2011

Bimolecular Coupling Reactions Involving Single Electron Oxidations: Method Development and Mechanistic Studies

Brian Michael Casey
Lehigh University

Bimolecular Coupling Reactions Involving Single Electron Oxidations: Method Development and Mechanistic Studies

by

Brian M. Casey

Presented to the Graduate and Research Committee
of Lehigh University
in Candidacy for the Degree of
Doctor of Philosophy

in

Department of Chemistry

Lehigh University

June 15, 2011

Approved and recommended for acceptance as a dissertation in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Brian M. Casey

Bimolecular Coupling Reactions Involving Single Electron Oxidations: Method Development and Mechanistic Studies

June 15, 2011

Defense Date

Dissertation Director
(Must Sign with Blue Ink)

Approved Date

Committee Members:

Professor Robert A. Flowers, II

Professor Ned D. Heindel

Professor Natalie M. Foster

Professor Bryan W. Berger

Acknowledgements

First and foremost, I would like to thank my research advisor, Professor Robert Flowers (a.k.a. "Boss"). Over the years, I have frequently been asked by friends, family, and colleagues, "How is it working for Dr. Flowers?" to which I always respond, "I really lucked out with choosing an advisor." He has been an excellent mentor to me over the last 4 ½ years and I am very proud of what we have accomplished together. On a personal note, I consider him my friend in addition to my research advisor. That he is also a huge fan of the New York Yankees, the New York Football Giants, and *The Big Lebowski* doesn't hurt. I would also like to thank my doctoral committee members (Professors Ned Heindel, Natalie Foster, and Bryan Berger) for their useful comments on my dissertation in addition to offering their support throughout the years.

I thank my parents (Val and Michaele Casey) for always believing in my abilities, and for instilling in me the idea that "anything worth doing, is worth doing right." I thank my sister and my brother-in-law (Catherine "Cat" and Jeremy Edmonds) for their constant encouragement, even when I wore my frustrations on my sleeve. I would not be where I am today without the love and support of my family.

I thank the past and present members of the Flowers's research group: Kim Choquette, Todd Maisano, Jim Devery, Dr. Dhandapani Sadasivam, Sherri Young, Dr. Esther Pesciotta, Dr. Rajni Singh, Dr. Larry Courtney, Niki Patel, and Gaby Haddad. Thanks for putting up with me over the last 5 years and for being the voice of reason when I was at my most frustrated. More importantly, thank you all for your friendship. A special thanks is needed for Cindy Eakin who, in addition to being an outstanding undergraduate researcher in my first 2 years at Lehigh, is an amazing friend.

Special thanks are also needed for Dr. Piercen Oliver (an honorary “Flowers’s group member”) and his wife, Kelli. Your friendship and support throughout our time here at Lehigh were more important than you know. Finally, I would like to thank Russell Confroy for listening to me complain (about both research and New York sports teams), and for just being a great friend. Being able to hang out in either PA or DC, especially when I was stressed out, made the difference.

Table of Contents

List of figures

List of tables

List of schemes

Abstract

The single electron oxidation of organic substrates provides access to powerful reactive intermediates that can be utilized by organic chemists to produce synthetically relevant compounds. While originally observed by Faraday almost two centuries ago, for many years single electron oxidations were not utilized to their full potential in organic synthesis primarily due to the lack of fundamental knowledge of how to interconvert reactive intermediates. It is our hypothesis that a thorough mechanistic understanding of the factors involved in single electron oxidations will lead to the development of efficient, selective and general synthetic protocols thereby expanding the range of reactions in the organic chemist's "toolbox." The doctoral research presented herein focuses on developing synthetic methods that utilize single electron oxidations to form new carbon-carbon and carbon-heteroatom bonds and on understanding the key mechanistic factors that contribute to the selective formation of products in several single electron oxidative bimolecular coupling reactions.

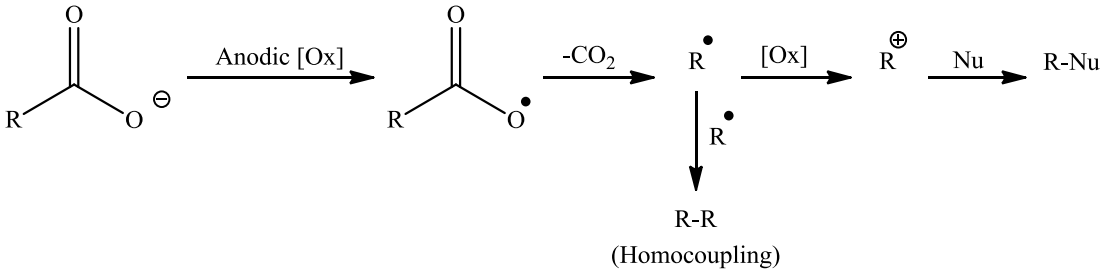
The research contained in this dissertation has achieved the following: 1) A novel method has been developed for the synthesis of γ-halogenated ketones which are important precursors for biologically active compounds such as haldol, 2) a solvent-dependent oxidative coupling of 1-aryl-1,3-dicarbonyls to styrene was developed and selective product formation was shown to be controlled by the lifetime of a radical cation intermediate, 3) a synthesis for β-tetralones via intramolecular cyclization of γ-aryl-β-dicarbonyls was developed and the impact of substrate electron density on product selectivity was interrogated with computational studies, and 4) the non-statistical oxidative heterocoupling of equimolar lithium enolates was investigated and it was

determined that product distributions were, in part, a consequence of lithium enolate aggregates.

Chapter 1: Introduction to single electron oxidations in organic synthesis

1.1 Origins

The single electron oxidation of organic substrates provides access to powerful reactive intermediates that can be utilized by organic chemists to produce synthetically relevant compounds. Though single electron oxidations are now ubiquitous in synthesis, experimental evidence of their existence has its foundation in work performed by Faraday in 1834 in which he reported the evolution of CO_2 gas at the anode during the electrolysis of acetate.[1] Subsequent work by Kolbe, after whom this reaction is named, showed that ethane gas was also produced in addition to CO_2.[2] The accepted mechanism for the Kolbe reaction (Scheme 1.1) is the initial electrochemical single electron oxidation of acetate ions to radicals. These radicals then decompose to expel CO_2 and generate methyl radicals which homocouple to produce ethane.[3] Depending on the reaction conditions and the organo-acetates employed, the radicals produced after decarboxylation can be oxidized further to produce cation intermediates that can couple with water, alcohols and other nucleophiles in solution.[4] Since the seminal work of Faraday and Kolbe, multitudes of sophisticated reaction systems have been developed that rely on the interconversion of anions, radicals, and cations to achieve the desired transformations.



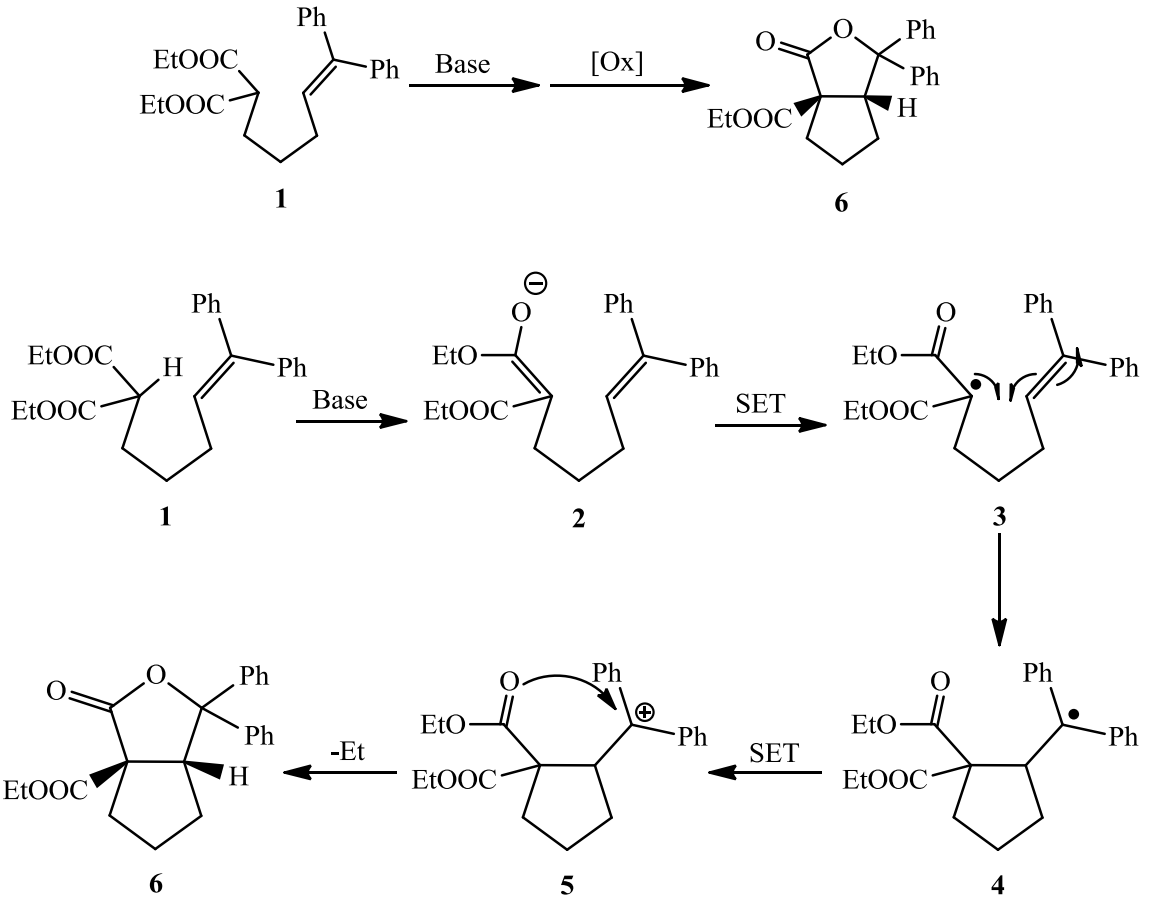
Scheme 1.1: Mechanism of the Kolbe reaction for the electrochemical oxidation of carboxylates. For the seminal work of Faraday, R = methyl.[1]

1.2 Importance of the interconversion of reactive intermediates in synthesis

Although the Kolbe reaction serves as a clear example of the potential of single electron transfers (SET) for organic synthesis, reactions involving radical intermediates were slow to develop. The primary reason that radical-mediated reactions were underutilized for decades was the lack of a fundamental understanding of how to efficiently interconvert between reactive intermediates. As Tanko points out in a recent review of radicals in organic synthesis, "radicals were viewed as a bit of a curiosity by most organic chemists—highly reactive, uncontrollable, and of little interest to anyone, save for the petroleum industry."[4] However, as chemists obtained more insight into the nature of radicals generated from SETs, new reaction systems were designed that fully harnessed the synthetic potential of these intermediates providing efficient pathways to structurally complex molecules.

The importance of the ability to interconvert reactive intermediates in synthesis is exemplified by the work of Jahn depicted in Scheme 1.2.[5] This reaction involves the oxidative intramolecular cyclization of malonate derivative **1** to form the bicyclic lactone **6**. In the first step of the reaction, compound **1** is deprotonated by base to generate enolate **2**. The single electron oxidation of intermediate **2** results in a radical species (**3**). This radical then cyclizes with the pendant olefin, which forms a 5-membered ring and produces another radical species (**4**). A second SET further oxidizes the radical to a cation (**5**) which is stabilized by the two phenyl groups. Finally, a second intramolecular cyclization with one of the esters followed by the loss of an ethyl group produces the bicyclic lactone (**6**). This reaction demonstrates how the ability to efficiently interconvert reactive intermediates can significantly impact syntheses. In this one-pot reaction, the

organic substrate is converted from a neutral molecule (**1**), to an anion (**2**), to a radical (**3**), to a cation (**5**), and ultimately to the neutral product molecule (**6**). Understanding the nature of reactive intermediates has dramatically increased the chemical diversity that can be accessed through single electron transfers. While both reductive and oxidative processes have significantly contributed to the field of organic chemistry, the research presented in this dissertation focuses on reaction systems involving single electron oxidations.



Scheme 1.2: Cyclizations of malonate derivatives through single electron oxidations[5]

1.3 Single electron oxidations

Today, radical and radical cation intermediates are routinely generated through a variety of methods. While numerous, the vast majority of the single electron oxidations in

organic chemistry are achieved via one of the following routes: transition metal-based oxidants, hypervalent iodine oxidants, electrochemical oxidations, or lanthanide-based oxidants. Often, multiple oxidative methods are capable of performing the desired chemical transformation. However, individual oxidants have discrete characteristics that can result in unique reactivity depending on the substrates and reaction conditions. The majority of the oxidative coupling reactions presented in the research chapters of this dissertation rely on lanthanide-based reagents. By understanding the important factors involved in single electron oxidations, new reaction systems can be rationally designed that are efficient, selective, and broadly applicable.

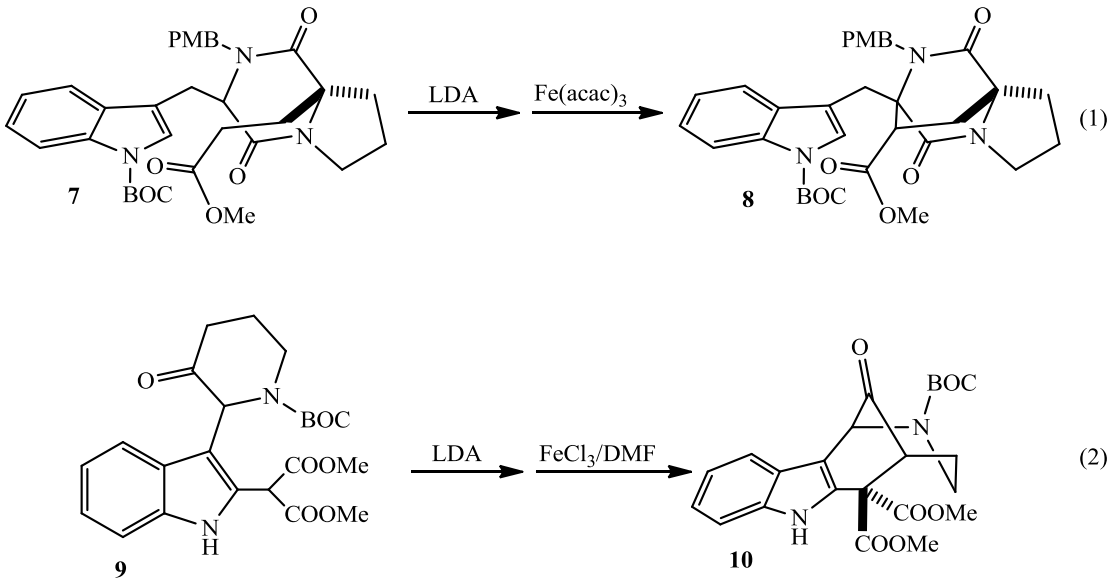
1.3.1 Transition metal-based oxidants

1.3.1.1 Fe(III) oxidants

Fe(III)-based reagents, such as iron(III) chloride ($FeCl_3$), are some of the most frequently used Lewis acid catalysts in organic synthesis.[6] In addition to serving as Lewis acid catalysts, Fe(III)-based reagents can act as stoichiometric single electron oxidants. The single electron oxidations to produce bicyclic lactones developed by Jahn (*vide supra*) were achieved using ferrocenium hexafluorophosphate ($FeCp_2PF_6$).[5] This Fe(III)-based oxidant has been shown to mediate a variety of other oxidative cyclizations involving malonate and ester enolate derivatives.[5, 7-10]

Fe(III)-based oxidants have also been extensively applied to the oxidative coupling of lithium enolates to generate 1,4-dicarbonyl compounds which are important structural components in many natural products and pharmaceutically active compounds. Several protocols have been developed for the synthesis of symmetric 1,4-dicarbonyls via the oxidative intermolecular homocoupling of enolates derived from ketones using

$FeCl_3$.[11-13] Additionally, intramolecular oxidative coupling of dienolates can be achieved with $FeCl_3$.[11] Both Baran *et al.* and Overman *et al.* have reported total syntheses in which an integral step was the intramolecular oxidative coupling of dienolates (Scheme 1.3).[14, 15] In reaction 1, deprotonation of both the amide and ester of **7** generates two enolates which are oxidatively coupled using iron(III) acetylacetonate ($Fe(acac)_3$) producing **8**.[14] In reaction 2, an $FeCl_3$/DMF complex is employed as the oxidant to couple the ketone enolate with the diester enolate of **9**.[15] The oxidative coupling of enolates including the intermolecular heterocoupling of enolates, which provides a direct route to asymmetric 1,4-dicarbonyls, is discussed in detail in Chapter 5 of this dissertation.

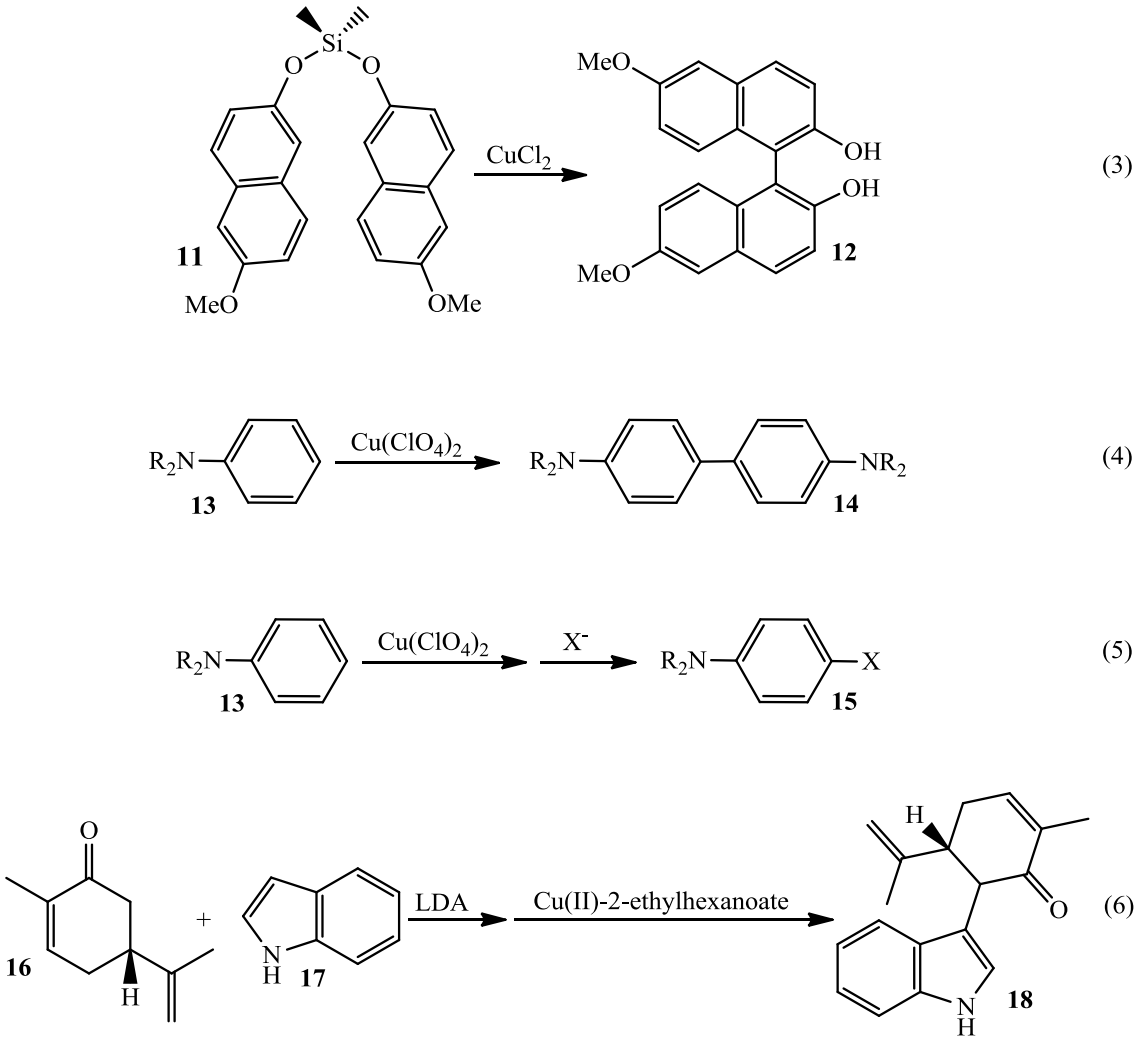


Scheme 1.3: Two examples of Fe(III)-mediated intramolecular cyclizations that are key steps in the total syntheses of avrainvillamide and stephacidins (1)[14] and actinophyllic acid (2).[15]

1.3.1.2 Cu(II) oxidants

Copper-catalyzed processes can be found in multiple chemical disciplines from biochemistry to materials science to organic synthesis. In addition to catalysis, Cu(II)-based reagents are commonly used as stoichiometric oxidants in a variety of carbon-

carbon bond forming reactions. Several examples of Cu(II)-mediated oxidative coupling reactions are shown in Scheme 1.4. In the first reaction, silyl bisnaphtholate **11** is oxidized with two equivalents of copper(II) chloride ($CuCl_2$) and after radical-radical coupling and elimination of the silyl group generates 1,1'-bi-2-naphthol (BINOL)



Scheme 1.4: Representative reactions involving the Cu(II)-mediated single electron oxidation of organic substrates

derivative **12**.[16] Asymmetric BINOL derivatives were also accessible via this method.[16] The synthesis of both symmetric and asymmetric BINOL derivatives is of interest because they are important ligands for numerous metal-mediated reactions in organocatalysis.[17] In another example (reaction 4), when aniline derivatives (R = alkyl) are oxidized with

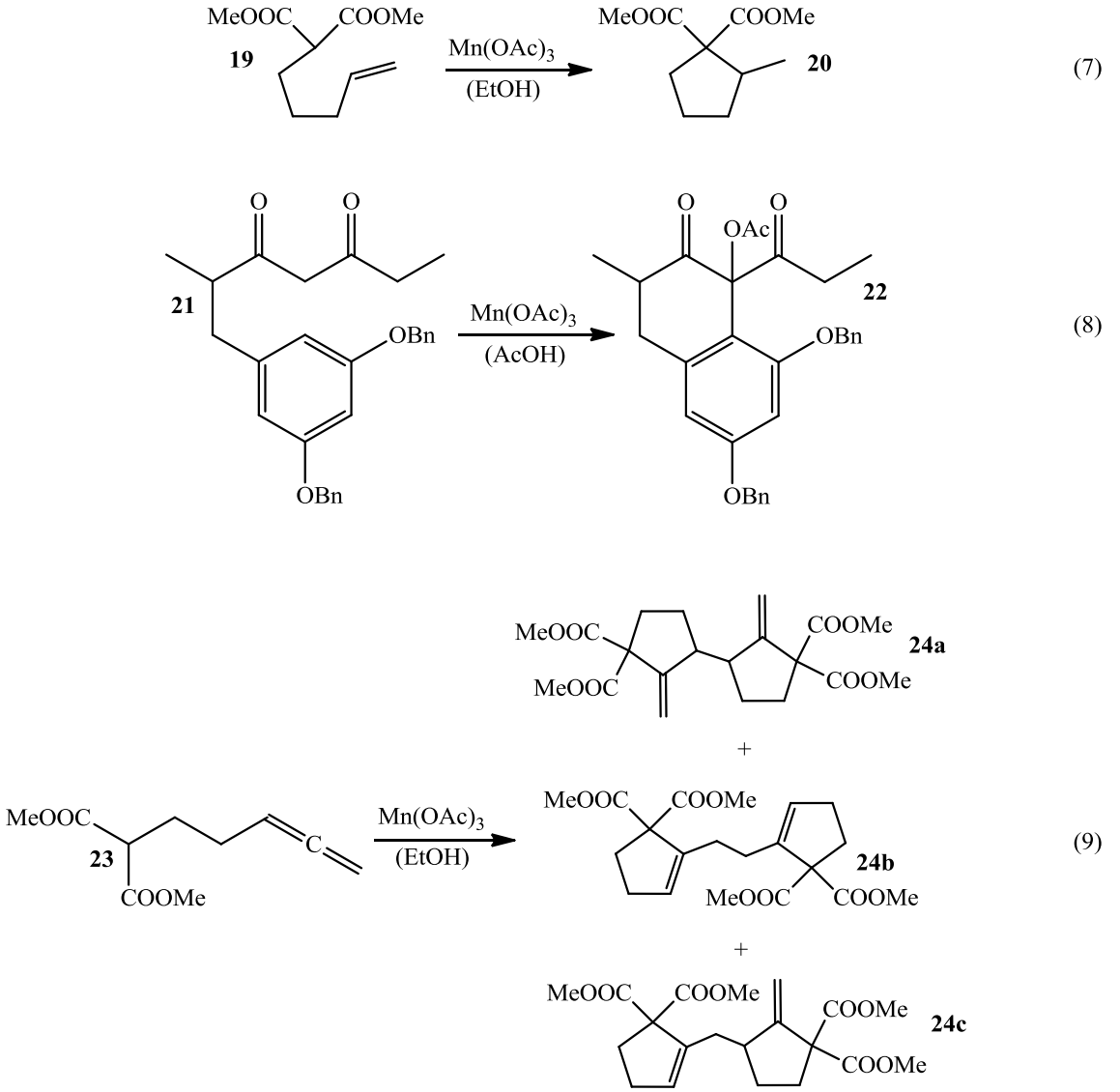
copper(II) perchlorate ($Cu(ClO_4)_2$), they dimerize to form biaryl products (**14**).[18] Interestingly, if the same reactions are performed in the presence of appropriate nucleophiles such as halides and thiocyanates, the dimerization of the radical cation intermediates is inhibited and *para*-substituted anilines (**15**) are obtained as the major products.[18] In the final example (reaction 6), Baran *et al.* were able to oxidatively couple carvone (**16**) with indole (**17**) to generate product **18**.[19] This reaction was shown to be general, allowing for a wide range of ketones, esters, and amides to be coupled with indoles and pyrroles.[19] Although a 3-5 equivalent excess of the indoles and pyrroles is necessary to obtain synthetically useful yields and limit homodimerization of the enolate species, this chemistry provides an efficient route to complex intermediates from relatively simple starting materials. Using this approach, Baran *et al.* were able to rapidly synthesize the natural products oxazinin 3 and acremoauxin A, a potent inhibitor of plant growth.[19]

In addition to reactions 3-6, Cu(II)-based oxidants are capable of mediating many of the same reactions as Fe(III)-based oxidants, in particular the oxidative coupling of lithium enolates. Both $CuCl_2$ and copper(II) triflate ($Cu(OTf)_2$) have been employed to oxidatively homocouple enolates[11, 20-22] as well as intramolecularly couple diketones[20, 21] and diesters.[20] Finally, Cu(II)-2-ethylhexanoate has been used by Baran *et al.* to produce asymmetric 1,4-dicarbonyl compounds through the heterocoupling of enolates.[23, 24]

1.3.1.3 Mn(III) oxidants

Although not as versatile as Fe(III)- and Cu(II)-based oxidants, Mn(III)-based oxidants are capable of mediating several SET reactions. Of these oxidants, manganese(III) acetate ($Mn(OAc)_3$) is the most frequently used in organic synthesis.[25] As the reactions in Scheme 1.5 indicate, the vast majority of Mn(III)-mediated reactions

involve intramolecular cyclizations via the single electron oxidation of dicarbonyl substrates. In the first example (reaction 7), dimethyl 4-pentenylmalonate (**19**) is oxidized by $Mn(OAc)_3$, generating a radical intermediate that cyclizes with the pendant olefin. This intramolecular cyclization generates a primary radical that abstracts a hydrogen atom, presumably from solvent or unreacted **19**, to form the cyclopentane derivative as the major product.[26] In reaction 8, β-tetralone derivative **22** is produced via the oxidative intramolecular cyclization of the 1,3- dicarbonyl moiety with the γ-aryl ring. The

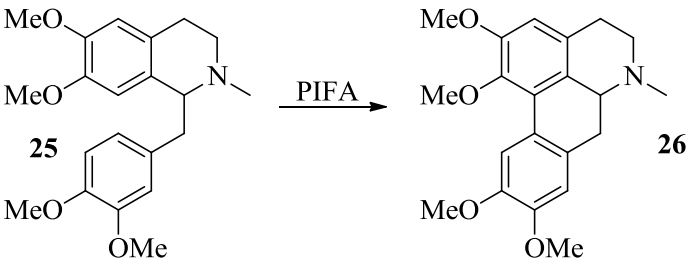


Scheme 1.5: Mn(III)-mediated oxidative intramolecular cyclizations

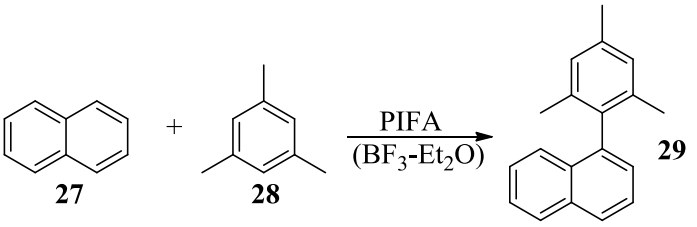
research in Chapter 4 of this dissertation describes an alternative synthesis of β-tetralone via single electron oxidations. Reaction 9[27] illustrates the most significant drawback and limitation of Mn(III)-mediated oxidations: the formation of multiple products.[25] In this example, although the initial oxidation of the enol tautomer of diester **23** and the cyclization with the allenyl group proceed efficiently, the subsequent radical is delocalized and oxidized very slowly by $Mn(OAc)_3$.[27] Consequently, though high yields of the dicyclopentane derivatives are produced, they are obtained as a complex mixture consisting of **24a-c**.[27]

1.3.2 Hypervalent iodine oxidants

Hypervalent iodine species, I(III) and I(V), represent another class of reagents that are capable of initiating a variety of bond forming reactions in organic synthesis through SETs. Of the I(III)-based oxidants, the most widely used is phenyliodine bis(trifluoroacetate) (PIFA).[28] PIFA has been shown to oxidize electron-rich arenes and aromatic heterocycles such as thiophenes and pyrroles.[28] Examples of both intramolecular (reaction 10) and intermolecular (reaction 11) bond formations that are initiated by PIFA are provided in Scheme 1.6. In the first reaction, both electron-rich aryl rings of **25** are oxidized to radical cations. Radical-radical coupling and rearomatization generate glaucine (**26**) as the major product.[29] In reaction 11, naphthalene (**27**) is selectively oxidized in the presence of mesitylene (**28**) to a radical cation.[30] Instead of dimerizing to binaphthalene, the radical cation adds to **28** generating the heterocoupled product (**29**) after a second single electron oxidation and deprotonation. A variety of substituted naphthalene and mesitylene substrates could be cross-coupled with this I(III)-mediated method without reducing product yields or selectivities.[30]



(10)

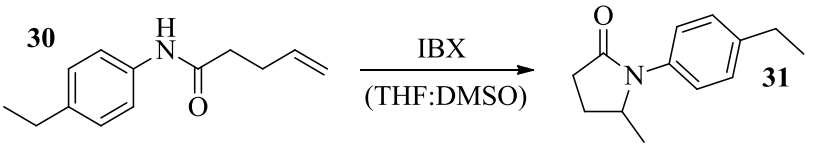


(11)

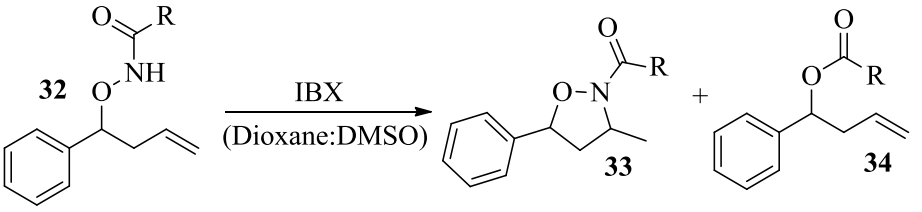
Scheme 1.6: Examples of I(III)-mediated oxidative coupling reactions

In addition to functional group oxidations,[31] several intramolecular cyclization reactions employing I(V)-based reagents, namely 2-iodoxybenzoic acid (IBX), have been shown to proceed through single electron oxidative pathways. Scheme 1.7 depicts two examples of IBX-mediated oxidative cyclizations. In reaction 12, the aryl amide (**30**) is oxidized generating a nitrogen-centered radical intermediate which undergoes a 5-*exo*-trig cyclization with the pendant olefin. Hydrogen atom abstraction produces **31** in a 90% yield.[32] Interestingly, a subsequent mechanistic study by Nicolaou *et al*. provided evidence that initial complexation of IBX to THF was integral to reaction efficiency.[33] Based on these synthetic and mechanistic studies, a new route to amino sugars was developed in which the key step in the synthesis was an IBX-mediated cyclization.[34] Using similar chemistry, Studer *et al*. oxidized methyl amide **32** (R = Me) to the cyclic product **33** in good yields.[35] Unfortunately, this reaction was not general. When the steric bulk of the amide was increased (R = aryl), only trace amounts of **33** were obtained. For

these substrates, esters (**34**) along with significant amounts of recovered starting material were obtained.[35]



(12)



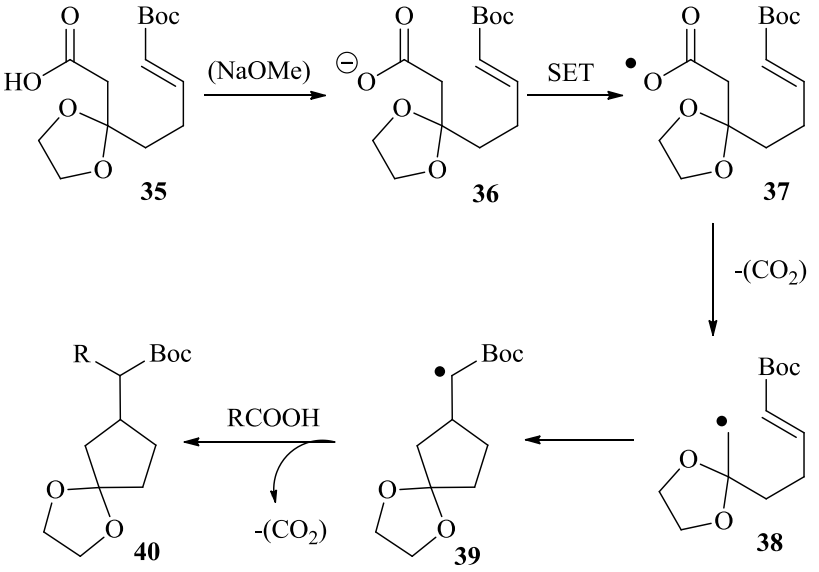
(13)

Scheme 1.7: Oxidative cyclization reactions initiated with I(V)

1.3.3 Electrochemical oxidations

Electrochemical methods are underutilized in modern synthetic laboratories primarily due to the misconception that specialized or overly involved set-ups are required. However, electrochemical techniques are applicable to a wide range of single electron transfer reactions and often times have simple experimental procedures for small scale reactions.[36] Adaptations of the Kolbe reaction (*vide supra*) are the most common examples of electrochemical SETs in modern organic syntheses.[37, 38] As shown in Scheme 1.8, compound **35** can be efficiently converted to product **40** in a 90% yield via a modified Kolbe reaction. In the presence of sodium methoxide (NaOMe), the carboxylate (**36**) of acid **35** is generated. When a constant current is passed through the reaction cell, a single electron oxidation of **36** occurs at the anode producing radical **37**. This radical rapidly eliminates CO_2 producing a primary radical species (**38**) which can cyclize with the electron-deficient olefin to generate intermediate **39**. This radical is then captured by an excess of another co-acid (for this reaction, R = Me) producing cyclopentane derivative

40 and another equivalent of CO_2.[38] Both the starting material and the R-group of the co-acid can be varied to generate 5- and 6-membered cyclic products in very good to excellent yields.[38]

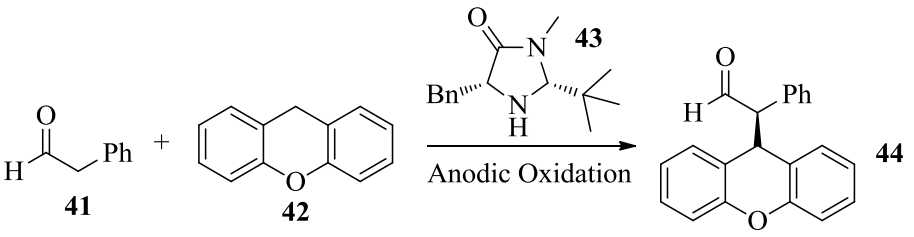


(14)

Scheme 1.8: Modern synthetic application of the Kolbe reaction via electrochemical anodic oxidation

Another area of research that has recently benefitted from electrochemical oxidations is organocatalysis. Recently, the singly occupied molecular orbital (SOMO)-activated asymmetric catalytic system developed by MacMillan has been achieved via electrochemical methods.[39, 40] In the example shown in Scheme 1.9, the reaction involves aldehyde **41** forming an enamine intermediate with the imidazolidinone catalyst (**43**).[40] It was proposed that both the intermediate enamine and xanthene (**42**) are oxidized at the anode when a constant current is passed through the reaction cell. After radical-radical coupling and release of the catalyst, compound **44** was produced in a 68% yield with 68% ee.[40] While this procedure was applied to several different substrates, 50 mol% of catalyst **43** had to be employed in many of the reactions in order to obtain synthetically useful yields.[40] Nonetheless, this research demonstrates the potential utility of electrochemistry

in the field of asymmetric organocatalysis and single electron oxidations, albeit on a millimolar scale.



(15)

Scheme 1.9: Electrochemical route to asymmetric α-substituted aldehydes

1.3.4 Lanthanide-based oxidants

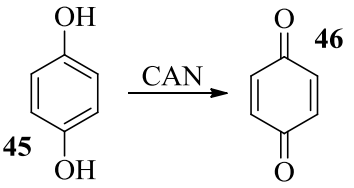
Discovered in the late 1780s, the lanthanide metals were originally termed "the rare earth metals.[41]" Surprisingly, many of the metals in the lanthanide series are actually more abundant in the earth's crust than other elements that are commonly used in organic syntheses.[42] In particular, cerium is the 25th most abundant element in the earth's crust making it more prevalent than tin, copper, bromine, lithium, iodine, and boron.[43] Despite being mislabeled as the "rare earth elements," lanthanide-based reagents have been utilized with increasing regularity in organic chemistry due to their unique chemical properties.[44] The lanthanides are the first elements in the periodic table to have electrons in the 4f orbitals. These 4f orbitals are contracted and buried under the 5d and 6s orbitals. As a result, lanthanide-ligand interactions are primarily ionic in nature.[45] Common to all lanthanides is the stable +3 oxidation state and many of their applications as Lewis acids and internal standards for NMR shift calibration rely on this oxidation state.[46, 47]

While the most stable oxidation state for the lanthanides is the +3 state, several lanthanides such as cerium, praseodymium, neodymium, terbium, and dysprosium have accessible +4 oxidation states allowing them to function as single electron oxidants. Of the lanthanide metals with stable +4 oxidation states, the most widely utilized in organic

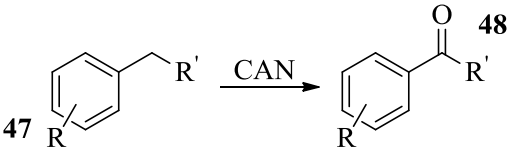
chemistry are Ce(IV)-based reagents, namely cerium(IV) ammonium nitrate (CAN). Though traditionally requiring highly acidic media, milder protocols in solvents such as methanol (MeOH), acetonitrile (MeCN), and 1,2-dimethoxyethane (DME) have led to increased applications of CAN in organic syntheses. Furthermore, replacement of the ammonium counterions of CAN with more lipophilic tetra-*n*-butylammoniums (CTAN) results in enhanced oxidant solubility in less polar solvents such as methylene chloride (CH_2Cl_2). The Ce(IV)-mediated processes provided in the following three sections of this dissertation are only a handful of examples of the multitude of reactions that have been developed.[48-53]

1.3.4.1 Functional group conversions and deprotections with Ce(IV)

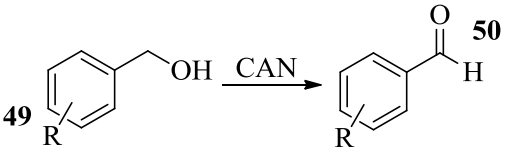
Many of the early reactions that utilized CAN in synthesis dealt with the oxidation of functional groups.[48, 53] Scheme 1.10 highlights a few of the functional group conversions that can be performed. In reaction 16, hydroquinone (**45**) is oxidized to quinone (**46**) quantitatively.[54] Reactions 17 and 18 involve the oxidation of substrates at the benzylic position. Depending on the substrate, alkyl benzenes (**47**) are oxidized to ketones (**48**) while benzyl alcohols (**49**) are converted to benzaldehydes (**50**).[53] Interestingly, Binnemans *et al.* recently reported that the oxidations of hydroquinones as well as benzylic substrates provide excellent yields when the reactions are performed in ionic liquids.[55] Functional group conversions mediated by CAN are not restricted to oxidations of carbon and oxygen. As shown in reaction 19, dialkyl- and diarylthioethers (**51**) can be oxidized to sulfoxides in high yields.[56]



(16)



(17)



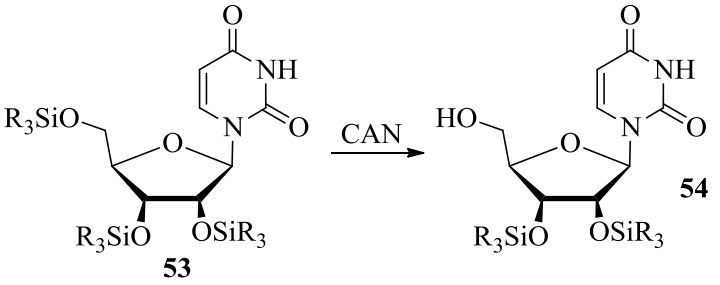
(18)

(19)

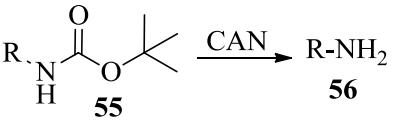
Scheme 1.10: Functional group conversions with CAN

In addition to functional group conversions, CAN has been extensively utilized in protecting group chemistry. Since protecting group chemistry adds two additional steps to the linear sequence of a total synthesis (one step to put the protecting group on the substrate and one step to remove it), the more efficient these steps are, the better. CAN and other Ce(IV)-based reagents have been used successfully in a variety of deprotection reactions (Scheme 1.11). Triisopropylsilyl (TIPS) and *tert*-butyldimethylsilyl (TBDMS) groups can be efficiently removed to produce alcohols. As shown in reaction 20, primary silylethers can be selectively desilylated to alcohols in the presence of protected secondary alcohols.[57] One of the most common protecting groups in organic synthesis for amines is *tert*-butyloxycarbonyl (Boc). Normally requiring the use of concentrated acid,[58] N-Boc amines (**55**) can be deprotected under mild reaction conditions to the free amines

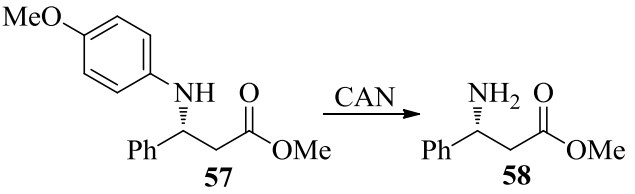
(**52**) using CAN.[59] Drawing from the oxidation of hydroquinones to quinones, amine **58** can be obtained through the CAN-mediated removal of the *p*-methoxyphenyl group from the protected amine (**57**).[60] Finally, the deprotection of ketals and acetals to ketones and aldehydes has been achieved both stoichiometrically and catalytically with CAN.[61]



53 (20)



55 **56** (21)



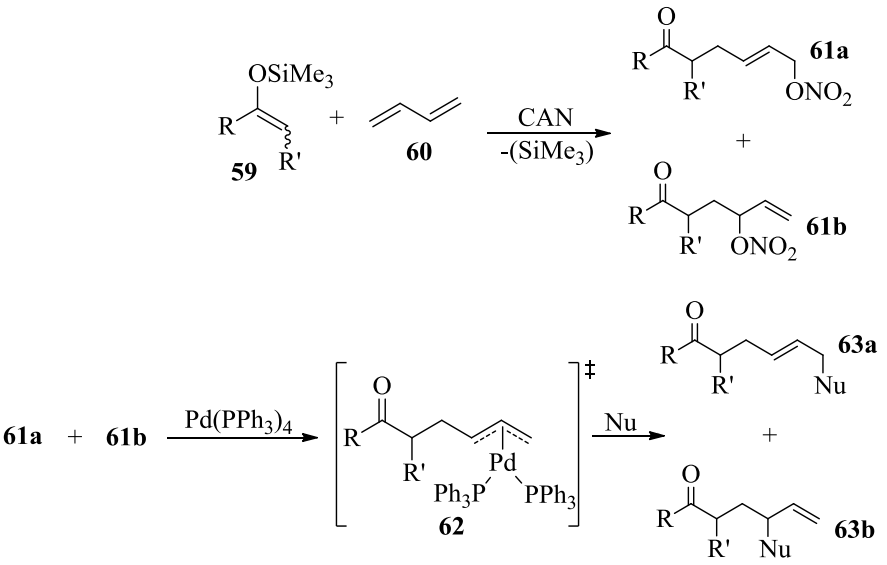
57 **58** (22)

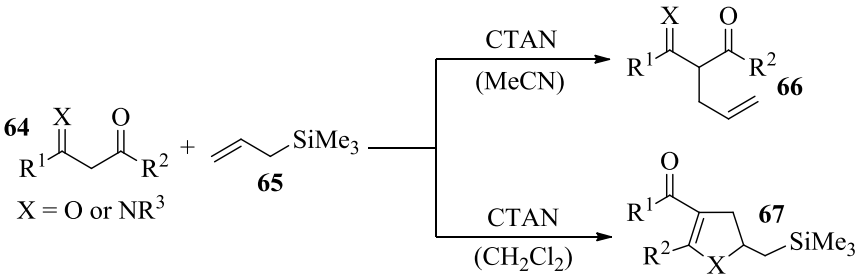
Scheme 1.11: Deprotection reactions initiated by CAN

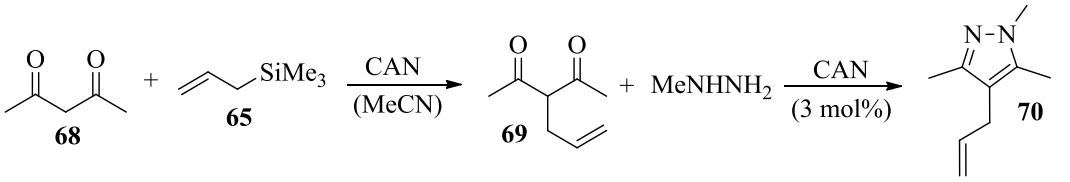
1.3.4.2 Carbon-carbon bond formations with Ce(IV)

While early applications focused primarily on functional group conversion and protecting group removal, many carbon-carbon bond forming reactions can be achieved through Ce(IV)-mediated oxidations.[48-50, 52] A number of CAN-mediated reactions proceed through radical cation and cation intermediates making them prone to rearrangements and other side reactions. However, judicious planning of reactions often can circumvent these alternative reaction pathways. For example, silylenolether **59** can be oxidized initially by CAN to generate a radical cation intermediate. Elimination of the

silyl-group, addition to diene **60**, oxidation of the product radical, and internal ligand transfer from CAN result in a 1:1 mixture of products **61a** and **61b** (reaction 23, Scheme 1.12).[62] However, when treated with $Pd(PPh_3)_4$ the nitrato groups are displaced forming the palladium complex **62**. Selective attack on the least hindered carbon atom by





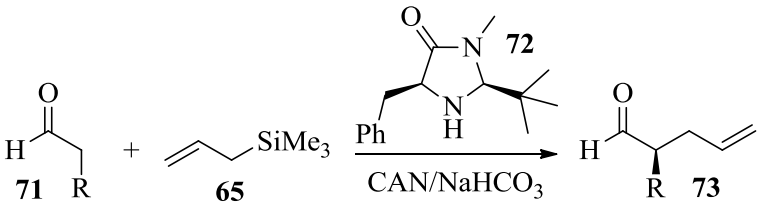


Scheme 1.12: CAN-mediated carbon-carbon bond forming reactions

an appropriate nucleophile selectively yields product **63a**.[62] Reaction 24 describes previous work from our research group which showed that the oxidative coupling of 1,3-

dicarbonyl derivatives (**64**) to allyltrimethylsilane (**65**) can be controlled to generate either allylated products (**66**) or dihydrofuran derivatives (**67**) through careful selection of solvent.[63, 64] Based on these results, we recently developed a method for tetra-substituted pyrazoles (reaction 25).[65] After initial allylation of 1,3-dicarbonyl **68** to generate **69**, treatment with methylhydrazine and a catalytic amount of CAN produced tetra-substituted pyrazoles (**70**) in very good yields.[65] Using this method, propylpyrazole triol (PPT), an estrogen receptor agonist, was efficiently synthesized.[65]

The enantioselective organocatalytic, SOMO-activated systems developed by MacMillan *et al*. are recent examples of the synthetic potential of Ce(IV)-based reagents in organic chemistry. These reactions involve the formation of an intermediate enamine from the condensation of an aldehyde (**71**) with the sterically encumbered imidazolidinone catalyst (**72**). A single electron oxidation of this enamine produces a radical cation that has one face completely blocked by the benzyl and *tert*-butyl groups of the catalyst. As a result, selective coupling with the radicophile (**65**) occurs at the opposite face of the radical cation. After a second single electron oxidation, deprotonation, and release of the catalyst, the enantiomerically enriched α-allylated aldehydes **73** are obtained in high yields.[66] Using similar procedures, the α-vinylation and α-enolation of aldehydes have also been achieved which employ CAN as the oxidant.[67, 68] Our research group in collaboration with MacMillan recently investigated the mechanism of these Ce(IV)-mediated reactions. Interestingly, by obtaining an intimate understanding of the complex roles of additives such as water in the catalytic cycle, the reaction time and catalyst loading were significantly reduced while preserving the high product yields and enantiomeric excesses.[69]

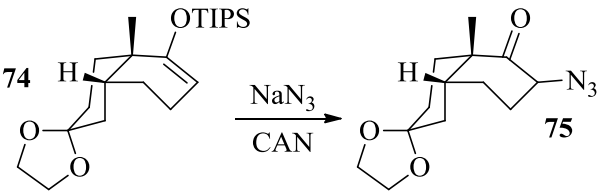


(26)

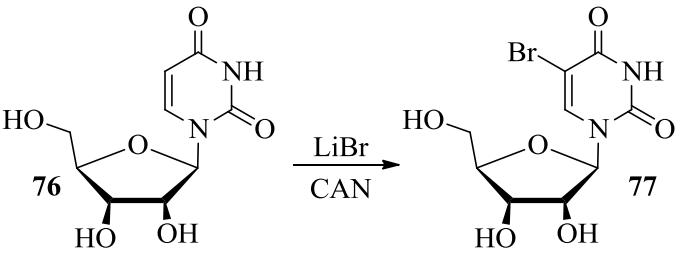
Scheme 1.13: Enantioselective α-allylation of aldehydes via SOMO-activated catalysis

1.3.4.3 Carbon-heteroatom bond formations with Ce(IV)

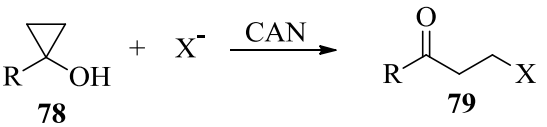
In addition to the carbon-carbon bond forming reactions mentioned in the previous section, CAN is capable of efficiently constructing carbon-heteroatom bonds as well.[48, 50, 51] Scheme 1.14 includes just a few of the Ce(IV)-mediated oxidative coupling reactions that have been developed. In reaction 27, the azide anion is oxidized to a



(27)



(28)



(29)

Scheme 1.14: Carbon-heteroatom bond construction via Ce(IV)-mediated oxidations

radical by CAN and adds to silylenolether **74** to generate the α-azido product (**75**).[70] These products are useful intermediates for the synthesis of α-amino ketones and acyl

enamines.[70] Oxidative addition of other inorganic anions such as bromide to uracil nucleosides (**76**), which results in regioselective mono-brominated products (**77**), can also be achieved using CAN.[71] Previous research from our group has shown that β-substituted ketones (**79**) are accessible by oxidizing inorganic anions with CAN in the presence of 1-substituted cyclopropanols (**78**).[72] The oxidative addition of iodides, bromides, azides, and thiocyanates proceeded efficiently via this method.[72] A novel synthetic method based on this research is discussed in detail in Chapter 2 of this dissertation.

1.4 Influencing reaction pathways

1.4.1 Preferential oxidation of substrates

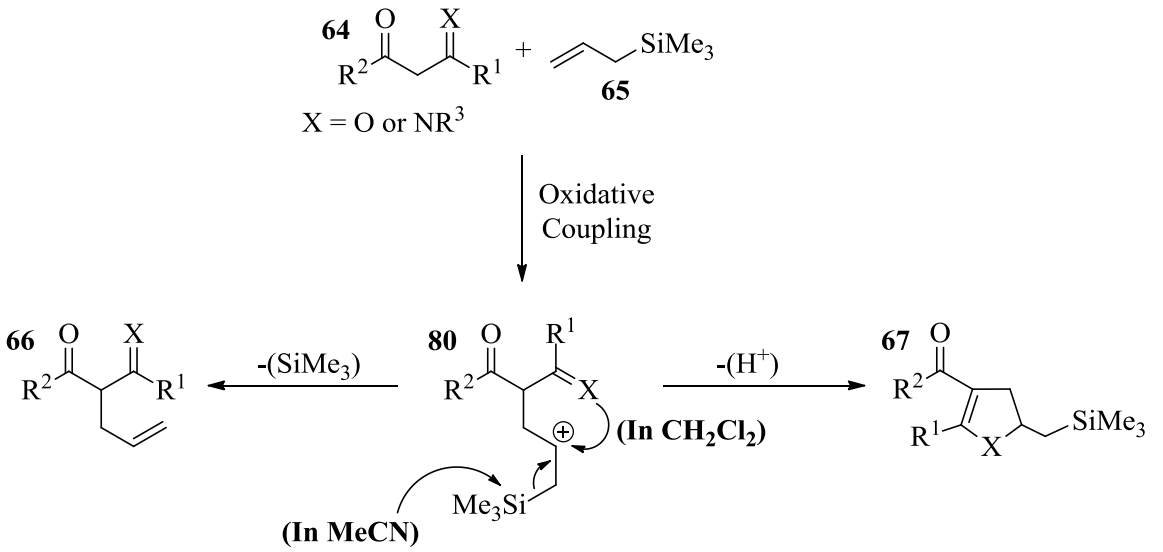
As demonstrated by the examples shown in the previous sections, many different substrates and functional groups are susceptible to single electron oxidations. As a result, multiple reaction pathways often can be envisioned for bimolecular oxidative coupling reactions. By knowing the relative rates of oxidation, these seemingly competitive processes may be avoided and selective coupling reactions can be developed by preferentially oxidizing one substrate over another. Two reaction systems exemplify the concept of preferential oxidation: organo-SOMO catalysis and oxidative addition of inorganic anions to cyclopropanols. In MacMillan's organo-SOMO systems, both the free imidazolidinone catalyst and the enamine are susceptible to single electron oxidation by CAN. However, the enamine intermediate is oxidized far more readily than free catalyst. Due to this difference in oxidation rate, preferential oxidation of the enamine occurs and catalyst deactivation through an oxidative pathway is not observed during the course of the reaction.[66-68]

Similarly, 1-substituted cyclopropanols can be oxidized to β-keto radicals through single electron oxidation. Previous research by Narasaka *et al.* has shown that these β-keto radicals can efficiently couple with radicophiles such as silylenolethers to generate 1,5-dicarbonyls as the major product.[73] However, the rate of oxidation of inorganic anions by CAN is much greater than the rate of oxidation of cyclopropanols. As a result, when CAN is added to a mixture of an inorganic anion and a cyclopropanol, the anion is preferentially oxidized to a radical which causes the cyclopropanol to act as the radicophile in the reaction.[72] This preferential oxidation of inorganic anions is critical for the efficient formation of the β-substituted ketone products. Components of the research presented in Chapters 2 and 5 of this dissertation involve the preferential oxidation of substrates to achieve selective bimolecular coupling reactions.

1.4.2 Impact of solvent

While the previous examples highlight how preferential oxidation of substrates can influence reaction pathways, the research performed in our group on the oxidative addition of 1,3-dicarbonyl derivatives to allyltrimethyl silane demonstrates that solvent can significantly impact some carbon-carbon bond forming reactions (reaction 24, Scheme 1.12).[63, 64] When oxidative couplings were performed in polar organic solvents such as MeCN, allylated products (**66**) were obtained, whereas dihydrofuran derivatives (**67**) were formed from reactions performed in less polar CH_2Cl_2. During the course of these reactions, a β-silyl cation (**80**) is generated (Scheme 1.15). More polar solvents such as MeCN and MeOH are able to promote the desilylation of this intermediate yielding the allylated products (**66**). In non-nucleophilic solvents such as CH_2Cl_2, elimination of the silyl group is slow, causing cyclization of the cation intermediate with one of the proximal

carbonyl groups to become the favored reaction pathway.[64] The research presented in Chapter 3 of this dissertation involves a detailed mechanistic study of a solvent-dependent reaction system.



Scheme 1.15: Solvent-dependent oxidative coupling of 1,3-dicarbonyl derivatives (**64**) with allyltrimethyl silane (**65**)

1.5 Expanding the organic chemist's "toolbox"

When planning the total synthesis of a complex synthetic molecule, it is important for organic chemists to have a variety of versatile, efficient reactions at their disposal. The improvement of a single reaction involved in a multistep synthesis can significantly enhance the overall yield of the target molecule. The driving force for the research presented in this dissertation is the expansion of the arsenal of reactions available in the organic chemist's "toolbox." Specifically, this research focuses on developing, understanding, and improving reactions that proceed through radical cation and radical intermediates. A selection of substrate classes that may participate in single electron oxidative coupling reactions are provided in Figure 1.1. Several of these substrates such as silylenolethers, cyclopropanols, and enamines are dual natured in that they can be oxidized to generate radical intermediates or they can act as radicophiles themselves to

trap an intermediate radical species. It is our belief that by understanding the mechanistic factors that are important to the single electron oxidation of substrates, new coupling reactions can be developed. Furthermore, exploiting differences in reactivity between substrate classes can lead to "fine-tuned" syntheses that selectively proceed through a single reaction pathway.

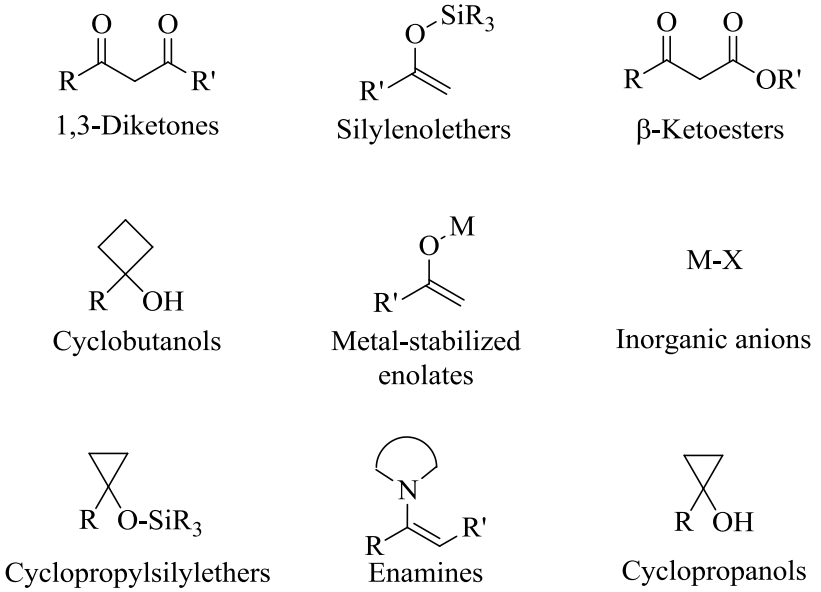


Figure 1.1: Examples of substrates useful in single electron oxidative couplings

1.6 Project summary

Chapters 2-5 of this dissertation present synthetic and mechanistic research on the following topics involving single electron oxidations in organic synthesis: 1) the synthesis of γ-halogenated ketones, which are important precursors for biologically active compounds such as haldol, via the Ce(IV)-mediated oxidative addition of inorganic halides to 1-substituted cyclobutanols; 2) the mechanism of the solvent-dependent oxidative coupling of 1-aryl-1,3-dicarbonyls to styrene; 3) the synthesis of β-tetralones via the oxidative intramolecular cyclization of γ-aryl-β-dicarbonyls and impact of substrate

electron density on product selectivity; and 4) the mechanistic basis for the non-statistical oxidative heterocoupling of equimolar lithium enolates.

Chapter 2: Synthesis of γ-halogenated ketones via the Ce(IV)-mediated oxidative coupling of inorganic halides to 1-substituted cyclobutanols

2.1 Background and significance

Ketones with γ-halogenated substitutions are routinely used as starting materials for the synthesis of biologically active compounds that contain γ-substituted ketone moieties in their structural backbone (Figure 2.1). The ketone moieties in neurological agents such as spiroperidol (**A**) and haldol (**B**) are incorporated by utilizing γ-chloro ketone precursors.[74, 75] The drug haldol is prescribed to patients suffering from severe cases of schizophrenia and delirium. Syntheses of antagonists (**C**) for the melanin-concentrating hormone (MCH_1) receptor require the use of γ-halogenated ketones.[76] Since the MCH_1 receptor is involved in the regulation of food in-take, these antagonists have potential applications as anti-obesity agents.[76] The ability to efficiently generate starting materials containing γ-halogenated ketone subunits[77] may greatly impact the synthesis of novel, pharmaceutically active compounds.

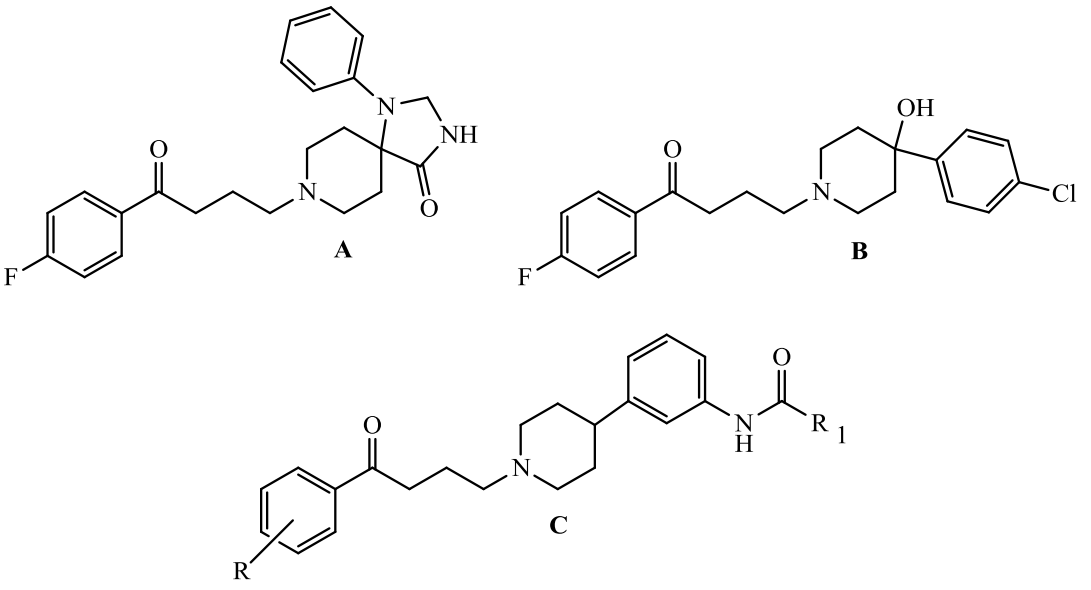
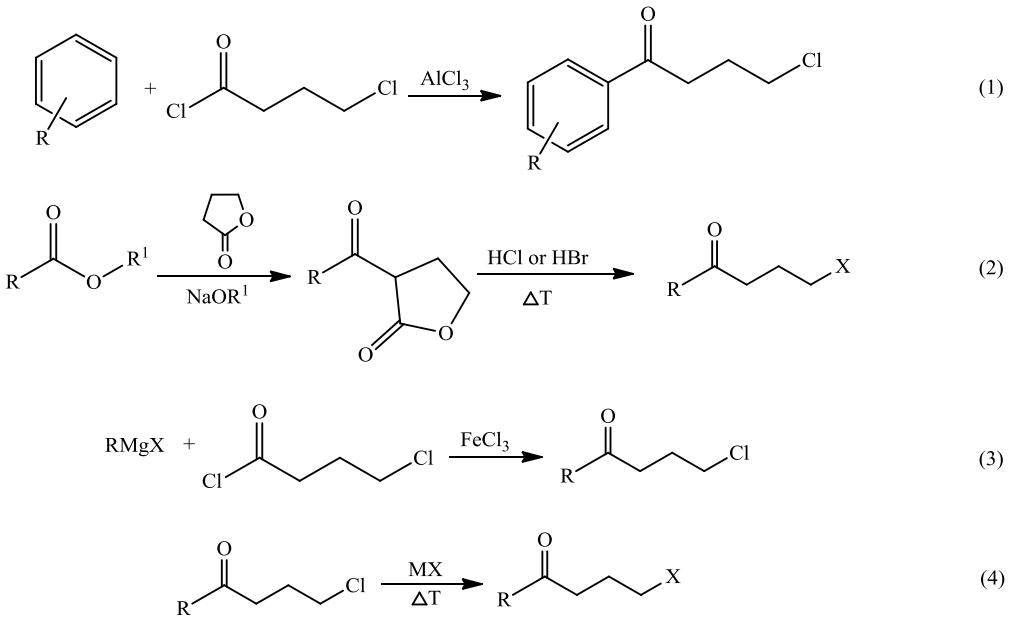


Figure 2.1: Structures of spiroperidol (**A**), haldol (**B**), and MCH_1 antagonists (**C**)

Although γ-substituted ketone functionalities traditionally have been incorporated into molecules through γ-chloro ketones, the use of other γ-halogenated ketones such as γ-iodo or bromo ketones may be synthetically beneficial since these halides are better leaving groups than chloride. However, the synthetic approaches to structurally diverse γ-halogenated ketones[77] have been limited to a handful of synthetic routes for γ-chloro and a sparse number of γ-bromo ketones. Scheme 2.1 includes some of the reactions routinely used in synthesis for the formation of γ-halogenated ketones. Friedel-Crafts reactions (eq. 1) can be utilized to generate a variety of 1-aryl-γ-chloro ketones.[78] The Claisen condensation of an ester with a γ-lactone can yield both 1-aryl and 1-alkyl substituted ketones upon treatment with strong acid (eq. 2).[79] Aliphatic γ-chloro ketones can also be prepared via the Grignard reaction using 4-chlorobutyryl chloride (eq. 3).[80] Typically, γ-iodo and -bromo ketones are produced by refluxing γ-chloro ketones in the presence of either iodide or bromide sources (eq. 4).[81]



(1)

(2)

(3)

(4)

Scheme 2.1: Previously established synthetic routes to γ-halogenated ketones

The conversions shown in Scheme 2.1 are not without drawbacks and limitations. Only 1-aryl-γ-chloro ketones can be synthesized via the Friedel-Crafts reaction, and yields (3-95%) are variable.[78] The Claisen condensation requires the use of strong acids at elevated temperatures.[79] Only low to moderate yields of 1-alkyl-γ-chloro ketones were obtained by Grignard reactions; 1-aryl-γ-chloro ketones were not accessible via this method.[80] While refluxing works well with a variety of substrates, it requires long reaction times and superstoichiometric amounts of the desired halide.[81] The development of a general and direct route to γ-iodo and -bromo ketones is of interest for the synthesis of more complex biologically active compounds.

As described in Chapter 1, cerium(IV) reagents, namely cerium(IV) ammonium nitrate (CAN), have been used extensively by organic chemists as single electron oxidants. CAN has proven to be a cost-effective, versatile reagent that is capable of mediating the formation of novel carbon-carbon and carbon-heteroatom bonds.[48-50, 52] Previous research from our group has shown that β-substituted ketones are accessible through the use of CAN.[72] By selectively oxidizing an inorganic anion with CAN in the presence of a 1-substituted cyclopropanol, the generated inorganic radical added to the cyclopropanol, resulting in ring-opening. Subsequent oxidation of the radical intermediate and deprotonation produced β-substituted ketones in very good to excellent yields. In addition to short reaction times, these reactions worked for both 1-aryl- and 1-alkyl-cyclopropanols as well as a variety of inorganic anions. Based on this precedent, we examined whether this method could be extended to 1-substituted cyclobutanols thereby providing access to γ-substituted ketones. The results of these studies are presented in this chapter.

2.2 Experimental

2.2.1 Materials

Diethyl ether, methylene chloride, tetrahydrofuran and acetonitrile were purified with a Pure Solv solvent purification system from Innovative Technology, Inc. using alumina columns. Dimethoxyethane was purchased from Acros Organics. Grignard reagents (phenylmagnesium bromide, *p*-methoxyphenylmagnesium bromide, *p*-fluorophenylmagnesium bromide, cyclohexylmagnesium chloride and *n*-hexylmagnesium bromide) were purchased from Acros Organics as solutions in diethyl ether. Cyclobutanone was purchased from both Acros Organics and Alfa Aesar and used without further purification. Sodium iodide, potassium bromide, and sodium azide were purchased from Acros Organics, Alfa Aesar, and Sigma Aldrich. CAN and copper(II) perchlorate hexahydrate ($CuClO_4$-$6H_2O$) were purchased from Alfa Aesar and Acros Organics, respectively, and were used without further purification. Ferrocenium hexafluorophosphate ($FeCp_2PF_6$) was prepared according to the literature.[8] Cyclohexyl ethyl ketone and molecular bromine were purchased from Alfa Aesar and Acros Organics, respectively.

2.2.2 Instrumentation

Proton and carbon NMR were recorded on a Bruker 500 MHz spectrometer. GC and GC-MS analyses were performed with an HP 5890 Series II Gas Chromatograph with an HP Mass Selector Detector. HR-MS was performed at the Mass Spectrometry Facility at Notre Dame University.

2.2.3 Methods

2.2.3.1 Procedure for the synthesis of 2-ethyl-cyclobutanone

Unsymmetric *N*,*N*-dimethylhydrazine (25 mmol, 1.2 equiv) was dissolved in 30 mL of benzene. Cyclobutanone (20 mmol, 1.0 equiv) was added to the reaction and a Dean-Stark apparatus was attached. The reaction was refluxed for 5 hours. The reaction mixture was dried with $MgSO_4$, filtered, and concentrated to yield 2.65 grams of the crude hydrazone. A solution of lithium diisopropylamine (LDA) (29.5 mmol in 16 mL THF, 1.25 equiv) was cooled to 0 ^oC. The hydrazone was dissolved in 10 mL of THF and added dropwise to the LDA. After stirring for 1 hour at 0 ^oC, the reaction was cooled to -78 ^oC. Ethyl iodide (26 mmol, 1.1 equiv) was dissolved in 10 mL of THF and added dropwise to the reaction at -78 ^oC. The reaction was allowed to slowly warm to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl, extracted with methylene chloride (CH_2Cl_2) (3x) and concentrated. The crude product was dissolved in acetone and stirred with "wet" Amberlyst (approx. 25 grams, 10 equiv) for 3 hours. The solution was filtered through Celite, concentrated, redissolved in ether, dried with $MgSO_4$, filtered, and concentrated to yield pure 2-ethyl-cyclobutanone.

2.2.3.2 General procedure for the synthesis of 1-substituted cyclobutanols

All glassware was flame-dried before use. Cyclobutanone (13.4 mmol) was dissolved in 25 mL of diethyl ether and purged with N_2 (2-ethyl-cyclobutanone was used for the synthesis of **1f**). The temperature was reduced to 0 ^oC. The appropriate Grignard reagent (14.7 mmol) was added dropwise with stirring. The reaction was allowed to stir for an additional 3 hours. Water was added slowly to quench the reaction. The organic layer was removed and the aqueous layer was extracted with diethyl ether (3x). The

organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. Pure 1-substituted cyclobutanols were then obtained by recrystallization from *n*-pentane at -20 ^oC, short-path low pressure distillation, or required no additional purification.

2.2.3.3 General procedure for the synthesis of γ-iodo ketones

Sodium iodide (0.33 mmol) was dissolved in 1 mL of H_2O and added to the 1-substituted cyclobutanol (0.33 mmol) in 2 mL of 1,2-dimethoxyethane (DME). The reaction was then purged with N_2. CAN (0.67 mmol) was dissolved in 2 mL of DME and added dropwise via syringe with stirring. After stirring for 30 minutes, the volatiles were removed from the reaction via rotary evaporation. Water was added and then the aqueous layer was extracted with diethyl ether (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The γ-iodo ketones were purified further by flash chromatography on a silica column using 15% ethyl acetate:hexanes as the eluting solvent.

2.2.3.4 Procedure for the synthesis of 2-ethyl-1-*p*-fluorophenyl-4-iodo-1-butanone

Sodium iodide (0.33 mmol) was dissolved in 1 mL of H_2O and added to the 2-ethyl-1-*p*-fluorophenyl-1-cyclobutanol (0.33 mmol) in 2 mL of MeCN. The reaction was then purged with N_2 and cooled to 0 ^oC. CAN (0.67 mmol) was dissolved in 2 mL of MeCN and added dropwise via syringe with stirring. After stirring for 30 minutes, the volatiles were removed from the reaction via rotary evaporation. Water was added and then the aqueous layer was extracted with diethyl ether (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The γ-iodo ketone was purified further by flash chromatography on a silica column using 15% ethyl acetate:hexanes as the eluting solvent.

2.2.3.5 General procedure for the synthesis of γ-bromo ketones

Potassium bromide (0.33 mmol) was dissolved in 1 mL H_2O and added to the 1-substituted cyclobutanol (0.33 mmol) in 3 mL of CH_2Cl_2. The reaction was purged with N_2. CAN (0.67 mmol) was dissolved in 2 mL H_2O and added dropwise via syringe with stirring. After stirring for 30 minutes, the volatiles were removed from the reaction via rotary evaporation. Water was added and then the aqueous layer was extracted with diethyl ether (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The γ-bromo ketones were purified further by flash chromatography on a silica column using 15% ethyl acetate:hexanes as the eluting solvent.

2.2.3.6 Procedure for the bromination of cyclohexyl ethyl ketone with molecular bromine

Cyclohexyl ethyl ketone (0.33 mmol) and molecular bromine (0.17 mmol) were added to 4 mL of 50% H_2O:CH_2Cl_2. The reaction was stirred for 30 minutes. The volatiles were removed from the reaction via rotary evaporation. Water was added and then the aqueous layer was extracted with diethyl ether (3x). The organic layers were combined, dried with $MgSO_4$, and filtered. The product distribution was determined by GC.

2.2.3.7 Procedure for the bromination of cyclohexyl ethyl ketone with KBr/CAN

Procedure 2.2.3.5 was followed, except that cyclohexyl ethyl ketone was employed in place of the 1-substituted cyclobutanol. The product distribution of the crude reaction mixture was determined by GC.

2.3 Results and discussion

In an initial study, sodium iodide (NaI) was oxidized with CAN in the presence of 1-phenyl-1-cyclobutanol (**1a**) using reaction conditions [20% H_2O: MeCN] previously employed for the oxidative addition of inorganic anions to 1-substituted cyclopropanols.[72] While the expected 4-iodo-1-phenyl-1-butanone (**2a**) was produced as the major product, analysis of the crude reaction mixture by ^{1}H NMR indicated the presence of multiple side products. Since changes in solvent can often impact the chemoselectivity of reactions initiated by CAN, several solvent systems were examined to determine if the reaction efficiency could be improved.[63, 64] Among the solvent systems screened, 20% H_2O:1,2-DME generated **2a** almost exclusively and did not show any formation of the side products by ^{1}H NMR.

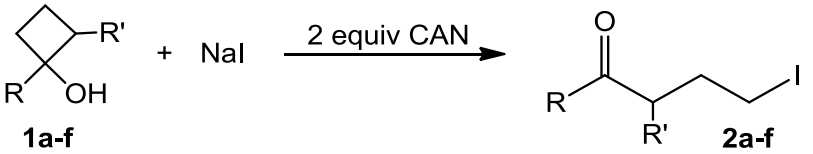
After determining the optimal reaction conditions, a variety of both 1-aryl- and 1-alkyl-1-cyclobutanols were synthesized to examine the breadth of γ-halogenated compounds that could be accessed from the oxidative addition of inorganic anions to 1-substituted cyclobutanols. These starting materials were generated via the reaction of cyclobutanone, or 2-ethyl-cyclobutanone for **1f**, with a variety of Grignard reagents.[82, 83] These reactions proceeded either quantitatively or required minimal purification using nonchromatographic methods.

With these starting materials in hand, iodinations of substrates **1a-e** were performed using the optimized reaction conditions. The results of these reactions are included in Table 2.1. The oxidative addition of iodide to unsubstituted, activated, or deactivated 1-aryl-1-cyclobutanols (substrates **1a-c**) generated the expected γ-iodo ketones (**2a-c**) in good to very good yields. Comparable yields of the desired γ-iodo

ketone products were obtained when 1-alkyl-1-cyclobutanols **1d** and **e** were employed. To examine the regioselectivity of the ring opening of the 1-substituted cyclobutanol, substrate **1f** was subjected to the same reaction conditions. While 2-ethyl-1-*p*-fluorophenyl-4-iodo-1-butanone (**2f**) was formed exclusively, the reaction mixture contained significant amounts of unreacted starting material. After scanning a series of solvent and reaction conditions, optimal yields of **2f** were obtained when the reaction was performed in 20% H_2O:MeCN at 0 ^oC. The exclusive formation of **2f** is consistent with the addition of the iodine atom occurring at the less hindered carbon of the cyclobutanol ring.

With synthetic studies of the iodination of 1-substituted cyclobutanols completed, the synthesis of γ-bromo ketones was examined. In the previous work on the synthesis of β-substituted ketones, the oxidation of bromide anion by CAN was shown to be relatively slow compared to the oxidation of iodide.[72] To avoid the possibility of direct oxidation of substrates **1a-f** by CAN, these brominations were performed in a two-phase solvent system of 50% H_2O:CH_2Cl_2.[84] In an initial experiment, the bromination of bromo-1-phenyl-1-butanone (**3a**) in an 87% isolated yield. Brominations of both 1-aryl- and 1-alkyl-1-cyclobutanols were performed using identical reaction conditions (Table 2.2). The bromination of 1-aryl substrates **1b-c** produced the desired γ-bromo ketones **3b-c** in good to excellent yields. While complete conversion to **3f** was not achieved even at reduced temperatures, bromination of the unsymmetric **1f** exhibited the same regioselectivity as the iodination reaction with the bromine atom addition occurring at the substrate **1a** using potassium bromide (KBr) as the bromide anion source provided 4- less hindered position of the cyclobutanol ring. Surprisingly, reactions of 1-alkyl-1-

Table 2.1: Synthesis of γ-iodo ketones



1a-f **2a-f**

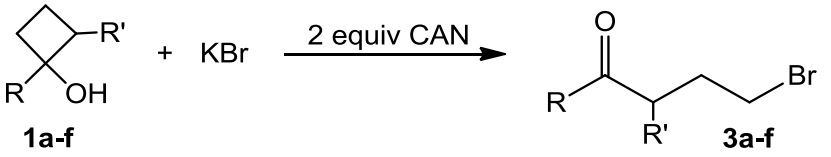
Substrate	Product	R	R'	Conditions[a]	Yield (%)[b]
1a	2a	Ph	H	A	79
1b	2b	*p*-CH_3O-Ph	H	A	67
1c	2c	*p*-F-Ph	H	A	79
1d	2d	cyclohexyl	H	A	64
1e	2e	*n*-hexyl	H	A	80
1f	2f	*p*-F-Ph	Et	B	80

[a] Conditions: (A) 20% H_2O:DME room temp. and (B) 20% H_2O:MeCN at 0°C
[b] Isolated yields

cyclobutanols **1d-e** produced **3d-e** in yields of less than 20%. Examination of crude reaction mixtures by GC-MS and ^{1}H NMR indicated that brominations of substrates **1d-e** resulted in a mixture of starting material, desired γ-bromo ketone, and α,γ-dibrominated ketones.

