UNIVERSITÉ DU QUÉBEC À MONTRÉAL

RÉACTION DE PRINS-PINACOL OXYDATIVE ET SYNTHÈSE ASYMÉTRIQUE DE LA FORTUCINE

THÈSE

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SCHÉMA

LISTE DES ABRÉVIATIONS, SIGLES ET ACRONYMES

Å	Angström
$A^{1,2}$	Tensions 1,2-allyliques
$A^{1,3}$	Tensions 1,3-allyliques
Ac	Acétyle
AcO^-	Ion acétate
Ac_2O	Anhydride acétique
AcOH	Acide acétique
AcOEt	Acétate d'éthyle
$AgNO_3$	Nitrate d'argent
AIBN	Azobisisobutyronitrile
aq.	Aqueux
Ar	Aryle
BF_3•OEt	Trifluorure de bore éthérate
Bn	Benzyle
Br	Brome
BuLi	Butyl lithium
Bu_3SnH	hydrure de tributylétain
Bu^t	Tert-butyle
Calcd	Calculé
Cat.	Catalytique
CD	Dichroïsme circulaire
$CDCl_3$	Chloroforme deutéré
CDI	*1,1'*-Carbonyldiimidazole
CH_3CN	Acétonitrile
$CHCl_3$	Chloroforme
Cl	Chlore
Cl^-	Chlorure

CO_2	Dioxyde de carbone
CO_2Me	Alcanoate de méthyle
$CuCl_2$	Chlorure de cuivre(II)
$Cu(OAc)_2$	Acétate de cuivre(II)
Cu(OTf)	Trifluorométhanesulfonate de cuivre
DBU	1,8-diazabicyclo[5.4.0]undéc-7-ène
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCM	Dichlorométhane
DIB	(Diacétoxy)iodobenzène
DIBAL-H	Hydrure de Diisobutylaluminium
DMAP	Dimethylaminopyridine
DMF	Diméthylformamide
DMP	Dess-Martin périodinane
DMSO	Diméthylsulfoxyde
DMTSF	Diméthyl(méthylthio)sulfonium tétrafluoroborate
dr	excès diastéréomérique
DRX	Diffractométrie des rayons X
E (E^+)	Électrophile
e^-	Électron
ee	Excès énantiomérique
ent	Énantiomère
RSE	Résonance de spin électronique
Et	Éthyle
Et_3N	Triéthylamine
EtOH	Éthanol
EtOAc	Acétate d'éthyle
ESI	Ionisation par électronébuliseur
Et_2O	Éther diéthylique
$FeSO_4$	Sulfate ferreux
H	Hydrogène

HBF_4	Acide tétrafluoroborique
HIO_4	Acide periodique
H_2O	Eau
H_2O_2	Peroxyde d'hydrogène
HFIP	Hexafluoroisopropanol
HMPA	Hexaméthylphosphoramide
HOBt	Hydroxybenzotriazole
HRMS	Sprectroscopie de Masse Haute Résolution
$HSiEt_3$	Triéthylsilane
Hz	Hertz
hυ	lumière (photochimie)
I_2	Diiode
IBX	acide 2-iodoxybenzoïque
IR	Infrarouge
K_2CO_3	Carbonate de potassium
KOH	Hydroxyde de potassium
$LiBH_4$	Borohydrure de lithium
LiI	Iodure de lithium
LiOOH	Hydroperoxyde de lithium
LDA	Diisopropylamidure de lithium
LN	Naphtalénide de lithium
LRMS	Sprectroscopie de Masse Basse Résolution
Me	Méthyle
MeMgBr	Bromure de méthylmagnésium
MeNHOMe	*N,O*-Diméthylhydroxylamine
MeOH	Méthanol
m-CPBA	Acide métachloroperbenzoïque
$MgSO_4$	Sulfate de magnésium
MHz	Mégahertz
$NaBH_4$	Borohydrure de sodium

n-Bu	Groupe linéraire butyle
n-Dec	Groupe linéaire décanyle
n-hexane	Alcane linéraire hexane
Na_2CO_3	Carbonate de sodium
$NaHCO_3$	Hydrogénocarbonate de sodium
$NaIO_4$	Periodate de sodium
Na_2SO_4	Sulfate de sodium
$Na_2S_2O_3$	Thiosulfate de sodium
NHC	Carbène hétérocyclique azoté
NH_4Cl	Chlorure d'ammonium
NSO_2R	Sulfonamide
Nu (Nu^-)	Nucléophile
o	*Ortho*
O_3	Ozone
Ortho Ns-Cl	Chlorure de 2-nitrobenzènesulfonyle
p	*Para*
PCC	chlorochromate de pyridinium
$Pd(PPh_3)_4$	Tétrakis(triphénylphosphine)palladium(0)
Ph	Phényle
PhI=NTs	(*N*-(*p*-toluènesulfonyl)imino)phényliodinane
PhIO	iodosobenzène
$PhI(OAc)_2$	Diacétoxyiodobenzène (DIB)
PIFA	Bis(trifluoracétoxy)iodobenzène
PhSH	Thiophénol
Pyr	Pyridine
R	Groupe alkyle
rt	Température ambiante
RMN	Résonance Magnétique Nucléaire
sat.	Saturée
SET	Transfert monoélectronique

SmI_2	Iodure de Samarium(II)
S_NAr	Substitution nucléophile aromatique
$SnCl_4$	Chlorure d'étain(IV)
$SOCl_2$	Chlorure de thionyle
sp^2	Hybridation sp^2
TBAF	Fluorure de tetrabutylammonium
TBDMSCl	Chlorure de *tert*-butyldiméthylsilyle
TBS	*Tert*-butyldiméthylsilyle
TBS-OTf	Trifluorométhanesulfonate de tert-butyldiméthylsilyle
t-Bu	*Tert*-butyle
TFA	Acide trifluoroacétique
TFE	Trifluoroéthanol
THF	Tétrahydrofurane
TIPS	Triisopropylsilyle
TIPSCl	Chlorure de triisopropylsilyle
TLC	Chromatographie sur couche mince
tp	Température ambiante
UV	Ultraviolet-Visible
w/w	Pourcentage massique
X-Ray	Diffractométrie des rayons X
π^*	Orbitale π^*
υ	Nombre d'onde
α	Position α
$[\alpha]_D^{20}$	Activité optique
β	Position β

RÉSUMÉ

Un nouveau procédé oxydatif tandem de la réaction de Prins-pinacol a été mis au point. La version *umpolung* aromatique de cette transformation a été développée à partir de phénols simples suivant un processus oxydatif impliquant l'utilisation d'un réactif à base d'iode hypervalent. Cette méthode a permis l'élaboration de systèmes compacts et polyfonctionnalisés de type spiro[4.5]décanyl contenant des centres quaternaires reliés à des carbones sp^2 à partir de simples phénols peu chers et rapidement accessibles. Les limites de la réaction ont été étudiées en utilisant des phénols contenant des alcènes et des alcynes plus ou moins encombrés. La stéréosélectivité de la transformation a aussi été étudiée à partir de phénols contenant déjà un centre asymétrique tertiaire ou quaternaire contrôlé. Enfin, l'application de ce procédé en synthèse de produits naturels a aussi été démontrée. En effet, la synthèse du squelette principal de la (-)-platensimycine, un antibiotique prometteur contre les staphylocoques dorés multirésistants, a été effectuée en appliquant cette méthodologie. Une fragmentation de type Schreiber-Fenton a aussi été employée afin de mettre en place le squelette désiré.

Dans le but de démontrer la versatilité synthétique associée aux transformations que peuvent permettre les réactifs à base d'iode hypervalent, la synthèse totale asymétrique de la fortucine a été effectuée. Cette molécule aurait des propriétés antivirales et antitumorales. La synthèse proposée met à profit la méthodologie de Wipf en utilisant le protocole de désaromatisation oxydante de Kita à partir d'un dérivé de la *L*-tyrosine. Cela a permis la formation, de façon hautement diastéréosélective, du squelette aza-bicyclique requis pour la suite de la synthèse. Une seconde étape clé consiste en l'élaboration du tétracycle pyrrolo[*d,e*]phénanthridine de la molécule cible via une carbopalladation de type Heck. Ensuite, dans le but de retirer l'acide carboxylique introduit en début de synthèse par la *L*-tyrosine pour contrôler la diastéréosélectivité des étapes subséquentes, le protocole de Boto, Hernandez et Suarez a été appliqué. Il s'agit à nouveau d'une méthode faisant intervenir la chimie de l'iode hypervalent. Enfin, dans le but de procéder à la migration de la double liaison, la stratégie de Zard a été exécutée en appliquant un procédé de type Julia-Lythgoe. Cette première synthèse asymétrique a permis de corriger la configuration absolue du produit naturel.

ABSTRACT

A novel oxidative Prins-pinacol tandem process has been developed. The *aromatic ring umpolung* version of this transformation has been achieved from cheap and readily accessible phenols following their oxidative activation by a hypervalent iodine reagent. This method allows the efficient construction of some very compact and highly functionalized scaffolds of spiro[4.5]decanyl type which bears quaternary centers connected to several sp^2 carbon centers. The scope of this transformation has been studied using phenols containing alkenes and alkynes more or less hindered. The stereoselectivity of this transformation has also been studied using phenols that already carry a controlled asymmetric center through a tertiary or a quaternary carbon center. Moreover, the application of this process in natural products synthesis has been demonstrated. Indeed, the formal synthesis of (-)-platensimycin, a novel class of antibiotic against multiresistant *Staphylococcus aureus*, has been accomplished using this methodology. A Schreiber-Fenton type fragmentation has also been employed in order to construct the desired cage compound.

In order to show the synthetic versatility of hypervalent iodine chemistry, the first asymmetric total synthesis of fortucine has been achieved. This molecule has already shown some antiviral and antitumoral activities. The herein proposed synthesis puts forward the Wipf's methodology concerning oxydative dearomatization using Kita's protocol from a *L*-tyrosine derivative. This allows the formation, in a highly diastereoselective way, of the aza-bicyclic system requisite for the subsequent steps. A second key step consists in the elaboration of the pyrrolo[*d,e*]phénanthridine tetracyclic core of the target molecule via a Heck-type carbopalladation. Furthermore, in order to remove the carboxylic acid moiety previously introduced through *L*-tyrosine that has controlled the diastereoselectivity of the synthesis, a Boto, Hernandez and Suarez's oxidative decarboxylation protocol has been used. Once again, this method involves hypervalent iodine chemistry. Finally, following Zard's strategy, the double bond migration has been done through a Julia-type process. In addition, this work has enabled to reassign the absolute configuration of the natural product.

INTRODUCTION

1. L'iode hypervalent en synthèse

Encore aujourd'hui, la synthèse totale de produits naturels et de dérivés bioactifs représente une des solutions afin de combattre plusieurs maladies. Parmi les molécules cibles, certaines sont très compactes et ne contiennent pas beaucoup d'hétéroatomes. Pour mettre en place ces architectures complexes, la chimie organique a fourni plusieurs outils permettant de créer les liens clés qui composent ces molécules. Parmi les méthodes connues, on retrouve celles qui impliquent l'utilisation de métaux lourds comme le palladium, le mercure, le plomb, etc. Ceux-ci peuvent être coûteux, toxiques et nocifs pour l'environnement. Voilà pourquoi plusieurs chercheurs tentent de mettre au point de nouvelles méthodologies de synthèse qui cadreraient davantage avec le développement durable. À cet effet, parmi les alternatives connues, l'utilisation de réactifs à base d'iode hypervalent constitue une solution viable qui gagne à être connue[1-2]. Mis à part le periodate de sodium ($NaIO_4$) ou l'acide periodique (HIO_4) permettant d'effectuer des clivages de diols vicinaux selon la procédure de Malaprade[3], des exemples bien connus de réactifs à base d'iodes hypervalents sont déjà utilisés depuis plusieurs années (**Figure 1**).

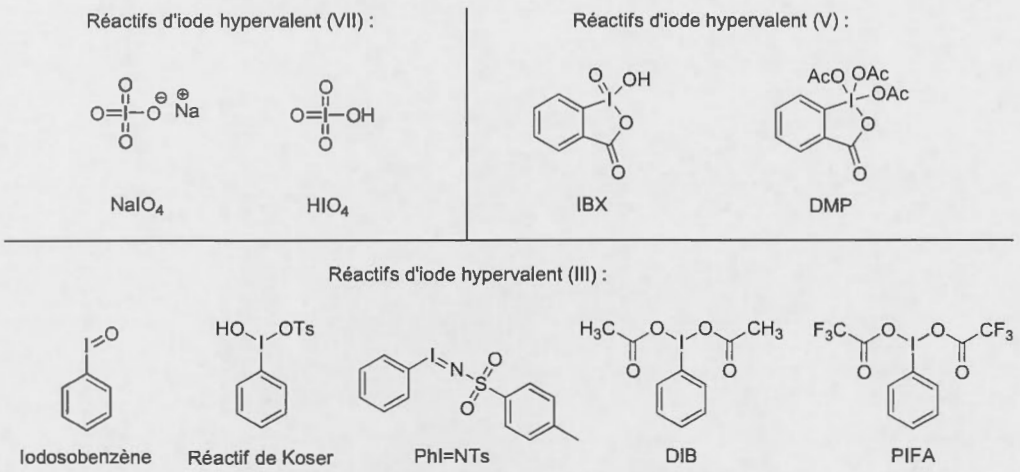

Figure 1: Réactifs à base d'iode hypervalent

Le periodinane de Dess Martin (DMP) est très utilisé pour oxyder des alcools en aldéhydes ou en cétones sous des conditions douces. L'acide 2-iodoxybenzoïque (IBX), encore plus doux, est aussi couramment utilisé. Par exemple, en 2000, Nicolaou a mis au point un procédé efficace permettant de former, en une étape, des cétones α,β-insaturées à partir d'alcools saturés, de cétones et d'aldéhydes en présence d'IBX[4] (**Schéma 1**). De nombreuses transformations impliquant des réactifs d'iode hypervalent (III) sont aussi venues outiller les chimistes de synthèse. Dans les années 1980, plusieurs méthodes d'α-oxygénation de cétones ou de leurs dérivés silylés ont été mises au point en utilisant un réactif d'iode hypervalent tel que le réactif de Koser ou l'iodosobenzène[5, 6]. En 2005, Ochiai a aussi proposé un procédé catalytique permettant d'effectuer des α-acétoxylations de cétones en utilisant *m-CPBA* comme co-oxydant de l'iodobenzène[7]. S'ajoutant à ces transformations, la chimie de l'iode hypervalent a aussi été employée pour la formation de liens carbone-carbone dans des réactions de couplage. Par exemple, en 1989, Zhdankin propose un procédé permettant le couplage entre des éthers d'énols silylés et différents nucléophiles carbonés (cyclohexène, allyltriméthylsilane, etc.) en utilisant un complexe d'iode hypervalent hautement électrophile ($PhIO/HBF_4$)[8]. Un procédé d'α-arylation chirale de cyclohexanones a aussi été proposé en 2005 par le groupe d'Aggarwal[9]. De plus, des méthodes d'aziridinations énantiosélectives

d'oléfines ont été développées à partir de PhI=NTs par Evans et Jacobsen[10, 11]. Des réactions de couplage biarylique et des procédés radicalaires basés sur l'utilisation de réactifs d'iode hypervalent ont aussi été appliqués en synthèse[12, 13]. Enfin, parmi les nombreux exemples démontrant l'utilité de tels réactifs à base d'iode hypervalent, la désaromatisation oxydative des phénols est l'une de celles qui a le plus retenu l'attention des chimistes de synthèse. À ce propos, en 1987, le groupe de Kita a proposé un procédé d'oxydation de phénols en présence de PIFA. Cette procédure simple a permis la formation de dérivés de *p*-benzoquinone et de spirolactones, des intermédiaires clés en synthèse de nombreux produits naturels[14].

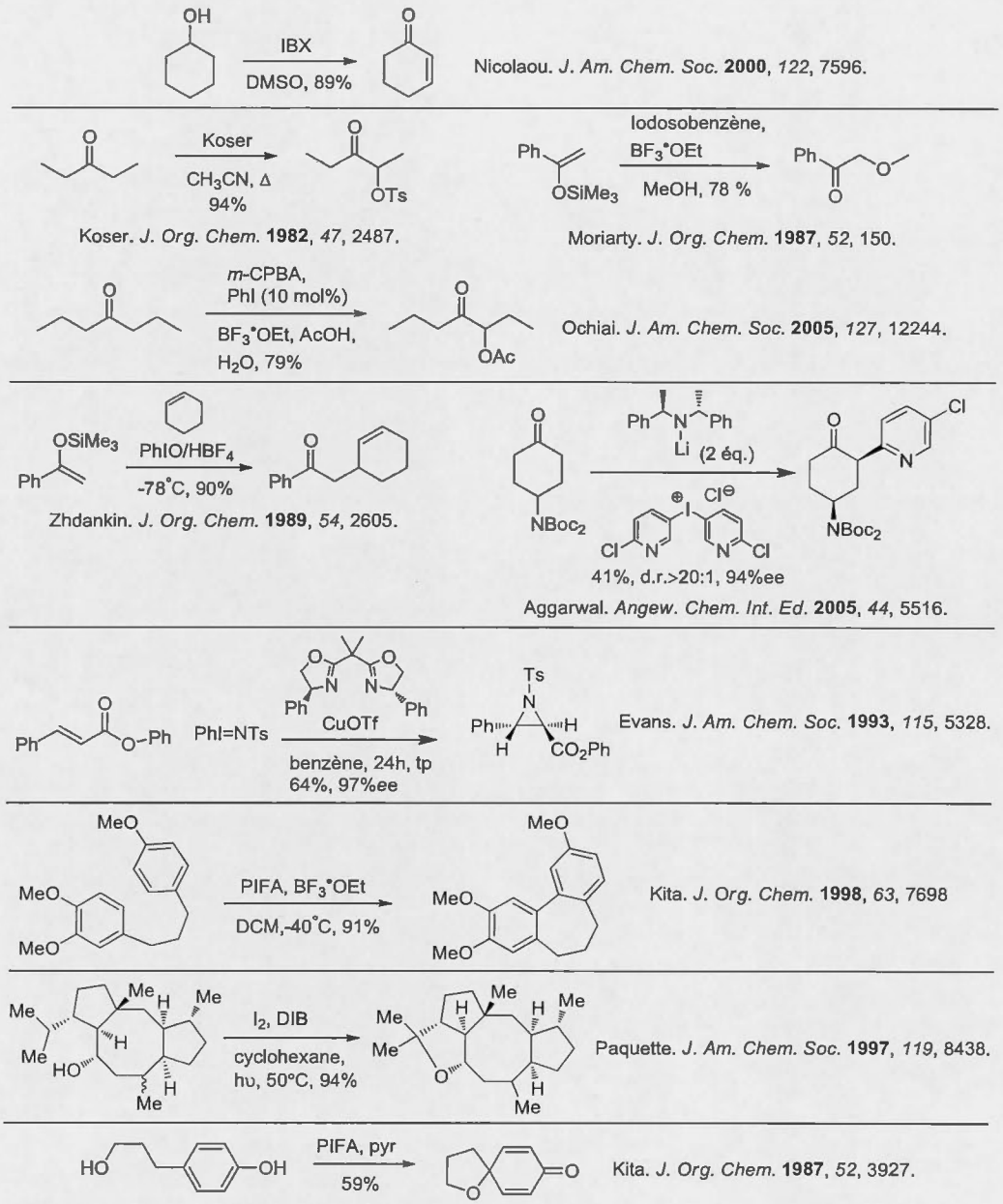

Schéma 1: Exemples de transformations utilisant l'iode hypervalent

2. *Umpolung* classique et *Umpolung* aromatique

En synthèse, il peut s'avérer utile d'inverser la polarité naturelle des espèces mises en jeu lors d'une réaction chimique. Par exemple, si l'atome de carbone d'un aldéhyde est chargé négativement, c'est que celui-ci, naturellement électrophile, a subi une inversion de polarité. L'espèce formée peut alors réagir à titre de nucléophile avec d'autres électrophiles. Des travaux publiés en 1975 par les chercheurs Seebach et Corey témoignent de la faisabilité d'une telle inversion de la réactivité naturelle des aldéhydes[15]. En effet, l'aldéhyde électrophile **1** est d'abord protégé sous forme de dithiane **2** (**Schéma 2**). Ensuite, en traitant ce dernier avec une base forte telle que le butyl-lithium, une déprotonation se produit et cela génère le carbanion **3**, maintenant nucléophile. Ce dernier peut alors attaquer un électrophile pour donner le produit **4**. C'est le principe de l'*umpolung* (inversion de polarité en allemand) classique.

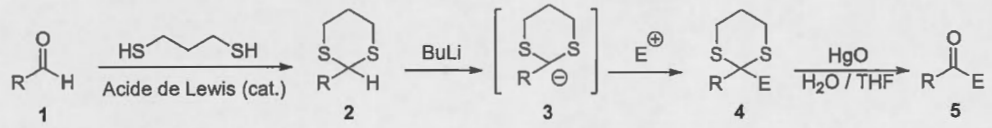

Schéma 2: *Umpolung* de Seebach et Corey

Des réactions très connues utilisent ce principe. La condensation benzoïne, découverte dans les années 1830, en est un bon exemple et consiste en une addition 1,2 du carbanion du benzaldéhyde sur une autre molécule de benzaldéhyde pour former la benzoïne. Plus de 140 ans plus tard, la réaction de Stetter permet de réaliser des additions 1,4 conjuguées de Michael à partir d'aldéhydes **6** ayant subi une activation *umpolung* catalysée au cyanure ou par des sels de thiazoliums **8**[16](**Schéma 3**). Plusieurs améliorations considérables, notamment l'emploi de sels de triazolium (NHC) chiraux, ont été apportées à cette transformation afin de la rendre hautement stéréosélective. Cela a permis plusieurs applications en synthèse[17, 18].

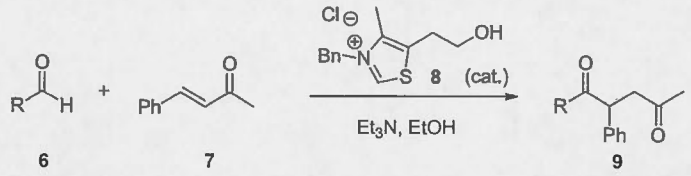

Schéma 3: Réaction de Stetter

Un autre exemple récent d'umpolung a été mis de l'avant par le groupe de Nicolaou lors de la synthèse de la (-)-platensimycine **12** (**Schéma 4**). En effet, à un stage avancé de la synthèse, le carbone de l'aldéhyde du produit **10** doit être connecté à l'énone de façon intramoléculaire. Pour ce faire, bien que la réaction de Stetter n'ait pas donné le résultat escompté selon l'auteur, l'activation *umpolung* au SmI_2 a permis d'obtenir le tricycle souhaité **11**[19].

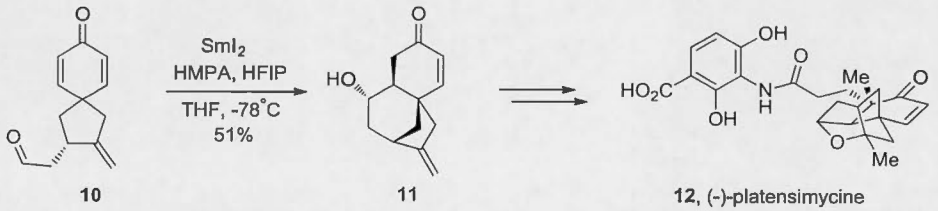

Schéma 4: Activation *umpolung* au SmI_2 en synthèse

Par analogie, le principe de l'*umpolung* aromatique consiste à renverser la réactivité naturelle d'espèces aromatiques riches en électrons afin de les rendre électrophiles. Étant électrodéficients, les réactifs à base d'iode hypervalent peuvent accomplir cette tâche suivant des échanges de ligands ou après des transferts monoélectroniques[20-31]. Ceci peut être réalisé sur des phénols[14, 29] ou des aryl-sulfonamides[30]. Une fois ces espèces oxydées, celles-ci peuvent maintenant réagir avec des nucléophiles. Cette activation *umpolung*, ou désaromatisation oxydative, est à la base de nombreuses stratégies de synthèse. L'utilisation de la chimie de l'iode hypervalent pour créer des liens carbone-carbone à partir de phénols a d'ailleurs suscité l'intérêt de plusieurs chercheurs ces dernières années[32-34].

Le groupe de Quideau propose trois mécanismes différents pour l'activation *umpolung* de phénols en utilisant des réactifs à base d'iode hypervalent[35] (**Schéma 5**).

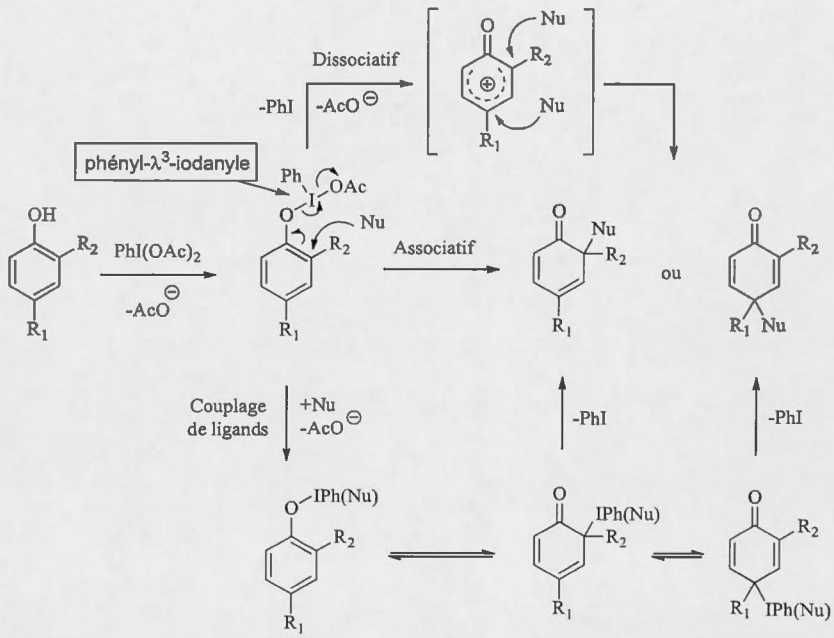

Schéma 5: Mécanismes d'activation *umpolung* de phénols à l'iode hypervalent

Ces trois propositions ont pour point commun la formation d'un intermédiaire de type phenyl-λ^3-iodanyle suite à un échange de ligand entre le phénol et l'iode hypervalent (ex : DIB). De plus, dans chacun des cas, la force motrice de la réaction consiste en la réduction du groupe phenyl-λ^3-iodanyle en iode monovalent (ex : iodobenzène). À ce niveau, trois possibilités sont envisageables. D'abord, un mécanisme par couplage de ligands pourrait être possible considérant le caractère pseudo-métallique et hypervalent des espèces mises en jeu. En effet, ces caractéristiques leur confèrent une qualité reconnue pour effectuer des réactions de couplage au même titre que d'autres composés organo-métalliques[36]. Un deuxième échange de ligand par un nucléophile externe pourrait ainsi permettre ce couplage de ligands conduisant aux espèces désaromatisées. Dans un autre ordre d'idées, il pourrait s'agir d'un

mécanisme associatif par lequel le départ du groupe phényl-λ^3-iodanyle se ferait de façon concertée avec l'entrée du nucléophile, ce qui s'apparenterait à un mécanisme de type S_N2'. Cependant, au niveau orbitalaire, cette réaction ne devrait pas se produire (**Schéma 6**).

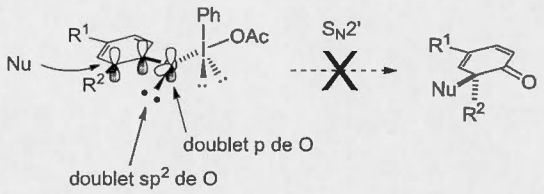

Schéma 6: Recouvrement orbitalaire impossible lors d'une S_N2'

Effectivement, puisque l'orbitale p de O se trouve à 90° de l'orbitale σ^*-sp^2 du nucléofuge, il ne peut y avoir de recouvrement orbitalaire adéquat lors de l'attaque du nucléophile. Peut-être qu'il s'agit alors d'un mécanisme de type S_N2' détendu, donc qui ne serait pas complètement associatif. En effet, un mécanisme dissociatif serait plus réaliste (**Schéma 5**). Ce dernier impliquerait d'abord le départ du groupe phényl-λ^3-iodanyle pour générer l'ion phénoxonium qui, par la suite, subirait l'attaque nucléophile en position *ortho* ou *para*. Étant donné le haut gain entropique des groupes partants de type phényl-λ^3-iodanyle, un tel mécanisme serait crédible. Aussi, il n'est pas rare de voir ces désaromatisations oxydatives se produire dans des solvants polaires perfluorés (HFIP, TFE), des conditions favorisant un mécanisme dissociatif. De plus, comme en témoignera ce document, ces conditions ont permis d'effectuer plusieurs transpositions cationiques (Wagner-Meerwein, Prins, Prins-pinacol, etc...), ce qui renforce l'hypothèse d'un mécanisme dissociatif dans les conditions utilisées. Enfin, considérant le caractère pseudo-métallique de l'iode, il est probable que le mécanisme réel impliquerait des réactions d'oxydo-réductions par transferts monoélectroniques (SET) sans nécessairement générer l'espèce phényl-λ^3-iodanyle de départ, notamment en présence de solvants protiques (**Schéma 7**). Le Pr. Kita a d'ailleurs démontré, par des analyses spectroscopiques UV et RSE, l'existence de radicaux cationiques obtenus par SET en oxydant, en utilisant du PIFA, des éthers phénoliques *para*-substitués dans le HFIP[37]. D'abord, le phénol **13** subirait le premier SET, ce qui génèrerait le radical cationique

14. Ce dernier se ferait déprotonner par un ion acétate relâché lors du SET pour donner le radical neutre **15**. Ensuite, un second SET surviendrait et générerait l'ion phénoxonium **16**. Ce faisant, l'iode retrouverait son état d'oxydation naturel (I) en formant l'iodobenzène, ce qui serait la force motrice de la réaction. La charge positive de l'ion phénoxonium peut être délocalisée dans le cycle via deux autres formes limites de résonnance (**17** et **18**).

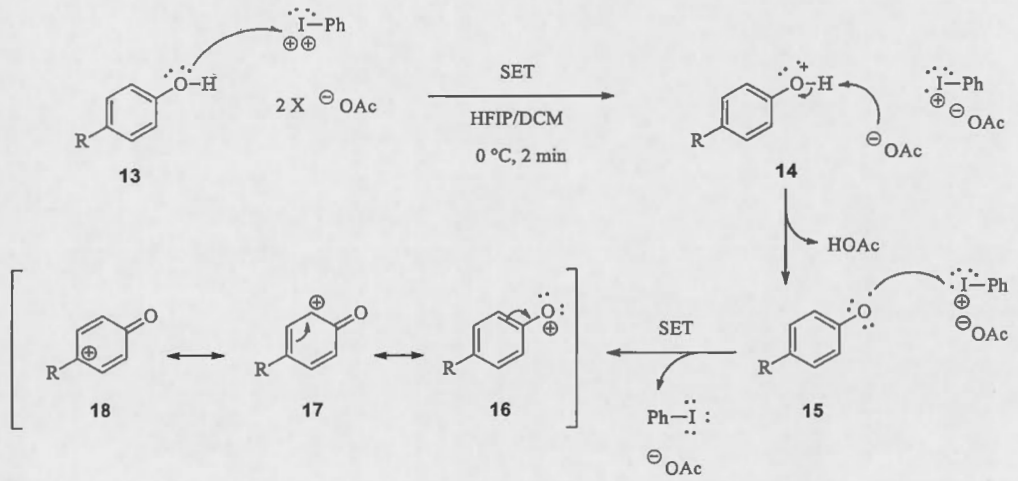

Schéma 7: Mécanisme d'oxydation de phénols à l'iode hypervalent par SET

Donc, lorsque des espèces aromatiques riches en électrons telles que des phénols **19** (ou aryl-sulfonamides) sont ainsi oxydés en présence de réactifs à base d'iode hypervalent, leur réactivité naturelle s'inverse (**Schéma 8**). C'est le concept de l'*umpolung* aromatique. Globalement, étant riches en électrons au départ, ces espèces réagissent normalement avec des électrophiles, comme c'est le cas lors d'une réaction de type Friedel-Crafts. Cependant, après une activation oxydative à l'iode hypervalent, ces espèces génèreraient un ion phénoxonium (ou phénoximinium) **20** hautement électrophile. Celui-ci peut donc maintenant réagir en tant qu'électrophile avec plusieurs types de nucléophiles. L'attaque peut survenir en position *ortho* ou *para* selon la nature du nucléophile utilisé. Si un nucléophile externe plus encombré est mis en jeu lors de l'activation umpolung, comme un nucléophile carboné, l'attaque survient surtout en position *ortho*, sans doute parce que celle-ci est plus dégagée

d'un point de vue stérique. Ceci donne lieu à la formation du produit **21** normalement obtenu lors d'une réaction de type Friedel-Crafts. Toutefois, si le nucléophile est faiblement encombré, la position *para* est favorisée, fort probablement parce que celle-ci correspond à la position où la charge positive est la plus stable, donc la moins exigeante en énergie à l'état de transition. Ce faisant, il y a formation d'un squelette hautement fonctionnalisé **22** contenant un carbone tétrasubstitué connecté à au moins deux centres sp^2 ainsi qu'une diénone prochirale hautement fonctionnalisable. Ceci fait de cet intermédiaire un excellent candidat pour la synthèse totale. Il est important de noter que, lorsque le nucléophile est délivré de façon intramoléculaire via un bras directeur porté par le groupement R, l'attaque se fera en position *para* pour donner le produit **23**, un squelette pouvant s'avérer intéressant en synthèse de produits naturels. En effet, de tels centres spiraniques sont présents dans de nombreuses molécules bioactives. C'est spécifiquement cet intermédiaire clé qui fera l'objet du présent document.

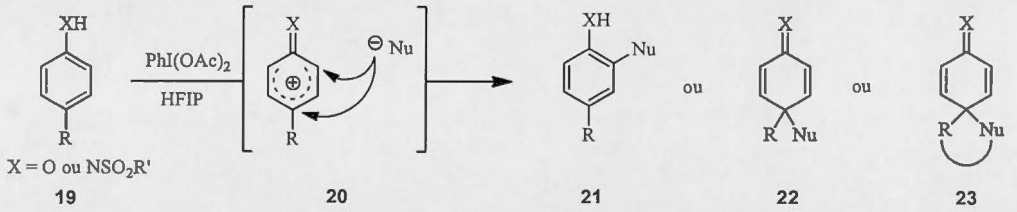

Schéma 8: Activation *umpolung* aromatique et régiosélectivité

Le Pr. Kita, pionnier dans ce domaine, a démontré qu'il était possible de réaliser ces réactions d'oxydations désaromatisantes en traitant des phénols au moyen de réactifs à base d'iode hypervalent. De plus, il a démontré que l'utilisation d'hexafluoroisopropanol (HFIP) comme solvant permettait la stabilisation de l'ion phénoxonium formé. En effet, l'ion phénoxonium constitue un intermédiaire instable qui peut réagir avec plusieurs nucléophiles présents dans le milieu, y compris le solvant. Afin de limiter la réactivité de cet intermédiaire instable au nucléophile désiré, l'ion phénoxonium doit être stabilisé par un solvant polaire, protique et non nucléophile, comme le HFIP ou le 2,2,2-trifluoroéthanol (TFE). Ainsi, en plus de stabiliser suffisamment l'ion phénoxonium pour lui donner le temps de vie nécessaire afin

que la réaction puisse avoir lieu, ce solvant n'effectue pas d'addition nucléophile. Cela permet donc au nucléophile souhaité de s'additionner afin d'obtenir le produit désiré[20-22, 30].

CHAPITRE I :

RÉACTION DE PRINS-PINACOL OXYDATIVE

1.1. Introduction

Les transpositions cationiques constituent depuis longtemps une avenue intéressante en synthèse de molécules complexes[38]. Les réarrangements de type Wagner-Meerwein sont au nombre des exemples les plus connus[39]. La réaction de Prins-pinacol fait aussi partie du lot et a été utilisée comme étape clé dans plusieurs synthèses totales de produits naturels. Le groupe de Overman a notamment utilisé cette transformation pour la synthèse énantiosélective de la (-)-magellanine[40] et de la shahamin K[41] (**Schéma 1.1**).

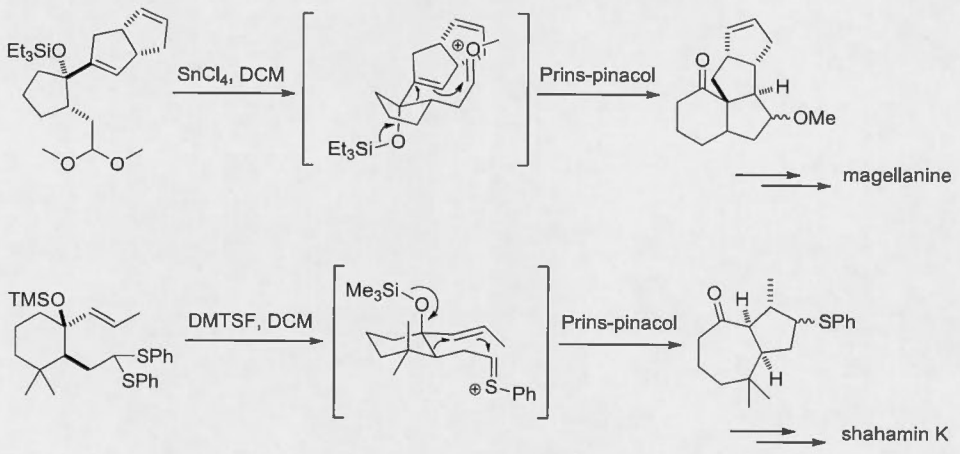

Schéma 1.1: Réaction de Prins-pinacol en synthèse de produits naturels

Sommairement, la réaction de Prins-pinacol est une combinaison de deux réactions en cascade, soit la réaction de Prins et un réarrangement pinacolique. En effet, suivant une activation appropriée au moyen d'un acide de Lewis ($SnCl_4$, DMTSF, etc.), l'ion oxonium (ou thiocarbénium) est piégé par une double liaison. C'est la "partie Prins" de la réaction. De façon concomitante, la stabilisation de la charge positive formée lors de la réaction de Prins

s'effectue via la rupture stéréospécifique du lien carbone-carbone périplanaire à l'orbitale π^* de la double liaison. Ce réarrangement cationique, au cours duquel s'effectue aussi la rupture de l'éther de silyle pour former la cétone correspondante, réfère à la "partie pinacol" de la réaction. Ce faisant, il se produit une élongation et une contraction de cycle de façon simultanée. Cette transformation a été utilisée en mode aliphatique par différents groupes de recherche pour synthétiser plusieurs molécules bioactives. Dans le présent document, la version *umpolung* aromatique de cette réaction sera décrite. En effet, suite à l'activation de phénols simples (**24** et **25**) en appliquant un processus oxydatif impliquant un réactif à base d'iode hypervalent, il a été possible de mettre au point la version *umpolung* aromatique de la réaction de Prins-pinacol (**Schéma 1.2**).

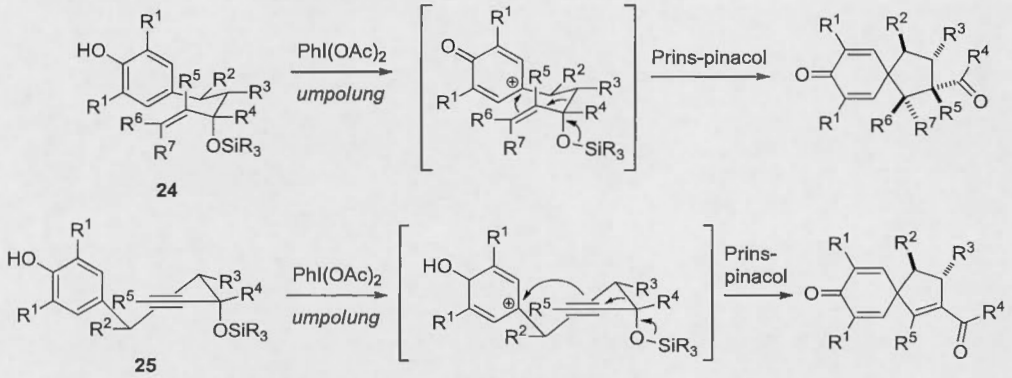

Schéma 1.2: Réaction de Prins-pinacol oxydative

Cette nouvelle méthodologie a non seulement été développée à partir de phénols **24** contenant des alcènes jouant le rôle de nucléophile, mais aussi à partir de phénols **25** comportant des alcynes. Dans le premier cas, l'état de transition serait de type chaise, alors que dans l'autre, il serait plutôt de type demi-chaise. Plusieurs exemples ont été réalisés dont certains avec des substrats très encombrés stériquement. En effet, un exemple avec un substrat contenant deux carbones quaternaires contigus a même été exécuté. De plus, la stéréosélectivité de la réaction a été étudiée en utilisant des phénols contenant déjà un centre asymétrique tertiaire ou quaternaire contrôlé. Il a alors été remarqué, par RMN^{19}F en employant la stratégie de

Mosher, que l'information chirale des produits de départ était, dans certains cas, totalement transmise aux produits finaux. Enfin, cette méthodologie a été appliquée à la synthèse formelle d'un antibiotique important, la (-)-platensimycine **12** (**Schéma 4**). Depuis sa découverte en 2006[42], cet antibiotique s'est révélé comme étant très efficace contre le staphylocoque doré. En effet, son mode d'action unique, par lequel il inhiberait la biosynthèse des acides gras de ces bactéries, a suscité l'intérêt de la communauté scientifique. En 2007, plusieurs chercheurs ont proposé différentes synthèses du système oxatétracyclique (composé cage) de cette molécule[43]. Toutefois, seuls Nicolaou et Ghosh ont réalisé la synthèse totale de cet antibiotique[44]. Afin de former le système spirobicyclique (**Schéma 1.3**), Nicolaou propose une cycloisomérisation de Trost en utilisant un catalyseur à base de ruthénium. Plus récemment, pour élaborer ce squelette, le même chercheur a proposé une alternative qui implique justement une désaromatisation oxydative en utilisant la chimie de l'iode hypervalent[19].

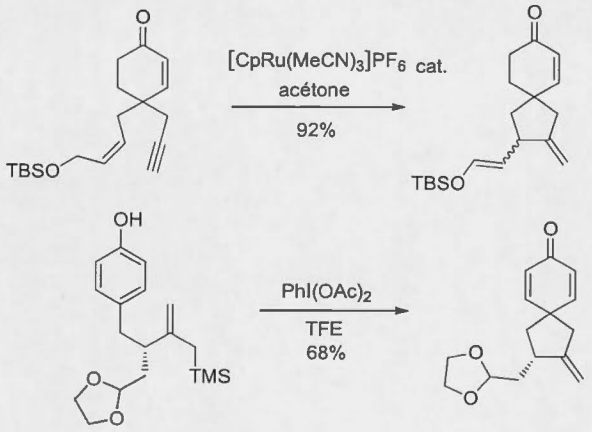

Schéma 1.3: Synthèses de la (-)-platensimycine de Nicolaou

La synthèse de ce système spirobicylcique a été effectuée en appliquant la méthodologie de Prins-pinacol oxydative. La synthèse formelle de cet antibiotique a donc été accomplie (**Schéma 1.4**).

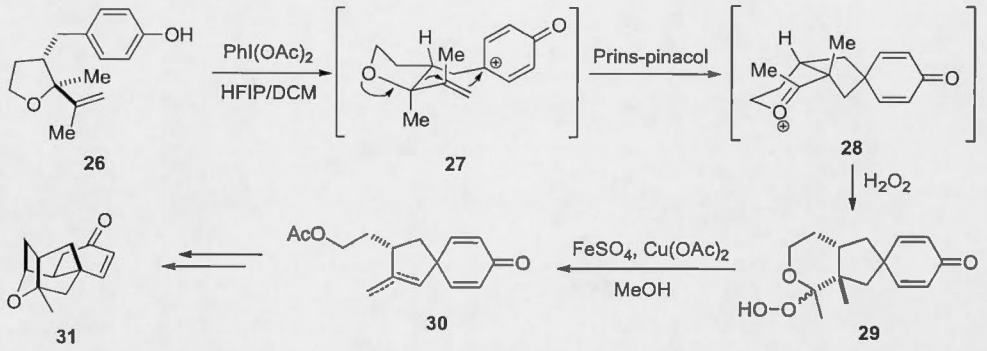

Schéma 1.4: Réaction de Prins-pinacol oxydative et son application à la synthèse de la (-)-platensimycine

Au cours de cette synthèse, le cycloéther *trans* **26** a été synthétisé de manière stéréosélective en utilisant la stratégie d'Evans. L'oxydation de ce dernier dans les conditions développées par Kita a permis d'effectuer le réarrangement de Prins-pinacol souhaité via l'état de transition présumé **27**. Ceci a généré l'intermédiaire cationique **28** qui, une fois traité par du peroxyde d'hydrogène, a donné l'hydroperoxycétal **29**. Ce dernier a subi une fragmentation de type Shreiber-Fenton, ce qui a permis d'obtenir le produit **30** sous forme d'un mélange 3:1 d'alcènes (exocyclique : endocyclique). Ce mélange a convergé vers un seul produit après quelques transformations et le composé cage **31** de la (-)-platensimycine a été obtenu.

1.2. "OXIDATIVE PRINS-PINACOL TANDEM PROCESS MEDIATED BY A HYPERVALENT IODINE REAGENT: SCOPE, LIMITATIONS, AND APPLICATIONS"
ARTICLE

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Auteurs: Marc-André Beaulieu, Kimiaka C. Guérard, Gaëtan Maertens, Cyrille Sabot et Sylvain Canesi*

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Oxidative Prins-Pinacol Tandem Process Mediated by a Hypervalent Iodine Reagent: Scope, Limitations, and Applications

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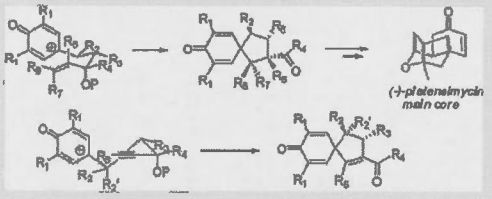
Supporting Information

ABSTRACT: An oxidative Prins-pinacol tandem process mediated by a hypervalent iodine reagent has been developed. This oxidative version of the famous tandem process fits within the concept of "aromatic ring umpolung" and allows the stereoselective transformation of simple phenols into highly elaborated spirocyclic dienone cores containing several quaternary carbon centers. The scope and the limitations of this process, including the study of its stereoselectivity, are described in this article. As a direct application of this stereoselective process, we describe the formal synthesis of (−)-platensimycin, an important antibiotic agent.



INTRODUCTION

Cationic molecular transpositions[1] provide an esthetically appealing route to complex molecular structures. A remarkable transformation of this type is the elegant Prins-pinacol tandem process; this method has been used as the key step in several total syntheses of natural products, as demonstrated by Overman and co-workers.[2] An extension of this aliphatic transformation to aromatic systems would open up several opportunities in chemical synthesis. Our interest in oxidative dearomatization of electron-rich aromatics[3] mediated by hypervalent iodine reagents[4−6] led us to question whether an analogous process could be initiated by oxidative activation. While electron-rich aromatic systems normally react as nucleophiles, oxidative activation converts them into highly electrophilic species, which may then be intercepted with appropriate nucleophiles. If one considers the behavior of intermediate 2, this reversal of reactivity may be thought of as involving "aromatic ring umpolung".[3,4d] Phenol dearomatization processes mediated by hypervalent iodine reagents such as (diacetoxyiodo)benzene (DIB), an environmentally benign reagent, are well-documented in the literature, and this has elicited substantial interest in the synthetic arena.[4−7] An indication of how the formation of the corresponding phenoxonium ion 2 can be efficiently achieved and sufficiently stabilized to be trapped by a nucleophile is well apparent in the work of Kita,[7] who has shown that such processes are best performed in solvents such as hexafluoroisopropanol (HFIP).[8] Extending the aromatic ring umpolung concept[9] to the famous Prins-pinacol transformation would allow the rapid conversion of simple and inexpensive cores, such as phenols, into more complex spirodienone architectures,[3i] while controlling the stereoselective formation of quaternary carbon centers, in a single step.[10] We assumed that during the umpolung activation, mediated by a single-electron transfer (SET), the phenoxonium ion 2 generated would be trapped via an oxidative Prins process by the double bond, possibly through a cydic chairlike transition state. This would be followed by a stereocontrolled ring contraction that should occur with retention of the configuration of the emerging quaternary carbon center (Figure 1).

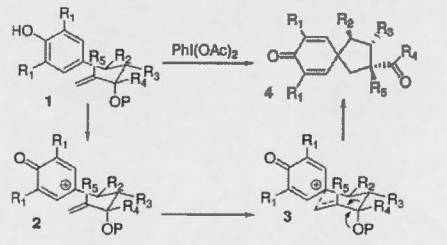


Figure 1. Presumed course of the oxidative Prins-pinacol tandem process.

Such spiro[4,5]decanyl scaffolds 4 are found in several natural products having interesting biological properties such as (+)-anhydro-β-rotunol 5,[11] an antifungal agent, (+)-dehydrosolanascone 6,[12] an antibacterial product resulting from a potential [2 + 2] cycloaddition process from 5, (−)-scopadulcic acid A 7,[13] an antiviral agent against herpes simplex virus type 1, and (+)-magellaninone 8,[14] a compound belonging to the lycopodium family[15] (Figure 2).

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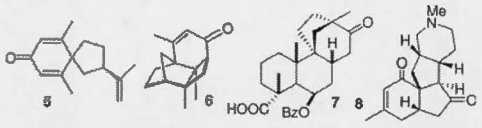


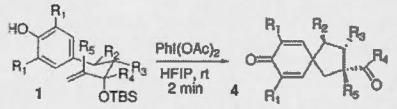
Figure 2. Natural products containing a spiro[4.5]decanyl core.

In this paper, we substantially extend the scope of the oxidative Prins-pinacol process to phenol derivatives containing allylic and propargylic alcohol moieties,[31] and we present an avenue for the stereoselective formation of tertiary and quaternary carbon centers. Furthermore, as a first application to this process, the synthesis of the known main cage of (−)-platensimycin, a novel important class of antibiotic agent is reported.

■ RESULTS AND DISCUSSION

We first investigated the scope and limitations of this process on different phenols 1 containing a terminal alkene as an internal nucleophile to trigger the oxidative Prins process followed by a semipinacol-type rearrangement to produce the main spirocyclic system 4. This reaction could be performed either in HFIP at room temperature or at −15 °C in an equal mixture of DCM/HFIP. To exemplify this transformation, different phenols substituted at any position on the lateral chain or at the *ortho*-positions were oxidized. A TBS moiety was first used as an alcohol protecting group in order to avoid the formation of the cyclic ether compound resulting from a direct attack by the alcohol on the phenoxonium ion 2 generated upon oxidation, as demonstrated by Kita and co-workers.[7] A summary of representative experiments appears in Table 1.

Table 1. Oxidative Prins-Pinacol Tandem Process of Olefinic Substrates



entry	R_1	R_2	R_3	R_4	R_5	yield (%)
a	H	H	H	Me	H	64
b	H	H	H	CH=CH$_2$	H	60
c	H	H	H	Ph	Me	58
d	H	H	H	Me	Me	68
e	Br	H	H	Me	Me	84
f	H	Me	H	Me	H	50
g	H	H	Me	Me	H	30
h	H	H	allyl	CH=CH$_2$	H	55

The anticipated ketones 4a–h emerged in good yields (up to 84%) and with very good diastereoselectivity, dictated by allylic strain interactions in the chairlike transition state (entries f–h), and only one other diastereoisomer was detectable by ^{1}H NMR (5–10%). This method produced compact polysubstituted scaffolds containing substituents located at any of the positions on the lateral chain. It should be noted that in the case of R_5 being an alkyl group, the reaction simultaneously produces two quaternary carbon atoms, one of which is also a spiro center. The presence of bromines in *ortho*-positions appears to lead to an increase of the global yield of this transformation. This may be explained by considering that the first intermediate is a highly delocalized carbonium ion, which can be represented by 2 (Figure 1, R_1 = Br) as one of its resonance structures. We believe that, because of the presence of the electron-withdrawing bromine atoms, 2 would be the dominant resonance form rather than the *ortho*-mesomer and thus would be less susceptible to a bimolecular attack by external nucleophiles at the *ortho*-position. As an additional advantage, the bromine atoms provide a handle for the introduction of other substituents, using transition metal chemistry. Compound 4g was obtained in a low 30% yield, about half of the yield recorded earlier for substrates without substituents in position 2 (R_3 = H). This result could shed light on the stereochemical course of the reaction: a 1:1 epimeric mixture of the tertiary alcohol moiety in 1g is oxidized, and it is possible that only one diastereoisomer, having minimal $A^{1,3}$ interactions, is a competent substrate for the requisite oxidative Prins-pinacol process. Indeed, the conformation of diastereomer 2g, which presumably undergoes reaction, is such that the OTBS group is subjected to minimal $A^{1,3}$ interaction with the "inside" vinylic hydrogen.[16] This contrast with diastereomer 2g′, where the allylic interaction is considerably more severe, due to the presence of a more sterically demanding methyl group in proximity to the same vinylic hydrogen. This interaction could slow the Prins step of diastereoisomer 2g′ and divert the reactive electrophilic species, created upon *umpolung* activation of the phenol, toward other reaction pathways. In either case, the major product of the reaction is *cis*-ketone 4g[17] (Scheme 1).

To support this hypothesis, compound 1h, containing an allyl substituent at position 2, was prepared. In this case, both vinyl groups at position 3 (R_4 = vinyl and R_5 = H) were able to trap the phenoxonium ion species, thus automatically placing the OTBS group in an axial position in the transition state 2h, to generate compound 4h in a 55% yield, comparable to that obtained with similar substrates.

This transformation is not restricted to the formation of ketones but can be extended to the formation of aldehydes from secondary allylic ethers. In this case, a protecting group more hindered than a TBS group must be used. Indeed, in the absence of a tertiary center, the phenoxonium ion, generated during umpolung activation, is more accessible to the oxygen atom and leads mainly to cycloether 10 via a five-membered ring, and only a small amount of the desired compound 12 was observed. In order to favor the 6-*endo* process, the secondary alcohol moiety was protected with the bulky TIPS protecting group. Moreover, the formation of aldehyde 12 required the use of PIFA (phenyliodine(III)bis(trifluoroacetate) instead of DIB, to prevent the formation of a mixed acetal, such as 15 in 43% yield. The formation of the latter resulted from the nucleophilic attack of an acetate ion, released upon umpolung activation, on intermediate 14. The presence of the less nucleophilic trifluoroacetate ligands on the hypervalent iodine complex (PIFA) allowed formation of the aldehyde 12 in 61% yield. It should be noted, however, that the mixed acetal function in 15 could be useful if a protected aldehyde is required in the synthesis (Scheme 2).

In order to broaden the scope and test the limitations of this transformation, we have also substituted the C-1 alkene position with two methyl groups.[9] This result suggests the potential for constructing highly hindered cores containing two contiguous quaternary carbon centers. Indeed, the elaboration of such challenging systems is often prevented by the steric hindrance of the first quaternary carbon center. During the

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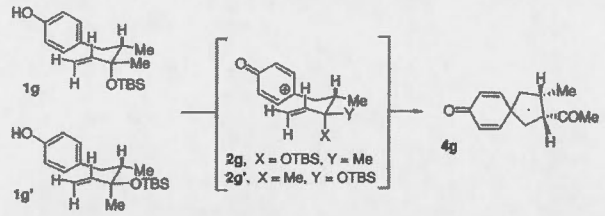
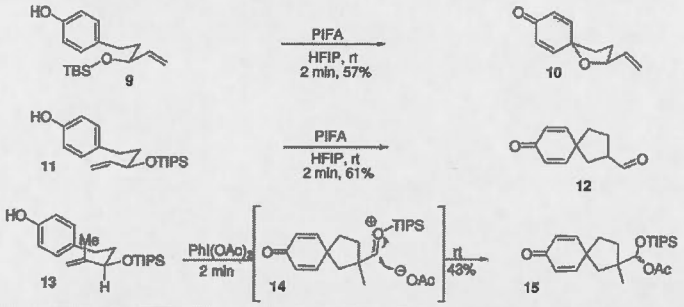
Scheme 1. $A^{1,3}$ Strain Interactions Involved during the Transition State of Compound 1g



Scheme 2. Formation of Aldehyde and Acetal Functionalities



oxidation of compound 16, the aldehyde 17 formed was not stable and further transformed into the corresponding tricyclic core 18 via a Michael addition on the dienone system mediated by the aldehyde functionality to produce hemiacetal 18 in 40% overall yield. It should be stressed that this is a one-pot multistep, stereoselective transformation producing a functionalized, highly congested tricyclic system 18 (Scheme 3).

Our next stage was to develop an enantioselective pathway enabling the formation of tertiary or quaternary carbon centers from an enantiopure (or an enantioenriched) substrate containing a stereogenic allylic alcohol functionality on the acyclic lateral chain, such as (+)-13.[18a] For this to be successful, the conformational equilibrium, involved during the chairlike transition state, had to be easily shifted to one conformer, considering all the possible $A^{1,2}$, $A^{1,3}$, and 1,3-diaxial steric interactions, as well as the stereoelectronic effects involved. Indeed, conformers 19 will lead stereoselectively, after a ring contraction, to the two opposite stereocenters of 20. In this case, the two conformers 19 and 19′ each have their own steric interactions, resulting in overall low enantioselectivity. Conformer 19′ has to accommodate $A^{1,3}$ and 1,3-diaxial steric interactions, whereas conformer 19 presents more severe $A^{1,2}$ interactions. The balance of these effects results in the formation of both enantiomers of compound 20 in 68% yield with low enantiomeric excess[19] (30%) (Scheme 4). Such a result suggests that, in principle, and depending on the protecting group used, the same enantiopure tertiary alcohol 13 could lead to an excess of either *R* or *S* compound 20. Indeed, an O-TBS version of (*R*)-13 that would favor conformer 19′ led to an excess of the opposite enantiomer (*R*)-20 with a similar ee.[19] To improve this enantioselectivity, we removed the mismatched steric $A^{1,2}$ interaction generated by the allylic methyl group and the smaller TBS protecting group was used. As a result, an enantioenriched form of compound (*R*)-1a (70% ee) was synthesized.[18b] During the umpolung activation, the two conformers 21 and 21′ can equilibrate, but the transition state originating from 21′ should be the most stable (Scheme 1). Compound (*R*)-4a was obtained with the same optical purity (70% ee)[19] as the starting material used, thus demonstrating the high reaction enantioselectivity in this case (Scheme 4).

In order to develop an efficient stereoselective route to compounds containing a quaternary carbon center, we resorted to a diastereoselective reaction where one transition state would be favored over the other. In the desired conformer 24, the set stereochemistry of the quaternary methyl group dictates the configuration of the emerging quaternary carbon center, such that chirality transfer takes place with retention of configuration (Scheme 5). Therefore, a *trans*-cycloether 23 was synthesized, and in this case, only the formation the bicyclic transition state 24 was permitted. The required tetrahydrofuran core 23, involving minimal $A^{1,2}$ interaction between the equatorial oxygen atom and the methyl group, and therefore presumably thermodynamically favored, was obtained by acid treatment of the mixture of triols 22 in 88% yield. The asymmetric version of 22 was assembled using Evans' asymmetric alkylation technology.[20] Umpolung activation of cycloether 23 led to the hemiketal 26 after the ring contraction, ring elongation process in 70% yield. Further treatment of the crude mixture of anomers 26 with Dess–Martin oxidation periodinate[21] led to keto-aldehyde 27 as a single diastereoisomer in 60% yield overall from compound 23. As anticipated, on the basis of our mechanistic hypothesis, compound 27 displayed a *cis*-relative configuration between the two carbonyl branches. It should be noted that, in this new process, we have efficiently created a pair of contiguous stereocenters, one tertiary and the other quaternary, with complete degree of stereocontrol, thus

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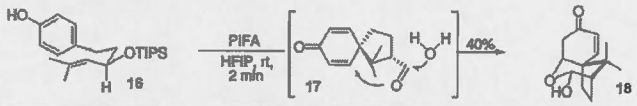
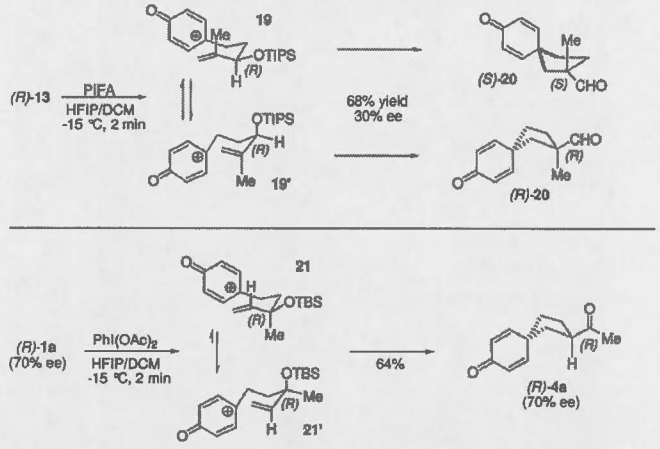
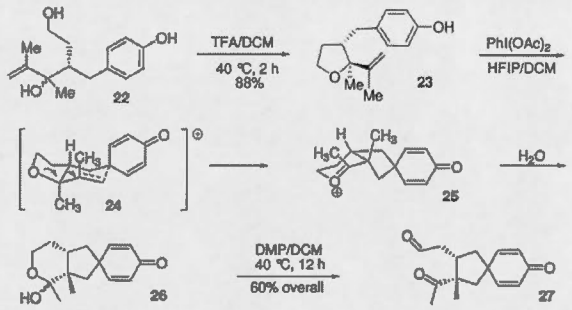
Scheme 3. Formation of Contiguous Quaternary Carbon Centers



Scheme 4. Stereoselectivity Issues Following the Conformational Equilibriums



Scheme 5. Efficient diastereoselective avenue for the formation of a quaternary carbon center



demonstrating the potential practical utility of this oxidative process in a diastereoselective pathway (Scheme 5).

We were also interested in extending this process to acetylenic substrates **28** to readily produce interesting polyfunctionalized and polysubstituted compact spiro[4,5]-decanyl systems **30**. In order to broaden the scope and limitation of this new transformation, different phenols, containing several substituents at any position on the lateral chain, were investigated. The desired compound **30** was obtained in 46–81% yield. A summary of representative experiments appears in Table 2.

This novel tandem process allows the production, in useful to good yield (up to 81%), of the scaffold **30**, a compact polysubstituted and functionalized subunit present in several natural products. This key functionalized core was easily obtained from simple and inexpensive phenols. It should be stressed that this process occurs even in presence of hindered alkynes with yields similar to those of unhindered alkynes and allows the generation of a contiguous quaternary carbon center and a tetrasubstituted alkene moiety. In addition, the geometry provided by the half-chair transition state **29** appears to tolerate a wide range of bulky substituents on the lateral chain. Indeed, the absence of 1,3-allylic strain interactions allows the presence of substituents in position 2 and leads to good yields of the desired system (up to 81%, **28f** and **28h**), by contrast with compound **4h** (Scheme 1). As already observed in Table 1, the presence of bromines in the *ortho*-position increased considerably the global yield of this transformation (**30e** versus **30f** and **30g** versus **30h**). This reaction can also generate a conjugated aldehyde functionality (**30m**) in 47% yield from compound **28m**. The presence of a more hindered TIPS as an oxygen protecting group was still required with a secondary alcohol moiety to efficiently produce the aldehyde functionality. As a demonstration of the potential of this new process,

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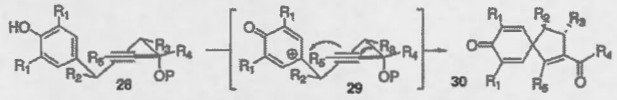
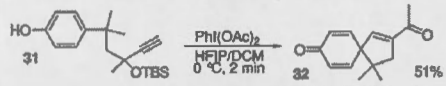
Table 2. Oxidative Prins-Pinacol Tandem Reaction with Alkynes



entry	P	R_1	R_2	R_3	R_4	R_5	yield (%)
a	TBS	H	H	H	Me	H	51
b	TBS	H	H	H	Me	*n*-Bu	48
c	TBS	H	H	H	Me	*n*-Dec	55
d	TBS	H	H	Me	Me	H	46
e	TBS	H	H	Me	≡—H	H	57
f	TBS	Br	H	Me	≡—H	H	78
g	TBS	H	H	Me	≡—*n*-Bu	*n*-Bu	60
h	TBS	Br	H	Me	≡—*n*-Bu	*n*-Bu	81
i	TBS	H	H	H	≡—*n*-Dec	*n*-Dec	50
j	TBS	H	H	Allyl	≡—*n*-Bu	*n*-Bu	53
k	TBS	H	Me	H	≡—*n*-Bu	*n*-Bu	56
l	TBS	H	Me	H	≡—H	H	53
m	TIPS	H	H	H	H	H	47

compound 31, containing a *gem*-dimethyl benzylic functionality, was prepared and the subsequent "umpolung activation" of this polysubstituted phenol resulted in compound 32 in 51% yield. In this case, the compact polyfunctionalized system contains two contiguous quaternary carbon centers and a trisubstituted alkene moiety. Such a hindered structure represents a difficult scaffold to synthesize. This new process represents an expeditious access to such challenging structures (Scheme 6).

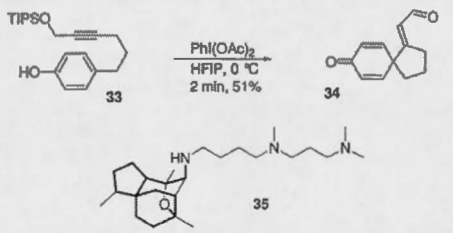
Scheme 6. Formation of Contiguous Quaternary Carbon Centers and a Trisubstituted Alkene Moiety



The process was also extended to compounds containing a propargylic ether in position 6 such as 33, producing the aldehyde 34 in 51% yield via an exocyclic Prins-pinacol process. In this case, a 5-*exo*-dig cyclization was observed instead of the standard 6-*endo*-dig mode normally observed with substrates such as 28 (Table 2), prompted by the sterically demanding ether moiety generated in position 3. In the case of an unsubstituted position 3, however, with an alkyne segment substituted in position 5, the process now proceeds via a 5-*exo*-dig mode cyclization, leading to the spiro[5.5]undecanyl structure 34 with good selectivity (9/1) in favor of the *E*-isomer, as observed by NMR. This new reaction course of compounds containing an alkyne functionality, which hinges on the position of the ether moiety during the oxidative Prins transformation, opens the door to novel opportunities such as the facilitated construction of the subunit present in the natural product (−)-hispidospermidin 35[22] (Scheme 7).

It should be noted that the oxidative Prins-pinacol reaction proceeded sometimes with formation of byproducts such as 37 (Scheme 8; in 5−10% yield). The formation of such spiro[5.5]undecanyl systems was rationalized by invoking an alkyl migration from intermediate 36, occurring in competition with ring contraction, albeit to a minor extent. While the ring contraction was the major pathway, migration of the acyclic moiety could occasionally be observed (Scheme 8).

Scheme 7. 5-*exo*-dig Cyclization of Substrate with Propargylic Ether at Position 7



As an initial application of the oxidative Prins-pinacol tandem sequence, we describe now a formal synthesis of (−)-platensimycin 53.[23] This substance is an exciting experimental antibiotic that is believed to act as a FabF inhibitor.[23a] Its unusual structure and potent bioactivity have elicited enormous interest in the synthetic community.[23] Our strategic approach to (−)-platensimycin targeted compound 52, an advanced intermediate in Nicolaou's total synthesis[24] (Figure 3).

The availability of a straightforward route to compounds such as 4 or 30 presents new opportunities for the formation of the main core of natural products such as (−)-platensimycin, 53. To that effect, the enantioenriched cycloether compound 23 was obtained using Evans's asymmetric alkylation technology from compound 38 (Scheme 5).[31] At this stage, we had assumed that a Baeyer−Villiger reaction or a similar transformation on the hemiketal 26 would produce the required tertiary alcohol functionality in a compound (43) which contains the carbon framework of the desired target. Unfortunately, direct treatment of compound 26 in presence of mCPBA failed to produce 43, and instead, an epoxide was recovered resulting from mCPBA over oxidation of alkene 42 (Scheme 9). Consequently, we proceeded to investigate alternatives to the Baeyer−Villiger process, such as the useful methodologies developed by Schreiber and co-workers.[25,26] Indeed, during the phenolic activation of cycloether 23 with the hypervalent iodine reagent, the resulting oxonium species 25 (Scheme 5) can be trapped in the same pot with hydrogen peroxide, affording a 3:2 mixture of unassigned diastereoisomers of hydroperoxyketal 39 in 64% yield from 23

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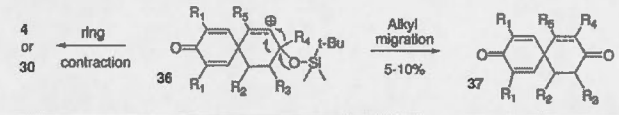
Scheme 8. Formation of Spiro[5.5]undecanyl Byproducts



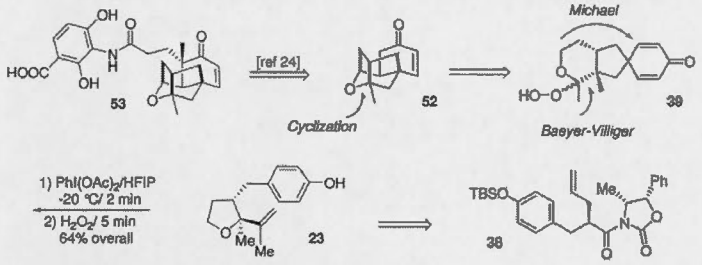
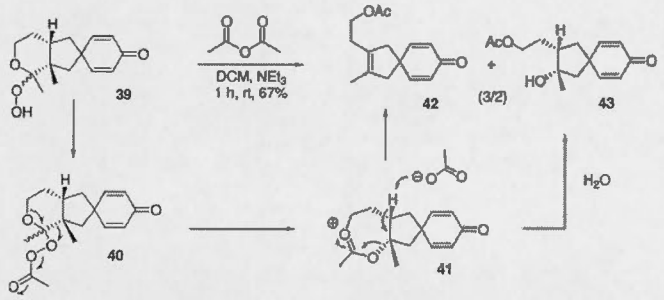


Figure 3. Structure of (−)-platensimycin and retrosynthetic logic.

Scheme 9. Schreiber Fragmentation Process on the Hydroperoxyketal 39

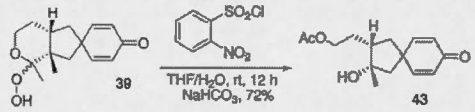


(Figure 3). Further treatment of this hydroperoxyketal in presence of acetic anhydride[25] furnished a mixture of the desired alcohol **43** and the unwanted tetrasubstituted alkene **42** in 67% yield in a 3:2 ratio in favor of the alkene. This alkene functionality presumably results from an elimination promoted by the released acetate ion on the anti-periplanar hydrogen on intermediate **41**; the desired compound **43** would result from the hydrolysis of the oxonium species **41** (Scheme 9).

To optimize the formation of alcohol **43**, we decided to perform this transformation in a biphasic medium using a Schotten–Baumann-type procedure on hydroperoxides **39**. Indeed, in such conditions, the presence of water favored the nucleophilic attack on the oxonium **41**, leading almost exclusively to the formation of the desired alcohol **43** with the required configuration, thereby demonstrating the stereoselectivity of the oxidative process (Scheme 5). This transformation could be performed with acetic anhydride; however, 2-nosyl chloride proved to be more convenient as a peroxide activator, affording **43** in 72% yield. During this transformation, the ketal function of **39** has been replaced by the desired alcohol functionality (**43**) with retention of configuration in good yield (Scheme 10).

Subsequently, the acetate group was removed and the primary alcohol obtained was selectively oxidized to the hemiketal **44** in presence of IBX in 80% yield. Further

Scheme 10. Stereoselective Formation of the Tertiary Alcohol Moiety



treatment of **44** with thiophenol and TFA produced thio-acetal **45** in 70% yield. Unfortunately, all radical or anionic attempts to produce the main cage core **52** from **45** failed, and only traces of the desired compound **52** was observed during the treatment of **45** with lithium naphthalenide (LN) (Scheme 11).

