Approaching a robust and versatile organocatalytic olefination methodology

Bryan Doonan, B.Sc. (Hons.)

Under the supervision of Dr Christopher O'Brien

A thesis presented to Dublin City University

for the degree of Master of Science

School of Chemical Sciences

Dublin City University

January 2014

Declaration

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of Master of Science is entirely my own work, that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

Bryan Doonan **ID No.:** 57519257

Signed: …… Date: .....

Acknowledgements

I wish to thank the following people for their help and support during my research project:

My supervisor Dr Chris O'Brien for design of the project and continuous efforts to improve the overall process.

Emma and Florie for their help, guidance and contributions.

DCU and Enterprise Ireland for funding the research.

Andy - a tremendous friend and colleague. Always good for help in the lab, a good laugh and a good summary of a documentary.

The rest of the lads -Niall, Eoin, Steve, Killian and Paul - for their continuous efforts to improve their skills at beer pong.

The technical staff at DCU who are always on hand to help out.

My family - Mam and Dad for giving all of their support no matter what, and Jess for always being there no matter what part of the world she's in.

Louise and Walt - for their love and support every hour of every day.

Contents

Abbreviations

Ad	Adamantyl
Alk	Alkyl group
Ar	Aryl group
Boc	*tert*-Butoxycarbonyl
BocO	*tert*-Butylcarbonate
br	Broad
$CDCl_3$	Deuterated chloroform
CH_3CN	Acetonitrile
CM	Cross metathesis
CO_2	Carbon dioxide
conv.	Conversion
COSY	Correlation spectroscopy
CPME	Cyclopentyl methyl ether
CWR	Catalytic Wittig reaction (in phosphine)
d	Doublet
dd	Doublet of doublets
DIPEA	*N,N*-diisopropylethylamine
DMC	Dimethylcarbonate
dq	Doublet of quartets
dt	Doublet of triplets
δ	Delta (chemical shift in ppm)
E	Entgegen (opposite)
EDG	Electron-donating group

ee	Enantiomeric excess
equiv	Equivalents
EtOAc	Ethyl acetate
EWG	Electron-withdrawing group
HRMS	High resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
IMDA	Intramolecular Diels-Alder
J	Coupling constant (in hertz)
KHMDS	Potassium hexamethyldisilazide
$KMnO_4$	Potassium permanganate
KO*t*Bu	Potassium *tert*-butoxide
m	Multiplet
$[M]^+$	Mass of molecular ion
Mes	Mesityl
2-Me THF	2-Methyl tetrahydrofuran
mp	Melting point
NaHMDS	Sodium hexamethyldisilazide
NaO*t*Bu	Sodium *tert*-butoxide
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser effect spectroscopy
pK_a	Acid dissociation constant
PMA	Phosphomolybdic acid
PMHS	Polymethylhydrosiloxane
ppm	Parts per million

q	Quartet
qn	Quintet
RCM	Ring-closing metathesis
ROM	Ring-opening metathesis
RT	Room temperature
s	Singlet
SCOOPY	α-Substitution plus carbonyl olefination via β-oxido phosphonium ylides
T	Temperature
t	Time
t	Triplet
td	Triplet of doublets
Teoc	2-(Trimethylsilyl)ethyl carbonate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TS	Transition state
UV	Ultraviolet
Z	Zusammen (together)

Abstract

The carbon-carbon double bond (C=C) is one of the most valuable functionalities available to synthetic chemists. Capable of a vast number of chemical transformations, molecules containing a C=C bond (olefins) are highly utilised as intermediates to a variety of diverse structures. In an effort to develop a catalytic olefination protocol that surpasses current methodologies, our group recently developed a Catalytic Wittig Reaction (CWR) that employs an organophosphine as the active catalytic species. Although a significant development, the first-generation CWR suffers from several drawbacks: (i) poor substrate diversity, (ii) high reaction temperature, (iii) potentially arduous purification and iv) low *E/Z* selectivity. This thesis outlines the steps taken to overcome these issues. Employment of a *masked form of a strong base* proved critical in facilitating semi-stabilised and non-stabilised ylides. An alternative method investigated was the concept of *ylide-tuning*, where the phosphine structure was altered to facilitate easier ylide formation. This concept proved successful in using a mild base for semi-stabilised ylide formation. Development of a pseudo-catalytic *pulse olefination* technique enabled ketones to be used as substrates in the CWR. The new protocols were used in the preparation of 39 different compounds and were also shown to proceed efficiently on multigram scale. The next issue that was addressed was the siloxane byproduct removal. The polymeric silane polymethylhydrosiloxane (PMHS) was successfully incorporated into the CWR resulting in a *cheaper, greener process* with significantly easier purification. A total of 25 compounds were prepared using the protocols optimised for PMHS. Lastly, the properties of phosphine structure were examined to determine a possible structural modification which could be used to design a selective CWR catalyst. Varying the properties of the 1-substituent provided no significant change in *E/Z* ratio. Aided by literature evaluation, a phosphine was identified which was significantly more *E*-selective in the CWR for all three ylide classes. Based on the results obtained, structures were proposed of second-generation pre-catalysts which could potentially result in an *E*-selective catalytic olefination facilitating all ylide classes.

1 Introduction

1.1 Olefins: *Versatile Building Blocks and Functional Molecules*

Olefins (alkenes) are molecules which contain a carbon-carbon double bond. The reactivity of a C=C bond makes alkenes capable of a broad range of chemical transformations. For this reason they are considered important building blocks of many molecules. Figure 1 shows a selection of some functional groups which can be constructed from alkenes. This shows how complex molecules can be constructed from relatively simple starting materials *via* short chemical syntheses.

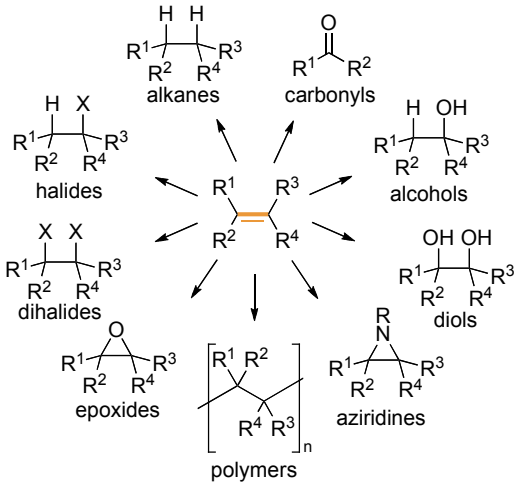
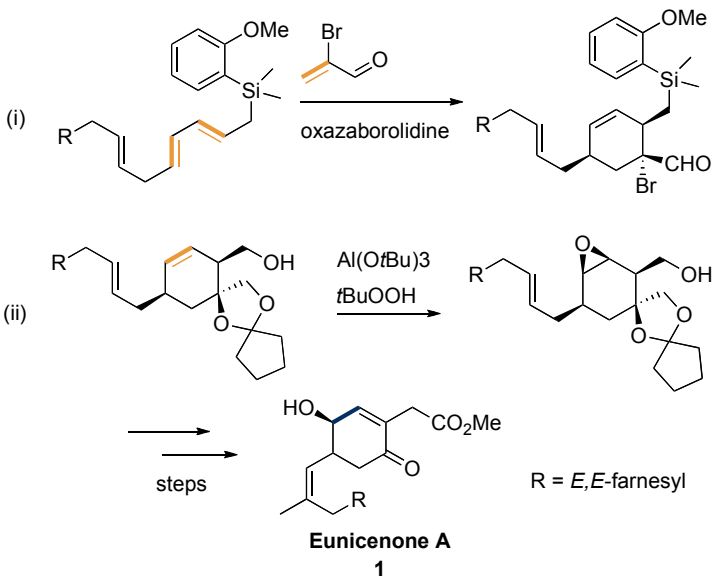


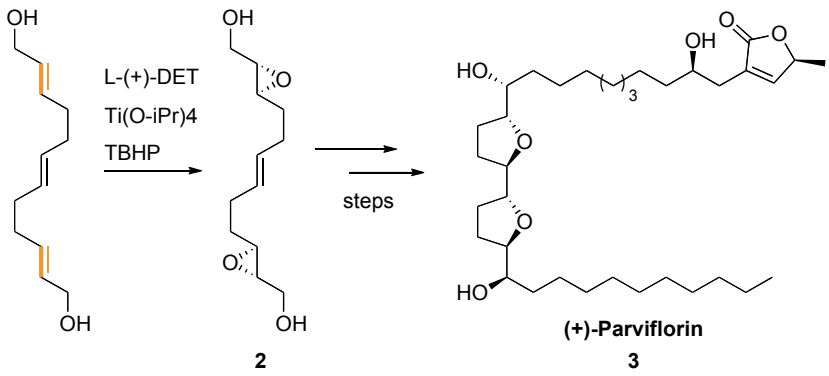
Figure 1: Some useful transformations of olefins

The difficulty involved in building a complicated molecule can sometimes be avoided if an alternate synthetic route *via* an alkene intermediate can be utilised. In the total synthesis of Eunicenone A (scheme 1, **1**), Corey *et al.* demonstrates the power of an alkene intermediate in two key steps.[1] Scheme 1 shows the Diels-Alder cycloaddition which not only constructed the 6-membered ring, but also formed 3 new chiral centres with 97% ee and endo:exo ratio of >98:2.



Scheme 1: Alkene intermediates in the total synthesis of eunicenone A

Pericyclic reactions of this nature are a very useful way to selectively form chiral centres without the need for transition metal catalysts or expensive chiral reagents. The newly formed double bond was later transformed into an epoxide enabling one of eunicenone A's two chiral centres to be constructed. Another example of selective epoxidation of an alkene was demonstrated in the synthesis of (+)-parviflorin (scheme 2, **3)**, a compound known to possess anti-tumor properties.[2]



Scheme 2: Alkene intermediates in the total synthesis of (+)-parviflorin

Using the Sharpless epoxidation method to form the diepoxide intermediate **2** in ~97% ee (99% ee after recrystallization) ensured that a selective synthesis of **3** could be carried out. AMF-26 (figure 2, **4**) has been recently identified by Ohashi, Yamori *et al.* as a potential anti-cancer agent, known to induce cell death by disruption of the Golgi apparatus.[3] The

first total synthesis of **4** utilised an intramolecular Diels-Alder (IMDA) reaction as a key step to form the core structure.[4] The IMDA precursor was prepared by Wittig reaction, and the subsequent IMDA formed four of AMF-26's seven chiral centres. An allylic phosphate fragment, constructed via a second Wittig reaction, was coupled to the core structure by a Horner-Wadsworth-Emmons (HWE) olefination to form the diene moiety.

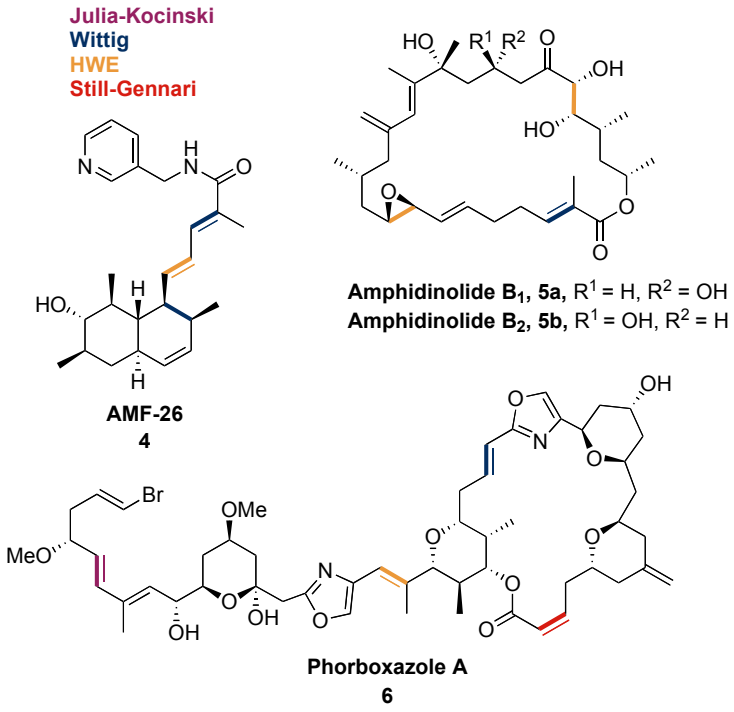


Figure 2: Bonds formed by classic olefination reactions

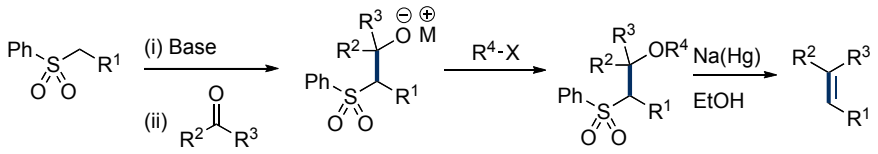
In 2008 Carter and co-workers disclosed the total synthesis of Amphidinolides B_1 and B_2 (figure 2, **5a** and **5b**), two macrolides which are highly cytotoxic to cancer cells.[5] An alkene fragment prepared by a HWE reaction was used to introduce a chiral diol portion. A Wittig reaction was utilised to form the tri-substituted alkene moiety. Upon oxidation of the alcohol to form the aldehyde functionality, spontaneous HWE olefination occurred. Driven to completion by addition of DIPEA, this one-pot process formed the closed-ring macrocycle. In 2003 Williams *et al.* demonstrated a total synthesis of the macrolide Phorboxazole A (figure 2, **6**) which incorporated four olefiation steps.[6] The first olefination was a HWE reaction of an aldehyde with a phosphonate to couple two key fragments in 88% yield and >95:5 *E/Z* selectivity. Attachment of the next major fragment was facilitated by forming a phosphonium salt using PBu_3 which subsequently reacted with the aldehyde substituent in a Wittig reaction. Again the olefination process was highly efficient in joining the fragments, proceeding in almost quantitative yield with the *E/Z* ratio >95:5 as before.

Formation of the diene portion of **6** was achieved using the Julia-Kocienski olefination conditions. The choice of heteroaromatic sulfone used for this process was shown to significantly impact the selectivity. Use of an *N*-phenyltetrazole sulphone primarily produced the *Z*-alkene. By switching the functionality to a benzothiazole sulphone the desired *E* double bond was constructed in 98% yield, *E/Z* >95:5. Lastly, a HWE type reaction at the end of the synthesis resulted in formation of the macrocycle of **6**, subsequent deprotection and hydrolysis steps produced the target molecule. For this olefination the *Z*-isomer was required, so Williams *et al.* utilised conditions similar to those of Still and Gennari.[7] A potassium base (K_2CO_3) and 18-crown-6 were used to produce the double bond in quantitative yield. On this occasion the *Z*-isomer was favoured (*Z:E* 4:1) and chromatographic purification post-deprotection allowed separation of the two diastereomers. This total synthesis clearly highlights the importance of olefination processes. The coupling of major fragments of **6** and formation of essential carbon-carbon double bonds was achieved efficiently and with controlled *E/Z* selectivity. Importantly, the olefinations all proceeded smoothly without adverse effects on the stereocentres of **6**, of which there are many. These few examples are minute compared to the wide range of alkene compounds which encompass an important biological function. If such compounds are to be made available to treat patients it is vital that suitable cost-effective synthetic methods are employed to make them. For this reason a significant amount of research continues to go into the development of olefination protocols.

1.2 Olefin Synthesis

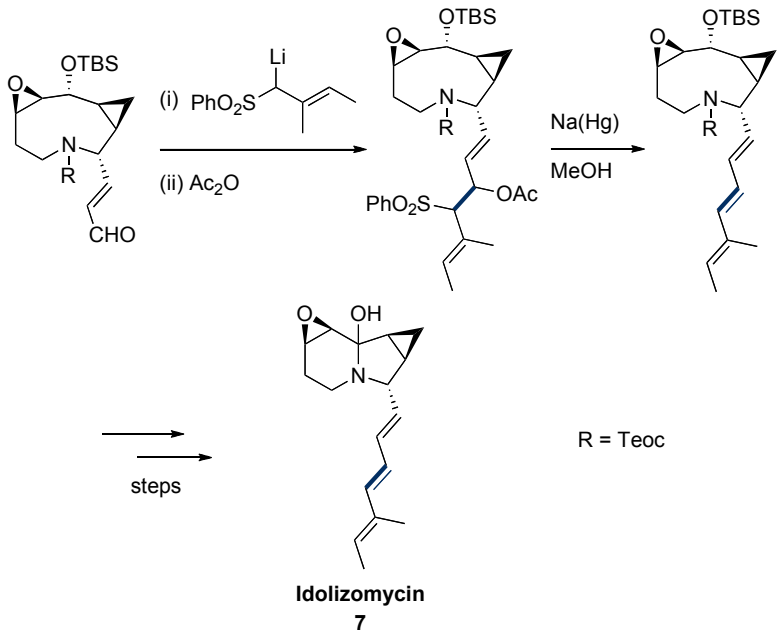
1.2.1 Julia-Lythgoe/Julia-Kocienski Olefination[8]

In 1973 Julia and Paris demonstrated a method for selective synthesis of alkenes.[8b] A study by Kocienski and Lythgoe explored the scope of the process and gave rise to what is known as the Julia-Lythgoe olefination.[9]



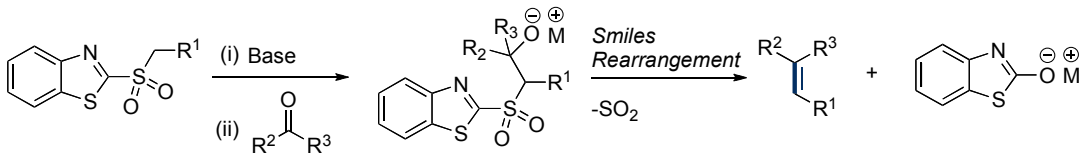
Scheme 3: Julia-Lythgoe olefination

The Julia-Lythgoe olefination involves reacting a phenyl sulphone with an aldehyde or ketone to form an alkene (scheme 3). A strong base is generally required for the initial step which is the formation of the sulphonium anion. Reaction of the sulphonium anion with the carbonyl forms an alkoxide intermediate. Subsequent reduction using sodium amalgam results in formation of the alkene. Free rotation of the carbon-carbon single bond during the reduction step leads to formation of the more thermodynamically stable alkene, hence the high *E*-selectivity of the reaction. This selective process was used in 1993 in the first total synthesis of the antibiotic indolizomycin (scheme 4, **7**), where Danishefsky and co-workers described the compound as "one of the most unstable products that has ever been obtained by total synthesis".[10]



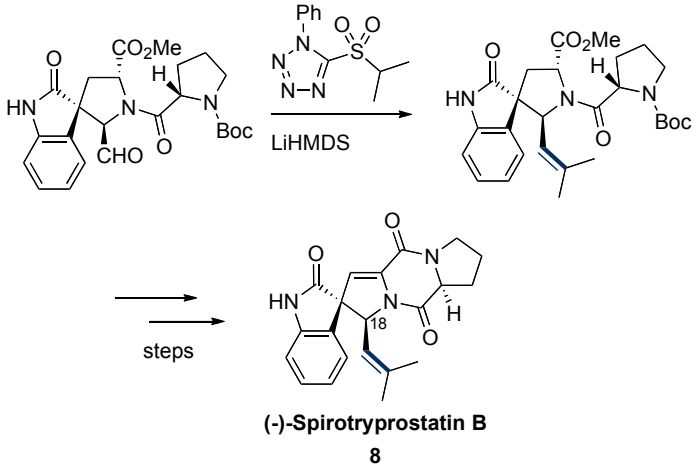
Scheme 4: Julia-Lythgoe olefination used in the synthesis of Indolizomycin

Construction of the trienyl side chain was a key part of the total synthesis. Reaction of a phenyl sulphone with the aldehyde functionality of the core molecule structure and subsequent reduction with sodium amalgam formed the new carbon-carbon double bond stereoselectively. This allowed the (*E,E,E*)-triene portion of Indolizomycin to be constructed with relative ease. The modified Julia olefination is similar to the traditional Julia-Lythgoe olefination but employs heteroaromatic sulphones instead of the phenyl-substituted type (scheme 5).[11] Deprotonation with a base and reaction with the carbonyl forms the alkoxide intermediate as before.



Scheme 5: Modified Julia olefination

On this occasion, however, the alkoxide undergoes a rapid Smiles rearrangement to a sulphonate. Loss of sulphur dioxide and a metallo-benzothiazolone spontaneously forms the alkene. This offers the advantage of a one-pot synthesis and removes the need to use sodium amalgam or an alternative reducing agent. However, the process does not undergo a free-radical reduction as in the traditional Julia-Lythgoe olefination so there is no stabilisation to form the favoured *E*-alkene. This ensures that steric interactions of the substituents are no longer useful in imparting selective control of the alkene product. Polarity of the reaction environment has been shown to impact the selectivity, meaning that experimenting with alternate solvents can offer stereo-control. Choice of metal counterion can also affect the outcome. A key step in the synthesis of (-)-spirotryprostatin B **8** was the formation of the tri-substituted C=C double bond (scheme 6).[12]

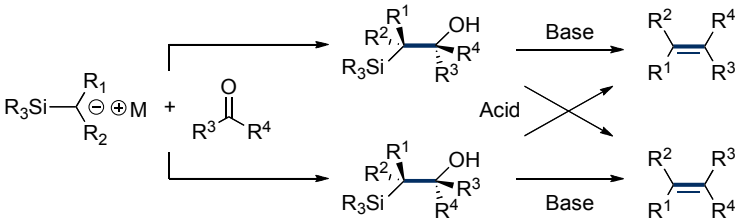


Scheme 6: Julia-Kocienski olefination used in the total synthesis of (-)-spirotryprostatin

Applying the traditional Julia-Lythgoe methods resulted in just 11% yield of the desired product, and also caused inversion of the chiral centre at C-18 (scheme 6). This issue was overcomeby employing the Kociensky-modified conditions. The double bond was formed without affecting the chirality at C-18 and the yield was significantly increased to 78%.

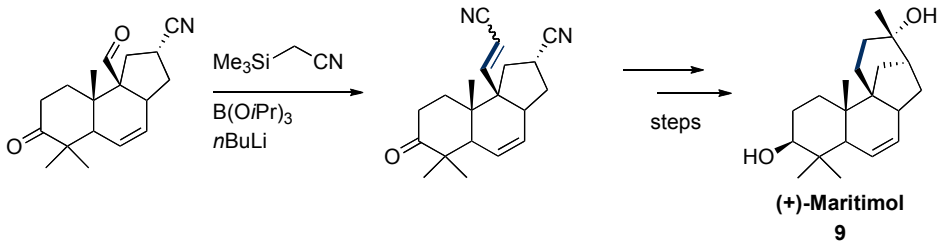
1.2.2 Peterson Reaction[13]

In 1968 D.J. Peterson devised a method of alkene synthesis which possessed interesting selectivity options.[13b] The process involves reacting an α-silyl carbanion with a carbonyl compound to produce a β-hydroxysilane. An elimination step results in the formation of the alkene (scheme 7). The power of this reaction is the ability to form either the *E*- or *Z*-alkene from the same β-hydroxysilane by choosing either acidic or basic conditions for the elimination step.



Scheme 7: Peterson olefination

This control offered by the Peterson reaction is overshadowed by the initial step, which inevitably produces both diastereomers of the β-hydroxysilane. Immediate elimination at this stage would result in formation of both the *E*- and *Z*-alkene, regardless of the conditions used. It is therefore often necessary to separate the two β-hydroxysilane diastereomers prior to the elimination step. Deslongchamps and co-workers made use of the Peterson olefination to construct the D-ring of (+)-maritimol (scheme 8, **9**).[14]



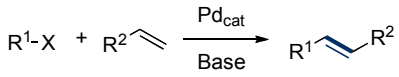
Scheme 8: Peterson reaction used in the synthesis of (+)-maritimol

The double bond was constructed without affecting the chirality of the α-carbon. The reaction proceeded in a somewhat selective manner, resulting in a *Z:E* ratio of 6:1. In this

case separation of the two diastereomers was performed with relative ease by flash column chromatography. As the next step required reduction of this new double bond to produce an alkyl nitrile, this separation was necessary so that appropriate reduction conditions could be applied to each diastereomer.

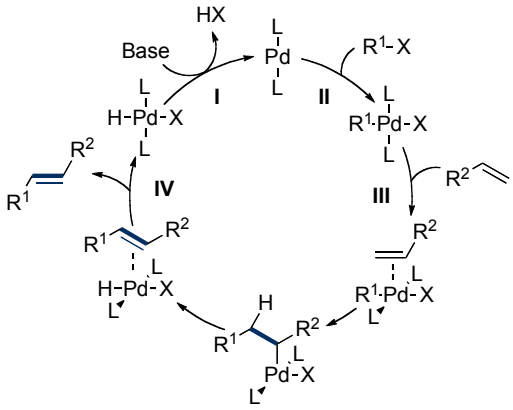
1.2.3 Heck Reaction[15]

In 1969 Richard Heck discovered a method of alkene synthesis by reacting an aryl palladium acetate compound with an alkene, a development which led to the award of the Nobel Prize in Chemistry to Heck, Negishi and Suzuki in 2010.[15b] New alkenes were produced by replacing a substituent of the reacting alkene with the aryl group.



Scheme 9: Heck reaction

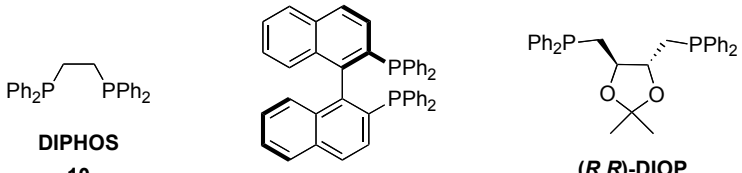
The aryl-palladium complex was formed in situ from an aryl-mercury compound and palladium acetate. The original substitution reaction was a stoichiometric process. This work was soon improved separately by Heck and Nolley[16] and Mizoroki *et al.*[17] resulting in an olefination process using a palladium catalyst (Heck reaction, scheme 9). This catalytic process had the added advantage of replacing the mercury compounds with simple aryl/vinyl halides. Although published later than Mizoroki's work, the work by Heck was important in showing that milder reaction conditions could be used. The Heck conditions used an amine base, no solvent and proceeded at a lower temperature than Mizoroki's process. Also, fewer equivalents of the reacting alkene and base were required.



Scheme 10: Mechanism of the Heck reaction

The proposed reaction mechanism consists of four key steps; (I) reductive elimination to form the reactive Pd(0) species, (II) oxidative addition of the aryl halide to the Pd, (III) insertion of the alkene into the Ar-Pd bond and (IV) β-hydride elimination to produce the alkene product (scheme 10). A base is required to activate the palladium from Pd(II) to a reactive Pd(0) state. Typically a secondary or tertiary amine is used, alternatively an acetate base can be used (eg. KOAc used by Mizoroki). In modern Heck reactions it has been shown that inorganic bases such as Na_2CO_3 and K_2CO_3 are more appropriate choices as it is believed that amines coordinate to the palladium *via* the nitrogen lone pair.[18] This creates a steric block at the metal centre which interferes with subsequent reaction steps. In the Pd(0) state the metal is more reactive and it spontaneously inserts into the carbon-halide bond of the aryl halide, oxidising the palladium back to the Pd(II) state. The choice of halide significantly impacts the rate at which this step occurs, or if it can occur at all. Aryl iodides are the most reactive owing to having the lowest bond strength: Ar-I < Ar-Br < Ar-Cl.[19] Originally Heck and others used aryl iodides. Modification of the catalyst was necessary to facilitate the Heck reaction of aryl bromides and chlorides. The reacting alkene then coordinates to the palladium *via* a π-electron donation. The aryl group forms a covalent bond with the alkene. This step can be termed a migration (of the aryl group) or an insertion (of the alkene into the R-Pd bond). Rotation to the *trans* orientation to minimise steric clashing of the R substituents ensures a more stable transition state. Then a transfer of a hydride anion (H^-) to the Pd centre occurs along with the formation of the new carbon-carbon double bond (β-hydride elimination). Of course, for this step to occur it is essential for the alkene reactant to contain β-hydrogens. Generally the Heck reaction works best with mono-substituted alkenes as substrates. The other limitation imposed by the β-hydride elimination process is that the scope of halide substrates is also narrowed. Soon after the reactions first reported by Heck and Mizoroki, the use of different ligands on the Pd was explored. In 1974 Dieck and Heck examined a range of phosphines, phosphites, arsines and amines as ligands and discovered that triphenylphosphine PPh_3 resulted in significantly improved Heck olefinations.[20] The new catalyst was produced in situ by reacting $Pd(OAc)_2$ with PPh_3. Using phosphine ligands on the Pd allowed the Heck reaction of aryl bromides to be carried out, while the rates of previously conducted reactions of aryl iodides were increased with the new catalyst. Importantly, the presence of the phosphine ligands also resulted in a certain degree of stereoselectivity. Early Heck reactions offered no selectivity, producing equal amounts of *E* and *Z* alkene product. The $Pd(PPh_3)_2$-catalysed process proceeded with a preference for formation of the *E*-alkene. This was a significant discovery, and immediate work went into exploring the use different phosphines as ligands. In 1978 Ziegler and Heck showed that aryl iodides and bromides containing electron-donating

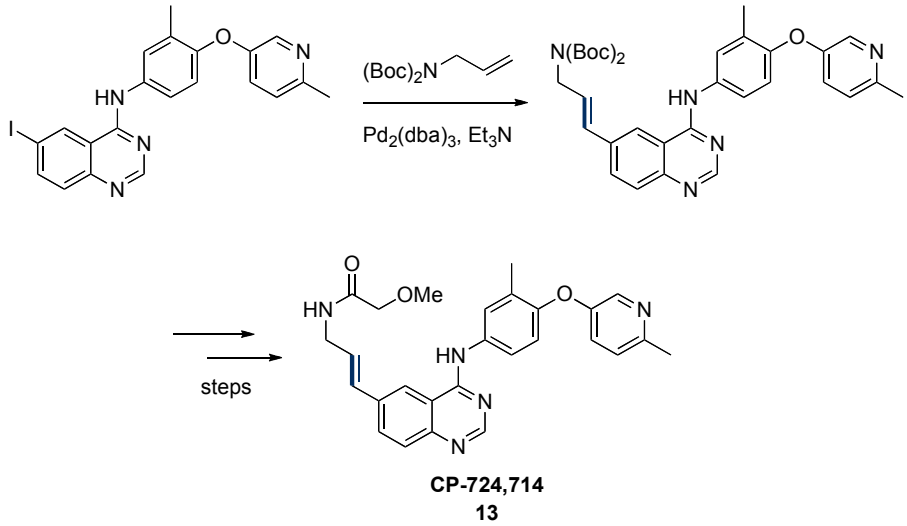
substituents could undergo the Heck olefination by replacing PPh_3 with P(*o*-tolyl)$_3$.[21] Iodo- and bromo-phenols and amines were adequate substrates, and even 2-amino-5-hydroxyiodobenzene reacted with styrene in 50% yield. This study not only showed that electron-rich bromides could be used, but importantly demonstrated that the Heck reaction could tolerate reactive functional groups without adverse side reactions. This is a useful property of a synthetic process, especially if is to be used in a multi-step synthesis. Later work by Hii and co-workers showed that there is a direct correlation between the Hammett paramaters of ligand substituents with the relative reaction rate.[22] The Heck reaction has been used to produce chiral materials enantioselectively.



DIPHOS **10** | **(*R*)-BINAP** **11** | **(*R,R*)-DIOP** **12**

Figure 3: Chiral ligands used in the first asymmetric Heck reactions

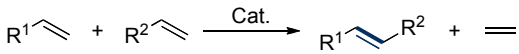
Chiral bidentate phosphine ligands were used successfully to catalyse epoxidations, hydrogenations and some cross-coupling reactions. It was therefore logical to employ them in the Heck process. The first asymmetric Heck-type reactions were performed independently by Shibasaki and co-workers[23] and Overman and co-workers[24] in 1989. A *cis*-decalin derivative was synthesised by Shibaski and co-workers *via* intramolecular Heck reaction using the bidentate ligand DIPHOS (figure 3, **10**). Optimisation led to an asymmetric synthesis of several cis-decalin derivatives using (*R*)-BINAP **11** as the ligand and Ag_2CO_3 as an inorganic base. Overman's group found that another chiral bis-phosphine ligand (*R,R*)-DIOP **12** in conjunction with triethylamine were efficient reagents for intramolecular Heck reactions. Although enantioselectivity was far from ideal in both cases (36-46% ee for Shibaski, 45% ee for Overman) this work marked the first successful use of the Heck reaction to selectively produce a chiral compound. A review by Dounay and Overman illustrates several examples asymmetric Heck couplings used in natural product synthesis.[25] In 2005 a team from Pfizer compared the use of the Sonagashira, Suziki and Heck reactions in their ~100 kg synthesis of anti-cancer compound CP-724,714 (scheme 11, **13**).[26] The Heck reaction proved far superior in overall reaction yield. Another important characteristic was that a low catalyst loading (2 mol %) was sufficient, resulting in low quantities of Pd waste post-reaction.



Scheme 11: Heck coupling used in the synthesis of CP-724,714

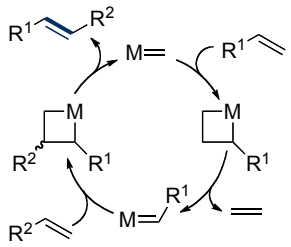
1.2.4 Olefin Metathesis[27]

Olefin metathesis is a catalytic olefination process which utilises two alkenes as starting materials.



Scheme 12: Olefin metathesis

Given its name in 1967 by Calderon *et al.*,[28] olefin metathesis has been used industrially since the 1960s, notably by Shell Higher Olefin Process using a nickel-phosphine based catalyst[29] and the Phillips Triolefin Process using molybdenum or tungsten oxide on silica.[30] In 1971 a mechanism was proposed by Chauvin and Herisson (scheme 13).[31] A metal-carbene catalyst reacts with an alkene via a 2+2 cycloaddition process to form a cyclic metallocyclobutane intermediate. Retro 2+2 cycloaddition of this species forms a new metal-carbene, which reacts with the other alkene substrate in similar fashion. This results in formation of new olefins by swapping the substituents of the olefin substrates.



Scheme 13: Chauvin's mechanism of olefin metathesis

This paved the way for the development of well-defined metathesis catalysts. Early research of olefin metathesis explored the use of tungsten (Grubbs, Katz and Schrock)[32][33][34] or titanium (Tebbe)[35] based catalysts. Modern metathesis utilises catalyst structures centred on molybdenum (Schrock, **14**)[36] and ruthenium (Grubbs and Hovedya, **15-17**, figure 4).[37][38][39] The ruthenium-based compounds are easier to handle due to their greater stability to oxygen and moisture. The applications of metathesis are many, with several variations on the traditional cross-metathesis enabling a wide variety of new structures to be constructed (scheme 14). In 2005 Chauvin, Grubbs and Schrock shared the Nobel Prize in Chemistry for their contributions to the development of olefin metathesis.

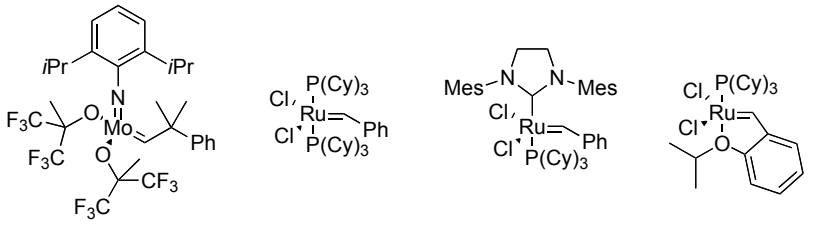
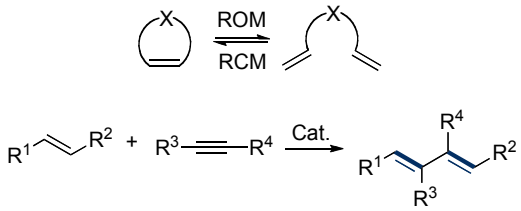


Figure 4: Conventional metathesis catalysts

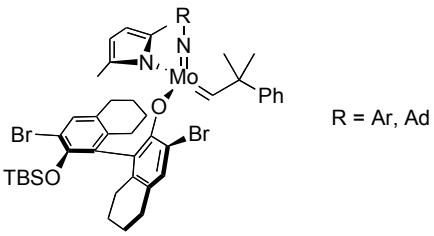
Recently extensive efforts have been made in enhancing the selectivity. In 2011 Schrock, Hoveyda and co-workers demonstrated an efficient *Z*-selective CM process.[40] High *Z*-selectivity was achieved by using stereogenic-at-Mo complexes which bear a bulky aryloxide ligand which is free to rotate about the Mo-O bond (figure 5, **18**). Initially, yields of *Z*-olefin were low and were improved by using 5 equivalents of the enol ether substrate.



Scheme 14: Ring-opening, ring-closing and enyne metathesis

However, when an expensive enol ether is the starting material, using a large excess becomes impractical, as illustrated in the group's preparation of natural product **20**. Using an excess of the alkene **19** would increase yield and selectivity, but would produce a significant quantity of ethylene, which would have the opposite effect. This issue was

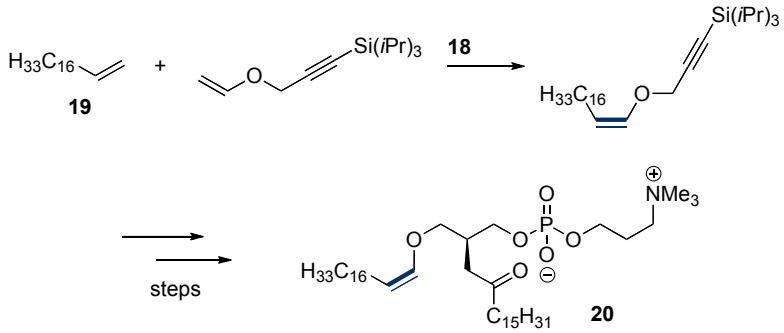
overcome by performing the reaction at reduced pressure to remove the volatile ethylene *in situ*.



18

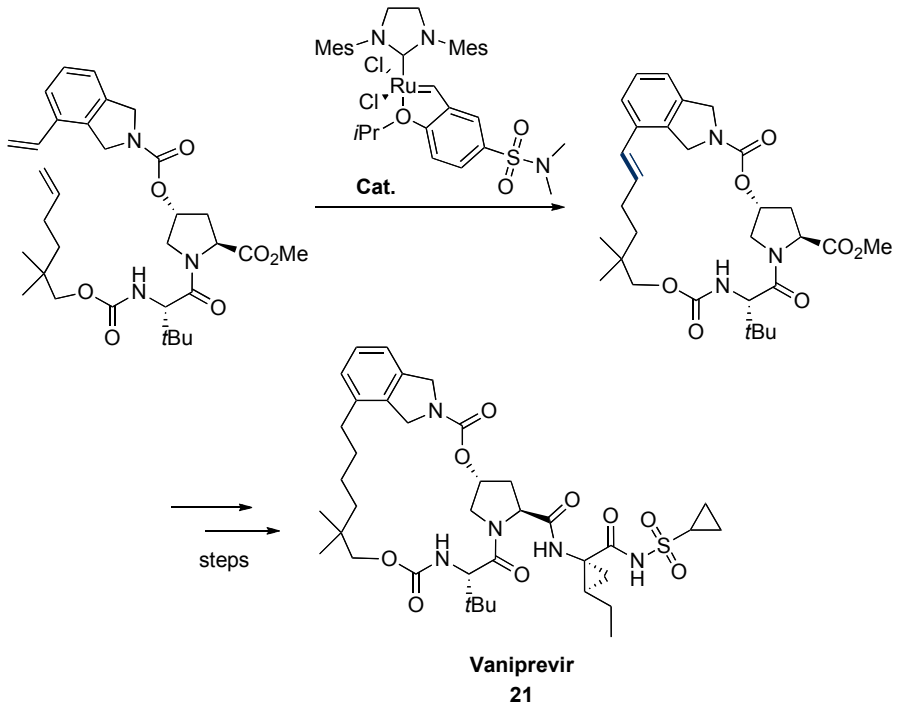
Figure 5: *Z*-Selective metathesis catalyst

The method was used to prepare a variety of *Z*-olefins in good yield, and was successfully applied to the synthesis of natural product **20**.



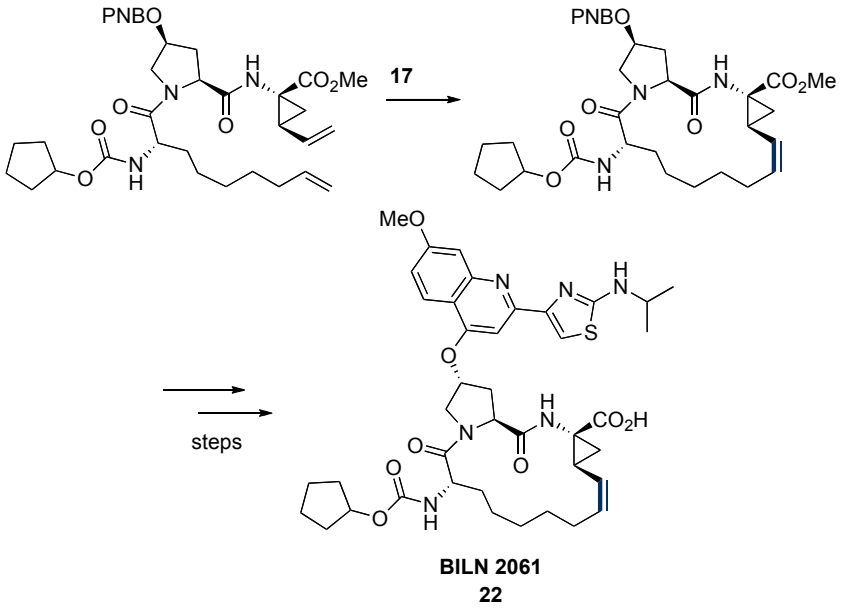
Scheme 15: *Z*-Selective metathesis reaction used in the synthesis of **20**

The use of chiral ligands in asymmetric metathesis is another phenomenon of current interest. Typical processes involve a ROM or RCM reaction of a symmetrical achiral alkene/diene which results in formation of a new chiral centre. A recent review by Blechert and Kress highlights the development and application of chiral Mo and Ru catalysts in asymmetric metathesis reactions.[41]



Scheme 16: RCM used in the synthesis of vaniprevir

A review by Nicolaou *et al.* highlights several examples of the use of olefin metathesis reactions in natural product synthesis.[42] Metathesis has also gained popularity in industrial preparations of pharmaceutical APIs such as HIV protease inhibitor vaniprevir (scheme 16, **21**)[43] and Hepatitis C protease inhibitor BILN 2061 (scheme 17, **22**).[44][45]

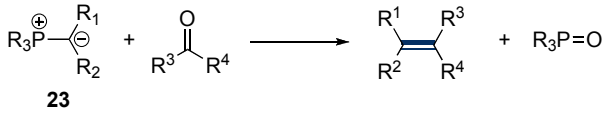


Scheme 17: RCM used in the synthesis of BILN 2061

1.3 Wittig and Related Reactions[46]

1.3.1 Witig Reaction

In 1953, some years prior to the discovery of the aforementioned olefination processes, G. Wittig and G. Geissler demonstrated an alkene synthesis by reaction of an aldehyde with a phosphonium ylide **23** (scheme 18).[47] This was the birth of the Wittig reaction, a milestone in the history of synthetic chemistry. In 1979 Wittig shared the Nobel Prize in Chemistry with H. C. Brown for their development of phosphorus and boron compounds respectively. Phosphonium ylides, were first made by Staudinger and Meyer early in the 20th century from a phosphonium salt.[48] Phosphonium salts can be readily produced by reacting a halide with triphenylphosphine. Deprotonation of the phosphonium salt with a base forms the ylide. These compounds can be viewed as the ylide form with a carbanion and phosphorus cation, or the ylene form with a carbon-phosphorus double bond. The nucleophilic carbanion readily reacts with a carbonyl (usually an aldehyde) and forms a 4-membered oxaphosphetane ring. The ring quickly collapses *via* a retro [2+2] cycloaddition to form the alkene and triphenylphosphine oxide.



Scheme 18: Wittig reaction

Ylides are divided into three categories based on the electronic properties of their substituents (figure 6). Stabilised ylides contain strongly electron-withdrawing substituents. Examples of such substituents include ester, cyano and EWG-substituted aromatic groups. The negative charge on the deprotonated carbon is stabilised by the substituent through resonance effects and to a lesser extent inductive effects.. This stabilisation makes ylides of this type relatively easy to form by deprotonation, i.e. the phosphonium salt is more acidic. Their stability also means that in some cases the ylide can be isolated, instead of being formed *in situ* during a reaction. However, the stabilisation renders the carbanion less nucleophilic making stabilised ylides less reactive.

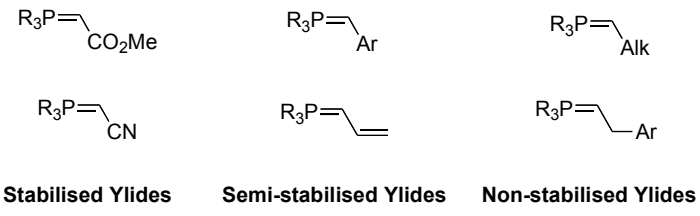
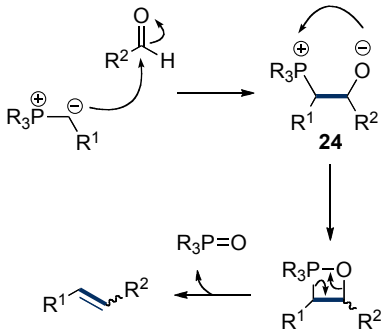


Figure 6: Classes of phosphonium ylides

Semi-stabilised ylides contain substituents which stabilise the carbanion by resonance effects. Typical substituents are benzylic or allylic groups. This makes them slightly more difficult to form than their stabilised counterparts, but more reactive. Non-stabilised contain no stabilising groups. Formation of ylides from alkyl phosphonium salts can be difficult and generally requires a strong base such as BuLi. The nature of the ylide has a significant impact on the stereoselectivity in the Wittig reaction. Stabilised ylides react to primarily produce the *E*-alkene, while reactions of non-stabilised ylides favour formation of the *Z*-alkene. To better understand why this is occurs it is important to gain a deeper insight into the reaction mechanism.

1.3.2 Mechanism and Selectivity

The first mechanism of the reaction was suggested by Wittig and Schöllkopf in 1954.[49] They proposed that the phosphonium ylide reacted with the aldehyde in a stepwise fashion, initially producing a betaine (scheme 19, **24**).



Scheme 19: Betaine mechanism of the Wittig reaction

The free rotation about the carbon-carbon single bond added some freedom to the intermediate. Through bond rotation the betaine could arrange itself to two different conformational structures and hence form two different oxaphosphetanes – one with the substituents (R^1 and R^2) on the same face of the ring (*cis*), and one where they are on opposite faces (*trans*). If the major intermediate is the oxaphosphetane with the substituents on the same face, the major product will be the *Z*-alkene, and likewise for favoured *E*-alkene formation. Betaine intermediates were never successfully characterised so their existence could only be proposed without providing direct evidence. In 1988 Vedejs and Marth set out to determine an alternate reaction mechanism which accounted for the selectivity based on different ylide types.[50][51]

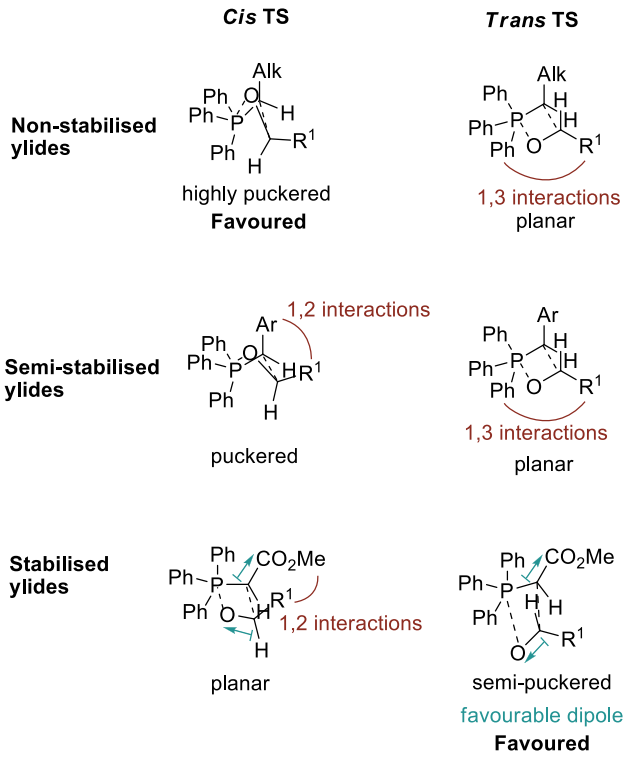
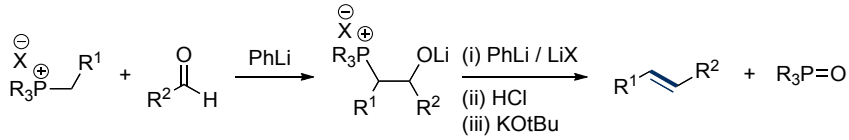


Figure 7: Harvey-Aggarwal model of Wittig transition states

The proposed mechanism suggests that the oxaphosphetane ring is formed in a one-step (concerted) process. This mechanism is kinetically controlled (as opposed to thermodynamic control) which agrees with *Z*-selective Wittig reactions. The *E/Z* selectivity in this case would be primarily influenced by the relative stabilities of the transition states leading to the ring formation. Vedejs stated that the fact that numerous ylides with different properties can undergo this reaction makes it impossible to suggest one transition state. The steric effects of ylide substituents significantly determine whether a planar or puckered transition state was preferred. Later computational studies by Harvey, Aggarwal and co-workers used density functional theory (DFT) calculations to support this theory.[52] The computational model also showed that electronic properties of the substituents also played a major role in selectivity for reactions of stabilised ylides. The electron-withdrawing properties of a stabilised ylide substituent create a strong dipole moment. This, coupled with the avoidance of 1,2 steric interactions, ensures that a puckered transition state is preferred for stabilised ylides, but with a smaller pucker angle than that of non-stabilised ylides. Wittig reactions of these ylides therefore favour formation of the *E*-alkene. A recent review by Gilheany and Byrne provides a thorough evaluation of several proposed mechanisms of the Wittig reaction.[53]

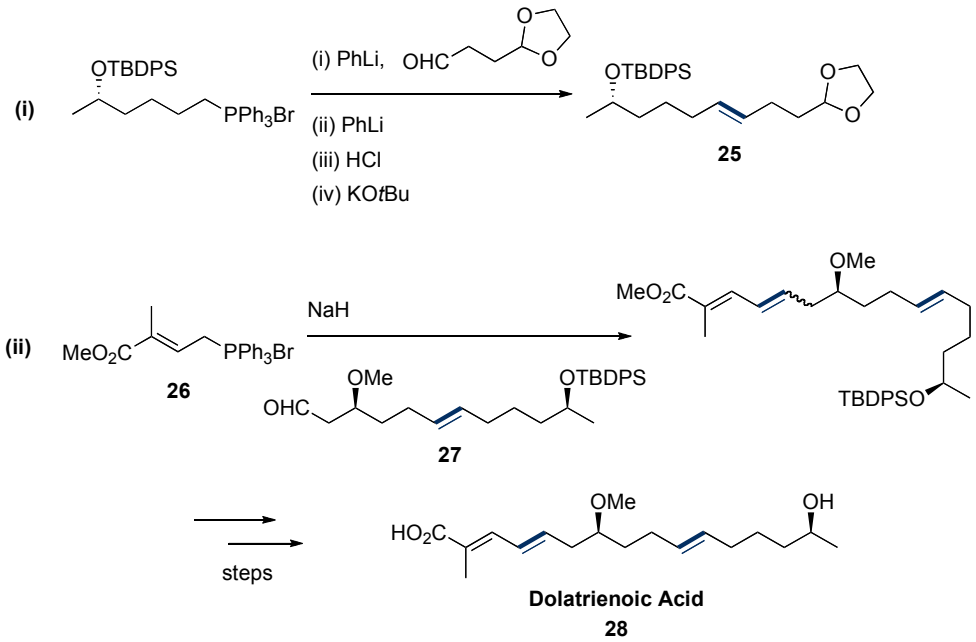
1.3.3 Schlosser Modification

In 1966 Schlosser and Christmann modified the Wittig reaction to selectively produce *E*-alkenes from non-stabilised ylides.[54] Whether the true mechanism of the Wittig reaction occurs via the betaine route or direct oxaphosphetane formation, both proposed pathways result in formation of the oxaphosphetane intermediate. Schlosser and Christmann decided to adapt this step to a reversible process (scheme 20).



Scheme 20: Schlosser-modified Wittig reaction

The presence of a lithium halide disconnects the phosphorus-oxygen bond to form a relatively stable lithio-betaine. Further deprotonation of the betaine with a lithium base (eg. PhLi) forms a carbanion. Free rotation of the carbon-carbon bond enables this structure to equilibrate to form the most stable *trans* conformation. Protonation with an acid such as HCl or an alcohol such as *t*BuOH re-forms the lithio-betaine.



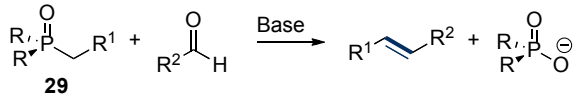
Scheme 21: (i) Schlosser and (ii) Wittig reactions used in the synthesis of dolatrienoic acid

The lithium halide is then removed using NaO*t*Bu or KO*t*Bu so that the betaine is no longer stabilised by the lithium cation. The oxaphosphetane reforms and subsequently collapses to

predominantly produce the *E*-alkene. By making the intermediate formation step a reversible process, more equilibration and stabilisation is allowed to occur, and thus the more stable product is produced. The protonation step leads to the *trans*-betaine, which later forms a di-substituted alkene. However, by using various electrophiles instead of protons, the Schlosser-modified Wittig reaction can be used to form tri-substituted alkenes. This was demonstrated by Schlosser *et al.* in 1971, a process which he termed SCOOPY (α-Substitution plus Carbonyl Olefination via β-Oxido Phosphorus Ylides).[55] A more modern study by Hodgson and Arif shows that tri-substitued *E*-bromo and iodoalkenes can be selectively produced by SCOOPY reactions.[56] In this case the halide is *trans* to the R group of the aldehyde. This demonstrates the power of the Schlosser modified reaction, whereby a carbon-carbon double bond and a carbon-halide bond are selectively formed in the one process. The nature of the R substituent significantly influenced the selectivity. When R = CH_3 the reaction produced the alkene with an *E/Z* ratio of <1:99, but as the steric bulk of the R substituent was increased, the *E*-selectivity increased also. This highlights the importance of having a range of olefination conditions available, as different methods will produce different results depending on the substrates. An example is observed in the total synthesis of dolatrienoic acid **28** by Pettit and Duffield (scheme 21).[57] The final step involved the coupling of aldehyde fragment **27** to phosphorus ylide **26** to form an *E*-double bond. This was successfully conducted using a classic Wittig reaction. However, when Wittig conditions were employed in an earlier step to form *E*-alkene fragment **25**, the *Z* form was preferred in a ratio of 1:9. By using the Schlosser modified conditions instead the fragment was predominantly formed as an *E*-alkene.

1.3.4 Horner-Wadsworth-Emmons Reaction

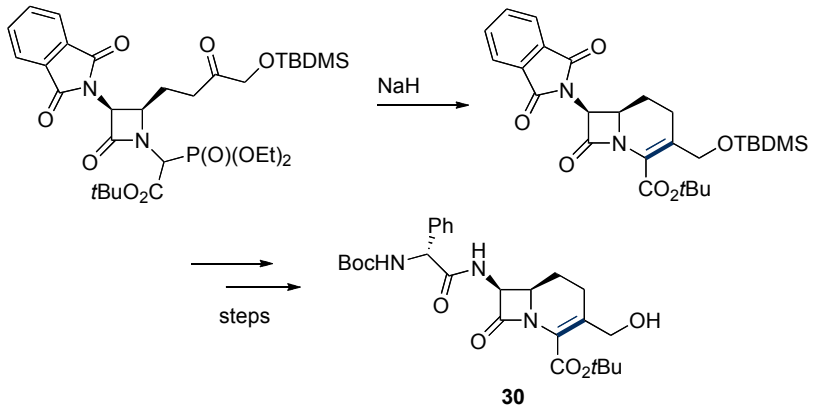
In 1958 Horner *et al.* discovered that alkenes could be synthesised using a Wittig-type reaction by replacing the phosphonium ylide with a phosphonate stabilised carbanion **29**.[58] Later in 1961 Wadsworth and Emmons, realising the potential of Horner's discovery, demonstrated the importance of the reaction.[59] This was the beginning of the Wittig-Horner or Horner-Wadsworth-Emmons reaction which has been a valuable alternative to the classical Wittig reaction since its discovery (HWE reaction, scheme 22).



29

Scheme 22: Horner-Wadsworth-Emmons reaction

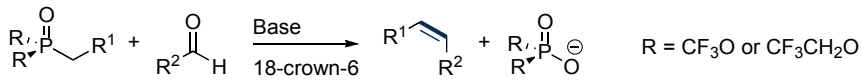
The phosphonate carbanions are generally easier and less expensive to prepare than corresponding ylides. A common method of phosphonate preparation is the Michaelis-Arbuzov reaction, which produces a phosphonate by heating a trialkyl phosphite in the presence of an alkyl halide.[60] The vast options of alkyl halides which are commercially available and inexpensive ensure that numerous phosphonates can be readily synthesised. As with ylide formation, the carbanion of the phosphonate is formed by deprotonation using a suitable base. The HWE was utilised by Miller and co-workers during the preparation of 3-(hydroxymethyl)carbacephalosporin **30**, with potential antibiotic properties (scheme 23).[61] An intramolecular HWE reaction of phosphonate and ketone functionalities formed the 6-membered ring portion of the cephalosporin core structure. The ketone reacted smoothly at room temperature in 2 hours to form one diastereomer of the product in 85% yield.



Scheme 23: Intramolecular HWE reaction used in the synthesis of **30**

The HWE olefination generally produces *E*-alkenes selectively. As the steric bulk of the R substituent of the phosphonate is increased, the preference for *E*-alkene formation also increases. The use of metal counter-ions has been shown to influence the HWE reaction. In one study HWE reactions were successfully carried out using LiCl and DBU as a base.[62] The chelation of the lithium cation to the oxygen lone electron pairs added stabilisation to the phosphonate carbanion, thus enabling the deprotonation to occur readily using a tertiary amine base. However, the selectivity of the reaction is also significantly influenced by chelation of metal cations, in particular lithium and magnesium. A study by Davies and co-workers showed that MeMgBr can be used similarly as a base for HWE reactions.[63] Their comparison with the LiCl/DBU conditions showed that both methods offered high *E/Z* selectivity (many >99:1, some >180:1 for MeMgBr), but the new conditions resulted in

greater conversion of reactant to product. In 1983 Still and Gennari devised a method for *Z*-selective olefination using phosphonate carbanions (scheme 24).[7]



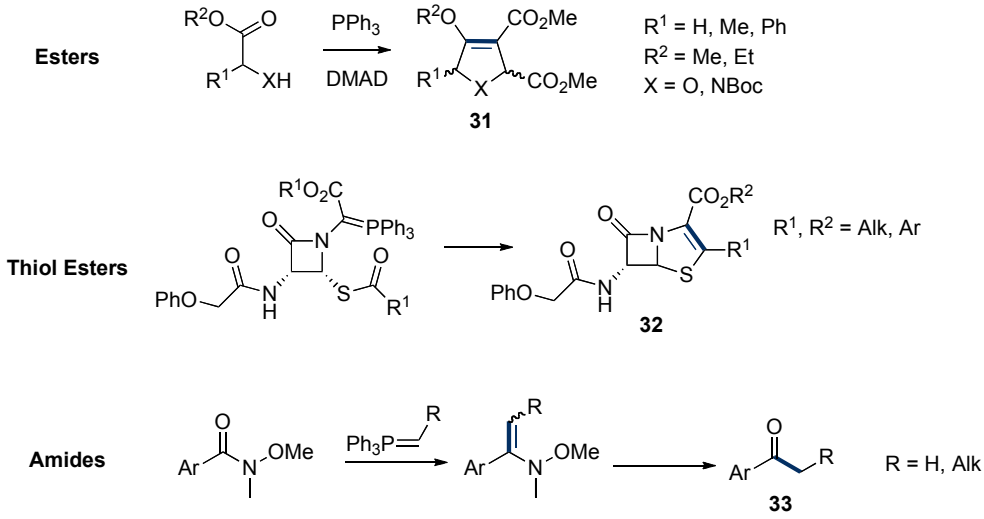
Scheme 24: Still-Gennari modified HWE reaction

Using trifluoroalkoxy substituents on the phosphorus, a strong base and 18-crown-6 the *Z*-alkene is formed predominantly. Electron-withdrawing groups are required to stabilise the phosphonate carbanion. A potassium base (e.g. KHMDS) is used in combination with 18-crown-6, as this crown ether is ideally suited in size to capture the potassium cations, with the subsequent anion acting as the base. This ensures that there is minimal chelation of the potassium cation to the oxygen atoms. It is believed that these conditions result in a quicker formation of the oxaphosphetane, which is irreversible. This kinetic control results in high *Z*-selectivity.

1.3.5 Non-Classical Wittig-Type Reactions

The wide substrate scope is an attractive property of the Wittig reaction. Phosphonium ylides can be easily prepared from phosphonium salts, which can be produced from halides. A substantial amount of structurally diverse halides are commercially available. A vast range of aldehydes and ketones are also either commercially available or can be readily synthesised, for example by oxidation of an alcohol. Although ketones are less reactive than aldehydes, they will undergo Wittig-type reactions. This can be aided by activating the ketone, i.e. making it more electrophilic and thus more reactive towards the carbanion of the ylide. Varying the temperature, base and solvent can also help affect the reactivity. Examples of reactions employing this methodology exist for carbonyl substrates other than aldehydes and ketones (scheme 25). Lin and co-workers demonstrated the preparation of substituted furans using an intramolecular Wittig reaction of esters.[64] Numerous tetra-substituted furans of type **31** were prepared in good yield. P.J. Murphy and co-workers, who also synthesised substituted furans using esters,[65] demonstrated the use of lactones as Wittig substrates.[66] Various substituted lactone substrates were shown to form bicyclic dihydrofurans in high yield. In 1978 Woodward and co-workers used the intramolecular Wittig reaction of thiol esters to synthesise a range of penems (scheme 25, **32**), a form of β-lactam antibiotics.[67] As expected, methyl ketones (R = CH_3) reacted smoothly under mild conditions (10 h, 70°C) while bulkier alkyl substituents were far less compliant with the isopropyl ketone (R = *i*Pr) only giving a 6% yield after 8 days (80-100°C). Strongly electron-withdrawing substituents assisted in activating the ketone to make it more

electrophilic, with R = *p*-nitrobenzyl producing the desired penem in 90% yield (17 h, 55°C).



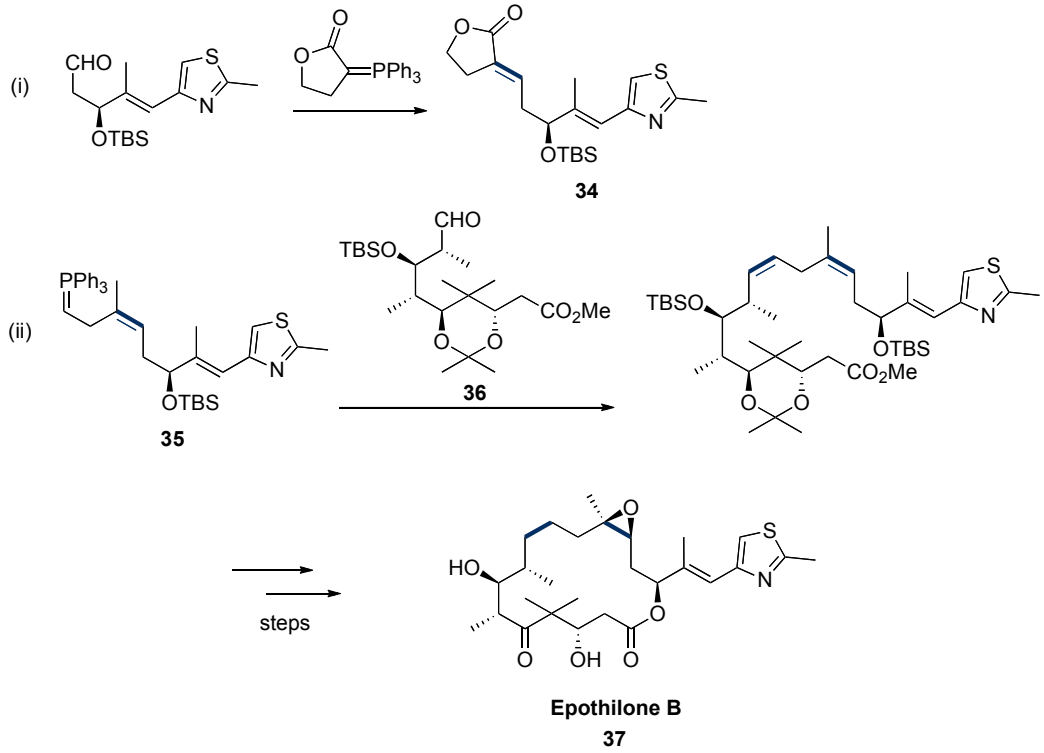
Scheme 25: Some examples of non-classical Wittig reactions

Amides are another subclass of compound which is part of the carbonyl group. In 1981 Weinreb and Nahm devised a method of ketone production which involved formation of an amide (called a Weinreb amide) from an acid chloride.[68] The Weinreb amide would then react with a Grignard reagent or organolithium compound to produce a ketone. Alternatively the amide could be reduced with $LiAlH_4$ to produce an aldehyde. An interesting Wittig reaction of amides was performed by J.A. Murphy *et al.* for the preparation of ketones (scheme 25, **33**) *via* Weinreb amides.[69] Instead of using a strong reducing agent or Grignard, the amide was subjected to a Wittig reaction to convert it to an alkene. Mild hydrolysis of the alkene would then form the ketone. Good yields were obtained for various substituted amides and the new conditions were far more tolerable than those of the conventional Weinreb process.

1.3.6 Synthetic Applications

It is important to show the application of the Wittig and related reactions in organic synthesis to demonstrate their importance. This section will highlight some examples of total synthesis and industrial process development projects where these reactions proved essential to prepare the desired compound. The epothilones are a class of compounds which have received much attention due to their anti-tumour properties. They are thought to function similar to the highly popular paclitaxel (Taxol®) by stabilising the microtubules of cells during mitosis and thus initiating apoptosis (programmed cell death).[70] In 2008 Keck

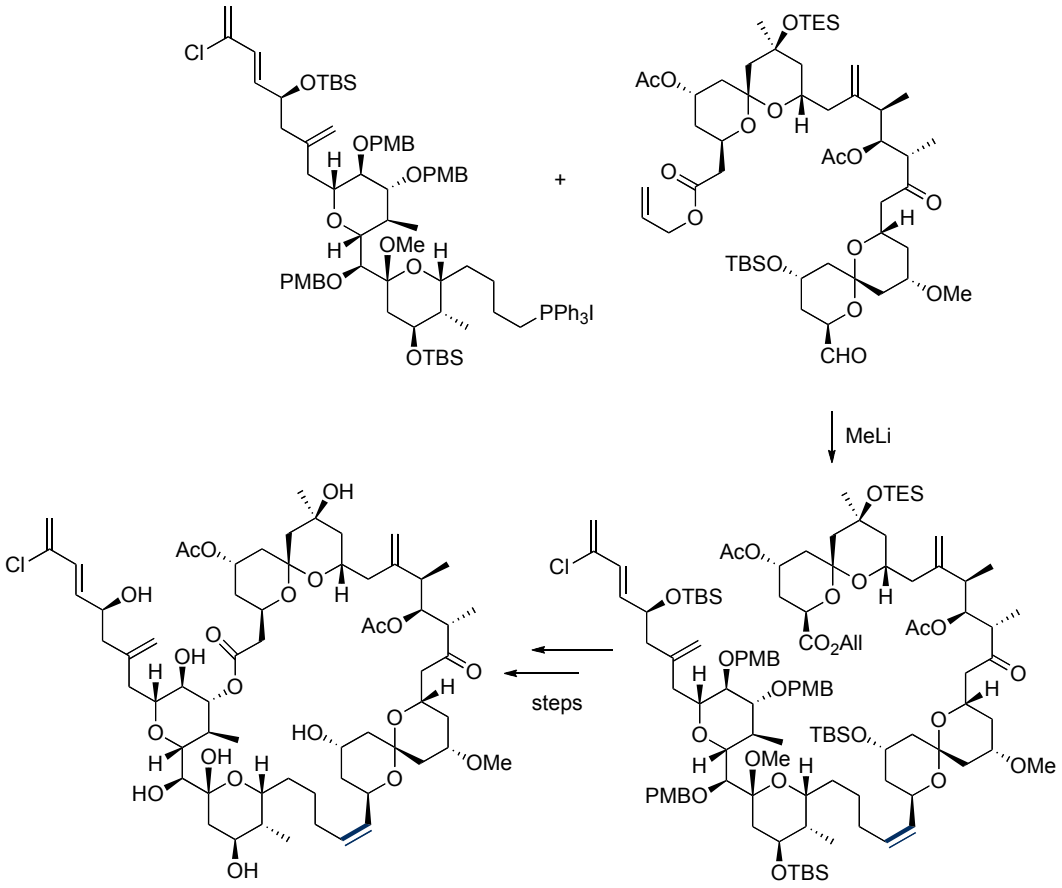
et al. synthesised epothilone B.[71] The initial plan was to form the main framework of epothilone B **37** *via* ring-closing metathesis but this method proved unsuitable. An alternate synthetic route was devised which utilised two Wittig reactions (scheme 26).



Scheme 26: Wittig reactions used in the synthesis of epothilone B

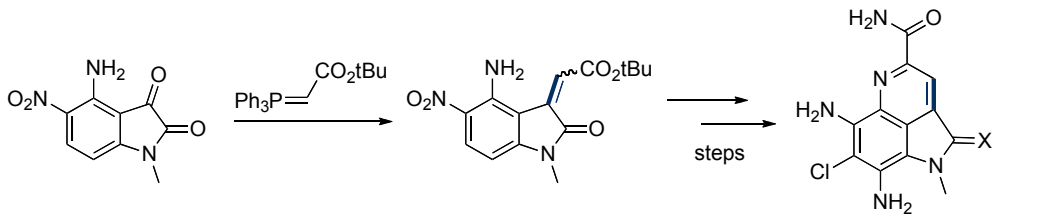
The first of these was used to construct a tri-substituted olefin fragment **34**. The resulting C=C double bond would eventually be used to form the epoxide of epothilone B in the final step of the synthesis. The Wittig reaction produced the desired intermediate in 94% yield with an *E/Z* ratio of >95:5. After the ylide **35** and aldehyde **36** fragments were both prepared, it was necessary to couple them together via a second Wittig reaction. This step, along with the macrolactonisation which soon followed, was essential to form the framework of the epothilone. Again good yield of alkene was obtained using the Wittig reaction (87%) and only the desired *Z*-diastereomer was formed. In the total synthesis of Spongistatin 1 (**38**), Ley and co-workers also used a Wittig reaction to combine two complex fragments to prepare the overall framework of the natural product.[72] Applying these conditions resulted in formation of the *Z*-alkene in 50% yield. In 2009 Fenical, Hughes and co-workers showed that ammosamides **39** and **40** are capable of interacting with the protein myosin.[73] This property is of value to medicinal chemists as myosin plays a pivotal role in cell division, so natural products which display activity against it may have

potential as anti-cancer therapeutics. Soon after discovering this activity of the ammosamides, Fenical and Hughes then demonstrated a total synthesis of the compounds from commercially available isatin (scheme 28).[74] A Wittig reaction (86% yield) and subsequent condensation formed a quinolone ring. Nitration and conversion of the hydroxyl group to a chloride resulted in the ammosamide scaffold. The two nitro groups and chloride substituent are functional groups which can be readily converted/substituted to prepare an array of ammosamide structures. The Wittig reaction was useful in constructing the fused heteroatomic ring structures.

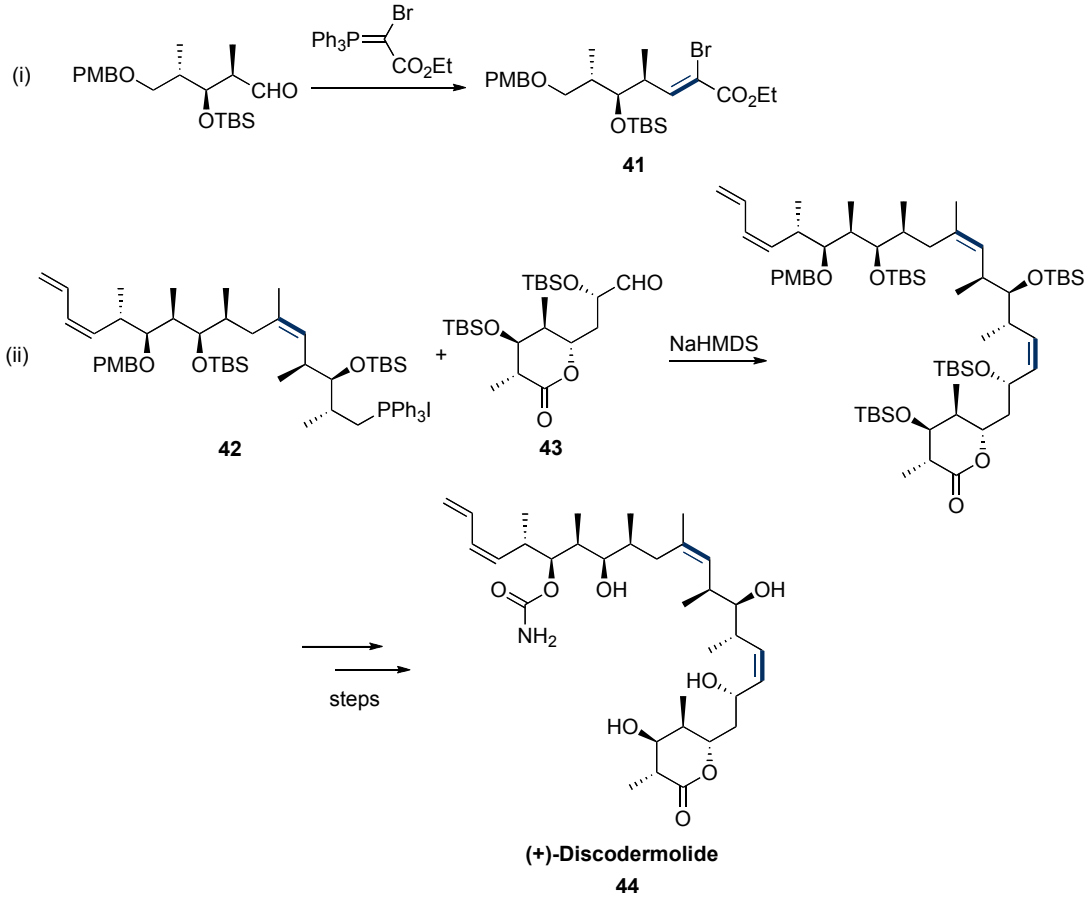


Spongistatin 1
38

Scheme 27: Wittig reaction used in the synthesis of spongistatin 1



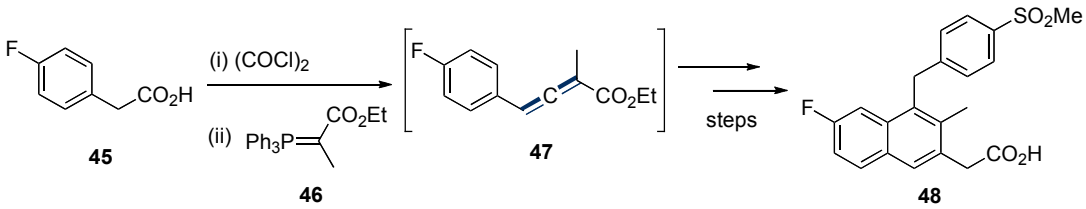
Scheme 28: Wittig reaction used in the synthesis of ammosamide core



Scheme 29: Wittig reactions used in the synthesis of (+)-discodermolide

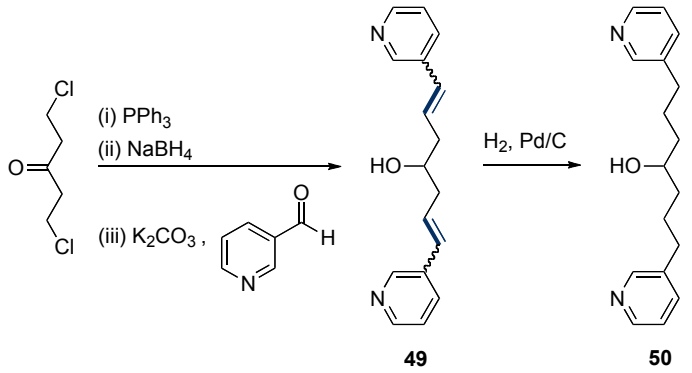
Another natural product which displays anti-tumour properties is (+)-discodermolide (**44**). In a complex synthesis of the compound by Smith *et al.*, the Wittig reaction again proved to be an essential synthetic tool (scheme 29).[75] Retrosynthetic analysis showed a route to **44** *via* coupling of three fragments, all of which were constructed in multistep processes. Preparation of the B fragment involved a Wittig reaction to form the tri-substituted alkene moiety **41**. The reaction yielded 84% of the desired intermediate with a *Z:E* ratio of 8.5:1. This formed the first of (+)-discodermolide's two *Z*-alkene functionalities. The second Wittig reaction was the challenging coupling of the phosphonium salt **42** to aldehyde **43**.

The reaction was highly efficient, forming the new double bond in 76% yield and with high *Z*-selectivity (*Z:E* ratio of >49:1).



Scheme 30: Wittig reaction used in the synthesis of CRTH2 receptor antagonist

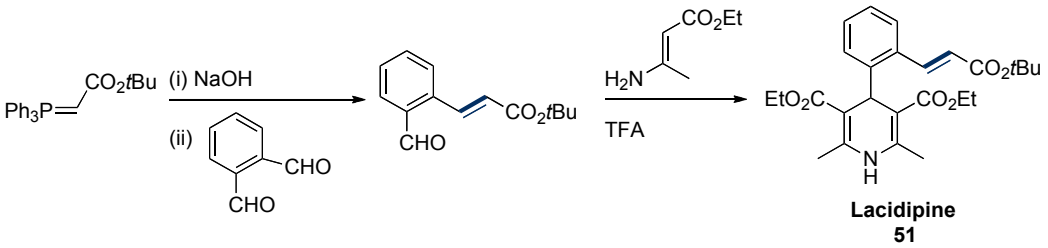
This Wittig reaction proved vital in achieving this multistep gram-scale synthesis. Recently, Shu *et al.* developed an optimised industrial route to produce the CRTH2 receptor antagonist **48**.[76] The reaction of the acid chloride derived from **45** with Wittig reagent **46** formed an allene intermediate **47**, which was subsequently converted to a tri-substituted olefin. Alcohols of type **50** are important precursors to several anti-cancer compounds developed by Vertex Pharmaceutical Inc.[77] The original synthesis of intermediate **49** was carried out by Heck reaction but the low reaction yield and high cost rendered this method impractical. By switching to a double Wittig reaction to form diene **49**, an efficient high-yielding synthesis of **50** was achieved (scheme 31).



Scheme 31: Double Wittig reaction used in the synthesis of precursor **50**

Lacidipine (**51**), a calcium channel blocker, is synthesised using the Wittig reaction to form the C=C double bond.[78] The entire synthesis of **51** proceeded without any chromatographic purification (scheme 32). Careful adjustment of reagent equivalents and reaction temperature produced high chemoselectivity in the Wittig reaction, with minimal reaction of the second aldehyde group. The advantages of the major stoichiometric olefination processes have been outlined. Their range of applications in organic synthesis, particularly the Wittig-type processes, has demonstrated their importance. However, there are

limitations associated with these methodologies. Each stoichiometric process requires the synthesis of a precursor in order to carry out the olefination – sulphone (Julia-lythgoe/Julia-Kocienski), α-silyl carbanion (Peterson), phosphonium ylide (Wittig) or a phosphonate (HWE).



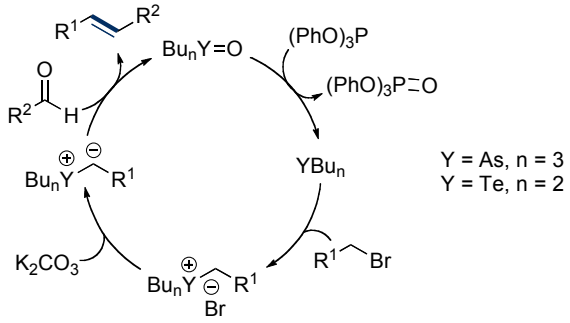
Scheme 32: Wittig reaction used in the synthesis of lacidipine

This adds an extra step to the overall synthetic process. Diastereoselectivity can also be an issue. Applying certain conditions to a particular combination of substrates can be performed to obtain high *E/Z* selectivity in several cases. However, this may not always be possible. For example the Wittig reaction of non-stabilised ylides (obtained from alkyl halides) usually favours formation of the *Z*-alkene. If the *E*-alkene was the desired product, the selective Wittig reaction of such halides becomes a major challenge. Another major issue associated with the stoichiometric processes is waste production. For each process a stoichiometric quantity of reactants are required. For example the Wittig reaction requires 1 molar equivalent (usually excess) of PPh_3 to form the phosphonium salt. Not only is this costly as more starting material is required, but it also means that a stoichiometric amount of waste byproduct is produced. In the case of the classic Wittig reaction the byproduct is triphenylphosphine oxide. Labourious chromatographic purifiation can be required to fully remove the byproducts, which is costly and time-consuming. A catalytic process has the potential to overcome all of these issues. Employing a catalyst would reduce quantities of reagents and waste, resulting in a less expensive and more environmentally friendly process. The current catalytic olefination methods (Heck and metathesis reactions) require transition metal catalyst and a olefin as the starting material. Development of a catalytic olefination process with a wide substrate scope would be highly advantageous. Tuning of the catalyst by modifying steric and electronic factors would result in a more selective process. These reasons ensure that the development of a catalytic olefination process is essential for synthetic and medicinal chemists.

1.4 Catalytic Wittig Reactions

1.4.1 Early Catalytic Wittig Reactions

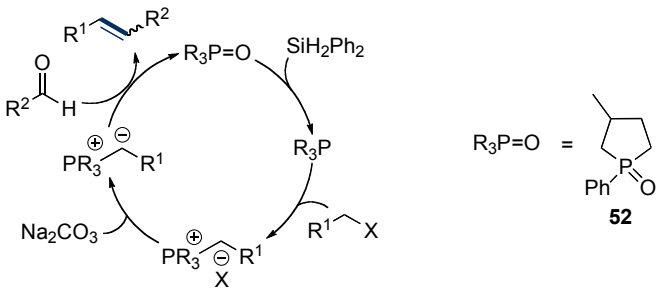
Of the many olefination processes that currently exist, those of the catalytic variety possess a distinct advantage over their stoichiometric variants in that waste is minimised. Unfortunately all of the catalytic olefination processes discussed require the use of a transition metal catalyst. Complexes of such metals are known to be toxic to the environment even in small quantities which is a concern for disposal of waste metal catalysts and their associated byproducts. The relative scarcity of these metals result in a significantly higher cost compared to similar quantities of organic compounds. The substrate diversity of the Heck reaction and olefin metathesis is also somewhat limited due to the requirement of an olefin starting material. A catalytic olefination protocol with a wide substrate scope would be of great benefit to synthetic chemists. In order to create such a process, several attempts have been made at devising a catalytic Wittig reaction. Such a process would have several advantages over the stoichiometric Wittig reaction. Removal of triphenylphosphine oxide byproduct would no longer be an issue. Perhaps a more interesting enhancement offered by a catalytic Wittig reaction would be the possibility of tuning the phosphine structure. It has been widely observed that varying the nature of the substituents at the phosphorus centre can lead to significant changes in the outcome of the reaction, in particular the *E/Z* selectivity of the olefin. As only a catalytic quantity of phosphine would be used it would be cost effective to explore the possibility of tuning the phosphine structure to alter the selectivity of the reaction. To make the reaction catalytic the triphenylphosphine oxide byproduct would have to be recycled back to triphenylphosphine. In isolation this appears a straightforward step but to reduce the phosphine oxide in the presence of other reactive reagents would necessitate a mild reducing agent.



Scheme 33: Catalytic Wittig-type reactions using arsenic and tellurium-based catalysts

With a bond strength of 132 kcal/mol, mild methods for P=O reduction proved difficult. To overcome this, the phosphorus was replaced with tellurium or arsenic resulting in a weaker bond and thus a more favoured oxide reduction (Te=O bond strength: 94 kcal/mol, Ar=O bond strength: 106 kcal/mol). In 1989 Shi, Huang *et al.* demonstrated the first catalytic Wittig-type reaction using tributylarsine[79] and dibutyltelluride[80] (scheme 33). Triphenylphosphite functioned as the reducing agent to convert the oxide to the active catalytic species. Although several examples of olefins were synthesised in good yield and selectivity, the high toxicity associated with arsenic[81] and tellurium[82] ensured the processes would not be widely adopted, particularly in industrial production.

1.4.2 First Organocatalytic Wittig Reaction



Scheme 34: Catalytic Wittig reaction (CWR) using an organophosphorus catalyst

In 2009 O'Brien *et al.* developed the first organocatalytic Wittig reaction which utilised a phosphine catalyst.[83] By employing cyclic phosphine oxide **52** as the pre-catalyst instead of triphenylphosphine oxide, reduction could be achieved using diphenylsilane. Contrary to previous experiments using chlorosilanes, the reduction proceeded with retention of configuration at the phosphorus centre. This factor may be of importance if later generation phosphine catalysts contain chiral moieties. 19 examples of olefins were synthesised from a variety of alkyl, aryl and heterocyclic aldehydes and activated bromides. A more thorough discussion of the CWR highlighted the necessity of the 5-membered ring in the pre-catalyst structure to obtain a viable rate of phosphine oxide reduction.[84] The full report also included slightly improved conditions whereby the insoluble sodium carbonate base was replaced with DIPEA and in total 50 olefin compounds were produced in good to high yield. This represented the beginning of the development of a versatile, environmentally friendly olefination process.

1.5 Thesis Proposal

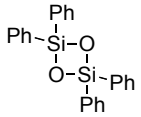
There are four key obstacles which must be overcome if the CWR is to be adopted as a useful methodology:

(i) Substrate scope

One of the initial reasons for the need of a new catalytic olefination process was the limited scope of the Heck and metathesis reactions. While a reasonable variety of aldehydes were used in the CWR, the reaction was limited to halides activated by strong electron withdrawing groups (esters, ketones, lactones and nitriles). Expansion of the protocol to include semi-stabilised and non-stabilised ylides would be a major advance in the CWR.

(ii) Purification

Another attractive prospect offered by the CWR is the omission of difficult phosphine oxide removal. While this has been achieved, there now exists a new byproduct which must be removed. The reduction of the phosphine oxide results in oxidation of the silane to a silanol. At the end of the reaction this is found to be in the form of a cyclic siloxane (figure 8, **53**).



53

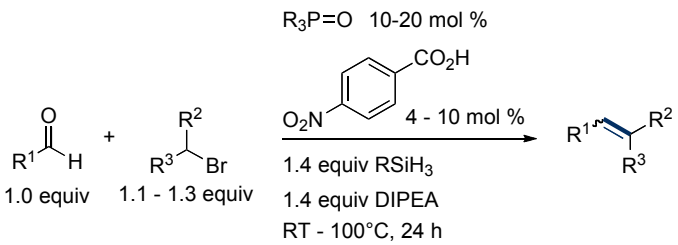
Figure 8: Siloxane byproduct

Removal of the siloxane **53** derived from diphenylsilane can be challenging, requiring arduous column chromatography. Replacement of diphenylsilane with an alternative which can be removed more easily by chromatography or ideally by crystallisation/filtration would make the CWR a much more user-friendly process.

(iii) Temperature

The first CWR required high tempertures to ensure a viable rate of phosphine oxide recycling. Lowering of this temperature would be advantageous; energy cost would be reduced for industrial scale applications and temperature labile compounds could be tolerated as starting materials. A lower reaction temperature relies on easier phosphine oxide reduction. This can be achieved either by modification of the phosphine oxide and/or silane structures to increase the rate of reduction or by including an additional reagent which

would influence the reaction. Recently, our group discovered that by using a catalytic amount of an ammonium benzoate species (formed *in situ*) the rate of reduction of phosphine oxides by silanes increased dramatically without compromising the retention of the phosphorus centre. This led to the development of the room temperature (RT) CWR using cyclic phosphines, and also allowed acyclic phosphines to be used at high temperatures.[85]

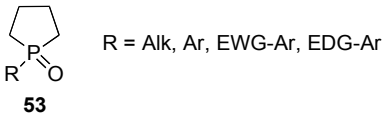


Scheme 35: Acid-enhanced CWR at RT or using acyclic phosphines

Simultaneously, Beller and co-workers discovered that using a catalytic amount of phosphoric acid in conjunction with a silane significantly increased the rate of phosphine oxide reduction.[86] The development of the RT-CWR will not be discussed in this thesis.

(iv) *E/Z* selectivity

The *E/Z* selectivity of the first CWR reactions ranged from 60:40 to >95:5. Probing the reaction showed that post-reaction isomerisation of the *Z*-olefin catalysed by the phosphine led to high selectivity. This effect was only observed for certain di-substituted ketone and ester-substituted olefins. The nature of the phosphonium ylide is known to play an important role in the eventual *E/Z* selectivity of the Wittig reaction.This is highlighted by the varying selectivities for the three ylide classes.



53

Figure 9: Propsed CWR pre-catalyst structure

The CWR offers the possibility to investigate the effect of varying the electronic and/or steric nature of the substituents at the phosphorus centre in order to increase the kinetic *E/Z* selectivity. The primary objective will be to screen pre-catalysts of type **53** (figure 9) where the properties of the 1-substituent R are varied.

2 Expanding the Substrate Scope: *Tuning the Phosphorus Ylide*

2.1 CWR Utilising Semi-Stabilised Ylides

A significant limitation of the CWR is that a strong electron-withdrawing substituent on the halide component is required. This limits the process to highly activated halides. Development of a protocol which could facilitate semi-stabilised ylides derived from benzylic and/or allylic halides would vastly widen the scope of the reaction. While two examples in the first CWR contained benzylic ylides, a strong EWG on the phenyl ring was required.[83] The key barrier to facilitating semi-stabilised ylides is the formation of the ylides via deprotonation of the phosphonium salt.

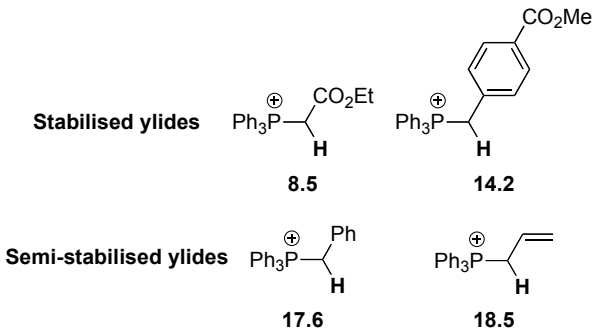
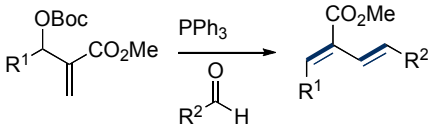
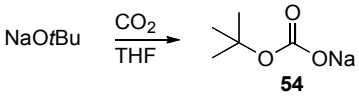


Figure 10: Experimental pK_a values (in DMSO) of some triphenylphosphonium ylide precursors[87]

The choice of base to perform this reaction is critical. For stabilised ylides the ylide-forming proton of the phosphonium salt typically had a pK_a of ~9, therefore Na_2CO_3 and DIPEA were ideally suited to form the ylide. Formation of benzylic ylides bearing an EWG was also possible with these mild bases. In the case of semi-stabilised ylides, the pK_a of the ylide-forming proton is 17-19 (DMSO) so a stronger base is required (figure 10). Conventional Wittig reactions have employed bases such as NaO*t*Bu, NaHMDS, NaOH and *n*BuLi to form semi-stabilised ylides. These strong bases are likely to react with the silane and halide reagent rendering them incompatible with the CWR. A publication in 2010 by Zhou *et al.* demonstrated Wittig reactions of MBH adducts with no base present.[88] Deprotonation is critical for ylide formation, so the likely occurrence is that phosphonium salt formation proceeds with the loss of the $BocO^-$ group which then acts as the base to form the ylide (scheme 36).



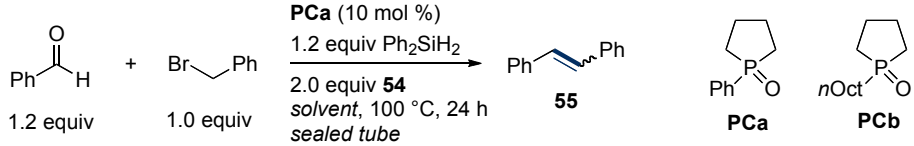
Scheme 36: "Base-free" Wittig reaction



Scheme 37: Preparation of NaOBoc **54**

NaOBoc (scheme 37, **54**) was prepared and tested in the synthesis of stilbene **55**. Pleasingly, the base was compatible with the CWR and the reaction proceeded in good yield (table 1).

Table 1: Optimisation of solvent using **54**

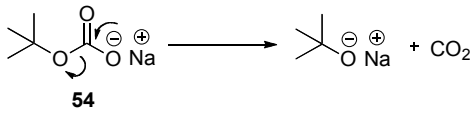


Entry	Solvent	Yield %	*E*/*Z*[a]
1	Acetonitrile (ACN)	37	66:34
2	Dimethyl carbonate (DMC)	38	66:34
3	1,2-Dimethoxyethane (DME)	49	66:34
4	1,4-Dioxane	53	66:34
5	*t*Butyl acetate (*t*BuOAc)	54	66:34
6	2-Methyl tetrahydrofuran (2-MeTHF)	73	66:34
7	Cyclopentyl methyl ether (CPME)	75	66:34
8	Toluene	81	66:34
9[b]	Toluene	74	80:20
10[c]	Toluene	80	80:20

[a] *E/Z* ratio was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [b] Result obtained using **PCb** at 100 °C. [c] Result obtained using **PCb** at 110 °C.

A solvent study revealed toluene to be the optimum solvent, with CPME and 2-methyl THF also resulting in good yields of stilbene. Other changes to the original protocol are the use of **PCb** as the pre-catalyst which gave increased *E/Z* selectivity (table 1, entry 9) and an increase of temperature to 110°C which gave a slight increase in yield (entry 10). The exact role of **54** remains unclear. We believe that **54** itself does not have the necessary pK_a to

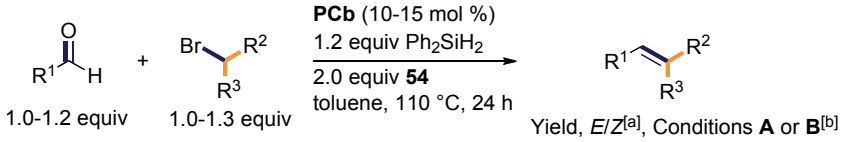
carry out the deprotonation, and that instead it acts as a masked form of NaO*t*Bu (scheme 38). Mechanistic studies have yet to be conducted.

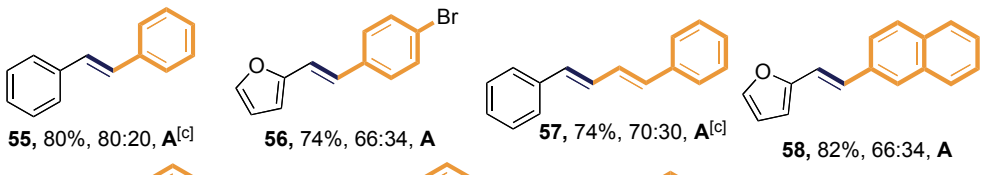


Scheme 38: Masked form of NaO*t*Bu

54 proved successful in the CWR of benzylic halides. Allylic bromides initially reacted poorly due to decomposition under high temperature and/or reaction with the base. This was overcome by portion-wise addition of the halide. Secondary halides also reacted efficiently to form tri-substituted olefins (table 2).

Table 2: Substrate study of semi-stabilised ylides using **54**





[a] *E/Z* ratio was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.
[b] Conditions **A**: all-in reaction, **B**: portion-wise addition (see appendix A for details).
[c] Following treatment with iodine at 110 °C (5 h) isomerisation to *E/Z* >95:5 was achieved.
[d] 27 mmol scale, see appendix A for details.

While **54** proved to be an ideal candidate in the CWR of semi-stabilised ylides, another approach was investigated. Instead of using a stronger base to carry out the deprotonation of the phosphonium salt, we considered lowering the pK_a of the ylide-forming salt. If the pK_a was lowered significantly it would be possible to use a mild, commercially available base.

As only a catalytic quantity of phosphine is used in the CWR it is cost-effective to modify its structure to alter the properties of the catalyst. Previous studies showed that the five-membered ring is critical for efficient reduction of phosphine oxide[84] so we considered altering the electronics by adding electron-withdrawing substituents to the phenyl ring in the 1-position.

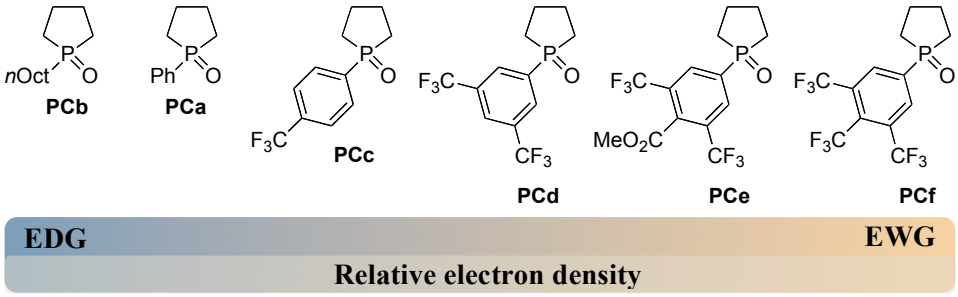
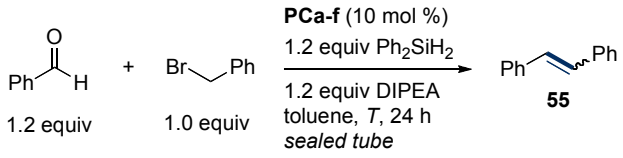


Figure 11: Library of pre-catalysts **PCa-f**

The idea is that withdrawal of electron density from the phosphorus centre will lower the pK_a of the ylide-forming proton sufficiently so that a mild base (DIPEA) could carry out the deprotonation. The drawback to adding EWGs is that the nucleophilicity of the phosphine and phosphine oxide will be lowered. This will likely impact the rate of phosphine oxide reduction and the rate of phosphonium salt formation. To compensate for this the reaction temperature was increased to 140 °C. A library of pre-catalysts (figure 11, **PCa-f**) was prepared and tested in the synthesis of stilbene (table 3).

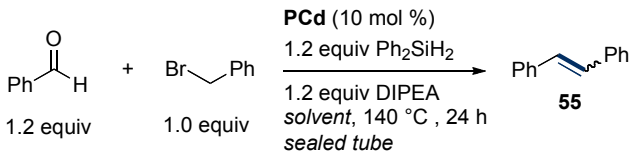
Table 3: Phosphine oxide screening using DIPEA and ylide tuning.



Entry	Pre-catalyst	*T*°C	Conversion (Yield %)[a]	*E*/*Z*[b]
1	**PCa**	100	trace	-
2	**PCb**	140	55 (37)	75:25
3	**PCa**	140	65 (43)	80:20
4	**PCc**	140	88 (61)	75:25
5	**PCd**	140	91 (72)	82:18
6	**PCe**	140	94 (66)	82:18
7	**PCf**	140	91 (72)	78:22

[a] Conversions were determined by ^{1}H NMR spectroscopy.
[b] *E*/*Z* ratio was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.

Table 4: Optimisation of solvent using DIPEA.



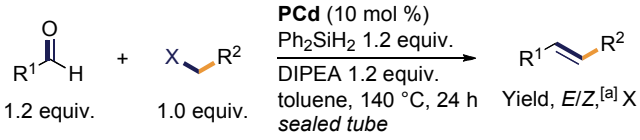
Entry	Solvent	Conversion (%)[a]	*E/Z*[b]
1	Cyclopentyl methyl ether (CPME)	75	81:19
2	tButyl acetate (tBuOAc)	84	81:19
3	Dimethyl carbonate (DMC)	87	75:25
4	Toluene	91	82:18
5	2-Methyl tetrahydrofuran (2-MeTHF)	92	77:23
6	α,α,α–Trifluorotoluene (CF_3Ph)	100	79:21

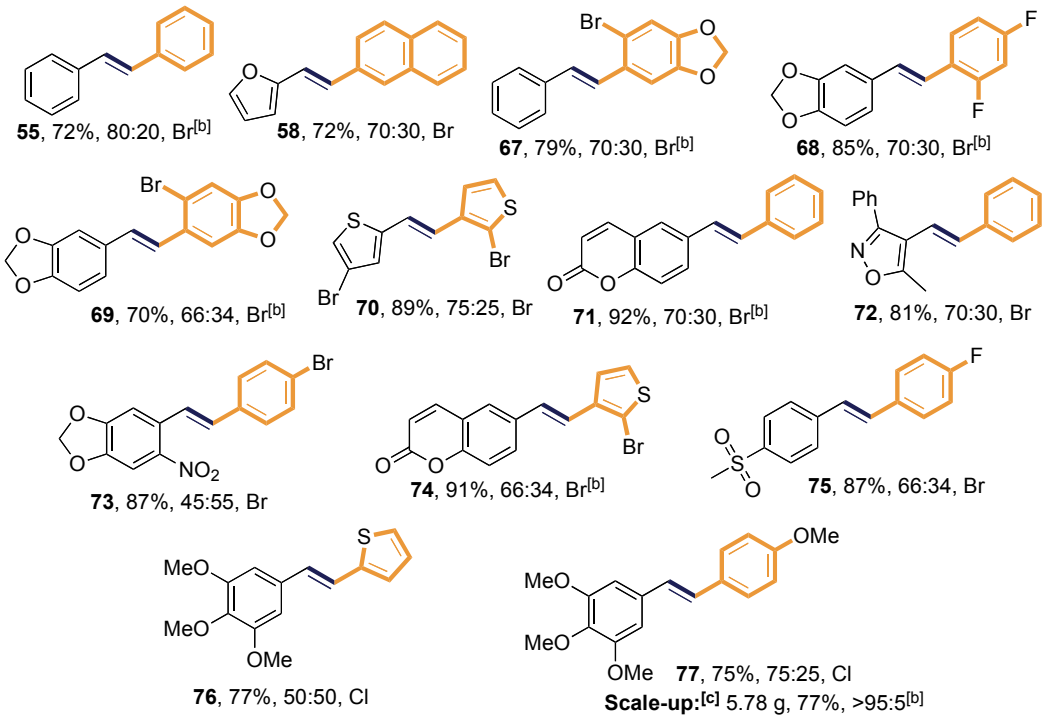
[a] Conversions were determined by ^{1}H NMR spectroscopy.
[b] *E/Z* ratio was determined by^{1}H NMR spectroscopy of the unpurified reaction mixture.

A clear trend is observed: as more EWGs are added to the pre-catalyst the reaction yields increase. Use of **PCd** as pre-catalyst gave a high yield (table 3, entry 5). However, a point is reached where addition of more EWGs fails to increase the yield (entries 6 and 7). This highlights the importance of finding a balance between lowering the pK_a of the phosphonium salt whilst maintaining viable rates of phosphine oxide reduction and phosphonium salt formation. A solvent study focusing on the use of green solvents showed that high conversions were obtained using toluene, 2-methyl THF and α,α,α-trifluorotoluene. No significant change in *E/Z* selectivity was observed by altering the solvent system. A substrate study was carried out to demonstrate the use of the CWR of semi-stabilised ylides utilising the concept of ylide-tuning (table 5). A wide array of aryl and heteroaryl aldehydes and organohalides were successfully tolerated. A notable example is DMU-212 (**77**), a resveratrol analogue which has been shown to possess more potent anti-cancer properties than resveratrol.[89] Compounds similar to **70** can be used as building blocks to prepare photochromic and conductive materials.[90] An aldehyde containing a 1-2 oxazole was employed in the synthesis of **72**; these heterocyclic fragments are found in some compounds of importance in medicinal chemistry.[91] Compounds similar to **73** can be used to form 1*H*-indoles,[92] which are also found in several pharmaceutical agents. The use of DIPEA is a significant achievement as this is the mildest base used to date for the formation of semi-stabilised ylides. For allylic and secondary benzylic halides **54** remains the base of choice. These halides react rapidly with DIPEA at high temperature and poor

yield of olefins were obtained even when using slow addition of the halide. The *E/Z* selectivity ranged from non-selective to 80:20, but was typically between 66:34 and 70:30.

Table 5: Substrate study of semi-stabilised ylides using DIPEA.





[a] *E/Z* ratio was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.
[b] Following treatment with iodine at 110 °C (5 h) isomerisation to *E/Z* >95:5 was achieved.
[c] 23 mmol scale, see appendix A for details.

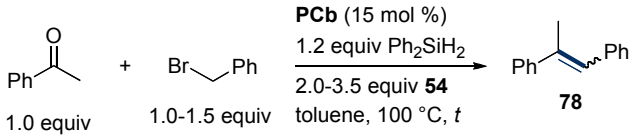
Pleasingly, many of the compounds isomerised fully to *E/Z* >95:5 when heated in the presence of a trace of iodine. Other isomerisation methods for stilbene derivatives including the use of acid or metal catalysis were not investigated. Further purification was not necessary after workup and pure *E*-olefin could be obtained with minimal loss of yield. This demonstrates that for the majority of the compounds prepared the intrinsic *E/Z* selectivity is trivial if the pure *E*-isomer is required.

2.2 CWR Utilising Ketones

The CWR of semi-stabilised ylides facilitates the use of benzylic and allylic halides which significantly enhances the substrate scope of the reaction. A further enhancement would be to employ ketones instead of aldehydes. This would be a useful method of preparing tri-

substituted olefins. The difficulty in using ketones lies with their low reactivity compared to aldehydes and their tendency to enolise.[93] The choice of pre-catalyst is important for the CWR of ketones. While **PCd** proved useful to facilitate easier ylide formation, the lowered nucleophilicity would be a problem when reacting the ylide with a ketone. **PCb** was chosen as the pre-catalyst as it would produce the most nucleophilic ylide. The first attempt to react acetophenone with benzyl bromide using **PCb** and **54** was met with failure, and the halide reactant was fully consumed (table 6, entry 1). Using potion-wise addition of the halide resulted in α-alkylation of the ketone instead of formation of **78** (table 6, entry 2).

Table 6: Development of the pulse olefination technique.

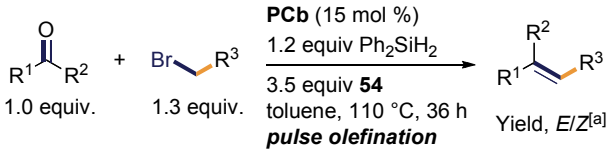


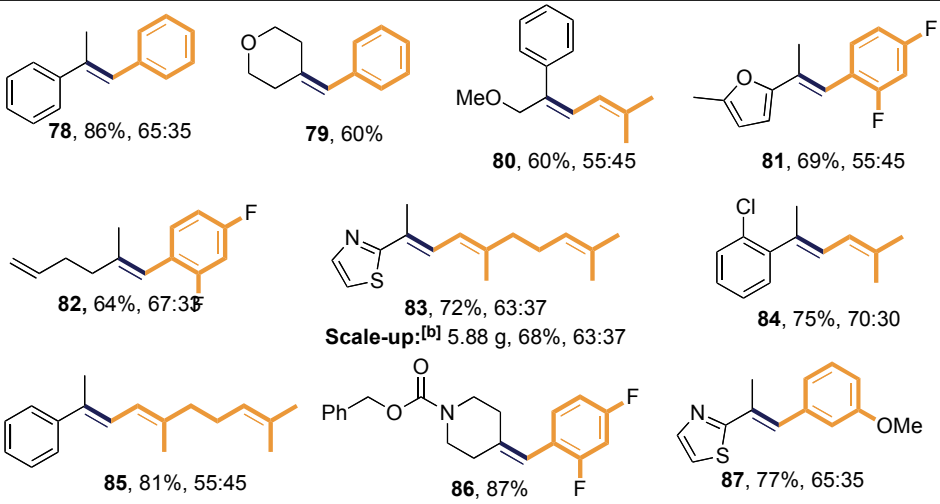
Entry	Halide (equiv)	Base (equiv)	Conditions	*t* (h)	Conv. (Yield %)[a]	*E/Z*[b]
1	1.50	2.0	All-in	24	0[c]	-
2	1.50	2.0	Portion-wise addition of halide (8 additions, 1 h intervals)	24	91[d]	-
3	1.05	2.0	Pulse olefination: halide (7 additions), base (2 x 1.0 equiv., 0 h and after 4th addition of halide); Heating cycle: 30 min at RT, 1.5 h heating	24	65 (58)	65:35
4	1.23	2.0	Pulse olefination: halide (7 additions), base (4 x 0.5 equiv., 0 h and after 3rd, 4th and 6th additions of halide); Heating cycle: 30 min at RT, 1.5 h heating	24	52	65:35
5	1.20	3.0	Pulse olefination: halide (8 additions), base (3 x 1.0 equiv., 0 h and after 3rd and 6th additions of halide); Heating cycle: 30 min at RT, 2.2 h heating[e]	31	75 (72)	63:37
6	1.35	3.5	Pulse olefination: halide (9 additions), base (3 x 1.0 equiv., 0 h and after 3rd and 6th additions of halide, 1 x 0.5 equiv. after 8th addition of halide); Heating cycle: 30 min at RT, 2.2 h heating[e]	36	97 (87)	66:34

[a] Conversions were determined by ^{1}H NMR spectroscopy, based on residual ketone. Isolated yields shown in parentheses.
[b] *E/Z* ratio was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.
[c] No halide or silane remaining.
[d] The only product observed was 1,3-diphenylpropanone, which is the result of α-deprotonation of the ketone.
[e] Stirred for 10 h at 110 °C between 5th and 6th cycles. Additional diphenylsilane (0.3 equiv.) was added after this time.

The success of the CWR of ketones relied on minimising the amount of halide in solution. This was achieved by the development of a pseudo-catalytic pulse-olefination technique whereby the halide is added portion-wise at room temperature to form the phosphonium salt. Once the phosphonium salt has formed the reaction mixture is heated to 110 °C for the subsequent steps of the catalytic cycle to occur. This procedure is repeated until all portions of the halide are added. Employing **PCb** as the pre-catalyst is important for this process as it ensures a high rate of phosphine oxide reduction and phosphonium salt formation are achieved. Using the pulse-olefination technique a range of olefins was prepared from aryl, heteroaryl and aliphatic ketones (table 7).

Table 7: Substrate study of semi-stabilised ylides with ketones using pulse olefination technique.





[a] *E/Z* ratio was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.
[b] 35 mmol scale, see appendix A for details.

E/Z selectivity was low for all substrates. However, the conventional Wittig reaction and even the Heck reaction of ketones typically proceeds with low selectivity compared to similar reactions of aldehydes.[93][94]

2.3 CWR Utilising Non-Stabilised Ylides

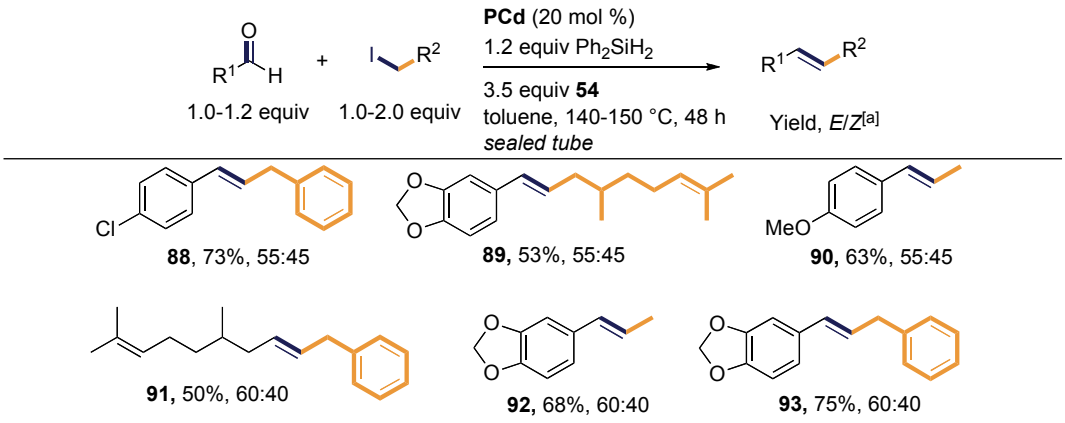
Expansion to include non-stabilised ylides presents two key challenges:

1) Formation of the phosphonium salt

2) Deprotonation of the phosphonium salt to form the ylide

The deprotonation issue can be approached similarly to that of the semi-stabilised ylides. A match between pK_a of phosphonium salt and base must be achieved. For semi-stabilised ylides this was achieved by either increasing the pK_a of the base (using **54**) *or* by lowering the pK_a of the ylide-forming proton (using **PCd**). To facilitate formation of non-stabilised ylides the natural progression is to combine these two methods i.e. use **PCd** in conjunction with **54**.

Table 8: Substrate study of non-stabilised ylides.



[a] *E/Z* ratio was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. See appendix A for sequence of reagent additions.

Initial application of these conditions using bromoethane indicated that phosphonium salt formation was an issue. This was not unexpected as preparation of phosphonium salts from PPh_3 and alkyl halides typically requires several hours under reflux. Replacing **PCd** with **PCb** as pre-catalyst could alleviate this problem, however the more electron-deficient phosphine is vital for efficient deprotonation to occur. The other option is to use iodides as the halide component instead of bromides or chlorides. Iodide is a better leaving group than bromide so the rate of salt formation should increase. Using (2-iodoethyl)benzene as the halide source, **88** was prepared in 73 % yield, albeit requiring 20 mol % catalyst loading and 48 h reaction time. Adding an extra equivalent of halide enabled good yields of olefin to be obtained when using iodoethane (table 8, **90** and **92**). Moderate yields of olefin were achieved using an aliphatic aldehyde (**91**) and using citronellyl iodide (**89**). The combination of ylide tuning and a masked base was successful in facilitating non-stabilised ylides in the CWR. Using iodides as the halide source was necessary for phosphonium salt formation. This is a minor setback in that a wider variety of alkyl bromides and chlorides are commercially available. However, alkyl iodides can be conveniently prepared by treating the corresponding alcohol with PPh_3 and iodine in the presence of imidazole.[95]

3 Waste Removal: *Use of a Polymeric Silane*

3.1 PMHS in the CWR of Stabilised Ylides

Expansion of the CWR to include all ylide types as well as ketones is a major improvement on the original protocol. The next major development is identification of the optimum silane. The CWR is superior to the conventional Wittig reaction in that triphenylphosphine oxide removal is not an issue. However, the stoichiometric amount of phosphine has been replaced with a stoichiometric amount of silane. The reduction of the phosphine oxide results in oxidation of the silane to a silanol. At the end of the reaction this is found to be in the form of a cyclic siloxane. Removal of the siloxane derived from diphenylsilane can be challenging, requiring arduous column chromatography. Replacement of diphenylsilane with an alternative which can be removed more easily by chromatography or ideally by crystallisation/filtration would make the CWR a much more user-friendly process. An ideal candidate is polymethylhydrosiloxane (PMHS), a cheap, commercially available polymeric reducing agent.

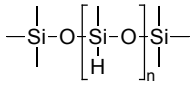
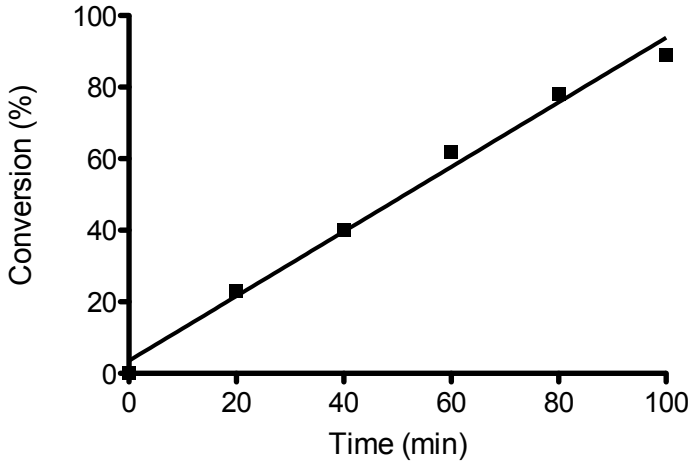


Figure 12: Polymethylhydrosiloxane (PMHS)

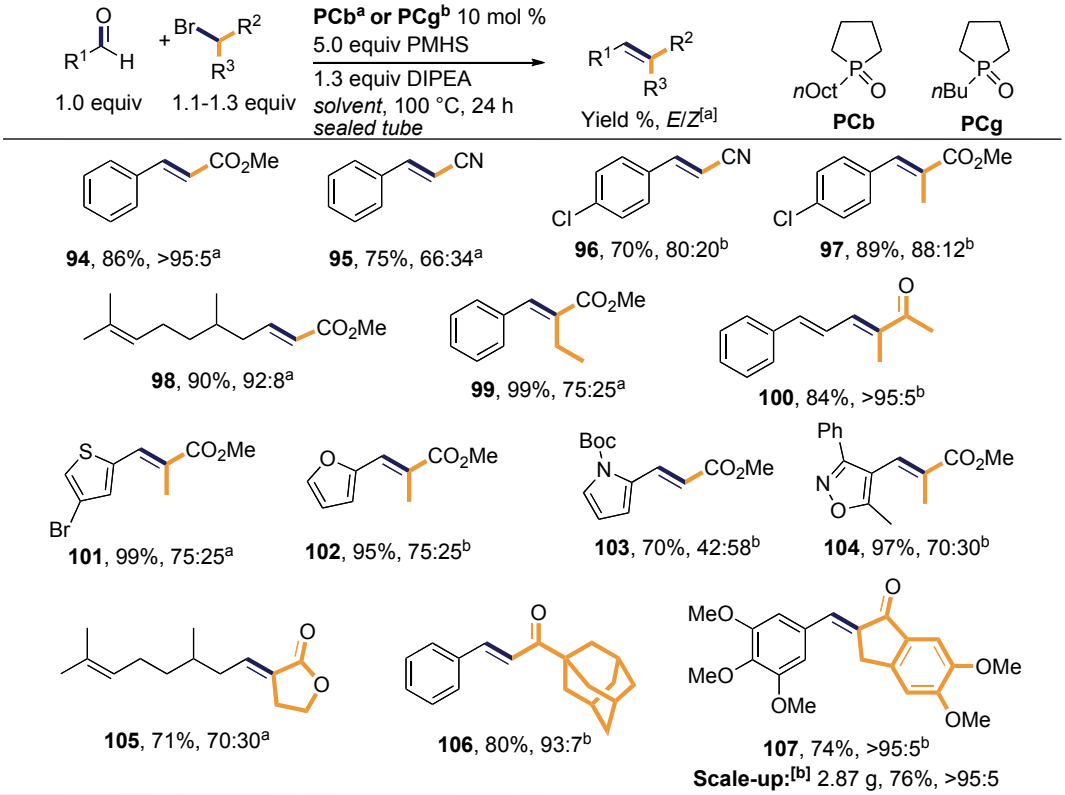
If PMHS is compatible in the CWR, removal of the byproduct would be possible by filtration. The overall cost would also be reduced dramatically, with PMHS (€9.00 / 25 g, Aldrich 176206) costing substantially less than the equivalent amount of diphenylsilane (€125.00 / 25 g, Aldrich 148482).[96] In addition, the overall process would be more environmentally friendly. A recent study by Huijbregts and co-workers showed that the overall energy demand and greenhouse gas emissions of the CWR are significantly lower than the classic Wittig reaction.[97] Furthermore, the study showed that a CWR using PMHS instead of diphenylsilane would lower the energy and emission figures significantly, resulting in a truly green process. For PMHS to be considered for the CWR it must be able to carry out phosphine oxide reduction at a suitable rate. Using 10 mol % of pre-catalyst, for the reaction to be complete in 24 h 50 % of phosphine oxide must be reduced in less than 1 h. To achieve a viable rate of reduction 50 molar equivalents of PMHS with respect to phosphine oxide were used. While not as efficient as diphenylsilane, at 100 °C reduction of **PCb** by PMHS proceeds at a rate deemed appropriate for the CWR (graph 1). However, when PMHS was applied to the CWR, solubility became an issue. Initially the siloxane was

soluble, but as the reaction proceeded and the polymeric chains became oxidised, the siloxane became insoluble and the reaction ceased to proceed efficiently.



Graph 1: Reduction of **PCb** by PMHS at 100 °C.
Conversions were determined by ^{31}P NMR spectroscopy.

