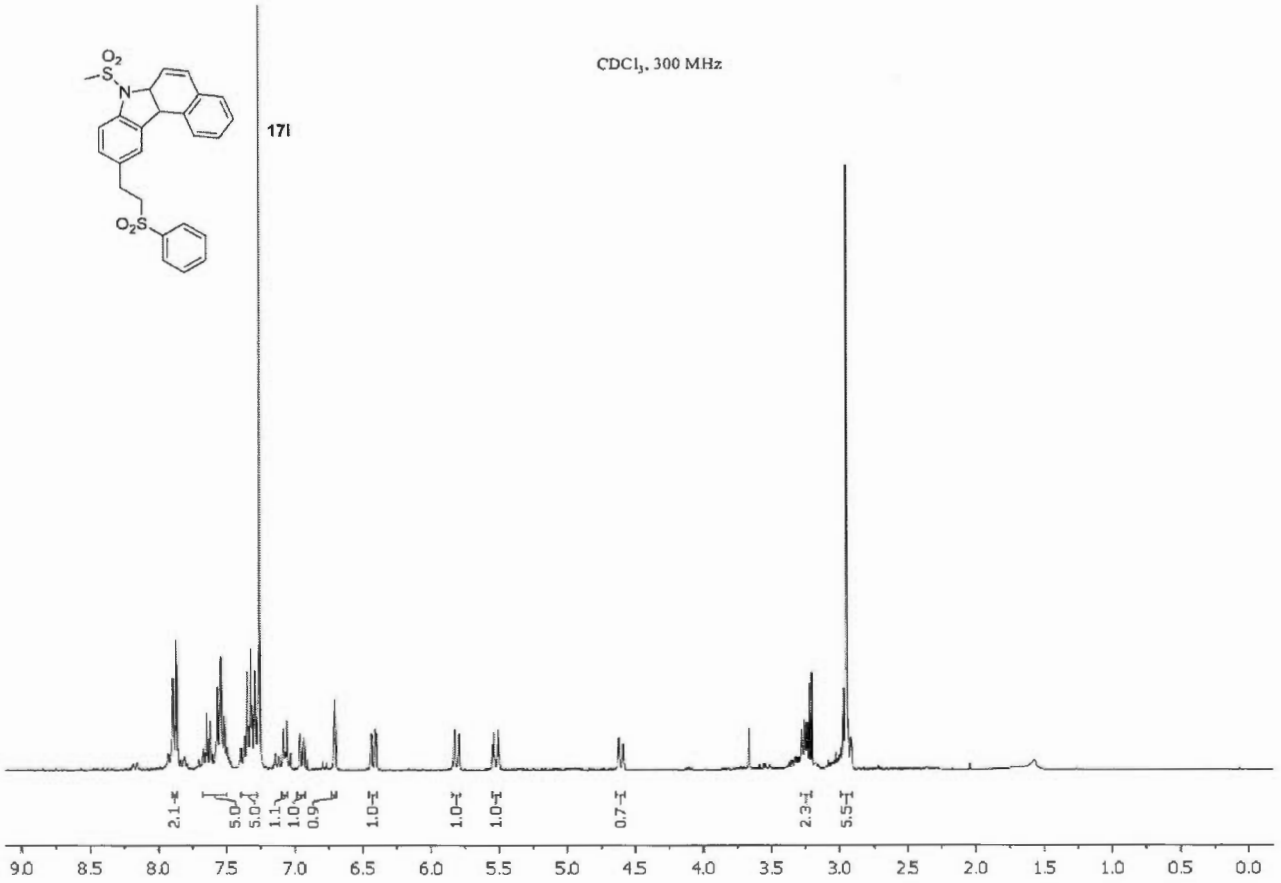
This journal is © The Royal Society of Chemistry 2013

17h

$CDCl_3$, 75 MHz



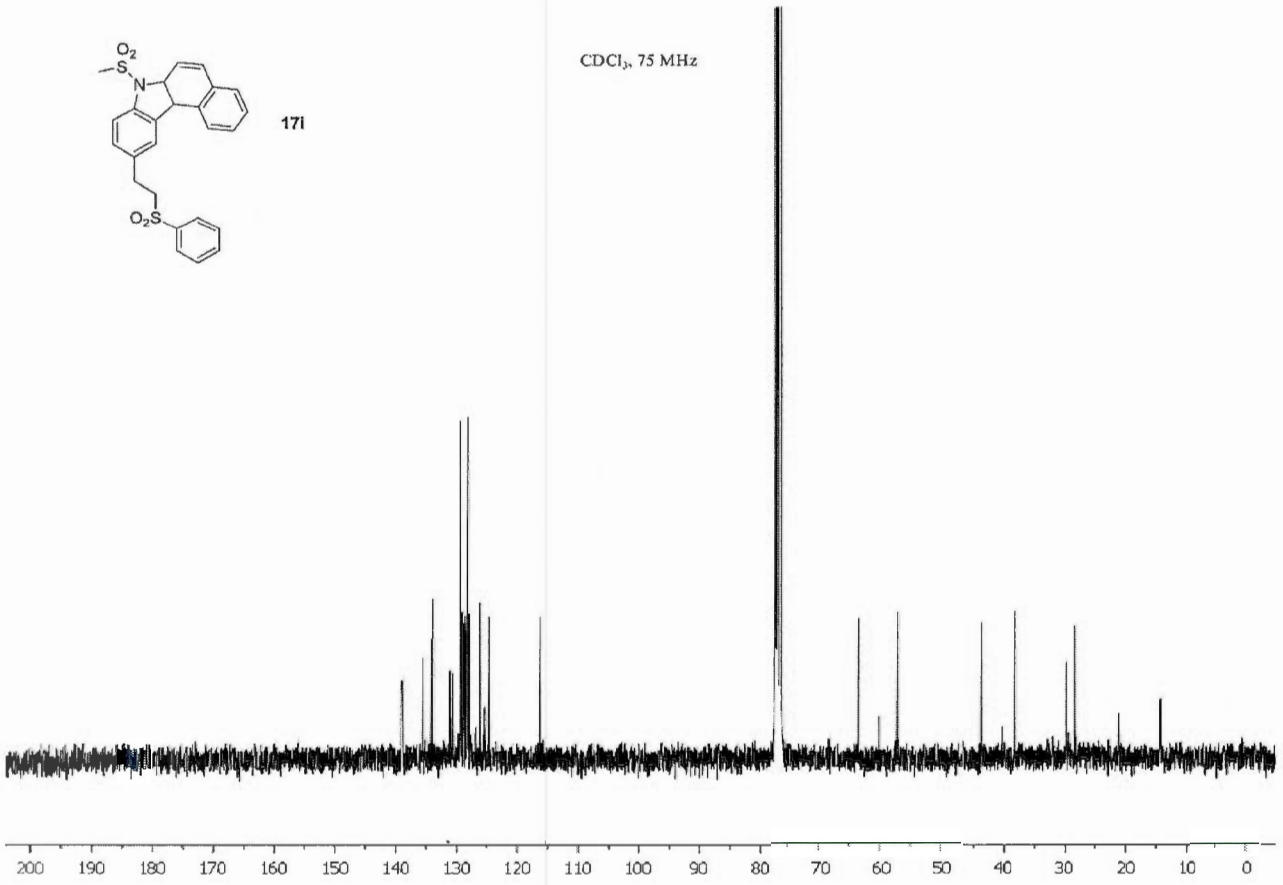
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013



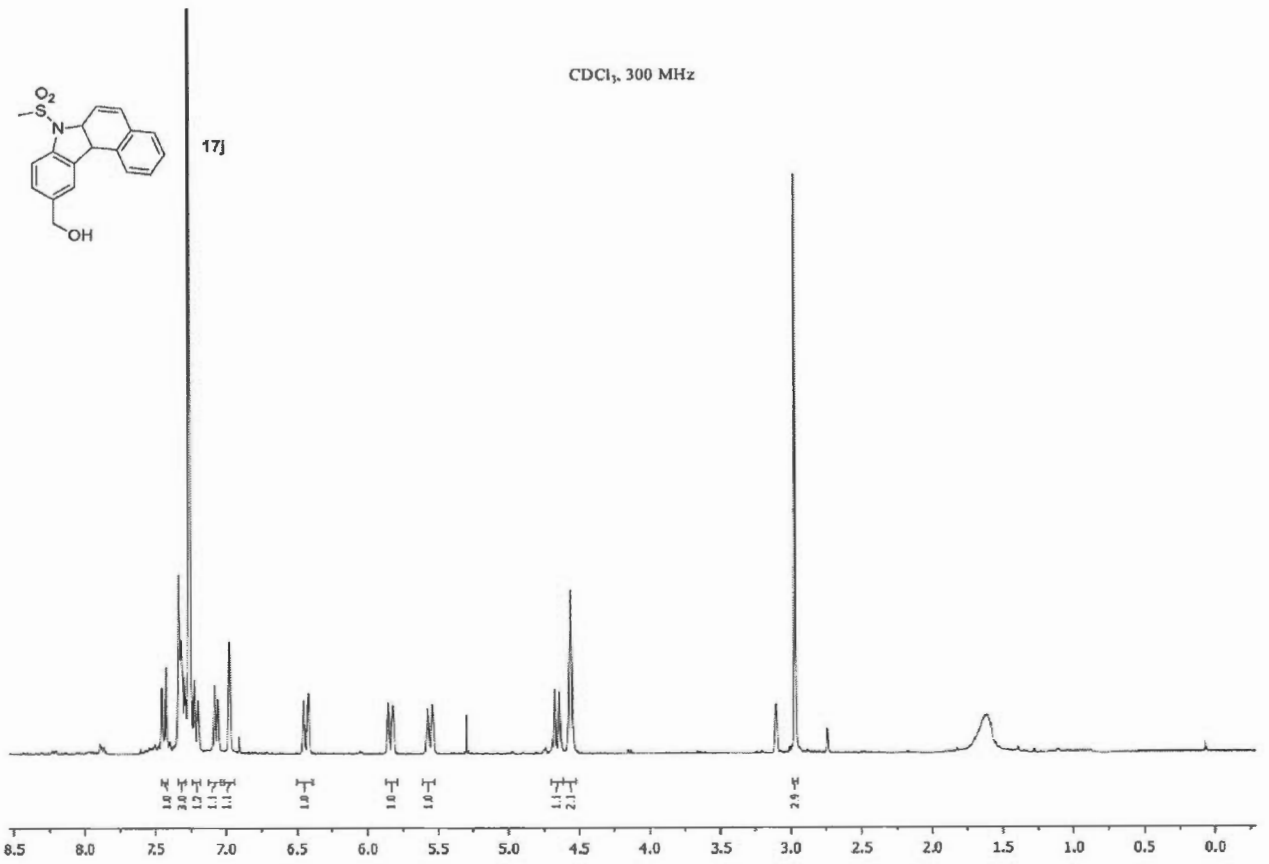
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

17l

$CDCl_3$, 75 MHz



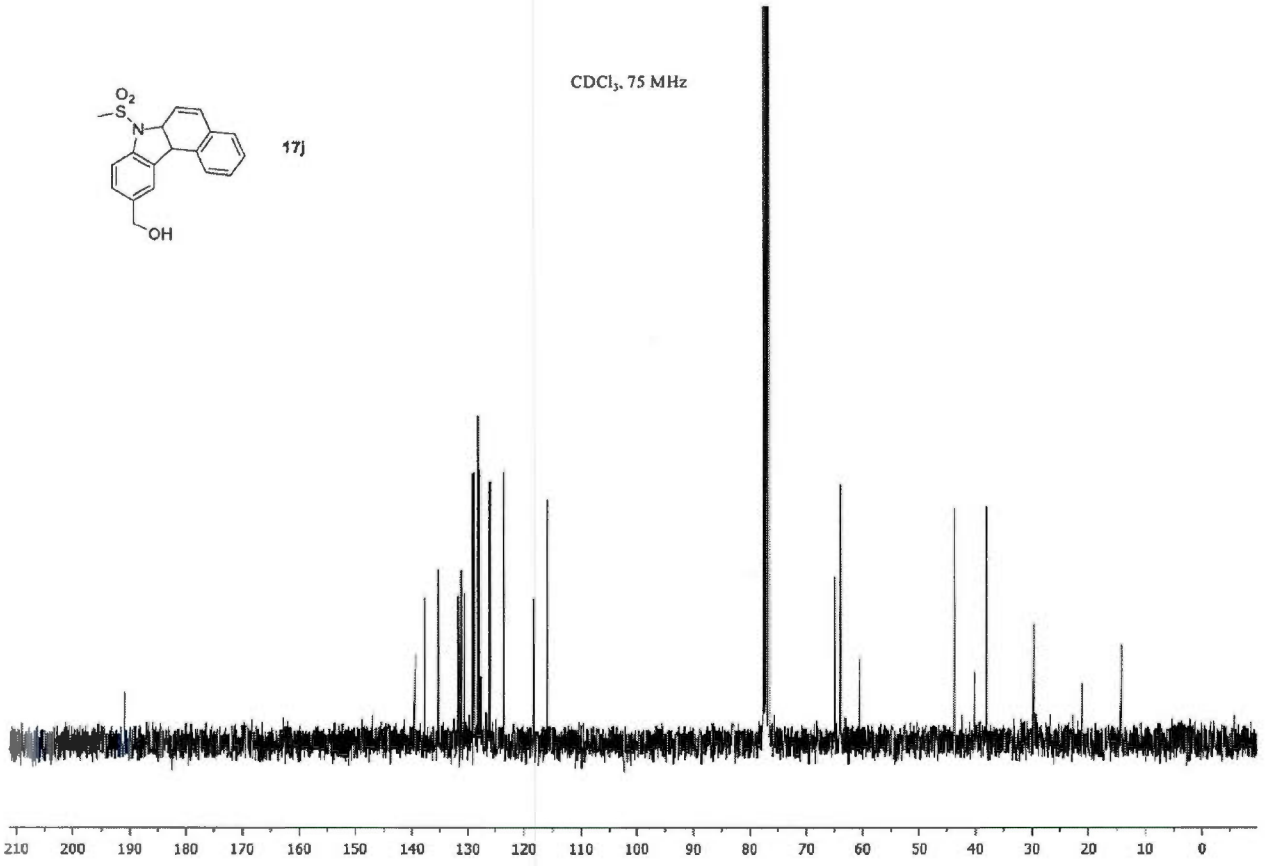
This journal is © The Royal Society of Chemistry 2013



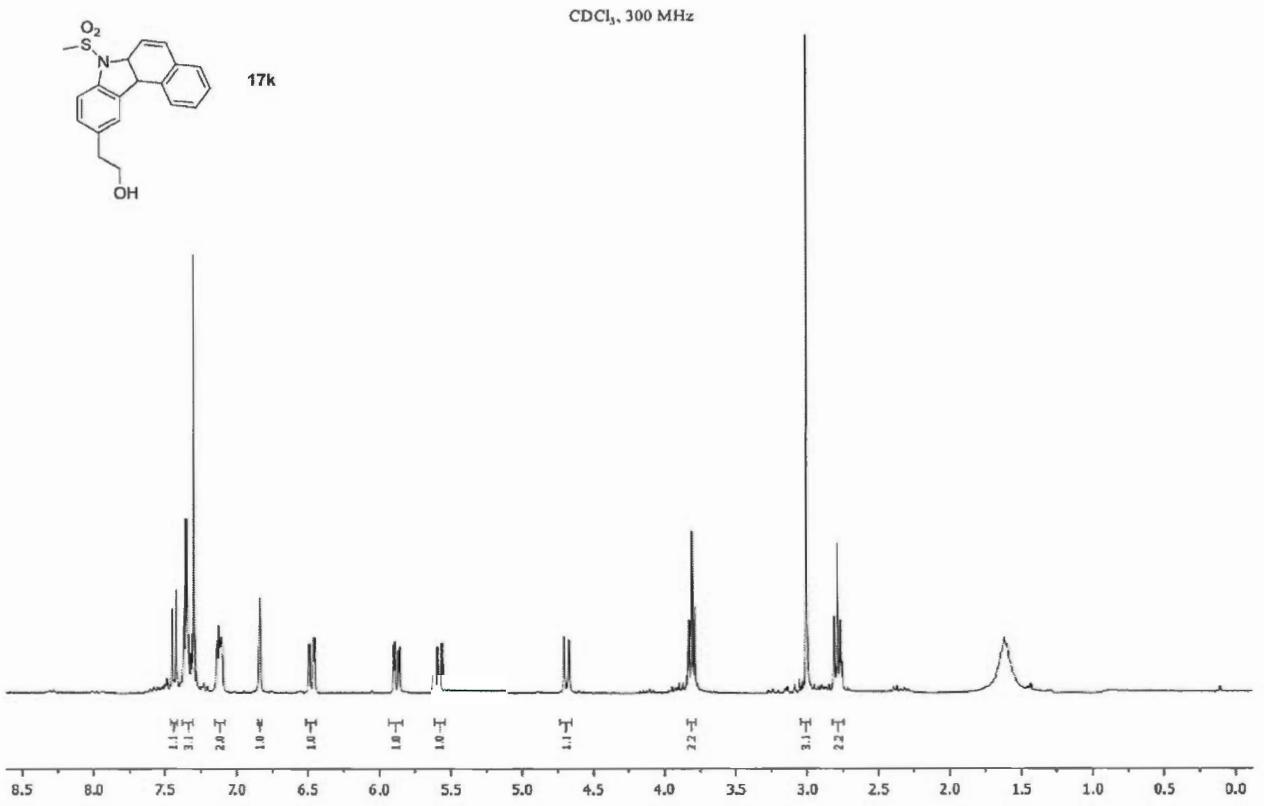
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

17j

$CDCl_3$, 75 MHz



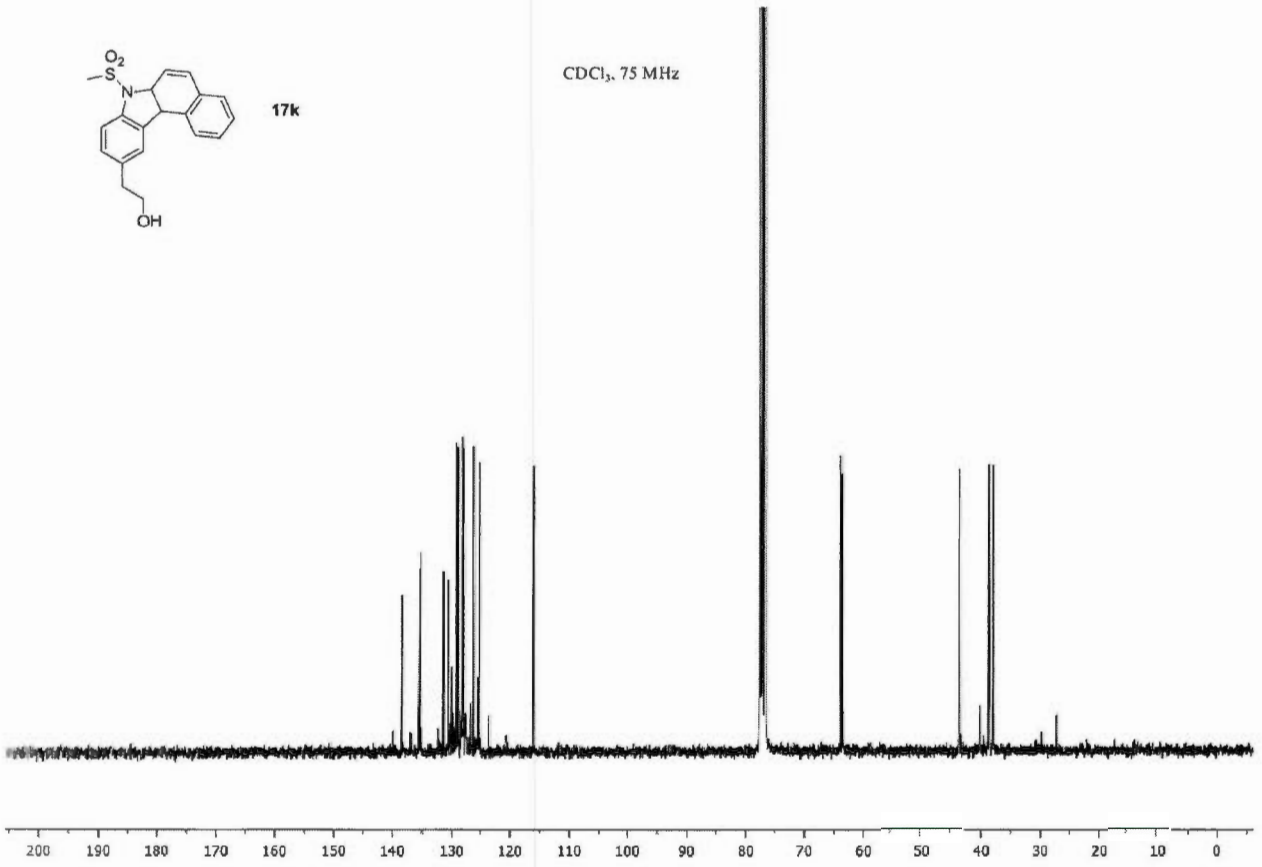
This journal is © The Royal Society of Chemistry 2013



This journal is © The Royal Society of Chemistry 2013

17k

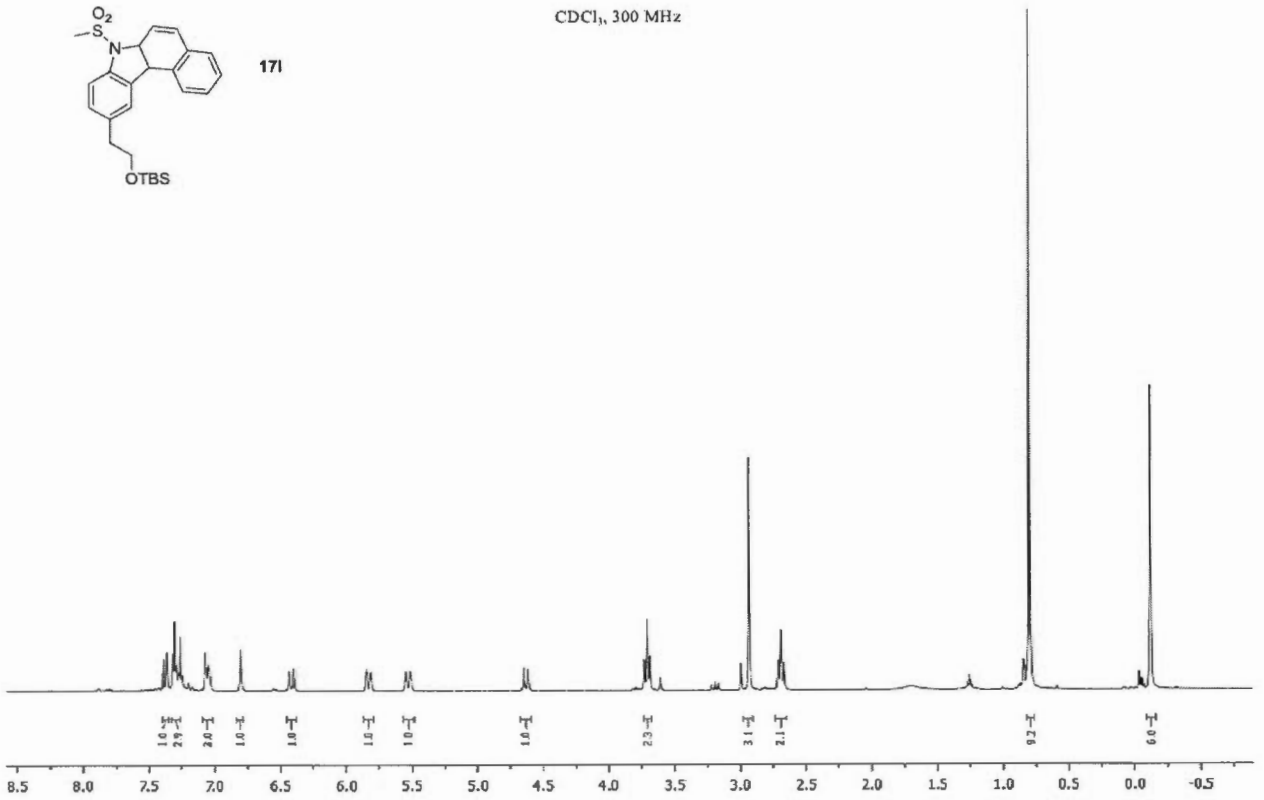
$CDCl_3$, 75 MHz



This journal is © The Royal Society of Chemistry 2013

17l

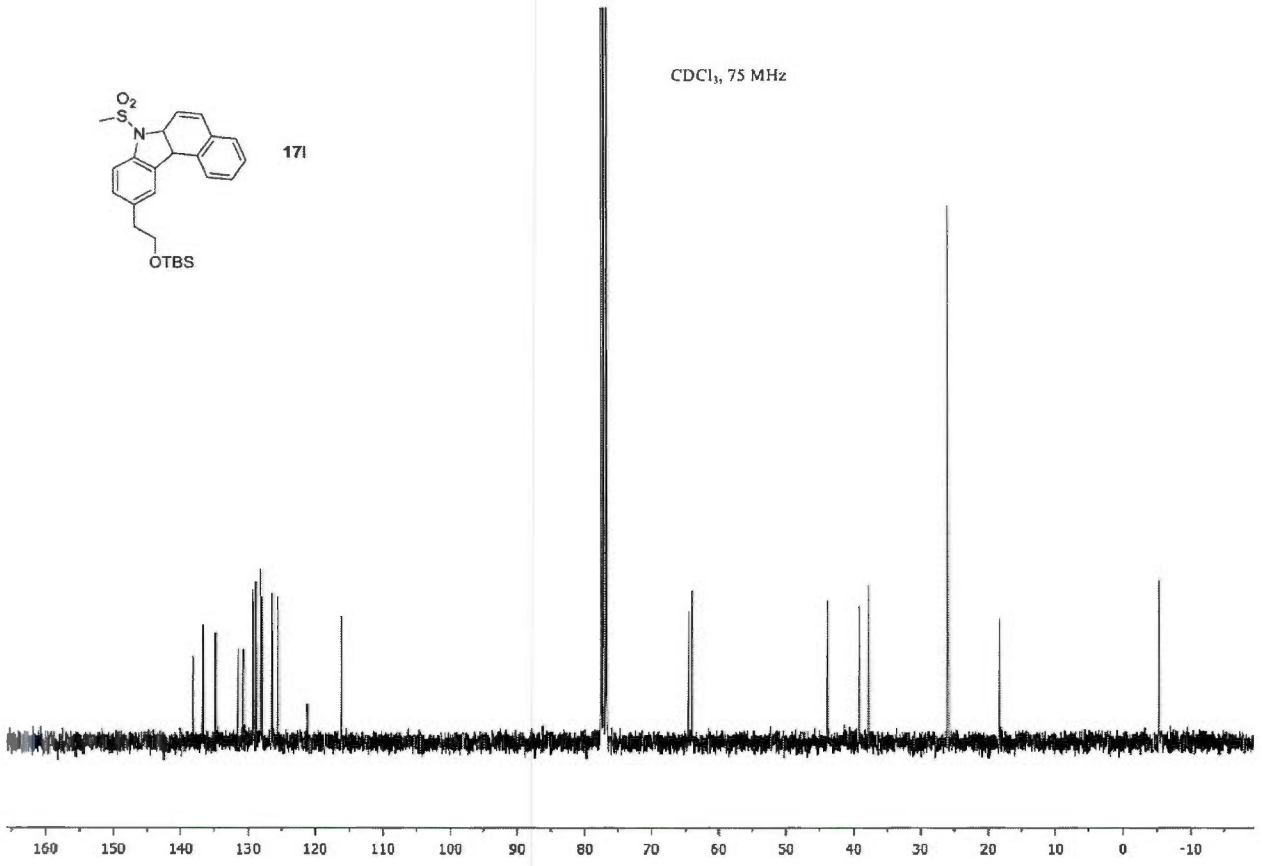
$CDCl_3$, 300 MHz



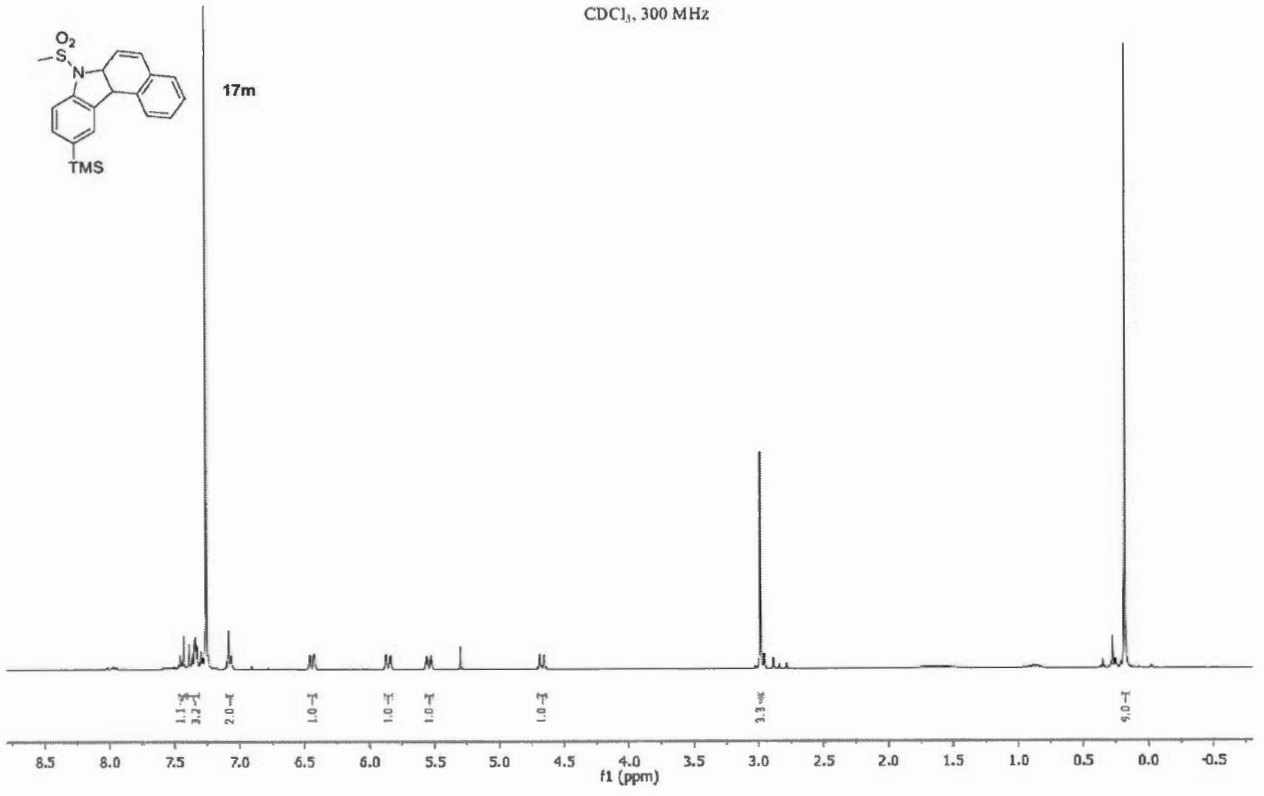
This journal is © The Royal Society of Chemistry 2013

17l

$CDCl_3$, 75 MHz



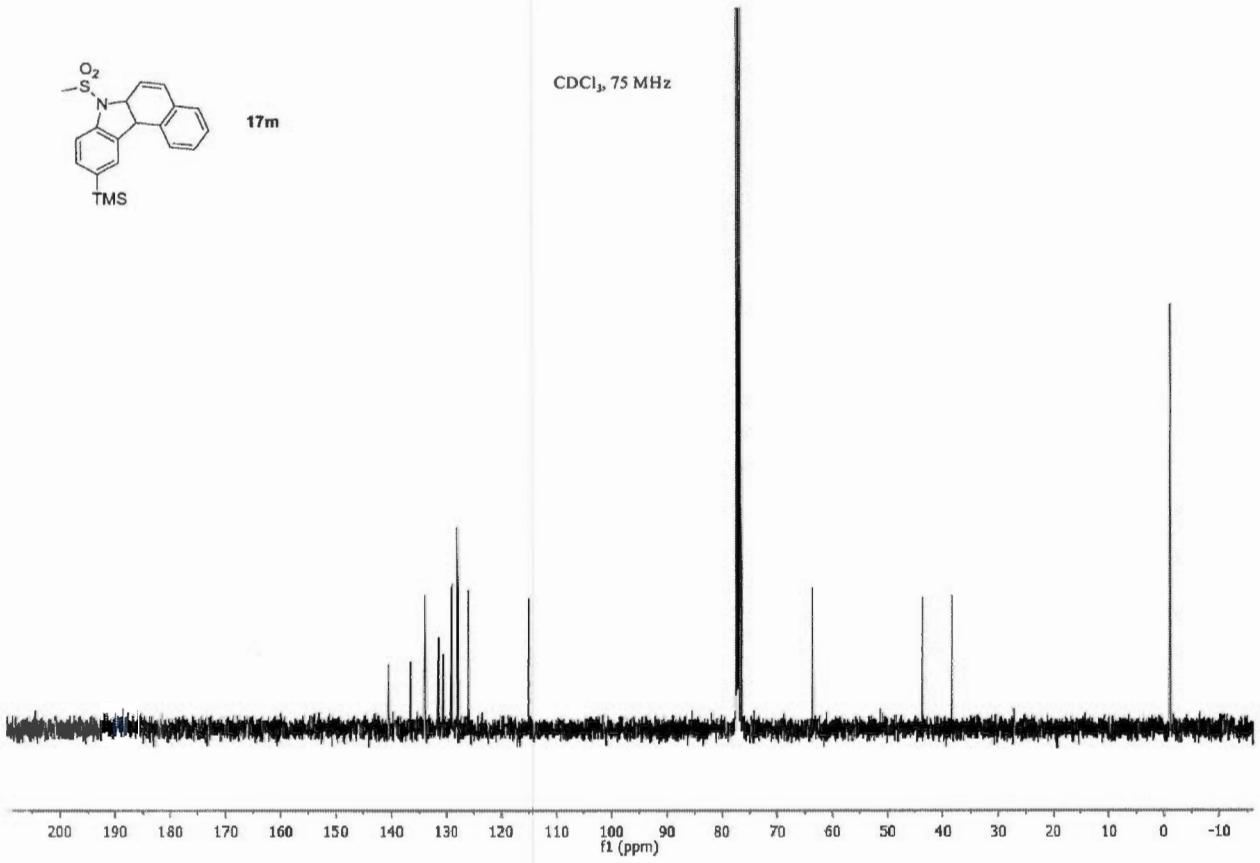
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013



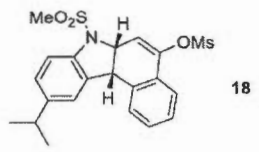
This journal is © The Royal Society of Chemistry 2013