The presence of α-brominated products for the reactions involving 1-alkyl-cyclobutanols **1d** and **e** suggested the formation of molecular bromine during the course of the reaction. Under the appropriate conditions, both acid- and base-promoted α-brominations of carbonyl-containing compounds can occur.[85] Reactions performed with methyl ketones under basic conditions are known as haloform reactions.[85] To determine whether molecular bromine was forming in the reactions involving the 1-alkyl-1-cyclobutanols, the series of experiments described in Table 2.3 was performed. For these experiments, cyclohexyl ethyl ketone (**4**) was used as a model substrate since it is

Table 2.2: Synthesis of γ-bromo ketones



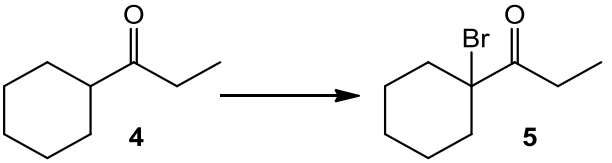
1a-f **3a-f**

Substrate	Product	R	R'	Conditions[a]	Yield (%)[b]
1a	3a	Ph	H	C	87
1b	3b	*p*-CH_3O-Ph	H	C	70
1c	3c	*p*-F-Ph	H	C	95
1d	3d	cyclohexyl	H	C	ND[c]
1e	3e	*n*-hexyl	H	C	ND[c]
1f	3f	*p*-F-Ph	Et	C	37[d]

[a] Conditions: (C) 50% H_2O:CH_2Cl_2
[b] Isolated yields
[c] Mixture of 1-alkyl-cyclobutanol, γ-bromo ketone and α,γ-dibrominated ketones
[d] Determined by ^{1}H NMR

structurally similar to both starting material **1d** and product **3d**. Initially, 1 equivalent of **4** was reacted with 0.5 equivalents of molecular bromine (entry 1). In a second experiment, substrate **4** was reacted with both 1 equivalent of both CAN and KBr under the same conditions the oxidative addition reactions were performed (entry 2). Bromine atom homocoupling following the single electron oxidation of bromine anion should generate an equal amount of molecular bromine. The results from experiments listed in entries 1 and 2 showed identical ratios of **5**:**4**, a finding consistent with *in situ* formation of molecular bromine. Interestingly, the use of excess CAN resulted in greater conversion to product **5** (entry 3). This observation suggested an additional role for CAN beyond oxidation, presumably through Lewis acid activation.

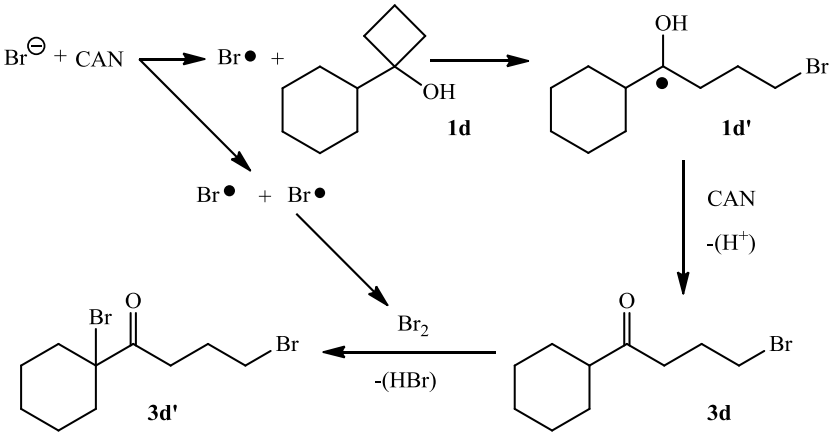
Table 2.3: α-Bromination of aliphatic substrates



Entry	Conditions[a]	Ratio (5:4)[b]
1	**4** (0.33 mmol), Br_2 (0.17 mmol)	3:1
2	**4** (0.33 mmol), KBr (0.33 mmol), CAN (0.66 mmol)	3:1
3	**4** (0.33 mmol), KBr (0.33 mmol), CAN (0.83 mmol)	9:1

[a] 50% H_2O:CH_2Cl_2
[b] Ratios determined by GC

From the data obtained, the mechanism provided in Scheme 2.2 was proposed. Initially, bromine anion is oxidized by CAN to bromine radical which adds to the 1-substituted cyclobutanol **1d** and ring-opens to produce intermediate **1d'**. Bromine atom addition to cyclobutanols is supported by the observation that no γ-substituted products were obtained when **1d** was treated with molecular bromine. The intermediate **1d'**, generated from the ring-opening of **1d**, is less stable than the corresponding benzylic radicals of 1-aryl-1-cyclobutanols **1a-c**. As a result, 1-alkyl-1-cyclobutanols are expected to be less reactive, causing homocoupling of bromine atoms to become a competitive pathway. A second single electron oxidation of intermediate **1d'** by CAN and subsequent



Scheme 2.2: Proposed mechanism for the bromination of 1-alkyl-cyclobutanols

deprotonation produce γ-bromo ketone **3d**. Addition of molecular bromine α to the carbonyl of **3d** produces the α,γ-dibrominated ketone **3d'**.

Because bromination was only successful in the case of 1-aryl-1-cyclobutanols, other oxidants were examined to determine whether the desired mono-brominated products could be obtained selectively for the 1-alkyl-1-cyclobutanol substrates. Both iodinations and brominations with NaI and KBr, respectively, were performed with $CuClO_4 \cdot 6H_2O$ in MeCN.[18] However, only a complex mixture of reaction products was obtained, none being the γ-haloketone. Additionally, the use of ferrocenium hexafluorophosphate in CH_2Cl_2 provided only unreacted starting material in all cases.[5, 8]

Due to the rapid evolution and applications of "click chemistry," direct routes for incorporation of azides into molecules would be synthetically useful. As a result, the methodology for the iodination and bromination of 1-substituted cyclobutanols was extended to the oxidative addition of azide anions. Unfortunately, oxidative addition of azide anions to 1-substituted-cyclobutanols has been disappointing thus far. When 1 equivalent of sodium azide (NaN_3) was oxidized by CAN in the presence of 1 equivalent of **1a-e**, evolution of nitrogen gas was observed even at reduced temperatures, and only starting material was recovered after reaction work-up. Even though azide anion was oxidized much faster than **1a-e** by CAN, the homocoupling of azide radicals and subsequent decomposition to evolve N_2 gas was favored over radical addition to the cyclobutanols. When 5 equivalent excesses of NaN_3 and CAN were used with 1 equivalent of **1a**, equal amounts of the desired γ-azido product and the γ-nitrato compound were generated with isolated yields of less than 20%. Although this method was inefficient for the synthesis of γ-azido ketones, subsequent transformations using the

accessible γ-iodo and -bromo products can produce other substrates including azides and nitriles.[86, 87]

Because CAN is a versatile single electron oxidant capable of oxidizing a variety of functional groups, this Ce-mediated protocol may appear to be incompatible with more complex substrates. However, rate studies performed by our research group have shown that the oxidation of inorganic anions by CAN is extremely fast, indicating that these reagents are oxidized preferentially to other functional groups. Additionally, previous studies on the relative rates of oxidation of substrates and functional groups have shown that selective oxidations can be achieved using CAN.[72, 88] As a result, this protocol should be applicable to complex molecules, provided that the substrates do not contain functional groups with rates of oxidation similar to inorganic anions.

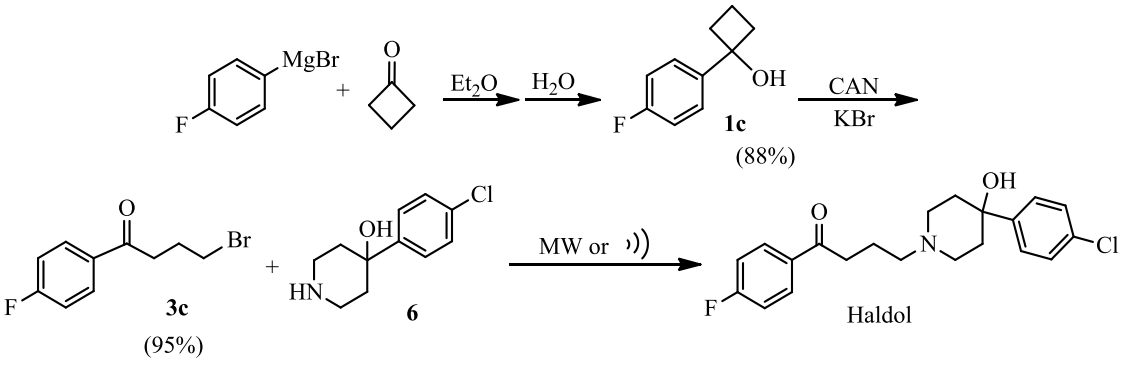
2.4 Conclusions

An alternative route to both γ-iodo and γ-bromo ketones has been developed. The synthesis of γ-iodo ketones from 1-substituted cyclobutanols is general, producing both aryl- and alkyl-γ-iodo ketones in good to very good yields. Although the iodination of 1-alkyl-1-cyclobutanols proceeded efficiently, brominations of these substrates lead to a mixture of the desired product and α,γ-dibrominated ketones. The formation of these side products resulted from the *in situ* formation of molecular bromine through bromine atom homocoupling. While the synthesis of aliphatic γ-bromo ketones proved to be more difficult, 1-aryl-γ-bromo ketones were obtained in good to excellent yields. For both the iodination and bromination reactions, the halide was shown to add selectively to the less hindered carbon of the cyclobutanol ring. The methodology described in this chapter has the advantage of short reaction times and provides access to a range of structurally diverse

γ-halogenated ketones that can be used as starting materials for the synthesis of more complex compounds. The research presented in this chapter was published in *Tetrahedron Letters*.[89]

2.5 Future work

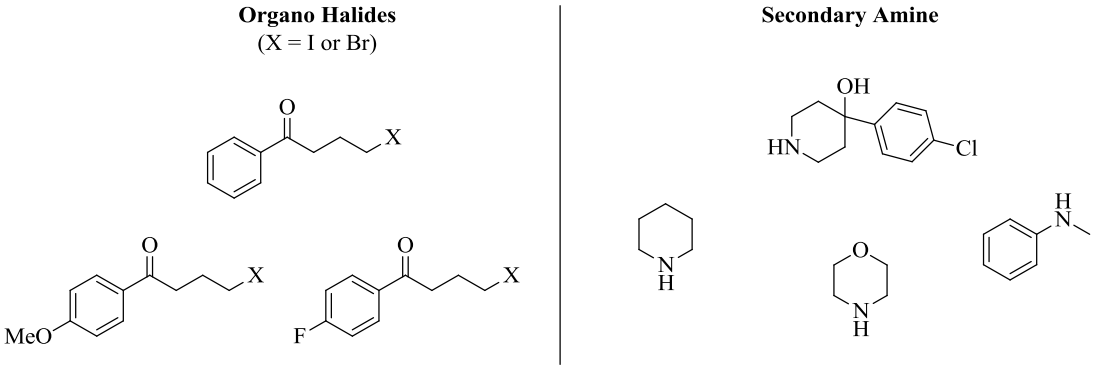
As stated in section 2.1, the synthesis of many pharmaceutically active compounds involves the use of γ-halogenated ketones as precursors. The most recent total synthesis of haldol consisted of 5 steps with an overall yield of 30%, starting from *p*-fluoro-benzaldehyde.[90] Using the methodology described in this chapter, the synthesis shown in Scheme 2.3 is a potential alternative route for the total synthesis of haldol. The first step to synthesize cyclobutanol **1c** is high yielding and requires no additional purification after working up the crude reaction. The CAN-mediated oxidative addition of bromine to substrate of **1c** to produce **3c** is quantitative. Rapid, high-yielding procedures exist for the coupling of organo halides and amines such as **6** through either sonication or microwave irradiation.[91] This alternative synthesis of haldol benefits from requiring two less steps and also from improving the overall yield.



Scheme 2.3: Total synthesis of haldol

While still readily prescribed for patients suffering from schizophrenia and delirium, the use of haldol is limited by the side effects associated with the drug.

Generation of a library of compounds related to haldol may lead to a therapeutic agent with the same antipsychotic activity but without the unfavorable side effects. In addition to the total synthesis of haldol, a range of haldol derivatives can be rapidly and efficiently generated via the method described in Scheme 2.3. As shown in Scheme 2.4, the γ-substituted ketone moiety as well as the amine moiety can be varied. Since both the iodination and bromination reactions tolerated substitutions on the aryl ring of the 1-substituted-1-cyclobutanol, the impact of electron density on drug efficacy can be investigated. In addition, cyclic and acyclic secondary amines can be introduced to assess how variations in the amine portion of the molecule affect the activity.



Scheme 2.4: Synthesis of a library of haldol derivatives and anaolgues

2.6 Synthesis and spectral data for starting materials and products

2.6.1 1-Substituted cyclobutanols

1-Phenyl-1-cyclobutanol (**1a**)

Procedure 2.2.3.2 was followed employing phenylmagnesium bromide. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 7.50 (m, 2H), 7.38-7.35 (m, 2H), 7.29-7.27 (m, 2H), 2.58-2.54 (m, 2H), 2.39-2.33 (m, 2H), 2.08-1.97 (m, 1H), 1.96 (s, 1H), 1.72-1.68 (m, 1H). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ146.22, 128.45, 127.25, 124.93, 36.81, 12.99.

1-*p*-Methoxyphenyl-1-cyclobutanol (**1b**)

Procedure 2.2.3.2 was followed employing *p*-methoxylphenylmagnesium bromide. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 7.42 (m, 2H), 6.90-6.89 (m, 2H), 3.80 (s, 3H), 2.55-2.50 (m, 2H), 2.37-2.32 (m, 2H), 2.01-1.92 (m, 1H), 1.94 (s, 1H), 1.65-1.62 (m, 1H). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 158.76, 126.34, 113.72, 109.31, 55.29, 36.84, 12.87. Bp 65-68 ^{o}C (at < 25 mtorr).

1-*p*-Fluorophenyl-1-cyclobutanol (**1c**)

Procedure 2.2.3.2 was followed employing *p*-fluorophenylmagnesium bromide. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 7.49-7.46 (m, 2H), 7.07-7.03 (m, 2H), 2.58-2.51 (m, 2H), 2.40-2.33 (m, 2H), 2.05-1.97(m, 1H), 2.01 (s, 1H), 1.72-1.63 (m, 1H). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 161.96 (d), 142.04 (d), 126.78 (d), 115.13 (d), 37.01, 12.87.

1-Cyclohexyl-1-cyclobutanol (**1d**)

Procedure 2.2.3.2 was followed employing cyclohexylmagnesium chloride. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 2.15-2.12 (m, 2H), 1.90-1.65 (m, 8H), 1.59-1.49 (m, 1H), 1.45 (s, 1H), 1.41-1.36 (m, 1H), 1.27-1.09 (m, 3H), 1.06-0.94 (m, 2H). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 78.02, 45.48, 33.85, 26.47, 26.44, 25.58, 12.36. Bp 34-35 ^{o}C (at < 70 mtorr).

1-*n*-Hexyl-1-cyclobutanol (**1e**)

Procedure 2.2.3.2 was followed employing *n*-hexylmagnesium bromide. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 2.05-1.92 (m, 4H), 1.76-1.68 (m, 1H), 1.57 (t, 3H, J = 6.75 Hz), 1.54-1.44 (m, 1H), 1.35-1.26 (m, 8H), 1.24 (s, 1H), 0.87 (t, 3H, J = 6.73 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 75.40, 39.54, 35.91, 31.88, 29.70, 23.33, 22.62, 14.0008, 12.11. Bp 33-35 ^{o}C (at < 50 mtorr).

2-Ethyl-1-*p*-fluorophenyl-1-cyclobutanol (**1f**)

Procedure 2.2.3.2 was followed employing *p*-fluorophenylmagnesium bromide. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 7.48-7.40 (m, 2H), 7.07-7.01 (m, 2H), 2.55-2.51 (m, 1H), 2.40-2.38 (m, 1H), 2.19-2.14 (m, 1H), 2.00-1.97 (m, 1H), 1.82-1.78 (m, 1H), 1.80 (s, 1H), 1.69-1.51 (m, 2H), 0.90-0.86 (t, 3H, J = 7.44 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 161.78 (d), 143.12 (d), 126.54 (d), 114.98 (d), 78.29, 47.59, 34.31, 22.33, 21.32, 11.38.

2.6.2 γ-Iodo ketones

4-Iodo-1-phenyl-1-butanone (**2a**)

Procedure 2.2.3.3 was followed. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 7.97-7.96 (m, 2H), 7.58-7.7.54 (m, 1H), 7.48-7.45 (m, 2H), 3.32 (t, 2H, J = 6.70 Hz), 3.12 (t, 2H, J = 6.97 Hz), 2.25 (quin, 2H, J = 6.83 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 198.62, 136.72, 133.24, 128.66, 128.02, 38.92, 27.52, 6.78.

4-Iodo-1-*p*-methoxyphenyl-1-butanone (**2b**)

Procedure 2.2.3.3 was followed. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 7.96-7.93 (m, 2H), 6.94-6.92 (m, 2H), 3.87 (s, 3H), 3.31 (t, 2H, J = 6.65 Hz), 3.07 (t, 2H, J = 7.04), 2.23 (quin, 2H, J = 6.84 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 197.16, 163.55, 130.28, 129.81, 113.76, 55.47, 38.52, 27.72, 7.02.

1-*p*-Fluorophenyl-4-iodo-1-butanone (**2c**)

Procedure 2.2.3.3 was followed. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 8.03-7.97 (m, 2H), 7.18-7.11 (m, 2H), 3.35-3.29 (t, 2H, J = 6.66 Hz), 3.13-3.08 (t, 2H, J = 7.01 Hz), 2.29-2.20 (quin, 2H, J = 6.84 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 196.93, 165.76 (d), 133.11 (d), 130.62 (d), 115.72 (d), 38.78, 27.39, 6.71.

1-Cyclohexyl-4-iodo-1-butanone (**2d**)

Procedure 2.2.3.3 was followed. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 3.20 (t, 2H, J = 6.61 Hz), 2.57 (t, 2H, J = 7.00 Hz), 2.34-2.30 (m, 1H), 2.04 (quin, 2H, J = 6.74 Hz), 1.86-1.62 (m, 5H), 1.36-1.13 (m, 5H). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 212.63, 50.96, 40.72, 28.48, 26.97, 25.80, 25.63, 6.97. HR-MS (FAB+): m/z 281.0397 $(M+H)^+$ for $C_{10}H_{18}OI$: Calcd. 281.04.

1-Iodo-4-decanone (**2e**)

Procedure 2.2.3.3 was followed. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 3.21 (t, 2H, J = 6.56 Hz), 2.54 (t, 2H, J = 6.91 Hz), 2.39 (t, 2H, J = 7.44 Hz), 2.05 (quin, 2H, J = 6.73 Hz), 1.58-1.52 (m, 2H), 1.30-1.24 (m, 6H), 0.87 (t, 3H, J = 6.91 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 209.76, 43.07, 42.79, 31.56, 28.87, 27.02, 23.81, 22.47, 14.02, 6.71.

2-Ethyl-1-*p*-fluorophenyl-4-iodo-1-butanone (**2f**)

Procedure 2.2.3.4 was followed. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 8.05-8.00 (m, 2H), 7.18-7.13 (m, 2H), 4.20-4.16 (m, 1H), 3.26-3.14 (m, 2H), 2.22-2.17 (m, 2H), 1.97-1.82 (m, 2H), 1.10-1.06 (t, 3H, J = 7.22 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 197.38, 165.78 (d), 133.15 (d), 130.66 (d), 115.71 (d), 41.66, 38.72, 34.25, 34.15, 14.12.

2.6.3 γ-Bromo ketones

4-Bromo-1-phenyl-1-butanone (**3a**)

Procedure 2.2.3.5 was followed. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 7.98-7.96 (m, 2H), 7.58-7.55 (m, 1H), 7.48-7.45 (m, 2H), 3.54 (t, 2H, J = 6.27 Hz), 3.18 (t, 2H, J = 6.86 Hz), 2.30 (quin, 2H, J = 6.64 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 198.81, 136.71, 133.24, 128.65, 128.01, 36.54, 33.64, 26.83.

4-Bromo-1-*p*-methoxyphenyl-1-butanone (**3b**)

Procedure 2.2.3.5 was followed. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 7.96-7.95 (m, 2H), 6.94-6.91 (m, 2H), 3.86 (s, 1H), 3.53 (t, 2H, J = 6.35 Hz), 3.12 (t, 2H, J = 6.96), 2.29 (quin, 2H, J = 6.60 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 197.31, 163.52, 130.24, 129.79, 113.72, 55.44, 36.12, 33.76, 27.01.

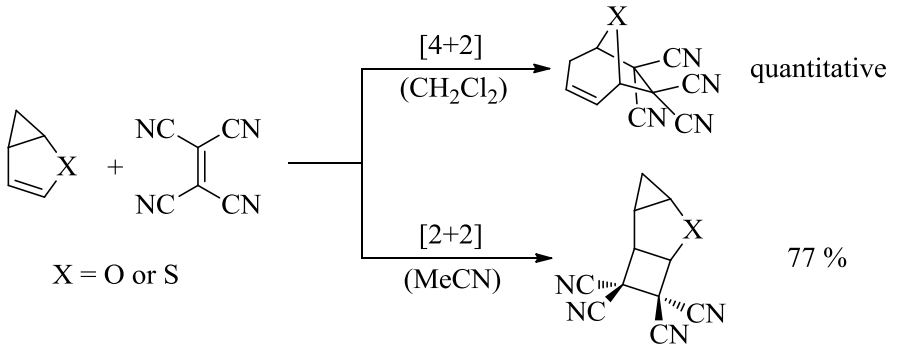
4-Bromo-1-*p*-fluorophenyl-1-butanone (**3c**)

Procedure 2.2.3.5 was followed. ^{1}H-NMR ($CDCl_3$, 500 MHz) – δ 8.03-7.98 (m, 2H), 7.17-7.11 (m, 2H), 3.57-3.53 (t, 2H, J = 6.33 Hz), 3.18-3.13 (t, 2H, J = 6.97 Hz), 2.33-2.26 (quin, 2H, J = 6.58 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) – δ 197.13, 165.77 (d), 133.12 (d), 130.62 (d), 115.72 (d), 36.41, 33.53, 26.74.

Chapter 3: Solvent-dependent oxidative coupling of 1-aryl-1,3-dicarbonyls and styrene via Ce(IV) reagents

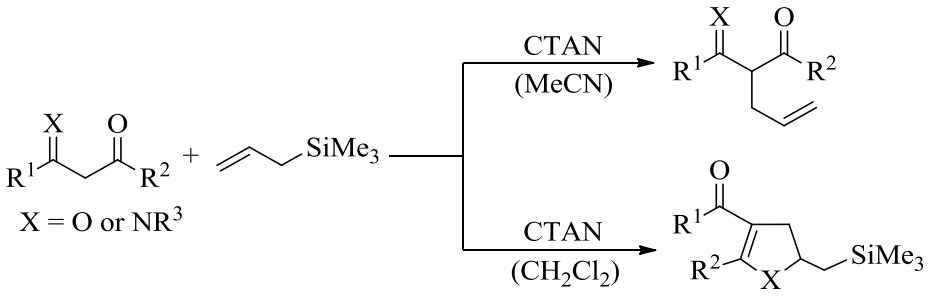
3.1 Background and significance

In addition to serving simply as a reaction medium, the solvent has been shown to be intimately involved in a variety of reaction systems. Numerous examples exist in which discrete products are formed depending on the solvent.[92] The types of reactions that can be affected by the solvent include but are not limited to, nucleophilic bimolecular substitutions,[93] nucleophilic intramolecular cyclizations,[94] Diels-Alder reactions,[95] photo-oxygenations,[96-99] fragmentations,[100] halogen eliminations,[101] and selective reduction of functional groups.[102] An example of a solvent-dependent Diels-Alder reaction is shown in Scheme 3.1. In this reaction system, the addition of 1,1,2,2-tetracyanoethene with either homofuran or homothiophene in polar, aprotic solvents such as MeCN results in a [2+2] cycloaddition generating a tricyclic product.[95] Conversely, when a less polar solvent such as CH_2Cl_2 is employed, the reaction proceeds through a [4+2] cycloaddition pathway yielding the 7-membered ring product quantitatively.[95] The authors reasoned that in more polar MeCN, the reaction pathway proceeded through a two-step process involving a zwitterionic intermediate, whereas a concerted cycloaddition occurred for the reaction performed in CH_2Cl_2.[95]



Scheme 3.1: Solvent-dependent Diels-Alder cycloadditions to homofuran (X = O) and homothiophene (X = S)[95]

While many of the reactions noted proceed through two-electron processes, solvent can dramatically impact reactions involving single electron oxidations as well. As described in detail in Chapter 1, cerium(IV) reagents, namely cerium(IV) ammonium nitrate (CAN), have been used extensively by organic chemists as single electron oxidants.[48-50, 52] Although traditionally restricted to aqueous or polar organic solvents, the replacement of the ammonium counterions of CAN with tetra-*n*-butylammonium ions yields cerium(IV) tetra-*n*-butylammonium nitrate (CTAN) which is more lipophilic, resulting in increased solubility in less polar organic solvents.[103] Previous research in our group has exploited the ability to perform Ce(IV)-mediated reactions in less polar media to develop two novel methods involving the oxidative coupling of 1,3-dicarbonyls and β-carbonyl imines to allyltrimethylsilane (Scheme 3.2).[63, 64] When reactions were performed in MeCN, allylated products were obtained, whereas reactions in CH_2Cl_2 resulted in dihydrofuran and dihydropyrrole derivatives. This solvent-dependent chemoselectivity is attributed to the solvent-assisted elimination of a β-silyl cation intermediate in more polar solvents such as MeCN leading to allylated products and inhibiting the intramolecular cyclization pathway which results in the dihydrofuran and dihydropyrrole derivatives.[63, 64]



Scheme 3.2: Solvent-dependent oxidative addition of 1,3-dicarbonyls and β-carbonyl imines to allyltrimethylsilane

The oxidative coupling of 1,3-dicarbonyls and β-carbonyl imines to allyltrimethylsilane highlights the ability of solvent to have a significant impact on the pathways of some carbon-carbon bond-forming reactions. Based on this precedent, the effect of solvent on the oxidative coupling of 1-aryl-1,3-dicarbonyl substrates to styrene was investigated. While previous research has examined similar synthetic systems, 1-aryl-1,3-dicarbonyl substrates were not used and reactions were performed only in polar solvents.[104-106] The synthetic and mechanistic details for the Ce(IV)-mediated oxidative coupling of 1-aryl-1,3-dicarbonyl compounds to styrene are presented in this chapter.

3.2 Experimental

3.2.1 Materials

MeCN and CH_2Cl_2 were purified with a Pure Solv solvent purification system from Innovative Technology, Inc. Methanol (MeOH) was dried with activated 3 Å molecular sieves and degassed with argon prior to use. All 1-aryl-1,3-dicarbonyl substrates were purchased commercially from Acros Organics, Sigma Aldrich, and Alfa Aesar and used without further purification. Styrene was purchased from Acros Organics and filtered through a plug of neutral alumina immediately before use to remove stabilizers. CAN was purchased from Alfa Aesar and used without further purification. CTAN was synthesized via established procedures.[103]

3.2.2 Instrumentation

Proton and carbon NMR were recorded on a Bruker 500 MHz spectrometer. GC-MS analyses were performed with an HP 5890 Series II Gas Chromatograph with an HP Mass Selector Detector. A Satellite FTIR from Thermo-Mattson was used to obtain IR spectra. LC-HRMS data were recorded at the Mass Spectrometry Facility at Notre Dame

University. Column chromatography was performed using the automated CombiFlash® Rf system from Teledyne Isco, Inc. Products were separated using prepacked silica gel columns with a gradient elution of either ethyl acetate:hexanes or ether:hexanes. Mechanistic rate data and time-resolved spectra were obtained using a computer-controlled stopped-flow reaction spectrophotometer from Applied Photophysics Limited. Temperature in the stopped-flow spectrophotometer was regulated using a NESLAB RTE-111.

3.2.3 Methods

3.2.3.1 General procedure for the synthesis of nitrate ester derivatives

All glassware was flame-dried before use. The 1-aryl-1,3-dicarbonyl substrate (1.0 mmol) was dissolved in 15 mL of either MeCN or CH_2Cl_2. Styrene (1.1 mmol) was added dropwise and the reaction was purged with N_2 gas. CAN or CTAN (2.1 mmol) was dissolved in 5 mL MeCN or CH_2Cl_2 respectively and added to the reaction via syringe with stirring. After stirring at room temperature for 2 hours, solvent was removed via rotary evaporation. Water was added and then the aqueous layer was extracted three times with ether. The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The nitrate ester products were purified via automated flash chromatography. Products were characterized by ^{1}H NMR, ^{13}C NMR, GC-MS, IR, and LC-HRMS.

3.2.3.2 General procedure for the synthesis of dihydrofuran derivatives

All glassware was flame-dried before use. The 1-aryl-1,3-dicarbonyl substrate (1.0 mmol) was dissolved in 15 mL of MeOH. Styrene (1.1 mmol) was added dropwise and the reaction was purged with N_2 gas. CAN (2.1 mmol) was dissolved in 5 mL MeOH

and added to the reaction via syringe with stirring. After stirring at room temperature for 2 hours, solvent was removed via rotary evaporation. Water was added and then the aqueous layer was extracted three times with ether. The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The dihydrofuran products were purified via automated flash chromatography. Products were characterized by ^{1}H NMR, ^{13}C NMR, GC-MS, IR, and LC-HRMS.

3.2.3.3 General procedure for kinetic rate studies

For the mechanistic studies, the Ce(IV) oxidants and substrates were prepared separately in the appropriate solvent in a glovebox, transported in airtight syringes, and injected into the stopped-flow spectrophotometer. The cellblock and the drive syringes of the stopped-flow spectrophotometer were flushed at least three times with dry, degassed solvent to make the system anaerobic. Rates studies were performed under pseudo-first-order conditions with the oxidant concentration kept low (1 mM) and substrate concentration kept high (20 mM). Reaction rates were monitored at 380 nm and 460 nm. Temperature in the stopped-flow spectrophotometer was maintained at 25^{o}C.

3.2.3.4 Procedure for time-resolved UV-vis study

The samples were prepared as described in procedure 3.2.3.3. The time-resolved absorption spectrum was obtained for CTAN (1 mM) and ethylbenzoylacetate (50 mM) in CH_2Cl_2 from 400-500 nm at 25^{o}C. The spectrum was obtained by taking 10 scans every 5 nm over a period of 50 msec.

3.2.3.5 Procedure for the synthesis of 2,2-dideuterio-1-phenyl-1,3-butanedione

1-Phenyl-1,3-butanedione (10.0 mmol) was added into D_2O (20 mL), potassium carbonate (14.0 mmol), and tetra-*n*-butylammonium bromide (3.0 mmol). The mixture

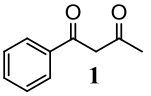
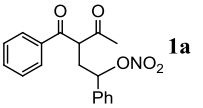
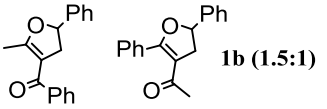
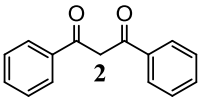
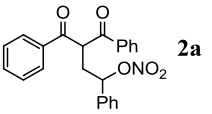
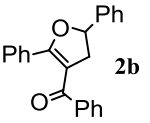
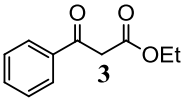
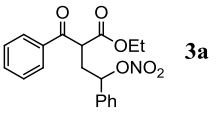
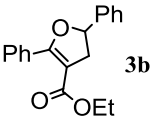
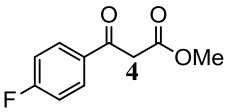
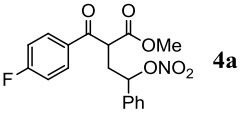
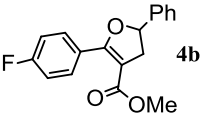
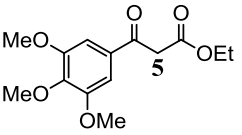
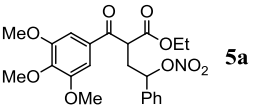
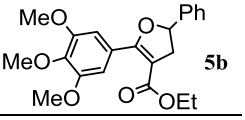
was stirred for 3 days at room temperature. The reaction mixture was filtered and extracted three times with diethyl ether. The organic layers were combined and concentrated to afford pure 2,2-dideuterio-1-phenyl-1,3-butanedione.

3.3 Results and discussion

3.3.1 Scope of reaction

In an initial study, when an equivalent of 1-phenyl-1,3-butanedione (**1**) was treated with 2 equivalents of CAN in MeCN in the presence of a slight excess of styrene, the nitrate ester derivative (**1a**) was formed as the major product with an isolated yield of 62% (Table 3.1, entry 1). Interestingly, when the same reaction was performed in MeOH with CAN, the dihydrofuran derivatives (**1b**) were produced in a combined 78% yield. To examine the scope of this solvent-dependent oxidative coupling reaction, a variety of 1-aryl-1,3-dicarbonyl compounds were examined as substrates. As shown in entries 1-3 of Table 3.1, the oxidative coupling reactions worked well for a 1-aryl-1,3-diketone (**1**), a 1,3-diaryl-1,3-diketone (**2**), and a 1-aryl-β-ketoester (**3**). For the dihydrofuran synthesis using the 1-aryl-β-ketoester, the product was obtained as a single isomer. Figure 3.1 shows the two dihydrofuran isomers that are possible for the oxidative addition of **3** to styrene. The selective formation of the dihydrofuran through cyclization with the ketone carbonyl (**3b**) as opposed to the ester (**3b'**) is presumably due to the relative stabilities of the isomers. The preferential formation of **3b** is consistent with previous oxidative additions of β-ketoesters to activated alkenes.[64, 104, 107, 108] The dihydrofuran derivatives from reactions with **4-5** were obtained as single isomers as well. Nitrate esters **1a** and **3a-**

Table 3.1: Ce(IV)-mediated oxidative coupling of 1-aryl-1,3-dicarbonyls to styrene

Entry	Substrate	Conditions[a]	Yield(%)[b]	Ratio (a:b)	Product[d]
1		A	62	78 : 22	 **1a**
		B	78	20 : 80	 **1b (1.5:1)**
2		A	50	60 : 40	 **2a**
		B	84	10 : 90	 **2b**
3		A	61	77 : 23	 **3a**
		B	78	16 : 84	 **3b**
4		A	25	33 : 67	 **4a**
		B	74	11 : 89	 **4b**
5		A	67	100 : trace	 **5a**
		B	25	70 : 30	 **5b**

[a] **Condition A:** 2 equiv CAN in MeCN, room temp., 2 hrs; **Condition B:** 2 equiv CAN in MeOH, room temp., 2 hrs

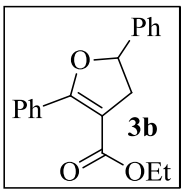
[b] Isolated yield

[c] Ratios determined by ^{1}H NMR by comparing the relative intensities of the proton signals from 5.6-6.0 ppm in the crude reaction mixture

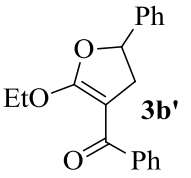
[d] Nitrate esters are mixtures of diastereomers

5a were obtained as mixtures of diastereomers. These diastereomers proved to be inseparable by column chromatography but could be distinguished by the NMR resonance of the benzylic proton.

In addition to varying the types of 1-aryl-1,3-dicarbonyl compounds used, the effect of altering the electron density of the 1-aryl ring was examined. As shown in entry 4, when an electron-withdrawing fluorine was incorporated into the ring, the major product for the reaction in MeCN was dihydrofuran **4b** instead of the expected nitrate ester **4a**. Similarly, when the ring was activated by the addition of three methoxy substituents, the selectivity shifted significantly towards the formation of nitrate ester **5a** in MeOH, producing **5b** in only a 25% yield. In addition, when the reaction was performed in MeCN, analysis of the crude reaction mixture by ^{1}H NMR showed only trace amounts of dihydrofuran **5b**. These results suggested a strong electronic effect with electron rich aryl rings favoring nitrate ester formation and electron poor aryl rings favoring the production of dihydrofurans.



Cyclization with ketone



Cyclization with ester

Figure 3.1: Possible dihydrofuran isomers from the oxidative addition of **3** to styrene

The experiments described demonstrate that both the solvent polarity and the electron density of the 1-aryl ring play a role in product distribution. Based on this observation, could the chemoselectivity be controlled further by the use of an even less polar solvent? To examine this hypothesis, the oxidative additions of substrates **1-4** to styrene were performed in CH_2Cl_2 using CTAN as the oxidant (Table 3.2). For all four

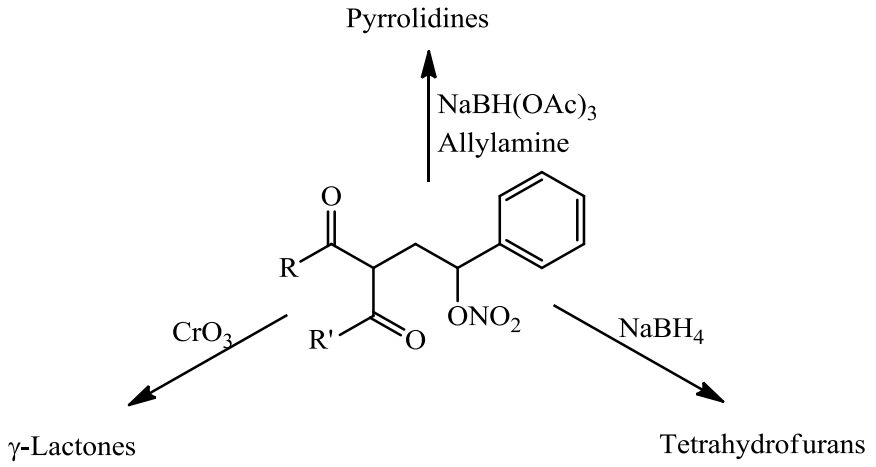
substrates, the selective formation of nitrate ester derivatives **1a-4a** was improved when the reactions were performed in CH_2Cl_2 with CTAN when compared to MeCN and CAN. Whereas substrate **4** favored dihydrofuran formation in MeCN, the reaction in CH_2Cl_2 produced the desired nitrate ester **4a** as the major product in 51% yield.

Table 3.2: Selective synthesis of nitrate ester derivatives in CH_2Cl_2[a]

Entry	Substrate	Product	Ratio (a:b)[b]	Yield (%)[c]
1	1	1a	88 : 12	66
2	2	2a	85 : 15	66
3	3	3a	82 : 18	66
4	4	4a	66 : 34	51

[a] 2 equiv CTAN in CH_2Cl_2, room temp., 2 hrs
[b] Ratios determined by ^1H NMR by comparing the relative intensities of the proton signals from 5.6-6.0 ppm in the crude reaction mixture
[c] Isolated yield

With a simple procedure and mild reaction conditions, the oxidative addition of 1-aryl-1,3-dicarbonyls to styrene provides an efficient approach to substituted nitrate esters and dihydrofurans selectively in moderate to very good yields. Scheme 3.3 illustrates the recent work by MacMillan *et al.* that highlights the accessibility of various cyclic products through benzylic nitrate esters with pendent carbonyls.[109] Additionally, the ability to produce dihydrofuran derivatives is synthetically useful[110, 111] because dihydrofuran



Scheme 3.3: Synthetic utility of benzylic nitrate esters

moieties are present in the backbone of natural products such as garcinielliptones K (**A**) (Figure 3.2).[112] Both Fristad[113] and Brun[114, 115] have demonstrated that 2,3-dihydrofurans can be efficiently converted to α-tetralones with $SnCl_4$. The synthesis of α-tetralones is of interest since they are important precursors to other natural products such as (+)-phyltetralin (**B**) and podophyllotoxin (**C**).[114]

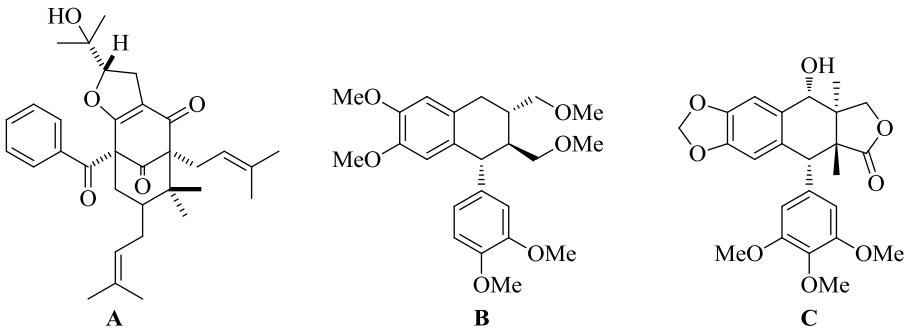


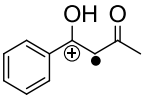
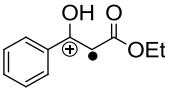
Figure 3.2: Structures of the natural products garcinielliptones K (**A**), (+)-phyltetralin (**B**), and podophyllotoxin (**C**)

3.3.2 Mechanistic studies

With the synthetic studies completed, a thorough mechanistic analysis was performed to fully elucidate the solvent-dependent chemoselectivity of the oxidative addition of 1-aryl-1,3-dicarbonyls to styrene. Preliminary studies focused on the initial oxidation of 1,3-diketone **1** and β-ketoester **3** in the absence of styrene to determine the impact of solvent on the mechanism of oxidation and the stability of the radical cation intermediates. Observed rate constants (k_{obs}) for the oxidation of substrates **1** and **3** were obtained in all three solvents using either CAN or CTAN (k_1 values, Table 3.3). These rate data were obtained by monitoring the decay of the Ce(IV) absorbance at 380 nm using stopped-flow spectrophotometry. While the λ_{max} of Ce(IV) is at 330 nm, the decay of Ce(IV) was monitored at 380 nm because the absorbance of the substrates overlapped at 330 nm. To assess the impact of solvent, rate studies were performed under pseudo-first-order conditions keeping the substrate in excess with respect to the oxidant. Based

on previous studies involving 1,3-dicarbonyls, the first step of the reaction was postulated to be the oxidation of the enol tautomer of the 1-aryl-1,3-dicarbonyl species by Ce(IV) generating a radical cation.[88, 116] This supposition is supported by the fact that many radical cations absorb in the range of 400 to 500 nm.[117-120] To obtain more insight into

Table 3.3: Rate data for the Ce(IV)-mediated oxidation of 1-phenyl-1,3-butanedione (**1**) and ethyl benzoylacetate (**3**) in the absence of styrene [a]

Substrate	Intermediate	Oxidant	Solvent	Rate constant of Ce(IV) decay at 380 nm k_1 (sec^{-1})[b]	Rate constant of radical cation formation at 460 nm k_2 (sec^{-1})[b]	Rate constant of radical cation decay at 460 nm k_3 (sec^{-1})[b]
1		CAN	MeOH	$5.8 \pm 0.6 \times 10^{2}$	$6.0 \pm 0.2 \times 10^{2}$	$4.1 \pm 0.1 \times 10^{-2}$
			MeCN	8.3 ± 0.2	8.7 ± 0.1	$5.8 \pm 0.2 \times 10^{-3}$
		CTAN	MeCN	6.0 ± 0.3	6.2 ± 0.1	$5.1 \pm 0.5 \times 10^{-3}$
			CH_2Cl_2	3.4 ± 0.3	3.4 ± 0.1	$1.7 \pm 0.1 \times 10^{-3}$
3		CAN	MeOH	$3.5 \pm 0.3 \times 10^{2}$	$3.7 \pm 0.2 \times 10^{2}$	$3.2 \pm 0.1 \times 10^{-1}$
			MeCN	6.2 ± 0.1	6.3 ± 0.1	$9.0 \pm 0.3 \times 10^{-2}$
		CTAN	MeCN	3.8 ± 0.4	3.9 ± 0.1	$8.8 \pm 0.2 \times 10^{-2}$
			CH_2Cl_2	1.4 ± 0.1	1.6 ± 0.1	$1.5 \pm 0.1 \times 10^{-2}$

[a] [Ce(IV)] = 1 mM, [substrate] = 20 mM at 25°C
[b] Average of at least two runs

this process, a time-resolved absorption spectrum was obtained for the oxidation of **3** by CTAN. As shown in the inset of Figure 3.3, a clear isosbestic point was observed at 420 nm. Since the 1-aryl-1,3-dicarbonyl substrates, Ce(IV), and Ce(III) do not absorb above 400 nm, the absorption observed at 460 nm was attributed to a radical cation intermediate. The observed rates of growth of the absorption at 460 nm for substrates **1** and **3** were recorded in each solvent and are included in Table 3.3. The growth of the radical cation absorption (k_2) was equal to the decay of Ce(IV) at 380 nm (k_1) within experimental error. This finding is consistent with earlier studies on the Ce(IV)-mediated oxidation of 1-alkyl-1,3-diketones.[88] In addition, since both CAN and CTAN are soluble in MeCN, the

rate data illustrate that only a modest decrease in reactivity occurs due to the bulky tetra-*n*-butylammonium counterions of CTAN.

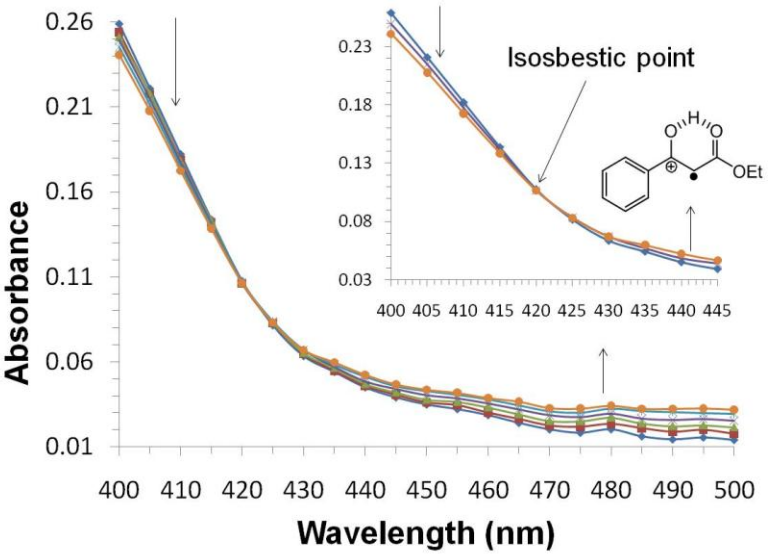


Figure 3.3: Time-resolved absorption spectra observed from CTAN and ethyl benzoylacetate (**3**) in CH_2Cl_2 ([**3**] = 50 mM, [CTAN] = 1 mM) from 400-500 nm at 25°C. Spectra were obtained by taking 10 scans every 5 nm over a period of 50 msec.

The rate data obtained indicated a clear trend based on the polarity of the solvent. The rate of decay of Ce(IV) increased with solvent polarity, being fastest in MeOH and slowest in CH_2Cl_2. Furthermore, the rates of oxidation of 1,3-diketone **1** and β-ketoester **3** are roughly 2 orders of magnitude faster in MeOH than in MeCN. The impact of solvent polarity and the relative rate differences among the solvents examined are consistent with earlier studies on 1-alkyl-1,3-diketones and related silyl enol ethers.[88] While both substrates exhibited the same trend in solvent polarity (MeOH > MeCN > CH_2Cl_2), the 1,3-diketone (**1**) was oxidized faster than the β-ketoester (**3**) in all three solvents. Previous research has shown that, in general, 1,3-diketones have more enol content than their related β-ketoesters.[121] Since the first step of the reaction involves the oxidation of the enol tautomer, the enol contents of **1** and **3** should impact their rates of oxidation. Rates of oxidation of **1** when compared to **3** were roughly 1.5 times faster in

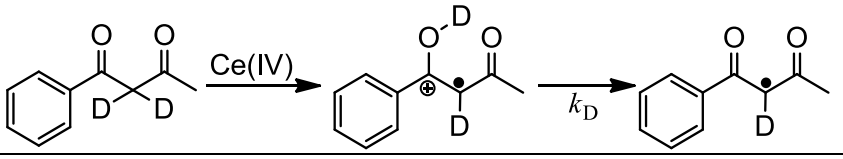
MeCN and MeOH, and 2.5 times faster in CH_2Cl_2. These findings are consistent with enhanced enol content for 1,3-dicarbonyls in less polar, aprotic solvents.[92]

Next, the impact of solvent on the lifetime of the radical cation intermediate was examined by monitoring its decay at 460 nm. Examination of the observed rate constants of radical cation decay (k_3) contained in Table 3.3 showed a clear dependence on solvent polarity in the order of MeOH > MeCN > CH_2Cl_2. The k_3 value is 4-7 times greater in MeOH than in MeCN, whereas k_3 is 3-6 times greater in MeCN than in CH_2Cl_2. While the general trend for the stability of radical cations in the solvents examined is the same as in previous studies of 1,3-diketones and β-silyl enol ethers, the difference in the rates of radical cation decay of **1** and **3** among the solvents screened is reduced.[88] Previous studies on radical cations derived from 1-alkyl-1,3-diketones showed a large difference among the solvents with decays in MeOH on the order of 15 to 100 times faster than in MeCN.[88] It is likely that the presence of the 1-phenyl group stabilizes the radical cation intermediate thereby tempering the impact of solvent.

To further probe the role of solvent, 2,2-dideuterio-1-phenyl-1,3-butanedione was prepared and the rate of decay of its radical cation was measured in all three solvents under conditions identical to those previously described. The data are displayed in Table 3.4. The k_H/k_D values for both MeCN and CH_2Cl_2 were greater than 2 (entries 2-3, Table 3.4), a finding consistent with studies reported by Schmittel for the deprotonation of the anisyldimesitylethenol radical cation.[122] The lower k_H/k_D value in MeOH of 1.5 (entry 1, Table 3.4) is likely due to deuterium exchange in the substrate and with bulk solvent. The deuterium-labelled studies indicate that, in the absence of styrene, the decay of the radical cation is due to deprotonation, resulting in a radical species. Both the observation that the

radical cations of 1-aryl-1,3-diketones and 1-aryl-β-ketoesters decay faster in more polar solvents and the results from the deuterium isotope study agree with the known solvent-assisted mechanism of O-H bond cleavage[123, 124] and are consistent with previous mechanistic studies on the role of solvent in the decay of radical cations derived from 1-alkyl-1,3-diketones.[88]

Table 3.4: Observed rate constants for the decay of the radical cation of 2,2-dideuterio-1-phenyl-1,3-butanedione in MeOH, MeCN, and CH_2Cl_2 in the absence of styrene[a]



Entry	Oxidant / Solvent	k_D (sec^{-1})[b]	k_H/k_D
1	CAN / MeOH	$2.7 \pm 0.1 \times 10^{-2}$	1.5 ± 0.1
2	CAN / MeCN	$2.7 \pm 0.1 \times 10^{-3}$	2.2 ± 0.1
3	CTAN / CH_2Cl_2	$7.3 \pm 0.1 \times 10^{-4}$	2.4 ± 0.1

[a] [Ce(IV)] = 1 mM, [substrate] = 20 mM at 25°C
[b] Average of at least two runs

The mechanistic studies described to this point support solvent playing an important role in the oxidation of the substrates and in the stability of the initial radical cation intermediates with the decay of the radical cation resulting from deprotonation in the absence of styrene. Next, a series of experiments was performed to determine the mechanistic role of styrene in the coupling reactions. In these studies, the decay of the radical cation of 1-phenyl-1,3-butanedione (**1**) was monitored in the presence of increasing concentrations of styrene in all three solvents under pseudo-first-order conditions with respect to the oxidant. The data from these experiments are contained in Table 3.5. These experiments clearly showed that the rate order of styrene was 1 in MeCN and CH_2Cl_2 whereas it was significantly less than unity (0.28) in MeOH. These

results indicated that reaction of the radical cation with styrene was the rate-limiting step of the reaction in MeCN and CH_2Cl_2. Previous results from our group have shown that radical cations derived from 1,3-diketones and related silyl enol ethers are deprotonated/desilylated by MeOH through a solvent-assisted process, whereas in CH_2Cl_2 and MeCN the radical cation intermediates are converted to radical species through a unimolecular mechanism.[88] Additionally, previous kinetic studies by our group have shown that MeOH is first order for the decay of radical cations generated from 1,3-dicarbonyls in CH_2Cl_2.[88] Based on these findings, the fractional rate order of styrene in MeOH was interpreted as being consistent with deprotonation of the radical cation by solvent occurring prior to the addition to styrene.

Table 3.5: Rate order of styrene for decay of radical cation at 460 nm[a]

Entry	Oxidant	Solvent	Styrene Rate Order[b,c]
1	CAN	MeOH	0.28 ± 0.01
2	CAN	MeCN	0.97 ± 0.05
3	CTAN	CH_2Cl_2	1.02 ± 0.06

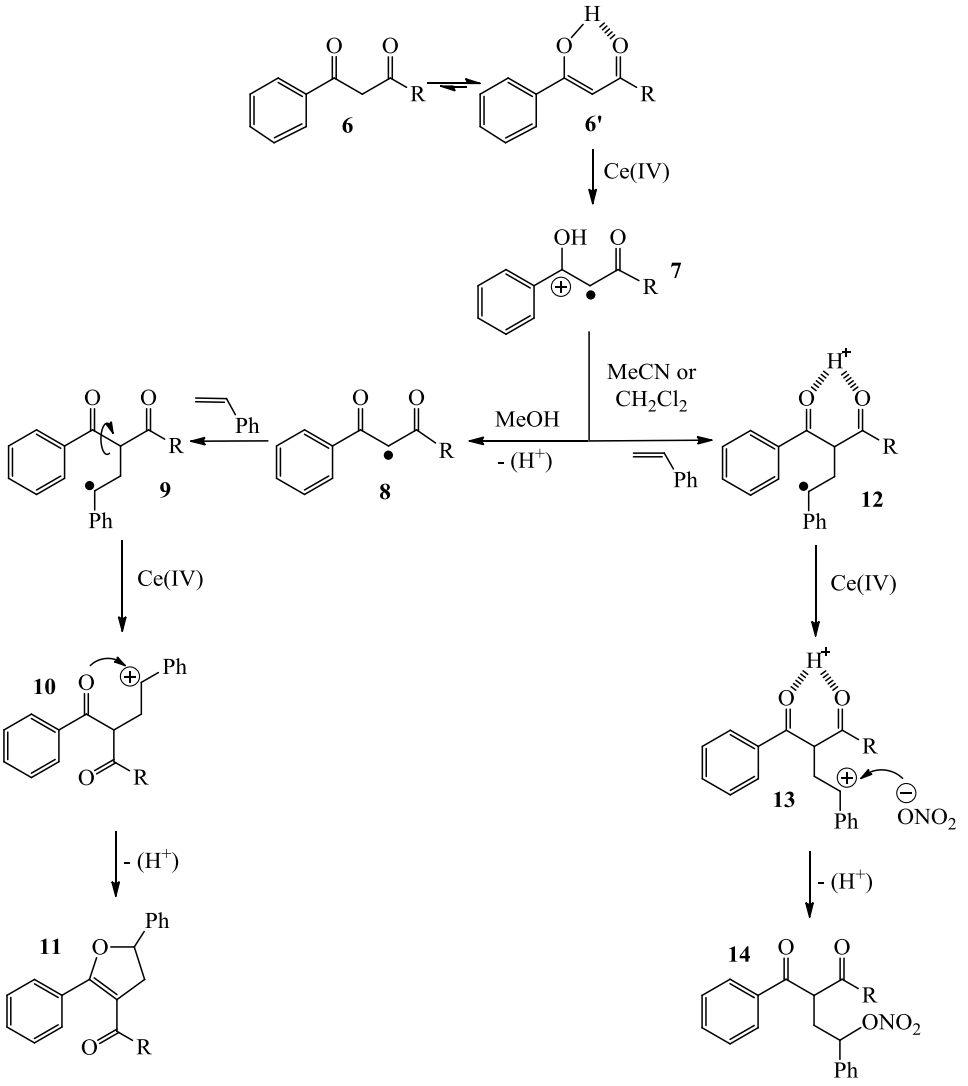
[a] Substrate = 1-phenyl-1,3-butanedione (**1**)
[b] Average of at least 2 runs
[c] Determined from the slope for the plot of lnk_{obs} vs. ln[styrene]

Taken together, these studies reveal several key details about the mechanism of the Ce(IV)-mediated oxidative coupling of 1-aryl-1,3-dicarbonyls to styrene. First, in the absence of styrene the rates of oxidation of substrates by Ce(IV), the rates of radical cation formation, and the rates of decay of the radical cations were solvent-dependent (MeOH > MeCN > CH_2Cl_2). Second, primary kinetic isotope effects were observed in all three solvents in the absence of styrene for the decay of the radical cation. Third, styrene was first order in both MeCN and CH_2Cl_2 for decay of the radical cation. Finally, a fractional rate order of styrene for the decay of the radical cation in MeOH indicated

solvent-assisted deprotonation of the radical cation to a radical species prior to the addition to styrene.

From the experimental results and points described in this chapter, the mechanism provided in Scheme 3.4 is proposed to explain the solvent-dependent chemoselectivity of the oxidative coupling of 1-aryl-1,3-dicarbonyls to styrene. Initial oxidation of the enol tautomer (**6'**) by Ce(IV) produces radical cation **7**. In MeOH, solvent-assisted deprotonation of the radical cation yields radical intermediate **8**. After the addition to styrene to form **9**, rotation around one of the carbonyl-CH bonds and another single electron oxidation by Ce(IV) produces cation **10**. Intramolecular cyclization and deprotonation of **10** result in the formation of dihydrofuran derivative **11**. Conversely, in less polar solvents such as MeCN and CH_2Cl_2, radical cation **7** adds directly to styrene producing intermediate **12**. This intermediate has restricted rotation since the enolic proton is shared by the two carbonyl groups. Oxidation to cation **13** followed by internal ligand transfer of a nitrate from cerium yields nitrate ester **14**. Observations from reactions involving substrates **4** and **5** indicate an electronic effect consistent with the proposed mechanism. Electron-donating groups on the aryl ring stabilize radical cation **7**. This enhanced stability assists in direct radical cation addition to styrene prior to deprotonation. Conversely, electron-withdrawing groups on the aryl ring destabilize radical cation **7** and, as a result, deprotonation to radical **8** becomes the favored pathway.

The key feature of the mechanism presented in Scheme 3.4 is that direct addition of the radical cation to styrene before deprotonation provides a conformationally restricted intermediate (12) that inhibits the intramolecular C-O bond formation that produces dihydrofurans. Based on this hypothesis, addition of a cosolvent to a reaction performed



Scheme 3.4: Proposed mechanism for the solvent-dependent oxidative addition of 1-aryl-1,3-dicarbonyls to styrene

in CH_2Cl_2 (or MeCN), which is capable of abstracting the enolic proton, should release this conformational restriction and lead to the formation of the dihydrofuran derivative as the major product. To test this supposition, the oxidative addition of substrate 2 to styrene employing CTAN as the oxidant was conducted in CH_2Cl_2 containing 5 equivalents of MeOH. Dihydrofuran 2b was obtained in an 80% yield.

3.4 Conclusions

A solvent-dependent chemoselective method for the Ce(IV)-mediated oxidative coupling of 1-aryl-1,3-dicarbonyls to styrene producing substituted dihydrofuran and nitrate ester derivatives has been developed. Reactions performed in MeOH yielded predominantly dihydrofuran derivatives whereas reactions in MeCN or CH_2Cl_2 favored the formation of nitrate esters. The reaction is general, working for a variety of 1-aryl-1,3-dicarbonyls and generating the desired products in good to very good yields. The reaction conditions are straightforward with short reaction times at room temperature. Both dihydrofurans and nitrate esters are useful intermediates in the synthesis of more complex, biologically active compounds. A thorough mechanistic analysis of the reaction system was consistent with the rate of solvent-assisted deprotonation of an initial radical cation intermediate playing an integral role in the selective formation of products. To the best of our knowledge, this approach is the first reported in which the reaction pathway is controlled by the lifetime of a radical cation intermediate. The work presented in this chapter was published in a special issue of *Tetrahedron* on single electron transfer reactions.[125, 126]

3.5 Synthesis and spectral data for products

3.5.1 Nitrate ester derivatives

3-Benzoyl-4-oxo-1-phenylpentyl-1-nitrate (**1a**): mixture of diastereomers

Procedure 3.2.3.1 was followed. Light yellow oil. ^{1}H NMR ($CDCl_3$, 500MHz) – δ 7.96-7.88 (m, 4H), 7.67-7.61 (m, 2H), 7.55-7.47 (m, 4H), 7.44-7.30 (m, 8H), 5.83 (t, 1H, J = 7.2 Hz), 5.75 (dd, 1H, J = 2.3 Hz, 6.0 Hz), 4.61-4.56 (m, 2H), 2.58-2.52 (m, 4H), 2.17-2.13 (s, 6H). ^{13}C NMR ($CDCl_3$, 125MHz) – δ 202.2, 195.4, 137.2, 134.3, 134.2,

129.3, 129.1, 129.0, 128.8, 128.7, 126.3, 83.2, 82.8, 58.7, 58.4, 33.4, 33.3, 28.8, 28.5. MS [*m*/*z* (rel int)] 264 (M^+, 1), 221 (65), 203 (18), 173 (15), 105 (98), 77 (90), 51 (30). IR (KBr) ν (cm^{-1}) 3508, 3448, 3062, 3035, 2962, 2930, 1720, 1635, 1555, 1447, 1358, 1274, 1071, 964, 855, 758, 698. LC-HRMS calcd. for $C_{18}H_{17}NNaO_5$ [M+Na] 350.0999, found 350.1006; calc. for $C_{18}H_{17}O_2$ [M-ONO_2] 265.1223, found 265.1225.

3-Benzoyl-4-oxo-1,4-diphenylbutyl-1-nitrate (**2a**)

Procedure 3.2.3.1 was followed. Yellow oil. ^{1}H NMR ($CDCl_3$, 500MHz) – δ 7.97-7.92 (m, 2H), 7.87-7.83 (m, 2H), 7.64-7.56 (m, 2H), 7.52-7.42 (m, 4H), 7.41-7.38 (m, 4H), 5.92 (dd, 1H, *J* = 3.7 Hz, 5.2 Hz), 5.38 (dd, 1H, *J* = 2.2 Hz, 5.5 Hz), 2.72-2.59 (m, 2H). ^{13}C NMR ($CDCl_3$, 125MHz) – δ 195.0, 194.9, 137.4, 135.4, 135.2, 134.0, 129.3, 129.1, 129.0 (2), 128.6, 128.5, 126.2, 83.3, 52.4, 33.9. MS [*m*/*z* (rel int)] 326 (M^+, 1), 239 (67), 222 (7), 161 (9), 105 (100), 77 (58), 51 (11). IR (KBr) ν (cm^{-1}) 3701, 3619, 3063, 2934, 1693, 1637, 1600, 1569, 1449, 1270, 1189, 1104, 995, 853, 853, 699. LC-HRMS calcd. for $C_{23}H_{20}NO_5$ [M+H] 390.1336, found 390.1324; calc. for $C_{23}H_{19}NNaO_5$ [M+Na] 412.1155, found 412.1143; $C_{23}H_{19}O_2$ [M-ONO_2] 327.1380, found 327.1391.

Ethyl 3-benzoyl-1-phenylbutan-4-oate-1-nitrate (3**a**): mixture of diastereomers

Procedure 3.2.3.1 was followed. Light yellow oil. ^{1}H NMR ($CDCl_3$, 500MHz) – δ 7.98-7.91 (m, 4H), 7.50-7.33 (m, 15H), 5.93 (dd, 1H, *J* = 3.2 Hz, 5.6 Hz), 5.83 (dd, 1H, *J* = 2.8 hz, 5.8 Hz), 4.50-4.42 (m, 2H), 4.20-4.12 (m, 4H), 2.66-2.54 (m, 4H), 1.21-1.15 (m, 6H). ^{13}C NMR ($CDCl_3$, 125MHz) – δ 193.9, 193.8, 168.9 (2), 137.2, 137.1, 135.6, 135.5, 134.0, 133.8, 129.2 (2), 129.0 (2), 128.9 (2), 128.8, 128.7, 128.6, 126.4, 126.3, 83.0 (2), 61.9 (2), 50.3, 50.2, 33.5, 13.9. MS [*m*/*z* (rel int)] 294 (M^+, 1), 238 (33), 133 (35), 105 (100), 77 (60), 51 (20). IR (KBr) ν (cm^{-1}) 3457, 3357, 3063, 3035, 2983, 2904, 1736,

1688, 1636, 1450, 1274, 1196, 1095, 1021, 855, 755, 696, 592. LC-HRMS calcd. for $C_{19}H_{20}NO_6$ [M+H] 358.1285, found 358.1288; calc. for $C_{19}H_{19}NNaO_6$ [M+Na] 380.1105, found 380.1099; $C_{19}H_{19}O_3$ [M-ONO_2] 295.1329, found 295.1346.

Methyl 3-(4-fluorobenzoyl)-1-phenylbutan-4-oate-1-nitrate(**4a**): mixture of diastereomers

Procedure 3.2.3.1 was followed. Colorless oil. ^{1}H NMR ($CDCl_3$, 500MHz) – δ 8.00-7.94 (m, 4H), 7.43-7.32 (m, 8H), 7.19-7.13 (m, 4H), 5.91 (dd, 1H, J = 3.6 Hz, 5.4 Hz), 5.81 (dd, 1H, J = 3.2 Hz, 5.6 Hz), 4.47-4.41 (m, 2H), 3.72-3.69 (s, 6H). ^{13}C NMR ($CDCl_3$, 125MHz) – δ 192.1 (2), 169.2, 167.2, 165.2 (2), 137.1, 137.0, 131.5, 131.5 (2), 131.4, 129.3 (2), 129.0 (2), 126.3 (2), 116.2, 116.0, 82.9 (2), 53.0, 50.0, 49.8, 33.6, 33.5. MS [*m*/*z* (rel int)] 384 (M^+, 10), 281 (11), 257 (13), 207 (100), 195 (92), 115 (19), 105 (27), 77 (16). IR (KBr) ν (cm^{-1}) 3472, 3361, 3069, 3033, 2955, 2902, 1741, 1687, 1638, 1600, 1506, 1442, 1273, 1240, 1161, 1097, 1009, 852, 744, 700. LC-HRMS calcd. for $C_{18}H_{17}FNO_6$ [M+H] 362.1034, found 362.1034; calc. for $C_{18}H_{16}FNNaO_6$ [M+Na] 384.0854, found 384.0843; $C_{18}H_{16}FO_3$ [M-ONO_2] 299.1078, found 299.1092.

Ethyl 3-(3,4,5-trimethoxybenzoyl)-1-phenylbutan-4-oate-1-nitrate (**5a**): mixture of diastereomers

Procedure 3.2.3.1 was followed. Colorless oil. ^{1}H NMR ($CDCl_3$, 500MHz) – δ 7.41-7.34 (m, 8H), 7.25, 7.20 (m, 4H), 5.89, (dd, 1H, J = 5.0 Hz, 4.8 Hz), 5.84 (dd, 1H, J = 2.3 Hz, 6.0 Hz), 4.46 (dd, 1H, J = 3.9 Hz, 5.0 Hz) 4.41 (t, 1H, J = 7.1 Hz), 4.24-4.15 (m, 4H), 3.96-3.88 (m, 18H), 2.64-2.49 (m, 4H), 1.26-1.19 (m, 6H). ^{13}C NMR ($CDCl_3$, 125MHz) – δ 192.6 (2), 169.0 (2), 153.2 (2), 137.3, 137.2, 130.7, 130.6, 129.3, 129.2, 129.0 (2), 126.3, 126.2, 106.2, 106.1, 83.2, 83.1, 62.0, 61.0, 56.3 (2), 50.3, 50.2, 33.8, 14.0 (2). MS [*m*/*z* (rel int)] 298 (M^+, 8), 265 (6), 170 (16), 123 (100), 95 (25). IR (KBr) ν

(cm^{-1}) 3644, 3553, 3337, 2978, 2944, 2839, 2255, 1734, 1681, 1636, 1584, 1502, 1456, 1416, 1332, 1272, 1237, 1125, 1004, 914, 854, 735, 704. LC-HRMS calcd. for $C_{22}H_{26}NO_9$ [M+H] 448.1602, found 448.1596; $C_{22}H_{25}O_6$ [M-ONO_2] 385.1646, found 385.1648.

3.5.2 Dihydrofuran derivatives

3-Benzoyl-4,5-dihydro-2-methyl-5-phenyl-furan (**1b**): major isomer

Procedure 3.2.3.2 was followed. Yellow oil. ^{1}H NMR ($CDCl_3$, 500MHz) – δ 7.62-7.58 (m, 2H), 7.51-7.34 (m, 8H), 5.66 (dd, 1H, *J* = 1.1 Hz, 9.0 Hz), 3.51 (ddd, 1H, *J* = 1.4 Hz, 4.1 Hz, 10.5 Hz), 3.17 (ddd, 1H, *J* = 1.4 Hz, 5.9 Hz, 8.8 Hz), 1.95 (br. t, 3H, *J* = 1.4 Hz). ^{13}C NMR ($CDCl_3$, 125MHz) – δ 168.5, 141.0, 131.1, 128.7, 128.3, 127.8, 125.8, 83.4, 39.5, 15.5. MS [*m*/*z* (rel int)] 264 (M^+, 36), 221 (15), 203 (8), 171 (9), 105 (94), 91 (17), 77 (100), 51 (35). IR (KBr) ν (cm^{-1}) 3448, 3417, 3385, 3355, 3060, 3033, 2927, 1714, 1639, 1563, 1448, 1352, 1274, 1225, 970, 895, 852, 700. LC-HRMS calcd. for $C_{18}H_{17}O_2$ [M+H] 265.1223, found 265.1223.

3-Benzoyl-4,5-dihydro-2,5-diphenyl-furan (**2b**)

Procedure 3.2.3.2 was followed. Colorless oil. ^{1}H NMR ($CDCl_3$, 500MHz) – δ 7.51-7.18 (m, 11H), 7.13-7.06 (m, 4H), 5.85 (t, 1H, *J* = 9.8 Hz), 3.72 (dd, 1H, *J* = 4.8 Hz, 10.3 Hz), 3.40 (dd, 1H, *J* = 6.2 Hz, 8.9Hz). ^{13}C NMR ($CDCl_3$, 125MHz) – δ 193.4, 165.4, 141.1, 139.0, 131.2, 130.1, 129.5, 128.9, 128.8, 128.3, 127.7 (2), 125.9, 111.8, 83.2, 41.2. MS [*m*/*z* (rel int)] 326 (M^+, 10), 223 (13), 134 (51), 121 (100), 105 (70), 91 (15), 77 (80), 51 (16). IR (KBr) ν (cm^{-1}) 3698, 3598, 3057, 2955, 2866, 1601, 1491, 1447, 1354, 1231, 1112, 1016, 918, 879, 695. LC-HRMS calcd. for $C_{23}H_{19}O_2$ [M+H] 327.1380, found 327.1389.

Ethyl-4,5-dihydro-2,5-diphenyl-3-furancarboxylate (**3b**)

Procedure 3.2.3.2 was followed. Light yellow oil. ^{1}H NMR ($CDCl_3$, 500MHz) – δ 7.88-7.85 (m, 2H), 7.46-7.33 (m, 8H), 5.73 (dd, 1H, J = 2.1 Hz, 8.7 Hz), 4.18-4.12 (m, 2H), 3.58 (dd, 1H, J = 4.5 Hz, 10.8 Hz), 3.16 (dd, 1H, 6.6 Hz, 8.6 Hz), 1.21 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 125MHz) – δ 198.9, 165.2, 164.8, 141.7, 130.4, 129.4, 128.7, 128.1, 127.6, 125.7, 102.1, 82.5, 59.8, 39.9, 14.2. MS [*m*/*z* (rel int)] 294 (M^+, 13), 247 (26), 220 (4), 115 (25), 105 (100), 77 (43). IR (KBr) ν (cm^{-1}) 3658, 3514, 3061, 3033, 2979, 1693, 1628, 1493, 1452, 1373, 1334, 1241, 1156, 1082, 1029, 928, 828, 758, 694. LC-HRMS calcd. for $C_{19}H_{19}O_3$ [M+H] 295.1329, found 295.1349.

Methyl-4,5-dihydro-2-(4-fluoro-phenyl)-5-phenyl-3-furancarboxylate (**4b**)

Procedure 3.2.3.2 was followed. Colorless oil. ^{1}H NMR ($CDCl_3$, 500MHz) – δ 7.97-7.91 (m, 2H), 7.44-7.38 (m, 4H), 7.38-7.32 (m, 1H), 7.13-7.06 (m, 2H), 5.73 (dd, 1H, J = 2.2 Hz, 8.6 Hz), 3.70 (s, 3H), 3.58 (dd, 1H, J = 4.6 Hz, 10.8 Hz), 3.16 (dd, 1H, J = 6.7 Hz, 8.6 Hz). ^{13}C NMR ($CDCl_3$, 125MHz) – δ 165.5, 164.9, 163.9, 162.9, 141.4, 131.7, 131.6, 128.8, 128.2, 125.7, 114.9, 114.7, 101.6, 82.5, 51.1, 39.8. MS [*m*/*z* (rel int)] 384 (M^+, 6), 370 (13), 281 (12), 207 (96), 195 (100), 105 (42), 77 (39). IR (KBr) ν (cm^{-1}) 3067, 3031, 2949, 2871, 1701, 1621, 1507, 1442, 1341, 1240, 1156, 1085, 913, 841, 759, 700. LC-HRMS calcd. for $C_{18}H_{16}FO_3$ [M+H] 299.1078, found 299.1097.

Ethyl-4,5-dihydro-5-phenyl-2-(3,4,5-trimethoxy-phenyl)-3-furancarboxylate (**5b**)

Procedure 3.2.3.2 was followed. Colorless oil. ^{1}H NMR ($CDCl_3$, 500MHz) – δ 7.44-7.33 (m, 5H), 7.33-7.30 (s, 2H), 5.71 (dd, 1H, J = 1.8 Hz, 8.9 Hz), 4.20-4.13 (m, 2H), 3.90 (s, 9H), 3.58 (dd, 1H, J = 4.5 Hz, 10.8 Hz), 3.16 (dd, 1H, J = 6.6 Hz, 8.8 Hz), 1.25 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 125MHz) – δ 165.2, 156.0, 152.4, 141.6,

128.7, 128.2, 125.7, 124.8, 107.1, 101.8, 82.3, 60.9, 59.8, 56.2, 40.4, 14.4. MS [*m*/*z* (rel int)] 298 (M^+, 1), 105 (100), 77 (60), 51 (25). IR (KBr) ν (cm^{-1}) 3632, 3502, 2944, 2839, 1692, 1635, 1583, 1501, 1459, 1417, 1348, 1293, 1241, 1125, 1094, 1007, 914, 851, 734. LC-HRMS calcd. for $C_{22}H_{25}O_6$ [M+H] 385.1646, found 385.1651.

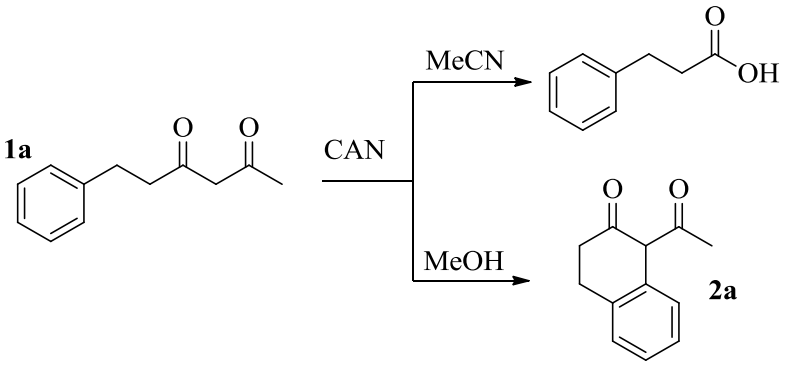
Chapter 4: CAN-mediated intramolecular cyclizations of δ-aryl-β-dicarbonyls

4.1 Background and significance

Cerium(IV) ammonium nitrate (CAN) is a versatile, inexpensive and nontoxic reagent used in organic syntheses for performing single electron oxidations.[48-53] Though traditionally restricted to aqueous and polar organic solvents, the solubility of CAN in less polar organic solvents such as CH_2Cl_2 can be significantly enhanced through the replacement of the ammonium counterions with more lipophilic tetra-*n*-butylammoniums (CTAN).[103] As discussed in Chapter 1, numerous carbon-carbon and carbon-heteroatom bond forming events are initiated by Ce(IV)-based reagents. In particular, organic transformations involving the single electron oxidation of enolizable carbonyl and 1,3-dicarbonyl substrates have received considerable interest.[107, 108, 127-131]

Recent research from our group reported the oxidative coupling of 1,3-dicarbonyls to radicophiles such as allyltrimethylsilane and styrene.[63, 64, 126] In addition to efficiently constructing carbon-carbon bonds, these reactions exhibited solvent-dependent chemoselectivities. As discussed in Chapter 3 of this dissertation, the oxidative coupling of 1-aryl-1,3-dicarbonyls to styrene generated discrete products depending on the solvent. Reactions performed in methanol (MeOH) yielded dihydrofuran derivatives as the major products whereas reactions in acetonitrile (MeCN) and methylene chloride (CH_2Cl_2) produced benzylic nitrate esters predominantly. A thorough mechanistic analysis of the reaction system was consistent with the rate of solvent-assisted deprotonation of an initial radical cation intermediate playing an integral role in the selective formation of products.[126]

We have shown previously that when 6-phenyl-2,4-hexanedione (**1a**) is oxidized by CAN in MeCN in the absence of a radicophile, 3-phenylpropionic acid is obtained exclusively over the cyclized β-tetralone product (Scheme 4.1).[132] Using this approach, a variety of 1,3-dicarbonyls can be converted under mild conditions to carboxylic acids in moderate to excellent yields.[132] Interestingly, others have shown that the formation of β-tetralones is possible through single electron oxidations of δ-aryl-β-dicarbonyls.[133, 134] Research in this area focused predominantly on the oxidation of β-ketoesters or used Mn(III)-based oxidants.[133, 134] Under the conditions of the reactions, secondary oxidations of the β-tetralones at the benzylic position also occurred.[133, 134] In a previous mechanistic study by our group on the Ce(IV)-mediated oxidation of 1,3-diketones, it was shown that β-tetralone product **2a** was obtained as the major product when **1a** was oxidized by CAN in MeOH (Scheme 4.1).[88] More importantly, when only a slight excess of CAN was employed, the β-tetralone was obtained cleanly without any secondary oxidations occurring at the benzylic positions. Based on this observation, the single electron oxidations of a variety of δ-aryl-β-dicarbonyl substrates with CAN in MeOH were performed, the results of which are presented in this chapter.