Table 9: Substrate study of stabilised ylides using PMHS.



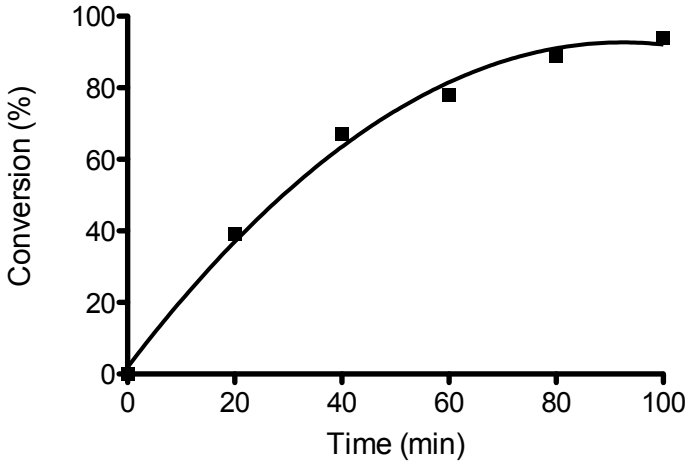
[a] *E/Z* ratio was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.
[b] 7.7 mmol scale, see appendix A for details.
Pre-catalyst was **PCb**^{a} or **PCg**^{b}

Reaction solvent was CPME or 2-methyl THF (see appendix A for details). Diluting the reaction mixture significantly enhanced the yields. A brief examination of solvents showed

that CPME and 2-methyl THF were superior to toluene. The advantage of using PMHS was clearly evident – by stirring the crude reaction mixture in EtOAc the siloxane precipitated and could be removed by filtration. A quick purification step was performed by column chromatography to isolate the pure compound. A substrate study was undertaken whereby several aryl, heteroaryl and aliphatic aldehydes were coupled with ester, ketone and cyano activated halides (table 9). 2-Methyl THF proved essential as the solvent when using cyano-containing substrates. Yields ranged from good to excellent, while the *E/Z* ratio was typically in the region of 66:34, similar to the selectivity obtained using diphenylsilane. Of particular interest is compound **107**, a somewhat resveratrol-like structure. Synthesis of **107** proceeded well on multigram scale (2.87 g, 7.7 mmol, 76%) and yielded only the *E*-isomer. Isolation of **107** was trivial in comparison to previous protocols, filtration and recrystallization steps were sufficient to purify the compound.

3.2 PMHS in the CWR of Semi-Stabilised Ylides

Adoption of PMHS into the CWR of semi-stabilised ylides would be a further improvement of the overall process, allowing two ylide classes to be facilitated using green conditions. Section 3.1 showed that **PCb** is reduced efficiently by PMHS at 100 °C. It was therefore expected that semi-stabilised ylides could be accomodated using **PCb**, PMHS and **54**. At 110 °C, the synthesis of **55** proceeded in good yield. Notably, toluene functioned well as the solvent, providing similar yields to reactions in CPME and 2-methyl THF.

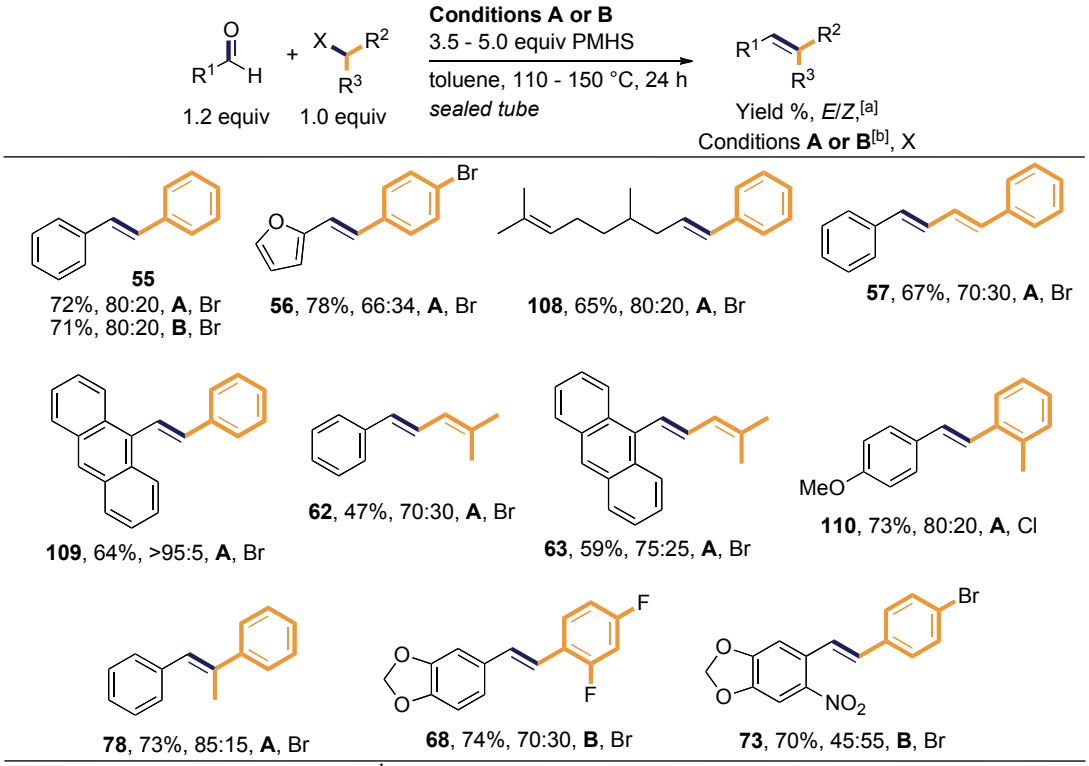


Graph 2: Reduction of **PCd** by PMHS at 150 °C.
Conversions were determined by ^{31}P NMR spectroscopy.

An interesting prospect would be to merge the PMHS conditions with the DIPEA conditions which rely on the ylide-tuning concept. A CWR employing semi-stabilised, a cheap, green silane and a mild base is an attractive option. The principle issue lies with the reduction of

an electron-poor phosphine oxide. Pleasingly, at 150 °C the reduction of **PCd** by PMHS proceeded efficiently (graph 2). The new conditions were tested using the synthesis of **55** as a model reaction. Initially low yields were obtained; this was found to be due to the reaction concentration. It became apparent that a more concentrated reaction mixture is necessary for an efficient rate of ylide formation. Reducing the equivalents of PMHS from 5.0 to 3.5 resulted in increased reaction yields. The lower equivalents of reducing agent did not have any significant impact on phosphine oxide reduction during the reaction. In comparison to toluene, the other green solvents screened provided no significant yield increase. A brief substrate study was undertaken to demonstrate the scope of the PMHS protocol (table 10).

Table 10: Substrate study of semi-stabilised ylides using PMHS



[a] *E/Z* ratio was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.
[b] Conditions **A**: **PCb** (10-20 mol %), 2.0 equiv **54**, 110 °C; **B**: **PCd** (10 mol %), 1.2 equiv DIPEA, 150 °C.

Aliphatic and heteroaryl aldehydes were tolerated, although in certain cases increasing the catalyst loading to 15 or 20 mol % was necessary to obtain acceptable yields. Using portion-wise addition of halide was again the key to employing allylic and secondary benzylic halides as substrates. Using **PCd** and DIPEA was also effective in the CWR using PMHS. As with the reactions of stabilised ylides using PMHS, purification was vastly improved by the ease of siloxane removal.

4 *E/Z* Selectivity: *Probing the Phosphine Structure*

4.1 Properties of the 1-Substituent

The CWR was developed in the hope of creating a broad-scope organocatalytic olefination process with minimal waste. Advances have been made in substrate expansion and waste removal in the CWR. The only central issue which remains is the relatively poor *E/Z* selectivity of the reaction. Upon analysis of the crude reaction mixture, the *E/Z* observed ratio typically ranges from 45:55 to 70:30. Some exceptions do exist, such as certain reactions involving ketone or ester stabilised ylides which undergo phosphine-mediated isomerisation resulting in a final *E/Z* ratio of >95:5. From an industrial viewpoint this, on occasion, is not detrimental to the process. In several cases the isomeric olefin mixture can be isomerised to the thermodynamically favoured *E*-olefin using UV light, heat or in conjunction with a catalytic amount of iodine, acid or a metal-based catalyst. If isomerisation can be performed easily with no significant loss in yield, the intrinsic *E/Z* selectivity holds no great value.

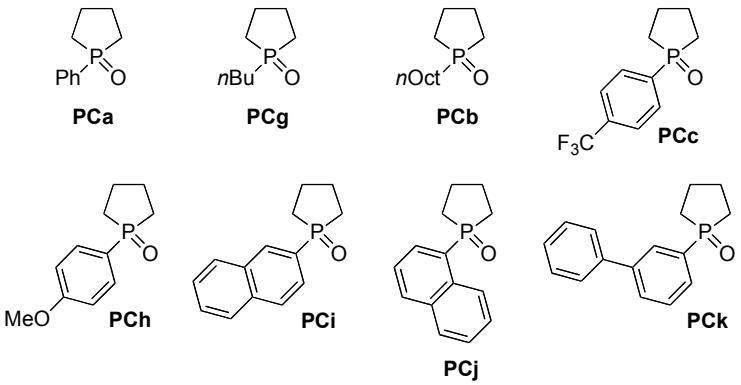


Figure 13: Pre-catalysts based on **53** used for selectivity studies

Alternatively, if both the *E*- and *Z*-olefin are useful products/intermediates and can be readily separated *via* chromatography, a non-selective olefination process can be useful in preparing two compounds in one synthetic step. However, often only one isomer is desired and application of isomerisation techniques is limited, so it would therefore be beneficial to develop a selective CWR method. From the literature it is evident that the substituents at the phosphorus centre, and thus reactivity of the ylide, are critical in determining the *E/Z* ratio of the olefin.[53] This accounts for the general trends associated with the varying selectivity between the three ylide classes. Varying the substituents of the phosphine becomes economically viable in the CWR. This was observed in section 2 when the phosphine was

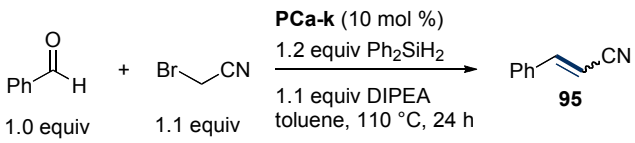
tuned to lower the pK_a of the ylide-forming proton. In this section the effect of substituent variation on the *E/Z* selectivity will be examined. Previous studies demonstrated that the 5-membered cyclic ring facilitates easier reduction of the phosphine oxide so for the *E/Z* study this fragment will remain intact. A library of phosphines based on structure **53** was chosen with various P-substituents in the 1-position (figure 13). **PCa-c and PCg-h** contain substituents with varying electronic properties, while **PCi-k** possess substituents which may impart a steric influence. The effect, if any, of the electronic or steric nature of the substituent on the selectivity will provide information on how to approach the design of a new catalyst.

Each pre-catalyst was screened in three key protocols:

- Standard conditions for stabilised ylides at 110 °C
- Acid-catalysed room temperature conditions for stabilised ylides
- Standard conditions for semi-stabilised ylides at 110 °C

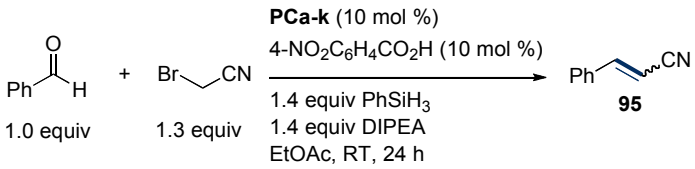
The synthesis of **95** was chosen as a model reaction for stabilised ylides, as no post-reaction phosphine-mediated *Z* to *E* isomerisation occurs for this compound. The synthesis of **55** was chosen as a model reaction for semi-stabilised ylides.

Table 11: Phosphine oxide screening for stabilised ylides at 110 °C



Entry	Pre-catalyst	*E/Z*
1	**PCa**	60:40
2	**PCb**	63:37
3	**PCg**	62:38
4	**PCc**	58:42
5	**PCh**	59:41
6	**PCi**	58:42
7	**PCj**	56:44
8	**PCk**	55:45
9	**PCl**	72:28
10	**PCm**	80:20

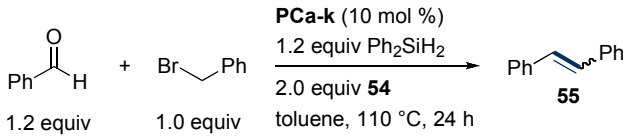
Table 12: Phosphine oxide screening for stabilised ylides at RT



Entry	Pre-catalyst	*E/Z*
1	**PCa**	67:33
2	**PCb**	71:29
3	**PCg**	71:29
4	**PCc**	64:35
5	**PCh**	60:40
6	**PCi**	66:34
7	**PCj**	60:40
8	**PCk**	54:46
9[a]	**PCl**	62:38
10	**PCm**	93:7

[a]Conversion for this reaction was 16%

Table 13: Phosphine oxide screening for semi-stabilised ylides

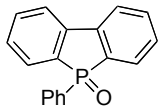


Entry	Pre-catalyst	*E/Z*
1	**PCa**	66:34
2	**PCb**	78:22
3	**PCg**	76:24
4	**PCc**	70:30
5	**PCh**	63:37
6	**PCi**	68:32
7	**PCj**	62:38
8	**PCk**	60:40
9	**PCl**	91:9
10	**PCm**	96:4

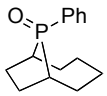
For **PCa-k** no significant leap in *E/Z* selectivity was observed. Addition of a strong EWG failed to impact the selectivity (tables 11-13, entry 4), as did the addition of a strong EDG (entry 5). No great change was observed for **PCi-k**, however their use did appear to favour the *Z*-olefin slightly more. This increased preference for *Z*-selectivity is marginal, but could suggest that the potential for creating a *Z*-selective CWR lies with varying the sterics of this P-substituent. The only improvement observed is entries 2 and 3, which highlights the greater selectivity when using an alkyl substituent in place of an aryl one. In terms of selectivity no phosphine appeared particularly suited to either ylide class.

4.2 An Alternative Approach

The next structural adjustment with the potential to impart selectivity into the CWR is to alter the cyclic component of the phosphine. Potential candidates include **PCl** and **PCm**, whose corresponding phosphines have been used in conventional Wittig reactions resulting in high *E*-selectivity (figure 14).[93]



PCl

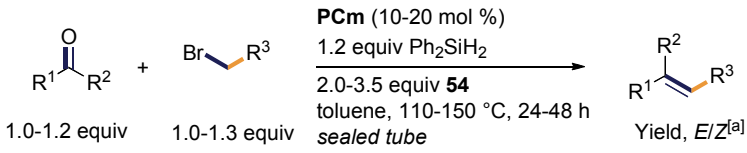


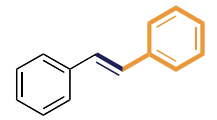
PCm

Figure 14: Alternate cyclic phosphine oxide pre-catalysts

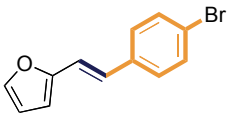
The core 5-membered ring is still present in both **PCl** and **PCm** so reduction of the phosphine oxide should not be hindered. Employment of **PCl** and **PCm** in the three CWR protocols produced interesting results. For the high temperature stabilised ylide reaction a significant increase in selectivity was observed (table 11, entries 9 and 10), while an *E/Z* ratio of 93:7 was obtained using **PCm** at room temperature (table 2, entry 10). Conversions using **PCl** were lower than for **PCm**, particularly at RT where only 16% conversion of aldehyde to olefin was obtained (table 12, entry 9). This is likely caused by the ring system of **PCl** adding increased stability to the ylide which significantly lowers its reactivity. A similar effect was observed with a previous reaction using an ester-activated bromide, where olefin yields using **PCl** were significantly lower than those using **PCa**. **PCl** and **PCm** performed remarkably in the semi-stabilised ylide conditions with both pre-catalysts imparting high *E/Z* ratios (table 14, entries 9 and 10). From these results it is clear that both **PCl** and **PCm** are far superior to **PCa-k** for obtaining high *E*-selectivity in the CWR.

Table 14: Substrate study using **PCm**

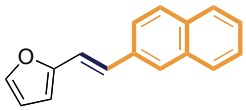




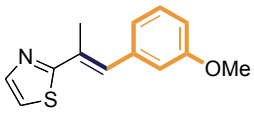
55, 82%, 95:5



56, 64%, 85:15

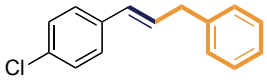


58, 65%, 90:10



87, 55%, 80:20

65, 63%, 85:15, **B**



88, 63%, 75:25

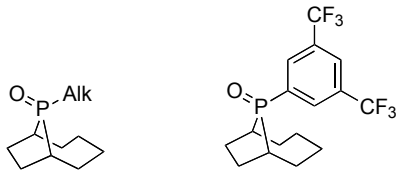
[a] *E/Z* ratio was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.

While **PCl** gave lower conversions for stabilised ylides, particularly in the room temperature conditions, **PCm** performed superbly for all protocols. A quick substrate study of semi-stabilised ylides using **PCm** showed that for all substrates a significant increase in selectivity was observed (table 14). Substrates were chosen for which iodine-mediated isomerisation of the olefin mixture was unsuccessful. A ketone was facilitated for preparation of **87**, and even **88** was prepared from a non-stabilised ylide in moderate yield with a reasonable increase in the *E/Z* ratio. This study illustrates that varying the P-substituent at the 1-position provided minimal influence on the selectivity. Use of **PCm** resulted in a CWR favouring formation of the *E*-olefin. The next stage of optimisation will focus on the development of a new catalyst based on **PCm** to impart high *E*-selectivity into the existing CWR protocols.

5 Conclusions

This work has outlined the steps taken to eradicate the issues associated with the CWR. Substrate scope was a major issue with only stabilised ylides tolerated in the original CWR. Expansion to semi-stabilised and non-stabilised ylides required efficient ylide formation *via* deprotonation of the phosphonium salt. Using strong bases such as NaO*t*Bu was shown to be incompatible with the CWR due to unwanted reaction with the silane. **54**, described as a *masked form of NaOtBu*, enabled semi-stabilised ylides to be used in the CWR, thus tolerating primary and secondary benzylic and allylic bromides and chlorides as substrates. The concept of *ylide tuning* was explored as an alternative method for ylide formation. By drawing electron density away from the phosphorus the pK_a of the ylide-forming proton was lowered. By using an electron-deficient phosphine **PCd**, formation of semi-stabilised ylides could be achieved using a mild, commercially available base (DIPEA). An alternative route to tri-substituted olefins was obtained by using ketones in place of aldehydes. The key to successful reactions of ketones was the limiting of the amount of halide in solution. This was achieved by developing a pseudo-catalytic *pulse olefination* technique, which ensured that the halide component was converted to phosphonium salt before any side-reaction or decomposition could occur. Substrate studies illustrated the wide application of the CWR, with a considerable amount of alkyl, aryl and heteroaryl aldehydes, ketones and organohalides utilised as substrates. The *E/Z* selectivity ranged from 45:55 to 80:20. For several examples, a post-reaction iodine-mediated isomerisation technique allowed full conversion to the *E*-olefin, minimising the significance of the poor *E/Z* selectivity. Non-stabilised ylides were facilitated using a combination of masked base **54** and ylide tuning. Use of organoiodides as substrates was critical to achieve phosphonium salt formation using an electron-deficient phosphine. These developments ensure that the CWR can now tolerate all three ylide classes as well as ketones. The protocols also transferred efficiently to multigram scale reactions. Siloxane removal was another significant drawback of the CWR, so the use of polymeric silane PMHS as an alternative reducing agent was investigated. While not as efficient as diphenylsilane for phosphine oxide reduction, PMHS was used successfully as a replacement in the CWR using stabilised and semi-stabilised ylides. Various primary and secondary cyano, ketone and ester-activated halides were utilised as substrates. Purification was improved considerably; the siloxane could be removed by simple filtration. Multigram synthesis of **108** proceeded in good yield and required only filtration and recrystallization steps to obtain the pure olefin. PMHS was successfully incorporated into the two CWR protocols for semi-stabilised ylides, using either **PCb** and **54** or **PCd** and DIPEA. Moderate to good yields were obtained using benzylic and allylic

halides. The use of PMHS in the CWR has eased the purification process immensely, while also reducing reagent cost, energy demand and greenhouse emissions. The final aspect of the CWR to be examined was the *E/Z* selectivity. With the exception of ketone or ester-substituted olefins which undergo phosphine-mediated isomerisation to *E/Z* >95:5, the selectivity of the CWR was typically 80:20 at best. To combat this issue the phosphine oxide pre-catalyst structure was probed to determine which structural properties influenced the *E/Z* ratio of the olefin. Initially, the substituent in the 1-position was varied to determine the effect of EWGs, EDGs and steric effect of bulky substituents.



PCm1 **PCm2**

Figure 15: Potential targets for second-generation CWR pre-catalysts

Aside from a slight increase in selectivity obtained using an alkyl substituent in place of an aryl group, no great improvements were observed. A second approach was taken whereby two phosphines known to give high *E*-selectivity in conventional Wittig reactions were tested in the CWR. The chosen candidates possessed a 5-membered cyclic structure which would ensure phosphine oxide reduction would not be hindered. **PCl** gave high *E/Z* ratios at high temperatures, albeit at lower conversions than pre-catalysts **PCa-k**. However, at room temperature only 16% conversion was obtained, likely due to the lower nucleophilicity of the phosphine. Pleasingly, **PCm** exhibited significantly increased *E*-selectivity and consistent yields for all CWR protocols. Future explorations will focus on designing a pre-catalyst using the core structure of **PCm** (figure 15, **PCm1** and **PCm2**). The ylide tuning concept explored in section 2 may be applied to **PCm**. Addition of EWGs should facilitate easier ylide formation, resulting in an *E*-selective phosphine which can be used in conjunction with DIPEA for semi-stabilised ylides or with **54** for non-stabilised ylides. Alternatively, adding an alkyl group in the 1-position instead of the phenyl group may increase selectivity as was observed for pre-catalysts **PCb** and **PCa**. The alkyl substituent may also increase the nucleophilicity of the phosphine to increase the rates of phosphine oxide reduction and phosphonium salt formation, two important factors for reactions involving ketone substrates. The final investigation will focus on combining these selective pre-catalysts based with PMHS as the reducing agent. If achieved, this would result in a cheap, green, selective organocatalytic olefination – a process which would be of substantial benefit to research and industrial synthetic chemists.

6 References

[1] T. W. Lee and E. J. Corey, *J. Am. Chem. Soc.,* **2001,** 123*,* 1872-1877.

[2] T. R. Hoye and Z. Ye, *J. Am. Chem. Soc.,* **1996,** 118*,* 1801-1802.

[3] Y. Ohashi, H. Iijima, N. Yamaotsu, K. Yamazaki, S. Sato, M. Okamura, K. Sugimoto, S. Dan, S. Hirono and T. Yamori, *J. Biol. Chem.*, **2012**, 287, 3885−3897.

[4] Y. Shiina, Y. Umezaki, Y. Ohashi, Y. Yamazaki, S. Dan and T. Yamori, *J. Med. Chem.*, **2013**, 56, 150-159.

[5] L. Lu, W. Zhang and R. G. Carter, *J. Am. Chem. Soc.*, **2008**, 130, 7253-7255.

[6] D. R. Williams, A. A. Kiryanov, U. Emde, M P. Clark, M. A. Berliner and J. T. Reeves, *Angew. Chem. Int. Ed.*, **2003**, 42, 1258-1262.

[7] W. C. Still and C. Gennari, *Tetrahedron Lett.*, **1983**, 24, 4405-4408.

[8] (a) P. R. Blackemore, *J. Chem. Rev., Perkin Trans. 1*, **2002**, 2563-2585. (b) M. Julia and J.-M. Paris, *Tetrahedron. Lett.*, **1973**, 14, 4833-4836.

[9] P. J. Kocienski, B. Lythgoe and S. Ruston, *J. Chem. Soc., Perkin Trans. 1*, **1978**, 829-834.

[10] G. Kim, M. Y. Chu-Moyer, S. J. Danishefsky and G. K. Schulte, *J. Am. Chem. Soc.,* **1993**, 115, 30-39.

[11] J. B. Baudin, G. Hareau, S. A. Julia and O. Ruel, *Tetrahedron Lett.*, **1991**, 32, 1175-1178.

[12] C. Meyers and E. M. Carreira, *Angew. Chem. Int. Ed.*, **2003**, 42, 694-696.

[13] (a) L. F. van Staden, D. Gravestock and D. J. Ager, *Chem. Soc. Rev.*, **2002**, 31, 195-200. (b) D. J. Peterson, *J. Org. Chem.*, **1968**, 33, 780-784.

[14] A. Toró, P. Nowak and P. Deslongchamps, *J. Am. Chem. Soc.*, **2000**, 122, 4526-4527.

[15] (a) I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, **2000**, 100, 3009-3066. (b) R. F. Heck, *J. Am. Chem. Soc.*, **1969**, 91, 6707-6714.

[16] R. F. Heck and J. P. Nolley Jr., *J. Org. Chem.*, **1972**, 37, 2320-2322.

[17] T. Mizoroki, K. Mori and A. Ozaki, *Bull. Chem. Soc. Jap.*, **1971**, 44, 581.

[18] F. E. Hahn, M. C. Jahnke, V. Gomez-Benitez, D. Morales-Morales and T. Pape, *Organometallics*, **2005**, 24, 6458-6463.

[19] N. J. Whitcombe, K. K. M. Hii and S. E. Gibson, *Tetrahedron*, **2001**, 57, 7449-7476.

[20] H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.*, **1974**, 96, 1133-1136.

[21] C. B. Ziegler Jr. And R. F. Heck, *J. Org. Chem.*, **1978**, 43, 2941-2946.

[22] M. Qadir, T. Möchel and K. K. M. Hii, *Tetrahedron*, **2000**, 56, 7975-7979.

[23] Y. Sato, M. Sodeoka and M. Shibasaki, *J. Org. Chem.*, **1989**, 54, 4738-4739.

[24] N. E. Carpenter, D. J. Kucera and L. E. Overman, *J. Org. Chem.*, **1989**, 54, 5846.

[25] A. B. Dounay and L. E. Overman, *Chem. Rev.*, **2003**, 103, 2945-2963.

[26] D. H. B. Ripin, D. E. Bourassa, T. Brandt, M. J. Castaldi, H. N. Frost, J. Hawkins, P. J. Johnson, S. S. Massett, K. Neumann, J. Phillips, J. W. Raggon, P. R. Rose, J. L. Rutherford, B. Sitter, A. M. Stewart III, M. G. Vetelino and L. Wei, *Org. Process. Res. Dev.*, **2005**, 9, 440-450.

[27] *Handbook of Metathesis* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, Germany, **2003**, vols. 1-3.

[28] N. Calderon, H. Y. Chen and K. W. Scott, *Tetrahedron Lett.* **1967**, 3327-3329.

[29] E. F. Lutz, *J. Chem. Educ.*, **1986**, 63, 202-203.

[30] R. L. Banks and G. C. Bailey, *Ind. Eng. Chem. Prod. Res. Dev.*, **1964**, 3, 170-173.

[31] J.-L. Hérisson and Y. Chauvin, *Macromol. Chem.*, **1971**, 141, 161-176.

[32] R. H. Grubbs and T. K. Brunck, *J. Am. Chem. Soc.*, **1972**, 94, 2538-2540.

[33] T. J. Katz and J. McGinnis, *J. Am. Chem. Soc.*, **1975**, 97, 1592-1594.

[34] J. H. Wengrovious, R. R. Schrock, M. R. Churchill, J. R. Missert and W. J. Youngs, *J. Am. Chem. Soc.*, **1980**, 102, 4515-4516.

[35] F. N. Tebbe, G. W. Parshall and G. S. Reddy, *J. Am. Chem. Soc.*, **1978**, 100, 3611-3613.

[36] R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare and M. O'Regan, *J. Am. Chem. Soc.*, **1990**, 112, 3875-3886.

[37] P. Schwab, R. H. Grubbs and G. W. Ziller, *J. Am. Chem. Soc.*, **1996**, 118, 100-110.

[38] M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, **1999**, 1, 953-956.

[39] S. B. Garber, J. S. Kingsbury, B. L. Gray and A. H. Hoveyda, *J. Am. Chem. Soc.*, **2000**, 122, 8168-8179.

[40] S. J. Meek, R. V. O'Brien, J. Llaveria, R. R. Schrock and A. H. Hoveyda, *Nature*, **2011**, 471, 461-466.

[41] S. Kress and S. Blechert, *Chem. Soc. Rev.*, **2012**, 41, 4389-4408.

[42] K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem. Int. Ed.*, **2005**, 44, 4490 – 4527.

[43] J. A. McCauley, C. J. McIntyre, M. T. Rudd, K. T. Nguyen, J. J. Romano, J. W. Butcher, K. F. Gilbert, K. J. Bush, M. K. Holloway, J. Swestock, B.-L. Wan, S. S. Carroll, J. M. DiMuzio, D. J. Graham, S. W. Ludmerer, S.-S. Mao, M. W. Stahlhut, C. M. Fandozzi, N. Trainor, D. B. Olsen, J. P. Vacca and N. J. Liverton, *J. Med. Chem.*, **2010**, 53, 2443–2463.

[44] T. Nicola, M. Brenner, K. Donsbach and P. Kreye, *Org. Process Res. Dev.*, **2005**, 9, 513-515.

[45] V. Farina, C. Shu, X. Zeng, X. Wei, Z. Han, N. K. Yee and C. H. Senanayake, *Org. Process Res. Dev.*, **2009**, 13, 250-254.

[46] M. Edmonds and A. Abell in *Modern Catalytic Olefination* (Ed.: T. Takeda), Wiley-VCH, Weinheim, Germany, **2004**, ch. 1.

[47] G. Wittig and G. Geissler, *Liebigs Ann. Chem.*, **1953**, 580, 44-57.

[48] H. Staudinger and M. Meyer, *Helv. Chim. Acta,* **1919**, 2, 635-646.

[49] G. Wittig and U. Schöllkopf *Chem. Ber.,* **1954**, 87, 1318.

[50] E. Vedejs and C. F. Marth, *J. Am. Chem. Soc.*, **1988**, 110, 3948-3958.

[51] E. Vedejs and C. F. Marth, *J. Am. Chem. Soc.*, **1990**, 112, 3905-3909.

[52] R. Robiette, J. Richardson, V. K. Aggarwal and J. N. Harvey, *J. Am. Chem. Soc.*, **2006**, 128, 2394-2409.

[53] P. A. Byrne and D. G. Gilheany, *Chem. Soc. Rev.*, **2013**, 42, 6670-6696.

[54] M. Schlosser and K. F. Christmann, *Angew. Chem. Int. Ed. Engl*., 1966, 5, 126.

[55] M. Schlosser, K. F. Christmann, A. Piskala and D. Coffinet, *Synthesis*, **1971**, 1, 29-31.

[56] D. M. Hodgson and T. Arif, *J. Am. Chem. Soc.*, **2008**, 130, 16500–16501.

[57] J. J. Duffield and G. R. Pettit, *J. Nat. Prod.,* **2001**, 64,472-479.

[58] L. Horner, H. M. R. Hoffmann and H. G. Wippel, *Chem. Ber.*, **1958**, 91, 61-63.

[59] W. S. Wadsworth Jr. and W. D. Emmons, *J. Am. Chem. Soc.*, **1961**, *83*, 1733–1738.

[60] B. A. Arbuzov, *Pure Appl. Chem.*, **1964**, 9, 307-353.

[61] M. G. Stocksdale, S. Ramurthy and M. J. Miller, *J. Org. Chem.*, **1998**, 63, 1221-1225.

[62] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, **1984**, 25, 2183-2186.

[63] T.D.W. Claridge, S.G. Davies, J.A. Lee, R.L. Nicholson, P.M. Roberts, A.J. Russell, A.D. Smith, S.M. Toms, *Org. Lett*., **2008**, 10, 5437-5440.

[64] T.-T. Kao, S. Syu, Y.-W. Jhang and W. Lin, *Org. Lett.,* **2010**, 12, 3066-3069.

[65] L. A. Evans, K. E. Griffiths, H. Guthmann and P. J. Murphy, *Tetrahedron Lett.*, **2002**, 43, 299–301.

[66] L. Heys, P. J. Murphy, S. J. Coles, T. Gelbrich and M. B. Hursthouse, *Tetrahedron Lett.*, **1999**, 40, 7151–7152.

[67] I. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler and R. B. Woodward, *J. Am. Chem. Soc.*, **1978**, 100, 8214-8222.

[68] S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, **1981**, 22, 3815-3818.

[69] J. A. Murphy, A. G. J. Commeureuc, T. N. Snaddon, T. M. McGuire, T. A> Khan, K. Hisler, M. L. Dewis and R. Carling, *Org. Lett.*, **2005**, 7, 1427-1429.

[70] D.M. Bollag, P.A. McQueney, J. Zhu, O. Hensens, L. Koupal, J. Liesch, M. Goetz, E. Lazarides, C.M. Woods, *Cancer Research*, **1995**, 55, 2325-2333.

[71] G. E. Keck, R. L. Giles, V. J. Cee, C. A. Wager, T. Yu and M. B. Kraft, *J. Org. Chem.* **2008**, 73, 9675–9691.

[72] M. Ball, M. J. Gaunt, D. F. Hook, A. S. Jessiman, S. Kawahara, P. Orsini, A. Scolaro, A. C. Talbot, H. R. Tanner, S. Yamanoi and S. V. Ley, *Angew. Chem. Int. Ed.*, **2005**, 44, 5433-5438.

[73] C. C. Hughes, J. B. MacMillan, S. P. Gaudêncio, W. Fenical and J. J. La Clair, *Angew. Chem. Int. Ed.*, **2009**, 48, 728-732.

[74] C. C. Hughes and W. Fenical, *J. Am. Chem. Soc.*, **2010**, 132, 2528–2529.

[75] A. B. Smith III, T. J. Beauchamp, M. J. LaMarche, M. D. Kaufman, Y. Qui, H. Arimoto, D. R. Jones and K. Kobayashi, *J. Am. Chem. Soc.* **2000,** 122, 8654-8664.

[76] L. Shu, P. Wang, C. Gu, W. Liu, L. M. Alabanza and Y. Zhang, *Org. Process Res. Dev.*, **2013**, 17, 651-657.

[77] M. Stivanello, L. Leoni and R. Bortolaso, *Org. Process Res. Dev.*, **2002**, 6, 807-810.

[78] V. V. N. K. V. P. Raju, V. Ravindra, V. T. Mathad, P. K. Dubey and P. P. Reddy, *Org. Process Res. Dev.*, **2009**, 13, 710-715.

[79] L. Shi, W. Wang, Y. Wang and Y.-Z. Huang, *J. Org. Chem.*, **1989**, 54, 2027-2028.

[80] Y.-Z. Huang, L.-L. Shi, S.-W. Li and X.-Q. Wen, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 2397-2399.

[81] M. F. Hughes, *Toxicology Letters*, **2002**, 133, 1-16.

[82] B. L. Sailer, N. Liles, S. Dickerson and T. G. Chasteen, *Arch. Toxicol.*, **2003**, 77, 30-36.

[83] C.J. O'Brien, J.L. Tellez, Z.S. Nixon, L.J. Kang, A.L. Carter, S.R. Kunkel, K.C. Przeworski, G.A. Chass, *Angew. Chem. Int. Ed*., **2009**, 48, 6836 –6839.

[84] C. J. O'Brien, Z. S. Nixon, A. J. Holohan, S. R. Kunkel, J. L. Tellez, B. J. Doonan, E. E. Coyle, F. Lavigne, L. J. Kang and K. C. Przeworski, *Chem. Eur. J.*, **2013**, 19, 15281-15289.

[85] C. J. O'Brien, F. Lavigne, E. E. Coyle, A. J. Holohan, B. J. Doonan, *Chem. Eur. J.*, **2013**, 19, 5854 – 5858.

[86] Y. Li, L.-Q. Lu, S. Das, S. Pisiewicz, K. Junge and M. Beller, *J. Am. Chem. Soc.*, **2012**, 134, 18325-18329.

[87] Y. Fu, H.-J. Wang, S.-S. Chong, Q.-X. Guo and L. Liu, *J. Org. Chem.*, **2009**, 74, 810-819.

[88] R. Zhou, C. Z. Wang, H. B. Song and Z. J. He, *Org. Lett.,* **2010**, 12, 976-979.

[89] S. Fulda, *Drug Discovery Today*, **2010**, *15*, 757-765.

[90] (a) G. Guirado, C. Coudret, M. Hliwa and J.-P. Launay, *J. Phys. Chem. B,* **2005**, 109*,* 17445-17459. (b) M. Irie, O. Miyatake and K. Uchida, *J. Am. Chem. Soc.*, **1992**, 114, 8716-8717.

[91] (a) P. Barraja, L. Caracausi, P. Diana, V. Spanò, A. Montalbano, A. Carbone, B. Parrino and G. Cirrincione, *ChemMedChem,* **2012**, 7, 1901-1904. (b) S. V. Drach, R. P. Litvinovskaya and V. A. Khripach, *Chem. Heterocycl. Compd.*, **2000**, 36, 233-255.

[92] P. Du, J. L. Brosmer and D. G. Peters, *Org. Lett.*, **2011**, 13, 4072-4075.

[93] E. Vedejs, M. J. Peterson, *Top. Stereochem.,* **1994**, 21, 1-157.

[94] D. De L. Martins, H. M. Alvarez, L. C. S. Aguiar and O. A. C. Antunes, *Appl. Catal., A*, **2011**, 408, 47-53.

[95] G. L. Lange and C. Gottardo, *Synth. Commun.*, **1990**, 20, 1473-1479.

[96] (a) http://www.sigmaaldrich.com/catalog/product/aldrich/176206?lang=en&region=IE

(b) http://www.sigmaaldrich.com/catalog/product/aldrich/148482?lang=en&region=IE

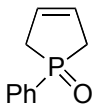
[97] H. A. van Kalkeren, A. L. Blom, F. P. J. T. Rutjes and M. A. J. Huijbregts, *Green Chem.*, **2013**, *15*, 1255-1263.

Appendix A: Experimental

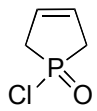
General Experimental

All reagents were purchased from commercial sources and were used without further purification, unless otherwise stated. Polymethylhydrosiloxane (PMHS) average M_n 1700-3200 amu was purchased from Sigma Aldrich or Gelest Inc. Dry solvents were purchased from Sigma Aldrich and Fisher (Acros Organics) and handled under argon. Toluene was freshly distilled from calcium hydride and handled under argon. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone and handled under argon. Deuterated solvents were purchased from Fluorochem. Thin Layer Chromatography (TLC) was performed on Macherey-Nagel ALUGRAM® Xtra SIL G/UV_{254} aluminum-backed plates, and spots were visualized using UV light (254 nm), $KMnO_4$, or PMA stains. Column chromatography purifications were carried out using the flash technique on DAVISIL LC60A (35-70 μm) or using the dry flash technique on Fluka TLC Grade silica gel.[1] NMR spectra were recorded on Bruker Avance 400 and Bruker Avance Ultrashield 600 spectrometers. The chemical shifts (δ) for ^1H and ^{13}C are given in ppm and referenced to the residual proton signal of the deuterated solvent ($CHCl_3$ at δ 7.26 ppm, 77.16 ppm, respectively), (H_2O at δ 4.79 ppm); coupling constants are expressed in Hz. Melting points were recorded on a Stuart Scientific SMP1 melting point apparatus and are uncorrected. All experiments were conducted under an atmosphere of dry argon or nitrogen, unless otherwise noted, using Schlenk technique.[1] Reaction vessels were sealed with a septum and purged with inert gas using the needle line from a Schlenk manifold and silicone oil bubbler. *E* and *Z* refer to the stereochemistry of the bond formed during the reaction (colored dark blue in tables 1-14). Compounds were named using ACD IUPAC naming tools. Phosphine oxides **PCa-m** were prepared by Dr Florie Lavigne, Dr Emma E. Coyle and Bryan J. Doonan.

Synthetic Procedures



1-Phenyl-3-phospholene-1-oxide:[2] A flame-dried sealed tube was charged with 2,6-di-*t*-butyl-4-methylphenol (110 mg, 0.5 mmol, 0.5 mol %) under nitrogen. 1,3-Butadiene (14.0 mL, 0.3 mol, 3.0 equiv.) was introduced by condensation at -78 °C in a liquid nitrogen/acetone bath, after which *P*,*P*-dichlorophenylphosphine (13.6 mL, 0.1 mol, 1.0 equiv.) was added. The tube was sealed and allowed to stand in darkness at RT for 15 days. After removal of excess 1,3-butadiene, ice water (30 mL) was added to the remaining red-brown viscous oil, which was stirred vigorously until residues dissolved fully. The solution was extracted in dichloromethane (3 x 30 mL) and the combined organic layers were neutralized using sodium carbonate (effervescence observed). The resultant solution was filtered, dried with magnesium sulfate, filtered and the solvent removed *in vacuo* to give a yellow-orange oil. Purification by dry flash column chromatography (methanol/dichloromethane, gradient 4-8%) yielded 1-phenyl-3-phospholene-1-oxide as a pale green solid (5.2 g, 30%). ^{1}H and ^{31}P NMR spectra are consistent with literature.

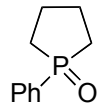


1-Chloro-3-phospholene-1-oxide:[3] A flame-dried sealed tube (100 mL ChemGlass CG-1880-25 or 125 mL AceGlass 8648-96) equipped with a stir-bar was charged with 2,6-di-*t*-butyl-4-methylphenol (55 mg, 0.25 mmol, 0.5 mol %) under nitrogen. 1,3-Butadiene (6.8 mL, 0.15 mol, 3.0 equiv.) was introduced by condensation at -78 °C in a liquid nitrogen/acetone bath, after which phosphorus trichloride (4.4 mL, 0.05 mol, 1.0 equiv.) and tris(2-chloroethyl) phosphite (6.0 mL, 0.03 mol, 0.6 equiv.) were introduced *via* syringe. The tube was sealed under nitrogen using a front-sealing bushing (back sealing bushings are unsuitable, as contact with hot reaction vapors causes swelling, resulting in loss of seal). The solution was stirred at 105 °C for 48 hours. A blast shield was placed around the reaction vessel for the duration of the reaction. A cloudy yellow solution resulted, which was filtered *via* needle cannula.[1] 1,2-Dichloroethane was removed in vacuo and the resultant pale yellow solid was shown to consist of 1-chloro-3-phospholene-1-oxide

and 1-hydroxy-3-phospholene-1-oxide (90:10). ^{1}H and ^{31}P NMR spectra are consistent with literature. Product was used without further purification.

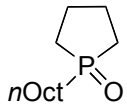
General procedure for 3-phospholene-1-oxide preparation: A round-bottom flask equipped with a stir-bar and reflux condenser was charged with magnesium turnings (1.2 equiv.), then flame dried *in vacuo*. Iodine (one crystal) and THF (1.0 mL) were introduced. A solution of organohalide (1.0 equiv) in THF was added dropwise until the brown color dissipated and the reaction was initiated by heating. The remaining organohalide solution was added slowly, maintaining reflux, and the resultant solution was stirred at reflux for a further 1 h. To a portion of this Grignard reagent (1.0 equiv.) at 0 °C was added 1-chloro-3-phospholene-1-oxide solution dropwise (1.0 equiv., 1 M in THF. Introduction of THF to crude 1-chloro-3-phospholene-1-oxide led to precipitation of the 1-hydroxy-3-phospholene by-product. 1-Chloro-3-phospholene-1-oxide solution was obtained following needle cannulation). The resultant solution was allowed to warm to RT and stirred for 16 h. The reaction mixture was quenched with water and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and solvent removed *in vacuo* to give the crude 3-phospholene-1-oxide. Purification by flash column chromatography yielded pure 3-phospholene-1-oxide.

General procedure for preparation of phospholane-1-oxides via hydrogenation of 3-phospholene-1-oxides: Pd/C (10% w/w, 6-10 mol %) was transferred to a round-bottom flask containing a magnetic stir-bar and sealed under nitrogen. Dichloromethane (1 mL) was added, followed by 3-phospholene-1-oxide dissolved in methanol (0.35 M). The vessel was purged with hydrogen using a balloon and silicon oil bubbler. The bubbler was removed and the mixture was stirred under hydrogen at room temperature for 24 h. The crude mixture was filtered through a plug of Celite® and the filtrate treated with activated charcoal to remove any residual dissolved palladium. After stirring for 1 h the solution was filtered through Celite® and solvent removed *in vacuo*.



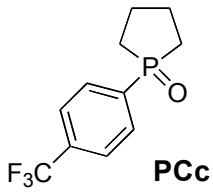
PCa

1-Phenylphospholane-1-oxide[4] (PCa) was prepared in accordance with the general procedure for hydrogenation from the reaction of 1-phenyl-3-phospholene-1-oxide (1.79 g, 10.0 mmol, 1.0 equiv.) with an excess of H_2 using Pd/C (10 % w/w; 1.10 g, 1.0 mmol, 10 mol %) in methanol/dichloromethane solution (30:1 mL) at room temperature for 24 h. **PCa** was obtained as a pale yellow, viscous oil (1.80 g, 99%). ^{1}H and ^{31}P NMR spectra are consistent with literature.



PCb

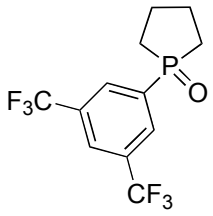
1-*n*-Octyl-3-phospholane-1-oxide (PCb) was prepared according to the general procedure from the reaction of magnesium turnings (0.29 g, 12.0 mmol, 1.2 equiv.), 1-bromooctane (1.7 mL, 10.0 mmol, 1.0 equiv., 1 M in THF) and 1-chloro-3-phospholene-1-oxide (0.98 g, 7.1 mmol, 1.0 equiv.). Purification by flash column chromatography (methanol/dichloromethane, gradient 1-3%) gave 1-*n*-octyl-3-phospholene-1-oxide as a yellow oil (0.93 g, 61%). Hydrogenation in accordance with the general procedure, from the reaction of 1-*n*-octyl-3-phospholene-1-oxide (0.93 g, 4.3 mmol, 1.0 equiv.) with an excess of H_2 using Pd/C (10% w/w; 0.42 g, 0.4 mmol, 10 mol %) in a methanol/dichloromethane solution (4:1 mL) at room temperature for 24 h yielded **PCb** as a colorless oil (0.90 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.69 (t, J = 7.2 Hz, 3H), 1.08-1.10 (m, 8H), 1.20-1.27 (m, 2H), 1.42-1.69 (m, 10H), 1.78-1.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 21.9 (d, J_{CP} = 4.4 Hz), 22.3, 24.3 (d, J_{CP} = 8.0 Hz), 26.3, 26.6 (d, J_{CP} = 64.9 Hz), 28.8 (d, J_{CP} = 10.9 Hz), 30.6 (d, J_{CP} = 61.8 Hz), 30.8 (d, J_{CP} = 13.1 Hz), 31.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 71.4; HRMS $[M+H]^+$ m/z calcd. 217.1721, found 217.1717.



PCc

1-(4-(Trifluoromethyl)phenyl)phospholane-1-oxide (PCc) was prepared according to the general procedure from the reaction of magnesium turnings (0.72 g, 36.0 mmol, 1.2 equiv.), 4-bromobenzotrifluoride (4.2 mL, 30.0 mmol, 1.0 equiv., 1 M in THF) and 1-chloro-3-phospholene-1-oxide (3.60 g, 26.3 mmol, 1.0 equiv.). Purification by flash column chromatography (methanol/dichloromethane, gradient 0.5-1.0%) gave 1-(4-

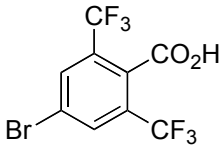
(trifluoromethyl)phenyl)-3-phospholene-1-oxide as a white solid (3.21 g, 49%). Hydrogenation in accordance with the general procedure, from the reaction of 1-(4-(trifluoromethyl)phenyl)-3-phospholene-1-oxide (2.36 g, 9.6 mmol, 1.0 equiv.) with an excess of H_2 using Pd/C (10% w/w; 0.96 g, 0.9 mmol, 9 mol %) in a methanol/dichloromethane solution (11:1 mL) at room temperature for 24 h yielded **PCc** as a white solid (2.21 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.88-2.22 (m, 8H), 7.88 (dd, J = 8.4, 2.0 Hz, 2H), 7.82 (dd, J = 10.8, 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3 (d, J_{CP} = 8.7 Hz), 29.7 (d, J_{CP} = 67.6 Hz), 123.6 (q, J_{CF} = 270.8 Hz), 125.5 (dq, J_{CP} = 3.6 Hz, J_{CF} = 11.6 Hz), 130.5 (d, J_{CP} = 10.2 Hz), 133.6 (qd, J_{CP} = 3.0 Hz, J_{CF} = 29.8 Hz), 138.9 (d, J_{CP} = 85.9 Hz); ^{31}P NMR (162 MHz, CDCl3) δ: 57.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.2; mp 59-61 °C; HRMS $[M+H]^+$ m/z calcd. 249.0656, found 249.0658.



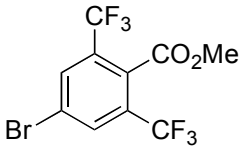
PCd

1-(3,5-Bis(trifluoromethyl)phenyl)phospholane-1-oxide (PCd) was prepared according to the general procedure from the reaction of magnesium turnings (0.69 g, 28.8 mmol, 1.2 equiv.), 1,3-bis(trifluoromethyl)-5-bromobenzene (4.1 mL, 24.0 mmol, 1.0 equiv., 0.5 M in THF) and 1-chloro-3-phospholene-1-oxide (3.00 g, 21.9 mmol, 1.0 equiv.). Purification by flash column chromatography (methanol/dichloromethane, gradient 0.5-1.0%) gave 1-(3,5-bis(trifluoromethyl)phenyl)-3-phospholene-1-oxide as a white solid (3.51 g, 51%). Hydrogenation in accordance with the general procedure, from the reaction of 1-(3,5-bis(trifluoromethyl)phenyl)-3-phospholene-1-oxide (3.50 g, 11.1 mmol, 1.0 equiv.) with an excess of H_2 using Pd/C (10% w/w; 1.08 g, 1.0 mmol, 10 mol %) in a methanol/dichloromethane solution (30:1 mL) at room temperature for 24 h yielded **PCd** as a yellow solid (3.42 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.87-2.19 (m, 8H), 7.89 (s, 1H), 8.07 (d, J = 10.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.2 (d, J_{CP} = 34.8 Hz), 29.6 (d, J_{CP} = 68.4 Hz), 122.8 (q, J_{CF} = 271.4 Hz), 125.3 (m), 130.1 (dd, J_{CP} = 2.9 Hz, J_{CF} = 9.5 Hz), 132.1 (qd, J_{CP} = 10.9 Hz, J_{CF} = 33.4 Hz), 138.1

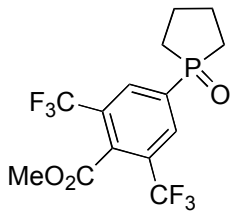
(d, J_{CP} = 83.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 54.98; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.17; mp 82-85 °C; HRMS $[M+H]^+$ m/z calcd. 317.0530, found 317.0530.



4-Bromo-2,6-bis(trifluoromethyl)benzoic acid:[5] 1,3-Dibromo-5,5-dimethylhydantoin (5.48 g, 19.2 mmol, 1.0 equiv) was dissolved at RT in conc. sulfuric acid (20 mL). The solution was cooled to 0 °C and 2,6-bis(trifluoromethyl)benzoic acid (5.00 g, 19.2 mmol, 1.0 equiv.) was added. The slurry was stirred at 0 °C for 2 h followed by stirring overnight at RT after which time it was poured into ice water (250 mL). The white precipitate was isolated by filtration and dried *in vacuo* to give 4-bromo-2,6-bis(trifluoromethyl)benzoic acid as a white solid (4.91 g, 77%). ^{1}H NMR spectrum is consistent with literature.



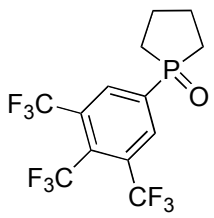
Methyl-4-bromo-2,6-bis(trifluoromethyl)benzoate:[6] To a solution of 4-bromo-2,6-bis(trifluoromethyl) benzoic acid (5.00 g, 14.8 mmol) in acetonitrile (56 mL) were added iodomethane (4.6 mL, 75.9 mmol) and K_2CO_3 (5.11 g, 37.0 mmol) at RT under N_2 atmosphere. After being stirred for 6 h at RT, the reaction mixture was quenched with sat. aq. $Na_2S_2O_3$, diluted with EtOAc, washed with water and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (1% ethyl acetate in hexane) gave methyl-4-bromo-2,6-bis(trifluoromethyl)benzoate as a white solid (4.21 g, 85%). ^{1}H NMR spectrum is consistent with literature.



PCe

1-(Methyl-2,6-bis(trifluoromethyl)benzoate)phospholane-1-oxide (PCe): A 50 mL round-bottom flask equipped with a stir-bar and reflux condenser was charged with magnesium turnings (0.43 g, 18.0 mmol, 1.2 equiv.), then flame dried in vacuo. Iodine (one crystal) and THF (1.0 mL) were introduced. A solution of 2-chloropropane (1.4 mL, 15.0 mmol, 1.0 equiv.) in THF (15.0 mL) was added dropwise until the brown color dissipated and the reaction was initiated by heating. The remaining halide solution was added slowly, maintaining reflux, and the resultant solution was stirred at reflux for a

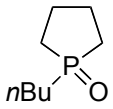
further 3 h. In a 100 mL round-bottom flask, methyl-4-bromo-2,6-bis(trifluoromethyl)benzoate (3.90 g, 11.0 mmol, 1.0 equiv.) was dissolved in THF (22 mL) under argon. The reaction mixture was cooled to –40 °C and charged slowly with a portion of the Grignard reagent (12.0 mL, 12.0 mmol, 1.1 equiv.). The reaction mixture was maintained at this temperature for 3 h, then 1-chloro-3-phospholene-1-oxide solution was added dropwise (1.50 g, 11.0 mmol, 1.0 equiv.). The resultant solution was stirred at –40 °C for 2 h, then warmed to RT and stirred for 16 h, resulting in a yellow solution. The reaction mixture was quenched with water and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and solvent removed *in vacuo* to give a yellow oil. Purification by flash column chromatography (methanol/dichloromethane, gradient 0.5-1.0%) gave 1-(methyl-2,6-bis(trifluoromethyl)benzoate)-3-phospholene-1-oxide as a white solid (2.73 g, 67%). Hydrogenation in accordance with the general procedure, from the reaction of 1-(methyl-2,6-bis(trifluoromethyl) benzoate)-3-phospholene-1-oxide (2.63 g, 7.1 mmol, 1.0 equiv.) with an excess of H_2 using Pd/C (10% w/w; 675 mg, 0.6 mmol, 8 mol %) in a methanol/dichloromethane solution (23:1 mL) at room temperature for 14 h yielded **PCe** as an off-white solid (2.58 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.88-2.30 (m, 8H), 3.90 (s, 3H), 8.18 (d, J = 10.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3 (d, J_{CP} = 8.7 Hz), 29.7 (d, J_{CP} = 68.4 Hz), 53.6, 122.4 (q, J_{CF} = 273.5 Hz), 129.6 (dq, J_{CP} = 10.9 Hz, J_{CF} = 32.7 Hz), 131.4 (m), 133.2 (m), 138.8 (d, J_{CP} = 82.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 55.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -60.1; mp 141-143 °C; HRMS $[M+H]^+$ m/z calcd. 375.0585, found 375.0585.



PCf

1-(3,4,5-Tris(trifluoromethyl)phenyl)phospholane-1-oxide (PCf) was prepared using the same procedure as 1-(methyl-2,6-bis(trifluoromethyl)benzoate)-3-phospholene-1-oxide by the reaction of magnesium turnings (260 mg, 11.0 mmol, 1.1 equiv.), 2-chloropropane

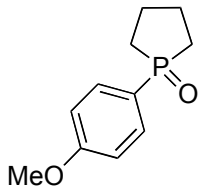
(910 mL, 10.0 mmol, 1.0 equiv.), 1-bromo-3,4,5-tris(trifluoromethyl)benzene (1.30 g, 3.7 mmol, 1.0 equiv.) and 1-chloro-3-phospholene-1-oxide (510 mg, 3.7 mmol, 1.0 equiv.). Purification by flash column chromatography (methanol/dichloromethane, gradient 0.5-1.0%) to give 1-(3,4,5-tris(trifluoromethyl)phenyl)-3-phospholene-1-oxide as a white solid (655 mg, 46%). Hydrogenation in accordance with the general procedure, from the reaction of 1-(3,4,5-tris(trifluoromethyl)phenyl)-3-phospholene-1-oxide (653 mg, 1.7 mmol, 1.0 equiv.) with an excess of H_2 using Pd/C (10% w/w; 138 mg, 0.1 mmol, 6 mol %) in a methanol/dichloromethane solution (5:1 mL) at room temperature for 24 h yielded **PCf** as an off-white solid (645 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.84-2.37 (m, 8H), 8.32 (d, J = 10.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3 (d, J_{CP} = 8.7 Hz), 29.6 (d, J_{CP} = 68.4 Hz), 121.2 (q, J_{CF} = 274.2 Hz), 122.1 (q, J_{CF} = 273.5 Hz), 130.4 (q, J_{CF} = 36.4 Hz), 125.3 (m), 131.4 (qd, J_{CP} = 10.9 Hz, J_{CF} = 33.5 Hz), 133.0 (m), 141.2 (d, J_{CP} = 81.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 58.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -55.3, -57.9; mp 103-105 °C; HRMS $[M+H]^+$ m/z calcd. 385.0404, found 385.0421.



PCg

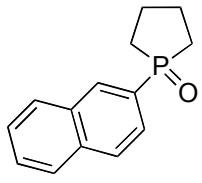
1-*n*-Butyl-3-phospholane-1-oxide (PCg)[7] was prepared according to the general procedure from the reaction of magnesium turnings (0.43 g, 18.0 mmol, 1.2 equiv.), 1-bromobutane (1.6 mL, 15.0 mmol, 1.0 equiv., 1 M in THF) and 1-chloro-3-phospholene-1-oxide (1.66 g, 12.0 mmol, 1.0 equiv.). Purification by flash column chromatography (methanol/dichloromethane, gradient 1-3%) gave 1-*n*-butyl-3-phospholene-1-oxide as a yellow oil (1.05 g, 55%). Hydrogenation in accordance with the general procedure, from the reaction of 1-*n*-butyl-3-phospholene-1-oxide (0.60 g, 3.8 mmol, 1.0 equiv.) with an excess of H_2 using Pd/C (10% w/w; 0.31 g, 0.4 mmol, 10 mol %) in a methanol/dichloromethane solution (9:1 mL) at room temperature for 48 h yielded **PCg** as a yellow oil (0.58 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (t, J = 7.4 Hz, 3H), 1.45 (m, 2H), 1.58-1.84 (m, 10H), 1.93-2.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 24.2 (d, J_{CP} = 13.8 Hz), 24.3 (d, J_{CP} = 4.4 Hz), 24.6 (d, J_{CP} = 8 Hz), 27.0 (d, J_{CP} = 64.7 Hz), 30.6 (d,

J_{CP} = 61.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 69.0; HRMS $[M+H]^+$: m/z calcd. 161.1095, found 161.1093.



PCh

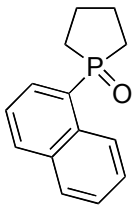
1-(4-Methoxyphenyl)phospholane-1-oxide (PCh) was prepared according to the general procedure from the reaction of magnesium turnings (0.18 g, 7.3 mmol, 1.2 equiv.), 4-bromoanisole (0.77 mL, 6.1 mmol, 1.0 equiv., 1 M in THF) and 1-chloro-3-phospholene-1-oxide (0.76 g, 5.5 mmol, 1.0 equiv.). Purification by flash column chromatography (methanol/dichloromethane, gradient 0-1%) gave 1-(4-methoxyphenyl)-3-phospholene-1-oxide as a colorless oil (0.58 g, 51%). Hydrogenation in accordance with the general procedure, from the reaction of 1-(4-methoxyphenyl)-3-phospholene-1-oxide (1.02 g, 4.9 mmol, 1.0 equiv.) with an excess of H_2 using Pd/C (10% w/w; 0.52 g, 0.5 mmol, 10 mol %) in a methanol/dichloromethane solution (4:1 mL) at room temperature for 48 h yielded **PCh** as a white solid (0.27 g, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.84-2.20 (m, 8H), 3.82 (s, 3H), 6.97 (dd, J = 8.8, 2.0 Hz, 2H), 7.63 (dd, J = 11.2, 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3 (d, J_{CP} = 8.1 Hz), 29.9 (d, J_{CP} = 68.4 Hz), 55.4, 114.3 (d, J_{CP} = 12.5 Hz), 125.4 (d, J_{CP} = 96.2 Hz), 131.8 (d, J_{CP} = 11.0 Hz), 162.4 (d, J_{CP} = 2.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 60.0.



PCi

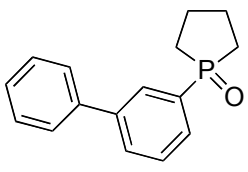
1-(Naphthalene-2-yl)phospholane-1-oxide (PCi) was prepared according to the general procedure from the reaction of magnesium turnings (0.13 g, 5.5 mmol, 1.1 equiv.), 2-bromonaphthalene (1.04 g, 5.0 mmol, 1.0 equiv., 1 M in THF) and 1-chloro-3-phospholene-1-oxide (0.61 g, 4.4 mmol, 1.0 equiv.). Purification by flash column chromatography (methanol/dichloromethane, gradient 0-2%) gave 1-(2-naphthyl)-3-phospholene-1-oxide as a green solid (0.49 g, 50%). Hydrogenation in accordance with the general procedure, from the reaction of 1-(naphthalene-2-yl)-3-phospholene-1-oxide (0.49 g, 2.2 mmol, 1.0 equiv.) with an excess of H_2 using Pd/C (10% w/w; 0.21 g, 0.2 mmol, 10 mol %) in a methanol/dichloromethane solution (4:1 mL) at room temperature for 48 h yielded **PCi** as

an off-white solid (0.39 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.88-2.20 (m, 8H), 7.47-7.57 (m, 3H), 7.78-7.89 (m, 3H), 8.34 (d, J = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4 (d, J_{CP} = 8.1 Hz), 29.7 (d, J_{CP} = 67.6 Hz), 124.5 (d, J_{CP} = 11.0 Hz), 127.0, 127.7, 128.0, 128.6 (d, J_{CP} = 11.7 Hz), 128.7, 131.1 (d, J_{CP} = 90.4 Hz), 132.0 (d, J_{CP} = 8.9 Hz), 132.4 (d, J_{CP} = 12.4 Hz), 134.5 (d, J_{CP} = 2.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 60.4.



PCj

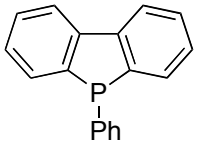
1-(Naphthalene-1-yl)phospholane-1-oxide (PCj) was prepared according to the general procedure from the reaction of magnesium turnings (0.13 g, 5.5 mmol, 1.1 equiv.), 1-bromonaphthalene (1.04 g, 5.0 mmol, 1.0 equiv., 1 M in THF) and 1-chloro-3-phospholene-1-oxide (0.78 g, 5.6 mmol, 1.1 equiv.). Purification by flash column chromatography (methanol/dichloromethane, gradient 0-3%) gave 1-naphthalene-1-yl)-3-phospholene-1-oxide as a white solid (0.89 g, 78%). Hydrogenation in accordance with the general procedure, from the reaction of 1-(naphthalene-1-yl)-3-phospholene-1-oxide (0.28 g, 1.2 mmol, 1.0 equiv.) with an excess of H_2 using Pd/C (10% w/w; 0.13 g, 0.1 mmol, 10 mol %) in a methanol/dichloromethane solution (4:1 mL) at room temperature for 48 h yielded **PCj** as a viscous oil (0.26 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.82-1.96 (m, 2H), 2.13-2.26 (m, 4H), 2.29-2.37 (m, 2H), 7.47-7.63 (m, 3H), 7.83 (ddd, J = 14.4, 7.2, 1.2 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 8.54 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.6 (d, J_{CP} = 8.8 Hz), 28.8 (d, J_{CP} = 70.0 Hz), 124.6 (d, J_{CP} = 13.2 Hz), 126.3 (d, J_{CP} = 5.2 Hz), 126.6, 127.6, 129.2, 129.8 (d, J_{CP} = 9.6 Hz), 130.1 (d, J_{CP} = 88.2 Hz), 132.9 (d, J_{CP} = 3.0 Hz), 133.0, 133.9 (d, J_{CP} = 8.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 63.1.



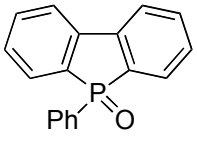
PCk

1-(Biphenyl-3-yl)phospholane-1-oxide (PCk) was prepared according to the general procedure from the reaction of magnesium turnings (0.13 g, 5.5 mmol, 1.1 equiv.), 2-bromobiphenyl (1.66 g, 5.0 mmol, 1.0 equiv., 1 M in THF) and 1-chloro-3-phospholene-1-oxide (0.73 g, 5.3 mmol, 1.1 equiv.). Purification by flash column chromatography (methanol/dichloromethane, gradient 0-2%) gave 1-(biphenyl-3-yl)-3-phospholene-1-oxide

as a green oil (0.88 g, 69%). Hydrogenation in accordance with the general procedure, from the reaction of 1-(biphenyl-3-yl)-3-phospholene-1-oxide (0.75 g, 2.9 mmol, 1.0 equiv.) with an excess of H_2 using Pd/C (10% w/w; 0.31 g, 0.3 mmol, 10 mol %) in a methanol/dichloromethane solution (4:1 mL) at room temperature for 48 h yielded **PCk** as a white solid (0.66 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40-1.52 (m, 2H), 1.65-1.71 (m, 4H), 1.81-1.95 (m, 2H), 7.35-7.48 (m, 5H), 7.51-7.57 (m, 3H), 7.91 (ddd, J = 12.4, 7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.1 (d, J_{CP} = 8.1 Hz), 29.0 (d, J_{CP} = 69.8 Hz), 127.3 (d, J_{CP} = 11.0 Hz), 128.2, 128.5, 129.7, 131.2 (d, J_{CP} = 8.8 Hz), 131.5 (d, J_{CP} = 2.1 Hz), 132.1 (d, J_{CP} = 9.5 Hz), 132.9 (d, J_{CP} = 88.9 Hz), 141.2 (d, J_{CP} = 3.6 Hz), 145.3 (d, J_{CP} = 8.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 64.1.



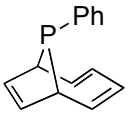
5-Phenyl-5*H*-benzo[b]phosphindole:[8] To a stirring solution of triphenylphosphine oxide (2.0 g, 7.2 mmol, 1.0 equiv.) in dry THF (52 mL) at 0 °C was added dropwise 2.0 M phenyllithium (7.22 mL, 14.4 mmol, 2.0 equiv.). The mixture was heated to reflux overnight. The solvent was removed *in vacuo*, water (70 mL) was added and the mixture was neutralised with 1 M aqueous HCl. The aqueous layer was extracted with dichloromethane (3 x 70 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash column chromatography (ethyl acetate/hexane, gradient 20-30%) yielded 5-phenyl-5*H*-benzo[b]phosphindole as a white solid (1.06 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23-7.29 (m, 3H), 7.31-7.38 (m, 4H), 7.49 (t, J = 7.6 Hz, 2H), 7.73 (t, J = 6.0 Hz, 2H), 7.98 (d, J = 8.0 Hz, 2H); ^{31}P NMR (162 MHz, $CDCl_3$) δ: -10.2.



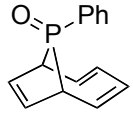
PCl

5-Phenyl-5*H*-benzo[b]phosphindole 5-oxide (PCl):[8] To a stirring solution of x (200 mg, 0.77 mmol, 1.0 equiv.) in diethyl ether (3.80 mL) was added dropwise hydrogen peroxide (30% wt/wt in water, 0.35 mL, 3.1 mmol, 4.0 equiv.). After stirring at room temperature for 0.5 h the reaction was filtered and washed with diethyl ether to yield pure PCl as a white solid (189 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.40 (m, 4H), 7.49 (td, J = 7.6, 1.2 Hz, 1H),

7.59 (t, *J* = 7.6 Hz, 2H), 7.62-7.67 (m, 2H), 7.70-7.74 (m, 2H), 7.82 (dd, *J* = 8.0, 2.8 Hz, 2H). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 34.4.

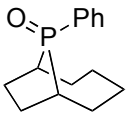


9-Phenyl-9-phosphabicyclo[4.2.1]nonatriene:[9] To a flame dried 2-neck round-bottom flask, equipped with a reflex condenser, argon inlet and connected to an oil bubbler, was added lithium (25% in mineral oil; 1.01 g, 36.4 mmol, 2.1 equiv.). The mineral oil was removed by washing with dry pentane (5 x 10 mL) and the lithium dried under a flow of argon. Anhydrous diethyl ether (54 mL) was introduced, followed by cyclooctatetraene (2.0 mL, 17.3 mmol, 1.0 equiv.). The resulting mixture was stirred at RT for 16 h, during which time the color changed from yellow to deep brown, with a large quantity of solid evident. A flame dried 2-neck round-bottom flask was charged with dichlorophenylphosphine (5.1 mL, 37.7 mmol, 2.2 equiv) and diethyl ether (27 mL) at 0 °C. The lithium cyclooctatetraene dianion solution was transferred *via* syringe to this flask over a 15 min period, and additional residues were transferred in diethyl ether washes (4 x 5 mL). The resultant yellow mixture was stirred at 0 °C for 1 h. The reaction was quenched using water (10 mL) and neutralized using saturated sodium carbonate solution (23 mL), then filtered through Celite®. The filter cake was washed repeatedly with diethyl ether. The resulting yellow biphasic solution was extracted and the aqueous layer washed with diethyl ether (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, toluene (54 mL) was added and the ether removed *in vacuo*. The residual yellow solution was refluxed for 2 h, until the solution was deep brown in color. The solvent was removed *in vacuo* to yield a brown solid, which was purified *via* flash column chromatography (2% diethyl ether in pentane, R_f = 0.33) to yield 9-phenyl-9-phosphabicyclo[4.2.1]nonatriene as a pale brown solid (1.99 g, 54%).



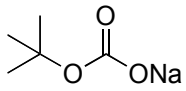
9-Phenyl-9-phosphabicyclo[4.2.1]nonatriene oxide:[9] To a stirring solution of 9-phenyl-9-phosphabicyclo[4.2.1]nonatriene (987 mg, 4.7 mmol, 1.0 equiv.) in chloroform (10 mL) at 0 °C was added hydrogen peroxide (35% w/w; 1.2 mL, 13.5 mmol, 2.9 equiv.). The resultant biphasic solution was stirred vigorously for 1.5 h.

Additional water (5 mL) was added and the layers separated. The aqueous layer was washed with chloroform (3 x 5 mL) and the combined organic layers dried over magnesium sulfate, filtered and dried *in vacuo*. 9-Phenyl-9-phosphabicyclo[4.2.1]nonatriene oxide was obtained as a pale yellow solid (1.04 g, 98%).



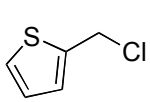
PCm

9-Phenyl-9-phosphabicyclo[4.2.1]nonane oxide[9] (PCm) was obtained in accordance with the general hydrogenation procedure, from the reaction of 9-phenyl-9-phosphabicyclo[4.2.1]nonatriene oxide (615 mg, 2.7 mmol), 1.0 equiv.) with an excess of H_2 using Pd/C (10% w/w; 860 mg, 0.8 mmol, 30 mol %) in a methanol/dichloromethane solution (10:1 mL) at room temperature for 24 h. **PCm** was obtained as an off-white solid (610 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02-1.12 (m, 2H), 1.36-1.45 (m, 2H), 1.50-1.67 (m, 2H), 1.77-1.86 (m, 4H), 2.68-2.82 (m, 4H), 7.46-7.54 (m, 3H), 7.66-7.72 (m, 2H); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 67.9.



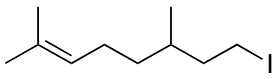
54

Sodium *tert*-butyl carbonate (54):[10] To a flame-dried 500 mL round-bottom flask equipped with a stir-bar was added NaO*t*Bu (8.46 g, 88.0 mmol) and dry THF (250 mL). The vessel was sealed with a rubber septum and purged with argon using a silicon oil bubbler. The solution was stirred vigorously until all of the alkoxide was dissolved. Solid CO_2 (dry ice) was added gradually in small portions (~20 g) until approximately 250 g was added in total. The turbid solution was stirred for 1 h under a flow of argon. The THF was removed *in vacuo* yielding a white solid. The solid was stirred in dry toluene (30 mL) for 15 min after which drying *in vacuo* yielded **54** as a white solid (11.20 g, 79.9 mmol, 91%). A 50 mg/mL solution of the **54** in water gave a pH of 9-10 on universal indicator paper. ^{1}H NMR (400 MHz, D_2O) δ: 1.19 (s, 9H); ^{13}C NMR (100 MHz, D_2O) δ: 29.6, 69.7, 161.8.



2-(Chloromethyl)thiophene:[11] To a stirring solution of 2-thiophenemethanol (470 µL, 5.0 mmol, 1.0 equiv.) in dry THF (5.0 mL) was added thionyl chloride (800 µL, 11.0 mmol, 2.2 equiv.) dropwise over 5 min at 0 °C. The solution was slowly warmed to RT and stirred for a further 30 min. The reaction was

quenched with aq. $NaHCO_3$ and the aqueous phase was extracted with dichloromethane (3 x 6 mL). The combined organic layers were dried over magnesium sulfate and dried *in vacuo* to yield 2-(chloromethyl)thiophene as a pale yellow oil (491 mg, 86%) which was used immediately for the synthesis of **76**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.82 (s, 2H), 6.96 (t, J = 4.4 Hz, 1H), 7.09 (d, J = 3.2 Hz, 1H), 7.32 (d, J = 4.8 Hz, 1H).



8-Iodo-2,6-dimethyloct-2-ene:[12] To a stirring solution of citronellol (8.7 g, 55.6 mmol 1.0 equiv.) in THF (150 mL) was added triphenylphosphine (16.0 g, 61.2 mmol, 1.1 equiv.), imidazole (4.16 g, 61.2 mmol, 1.1 equiv.) and iodine (15.5 g, 61.2 mmol, 1.1 equiv.). The mixture was stirred at room temperature for 24 h and then concentrated *in vacuo*. Purification *via* dry flash chromatography (hexane, R_f = 0.61) afforded 8-iodo-2,6-dimethyloct-2-ene as a colourless liquid (10.6 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (d, J = 6.8 Hz, 3H), 1.12-1.21 (m, 1H), 1.25-1.38 (m, 1H), 1.53-1.71 (m, 1H), 1.61 (s, 3H), 1.68 (d, J = 1.2 Hz, 3H), 1.83-2.05 (m, 3H), 3.13-3.28 (m, 2H), 5.06-5.11 (m, 1H).

Optimization studies

General procedure for solvent study using 54: In air, a 1-dram vial equipped with a stir-bar was charged with **PCb** (18 mg, 0.1 mmol, 10 mol %) and **54** (280 mg, 2.0 mmol, 2.0 equiv.). The vial was then sealed with a rubber septum and purged with argon *via* needle inlet. Solvent (1.0 mL), benzaldehyde (122 µL, 1.2 mmol, 1.2 equiv.), benzyl bromide (120 µL, 1.0 mmol, 1.0 equiv.) and diphenylsilane (223 µL, 1.2 mmol, 1.2 equiv.) were introduced, the septum was replaced with a PTFE-lined screw cap under an inert atmosphere,[1] and the reaction was heated at 100 °C for 24 h. The crude reaction mixture was filtered through Celite®, concentrated *in vacuo*, and purified *via* flash column chromatography to afford pure **55**, as detailed in table 1.

General procedure for phosphine oxide screening using DIPEA: In air, a 4 mL pressure vessel equipped with a stir-bar was charged with phosphine oxide **PCa-f** (0.10 mmol, 10

mol %). The vessel was then sealed with a rubber septum and purged with argon *via* needle inlet. Toluene (0.33 mL), benzaldehyde (122 μL, 1.2 mmol, 1.2 equiv.), benzyl bromide (120 μL, 1.0 mmol, 1.0 equiv.), DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) and diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) were introduced, the septum was replaced with a PTFE-lined screw cap under an inert atmosphere,[1] and the reaction was heated at 100 or 140 °C for 24 h. The crude reaction mixture was filtered through Celite®, concentrated *in vacuo* and purified *via* flash column chromatography to afford pure **55**, as detailed in table 3.

General procedure for solvent study using DIPEA: In air, a 4 mL pressure vessel equipped with a stir-bar was charged with **PCd** (32 mg, 0.10 mmol, 10 mol %). The vessel was then sealed with a rubber septum and purged with argon *via* needle inlet. Solvent (0.33 mL), benzaldehyde (122 μL, 1.2 mmol, 1.2 equiv.), benzyl bromide (120 μL, 1.0 mmol, 1.0 equiv.), DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) and diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) were introduced, the septum was replaced with a PTFE-lined screw cap under an inert atmosphere,[1] and the reaction was heated at 140 °C for 24 h. The crude reaction mixture was filtered through Celite®, concentrated *in vacuo* and ^{1}H NMR spectroscopy analysis was used to determine conversion and *E*/*Z* ratio, as shown in table 4.

Development of the pulse olefination protocol: In air, a 1-dram vial equipped with a stir-bar was charged with **PCb** (0.15 mmol, 15 mol %) and **54** (0.5-1.0 equiv.). The vial was then sealed with a rubber septum and purged with argon *via* needle inlet. Toluene (1.0 mL), acetophenone (117 μL, 1.2 mmol, 1.2 equiv.) and diphenylsilane (1.2 mmol, 1.2 equiv.) were introduced at this time. Addition of **54** and benzyl bromide (1.0-1.35 equiv.) was varied as detailed in table 6. The reactions were conducted at 110 °C unless otherwise stated. The crude reaction mixture was filtered through Celite®, concentrated *in vacuo* and ^{1}H NMR spectroscopy analysis was used to determine conversion and *E*/*Z* ratio, as shown in table 6.

Catalytic Wittig Olefination Procedures

General procedure A1: *(table 2, conditions **A**) preparation of compounds **55-58, 60** and **61** via catalytic Wittig reaction using **54**.*

In air, a 1-dram vial equipped with a stir-bar was charged with **PCb** (0.10-0.20 mmol, 10-20 mol %) and **54** (2.0 mmol, 2.0 equiv.). Any other solid reagents were also added at this point, in the following quantities: aldehyde (1.1-1.2 mmol, 1.1-1.2 equiv.) and organohalide (1.0 mmol, 1.0 equiv.). The vial was then sealed with a rubber septum and purged with argon *via* needle inlet. Toluene (1.0 mL) and liquid reagents were introduced in the following quantities: aldehyde (1.1-1.2 mmol, 1.1-1.2 equiv.), organohalide (1.0 mmol, 1.0 equiv.). Diphenylsilane (1.1-1.4 mmol, 1.1-1.4 equiv.) was introduced and the septum was replaced with a PTFE-lined screw cap under an inert atmosphere,[1] and the reaction was heated at 110 °C for 24 h. The crude reaction mixture was filtered through Celite®, concentrated *in vacuo*, and purified *via* flash column chromatography.

General procedure A2: *(table 2, conditions **B**) preparation of compounds **59** and **62-66** via catalytic Wittig reaction using **54** with portion-wise addition.*

In air, a 1-dram vial equipped with a stir-bar was charged with **PCb** (0.15 mmol, 15 mol %) and **54** (0.66 mmol, 0.66 equiv.). The vial was then sealed with a rubber septum and purged with argon *via* needle inlet. Toluene (1.0 mL) and diphenylsilane (0.9 mmol, 0.9 equiv.) were introduced and the septum was replaced with a PTFE-lined screw cap under an inert atmosphere.[1] The reaction solution was heated at 110 °C for 45 min, then aldehyde (0.33 mmol, 0.33 equiv.) and organohalide (0.15 mmol, 0.15 equiv.) were introduced and the reaction solution stirred at RT for 5-10 min, before returning to 110 °C for a further hour. Additional halide (0.15 mmol, 0.15 equiv.) was added hourly (total of 7 additions) and additional **54** (2 x 0.66 mmol, 0.66 equiv.) and aldehyde (2 x 0.33 mmol, 0.33 equiv.) were added after 2 h and 5 h. Diphenylsilane (0.3 mmol, 0.3 equiv.) was added after 5 h. After all additions were complete the reaction solution was stirred at 110 °C for a total time of 24 h. The crude reaction mixture was filtered through Celite®, concentrated *in vacuo*, and purified *via* flash column chromatography.

General procedure B: *(table 5) preparation of compounds **55, 58 and 67-77** via catalytic Wittig reaction using DIPEA.*

In air, a 4 mL pressure vessel equipped with a stir-bar was charged with phosphine oxide **PCd** (0.10 mmol, 10 mol %). Any other solid reagents were also added at this point, in the following quantities: aldehyde (1.2 mmol, 1.2 equiv.) and organohalide (1.0 mmol, 1.0 equiv.). The vessel was then sealed with a rubber septum and purged with argon *via* needle inlet. Toluene (0.33 mL) and liquid reagents were introduced in the following quantities: aldehyde (1.2 mmol, 1.2 equiv.), organohalide (1.0 mmol, 1.0 equiv.), DIPEA (1.2 mmol, 1.2 equiv.). Diphenylsilane (1.2 mmol, 1.2 equiv.) was introduced and the septum was replaced with a PTFE-lined screw cap under an inert atmosphere,[1] and the reaction was heated at 140 °C for 24 h. The crude reaction mixture was concentrated *in vacuo*, and purified *via* flash column chromatography.

General procedure C: *(table 7) preparation of compounds **78-87** via catalytic Wittig reaction using pulse olefination.*

In air, a 1-dram vial equipped with a stir-bar was charged with **PCb** (0.15 mmol, 15 mol %) and **54** (1.0 mmol, 1.0 equiv.). If solid, ketone (1.0 mmol, 1.0 equiv.) was also added at this point. The vial was then sealed with a rubber septum and purged with argon *via* needle inlet. Toluene (1.0 mL) and ketone (1.0 mmol, 1.0 equiv.), if liquid, were added via syringe. Diphenylsilane (1.2 mmol, 1.2 equiv.) was introduced and the septum was replaced with a PTFE-lined screw cap under an inert atmosphere,[1] and the reaction was heated at 110 °C for 30 min. The reaction was cooled to RT and organohalide (0.15 mmol, 0.15 equiv.) was added. The reaction was stirred at RT for 30 min, then returned to 110 °C for 2 h. This process was repeated until 9 additions of halide were carried out. Additional base was introduced after the 3rd (1.0 mmol, 1.0 equiv.), 6th (1.0 mmol, 1.0 equiv.) and 8th (0.5 mmol, 0.5 equiv.) additions. If required, the reaction was allowed to stir at 110 °C overnight (10 h) between the 5th and 6th addition. The crude reaction mixture was filtered through Celite®, concentrated *in vacuo*, and purified *via* flash column chromatography.

General procedure D: *(table 8) preparation of compounds* ***88-93*** *via catalytic Wittig reaction.*

In air, a 1-dram vial equipped with a stir-bar was charged with **PCd** (0.2 mmol, 20 mol %) and **54** (2.0-3.5 mmol, 2.0-3.5 equiv.). If solid, aldehyde (1.0-1.2 mmol, 1.0-1.2 equiv.) was also added at this point. The vial was then sealed with a rubber septum and purged with argon *via* needle inlet. Toluene (1.4 mL) and liquid reagents were introduced in the following quantities: aldehyde (1.2 mmol, 1.2 equiv.) and organohalide (1.0 mmol, 1.0 equiv.). Diphenylsilane (1.2 mmol, 1.2 equiv.) was introduced and the septum was replaced with a PTFE-lined screw cap under an inert atmosphere.[1] The reaction was heated at 140 °C or 150 °C for 24-48 h. Additional portions of base and halide were added at 24 h for 48 h reactions. The crude reaction mixture was filtered through Celite®, concentrated *in vacuo*, and purified *via* flash column chromatography.

General procedure E1: *(table 10, conditions A) preparation of compounds* ***55-57 and 108-110*** *using PMHS and* ***54***

In air, a 1-dram vial equipped with a stir-bar was charged with **PCb** (0.10-0.20 mmol, 10-20 mol %) Any solid reagents were also added at this point, in the following quantities: **54** (2.0 mmol, 2.0 equiv.), aldehyde (1.0-1.2 mmol, 1.0-1.2 equiv.) and organohalide (1.0-1.3 mmol, 1.0-1.3 equiv.). The vial was then sealed with a rubber septum and purged with argon *via* needle inlet. Solvent (0.4 -1.0 mL) and liquid reagents were introduced in the following quantities: aldehyde (1.0-1.2 mmol, 1.0-1.2 equiv.), organohalide (1.0-1.3 mmol, 1.0-1.3 equiv.). PMHS (3.5-5.0 mmol, 3.5-5.0 equiv.) was introduced and the septum was replaced with a PTFE-lined screw cap under an inert atmosphere,[1] and the reaction was heated at 110 °C for 24 h. The crude reaction mixture was stirred in ethyl acetate, filtered through Celite®, concentrated *in vacuo*, and purified *via* flash column chromatography.

General procedure E2: *(table 10, conditions A) preparation of compounds* ***62, 63 and 78*** *using PMHS and* ***54*** *with portion-wise addition*

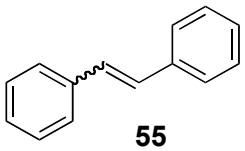
In air, a 1-dram vial equipped with a stir-bar was charged with **PCb** (0.15 mmol, 15 mol %) and **54** (0.66 mmol, 0.66 equiv.). The vial was then sealed with a rubber septum and purged with argon *via* needle inlet. Toluene (1.0 mL) and PMHS (5.0 mmol, 5.0 equiv.) were introduced and the septum was replaced with a PTFE-lined screw cap under an inert atmosphere.[1] The reaction solution was heated at 110 °C for 45 min, then aldehyde (0.33 mmol, 0.33 equiv.) and organohalide (0.15 mmol, 0.15 equiv.) were introduced and the reaction solution stirred at RT for 5-10 min, before returning to 110 °C for a further hour. Additional halide (0.15 mmol, 0.15 equiv.) was added hourly (total of 7 additions) and additional **54** (2 x 0.66 mmol, 0.66 equiv.) and aldehyde (2 x 0.33 mmol, 0.33 equiv.) were added after 2 h and 5 h. After all additions were complete the reaction solution was stirred at 110 °C for a total time of 24 h. The crude reaction mixture was filtered through Celite®, concentrated *in vacuo*, and purified *via* flash column chromatography.

General procedure F: *(table 9 and table 10, conditions **B**) preparation of compounds **55, 68, 73 and 94-107** using PMHS and DIPEA*

In air, a 1-dram vial (or 4 mL pressure vessel for reactions at 150 °C) equipped with a stir-bar was charged with **PCb or PCd** (0.10 mmol, 10 mol %) Any solid reagents were also added at this point, in the following quantities: aldehyde (1.0-1.2 mmol, 1.0-1.2 equiv.) and organohalide (1.0-1.3 mmol, 1.0-1.3 equiv.). The vial was then sealed with a rubber septum and purged with argon *via* needle inlet. Solvent (0.4 -1.0 mL) and liquid reagents were introduced in the following quantities: aldehyde (1.0-1.2 mmol, 1.0-1.2 equiv.), organohalide (1.0-1.3 mmol, 1.0-1.3 equiv.) and DIPEA (1.1-1.3 mmol, 1.1-1.3 equiv.). PMHS (3.5-5.0 mmol, 3.5-5.0 equiv.) was introduced and the septum was replaced with a PTFE-lined screw cap under an inert atmosphere,[1] and the reaction was heated at 110 °C or 150 °C for 24 h. The crude reaction mixture was stirred in ethyl acetate, filtered through Celite®, concentrated *in vacuo*, and purified *via* flash column chromatography.

General procedure for iodine-catalyzed olefin isomerization: In air, a 1-dram vial equipped with a stir-bar was charged with the pure *E/Z* olefin mixture obtained *via* catalytic

Wittig reaction (1.0 mmol) and iodine (1 crystal). The vial was then sealed with a rubber septum and purged with argon *via* needle inlet, before introduction of toluene (1.0 mL). The septum was replaced with a PTFE-lined screw cap under an inert atmosphere,[1] and the reaction was heated at 110 °C for 5 h. The mixture was diluted with diethyl ether (5 mL) and washed with saturated aq. $NaHSO_3$ and brine. The diethyl ether layer was dried over magnesium sulfate and the solvent was removed *in vacuo* to yield pure *E*-olefin in quantitative yield.



55

1,2-Diphenylethene[13] (55) was obtained in accordance with **general procedure A1** from the reaction of benzaldehyde (122 μL, 1.2 mmol, 1.2 equiv.), benzyl bromide (120 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (22 mg, 0.1 mmol, 10 mol %) in toluene (1.0 mL) at 110 °C for 24 h. The crude product was purified *via* flash column chromatography (hexane, *E*-**55**: R_f = 0.44, *Z*-**55**: R_f = 0.52) to afford *E*-**55** as a white solid and *Z*-**55** as a colorless oil (128 mg, 71%, *E/Z* 80:20). *E*-**55**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12 (s, 2H), 7.25-7.29 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 4H), 7.53 (d, *J* = 7.6 Hz, 4H). *Z*-**55**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.62 (s, 2H), 7.19-7.29 (m, 10H).

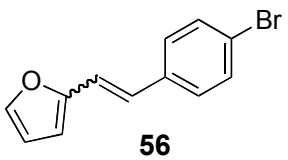
When **55** was prepared in accordance with **general procedure A1** from the reaction of benzaldehyde (122 μL, 1.2 mmol, 1.2 equiv.), benzyl bromide (120 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCm** (23 mg, 0.1 mmol, 10 mol %) in toluene (1.0 mL) at 110 °C for 24 h, yield was 82% (148 mg, *E*/*Z* 95:5).

When **55** was prepared in accordance with **general procedure B** from the reaction of benzaldehyde (122 μL, 1.2 mmol, 1.2 equiv.), benzyl bromide (120 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h, yield was 72% (129 mg, *E/Z* 80:20).

When **55** was prepared in accordance with **general procedure E1** from the reaction of benzaldehyde (122 μL, 1.2 mmol, 1.2 equiv.), benzyl bromide (120 μL, 1.0 mmol, 1.0 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (23 mg, 0.1 mmol, 10 mol %) in in toluene (1.0 mL) at 110 °C for 24 h, yield was 72% (130 mg, *E/Z* 80:20).

When **55** was prepared in accordance with **general procedure F** from the reaction of benzaldehyde (122 μL, 1.2 mmol, 1.2 equiv.), benzyl bromide (120 μL, 1.0 mmol, 1.0 equiv.), PMHS (217 μL, 3.5 mmol, 3.5 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 10 mol %) in toluene (0.40 mL) at 150 °C for 24 h, yield was 71% (128 mg, *E/Z* 80:20).

Isomerization of **55** (126 mg, 0.7 mmol) using iodine (one crystal) was carried out in accordance with the general procedure, and *E*-**55** was obtained in 99% yield.



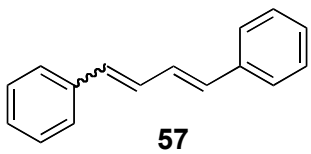
56

2-(4-Bromophenyl)-1-(2-furyl)ethene (56) was obtained in accordance with **general procedure A1** from the reaction of furfural (100 μL, 1.2 mmol, 1.2 equiv.), 4-bromobenzyl bromide (250 mg, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (22 mg, 0.1 mmol, 10 mol %) in toluene (1.0 mL) at 110 °C for 24 h. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.33) to afford an isomeric mixture of **56** as a white solid (185 mg, 74%, *E/Z* 66:34). *E*-**56**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.39-6.40 (m, 1H), 6.46 (dd, *J* = 3.6 Hz, 1.8 Hz, 1H), 6.89 (d, *J* = 16.2 Hz, 1H), 6.99 (d, *J* = 16.2 Hz, 1H), 7.31-7.37 (m, 2H), 7.44 (d, *J* = 1.8 Hz, 1H), 7.47-7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 109.3, 111.8, 117.2, 121.3, 125.8, 127.8, 131.8, 136.0, 142.5, 153.0. *Z*-**56**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.31 (d, *J* = 3.6 Hz, 1H), 6.37 (dd, *J* = 3.6 Hz, 1.8 Hz, 1H), 6.38 (d, *J* = 12.0 Hz, 1H), 6.41 (d, *J* = 12.6 Hz, 1H), 7.31-7.37 (m, 2H), 7.34 (d, *J* = 1.2 Hz, 1H), 7.47-7.50 (m, 2H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ: 110.7, 111.4, 118.5, 121.3, 126.5, 130.5, 131.3, 136.3, 141.9, 151.9. HRMS $[M]^+$ m/z calcd. 247.9837, found 247.9835.

When **56** was prepared in accordance with **general procedure A1** from the reaction of furfural (100 μL, 1.2 mmol, 1.2 equiv.), 4-bromobenzyl bromide (250 mg, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCm** (23 mg, 0.1 mmol, 10 mol %) in toluene (1.0 mL) at 110 °C for 24 h, yield was 64% (159 mg, *E*/*Z* 85:15).

When **56** was prepared in accordance with **general procedure E1** from the reaction of furfural (100 μL, 1.2 mmol, 1.2 equiv.), 4-bromobenzyl bromide (250 mg, 1.0 mmol, 1.0 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (42 mg, 0.2 mmol, 20 mol %) in in toluene (1.0 mL) at 110 °C for 24 h, yield was 78% (195 mg, *E*/*Z* 66:34).



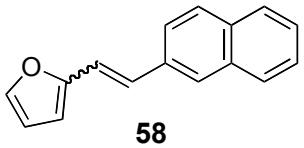
57

(1*E*)-1,4-Diphenylbuta-1,3-diene[14] (57) was obtained in accordance with **general procedure A1** from the reaction of benzaldehyde (122 μL, 1.2 mmol, 1.2 equiv.), 3-bromo-1-phenyl-1-propene (197 mg, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (22 mg, 0.1 mmol, 10 mol %) in toluene (1.0 mL) at 110 °C for 24 h. The crude product was purified *via* flash column chromatography (hexane, *E*-**57**: R_f = 0.26, *Z*-**57**: R_f = 0.36) to afford both *E*-**57** and *Z*-**57** as white solids (152 mg, 74%, *E*/*Z* 70:30). *E*-**57** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.65-6.73 (m, 2H), 6.94-7.01 (m, 2H), 7.25 (t, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 4H), 7.46 (d, *J* = 7.6 Hz, 4H). *Z*-**57** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.45 (t, *J* = 11.6 Hz, 1H), 6.55 (d, *J* = 11.6 Hz, 1H), 6.74 (d, *J* = 15.6 Hz, 1H), 7.22-7.43 (m, 11H).

When **57** was prepared in accordance with **general procedure E1** from the reaction of benzaldehyde (122 μL, 1.2 mmol, 1.2 equiv.), 3-bromo-1-phenyl-1-propene (197 mg, 1.0 mmol, 1.0 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and **54** (280 mg, 2.0 mmol, 2.0

equiv.) using **PCb** (21 mg, 0.1 mmol, 10 mol %) in in toluene (1.0 mL) at 110 °C for 24 h, yield was 67% (139 mg, *E*/*Z* 70:30).

Isomerization of **57** (134 mg, 0.65 mmol) using iodine (one crystal) was carried out in accordance with the general procedure, and *E*-**57** was obtained in 98% yield.

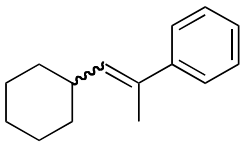


58

1-(2-Furyl)-2-(2-naphthyl)ethene[15] **(58)** was obtained in accordance with **general procedure A1** from the reaction of furfural (100 μL, 1.2 mmol, 1.2 equiv.), 2-(bromomethyl)naphthalene (221 mg, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (22 mg, 0.1 mmol, 10 mol %) in toluene (1.0 mL) at 110 °C for 24 h. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.31) to afford **58** as a white solid (181 mg, 82%, *E/Z* 66:34). *E*-**58**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.47 (d, *J* = 3.2 Hz, 1H), 6.52 (dd, *J* = 3.2 Hz, 1.6 Hz, 1H), 7.10 (d, *J* = 16.4 Hz, 1H), 7.31 (d, *J* = 16.4 Hz, 1H), 7.50-7.56 (m, 3H), 7.74 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.86-7.92 (m, 4H); *Z*-**58**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.39 (d, *J* = 0.8 Hz, 2H), 6.58 (d, *J* = 12.8 Hz, 1H), 6.71 (d, *J* = 12.8 Hz, 1H), 7.39 (br. s, 1H), 7.50-7.56 (m, 2H), 7.69 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.86-7.92 (m, 3H), 8.00 (br. s, 1H).

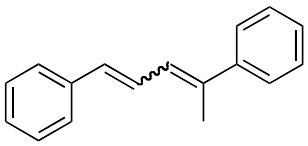
When **58** was prepared in accordance with **general procedure A1** from the reaction of furfural (100 μL, 1.2 mmol, 1.2 equiv.), 2-(bromomethyl)naphthalene (221 mg, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCm** (23 mg, 0.1 mmol, 10 mol %) in toluene (1.0 mL) at 110 °C for 24 h, yield was 65% (143 mg, *E*/*Z* 90:10).

When **58** was obtained in accordance with **general procedure B** from the reaction of furfural (100 μL, 1.2 mmol, 1.2 equiv.), 2-(bromomethyl)naphthalene (221 mg, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h, yield was 72% (160 mg, *E/Z* 70:30).



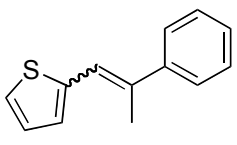
59

1-Cyclohexyl-2-phenylprop-1-ene[16] (59) was obtained in accordance with **general procedure A2** using a portion-wise addition of organohalide (7 x 0.14 mmol portions added at 1 h intervals) from the reaction of cyclohexanecarboxaldehyde (145 μL, 1.2 mmol, 1.2 equiv.), (1-bromoethyl)benzene (136 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (22 mg, 10 mol %) in toluene (1.0 mL) at 110 °C for 24 h. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.69) to afford an isomeric mixture of **59** as a colorless liquid (141 mg, 79%, *E/Z* 70:30). *E*-**59**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05-1.41 (m, 5H), 1.60-1.79 (m, 5H), 2.07 (d, *J* = 1.2 Hz, 3H), 2.32-2.42 (m, 1H), 5.65 (dd, *J* = 8.8 Hz, 1.2 Hz, 1H), 7.18-7.42 (m, 5H). *Z*-**59**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05-1.41 (m, 6H), 1.60-1.79 (m, 5H), 2.02 (d, *J* = 1.2 Hz, 3H), 5.29 (dd, *J* = 10.0 Hz, 1.2 Hz, 1H), 7.18-7.42 (m, 5H).



60

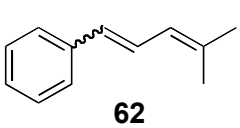
1,4-Diphenylpenta-1,3-diene[17] (60) was obtained in accordance with **general procedure A1** from the reaction of *trans*-cinnamaldehyde (150 μL, 1.2 mmol, 1.2 equiv.), (1-bromoethyl)benzene (136 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (22 mg, 0.1 mmol, 10 mol %) in toluene (1.0 mL) at 110 °C for 24 h. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.29) to afford an isomeric mixture of **60** as a white solid (174 mg, 79%, *E/Z* 70:30). *E*-**60**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 6.68 (d, *J* = 10.8 Hz, 1H), 6.70 (d, *J* = 15.2 Hz, 1H), 7.16-7.44 (m, 7H), 7.48-7.54 (m, 4H). *Z*-**60**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.22 (s, 3H), 6.34 (d, *J* = 11.2 Hz, 1H), 6.57 (d, *J* = 15.6 Hz, 1H), 6.89 (dd, *J* = 15.6 Hz, 11.2 Hz, 1H), 7.16-7.44 (m, 10H).



61

2-Phenyl-1-(2-thienyl)-prop-1-ene[18] (61) was obtained in accordance with **general procedure A1** from the reaction of 2-

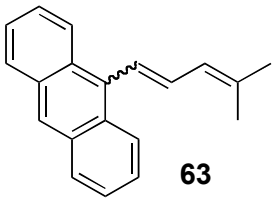
thiophenecarboxaldehyde (112 μL, 1.2 mmol, 1.2 equiv.), (1-bromoethyl)benzene (136 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (22 mg, 0.1 mmol, 10 mol %) in toluene (1.0 mL) at 110 °C for 24 h. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.26) to afford an isomeric mixture of **61** as a pale yellow oil (154 mg, 77%, *E/Z* 80:20). *E*-**61**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.54 (d, *J* = 1.2 Hz, 3H), 7.09 (br. s, 1H), 7.17 (dd, *J* = 4.8 Hz, 3.6 Hz, 1H), 7.21 (br. d, *J* = 3.6 Hz, 1H), 7.36-7.62 (m, 6H). *Z*-**61**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.29 (d, *J* = 1.2 Hz, 3H), 6.74 (d, *J* = 1.2 Hz, 1H), 6.85 (br. d, *J* = 3.6 Hz, 1H), 6.92 (dd, *J* = 4.8 Hz, 3.6 Hz, 1H), 7.04 (br. d, *J* = 5.2 Hz, 1H), 7.36-7.62 (m, 5H).



62

4-Methyl-1-phenylpenta-1,3-diene[19] (62) was obtained in accordance with **general procedure A2** from the reaction of benzaldehyde (100 μL, 1.0 mmol, 1.0 equiv.), 3,3-dimethylallyl bromide (140 μL, 1.2 mmol, 1.2 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) at 110 °C for 24 h using a portion-wise addition process. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.38) to afford an isomeric mixture of **62** as a colorless liquid (112 mg, 71%, *E/Z* 66:34). *E*-**62**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.90 (s, 3H), 1.92 (s, 3H), 6.06 (d, *J* = 10.8 Hz, 1H), 6.48 (d, *J* = 15.6 Hz, 1H), 7.05 (dd, *J* = 15.6 Hz, 10.8 Hz, 1H), 7.21-7.45 (m, 5H). *Z*-**62**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.88 (s, 3H), 1.89 (s, 3H), 6.36-6.51 (m, 3H), 7.21-7.45 (m, 5H).

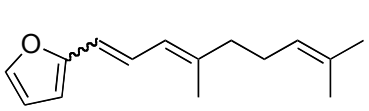
1H), 7.16-7.44 (m, 10H).



63

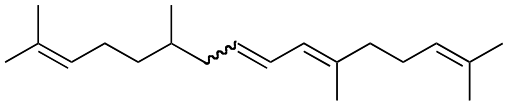
1-(9-Anthryl)-4-methylpenta-1,3-diene (63) was obtained in accordance with **general procedure A2** from the reaction of 9-anthracenecarboxaldehyde (206 mg, 1.0 mmol, 1. 0 equiv.), 3,3-dimethylallyl bromide (140 μL, 1.2 mmol, 1.2 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) at 110 °C for 24 h using a portion-

wise addition process. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.38) to afford an isomeric mixture of **63** as a bright yellow oil (188 mg, 73%, *E/Z* 80:20). *E*-**63**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.86 (s, 3H), 1.98 (s, 3H), 6.37 (d, *J* = 10.8 Hz, 1H), 6.85-6.94 (m, 1H), 7.27 (d, *J* = 15.6 Hz, 1H), 7.48-7.50 (m, 4H), 8.01-8.06 (m, 2H), 8.36-8.38 (m, 3H). *Z*-**63**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.57 (s, 3H), 1.92 (s, 3H), 5.48 (d, *J* = 10.8 Hz, 1H), 6.85-6.94 (m, 1H), 7.05 (t, *J* = 11.2 Hz, 1H), 7.48-7.50 (m, 4H), 8.01-8.06 (m, 2H), 8.19-8.22 (m, 2H), 8.44 (br. s, 1H). *E*+*Z*-**63**: ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.6, 18.7, 26.3, 26.4, 122.2, 123.6, 125.2, 125.2, 125.3, 125.4, 125.8, 126.1, 126.2, 126.3, 126.8, 128.7, 128.7, 129.7, 130.3, 131.5, 131.6, 132.6, 133.7, 134.6, 137.1, 138.1. HRMS $[M]^+$ m/z calcd. 258.1409, found 258.1403.



64

(3*E*)-1-(2-Furyl)-4,8-dimethylnona-1,3,7-triene (64) was obtained in accordance with **general procedure A2** from the reaction of furfural (83 μL, 1.0 mmol, 1.0 equiv.), geranyl bromide (238 μL, 1.2 mmol, 1.2 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) at 110 °C for 24 h using a portion-wise addition process. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.42) to afford an isomeric mixture of **64** as a pale yellow liquid (139 mg, 64%, *E/Z* 66:34). *E*-**64**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.64 (s, 3H), 1.71 (s, 3H), 1.86 (s, 3H), 2.00-2.31 (m, 4H), 5.11-5.19 (m, 1H), 5.96 (d, *J* = 11.2 Hz, 1H), 6.21 (d, *J* = 3.2 Hz, 1H), 6.26 (d, *J* = 15.6 Hz, 1H), 6.40 (br. d, *J* = 11.6 Hz, 1H), 6.93 (dd, *J* = 15.2 Hz, 11.6 Hz, 1H), 7.35 (br. s, 1H). *Z*-**64**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65 (s, 3H), 1.71 (s, 3H), 1.85 (s, 3H), 2.00-2.31 (m, 4H), 5.11-5.19 (m, 1H), 6.06 (d, *J* = 12.0 Hz, 1H), 6.28 (d, *J* = 11.6 Hz, 1H), 6.32 (d, *J* = 2.8 Hz, 1H), 6.40 (br. d, *J* = 11.6 Hz, 1H), 6.79 (d, *J* = 11.2 Hz, 1H), 7.43 (br. s, 1H). *E*+*Z*-**64**: ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.8, 17.1, 17.9, 18.0, 25.9, 26.7, 26.8, 27.1, 40.3, 40.6, 107.3, 109.8, 111.4, 111.6, 114.6, 117.8, 122.2, 123.8, 124.0, 124.1, 124.6, 132.0, 140.7, 141.7, 142.0, 142.7, 154.0, 154.1. HRMS $[M]^+$ m/z calcd. 216.1514, found 216.1507.



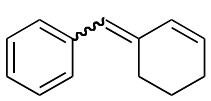
65

(6*E*)-2,6,11,15-Tetramethylhexadeca-2,6,8,14-tetraene (65) was obtained in accordance with **general procedure A2** from the reaction of (±)-citronellal (180 μL, 1.0 mmol, 1.0 equiv.), geranyl bromide (238 μL, 1.2 mmol, 1.2 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) at 110 °C for 24 h using a portion-wise addition process. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.71) to afford an isomeric mixture of **65** as a clear liquid (203 mg, 74%, *E/Z* 70:30). *E*-**65**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (d, *J* = 6.8 Hz, 3H), 1.12-1.22 (m, 1H), 1.34-1.44 (m, 1H), 1.47-1.57 (m, 1H), 1.62 (br. s, 6H), 1.70 (br. s, 6H), 1.76 (s, 3H), 1.92-2.23 (m, 8H), 5.10-5.15 (m, 2H), 5.58 (dt, *J* = 15.2 Hz, 7.2 Hz, 1H), 5.83 (br. d, *J* = 10.8 Hz, 1H), 6.21-6.28 (m, 1H). *Z*-**65**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (d, *J* = 6.8 Hz, 3H), 1.12-1.22 (m, 1H), 1.34-1.44 (m, 1H), 1.47-1.57 (m, 1H), 1.62 (br. s, 6H), 1.70 (br. s, 6H), 1.76 (s, 3H), 1.92-2.23 (m, 8H), 5.10-5.15 (m, 2H), 5.38 (dt, *J* = 10.8 Hz, 7.6 Hz, 1H), 6.09 (br. d, *J* = 11.6 Hz, 1H), 6.21-6.28 (m, 1H). *E*+*Z*-**65**: ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.6, 16.7, 17.8, 17.8, 17.8, 19.6, 19.7, 25.8, 25.8, 25.8, 25.9, 26.8, 33.1, 33.3, 34.8, 36.8, 36.9, 40.0, 40.4, 40.6, 120.3, 124.3, 124.3, 124.9, 125.0, 125.6, 128.0, 128.7, 131.1, 131.2, 131.6, 136.3, 138.4; HRMS $[M]^+$ m/z calcd. 274.2661, found 274.2666.

When **65** was prepared in accordance with **general procedure A2** from the reaction of (±)-citronellal (180 μL, 1.0 mmol, 1.0 equiv.), geranyl bromide (238 μL, 1.2 mmol, 1.2 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCm** (35 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) at 110 °C for 24 h, yield was 63% (173 mg, *E*/*Z* 85:15).

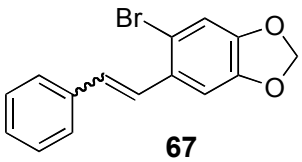
65 was obtained on a 28.0 mmol scale in accordance with **general procedure A2** from the reaction of (±)-citronellal (5.3 mL, 28.0 mmol, 1.0 equiv.), geranyl bromide (7.0 mL, 33.6 mmol, 1.2 equiv.), diphenylsilane (6.2 mL, 33.6 mmol, 1.2 equiv.) and **54** (7.85 g, 56.0 mmol, 2.0 equiv.) using **PCb** (908 mg, 4.2 mmol, 15 mol %) in toluene (28 mL). The

reaction was prepared in a 100 mL pressure vessel under an inert atmosphere and run at .110 °C for 24 h to afford **65** in 84% yield (6.42 g, *E/Z* 70:30).



66

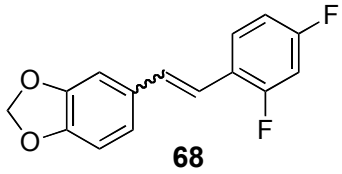
3-Benzylidenecyclohex-2-ene[20] (66) was obtained in accordance with **general procedure A2** from the reaction of benzaldehyde (100 µL, 1.0 mmol, 1.0 equiv.), 3-bromocyclohexene (138 µL, 1.2 mmol, 1.2 equiv.), diphenylsilane (223 µL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) at 110 °C for 24 h using a portion-wise addition process. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.59) to afford an isomeric mixture of **66** as a colorless liquid (116 mg, 68%, *E/Z* 55:45). *E*-**66**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.76 (qn, *J* = 6.0 Hz, 1H), 1.87 (qn, *J* = 6.0 Hz, 1H), 2.21-2.27 (m, 2H), 2.49 (dt, *J* = 6.0 Hz, 1.2 Hz, 1H), 2.70 (dt, *J* = 6.0 Hz, 1.6 Hz, 1H), 5.93-6.00 (m, 1H), 6.25-6.32 (m, 2H), 7.22-7.39 (m, 5H). *Z*-**66**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.76 (qn, *J* = 6.0 Hz, 1H), 1.87 (qn, *J* = 6.0 Hz, 1H), 2.21-2.27 (m, 2H), 2.49 (dt, *J* = 6.0 Hz, 1.2 Hz, 1H), 2.70 (dt, *J* = 6.0 Hz, 1.6 Hz, 1H), 5.93-6.00 (m, 1H), 6.28 (s, 1H), 6.68 (d, *J* = 10.4 Hz, 1H), 7.22-7.39 (m, 5H).



67

1-(6-Bromo-1,3-dioxa-5-indanyl)-2-phenylethene[21] (67) was obtained in accordance with **general procedure B** from the reaction of benzaldehyde (122 µL, 1.2 mmol, 1.2 equiv.), 5-bromo-6-bromomethyl-1,3-benzodioxole (294 mg, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 µL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 µL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 0.1 mmol, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h. The crude product was purified *via* flash column chromatography (hexane, *E*-**67**: R_f = 0.15, *Z*-**67**: R_f = 0.24) to afford both *E*-**67** and *Z*-**67** as white solids (239 mg, 79%, *E/Z* 70:30). *E*-**67**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.99 (s, 2H), 6.90 (d, *J* = 16.4 Hz, 1H), 7.05 (s, 1H), 7.16 (s, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 16.0 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 2H). *Z*-**67**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.92 (s, 2H), 6.54 (d, *J* = 11.6 Hz, 1H), 6.63 (d, *J* = 11.2 Hz, 1H), 6.64 (s, 1H), 7.07 (s, 1H), 7.17-7.26 (m, 5H).

Isomerization of **67** (172 mg, 0.65 mmol) using iodine (one crystal) was carried out in accordance with the general procedure, and *E*-**67** was obtained in 97% yield.



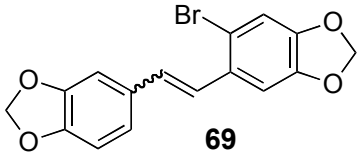
68

5-(2-(2,4-Difluorophenyl)ethenyl)-1,3-benzodioxole (68) was obtained in accordance with **general procedure B** from the reaction of piperonal (180 mg, 1.2 mmol, 1.2 equiv.), 2,5-difluorobenzyl bromide (128 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 0.1 mmol, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h. The crude product was purified *via* flash column chromatography (benzene/hexane, 10:90, *E*-**68**: R_f = 0.32, *Z*-**68**: R_f = 0.36) to afford both *E*-**68** and *Z*-**68** as white solids (222 mg, 85%, *E/Z* 70:30, *Z*-**68** inseparable from *E*-**68**). *E*-**68**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.98 (s, 2H), 6.79-6.90 (m, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.94 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.01 (s, 2H), 7.07 (d, *J* = 1.6 Hz, 1H), 7.52 (dt, *J* = 8.8 Hz, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 101.3, 104.2 (t, J_{CF} = 25.8 Hz), 105.6, 108.5, 111.6 (dd, J_{CF} = 21.3 Hz, 3.6 Hz), 118.2 (dd, J_{CF} = 2.9 Hz, 1.5 Hz), 121.7-121.9 (m), 121.8, 127.6 (dd, J_{CF} = 9.6 Hz, 5.1 Hz), 130.3 (dd, J_{CF} = 5.1 Hz, 2.9 Hz), 131.7, 147.7, 148.3, 159.9 (dd, J_{CF} = 178.2 Hz, 11.7 Hz), 162.4 (dd, J_{CF} = 177.7 Hz, 11.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -114.0 (d, *J* = 7.1 Hz, 1F), -111.3 (d, *J* = 7.1 Hz, 1F); mp 84-85 °C. *Z*-**68**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.92 (s, 2H), 6.45 (d, *J* = 12.0 Hz, 1H), 6.62 (d, *J* = 12.0 Hz, 1H), 6.70-6.76 (m, 4H), 6.80-6.90 (m, 1H), 7.24 (dt, *J* = 8.8 Hz, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 101.1, 104.1 (t, J_{CF} = 25.8 Hz), 108.3, 108.6, 111.2 (dd, J_{CF} = 21.3 Hz, 3.6 Hz), 120.5 (d, J_{CF} = 2.2 Hz), 121.2 (dd, J_{CF} = 14.6 Hz, 3.6 Hz), 123.1, 130.7, 131.3 (dd, J_{CF} = 9.5 Hz, 5.1 Hz), 132.0, 147.0, 147.6, 160.0 (dd, J_{CF} = 183.6 Hz, 11.7 Hz), 162.6 (dd, J_{CF} = 181.5 Hz, 11.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -110.8 (d, *J* = 7.1 Hz, 1F), -110.4 (d, *J* = 7.1 Hz, 1F). HRMS $[M]^+$ m/z calcd. 260.0649, found 260.0645.

When **68** was prepared in accordance with **general procedure F** from the reaction of piperonal (180 mg, 1.2 mmol, 1.2 equiv.), 2,5-difluorobenzyl bromide (128 μL, 1.0 mmol, 1.0 equiv.), PMHS (217 μL, 3.5 mmol, 3.5 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2

equiv.) using **PCd** (32 mg, 10 mol %) in toluene (0.40 mL) at 150 °C for 24 h, yield was 74% (193 mg, *E/Z* 70:30).

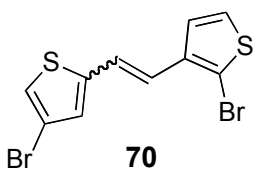
Isomerization of **68** (182 mg, 0.7 mmol) using iodine (one crystal) was carried out in accordance with the general procedure, and *E*-**68** was obtained in 98% yield.



69

5-(2-(1,3-Benzodioxol-5-yl)ethenyl)-6-bromo-1,3-benzodioxole (69) was obtained in accordance with **general procedure B** from the reaction of piperonal (180 mg, 1.2 mmol, 1.2 equiv.), 5-bromo-6-bromomethyl-1,3-benzodioxole (294 mg, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 0.1 mmol, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h. The crude product was purified *via* flash column chromatography (benzene/hexane, 20:80, R_f = 0.32) to afford both *E*-**69** and *Z*-**69** as white solids (243 mg, 70%, *E/Z* 66:34, *Z*-**69** inseparable from *E*-**69**). *E*-**69**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.98 (s, 4H), 6.79 (d, *J* = 16.4 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.93 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.02 (s, 1H), 7.08 (d, *J* = 1.6 Hz, 1H), 7.10 (s, 1H), 7.21 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 101.3, 101.9, 105.7, 105.8, 108.5, 112.9, 115.2, 121.8, 125.7, 129.5, 130.7, 131.8, 147.6, 147.8, 147.9, 148.3. *Z*-**69**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.91 (s, 2H), 5.93 (s, 2H), 6.40 (d, *J* = 12.0 Hz, 1H), 6.50 (d, *J* = 12.0 Hz, 1H), 6.64-6.69 (m, 4H), 7.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 101.1, 101.8, 108.3, 108.9, 110.2, 112.7, 114.8, 123.4, 128.1, 130.4, 130.4, 130.9, 146.9, 147.1, 147.5, 147.7. HRMS $[M]^+$ m/z calcd. 345.9841, found 345.9832.

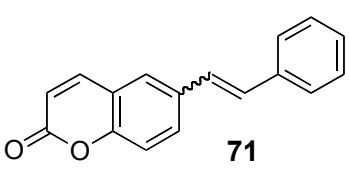
Isomerization of **69** (208 mg, 0.6 mmol) using iodine (one crystal) was carried out in accordance with the general procedure, and *E*-**69** was obtained in 99% yield.



70

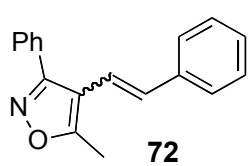
1-(2-Bromo-3-thienyl)-2-(4-bromo-2-thienyl)ethene (70) was obtained in accordance with **general procedure B** from the reaction of 4-bromo-2-thiophenecarboxaldehyde (229 mg, 1.2 mmol, 1.2 equiv.), 2-bromo-3-(bromomethyl)thiophene (130 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.)

using **PCd** (32 mg, 0.1 mmol, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h. The crude product was purified *via* flash column chromatography (hexane, *E*-**70**: R_f = 0.44, *Z*-**70**: R_f = 0.66) to afford both *E*-**70** and *Z*-**70** as pale yellow oils (312 mg, 89%, *E/Z* 75:25). *E*-**70**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.91 (d, *J* = 16.0 Hz, 1H), 7.00 (d, *J* = 16.0 Hz, 1H), 7.00 (d, *J* = 1.2 Hz, 1H), 7.11 (d, *J* = 1.2 Hz, 1H), 7.15 (d, *J* = 6.0 Hz, 1H), 7.27 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.5, 112.3, 121.8, 121.9, 122.3, 124.5, 126.5, 128.3, 137.4, 143.4. *Z*-**70**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.33 (d, *J* = 12.0 Hz, 1H), 6.68 (d, 12.0 Hz, 1H), 6.88 (d, *J* = 5.6 Hz, 1H), 6.90 (br. s, 1H), 7.08 (d, *J* = 1.2 Hz, 1H), 7.25 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 109.7, 113.2, 123.3, 123.6, 124.1, 126.4, 127.9, 130.4, 136.9, 140.6. HRMS $[M]^+$ m/z calcd. 347.8278, found 347.8282.


71

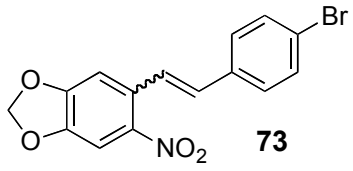
6-(2-Phenylethenyl)-2*H*-chromen-2-one (71) was obtained in accordance with **general procedure B** from the reaction of 2-oxo-2*H*-chromene-6-carbaldehyde (209 mg, 1.2 mmol, 1.2 equiv.), benzyl bromide (120 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 0.1 mmol, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h. The crude product was purified *via* flash column chromatography (ethyl acetate/benzene/hexane, 7:30:63, *E*-**71**: R_f = 0.20, *Z*-**71**: R_f = 0.29) to afford *E*-**71** as a white solid and *Z*-**71** as a pale yellow oil (228 mg, 92%, *E/Z* 70:30). *E*-**71**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.44 (d, *J* = 9.6 Hz, 1H), 7.10 (s, 2H), 7.27-7.33 (m, 2H), 7.38 (br. t, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 9.2 Hz, 2H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.70 (t, *J* = 9.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 117.1, 117.3, 119.1, 125.6, 126.7, 126.7, 128.1, 128.9, 129.8, 129.8, 134.1, 136.8, 143.4, 153.4, 160.7; mp 136-138 °C. *Z*-**71**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.39 (d, *J* = 9.6 Hz, 1H), 6.59 (d, *J* = 12.4 Hz, 1H), 6.69 (d, *J* = 12.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.22-7.28 (m, 5H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.40 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.56 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 116.8, 116.8, 118.8, 127.6, 128.0, 128.3, 128.6, 128.9, 131.5, 132.7, 133.8, 136.7, 143.5, 153.0, 160.8. HRMS $[M+H]^+$ m/z calcd. 249.0916, found 249.0911.

