ABSTRACT

Title of Document:	APPLICATIONS OF 2,3-DIKETOESTERS IN ORGANIC SYNTHESIS AND STEREOSELECTIVE TRANSFORMATIONS.
	Phong Minh Truong, Doctor of Philosophy, 2014
Directed By:	Professor, Michael P. Doyle, Department of Chemistry and Biochemistry

Dimethyldioxyrane oxidation of *δ*-hydroxy-*α*-diazo-*β*-ketoesters that are prepared by zinc triflate catalyzed Mukaiyama-aldol condensation of methyl diazoacetoacetates with aldehydes, occurred in quantitative yield to form dihydrofuranols that undergo acid catalyzed dehydration under mild conditions to generate 3-methoxyfuran-2-carboxylates in good yield.

Oxidation of *ζ*-keto-*α*-diazo-*β*-ketoesters that are formed by zinc triflate catalyzed Mukaiyama-Michael condensation of methyl diazoacetoacetate enones procduced their 2,3,7-diketoester derivative in quantitative yield. The intramolecular acid catalyzed aldol cyclization of 2,3,7-triketoesters provides highly functionalized cyclopentanones with good diastereoselectivity in high overall yields via kinetically controlled and stereodivergent catalytic processes. Lewis acid catalysis gives high selectivity for the 1,3-*anti* tetrasubstituted cyclopentanones, whereas Brønsted acid catalysis produces the corresponding 1,3-*syn* diastereomer.

The first enantioselective transformation of 2,3-diketoesters was demonstrated in carbonyl-ene reactions catalyzed by [Cu((*S*,*S*)-*tert*-Bu-box)](SbF$_6$)$_2$ generating chiral α-functionalized-α-hydroxy-β-ketoesters in up to 94% yield and 97% ee. The suggested mode of activation is bi-dentate coordination between copper and the oxygen atoms of the two keto-carbonyl groups. The 2,3-diketoesters are conveniently accessed from the corresponding α-diazo-β-ketoester, and catalyst loading as low as 1.0 mol % is achieved.

APPLICATIONS OF 2,3-DIKETOESTERS IN ORGANIC SYNTHESIS AND STEREOSELECTIVE TRANSFORMATIONS

By

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Dedication

To my wife, Anna Vu for her incredible support throughout this program, and to my parents, Binh Truong and Anh Nguyen

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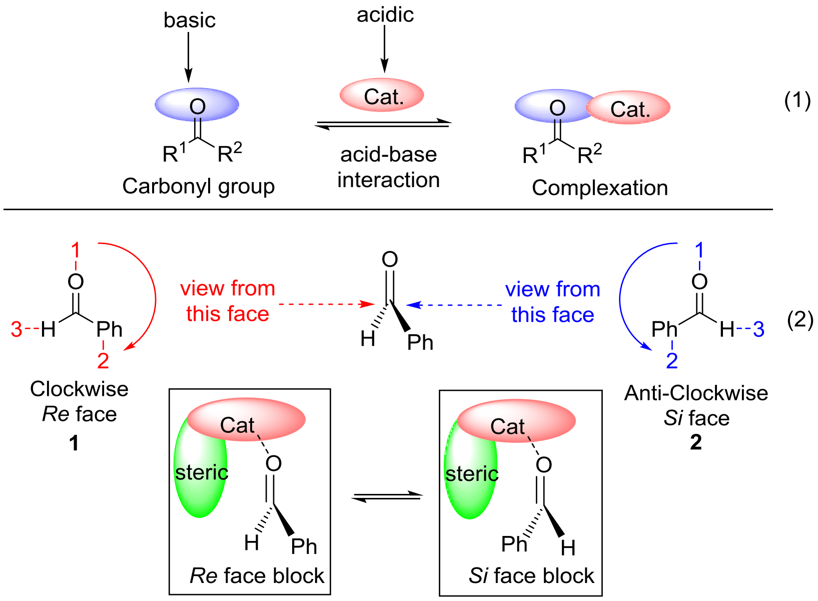
Chapter 1: Vicinal Tricarbonyl Systems and the Synthesis of Substituted Furans

1.1 Introduction to Carbonyl Functional Group

One of the fundamental and challenging tasks in modern chemistry is having the ability to control the stereochemical outcome in a chemical reaction. Tremendous efforts have been devoted into the field of catalytic diastereo- and enantioselective transformations over the last 3 decades.[1] In the subcategory of catalytic stereoselective synthesis Lewis acid catalysis of nucleophilic addition to carbonyl compounds, particularly aldehydes and ketones, is one of the most studied chemical process in organic synthesis due to the reactivity offered by the polarized carbon–oxygen double bond.[2] The property of a carbonyl group that plays a crucial role in stereoselective reactions is the weakly basic electron pairs on the oxygen atom that allow them to interact with the Lewis acidic catalyst (Figure 1.1, eq. 1). The interaction between a carbonyl group and a catalyst can be viewed as a simple acid-base complexation. As the result of this interaction, the carbonyl group is activated through electronic induction by the catalyst, which leads to a lower activation energy in reactions with electron rich nucleophiles. In stereoselective reactions, the essential role of the catalyst upon complexation with the carbonyl group is to create a different facial steric environment between the *Re* face **1** and *Si* face **2** of the carbonyl group, thus driving the chemical reaction to selectively occur on one face over the other (Figure 1.1, eq. 2).[3]

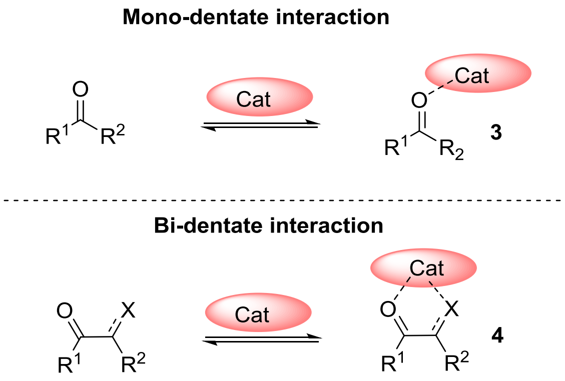
Figure 1.1 Explanations of Carbonyl *Re* Face and *Si* Face.



basic
acidic
Cat.
O
R1
R2
Carbonyl group
acid-base interaction
Cat.
Complexation
(1)
1
O
3--H
Ph
2
Clockwise
Re face
1
view from this face
O
H
Ph
view from this face
1
O
Ph
H--3
2
(2)
Anti-Clockwise
Si face
2
Cat
steric
O
H
Ph
Re face block
Cat
steric
O
Ph
H
Si face block

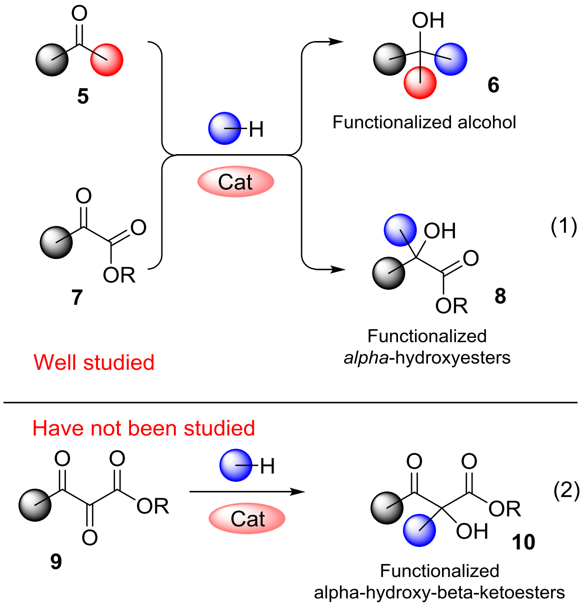
Single point binding (mono-dentate) **(3)** and two-point binding (bi-dentate) **(4)** are the two common modes of interaction between carbonyl groups and Lewis acid catalysts (Figure 1.2). Although many mono-dentate Lewis acid catalyst systems have been successfully developed, in general the selectivity of these systems is difficult to control compared to that in bi-dentate catalytic systems due to the possibility of rotation about the catalyst-carbonyl oxygen bond, leading to different activated conformations.[4] On the other hand, bi-dentate complexation with Lewis acids having two open coordination sites provides a conformationally more restricted adduct compared to that from one-point binding and reduces the number of possible transition states. Furthermore, the tight chelation of a bidentate complex increases the equilibrium constant between the unbound substrate and catalyst-substrate, leading to a greater concentration of the activated adduct which increases the activities of the catalyst.[5]

Figure 1.2 Mono-dentate and Bi-dentate Interaction.



Nucleophilic additions to mono-carbonyl **(5)** and 1,2-dicarbonyl **(7)** systems are essential transformations in organic chemistry because they provide direct access to functionalized alcohol **(6)** and α-hydroxyester **(8)** derivatives respectively, which are extremely important building blocks in natural product synthesis and the pharmaceutical industry (Scheme 1.1, eq. 1).[7,8] Although extensive efforts have been devoted to the exploration of stereoselective Lewis acid catalysis reactions with mono-carbonyl and 1,2-dicarbonyl systems, surprisingly, these studies have not been applied to the well-known highly electrophilic 2,3-diketoesters **(9)**, even though the desired product of nucleophilic addition to the central carbonyl of 2,3-diketoester would generate highly functionalized *α*-hydroxy-*β*-ketoester **(10)** (Scheme 1.1, eq. 2).[8] *α*-Hydroxy-*β*-ketoesters are important structural motifs in biological molecules, drug candidates, and key intermediates in natural product synthesis.[9] In combination with their highly electrophilic character and multiple oxygen-rich coordination sites, we envision that the 2,3-diketoester system would be an excellent candidate in catalytic stereoselective nucleophilic addition reactions.

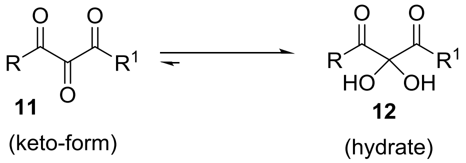
Scheme 1.1 Nucleophilic Addition to Carbonyl Compounds.


O
5
H
Cat
O
O
OR
7
Well studied
OH
6
Functionalized alcohol
OH
O
OR
8
(1)
Functionalized
alpha-hydroxyesters
Have not been studied
O
O
OR
O
9
H
Cat
O
O
OR
OH
10
(2)
Functionalized
alpha-hydroxy-beta-ketoesters

1.2 Background of Vicinal Tricarbonyl Systems

2,3-Diketoesters are a subcategory of vicinal tricarbonyl (VTC) compounds that have a rich history of interest in organic synthesis.[8] The carbon of the central carbonyl is the most electrophilic site and normally forms a hydrate in the presence of water. In general, vicinal tricarbonyl compounds exist in equilibrium between the keto-form (minor) **(11)** and the hydrate (major) **(12)** (Scheme 1.2). The hydrates can be converted to their keto-forms **(11)** by distillation, heating in vacuum, or treatment with a drying agent such as phosphorus pentoxide.[32, 53] However, obtaining the completely pure keto-form of vicinal tricarbonyl compounds is a difficult task.[53] For simplicity, the vicinal tricarbonyl products described in this chapter will refer only to the keto-form unless noted otherwise.

Scheme 1.2 Keto-form and Hydrate of Vicinal Tricarbonyl Compounds (VTC).

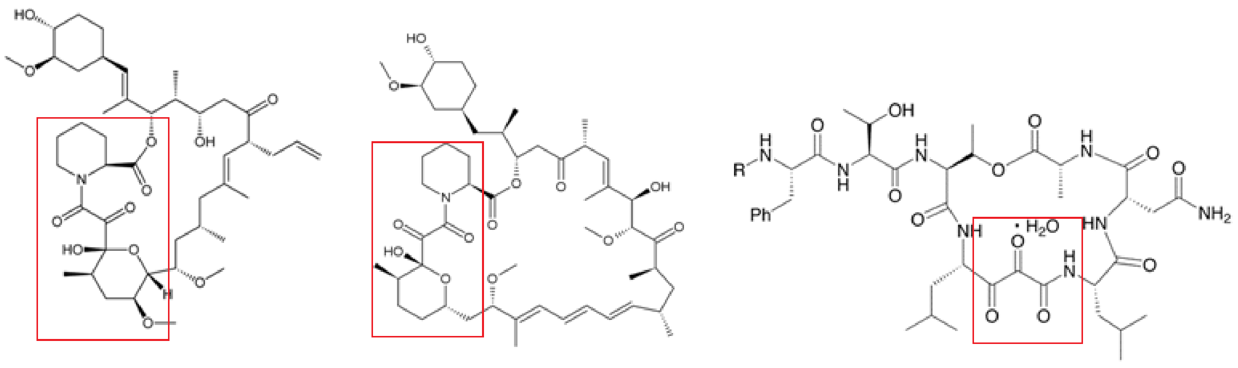


11
(keto-form)

12
(hydrate)

Vicinal tricarbonyl compounds received considerable attention in the late 1980s as a result of the isolation of FK-506,[10] a potent immunosuppressant, and the antibiotic rapamycin[11] that contain a vicinal tricarbonyl functional group in the form of a hemiketal (Figure 1.3). Later, Kaniwa et al. reported the isolation of the cyclic peptide protease inhibitors YM-47141 and YM-47142 from Flexibacter sp. Q17897 containing a vicinal tricarbonyl unit in hydrated form (Figure 1.3).[12] However, their applications in organic synthesis have come to a halt since the last review by Wasserman in 2004.[8c]

Figure 1.3 Natural Products Containing VTC Functional Group.



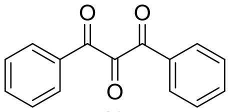
FK 506

Rapamycin

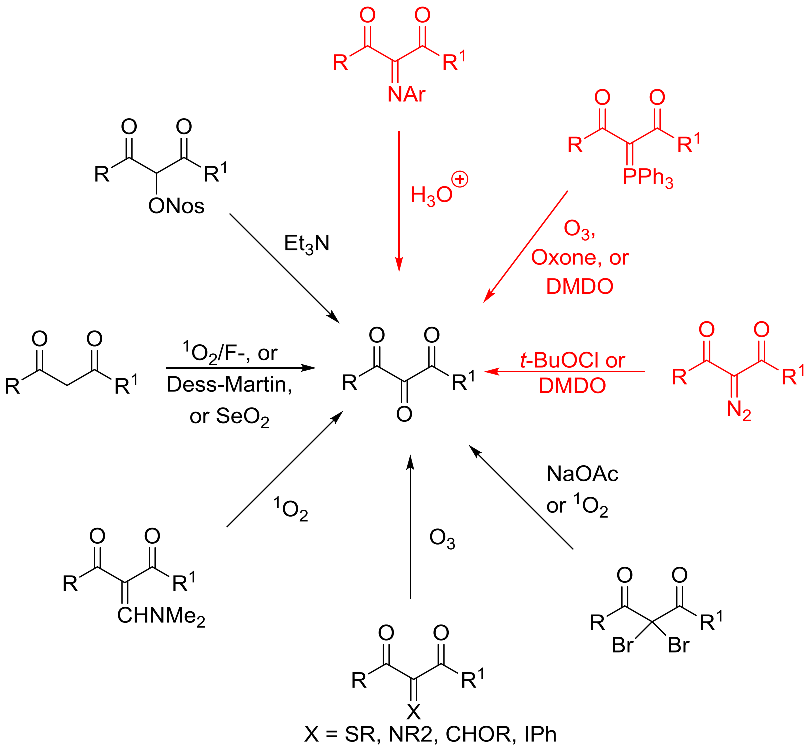
YM-47141 R = $COCH_2Ph$
YM-47142 R = $COCH_2CH(CH_3)_2$

1,3-Diphenylpropane-1,2,3-trione **(13)** was the first reported vicinal triketone compound and was published by Neufville and Pechmann in 1890.[13] As a consequence of “interested in the questions of how many carbonyl group may be juxtaposed and what will be the properties of the resulting vicinal polyketone,” stated by Rubin,[8a] there have been a large number of methods developed for their preparation, as summarized in Scheme 1.3.[14-31] In general, VTC compounds are synthesized by oxidation of 1,3-dicarbonyl systems that include the following procedures: hydrolysis of imines,[14] oxidation of phophonium ylides with ozone,[15] potassium peroxymonosulfate (oxone),[17] or dimethyldioxirane (DMDO),[18] oxidation of α-diazo-β-dicarbonyl derivatives with *tert*-butyl hypochlorite[19] or DMDO,[20] reaction of 2,2-dibromo-1,3-dicarbonyl with singlet oxygen[21] or sodium acetate,[22] ozonolysis of other ylides containing either sulfur,[23] nitrogen,[24] iodide[25] and enol ethers,[26] oxidation of enamine with singlet oxygen,[27] oxidation of 1,3-dicarbonyl compounds with singlet oxygen in the present of fluoride ion,[28] Dess-Martin reagent,[29] or selenium dioxide,[30] elimination of the nosyl group in the α-nosyl-1,3-dicarbonyl compounds.[31] The methods highlighted in red in scheme 1.3 will be further discussed because they often employed in organic synthesis.

Scheme 1.3 Preparation of VTC Compounds From 1,3-Dicarbonyl Precursors.



13



NAr
$H_3O^{\oplus}$
ONos
Et_3N
PPh$_3$
O$_3$, Oxone, or DMDO
$^1O_2$/F-, or Dess-Martin, or SeO$_2$
t-BuOCl or DMDO
N$_2$
$^1O_2$
CHNMe$_2$
O$_3$
NaOAc or $^1O_2$
Br Br
X = SR, NR2, CHOR, IPh

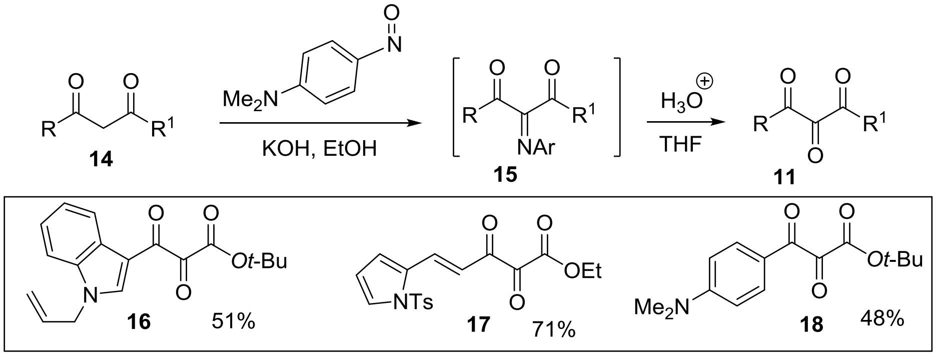
1.2.1 Synthesis

1.2.1.1 Condensation Reactions

Methods for the preparation of vicinal tricarbonyl compounds often involve oxidation chemistry that is incompatible with other electron rich functional groups such as activated olefins, primary amines, electron rich ring systems, and others. The oldest procedure reported by Sachs and Barschall more than 100 years ago is still being employed in several cases to avoid oxidation conditions such as in the synthesis of indole **(16)**,[33] vinylpyrrole **(17)**,[34] and *p*-dimethylaminophenyl **(18).**[35] This method involves in a condensation reaction between a 1,3-dicarbonyl compound **(14)** and *p*-

nitroso-*N*,*N*-dimethylaniline under basic conditions, forming imine intermediates **(15)** that hydrolyze under acidic conditions to vicinal tricarbonyl compounds **(11)** (scheme 1.4).[14] Although oxidation conditions are avoided by this method, strongly basic and acidic conditions are required.

Scheme 1.4 Sachs and Barschall's Procedure.

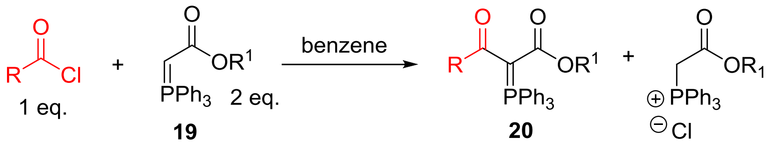


1.2.1.2 From Phosphonium Ylides

The synthesis of phosphonium ylides of *β*-ketoesters **(20)** were first reported by Cooke and Burman from the reaction of acid chlorides and phosphonium ylide **(19)**.[36] This procedure required two equivalents of the high molecular weight phosphonium ylide **(19)**, with the second equivalent of **(19)** functions as a proton acceptor (Scheme 1.5). Later, Wasserman and coworkers made an improvement to this method by introducing a proton sponge, bis(trimethylsilyl)acetamide (BSA), which enabled reducing the amount of phosphonium ylide **(19)** from 2 to 1 equivalent (Scheme 1.6).[37] In the same report, they were able to substitute acyl chlorides with carboxylic acids in coupling reactions with phosphonium ylide **(19)**, using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCl) as the coupling reagent to generate *β*-

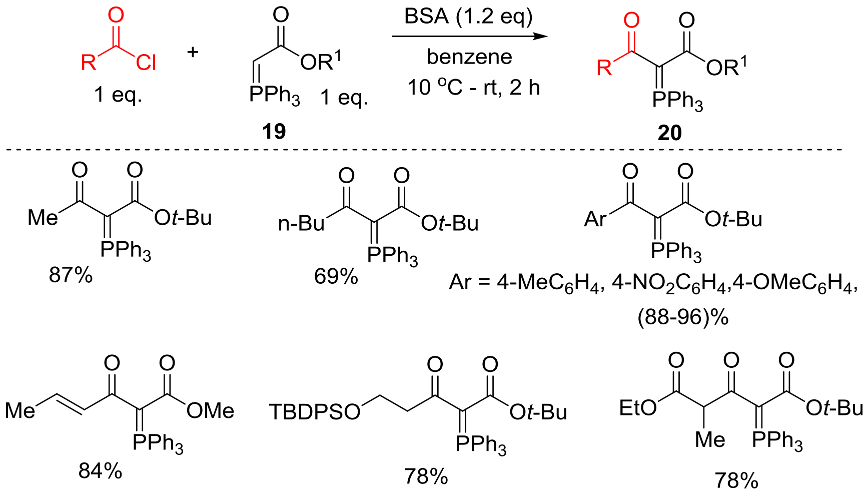
ketoester phosphorus ylides **(20)** (Scheme 1.7).[37] Both acid chloride and carboxylic acid reactions give similar yields, however carboxylic acid derivatives are easier to access.