As first demonstrated by Nicolaou,[24] it appears that the formation of the main cage was not so straightforward, most probably due to the presence of the quaternary carbon center. Indeed, in the literature, few reactions allowing the formation of such a system by a Michael addition have been reported;[24] as an example, the Stetter transformation did not proceed.[24] To be able to produce a formal synthesis of (−)-platensimycin, we decided to sacrifice the second quaternary carbon center generated with total stereocontrol during the "umpolung activation" to obtain a flat and less hindered cyclopentene moiety, in order to favor the Michael addition required. In the

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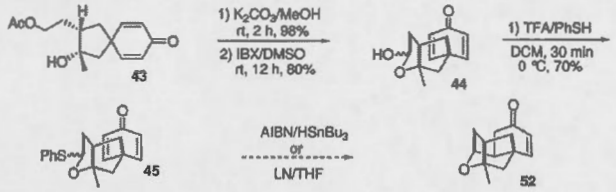
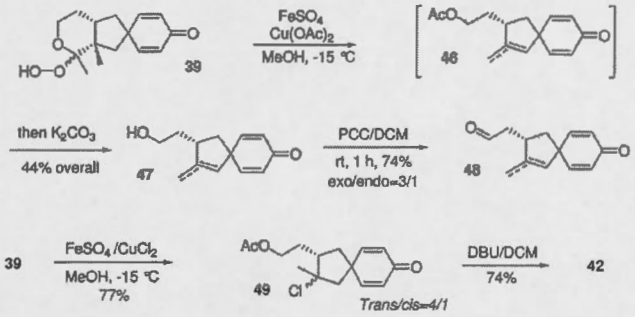
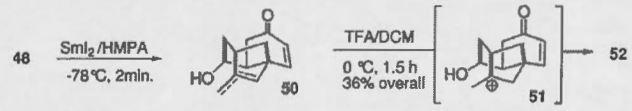
Scheme 11. First Unsuccessful Pathway to the Main Core



Scheme 12. Schreiber–Fenton Fragmentation Process



Scheme 13. Formal Synthesis of (−)-Platensimycin



event, hydroperoxide **39** was treated with a mixture of the Fenton reagent ($FeSO_4$) and $Cu(OAc)_2$ in MeOH to produce the intermediate **46**, and a subsequent addition of K_2CO_3 to the reaction mixture induced conversion to **47** in 44% overall yield from **29**. Compound **47** was obtained as a 3:1 mixture of exocyclic (major) and endocyclic alkenes. The substitution of $Cu(OAc)_2$ by $CuCl_2$ during the Schreiber fragmentation[26] led exclusively to the chloro compound **49** in good yield (74%) with 4:1 selectivity in favor of the *trans* isomer but, as presumed, subsequent treatment with DBU led mainly to the undesired tetrasubstituted alkene **42**. As demonstrated first by Nicolaou et al.,[24] both isomers of compound **48** converge to the tetracyclic main core of platensimycin **52**. Accordingly to this hypothesis, no separation was required at this stage. The alcohol mixture **47** was thus advanced to a mixture of the corresponding aldehydes **48** in 74% yield by PCC oxidation (Scheme 12).

Both compounds in the mixture **48** are known synthetic precursors[24] for (−)-platensimycin. Accordingly, they were treated by Kagan's reagent (SmI_2),[27] whereupon stereoselective cyclization to alcohols **50** occurred via a regular aliphatic umpolung transformation (Scheme 13).[28] Finally, the alkene mixture **50** was transformed to the known cage compound **52** upon treatment with TFA via the formation of a common tertiary carbocation **51**. The final elaboration of **52** to (−)-platensimycin is well-known in the literature.[24] Therefore, the synthesis of **52** represents a formal synthesis of (−)-platensimycin (Scheme 13).

■ CONCLUSION

In summary, an oxidative Prins-pinacol tandem process has been developed. This version represents an extension to aromatic systems of this important transformation and allows the generation of compact polyfunctionalized and polysubstituted spiro[4.5]decanyl systems containing several quaternary carbon centers from inexpensive phenol derivatives. In addition, we have devised an enantioselective and a diastereoselective pathway to compounds containing tertiary and quaternary carbon centers; these scaffolds are present in numerous natural products that bear important biological activities. As the first application of this novel process, a formal synthesis of (−)-platensimycin has been achieved. This demonstrates the synthetic potential of this novel oxidative extension of the Prins-pinacol process, as well as the utility of the "aromatic ring umpolung" concept.

■ EXPERIMENTAL SECTION

Unless otherwise indicated, ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in parts per million 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 hertz. IR spectra (cm^{-1}) were

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recorded from thin films. Mass spectra (m/e) were measured in the electrospray (ESI) mode.

General Procedure for the Oxidative Prins-Pinacol Process. A solution of $PhI(OAc)_2$ ("DIB", 38 mg, 0.11 mmol, 1.1 equiv) in $(CF_3)_2CHOH$ ("HFIP", 0.25 mL) was added over 5 s to a vigorously stirred solution of phenol (0.1 mmol, 1 equiv) in 0.75 mL of a solution of CH_2Cl_2/HFIP (2/1) cooled to −15 °C for a few seconds (to avoid precipitation of HFIP) or in 0.75 mL of HFIP at room temperature. After addition of DIB, the solution was stirred for 2 min, quenched with 0.1 mL of acetone, filtered directly over silica gel (*n*-hexane/EtOAc, 1:1), and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane to afford the corresponding dienone.

2-Acetylspiro[4.5]deca-6,9-dien-8-one (4a): Pale yellow oil, 0.064 mmol, 12.2 mg, 64% yield; IR ν (cm^{-1}) 2957, 1707, 1660, 1623; ^1H NMR (600 MHz, $CDCl_3$) δ 6.87 (dd, J = 10.2, 3.0 Hz, 1H), 6.86 (dd, J = 10.2, 3.0 Hz, 1H), 6.21 (d, J = 10.8 Hz, 2H), 3.31 (quin, J = 7.8 Hz, 1H), 2.22 (s, 3H), 2.21−2.10 (m, 3H), 1.95−1.78 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7, 185.9, 154.1, 152.9, 127.7, 127.6, 51.3, 48.5, 38.9, 37.5, 29.2, 28.0; HRMS (ESI) calcd for $C_{13}H_{15}O_2$ $(M + H)^+$ 191.1067, found 191.1065.

2-Acryloylspiro[4.5]deca-6,9-dien-8-one (4b): Pale yellow oil, 0.060 mmol, 12.0 mg, 60% yield; IR ν (cm^{-1}) 2935, 1661, 1615, 1404; ^1H (600 MHz, $CDCl_3$) δ 6.91 (d, J = 9.6 Hz, 2H), 6.43 (dd, J = 17.4, 9.6 Hz, 1H), 6.40 (d, J = 17.4 Hz, 1H), 6.23 (d, J = 9.6 Hz, 2H), 5.89 (d, J = 9.6 Hz, 1H), 3.58 (quin, J = 8.4 Hz, 1H), 2.21−2.17 (m, 3H), 1.99−1.82 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.6, 186.0, 154.2, 152.9, 135.4, 129.1, 127.7, 127.7, 48.7, 47.6, 39.1, 37.7, 28.5; HRMS (ESI) calcd for $C_{13}H_{15}O_2$ $(M + H)^+$ 203.1067, found 203.1063.

2-Benzoyl-2-methylspiro[4.5]deca-6,9-dien-8-one (4c): Pale yellow oil, 0.058 mmol, 15.5 mg, 58% yield; IR ν (cm^{-1}) 2935, 1667, 1622, 1445, 1260; ^1H (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.6 Hz, 2H), 6.93 (dd, J = 10.0, 2.9 Hz, 2H), 6.80 (dd, J = 10.0, 2.9 Hz, 1H), 6.23 (dd, J = 10.0, 1.7 Hz, 1H), 6.15 (dd, J = 10.0, 1.7 Hz, 1H), 2.81 (dt, J = 12.9, 7.0 Hz, 1H), 2.78 (d, J = 14.0 Hz, 1H), 2.06 (dt, J = 12.9, 7.0 Hz, 1H), 2.00 (dt, J = 12.9, 7.0 Hz, 1H), 1.93 (d, J = 14.0 Hz, 1H), 1.84 (dt, J = 12.9, 7.0 Hz, 1H), 1.64 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.1, 185.9, 154.5, 153.6, 135.1, 132.3, 129.2, 128.3, 127.6, 127.0, 55.5, 48.7, 47.8, 37.5, 37.3, 28.6; HRMS (ESI) calcd for $C_{18}H_{19}O_2$ $(M + H)^+$ 267.1380, found 267.1381.

2-Acetyl-2-methylspiro[4.5]deca-6,9-dien-8-one (4d): Pale yellow oil, 0.059 mmol, 12.1 mg, 59% yield; IR ν (cm^{-1}) 2928, 1701, 1662, 1623; ^1H NMR (600 MHz, $CDCl_3$) δ 6.86 (d, J = 10.2 Hz, 2H), 6.17 (d, J = 10.2 Hz, 1H), 6.15 (d, J = 10.2 Hz, 1H), 2.48 (d, J = 14.4 Hz, 1H), 2.41−2.37 (m, 1H), 2.21 (s, 3H), 1.92−1.73 (m, 3H), 1.59 (d, J = 14.4 Hz), 1.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.1, 185.9, 154.4, 154.1, 127.2, 126.9, 56.7, 48.4, 45.3, 37.2, 36.1, 25.8, 25.2; HRMS (ESI) calcd for $C_{13}H_{17}O_2$ $(M + H)^+$ 205.1223, found 205.1222.

2-Acetyl-7,9-dibromo-2-methylspiro[4.5]deca-6,9-dien-8-one (4e): Pale yellow oil, 0.084 mmol, 30.2 mg, 84% yield; ^1H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, J = 2.9 Hz, 1H), 7.33 (d, J = 2.9 Hz, 1H), 2.64 (d, J = 14.1 Hz, 1H), 2.37 (m, 1H), 2.24 (s, 3H), 2.41−2.37 (m, 1H), 2.21 (s, 3H), 1.97 (m, 1H), 1.91−1.82 (m, 2H), 1.65 (d, J = 14.1 Hz), 1.44 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.7, 172.5, 154.4, 120.4, 120.2, 56.8, 53.9, 44.2, 36.7, 36.3, 25.4, 25.1; HRMS (ESI) calcd for $C_{13}H_{15}Br_2O_2$ $(M + H)^+$ 362.9412, found 362.9416.

trans-3-Acetyl-1-methylspiro[4.5]deca-6,9-dien-8-one (4f): Pale yellow oil, 0.050 mmol, 10.1 mg, 50% yield; IR ν (cm^{-1}) 2924, 1711, 1663, 1624; ^1H NMR (300 MHz, $CDCl_3$) δ 6.86 (dd, J = 10.4, 2.2 Hz, 1H), 6.74 (dd, J = 10.4, 2.2 Hz, 1H), 6.36 (d, J = 10.4 Hz, 1H), 6.33 (d, J = 10.2 Hz, 1H), 3.34 (m, 1H), 2.40−2.10 (m, 3H), 2.23 (s, 3H), 1.94 (dd, J = 13.2, 8.2 Hz, 1H), 1.85 (d, J = 13.2, 8.2 Hz), 0.77 (d, J = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.8, 186.4, 154.5, 149.4, 129.9, 129.8, 53.0, 49.0, 44.4, 39.3, 34.9, 29.1, 14.1; HRMS (ESI) calcd for $C_{13}H_{17}O_2$ $(M + H)^+$ 205.1223, found 205.1218.

cis-2-Acetyl-3-methylspiro[4.5]deca-6,9-dien-8-one (4g): Pale yellow oil, 0.030 mmol, 6.0 mg, 30% yield; IR ν (cm^{-1}) 2958, 2930, 1707, 1661, 1620; ^1H (300 MHz, $CDCl_3$) δ 7.20 (dd, J = 9.9, 2.7 Hz, 1H), 6.93 (dd, J = 9.9, 2.7 Hz, 1H), 6.20 (d, J = 9.9 Hz, 1H), 6.16 (d, J = 9.9 Hz, 1H), 3.39 (q, J = 8.1 Hz, 1H), 2.81−2.70 (m, 1H), 2.32 (dd, J = 14.4, 7.8 Hz, 1H), 2.22 (s, 3H), 1.92−1.72 (m, 3H), 1.30 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 186.0, 155.8, 153.6, 127.5, 126.5, 54.7, 46.9, 44.8, 38.3, 36.9, 31.8, 16.5; HRMS (ESI) calcd for $C_{13}H_{17}O_2$ $(M + H)^+$ 205.1223, found 205.1226.

cis-2-Acryloyl-3-allylspiro[4.5]deca-6,9-dien-8-one (4h): Pale yellow oil, 0.055 mmol, 11.2 mg, 55% yield; IR ν (cm^{-1}) 2928, 1701, 1662, 1623; ^1H NMR (600 MHz, $CDCl_3$) δ 6.82 (d, J = 10.0 Hz, 1H), 6.74 (d, J = 10.0 Hz, 1H), 6.38 (d, J = 10.0 Hz, 1H), 6.35 (d, J = 10.0 Hz, 1H), 5.68 (m, 2H), 5.09 (d, J = 17 Hz, 1H), 5.07 (d, J = 10 Hz, 1H), 4.94 (d, J = 16.4 Hz, 1H), 4.91 (d, J = 10 Hz, 1H), 2.57 (m, 2H), 2.45 (m, 1H), 2.39 (t, J = 7.6 Hz, 1H), 2.26 (m, 1H), 2.09 (dd, J = 13.5, 8.8 Hz, 1H), 1.91 (t, J = 11.7 Hz), 1.83 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.2, 185.8, 154.1, 148.2, 135.1, 134.3, 130.8, 130.4, 118.1, 117.3, 58.8, 48.2, 45.5, 38.4, 35.3, 30.6; HRMS (ESI) calcd for $C_{16}H_{19}O_2$ $(M + H)^+$ 243.1380, found 243.1377.

8-Oxospiro[4.5]deca-6,9-diene-2-carbaldehyde (12): Pale yellow oil, 0.061 mmol, 10.7 mg, 61% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H), 6.87 (d, J = 9.8 Hz, 1H), 6.77 (d, J = 9.8 Hz, 1H), 6.17 (d, J = 10.2 Hz, 1H), 6.22 (d, J = 9.8 Hz, 2H), 3.18 (m, 1H), 2.29−2.14 (m, 3H), 1.99 (dd, J = 13.7, 9.4 Hz, 1H), 1.83 (t, J = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 185.8, 153.4, 152.5, 128.0, 127.8, 51.0, 48.3, 37.4, 36.7, 25.5; HRMS (ESI) calcd for $C_{11}H_{13}O_2$ $(M + H)^+$ 177.0910, found 177.0908.

2-Hydroxy-10,10-dimethyl-4,5,9,9a-tetrahydro-2H-3,5a-methanobenzo-oxepin-8(3H)-one (18): Pale yellow oil, 40% yield; ^1H NMR (600 MHz, $CDCl_3$) δ 6.52 (dd, J = 10.2, 2.3 Hz, 2H), 6.17 (d, J = 10.4 Hz, 1H), 5.35 (m, 1H), 4.09 (m, 1H), 2.77 (dd, J = 7.8, 3.4 Hz, 1H), 2.20 (dd, J = 7.8, 3.4 Hz, 1H), 1.94 (s, 1H), 1.94 (dd, J = 7.8, 3.4 Hz, 1H), 1.33 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.8, 152.3, 126.8, 82.8, 80.7, 68.5, 56.2, 38.3, 33.0, 31.4, 31.1, 29.6, 23.2; HRMS (ESI) calcd for $C_{13}H_{19}O_3$ $(M + H)^+$ 223.1329, found 223.1327.

2-Methyl-8-oxospiro[4.5]deca-6,9-diene-2-carbaldehyde (20): Pale yellow oil, 68% yield; IR ν (cm^{-1}) 2930, 1718, 1663, 1623; ^1H NMR (600 MHz, $CDCl_3$) δ 9.57 (s, 1H), 6.92 (dd, J = 10.2, 3.2 Hz, 1H), 6.87 (dd, J = 10.2, 3.2 Hz, 1H), 6.21 (dd, J = 10.2, 3.2 Hz, 1H), 6.20 (dd, J = 10.2, 3.2 Hz, 1H), 2.40 (d, J = 14.4 Hz, 1H), 1.92−1.77 (m, 3H), 1.62 (d, J = 14.4 Hz, 1H), 1.92−1.73 (m, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 185.7, 153.8, 153.6, 127.3, 127.3, 54.8, 48.5, 43.3, 37.2, 34.2, 22.4; HRMS (ESI) calcd for $C_{12}H_{15}O_2$ $(M + H)^+$ 191.1067, found 191.1066.

2-Acetylspiro[4.5]deca-1,6,9-trien-8-one (30a): Pale yellow oil, 0.05 mmol, 9.7 mg, 51% yield; IR ν (cm^{-1}) 2923, 1667, 1621, 1367; ^1H (300 MHz, $CDCl_3$) δ 6.80 (d, J = 9.6 Hz, 2H), 6.29 (d, J = 9.6 Hz, 2H), 6.11 (s, 1H), 2.82 (t, J = 7.5 Hz, 2H), 2.35 (s, 3H), 2.17 (t, J = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 185.2, 150.3, 148.7, 141.9, 128.7, 54.8, 34.6, 30.5, 26.9; HRMS (ESI) calcd for $C_{12}H_{13}O_2$ $(M + H)^+$ 189.0910, found 189.0907.

2-Acetyl-1-butylspiro[4.5]deca-1,6,9-trien-8-one (30b): Pale yellow oil, 0.045 mmol, 10.9 mg, 45% yield; IR ν (cm^{-1}) 2925, 1665, 1615, 1370; ^1H (600 MHz, $CDCl_3$) δ 6.74 (d, J = 9.9 Hz, 2H), 6.24 (d, J = 9.9 Hz, 2H), 2.43 (t, J = 7.2 Hz, 2H), 2.15 (t, J = 7.2 Hz, 2H), 2.11 (s, 3H), 2.10 (t, J = 7.2 Hz, 2H), 1.46−1.22 (m, 4H), 0.87 (t, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.7, 185.0, 150.9, 149.9, 129.4, 128.3, 84.7, 76.1, 38.8, 38.2, 33.6, 30.5, 30.1, 21.8, 18.3, 13.5; HRMS (ESI) calcd for $C_{16}H_{21}O_2$ $(M + H)^+$ 245.1536, found 245.1539.

2-Acetyl-1-decylspiro[4.5]deca-1,6,9-trien-8-one (30c): Pale yellow oil, 0.055 mmol, 18.0 mg, 55% yield; IR ν (cm^{-1}) 2925, 2854, 1720, 1673, 1628; ^1H (600 MHz, $CDCl_3$) δ 6.75 (d, J = 9.8 Hz, 2H), 6.25 (d, J = 9.8 Hz, 2H), 2.43 (t, J = 7.8 Hz, 2H), 2.15 (t, J = 7.8 Hz, 2H), 2.11 (s, 3H), 2.10 (t, J = 7.8 Hz, 2H), 1.46 (quin, J = 7.8 Hz, 1H), 1.47 (quin, J = 7.8 Hz, 2H), 1.36−1.21 (m, 16H), 0.87 (t, J = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.7, 185.0, 150.9, 150.0, 129.4, 128.3, 84.8, 38.8, 38.2, 33.6, 31.8, 30.1, 29.5, 29.4, 29.2, 29.0,

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28.7, 28.5, 22.6, 18.6, 14.0; HRMS (ESI) calcd for $C_{22}H_{32}NaO_2$ $(M + Na)^+$ 351.2295, found 351.2297.

2-Acetyl-3-methylspiro[4.5]deca-1,6,9-trien-8-one (30d): Pale yellow oil, 0.046 mmol, 9.3 mg, 46% yield; IR ν (cm^{-1}) 3482, 2959, 1663, 1622, 1666; ^1H (600 MHz, $CDCl_3$) δ 6.84 (dd, J = 10.0, 2.3 Hz, 1H), 6.72 (dd, J = 10.0, 2.3 Hz, 1H), 6.3 (d, J = 10.0 Hz, 1H), 6.28 (d, J = 10.0 Hz, 1H), 6.07 (s, 1H), 3.34 (hex, J = 7.0 Hz, 1H), 2.40 (ddd, J = 13.5, 8.2, 1.1 Hz, 1H), 2.34 (s, 3H), 1.79 (ddd, J = 13.5, 5.9, 1.1 Hz, 1H), 1.28 (d, J = 8.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.3, 185.1, 152.3, 151.6, 151.0, 141.5, 128.6, 128.5, 53.7, 42.8, 39.2, 27.5, 20.6; HRMS (ESI) calcd for $C_{13}H_{15}O_2$ $(M + H)^+$ 203.1067, found 203.1064.

3-Methyl-2-propioloylspiro[4.5]deca-1,6,9-trien-8-one (30e): Pale yellow oil, 0.057 mmol, 12 mg, 57% yield; IR ν (cm^{-1}) 2092, 1662, 1636, 857; ^1H (300 MHz, $CDCl_3$) δ 6.84 (dd, J = 10.4, 3.3 Hz, 1H), 6.73 (dd, J = 10.4, 3.3 Hz, 1H), 6.52 (d, J = 9.6 Hz, 1H), 6.34 (dd, J = 10.4, 3.3 Hz, 1H), 6.31 (dd, J = 10.4, 3.3 Hz, 1H), 3.37 (m, 1H), 3.25 (s, 1H), 2.47 (dd, J = 13.7, 8.8 Hz, 1H), 1.87 (dd, J = 13.7, 8.8 Hz, 1H), 1.33 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 174.3, 152.3, 150.9, 150.1, 148.2, 129.0, 128.9, 80.1, 78.6, 53.5, 43.3, 38.5, 20.3; HRMS (ESI) calcd for $C_{14}H_{13}O_2$ $(M + H)^+$ 213.0910, found 213.0905.

7,9-Dibromo-3-methyl-2-propioloylspiro[4.5]deca-1,6,9-trien-8-one (30f): Pale yellow oil, 78% yield; IR ν (cm^{-1}) 2092, 1733, 1677, 1641, 1072; ^1H (300 MHz, $CDCl_3$) δ 7.31 (d, J = 2.7 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 6.52 (d, J = 1.6 Hz, 1H), 3.37 (m, 1H), 3.30 (s, 1H), 2.56 (dd, J = 13.7, 8.8 Hz, 1H), 1.97 (dd, J = 13.7, 8.8 Hz, 1H), 1.33 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 172.0, 153.0, 150.9, 150.2, 144.9, 129.3, 122.5, 122.3, 80.0, 79.2, 58.5, 42.7, 38.7, 25.5, 20.0; HRMS (ESI) calcd for $C_{14}H_{11}Br_2O_2$ $(M + H)^+$ 370.9100, found 370.9094.

1-Butyl-2-(hept-2-ynoyl)-3-methylspiro[4.5]deca-1,6,9-trien-8-one (30g): Pale yellow oil, 60% yield; IR ν (cm^{-1}) 2933, 2205, 1667, 1626; ^1H (600 MHz, $CDCl_3$) δ 6.78 (d, J = 9.9 Hz, 1H), 6.76 (d, J = 9.9 Hz, 1H), 6.28 (d, J = 9.9 Hz, 1H), 6.22 (d, J = 9.9 Hz, 1H), 2.67 (dd, J = 14.0, 8.2 Hz, 1H), 2.60 (qd, J = 8.2, 2.9 Hz, 1H), 2.37 (t, J = 7.0 Hz, 2H), 2.17 (t, J = 7.0 Hz, 2H), 1.70 (dd, J = 13.4, 2.9 Hz, 1H), 1.60–1.56 (m, 4H), 1.50–1.37 (m, 5H), 1.20 (d, J = 7.0 Hz, 3H), 0.94 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 185.0, 150.1, 149.9, 128.4, 128.2, 96.4, 84.9, 80.0, 76.1, 44.8, 42.4, 39.2, 30.5, 29.6, 21.9, 21.8, 18.8, 18.6, 18.3, 13.5, 13.4; HRMS (ESI) calcd for $C_{22}H_{29}O_2$ $(M + H)^+$ 325.2162, found 325.2156.

7,9-Dibromo-1-butyl-2-(hept-2-ynoyl)-3-methylspiro[4.5]deca-1,6,9-trien-8-one (30h): Pale yellow oil, 81% yield; IR ν (cm^{-1}) 2923, 2205, 1733, 1677; ^1H (600 MHz, $CDCl_3$) δ 7.21 (d, J = 2.7 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 2.67 (dd, J = 14.3, 9.3 Hz, 1H), 2.59 (m, 1H), 2.39 (t, J = 7.0 Hz, 2H), 2.18 (t, J = 7.0 Hz, 2H), 1.79 (dd, J = 13.7, 2.7 Hz, 1H), 1.63–1.27 (m, 8H), 1.20 (d, J = 7.0 Hz, 3H), 0.94 (t, J = 7.0 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.7, 171.9, 150.3, 149.8, 121.8, 97.2, 86.8, 80.0, 73.4, 44.7, 44.5, 42.8, 30.3, 29.6, 21.9, 21.9, 18.7, 18.4, 13.5, 13.4; HRMS (ESI) calcd for $C_{22}H_{27}Br_2O_2$ $(M + H)^+$ 483.0353, found 483.0343.

1-Decyl-2-(tridec-2-ynoyl)spiro[4.5]deca-1,6,9-trien-8-one (30i): Pale yellow oil, 0.05 mmol, 23.9 mg, 50% yield; IR ν (cm^{-1}) 2925, 2854, 1674, 1627; ^1H (600 MHz, $CDCl_3$) δ 6.76 (d, J = 9.8 Hz, 2H), 6.26 (d, J = 9.6 Hz, 2H), 2.57 (t, J = 7.8 Hz, 2H), 2.16 (t, J = 7.2 Hz, 4H), 1.56 (quin, J = 7.8 Hz, 1H), 1.47 (quin, J = 7.8 Hz, 2H), 1.40–1.21 (m, 28H), 0.87 (t, J = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.9, 185.0, 149.7, 132.9, 128.4, 115.2, 95.5, 85.1, 80.5, 80.5, 75.8, 40.4, 38.7, 33.9, 31.8, 29.5, 29.5, 29.4, 29.2, 28.9, 29.2, 29.0, 28.9, 28.8, 28.8, 28.5, 27.6, 22.6, 18.9, 18.6, 14.0; HRMS (ESI) calcd for $C_{33}H_{50}NaO_2$ $(M + Na)^+$ 501.3703, found 501.3700.

3-Allyl-1-butyl-2-(hept-2-ynoyl)spiro[4.5]deca-1,6,9-trien-8-one (30j): Pale yellow oil, 53% yield; IR ν (cm^{-1}) 2923, 2205, 1667, 1625, 1461; ^1H (300 MHz, $CDCl_3$) δ 6.75 (dd, J = 9.8, 2.7 Hz, 1H), 6.71 (dd, J = 9.8, 2.7 Hz, 1H), 6.28 (d, J = 9.8, 1.7 Hz, 1H), 6.21 (d, J = 9.8, 1.7 Hz, 1H), 5.65 (m, 1H), 5.11 (d, 17.0 Hz, 1H), 5.08 (d, J = 8.0, 1H), 2.59 (m, 2H), 2.45 (m, 1H), 2.37 (t, J = 7.0 Hz, 2H), 2.22 (m, 1H), 2.17 (t, J = 7.0 Hz, 2H), 1.80 (dt, J = 12.1, 7.1 Hz, 1H), 1.60–1.31 (m, 6H), 1.25 (d, J = 9.2 Hz, 1H), 0.93 (t, J = 7.8 Hz, 3H). 0.90 (t, J = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 185.0, 150.1, 149.8, 133.9, 128.5, 128.2, 118.3, 96.6, 85.0, 80.4, 49.7, 39.5, 39.1, 37.2, 30.5, 29.6, 21.9, 18.7, 18.4, 13.5; HRMS (ESI) calcd for $C_{24}H_{31}O_2$ $(M + H)^+$ 351.2319, found 351.2305.

1-Butyl-2-(hept-2-ynoyl)-4-methylspiro[4.5]deca-1,6,9-trien-8-one (30k): Pale yellow oil, 56% yield; IR ν (cm^{-1}) 2929, 2854, 2210, 1670; ^1H (300 MHz, $CDCl_3$) δ 6.80 (dd, J = 9.8, 2.7 Hz, 1H), 6.72 (dd, J = 9.8, 2.7 Hz, 1H), 6.32 (d, J = 9.8 Hz, 2H), 2.88 (dd, J = 16.4, 2.2 Hz, 1H), 2.61 (m, 1H), 2.59 (m, 2H), 2.45 (m, 1H), 2.38 (t, J = 7.0 Hz, 2H), 2.34 (dd, J = 16.4, 9.8 Hz, 1H), 2.20 (t, J = 7.0 Hz, 2H), 1.60–1.31 (m, 6H), 1.03 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.8 Hz, 3H). 0.91 (t, J = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.0, 185.2, 167.1, 148.7, 148.6, 133.0, 129.4, 129.2, 115.2, 95.2, 85.7, 80.8, 75.7, 48.0, 43.2, 37.9, 30.5, 29.6, 21.9, 21.9, 18.6, 18.4, 15.3, 13.5, 13.4; HRMS (ESI) calcd for $C_{22}H_{29}O_2$ $(M + H)^+$ 325.2162, found 325.2164.

4-Methyl-2-propioloylspiro[4.5]deca-1,6,9-trien-8-one (30l): Pale yellow oil, 54% yield; IR ν (cm^{-1}) 2925, 2854, 1674, 1627; ^1H (300 MHz, $CDCl_3$) δ 6.79 (dd, J = 10.4, 3.3 Hz, 1H), 6.71 (dd, J = 10.4, 3.3 Hz, 1H), 6.61 (s, 1H), 6.41 (dd, J = 8.8, 3.3 Hz, 2H), 3.27 (s, 1H), 3.03 (dd, J = 16.5, 8.2 Hz, 1H), 3.03 (dd, J = 16.5, 8.2 Hz, 1H), 2.69 (m, 1H), 2.46 (ddd, J = 16.4, 10.4, 2.2 Hz, 1H), 0.99 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.4, 174.1, 167.1, 150.3, 148.6, 146.3, 130.8, 130.6, 79.7, 79.2, 57.6, 44.6, 36.8, 14.4; HRMS (ESI) calcd for $C_{14}H_{13}O_2$ $(M + H)^+$ 213.0910, found 213.0907.

8-Oxospiro[4.5]deca-1,6,9-triene-2-carbaldehyde (30m): Pale yellow oil, 45% yield; IR ν (cm^{-1}) 2928, 1701, 1662, 1623; ^1H NMR (600 MHz, $CDCl_3$) δ 9.86 (s, 1H), 6.79 (d, J = 10.0 Hz, 2H), 6.33 (d, J = 10.0 Hz, 2H), 6.30 (s, 1H), 2.83 (d, J = 7.6 Hz, 2H), 2.25 (d, J = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ189.2, 185.3, 149.9, 149.8, 149.7, 129.3, 54.6, 35.1, 28.7; HRMS (ESI) calcd for $C_{11}H_{11}O_2$ $(M + H)^+$ 175.0754, found 175.0751.

2-Acetyl-4,4-dimethylspiro[4.5]deca-1,6,9-trien-8-one (32): Pale yellow oil, 51% yield; IR ν (cm^{-1}) 1667, 1621; ^1H NMR (600 MHz, $CDCl_3$) δ 6.85 (d, J = 10.2 Hz, 2H), 6.37 (d, J = 10.2 Hz, 1H), 6.16 (t, J = 1.6 Hz, 1H), 2.64 (d, J = 1.6 Hz, 1H), 2.34 (s, 3H), 1.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 184.9, 148.5, 148.0, 142.0, 130.4, 59.8, 49.7, 44.9, 26.4, 25.8; HRMS (ESI) calcd for $C_{14}H_{17}O_2$ $(M + H)^+$ 217.1223, found 217.1232.

(E)-2-(8-Oxospiro[4.5]deca-6,9-dien-1-ylidene)acetaldehyde (34): 9.6 mg, 0.051 mmol, 51%, as an oil; IR ν (cm^{-1}) 2923, 2858, 1667, 1622, 1403, 1253, 1154, 863; ^1H NMR (300 MHz, $CDCl_3$) δ 9.84 (d, 1H, J = 7.0 Hz), 6.76 (d, 2H, J = 10.1 Hz), 6.31 (d, 2H, J = 10.1 Hz), 5.77 (dt, 1H, J = 7.0, 2.5 Hz), 3.11 (td, 2H, J = 7.0, 2.5 Hz), 2.14 (m, 2H), 2.06 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.7, 185.5, 168.4, 149.7, 128.1, 125.1, 53.9, 37.2, 30.7, 24.0; HRMS (ESI) calcd for $C_{12}H_{13}O_2$ $(M + H)^+$ 189.0910, found 189.0910.

4-(((2S,3S)-2-methyl-2-(prop-1-en-2-yl)tetrahydrofuran-3-yl)-methyl)phenol (23). To a solution of the triols 22[31] (50 mg, 0.2 mmol) in dry CH_2Cl_2 (2 mL) was added TFA (45 mg, 0.4 mmol, 2 equiv) and the solution was stirred for 90 min at 40 °C. The crude mixture is purified directly on silica gel (*n*-hexane/EtOAc, 7:3) to afford 23 compound 35 mg, 0.15 mmol) in 75% yield as an oil: IR ν (cm^{-1}) 3312, 1610, 1221, 1164; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J = 8.2 Hz, 2H), 6.77 (d, J = 8.2 Hz, 2H), 4.99 (s, 1H), 4.85 (s, 1H), 3.74 (q, J = 8.2 Hz, 1H), 2.78 (d, J = 10.4 Hz, 1H), 2.31 (m, 2H), 1.89 (m, 1H), 1.82 (s, 3H), 1.71 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.9, 149.7, 133.1, 129.7, 115.2, 109.8, 86.1, 65.9, 47.4, 35.4, 31.4, 20.8, 18.8; HRMS (ESI) calcd for $C_{15}H_{21}O_2$ $(M + H)^+$ 233.1536, found 233.1536.

3-Acetyl-3-methyl-8-oxospiro[4.5]deca-6,9-dien-2-yl)-acetaldehyde (27). The crude mixture 26 resulting from the direct oxidation of compound 23 (0.1 mmol, 25 mg) was quickly filtrated by chromatography (EtOAc), concentrated under reduced pressure, and dissolved in dry CH_2Cl_2 (0.75 mL). Dess–Martin periodinane (85 mg, 0.2 mmol) was added. The solution was stirred overnight (and verified by TLC) at 40 °C. Then a solution of 2 mL of saturated aqueous $NaHCO_3$ and 2 mL of saturated aqueous sodium thiosulfate were added. The mixture was diluted with 4 mL of ethyl acetate, the organic

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layer removed, and the aqueous phase extracted with EtOAc (2 × 4 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by chromatography (*n*-hexane/EtOAc, 1:1) to afford 263 mg (60% over two steps) of compound **27** as a colorless oil: IR ν (cm^{-1}) 2932, 1723, 1692, 1656; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 6.98 (d, J = 9.8 Hz, 2H), 6.16 (d, J = 9.8 Hz, 2H), 2.73–2.48 (m, 3H), 2.36 (d, J = 14.3 Hz, 1H), 2.19 (s, 3H), 1.99 (d, J = 9.8 Hz, 2H), 1.71 (d, J = 14.3 Hz, 1H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 185.7, 155.0, 154.6, 127.0, 126.1, 57.9, 47.5, 45.7, 44.2, 43.9, 42.0, 28.2, 24.1; HRMS (ESI) calcd for $C_{15}H_{18}O_3Na$ $(M + Na)^+$ 269.1148, found 269.1147.

2-(3-Methyl-8-oxospiro[4.5]deca-2,6,9-trien-2-yl)ethyl acetate (42). A solution of $PhI(OAc)_2$ ("DIB", 80 mg, 0.25 mmol) in $(CF_3)_2CHOH$ ("HFIP", 0.75 mL) was added over 10 s to a vigorously stirred solution of phenol **23**[31] (0.2 mmol, 1 equiv) in 2 mL of a solution of CH_2Cl_2/HFIP (3/2) cooled to −17 °C for a few seconds (to avoid precipitation of HFIP). After addition of DIB, the solution was stirred for 1 min, and H_2O_2 (35%, 0.75 mL) was added to the medium. The reaction was stirred for 5 min and filtered directly over silica gel (*n*-hexane/EtOAc, 1:1), and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane, 3:1) to afford a mixture (37 mg, 64%) of two diastereoisomers **39** as an oil.[31] The epimeric mixture of compound **39** was rapidly used (17 mg, 0.064 mmol) in dry DCM (0.6 mL); NEt_3 (30 μL, 0.200 mmol, 3.1 equiv) was added followed by Ac_2O (20 μL, 0.200 mmol, 3.1), and the solution was stirred for 1 h under argon and filtered directly over silica gel (*n*-hexane/EtOAc, 1:1). The crude product was purified by chromatography (*n*-hexane/EtOAc, 1:1) to afford 6.0 mg (38%) of compound **42** as well as 4.0 mg (24%) of compound **43** (oils): IR ν (cm^{-1}) 1738, 1664, 1233; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, J = 10.0 Hz, 2H), 6.21 (d, J = 10.0 Hz, 2H), 4.12 (t, J = 7.5 Hz, 2H), 2.53 (s, 2H), 2.50 (s, 2H), 2.43 (t, J = 7.5 Hz, 2H), 2.06 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 170.9, 154.9, 132.5, 129.3, 127.1, 62.4, 47.8, 45.8, 27.5, 20.9, 13.6; HRMS (ESI) calcd for $C_{15}H_{19}O_3$ $(M + H)^+$ 247.1329, found 247.1336.

2-((2S,3S)-3-Hydroxy-3-methyl-8-oxospiro[4.5]deca-6,9-dien-2-yl)ethyl acetate (43). To a solution of compound **39** (see formation of compound **42**, 63 mg, 0.239 mmol) in THF (2.5 mL) was added a solution (2.5 mL) of saturated aqueous $NaHCO_3$ followed by *ortho*-NsCl (320 mg, 1.448 mmol, 6.0 equiv), then the solution was stirred for 12 h and H_2O (10.0 mL) was added. The aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by chromatography (*n*-hexane/EtOAc, 1:1) to afford 45.5 mg (72%) of the desired alcohol as an oil: IR ν (cm^{-1}) 2921, 1732, 1660, 1557; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, J = 10.0, 2.7 Hz, 1H), 6.86 (dd, J = 10.0, 2.7 Hz, 1H), 6.16 (dd, J = 10.0, 2.7 Hz, 1H), 6.13 (dd, J = 10.0, 2.7 Hz, 1H), 4.12 (m, 2H), 2.06 (s, 3H), 2.01–1.89 (m, 7H), 1.68 (m, 2H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.1, 171.0, 157.0, 155.4, 126.1, 125.8, 81.1, 63.3, 51.4, 46.4, 44.8, 41.3, 27.2, 25.9, 20.9; HRMS (ESI) calcd for $C_{15}H_{20}NaO_4$ $(M + Na)^+$ 287.1254, found 287.1267.

(3a'S,6a'S)-2'-Hydroxy-6a'-methyl-2',3',3a',4',6',6a'-hexahydrospiro[cyclohexa[2,5]diene-1,5'-cyclopenta[b]furan]-4-one (44). To a solution of compound **43** (23 mg, 0.85 mmol) in methanol (2.0 mL) was added finely powdered potassium carbonate (12.0 mg, 0.9 mmol, 1.05 equiv). The reaction mixture was stirred for 25 min, and the methanol was partly removed by evaporation under reduced pressure. The crude product was directly purified by chromatography (DCM/MeOH, from 9:1 to 8:2) to afford 18.5 mg (97%) of the desired compound. The corresponding diol (15.5 mg, 0.07 mmol) was dissolved in a (1/1) DMSO/EtOAc mixture (2 mL), and then was added IBX (30 mg, 0.11 mmol, 1.5 equiv). The reaction mixture was stirred for 2 h, and H_2O (5.0 mL) was added. The aqueous phase was extracted with EtOAc (4 × 5 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford 24.0 mg (80%) of the desired mixture of hemiketals: HRMS (ESI) calcd for $C_{13}H_{15}O_2$ $(M + H - H_2O)^+$ 203.1067, found 203.1074.

(3a'S,6a'S)-6a'-Methyl-2'-(phenylthio)-2',3',3a',4',6',6a'-hexahydrospiro[cyclohexa[2,5]diene-1,5'-cyclopenta[b]furan]-4-one (45). To a solution of the compound **44** (8.0 mg, 0.036 mmol) in DCM (1.0 mL) were added PhSH (5 μL, 0.048 mmol, 1.4 equiv) and TFA (5 μL, 0.068 mmol, 1.9 equiv). The reaction mixture was stirred for 1 h. The crude product was directly purified by chromatography (*n*-hexane/EtOAc, 80:20) to afford 7.0 mg (62%) of the desired diastereomeric mixture as an oil: HRMS (ESI) for $C_{19}H_{20}NaO_2S$ $(M + Na)^+$ 335.1076, found 335.1073.

(S)-2-(2-Hydroxyethyl)-3-methylenespiro[4.5]deca-6,9-dien-8-one (47). To a solution of compounds **39** (see formation of compound **42**, 18 mg, 0.068 mmol) in degassed MeOH at −15 °C was dissolved $Cu(OAc)_2$ (27 mg, 2 equiv), and the solution was stirred 5 min until the salt was soluble, then $FeSO_4$ (12.5 mg, 1.2 equiv) was added at −20 °C . The reaction was stirred until the starting material disappeared by TLC (ethyl acetate/hexane 1:1), then the solution was filtrated on silica gel chromatography and concentrated under vacuum. The residue was dissolved in methanol (2 mL); K_2CO_3 solid (14 mg, 0.1 mmol) was added, and the solution was stirred until the starting material disappeared by TLC, affording a mixture of alkenes **47** (6 mg, 44%) in a ratio ~3/1 in favor of the exo isomer: colorless oil; ^1H NMR (exo isomer, 300 MHz, $CDCl_3$) δ 6.98 (dd, J = 9.8, 3.3 Hz, 1H), 6.81 (dd, J = 9.8, 2.3 Hz, 1H), 6.16 (t, J = 9.8, 1.6 Hz, 2H), 5.08 (s, 1H), 5.02 (s, 1H), 3.74 (m, 2H), 2.92, (m,1H), 2.67 (dq, J = 15.9, 2.2 Hz, 1H), 2.43 (dd, J = 15.9, 1.6 Hz, 1H), 2.06 (m, 2H), 1.75 (m, 2H); LRMS (ESI) for $C_{13}H_{16}O_2Na$ $(M + Na)^+$ 227, identical to the literature.[24]

(S)-2-(3-Methylene-8-oxospiro[4.5]deca-6,9-dien-2-yl)-acetaldehyde (48). The alkene mixture **47** (11 mg, 0.054 mmol) was dissolved in 2 mL of DCM, and PCC (24 mg, 0.11 mmol) was added; the reaction was stirred until the starting material disappeared by TLC (ethyl acetate/hexane 3:1) and filtered directly over silica gel (*n*-hexane/EtOAc, 1:3). The filtrate was concentrated under reduced pressure and purified by silica gel chromatography with a mixture of ethyl acetate/hexane (3:1) to afford a mixture of aldehydes **48** (8.1 mg, 74%) as a colorless oil: ^1H NMR (exo isomer, 300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 6.98–6.95 (m, 1H), 6.79–6.76 (m, 1H), 6.27–6.23 (m, 2H), 5.10 (s, 1H), 4.98 (s, 1H), 3.30 (m, 1H), 2.90 (dd, J = 18.1, 5.5 Hz, 1H), 2.66 (m, 2H), 2.47 (m, 1H), 2.15 (ddd, J = 13.0, 8.0, 1.6 Hz, 1 H), 1.69 (m, J = 13.0, 10.3 Hz, 1H); LRMS (ESI) $C_{13}H_{14}O_2Na$ $(M + Na)^+$ 225, identical to the literature.[24]

2-(3-Chloro-3-methyl-8-oxospiro[4.5]deca-6,9-dien-2-yl)ethyl acetate (49). To a solution of compounds **39** (see formation of compound **42**, 26.5 mg, 0.1 mmol) in degassed MeOH (2 mL) at rt was dissolved $Cu(Cl)_2$ (27 mg, 0.2 mmol, 2 equiv), and the solution was stirred 5 min until the salt was soluble. The mixture was cooled at −30 °C, and $FeSO_4$ (41 mg, 0.15 mmol, 1.5 equiv) was added. The reaction was stirred 10 min at −30 °C, and the crude product was directly purified by chromatography (*n*-hexane/EtOAc, 1:1), affording a mixture of alkenes **47** (20.4 mg, 74%) in a ratio ~4/1 in favor of the *trans* isomer as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (dd, J = 9.8, 3.8 Hz, 1H), 6.86 (dd, J = 9.8, 3.8 Hz, 1H), 6.20 (dd, J = 9.8, 3.8 Hz, 1H), 6.17 (t, J = 9.8, 3.8 Hz, 1H), 4.14 (m, 2H), 2.50 (d, J = 15.4 Hz, 1H), 2.20 (d, J = 15.4 Hz, 1H), 2.17–1.98 (m, 2H), 2.08 (s, 3H), 1.79 (m, 1H), 1.71 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.6, 171.1, 154.3, 154.3, 127.8, 126.6, 74.6, 63.1, 53.4, 49.9, 44.9, 41.3, 28.5, 27.2, 21.2; HRMS (ESI) calcd for $C_{15}H_{19}ClNaO_3$ $(M + Na)^+$ 305.0915, found 305.0919.

(4aS,5S,7R,8S,9aS)-8-Methyl-4a,5,6,7,8,9-hexahydro-5,8-epoxy-7,9a-methanobenzo[7]annulen-3(4H)-one (Cage Compound 52). To a vigorously stirred solution of compound **48** (8 mg, 0.04 mmol), HMPA (73 mg, 0.4 mmol), and HFIP (10 mg, 0.06 mmol) in THF (1.2 mL) at −78 °C was rapidly added SmI_2 (0.09 mmol, 0.53 mL, 0.17 M in THF). The resulting mixture was stirred at that temperature for 20 s before it was quenched with saturated aqueous NH_4Cl solution (4 mL). After extraction with EtOAc (3 × 5 mL), the combined organic phase was dried over Na_2SO_4 and filtered. The solvent was removed under vacuum, and the residue was dissolved in

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CH_2Cl_2 (0.1 mL). To the resulting solution at 0 °C was added TFA (0.25 mL), and the resulting mixture was stirred at that temperature for 1.5 h. The solvent was then removed by a stream of argon, and the residue was dissolved in EtOAc (5 mL). The resulting organic phase was washed with saturated aqueous $NaHCO_3$ solution (4 mL) and brine (4 mL) and dried over Na_2SO_4. After filtration and removal of the solvent under vacuum, the residue was purified by flash column chromatography with EtOAc/hexanes (2/3) as eluent to give cage compound 31 (2.8 mg, 36%): $[\alpha]_D^{20} = -21$ ($c = 0.5$ in $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 6.62 (d, J = 10.0 Hz, 1H), 5.94 (d, J = 10.0 Hz, 1H), 4.17 (t, J = 3.4 Hz, 1H), 2.43–2.29 (m, 4H), 1.97–1.94 (m, 2H), 1.90 (d, J = 11.6 Hz, 1H), 1.79–1.74 (m, 2H), 1.66 (d, J = 11.2 Hz, 1H), 1.45 (s, 3H); LRMS (ESI) $C_{13}H_{16}O_2Na$ $(M + Na)^+$ found 227, identical to the literature.[24]

■ 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.

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(20) The preparation of these materials is provided in ref 3i or as Supporting Information.

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1.3. Conclusion

En conclusion, la réaction de Prins-pinacol oxydative a été développée. Il s'agit de la version *umpolung aromatique* de cette transposition cationique rendue possible par l'utilisation d'un réactif à base d'iode hypervalent. Plusieurs exemples ont été étudiés (alcènes et alcynes), dont certains étaient très encombrés stériquement. La stéréosélectivité de la réaction a aussi été démontrée et une synthèse formelle de la (-)-platensimycine a été accomplie en appliquant cette nouvelle méthodologie. Éventuellement, la synthèse d'autres molécules spirobicycliques bioactives (ex : (+)-anhydro-β-rotunol, acide (-)-scopadulcique A, etc.) pourrait être réalisée en appliquant cette méthodologie.

1.4. Informations supplémentaires

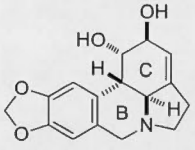
Les informations supplémentaires, contenant les protocoles expérimentaux ainsi que les caractérisations et spectres RMN, sont présentées à l'Annexe A.

CHAPITRE II :

SYNTHÈSE ASYMÉTRIQUE DE LA FORTUCINE

2.1. Introduction

Le second volet de ce document portera sur la synthèse asymétrique de la fortucine, une molécule aux propriétés antivirales et antitumorales. Cette molécule appartient à la classe des lycorines, des alcaloïdes isolés des espèces Amaryllidacées de plantes[45]. Ces molécules bioactives ont un squelette tétracyclique de type pyrrolo[*d,e*]phénanthridine. La plupart possèdent une jonction cyclique B/C *trans*. C'est le cas de la (-)-lycorine **32**, la plus répandue de cette classe d'alcaloïdes (**Figure 2.1**). Toutefois, certaines de ces molécules possèdent une jonction cyclique B/C *cis*, comme la (+)-fortucine **33**, la (+)-kirkine **34** et la (-)-siculinine **35**.



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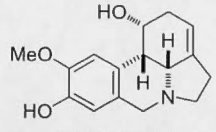
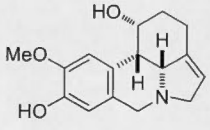
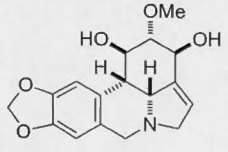


33, (+)-fortucine
(configuration absolue présumée)



34



35

Figure 2.1: Structures des alcaloïdes de type lycorines rapportées dans la littérature

Une seule synthèse non-asymétrique de cette molécule a été rapportée dans la littérature et il s'agit de celle proposée en 2008 par le groupe de Zard[46]. Au cours de cette synthèse, un

procédé radicalaire élégant est utilisé pour élaborer le tétracycle de type pyrrolo[*d,e*]phénanthridine de la molécule (**Schéma 2.1**).

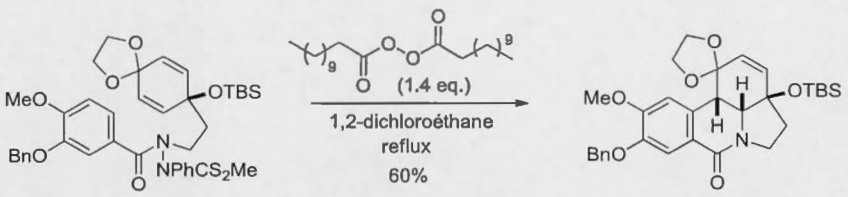


Schéma 2.1: Cascade radicalaire proposée par le groupe de Zard

Le présent document traitera de la première synthèse asymétrique de la fortucine **33** et de la réassignation de la configuration absolue du produit naturel. Le squelette principal **36** de la fortucine a été mis en place via une carbopalladation de type Heck à partir de l'éther d'énol silylé **37** (**Schéma 2.2**). La stratégie de Zard a ensuite été employée pour procéder à l'isomérisation de la double liaison selon un procédé de type Julia-Lythgoe afin d'obtenir la fortucine **33**. L'azabicycle **37** a été mis en place en appliquant la méthodologie de Wipf, élégante et efficace, qui consiste en une désaromatisation oxydative du phénol **38** dérivé de la *L*-tyrosine en utilisant un réactif à base d'iode hypervalent, suivie d'une addition conjuguée de type aza-Michael en milieu basique. Cette synthèse débute par le couplage de Schotten-Baumann entre l'ester méthylique **39** de la *L*-tyrosine et un dérivé silylé **40** du chlorure d'acyle de l'aldéhyde commercial **41**.

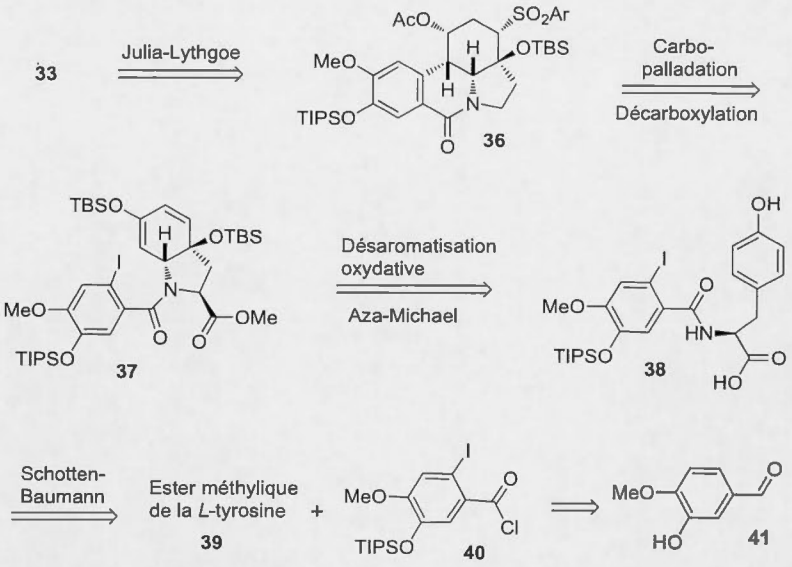


Schéma 2.2: Analyse rétrosynthétique de la synthèse asymétrique de la fortucine

Cette synthèse a permis de mettre en valeur, à deux reprises, la chimie de l'iode hypervalent. En effet, dans un premier temps, la méthodologie de Wipf a été utilisée pour mette en place le système azabicyclique du produit **37**. En 1995, le groupe de Wipf a mis au point une méthode générale permettant de synthétiser ces systèmes (**45** et **46**) à partir de dérivés *N*-protégés **42** de la *L*-tyrosine **(Schéma 2.3)**[47].

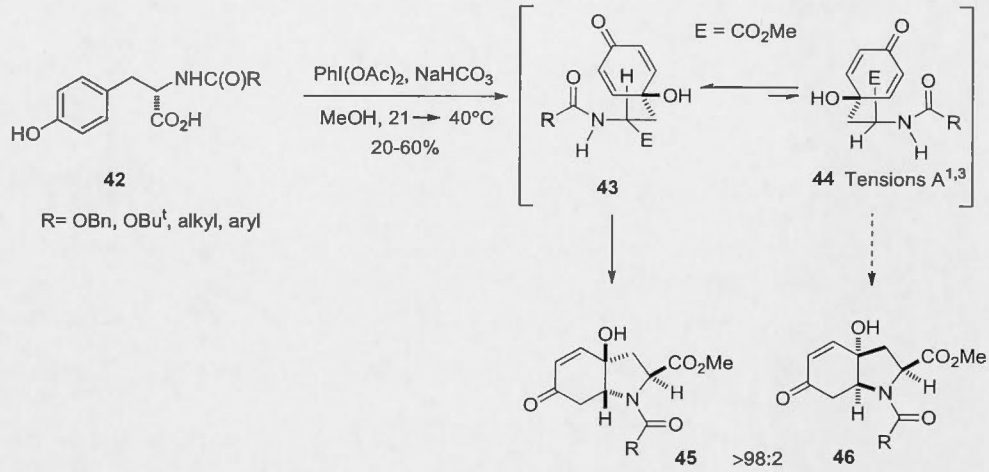


Schéma 2.3: Méthodologie de Wipf pour la synthèse de systèmes azabicycliques

Il s'agit d'une désaromatisation oxydative en présence d'un réactif d'iode hypervalent, le DIB. Selon Wipf, les produits **45** et **46** seraient obtenus via les approches représentées ci-dessus. Afin d'expliquer la haute diastéréosélectivité de cette transformation, l'auteur a suggéré l'implication, au niveau du conformère **44**, de grandes tensions $A^{1,3}$ (E vs amide) et d'une plus grande répulsion stérique entre E et l'environnement relativement encombré sous la diénone. Le conformère **43** serait donc bien plus favorisé et donnerait lieu à la formation quasi exclusive du diastéréoisomère désiré **45**. Enfin, Wipf a démontré que cet intermédiaire était très intéressant en synthèse de produits naturels[48]. C'est cette méthode qui a été choisie au laboratoire pour effectuer notre synthèse du système azabicyclique de la fortucine (**Schéma 2.4**).

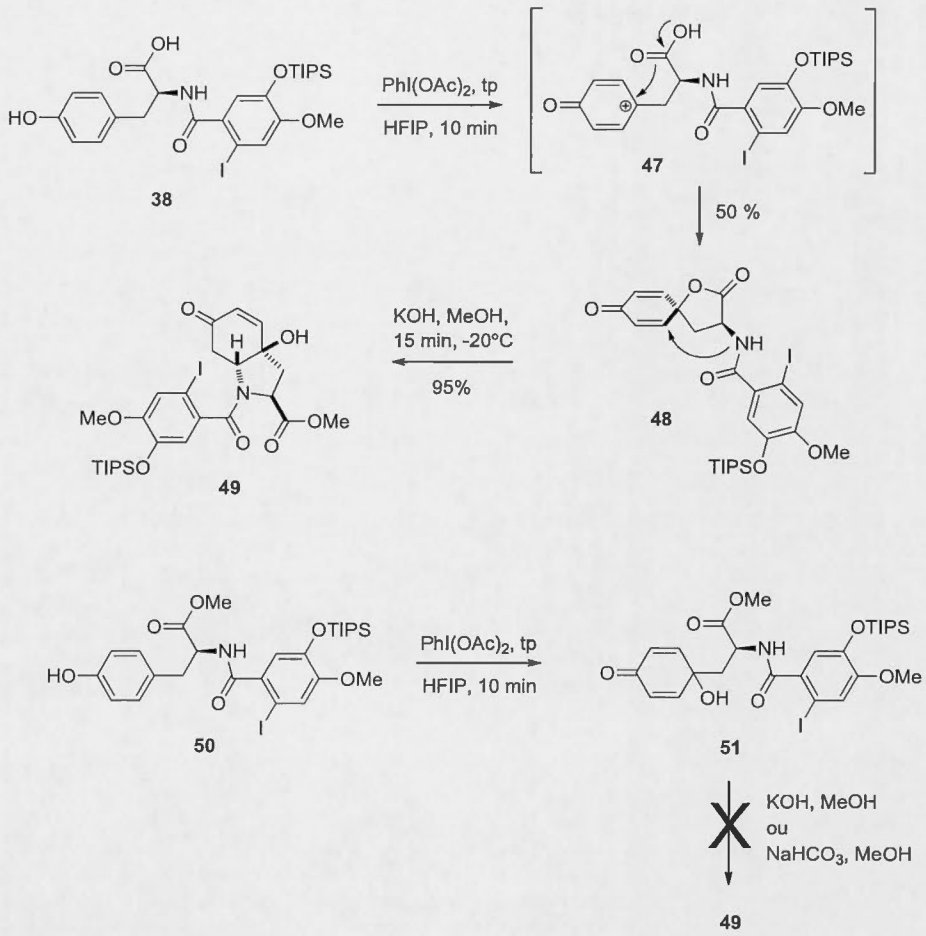


Schéma 2.4: Application de la méthodologie de Wipf à la synthèse de la fortucine

Tout d'abord, au cours de ce procédé, notre phénol **38** subit l'activation *umpolung* aromatique (ou désaromatisation oxydative) en présence d'un réactif d'iode hypervalent selon les conditions développées par le groupe de Kita. L'ion phénoxonium **47** ainsi formé induirait la spirolactonisation pour donner la spirolactone **48**. Un produit semblable a d'ailleurs déjà été obtenu par le groupe de Pettus en appliquant le même procédé oxydatif à base de DIB[49]. L'isolation de ce produit suggère une autre approche que celle décrite par Wipf. En effet, expérimentalement, il a été remarqué que le produit ouvert **51**, obtenu lors de la désaromatisation oxydative du phénol **50** suivant l'addition d'une molécule d'eau sur l'ion

phénoxonium généré, ne parvenait pas à réaliser la cyclisation souhaitée en milieu basique. Donc, il serait probable que l'étape de désymétrisation de la diénone s'effectue plutôt via la spirolactone **48** qui rapprocherait dans l'espace l'amide et l'énone dans une orientation plus propice à l'addition conjuguée de type aza-Michael. Ce serait uniquement à la suite de cette cyclisation, conduisant à un intermédiaire très tendu, que s'effectuerait la réouverture de la spirolactone par transestérification en milieu basique. Effectivement, en présence de méthylate de potassium, la spirolactone **48** fournit l'azabicycle souhaité **49** de façon hautement stéréosélective avec un excellent rendement.

Dans un deuxième temps, afin d'obtenir le produit **36** (**Schéma 2.2**), il a été nécessaire de procéder à la décarboxylation de l'ester méthylique présent dans le produit **37**. Il convient ici de rappeler que le centre asymétrique au pied de cet ester est celui de la *L*-tyrosine et qu'il avait été introduit en début de synthèse afin de contrôler la diastéréosélectivité des étapes subséquentes. Pour retirer ce fragment, le protocole de Boto, Hernandez et Suarez a été appliqué[50]. Développée en 2000, il s'agit d'une méthode faisant à nouveau appel à la chimie de l'iode hypervalent. Ce groupe a alors démontré que, en traitant des acides aminés *N*-substitués tels que **52** en présence de DIB (2.0 éq.) et d'I_2 (0.5 éq.), il se produit une décarboxylation oxydative (**Schéma 2.5**).

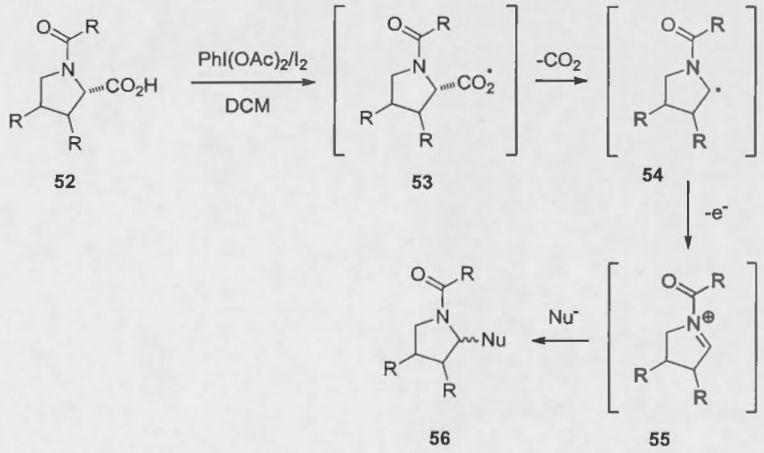
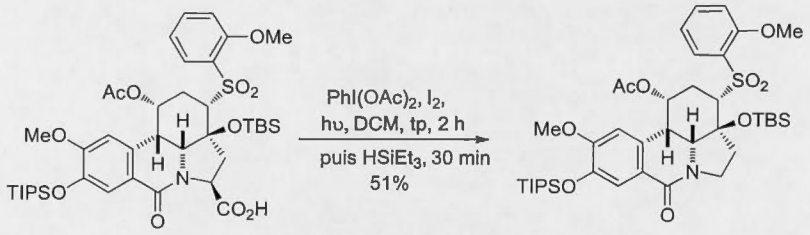


Schéma 2.5: Décarboxylation radicalaire oxydative d'acides aminés *N*-substitués

Le radical carboxyle **53**, formé après un premier SET, évolue en l'espèce radicalaire **54** suivant une perte de CO_2. Ensuite, après un second SET, l'ion *N*-acyliminium **55** peut être piégé par un nucléophile dans le milieu (ex : ion acétate, méthanol, etc.) pour donner le produit **56**. Dans le cas de la synthèse de la fortucine, la même stratégie a été employée. En effet, pour retirer l'acide carboxylique du produit **57**, celui-ci a été traité dans des conditions similaires pour donner le produit décarboxylé **36** après un traitement subséquent au triéthylsilane (**Schéma 2.6**).



57 **36**

Schéma 2.6: Décarboxylation oxydative lors de la synthèse de la fortucine

Enfin, la première synthèse asymétrique de la fortucine **33** (**Figure 2.1**) a été achevée. Afin de vérifier la configuration absolue du produit naturel, une analyse par diffraction des rayons X a été effectuée sur le produit **58** (**Figure 2.2**). Il a donc été possible de démontrer, après l'oléfination de type Julia-Lythgoe subséquente, que le produit **33** synthétisé était bien de même configuration absolue que celle rapportée dans la littérature concernant le produit naturel. Cependant, selon l'activité optique obtenue et les analyses de dichroïsme circulaire, ce travail a permis de réassigner la configuration absolue du produit naturel *ent*-**33**.

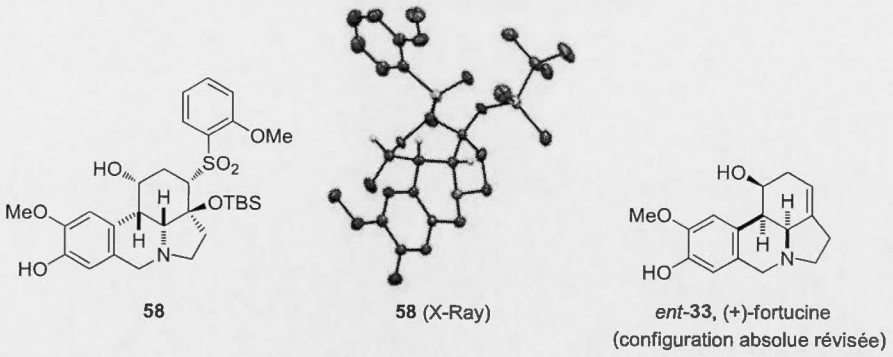


Figure 2.2: Résultats des analyses DRX

2.2. "ASYMMETRIC SYNTHESIS OF FORTUCINE AND REASSIGNMENT OF ITS ABSOLUTE CONFIGURATION" *ARTICLE*

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Asymmetric Synthesis of Fortucine and Reassignment of its Absolute Configuration

Marc-André Beaulieu[a] and Sylvain Canesi*[a]

Lycorine alkaloids are natural products isolated from amaryllidaceae species.[1] These compounds have been reported to possess antiviral and antitumor activities.[2] Their main core contains a tetracyclic pyrrolo[d,e]phenanthridine skeleton as illustrated in the structure of lycorine **1**, which is the most prevalent phenanthridine Amaryllidaceae alkaloid. Compounds belonging to this family have attracted substantial interest in the synthetic community since the isolation and characterization of (-)-lycorine **1**.[3] While most have a *trans* B/C-ring junction, a few have a *cis* junction, including (+)-fortucine **2**,[4] (+)-kirkine **3**,[5] and (-)-siculinine **4**.[6] Although no experimental evidence was provided for establishing the absolute configuration of (+)-fortucine,[4] the authors proposed the structure of compound **2** described in Chart 1, most probably by analogy with (-)-lycorine **1**, a related parent and more studied alkaloid.

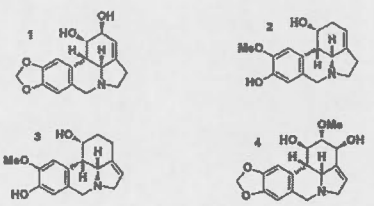
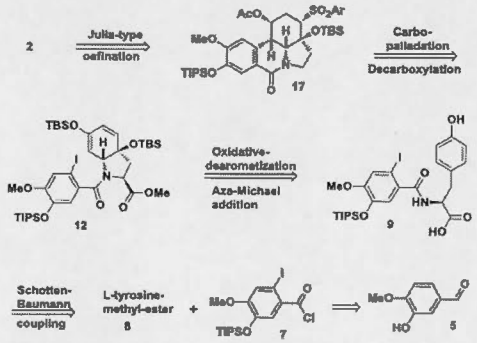


Chart 1. Lycorine alkaloid members reported in the literature.

In this paper, we present a convergent asymmetric synthesis of one enantiomer of fortucine, **2**, a molecule isolated from the fortune variety of narcissus. The only synthesis of fortucine in the literature was reported by Zard and coworkers,[7] whose preparation of the main tetracyclic core of fortucine employed an elegant radical cascade transformation as a key step. However, since it is a racemic synthesis, the authors could not confirm the absolute configuration of natural fortucine. Meanwhile, the same group also revised the initial proposed structure of kirkine **3**, a natural related isomer which has probably the same absolute configuration than fortucine. A significant advantage of our asymmetric synthesis is that we were able to determine the correct absolute configuration of natural fortucine. Our asymmetric synthesis of fortucine starts from L-tyrosine-methyl ester **8** and 3-hydroxy-4-methoxybenzaldehyde **5** along a retrosynthetic pathway presented in Scheme 1. These segments are joined through an amide functionality **9**, which is used as an amine-protecting group and is later reduced to install the required cycloamine. This approach presents an interesting alternative to common protecting-group-free strategies,[8] since a functional protecting group not only masks the reactivity of a sensitive ensemble but also carries a moiety of the final target. We also decided to involve hypervalent iodine reagents in several steps of the synthesis due to their lower environmental impact compared with heavy metal reagents. Thus, a Wipf-type strategy[9] based on the Kita oxidative dearomatization process[10] was used to provide stereoselectivity and was followed by an oxidative decarboxylation process[11] to yield the final product.



Scheme 1. Retrosynthesis of enantiopure fortucine.

The hydroxyl group of the inexpensive starting material 3-hydroxy-4-methoxybenzaldehyde **5** was protected using TIPSCl. Subsequent treatment with iodine and silver nitrate produced compound **6** in 73% yield over two steps. The aldehyde functionality was oxidized into the desired acyl chloride in the

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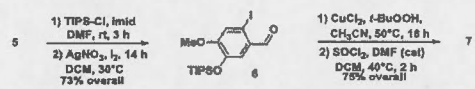
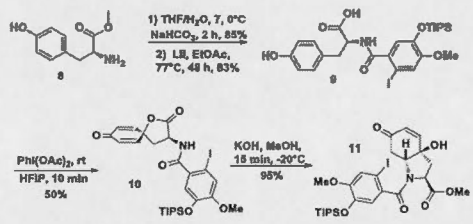
presence of $CuCl_2$ and *t*-BuOOH,[12] followed by a Vilsmeier activation[13] to yield compound **7** in 75% overall yield, Scheme 2.



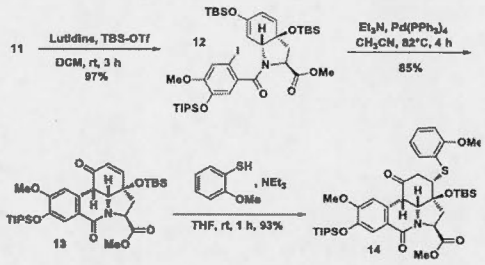
Scheme 2. Formation of the aromatic subunit.

At this stage, compound **7** was attached through the amino group to L-tyrosine methyl ester **8** using the Schotten-Baumann reaction and the ester functionality was selectively transformed into a carboxylic acid under mild Krapcho-like conditions[14] to avoid deprotecting the phenol group, leading to intermediate **9** in 71% overall yield. Compound **9** represents the first key intermediate in the synthesis. Using a remarkable methodology developed by Wipf and coworkers, this phenol was readily dearomatized and stereoselectively transformed into the functionalized bicyclic system **11**. The stereochemistry is guided by the chiral center of the tyrosine.[15] This elegant process[9] occurs through an oxidative lactonization mediated by the hypervalent iodine reagent leading to compound **10** in 50% yield. Subsequent treatment in the presence of potassium methoxide produces the desired bicyclic core **11** in 95% yield with high stereoselectivity, Scheme 3.



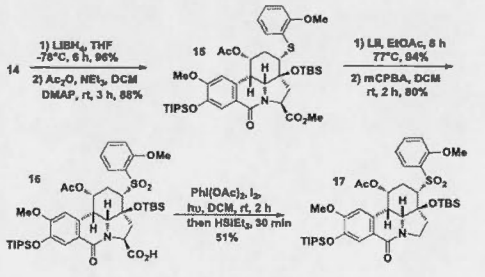
Scheme 3. Formation of the bicyclic core.

The required tetracyclic system was produced from the functionalized synthon **11** via a Heck-type carbopalladation process. First, the ketone functionality was quantitatively transformed into the pre-activated enol-ether **12** in the presence of TBS-triflate, which also converted the tertiary alcohol moiety into the corresponding silyl ether required at the end of the synthesis. The intramolecular C-C coupling was performed by treatment of **12** with tetrakis(tripbenylphosphine)palladium, to yield the desired *cis* tetracyclic pyrrolo[d,e]phenanthridine skeleton **13** in 85% yield. The observed *cis* stereoselectivity is rationalized by the planar geometry of the lactam segment. It should be noted that compound **13** represents the main core of several natural products of the same family (Chart 1). The alkene migration necessary to reach final product **2** entails the Julia-type transformation[16] brilliantly used by Zard and co-workers during their synthesis of fortucine. Following their approach, treatment of compound **13** with ortho-methoxythiophenol and NEt_3 enabled the kinetic formation of **14** through a 1-4 addition in 93% yield, Scheme 4.



Scheme 4. Formation of the main tetracyclic system.