Scheme 4.1: Oxidative conversion of 1,3-dicarbonyls to carboxylic acids with CAN

4.2 Experimental

4.2.1 Materials

Methanol (MeOH) was degassed with argon and dried with activated 3Å molecular sieves prior to use. THF was purified with a Pure Solv solvent purification system from Innovative Technology, Inc. CAN was purchased from Alfa Aesar and used without further purification. The organohalides, 2,4-pentanedione, and methyl acetoacetate were all purchased from Acros Organics, Alfa Aesar, and Sigma Aldrich and required no additional purification. Sodium hydride and *n*-butyllithium were purchased from Sigma Aldrich and Alfa Aesar respectively and stored under an inert atmosphere.

4.2.2 Instrumentation

Proton and carbon NMR were recorded on a Bruker 500 MHz spectrometer. GC-MS analyses were performed with an HP 5890 Series II Gas Chromatograph with an HP Mass Selector Detector. A Satellite FTIR from Thermo-Mattson was used to obtain IR spectra. LC-HRMS data were recorded at the Mass Spectrometry Facility at Notre Dame University. Column chromatography was performed using the automated CombiFlash® Rf system from Teledyne Isco, Inc. Products were separated using prepacked silica gel columns with a gradient elution of either ethyl acetate:hexanes or diethyl ether:hexanes. Computational studies for the electron densities of substrates were carried out using Spartan '08. Mulliken charges were calculated for each substrate after the structures were optimized at the HF/6-31G* level. Theoretical calculations for the intramolecular cyclization of 6-(2-naphthyl)-2,4-hexanedione were performed using Gaussian 03.[135] The structures were optimized at the UHF/6-31G(d,p) level and CHELPG charges were calculated at both the UHF/6-31+G(d,p) and UB3LYP/6-31+G(d,p) levels.

4.2.3 Methods

4.2.3.1 General procedure for the synthesis of δ-aryl-β-dicarbonyls

Sodium hydride (11 mmol) was dissolved in 25 mL of THF and cooled to 0 ^{o}C. Next, 10 mmol of 2,4-pentanedione (or methyl acetoacetate for the δ-aryl-β-ketoester substrates) was added dropwise to the flask, causing the evolution of H_2 gas and forming an opaque, white solution. After stirring for 10 min, 10.5 mmol of *n*-butyllithium was added dropwise forming a clear yellow solution that was allowed to stir for an additional 10 min. The appropriate organohalide (11 mmol) was dissolved in 2 mL of THF and rapidly injected into the reaction at 0 ^{o}C. The reaction mixture was warmed gradually to room temperature in 30 min. The reaction was slowly quenched with an HCl solution (2 mL of concentrated HCl diluted with 5 mL H_2O). The organic layer was separated and the aqueous layer was extracted three times with diethyl ether. The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered, and concentrated. The crude product was purified via automated flash chromatography with a gradient elution of either ethyl acetate:hexanes or diethyl ether:hexanes. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, GC-MS, IR, and LC-HRMS.

4.2.3.2 General procedure for the oxidation of δ-aryl-β-dicarbonyls with CAN in MeOH

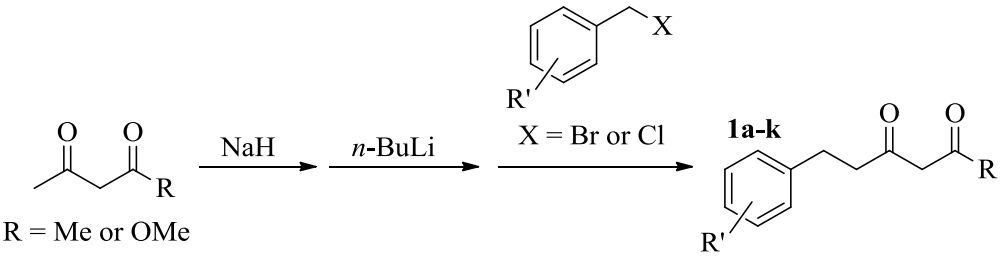
CAN (1.1 mmol) was dissolved in 4 mL MeOH. This CAN solution was then added dropwise in 1 min to the δ-aryl-β-dicarbonyl (0.5 mmol) which was dissolved in 15 mL of MeOH. The reaction was allowed to stir for 30 min. Solvent was then removed by rotary evaporation. Ice cold H_2O (15 mL) was poured into the reaction mixture, which was extracted three times with CH_2Cl_2. The organic layers were combined, dried with

$MgSO_4$, filtered, and concentrated. The crude product was purified via automated flash chromatography with a gradient elution of either ethyl acetate:hexanes or diethyl ether:hexanes. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, GC-MS, IR, and LC-HRMS.

Best synthetic results for electron-rich substrates were obtained when the reactions were quenched 5 minutes after introduction of the oxidant with an equal volume of cold H_2O. The rest of the work-up and purification procedure was identical to the 30min reactions.

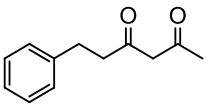
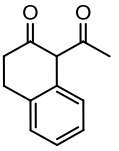
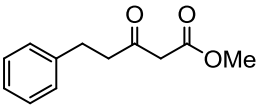
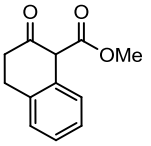
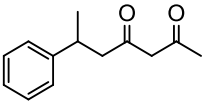
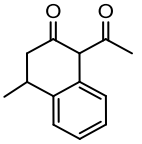
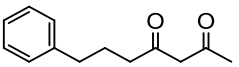
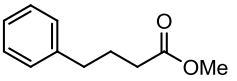
4.3 Results and discussion

In an initial experiment, when compound **1a** was oxidized in MeOH with 2.2 equivalents of CAN, the corresponding β-tetralone **2a** was generated in a 73% yield. To examine the breadth of this method, a series of δ-aryl-β-dicarbonyl substrates were prepared by a previously reported procedure (Scheme 4.2).[136] As shown in Table 4.1, the intramolecular cyclization of δ-aryl-β-diketones with unsubstituted aryl rings (entries 1 and 3) afforded β-tetralone products in moderate to good yields. Additionally, cyclization of the β-ketoester substrate (**1b**) proceeded efficiently, generating β-tetralone **2b** in an 85% yield. The oxidation of substrate **1d** indicated that products with 7-membered ring systems were not accessible by this method.



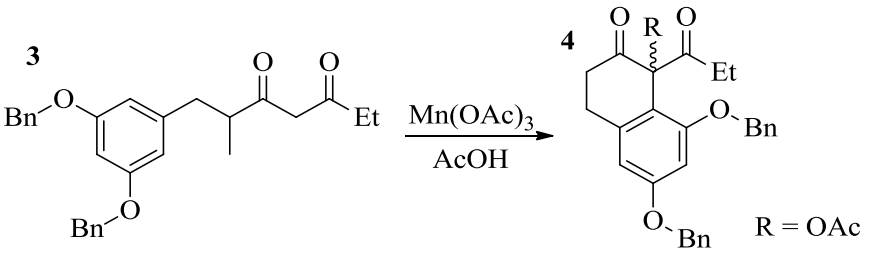
Scheme 4.2: Synthesis of δ-aryl-β-dicarbonyl starting materials

Table 4.1: CAN-mediated oxidation of δ-aryl-β-dicarbonyls in MeOH[a]

Entry	Substrate		Product		Yield (%)[b]
1	1a		2a		73
2	1b		2b		85
3	1c		2c		59
4	1d		2d		--[c]

[a] Reaction conditions: 1 equiv δ-aryl-β-dicarbonyl, 2.2 equiv CAN, MeOH, r.t., N_2, 4 hrs.
[b] Isolated yield. [c] GC data indicated that major product was the methyl ester. Attempts were not made to isolate the methyl ester.

Previous work by Rickards *et al.* on a related system reported strong electronic effects when electron-donating substituents were incorporated onto the δ-aryl ring of the starting material.[134] For example, the oxidative intramolecular cyclization of **3** shown in Scheme 4.3 generated the β-tetralone derivative (**4**) in a 93% yield. To probe the impact of electron density of the δ-aryl ring on intramolecular cyclization, several substrates with both electron-donating and electron-withdrawing groups were synthesized and subjected

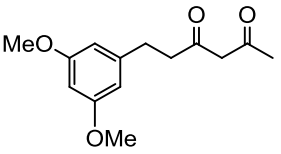
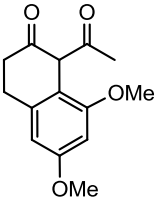
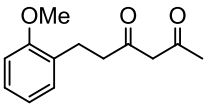
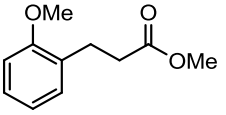
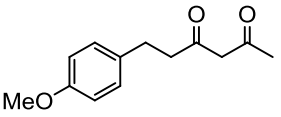
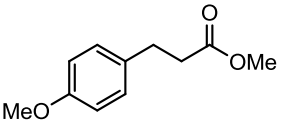
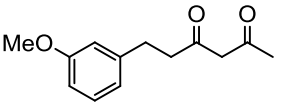
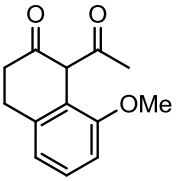
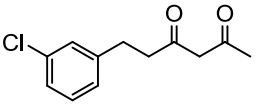
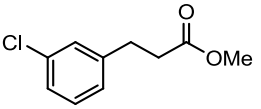
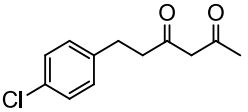
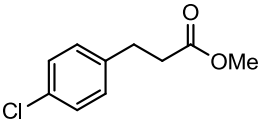
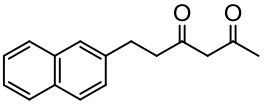
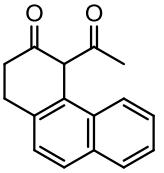


Scheme 4.3: Efficient oxidative cyclization of electron-rich δ-aryl-β-dicarbonyl **3**

to our reaction conditions. The results of these experiments are summarized in Table 4.2. As shown in entry 1, dimethoxylated substrate **1e** oxidatively cyclized to the β-tetralone derivative in a 76% yield. However, when only one methoxy group was incorporated onto the δ-aryl ring, the expected β-tetralone derivative was only produced when the methoxy group was *meta* to the dicarbonyl (entry 4). For substrates **1f** and **1g** with the methoxy group at either the *ortho* or *para* position respectively, methylesters **2c** and **2d** (entries 2 and 3) were the major products. Additionally, intramolecular cyclizations with electron-deficient δ-aryl rings (entries 5 and 6) did not occur and oxidation of **1i** and **2j** instead favored the formation of methylesters **2i** and **2j** as the major products. Finally, the tricyclic product (**2k**) was generated in an isolated yield of 61% when substrate **1k** was oxidized. It is important to note that products **2h** and **2k** were isolated as single isomers. Additionally, the regioisomers formed from these reactions result from cyclization occurring at the more hindered carbon atom of the δ-aryl ring. This observed regioselectivity is consistent with previous research by both MacMillan *et al*. and Nicolaou *et al.* on the α-arylation of aldehydes through organo-SOMO activation.[137-140] The preferential formation of regioisomers will be discussed *vide infra*.

While alkyl radicals are generally considered nucleophilic, the radicals generated from β-dicarbonyls have been shown to display more electrophilic character.[106, 141, 142] As a consequence, these radicals should favor coupling with more nucleophilic, electron-rich carbon centers. The observation that intramolecular cyclization did not occur in either of the electron-deficient substrates (compounds **1i** and **1j**) is consistent with electrophilic radical intermediates. To gain a better understanding of the impact that the electron density of the δ-aryl ring has on intramolecular cyclization, theoretical calculations were

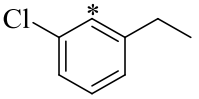
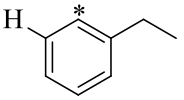
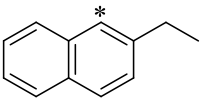
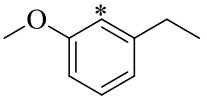
Table 4.2: Impact of ring substituents on the CAN-mediated oxidation of δ-aryl-β-dicarbonyls in MeOH[a]

Entry	Substrate		Product		Yield (%)[b]
1	1e		2e		76
2	1f		2f		--[c]
3	1g		2g		--[c]
4	1h		2h		83
5	1i		2i		--[c]
6	1j		2j		--[c]
7	1k		2k		61

[a] Reaction conditions: 1 equiv δ-aryl-β-dicarbonyl, 2.2 equiv CAN, MeOH, r.t., N_2, 4 hrs. [b] Isolated yield. [c] GC data indicated that the major products (50-80% conversion) were the methyl esters. Attempts were not made to isolate the methyl esters.

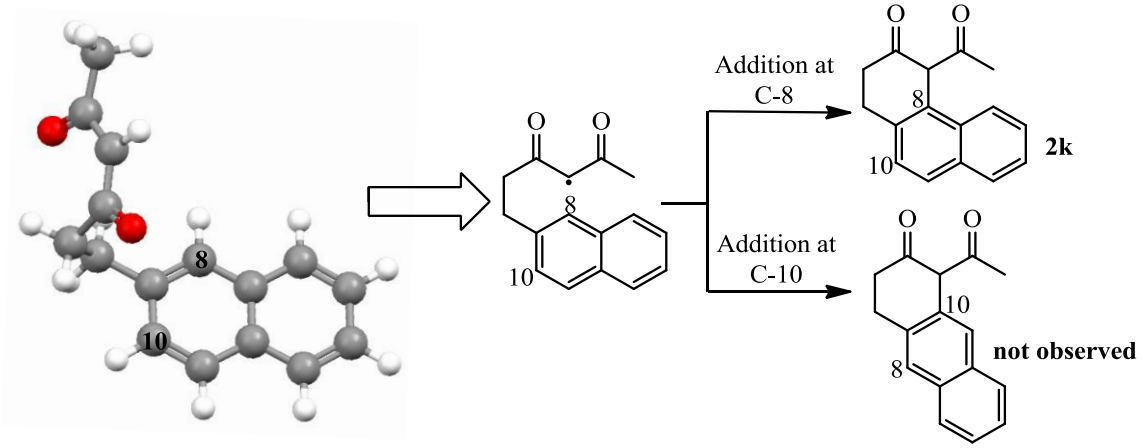
performed using Spartan '08 (Table 4.3). In these studies, the structures of substituted derivatives of ethylbenzene were optimized at the HF/6-31G* level. For these studies, the β-dicarbonyl group was replaced with an ethyl group for ease of calculation. Mulliken charges were then calculated to determine the effect of these substituents on the electron density at C2, the position where cyclization occurred for substrates **1h** and **1k**. The results of these computational studies show that a chloro group *meta* to the ethyl group significantly reduced the Mulliken charge at the C2 position when compared to the unsubstituted ethylbenzene (from -0.225 to -0.206). Conversely, both the naphthyl- and the *meta*-methoxy-substituted structures exhibited more electron density at the C2 position in comparison to ethylbenzene (entries 3 and 4). Since β-tetralone derivatives were obtained for substrates **1a**, **1h**, and **1k**, these computational studies affirm that there is a minimum electron density that must be met in order for cyclization with an electrophilic radical intermediate to occur.

Table 4.3: Substituent-effect on electron density at C2 of model aryl substrates

Entry	Structure[a]	Mulliken Charge at C2[b]
1		-0.206
2		-0.225
3		-0.241
4		-0.318

[a] Structures optimized at HF/6-31G* using Spartan '08
[b] The C2 position is marked with an "*" in each structure

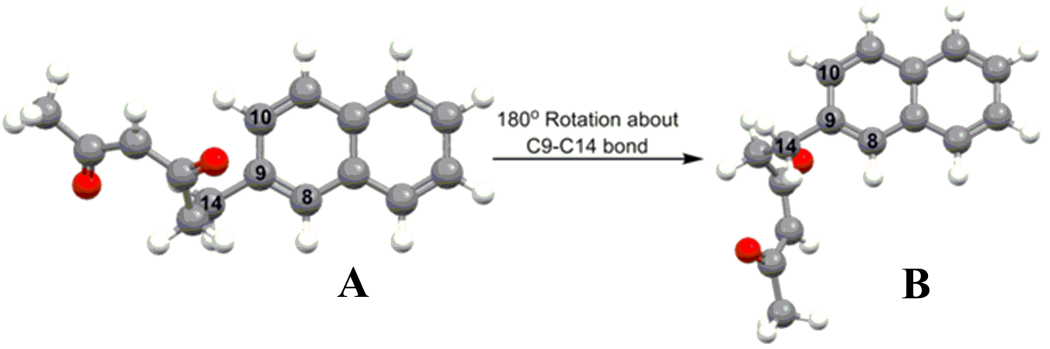
Having established a theoretical threshold for oxidative intramolecular cyclization, our efforts focused on understanding the nature of the observed regioselectivity in β-tetralone formation. While MacMillan and Houk have performed detailed computational studies to explain the regioselective radical cyclization with *m*-methoxylated rings, the selectivity of naphthyl substrates was not investigated.[138] As shown in Scheme 4.4, both a phenanthrene- and an anthracene-derived product are possible for the oxidative cyclization of **1k**. The formation of these regioisomers is dependent upon the position of attack on the naphthyl ring by a radical intermediate with cyclization at C8 and C10 leading to the phenanthrene and anthracene derivative, respectively. Additional computational studies were performed using Gaussian 03 to obtain further insight into the regioselectivity of the oxidative intramolecular cyclization of substrate **1k**,.[135] The intermediate radical structures were optimized at the UHF/6-31G(d,p) level and charges from electrostatic potentials using grid-based method (CHELPG) were calculated at both the UHF/6-31+G(d,p) and UB3LYP/6-31+G(d,p) levels. The data from these calculations (Table 4.4) clearly indicate that there is a significant difference in the electron density at the two positions on the δ-aryl ring where intramolecular cyclization with the



Scheme 4.4: Regioselectivity for the intramolecular cyclization of **1k**

electrophilic radical can occur (C8 and C10). Independent of the orientation of the α-carbonyl radical (structure A *versus* B), the carbon atom that should lead to phenanthrene derivative **2k** (C8) is approximately 3 times more electronegative than the carbon atom that should lead to the anthracene derivative (C10).

Table 4.4: CHELPG charges for optimized radical intermediates of **1k**[a]



Structure	Level	C-8	C-10
A	UHF/6-31+G(d,p)	-0.359	-0.085
B	UHF/6-31+G(d,p)	-0.392	-0.176
A	UB3LYP/6-31+G(d,p)	-0.289	-0.048
B	UB3LYP/6-31+G(d,p)	-0.320	-0.134

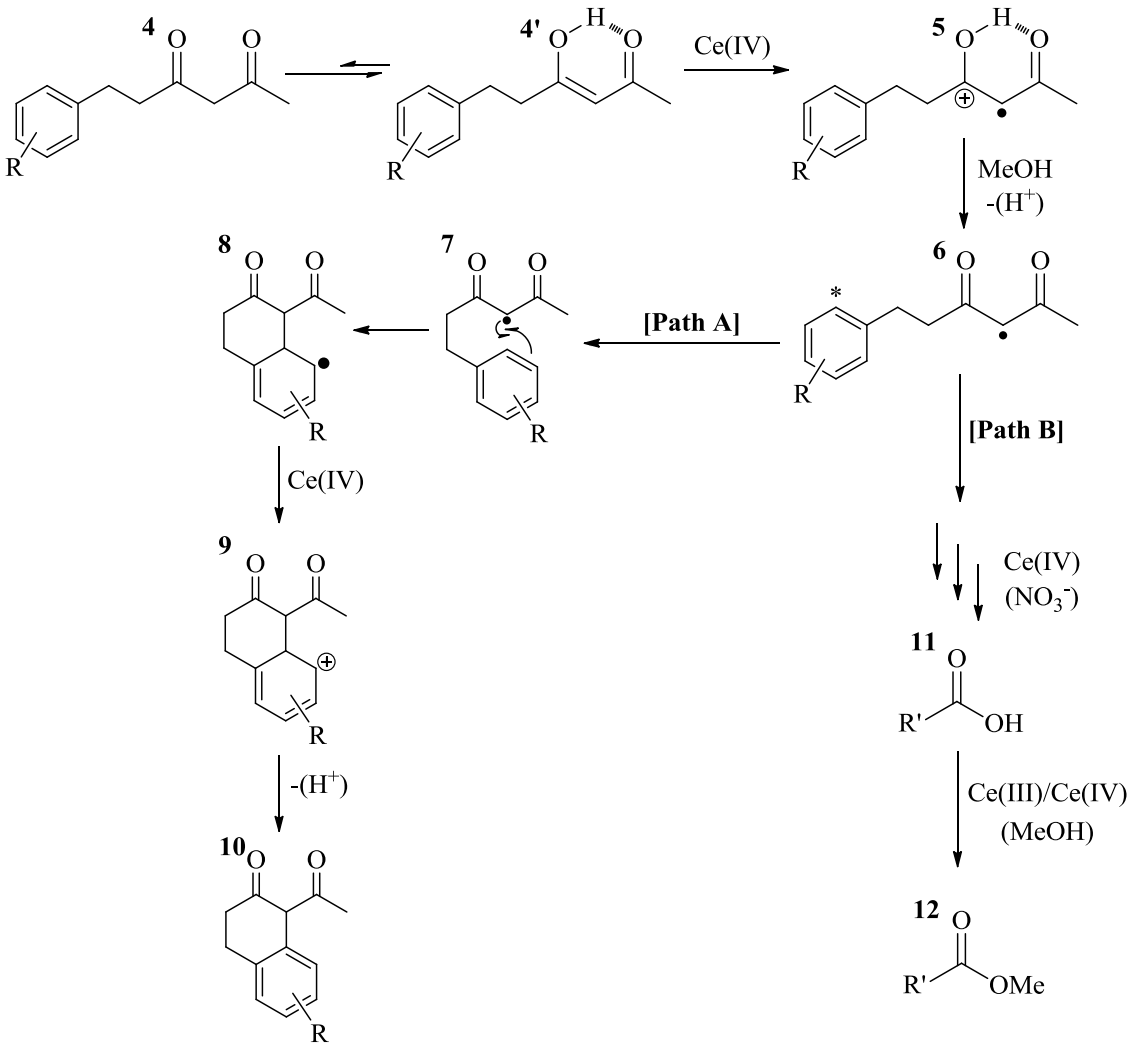
[a] Structures A and B optimized using Gaussian 03

In a previous study by our research group, the rates of oxidation of several β-diketones and their related silylenol ethers by CAN and CTAN were measured in MeOH, MeCN and CH_2Cl_2 using stopped-flow spectrophotometry.[88] The rates of formation and subsequent decay of radical cations formed after the initial oxidation were measured in all three solvents as well. The data discussed in this chapter in concert with the results from the oxidation of 1,3-dicarbonyls to carboxylic acids[88, 132] provide several key insights into the mechanism of the oxidation of δ-aryl-β-dicarbonyls in MeOH. First, MeOH is intimately involved in the decay of the initial radical cation through solvent-assisted deprotonation. Second, intramolecular cyclization of **1a** occurs after the rate-limiting step of the reaction. Third, the oxidations of non-aromatic β-diketones and their silylenol

ethers in MeOH result in conversion to their methylesters. In addition, the nitrate ligand of CAN plays an integral role in formation of carboxylic acids and their methylester equivalents. Finally, computational studies indicate that only substrates with sufficiently electron-rich δ-aryl rings undergo intramolecular cyclization.

Based on these previous findings as well as the synthetic and computational data presented herein, the mechanism in Scheme 4.5 is proposed for the oxidation of δ-aryl-β-dicarbonyls in MeOH with CAN. Initial oxidation of the enol tautomer (**4'**) by CAN produces radical cation **5**. Intermediate **5** is rapidly deprotonated by MeOH to radical species **6**. When the radical contains a δ-aryl group with sufficient electron density at the * position, Path A is followed. Intramolecular cyclization (**7**) occurs through radical addition to the aromatic ring forming intermediate **8**. As demonstrated by the oxidation of substrate **1k**, intramolecular cyclization of this radical occurs at the more electron rich carbon atom of asymmetric δ-aryl rings. A second equivalent of CAN oxidizes **8** to cation **9**. Rearomatization through deprotonation of intermediate **9** yields the β-tetralone derivative **10**. Close inspection of cation **9** reveals that only the substrate with the methoxy group at the *meta* position on the δ-aryl ring (Table 4.2, entry 4) can stabilize this cation through resonance.

Conversely, when the δ-aryl ring is electron-deficient (Table 4.2, entries 5-6), the reaction follows Path B which is similar to the pathway previously established for the conversion of β-dicarbonyls to carboxylic acids.[88] Both a second single electron oxidation and internal ligand transfer of a nitrate are required for the conversion of radical **6** to the carboxylic acid (**11**).[88] Methylester **12** is produced by the Lewis acid-promoted esterification of **11** with Ce(III)/Ce(IV) and MeOH.[143-145]

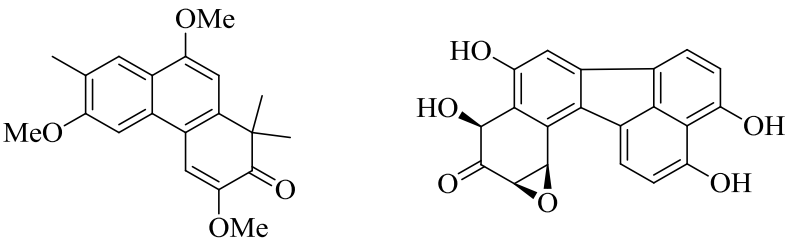


Scheme 4.5 Proposed mechanism for the conversion of δ-aryl-β-dicarbonyls to β-tetralones (Path A) and methylesters (Path B)

4.4 Conclusions

A protocol for the conversion of δ-aryl-β-tetralones using CAN has been developed. The method presented in this chapter demonstrates that a series of δ-aryl-β-dicarbonyls can be efficiently oxidized with CAN to form β-tetralones which are structural motifs in several natural products such as trigonostemone and daldinone B (Figure 4.1).[146, 147] In addition, β-tetralones have been used as precursors in the synthesis of a variety of pharmaceutically active compounds and biologically relevant molecules.[148, 149] As a result, a great deal of research has been devoted to developing efficient routes to

β-tetralone derivatives.[150-152] The Ce(IV)-mediated syntheses of β-tetralones presented in this chapter had short reaction times, mild conditions, and afforded the desired products in moderate to very good yields. While β-tetralones were not generated for all substrates, the data suggest that a general method for the conversion of aliphatic β-dicarbonyls and electron-deficient δ-aryl-β-dicarbonyls to esters may be achieved. Furthermore, the results of computational studies presented herein helped establish for the first time that a threshold based on electron density of the δ-aryl ring exists for efficient intramolecular cyclization. Finally, the regioselective formation of phenanthrene derivative **2k** was shown to be a consequence of intramolecular cyclization occurring at the most electron-rich carbon atom. The manuscript for this research is currently in preparation for *Organic Letters*.



A **B**

Figure 4.1: Structures of trigonostemone (**A**) and daldinone B (**B**)

4.5 Synthesis and spectral data for starting materials and products

4.5.1 δ-Aryl-β-dicarbonyls substrates

6-Phenyl-2,4-hexanedione (**1a**)

Procedure 4.2.3.1 was followed using 2,4-pentanedione and benzyl bromide. Clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 15.46 (br. s, 1H), 7.32-7.27 (m, 2H), 7.24-7.17 (m, 3H), 5.49 (s, 1H), 2.94 (t, 2H, J = 8.1 Hz), 2.60 (t, 2H, J = 8.2 Hz), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 193.2, 191.0, 140.6, 128.8,

128.5, 128.5, 128.4, 128.3, 128.2, 126.4, 126.2, 100.0, 58.0, 45.2, 40.0, 38.1, 31.4, 29.4, 24.8. MS [*m*/*z* (rel int)] 190 (M^+, 72), 172 (11), 129 (10), 104 (67), 91 (86), 85 (100), 77 (31).

Methyl 3-oxo-5-phenyl-pentanoate (**1b**)

Procedure 4.2.3.1 was followed using methylacetoacetate and benzyl bromide. Clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (keto tautomer) δ 7.31-7.27 (m, 2H), 7.22-7.17 (m, 3H), 3.72 (s, 3H), 3.44 (s, 2H), 2.95-2.86 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 201.7, 167.5, 140.4, 128.5, 128.4, 128.3, 126.2, 52.4, 49.2, 44.5, 29.4. MS [*m*/*z* (rel int)] 206 (M^+, 28), 188 (41), 174 (25), 133 (50), 128 (34), 104 (100), 91 (100), 77 (47).

6-Methyl-6-phenyl-2,4-hexanedione (**1c**)

Procedure 4.2.3.1 was followed using 2,4-pentanedione and (1-bromoethyl)benzene. Clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 15.52 (br. s, 1H), 7.34-7.29 (m, 2H), 7.26-7.20 (m, 3H), 5.43 (s, 1H), 3.29 (apparent sext, 1H, J = 7.1 Hz), 2.61 (dd, 1H, J = 14.7, 6.8 Hz), 2.49 (dd, 1H, J = 14.3, 8.2 Hz), 2.02 (s, 3H), 1.32 (d, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 202.9, 201.8, 191.9, 191.6, 145.8, 145.6, 128.4, 128.3, 126.6, 126.2, 100.6, 58.3, 51.6, 46.6, 46.5, 36.7, 36.6, 35.1, 35.1, 24.9, 24.8, 21.6, 21.5. MS [*m*/*z* (rel int)] 204 (M^+, 36), 186 (9), 143 (18), 118 (41), 105 (100), 91 (23), 85 (54), 77 (32).

7-Phenyl-2,4-heptanedione (**1d**)

Procedure 4.2.3.1 was followed using 2,4-pentanedione and (2-bromoethyl)benzene. Clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 15.50 (br. s, 1H), 7.32-7.28 (m, 2H), 7.22-7.17 (m, 2H), 5.49 (s, 1H), 2.66 (t,

2H, J = 7.7 Hz), 2.31 (t, 2H, J = 7.7 Hz), 2.06 (s, 3H), 1.95 (apparent pentet, 2H, J = 7.7 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 193.8, 191.3, 141.5, 128.4, 128.4, 126.0, 99.9, 37.5, 35.2, 27.2, 24.9. MS [*m*/*z* (rel int)] 204 (M^+, 6), 186 (6), 105 (75), 100 (94), 91 (69), 85 (100), 77 (12).

6-(3,5-Dimethoxyphenyl)-2,4-hexanedione (**1e**)

Procedure 4.2.3.1 was followed using 2,4-pentanedione and 3,5-dimethoxybenzyl chloride. Clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 15.44 (br. s, 1H), 6.37-6.26 (m, 3H), 5.46 (s, 1H), 3.75 (s, 6H), 2.85 (t, 2H, J = 7.9 Hz), 2.56 (t, 2H, J = 7.9 Hz), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 193.3, 190.9, 160.8, 143.1, 106.3, 100.0, 98.1, 55.2, 39.8, 31.7, 24.7. MS [*m*/*z* (rel int)] 250 (M^+, 21), 232 (9), 165 (100), 151 (14), 91 (12), 85 (16), 77 (13).

6-(2-Methoxyphenyl)-2,4-hexanedione (**1f**)

Procedure 4.2.3.1 was followed using 2,4-pentanedione and 2-methoxybenzyl chloride. Clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 15.47 (br. s, 1H), 7.23-7.18 (m, 1H), 7.15-7.12 (m, 1H), 6.91-6.83 (m, 2H), 5.49 (s, 1H), 3.83 (s, 3H), 2.92 (t, 2H, J = 7.7Hz), 2.58 (t, 2H, J = 7.7Hz), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 193.9, 191.0, 157.4, 129.8, 129.0, 127.5, 120.4, 110.2, 99.8, 55.18, 38.3, 26.6, 24.9. MS [*m*/*z* (rel int)] 220 (M^+, 27), 146 (13), 134 (33), 121 (77), 91 (100), 85 (46), 77 (33).

6-(4-Methoxyphenyl)-2,4-hexanedione (**1g**)

Procedure 4.2.3.1 was followed using 2,4-pentanedione and 4-methoxybenzyl chloride. Clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 15.46 (br. s, 1H), 7.13-7.09 (m, 2H), 6.85-6.81 (m, 2H), 5.47 (s, 1H), 3.79 (s, 3H), 2.88 (t, 2H, J

= 7.6 Hz), 2.56 (t, 2H, *J* = 7.6 Hz), 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 193.2, 191.1, 158.0, 132.7, 129.2, 129.2, 113.9, 113.8, 100.0, 55.2, 40.2, 30.6, 24.9. MS [*m*/*z* (rel int)] 220 (M^+, 39), 163 (7), 134 (36), 121 (100), 91 (21), 85 (16), 77 (20).

6-(3-Methoxyphenyl)-2,4-hexanedione (**1h**)

Procedure 4.2.3.1 was followed using 2,4-pentanedione and 3-methoxybenzyl chloride. Clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 15.46 (br. s, 1H), 7.23-7.19 (m, 1H), 6.81-6.72 (m, 3H), 5.49 (s, 1H), 3.80 (s, 3H), 2.92 (t, 2H, *J* = 7.9 Hz), 2.60 (t, 2H, *J* = 7.9 Hz), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 193.3, 191.0, 159.7, 142.3, 129.5, 120.6, 114.0, 111.5, 100.0, 55.1, 39.9, 31.5, 24.8. MS [*m*/*z* (rel int)] 220 (M^+, 38), 202 (11), 162 (11), 135 (100), 121 (71), 105 (27), 91 (73), 85 (91), 77 (40).

6-(3-Chlorophenyl)-2,4-hexanedione (**1i**)

Procedure 4.2.3.1 was followed using 2,4-pentanedione and 3-chlorobenzyl chloride. Clear, yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 15.41 (br. s, 1H), 7.22-7.17 (m, 3H), 7.09-7.06 (m, 1H), 5.47 (s, 1H), 2.92 (t, 2H, *J* = 8.1 Hz), 2.59 (t, 2H, *J* = 8.1 Hz), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 192.9, 190.8, 142.7, 134.2, 129.8, 129.7, 128.5, 128.4, 126.5, 126.4, 100.0, 58.0, 44.8, 39.7, 31.0, 28.9, 24.7. MS [*m*/*z* (rel int)] 224 (M^+, 38), 138 (33), 125 (42), 103 (35), 85 (100), 77 (28). IR (KBr) ν (cm^{-1}) 3644, 3167, 3064, 2939, 2670, 2365, 1843, 1592, 1438, 1330, 1262, 1142, 1038, 893, 785, 688. LC-HRMS calcd. for $C_{12}H_{14}ClO_2$ [M+H] 225.0677, found 225.0665.

6-(4-Chlorophenyl)-2,4-hexanedione (**1j**)

Procedure 4.2.3.1 was followed using 2,4-pentanedione and 4-chlorobenzyl chloride. White solid (mp 34-36 ^{o}C). ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ

15.42 (br. s, 1H), 7.26-7.23 (m, 2H), 7.14-7.10 (m, 2H), 5.46 (s, 1H), 2.91 (t, 2H, J = 7.9 Hz), 2.57 (t, 2H, J = 7.9 Hz), 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 192.9, 190.9, 139.1, 132.0, 129.6, 128.6, 100.1, 39.8, 30.7, 24.8. MS [*m*/*z* (rel int)] 224 (M^+, 65), 138 (59), 125 (76), 103 (29), 85 (100), 77 (24). IR (KBr) ν (cm^{-1}) 3491, 2884, 2396, 2283, 1894, 1808, 1608, 1498, 1427, 1251, 1097, 1006, 940, 807. LC-HRMS calcd. for $C_{12}H_{13}ClNaO_2$ [M+Na] 247.0496, found 247.0487.

6-(2-Naphthyl)-2,4-hexanedione (**1k**)

Procedure 4.2.3.1 was followed using 2,4-pentanedione and 2-(bromomethyl)naphthalene. White solid (mp 57-58 ^{o}C). ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 15.51 (br. s, 1H), 7.84-7.75 (m, 3H), 7.67-7.62 (s, 1H), 7.51-7.42 (m, 2H), 7.37-7.32 (m, 1H), 5.50 (s, 1H), 3.12 (t, 2H, J = 8.0 Hz), 2.70 (t, 2H, J = 8.0 Hz), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 193.1, 191.0, 138.2, 133.5, 132.1, 128.1, 127.6, 127.4, 126.9, 126.4, 126.0, 125.3, 100.0, 39.9, 31.6, 24.8. MS [*m*/*z* (rel int)] 240 (M^+, 55), 182 (12), 154 (65), 141 (100), 128 (35), 115 (62), 85 (40).

4.5.2 β-Tetralone derivatives

1-Acetyl-3,4-dihydro-2(*2H*)-naphthalenone (**2a**)

Procedure 4.2.3.2 was followed. Clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 16.53 (br. s, 1H), 7.25-7.18 (m, 3H), 7.15-7.10 (m, 1H), 2.86 (t, 2H, J = 6.9 Hz), 2.56 (t, 2H, J = 6.9 Hz), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 200.0, 183.8, 135.4, 132.8, 127.4, 126.5, 126.4, 125.4, 110.9, 35.3, 27.8, 23.3. MS [*m*/*z* (rel int)] 188 (M^+, 26), 173 (23), 146 (21), 141 (21), 128 (24), 115 (100), 102 (10), 91 (24), 77 (16).

Methyl 3,4-dihydro-2(*2H*)-naphthalenone-1-carboxylate (**2b**)

Procedure 4.2.3.2 was followed. Clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 13.32 (br. s, 1H), 7.72-7.67 (m, 1H), 7.22-7.18 (m, 1H), 7.15-7.12 (m, 1H), 7.10-7.06 (m, 1H), 3.93 (s, 3H), 2.83 (t, 2H, J = 7.4 Hz), 2.55 (t, 2H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 178.4, 172.4, 133.2, 131.3, 127.2, 126.4, 125.8, 125.0, 99.9, 51.7, 29.5, 27.7. MS [*m*/*z* (rel int)] 204 (not observed), 189 (2), 146 (56), 117 (44), 104 (100), 91 (23), 78 (33).

1-Acetyl-3,4-dihydro-4-methyl-2(*2H*)-naphthalenone (**2c**)

Procedure 4.2.3.2 was followed. Clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 16.56 (br. s, 1H), 7.26-7.15 (m, 4H), 3.07-3.00 (m, 1H), 2.66 (dd, 1H, J = 16.2, 5.1 Hz), 2.40 (s, 3H), 2.39 (dd, 1H, J = 7.6 Hz), 1.31 (d, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 199.1, 183.6, 139.8, 132.1, 126.7, 126.2, 125.7, 110.8, 42.7, 32.4, 23.4, 18.9. MS [*m*/*z* (rel int)] 202 (M^+, 62), 187 (25), 141 (44), 128 (38), 115 (100), 105 (25), 91 (31). IR (KBr) ν (cm^{-1}) 3089, 2958, 2549, 2411, 1595, 1408, 1271, 984, 759. LC-HRMS calcd. for $C_{13}H_{15}O_2$ [M+H] 203.1067, found 203.1060.

1-Acetyl-6,8-dimethoxy-3,4-dihydro-2(*2H*)-naphthalenone (**2e**)

Procedure 4.2.3.2 was followed. Clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 15.56 (br. s, 1H), 6.41-6.32 (m, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.19-2.37 (m, 4H), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 206.4, 203.3, 198.2, 183.8, 160.2, 158.9, 157.4, 155.7, 138.8, 138.7, 114.6, 114.0, 107.4, 104.4, 104.2, 96.9, 96.8, 62.6, 55.4, 55.3, 55.0, 37.7, 35.2, 29.6, 29.0, 28.5, 23.1. MS [*m*/*z* (rel int)] 248 (M^+, 32), 233 (6), 215 (21), 206 (100), 191 (30), 177 (34), 161 (13), 147 (11), 131 (11), 115 (11), 103 (11), 91 (15), 77 (13).

1-Acetyl-8-methoxy-3,4-dihydro-2(*2H*)-naphthalenone (**2h**)

Procedure 4.2.3.2 was followed. Single isomer existing in keto, *cis*-enol and *trans*-enol tautomers. Clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomers) δ 16.32 (br. s, 1H), 15.75 (br. s, 1H), 7.26-7.09 (m, 2H), 6.88-6.76 (m, 4H), 3.82 (s, 6H), 3.24-2.42 (m, 8H), 2.06 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 206.2, 202.9, 197.7, 185.5, 182.0, 157.4, 156.4, 154.6, 138.1, 137.8, 137.0, 128.6, 127.5, 126.8, 125.3, 121.8, 121.7, 120.5, 119.6, 113.2, 111.4, 110.5, 109.6, 108.5, 107.6, 63.0, 55.4, 55.3, 55.0, 37.7, 35.5, 34.9, 29.9, 28.5, 28.2, 28.1, 23.4, 23.0. MS [*m*/*z* (rel int)] 218 (M^+, 31), 203 (14), 185 (17), 176 (100), 161 (48), 131 (31), 115 (43), 103 (28), 91 (20), 77 (20). IR (KBr) ν (cm^{-1}) 3635, 2948, 2823, 1712, 1597, 1461, 1425, 1260, 1167, 1086, 969. LC-HRMS calcd. for $C_{13}H_{15}O_3$ [M+H] 219.1016, found 219.1006.

4-Acetyl-1,2-dihydro-3(*2H*)-phenanthrenone (**2k**)

Procedure 4.2.3.2 was followed. Clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) – (enol tautomer) δ 15.51 (br. s, 1H), 7.91-7.81 (m, 1H), 7.71 (d, 1H, J = 8.3 Hz), 7.64 (d, 1H, J = 8.2 Hz), 7.50-7.42 (m, 2H), 7.39 (d, 1H, J = 8.2 Hz), 3.18 (td, 1H, J = 15.0, 4.3 Hz), 2.93-2.85 (m, 1H), 2.71-2.62 (m, 1H), 2.51 (td, 1H, J = 15.6, 5.4 Hz), 1.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 206.4, 202.8, 201.7, 179.7, 135.4, 134.6, 133.1, 133.0, 131.3, 130.0, 129.4, 129.2, 128.6, 127.3, 126.9, 126.5, 125.8, 125.7, 125.7, 125.4, 125.0, 122.2, 110.1, 65.8, 37.3, 36.2, 29.2, 28.8, 28.7, 23.1. MS [*m*/*z* (rel int)] 238 (M^+, 23), 196 (63), 178 (32), 165 (100), 152 (47), 139 (25), 115 (15). IR (KBr) ν (cm^{-1}) 3420, 3048, 2953, 2254, 1712, 1601, 1402, 1248, 1026, 915, 818, 739. LC-HRMS calcd. for $C_{16}H_{15}O_2$ [M+H] 239.1067, found 239.1062.

4.5.3 Methyl ester derivatives

Methyl 4-phenyl-butanoate (**2d**)

Procedure 4.2.3.2 was followed and the crude reaction was analyzed by GC-MS. MS [*m*/*z* (rel int)] 178 (M^+, 28), 147 (31), 104 (79), 91 (100).

Methyl 3-(2-methoxyphenyl)-propionate (**2f**)

Procedure 4.2.3.2 was followed and the crude reaction was analyzed by GC-MS. MS [*m*/*z* (rel int)] 194 (M^+, 34), 121 (80), 91 (100).

Methyl 3-(4-methoxyphenyl)-propionate (**2g**)

Procedure 4.2.3.2 was followed and the crude reaction was analyzed by GC-MS. MS [*m*/*z* (rel int)] 194 (M^+, 16), 121 (100), 91 (25).

Methyl 3-(3-chlorophenyl)-propionate (**2i**)

Procedure 4.2.3.2 was followed and the crude reaction was analyzed GC-MS. MS [*m*/*z* (rel int)] 198 (M^+, 9), 138 (100), 125 (31), 103 (53), 89 (22), 77 (45).

Methyl 3-(4-chlorophenyl)-propionate (**2j**)

Procedure 4.2.3.2 was followed and the crude reaction was analyzed by GC-MS. MS [*m*/*z* (rel int)] 198 (M^+, 33), 138 (100), 103 (61), 77 (39).

Chapter 5: On the nature of the oxidative heterocoupling of lithium enolates

5.1 Background and significance

The coupling of enolates through single electron oxidation is one of the most direct routes to generating 1,4-dicarbonyls, which are important structural motifs in a variety of natural products[153-156] and pharmaceutically active compounds (Figure 5.1).[157, 158] Reactions of this kind provide one-step synthetic routes to complex products from relatively simple starting materials. Direct routes to complex structures and molecular

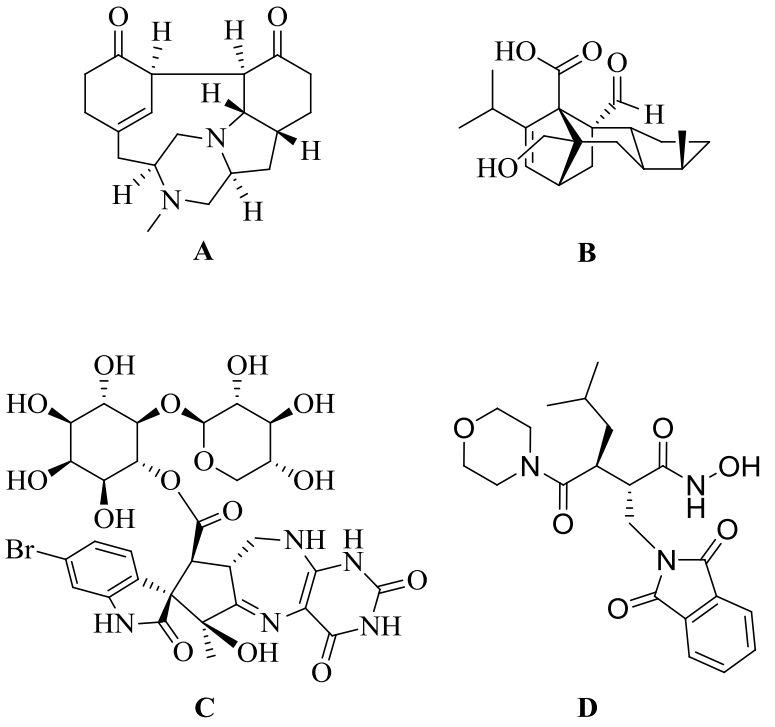


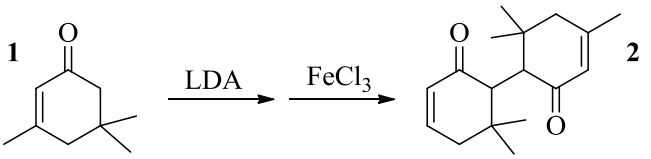
Figure 5.1: 1,4-Dicarbonyl structures in the natural products herquline A (**A**), sordaricin (**B**), neosurugatoxin (**C**) and pharmaceutics such as matrix metalloprotease inhibitors (**D**)

scaffolds are of paramount importance to synthetic chemists. In recent years, increasing consideration has been given to the concepts of "atom economy" and "protecting-group-free" approaches in the total synthesis of biologically relevant compounds.[159-161] Unlike other synthetic routes to 1,4-dicarbonyls,[23, 24, 162, 163] the single electron oxidative coupling

of equimolar amounts of enolates can afford the same products while requiring no prefunctionalization steps.

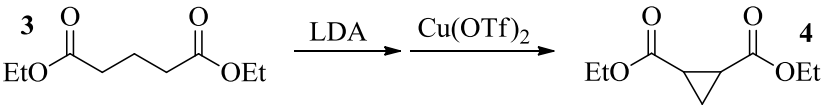
Numerous protocols have been developed for the oxidative homocoupling of enolates which use a variety of oxidants and are applicable to many different substrates.[11-13, 20-22, 164-167] Reaction 1 in Scheme 5.1 depicts the intermolecular oxidative homocoupling of isophorone (**1**).[12] After deprotonation with lithium diisopropylamine (LDA), the enolate is oxidized by iron(III) chloride ($FeCl_3$) dimerizing to produce the symmetric 1,4-diketone product (**2**).[12] In addition to intermolecular homocoupling reactions, intramolecular cyclizations can be achieved through the single electron oxidation of dienolates.[20, 168] As shown in reaction 2, diester **3** can be deprotonated with two

Intermolecular homocoupling



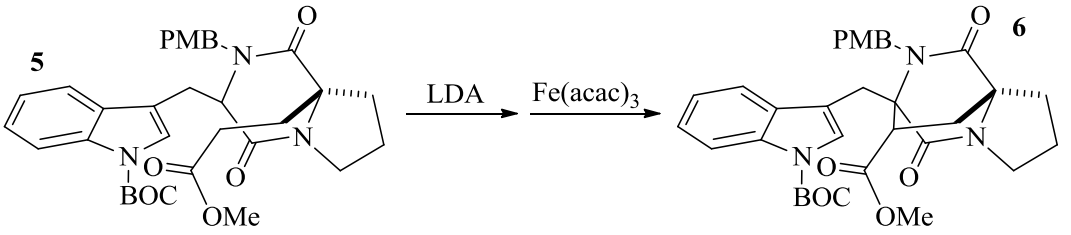
(1)

Intramolecular homocoupling



(2)

Intramolecular heterocoupling



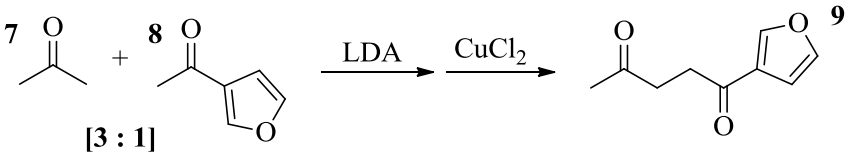
(3)

Scheme 5.1: Synthesis of 1,4-dicarbonyls via the oxidative coupling of metal-stabilized enolates

equivalents of LDA to generate a dienolate.[20] After oxidation with copper(II) triflate [$Cu(OTf)_2$], the cyclopropane derivative (**4**) is produced via intramolecular radical-radical coupling.[20] As demonstrated by Baran *et al*., intramolecular cyclizations can also occur through the oxidative coupling of two different enolates.[14] In reaction 3, deprotonation of both the amide and ester of **5** generates a dienolate which oxidatively heterocouples using iron(III) acetylacetonate ($Fe(acac)_3$) to produce **6**.[14]

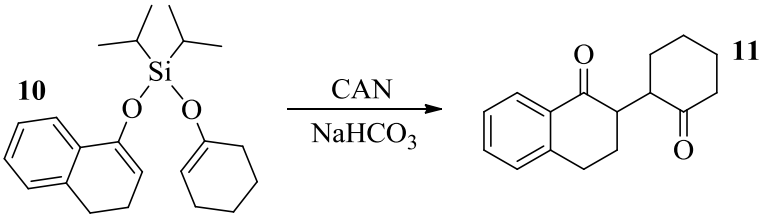
Despite the large amount of research on intra- and intermolecular oxidative coupling of enolates, the synthesis of unsymmetric 1,4-dicarbonyls via the single electron oxidation of two different metal-stabilized enolates has been slow to develop. Applications of traditional oxidative procedures require the use of superstoichiometric amounts of one enolate relative to the other to obtain synthetically useful yields of the heterocoupled product (i.e. better than 50%).[21, 22] As shown in reaction 4 of Scheme 5.2, when a 3 equivalent excess of acetone (**7**) relative to ketone **8** is employed the heterocoupled product (**9**) is generated in 59% yield.[21] Thomson *et al*. have shown that

Intermolecular heterocoupling



(4)

Silyl bis-enol ether heterocoupling

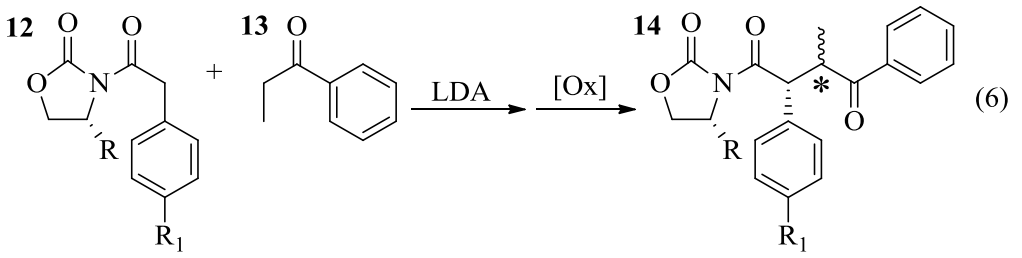


(5)

Scheme 5.2: Previous synthetic approaches to the oxidative heterocoupling of enolates

unsymmetric 1,4-dicarbonyls are produced through the oxidation of silyl bis-enol ethers.[169] In reaction 5, the silyl bis-enol ether (**10**) is oxidized with two equivalents of cerium(IV) ammonium nitrate (CAN) to produce **11**. While unsymmetric 1,4-dicarbonyls have been generated in acceptable yields (40-82%) by this method, multistep syntheses are required to make the silyl bis-enol ethers reducing the appeal of this approach in terms of atom economy.[169]

Recently, Baran *et al.* reported the intermolecular oxidative heterocoupling of enolates.[23, 24] In all reported cases, when equimolar amounts of two different enolates (**12** and **13**) were oxidized with Fe(III)- or Cu(II)-based oxidants, the heterocoupled product (**14**) was obtained in greater than 50% yield with some products being obtained in 70-90% yields (Scheme 5.3). These findings are intriguing because statistically the oxidation of equimolar amounts of two enolates, at best, should result in 50% yield of the heterocoupled product along with 25% of each of the homodimers. Interestingly, they also found that the diastereoselectivity was oxidant-dependent, with Fe(III)-oxidants favoring β-stereochemistry at the "*" position and Cu(II)-oxidants favoring α-stereochemistry.[23] While synthetic studies were performed to probe the basis for diastereoselectivity,[23] **the underlying mechanistic basis for the selective formation of heterocoupled products has not been elucidated**. The research presented in this chapter uses mechanistic and synthetic studies to test two possibilities for enhanced



Scheme 5.3: Oxidative heterocoupling of an equimolar mixture of two different enolates

heterocoupling yields: 1) selective heterocoupling as a result of preferential oxidation of enolates, and 2) selective heterocoupling as a result of non-statistical distributions of lithium heteroaggregates.

5.2 Experimental

5.2.1 Materials

5.2.1.1 ^{7}Li NMR experiments

THF was purified with a Pure Solv solvent purification system from Innovative Technology, Inc. Toluene was degassed with argon for 1 hour and then stored over activated 3 Å molecular sieves under an inert atmosphere. A stock solution of 2.0 M THF/toluene was prepared by diluting 8.1 mL of THF to a final volume of 50 mL with toluene. LiHMDS was purchased from Sigma Aldrich as a white solid and used without further purification. All ketones were purchased from Alfa Aesar or Acros Organics and purified by short-path distillation, recrystallization from *n*-pentane, or column chromatography prior to use. As a reference and locking signal, 0.3 M LiCl in CD_3OD was prepared and flame-sealed inside melting point capillaries. All solutions and substrates were stored inside a glovebox filled with argon.

5.2.1.2 Oxidative heterocoupling reactions

THF was purified with a Pure Solv solvent purification system from Innovative Technology, Inc. LiHMDS was purchased from Sigma Aldrich as a white solid and used without further purification. All ketones were purchased from Alfa Aesar or Acros Organics and purified by short-path distillation, recrystallization from *n*-pentane, or column chromatography prior to use. Molecular iodine was purchased from Acros

Organics and used without further purification. Anhydrous *N*,*N*-dimethylforamide (DMF) was purchased from Acros Organics.

5.2.2 Instrumentation

Proton, carbon, and lithium NMR were recorded on a Bruker 500 MHz spectrometer. GC-MS analyses were performed with an HP 5890 Series II Gas Chromatograph with an HP Mass Selector Detector. LC-HRMS data were recorded at the Mass Spectrometry Facility at Notre Dame University. Column chromatography was performed using the automated CombiFlash® Rf system from Teledyne Isco, Inc. Products were separated using prepacked silica gel columns with a gradient elution of either ethyl acetate:hexanes or diethyl ether:hexanes.

5.2.3 Methods

5.2.3.1 General procedure for the determination of lithium enolate aggregation

All glassware was flame-dried before use. Two portions of LiHMDS (0.304 mmol each) were dissolved in 0.5 mL of 2.0 M THF/toluene each in septated vials with magnetic stirrers and cooled to -10 ^{o}C. Each ketone (0.300 mmol) was dissolved separately in 0.5 mL 2.0M THF/toluene and added dropwise to one of the vials of LiHMDS. The two solutions were stirred at -10 ^{o}C for 45 minutes. The enolate solutions were then cooled to -78 ^{o}C, combined via syringe (stirred for 5 minutes), warmed to -10 ^{o}C (stirred for 5 minutes), and recooled to -78 ^{o}C. The solution was transferred to a septated NMR tube containing a sealed insert (0.3 M LiCl in CD_3OD). The sample temperature was maintained at -78 ^{o}C until it was placed in the NMR spectrometer (NMR probe temperature was -30 ^{o}C). The sample was locked and shimmed extensively using the CD_3OD. A pre-thermal equilibrated ^{7}Li NMR spectrum was obtained for the sample

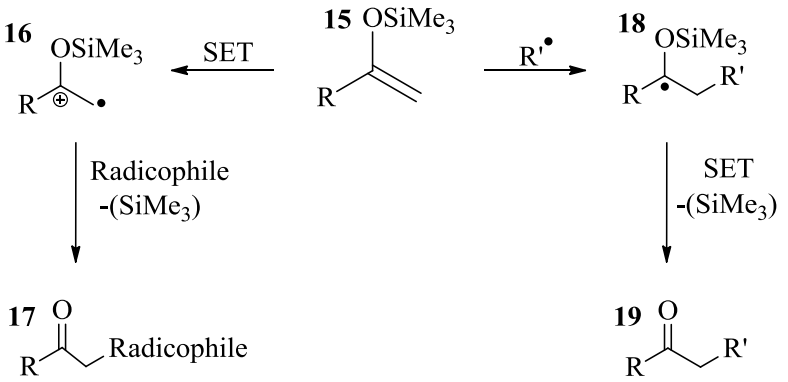
at -30 ^{o}C. The NMR tube was then ejected from the spectrometer, warmed in-hand for 2 minutes, recooled to -30 ^{o}C inside the spectrometer, and the ^{7}Li NMR spectrum was recorded again. The peaks were integrated with the signal corresponding to the A_4 aggregate set to a value of 1. The shift values are reported relative to the signal for LiCl (0.00 ppm). For all equimolar enolate mixtures reported, the lithium aggregates were ensembles of tetramers (A_4 : A_3B_1 : A_2B_2 : A_1B_3 : B_4) consistent with those reported by Collum *et al*.[170]

5.2.3.2 General procedure for the oxidative heterocoupling of lithium enolates

All glassware was flame-dried before use. The ketone substrates (0.30 mmol of each) were dissolved together in 1.0 mL of THF in a septated vial with a magnetic stirrer. The vial was then cooled to -10 ^{o}C. LiHMDS (0.64 mmol) was dissolved in 1.0 mL of THF and added dropwise to the solution of ketones. The solution was stirred at -10 ^{o}C for 45 minutes. The enolate solution was placed in a water bath at room temperature (stirred for 5 minutes) and then cooled to -78 ^{o}C. Molecular iodine (0.30 mmol) was dissolved in 1.0 mL of THF and added to the enolate solution dropwise via syringe with vigorous stirring. The reaction solution was removed from the -78 ^{o}C bath and allowed to slowly warm to room temperature over 30 minutes. The reaction was quenched with an equal volume of brine, separated, and the aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, rotary evaporated to dryness, and the crude reaction mixture was redissolved in $CDCl_3$. DMF (0.3 mmol) was added. Product yields and ratios (heterocoupled product:homocoupled product) were determined by ^{1}H NMR. The heterocoupled products were purified via automated flash chromatography and characterized by ^{1}H NMR, ^{13}C NMR, GC-MS, and LC-HRMS.

5.3 Results and discussion

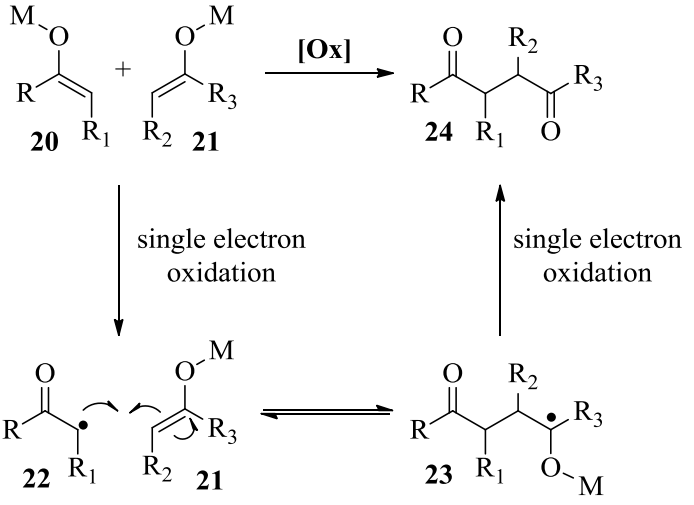
Depending on the conditions of the reaction system, some substrates can either be oxidized to radical cation/radical species, thereby initiating bond-forming events, or act as radicophiles themselves. As depicted in Scheme 5.4, the single electron oxidation of silylenol ether **15** generates radical cation **16**. Coupling with an appropriate radicophile (such as allyltrimethylsilane) and elimination of the silyl group, results in the α-substituted carbonyl product (**17**). Alternatively, if another radical species is present in the reaction mixture, silylenol ether **15** can instead act as a radicophile generating radical intermediate **18**. The single electron oxidation of this radical generates a carbocation which after desilylation produces a different α-substituted carbonyl compound (**19**). With a complete understanding of the important mechanistic factors of a system, new reactions can be designed that proceed through a specific pathway.



Scheme 5.4: Dual nature of silylenol ethers in reactions involving single electron oxidations

As highlighted in the research presented in Chapter 2 of this dissertation, preferential oxidation is one way to influence reaction pathways. Because metal-stabilized enolates are structurally related to silylenol ethers, if two enolates of different stabilities are present, one enolate may be preferentially oxidized to a radical as shown in

Scheme 5.5. Faster oxidation of enolate **20** leads to radical **22**. Preferential reaction of **22** with enolate **21** (as opposed to homodimerization) provides the intermediate **23**. A second single electron oxidation leads to heterodimer **24**. Two enolates that efficiently heterocoupled having very different rates of oxidation would provide strong evidence that preferential oxidation may be involved in the selective formation of heterocoupled products. To test this possibility, the oxidations of several enolates derived from the reaction of ketones, esters, and amides with lithium hexamethyldisilazide (LiHMDS) were examined with cerium(IV) tetra-*n*-butylammonium nitrate (CTAN) using stopped flow spectrophotometry. Surprisingly, all reactions were too fast to monitor and occurred in the mixing time of the instrument even at reduced temperatures. Although these experiments did not provide the expected results, the data suggested that differential rates of oxidation may not provide the basis for the selectivity observed in these oxidative enolate heterocouplings.



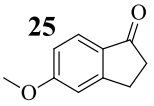
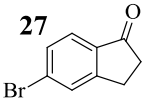
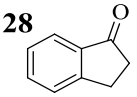
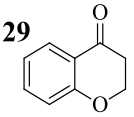
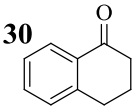
Scheme 5.5: Selective formation of heterocoupled products through preferential oxidation

Careful inspection of the literature describing successful enolate coupling through oxidation reveals a common factor: the use of lithium bases. Lithium coordination to

anions, alkoxides, and carbanions often leads to highly ordered aggregates in solution. The work of Reich[171, 172] and Collum[173-178] has demonstrated that the unique coordination chemistry of lithium is responsible for the reactivity observed when lithium bases are employed as reagents in many bond-forming reactions. Interestingly, Collum *et al.* have shown that equimolar mixtures of two different enolates in tetramethylethylenediamine (TMEDA)/toluene preferentially formed heteroaggregated dimers depending on the steric congestion of the carbonyl precursors.[179] Given these previous findings, spectroscopic and synthetic studies were performed to determine the mechanistic role of lithium aggregation in the non-statistical oxidative heterocoupling of enolates.

Many successful oxidative couplings of enolates are performed in THF.[11-13, 20-24, 165] Collum's work on the impact of solvent on lithium aggregation shows that enolates are tetrameric in THF.[170] Given the complexity of the system, we chose to study the lithium enolate of pinacolone with an equimolar amount of lithium enolates derived from a series of cyclic ketones. Ketones with similar pK_a values were chosen so that rates of enolization and stabilities were comparable. As a consequence, the relative rates of oxidation should be similar as well.[180] Pinacolone was selected as one of the ketone partners because it is sterically bulky and has been shown previously to preferentially form lithium heteroaggregate dimers in TMEDA/toluene.[179] To determine the impact of structure on heteroaggregation of equimolar mixtures of two different lithium enolates, ^{7}Li NMR experiments were performed on a series of ketone-ketone mixtures (Table 5.1). In these experiments, the lithium enolate of pinacolone (**26**) was mixed with an equal amount of another lithium enolate derived from cyclic aryl ketones (**25**, **27-30**).

Table 5.1: Lithium aggregate distributions[a] of equimolar mixtures of enolates[b]

Entry	Ketone A	Ketone B	$\frac{A_2B_2}{A_4 + B_4}$
1	**25** 	**26** 	15.7 : 1
2	**27** 	**26** 	14.7 : 1
3	**28** 	**26** 	14.3 : 1
4	**29** 	**26** 	8.5 :1
5	**30** 	**26** 	4.4 : 1

[a] Distributions obtained by integrating ^{7}Li NMR spectra at -30 ^{o}C
[b] [A] = [B] = 0.15 M and [LiHMDS] = 0.304 M in 2.0 M THF:Toluene

The results of the ^{7}Li NMR experiments revealed several important features of the aggregation of lithium enolates in THF. For all the equimolar enolate mixtures of ketone-ketone partners examined, the lithium aggregates were ensembles of homoaggregated and heteroaggregated tetramers (A_4 : A_3B_1 : A_2B_2 : A_1B_3 : B_4) consistent with those reported by Collum *et al*.[170] As illustrated in Figure 5.2 (Spectrum 1), when lithium enolates of **26** and **28** were generated separately and mixed at -78 ^{o}C, the homotetramer of **28** (A_4) as well as smaller amounts of other aggregates including the homotetramer of **26** (B_4) were the predominant species indicating minimal interaggregate exchange at reduced temperatures. However, upon warming and recooling the solution, the aggregate distribution shifted dramatically to favor the heteroaggregated A_2B_2 tetramer (Figure 5.2,

Spectrum 2). This finding indicates that an energy barrier exists for rearrangement to the more thermodynamically stable enolate heteroaggregates.

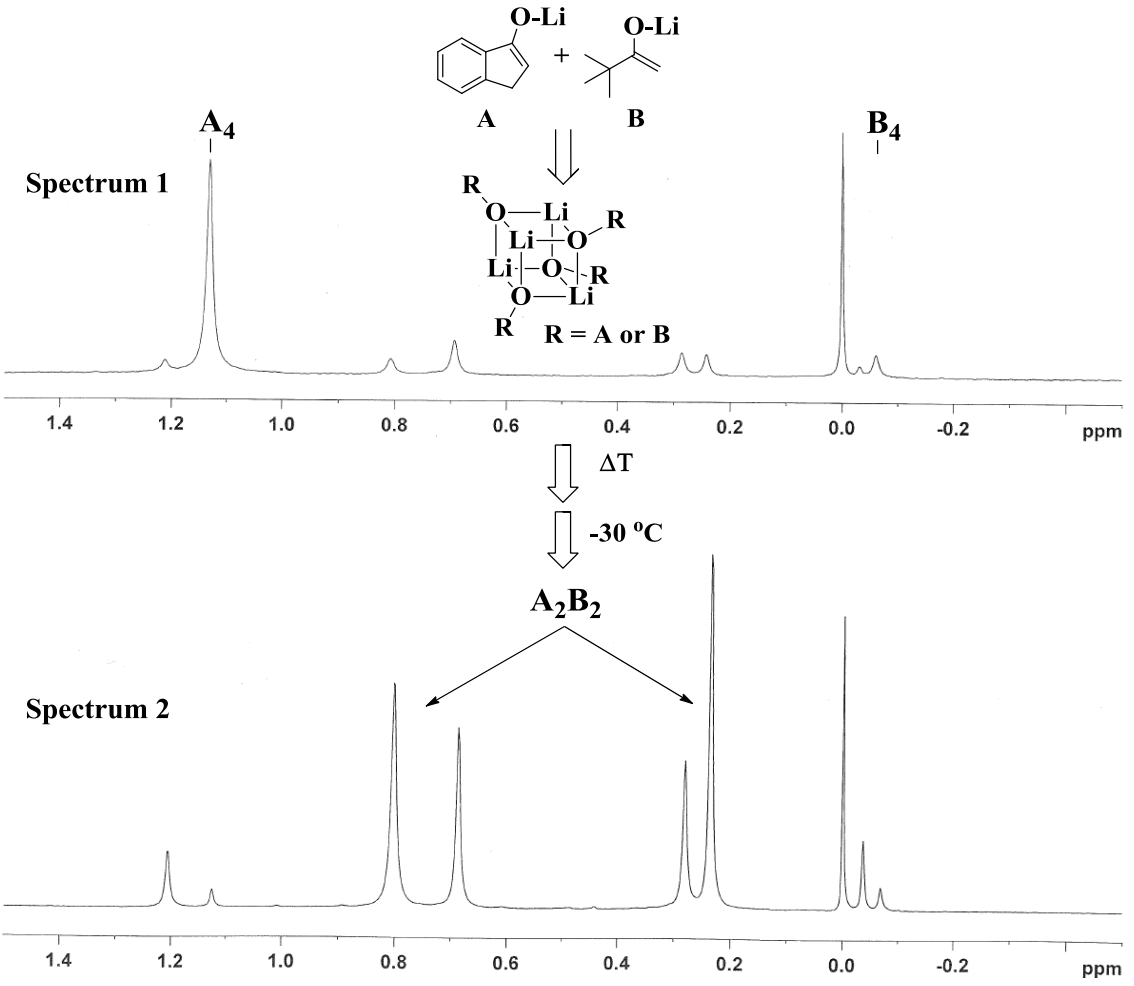


Figure 5.2: ^{7}Li NMR at -30 ^{o}C of 1:1 mixture of **26** and **28** with LiHMDS. Enolized separately and combined at -78 ^{o}C (Spectrum 1). Warming and recooling to -30 ^{o}C (Spectrum 2).

To assess the impact of substrate structure on the heteroaggregate distribution of equimolar mixtures of lithium enolates, the ratio between the most abundant heteroaggregate (A_2B_2) was compared to the individual homotetramers (A_4 and B_4) for every ketone-ketone mixture. As shown in Table 5.1, a unique ratio was obtained for each mixture of lithium enolates. Interestingly, even the ratio for the lithium enolates

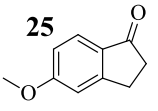
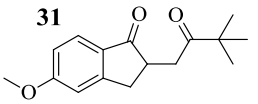
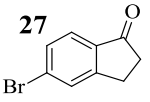
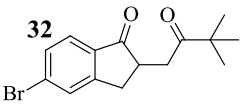
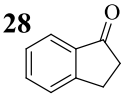
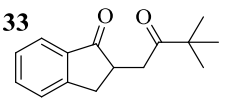
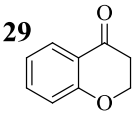
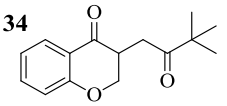
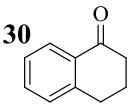
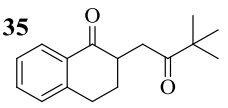
derived from **26** and **30**, which was the lowest of the mixtures examined, was still above the statistically predicted distribution for an ensemble of tetramers. Based on Pascal's triangle, the statistical distribution of an equimolar mixture of two enolates in an ensemble of tetramers should be 1 : 4 : 6 : 4 : 1. For this distribution, the ratio of heteroaggregate A_2B_2 to the homoaggregates A_4 and B_4 would be 3 : 1. While placing substituents on the aromatic ring of ketone A (substrates **25** and **27**) did not significantly impact the lithium aggregation, increasing the size of the adjacent ring (substrates **29** and **30**) greatly reduced the amount of heteroaggregated tetramers. These observations are consistent with Collum's work on lithium heterodimers, which showed that statistically predicted aggregate distributions were obtained when both enolates were sterically bulky.[179]

With the ^{7}Li NMR data in hand, the question remained whether these non-statistical distributions of lithium aggregates are involved in the selective oxidative heterocoupling of lithium enolates. To investigate the role of heteroaggregation, optimal reaction conditions were determined for the coupling of substrates **26** and **28**. By screening several different oxidants, reactions using CTAN and I_2 were found to provide the best yields and reproducibility. Iodine was employed as the oxidant in subsequent reactions (Table 5.2) because it is an attractive oxidant in terms of atom economy in that one equivalent of I_2 carries out two single electron oxidations.[167] Furthermore, oxidations using I_2 benefited from improved synthetic work up procedures because the tetra-*n*-butylammonium counterions of CTAN are lipophilic and act as phase-transfer reagents, complicating reaction workup.

The oxidative coupling of equimolar mixtures of two different enolates preferentially generated the heterocoupled products (Table 5.2). More importantly, in all

cases the product ratio of heterocoupled product to homodimer of **26** was better than statistically predicted (2 : 1). Interestingly, both product yields and selectivity were negatively impacted when LiHMDS was replaced by Na- or KHMDS. In addition, omission of the warming and recooling steps (*vide supra*) prior to oxidation by I_2 dampened product selectivity dramatically. These observations provide strong evidence that not only is the lithium counterion integral to reaction efficiency, but the distribution of lithium homo- and heteroaggregates is as well. It is important to note that the homodimers of ketone A were never observed, and the starting ketones were recovered

Table 5.2: Product distributions from the oxidative coupling of lithium enolates[a]

Entry	Ketone A	Ketone B	Heterocoupled Product	Product Distribution[b]	Yield (%)[c, d]
1	 **25**	 **26**	 **31**	13.8 : 1	62
2	 **27**	 **26**	 **32**	12.8 : 1	58
3	 **28**	 **26**	 **33**	12.4 : 1	62
4	 **29**	 **26**	 **34**	7.0 : 1	46
5	 **30**	 **26**	 **35**	3.0 : 1	47

[a] [A] = [B] = 0.12 M in THF, [LiHMDS] = 0.26 M in THF, [I_2] = 0.12 M in THF
[b] Ratios (heterocoupled product:homodimer of **26**) were determined by ^{1}H NMR. Trace, if any, amounts of homodimer of ketone A were observed by GC and ^{1}H NMR.
[c] Determined by ^{1}H NMR with ± 3% error.
[d] 15-25% of ketone A was recovered in these reactions.

in all cases. While experimental observations indicate that enolates derived from these ketones are oxidized, hydrogen atom abstraction from THF coordinated to the lithium centers of the aggregates becomes a competitive pathway.[167, 171]

With the synthetic studies completed, the degree of lithium enolate heteroaggregation was compared to the product ratios obtained after oxidation. As shown in Figure 5.3, there is a direct, linear correlation between the amount of lithium enolate heteroaggregation and the formation of heterocoupled product. Furthermore, the high degree of correlation between the heteroaggregate content and the degree of heterodimer product suggests that **aggregation is the major driving force for the selective heterocoupling of two different lithium enolates**. In the predominant A_2B_2

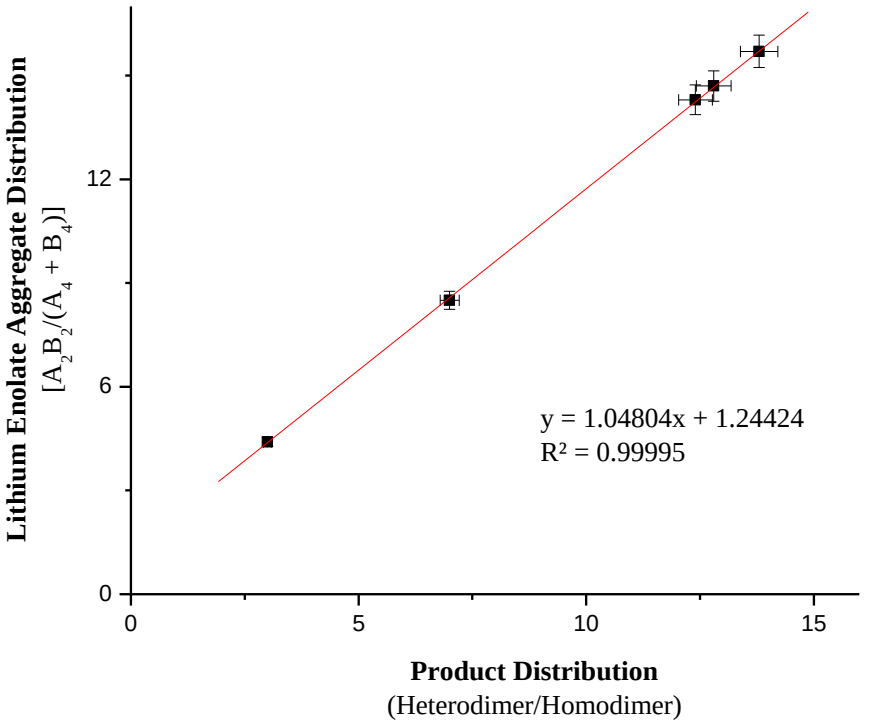


Figure 5.3: Impact of heteroaggregation on the oxidative heterocoupling of lithium enolates

heteroaggregate, two different enolates are tethered to one another in solution. Having these enolates in close proximity transforms a bimolecular oxidative carbon-carbon bond-forming event into a unimolecular process and provides a mechanism for non-statistical heterocoupling. As a consequence, equimolar mixtures of lithium enolates that exist predominantly as heteroaggregated enolates (A_2B_2) generate the most heterocoupled product when oxidized.