17m

$CDCl_3$, 75 MHz

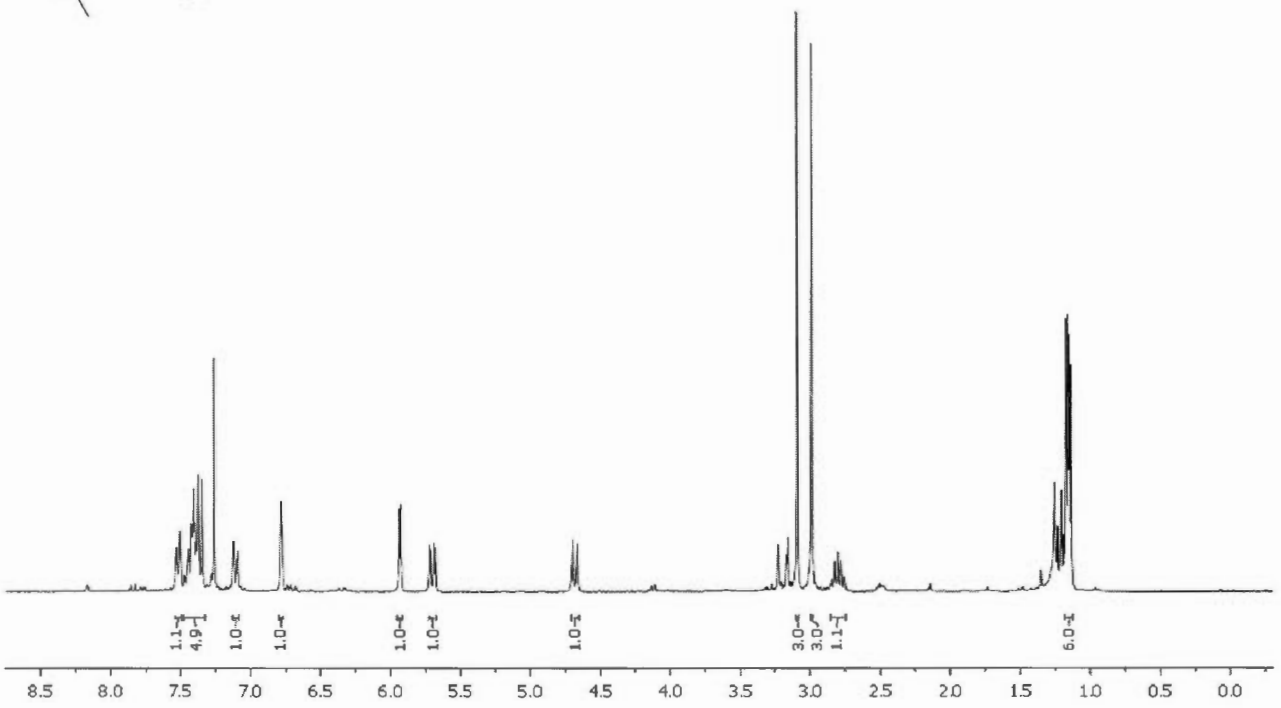


Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013



18

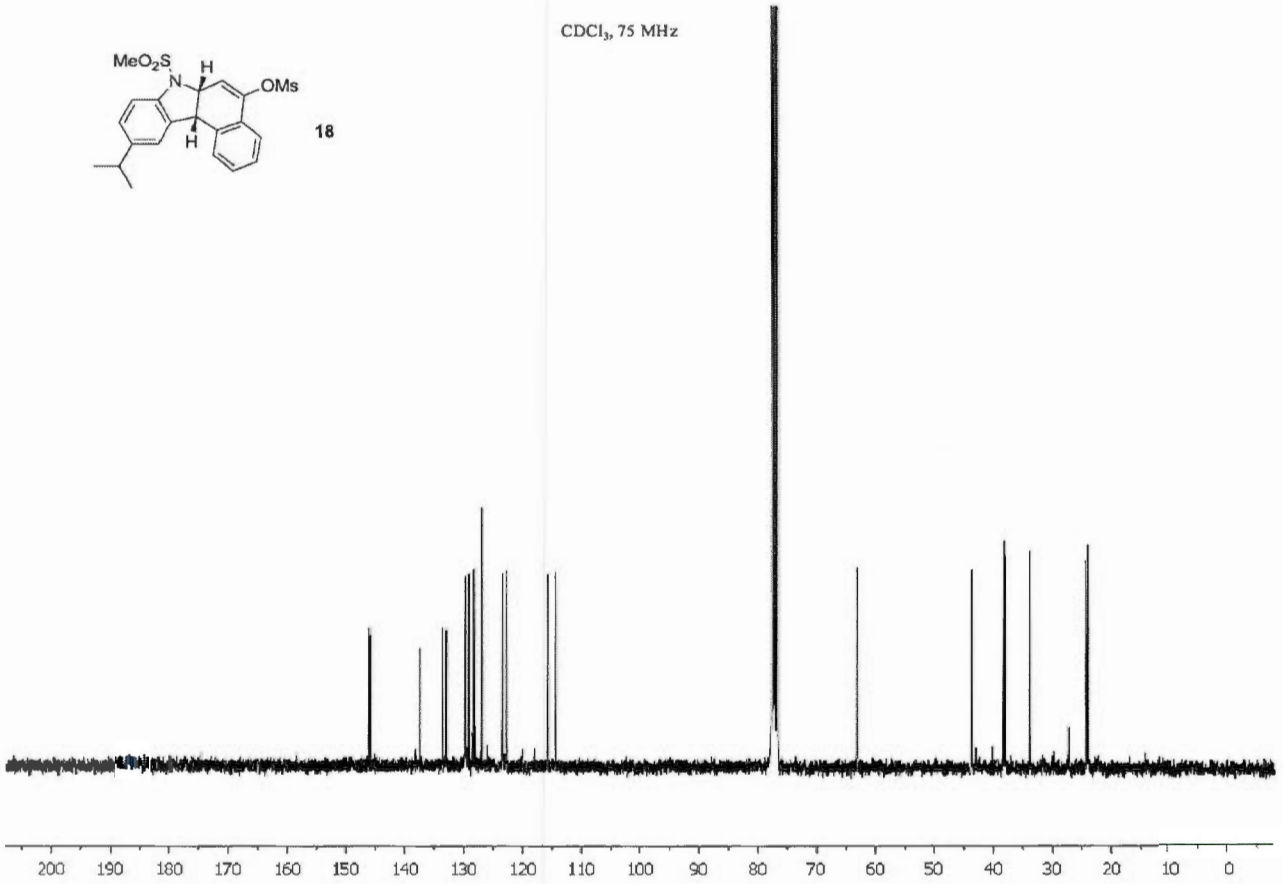
$CDCl_3$, 300 MHz



This journal is © The Royal Society of Chemistry 2013

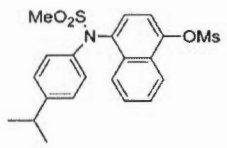
18

CDCl3, 75 MHz

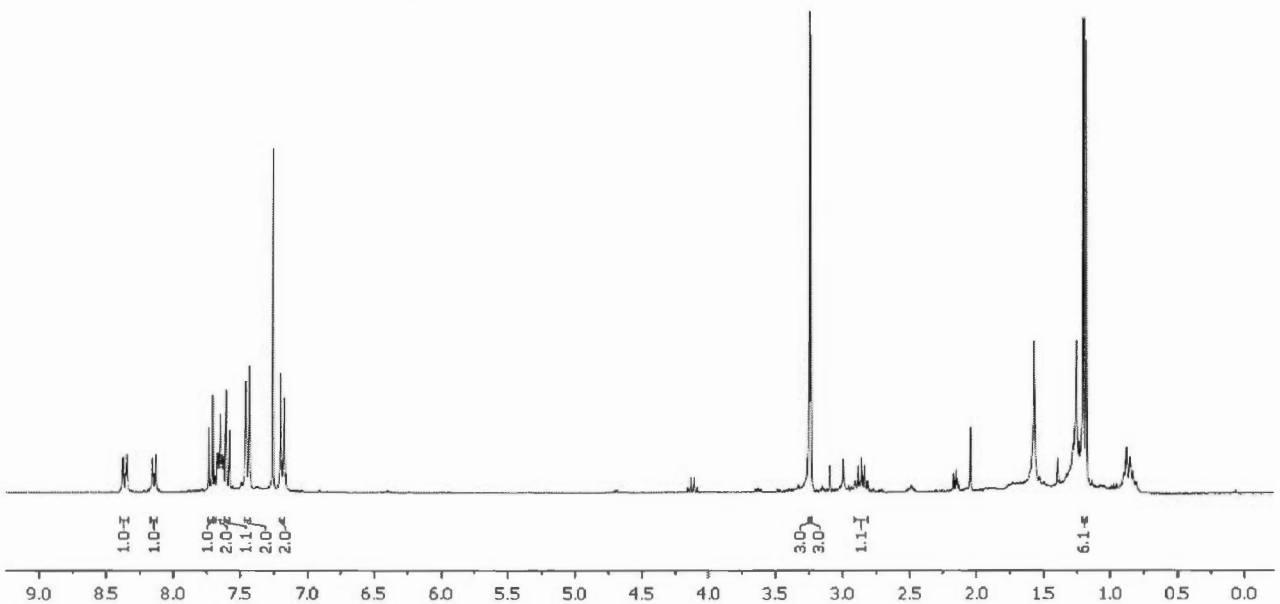


This journal is © The Royal Society of Chemistry 2013

$CDCl_3$, 300 MHz



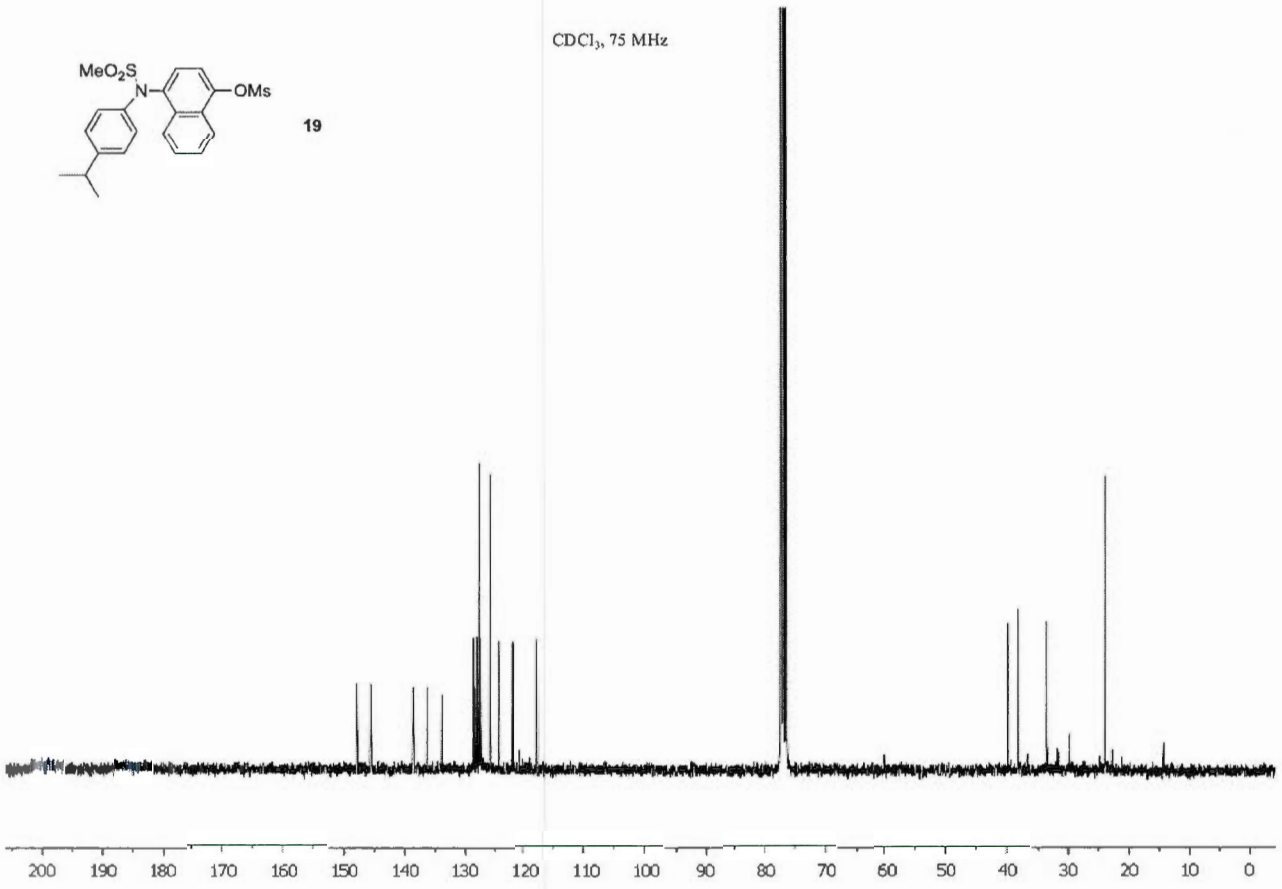
19



This journal is © The Royal Society of Chemistry 2013

19

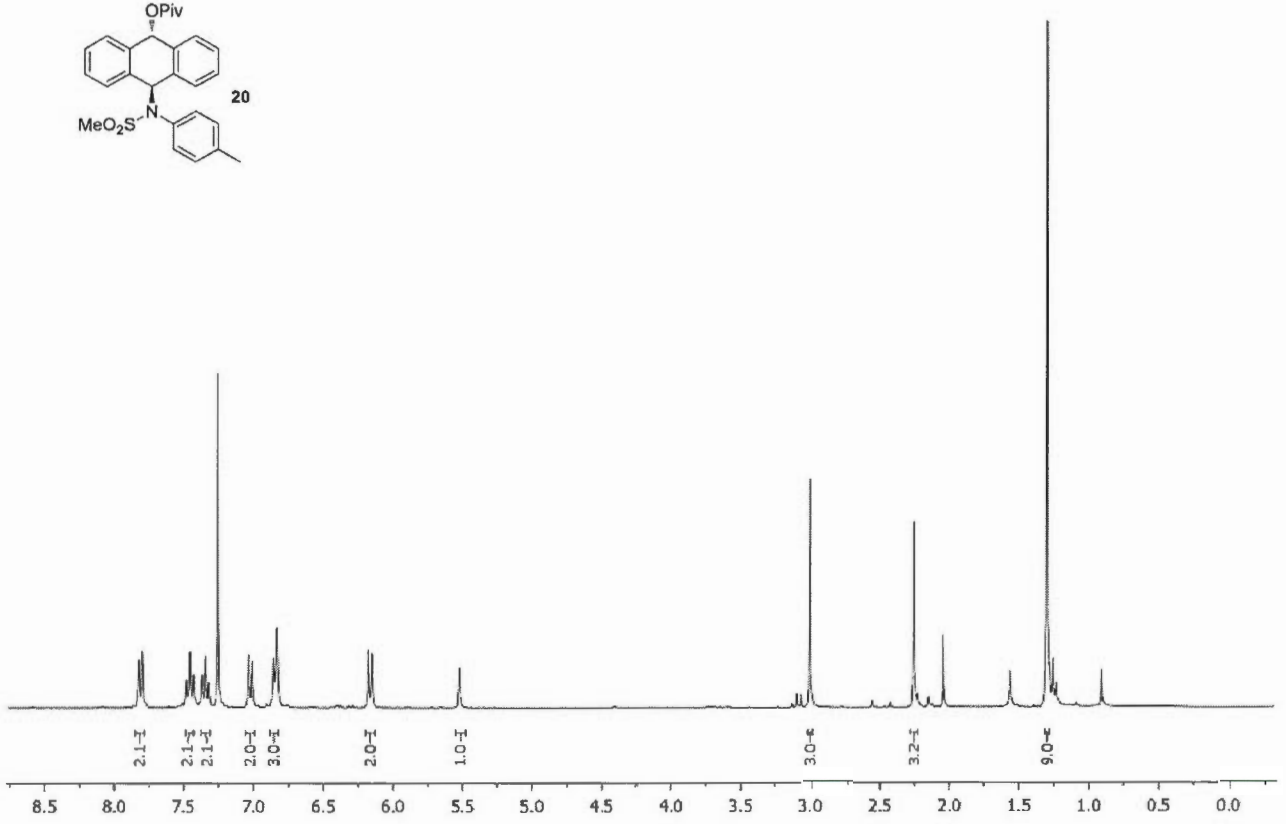
$CDCl_3$, 75 MHz



Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

$CDCl_3$, 300 MHz

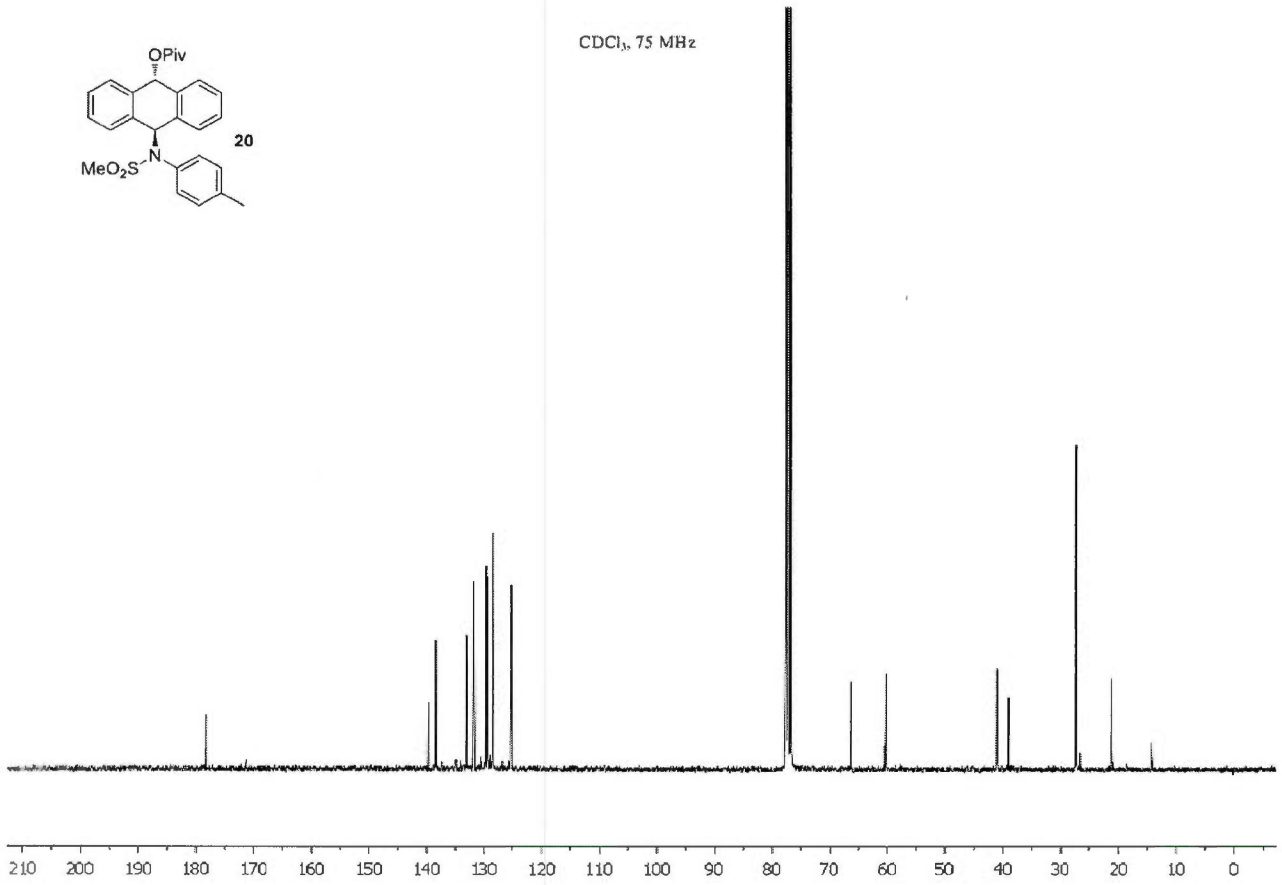
20



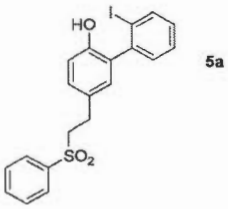
This journal is © The Royal Society of Chemistry 2013

20

$CDCl_3$, 75 MHz

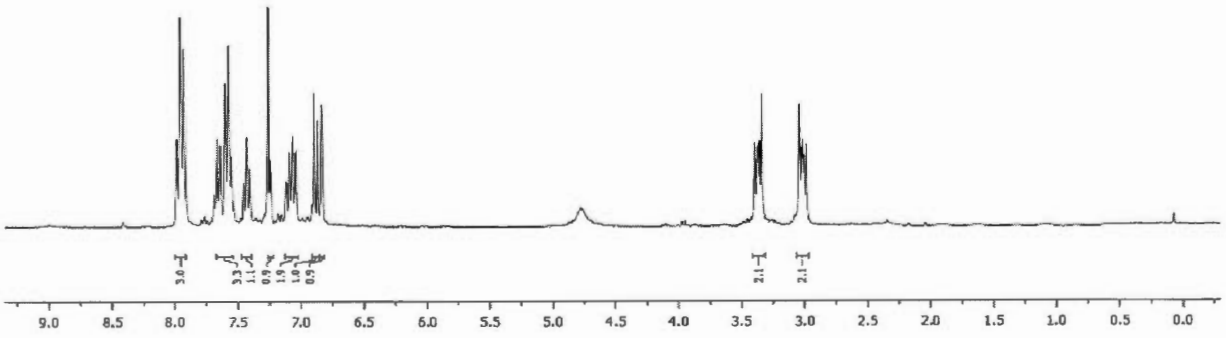


Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013



5a

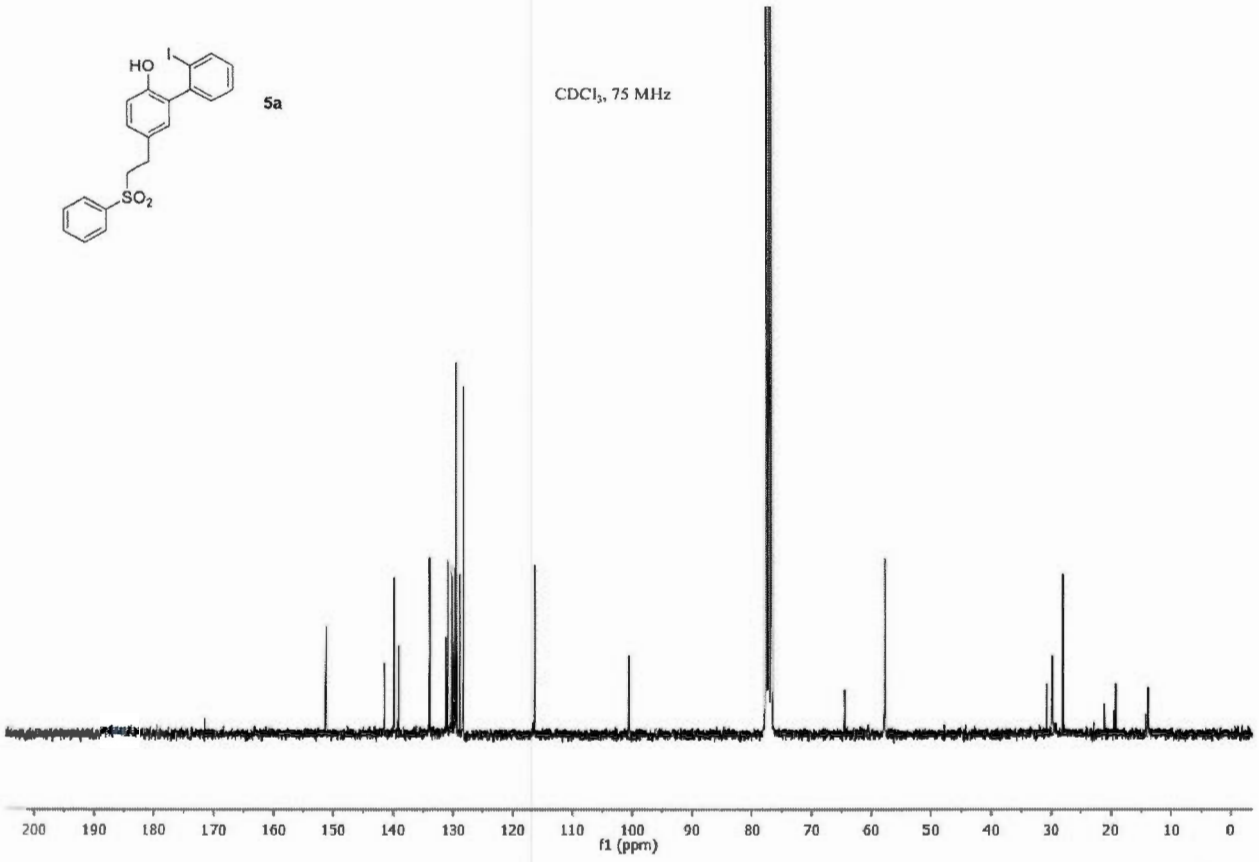
$CDCl_3$, 300 MHz



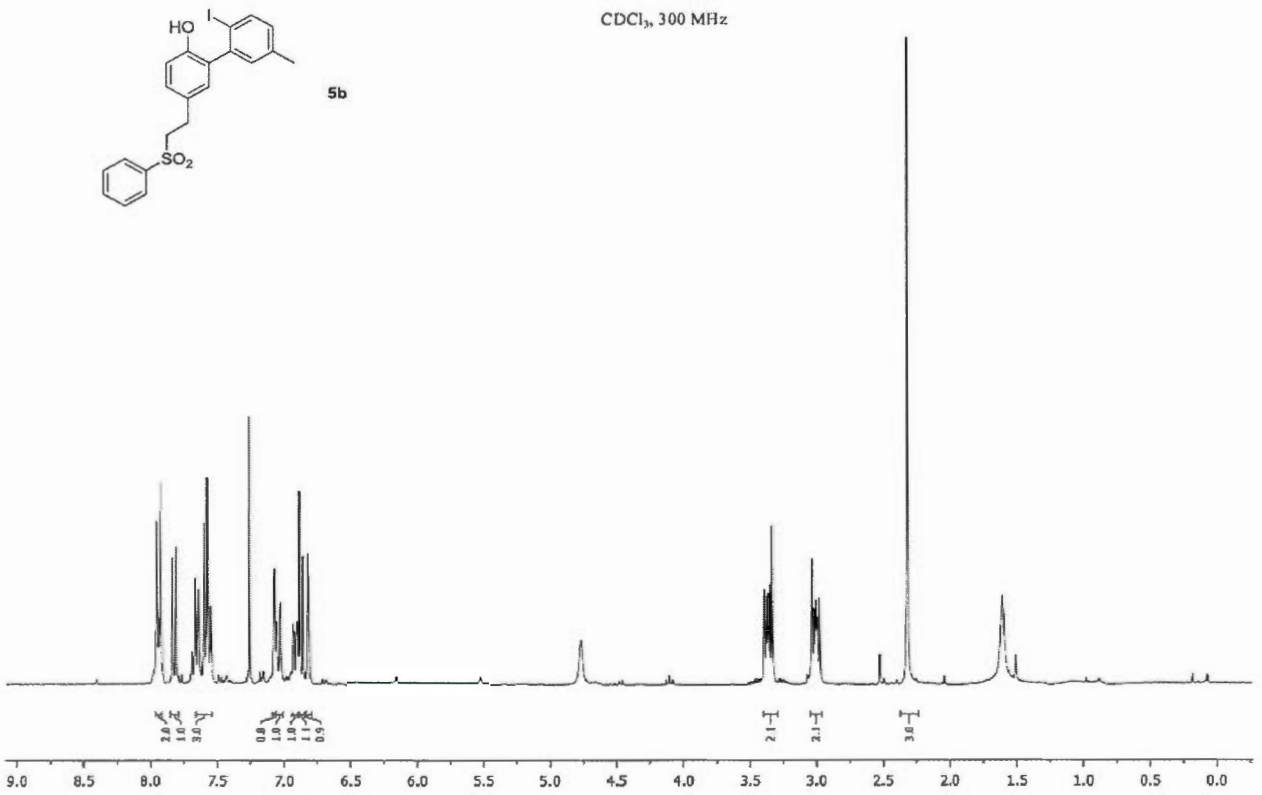
This journal is © The Royal Society of Chemistry 2013

5a

$CDCl_3$, 75 MHz



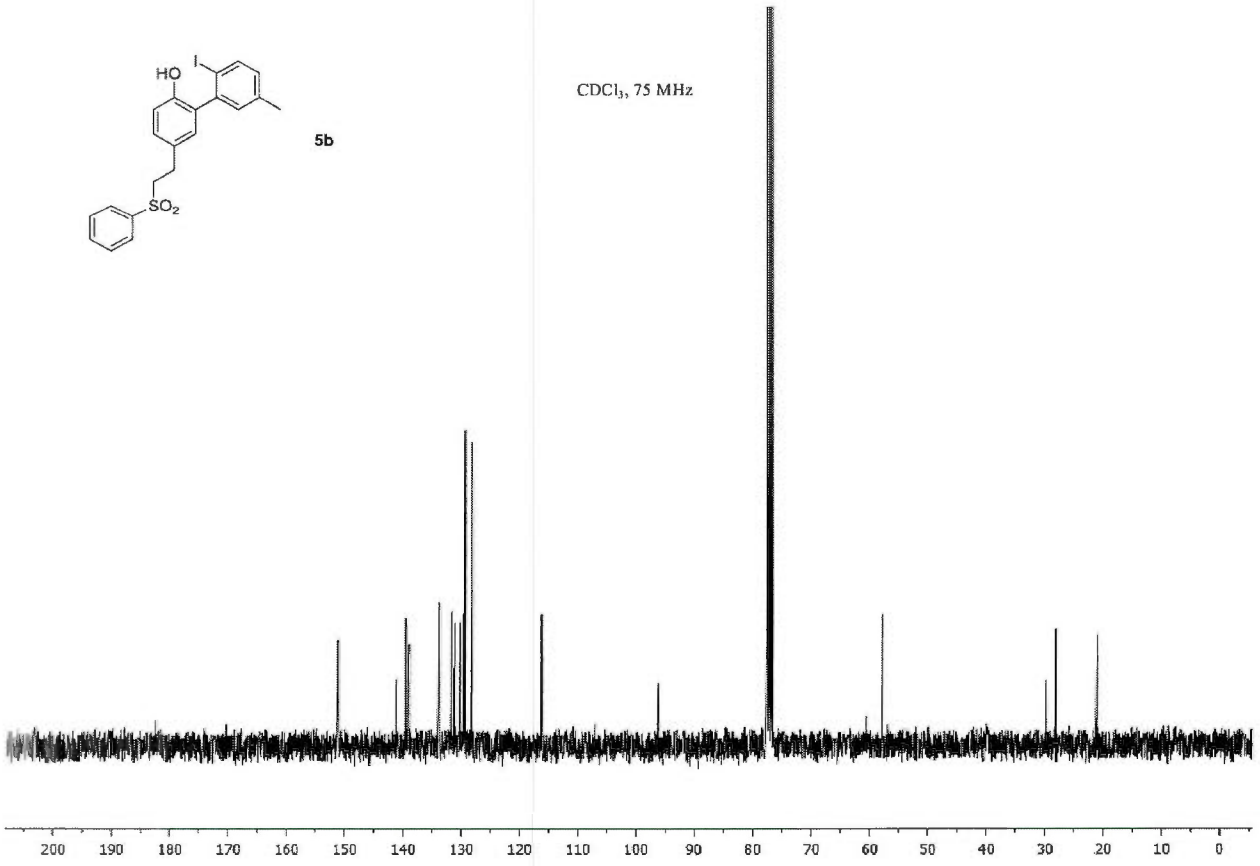
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013



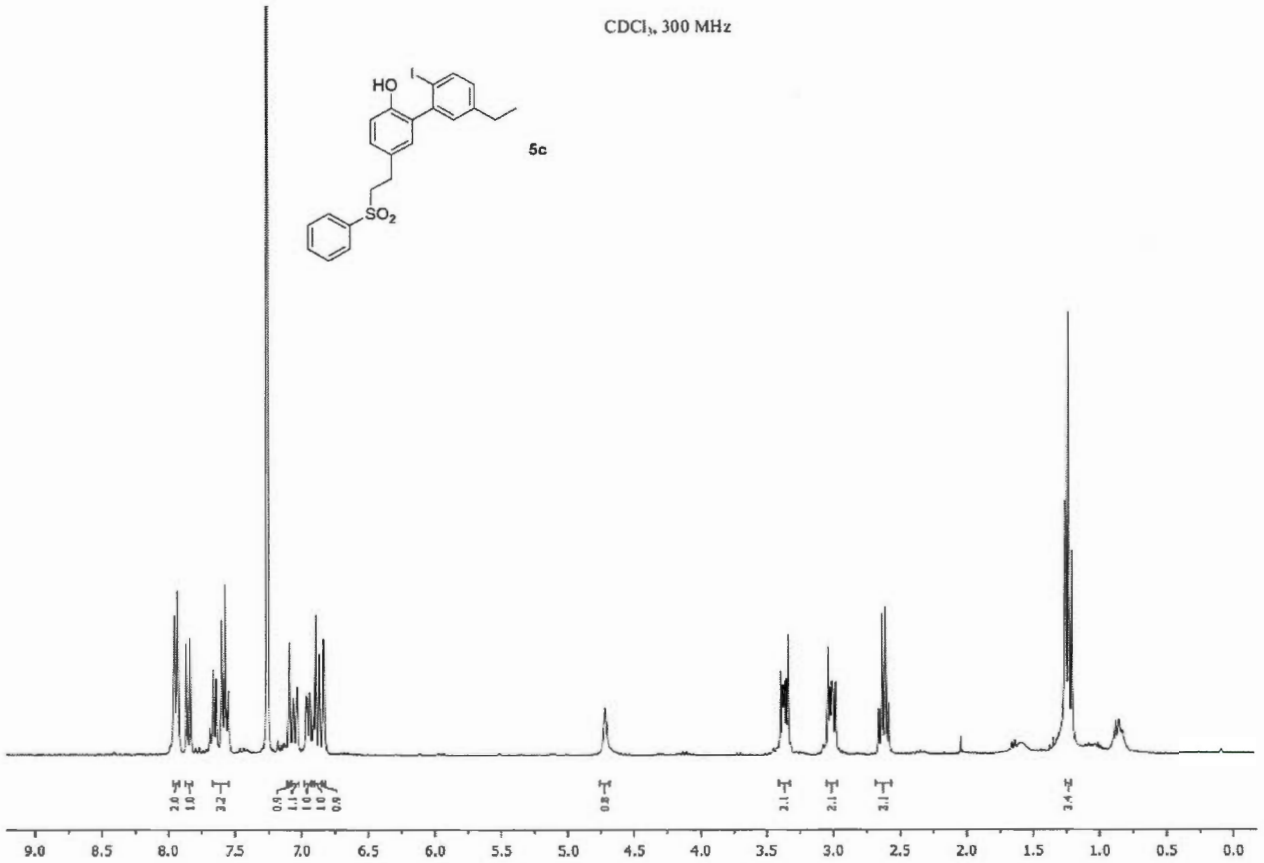
This journal is © The Royal Society of Chemistry 2013