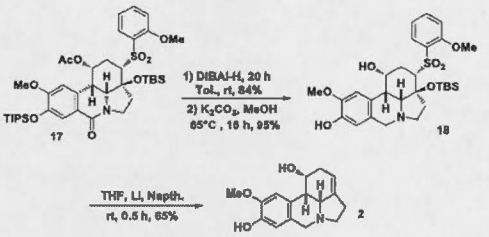
The secondary alcohol functionality in the structure of enantiopure fortucine was obtained in 96% yield by treatment of **14** with $LiBH_4$, which was chosen based on its superior stereoselectivity. Subsequently, an acetate group was quantitatively introduced on the alcohol moiety as a protecting group to yield compound **15**. The enantiopurity of **15** was verified by NMR by coupling the acid derivative of **15** with (S)-(-)-alpha-methylbenzylamine. Only one diastereoisomer of the product was apparent within the limits of ^{1}H-NMR spectroscopy (300 MHz), establishing a lower limit of 95% for the enantiomeric excess of compound **15**. At this stage, the ester functionality was quantitatively transformed into a carboxylic acid using a Krapcho-like transformation that is mild enough to avoid deprotecting the hydroxyl groups. Further treatment with mCPBA produced sulfone **16** in 98% yield. The sulfonyl group was required for the final step to enable the introduction of the alkene functionality by a Julia-like transformation. The carboxylic acid moiety that enabled us to control the diastereoselectivity of the tetracyclic core was removed using a second strategic step mediated by a hypervalent iodine reagent,[17] following a noteworthy protocol developed by Boto, Hernandez, and Suarez.[11] However, this strategy was only successful when the secondary alcohol moiety was previously protected as an acetate to prevent its oxidation into a ketone promoted by the hypervalent species. An oxidative decarboxylation process mediated by diacetoxyiodo-benzene and iodine was used to first generate an iminium ion which was further reduced to **17** by the addition of triethylsilylane in 51% yield, Scheme 5.



Scheme 5. Elaboration of the main core of fortucine.

To conclude the synthesis, the lactam subunit used as a pyrrolidine protecting group and the acetate functionality were

reduced in the presence of DIBAl-H in 80% yield. Subsequent treatment with K_2CO_3 in methanol resulted in TIPS deprotection, producing phenol **18** in 95% yield. Compound **18** is the final precursor to fortucine and has been transformed into the target by treatment with lithium naphthalene (Julia-type conditions[18]) in 65% yield, Scheme 6. A similar transformation with sodium amalgam in methanol was first demonstrated by Zard et al. during their synthesis. [7] Formaly, the transformation of the enone moiety present in **13** into fortucine represents a reductive isomerization process.



Scheme 6. Final steps of the synthesis.

The confirmation of the structure and absolute configuration of **2** was carried out using several techniques. At this stage, the NMR and mass spectrometry data for **2** were in agreement with the literature.[5,7] However, the optical rotation of our synthetic **2**, $[\alpha_D]_{20}$ = –63 (c = 0.04 in ethanol), had the opposite sign from what is reported in the literature for natural fortucine, $[\alpha_D]_{20}$ = +66 (c = 0.23 in ethanol).[4a] In addition, our synthesized fortucine has the opposite Cotton effect at 285 nm compared with the natural product, as assessed by circular dichroism spectroscopy.[4] In order to determine the actual absolute configuration of our enantiopure compound, we performed a crystallographic analysis of four crystals of the final precursor **18** (Figure 1a).[19] The presence of S and Si heavy elements in this molecule guarantees unequivocal assignment of the absolute configuration as drawn in Scheme 6 (Flack parameter of 0.00(2)). Circular dichroism experiments also confirmed that the crystals had the same positive Cotton effect at 285 nm as the whole sample, further confirming that the X-ray structure is representative of the whole sample.[20] Hence, we undoubtedly synthesized the reported enantiomer of fortucine, but the isolated natural product **ent-2** is actually its mirror image, with the correct absolute structure reassigned as drawn in Figure 1b. By analogy, we reason that the absolute configuration of (+)-kirkine,[5,7] which appears as a natural related isomer of fortucine, is probably also incorrect.

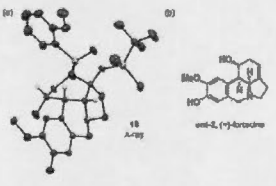


Figure 1: (a) ORTEP representation at 50% ellipsoid probability of **18** in the solid-state structure of **18**·$\frac{1}{2}H_2O$. Hydrogen atoms were removed for clarity, except those on the asymmetric carbons. (b) Corrected absolute configuration of (+)-fortucine.

In summary, an asymmetric synthesis of fortucine was achieved using L-tyrosine-methyl ester as the sole precursor of chirality on three asymmetric carbons. The synthesis was based on two key steps mediated by hypervalent iodine reagents. In addition, this work has enabled to reassign the absolute configuration of this natural product

Acknowledgements

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Keywords: hypervalent iodine · aromatic ring umpolung · total synthesis · oxidation · natural product

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[19] See the experimental information section for details.

[20] By comparison, natural (+)-fortucine has a negative Cotton effect at 282 nm.[4a]

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Published online: ((will be filled in by the editorial staff))

2.3. Conclusion

La première synthèse asymétrique de la fortucine a été réalisée. Parmi les étapes clés de cette synthèse, deux impliquent l'utilisation de la chimie de l'iode hypervalent. En effet, la stéréosélectivité de cette synthèse est dû à l'application de la méthodologie de Wipf qui consiste en une désaromatisation oxydative d'un dérivé de la *L*-tyrosine en utilisant un réactif d'iode hypervalent. Cela a permis de mettre en place le système azabicyclique de la molécule. C'est l'unique centre chiral présent sur la *L*-tyrosine qui a permis un contrôle de tous les autres centres stéréogéniques de la fortucine. Cette synthèse n'implique donc pas l'utilisation ni le gaspillage d'auxiliaires chiraux ou encore de systèmes catalytiques à base de métaux coûteux et de ligands dont la synthèse est très souvent ardue. De plus, une décarboxylation oxydative permet d'obtenir un substrat clé à partir duquel il a été possible d'appliquer la stratégie de Zard afin de procéder à l'isomérisation de la double liaison. Enfin, cette synthèse a non seulement permis de mettre en valeur la chimie de l'iode hypervalent en synthèse totale, mais elle a aussi permis la réassignation de la configuration absolue du produit naturel. La stratégie développée au laboratoire pour la synthèse du tétracycle pyrrolo[*d,e*]phénanthridine pourrait être mise à profit lors d'éventuelles synthèses d'autres molécules de la classe des lycorines, telles que la (+)-kirkine ou la (-)-siculinine. Il serait alors intéressant de vérifier l'exactitude de l'attribution de la configuration absolue de ces produits naturels.

2.4. Informations supplémentaires

Les informations supplémentaires contenant les protocoles expérimentaux ainsi que les caractérisations et spectres RMN, sont présentées à l'Annexe B.

ANNEXE A: "OXIDATIVE PRINS-PINACOL TANDEM PROCESS MEDIATED BY A HYPERVALENT IODINE REAGENT: SCOPE, LIMITATIONS, AND APPLICATIONS"
SUPPORTING INFORMATION

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Titre: Oxidative Prins-Pinacol Tandem Process Mediated by a Hypervalent Iodine Reagent: Scope, Limitations, and Applications

Auteurs: Marc-André Beaulieu, Kimiaka C. Guérard, Gaëtan Maertens, Cyrille Sabot et Sylvain Canesi*

An Oxidative Prins-Pinacol Tandem Process Mediated by a Hypervalent Iodine Reagent: Scope, Limitations and Applications

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Supporting Information

Table of Contents

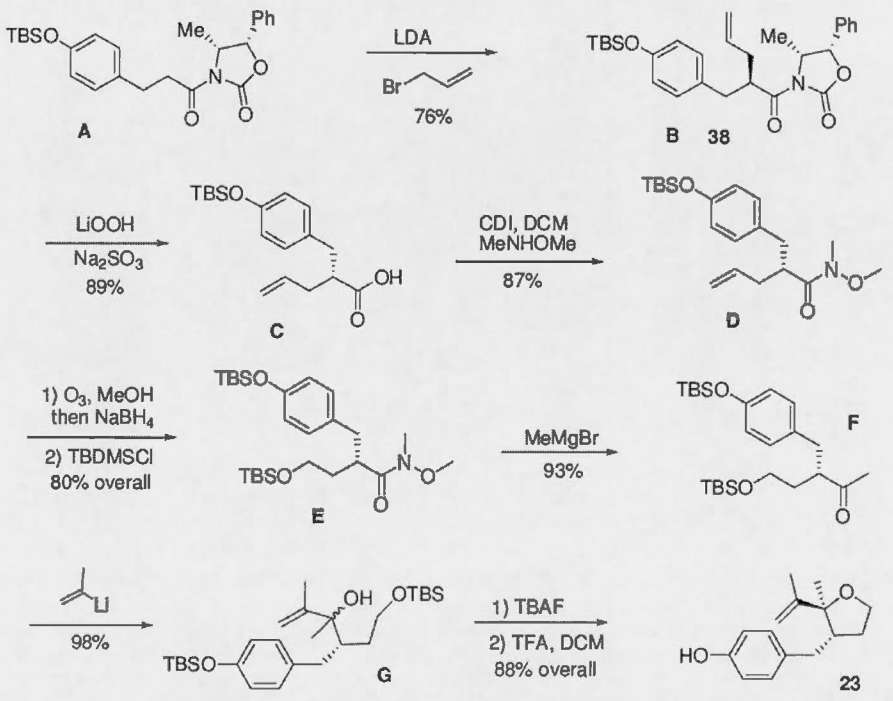
I. General information and materials

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

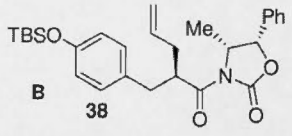
II.4: Representative procedures for the formal synthesis of (-)-Platensimycin:

This experimental part is also present in reference 3i of this manuscript.

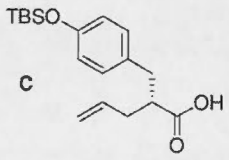
a) Synthesis of compound ***23***.



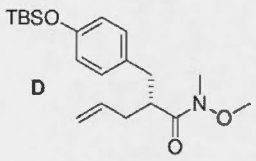
b) Procedures. (see reference 3i)



To a solution of the Evans oxazolidinone **A** (1.4 mmol, 615 mg) in THF (4.5 mL) was added LDA (4.2 mmol, 4.2 mL) at -78°C. After 20 minutes, allyl bromide (7 mmol, 0.61 mL) was added dropwise. The reaction was then slowly warmed at 5°C and stirred until completion by TLC. The reaction was quenched by the addition of saturated NH_4Cl solution, the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO4), filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel chromatography (hexane/ethyl acetate 90/10) to yield a yellow oil **B** (or **38**) (76%, 510 mg). $[\alpha_D]20 = -50$ ($c = 1$, in $CHCl_3$); **IR** υ (cm^{-1}) 1782, 1648,1607, 1342, 1253, 1195; **^{1}H** (600 MHz, $CDCl_3$): δ= 7.38 (t, J = 8.2 Hz, 3H); 7.25 (t, J = 8.2 Hz, 2H); 7.09 (d, J = 8.2 Hz, 2H); 6.77 (d, J = 8.2 Hz, 2H); 5.83 (m, 1H), 5.28 (d, J = 7.1 Hz, 1H); 5.07 (d, J = 17.0 Hz, 1H); 5.03 (d, J = 9.4 Hz, 1H); 4.57 (q, J = 6.6 Hz, 1H); 4.29 (m, 1H); 2.88 (dd, J = 13.7, 9.4 Hz, 1H); 2.78 (dd, J = 13.7, 6.6 Hz, 1H); 2.50 (m, 1H), 2.33 (m, 1H); 0.96 (s, 9H); 0.82 (d, J = 13.7 Hz, 3H); 0.18 (s, 6H); 0.16 (s, 6H); **^{13}C** NMR (75 MHz, $CDCl_3$): δ= 175.2, 154.1, 152.5, 134.9, 133.1, 131.5, 130.0, 128.5, 125.5, 119.8, 117.1, 78.6, 54.9, 44.1, 37.6, 36.3, 25.6, 18.1, 14.5, -4.4; **HRMS** (ESI): Calc. for $C_{28}H_{38}NO_4Si$ $(M+H)^+$: 480.2565; found: 480.2573.

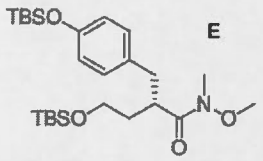


To a solution of compound **B** (1.2 mmol, 575 mg) in THF/H_2O (3/1, 24 mL) was added H_2O_2 (30% in H_2O, ~9.6 mmol) followed by $LiOH,H_2O$ (2.4 mmol, 101 mg). The mixture was allowed to warm to room temperature and stirred until completion by TLC (~ 10 min.). The mixture was cooled to 0°C and quenched with saturated Na_2SO_3 solution, and diluted with ethyl acetate (25 mL) then citric acid was added (460 mg, 3.6 mmol, 1.5 equiv. PH~3), the aqueous layer was extracted with ethyl acetate (3*20 mL). The combined organic phases were washed with brine (30 ml), dried (Na_2SO_4), filtered and the solvent removed in vacuo, the crude product was purified by silica gel chromatography (hexane/ethyl acetate 25/75) to yield a colourless oil **C** (89%, 342 mg). $[\alpha_D]20 = +20$ ($c = 0.6$ in $CHCl_3$); **IR** υ (cm^{-1}) 2922, 1705, 1503, 1249; **^{1}H NMR** (300 MHz, $CDCl_3$): δ= 7.04 (d, J = 8.2 Hz, 2H); 6.75 (d, J = 8.2 Hz, 2H); 5.78 (m, 1H); 5.10 (d, J = 8.2 Hz, 1H); 5.08 (d, J = 18.1 Hz, 1H); 2.92 (dd, J = 10.4, 15.9 Hz, 1H); 2.73 (m, 2H); 2.33 (m, 2H); 0.98 (s, 9H); 0.19 (s, 6H). **^{13}C** NMR (75 MHz, $CDCl_3$): δ= 180.7, 154.1, 134.8, 131.4, 129.8, 119.9, 117.3, 47.1, 36.5, 35.4, 25.6, 18.1, -4.4; **HRMS** (ESI): Calc. for $C_{18}H_{29}O_3Si$ $(M+H)^+$: 321.1880; found: 321.1884.

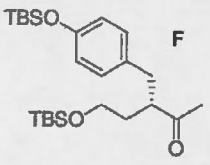


To a solution of compound **C** (320 mg, 1 mmol) in dichloromethane (5 mL) at 0°C was added carbonyldiimidizole (210 mg, 1.3 mmol) and a catalytic amount of DMAP (10 %, 12 mg, 0.1 mmol). The resulting solution was stirred for 1 hour. To this solution was added O,N-dimethylhydroxylamine hydrochloride (300 mg, 3 mmol) and the reaction was stirred overnight. The reaction solution was then quenched with saturated NH_4Cl solution (10 mL) then diluted with ethyl acetate (20 mL). The combined organic phases were washed with brine (30 ml), dried (Na_2SO_4), filtered and the solvent removed in vacuo, the crude product was purified by silica gel chromatography (hexane/ethyl acetate 80/20) to yield a pale yellow oil **D** (87%, 317 mg). $[\alpha_D]20 = -26$ ($c = 0.5$ in $CHCl_3$); **IR** υ (cm^{-1}) 2929, 1661, 1608, 1510,

1256; ^{1}**H** (300 MHz, $CDCl_3$): δ= 7.03 (d, *J* = 8.2 Hz, 2H); 6.73 (d, *J* = 8.2 Hz, 2H); 5.76 (m, 1H); 5.07 (d, *J* = 17.0 Hz, 1H); 5.01 (d, *J* = 12.0 Hz, 1H); 3.31 (s, 3H); 3.15 (m, 1H); 3.08 (s, 3H); 2.89 (dd, *J* = 13.2; 9.3 Hz, 1H); 2.64 (dd, *J* = 13.2; 5.5 Hz, 1H); 2.42 (m, 1H); 2.23 (m, 1H); 0.97 (s, 9H); 0.16 (s, 6H); ^{13}**C** NMR (75 MHz, $CDCl_3$): δ= 175.8, 153.9, 135.7, 132.7, 129.9, 119.9, 116.6, 61.1, 43.3, 37.5, 36.7, 31.9, 25.6, 18.1, -4.4; **HRMS** (ESI): Calc. for $C_{20}H_{34}NO_3Si$ $(M+H)^+$: 364.2302; found: 364.2300.

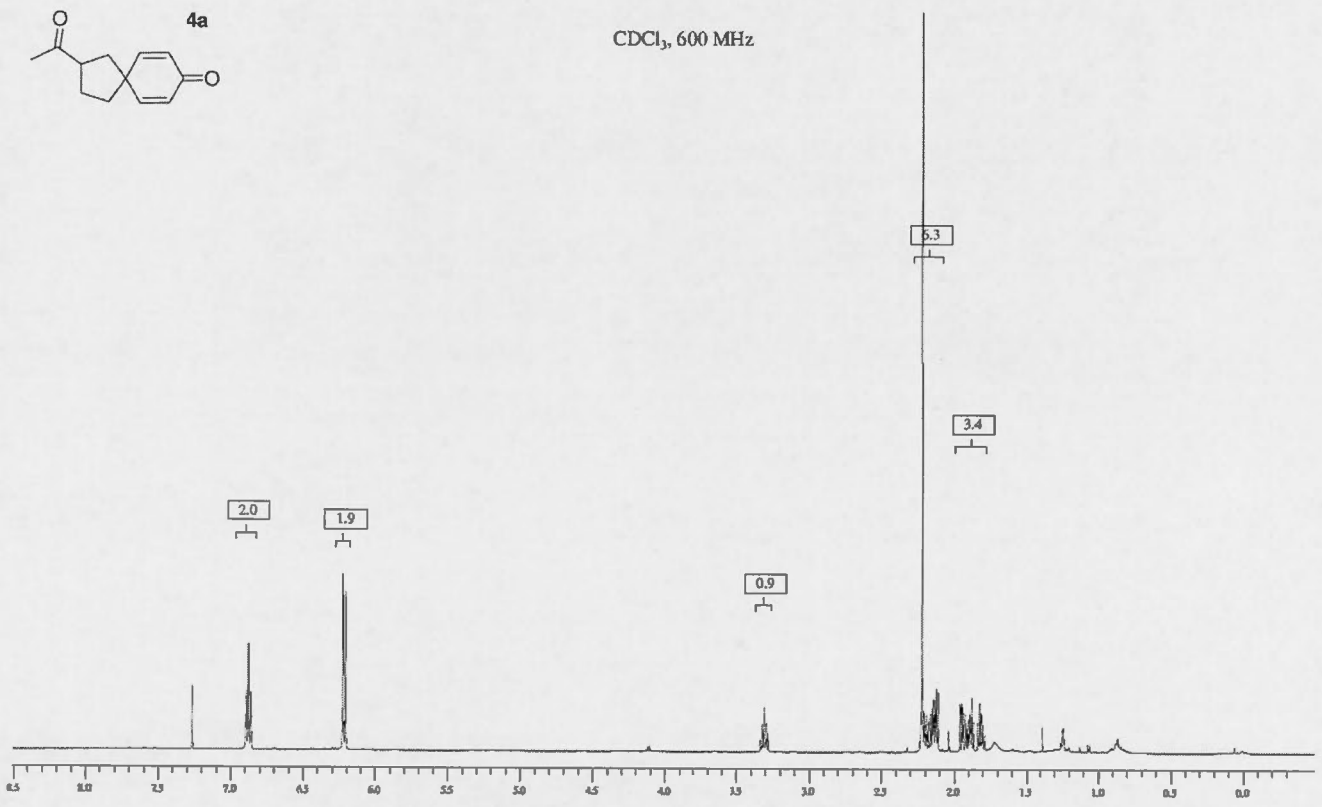


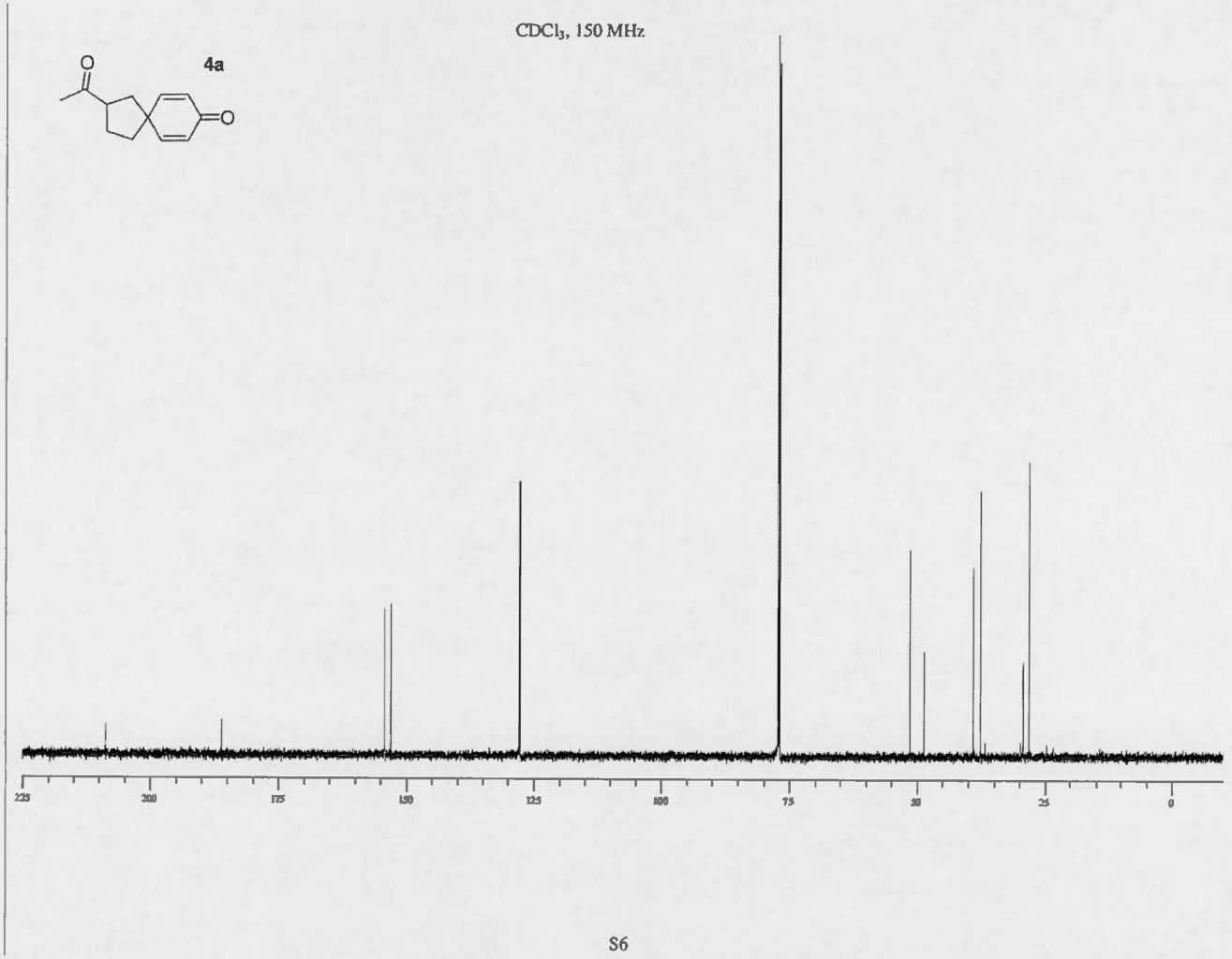
A solution of the allyl compound **D** (1.36 g, 3.74 mmol) in methanol (25 ml) at -78°C was treated with ozone (bubbled through the solution until appearance of blue color). Argon was bubbled through the solution for 3 min. and $NaBH_4$ (150 mg, 3.74 mmol) was added. The reaction was allowed to warm to room temperature and was stirred until the starting material disappears by TLC. The reaction was quenched with NH_4Cl (20 ml) and the mixture was concentrated in vacuo. The reaction was diluted with ethyl acetate (30 ml). The organic layer was removed and the aqueous lawer washed two times with ethyl aketale (15 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated in vacuo. The crude alcohol obtained was diluted as it in dry DMF at 0 °C and imidazole (620 mg, 9 mmol), *tert*-butyldimethylsilyl chloride (685 mg, 4.50 mmol) were added. The resulting solution was stirred at room temperature for 12 hours and then was treated with sat. aq. $NaHCO_3$ (10 mL). The aqueous phase was extracted with EtOAc (4 x 20 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (*n*-hexane/ EtOAc, 88:12) to afford 1.45 g (80%, overall) of the product **E** as a yellow oil. $[\alpha_D]20 = -9$ (*c* = 0.75 in $CHCl_3$); **IR** υ (cm^{-1}) 2930, 1663, 1510, 1256; ^{1}**H** (300 MHz, $CDCl_3$): δ= 7.04 (d, *J* = 8.2 Hz, 2H); 6.73 (d, *J* = 8.2 Hz, 2H); 3.60 (m, 2H); 3.38 (s, 3H); 3.08 (s, 3H); 2.88 (dd, *J* = 13.2; 8.8 Hz, 1H); 2.62 (dd, *J* = 13.2; 6.0 Hz, 1H); 1.89 (m, 1H); 1.67 (m, 1H); 0.97 (s, 9H); 0.87 (s, 9H); 0.16 (s, 6H); 0.01 (s, 6H); ^{13}**C** NMR (75 MHz, $CDCl_3$): δ= 176.4, 153.9, 132.8, 129.9, 119.8, 61.0, 60.7, 39.7, 37.7, 35.1, 31.9, 25.8, 25.6, 18.1, -4.4, -5.3; **HRMS** (ESI): Calc. for $C_{25}H_{48}NO_4Si_2$ $(M+H)^+$: 482.3116; found: 482.3113.

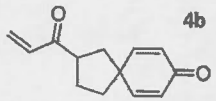


To a solution of the Weinreb amide **E** (1.45 g, 3 mmol) in dry THF (13 mL) at 0 °C was added methylmagnesium bromide (3M in THF, 2 mL, 6 mmol, 2 equiv.) dropwise. The reaction mixture was stirred 0°C for 1 h and then a solution of 10 mL of sat. aq. NH_4Cl was added. The aqueous phase was extracted with EtOAc (3 * 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by chromatography (*n*-hexane:EtOAc, 9:1) to afford 1.22 g (93%) of the compound **F** desired as a colorless oil. $[\alpha_D]20 = -20$ (*c* = 0.9 in THF); **IR** υ (cm^{-1}) 2954, 1715, 1510, 1256, 1106; ^{1}**H** (300 MHz, $CDCl_3$): δ= 7.00 (d, *J* = 8.8 Hz, 2H); 6.74 (d, *J* = 8.8 Hz, 2H); 3.58 (t, *J* = 6.0 Hz, 2H); 2.96 (m, 1H); 2.80 (dd, *J* = 13.7; 8.2 Hz, 1H); 2.61 (dd, *J* = 13.7; 7.1 Hz, 1H); 1.98 (s, 3H); 1.87 (m, 1H); 1.62 (m, 1H); 0.98 (s, 9H); 0.88 (s, 9H); 0.18 (s, 6H); 0.02 (s, 6H). ^{13}**C** NMR (75 MHz, $CDCl_3$): δ= 212.5, 154.0, 132.1, 129.7, 120.0, 60.9, 51.4, 37.4, 34.4, 30.6, 25.8, 25.6, 18.2, 18.1, -4.4, -5.4. **HRMS** (ESI): Calc. for $C_{24}H_{45}O_3Si$ $(M+H)^+$: 437.2902; found: 437.2899.

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

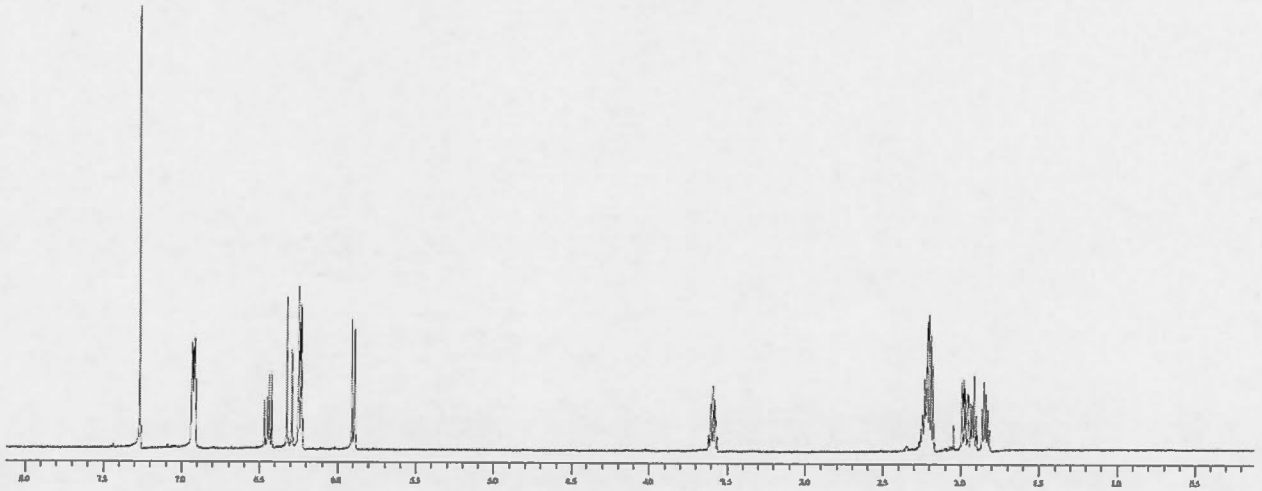

4a
CDCl3, 600 MHz
6.3
3.4
2.0
1.9
0.9

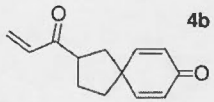

CDCl3, 150 MHz
4a
O
O
225
200
175
150
125
100
75
50
25
0



4b

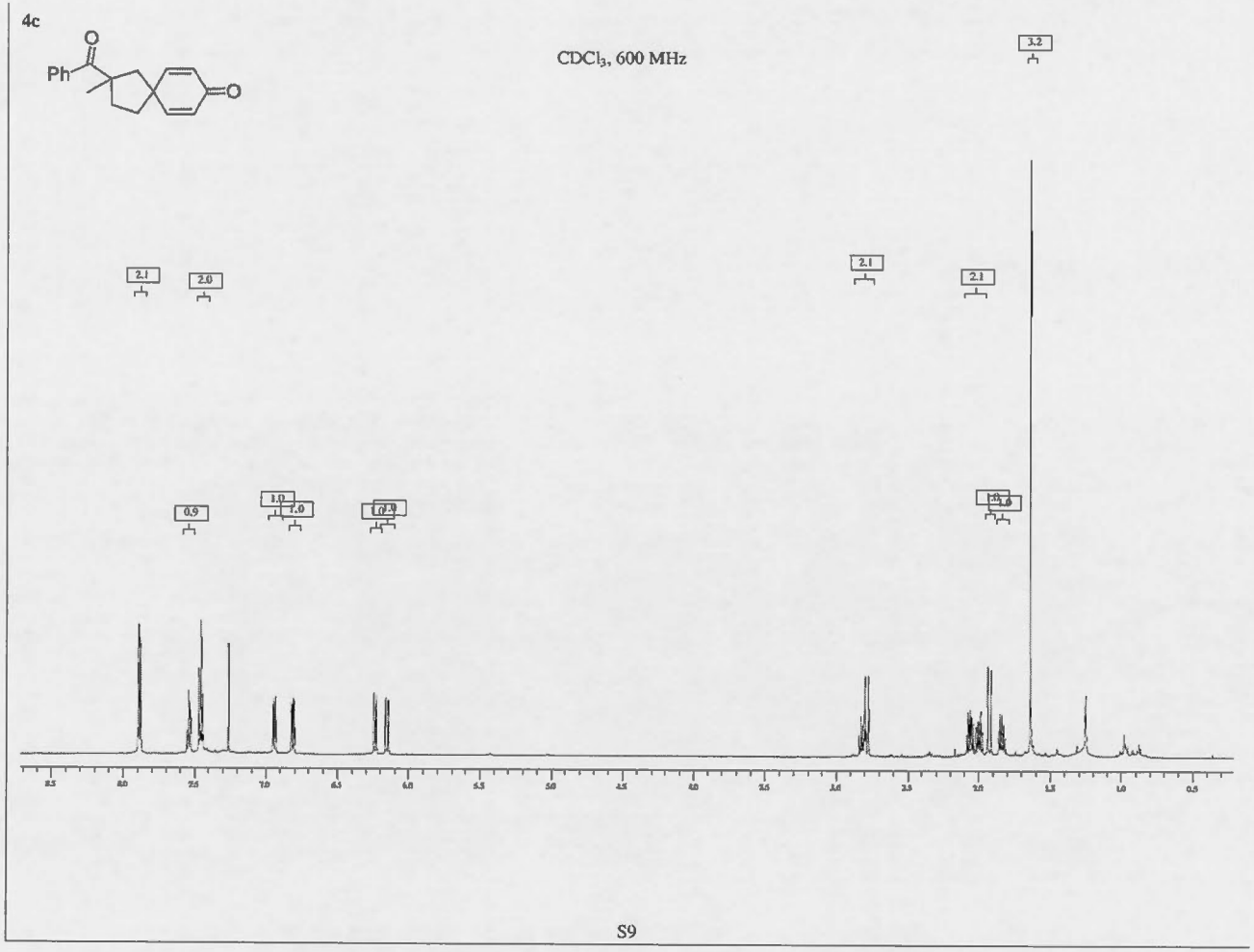
$CDCl_3$, 600 MHz





4b

$CDCl_3$, 150 MHz


4c
Ph
O
O
CDCl3, 600 MHz
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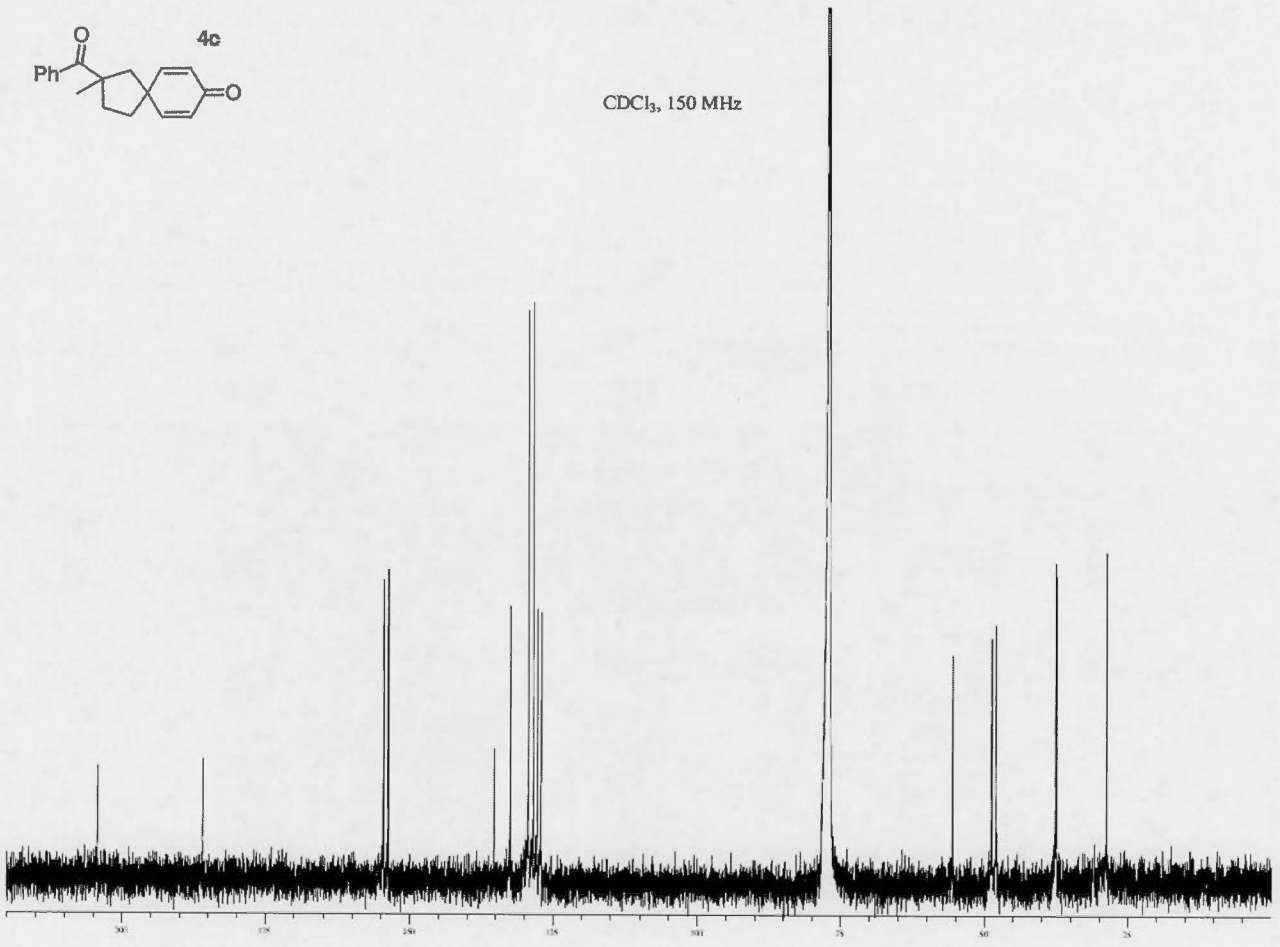
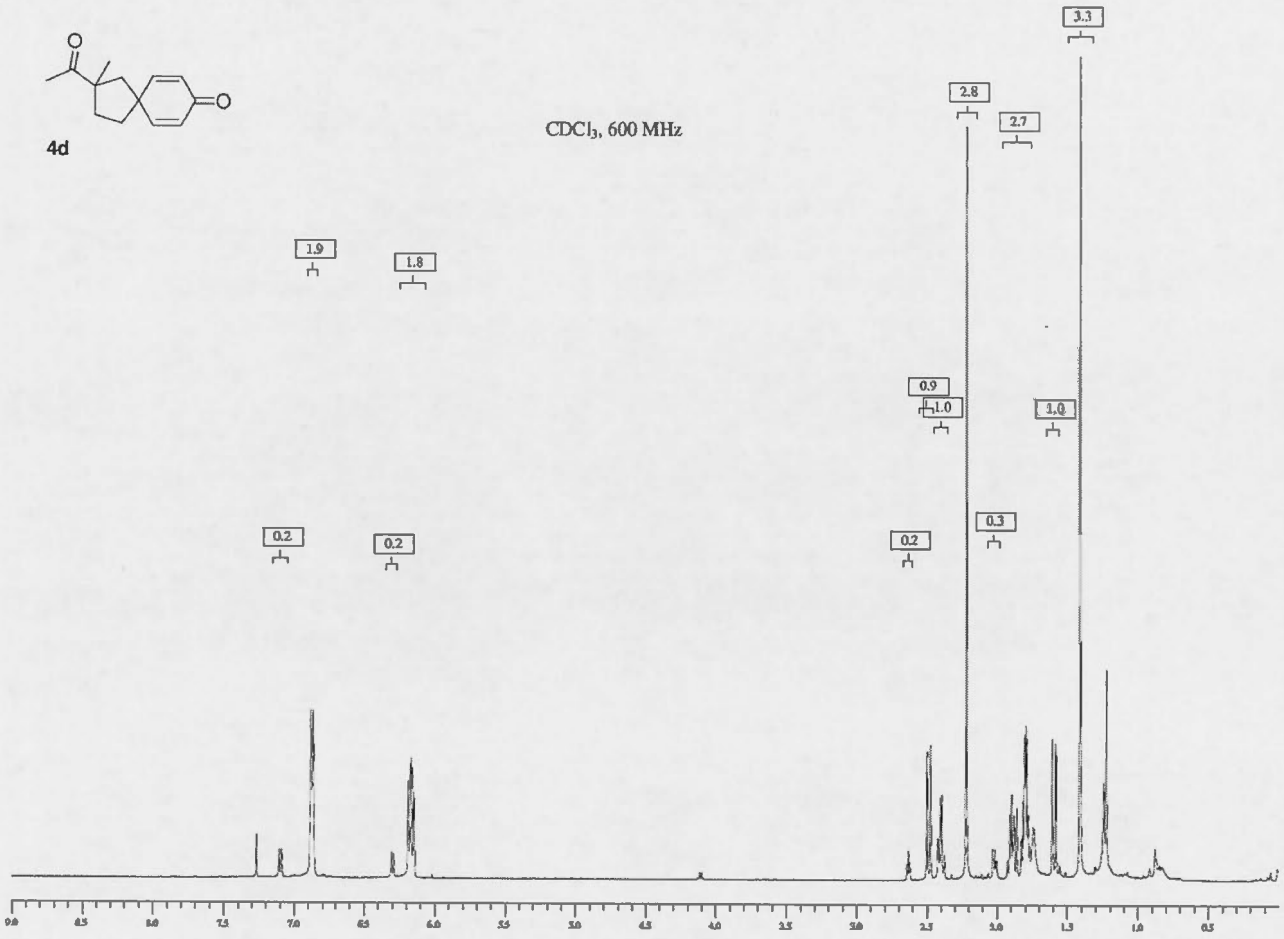
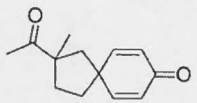
2.1
2.0
2.1
2.1
0.9
1.0
1.0
1.0
S9



S10

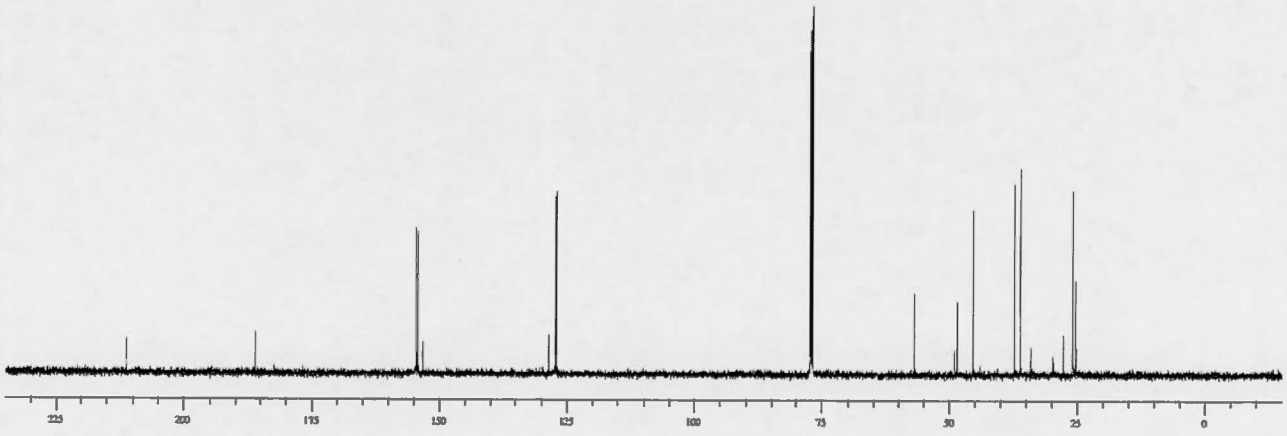


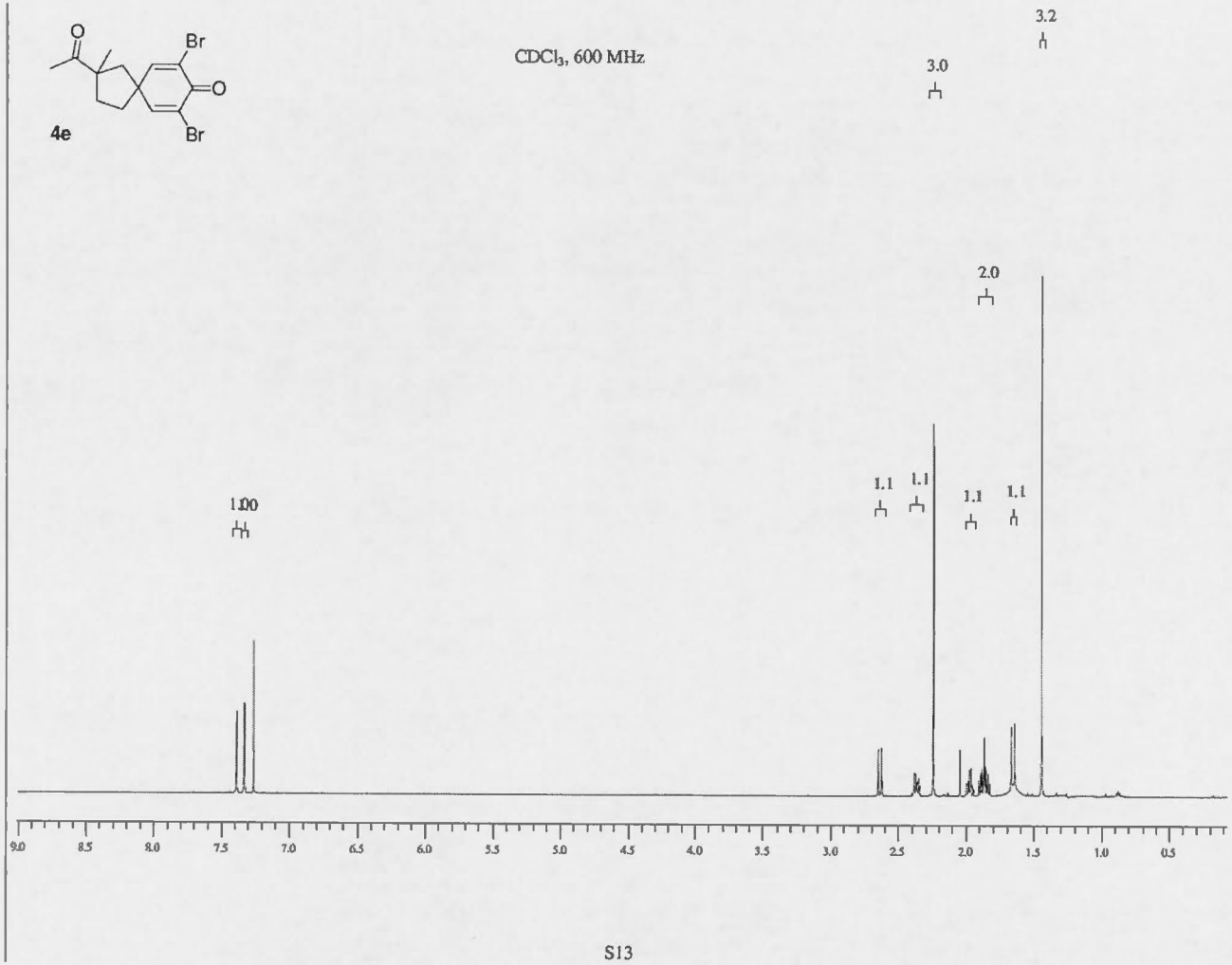
S11

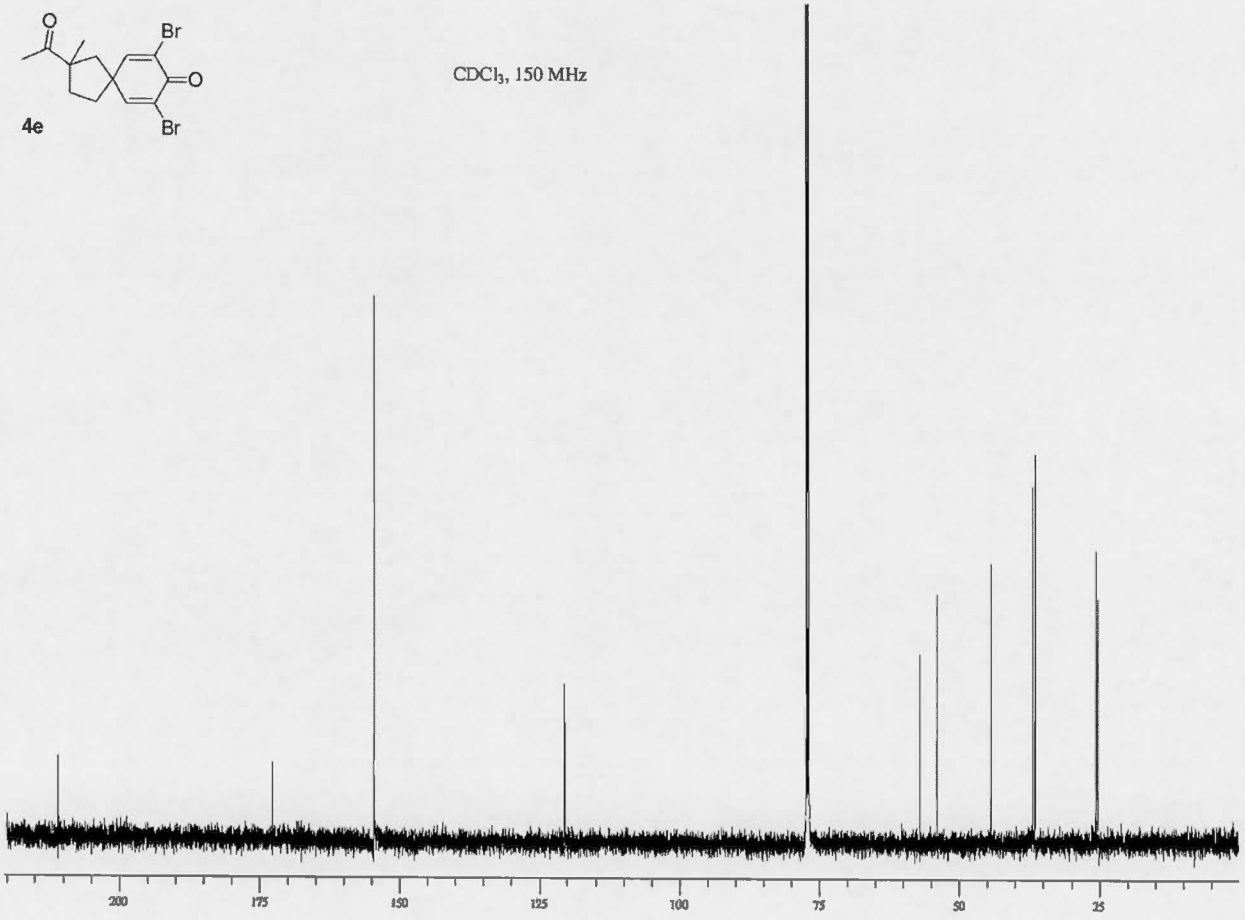


4d

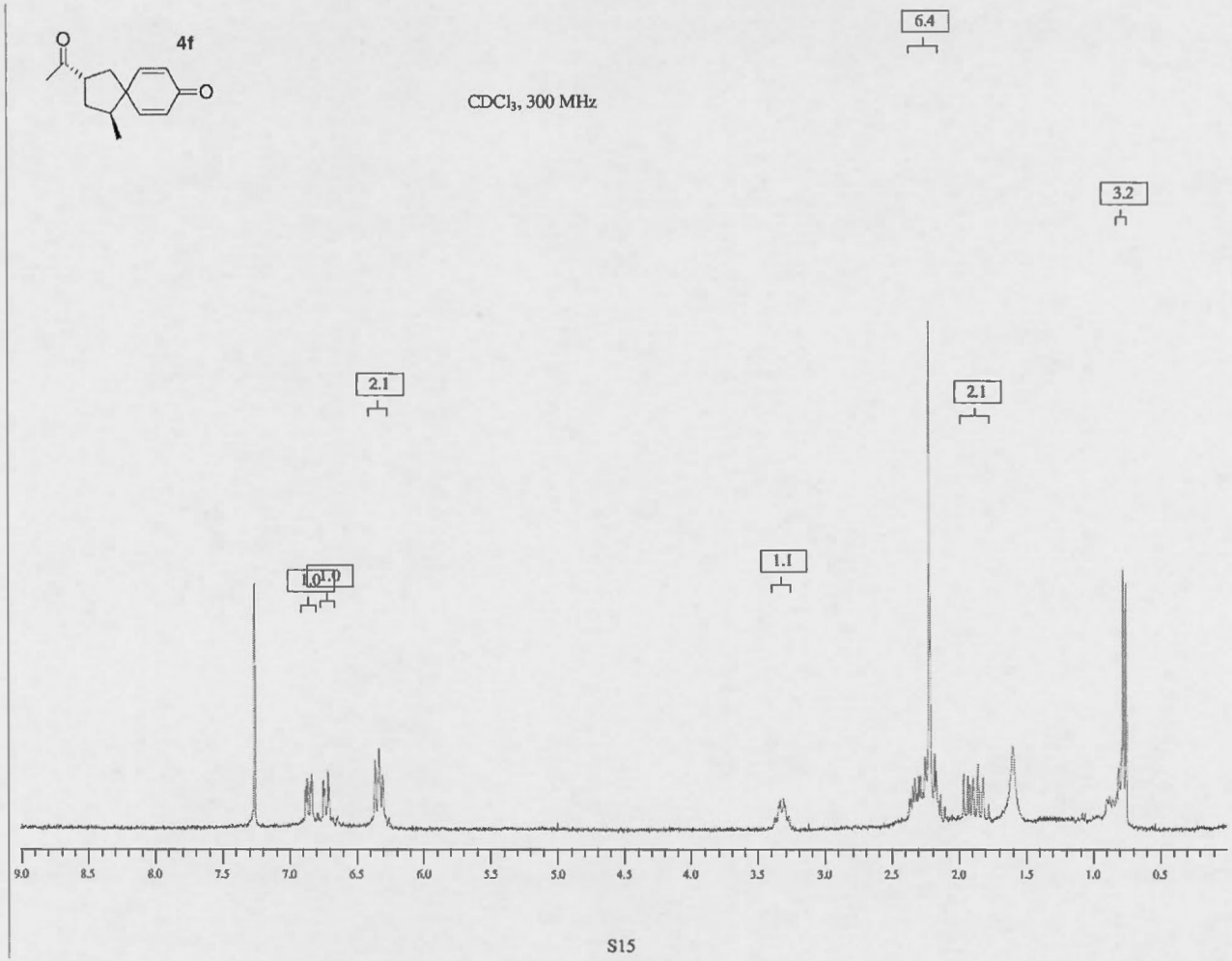
$CDCl_3$, 150 MHz




O
Br
O
Br
4e
CDCl3, 600 MHz
3.2
3.0
2.0
1.1
1.1
1.1
1.1
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5



S14


4f
CDCl3, 300 MHz
6.4
3.2
2.1
2.1
1.1
1.0
1.0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
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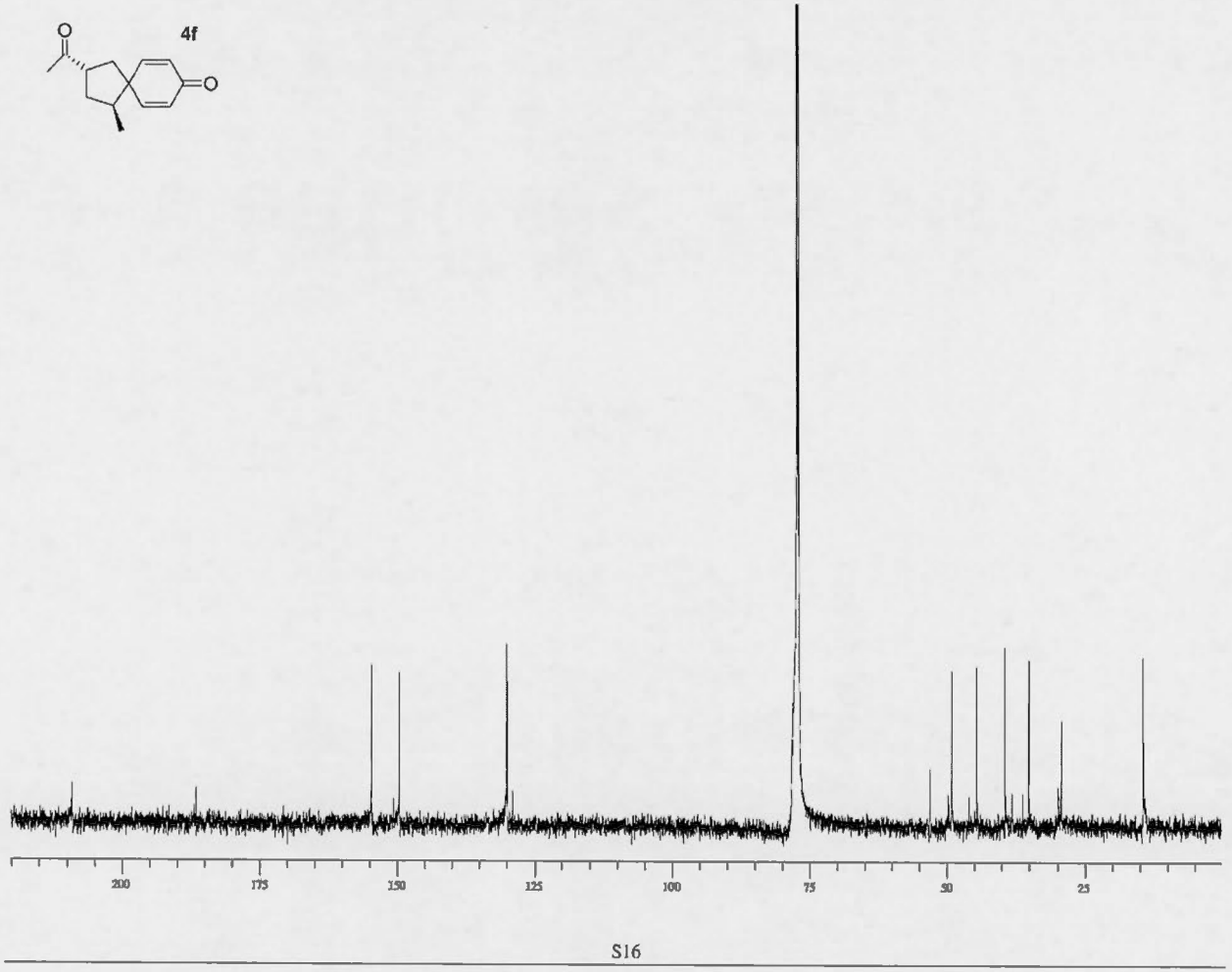
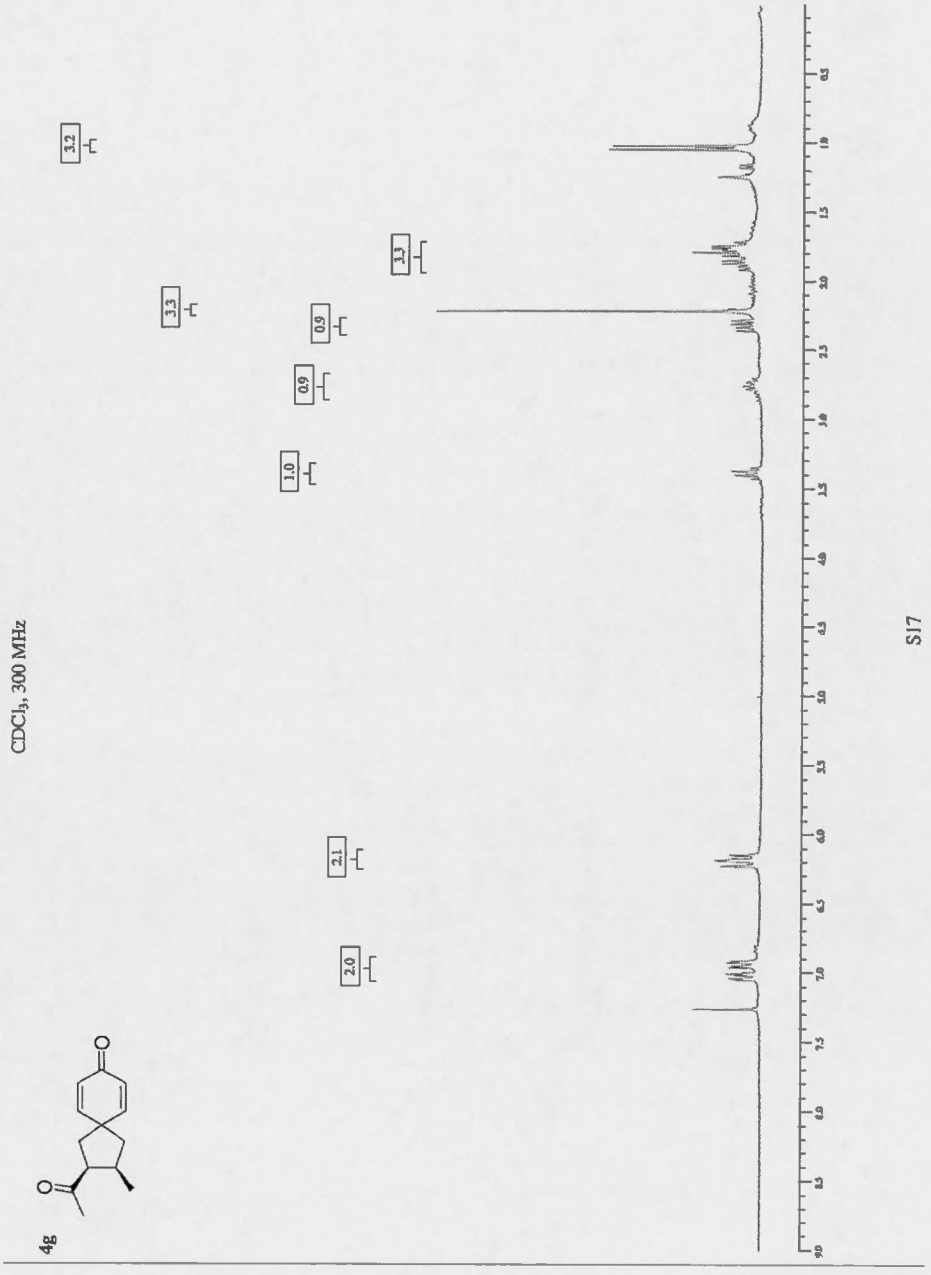
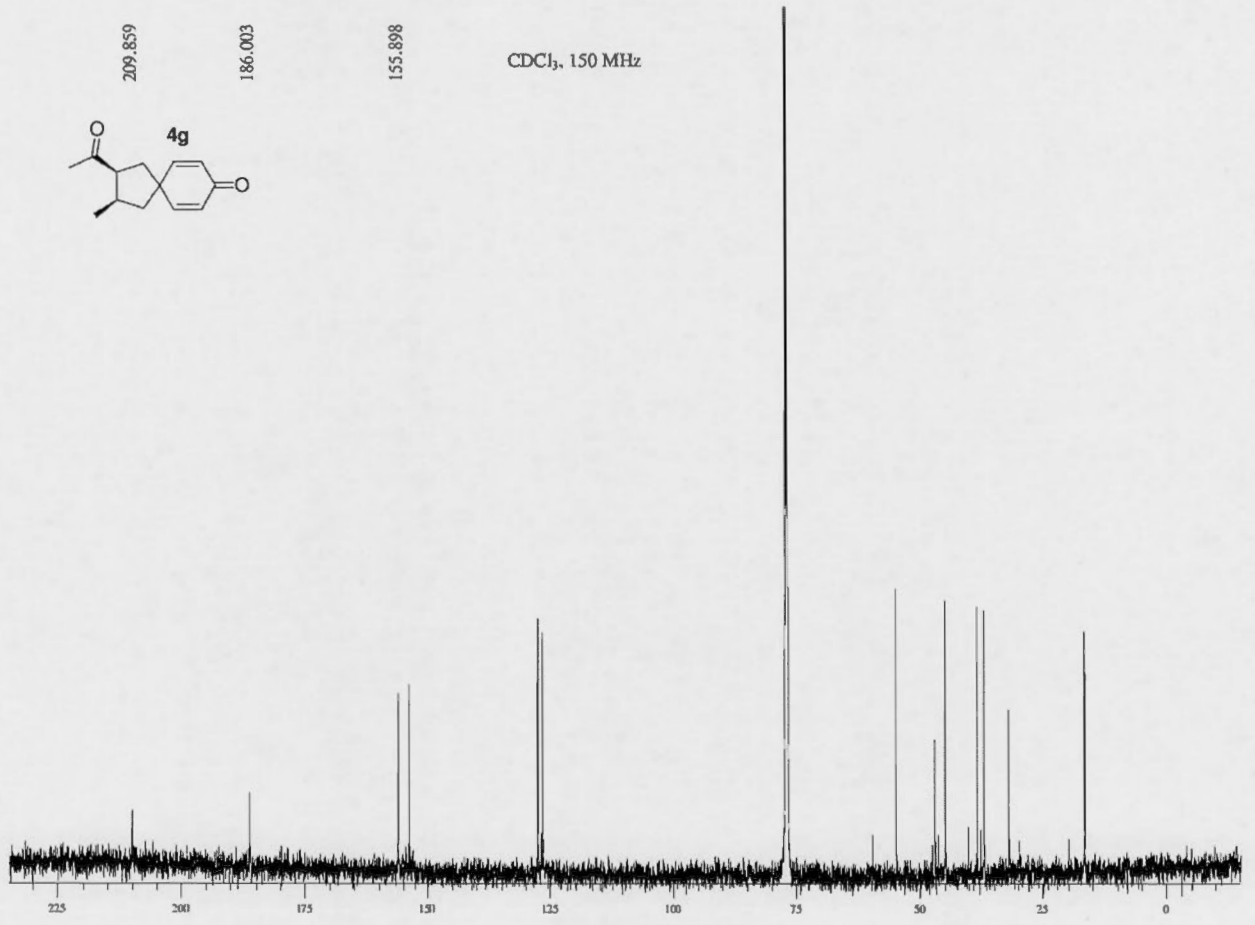
1.5
1.0
0.5

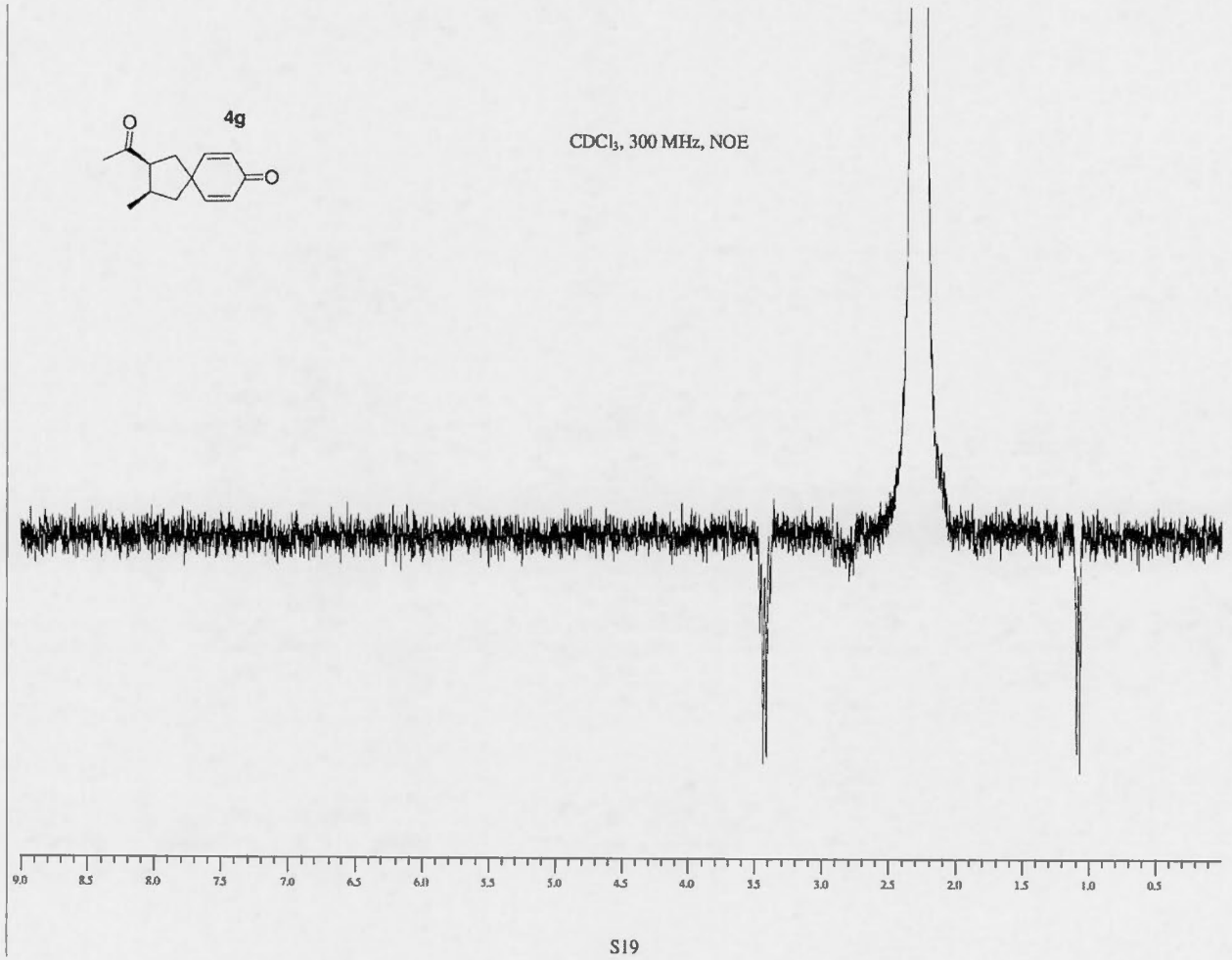
S15


4f
200
175
150
125
100
75
50
25

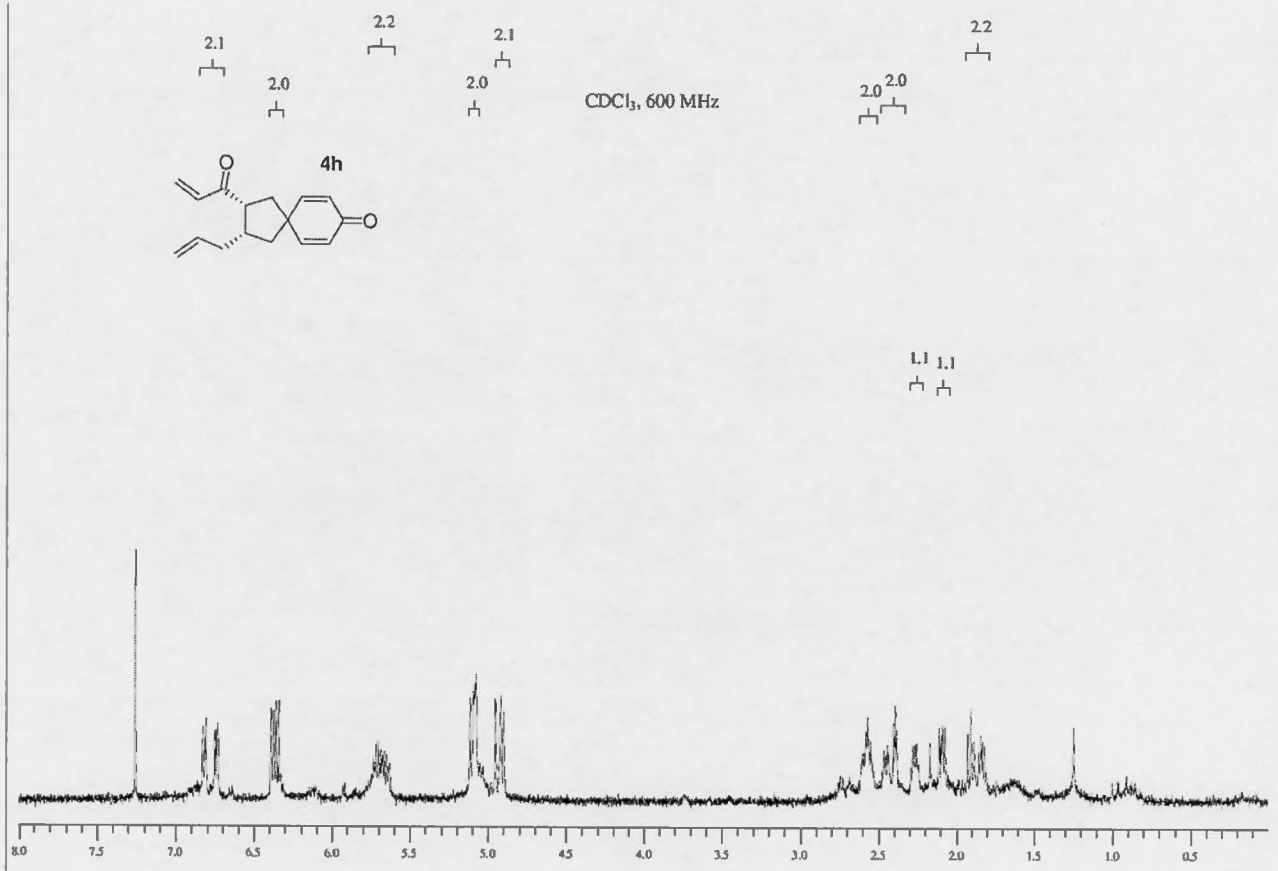


S17

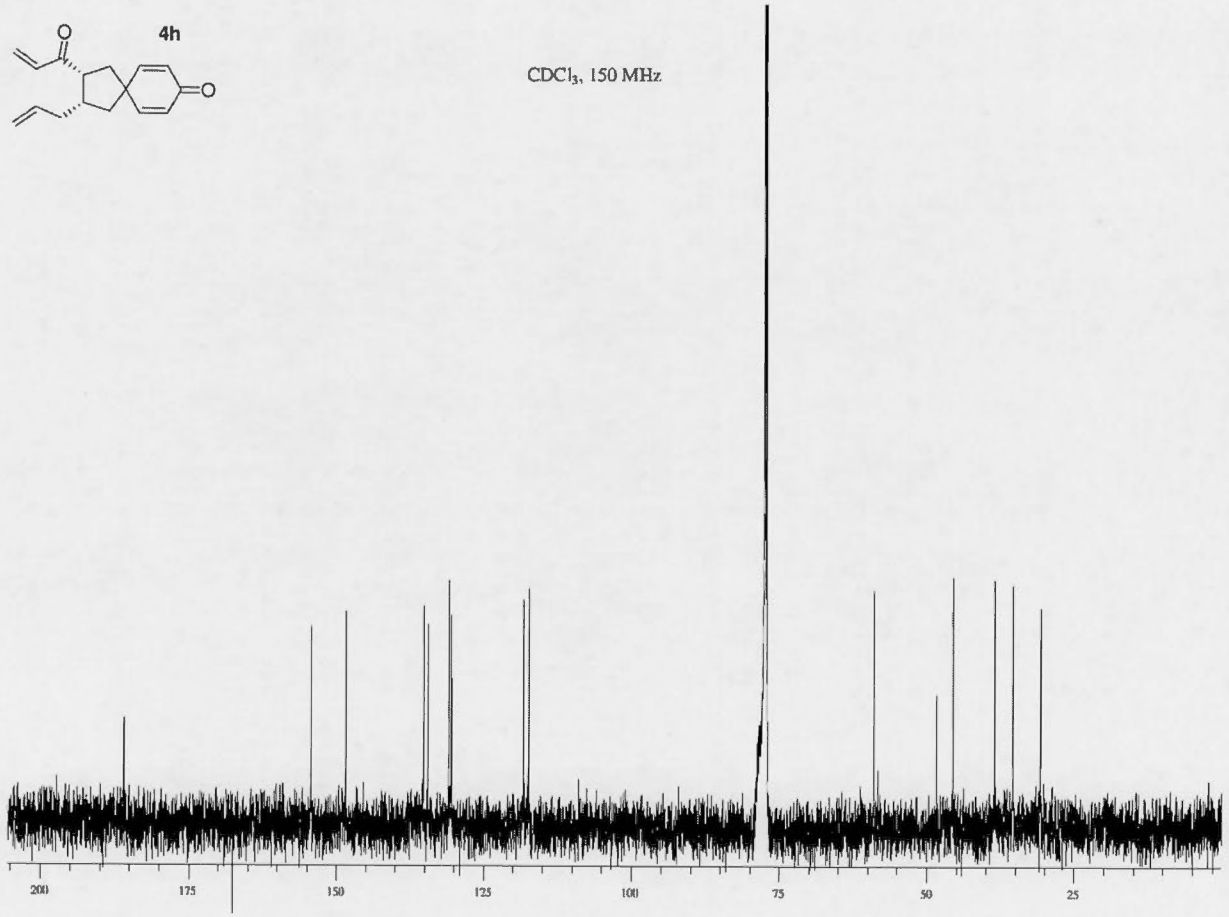

209.859
186.003
155.898
CDCl3, 150 MHz
4g
O
O
225
200
175
150
125
100
75
50
25
0

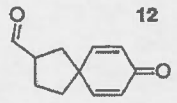

4g
CDCl3, 300 MHz, NOE
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

S19


2.1
2.0
2.2
2.1
2.0
CDCl3, 600 MHz
2.0
2.0
2.2
4h
O
O
1.1
1.1
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