Previous coupling reactions performed by both Saegusa[21] and Baran[23, 24] have shown that synthetically useful yields of heterocoupled products can be obtained by employing an excess of one enolate relative to another. To further demonstrate the importance of lithium aggregation in the oxidative coupling of lithium enolates, the ^{7}Li NMR spectra for a 1 : 1 and a 2 : 1 mixture of enolates from substrates **29** and **26** were obtained (Figure 5.4). Spectrum 1 containing equimolar amounts of enolates derived from **26** and **29** exhibits a symmetric distribution of tetrameric aggregates. When oxidized, the heterocoupled product **34** to homodimer of **26** ratio was 7 : 1 (Table 5.2). Spectrum 2 shows the ^{7}Li NMR spectrum of a 2 : 1 ratio of enolates derived from **29** and **26**. Interestingly, the lithium enolate aggregate distribution dramatically shifts for the 2 : 1 mixture to favor A_2B_2 over the homotetramer of **26** (B_4). When the 2 : 1 mixture was oxidized with I_2, the selective formation of **34** improved to 26 : 1, well above the ratio expected from employing a one equivalent excess of **29** relative to **26**. Additionally, the yield of heterocoupled product **34** improved to 60%. The enolate derived from **29** does not tend to homocouple upon oxidation (*vide supra*), and the homotetramer of **26** is drastically reduced in the 2 : 1 mixture. As a consequence, the likelihood of **26** being in close proximity to **29** is significantly increased and the presence of excess A_4 is not

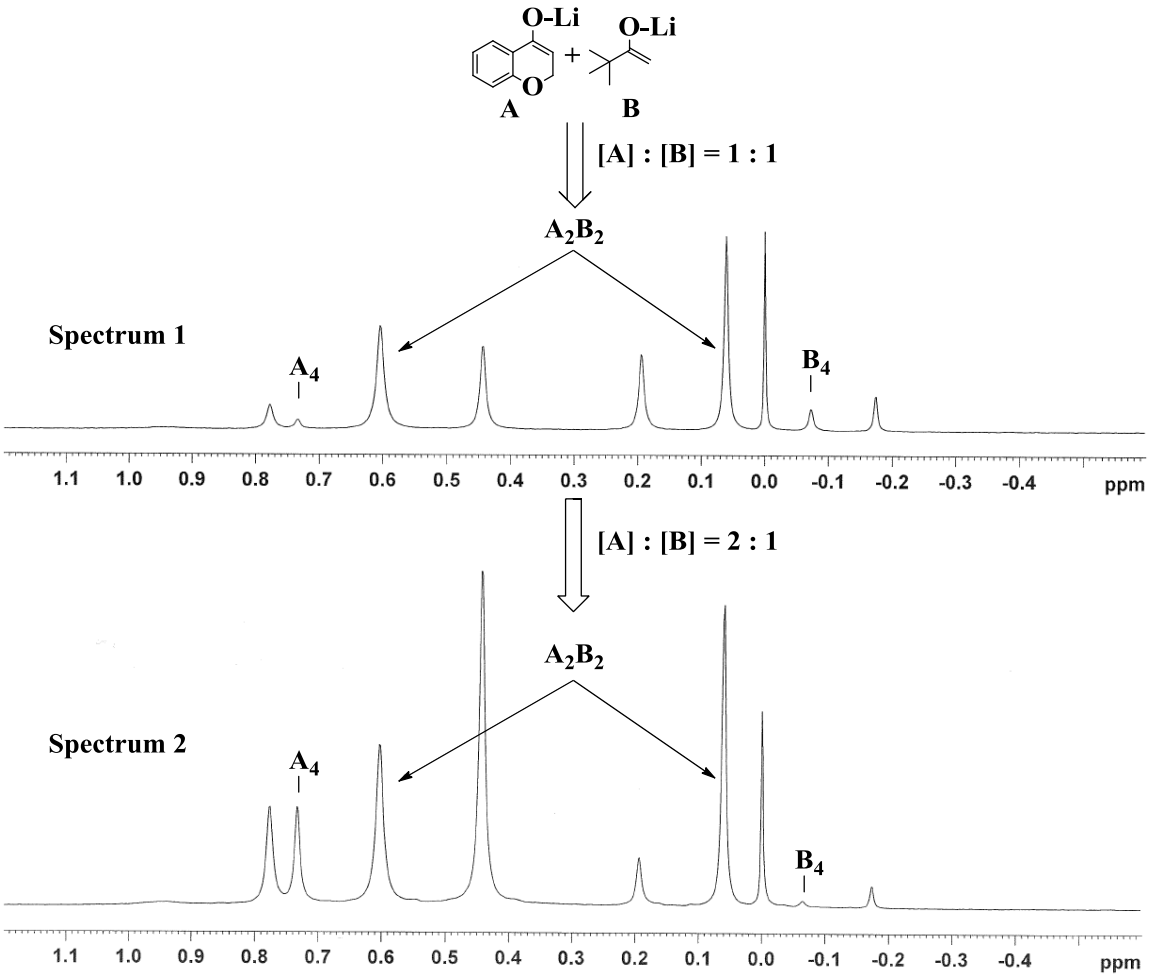


Figure 5.4: ^{7}Li NMR at -30 ^{o}C for 1 : 1 enolate mixture of **26** and **29** (Spectrum 1) and 2 : 1 mixture (Spectrum 2)

detrimental since **29** does not homocouple. This combination of factors leads to the increase in selectivity and yield, reaffirming the integral role that lithium aggregation plays in the oxidative coupling of enolates.

5.4 Conclusions

Taken together, the mechanistic and synthetic experiments described in this chapter have shown the following: 1) Equimolar mixtures of two different lithium enolates are ensembles of tetramers in THF, a finding consistent with the work of Collum.[170] 2) The distribution of homo- and heteroaggregates in THF is dependent on substrate structure. 3) The major component of the mixture is heteroaggregate A_2B_2 when

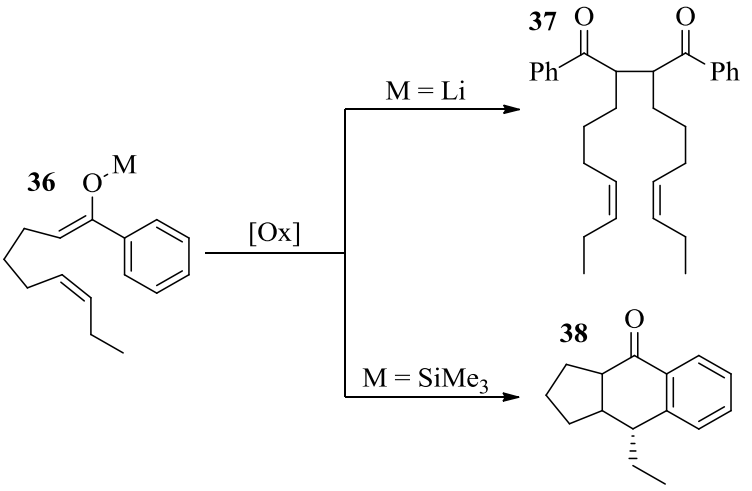
one enolate is sterically encumbered. 4) Single electron oxidation of solutions containing predominantly heteroaggregate A_2B_2 furnish the heterocoupled product selectively. 5) A direct correlation exists between the amount of heteroaggregate A_2B_2 and the ratio of heterocoupled to homocoupled products.

The rational design of efficient syntheses is best facilitated by identifying and understanding the important mechanistic factors involved in the reaction system. Simple empirical models that discount aggregation are often insufficient to explain their role in bond-forming reactions. While a great deal of research has been dedicated to understanding and elucidating the solution structures of lithium complexes, the impact of lithium aggregation on organic reactions is often overlooked. Overall, the results presented herein serve as yet another example of lithium aggregation driving selectivity in organic reactions. The work presented in this chapter was recently submitted to the *Journal of the American Chemical Society*.

5.5 Impact of lithium enolate aggregation on other reaction systems

The data presented in this chapter suggest that the success (or failure) of previously reported reactions proceeding through the single electron oxidation of enolates may be explained by considering the mechanistic role of lithium aggregation. Previous work by Snider *et al.* on the oxidative intramolecular cyclization of metal-stabilized enolates (**36**) with pendent olefins found that discrete products were obtained depending on the metal employed (Scheme 5.6).[181] The expected cyclized product (**38**) was obtained when **36** was a silylenol ether (M = $SiMe_3$) whereas the single electron oxidation of the lithium enolate resulted in homodimer **37**. At the time this work was published, it was suggested that "intramolecular coupling of the enol radical with the alkene cannot

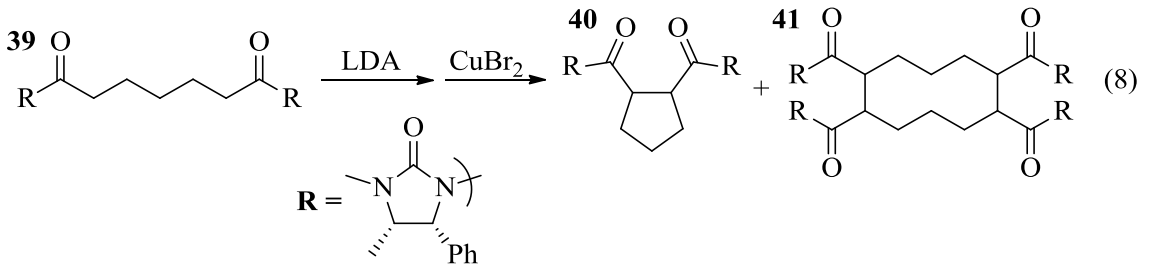
compete with intermolecular coupling with the very reactive enolate."[181] However, given the research detailed in this chapter, it is likely that lithium enolates tethered through an aggregate drive formation of the dimer (**37**), even over the relatively fast intramolecular cyclization with the olefin. Successful cyclization of the silylenol ether can be attributed to the increased steric bulk around the radical intermediate, inhibiting dimerization and allowing intramolecular cyclization with the pendent olefin to occur.



(7)

Scheme 5.6: Competitive dimerization in the oxidative intramolecular cyclization of metal-stabilized enolates with pendant olefins

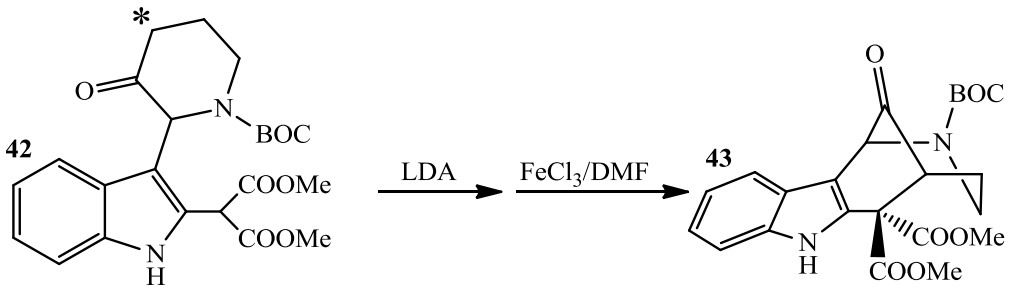
The reaction shown in Scheme 5.7 involves oxidation of the lithium dienolate derived from diamide **39**. When oxidized with excess copper(II) bromide ($CuBr_2$), both the expected cyclopentane product (**40**) and the macrocycle (**41**) were generated in equal amounts.[165] As in the previous example by Snider, the intramolecular cyclization to produce **40** should proceed more readily than dimerization, which is a bimolecular process. However, since the dienolate of **39** is in close proximity to other dienolates through lithium aggregation, the rate of formation of macrocycle **41** through two radical-radical coupling steps is comparable to intramolecular cyclization.



Scheme 5.7: Macrocyclization *versus* intramolecular cyclization of substrate **39**

As a final example, Scheme 5.8 depicts an intramolecular cyclization developed by Overman *et al.* involving the Fe(III)-mediated oxidative coupling of lithium enolates derived from a ketone and a diester (**42**).[15] Interestingly, the intermolecular dimerization at the "*" position of the lithium dienolate was found to be a competing process. While optimizing the production of **43**, they noticed that the intramolecular cyclization to **43** improved as the dienolate concentration was *increased.*[15] This finding is seemingly at odds with a classic bimolecular process in which *dimerization* should increase as the concentration of enolates is increased. Although Overman's system is expected to be more complex than the lithium enolate mixtures detailed in this chapter, a plausible mechanism involving lithium aggregation can be envisioned for the observed inverse relationship between dimerization and concentration. If the lithium dienolate of **42** is in a homoaggregated state, intermolecular dimerization becomes a competing pathway to the intramolecular cyclization at low enolate concentrations. However, as the dienolate concentration increases, the amine concentration (from LDA) increases as well. Previously, Collum *et al*. have shown in some systems that diisopropylamine (or LDA) is able to form mixed aggregates with simple lithium enolates.[170, 173, 182] If more mixed amine-enolate aggregates are formed at higher concentrations, the dienolate should be

more "monomeric" in nature, which would facilitate the intramolecular cyclization to **43** becoming the dominant reaction pathway.



Scheme 5.8: Concentration dependent intramolecular cyclization of enolates derived from a ketone and a diester

5.6 Spectral data

5.6.1 ^{7}Li NMR spectra of lithium enolate aggregates

5-Methoxy1-indanone (**A**) with pinacolone (**B**)

Procedure 5.2.3.1 was followed. ^{7}Li NMR (2.0M THF/toluene, 194 MHz, shifts relative to 0.3M LiCl in CD_3OD) – δ 1.18 (A_3**B**$_1$), 1.12 (**A**$_4$), 0.79 (**A**$_2$B$_2$), 0.69 (**A**$_3$B$_1$), 0.27 (A_1**B**$_3$), 0.24 (A_2**B**$_2$), -0.03 (**A**$_1$B$_3$), -0.07 (**B**$_4$).

5-Bromo-1-indanone (**A**) and pinacolone (**B**)

Procedure 5.2.3.1 was followed. ^{7}Li NMR (2.0M THF/toluene, 194 MHz, shifts relative to 0.3M LiCl in CD_3OD) – δ 0.99 (A_3**B**$_1$), 0.88 (**A**$_4$), 0.66 (**A**$_2$B$_2$), 0.51 (**A**$_3$B$_1$), 0.20 (A_1**B**$_3$), 0.12 (A_2**B**$_2$), -0.06 (**B**$_4$), -0.09 (**A**$_1$B$_3$).

1-Indanone (**A**) and pinacolone (**B**)

Procedure 5.2.3.1 was followed. ^{7}Li NMR (2.0M THF/toluene, 194 MHz, shifts relative to 0.3M LiCl in CD_3OD) – δ 1.21 (A_3**B**$_1$), 1.13 (**A**$_4$), 0.80 (**A**$_2$B$_2$), 0.69 (**A**$_3$B$_1$), 0.28 (A_1**B**$_3$), 0.24 (A_2**B**$_2$), -0.04 (**A**$_1$B$_3$), -0.07 (**B**$_4$).

4-Chromanone (**A**) and pinacolone (**B**)

Procedure 5.2.3.1 was followed. ^{7}Li NMR (2.0M THF/toluene, 194 MHz, shifts relative to 0.3M LiCl in CD_3OD) – δ 0.78 ($A_3\mathbf{B_1}$), 0.73 ($\mathbf{A_4}$), 0.60 ($\mathbf{A_2}B_2$), 0.44 ($\mathbf{A_3}B_1$), 0.20 ($A_1\mathbf{B_3}$), 0.06 ($A_2\mathbf{B_2}$), -0.07 ($\mathbf{B_4}$), -0.17 ($\mathbf{A_1}B_3$).

1-Tetralone (**A**) and pinacolone (**B**)

Procedure 5.2.3.1 was followed. ^{7}Li NMR (2.0M THF/toluene, 194 MHz, shifts relative to 0.3M LiCl in CD_3OD) – δ 0.97 ($A_3\mathbf{B_1}$), 0.95 ($\mathbf{A_4}$), 0.70 ($\mathbf{A_2}B_2$), 0.61 ($\mathbf{A_3}B_1$), 0.27 ($A_1\mathbf{B_3}$), 0.19 ($A_2\mathbf{B_2}$), -0.06 ($\mathbf{A_1}B_3$), -0.10 ($\mathbf{B_4}$).

5.6.2 Synthesis and spectral data for heterocoupled products

2-(3,3-Dimethyl-2-oxobutyl)-5-methoxy-indan-1-one (**31**)

Procedure 5.2.3.2 was followed. Clear, colorless oil. 62% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) – δ 7.68-7.63 (m, 1H), 6.89-6.84 (m, 1H), 6.84-6.81 (m, 1H), 3.84 (s, 3H), 3.38 (dd, 1H, *J* = 7.8 Hz, 17.7 Hz), 3.16 (dd, 1H, *J* = 3.4 Hz, 18.3 Hz), 3.01-2.94 (m, 1H), 2.75 (dd, 1H, 9.5 Hz, 18.3 Hz), 2.56 (dd, 1H, *J* = 4.2 Hz, 17.2 Hz), 1.13 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 214.2, 206.3, 165.3, 156.5, 129.8, 125.4, 115.3, 109.5, 55.6, 43.9, 43.0, 38.4, 33.6, 26.4. MS [*m*/*z* (rel int)] 260 (M^+, 9), 203 (22), 175 (100), 161 (10), 147 (36), 131 (9), 115 (13), 103 (11), 91 (12), 77 (9), 57 (31) . LC-HRMS calcd. for $C_{16}H_{21}O_3$ [M+H] 261.1485, found 261.1480.

5-Bromo-2-(3,3-dimethyl-2-oxobutyl)-indan-1-one (**32**)

Procedure 5.2.3.2 was followed. Light yellow oil. 58% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) – δ 7.63-7.57 (m, 2H), 7.51-7.46 (m, 1H), 3.39 (dd, 1H, *J* = 8.0 Hz, 17.3 Hz), 3.18 (dd, 1H, *J* = 2.7 Hz, 17.7 Hz), 2.97-2.92 (m, 1H), 2.88 (dd, 1H, *J* = 8.3 Hz, 18.0 Hz), 2.64 (dd, 1H, *J* = 4.4 Hz, 17.5 Hz) 1.14 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 213.9, 206.8, 155.0, 135.5, 131.0, 130.0, 129.8, 125.0, 43.9, 43.0, 38.0, 33.0, 26.5. MS [*m*/*z* (rel

int)] 308/310 (M^+, 9), 251/253 (29), 223/225 (76), 145 (22), 115 (88), 89 (21), 57 (100). LC-HRMS calcd. for $C_{15}H_{18}BrO_2$ [M+H] 309.0485, found 309.0462.

2-(3,3-Dimethyl-2-oxobutyl)-indan-1-one (**33**)

Procedure 5.2.3.2 was followed. Clear, colorless oil. 62% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) – δ 7.80-7.75 (m, 1H), 7.62-7.56 (m, 1H), 7.47-7.43 (m, 1H), 7.41-7.35 (m, 1H), 3.46 (dd, 1H, J = 8.0 Hz, 17.2 Hz), 3.22 (dd, 1H, J = 3.4 Hz, 18.5 Hz), 3.05-2.98 (m, 1H), 2.86 (dd, 1H, J = 8.8 Hz, 18.5 Hz), 2.67 (dd, 1H, J = 4.6 Hz, 17.6 Hz), 1.18 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 214.1, 208.2, 153.5, 136.6, 134.7, 127.4, 126.5, 123.8, 44.0, 43.0, 38.2, 33.5, 26.5. MS [*m*/*z* (rel int)] 230 (M^+, 8), 173 (16), 145 (100), 131 (11), 115 (67), 91 (21), 57 (27). LC-HRMS calcd. for $C_{15}H_{19}O_2$ [M+H] 231.1380, found 231.1383.

3-(3,3-Dimethyl-2-oxobutyl)-chroman-4-one (**34**)

Procedure 5.2.3.2 was followed. Off-white solid. 46% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) – δ 7.88-7.83 (m, 1H), 7.49-7.42 (m, 1H), 7.03-6.97 (m, 1H), 6.97-6.92 (m, 1H), 4.48 (dd, 1H, J = 5.2 Hz, 11.1 Hz), 4.20 (t, 1H, J = 11.3 Hz), 3.42-3.35 (m, 1H), 3.10 (dd, 1H, J = 4.4 Hz, 18.4 Hz), 2.57 (dd, 1H, J = 8.0 Hz, 18.1 Hz), 1.18 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 212.9, 193.7, 161.8, 135.9, 127.3, 121.4, 120.7, 117.8, 70.3, 44.3, 41.7, 32.6, 26.5. MS [*m*/*z* (rel int)] 246 (M^+, 3), 189 (100), 171 (9), 161 (24), 147 (40), 133 (6), 121 (16), 92 (14), 57 (36). LC-HRMS calcd. for $C_{15}H_{19}O_3$ [M+H] 247.1329, found 247.1330.

2-(3,3-Dimethyl-2-oxobutyl)-tetral-1-one (**35**)

Procedure 5.2.3.2 was followed. Light yellow oil. 47% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) – δ 8.01-7.96 (m, 1H), 7.47-7.40 (m, 1H), 7.30-7.25 (m, 1H), 7.23-7.19 (m,

1H), 3.26 (dd, 1H, J = 5.1 Hz, 18.0 Hz), 3.17-3.06 (m, 2H), 2.96-2.89 (m, 1H), 2.56 (dd, 1H, J = 6.8 Hz, 18.1 Hz), 2.15-2.08 (m, 1H), 1.89 (dddd, 1H, J = 4.4 Hz, 12.9 Hz, 13.7 Hz, 13.1 Hz) 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) – δ 214.2, 199.3, 144.1, 133.2, 132.4, 128.7, 127.4, 126.6, 44.2, 43.8, 37.4, 29.4, 26.5. MS [m/z (rel int)] 244 (M^+, 1) 187 (100), 169 (16), 159 (5), 145 (11), 131 (27), 115 (11), 91 (16), 57 (21). LC-HRMS calcd. for $C_{16}H_{21}O_2$ [M+H] 245.1536, found 245.1519.

References

1. Faraday, M. *Philosophical Transactions of the Royal Society of London.* **1834,** *124,* 77.

2. Kolbe, H. *Justus Liebigs Ann. Chem.* **1849,** *69,* 257.

3. Vijh, A.K.; Conway, B. E. *Chem. Rev.* **1967,** *67,* 623.

4. Walling C. *Free radicals in solution*. Wiley; Chapman & Hall; **1957**.

5. Jahn, U.; Hartmann, P. *Journal of the Chemical Society-Perkin Transactions 1.* **2001,** 2277.

6. Correa, A.; Mancheno, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008,** *37,* 1108.

7. Jahn, U.; Hartmann, P.; Kaasalainen, E. *Org. Lett.* **2004,** *6,* 257.

8. Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. *European Journal of Organic Chemistry.* **2001,** 3333.

9. Jahn, U.; Hartmann, P. *Chem. Commun.* **1998,** 209.

10. Jahn, U.; Dinca, E. *Chemistry: A European Journal.* **2009,** *15,* 58.

11. Paquette, L.A.; Bzowej, E. I.; Branan, B. M.; Stanton, K. J. *J. Org. Chem.* **1995,** *60,* 7277.

12. Frazier, R.H.; Harlow, R. L. *J. Org. Chem.* **1980,** *45,* 5408.

13. Csaky, A.G.; Plumet, J. *Chem. Soc. Rev.* **2001,** *30,* 313.

14. Baran, P.S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006,** *128,* 8678.

15. Martin, C.L.; Overman, L. E. Rohde, J. M. *J. Am. Chem. Soc.* **2010,** *132,* 4894.

16. Schmittel, M.; Haeuseler, A. *Zeitschrift Fur Naturforschung Section B-a Journal of Chemical Sciences.* **2003,** *58,* 211.

17. Chen, Y.; Yekta, S. Yudin, A. K. *Chem. Rev.* **2003,** *103,* 3155.

18. Kirchgessner, M.; Sreenath, K.; Gopidas, K. R. *J. Org. Chem.* **2006,** *71,* 9849.

19. Richter, J.M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007,** *129,* 12857.

20. Kobayashi, Y.; Taguchi, T.; Morikawa, T.; Tokuno, E. Sekiguchi, S. *Chem. Pharm. Bull.* **1980,** *28,* 262.

21. Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977,** *99,* 1487.

22. Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975,** *97,* 2912.

23. DeMartino, M.P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008,** *130,* 11546.

24. Baran, P.S.; DeMartino, M. P. *Angew. Chem. Int. Ed.* **2006,** *45,* 7083.

25. Snider, B.B. *Tetrahedron.* **2009,** *65,* 10738.

26. Snider, B.B.; Mccarthy, B. A. *J. Org. Chem.* **1993,** *58,* 6217.

27. Curry, L.; Hallside, M. S.; Powell, L. H.; Sprague, S. J.; Burton, J. W. *Tetrahedron.* **2009,** *65,* 10882.

28. Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron.* **2009,** *65,* 10797.

29. Huang, W.; Singh, O. V.; Chen, C.; Lee, S. *Helv. Chim. Acta.* **2004,** *87,* 167.

30. Dohi, T.; Ito, M.; Morimoto, K.; Wata, M.; Kita, Y. *Angew. Chem. Int. Ed.* **2008,** *47,* 1301.

31. Ladziata, U.; Zhdankin, V. V. *ARKIVOC.* **2006,** 26.

32. Nicolaou, K.C.; Zhong, Y. L.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000,** *39,* 625.

33. Nicolaou, K.C.; Baran, P. S.; Kranich, R.; Zhong, Y. L.; Sugita, K.; Zou, N. *Angew. Chem. Int. Ed.* **2001,** *40,* 202.

34. Nicolaou, K.C.; Baran, P. S.; Zhong, Y. L.; Vega, J. A. *Angew. Chem. Int. Ed.* **2000,** *39,* 2525.

35. Janza, B.; Studer, A. *J. Org. Chem.* **2005,** *70,* 6991.

36. Moeller, K.D. *Tetrahedron.* **2000,** *56,* 9527.

37. Kurihara, H.; Fuchigami, T.; Tajima, T. *J. Org. Chem.* **2008,** *73,* 6888.

38. Lebreux, F.; Buzzo, F.; Marko, I. E. *Synlett.* **2008,** 2815.

39. Bui, N.; Ho, X.; Mho, S.; Jang, H. *European Journal of Organic Chemistry.* **2009,** 5309.

40. Ho, X.; Mho, S.; Kang, H.; Jang, H. *European Journal of Organic Chemistry.* **2010,** *2010,* 4436.

41. Moeller T. *The chemistry of the lanthanides*. New York, NY: Reinhold; **1963**.

42. Falconnet, P. *J. Alloys Compounds.* **1993**, *192,* 114.

43. Emsley J. *The elements*. 3rd ed. New York, NY: Oxford University Press, Inc.; **2000**.

44. Steel, P.G. *Journal of the Chemical Society-Perkin Transactions 1.* **2001,** 2727.

45. Anwander, R. *Lanthanides: Chemistry and use in organic synthesis*. Kobayashi S, editor. New York, NY: Springer-Verlag; **1999**.

46. Danishefsky, S.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1984,** *106,* 2453.

47. Wenzel, T.J.; Morin, C. A.; Brechting, A. A. *J. Org. Chem.* **1992,** *57,* 3594.

48. Nair, V.; Deepthi, A. *Chem. Rev. (Washington, DC, US).* **2007,** *107,* 1862.

49. Nair, V.; Deepthi, A. *Tetrahedron.* **2009,** *65,* 10745.

50. Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2004,** *37,* 21.

51. Nair, V.; Panicker, S. B.; Nair, L. G.; George, T. G.; Augustine, A. *Synlett.* **2003,** 156.

52. Nair, V.; Mathew, J.; Prabhakaran, J. *Chem. Soc. Rev.* **1997,** *26,* 127.

53. Molander, G.A. *Chem. Rev.* **1992,** *92,* 29.

54. Fischer, A.; Henderson, G. N. *Synthesis-Stuttgart.* **1985,** 641.

55. Mehdi, H.; Bodor, A.; Lantos, D.; Horvath, I. T.; De Vos, D. E.; Binnemans, K. *J. Org. Chem.* **2007,** *72,* 517.

56. Ho, T.L.; Wong, C. M. *Synthesis-International Journal of Methods in Synthetic Organic Chemistry.* **1972,** 561.

57. Hwu, J.R.; Jain, M. L.; Tsai, F. Y.; Tsay, S. C.; Balakumar, A.; Hakimelahi, G. H. *J. Org. Chem.* **2000,** *65,* 5077.

58. Han, G.; Tamaki, M.; Hruby, V. J. *The Journal of Peptide Research.* **2001,** *58,* 338.

59. Jih Ru Hwu, ; Jain, M. L.; Shwu-Chen, T.; Hakimelahi, G. H. *Tetrahedron Lett.* **1996,** *37,* 2035.

60. Hata, S.; Iguchi, M.; Iwasawa, T.; Yamada, K.; Tomioka, K. *Org. Lett.* **2004,** *6,* 1721.

61. Maulide, N.; Vanherck, J.; Gautier, A.; Marko, I. E. *Acc. Chem. Res.* **2007,** *40,* 381.

62. Paolobelli, A.; Ceccherelli, P.; Pizzo, F.; Ruzziconi, R. *J. Org. Chem.* **1995,** *60,* 4954.

63. Zhang, Y.; Raines, A. J.; Flowers, R. A. *J. Org. Chem.* **2004,** *69,* 6267.

64. Zhang, Y.; Raines, A. J.; Flowers, R. A. *Org. Lett.* **2003,** *5,* 2363.

65. Devery,James J.,,III; Mohanta, P. K.; Casey, B. M.; Flowers, R. A.,II. *Synlett.* **2009,** 1490.

66. Beeson, T.D.; Mastracchio, A.; Hong, J.; Ashton, K.; MacMillan, D. W. C. *Science.* **2007,** *316,* 582.

67. Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008,** *130,* 398.

68. Jang, H.; Hong, J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007,** *129,* 7004.

69. Devery,James J.,,III; Conrad, J. C.; MacMillan, D. W. C.; Flowers, R. A.,II. *Angew. Chem. Int. Ed.* **2010,** *49,* 6106.

70. Magnus, P.; Barth, L. *Tetrahedron.* **1995,** *51,* 11075.

71. Asakura, J.; Robins, M. *J. Org. Chem.* **1990,** *55,* 4928.

72. Jiao, J.; Nguyen, L. X.; Patterson, D. R.; Flowers, R. A. *Org. Lett.* **2007,** *9,* 1323.

73. Chiba, S.; Cao, Z. Y.; El Bialy, S. A. A.; Narasaka, K. *Chem. Lett.* **2006,** *35,* 18.

74. Vanwijngaarden, I.; Kruse, C. G.; Vanderheyden, J. A. M.; Tulp, M. T. M. *J. Med. Chem.* **1988,** *31,* 1934.

75. Iorio, M.A.; Paszkowska Reymer, T.; Frigeni, V. *J. Med. Chem.* **1987,** *30,* 1906.

76. Chen, C.; Jiang, Y.; Lu, K.; Daniewska, I.; Mazza, C. G.; Negron, L.; Forray, C.; Parola, T.; Li, B.; Hegde, L. G.; Wolinsky, T. D.; Craig, D. A.; Kong, R.; Wetzel, J. M.; Andersen, K.; Marzabadi, M. R. *J. Med. Chem.* **2007,** *50,* 3883.

77. Roman, B.I.; De Kimpe, N.; Stevens, C. V. *Chem. Rev.* **2010,** *110,* 5914.

78. Uchida, M.; Komatsu, M.; Morita, S.; Kanbe, T.; Yamasaki, K.; Nakagawa, K. *Chem. Pharm. Bull.* **1989,** *37,* 958.

79. Sato, M.; Tagawa, H.; Kosasayama, A.; Uchimaru, F.; Kojima, H.; Yamasaki, T.; Sakurai, T. *Chem. Pharm. Bull.* **1978,** *26,* 3296.

80. Eberle, M.K.; Kahle, G. G. *Tetrahedron Lett.* **1980,** *21,* 2303.

81. Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003,** *125,* 14726.

82. Hahn, R.C.; Corbin, T. F.; Shechter, H. *J. Am. Chem. Soc.* **1968,** *90,* 3404.

83. Celebi, S.; Leyva, S.; Modarelli, D. A.; Platz, M. S. *J. Am. Chem. Soc.* **1993,** *115,* 8613.

84. Nair, V.; Panicker, S. B.; Augustine, A.; George, T. G.; Thomas, S.; Vairamani, M. *Tetrahedron.* **2001,** *57,* 7417.

85. Solomons, T.W.G.; Fryhle, C.B. *Organic chemistry*. 8th ed. Brennan, D, editor. Hoboken, NJ, USA: Wiley; **2004**.

86. Singh, P.N.D.; Muthukrishnan, S.; Murthy, R. S.; Klima, R. F.; Mandel, S. M.; Hawk, M.; Yarbrough, N.; Gudmundsdottir, A. D. *Tetrahedron Lett.* **2003,** *44,* 9169.

87. Iida, S.; Togo, H. *Synlett.* **2008,** 1639.

88. Jiao, J.; Zhang, Y.; Devery, J. J.; Xu, L.; Deng, J.; Flowers, R. A. *J. Org. Chem.* **2007,** *72,* 5486.

89. Casey, B. M.; Eakin, C. A.; Flowers, R. A.,II. *Tetrahedron Lett.* **2009,** *50,* 1264.

90. Anjaiah, S.; Chandrasekhar, S.; Gree, R. *Advanced Synthesis & Catalysis.* **2004,** *346,* 1329.

91. Ju, Y.H.; Varma, R. S. *Green Chem.* **2004,** *6,* 219.

92. Reichardt C. *Solvents and solvent effects in organic chemistry*. 3rd ed. Weinheim, Germany: Wiley-VCH; **2003**.

93. Bertho, A. *Annalen Der Chemie-Justus Liebig.* **1968,** *714,* 155.

94. Duggan, P.G.; Murphy, W. S. *Journal of the Chemical Society-Perkin Transactions 2.* **1975,** 1291.

95. Herges, R.; Ugi, I. *Angew. Chem. Int. Ed.* **1985,** *24,* 594.

96. Frimer, A.A. *Chem. Rev.* **1979,** *79,* 359.

97. Jefford, C.W.; Kohmoto, S. *Helv. Chim. Acta.* **1982,** *65,* 133.

98. Jefford, C.W.; Grant, H. G.; Jaggi, D.; Boukouvalas, J.; Kohmoto, S. *Helv. Chim. Acta.* **1984,** *67,* 2210.

99. Frimer, A.A.; Bartlett, P. D.; Boschung, A. F.; Jewett, J. G. *J. Am. Chem. Soc.* **1977,** *99,* 7977.

100. Grob, C.A.; Schiess, P. W. *Angew. Chem. Int. Ed.* **1967,** *6,* 1.

101. Avraamid, J.; Parker, A. J. *Tetrahedron Lett.* **1971,** 4043.

102. Krishnamurthy, S. *J. Org. Chem.* **1980,** *45,* 2550.

103. Muathen, H.A. *Indian Journal of Chemistry Section B-Organic Chemistry Including Medicinal Chemistry.* **1991,** *30,* 522.

104. Baciocchi, E.; Ruzziconi, R. *J. Org. Chem.* **1991,** *56,* 4772.

105. Baciocchi, E.; Giese, B.; Farshchi, H.; Ruzziconi, R. *J. Org. Chem.* **1990,** *55,* 5688.

106. Heiba, E.I.; Dessau, R. M. *J. Org. Chem.* **1974,** *39,* 3456.

107. Baciocchi, E.; Ruzziconi, R. *J. Org. Chem.* **1986,** *51,* 1645.

108. Hwu, J.; Chen, C. Shiao, S. *J. Org. Chem.* **1995,** *60,* 856.

109. Graham, T.H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008,** *130,* 16494.

110. Davies, H.M.L.; Ahmed, G.; Calvo, R. L.; Churchill, M. R.; Churchill, D. G. *J. Org. Chem.* **1998,** *63,* 2641.

111. Gais, H.J.; Reddy, L. R.; Babu, G. S.; Raabe, G. *J. Am. Chem. Soc.* **2004,** *126,* 4859.

112. Weng, J.R.; Tsao, L. T.; Wang, J. P.; Wu, R. R.; Lin, C. N. *J. Nat. Prod.* **2004,** *67,* 1796.

113. Yang, F.; Trost, M.; Fristad, W. *Tetrahedron Lett.* **1987,** *28,* 1493.

114. Garzino, F.; Meou, A.; Brun, P. *European Journal of Organic Chemistry.* **2003,** 1410.

115. Garzino, F.; Meou, A.; Brun, P. *Tetrahedron Lett.* **2002,** *43,* 5049.

116. Schmittel, M.; Burghart, A. *Angew. Chem. Int. Ed.* **1997,** *36,* 2550.

117. Courtneidge, J.; Davies, A. *Acc. Chem. Res.* **1987,** *20,* 90.

118. Schepp, N.P. *J. Org. Chem.* **2004,** *69,* 4931.

119. Dombrowski, G.W.; Dinnocenzo, J. P.; Zielinski, P. A.; Farid, S.; Wosinska, Z. M.; Gould, I. R. *J. Org. Chem.* **2005,** *70,* 3791.

120. Bietti, M.; Capone, A. *J. Org. Chem.* **2006,** *71,* 5260.

121. Cook, G.; Feltman, P. M. *J. Chem. Educ.* **2007,** *84,* 1827.

122. Schmittel, M.; Gescheidt, G.; Rock, M. *Angew. Chem. Int. Ed.* **1994,** *33,* 1961.

123. Bockman, T.M.; Shukla, D.; Kochi, J. K. *Journal of the Chemical Society-Perkin Transactions 2.* **1996,** 1623.

124. Schmittel, M.; Heinze, J.; Trenkle, H. *J. Org. Chem.* **1995,** *60,* 2726.

125. Casey, B.M.; Eakin, C. A.; Jiao, J.; Sadasivam, D. V.; Flowers, R. A. *Tetrahedron.* **2009,** *65,* 10762.

126. Casey, B.M.; Eakin, C. A.; Jiao, J.; Sadasivam, D. V.; Flowers, R.A. *Tetrahedron.* **2010,** *66,* 5719.

127. Roy, S.C.; Mandal, P. K. *Tetrahedron.* **1996,** *52,* 12495.

128. Roy, S.C.; Mandal, P. K. *Tetrahedron.* **1996,** *52,* 2193.

129. Citterio, A.; Sebastiano, R.; Marion, A. Santi, R. *J. Org. Chem.* **1991,** *56,* 5328.

130. Lee, Y.R.; Kim, B. S.; Kim, D. H. *Tetrahedron.* **2000,** *56,* 8845.

131. Lee, Y.R.; Kim, B. S. *Tetrahedron Lett.* **1997,** *38,* 2095.

132. Zhang, Y.; Jiao, J.; Flowers, R. A. *J. Org. Chem.* **2006,** *71,* 4516.

133. Citterio, A.; Pesce, L.; Sebastiano, R.; Santi, R. *Synthesis-Stuttgart.* **1990,** 142.

134. Jamie, J.F.; Rickards, R. W. *Journal of the Chemical Society-Perkin Transactions 1.* **1996,** 2603.

135. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery J, J. A., Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, and Pople JA. Gaussian 03, revision C.02. Wallingford, CT: Gaussian, Inc.; **2004**.

136. Huckin, S.N.; Weiler, L. *J. Am. Chem. Soc.* **1974,** *96,* 1082.

137. Conrad, J.C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009,** *131,* 11640.

138. Um, J.M.; Gutierrez, O.; Schoenebeck, F.; Houk, K. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010,** *132,* 6001.

139. Nicolaou, K.C.; Reingruber, R.; Sarlah, D.; Braese, S. *J. Am. Chem. Soc.* **2009,** *131*, 6640.

140. Nicolaou, K.C.; Reingruber, R.; Sarlah, D.; Braese, S. *J. Am. Chem. Soc.* **2009,** *131*, 2086.

141. Fristad, W.E.; Hershberger, S. S. *J. Org. Chem.* **1985,** *50,* 1026.

142. Corey, E.J.; Kang, M. C. *J. Am. Chem. Soc.* **1984,** *106*, 5384.

143. Goswami, P.; Chowdhury, P. *New Journal of Chemistry.* **2000,** *24,* 955.

144. Iranpoor, N.; Shekarriz, M. *Bull. Chem. Soc. Jpn.* **1999,** *72,* 455.

145. Pan, W.B.; Chang, F. R.; Wei, L. M.; Wu, M. J.; Wu, Y. C. *Tetrahedron Lett.* **2003,** *44*, 331.

146. Quang, D.N.; Hashimoto, T.; Tanaka, M.; Baumgartner, M.; Stadler, M.; Asakawa, Y. *J. Nat. Prod.* **2002,** *65,* 1869.

147. Seephonkai, P.; Sangdee, A.; Bunchalee, P.; Pyne, S. G. *J. Nat. Prod.* **2009,** *72*, 1892.

148. Ghoneim, O.M.; Legere, J. A.; Golbraikh, A.; Tropsha, A.; Booth, R. G. *Bioorg. Med. Chem.* **2006,** *14*, 6640.

149. Kokpol, U.; Thebpatiphat, S.; Boonyaratavej, S.; Chedchuskulcai, V.; Ni, C. Z.; Clardy, J.; Chaichantipyuth, C.; Chittawong, V.; Miles, D. H. *J. Nat. Prod.* **1990,** *53,* 1148.

150. Carreno, M.C.; Garcia-Cerrada, S.; Urbano, A. *J. Am. Chem. Soc.* **2001,** *123,* 7929.

151. Silveira, C.C.; Braga, A. L.; Kaufman, T. S.; Lenardao, E. J. *Tetrahedron.* **2004,** *60,* 8295.

152. Hon, Y.; Devulapally, R. *Tetrahedron Lett.* **2009,** *50,* 2831.

153. Mander, L.N.; Thomson, R. J. *Org Lett.* **2003,** *5,* 1321.

154. Furusaki, A.; Matsumoto, T.; Ogura, H.; Takayanagi, H.; Hirano, A.; Omura, S. *Chem. Commun.* **1980,** 698.

155. Omura, S.; Hirano, A.; Iwai, Y.; Masuma, R. *J Antibiot.* **1979,** *32,* 786.

156. Kosuge, T.; Tsuji, K.; Hirai, K.; Yamaguchi, K.; Okamoto, T.; Iitaka, Y. *Tetrahedron Lett.* **1981,** *22,* 3417.

157. Whittaker, M.; Floyd, C. D.; Brown, P. Gearing, A. J. H. *Chem Rev.* **1999,** *99,* 2735.

158. Fujisawa, T.; Igeta, K.; Odake, S.; Morita, Y.; Yasuda, J. Morikawa, T. *Bioorg Med Chem.* **2002,** *10,* 2569.

159. Hoffmann, R. *Synthesis.* **2006,** *2006,* 3531.

160. Young, I.S.; Baran, P. S. *Nature Chemistry.* **2009,** *1,* 193.

161. Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010,** *75,* 4657.

162. Shen, Z.; Goh, K. K. K.; Cheong, H.; Wong, C. H. A.; Lai, Y.; Yang, Y.; Loh, T. *J. Am. Chem. Soc.* **2010,** *132,* 15852.

163. Setzer, P.; Beauseigneur, A.; Pearson-Long, M. S. M.; Bertus, P. *Angew. Chem. Int. Ed.* **2010,** *49,* 8691.

164. Kim, J.W.; Lee, J. J.; Lee, S. H.; Ahn, K. H. *Synthetic Communications.* **1998,** *28,* 1287.

165. Langer, T.; Illich, M.; Helmchen, G. *Tetrahedron Lett.* **1995,** *36,* 4409.

166. AlvarezIbarra, C.; Csaky, A. G.; Colmenero, B.; Quiroga, M. L. *J. Org. Chem.* **1997,** *62,* 2478.

167. Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988,** *53,* 3745.

168. Babler, J.H.; Sarussi, S. J. *J. Org. Chem.* **1987,** *52,* 3462.

169. Avetta, C.T., Jr.; Konkol, L. C.; Taylor, C. N.; Dugan, K. C.; Stern, C. L.; Thomson, R. J. *Org. Lett.* **2008,** *10,* 5621.

170. Liou, L.R.; McNeil, A. J.; Ramirez, A.; Toombes, G. E. S.; Gruver, J. M.; Collum, D. B. *J. Am. Chem. Soc.* **2008,** *130,* 4859.

171. Kolonko, K.J.; Biddle, M. M.; Guzei, I. A.; Reich, H. J. *J. Am. Chem. Soc.* **2009,** *131,* 11525.

172. Jones, A.C.; Sanders, A. W.; Bevan, M. J.; Reich, H. J. *J. Am. Chem. Soc.* **2007,** *129,* 3492.

173. Collum, D.B.; McNeil, A. J.; Ramirez, A. *Angew. Chem. Int. Ed.* **2007,** *46,* 3002.

174. Godenschwager, P.F.; Collum, D. B. *J. Am. Chem. Soc.* **2008,** *130,* 8726.

175. Ma, Y.; Hoepker, A. C.; Gupta, L.; Faggin, M. F.; Collum, D. B. *J. Am. Chem. Soc.* **2010,** *132,* 15610.

176. Godenschwager, P.F.; Collum, D. B. *J. Am. Chem. Soc.* **2007,** *129,* 12023.

177. Singh, K.J.; Collum, D. B. *J. Am. Chem. Soc.* **2006,** *128,* 13753.

178. Zuend, S.J.; Ramirez, A.; Lobkovsky, E.; Collum, D. B. *J. Am. Chem. Soc.* **2006,** *128,* 5939.

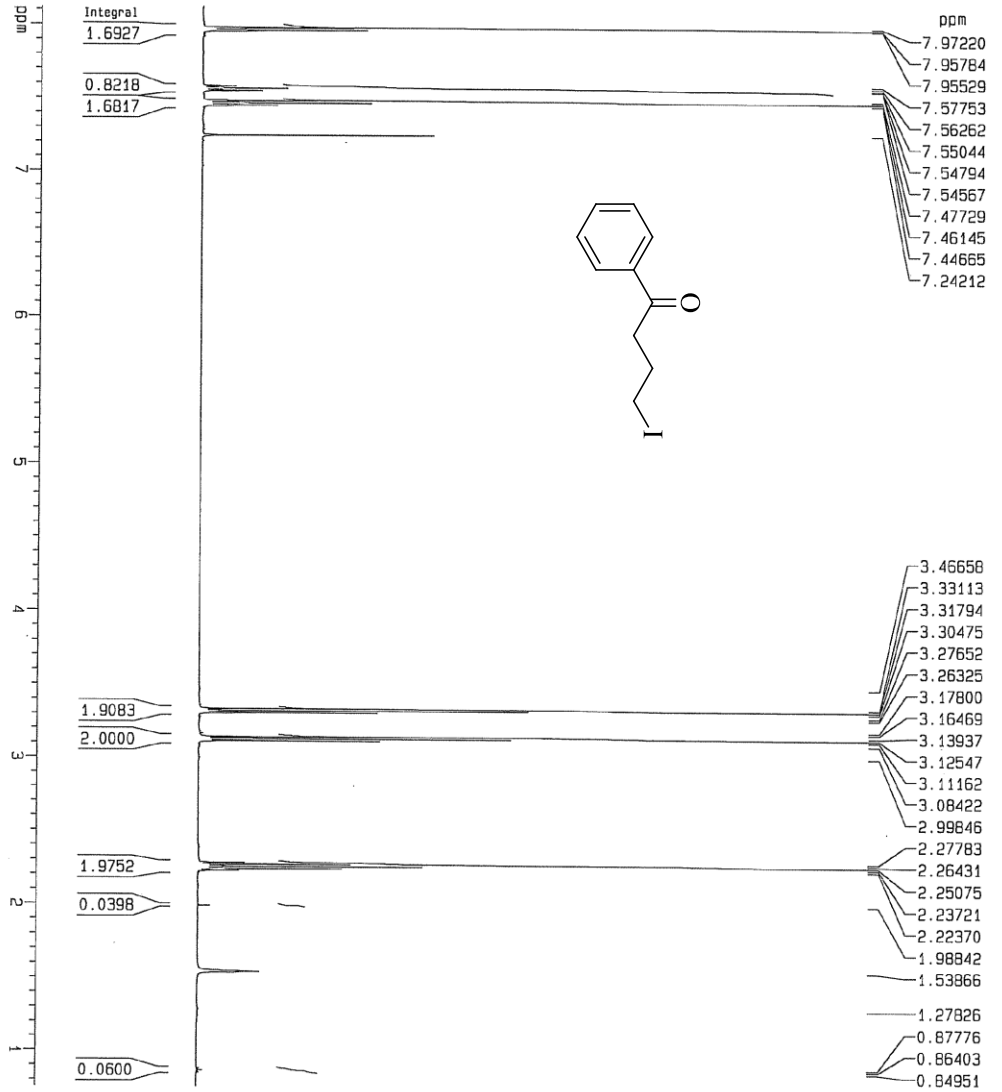
179. Gruver, J.M.; Liou, L. R.; McNeil, A. J.; Ramirez, A.; Collum, D. B. *J. Org. Chem.* **2008,** *73,* 7743.

180. Bordwell, F.G.; Zhang, X. M.; Filler, R. *J. Org. Chem.* **1993,** *58,* 6067.

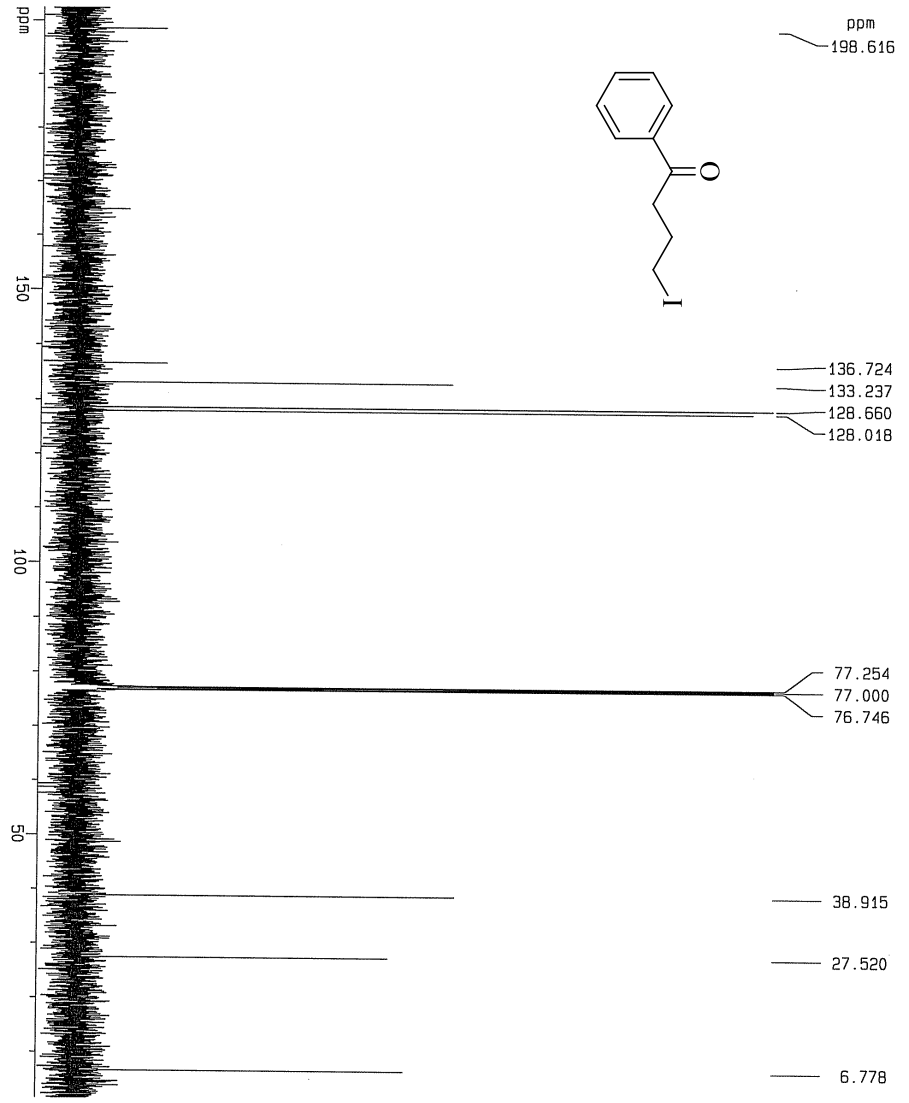
181. Snider, B.; Kwon, T. *J. Org. Chem.* **1992,** *57,* 2399.

182. Sun, X.F.; Collum, D. B. *J. Am. Chem. Soc.* **2000,** *122,* 2459.

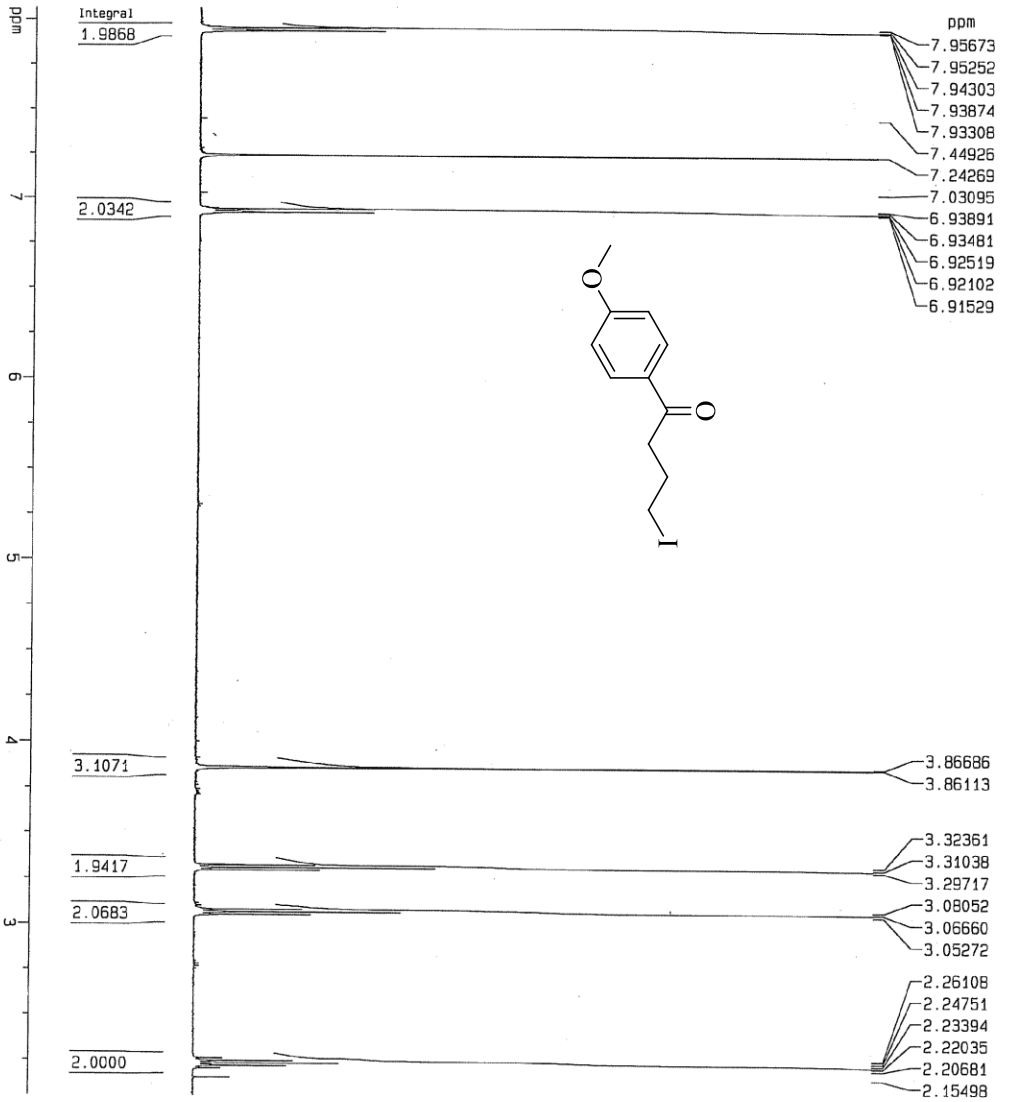
^{1}H NMR and ^{13}C NMR spectra for γ-halogenated ketones



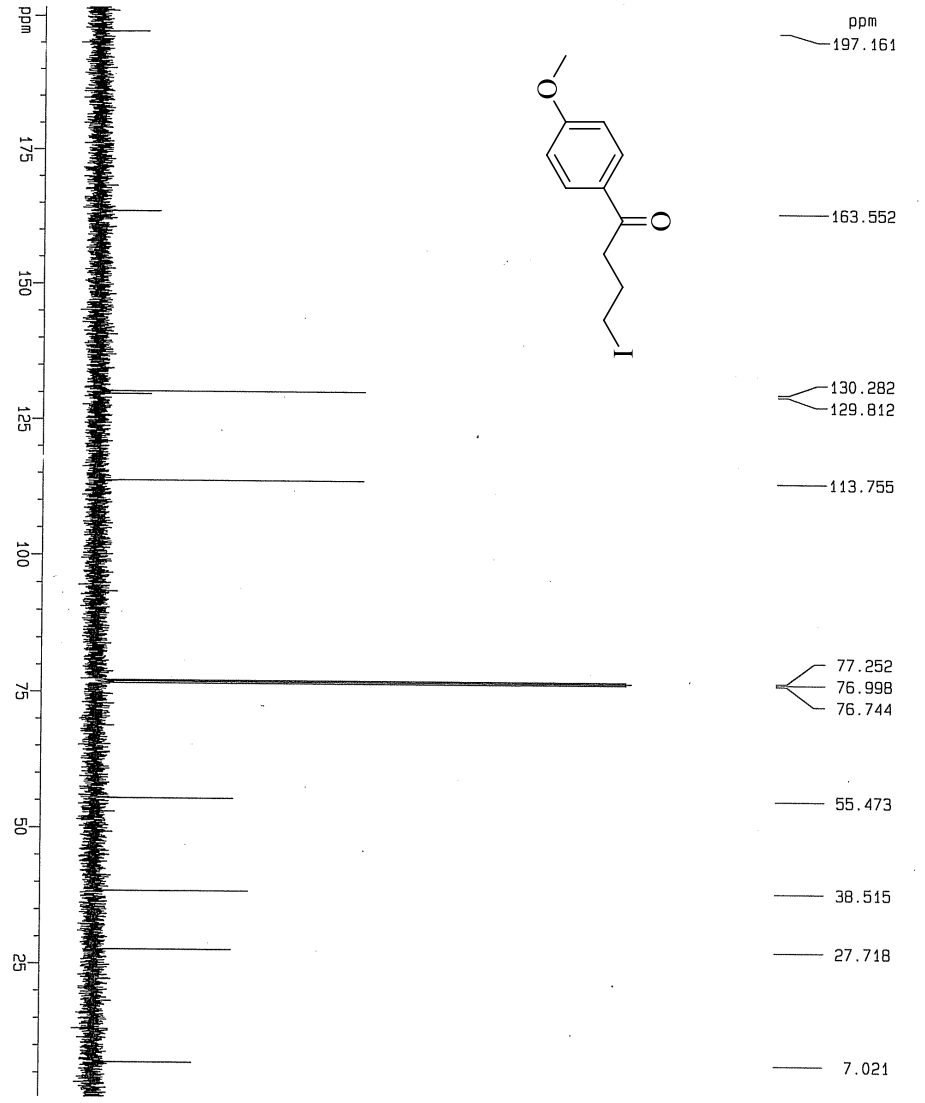

```
Current Data Parameters
NAME          4-I-ButPhenone-051408
EXPNO                            3
PROCNO                           1

F2 - Acquisition Parameters
Date_                     20080515
Time                         13.51
INSTRUM                       spect
PROBHD     5 mm PABBO BB-
PULPROG                        zg
TD                            32768
SOLVENT                     CDCl3
NS                               10
DS                                0
SWH                        7507.507 Hz
FIDRES                        0.229111 Hz
AQ                         2.1824653 sec
RG                              287.4
DW                             66.600 usec
DE                              7.00 usec
TE                             298.2 K
D1                         1.00000000 sec
d11                        0.03000000 sec
MCREST                     0.00000000 sec
MCWRK                      0.01500000 sec

======== CHANNEL f1 ========
NUC1                              1H
P1                              6.00 usec
PL1                           -4.00 dB
SFO1                     500.1323989 MHz

======== CHANNEL f2 ========
CPDPRG2                     waltz16
NUC2                             off
PCPD2                      100.00 usec
PL2                          120.00 dB
PL12                         120.00 dB
SFO2                     500.1300000 MHz

F2 - Processing parameters
SI                            32768
SF                       500.1300225 MHz
WDW                              EM
SSB                               0
LB                             0.20 Hz
GB                                0
PC                             4.00

1D NMR plot parameters
CX                           20.00 cm
CY                            0.00 cm
F1P                           8.119 ppm
F1                         4060.34 Hz
F2P                           0.753 ppm
F2                           376.75 Hz
PPMCM                      0.35826 ppm/cm
HZCM                     184.17952 Hz/cm
```




```
Current Data Parameters
NAME                  4-I-ButPhenone-DS140B
EXPNO                        4
PROCNO                       1

F2 - Acquisition Parameters
Date_              20080515
Time                    13.56
INSTRUM                 spect
PROBHD     5 mm PABBO BB-
PULPROG                 zgdc
TD                     65536
SOLVENT                CDCl3
NS                       252
DS                         0
SWH                30030.029 Hz
FIDRES                 0.458222 Hz
AQ                     1.091410 sec
RG                      1290.2
DW                     16.650 usec
DE                      7.00 usec
TE                     298.2 K
D1                     2.00000000 sec
d11                    0.03000000 sec
MCREST                 0.00000000 sec
MCWRK                  0.01500000 sec

========== CHANNEL f1 ==========
NUC1                        13C
P1                         5.00 usec
PL1                       -1.00 dB
SFO1                125.7715390 MHz

========== CHANNEL f2 ==========
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                    110.00 usec
PL2                       17.50 dB
PL12                      17.00 dB
SFO2                500.1325000 MHz

F2 - Processing parameters
SI                         65536
SF                  125.7577921 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40

1D NMR plot parameters
CX                         20.00 cm
CY                         12.50 cm
F1P                      202.486 ppm
F1                     25464.18 Hz
F2P                        1.632 ppm
F2                       205.28 Hz
PPMCM                   10.04268 ppm/cm
HZCM                 1262.94531 Hz/cm
```

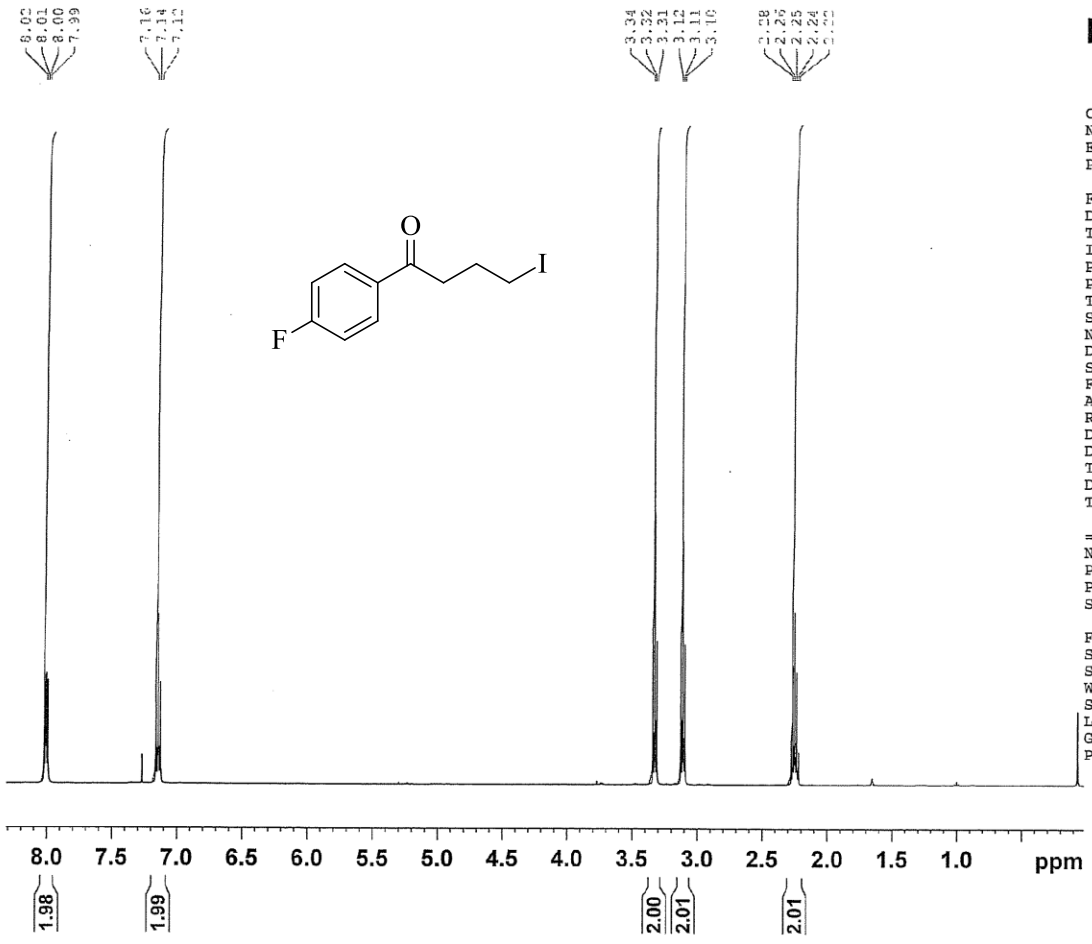



```
Current Data Parameters
NAME                  4-I-pMeOPhBut-062308
EXPNO                                    4
PROCNO                                   1

F2 - Acquisition Parameters
Date_                             20080624
Time                                 17.05
INSTRUM                                spect
PROBHD     5 mm PHBBO BB-
PULPROG                              zg30
TD                                   32768
SOLVENT                              CDCl3
NS                                       8
DS                                       0
SWH                             7507.507 Hz
FIDRES                          0.229111 Hz
AQ                              2.1824653 sec
RG                                     362
DW                                66.600 usec
DE                                 7.00 usec
TE                                 296.8 K
D1                              1.00000000 sec
MCREST                          0.00000000 sec
MCWRK                           0.01500000 sec

======== CHANNEL f1 ========
NUC1                                   1H
P1                                  7.90 usec
PL1                                -4.00 dB
SFO1                    500.1323999 MHz

F2 - Processing parameters
SI                                   32768
SF                      500.1300225 MHz
WDW                                     EM
SSB                                      0
LB                                  0.20 Hz
GB                                       0
PC                                    4.00

1D NMR plot parameters
CX                                  20.00 cm
CY                                   0.00 cm
F1P                                  8.067 ppm
F1                                4034.43 Hz
F2P                                  2.055 ppm
F2                                1027.89 Hz
PPMCM                             0.30058 ppm/c
HZCM                              150.32701 Hz/cm
```




```
Current Data Parameters
NAME                  4-I-pMeOPhBut-062308
EXPNO                              5
PROCNO                             1

F2 - Acquisition Parameters
Date_                       20080624
Time                           17.17
INSTRUM                        spect
PROBHD     5 mm PHBBO BB-
PULPROG                     zgdc30
TD                           65536
SOLVENT                      CDCl3
NS                              53
DS                               0
SWH                      30030.029 Hz
FIDRES                       0.458222 Hz
AQ                        1.0912410 sec
RG                           2580.3
DW                          16.650 usec
DE                           7.00 usec
TE                          297.0 K
D1                       1.00000000 sec
d11                      0.03000000 sec
MCREST                   0.00000000 sec
MCWRK                    0.01500000 sec

======== CHANNEL f1 ========
NUC1                           13C
P1                            9.30 usec
PL1                           1.00 dB
SFO1                    125.7715390 MHz

======== CHANNEL f2 ========
CPDPRG2                     waltz16
NUC2                           1H
PCPD2                       100.00 usec
PL2                           17.50 dB
PL12                          17.50 dB
SFO2                    500.1325000 MHz

F2 - Processing parameters
SI                           65536
SF                      125.7577949 MHz
WDW                            EM
SSB                             0
LB                           1.00 Hz
GB                              0
PC                           1.40

1D NMR plot parameters
CX                          20.00 cm
CY                           5.00 cm
F1P                       201.685 ppm
F1                       25363.50 Hz
F2P                         0.582 ppm
F2                         73.19 Hz
PPMCM                     10.05517 ppm/cm
HZCM                   1264.51538 Hz/cm
```