Scheme 1.5 Cooke's Procedure for the Synthesis of Phosphonium Ylide **(20).**



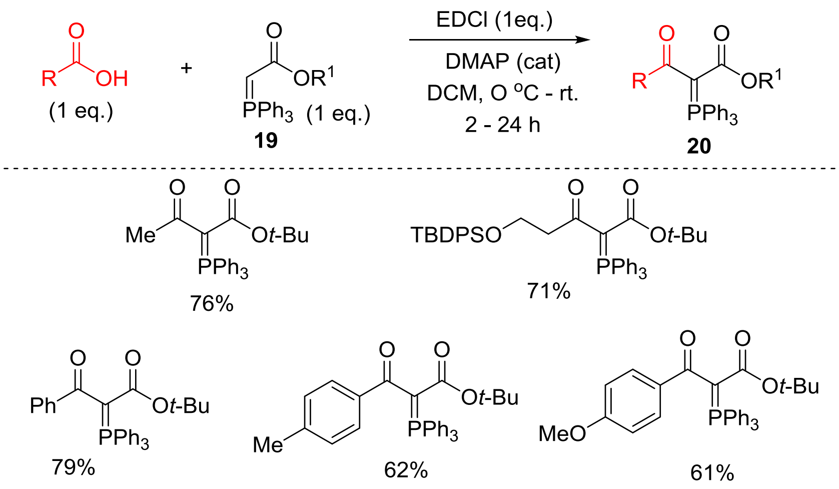
R
Cl
1 eq.
+
OR1
PPh3 2 eq.
19
benzene
OR1
PPh3
20
+
OR1
PPh3
Cl

Scheme 1.6 Reactions of Acid Chloride with Phosphonium Ylide **(19).**



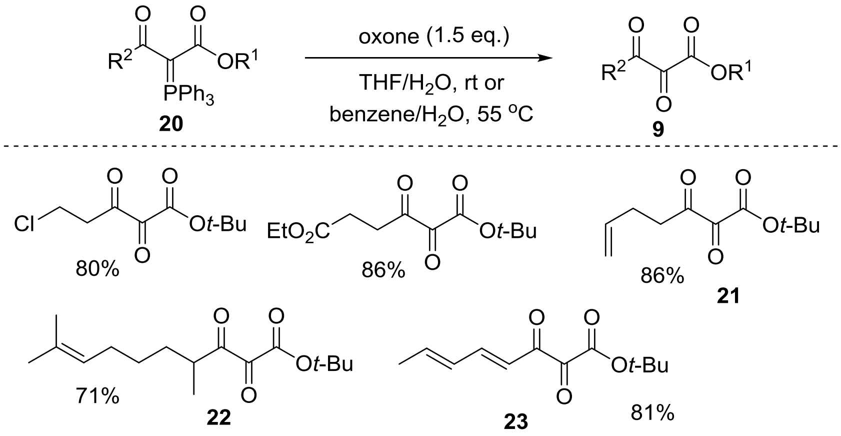
R
Cl
1 eq.
+
OR1
PPh3 1 eq.
19
BSA (1.2 eq)
benzene
10 °C - rt, 2 h
OR1
PPh3
20
Me
Ot-Bu
PPh3
87%
n-Bu
Ot-Bu
PPh3
69%
Ar
Ot-Bu
PPh3
Ar = 4-MeC6H4, 4-NO2C6H4,4-OMeC6H4,
(88-96)%
Me
OMe
PPh3
84%
TBDPSO
Ot-Bu
PPh3
78%
EtO
Ot-Bu
Me
PPh3
78%

Scheme 1.7 Reactions of Carboxylic Acids and Phosphonium Ylides **(19)**.


EDCI (1eq.)
DMAP (cat)
DCM, O °C - rt.
2 - 24 h
(1 eq.)
(1 eq.)
19
20
76%
71%
79%
62%
61%

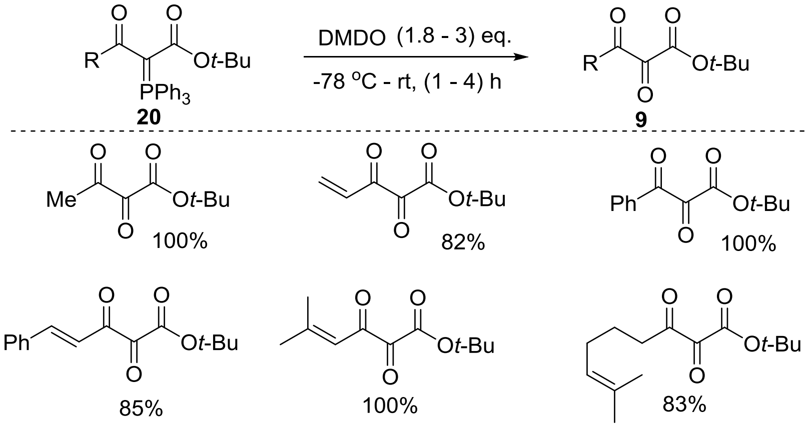
Oxidation of phophonium ylides to vicinal tricarbonyl compounds was first reported by Bestmann and Kloeters in the synthesis of nynhydrin.[15] More than a decade later, Wasserman found that potassium peroxymonosulfate (oxone) in a mixture of organic solvent and water can also convert phophonium ylides **(20)** to 1,2-diketoesters **(9)** in high yield (scheme 1.8).[17] Remarkably, the oxidation process was selective in the presence of alkenes such as in **(21-22)** and conjugated enones **(23)**. The reaction is mild in most cases, except for compound **(22)** for which the reaction solution had to be heated to 55 °C.

Scheme 1.8 Oxidation of Phophonium Ylides with Oxone.


oxone (1.5 eq.)
THF/H2O, rt or
benzene/H2O, 55 °C
20
9
80%
86%
86%
21
71%
22
23
81%

Later, Wasserman and coworkers also found dimethyldioxyrane (DMDO) to be an effective oxidant for the conversion of phophonium ylides **(20)** to 1,2-diketoester derivatives **(9)** (Scheme 1.9).[18] Similar to oxone, DMDO also showed a high level of selectivity in the presence of an olefin functional group. In some cases, the yield is quantitative. Out of the three available oxidants - ozone, oxone, and DMDO - oxone seems to be the superior oxidant for this process because it is an extremely inexpensive, commercially available material.

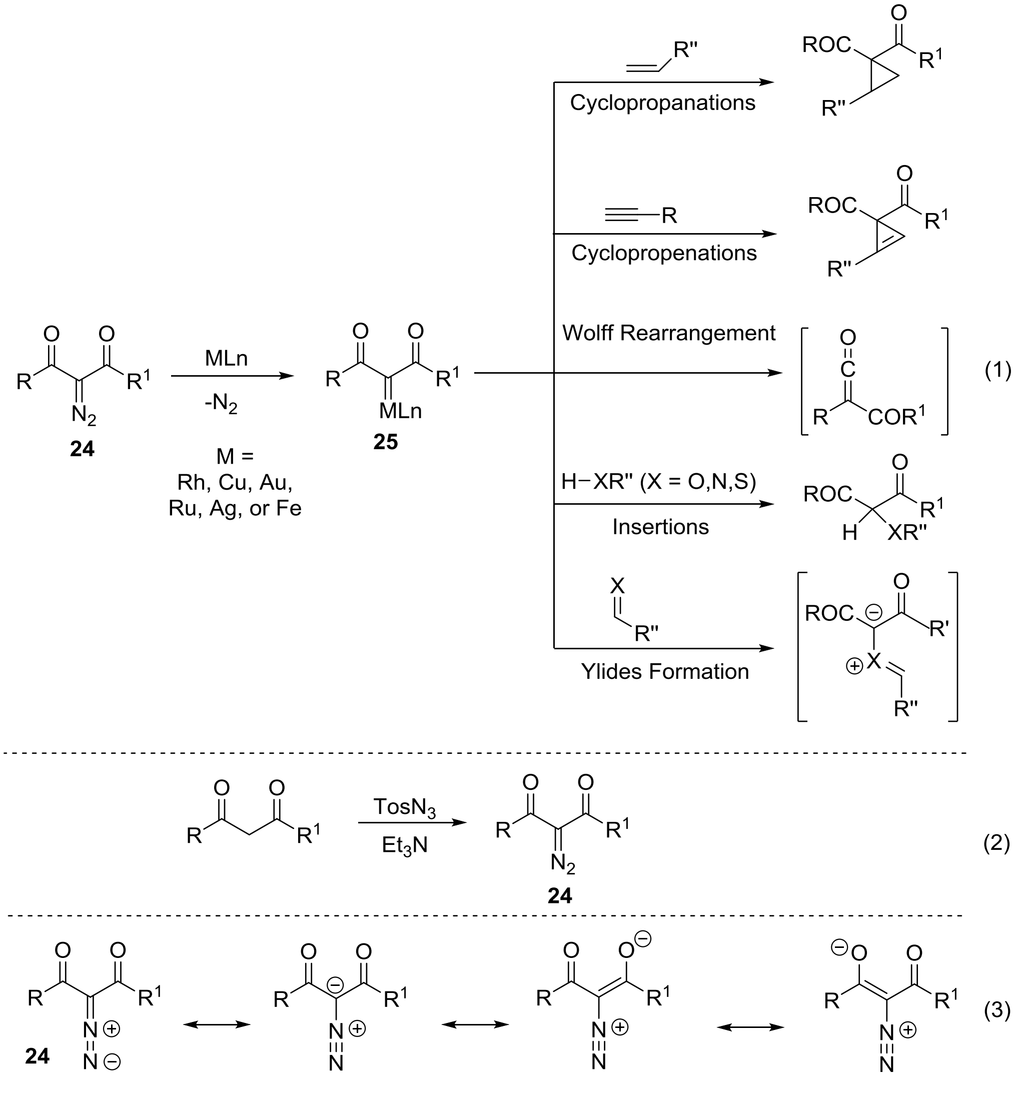
Scheme 1.9 Oxidation of Phophonium Ylides with DMDO.



1.2.1.3 From *α*-Diazo-*β*-dicarbonyl Compounds

The chemistry of *α*-diazo-*β*-dicarbonyl compounds **(24)** has been, for the most part, applied in metal catalyzed dinitrogen extrusion reactions with diazo compounds, forming metal carbene intermediates **(25)** that undergo a variety of transformations such as cyclopropanation, cyclopropenation, Wolff rearrangement, insertion, ylide formation, and others (Scheme 1.10, eq. 1).[38] One of the easiest and commonly used method for the preparation of *α*-diazo-*β*-dicarbonyl compounds **(24)** is through a diazo transfer reaction between *β*-dicarbonyl compounds and sulfonyl azides under basic conditions (Scheme 1.10, eq. 2).[39] These diazo compounds are highly stable compared to alkyldiazo compounds which can be explained by resonance stabilization with the adjacent carbonyl groups (Scheme 1.10, eq. 3).[40] They can be stored in a capped vial at room temperature for many years without decomposition.

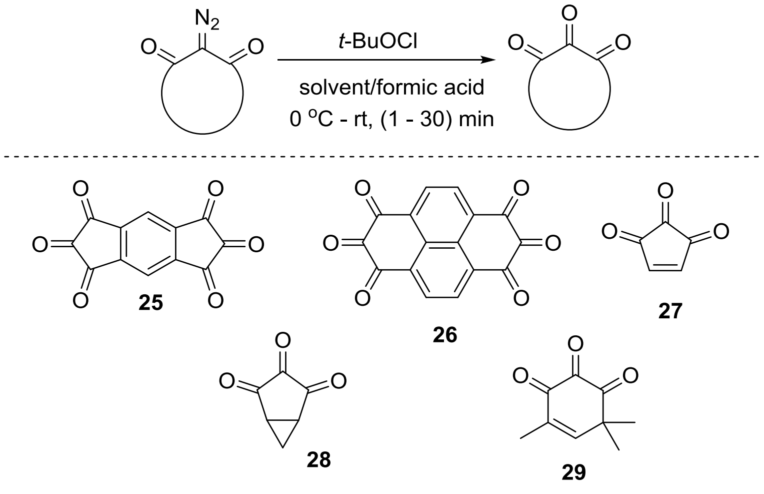
Scheme 1.10 Chemistry of *α*-Diazo-*β*-dicarbonyl Compounds.



Cyclopropanations
Cyclopropenations
Wolff Rearrangement
H−XR" (X = O,N,S)
Insertions
Ylides Formation
MLn
-N2
M =
Rh, Cu, Au,
Ru, Ag, or Fe
24
25
(1)
TosN3
Et3N
(2)
(3)

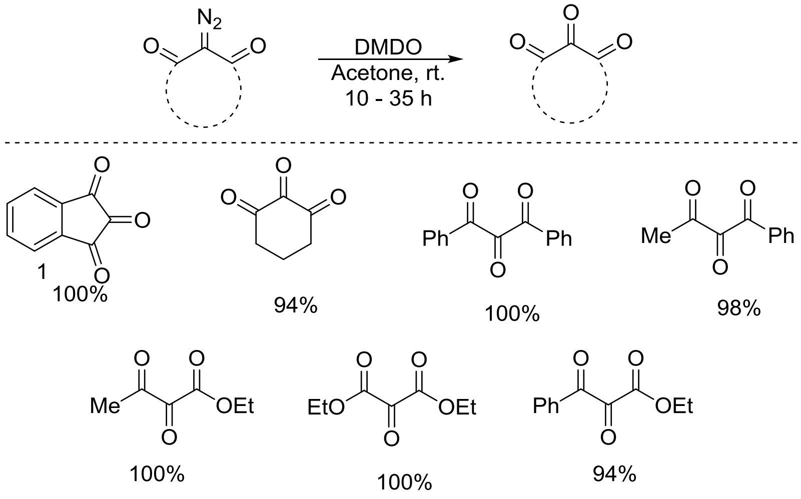
Beside metal catalyzed decomposition, *α*-diazo-*β*-dicarbonyl compounds **(24)** have been an attractive precursor to vicinal tricarbonyl compounds by oxidation with either *tert*-butyl hypochlorite[19] or dimethyldioxirane (DMDO).[20] *tert*-Butyl hypochlorite has been used for the preparation of variety of cyclic triketones including tri-cyclic trione **(25)** and tetracyclic trione **(26)**,[41] cyclopentene trione **(27)**,[42] bicyclotrione **(28)**,[43] and cyclohexenetrione **(29)**[44] from the *α*-diazo-*β*-dicarbonyl precursor (Scheme 1.11). In addition to the fast oxidation reaction time, *tert*-butyl hypochlorite can be easy prepared from commercial household bleach solution that contains ~5% of sodium hypochlorite and *tert*-butyl alcohol.[45] The isolation of *tert*-butyl hypochlorite was done by a simple separatory funnel extraction.

Scheme 1.11 Oxidation of *α*-Diazo-*β*-dicarbonyl Compounds by *tert*-Butyl Hypochlorite.



Saba reported that DMDO is an effective oxidant for the conversion of *α*-diazo-*β*-dicarbonyl compounds into vicinal tricarbonyl units in qunatitiative yield for most cases (Scheme 1.12).[12] Since acetone is the by-product of the reaction, the vicinal tricarbonyl compounds was able to be obtained by evaporation of the solvent. The reaction time of this process was from 10 to 36 hours. DMDO is a highly volatile gas prepared from very cheap starting materials: acetone, sodium bicarbonate, and oxone.[46,47] However, a typical isolated yield of DMDO is less than 3% in a dilute solution of acetone (0.05-0.1 M).[46] Therefore, preparing a DMDO solution for a large scale reaction is a challenging task.[46] Very recently, procedures with simple set-up apparatus for large scale preparation of DMDO have been reported.[47]

Scheme 1.12 Oxidation of α-Diazo-β-Dicarbonyl Compounds by DMDO.



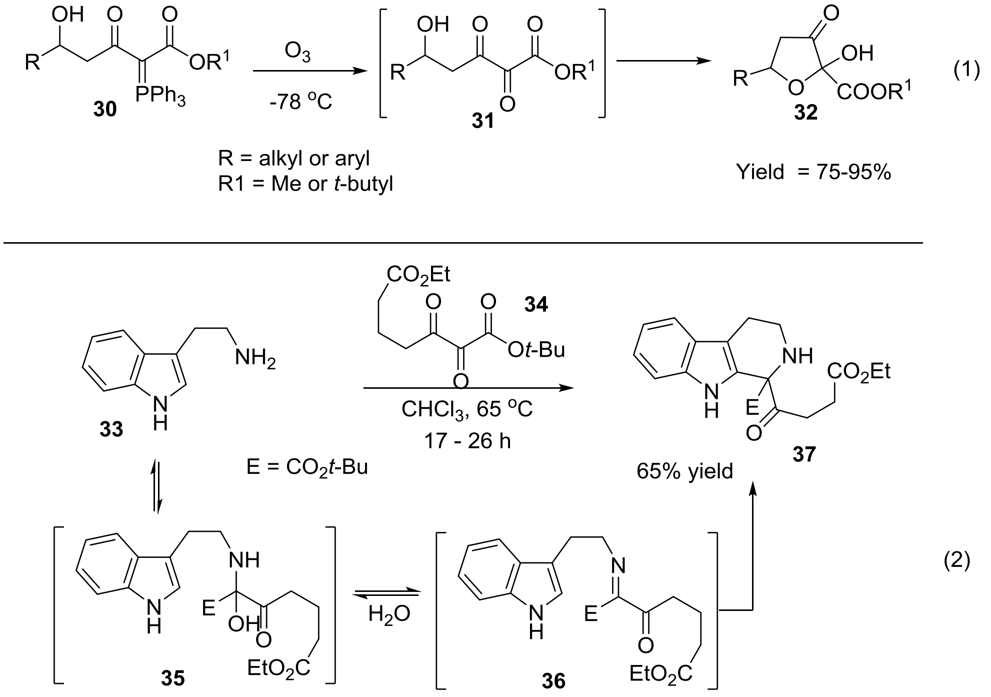
1.2.2 Reactivity with Nucleophiles

1.2.2.1 Oxygen and Nitrogen Nucleophiles

Anhydrous vicinal tricarbonyl compounds react rapidly with water at room temperature at the carbon of the central carbonyl group to form hydrates. Similar reactions also occur with alcohols and amines, forming hemiketals and hemiaminals respectively. For example, oxidation of phosphonium ylides **(30)** with ozone at -78

°C produces the VTC compound **(31)**, which immediately undergoes intramolecular nucleophilic addition by the tethered alcohol group to form the hemiacetal dihydrofuranone **(32)** (Scheme 1.13, eq. 1)). These compounds are isolable in high yield.[48] Primary amines generally react with the central carbonyl group of vicinal tricarbonyl compounds to form hemiaminal intermdiates, followed by dehydration to generate imines. For example, the primary amine of tryptamine **(33)** reacts with VTC **(34)** to produce the cyclic indole **(37)** in 65% yield. Upon dehydration to **(36)**, the imine intermediate further cyclizes with aromatization to furnish indole **(37)** (Scheme 1.13, eq. 2).[49]

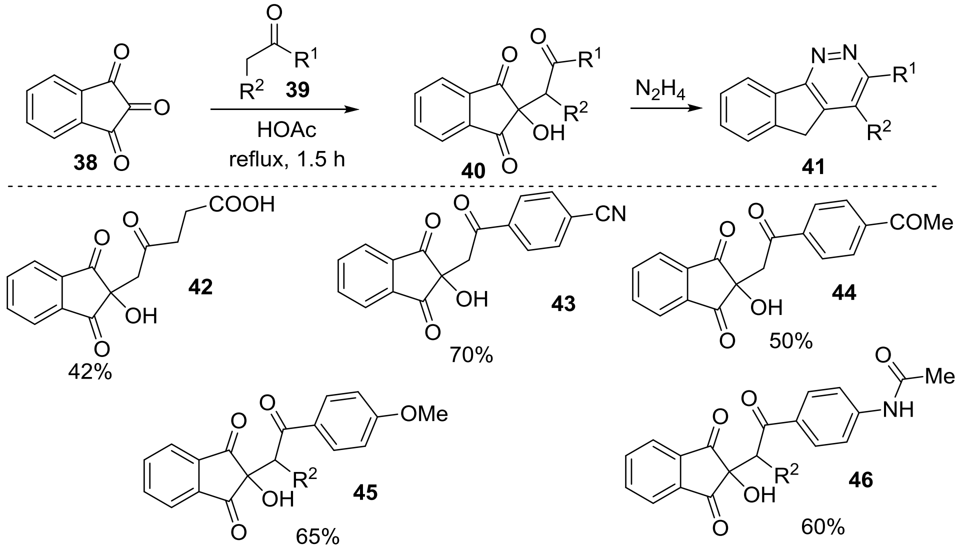
Scheme 1.13. Reaction of Alcohol and Amine to VTC Compounds.