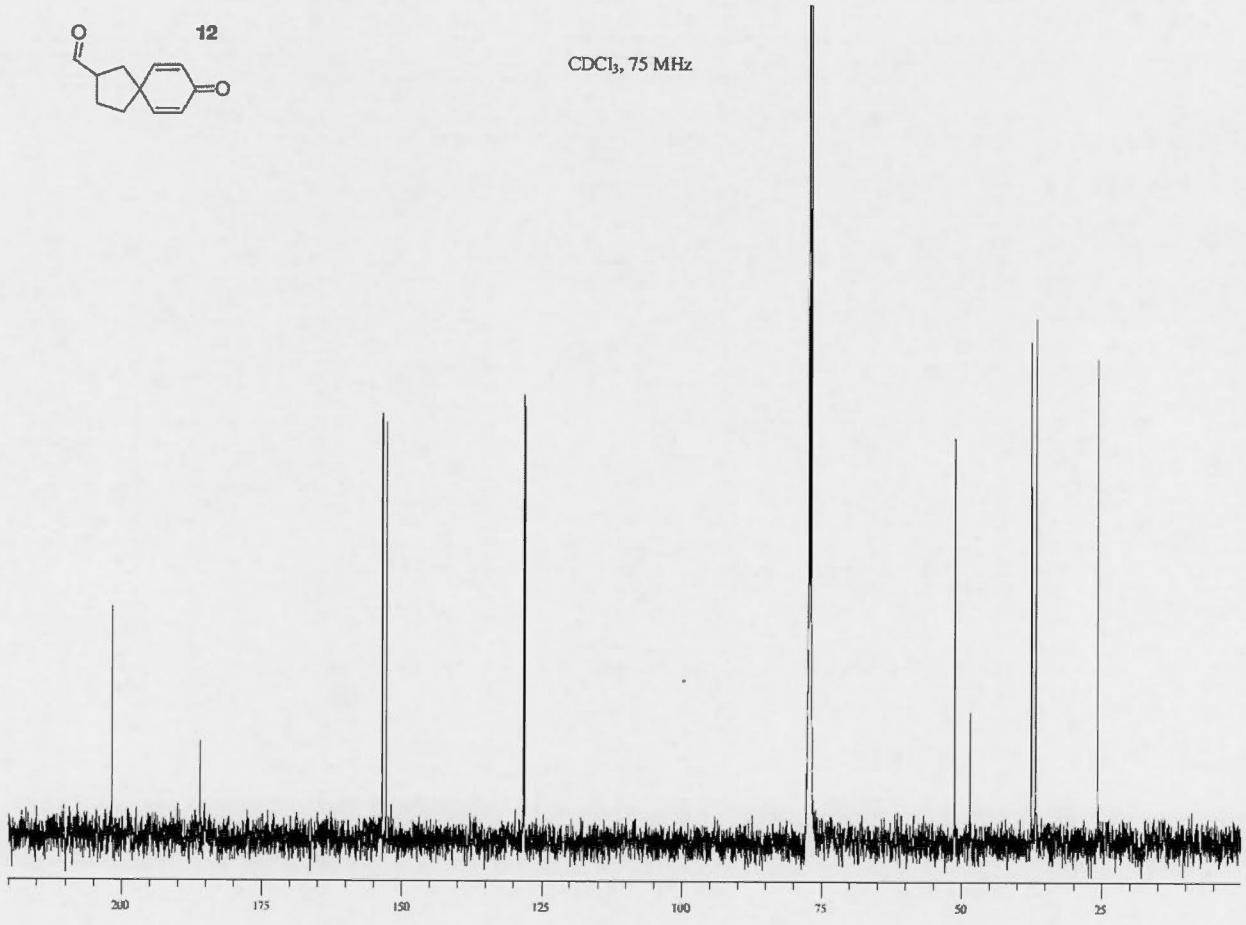
S20


4h
CDCl3, 150 MHz
200
175
150
125
100
75
50
25

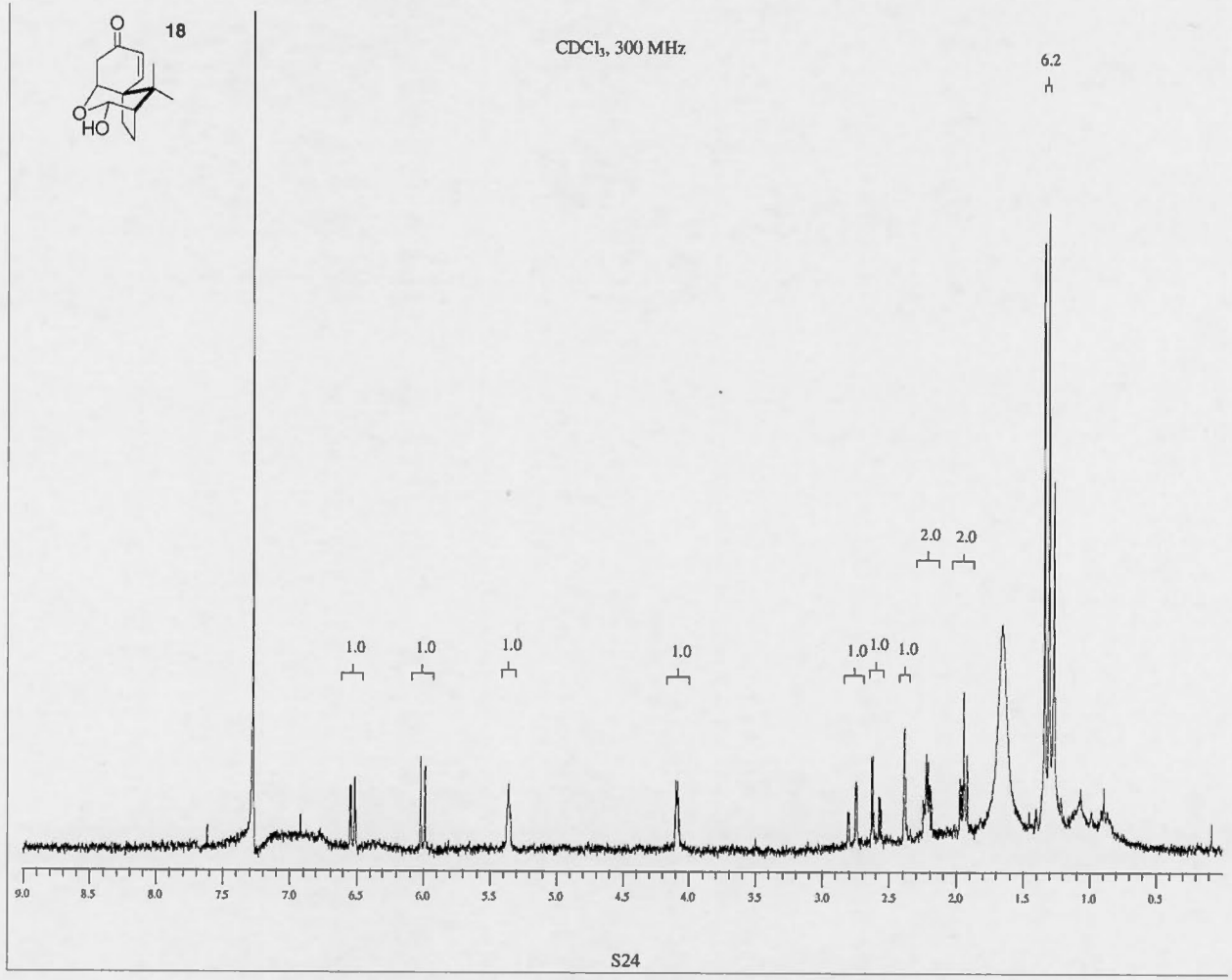


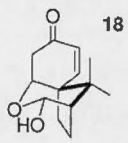
12

$CDCl_3$, 300 MHz



S23

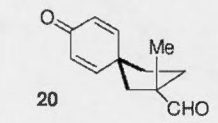

18
CDCl3, 300 MHz
6.2
2.0
2.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
S24



18

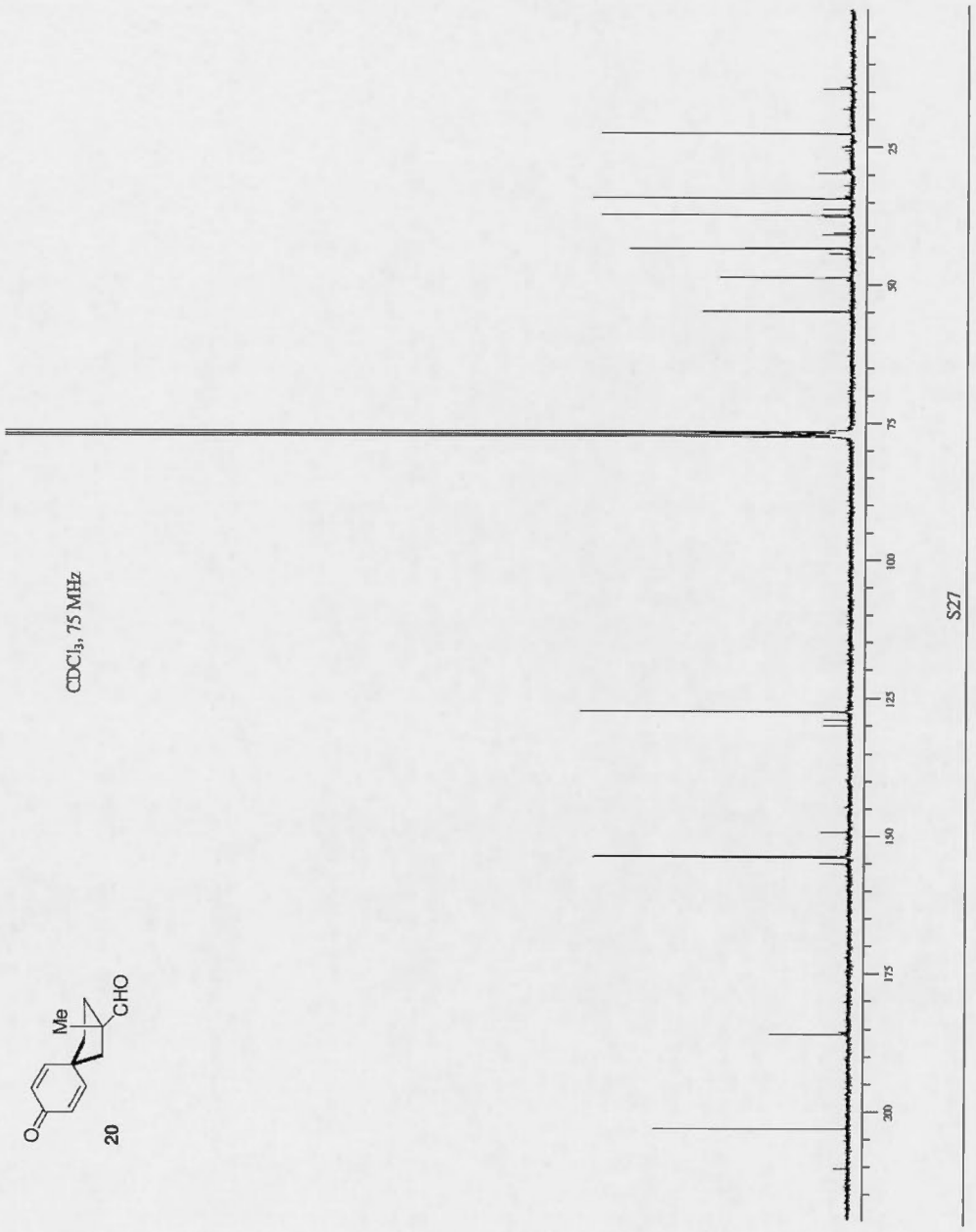
$CDCl_3$, 75 MHz

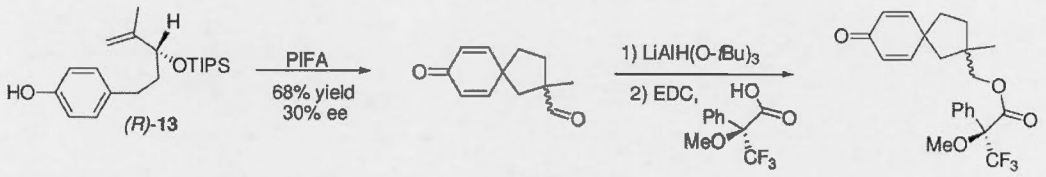
S25



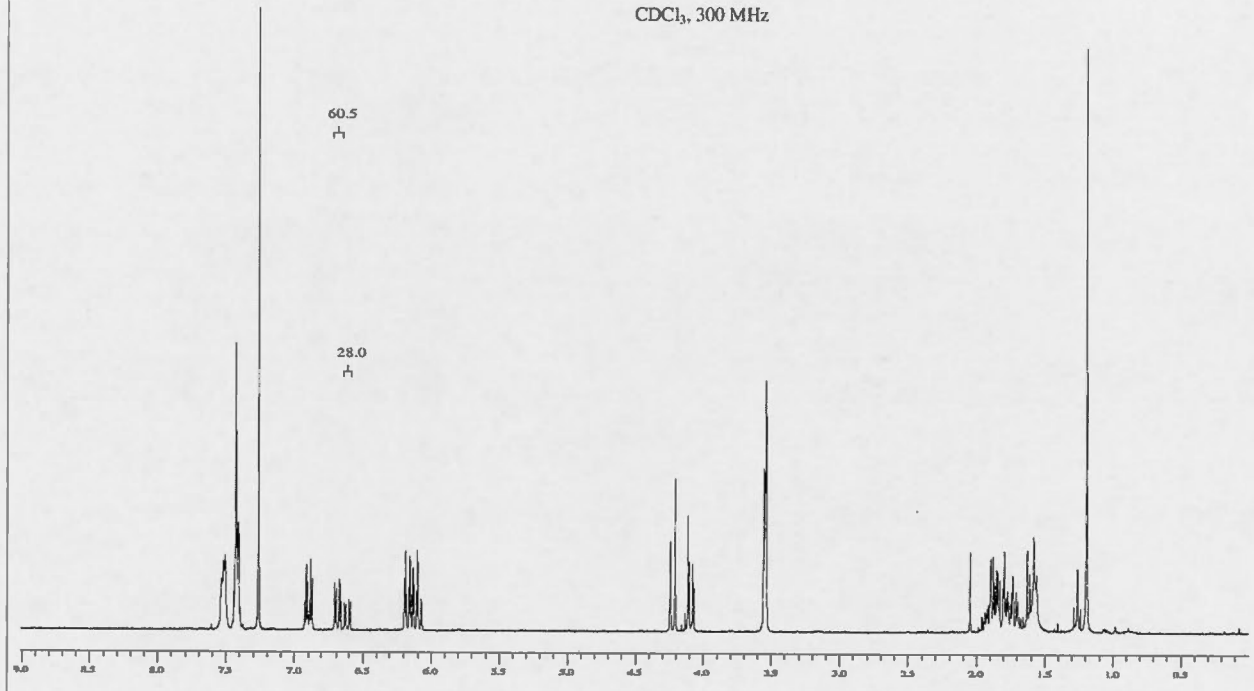
20

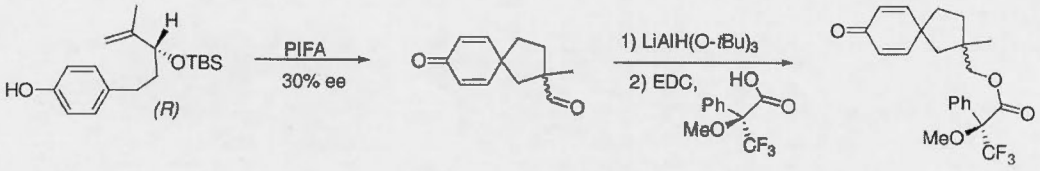
$CDCl_3$, 300 MHz


Me
CHO
O
20
CDCl3, 75 MHz
25
50
75
100
125
150
175
200
S27

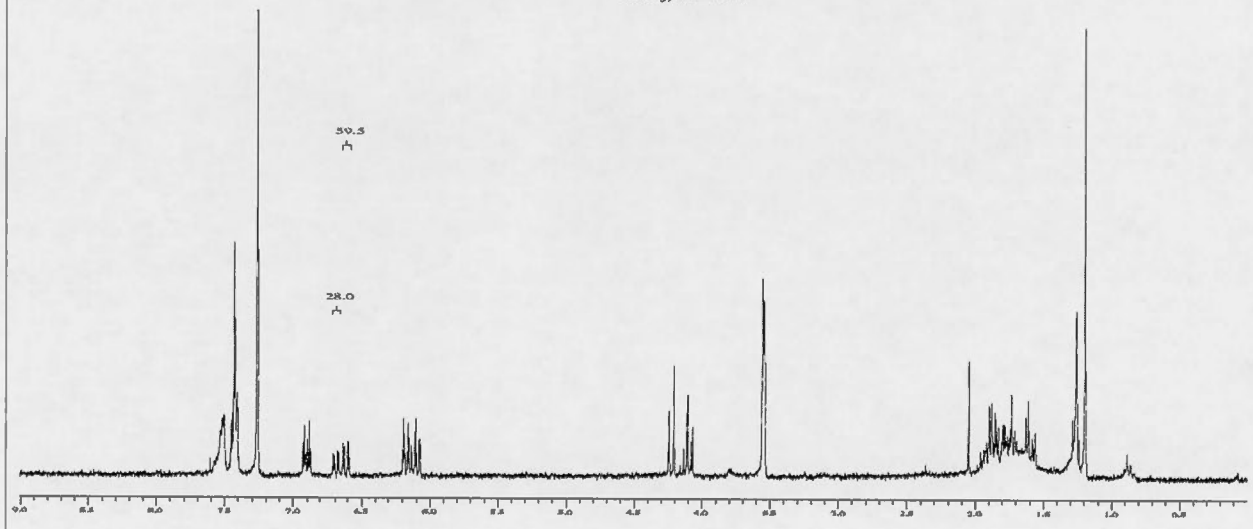


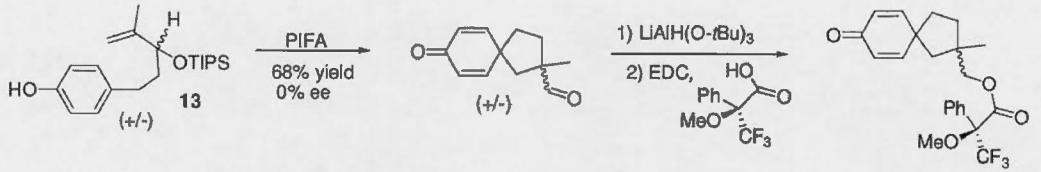
$CDCl_3$, 300 MHz



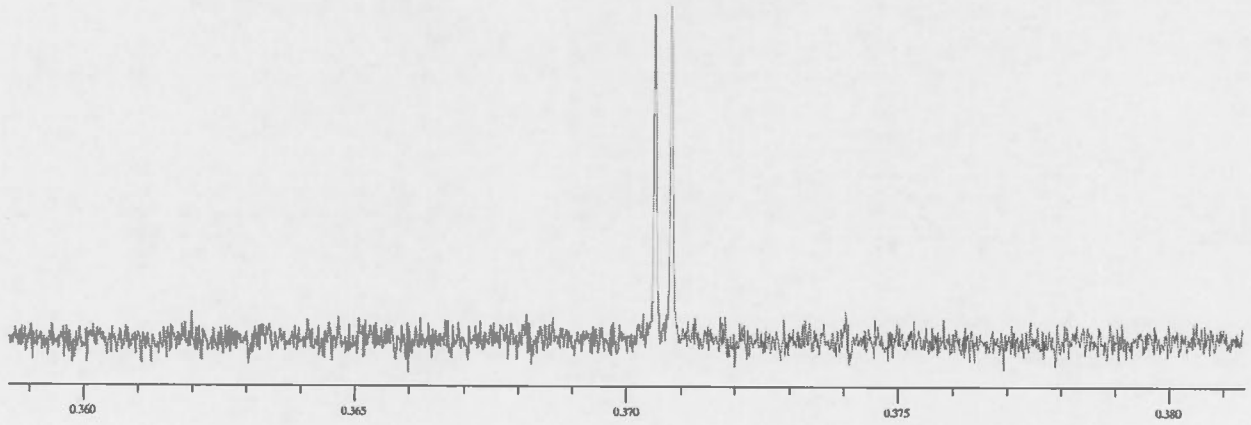


$CDCl_3$, 300 MHz

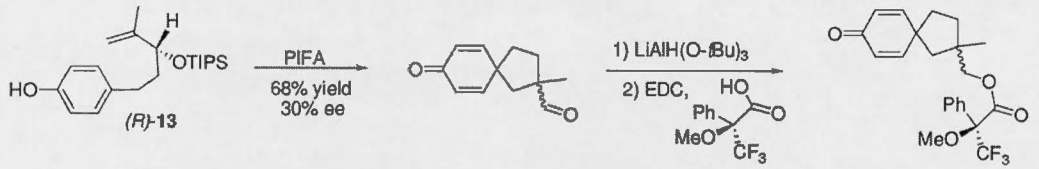


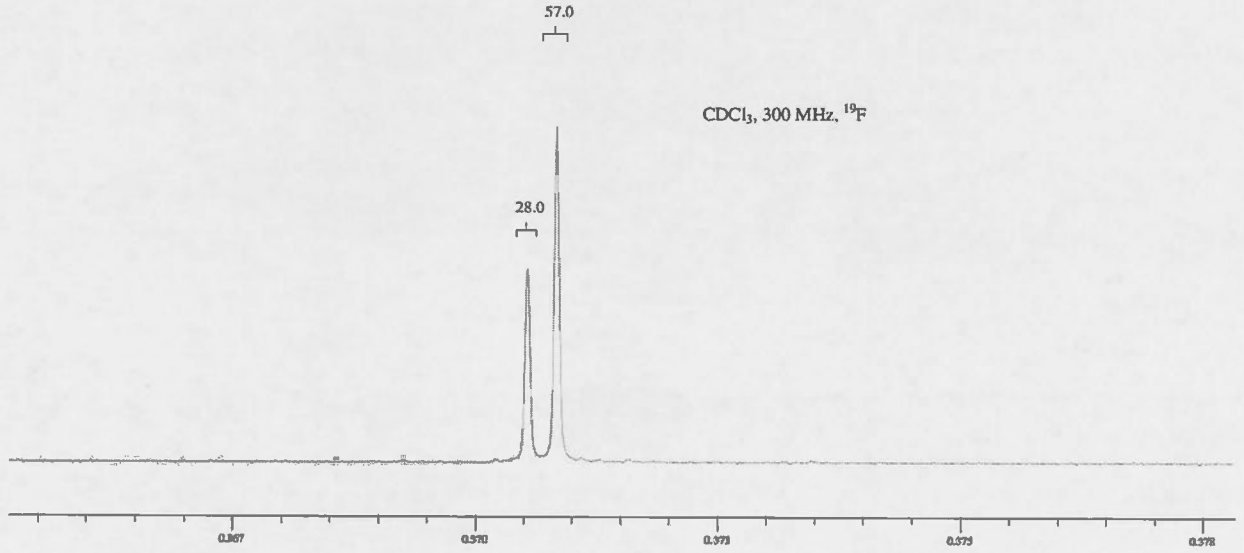


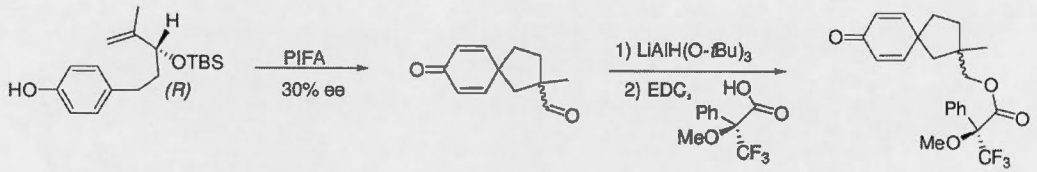
$CDCl_3$, 300 MHz, ^{19}F

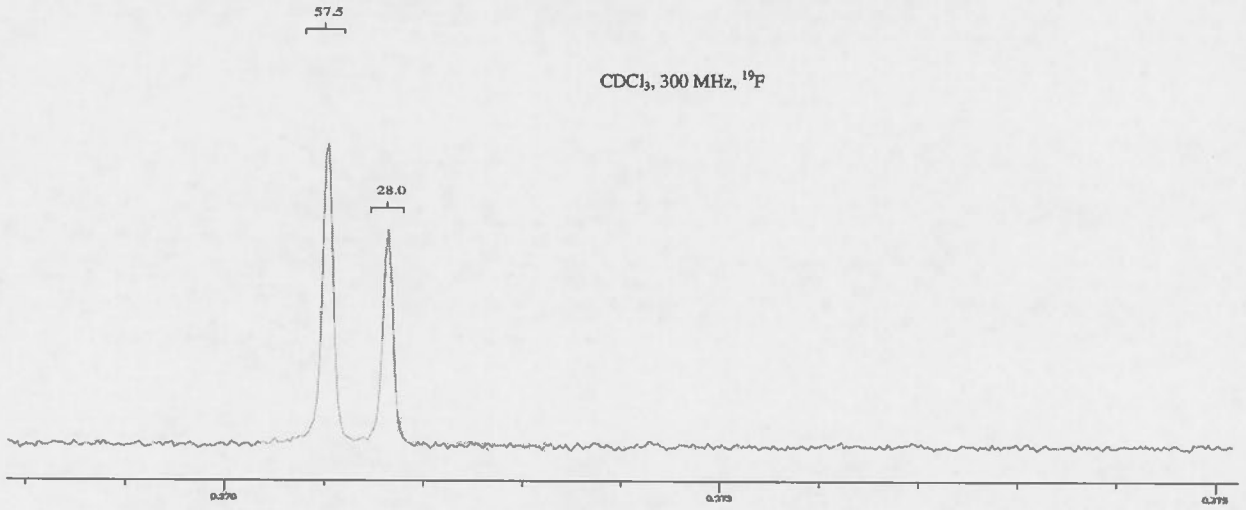


S30

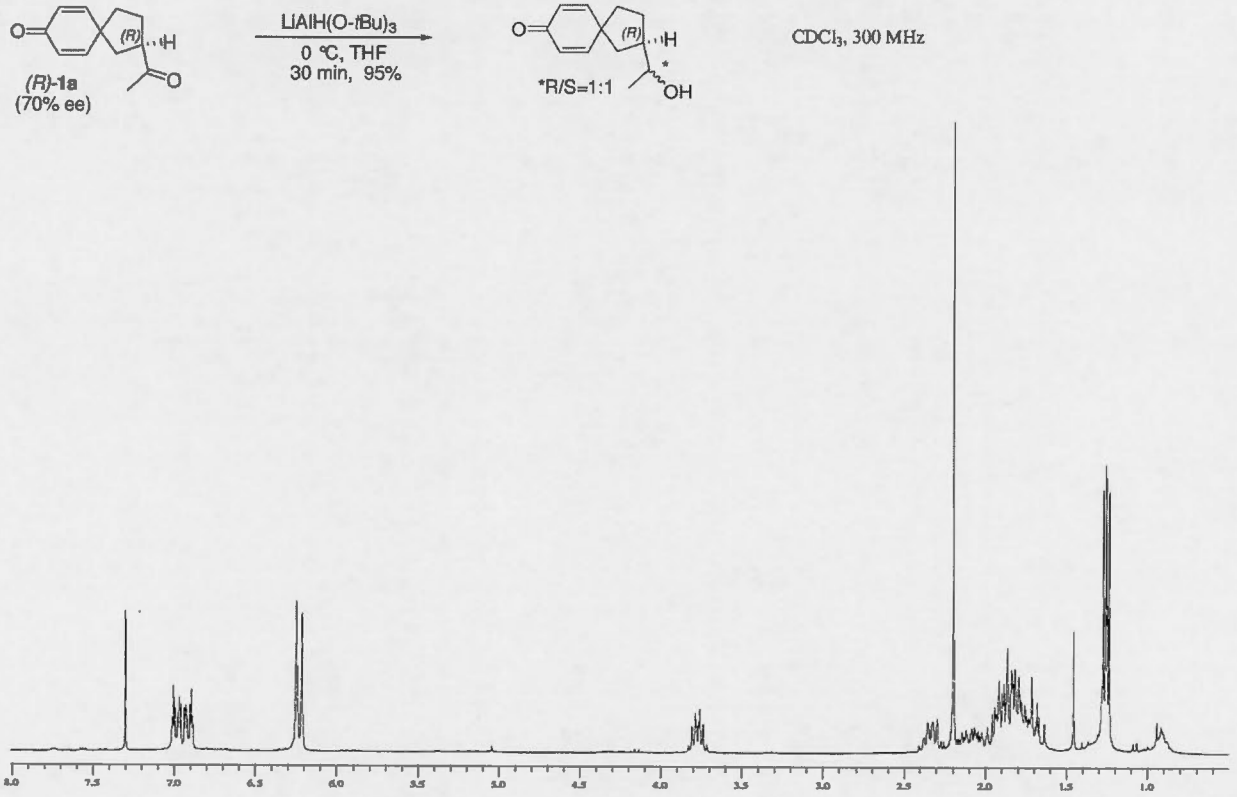

H
OTIPS
HO
(R)-13
PIFA
68% yield
30% ee
1) LiAlH(O-tBu)3
2) EDC,
HO
Ph
MeO
CF3
O
O
O
Ph
MeO
CF3

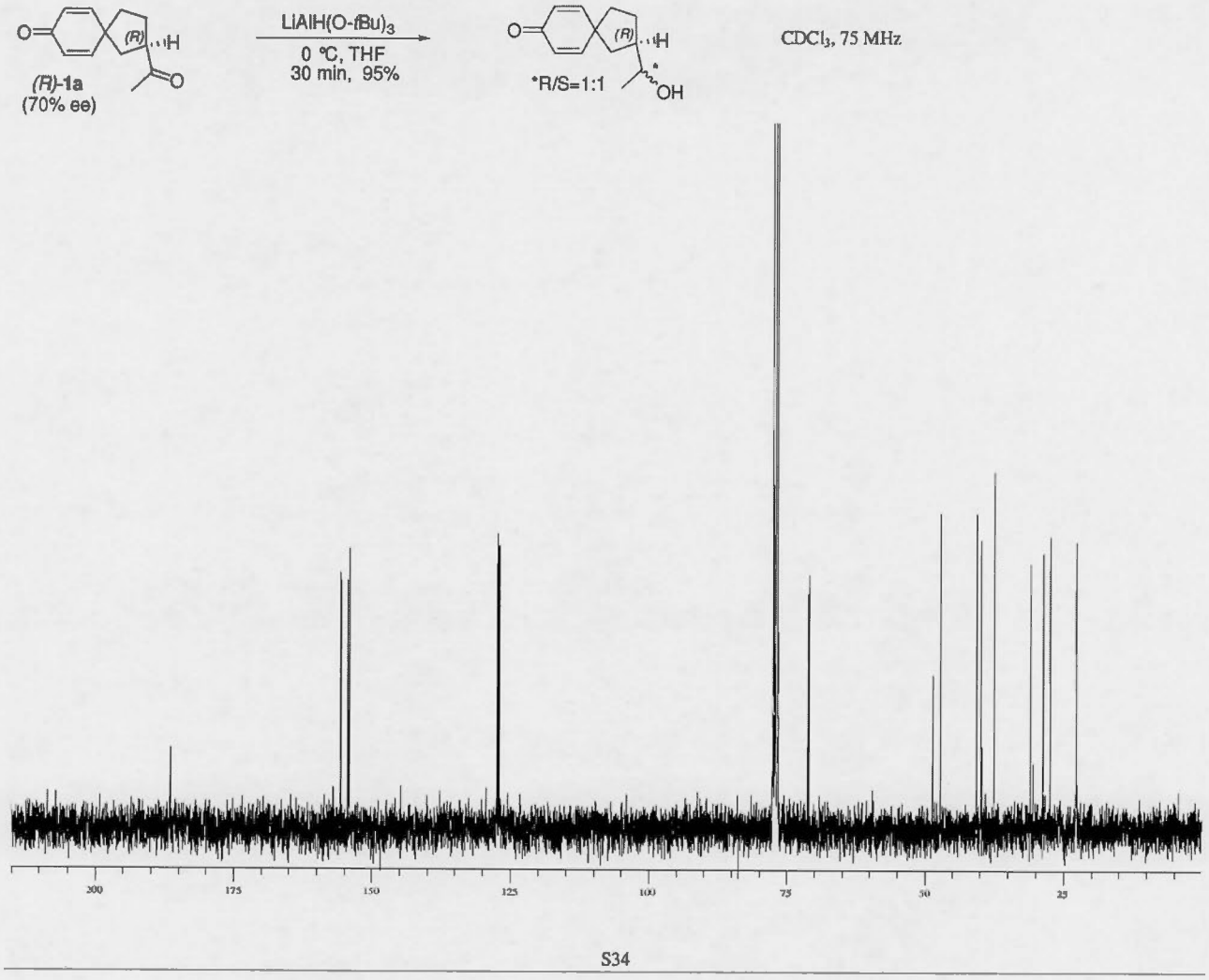

57.0
CDCl3, 300 MHz, 19F
28.0
0.367
0.370
0.373
0.375
0.378

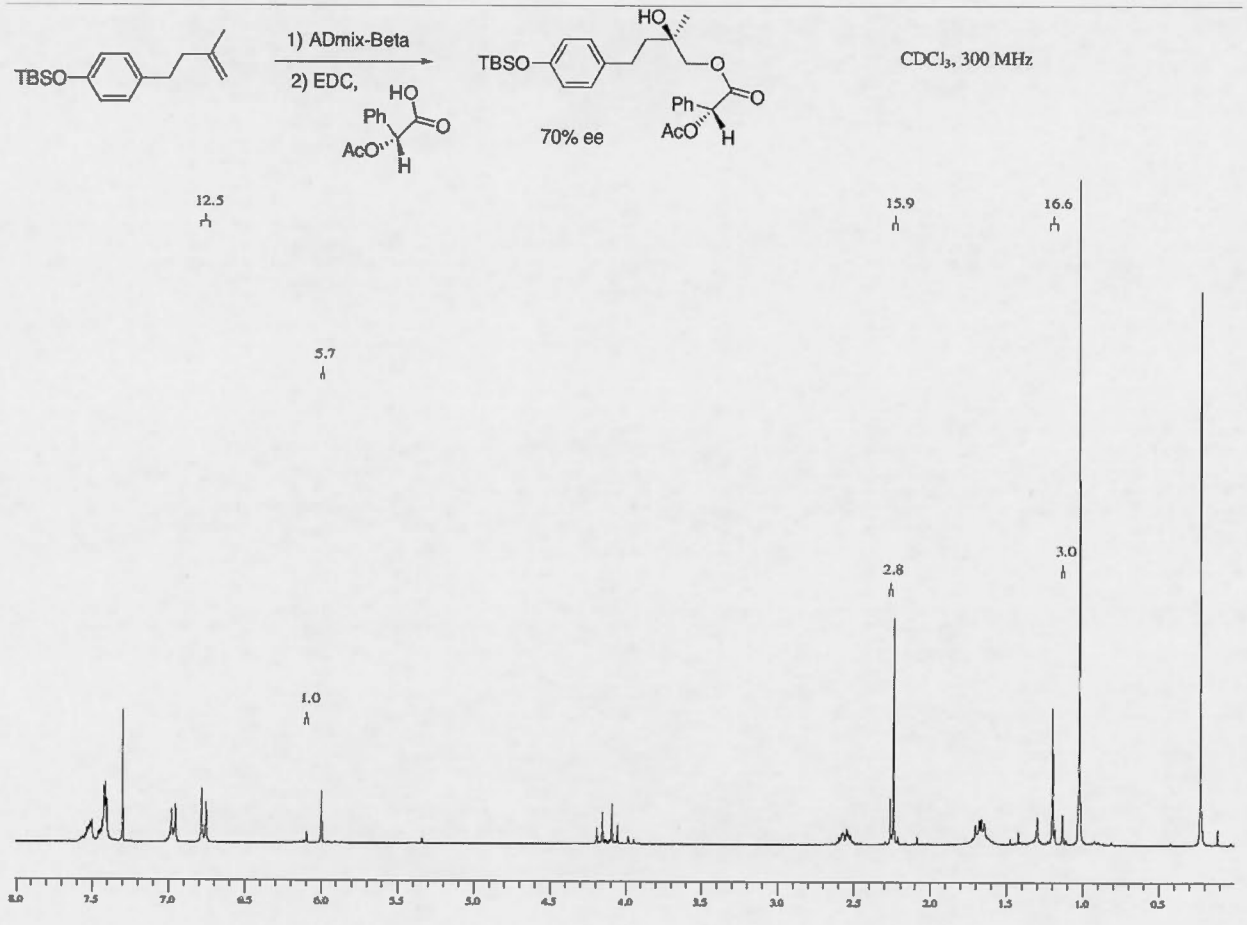




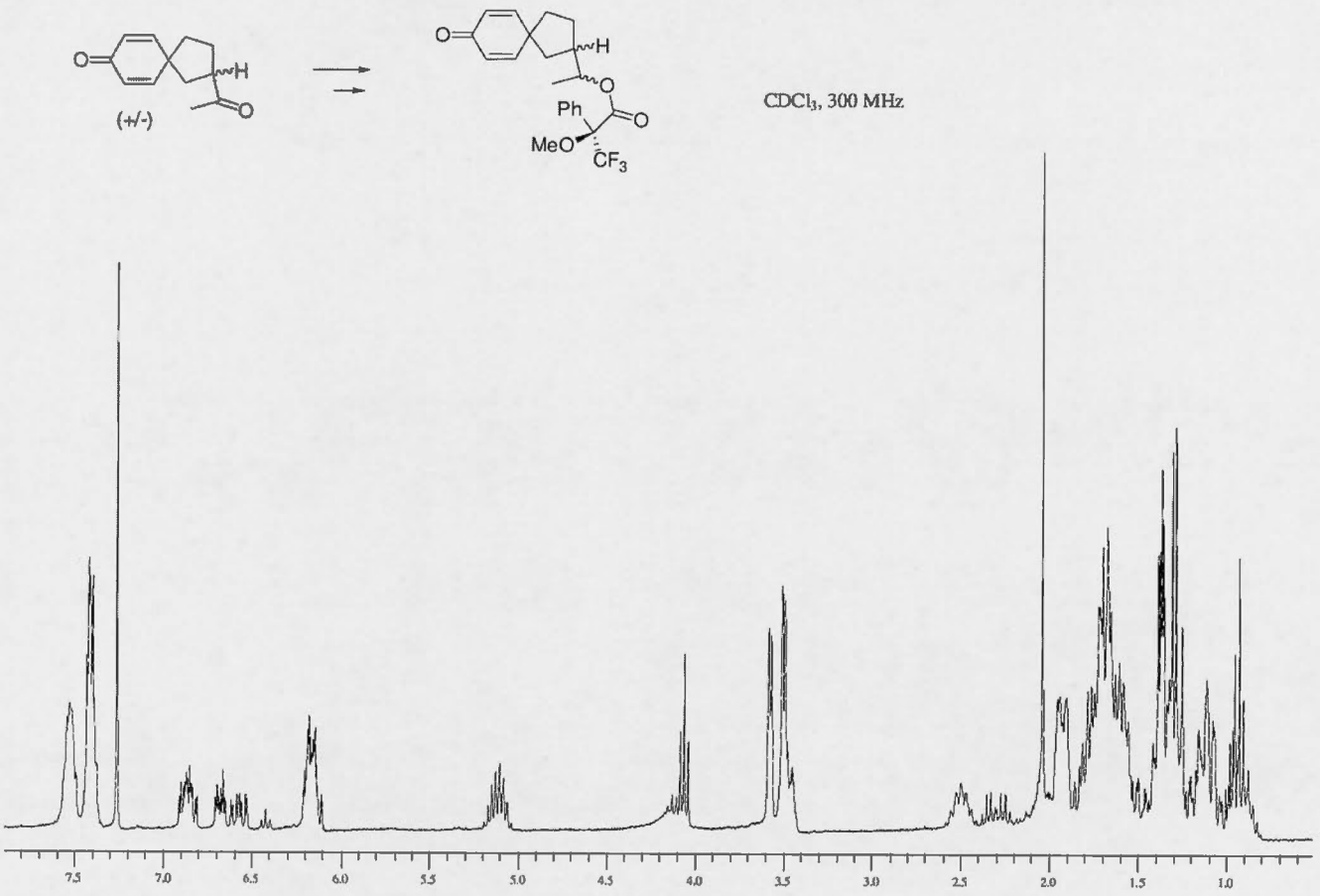
$CDCl_3$, 300 MHz, ^{19}F

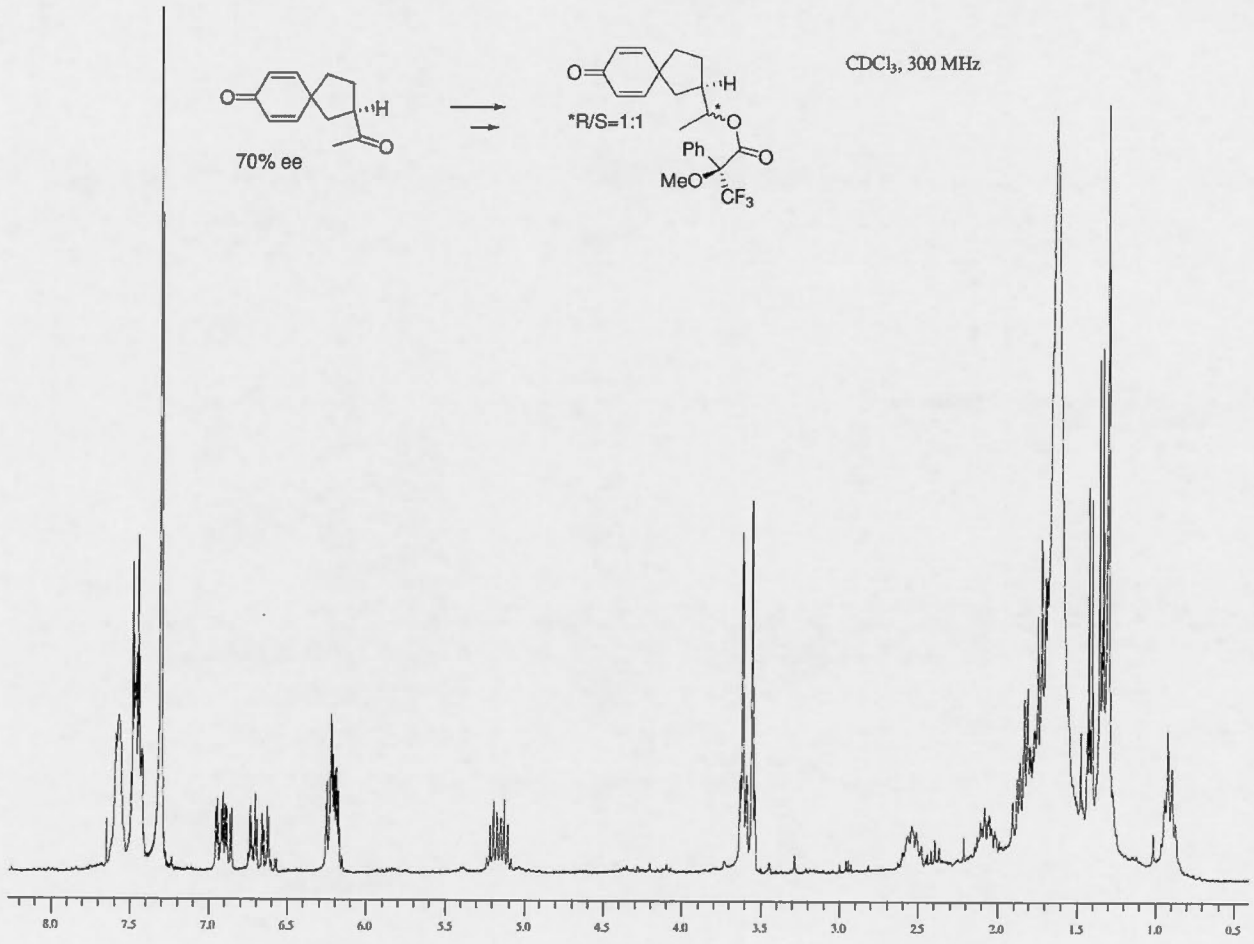

(R)-1a
(70% ee)
LiAlH(O-tBu)3
0 °C, THF
30 min, 95%
*R/S=1:1
OH
CDCl3, 300 MHz


LiAlH(O-tBu)3
0 °C, THF
30 min, 95%
(R)-1a
(70% ee)
*R/S=1:1
OH
CDCl3, 75 MHz
200
175
150
125
100
75
50
25

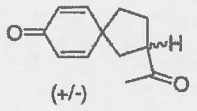

TBSO
1) ADmix-Beta
2) EDC,
HO
Ph
AcO
H
O
TBSO
HO
O
Ph
AcO
H
O
70% ee
CDCl3, 300 MHz
12.5
5.7
15.9
16.6
2.8
3.0
1.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

S35

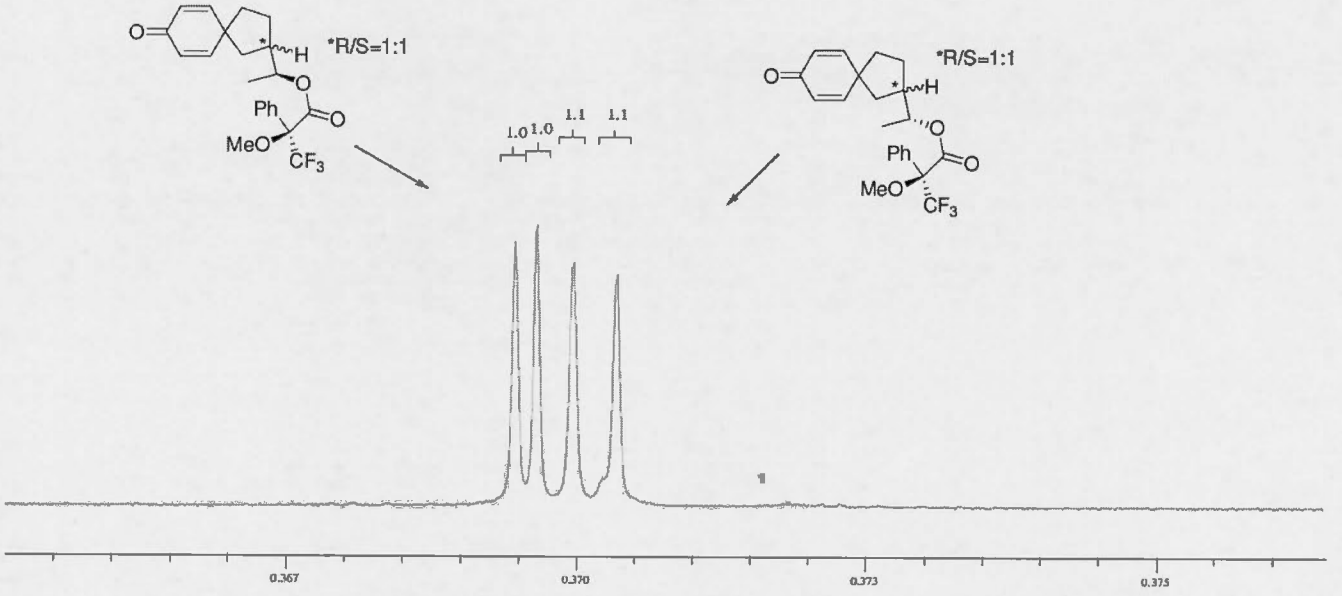

(+/-)
Ph
MeO
CF3
CDCl3, 300 MHz
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

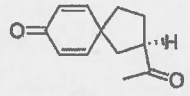

70% ee
*R/S=1:1
Ph
MeO
CF3
CDCl3, 300 MHz
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

S37

From:  (+/-)