5b

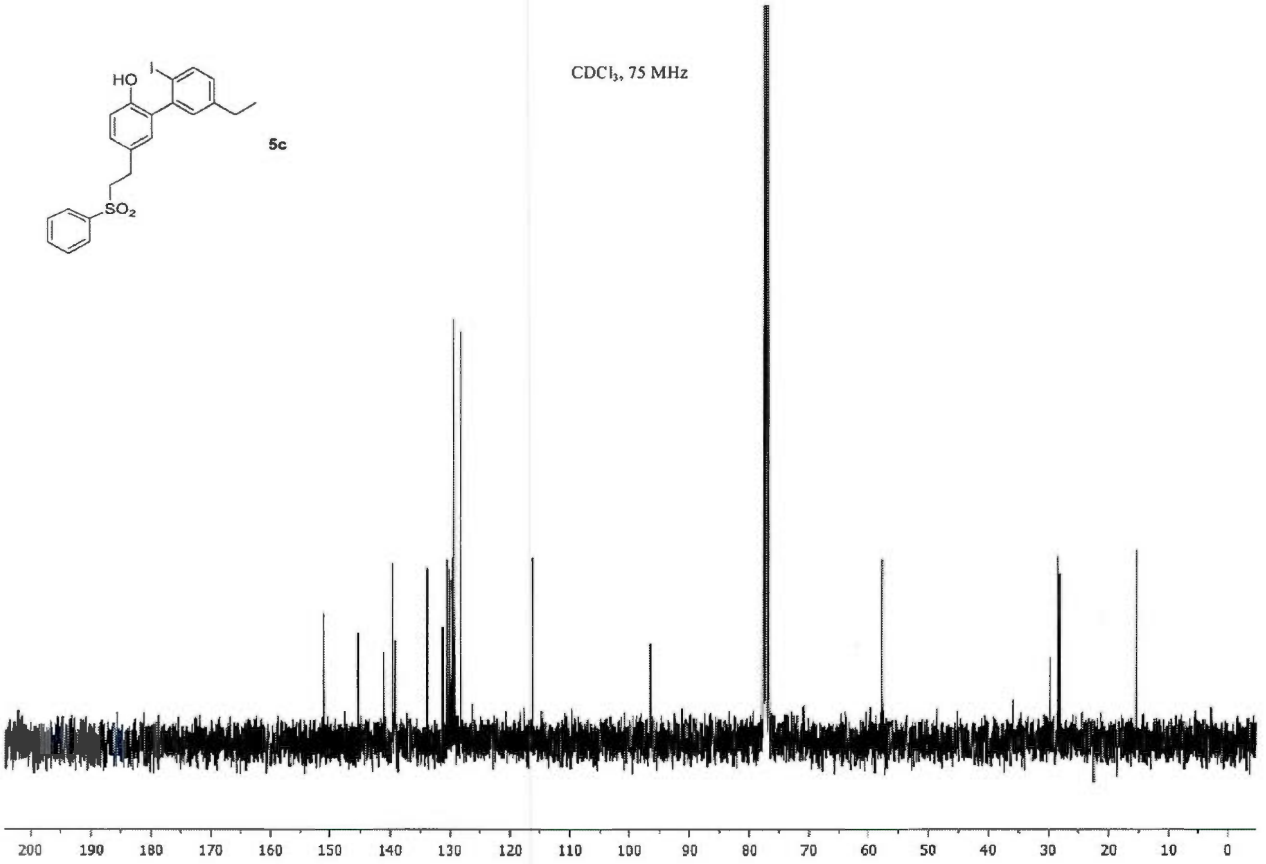
$CDCl_3$, 75 MHz



This journal is © The Royal Society of Chemistry 2013

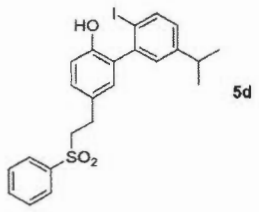


Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

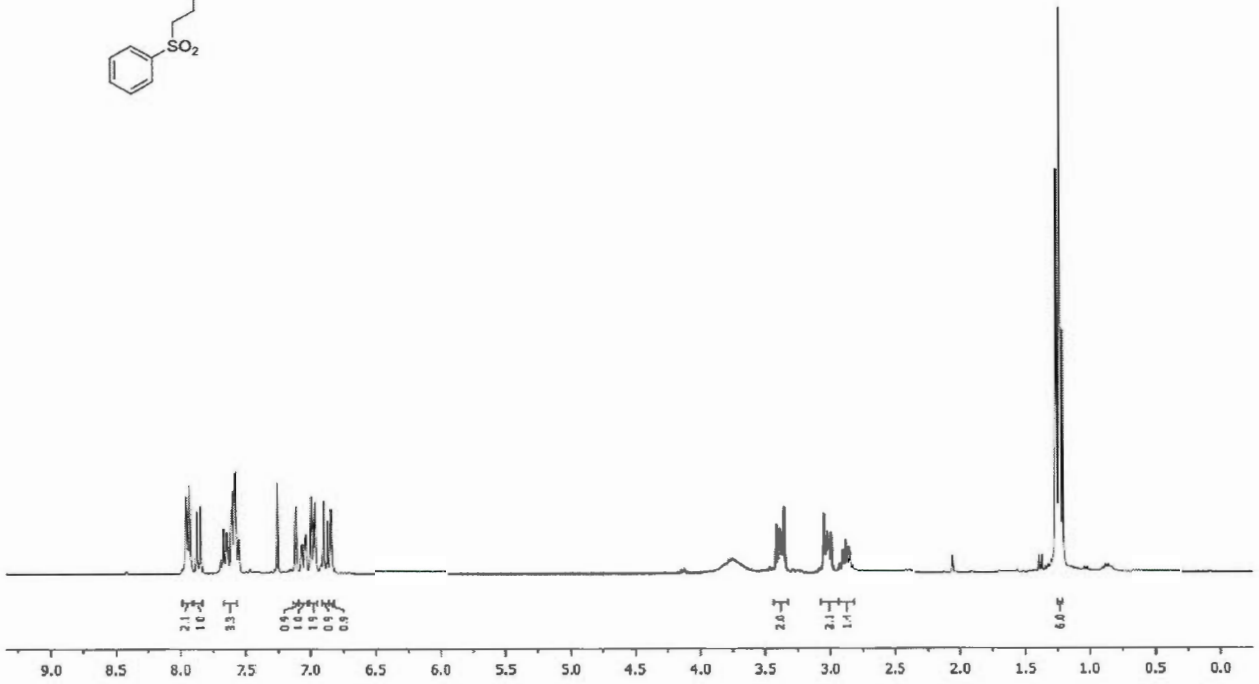


Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

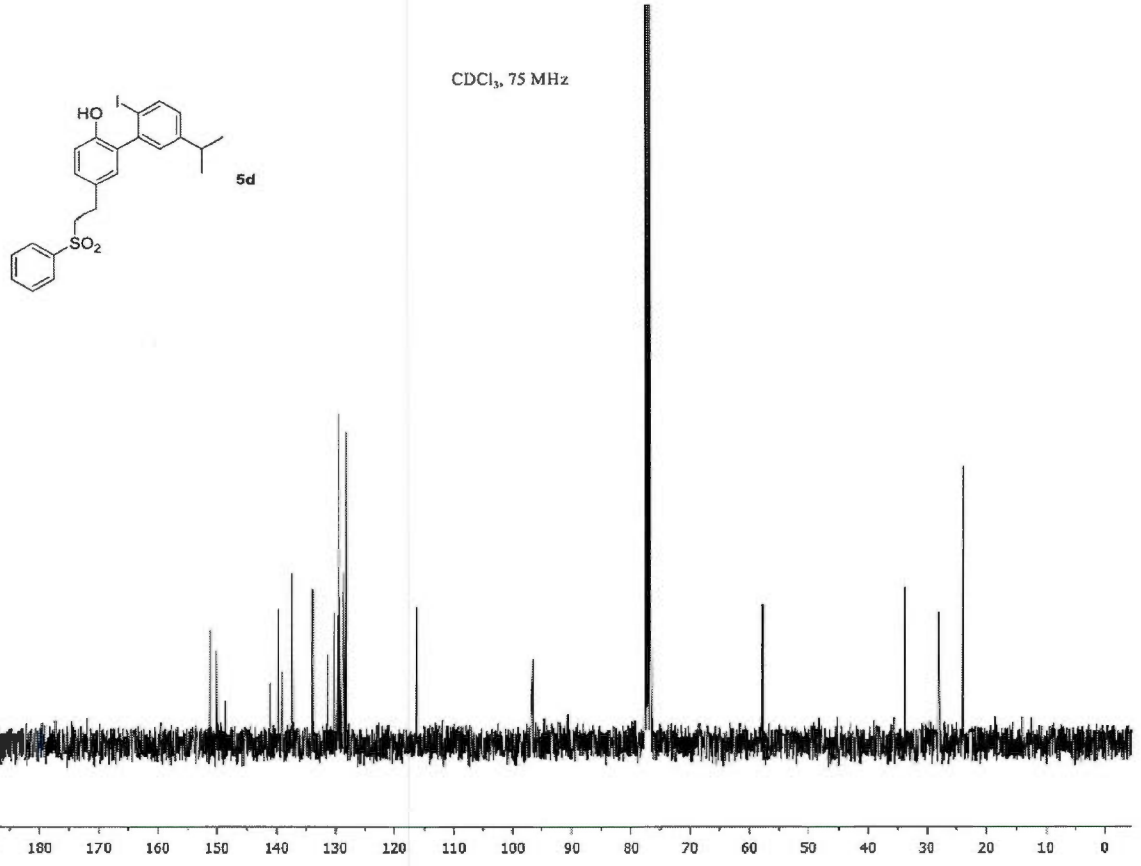
$CDCl_3$, 300 MHz



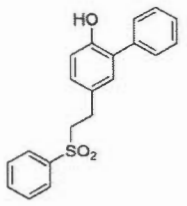
5d



This journal is © The Royal Society of Chemistry 2013

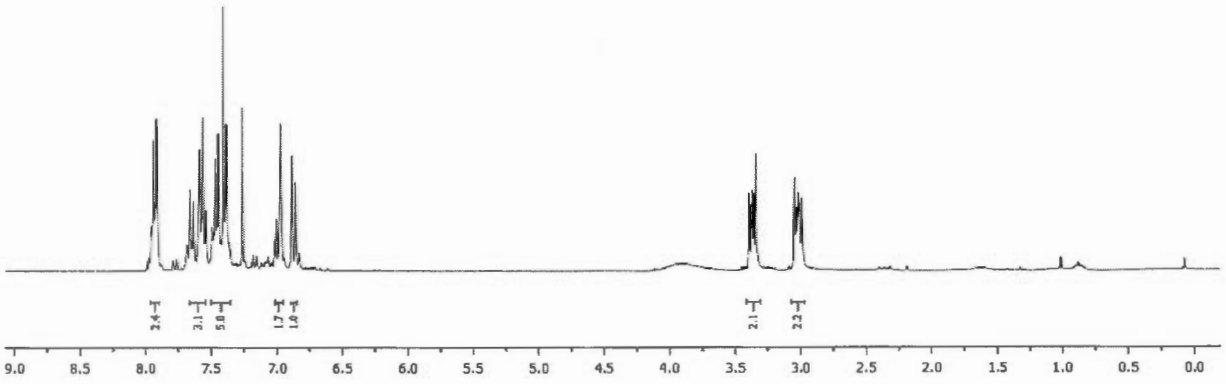


This journal is © The Royal Society of Chemistry 2013



5e

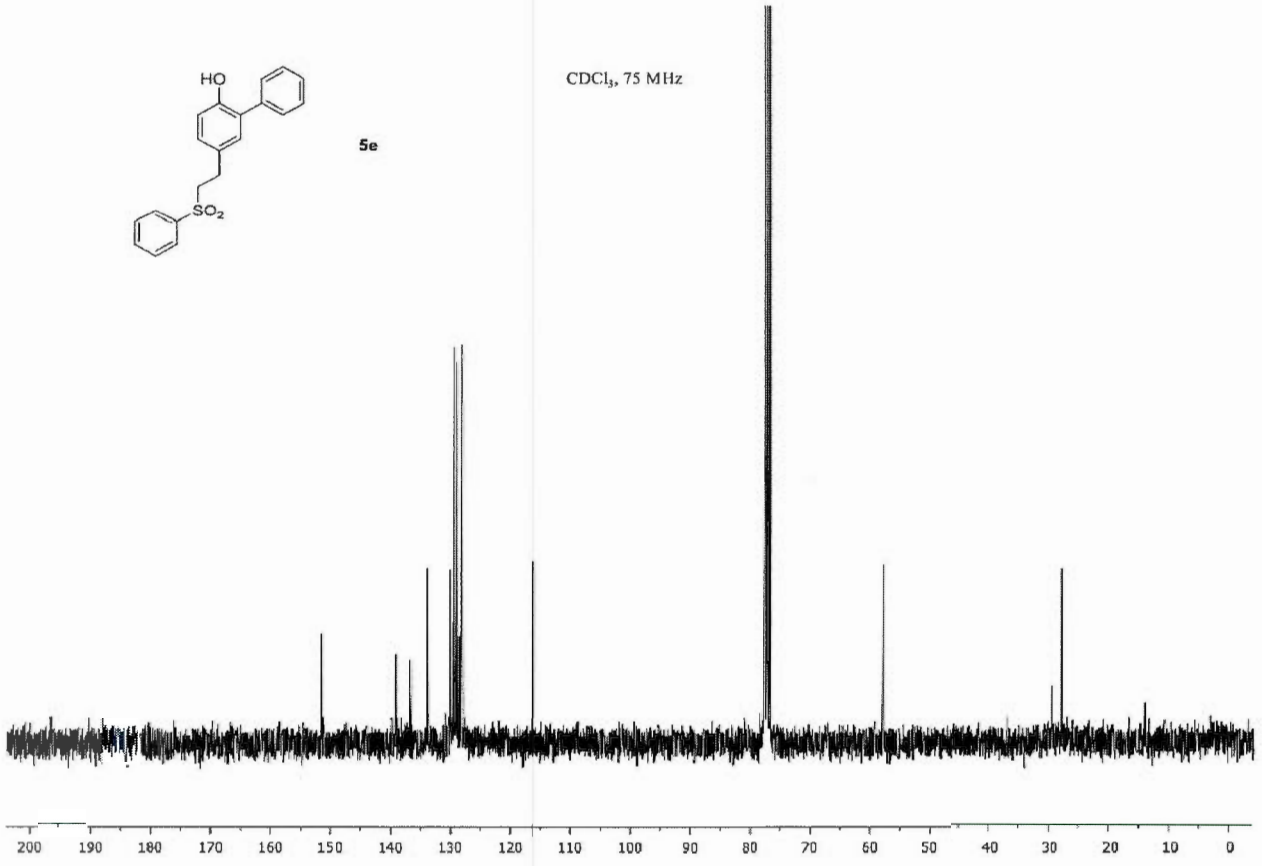
$CDCl_3$, 300 MHz



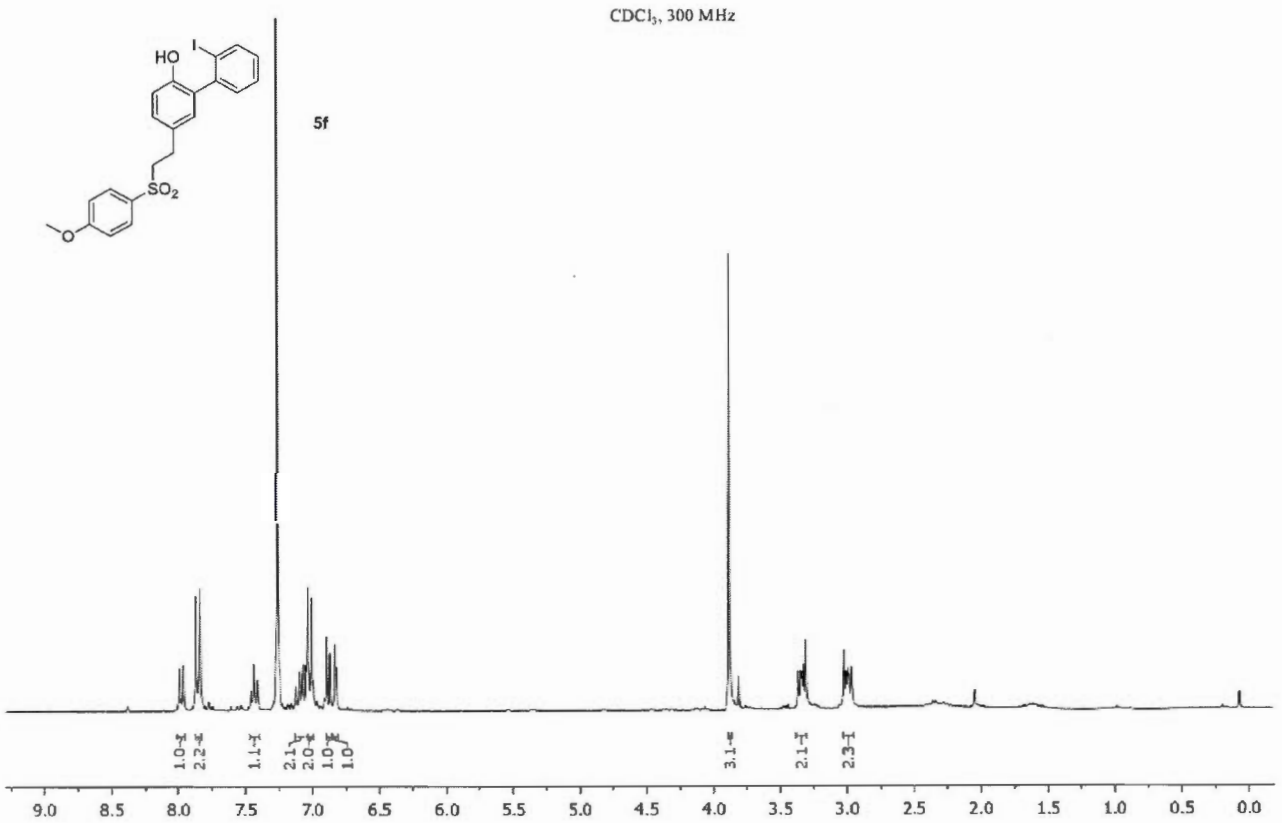
This journal is © The Royal Society of Chemistry 2013

5e

$CDCl_3$, 75 MHz



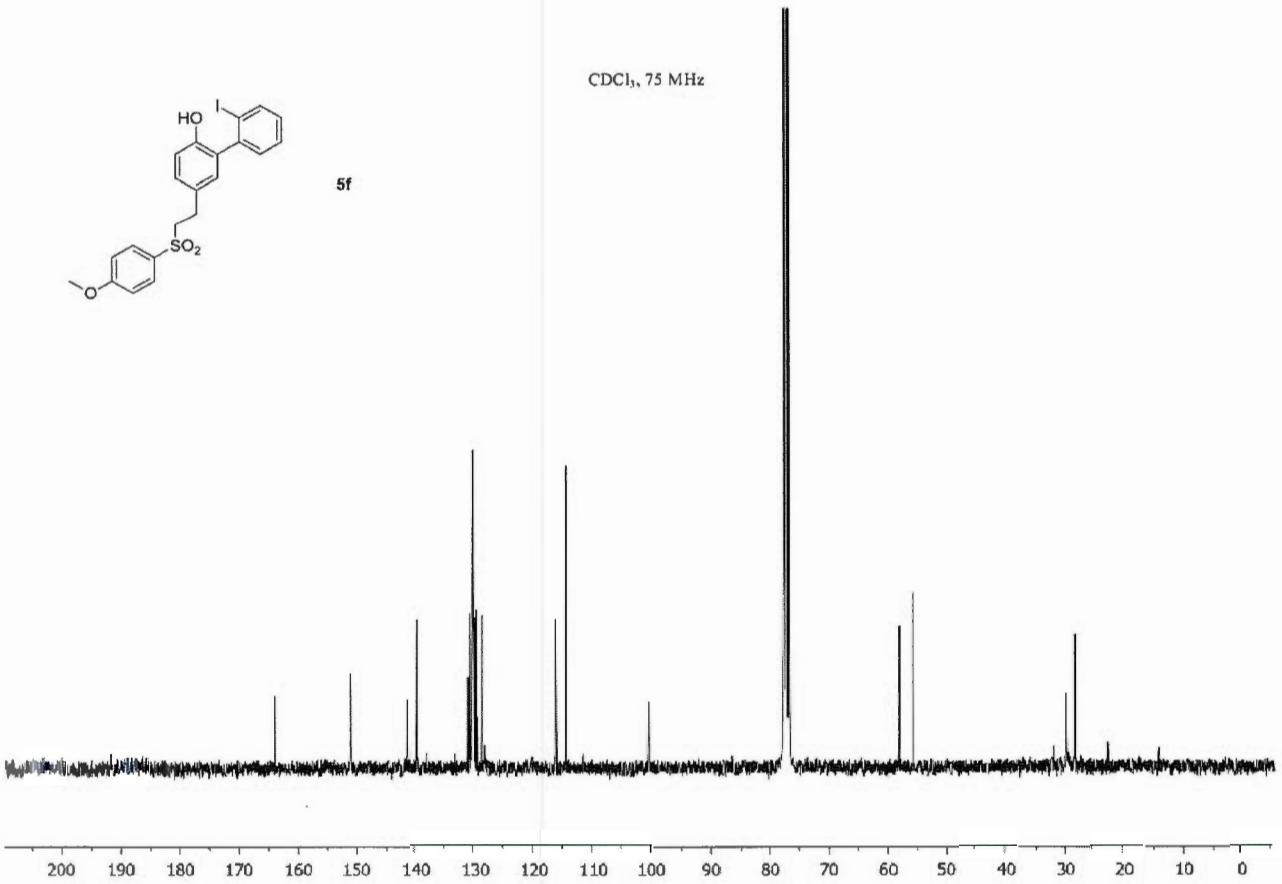
This journal is © The Royal Society of Chemistry 2013



Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

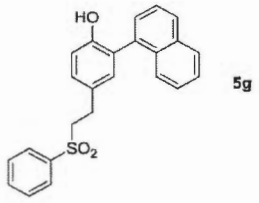
5f

$CDCl_3$, 75 MHz

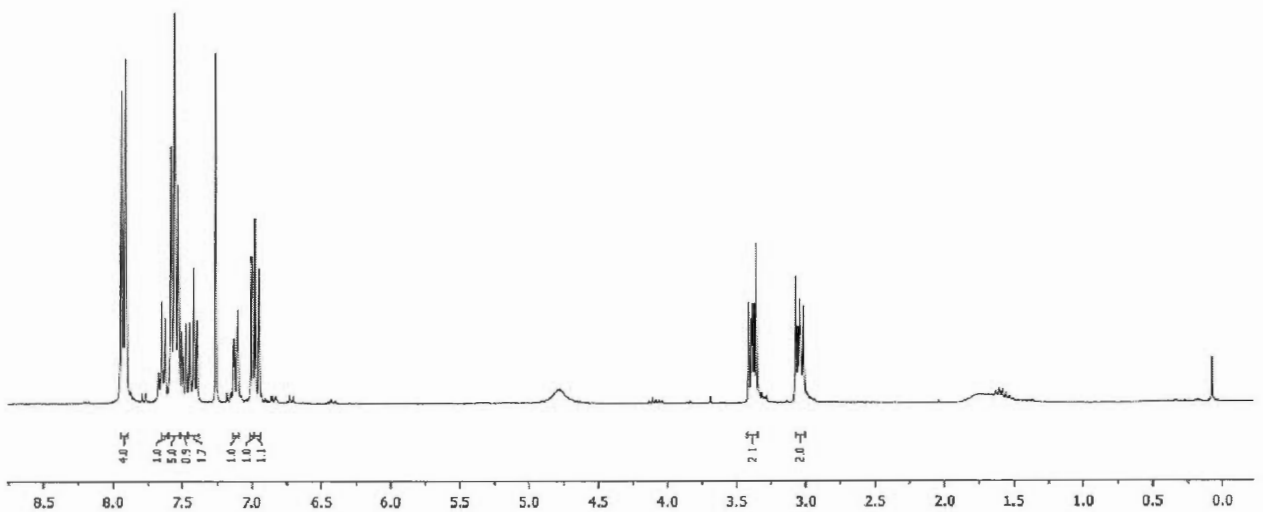


This journal is © The Royal Society of Chemistry 2013

$CDCl_3$, 300 MHz



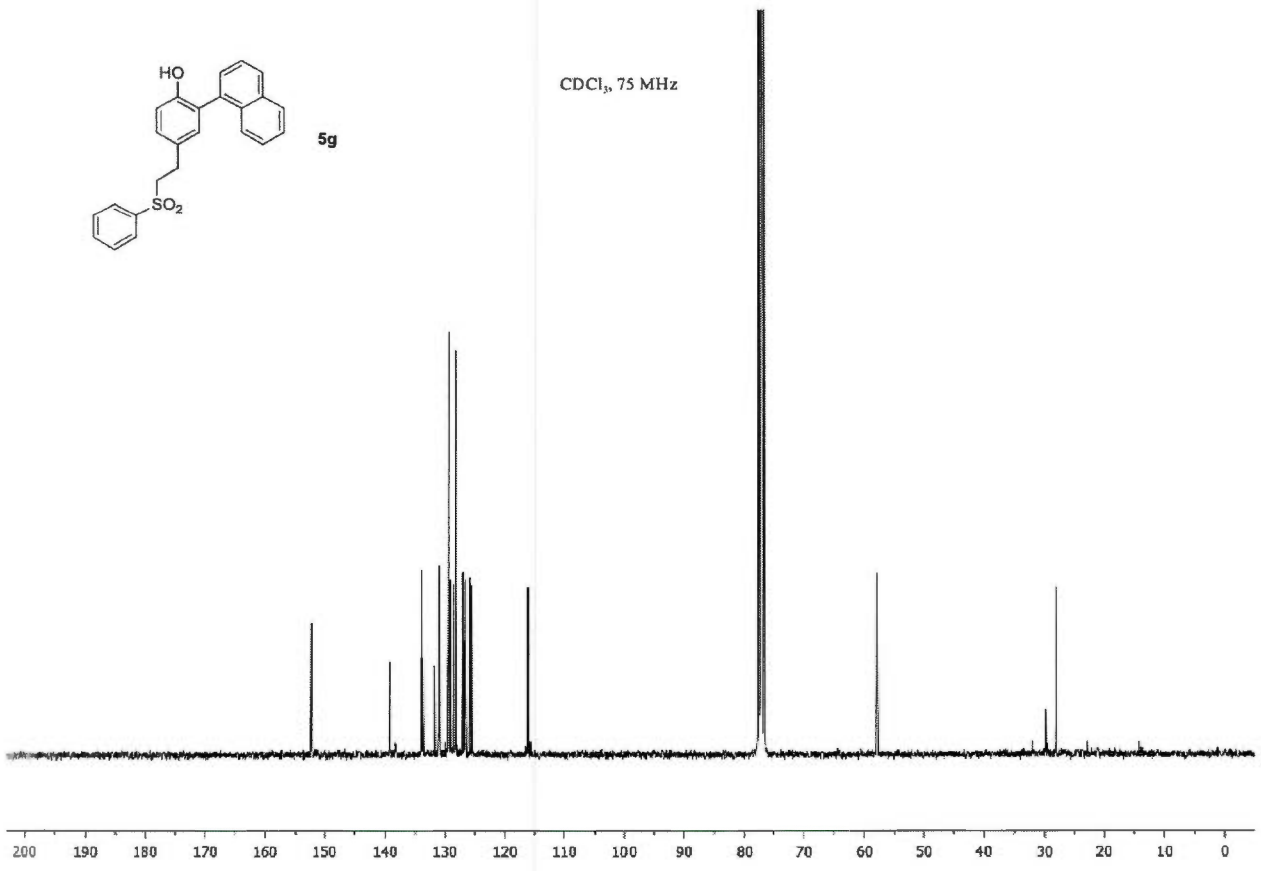
5g



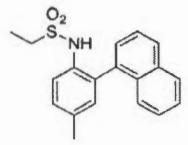
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

5g

$CDCl_3$, 75 MHz

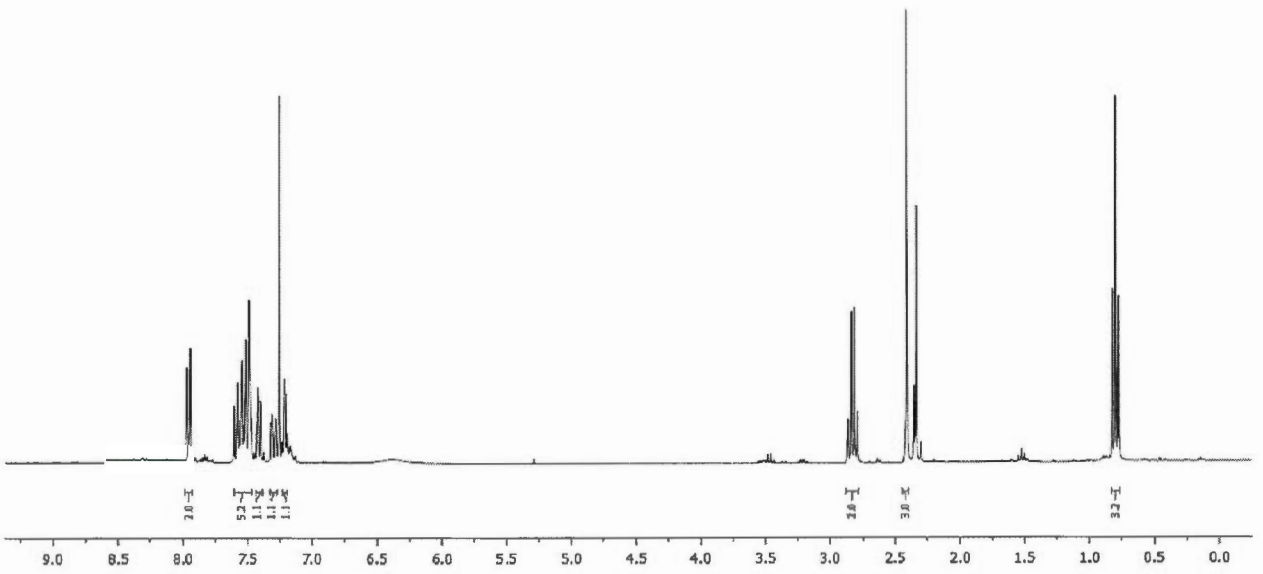


Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013



5h

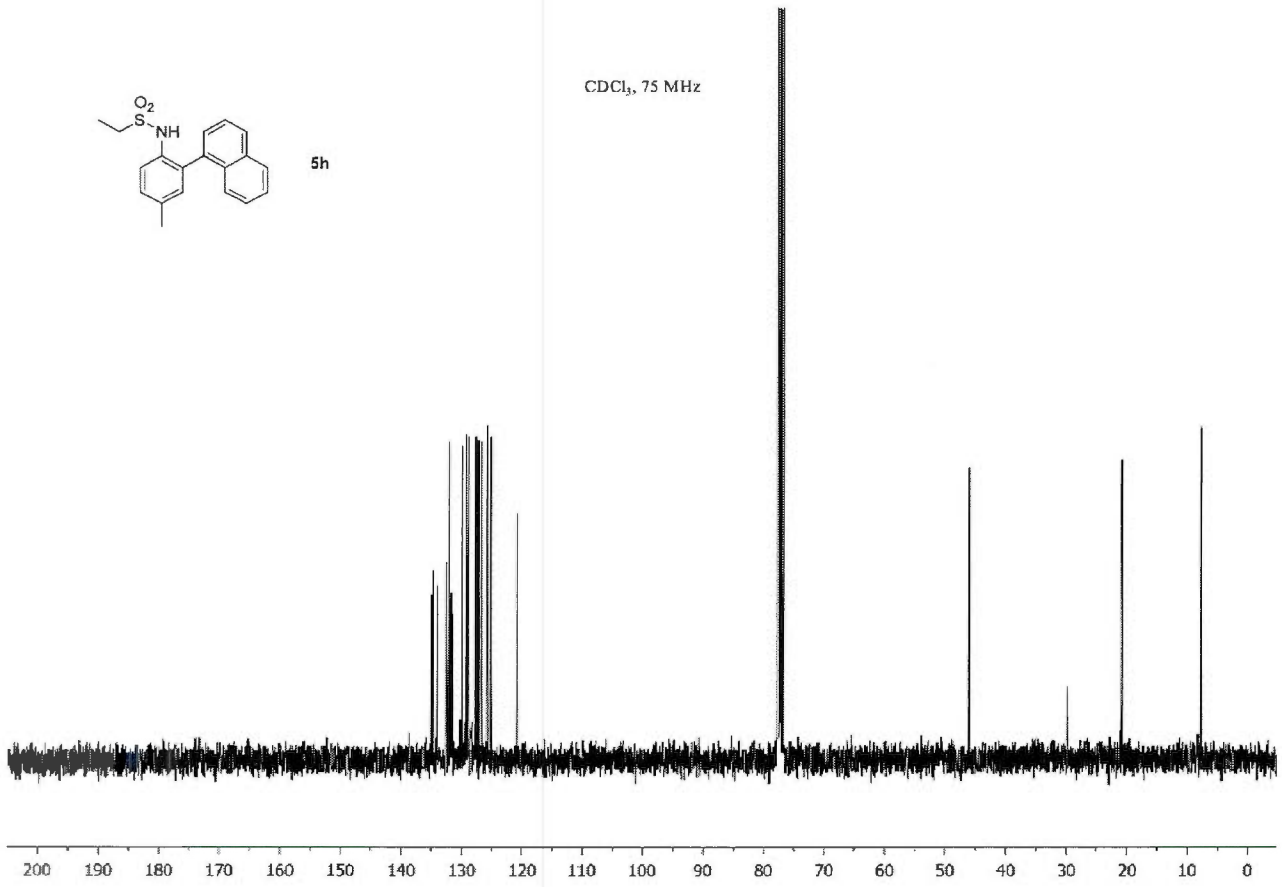
$CDCl_3$, 300 MHz



Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

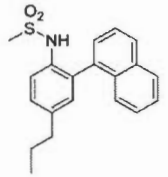
5h

$CDCl_3$, 75 MHz

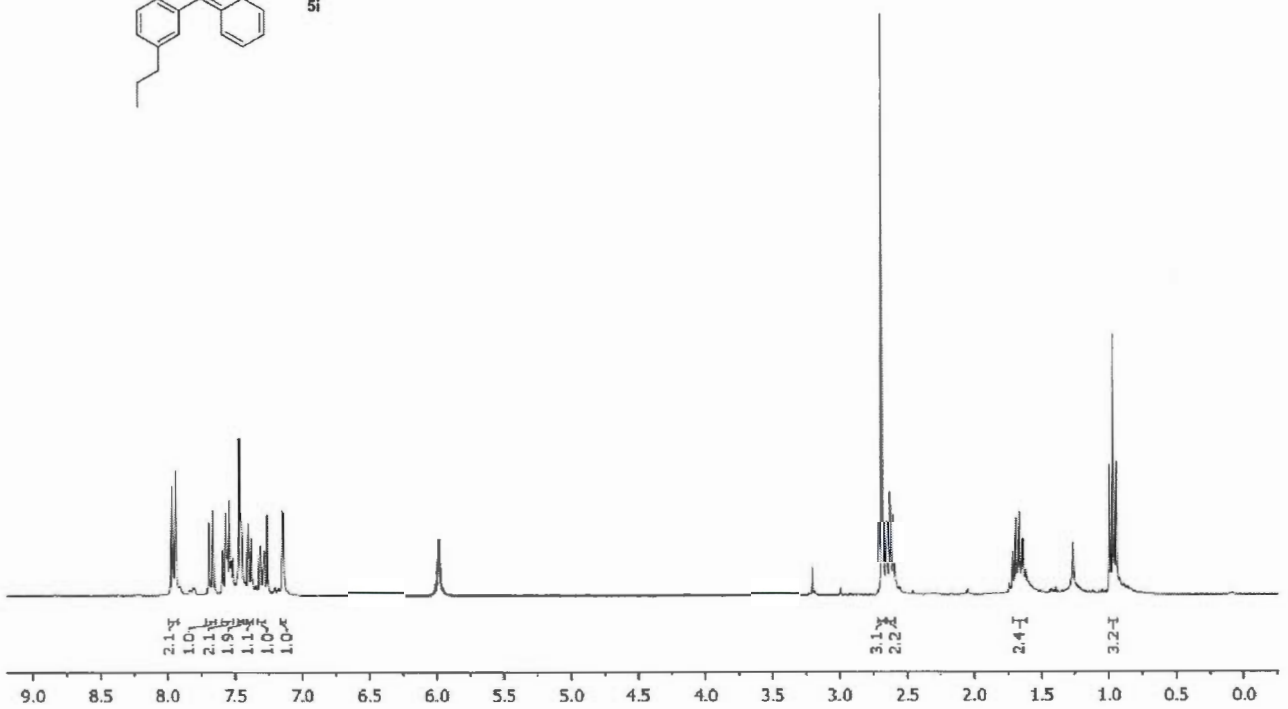


This journal is © The Royal Society of Chemistry 2013

$CDCl_3$, 300 MHz



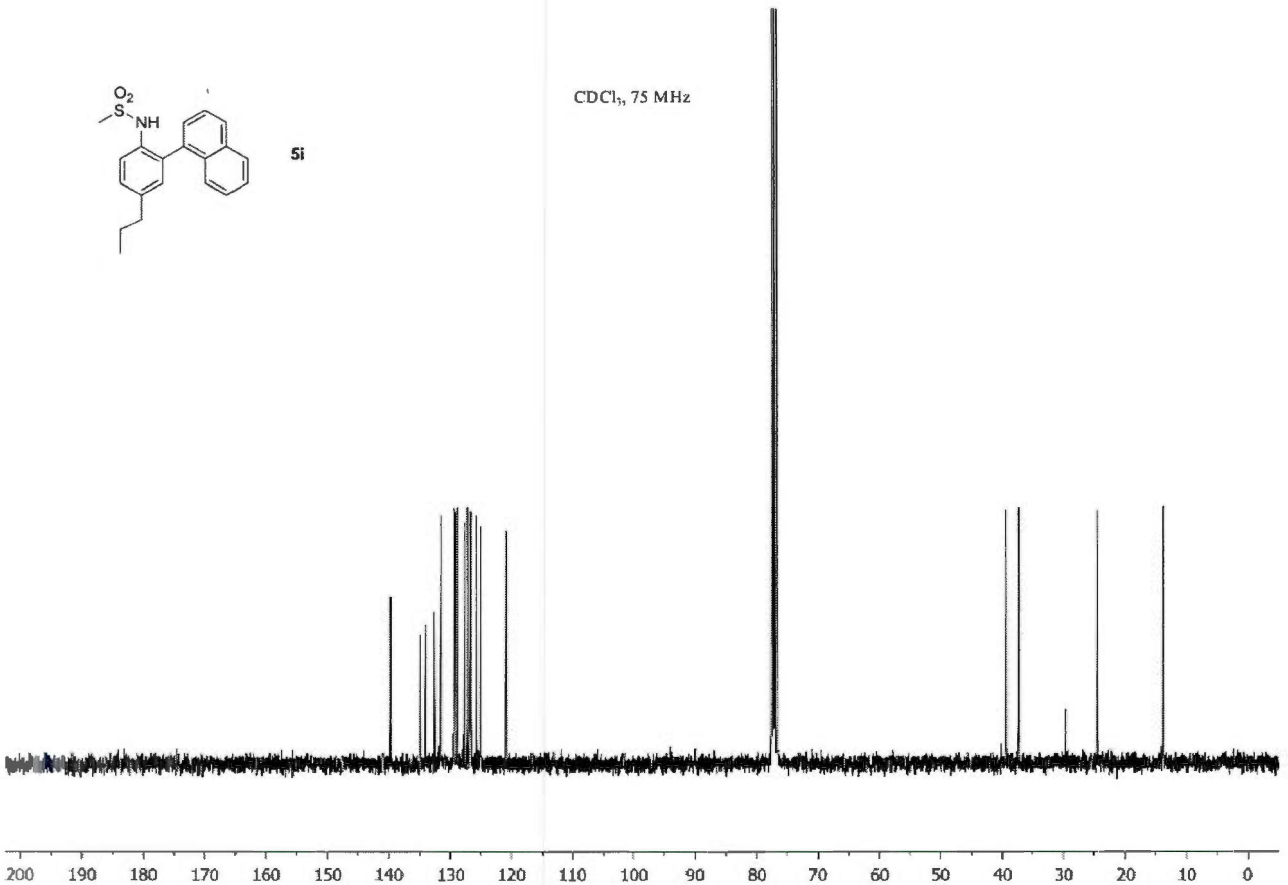
5i



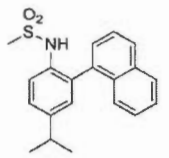
This journal is © The Royal Society of Chemistry 2013