Isomerization of **71** (199 mg, 0.8 mmol) using iodine (one crystal) was carried out in accordance with the general procedure, and *E*-**71** was obtained in 98% yield.



72

1-(5-Methyl-3-phenyl-4-isoxazolyl)-2-phenylethene (72) was obtained in accordance with **general procedure B** from the reaction of 5-methyl-3-phenylisoxazole-4-carboxaldehyde (225 mg, 1.2 mmol, 1.2 equiv.), benzyl bromide (120 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 0.1 mmol, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h. The crude product was purified *via* flash column chromatography (benzene/hexane, 50:50, *E*-**72**: R_f = 0.17, *Z*-**72**: R_f = 0.31) to afford both *E*-**72** and *Z*-**72** as pale yellow oils (211 mg, 81%, *E/Z* 70:30). *E*-**72**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.51 (s, 3H), 6.60 (d, *J* = 16.4 Hz, 1H), 6.71 (d, *J* = 16.4 Hz, 1H), 7.15-7.20 (m, 1H), 7.25 (br. t, *J* = 7.2 Hz, 2H), 7.30-7.32 (m, 2H), 7.37-7.40 (m, 3H), 7.57-7.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.5, 112.7, 116.7, 126.3, 128.0, 128.7, 128.8, 128.9, 129.5, 129.7, 132.3, 137.0, 161.7, 166.3. *Z*-**72**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.95 (d, *J* = 0.8 Hz, 3H), 6.28 (dd, *J* = 12.0 Hz, 0.8 Hz, 1H), 6.79 (d, *J* = 12.0 Hz, 1H), 7.18-7.29 (m, 5H), 7.44-7.47 (m, 3H), 7.81-7.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.0, 111.5, 118.1, 127.6, 127.9, 128.4, 128.7, 128.8, 129.6, 129.8, 134.1, 136.8, 161.7, 166.3. HRMS $[M+H]^+$ m/z calcd 262.1232, found 262.1228.

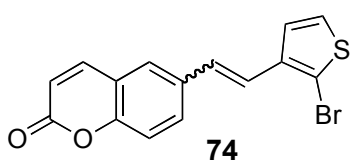


73

5-(2-(4-bromophenyl)ethenyl)-6-nitro-1,3-benzodioxole (73) was obtained in accordance with **general procedure B** from the reaction of 6-nitropiperonal (234 mg, 1.2 mmol, 1.2 equiv.), 4-bromobenzyl bromide (250 mg, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 0.1 mmol, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h. The crude product was purified *via* flash column chromatography (benzene/hexane, 40:60, R_f = 0.30) to afford an inseparable mixture of **73** as a bright yellow solid (302 mg, 87%, *E/Z* 45:55). *E*-**73**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.13 (s, 2H), 6.87 (d, *J* = 16.0 Hz, 1H), 7.09

(s, 1H), 7.37 (br. d, J = 8.4 Hz, 2H), 7.49 (br. d, J = 8.4 Hz, 2H), 7.51 (s, 1H), 7.63 (d, J = 16.0 Hz, 1H). *Z*-**73**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.08 (s, 2H), 6.54 (s, 1H), 6.62 (d, J = 12.0 Hz, 1H), 6.87 (d, J = 12.0 Hz, 1H), 6.95 (br. d, J = 8.4 Hz, 2H), 7.32 (br. d, J = 8.4 Hz, 2H), 7.63 (s, 1H). *E*+*Z*-**73**: ^{13}C NMR (100 MHz, $CDCl_3$) δ: 103.1, 103.2, 105.6, 105.7, 106.7, 110.5, 121.6, 122.4, 125.2, 128.3, 128.5, 129.7, 130.2, 130.4, 130.8, 131.6, 132.0; mp 143-152 °C; HRMS $[M]^+$ m/z calcd. 346.9793, found 346.9782.

When **73** was prepared in accordance with **general procedure F** from the reaction of 6-nitropiperonal (234 mg, 1.2 mmol, 1.2 equiv.), 4-bromobenzyl bromide (250 mg, 1.0 mmol, 1.0 equiv.), PMHS (217 μL, 3.5 mmol, 3.5 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 10 mol %) in toluene (0.40 mL) at 150 °C for 24 h, yield was 70% (244 mg, *E/Z* 45:55).

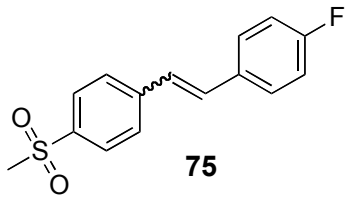


74

6-(2-(2-bromothiophen-3-yl)ethenyl)-2*H*-chromen-2-one (74) was obtained in accordance with **general procedure B** from the reaction of coumarin-6-carboxaldehyde (209 mg, 1.2 mmol, 1.2 equiv.), 2-bromo-3-(bromomethyl)thiophene (130 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 0.1 mmol, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h. The crude product was purified *via* flash column chromatography (ethyl acetate/benzene/hexane, 7:30:63, *E*-**74**: R_f = 0.20, *Z*-**74**: R_f = 0.30) to afford *E*-**74** as a pale green solid and *Z*-**74** as a white solid (303 mg, 91%, *E/Z* 66:34). *E*-**74**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.46 (d, J = 9.6 Hz, 1H), 6.98 (d, J = 16.4 Hz, 1H), 7.10 (d, J = 16.4 Hz, 1H), 7.23 (d, J = 5.6 Hz, 1H), 7.29 (dd, J = 5.6 Hz, 0.8 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.70 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 112.3, 117.2, 117.5, 119.2, 122.0, 124.6, 125.6, 126.5, 128.5, 129.9, 133.8, 137.8, 143.4, 153.7, 160.7; mp 195-200 °C. *Z*-**74**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.29 (d, J = 9.6 Hz, 1H), 6.38 (d, J = 12.4 Hz, 1H), 6.48 (d, J = 6.0 Hz, 1H), 6.56 (d, J = 12.0 Hz, 1H), 6.98 (d, J = 5.2 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 1.6 Hz, 1H), 7.29 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.50 (d, J =

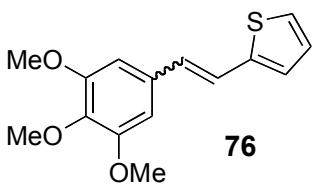
9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 113.2, 116.8, 116.9, 118.7, 123.8, 125.8, 127.4, 127.9, 129.4, 132.4, 133.5, 136.9, 143.3, 153.2, 160.5; mp 101-105 °C. HRMS $[M]^+$ m/z calcd. 331.9507, found 331.9514.

Isomerization of **74** (233 mg, 0.7 mmol) using iodine (one crystal) was carried out in accordance with the general procedure, and *E*-**74** was obtained in 99% yield.



75

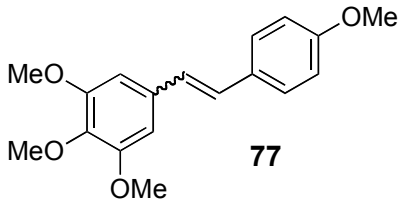
1-Fluoro-4-(2-(4-(methylsulfonyl)phenyl)ethenyl) benzene[22] **(75)** was obtained in accordance with **general procedure B** from the reaction of 4-(methylsulfonyl) benzaldehyde (221 mg, 1.2 mmol, 1.2 equiv.), 4-fluorobenzyl bromide (125 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 0.1 mmol, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h. The crude product was purified *via* flash column chromatography (0.5% ethyl acetate in benzene, R_f = 0.28) to afford an isomeric mixture of **75** as a white solid (240 mg, 87%, *E/Z* 66:34). *E*-**75**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.07 (s, 3H), 7.04 (d, *J* = 16.4 Hz, 1H), 7.07 (t, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 16.4 Hz, 1H), 7.51 (dd, *J* = 8.8 Hz, 5.6 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 2H). *Z*-**75**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.05 (s, 3H), 6.58 (d, *J* = 12.0 Hz, 1H), 6.72 (d, *J* = 12.0 Hz, 1H), 6.94 (t, *J* = 8.4 Hz, 2H), 7.17 (dd, *J* = 8.4 Hz, 5.6 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H).



76

1-(2-Thienyl)-2-(3,4,5-trimethoxyphenyl)ethene[23] **(76)** was obtained in accordance with **general procedure B** from the reaction of 3,4,5-trimethoxybenzaldehyde (235 mg, 1.2 mmol, 1.2 equiv.), 2-(chloromethyl)thiophene (133 mg, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 μL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 0.1 mmol, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h. The crude product was purified *via* flash column chromatography (80:20 benzene/hexane, *E*-**76**: R_f = 0.22, *Z*-**76**: R_f = 0.32) to afford both *E*-**76** and *Z*-**76** as pale yellow oils (213 mg, 77%, *E/Z*

50:50). *E*-**76**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.88 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 6.69 (d, *J* = 8.4 Hz, 1H), 7.00 (dd, *J* = 4.8 Hz, 3.6 Hz, 1H), 7.05 (d, *J* = 3.6 Hz, 1H), 7.12 (d, *J* = 16.0 Hz, 1H), 7.17-7.18 (m, 1H), 7.19 (d, *J* = 16.4 Hz, 1H), 7.25 (d, *J* = 9.6 Hz, 1H). *Z*-**76**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.83 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 6.50 (d, *J* = 11.6 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 11.6 Hz, 1H), 6.89 (dd, *J* = 4.8 Hz, 3.2 Hz, 1H), 6.98 (d, *J* = 3.2 Hz, 1H), 7.05-7.08 (m, 2H).

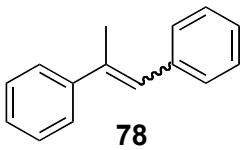


77

1,2,3-Trimethoxy-5-(2-(4-methoxyphenyl)ethenyl)benzene[24] (77) was obtained in accordance with **general procedure B** from the reaction of 3,4,5-trimethoxybenzaldehyde (235 mg, 1.2 mmol, 1.2 equiv.), 4-methoxybenzyl chloride (136 µL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 µL, 1.2 mmol, 1.2 equiv.) and DIPEA (210 µL, 1.2 mmol, 1.2 equiv.) using **PCd** (32 mg, 0.1 mmol, 10 mol %) in toluene (0.33 mL) at 140 °C for 24 h. The crude product was purified *via* flash column chromatography (ethyl acetate/benzene, gradient 0-2%, *E*-**77**: R_f = 0.34, *Z*-**77**: R_f = 0.31) to afford *E*-**77** as a light yellow solid and *Z*-**77** as a pale yellow oil (225 mg, 75%, *E/Z* 75:25). *E*-**77**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.83 (s, 3H), 3.87 (s, 3H), 3.91 (s, 6H), 6.72 (s, 2H), 6.90 (br. d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 16.0 Hz, 1H), 6.98 (d, *J* = 16.0 Hz, 1H), 7.45 (br. d, *J* = 8.8 Hz, 1H). *Z*-**77**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.69 (s, 6H), 3.79 (s, 3H), 3.85 (s, 3H), 6.42 (d, *J* = 12.0 Hz, 1H), 6.51 (s, 2H), 6.52 (d, *J* = 12.0 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H).

77 was obtained on a 25.0 mmol scale in accordance with **general procedure B** from the reaction of 3,4,5-trimethoxybenzaldehyde (5.90 g, 30.0 mmol, 1.2 equiv.), 4-methoxybenzyl chloride (3.5 mL, 25.0 mmol, 1.0 equiv.), diphenylsilane (5.7 mL, 30.0 mmol, 1.2 equiv.) and DIPEA (5.3 mL, 30.0 mmol, 1.2 equiv.) using **PCd** (790 mg, 0.1 mmol, 10 mol %) in toluene (8.30 mL). The reaction was prepared in a 100 mL pressure vessel under an inert atmosphere and run at .140 °C for 24 h before purification by dry flash chromatography (ethyl acetate/benzene, gradient 0-2%) to afford **77** in 81% yield (6.42 g, *E/Z* 75:25).

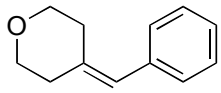
Isomerization in accordance with the general procedure produced *E*-**77** in 77% yield (5.78 g, 19.0 mmol).



78

1,2-Diphenylprop-1-ene[25] **(78)** was obtained in accordance with **general procedure C** from the reaction of acetophenone (117 µL, 1.0 mmol, 1.0 equiv.), benzyl bromide (160 µL, 1.3 mmol, 1.3 equiv.), diphenylsilane (279 µL, 1.2 mmol, 1.2 equiv.) and **54** (490 mg, 3.5 mmol, 3.5 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) using the pulse olefination technique. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.28) to afford an isomeric mixture of **78** as a white solid (168 mg, 86%, *E/Z* 65:35). *E*-**78**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.18 (d, *J* = 1.5 Hz, 3H), 6.74 (br. d, *J* = 1.2 Hz, 1H), 6.83-7.44 (m, 5H). *Z*-**78**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10 (d, *J* = 1.5 Hz, 3H), 6.37 (br. d, *J* = 1.3 Hz, 1H), 6.83-7.44 (m, 5H).

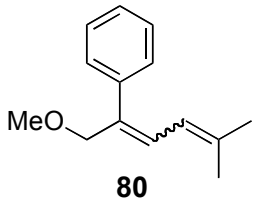
When **78** was prepared in accordance with **general procedure E2** using a portion-wise addition of organohalide (7 x 0.17 mmol portions added at 1 h intervals) from the reaction of benzaldehyde (101 µL, 1.0 mmol, 1.0 equiv.), (1-bromoethyl)benzene (177 µL, 1.3 mmol, 1.3 equiv.), diphenylsilane (223 µL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (32 mg, 15 mol %) in toluene (1.0 mL) at 110 °C for 24 h the yield was 73% (141 mg, *E/Z* 85:15)



79

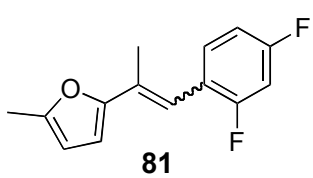
4-Benzylidenetetrahydro-2*H*-pyran[26] **(79)** was obtained in accordance with **general procedure C** from the reaction of tetrahydro-4*H*-pyran-4-one (92 µL, 1.0 mmol, 1.0 equiv.), benzyl bromide (160 µL, 1.3 mmol, 1.3 equiv.), diphenylsilane (279 µL, 1.2 mmol, 1.2 equiv.) and **54** (490 mg, 3.5 mmol, 3.5 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) using the pulse olefination technique. The crude product was purified *via* flash column chromatography (benzene/hexane gradient 5-100%, R_f (benzene) = 0.36) to afford **79** as a yellow oil (105 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.41 (td, *J* = 5.6 Hz, 1.3 Hz, 2H), 2.54 (td, *J* = 5.6 Hz, 1.3 Hz, 2H), 3.67 (t, *J* = 5.6 Hz, 2H), 3.80 (t, *J* = 5.6 Hz, 2H), 6.35 (s,

1H), 7.19-7.23 (m, 3H), 7.31-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.7, 37.3, 68.6, 69.5, 124.0, 126.3, 128.3, 128.9, 137.5, 137.8.



80

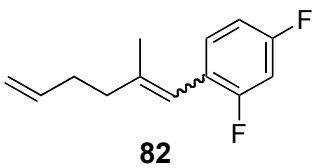
1-Methoxy-5-methyl-2-phenylhexa-2,4-diene (80) was obtained in accordance with **general procedure C** from the reaction of 2-methoxyacetophenone (138 μL, 1.0 mmol, 1.0 equiv.), 3,3-dimethylallyl bromide (150 μL, 1.3 mmol, 1.3 equiv.), diphenylsilane (279 μL, 1.2 mmol, 1.2 equiv.) and **54** (490 mg, 3.5 mmol, 3.5 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) using the pulse olefination technique. The crude product was purified *via* flash column chromatography (benzene in hexane, gradient 5-50%, R_f (50% benzene in hexane) = 0.32) to afford an isomeric mixture of **80** as a colorless oil (121 mg, 60%, *E/Z* 60:40). *E*-**80**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.70 (s, 3H), 1.80 (s, 3H), 3.31 (s, 3H), 4.18 (s, 2H), 5.86-5.90 (m, 1H), 6.49 (d, *J* = 11.3 Hz, 1H), 7.17-7.48 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 18.6, 26.5, 57.8, 77.8, 121.7, 126.2, 127.1, 128.2, 129.0, 135.7, 137.7, 139.1. *Z*-**80**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.83 (s, 3H), 1.86 (s, 3H), 3.33 (s, 3H), 4.42 (s, 2H), 6.26-6.30 (m, 1H), 6.76 (d, *J* = 11.3 Hz, 1H), 7.17-7.48 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 18.6, 26.9, 58.0, 69.2, 121.1, 125.6, 127.0, 128.2, 128.5, 133.6, 139.4, 142.1. HRMS $[M]^+$ m/z calcd. 202.1358, found 202.1351.



81

1-(2,4-Difluorophenyl)-2-(5-methyl-2-furyl)prop-1-ene (81) was obtained in accordance with **general procedure C** from the reaction of 2-acetyl-5-methylfuran (116 μL, 1.0 mmol, 1.0 equiv.), 2,4-difluorobenzyl bromide (167 μL, 1.3 mmol, 1.3 equiv.), diphenylsilane (279 μL, 1.2 mmol, 1.2 equiv.) and **54** (490 mg, 3.5 mmol, 3.5 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) using the pulse olefination technique. The crude product was purified *via* flash column chromatography (pentane, R_f = 0.30) to afford an isomeric mixture of **81** as a colorless oil (162 mg, 69%, *E/Z* 55:45). *E*-**81**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.06 (br. t, *J* = 1.1 Hz, 3H), 2.36 (s, 3H), 6.02-6.04 (m, 1H), 6.31 (d, *J* = 3.4 Hz, 1H), 6.82-6.90 (m, 2H), 6.97 (br. s, 1H), 7.28-7.33 (m, 1H); ^{13}C NMR (151 MHz,

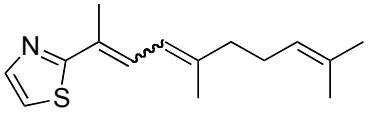
$CDCl_3$) δ: 13.8, 14.9, 103.9 (t, J_{CF} = 25.9 Hz), 107.6, 108.2, 110.9 (dd, J_{CF} = 20.9 Hz, 4.4 Hz), 114.4 (d, J_{CF} = 2.2 Hz), 121.8 (dd, J_{CF} = 14.3 Hz, 4.4 Hz), 128.4, 131.4 (dd, J_{CF} = 8.8 Hz, 5.5 Hz), 152.4, 154.1, 160.4 (dd, J_{CF} = 220.2 Hz, 12.1 Hz), 161.9 (dd, J_{CF} = 216.8, 11.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.8 (d, J = 8.0 Hz, 1F), -110.7 (d, J = 8.0 Hz, 1F). *Z*-**81**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.16 (s, 3H), 2.18 (s, 3H), 5.91-5.93 (m, 1H), 6.10 (d, J = 3.4 Hz, 1H), 6.18 (br. s, 1H), 6.76-6.80 (m, 2H), 7.22-7.27 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 13.5, 22.3, 103.4 (t, J_{CF} = 25.9 Hz), 107.2, 110.4, 110.5 (dd, J_{CF} = 20.9 Hz, 3.3 Hz), 116.5 (d, J_{CF} = 2.2 Hz), 122.5 (dd, J_{CF} = 15.4 Hz, 4.4 Hz), 128.6, 131.8 (dd, J_{CF} = 9.9 Hz, 5.5 Hz), 151.8, 152.0, 160.3 (dd, J_{CF} = 218.0 Hz, 12.1 Hz), 162.0 (dd, J_{CF} = 216.9 Hz, 12.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -112.0 (d, J = 6.8 Hz, 1F), -112.3 (d, J = 6.8 Hz, 1F). HRMS $[M]^+$ m/z calcd. 234.0856, found 234.0865.



82

1-(2,4-Difluorophenyl)-2-methylhexa-1,5-diene (82) was obtained in accordance with **general procedure C** from the reaction of 5-hexen-2-one (116 μL, 1.0 mmol, 1.0 equiv.), 2,4-difluorobenzyl bromide (167 μL, 1.3 mmol, 1.3 equiv.), diphenylsilane (279 μL, 1.2 mmol, 1.2 equiv.) and **54** (490 mg, 3.5 mmol, 3.5 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) using the pulse olefination technique. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.36) to afford an isomeric mixture of **82** as a colorless oil (133 mg, 64%, *E/Z* 68:32). *E*-**82**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.76 (br. t, J = 1.3 Hz, 3H), 2.27-2.31 (m, 4H), 4.97-5.11 (m, 2H), 5.79-5.93 (m, 1H), 6.16 (s, 1H), 6.75-6.85 (m, 2H), 7.10-7.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.0, 32.3, 39.6, 103.7 (t, J_{CF} = 25.9 Hz), 110.7 (dd, J_{CF} = 20.9, 4.4 Hz), 114.9, 117.0 (d, J_{CF} = 2.2 Hz), 122.4 (dd, J_{CF} = 15.4 Hz, 4.4 Hz), 131.5 (dd, J_{CF} = 8.8, 5.5 Hz), 138.2, 141.1, 160.2 (dd, J_{CF} = 248.8, 12.1 Hz), 161.6 (dd, J_{CF} = 247.6, 12.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -110.9 (d, J = 6.9 Hz, 1F), -112.8 (d, J = 6.8 Hz, 1F). *Z*-**82**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.91 (d, J = 1.5 Hz, 3H), 2.20-2.22 (m, 4H), 4.93-5.06 (m, 2H), 5.71-5.81 (m, 1H), 6.16 (s, 1H), 6.75-6.85 (m, 2H), 7.10-7.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.6, 32.0, 32.2,

103.8 (t, J_{CF} = 25.3 Hz), 110.8 (dd, J_{CF} = 20.9 Hz, 3.3 Hz), 114.9, 117.8 (d, J_{CF} = 2.2 Hz), 122.2 (dd, J_{CF} = 15.4 Hz, 4.4 Hz), 131.3 (dd, J_{CF} = 8.8 Hz, 5.5 Hz), 138.1, 141.4, 160.2 (dd, J_{CF} = 246.6 Hz, 12.1 Hz), 161.7 (dd, J_{CF} = 247.6 Hz, 12.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -111.0 (d, J = 6.9 Hz, 1F), -112.9 (d, J = 6.9 Hz, 1F). HRMS $[M]^+$ m/z calcd. 208.1064, found 208.1063.

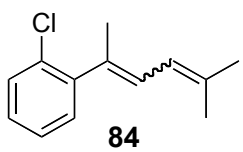


83

5,9-Dimethyl-2-(1,3-thiazol-2-yl)-deca-2,4,8-triene (83) was obtained in accordance with **general procedure C** from the reaction of 2-acetylthiazole (104 µL, 1.0 mmol, 1.0 equiv.), geranyl bromide (258 µL, 1.3 mmol, 1.3 equiv.), diphenylsilane (279 µL, 1.2 mmol, 1.2 equiv.) and **54** (490 mg, 3.5 mmol, 3.5 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) using the pulse olefination technique. The crude product was purified *via* flash column chromatography (benzene/hexane, gradient 5-50%, R_f (50% benzene in hexane) = 0.23) to afford an isomeric mixture of **83** as a yellow oil (178 mg, 72%, *E/Z* 63:37). *E*-**83**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.63 (s, 3H), 1.71 (s, 3H), 1.91 (br. d, J = 0.8 Hz, 3H), 2.16-2.21 (m, 4H), 2.26 (br. d, J = 0.7 Hz, 3H), 5.10-5.15 (m, 1H), 6.23 (dd, J = 11.3 Hz, 1.1 Hz, 1H), 7.16 (d, J = 3.4 Hz, 1H), 7.28 (dd, J = 11.7 Hz, 1.5 Hz, 1H), 7.75 (d, J = 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.1, 17.2, 17.8, 25.7, 26.6, 40.7, 117.3, 120.8, 123.8, 126.8, 127.7, 131.9, 143.1, 144.1, 172.3. *Z*-**83**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.62 (s, 3H), 1.69 (s, 3H), 1.86 (s, 3H), 2.10-2.37 (m, 4H), 2.31 (s, 3H), 5.12-5.19 (m, 1H), 6.58 (dd, J = 11.7 Hz, 1.1 Hz, 1H), 6.96 (d, J = 11.6 Hz, 1H), 7.29 (d, J = 3.4 Hz, 1H), 7.85 (d, J = 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.0, 17.8, 24.5, 25.8, 26.7, 40.6, 118.3, 122.0, 124.0, 126.0, 128.4, 131.8, 142.8, 143.9, 167.9. HRMS $[M+H]^+$ m/z calcd. 248.1473, found 248.1469.

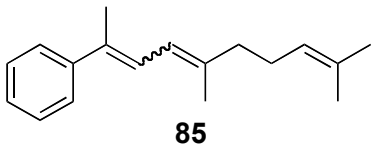
83 was obtained on a 25.0 mmol scale according to **general procedure C** from the reaction of 2-acetylthiazole (3.7 mL, 35.0 mmol, 1.0 equiv.), geranyl bromide (9.9 mL, 47.3 mmol 1.35 equiv.), diphenylsilane (9.8 mL, 51.2 mmol, 1.5 equiv.) and **54** (17.20 g, 122.5 mmol, 3.5 equiv.) using **PCb** (1.14 g, 5.3 mmol, 15 mol %) in toluene (35 mL). The reaction was

prepared in a 100 mL pressure vessel under an inert atmosphere and run at 110 °C for 24 h before purification by dry flash chromatography (benzene/hexane, gradient 10-100%) to afford **83** in 68% yield (5.89 g, *E/Z* 75:25).



84

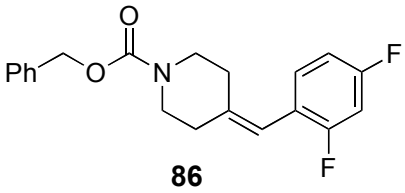
2-(2-Chlorophenyl)-5-methylhexa-2,4-diene (84) was obtained in accordance with **general procedure C** from the reaction of 2'-chloroacetophenone (130 µL, 1.0 mmol, 1.0 equiv.), 3,3-dimethylallyl bromide (150 µL, 1.3 mmol, 1.3 equiv.), diphenylsilane (279 µL, 1.2 mmol, 1.2 equiv.) and **54** (490 mg, 3.5 mmol, 3.5 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) using the pulse olefination technique. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.38) to afford an isomeric mixture of **84** as a yellow oil (143 mg, 69%, *E/Z* 70:30). *E*-**84**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.81 (s, 3H), 1.91 (s, 3H), 2.14 (s, 3H), 6.16-6.21 (m, 1H), 6.27 (br. dq, *J* = 11.4 Hz, 1.3 Hz, 1H), 7.13-7.29 (m, 3H), 7.36-7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.8, 18.5, 26.7, 121.3, 126.6, 126.7, 127.9, 129.7, 130.2, 132.5, 133.7, 136.8, 144.7. *Z*-**84**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.69 (s, 3H), 1.82 (s, 3H), 2.11 (s, 3H), 5.42-5.47 (m, 1H), 6.40 (br. dq, *J* = 11.4 Hz, 1.3 Hz, 1H), 7.13-7.29 (m, 3H), 7.41-7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.4, 24.8, 26.3, 122.0, 125.0, 126.8, 128.2, 129.6, 130.7, 132.7, 134.0, 134.7, 141.1. HRMS $[M]^+$ m/z calcd. 206.0862, found 206.0867.



85

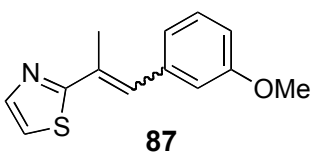
5,9-Dimethyl-2-phenyldeca-2,4,8-triene[27] (85) was obtained in accordance with **general procedure C** from the reaction of acetophenone (117 µL, 1.0 mmol, 1.0 equiv.), geranyl bromide (258 µL, 1.3 mmol, 1.3 equiv.), diphenylsilane (279 µL, 1.2 mmol, 1.2 equiv.) and **54** (490 mg, 3.5 mmol, 3.5 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) using the pulse olefination technique. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.34) to afford an isomeric mixture of **85** as a colorless oil (195 mg, 81%, *E/Z* 55:45). *E*-**85**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.63 (s, 3H), 1.70 (s, 3H), 1.84 (s, 3H), 1.95-2.20 (m, 4H), 2.15 (s, 3H), 5.14 (m, 1H), 6.21

(dd, J = 7.5 Hz, 0.8 Hz, 1H), 6.63 (dd, J = 7.5 Hz, 0.8 Hz, 1H), 7.20-7.50 (m, 5H). *Z*-**85**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54 (s, 3H), 1.66 (s, 3H), 1.79 (s, 3H), 1.95-2.20 (m, 4H), 2.13 (s, 3H), 5.04 (tt, J = 4.2 Hz, 0.8 Hz, 1H), 6.21 (dd, J = 7.5 Hz, 0.8 Hz, 1H), 6.63 (dd, J = 7.5 Hz, 0.8, 1H), 7.20-7.50 (m, 5H).



86

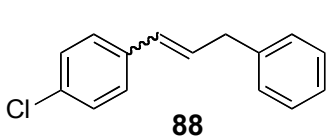
Benzyl 4-(2,4-difluorobenzylidene) piperidine-1-carboxylate (86) was obtained in accordance with **general procedure C** from the reaction of 2-acetyl-5-methylfuran (116 μL, 1.0 mmol, 1.0 equiv.), 2,4-difluorobenzyl bromide (167 μL, 1.3 mmol, 1.3 equiv.), diphenylsilane (279 μL, 1.2 mmol, 1.2 equiv.) and **54** (490 mg, 3.5 mmol, 3.5 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) using the pulse olefination technique. The crude product was purified *via* flash column chromatography (benzene, R_f = 0.30) to afford **86** as a colorless oil (299 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25-2.45 (m, 4H), 3.51 (t, J = 5.8 Hz, 2H), 3.61 (t, J = 5.8 Hz, 2H), 5.17 (s, 2H), 6.22 (s, 1H), 6.76-6.88 (m, 2H), 7.12 (q, J = 7.8 Hz, 1H), 7.29-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 44.7, 45.6, 67.2, 103.9 (t, J_{CF} = 25.5 Hz), 110.9 (dd, J_{CF} = 21.1 Hz, 3.6 Hz), 116.6 (d, J_{CF} = 1.5 Hz), 121.0 (dd, J_{CF} = 15.3 Hz, 3.6 Hz), 128.0, 128.1, 128.6, 131.5 (dd, J_{CF} = 9.5 Hz, 5.1 Hz), 134.3-134.7 (m, 2C), 136.8, 140.6, 155.3, 160.1 (dd, J_{CF} = 247.3 Hz, 11.6 Hz), 161.8 (dd, J_{CF} = 247.3 Hz, 11.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -110.3 (d, J = 43.5 Hz, 1F), -110.7 (br. s, 1F). HRMS $[M+H]^+$ m/z calcd. 344.1462, found 344.1457.



87

2-(1-(3-Methoxyphenyl)prop-1-en-2-yl]-1,3-thiazole (87) was obtained in accordance with **general procedure C** from the reaction of 2-acetylthiazole (104 μL, 1.0 mmol, 1. 0 equiv.), 3-methoxybenzyl bromide (182 μL, 1.3 mmol, 1.3 equiv.), diphenylsilane (279 μL, 1.2 mmol, 1.2 equiv.) and **54** (490 mg, 3.5 mmol, 3.5 equiv.) using **PCb** (32 mg, 0.15 mmol, 15 mol %) in toluene (1.0 mL) using the pulse olefination technique. The crude product was purified *via* flash column chromatography (benzene, R_f = 0.26) to afford an

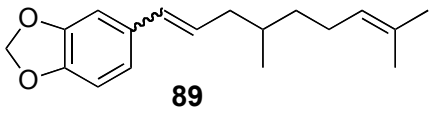
isomeric mixture of **87** as a yellow oil (178 mg, 77%, *E/Z* 65:35). *E*-**87**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 3.83 (s, 3H), 6.85 (dd, *J* = 8.6 Hz, 2.6 Hz, 1H), 6.96 (br. s, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 7.25 (br. s, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.48 (br. s, 1H), 7.81 (d, *J* = 3.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 16.8, 55.3, 113.2, 115.0, 118.4, 122.0, 129.4, 130.8, 131.9, 138.0, 143.3, 159.6, 171.9. *Z*-**87**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 3.71 (s, 3H), 6.71 (br. s, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.82 (dd, *J* = 8.3 Hz, 2.6 Hz, 1H), 6.84 (br. s, 1H), 7.48 (br. d, *J* = 2.6 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.75 (d, *J* = 3.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 24.4, 55.2, 113.7, 114.1, 119.9, 121.5, 129.7, 131.5, 132.0, 138.3, 142.0, 159.8, 167.0. HRMS $[M+H]^+$ m/z calcd. 232.0796, found 232.0804.



88

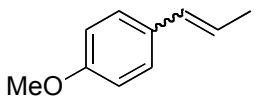
1-(4-Chlorophenyl)-3-phenylprop-1-ene[28] **(88)** was obtained in accordance with **general procedure D** from the reaction of 4-chlorobenzaldehyde (169 mg, 1.2 mmol, 1.2 equiv.), (2-iodoethyl)benzene (145 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCd** (63 mg, 20 mol %) in toluene (1.4 mL) at 140 °C for 48 h. An additional portion of **54** (210 mg, 1.5 mmol, 1.5 equiv.) was added at 24 h. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.45) to afford an isomeric mixture of **88** as a colorless liquid (166 mg, 73%, *E/Z* 55:45). *E*-**88**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.54 (d, *J* = 6.0 Hz, 2H), 6.33 (dt, *J* = 16.0 Hz, 6.0 Hz, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 7.21-7.34 (m, 9H). *Z*-**88**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.64 (d, *J* = 7.6 Hz, 2H), 5.89 (dt, *J* = 11.6 Hz, 7.6 Hz, 1H), 6.54 (d, *J* = 11.6 Hz, 1H), 7.18-7.34 (m, 9H).

When **88** was prepared in accordance with **general procedure D** from the reaction of 4-chlorobenzaldehyde (169 mg, 1.2 mmol, 1.2 equiv.), (2-iodoethyl)benzene (145 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (490 mg, 3.5 mmol, 3.5 equiv.) using **PCm** (47 mg, 20 mol %) in toluene (1.4 mL) at 140 °C for 48 h, yield was 63% (144 mg, *E*/*Z* 75:25).



89

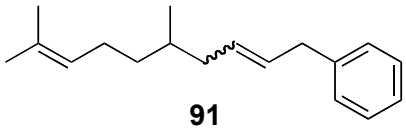
5-(4,8-Dimethylnona-1,7-dien-1-yl)-1,3-benzodioxole (89) was obtained in accordance with **general procedure D** from the reaction of piperonal (180 mg, 1.2 mmol, 1.2 equiv.), 8-iodo-2,6-dimethyl-oct-2-ene (266 mg, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCd** (63 mg, 20 mol %) in toluene (1.4 mL) at 140 °C for 48 h. An additional portion of **54** (210 mg, 1.5 mmol, 1.5 equiv.) was added at 24 h. The crude product was purified *via* flash column chromatography (8% benzene in hexane, R_f = 0.34) to afford an isomeric mixture of **89** as a colorless liquid (144 mg, 53%, *E/Z* 55:45). *E*-**89**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97 (d, *J* = 6.8 Hz, 3H), 1.18-1.51 (m, 3H), 1.66 (s, 3H), 1.76 (s, 3H), 1.98-2.40 (m, 4H), 4.71-4.74 (m, 1H), 5.94 (s, 2H), 6.08 (dt, *J* = 15.6 Hz, 7.2 Hz, 1H), 6.32 (d, *J* = 15.6 Hz, 1H), 6.75-7.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.7, 19.6, 25.7, 25.8, 33.1, 36.8, 40.5, 101.0, 105.5, 108.2, 121.1, 124.9, 127.9, 130.6, 131.2, 132.6, 146.6, 148.0. *Z*-**89**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97 (d, *J* = 6.8 Hz, 3H), 1.18-1.51 (m, 3H), 1.64 (s, 3H), 1.73 (s, 3H), 1.98-2.40 (m, 4H), 5.14-5.16 (m, 1H), 5.63 (dt, *J* = 11.6 Hz, 7.2 Hz, 1H), 5.96 (s, 2H), 6.39 (d, *J* = 11.6 Hz, 1H), 6.75-7.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.7, 19.7, 25.7, 25.8, 33.5, 35.8, 36.9, 100.9, 108.1, 109.1, 120.3, 122.6, 124.9, 129.1, 130.8, 132.1, 146.1, 147.5. HRMS $[M]^+$ m/z calcd. 272.1776, found 272.1770.



90

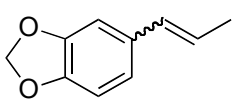
1-Methoxy-4-(prop-1-en-1-yl)benzene[29] (90) was obtained in accordance with **general procedure D** from the reaction of 4-anisaldehyde (122 μL, 1.0 mmol, 1.0 equiv.), iodoethane (80 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCd** (63 mg, 20 mol %) in toluene (1.4 mL) at 150 °C for 48 h. Additional portions of **54** (210 mg, 1.5 mmol, 1.5 equiv.) and iodoethane (80 μL, 1.0 mmol, 1.0 equiv.) were added at 24 h. The crude product was purified *via* flash column chromatography (gradient 5-10% benzene in hexane, R_f (7% benzene in hexane) = 0.31) to afford an isomeric mixture of **90** as a colorless liquid (94 mg, 63%, *E/Z* 55:45). *E*-**90**: ^{1}H

NMR (400 MHz, $CDCl_3$) δ: 1.90 (dd, *J* = 6.4 Hz, 1.6 Hz, 3H), 3.83 (s, 3H), 6.14 (dq, *J* = 15.6 Hz, 6.8 Hz, 1H), 6.37-6.43 (m, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.27-7.31 (m, 2H). *Z*-**90**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.94 (dd, *J* = 7.2 Hz, 1.6 Hz, 3H), 3.85 (s, 3H), 5.75 (dq, *J* = 11.6 Hz, 6.8 Hz, 1H), 6.37-6.43 (m, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 7.27-7.31 (m, 2H).



91

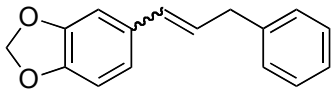
5,9-Dimethyl-1-phenyl-2,8-decadiene (91) was obtained in accordance with **general procedure D** from the reaction of (±)-citronellal (216 μL, 1.2 mmol, 1.2 equiv.), (2-iodoethyl)benzene (145 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCd** (63 mg, 20 mol %) in toluene (1.4 mL) at 140 °C for 48 h. An additional portion of **54** (210 mg, 1.5 mmol, 1.5 equiv.) was added at 24 h. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.82) to afford an isomeric mixture of **91** as a colorless liquid (121 mg, 50%, *E/Z* 60:40). *E*-**91**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (d, *J* = 6.8 Hz, 3H), 1.19-1.61 (m, 3H), 1.65 (s, 3H), 1.73 (s, 3H), 1.88-2.24 (m, 4H), 3.44 (d, *J* = 7.2 Hz, 2H), 5.13-5.17 (m, 1H), 5.53-5.68 (m, 2H), 7.20-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.8, 19.7, 25.8, 25.9, 33.2, 33.7, 34.6, 37.0, 125.0, 125.9, 128.5, 128.5, 129.0, 129.7, 131.3, 141.4. *Z*-**91**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (d, *J* = 6.4 Hz, 3H), 1.19-1.61 (m, 3H), 1.64 (s, 3H), 1.73 (s, 3H), 1.88-2.24 (m, 4H), 3.39 (d, *J* = 7.2 Hz, 2H), 5.13-5.17 (m, 1H), 5.58-5.68 (m, 2H), 7.20-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.8, 19.6, 25.7, 25.9, 32.9, 33.5, 34.7, 36.8, 125.0, 126.0, 127.0, 128.5, 130.1, 130.7, 131.2, 141.2. HRMS $[M]^+$ m/z calcd. 242.2035, found 242.2033.



92

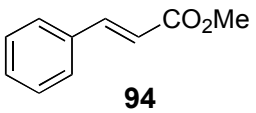
5-(Prop-1-en-1-yl)-1,3-benzodioxole[30] (92) was obtained in accordance with **general procedure D** from the reaction of piperonal (150 mg, 1.0 mmol, 1.0 equiv.), iodoethane (80 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCd** (63 mg, 20 mol %) in toluene (1.4 mL) at 150 °C for 48 h. Additional portions of **54** (210 mg, 1.5 mmol, 1.5 equiv.) and iodoethane (80 μL, 1.0 mmol, 1.0 equiv.)

were added at 24 h. The crude product was purified *via* flash column chromatography (5% benzene in hexane, R_f = 0.34) to afford an isomeric mixture of **92** as a colorless liquid (111 mg, 68%, *E/Z* 60:40). *E*-**92**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.86 (dd, *J* = 6.8 Hz, 1.6 Hz, 3H), 5.94 (s, 2H), 6.07 (dq, *J* = 16.0 Hz, 6.8 Hz, 1H), 6.23-6.36 (m, 1H), 6.73-6.89 (m, 3H). *Z*-**92**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.89 (dd, *J* = 7.2 Hz, 2.0 Hz, 3H), 5.71 (dq, *J* = 11.6 Hz, 7.2 Hz, 1H), 5.96 (s, 2H), 6.23-6.36 (m, 1H), 6.73-6.89 (m, 3H).



93

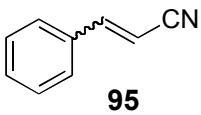
5-(3-phenylprop-1-en-1-yl)-1,3-benzodioxole (93) was obtained in accordance with **general procedure D** from the reaction of piperonal (180 mg, 1.2 mmol, 1.2 equiv.), (2-iodoethyl)benzene (145 μL, 1.0 mmol, 1.0 equiv.), diphenylsilane (223 μL, 1.2 mmol, 1.2 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCd** (63 mg, 20 mol %) in toluene (1.4 mL) at 140 °C for 48 h. An additional portion of **54** (210 mg, 1.5 mmol, 1.5 equiv.) was added at 24 h. The crude product was purified *via* flash column chromatography (hexane/benzene, 80:20, R_f = 0.33) to afford an isomeric mixture of **93** as a pale yellow liquid (179 mg, 75%, *E/Z* 60:40). *E*-**93**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.57 (d, *J* = 6.8 Hz, 2H), 5.96 (s, 2H), 6.24 (dt, *J* = 16.0 Hz, 6.8 Hz, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.78-6.86 (m, 2H), 6.97 (br. s, 1H), 7.25-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.3, 101.0, 108.3, 120.7, 126.3, 127.6, 128.6, 128.7, 130.7, 132.1, 134.4, 140.4, 146.9, 148.9. *Z*-**93**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.72 (d, *J* = 7.6 Hz, 2H), 5.84 (dt, *J* = 11.6 Hz, 7.6 Hz, 1H), 5.98 (s, 2H), 6.55 (d, *J* = 11.6 Hz, 1H), 6.78-6.86 (m, 2H), 6.90 (br. s, 1H), 7.25-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.8, 108.3, 109.0, 122.5, 126.2, 128.4, 128.6, 129.6, 129.8, 130.2, 131.4, 140.9, 146.5, 147.6. HRMS $[M]^+$ m/z calcd. 238.0994, found 238.0997.



94

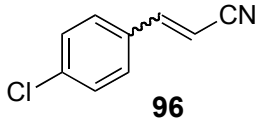
Methyl (2*E*)-3-phenylprop-2-enoate[31] (94) was obtained in accordance with **general procedure F** from the reaction of benzaldehyde (100 μL, 1.0 mmol, 1.0 equiv.), methyl bromoacetate (105 μL, 1.1 mmol, 1.1 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 μL, 1.3 mmol, 1.3 equiv.) using **PCb** (21 mg, 0.1 mmol, 10 mol %) in CPME (1.0 mL) at 100 °C for 24 h. The crude

product was purified *via* flash column chromatography (6% diethyl ether/hexane, R_f = 0.31) to afford **94** as a white solid (140 mg, 86%, *E/Z* >95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.75 (s, 3H), 6.41 (d, *J* = 16.0 Hz, 1H), 7.32-7.33 (m, 3H), 7.45-7.47 (m, 2H), 7.66 (d, *J* = 16.0 Hz, 1H).



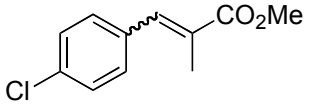
95

3-Phenylprop-2-enenitrile[32] (95) was obtained in accordance with **general procedure F** from the reaction of benzaldehyde (100 μL, 1.0 mmol, 1.0 equiv.), bromoacetonitrile (86 μL, 1.3 mmol, 1.3 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 μL, 1.3 mmol, 1.3 equiv.) using **PCb** (21 mg, 0.1 mmol, 10 mol %) in 2-methyl THF (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (6% diethyl ether/hexane, *E*-**95**: R_f = 0.23, *Z*-**95**: R_f = 0.26) to afford both *E*-**95** and *Z*-**95** as colorless oils (97 mg, 75%, *E/Z* 70:30). *E*-**95**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.88 (d, *J* = 16.7 Hz, 1H), 7.39-7.46 (m, 6H). *Z*-**95**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.45 (d, *J* = 12.4 Hz, 1H), 7.13 (d, *J* = 12.4 Hz, 1H), 7.44-7.45 (m, 3H), 7.80-7.81 (m, 2H).



96

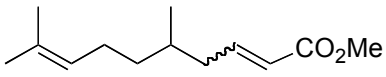
3-(4-Chlorophenyl)acrylate[32] (96) was obtained in accordance with **general procedure F** from the reaction of 4-chlorobenzaldehyde (141 mg, 1.0 mmol, 1.0 equiv.), bromoacetonitrile (86 μL, 1.3 mmol, 1.3 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 μL, 1.3 mmol, 1.3 equiv.) using **PCg** (16 mg, 0.1 mmol, 10 mol %) in 2-methyl THF (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (6% diethyl ether/hexane, R_f = 0.28) to afford an isomeric mixture of **96** as a colorless oil (138 mg, 70%, *E/Z* 80:20). *E*-**96**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.86 (d, *J* = 16.8 Hz, 1H), 7.33-7.41 (m, 5H). *Z*-**96**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.47 (d, *J* = 12.0 Hz, 1H), 7.08 (d, *J* = 12.0 Hz, 1H), 7.33-7.41 (m, 2H), 7.74 (d, *J* = 8.8 Hz, 2H).



97

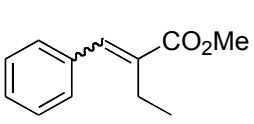
Methyl (2*E*)-3-(4-chlorophenyl)-2-methylprop-2-enoate[33] (97) was obtained in accordance with **general**

procedure F from the reaction of 4-chlorobenzaldehyde (141 mg, 1.0 mmol, 1.0 equiv.), methyl 2-bromopropionate (145 μL, 1.3 mmol, 1.3 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 μL, 1.3 mmol, 1.3 equiv.) using **PCg** (16 mg, 0.1 mmol,10 mol %) in CPME (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (5% ethyl acetate in hexane, R_f = 0.33) to afford an isomeric mixture of **97** as a colorless liquid (188 mg, 89%, *E/Z* 88:12). *E*-**97**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.08 (d, *J* = 1.5 Hz, 3H), 3.80 (s, 3H), 7.29-7.35 (m, 4H), 7.61 (br. s, 1H). *Z*-**97**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10 (s, 3H), 3.66 (s, 3H), 6.65 (br s, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H).



98

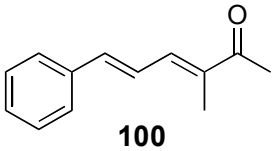
Methyl (2*E*)-5,9-dimethyldeca-2,8-dienoate[34] (98) was obtained in accordance with **general procedure F** from the reaction of (±)-citronellal (180 μL, 1.0 mmol, 1.0 equiv.), methyl bromoacetate (125 μL, 1.3 mmol, 1.3 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 μL, 1.3 mmol, 1.3 equiv.) using **PCb** (21 mg, 0.1 mmol, 10 mol %) in CPME (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (pentane/benzene, 70:30, R_f = 0.17) to afford **98** as a colorless oil (189 mg, 90%, *E/Z* 92:8). *E*-**98**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (d, *J* = 6.9 Hz, 3H), 1.14-1.21 (m, 1H), 1.31-1.38 (m, 1H), 1.56-1.70 (m, 1H), 1.59 (s, 3H), 1.67 (s, 3H), 1.90-2.06 (m, 3H), 2.18-2.23 (m, 1H), 3.72 (s, 3H), 5.07 (t, *J* = 7.1 Hz, 1H), 5.81 (d, *J* = 15.6 Hz, 1H), 6.91-6.97 (m, 1H).



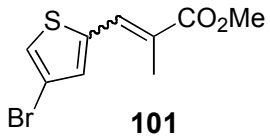
99

Methyl 2-benzylidenebutanoate[35] (99) was obtained in accordance with **general procedure F** from the reaction of benzaldehyde (100 μL, 1.0 mmol, 1.0 equiv.), methyl 2-bromobutyrate (150 μL, 1.3 mmol, 1.3 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 μL, 1.3 mmol, 1.3 equiv.) using **PCb** (21 mg, 0.1 mmol, 10 mol %) in CPME (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (5% diethyl ether/hexane, R_f = 0.33) to afford an isomeric mixture of **99** as

a colorless oil (188 mg, 99%, *E/Z* 75:25). *E*-**99**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (t, J = 7.6 Hz, 3H), 2.57 (q, J = 7.6 Hz, 2H), 3.82 (s, 3H), 7.23-7.42 (m, 5H), 7.68 (s, 1H). *Z*-**99**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (t, J = 7.6 Hz, 3H), 2.47 (qd, J = 7.6, 1.6 Hz, 2H), 3.66 (s, 3H), 6.63 (br s, 1H), 7.23-7.42 (m, 5H).

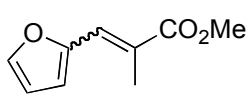

100

(3*E*, 5*E*)-3-Methyl-6-phenylhexa-3,5-dien-2-one (100) was obtained in accordance with **general procedure F** from the reaction of *trans*-cinnamaldehyde (126 μL, 1.0 mmol, 1.0 equiv.), 3-bromobutan-2-one (138 μL, 1.3 mmol, 1.3 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 μL, 1.3 mmol, 1.3 equiv.) using **PCg** (16 mg, 0.1 mmol, 10 mol %) in CPME (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (pentane/benzene/diethyl ether, 63:30:7, R_f = 0.31) to afford **100** as a pale yellow solid (157 mg, 84%, *E/Z* >95:5). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.99 (d, *J* = 1.2 Hz, 3H), 2.39 (s, 3H), 6.91 (d, *J* = 15.0 Hz, 1H), 7.11-7.16 (m, 1H), 7.20 (dd, *J* = 11.4 Hz, 1.2 Hz, 1H), 7.30-7.32 (m, 1H), 7.35-7.38 (br. t, *J* = 7.2 Hz, 2H), 7.50 (br. d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.7, 25.6, 124.4, 127.1, 128.8, 128.9, 136.3, 136.4, 139.3, 139.6, 199.4; HRMS $[M]^+$: m/z calcd. 186.1045, found 186.1043.


101

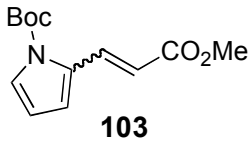
Methyl 3-(4-bromo-2-thienyl)-2-methylprop-2-enoate (101) was obtained in accordance with **general procedure F** from the reaction of 4-bromothiophene-2-carboxaldehyde (212 mg, 1.0 mmol, 1.0 equiv.), methyl 2-bromopropionate (145 μL, 1.3 mmol, 1.3 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 μL, 1.3 mmol, 1.3 equiv.) using **PCb** (21 mg, 0.1 mmol, 10 mol %) in CPME (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (pentane/benzene, 60:40, *E*-**101**: R_f = 0.37, *Z*-**101**: R_f = 0.26) to afford *E*-**101** and *Z*-**101** as yellow solids (259 mg, 99%, *E/Z* 75:25). *E*-**101**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.16 (d, *J* = 0.8 Hz, 3H), 3.79 (s, 3H), 7.14 (s, 1H), 7.34 (s, 1H), 7.69 (br. s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 52.4, 110.9, 126.0, 126.6, 130.2, 133.2, 140.2, 168.5. *Z*-**101**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.02 (d, *J* = 1.2 Hz, 3H), 3.74 (s,

3H), 6.75 (s, 1H), 7.04 (s, 1H), 7.18 (br. d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 52.0, 109.4, 125.4, 126.6, 130.3, 134.4, 139.2, 168.2; HRMS $[M]^+$: m/z calcd. 259.9507, found 259.9513.



102

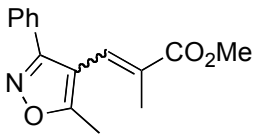
Methyl 3-(2-furyl)-2-methylprop-2-enoate[36] (102) was obtained in accordance with **general procedure F** from the reaction of furfural (83 μL, 1.0 mmol, 1.0 equiv.), methyl 2-bromopropionate (145 μL, 1.3 mmol, 1.3 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 μL, 1.3 mmol, 1.3 equiv.) using **PCg** (16 mg, 0.1 mmol, 10 mol %) in CPME (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (5% diethyl ether/hexane, R_f = 0.33) to afford an isomeric mixture of **102** as a brown oil (158 mg, 95%, *E/Z* 75:25). *E*-**102**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.20 (s, 3H), 3.76 (s, 3H), 6.45 (dd, J = 3.4, 1.8 Hz, 1H), 6.57 (d, J = 3.6 Hz, 1H), 7.42 (br. s, 1H), 7.49 (d, J = 1.2 Hz, 1H). *Z*-**102**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.05 (d, J = 0.8 Hz, 3H), 3.77 (s, 3H), 6.38 (dd, J = 3.6, 1.8 Hz, 1H), 6.49 (br. s, 1H), 6.90 (d, J = 3.6 Hz, 1H), 7.35 (d, J = 1.2 Hz, 1H).



103

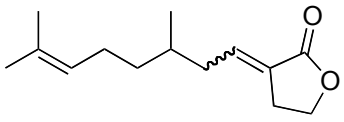
***tert*-Butyl 2-(3-methoxy-3-oxoprop-1-en-1-yl)-1*H*-pyrrole-1-carboxylate[37] (103)** was obtained in accordance with **general procedure F** from the reaction of *tert*-butyl 2-formyl-1*H*-pyrrole-1-carboxylate (195 mg, 1.0 mmol, 1.0 equiv.), methyl bromoacetate (123 μL, 1.3 mmol, 1.3 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 μL, 1.3 mmol, 1.3 equiv.) using **PCg** (16 mg, 0.1 mmol, 10 mol %) in CPME (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (benzene/diethyl ether, 80:20, *E*-**103**: R_f = 0.33, *Z*-**103**: R_f = 0.31) to afford both *E*-**103** and *Z*-**103** as brown oils (177 mg, 70%, *E/Z* 42:58). *E*-**103**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.62 (s, 9H), 3.76 (s, 3H), 6.20 (t, J = 3.2 Hz, 1H), 6.21 (d, J = 16.0 Hz, 1H), 6.69 (br. d, J = 3.2 Hz, 1H), 7.38 (dd, J = 3.6, 2.0 Hz, 1H), 8.30 (d, J = 16.0 Hz, 1H). *Z*-**103**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.59 (s, 9H), 3.71

(s, 3H), 5.78 (d, *J* = 12.8 Hz, 1H), 6.23 (dd, *J* = 6.8, 3.6 Hz, 1H), 7.24 (br. d, *J* = 3.6 Hz, 1H), 7.32 (dd, *J* = 3.2, 1.6 Hz, 1H), 7.48 (d, *J* = 13.2 Hz, 1H).



104

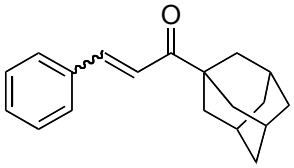
Methyl 2-methyl-3-(5-methyl-3-phenyl-1,2-oxazol-4-yl)prop-2-enoate (104) was obtained in accordance with **general procedure F** from the reaction of 5-methyl-3-phenylisoxazole-4-carboxaldehyde (187 mg, 1.0 mmol, 1.0 equiv.) and methyl 2-bromopropionate (145 µL, 1.3 mmol, 1.3 equiv.), PMHS (310 µL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 µL, 1.3 mmol, 1.3 equiv.) using **PCg** (16 mg, 0.1 mmol, 10 mol %) in CPME (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (1% diethyl ether in benzene, *E*-**104**: R_f = 0.30, *Z*-**104**: R_f = 0.17) to afford both *E*-**104** as a yellow solid and *Z*-**104** as a yellow oil (250 mg, 97%, *E/Z* 70:30). *E*-**104**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.79 (d, *J* = 1.6 Hz, 3H), 2.38 (d, *J* = 0.4 Hz, 3H), 3.81 (s, 3H), 7.36 (br. s, 1H), 7.42-7.45 (m, 3H), 7.61-7.66 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 12.5, 14.9, 52.3, 110.7, 128.0, 128.0, 128.9, 129.2, 129.9, 132.2, 161.4, 167.2, 168.0; mp 93-95 °C. *Z*-**104**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.11 (d, *J* = 1.6 Hz, 3H), 2.33 (s, 3H), 3.52 (s, 3H), 6.47 (br. s, 1H), 7.35-7.50 (m, 3H), 7.60-7.70 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 12.1, 21.3, 51.9, 111.3, 125.4, 128.0, 128.8, 129.6, 129.7, 133.3, 161.2, 167.2, 168.0; HRMS $[M+H]^+$: m/z calcd. 258.1130, found 258.1129.



105

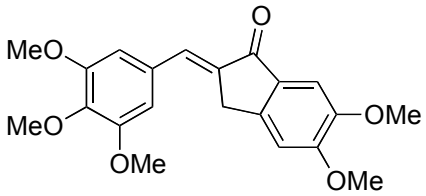
3-(3,7-Dimethyloct-6-en-1-ylidene)dihydrofuran-2(3*H*)-one[38] (105) was obtained in accordance with **general procedure F** from the reaction of (±)-citronellal (180 µL, 1.0 mmol, 1.0 equiv.), a-bromo-g-butyrolactone (120 µL, 1.3 mmol, 1.3 equiv.), PMHS (310 µL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 µL, 1.3 mmol, 1.3 equiv.) using **PCb** (21 mg, 0.1 mmol, 10 mol %) in CPME (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (benzene, *E*-**105**: R_f = 0.19, *Z*-**105**: R_f = 0.32) to afford *E*-**105** and *Z*-**105** as pale yellow oils (258 mg, 71%, *E/Z* 70:30). *E*-**105**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (d, *J* = 6.8 Hz, 3H), 1.13-1.22 (m, 1H), 1.29-1.40 (m, 1H), 1.57 (br. s,

3H), 1.61-1.69 (m, 4H), 1.88-2.05 (m, 3H), 2.13-2.20 (m, 1H), 2.81-2.86 (m, 2H), 4.35 (t, *J* = 7.6 Hz, 2H), 5.02-5.07 (m, 1H), 6.74 (tt, *J* = 7.6, 2.8 Hz, 1H). *Z*-**105**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (d, *J* = 6.4 Hz, 3H), 1.13-1.22 (m, 1H), 1.29-1.40 (m, 1H), 1.54-1.62 (m, 4H), 1.66 (d, *J* = 0.8 Hz, 3H), 1.89-2.06 (m, 2H), 2.57-2.70 (m, 2H), 2.91 (tq, *J* = 7.2, 2.0 Hz, 2H), 4.30 (t, *J* = 7.2 Hz, 2H), 5.05-5.09 (m, 1H), 6.24 (tt, *J* = 7.6, 2.4 Hz 1H).



106

3-Phenyl-1-(adamant-1-yl)prop-2-en-1-one[39] **(106)** was obtained in accordance with **general procedure F** from the reaction of benzaldehyde (100 µL, 1.0 mmol, 1.0 equiv.), 1-(1-adamantyl)-2-bromoethanone (334 mg, 1.3 mmol, 1.3 equiv.), PMHS (310 µL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 µL, 1.3 mmol, 1.3 equiv.) using **PCg** (16 mg, 0.1 mmol, 10 mol %) in CPME (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (benzene/hexane, 50:50, R_f = 0.33) to afford an isomeric mixture of **106** as a white solid (213 mg, 80%, *E/Z* 93:7). *E*-**106**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.76 (br q, *J* = 12.4 Hz, 6H), 1.89 (d, *J* = 2.0 Hz, 6H), 2.09 (br s, 3H), 7.16 (d, *J* = 15.6 Hz, 1H), 7.37-7.39 (m, 3H), 7.57-7.59 (m, 2H), 7.67 (d, *J* = 15.6 Hz, 1H).

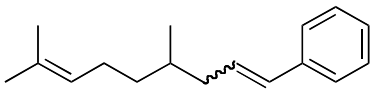


107

(*E*)-5,6-Dimethoxy-2-(3,4,5-trimethoxybenzylidene)-2,3-dihydro-1*H*-inden-1-one (107) was obtained in accordance with **general procedure F** from the reaction of 3,4,5-trimethoxybenzaldehyde (196 mg, 1.0 mmol, 1.0 equiv.), 2-bromo-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (351 mg, 1.3 mmol, 1.3 equiv.), PMHS (310 µL, 5.0 mmol, 5.0 equiv.) and DIPEA (226 µL, 1.3 mmol, 1.3 equiv.) using **PCg** (16 mg, 0.1 mmol, 10 mol %) in CPME (1.0 mL) at 100 °C for 24 h. The crude product was purified *via* flash column chromatography (benzene/diethyl ether, 50:50, R_f = 0.29) to afford **107** as a pale yellow solid (275 mg, 74%, *E/Z* >95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.90 (s, 3H), 3.90-3.95 (m, 11H), 3.99 (s, 3H), 6.86 (s, 2H), 6.98 (s, 1H), 7.31 (s,

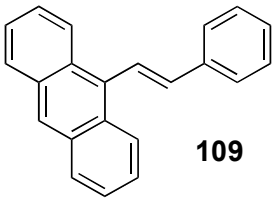
1H), 7.48 (br. s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 32.0, 56.2, 56.4, 61.1, 105. 1, 107.3, 107.9, 131.1, 132.7, 134.5, 139.5, 144.7, 149.7, 153.4, 155.4, 193.1; mp 207-208 °C; HRMS $[M+H]^+$: m/z calcd. 371.1495, found 371.1502.

107 was obtained on a 7.7 mmol scale according to **general procedure F** from the reaction of 3,4,5-trimethoxybenzaldehyde (2.0 g, 10.2 mmol, 1.0 equiv.), 2-bromo-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (3.6 g, 13.2 mmol 1.3 equiv.), PMHS (3.2 mL, 51.0 mmol, 5.0 equiv.) and DIPEA (2.3 mL, 13.2 mmol, 1.3 equiv.) using **PCg** (160 mg, 1 mmol, 10 mol %) in CPME (10 mL). The reaction was prepared in a 100 mL pressure vessel under an inert atmosphere and run at 100 °C for 24 h. The crude reaction mixture was stirred in EtOAc, filtered through Celite®, dried *in vacuo* and recrystallised from EtOH to yield pure **107** as a yellow solid (2.87 g, 76%, *E/Z* >95:5).



108

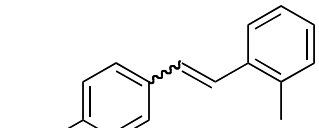
4,8-Dimethylnona-1,7-dien-1-yl)benzene[40] (108) was prepared in accordance with **general procedure E1** from the reaction of (±)-citronellal (216 μL, 1.2 mmol, 1.2 equiv.), benzyl bromide (120 μL, 1.0 mmol, 1.0 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (42 mg, 0.2 mmol, 20 mol %) in in toluene (1.0 mL) at 110 °C for 24 h. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.49) to afford an isomeric mixture of **108** as a colourless liquid (148 mg, 65%, *E*/*Z* 80:20). *E*-**108**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (d, *J* = 6.4 Hz, 3H), 1.16-1.29 (m, 1H), 1.38-1.48 (m, 1H), 1.54-1.72 (m, 1H), 1.64 (s, 3H), 1.72 (s, 3H), 1.96-2.41 (m, 4H), 5.10-5.16 (m, 1H), 6.24 (dt, *J* = 15.6, 7.6 Hz, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 7.20-7.38 (m, 5H). *Z*-**108**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (d, *J* = 6.4 Hz, 3H), 1.16-1.29 (m, 1H), 1.38-1.48 (m, 1H), 1.54-1.72 (m, 7H), 1.96-2.41 (m, 4H), 5.10-5.16 (m, 1H), 5.72 (dt, *J* = 11.6, 7.2 Hz, 1H), 6.48 (d, *J* = 11.6 Hz, 1H), 7.20-7.38 (m, 5H).



109

9-[(*E*)-2-Phenylethenyl]anthracene (109) was prepared in accordance with **general procedure E1** from the reaction of 9-

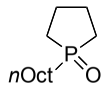
anthracenecarboxaldehyde (247 mg, 1.2 mmol, 1.2 equiv.), benzyl bromide (120 μL, 1.0 mmol, 1.0 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (21 mg, 0.1 mmol, 10 mol %) in in toluene (1.0 mL) at 110 °C for 24 h. The crude product was purified *via* flash column chromatography (hexane, R_f = 0.19) to afford **109** as a bright yellow solid (180 mg, 64%, *E*/*Z* >95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.97 (d, *J* = 16.4 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.45-7.50 (m, 6H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.93 (d, *J* = 16.8 Hz, 1H), 8.01-8.05 (m, 2H), 8.35-8.38 (m, 2H), 8.42 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 125.0, 125.3, 125.6, 126.2, 126.6, 126.7, 128.2, 128.8, 129.0, 129.9 131.6, 132.9, 137.5; HRMS $[M]^+$: m/z calcd. 280.1252, found 280.1253.



110

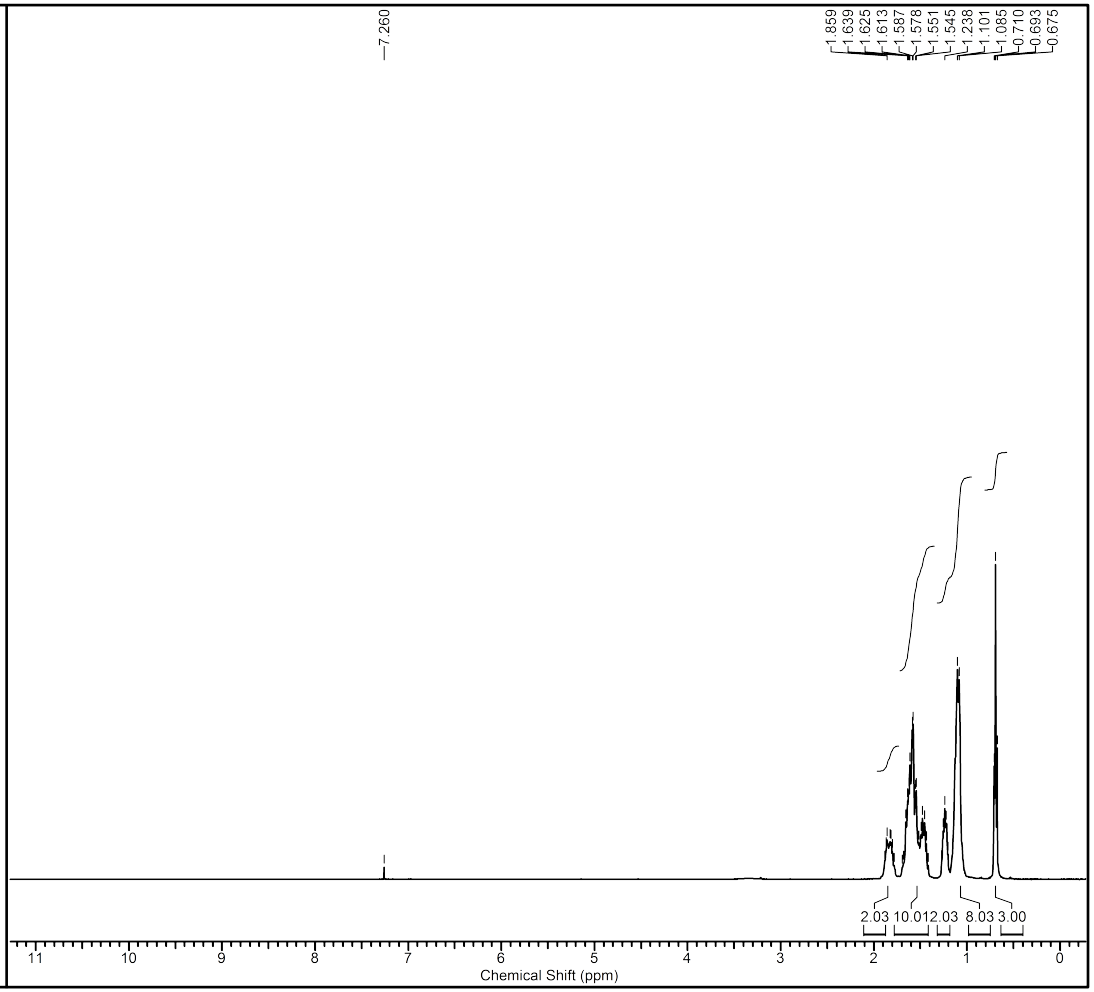
1-[2-(4-Methoxyphenyl)ethenyl]-2-methylbenzene[41] (110) was prepared in accordance with **general procedure E1** from the reaction of 4-anisaldehyde (146 μL, 1.2 mmol, 1.2 equiv.), 2-methylbenzyl chloride (132 μL, 1.0 mmol, 1.0 equiv.), PMHS (310 μL, 5.0 mmol, 5.0 equiv.) and **54** (280 mg, 2.0 mmol, 2.0 equiv.) using **PCb** (21 mg, 0.1 mmol, 10 mol %) in in toluene (1.0 mL) at 110 °C for 24 h. the crude product was purified *via* flash column chromatography (5% ethyl acetate/hexane, *E*-**110** R_f = 0.36, *Z*-**110** R_f = 0.42) to afford an isomeric mixture of **110** as a colourless oil (164 mg, 73%, *E*/*Z* 80:20). *E*-**110** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (s, 3H), 3.86 (s, 3H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 16.0 Hz, 1H), 7.20-7.27 (m, 3H), 7.24 (d, *J* = 16.0 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 1H). *Z*-**110** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 3.78 (s, 3H), 6.59 (d, *J* = 2.0 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.20-7.27 (m, 3H).

File Name	nOct
Acquisition Time (sec)	3.9584
Date Stamp	11 May 2013 05:41
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2460.6958
Origin	spect
Receiver Gain	18.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

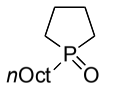


PCb

O'Brien™
Group NMR Data

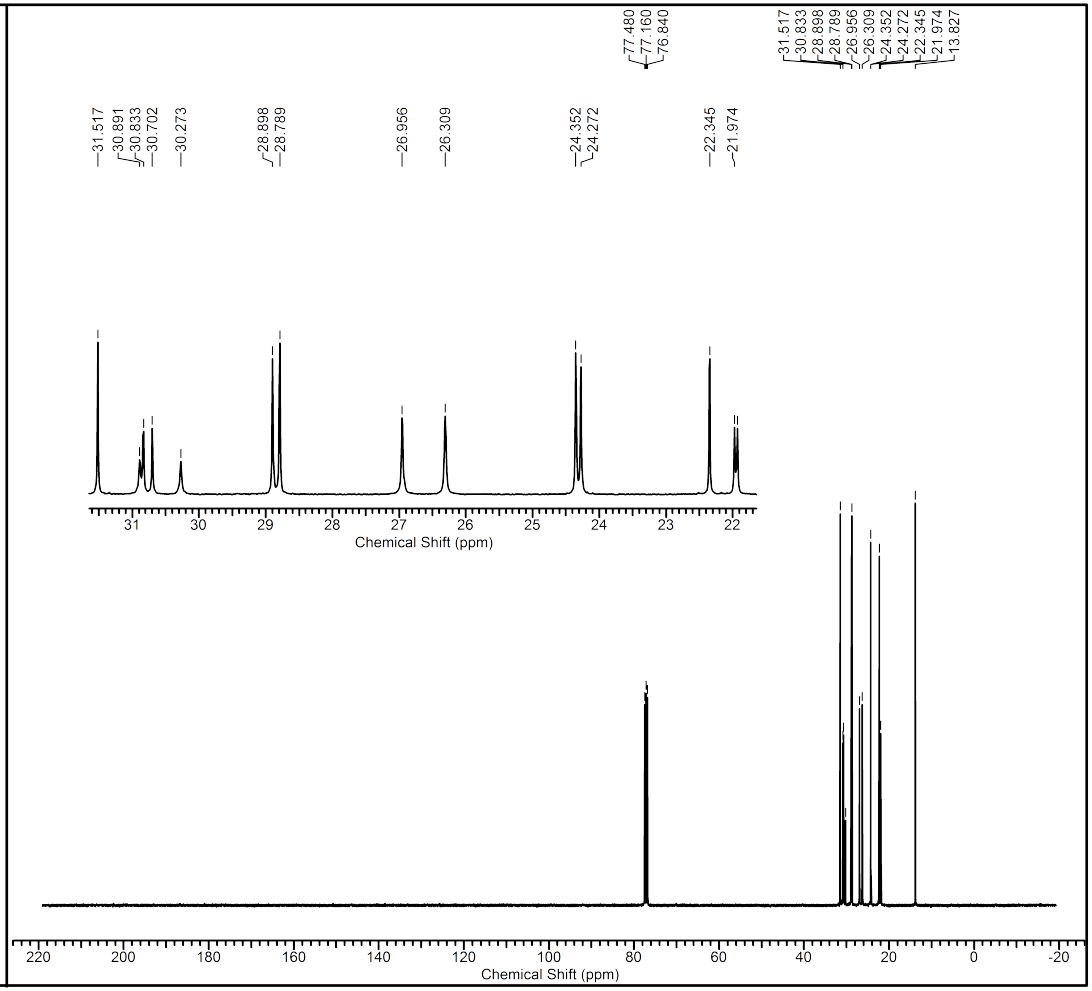


File Name	nOct
Acquisition Time (sec)	1.3664
Date Stamp	11 May 2013 06:45
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10048.4414
Origin	spect
Receiver Gain	10321.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

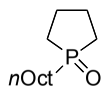


PCb

O'Brien™
Group NMR Data

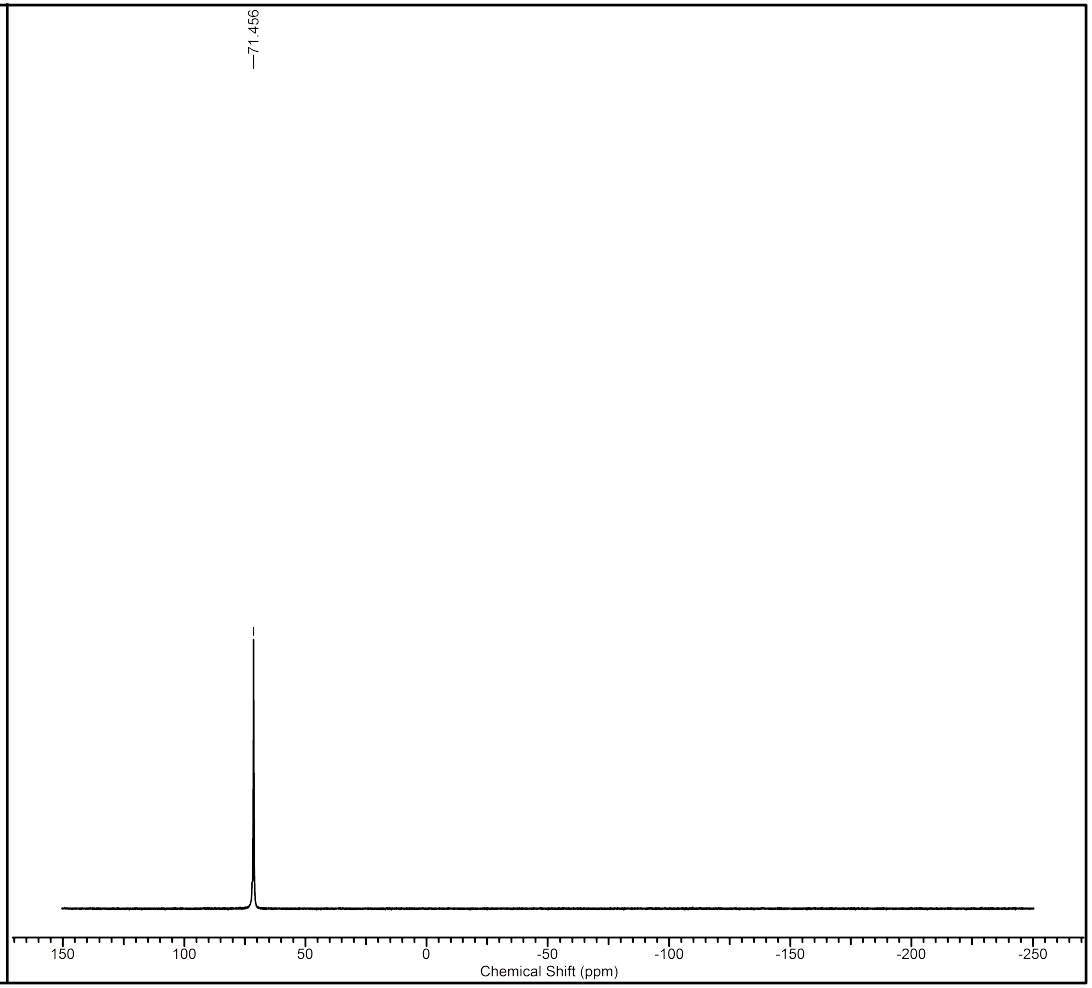


File Name	nOct
Acquisition Time (sec)	0.5046
Date Stamp	11 May 2013 05:45
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	31P
Points Count	32768
Number of Transients	64
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	-8098.8086
Origin	spect
Receiver Gain	3649.10
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09

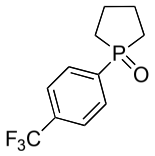


PCb

O'Brien™
Group NMR Data

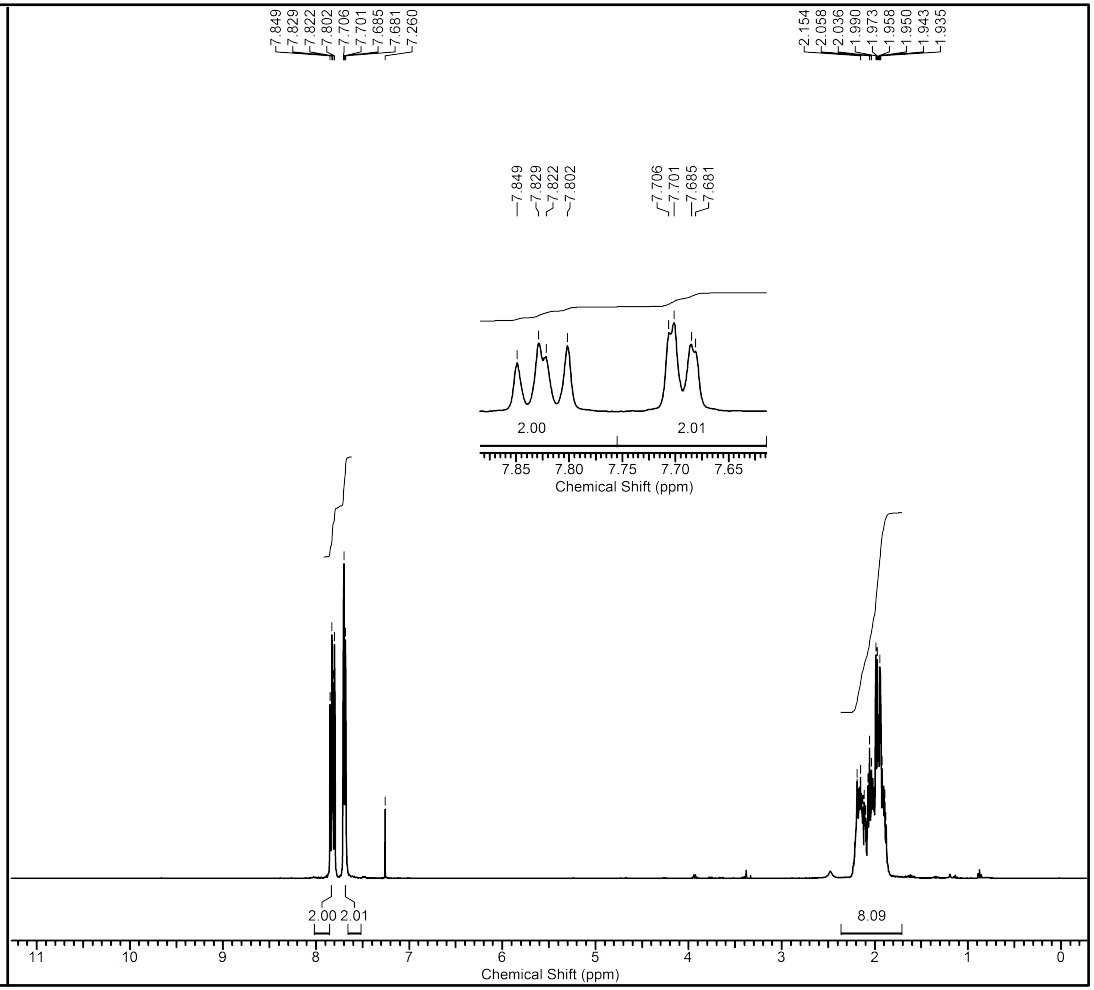


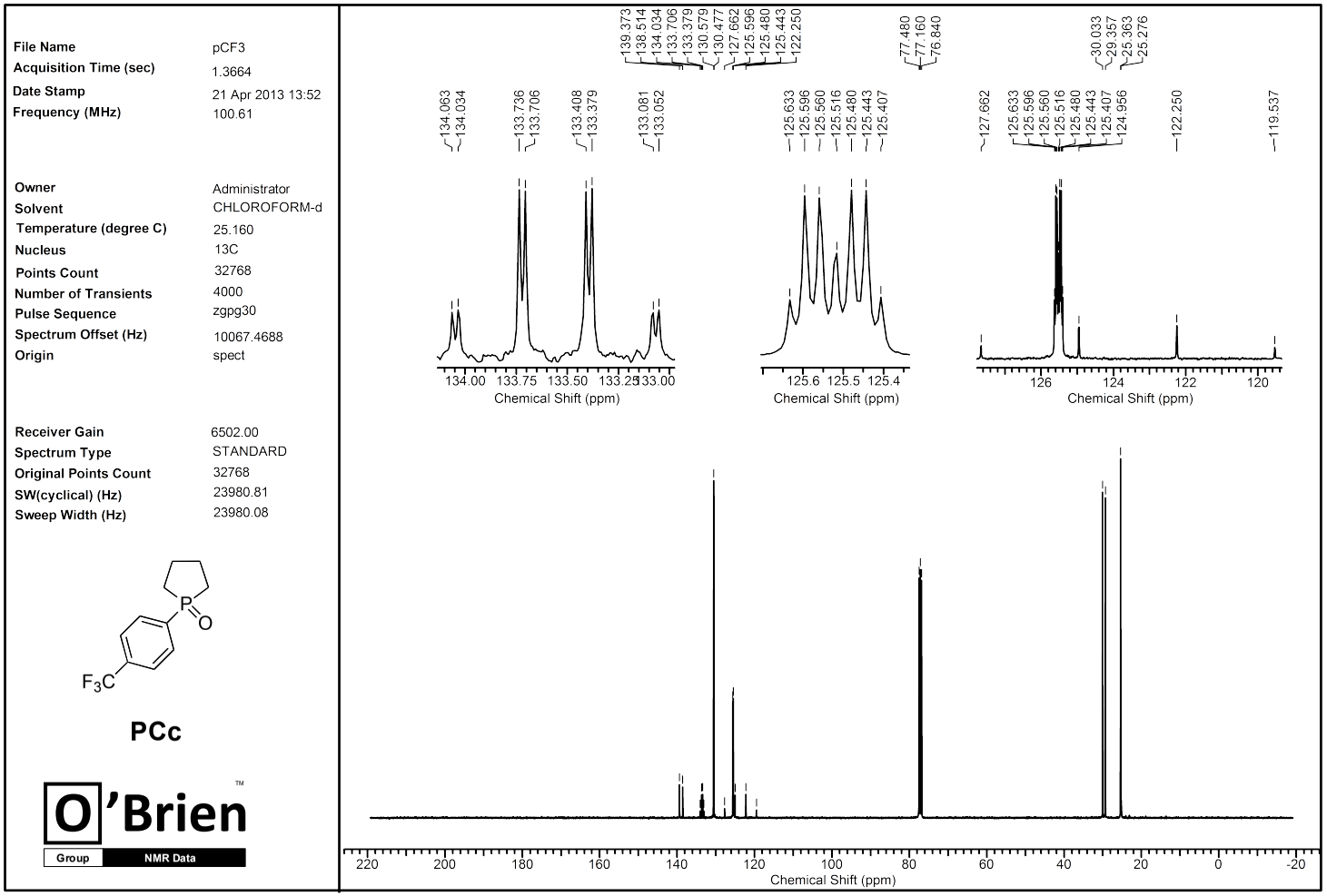
File Name	pCF3
Acquisition Time (sec)	3.9584
Date Stamp	21 Apr 2013 09:51
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4539
Origin	spect
Receiver Gain	64.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89



PCc

O'Brien™
Group NMR Data

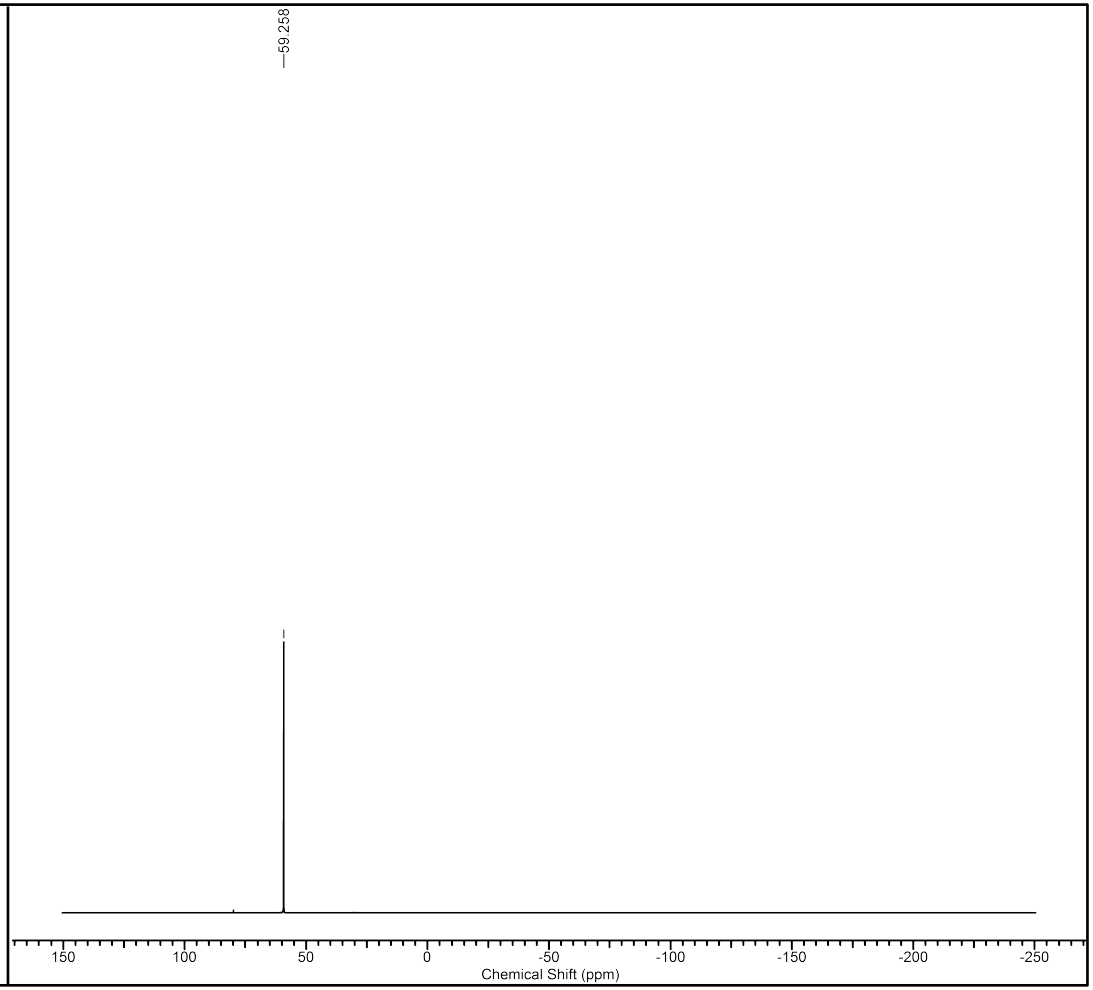



File Name pCF3
Acquisition Time (sec) 1.3664
Date Stamp 21 Apr 2013 13:52
Frequency (MHz) 100.61
Owner Administrator
Solvent CHLOROFORM-d
Temperature (degree C) 25.160
Nucleus 13C
Points Count 32768
Number of Transients 4000
Pulse Sequence zgpg30
Spectrum Offset (Hz) 10067.4688
Origin spect
Receiver Gain 6502.00
Spectrum Type STANDARD
Original Points Count 32768
SW(cyclical) (Hz) 23980.81
Sweep Width (Hz) 23980.08
PCc
O'Brien
Group NMR Data
Chemical Shift (ppm)

File Name	pCF3
Acquisition Time (sec)	0.5046
Date Stamp	21 Apr 2013 10:01
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	31P
Points Count	32768
Number of Transients	128
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	-8098.8086
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09

PCc

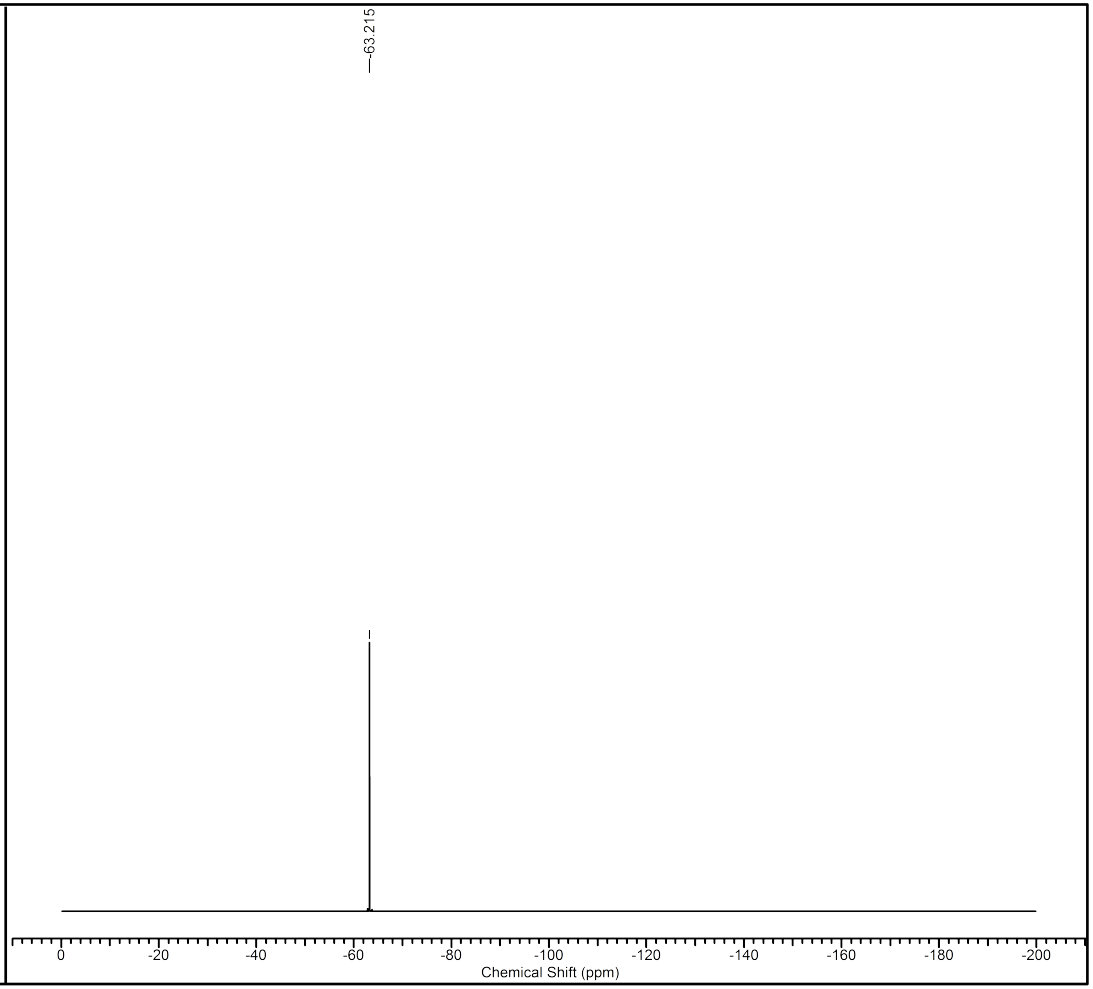
O'Brien™
Group NMR Data



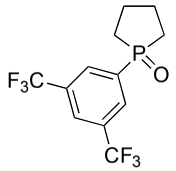
File Name	pCF3
Acquisition Time (sec)	0.8716
Date Stamp	21 Apr 2013 09:55
Frequency (MHz)	376.50
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	19F
Points Count	65536
Number of Transients	16
Pulse Sequence	zgfhigqn
Spectrum Offset (Hz)	-37649.6211
Origin	spect
Receiver Gain	456.10
Spectrum Type	STANDARD
Original Points Count	65536
SW(cyclical) (Hz)	75187.97
Sweep Width (Hz)	75186.82

PCc

O'Brien™
Group NMR Data

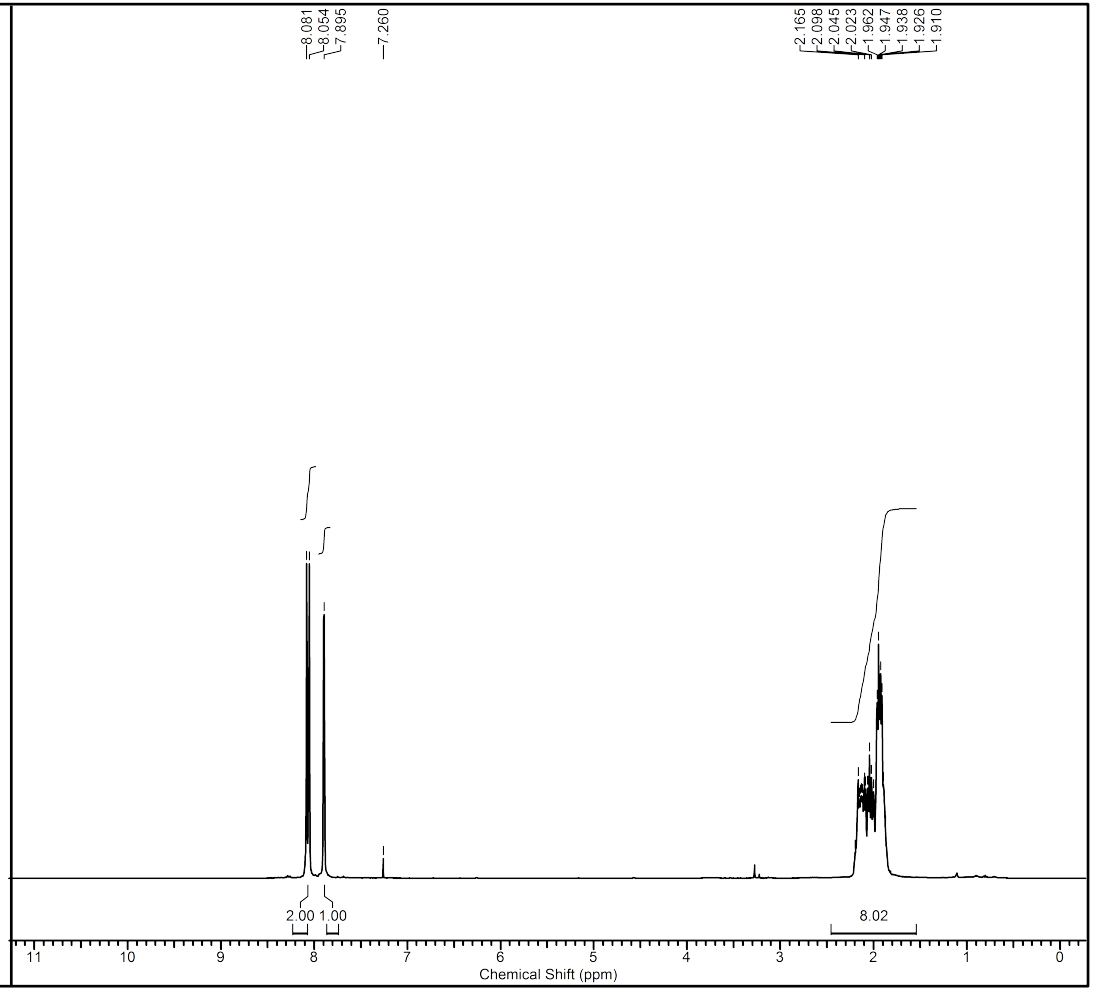


File Name	2mCF3
Acquisition Time (sec)	3.9584
Date Stamp	04 May 2013 18:10
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4539
Origin	spect
Receiver Gain	32.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

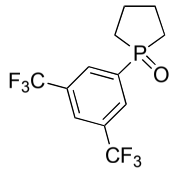


PCd

O'Brien™
Group NMR Data

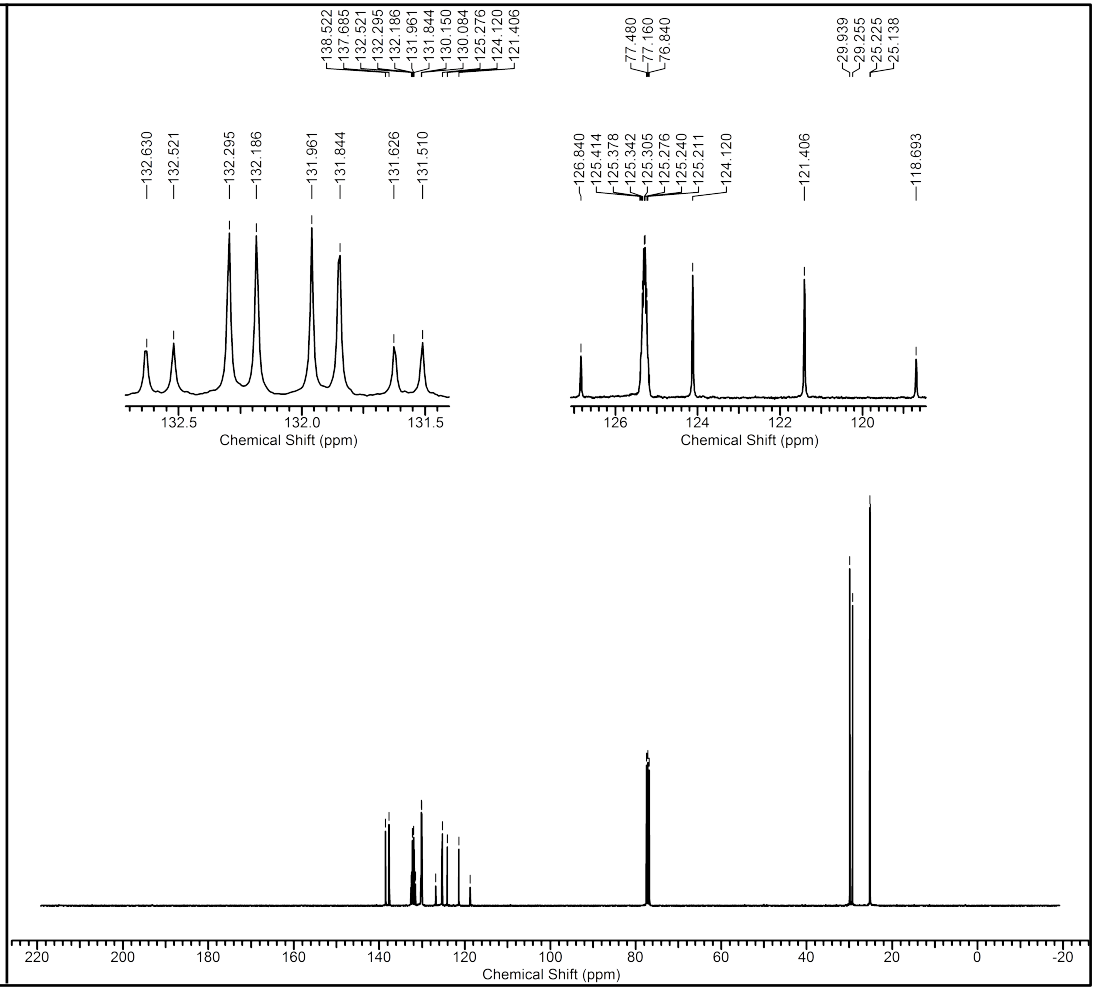


File Name	2mCF3
Acquisition Time (sec)	1.3664
Date Stamp	04 May 2013 21:03
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	3000
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10062.3457
Origin	spect
Receiver Gain	4096.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

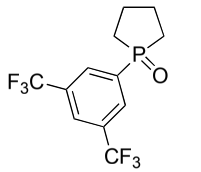


PCd

O'Brien™
Group NMR Data

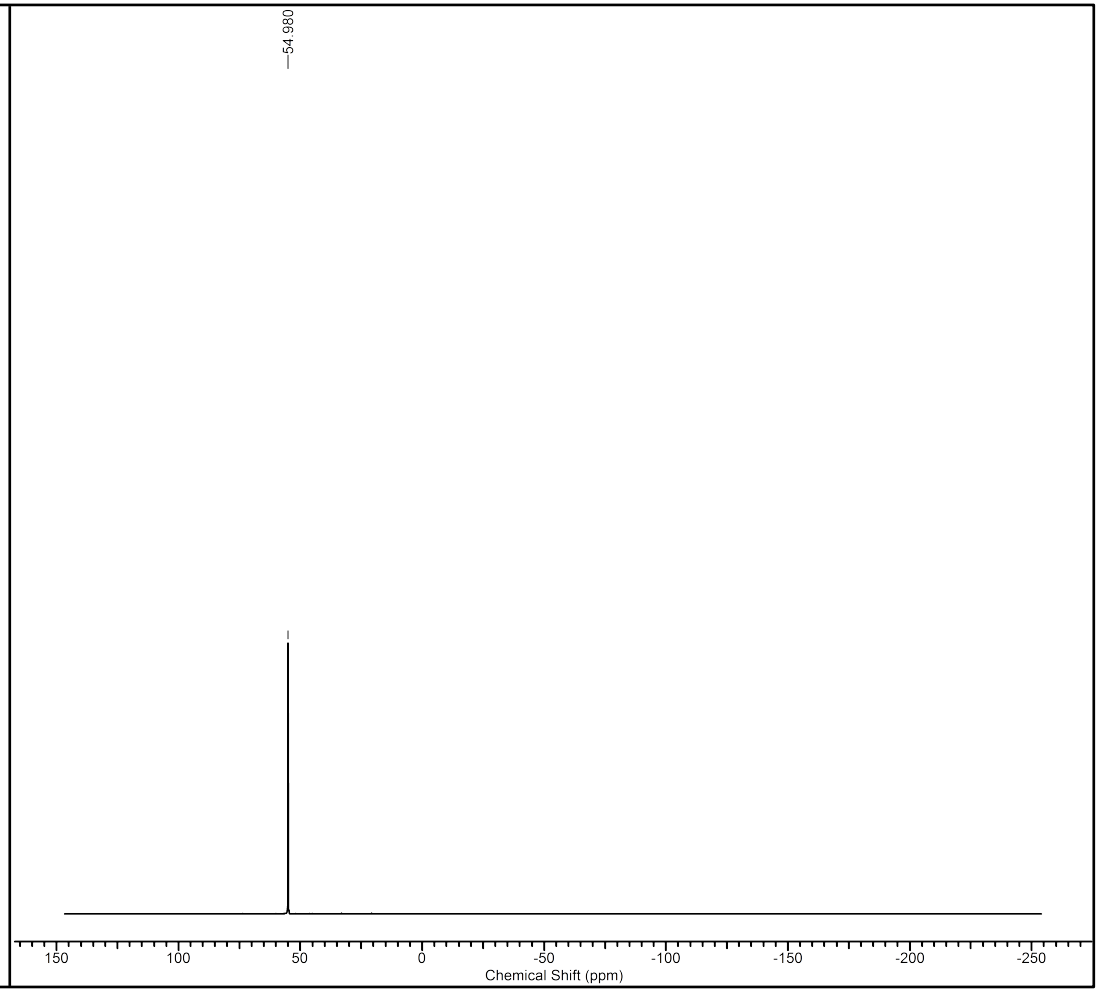


File Name	2mCF3
Acquisition Time (sec)	0.5046
Date Stamp	04 May 2013 21:11
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	31P
Points Count	32768
Number of Transients	128
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	-8688.7588
Origin	spect
Receiver Gain	1824.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09

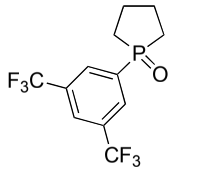


PCd

O'Brien™
Group NMR Data



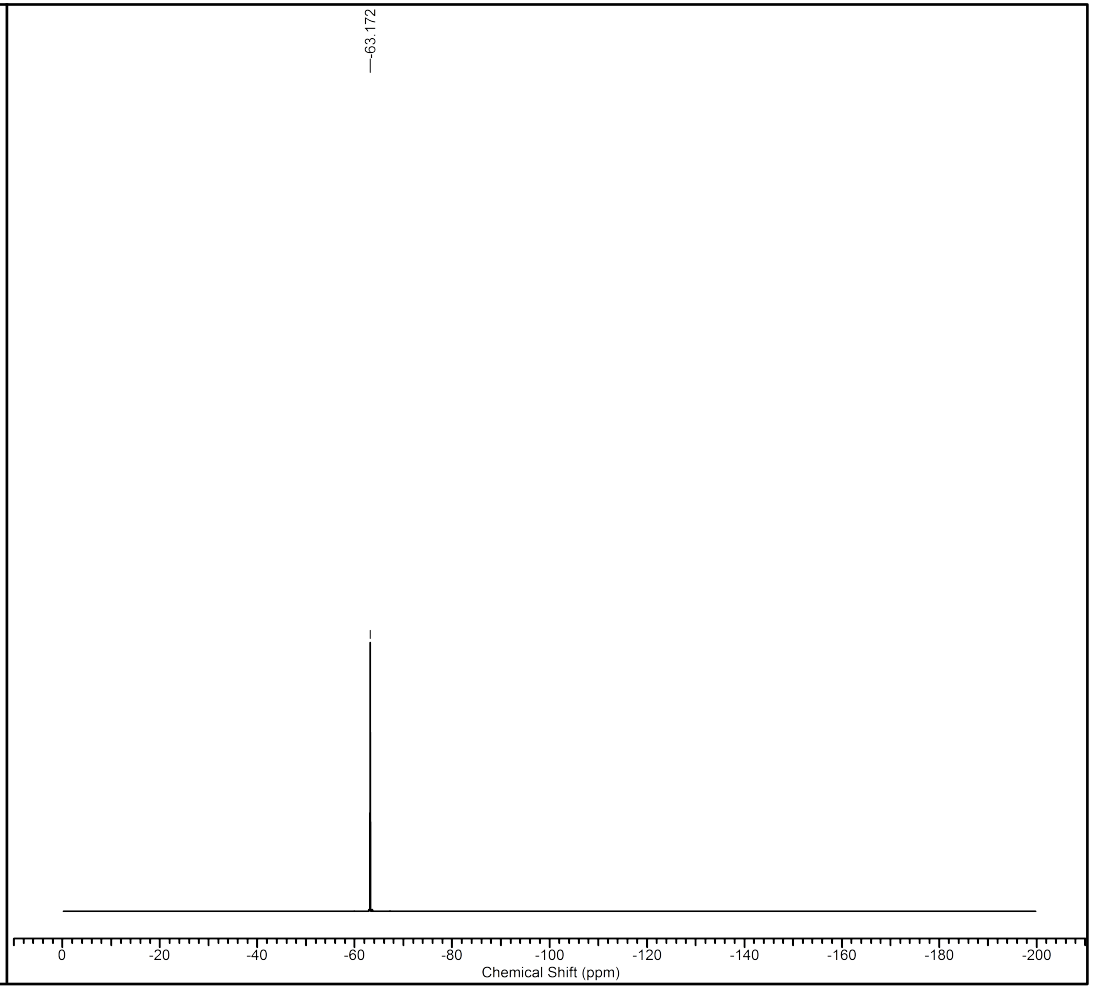
File Name	2mCF3
Acquisition Time (sec)	0.8716
Date Stamp	04 May 2013 21:05
Frequency (MHz)	376.50
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	19F
Points Count	65536
Number of Transients	16
Pulse Sequence	zgfhigqn
Spectrum Offset (Hz)	-37649.6211
Origin	spect
Receiver Gain	90.50
Spectrum Type	STANDARD
Original Points Count	65536
SW(cyclical) (Hz)	75187.97
Sweep Width (Hz)	75186.82



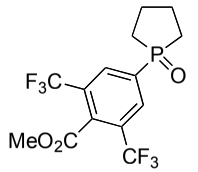
PCd

O'Brien™

Group NMR Data

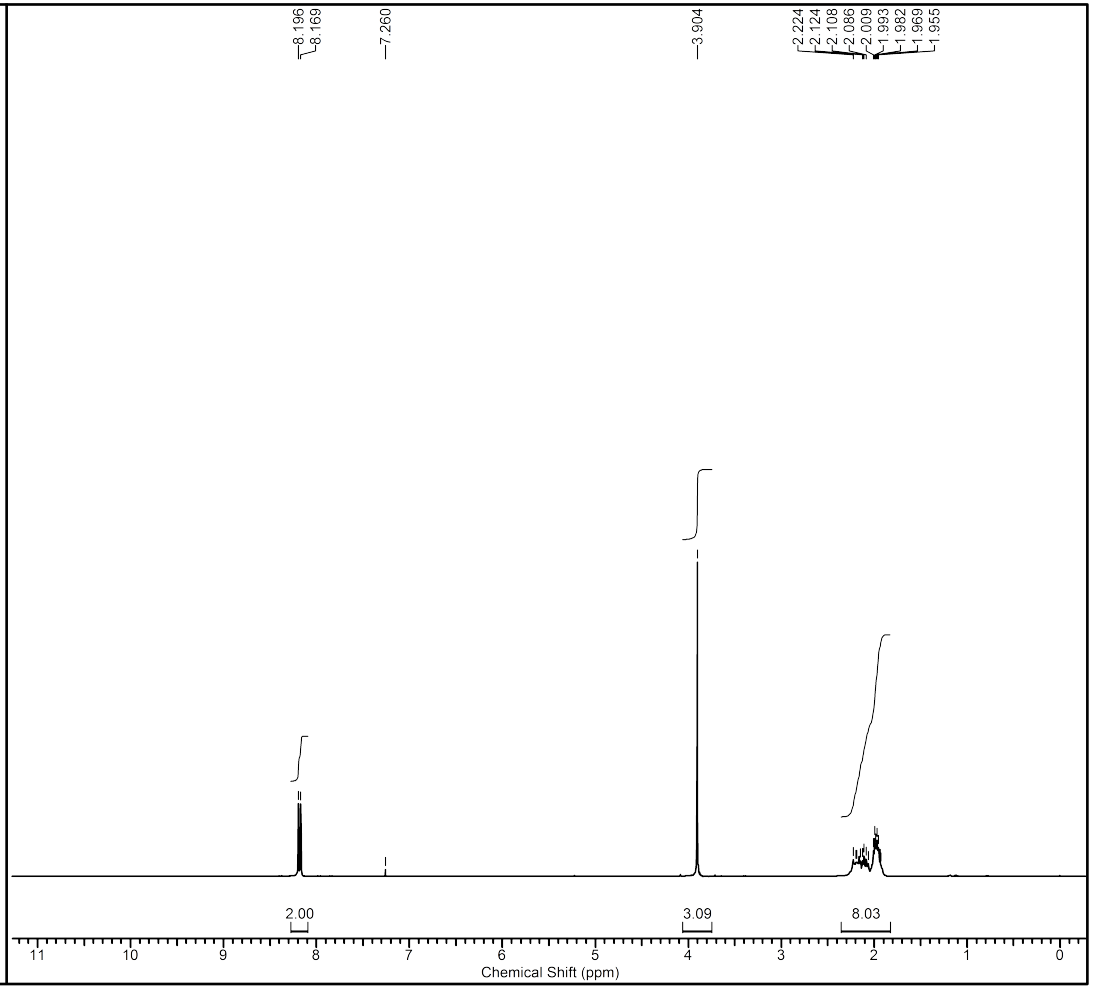


File Name	2mCF3_pCO2Me
Acquisition Time (sec)	3.9584
Date Stamp	21 Apr 2013 18:16
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.7063
Origin	spect
Receiver Gain	50.80
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

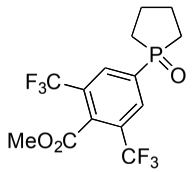


PCe

O'Brien™
Group NMR Data

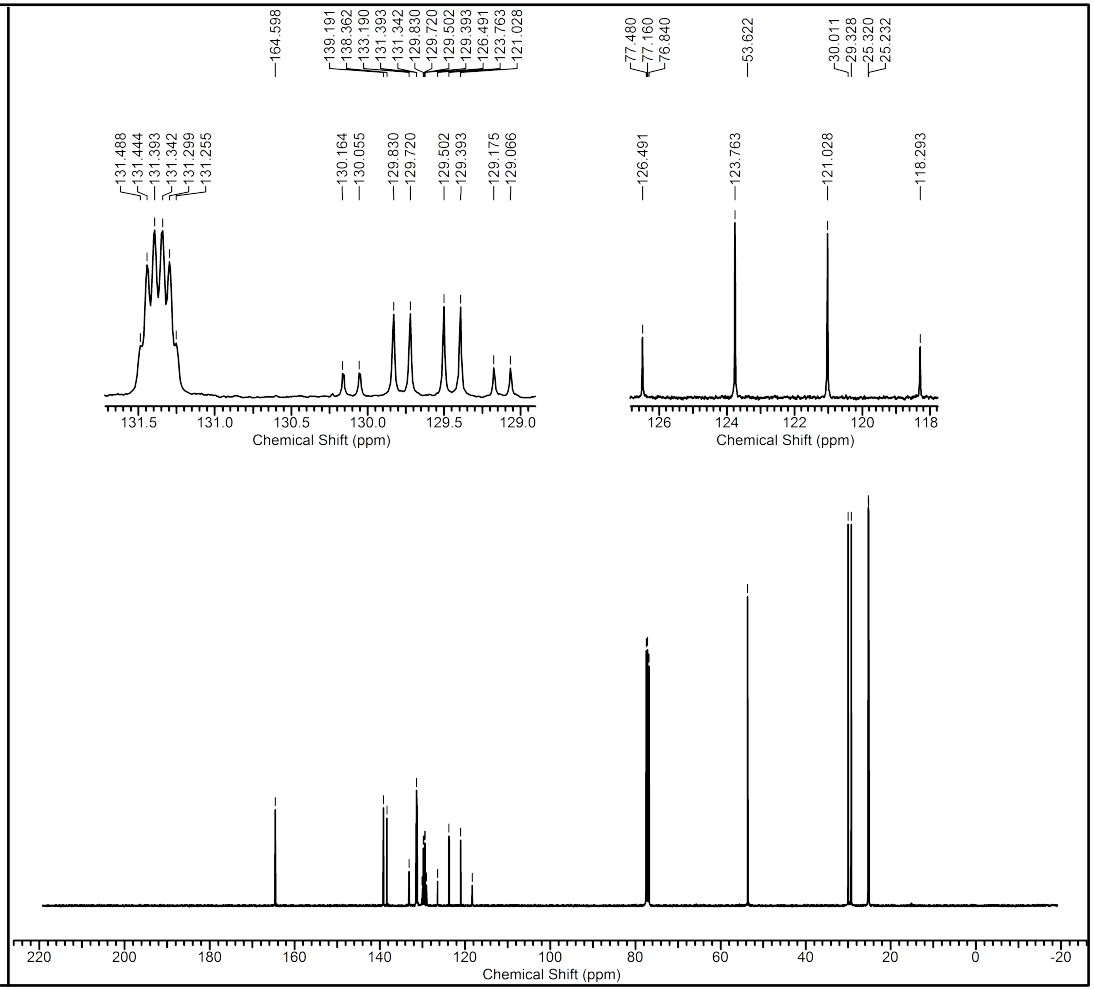


File Name	2mCF3_pCO2Me
Acquisition Time (sec)	1.3664
Date Stamp	21 Apr 2013 22:17
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	13C
Points Count	32768
Number of Transients	4000
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10068.2002
Origin	spect
Receiver Gain	1625.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

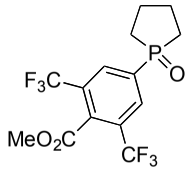


PCe

O'Brien™
Group NMR Data

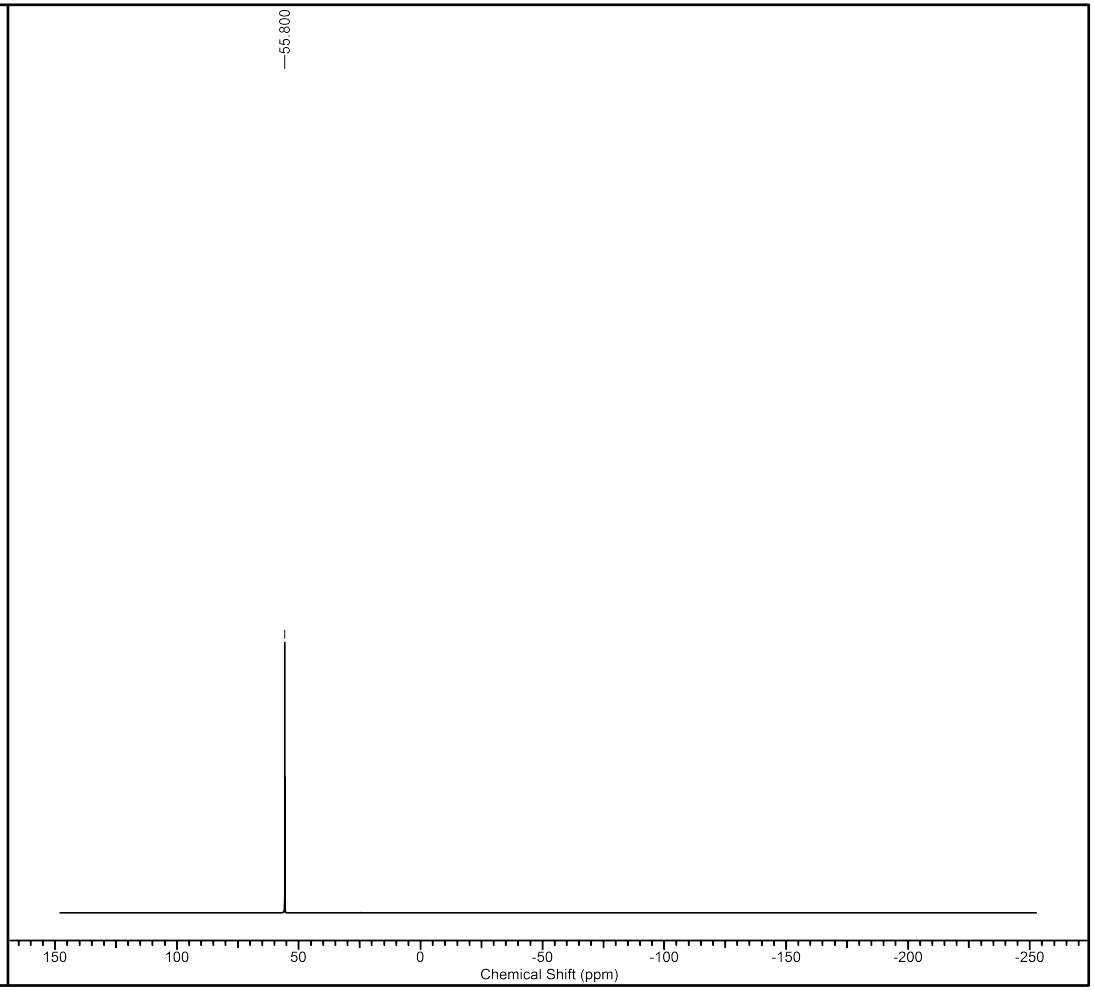


File Name	2mCF3_pCO2Me
Acquisition Time (sec)	0.5046
Date Stamp	21 Apr 2013 18:25
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	31P
Points Count	32768
Number of Transients	128
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	-8480.6367
Origin	spect
Receiver Gain	5160.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09