30
31
32
33
34
35
36
37
O_3
-78 °C
R = alkyl or aryl
R1 = Me or *t*-butyl
Yield = 75-95%
(1)
$CHCl_3$, 65 °C
17 - 26 h
E = CO_2*t*-Bu
65% yield
H_2O
(2)

1.2.2.2 Carbon Nucleophiles

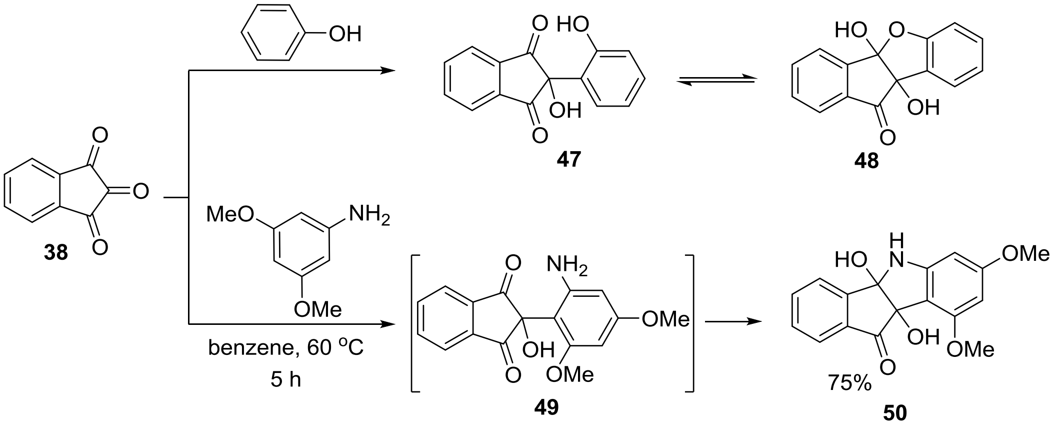
The highly electrophilic central carbonyl is reactive towards variety of carbon nucleophiles such as enolizable carbonyl compounds, electron rich aromatic compounds, enamines, olefins, ylides, and others.[50-55, 66] Testa and coworkers demonstrated that a variety of enolizable ketones **(39)** undergo aldol reactions with indane-1,2,3-trione **(38)** in refluxing acetic acid, forming the aldol adducts **(40)**, which were trapped with hydrazine to provide pyridazines **(41)** (Scheme 1.14).[50] In this report, they made 66 different derivatives of the pyridazines **(41)** for biological testing, and in most cases, the aldol adduct **(40)** was formed as an intermediate with the exception of compounds **42-46**.

Scheme 1.14. Carbon Nucleophiles from Enolizable Ketones.



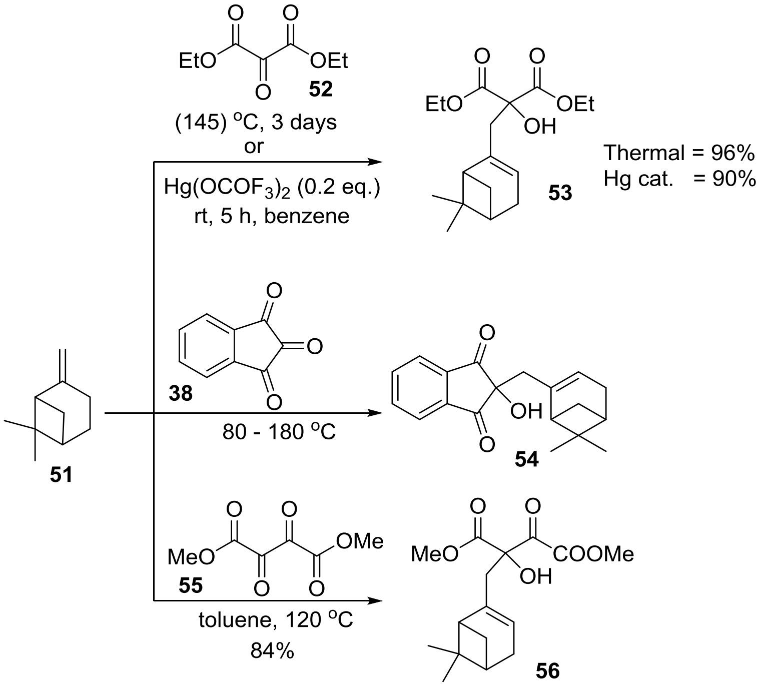
Electron rich aromatic compounds such as phenol[51] and aniline[52] derivatives undergo Friedel-Crafts alkylation to the central carbonyl of vicinal tricarbonyl compounds (Scheme 1.15). For example, Poupelin and coworkers have shown that a variety of phenol derivatives undergo Friedel-Crafts alkylation at the ortho position of the phenol or aniline with the central carbonyl of indane-1,2,3-trione **(38).** The tertiary alcohol product **(47)** existed in equilibrium with the cyclized hemiacetal **(48)** because of intramolecular nucleophilic addition of the aryl alcohol to the proximate ketone. A similar reaction was observed with aniline derivatives; for example, 3,5-dimethoxyaniline also alkylates indane-1,2,3-trione **(38)**, forming intermediate **(49)** that cyclizes to the tetracyclic **(50)**. It is interesting that a 75% yield of **(50)** was observed in this process because other reaction pathways, such as alkylation at the C-4 position or a condensation reaction between of the amine and carbonyl group, can occur.

Scheme 1.15. Friedel-Crafts Alkylation.



Vicinal tricarbonyl compounds have been employed in carbonyl-ene reactions on several occasions. Scheme 1.16 shows some representative examples of *β*-pinene **(51)** undergoing carbonyl-ene reactions with several types of vicinal tricarbonyl systems. Solomon and coworkers reported carbonyl-ene reactions for a series of olefins condensing with the central carbonyl of diethyl ketomalonate **(52)** under thermal and Lewis acid conditions.[53] For example, β-pinene **(51)** reacts with diethyl ketomalonate at 145 °C for 3 days to product in 96% yield the carbonyl-ene product **(53)**. When 0.2 equivalent of mercury trifluoroacetate [$Hg(OCOF_3)_2$] is introduced as a Lewis acid catalyst, the same product was formed in 90% yield at room temperature in 5 hours. In this report, tin tetrachloride ($SnCl_4$) and zinc chloride ($ZnCl_2$) were also effective Lewis acid catalysts. Later, Gill and Kirollos applied a variety of olefins to the carbonyl-ene reaction with indane-1,2,3-trione system **(38)**.[54] This thermal carbonyl-ene reaction was also extended to the tetra-vicinal carbonyl dimethyl dioxosuccinate **(65)** that with β-pinene gave **(56)** in 84% yield.[55]

Scheme 1.16 Carbonyl-ene Reactions with Vicinal Tricarbonyl Compounds.



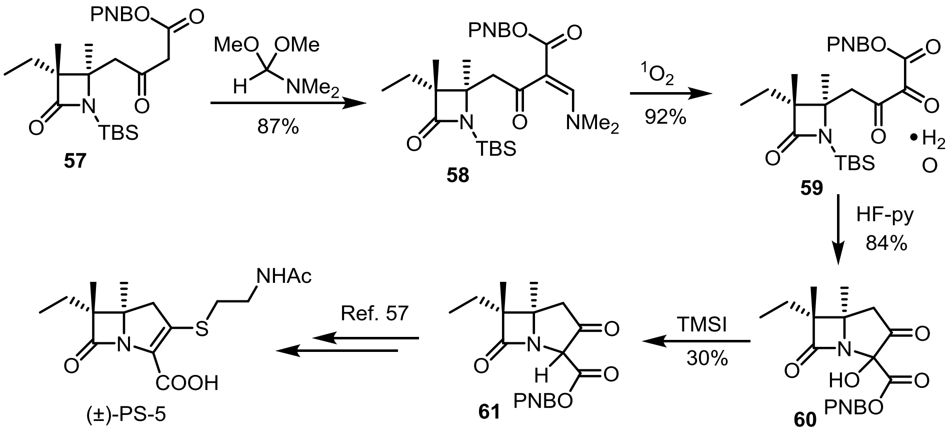
EtO
OEt
52
(145) °C, 3 days
or
Hg(OCOF$_3$)$_2$ (0.2 eq.)
rt, 5 h, benzene
EtO
OEt
OH
53
Thermal = 96%
Hg cat. = 90%
38
80 - 180 °C
OH
54
51
MeO
OMe
55
toluene, 120 °C
84%
MeO
COOMe
OH
56

1.2.3 Applications in Natural Product Synthesis

1.2.3.1 Formal Synthesis of Antibiotic (±)-PS-5

Wasserman and coworkers have been the leaders in applications of VTC compounds to natural product synthesis. The first application of the VTC functional group in natural product synthesis was the formal synthesis of antibiotic (±)-PS-5 (Scheme 1.17).[56] The functionalized VTC **(59)** was synthesized in high yield by condensation of the 1,3-dicarbonyl compound **(57)** and 1,1-dimethoxy-*N*,*N*-dimethylmethanamine to form enamine **(58)**, followed by photooxidation. Upon removal of the *tert*-butyldimethylsilyl (TBS) protecting group, the amide intermediate cyclized to form bicyclic hemiaminal **(60)**. Compound **(60)** undergoes reduction using trimethylsilyl iodide (TMSI) to generate **(61)** as a formal synthesis of antibiotic (±)-PS-5.[57]

Scheme 1.17 Formal Synthesis of Antibiotic (±)-PS-5.

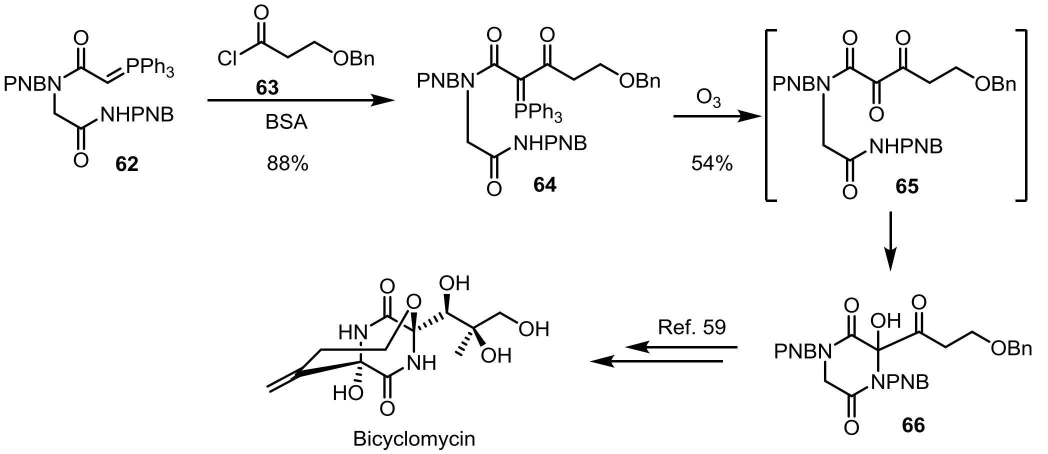


1.2.3.2 Formal Synthesis of Natural Product Bicyclomycin

Intramolecular nucleophilic addition of an amide to a vicinal tricarbonyl compound was applied to the formal synthesis of antibiotic bicyclomycin (Scheme 1.18).[58] The phosphoniun ylide **(62)** reacted with acid chloride **(63)** in the presence of

N,*O*-bis(trimethylsilyl)acetamide (BSA) to yield the diacyl ylide **(64)**. Oxidative cleavage of **(64)** gave the VTC **(65)** intermediate that quickly underwent intermolecular reaction with the amide group to generate cyclic **(66)**, which is a precursor to the natural product bicyclomycin.[59]

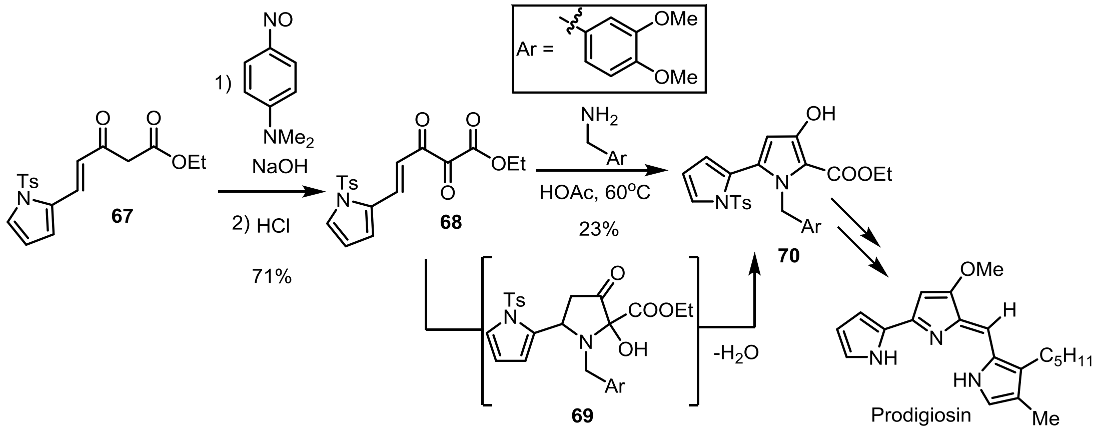
Scheme 1.18. Formal Synthesis of Natural Product Bicyclomycin.



1.2.3.3 Total Synthesis of Prodigiosin

Previously, Wasserman and coworkers discovered vinyl tricarbonyl esters such as **(68)** react with variety of primary amines to form 3-hydroxypyrroles.[60] They utilized this methodology in the total synthesis of prodigiosin, as shown in Scheme 1.19.[61] The vinyl tricarbonyl ester **(68)** was synthesized via a condensation reaction between 2,3-dicarbonyl compound **(67)** and *N*,*N*-dimethyl-4-nitrosoaniline, followed by hydrolysis with aqueous HCl. Next, 2,3-dimethoxybenzylamine underwent Michael and carbonyl addition to VTC **(68)** forming the intermediate pyrrolidinone **(69)**, which underwent dehydration to 3-hydroxypyrrole (**70)**. This compound was then converted to prodigiosin in a few subsequent steps.

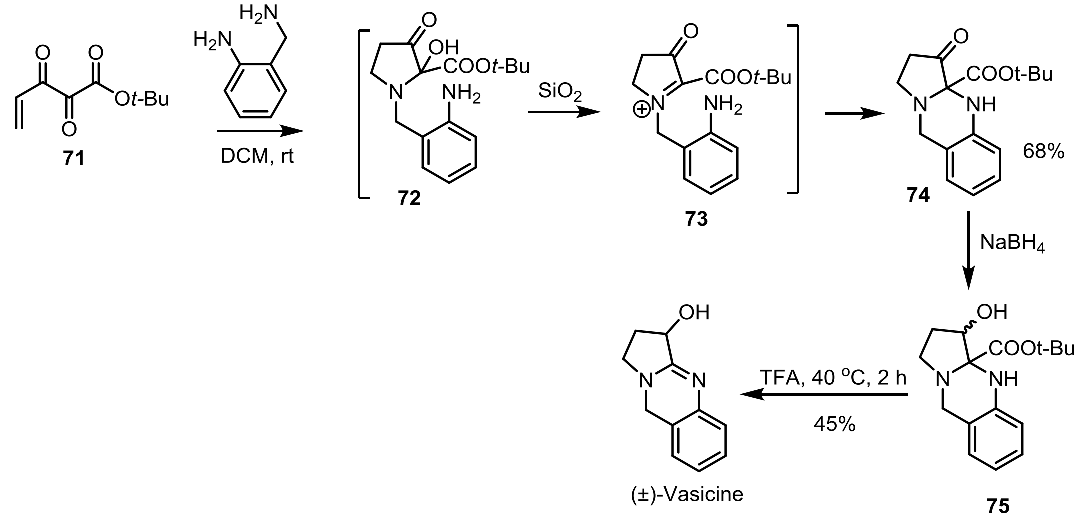
Scheme 1.19 Total Synthesis of Prodigiosin.



1.2.3.4 Total Synthesis of (±)-Vasicine

Vinyl tricarbonyl esters such as **(68)** are dielectrophilic systems that can react with nucleophiles via Michael and/or carbonyl addition. Wasserman and Kuo took advantage of this unique reactivity and applied it to a short synthesis of a natural product vasicine (Scheme 1.20).[62] Reaction of 2-aminobenzylamine and vinyl vicinal tricarbonyl **(71)** formed the intermediate pyrrolidinone **(72)** by Michael and carbonyl addition of the alkyl amine group. This intermediate was able to be isolated when the reaction was run without silica gel (SiO_2). In the presence of silica gel (SiO_2), intermediate **(72)** cyclized to **(74)**, probably through the iminium ion intermediate **(73)**. Then reduction of the keto group with sodium borohydride ($NaBH_4$) to the alcohol **(75)**, and removal of COO*tert*-Bu with trifluoroacetic acid (TFA) gave the natural product vasicine. In addition to the above examples, VTC compounds have also been applied to the synthesis of other natural products and biological relevant compounds such as papaveraldine,[63] eburnamonine,[49] immunosuppressant KF-506,[64] protease inhibitors YM-47141, and YM-47142.[65]

Scheme 1.20 Total Synthesis of (±)-Vasicine.

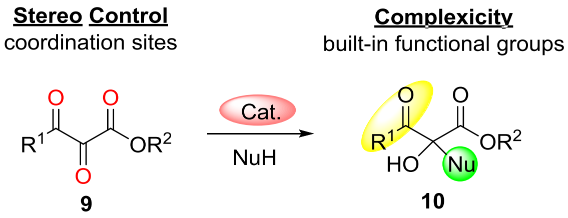


O
O
Ot-Bu
O
71
H2N
H2N
DCM, rt
O
OH
COOt-Bu
N
NH2
72
SiO2
O
COOt-Bu
N
NH2
73
O
COOt-Bu
N
NH
74
68%
NaBH4
OH
COOt-Bu
N
NH
75
TFA, 40 °C, 2 h
45%
OH
N
N
(±)-Vasicine

1.3 Our Vision of Vicinal Tricarbonyl Systems

Vicinal tricarbonyl systems such as in 2,3-diketoester derivatives **(9)** are useful in organic synthesis because of they offer a electrophilic carbon site for new C-C, C-O, or C-N bond formation, as Wasserman and coworkers have described previously.[8c] However, one important aspect of their work that was not addressed to this point is stereocontrol of the nucleophile attacking the central carbonyl. Thus far, the valuable chiral center generated from nucleophilic addition to the central carbonyl is generally lost by aromatization. We envisioned that the 2,3-diketoester system is a functional unit with a potential to deliver both complexity and stereoselectivity upon nucleophilic addition to the central carbonyl group. The possible elements for stereocontrol are the multiple oxygen coordination sites of the starting material, while complexity comes from the acyl and nucleophile groups incorporated in the product (Scheme 1.21). As result of our investigations with the 2,3-diketoester systems, we have developed a method for the synthesis of substituted furans, but more importantly, we discovered the stereocontrol elements in these system that have not been previously realized.

Scheme 1.21 Nucleophilic Addition to 2,3-Diketoesters

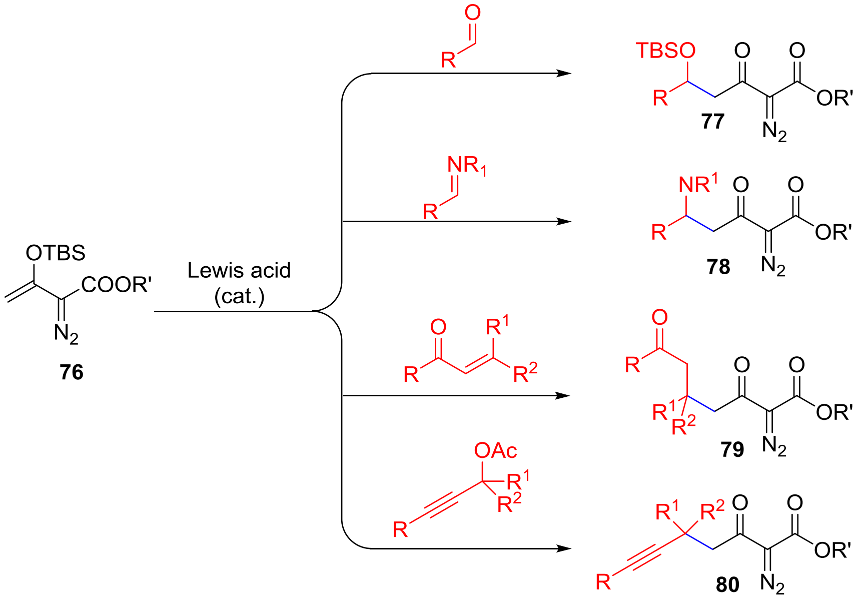


1.4 Synthesis of Substituted Furans

1.4.1 Introduction

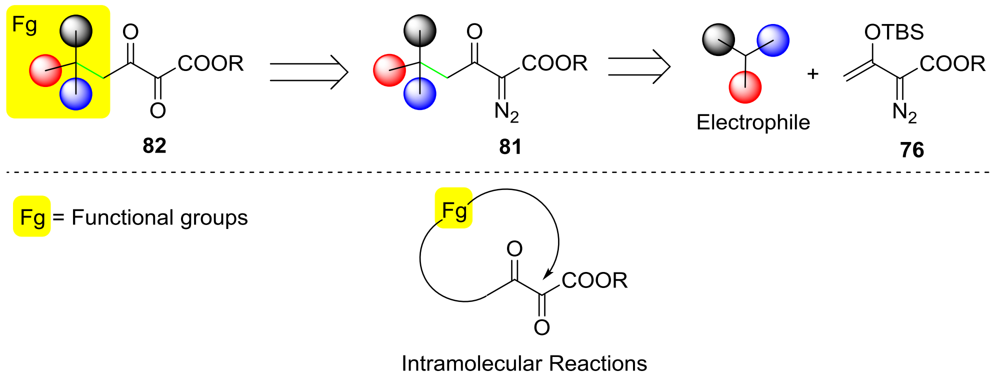
The syntheses and applications of functionalized *α*-diazo-*β*-ketoesters have been widely utilized in organic synthesis due to their diverse reactivity and selective metal catalyzed diazo decomposition reactions in complex environments.[38, 40] Our research group has been focused on enol silyldiazoacetates of type **(76)** as a coupling partner with other electrophiles toward the synthesis of highly functionalized *α*-diazo-*β*-ketoester. To that end, we have recently reported methodologies to access to *α*-diazo-*β*-keto-*δ*-functionalized esters via Mukaiyama-(aldol, Manich, Michael) condensation reactions catalyzed by Lewis acid as well as the propargyl acetates coupling partner **(77-80)** (Scheme 1.22).[67] These new methods have provided access to highly functionalized diazo compounds that have allowed us to study increasingly complex materials by way of transition metal catalyzed dinitrogen extrusion reactions.