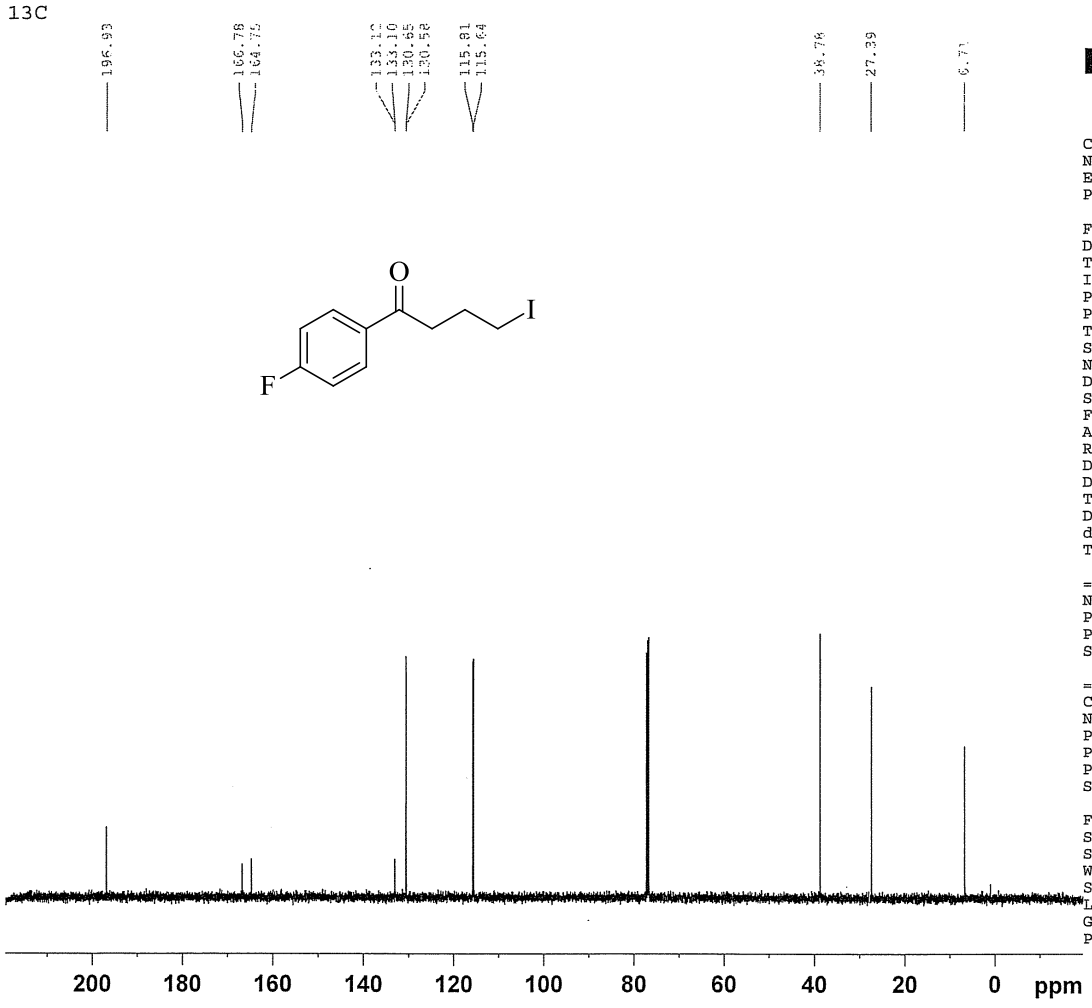
Frac3-4



BRUKER

```
Current Data Parameters
NAME      4-I-pF-PhBut-090808
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_              20080908
Time                  13.56
INSTRUM               spect
PROBHD   5 mm BBO BB-1H
PULPROG               zg30
TD                   32768
SOLVENT              CDCl3
NS                       6
DS                       0
SWH                6009.615 Hz
FIDRES            0.183399 Hz
AQ                2.7264309 sec
RG                     90.5
DW                   83.200 usec
DE                    6.00 usec
TE                   296.4 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   7.35 usec
PL1                  1.00 dB
SFO1          500.1327510 MHz

F2 - Processing parameters
SI                   32768
SF            500.1300102 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

13C



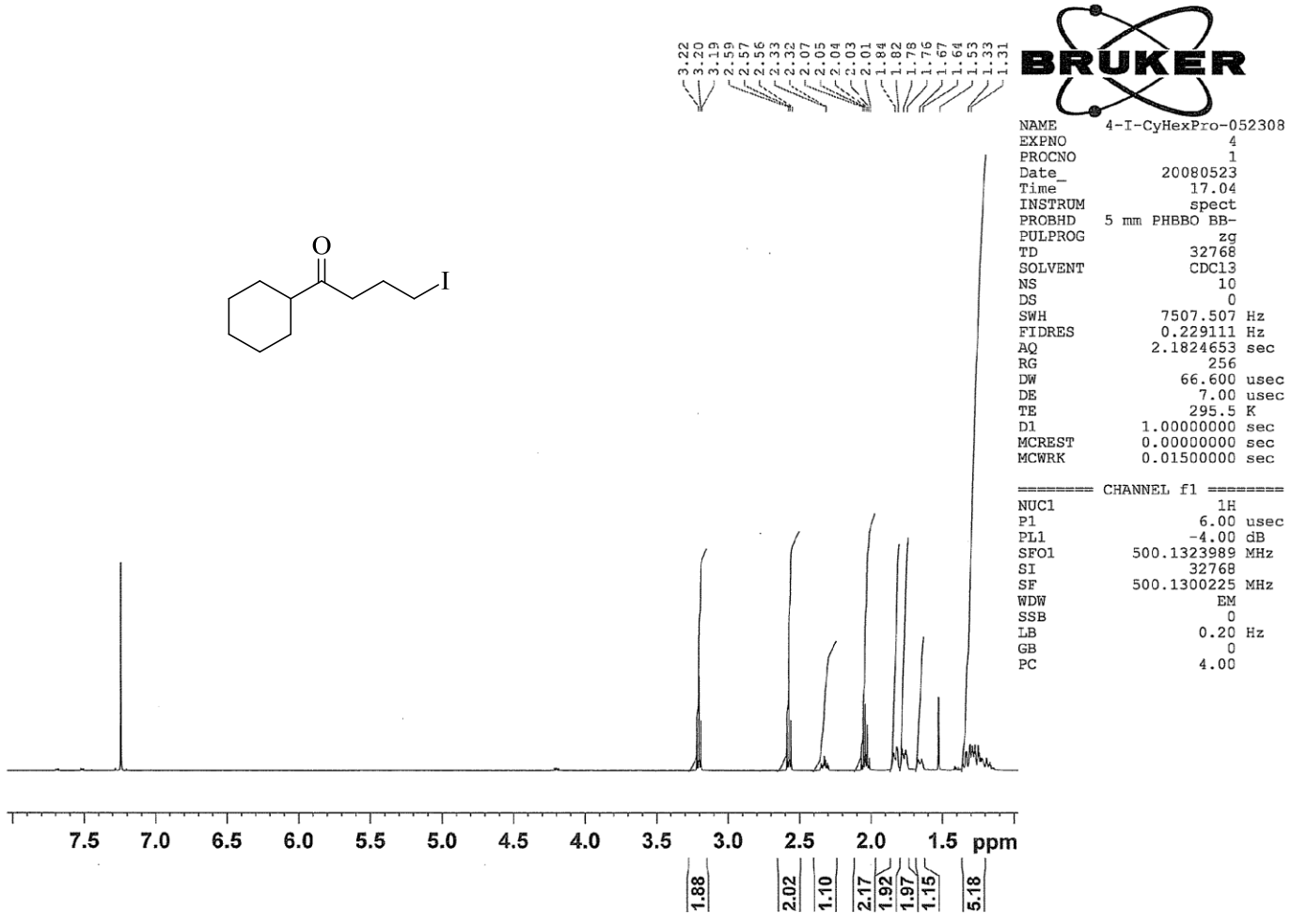
Current Data Parameters
NAME 4-I-pF-PhBut-090808
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20080908
Time 13.59
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 85
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 1448.2
DW 16.650 usec
DE 7.00 usec
TE 297.5 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 5.00 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

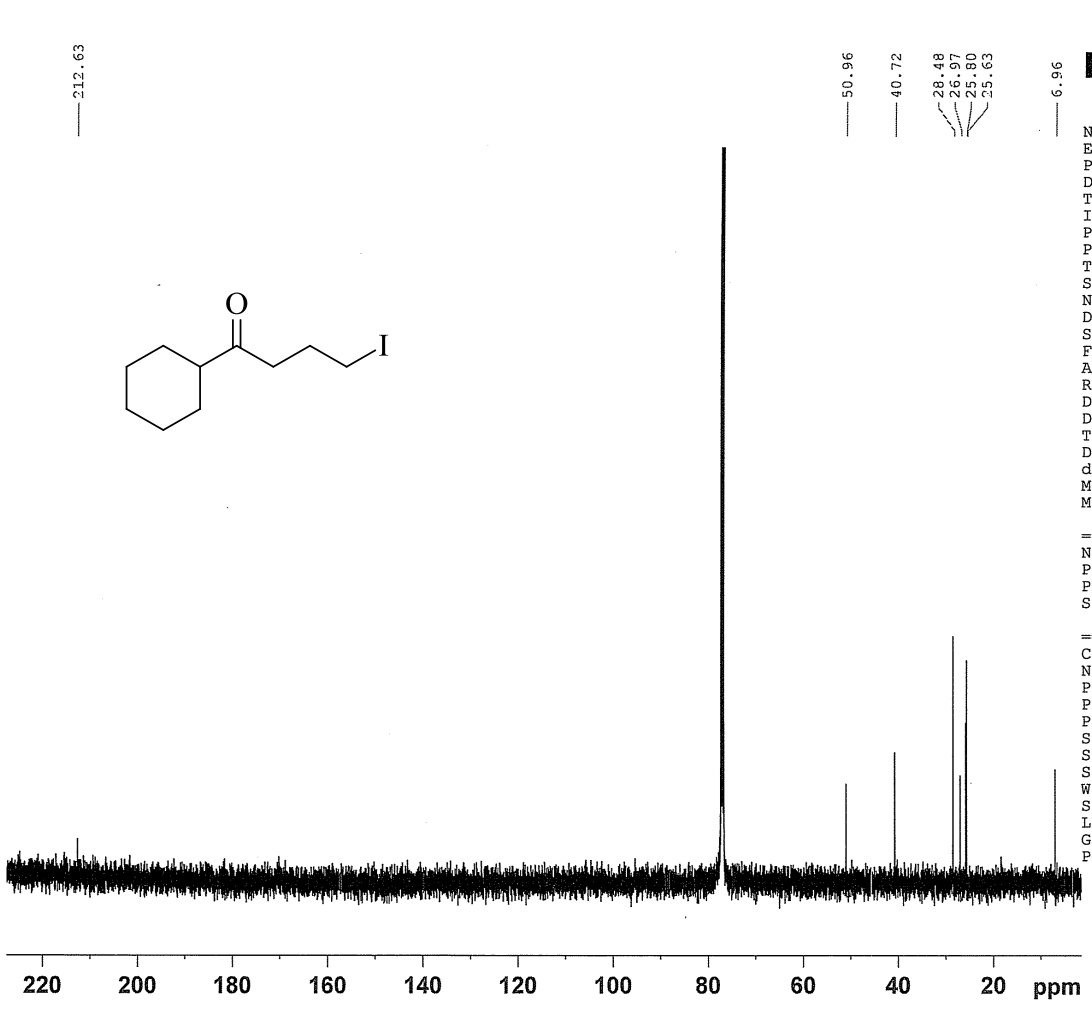
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 24.00 dB
PL12 24.00 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577969 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



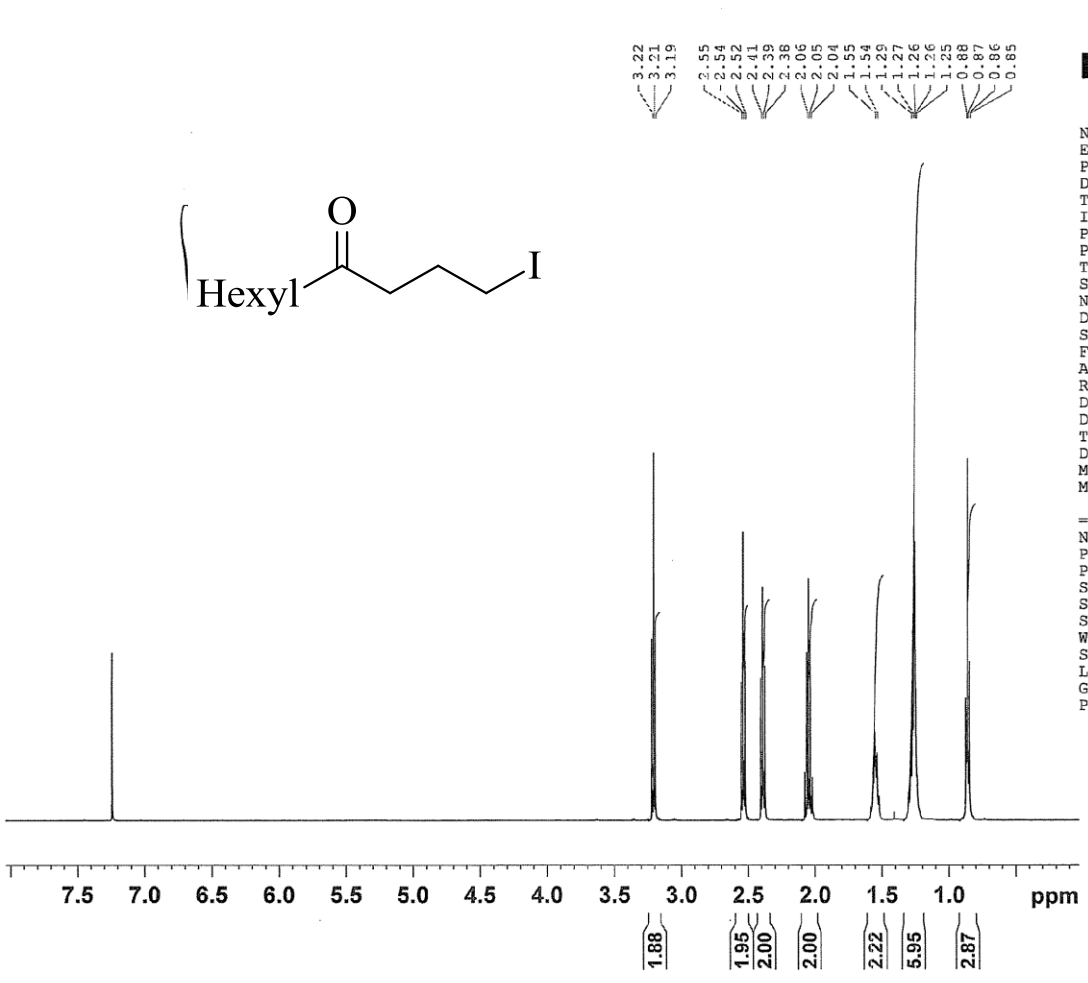
BRUKER

NAME	4-I-CyHexPro-052308
EXPNO	4
PROCNO	1
Date_	20080523
Time	17.04
INSTRUM	spect
PROBHD	5 mm PHBBO BB-
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	10
DS	0
SWH	7507.507 Hz
FIDRES	0.229111 Hz
AQ	2.1824653 sec
RG	256
DW	66.600 usec
DE	7.00 usec
TE	295.5 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	6.00 usec
PL1	-4.00 dB
SFO1	500.1323989 MHz
SI	32768
SF	500.1300225 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	4.00



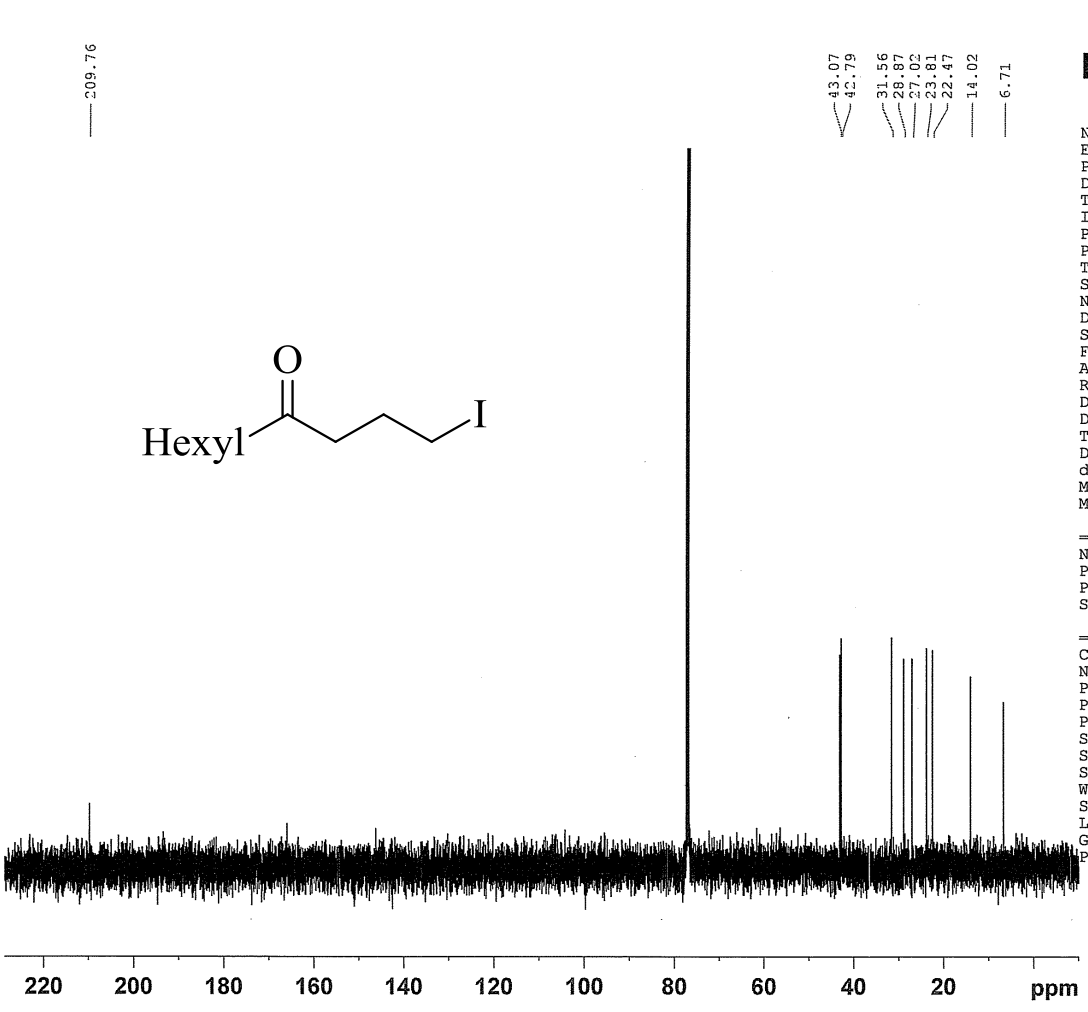
BRUKER

NAME	4-I-CyHexPro-052308
EXPNO	3
PROCNO	1
Date_	20080523
Time	13.11
INSTRUM	spect
PROBHD	5 mm PHBBO BB-
PULPROG	zgdc
TD	65536
SOLVENT	CDCl3
NS	2789
DS	0
SWH	30030.029 Hz
FIDRES	0.458222 Hz
AQ	1.0912410 sec
RG	5160.6
DW	16.650 usec
DE	7.00 usec
TE	296.1 K
D1	2.00000000 sec
d11	0.03000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec
======== CHANNEL f1 ========	
NUC1	13C
P1	5.00 usec
PL1	-1.00 dB
SFO1	125.7715390 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	110.00 usec
PL2	17.50 dB
PL12	17.00 dB
SFO2	500.1325000 MHz
SI	65536
SF	125.7577926 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

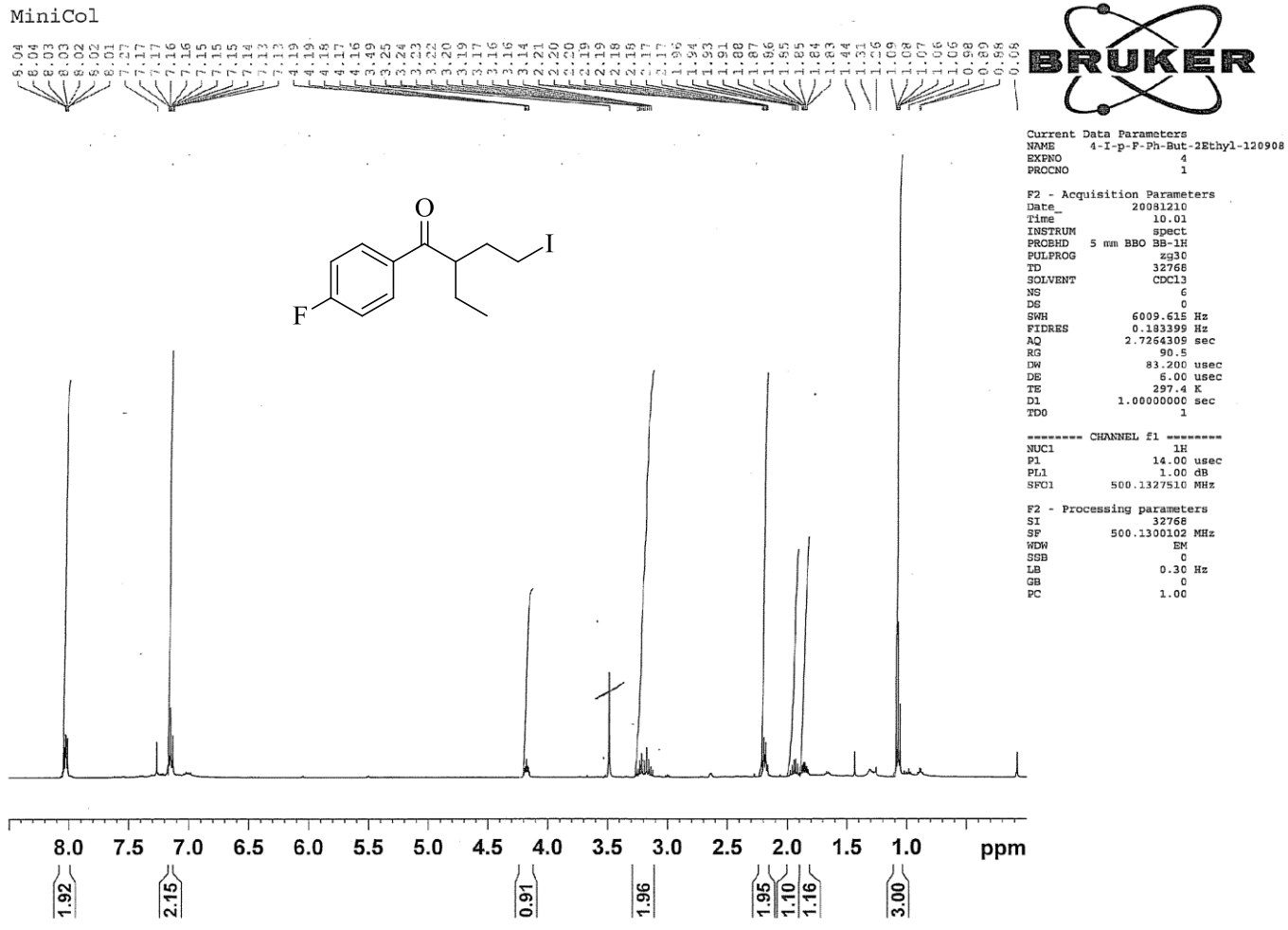


BRUKER

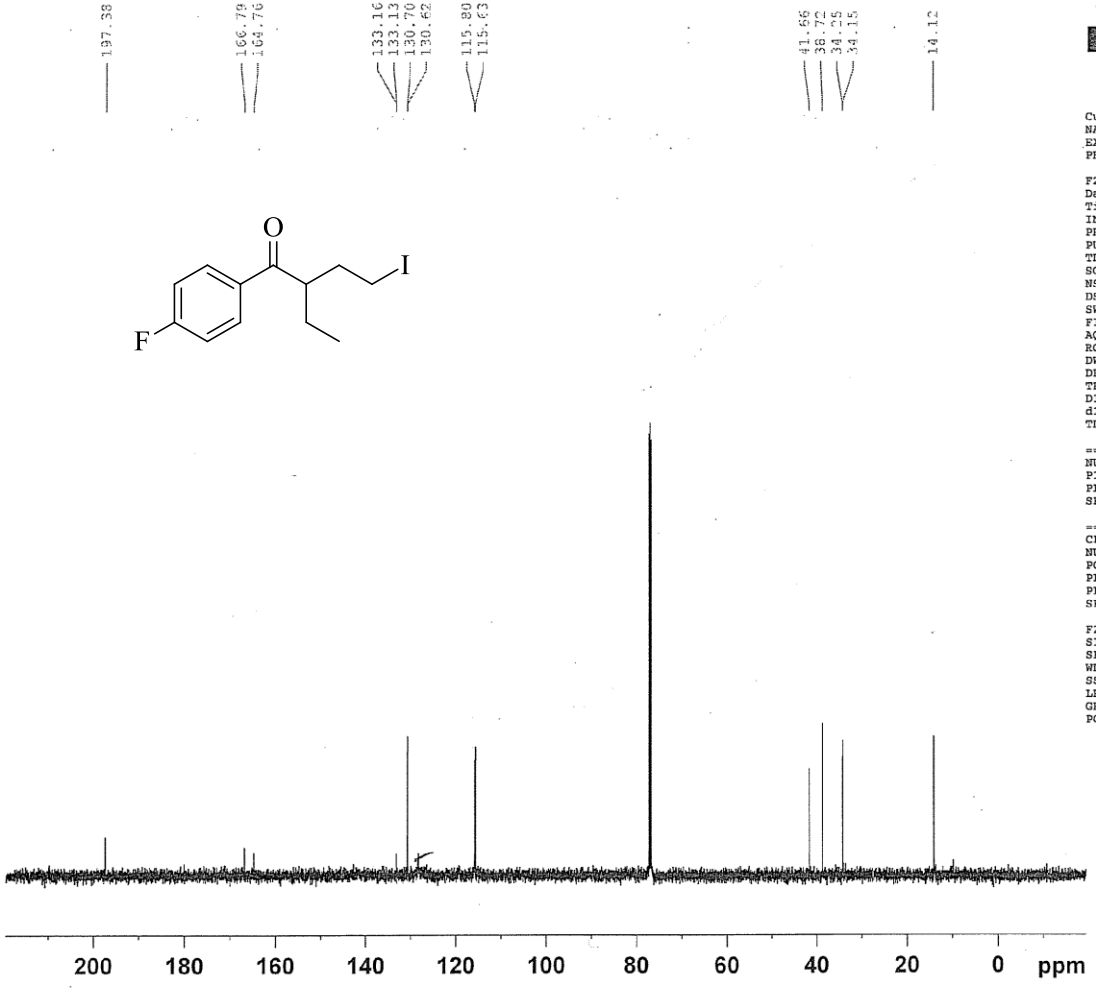
NAME	4-I-HexBut2-060408
EXPNO	1
PROCNO	1
Date_	20080604
Time	16.31
INSTRUM	spect
PROBHD	5 mm PHBBO BB-
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	8
DS	0
SWH	7507.507 Hz
FIDRES	0.229111 Hz
AQ	2.1824653 sec
RG	161.3
DW	66.600 usec
DE	7.00 usec
TE	295.4 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	6.00 usec
PL1	-4.00 dB
SFO1	500.1323989 MHz
SI	32768
SF	500.1300225 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	4.00



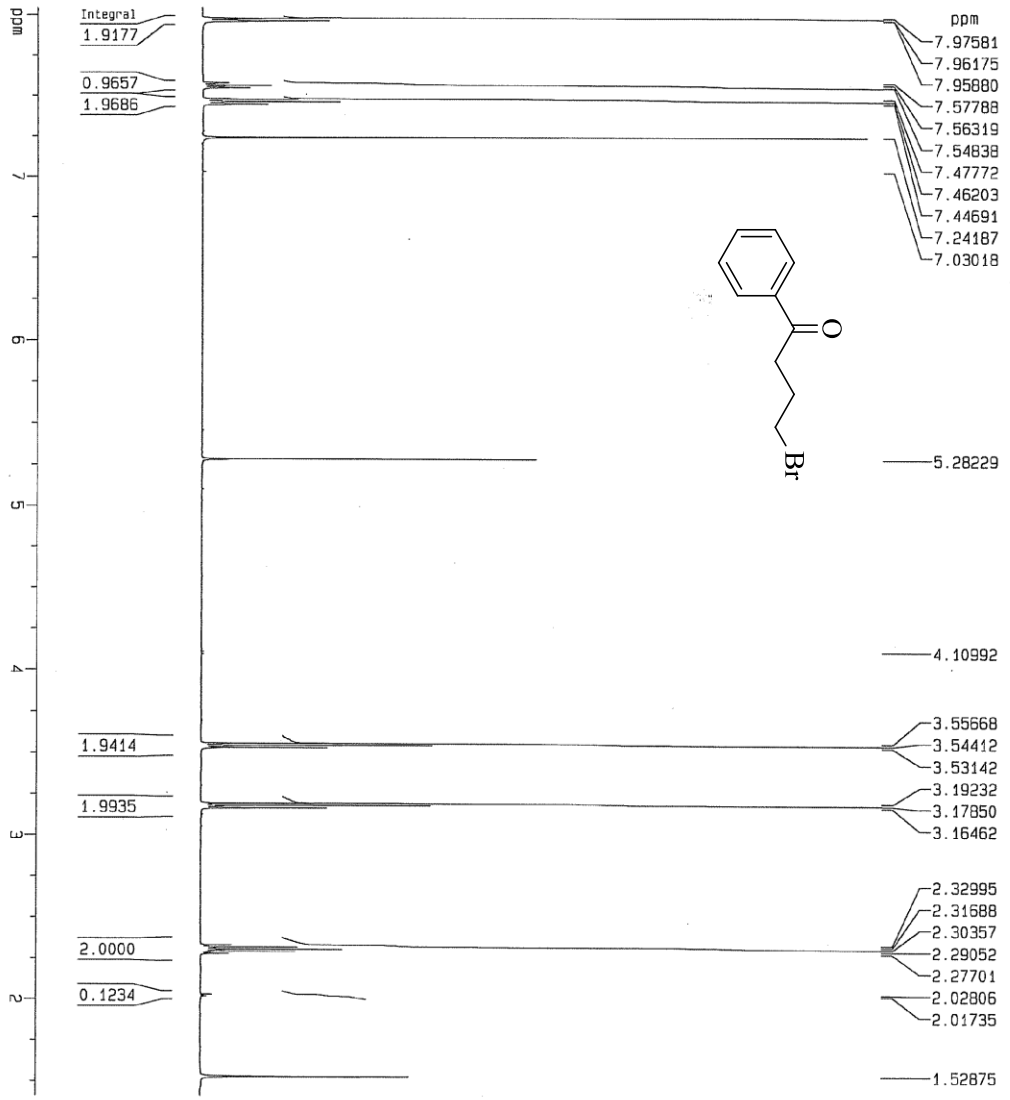
NAME	4-I-HexBut-060408
EXPNO	3
PROCNO	1
Date_	20080604
Time	16.25
INSTRUM	spect
PROBHD	5 mm PHBBO BB-
PULPROG	zgdc30
TD	65536
SOLVENT	CDCl3
NS	92
DS	0
SWH	30030.029 Hz
FIDRES	0.458222 Hz
AQ	1.0912410 sec
RG	1625.5
DW	16.650 usec
DE	7.00 usec
TE	295.6 K
D1	2.00000000 sec
d11	0.03000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec
======== CHANNEL f1 ========	
NUC1	13C
P1	9.30 usec
PL1	1.00 dB
SFO1	125.7715390 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	110.00 usec
PL2	-4.00 dB
PL12	18.88 dB
SFO2	500.1325000 MHz
SI	65536
SF	125.7577935 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40


MiniCol
BRUKER
Current Data Parameters
NAME 4-I-p-F-Ph-But-2Ethyl-120908
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20081210
Time 10.01
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 6009.615 Hz
FIDRES 0.183399 Hz
AQ 2.7264309 sec
RG 90.5
DW 83.200 usec
DE 6.00 usec
TE 297.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1327510 MHz
F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
I
F
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.92
2.15
0.91
1.96
1.95
1.10
1.16
3.00

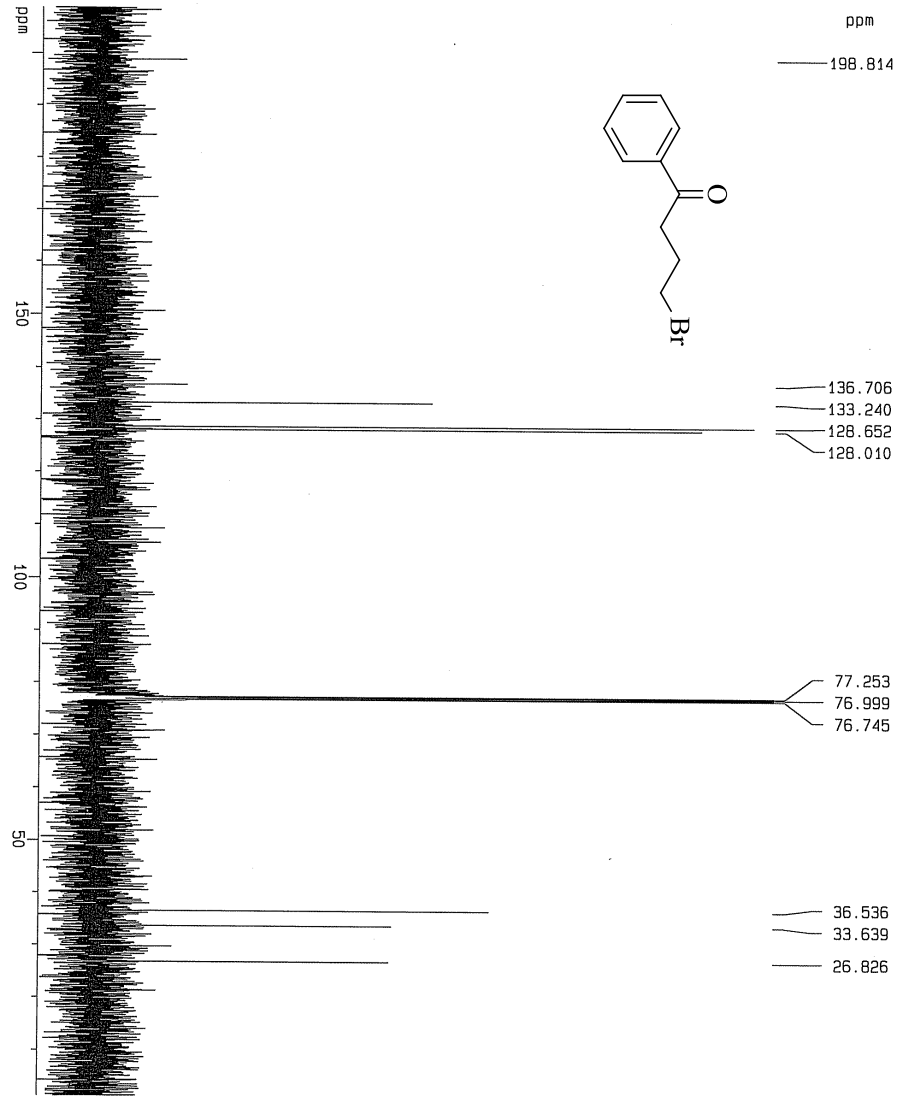
13C-NMR-Crude



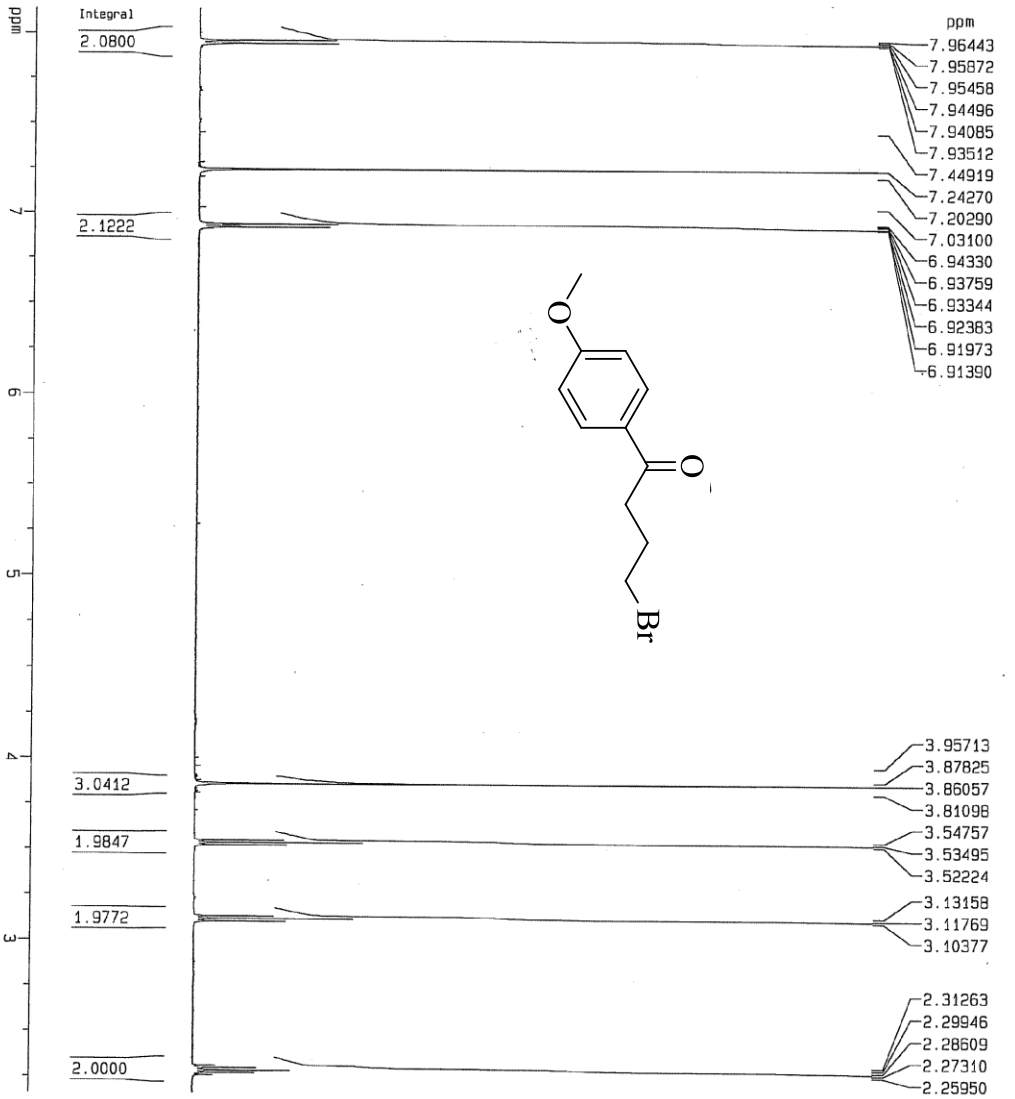

```
Current Data Parameters
NAME      4-I-p-F-Ph-But-2Ethyl-120908
EXPNO                3
PROCNO               1

F2 - Acquisition Parameters
Date_         20081209
Time              18.17
INSTRUM           spect
PROBHD   5 mm BBO BB-1H
PULPROG         zgdc30
TD               65536
SOLVENT          CDCl3
NS                 121
DS                   4
SWH           30030.029 Hz
FIDRES         0.458222 Hz
AQ             1.0912410 sec
RG                3251
DW               16.650 usec
DE                7.00 usec
TE                298.1 K
D1            1.00000000 sec
d11           0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.35 usec
PL1                1.00 dB
SFO1        125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2             100.00 usec
PL2                17.50 dB
PL12               17.50 dB
SFO2        500.1322150 MHz

F2 - Processing parameters
SI                 32768
SF          125.7577976 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```



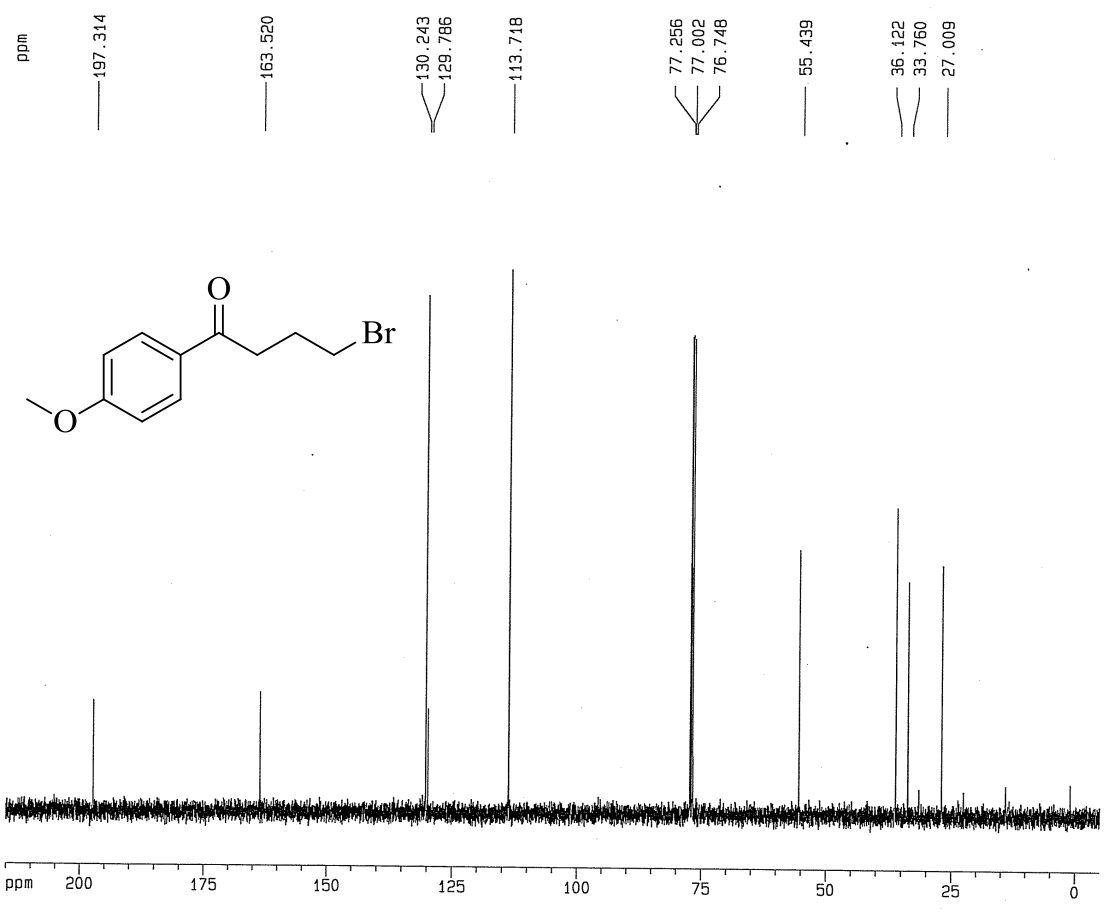

```
Current Data Parameters
NAME                  4-Br-PhBut-053008
EXPNO                              3
PROCNO                             1

F2 - Acquisition Parameters
Date_                       20080530
Time                           11.47
INSTRUM                         spect
PROBHD     5 mm TXI 1H/2H
PULPROG                         zg30
TD                             32768
SOLVENT                       CDCl3
NS                                 8
DS                                 0
SWH                       7507.507 Hz
FIDRES                    0.229111 Hz
AQ                        2.1824653 sec
RG                             724.1
DW                            66.600 usec
DE                             7.00 usec
TE                            294.7 K
D1                        1.00000000 sec
MCREST                    0.00000000 sec
MCWRK                     0.01500000 sec

========== CHANNEL f1 ==========
NUC1                             1H
P1                             8.30 usec
PL1                            1.00 dB
SFO1                  500.1323989 MHz

F2 - Processing parameters
SI                             32768
SF                  500.1300225 MHz
WDW                               EM
SSB                                0
LB                              0.20 Hz
GB                                 0
PC                              4.00

1D NMR plot parameters
CX                            20.00 cm
CY                             0.00 cm
F1P                            8.041 ppm
F1                          4021.73 Hz
F2P                            1.412 ppm
F2                           706.17 Hz
PPMCM                          0.33147 ppm
HZCM                       165.77797 Hz/
```




```
Current Data Parameters
NAME                  4-Br-PhBut-060408
EXPNO                            1
PROCNO                           1

F2 - Acquisition Parameters
Date_              20080604
Time                    11.37
INSTRUM                 spect
PROBHD     5 mm PHBBO BB-
PULPROG                 zgdc
TD                     65536
SOLVENT                CDCl3
NS                       256
DS                         0
SWH                30030.029 Hz
FIDRES             0.458222 Hz
AQ                 1.0912410 sec
RG                    1625.5
DW                  16.650 usec
DE                   7.00 usec
TE                  295.5 K
D1                 2.00000000 sec
d11                0.03000000 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                       5.00 usec
PL1                    -1.00 dB
SFO1             125.77115390 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                 110.00 usec
PL2                    17.50 dB
PL12                   17.00 dB
SFO2             500.1326000 MHz

F2 - Processing parameters
SI                       65536
SF               125.7577930 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40

1D NMR plot parameters
CX                    20.00 cm
CY                    12.50 cm
F1P                 208.895 ppm
F1                 26270.16 Hz
F2P                  1.346 ppm
F2                 169.30 Hz
PPMCM              10.37743 ppm/cm
HZCM               1305.04321 Hz/cm
```

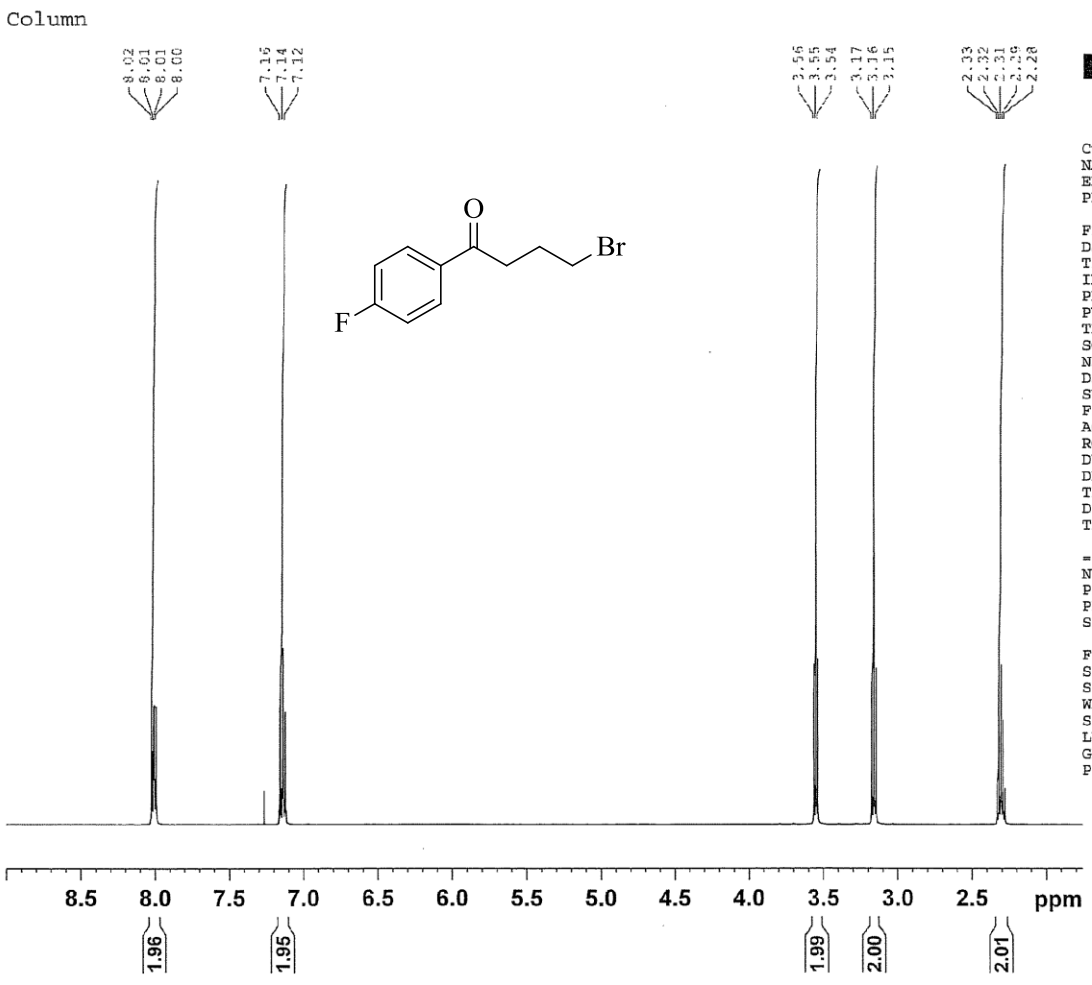



```
Current Data Parameters
NAME          4-Br-pMeOPhBut-061608
EXPNO                            2
PROCNO                           1

F2 - Acquisition Parameters
Date_                     20080616
Time                         14.46
INSTRUM                       spect
PROBHD     5 mm PHBBO BB-
PULPROG                       zg30
TD                           32768
SOLVENT                      CDCl3
NS                               8
DS                               0
SWH                       7507.507 Hz
FIDRES                    0.229111 Hz
AQ                        2.1824653 sec
RG                             912.3
DW                        65.600 usec
DE                         7.00 usec
TE                           296.1 K
D1                        1.00000000 sec
MCREST                    0.00000000 sec
MCWRK                     0.01500000 sec

========== CHANNEL f1 ==========
NUC1                             1H
P1                         8.30 usec
PL1                        1.00 dB
SFO1                  500.1323989 MHz

F2 - Processing parameters
SI                           32768
SF                    500.1300225 MHz
WDW                             EM
SSB                              0
LB                         0.20 Hz
GB                               0
PC                         4.00

1D NMR plot parameters
CX                        20.00 cm
CY                         0.00 cm
F1P                        8.137 ppm
F1                      4069.80 Hz
F2P                        2.161 ppm
F2                      1080.94 Hz
PPMCM                  0.29881 ppm/cm
HZCM                 149.44272 Hz/cm
```




```
Current Data Parameters
NAME      4-Br-pMeOPhBut-061608
EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_              20080616
Time                  17.58
INSTRUM                spect
PROBHD   5 mm PHBBO BB-
PULPROG             zgdc30
TD                   65536
SOLVENT              CDCl3
NS                      37
DS                       0
SWH              30030.029 Hz
FIDRES            0.458222 Hz
AQ                1.0912410 sec
RG                    2048
DW                  16.650 usec
DE                   7.00 usec
TE                   296.9 K
D1               1.00000000 sec
d11              0.03000000 sec
MCREST           0.00000000 sec
MCWRK            0.01500000 sec

======== CHANNEL f1 ========
NUC1                    13C
P1                    9.30 usec
PL1                   1.00 dB
SFO1           125.7715390 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2               100.00 usec
PL2                   17.50 dB
PL12                  17.50 dB
SFO2           500.1325000 MHz

F2 - Processing parameters
SI                   65536
SF             125.7577976 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40

1D NMR plot parameters
CX                   20.00 cm
CY                   10.00 cm
F1P                 215.000 ppm
F1                27037.93 Hz
F2P                  -5.000 ppm
F2                 -628.79 Hz
PPMCM              11.00000 ppm/cm
HZCM             1383.33582 Hz/cm
```

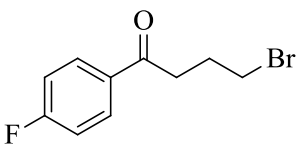
Column

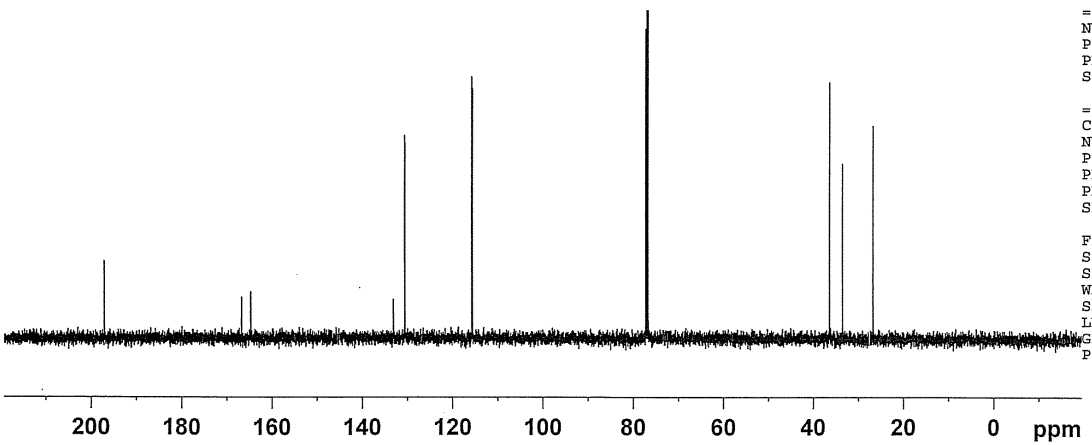


BRUKER

```
Current Data Parameters
NAME      4-Br-pF-PhBut-090808
EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_              20080909
Time                  11.47
INSTRUM               spect
PROBHD   5 mm BBO BB-1H
PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                        6
DS                        0
SWH                6009.615 Hz
FIDRES            0.183399 Hz
AQ                2.7264309 sec
RG                      128
DW                 83.200 usec
DE                  6.00 usec
TE                  296.3 K
D1              1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    1H
P1                   7.35 usec
PL1                  1.00 dB
SFO1          500.1327510 MHz

F2 - Processing parameters
SI                    32768
SF            500.1300102 MHz
WDW                      EM
SSB                       0
LB                   0.30 Hz
GB                        0
PC                    1.00
```

Column





Current Data Parameters

NAME	4-Br-pF-PhBut-090808
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20080909
Time	11.51
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zgdc30
TD	65536
SOLVENT	CDCl3
NS	42
DS	4
SWH	30030.029 Hz
FIDRES	0.458222 Hz
AQ	1.0912410 sec
RG	3251
DW	16.650 usec
DE	7.00 usec
TE	297.0 K
D1	1.00000000 sec
d11	0.03000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	13C
P1	5.00 usec
PL1	1.00 dB
SFO1	125.7703640 MHz

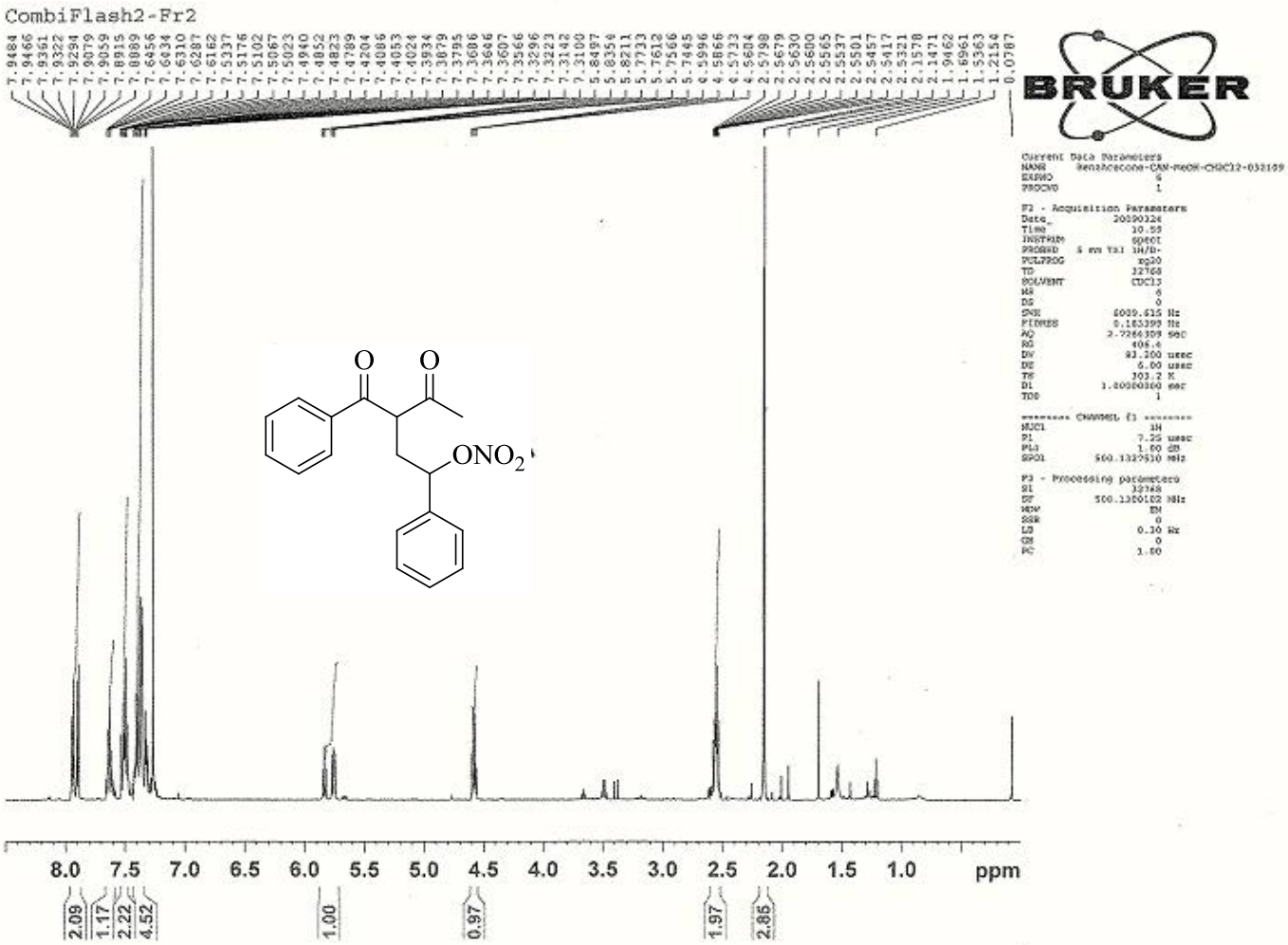
======== CHANNEL f2 ========

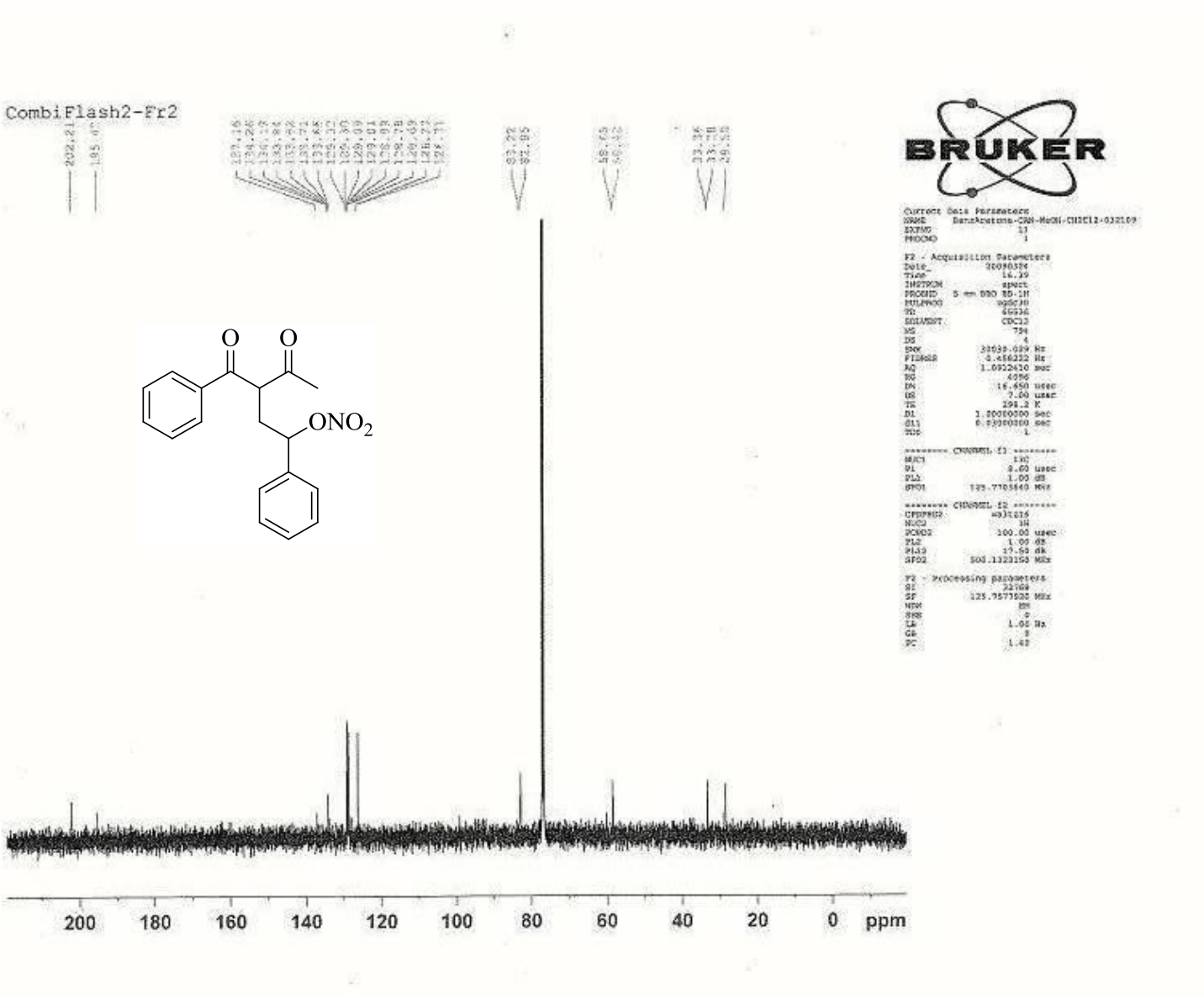
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	24.00 dB
PL12	24.00 dB
SFO2	500.1322150 MHz

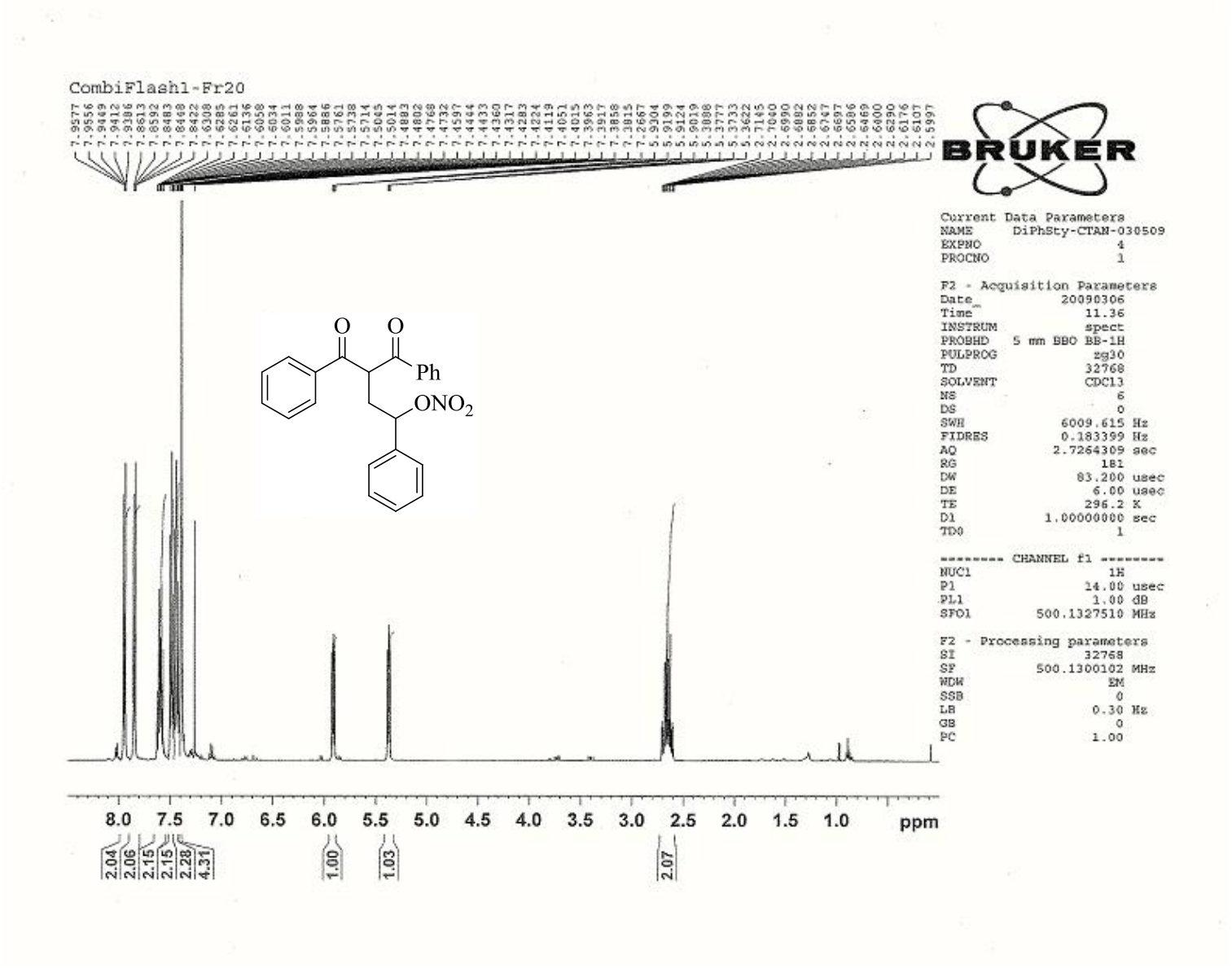
F2 - Processing parameters

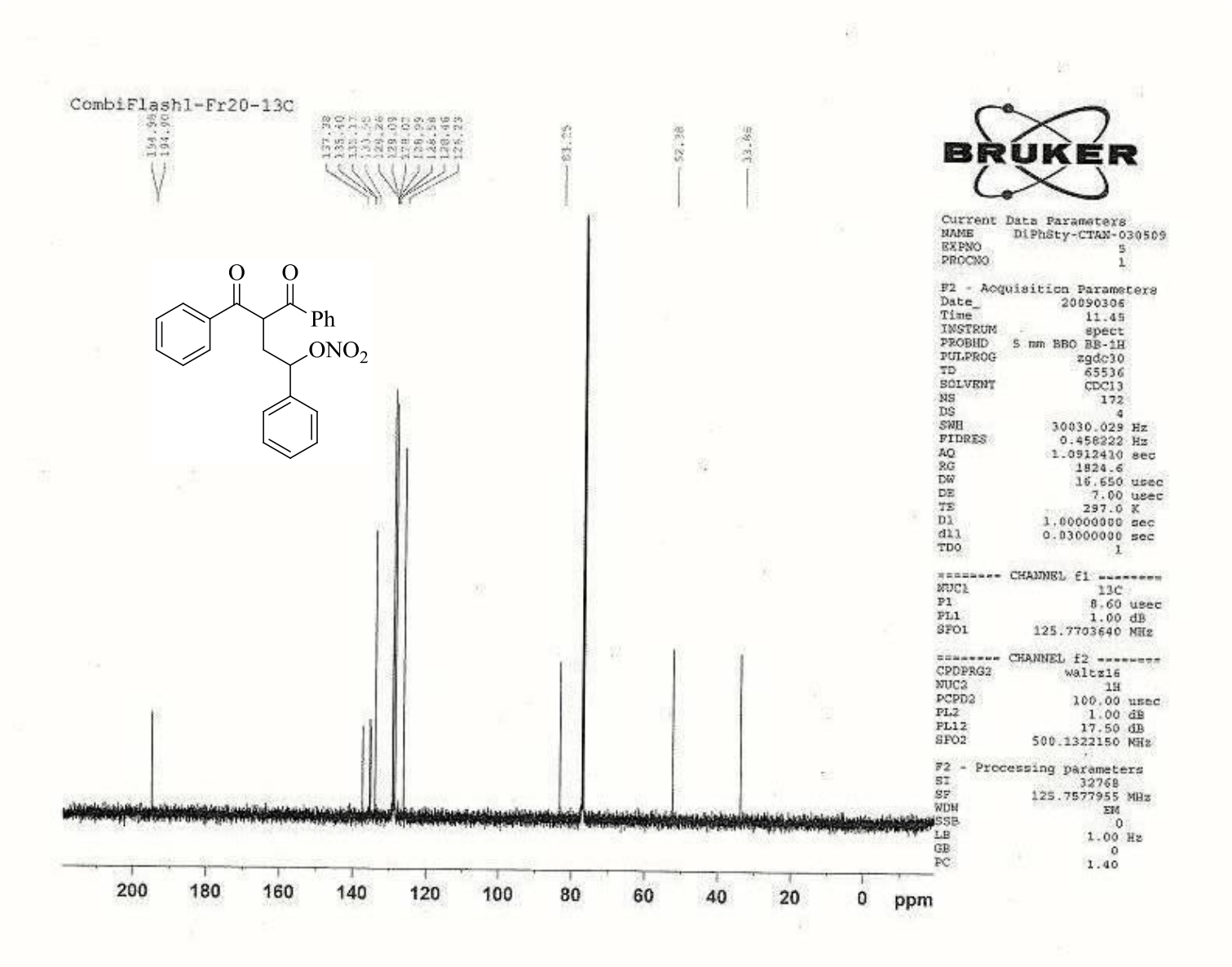
SI	32768
SF	125.7577962 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

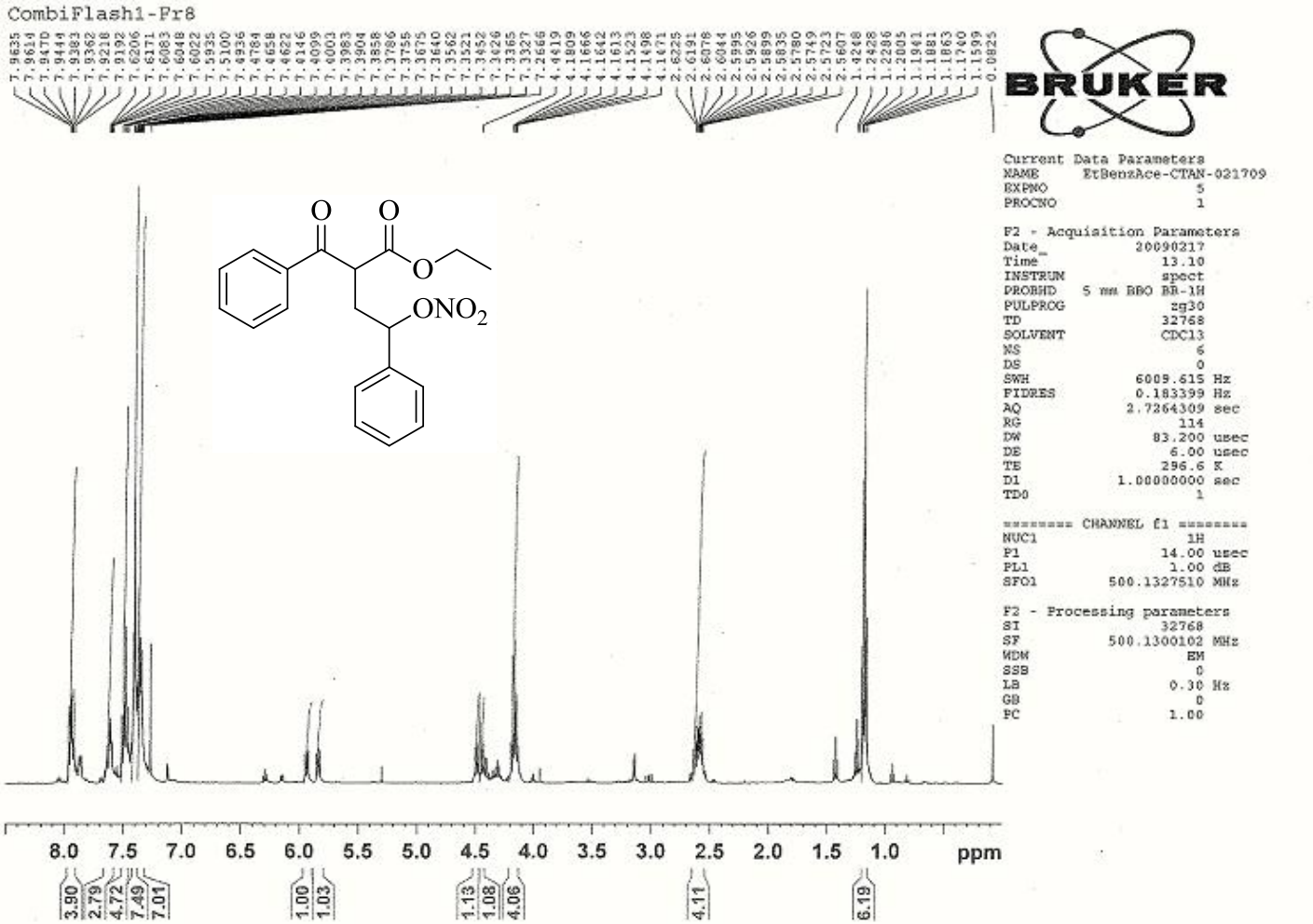
^{1}H NMR and ^{13}C NMR spectra for nitrate ester and dihydrofuran derivatives


CombiFlash2-Fr2
BRUKER
Current Data Parameters
NAME Renaissance-CAN-MeOH-CHCl2-032109
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090324
Time 10.59
INSTRUM spect
PROBHD 5 mm TXI 1H/D-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 6009.615 Hz
FIDRES 0.183399 Hz
AQ 2.7266309 sec
RG 406.4
DW 83.200 usec
DE 6.00 usec
TE 303.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 7.25 usec
PL1 1.00 dB
SFO1 500.1327930 MHz
F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ONO2
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.09
1.17
2.22
4.52
1.00
0.97
1.97
2.85

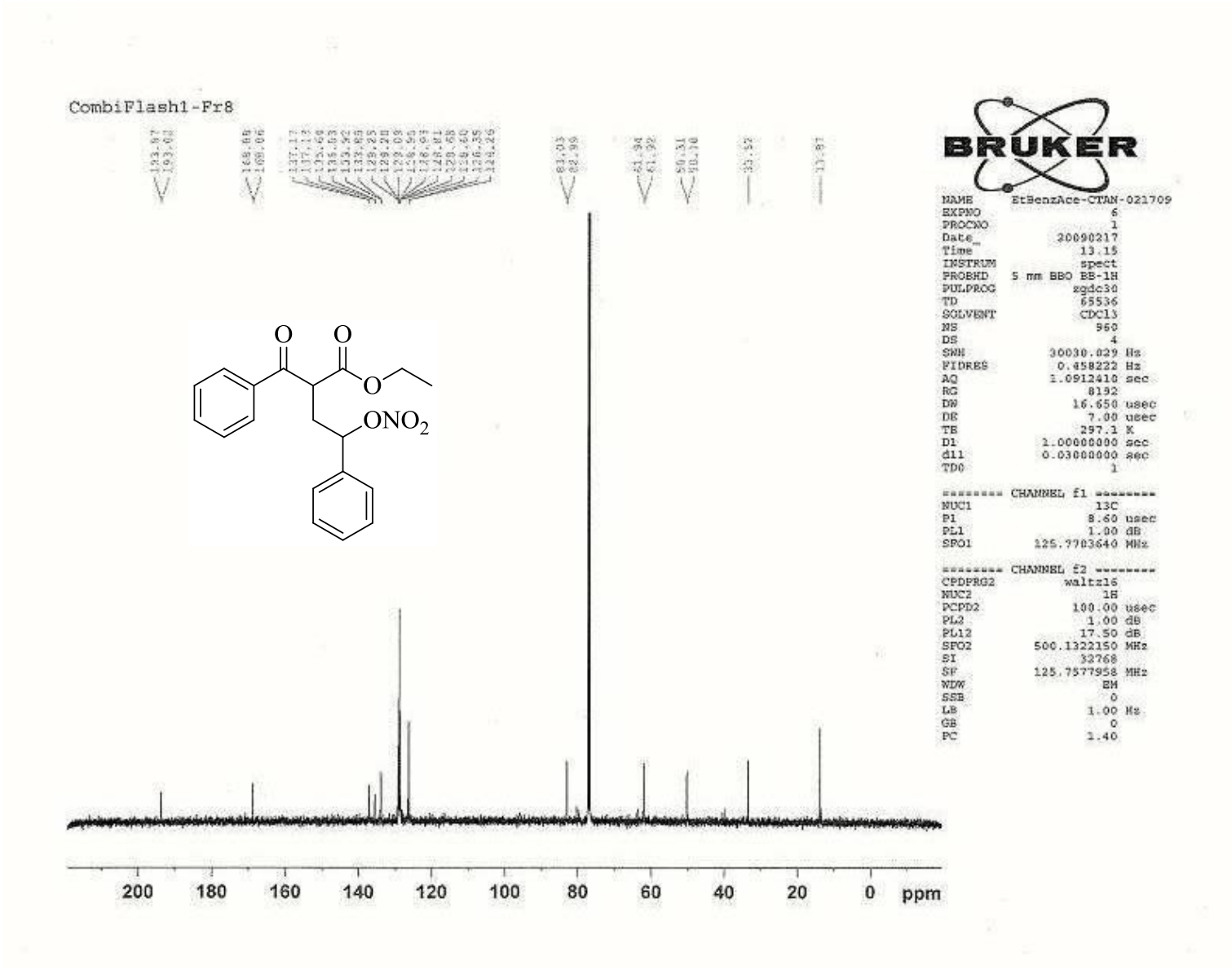

CombiFlash2-Fr2
BRUKER
O
O
ONO2
200
180
160
140
120
100
80
60
40
20
0
ppm

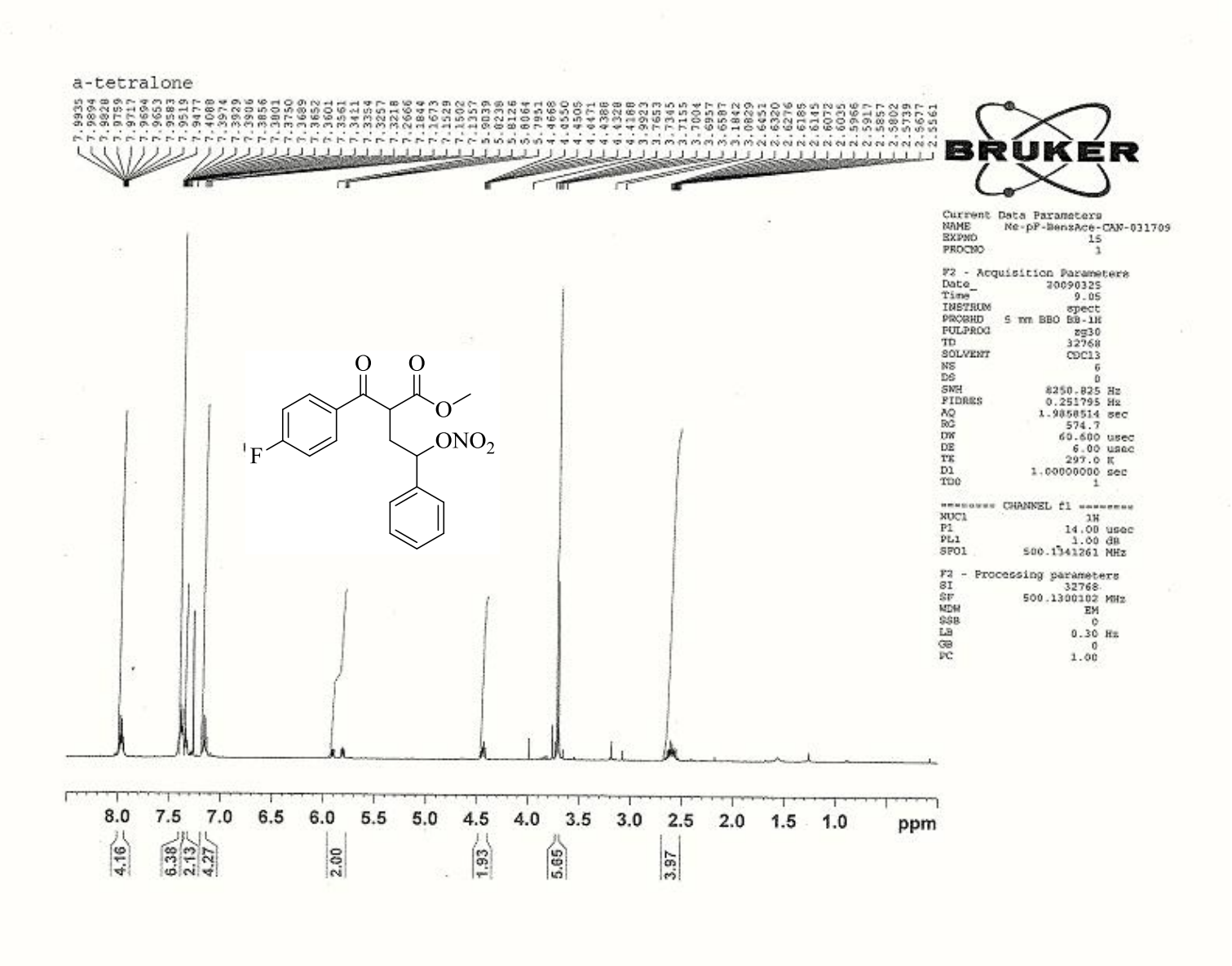

CombiFlash1-Fr20
BRUKER
Current Data Parameters
NAME DiPhSty-CTAN-030509
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date 20090306
Time 11.36
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 6009.615 Hz
FIDRES 0.183399 Hz
AQ 2.7264309 sec
RG 181
DW 83.200 usec
DE 6.00 usec
TE 296.2 K
D1 1.00000000 sec
TD0 1
-------- CHANNEL f1 --------
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1327510 MHz
F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
O
Ph
ONO2
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.04
2.06
2.15
2.15
2.28
4.31
1.00
1.03
2.07

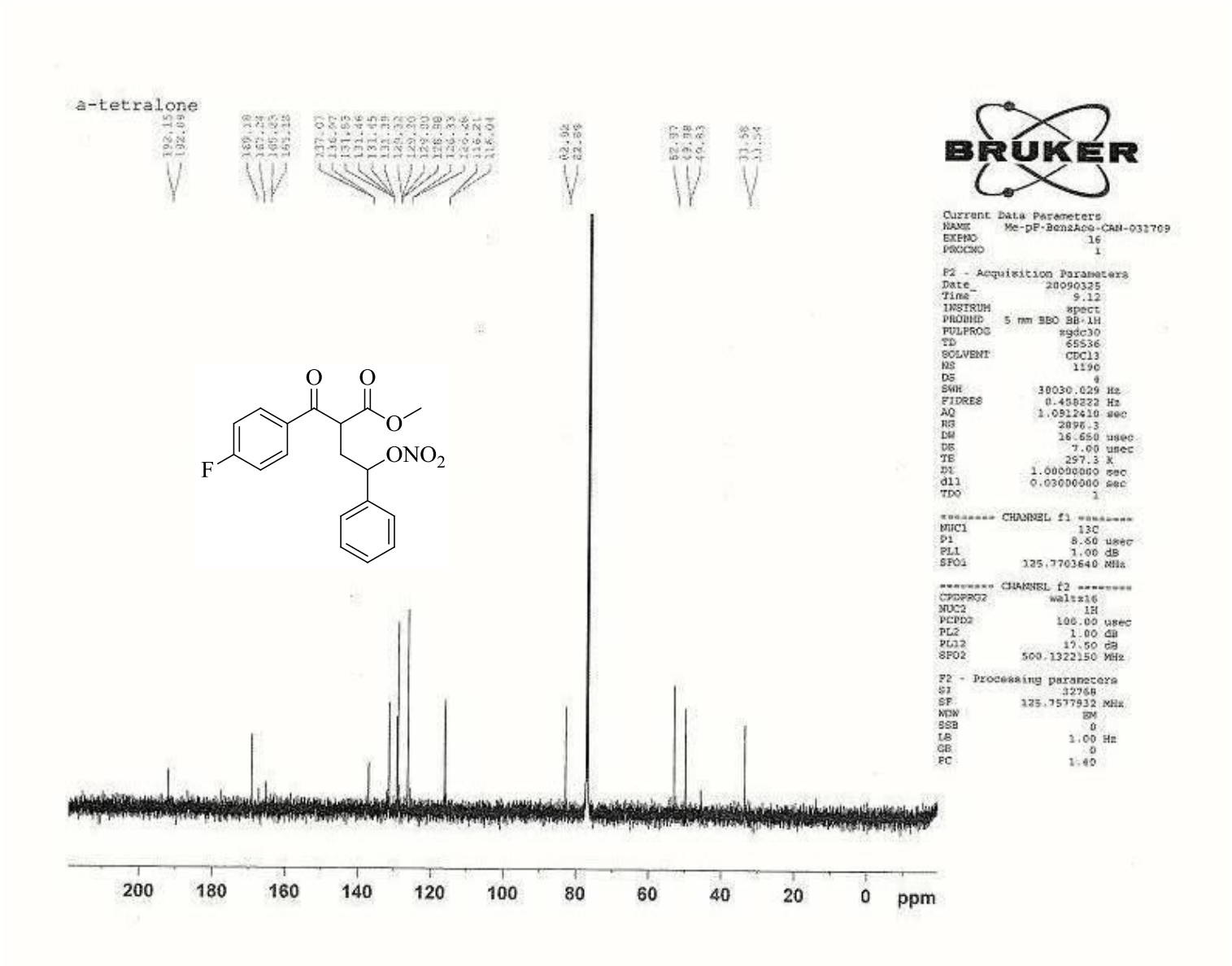

CombiFlash1-Fr20-13C
194.98
194.90
137.38
135.40
135.17
133.75
129.26
129.09
128.87
128.99
128.58
128.46
126.23
81.25
52.38
33.86
O
O
Ph
ONO2
200
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER
Current Data Parameters
NAME DiPhSty-CTAN-030509
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090306
Time 11.45
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 172
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 1824.6
DW 16.650 usec
DE 7.00 usec
TE 297.0 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz
F2 - Processing parameters
SI 32768
SF 125.7577955 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