5i

$CDCl_3$, 75 MHz

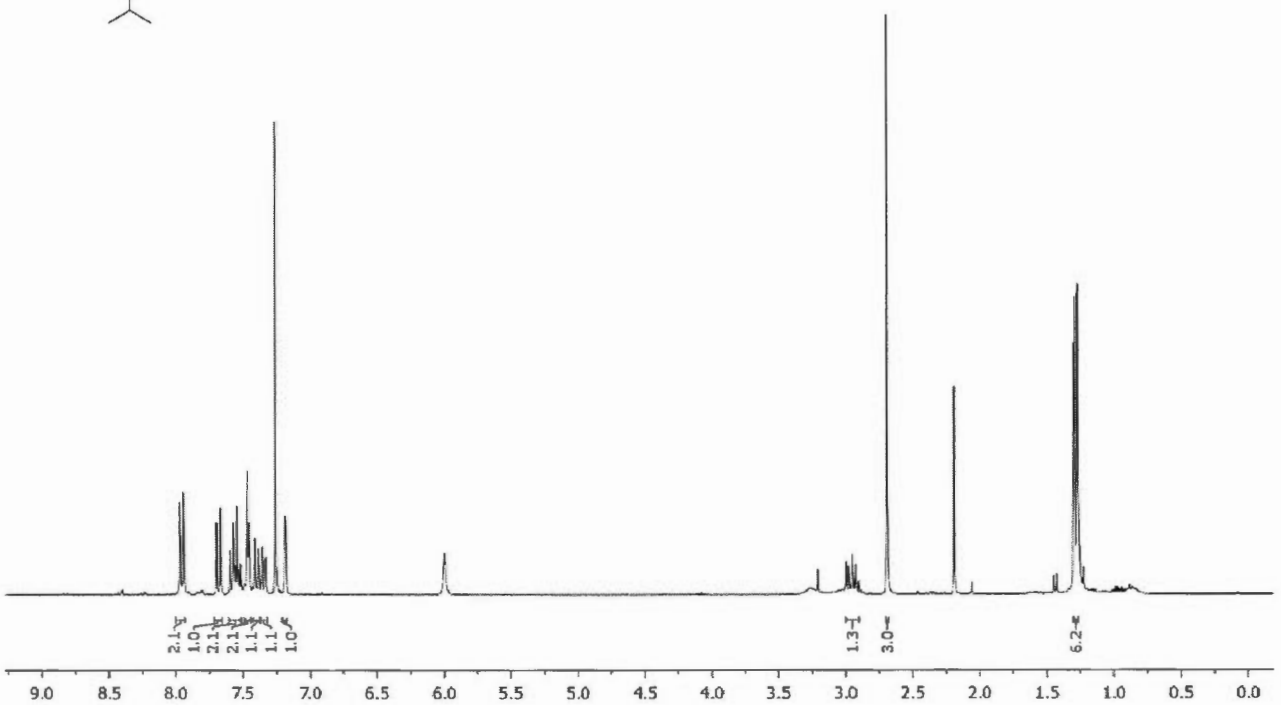


This journal is © The Royal Society of Chemistry 2013

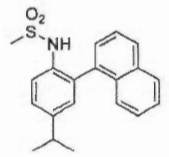


5j

$CDCl_3$, 300 MHz

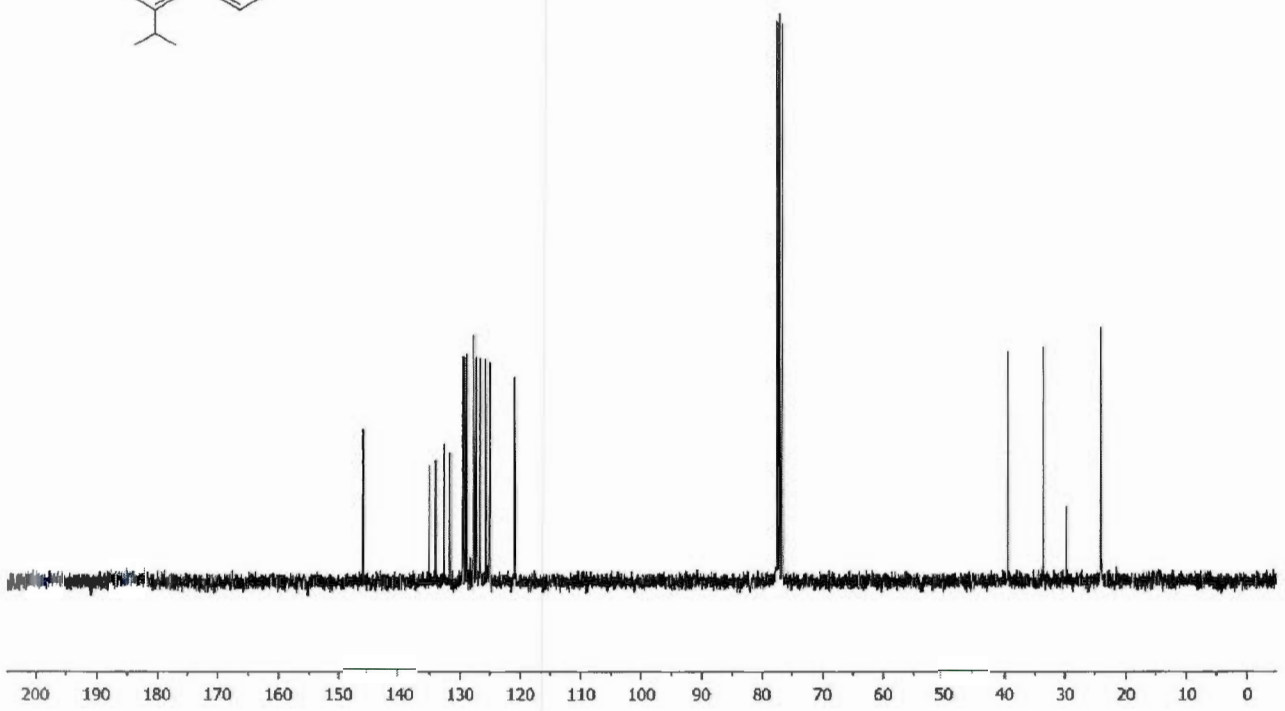


This journal is © The Royal Society of Chemistry 2013



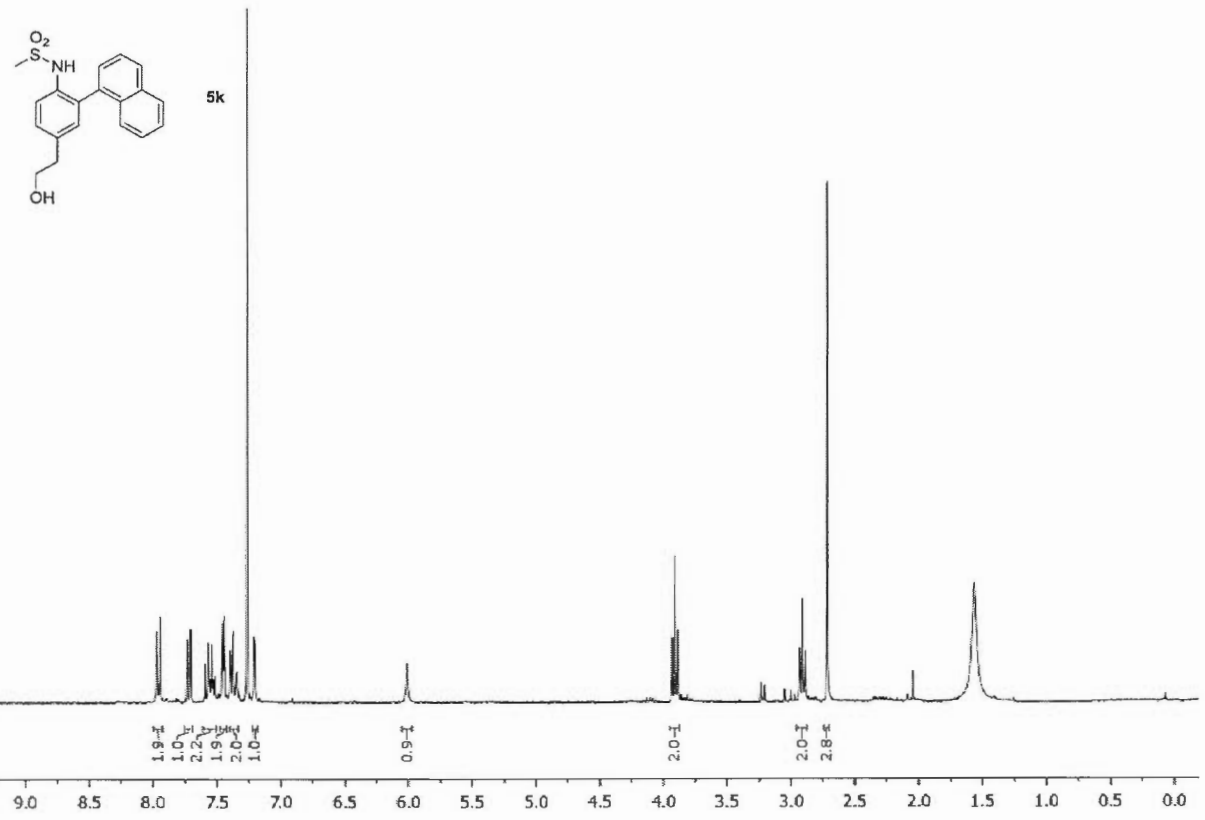
5j

$CDCl_3$, 75 MHz



This journal is © The Royal Society of Chemistry 2013

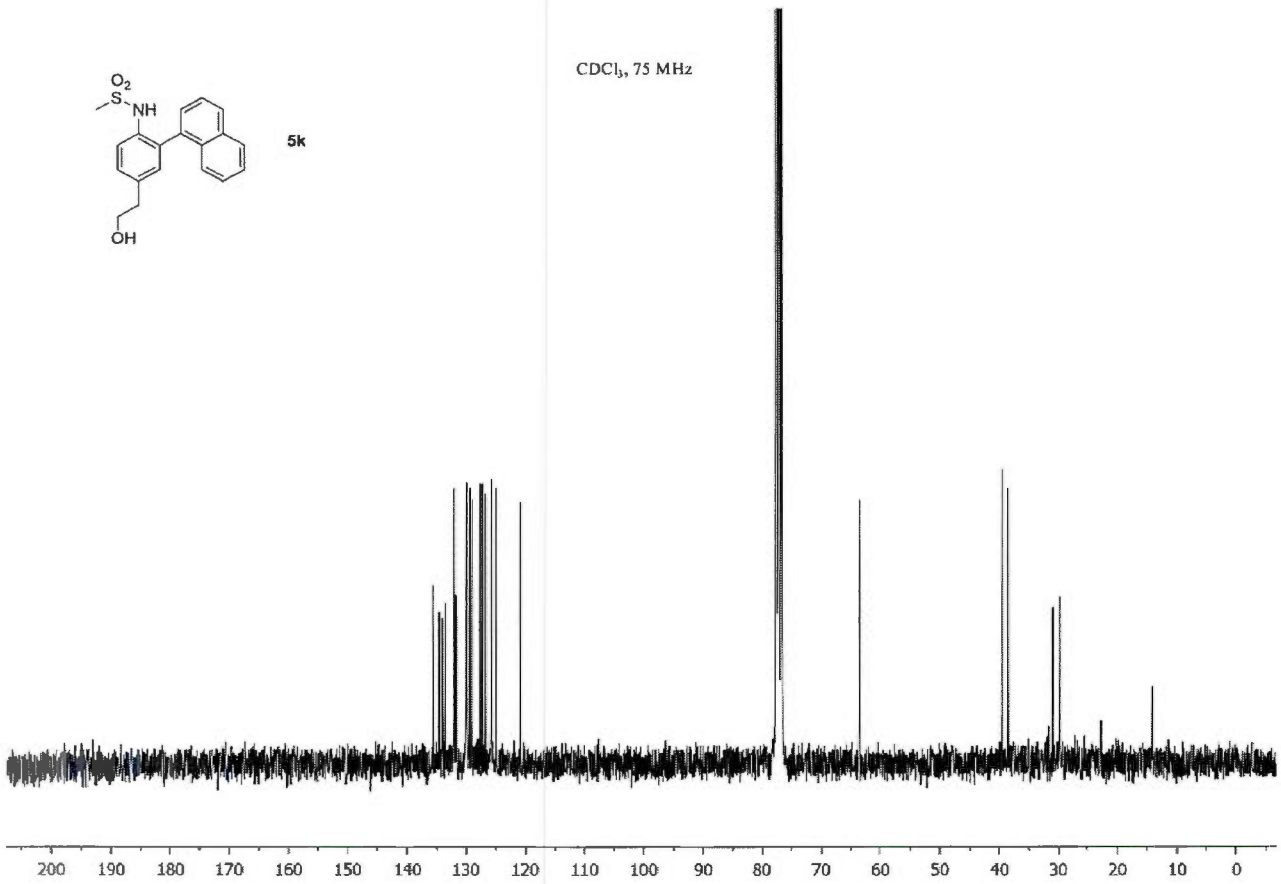
$CDCl_3$, 300 MHz



Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

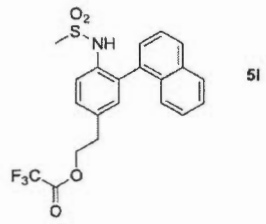
5k

$CDCl_3$, 75 MHz

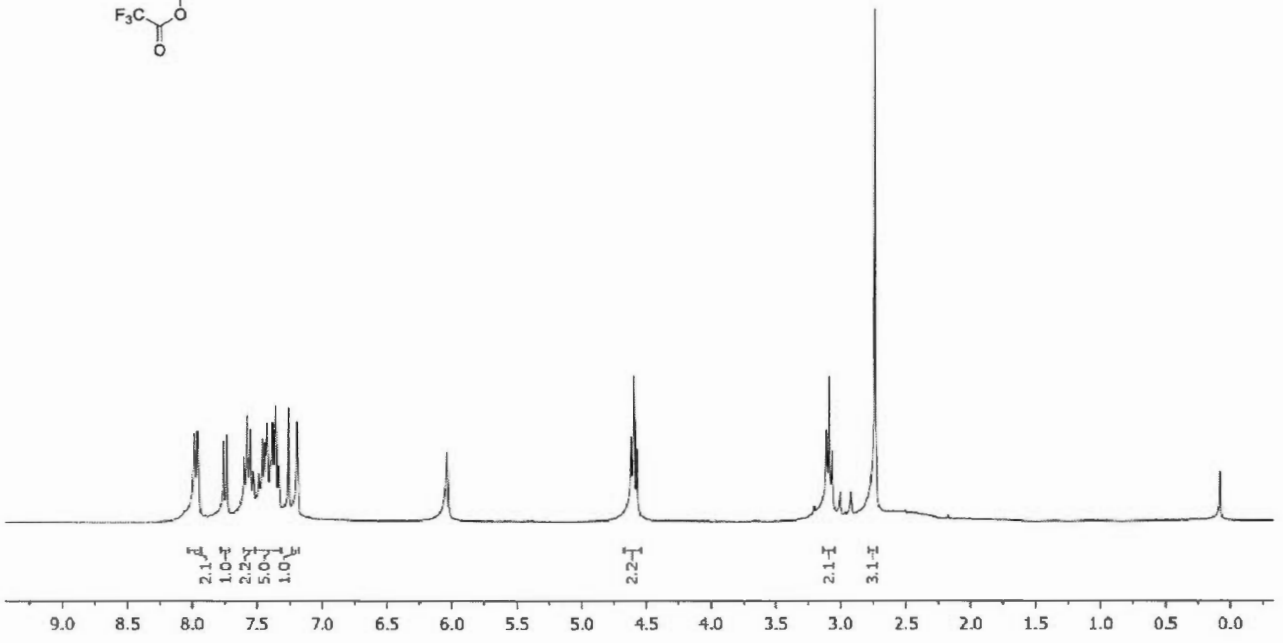


This journal is © The Royal Society of Chemistry 2013

$CDCl_3$, 300 MHz



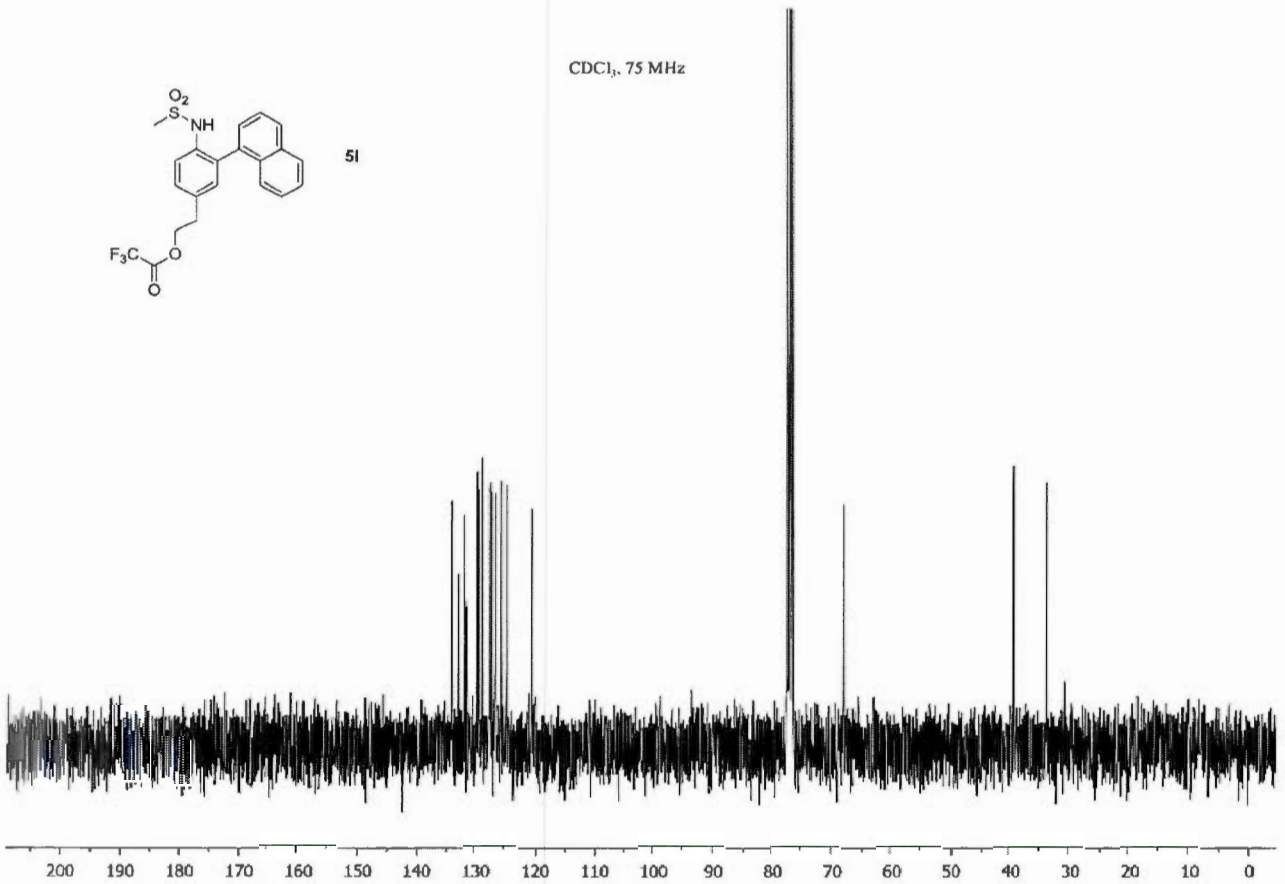
5l



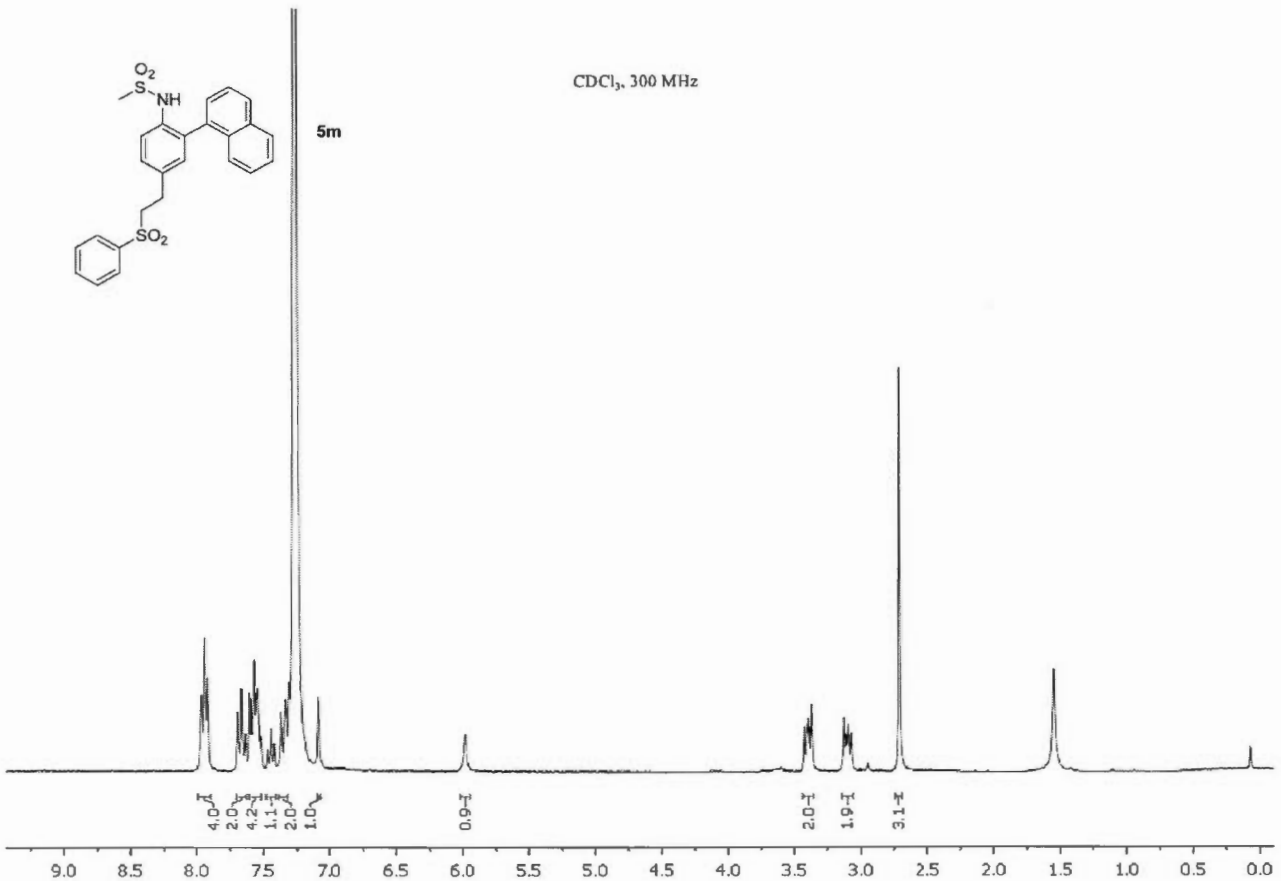
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

5l

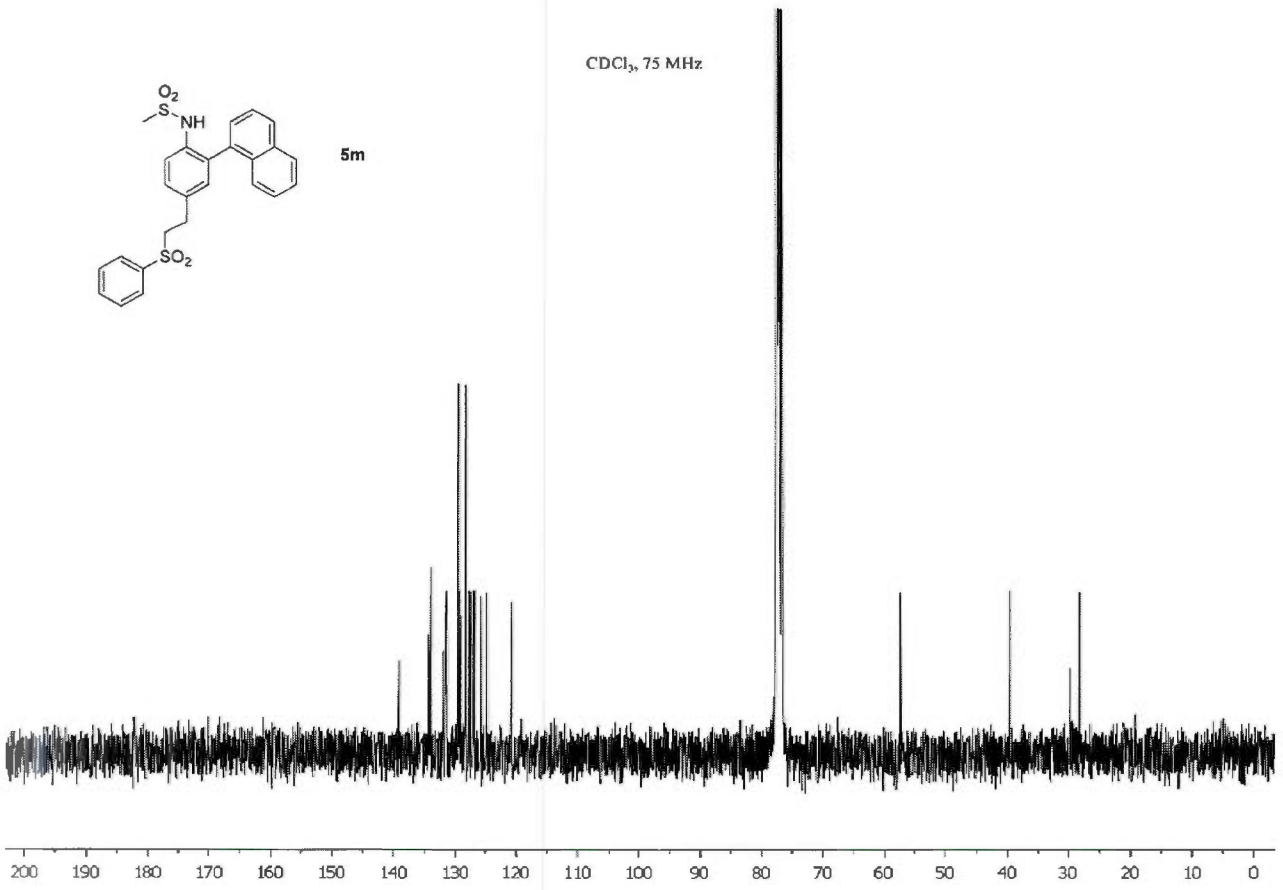
$CDCl_3$, 75 MHz



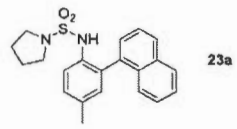
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013



This journal is © The Royal Society of Chemistry 2013

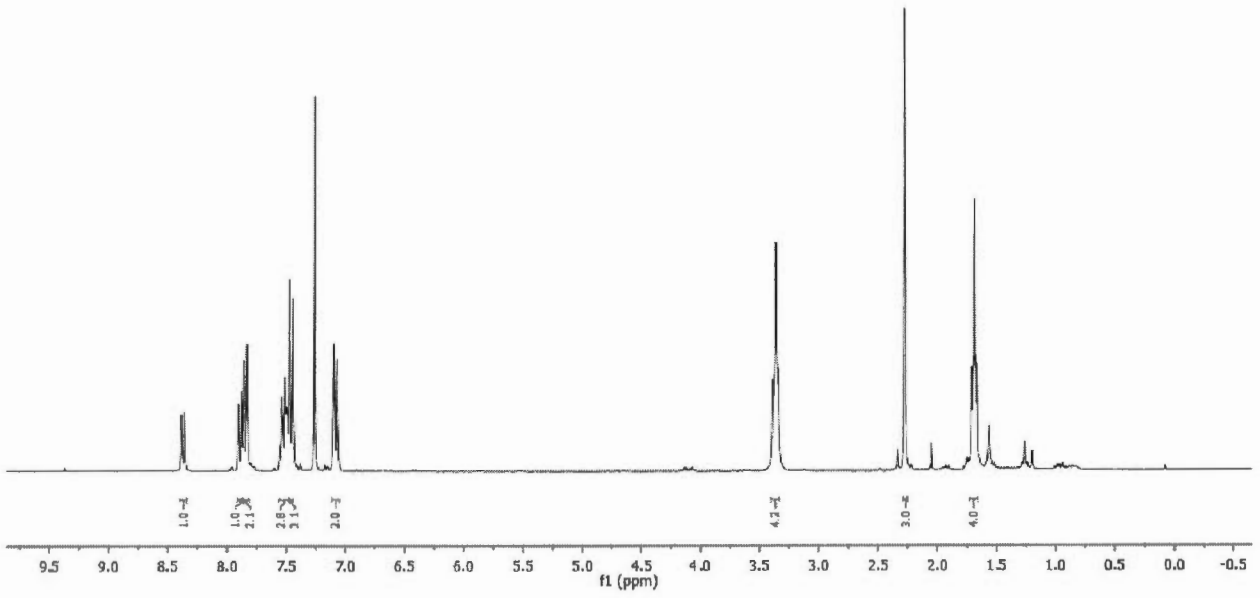


Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013



23a

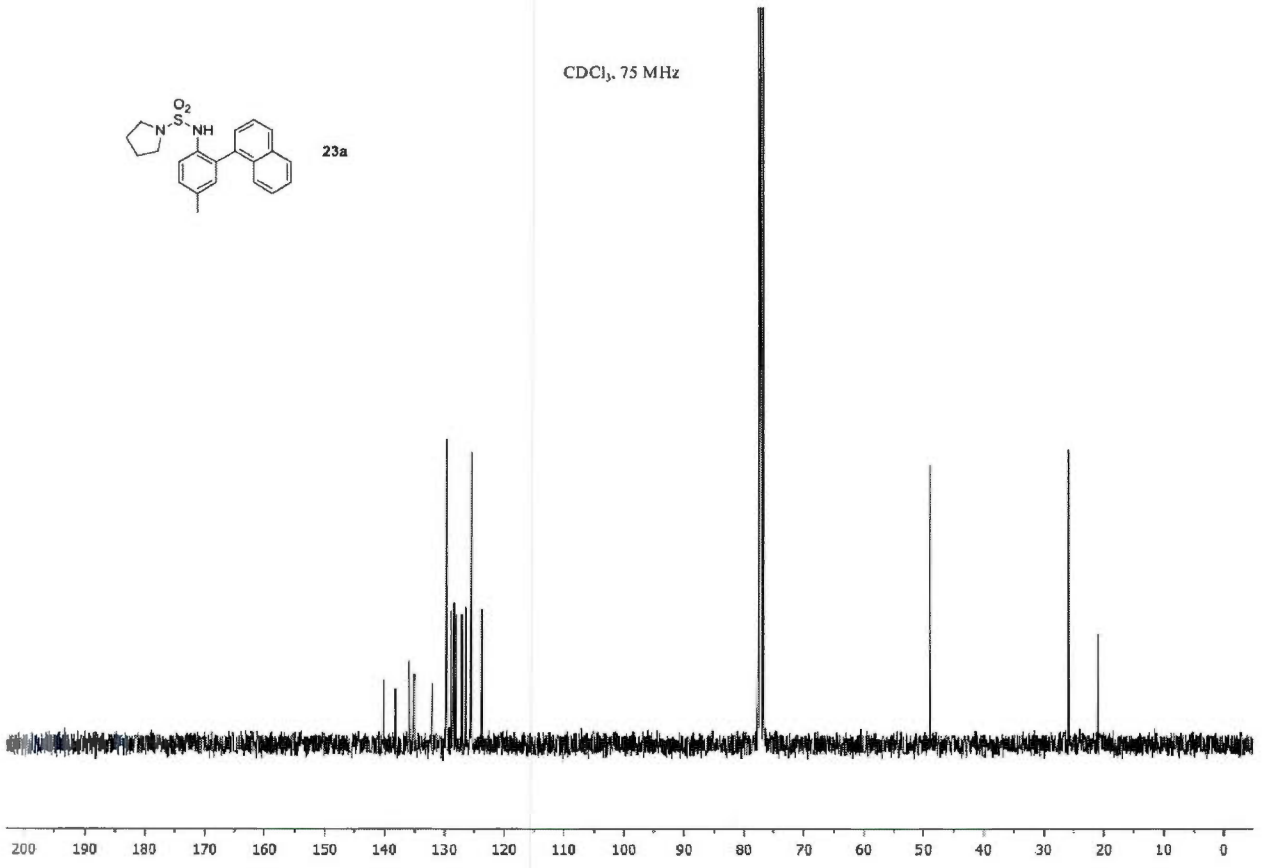
$CDCl_3$, 300 MHz



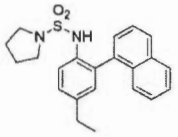
This journal is © The Royal Society of Chemistry 2013