Scheme 1.22 Reaction of Enol Silyldiazoacetates **(76)** with Electrophiles.


OTBS
COOR'
N2
76
Lewis acid
(cat.)
O
R
NR1
R
O
R1
R
R2
OAc
R1
R2
R
TBSO
O
O
R
OR'
77
N2
NR1
O
O
R
OR'
78
N2
O
R
O
O
R1
R2
OR'
79
N2
R1
R2
O
O
OR'
R
80
N2

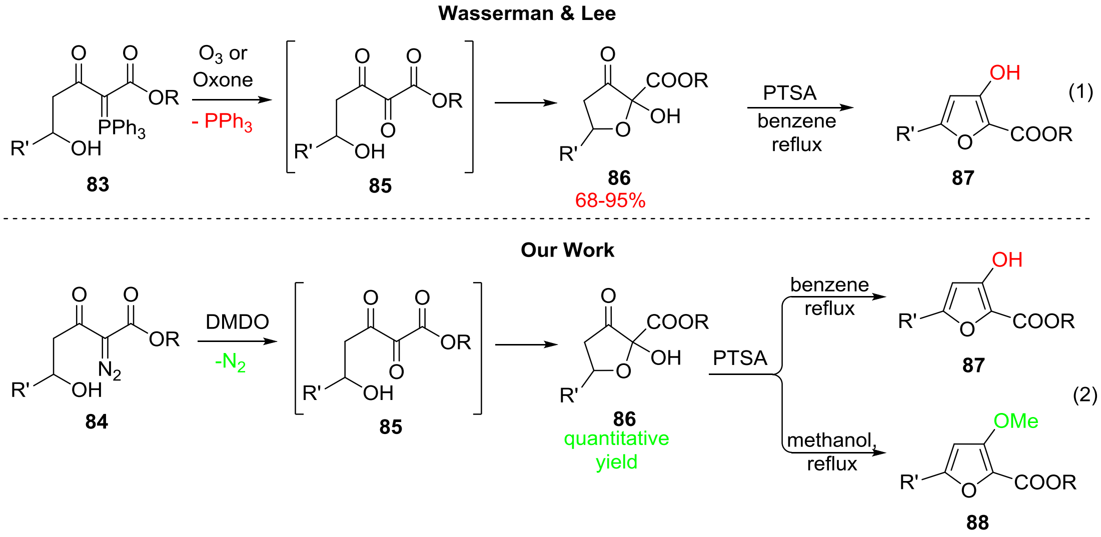
We have been intrigued with vicinal tricarbonyl systems because of the electrophilic carbon atom on the central carbonyl group. Since functionalized *α*-diazo-*β*-ketoesters **(81)** are accessible via reactions of enol silyldiazoacetate **(76)** with different types of electrophile, we thought that oxidation of complex diazo compounds **(81)** would give us access to functionalized 2,3-diketoesters **(83)**. This strategy would allow us to studies intramolecular reactions of the previous installed functional group with the central carbonyl of the 2,3-diketoesters (Figure 1.4).

Figure 1.4 Our Plans to Study Intramolecular Reactions of 2,3-Diketoesters



Furans represent an important class of compounds due to their wide applications in organic synthesis, polymers, the pharmaceutical industry, and in their abundance in natural products.[68] Previously, Wasserman and Lee[48] reported a novel synthesis of 3-hydroxyfurans **(87)** via oxidation of phosphorus ylides **(83)** that were prepared from enolates of acyl phosphoranylidine carboxylates. Subsequent dehydration of the furanones **(86)** using *p*-toluenesulfonic acid (PTSA) yielded 3-hydroxyfuran-2-carboxylates **(87)** in moderate to high yields (Scheme 1.23, eq. 1). In our first entry into the chemistry of vicinal tricarbonyl compounds, we were able to make an improvement to the Wasserman's procedures for the preparation of 3-hydroxy furans **(87)** as well as developing an efficient methodology for the synthesis of 3-methoxyfuran-2-carboxylate derivatives. Our approach for the synthesis of substituted furans **(87)** and **(88)** was by oxidation of *α*-diazo-*β*-keto-*δ*-hydroxyacetates **(84)**, formed by zinc triflate catalyzed Mukaiyama-aldol condensation of diazoacetoacetates with aldehydes. Oxidation of *α*-diazo-*β*-keto-*δ*-hydroxyacetates **(84)** to the furanones **(7)** was achieved by dimethyldioxirane (DMDO) in quantitative yield (Scheme 1.23, eq. 2). The advantages of this procedure are the ease of preparation and handling of the diazoacetoacetate reactants, the quantitative yield of furanones **(7)** under neutral conditions, and the conversion of furanones **(7)** to 3-methoxyfurans **(88)** under mild conditions.

Scheme 1.23 Methods to Substituted Furans.


Wasserman & Lee
O₃ or Oxone
- PPh₃
OR
PPh₃
R'
OH
83
85
86
68-95%
COOR
PTSA
benzene
reflux
87
(1)
Our Work
DMDO
-N₂
N₂
84
quantitative yield
methanol, reflux
88
OMe
(2)

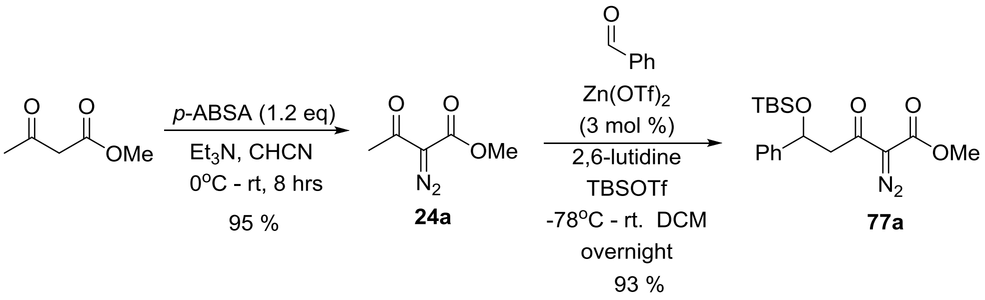
1.4.2 Results and Discussion

1.4.2.1 Strategy to Dihydrofuranones

Lewis acid catalyzed Mukaiyama-aldol reactions of enol silyldiazoacetates of type **(76)** with aldedydes are a versitle and efficient process to acess δ-oxy-α-diazo-β-ketoesters.[67a,b] Our strategic plans were to oxidize δ-oxy-α-diazo-β-ketoesters into δ-oxy-α-β-diketoesters, and then study their reactivity with nucleophiles. Our investigation began with methyl-α-diazoacetoacetate **24a** that is easily prepared in gram quantities by diazo transfer from 4-acetamidobenzenesulfonyl azide (*p*-ABSA) to methyl acetoacetate in 95% isolated yield (Scheme 1.24).[39] α-Diazoacetoacetates including **(24a)** are stable under a wide range of conditions. For example, compound

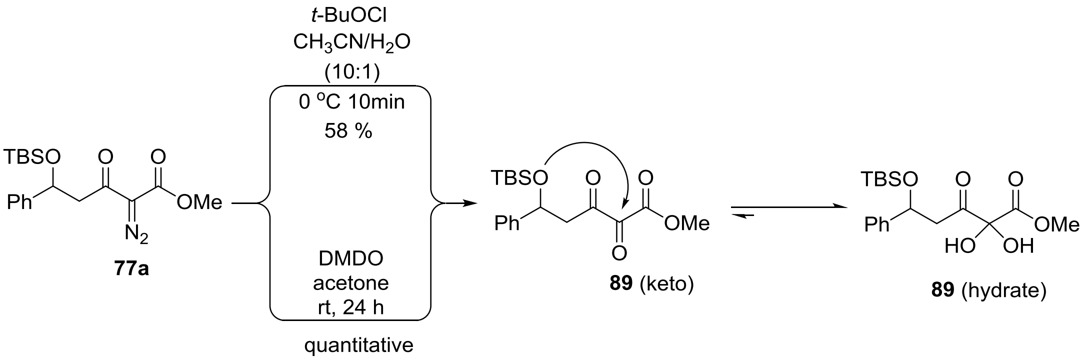
(24a) does not show any sign of decomposition after four years stored at room temperature in a capped vial as checked by ^{1}H NMR spectroscopic analysis. Reaction of methyl α-diazoacetoacetate **(24a)** with benzaldehyde via a one-pot Mukaiyama-aldol procedure produced the functionalized diazo compound **(77a)** in 93% isolated yield (Scheme 1.24).[67b]

Scheme 1.24 Preparation of Functionalized Methyl α-Diazoacetoacetate **(77a)**.



With functionalized diazo compound **(77a)** in hand, we next sought to oxidize the diazo group to a carbonyl group. We initially began with *tert*-butyl hypochlorite as the oxidant, since several reports have shown that *tert*-butyl hypochlorite can generate vicinal tricarbonyl compounds from α-diazo-β-dicarbonyl compounds.[19, 41-44] In our hands, however, the use of *tert*-butyl hypochlorite afforded the desired tricarbonyl compound **(89)** that existed in equilibrium between the keto-form and hydrate in moderate yield along with other unidentified by-products (Scheme 1.25). As Saba[20] reported that α-diazo-β-dicarbonyl compounds were oxidized to vicinal tricarbonyl derivatives using dimethyldioxirane (DMDO) in excellent to quantitative yield, we subjected diazo substrate **(77a)** to DMDO. This process resulted in the quantitative oxidation of **(77a)** to the desired product **(89)** that existed as hydrate in the presence of water (Scheme 1.25).

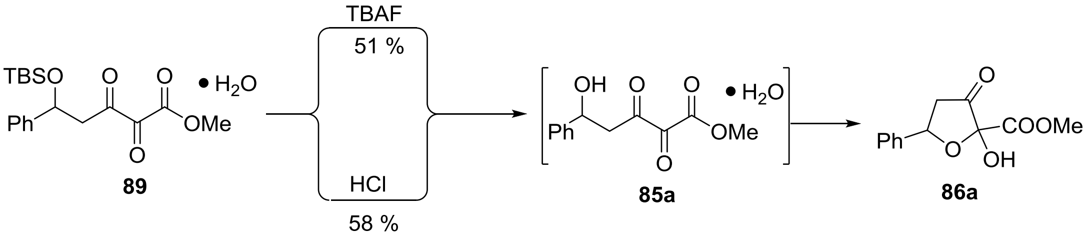
Scheme 1.25 Oxidation of α-Diazo-β-ketoester **(77a)**.



t-BuOCl
CH_3CN/H_2O
(10:1)
0 °C 10min
58 %
TBSO
Ph
OMe
N_2
77a
DMDO
acetone
rt, 24 h
quantitative
89 (keto)
89 (hydrate)
HO
OH

Then we attempted to remove the TBS group from **(89)** to form the corresponding alcohol **(85a)**. Unfortunately, standard methods for removal of the TBS group, such as treatment of *tert*-butylammonium fluoride (TBAF) or hydrochloric acid (HCl), only resulted in low yields of **(85a)** which immediately cyclized to the dihydrofuranone **(86a)** (Scheme 1.26).

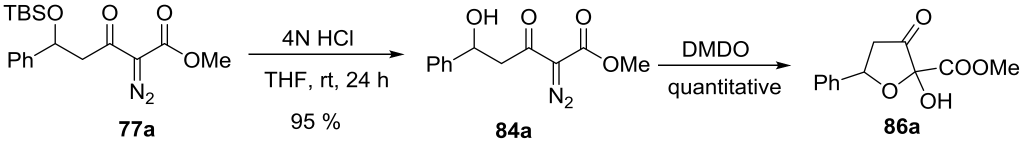
Scheme 1.26 Deprotection of the TBS Group.



TBSO
• H_2O
Ph
OMe
89
TBAF
51 %
HCl
58 %
OH
• H_2O
85a
COOMe
OH
86a

Since removal to the TBS group on **(89)** only provided **(86a)** in low yield, we decided to remove the TBS group prior to the oxidation process. Removal of the TBS group from functionalized α-diazoacetate **(77a)** with 4N HCl produce in 95% yield the desired alcohol **(84a)** (Scheme 1.27). Remarkably, compound **(84a)** oxidized to furananone **(86a)** in quantitative yield using DMDO (Scheme 1.27). Since the by-product of the oxidation reaction is acetone, pure **(86a)** was isolated after evaporation of solvent.

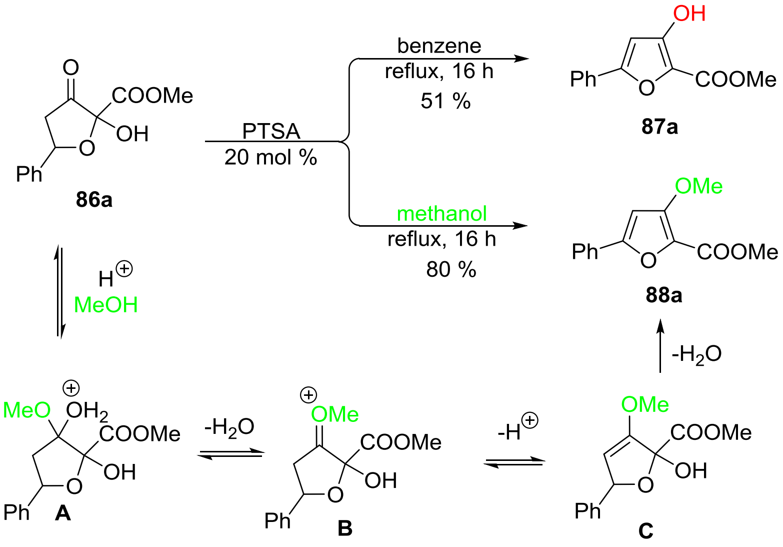
Scheme 1.27 Preparation of Dihydrofuranone **86a**.



1.4.2.2 Formation of Substituted Furans and a Proposed Mechanism

The dihydrofuranone **(86a)** underwent acid catalyzed dehydration to form 3-hydroxyfuran-2-carboxylate **(87a)** by the same procedure as that employed by Wasserman and Lee (Scheme 1.28).[48] However, reactions in refluxing benzene together with catalytic PTSA results in product decomposition, and isolation of **(87a)** by silica gel chromatography occurred in relatively low yield (51%). However, changing the reaction solvent to methanol gave the expected conversion of hemiketal **(86a)** to 3-methoxyfuran-2-carboxylates **(88a)** (Scheme 1.28). This modification also allowed for ease in purification since the 3-hydroxyfuran-2-carboxylates **(87a)** were otherwise difficult to purify. A proposed mechanism for the formation of 3-methoxyfuran-2-carboxylates **(88a)** is outlined in Scheme 1.28. Nucleophilic addition of methanol to the acid activated keto group of **(86a)**, then followed by loss of water to form the oxonium intermediate B. Upon proton transfer to form the vinyl ether C, subsequent acid catalyzed dehydration generated furan **(88a)**.

Scheme 1.28 Formation of Substituted Furans and a Proposed Mechanism.



PTSA
20 mol %
benzene
reflux, 16 h
51 %
methanol
reflux, 16 h
80 %
86a
87a
88a
A
B
C
H⊕
MeOH
-H2O
-H⊕
-H2O
COOMe
OH
OMe
Ph

1.4.2.3 Substrate Scope of Functionalized Diazo Compounds and Dihydrofuranones

With these methods in hand, we tested the substrate scope of this transformation. Varieties of OTBS functionalized diazo compounds **(77)** were prepared by the previously reported one-pot Mukaiyama-aldol reaction.[67b] Removal of the TBS group with 4*N* HCl in THF solution provided the corresponding alcohols in high yield **84(a-i)** (Table 1.1). A full range of diazo compounds **(84)** was quantitatively oxidized to the vicinal tricarbonyl intermediates **(85)** that existed as the cyclized dihydrofuranones **(86)** form (Table 1.2). Compounds **(86)** were readily isolated by evaporation of acetone and taken to the next step without further purification.

Table 1.1 Synthesis of Functionalized Diazo Compounds **(84)**.

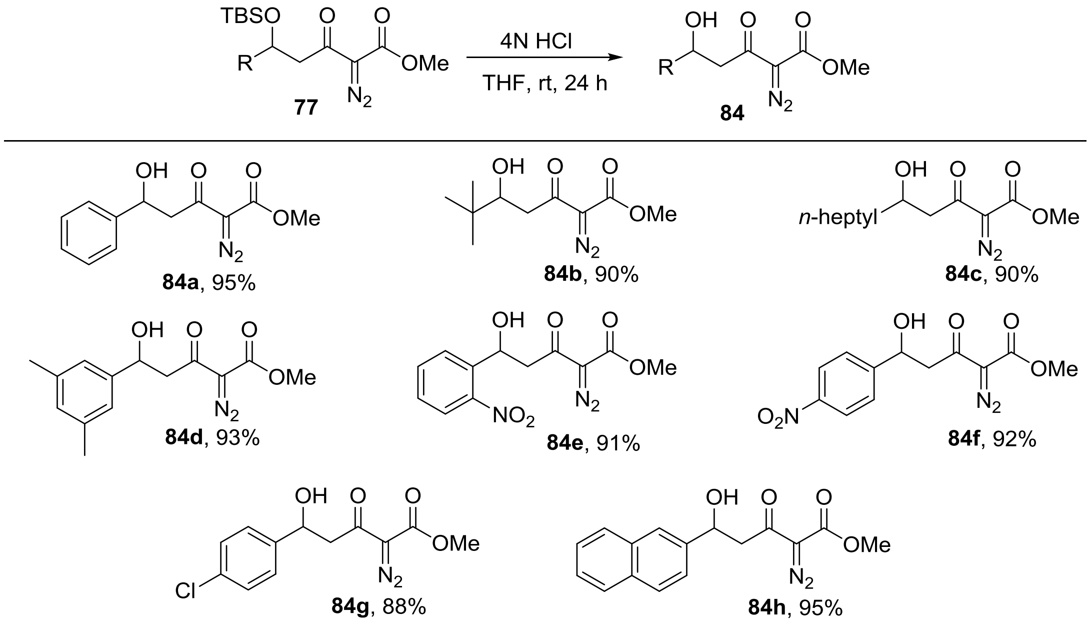
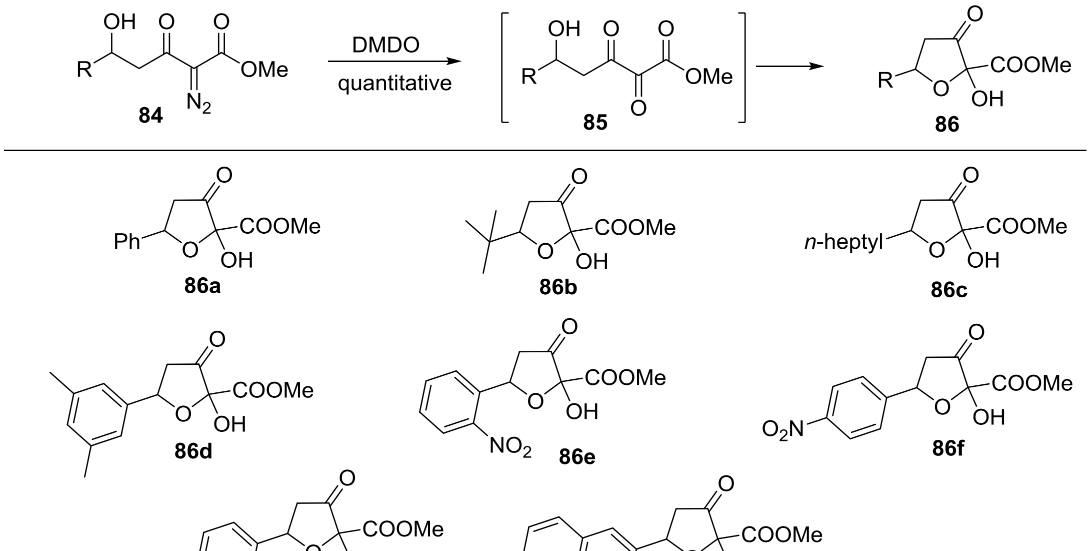

TBSO
R
77
N2
OMe
4N HCl
THF, rt, 24 h
OH
84
84a, 95%
84b, 90%
n-heptyl
84c, 90%
84d, 93%
NO2
84e, 91%
O2N
84f, 92%
Cl
84g, 88%
84h, 95%

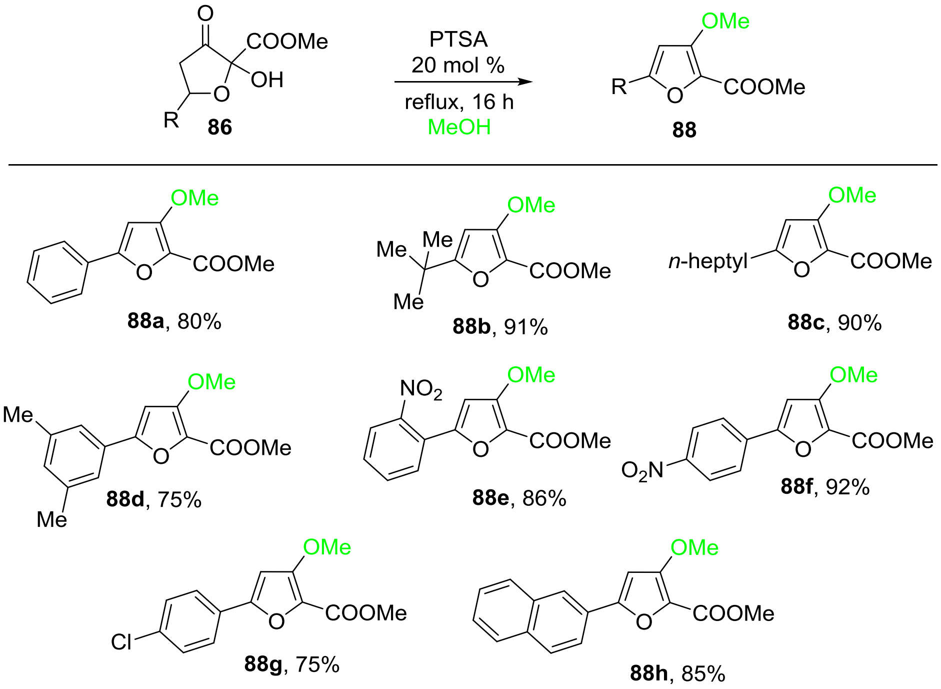
Table 1.2 Oxidation of Diazo Compound **(84)** to Dihydrofuranone **(86)**.