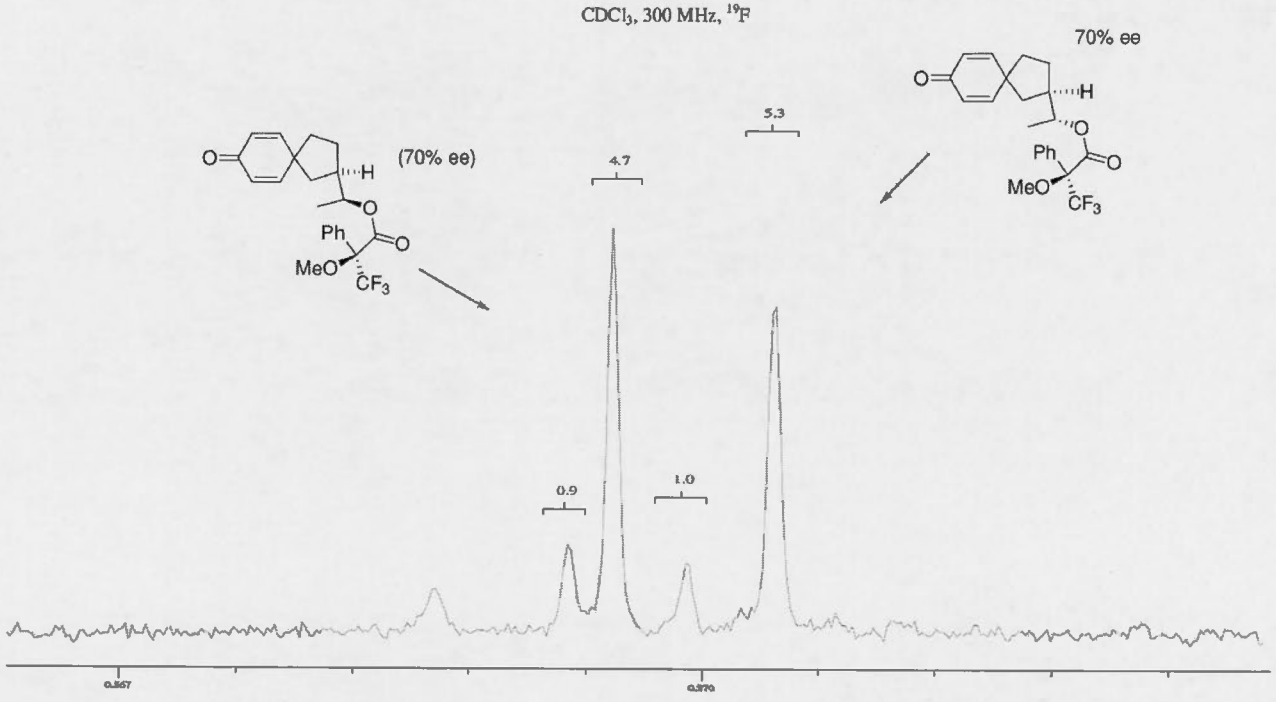
$CDCl_3$, 300 MHz, ^{19}F

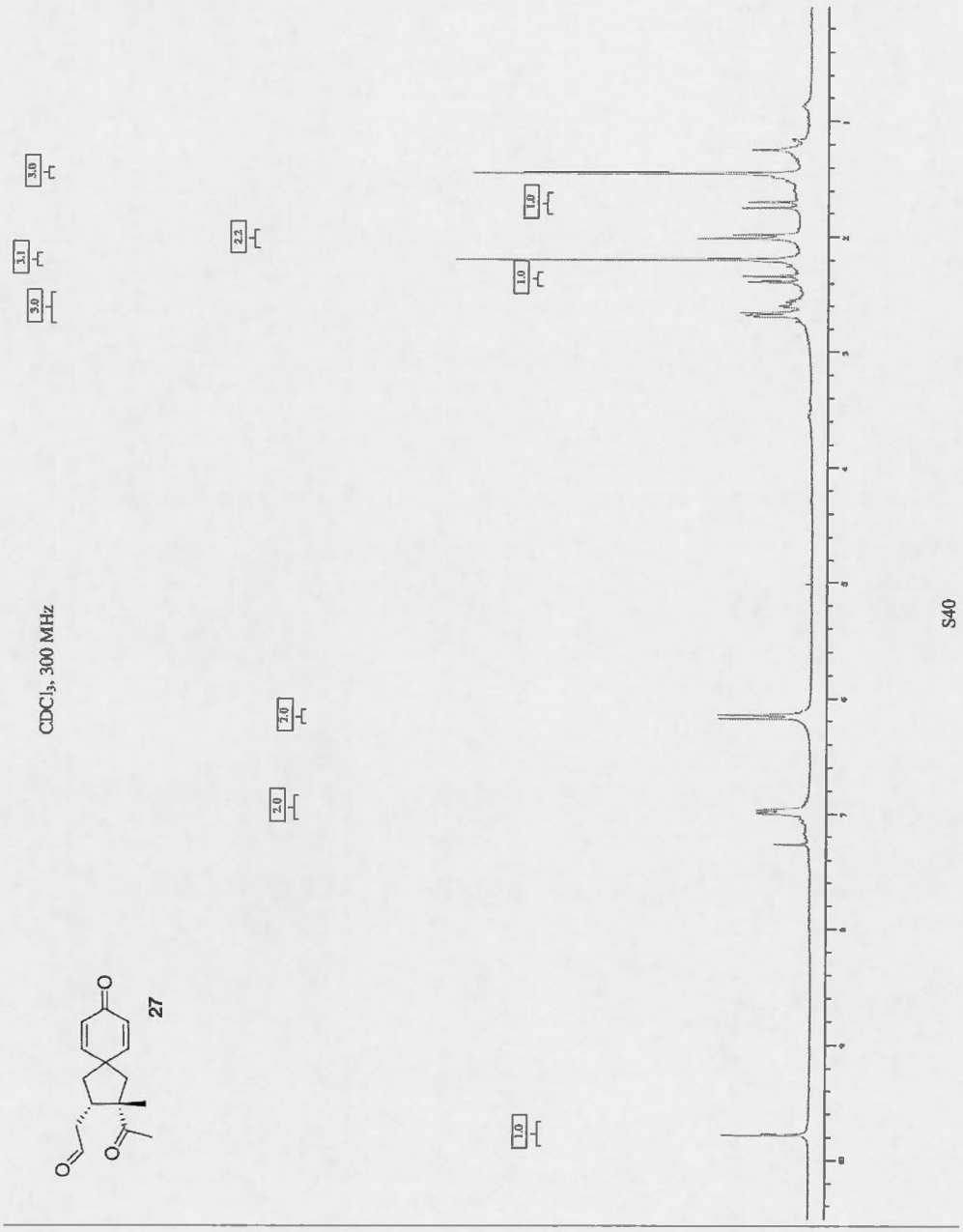


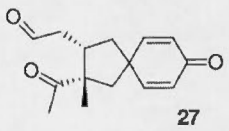


70% ee

From



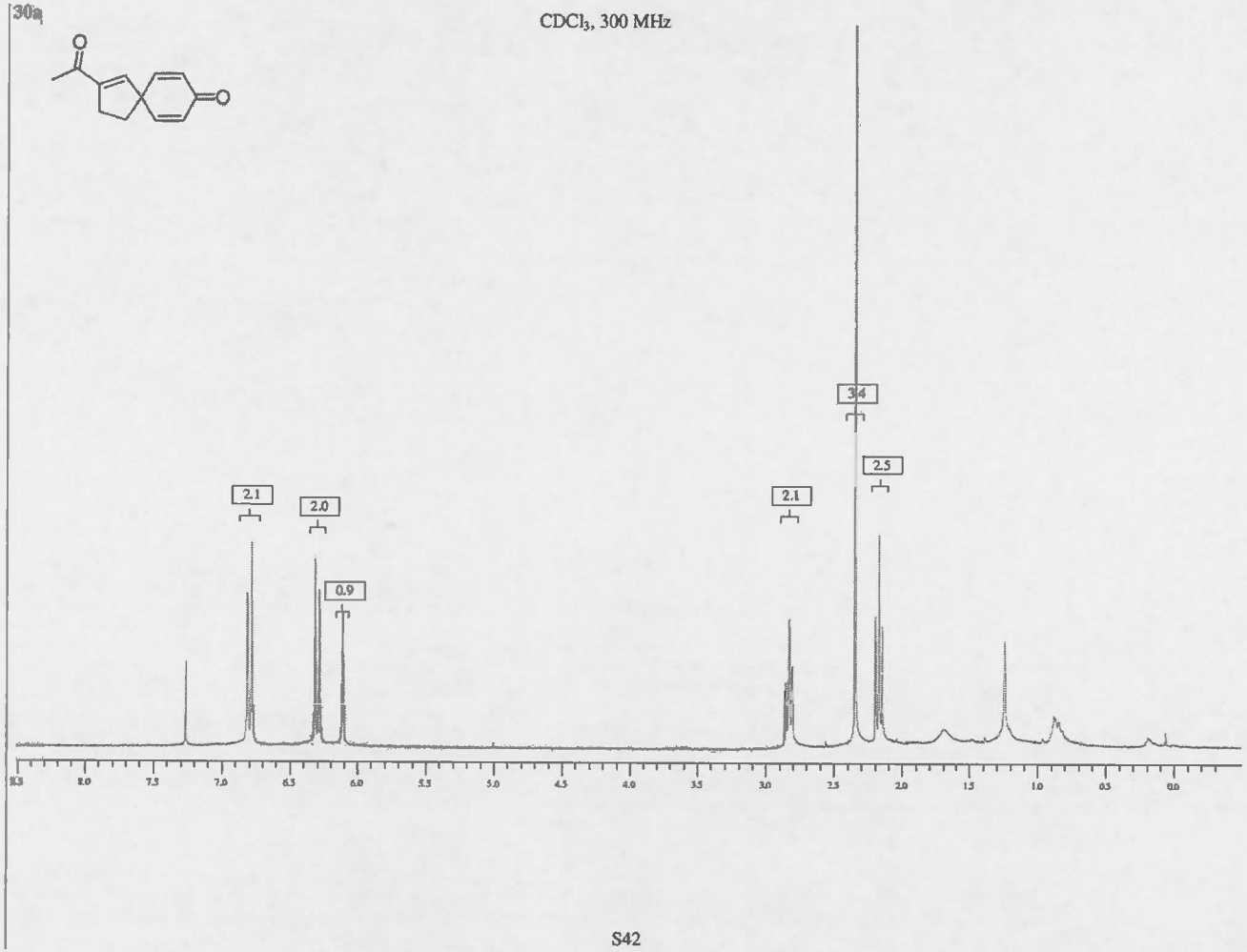

CDCl3, 300 MHz
27
S40

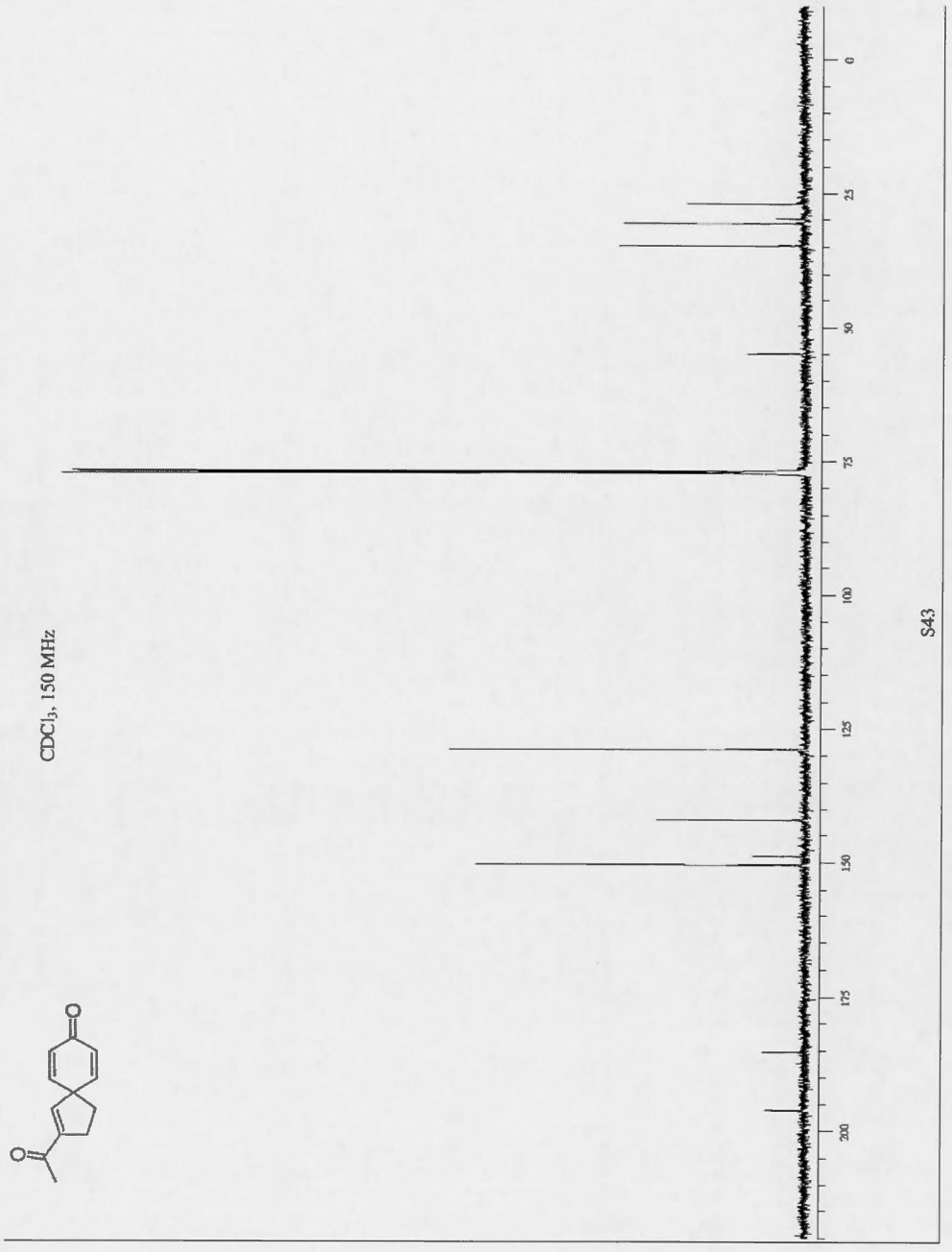


27

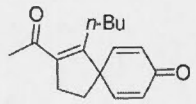
$CDCl_3$, 75 MHz

S41

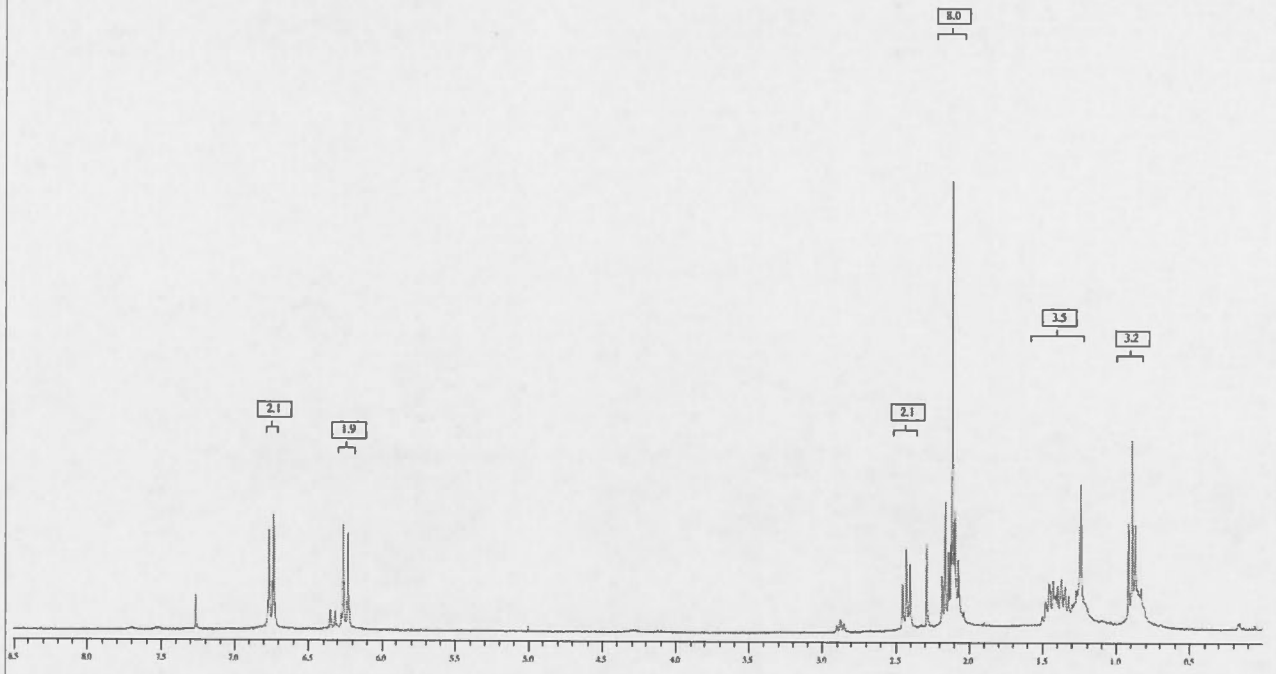

30a
CDCl3, 300 MHz
2.1
2.0
0.9
2.1
3.4
2.5


CDCl3, 150 MHz
S43
200
175
150
125
100
75
50
25
0

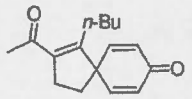
30b



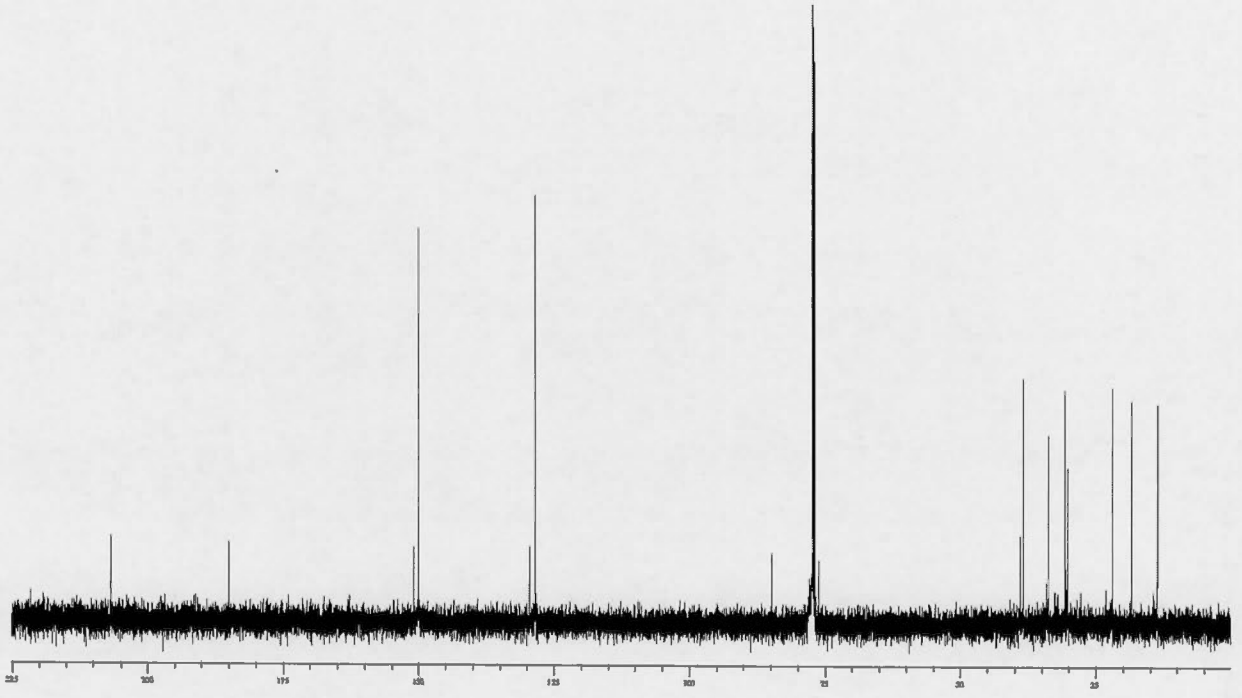
$CDCl_3$, 300 MHz

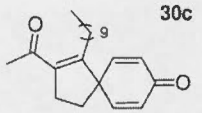


30b



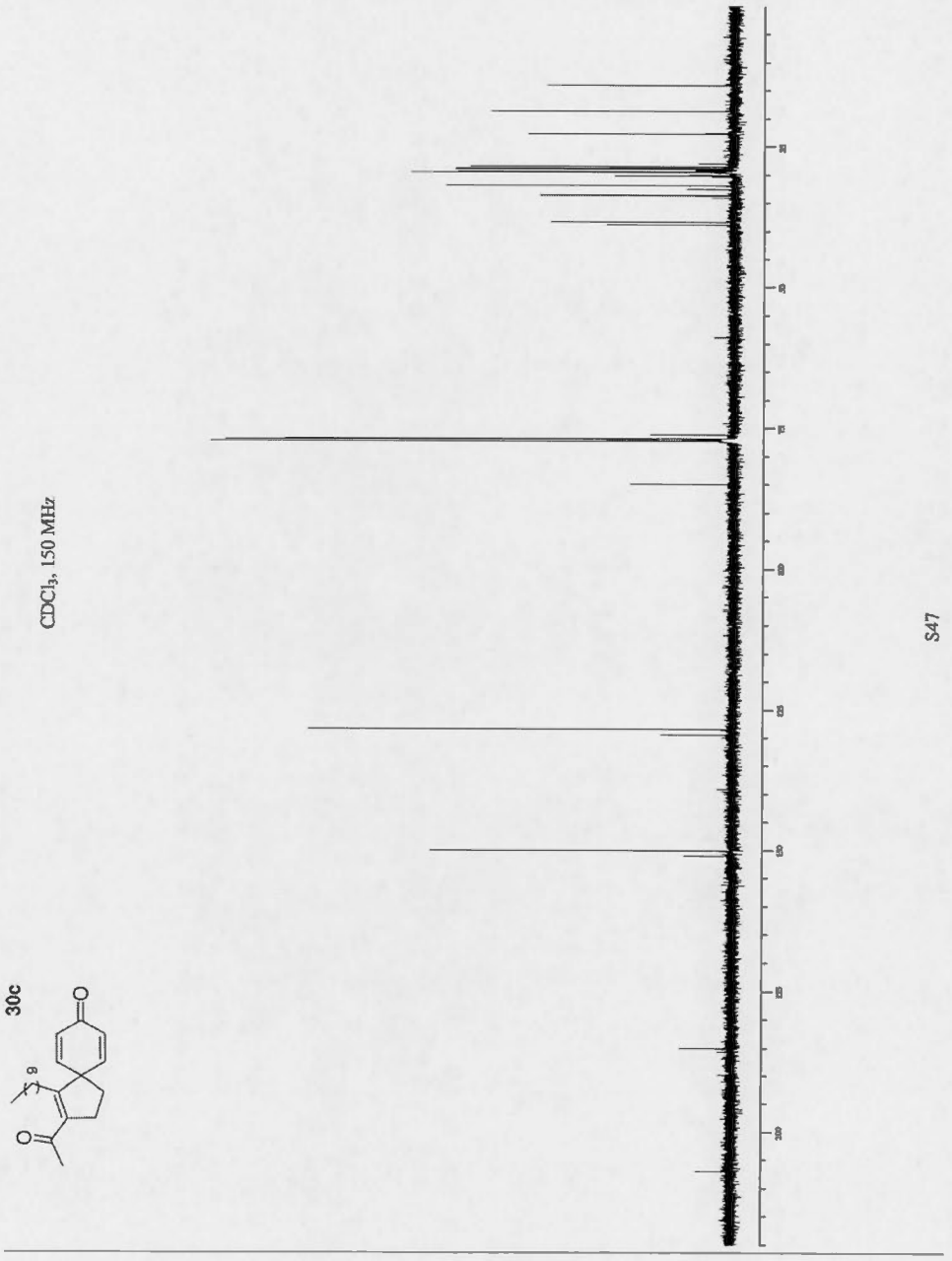
$CDCl_3$, 150 MHz

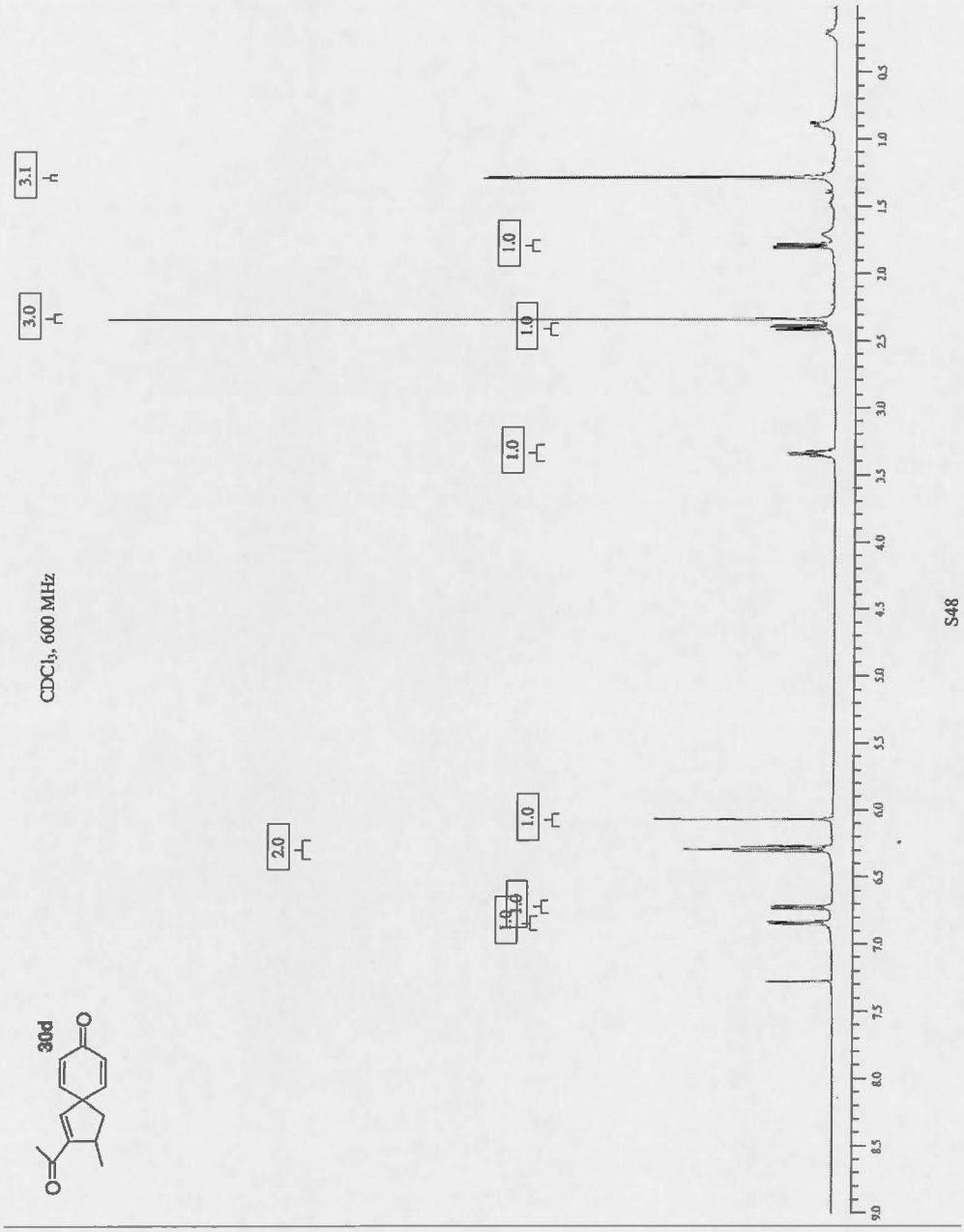


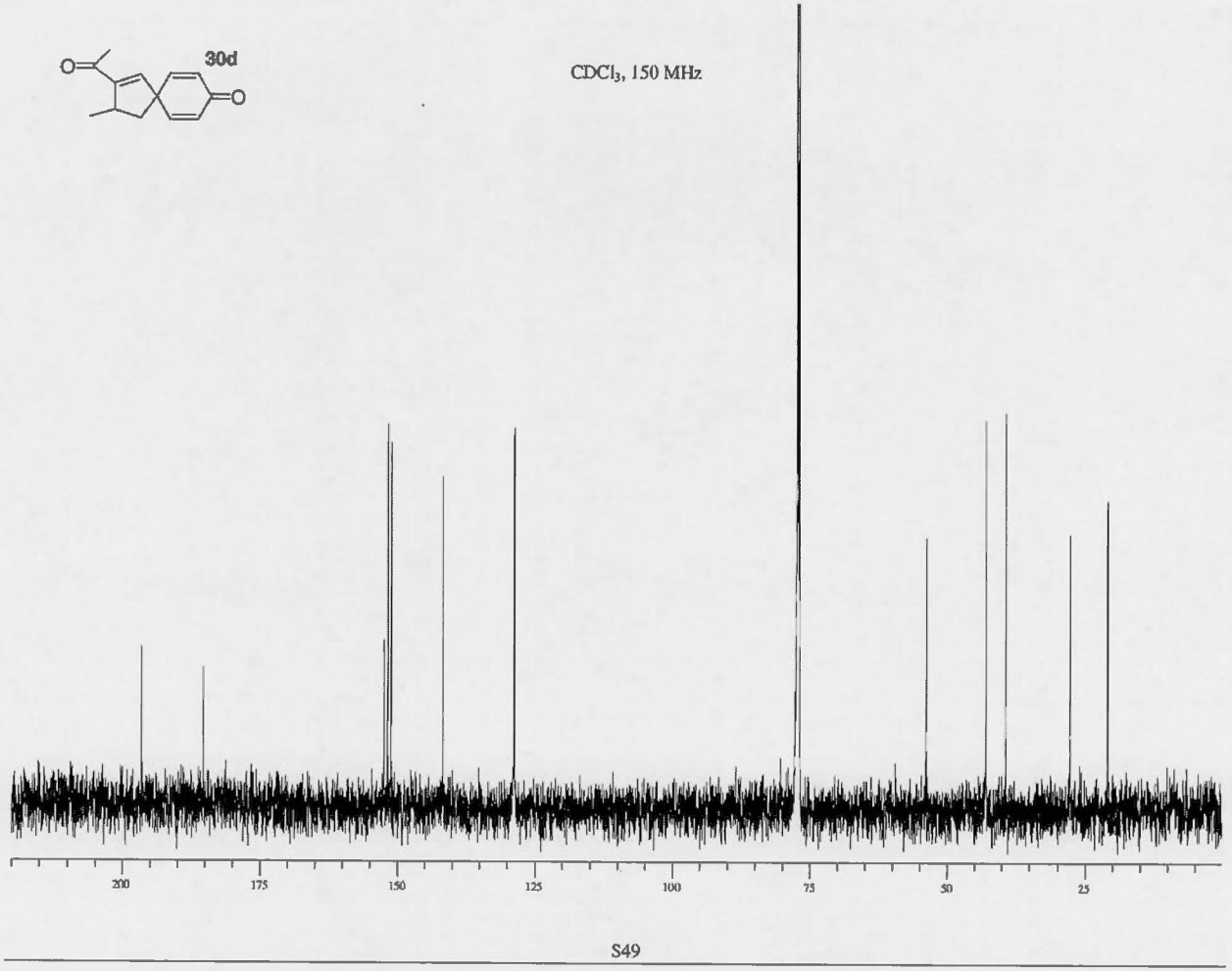


30c

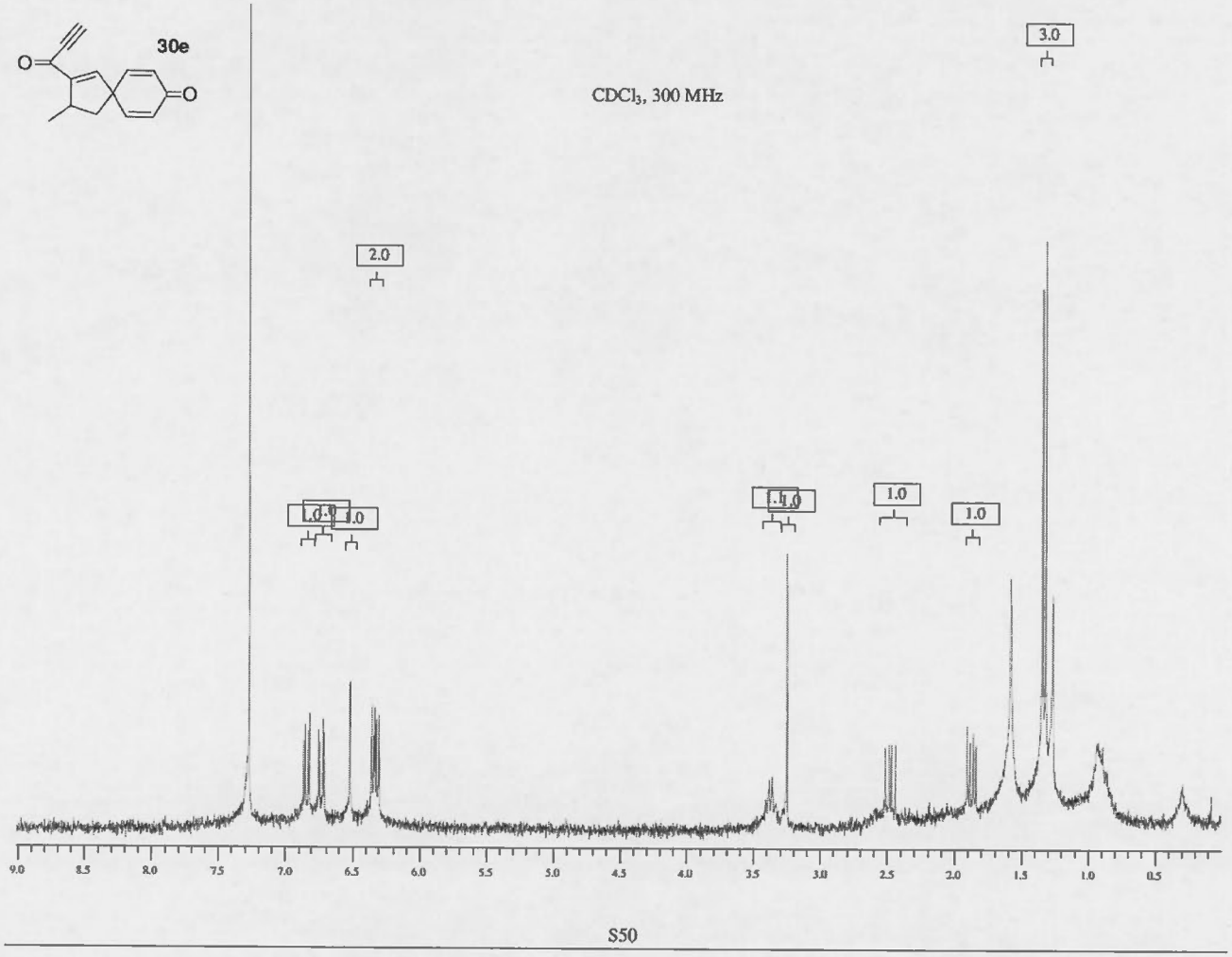
$CDCl_3$, 600 MHz


30c
CDCl3, 150 MHz
S47

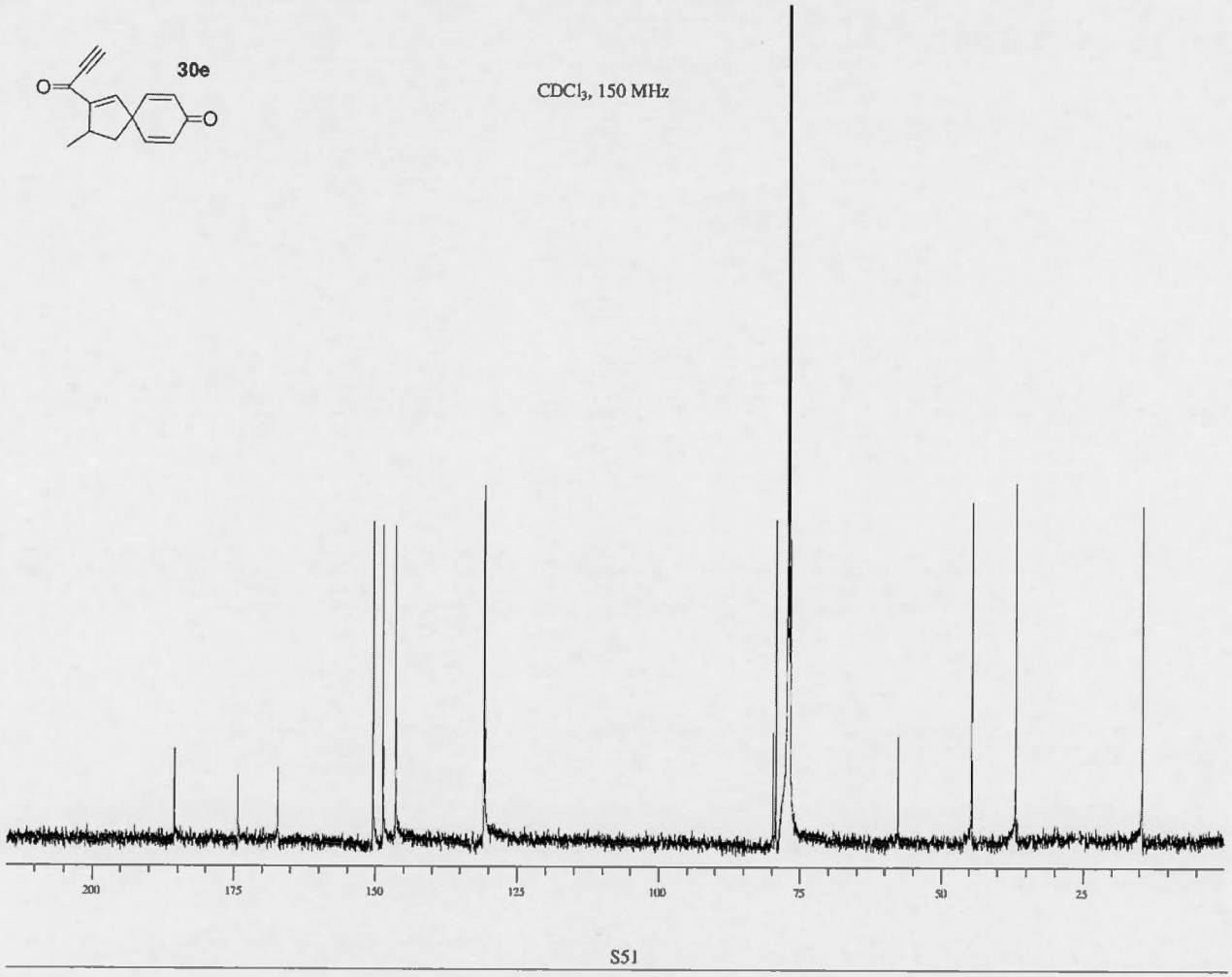

30d
CDCl3, 600 MHz
3.0
3.1
2.0
1.0
1.0
1.0
1.0
1.0
1.0
S48



S49

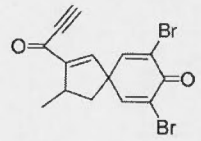

30e
CDCl3, 300 MHz
3.0
2.0
1.0
1.0
1.0
1.0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

S50



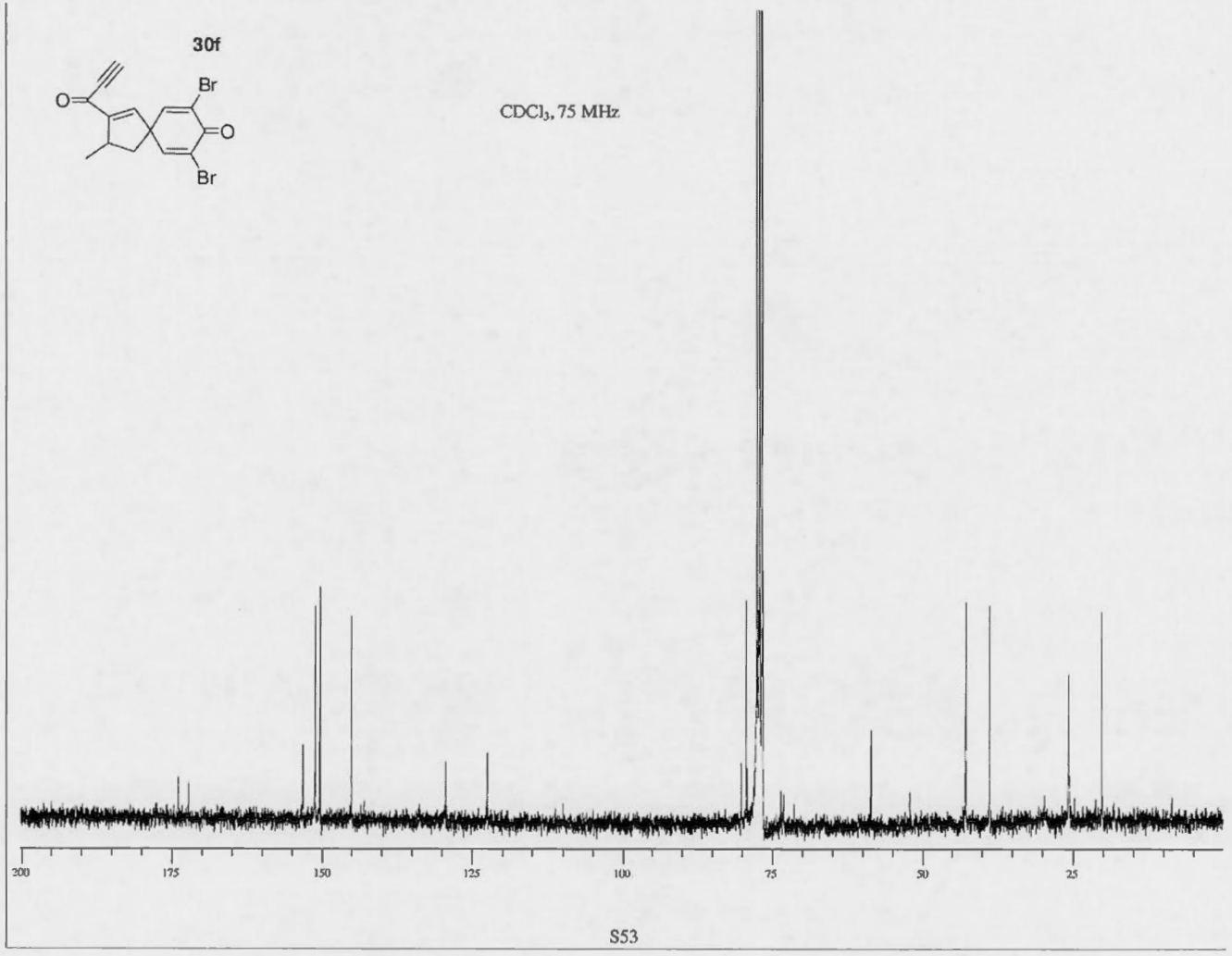
S51

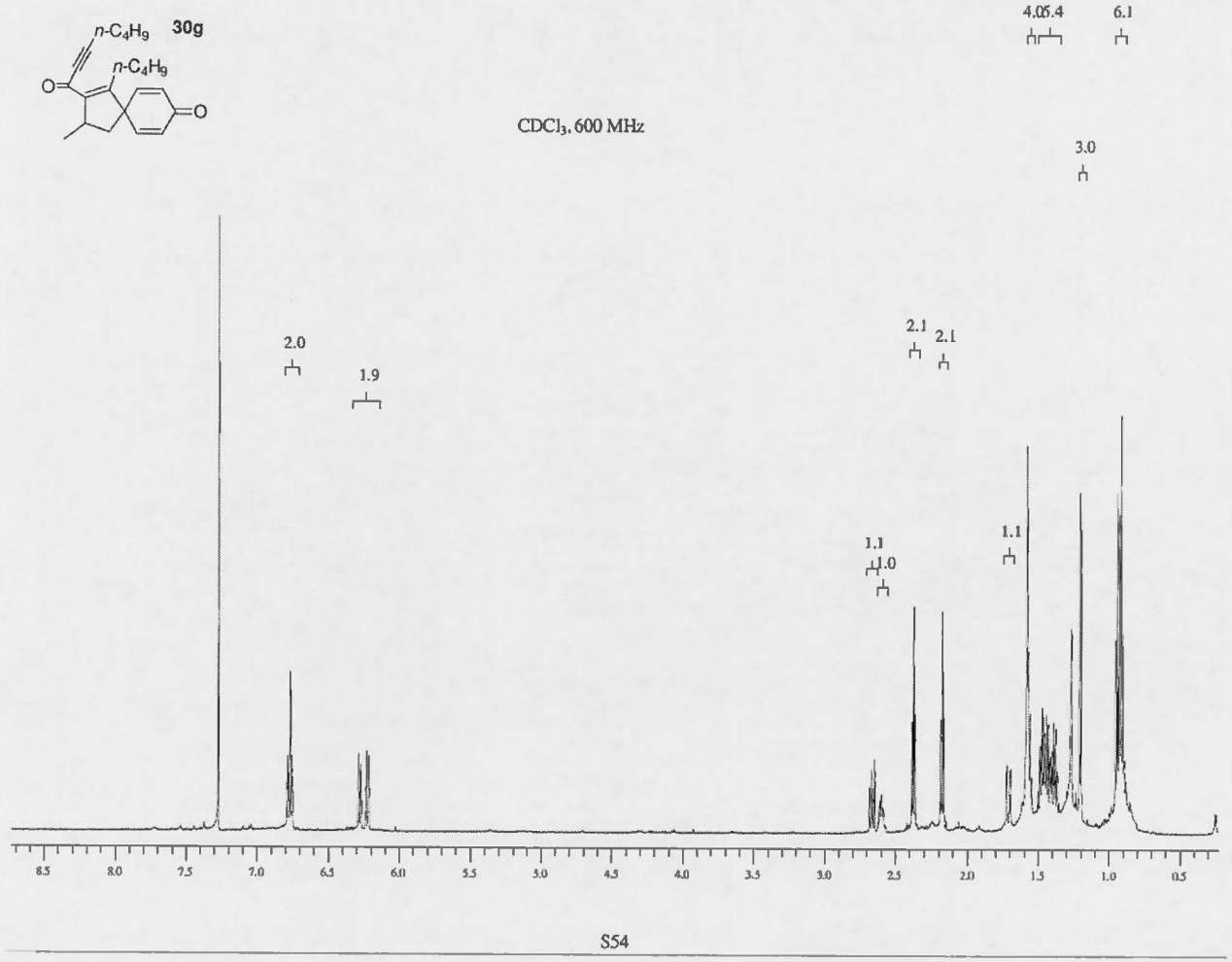
30f



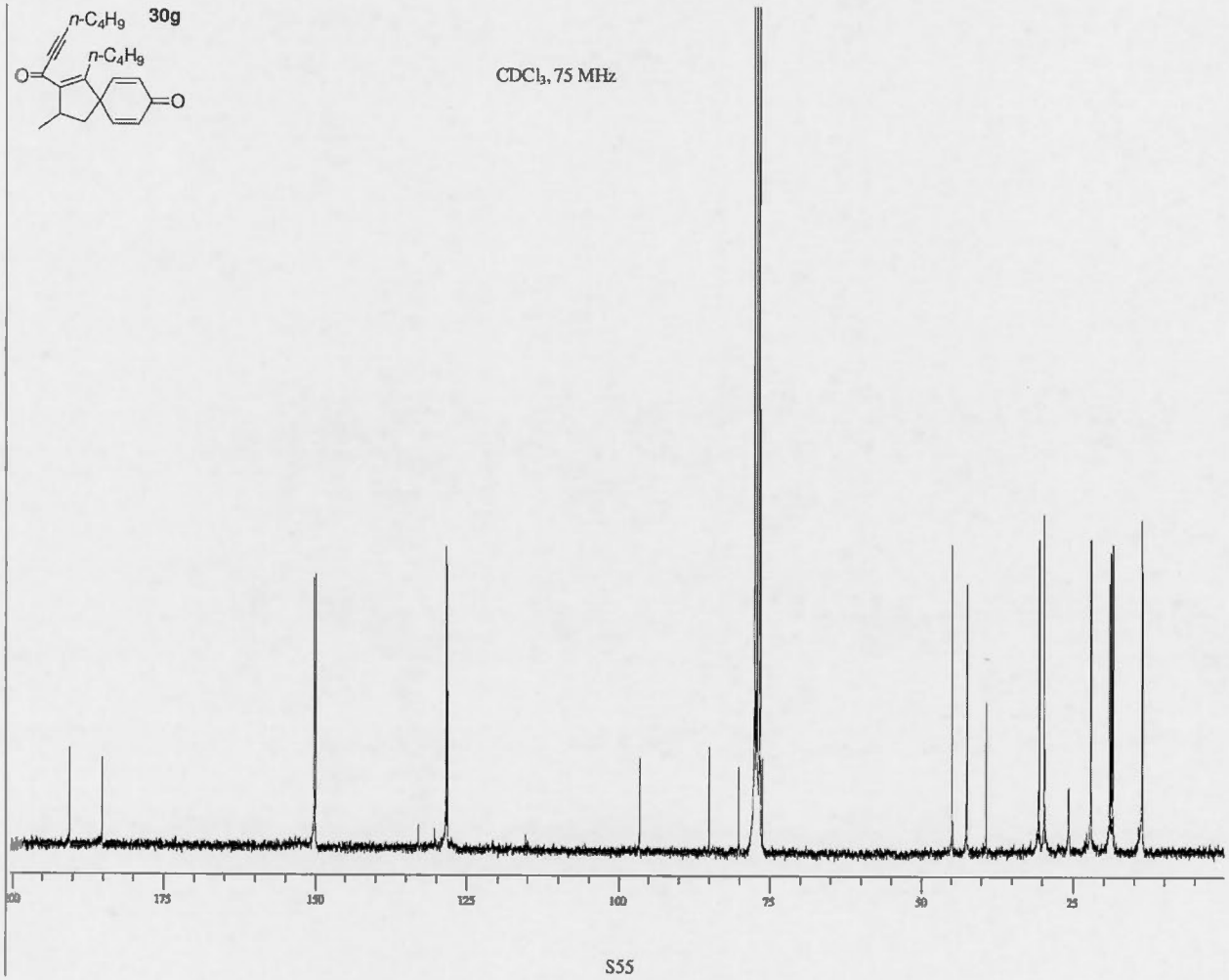
$CDCl_3$, 300 MHz

S52

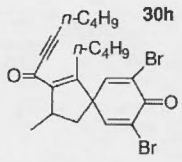

30f
Br
O
O
Br
CDCl3, 75 MHz
200
175
150
125
100
75
50
25
S53


n-C4H9
30g
n-C4H9
O
O
CDCl3, 600 MHz
4.0
5.4
6.1
3.0
2.0
1.9
2.1
2.1
1.1
1.0
1.1
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

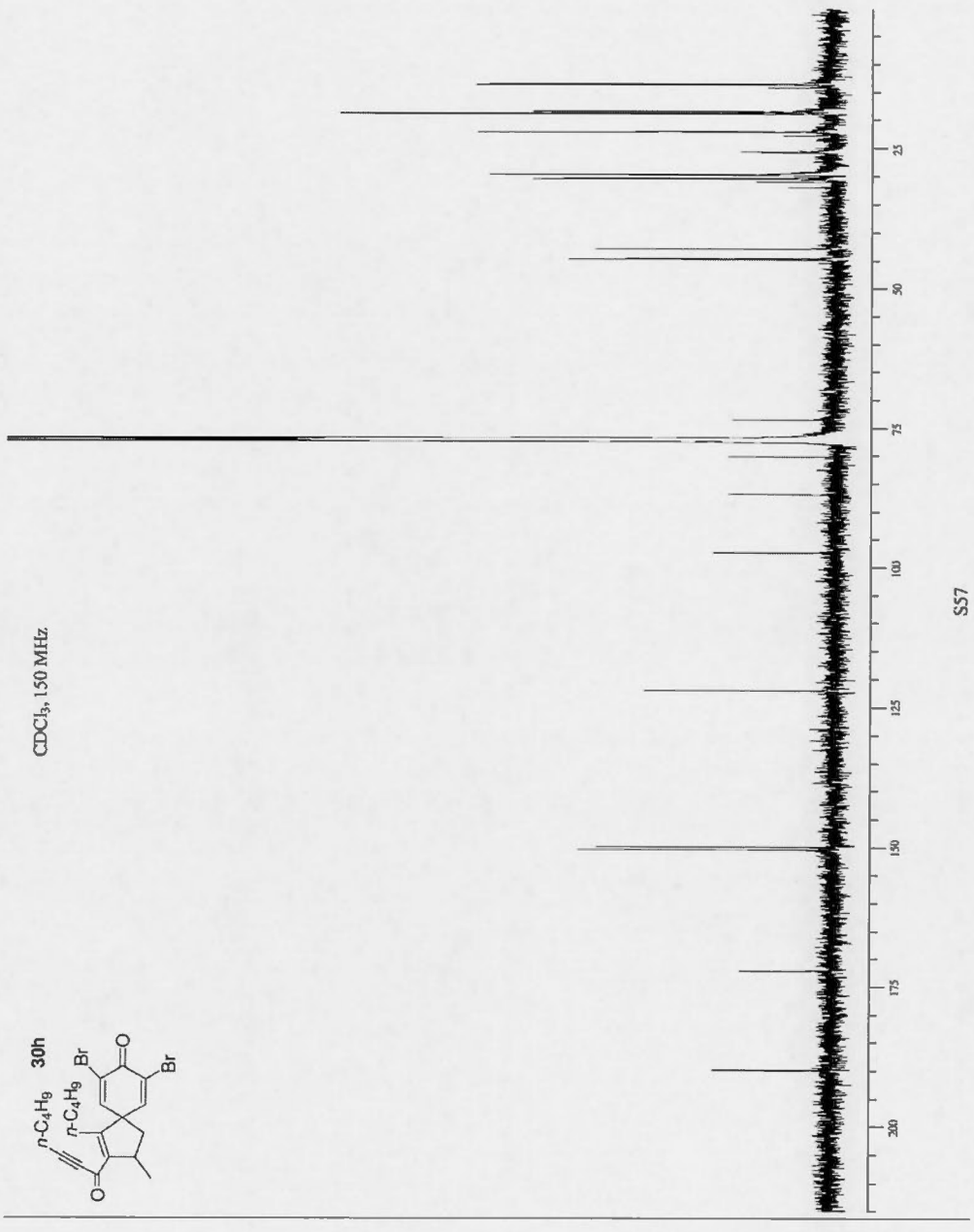
S54



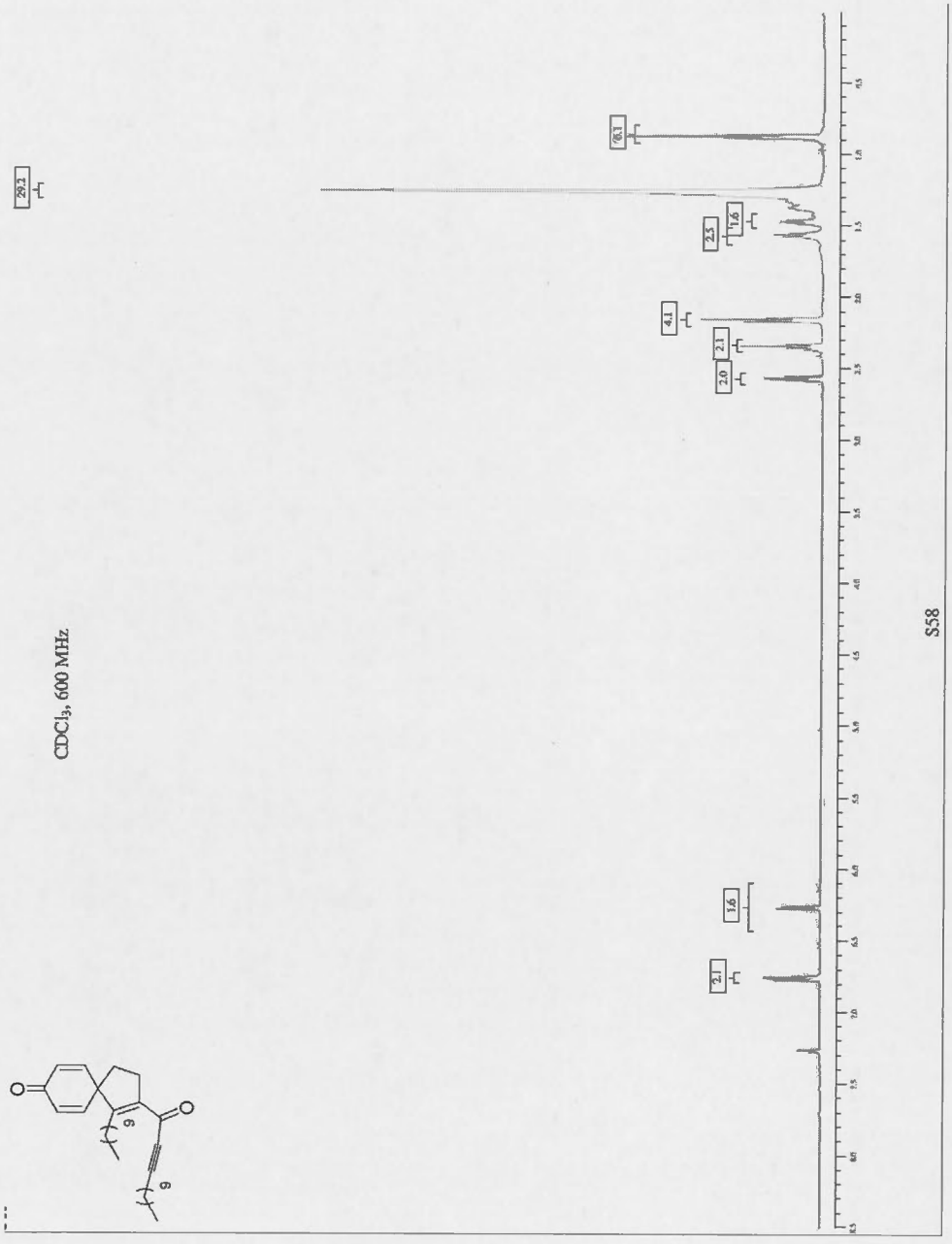
S55



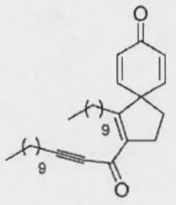
CDCl3, 300 MHz


30h
n-C4H9
n-C4H9
Br
Br
O
O
CDCl3, 150 MHz
200
175
150
125
100
75
50
25

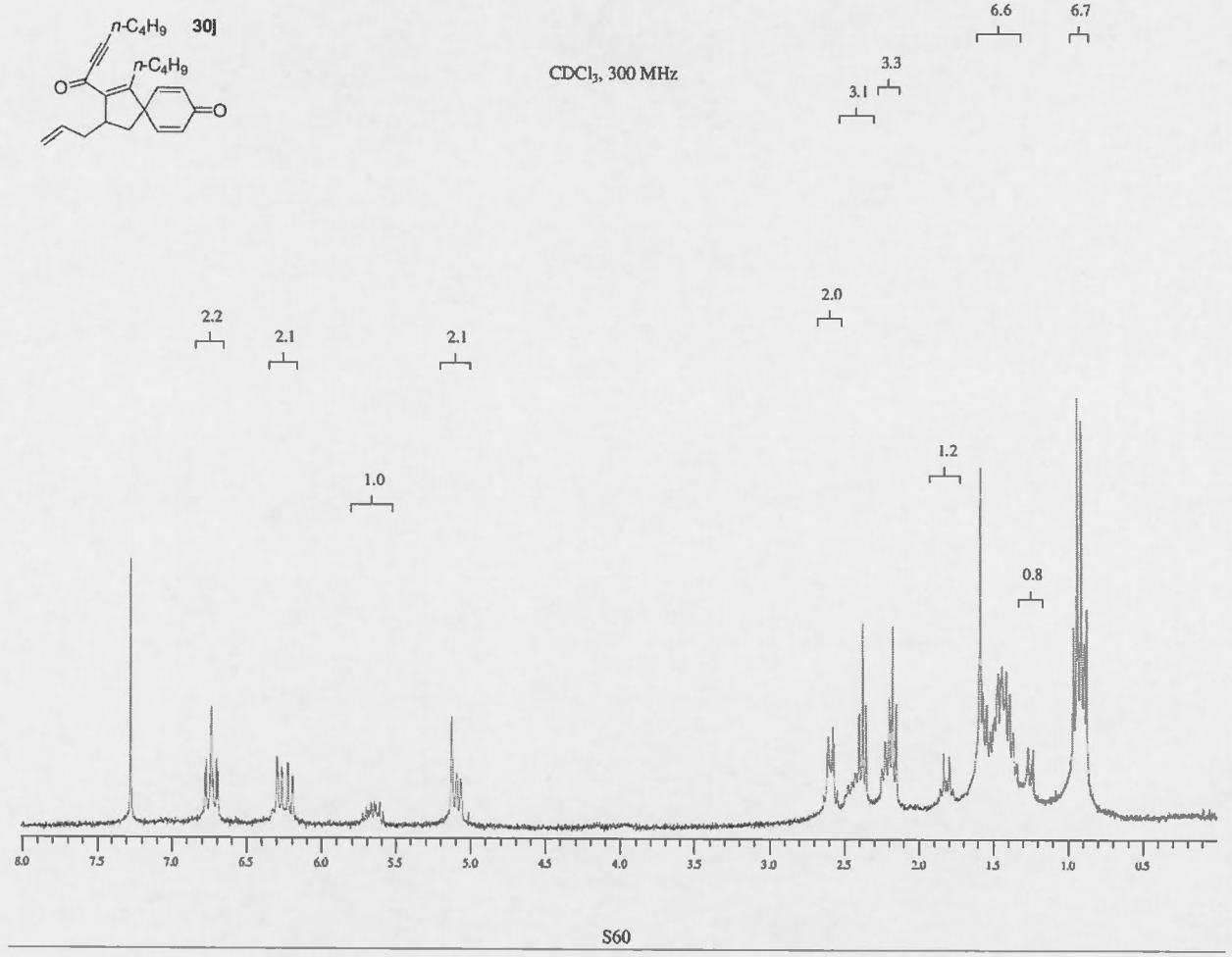
S57

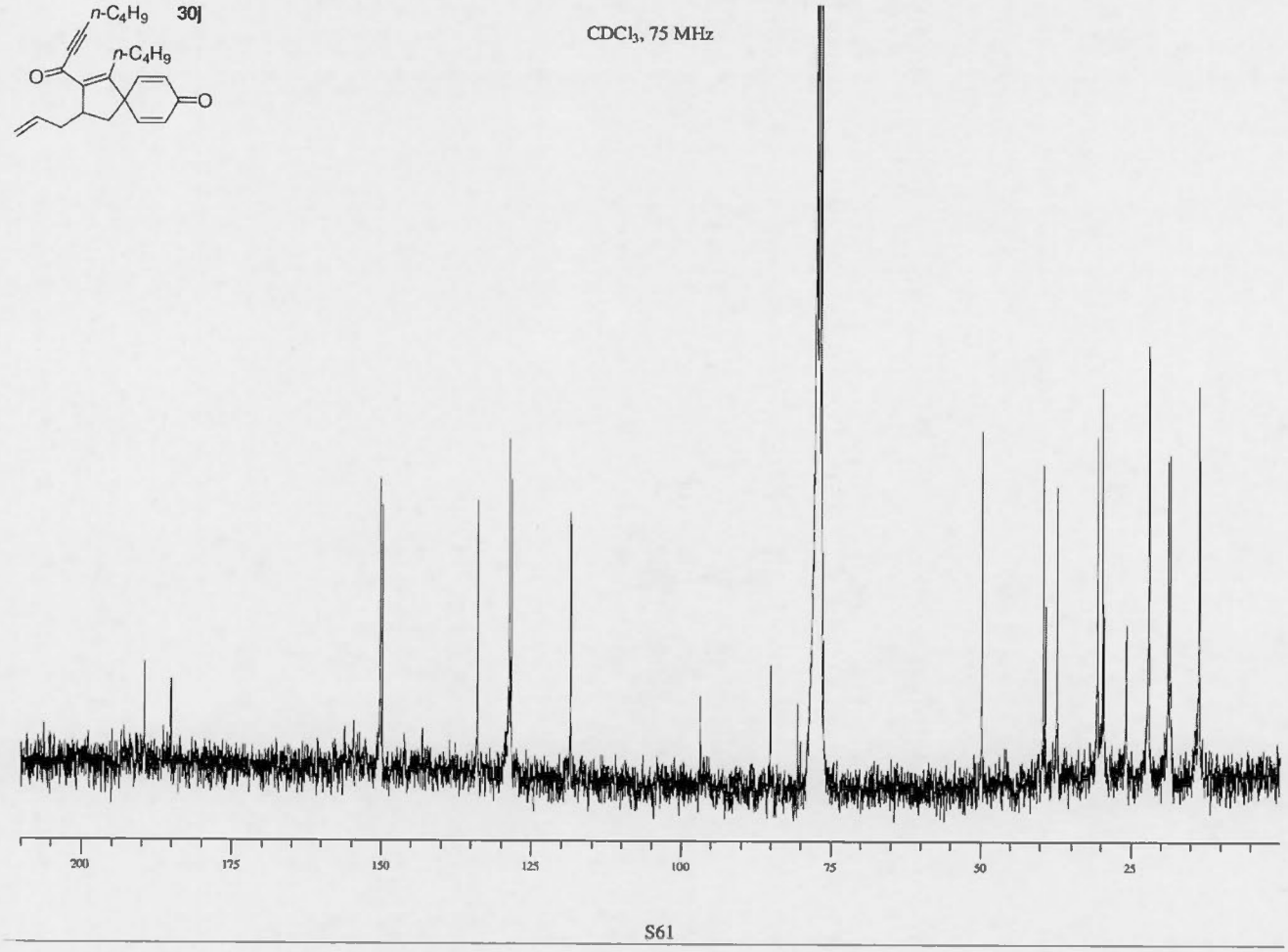

CDCl3, 600 MHz
S58

30i

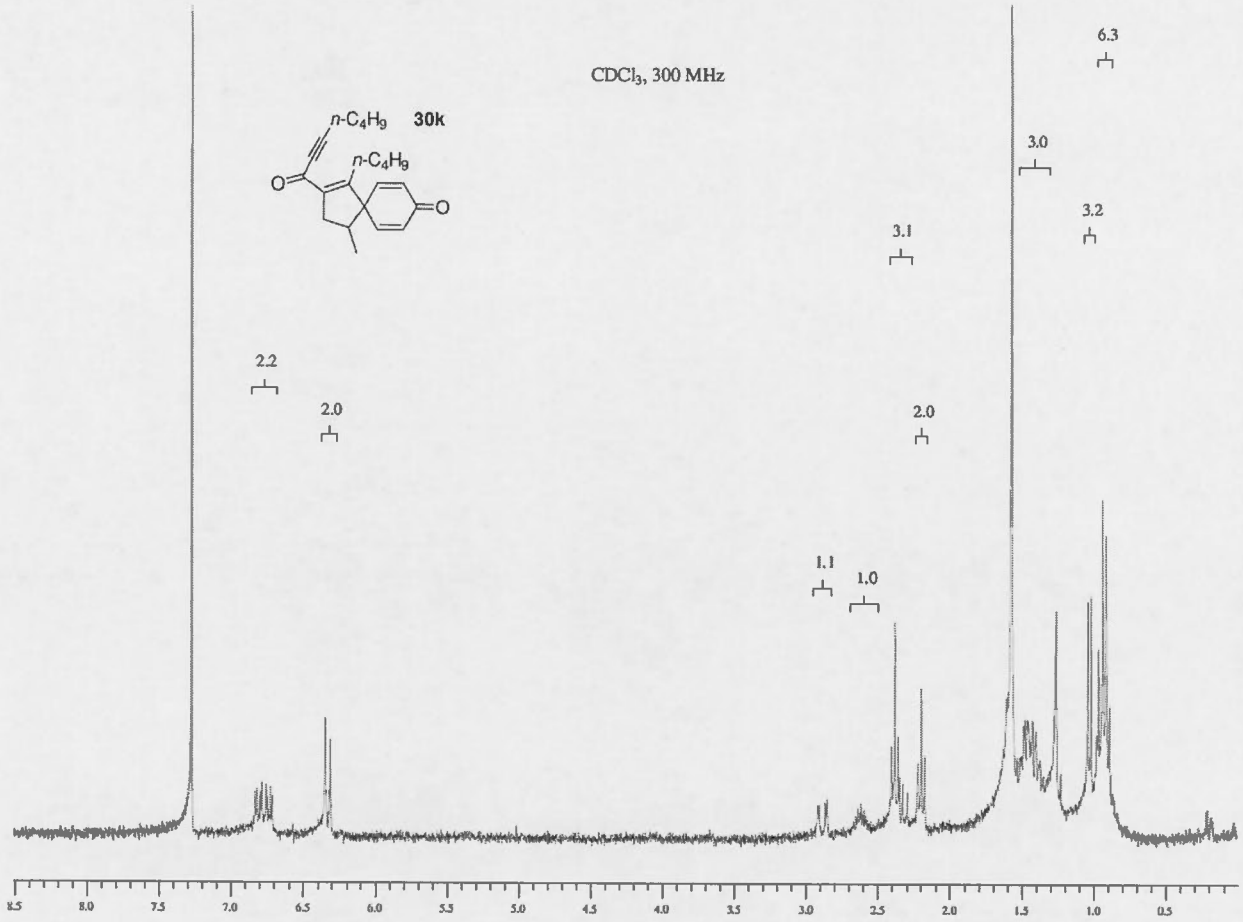


$CDCl_3$, 150 MHz

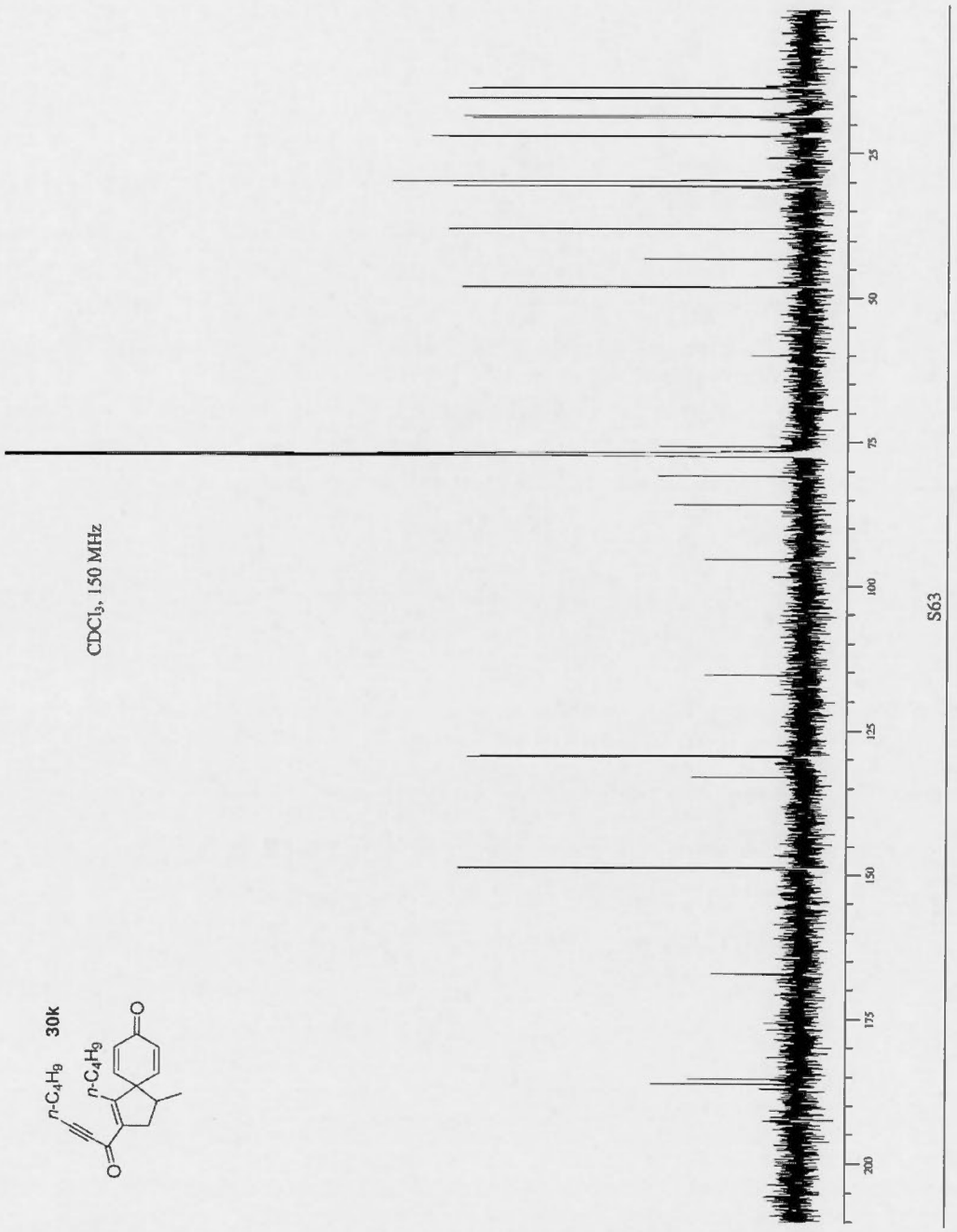

n-C4H9
30j
n-C4H9
O
O
CDCl3, 300 MHz
6.6
6.7
3.3
3.1
2.2
2.1
2.1
2.0
1.2
1.0
0.8
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
S60

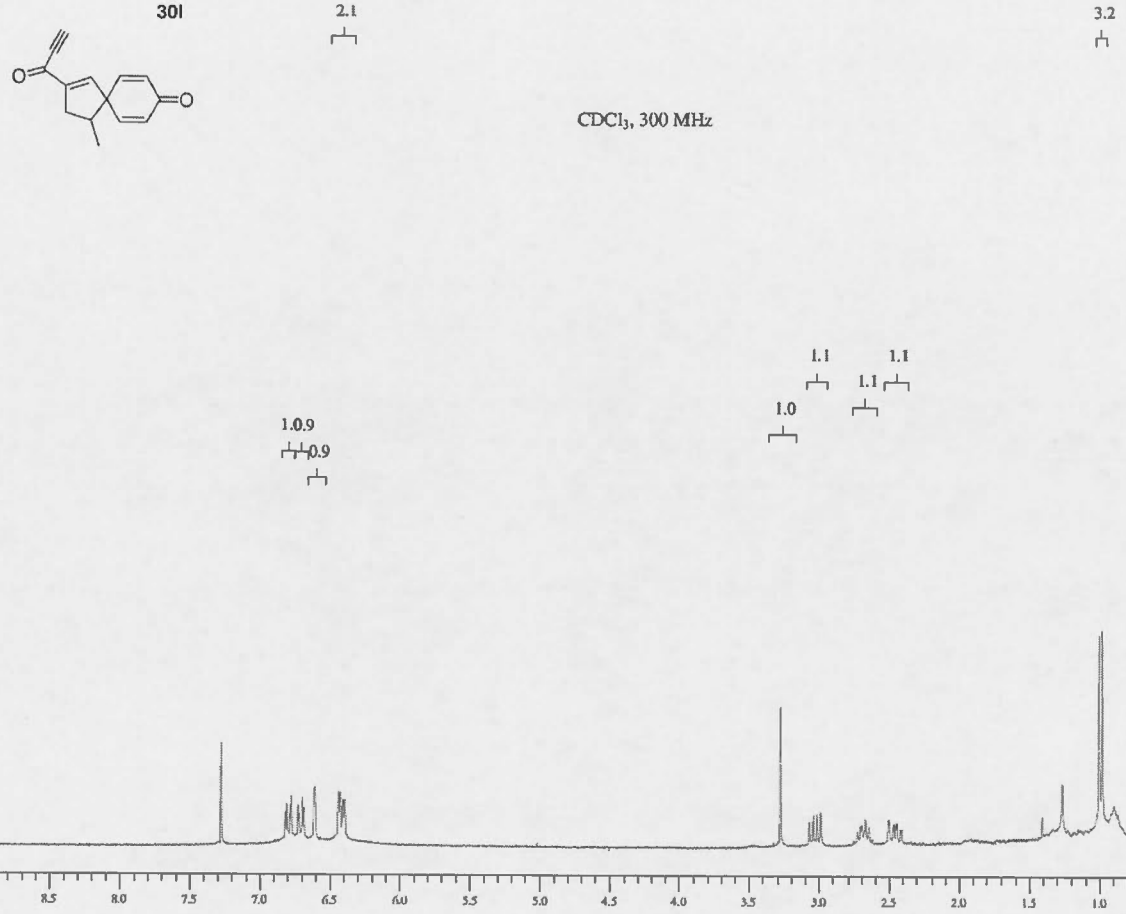


S61

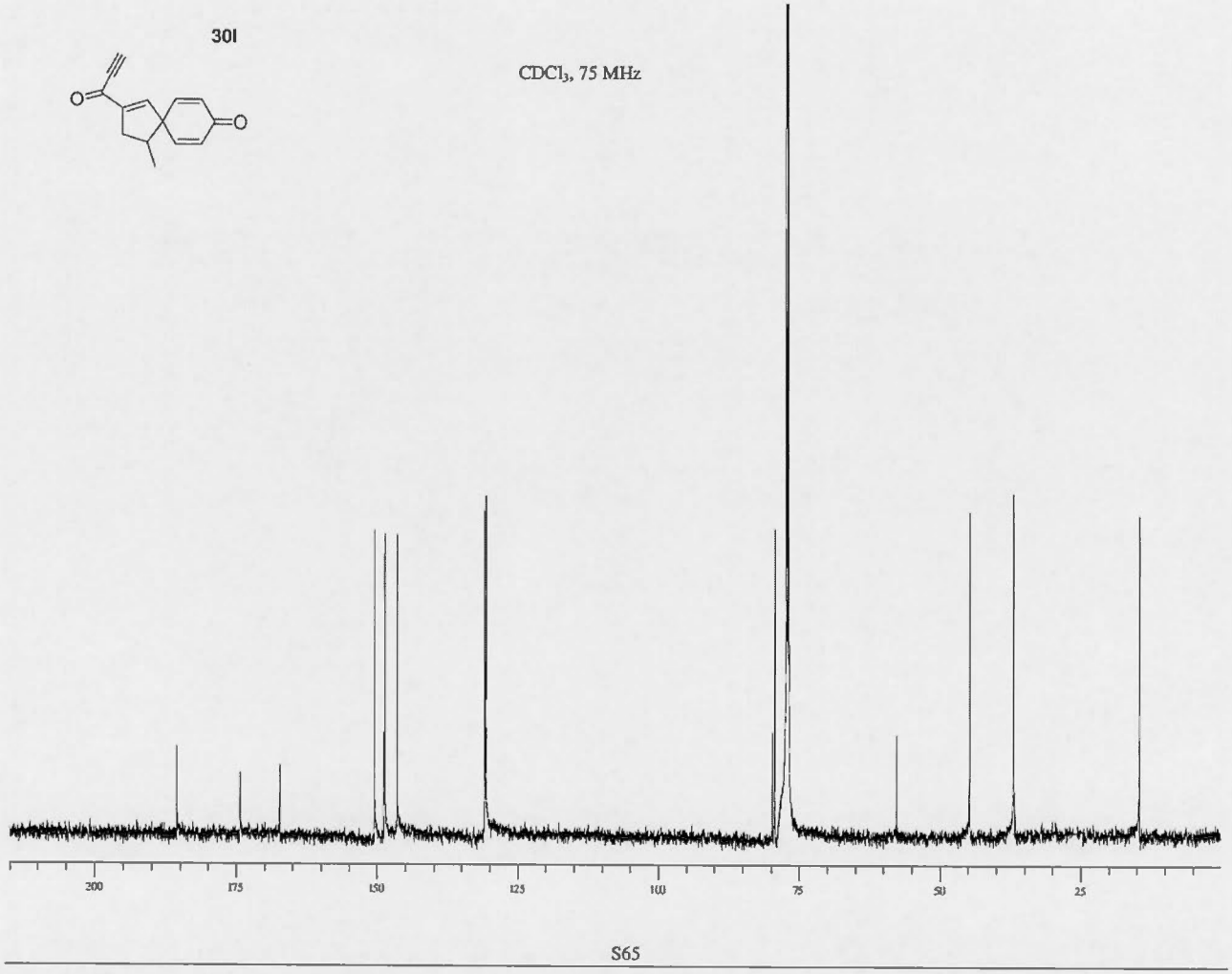

CDCl3, 300 MHz
n-C4H9
30k
n-C4H9
O
O
6.3
3.0
3.2
3.1
2.2
2.0
2.0
1.1
1.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

S62

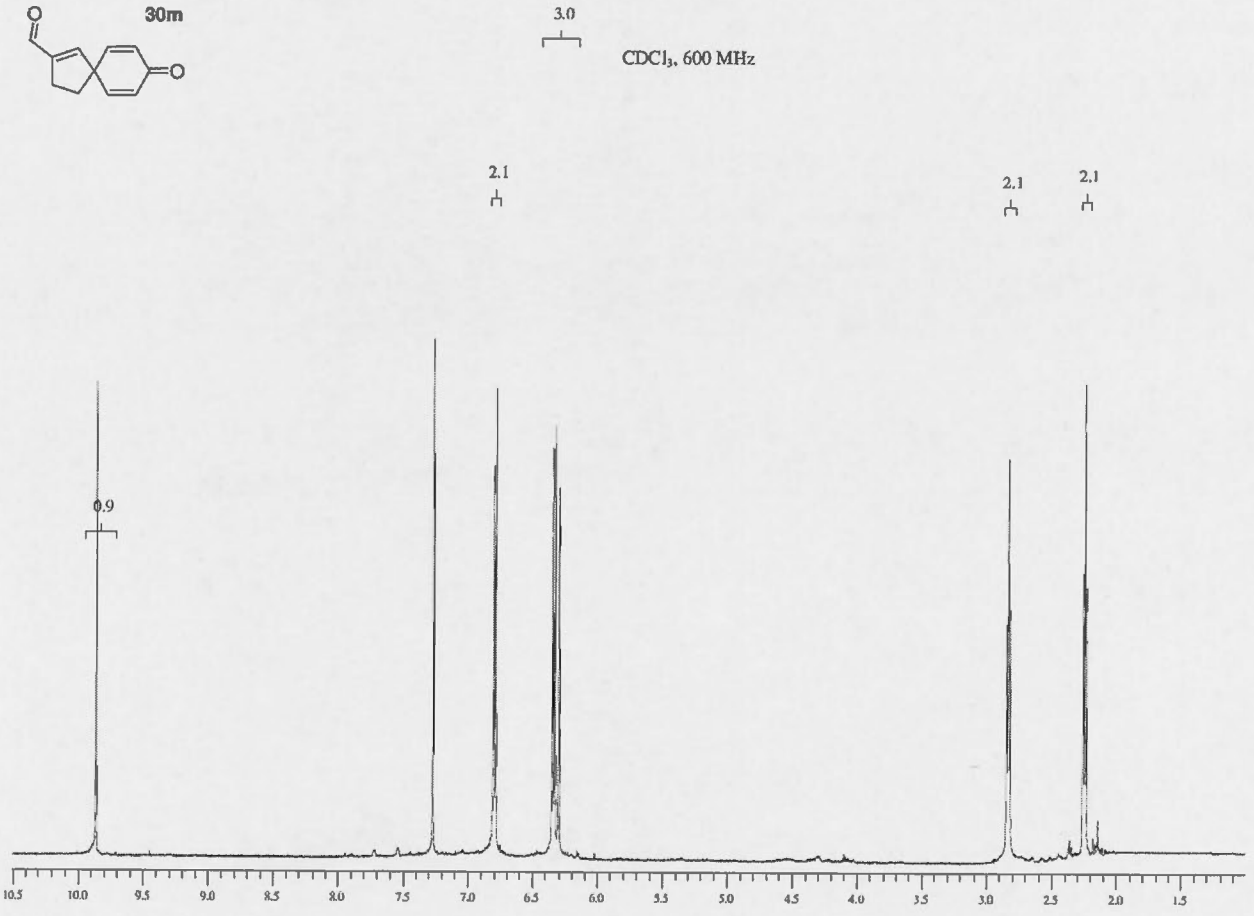

30k
n-C4H9
n-C4H9
O
O
CDCl3, 150 MHz
200
175
150
125
100
75
50
25
S63

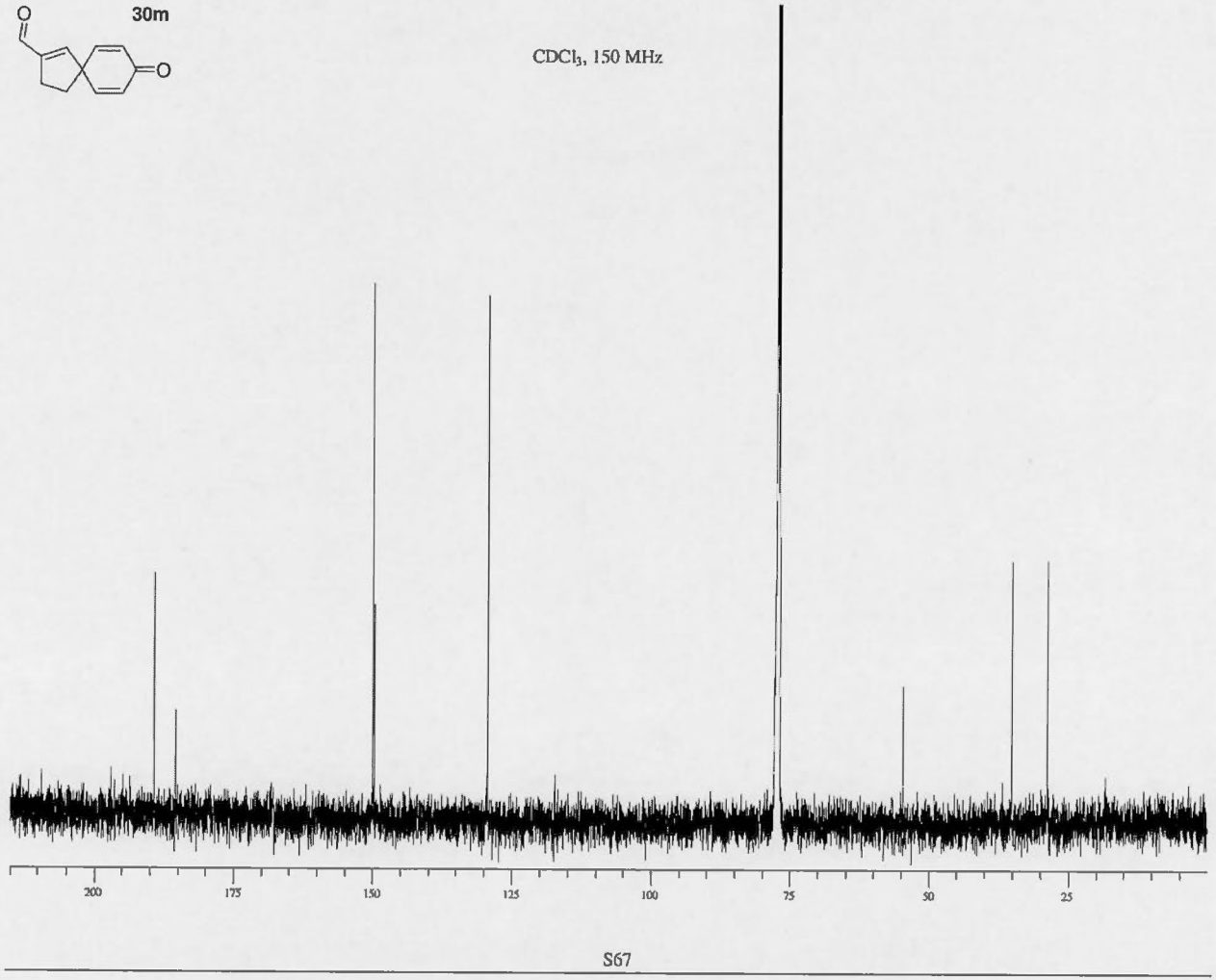

301
2.1
3.2
CDCl3, 300 MHz
1.1
1.1
1.1
1.0
1.0.9
0.9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

S64

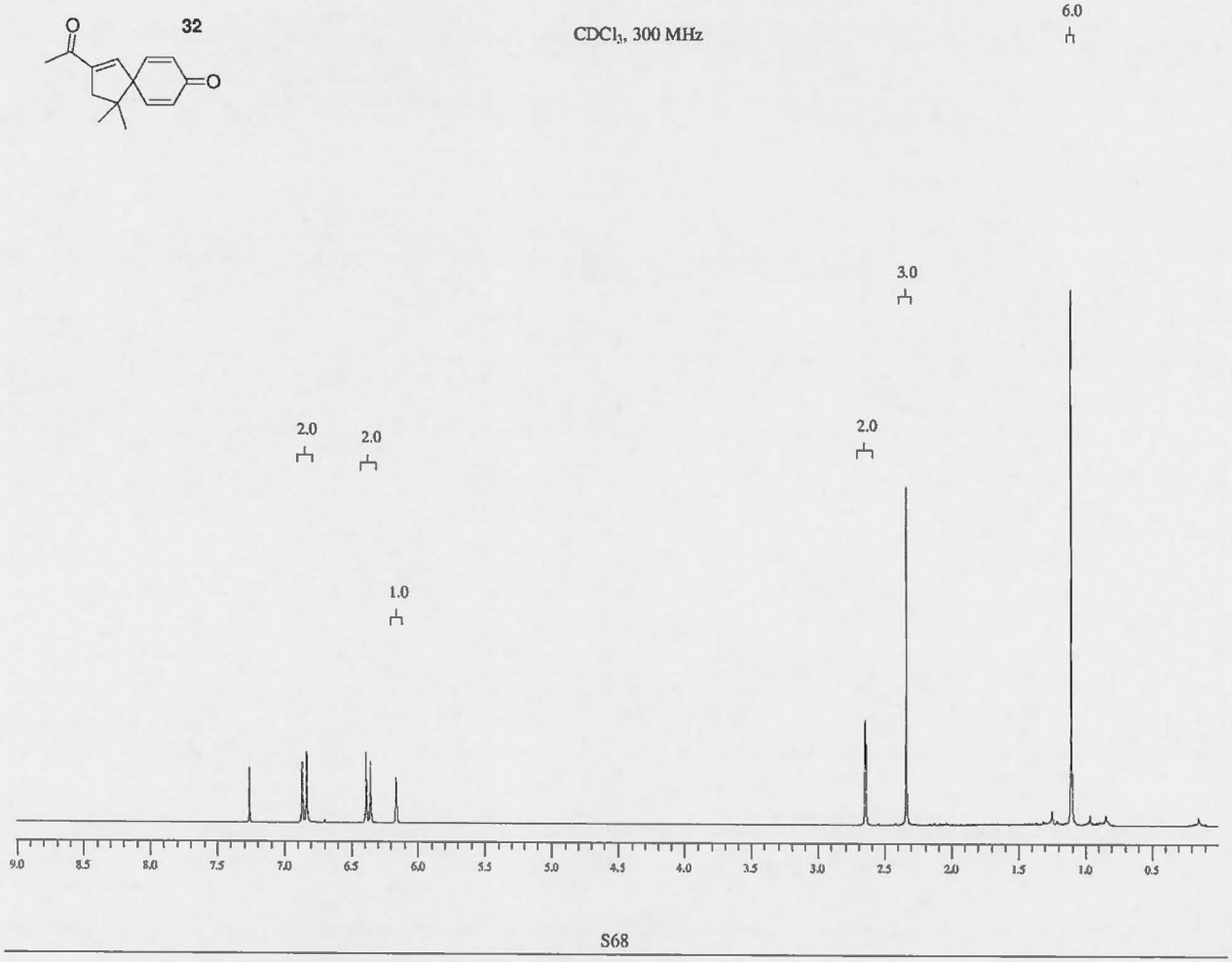


S65

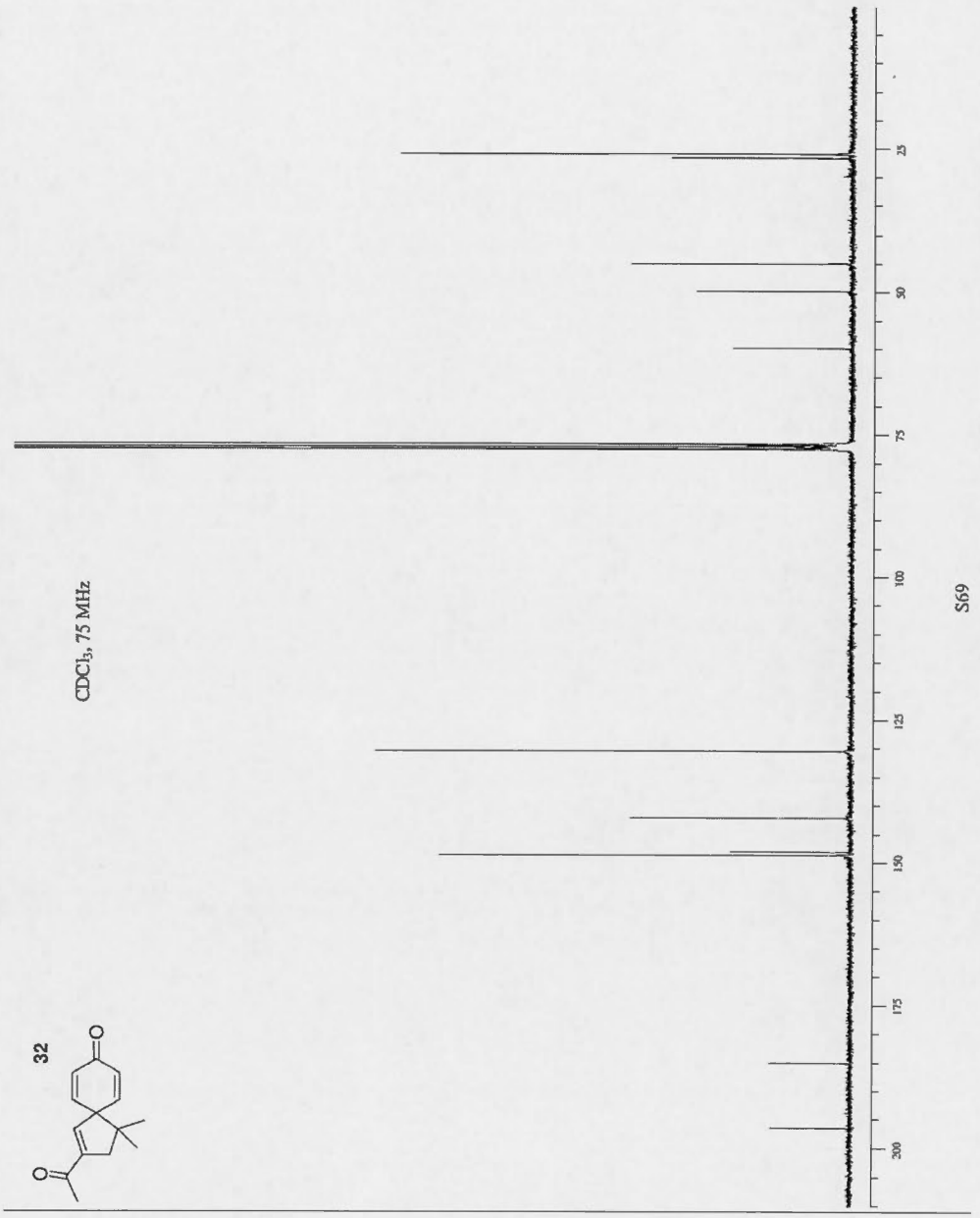

30m
3.0
CDCl3, 600 MHz
2.1
2.1
2.1
0.9
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