23a

$CDCl_3$, 75 MHz

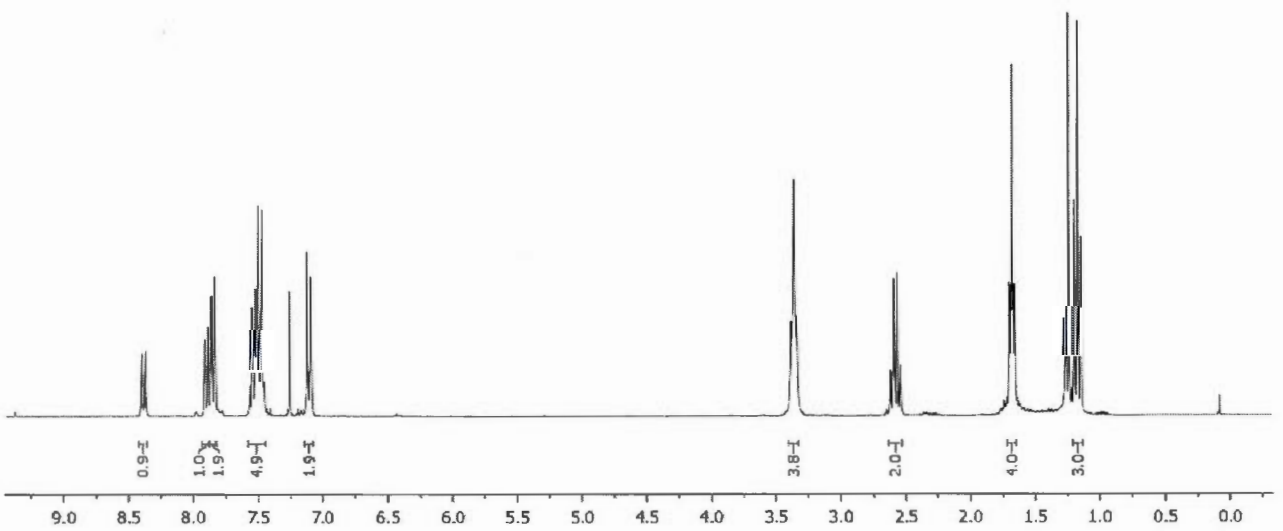


Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013



23b

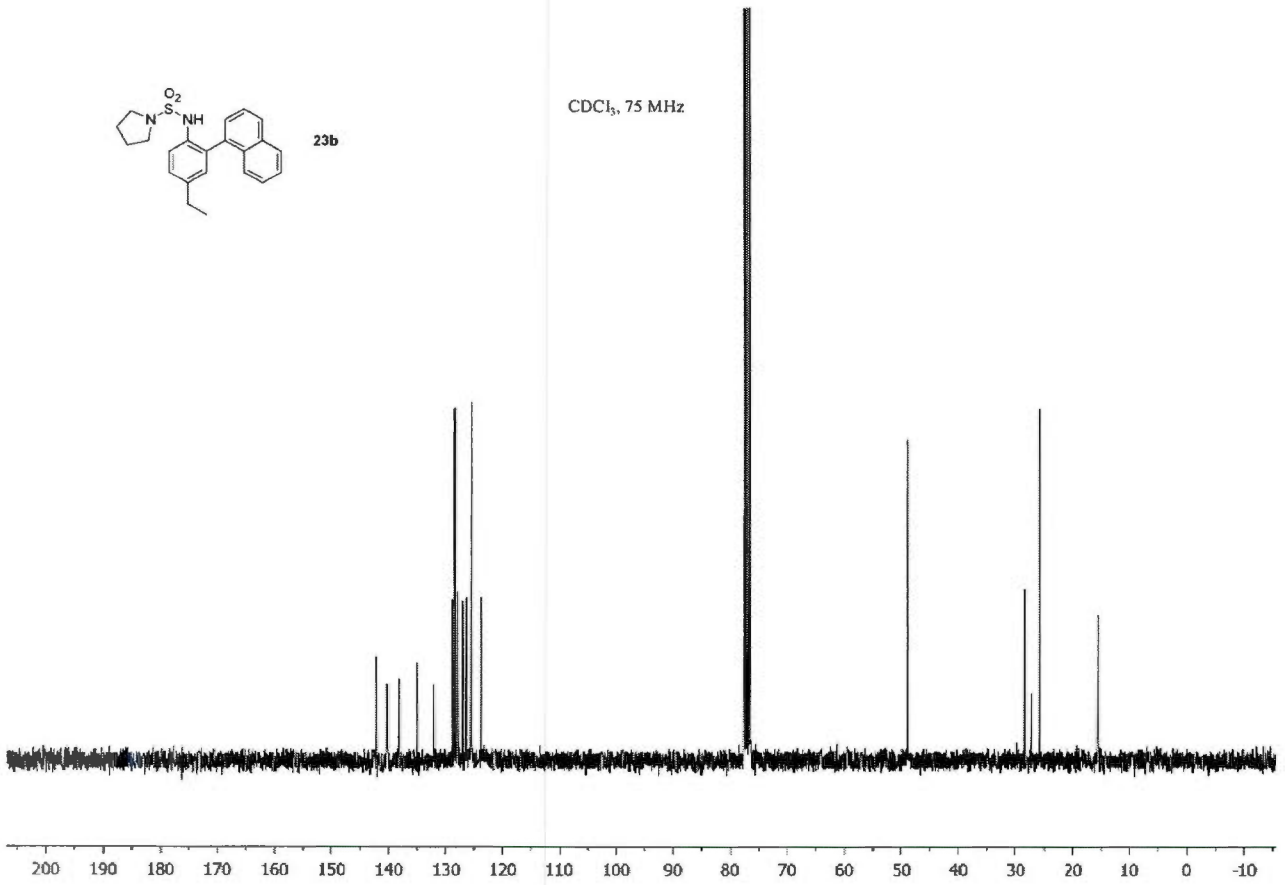
$CDCl_3$, 300 MHz



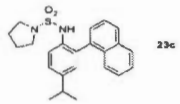
This journal is © The Royal Society of Chemistry 2013