OH
R
84
N2
OMe
DMDO
quantitative
85
COOMe
86
Ph
86a
86b
n-heptyl
86c
86d
NO2
86e
O2N
86f
Cl
86g
86h

1.4.2.4 Substrate Scope of Substituted 3-Methoxyfurans

The hemiketal furanone **(86)** underwent acid catalyzed methanolysis and dehydration to form 3-methoxyfuran-2-carboxylates **(88)** (Table 1.3). The substrate scope is general toward both aromatic and aliphatic substituents. Electron-rich, electron-poor, ortho, and halogenated substituents on the phenyl ring were tolerated.

Table 1.3 Synthesis of 3-Methoxyfuran Derivatives **88**.



O
COOMe
OH
O
R
86
PTSA
20 mol %
reflux, 16 h
MeOH
OMe
R
O
COOMe
88
OMe
O
COOMe
88a, 80%
OMe
Me
Me
Me
O
COOMe
88b, 91%
OMe
n-heptyl
O
COOMe
88c, 90%
OMe
Me
Me
O
COOMe
88d, 75%
NO_2
OMe
O
COOMe
88e, 86%
OMe
O_2N
O
COOMe
88f, 92%
OMe
Cl
O
COOMe
88g, 75%
OMe
O
COOMe
88h, 85%

1.4.3 Conclusion

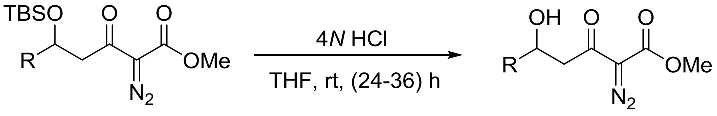
Enol silyldiazoacetate of type **(76)** is an effective precursor of functionalized α-diazo-ß-ketoesters **(77-80)** via coupling with compatible electrophiles under Lewis acid catalyzed conditions. The product α-diazo-β-keto-δ-hydroxyesters **(84)** prepared from the Mukaiyama-aldol reaction underwent quantitative oxidation to dihydrofuranones **(86)**. Acid catalyzed methanolysis and subsequent dehydration of **(86)** provided an efficient method for the synthesis of 3-methoxyfuran-2-carboxylates **88** under mild conditions. This work opened the possibility for further functionalization at the C-3 position with other nucleophiles. In addition, our studies have provided an alternative method for the preparation of 3-hydroxyfuran-2-carboxylates with several advantages including higher product yields and atom-economy.

1.4.4 Experimental

1.4.4.1 General Information

Thin layer chromatography (TLC) was carried out using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm), *p*-anisaldehyde (PAA), potassium permanganate (KMnO4) or ceric ammonium molybdate (CAM) reagents. Liquid chromatography was performed using a force flow (flash chromatography) of the indicated system on silica gel (230-400 mesh). Methanol and acetone were purchased from Aldrich and used as receive. α-Diazo-β-keto-δ-oxysilylesters **77** were prepared according to literature.[67b] *tert*-Butyl hypochlorite[45] and DMDO[46] were prepared according to the literature. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Advance 400 MHz spectrometer. Chemical shifts are reported in ppm with the solvent signals as reference, and coupling constants (*J*) are given in Hertz. The peak information is described as: br = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, comp = complex multiplet of magnetically inequivalent protons. High-resolution mass spectra (HRMS) were performed on a JEOL AccuTOF-ESI mass spectrometer using CsI as the standard.

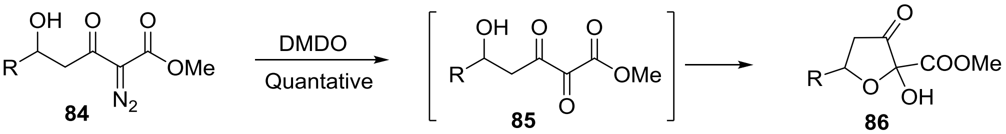
1.4.4.2 Preparation of α-Diazo-β-keto-δ-hydroxyesters



77 **84**

α-Diazo-β-keto-δ-oxysilylesters **77** (0.10 mmol) was dissolved in 4 mL of THF. The reaction flask was cooled to 0 °C in an ice bath. Then 4 mL of 4*N* HCl was added dropwise and stirred for 24-36 h at room temperature until TLC analysis indicated complete loss of starting material. Then the reaction was quenched by slow addition of saturated sodium bicarbonate solution until basic to pH paper. The resulting solution was extracted with 15 mL (3x) with diethyl ether. The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2), eluting with hexane and ethyl acetate to provide α-diazo-β-keto-γ-hydroxyesters **84**.

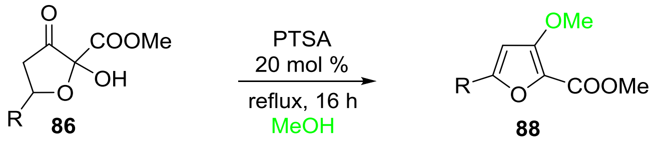
1.4.4.3 Procedures for the Preparation of Dihydrofuranones



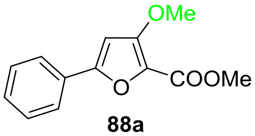
84 **85** **86**

α-Diazo-β-keto-δ-hydroxyester **84** (0.05 mmol) was dissolved in 1 mL of acetone, under nitrogen atmosphere was cooled to 0 °C. A solution of dimethyldioxirane in acetone (10 mL, 2.6 eq., 0.06 M) was added all at once via syringe and stirred for 24 h at room temperature. Evaporation of solvent provided dihydrofuranones **86** in quantitative yield.

1.4.4.4 Procedure for the Synthesis of 3-Methoxyfurans

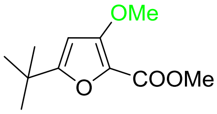


Dihydrofuranone **86** (0.50 mmol) and *p*-toluenesulfonic acid monohydrate (PTSA) (19 mg, 0.10 mmol) were dissolved in 3 mL of methanol. The resulting reaction solution was refluxed for 16 h and concentrated under reduced pressure, The residue was purified by flash column chromatography (SiO_2), eluting with hexane and ethyl acetate to provide 3-methoxyfurans **88** in the indicated yield.



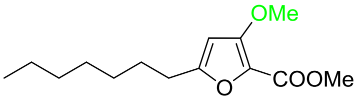
88a

Methyl 3-methoxy-5-phenylfuran-2-carboxylate 88a: yield 80%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.36-7.42 (comp, 3H), 6.64 (s, 1H), 3.99 (s, 3H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 159.2, 156.3, 155.6, 129.3, 129.2, 128.9, 128.7, 124.8, 96.8, 58.9, 51.4; HRMS (ESI) calcd for $C_{13}H_{13}O_4$ $(M+H)^+$ 233.0808, found 233.0826.



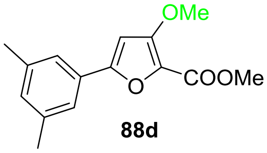
88b

Methyl 5-(tert-butyl)-3-methoxyfuran-2-carboxylate 88b: yield 91%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.02 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 167.6, 159.4, 155.9, 99.0, 95.4, 58.7, 51.2, 28.5, 26.9; HRMS (ESI) calcd for $C_{11}H_{17}O_4$ $(M+H)^+$ 213.1121, found 213.1116.



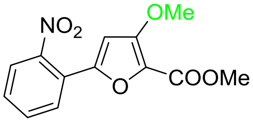
88c

Methyl 3-methoxy-5-phenylfuran-2-carboxylate 88c: yield 90%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.04 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.60 (t, *J* = 8.0 Hz, 2H), 0.84-1.65 (comp, 13H); ^{13}C NMR (CDCl$_3$, 400 MHz) δ 160.5, 159.1, 156.1, 126.4, 98.1, 58.7, 51.2, 31.6, 31.6, 29.0, 28.8, 27.4, 22.5, 13.9.; HRMS (ESI) calcd for $C_{14}H_{23}O_4$ (M+H)$^+$ 255.1591, found 255.1574.



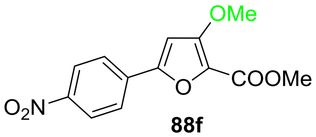
88d

Methyl 5-(3,5-dimethylphenyl)-3-methoxyfuran-2-carboxylate 88d: yield 75%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.39 (s, 2H), 7.01 (s, 1H), 6.61 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 2.36 (s, 6H); ^{13}C NMR (CDCl$_3$, 400 MHz) δ 159.2, 156.4, 156.0, 138.4, 131.1, 129.0. 127.1, 122.6, 96.6, 58.9, 51.4, 21.2; HRMS (ESI) calcd for $C_{15}H_{17}O_4$ (M+H)$^+$ 261.1121, found 261.1100.

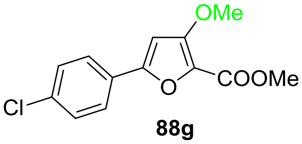


88e

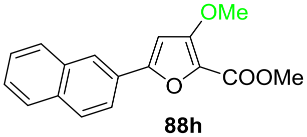
Methyl 3-methoxy-5-(2-nitrophenyl)furan-2-carboxylate 88e: yield 86%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.55-7.82 (comp, 4H), 6.60 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (CDCl$_3$, 400 MHz) δ 158.8, 155.4, 149.6, 147.8, 132.3, 130.0, 129.8, 128.7, 124.1, 123.2, 101.5, 59.1, 51.6; HRMS (ESI) calcd for $C_{13}H_{12}NO_6$ $(M+H)^+$ 278.0659, found 278.0686.


88f

Methyl 3-methoxy-5-(2-nitrophenyl)furan-2-carboxylate 88f: yield 92%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 8.0 Hz, 2H), 6.83 (s, 1H), 4.00 (s, 3H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 158.9, 155.8, 152.5, 147.7, 134.7. 129.0, 125.2, 124.7, 99.9, 59.1, 51.6; HRMS (ESI) calcd for $C_{13}H_{12}NO_6$ $(M+H)^+$ 278.0659, found 278.0685.

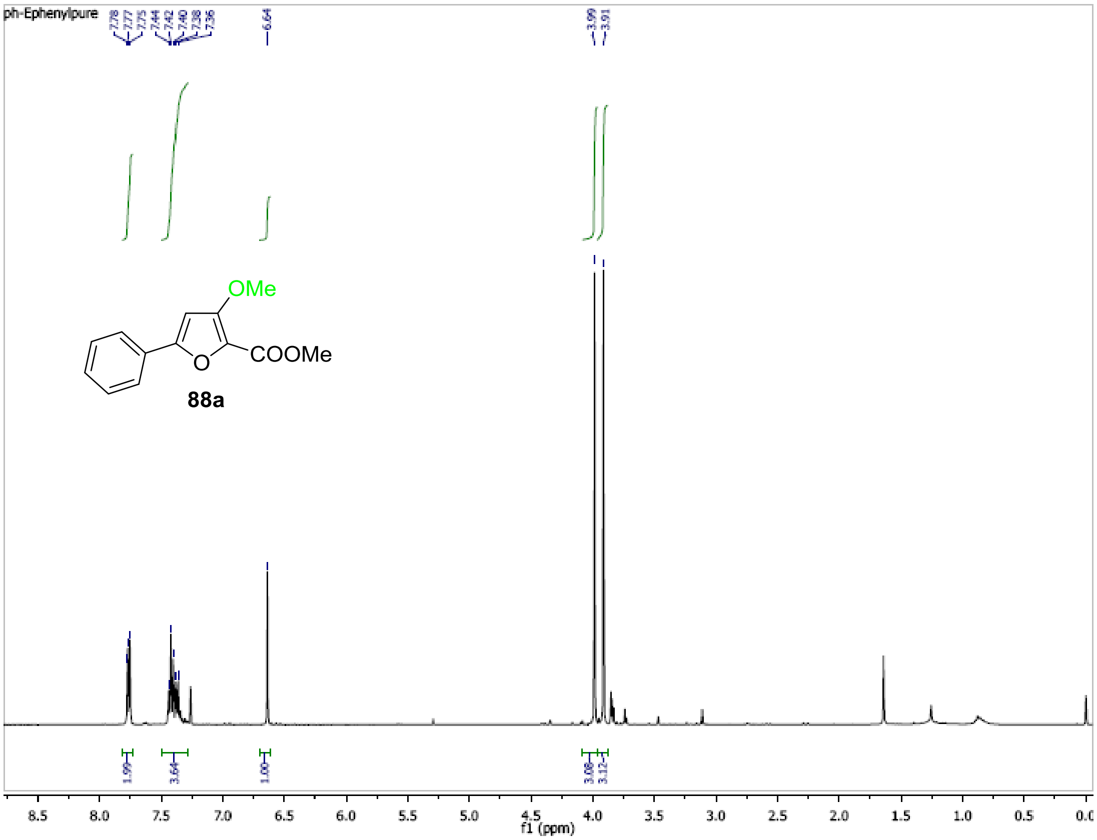

88g

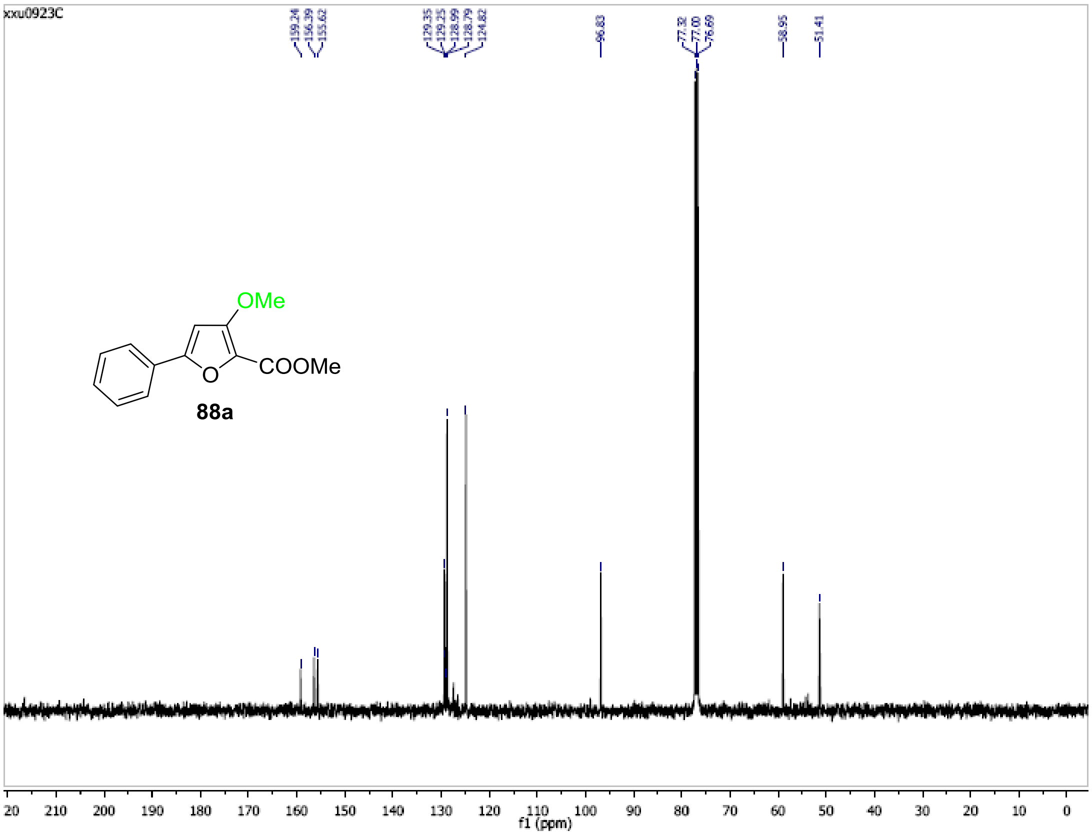
Methyl 5-(4-chlorophenyl)-3-methoxyfuran-2-carboxylate 88g: yield 75%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.61 (s, 1H), 3.96 (s, 3H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 159.1, 156.2, 154.3, 135.2, 129.0, 127.7, 127.6, 126.0, 97.2, 58.9, 51.4; HRMS (ESI) calcd for $C_{13}H_{12}ClO_4$ $(M+H)^+$ 267.0419, found 267.0435.