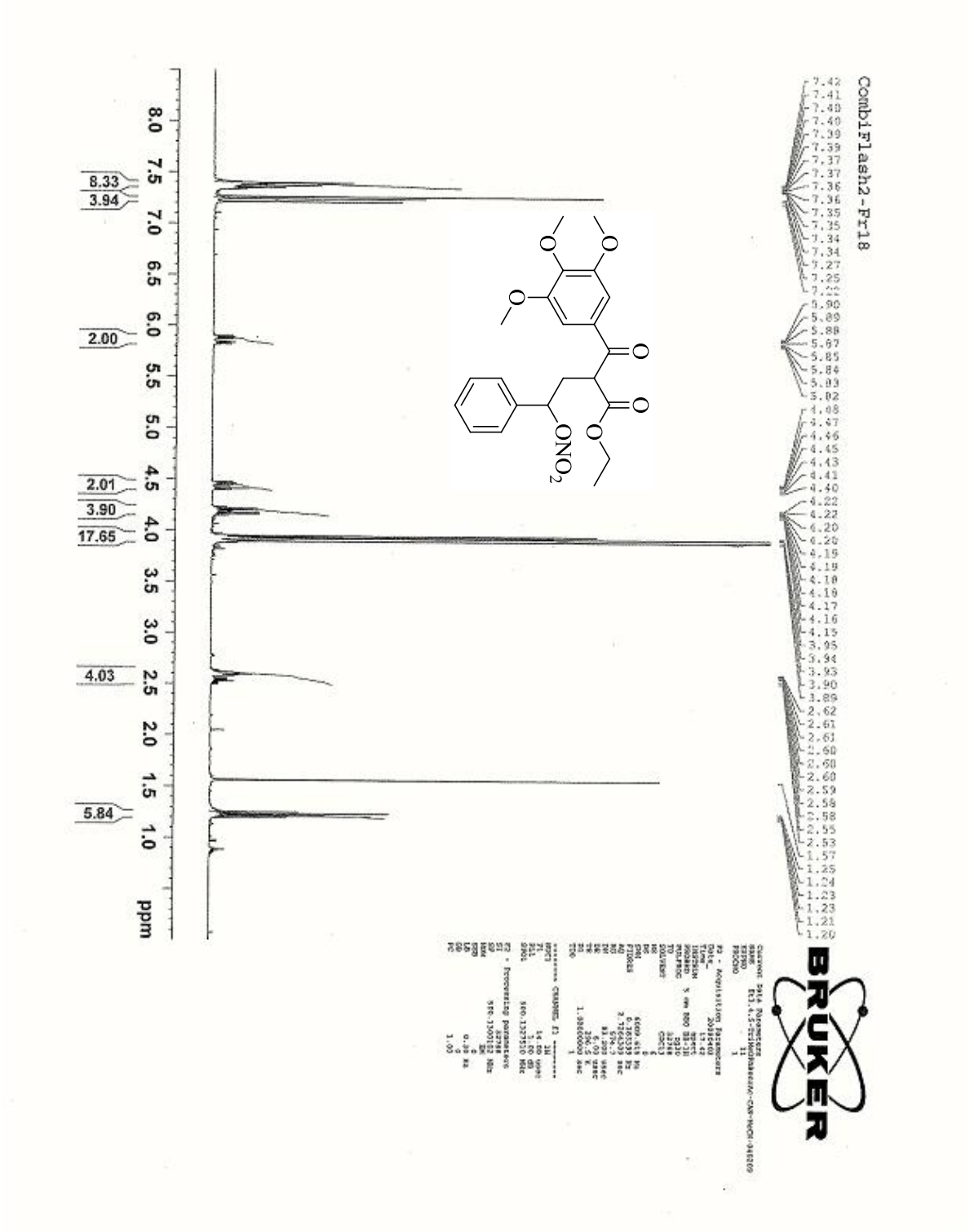


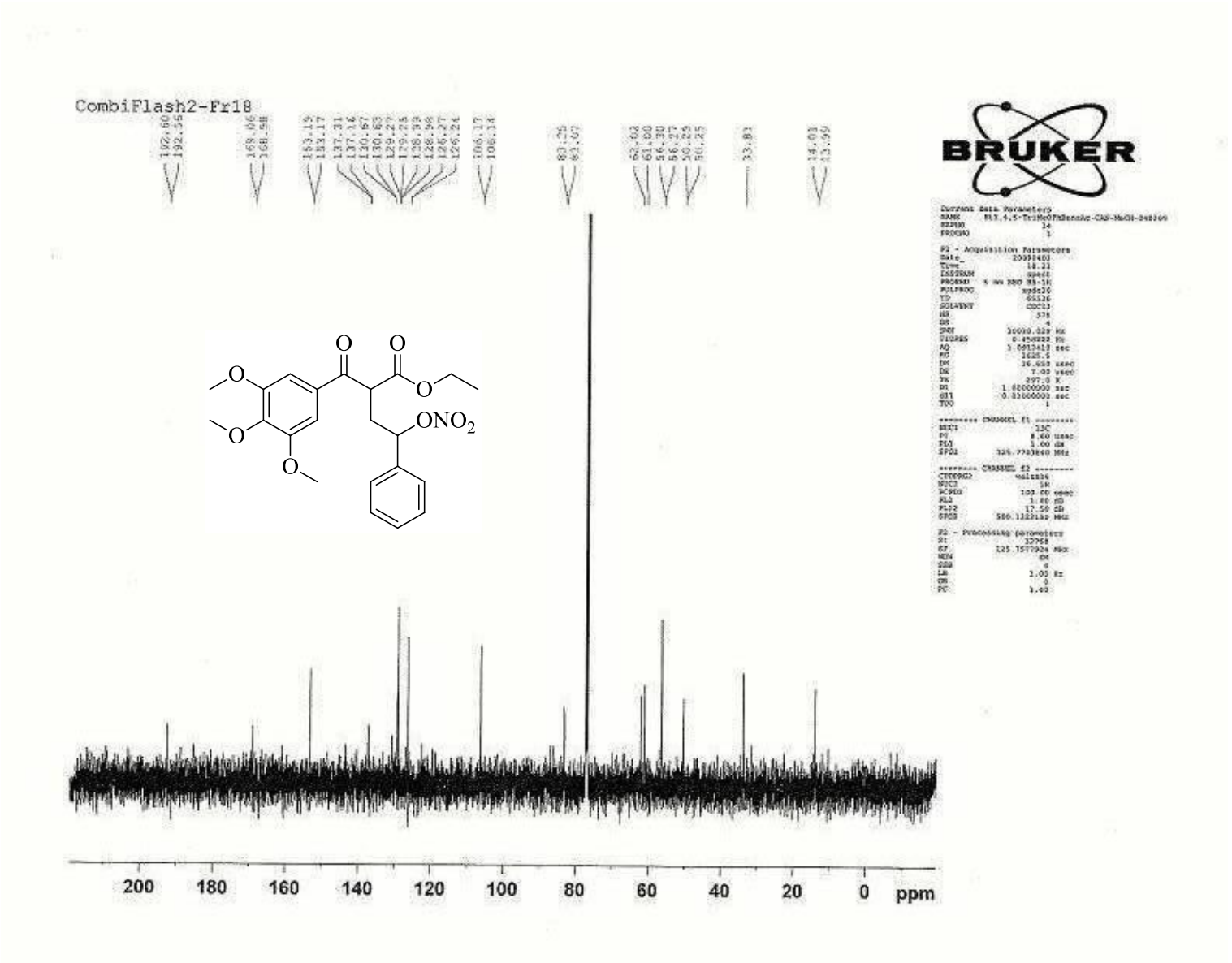

```
Current Data Parameters
NAME      EtBenzAce-CTAN-021709
EXPNO                        5
PROCNO                       1

F2 - Acquisition Parameters
Date_              20090217
Time                 13.10
INSTRUN              spect
PROBHD    5 mm BBO BR-1H
PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
NS                      6
DS                      0
SWH               6009.615 Hz
FIDRES           0.183399 Hz
AQ               2.7264309 sec
RG                    114
DW                 83.200 usec
DE                  6.00 usec
TE                296.6 K
D1              1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                 14.00 usec
PL1                 1.00 dB
SFO1          500.1327510 MHz

F2 - Processing parameters
SI                  32768
SF            500.1300102 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

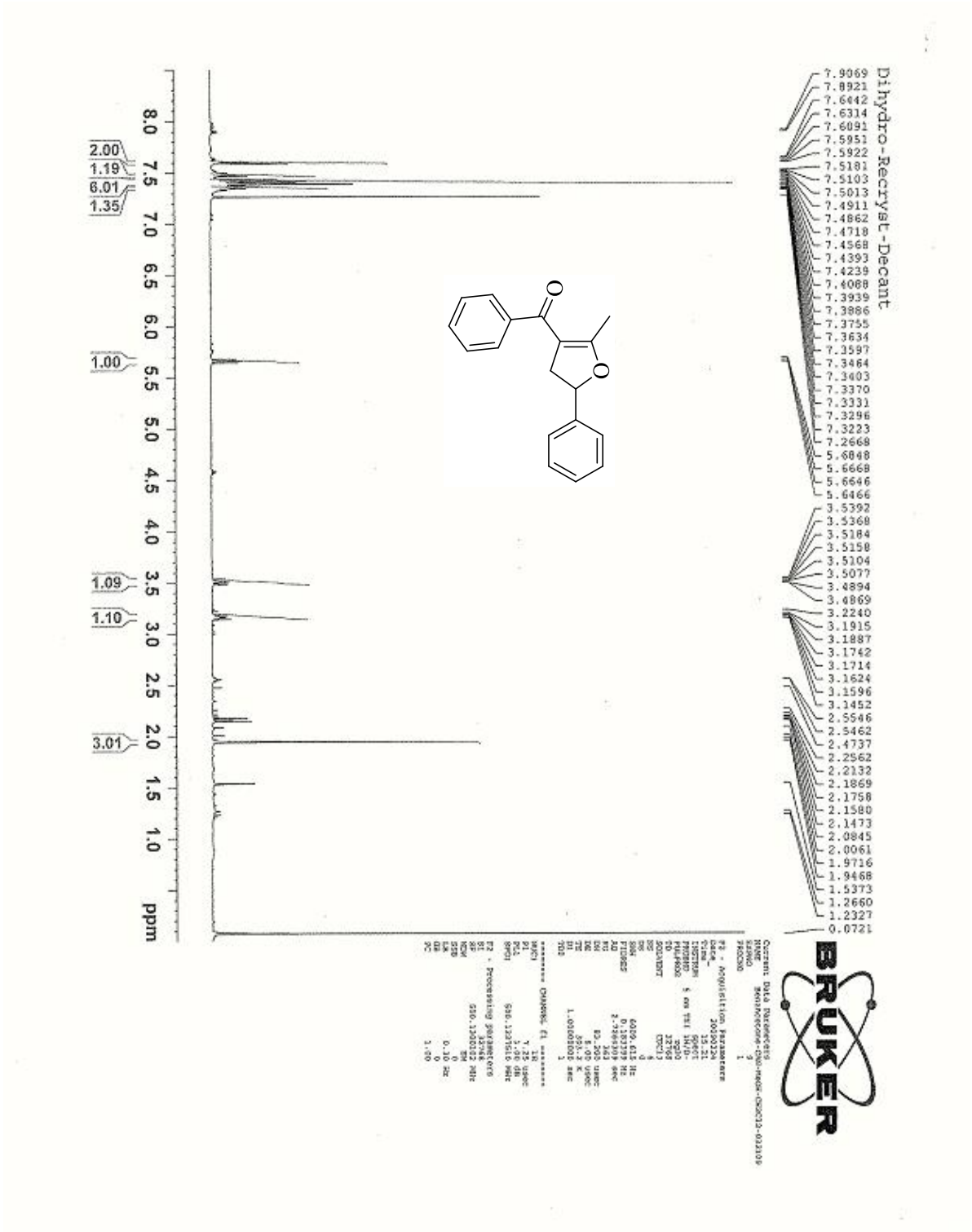

CombiFlash1-Fr8
BRUKER
NAME EtBenzAce-CTAN-021709
EXPNO 6
PROCNO 1
Date_ 20090217
Time 13.15
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 960
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 8192
DW 16.650 usec
DE 7.00 usec
TE 297.1 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz
SI 32768
SF 125.7577958 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
O
O
O
ONO2
200
180
160
140
120
100
80
60
40
20
0
ppm

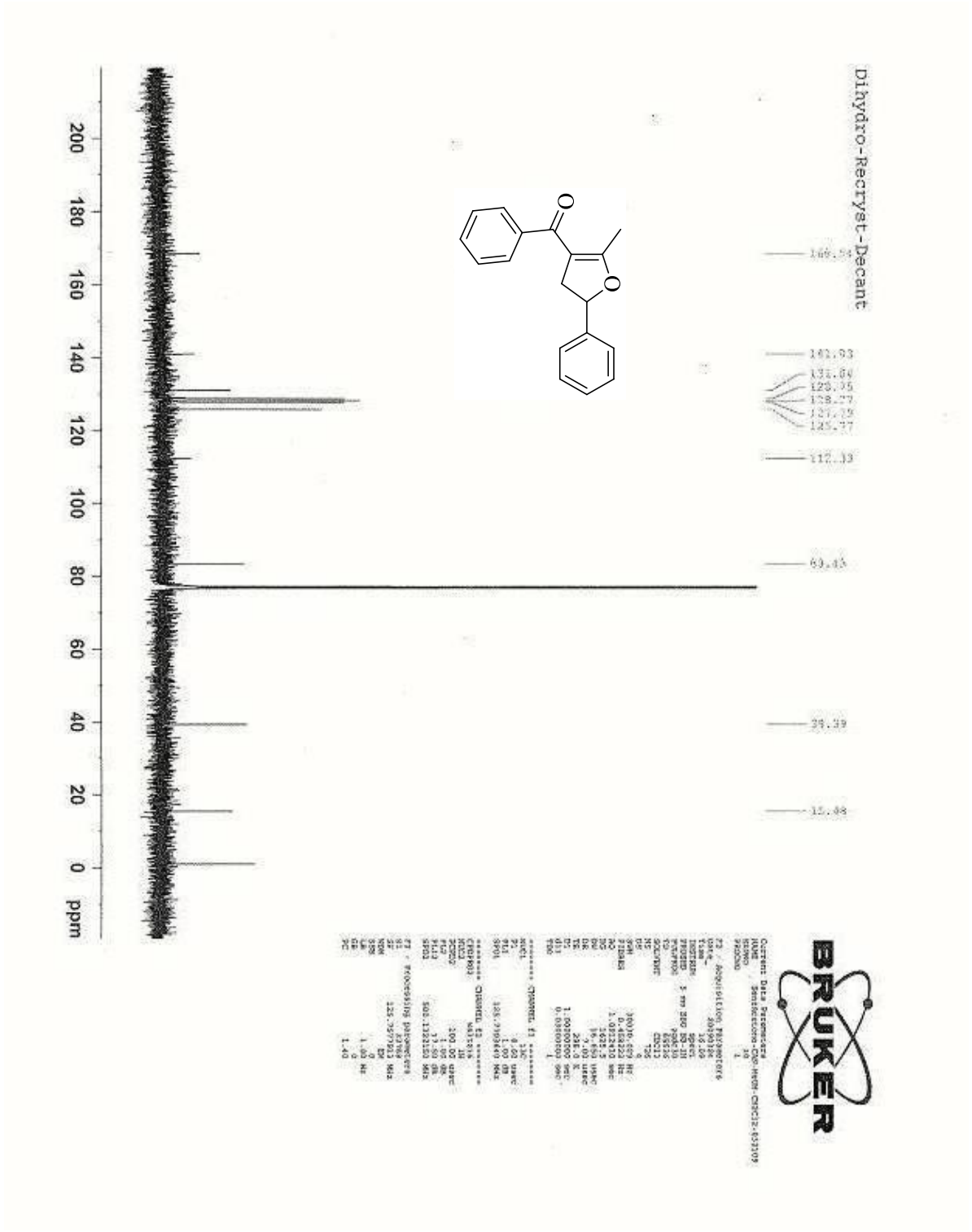

a-tetralone
7.9935 7.9894 7.9828 7.9759 7.9717 7.9694 7.9653 7.9583 7.9519 7.9477 7.4008 7.3974 7.3929 7.3906 7.3856 7.3801 7.3750 7.3689 7.3652 7.3601 7.3561 7.3411 7.3354 7.3257 7.3218 7.2666 7.1844 7.1673 7.1529 7.1502 7.1357 5.9039 5.8238 5.8126 5.8064 5.7951 4.4668 4.4550 4.4505 4.4471 4.4388 4.4328 4.4188 3.9923 3.7653 3.7345 3.7155 3.7004 3.6957 3.6587 3.1842 3.0829 2.6451 2.6320 2.6276 2.6185 2.6145 2.6072 2.6035 2.5966 2.5917 2.5857 2.5802 2.5739 2.5677 2.5561
BRUKER
Current Data Parameters
NAME Me-pF-BenzAce-CAN-031709
EXPNO 15
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090325
Time 9.05
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8250.825 Hz
FIDRES 0.251795 Hz
AQ 1.9858514 sec
RG 574.7
DW 60.600 usec
DE 6.00 usec
TE 297.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1341261 MHz
F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
O
O
ONO2
F
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
4.16
6.38
2.13
4.27
2.00
1.93
5.65
3.97

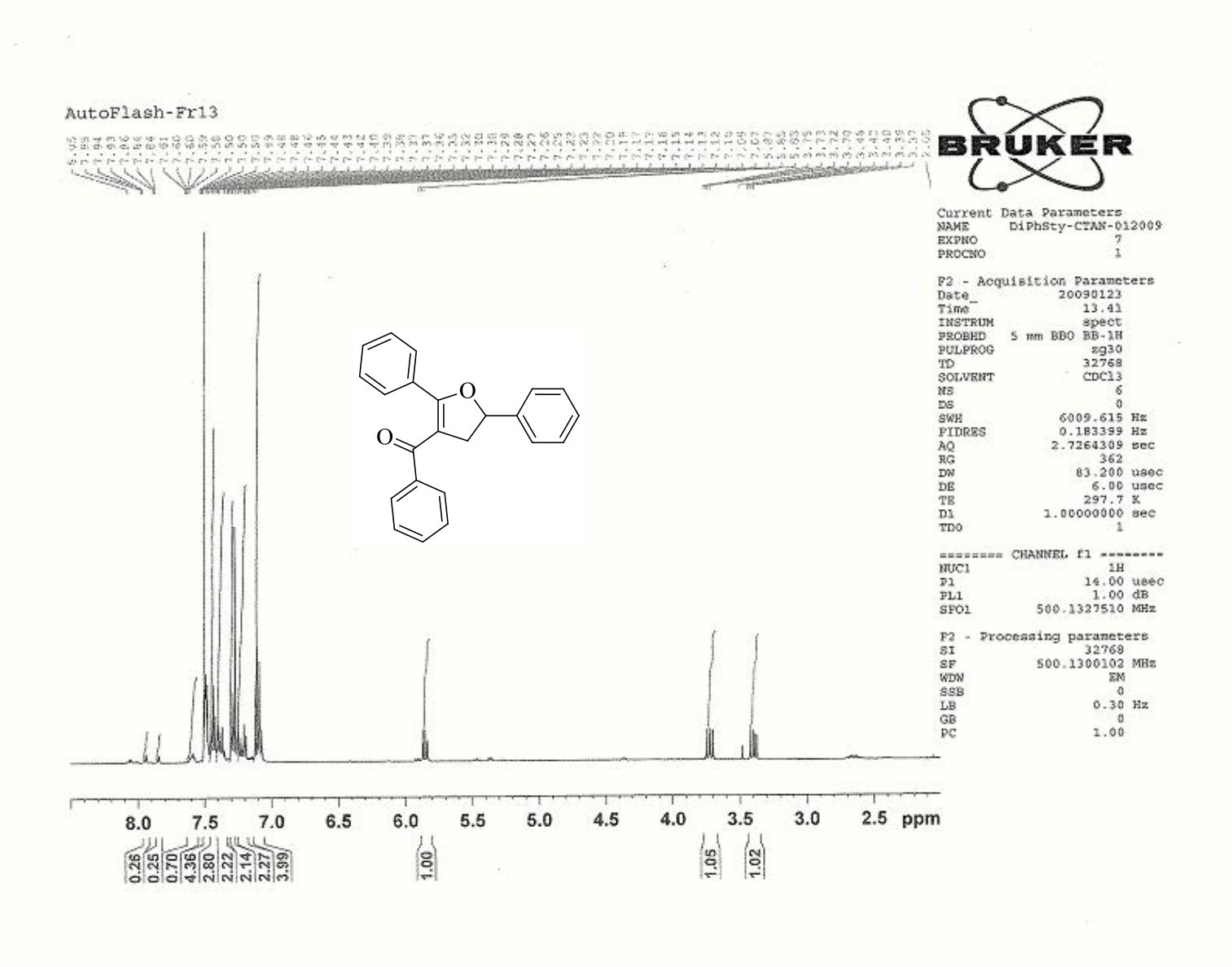

a-tetralone
192.15
192.09
169.18
167.24
165.25
165.18
137.07
136.67
131.65
131.46
131.45
131.35
129.32
129.30
129.00
126.98
126.33
126.26
116.21
116.04
82.92
82.89
52.37
49.98
49.83
31.58
31.34
O
O
O
F
ONO2
200
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER
Current Data Parameters
NAME Me-pF-BenzAco-CAN-031709
EXPNO 16
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090325
Time 9.12
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 1196
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 2896.3
DW 16.650 usec
DE 7.00 usec
TE 297.3 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 1.00 dB
SFO1 125.7703640 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz
F2 - Processing parameters
SI 32768
SF 125.7577932 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

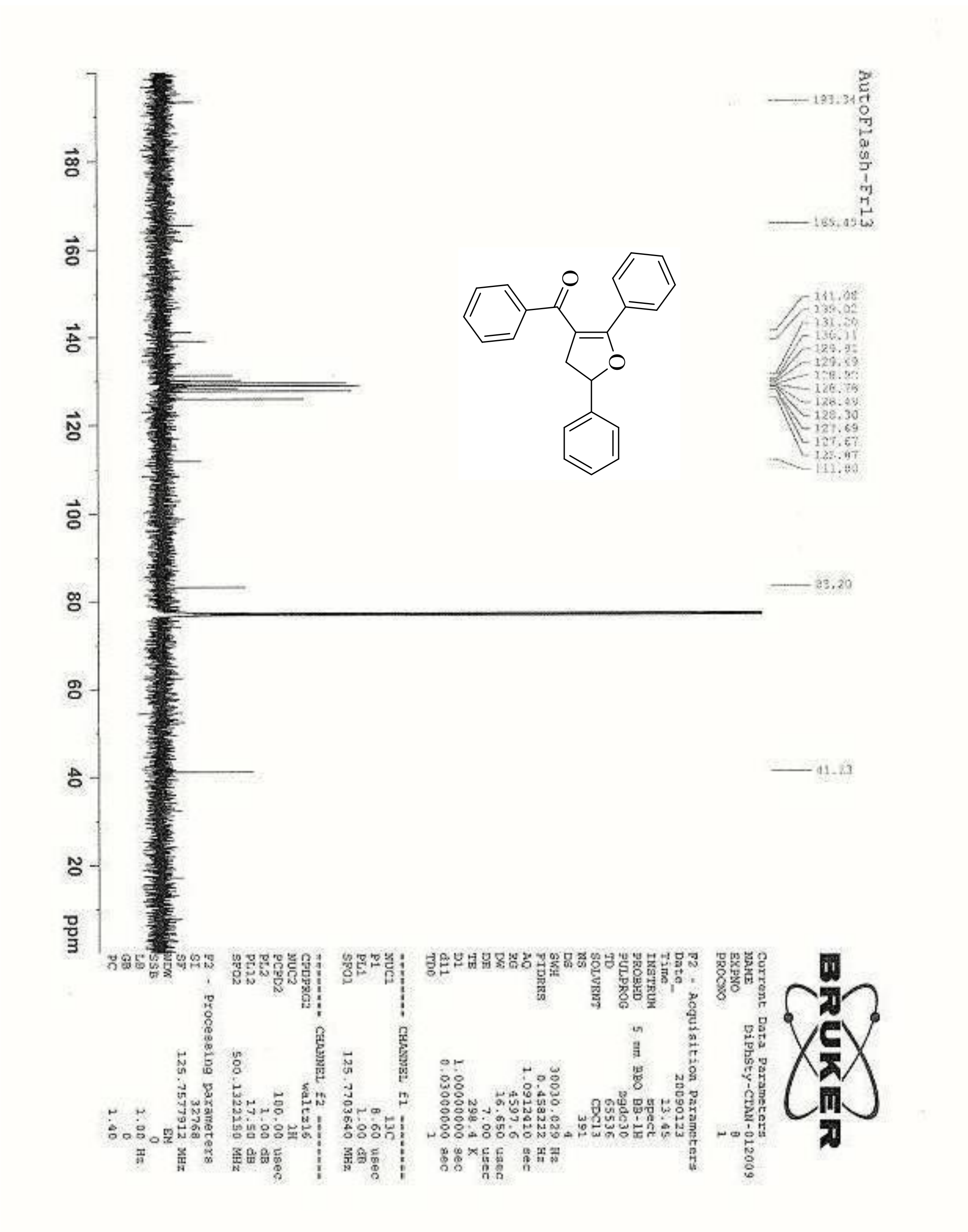

CombiFlash2-Fr18
8.33
3.94
2.00
2.01
3.90
17.65
4.03
5.84
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
BRUKER

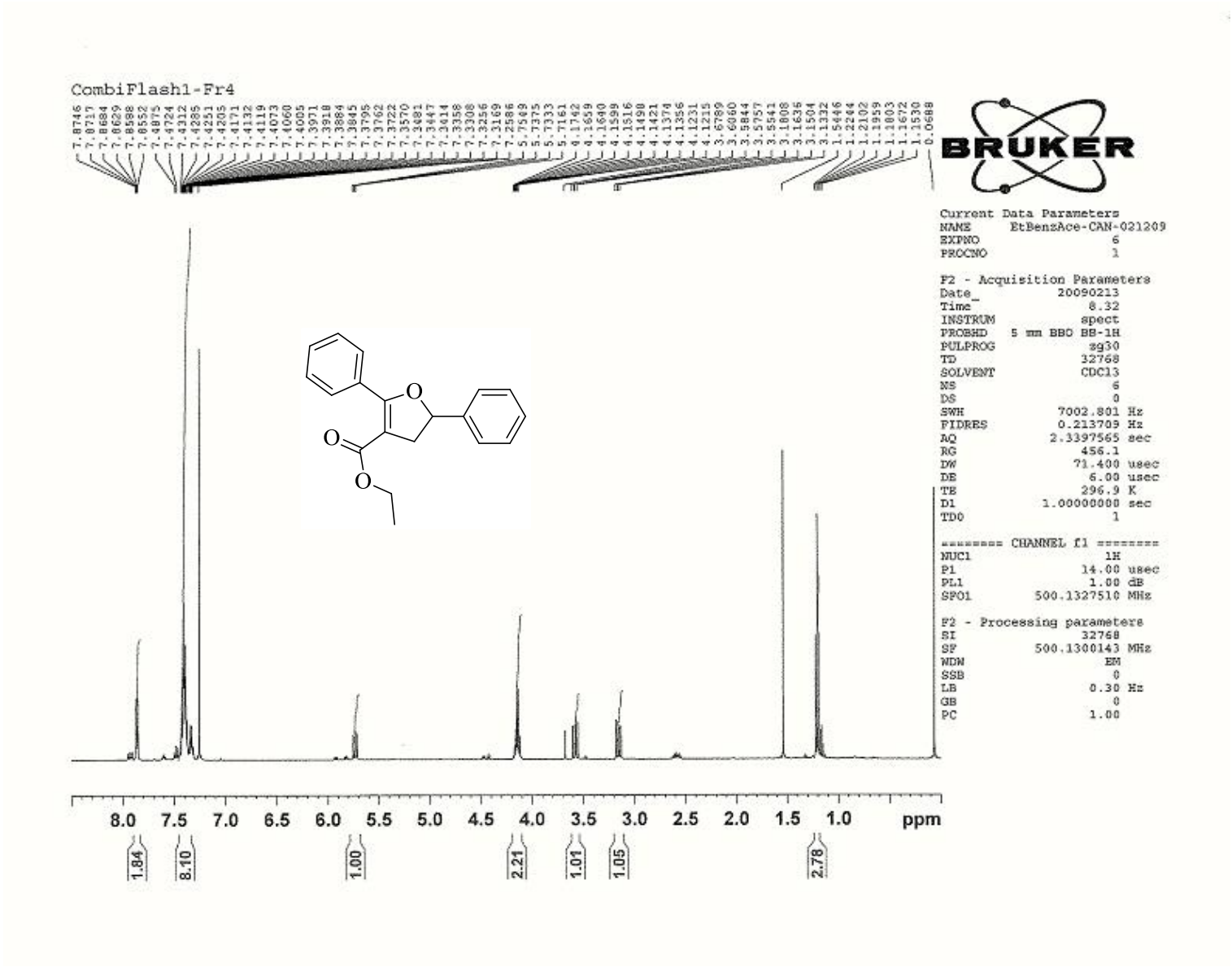

CombiFlash2-Fr18
192.60
192.55
169.06
168.98
153.19
153.17
137.31
137.16
130.67
130.63
129.27
129.25
128.93
128.96
126.27
126.24
106.17
106.14
83.29
83.07
62.03
61.90
56.30
56.27
50.25
50.25
33.81
14.03
13.99
O
O
O
O
O
O
ONO2
200
180
160
140
120
100
80
60
40
20
0
ppm

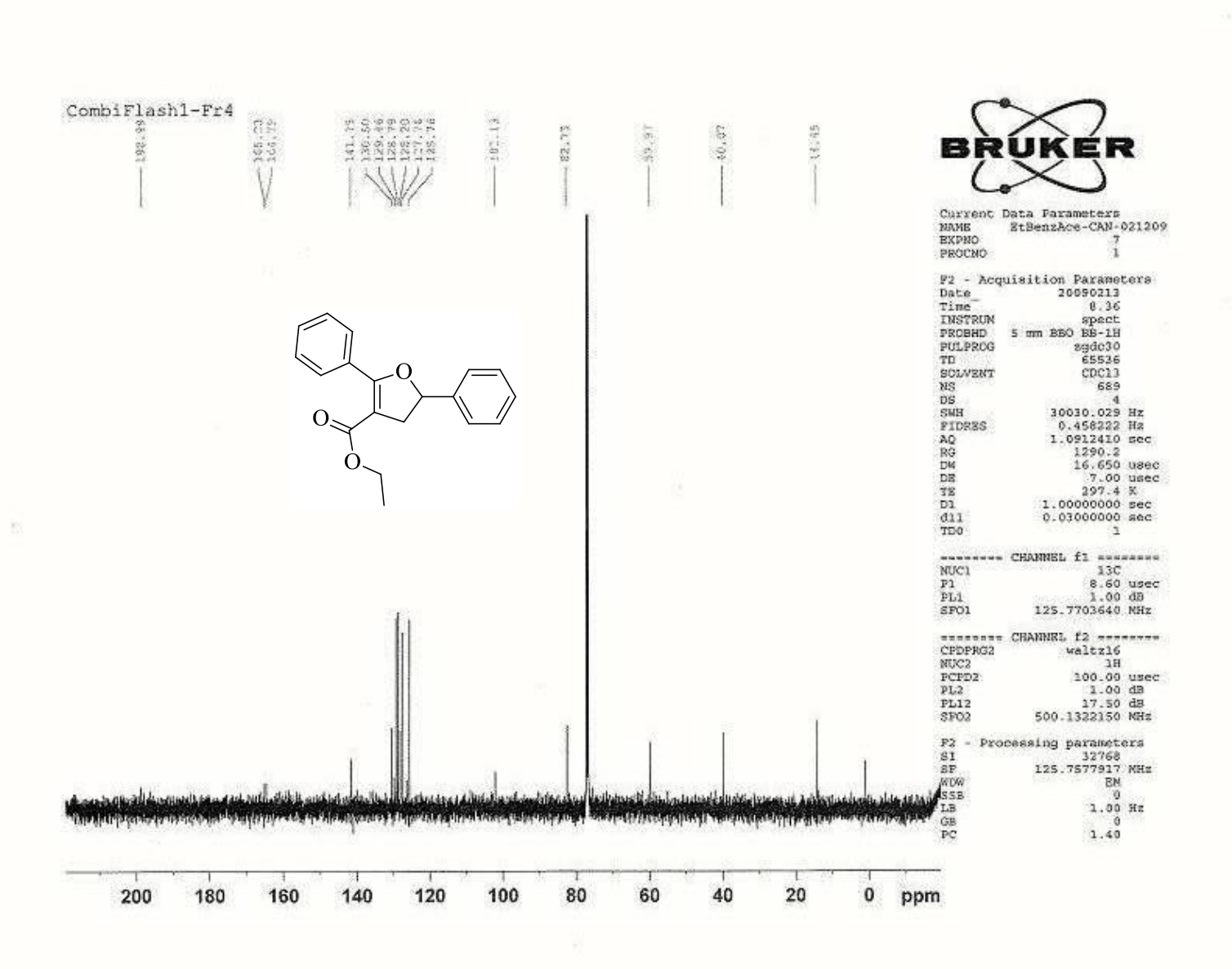

Dihydro-Recryst-Decant
7.9069
7.8921
7.6442
7.6314
7.6091
7.5951
7.5922
7.5181
7.5103
7.5013
7.4911
7.4862
7.4718
7.4568
7.4393
7.4239
7.4088
7.3939
7.3886
7.3755
7.3634
7.3597
7.3464
7.3403
7.3370
7.3331
7.3296
7.3223
7.2668
5.6048
5.6668
5.6646
5.6466
3.5392
3.5368
3.5184
3.5158
3.5104
3.5077
3.4894
3.4869
3.2240
3.1915
3.1887
3.1742
3.1714
3.1624
3.1596
3.1452
2.5546
2.5462
2.4737
2.2562
2.2132
2.1869
2.1758
2.1580
2.1473
2.0845
2.0061
1.9716
1.9468
1.5373
1.2660
1.2327
0.0721
2.00
1.19
6.01
1.35
1.00
1.09
1.10
3.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
BRUKER

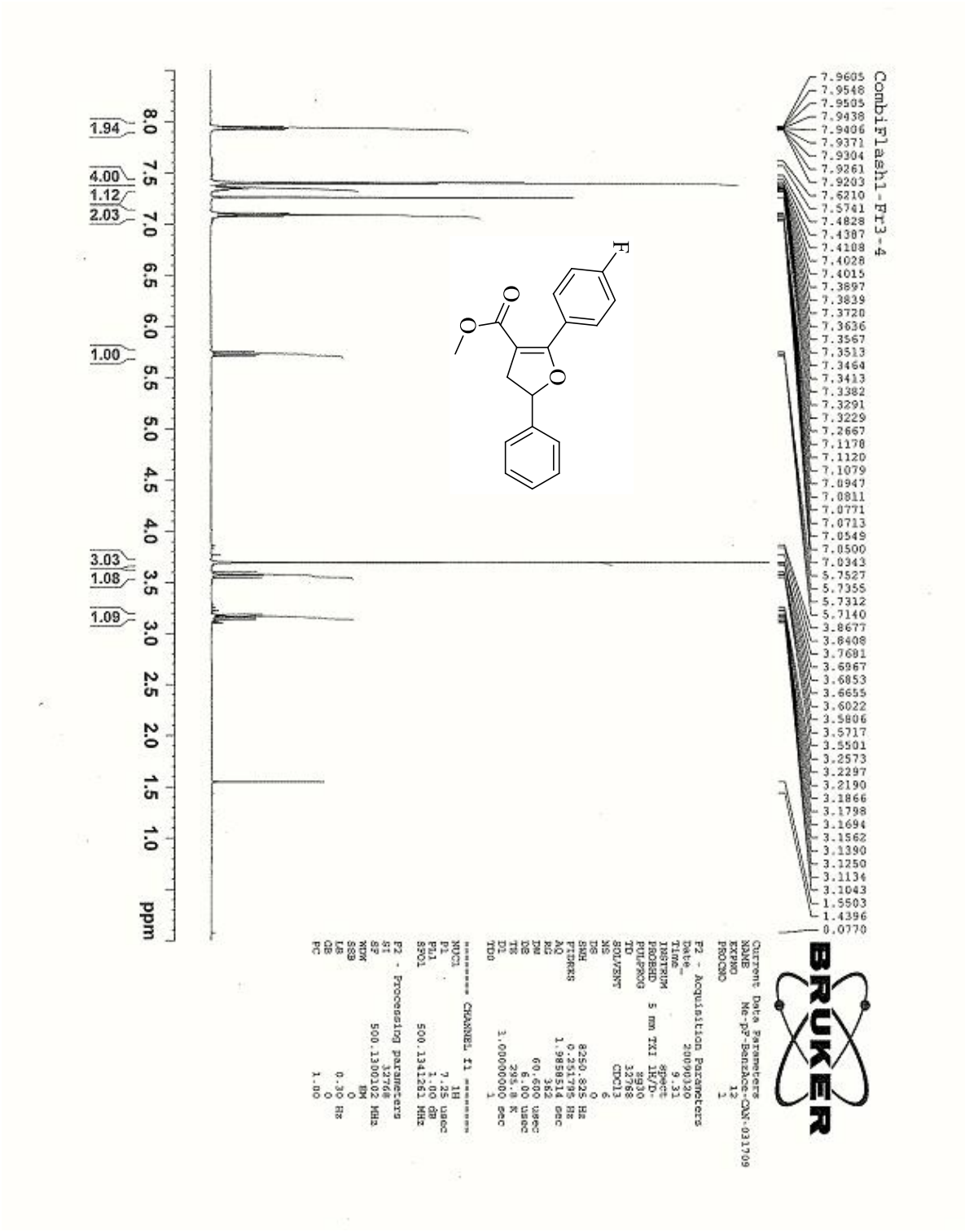

Dihydro-Recryst-Decant
169.54
161.93
131.84
129.95
128.77
127.79
125.77
117.33
60.45
39.39
15.48
200
180
160
140
120
100
80
60
40
20
0
ppm

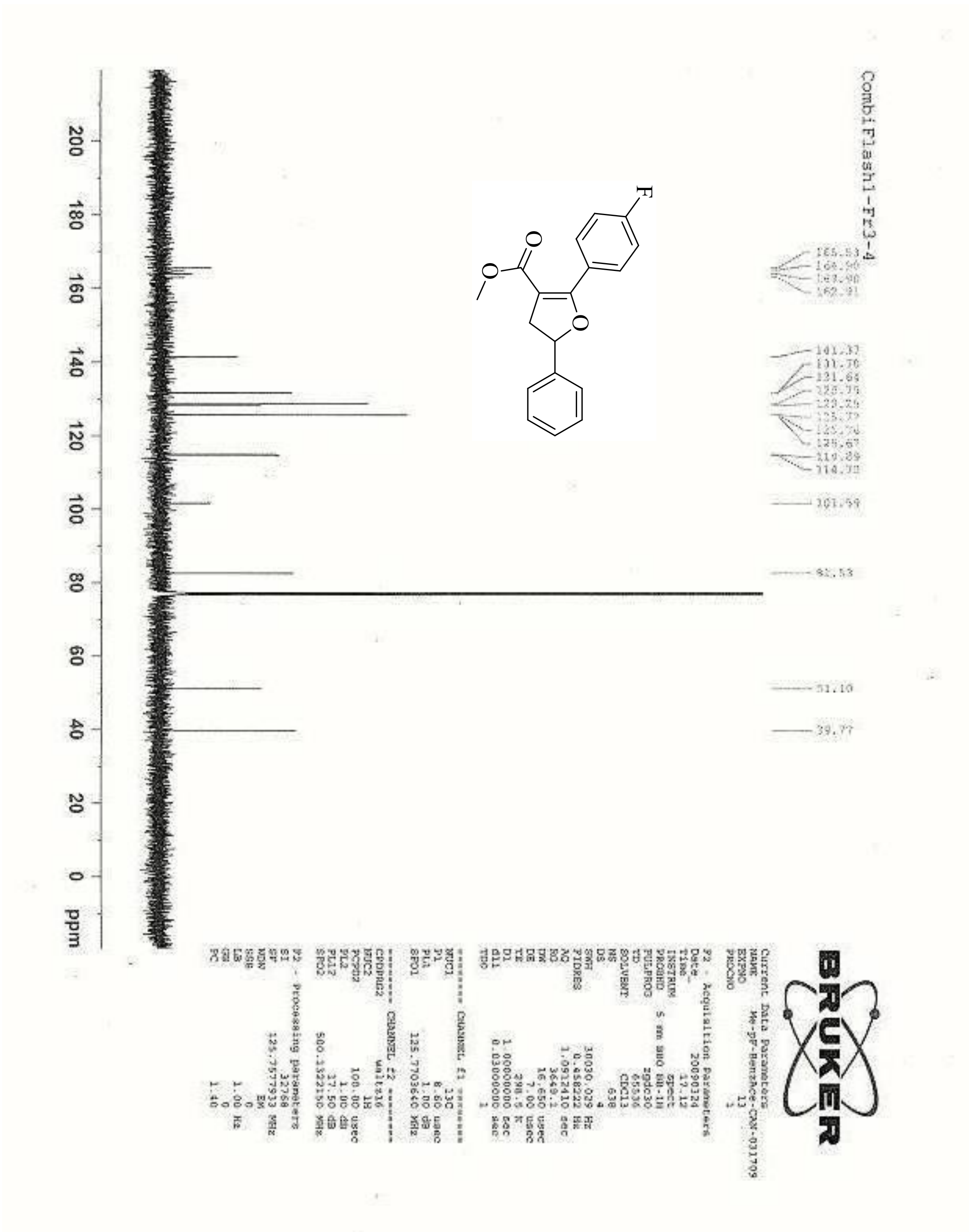

AutoFlash-Fr13
BRUKER
Current Data Parameters
NAME DiPhSty-CTAN-012009
EXPNO 7
PROCNO 1
P2 - Acquisition Parameters
Date_ 20090123
Time 13.41
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 6009.615 Hz
FIDRES 0.183399 Hz
AQ 2.7264309 sec
RG 362
DW 83.200 usec
DE 6.00 usec
TE 297.7 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1327510 MHz
P2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
O
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 ppm
0.26 0.25 0.70 4.36 2.80 2.22 2.14 2.27 3.99
1.00
1.05
1.02

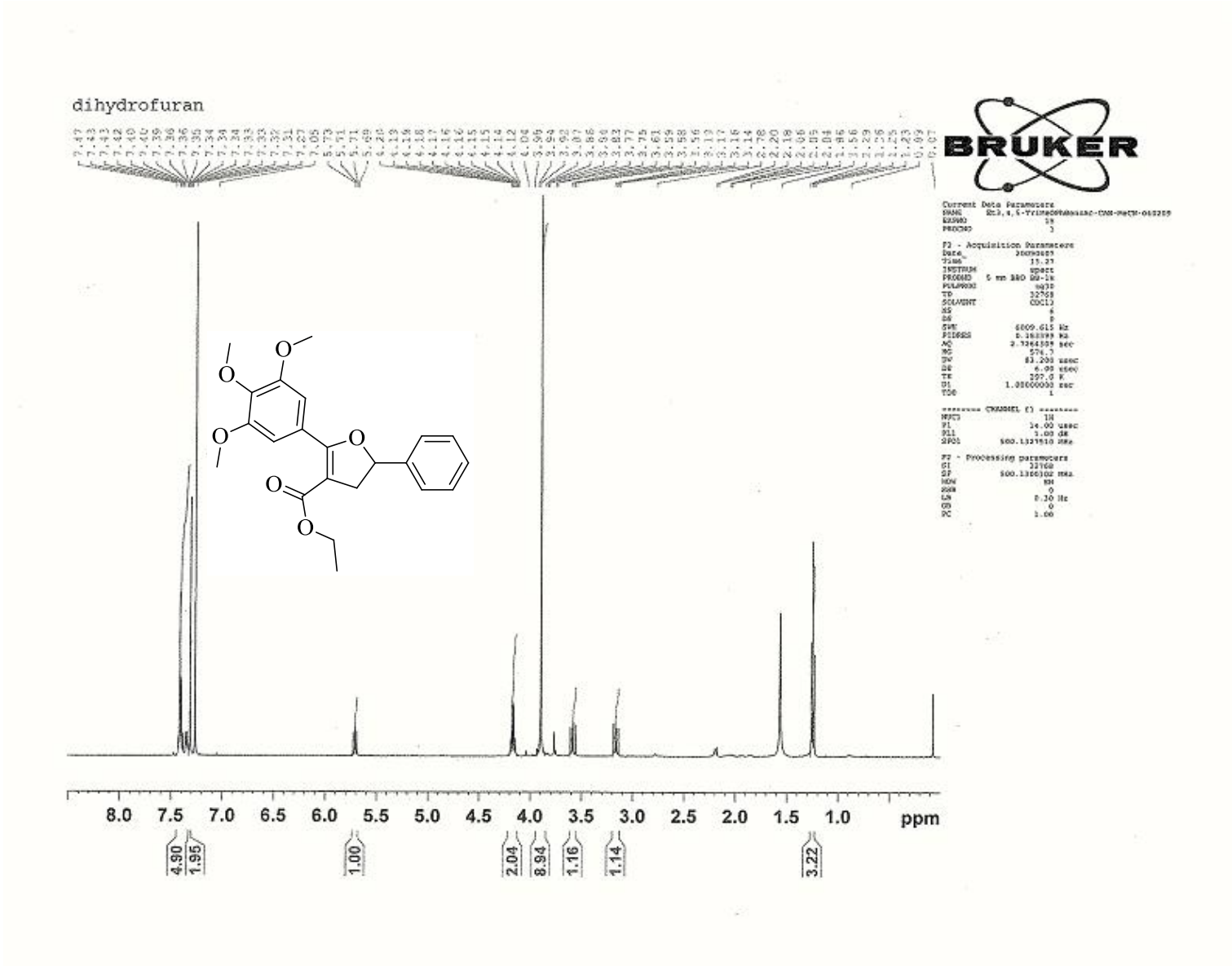

AutoFlash-Fr13
193.34
165.45
141.08
111.80
83.20
41.13
O
O
BRUKER
Current Data Parameters
NAME DiPhSty-CTAN-012009
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090123
Time 13.45
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 391
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 4597.6
DW 16.650 usec
DE 7.00 usec
TE 298.4 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz
F2 - Processing parameters
SI 32768
SF 125.7577912 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
180 160 140 120 100 80 60 40 20 ppm

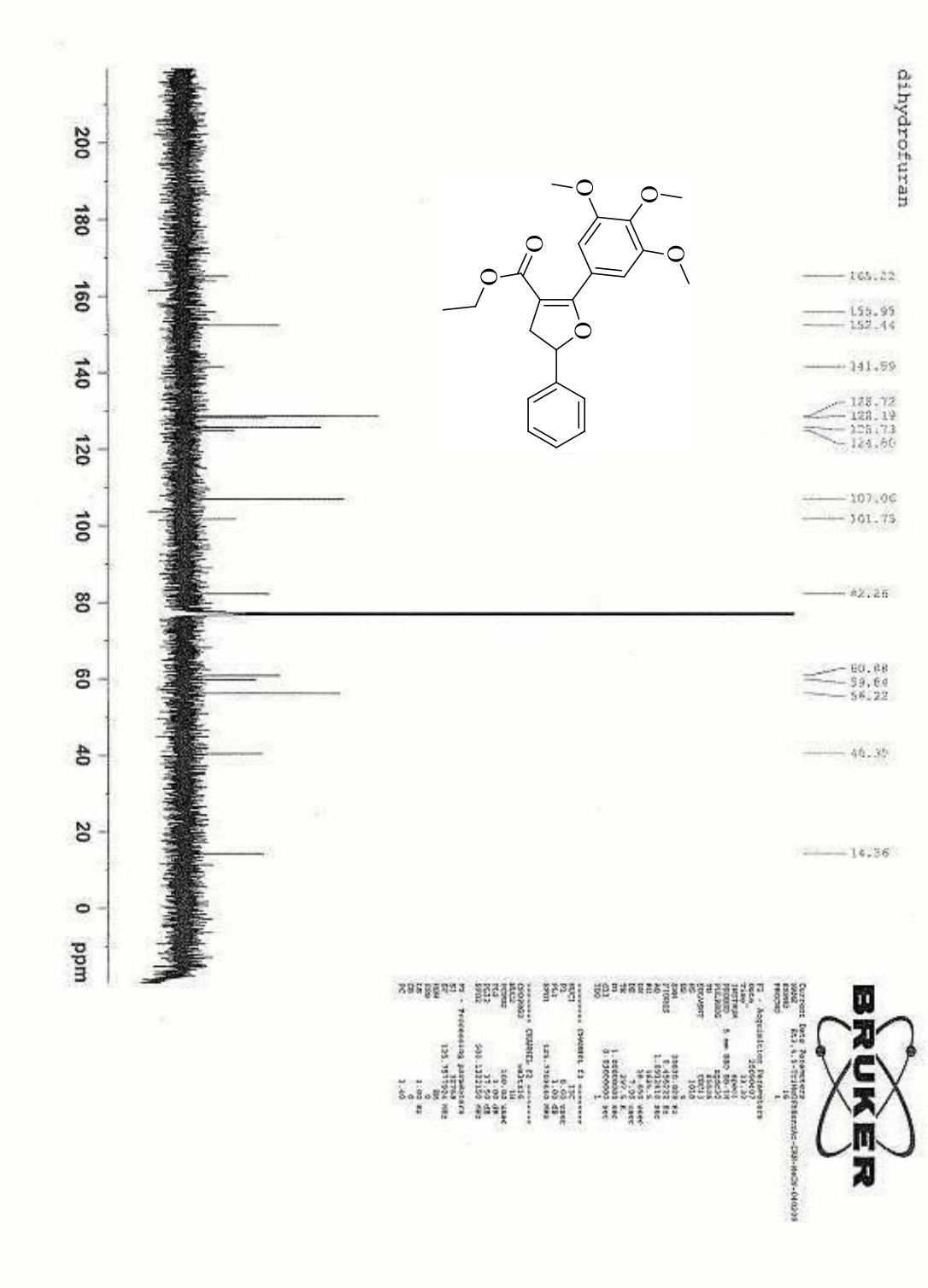

CombiFlash1-Fr4
BRUKER
Current Data Parameters
NAME EtBenzAce-CAN-021209
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090213
Time 8.32
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 7002.801 Hz
FIDRES 0.213709 Hz
AQ 2.3397565 sec
RG 456.1
DW 71.400 usec
DE 6.00 usec
TE 296.9 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1327510 MHz
F2 - Processing parameters
SI 32768
SF 500.1300143 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
O
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.84
8.10
1.00
2.21
1.01
1.05
2.78


CombiFlash1-Fr4
192.99
165.23
164.79
141.13
130.50
129.46
128.79
128.20
127.76
125.76
102.13
82.73
59.97
40.07
14.45
O
O
O
200
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER
Current Data Parameters
NAME StBenzAce-CAN-021209
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090213
Time 8.36
INSTRUN spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 689
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 1290.2
DW 16.650 usec
DE 7.00 usec
TE 297.4 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz
F2 - Processing parameters
SI 32768
SF 125.7577917 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

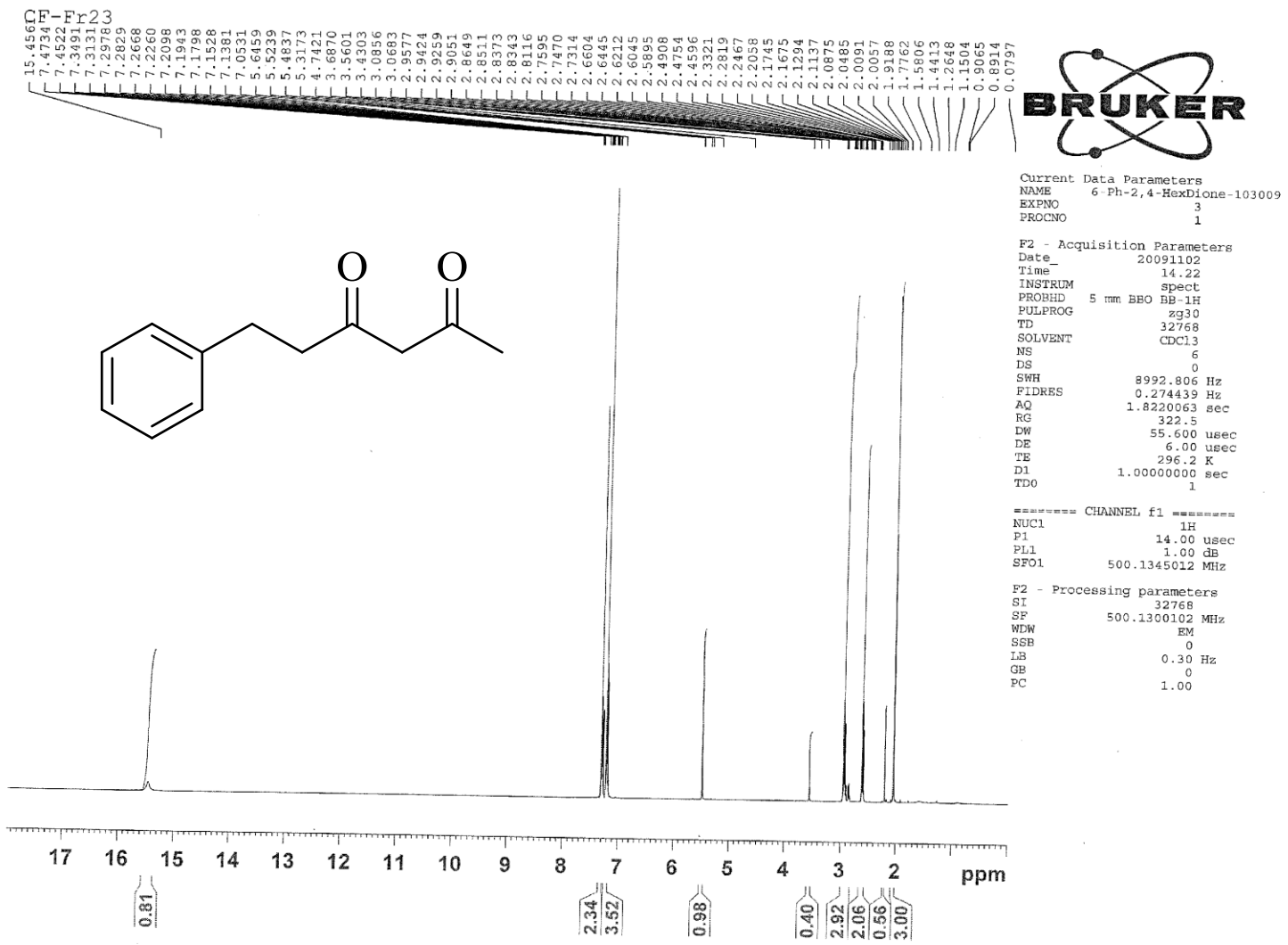

CombiFlash1-Fr3-4
7.9605
7.9548
7.9505
7.9438
7.9406
7.9371
7.9304
7.9261
7.9203
7.6210
7.5741
7.4828
7.4387
7.4108
7.4028
7.4015
7.3897
7.3839
7.3720
7.3636
7.3567
7.3513
7.3464
7.3413
7.3382
7.3291
7.3229
7.2667
7.1178
7.1120
7.1079
7.0947
7.0811
7.0771
7.0713
7.0549
7.0500
7.0343
5.7527
5.7355
5.7312
5.7140
3.8677
3.8408
3.7681
3.6967
3.6853
3.6655
3.6022
3.5806
3.5717
3.5501
3.2573
3.2297
3.2190
3.1866
3.1798
3.1694
3.1562
3.1390
3.1250
3.1134
3.1043
1.5503
1.4396
0.0770
F
O
O
O
1.94
4.00
1.12
2.03
1.00
3.03
1.08
1.09
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
BRUKER
Current Data Parameters
NAME Me-p9-Benzace-CN-031709
EXPNO 12
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090320
Time 9.31
INSTRUM spect
PROBHD 5 mm TXI 1H/D-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8250.825 Hz
FIDRES 0.251795 Hz
AQ 1.9858514 sec
RG 362
DW 60.600 usec
DE 6.00 usec
TE 295.8 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 7.25 usec
PL1 1.00 dB
SFO1 500.1341261 MHz
F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


CombiFlash1-Fr3-4
ppm

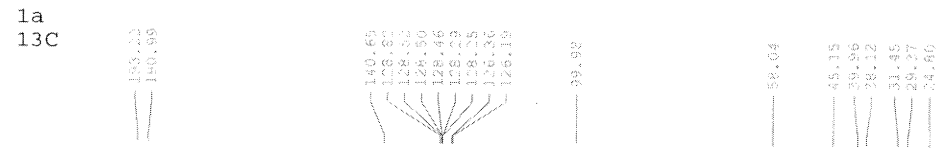

dihydrofuran
BRUKER
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
4.90
1.95
1.00
2.04
8.94
1.16
1.14
3.22

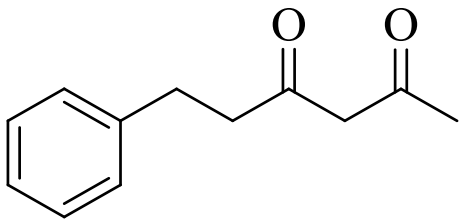

dihydrofuran
165.22
155.95
152.44
141.59
128.72
128.19
125.73
124.60
107.06
101.75
82.26
60.88
59.64
56.22
46.35
14.36
200
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER

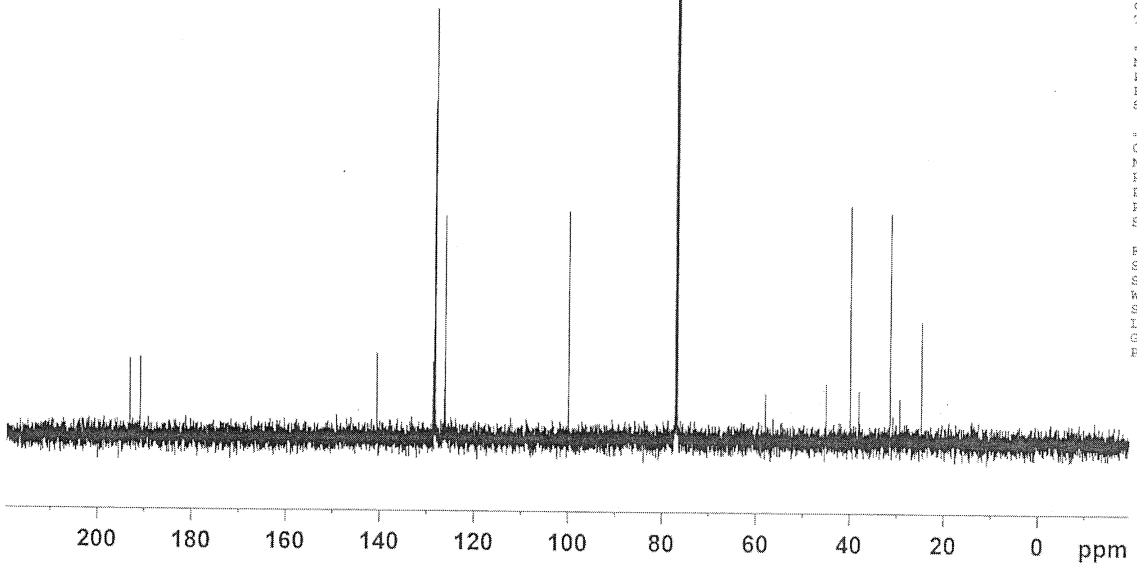
^{1}H NMR and ^{13}C NMR spectra for γ-aryl-β-dicarbonyls and β-tetralones


CF-Fr23
15.4566
7.4734
7.4522
7.3491
7.3131
7.2978
7.2829
7.2668
7.2260
7.2098
7.1943
7.1798
7.1528
7.1381
7.0531
5.6459
5.5239
5.4837
5.3173
4.7421
3.6870
3.5601
3.4303
3.0856
3.0683
2.9577
2.9424
2.9259
2.9051
2.8649
2.8511
2.8373
2.8343
2.8116
2.7595
2.7470
2.7314
2.6604
2.6445
2.6212
2.6045
2.5895
2.4908
2.4754
2.4596
2.3321
2.2819
2.2467
2.2058
2.1745
2.1675
2.1294
2.1137
2.0875
2.0485
2.0091
2.0057
1.9188
1.7762
1.5806
1.4413
1.2648
1.1504
0.9065
0.8914
0.0797
BRUKER
Current Data Parameters
NAME 6-Ph-2,4-HexDione-103009
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20091102
Time 14.22
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220063 sec
RG 322.5
DW 55.600 usec
DE 6.00 usec
TE 296.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz
F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
O
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
ppm
0.81
2.34
3.52
0.98
0.40
2.92
2.06
0.56
3.00

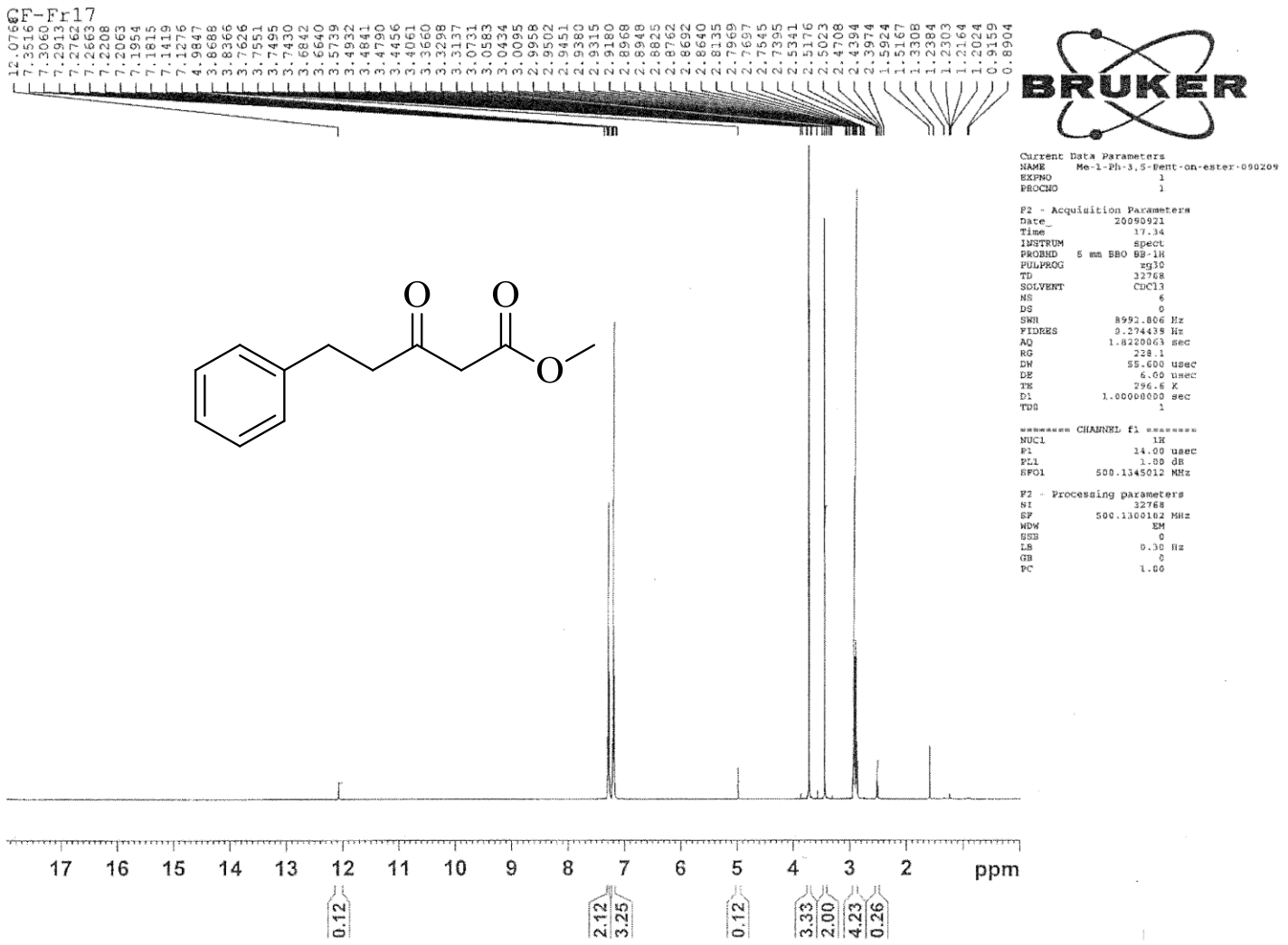
1a
13C



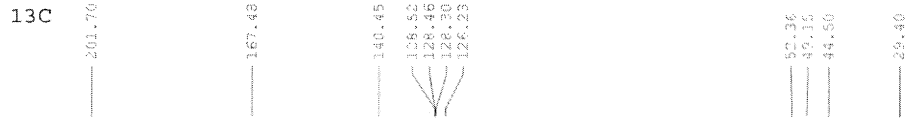


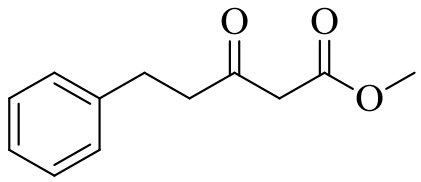


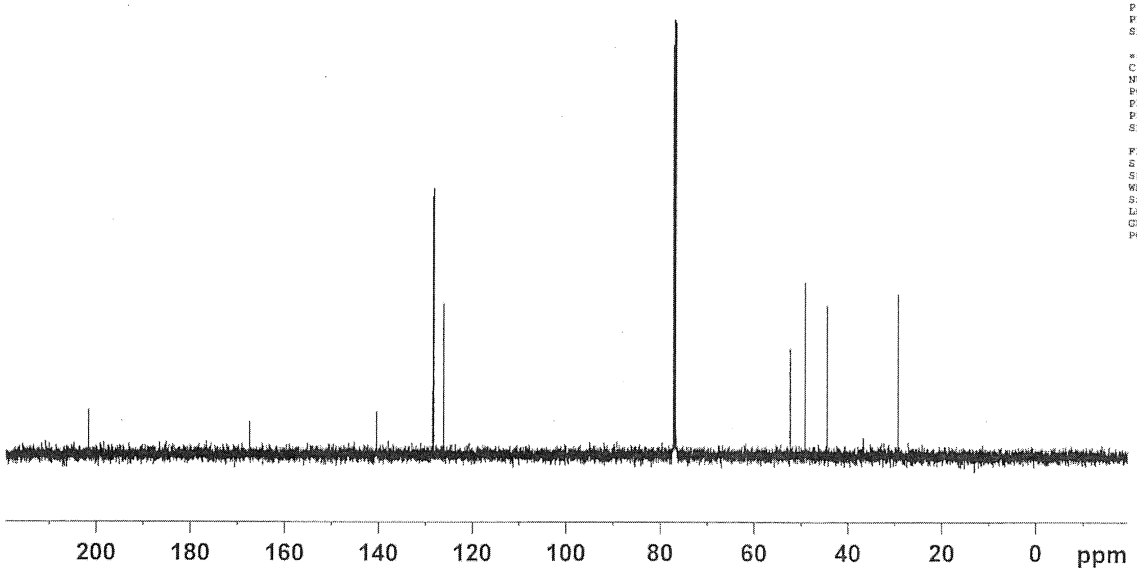

```
Current Data Parameters
NAME      6-Ph-2,4-PentDione-090209
EXPNO                  5
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090921
Time              15.14
INSTRUM           spect
PROBHD   5 mm BBO BB-1H
PULPROG          zgdc30
TD                65536
SOLVENT           CDCl3
NS                   29
DS                    4
SWH           30030.029 Hz
FIDRES         0.458222 Hz
AQ            1.0912410 sec
RG               2580.3
DW              16.650 usec
DE               7.00 usec
TE              297.2 K
D1          1.00000000 sec
d11         0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                 8.60 usec
PL1                1.00 dB
SFO1        125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2           100.00 usec
PL2                1.00 dB
PL12              17.50 dB
SFO2        500.1322150 MHz

F2 - Processing parameters
SI                32768
SF          125.7577962 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```


GF-Fr17
12.0767
7.3516
7.3060
7.2913
7.2762
7.2663
7.2208
7.2063
7.1954
7.1815
7.1419
7.1276
4.9847
3.8688
3.8366
3.7626
3.7551
3.7485
3.7430
3.6842
3.6640
3.5739
3.4932
3.4841
3.4790
3.4456
3.4061
3.3660
3.3298
3.3137
3.0731
3.0583
3.0434
3.0095
2.9958
2.9502
2.9451
2.9380
2.9315
2.9180
2.8968
2.8948
2.8825
2.8762
2.8692
2.8640
2.8135
2.7969
2.7697
2.7545
2.7395
2.5341
2.5176
2.5023
2.4708
2.4394
2.3974
1.5924
1.5167
1.3308
1.2384
1.2303
1.2164
1.2024
0.9159
0.8904
BRUKER
Current Data Parameters
NAME Me-1-Ph-3,5-Pent-on-ester-090209
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090921
Time 17.34
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220063 sec
RG 228.1
DW 55.600 usec
DE 6.00 usec
TE 296.6 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz
F2 - Processing parameters
SI 32768
SF 500.1300162 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
O
O
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
ppm
0.12
2.12
3.25
0.12
3.33
2.00
4.23
0.26

CF-Fr17
13C







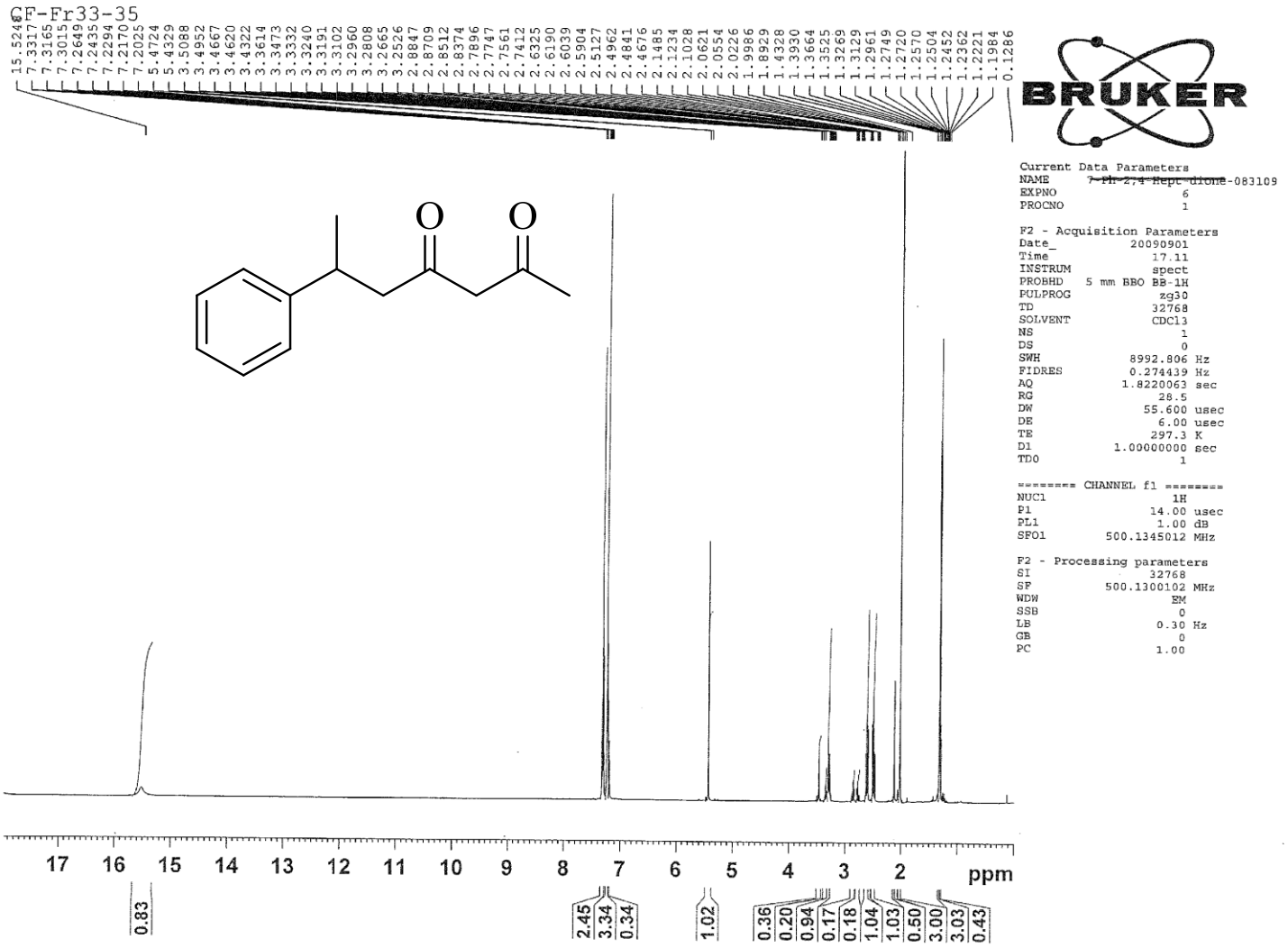
Current Data Parameters
NAME Me-1-Ph-3,5-Pent-on-ester-090209
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090921
Time 17.41
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 65
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 4096
DW 16.650 usec
DE 7.00 usec
TE 296.9 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577942 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



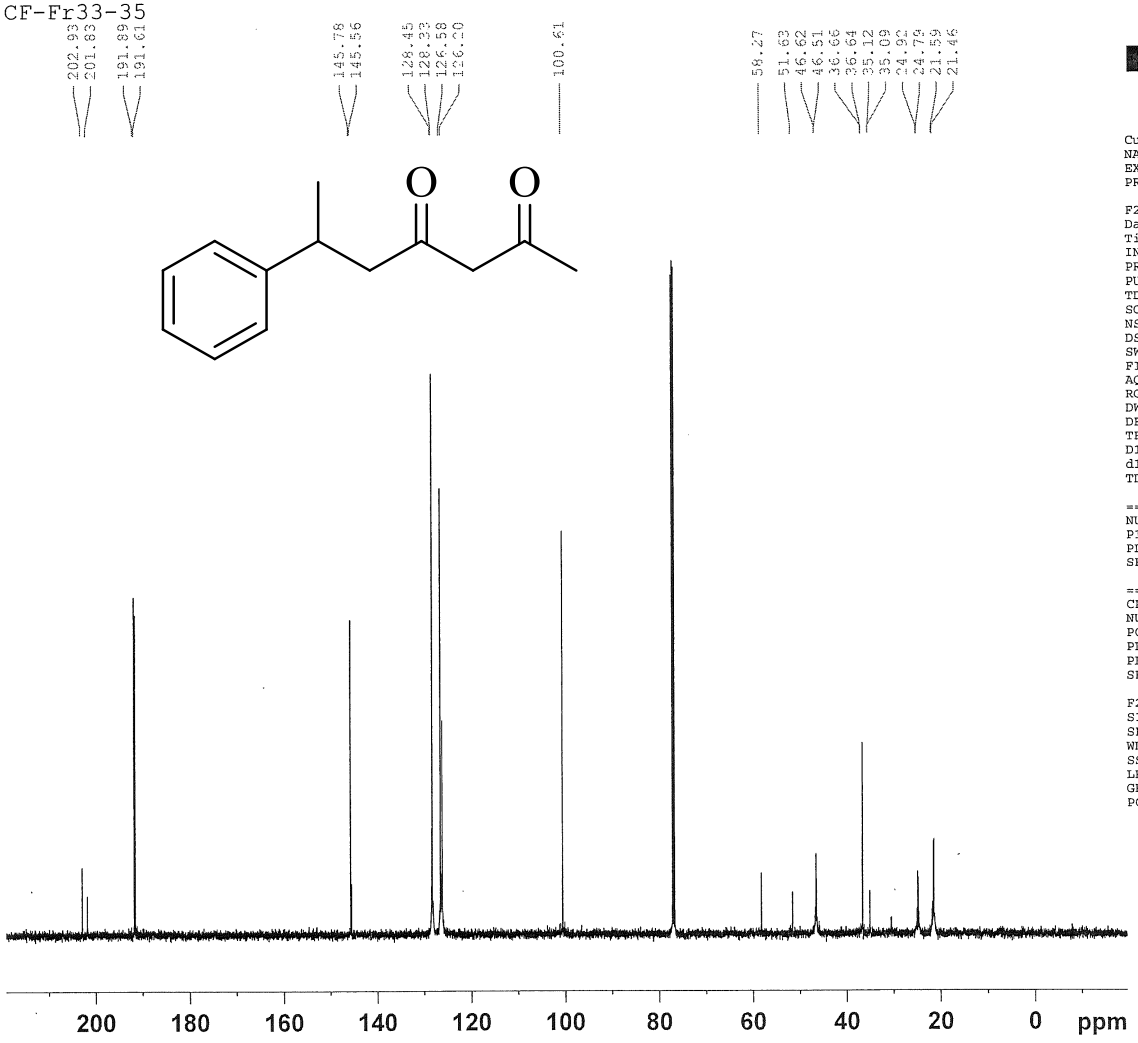
Current Data Parameters
NAME ~~7-Ph-2,4-Hept-dione~~-083109
EXPNO 6
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090901
Time 17.11
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 1
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220063 sec
RG 28.5
DW 55.600 usec
DE 6.00 usec
TE 297.3 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz

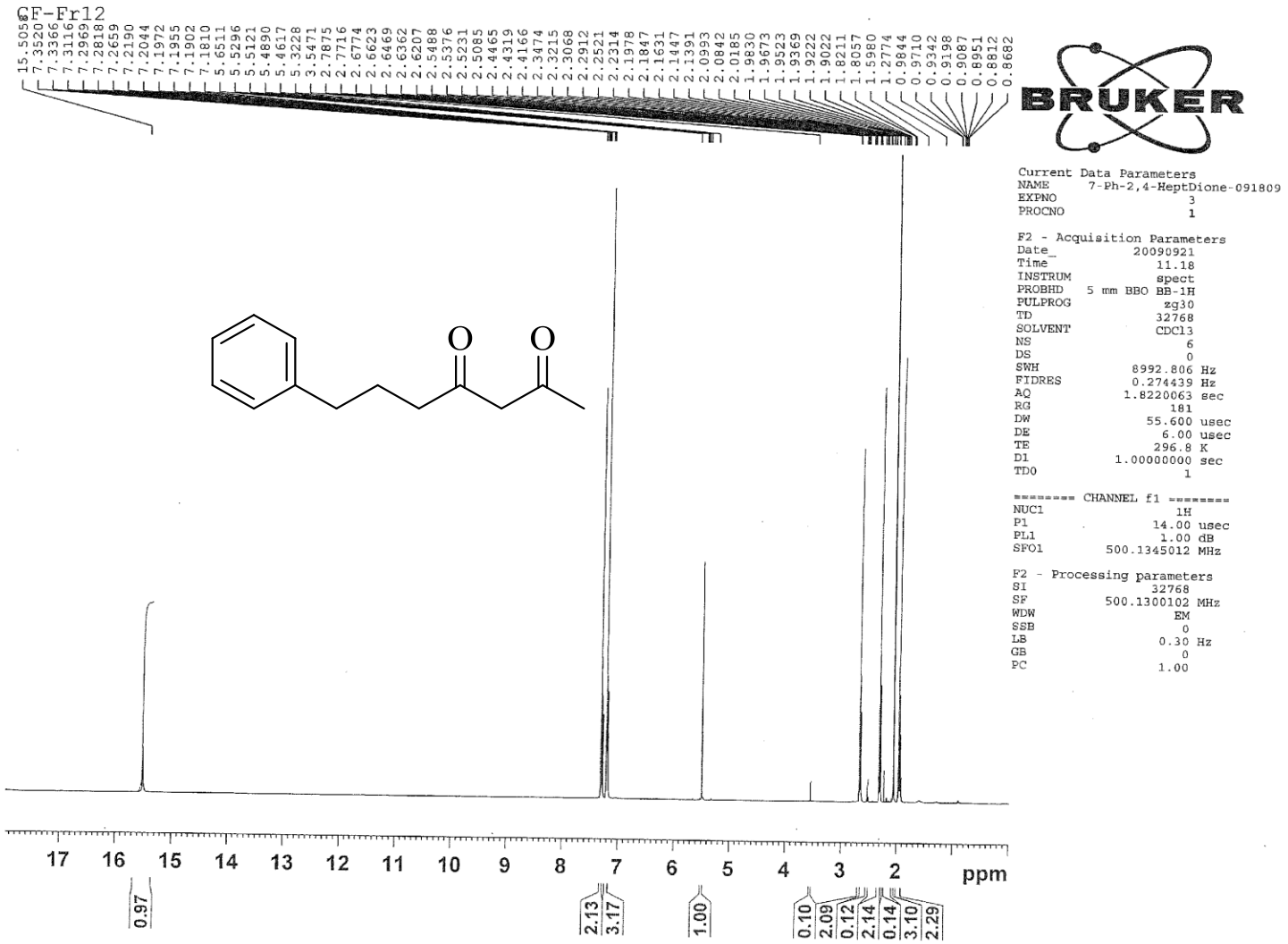
F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