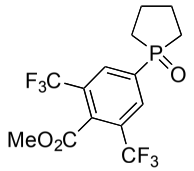


PCe

O'Brien™
Group NMR Data



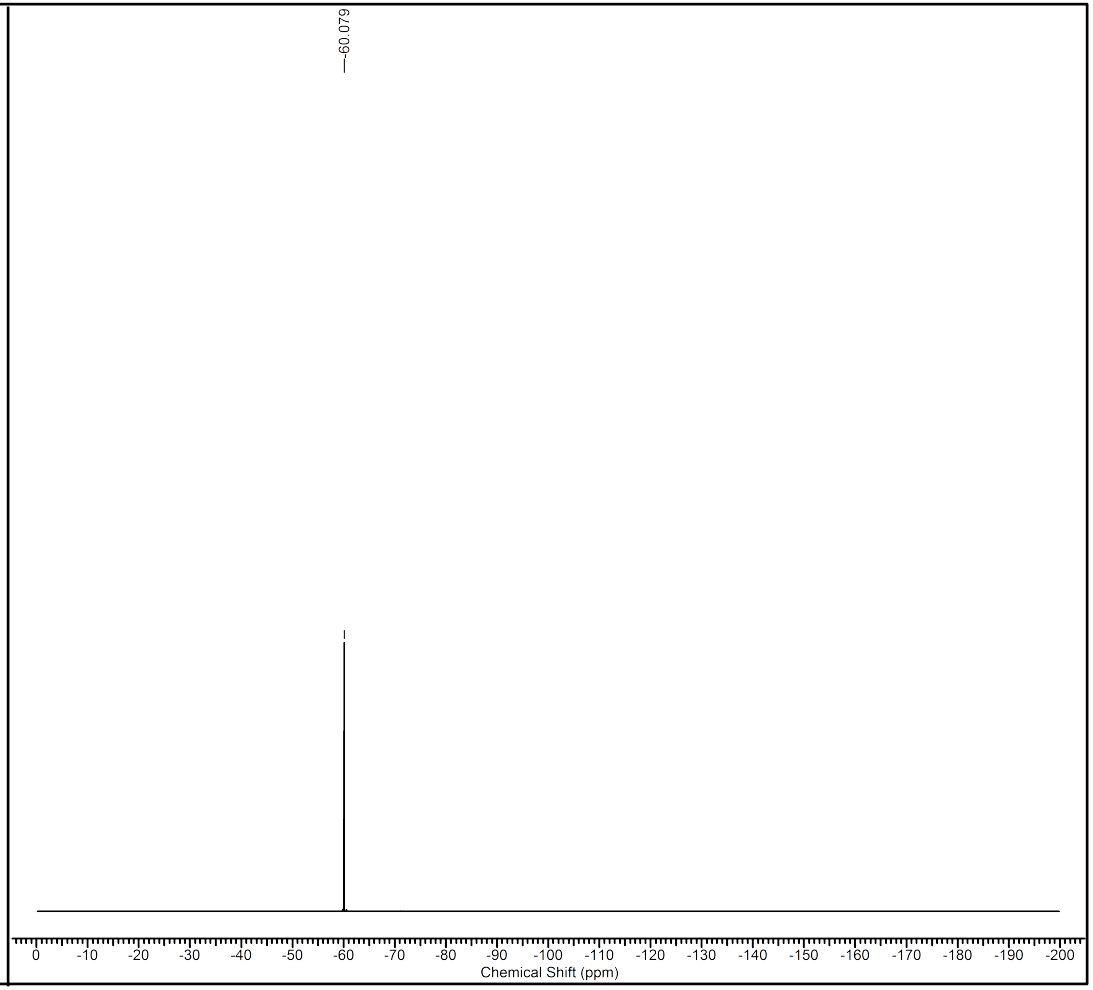
File Name	2mCF3_pCO2Me
Acquisition Time (sec)	0.8716
Date Stamp	21 Apr 2013 18:18
Frequency (MHz)	376.50
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	19F
Points Count	65536
Number of Transients	16
Pulse Sequence	zgfhigqn
Spectrum Offset (Hz)	-37649.6211
Origin	spect
Receiver Gain	143.70
Spectrum Type	STANDARD
Original Points Count	65536
SW(cyclical) (Hz)	75187.97
Sweep Width (Hz)	75186.82



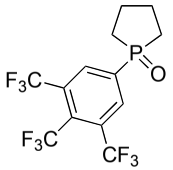
PCe

O'Brien™

Group NMR Data



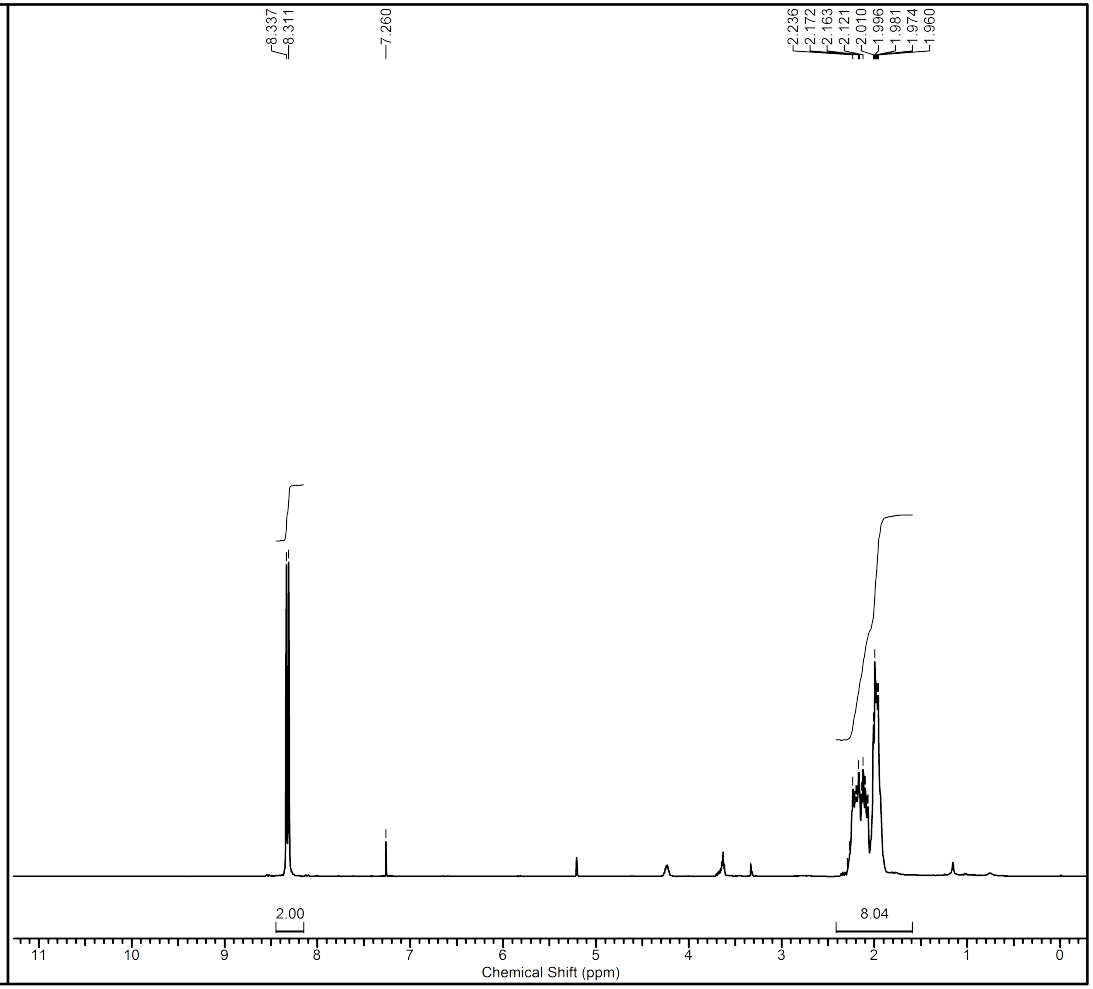
File Name	TriCF3
Acquisition Time (sec)	3.9584
Date Stamp	14 May 2013 21:26
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4539
Origin	spect
Receiver Gain	40.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89



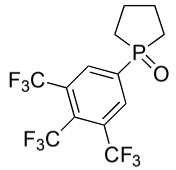
PCf

O'Brien™

Group NMR Data

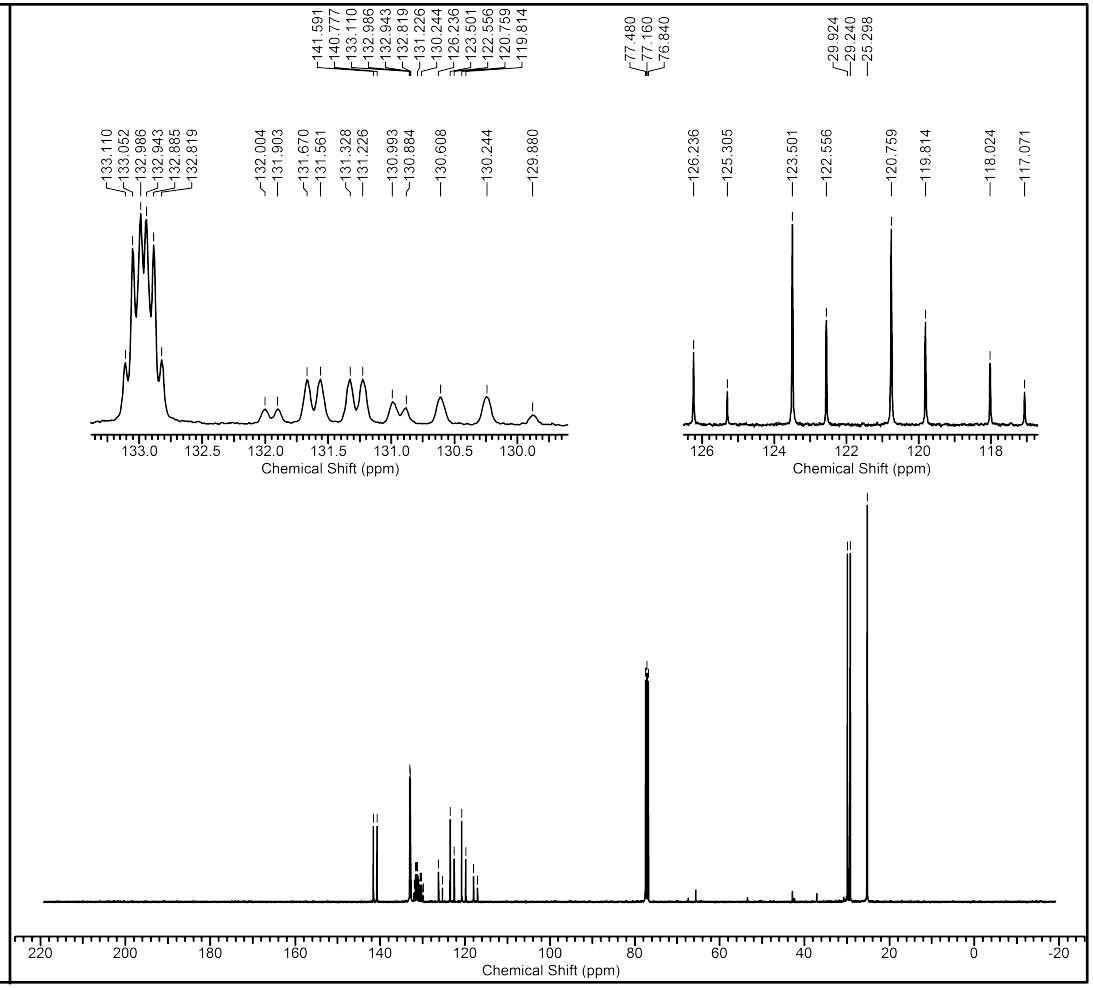


File Name	TriCF3
Acquisition Time (sec)	1.3664
Date Stamp	15 May 2013 01:17
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	4000
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10066.7373
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

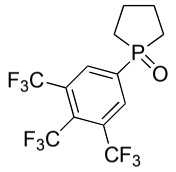


PCf

O'Brien™
Group NMR Data



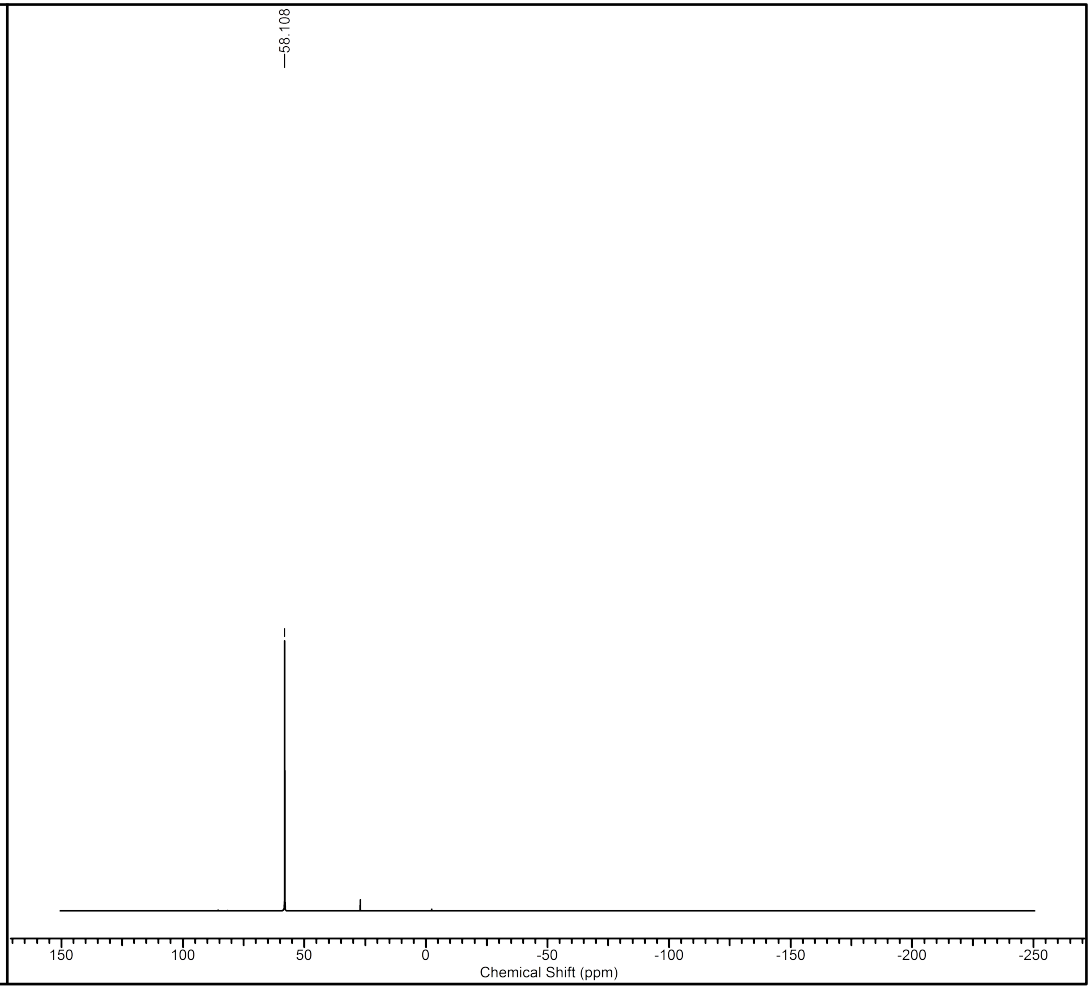
File Name	TriCF3
Acquisition Time (sec)	0.5046
Date Stamp	15 May 2013 01:21
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	31P
Points Count	32768
Number of Transients	64
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	-8098.8086
Origin	spect
Receiver Gain	2298.80
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09



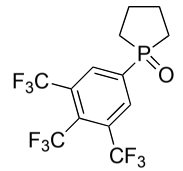
PCf

O'Brien™

Group NMR Data

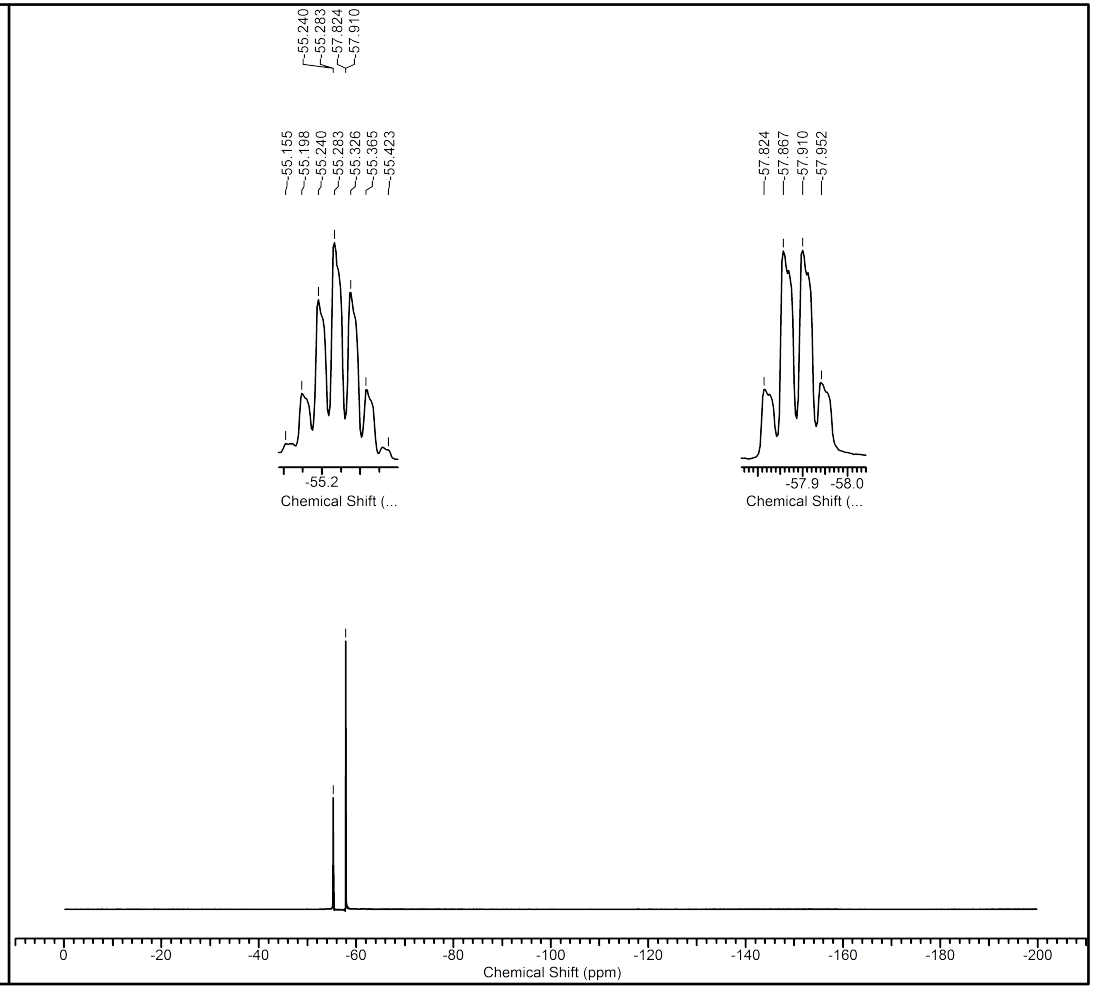


File Name	TriCF3
Acquisition Time (sec)	0.8716
Date Stamp	15 May 2013 01:17
Frequency (MHz)	376.50
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	19F
Points Count	65536
Number of Transients	16
Pulse Sequence	zgfhigqn
Spectrum Offset (Hz)	-37649.6211
Origin	spect
Receiver Gain	80.60
Spectrum Type	STANDARD
Original Points Count	65536
SW(cyclical) (Hz)	75187.97
Sweep Width (Hz)	75186.82



PCf

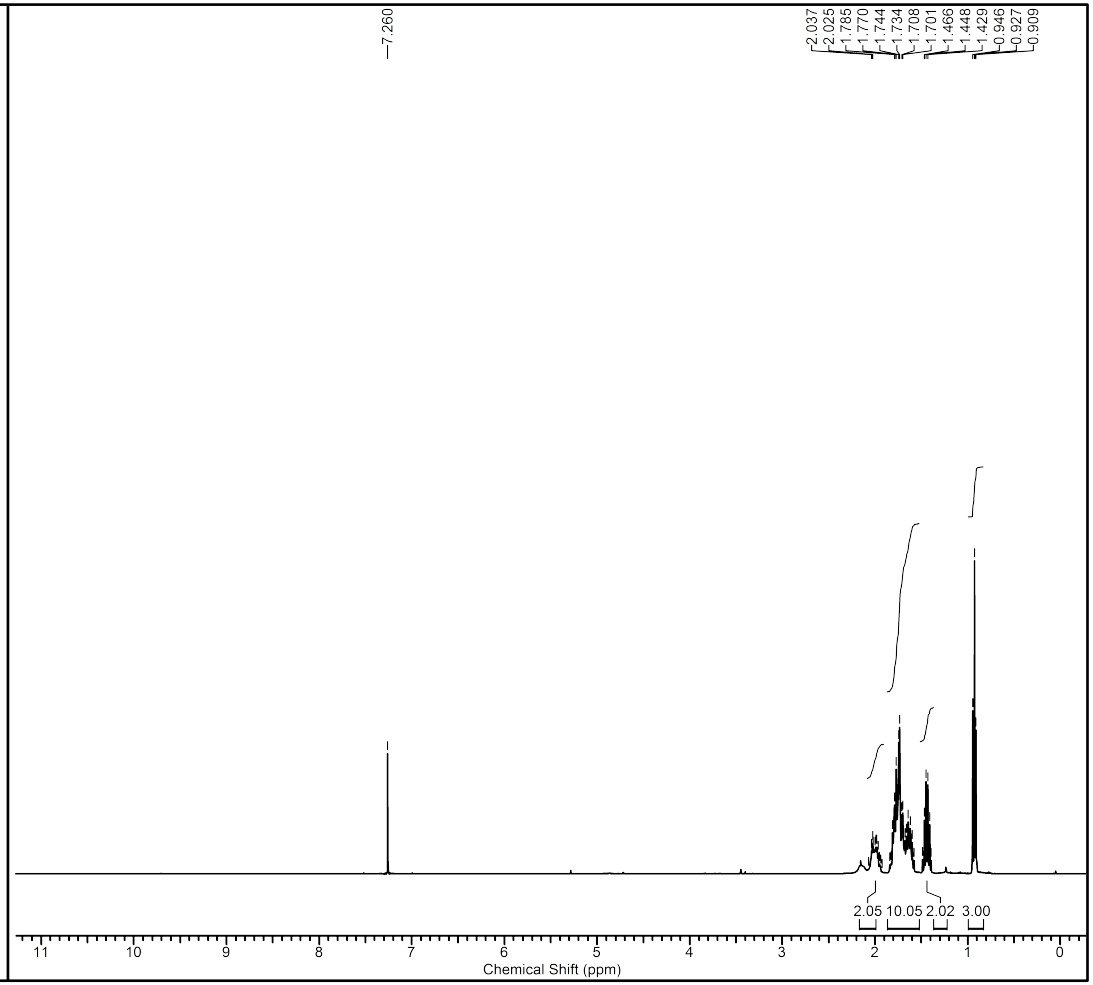
O'Brien™
Group NMR Data



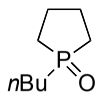
File Name	nBu_2
Acquisition Time (sec)	3.9584
Date Stamp	23 May 2012 19:42
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	22.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.2014
Origin	spect
Receiver Gain	128.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

PCg

O'Brien™
Group NMR Data

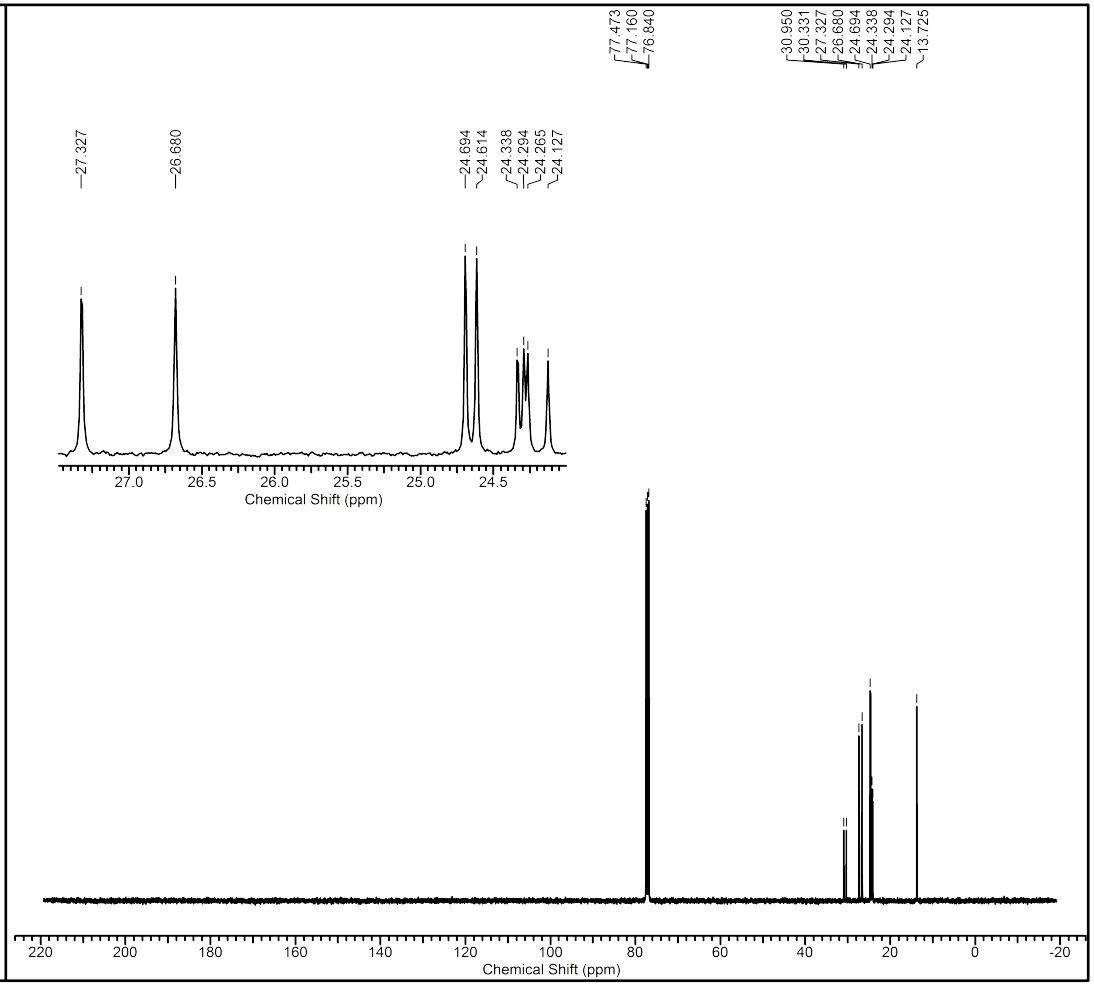


File Name	nBu_2
Acquisition Time (sec)	1.3664
Date Stamp	19 Oct 2012 00:02
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10068.9316
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

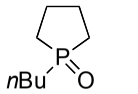


PCg

O'Brien™
Group NMR Data

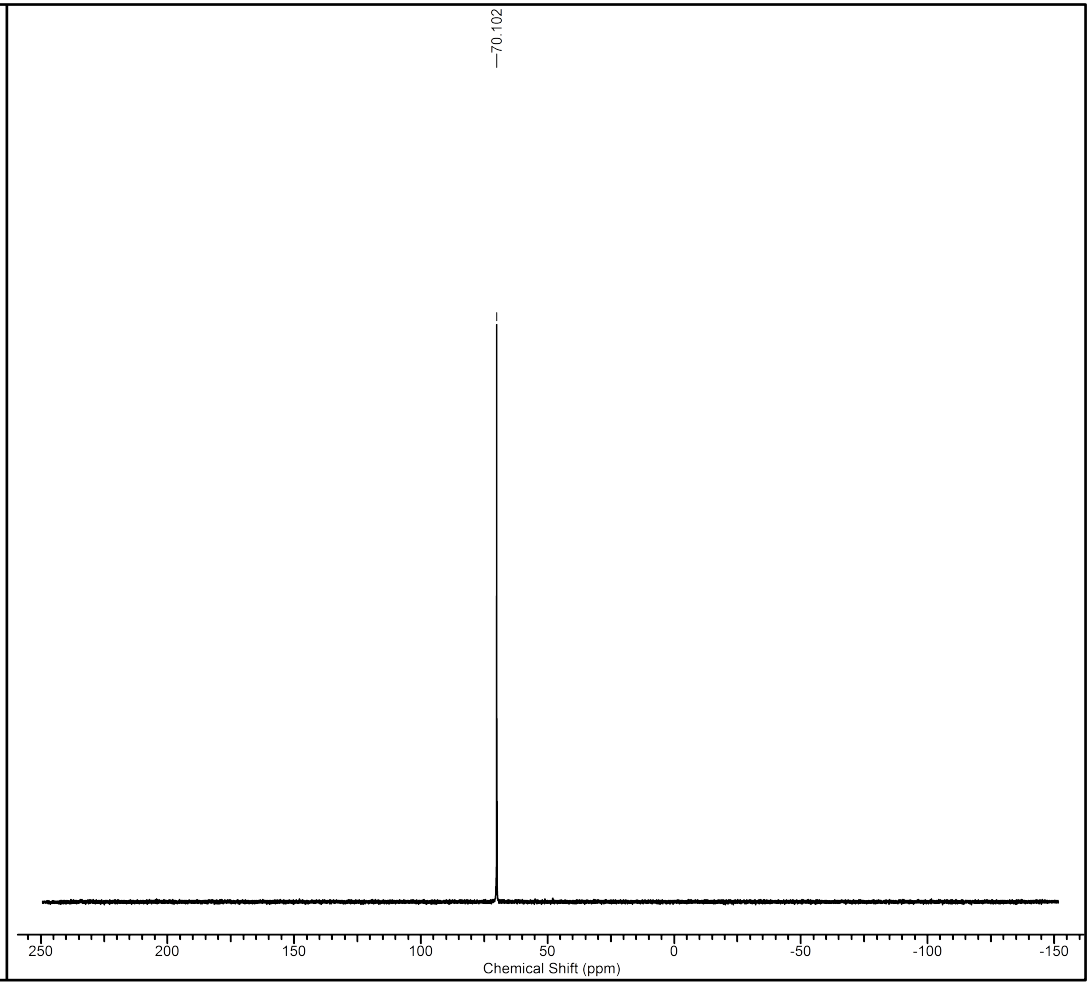


File Name	nBu_2
Acquisition Time (sec)	0.5046
Date Stamp	23 May 2012 19:40
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	22.160
Nucleus	31P
Points Count	32768
Number of Transients	128
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	7905.7319
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09

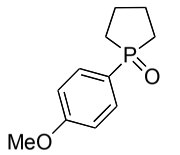


PCg

O'Brien™
Group NMR Data



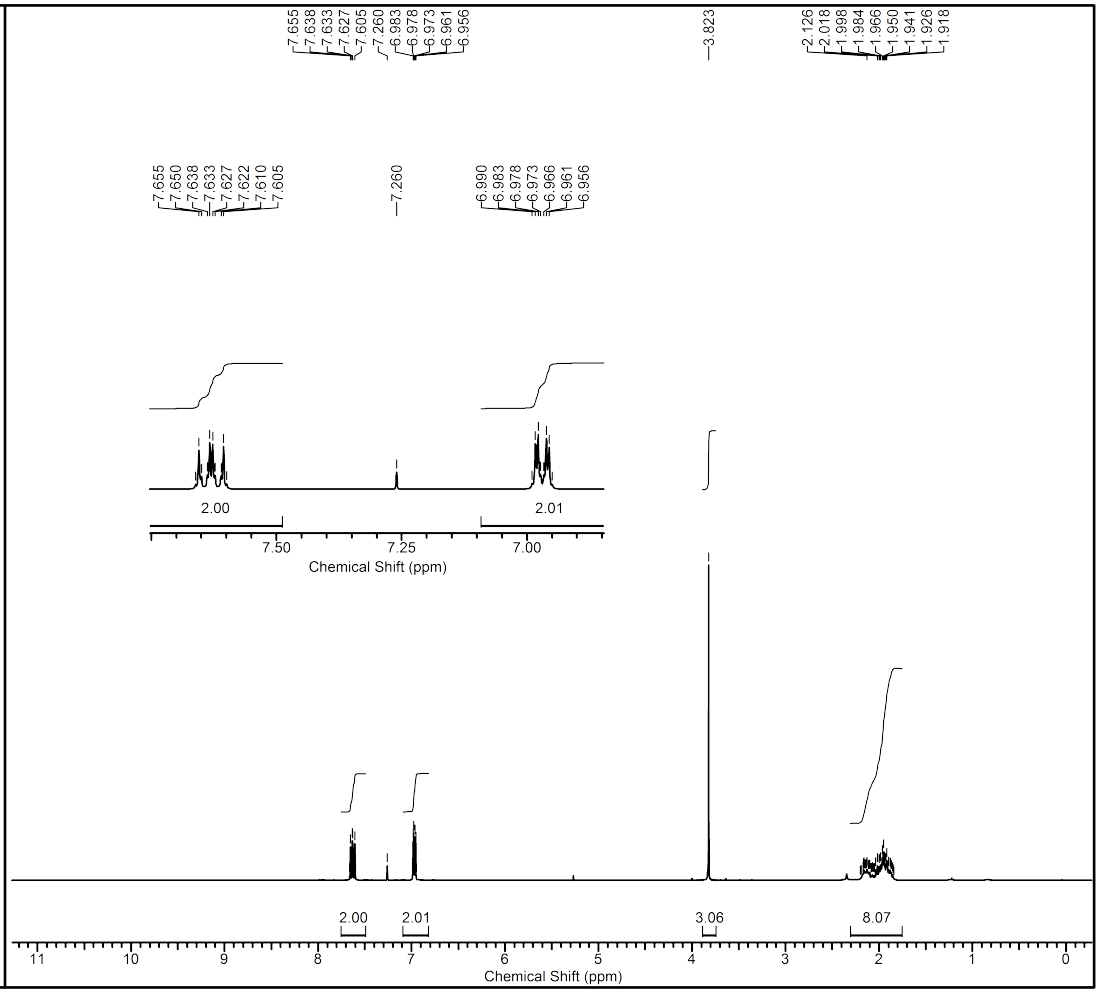
File Name	OMe_P=O
Acquisition Time (sec)	3.9584
Date Stamp	09 May 2012 17:12
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	22.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	90.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

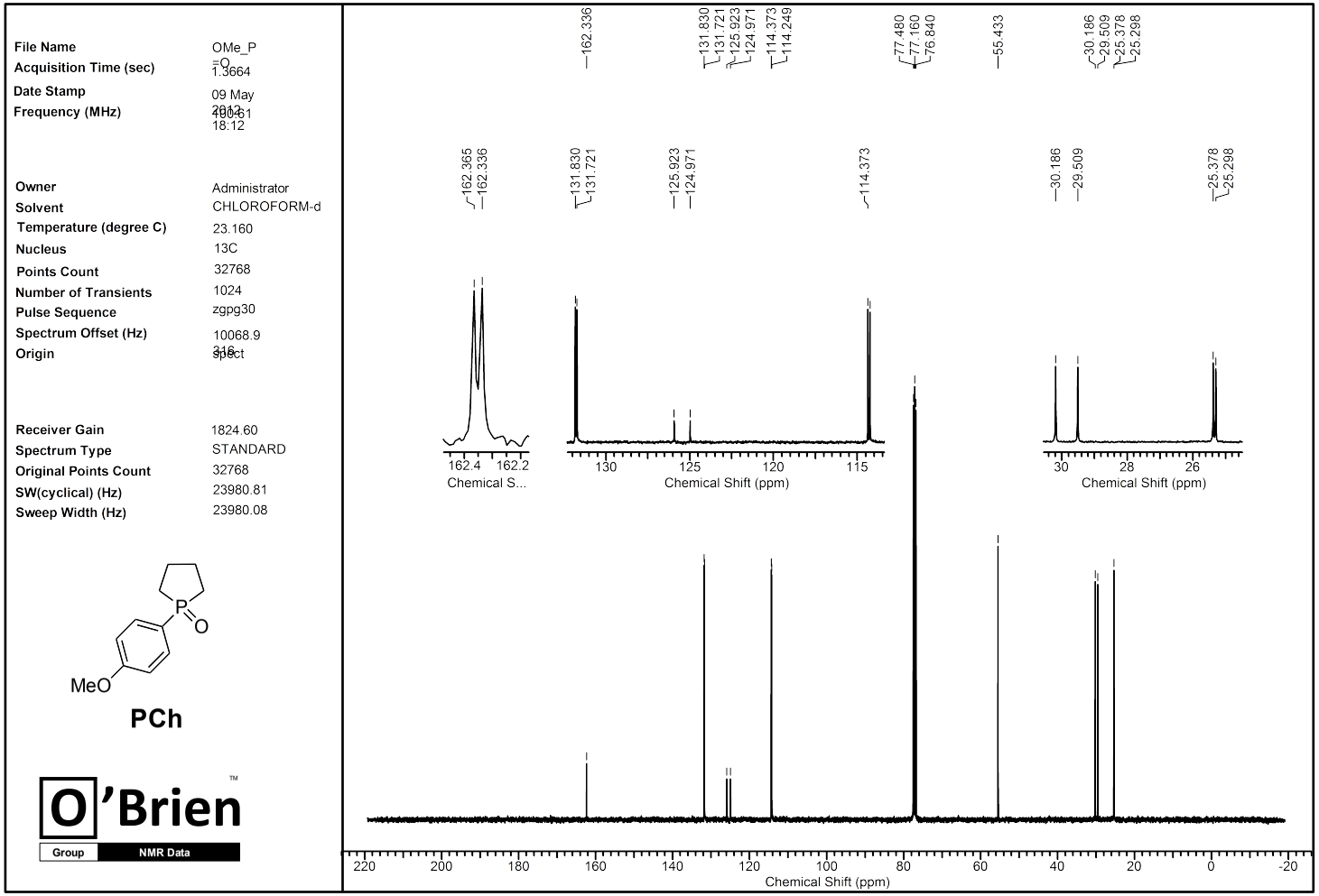


PCh

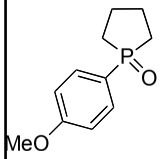
O'Brien™

Group NMR Data



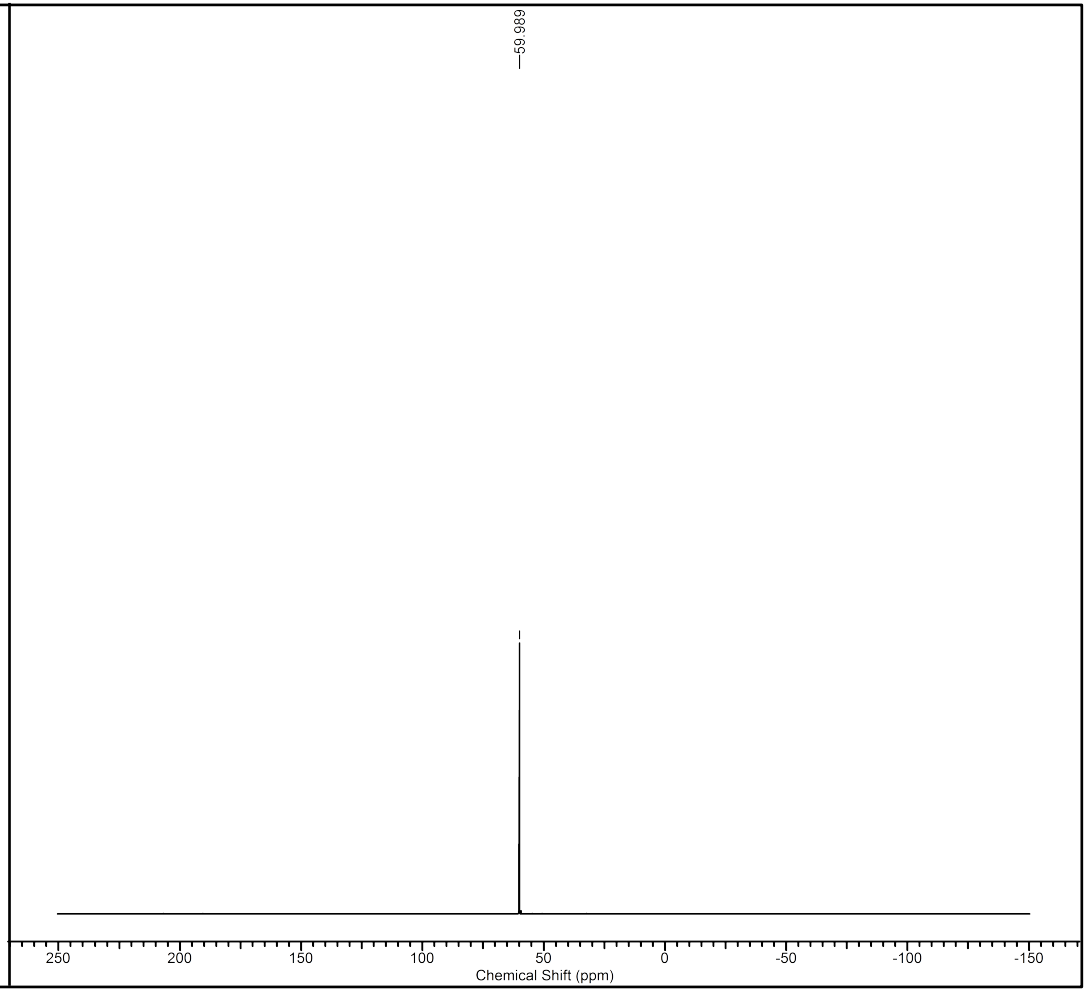

File Name OMe_P
Acquisition Time (sec) 1.3664
Date Stamp 09 May 2012
Frequency (MHz) 100.61
18:12
Owner Administrator
Solvent CHLOROFORM-d
Temperature (degree C) 23.160
Nucleus 13C
Points Count 32768
Number of Transients 1024
Pulse Sequence zgpg30
Spectrum Offset (Hz) 10068.9
Origin spect
Receiver Gain 1824.60
Spectrum Type STANDARD
Original Points Count 32768
SW(cyclical) (Hz) 23980.81
Sweep Width (Hz) 23980.08
MeO
P
O
PCh
O'Brien
Group NMR Data
162.336
131.830
131.721
125.923
124.971
114.373
114.249
77.480
77.160
76.840
55.433
30.186
29.509
25.378
25.298
Chemical Shift (ppm)

File Name	OMe_P=O
Acquisition Time (sec)	0.5046
Date Stamp	04 May 2012 16:06
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	23.160
Nucleus	31P
Points Count	32768
Number of Transients	128
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	8098.7822
Origin	spect
Receiver Gain	5792.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09

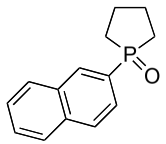


PCh

O'Brien™
Group NMR Data

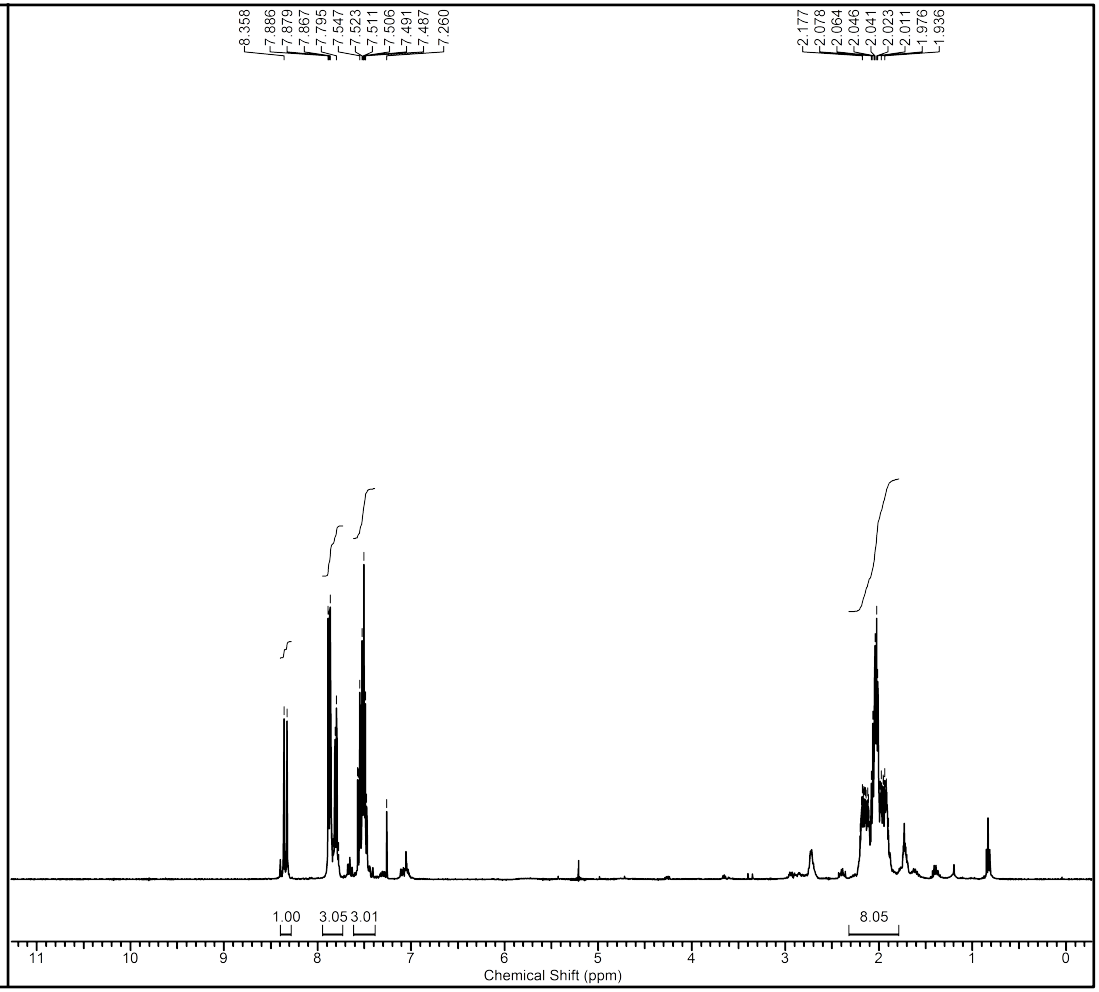


File Name	1-n_P=O
Acquisition Time (sec)	3.9584
Date Stamp	03 Oct 2013 21:01
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	40.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

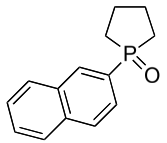


PCi

O'Brien™
Group NMR Data

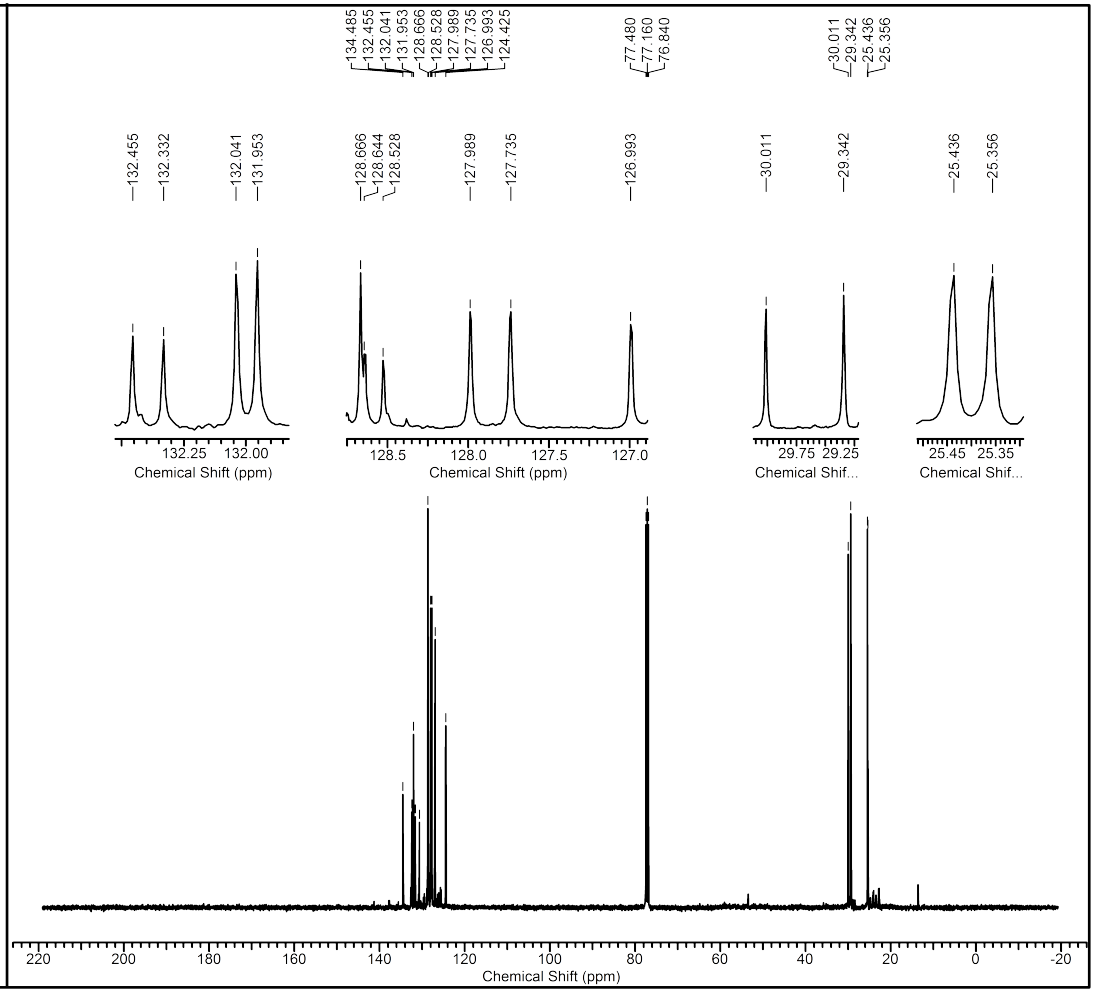


File Name	1-n_P=O
Acquisition Time (sec)	1.3664
Date Stamp	03 Oct 2013 20:50
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10054.2959
Origin	spect
Receiver Gain	10321.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

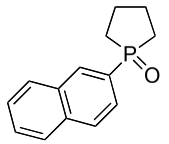


PCi

O'Brien™
Group NMR Data

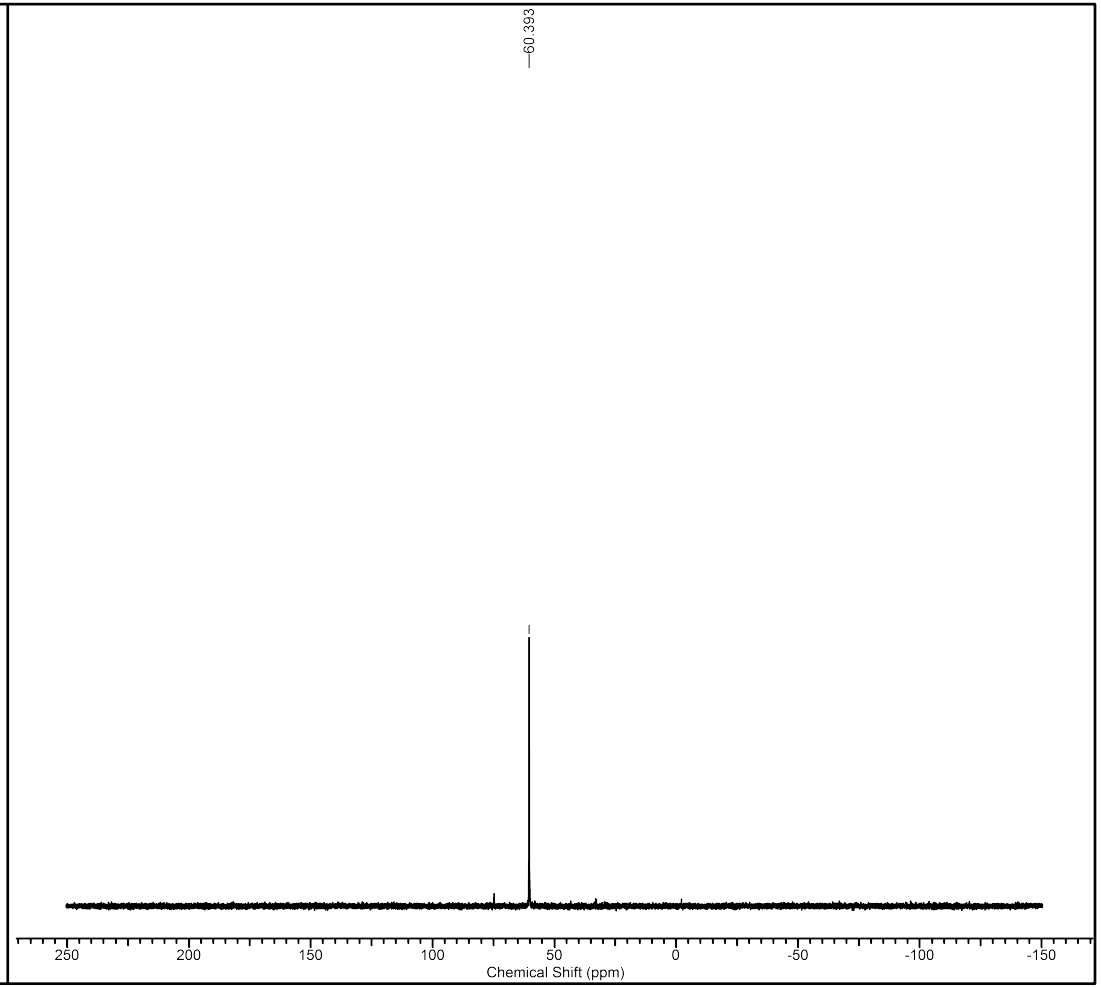


File Name	1-n_P=O
Acquisition Time (sec)	0.5046
Date Stamp	16 Sep 2013 16:30
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	31P
Points Count	32768
Number of Transients	128
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	8098.7822
Origin	spect
Receiver Gain	7298.20
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09

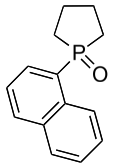


PCi

O'Brien™
Group NMR Data

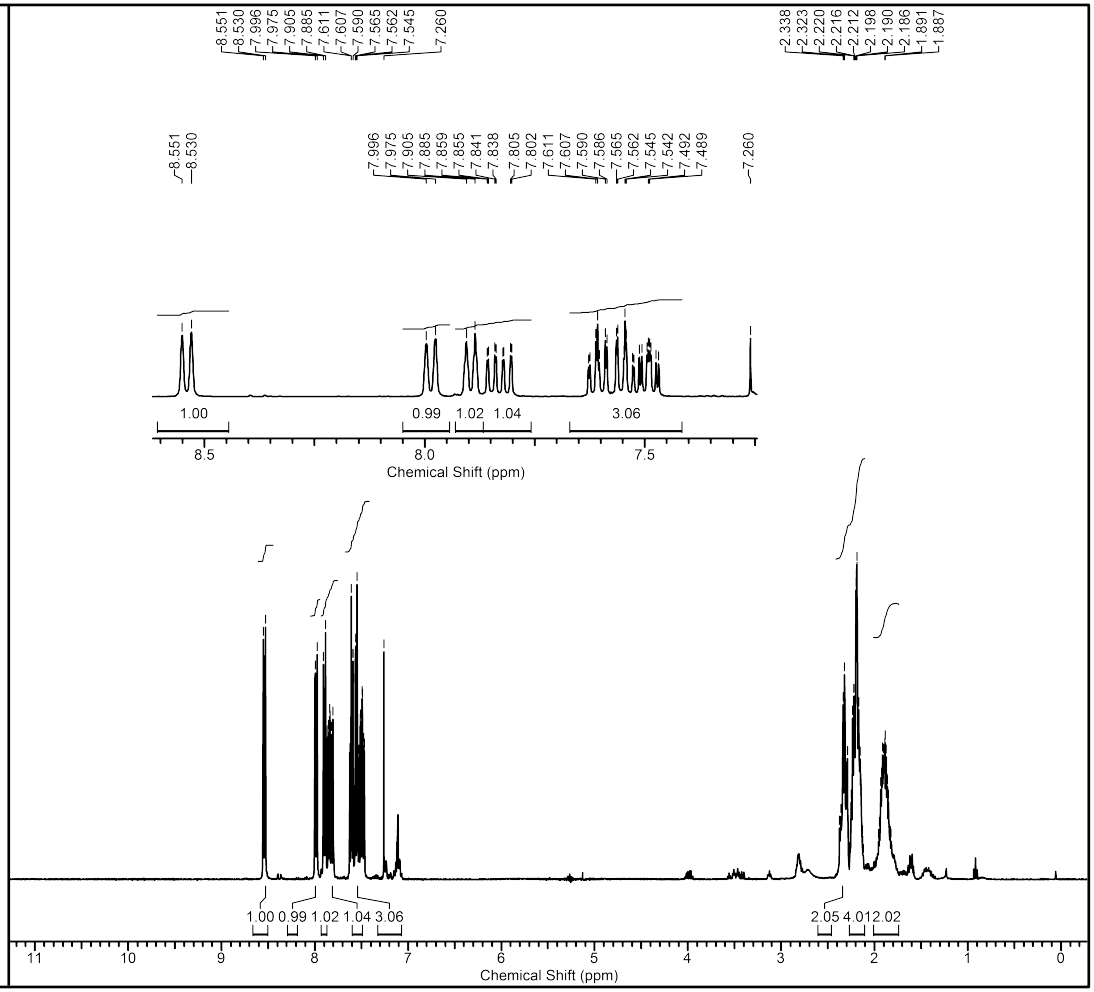


File Name	2-n_P=O
Acquisition Time (sec)	3.9584
Date Stamp	03 Oct 2013 22:07
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4543
Origin	spect
Receiver Gain	80.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

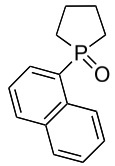


PCj

O'Brien™
Group NMR Data

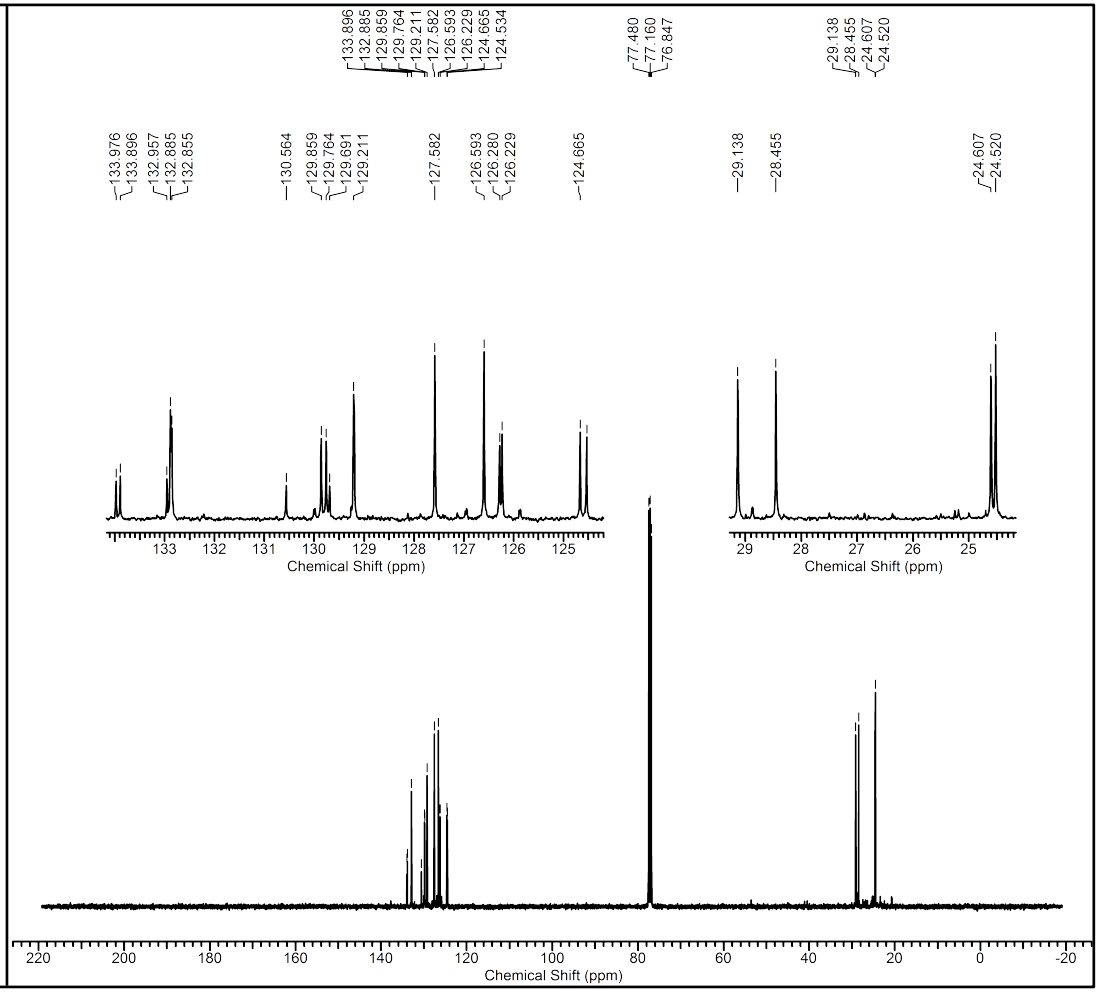


File Name	2-n_P=O
Acquisition Time (sec)	1.3664
Date Stamp	03 Oct 2013
Frequency (MHz)	150.91
	22:05
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10065.2
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

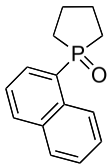


PCj

O'Brien™
Group NMR Data

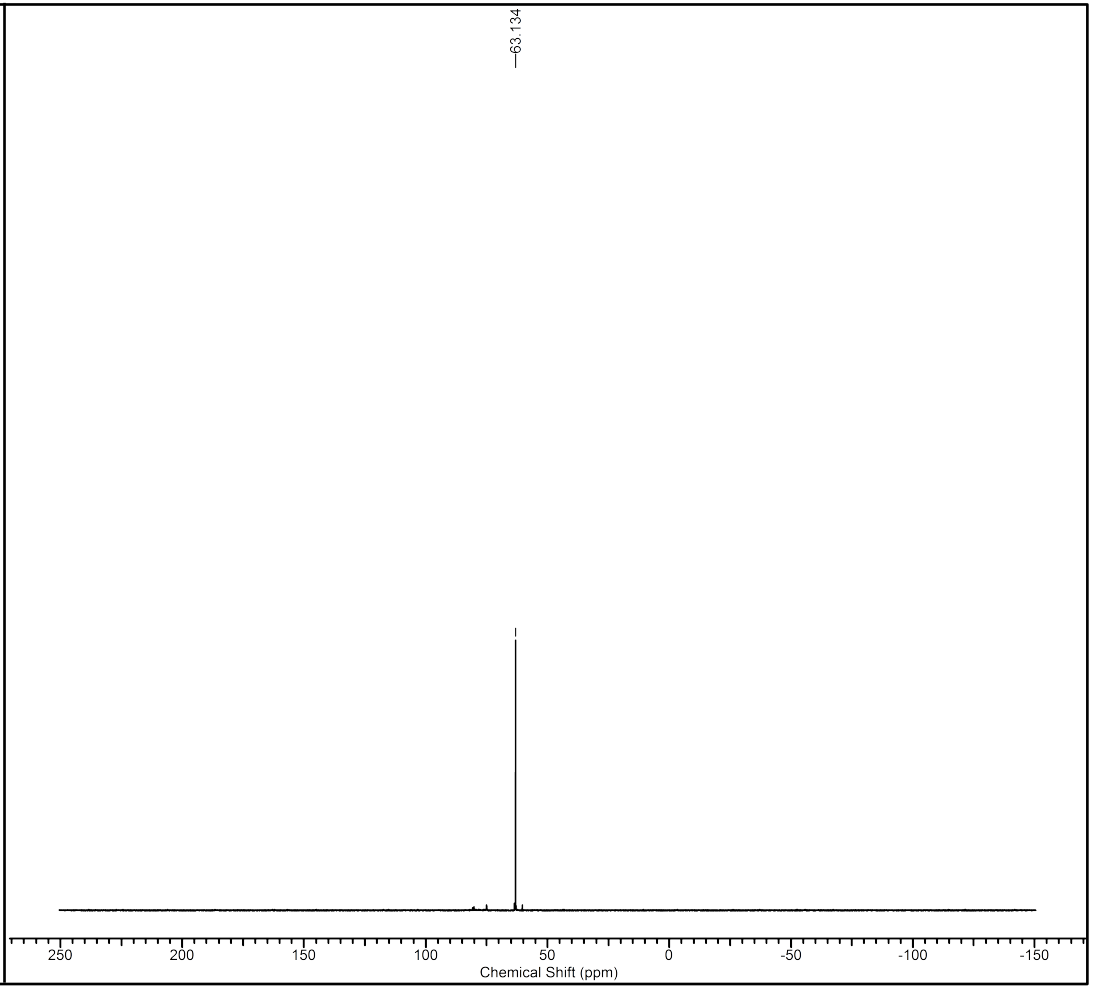


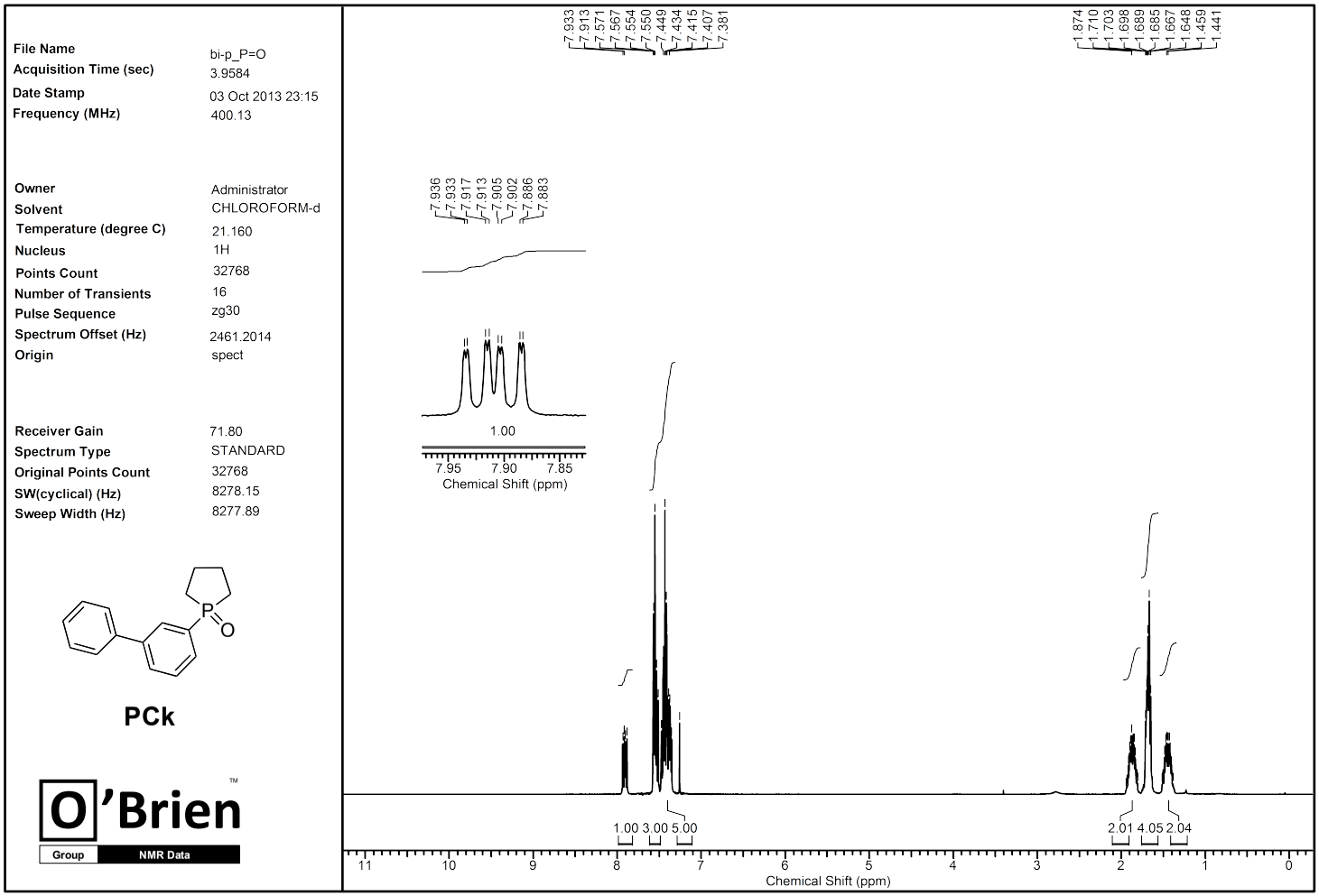
File Name	2-n_P=O
Acquisition Time (sec)	0.5046
Date Stamp	18 Sep 2013 16:36
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	31P
Points Count	32768
Number of Transients	128
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	8098.7822
Origin	spect
Receiver Gain	5160.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09



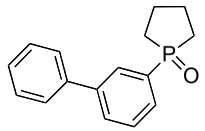
PCj

O'Brien™
Group NMR Data



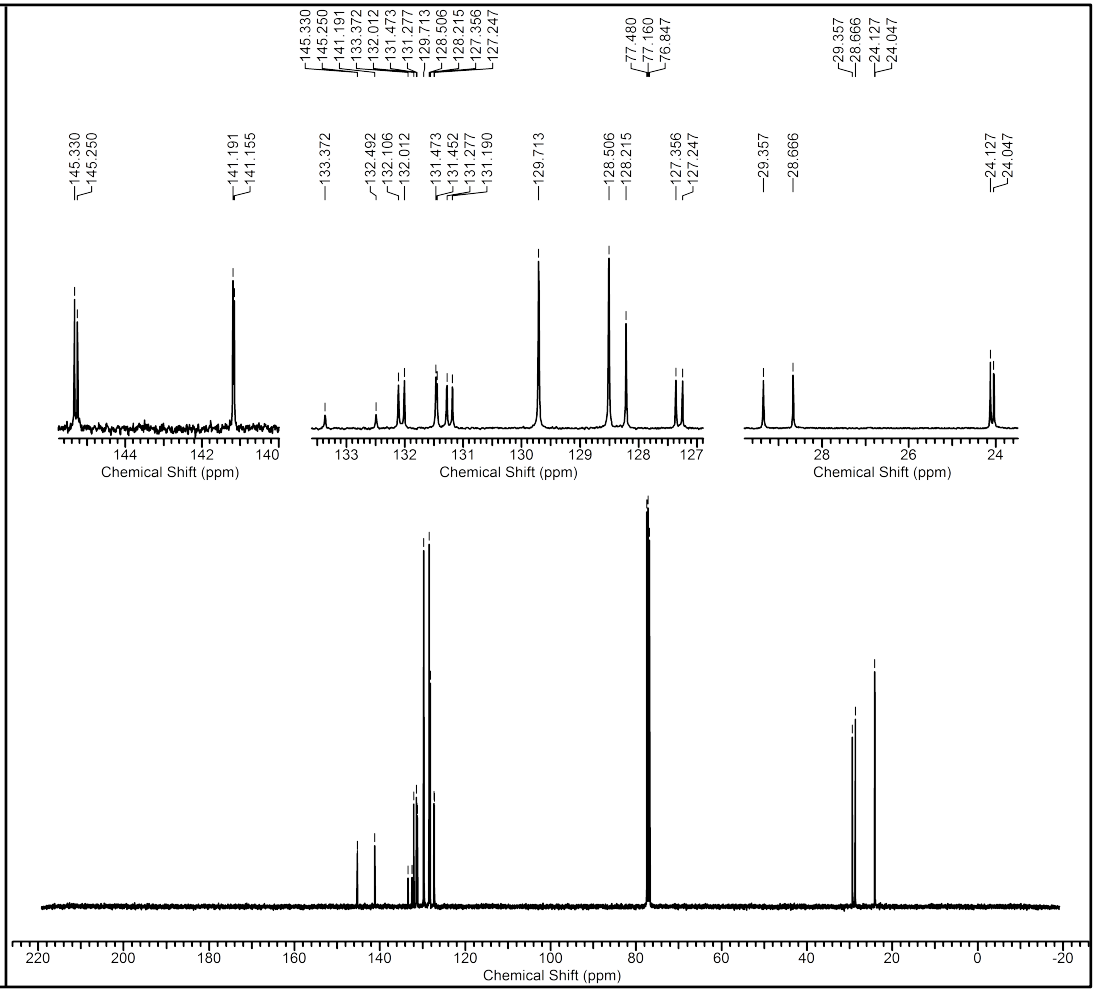

File Name bi-p_P=O
Acquisition Time (sec) 3.9584
Date Stamp 03 Oct 2013 23:15
Frequency (MHz) 400.13
Owner Administrator
Solvent CHLOROFORM-d
Temperature (degree C) 21.160
Nucleus 1H
Points Count 32768
Number of Transients 16
Pulse Sequence zg30
Spectrum Offset (Hz) 2461.2014
Origin spect
Receiver Gain 71.80
Spectrum Type STANDARD
Original Points Count 32768
SW(cyclical) (Hz) 8278.15
Sweep Width (Hz) 8277.89
PCk
O'Brien
Group NMR Data
7.933 7.913 7.571 7.567 7.554 7.550 7.449 7.434 7.415 7.407 7.381
1.874 1.710 1.703 1.698 1.689 1.685 1.667 1.648 1.459 1.441
7.936 7.933 7.917 7.913 7.905 7.902 7.886 7.883
1.00
7.95 7.90 7.85
Chemical Shift (ppm)
1.00 3.00 5.00
2.01 4.05 2.04
11 10 9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)

File Name	bi-p_P=O
Acquisition Time (sec)	1.3664
Date Stamp	03 Oct 2013 23
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10066.0049
Origin	spect
Receiver Gain	9195.20
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

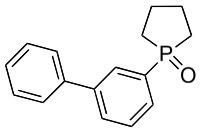


PCk

O'Brien™
Group NMR Data

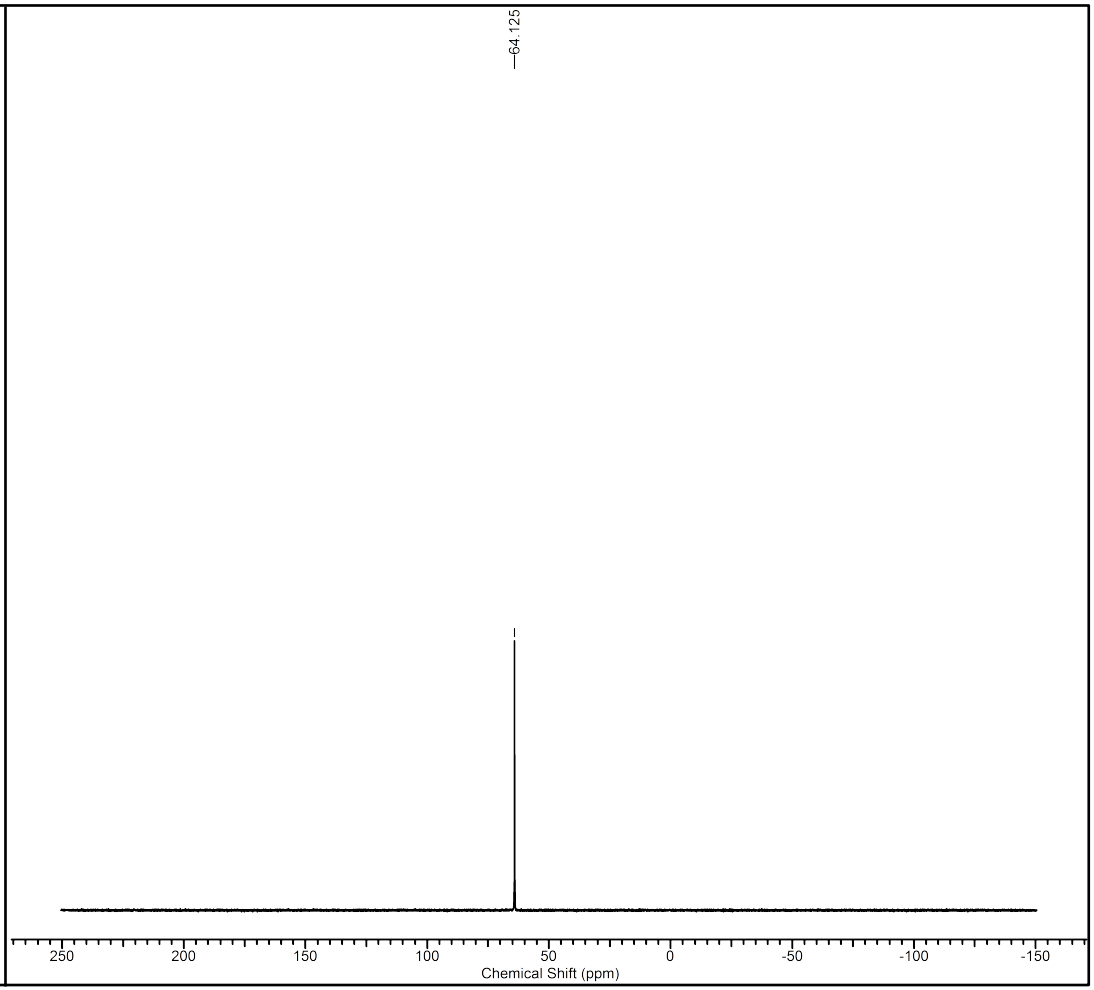


File Name	bi-p_P=O
Acquisition Time (sec)	0.5046
Date Stamp	18 Sep 2013 16:21
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	31P
Points Count	32768
Number of Transients	128
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	8098.7822
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09

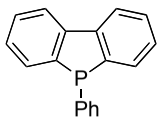


PCk

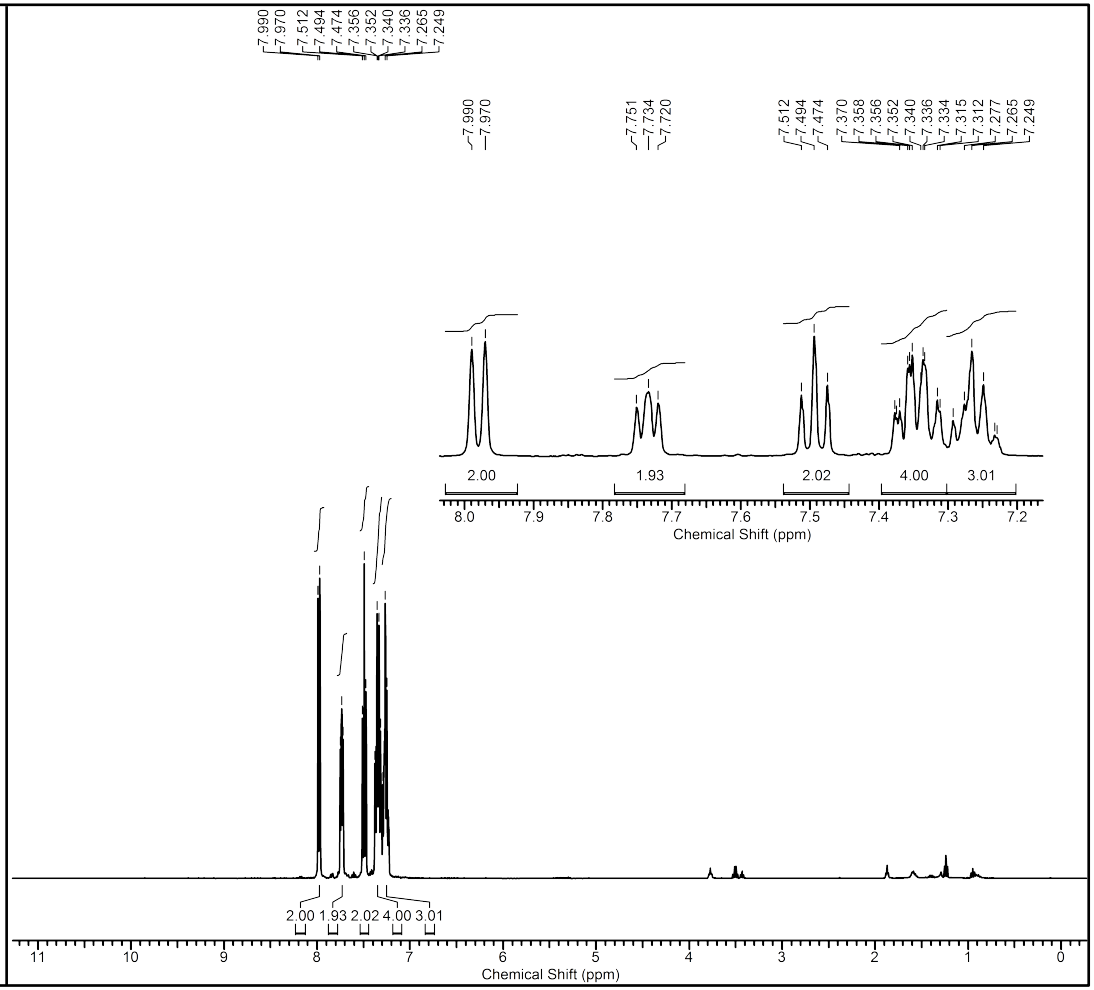
O'Brien™
Group NMR Data



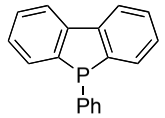
File Name	017-19a
Acquisition Time (sec)	3.9584
Date Stamp	22 Feb 2013 15:04
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2463.3804
Origin	spect
Receiver Gain	128.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89



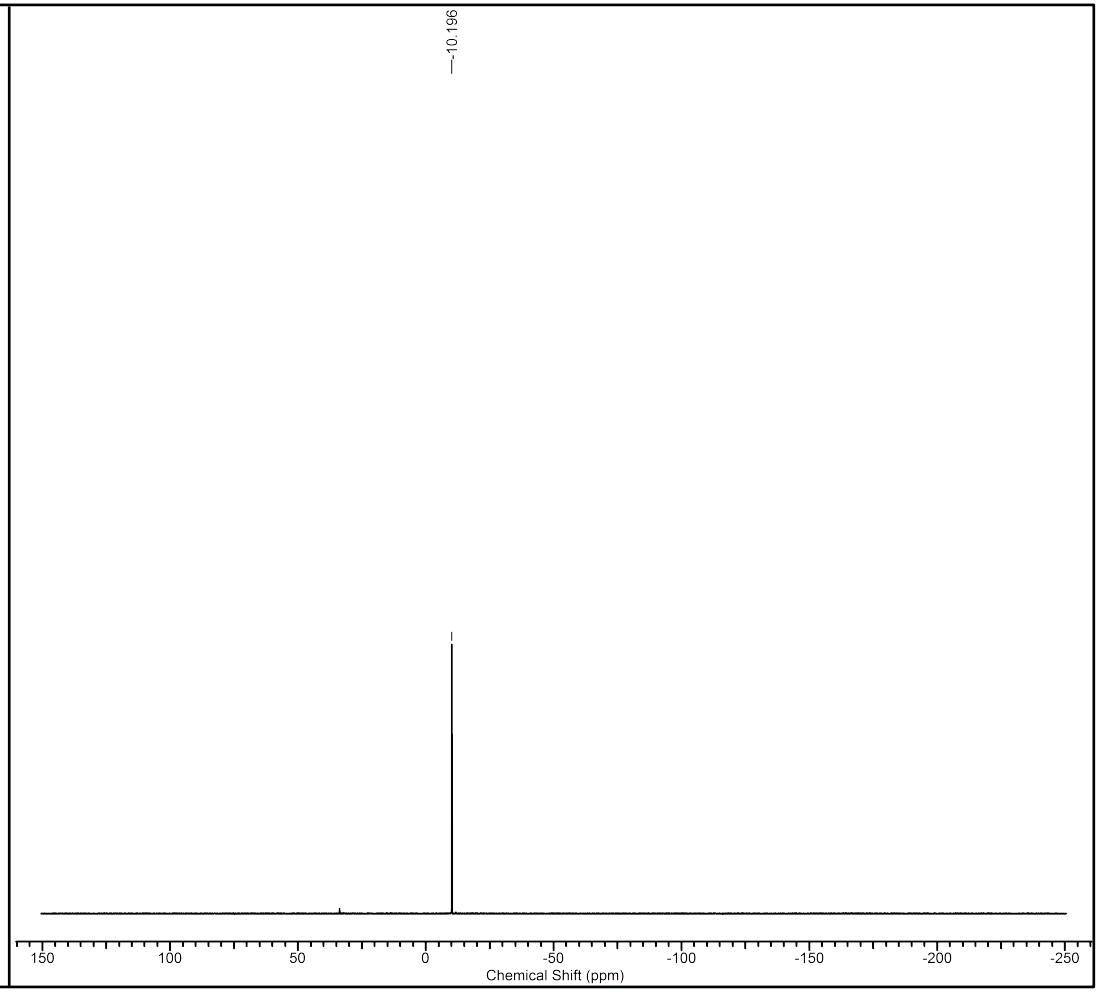
O'Brien™
Group NMR Data



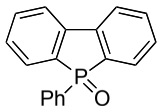
File Name	017-19a
Acquisition Time (sec)	0.5046
Date Stamp	22 Feb 2013 15:06
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	31P
Points Count	32768
Number of Transients	64
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	-8098.8086
Origin	spect
Receiver Gain	7298.20
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09



O'Brien™
Group NMR Data

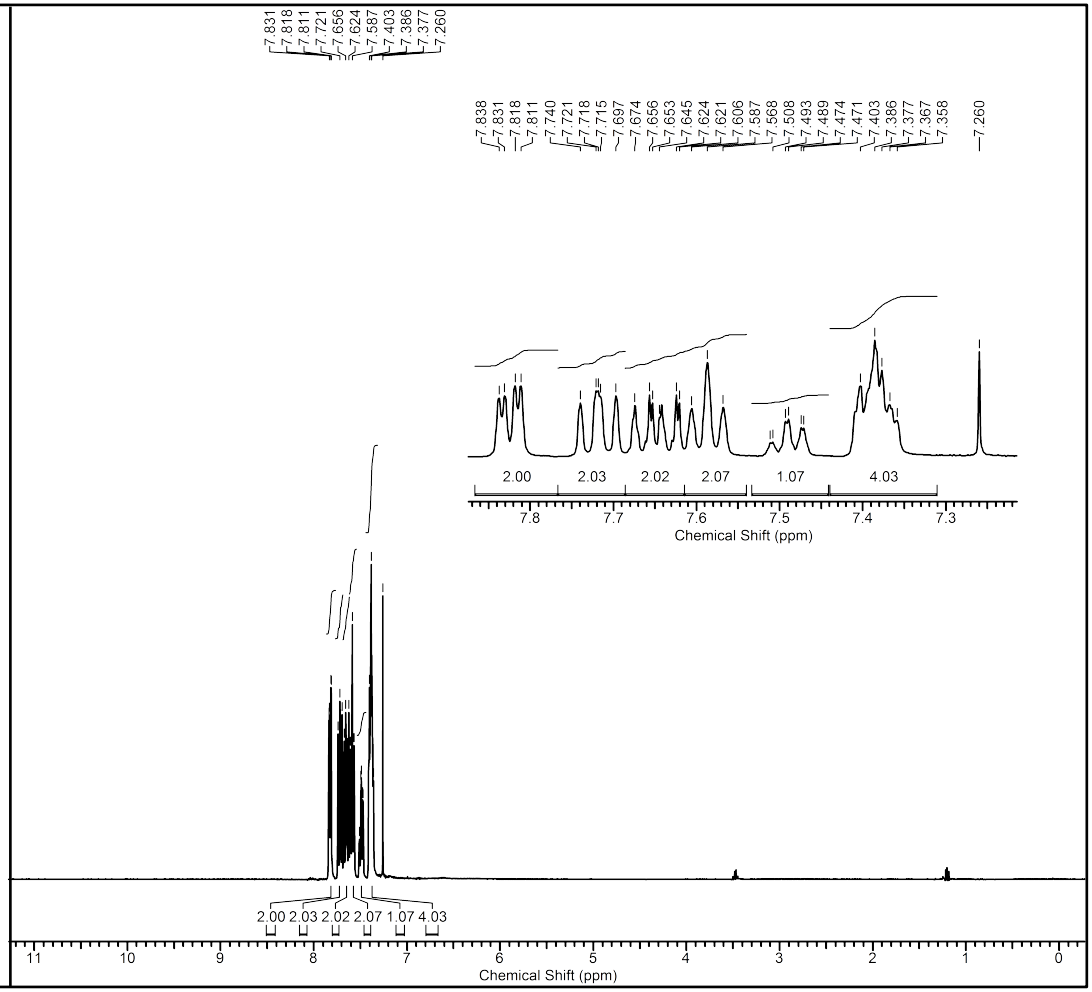


File Name	017-19
Acquisition Time (sec)	3.9584
Date Stamp	18 Oct 2013 14:43
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	22.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	181.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

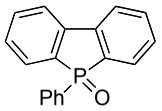


PCl

O'Brien™
Group NMR Data

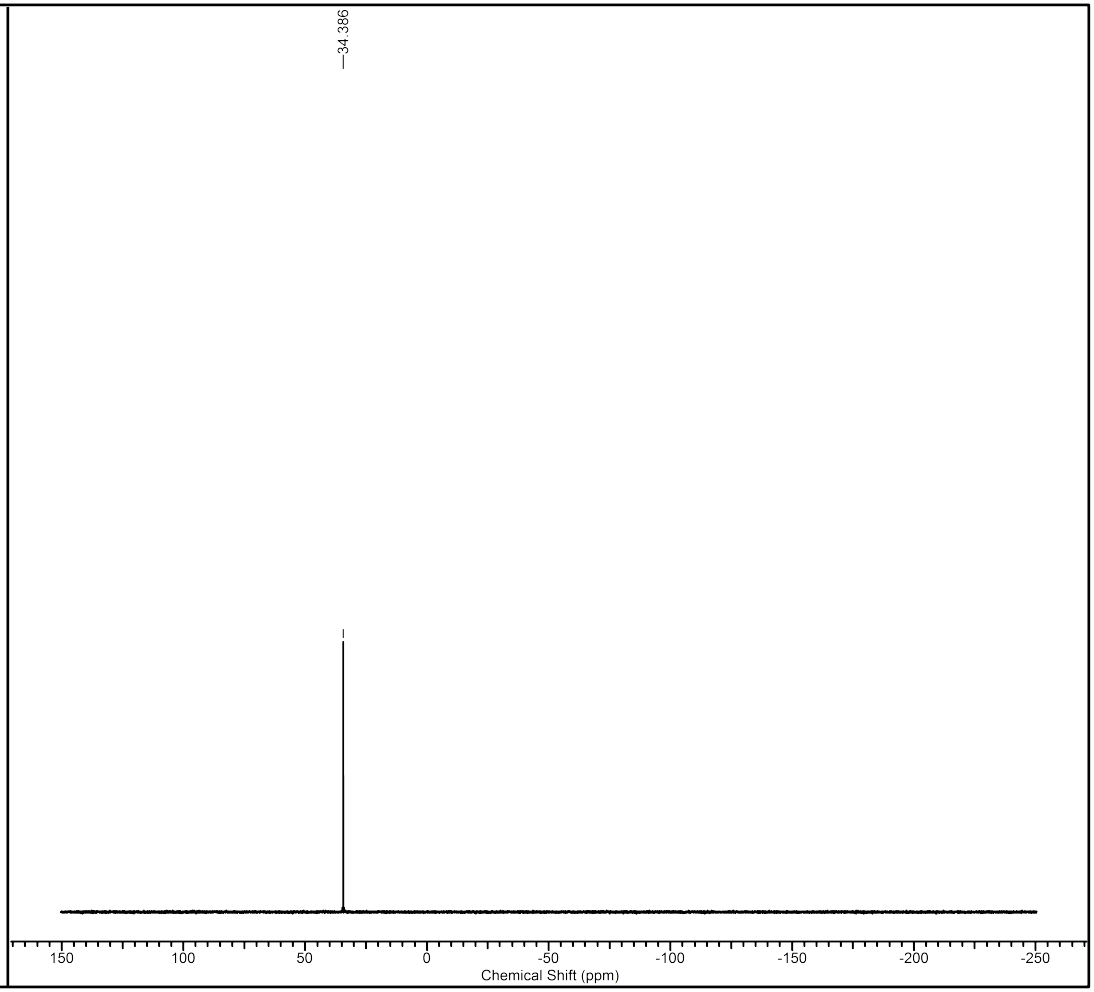


File Name	017-19
Acquisition Time (sec)	0.5046
Date Stamp	18 Oct 2013 14:45
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	22.160
Nucleus	31P
Points Count	32768
Number of Transients	32
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	-8098.8086
Origin	spect
Receiver Gain	11585.20
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09

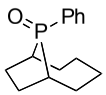


PCI

O'Brien™
Group NMR Data

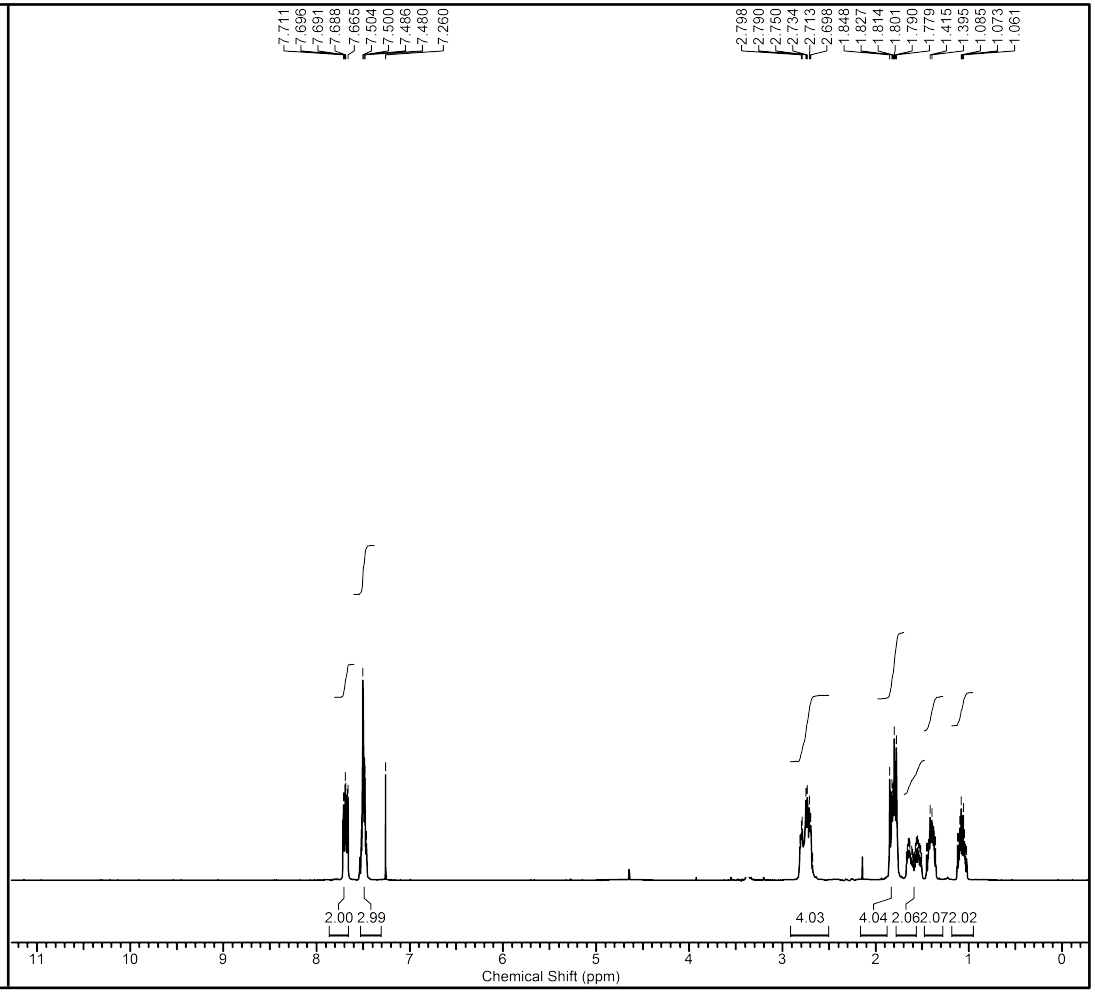


File Name	020-63
Acquisition Time (sec)	3.9584
Date Stamp	09 Aug 2013 16:45
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4539
Origin	spect
Receiver Gain	80.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

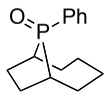


PCm

O'Brien™
Group NMR Data

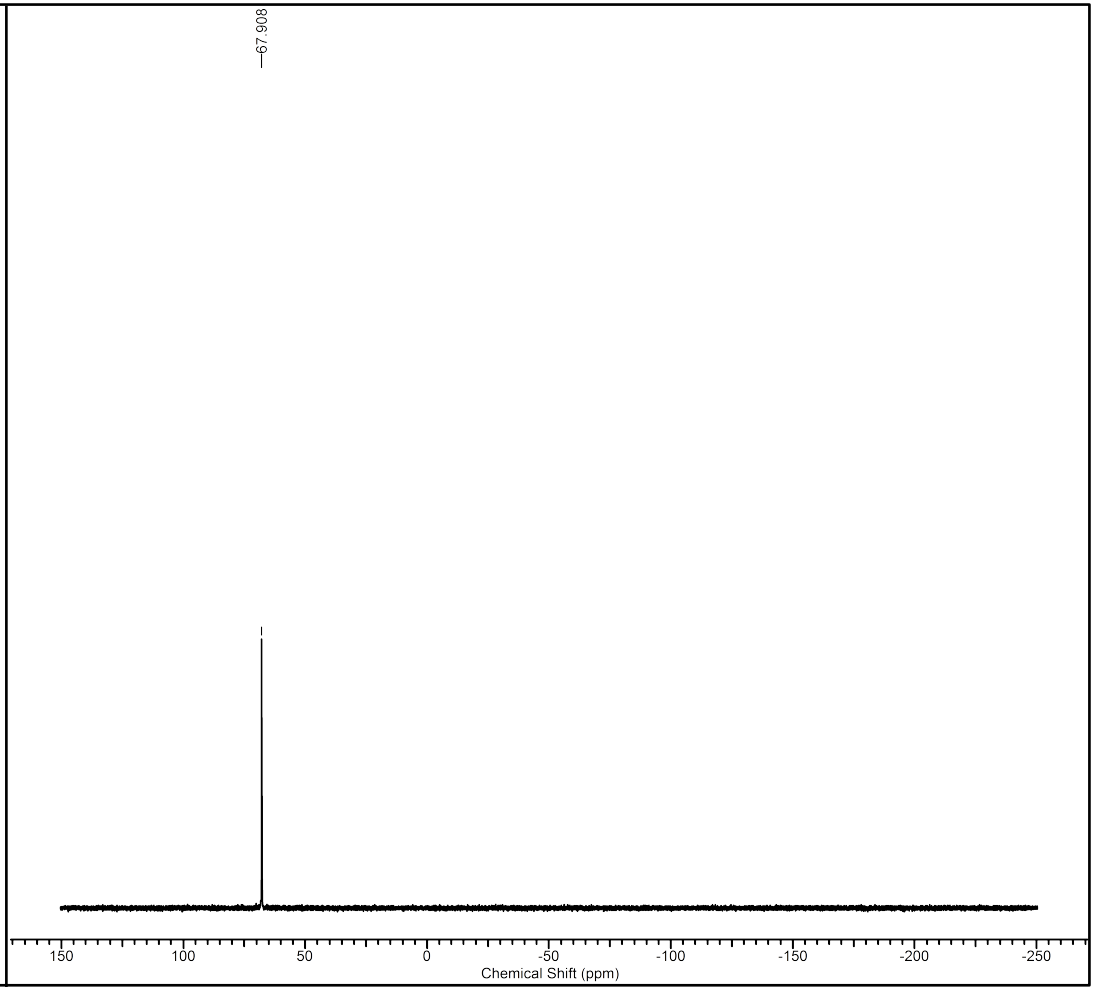


File Name	020-63
Acquisition Time (sec)	0.5046
Date Stamp	09 Aug 2013 16:47
Frequency (MHz)	161.98
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	31P
Points Count	32768
Number of Transients	16
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	-8098.8086
Origin	spect
Receiver Gain	8192.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	64935.07
Sweep Width (Hz)	64933.09

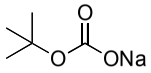


PCm

O'Brien™
Group NMR Data

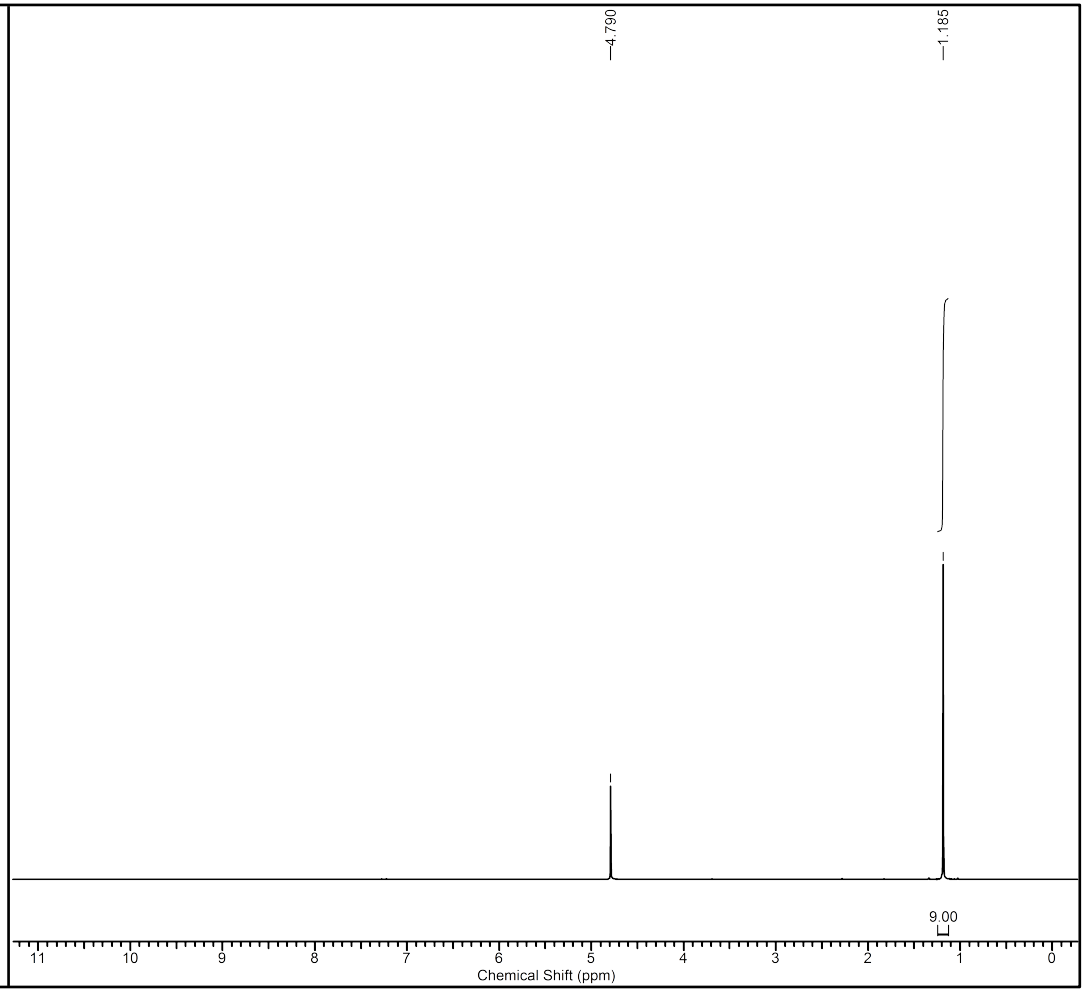


File Name	NaOC(O)OtBu
Acquisition Time (sec)	3.9584
Date Stamp	09 Oct 2013 18:25
Frequency (MHz)	400.13
Owner	Administrator
Solvent	DEUTERIUM OXIDE
Temperature (degree C)	21.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2506.3850
Origin	spect
Receiver Gain	80.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

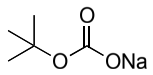


54

O'Brien™
Group NMR Data

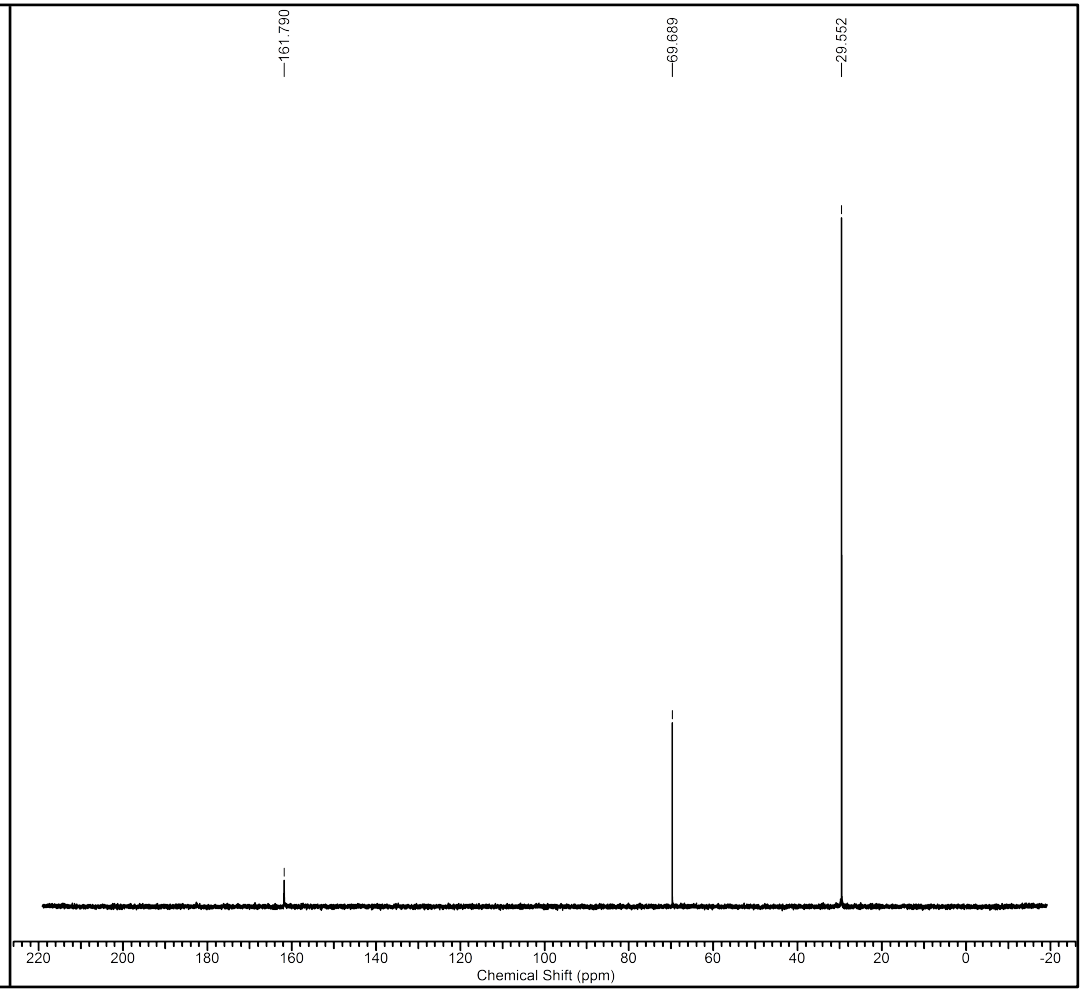


File Name	NaOC(O)OtBu
Acquisition Time (sec)	1.3664
Date Stamp	09 Oct 2013
Frequency (MHz)	100.61
	19:25
Owner	Administrator
Solvent	DEUTERIUM OXIDE
Temperature (degree C)	21.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10060.8
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

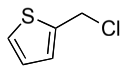


54

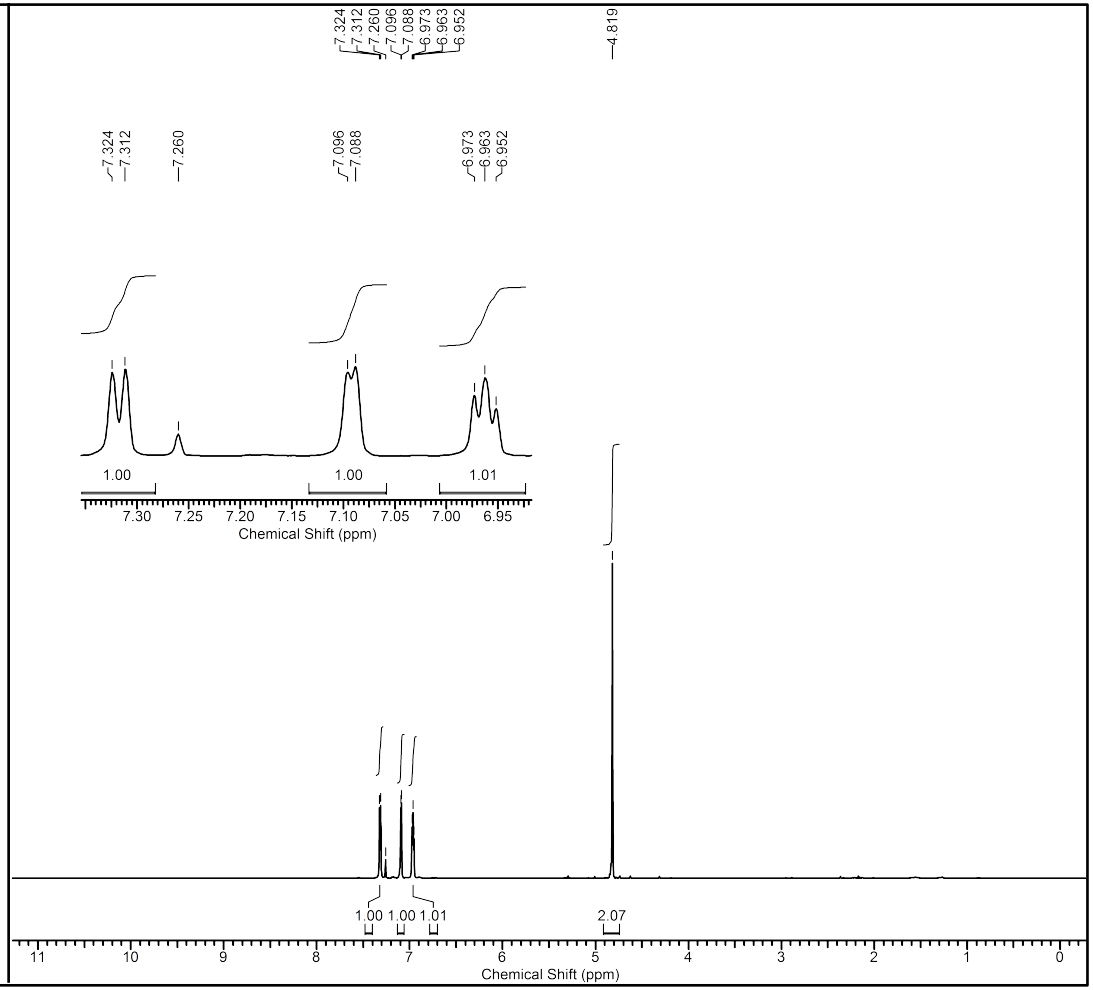
O'Brien™
Group NMR Data

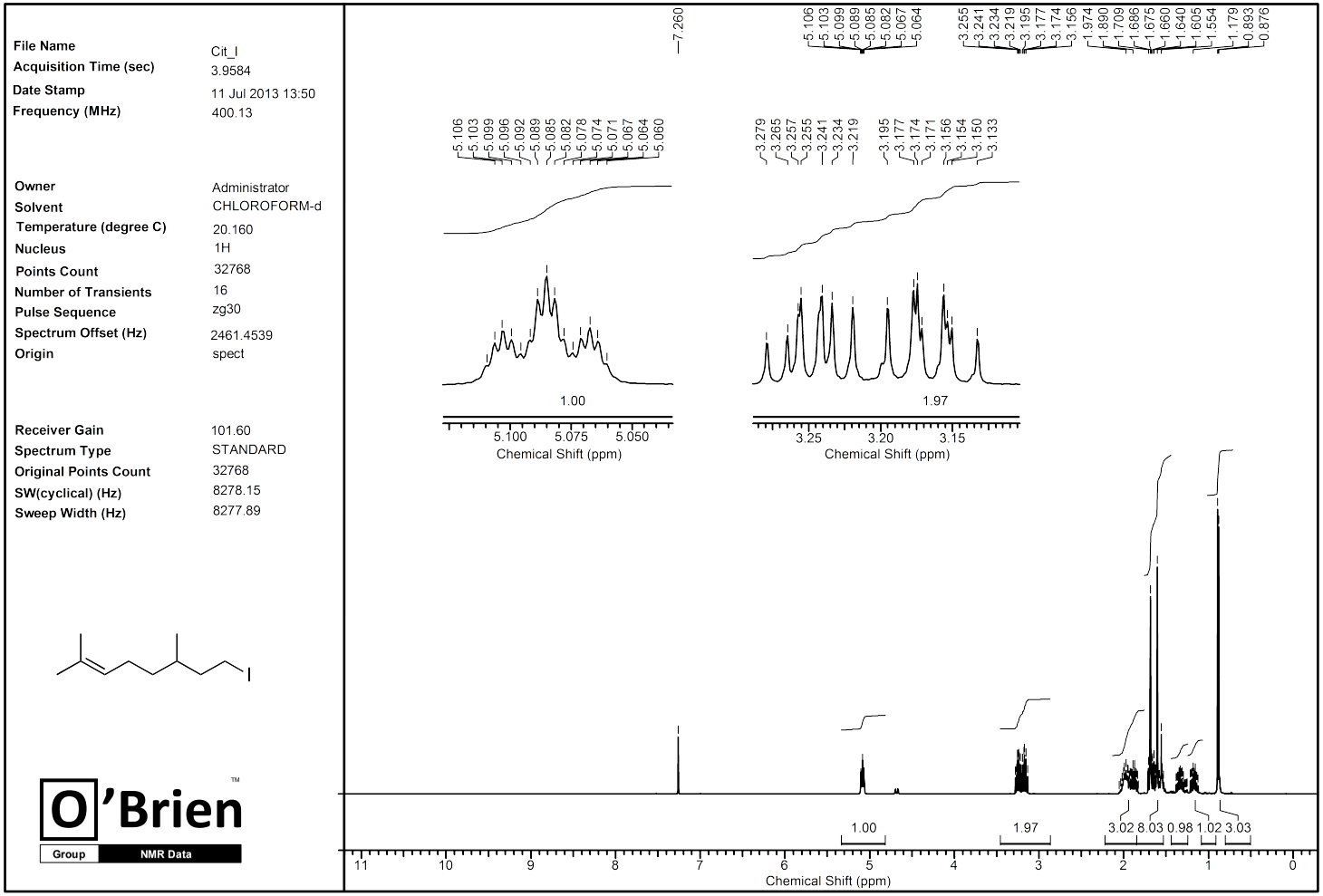


File Name	Thio_Cl
Acquisition Time (sec)	3.9584
Date Stamp	17 Apr 2013 17:00
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	143.70
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

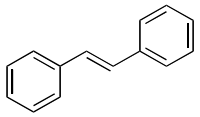


O'Brien™
Group NMR Data



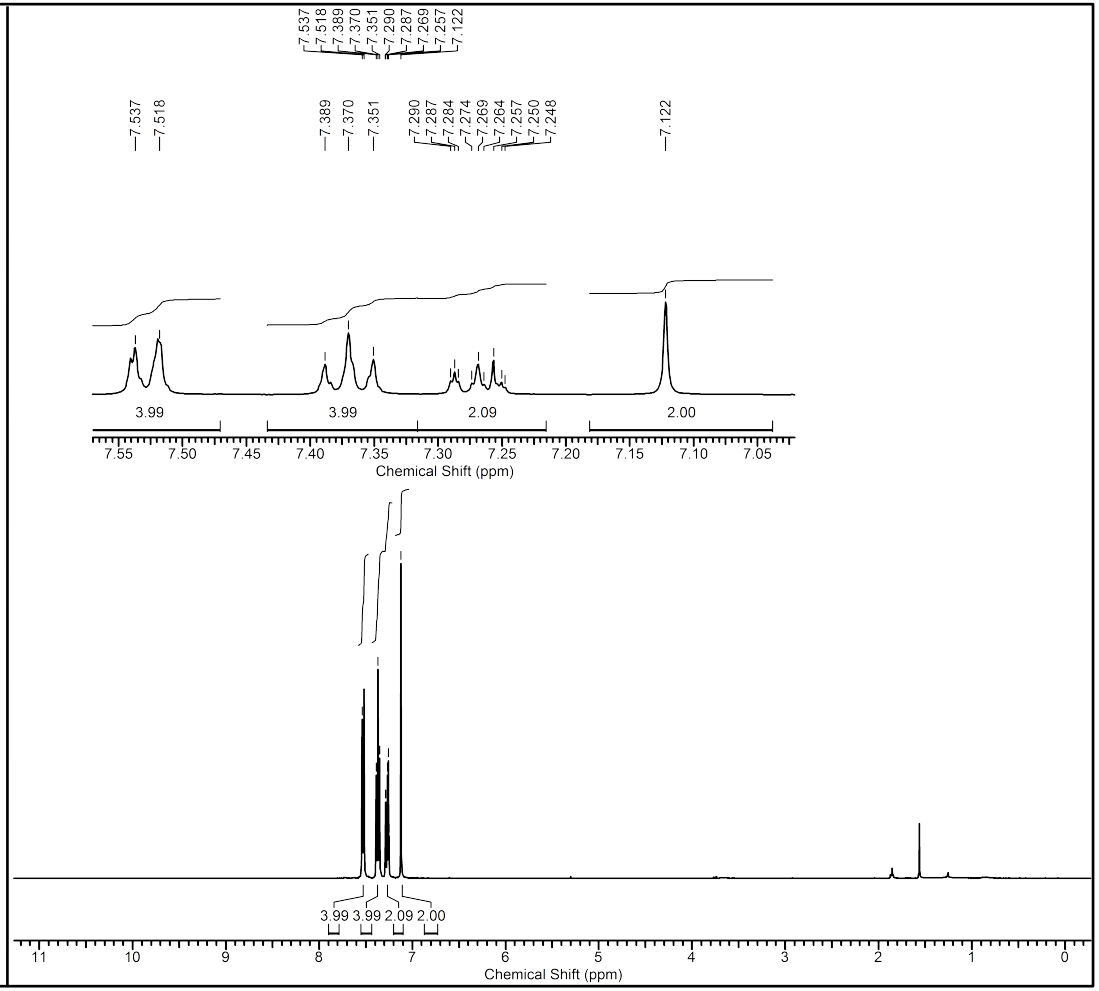

File Name Cit_I
Acquisition Time (sec) 3.9584
Date Stamp 11 Jul 2013 13:50
Frequency (MHz) 400.13
Owner Administrator
Solvent CHLOROFORM-d
Temperature (degree C) 20.160
Nucleus 1H
Points Count 32768
Number of Transients 16
Pulse Sequence zg30
Spectrum Offset (Hz) 2461.4539
Origin spect
Receiver Gain 101.60
Spectrum Type STANDARD
Original Points Count 32768
SW(cyclical) (Hz) 8278.15
Sweep Width (Hz) 8277.89
O'Brien
Group NMR Data
7.260
5.106 5.103 5.099 5.089 5.085 5.082 5.067 5.064
3.255 3.241 3.234 3.219 3.195 3.177 3.174 3.156
1.974 1.890 1.709 1.686 1.675 1.660 1.640 1.605 1.554 1.179 0.893 0.876
1.00
1.97
Chemical Shift (ppm)
3.02 8.03 0.98 1.02 3.03

File Name	017-04_E
Acquisition Time (sec)	3.9584
Date Stamp	21 Jan 2013 10:52
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	14.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2460.0962
Origin	spect
Receiver Gain	322.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