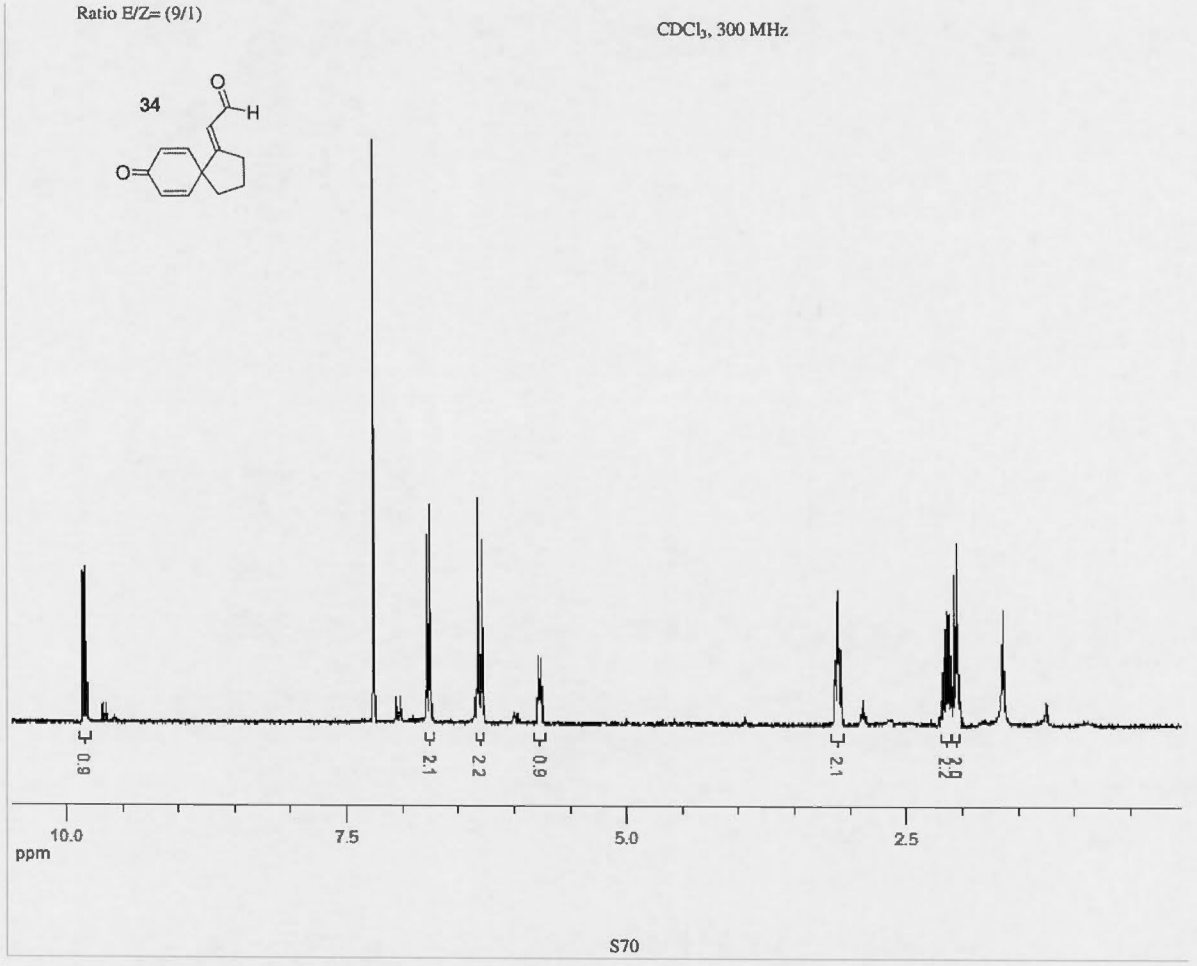


S67

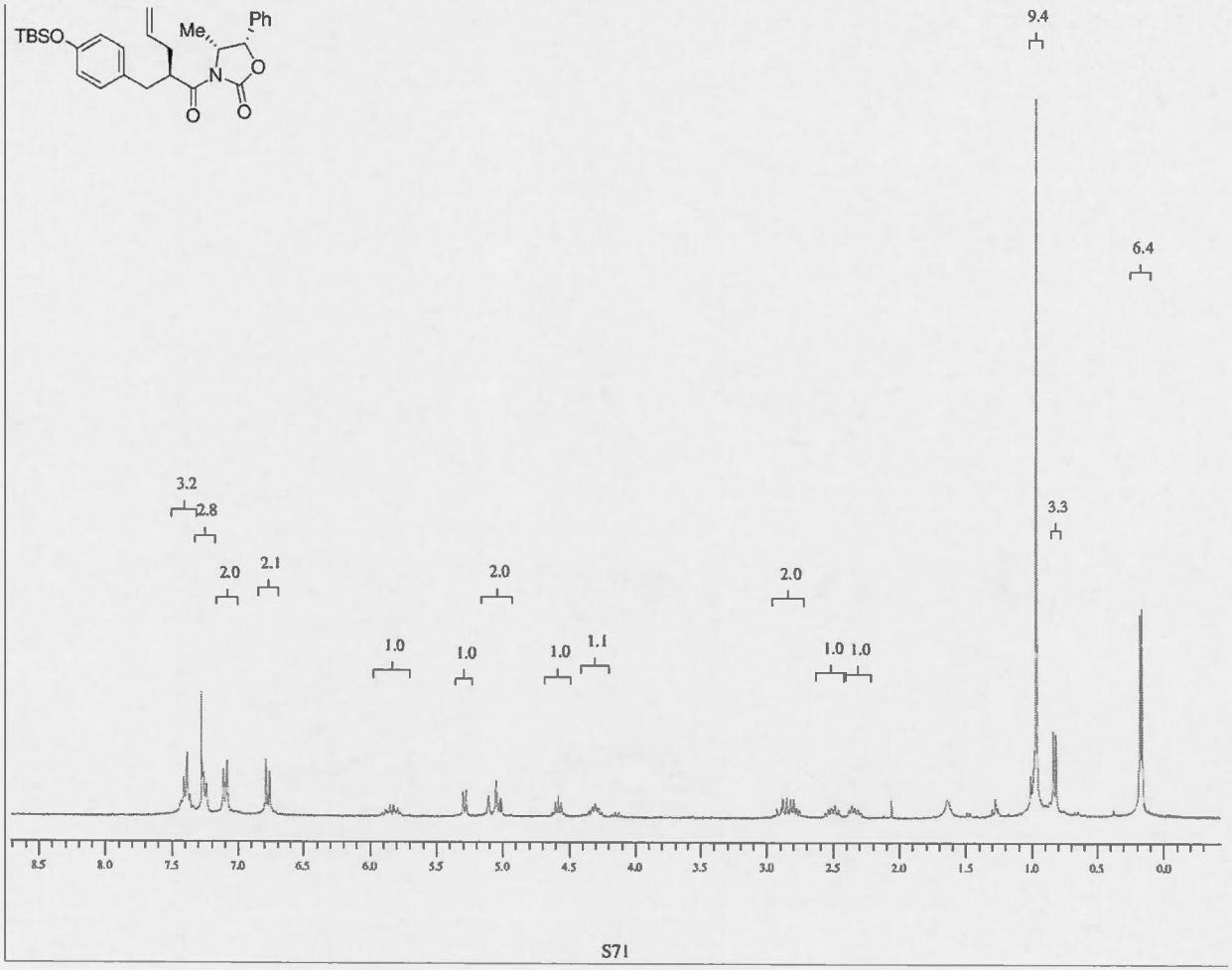

32
CDCl3, 300 MHz
6.0
3.0
2.0
2.0
2.0
1.0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

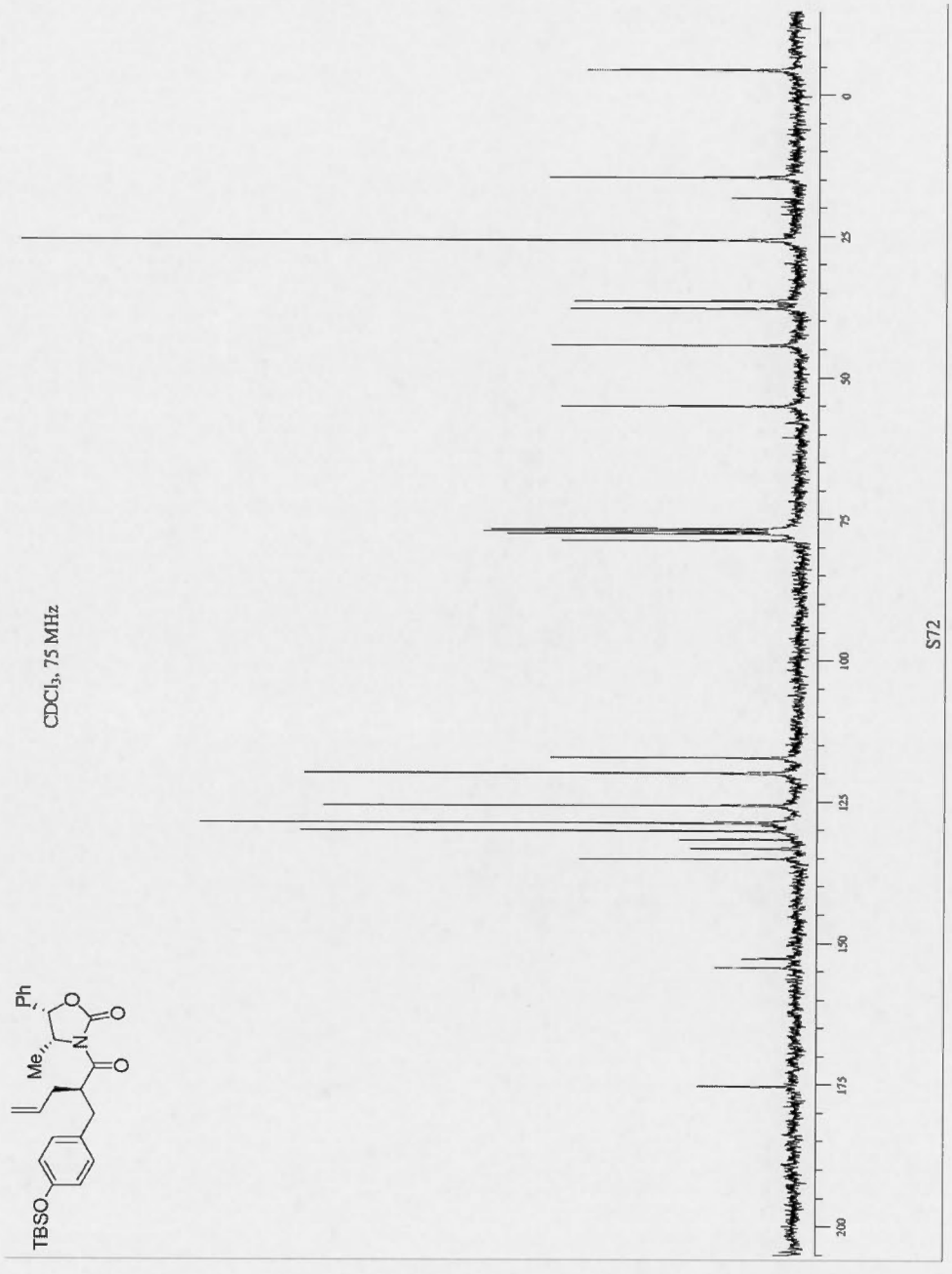
S68

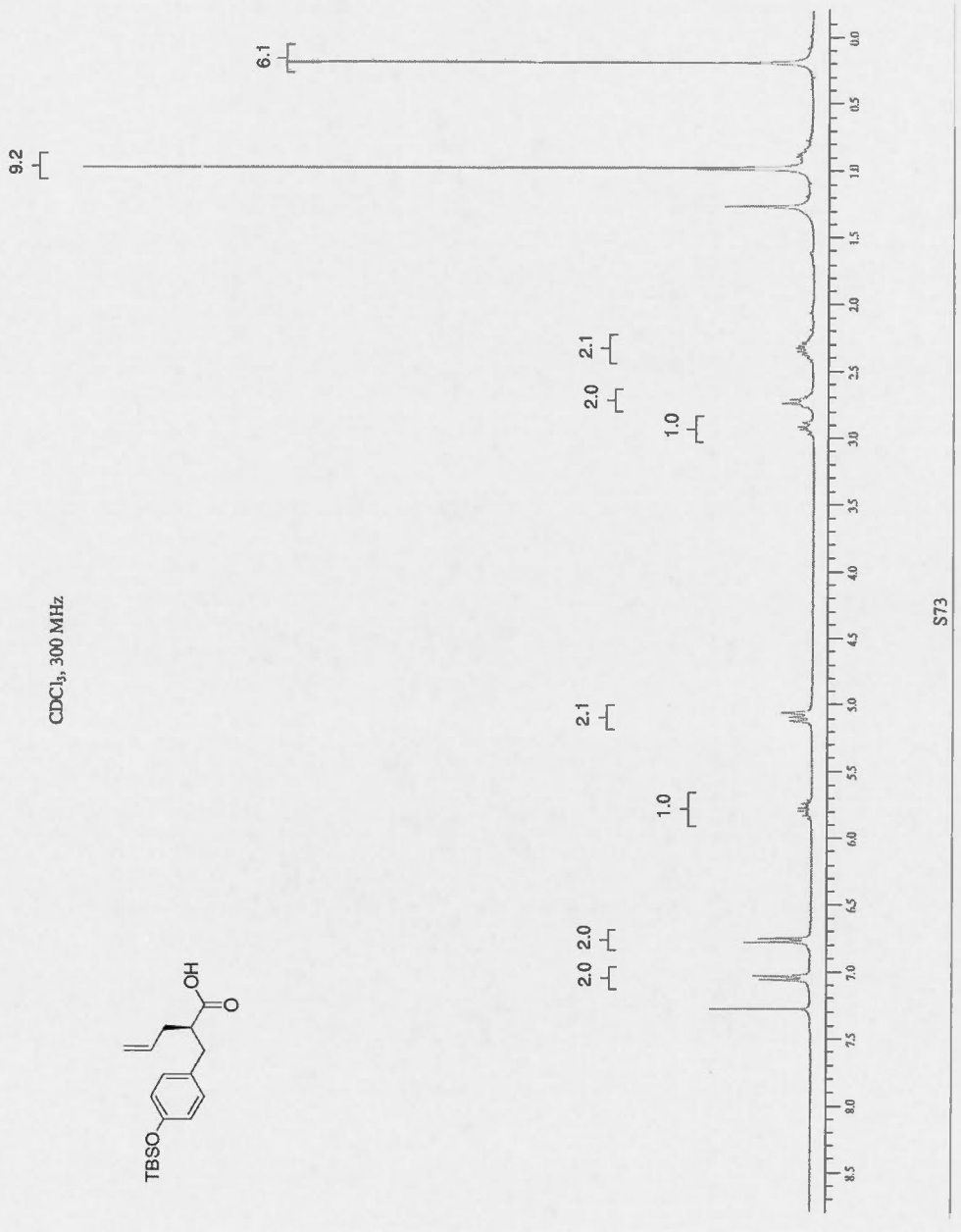

32
CDCl3, 75 MHz
25
50
75
100
125
150
175
200
S69

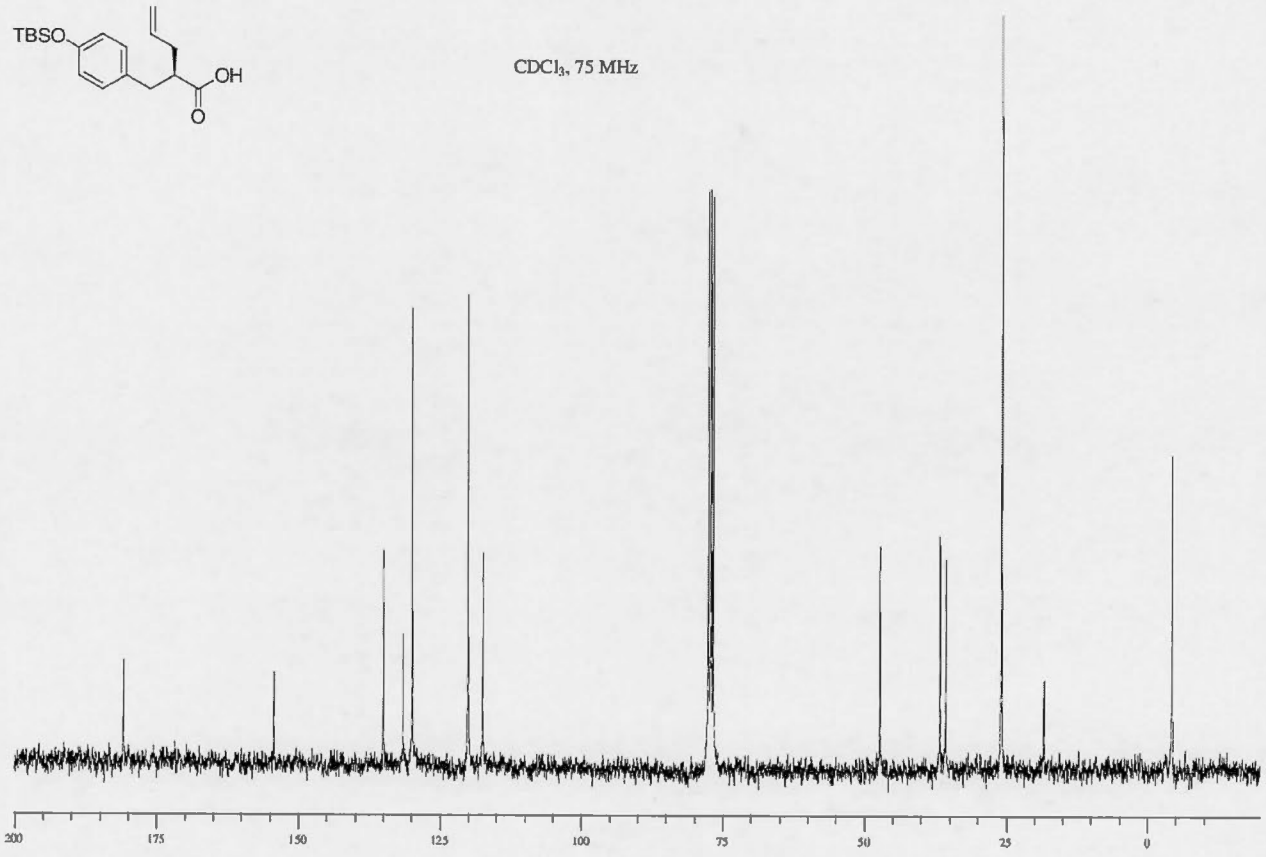

Ratio E/Z= (9/1)
CDCl3, 300 MHz
34
O
H
O
0.8
2.1
2.2
0.9
2.1
2.9
2.2
10.0
ppm
7.5
5.0
2.5

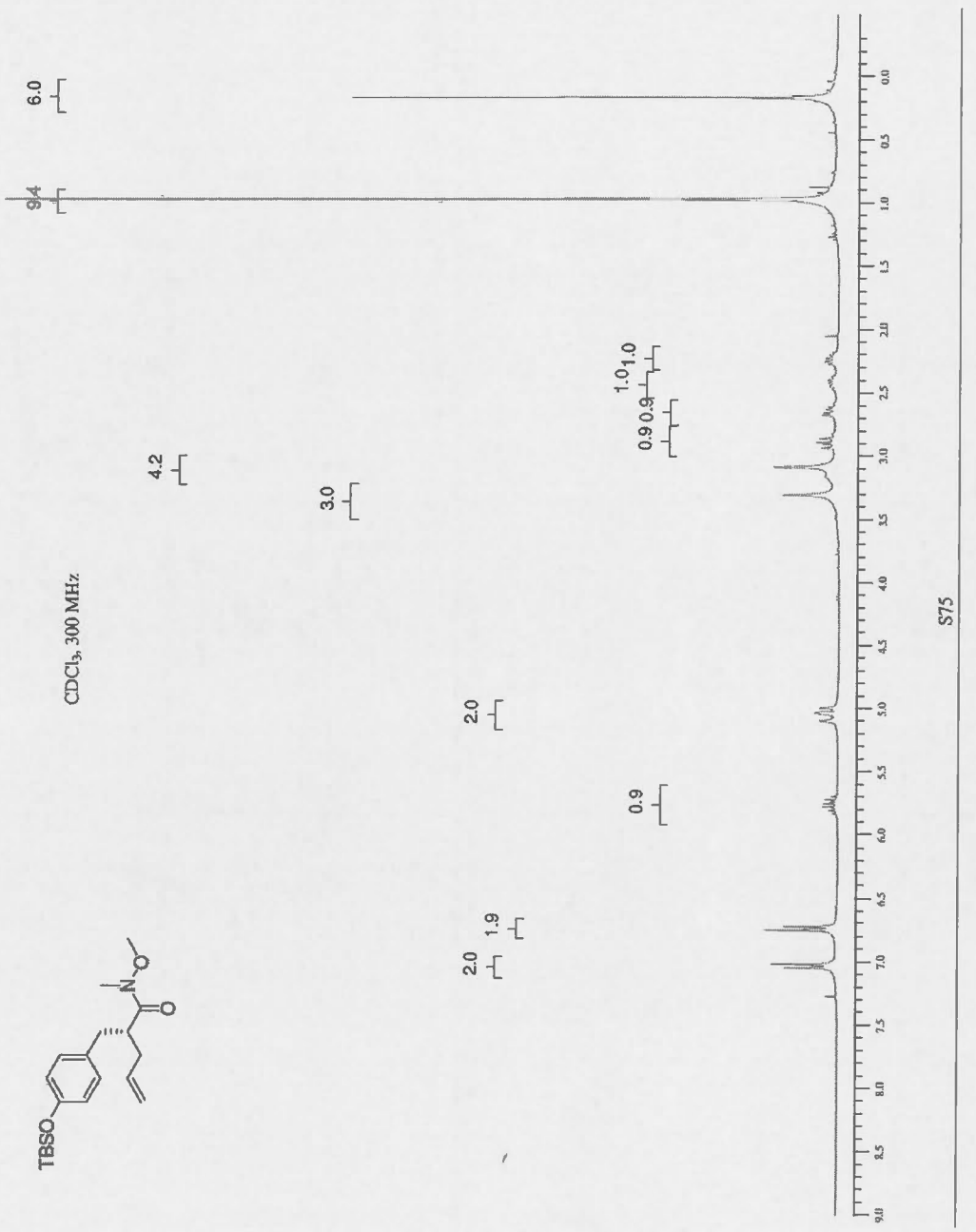
S70

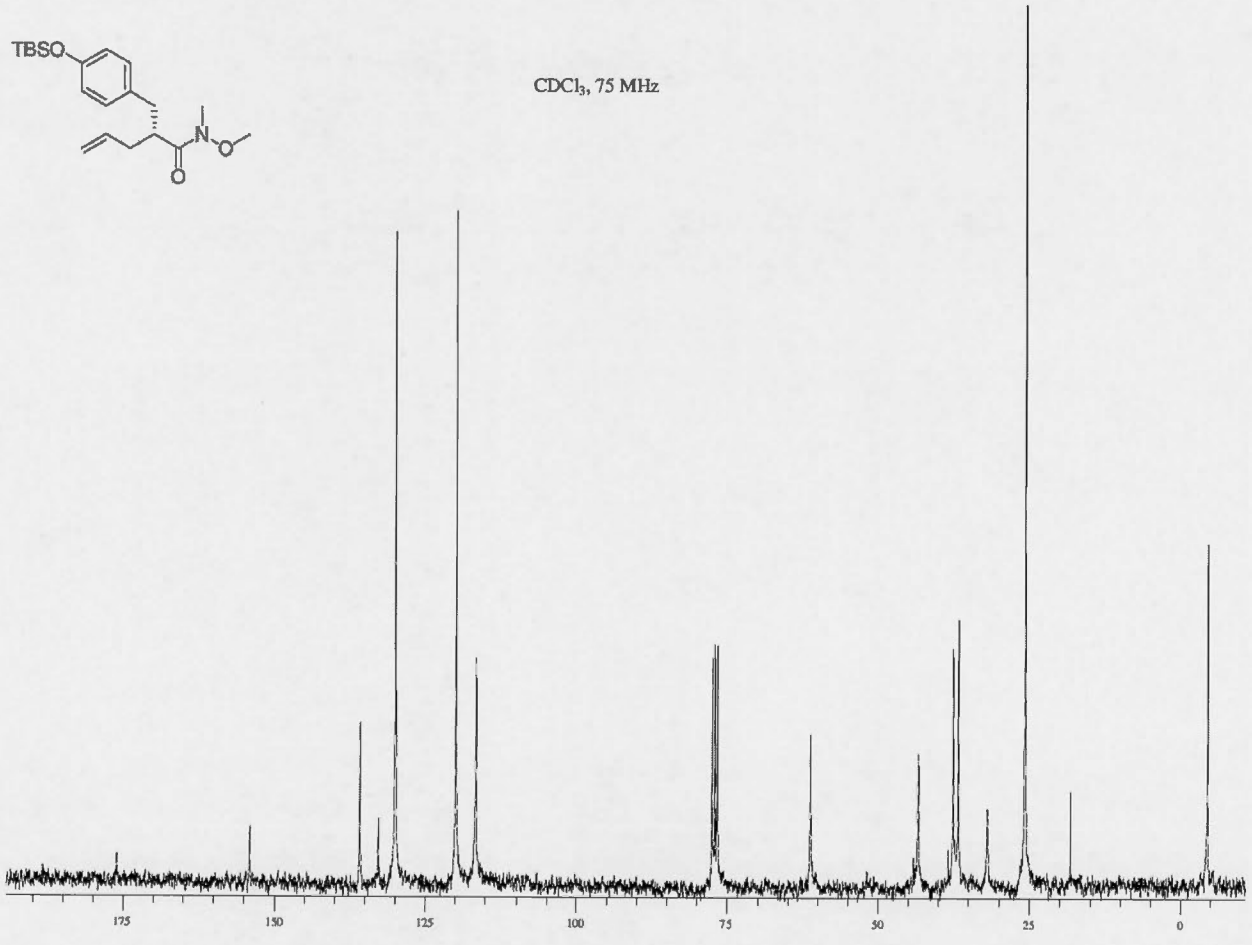

TBSO
Me
Ph
N
O
O
O
9.4
6.4
3.3
3.2
2.8
2.0
2.1
2.0
2.0
1.0
1.0
1.0
1.1
1.0
1.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
S71


Ph
Me
O
O
N
O
TBSO
CDCl3, 75 MHz
0
25
50
75
100
125
150
175
200
S72

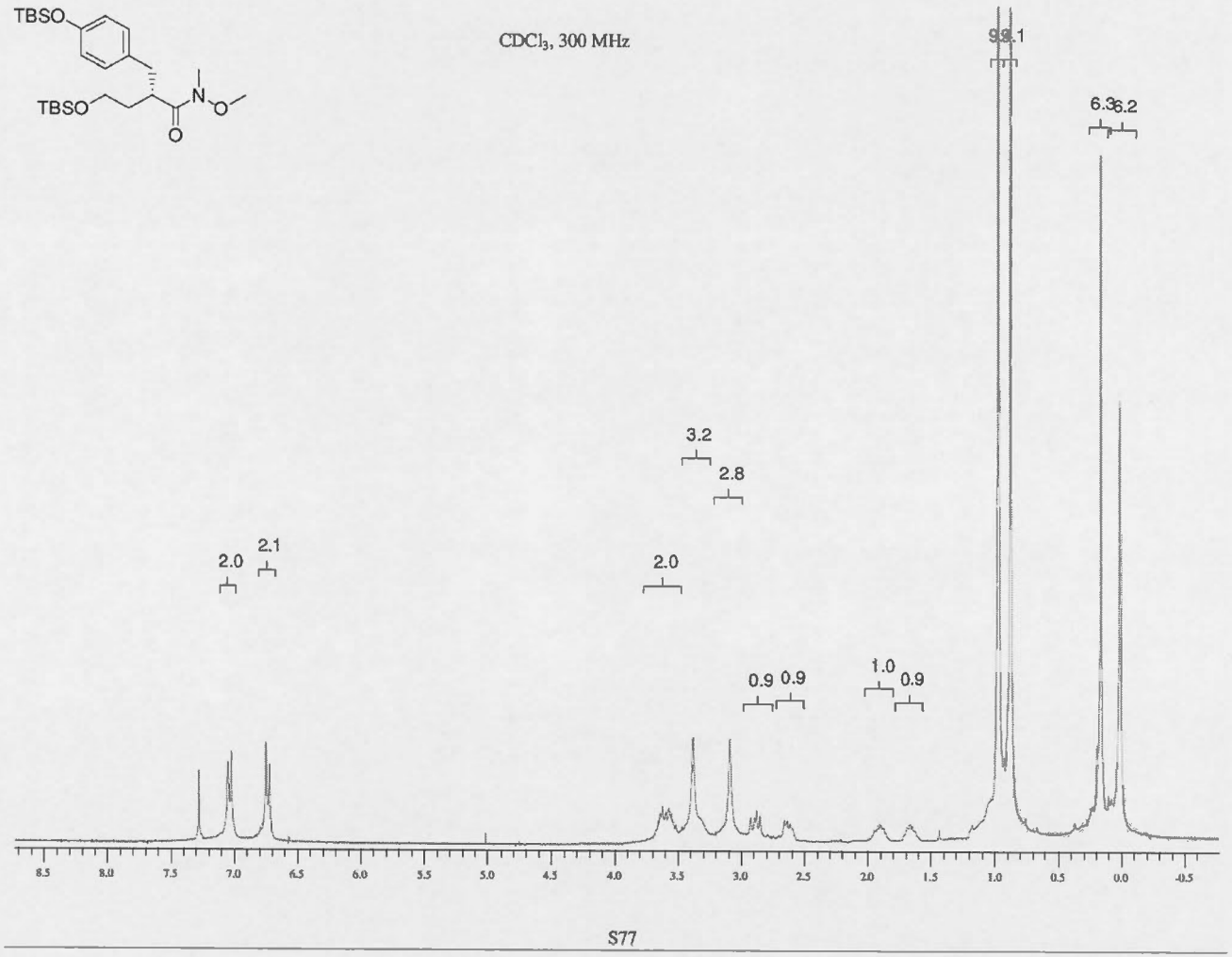

CDCl3, 300 MHz
TBSO
OH
O
9.2
6.1
2.1
2.0
1.0
2.0 2.0
2.1
1.0
S73


TBSO
OH
O
CDCl3, 75 MHz
200
175
150
125
100
75
50
25
0

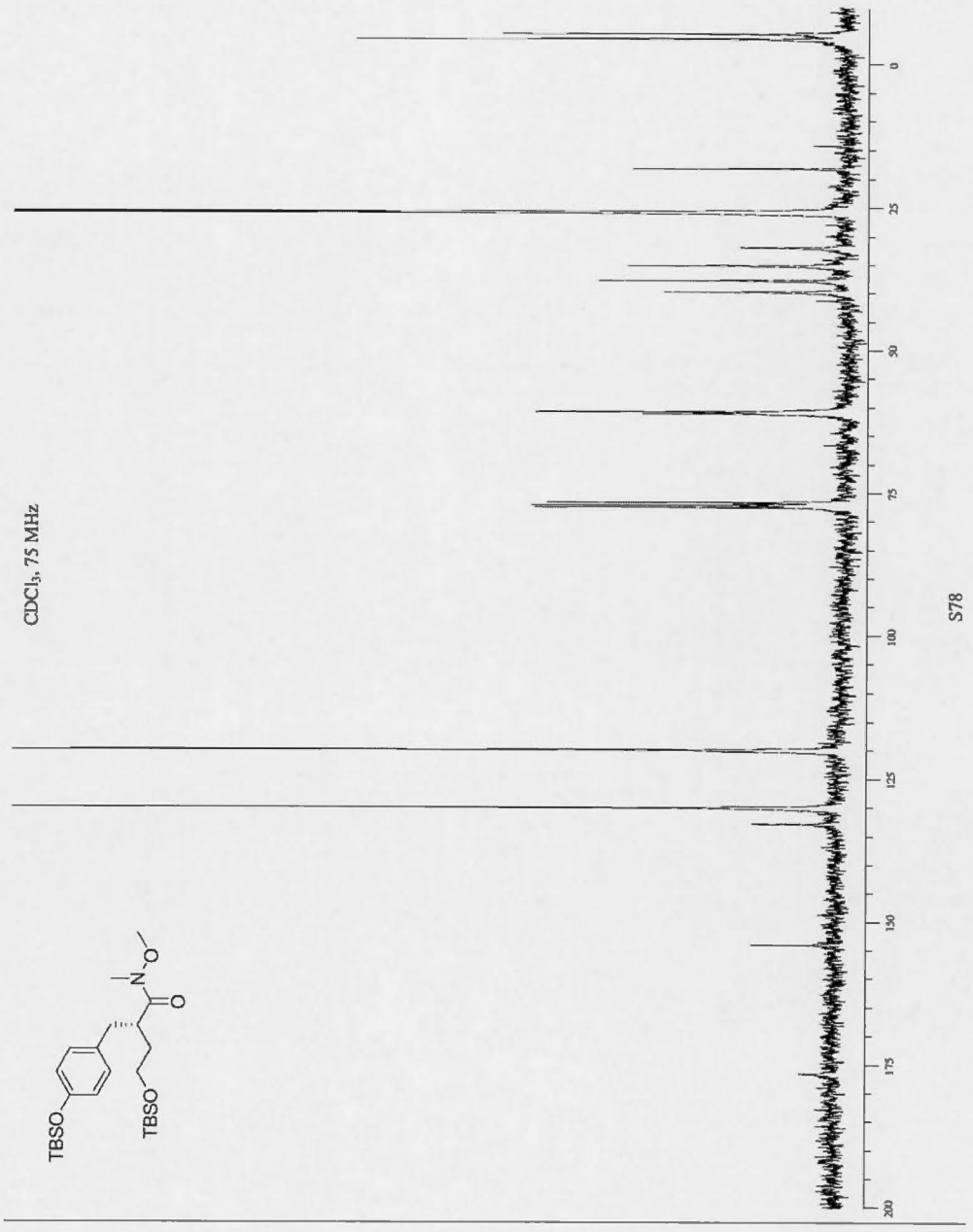

TBSO
N
O
O
CDCl3, 300 MHz
6.0
9.4
4.2
3.0
2.0
1.9
2.0
0.9
1.0
1.0
0.9
0.9
S75



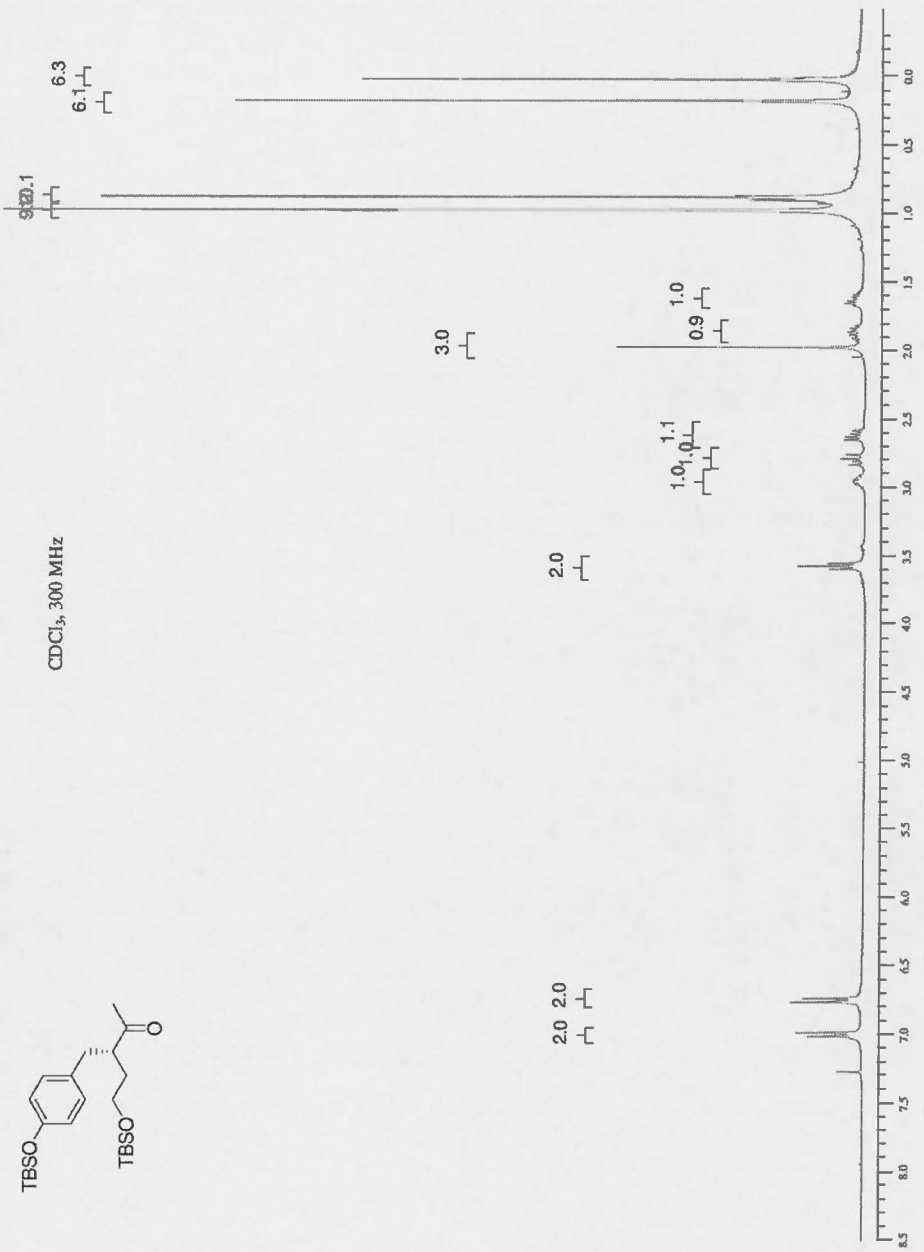
S76


TBSO
TBSO
N
O
O
CDCl3, 300 MHz
2.0
2.1
2.0
3.2
2.8
0.9
0.9
1.0
0.9
6.3
6.2
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
-0.5

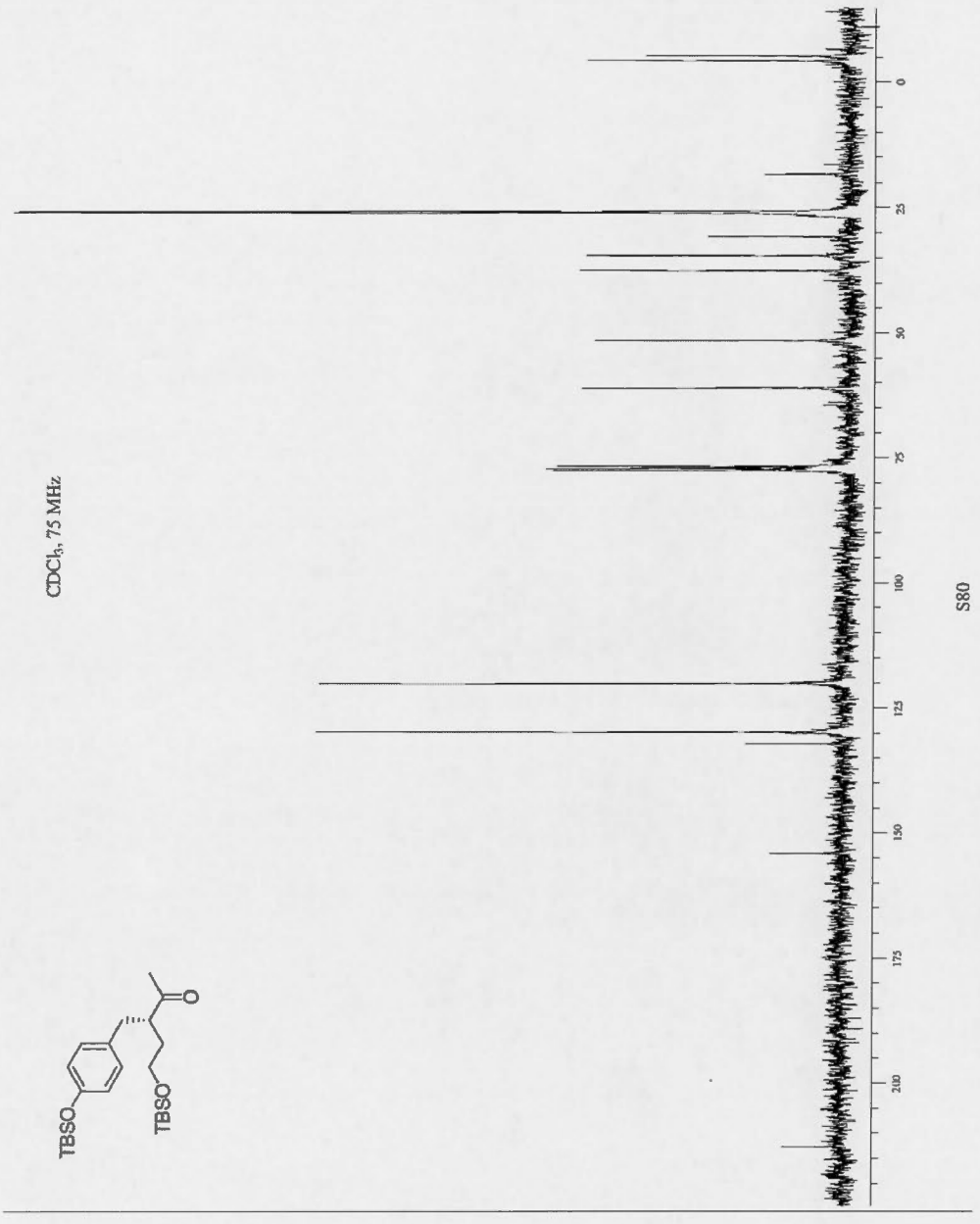
S77

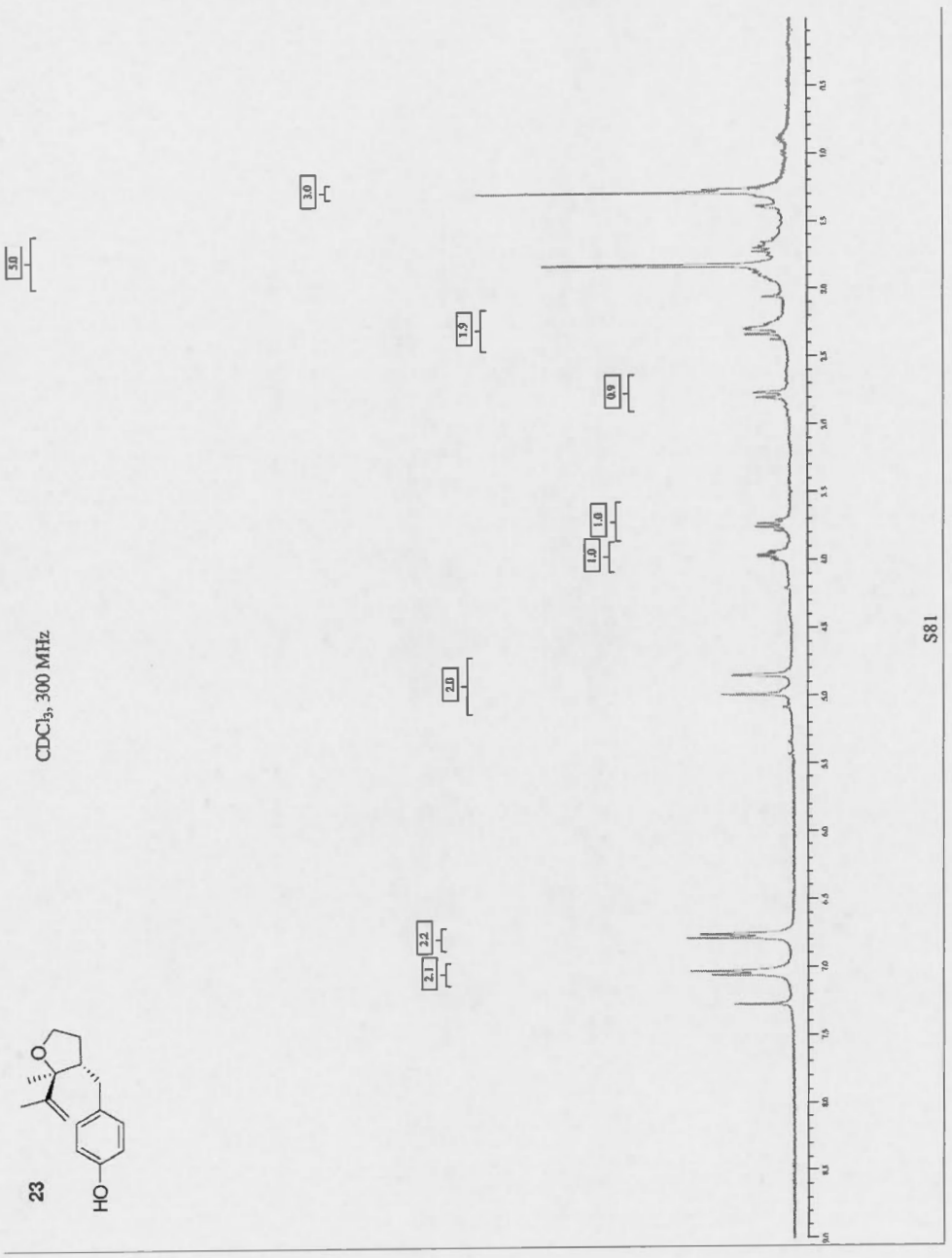


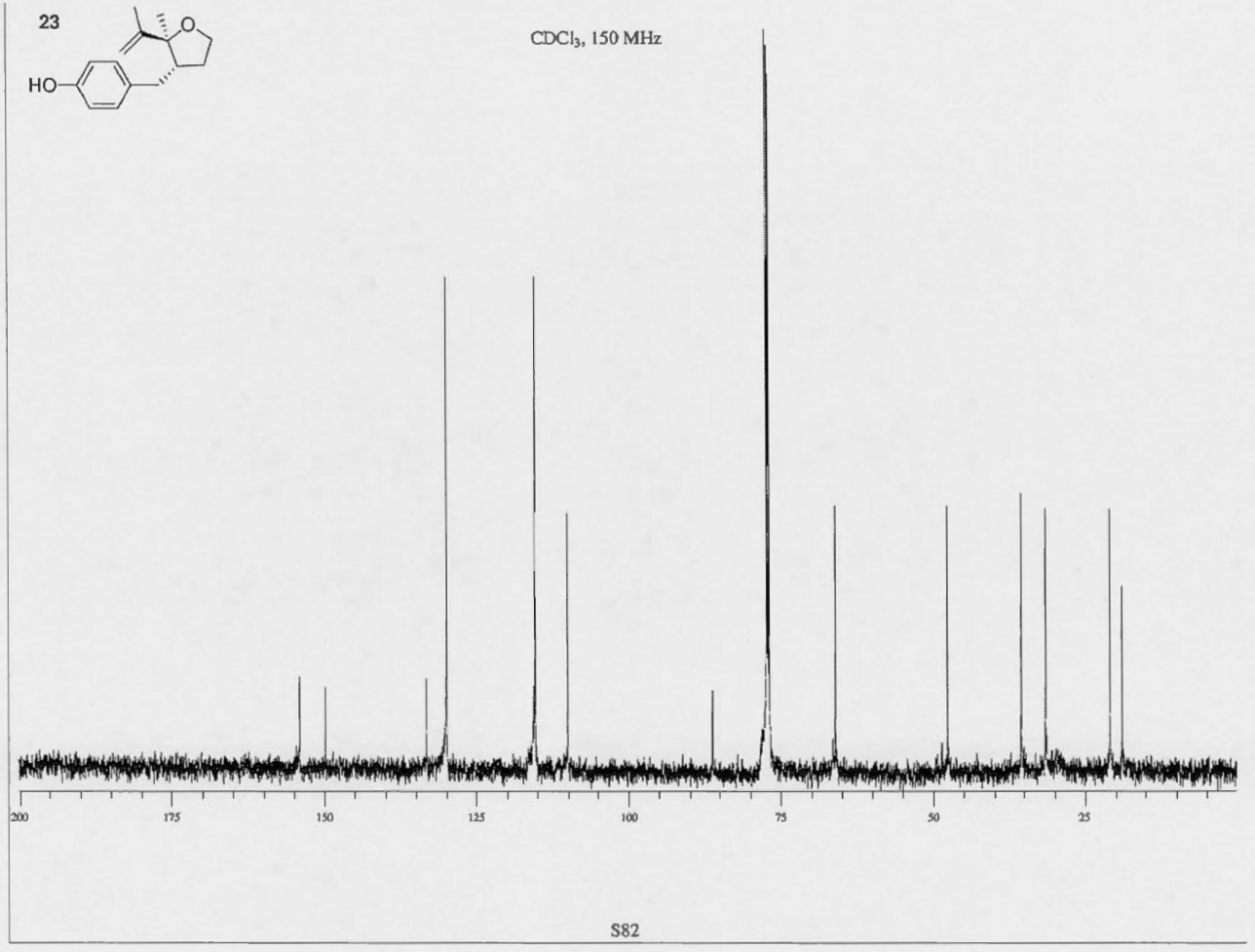
S78

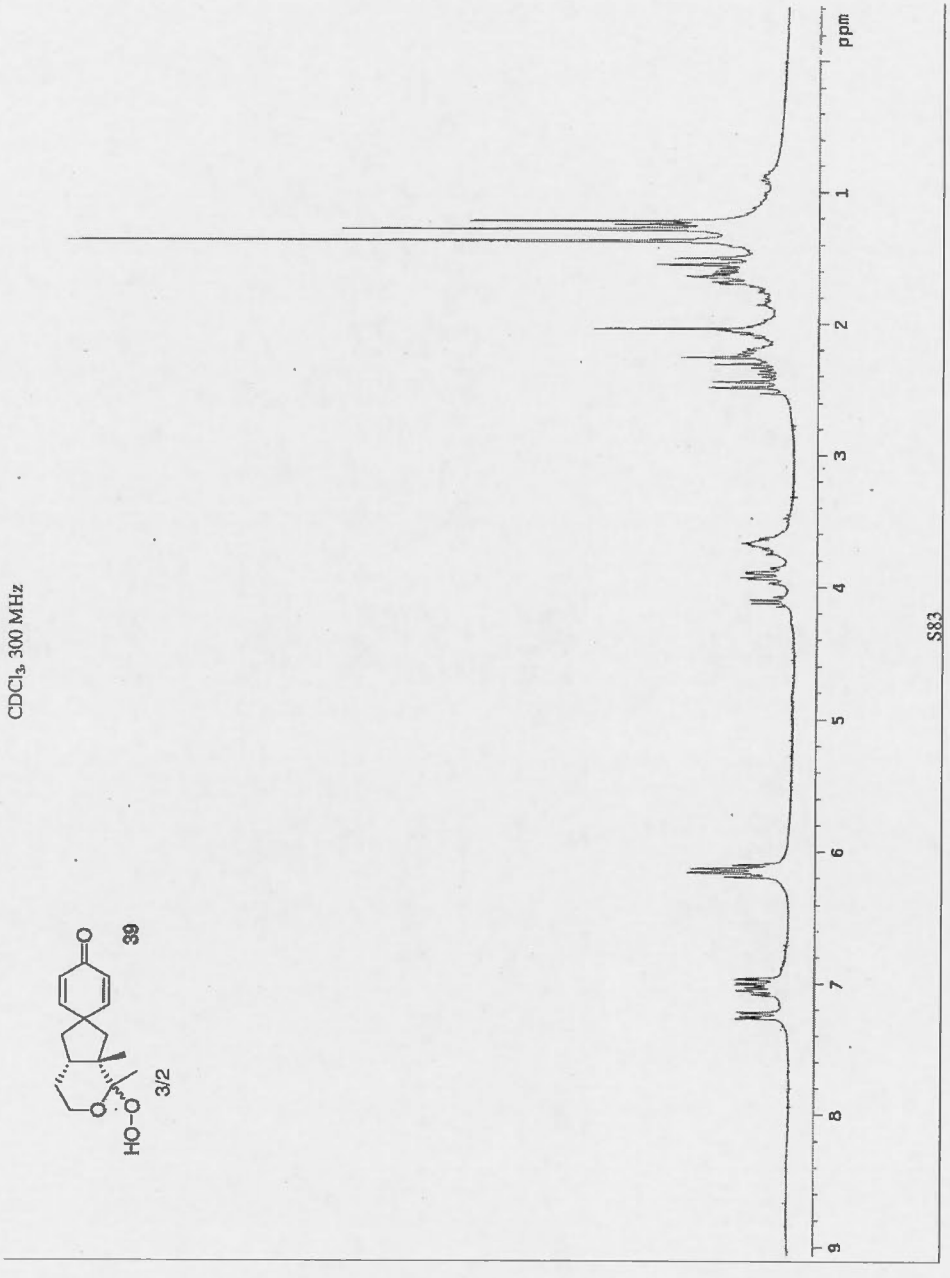


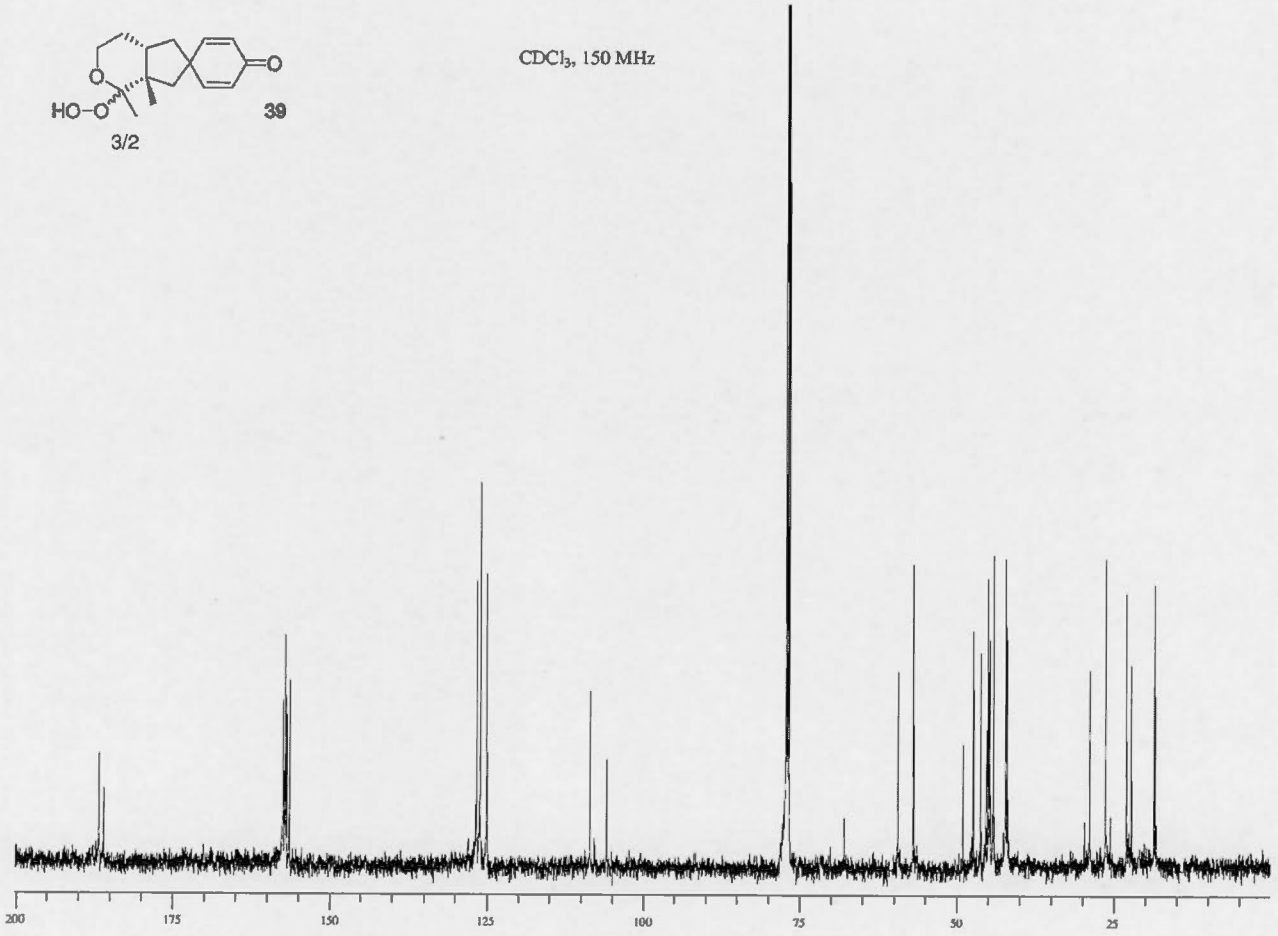
S79

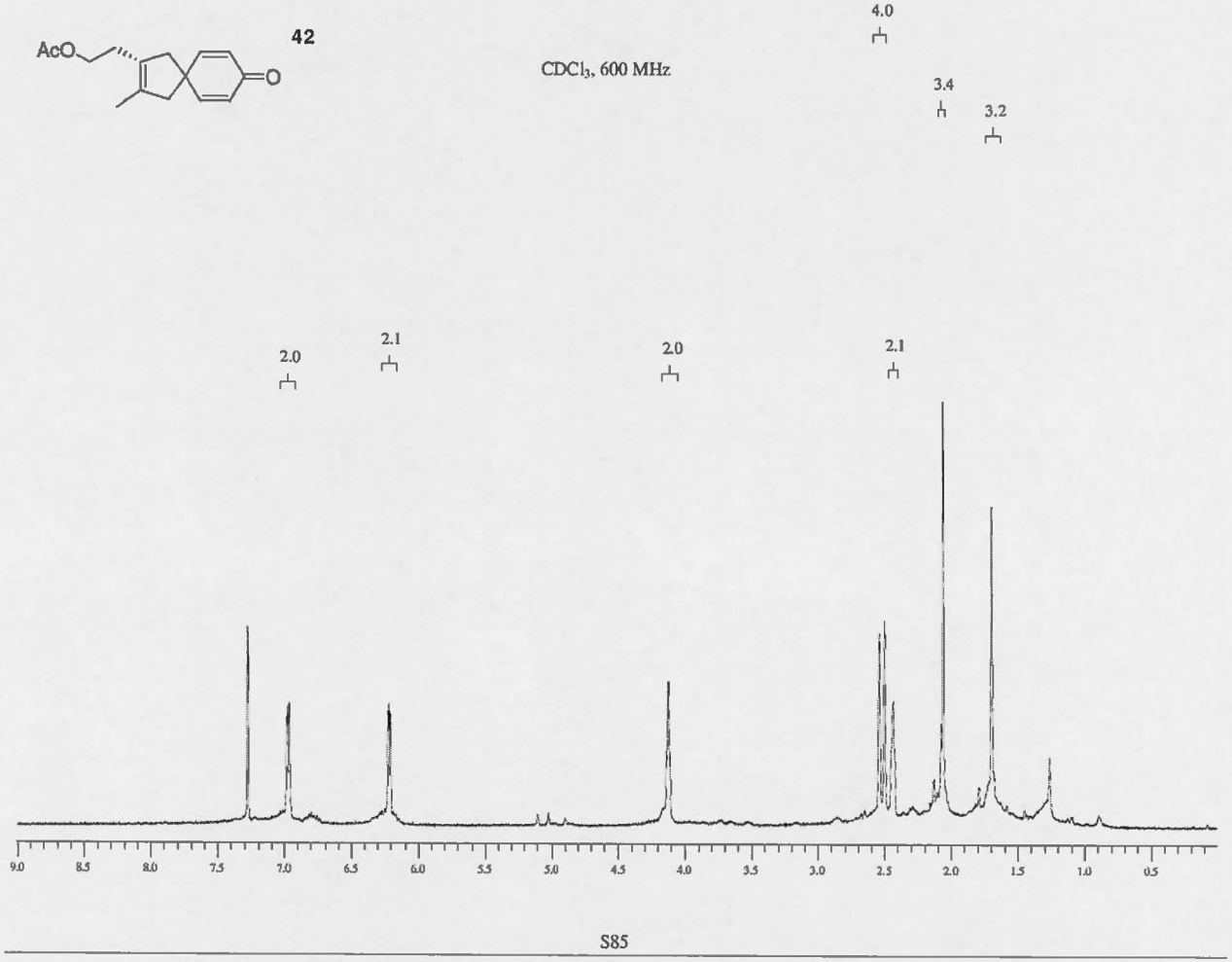

TBSO
TBSO
O
CDCl3, 75 MHz
0
25
50
75
100
125
150
175
200
S80


23
HO
$CDCl_3$, 300 MHz
5.0
3.0
1.9
0.9
1.0
1.0
2.0
2.1
2.2
S81

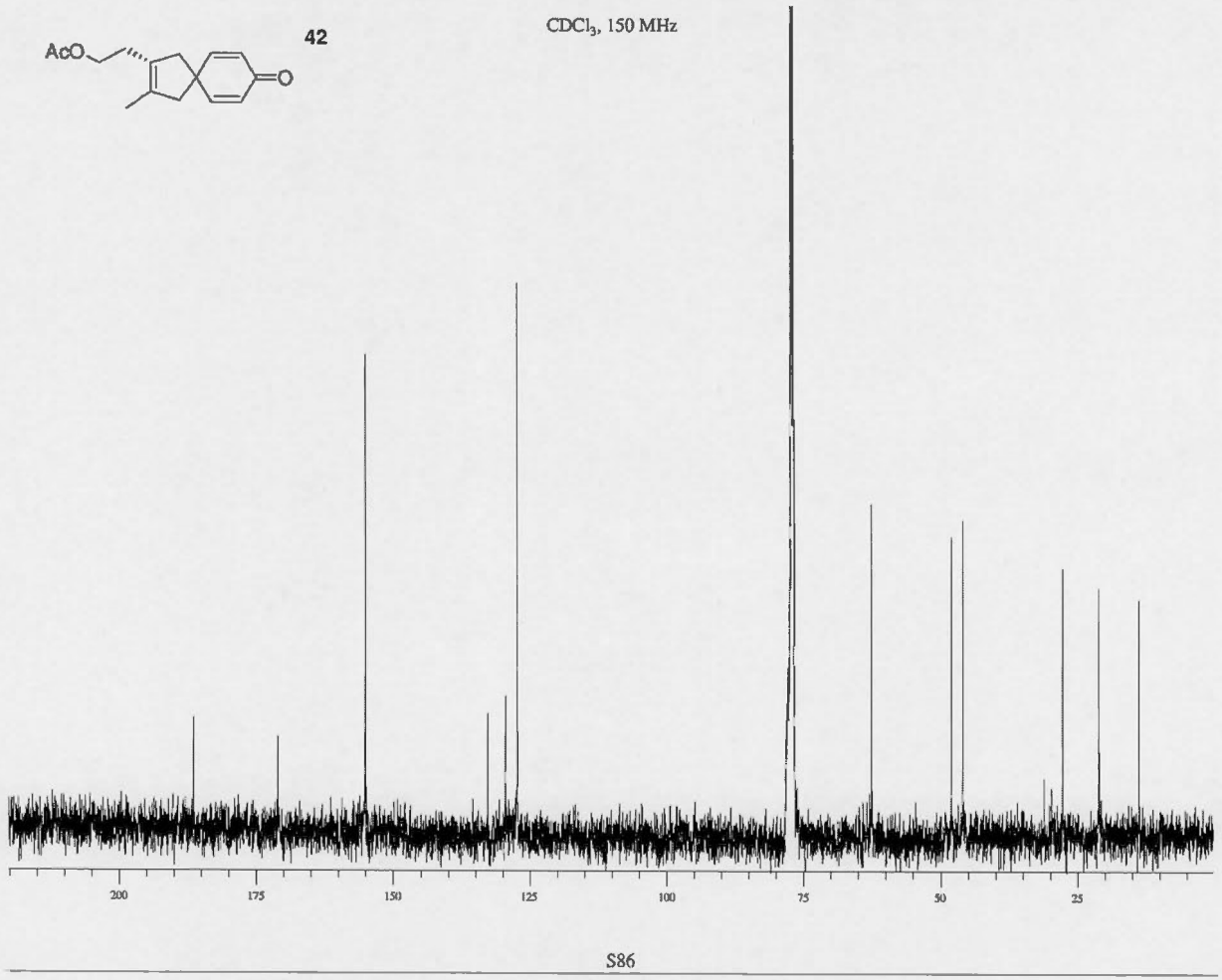

23
HO
O
CDCl3, 150 MHz
200
175
150
125
100
75
50
25
S82

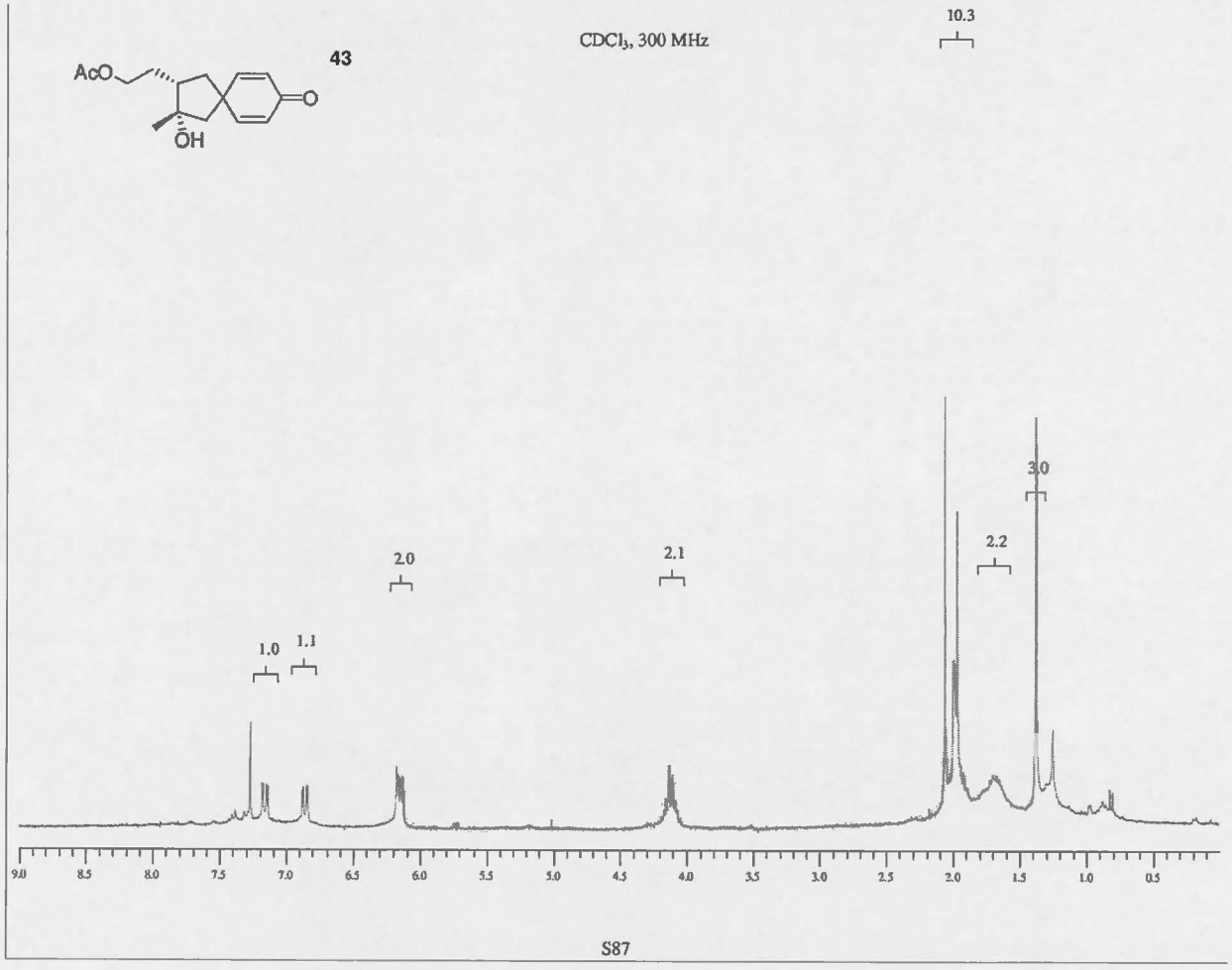

CDCl3, 300 MHz
39
HO-O
3/2
ppm
S83

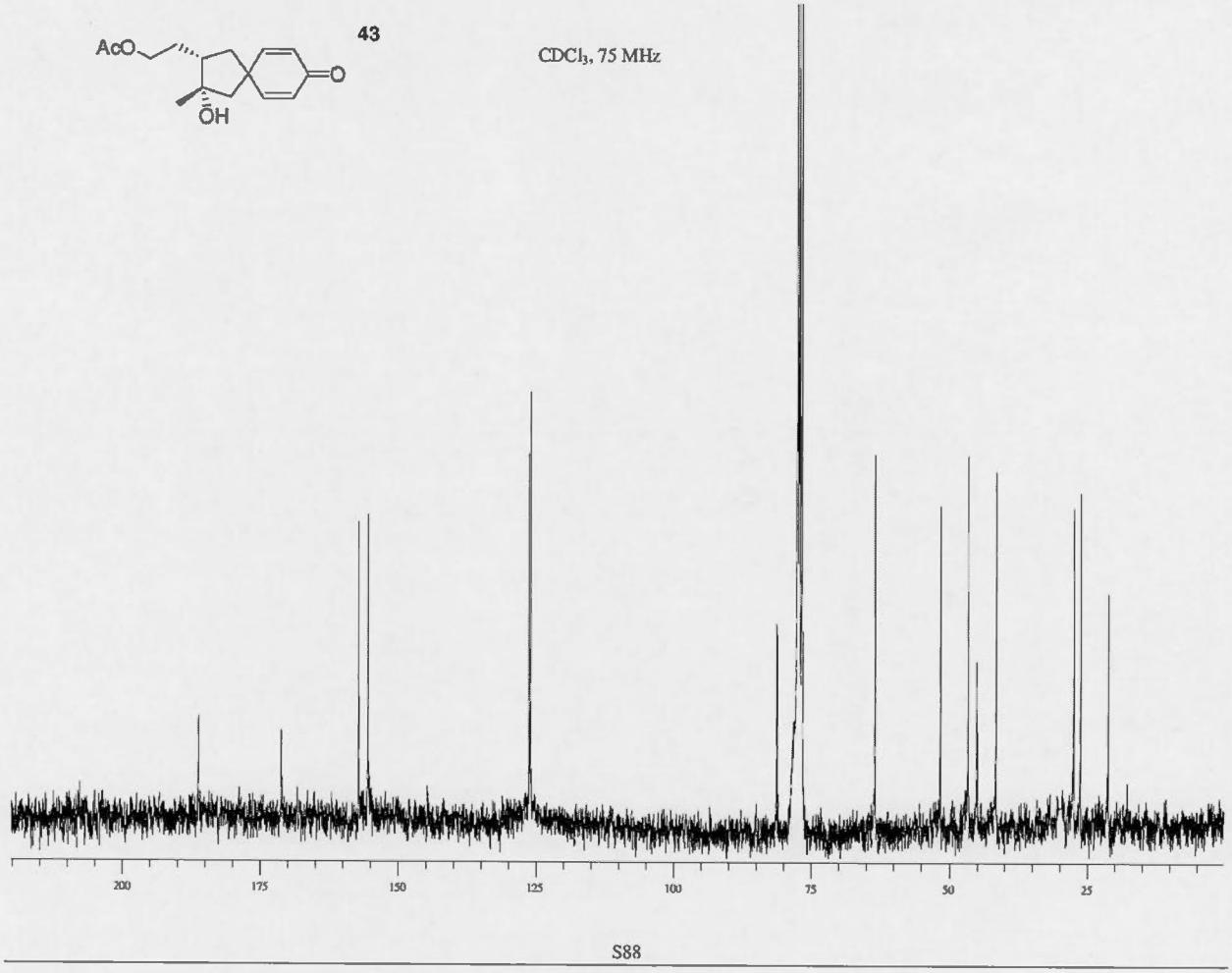

HO–O
O
O
39
3/2
CDCl3, 150 MHz
200
175
150
125
100
75
50
25

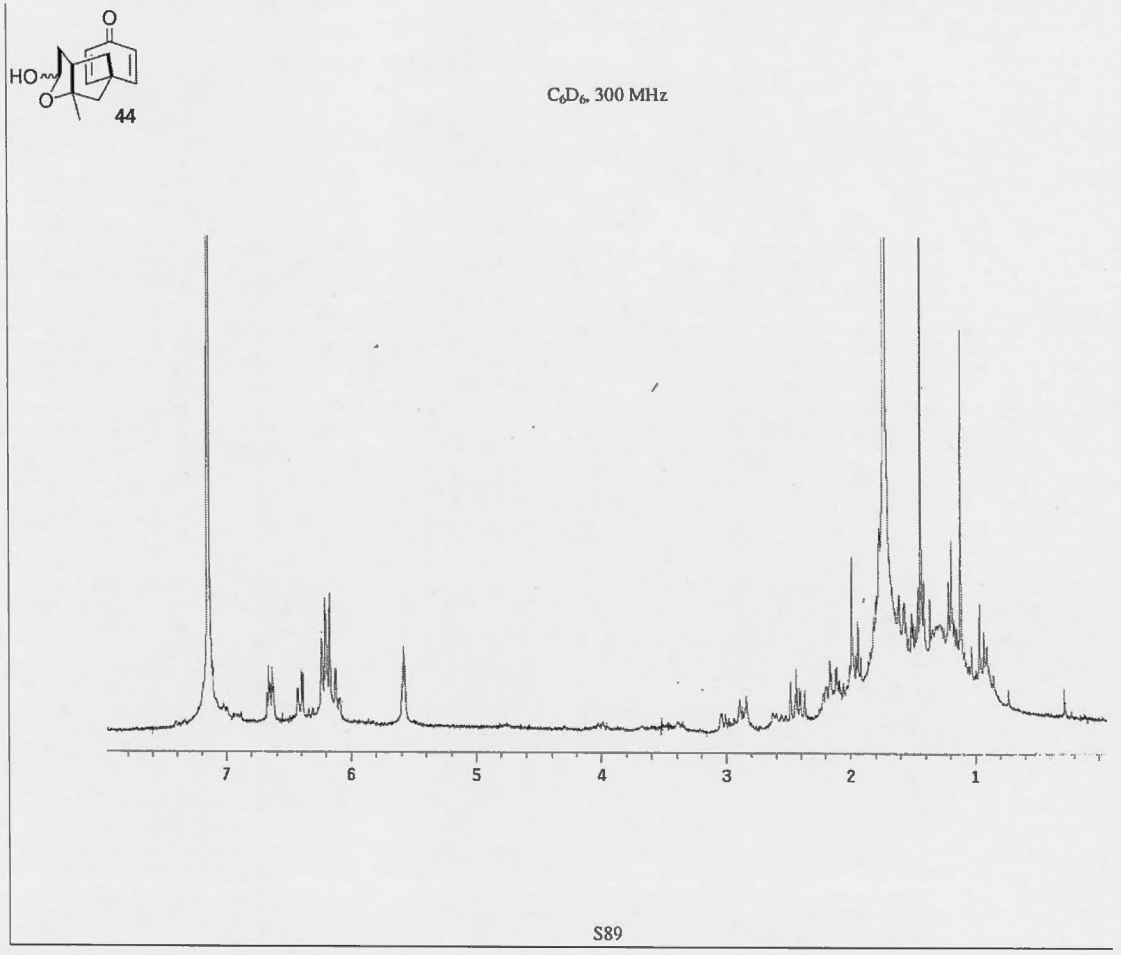

AcO
O
42
CDCl3, 600 MHz
4.0
3.4
3.2
2.0
2.1
2.0
2.1
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