CF-Fr33-35



BRUKER

```
Current Data Parameters
NAME      7-Ph-2,4-Hept-dione-083109
EXPNO                  7
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090901
Time              17.03
INSTRUM           spect
PROBHD   5 mm BBO BB-1H
PULPROG          zgdc30
TD                65536
SOLVENT           CDCl3
NS                  214
DS                    4
SWH           30030.029 Hz
FIDRES         0.458222 Hz
AQ             1.0912410 sec
RG                5160.6
DW               16.650 usec
DE                7.00 usec
TE                297.2 K
D1            1.00000000 sec
d11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                  5.00 usec
PL1                 1.00 dB
SFO1         125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2              90.00 usec
PL2                24.00 dB
PL12               24.00 dB
SFO2         500.1322150 MHz

F2 - Processing parameters
SI                  32768
SF           125.7578145 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```



BRUKER

Current Data Parameters
NAME 7-Ph-2,4-HeptDione-091809
EXPNO 3
PROCNO 1

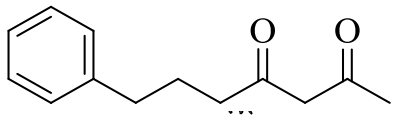
F2 - Acquisition Parameters
Date_ 20090921
Time 11.18
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220063 sec
RG 181
DW 55.600 usec
DE 6.00 usec
TE 296.8 K
D1 1.00000000 sec
TD0 1

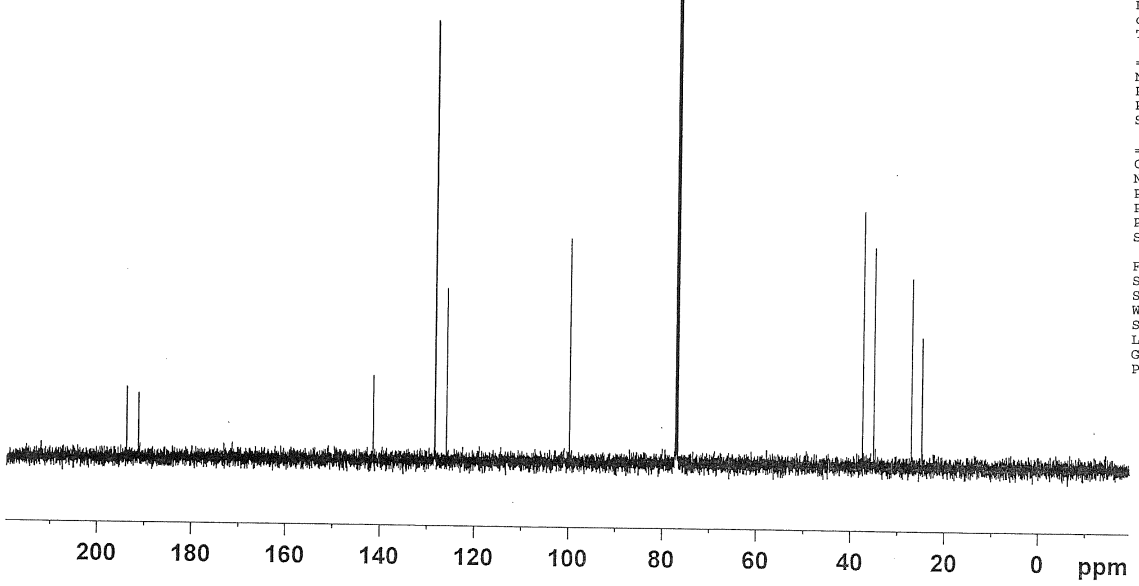
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz

F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

CF-Fr12
13C

193.84
191.33
141.47
128.44
128.37
125.97
99.87
37.54
35.19
27.15
24.94





BRUKER

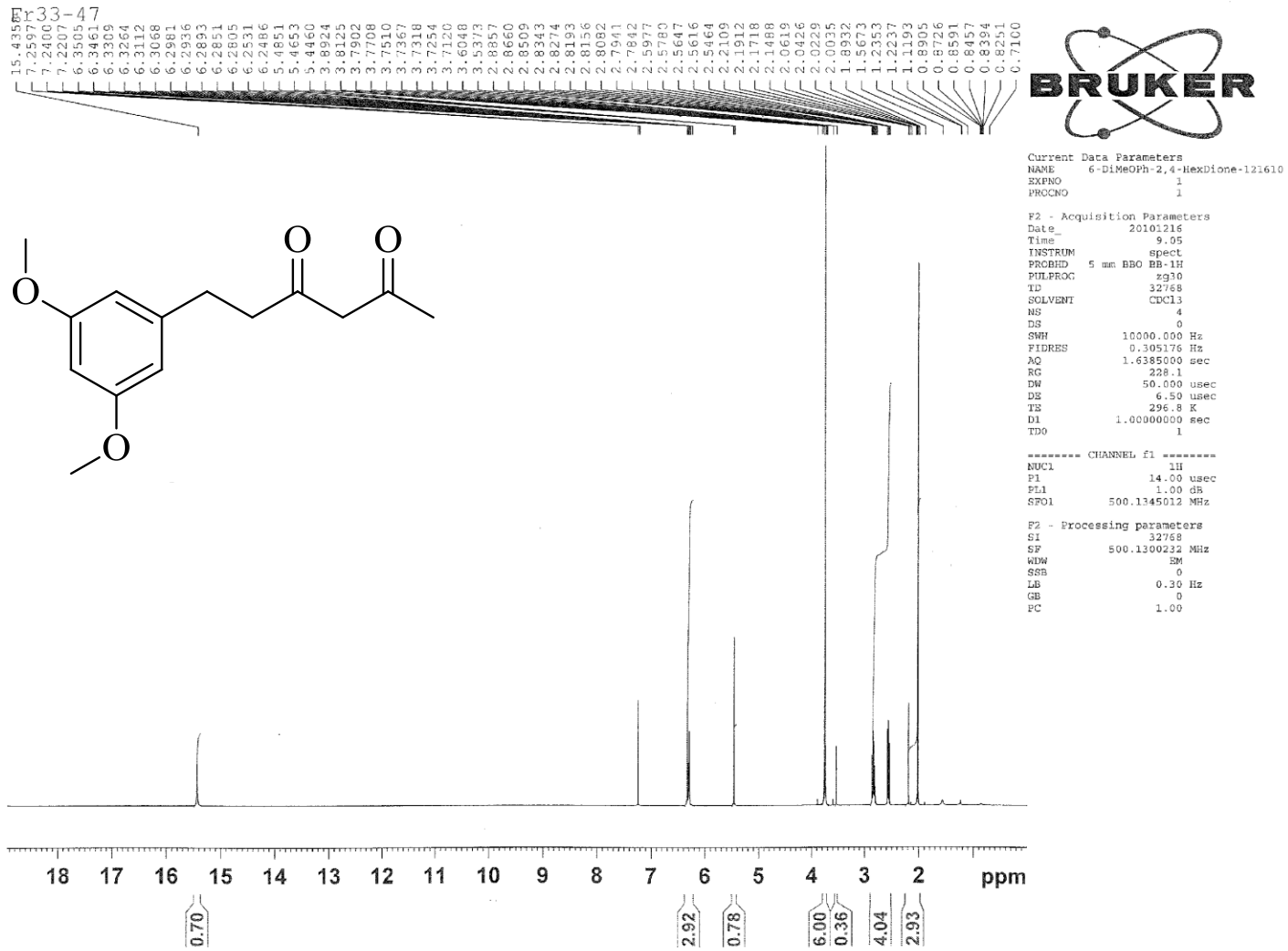
Current Data Parameters
NAME 7-Ph-2,4-HeptDione-091809
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090921
Time 11.22
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 73
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 2580.3
DW 16.650 usec
DE 7.00 usec
TE 297.5 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577941 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



BRUKER

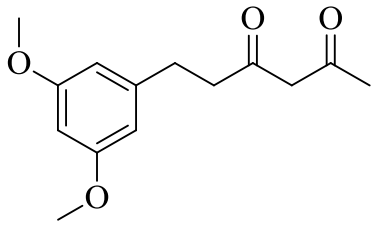
Current Data Parameters
NAME 6-DiMeOPh-2,4-HexDione-121610
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20101216
Time 9.05
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 1.6385000 sec
RG 228.1
DW 50.000 usec
DE 6.50 usec
TE 296.8 K
D1 1.00000000 sec
TD0 1

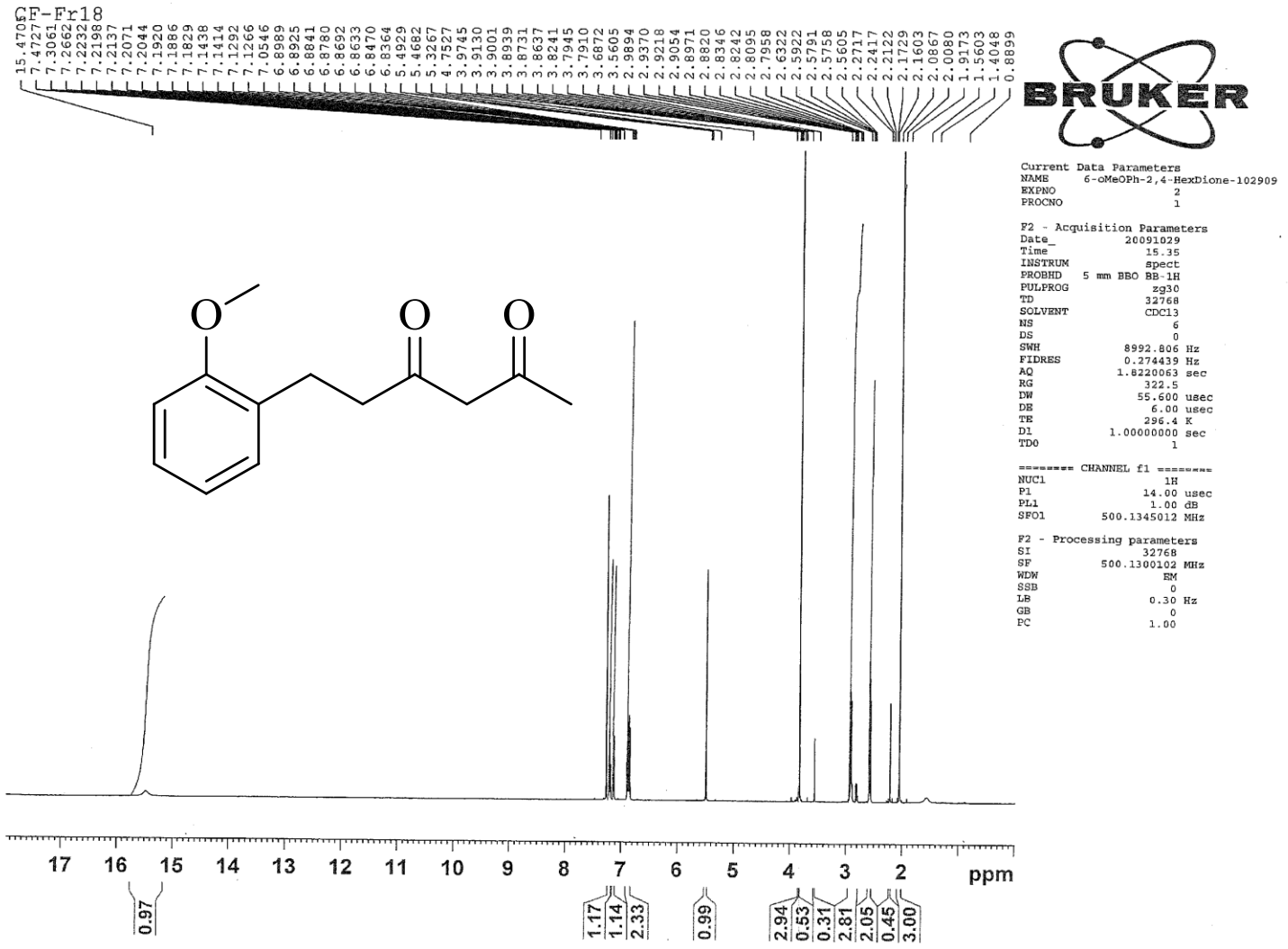
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz

F2 - Processing parameters
SI 32768
SF 500.1300232 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Fr33-47




```
Current Data Parameters
NAME      6-DiMeOPh-2,4-HexDione-121610
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20101216
Time               9.12
INSTRUM           spect
PROBHD   5 mm BBO BB-1H
PULPROG         zgdc30
TD              65536
SOLVENT           CDCl3
NS                   52
DS                    4
SWH           30030.029 Hz
FIDRES            0.458222 Hz
AQ                1.0912410 sec
RG                7298.2
DW                16.650 usec
DE                 7.00 usec
TE                297.2 K
D1             1.00000000 sec
d11            0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                  8.60 usec
PL1                 1.00 dB
SFO1         125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                 1.00 dB
PL12               17.50 dB
SFO2         500.1322150 MHz

F2 - Processing parameters
SI                32768
SF          125.7577932 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```



BRUKER

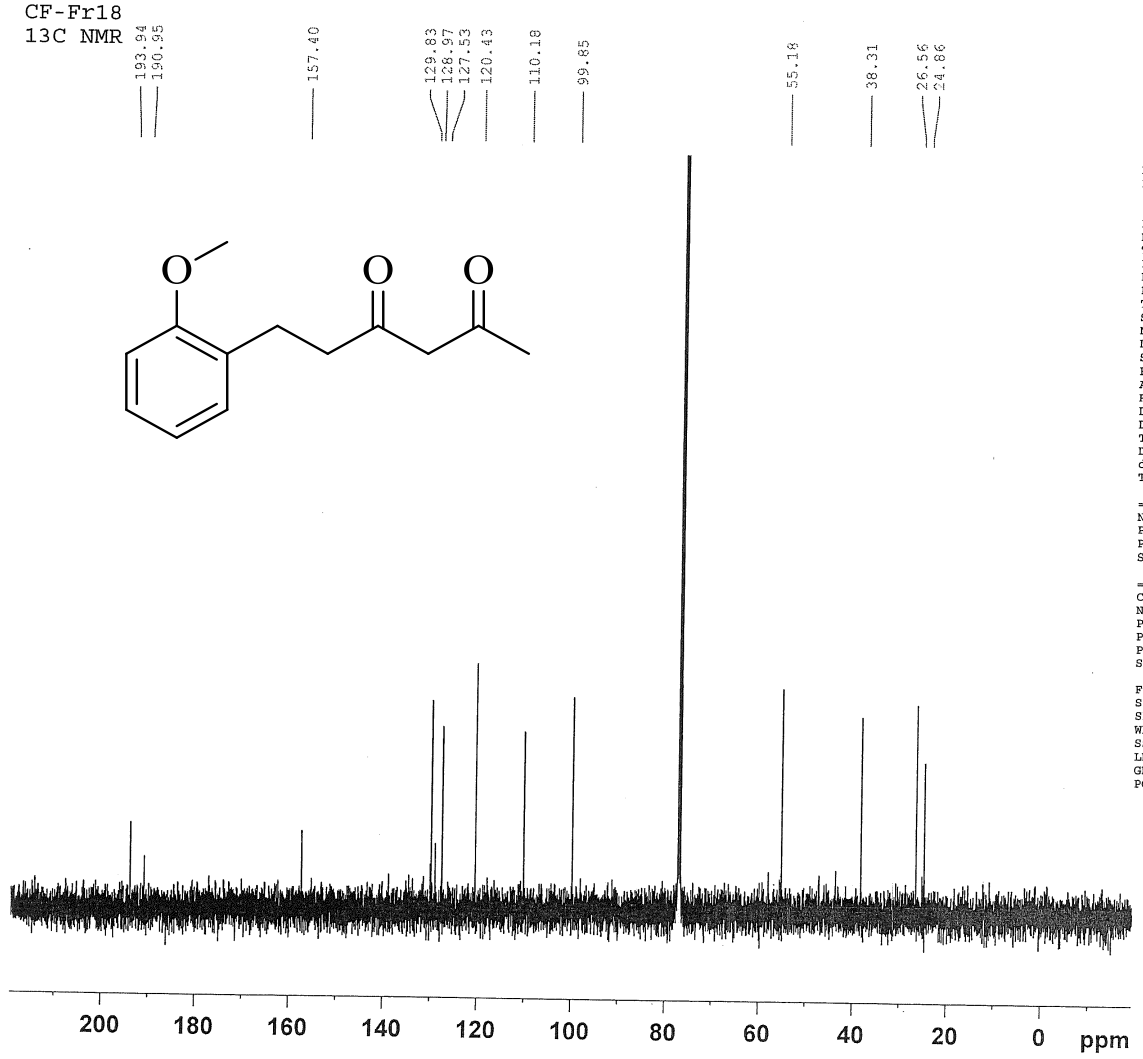
Current Data Parameters
NAME 6-oMeOPh-2,4-HexDione-102909
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20091029
Time 15.35
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220063 sec
RG 322.5
DW 55.600 usec
DE 6.00 usec
TE 296.4 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz

F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

CF-Fr18
13C NMR



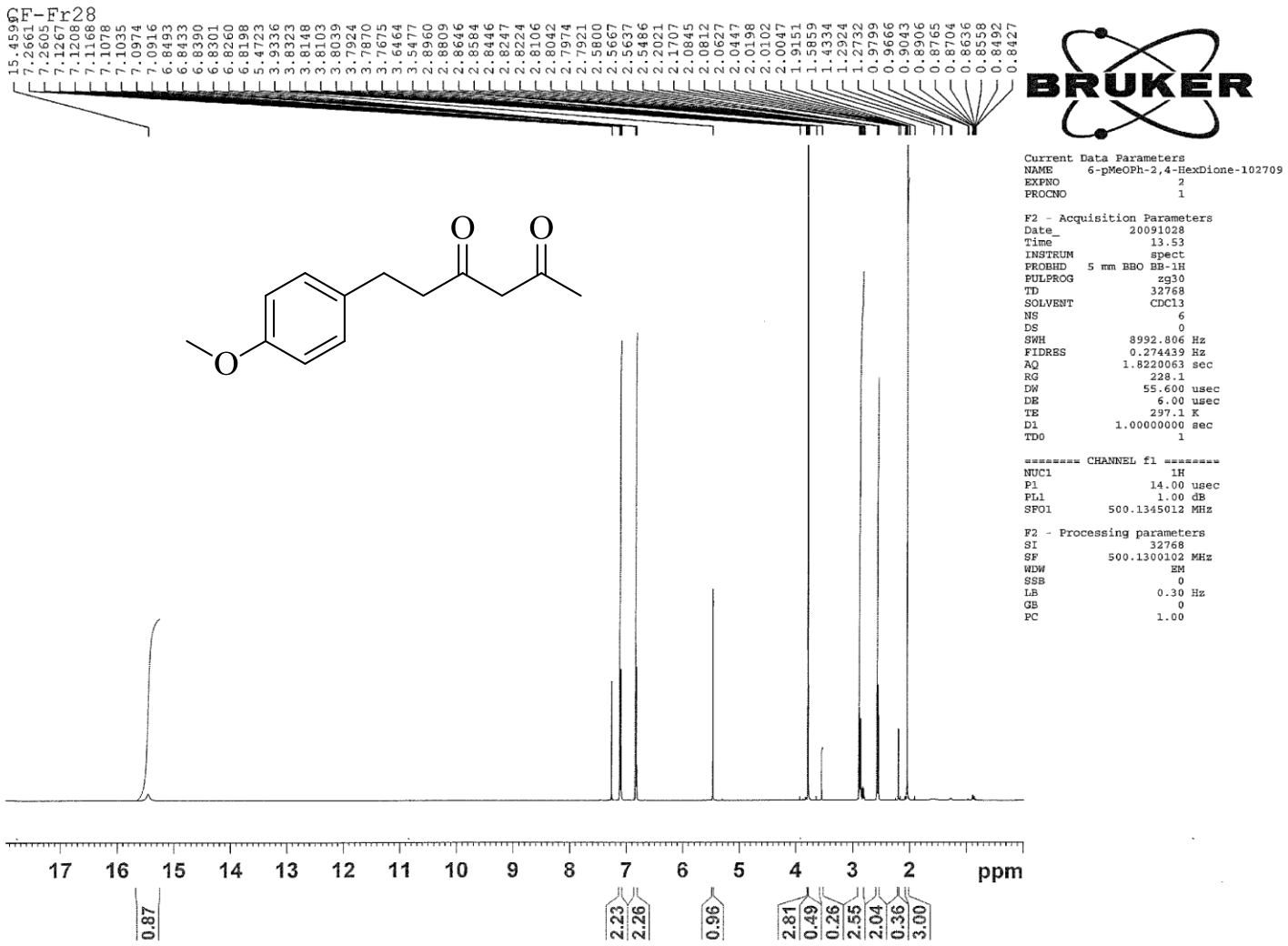
Current Data Parameters
NAME 6-oMeOPh-2,4-HexDione-102909
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20091029
Time 15.38
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 291
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 4096
DW 16.650 usec
DE 7.00 usec
TE 296.8 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

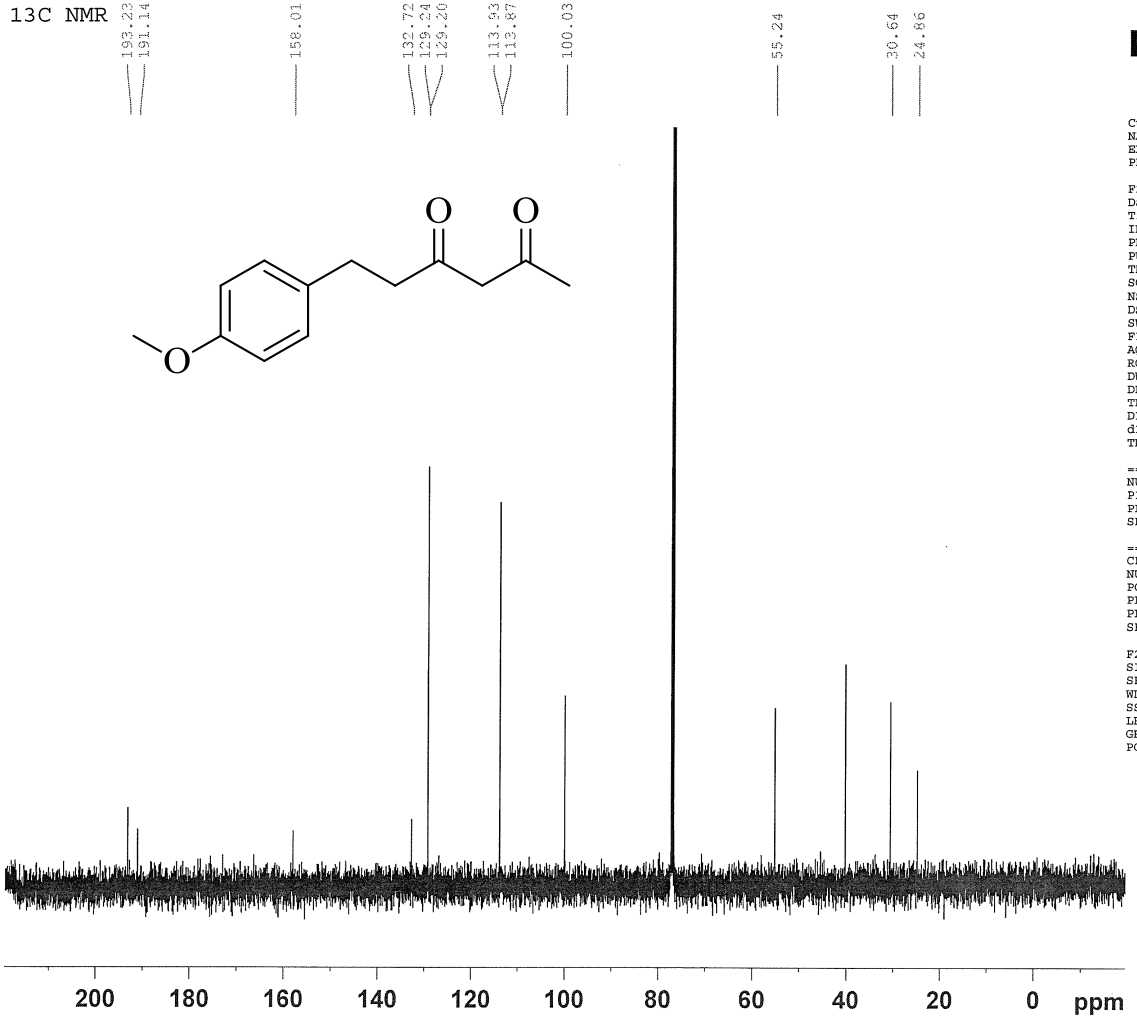
F2 - Processing parameters
SI 32768
SF 125.7577924 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



BRUKER

```
Current Data Parameters
NAME      6-pMeOPh-2,4-HexDione-102709
EXPNO                2
PROCNO               1

F2 - Acquisition Parameters
Date_          20091028
Time              13.53
INSTRUM           spect
PROBHD   5 mm BBO BB-1H
PULPROG           zg30
TD               32768
SOLVENT          CDCl3
NS                   6
DS                   0
SWH           8992.806 Hz
FIDRES        0.274439 Hz
AQ            1.8220063 sec
RG                228.1
DW               55.600 usec
DE                6.00 usec
TE               297.1 K
D1          1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                 1H
P1                14.00 usec
PL1                1.00 dB
SFO1        500.1345012 MHz

F2 - Processing parameters
SI                32768
SF          500.1300102 MHz
WDW                  EM
SSB                  0
LB                0.30 Hz
GB                   0
PC                1.00
```

CF-Fr28
13C NMR



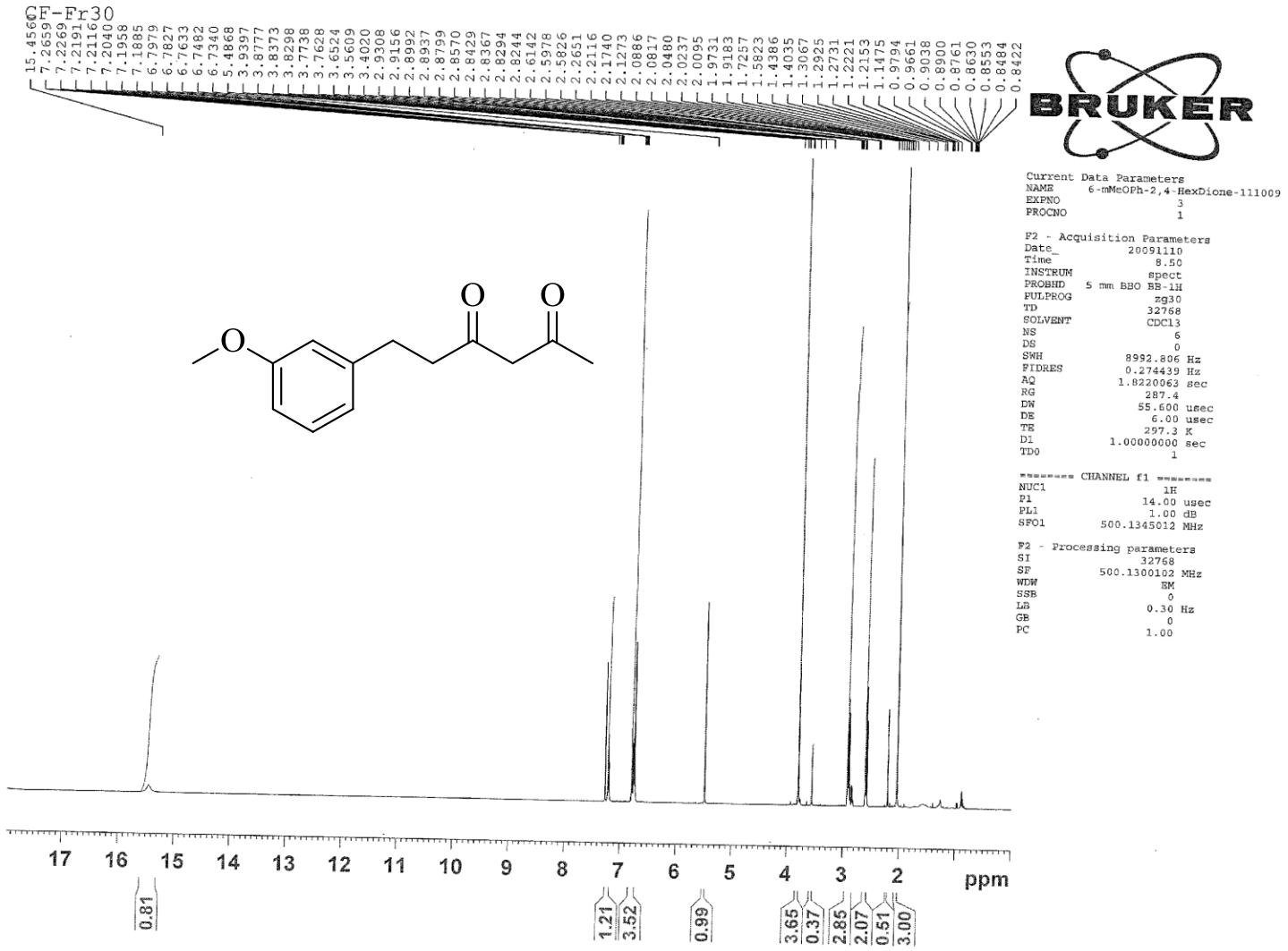
Current Data Parameters
NAME 6-pMeOPh-2,4-HexDione-102709
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20091028
Time 13.56
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 48
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 1448.2
DW 16.650 usec
DE 7.00 usec
TE 297.4 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577929 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



BRUKER

Current Data Parameters
NAME 6-mMeOPh-2,4-HexDione-111009
EXPNO 3
PROCNO 1

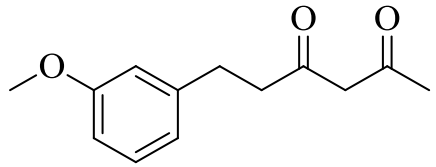
F2 - Acquisition Parameters
Date_ 20091110
Time 8.50
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220063 sec
RG 287.4
DW 55.600 usec
DE 6.00 usec
TE 297.3 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz

F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

CF-Fr9-13
13C NMR

193.26
190.95
159.69
142.31
129.47
120.62
114.05
111.51
100.01
55.14
39.90
31.49
24.80



BRUKER

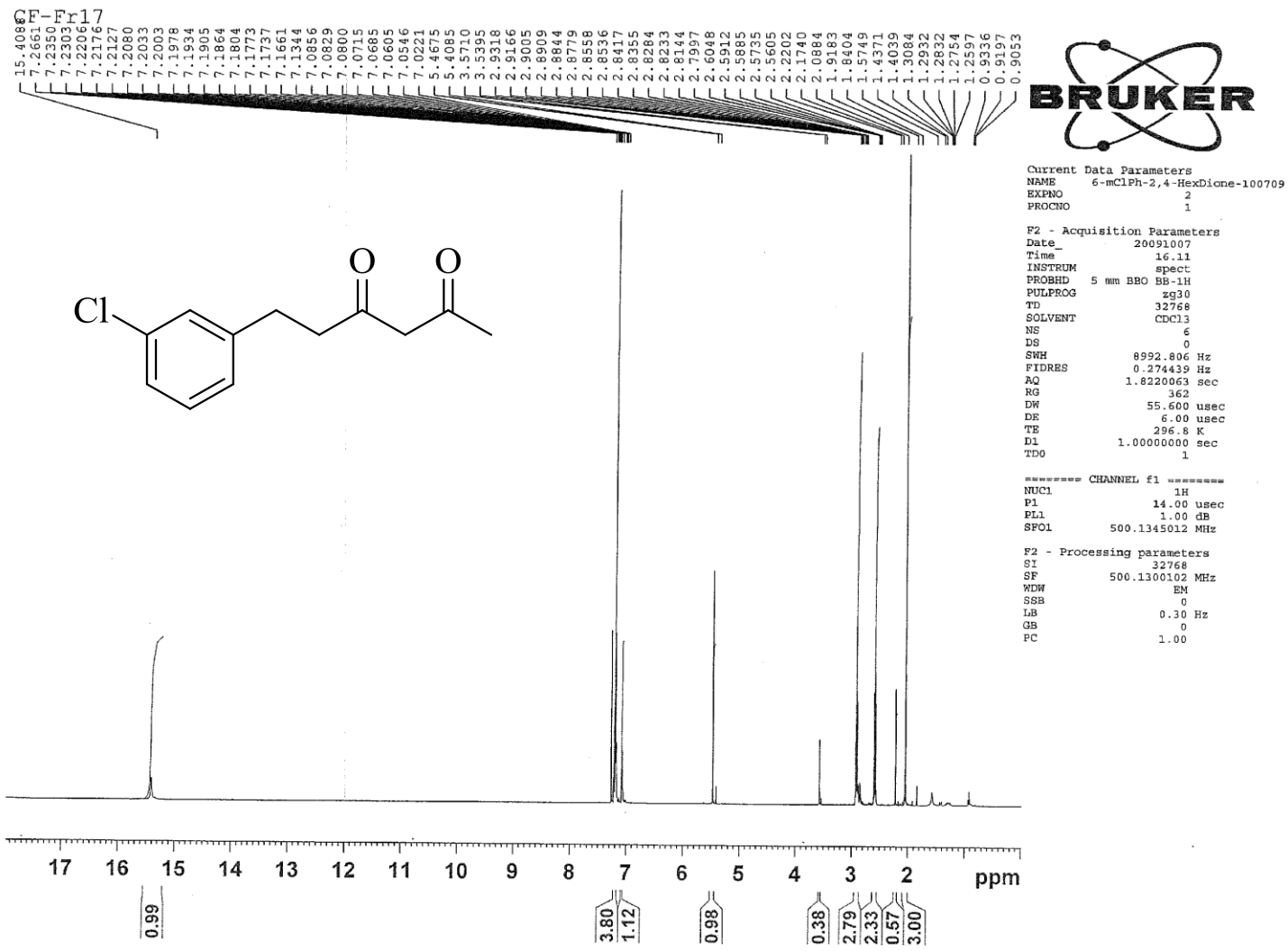
Current Data Parameters
NAME 6-mMeOPh-2,4-HexDione-102109
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20091021
Time 14.49
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 105
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 2896.3
DW 16.650 usec
DE 7.00 usec
TE 297.6 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577920 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



BRUKER

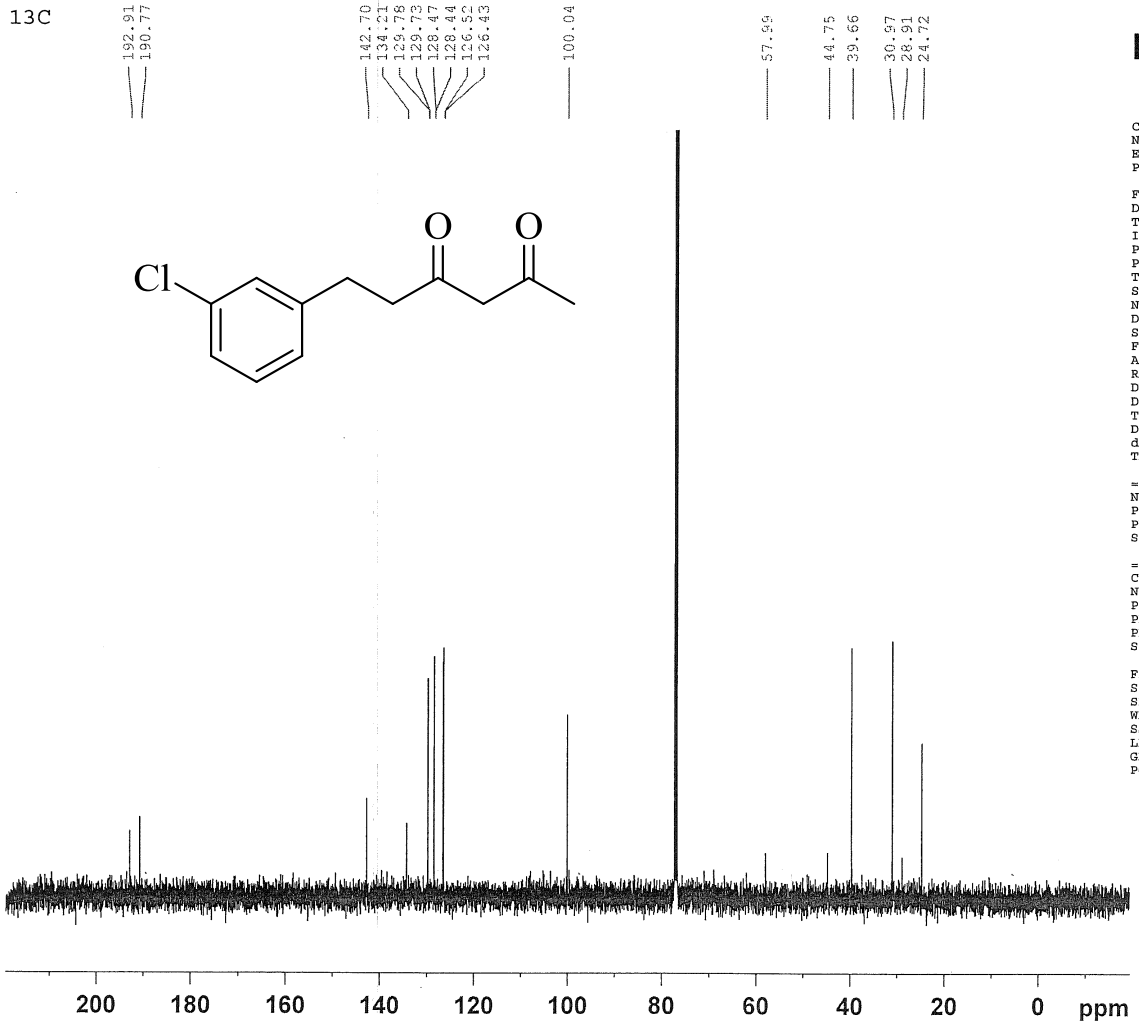
Current Data Parameters
NAME 6-mClPh-2,4-HexDione-100709
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20091007
Time 16.11
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220063 sec
RG 362
DW 55.600 usec
DE 6.00 usec
TE 296.8 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz

F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

CF-Fr17
13C



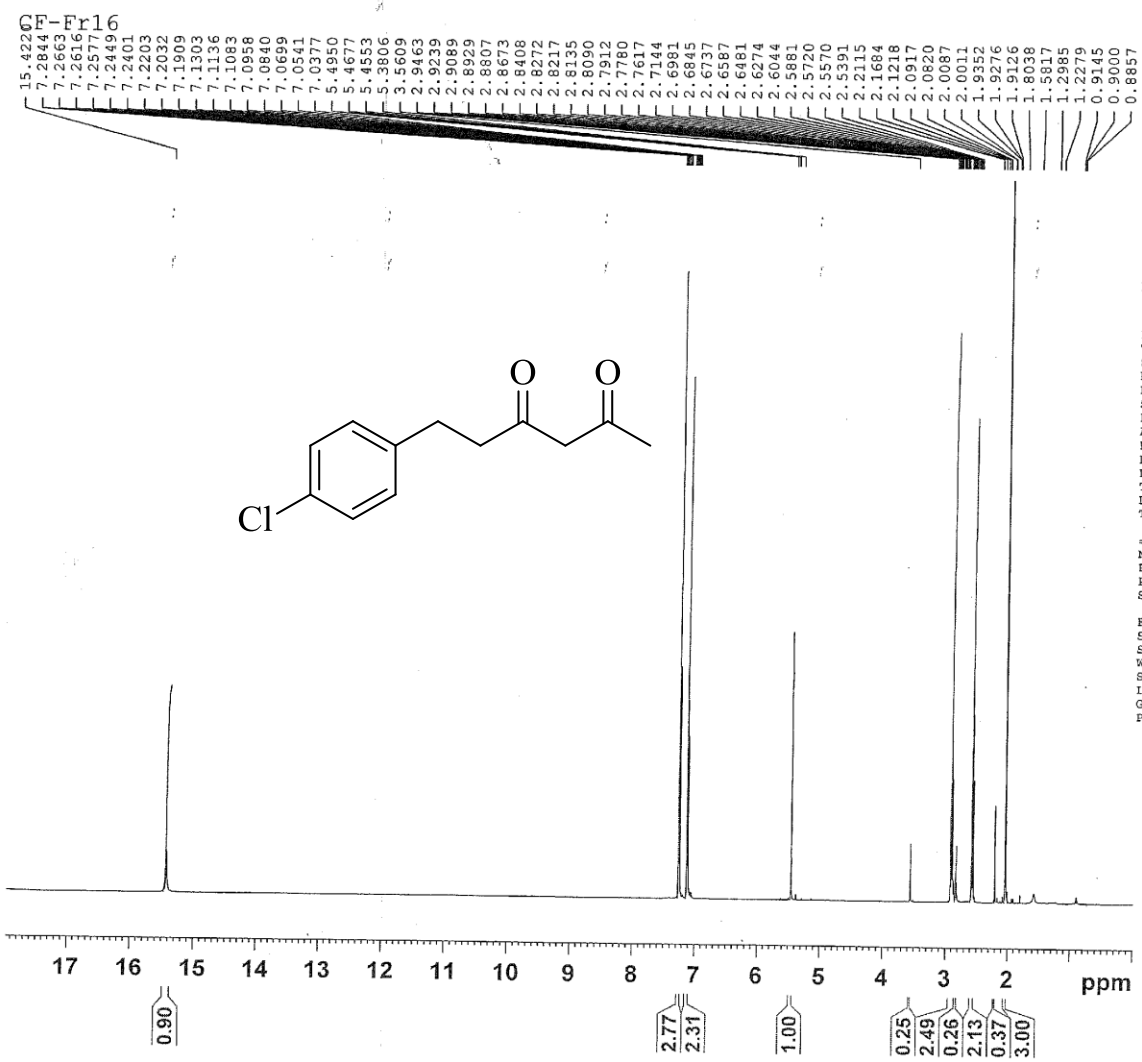
Current Data Parameters
NAME 6-mClPh-2,4-HexDione-100709
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20091007
Time 16.15
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 177
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 3649.1
DW 16.650 usec
DE 7.00 usec
TE 297.4 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577921 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



BRUKER

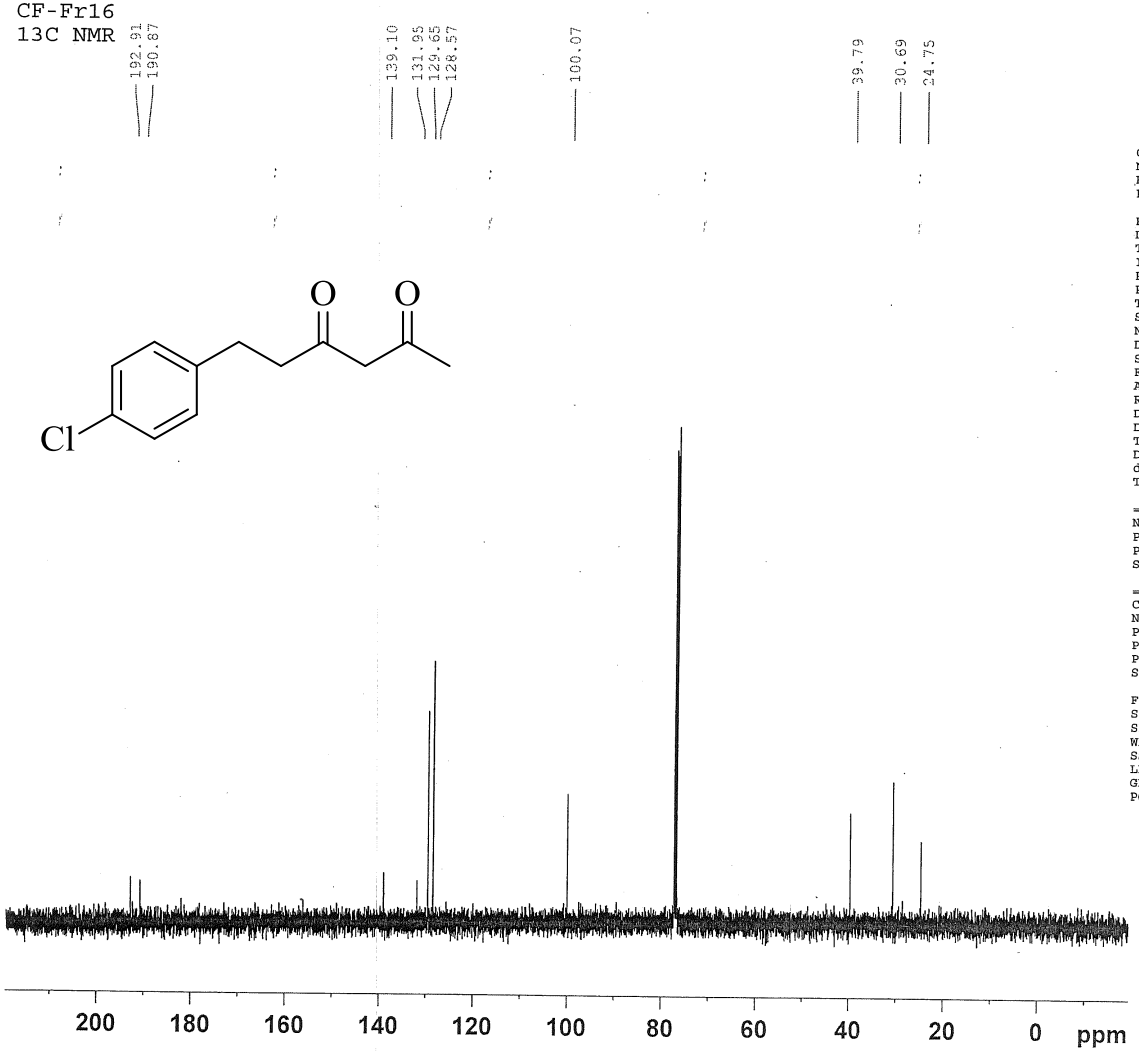
Current Data Parameters
NAME 6-pClPh-2,4-HexDione-093009
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090930
Time 14.54
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220063 sec
RG 256
DW 55.600 usec
DE 6.00 usec
TE 296.9 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz

F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

CF-Fr16
13C NMR



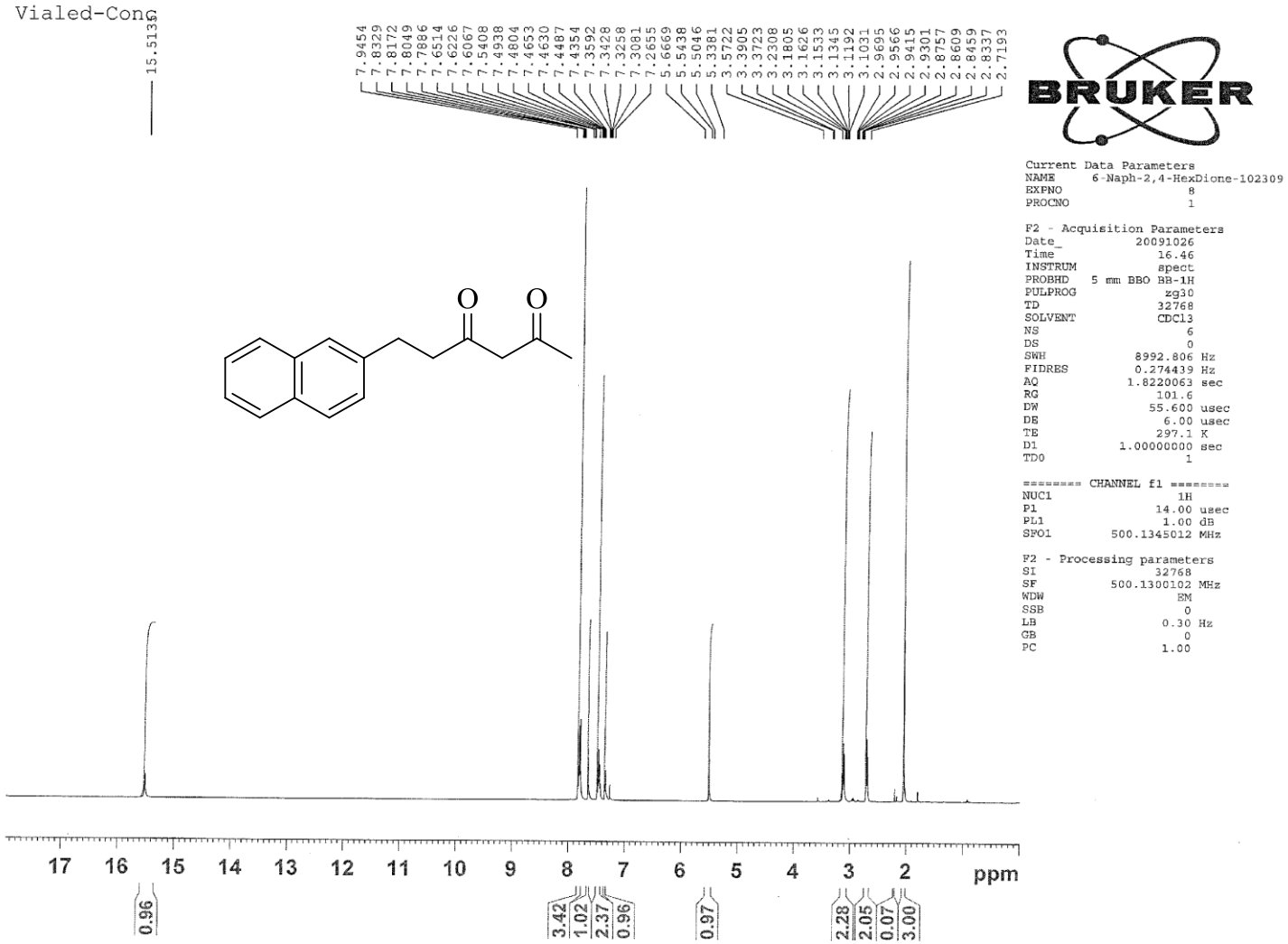
Current Data Parameters
NAME 6-pClPh-2,4-HexDione-093009
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090930
Time 15.19
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 35
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 4096
DW 16.650 usec
DE 7.00 usec
TE 297.4 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577935 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



BRUKER

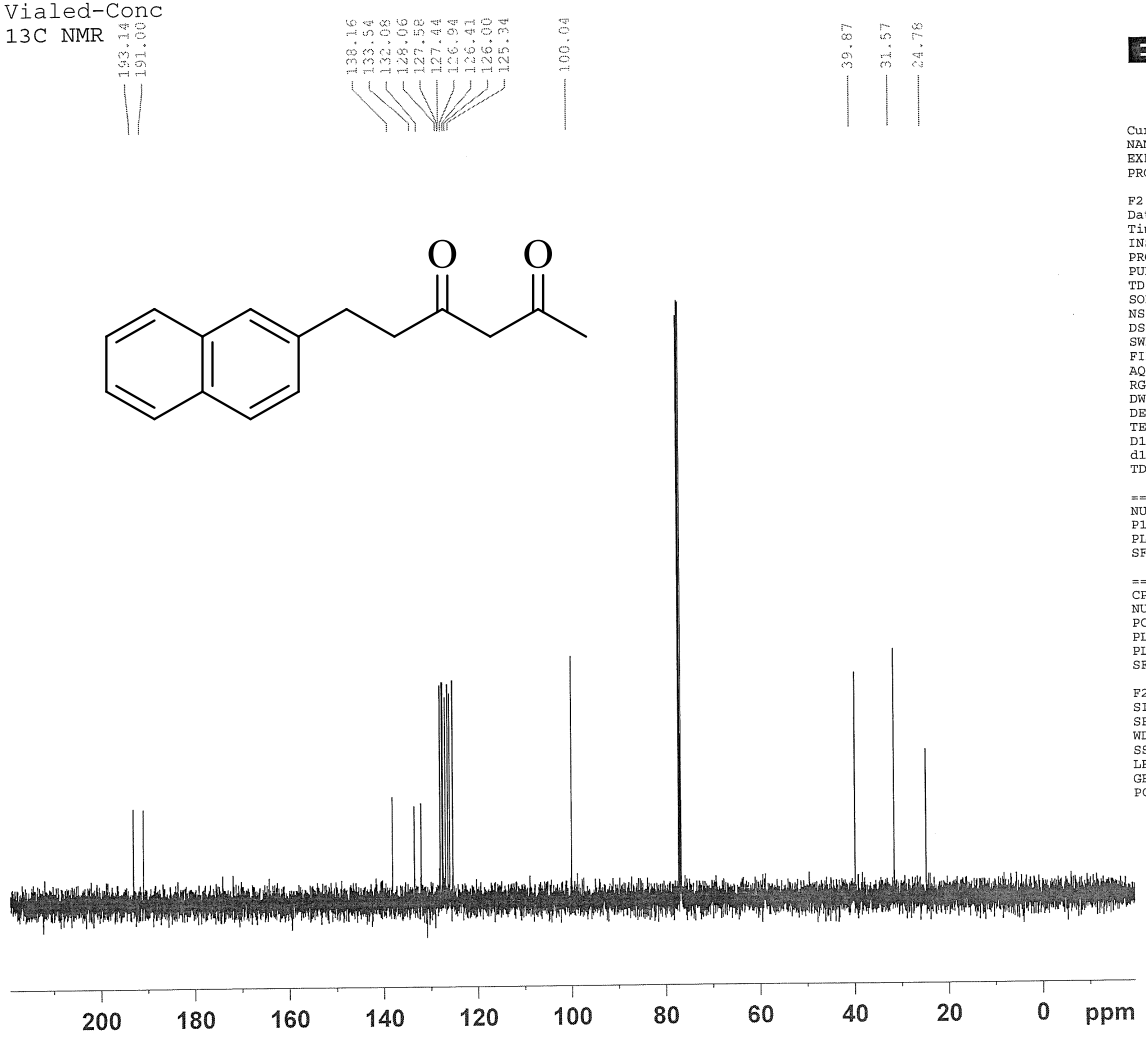
Current Data Parameters
NAME 6-Naph-2,4-HexDione-102309
EXPNO 8
PROCNO 1

F2 - Acquisition Parameters
Date_ 20091026
Time 16.46
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220063 sec
RG 101.6
DW 55.600 usec
DE 6.00 usec
TE 297.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz

F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Vialed-Conc
13C NMR



BRUKER

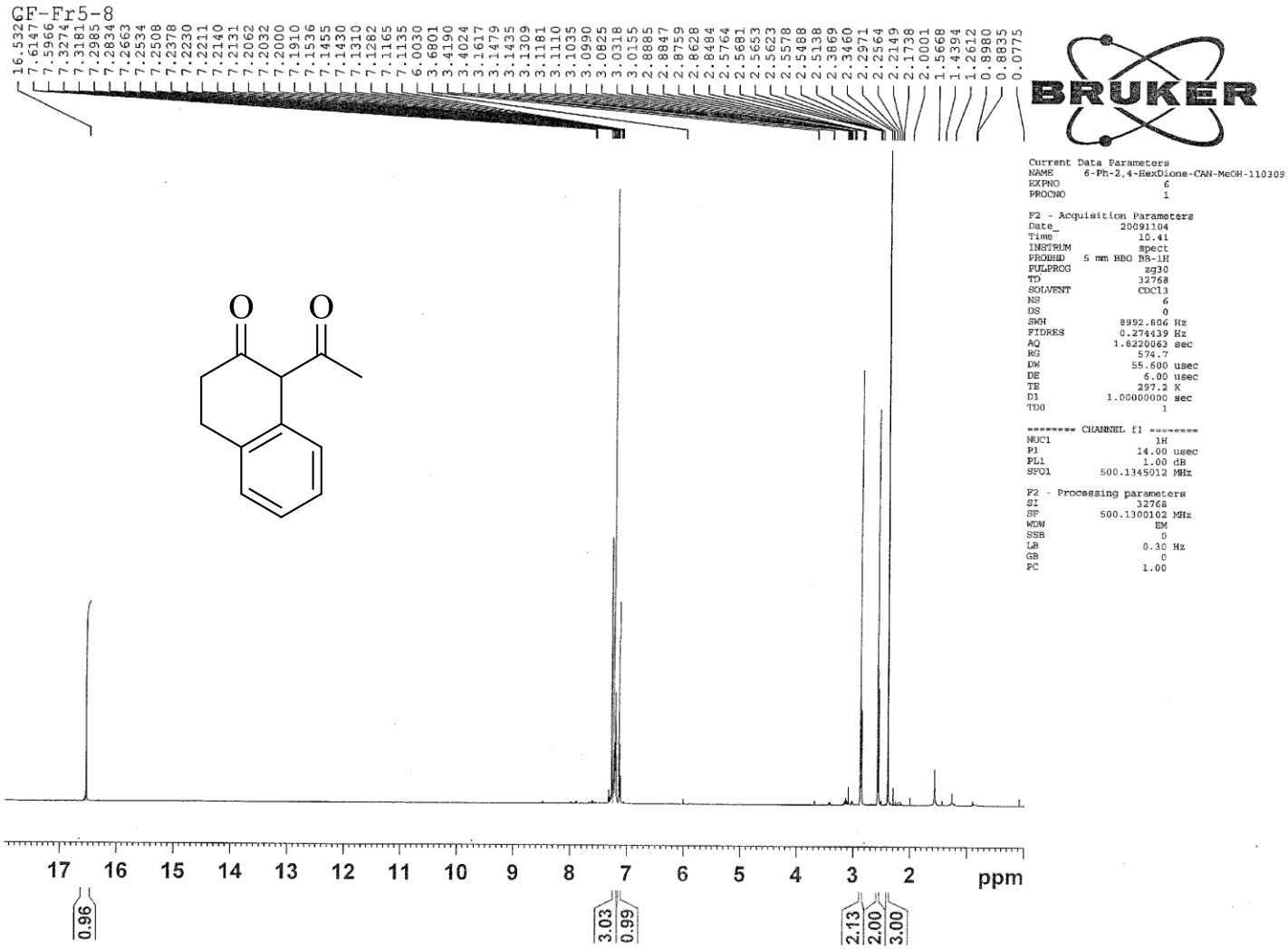
Current Data Parameters
NAME 6-Naph-2,4-HexDione-102309
EXPNO 9
PROCNO 1

F2 - Acquisition Parameters
Date_ 20091026
Time 16.49
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 21
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 4096
DW 16.650 usec
DE 7.00 usec
TE 297.5 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577984 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



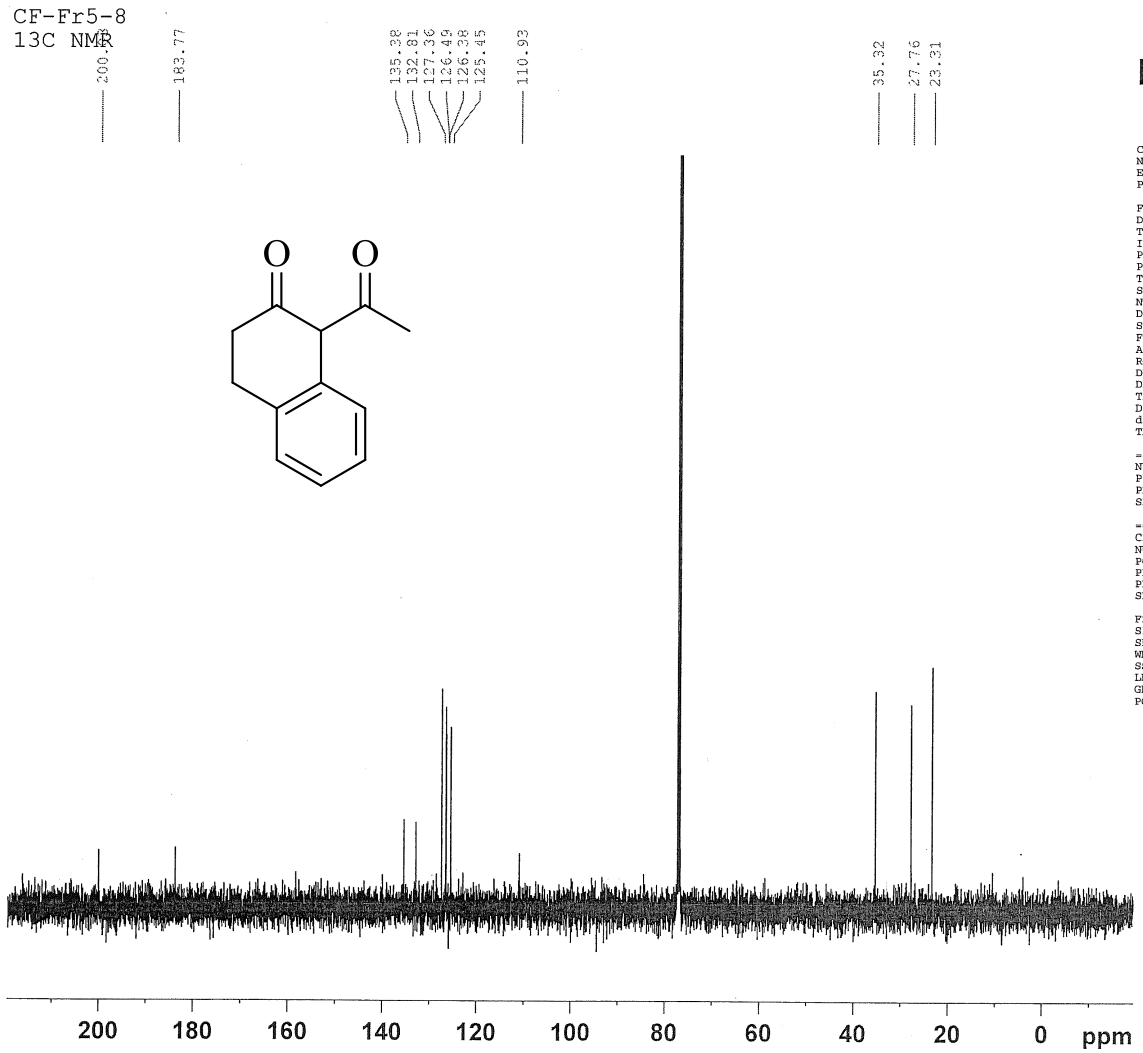
Current Data Parameters
NAME 6-Ph-2,4-HexDione-CAN-MeOH-110309
EXPNO 6
PROCNO 1

F2 - Acquisition Parameters
Date_ 20091104
Time 10.41
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220063 sec
RG 574.7
DW 55.600 usec
DE 6.00 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz

F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

CF-Fr5-8
13C NMR



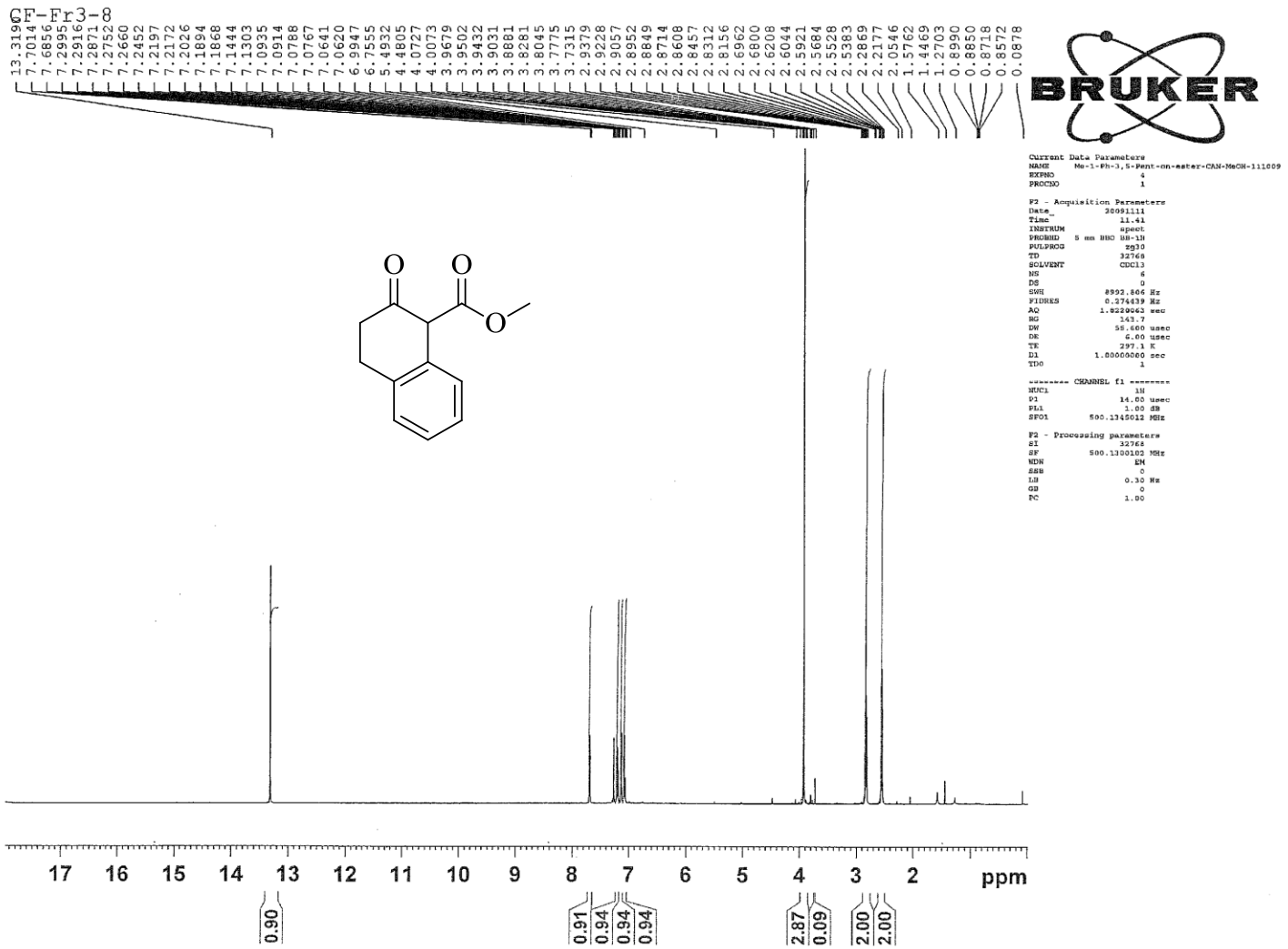
Current Data Parameters
NAME 6-Ph-2,4-HexDione-CAN-MeOH-110309
EXPNO 7
PROCNO 1

F2 - Acquisition Parameters
Date_ 20091104
Time 10.43
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 128
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 3251
DW 16.650 usec
DE 7.00 usec
TE 297.8 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

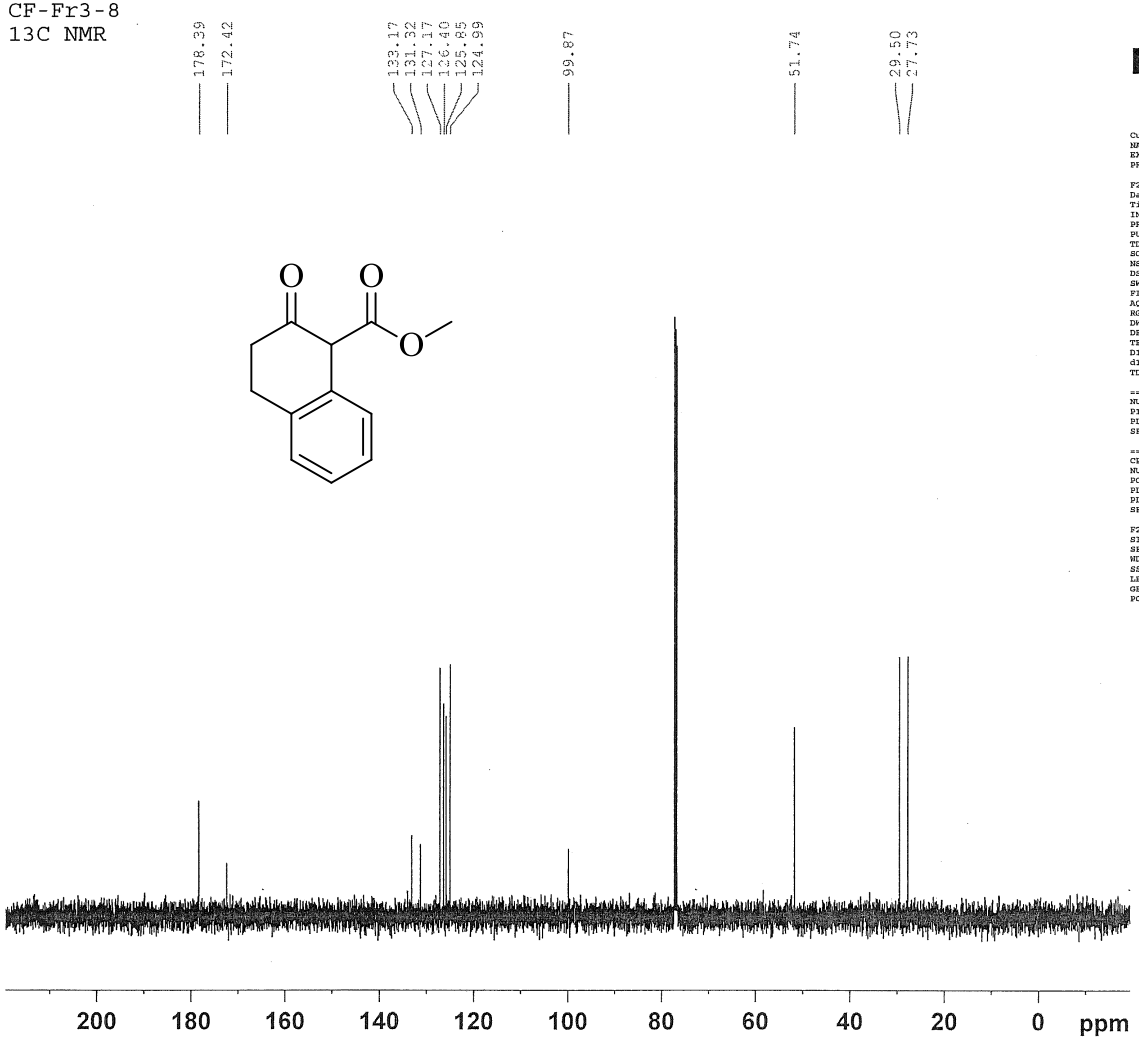
======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577923 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


CF-Fr3-8
13.3199
7.7014
7.6856
7.2995
7.2916
7.2871
7.2752
7.2660
7.2452
7.2197
7.2172
7.2026
7.1894
7.1868
7.1444
7.1303
7.0935
7.0914
7.0788
7.0767
7.0641
7.0620
6.9947
6.7555
5.4932
4.4805
4.0727
4.0073
3.9679
3.9502
3.9432
3.9031
3.8881
3.8281
3.8045
3.7775
3.7315
2.9379
2.9228
2.9057
2.8952
2.8849
2.8714
2.8608
2.8457
2.8312
2.8156
2.6962
2.6800
2.6208
2.6044
2.5921
2.5684
2.5528
2.5383
2.2869
2.2177
2.0546
1.5762
1.4469
1.2703
0.8990
0.8850
0.8718
0.8572
0.0878
BRUKER
Current Data Parameters
NAME Me-1-Ph-3,5-Pent-on-ester-CAN-MeCN-111609
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20091111
Time 11.41
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220963 sec
RG 143.7
DW 55.600 usec
DE 6.00 usec
TE 297.1 K
D1 1.80000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz
F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
O
O
17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 ppm
0.90
0.91
0.94
0.94
0.94
2.87
0.09
2.00
2.00

CF-Fr3-8
13C NMR



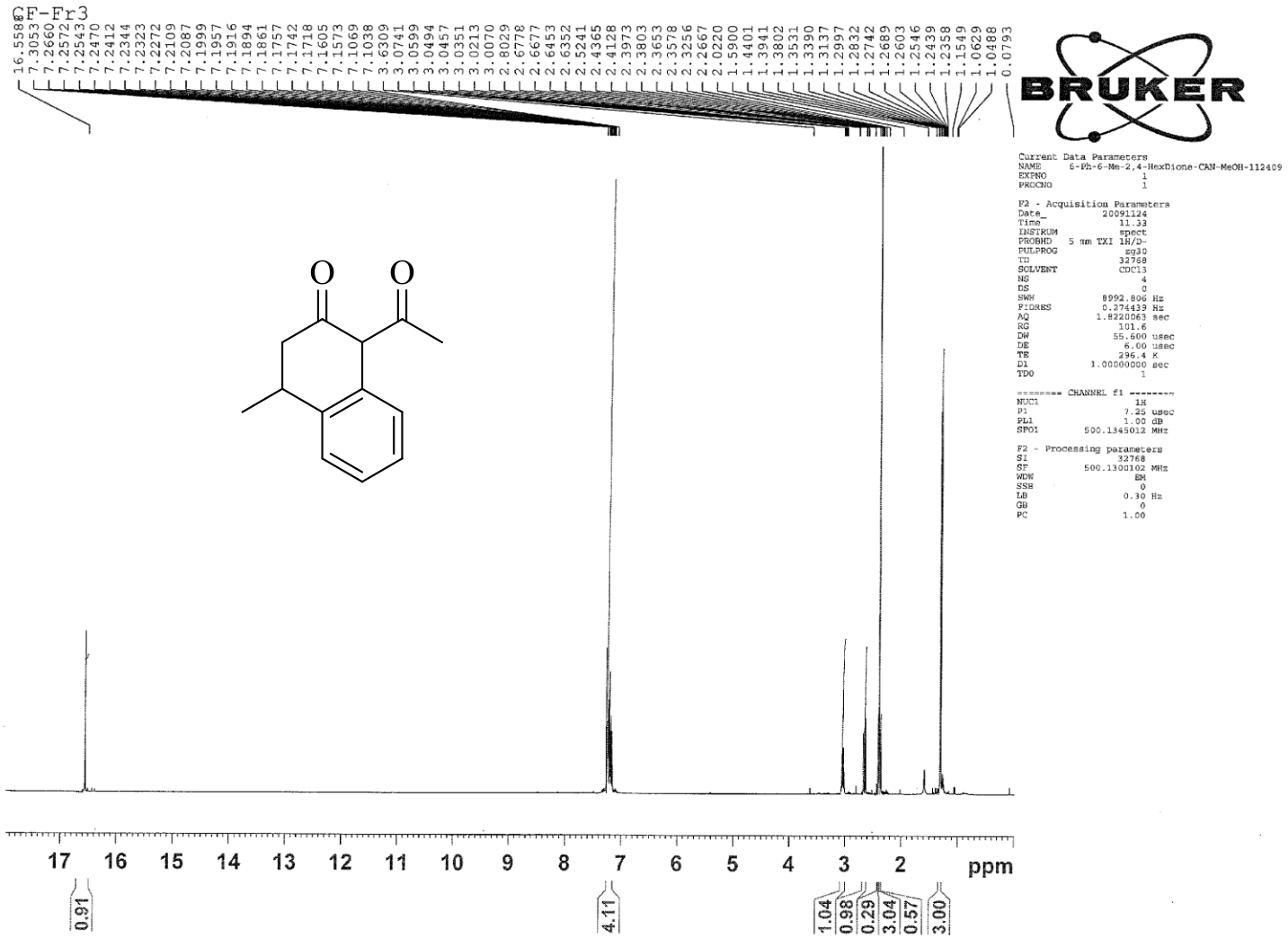
Current Data Parameters
NAME Me-1-Ph-3,5-Pent-on-ester-CAN-MeOH-111009
EXPNO 5
PROCNO 1

F2 - Acquisition Parameters
Date_ 20091111
Time 11.44
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 30
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 2580.3
DW 16.650 usec
DE 7.00 usec
TE 297.6 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577942 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



BRUKER

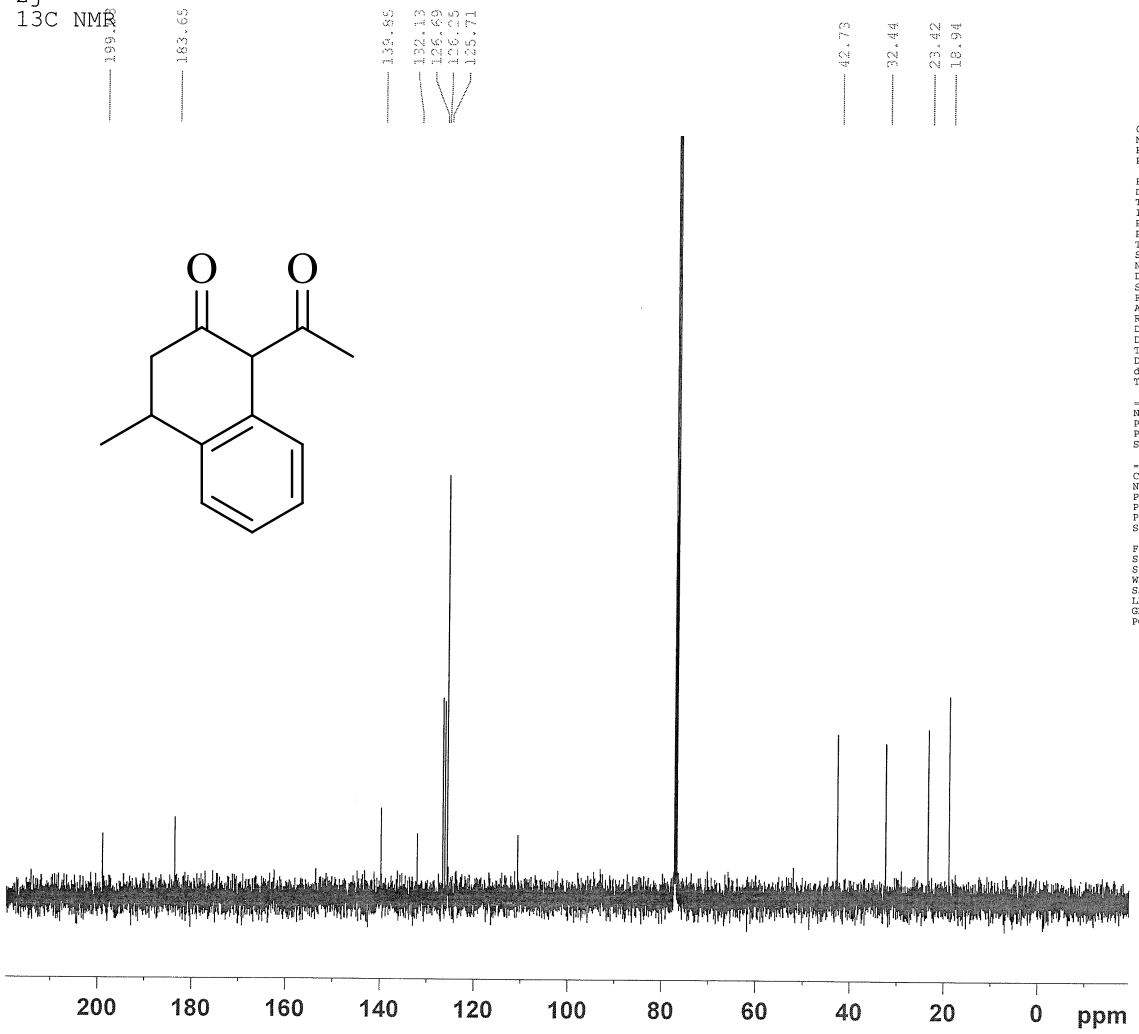
Current Data Parameters
NAME 6-Ph-6-Me-2,4-HexDione-CAN-MeOH-112409
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20091124
Time 11.33
INSTRUM spect
PROBHD 5 mm TXI 1H/D-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220063 sec
RG 101.6
DW 55.600 usec
DE 6.00 usec
TE 296.4 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 7.25 usec
PL1 1.00 dB
SFO1 500.1345012 MHz

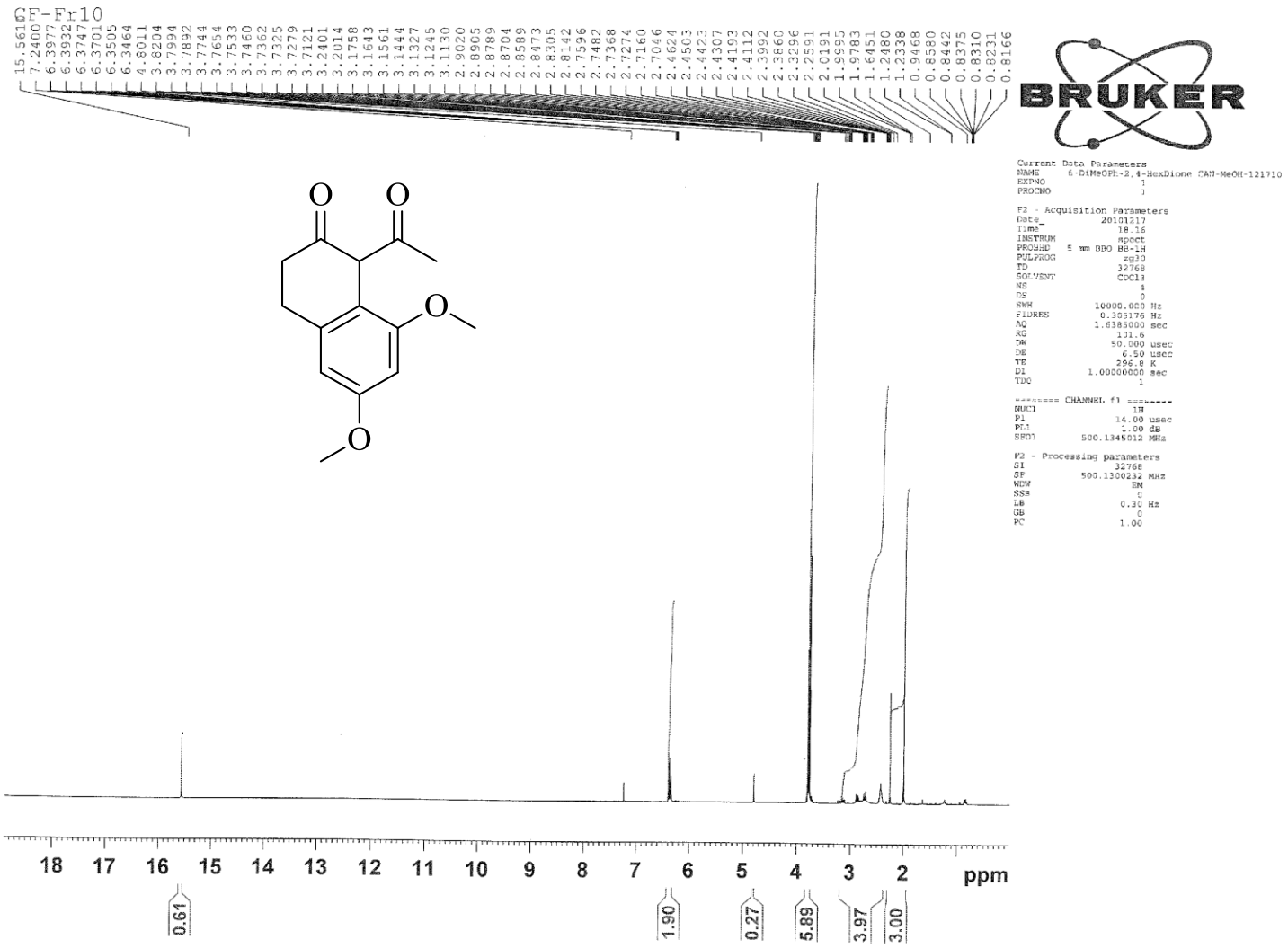
F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