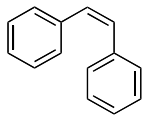


E-**55**

O'Brien™
Group NMR Data

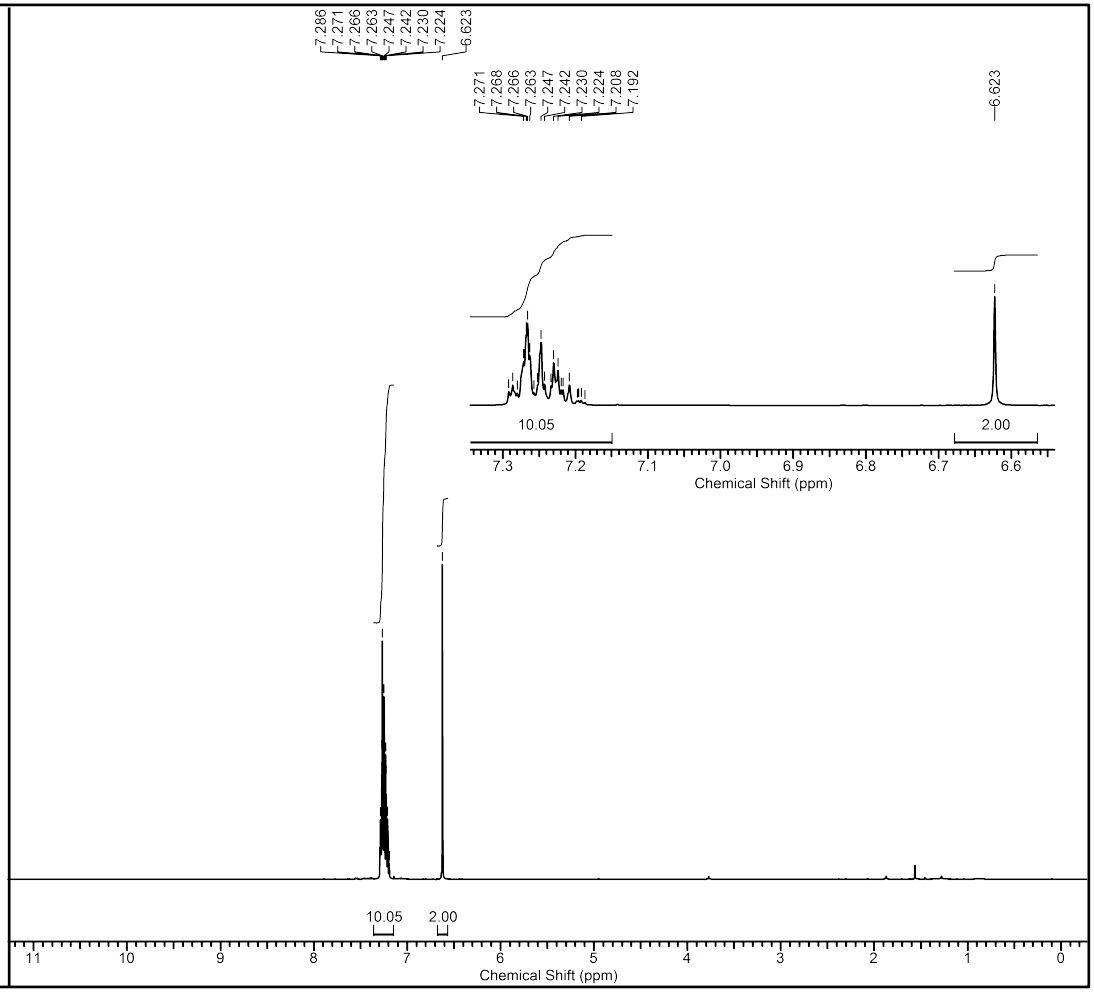


File Name	017-04_Z
Acquisition Time (sec)	3.9584
Date Stamp	21 Jan 2013 10:44
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	14.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.9790
Origin	spect
Receiver Gain	128.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

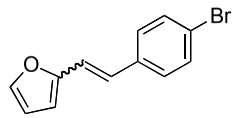


***Z*-55**

O'Brien™
Group NMR Data

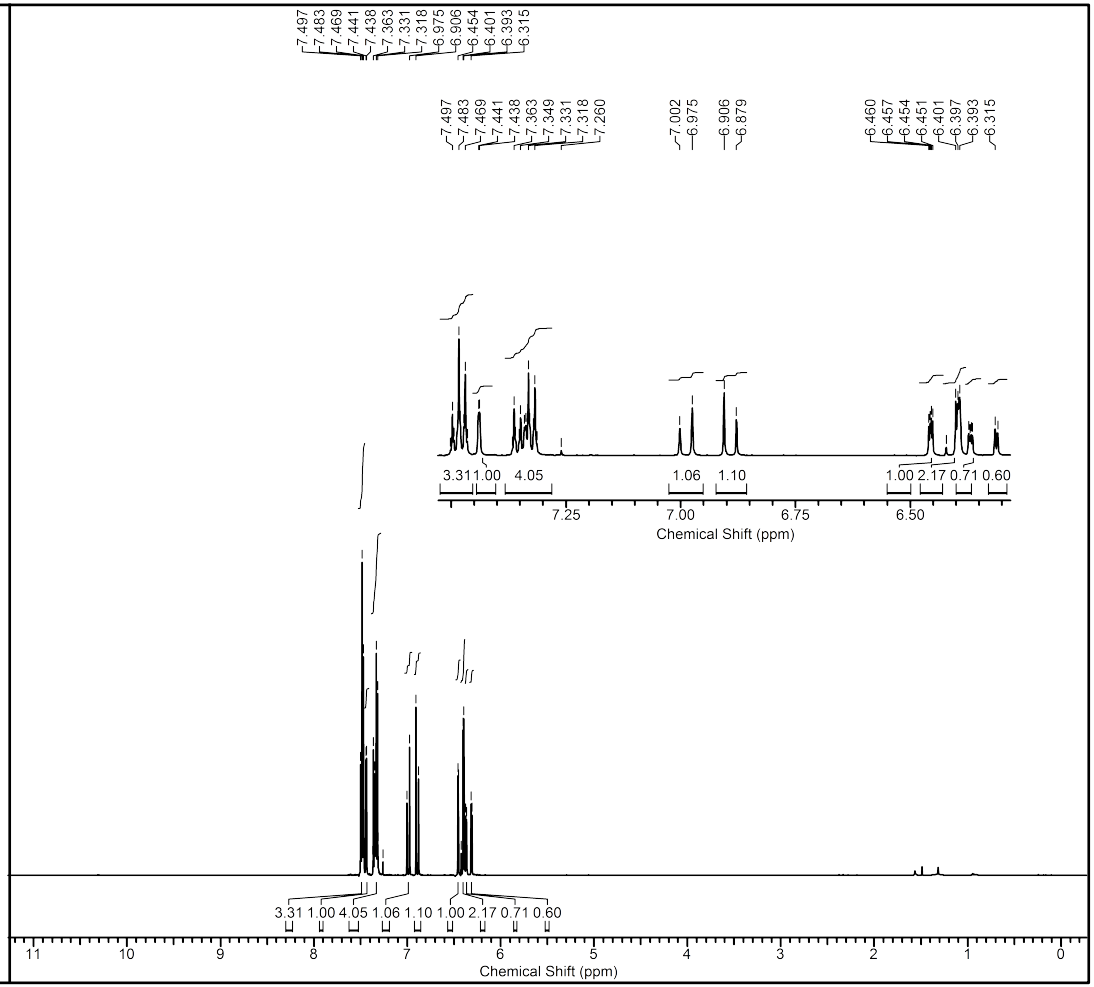


File Name	017-13_Mix
Acquisition Time (sec)	2.6564
Date Stamp	12 Feb 2013 12:09
Frequency (MHz)	600.32
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	19.960
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	3687.3223
Origin	spect
Receiver Gain	50.80
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	12335.53
Sweep Width (Hz)	12335.15

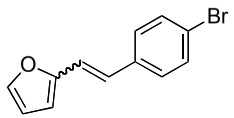


56

O'Brien™
Group NMR Data

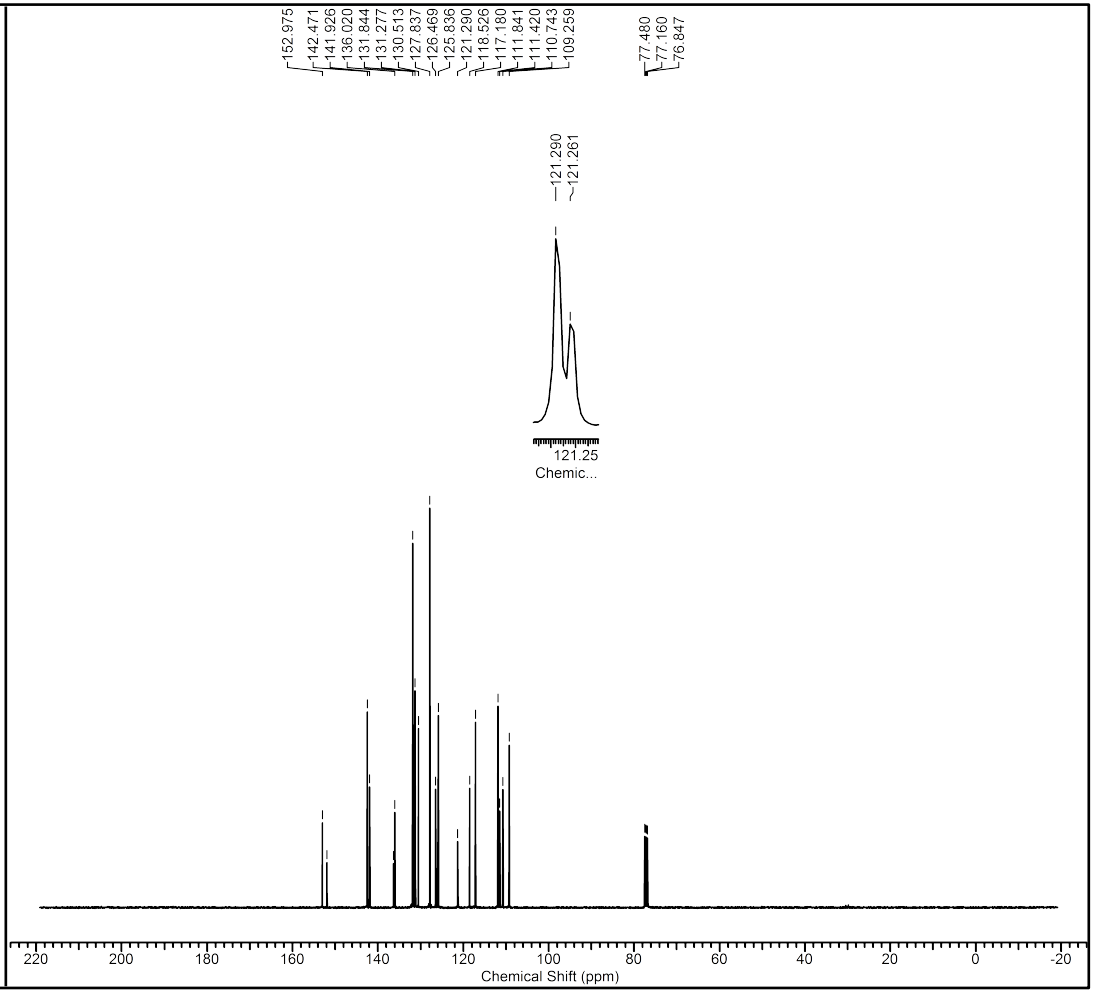


File Name	017-13_Mix
Acquisition Time (sec)	1.3664
Date Stamp	11 Feb 2013 18:10
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10061.6143
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

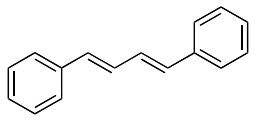


56

O'Brien™
Group NMR Data

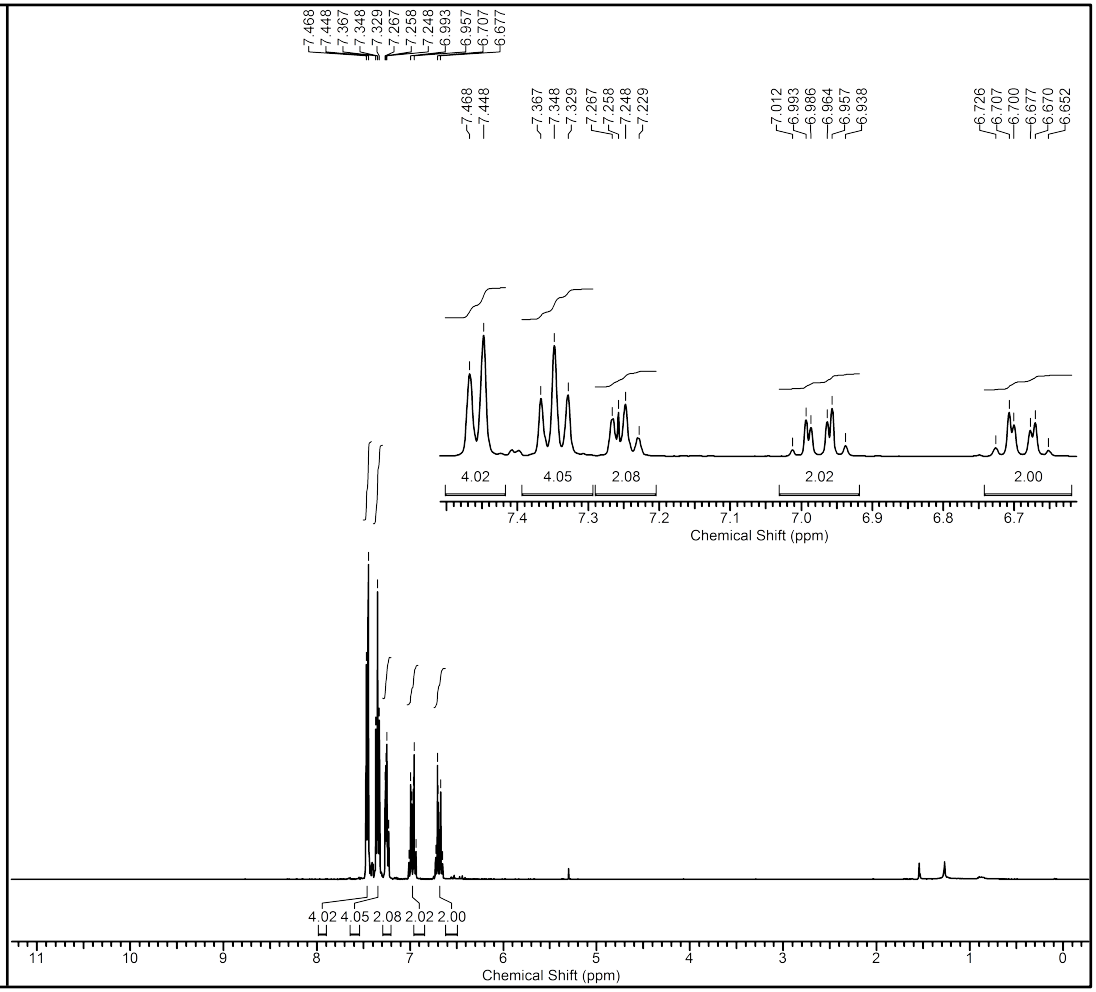


File Name	017-11_E
Acquisition Time (sec)	3.9584
Date Stamp	31 Jan 2013 20:52
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2460.6016
Origin	spect
Receiver Gain	143.70
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

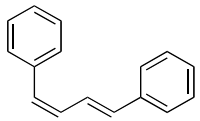


E-**57**

O'Brien™
Group NMR Data

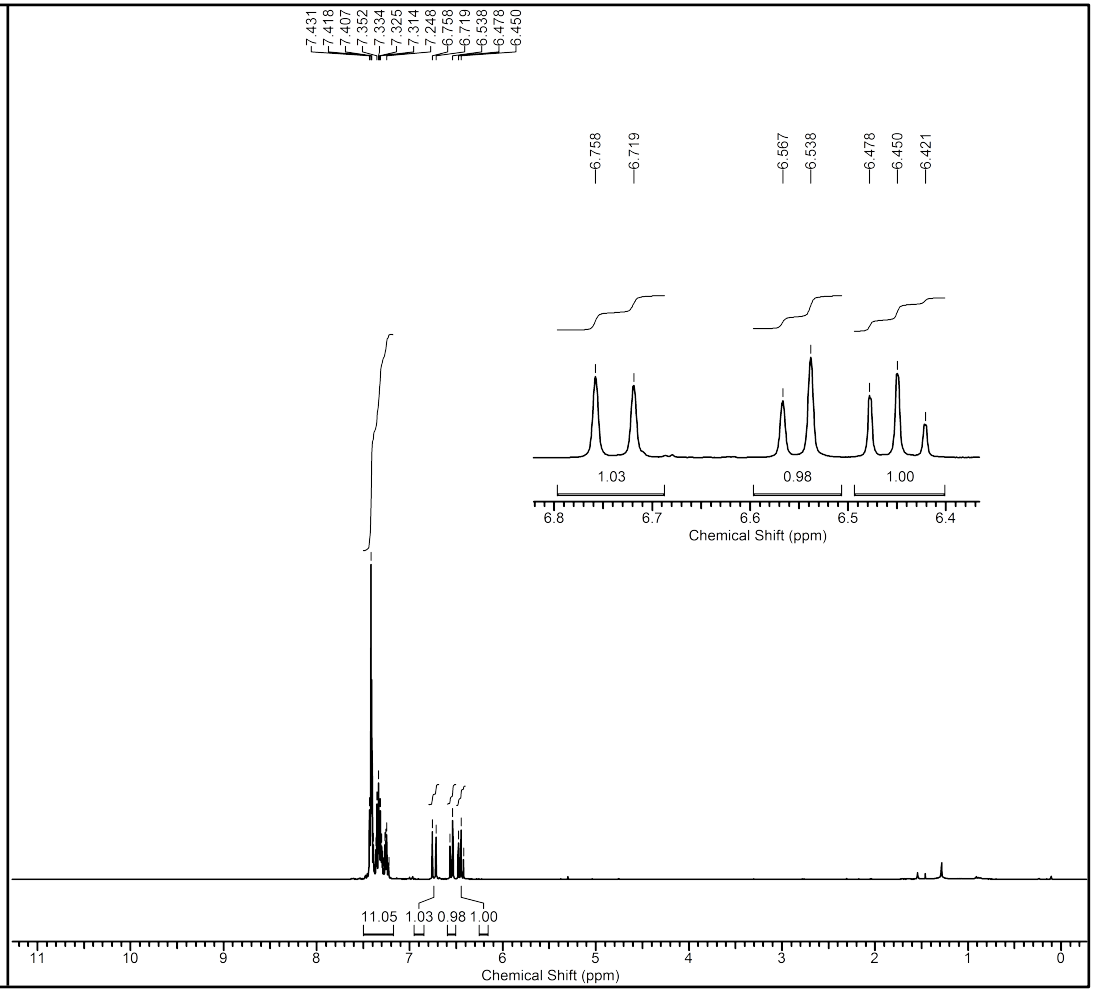


File Name	017-11_Z
Acquisition Time (sec)	3.9584
Date Stamp	31 Jan 2013 20:43
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2459.8438
Origin	spect
Receiver Gain	101.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

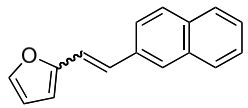


Z-57

O'Brien™
Group NMR Data

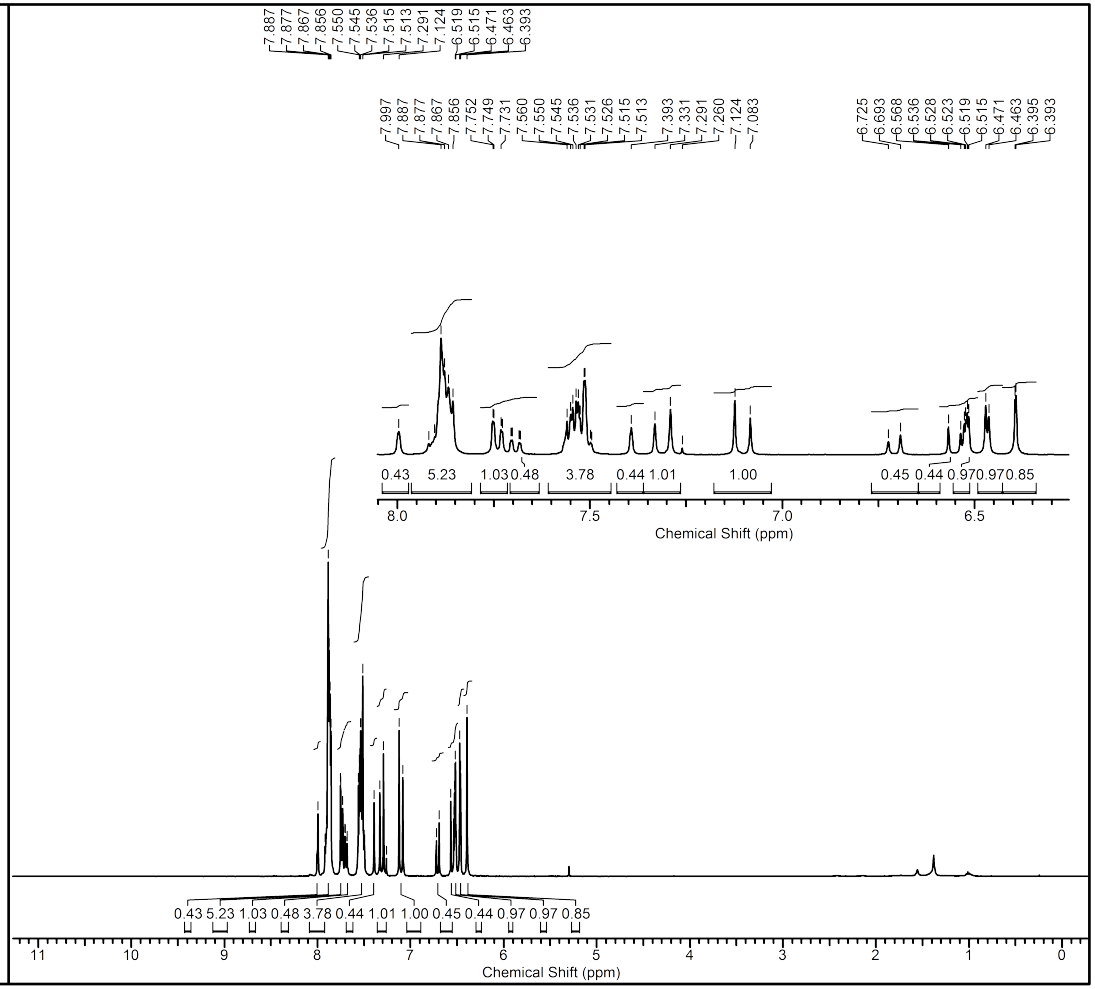


File Name	017-22B
Acquisition Time (sec)	3.9584
Date Stamp	11 Jun 2013 15:26
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4539
Origin	spect
Receiver Gain	40.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

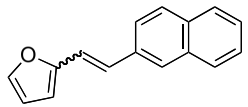


58

O'Brien™ Group NMR Data

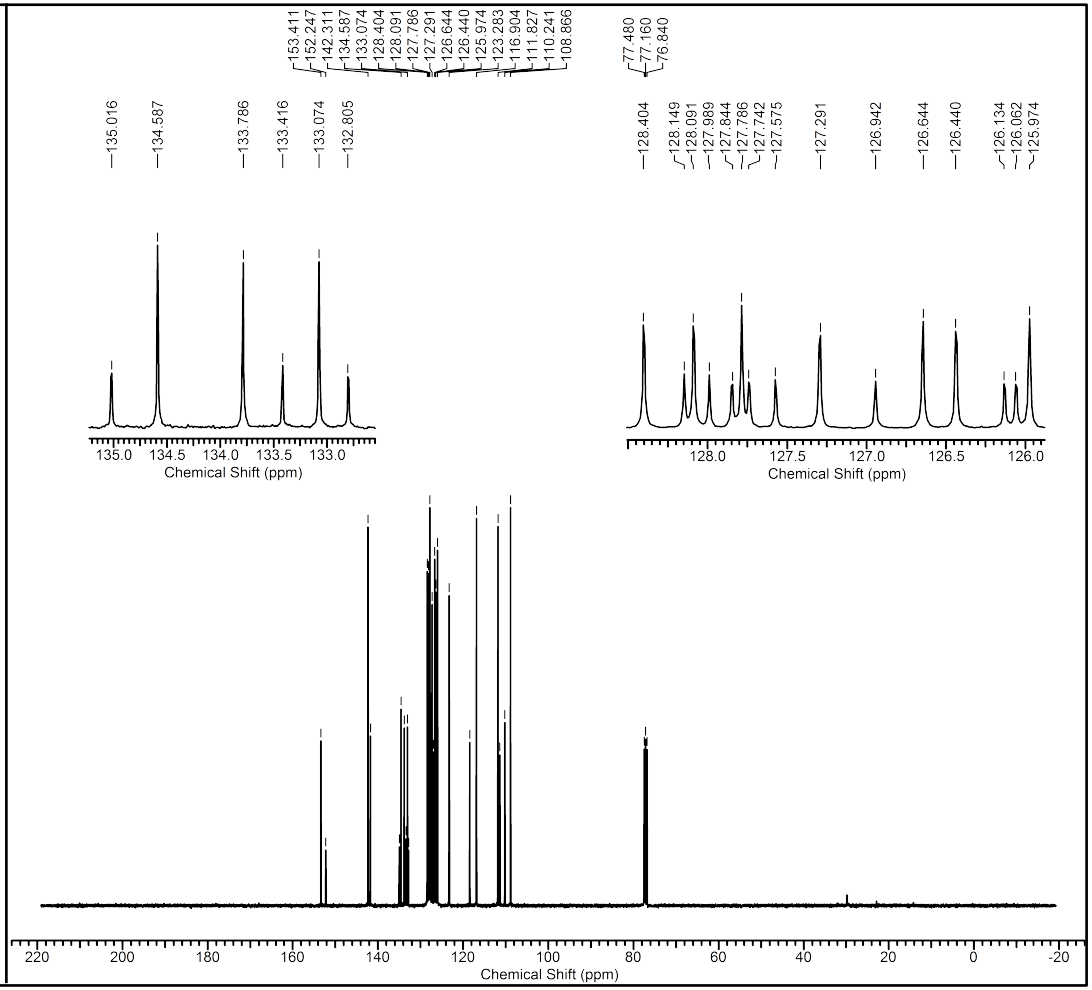


File Name	017-22B
Acquisition Time (sec)	1.3664
Date Stamp	11 Jun 2013 20:41
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10056.4912
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

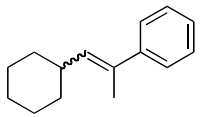


58

O'Brien™
Group NMR Data

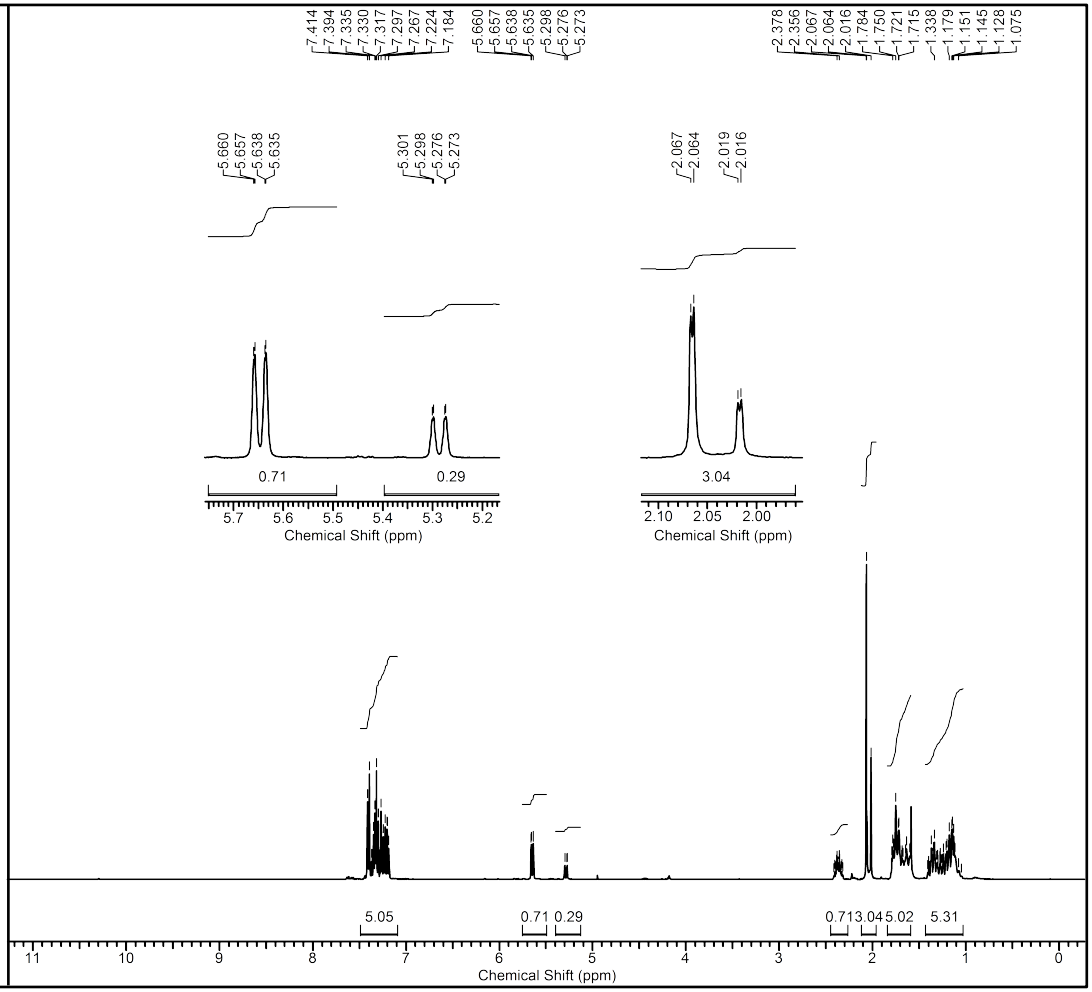


File Name	017-54A
Acquisition Time (sec)	3.9584
Date Stamp	07 May 2013 18:10
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2464.2856
Origin	spect
Receiver Gain	90.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

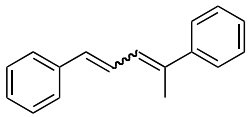


59

O'Brien™
Group NMR Data

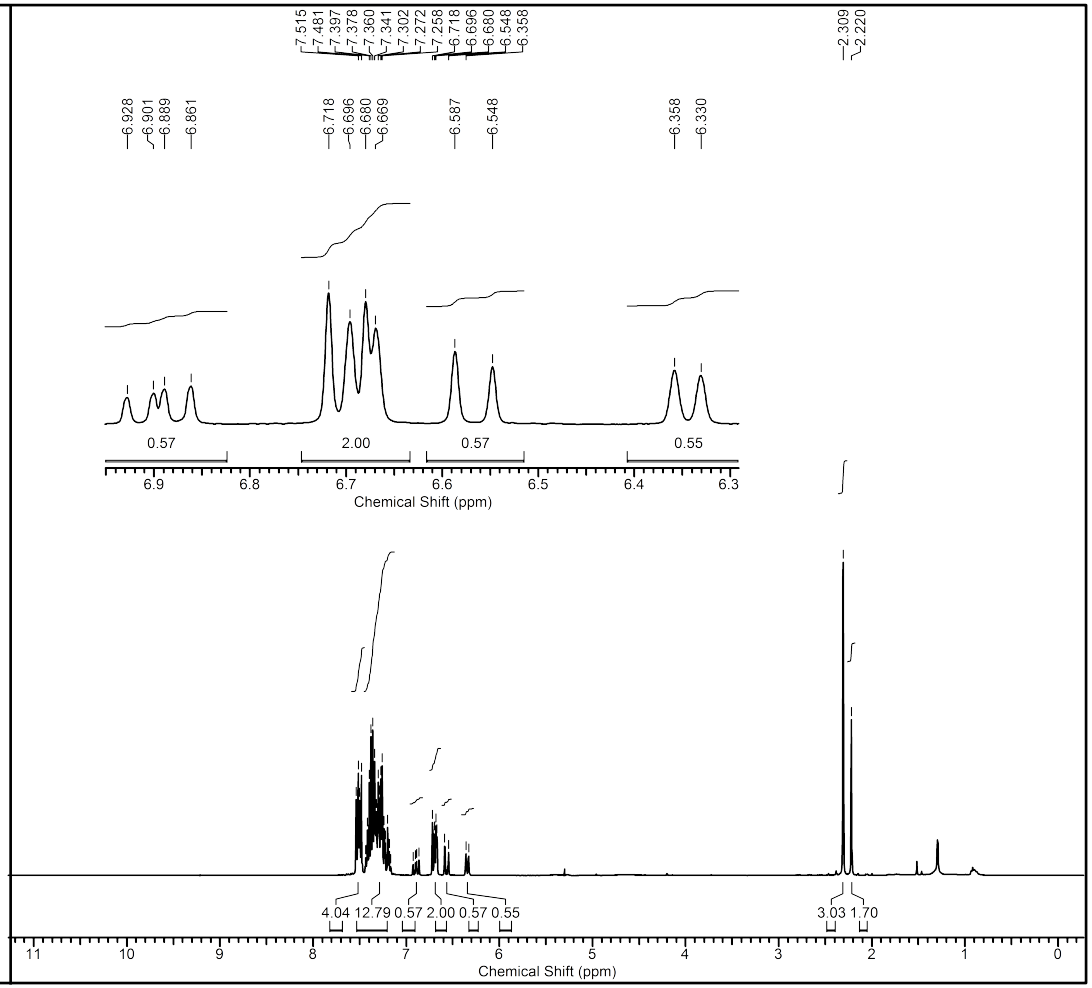


File Name	017-38A
Acquisition Time (sec)	3.9584
Date Stamp	04 Apr 2013 17:19
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2460.8540
Origin	spect
Receiver Gain	90.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

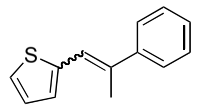


60

O'Brien™ Group NMR Data

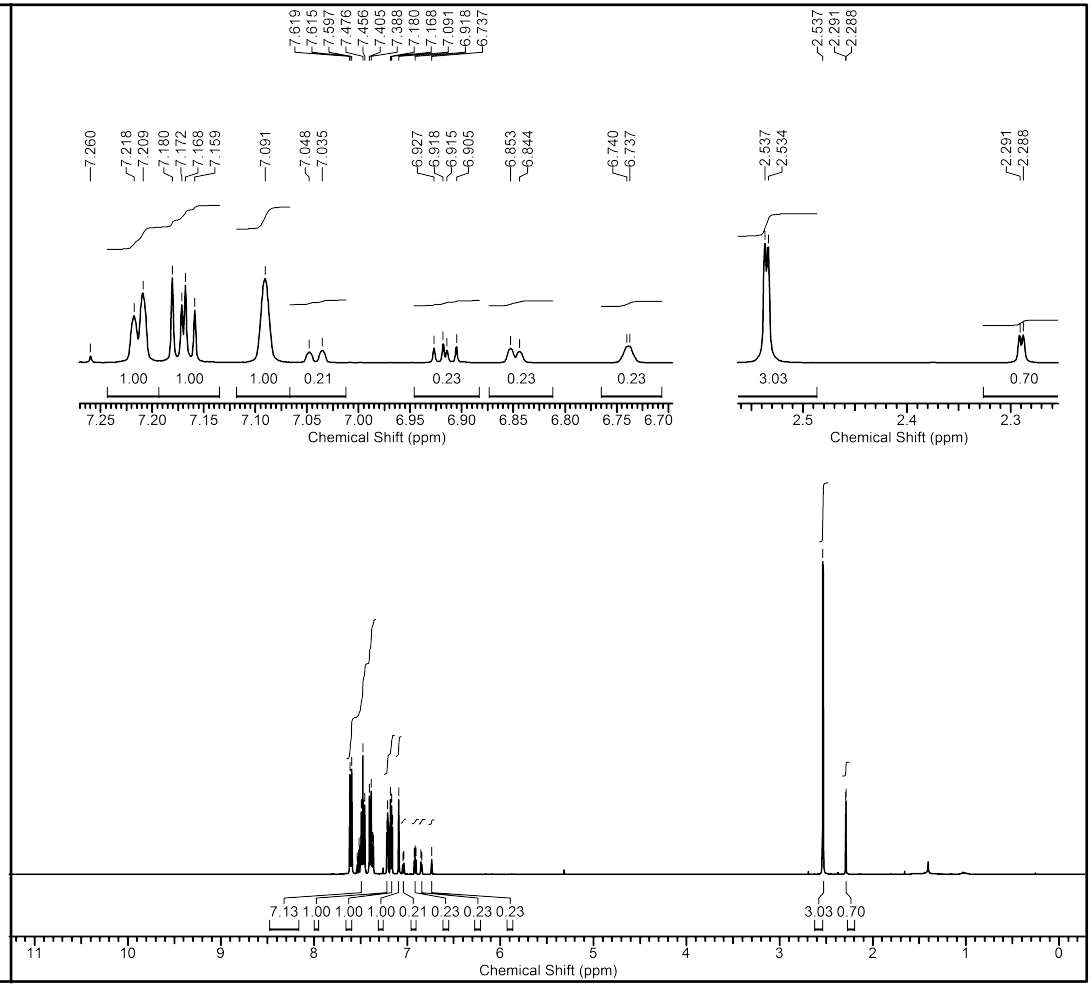


File Name	016-26A
Acquisition Time (sec)	3.9584
Date Stamp	17 May 2013 01:06
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4539
Origin	spect
Receiver Gain	32.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

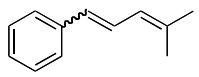


61

O'Brien™
Group NMR Data

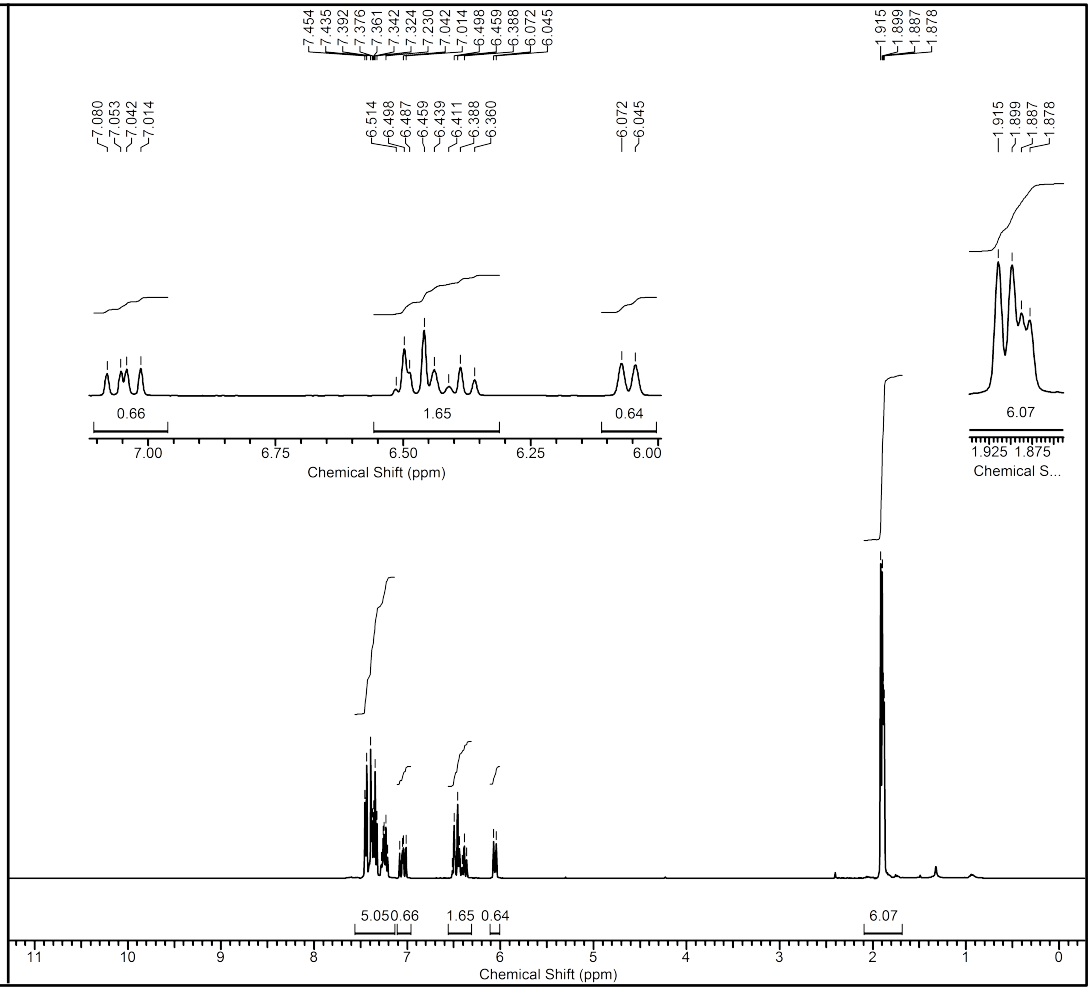


File Name	017-49A
Acquisition Time (sec)	3.9584
Date Stamp	19 Apr 2013
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.3591
Origin	spect
Receiver Gain	45.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

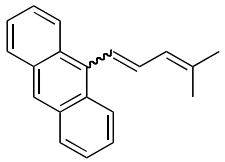


62

O'Brien™
Group NMR Data

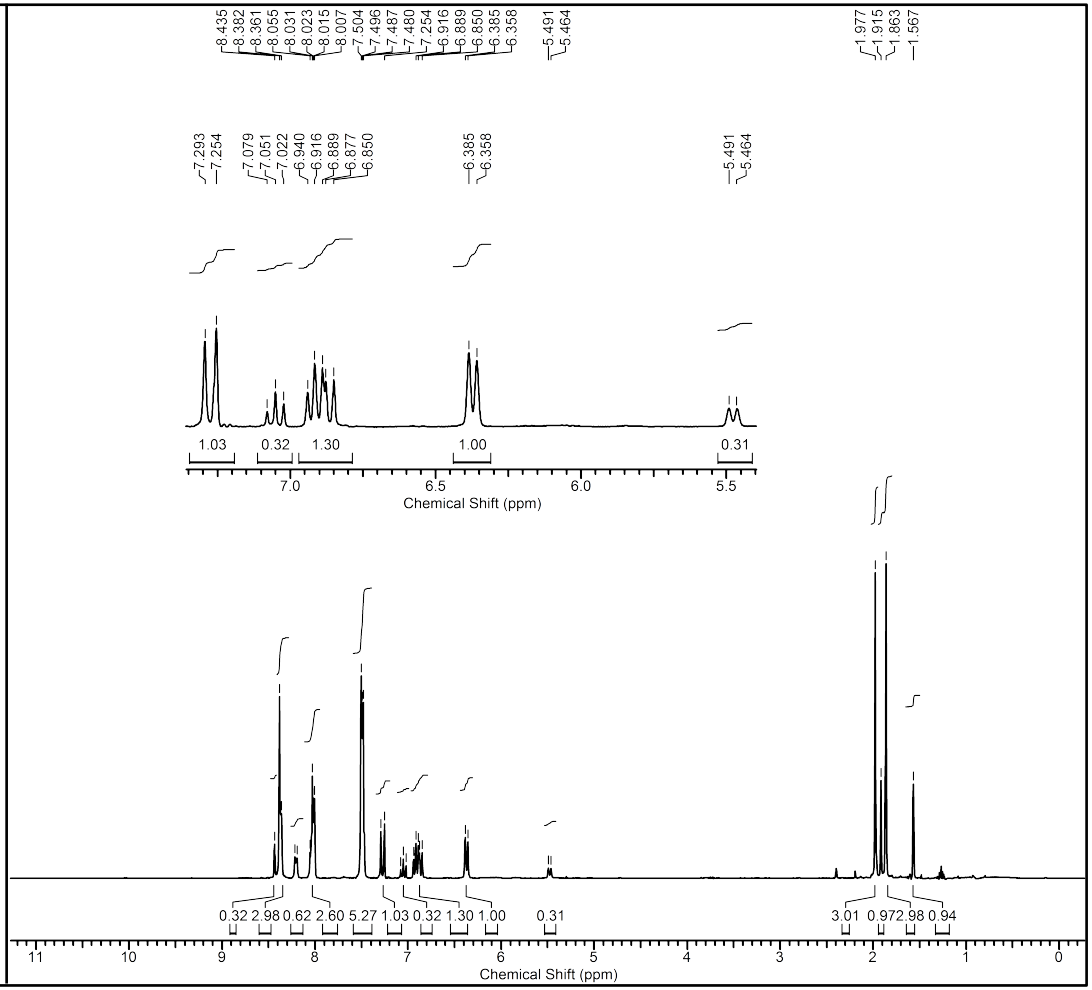


File Name	017-50A
Acquisition Time (sec)	3.9584
Date Stamp	24 Apr 2013 13:39
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2462.8750
Origin	spect
Receiver Gain	71.80
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

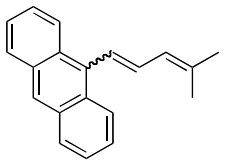


63

O'Brien™
Group NMR Data

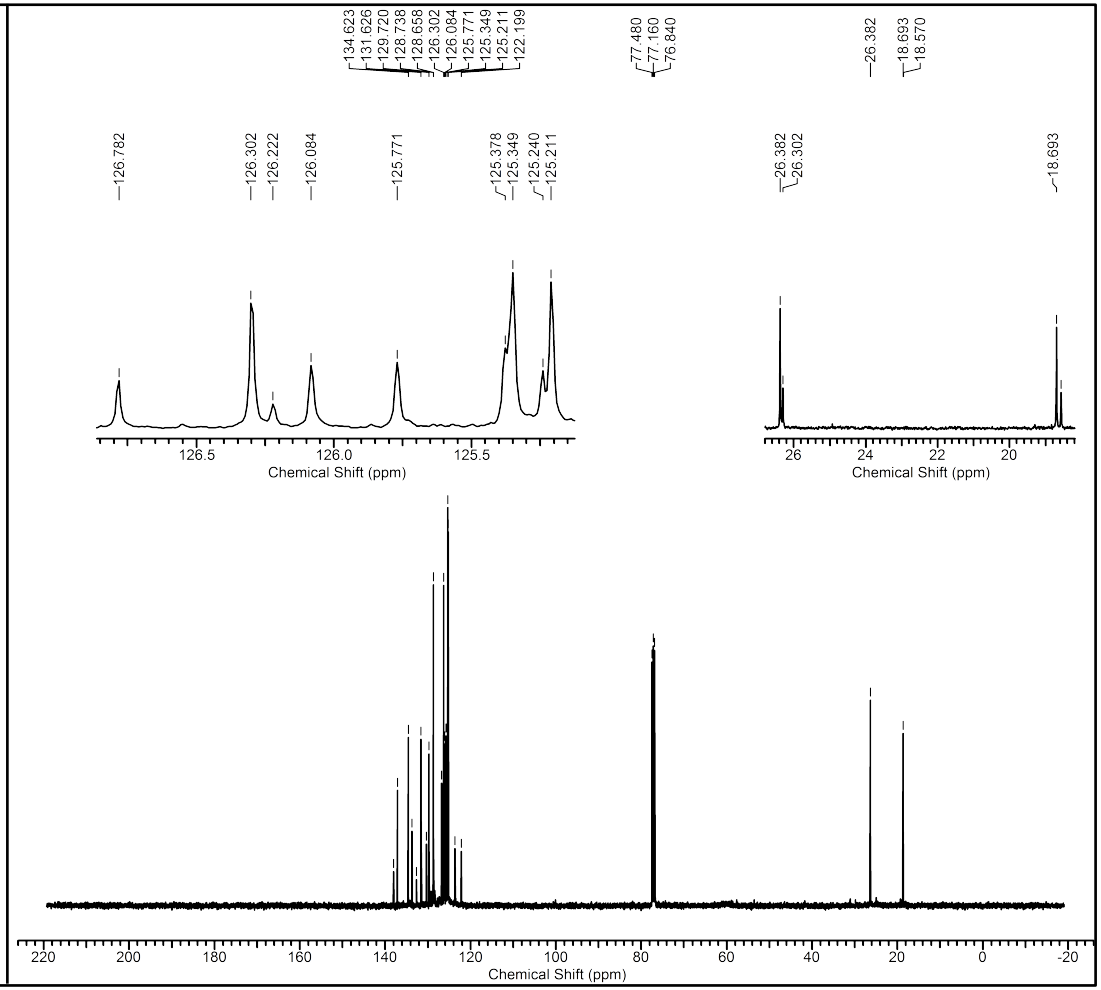


File Name	017-50A
Acquisition Time (sec)	1.3664
Date Stamp	25 Apr 2013 21:28
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10068.2002
Origin	spect
Receiver Gain	1290.20
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

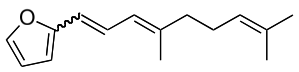


63

O'Brien™
Group NMR Data

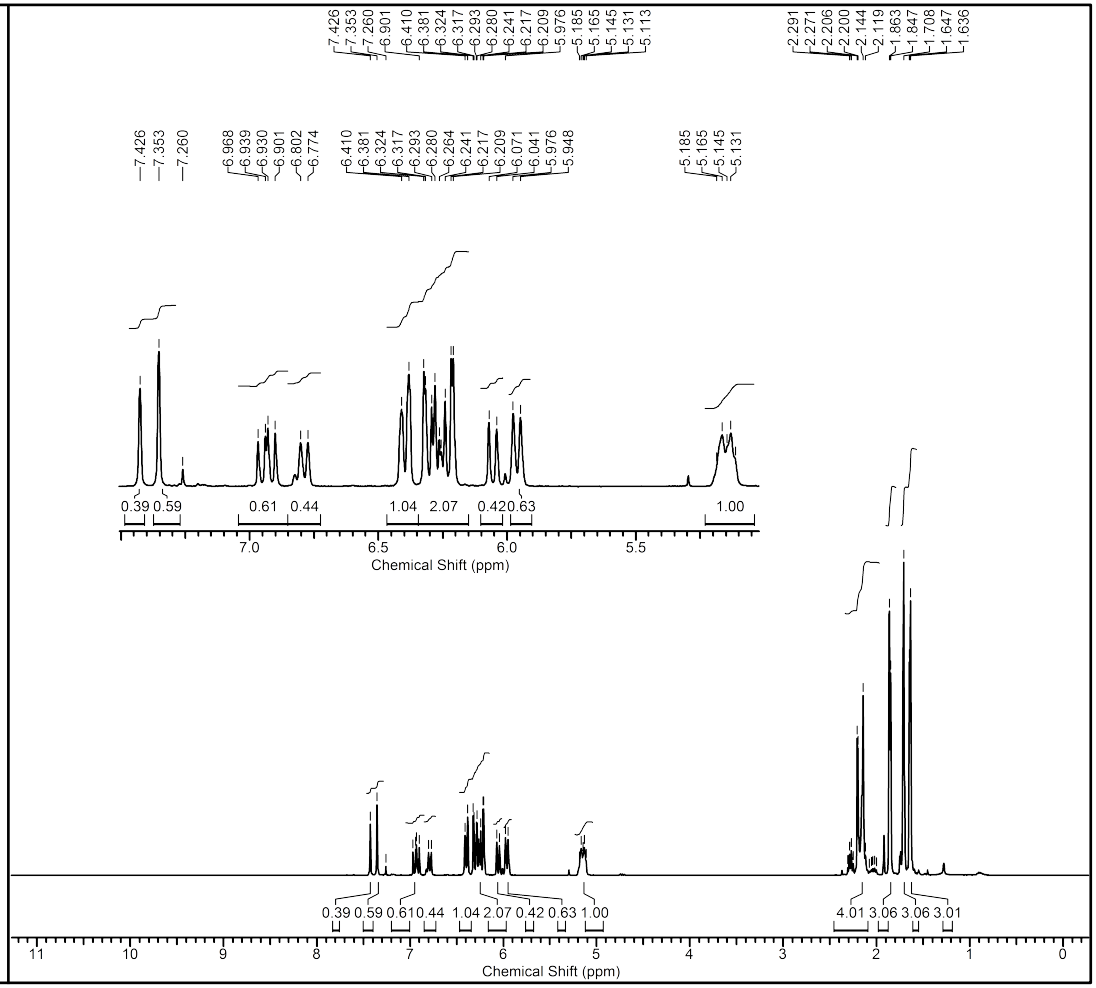


File Name	017-50D
Acquisition Time (sec)	3.9584
Date Stamp	25 Apr 2013 18:59
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.2012
Origin	spect
Receiver Gain	45.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

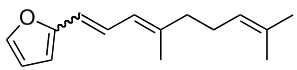


64

O'Brien™
Group NMR Data

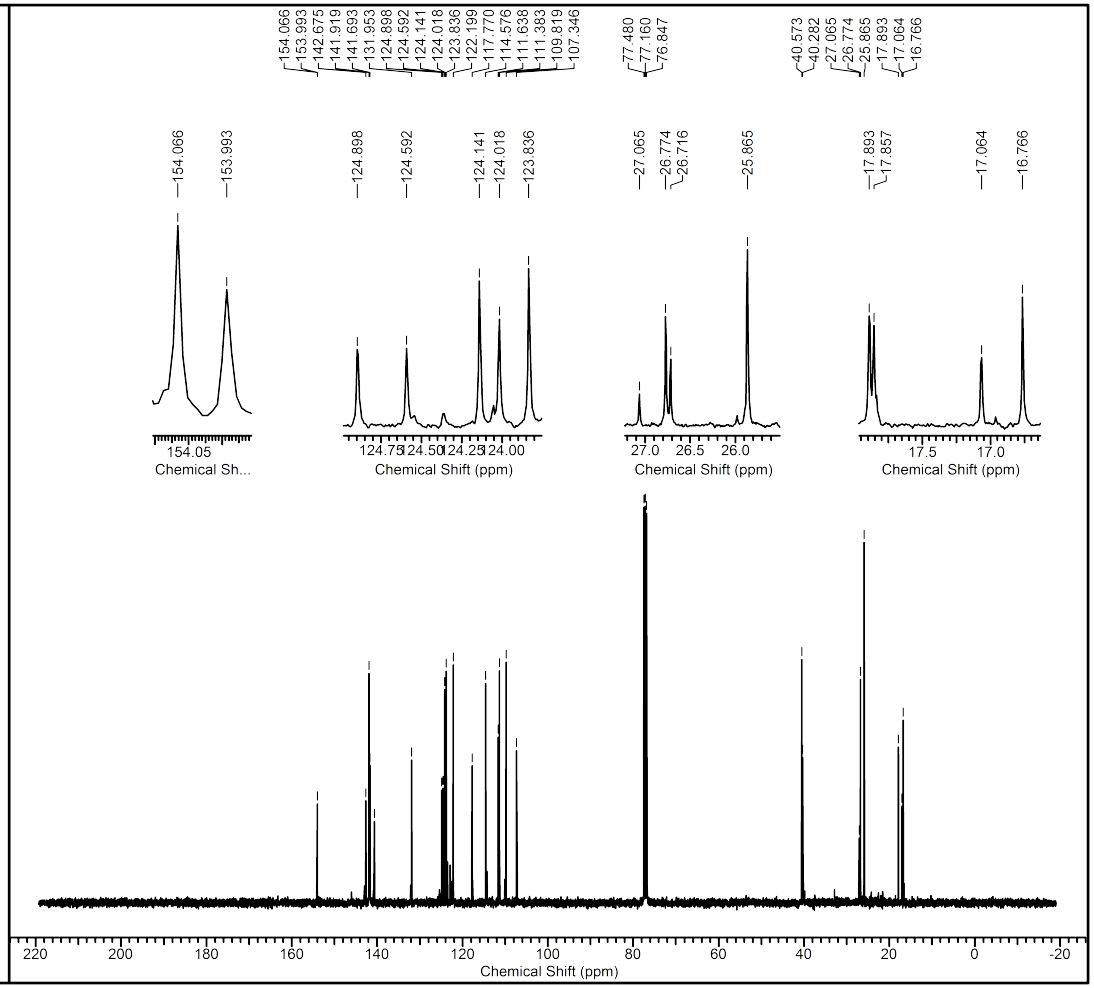


File Name	017-50D
Acquisition Time (sec)	1.3664
Date Stamp	25 Jun 2013 08:19
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10073.3232
Origin	spect
Receiver Gain	2048.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

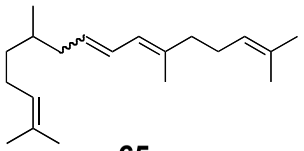


64

O'Brien™
Group NMR Data

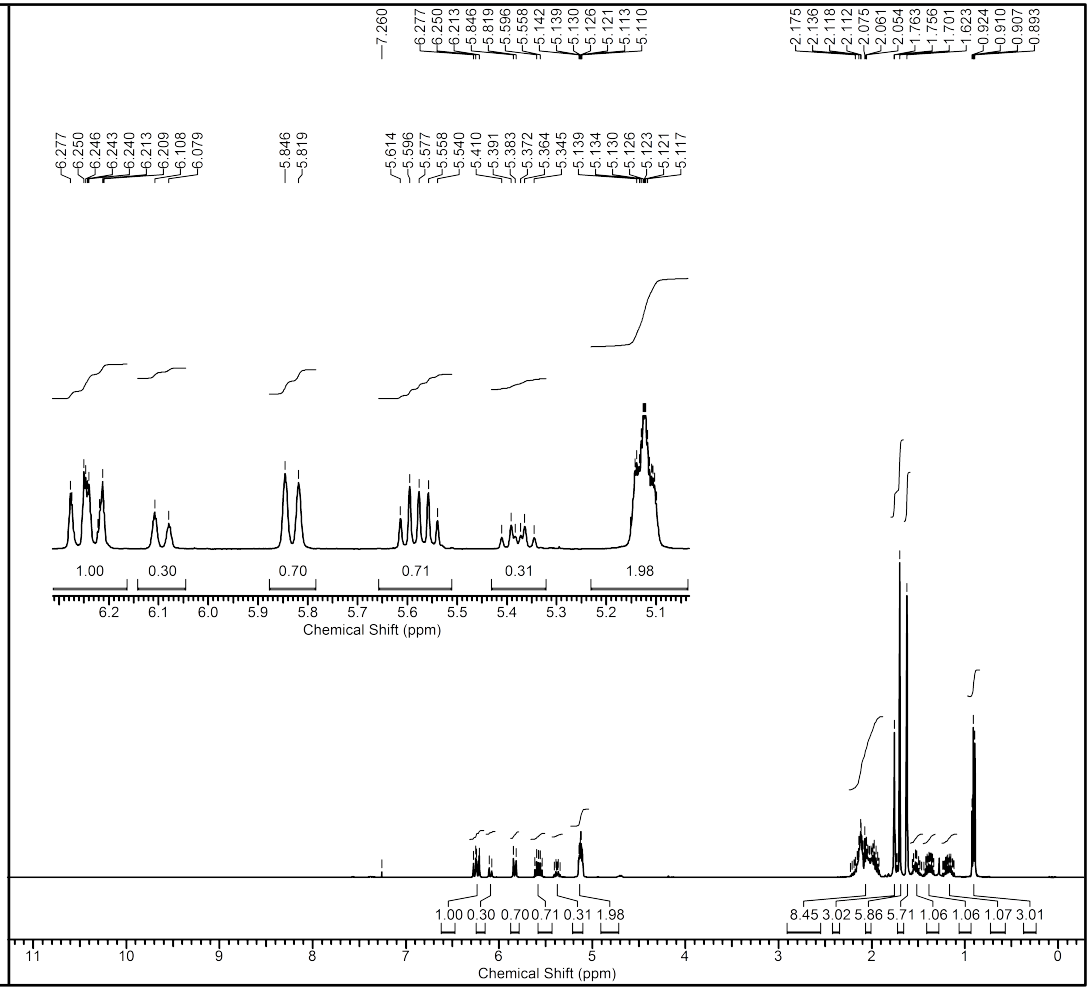


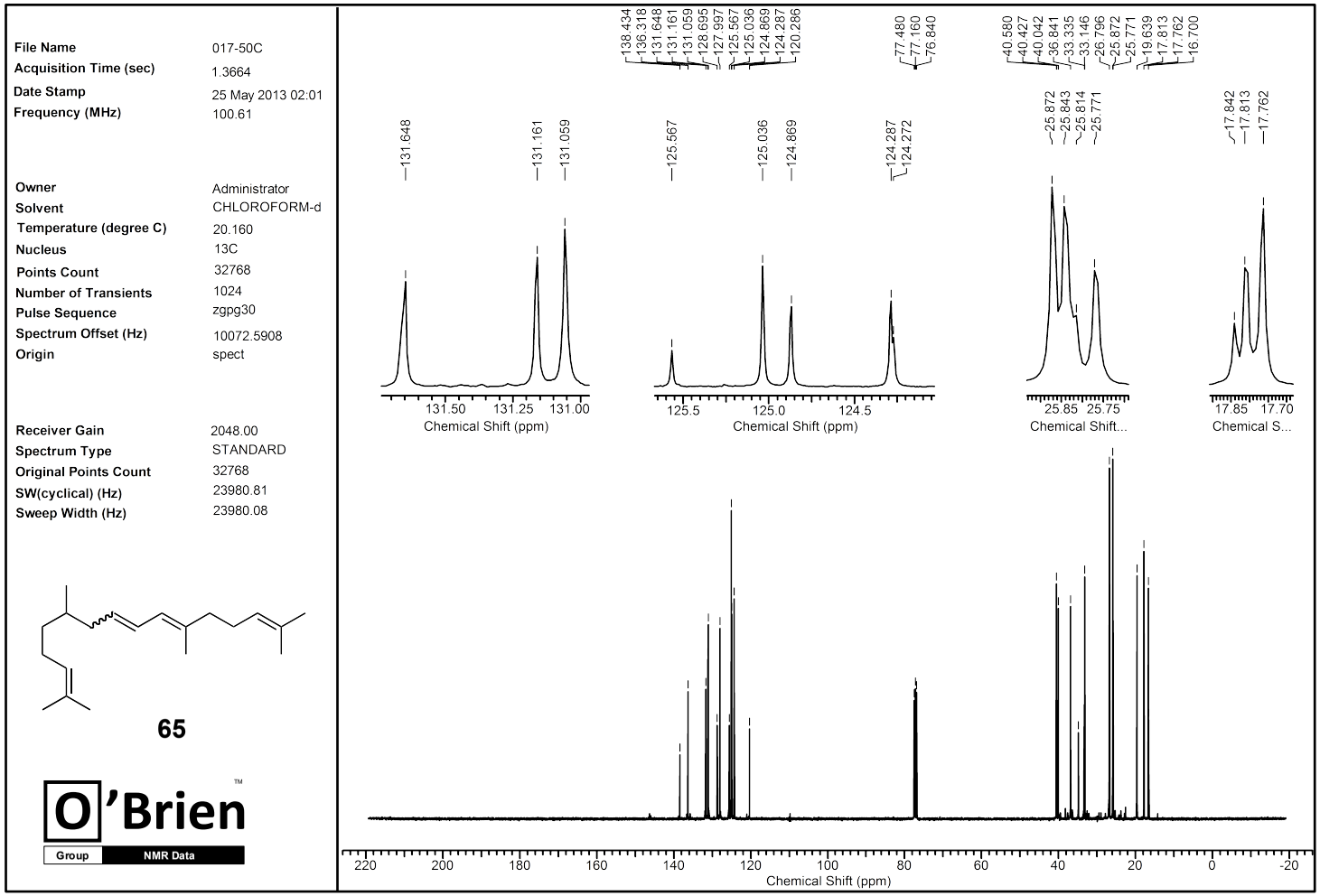
File Name	017-50C
Acquisition Time (sec)	3.9584
Date Stamp	25 May 2013 01:02
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	19.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.2014
Origin	spect
Receiver Gain	18.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89



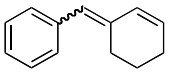
65

O'Brien™
Group NMR Data



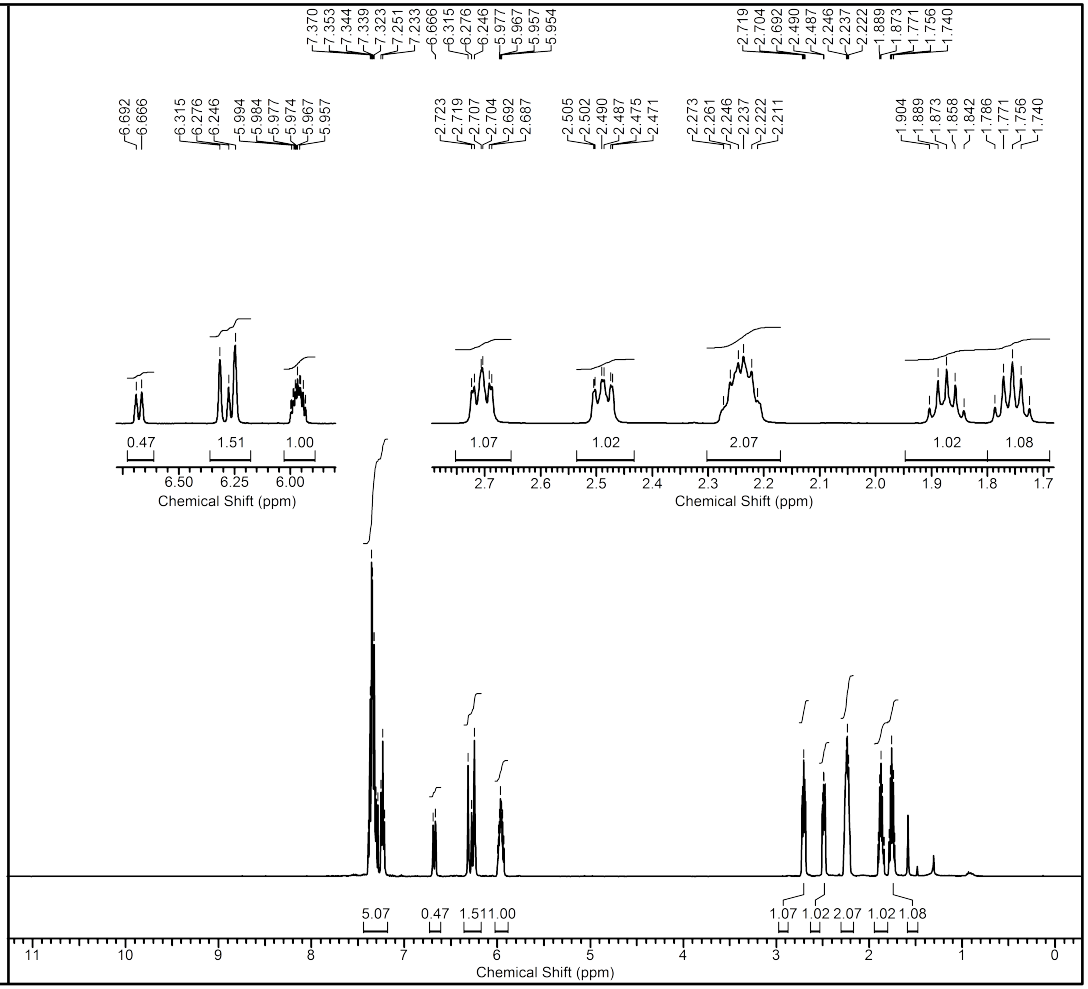

File Name 017-50C
Acquisition Time (sec) 1.3664
Date Stamp 25 May 2013 02:01
Frequency (MHz) 100.61
Owner Administrator
Solvent CHLOROFORM-d
Temperature (degree C) 20.160
Nucleus 13C
Points Count 32768
Number of Transients 1024
Pulse Sequence zgpg30
Spectrum Offset (Hz) 10072.5908
Origin spect
Receiver Gain 2048.00
Spectrum Type STANDARD
Original Points Count 32768
SW(cyclical) (Hz) 23980.81
Sweep Width (Hz) 23980.08
65
O'Brien
Group NMR Data
138.434 136.318 131.648 131.161 131.059 128.695 127.997 125.567 125.036 124.869 124.287 120.286
77.480 77.160 76.840
40.580 40.427 40.042 36.841 33.335 33.146 26.796 25.872 25.771 19.639 17.813 17.762 16.700
131.648 131.161 131.059
125.567 125.036 124.869 124.287 124.272
25.872 25.843 25.814 25.771
17.842 17.813 17.762
Chemical Shift (ppm)
Chemical Shift (ppm)
Chemical Shift...
Chemical S...
Chemical Shift (ppm)

File Name	017-55B
Acquisition Time (sec)	3.9584
Date Stamp	07 May 2013 18:18
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2470.9668
Origin	spect
Receiver Gain	71.80
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

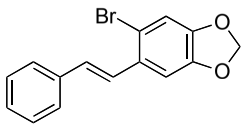


66

O'Brien™
Group NMR Data

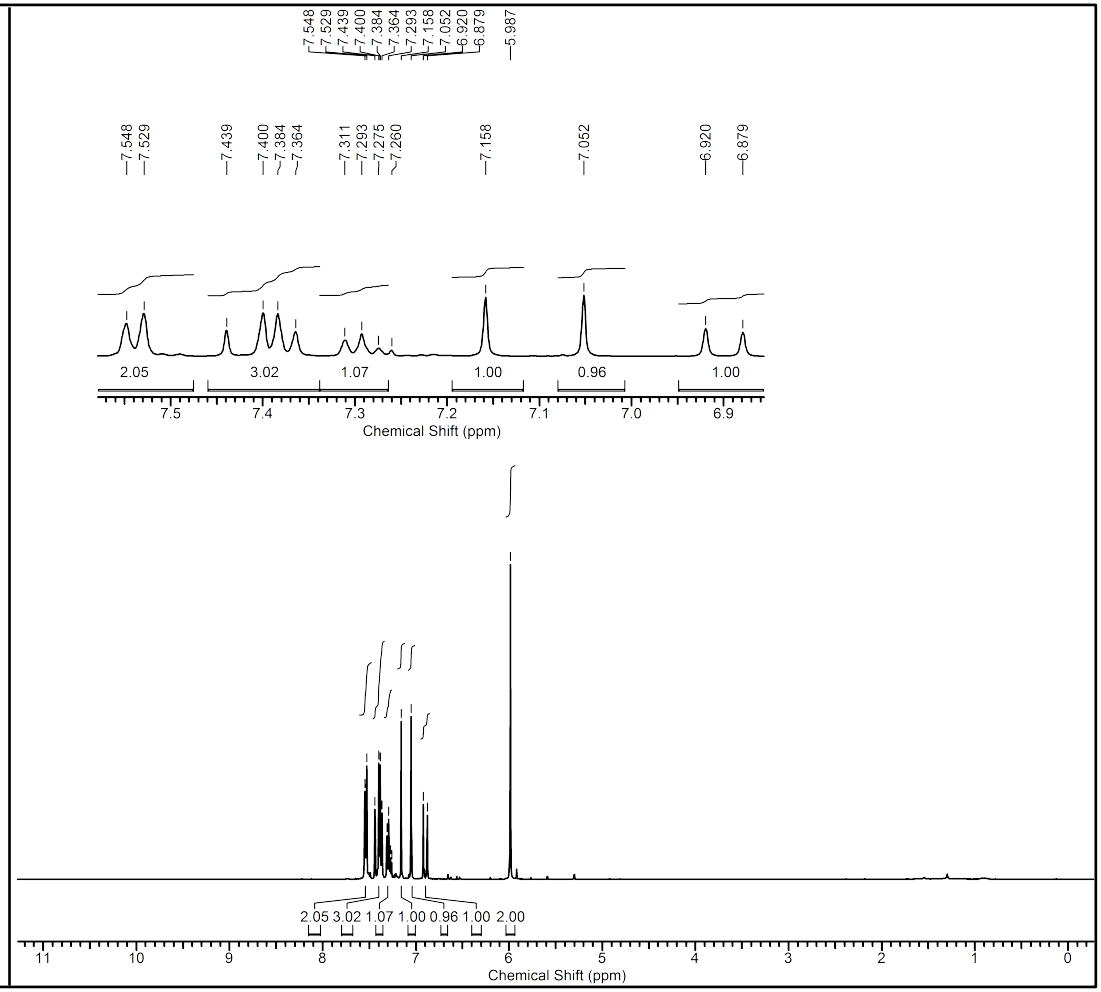


File Name	017-34A_E
Acquisition Time (sec)	3.9584
Date Stamp	27 Mar 2013 15:08
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.9595
Origin	spect
Receiver Gain	71.80
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

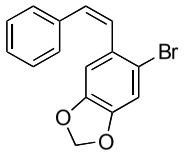


E-**67**

O'Brien™
Group NMR Data

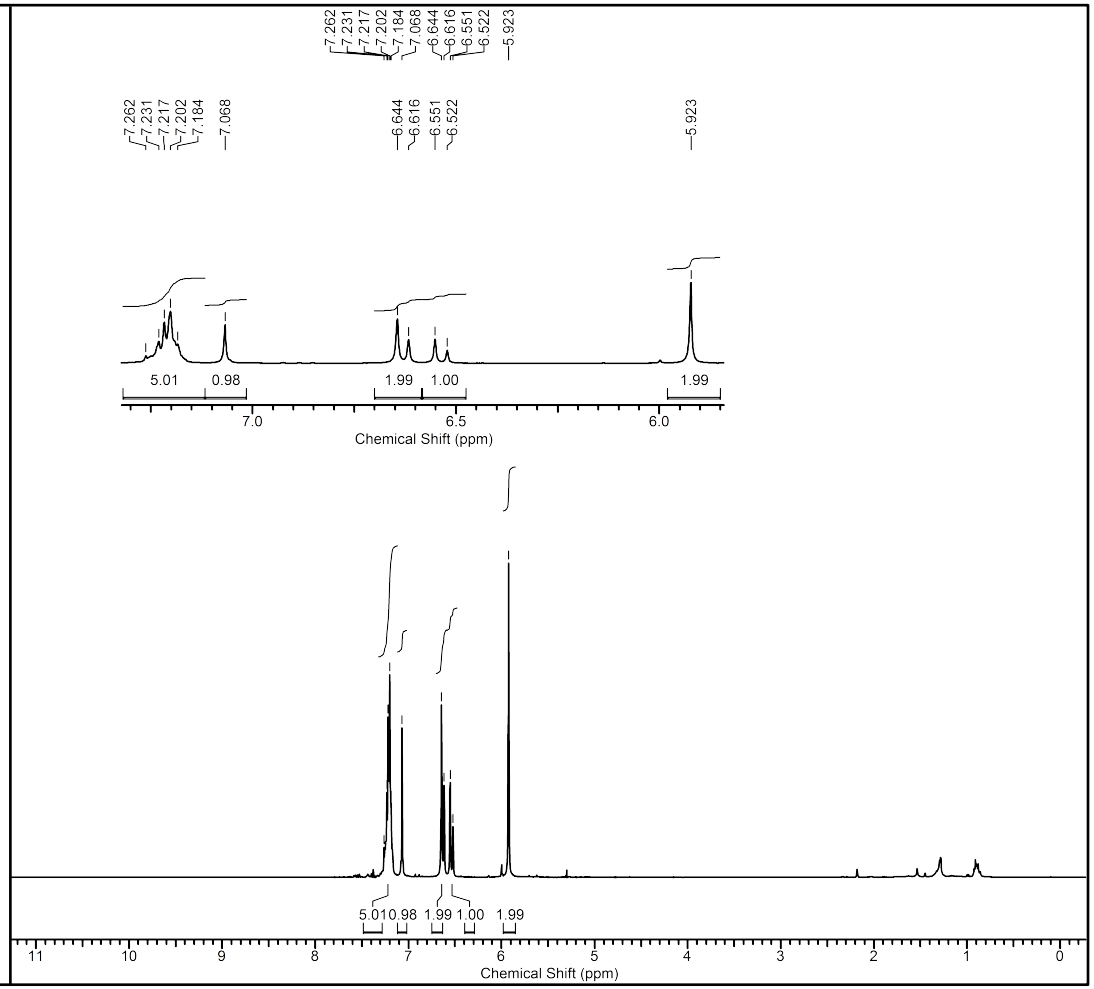


File Name	017-34A_Z
Acquisition Time (sec)	3.9584
Date Stamp	27 Mar 2013 15:00
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2462.8750
Origin	spect
Receiver Gain	101.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

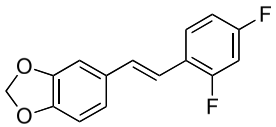


***Z*-67**

O'Brien™
Group NMR Data

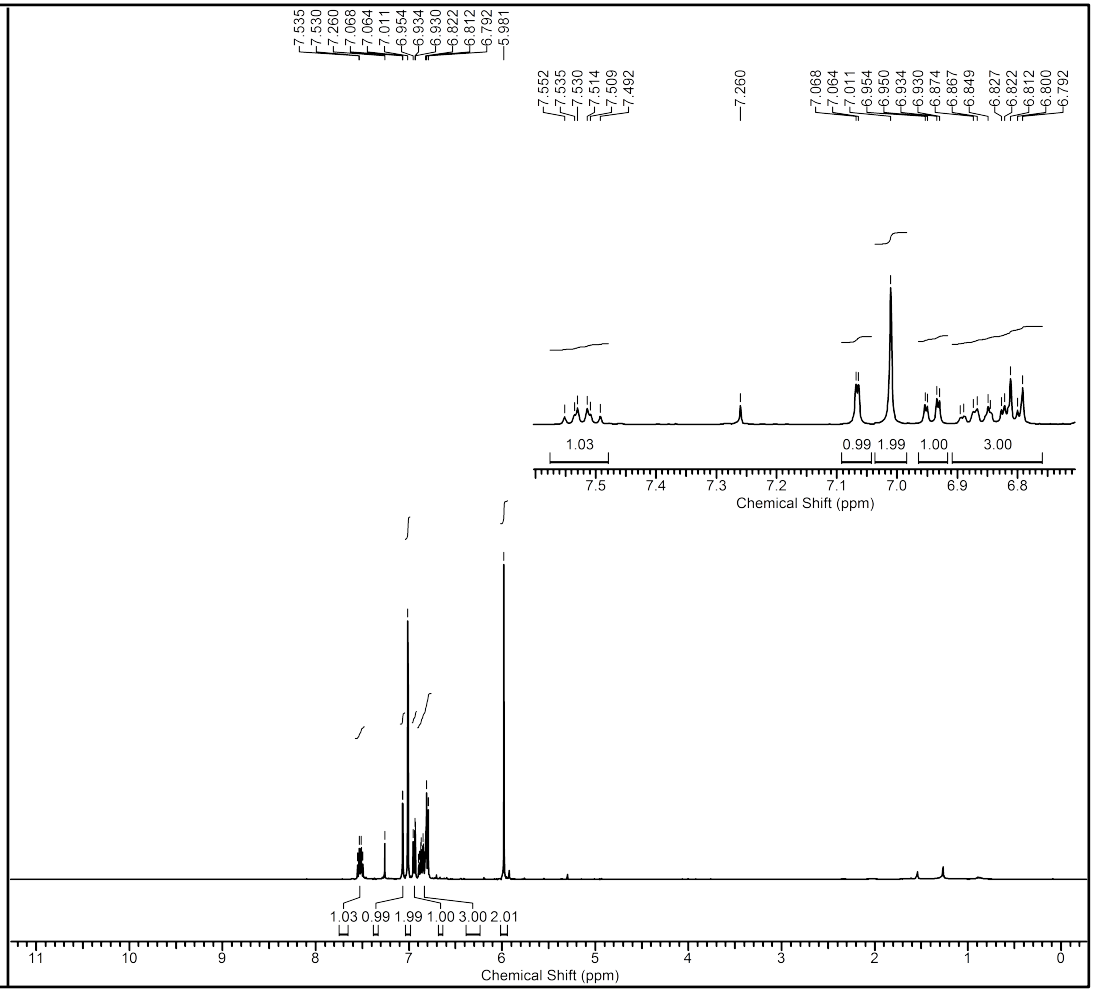


File Name	017-30A_E
Acquisition Time (sec)	3.9584
Date Stamp	14 Mar 2013 13:17
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.7065
Origin	spect
Receiver Gain	143.70
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

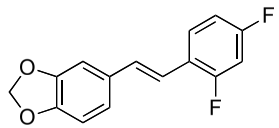


E-68

O'Brien™ Group NMR Data

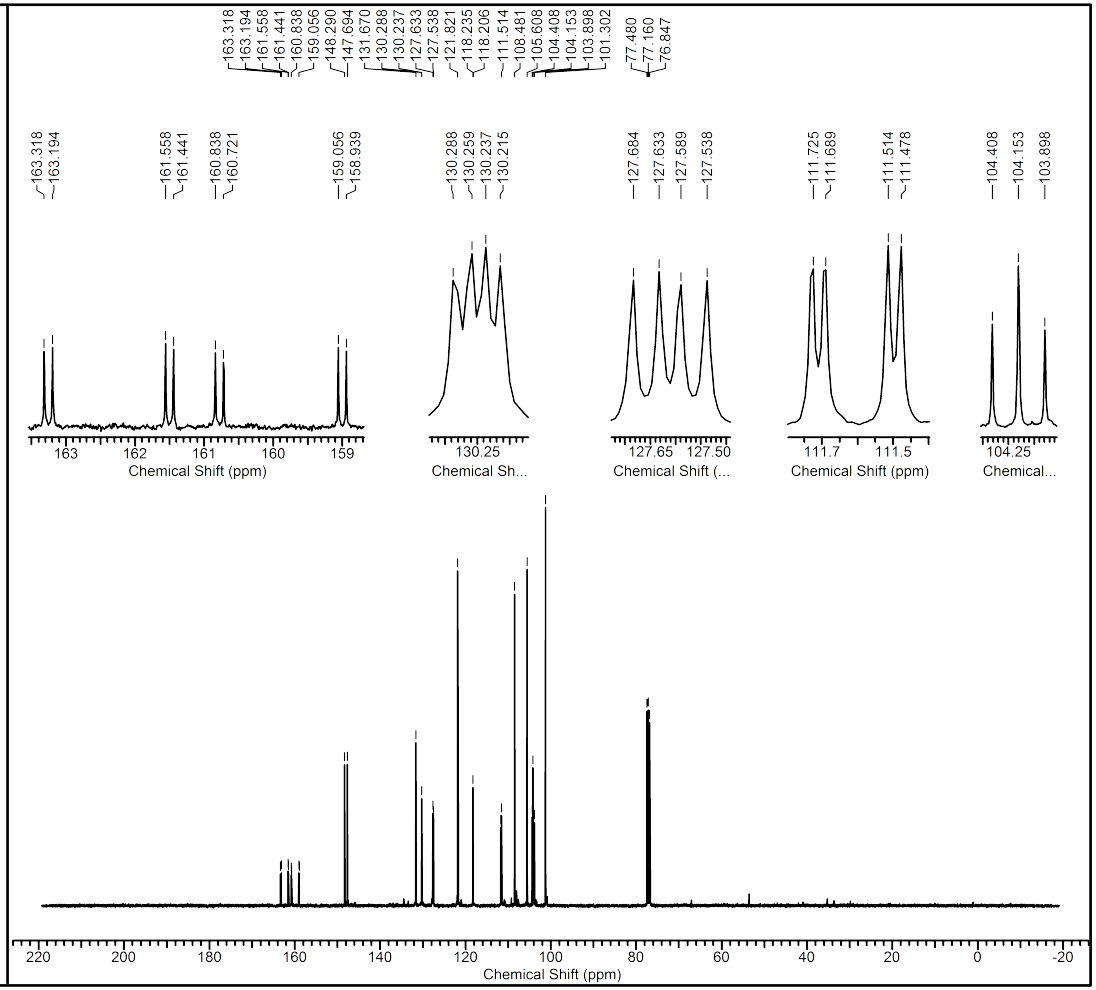


File Name	017-30A_E
Acquisition Time (sec)	1.3664
Date Stamp	14 Jun 2013 18:06
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10066.7451
Origin	spect
Receiver Gain	812.70
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

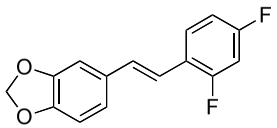


***E*-68**

O'Brien™
Group NMR Data

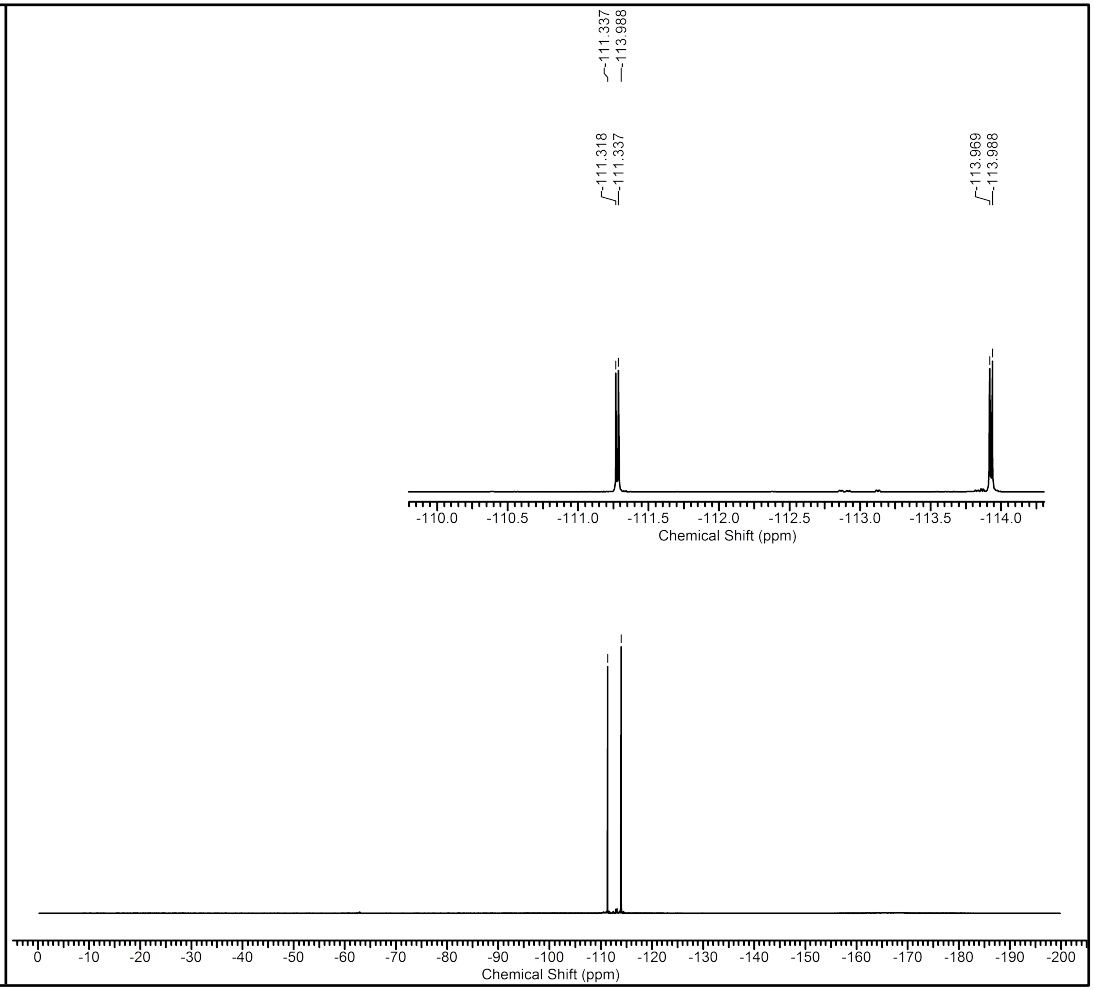


File Name	017-30A_E
Acquisition Time (sec)	0.8716
Date Stamp	14 Jun 2013 16:23
Frequency (MHz)	376.50
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	19F
Points Count	65536
Number of Transients	16
Pulse Sequence	zgfhigqn
Spectrum Offset (Hz)	-37649.6211
Origin	spect
Receiver Gain	322.50
Spectrum Type	STANDARD
Original Points Count	65536
SW(cyclical) (Hz)	75187.97
Sweep Width (Hz)	75186.82

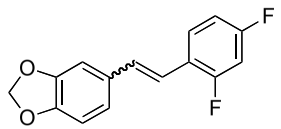


***E*-68**

O'Brien™
Group NMR Data

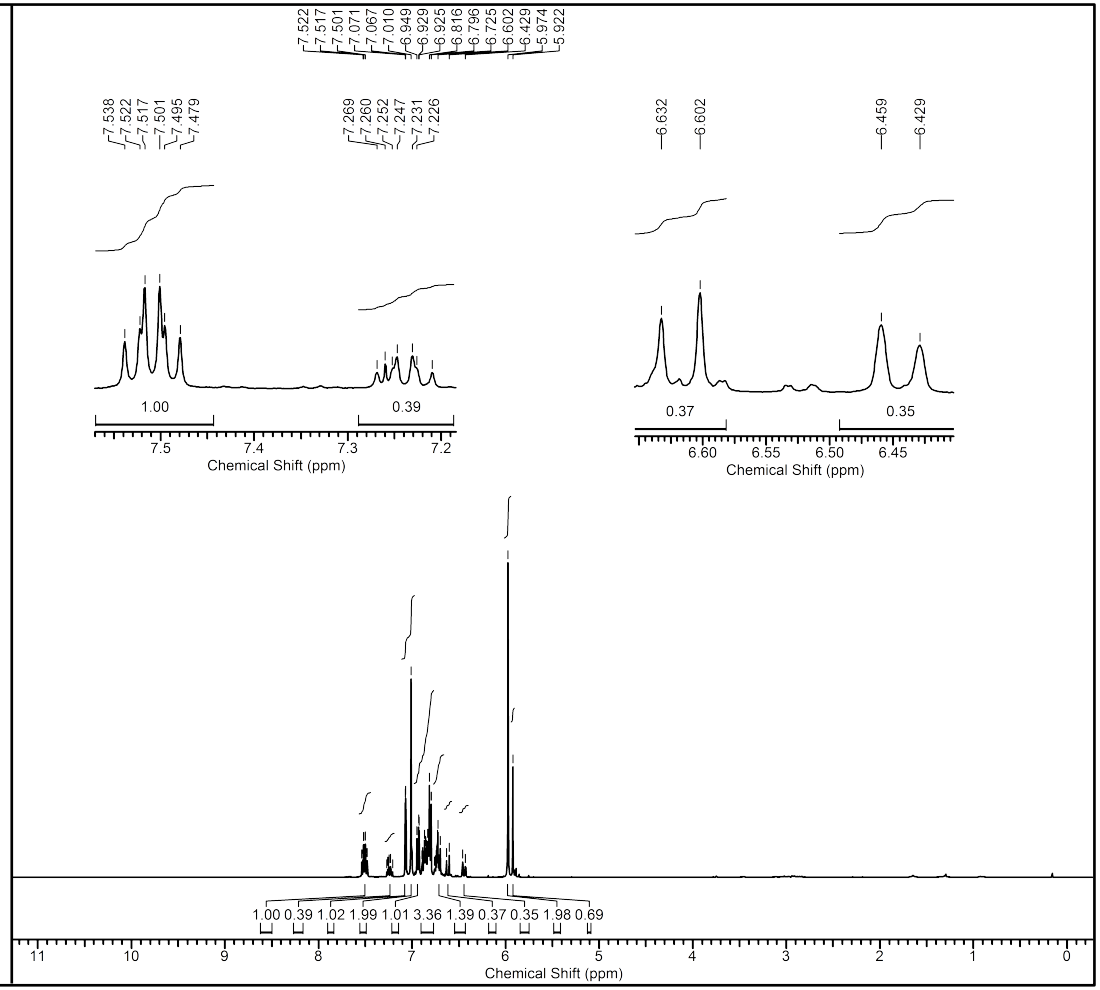


File Name	017-30A
Acquisition Time (sec)	3.9584
Date Stamp	13 Jun 2013 15:24
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.7068
Origin	spect
Receiver Gain	35.90
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

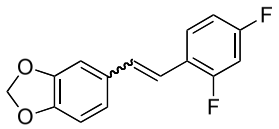


68

O'Brien™
Group NMR Data

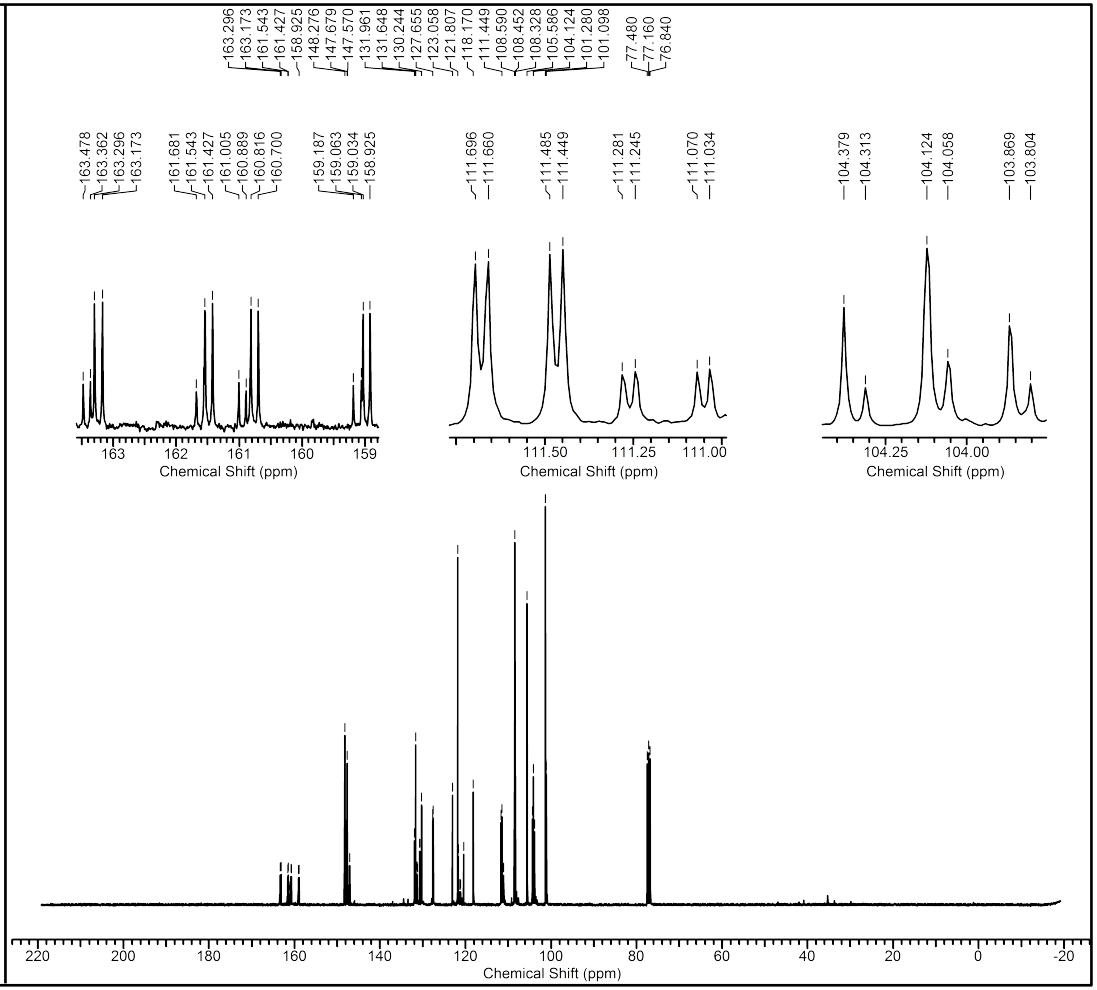


File Name	017-30A
Acquisition Time (sec)	1.3664
Date Stamp	13 Jun 2013 21:41
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10063.8096
Origin	spect
Receiver Gain	1149.40
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

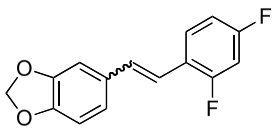


68

O'Brien™
Group NMR Data

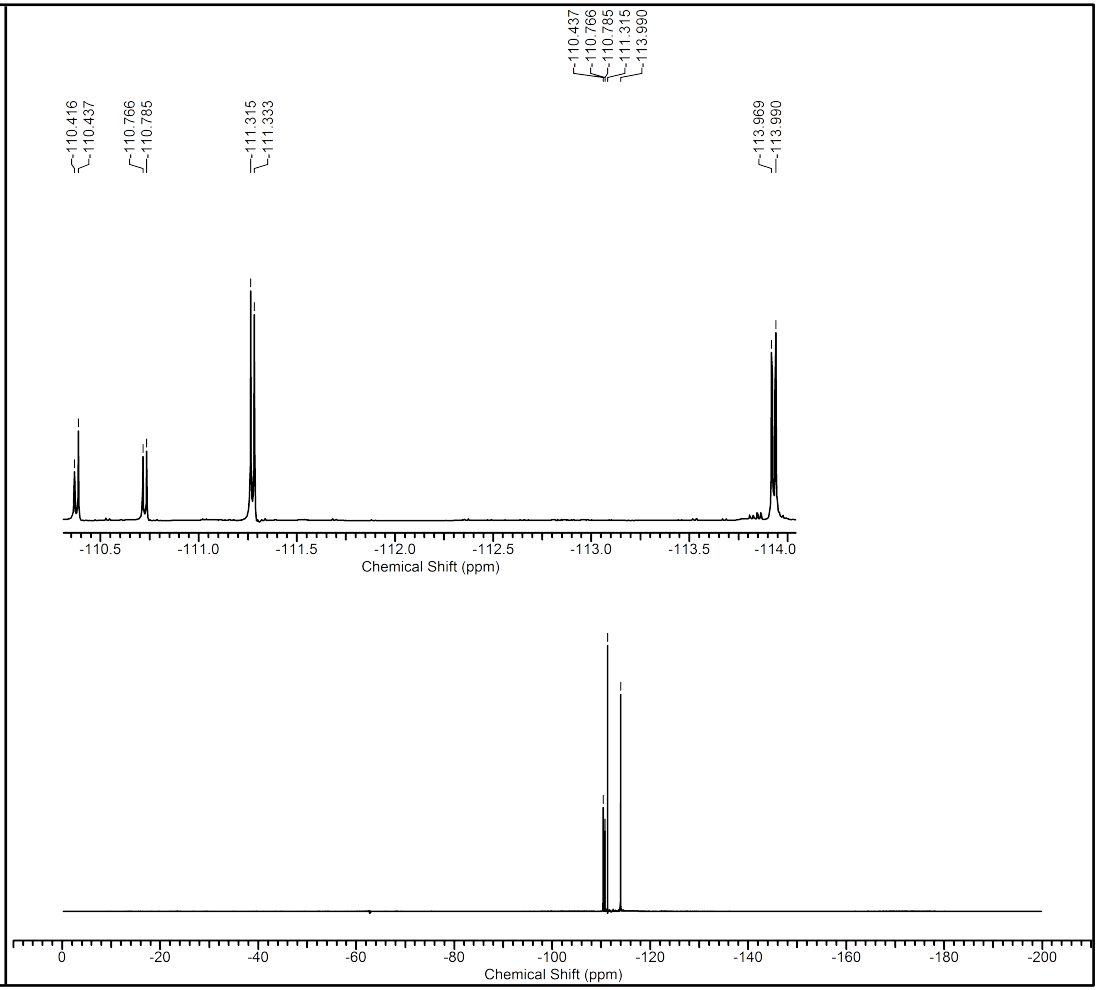


File Name	017-30A
Acquisition Time (sec)	0.8716
Date Stamp	13 Jun 2013 15:24
Frequency (MHz)	376.50
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	19F
Points Count	65536
Number of Transients	16
Pulse Sequence	zgfhigqn
Spectrum Offset (Hz)	-37658.6250
Origin	spect
Receiver Gain	181.00
Spectrum Type	STANDARD
Original Points Count	65536
SW(cyclical) (Hz)	75187.97
Sweep Width (Hz)	75186.82

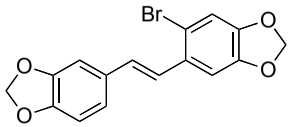


68

O'Brien™
Group NMR Data

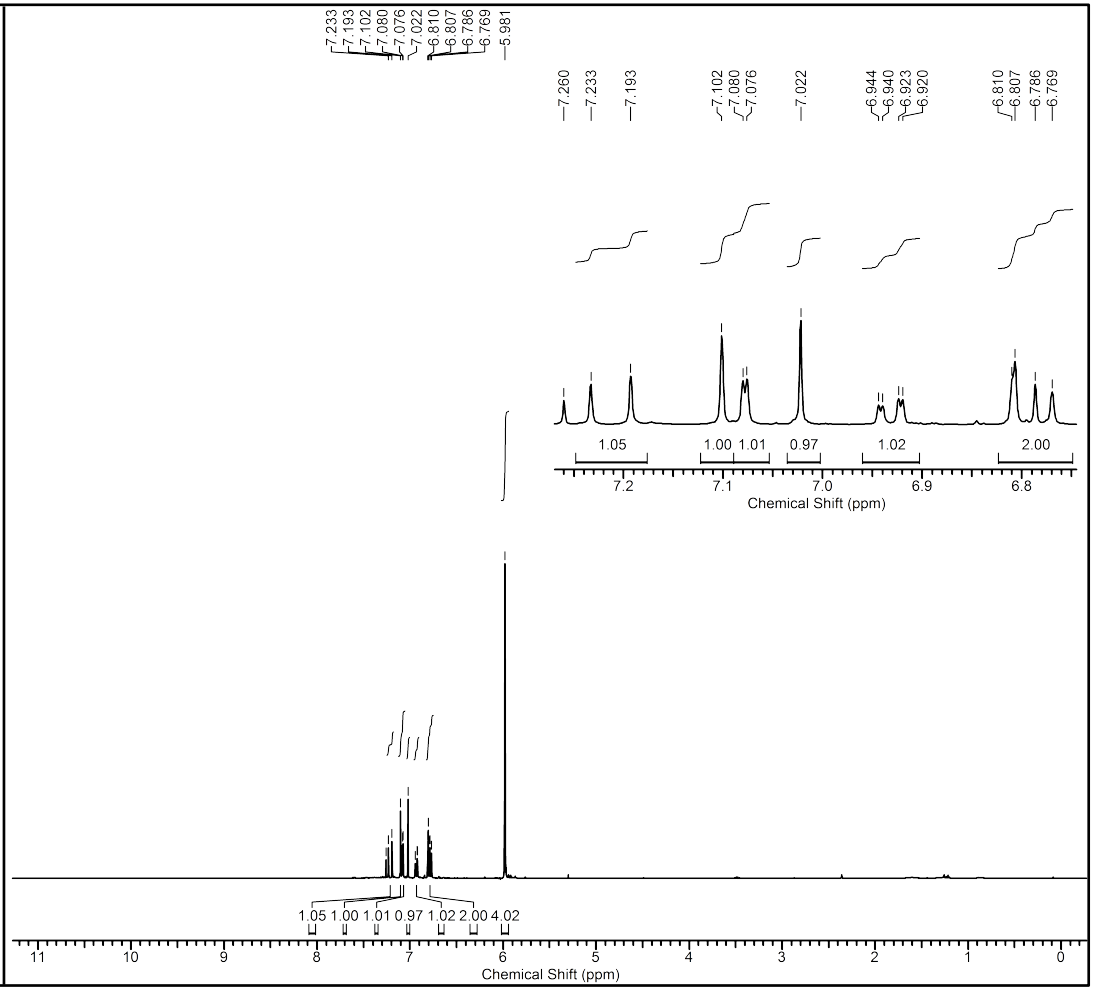


File Name	017-57C_E
Acquisition Time (sec)	3.9584
Date Stamp	07 Jun 2013 15:15
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.2014
Origin	spect
Receiver Gain	128.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

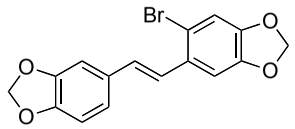


***E*-69**

O'Brien™
Group NMR Data

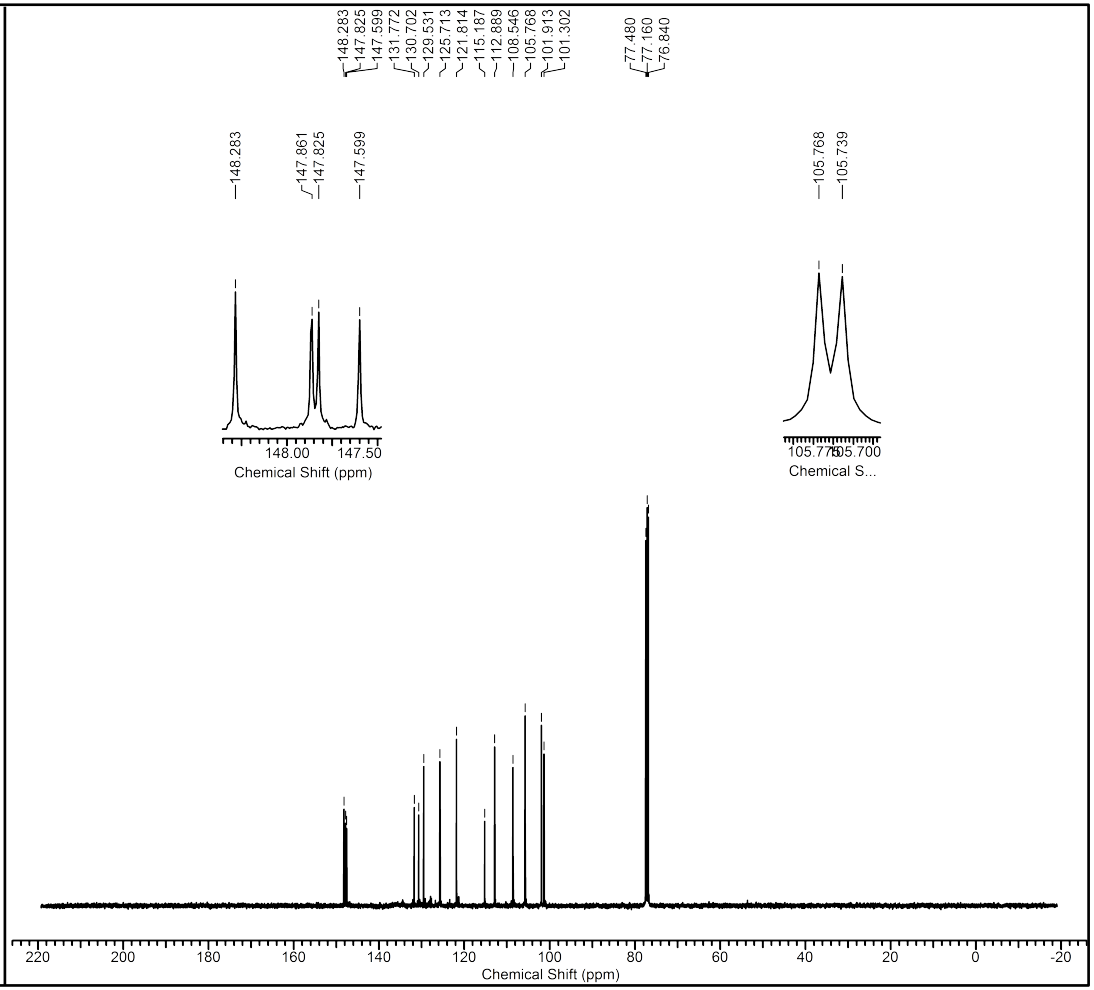


File Name	017-57C_E
Acquisition Time (sec)	1.3664
Date Stamp	07 Jun 2013 20:14
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10070.3955
Origin	spect
Receiver Gain	1448.20
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

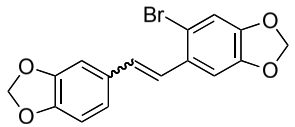


E-**69**

O'Brien™
Group NMR Data

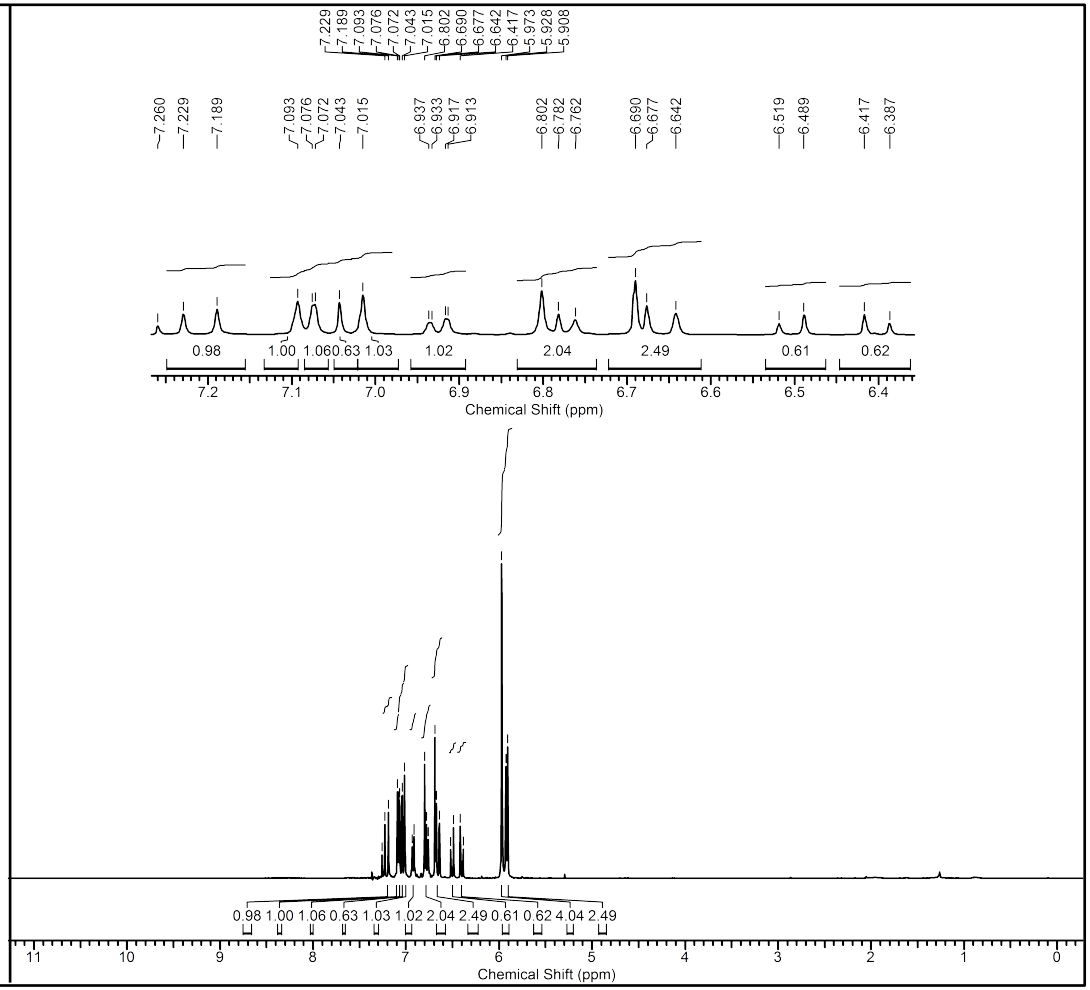


File Name	017-57C
Acquisition Time (sec)	3.9584
Date Stamp	22 May 2013 18:14
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2460.9487
Origin	spect
Receiver Gain	71.80
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

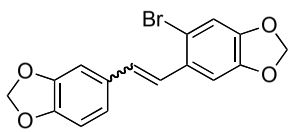


69

O'Brien™
Group NMR Data

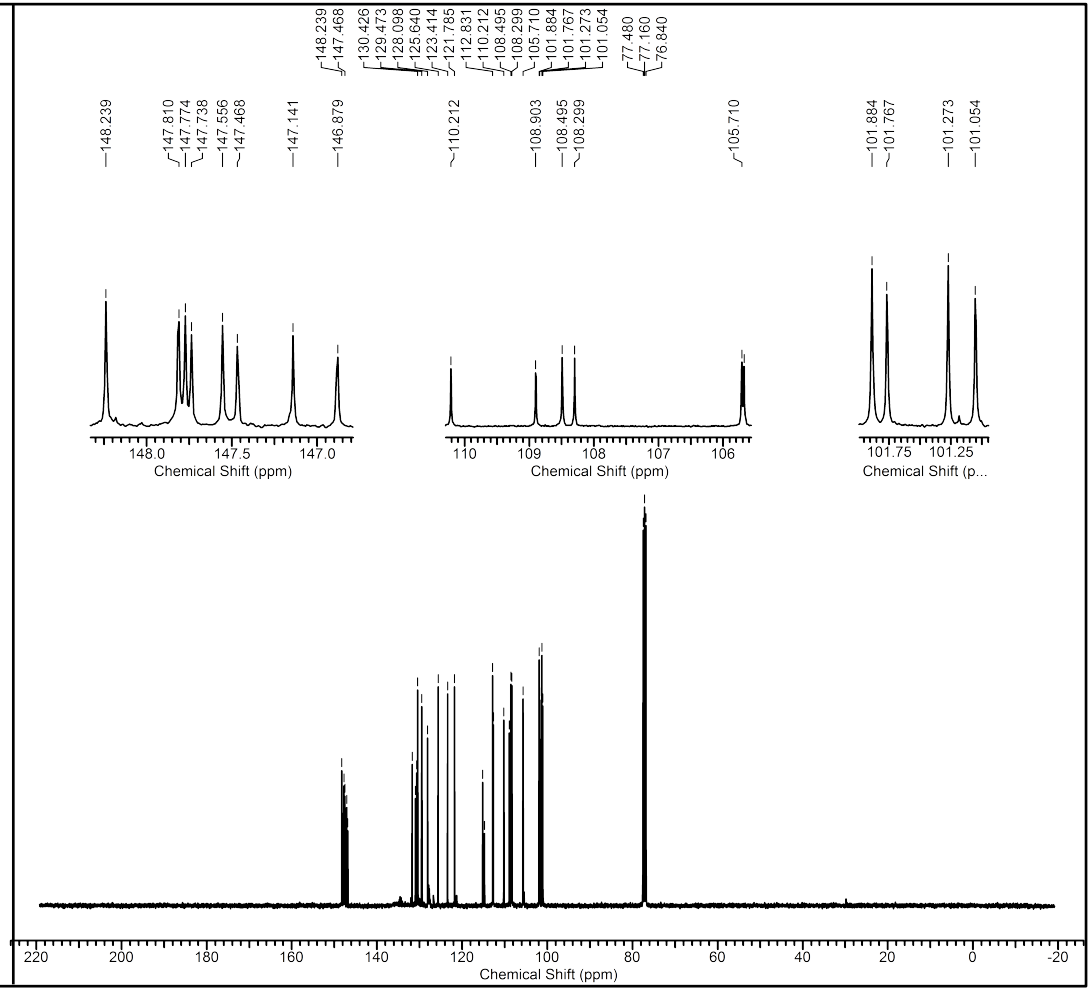


File Name	017-57C
Acquisition Time (sec)	1.3664
Date Stamp	24 May 2013 23:28
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10065.2725
Origin	spect
Receiver Gain	1625.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

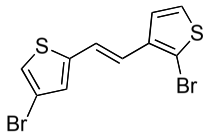


69

O'Brien™
Group NMR Data

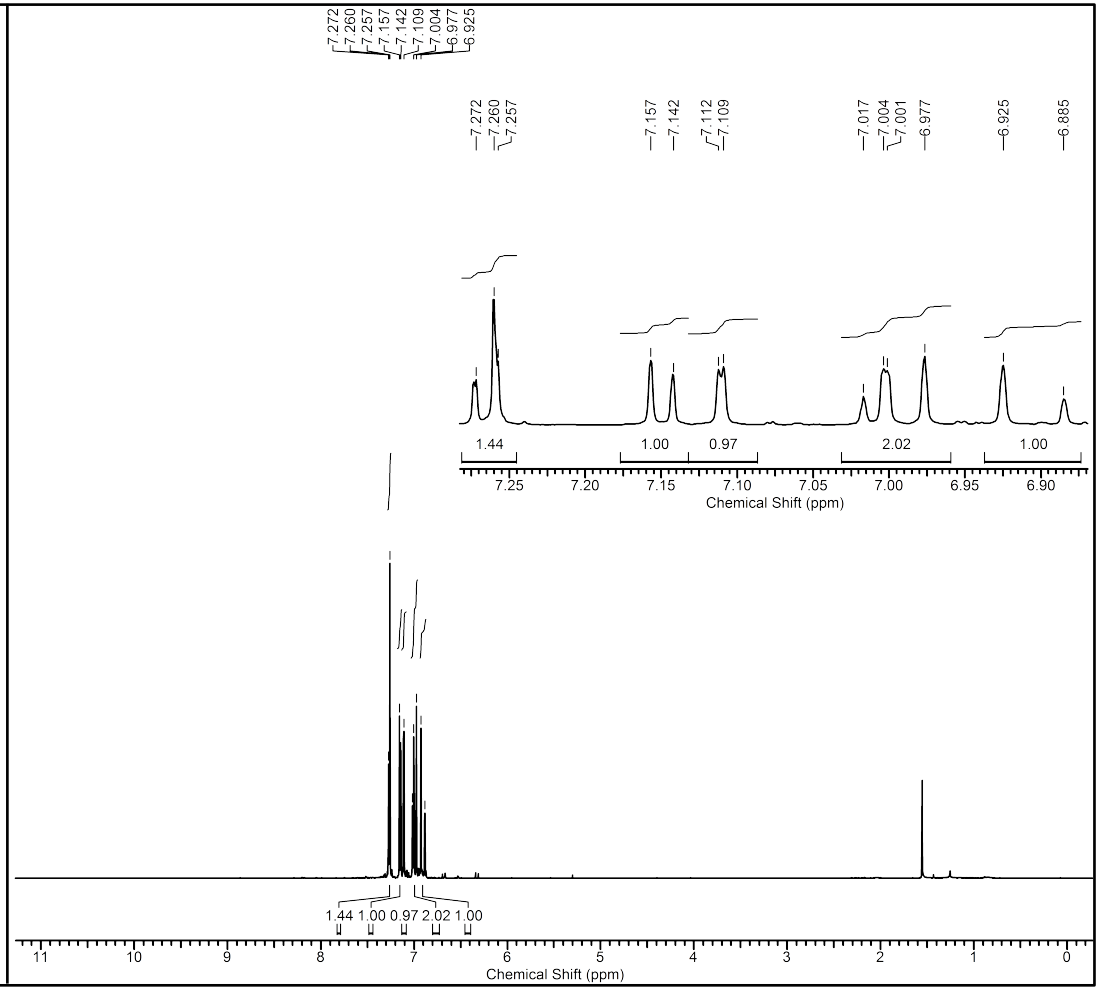


File Name	017-59A_E
Acquisition Time (sec)	3.9584
Date Stamp	17 May 2013 18:18
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4539
Origin	spect
Receiver Gain	574.70
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

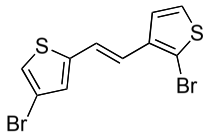


***E*-70**

O'Brien™
Group NMR Data

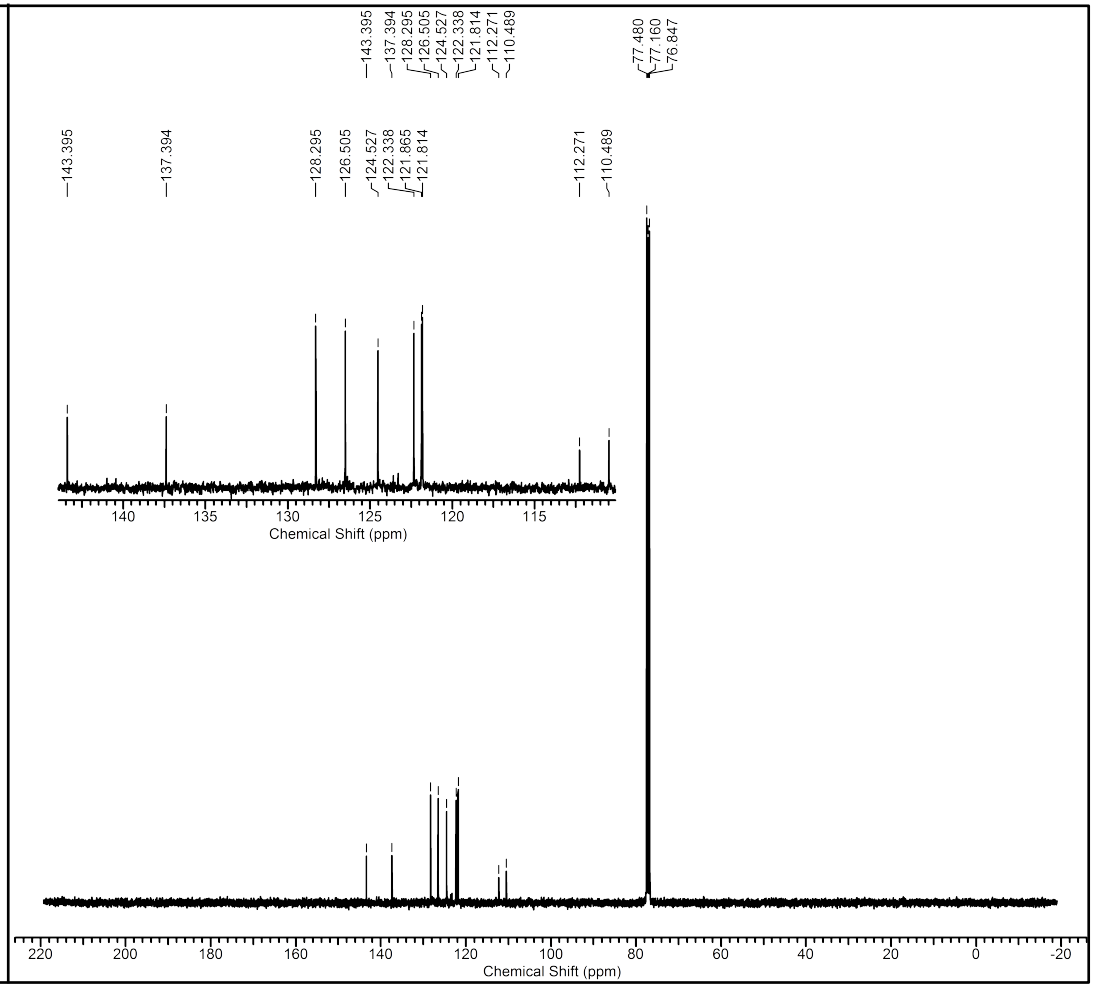


File Name	017-59A_E
Acquisition Time (sec)	1.3664
Date Stamp	17 May 2013 21:39
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10073.3232
Origin	spect
Receiver Gain	4096.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