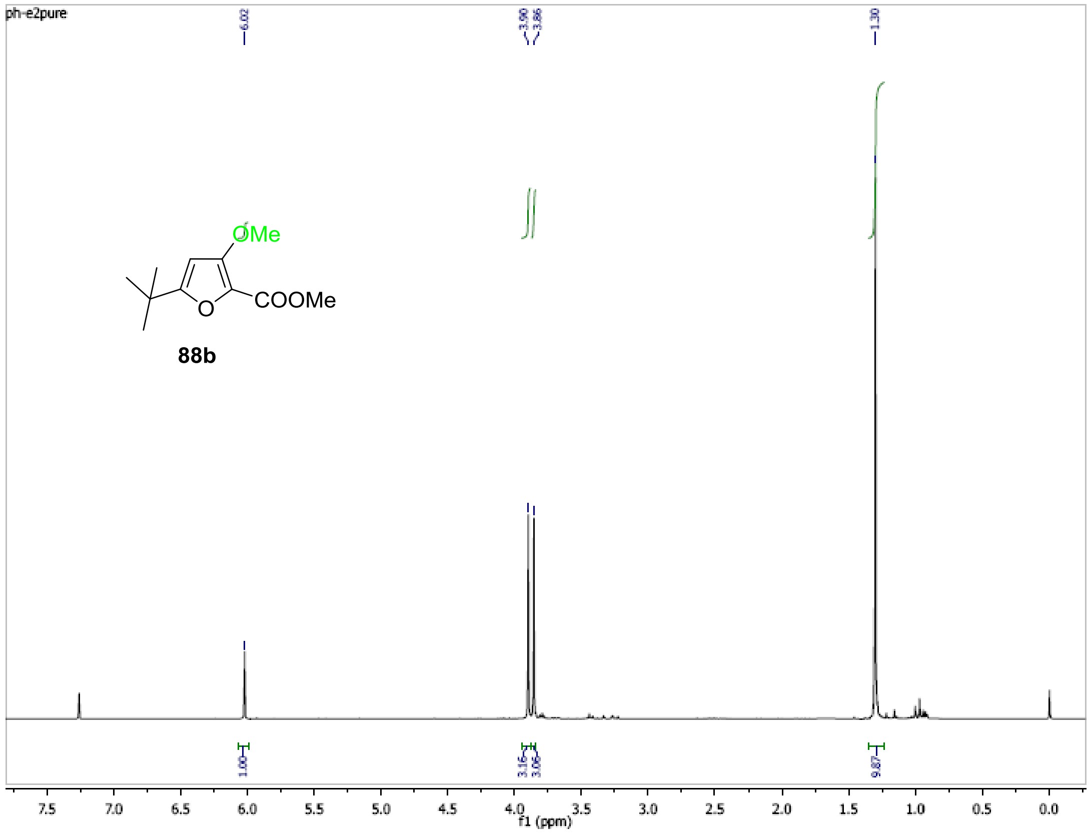

88h

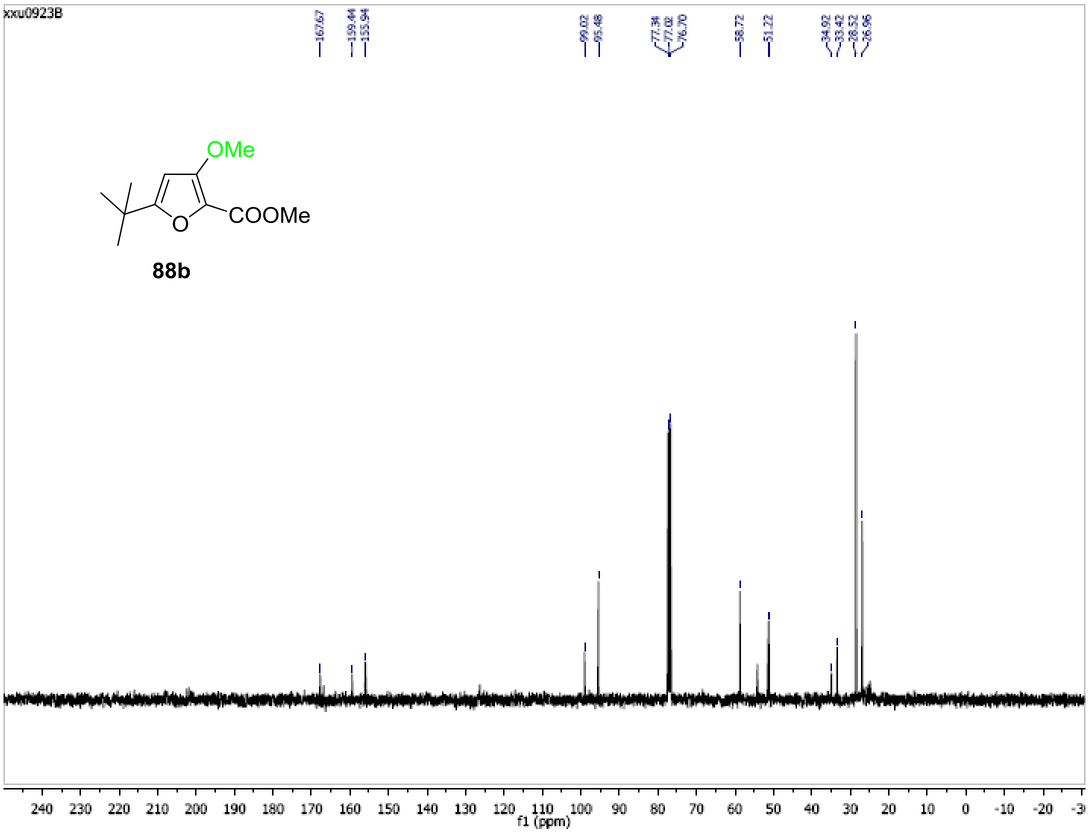
Methyl 3-methoxy-5-(naphthalen-2-yl)furan-2-carboxylate 88h: yield 85%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.28 (s, 1H), 7.49-7.87 (comp, 6H), 6.74 (s, 1H)4.01 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (CDCl$_3$, 400 MHz) δ 159.7, 156.2, 155.7, 154.4, 135.2, 133.5, 133.1, 129.0, 128.6. 127.7, 126.8, 126.0, 124.2, 122.1, 97.2, 58.9, 51.4; HRMS (ESI) calcd for $C_{17}H_{15}O_4$ (M+H)$^+$ 283.0965, found 283.0938.

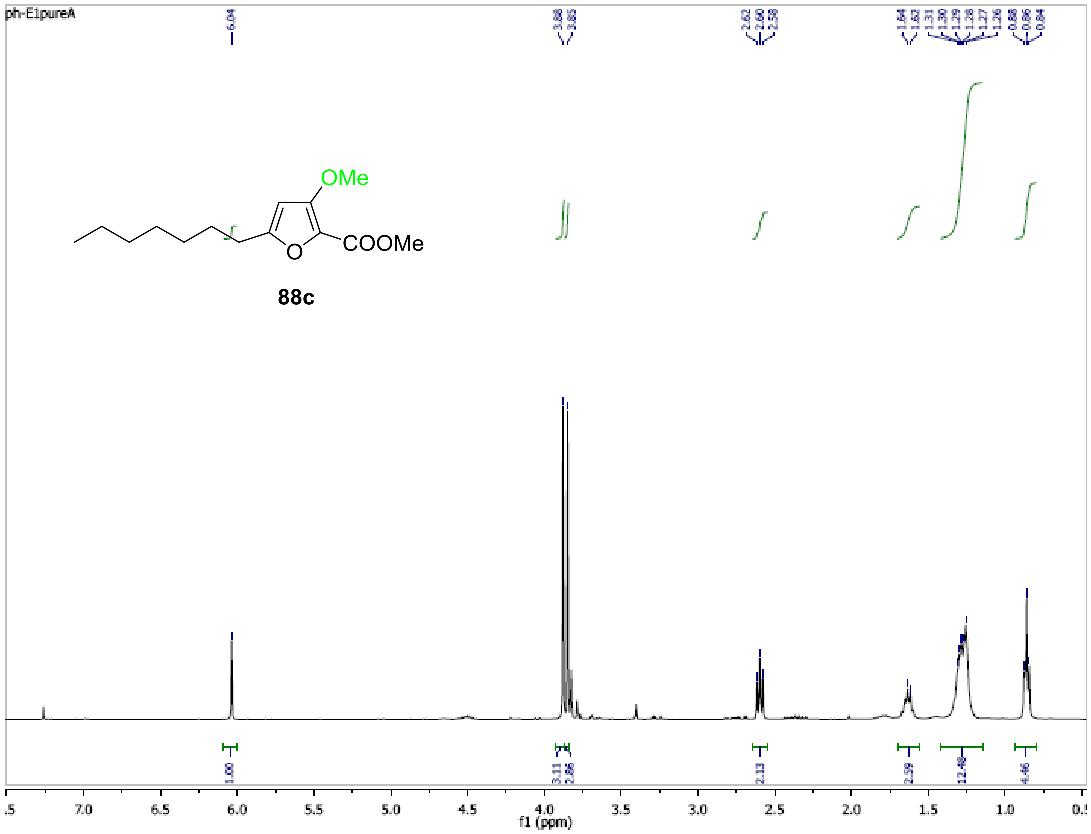
1.4.4.5 ^{1}H NMR and ^{13}C NMR Spectra

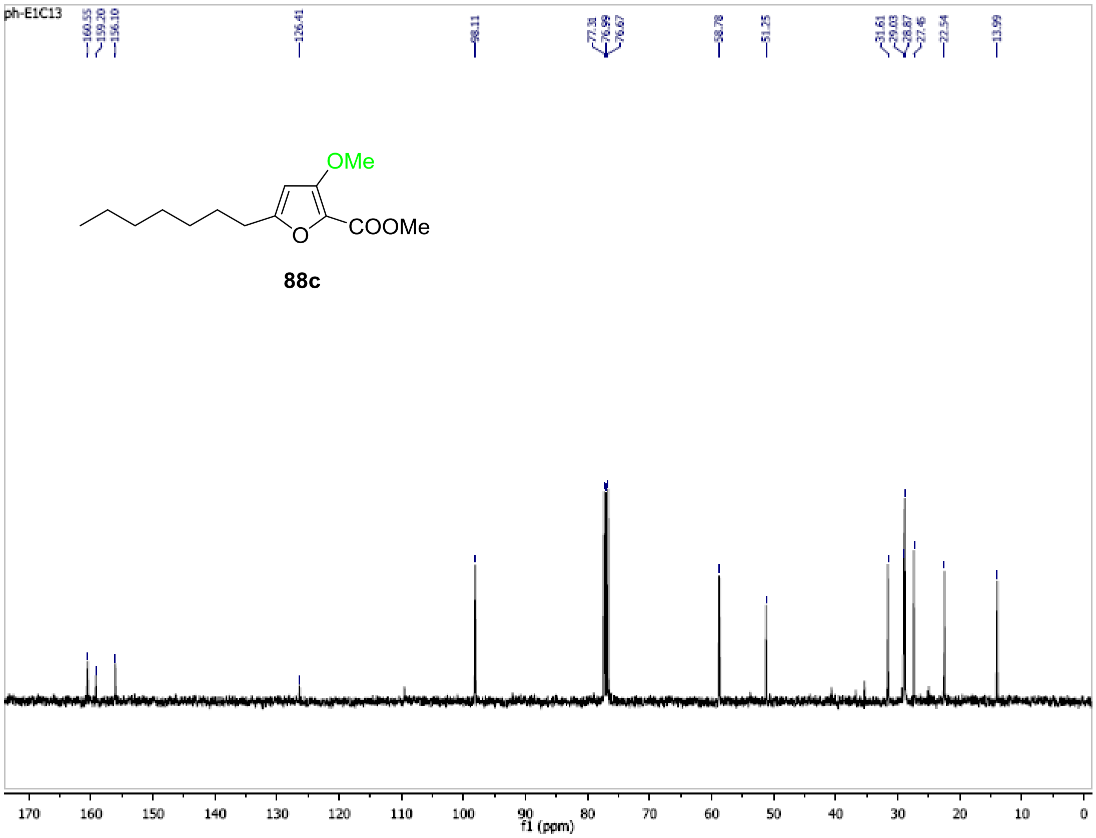

ph-Ephenylpure
7.78
7.77
7.75
7.44
7.42
7.40
7.38
7.36
6.64
3.99
3.91
OMe
COOMe
O
88a
1.99
3.64
1.00
3.08
3.12
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

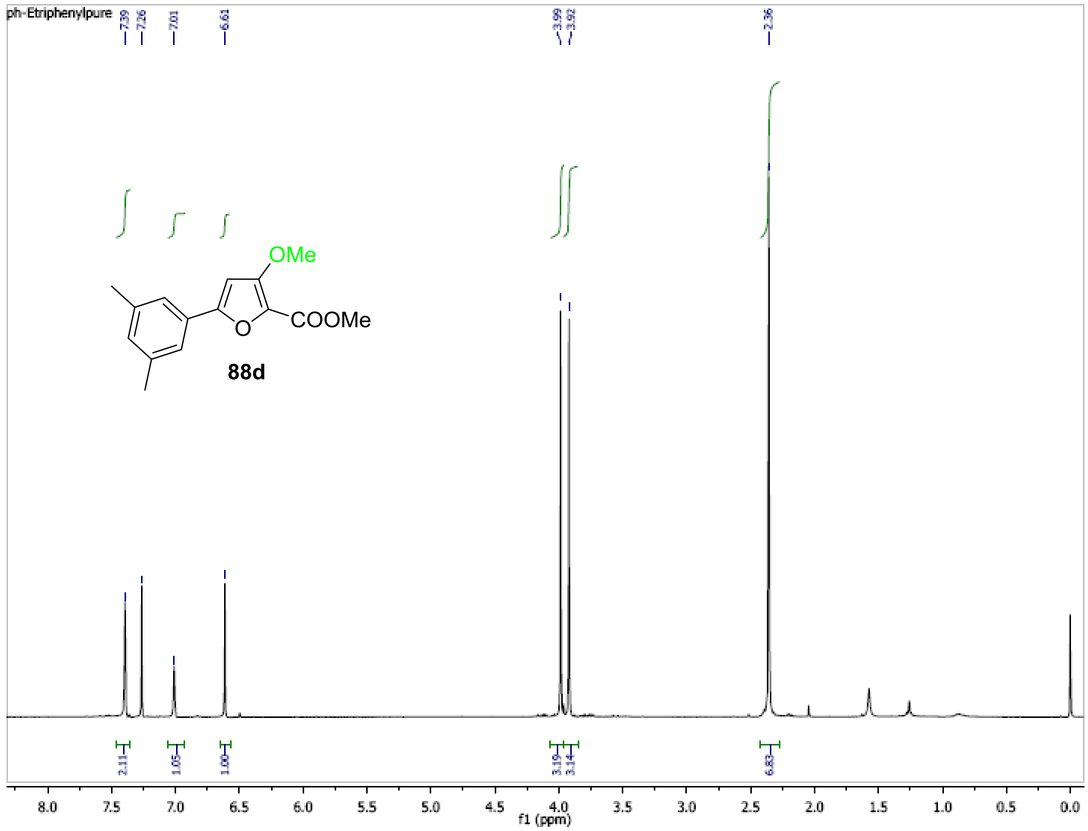

xxu0923C
159.24
156.39
155.62
129.35
129.25
128.99
128.79
124.82
96.83
77.32
77.00
76.69
58.95
51.41
OMe
COOMe
O
88a
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

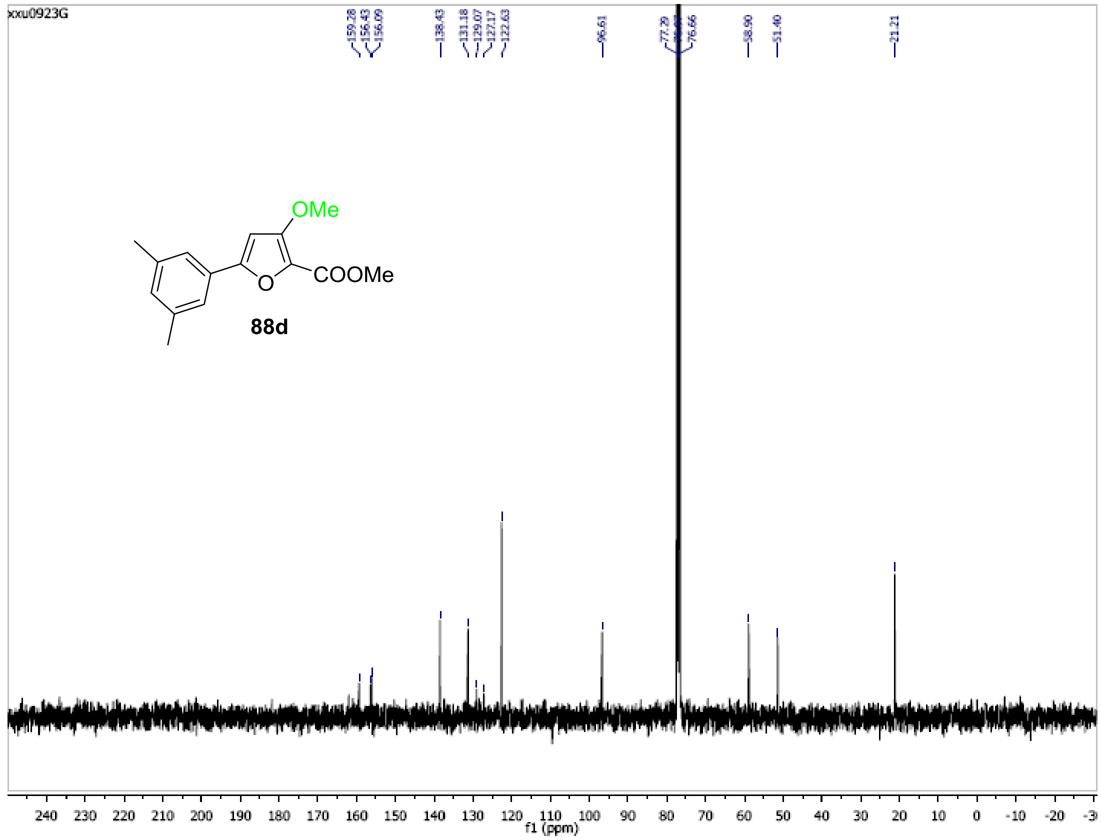

ph-e2pure
6.02
3.90
3.86
1.30
OMe
COOMe
O
88b
1.00
3.16
3.06
9.87
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


xxu0923B
167.67
159.44
155.94
99.02
95.48
77.34
77.02
76.70
58.72
51.22
34.92
33.42
28.52
26.96
OMe
COOMe
O
88b
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-3
f1 (ppm)


ph-E1pureA
6.04
3.88
3.85
2.62
2.60
2.58
1.64
1.62
1.31
1.30
1.29
1.28
1.27
1.26
0.88
0.86
0.84
OMe
O
COOMe
88c
1.00
3.11
2.86
2.13
2.59
12.48
4.46
.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


ph-E1C13
160.55
159.20
156.10
126.41
98.11
77.31
76.99
76.67
58.78
51.25
31.61
29.03
28.87
27.45
22.54
13.99
OMe
O
COOMe
88c
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


ph-Etriphenylpure
7.39
7.26
7.01
6.61
3.99
3.92
2.36
OMe
COOMe
O
88d
2.11
1.05
1.00
3.19
3.14
6.83
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