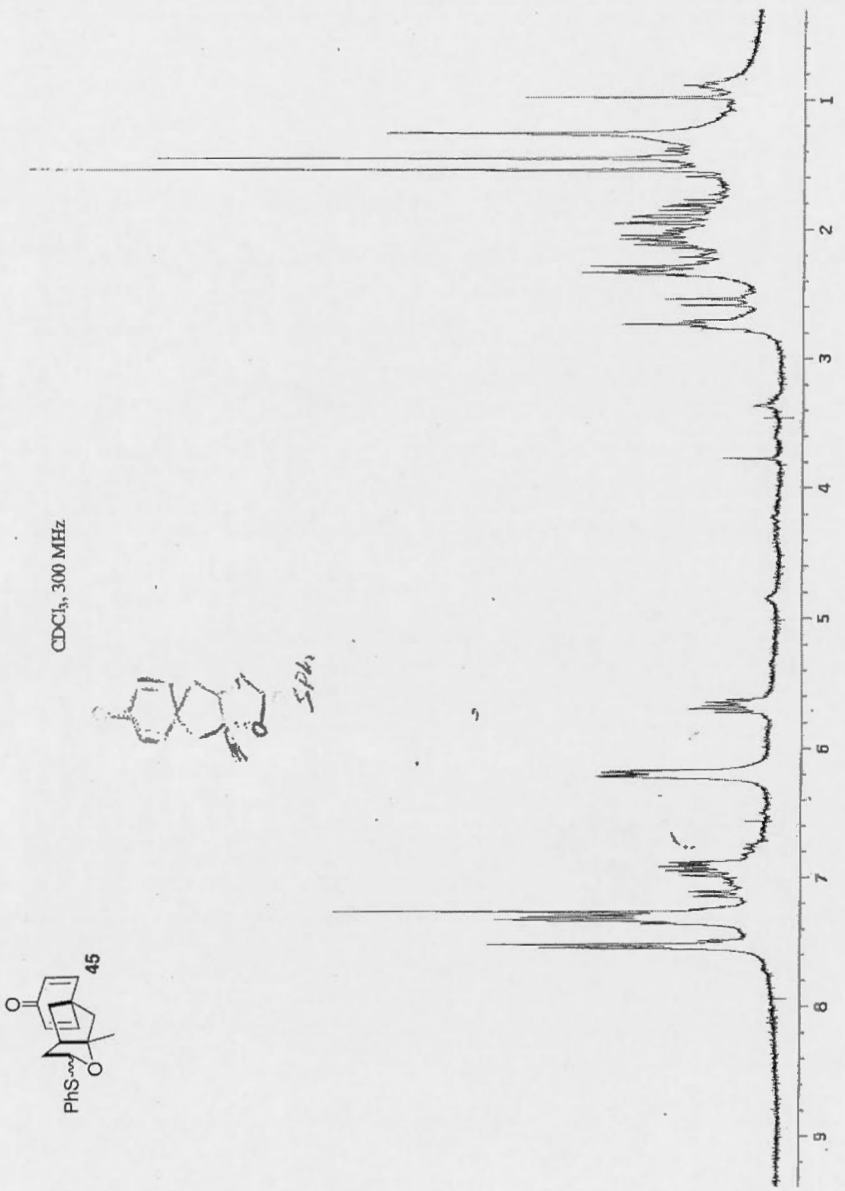
S85


AcO
O
42
CDCl3, 150 MHz
200
175
150
125
100
75
50
25
S86

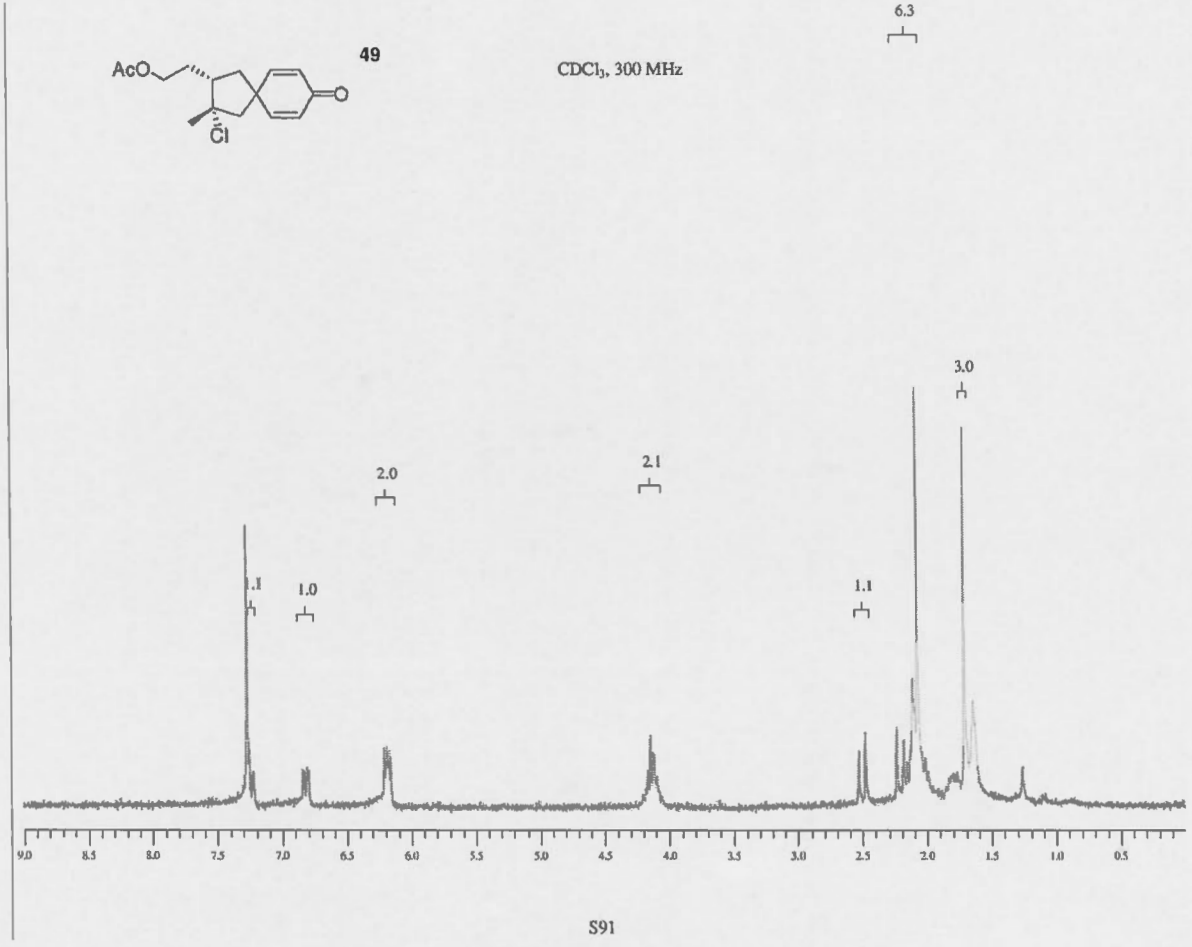

AcO
OH
O
43
CDCl3, 300 MHz
10.3
3.0
2.2
2.1
2.0
1.1
1.0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
S87


AcO
43
O
OH
CDCl3, 75 MHz
200
175
150
125
100
75
50
25
S88

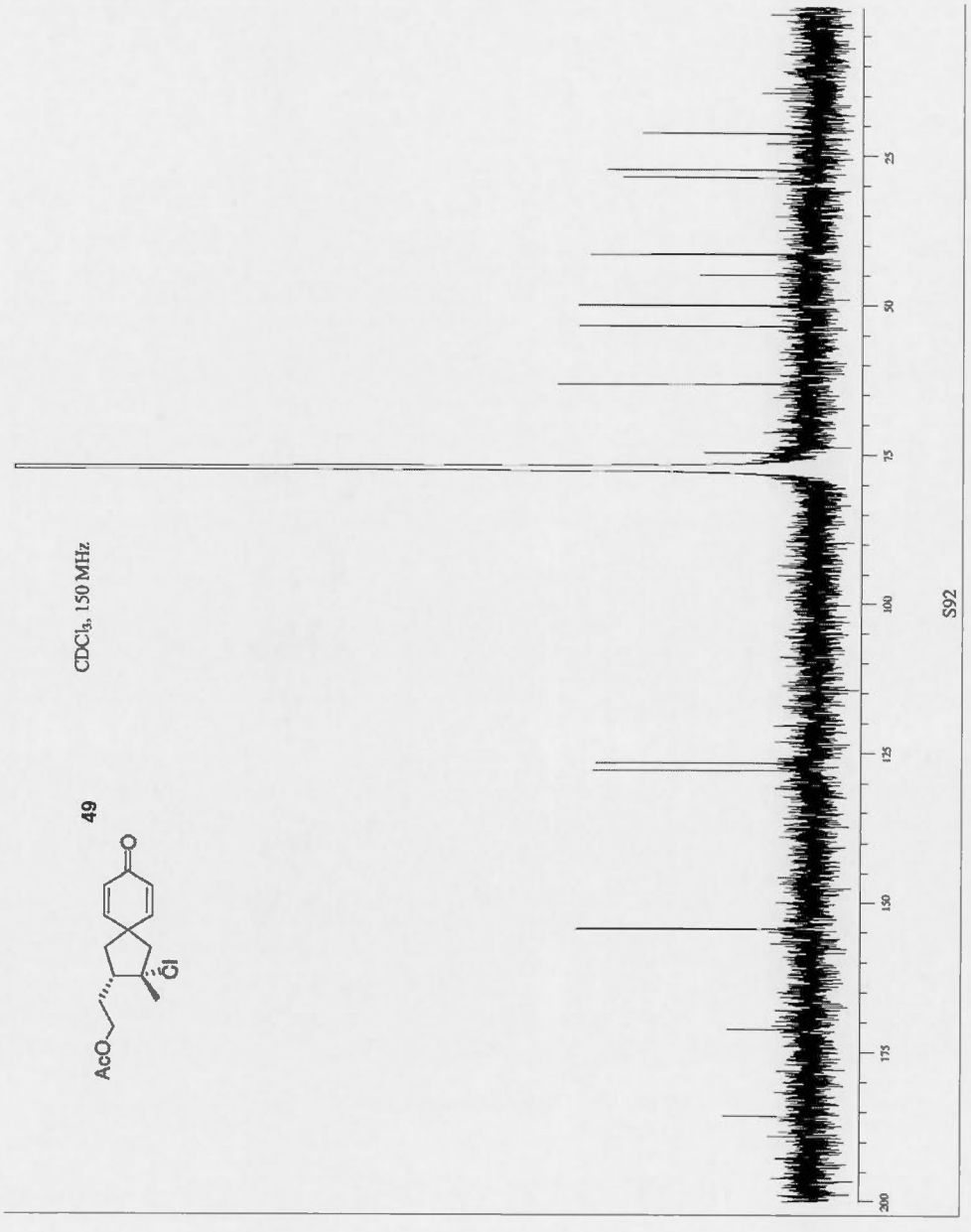

HO
O
O
44
C6D6, 300 MHz
7
6
5
4
3
2
1
S89

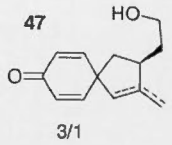


S90


AcO
Cl
O
49
CDCl3, 300 MHz
6.3
3.0
2.1
2.0
1.1
1.0
1.1
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

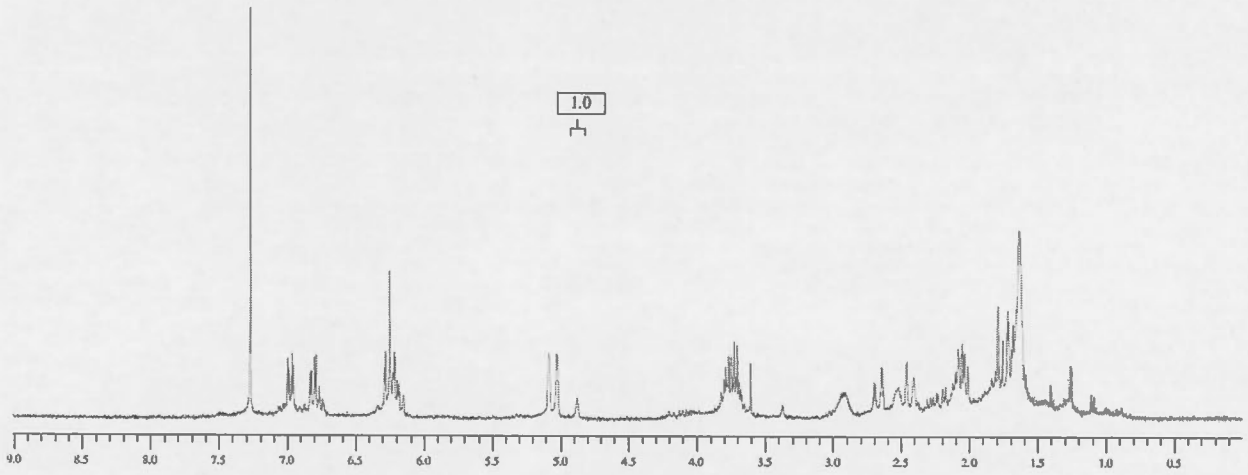
S91


49
AcO
Cl
CDCl3, 150 MHz
200
175
150
125
100
75
50
25
S92

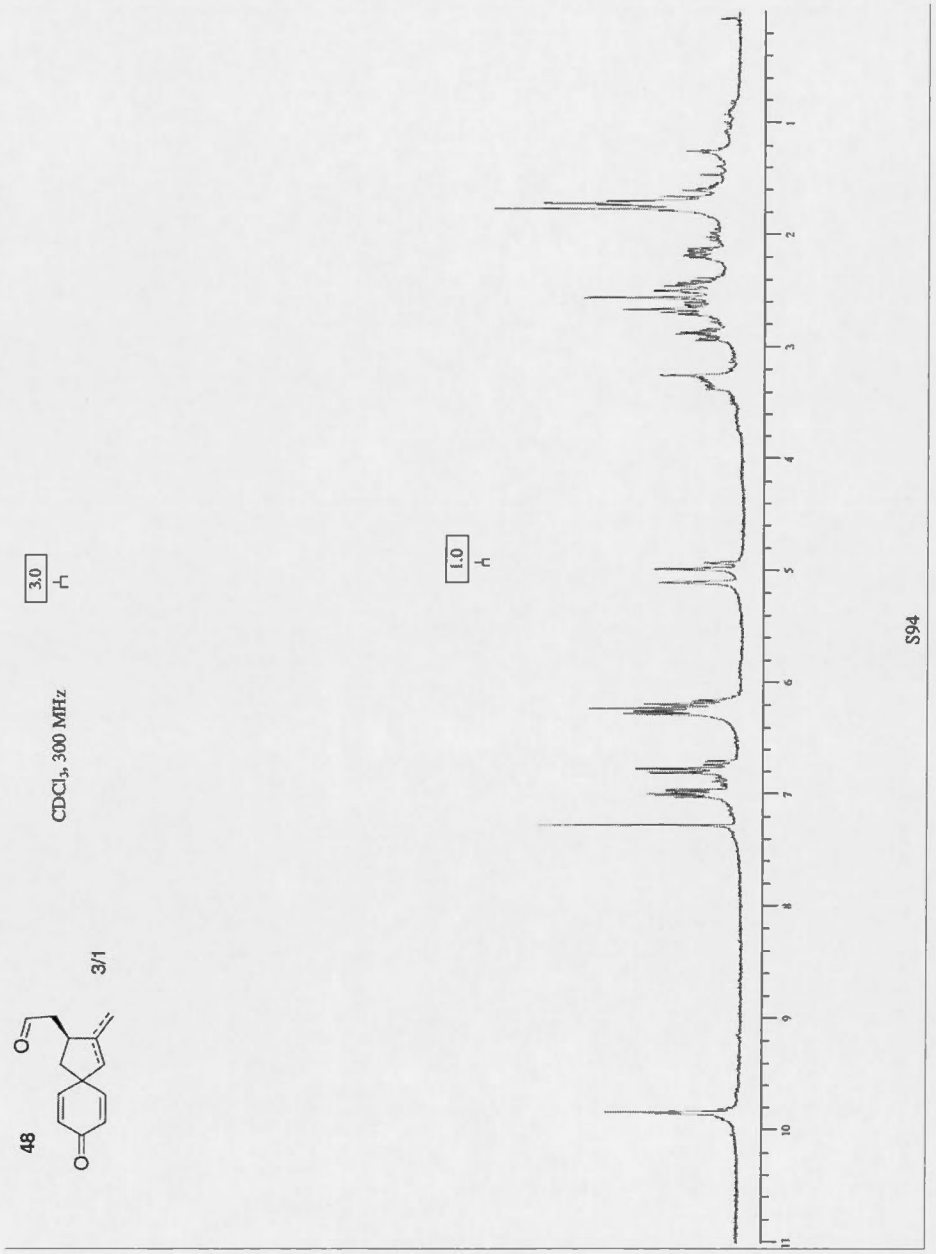


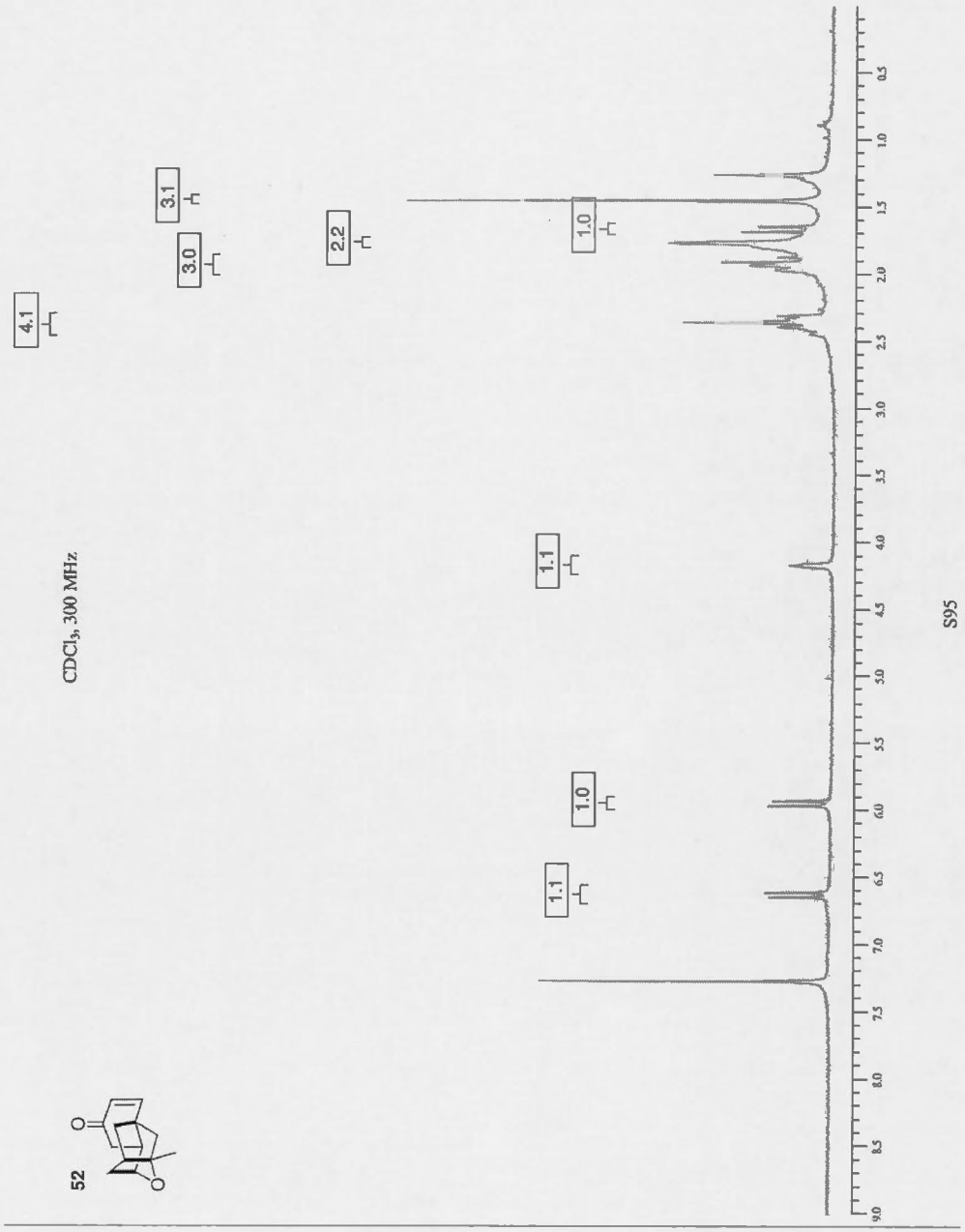
3/1

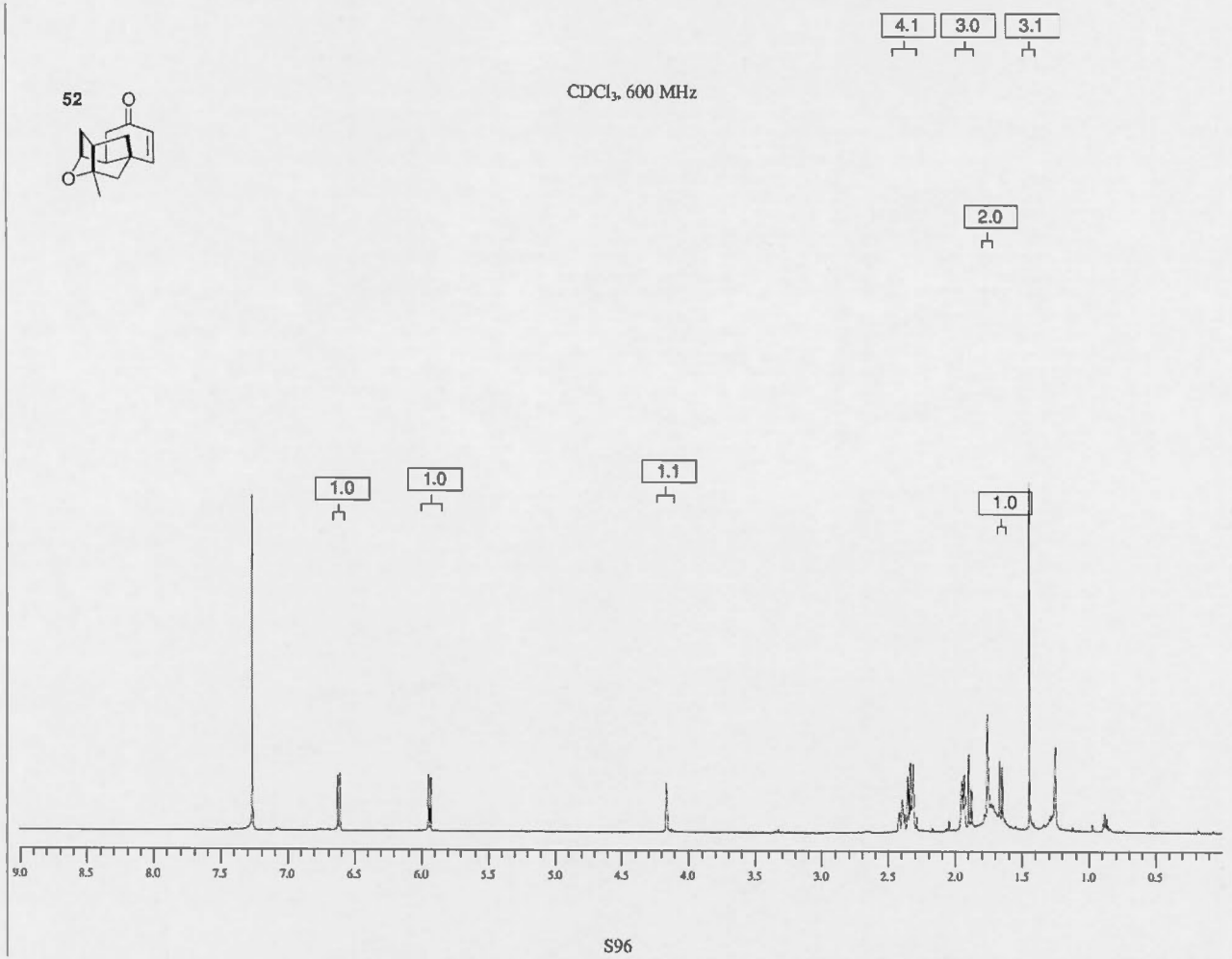
$CDCl_3$, 300 MHz



S93


48
3/1
CDCl3, 300 MHz
3.0
H
1.0
H
S94


52
CDCl3, 300 MHz
4.1
3.1
3.0
2.2
1.1
1.0
1.1
1.0
S95


52
CDCl3, 600 MHz
4.1
3.0
3.1
2.0
1.0
1.0
1.1
1.0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

S96

ANNEXE B: "ASYMMETRIC SYNTHESIS OF FORTUCINE AND REASSIGNMENT OF ITS ABSOLUTE CONFIGURATION" SUPPORTING INFORMATION

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Titre: Asymmetric Synthesis of Fortucine and Reassignment of its Absolute Configuration

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Asymmetric Synthesis of Fortucine and Correction of its Absolute Configuration

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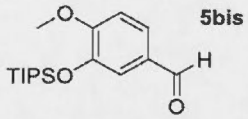
Contents

I. General information and materials

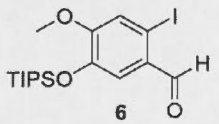
^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quartet), p (pentuplet), hept (heptuplet), m (multiplet), b (broad). Coupling constants, *J*, are reported in Hz. Mass spectra (m/e) were measured in the electrospray (ESI) mode.

II. Experimental procedures and descriptions



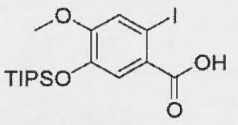
5bis

To a stirred solution of the commercial aldehyde **5** (2.96 g, 19.4 mmol) in dry DMF (20 mL) and under argon atmosphere was added imidazole (3.17 g, 46.6 mmol) and triisopropylsilyl chloride (5.0 mL, 23.3 mmol). The solution was stirred for 3 h (monitored by TLC) at room temperature. The crude mixture was then poured in water (200 mL) and the organic layer was diluted with a 1:1 mix of n-hexane an EtOAc (40 mL). The organic layer was removed and the aqueous phase extracted with a 1:1 mix of n-hexane an EtOAc (2 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 9:1) to afford 5.95 g (99%) of the protected compound **5bis** as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.44 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.38 (s, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 3.88 (s, 3H), 1.30 – 1.21 (m, 3H), 1.09 (d, *J* = 7.1 Hz, 18H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 191.23, 156.87, 146.38, 130.43, 126.42, 119.63, 111.42, 55.86, 18.16, 13.15. **HRMS** (ESI) calculated for $C_{17}H_{29}O_3Si$ $(M + H)^+$: 309.1880; found: 309.1885.



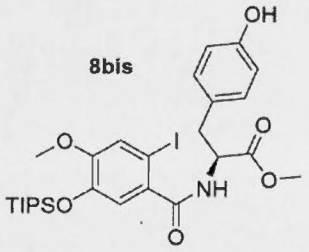
6

To a stirred solution of the previously prepared protected aldehyde **5bis** (2.00 g, 6.5 mmol) in dry DCM (20 mL) and under argon atmosphere was added silver nitrate (1.21 g, 7.1 mmol). Then, a freshly prepared I_2 (1.81 g, 7.1 mmol)/ DCM (80 mL) solution was added in the previous mixture by canulation under argon atmosphere over 15 min at room temperature. The solution was stirred for 14 h (monitored by TLC) at 30°C. The crude mixture was then treated with a 0.1M $Na_2S_2O_3$ aqueous solution (80 mL) for 5 min. The mixture was filtered on celite (rinsed with DCM) and the filtrate was poured in water (100 mL). The organic layer was removed and the aqueous phase extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 9:1) to afford 2.10 g (74%) of compound **6** as an orange oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.40 (s, 1H), 7.28 (s, 1H), 3.88 (s, 3H), 1.30 – 1.20 (m, 3H), 1.08 (d, *J* = 7.0 Hz, 18H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.10, 156.99, 146.68, 128.78, 122.76, 120.81, 92.65, 56.24, 18.16, 13.13. **HRMS** (ESI) calculated for $C_{17}H_{28}IO_3Si$ $(M + H)^+$: 435.0847; found: 435.0836.



6bis

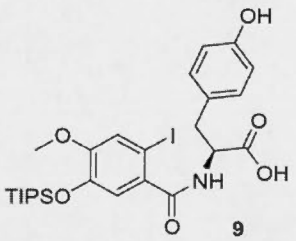
To a stirred solution of the iodoaryle **6** (2.00 g, 4.6 mmol) in CH_3CN (6.0 mL) was added copper(II) chloride (673 mg, 5.0 mmol), followed by a 70% (w/w in H_2O) solution of tert-butyl hydroperoxyde (10 mL) at room temperature. The solution was stirred for 16 h (monitored by TLC) at 50 °C (not more to avoid S_NAr iodine substitution by chloride from $CuCl_2$). The crude mixture was then poured in water (150 mL) and filtered on celite (rinsed with EtOAc). The organic layer was diluted with EtOAc (40 mL) and removed. The aqueous phase was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 9:1 following an increasing gradient up to 6:4) to afford 1.55 g (75%) of the desired carboxylic acid **6bis** as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.41 (s, 1H), 3.86 (s, 3H), 1.29 – 1.22 (m, 3H), 1.09 (d, J = 7.2 Hz, 18H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.12, 155.09, 145.65, 125.15, 124.25, 85.92, 56.11, 18.18, 13.16. **HRMS** (ESI) calculated for $C_{17}H_{26}IO_4Si$ $(M - H)^-$: 449.0651; found: 449.0667.



8bis

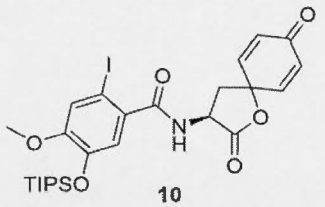
To a stirred solution of the previously prepared carboxylic acid **6bis** (3.86 g, 8.57 mmol) in dry DCM (20 mL) and under argon atmosphere, DMF (133 µL, 1.71 mmol) was added, followed by thionyl chloride (1.25 mL, 17.1 mmol) at room temperature. The solution was stirred for 2 h at refluxing temperature. The crude mixture (acyl chloride **7**) was concentrated under reduced pressure. In another flask, to a solution of commercial *L*-tyrosine (3.10 g, 17.1 mmol) in MeOH (35 mL), thionyl chloride (3.8 mL, 51.4 mmol) was slowly added dropwise at 0°C. The solution was stirred at this temperature for 30 min and at room temperature for 2 h. The crude mixture (*L*-tyrosine methyl ester **8**) was concentrated under reduced pressure and dissolved in a 1:1 mix of THF and H_2O (50 mL). To the resulting mixture, at 0°C, solid sodium carbonate (2.90 g, 34.3 mmol) was slowly added (be careful). The mixture was allowed to stir at this temperature for about 5 min and the acyl chloride **7**, prepared above in the previous flask and dissolved in THF (25 mL), was added to the mixture. The pasty mixture was stirred for 2 h (monitored by TLC) at 0°C. The crude mixture was then treated with saturated NH_4Cl aqueous solution (50 mL) and filtered on celite (rinsed with EtOAc). The filtrate was poured in water (50 mL). The organic layer was removed and the aqueous phase extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel

chromatography (n-hexane/EtOAc, 9:1 following an increasing gradient up to 1:1) to afford 4.57 g (85%) of the desired Schotten-Baumann product **8bis** as a white foam. $[\alpha_D]_{20}$ = +34 (c = 0.93 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.91 (s, 1H), 6.71 (d, *J* = 8.5 Hz, 2H), 6.33 (d, *J* = 7.7 Hz, 1H), 5.00 (dt, *J* = 7.6, 5.8 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.16 (ddd, *J* = 31.0, 14.1, 5.8 Hz, 2H), 1.24 – 1.14 (m, 3H), 1.05 (d, *J* = 6.9 Hz, 18H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.20, 168.55, 155.59, 153.13, 146.02, 133.22, 130.75, 127.55, 123.52, 120.91, 115.94, 81.79, 56.02, 54.28, 52.77, 37.40, 18.17, 13.15. **HRMS** (ESI) calculated for $C_{27}H_{39}INO_6Si$ $(M + H)^+$: 628.1586; found: 628.1581.



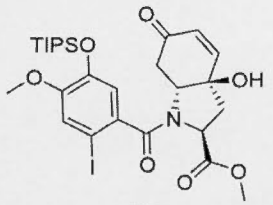
9

To a stirred solution of the previously prepared Schotten-Baumann product **8bis** (2.93 g, 4.67 mmol) in EtOAc (20 mL), LiI xH_2O (6.24 g, 46.6 mmol) was added at room temperature. The solution was stirred for 2 days (monitored by TLC) at refluxing temperature (it may be necessary to concentrate the mixture under air flux to allow the completion of the reaction).The crude mixture was then treated with saturated NH_4Cl aqueous solution (50 mL) and monohydrate citric acid (10.8 g, 51.4 mmol) was added. After about 5 min, the mixture was poured in water (50 mL). The organic layer was diluted with EtOAc (20 mL) and removed. The aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 1:1 following an increasing gradient up to 1:4) to afford 2.38 g (83%) of the desired carboxylic acid **9** as a beige foam. $[\alpha_D]_{20}$ = +31 (c = 0.78 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.03 (d, *J* = 7.0 Hz, 2H), 6.92 (s, 1H), 6.71 (d, *J* = 7.2 Hz, 2H), 6.39 (d, *J* = 6.1 Hz, 1H), 5.01 (s, 1H), 3.79 (s, 3H), 3.20 (dd, *J* = 28.6, 11.5 Hz, 2H), 1.25 – 1.15 (m, 3H), 1.05 (d, *J* = 7.0 Hz, 18H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.16, 155.44, 153.29, 146.07, 132.88, 130.92, 127.44, 123.60, 120.99, 116.12, 81.91, 56.06, 36.93, 18.19, 13.16. **HRMS** (ESI) calculated for $C_{26}H_{37}INO_6Si$ $(M + H)^+$: 614.1429; found: 614.1408.



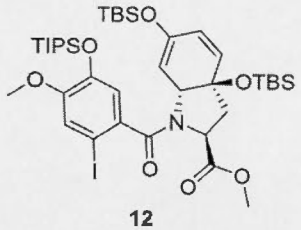
10

To a stirred solution of the carboxylic acid **9** (450 mg, 0.733 mmol) in a mix of DCM: HFIP 5:2 (14 mL), DIB (354 mg, 1.10 mmol), previously dissolved in HFIP (2.0 mL), was added at room temperature. The solution was stirred for 10 min (monitored by TLC) and was treated with saturated $NaHCO_3$ aqueous solution (2.0 mL). The mixture was poured in water (20 mL), the organic layer was removed and the aqueous phase was extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 9:1 following an increasing gradient up to 3:2) to afford 224 mg (50 %) of the desired spirolactone **10** as a beige foam. $[\alpha_D]_{20}$ = -110 (c = 0.58 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20 (s, 1H), 7.01 (s, 1H), 6.94 (ddd, *J* = 10.0, 8.3, 3.3 Hz, 2H), 6.86 – 6.71 (m, 1H), 6.30 – 6.21 (m, 2H), 4.89 (ddd, *J* = 11.0, 9.4, 6.5 Hz, 1H), 3.80 (s, 3H), 2.92 – 2.78 (m, 1H), 2.61 (dd, *J* = 12.5, 11.9 Hz, 1H), 1.26 – 1.14 (m, 3H), 1.05 (d, *J* = 7.3 Hz, 18H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 184.33, 173.38, 169.04, 153.40, 146.46, 146.17, 144.64, 132.07, 129.99, 129.39, 123.29, 121.19, 81.90, 55.95, 50.05, 38.39, 18.15, 13.15. **HRMS** (ESI) calculated for $C_{26}H_{35}INO_6Si$ $(M + H)^+$: 612.1273; found: 612.1277.



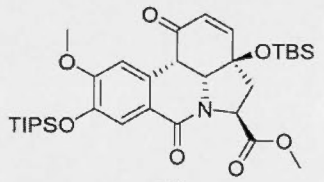
11

To a stirred 3.0 M potassium hydroxide aqueous solution (33 mL), 33 mL of MeOH was added. This solution was cooled at -20°C and the prepared compound **10** (2.05 g, 3.35 mmol), previously dissolved in 33 mL MeOH and also cooled at -20°C , was added quickly. The solution was vigorously stirred for 15 min (monitored by TLC) at -20°C and treated with saturated NH_4Cl aqueous solution (20 mL). The mixture was poured in water (150 mL), the organic layer was removed and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 8:2 following an increasing gradient up to 3:7) to afford 2.05 g (95 %) of the desired compound **11** as a beige foam. $[\alpha_D]_{20}$ = -72 (c = 1.0 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): see spectrum (rotamers mix). **^{13}C NMR** (300 MHz, $CDCl_3$): see spectrum (rotamers mix). **HRMS** (ESI) calculated for $C_{27}H_{39}INO_7Si$ $(M + H)^+$: 644.1535; found: 644.1561.



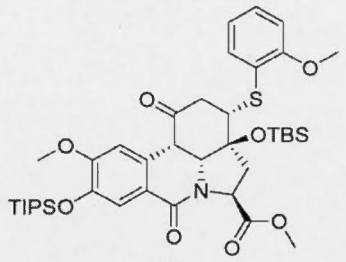
12

To a stirred solution of the prepared compound **11** (2.50 g, 3.88 mmol) in dry DCM (35mL) and under argon atmosphere was added 2,6-Lutidine (3.0 mL, 26.0 mmol) and TBS-OTf (3.0 mL, 13.1 mmol) at room temperature. The solution was stirred for 3 h (monitored by TLC) and the mixture was poured in water (150 mL), the organic layer was removed and the aqueous phase was extracted with DCM (2 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 9:1) to afford 3.30 g (97 %) of the desired compound **12** as a white foam. $[\alpha_D]_{20}$ = -104 (c = 1.8 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): see spectrum (rotamers mix). **^{13}C NMR** (300 MHz, $CDCl_3$): see spectrum (rotamers mix). **HRMS** (ESI) calculated for $C_{39}H_{67}INO_7Si_3(M + H)^+$: 872.3265; found: 872.3276.



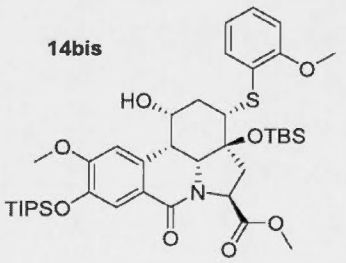
13

To a stirred solution of the prepared compound **12** (2.10 g, 2.41 mmol) in dry (and previously degazed under argon atmosphere) CH_3CN (30 mL) and under argon atmosphere was added Et_3N (3.4 mL, 24.1 mmol) followed by a 0.02 M (in THF) solution of $Pd(PPh_3)_4$ (11 mL) at room temperature. The solution was stirred for 4 h (monitored by TLC) at refluxing temperature. The crude mixture was directly filtered on silica gel (eluted with EtOAc) and concentrated under reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 8:2 following an increasing gradient up to 5:2) to afford 1.30 g (85 %) of the desired tetracycle **13** as a beige solid. $[\alpha_D]_{20}$ = -148 (c = 0.30 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 6.80 (s, 1H), 6.68 (dd, *J* = 10.2, 2.1 Hz, 1H), 6.14 (d, *J* = 10.2 Hz, 1H), 4.59 (dd, *J* = 4.5, 2.0 Hz, 1H), 4.24 (dd, *J* = 10.4, 7.5 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 3.67 (d, *J* = 4.6 Hz, 1H), 2.56 (dd, *J* = 12.5, 7.5 Hz, 1H), 2.30 (dd, *J* = 12.4, 10.6 Hz, 1H), 1.30 – 1.20 (m, 3H), 1.07 (d, *J* = 7.1 Hz, 18H), 0.88 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.17, 172.25, 162.97, 154.40, 146.63, 145.83, 130.57, 128.85, 121.37, 119.45, 113.61, 75.28, 64.41, 56.43, 55.88, 52.94, 45.44, 42.84, 25.83, 18.23, 13.21, -1.83, -1.94. **HRMS** (ESI) calculated for $C_{33}H_{52}NO_7Si_2Na$ $(M + H)^+$: 630.3277; found: 630.3304.



14

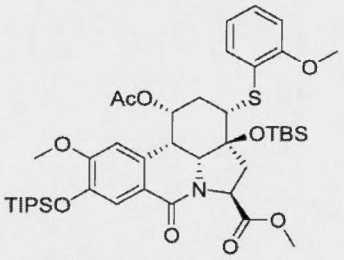
To a stirred solution of the prepared tetracycle **13** (250 mg, 0.397 mmol) in dry THF (4.0 mL) and under argon atmosphere, was added 2-methoxythiophenol (966 μL, 7.94 mmol) followed by Et_3N (941 µL, 6.75 mmol). The solution was stirred for 60 min (monitored by TLC) at room temperature. The crude mixture was treated with saturated NH_4Cl aqueous solution (5.0 mL) and poured in water (50 mL). The organic layer was diluted with EtOAc (15 mL) and removed. The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 9:1 following an increasing gradient up to 7:3) to afford 283 mg (93 %) of the desired product **14** as an orange foam. $[\alpha_D]_{20}$ = +40 (c = 0.93 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.40 – 7.27 (m, 2H), 6.89 (dd, *J* = 7.3, 5.7 Hz, 2H), 6.63 (s, 1H), 4.94 (dd, *J* = 9.5, 5.8 Hz, 1H), 4.68 (d, *J* = 6.5 Hz, 1H), 3.99 – 3.92 (m, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 3.72 (d, *J* = 6.5 Hz, 1H), 3.17 (dd, *J* = 13.2, 9.5 Hz, 1H), 2.96 (dd, *J* = 15.4, 4.2 Hz, 1H), 2.38 (dd, *J* = 15.4, 6.9 Hz, 1H), 2.25 (dd, *J* = 13.3, 5.8 Hz, 1H), 1.37 – 1.15 (m, 3H), 1.09 (d, *J* = 7.1 Hz, 18H), 0.91 (s, 9H), 0.26 (s, 3H), 0.19 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.61, 172.59, 163.12, 159.77, 154.34, 145.77, 136.66, 130.68, 127.60, 121.60, 121.42, 120.55, 119.47, 113.64, 111.59, 82.47, 67.63, 57.86, 56.09, 55.88, 52.79, 51.97, 49.11, 42.18, 39.81, 26.02, 18.47, 18.28, 13.23, -2.22, -2.23. **HRMS** (ESI) calculated for $C_{40}H_{60}NO_8SSi_2$ $(M + H)^+$: 770.3573; found: 770.3566.



14bis

To a stirred solution of the prepared compound **14** (272 mg, 0.354 mmol) in dry THF (5.0 mL) and under argon atmosphere was added a 2.0 M solution of $LiBH_4$ in THF (800 μL, 1.60 mmol) at -78°C. The solution was stirred for 6 h at this temperature. The crude mixture was slowly treated with saturated NH_4Cl aqueous solution (5.0 mL) and water (10 mL) was added. The organic layer was diluted with EtOAc (5.0 mL) and was removed. The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under

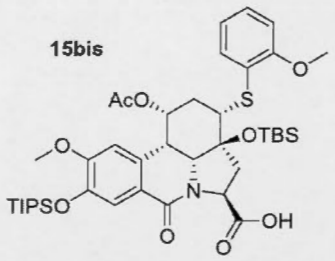
reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 9:1 following an increasing gradient up to 6:4) to afford 261 mg (96%) of the desired alcohol **14bis** as a beige foam. $[\alpha_D]_{20}$ = -1.9 (c = 0.94 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.48 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.33 (td, *J* = 7.9, 1.6 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 2H), 6.71 (s, 1H), 5.01 (t, *J* = 8.5 Hz, 1H), 4.16 (d, *J* = 6.0 Hz, 1H), 4.10 – 3.99 (m, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 3.64 (t, *J* = 2.9 Hz, 1H), 3.13 (m, 3H), 2.36 – 2.19 (m, 2H), 1.98 (dd, *J* = 12.6, 8.2 Hz, 1H), 1.34 – 1.20 (m, 3H), 1.09 (d, *J* = 7.1 Hz, 18H), 0.85 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.31, 163.80, 159.50, 154.83, 145.22, 135.60, 132.96, 130.46, 123.65, 123.05, 121.66, 119.51, 111.61, 110.37, 81.37, 69.52, 62.47, 58.19, 56.07, 55.82, 52.68, 48.81, 40.93, 40.61, 31.07, 25.92, 18.29, 13.25, -2.48, -2.67. **HRMS** (ESI) calculated for $C_{40}H_{62}NO_8SSi_2$ $(M + H)^+$: 772.3729; found: 772.3753.



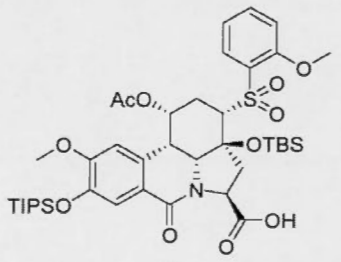
15

To a stirred solution of the previously prepared alcohol **14bis** (238 mg, 0.309 mmol) in DCM (3.0 mL) and under argon atmosphere was added Et_3N (258 μL, 1.85 mmol), Ac_2O (88.0 μL, 0.926 mmol) and DMAP (7.6 mg, 0.062 mmol), respectively at room temperature. The solution was stirred for 3 h at this temperature. The crude mixture was then treated with saturated NH_4Cl aqueous solution (5.0 mL) and water (15 mL) was added. The organic layer was diluted with DCM (5.0 mL) and was removed. The aqueous phase was extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 9:1 following an increasing gradient up to 6:4) to afford 220 mg (88%) of compound **15** as a beige foam. $[\alpha_D]_{20}$ = -66 (c = 0.75 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.52 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.37 – 7.27 (m, 1H), 7.01 – 6.84 (m, 2H), 6.68 (s, 1H), 5.28 (t, *J* = 8.6 Hz, 1H), 5.16 (d, *J* = 2.6 Hz, 1H), 4.17 (d, *J* = 6.0 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.53 (d, *J* = 2.5 Hz, 1H), 3.15 (dd, *J* = 5.9, 4.2 Hz, 1H), 2.83 (dd, *J* = 12.5, 8.6 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.49 – 2.36 (m, 1H), 1.86 (dd, *J* = 12.5, 8.7 Hz, 1H), 1.71 (s, 3H), 1.32 – 1.19 (m, 3H), 1.07 (d, *J* = 7.1 Hz, 18H), 0.82 (s, 9H), -0.08 (s, 3H), -0.14 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.50, 170.47, 162.97, 159.06, 154.58, 145.34, 134.11, 131.46, 130.00, 126.68, 123.76, 121.67, 119.43, 111.50, 110.52, 82.24, 69.53, 62.13, 58.83, 55.99, 55.87, 52.66, 49.67, 40.57, 38.65, 31.65, 25.88, 21.31, 18.26, 13.22, -2.74, -3.01. **HRMS** (ESI) calculated for $C_{42}H_{64}NO_9SSi_2$ $(M + H)^+$: 814.3835; found: 814.3859.

15bis



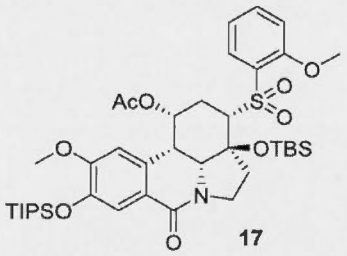
To a stirred solution of the prepared compound **15** (195 mg, 0.240 mmol) in EtOAc (4.0 mL), LiI xH_2O (320 mg, 2.39 mmol) was added at room temperature. The solution was stirred for 8 h (monitored by TLC) at refluxing temperature (it may be necessary to concentrate the mixture under air flux to allow the completion of the reaction). The crude mixture was then treated with saturated NH_4Cl aqueous solution (5.0 mL) and water (15 mL) was added. The organic layer was diluted with EtOAc (5.0 mL) and was removed. The aqueous phase was extracted with EtOAc (2 × 10 mL). It should be note here that the carboxylate is liposoluble enough to be extracted that way. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (DCM/MeOH, 9:1) to afford 180 mg (94%) of the desired carboxylic acid **15bis** as a colorless oil. $[\alpha_D]_{20}$ = -83 (c = 1.5 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.35 – 7.27 (m, 1H), 6.92 (dd, *J* = 15.4, 7.8 Hz, 2H), 6.69 (s, 1H), 5.59 (t, *J* = 8.2 Hz, 1H), 5.11 (d, *J* = 2.2 Hz, 1H), 4.04 (d, *J* = 6.2 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.54 (d, *J* = 2.8 Hz, 1H), 3.17 (dd, *J* = 6.1, 4.0 Hz, 1H), 2.79 – 2.54 (m, 2H), 2.52 – 2.37 (m, 2H), 1.74 (s, 3H), 1.32 – 1.18 (m, 3H), 1.08 (d, *J* = 7.2 Hz, 18H), 0.83 (s, 9H), -0.09 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.15, 165.63, 158.95, 155.36, 145.55, 134.23, 131.26, 130.23, 126.35, 122.56, 121.82, 119.44, 111.55, 110.46, 81.10, 69.55, 62.27, 60.77, 56.01, 55.93, 50.15, 38.81, 38.26, 31.47, 30.04, 25.91, 21.28, 18.22, 18.21, 13.15, -2.69, -3.12. **HRMS** (ESI) calculated for $C_{41}H_{62}NO_9SSi_2$ $(M + H)^+$: 800.3678; found: 800.3669.



16

To a stirred solution of the previously prepared carboxylic acid **15bis** (140 mg, 0.175 mmol) in DCM (2.0 mL) and under argon atmosphere, *m*CPBA (121 mg, 0.7 mmol) was added at room temperature. The solution was stirred for 2 h (monitored by TLC) at this temperature. The crude mixture was treated with a 0.1M $Na_2S_2O_3$ aqueous solution (3.0 mL) for 5 min and then with saturated $NaHCO_3$ aqueous solution (3.0 mL). Water was added (10 mL) and the organic layer was diluted with DCM (5.0 mL) and was removed. The aqueous phase was extracted with DCM (2 × 5.0 mL). The combined organic layers

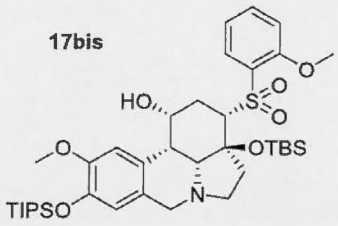
were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (DCM/MeOH, 9:1) to afford 116 mg (80%) of compound **16** as a pale yellow oil. $[\alpha_D]_{20}$ = -24 (c = 0.33 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 6.7 Hz, 1H), 7.68 – 7.58 (m, 1H), 7.56 (s, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.65 (s, 1H), 5.27 (t, *J* = 7.7 Hz, 1H), 5.11 (dd, *J* = 10.3, 5.1 Hz, 1H), 4.14 (d, *J* = 5.3 Hz, 2H), 3.98 (s, 3H), 3.84 (s, 3H), 3.64 (s, 1H(*not always present*)), 3.26 (t, *J* = 5.8 Hz, 1H), 3.24 – 3.06 (m, 1H), 2.86 (dd, *J* = 13.6, 8.7 Hz, 1H), 2.63 – 2.43 (m, 1H), 2.26 – 2.09 (m, 1H), 1.65 (s, 3H), 1.33 – 1.19 (m, 3H), 1.09 (d, *J* = 7.1 Hz, 18H), 0.87 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.42, 165.29, 157.25, 155.15, 145.71, 136.26, 130.80, 130.16, 128.66, 122.36, 121.70, 119.55, 113.13, 110.99, 79.95, 67.08, 66.16, 65.85, 59.40, 56.77, 55.96, 38.08, 30.04, 26.96, 25.95, 20.79, 18.32, 18.22, 13.16, -2.49, -2.92. **HRMS** (ESI) calculated for $C_{41}H_{62}NO_{11}SSi_2$ $(M + H)^+$: 832.3577; found: 832.3535.



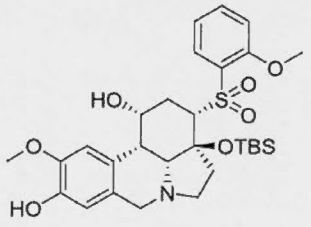
17

To a stirred solution of the prepared compound **16** (95 mg, 0.114 mmol) in DCM (1.0 mL) and under argon atmosphere, DIB (92 mg, 0.286 mmol) and I_2 (9.0 mg, 0.034 mmol) was added simultaneously at room temperature. The solution was stirred for 2 h (monitored by LRMS) under a 100W light at this temperature. The solution was carefully treated with Et_3SiH (145 μL, 0.908 mmol) for 30 min (monitored by LRMS). The crude mixture was treated with a 0.1M $Na_2S_2O_3$ aqueous solution (3.0 mL) and with saturated $NaHCO_3$ aqueous solution (3.0 mL) for 5 min. Water (10 mL) was added, the organic layer was diluted with DCM (5.0 mL) and was removed. The aqueous phase was extracted with DCM (2 × 10 mL). The combined .organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 9:1 following an increasing gradient up to 6:4) to afford 46 mg (51%) of compound **17** as a yellow oil. $[\alpha_D]_{20}$ = +61 (c = 1.5 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.54 (s, 1H), 7.09 (dd, *J* = 17.3, 8.0 Hz, 2H), 6.57 (s, 1H), 5.21 (dd, *J* = 7.5 Hz, 1H), 4.11 – 3.95 (m, 3H), 3.99 (s, 3H), 3.88 – 3.75 (m, 1H), 3.80 (s, 3H), 3.25 – 3.10 (m, 2H), 2.41 – 2.26 (m, 1H), 2.02 (t, *J* = 8.6 Hz, 2H), 1.52 (s, 3H), 1.33 – 1.19 (m, 3H), 1.08 (d, *J* = 7.1 Hz, 18H), 0.90 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.46, 162.89, 157.65, 153.89, 145.49, 136.10, 131.38, 129.55, 127.45, 124.08, 121.34, 119.24, 113.11, 111.57, 82.49, 69.00, 67.74, 65.46, 56.72, 55.93, 43.65, 38.40, 34.51, 28.96, 26.17, 20.74, 18.57, 18.23, 13.17, -2.02, -2.18. **HRMS** (ESI) calculated for $C_{40}H_{62}NO_9SSi_2$ $(M + H)^+$: 788.3678; found: 788.3689.

17bis



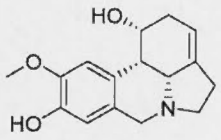
To a stirred solution of the prepared compound **17** (30 mg, 0.038 mmol) in toluene (1.0 mL) and under argon atmosphere, was slowly added a 1.0 M solution of diisobutylaluminium hydride in toluene (300 μL, 0.3 mmol) at room temperature. The solution was stirred for 20 h (monitored by LRMS and TLC) at this temperature. The solution was treated with EtOAc (1.0 mL) and water (1.0 mL) for 5 min. The mixture was then filtrated on celite (rinsed with 5.0 mL EtOAc) and the filtrate was poured in water (15 mL). The organic layer was removed and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel chromatography (n-hexane/EtOAc, 9:1 following an increasing gradient up to 6:4) to afford 17 mg (84%) of the desired reduced compound **17bis** as a pale yellow oil. $[\alpha_D]_{20}$ = +33 (c = 0.47 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.56 (dd, *J* = 12.4, 5.1 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.60 (s, 1H), 6.58 (s, 1H), 4.08 – 3.89 (m, 3H), 3.98 (s, 3H), 3.74 (s, 3H), 3.47 (d, *J* = 14.3 Hz, 1H), 3.29 (t, *J* = 7.8 Hz, 1H), 3.04 – 2.90 (m, 1H), 2.90 – 2.81 (m, *J* = 8.1 Hz, 2H), 2.71 – 2.58 (m, 1H), 2.35 – 2.02 (m, 4H), 1.25 – 1.15 (m, 3H), 1.08 (d, *J* = 6.8 Hz, 18H), 0.90 (s, 9H), 0.19 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.54, 150.01, 144.74, 135.52, 131.52, 128.52, 127.89, 127.35, 121.20, 118.23, 112.76, 112.28, 82.44, 75.53, 68.73, 65.64, 56.58, 55.82, 55.48, 52.75, 40.13, 35.30, 33.27, 26.40, 18.73, 18.29, 13.27, -1.18, -1.44. **HRMS** (ESI) calculated for $C_{38}H_{62}NO_7SSi_2$ $(M + H)^+$: 732.3780; found: 732.3742.



18

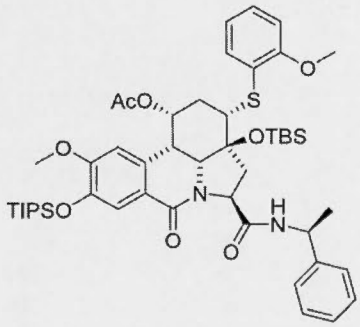
To a stirred solution of the previously prepared reduced compound **17bis** (8.0 mg, 0.011 mmol) in MeOH (1.0 mL), K_2CO_3 (10 mg, 0.072 mmol) was added at room temperature. The solution was stirred for 16 h (monitored by TLC) at refluxing temperature. The crude mixture was directly filtered on a silica gel pad using MeOH as eluent. The crude was then concentrated under reduced pressure and purified by silica gel chromatography (DCM/MeOH, 9:1) to afford 6.0 mg (95%) of compound **18** as a pale solid. $[\alpha_D]_{20}$ = +56 (c = 0.36 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.62 – 7.52 (m, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 5.54 (s, 1H), 4.07 (d, *J* = 14.3 Hz, 1H), 3.98 (s, 3H), 3.95 – 3.88 (m, 1H), 3.84 (s, 3H), 3.50 (d, *J* = 14.3 Hz, 1H), 3.29 (t, *J* = 7.8 Hz, 1H), 3.04 – 2.91 (m, 1H), 2.92 – 2.82 (m,

2H), 2.72 – 2.58 (m, 1H), 2.36 – 2.03 (m, 4H), 0.90 (s, 9H), 0.18 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.56, 145.96, 144.89, 135.55, 131.53, 128.54, 128.49, 126.38, 121.20, 112.79, 112.56, 110.69, 82.43, 75.71, 68.85, 65.53, 56.61, 56.16, 55.55, 52.77, 40.16, 35.29, 33.39, 26.39, 18.72, -1.18, -1.42. **HRMS** (ESI) calculated for $C_{29}H_{42}NO_7SSi$ $(M + H)^+$: 576.2446; found: 576.2464.



2

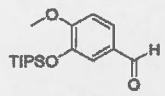
To a stirred solution of the prepared compound **18** (7.0 mg, 0.012 mmol) in anhydrous THF (0.5 mL) and under argon atmosphere, was added a freshly prepared 0.66 M solution of lithium naphtalenide in THF (300 μL, 0.198 mmol) dropwise at room temperature. The solution was stirred for 30 min (monitored by LRMS and TLC) at this temperature. The solution was then cooled at 0°C and treated with water (0.5 mL) and brine (10 mL). The organic layer was diluted with EtOAc (5.0 mL) and removed. The aqueous phase was extracted with EtOAc (2 × 5.0 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (CH_2Cl_2/MeOH, 10:0 following an increasing gradient up to 7:3) to afford 2.1 mg (65%) of the desired (-)-fortucine as a pale yellow residue. $[\alpha_D]_{20}$ = -63 (c = 0.04 in ethanol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.65 (s, 1H), 5.54 (d, *J* = 7.6 Hz, 1H), 4.26 (d, *J* = 2.5 Hz, 1H), 3.94 (d, *J* = 13.9 Hz, 1H), 3.89 (s, 3H), 3.31 (d, *J* = 13.1 Hz, 2H), 2.97 (s, 1H), 2.70 (s, 1H), 2.58 – 2.26 (m, 6H).



To a stirred solution of the prepared compound **15bis** (3.3 mg, 0.0041 mmol) in anhydrous DMF (0.3 mL) and under argon atmosphere, was added $CuCl_2$ (0.8 mg, 0.006 mmol) at 0°C followed by HOBT (0.8 mg, 0.006 mmol) and DCC (1.2 mg, 0.006). After being stirred for 15 min at 0°C, (S)-(-)-α-Methylbenzylamine (1.0 μL, 0.008 mmol) was added (the color of the mixture immediately changed from yellow to green) at the same temperature and the reaction mixture was allowed to warm gradually at room temperature. After 16 hours (monitored by TLC), the reaction mixture was diluted with EtOAc (5.0 mL) and washed with a saturated $NaHCO_3$ aqueous solution (10 mL). The organic layer was removed and the aqueous phase was extracted with EtOAc (2 × 5.0 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under

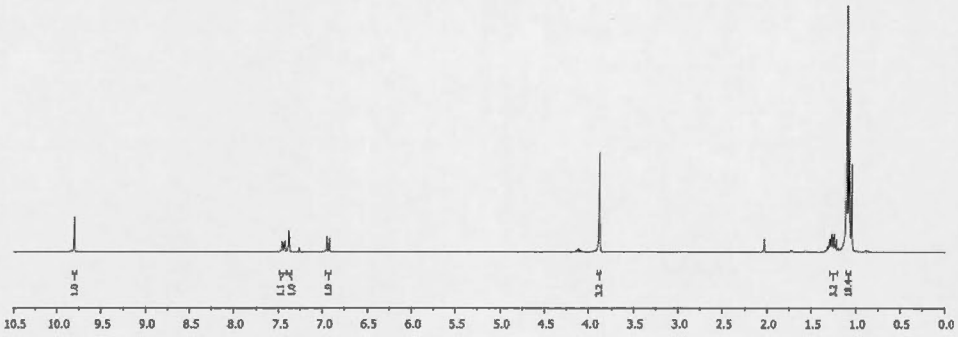
reduced pressure. The crude was purified by silica gel chromatography (Hex/EtOAc, 9:1 following an increasing gradient up to 7:3) to afford 2.0 mg (54%) of the desired product as a pale yellow residue. $[\alpha_D]_{20}$ = +49 (c = 0.06 in $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94 – 7.86 (m, 1H), 7.58 (s, 1H), 7.48 – 7.29 (m, 6H), 6.95 – 6.83 (m, 2H), 6.69 (s, 1H), 5.24 (t, *J* = 7.8 Hz, 1H), 5.07 (m, 2H), 4.07 – 3.95 (m, 2H), 3.85 (s, 6H), 3.52 – 3.44 (m, 1H), 3.20 – 3.10 (m, 1H), 2.75 – 2.42 (m, 4H), 1.74 (s, 3H), 1.46 (d, *J* = 7.0 Hz, 3H), 1.34 – 1.17 (m, 3H, ROSiC**H**$(CH_3)_2$ behind grease signals), 1.10 (d, *J* = 5.9 Hz, 18H), 0.84 (s, 9H), -0.03 (s, 3H),-0.08 (s, 3H).