23b

$CDCl_3$, 75 MHz

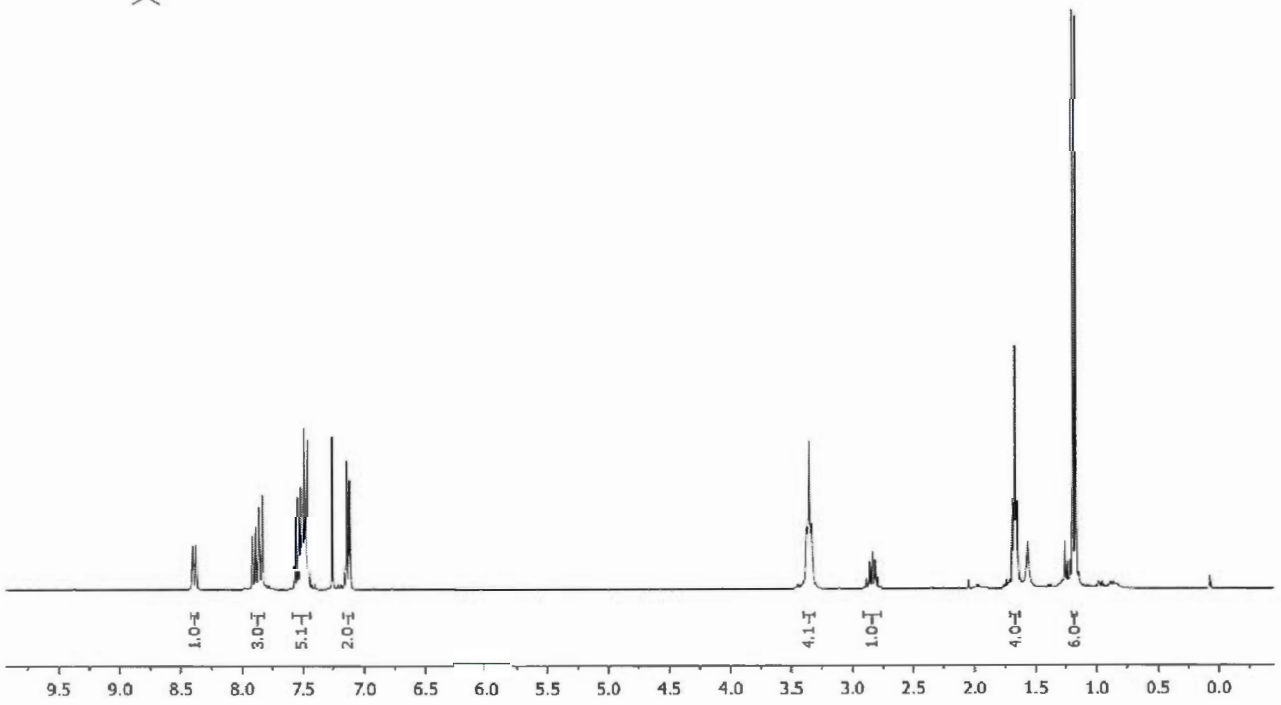


This journal is © The Royal Society of Chemistry 2013



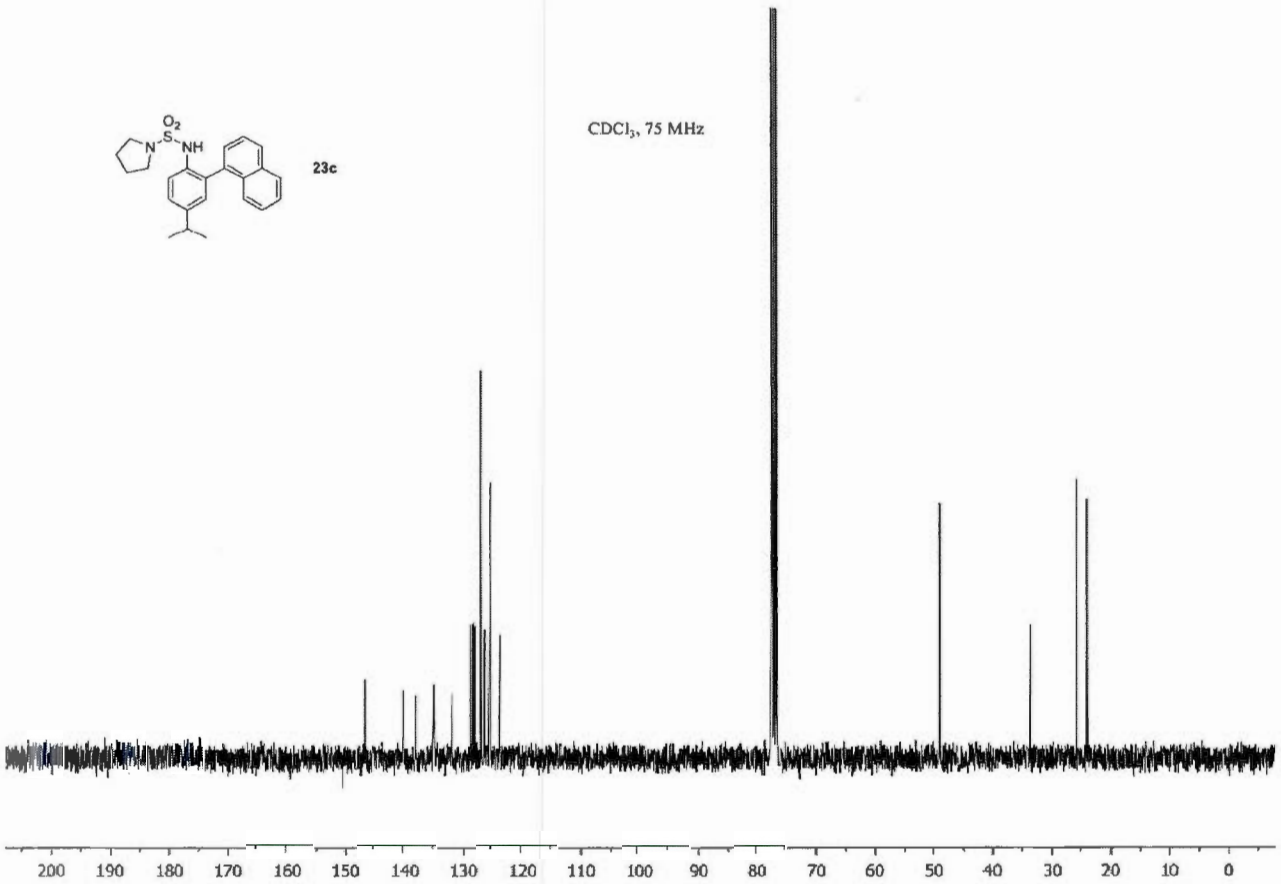
23c

$CDCl_3$, 300 MHz

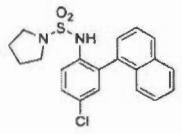


23c

$CDCl_3$, 75 MHz

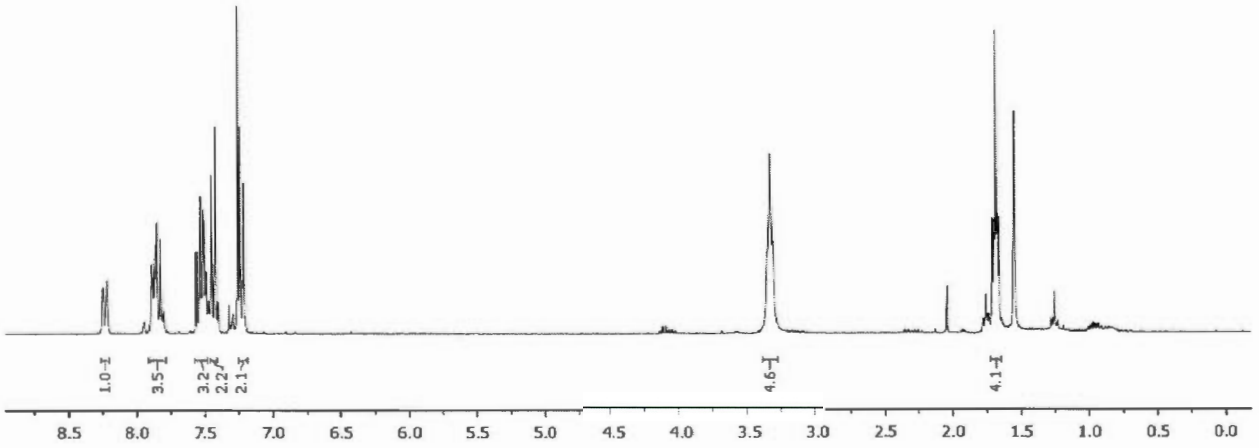


This journal is © The Royal Society of Chemistry 2013



23d

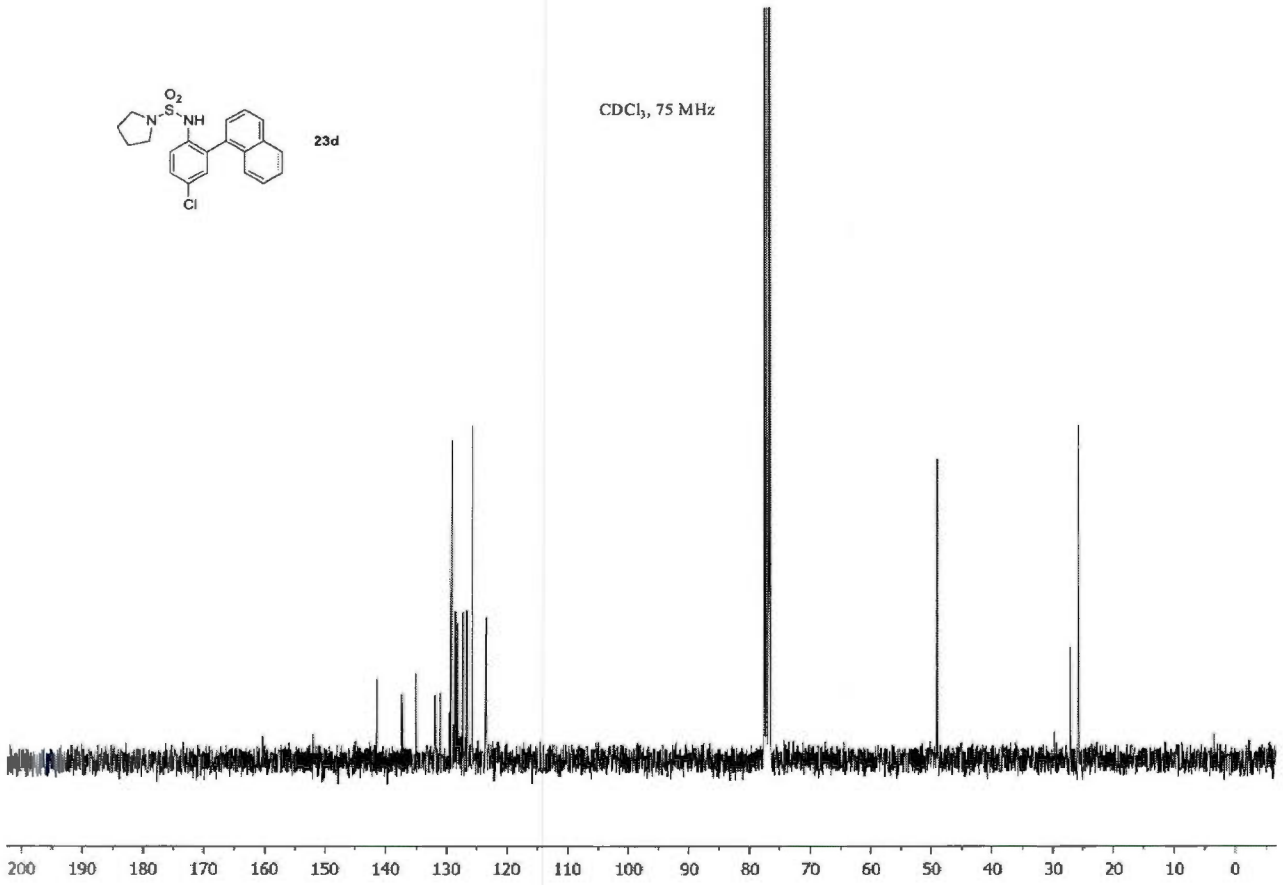
$CDCl_3$, 300 MHz



This journal is © The Royal Society of Chemistry 2013

23d

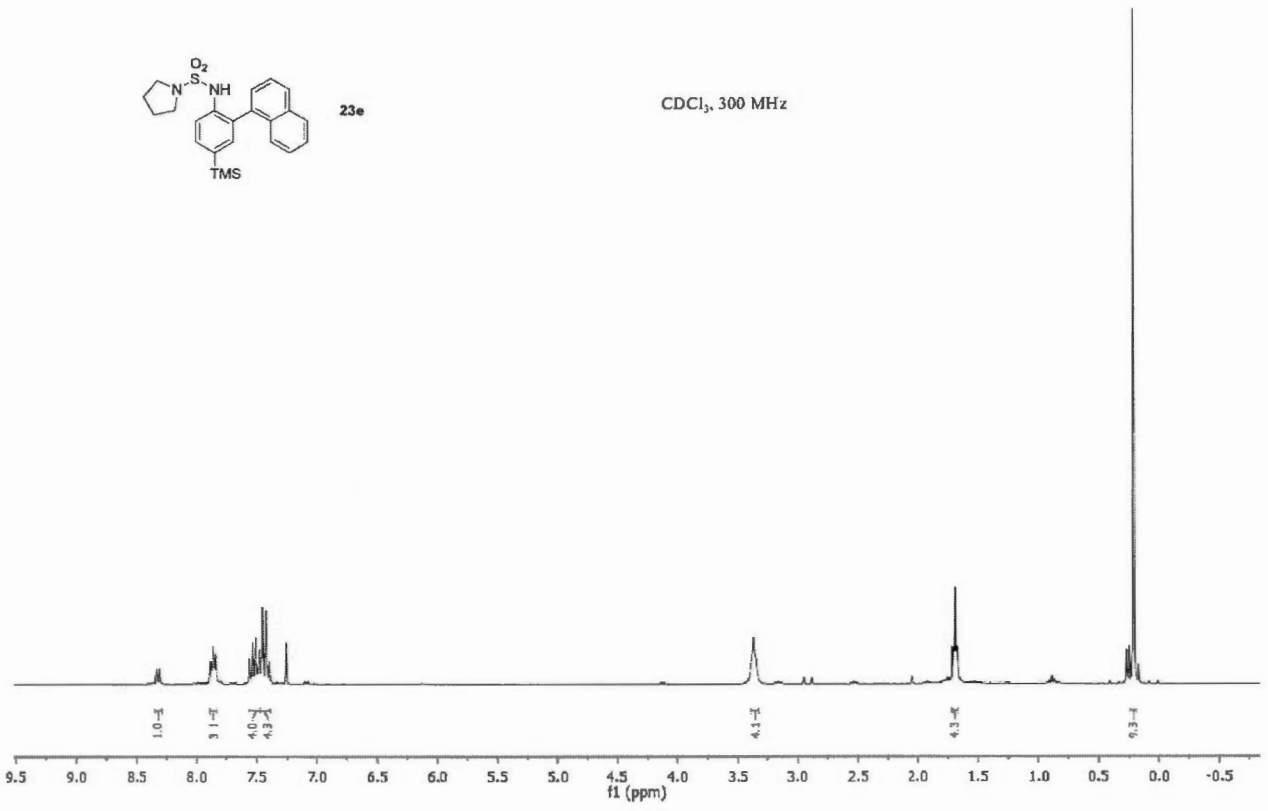
$CDCl_3$, 75 MHz



Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

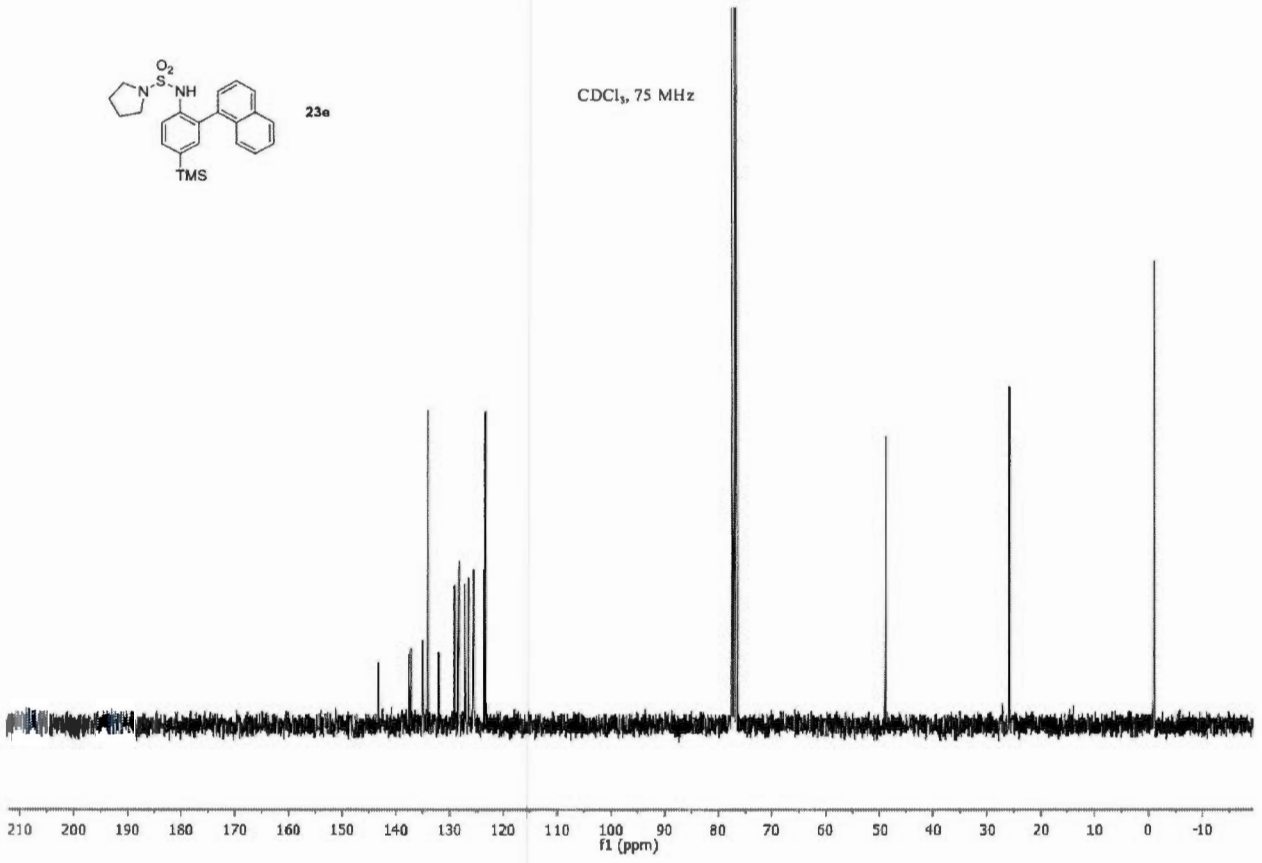
23e

$CDCl_3$, 300 MHz

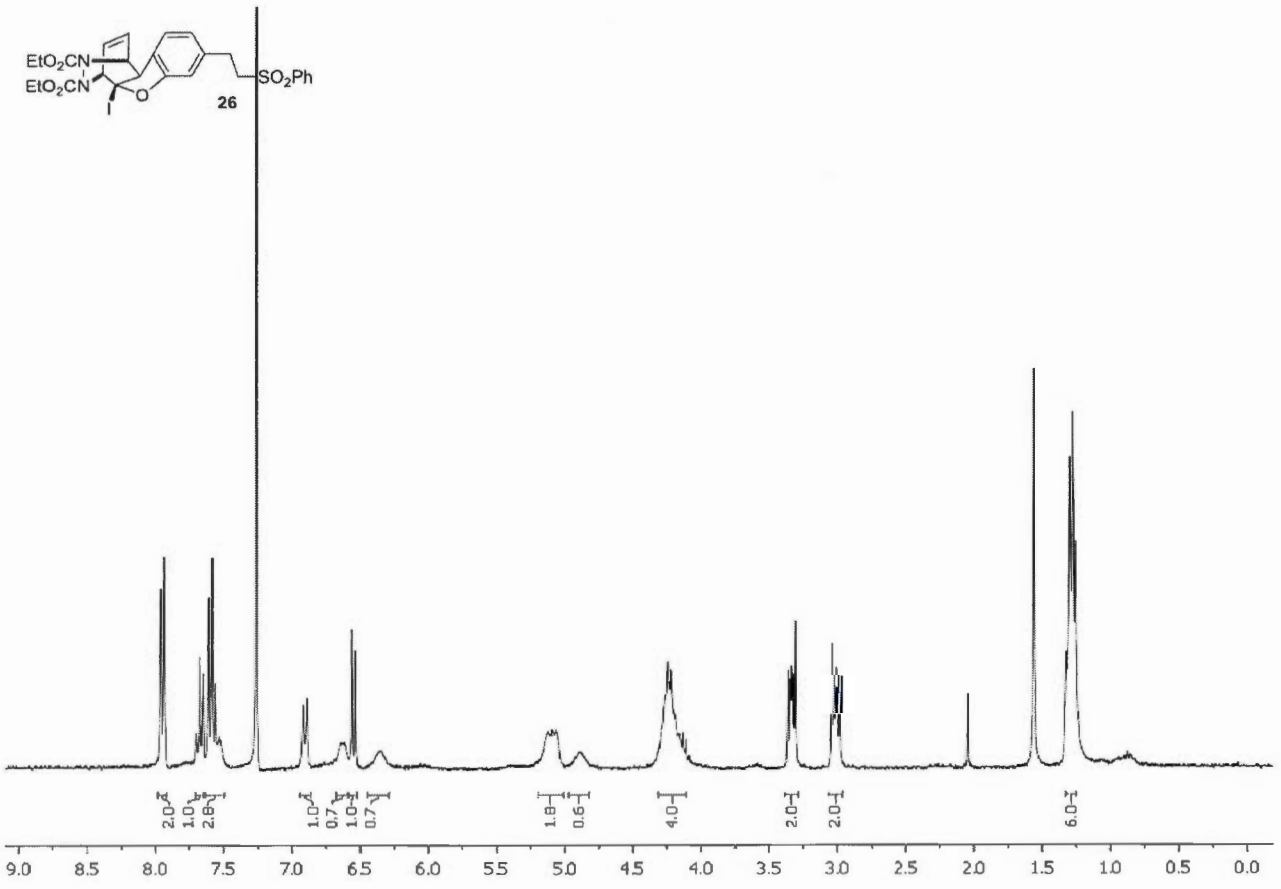


O2
S
N
NH
TMS

23e

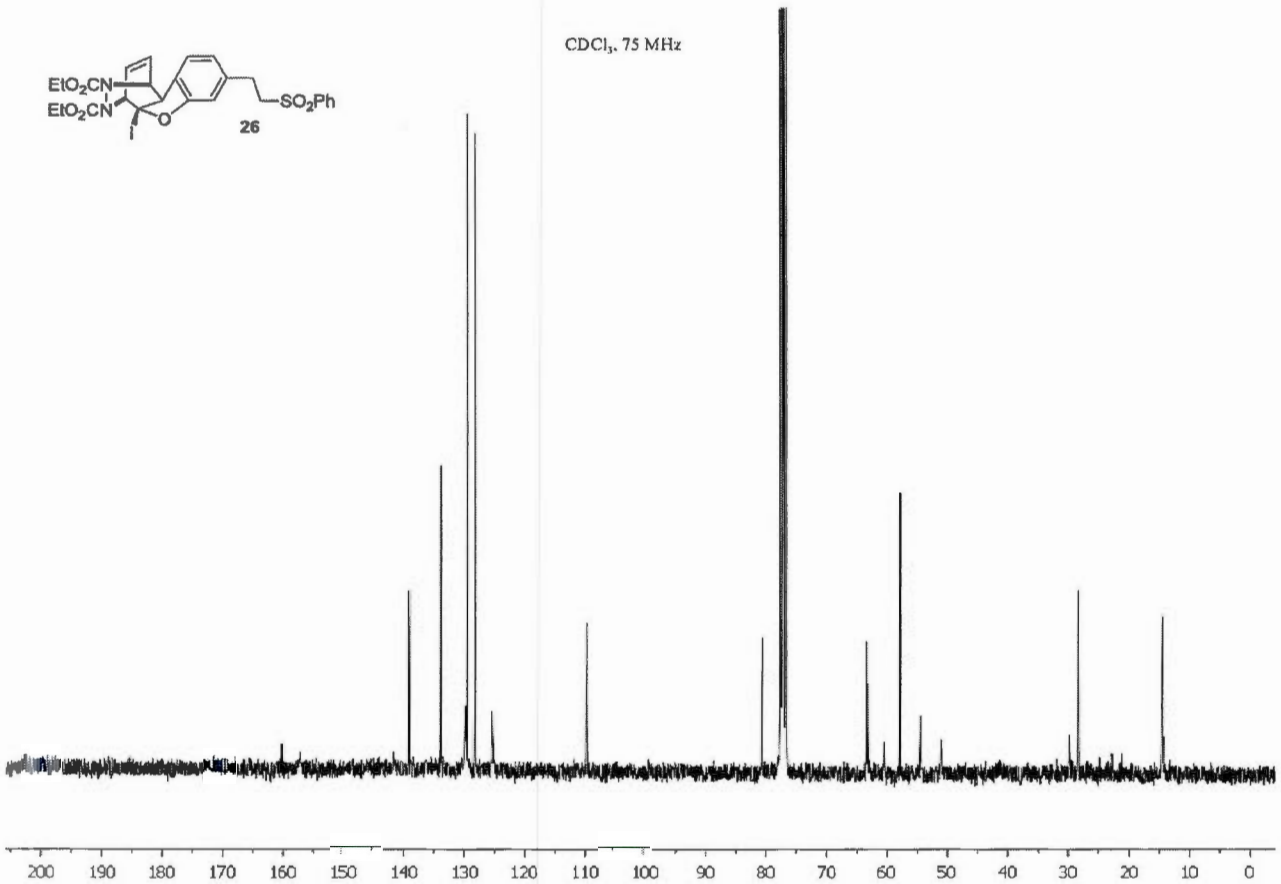

CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

This journal is © The Royal Society of Chemistry 2013

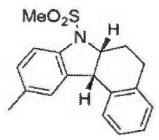


26

$CDCl_3$, 75 MHz

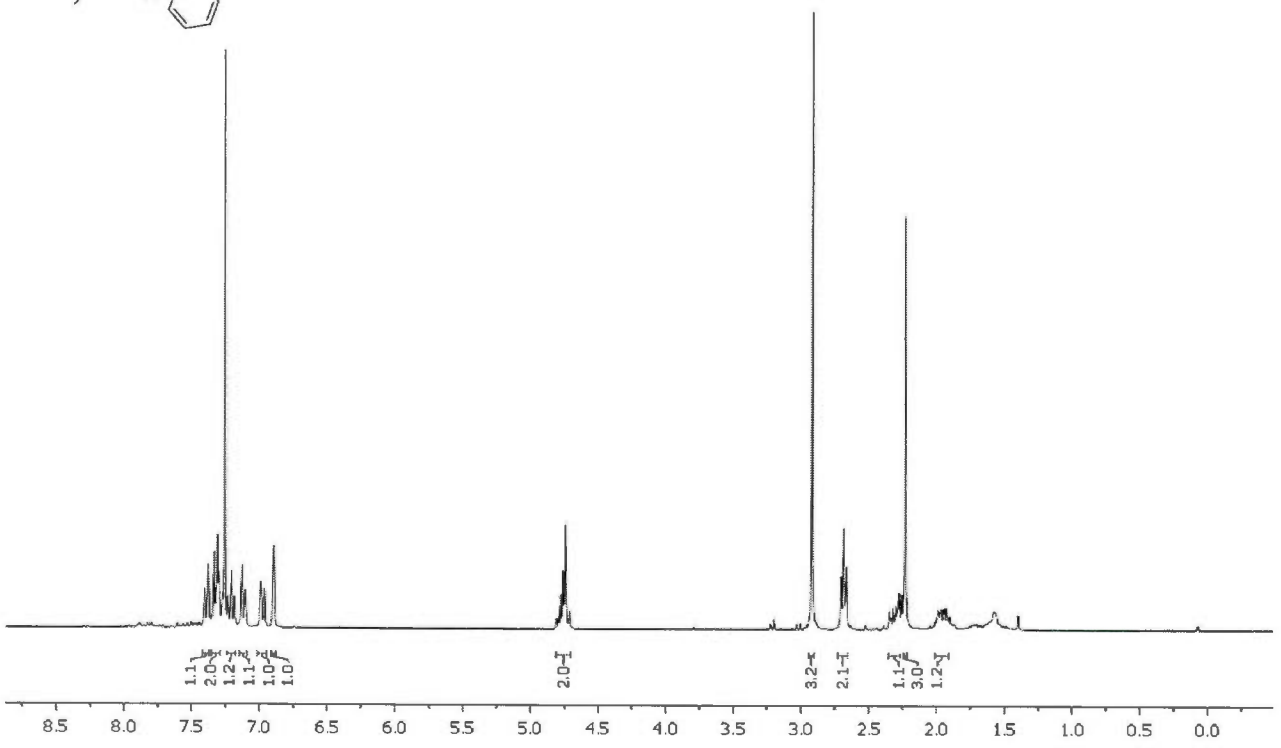


This journal is © The Royal Society of Chemistry 2013



27

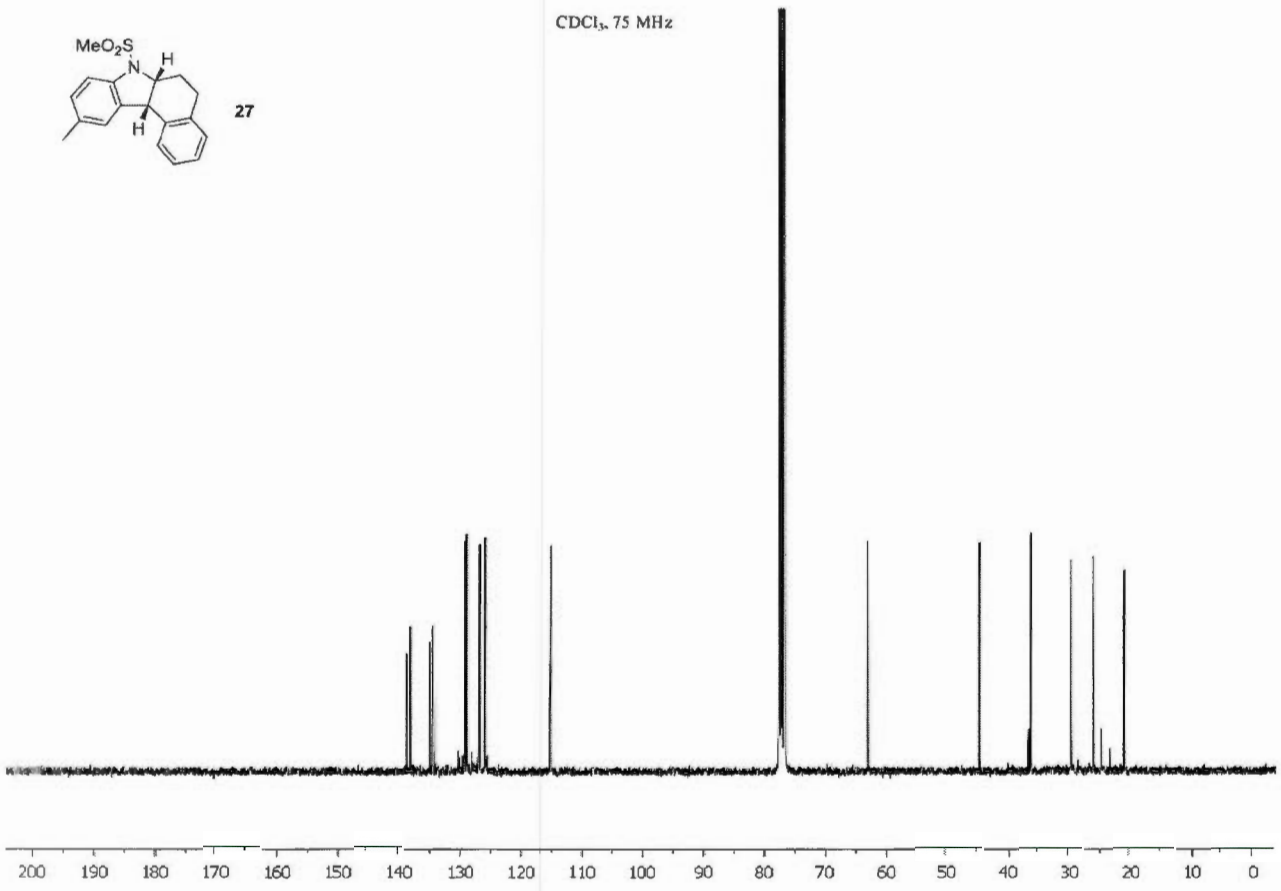
$CDCl_3$, 300 MHz



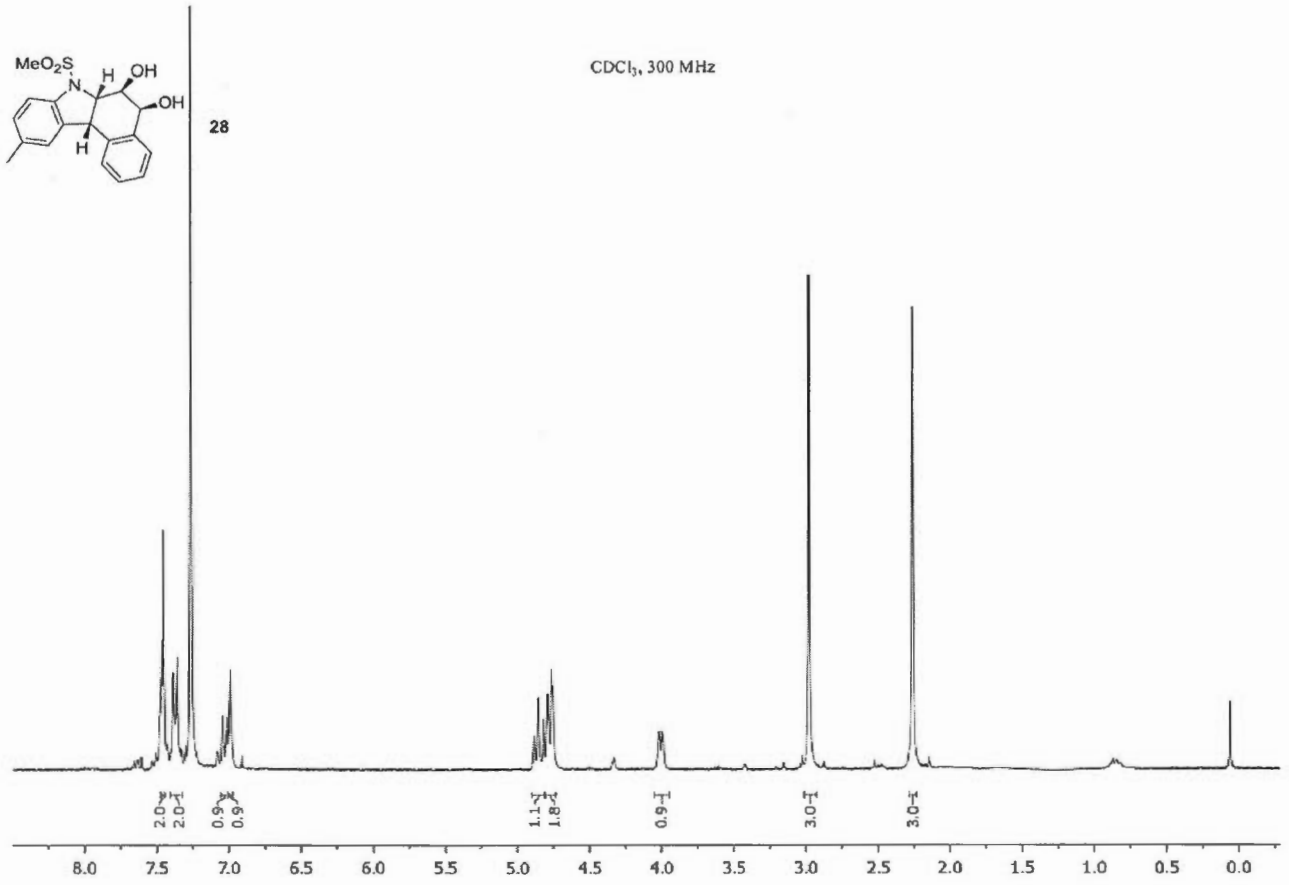
This journal is © The Royal Society of Chemistry 2013

27

$CDCl_3$, 75 MHz

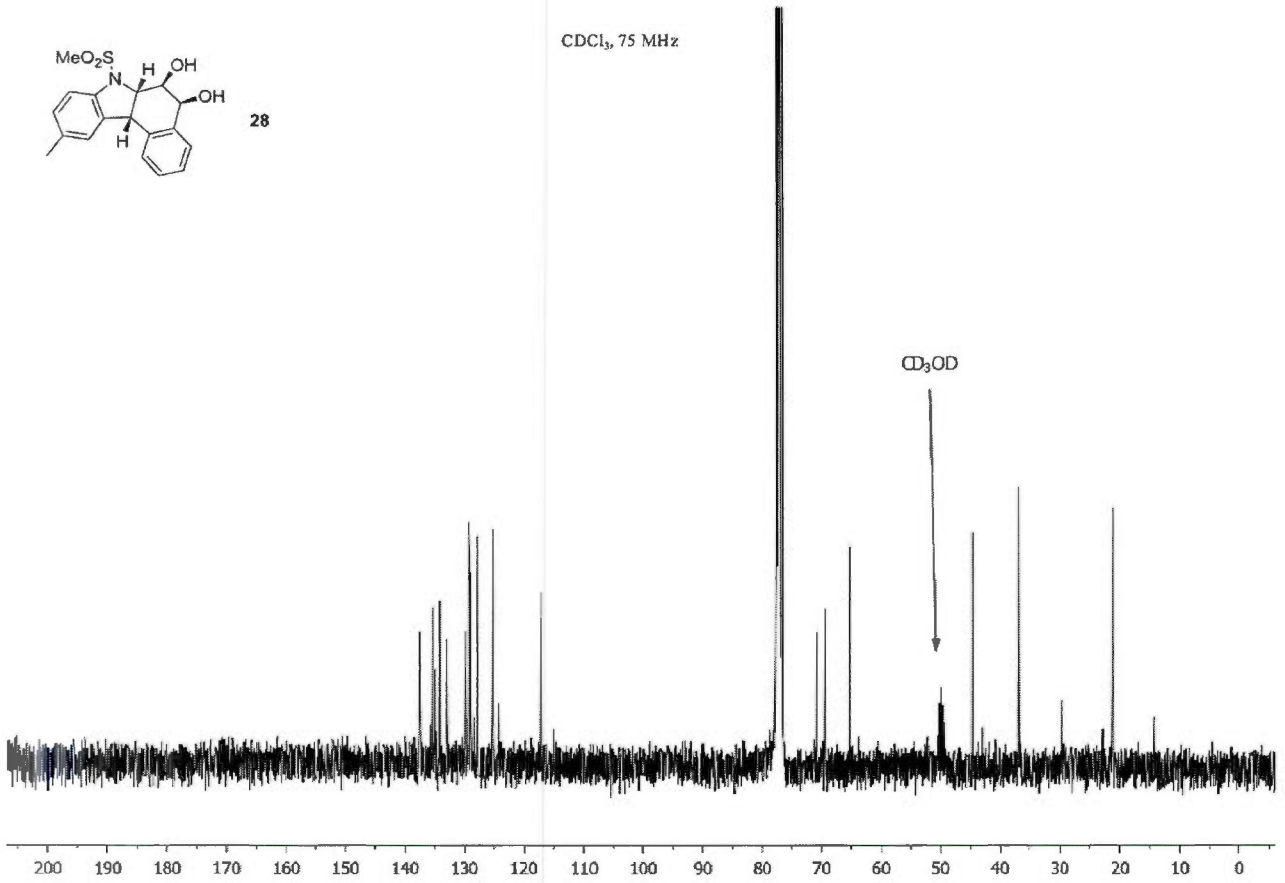


This journal is © The Royal Society of Chemistry 2013



Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013

28



ANNEXE E :

"A CONCISE FORMAL SYNTHESIS OF STRYCHNINE" ARTICLE

L'article sera soumis sous peu.

Titre: A Concise Formal Synthesis of Strychnine

Auteurs: Guillaume Jacquemot et Sylvain Canesi*

A Concise Formal Synthesis of Strychnine

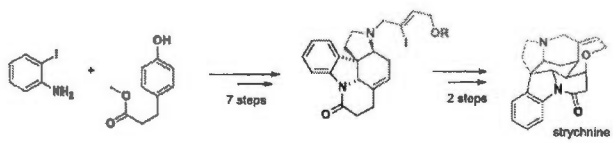
Guillaume Jacquemot and Sylvain Canesi*

Laboratoire de Méthodologie et Synthèse de Produits Naturels, Université du Québec à Montréal, C.P. 8888, Succ. Centre-Ville, Montréal, H3C 3P8, Québec, Canada.

**canesi.sylvain@uqam.ca*

Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT



A concise synthesis of the main pentacyclic core of strychnine has been achieved from available 3-(4-Hydroxyphenyl)propionic acid methyl ester in nine steps. This synthesis involves an oxidative dearomatization transformation mediated by a hypervalent iodine reagent, a novel aza Michael-ether-enol tandem process, a heck type cyclization and a reductive isomerization reaction.

(+)-Strychnine has been mainly isolated from the seeds of the trees *Strychnos Ignatii Bergius* and *Strychnos nux-vomica*.[1] This compound is one of the most known alkaloid in the world by chemists as well as the population due to its dangerous biological properties. Indeed, the acting poison effect of nuts containing strychnine has been involved in several famous murders and legends down the ages.[2] Firstly isolated by Pelletier and Caventou in 1818,[3] this alkaloid is also considered to be the first complex total synthesis that has been achieved in the organic chemistry history by Woodward and coworkers in 1954[4] and none other synthesis of this molecule has been accomplished during almost forty years after. In the 1990s, several beautiful total and formal syntheses have been subsequently reported in the literature. This alkaloid has been a wonderful source of inspiration that has allowed developing numerous advancements in organic synthesis and training several chemists.[5] A very interesting review by Overman and Cannon outlines the main strategies and accomplishments that have been reported on strychnine syntheses.[6] Strychnine **1** belongs to the strychnos alkaloids which represent a large family of bioactive natural products such as icajine **2**,[7] or akuammicine **3**,[8] Figure 1.

(1) Creasey, W. A. *in Monoterpenoid Indole Alkaloids, Supplement to Vol. 25, Part 4* (Ed.: J. E. Saxton), Wiley, New York, **1994**, pp. 715.

(2) Buckingham, J. *Bitter Nemensis*. The Intimate History of Strychnine, CRC, Boca Raton, FL, **2008**.

(3) (a) Pelletier, P. J., Caventou, J. B. *Ann. Chim. Phys.* **1818**, *8*, 323; (b) Pelletier, P. J., Caventou, J. B. *Ann. Chim. Phys.* **1819**, *10*, 142.

(4) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; H. U. Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749.

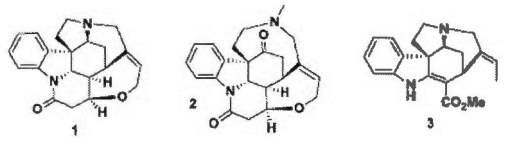
(5) (a) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403. (b) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293. (c) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490. (d) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685. (e) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9427. (f) Solé, D.; Bonjoch, J.; Garcia-Rubio, S.; Peidró, E.; Bosch, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 395. (g) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003. (h) Eichberg, M. J.; Dorta, R. L.; Lamottke, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *2*, 2479. (i) Nakanishi, M.; Mori, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1934. (j) Bodwell, G. J.; Li, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3261. (k) Ohshima, T.; Xu, Y.; Takita, R.; Shimuzu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546. (l) Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 10246. (m) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, *9*, 279. (n) Sirasani, G.; Paul, T.; Dougherty, W. Jr.; Kassel, S.; Andrade, R. B. *J. Org. Chem.* **2010**, *75*, 3529. (o) Beemelmanns, C.; Reissig, H. U. *Angew. Chem., Int. Ed.* **2010**, *49*, 8021. (p) Martin, D. B. C.; Vanderwal, C. D. *Chem. Sci.* **2011**, *2*, 649. (q) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 185. (r) Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455. (s) Mori, M. *Heterocycles* **2010**, *81*, 259. (t) Furst, L.; Stephenson, C. R. *J. Nat. Chem. Biol.* **2011**, *7*, 582. (u) Beemelmanns, C.; Reissig, H.-U. *Chem. Soc. Rev.* **2011**, *40*, 2199. (v) Martin, D. B. C.; Nguyen, L. Q.; Vanderwal, C. D. *J. Org. Chem.* **2012**, *77*, 17.

(6) Cannon, J. S.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 4288.

(7) (a) Delle, M. F.; Gelabert, B. A.; Corio, E.; Marin, G. *J. Chromatogr.* **1968**, *32*, 178.

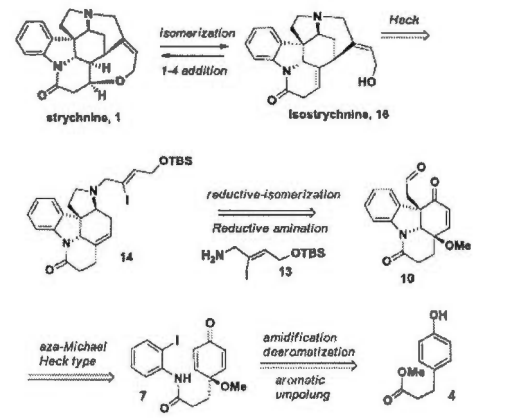
(8) Tan, S. J.; Low, Y. Y.; Choo, Y. M.; Abdullah, Z.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T. S. *J. Nat. Prod.* **2010**, *73*, 1891.

Figure 1. Strychnine and Related Alkaloids



Despite the fact that several syntheses of strychnine have been reported, our interest in oxidative dearomatizing processes[9] mediated by hypervalent iodine reagents[10] has conducted us to think about an unexplored formal synthesis of this target. In this paper, we propose a new concise synthesis of the main pentacyclic core of strychnine involving several key steps such as an aromatic dearomatization transformation, a Heck type cyclization, an unprecedented aza-Michael-enol-ether tandem process, a reductive isomerization and a double reductive amination. The end of synthesis has been achieved following the remarkable protocol reported by Rawal and coworkers,[5d] Figure 2.

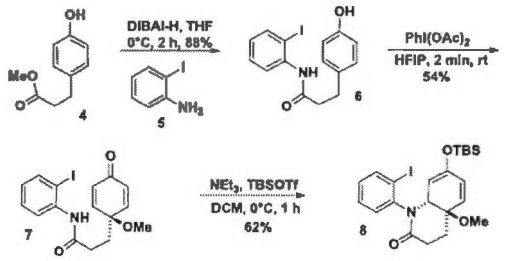
Figure 2. Strychnine Retrosynthesis



(9) (a) Guérard, K. C.; Sabot, C.; Racicot, L.; Canesi, S. *J. Org. Chem.* **2009**, *74*, 2039. (b) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941. (c) Guérard, K. C.; Chapelle, C.; Giroux, M. A.; Sabot, C.; Beaulieu, M. A.; Achache, N.; Canesi, S. *Org. Lett.* **2009**, *11*, 4756. (d) Guérard, K. C.; Sabot, C.; Beaulieu, M. A.; Giroux, M. A.; Canesi, S. *Tetrahedron* **2010**, *66*, 5893. (e) Andrez, J. A.; Giroux, M. A.; Lucien, J.; Canesi, S. *Org. Lett.* **2010**, *12*, 4368. (f) Beaulieu, M. A.; Sabot, C.; Achache, N.; Guérard, K. C.; Canesi, S. *Chem. Eur. J.* **2010**, *16*, 11224. (g) Desjardins, S.; Andrez, J. A.; Canesi, S. *Org. Lett.* **2011**, *13*, 3406. (h) Beaulieu, M. A.; Guérard, K. C.; Maertens, G.; Sabot, C.; Canesi, S. *J. Org. Chem.* **2011**, *76*, 9460. (i) Guérard, K. C.; Guerinot, A.; Bouchard-Aubin, C.; Ménard, M.A.; Lepage, M.; Beaulieu, M. A.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 2121 (j) Sabot, C.; Commare, B.; Nahi, S.; Duceppe, M. A.; Guérard, K. C.; Canesi, S. *Synlett* **2008**, 3226. (k) Jacquemot, G.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 7588. (l) Jacquemot, G.; Menard, M. A.; L'Homme, C.; Canesi, S. *Chem. Sci.* **2013**, *4*, 1287.

Our synthesis starts from available phenol **4**. This compound reacts with the aluminum salt[11] of iodo-aniline to produce the amide **6** in 88% yield. Subsequently, an oxidative dearomatization process well developed by Kita and coworkers[12] has been performed to yield the dienone core **7** in 54% yield. This compound is accompanied by a small amount of a spirolactam[13] as a side product resulting from a direct nitrogen attack. At this stage, a new method enabling to generate the bicyclic enol-ether **8** has been developed via an aza-Michael process provoked by a siliconium Lewis acid in 62% yield. This transformation should firstly occur by an imino-ether formation followed by an activation of the enone moiety with TBS-triflate enabling the nitrogen attack in a Michael pathway to produce the desired enol-ether **8**. To the best of our knowledge, such transformation is unreported in the literature. It should be stressed that compound **7** is a prochiral dienone system and an asymmetric aza-Michael process on this species would lead to an enantioselective synthesis of strychnine and its congeners, Scheme 1.

Scheme 1. Bicyclic System Formation



Compound **8** is the required intermediate to produce the tetracore of strychnine **1**. Indeed, the enol-ether moiety generated during the previous tandem process has been involved in a further carbopalladation such as a Heck type cyclization to produce **9** in 73% yield. The first quaternary carbon center has been generated at this step by an

(8) (a) Quideau, S.; Looney, M. A.; Pouységu, L. *Org. Lett.* **1999**, *1*, 1651. (b) Quideau, S.; Lyvinec, G.; Marguerit, Bathany, K.; Ozanne-Beaudenon, A.; Bufeteau, T.; Cavagnat, D.; Chenede, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605. (c) Quideau, S.; Looney, M. A.; Pouységu, L. *J. Org Chem.* **1998**, *63*, 9597. (d) Pouységu, L. ; Sylla, T.; Garnier, T.; L. B. Rojas, L. B.; Charris, J.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 5908. (e) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (f) Liang, H.; Ciufolini. M. A. *Org. Lett.* **2010**, *12*, 1760. (g) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539. (h) Liang, H.;. Ciufolini, M. A. *Tetrahedron* **2010**, *66*, 5884. (i) Lewis, N.; Wallbank, P. *Synthesis* **1987**, 1103.

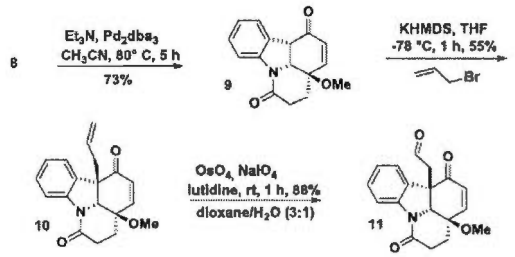
(11) Huang, P.-Q.; Zheng, X.; Deng, X.-M. *Tetrahedron Lett.* **2001**, *42*, 9039.

(12) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (c) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775.

(13) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, *24*, 3759.

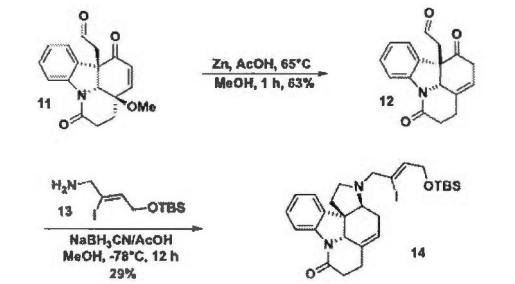
allylation in basic conditions and controlled by the bowl shape of the molecule to afford **10** in 55% yield. A Lemieux-Johnson transformation[14] realized on **10** yields the aldehyde **11** in 88% yield, Scheme 2.

Scheme 2. Tetracycle Formation



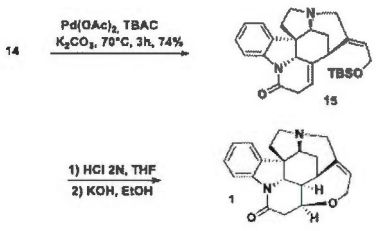
A reductive isomerization process developed by Wipf and coworkers on compound **11** produces the key adduct **12** in 63% yield. This reaction is promoted by zinc in acetic acid[15] and allows installing the double bond at a strategic position for the elaboration of the hexacyclic system desired as noteworthy demonstrated by Rawal and coworkers. At this stage, a double reductive amination with the known amine[5d] **13** is performed on **12** and enables producing the desired substituted pentacyclic core **14**, Scheme 3.

Scheme 3. Pentacyclic Core Formation



By this strategy, a concise synthesis of the main substituted-pentacyclic core of strychnine has been achieved in seven steps from readily available phenol **4**. The end of synthesis has already been demonstrated by Rawal and coworkers in their noteworthy synthesis.[5d] Indeed, a Heck transformation performed on **14** leads to the hexacyclic core **15**, which represents the tertbutyldimethylsilane protected form of isostrychnine **16**. A deprotection with HCl followed by a treatment in basic conditions led them to a short and efficient synthesis of strychnine **1**, Figure 3.

Figure 3. Rawal and Coworkers end of Synthesis



In summary, a formal synthesis of strychnine has been accomplished in 9 steps from a readily available and inexpensive phenol. This synthesis outlines several transformations such as an oxidative dearomatization mediated by a hypervalent iodine reagent, an unprecedented aza-Michael-ether-enol tandem process, a heck type cyclization and a reductive isomerization transformation. The main strategy focused on hypervalent iodine chemistry as a rapid application in total synthesis of complex natural products.

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) 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.

(14) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(15) Wipf, P.; Methot, J.L. *Org. Lett.* **2000**, *2*, 4213.

ANNEXE F :

"A CONCISE FORMAL SYNTHESIS OF STRYCHNINE" SUPPORTING INFORMATION

L'article sera soumis sous peu.

Titre: A Concise Formal Synthesis of Strychnine

Auteurs: Guillaume Jacquemot et Sylvain Canesi*

A Concise Formal Synthesis of Strychnine

Guillaume Jacquemot and Sylvain Canesi*

Laboratoire de Méthodologie et Synthèse de Produit Naturels.

Université du Québec à Montréal, C.P.8888, Succ. Centre-Ville, Montréal. H3C 3P8,

Québec, Canada.

Supporting Information

Table of Contents

1. General information -S2-

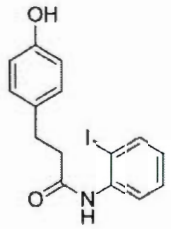
2. Experimental procedures and analytical data -S2-S7

3. Copies of ^{1}H and ^{13}C NMR spectra for all compounds -S8-S22

I. General information and materials

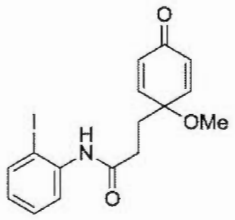
Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, 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

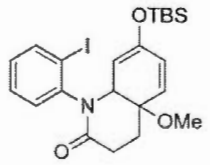


3-(4-hydroxyphenyl)-N-(2-iodophenyl)propanamide (6): To a solution of 2-iodoaniline **5** (2.467 g, 11.26 mmol, 2.8 equiv.) in THF (15 mL) at 0°C, DIBAL-H (11.3 mL, 11.26 mmol, 2.8 equiv.) was added and the solution was stirred during 1.5 h at room temperature. A solution of methyl 3-(4-hydroxyphenyl)propanoate **4** (725.0 mg, 4.02 mmol, 1.0 equiv.) in THF (2 mL) was then added at room temperature and the reaction was followed by TLC. After completion, HCl 1M was added, followed by ethyl acetate. The aqueous phase was extracted with ethyl acetate, and the organic phases were then dried with Na_2SO_4. The solution was filtered, concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 1.294 g (88 %) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 7.3 Hz, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.08 (d, J = 8.3 Hz, 2H), 6.82

(t, J = 7.2 Hz, 1H), 6.75 (d, J = 8.4 Hz, 2H), 2.98 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.23, 155.16, 138.90, 137.97, 131.38, 129.39, 129.18, 126.43, 122.89, 115.57, 90.75, 39.78, 30.73; HRMS (ESI): Calc. for $C_{15}H_{15}INO_2$ (M+H)+: 368.0142; found: 368.0133.

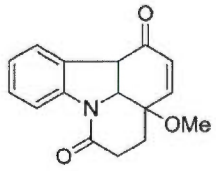


N-(2-iodophenyl)-3-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)propanamide (7): To a solution of **6** (867.0 mg, 2.36 mmol, 1.0 equiv.) in MeOH (12 mL) at room temperature, a solution of diacetoxyiodobenzene ("DIB", 912.0 mg, 2.83 mmol, 1.2 equiv.) in MeOH (3 mL) was added and the reaction was followed by TLC. After completion, the solution was filtreted through a pad of silica gel and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 511.3 mg (54 %) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.41 (s, 1H), 7.33 (t, J = 7.8 Hz, 1H), 6.85 (t, J = 6.9 Hz, 1H), 6.78 (d, J = 10.2 Hz, 2H), 6.40 (d, J = 10.2 Hz, 2H), 3.24 (s, 3H), 2.44 (t, J = 7.6 Hz, 2H), 2.21 (t, J = 7.6 Hz, 2H; ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.15, 169.96, 150.28, 138.99, 138.09, 132.13, 129.41, 129.17, 128.36, 126.35, 122.44, 75.09, 53.38, 34.40; HRMS (ESI): Calc. for $C_{16}H_{17}INO_3$ (M+H)+: 398.0248; found: 398.0235.



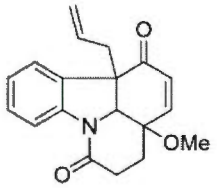
7-((tert-butyldimethylsilyl)oxy)-1-(2-iodophenyl)-4a-methoxy-1,4,4a,8a-tetrahydroquinolin-2(3H)-one (8): To a solution of **7** (513.0 mg, 1.291 mmol, 1.0

equiv.) in DCM (6.5 mL) at 0°C, Et_3N (392.1 mg, 3.874 mmol, 3.0 equiv.) was added followed by TBSOTf (512.0 mg, 1.937 mmol, 1.5 equiv.) and the reaction was followed by TLC. After completion, NH_4Cl was added, followed by DCM. The aqueous phase was extracted with DCM, and the organic phases were then dried with Na_2SO_4. The solution was filtered, concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 413.4 mg (62 %) of **8** as a mixture of atropoisomers. ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.6 Hz, 2H), 7.41 – 7.30 (m, 2H), 7.17 (d, J = 7.7 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 6.97 (d, J = 4.3 Hz, 2H), 5.96 (d, J = 10.0 Hz, 1H), 5.80 (s, 2H), 5.67 (d, J = 10.0 Hz, 1H), 4.84 (d, J = 13.1 Hz, 1H), 4.61 (d, J = 14.9 Hz, 1H), 3.34 (d, J = 3.0 Hz, 3H), 3.29 (d, J = 2.7 Hz, 3H), 2.70 – 1.80 (m, 7H), 1.25 – 1.11 (m, 1H), 0.86 (s, 18H), 0.07 (d, J = 6.9 Hz, 6H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.22, 169.06, 148.33, 147.09, 144.33, 142.05, 140.12, 139.73, 132.30, 131.70, 131.49, 129.77, 129.48, 129.27, 128.87, 128.59, 128.43, 128.24, 102.28, 101.85, 101.05, 98.78, 75.44, 73.64, 63.75, 60.15, 51.45, 50.94, 30.42, 29.00, 28.19, 26.65, 25.58, 25.51, 25.48, 20.95, 17.87, 17.85, 14.15, -4.39, -4.56, -4.58; HRMS (ESI): Calc. for $C_{22}H_{31}INO_3Si$ (M+H)+: 512.1112; found: 512.1111.

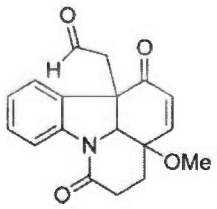


3a-methoxy-3a1,4,5,11b-tetrahydro-1H-pyrido[3,2,1-jk]carbazole-1,6(3aH)-dione (9): To a solution of **8** (17.1 mg, 0.033 mmol, 1.0 equiv.) in MeCN (1 mL), Et_3N (33.8 mg, 0.334 mmol, 10.0 equiv.) was added followed by Pd_2dba_3 (6.2 mg, 0.0066 mmol, 0.20 equiv.). The solution was then refluxed and the reaction was followed by TLC. After completion, the solution was filtreted through a pad of silica gel and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 6.6 mg (73%) of a brown oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.27 (t, J = 7.7 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.78 (dd, J = 10.3, 2.0 Hz, 1H), 6.37 (d, J = 10.3 Hz, 1H), 4.62 (dd, J = 7.7, 2.0 Hz, 1H), 4.00 (d, J = 7.7 Hz, 1H), 3.37 (s, 3H), 2.79 (dt, J = 17.5, 5.5 Hz, 1H), 2.55 – 2.38

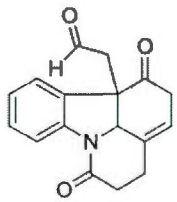
(m, 1H), 2.33 – 2.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.13, 167.70, 146.60, 141.90, 134.37, 129.04, 128.18, 126.08, 125.02, 117.05, 69.87, 65.66, 51.15, 48.94, 30.63, 30.16; HRMS (ESI): Calc. for $C_{16}H_{16}NO_3$ (M+H)+: 270.1125; found: 270.1112.