xxu0923G
159.28
156.43
156.09
138.43
131.18
129.07
127.17
122.63
96.61
77.29
76.66
58.90
51.40
21.21
OMe
COOMe
O
88d
240
230
220
210
200
190
180
170
160
150
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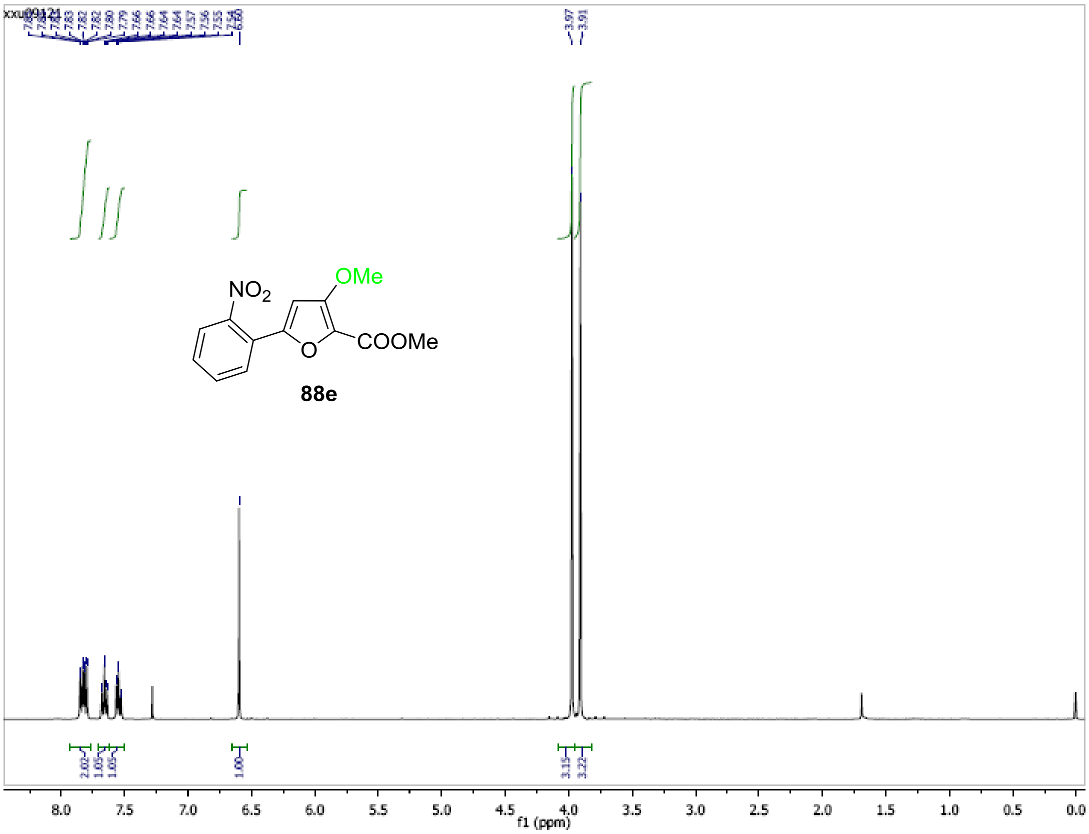
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7.54
6.60
3.97
3.91
NO2
OMe
O
COOMe
88e
2.02
1.05
1.05
1.00
3.15
3.22
8.0
7.5
7.0
6.5
6.0
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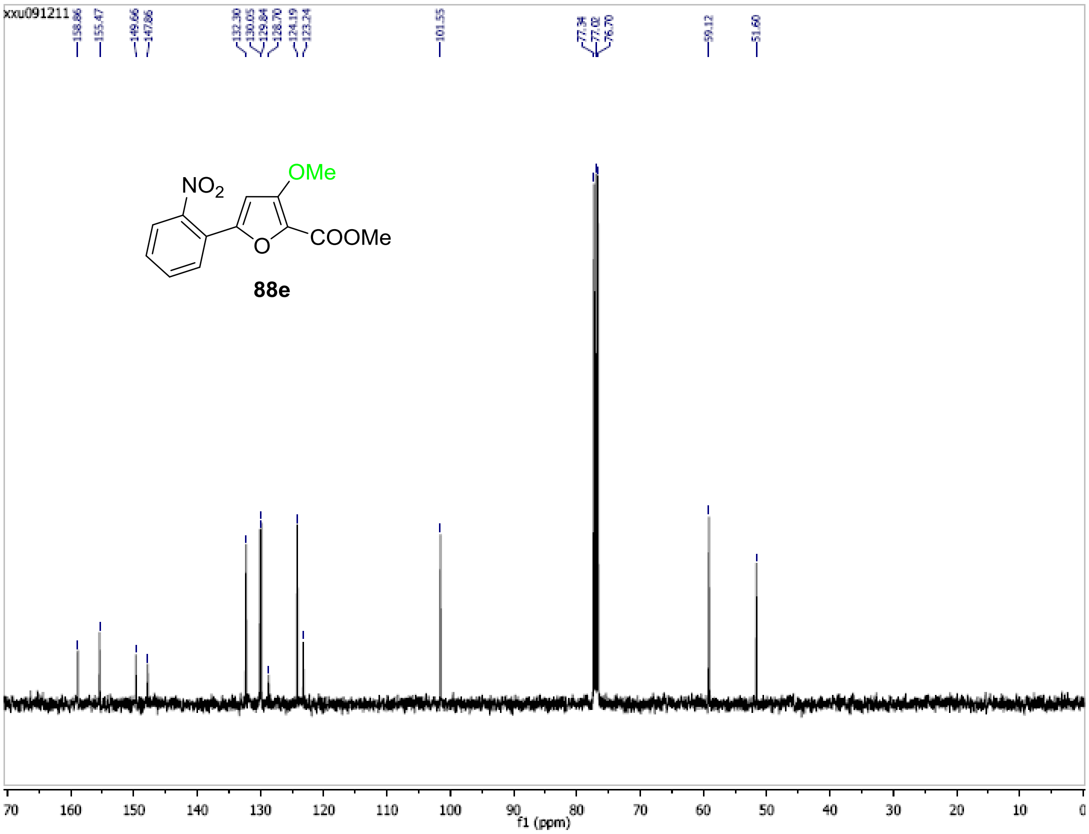
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77.34
77.02
76.70
59.12
51.60
NO2
OMe
O
COOMe
88e
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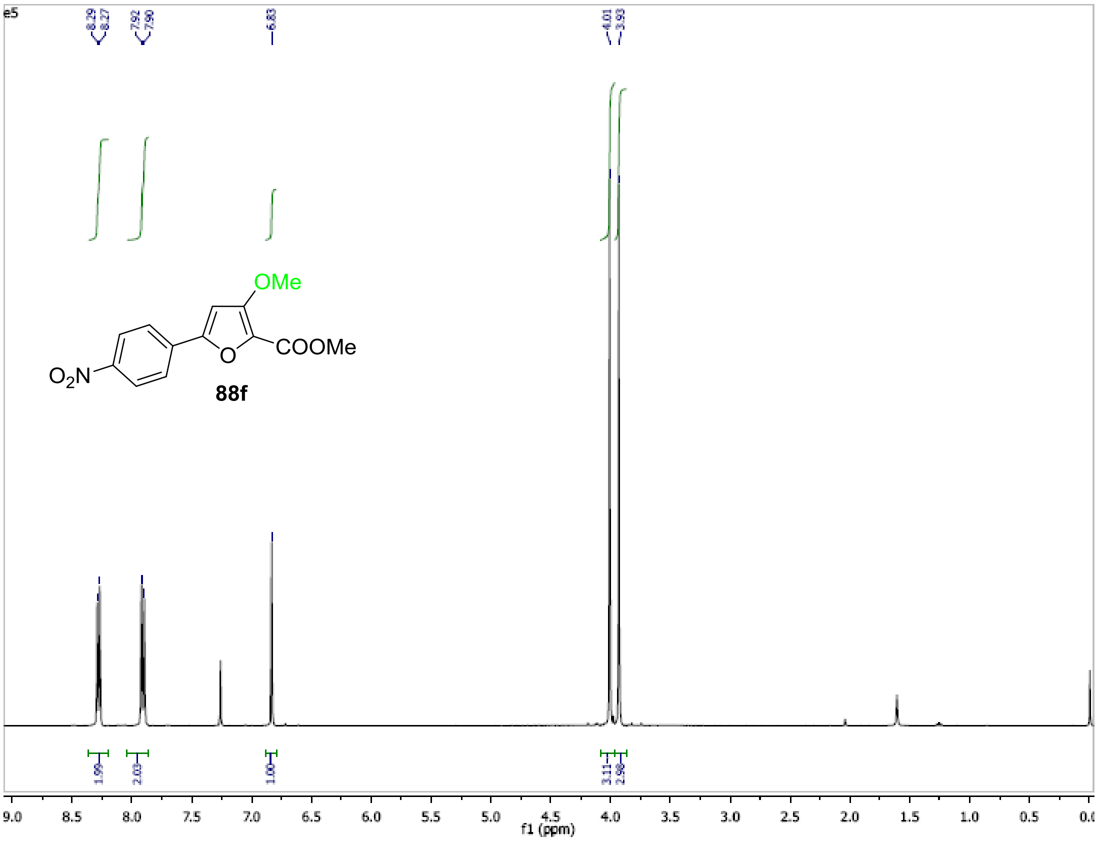
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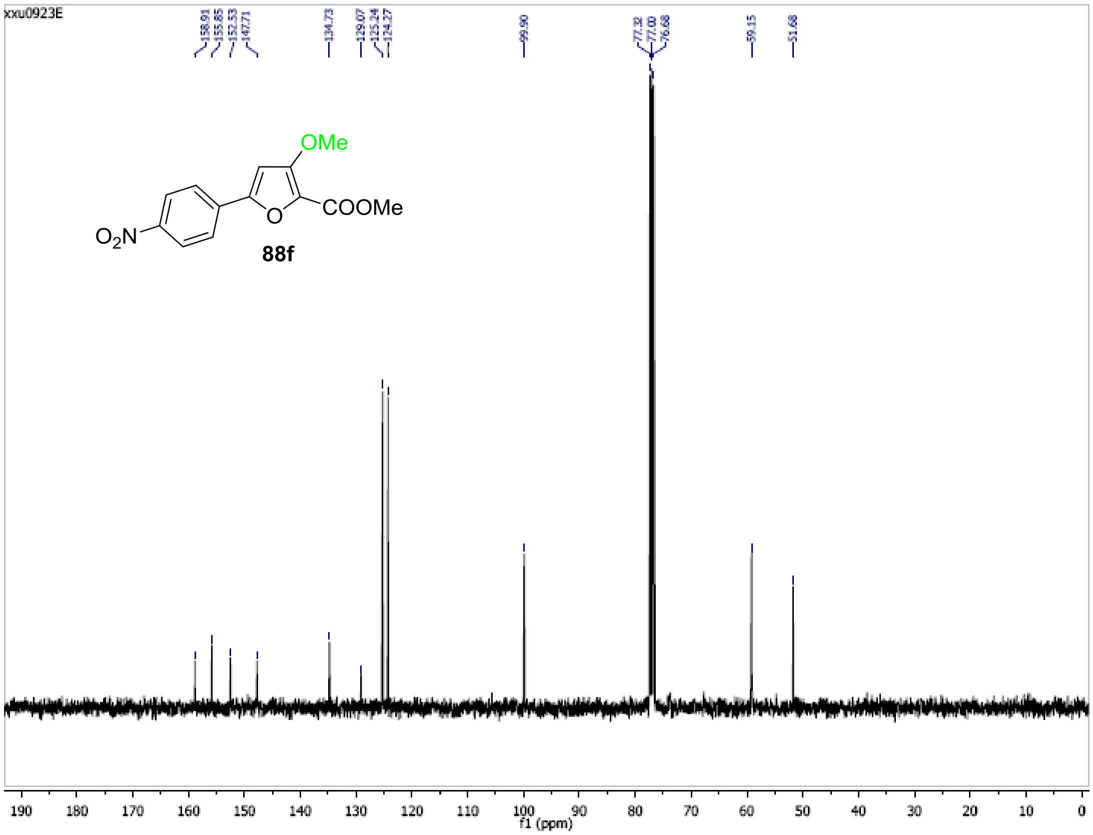
2.03
1.00
3.11
2.98
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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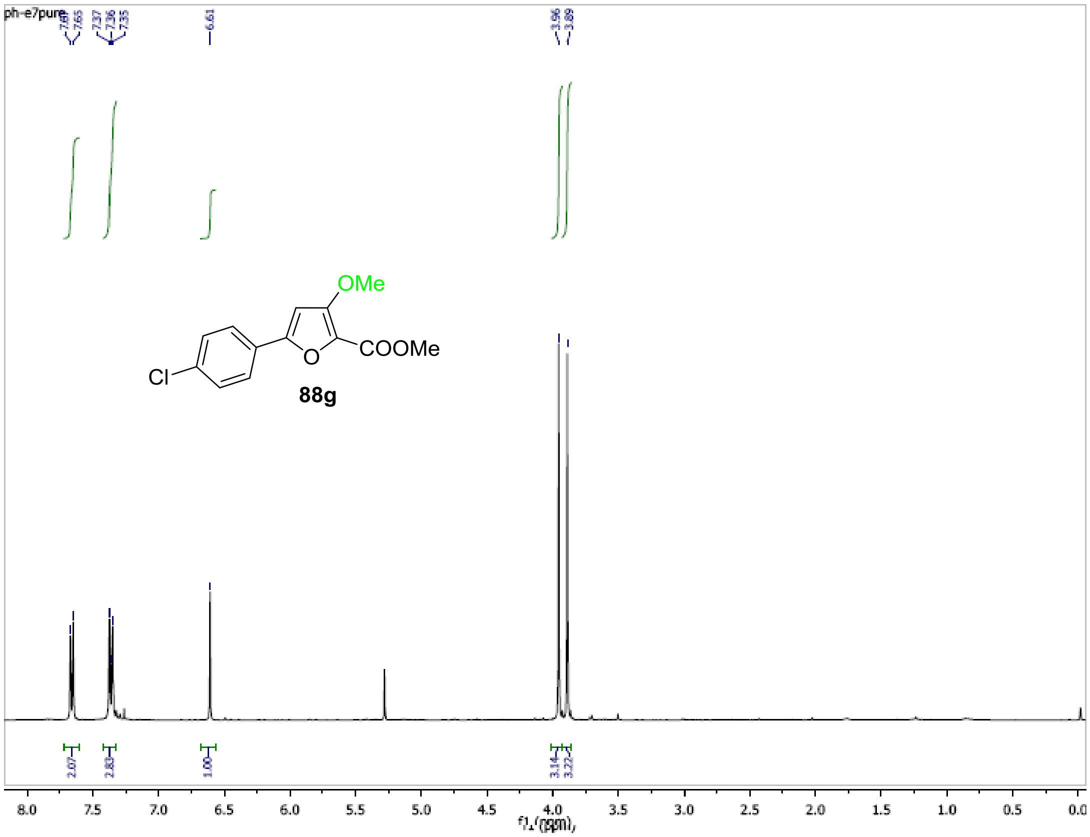
f1 (ppm)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1.00
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3.22
8.0
7.5
7.0
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6.0
5.5
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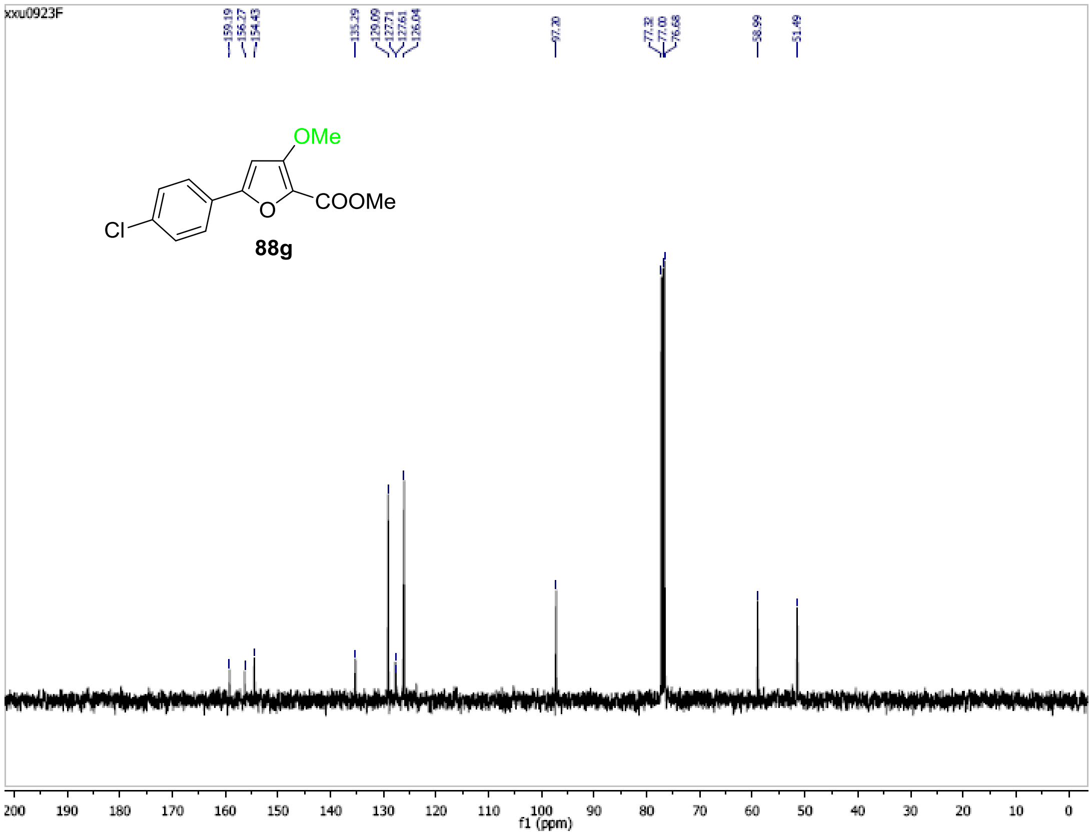
f1 (ppm)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51.49
OMe
COOMe
O
Cl
88g
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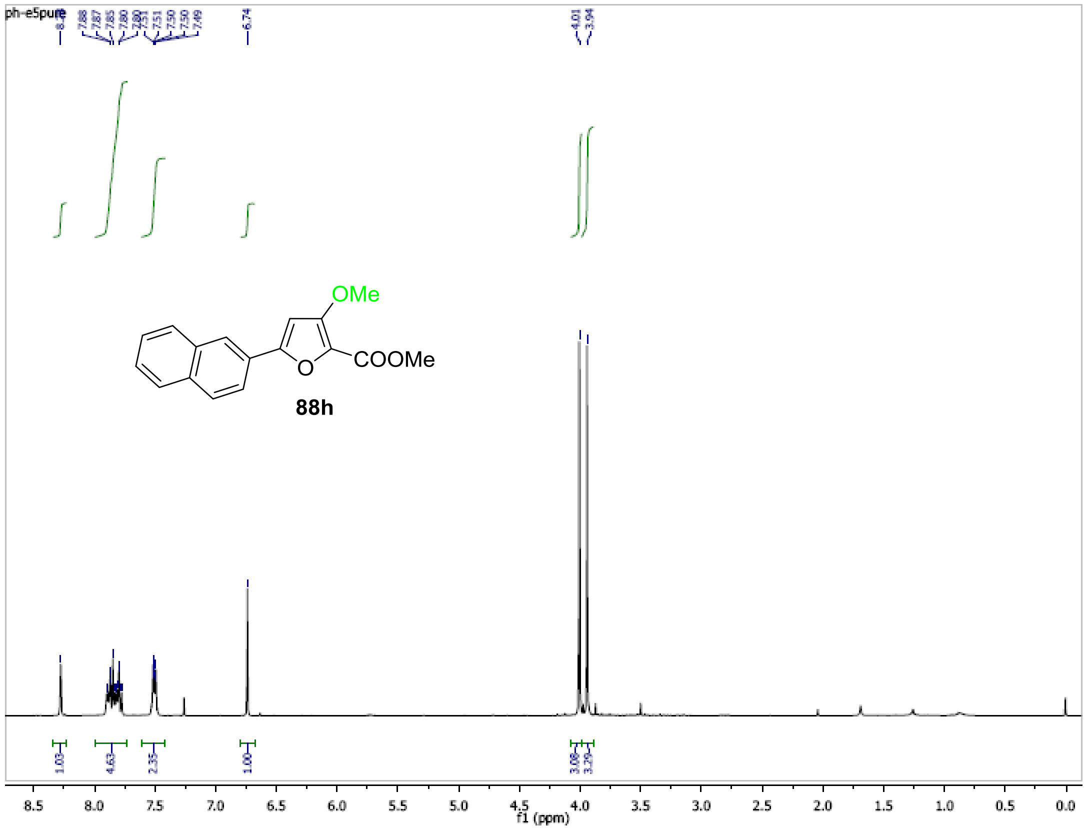
f1 (ppm)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4.01
3.94
OMe
COOMe
O
1.03
4.63
2.35
1.00
3.08
3.29
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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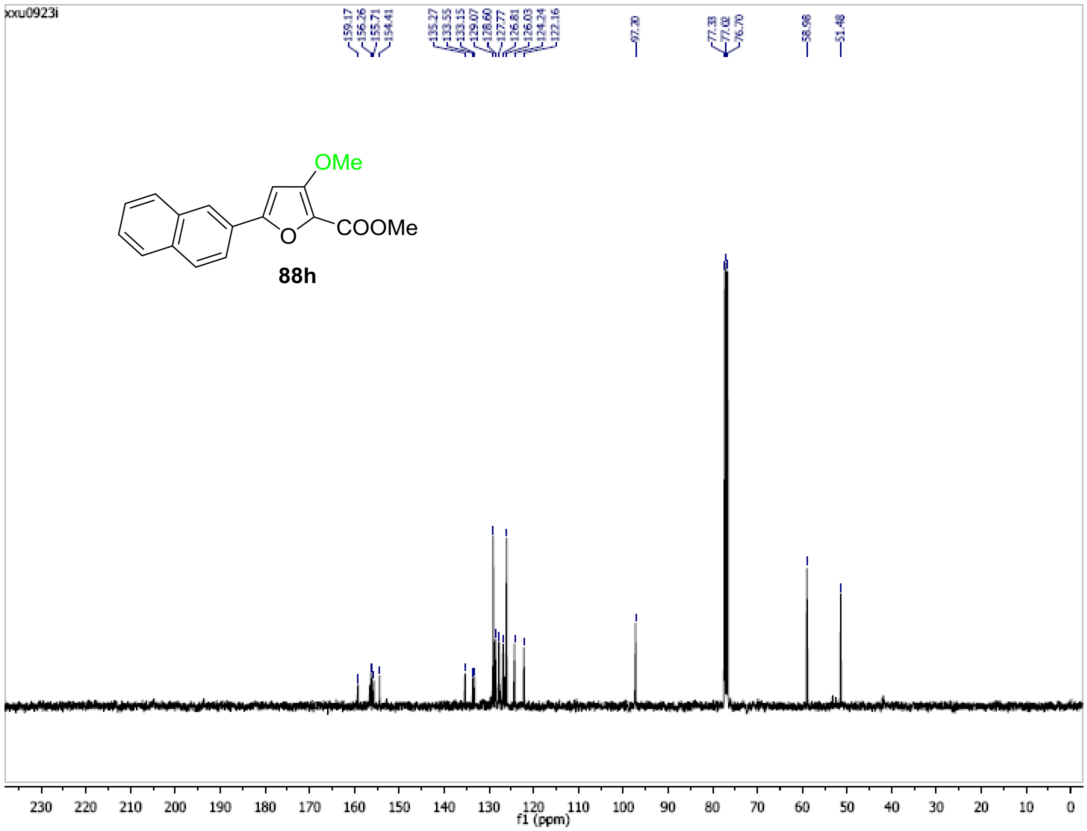
f1 (ppm)

88h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124.24
122.16
97.30
77.33
77.02
76.70
58.98
51.48
OMe
COOMe
O
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220
210
200
190
180
170
160
150
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70
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50
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30
20
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f1 (ppm)

88h

1.5 References

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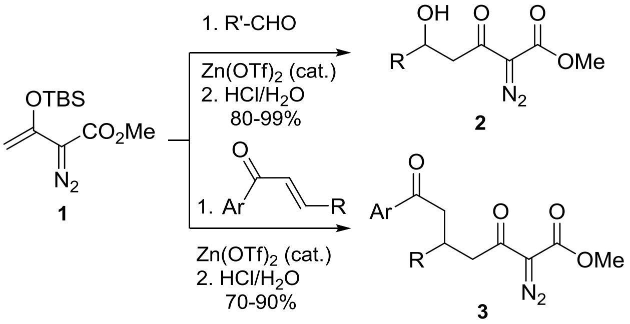
Chapter 2: Divergent Stereocontrol of Acid Catalyzed Intramolecular Aldol Reactions of 2,3,7-Triketoesters: Synthesis of Highly Functionalized Cyclopentanones

2.1 Introduction

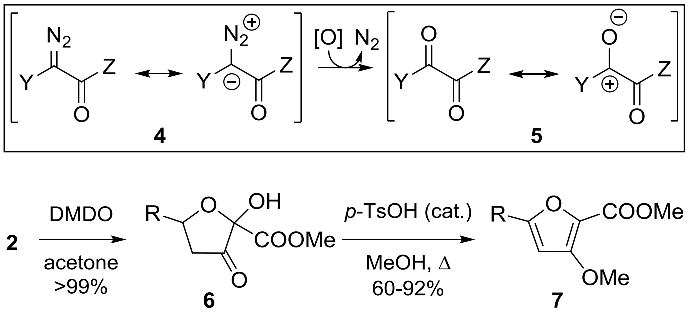
New strategies for the synthesis and application of complex diazo compounds have proven fruitful in the preparation of carbocyclic and heterocyclic ring systems due to the utility of selective diazo decomposition reactions in complex enviroments.[1] A longstanding interest in our research group has been the application of enol diazoacetates of type **(1)** toward the synthesis of more complex diazo compounds by developing methods that take advantages of the remarkable stability of the diazo-*β*-ketoester functional group (Scheme 2.1).[2] To that end, our group has recently reported the Mukaiyama-aldol reactions of **(1)** to give *δ*-hydroxy diazo-*β*-ketoesters **(2)**[2a] as well as a Mukaiyama-Michael variant with enones to provide ζ-keto-α-diazo-β-ketoester **(3)** (Scheme 2.1).[2b] These new methods have provided access to highly functionalized diazo compounds that have allowed us to study increasingly complex material by way of transition metal catalyzed dinitrogen extrusion reactions.[1]

Scheme 2.1 Mukaiyama Reactions of Silyl Enoldiazoacetate **(1)**.