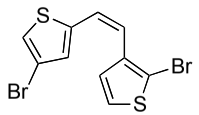


***E*-70**

O'Brien™
Group NMR Data



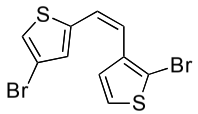
File Name	017-59A_Z
Acquisition Time (sec)	3.9584
Date Stamp	17 May 2013 18:10
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.2014
Origin	spect
Receiver Gain	322.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89



***Z*-70**

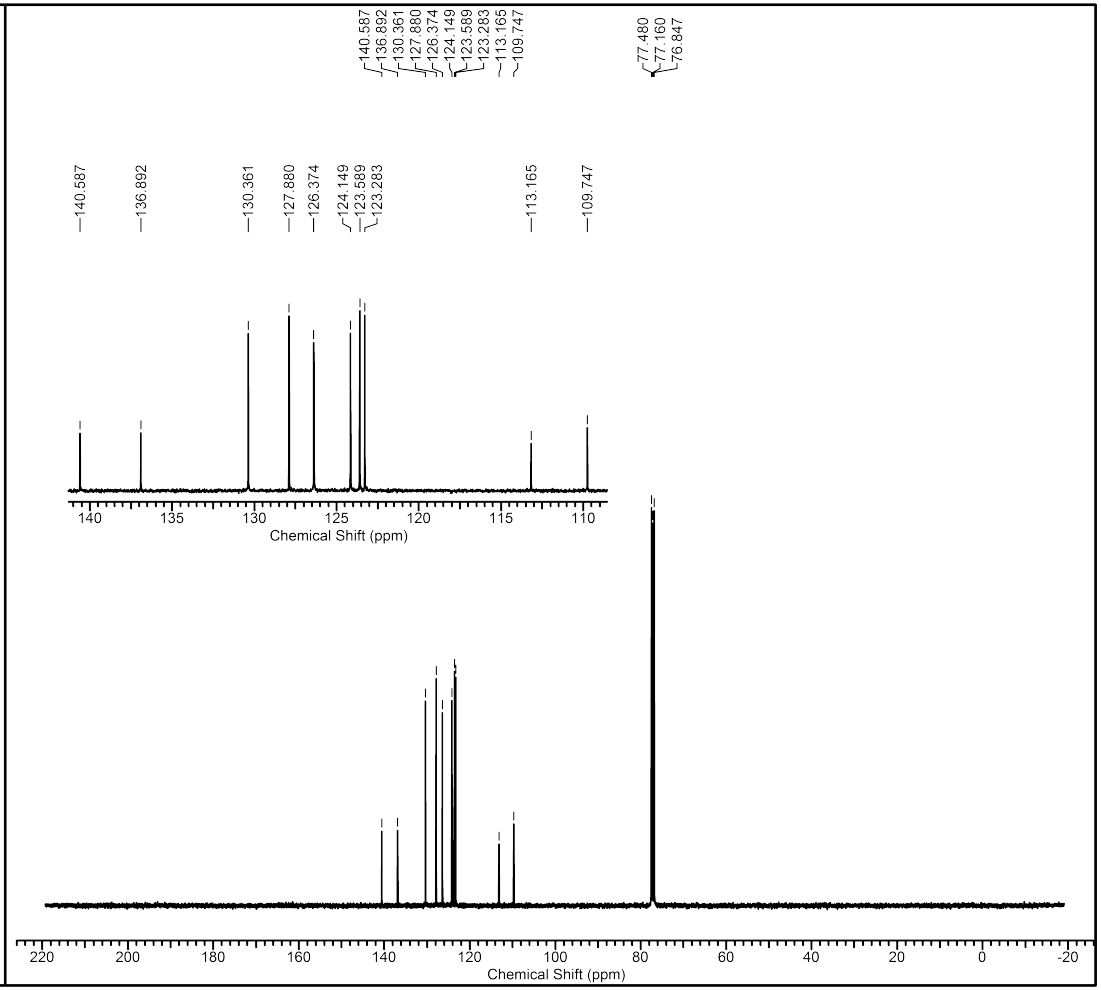
O'Brien™
Group NMR Data

File Name	017-59A_Z
Acquisition Time (sec)	1.3664
Date Stamp	17 May 2013 20:35
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10071.1279
Origin	spect
Receiver Gain	1824.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

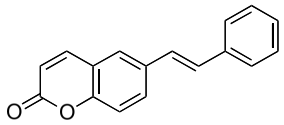


***Z*-70**

O'Brien™
Group NMR Data

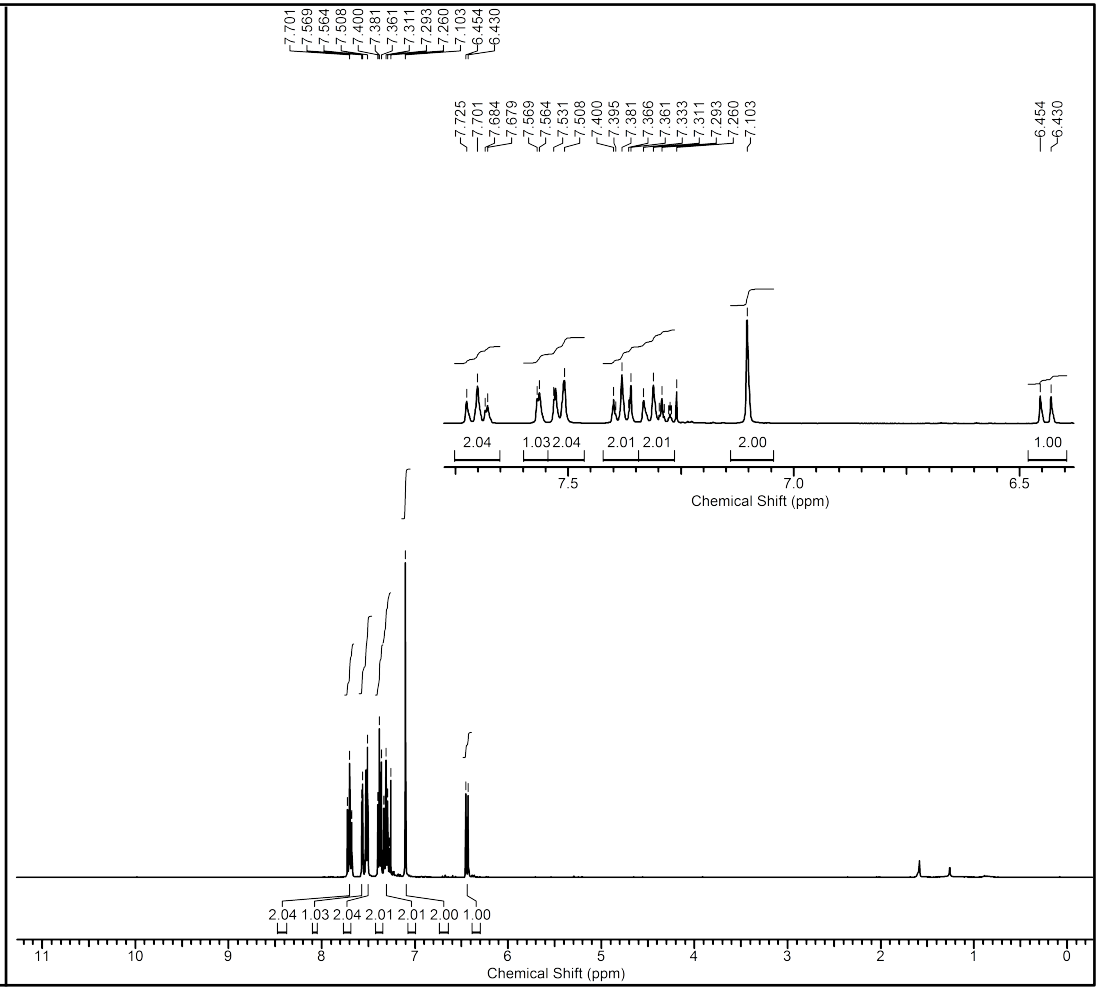


File Name	017-31A_E
Acquisition Time (sec)	3.9584
Date Stamp	15 Mar 2013 22:43
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.7065
Origin	spect
Receiver Gain	228.10
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

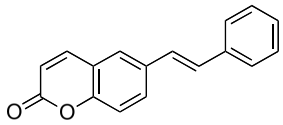


E-**71**

O'Brien™ Group NMR Data

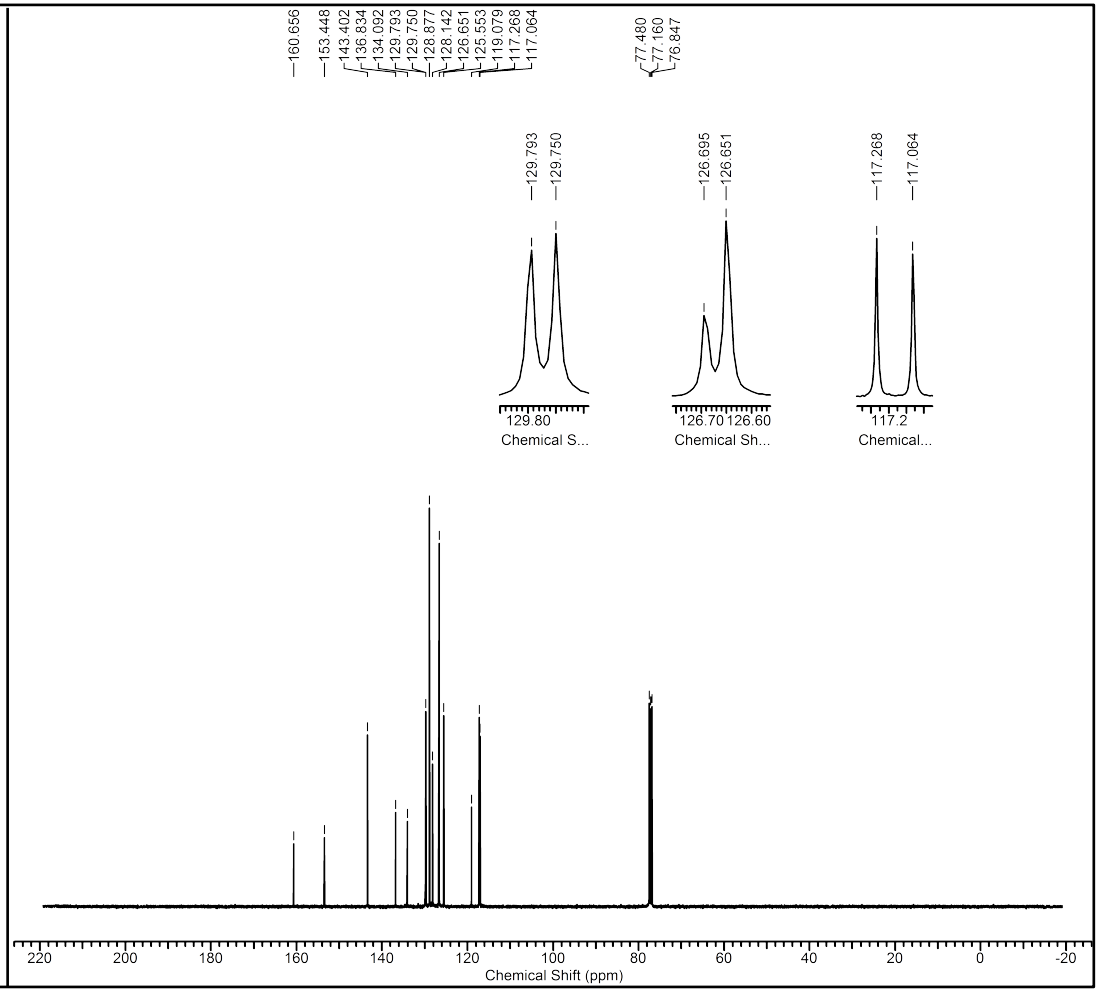


File Name	017-31A_E
Acquisition Time (sec)	1.3664
Date Stamp	19 Mar 2013 18:35
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10067.4688
Origin	spect
Receiver Gain	287.40
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

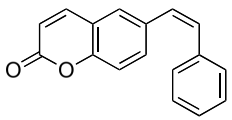


E-71

O'Brien™
Group NMR Data

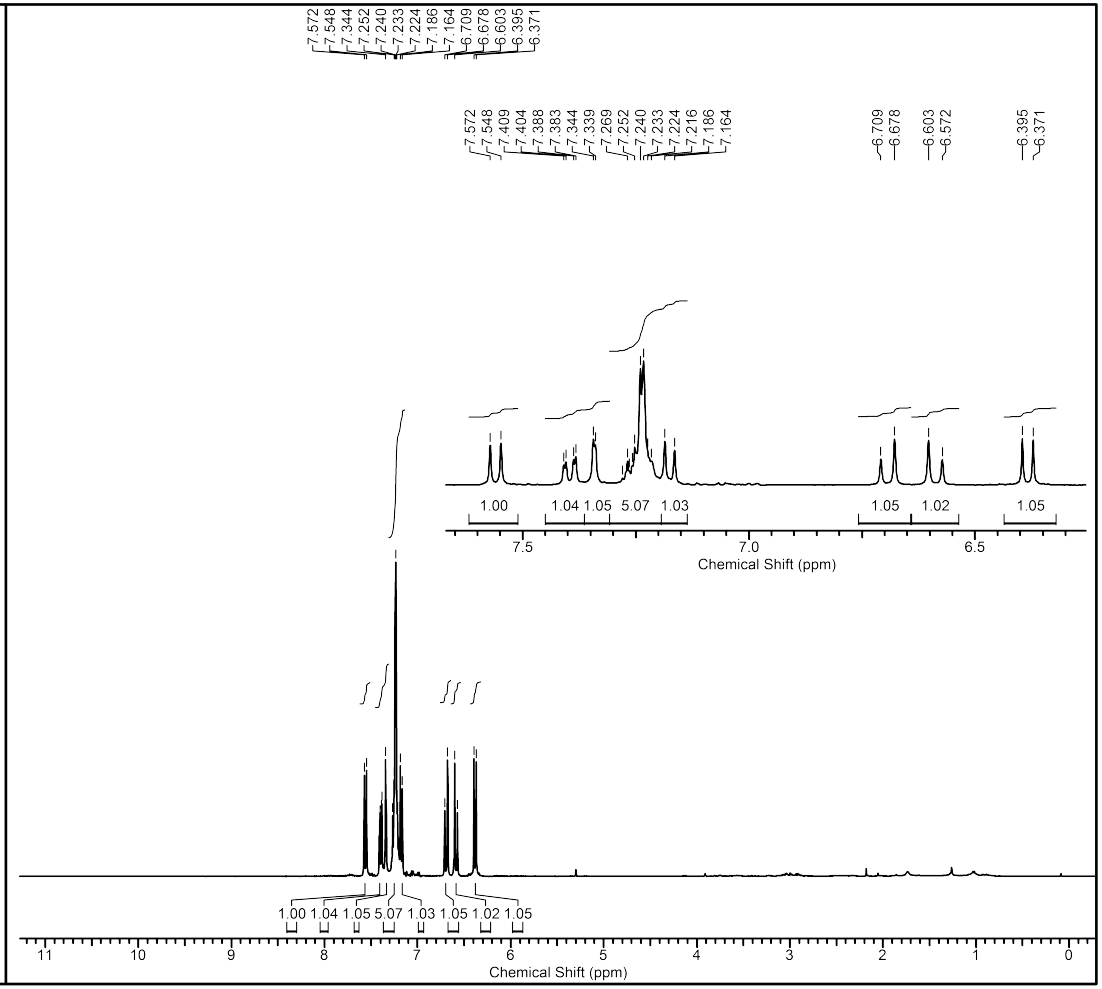


File Name	017-31A_Z
Acquisition Time (sec)	3.9584
Date Stamp	07 Jun 2013 13:03
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2464.6438
Origin	spect
Receiver Gain	101.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

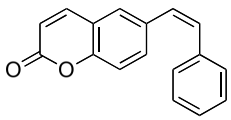


Z-71

O'Brien™
Group NMR Data

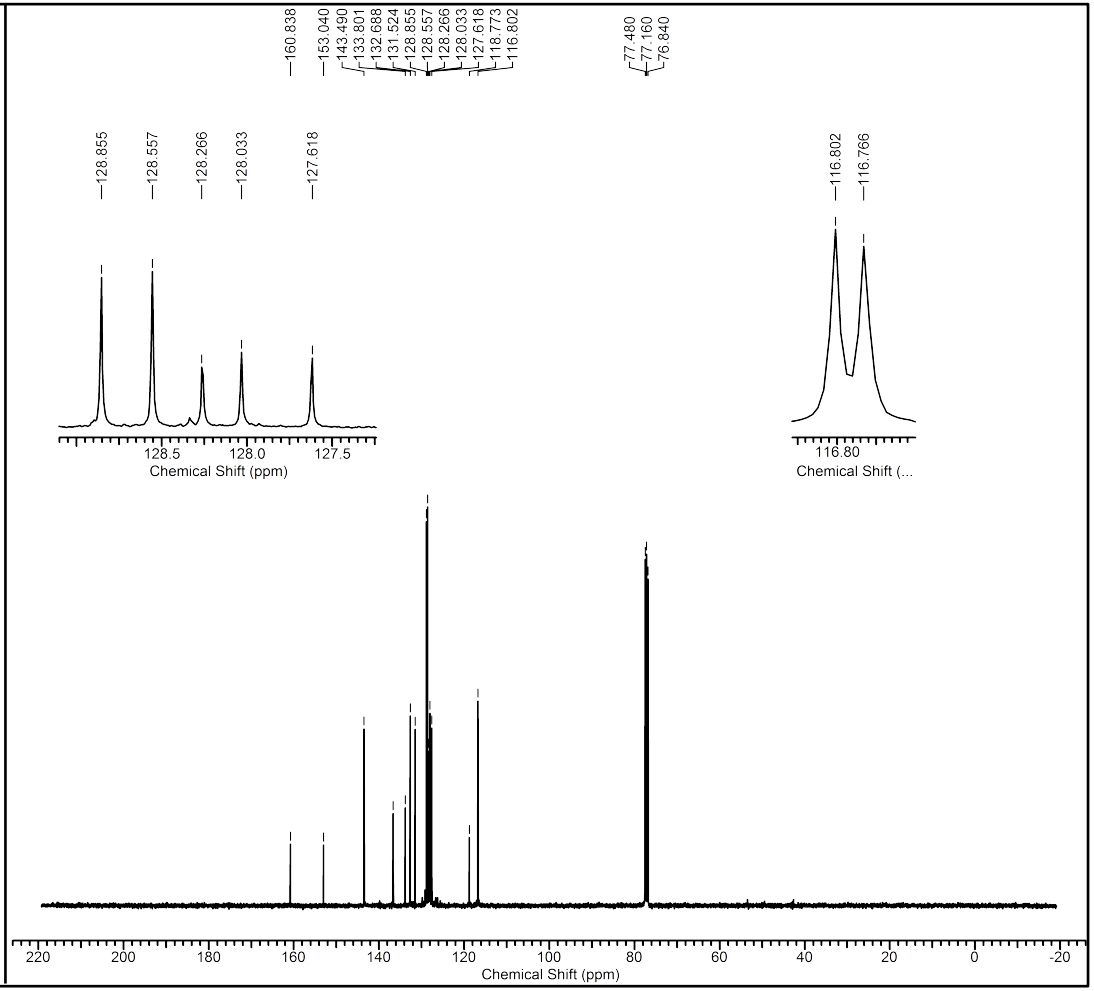


File Name	017-31A_Z
Acquisition Time (sec)	1.3664
Date Stamp	07 Jun 2013 19:10
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10068.2002
Origin	spect
Receiver Gain	13004.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

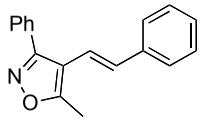


Z-71

O'Brien™
Group NMR Data

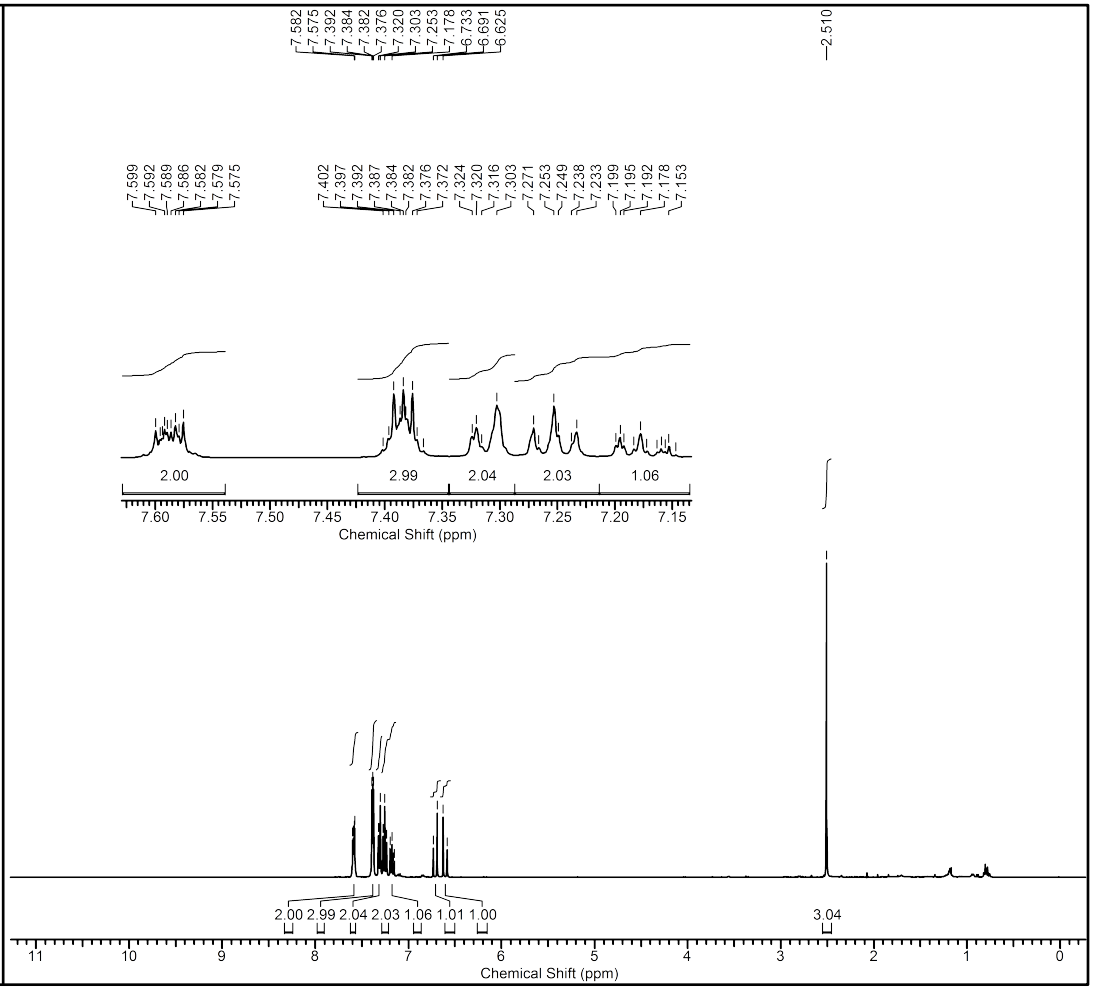


File Name	017-31B_E
Acquisition Time (sec)	3.9584
Date Stamp	12 Jun 2013 16:25
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2418.6697
Origin	spect
Receiver Gain	57.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

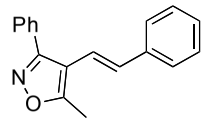


E-72

O'Brien™
Group NMR Data

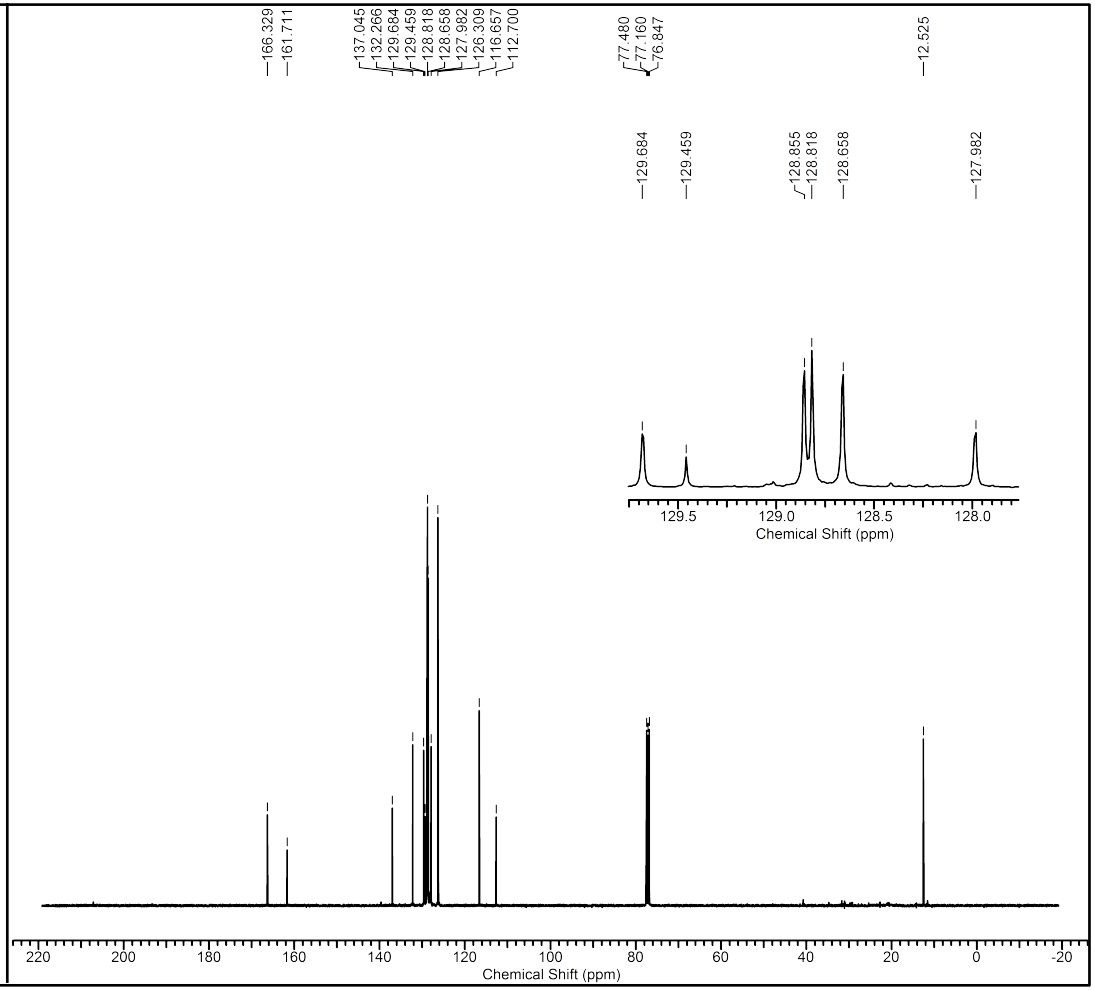


File Name	017-31B_E
Acquisition Time (sec)	1.3664
Date Stamp	13 Jun 2013 07:19
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10063.8096
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

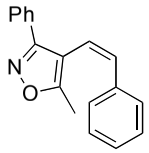


E-**72**

O'Brien™
Group NMR Data

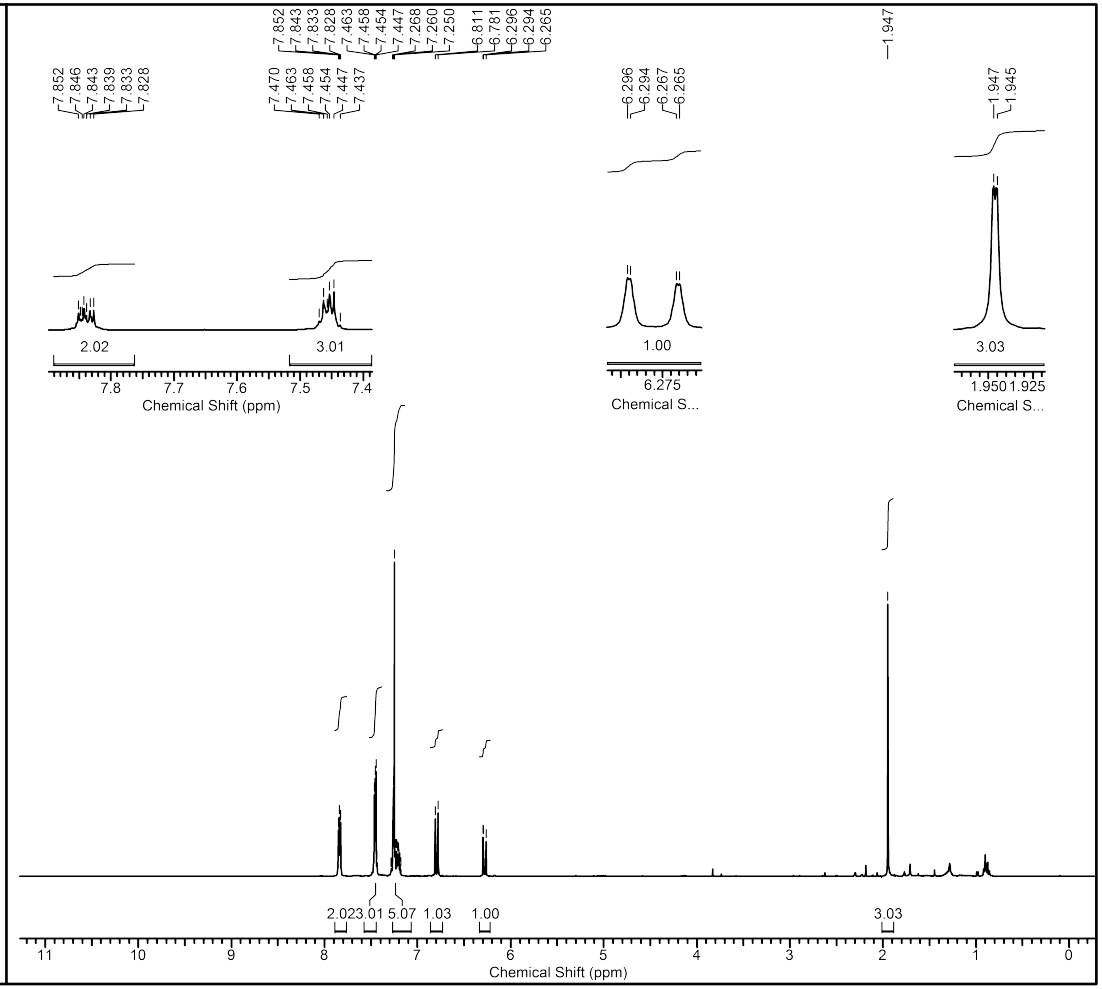


File Name	017-31B_Z
Acquisition Time (sec)	3.9584
Date Stamp	12 Jun 2013 16:13
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2464.7197
Origin	spect
Receiver Gain	80.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

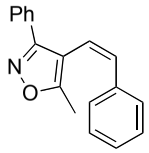


Z-72

O'Brien™
Group NMR Data

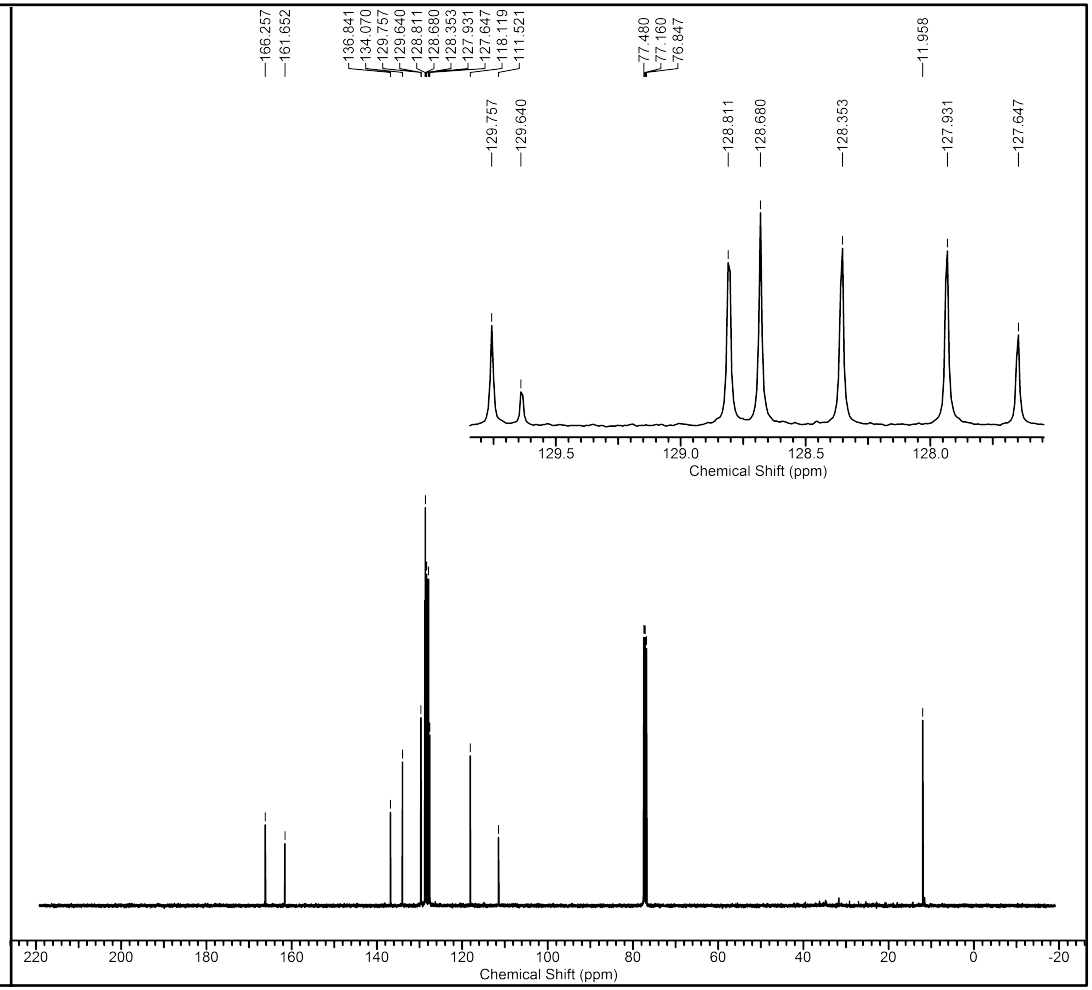


File Name	017-31B_Z
Acquisition Time (sec)	1.3664
Date Stamp	13 Jun 2013 03:57
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10068.9316
Origin	spect
Receiver Gain	3251.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

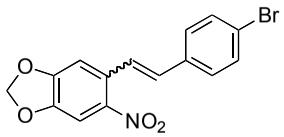


Z-72

O'Brien™
Group NMR Data

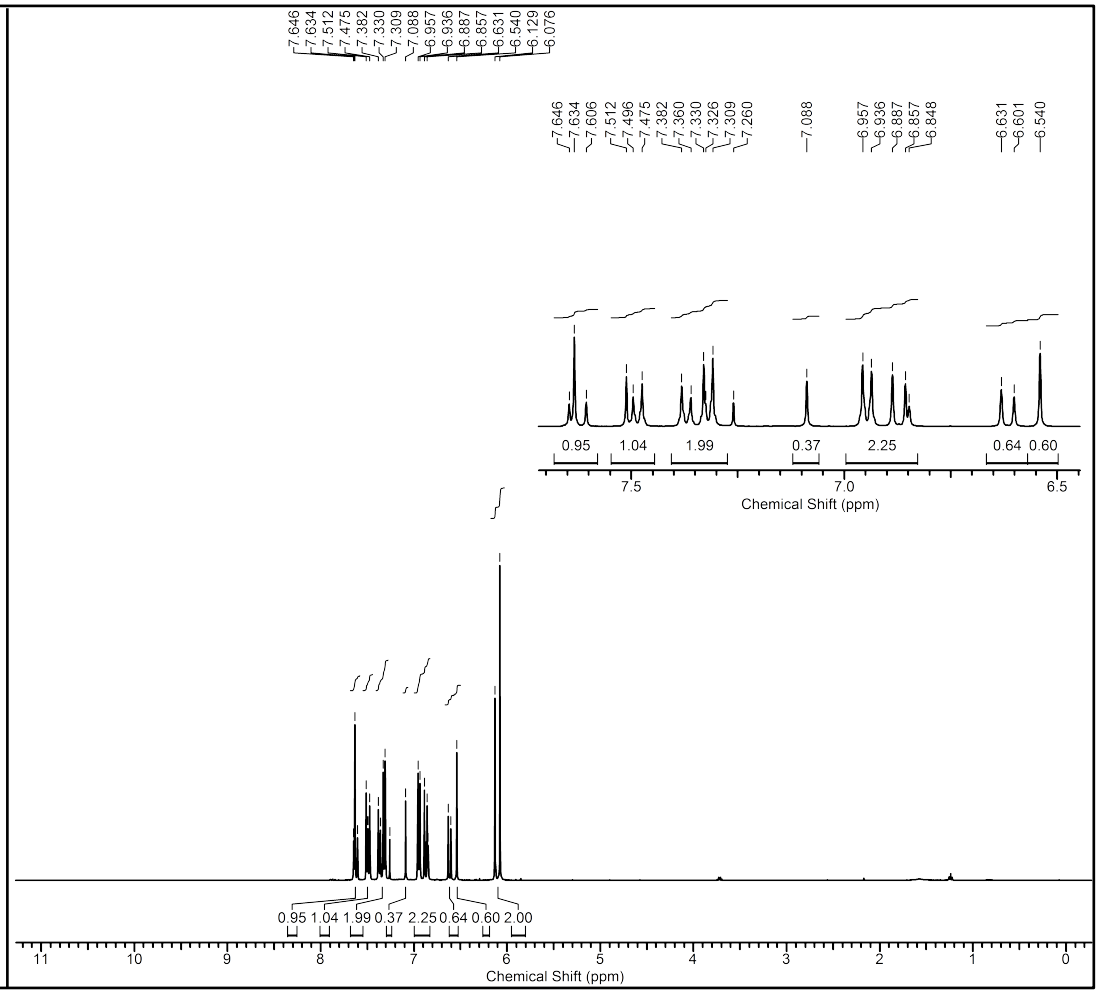


File Name	017-30B_Mix
Acquisition Time (sec)	3.9584
Date Stamp	09 May 2013 17:14
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4539
Origin	spect
Receiver Gain	128.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

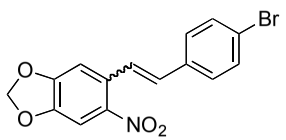


73

O'Brien™
Group NMR Data

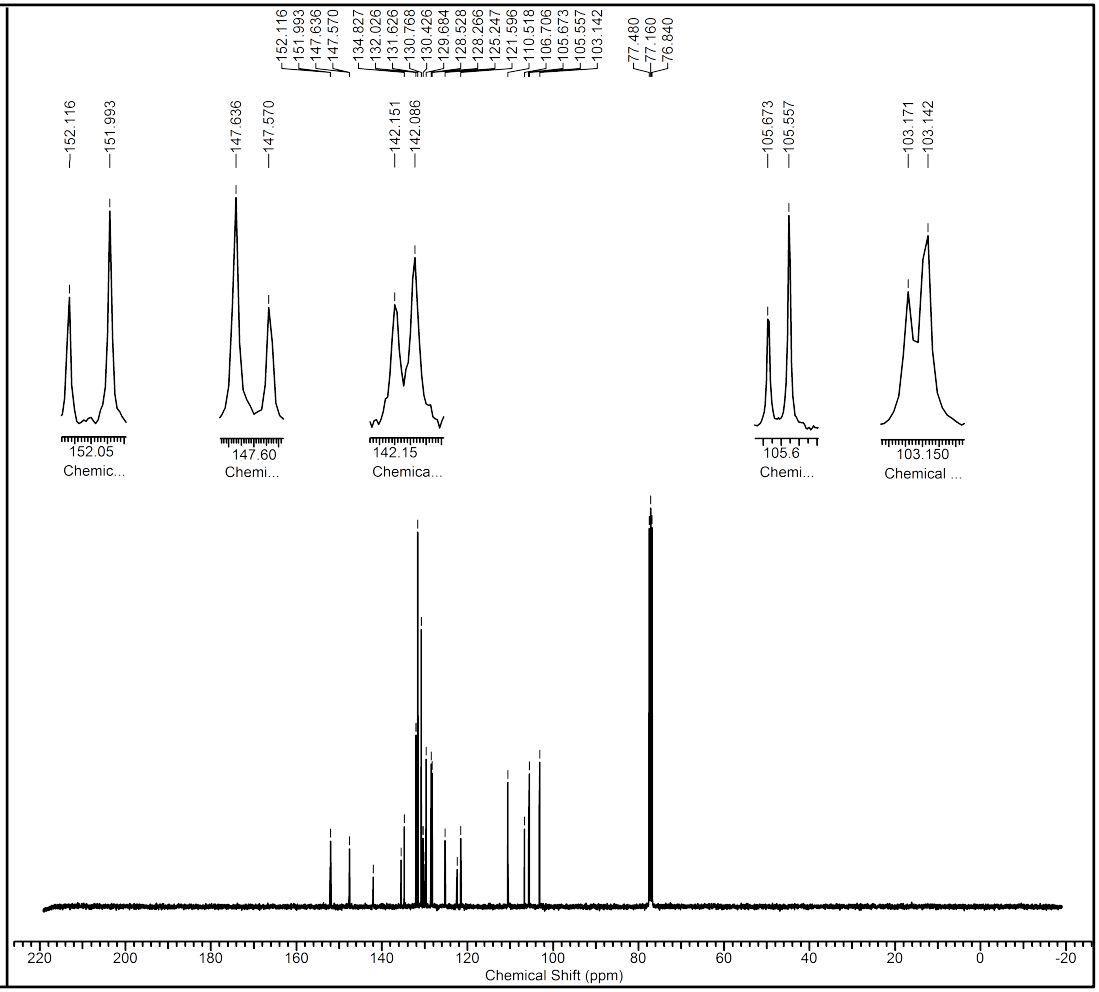


File Name	017-30B_Mix
Acquisition Time (sec)	1.3664
Date Stamp	09 May 2013 18:14
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10069.6641
Origin	spect
Receiver Gain	2048.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

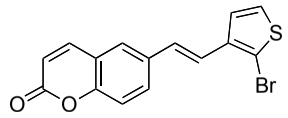


73

O'Brien™
Group NMR Data

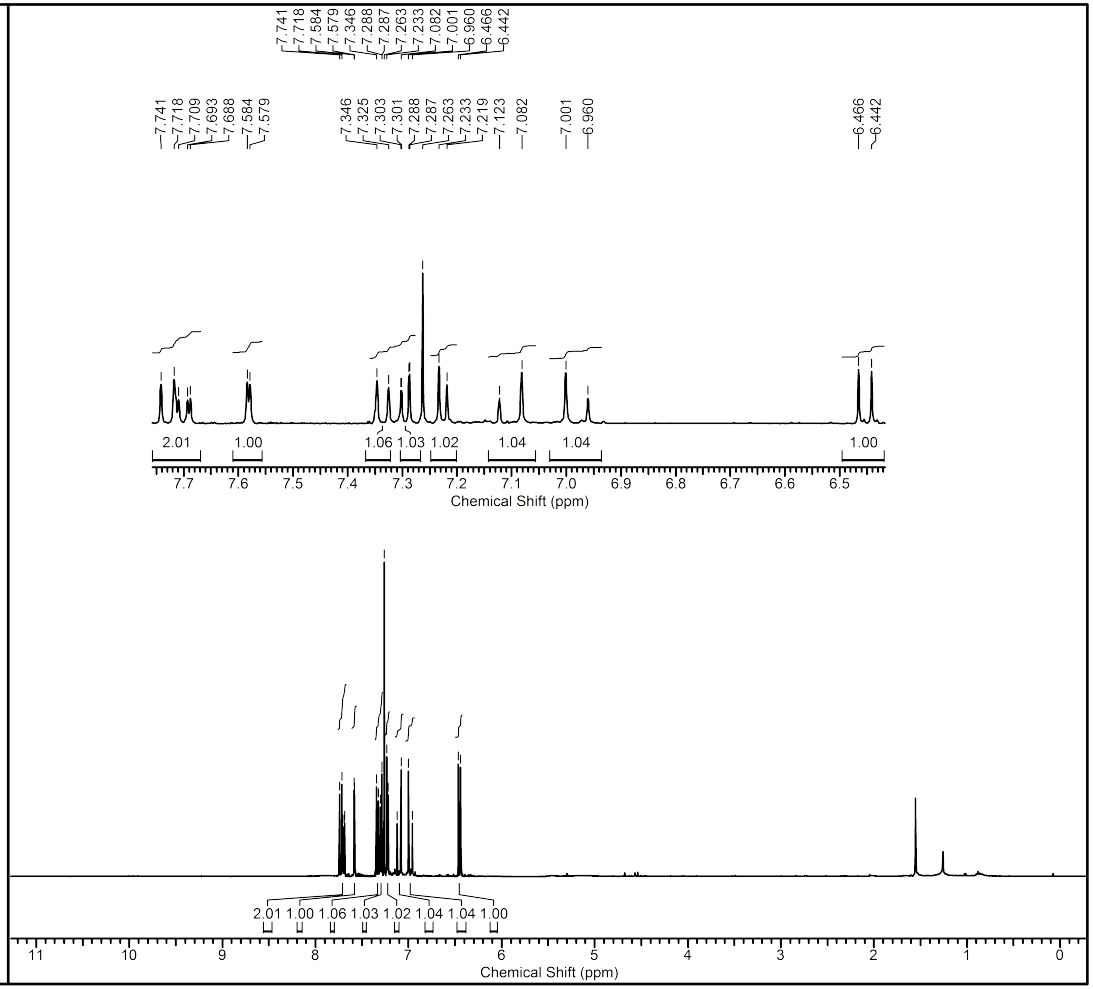


File Name	017-33_E
Acquisition Time (sec)	3.9584
Date Stamp	21 Mar 2013 15:08
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2462.8750
Origin	spect
Receiver Gain	456.10
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

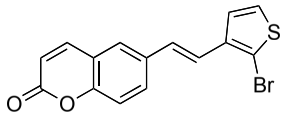


***E*-74**

O'Brien™
Group NMR Data

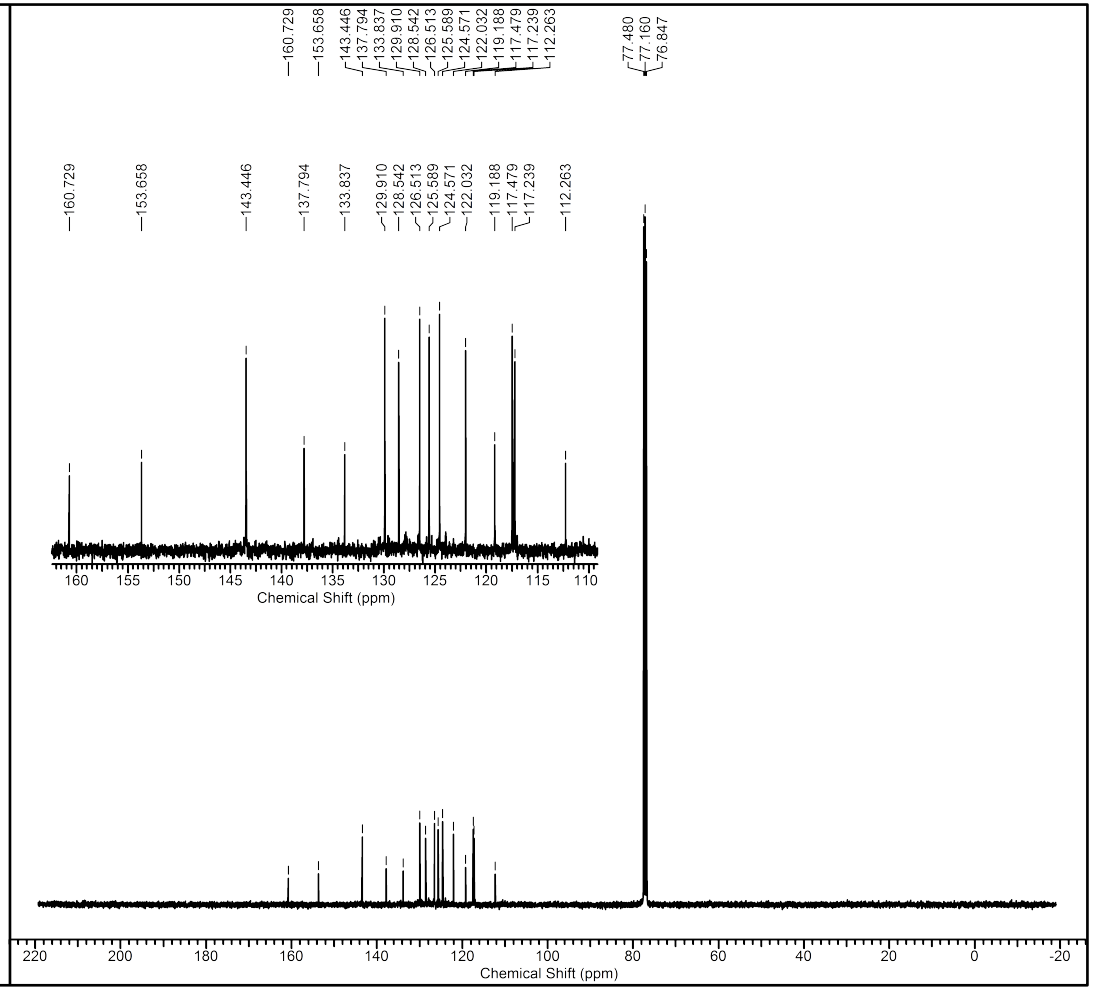


File Name	017-33_E
Acquisition Time (sec)	1.3664
Date Stamp	20 Jun 2013 23:06
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	2048
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10072.5908
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

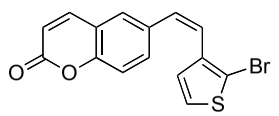


E-**74**

O'Brien™
Group NMR Data

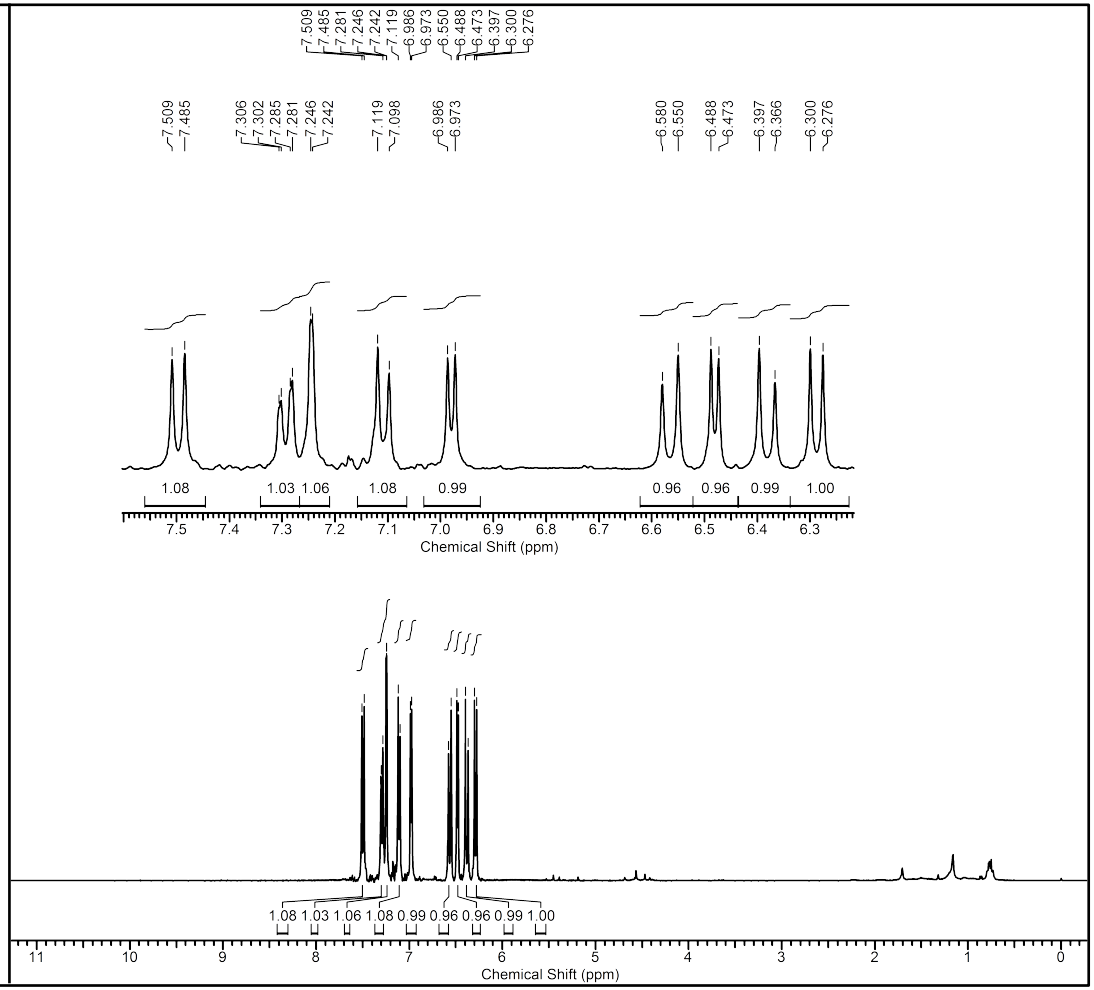


File Name	017-33_Z
Acquisition Time (sec)	3.9584
Date Stamp	25 Mar 2013 19:29
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2427.7891
Origin	spect
Receiver Gain	50.80
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

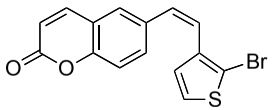


Z-74

O'Brien™
Group NMR Data

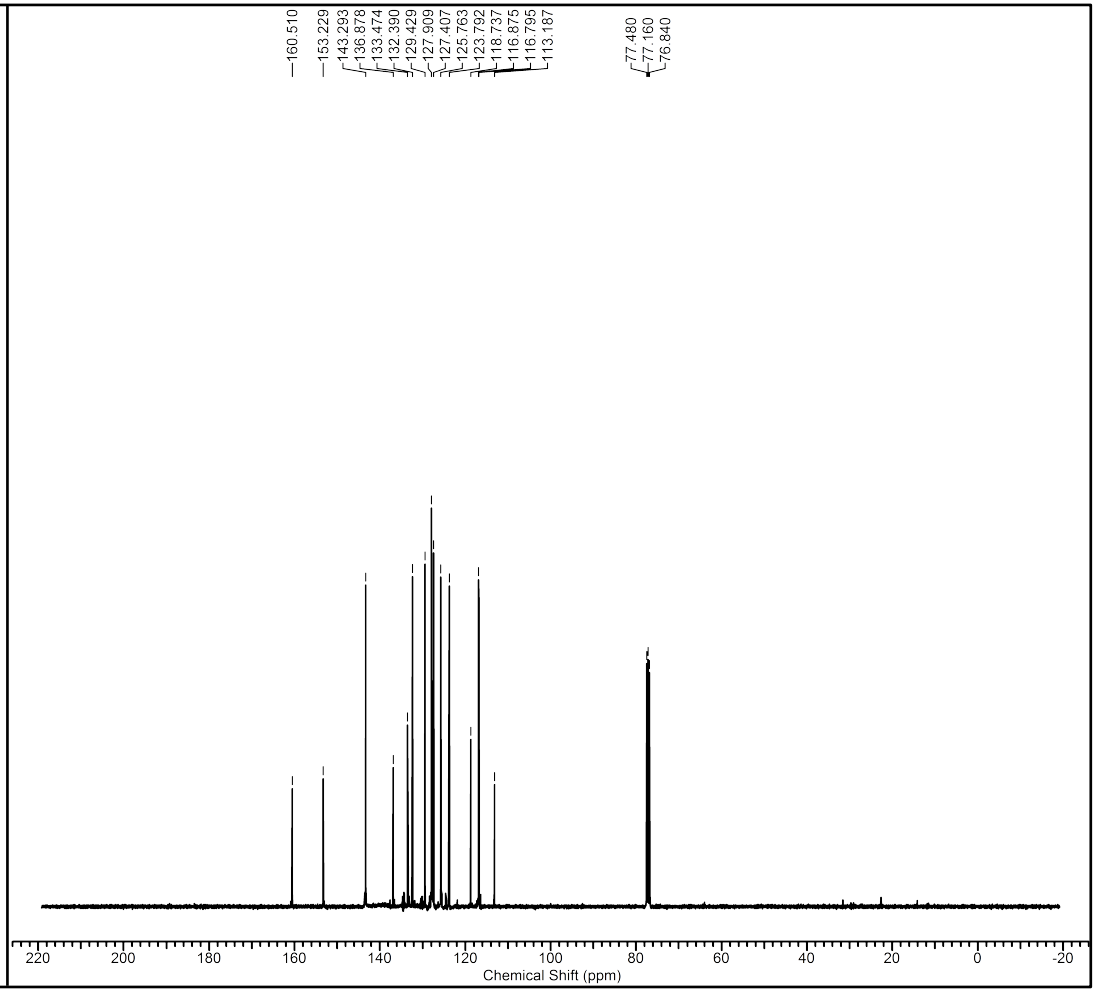


File Name	017-33_Z
Acquisition Time (sec)	1.3664
Date Stamp	25 Mar 2013 20:28
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10060.8818
Origin	spect
Receiver Gain	2580.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

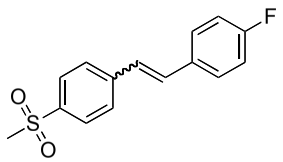


Z-**74**

O'Brien™
Group NMR Data

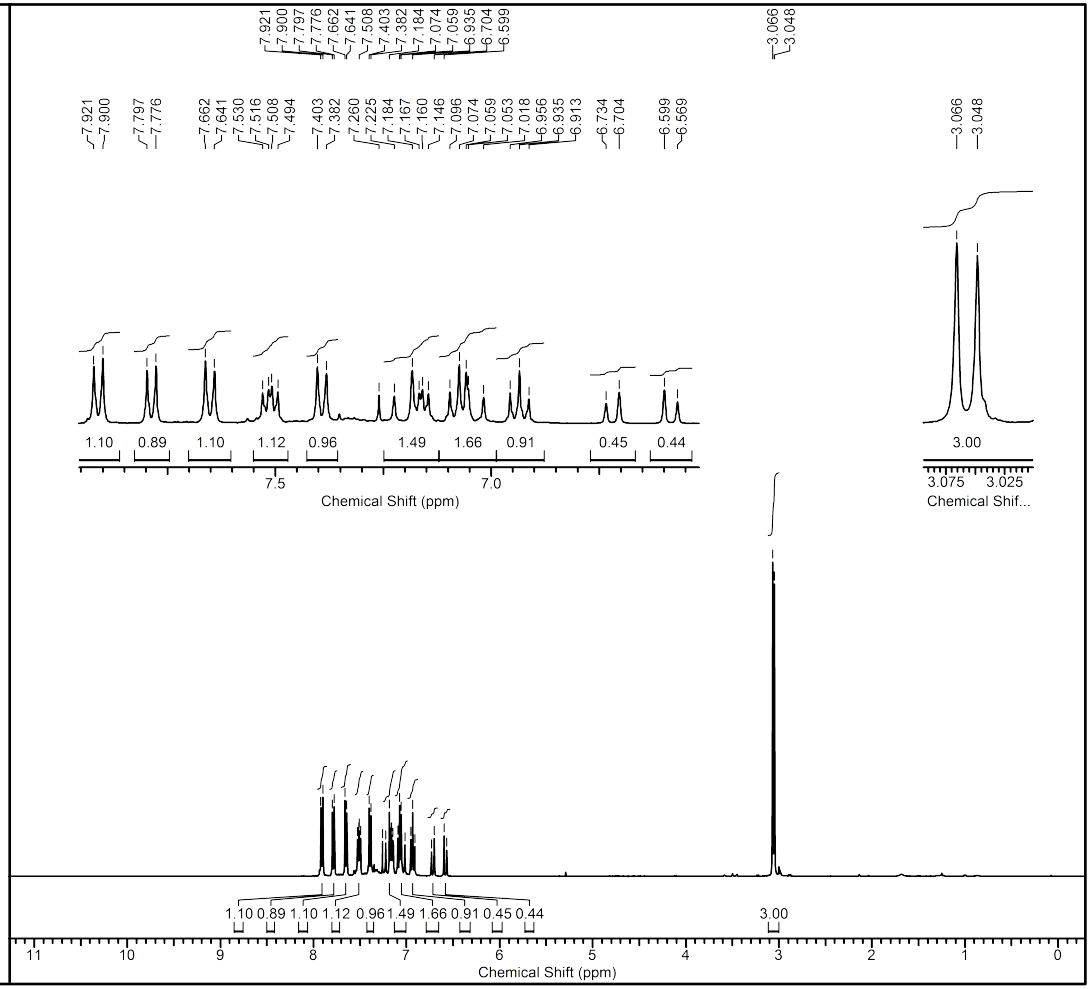


File Name	017-53A
Acquisition Time (sec)	3.9584
Date Stamp	08 May 2013 17:29
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	90.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

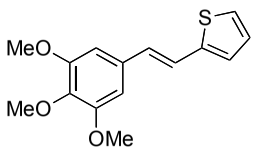


75

O'Brien™
Group NMR Data

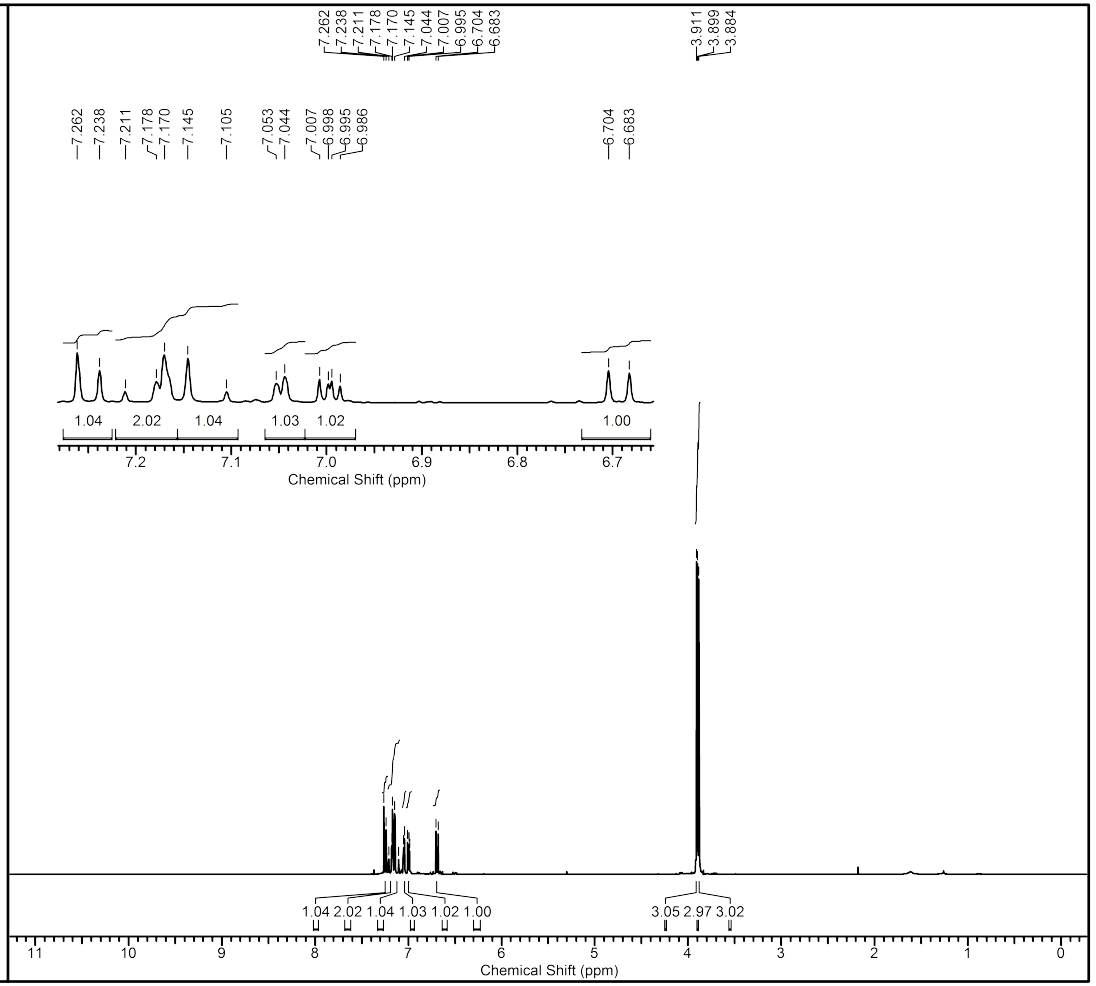


File Name	017-59B_E
Acquisition Time (sec)	3.9584
Date Stamp	08 May 2013 14:52
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2462.1172
Origin	spect
Receiver Gain	143.70
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

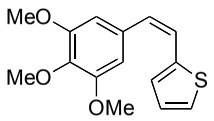


***E*-76**

O'Brien™
Group NMR Data

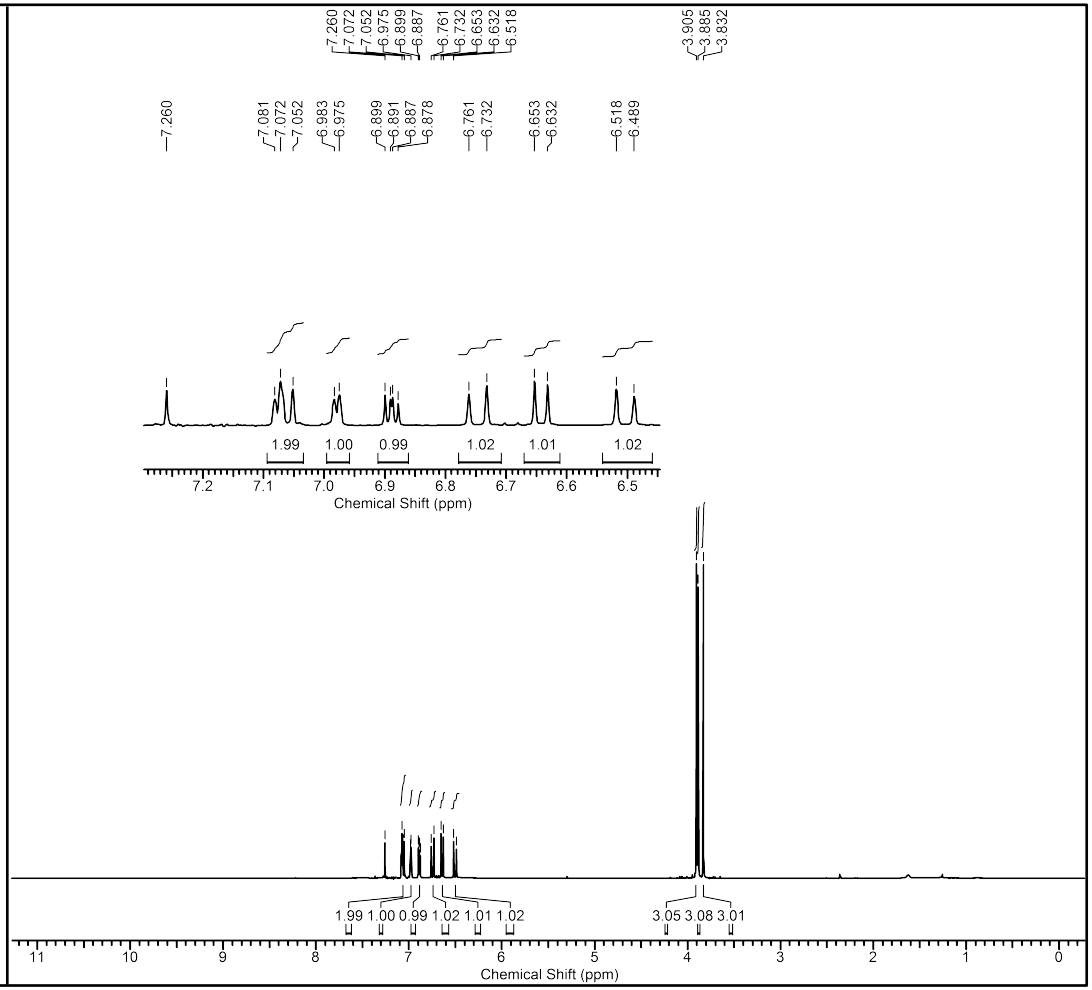


File Name	017-59B_Z
Acquisition Time (sec)	3.9584
Date Stamp	08 May 2013 14:43
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.2012
Origin	spect
Receiver Gain	114.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

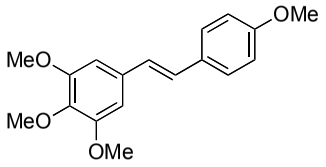


***Z*-76**

O'Brien™
Group NMR Data

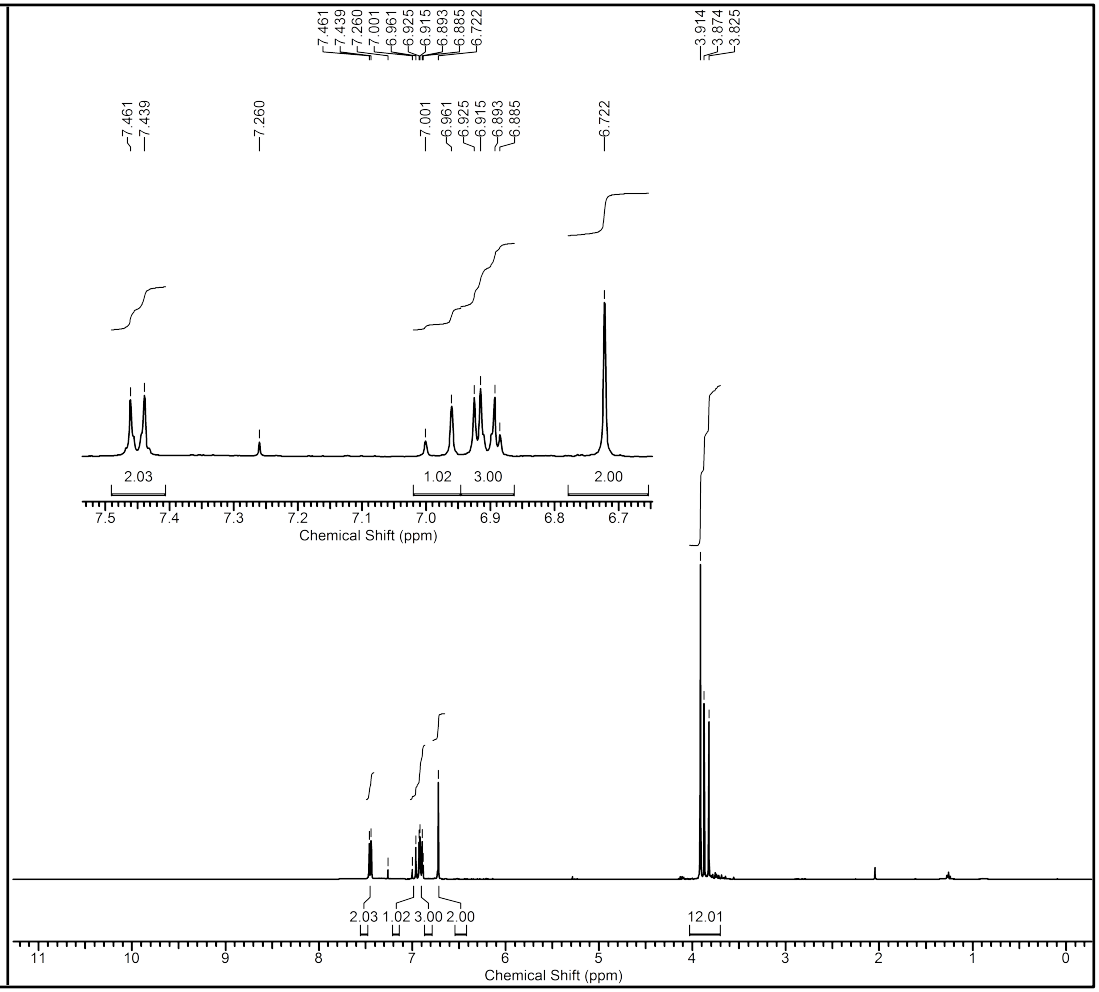


File Name	017-58A_E
Acquisition Time (sec)	3.9584
Date Stamp	17 May 2013 13:45
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	57.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

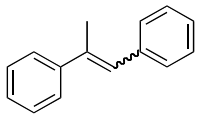


E-77

O'Brien™
Group NMR Data

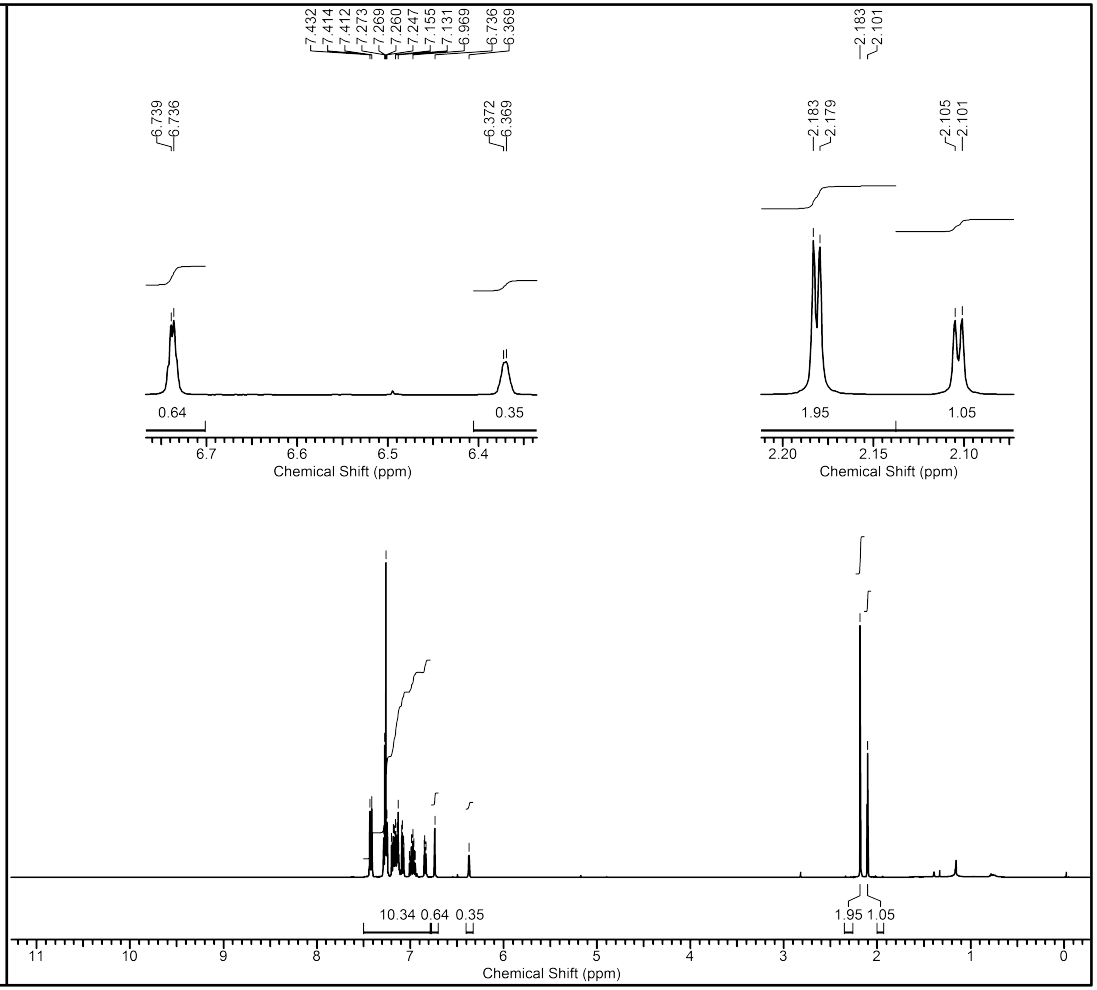


File Name	016-88
Acquisition Time (sec)	3.9584
Date Stamp	03 Apr 2013 11:48
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2409.9180
Origin	spect
Receiver Gain	114.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

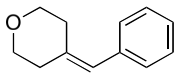


78

O'Brien™
Group NMR Data

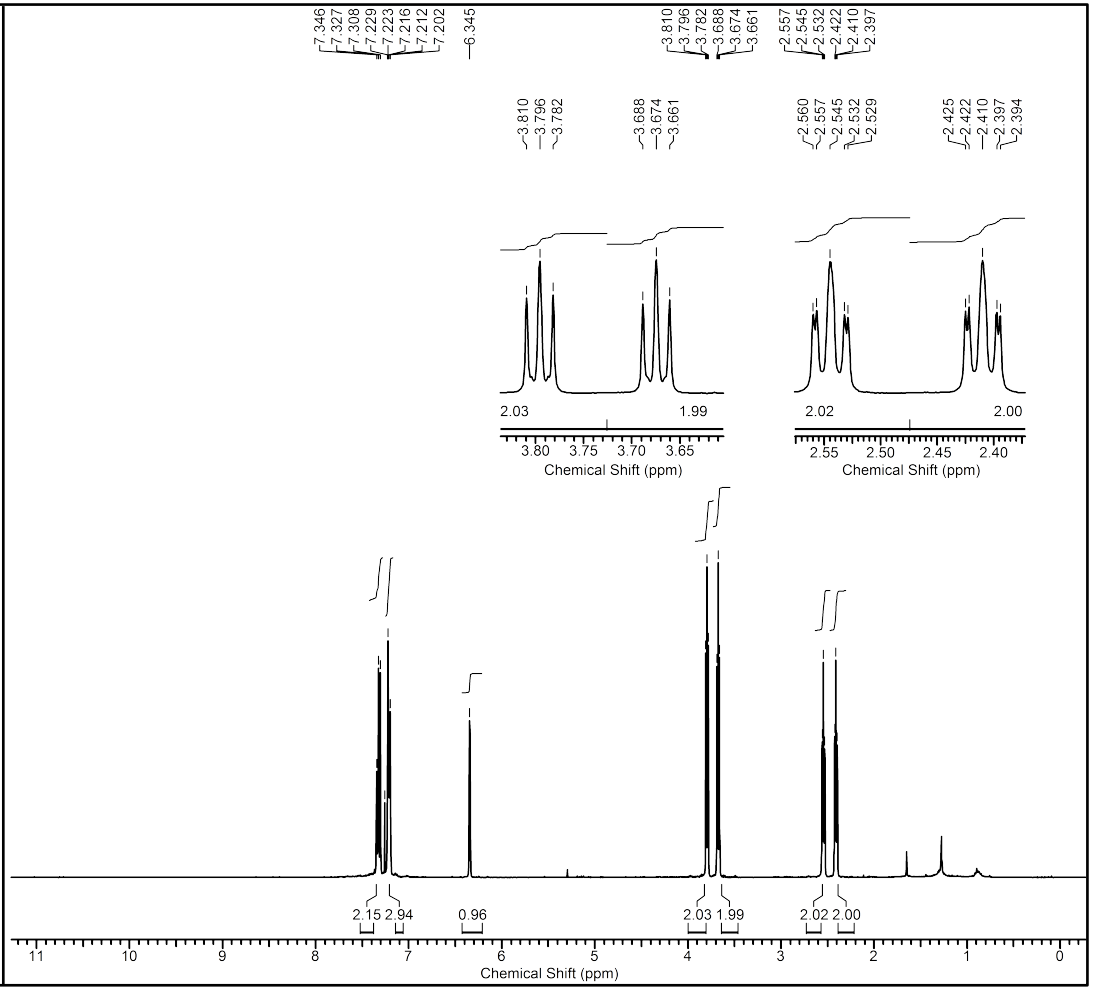


File Name	016-83
Acquisition Time (sec)	3.9584
Date Stamp	11 Apr 2013 11:16
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	25.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4543
Origin	spect
Receiver Gain	80.60
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

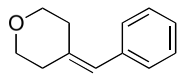


79

O'Brien™ Group NMR Data

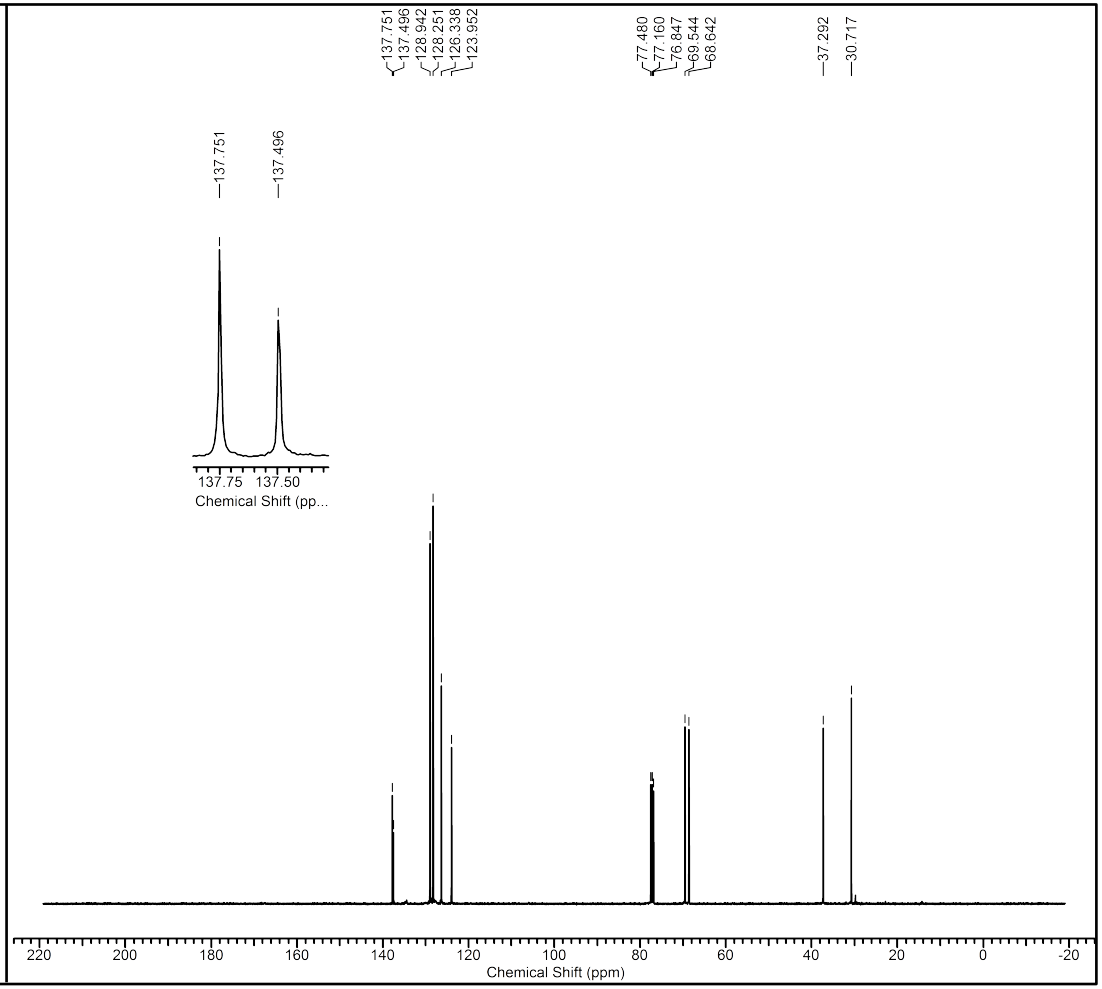


File Name	016-83
Acquisition Time (sec)	1.3664
Date Stamp	25 Jun 2013 07:11
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10064.5410
Origin	spect
Receiver Gain	2896.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

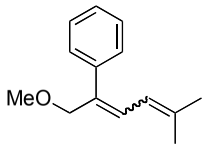


79

O'Brien™
Group NMR Data

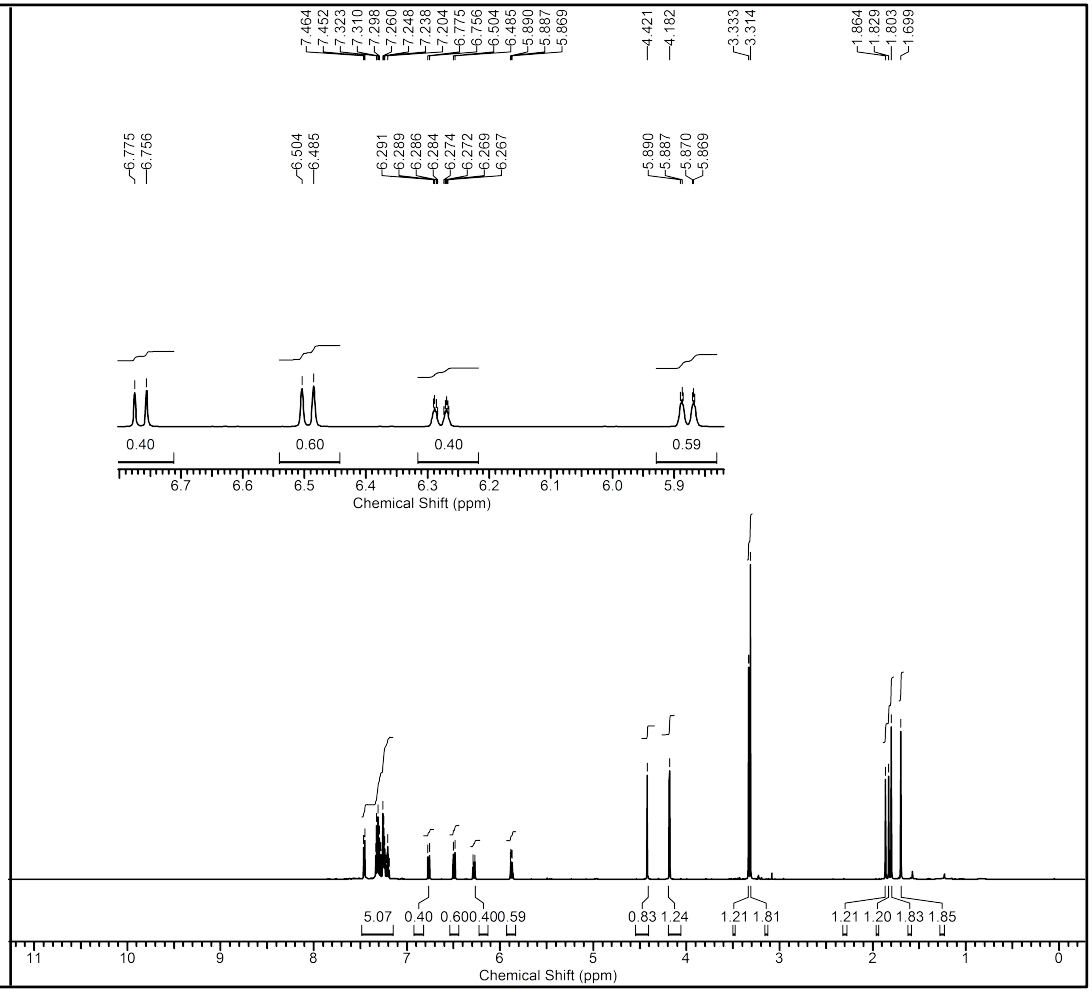


File Name	020-37
Acquisition Time (sec)	3.9584
Date Stamp	21 Jun 2013 22:07
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	19.860
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	3653.4421
Origin	spect
Receiver Gain	64.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

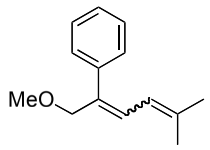


80

O'Brien™
Group NMR Data

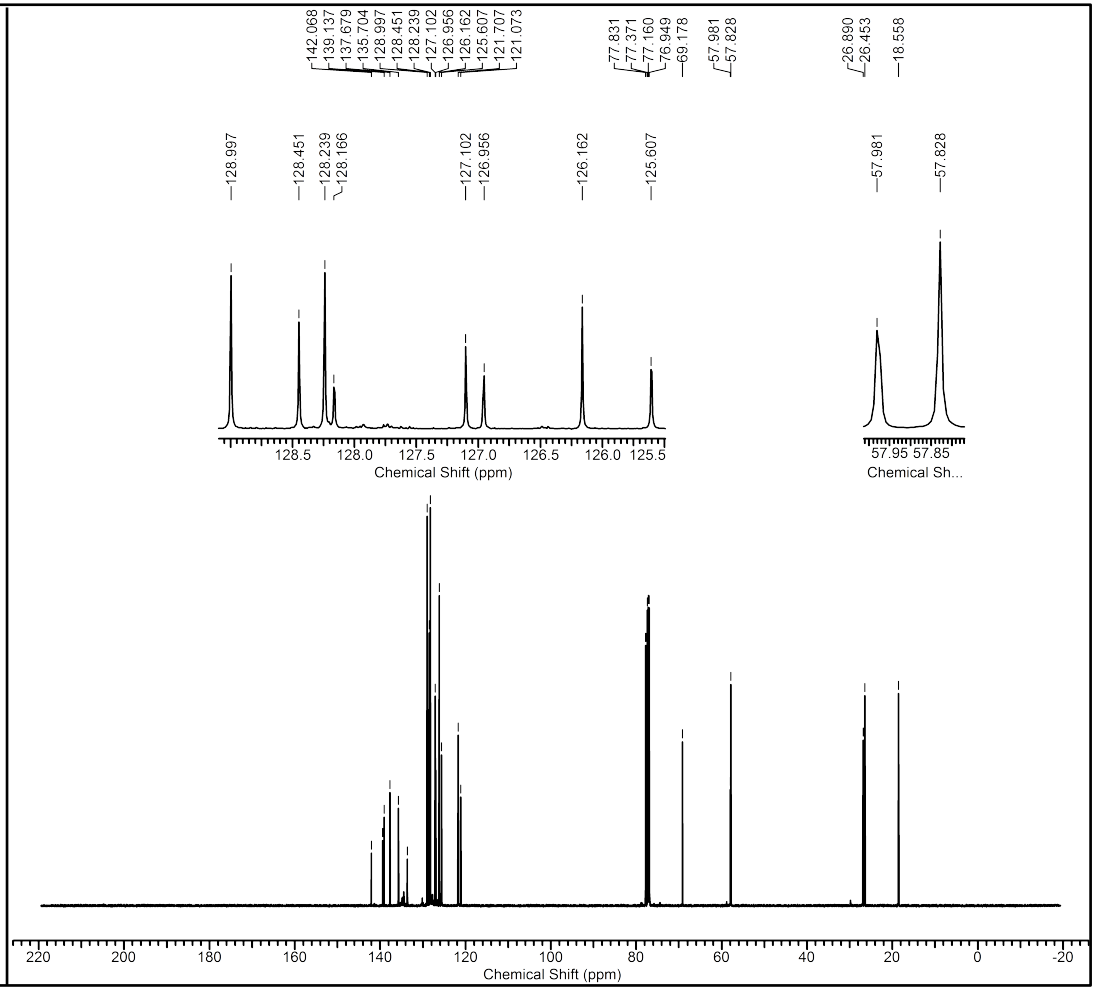


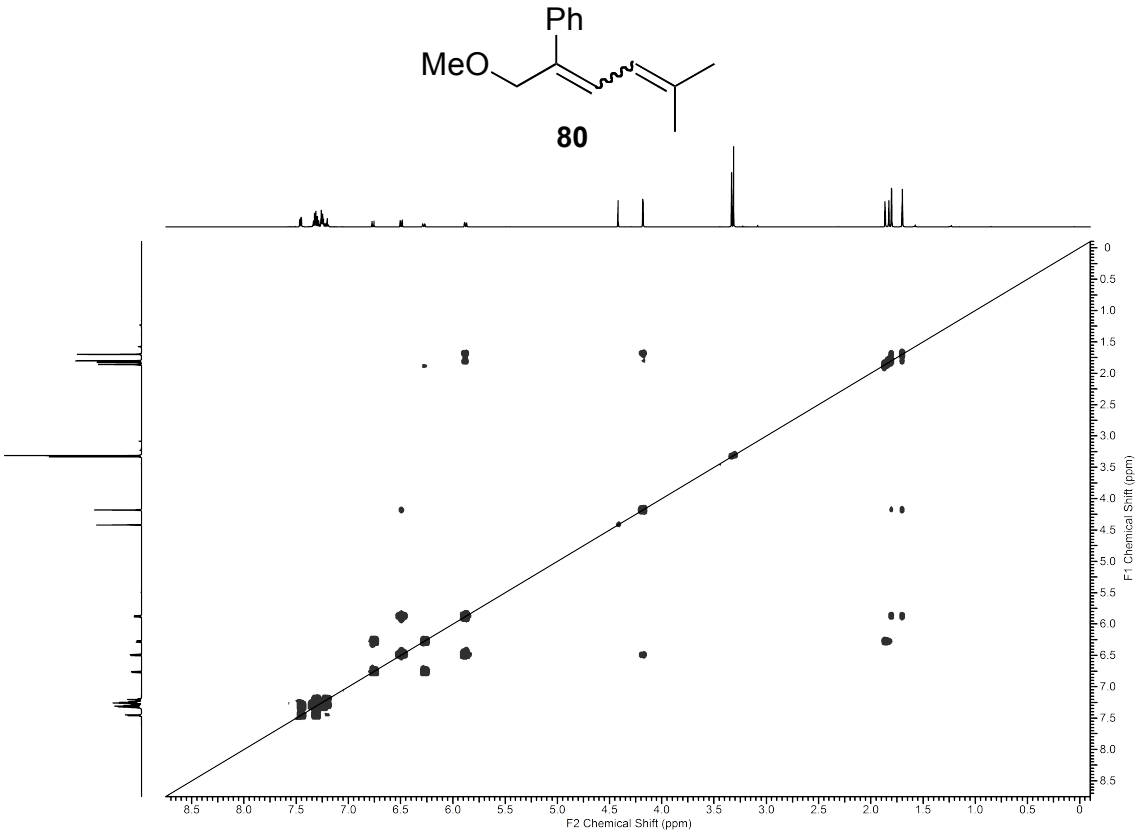
File Name	020-37
Acquisition Time (sec)	1.3664
Date Stamp	22 Jun 2013 02:08
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.860
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	15105.3916
Origin	spect
Receiver Gain	2050.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08



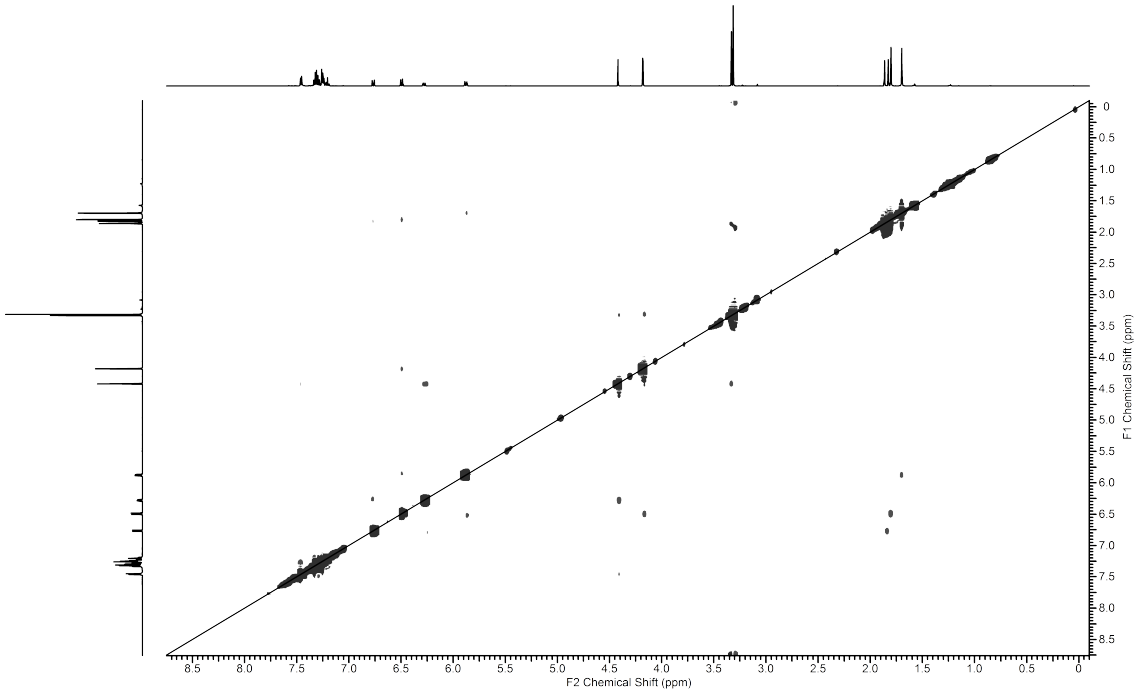
80

O'Brien™
Group NMR Data



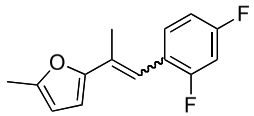


$^1H/^1H$ COSY (600 MHz, $CDCl_3$)



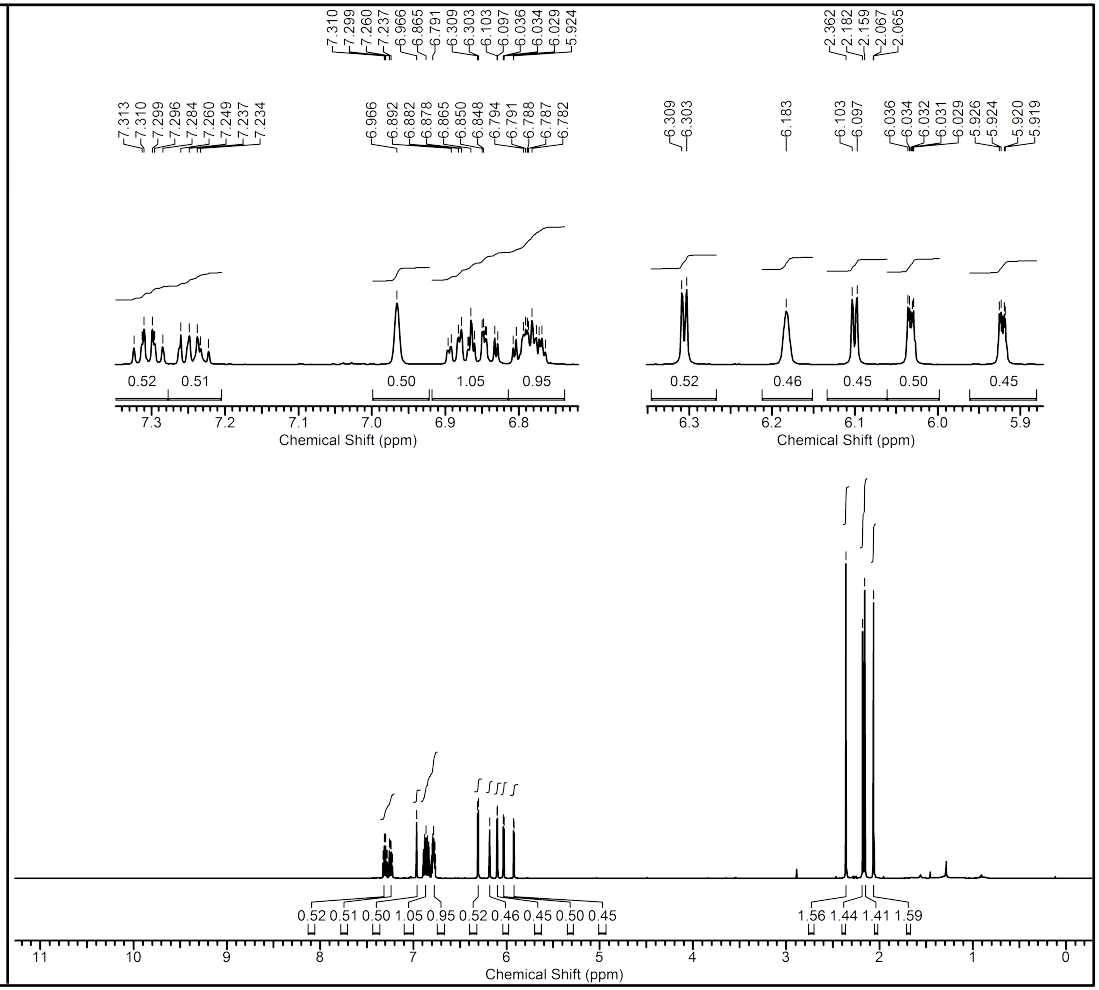
$^1H/^1H$ NOESY (600 MHz, $CDCl_3$)

File Name	020-43B
Acquisition Time (sec)	2.6564
Date Stamp	21 Jun 2013 17:57
Frequency (MHz)	600.32
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.060
Nucleus	1H
Points Count	32768
Number of Transients	128
Pulse Sequence	zg30
Spectrum Offset (Hz)	3686.9468
Origin	spect
Receiver Gain	71.80
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	12335.53
Sweep Width (Hz)	12335.15

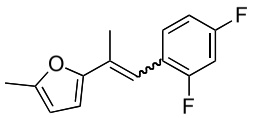


81

O'Brien™
Group NMR Data

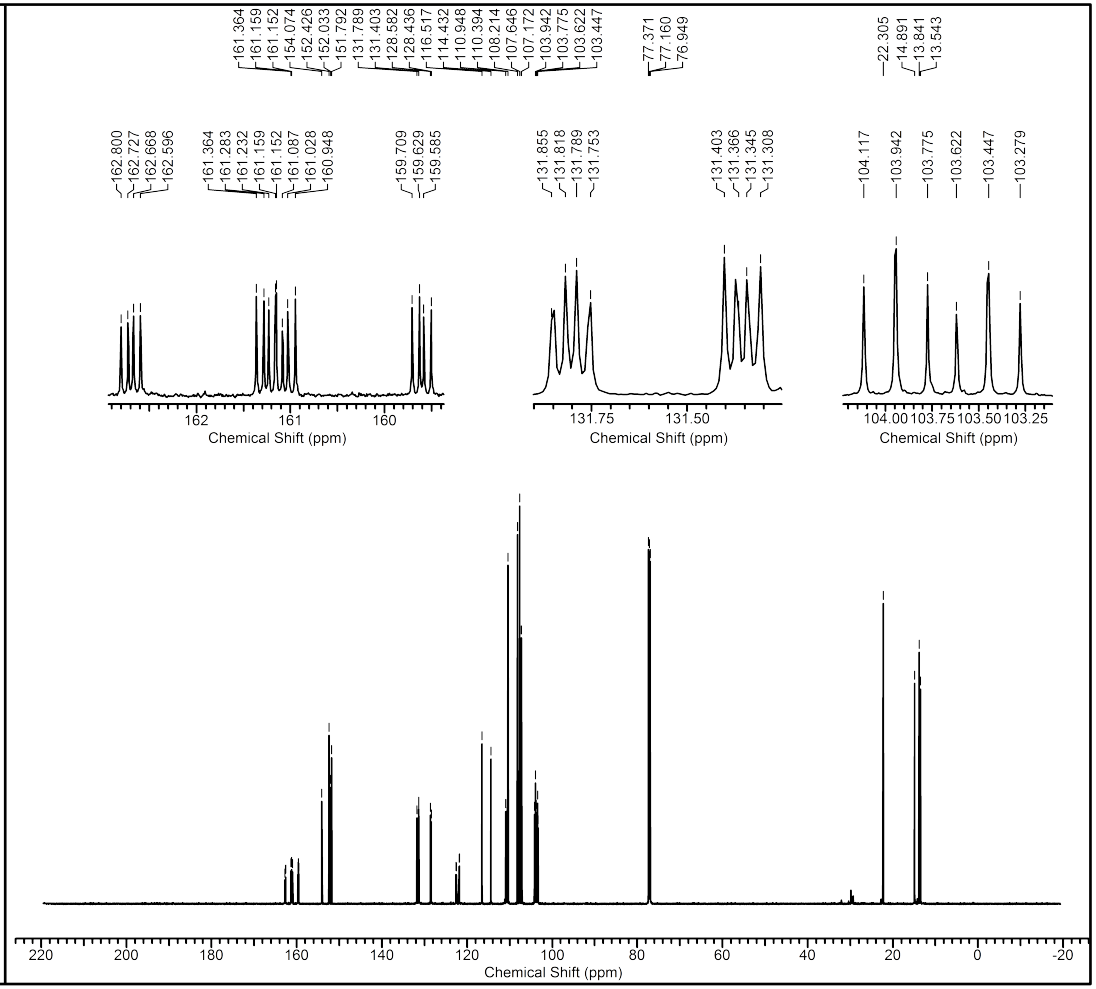


File Name	020-43B
Acquisition Time (sec)	0.9088
Date Stamp	26 Jun 2013 04:07
Frequency (MHz)	150.95
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.860
Nucleus	13C
Points Count	32768
Number of Transients	4096
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	15109.7939
Origin	spect
Receiver Gain	2050.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	36057.69
Sweep Width (Hz)	36056.59

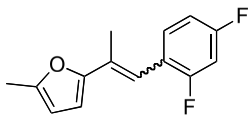


81

O'Brien™
Group NMR Data

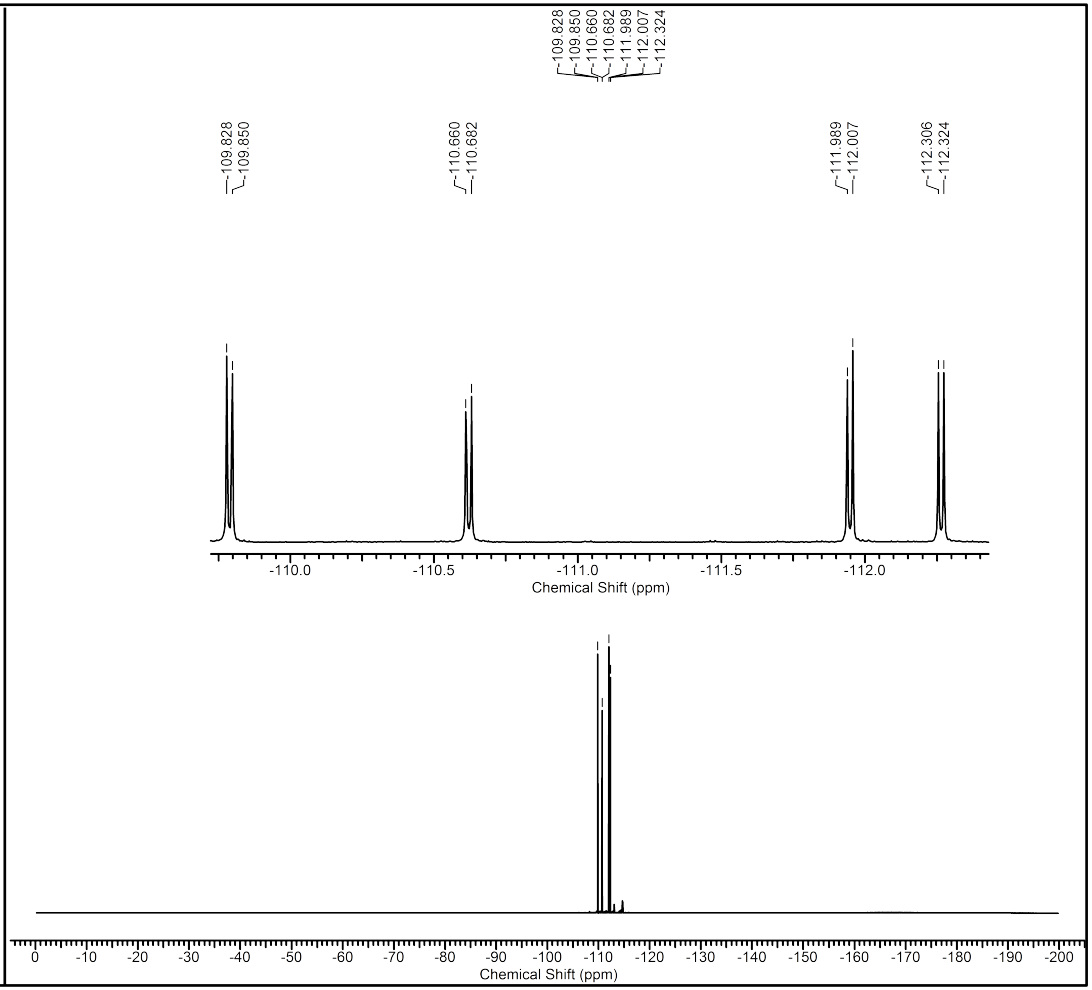


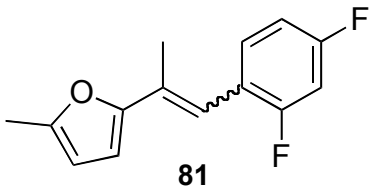
File Name	020-43B
Acquisition Time (sec)	0.8716
Date Stamp	21 Jun 2013 12:18
Frequency (MHz)	376.50
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	19F
Points Count	65536
Number of Transients	16
Pulse Sequence	zgfhigqn
Spectrum Offset (Hz)	-37649.6211
Origin	spect
Receiver Gain	362.00
Spectrum Type	STANDARD
Original Points Count	65536
SW(cyclical) (Hz)	75187.97
Sweep Width (Hz)	75186.82



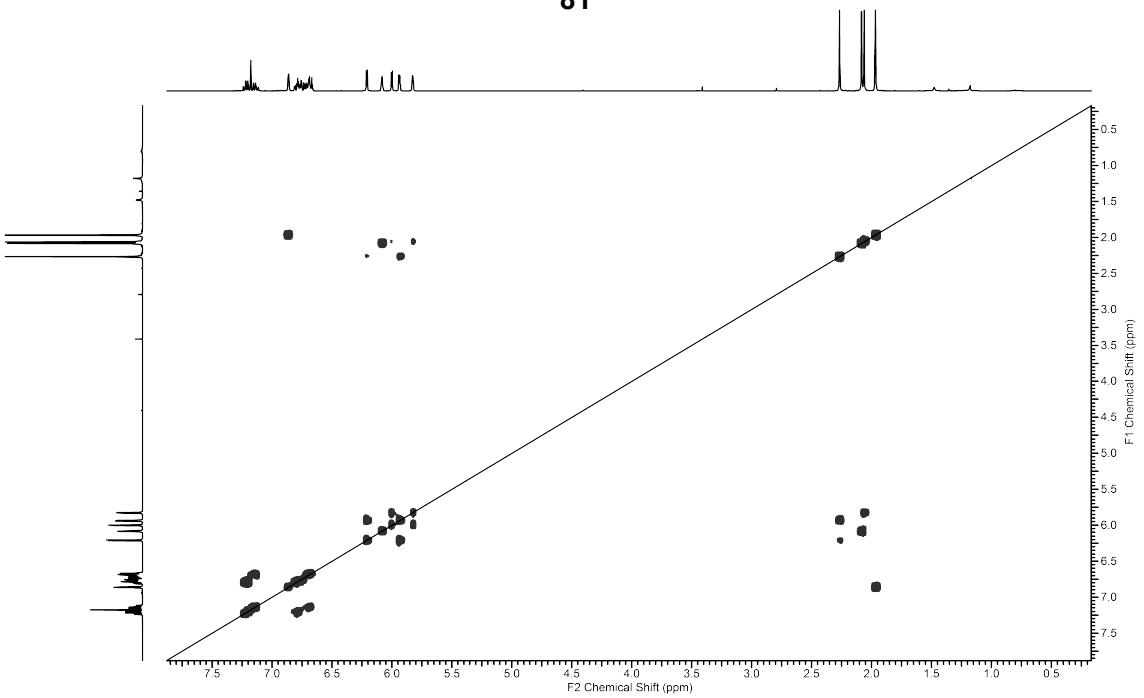
81

O'Brien™
Group NMR Data

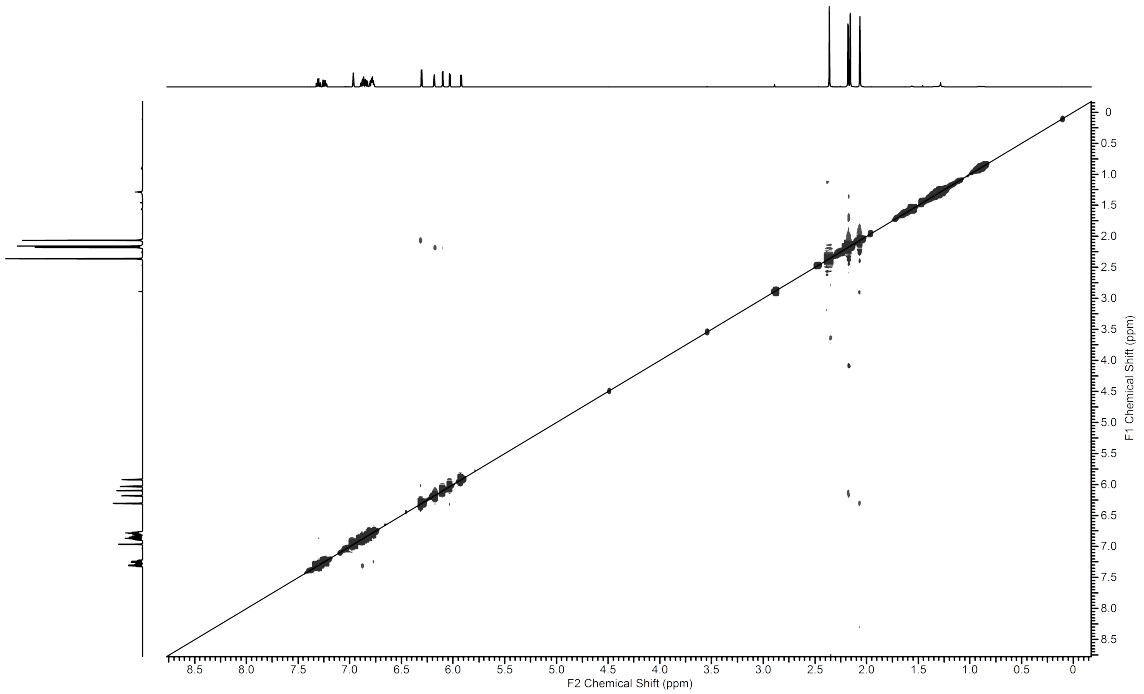




81

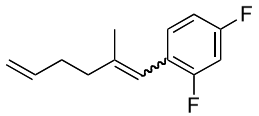


$^{1}H/^{1}H$ COSY (600 MHz, $CDCl_3$)



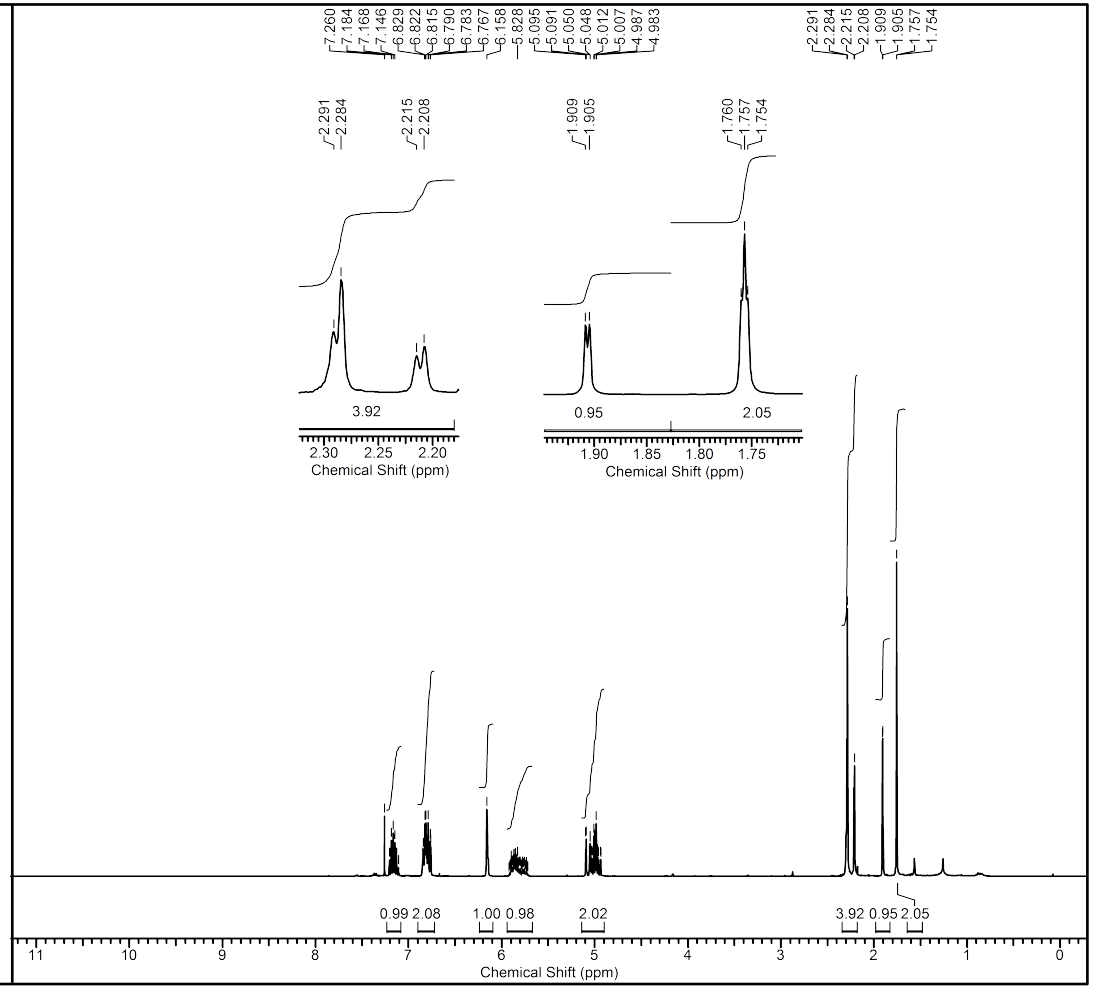
$^{1}H/^{1}H$ NOESY (600 MHz, $CDCl_3$)

File Name	020-35
Acquisition Time (sec)	3.9584
Date Stamp	13 Jun 2013 11:20
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	90.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

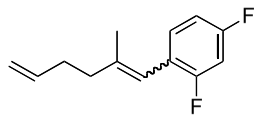


82

O'Brien™
Group NMR Data

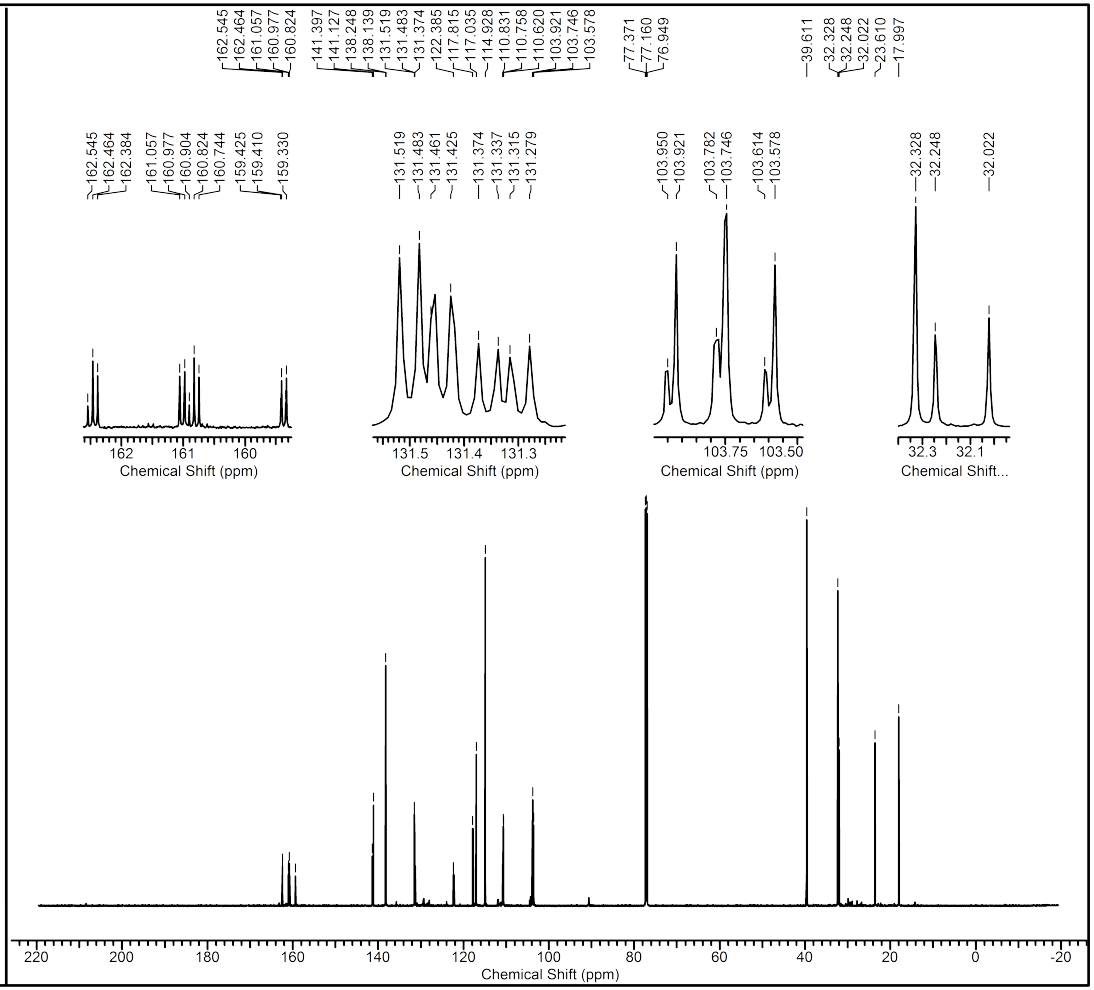


File Name	020-35
Acquisition Time (sec)	1.3664
Date Stamp	26 Jun 2013 15:32
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.960
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	15114.1953
Origin	spect
Receiver Gain	2050.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