11b-allyl-3a-methoxy-3a1,4,5,11b-tetrahydro-1H-pyrido[3,2,1-jk]carbazole-1,6(3aH)-dione (10): To a solution of **9** (36.6 mg, 0.136 mmol, 1.0 equiv.) in THF (3 mL) at -78°C, KHMDS (544 µL, 0.272 mmol, 2.0 equiv.) was added and the solution was stirred 10 minutes at -78°C. Allyl bromide (49.3 mg, 0.408 mmol, 3.0 equiv.) was then added. The solution was allowed to warm to 0°C and the reaction was followed by TLC. After completion, NH_4Cl was added, followed by EtOAc. The aqueous phase was extracted with EtOAc, and the organic phases were then dried with Na_2SO_4. The solution was filtered, concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 23.0 mg (55 %) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 7.3 Hz, 1H), 7.25 (t, J = 7.1 Hz, 2H), 7.12 (t, J = 7.5 Hz, 1H), 6.84 (dd, J = 10.2, 2.0 Hz, 1H), 6.30 (d, J = 10.2 Hz, 1H), 5.54 (dtd, J = 16.9, 9.7, 5.0 Hz, 1H), 5.21 – 5.06 (m, 2H), 4.51 (d, J = 2.0 Hz, 1H), 3.36 (s, 3H), 3.24 (dd, J = 14.2, 4.9 Hz, 1H), 2.83 – 2.69 (m, 2H), 2.51 – 2.10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.80, 167.38, 146.28, 142.22, 134.23, 133.23, 130.52, 129.10, 125.25, 124.92, 120.17, 117.19, 70.68, 66.97, 56.37, 50.52, 39.14, 30.05, 29.11; HRMS (ESI): Calc. for $C_{19}H_{20}NO_3$ (M+H)+: 310.1438; found: 310.1438.

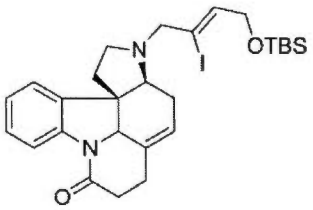


2-(3a-methoxy-1,6-dioxo-3a,3a1,4,5,6,11b-hexahydro-1H-pyrido[3,2,1-jk]carbazol-11b-yl)acetaldehyde (11): To a solution of **10** (23.0 mg, 0.074 mmol, 1.0 equiv.) in 1,4-Dioxane/H_2O (3:1, 1.3 mL), 2,6-lutidine (15.9 mg, 0.149 mmol, 2.0 equiv.) was added followed by OsO_4 (9.4 mg, 0.0015 mmol, 0.02 equiv.) and $NaIO_4$ (63.6 mg, 0.297 mmol, 4.0 equiv.). The solution was stirred at room temperature and the reaction was followed by TLC. After completion, NH_4Cl was added, followed by DCM. The aqueous phase was extracted with DCM, and the organic phases were then dried with Na_2SO_4. The solution was filtered, concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 20.5 mg (88 %) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 5.8 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.91 (dd, J = 10.2, 1.8 Hz, 1H), 6.38 (d, J = 10.2 Hz, 1H), 4.59 (s, J = 1.7 Hz, 1H), 3.32 (s, 3H), 3.30 (s, J = 2.4 Hz, 2H), 2.87 – 2.75 (m, 1H), 2.53 – 2.34 (m, 2H), 2.23 – 2.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.30, 194.08, 166.88, 147.21, 142.03, 134.65, 130.04, 129.71, 125.56, 124.22, 117.43, 70.58, 69.34, 54.02, 50.46, 49.32, 29.92, 28.73; HRMS (ESI): Calc. for $C_{18}H_{18}NO_4$ (M+H)+: 312.1230; found: 312.1213.

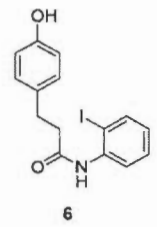


2-(1,6-dioxo-2,3a1,4,5,6,11b-hexahydro-1H-pyrido[3,2,1-jk]carbazol-11b-yl)acetaldehyde (12): To a solution of **11** (11.9 mg, 0.038 mmol, 1.0 equiv.) in MeOH (2.0 mL), Zn (25.0 mg, 0.382 mmol, 10.0 equiv.) was added followed by acetic acid (22.9 mg, 0.382 mmol, 10.0 equiv.). The solution was then refluxed and the reaction was followed by TLC. After completion, the solution was filtreted through a pad of silica gel and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 6.8 mg (63%) of a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.16 (d, J = 6.6 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 5.67 (s, 1H), 4.61 (s, 1H), 3.72 (d,

J = 18.9 Hz, 1H), 3.12 (d, J = 22.5 Hz, 1H), 2.96 (d, J = 23.0 Hz, 1H), 2.91 (d, J = 18.9 Hz, 1H), 2.78 – 2.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.59, 199.60, 170.68, 141.41, 130.40, 129.97, 129.21, 124.46, 123.96, 118.52, 116.55, 67.91, 55.74, 54.34, 36.64, 32.57, 25.91; HRMS (ESI): Calc. for $C_{17}H_{16}NO_3$ (M+H)+: 282.1125; found: 282.1122.

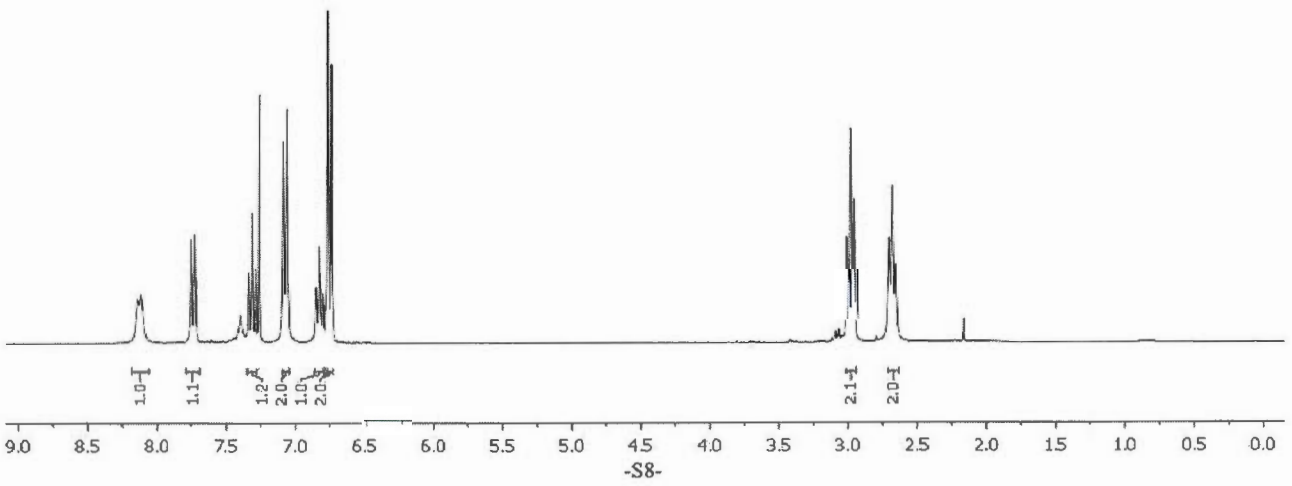


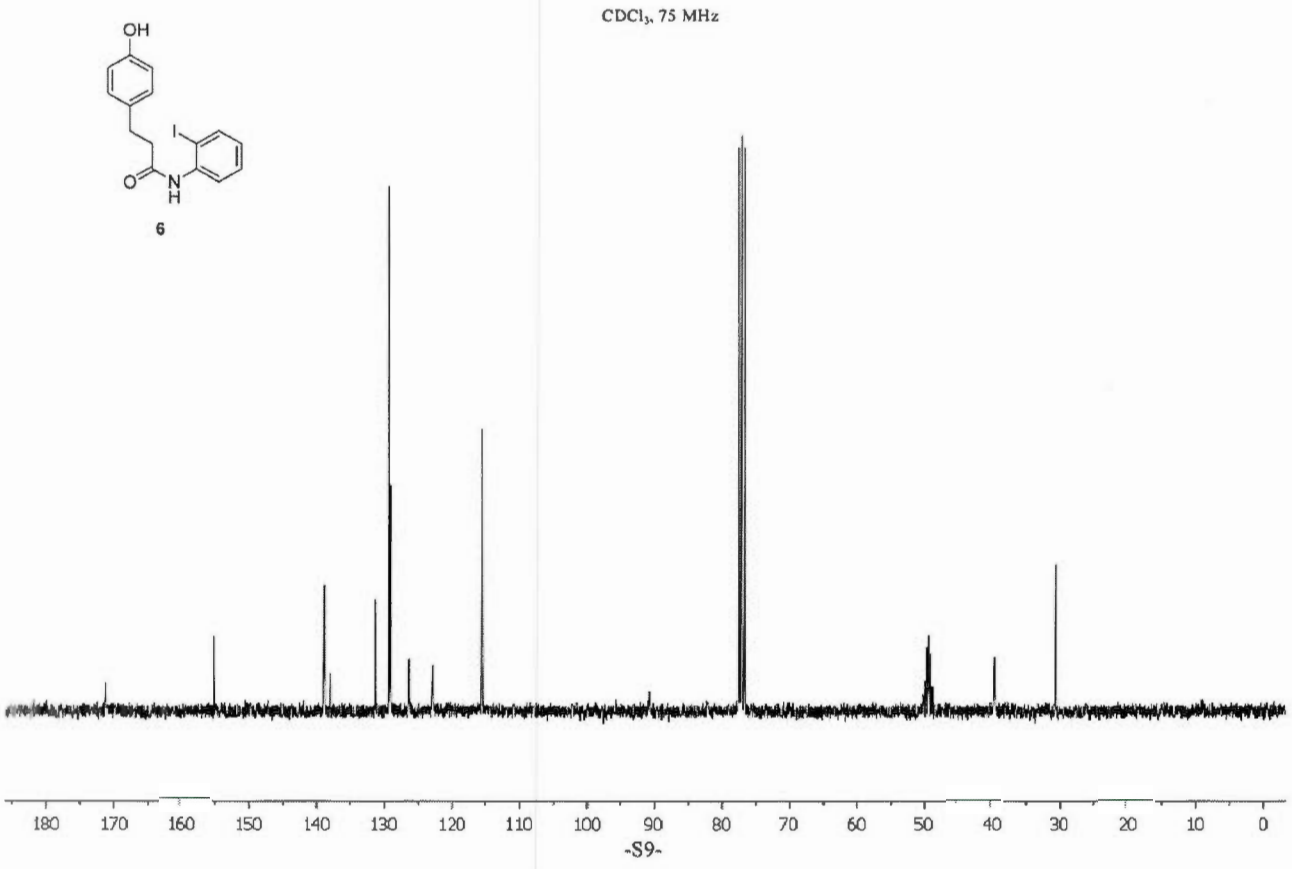
(Z)-3-(4-((tert-butyldimethylsilyl)oxy)-2-iodobut-2-en-1-yl)-2,3,3a,4,6,7-hexahydro-1H-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazol-8(5a1H)-one (14): To a solution of **12** (9.1 mg, 0.032 mmol, 1.0 equiv.) and amine **13** (12.7 mg, 0.039 mmol, 1.2 equiv.) in MeOH at -78°C, $NaBH_3CN$ (3.8 mg, 0.055 mmol, 1.7 equiv.) was added. After 1h, another portion of $NaBH_3CN$ (3.8 mg, 0.055 mmol, 1.7 equiv.) was added, followed by a drop of AcOH. The solution was slowly warmed overnight. After completion $NaHCO_3$ was added, followed by Et_2O. The aqueous phase was extracted with Et_2O, and the organic phases were then dried with Na_2SO_4. The solution was filtered, concentrated under vacuum, and the residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to give 5.4 mg (29 %) of a **14** as a 1:1 mixture of diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 6.8 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.09 (t, J = 5.0 Hz, 1H), 5.69 (d, J = 6.0 Hz, 1H), 4.33 (s, 1H), 4.25 (d, J = 4.9 Hz, 2H), 3.55 (d, J = 13.9 Hz, 1H), 3.44 (d, J = 13.9 Hz, 1H), 3.25 – 3.15 (m, 1H), 2.90 (dd, J = 8.6, 5.7 Hz, 1H), 2.78 – 2.51 (m, 5H), 2.26 – 2.01 (m, 4H), 0.90 (s, 9H), 0.08 (s, 6H).



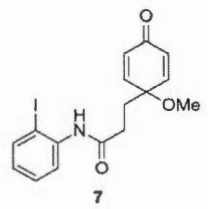
6

$CDCl_3$, 300 MHz

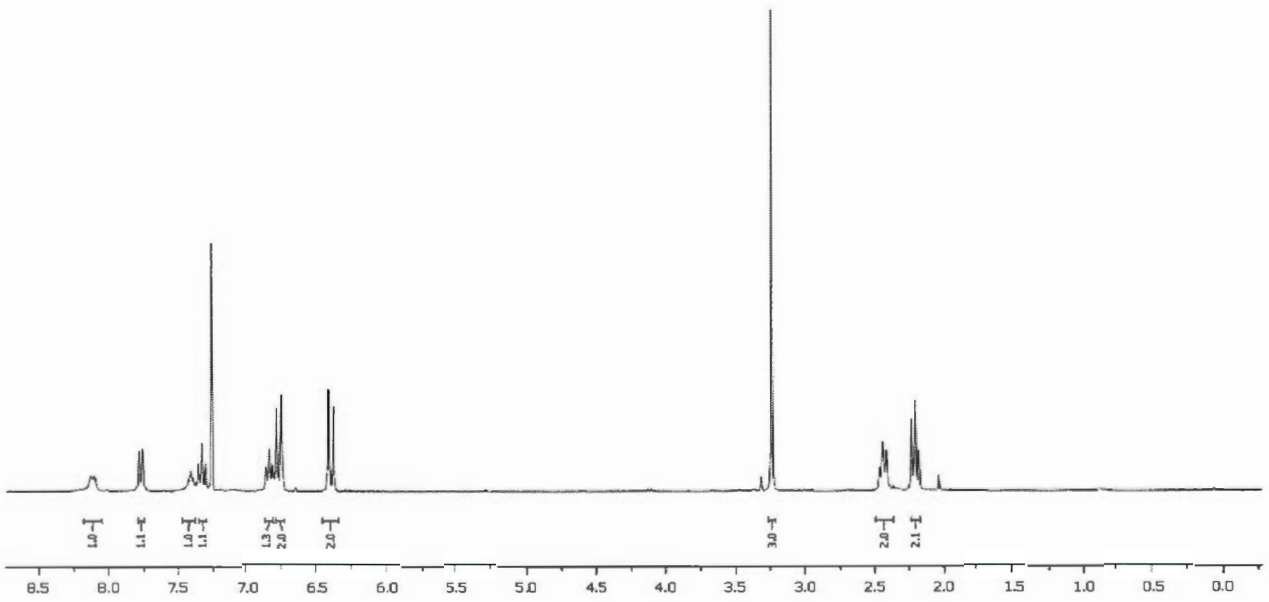


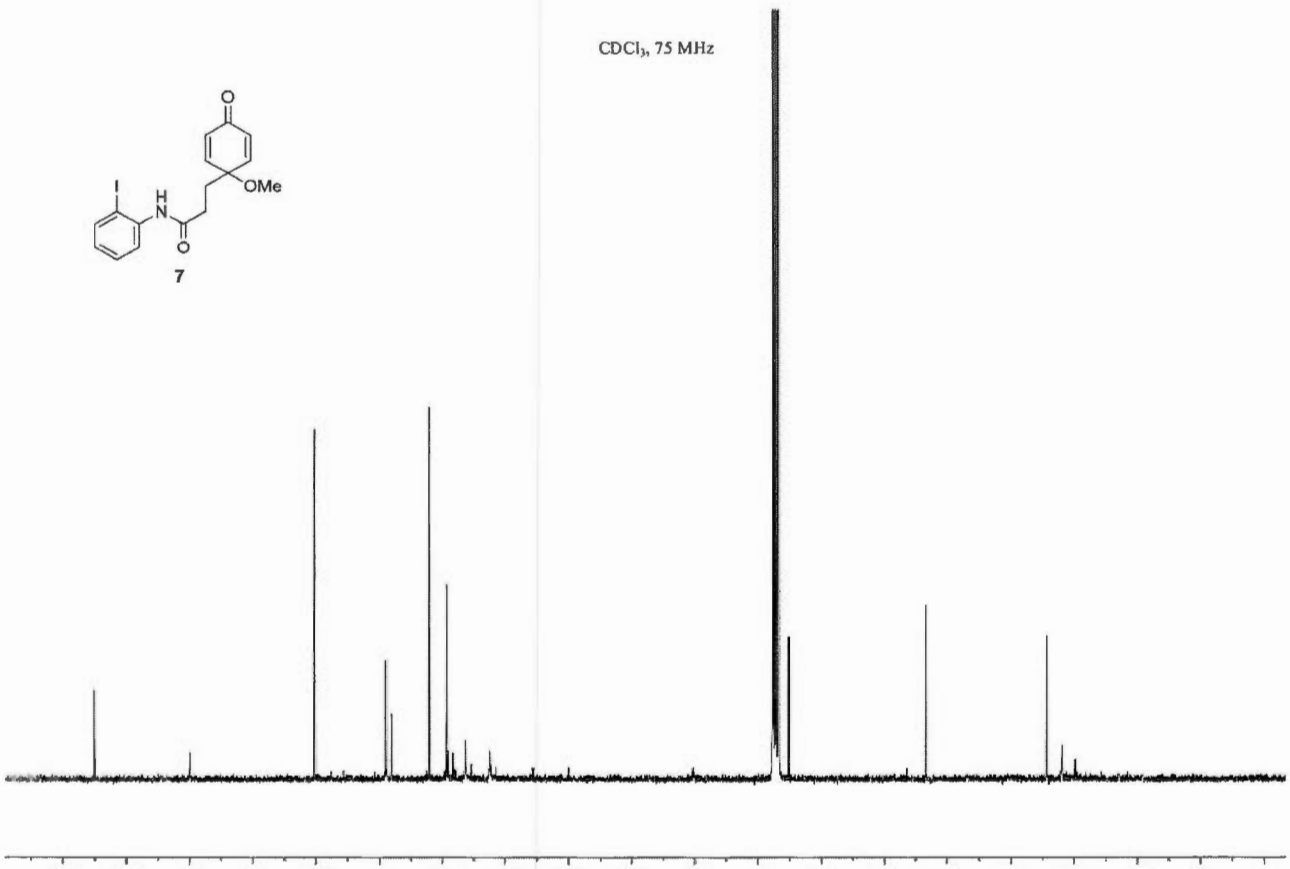

OH
I
O
N
H
6
CDCl3, 75 MHz
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

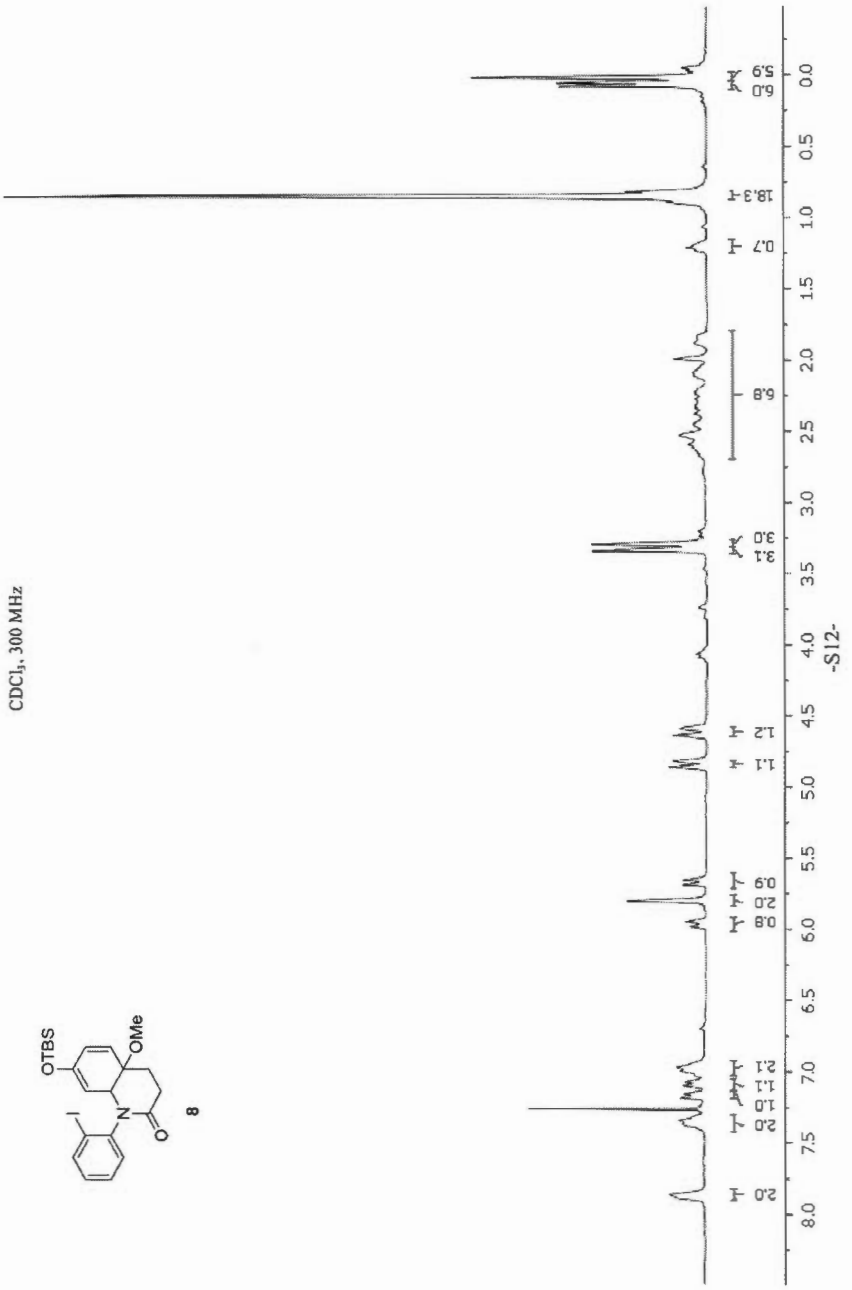
$CDCl_3$, 300 MHz



7

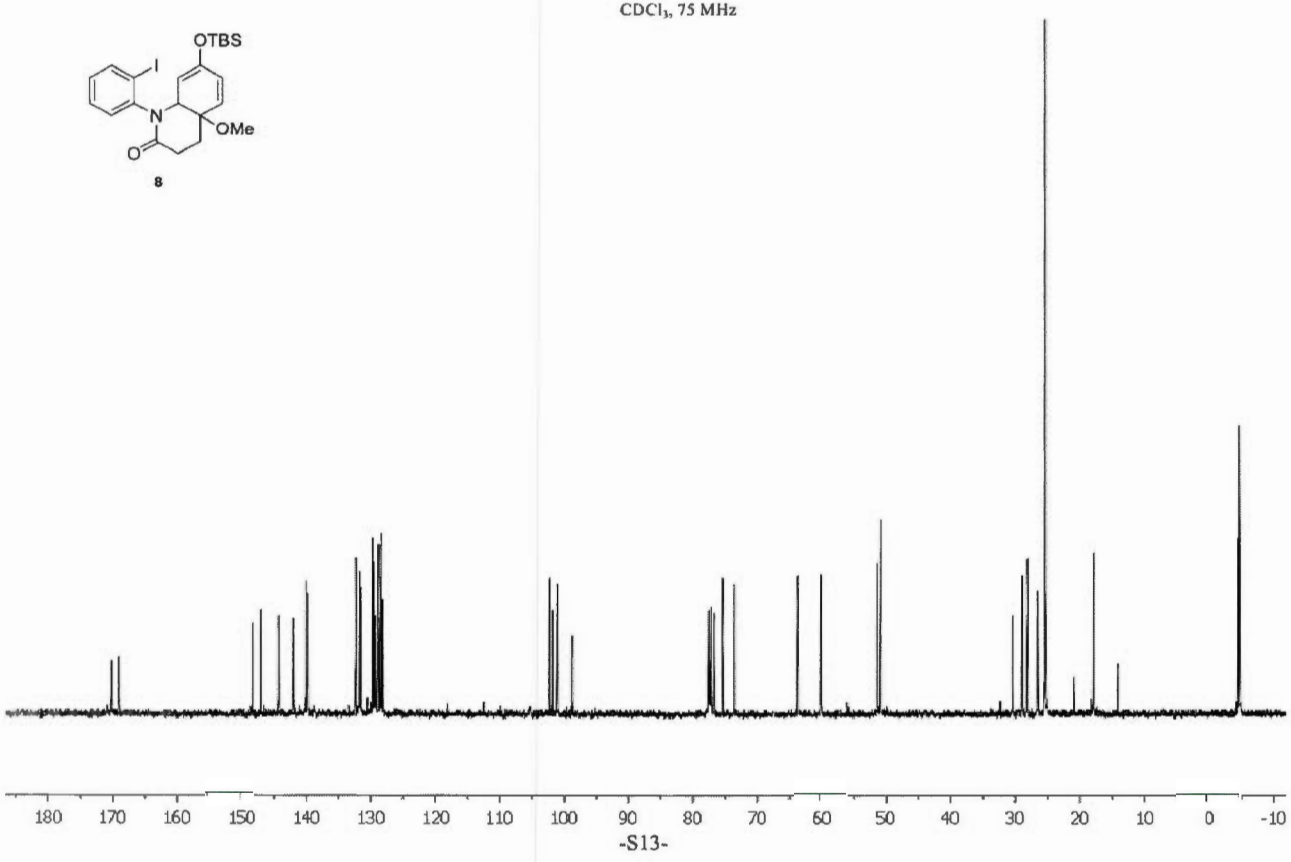


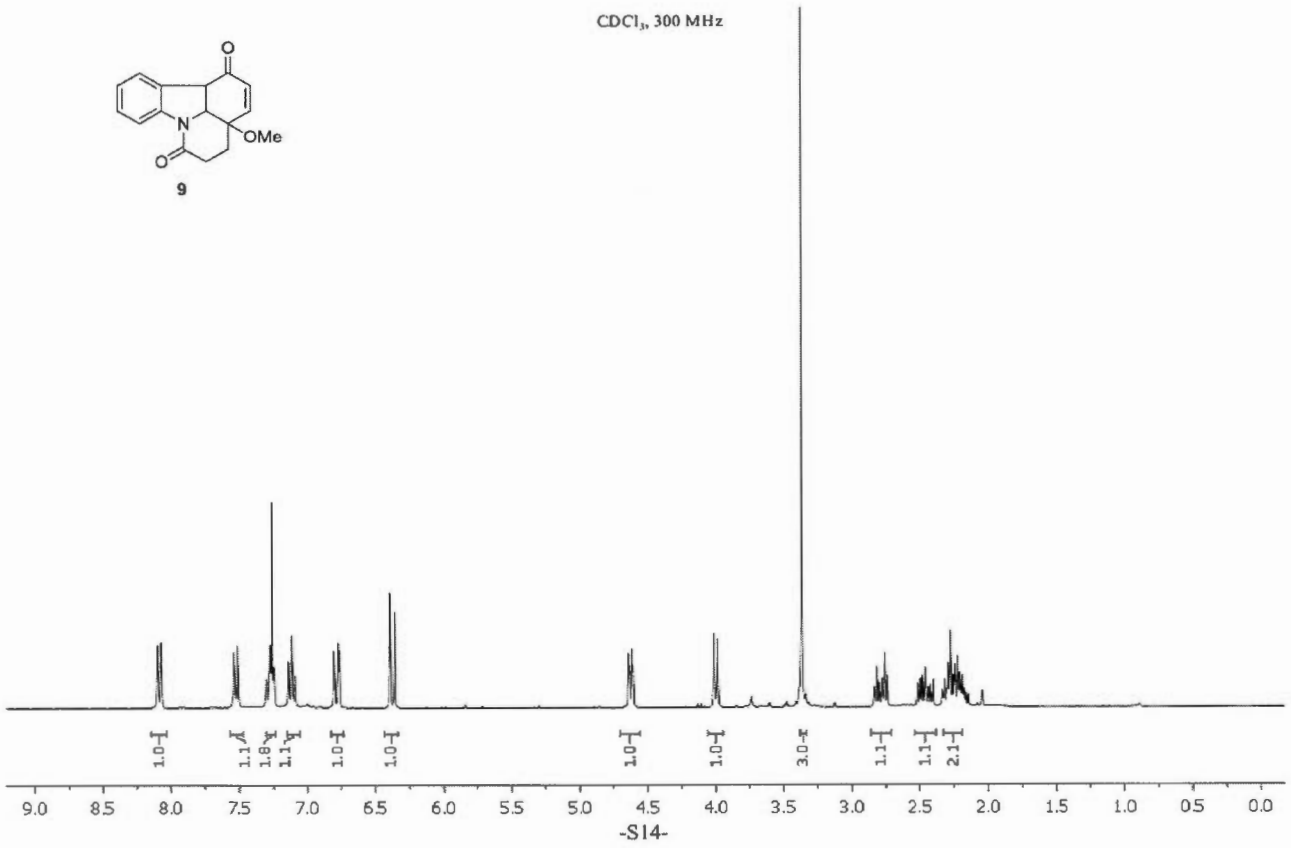

CDCl3, 75 MHz
I
H
N
O
OMe
O
7
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

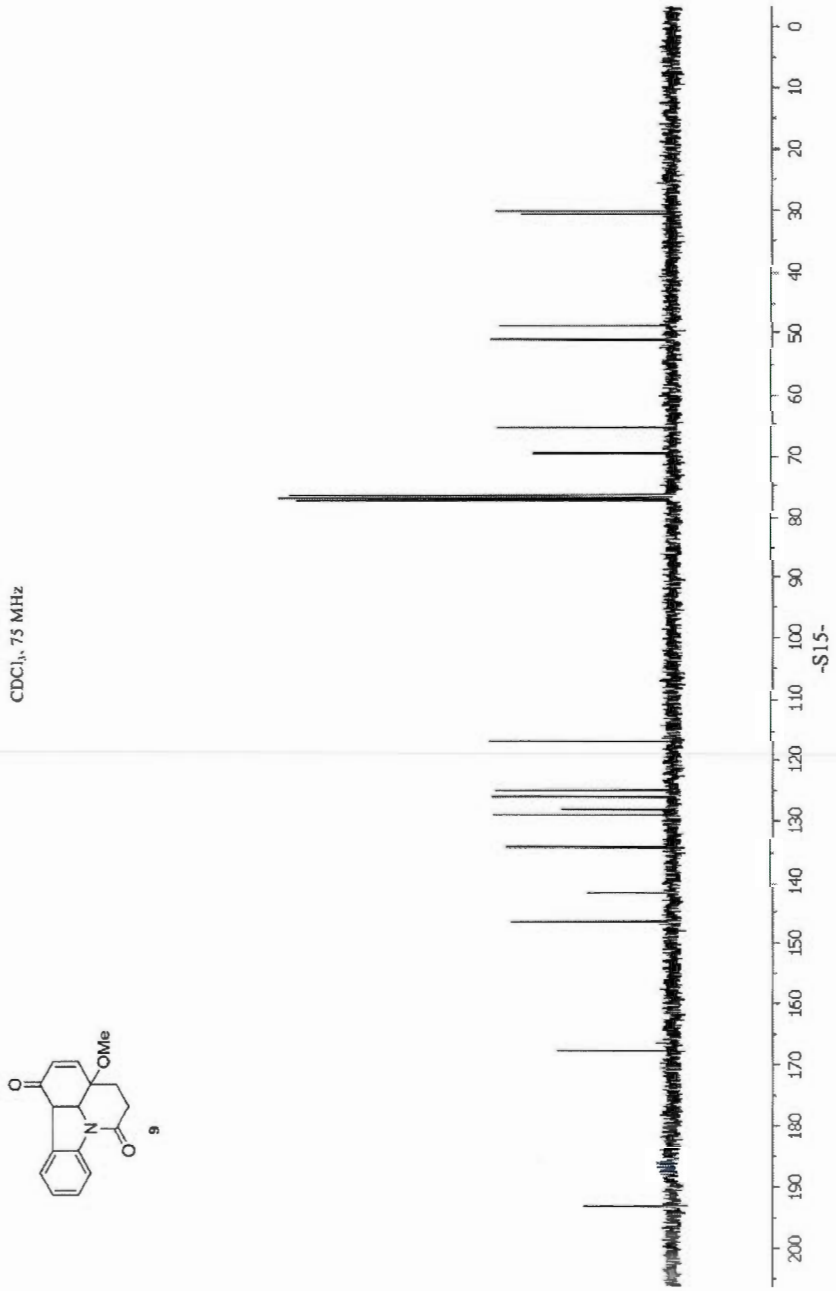

CDCl3, 300 MHz
OTBS
OMe
I
N
O
8
-S12-

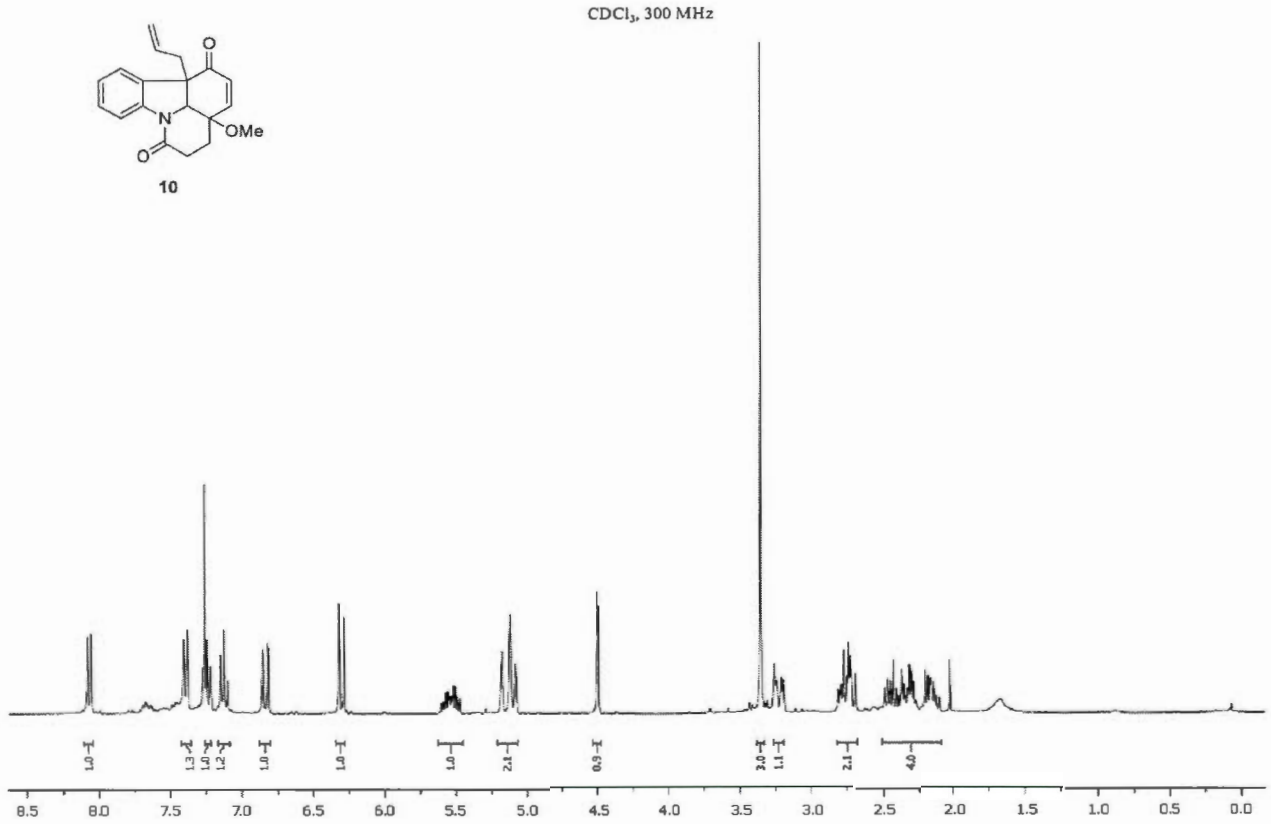
8

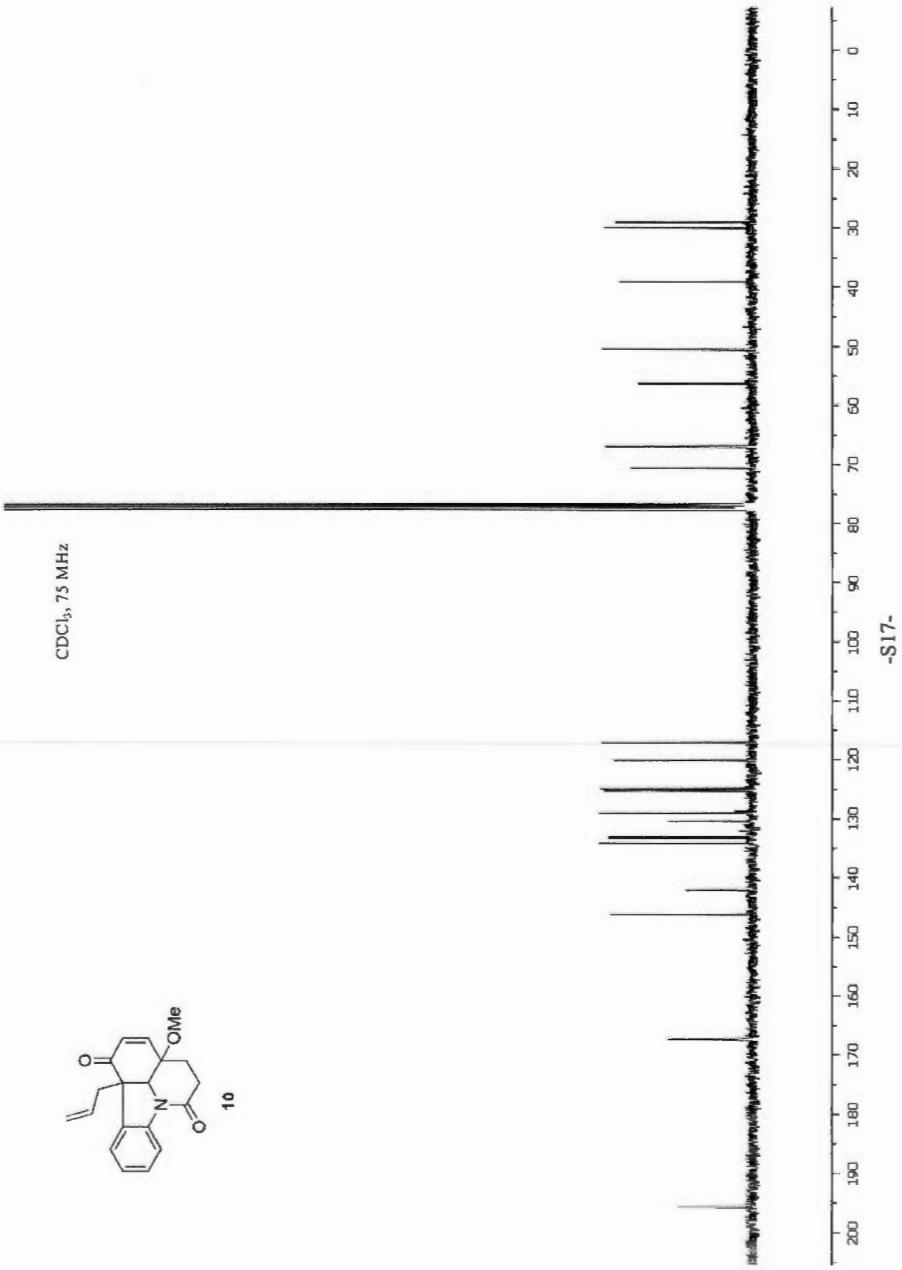
$CDCl_3$, 75 MHz




CDCl3, 300 MHz
O
N
OMe
O
9
1.0
1.1
1.8
1.1
1.0
1.0
1.0
1.0
3.0
1.1
1.1
2.1
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