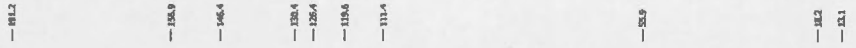
III. Copies of 1H and 13C NMR spectra

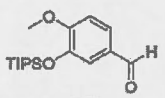


5bis

$CDCl_3$, 300 MHz

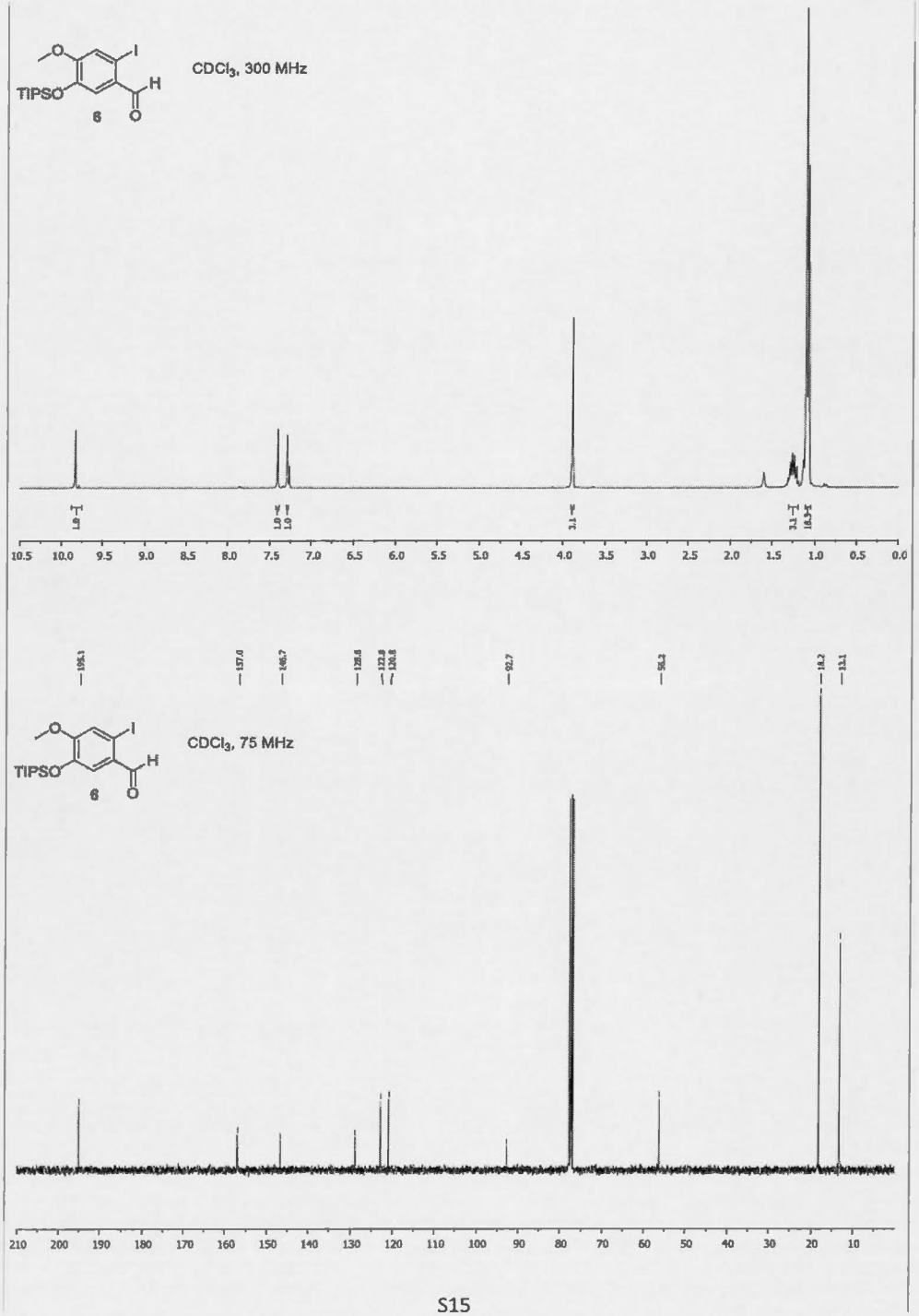


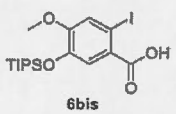




5bis

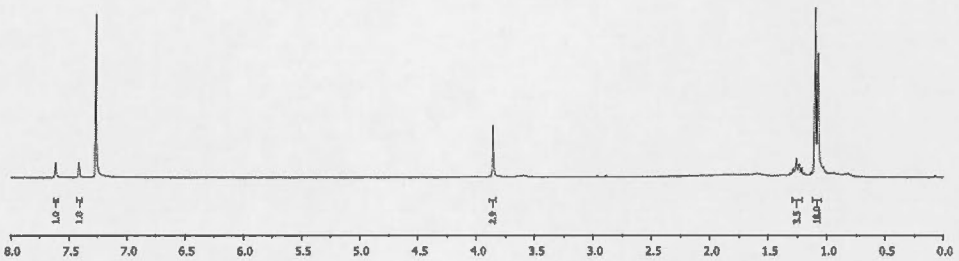
$CDCl_3$, 75 MHz

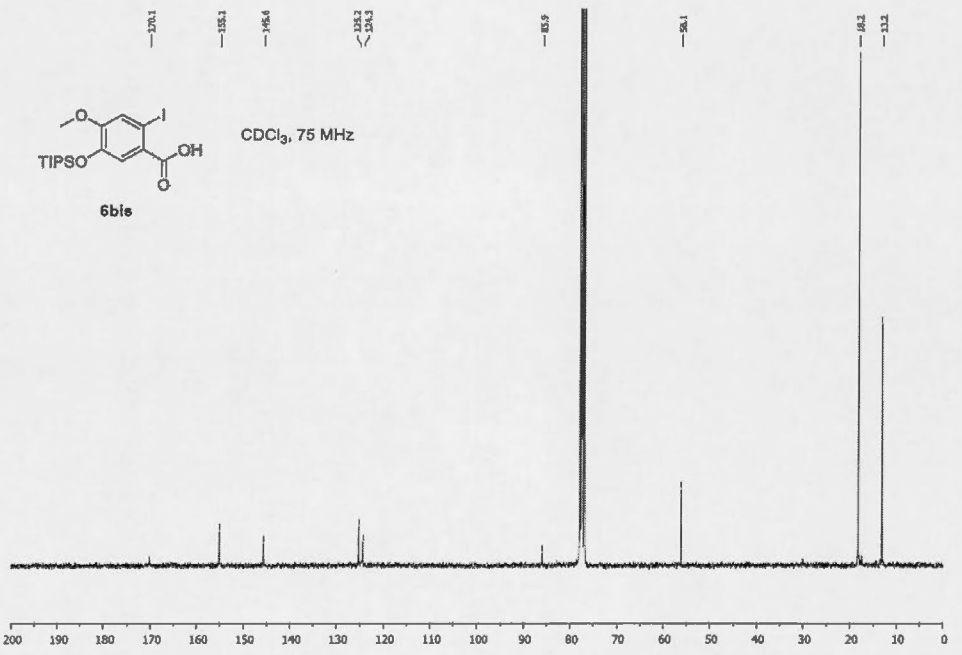

TIPSO
I
H
O
6
CDCl3, 300 MHz
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
195.1
157.0
146.7
128.6
122.8
120.8
92.7
56.3
18.2
13.1
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10



6bis

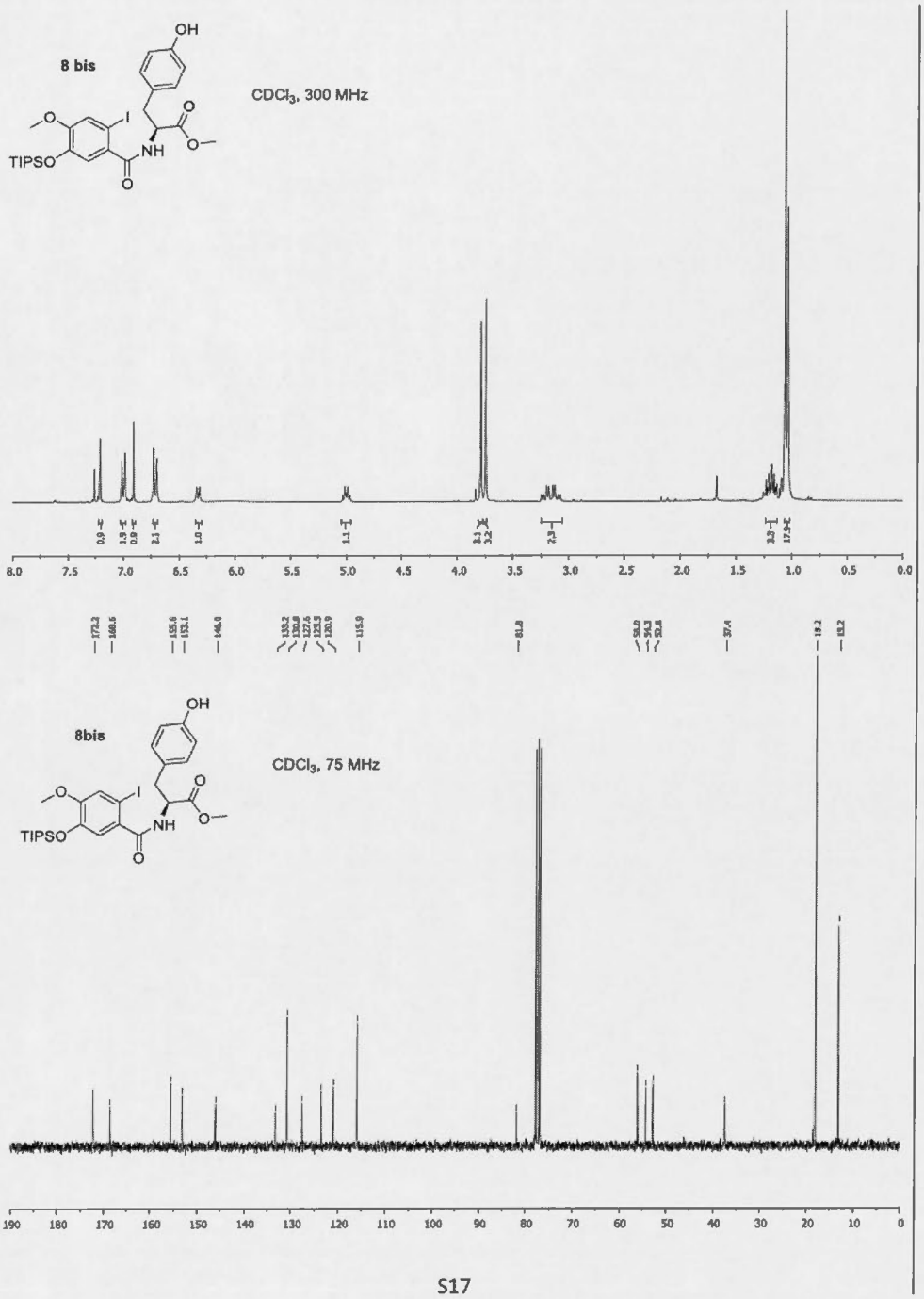
$CDCl_3$, 300 MHz

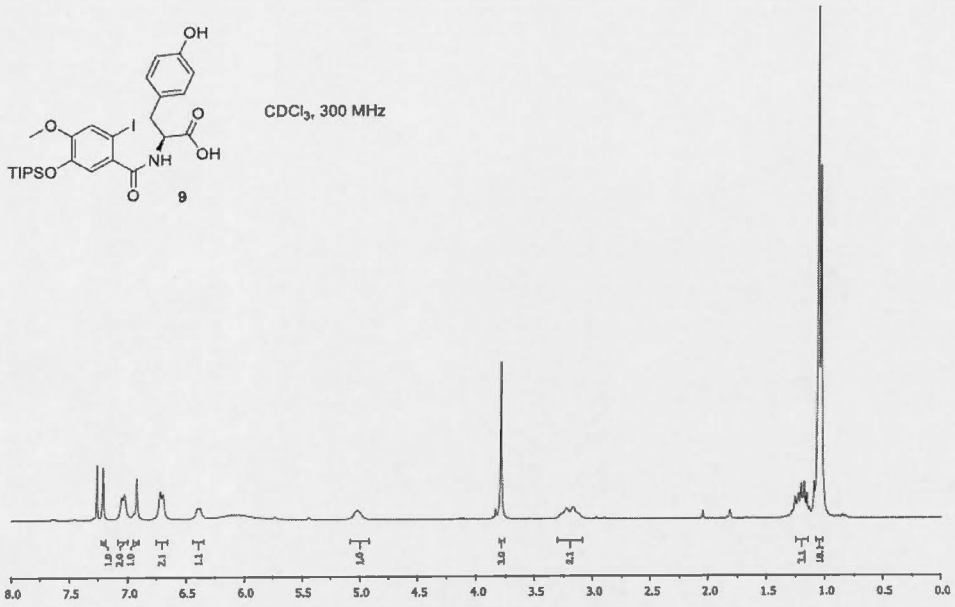


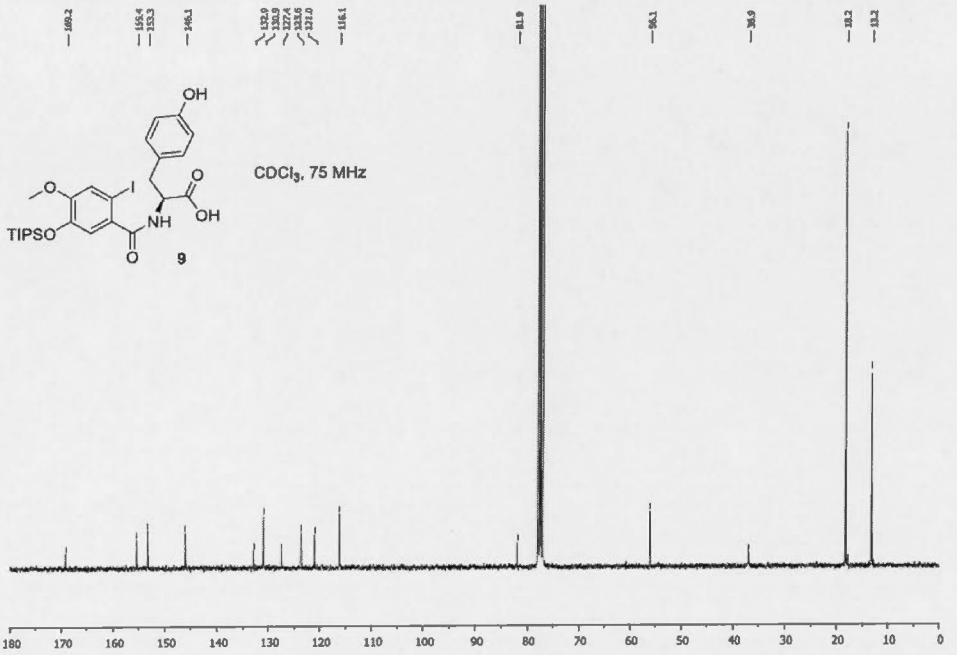


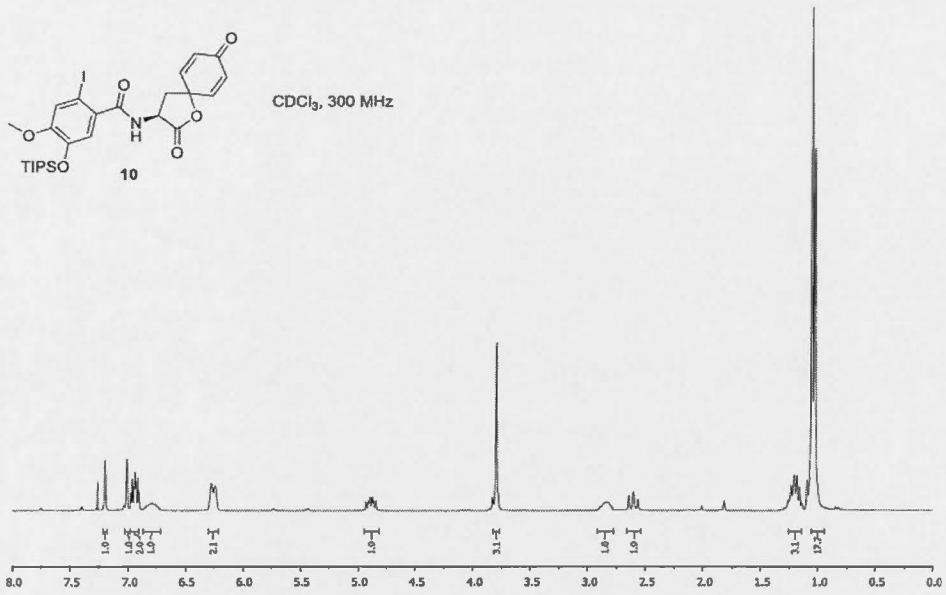
6bis

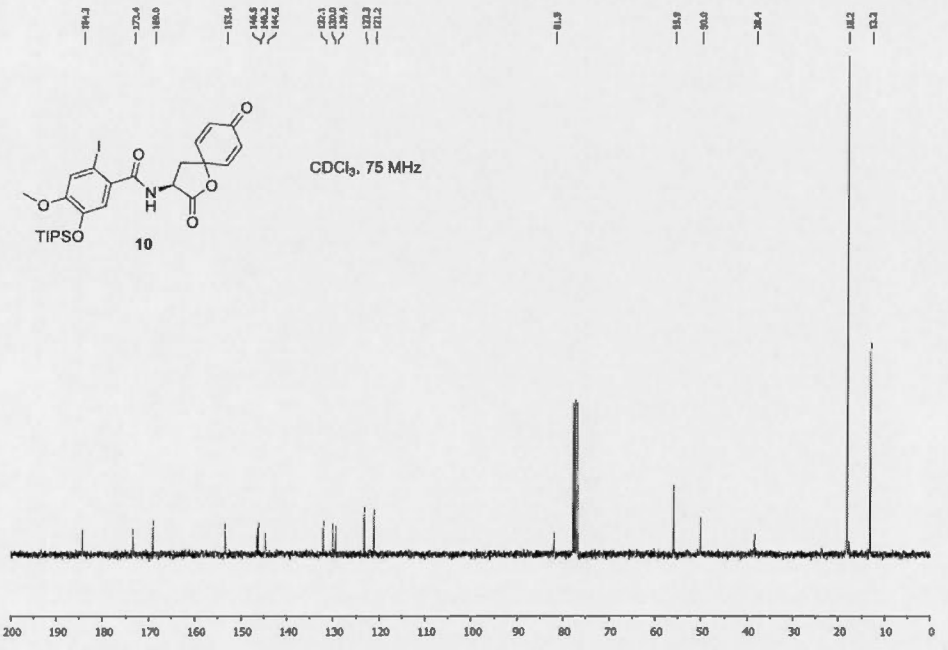
$CDCl_3$, 75 MHz

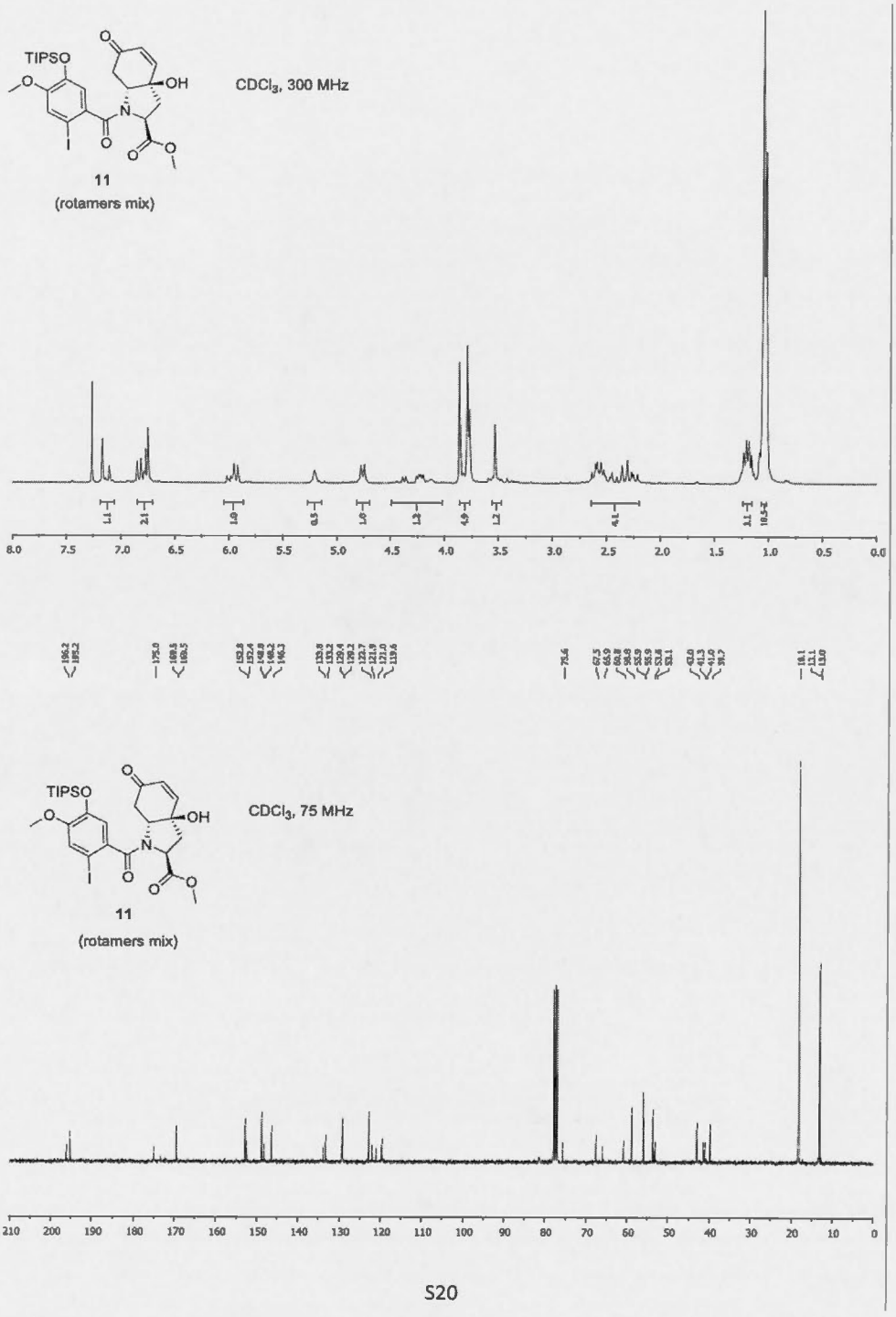

8 bis
CDCl3, 300 MHz
8bis
CDCl3, 75 MHz

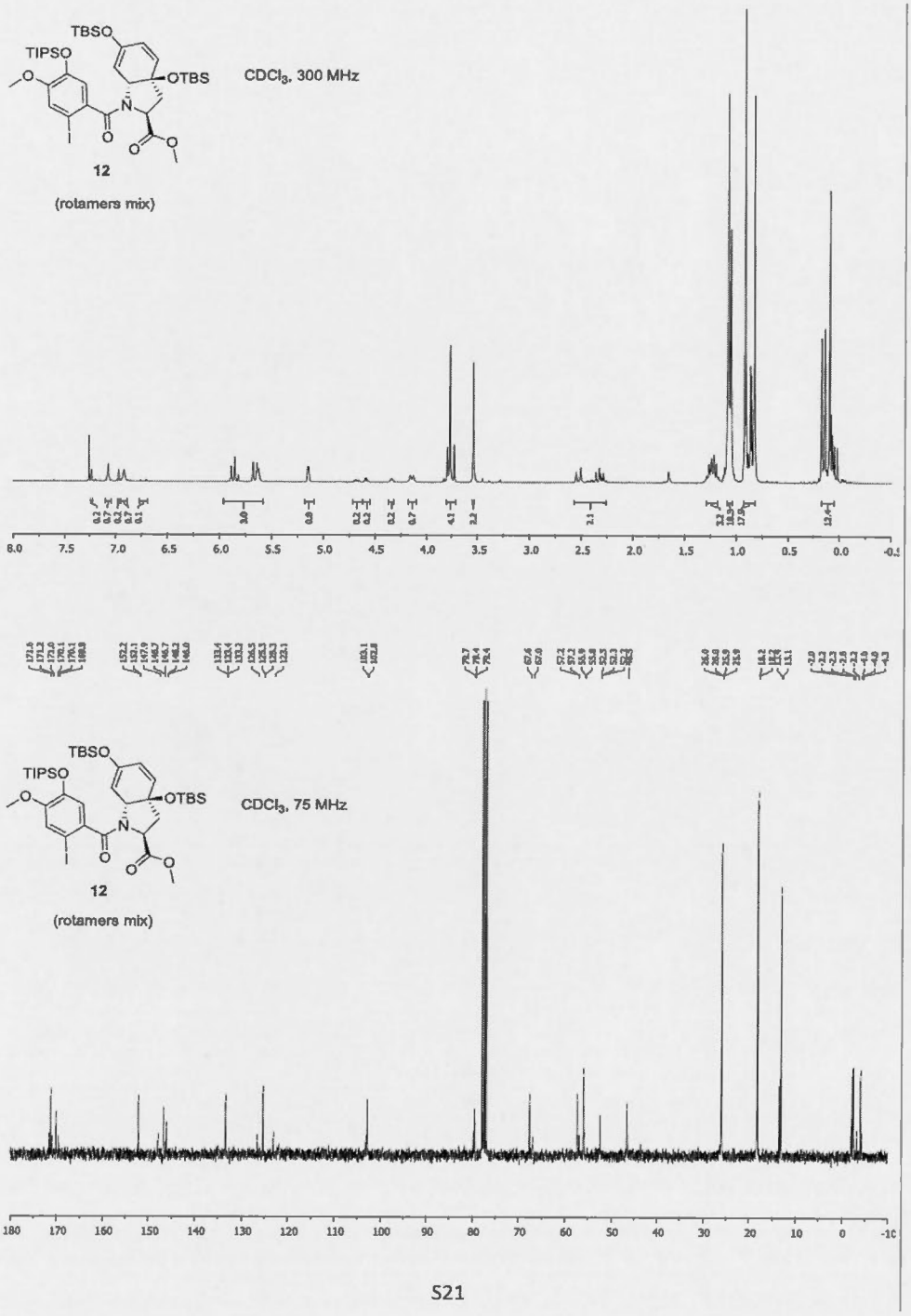

OH
O
I
O
NH
OH
TIPSO
O
9
CDCl3, 300 MHz
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

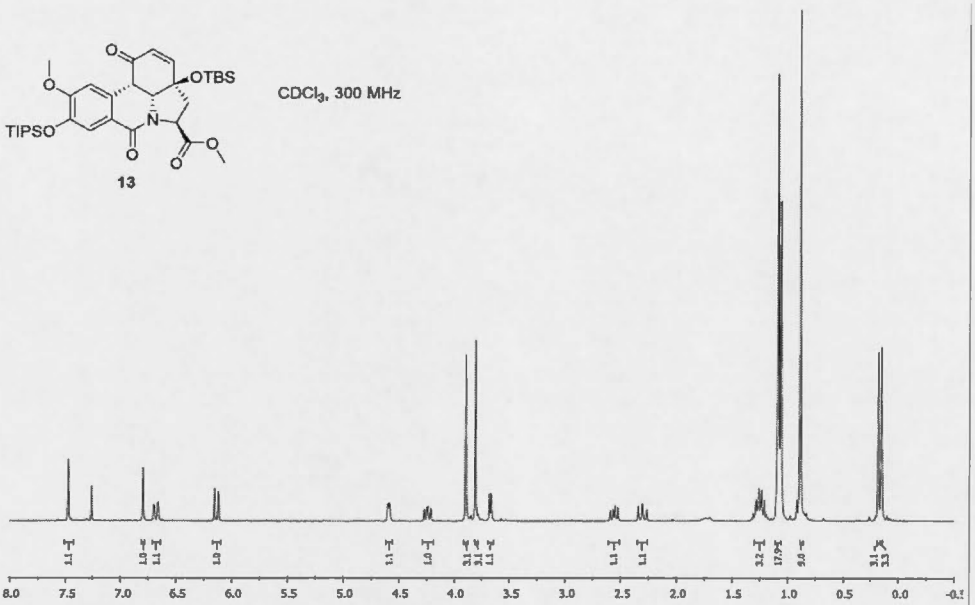

169.2
155.4
153.3
146.1
132.9
130.9
127.4
123.6
121.0
116.1
81.9
56.1
38.9
18.2
13.2
OH
O
I
O
NH
OH
TIPSO
O
9
CDCl3, 75 MHz
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

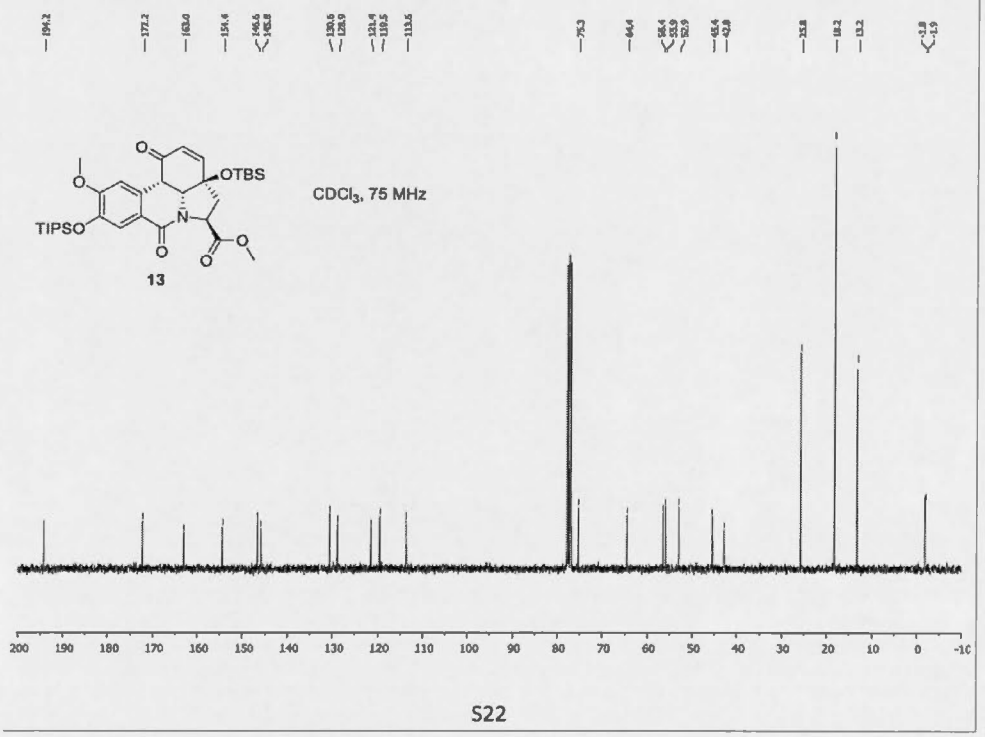

CDCl3, 300 MHz
TIPSO
10

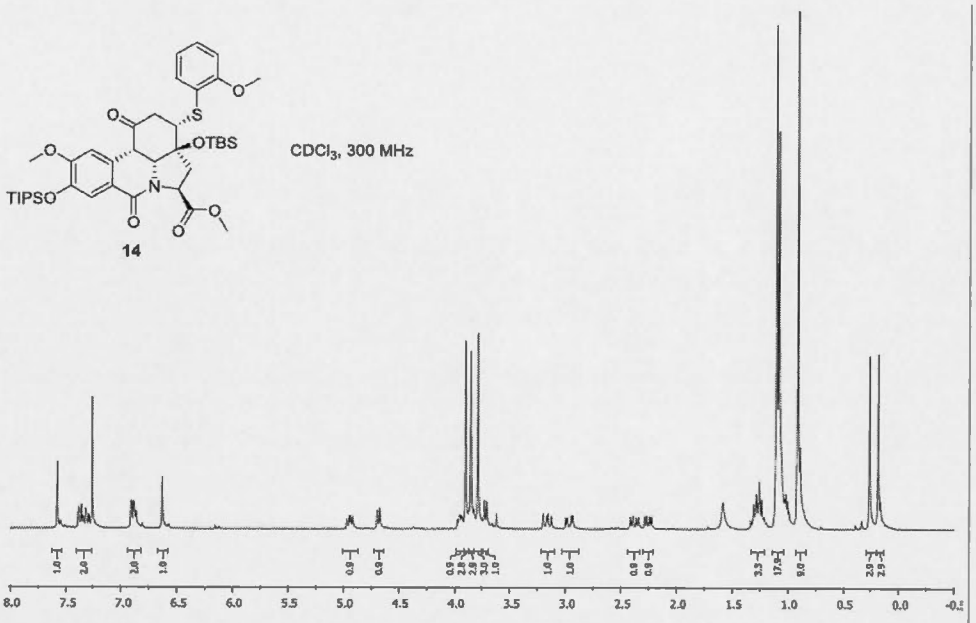

CDCl3, 75 MHz
TIPSO
10

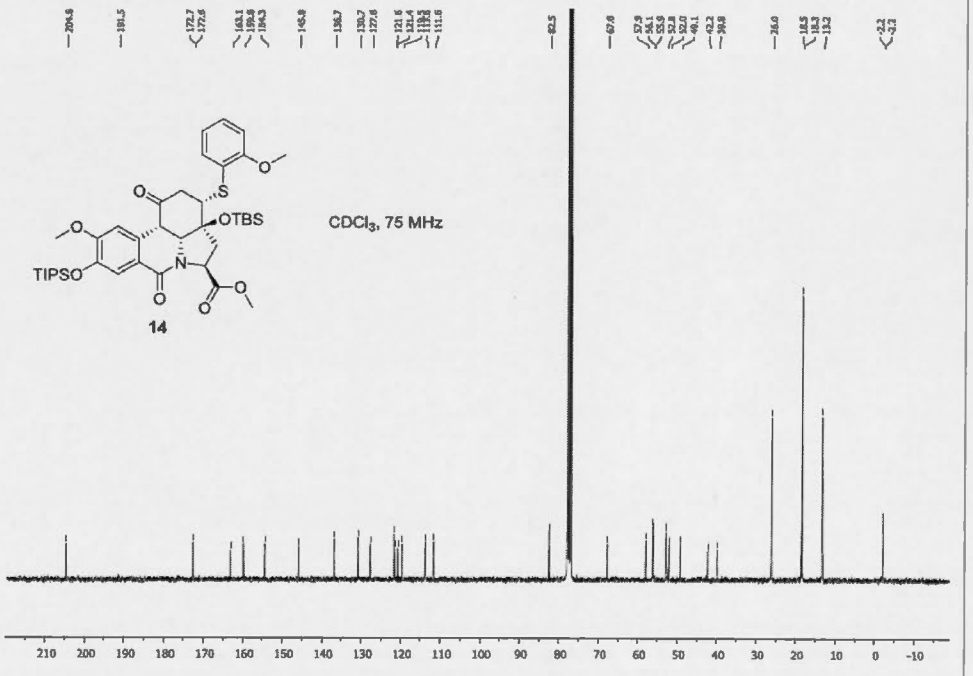

TIPSO
OH
CDCl3, 300 MHz
11
(rotamers mix)
CDCl3, 75 MHz
11
(rotamers mix)

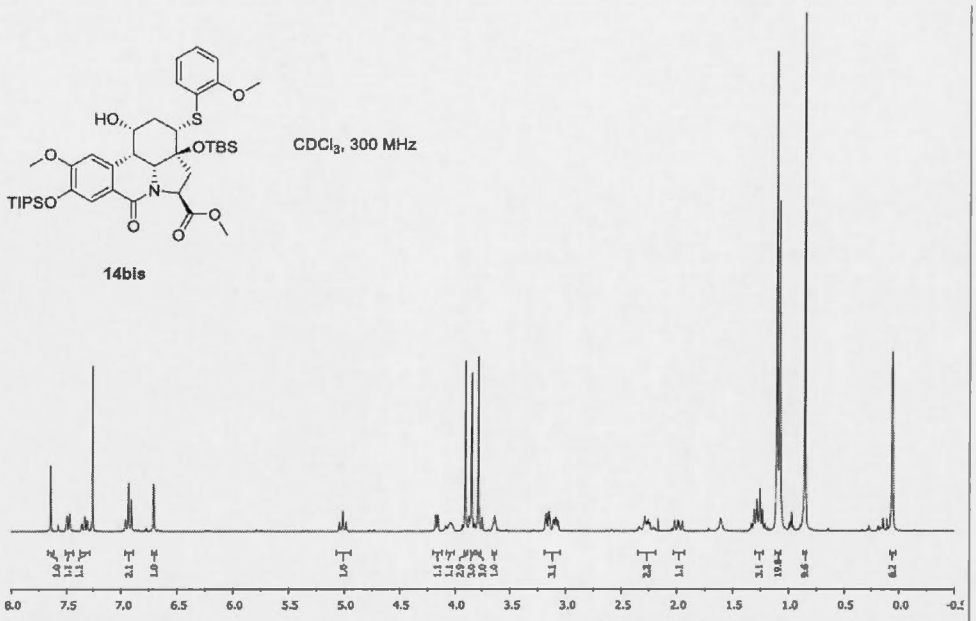

TBSO
TIPSO
OTBS
N
O
I
O
O
12
(rotamers mix)
CDCl3, 300 MHz
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
TBSO
TIPSO
OTBS
N
O
I
O
O
12
(rotamers mix)
CDCl3, 75 MHz
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

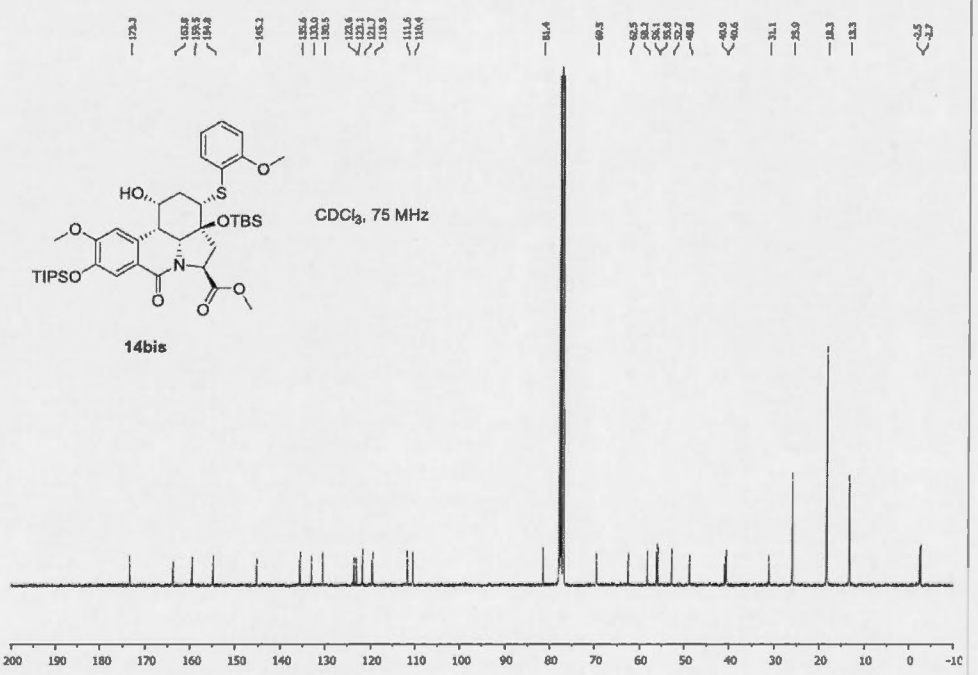

OTBS
TIPSO
13
CDCl3, 300 MHz

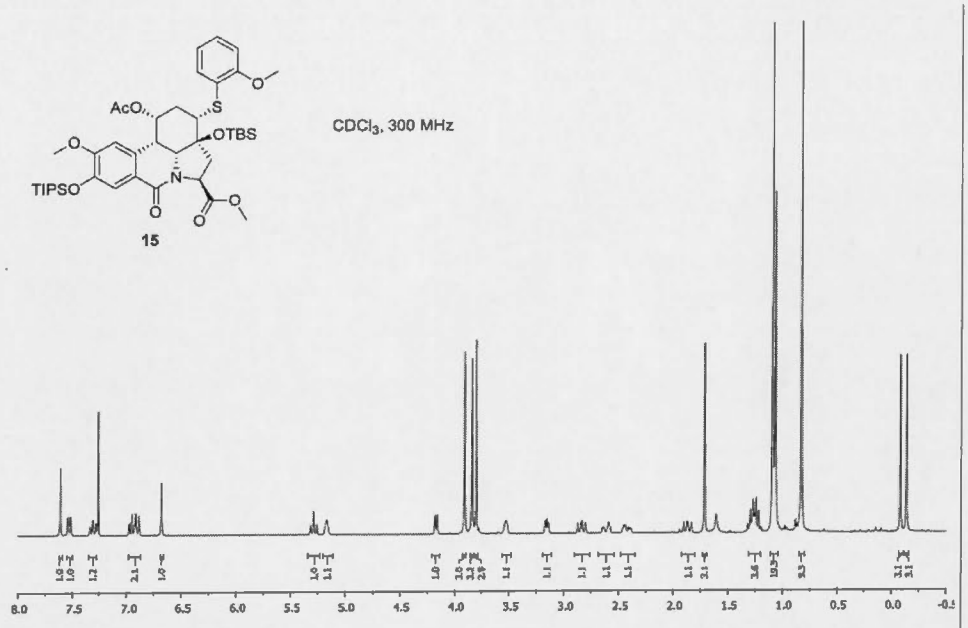

OTBS
TIPSO
13
CDCl3, 75 MHz

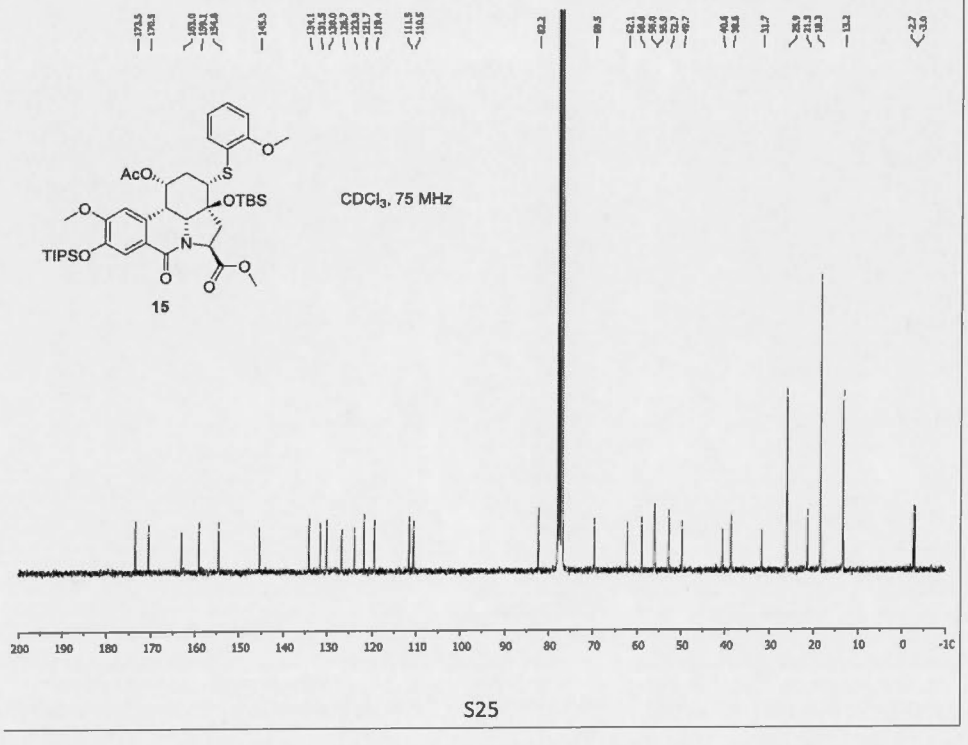

CDCl3, 300 MHz
OTBS
TIPSO
14

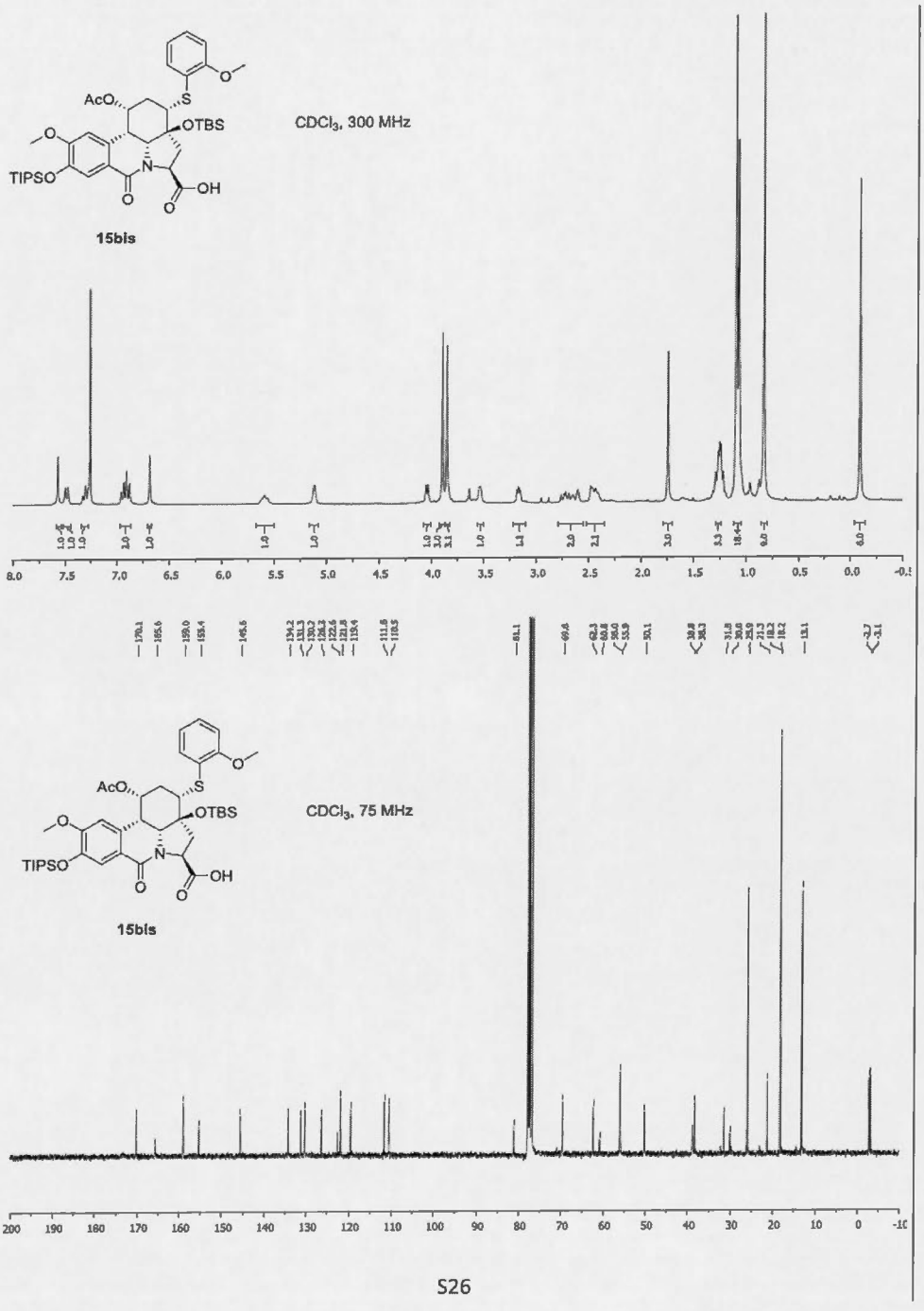

CDCl3, 75 MHz
OTBS
TIPSO
14

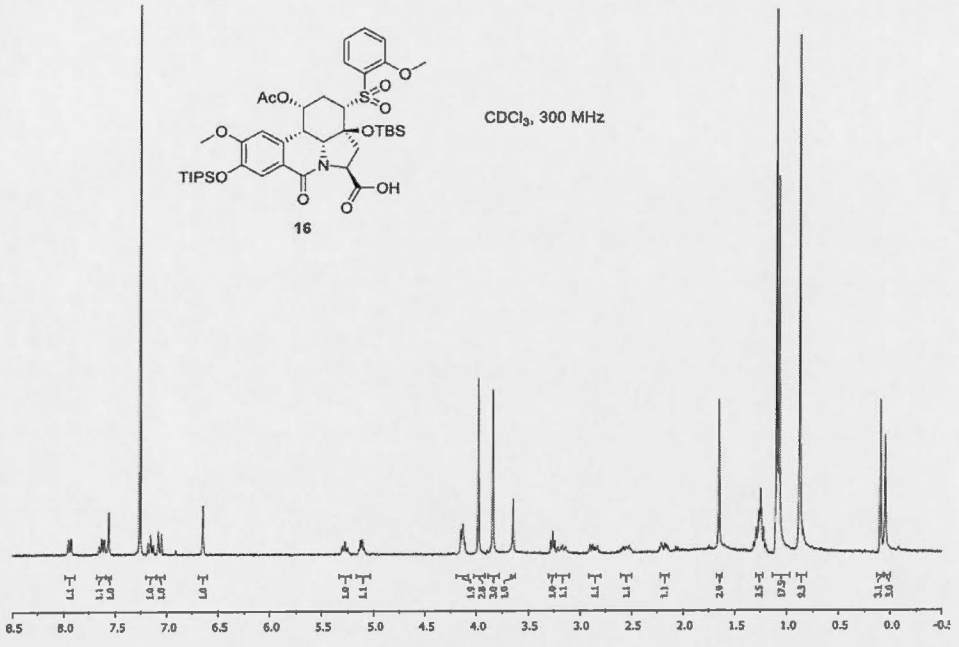

HO
S
OTBS
TIPSO
N
O
O
O
O
14bis
CDCl3, 300 MHz

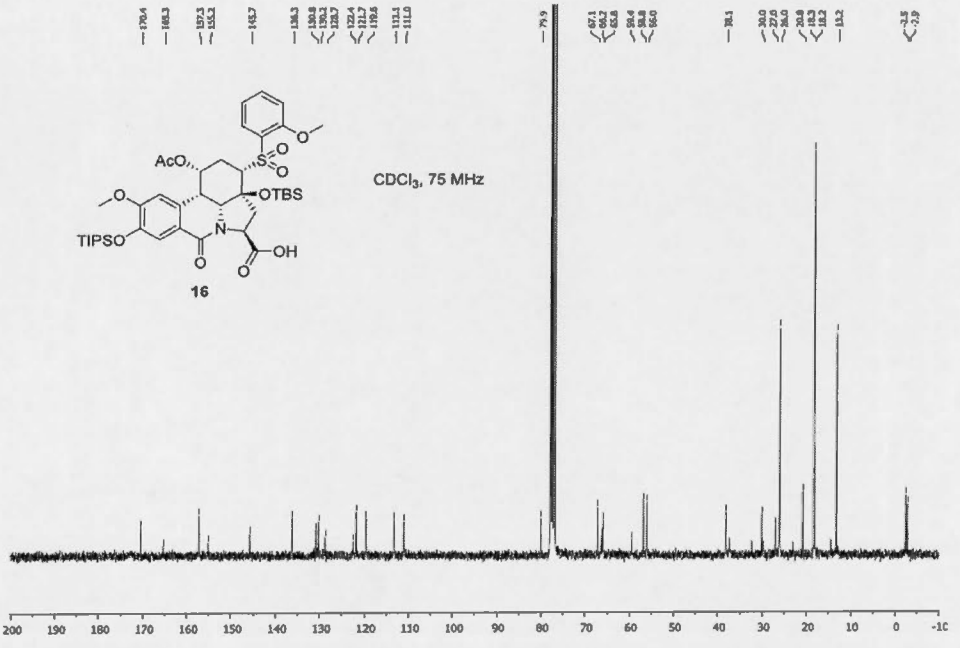

HO
S
OTBS
TIPSO
N
O
O
O
O
14bis
CDCl3, 75 MHz

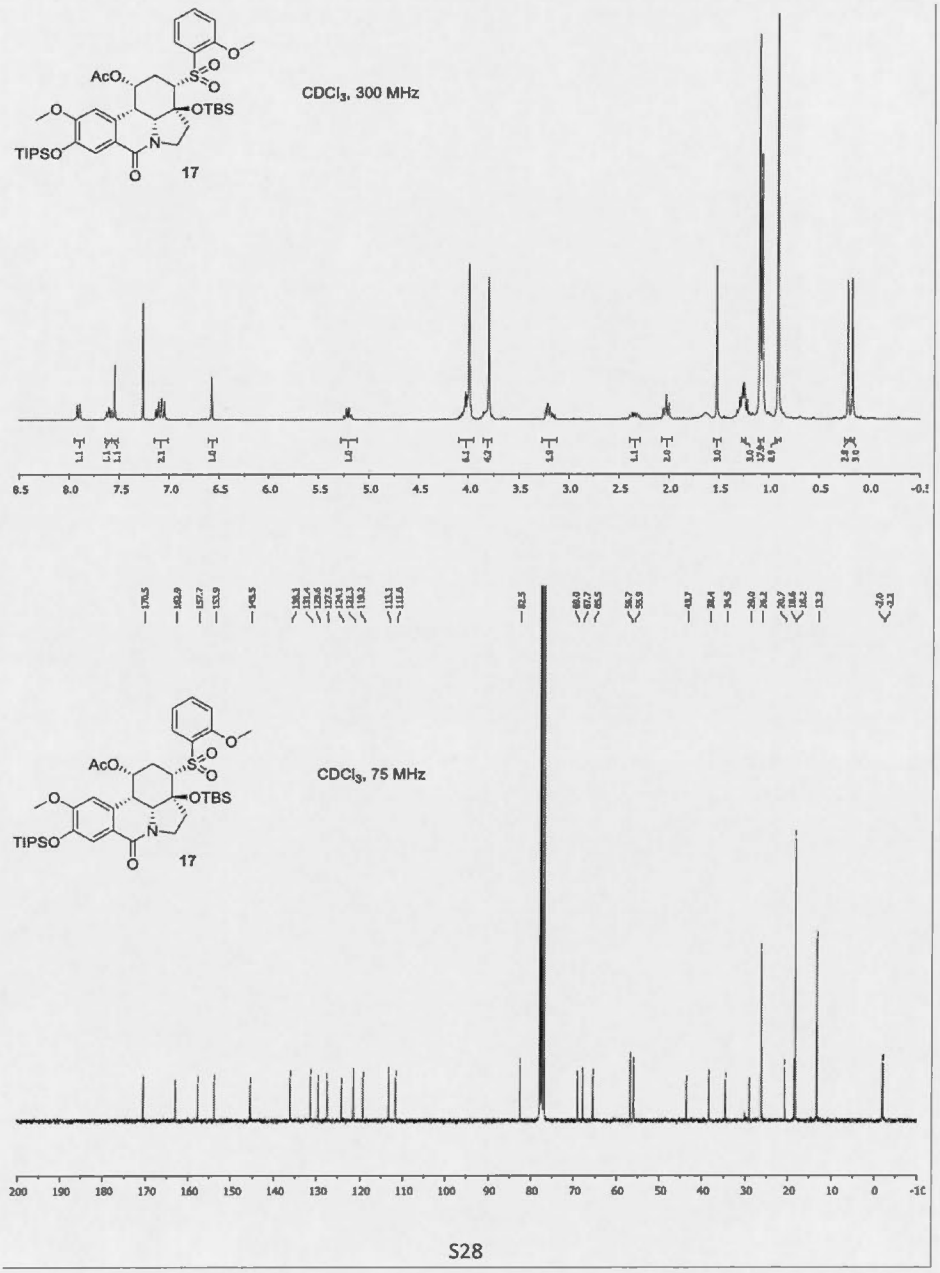

AcO
S
OTBS
O
TIPSO
N
O
O
O
15
CDCl3, 300 MHz

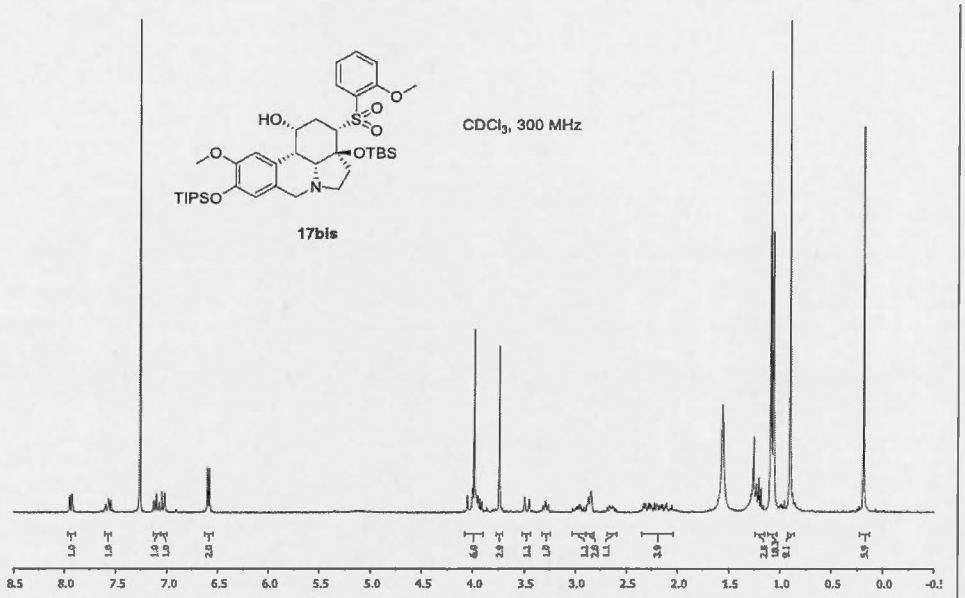

AcO
S
OTBS
O
TIPSO
N
O
O
O
15
CDCl3, 75 MHz

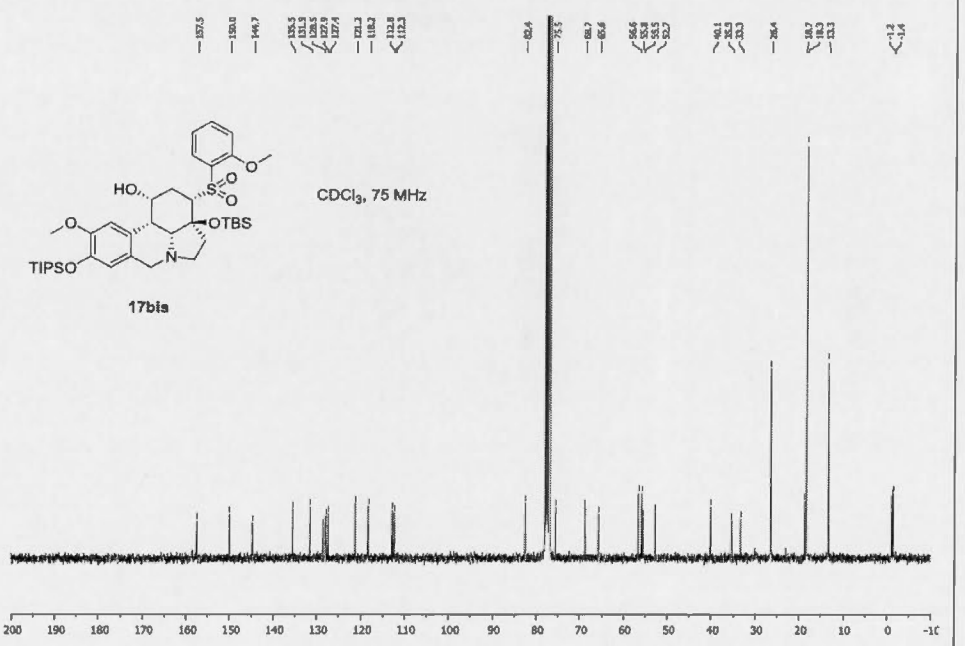

AcO
S
O
OTBS
O
N
TIPSO
O
OH
O
15bis
CDCl3, 300 MHz
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
AcO
S
O
OTBS
O
N
TIPSO
O
OH
O
15bis
CDCl3, 75 MHz
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

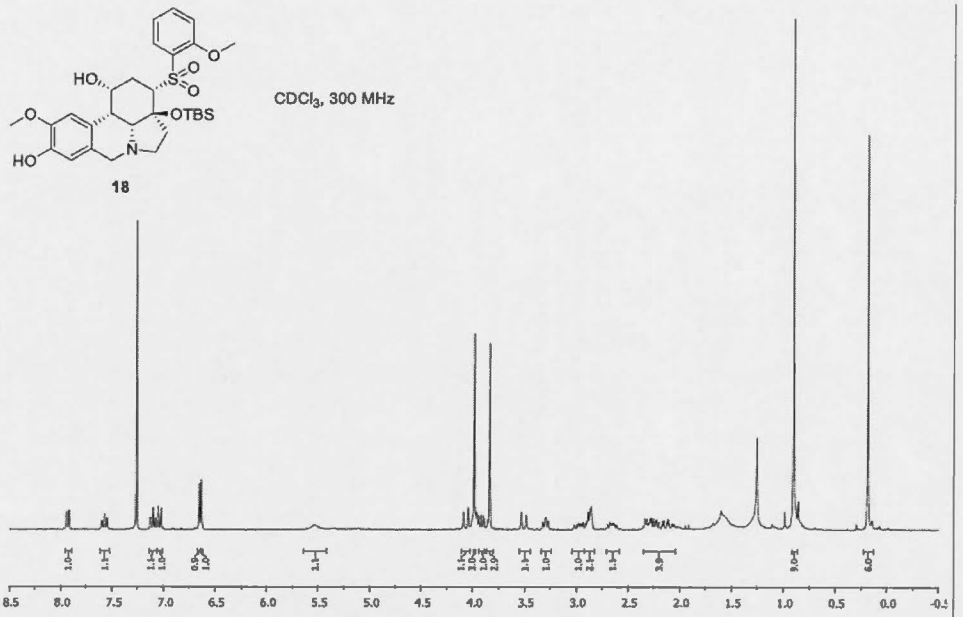

AcO
OTBS
TIPSO
OH
16
CDCl3, 300 MHz

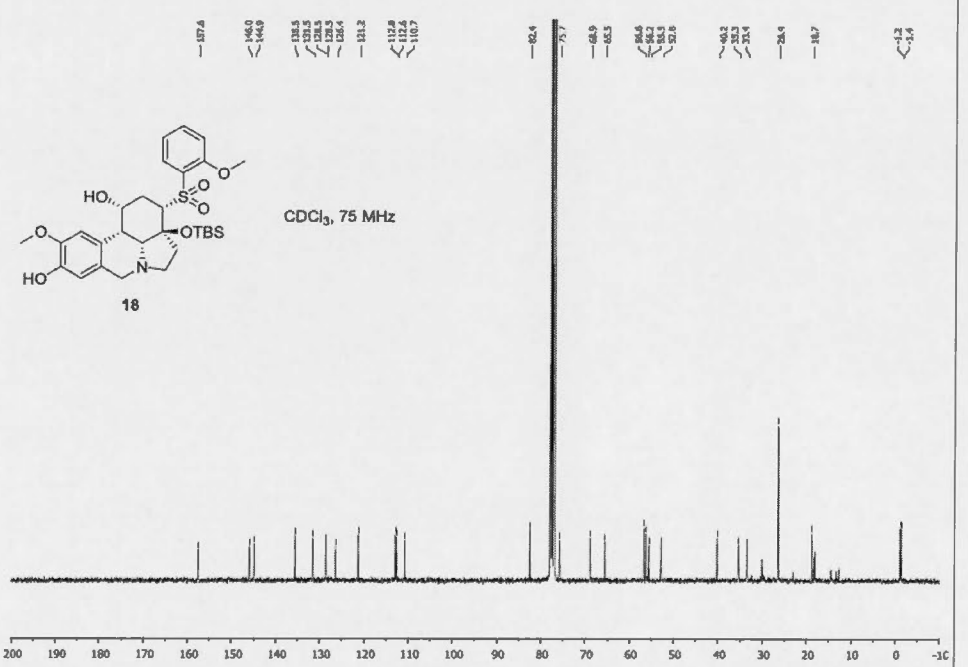

AcO
OTBS
TIPSO
OH
16
CDCl3, 75 MHz


AcO
OTBS
TIPSO
17
CDCl3, 300 MHz
CDCl3, 75 MHz


HO
O
S
O
O
OTBS
O
N
TIPSO
17bis
CDCl3, 300 MHz


HO
O
S
O
O
OTBS
O
N
TIPSO
17bis
CDCl3, 75 MHz


HO
O
S
O
O
OTBS
O
HO
N
18
CDCl3, 300 MHz


HO
O
S
O
O
OTBS
O
HO
N
18
CDCl3, 75 MHz

X-ray crystallographic analysis

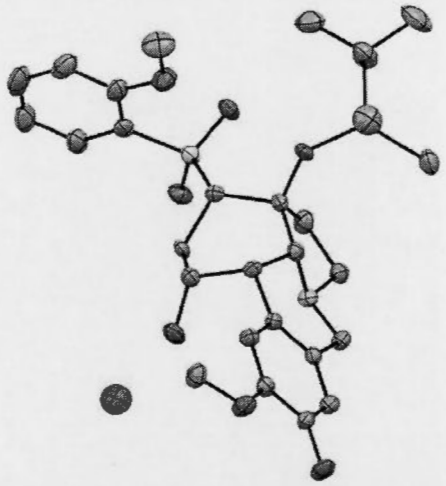


Figure 1: ORTEP at 50% thermal ellipsoid probability of the elementary unit cell of $(\mathbf{18})_3 \cdot H_2O$. Hydrogen atoms omitted for clarity.

Crystallographic analysis was performed on a Bruker APEX-DUO diffractometer. A clear colourless needle-like specimen of $(\mathbf{18})_3 \cdot H_2O$, of approximate dimensions 0.035 mm x 0.038 mm x 0.473 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 5856 frames were collected. The total exposure time was 16.27 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a trigonal unit cell yielded a total of 25636 reflections to a maximum θ angle of 66.95° (0.84 Å resolution), of which 5353 were independent (average redundancy 4.789, completeness = 99.4%, R_{int} = 13.29%) and 3898 (72.82%) were greater than $2\sigma(F^2)$. The final cell constants of a = 33.1514(10) Å, b = 33.1514(10) Å, c = 7.1798(3) Å, volume = 6833.6(5) $Å^3$, are based upon the refinement of the XYZ-centroids of 9981 reflections above 20 σ(I) with 5.331° < 2θ < 133.7°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.837. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.4990 and 0.9430.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group R3, with Z = 3 for the formula unit, $C_{87}H_{123}N_3O_{22}S_3Si_3$. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were generated in idealized positions, riding on the carrier atoms with isotropic thermal parameters.The final anisotropic full-matrix least-squares refinement on F^2 with 364 variables converged at R_1 = 4.88%, for the observed data and wR_2 = 10.73% for all data. The goodness-of-fit was 0.970. The largest peak in the final difference electron density synthesis was 0.232 $e^-/Å^3$ and the largest hole was -0.380 $e^-/Å^3$ with an RMS deviation of 0.051 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.271 g/cm^3 and F(000), 2796 e^-.

We were not able to locate the two hydrogen atoms on the water molecule by analyzing the difference map, nor did we constrain them at idealized positions because the O atom lies on a 3-fold axis. In addition, the molecule of interest is the organic moiety and the data was of sufficient quality for structural confirmation of this molecule.

Table 1: Sample and crystal data for $(\mathbf{18})_3 \cdot H_2O$.

CCDC deposition number	985620	
Chemical formula	$C_{87}H_{123}N_3O_{22}S_3Si_3$	
Formula weight	1743.33 g/mol	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal size	0.035 x 0.038 x 0.473 mm	
Crystal habit	clear colourless needle	
Crystal system	trigonal	
Space group	R 3	
Unit cell dimensions	a = 33.1514(10) Å	α = 90°
	b = 33.1514(10) Å	β = 90°
	c = 7.1798(3) Å	γ = 120°
Volume	6833.6(5) $Å^3$	
Z	3	
Density (calculated)	1.271 g/cm^3	
Absorption coefficient	1.709 mm^{-1}	
F(000)	2796	

Table 2: Data collection and structure refinement for $(\mathbf{18})_3 \cdot H_2O$.

Theta range for data collection	4.62 to 66.95°	
Index ranges	$-38 \le h \le 39$, $-39 \le k \le 39$, $-8 \le l \le 8$	
Reflections collected	25636	
Independent reflections	5353 [R(int) = 0.1329]	
Coverage of independent reflections	99.4%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9430 and 0.4990	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick, 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2013 (Sheldrick, 2013)	
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	5353 / 1 / 364	
Goodness-of-fit on F^2	0.970	
Final R indices	3898 data; $I>2\sigma(I)$	$R_1 = 0.0488$, $wR_2 = 0.0933$
	all data	$R_1 = 0.0895$, $wR_2 = 0.1073$
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0469P)^2]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	0.0(0)	
Largest diff. peak and hole	0.232 and -0.380 e $Å^{-3}$	
R.M.S. deviation from mean	0.051 e $Å^{-3}$	

Atomic coordinates and equivalent isotropic atomic displacement parameters, bond

lengths, bond angles, torsion angles, anisotropic atomic displacement parameters are provided in the attached CIF file, which can also be retrieved from the Cambridge Crystallographic Data Centre using deposition number 985620 at the following URL: http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/Requestastructure.aspx

Circular dichroism analysis

Circular dichroism experiments were carried out on a Jasco J-710 spectropolarimeter in methanol solutions at 1.0 mm pathlength. Spectra were corrected from a baseline (pure solvent) that was collected the same number of times as the spectra.

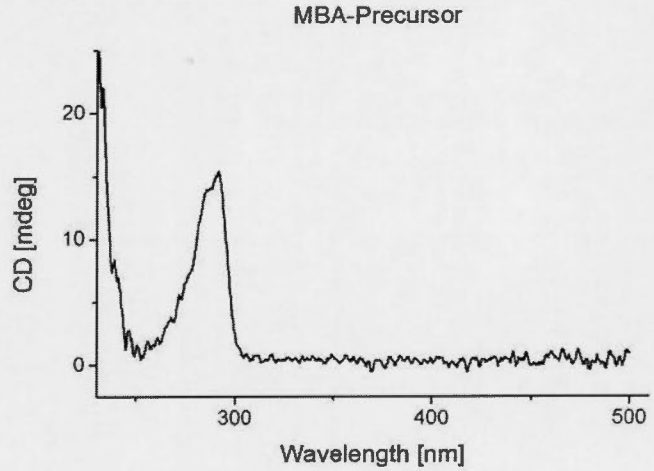


Figure 2: CD spectrum of a sample of **18** in MeOH (3 scans).

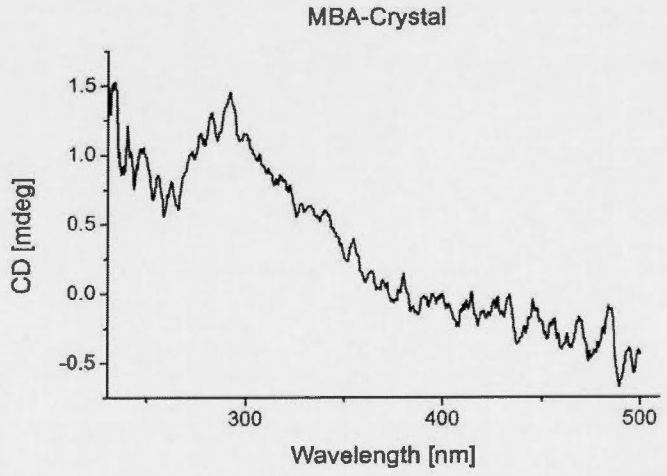
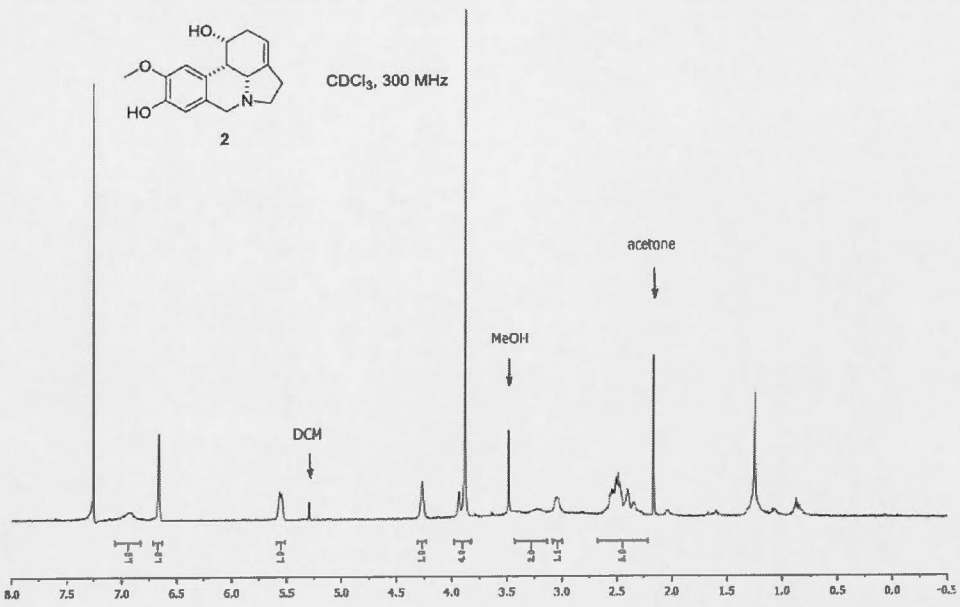


Figure 3: CD spectrum in MeOH of three crystals of **18** (20 scans), which absolute configuration was confirmed by X-ray diffraction.


HO
O
HO
N
2
CDCl3, 300 MHz
acetone
MeOH
DCM
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

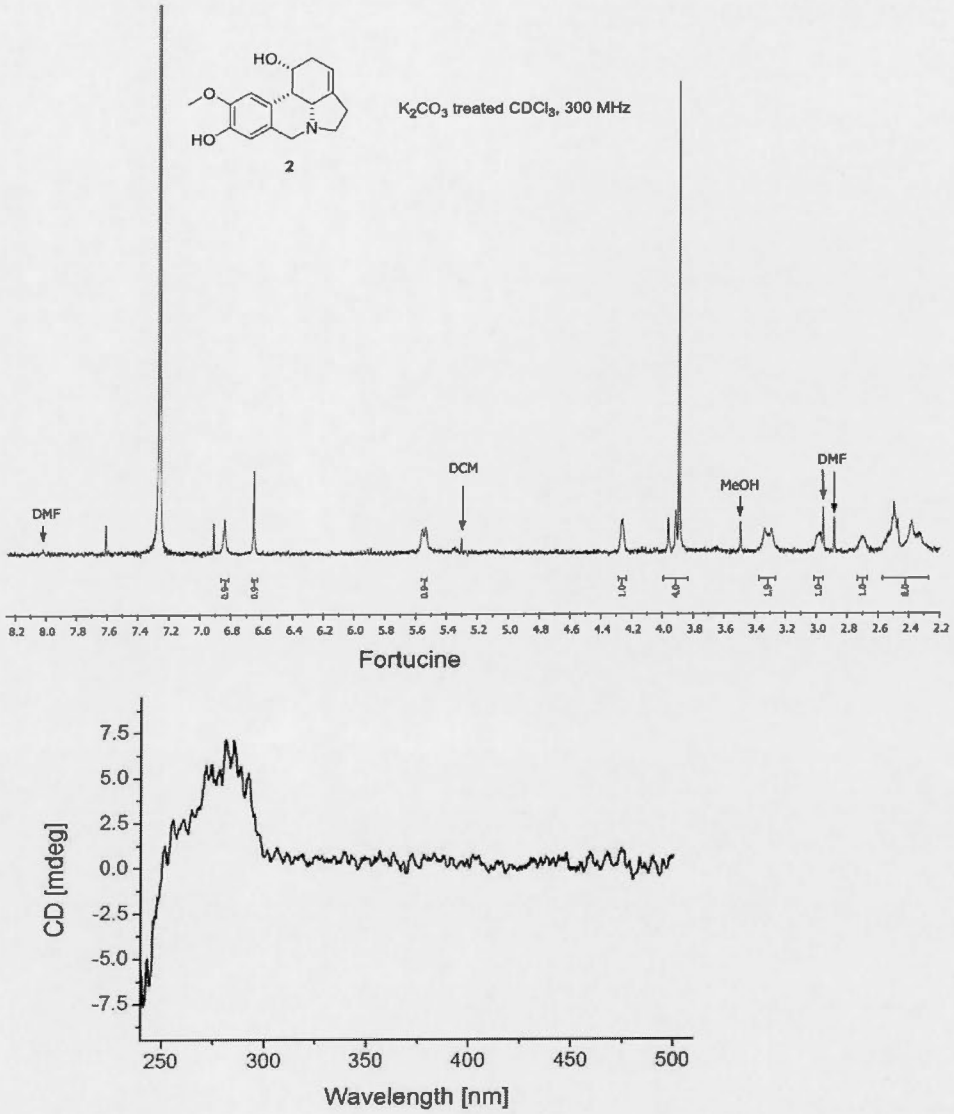
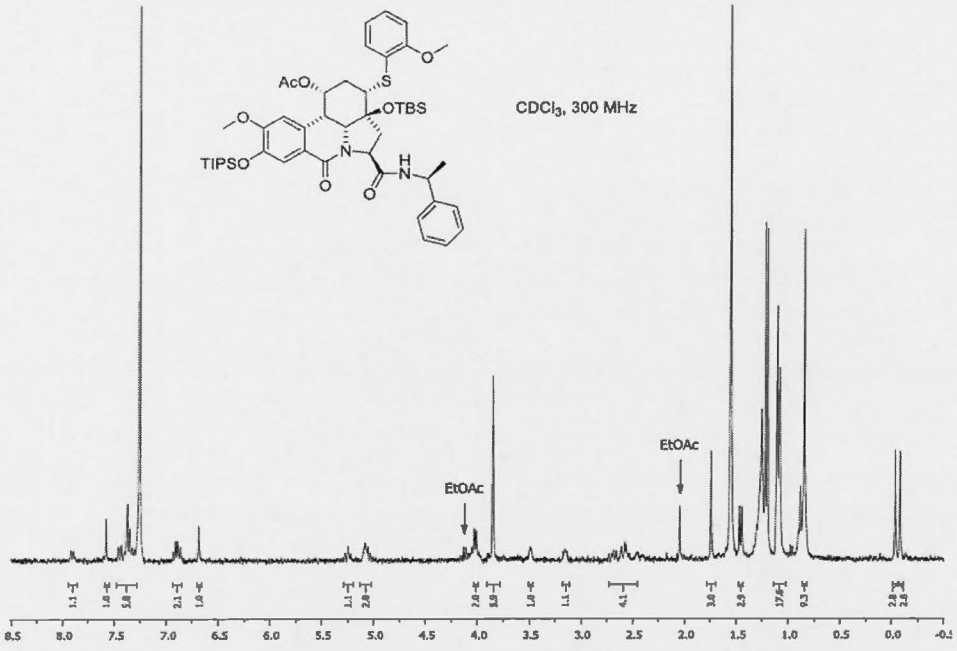


Figure 4: CD spectrum of our enantiopure fortucine sample (0.003 M in MeOH, $[\Theta]_{285} \approx +2000$, 10 scans), showing the opposite Cotton effects compared with reports on natural fortucine (for which $[\Theta]_{236} = +4000$, $[\Theta]_{282} = -2000$ (c $2.92 \cdot 10^{-4}$ M).


AcO
S
O
OTBS
TIPSO
N
H
N
O
O
CDCl3, 300 MHz
EtOAc
EtOAc
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

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