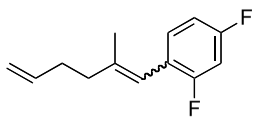


82

O'Brien™
Group NMR Data

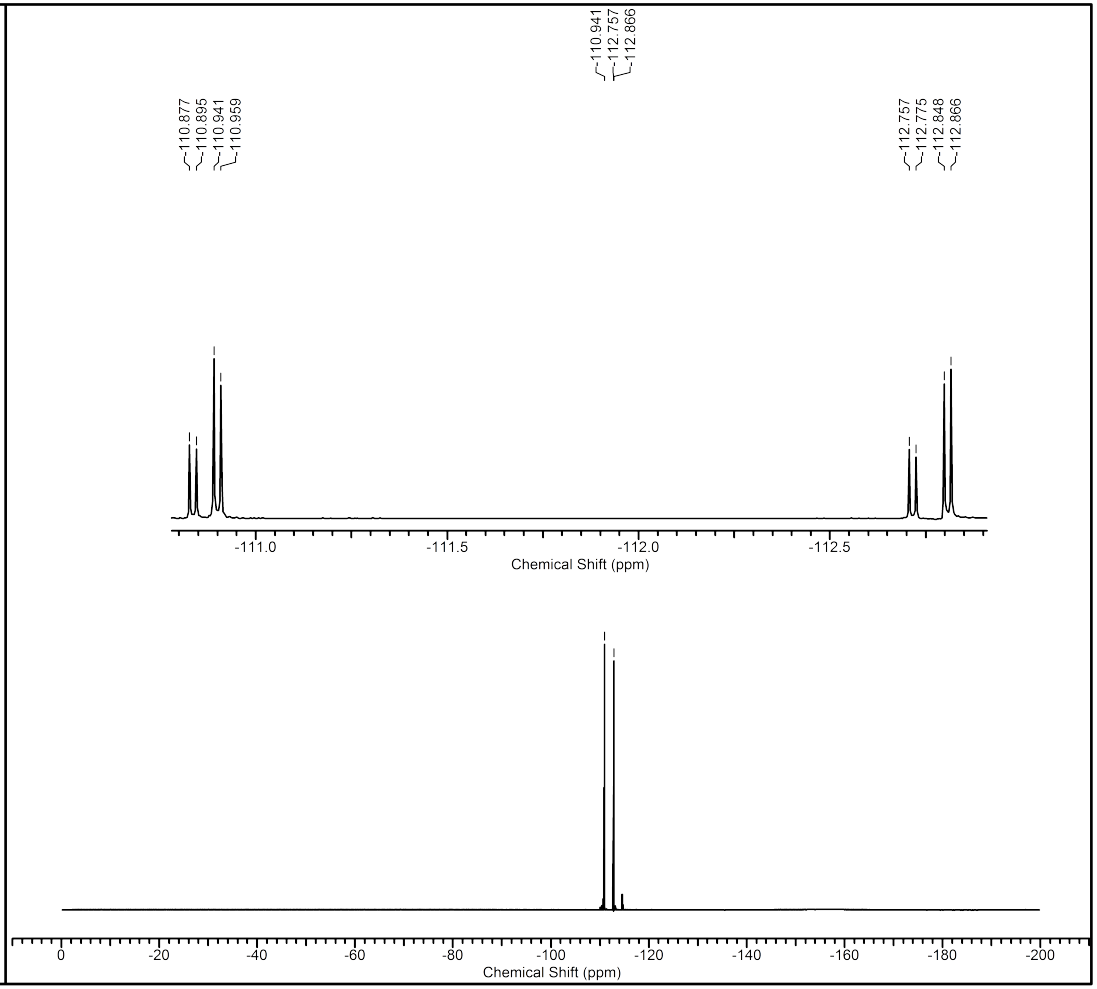


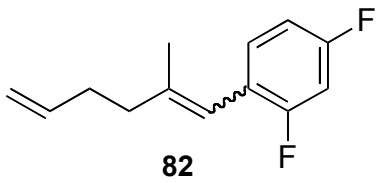
File Name	020-35
Acquisition Time (sec)	0.8716
Date Stamp	13 Jun 2013 11:22
Frequency (MHz)	376.50
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	19F
Points Count	65536
Number of Transients	16
Pulse Sequence	zgfhigqn
Spectrum Offset (Hz)	-37649.6211
Origin	spect
Receiver Gain	574.70
Spectrum Type	STANDARD
Original Points Count	65536
SW(cyclical) (Hz)	75187.97
Sweep Width (Hz)	75186.82



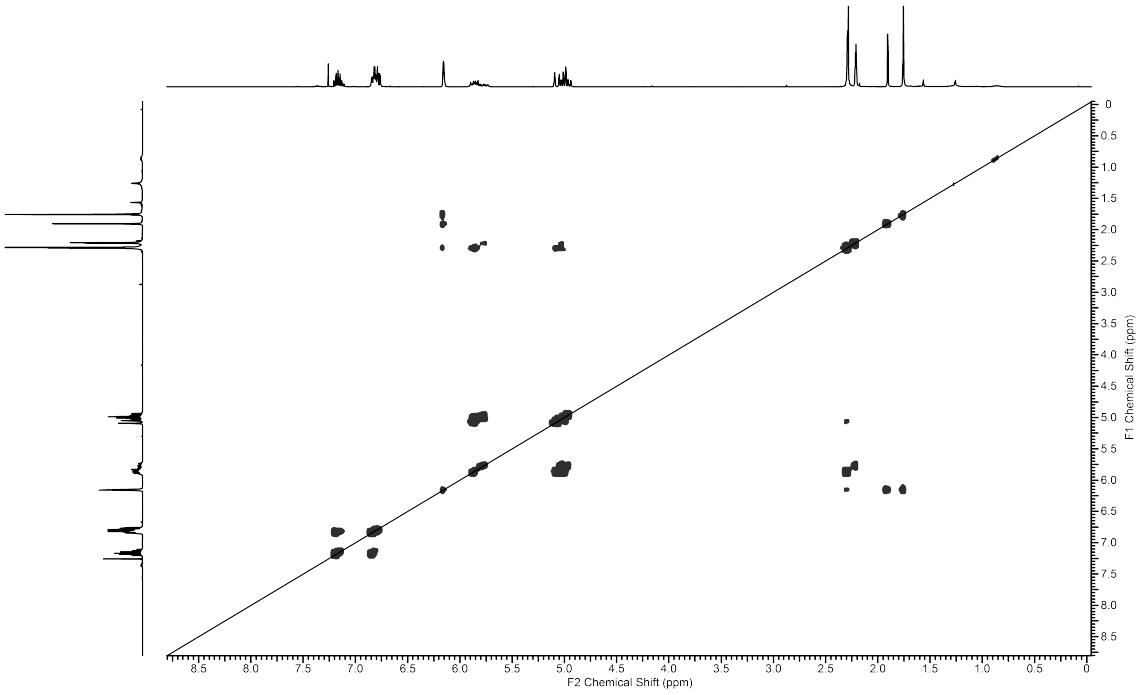
82

O'Brien™
Group NMR Data

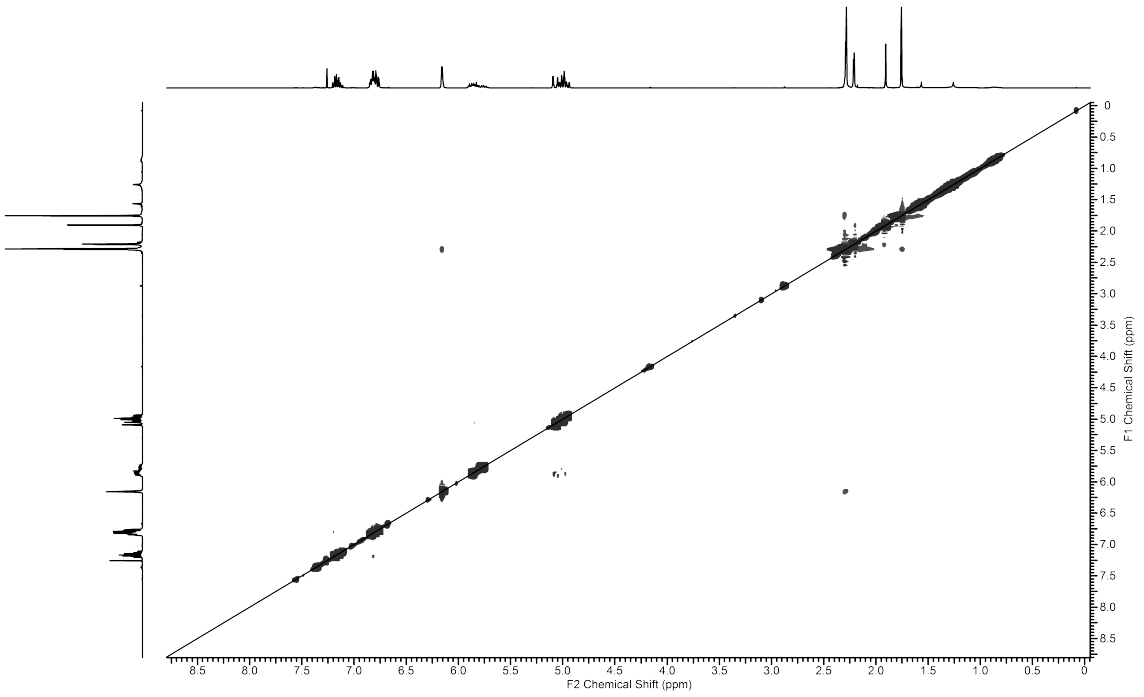




82

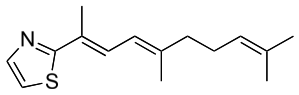


$^{1}H/^{1}H$ COSY (600 MHz, $CDCl_3$)



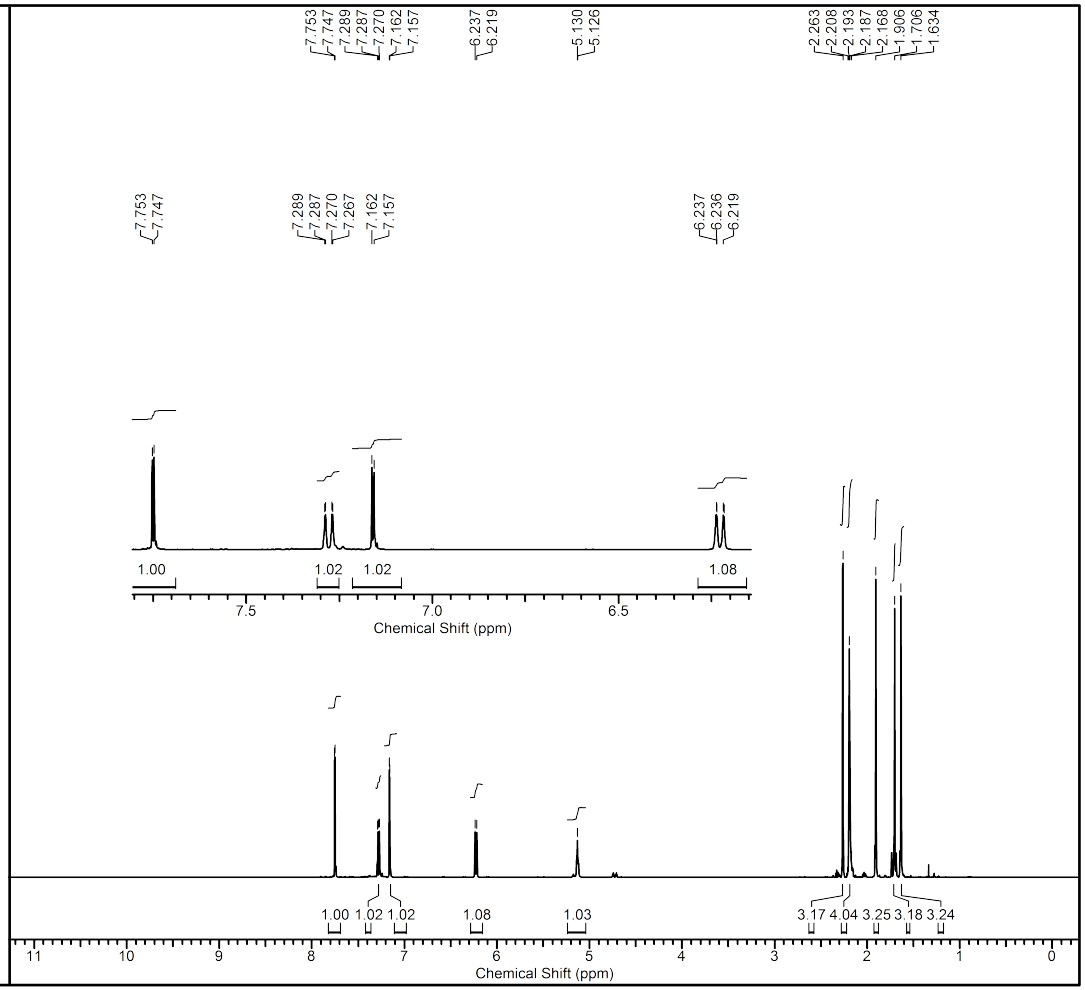
$^{1}H/^{1}H$ NOESY (600 MHz, $CDCl_3$)

File Name	020-56_E
Acquisition Time (sec)	3.9584
Date Stamp	17 Jun 2013 22:05
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	19.960
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	3706.6719
Origin	spect
Receiver Gain	20.20
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

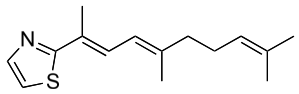


***E*-83**

O'Brien™
Group NMR Data

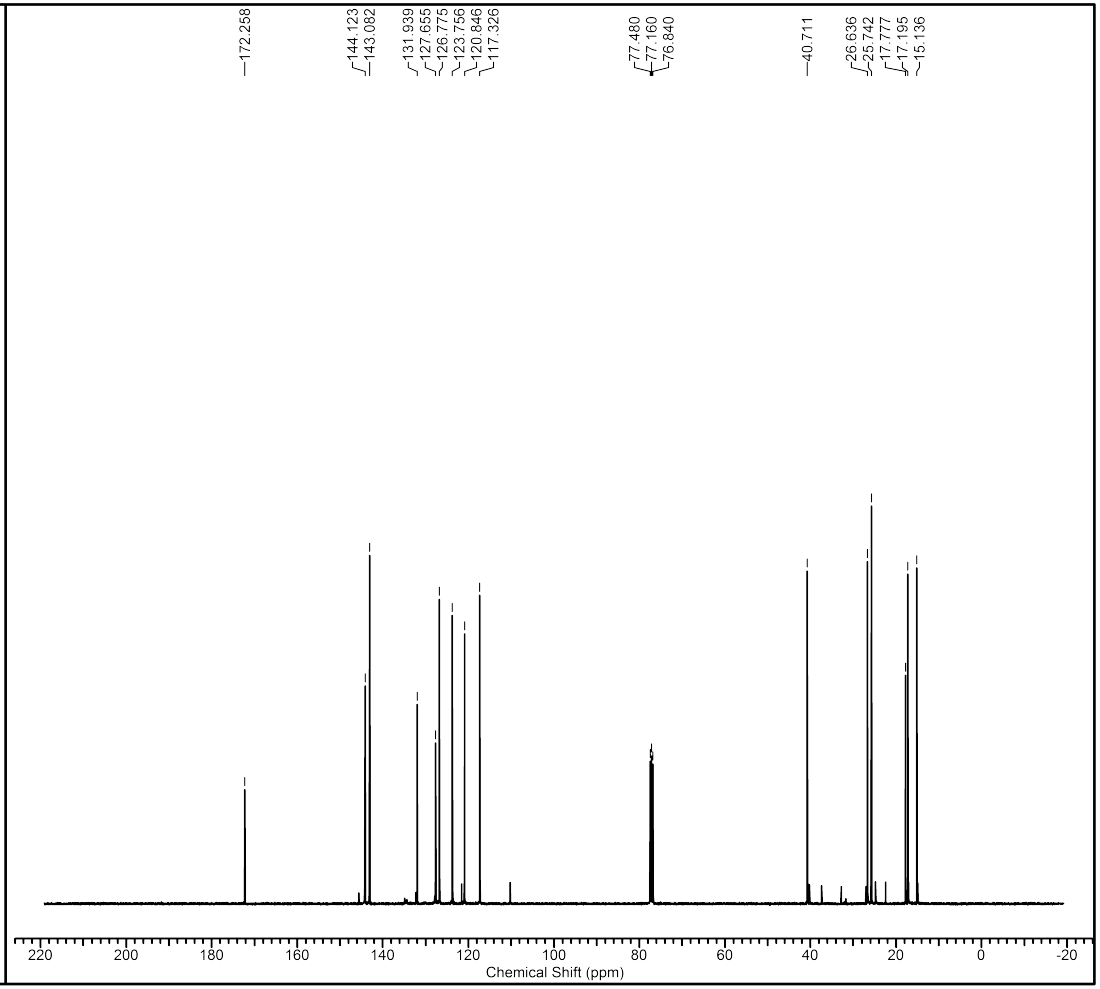


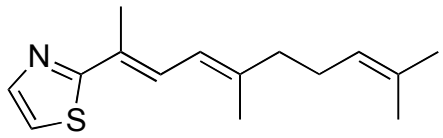
File Name	020-56_E
Acquisition Time (sec)	1.3664
Date Stamp	13 Jun 2013 19:46
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10062.3457
Origin	spect
Receiver Gain	1625.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08



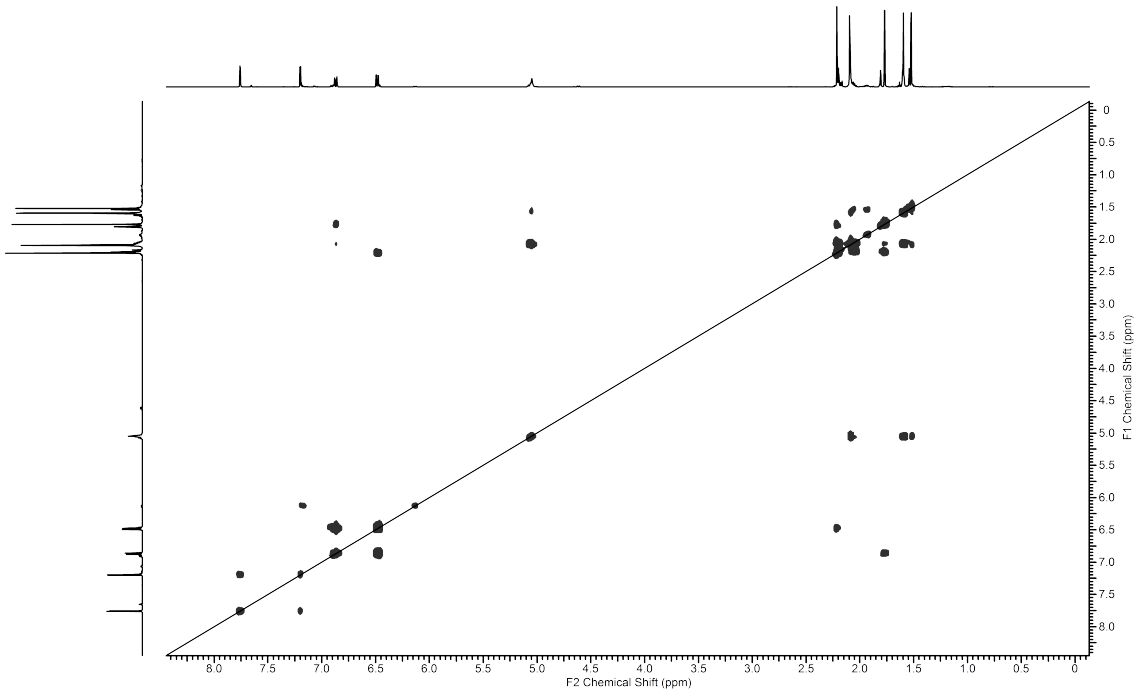
***E*-83**

O'Brien™
Group NMR Data

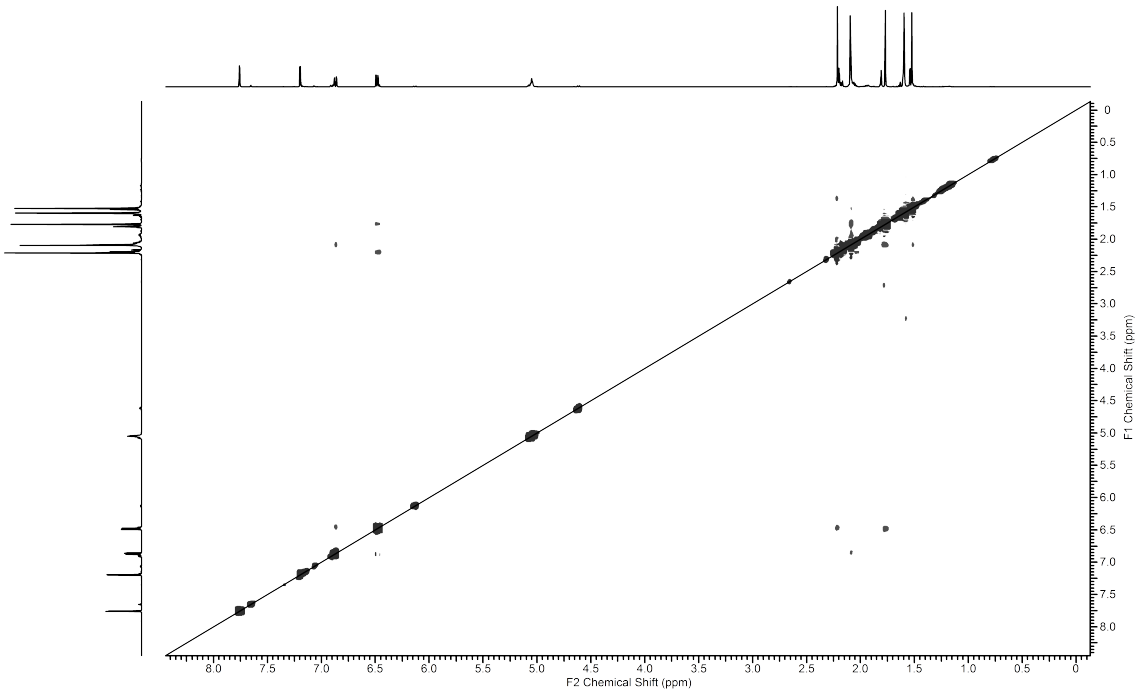




E-**83**

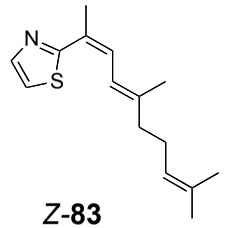


$^{1}H/^{1}H$ COSY (600 MHz, $CDCl_3$)



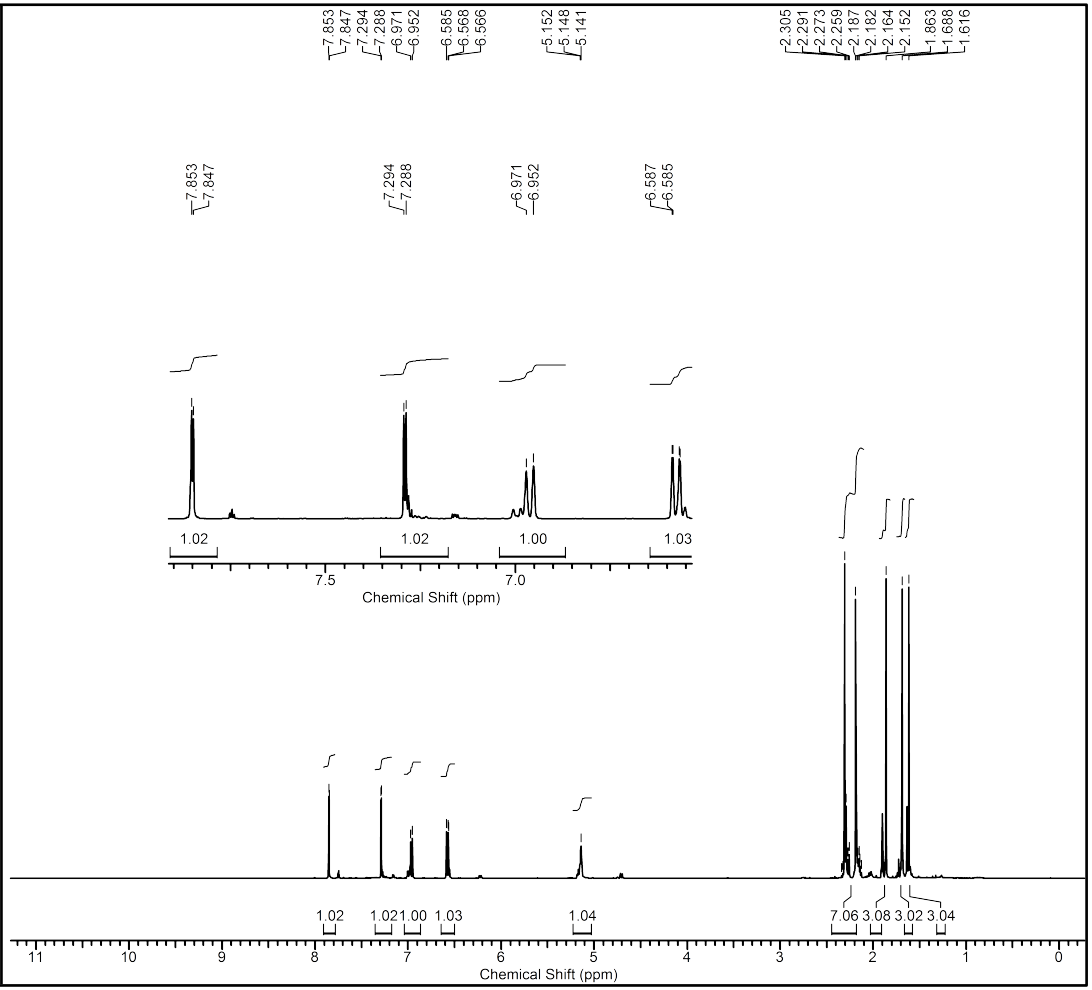
$^{1}H/^{1}H$ NOESY (600 MHz, $CDCl_3$)

File Name	020-56_Z
Acquisition Time (sec)	3.9584
Date Stamp	17 Jun 2013 13:07
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	19.860
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	3694.8022
Origin	spect
Receiver Gain	25.40
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

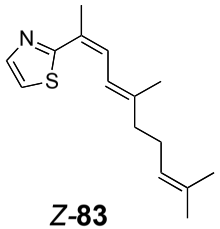


Z-83

O'Brien™
Group NMR Data

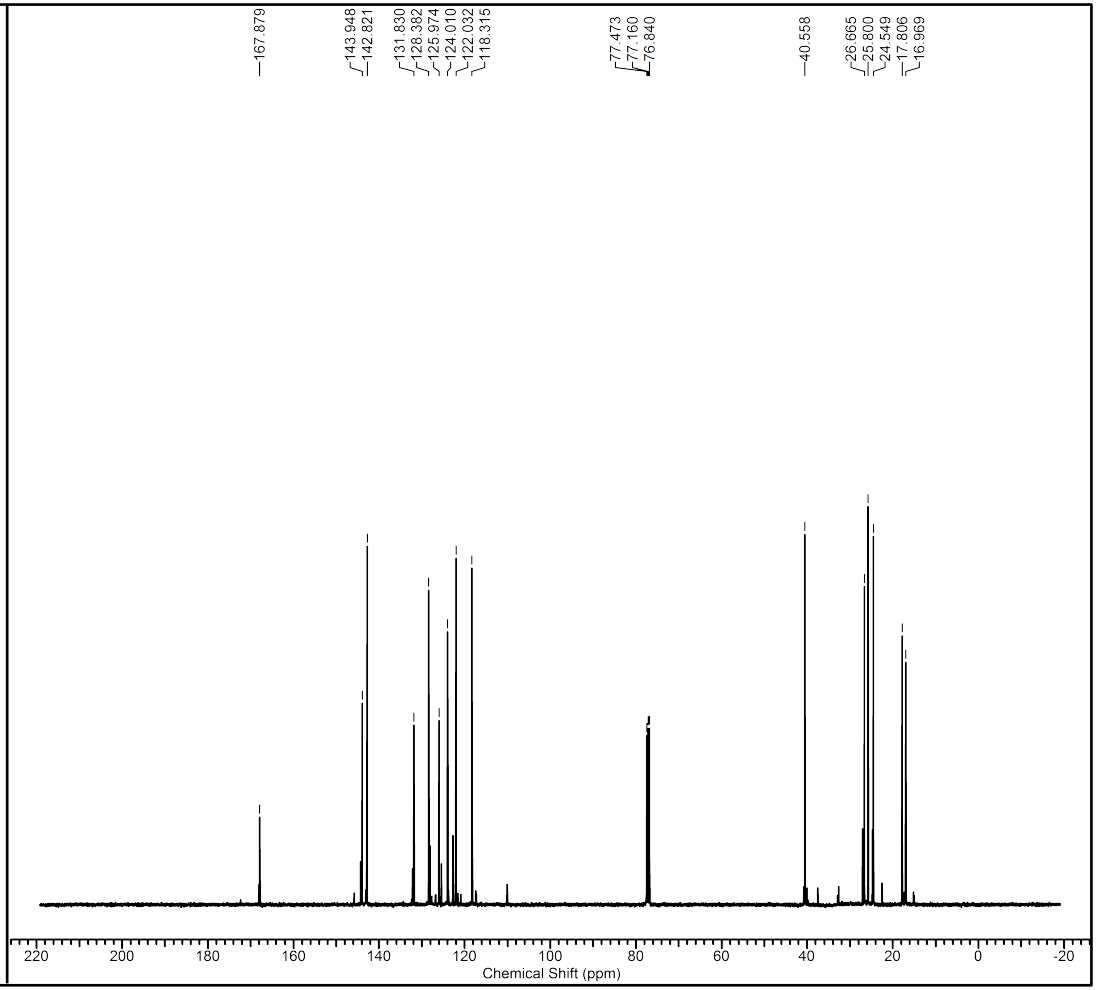


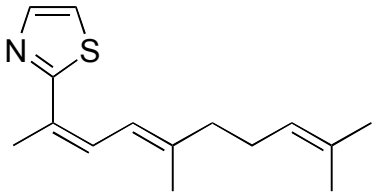
File Name	020-56_Z
Acquisition Time (sec)	1.3664
Date Stamp	13 Jun 2013 01:25
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10066.0049
Origin	spect
Receiver Gain	1024.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08



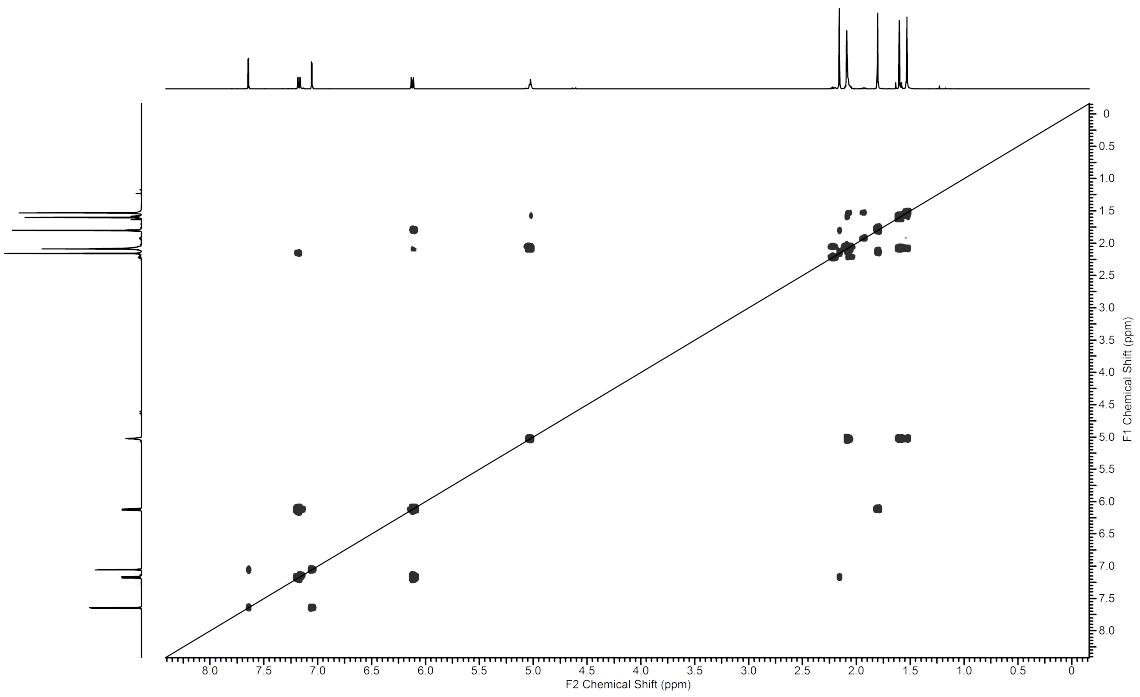
Z-83

O'Brien™
Group NMR Data

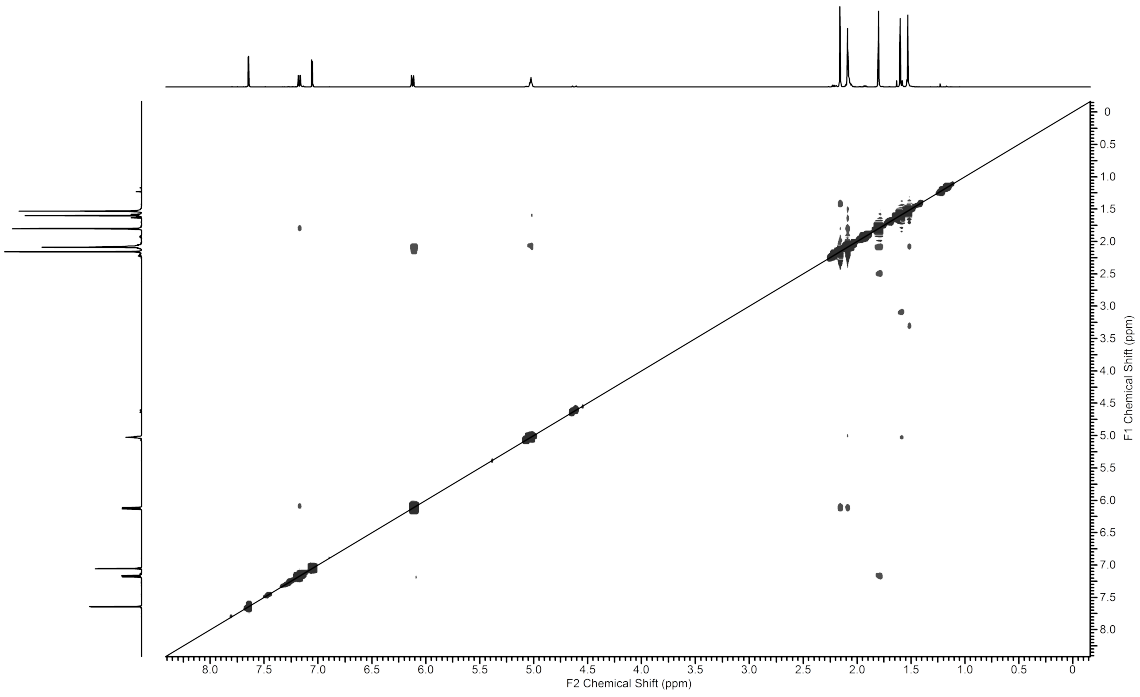




Z-**83**

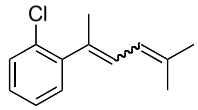


$^1H/^1H$ COSY (600 MHz, $CDCl_3$)



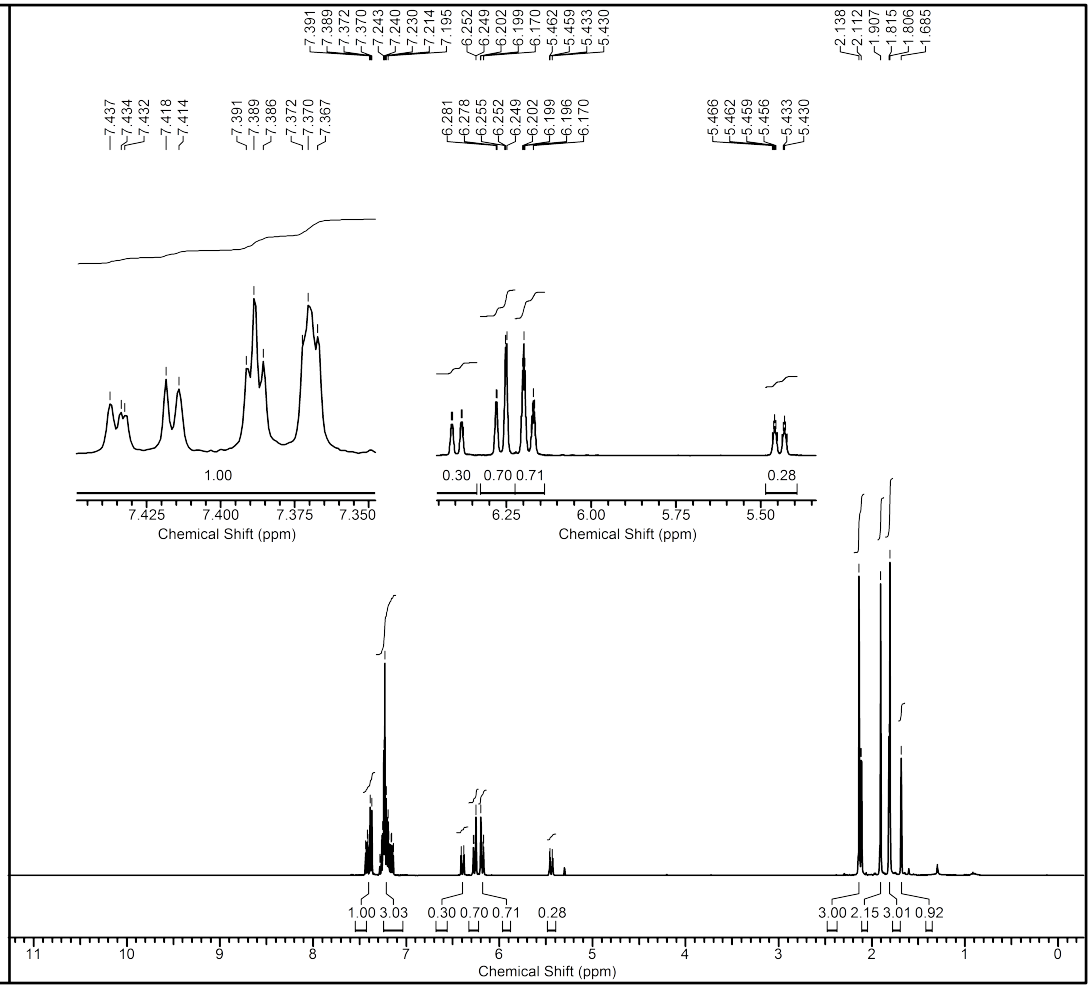
$^1H/^1H$ NOESY (600 MHz, $CDCl_3$)

File Name	020-38
Acquisition Time (sec)	3.9584
Date Stamp	04 Jun 2013 20:22
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.2019
Origin	spect
Receiver Gain	35.90
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

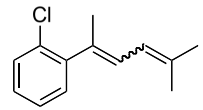


84

O'Brien™
Group NMR Data

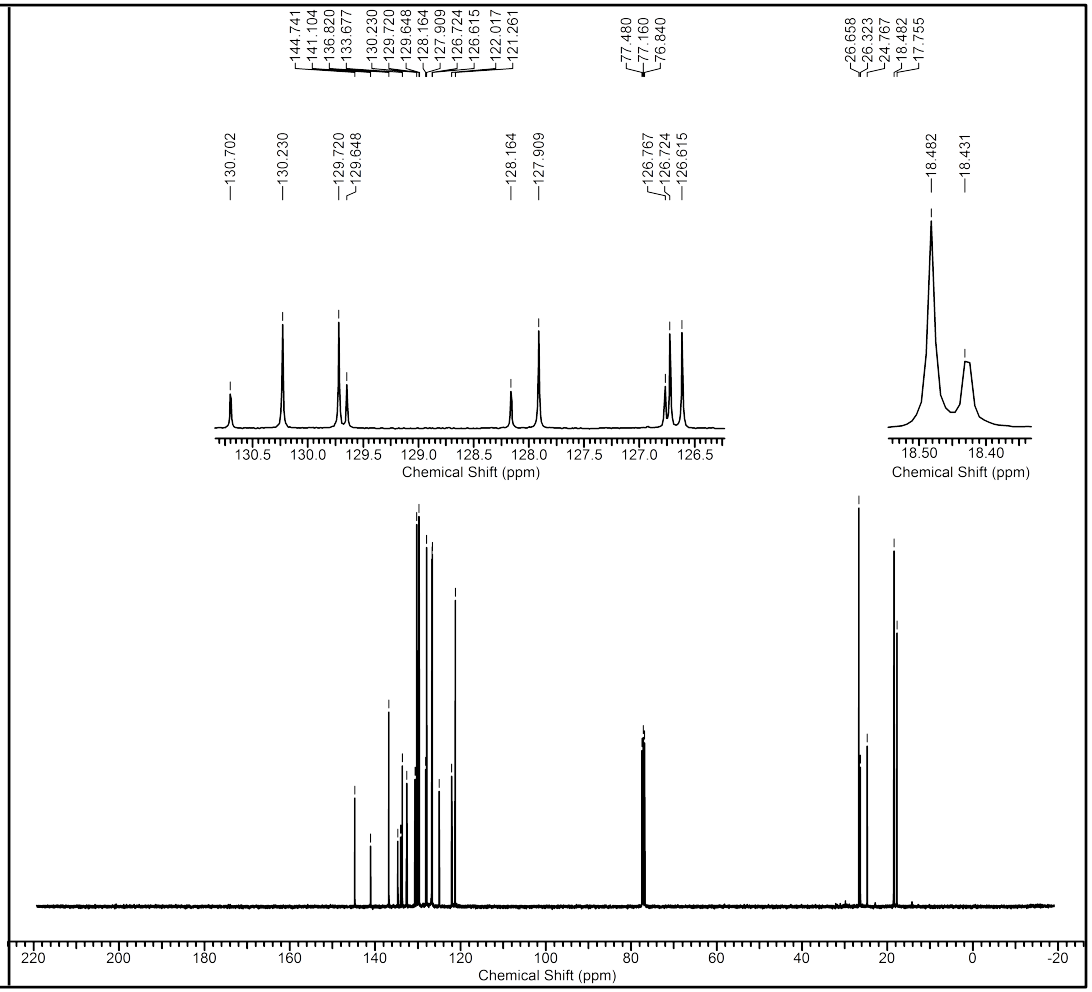


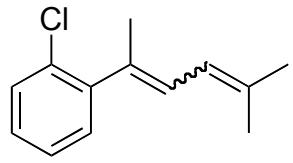
File Name	020-38
Acquisition Time (sec)	1.3664
Date Stamp	07 Jun 2013 18:06
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10068.2002
Origin	spect
Receiver Gain	2896.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08



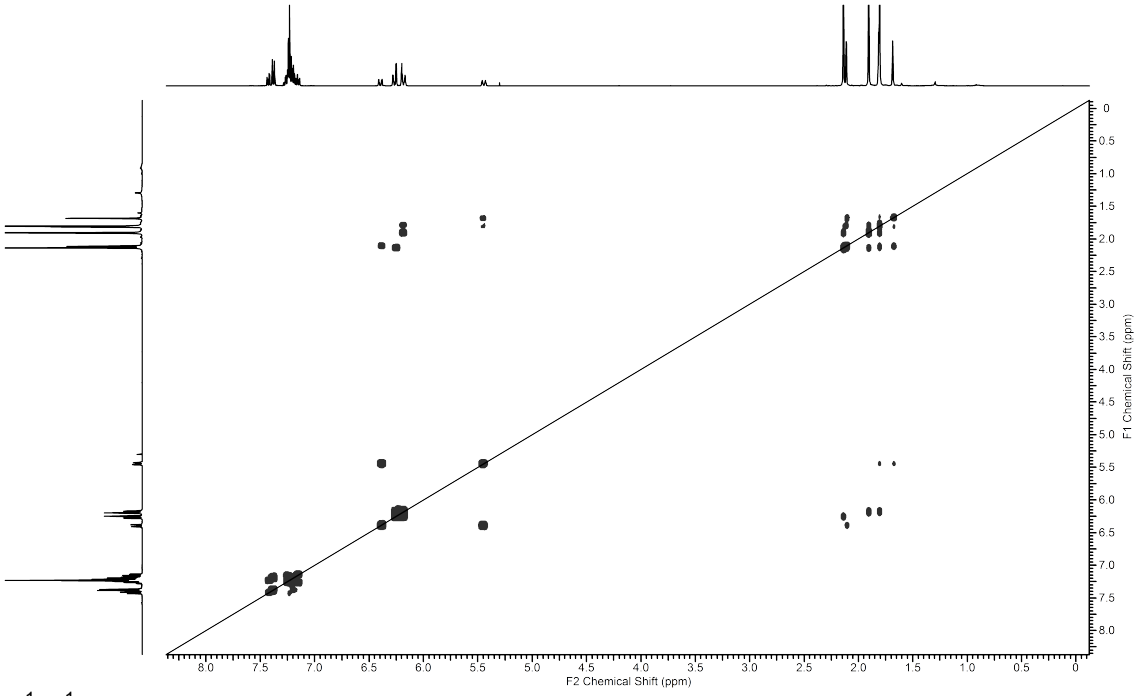
84

O'Brien™
Group NMR Data

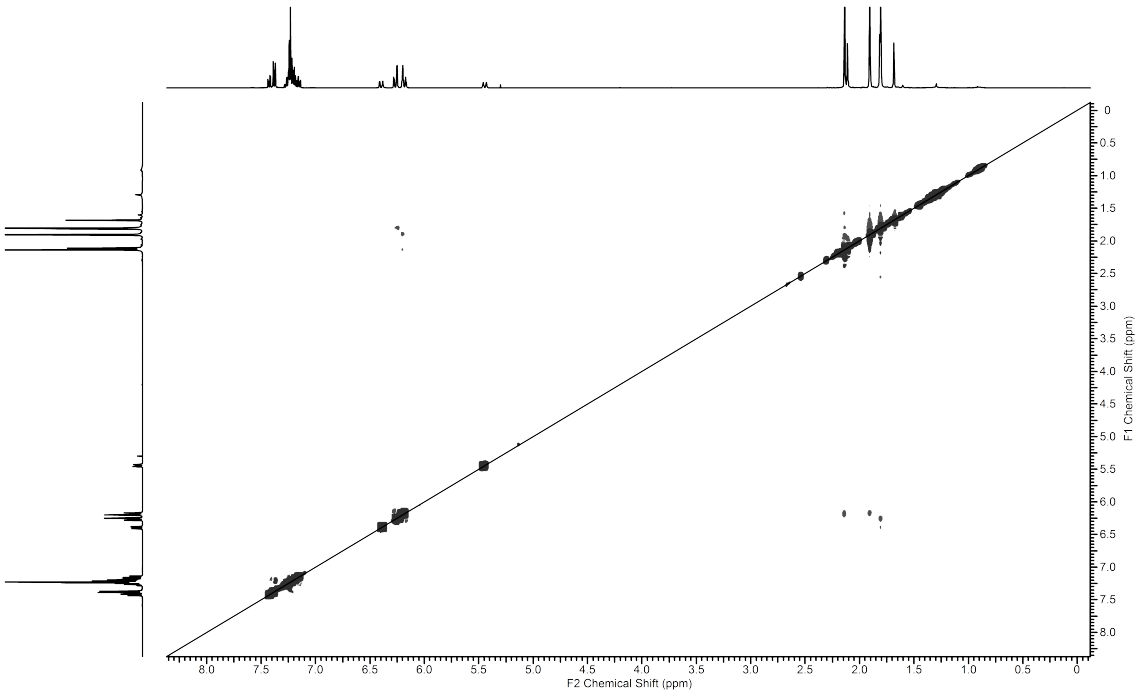




84

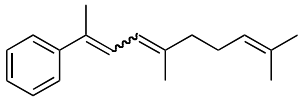


$^{1}H/^{1}H$ COSY (600 MHz, $CDCl_3$)



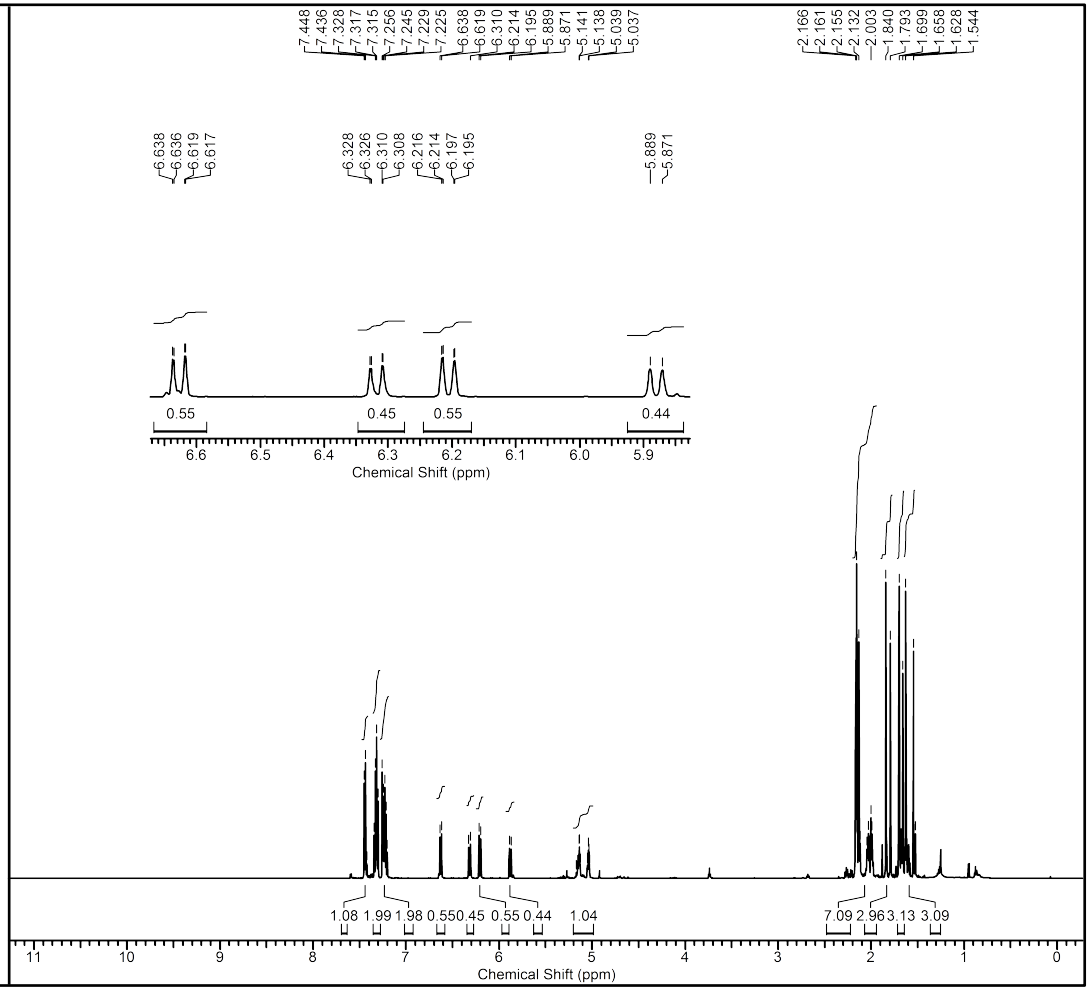
$^{1}H/^{1}H$ NOESY (600 MHz, $CDCl_3$)

File Name	020-07
Acquisition Time (sec)	3.9584
Date Stamp	22 May 2013 17:57
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	17.760
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	3668.62
Origin	spect
Receiver Gain	64.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

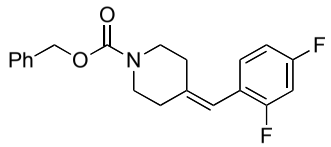


85

O'Brien™
Group NMR Data

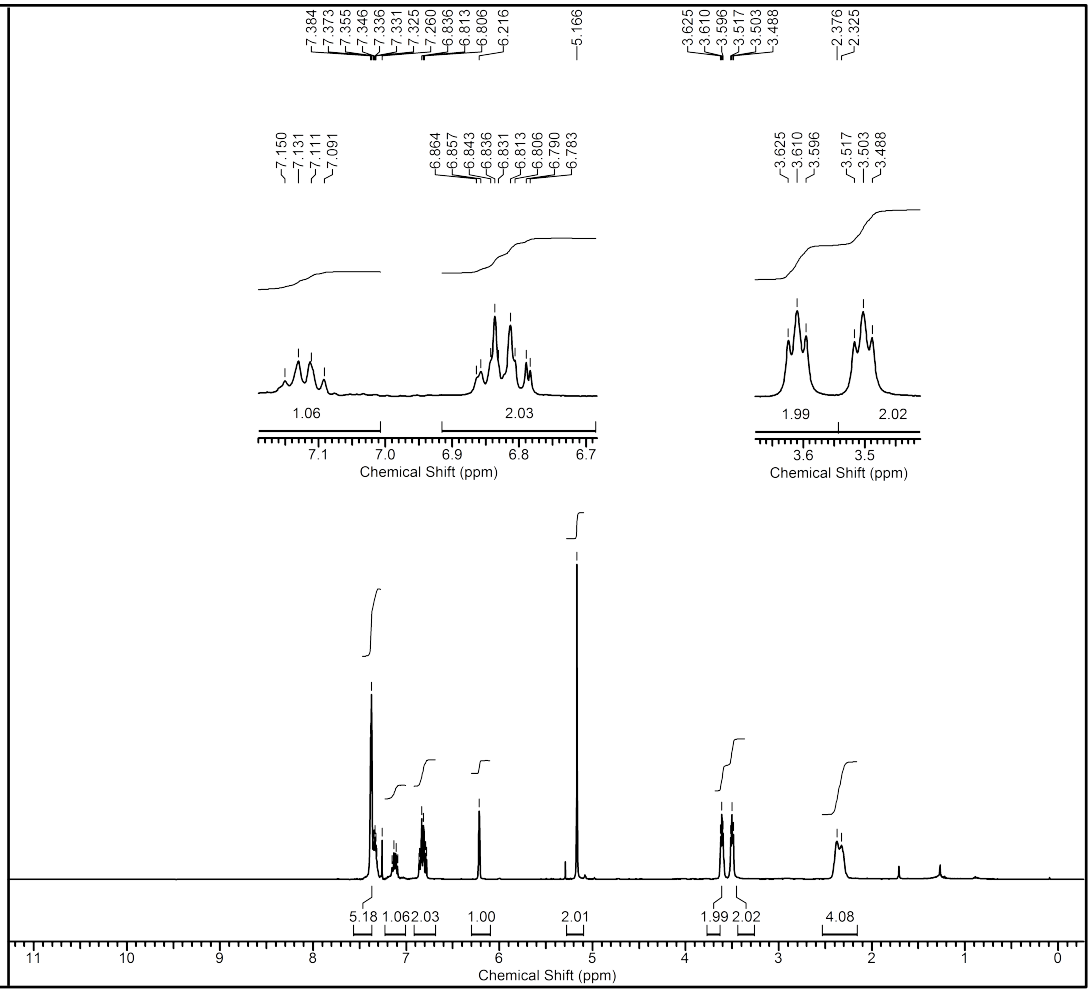


File Name	020-58
Acquisition Time (sec)	3.9584
Date Stamp	19 Jun 2013 11:37
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.7065
Origin	spect
Receiver Gain	71.80
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

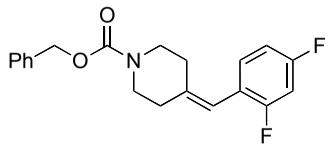


86

O'Brien™
Group NMR Data

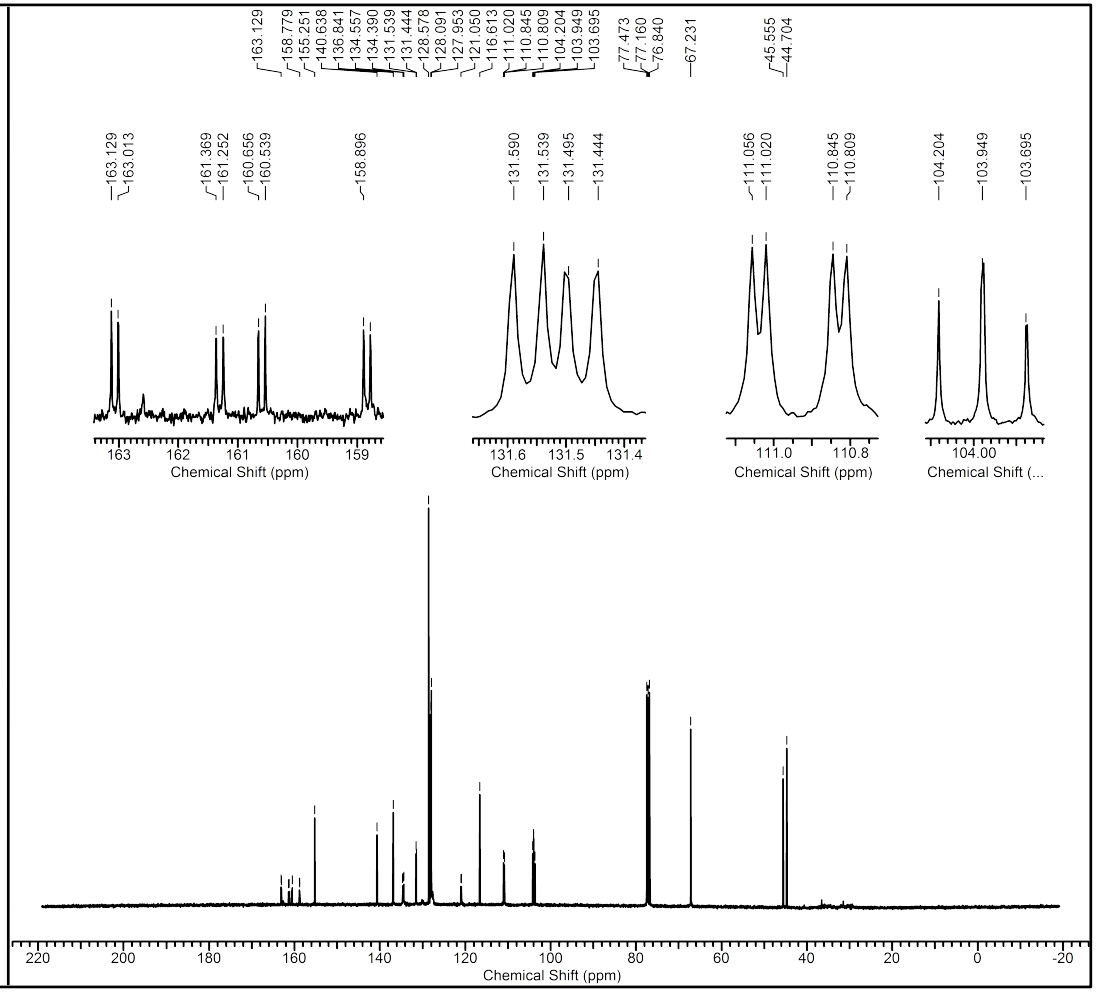


File Name	020-58
Acquisition Time (sec)	1.3664
Date Stamp	20 Jun 2013 03:03
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10064.5410
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

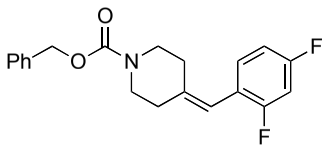


86

O'Brien™
Group NMR Data

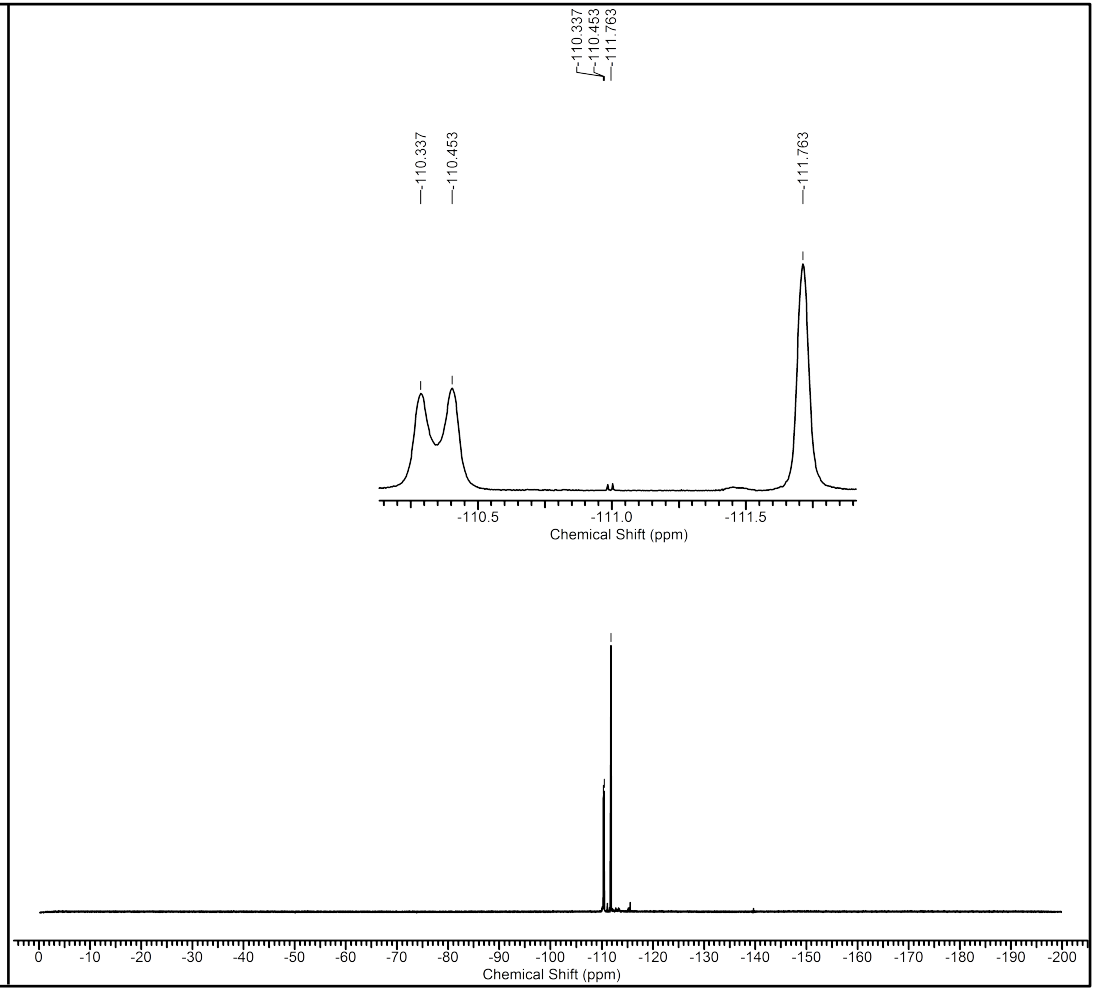


File Name	020-58
Acquisition Time (sec)	0.8716
Date Stamp	19 Jun 2013 11:40
Frequency (MHz)	376.50
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	19F
Points Count	65536
Number of Transients	16
Pulse Sequence	zgfhigqn
Spectrum Offset (Hz)	-37649.6211
Origin	spect
Receiver Gain	574.70
Spectrum Type	STANDARD
Original Points Count	65536
SW(cyclical) (Hz)	75187.97
Sweep Width (Hz)	75186.82

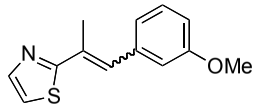


86

O'Brien™
Group NMR Data

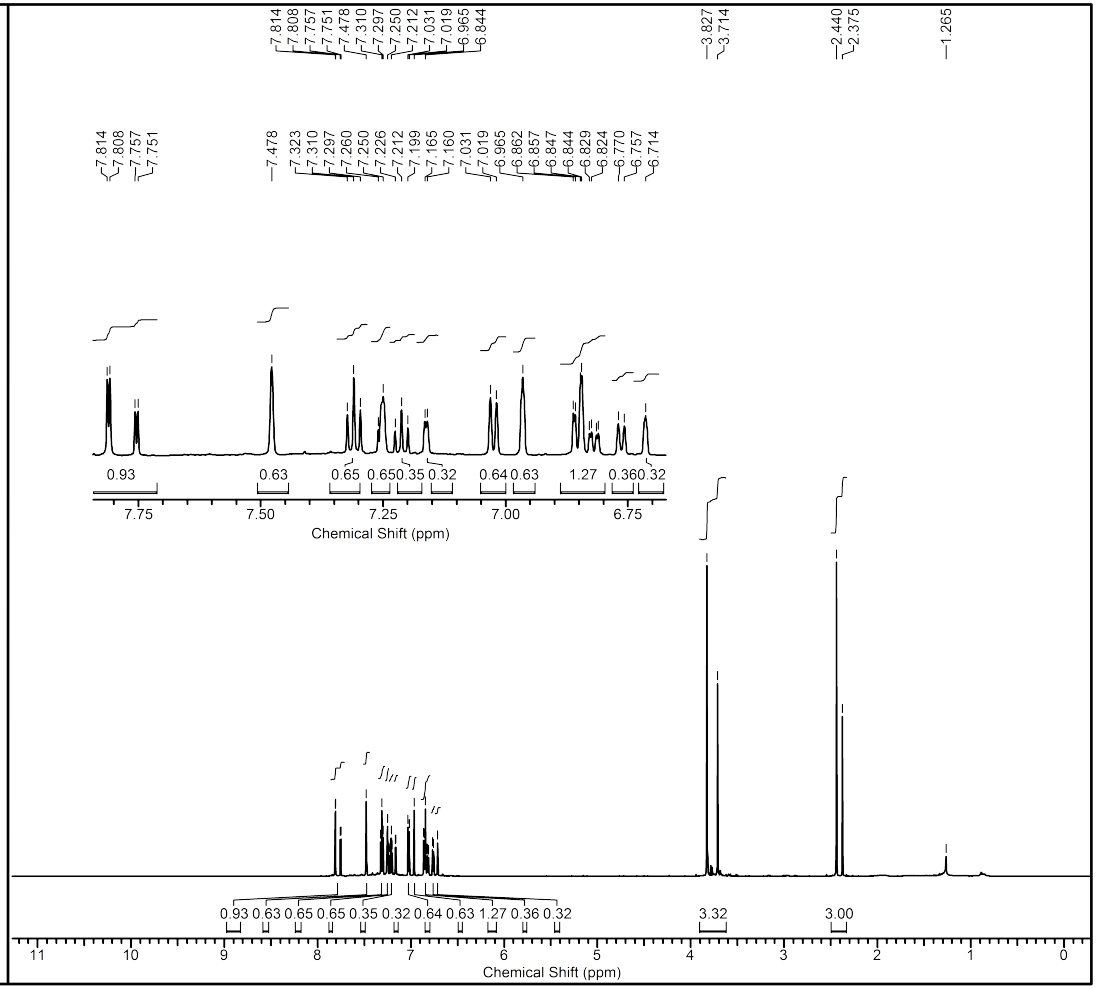


File Name	020-42A
Acquisition Time (sec)	3.9584
Date Stamp	22 Jun 2013 02:57
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.060
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	3688.4521
Origin	spect
Receiver Gain	64.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

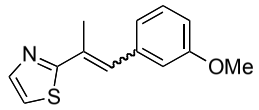


87

O'Brien™
Group NMR Data

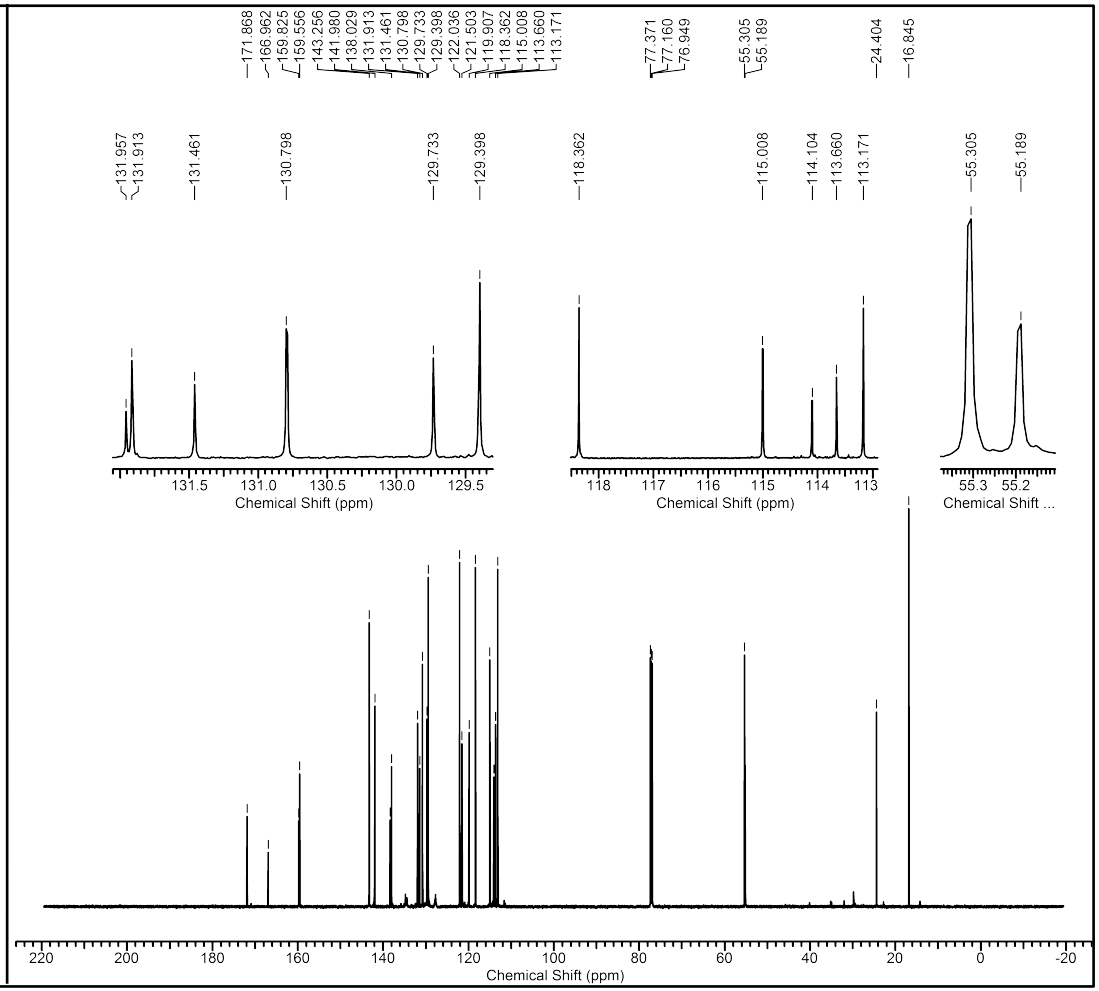


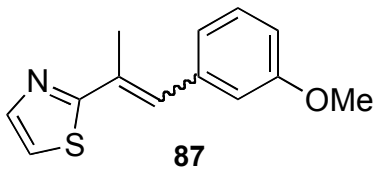
File Name	020-42A
Acquisition Time (sec)	1.3664
Date Stamp	22 Jun 2013 07:02
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.560
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	15100.9912
Origin	spect
Receiver Gain	2050.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08



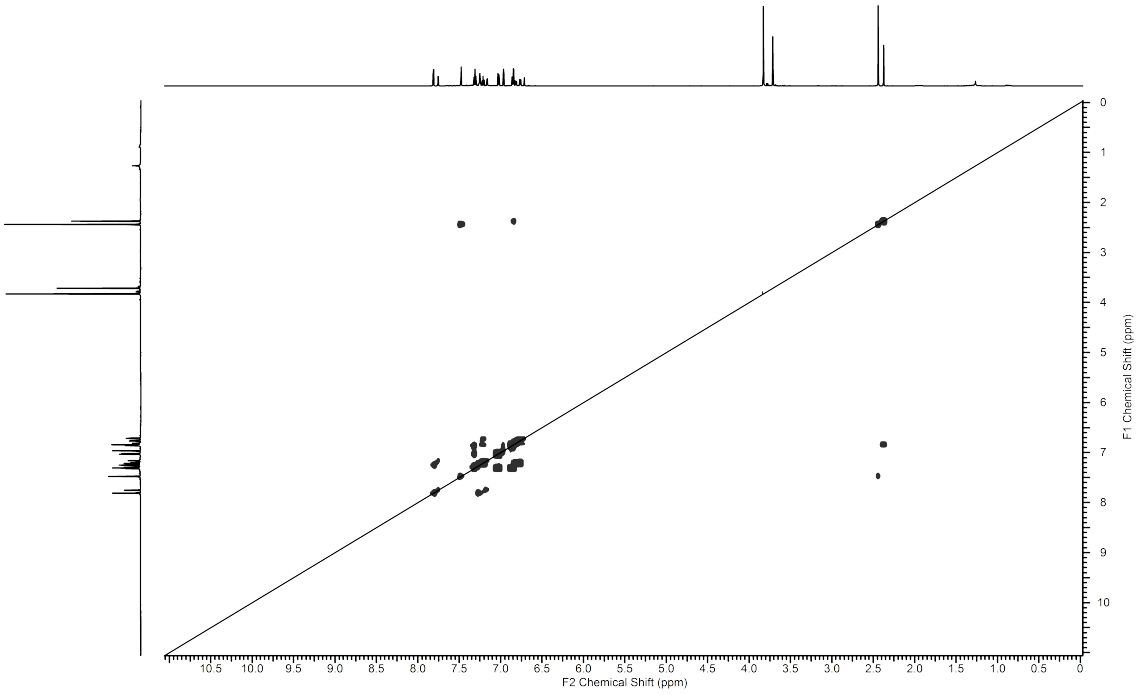
87

O'Brien™
Group NMR Data

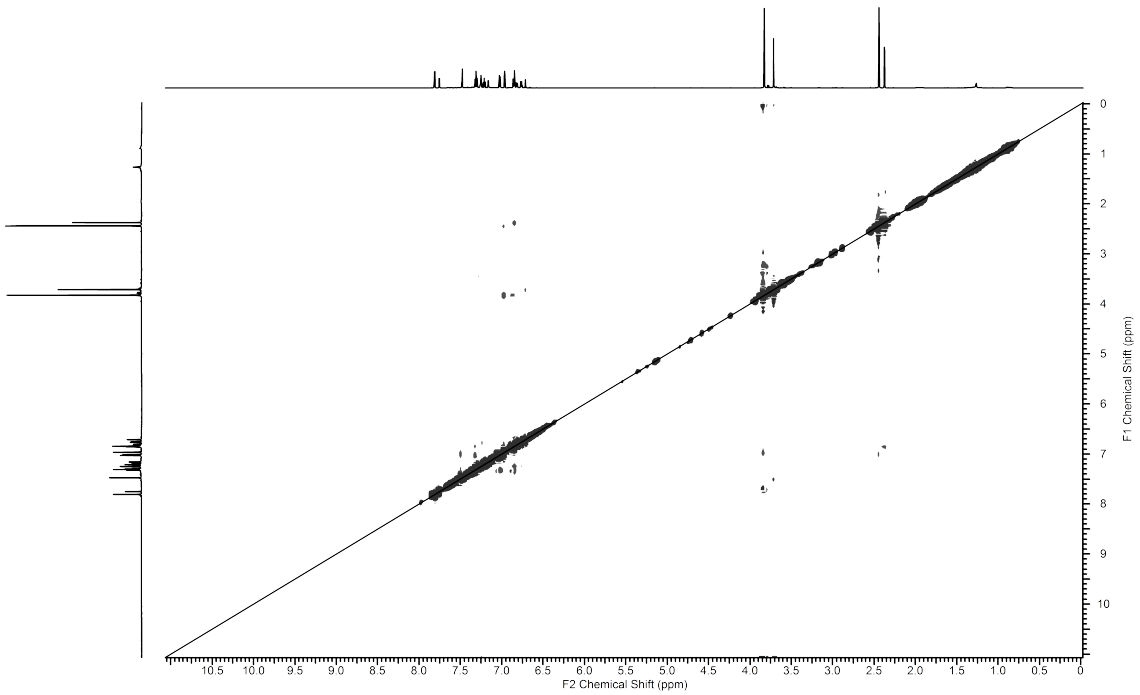




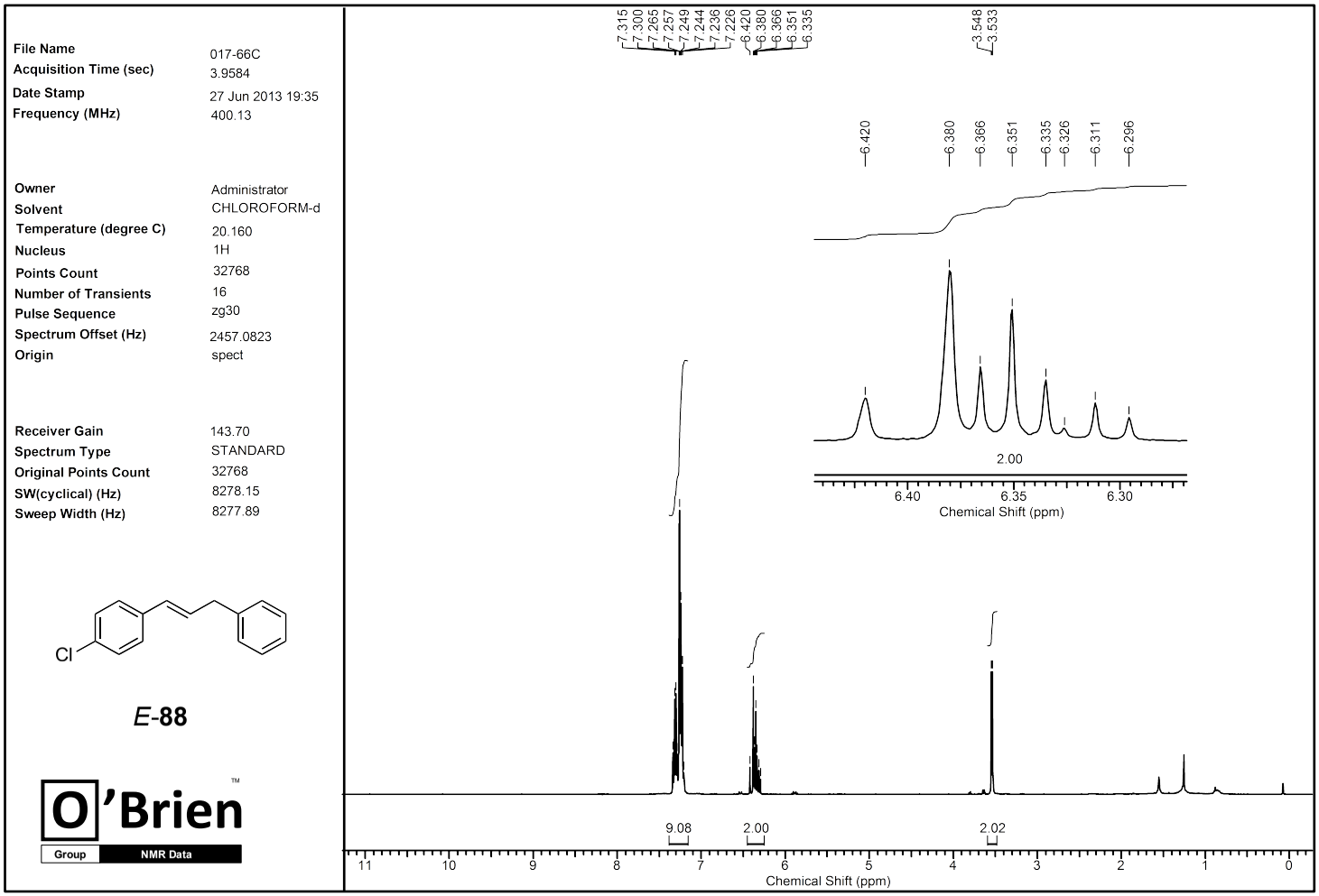
87



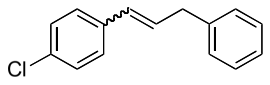
$^{1}H/^{1}H$ COSY (600 MHz, $CDCl_3$)



$^{1}H/^{1}H$ NOESY (600 MHz, $CDCl_3$)

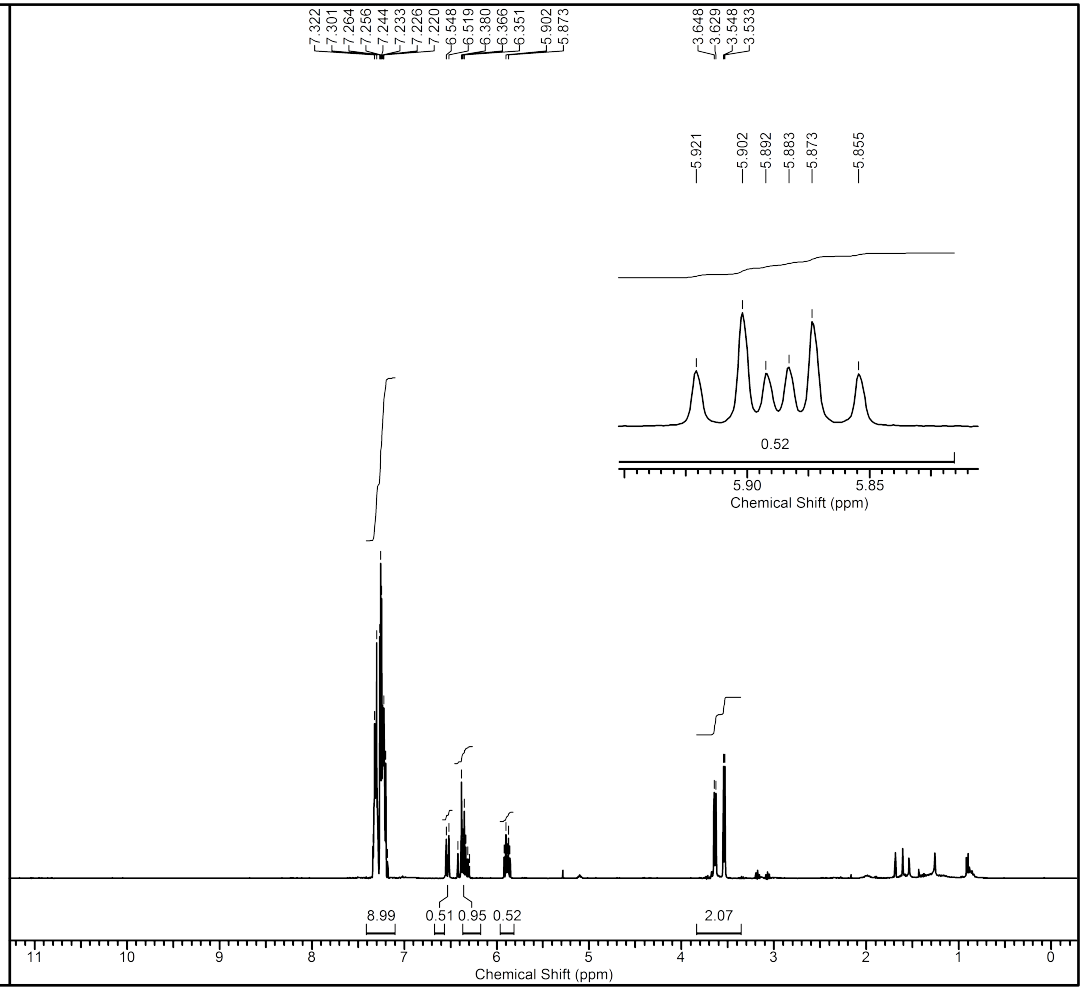

File Name 017-66C
Acquisition Time (sec) 3.9584
Date Stamp 27 Jun 2013 19:35
Frequency (MHz) 400.13
Owner Administrator
Solvent CHLOROFORM-d
Temperature (degree C) 20.160
Nucleus 1H
Points Count 32768
Number of Transients 16
Pulse Sequence zg30
Spectrum Offset (Hz) 2457.0823
Origin spect
Receiver Gain 143.70
Spectrum Type STANDARD
Original Points Count 32768
SW(cyclical) (Hz) 8278.15
Sweep Width (Hz) 8277.89
Cl
E-88
O'Brien
Group NMR Data
7.315 7.300 7.265 7.257 7.249 7.244 7.236 7.226 6.420 6.380 6.366 6.351 6.335
3.548 3.533
6.420 6.380 6.366 6.351 6.335 6.326 6.311 6.296
2.00
6.40 6.35 6.30
Chemical Shift (ppm)
9.08 2.00 2.02
11 10 9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)

File Name	017-66C
Acquisition Time (sec)	3.9584
Date Stamp	17 Jul 2013 13:58
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2454.8696
Origin	spect
Receiver Gain	114.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

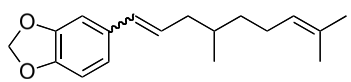


88

O'Brien™
Group NMR Data

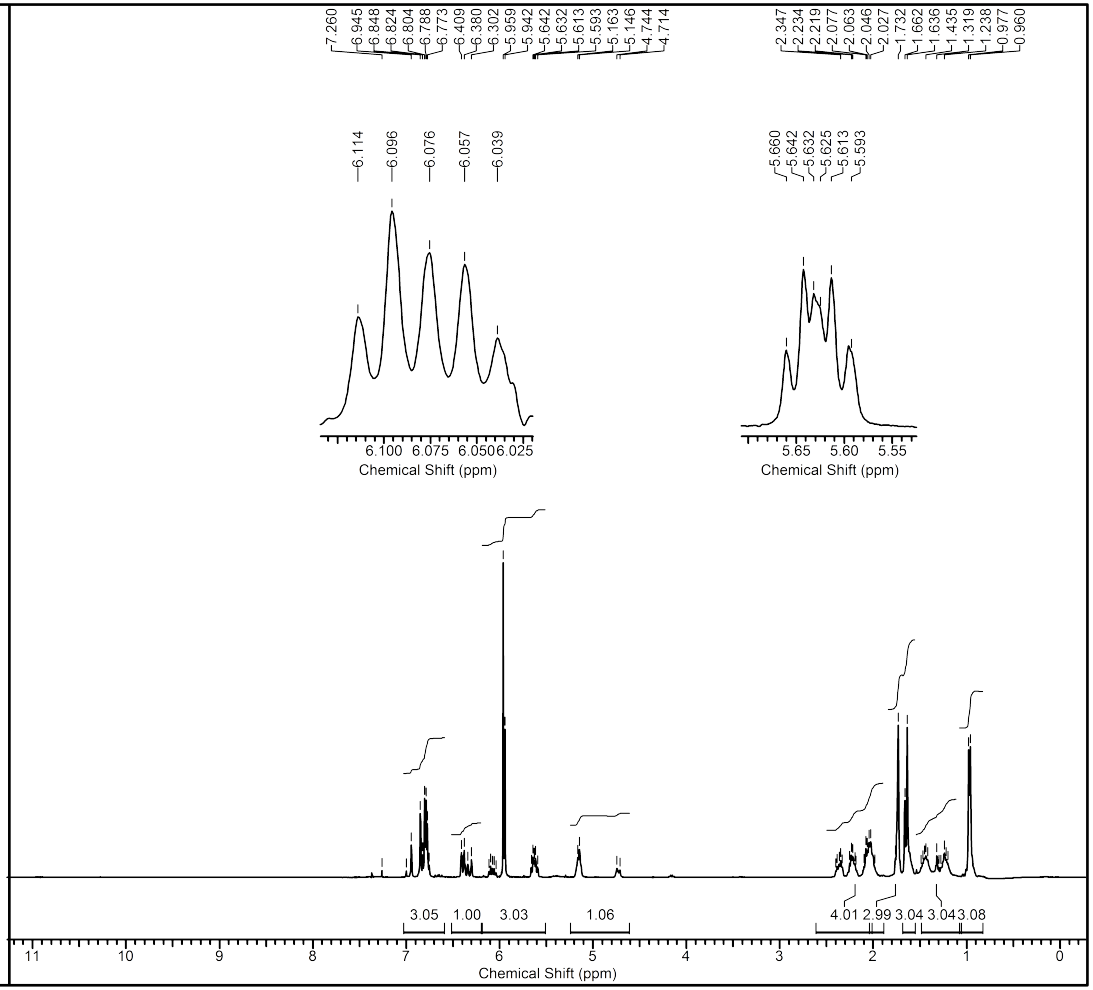


File Name	017-74C
Acquisition Time (sec)	3.9584
Date Stamp	13 Aug 2013 15:36
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	22.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.9590
Origin	spect
Receiver Gain	16.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

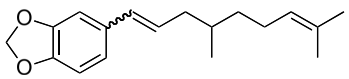


89

O'Brien™ Group NMR Data

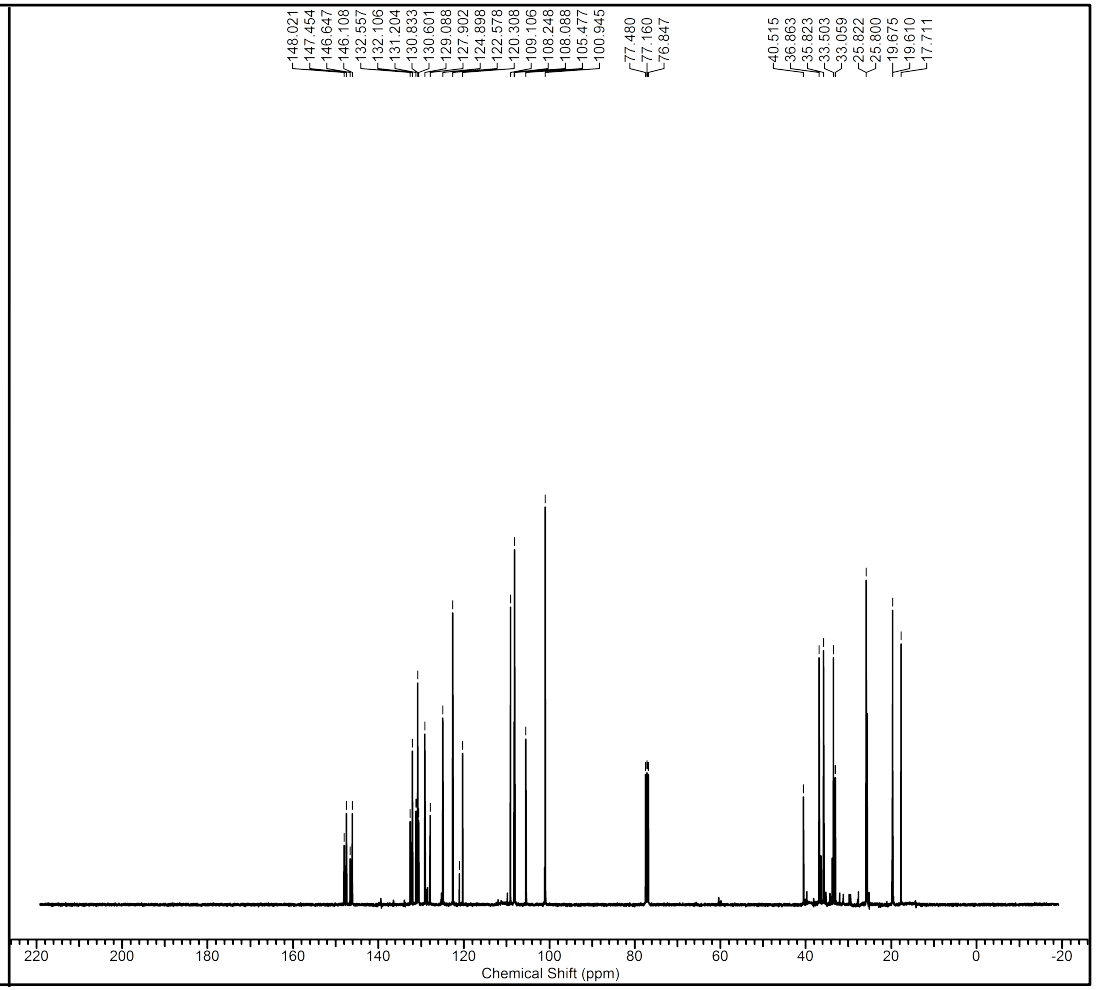


File Name	017-74C
Acquisition Time (sec)	1.3664
Date Stamp	13 Aug 2013 17:40
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	22.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10064.5410
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

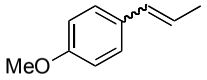


89

O'Brien™
Group NMR Data

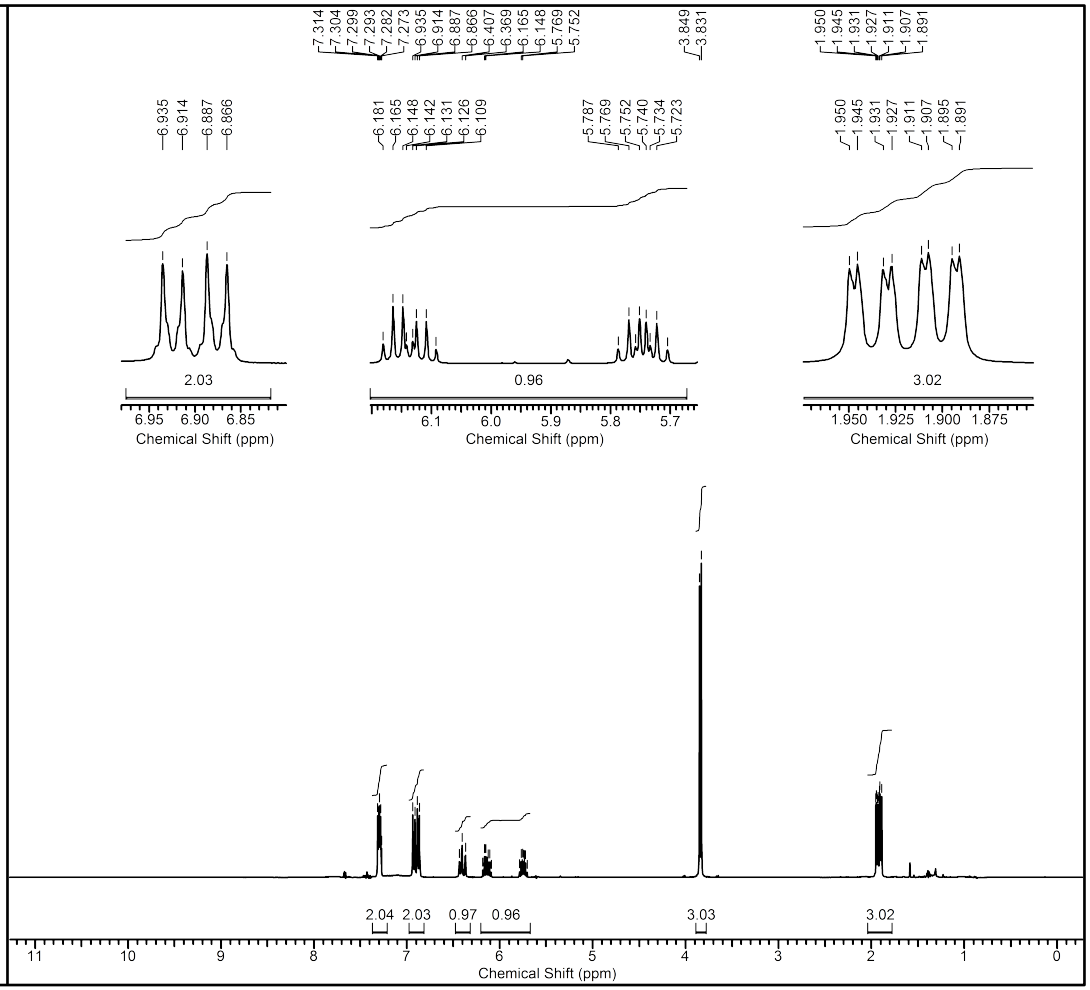


File Name	017-77B
Acquisition Time (sec)	3.9584
Date Stamp	06 Aug 2013 09:42
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2466.5649
Origin	spect
Receiver Gain	57.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

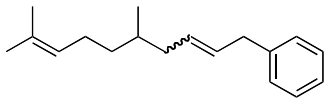


90

O'Brien™
Group NMR Data

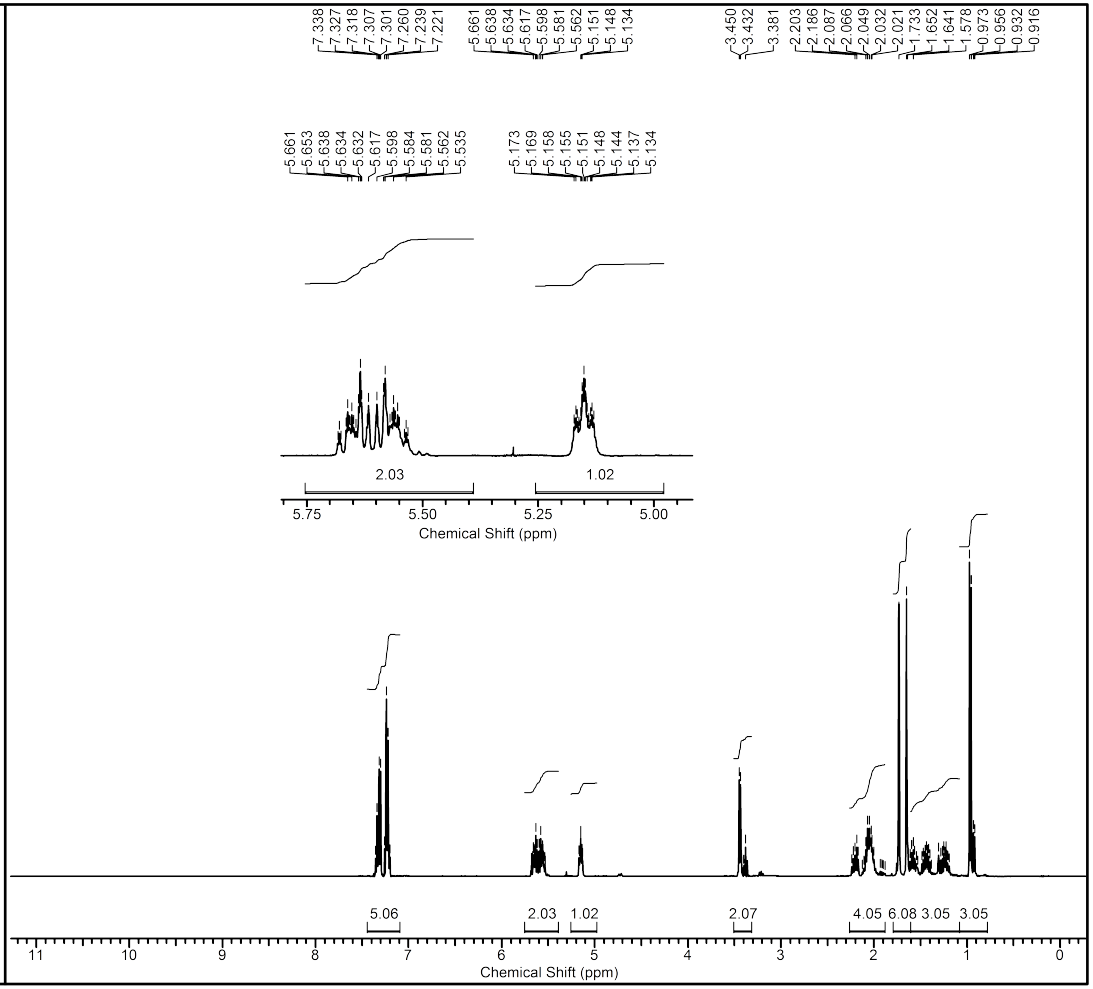


File Name	017-70F
Acquisition Time (sec)	3.9584
Date Stamp	15 Aug 2013 16:40
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	22.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4539
Origin	spect
Receiver Gain	35.90
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

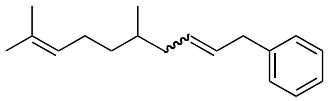


91

O'Brien™
Group NMR Data

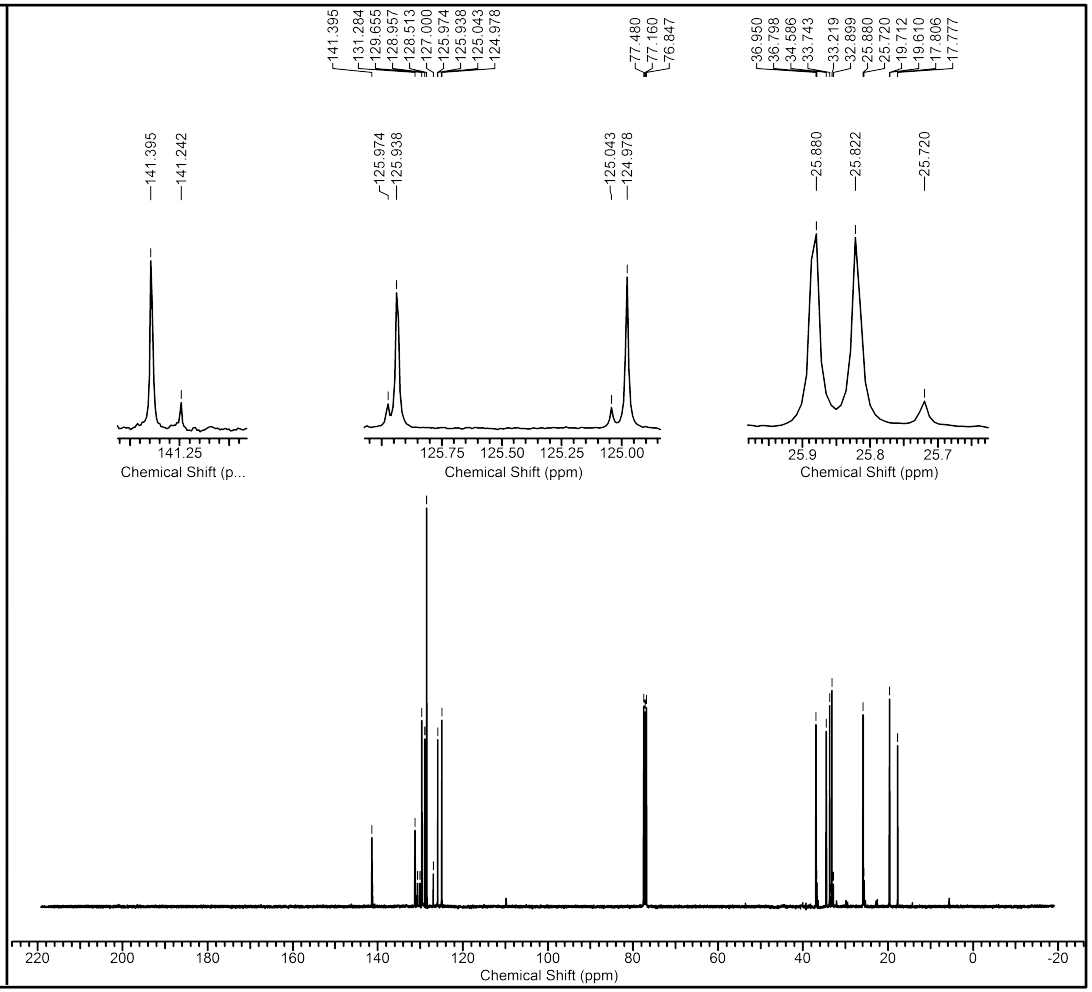


File Name	017-70F
Acquisition Time (sec)	1.3664
Date Stamp	15 Aug 2013 21:09
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	22.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10069.6641
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

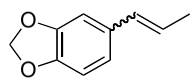


91

O'Brien™
Group NMR Data

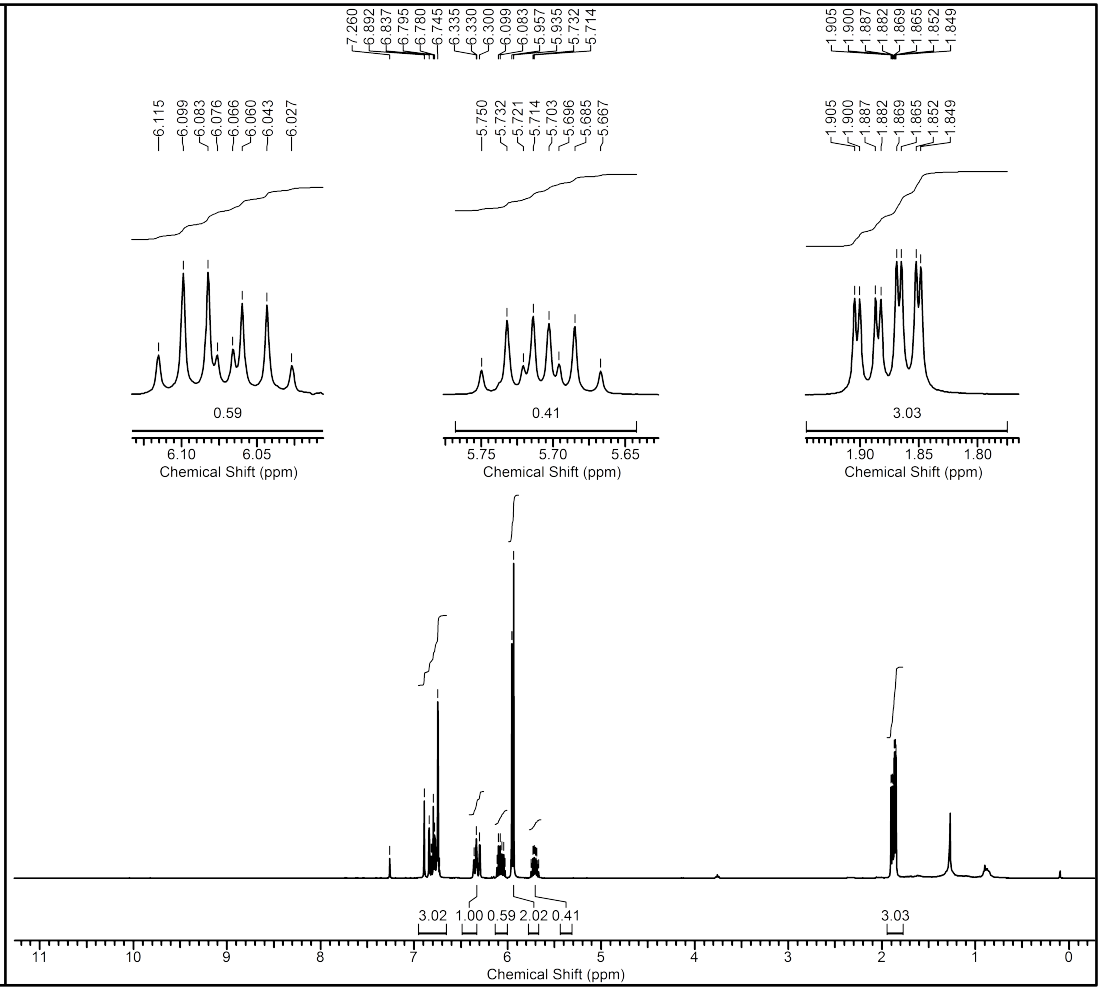


File Name	019-74D
Acquisition Time (sec)	3.9584
Date Stamp	22 May 2013 20:22
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4543
Origin	spect
Receiver Gain	64.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

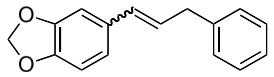


92

O'Brien™
Group NMR Data

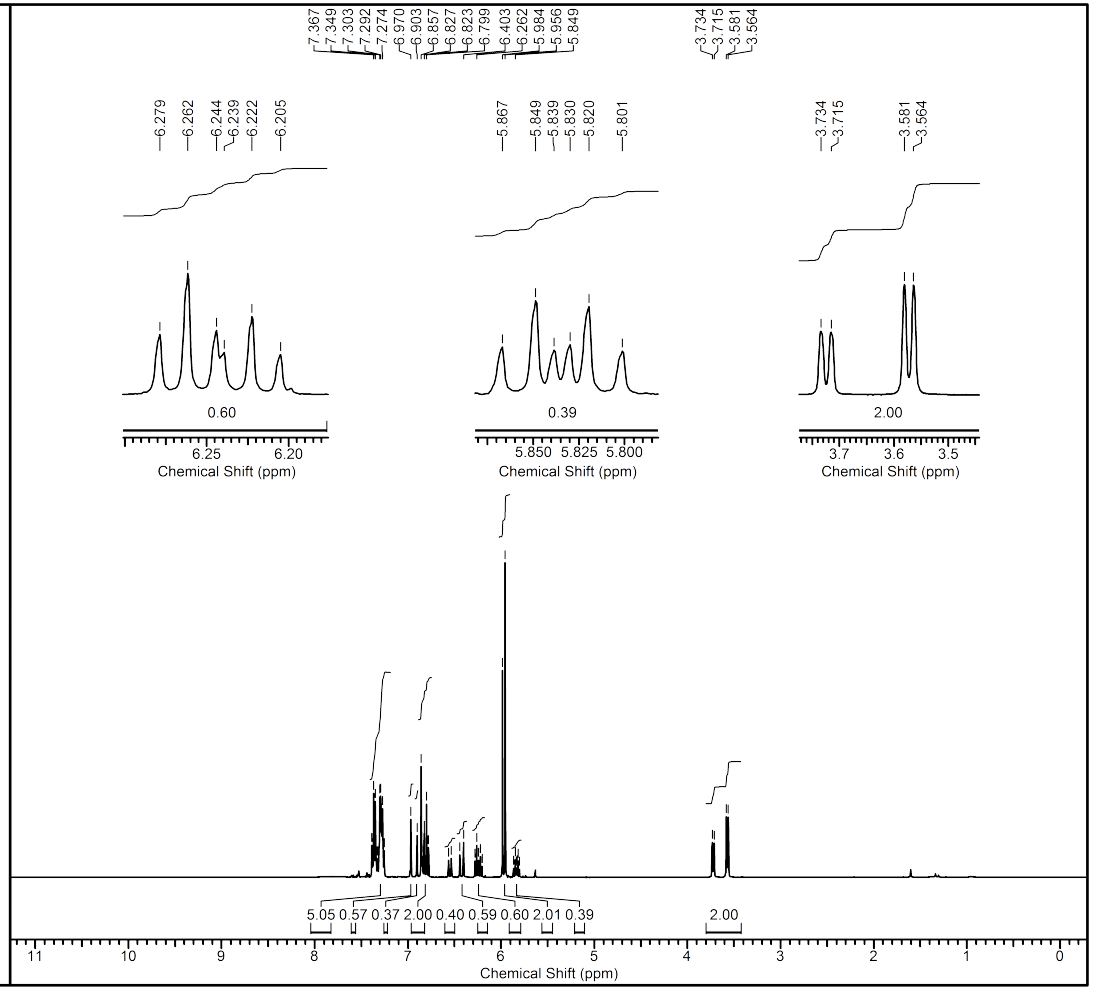


File Name	017-70C
Acquisition Time (sec)	3.9584
Date Stamp	06 Aug 2013 09:36
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2459.3420
Origin	spect
Receiver Gain	40.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

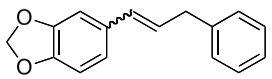


93

O'Brien™
Group NMR Data

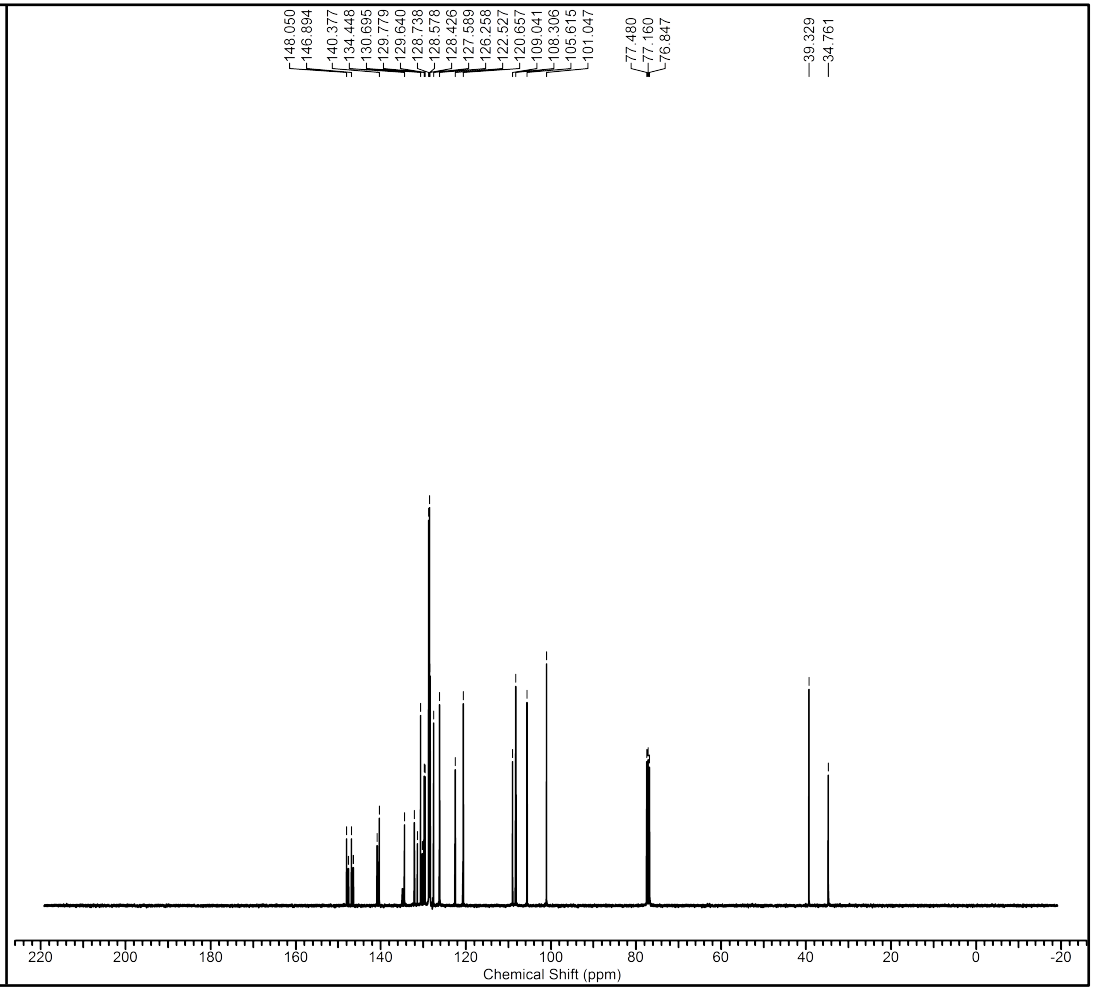


File Name	017-70C
Acquisition Time (sec)	1.3664
Date Stamp	06 Aug 2013 18:14
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10061.6143
Origin	spect
Receiver Gain	11585.20
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

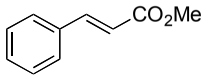


93

O'Brien™
Group NMR Data

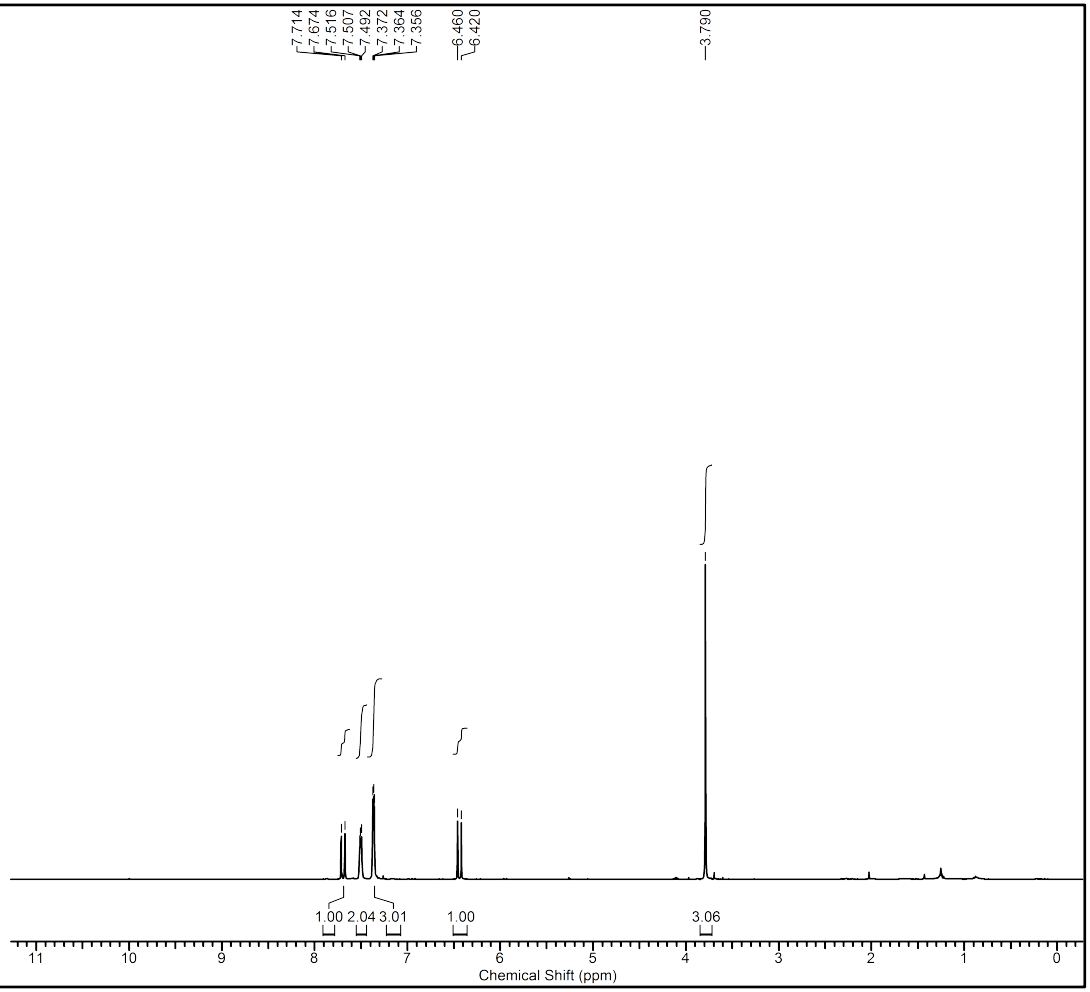


File Name	E_MeCinn
Acquisition Time (sec)	3.9584
Date Stamp	06 Dec 2012 10:29
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	17.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.9595
Origin	spect
Receiver Gain	32.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

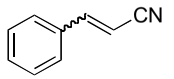


E-**94**

O'Brien™ Group NMR Data

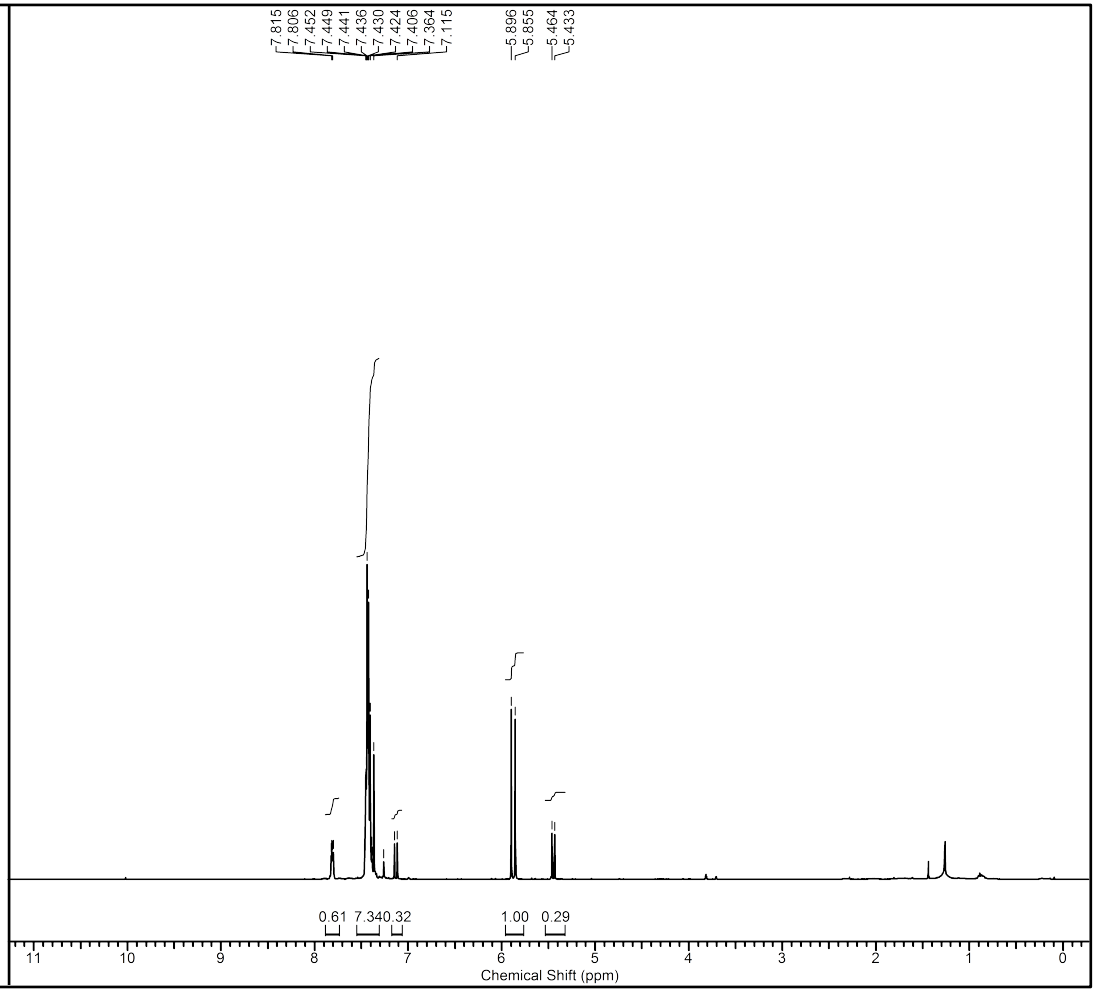


File Name	BCN_Mix
Acquisition Time (sec)	3.9584
Date Stamp	19 Nov 2012 16:19
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	17.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	57.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