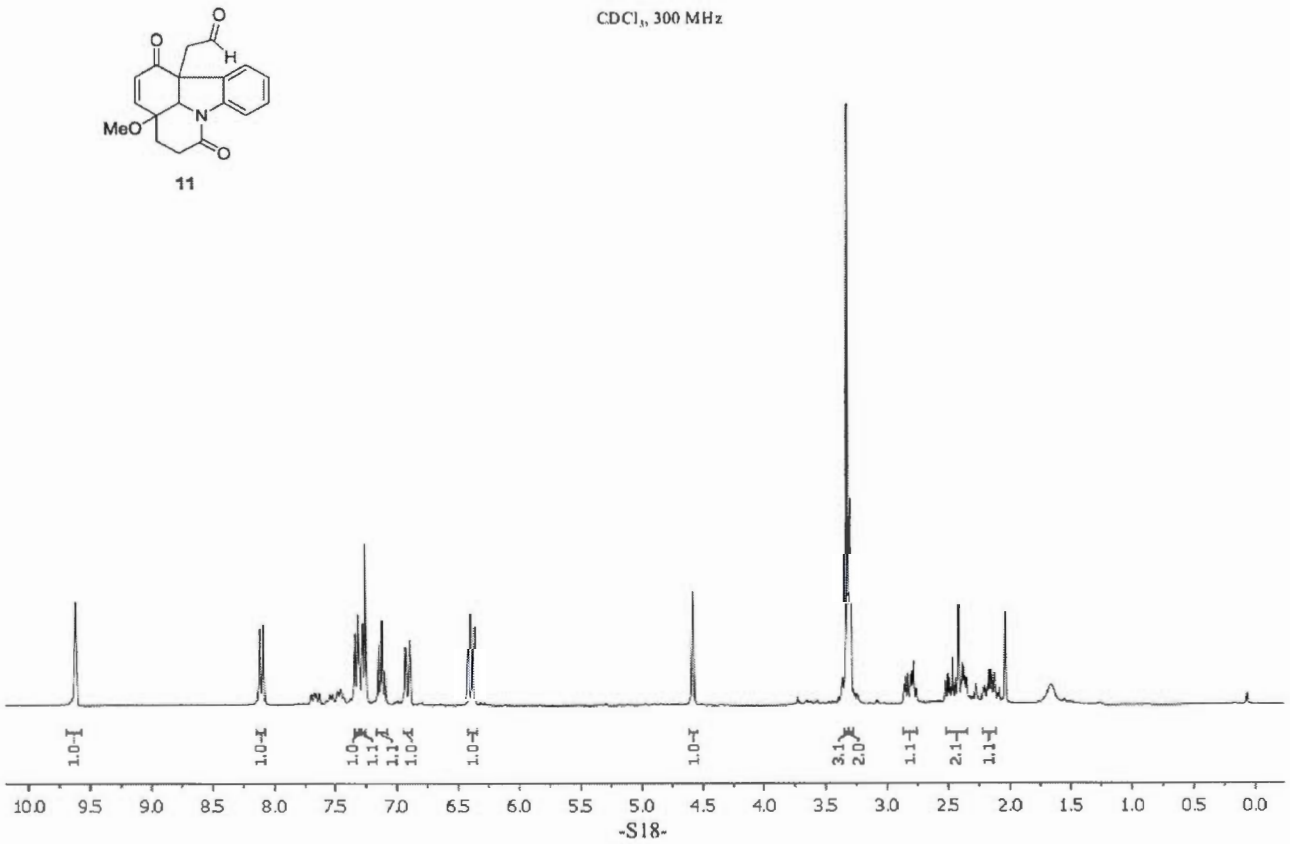

CDCl3, 75 MHz
OMe
O
N
O
9
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

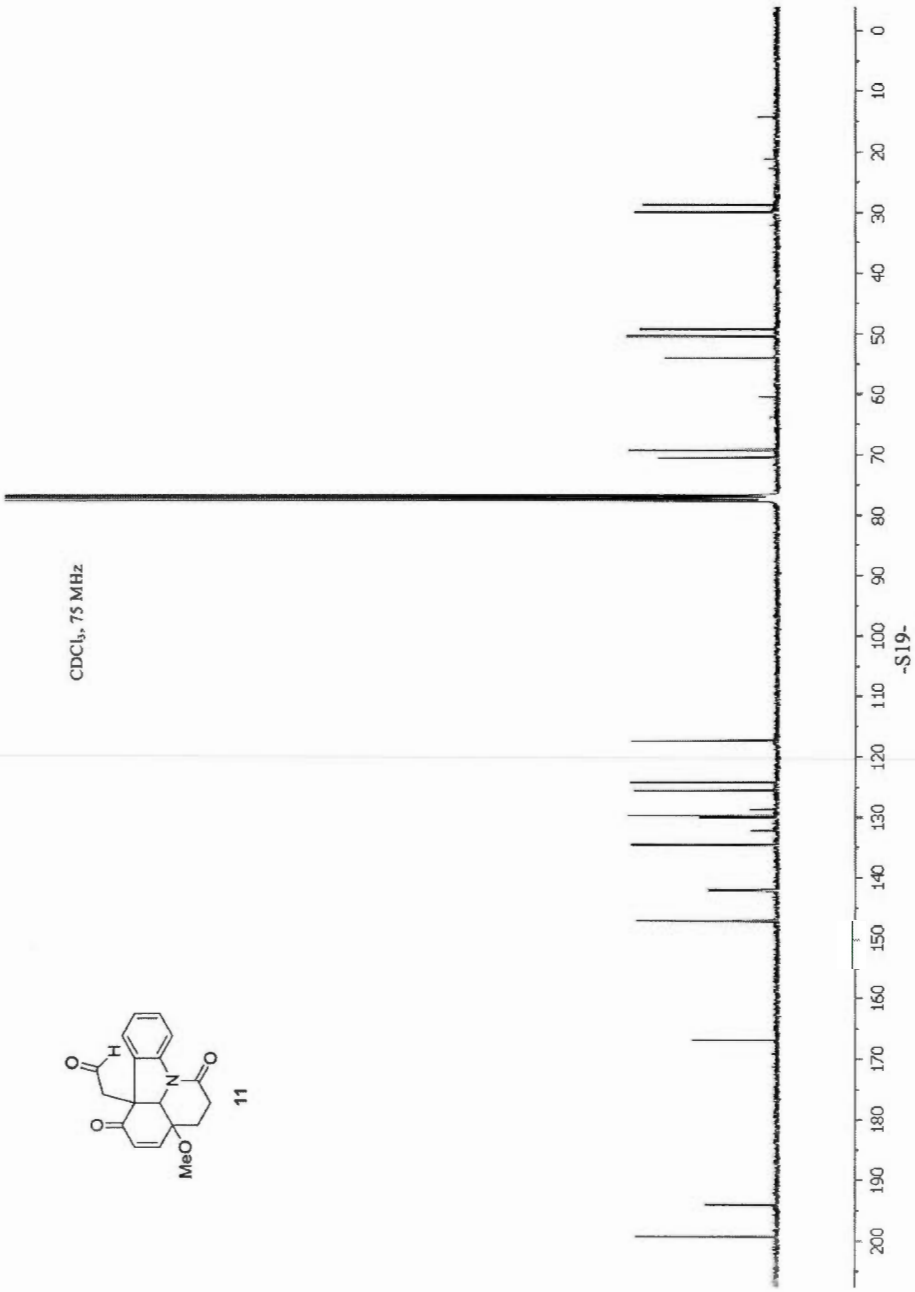

CDCl3, 300 MHz
O
N
OMe
O
10
1.0
1.3
1.1
1.2
1.0
1.0
1.0
2.1
0.9
2.0
1.1
2.1
4.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

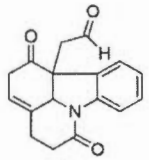

CDCl3, 75 MHz
OMe
O
N
O
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

O
O
H
MeO
N
O

11

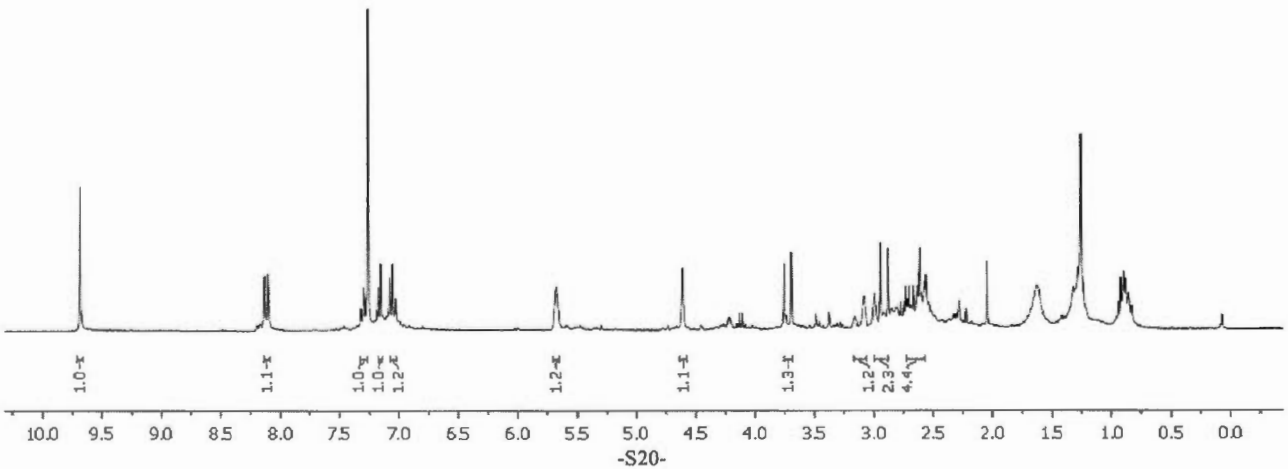

CDCl3, 300 MHz
1.0
1.0
1.1
1.1
1.0
1.0
1.0
3.1
2.0
1.1
2.1
1.1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


CDCl3, 75 MHz
MeO
11
-S19-



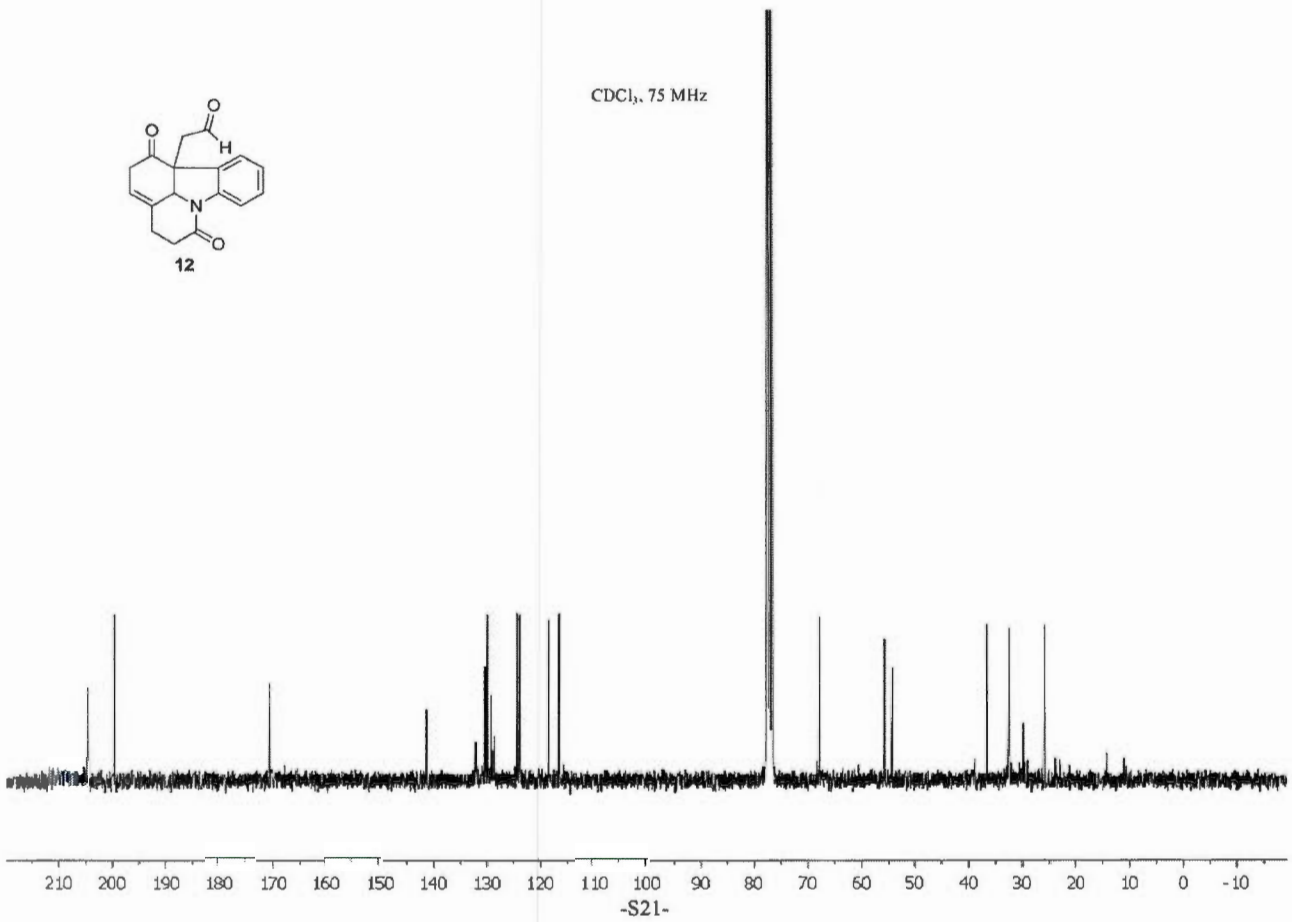
12

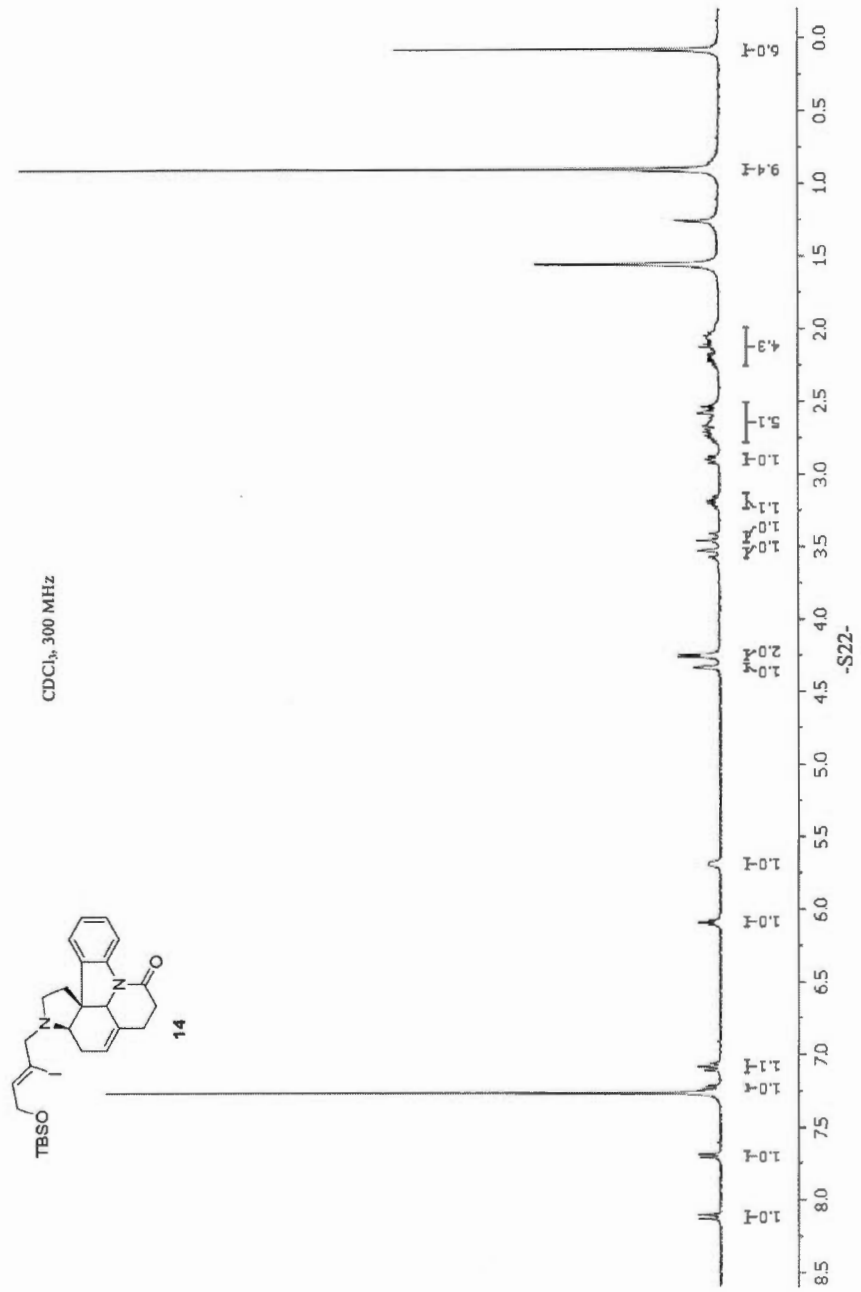
$CDCl_3$, 300 MHz



12

$CDCl_3$, 75 MHz




CDCl3, 300 MHz
TBSO
I
N
N
O
14
-S22-

RÉFÉRENCES

1. Stang. P.J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123−1178.
2. Silva, L, F; Olofsson, B. *Nat. Prod. Rep.* **2011**, *28*, 1722–1754.
3. Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111-124.
4. a) Ochiai, M. *J. Am. Chem. Soc.* **2005**, 12244. b) Evans, *J. Am. Chem. Soc.* **1993**, 5328. Evans, *J. Am. Chem. Soc.* **1994**, 2742. c) Brand, J. P.; Gonzalez, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.*, **2011**, *47*, 102–11515.
5. Pouységu, P.; Deffieux, D.; Quideau. S. *Tetrahedron,* **2010**, *66*, 2235–226115.
6. Okuyama, T.; Takino, T.; Sueda, T.; Ochiai. M. *J. Am. Chem. Soc.* **1995**, *117*, 3360-3367.
7. Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S.; *J. Am. Chem. Soc.* **1994**, *116*, 3684-3691.
8. Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.,* **2002**, *4,* 285-288.
9. Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 3787 –3790.
10. Seebach, D., *Angew. Chem. Int. Ed.* **1979**, *18*, 239; Seebach, D.; Corey, E., *J. Org. Chem.* **1975**, *40*, 231.
11. Stetter, H.; Schreckenberg, M. *Angew. Chem. internat. Edit.* **1973**, *12*, 81.
12. White, N. A.; DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 8504−8507.
13. Jang, K. P.; Hutson, G. E.; Johnston, R. C.; McCusker, E. O.; Cheong, P. H. Y.; Scheidt. K. A. *J. Am. Chem. Soc.* **2014**, *136*, 76−79.
14. (a) Bérard, D.; Jean, *A.;* Canesi, S., *Tetrabedron Lett.* **2007**, *48*, 8238; (b) Jean, A.; Cantat, J.; Bérard, D.; Bouchu, D.; Canesi, S., *Org. Lett.* **2007**, *9*, 2553. (c) Sabot, C.; Bérard, D.; Canesi, S. *Org. Lett.* **2008**, *10*, 4629 (d) Sabot, C.; Commare, B.; Nahi, S.; Duceppe, M.A.; Guérard, K. C.; Canesi, S. *Synlett*, **2008**, 3226; (e) Guérard, K. C.; Sabot, C.; Racicot, L.; Canesi, S. *J. Org. Chem.*, **2009**, *74*, 2039; (f) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.*, **2009**, 2941; (g) Guérard, K. C.; Chapelle, C.; Giroux, M. A.; Sabot, C.; Beaulieu, M. A.; Achache, N.; Canesi, S.

Org. Lett., **2009**, *11*, 4756; (h) Andrez, J, A.; Giroux, M. A.; Lucien, J; Canesi, S. *Org. Lett.*, **2010**, *12*, 4368; (i) Beaulieu, M. A.; Sabot, C.; Achache, N.; Guérard, K. C.; Canesi, S. *Chem.–Eur. J.*, **2010**, *16*, 11224; (j) Beaulieu, M. A.; Guérard, K. C.; Maertens, G.; Sabot, C.; Canesi, S. *J. Org. Chem.*, **2011**, *76*, 9460; (k) Guérard, K. C.; Guerinot, A.; Bouchard-Aubin, C.; Ménard, M. A.; Lepage, M.; Beaulieu, M. A.; Canesi, S. *J. Org. Chem.*, **2012**, *77*, 2121; (l) Jacquemot, G.; Canesi, S. *J. Org. Chem.*, **2012**, *77*, page 7588. (m) Jacquemot, G.; Ménard, M. A.; L'Homme, C.; Canesi, S. *Chem. Sci.*, **2013**, *4*, 1287.

15. Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y., *Angew. Chem. Int. Ed.* **2008**, *47*,3787.

16. Akai, S.; Kawashita, N.; Morita, N.; Nakamura, Y.; lio, K.; Kita, Y., *Heterocycles* **2002**, *58*, 75; Dohi, T.; Kita, Y., *Chem. Commun.* **2009**, 2073; Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J., 1. *Org. Chem.* **1996**, *61*, 5857.

17. Arisawa, M.; Utsumi, S.; Nakajima, M.; Ramesh, N. G.; Tohma, H.; Kita, Y., *Chem. Commun.* **1999**, 469; Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T., *Chem. Commun.* **1996**, 1481; Kita., Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S., *J. Am. Chem. Soc.* **1994**, *116*, 3684; Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y, *J Org. Chem.* **1998**, *63*, 7698.

18. Bérard, D.; Racicot, L.; Sabot, c.; Canesi, S., *Synlett.* **2008**, *1076*; Canesi, S.; Bouchu, D.; Ciufolini, M. A., *Angew. Chem. Int. Ed.* **2004**, *43*, 4336; Canesi, S.; Bouchu, D.; Ciufolini, M. A., *Angew. Chem.* **2004**, *116*, 4436.

19. Braun, N. A.; Bray, J.; Ousmer, M.; Peters, K.; Peters, E. M.; Bouchu, D.; Ciufolini, M. A., *J. Org. Chem.* **2000**, *65*, 4397; Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E. M., *Tetrahedron Lett.* **1998**, *39*, 4667; Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A., *Tetrahedron Lett.* **2002**, *43*, 5193; Canesi, S.; Bouchu, D.; Ciufolini, M. A., *Org. Lett.* **2005**, *7*, 175; Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S., *J. Org. Chem.* **1992**, *57*, 2135; Liang, H.; Ciufolini, M. A., *J. Org. Chem.* **2008**, 4299; Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A., *Org. Lett.* **2009**, *11*, 1539; Nicolaou, K. C.; Edmonds, D. J; Li, A.; Tria, G. S., *Angew. Chem.* **2007**, *119*, 4016; Ousmer, M.;

Braun, N. A.; Bavoux, c.; Perrin, M.; Ciufolini, M. A, *J. Am. Chem. Soc.* **2001**, *123*, 7534; Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A. M.; Miqueu, K.; Sotiropoulos, J M.; Quideau, S., *Angew. Chem. Int. Ed.* **2008**, *47*, 3552 ; Pouységu, L.; Marguerlt, M.; Gagnepain, J; Lyvinec, *G.;* Eatherton, A. J; Quideau. S., *Org. Lett.* **2008**, *10*, 5211; Quideau, S.; Pouységu, L.; Deffieux, D., *Synlett.* **2008**, 467; Quideau, S.; Pouységu, L.; Looney, M. A., *J Org. Chem.* **1998**, *63*, 9597; Zhdankin, V. V.; Stang, P. J, Chem. Rev. **2008**, *108*, 5299.

20. Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D., *Synthesis* **2007**, *24*, 3759 ; Ciufolini, M. A.; Canesi, S.; Ousmer, M.; Braun, N. *A., Tetrahedron* **2006**, *62*, 5318.

21. Drutu, 1.; Njardarson, J. T.; Wood, J L., *Org. Lett.* **2002**, *4*, 493; Ozanne-Beaudenon, A; Quideau, S., *Angew. Chem. Int. Ed.* **2005**, *44*, 7065; Pelter, A.; Drake, R. A., *Tetrahedron Lett.* **1988**, *29*, 4181; Quideau, S.; Looney, M. A.; Pouységu, 1., *Org. Lett.* **1999**, *l*, 1651; Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; OzanneBeaudenon, A.; Bufeteau, T; Cavagnat, D.; Chenede, A., *Angew. Chem. Int. Ed.* **2009**, *48*, 4605; Quideau, S.; Pouységu, 1.; Oxoby, M.; Looney, M. A., *Tetrahedron* **2001**, *57*, 319; Scheffler, G.; Seike, H.; Sorensen, E. I., *Angew. Chem. Int. Ed.* **2000**, *39*, 4593.

22. Giroux, M. A.; Guérard, K. *C.;* Beaulieu, M. A.; Sabot, c.; Canesi, S., *Eur. J. Org. Chem.* **2009**, 3871.

23. Lewis, N.; Wallbank, P., Synthesis 1987, 1103; Pelter, A.; Elgendy, S., *Tetrahedron Lett.* **1988**, *29*, 677.

24. Tamura, Y.; Yakura, T; Haruta, J. 1.; Kita, K., *J. Org. Chem.* **1987**, *52*, 3927.

25. Wells, G.; Berry, 1. M.; Bradshaw, T D.; Burger, A. M.; Seaton, A.; Wang, B.; Westwell, A. D.; Stevens, M. F. G., *J. Med. Chem.* **2003**, *46*, 532; Zawada, P. V.; Banfield, S. *C.;* Kerr, M. A., *Synlett.* **2003**, 971.

26. Kita, Y.; Tohma, H.; Kikuchi, K.; Iilagaki, M.; Yakuni, T., *J. Org. Chem.* **1991**, *56*, 435.

27. Traynham, J. G. *Chemical Rev.* **1979**, *79*, 323.

28. Moodie, R. B.; Schofield, K. *Acc. Chem. Res.***1976**, *9*, 287.

29. (a) Jeffs, W.; Capps, T. M.; Johnson, D. B.; Karle, J. M.; Martin, N. H.; Rauckman, B. *J. Org. Chem.* **1974**, *39*, 2703. (b) Sanchez, I. H.; Larraza, M. I.; Flores, H. J.; Rojas, I.; Alcala, R. *Synth. Commun.* **1983**, *13*, 35. (c) Jeffs, P. W.; Karle, J. M.; Martin, N. H. *Phytochemistry* **1978**, *17*, 719. (d) Gaffney, C. D. Dissertation, University of Johannesburg, **2008**.

30. Huisgen, R. *Angew. Chem. internat. Edit.* **1963**, *2*, 565.

31. (a) F. Caramella and P. Grunanger, 1,3-Dipolar Cycloaddition Chemistry, ed. A. Padwa, Wiley-Intersciences, New York, NY, **1984**, p. 291; (b) V. Jager and P. A. Colinas, Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, ed. A. Padwa and W. H. Pearson, John Wiley and Sons, New Jersey, NJ, 2003, 361.

32. Zhou, G.; Corey. E. J. *J. Am. Chem. Soc.* **2005**, *127*, 11958-11959.

33. Creasey, W. A. *in Monoterpenoid Indole Alkaloids, Supplement to Vol. 25, Part 4* (Ed.: J. E. Saxton), Wiley, New York, **1994**, 715.

34. Buckingham, J. *Bitter Nemensis.* The Intimate History of Strychnine, CRC, Boca Raton, FL, **2008**.

35. Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749.

36. a) P. J. Pelletier, J. B. Caventou, *Ann. Chim. Phys.* **1818**, *8*, 323; b) P. J. Pelletier, J. B. Caventou, *Ann. Chim. Phys.* **1819**, *10*, 142.

37. Cannon, J. S.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 4288.

38. S. I. Heimberger, A. I. Scott, *J. Chem. Soc. Chem. Commun.* **1973**, 217 – 218.

39. C. Schlatter, E. E. Waldner, H. Schmid, W. Maier, D. Gröger, *Helv. Chim. Acta* **1969**, *52*, 776 – 789.

40. Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403. (c) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293. (d) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490. (e) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685. (f) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9427. (g) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 395. (h) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**,

123, 8003. (i) Eichberg, M. J.; Dorta, R. L.; Lamottke, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *2*, 2479. (j) Nakanishi, M.; Mori, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1934. (k) Bodwell, G. J.; Li, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3261. (l) Ohshima, T.; Xu, Y.; Takita, R.; Shimuzu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546. (m) Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 10246. (n) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, 9, 279. (o) Sirasani, G.; Paul, T.; Dougherty, W. Jr.; Kassel, S.; Andrade, R. B. *J. Org. Chem.* **2010**, *75*, 3529. (p) Beemelmanns, C.; Reissig, H. U. *Angew. Chem., Int. Ed.* **2010**, *49*, 8021. (q) Martin, D. B. C.; Vanderwal, C. D. *Chem. Sci.* **2011**, *2*, 649. (r) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 185. (s) Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455. (t) Mori, M. *Heterocycles* **2010**, *81*, 259. (u) Furst, L.; Stephenson, C. R. *J. Nat. Chem. Biol.* **2011**, *7*, 582. (v) Beemelmanns, C.; Reissig, H.-U. *Chem. Soc. Rev.* **2011**, *40*, 2199. (w) Martin, D. B. C.; Nguyen, L. Q.; Vanderwal, C. D. *J. Org. Chem.* **2012**, *77*, 17.

41. a) R. B. Herbert in *Monoterpenoid Indole Alkaloids, Supplement to Vol. 25*, Part 4 (Ed.: J. E. Saxton), Wiley, New York, **1994**, pp. 1 – 13; b) J. Sapi, G. Massiot in *Monoterpenoid Indole Alkaloids, Supplement to Vol. 25*, Part 4 (Ed.: J. E. Saxton), Wiley, New York, **1994**, pp. 279 – 356. [19] a) N. G. Bisset in Indole *and Biogenetically Related Alkaloids* (Eds.: J. D. Phillipson, M. H. Zenk), Academic Press, London, **1980**, pp. 27 – 61; b) M. V. Kisak_rek, A. J. M. Leeuwenberg,M. Hesse in *Alkaloids: Chemical and Biological Perspecitves*, Vol. 1 (Ed.: S.W. Pelletier), Wiley, New York, **1983**, pp. 211 – 376; c) Atta-ur-Rahman, A. Basha in *Biosynthesis of Indole Alkaloids*, Clarendon Press, Oxford, **1983**, pp. 45 – 93; d) P. M. Dewick in *Medicinal Natural Products. A Biosynthetic Approach*, Wiley, Chichester, **1998**, pp. 324 – 334.

42. Gu, Q.; You, S. L. *Chem. Sci.*, **2011**, *2*, 1519.