2j
13C NMR



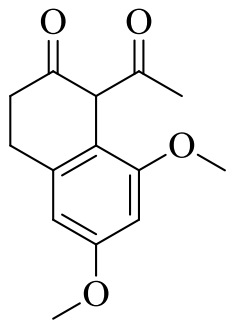
BRUKER

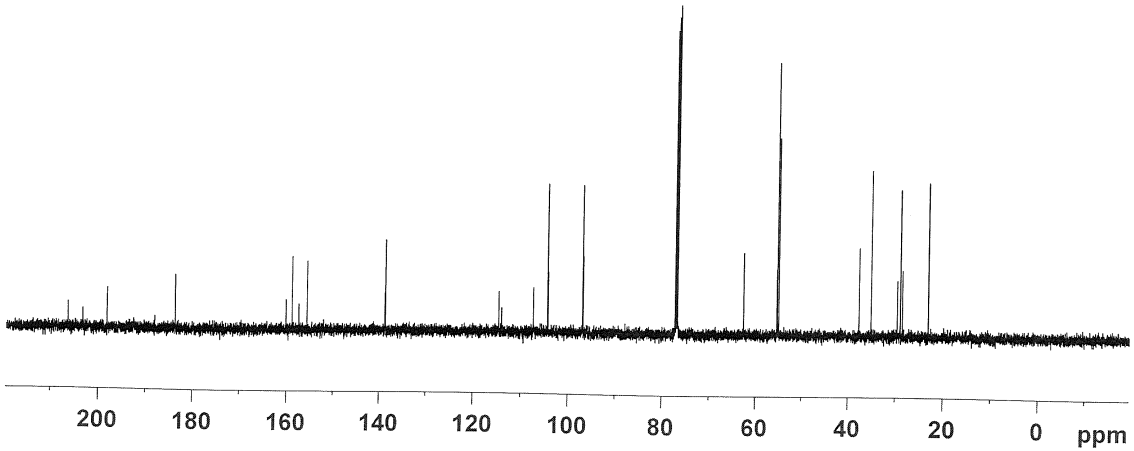
```
Current Data Parameters
NAME        6-Ph-6-Me-2,4-HexDione-CAN-MeOH-112409
EXPNO                4
PROCNO               1

F2 - Acquisition Parameters
Date_         20091201
Time              9.18
INSTRUM          spect
PROBHD   5 mm BBO BB-1H
PULPROG         zgdc30
TD               65536
SOLVENT          CDCl3
NS                 120
DS                   4
SWH          30030.029 Hz
FIDRES         0.458222 Hz
AQ             1.0912410 sec
RG                4096
DW               16.650 usec
DE                7.00 usec
TE              297.0 K
D1           1.00000000 sec
d11          0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1               13C
P1                8.60 usec
PL1               1.00 dB
SFO1       125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2               1H
PCPD2           100.00 usec
PL2               1.00 dB
PL12             17.50 dB
SFO2       500.1322150 MHz

F2 - Processing parameters
SI                32768
SF         125.7577890 MHz
WDW                EM
SSB                 0
LB               1.00 Hz
GB                  0
PC               1.40
```


GF-Fr10
15.5616
7.2400
6.3977
6.3932
6.3747
6.3701
6.3505
6.3464
4.8011
3.8204
3.7994
3.7892
3.7744
3.7654
3.7533
3.7460
3.7362
3.7325
3.7279
3.7121
3.2401
3.2014
3.1758
3.1643
3.1561
3.1444
3.1327
3.1245
3.1130
2.9020
2.8905
2.8789
2.8704
2.8589
2.8473
2.8305
2.8142
2.7596
2.7482
2.7368
2.7274
2.7160
2.7046
2.4624
2.4503
2.4423
2.4307
2.4193
2.4112
2.3992
2.3860
2.3296
2.2591
2.0191
1.9995
1.9783
1.6451
1.2480
1.2338
0.9468
0.8580
0.8442
0.8375
0.8310
0.8231
0.8166
BRUKER
Current Data Parameters
NAME 6-DiMeOPh-2,4-HexDione CAN-MeOH-121710
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20101217
Time 18.16
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 1.6385000 sec
RG 101.6
DW 50.000 usec
DE 6.50 usec
TE 296.8 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz
F2 - Processing parameters
SI 32768
SF 500.1300232 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
O
O
O
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
ppm
0.61
1.90
0.27
5.89
3.97
3.00

Fr10
13C

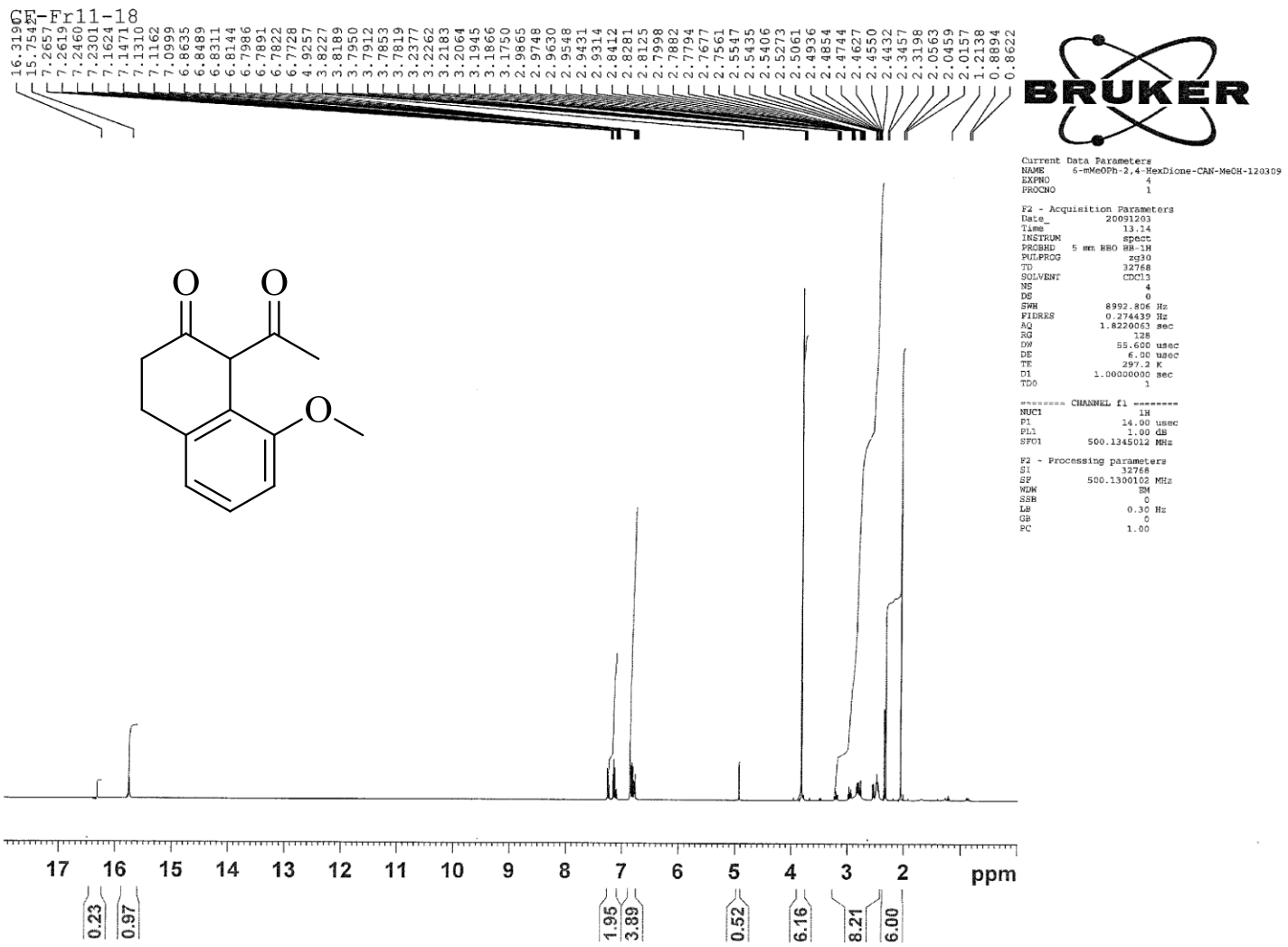
206.42
203.32
198.19
133.73
160.17
158.66
157.43
155.66
138.84
138.74
114.62
114.03
107.38
104.35
104.22
94.93
86.85
62.59
55.44
55.33
55.02
37.72
35.15
29.62
29.00
28.55
23.11

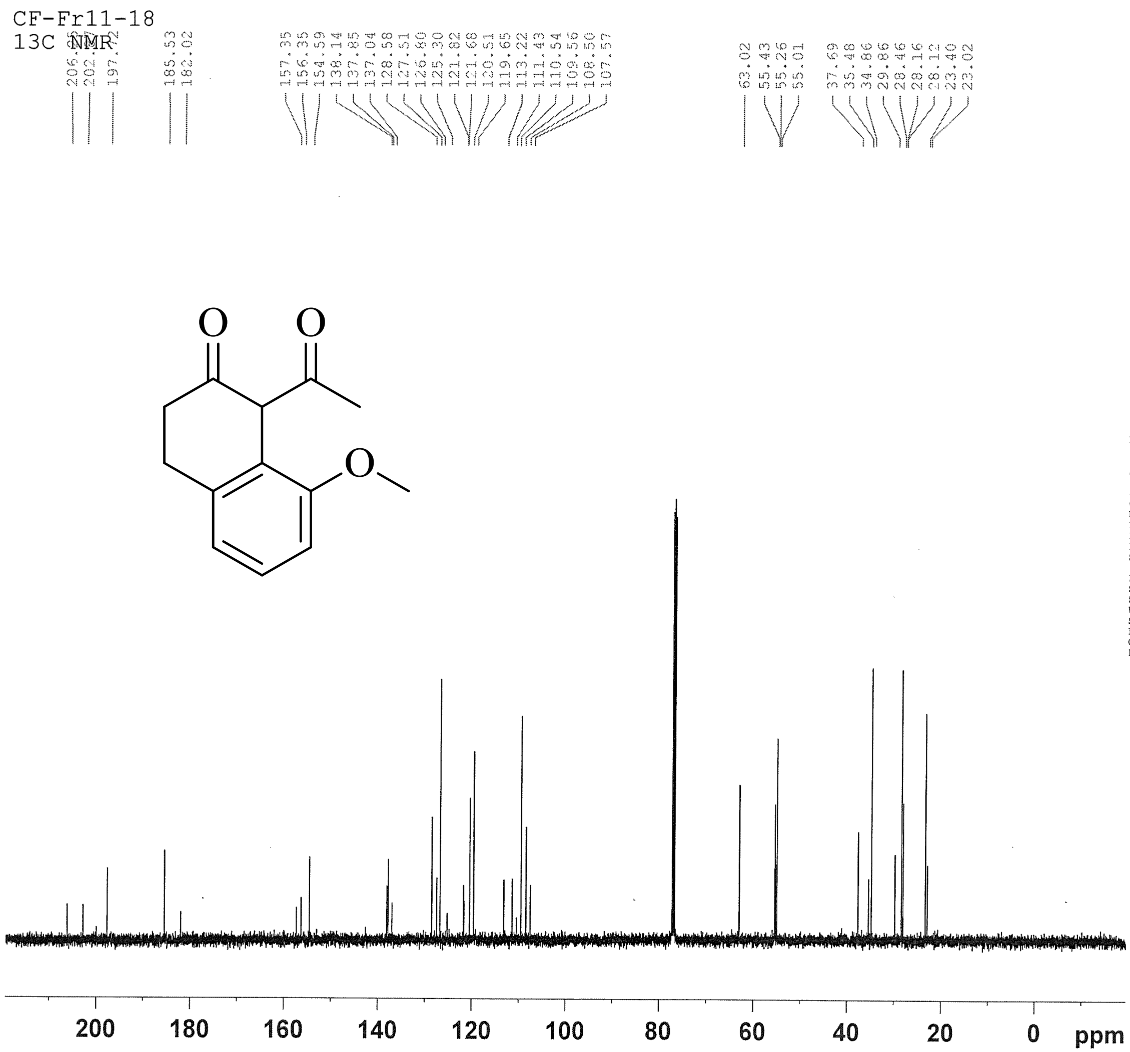




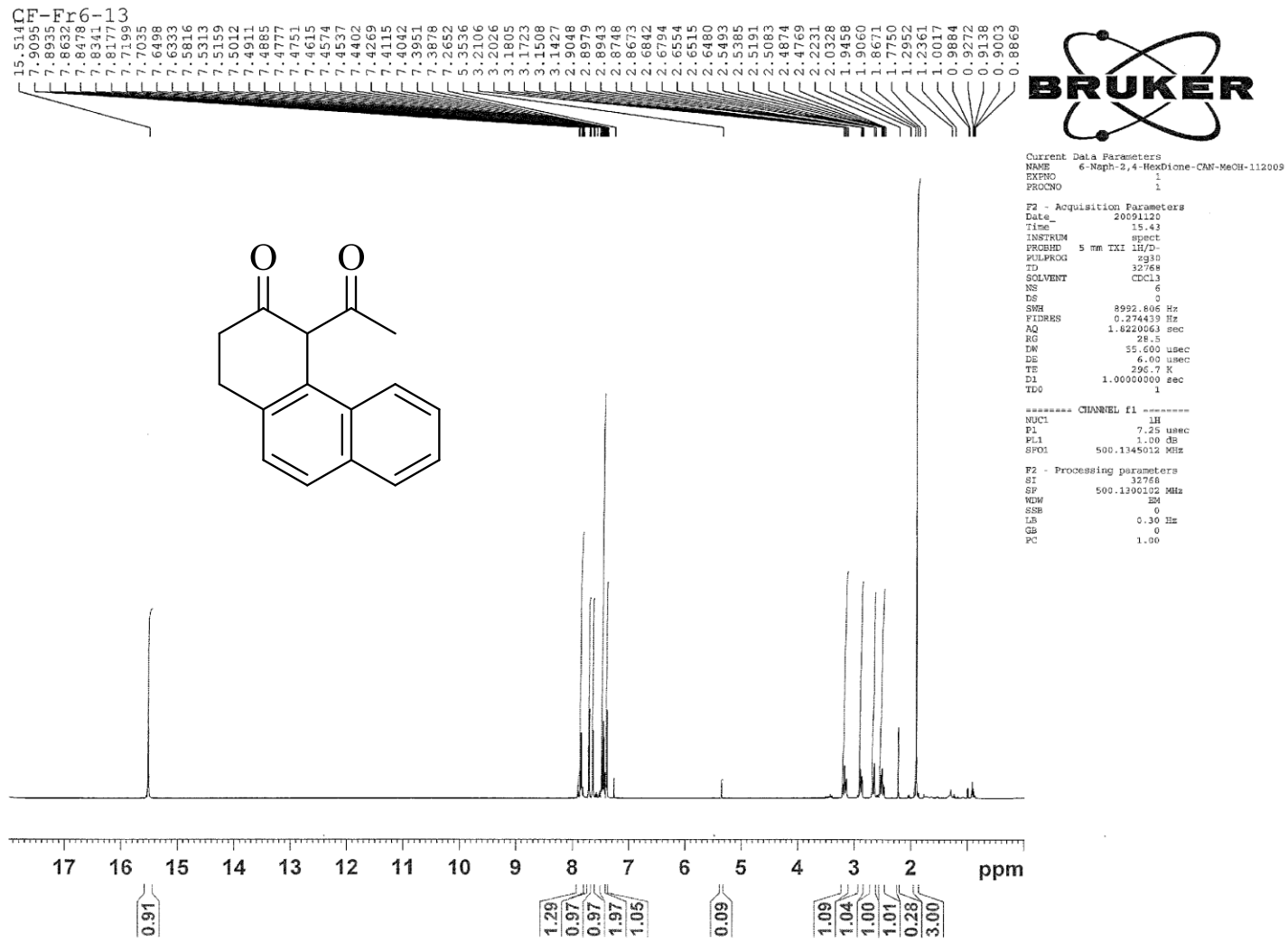
BRUKER

```
Current Data Parameters
NAME      6-DiMeOPh-2,4-HexDione-CAN-MeOH-121710
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20101217
Time_              18.20
INSTRUM            spect
PROBHD   5 mm BBO BB-1H
PULPROG          zgdc30
TD                65536
SOLVENT           CDCl3
NS                   62
DS                    4
SWH           30030.029 Hz
FIDRES         0.458222 Hz
AQ             1.0912410 sec
RG                7298.2
DW               16.650 usec
DE                7.00 usec
TE                297.2 K
D1            1.00000000 sec
d11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                  8.60 usec
PL1                 1.00 dB
SFO1         125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2           100.00 usec
PL2                1.00 dB
PL12              17.50 dB
SFO2         500.1322150 MHz

F2 - Processing parameters
SI                  32768
SF           125.7577983 MHz
WDW                    EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```


CF-Fr11-18
16.3196
15.7548
7.2657
7.2619
7.2460
7.2301
7.1624
7.1471
7.1310
7.1162
7.0999
6.8635
6.8489
6.8311
6.8144
6.7986
6.7891
6.7822
6.7728
4.9257
3.8227
3.8189
3.7950
3.7912
3.7853
3.7819
3.2377
3.2262
3.2183
3.2064
3.1945
3.1866
3.1750
2.9965
2.9748
2.9630
2.9548
2.9431
2.9314
2.8412
2.8281
2.8125
2.7998
2.7882
2.7794
2.7677
2.7561
2.5547
2.5435
2.5406
2.5273
2.5061
2.4936
2.4854
2.4744
2.4627
2.4550
2.4432
2.3457
2.3198
2.0563
2.0459
2.0157
1.2138
0.8894
0.8622
BRUKER
Current Data Parameters
NAME 6-mMeOPh-2,4-HexDione-CAN-MeOH-120309
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20091203
Time 13.14
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8220063 sec
RG 128
DW 55.600 usec
DE 6.00 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz
F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
O
O
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
ppm
0.23
0.97
1.95
3.89
0.52
6.16
8.21
6.00

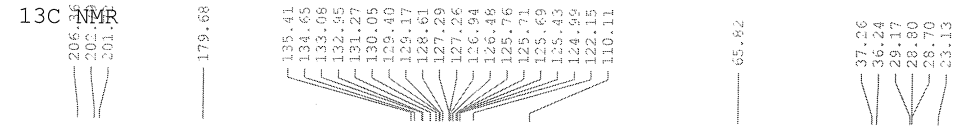


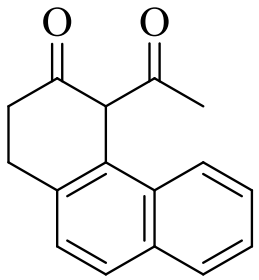

```
Current Data Parameters
NAME     6-mMeOPh-2,4-HexDione-CAN-MeOH-120309
EXPNO                5
PROCNO               1

F2 - Acquisition Parameters
Date_            20091203
Time                13.18
INSTRUM             spect
PROBHD   5 mm BBO BB-1H
PULPROG           zgdc30
TD                  65536
SOLVENT             CDCl3
NS                    135
DS                      4
SWH          30030.029 Hz
FIDRES        0.458222 Hz
AQ           1.0912410 sec
RG                   4096
DW             16.650 usec
DE               7.00 usec
TE               297.8 K
D1          1.00000000 sec
d11         0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1               8.60 usec
PL1               1.00 dB
SFO1       125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2           100.00 usec
PL2               1.00 dB
PL12             17.50 dB
SFO2       500.1322150 MHz

F2 - Processing parameters
SI                  32768
SF         125.7577973 MHz
WDW                    EM
SSB                     0
LB                1.00 Hz
GB                      0
PC                   1.40
```

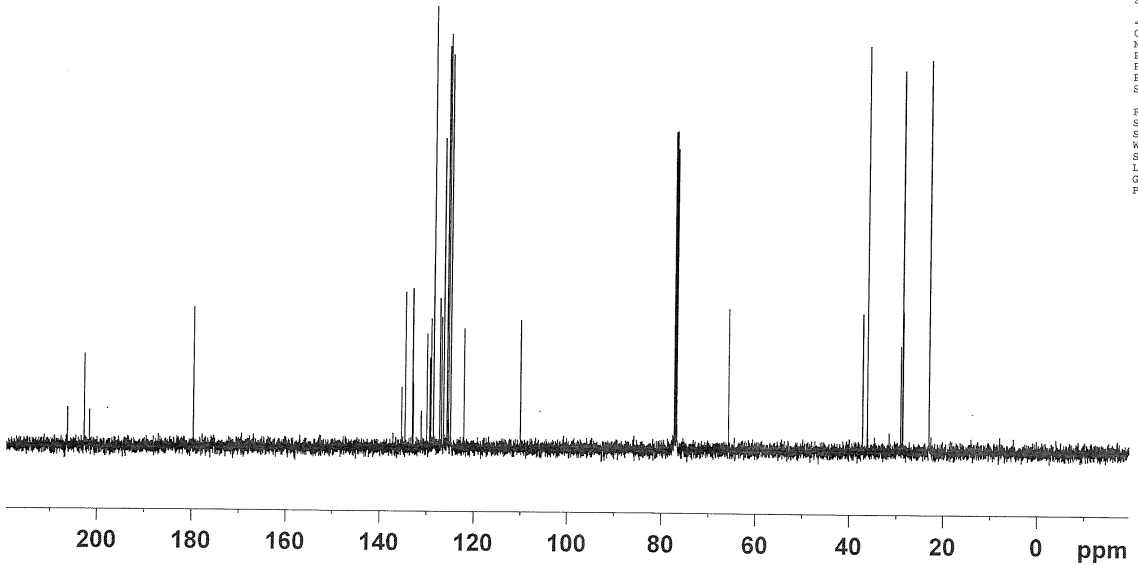

CF-Fr6-13
15.5141
7.9095
7.8935
7.8632
7.8478
7.8341
7.8177
7.7199
7.7035
7.6498
7.6333
7.5816
7.5313
7.5159
7.5012
7.4911
7.4885
7.4777
7.4751
7.4615
7.4574
7.4537
7.4402
7.4269
7.4115
7.4042
7.3951
7.3878
7.2652
5.3536
3.2106
3.2026
3.1805
3.1723
3.1508
3.1427
2.9048
2.8979
2.8943
2.8748
2.8673
2.6842
2.6794
2.6554
2.6515
2.6480
2.5493
2.5385
2.5191
2.5083
2.4874
2.4769
2.2231
2.0328
1.9458
1.9060
1.8671
1.7750
1.2952
1.2361
1.0017
0.9884
0.9272
0.9138
0.9003
0.8869
BRUKER
Current Data Parameters
NAME 6-Naph-2,4-HexDione-CAN-MeOH-112009
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20091120
Time 15.43
INSTRUM spect
PROBHD 5 mm TXI 1H/D-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 8992.806 Hz
FIDRES 0.274419 Hz
AQ 1.8220063 sec
RG 28.5
DW 55.600 usec
DE 6.00 usec
TE 296.7 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 7.25 usec
PL1 1.00 dB
SFO1 500.1345012 MHz
F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
O
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
ppm
0.91
1.29
0.97
0.97
1.97
1.05
0.09
1.09
1.04
1.00
1.01
0.28
3.00

2i

13C NMR





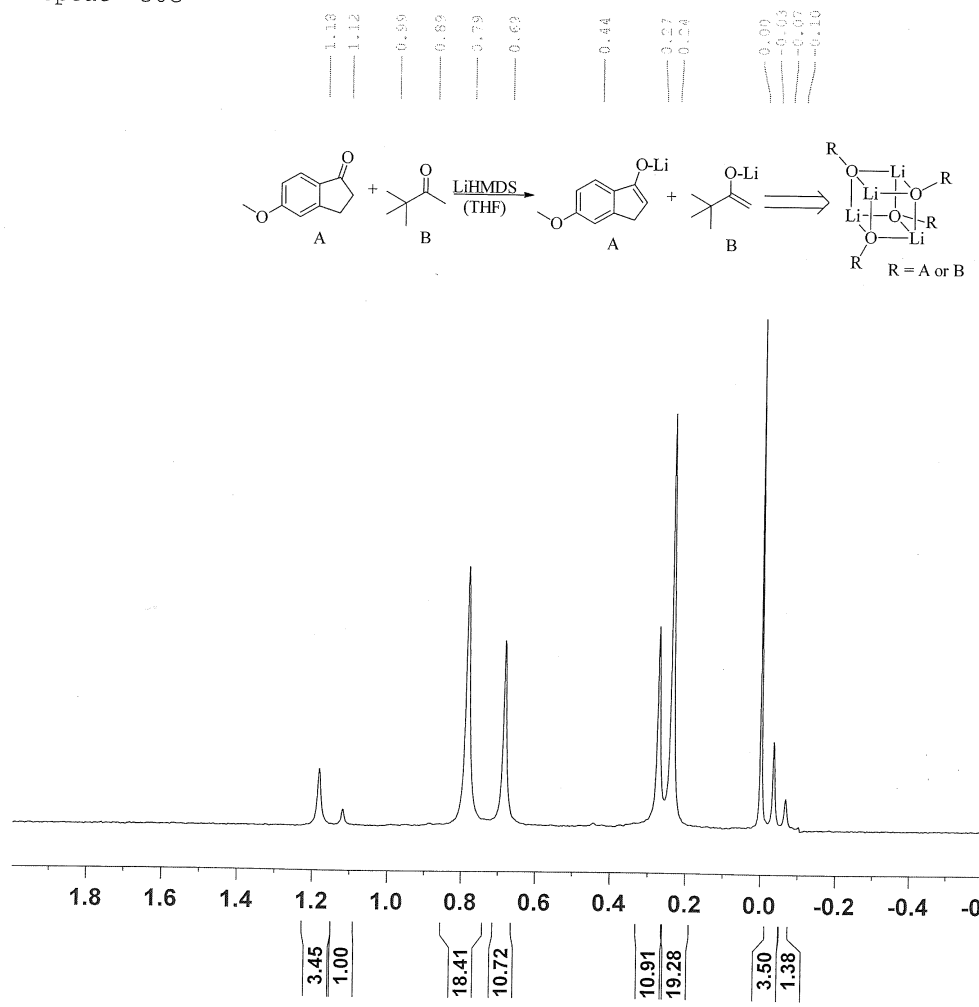


BRUKER

```
Current Data Parameters
NAME        6-Naph-2,4-HexDione-CAN-MeOH-112009
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_          20091201
Time               9.09
INSTRUM           spect
PROBHD   5 mm BBO BB-1H
PULPROG         zgdc30
TD               65536
SOLVENT          CDCl3
NS                  61
DS                   4
SWH          30030.029 Hz
FIDRES         0.458222 Hz
AQ             1.0912410 sec
RG                4096
DW              16.650 usec
DE               7.00 usec
TE              297.0 K
D1           1.00000000 sec
d11          0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                13C
P1                 8.60 usec
PL1                1.00 dB
SFO1       125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2          100.00 usec
PL2                1.00 dB
PL12              17.50 dB
SFO2       500.1322150 MHz

F2 - Processing parameters
SI                32768
SF         125.7577890 MHz
WDW                  EM
SSB                  0
LB                1.00 Hz
GB                   0
PC                1.40
```

^{7}Li NMR spetra of lithium enolate aggregates

5MeOInda-Pina-0.15M Each-042011
Repeat -30C



Current Data Parameters

NAME	7Li_BBO5
EXPNO	60
PROCNO	1

F2 - Acquisition Parameters

Date_	20110420
Time	11.26
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	MeOD
NS	8
DS	0
SWH	10000.000 Hz
FIDRES	0.152588 Hz
AQ	3.2769001 sec
RG	4597.6
DW	50.000 usec
DE	7.00 usec
TE	241.2 K
D1	1.00000000 sec
TD0	1

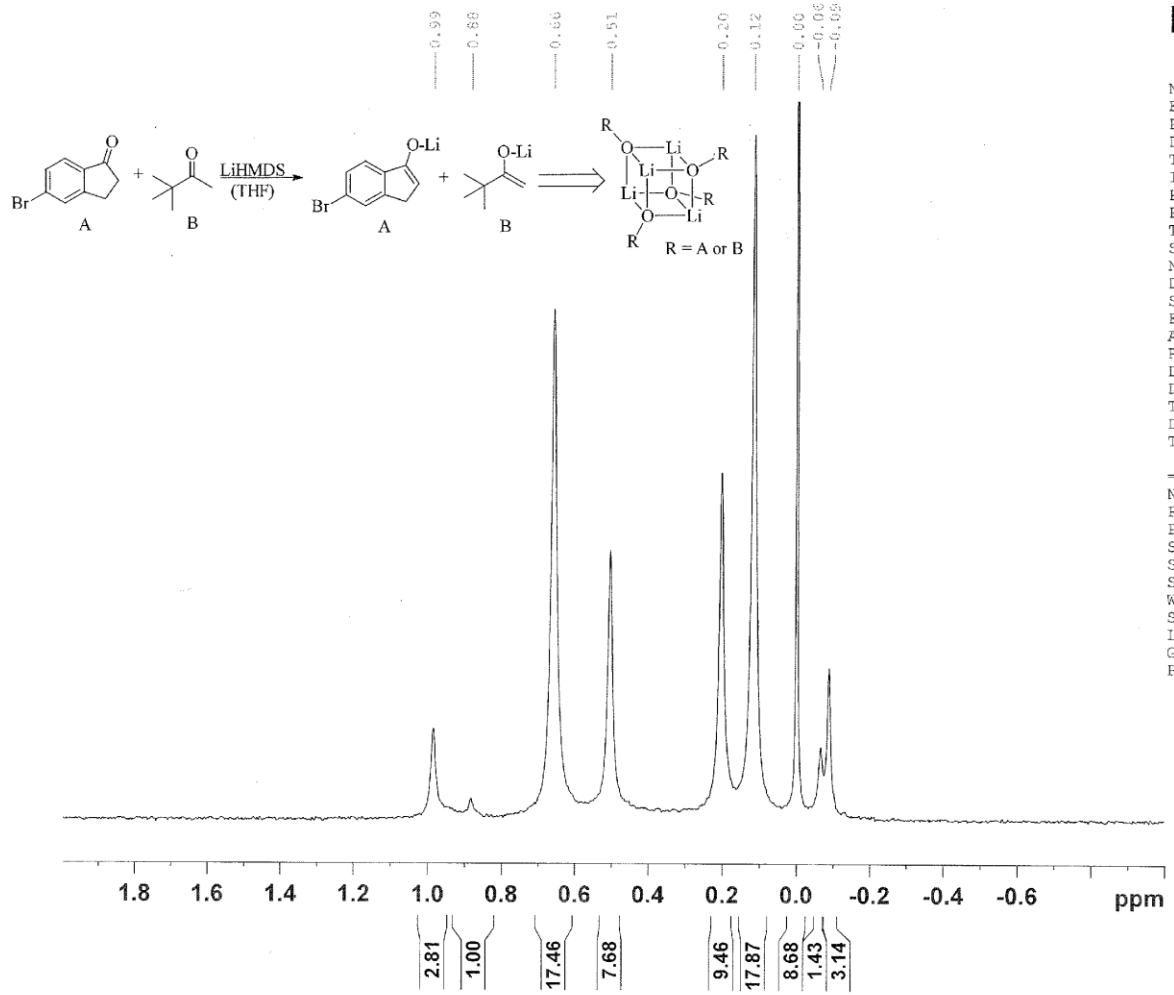
======== CHANNEL f1 ========

NUC1	7Li
P1	9.10 usec
PL1	-2.00 dB
SFO1	194.3695080 MHz

F2 - Processing parameters

SI	32768
SF	194.3694464 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

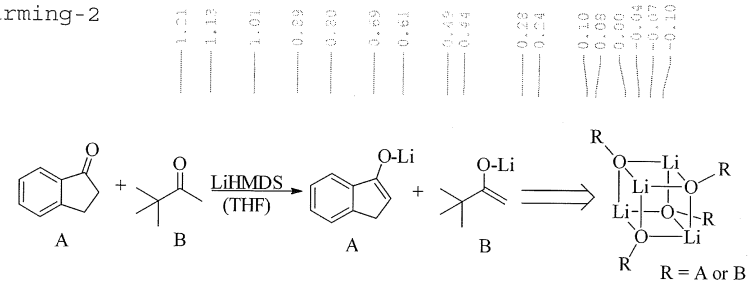
Br-Inda-Pina-0.15M Each-042011
Repeat-warming

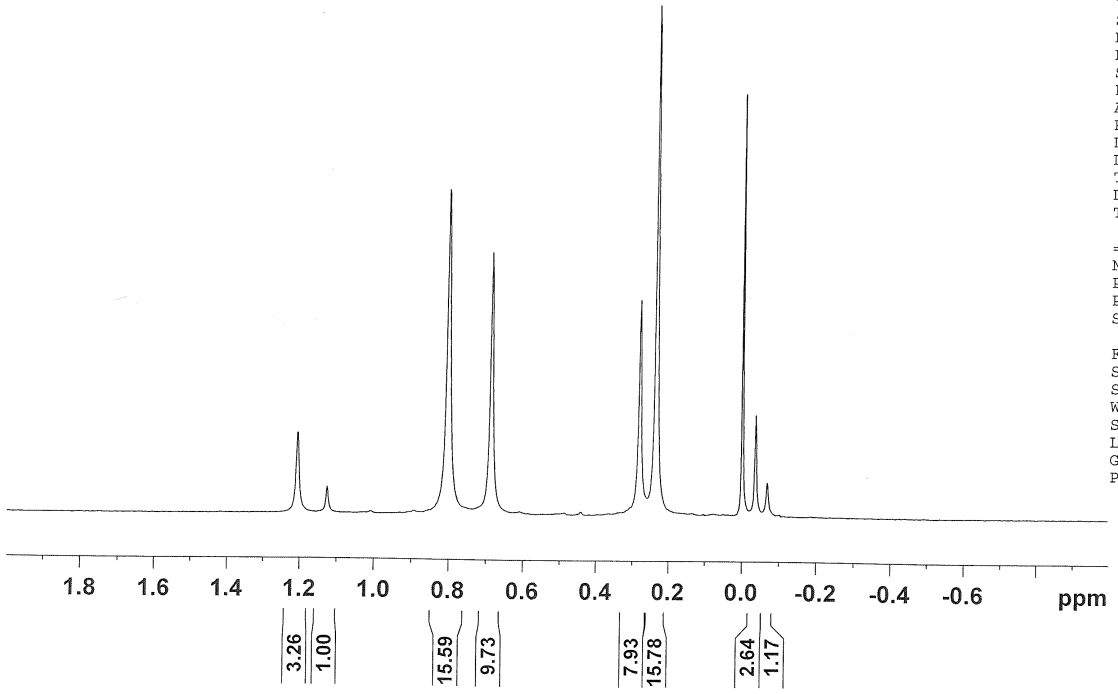


BRUKER

NAME	7Li_BBO5
EXPNO	59
PROCNO	1
Date_	20110420
Time	11.17
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	MeOD
NS	8
DS	0
SWH	10000.000 Hz
FIDRES	0.152588 Hz
AQ	3.2769001 sec
RG	4597.6
DW	50.000 usec
DE	7.00 usec
TE	241.1 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	7Li
P1	9.10 usec
PL1	-2.00 dB
SFO1	194.3695080 MHz
SI	32768
SF	194.3694464 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

IndaPina-Enolates-0.15M Each-062310
LiCl in MeOh-d4
Repeat/Warming-2





BRUKER

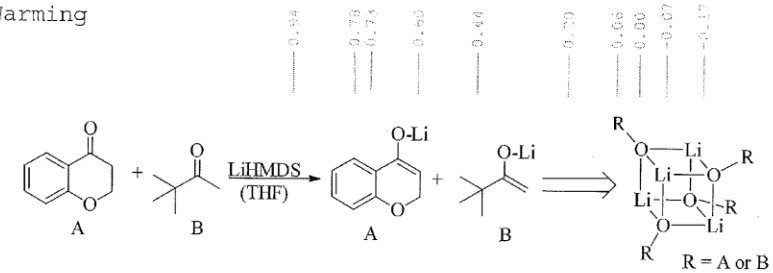
Current Data Parameters
NAME 7Li_BBO5
EXPNO 25
PROCNO 1

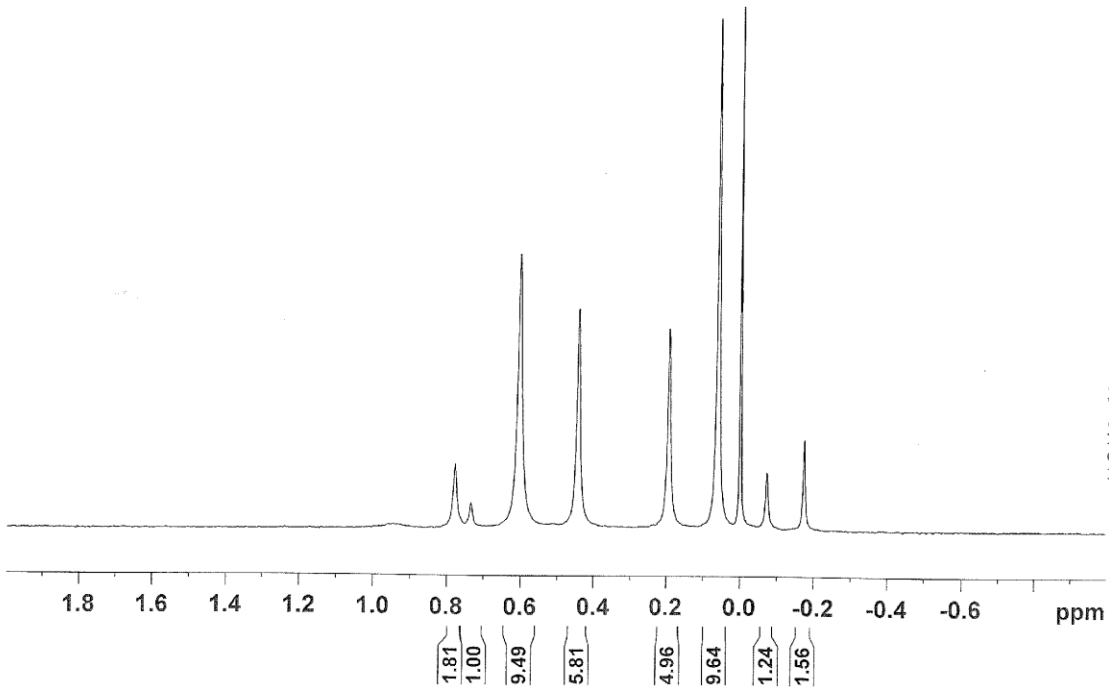
F2 - Acquisition Parameters
Date_ 20100623
Time 11.33
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 5160.6
DW 50.000 usec
DE 7.00 usec
TE 239.6 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 7Li
P1 9.10 usec
PL1 -2.00 dB
SFO1 194.3695080 MHz

F2 - Processing parameters
SI 32768
SF 194.3694465 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

4-Chroma-Pina-Enolates-0.15M Each-063010
LiCl in MeOh-d4
Repeat/Warming





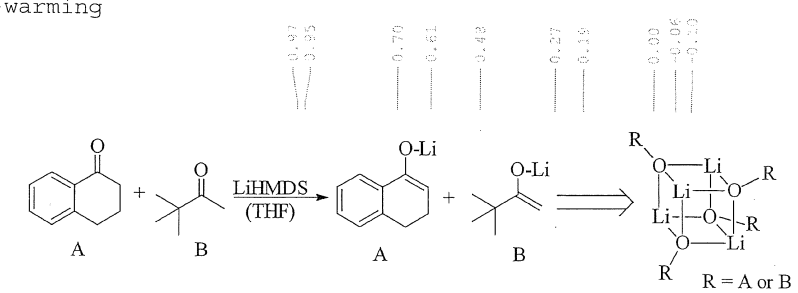
Current Data Parameters
NAME 7Li_BBO5
EXPNO 31
PROCNO 1

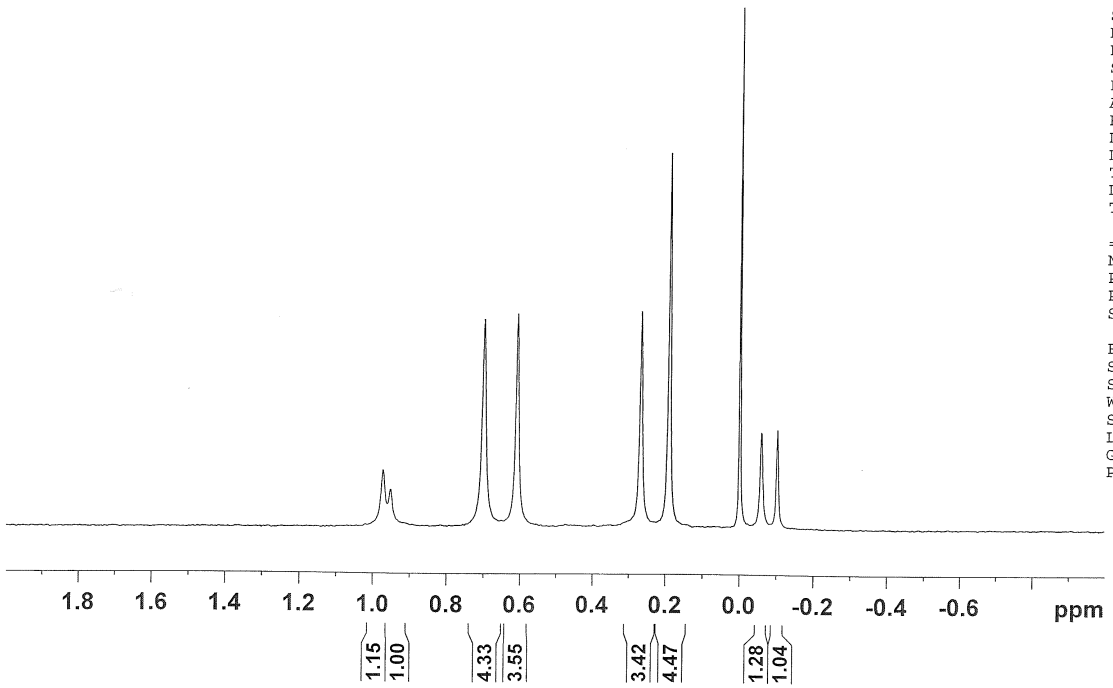
F2 - Acquisition Parameters
Date_ 20100630
Time 10.20
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 5160.6
DW 50.000 usec
DE 7.00 usec
TE 241.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 7Li
P1 9.10 usec
PL1 -2.00 dB
SFO1 194.3695080 MHz

F2 - Processing parameters
SI 32768
SF 194.3694468 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

aTet-Pina-0.15M Each-040311
repeat-warming





Current Data Parameters
NAME 7Li_BBO5
EXPNO 53
PROCNO 1

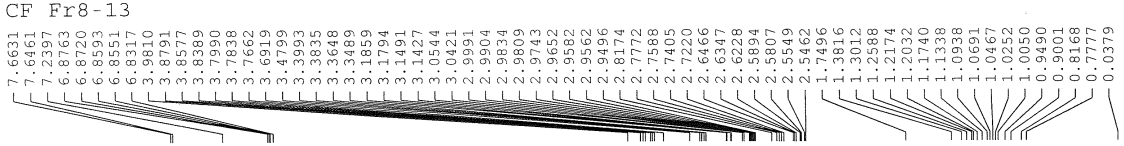
F2 - Acquisition Parameters
Date_ 20110403
Time 18.05
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 4597.6
DW 50.000 usec
DE 7.00 usec
TE 241.2 K
D1 1.00000000 sec
TD0 1

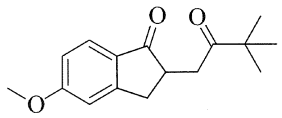
======== CHANNEL f1 ========
NUC1 7Li
P1 9.10 usec
PL1 -2.00 dB
SFO1 194.3695080 MHz

F2 - Processing parameters
SI 32768
SF 194.3702125 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

^{1}H NMR and ^{13}C NMR spectra of heterocoupled products

CF Fr8-13





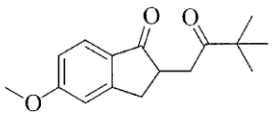
Current Data Parameters
NAME 5-MeOIndaPina-LiHMDS-I2-041211
EXPNO 2
PROCNO 1

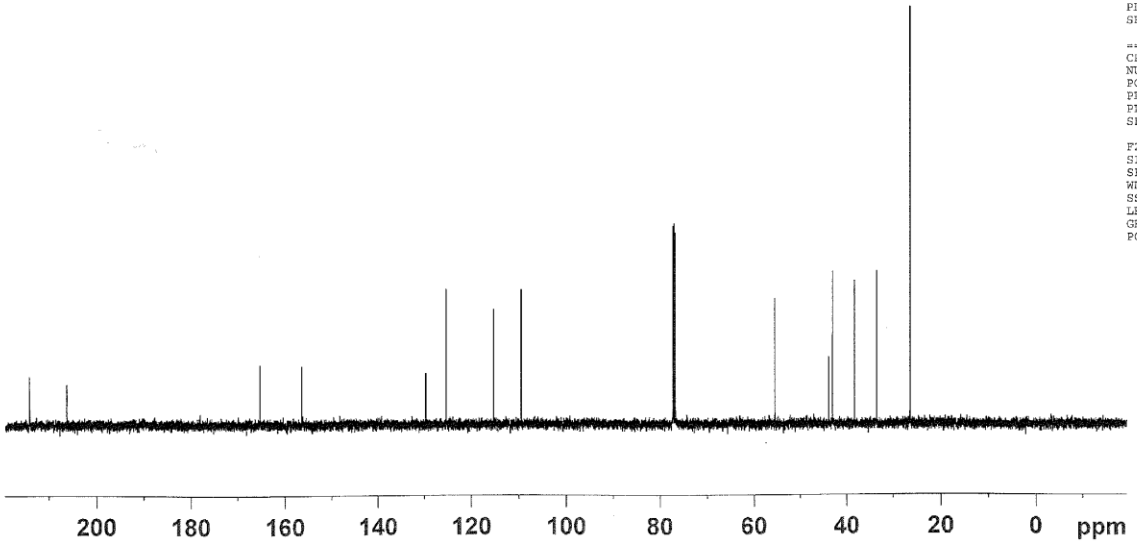
F2 - Acquisition Parameters
Date_ 20110413
Time 7.55
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 1.6385000 sec
RG 101.6
DW 50.000 usec
DE 6.50 usec
TE 296.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz

F2 - Processing parameters
SI 32768
SF 500.1300232 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

CF Fr8-13
13C





BRUKER

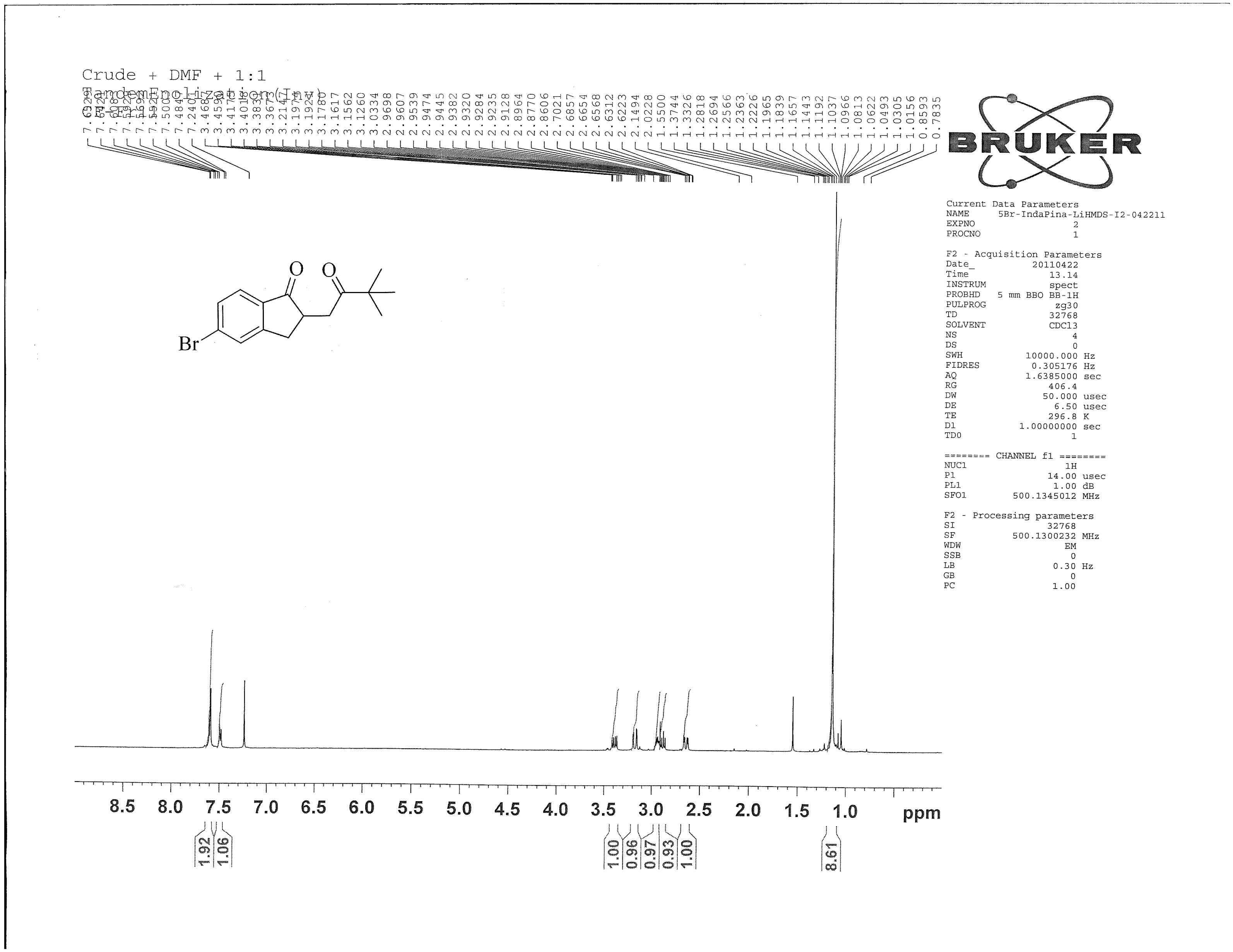
Current Data Parameters
NAME 5-MeOIndaPina-LiHMDS-I2 041211
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110413
Time 8.00
INSTRUM spect
PROBHD 5 mm BBO BB 1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 34
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 2048
DW 16.650 usec
DE 7.00 usec
TE 296.6 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

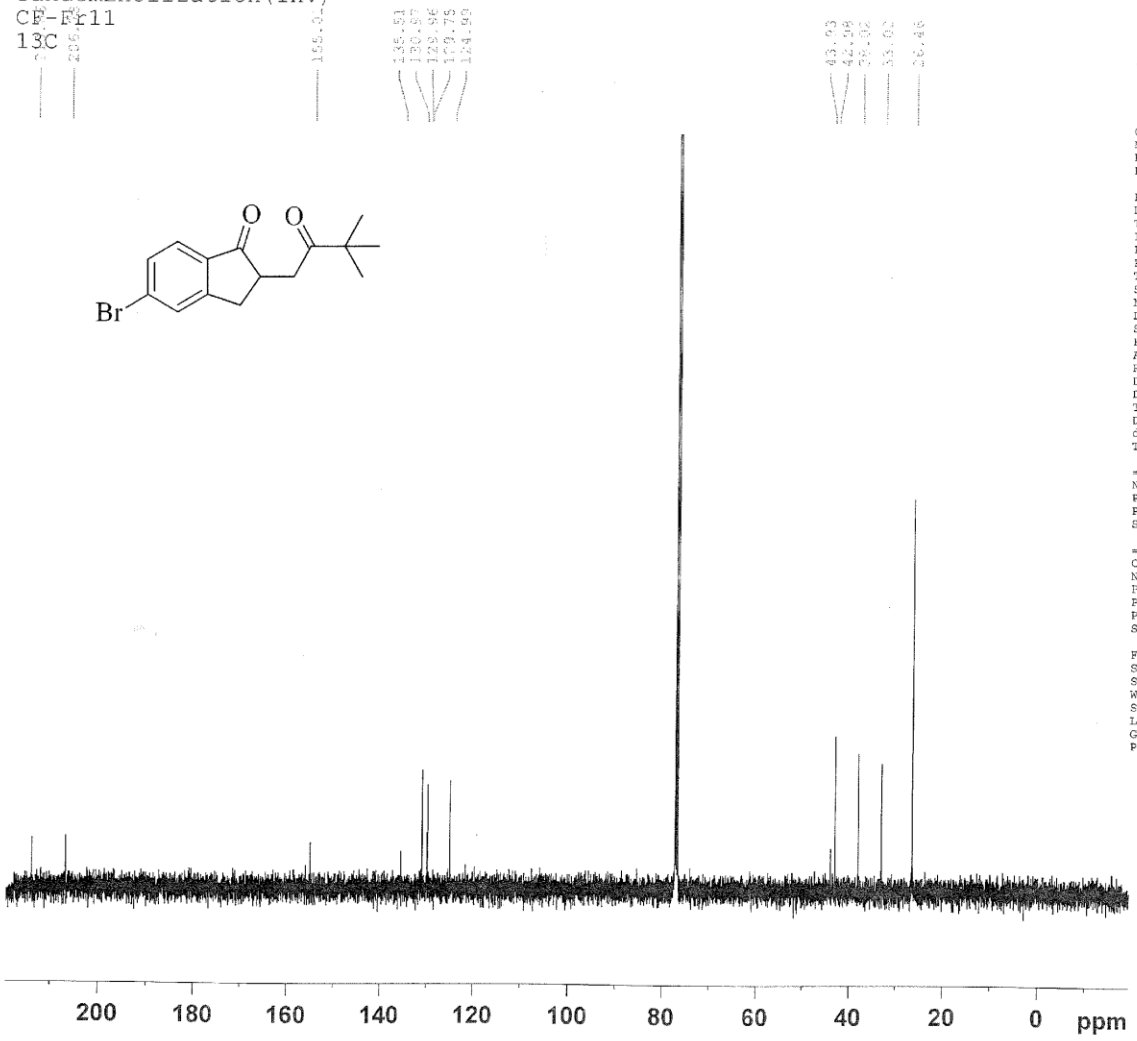
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577980 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Crude + DMF + 1:1
Br
O
O
3.1617
3.1562
3.1260
3.0334
2.9698
2.9607
2.9539
2.9474
2.9445
2.9382
2.9320
2.9284
2.9235
2.9128
2.8964
2.8770
2.8606
2.7021
2.6857
2.6654
2.6568
2.6312
2.6223
2.1494
2.0228
1.5500
1.3744
1.3326
1.2818
1.2694
1.2566
1.2363
1.2226
1.1965
1.1839
1.1657
1.1443
1.1192
1.1037
1.0966
1.0813
1.0622
1.0493
1.0305
1.0156
0.8593
0.7835
Current Data Parameters
NAME 5Br-IndaPina-LiHMDS-I2-042211
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110422
Time 13.14
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 1.6385000 sec
RG 406.4
DW 50.000 usec
DE 6.50 usec
TE 296.8 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz
F2 - Processing parameters
SI 32768
SF 500.1300232 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.92
1.06
1.00
0.96
0.97
0.93
1.00
8.61

TandemEnolization(Inv)
CF-Fr11
13C



Current Data Parameters
NAME 5Br-IndaPina-LiHMDS-I2-042211
EXPNO 3
PROCNO 1

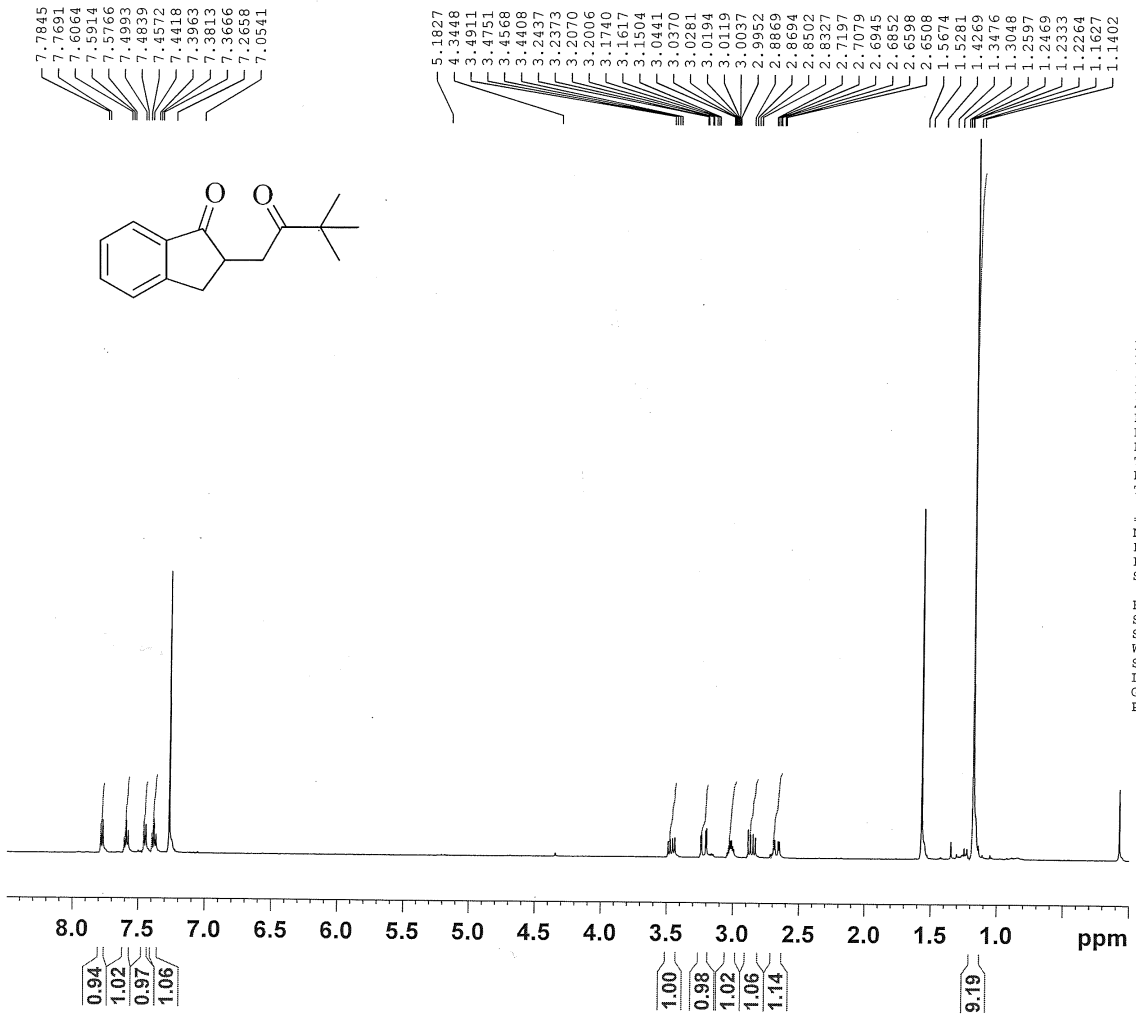
F2 - Acquisition Parameters
Date_ 20110422
Time 13.20
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 210
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 2048
DW 16.650 usec
DE 7.00 usec
TE 297.2 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577921 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

CombiFlash2-Fr12-13



BRUKER

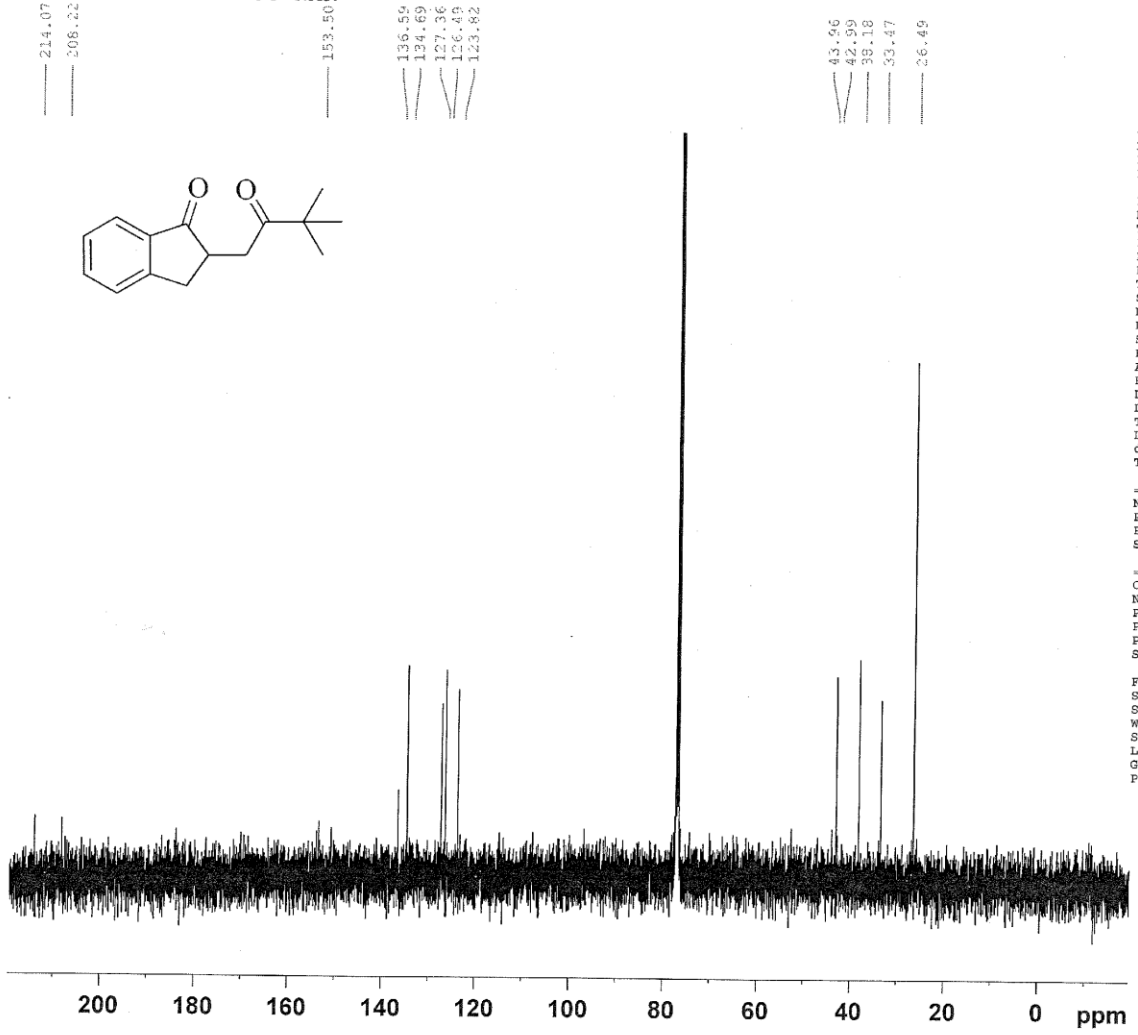
Current Data Parameters
NAME Inda-Pina-LDA-CTAN-070209
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090702
Time 14.09
INSTRUM spect
PROBHD 5 mm TXI 1H/D-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 6
DS 0
SWH 7002.801 Hz
FIDRES 0.213709 Hz
AQ 2.3397565 sec
RG 406.4
DW 71.400 usec
DE 6.00 usec
TE 295.8 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 7.25 usec
PL1 1.00 dB
SFO1 500.1335009 MHz

F2 - Processing parameters
SI 32768
SF 500.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

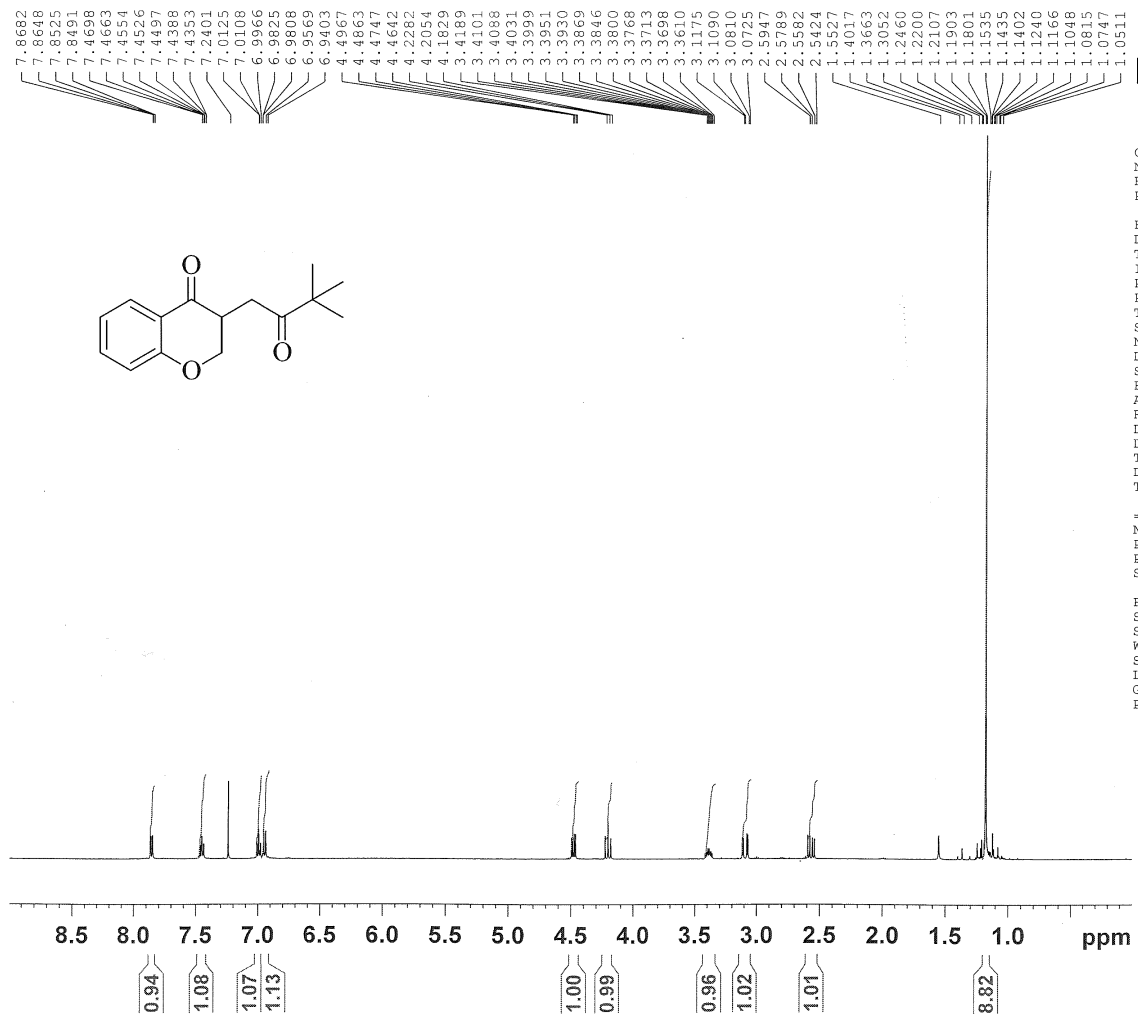
CombiFlash-Fr8-13C NMR



BRUKER

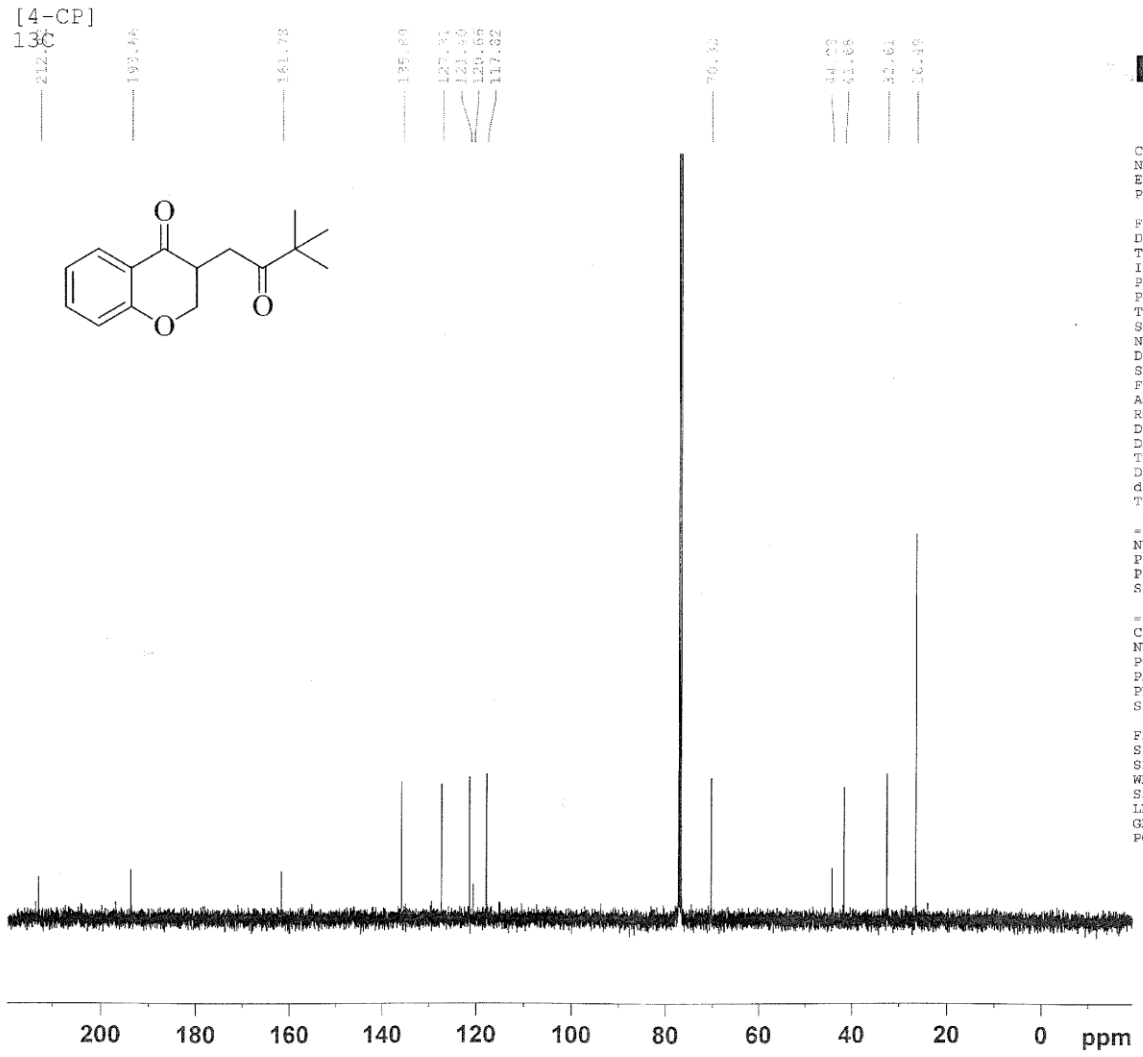
```
Current Data Parameters
NAME      Inda-Pina-LDA-CTAN-061809-2
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_          20090622
Time              10.27
INSTRUM           spect
PROBHD   5 mm BBO BB-1H
PULPROG          zgdc30
TD                65536
SOLVENT           CDCl3
NS                  705
DS                    4
SWH           30030.029 Hz
FIDRES         0.458222 Hz
AQ             1.0912410 sec
RG                 4096
DW               16.650 usec
DE                7.00 usec
TE               296.9 K
D1             1.00000000 sec
d11            0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 8.60 usec
PL1                1.00 dB
SFO1         125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2           100.00 usec
PL2                1.00 dB
PL12              17.50 dB
SFO2         500.1322150 MHz

F2 - Processing parameters
SI                 32768
SF           125.7577923 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

[4-CP]



BRUKER

```
Current Data Parameters
NAME      IndaPina-LiHMDS-I2-041411
EXPNO                3
PROCNO               1

F2 - Acquisition Parameters
Date_          20110418
Time              11.58
INSTRUM           spect
PROBHD   5 mm BBO BB-1H
PULPROG           zg30
TD               32768
SOLVENT          CDCl3
NS                   4
DS                   0
SWH          10000.000 Hz
FIDRES           0.305176 Hz
AQ            1.6385000 sec
RG                 322.5
DW              50.000 usec
DE               6.50 usec
TE              296.6 K
D1           1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                 1H
P1              14.00 usec
PL1              1.00 dB
SFO1        500.1345012 MHz

F2 - Processing parameters
SI               32768
SF          500.1300232 MHz
WDW                 EM
SSB                  0
LB               0.30 Hz
GB                   0
PC                1.00
```



Current Data Parameters
NAME IndaPina-LiHMDS-12-041411
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110418
Time 12.02
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 225
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 4597.6
DW 16.650 usec
DE 7.00 usec
TE 297.1 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 1

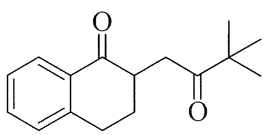
======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 17.50 dB
SFO2 500.1322150 MHz

F2 - Processing parameters
SI 32768
SF 125.7577919 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

CF-Fr15-16

7.9967 7.9810 7.4557 7.4531 7.4408 7.4383 7.4259 7.4233 7.2894 7.2745 7.2596 7.2401 7.2218 7.2064 3.2818 3.2719 3.2458 3.2360 3.1587 3.1493 3.1455 3.1397 3.1361 3.1319 3.1226 3.1180 3.1137 3.1089 3.0996 3.0897 3.0807 2.9518 2.9457 2.9391 2.9319 2.9122 2.9056 2.8984 2.5820 2.5685 2.5461 2.5326 2.1389 2.1299 2.1242 2.1134 2.1073 2.1041 2.0985 2.0952 2.0895 2.0237 1.8846 1.8761 1.8584 1.8499 1.8322 1.5617 1.2372 1.2303 1.2009 1.1899 1.1535 1.1499 1.1139 0.9055



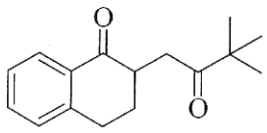
Current Data Parameters
NAME aTetPina-LiHMDS-I2-042711
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110427
Time 16.30
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 1.6385000 sec
RG 406.4
DW 50.000 usec
DE 6.50 usec
TE 296.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 1.00 dB
SFO1 500.1345012 MHz

F2 - Processing parameters
SI 32768
SF 500.1300232 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

CF-Fr15-16
13C



BRUKER

```
Current Data Parameters
NAME      aTetPina-LiHMDS-I2-042711
EXPNO                4
PROCNO               1

F2 - Acquisition Parameters
Date_            20110427
Time               16.35
INSTRUM            spect
PROBHD   5 mm BBO BB-1H
PULPROG          zgdc30
TD                65536
SOLVENT           CDCl3
NS                  401
DS                    4
SWH           30030.029 Hz
FIDRES         0.458222 Hz
AQ            1.0912410 sec
RG                 4096
DW               16.650 usec
DE                7.00 usec
TE               296.5 K
D1            1.00000000 sec
d11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                  8.60 usec
PL1                 1.00 dB
SFO1        125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                 1.00 dB
PL12               17.50 dB
SFO2        500.1322150 MHz

F2 - Processing parameters
SI                  32768
SF          125.7577924 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

Curriculum Vitae

Highlights

- Expertise in organic reactions involving single electron transfers
- Experienced in interrogating mechanisms of complex reaction systems with spectroscopic, kinetic, and thermodynamic data
- Broad knowledge in organic synthesis and in methodology development

Education

- Ph.D, Chemistry, Lehigh University, Bethlehem, PA (GPA 3.97), Spring 2011
  Dissertation title: Bimolecular coupling reactions involving single electron oxidations: Methodology development and mechanistic studies
  Adviser: Dr. Robert A. Flowers, II
- B.S., Biochemistry (Minor: Spanish), *summa cum laude*, Ramapo College of New Jersey, Mahwah, NJ (GPA 3.98), 2006
  Research project title: Synthesis of novel di- and tri-pegylating reagents
  Adviser: Dr. Arthur M. Felix

Research Accomplishments

- Developed methodology for synthesis of γ-halogenated ketones, important precursors for biologically active compounds such as haldol
- Determined, for first time, that solvent-dependent oxidative coupling of 1-aryl-1,3-dicarbonyls to styrene was controlled by lifetime of radical cation intermediate
- Developed synthesis for β-tetralones via intramolecular cyclization of γ-aryl-β-dicarbonyls and interrogated impact of substrate electron density on product selectivity with computational studies
- Investigated non-statistical oxidative heterocoupling of lithium enolates and determined that product distributions were, in part, a consequence of lithium enolate aggregates

Honors/Awards

- Lehigh University Edward D. Amstutz Doctoral Fellowship Recipient (2009-2010)
- Ramapo College, Summa Cum Laude, Biochemistry (2006)
- Ramapo College Research Honors (2006)
- Ramapo College Award for Excellence in Biochemistry (2006)
- Ramapo College Dean's List (Fall 2002-Spring 2006)
- CRC Press Freshman Chemistry Achievement Award (2003)
- Edward J. Bloustein Distinguished Scholar (2002)
- Ramapo College of New Jersey Presidential Scholar Recipient (2002)

Teaching/Employment

- Lehigh University: Teaching assistant for Introduction to Chemical Properties (Fall 2006 and 2010), Organic Chemistry I and II (Fall 2007-Spring 2009)
- Referee for *Tetrahedron*
- Mentored two undergraduate researchers: one is currently attending medical school at Touro University Nevada and other will graduate in Spring 2011 and pursue industrial work
- ExxonMobil Biomedical Sciences Inc.: Core author of material safety data sheets in Toxicology Department (Summers 2004, 2005 and 2006)
- Ramapo College of New Jersey: Undergraduate tutor for Organic Chemistry I and II (Fall 2004-Spring 2005)

Technical Skills

- Instrumentation: GC, GC-MS, FT-IR, NMR (including ^{7}Li NMR), Stopped-flow spectrophotometry, Automated flash chromatography and UV-Vis
- Laboratory techniques: Flash column chromatography, TLC and inert atmosphere/anhydrous chemistry

Publications

- Casey, B.M.; Flowers, R.A. II "On the nature of the oxidative heterocoupling of lithium enolates" *J. Am. Chem. Soc.* Under review.
- Casey, B.M.; Sadasivam, D.V.; Flowers, R.A. II. "CAN-mediated intramolecular cyclizations of γ-aryl-β-dicarbonyls" In preparation for *Organic Letters*.
- Casey, B.M.; Eakin, C.A.; Jiao, J.; Sadasivam, D.V.; Flowers, R.A. II. "Solvent-dependent oxidative coupling of 1-aryl-1,3-dicarbonyls and styrene" *Special Issue of Tetrahedron* **2010**, *66*, 5720.
- Devery, J.J. III; Mohanta, P.K.; Casey, B.M.; Flowers, R.A. II. "Facile route to tetra-substituted pyrazoles utilizing ceric ammonium nitrate" *Synlett*, **2009**, *9*, 1490-1494.
- Casey, B.M.; Eakin, C.A.; Flowers, R.A. II. "Synthesis of γ-halogenated ketones via the Ce(IV)-mediated oxidative coupling of cyclobutanols and inorganic halides" *Tetrahedron Letters*, **2009**, *50*, 1264-1266.

Poster Presentations/Symposiums

- Casey, B.M.; Flowers, R.A., II "On the nature of the oxidative heterocoupling of lithium enolates" 42nd National Organic Chemistry Symposium. Princeton, NJ (June 2011)
- Casey, B.M.; Jiao, J.; Flowers, R.A., II "Solvent-dependent oxidative coupling of 1-aryl-1,3-dicarbonyls and styrenes via Ce (IV) reagents" 236th National Meeting of the ACS. Philadelphia, PA (August 2008)

- Casey, B.M.; Felix, A.M. "Synthesis of novel di- and tri-pegylating reagents" 8th Annual Hudson Bergen County ACS Undergraduate Research Symposium. Fairleigh Dickinson University (May 2006)
- Casey, B.M.; Felix, A.M. "Synthesis of novel di- and tri-pegylating reagents" 54th Annual New York ACS Undergraduate Research Symposium. St. John's University (April 2006)
- Casey, B.M.; Felix, A.M. "Synthesis of novel di- and tri-pegylating reagents" 5th Annual Ramapo Undergraduate Research Symposium. Ramapo College of New Jersey (April 2006)

Professional Induction/Membership

- Associate Member of the American Chemical Society
- Associate Member of Sigma Xi
- Alpha Lamba Delta Honors Society
- Beta Beta Beta Honors Society