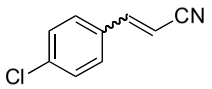


95

O'Brien™
Group NMR Data

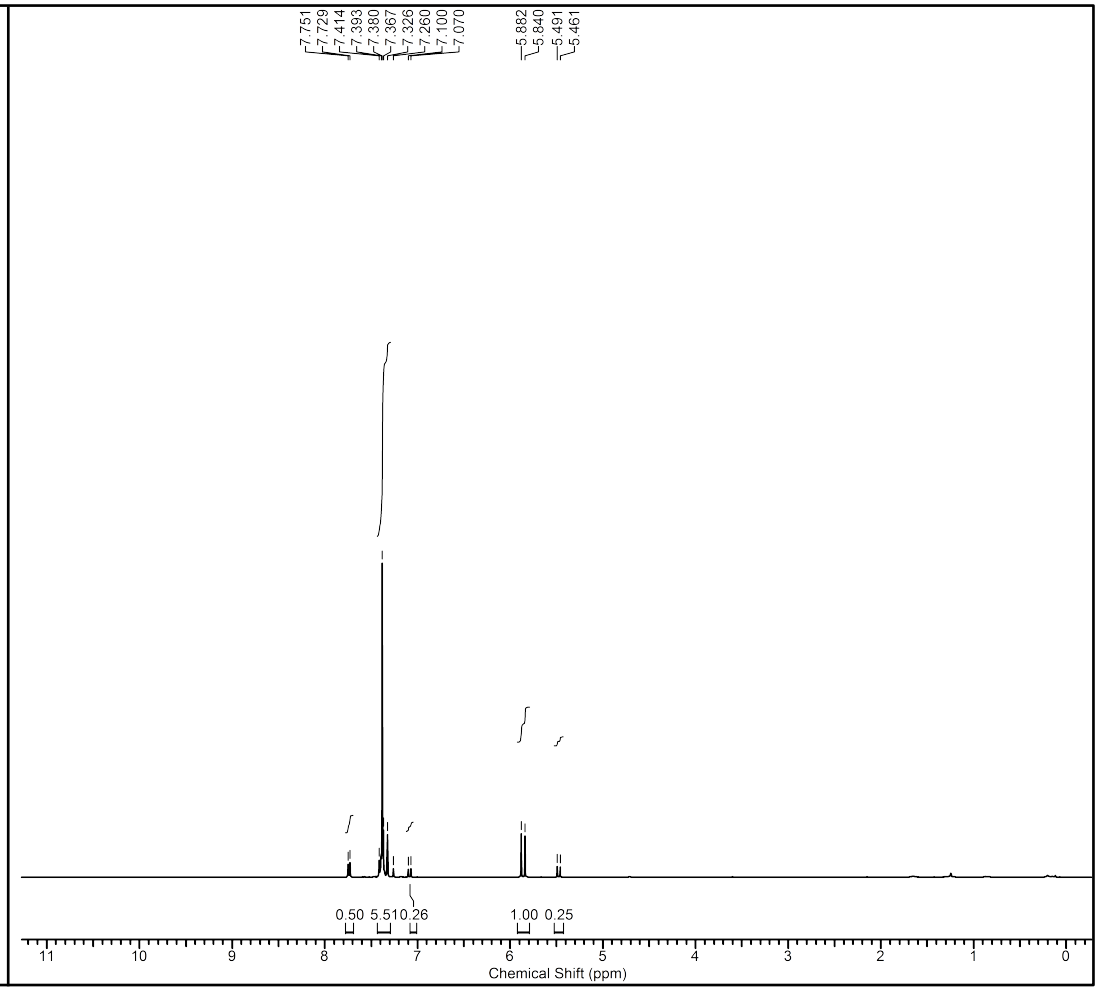


File Name	Cmpd_9
Acquisition Time (sec)	3.9584
Date Stamp	13 Nov 2012 18:05
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4546
Origin	spect
Receiver Gain	114.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

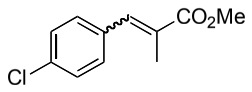


96

O'Brien™
Group NMR Data

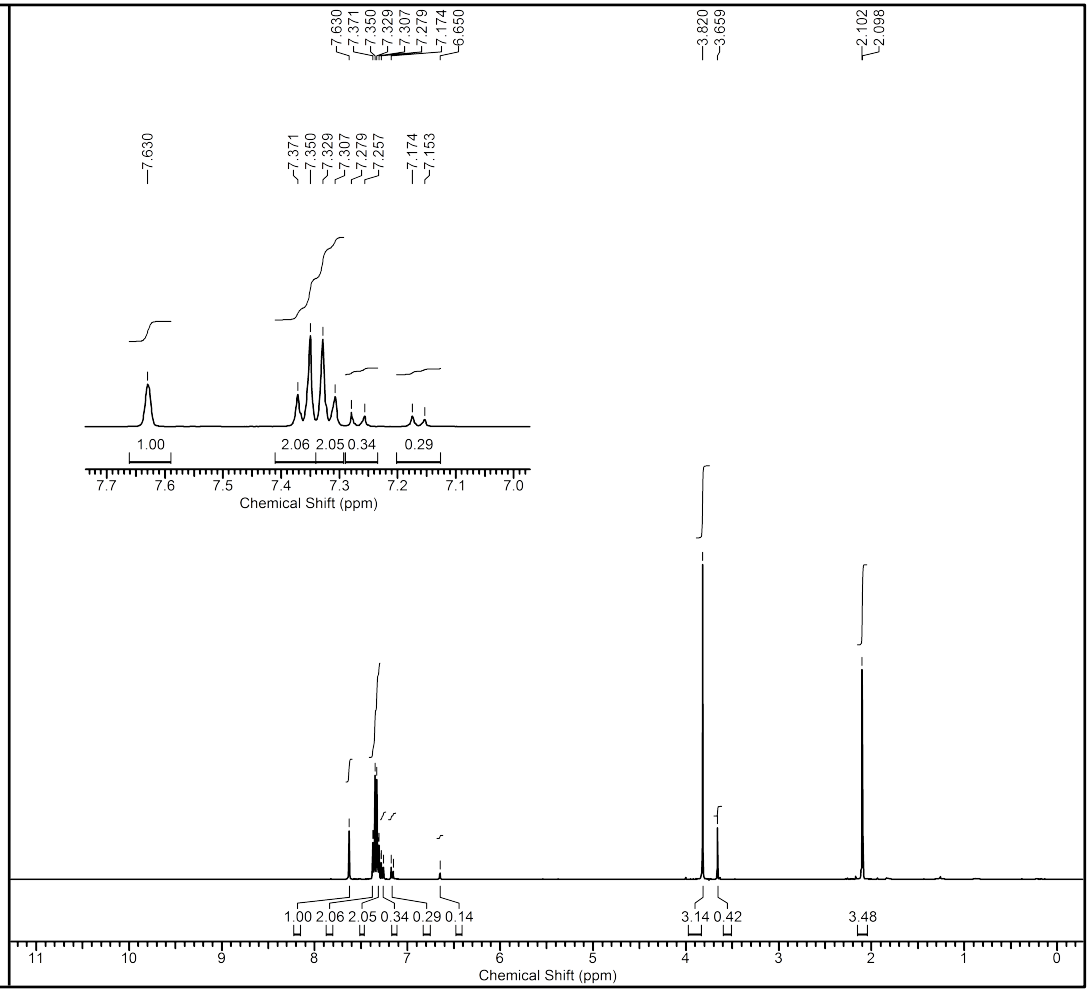


File Name	SK-60a
Acquisition Time (sec)	3.9584
Date Stamp	12 Nov 2012 16:21
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	19.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2469.4133
Origin	spect
Receiver Gain	45.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

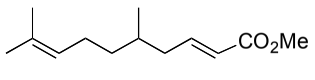


97

O'Brien™
Group NMR Data

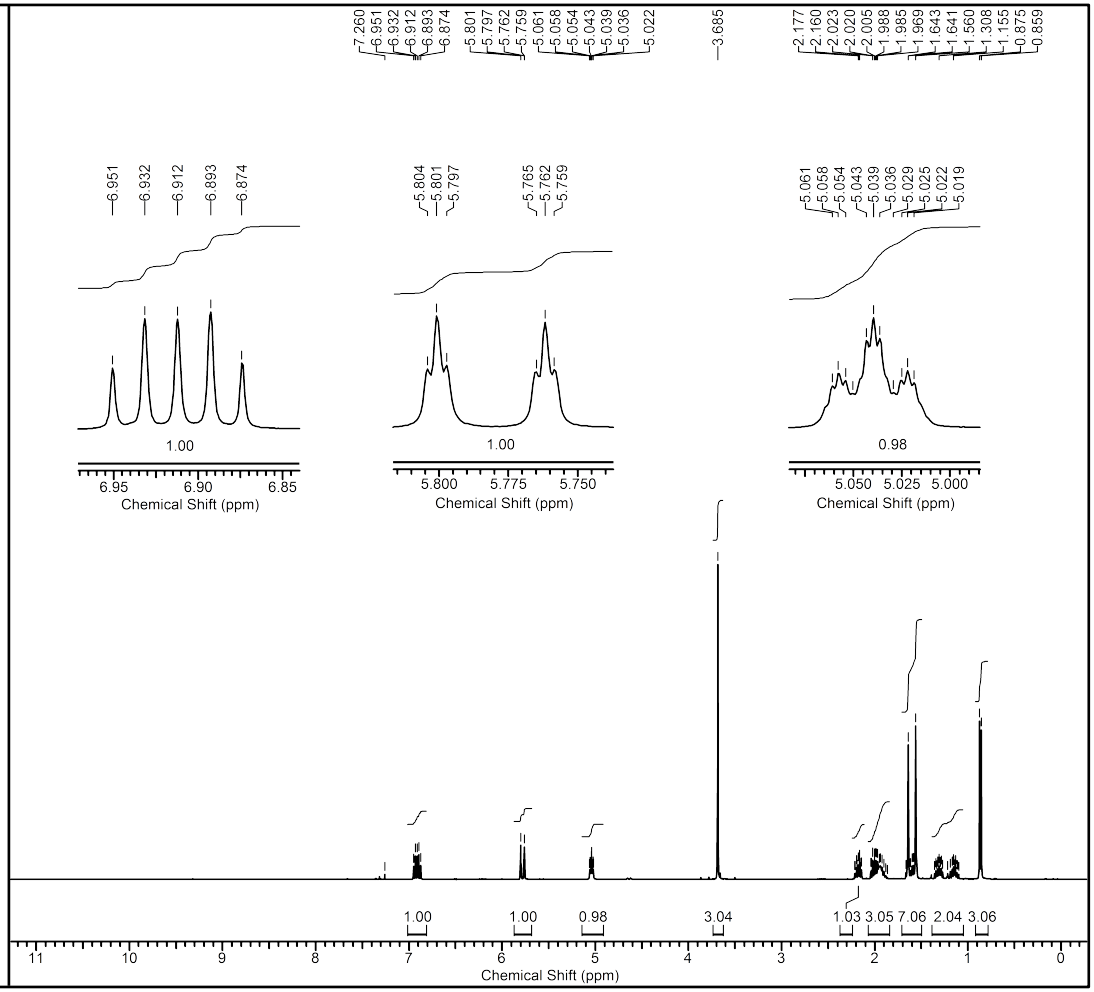


File Name	CitEst
Acquisition Time (sec)	3.9584
Date Stamp	27 Nov 2012 00:55
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	17.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2465.4553
Origin	spect
Receiver Gain	20.20
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

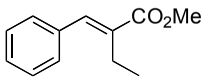


E-98

O'Brien™
Group NMR Data

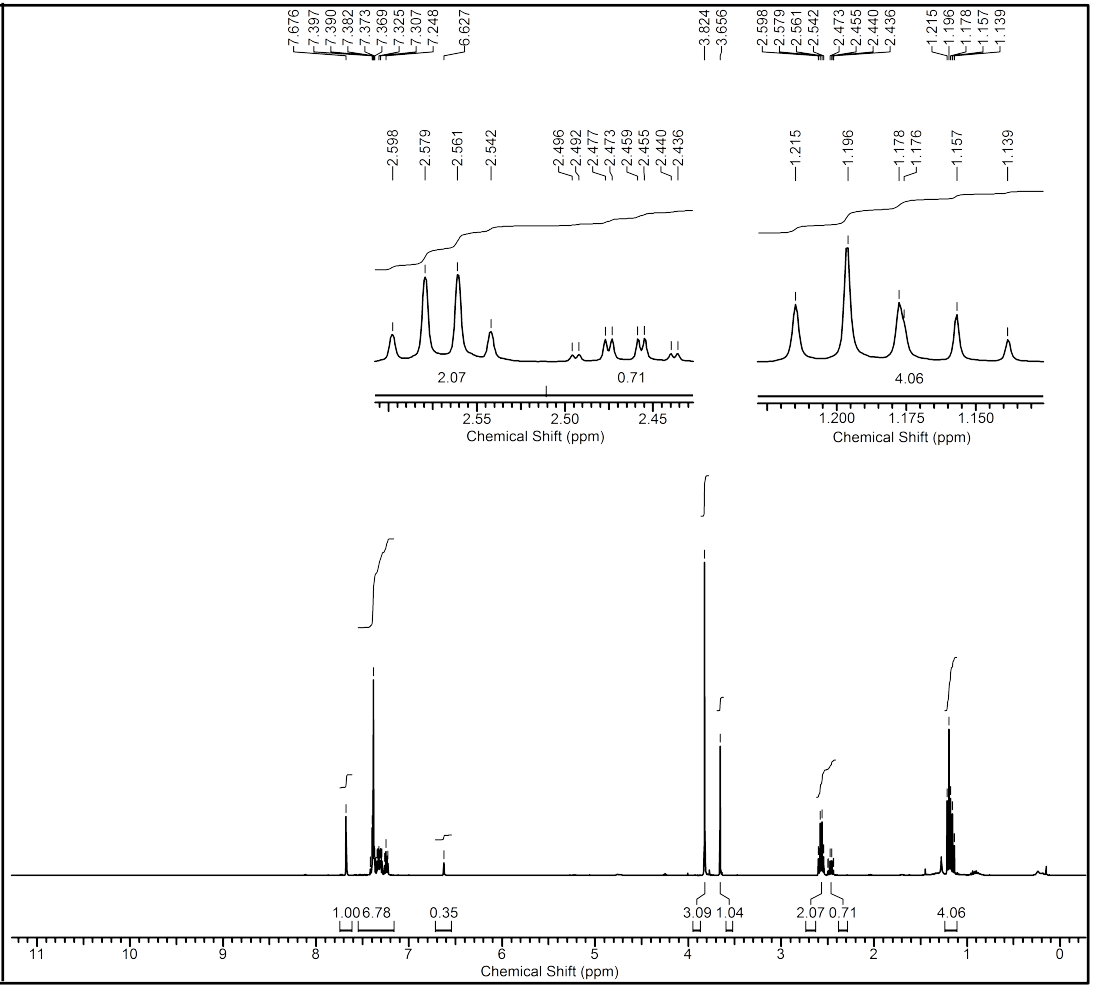


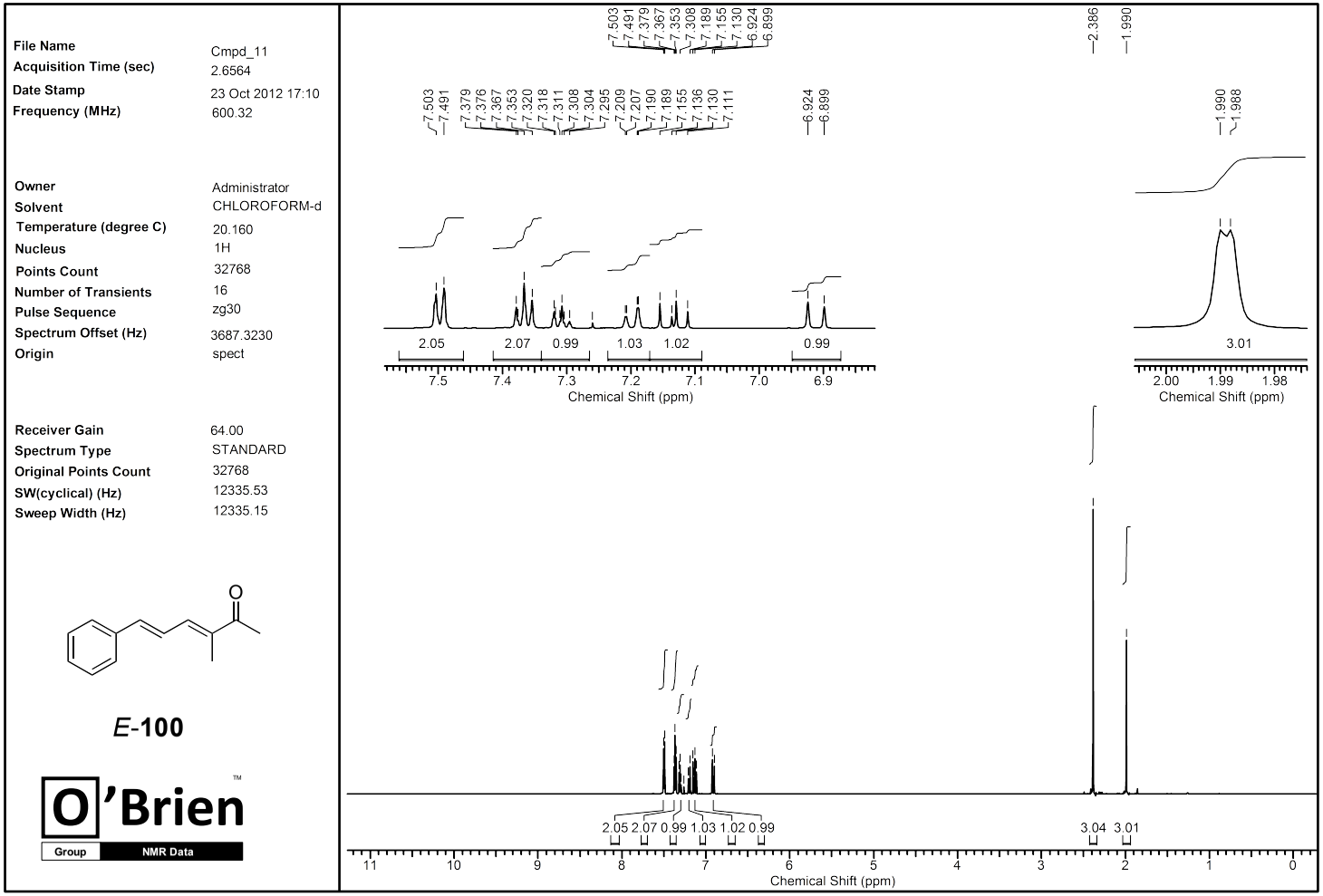
File Name	Cmpd_7
Acquisition Time (sec)	3.9584
Date Stamp	05 Sep 2012 12:05
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	19.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2463.3269
Origin	spect
Receiver Gain	28.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89



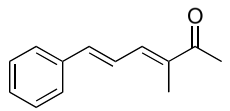
E-**99**

O'Brien™
Group NMR Data



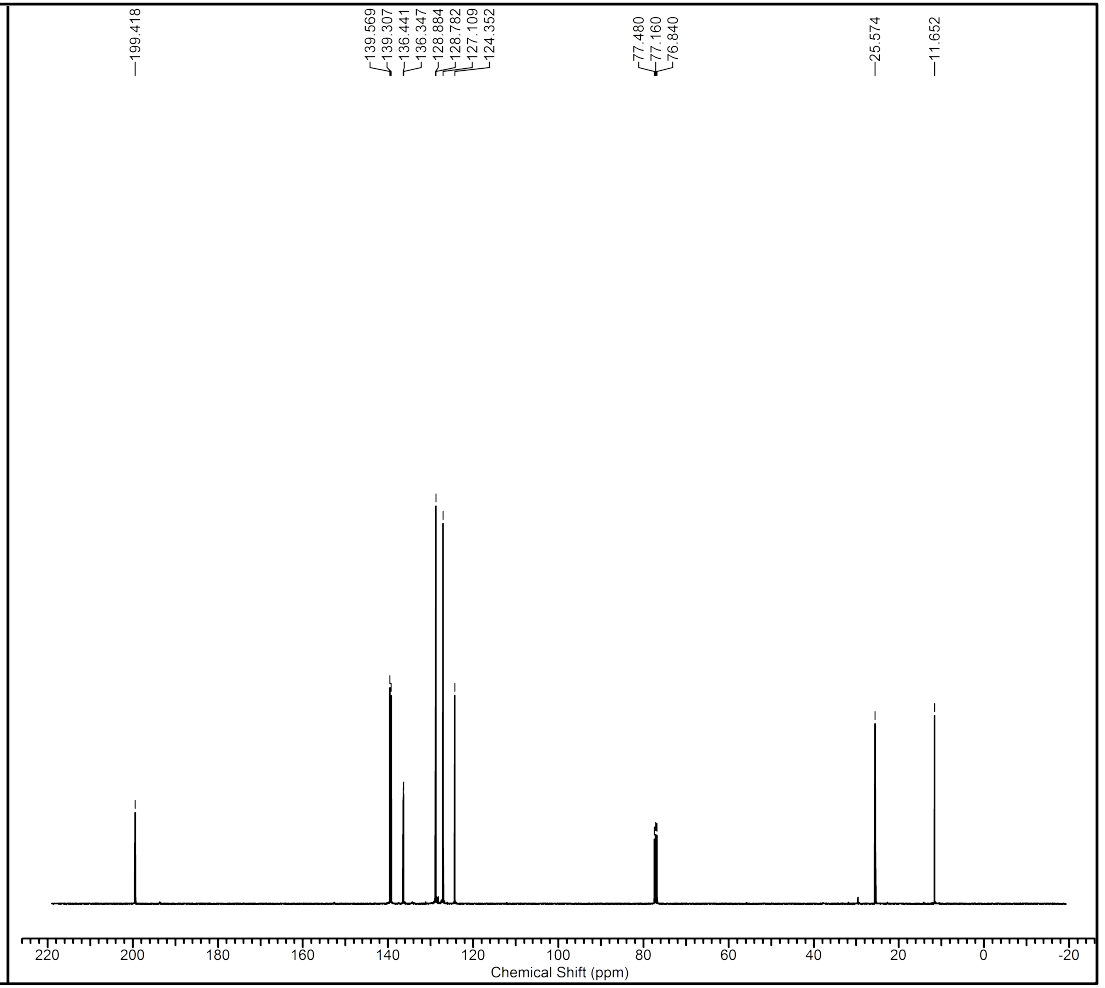

File Name Cmpd_11
Acquisition Time (sec) 2.6564
Date Stamp 23 Oct 2012 17:10
Frequency (MHz) 600.32
Owner Administrator
Solvent CHLOROFORM-d
Temperature (degree C) 20.160
Nucleus 1H
Points Count 32768
Number of Transients 16
Pulse Sequence zg30
Spectrum Offset (Hz) 3687.3230
Origin spect
Receiver Gain 64.00
Spectrum Type STANDARD
Original Points Count 32768
SW(cyclical) (Hz) 12335.53
Sweep Width (Hz) 12335.15
O
E-100
O'Brien
Group NMR Data
7.503 7.491 7.379 7.367 7.353 7.308 7.189 7.155 7.130 6.924 6.899
2.386 1.990
2.05 2.07 0.99 1.03 1.02 0.99
3.01
Chemical Shift (ppm)
2.05 2.07 0.99 1.03 1.02 0.99
3.04 3.01
Chemical Shift (ppm)

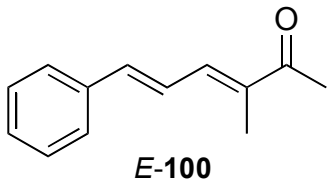
File Name	Cmpd_11
Acquisition Time (sec)	1.3664
Date Stamp	22 Jun 2012 18:57
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	21.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10052.1113
Origin	spect
Receiver Gain	2048.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08



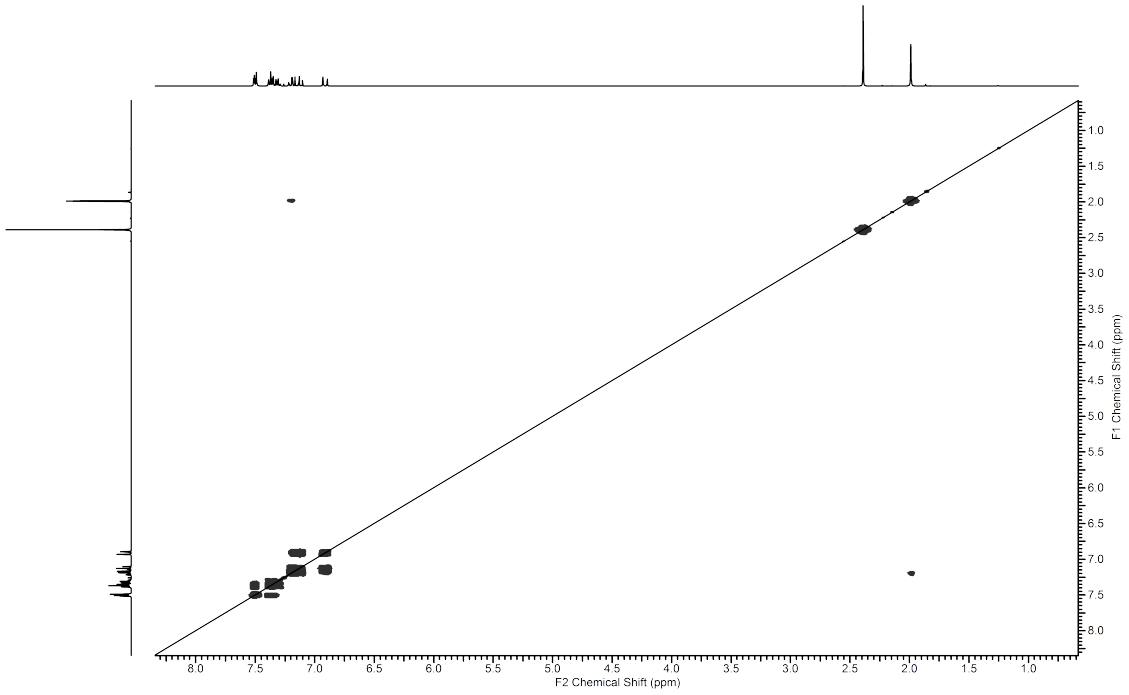
E-100

O'Brien™
Group NMR Data

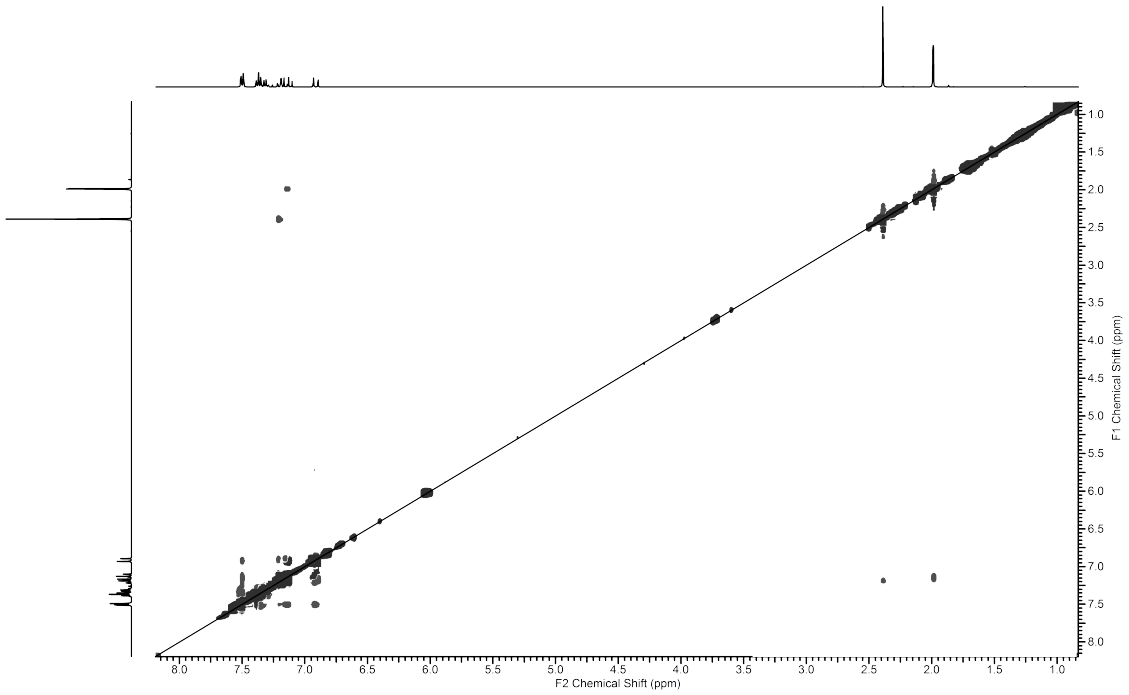




E-**100**

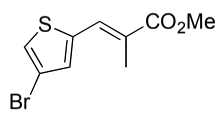


$^{1}H/^{1}H$ COSY (600 MHz, $CDCl_3$)



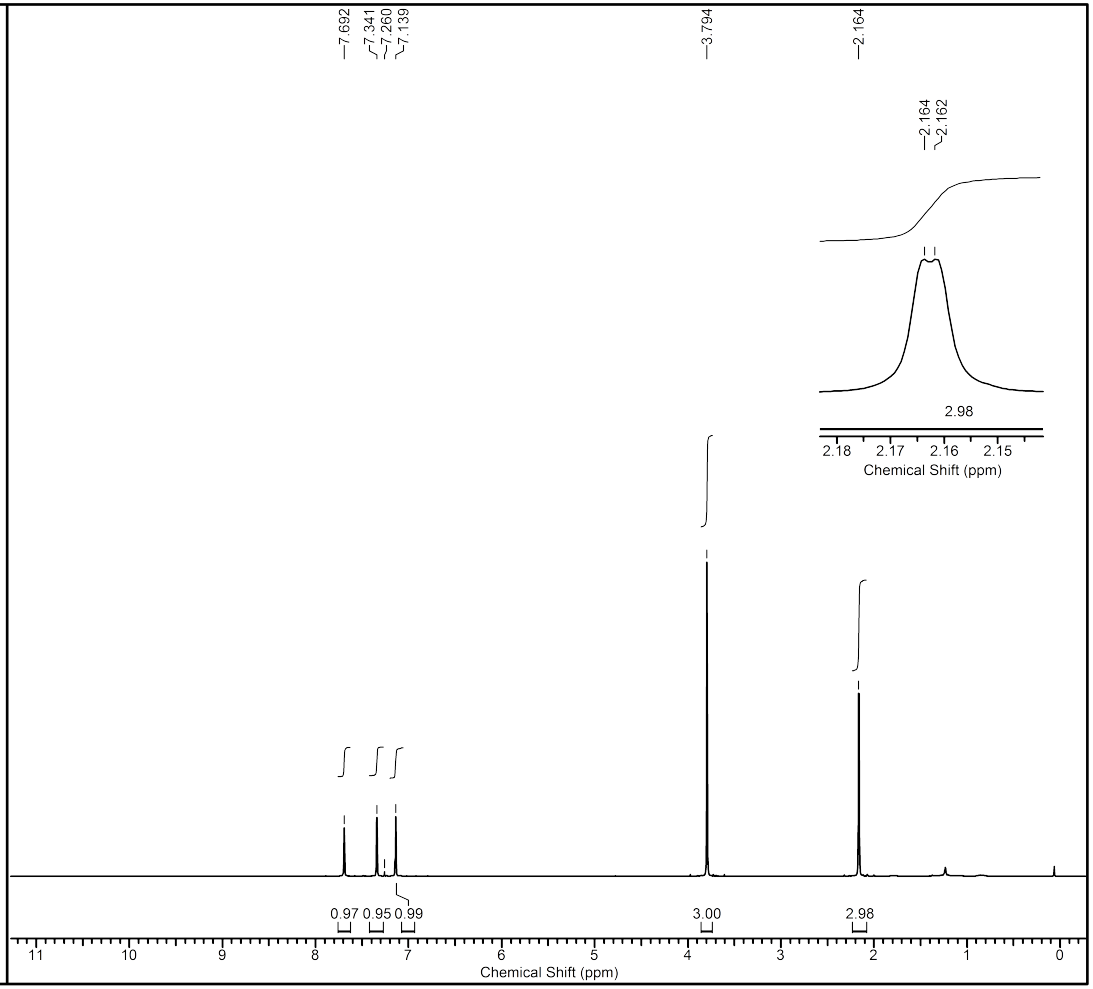
$^{1}H/^{1}H$ NOESY (600 MHz, $CDCl_3$)

File Name	Cmpd_3
Acquisition Time (sec)	3.9584
Date Stamp	20 Apr 2012 02:48
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	57.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

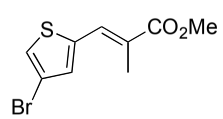


***E*-101**

O'Brien™
Group NMR Data

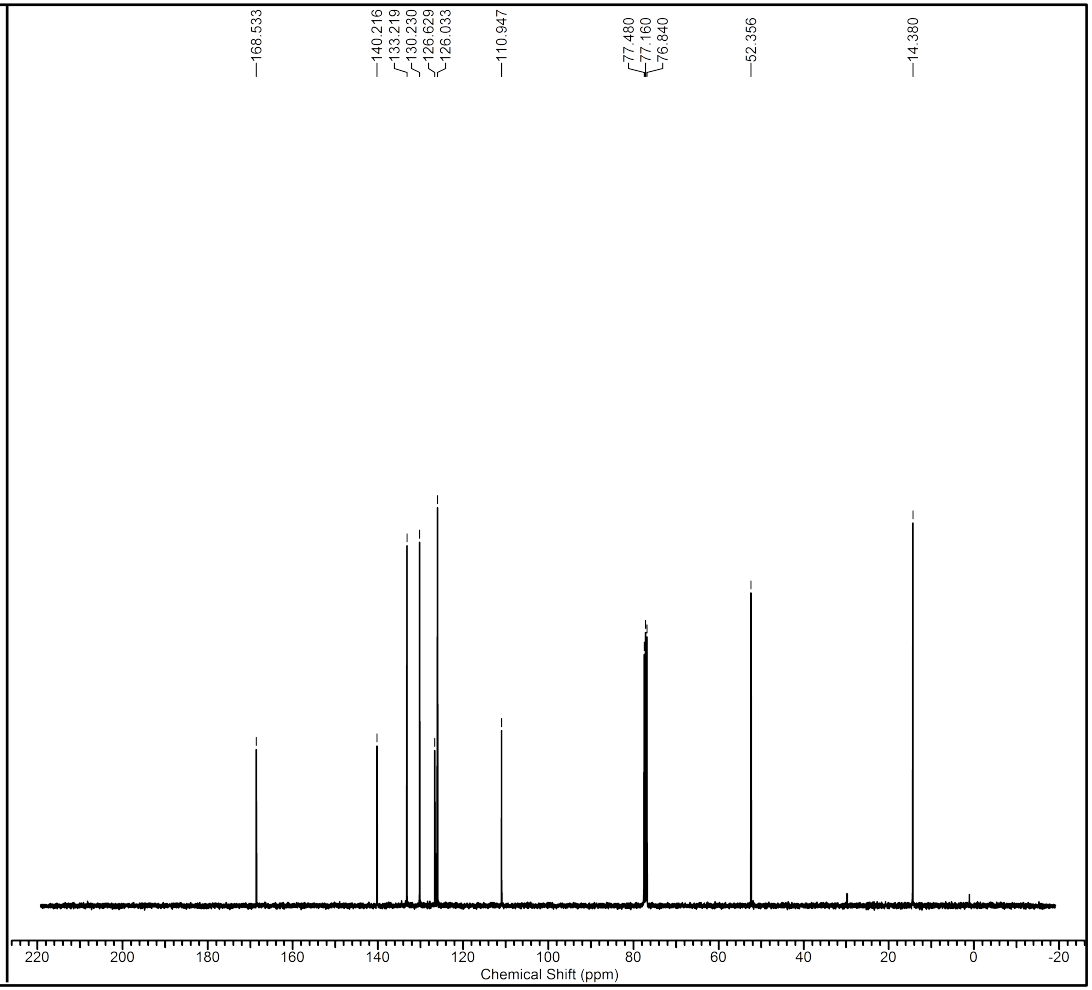


File Name	Cmpd_3
Acquisition Time (sec)	1.3664
Date Stamp	20 Apr 2012 03:48
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10066.0127
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08

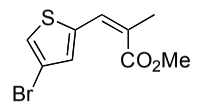


E-**101**

O'Brien™
Group NMR Data

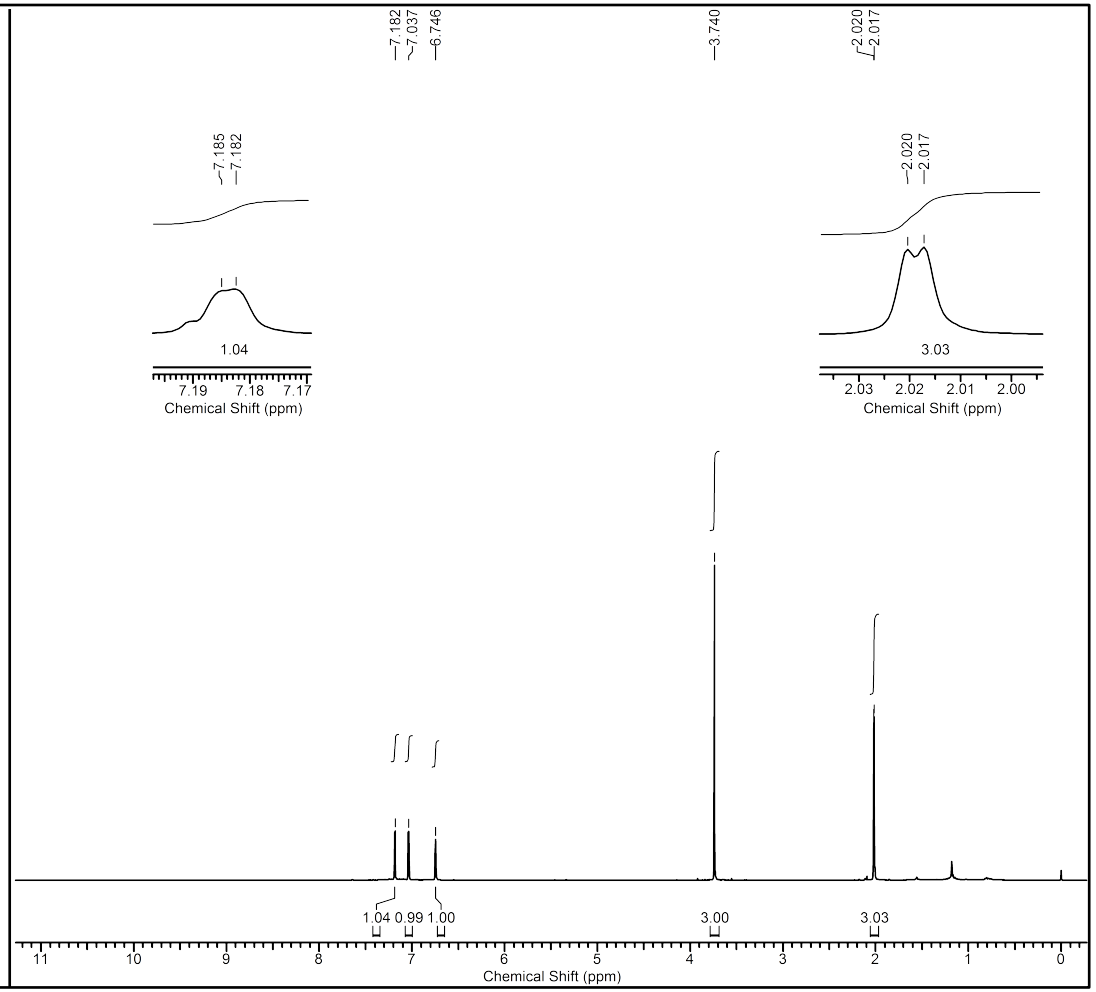


File Name	Cmpd_3
Acquisition Time (sec)	3.9584
Date Stamp	20 Apr 2012 01:32
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2433.7009
Origin	spect
Receiver Gain	90.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

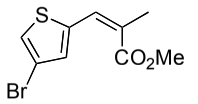


Z-101

O'Brien™
Group NMR Data

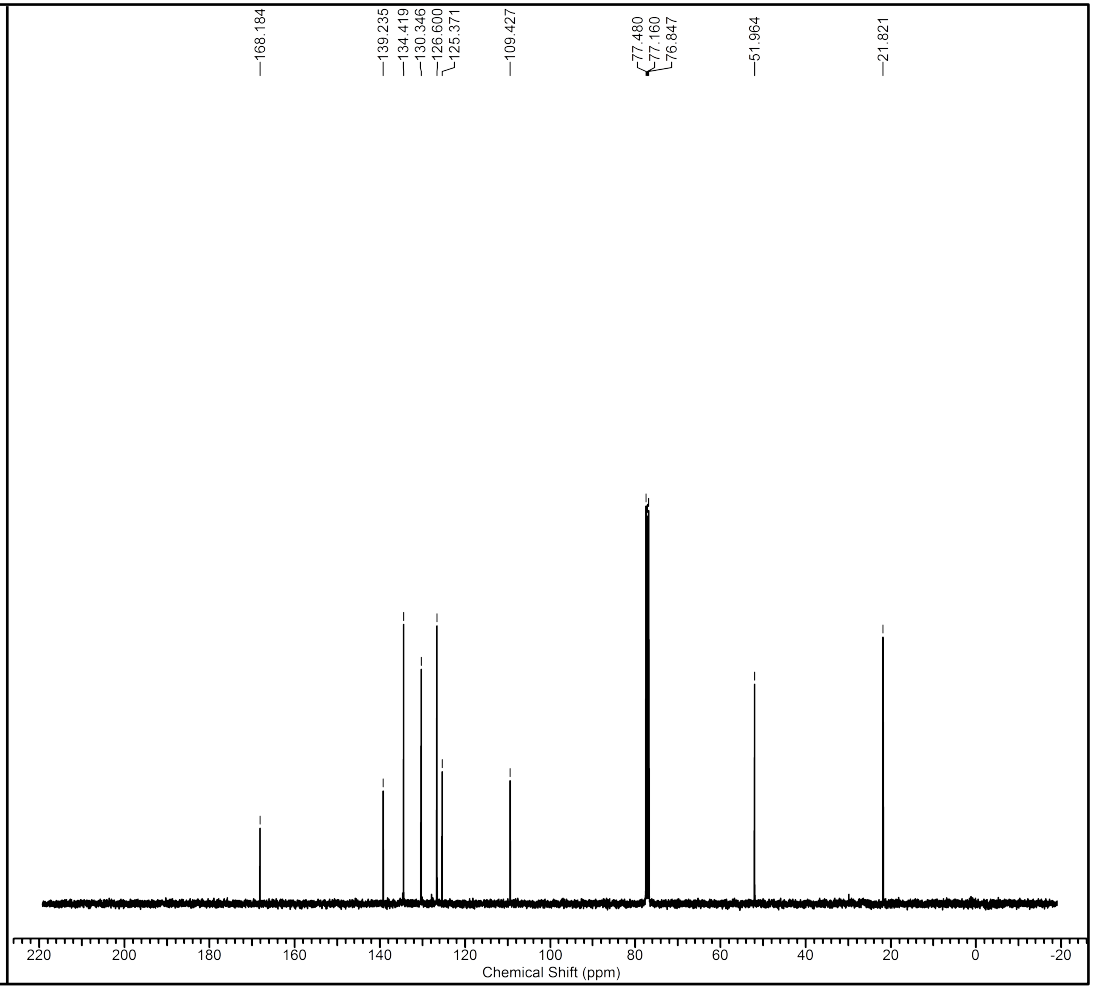


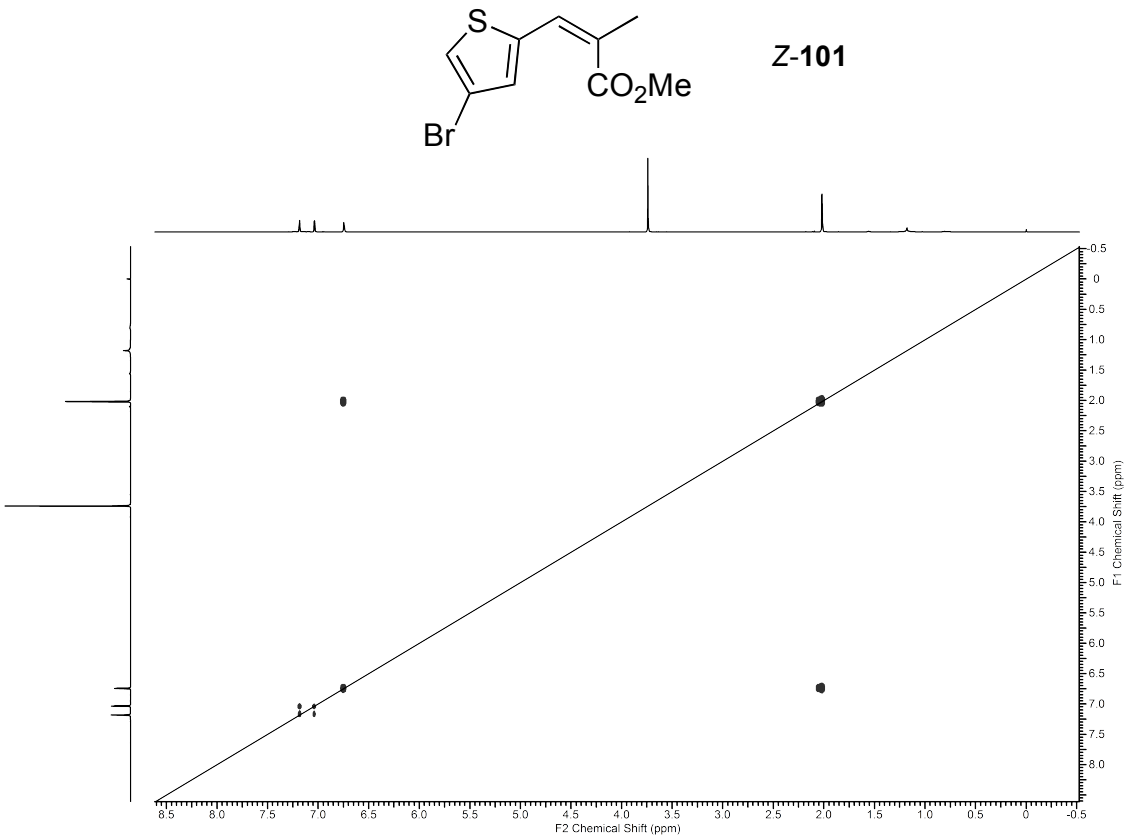
File Name	Cmpd_3
Acquisition Time (sec)	1.3664
Date Stamp	20 Apr 2012 02:31
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10070.3955
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08



***Z*-101**

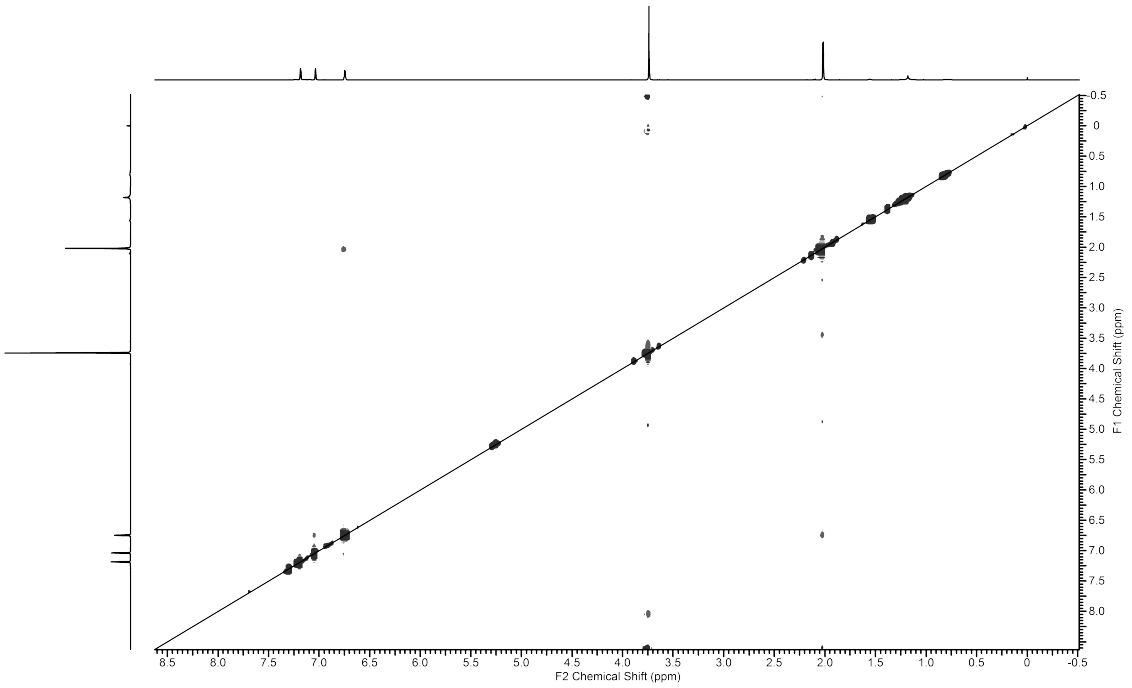
O'Brien™
Group NMR Data





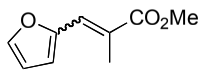
Z-**101**

$^1H/^1H$ COSY (600 MHz, $CDCl_3$)



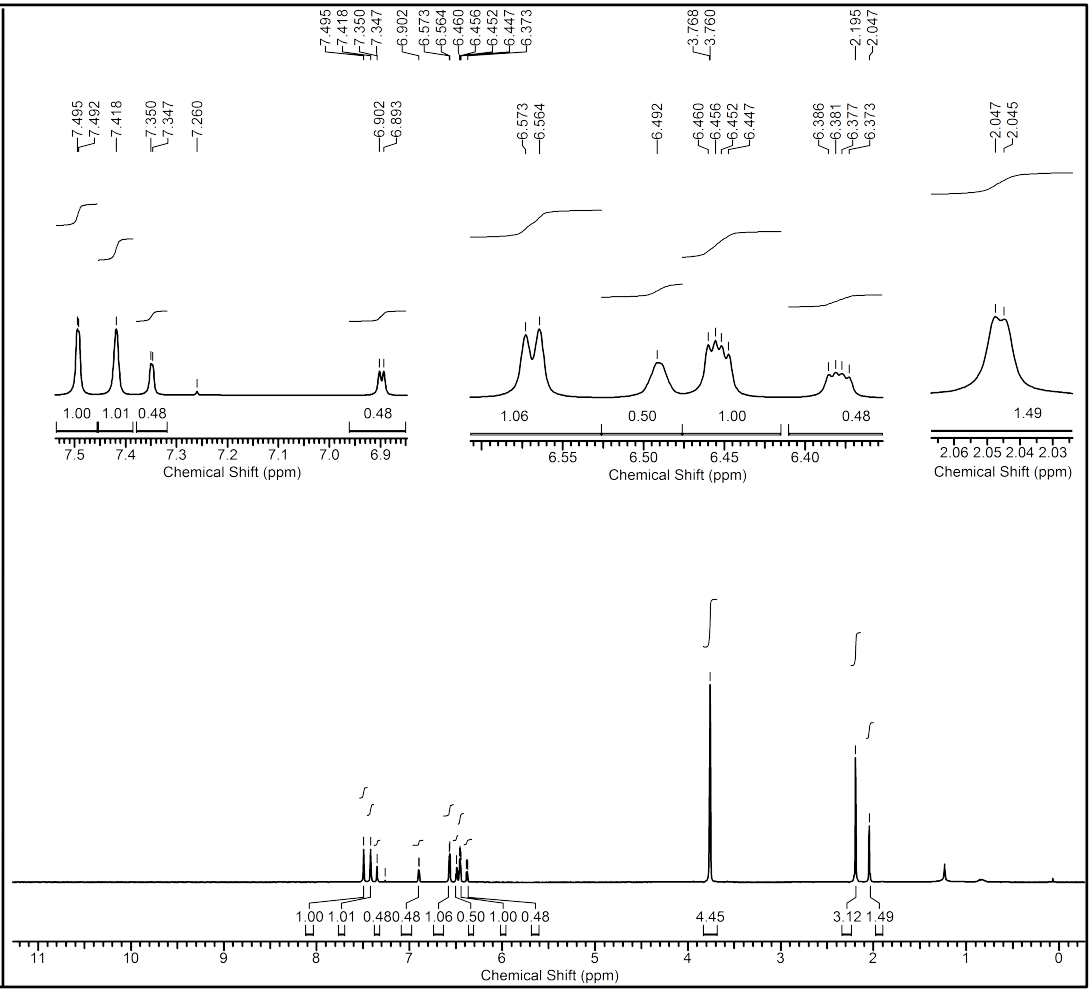
$^1H/^1H$ NOESY (600 MHz, $CDCl_3$)

File Name	Cmpd_2
Acquisition Time (sec)	3.9584
Date Stamp	07 Jun 2012 11:57
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	22.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.7065
Origin	spect
Receiver Gain	28.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

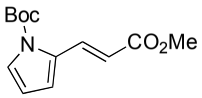


102

O'Brien™
Group NMR Data

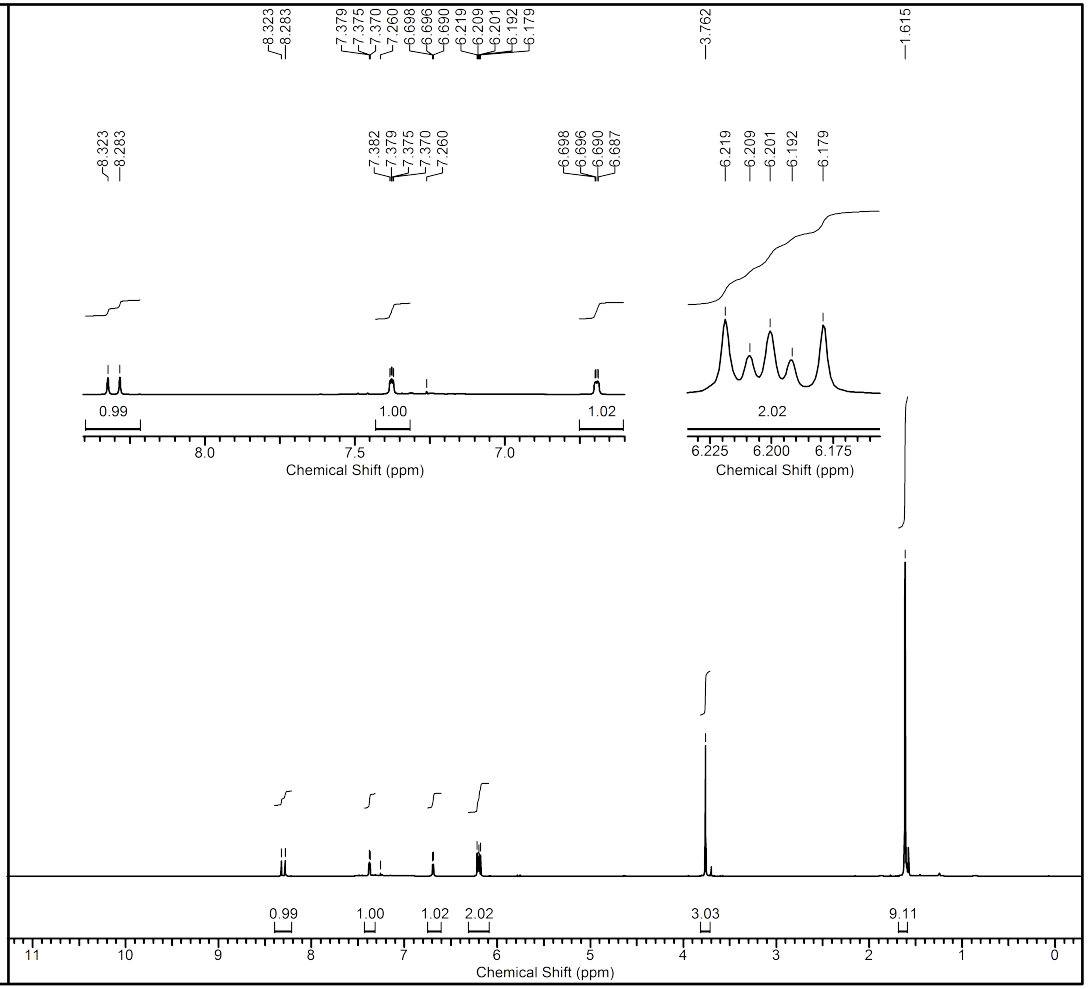


File Name	Cmpd_10
Acquisition Time (sec)	3.9584
Date Stamp	01 Aug 2012 18:18
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	19.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	45.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

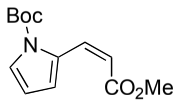


***E*-103**

O'Brien™
Group NMR Data

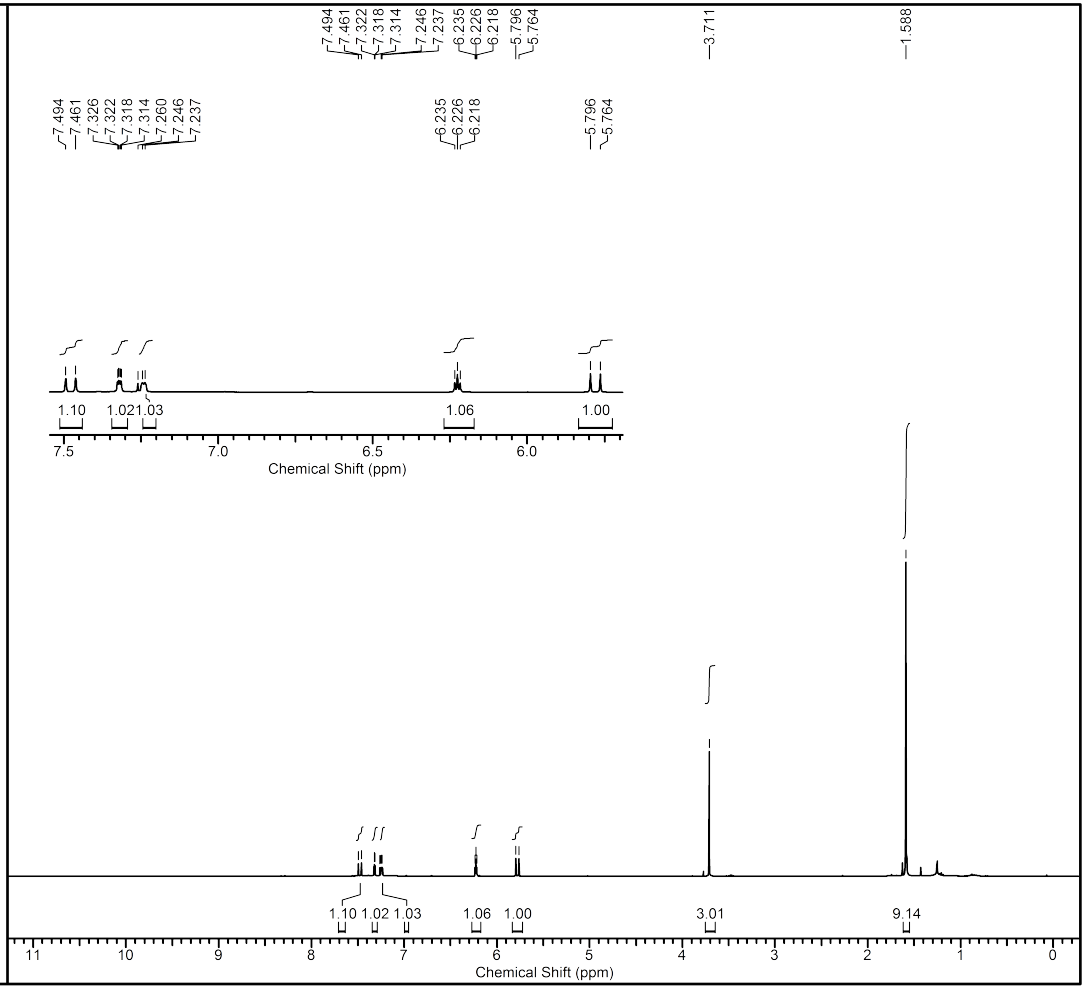


File Name	Cmpd_10
Acquisition Time (sec)	3.9584
Date Stamp	22 Oct 2012 23:41
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	90.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

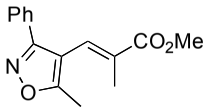


***Z*-103**

O'Brien™
Group NMR Data

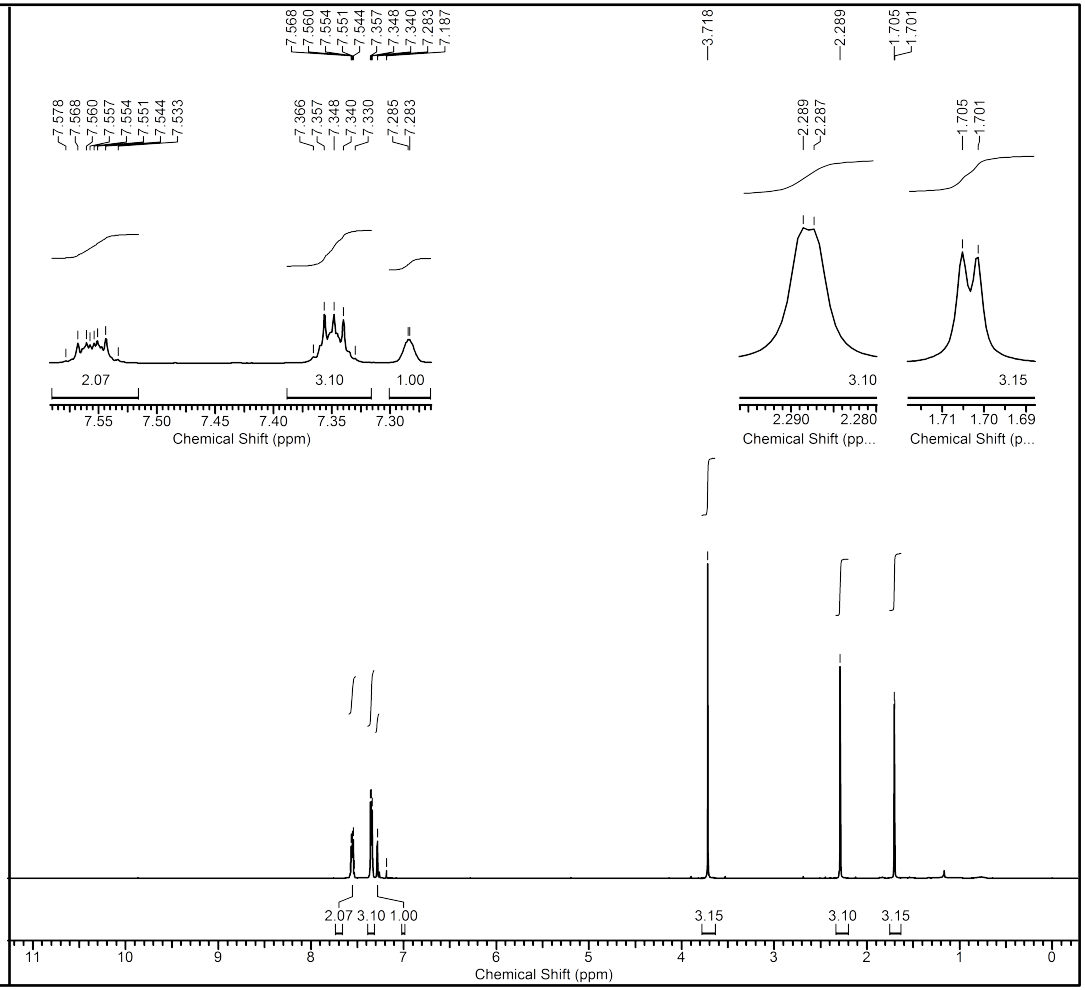


File Name	Cmpd_11
Acquisition Time (sec)	3.9584
Date Stamp	05 Nov 2012 20:48
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	18.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2432.3828
Origin	spect
Receiver Gain	45.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

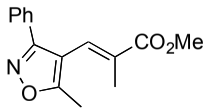


***E*-104**

O'Brien™
Group NMR Data

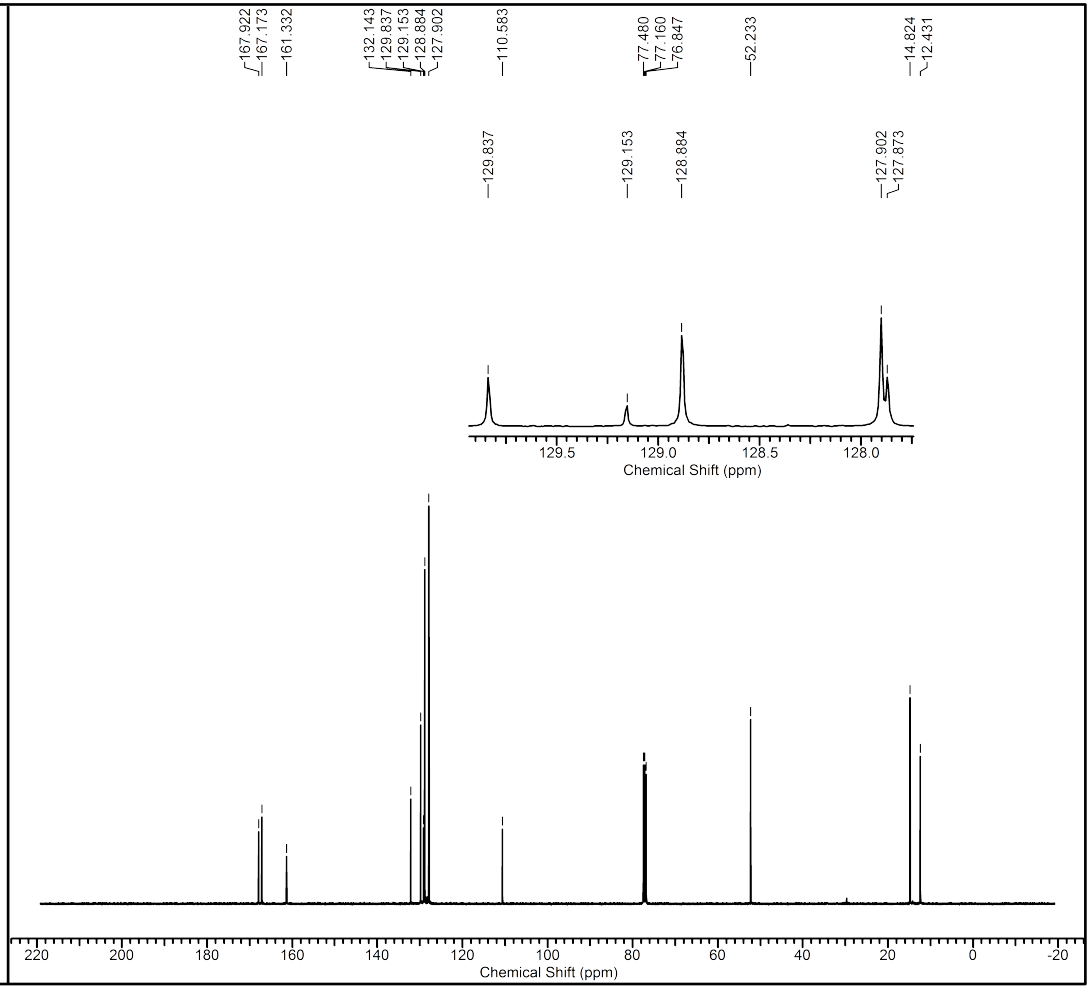


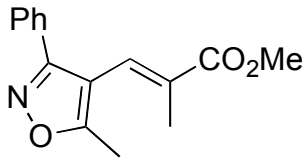
File Name	Cmpd_11
Acquisition Time (sec)	1.3664
Date Stamp	05 Nov 2012 21:47
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	19.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10063.8096
Origin	spect
Receiver Gain	13004.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08



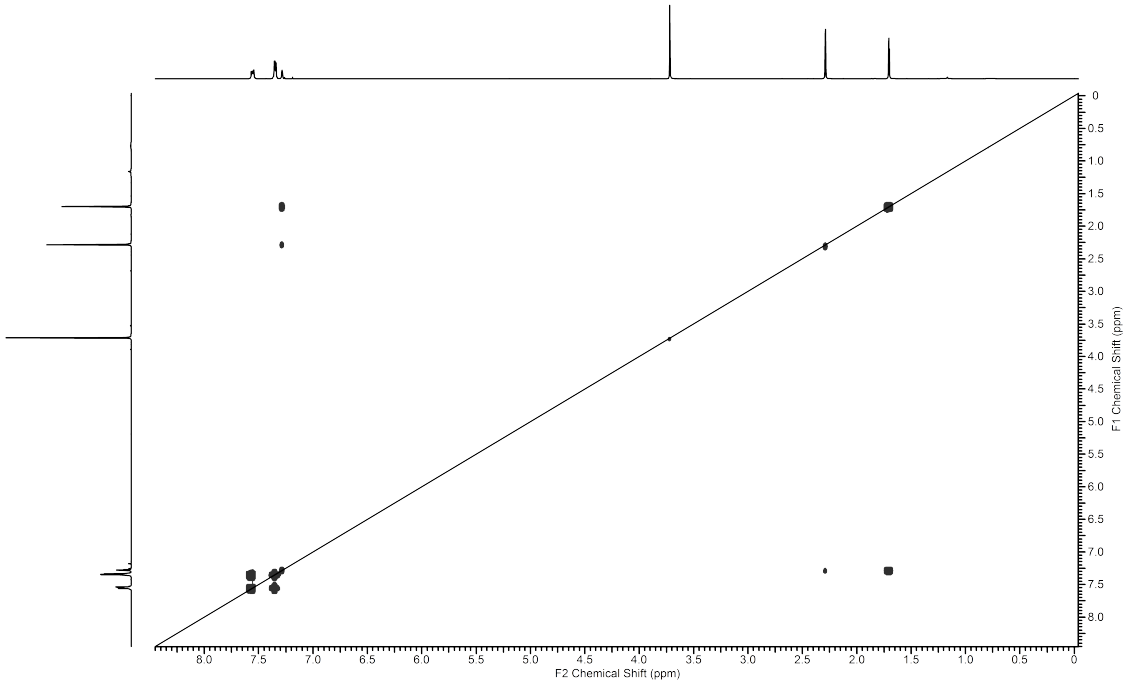
***E*-104**

O'Brien™
Group NMR Data

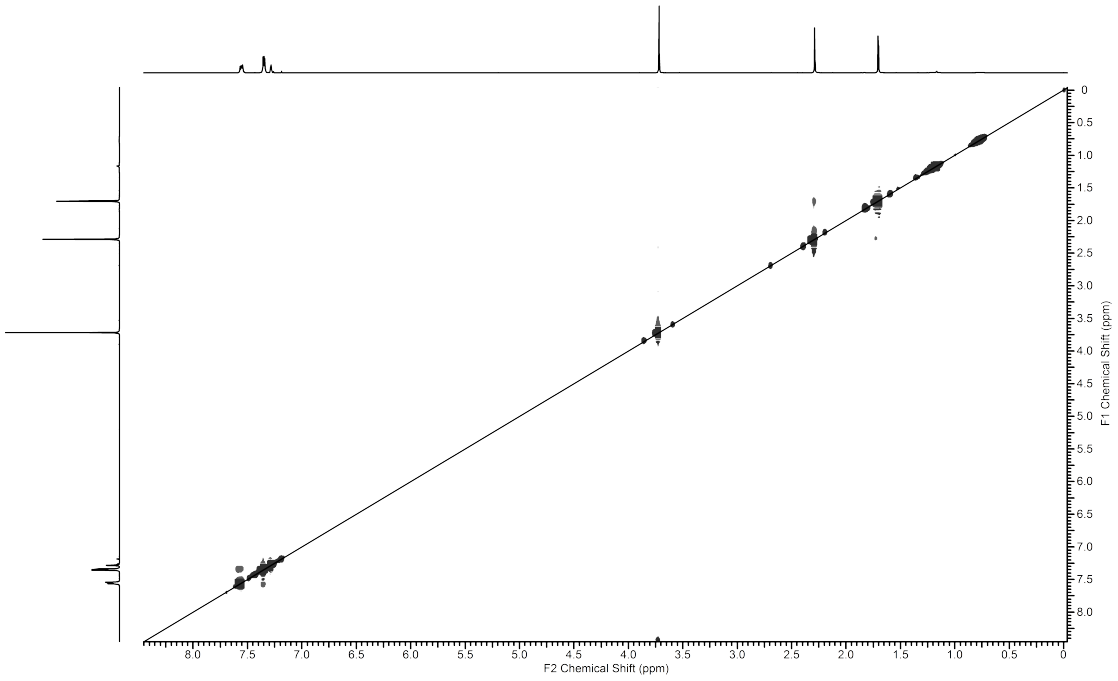




E-**104**

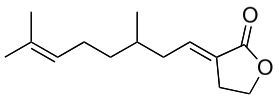


$^1H/^1H$ COSY (600 MHz, $CDCl_3$)



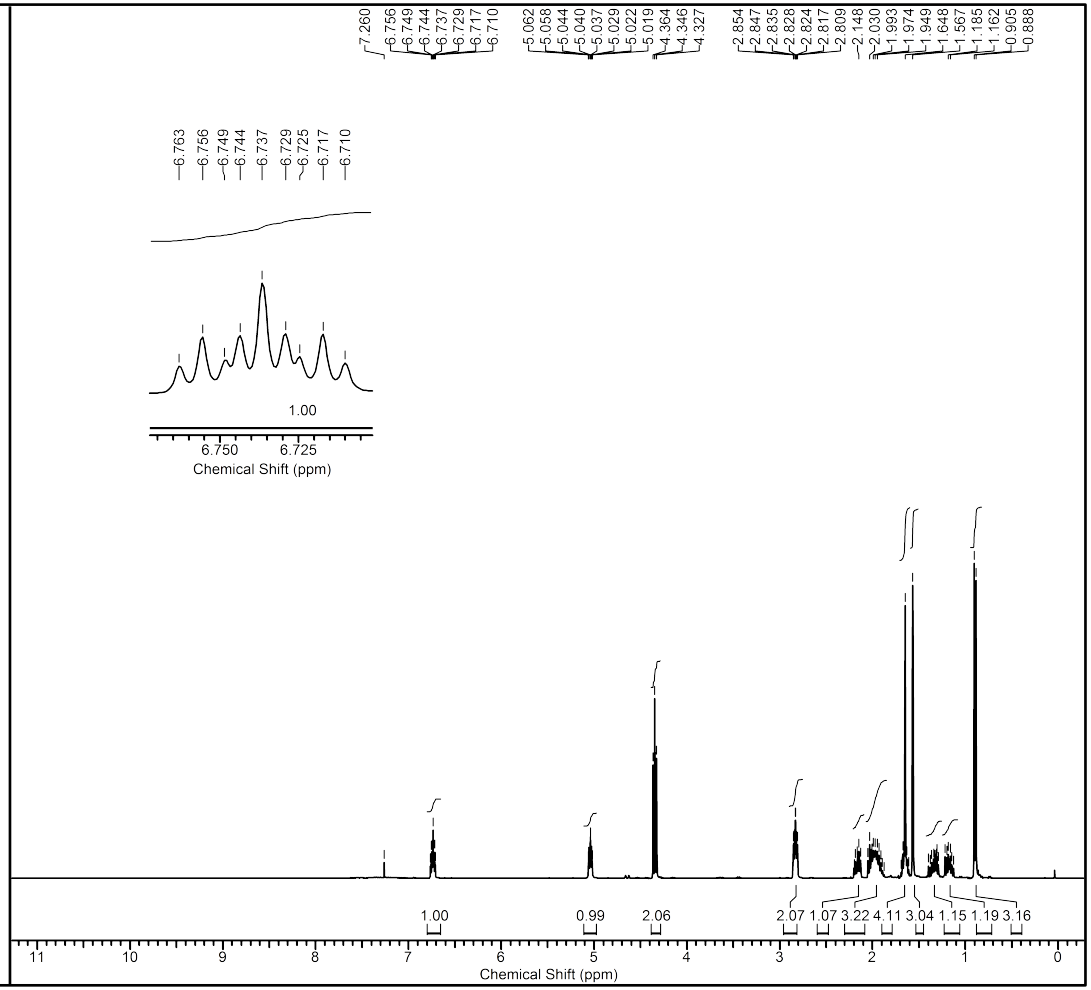
$^1H/^1H$ NOESY (600 MHz, $CDCl_3$)

File Name	Cmpd_5
Acquisition Time (sec)	3.9584
Date Stamp	05 Apr 2012 11:12
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	18.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.7068
Origin	spect
Receiver Gain	35.90
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

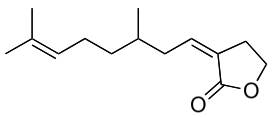


E-105

O'Brien™ Group NMR Data

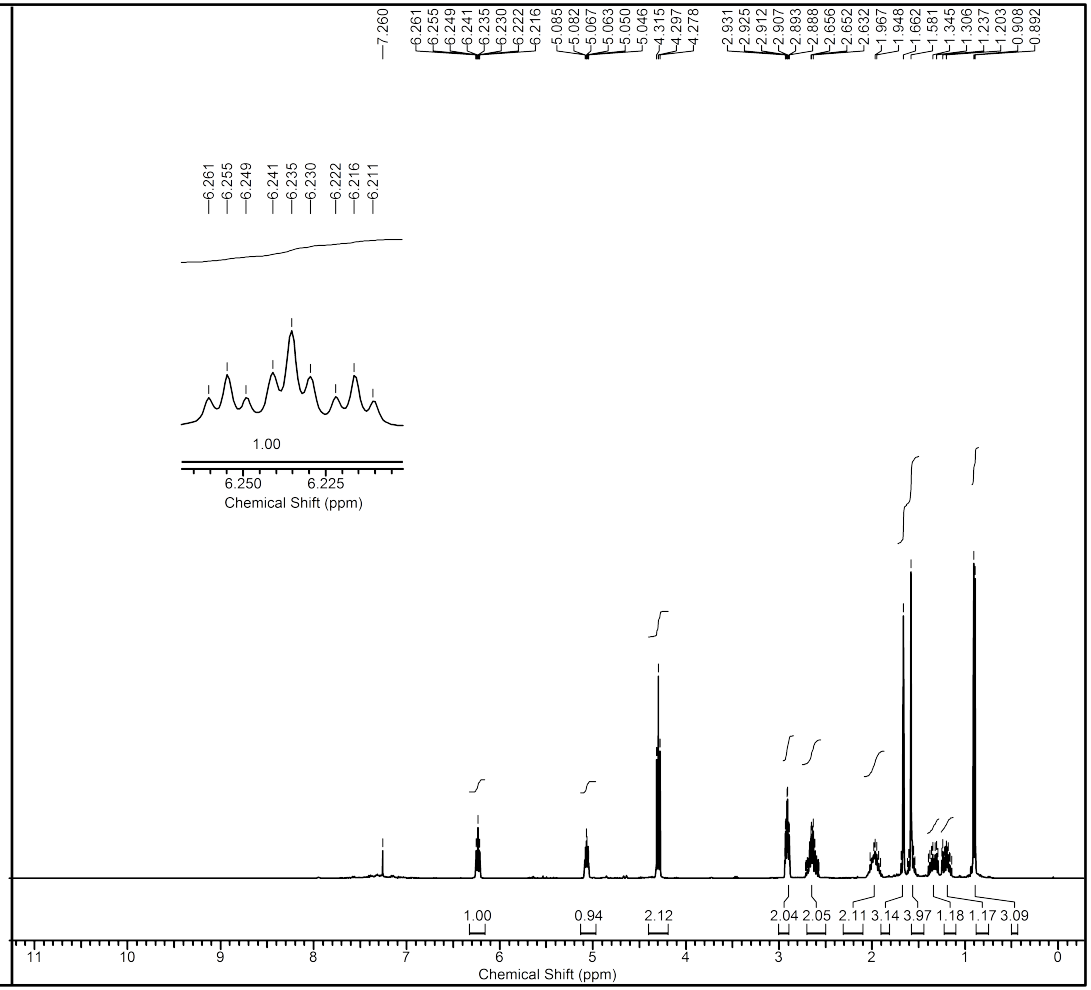


File Name	Cmpd_5
Acquisition Time (sec)	3.9584
Date Stamp	11 Jul 2012 13:28
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	19.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	50.80
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

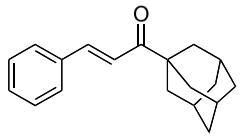


Z-105

O'Brien™
Group NMR Data

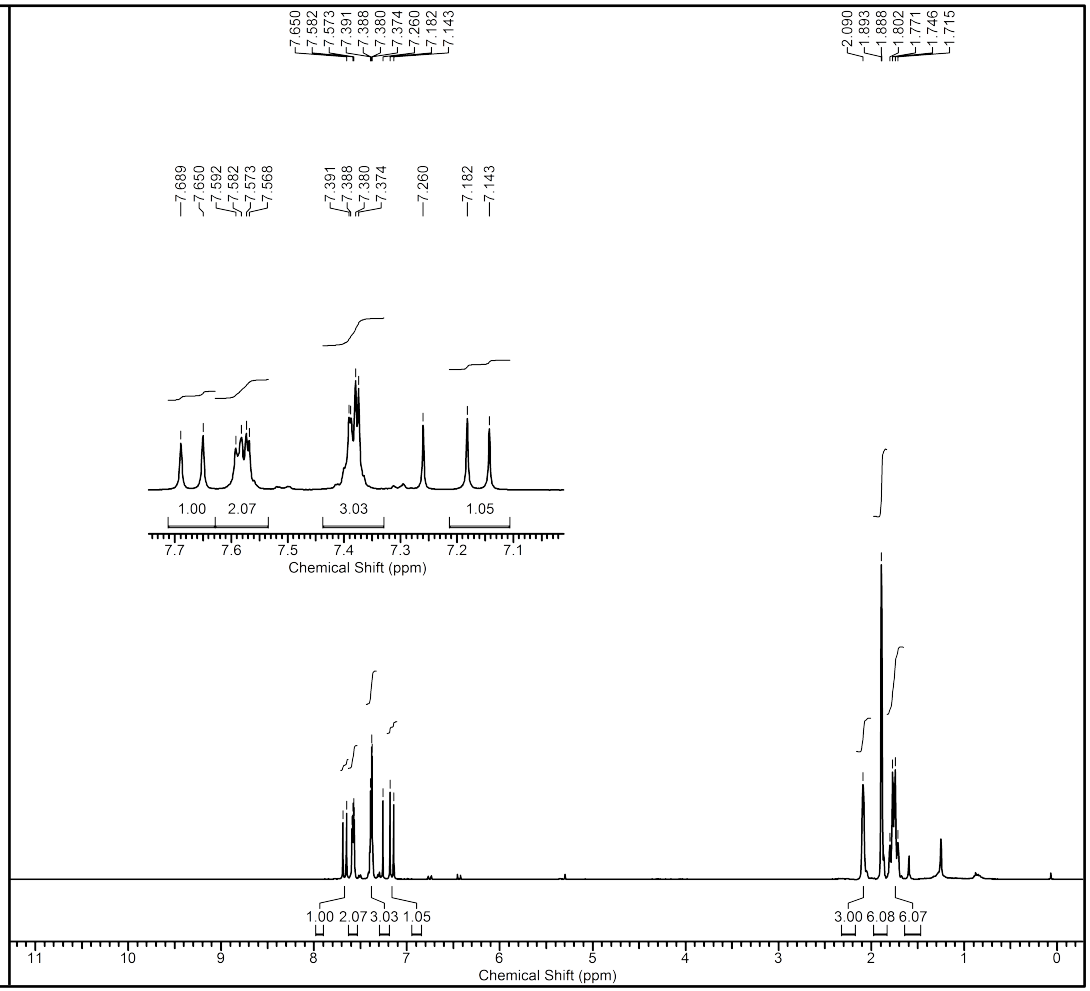


File Name	BenzAd
Acquisition Time (sec)	3.9584
Date Stamp	15 Nov 2012 12:45
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.2014
Origin	spect
Receiver Gain	322.50
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

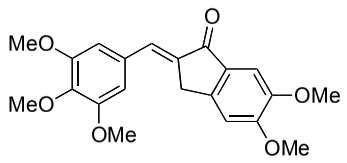


***E*-106**

O'Brien™
Group NMR Data

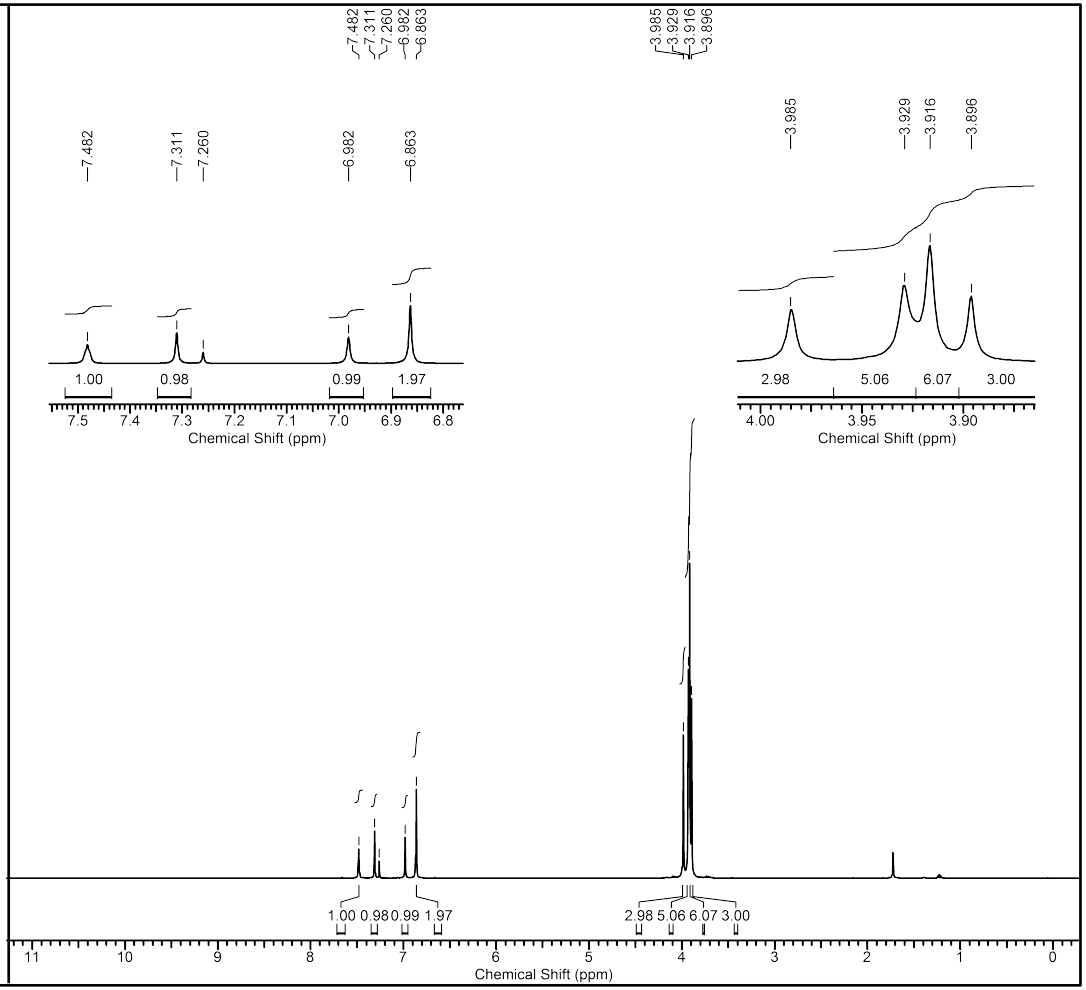


File Name	Cmpd_17
Acquisition Time (sec)	3.9584
Date Stamp	08 Aug 2012 11:57
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	19.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.2017
Origin	spect
Receiver Gain	128.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

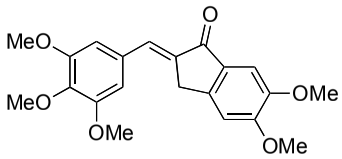


***E*-107**

O'Brien™
Group NMR Data

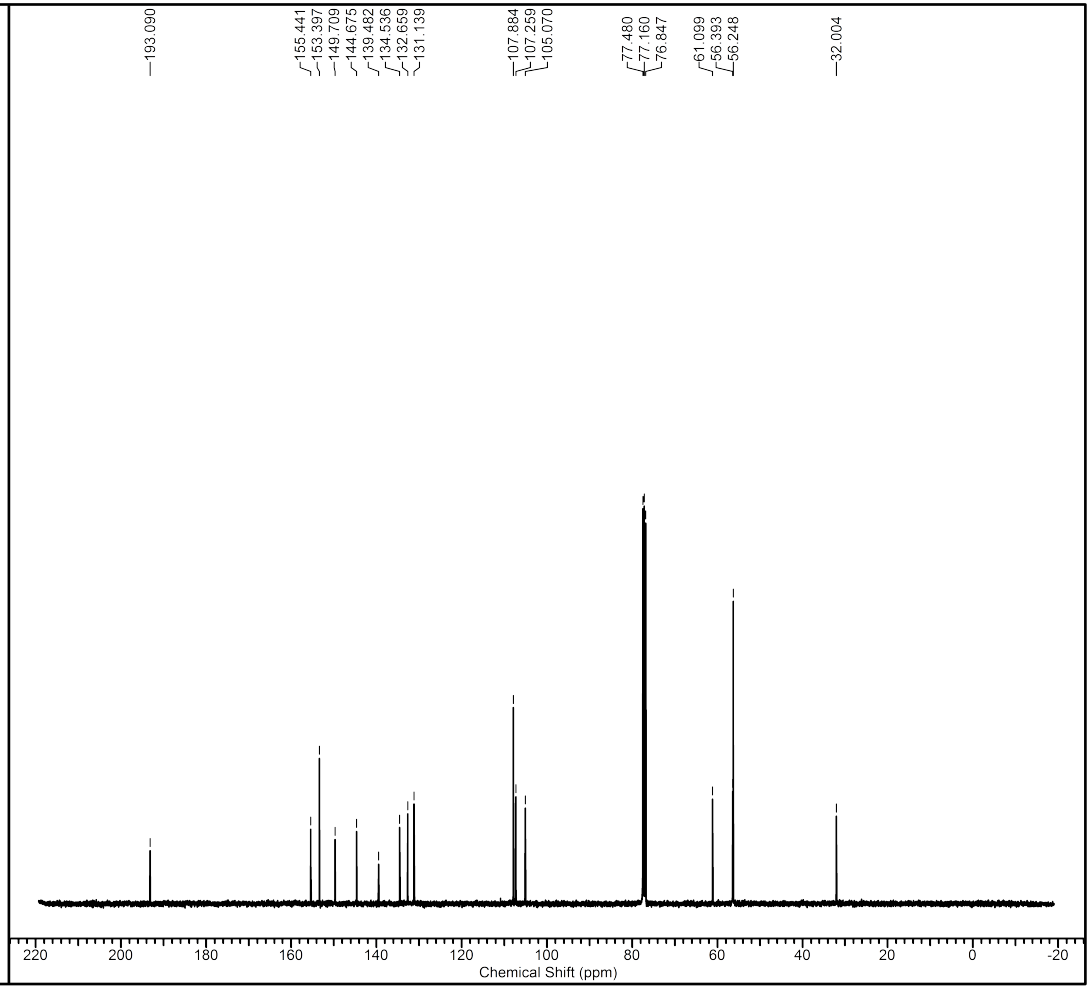


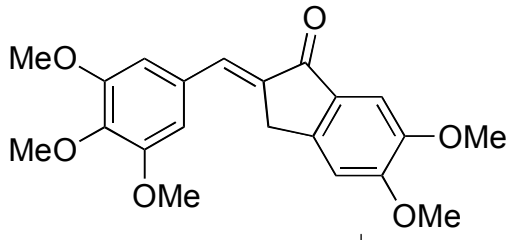
File Name	Cmpd_17
Acquisition Time (sec)	1.3664
Date Stamp	10 Aug 2012 02:23
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	19.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10068.9316
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08



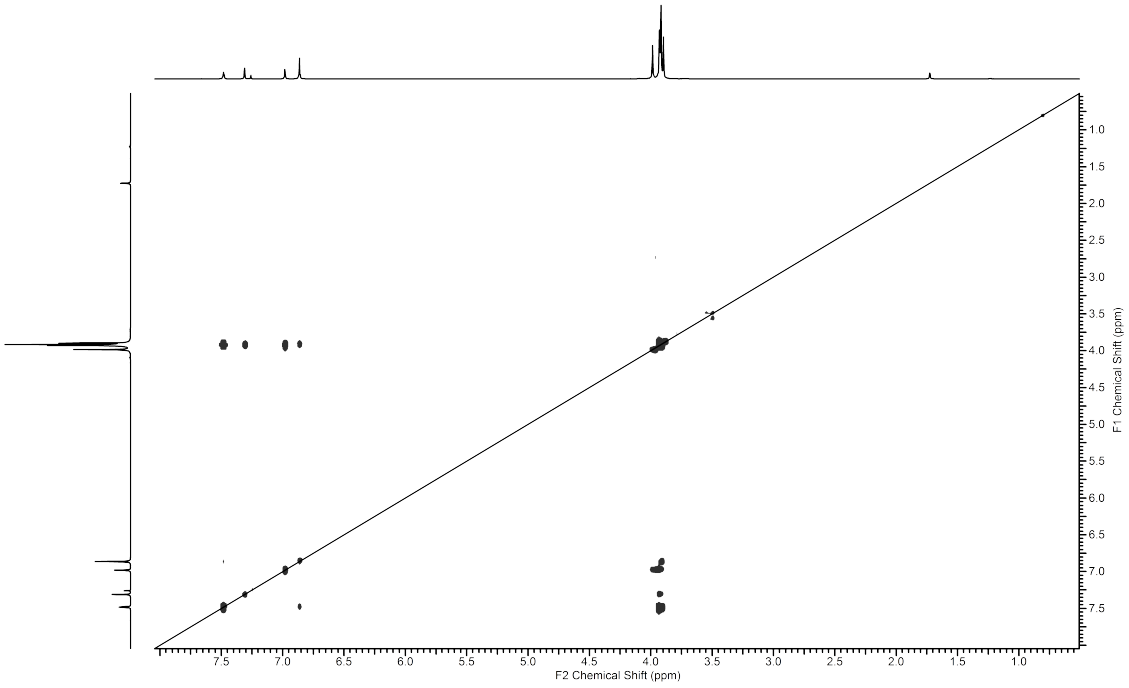
***E*-107**

O'Brien™
Group NMR Data

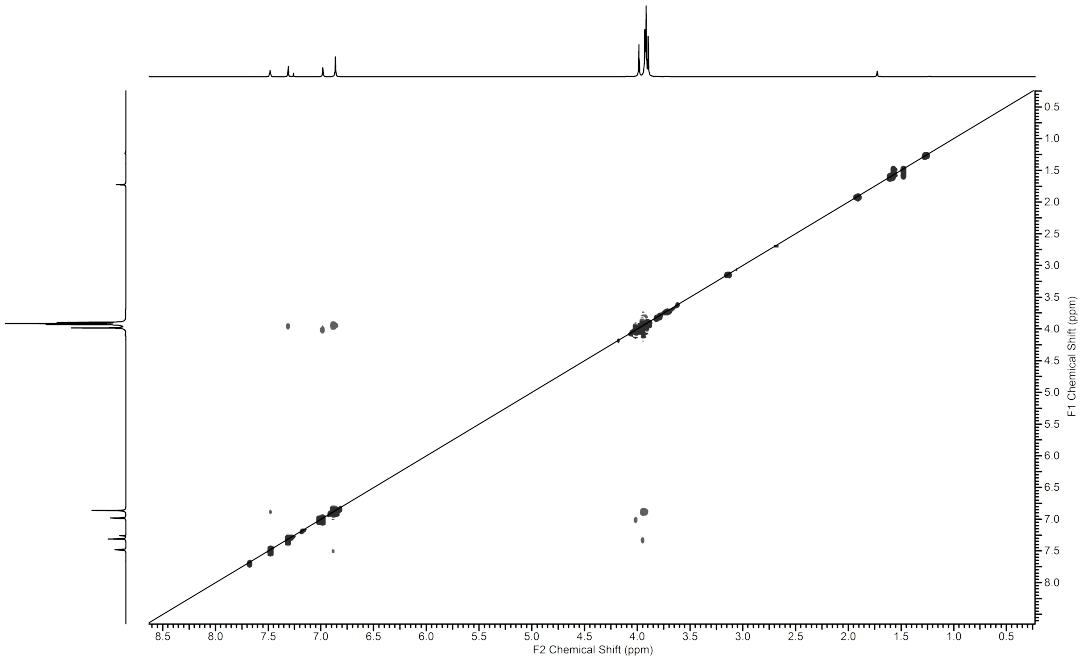




***E*-107**

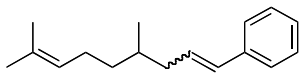


$^1H/^1H$ COSY (600 MHz, $CDCl_3$)



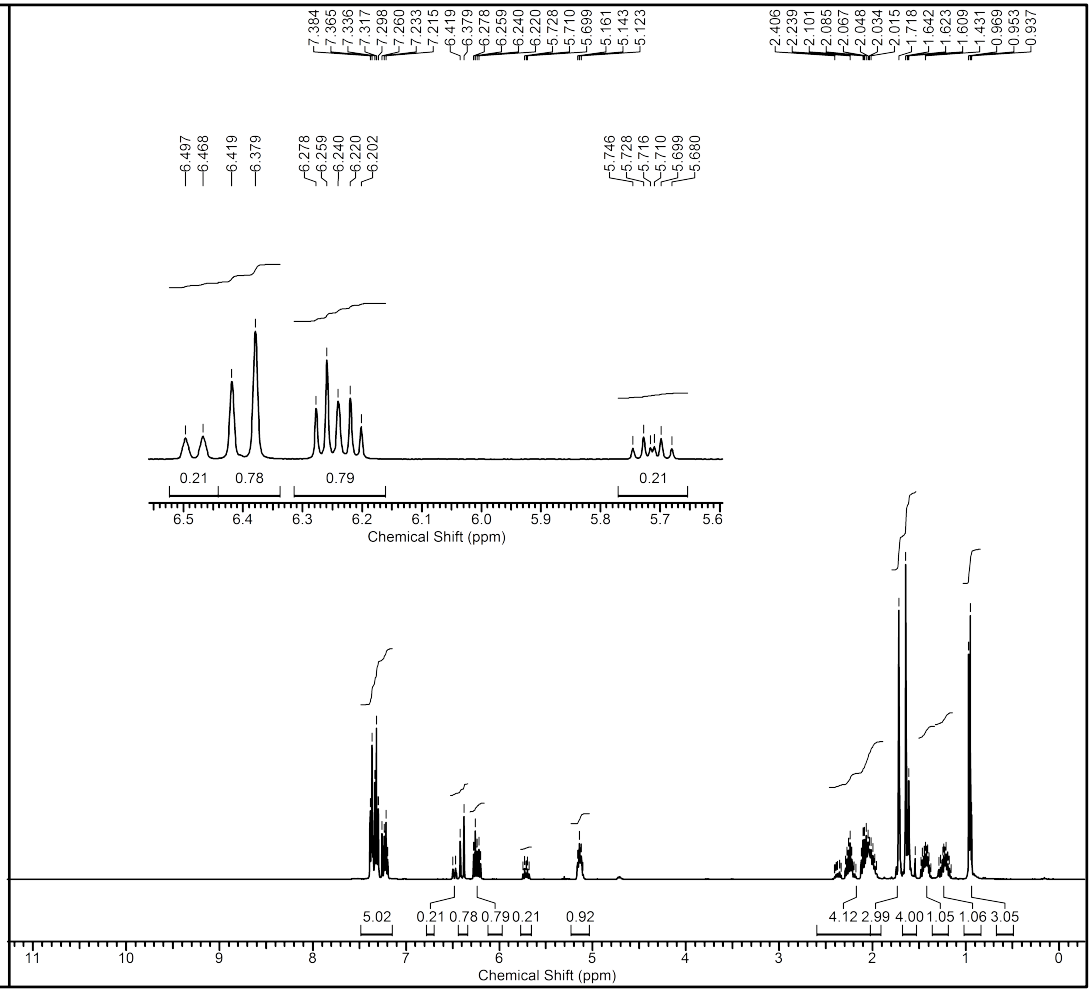
$^1H/^1H$ NOESY (600 MHz, $CDCl_3$)

File Name	017-06_Mix
Acquisition Time (sec)	3.9584
Date Stamp	30 Jan 2013 22:00
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4543
Origin	spect
Receiver Gain	50.80
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

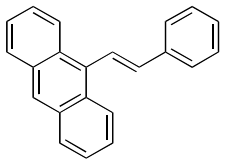


108

O'Brien™
Group NMR Data

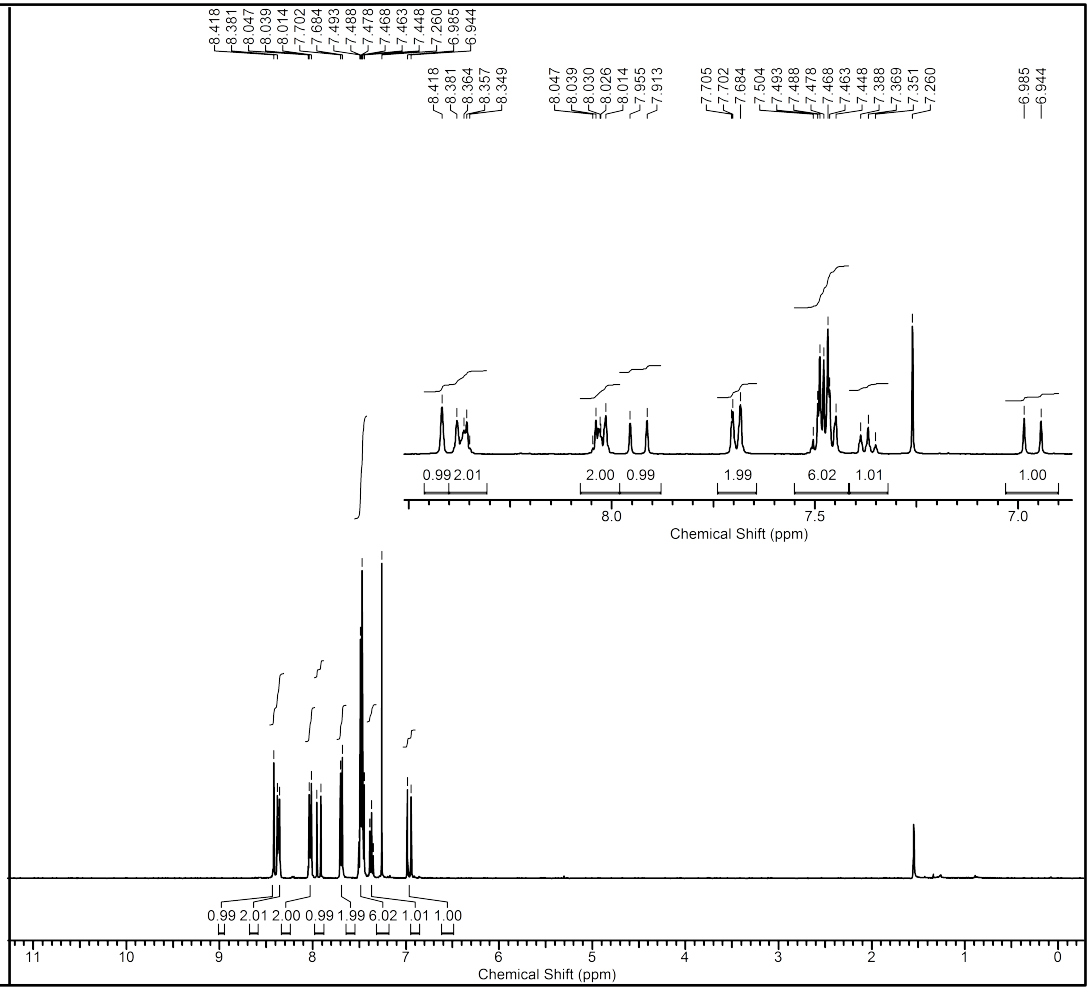


File Name	017-22A_E
Acquisition Time (sec)	3.9584
Date Stamp	27 Feb 2013 19:37
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2461.4541
Origin	spect
Receiver Gain	574.70
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89

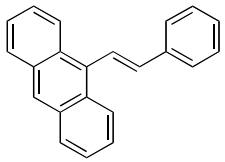


***E*-109**

O'Brien™ Group NMR Data



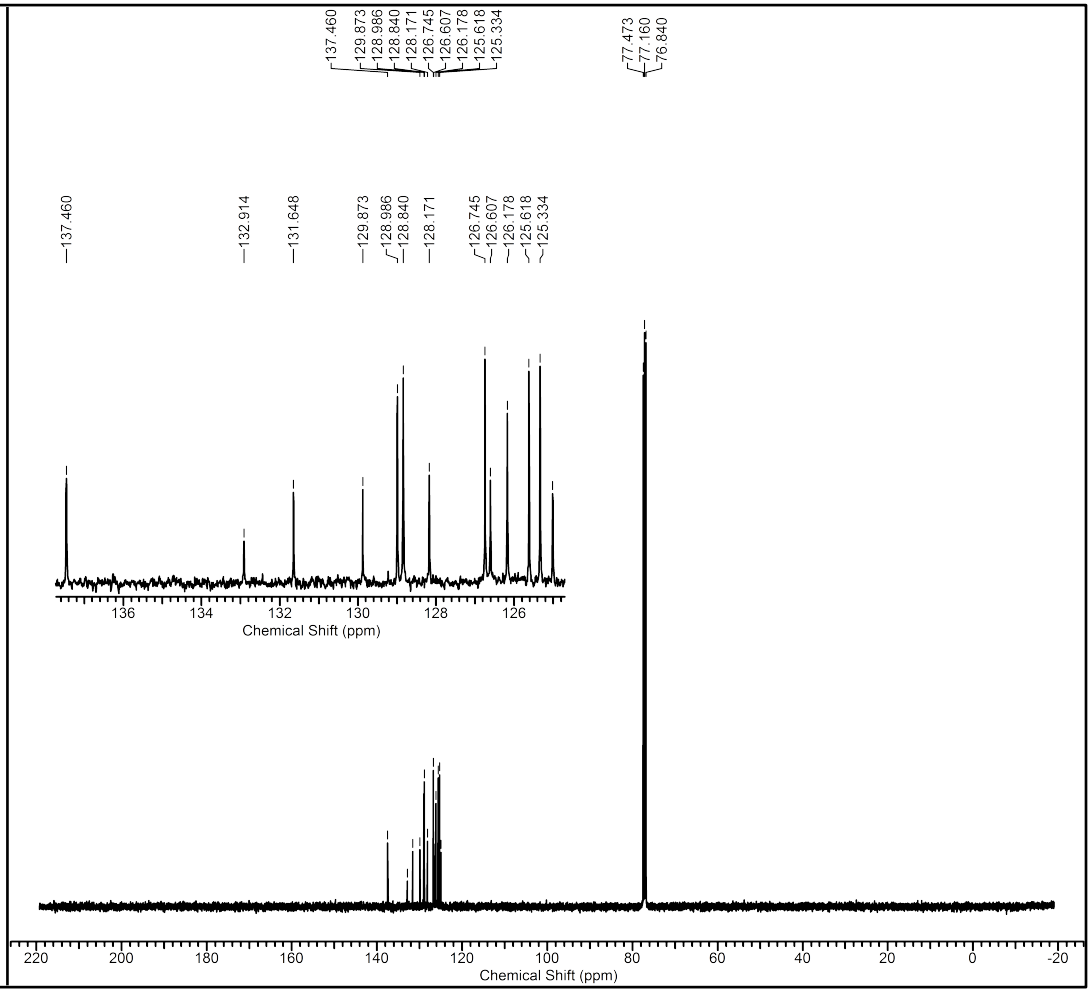
File Name	017-22A_E
Acquisition Time (sec)	1.3664
Date Stamp	28 Feb 2013 22:41
Frequency (MHz)	100.61
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	13C
Points Count	32768
Number of Transients	1024
Pulse Sequence	zgpg30
Spectrum Offset (Hz)	10074.0547
Origin	spect
Receiver Gain	6502.00
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	23980.81
Sweep Width (Hz)	23980.08



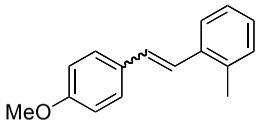
E-109

O'Brien™

Group NMR Data

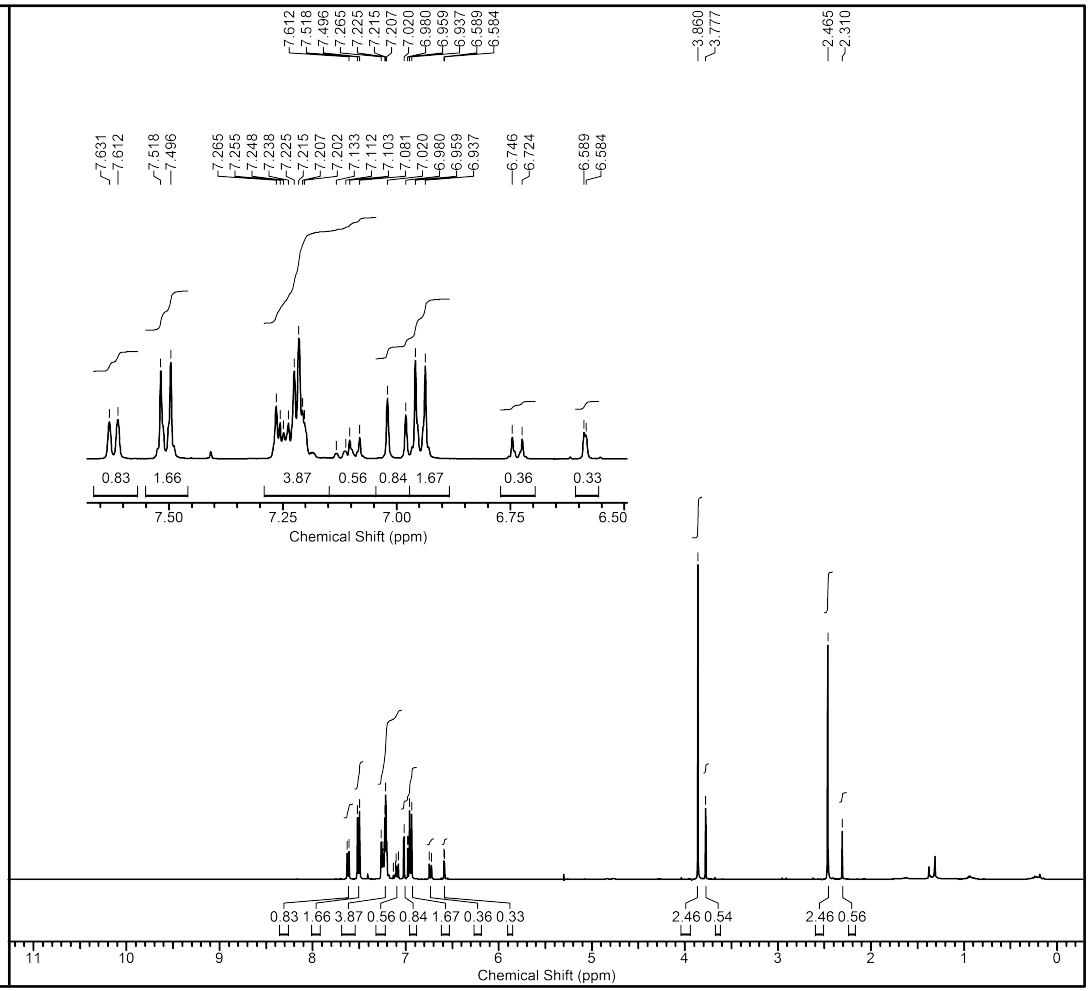


File Name	022-22
Acquisition Time (sec)	3.9584
Date Stamp	30 Jul 2013 13:05
Frequency (MHz)	400.13
Owner	Administrator
Solvent	CHLOROFORM-d
Temperature (degree C)	20.160
Nucleus	1H
Points Count	32768
Number of Transients	16
Pulse Sequence	zg30
Spectrum Offset (Hz)	2459.8438
Origin	spect
Receiver Gain	45.30
Spectrum Type	STANDARD
Original Points Count	32768
SW(cyclical) (Hz)	8278.15
Sweep Width (Hz)	8277.89



110

O'Brien™
Group NMR Data



References

[1] J. Leonard, B. Lygo and G. Procter, *Advanced Practical Organic Chemistry,* Blackie Academic & Professional: Oxford, **1995.**

[2] G. Keglevich, M. Fekete, T. Chuluunbaatar, A. Dobó, Z. Böcskei and L. Töke, *Synth. Commun.* **2000,** *30,* 4221-4231.

[3] K. Moedritzer and R. E. Miller, *Synth. React. Inorg. Met.-Org. Chem.* **1977,** *7,* 311-332.

[4] **(**a) J. H. Davies, J. D. Downer and P. Kirby, *J. Chem. Soc. C* **1966,** 245-247; (b) W. B. McCormack, **1953,** US patent 2663737 19531222.

[5] W. Dmowski and K. Piasecka-Maciejewska, *Tetrahedron* **1998,** *54,* 6781- 6792.

[6] Y. Nakamura, S. Inomata, M. Ebine, Y. Manabe, I. Iwakurab and M. Ueda, *Org. Biomol. Chem.,* **2011,** *9,* 83-85.

[7] (a) B. D. Cuddy, K. Treon, B. J. Walker, *Tetrahedron Lett.*, **1971**, 4433-4434; (b) B. D. Cuddy, J. C. P. Murray, B.J. Walker, *Tetrahedron Lett.*, **1971**, 2397-2400.

[8] (a) S. Ogawa, Y. Tajiri and N. Furukawa, *Bull. Chem. Soc. Jpn.,* **1991**, *64*, 3182-3184; (b) H. A. van Kalkeren, S. H. A. M. Leenders, C. R. A. Hommersom, F. P. J. T. Rutjes and F. L. van Delft, *Chem. Eur. J.*, **2011**, *17*, 11290-11295.

[9] E. W. Turnblom and T. J. Katz, *J. Am. Chem. Soc.* **1973,** *95,* 4292-4311.

[10] (a) C. S. Dean, D. S. Tarbell and A. W. Friederang, *J. Org. Chem.*, **1970**, *35*, 3393-3397; (b) B. M. Pope, Y. Yamamoto and D. S. Tarbell, *Org. Synth.*, *Coll. Vol.,* **1988**, *6*, 418-422.

[11] M. C. Davies, *Synth. Commun.* **2005**, *35,* 2079–2083.

[12] D. B. Berkowitz, M. Bose and N. G. Asher, *Org. Lett.*, **2001**, *3*, 2009-2012.

[13] K. Hamza, R. Abu-Reziq, D. Avnir and J. Blum, *Org. Lett.* **2004**, *6,* 925-927.

[14] V. K. Aggarwal, J. R. Fulton, C. G. Sheldon and J. de Vicente, *J. Am. Chem. Soc.* **2003,** *125,* 6034-6035.

[15] A. B. S. Maya, C. Perez-Melero, C. Mateo, D. Alonso, J. L. Fernandez, C. Gajate,

F. Mollinedo, R. Pelaez, E. Caballero and M. Medarde, *J. Med. Chem.* **2005,** 48, 556-568.

[16] A. Krasovskiy, C. Duplais and B. H. Lipshutz, *Org. Lett.* **2010,** *12,* 4742-4744.

[17] A. R. Katritzky, D. Cheng, S. A. Henderson and J. Li, *J. Org. Chem.* **1998,** *63,* 6704-6709.

[18] E.-I. Negishi, T. Tobrman, H. Rao, S. Xu and C.-T. Lee, *Isr. J. Chem.* **2010,** *50,* 696-701.

[19] (a) J.-P. Ebran, A. L. Hansen, T. M., Gogsig and T Skrydstrup, *J. Am. Chem. Soc.* **2007,** *129,* 6931-6942; (b) Q. Wang, M. El Khoury, M. Schlosser, *Chem. Eur. J.* **2000,** *6,* 420-426.

[20] R.-H. Fan, X.-L. Hou and L.-X. Dai, *J. Org. Chem.* **2004,** *69,* 689-694.

[21] M. E. Jung, P. Y.-S. Lam, M. M. Mansuri and L. M. Speltz, *J. Org. Chem.* **1985,** 50, 1087-1105.

[22] A. Shafiee, M. Z. Kassaee and A. R. Bekhradnia, *J. Heterocyclic. Chem.* **2007,** 44, 471-474.

[23] T. T. B. Nguyen, T. Lomberget, N. C. Tran and R. Barret, *Tetrahedron,* **2013,** 69, 2336-2347.

[24] W. Zhang and M. L. Go, *Eur. J. Med. Chem.* **2007,** 42, 841-850.

[25] a) J. Cotter, A.-M. L. Hogan and D. F. O'Shea, *Org. Lett.* **2007,** *9,* 1493-1496; b) J. J. Eisch and A. A. Adeosun, *Eur. J. Org. Chem.* **2005,** 993-997.

[26] A. Kunugi, Y. Kudo and H. Uno, *J. Electroanal. Chem.* **2001,** *507,* 37-45.

[27] H. J. Bestmann and E. Kranz, *Chem. Ber.* **1969,** *102,* 1802-1815.

[28] M. L. N. Rao, D. Banerjee and S. Giri, *J. Organomet. Chem.,* **2010,** *695,* 1518-1525.

[29] I. R. Green and N. October, *ARKIVOC,* **2010,** *ii,* 71-96.

[30] D. Gauthier, A. T. Lindhardt, E. P. K. Olsen, J. Overgaard and T. Skrydstrup, *J. Am. Chem. Soc.*, **2010**, *132*, 7998-8009.

[31] http://www.sigmaaldrich.com/spectra/fnmr/FNMR002084.PDF

[32] C. Qin and N. Jiao, *J. Am. Chem. Soc.*, **2010**, *132*, 15893-15895.

[33] Y. Liu, D. Xu, Z. Xu and Y. Zhang, *Heteroatom Chemistry*, **2008**, *19*, 188-198.

[34] C. J. O'Brien, J. L. Tellez, Z. S. Nixon, L. J. Kang, A. L. Carter, S. R. Kunkel, K. C. Przeworski, G. A. Chass, *Angew. Chem. Int. Ed.*, **2009**, *48*, 6836-6839.

[35] A. Novak, M. J. Calhorda, P. J. Costa and S. Woodward, *Eur. J. Org. Chem.,* **2009**, 898-903.

[36] U. Shadakshari and S. K. Nayak, *Tetrahedron,* **2001**, 57, 4599-4602.

[37] H. You, H-S. Youn, I. Im, M-H. Bae, S-K. Lee, H. Ko, S.H. Eom and Y-C. Kim, *Eur. J. Med. Chem.*, **2011**, 46, 1153-1164.

[38] F. Beji, R. Besbes and H. Amri, *Synth. Commun.*, **2000**, 30, 3947-3954.

[39] G. L., Anderson and T. A.-R. Kaimari, **2005,** US patent 6864264.

[40] Y. Gan, D. H. Blank,J. E. Ney and T. A. Spencer, *J. Org. Chem.*, **2006**, 71, 5864-5869.

[41] J.-Y. Yu, R. Shimizu and R. Kuwano, *Angew. Chem. Int. Ed.*, **2010**, *49*, 6396-6399.