1. R'-CHO
Zn(OTf)2 (cat.)
2. HCl/H2O
80-99%
OTBS
CO2Me
N2
1
OH
O
O
R
OMe
N2
2
O
1. Ar
R
Zn(OTf)2 (cat.)
2. HCl/H2O
70-90%
O
Ar
O
O
R
OMe
N2
3

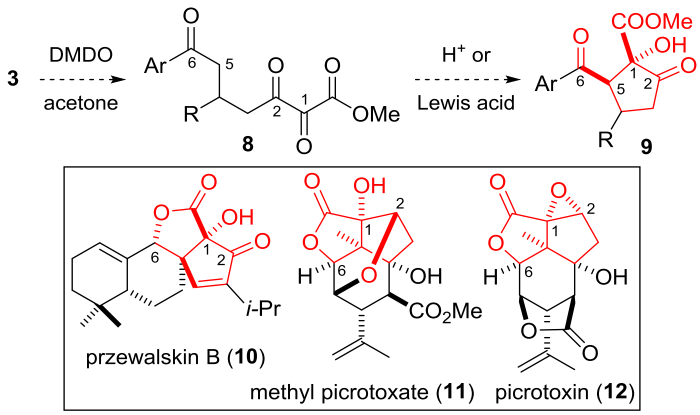
We have also been intrigued by the umpolung in reactivity provided by the conversion of the diazo functional group to the keto functional group that has been made possible through the use of DMDO.[5] In general, conversion of a diazo functionality **(4)** to a carbonyl functionality **(5)** causes a reversal in the polarity of carbon (Scheme 2.2). Upon reaction of DMDO with δ-hydroxy-α-diazoacetoacetate **(2)** (Scheme 2.2), the polarity inversion invites an intramolecular nucleophilic attack from the remote hydroxyl group into the newly formed carbonyl unit to generate hemiketal **(6)**.[2c] Hemiketal **(6)** could then be further manipulated to provide 3-alkoxyfuran derivatives such as **(7)** by acid catalyzed dehydration/methanolysis.

Scheme 2.2 Oxidation of δ-Hydroxy-α-diazoacetoacetates as a Route to Furanones and Furans.


N2
Y
Z
O
N2⊕
Y
⊖
Z
O
4
[O]
N2
O
Y
Z
O
⊖
O
Y
⊕
Z
O
5
2
DMDO
acetone
>99%
R
O
OH
COOMe
O
6
p-TsOH (cat.)
MeOH, Δ
60-92%
R
O
COOMe
OMe
7

With the success of these early studies, we directed our attention to the application of this umpolung strategy to the previously reported[2b] Mukaiyama-Michael adducts **(3)** (Scheme 2.3). Our hypothesis was that oxidation of this class of diazo compounds would provide tetracarbonyl compounds **(8)**, which we envisioned as candidates for intramolecular aldol reactions for the construction of the highly functionalized cyclopentanones **(9)**. Our interested in this strategy was piqued by the knowledge that a number of biologically active natural products such as prezawlskin B **(10)**[3] and the picrotoxanes (e.g **11-12**)[4] share a similarly functionalized cyclopentanone system to which the proposed methodology may allow access.

Scheme 2.3 Diazo-umpolung Route to Cyclopentanones.

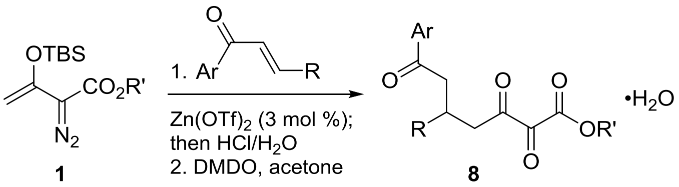


2.2 Results and Discussion

2.2.1 Synthesis of 2,3,7-Triketoesters

Our investigation began by first preparing a family of tetracarbonyl compounds, which were available via a two-step sequence involving the intermolecular Mukaiyama-Michael reaction of enol diazoacetate **(1)** followed by oxidation of the diazoacetoacetate with DMDO (Table 2.1).[2b] Yields from the two step process ranged from 69-92%.[5,2c] It should be noted that the oxidation step in all cases proceeded in virtually quantitative yields, and the products were isolated as hydrates.[6] Thus, yields of Michael adduct **(8)** reflect limitations in the Mukaiyama-Michael reaction.

Table 2.1. Synthesis of 2,3,7-Triketoesters[a]



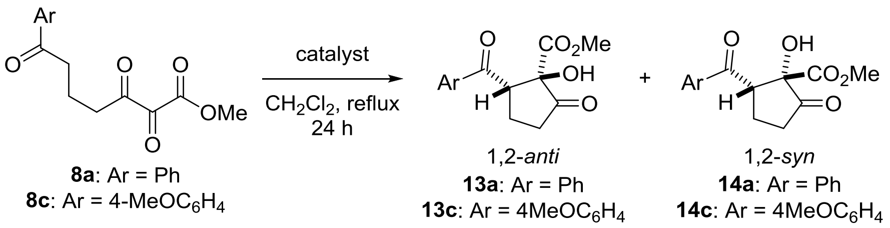
8	Ar	R	R′	Yield (%)[b,c]
A	C_6H_5	H	Me	80
B	2-naphthyl	H	Me	83
C	4-$MeOC_6H_4$	H	Me	92
D	4-ClC_6H_4	H	Me	83
E	9-anthryl	H	Me	71
F	mesityl	H	Me	69
G	4-$CF_3C_6H_4$	H	Me	81
H	4-$CF_3C_6H_4$	H	Bn	73
I	C_6H_5	Ph	Me	90

[a] Mukaiyama-Michael reactions were carried out in a 5.0 mmol scale of enones, 7.0 mmol of **1** and $Zn(OTf)_2$ (3 mol %) in 25 mL of CH_2Cl_2 at room temperature. [b] Isolated yield following purification via column chromatography. [c] Overall yields are reported starting from **1** and the respective enone used.

2.2.2 Acid Catalyzed Intramolecular Aldol Condensation of 2,3,7-Triketoesters

The capabilities of Lewis acids to catalyze aldol condensation reactions with high stereocontrol are well known.[7] However, applications to vicinal tricarbonyl compounds have not been reported. Copper(II), scandium(III), and ytterbium(III) triflates are reported to be effective for aldol condensation reactions,[8] and tin(II) triflate has also been described.[9] These catalysts were evaluated for their effectiveness in mediating carbocyclization of **(8a)** in refluxing dichloromethane (Table 2.2, entries 1-7). Each of these catalysts exhibited a high degree of diastereocontrol, but Yb(OTf)$_3$ provided the highest level of diastereoselectivity. Alternative catalysts such as La(Otf)$_3$,[9d,11] Zn(Otf)$_2$,[9a,3,4] Ni(Otf)$_2$,[12] and Mg(Otf)$_2$[13] showed little or no activity for this transformation under the reaction conditions.

Table 2.2 Optimization of the Intramolecular Aldol Reaction of 2,3,7-Triketoester **(8a)**.


Ar
O
O
O
OMe
O
catalyst
CH2Cl2, reflux
24 h
8a: Ar = Ph
8c: Ar = 4-MeOC6H4
O
CO2Me
OH
Ar
H
O
+
O
OH
CO2Me
Ar
H
O
1,2-anti
13a: Ar = Ph
13c: Ar = 4MeOC6H4
1,2-syn
14a: Ar = Ph
14c: Ar = 4MeOC6H4

Entry [a]	Catalyst [b]	*anti*:*syn* [c]	% Conversion [c]
1	Yb(Otf)$_3$ [d]	N.D.	<5
2	Yb(Otf)$_3$ [e]	95:5	65
3	Yb(Otf)$_3$ [f]	95:5	>95
4	Yb(Otf)$_3$	95:5	>95
5	Sn(Otf)$_2$	85:15	93
6	Sc(Otf)$_3$	87:13	>95
7	Cu(Otf)$_2$	89:11	>95
8	H_2PO_4 [g]	25:75	75
9	*p*-TsOH	32:68	84
10	Mes-SO_3H	30:70	90
11	Mes-SO_3H [h]	30:70	>95
12 [i]	Yb(Otf)$_3$	93:7	>95

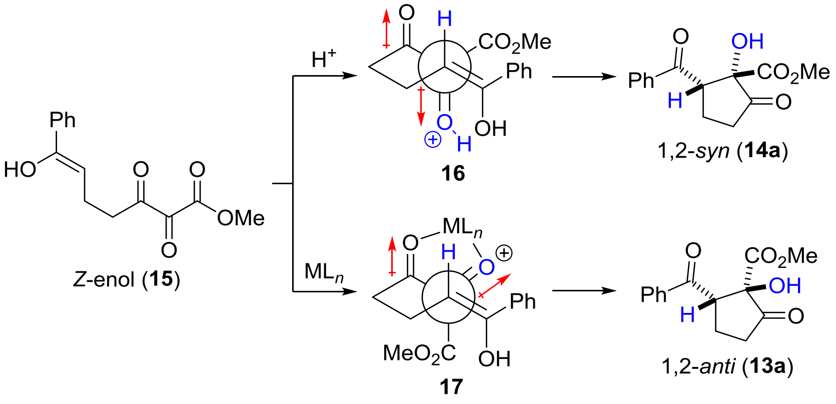
[a] Reaction performed with substrate **8a**. [b] Reaction performed with 10 mol % catalyst. [c] Determined by ^{1}H NMR spectroscopy. [d] 10 mol% catalyst at room temp for 24 h. [e] 5 mol % catalyst. [f] 20 mol % catalyst. [g] 4 equivalents of acid used. [h] 30 mol % of the acid used. [I] The

stereochemistry of the process was confirmed by a reaction with **8c** using 10 mol% Yb(Otf)$_3$, and the stereochemistry of product **13c** was varified by X-ray analysis.

2.2.3 Proposed Stereocontrol of Cyclopentanone Formation

We were surprised to find a significant divergence in stereocontrol between Lewis acid and Brønsted acid catalysts. The use of a Lewis acid gave the 1,2-*anti* product **(13a)** predominantly, whereas Brønsted acids greatly favored formation of the 1,2-*syn* product **(14a)**. Furthermore, given the prevalence of *syn*-selective aldol reactions of 1,*n*-dicarbonyl compounds under both Brønsted and Lewis acid catalyzed conditions,[12] the fact that the *anti*-aldol product **(13)** is formed with high selectively is notable. Our initial thought regarding the observation that Lewis and Brønsted acid provided divergent reactivity was that we had simply discovered conditions for both the kinetically and thermodynamically controlled processes; however, as described below, extensive investigations have revealed that the aldol adducts themselves are resistant to equilibration between their *syn*- and *anti*-forms under any of the optimized reaction conditions. When either purified **(13a)** or **(14a)** was resubjected to the standard reaction conditions (Table 2.2, Entries 4 & 11), no interconversion of these products was observed. Interconversion was observed after 7 days in refluxing $CDCl_3$, however, but interconversion under these more forcing conditions was accompanied by a significant amount of by-product formation (>30% relative to **(13a)** and **(14b)** based on ^1H NMR). The absence of product interconversion under the standard reaction conditions suggests that this unique stereochemical divergence between Lewis and Brønsted acid catalysis is the result of a kinetically controlled process. In this scenario Lewis acids alter the course of the reaction to give the less common *anti*-aldol product. We believe that the stereochemical outcomes of the Brønsted and Lewis acid catalyzed aldol reactions can be rationalized by analyzing the transition states *en route* to the respective products (Scheme 2.4). Activation of the central carbonyl by Brønsted acid presumably results in the dipole minimized orientation of the 1,2-diketo unit, which can then be attacked by the tethered *Z*-enol via the lower energy intermediate **(16)** thus providing *syn*-adduct (**14a)**. Lewis acid activation, however, has the ability to coordinate the 1,2-diketo unit thus locking the carbonyls in a *syn*-orientation. The *Z*-enol then reacts with the central carbonyl *via* intermediate **(17)** to give *anti*-product **(13a)**.

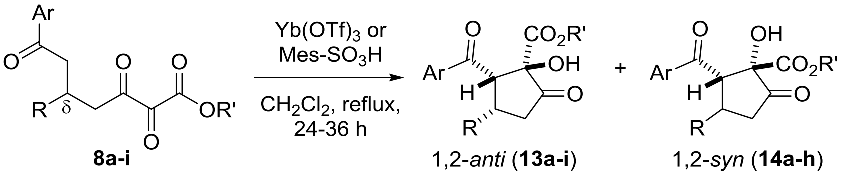
Scheme 2.4 Stereochemical Rationale for the Diastereoselectivity of Lewis and Brønsted Acids.

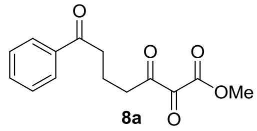
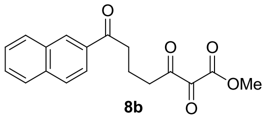


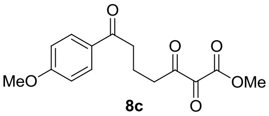
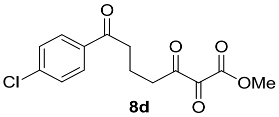
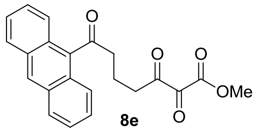
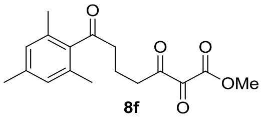
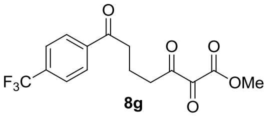
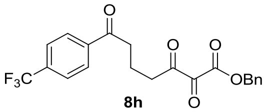
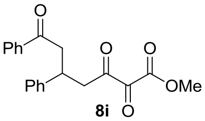
2.2.4 Substrate Scope

Expanding on these initial results, we applied the optimized conditions for the Lewis and Brønsted acid catalyzed processes to representative substrates (Table 2.3). Both electron-withdrawing and -donating aromatic rings were tolerated, as were those with sterically demanding aromatic substituents. In the case of the *o,o*-disubstitued substrates **(13e)** and **(13f)** (Table 2.3, entries 5 and 6), however, a significant deterioration in *anti:syn* selectivity was observed under Lewis acid catalyzed conditions. In fact, in the mesityl example (Table 2.3, entry 6) selectivity was inverted, and the *syn*-diastereomer was formed preferentially. This anomaly seems to highlight the fact that the *anti*-transition state is inherently more sterically demanding; and thus, when the steric demand is too high, an alternative acid coordination such that in **(16)** is favored due to the fewer number of Gauche interactions. We were also interested in studying the effect of a δ-substituent on the stereochemical course of the reaction (Table 2.3, entry 9). To that end, when **(8i)** was subjected to standard Lewis acid catalyzed conditions the reaction provided **(13i)** as the major product (*dr* = 93:7) with the usual 1,2-*anti* geometry where the 3-phenyl substituent is positioned *syn* to the aryl ketone moiety, which further exemplifies the stereocontrol predicted by **(17)**.[13]

Table 2.3 Scope and Limitations.



Entry	Substrates	Method	Yield (%)[a]	*anti*:*syn* ratio[b]
1	 **8a**	A[c] B[d]	98 81	95:5 24:76
2	 **8b**	A B	92 80	95:5 33:67

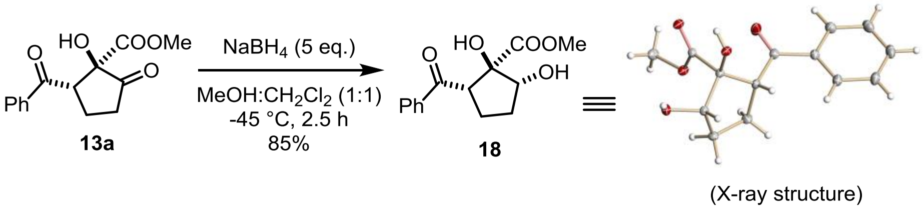
3	 **8c**	A B	94 67	93:7 25:75
4	 **8d**	A B	96 75	95:5 43:57
5	 **8e**	A B	70 82	57:43 10:90
6	 **8f**	D[f] B	51 61	30:70 5:95
7	 **8g**	A B	96 75	94:6 16:84
8	 **8h**	A B	92 77	93:7 23:77
9	 **8i**	C[e] -	92 -	93:7 -

[a] Isolated yield. [b] Diastereomeric ratios determined by ^{1}H NMR spectroscopy (see Supporting Information, page 77). [c] Method A: Reaction was performed with 10 mol% Yb(OTf)$_3$. [d] Method B: Reaction was performed with 30 mol% mesitylenesulfonic acid (Mes-SO$_3$H). [e] Method C: Reaction was performed with 10 mol% Sn(OTf)$_2$. [f] Method D: Reaction was performed with 10 mol % Sc(OTf)$_3$.

2.2.5 Selective Reduction to 1,2-Diols

With the cyclopentanone system bearing two ketone groups we next queried whether these carbonyl groups could be orthogonally reacted, thus enhancing the synthetic utility of these novel cyclopentanone products. We found that reduction of the cyclic ketone could be performed with high chemo- and stereo-selectivity to give diol **(18)** in 85% yield as only one diastereomer (Scheme 2.5).[14] The stereochemistry of **(18)** was confirmed by X-ray crystallography to be the 1,2-*anti* diol resulting from a chelation controlled delivery of the hydride.

Scheme 2.5 Chemo- and Stereoselective Reduction of Dione **(13a)**.[a]



[a] No trace of the aryl ketone reduction product under these conditions.

2.3 Conclusion

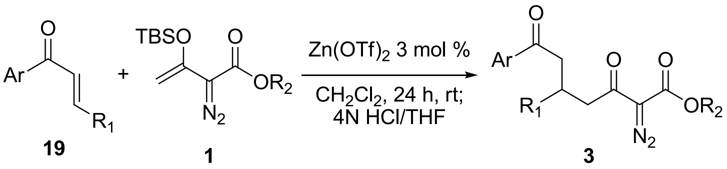
The Mukaiyama-Michael reaction of silyl enoldiazoaceates was exploited to prepare a series of highly functionalized ζ-keto-α-diazo-β-ketoesters. The diazo groups of these compounds were oxidized with DMDO to generate 2,3,7-triketoesters in virtually quantitative yields, which set up highly stereoselective intramolecular aldol reactions to provide usefully functionalized cyclopentanones. Lewis acid catalysts provided high degrees of 1,2-*anti* diastereoselectivity, while Brønsted acids selectively provided the 1,2-*syn* diastereomer, a fact that we believe makes this methodology even more synthetically attractive. The prospect of using chiral acid catalysts to achieve an asymmetric variant of this reaction, and application of the overall strategy toward natural product synthesis are currently being explored.

2.4 Experimental

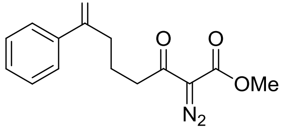
2.4.1 General Information

Dichloromethane (DCM) and tetrahydrofuran (THF) were passed through a column of molecular sieves prior to use, not distilled. Thin layer chromatography (TLC) was carried out using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolate phosphomolybdic acid, potassium permanganate (KMnO4) or cerium ammonium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated system on silica gel (230-400 mesh). Metal triflate salts and Brønsted acids were purchased from Aldrich and used as received. Methyl 3-*tert*-butyldimethylsilyloxy-2-diazobut-3-enoate (**1**) was prepared by the literature method.[15] Dimethyldioxirane (DMDO) was prepared by the method described by Adam.[16] Functionalized α-diazo-β-ketoesters (**3**) were prepared by method described by Liu.[2b] ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Advance 400 MHz spectrometer. Chemical shifts are reported in ppm with the solvent signals as reference, and coupling constants (*J*) are given in Hertz. The peak information is described as: br = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, comp = complex multiplet of magnetically inequivalent protons. IR spectra were recorded on a Thermo Nicolet IR200 spectrometer. Melting points were obtained from Electro Thermo Mel-Temp DLX 104. High-resolution mass spectra (HRMS) were performed on a JEOL AccuTOF-ESI mass spectrometer using CsI as the standard.

2.4.2 General Procedure for the Preparation of Functionalized *α*-Diazo-*β*-ketoesters



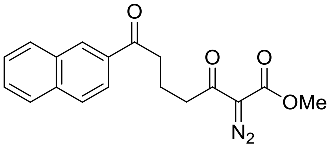
A solution of methyl 3-*tert*-butyldimethylsilyloxy-2-diazobut-3-enoate **1** (7.0 mmol, 1.4 eq) in anhydrous CH_2Cl_2 (3 mL) was added via syringe pump over 1 h to a solution of aryl vinyl ketone **19** (5.0 mmol, 1.0 eq) and $Zn(OTf)_2$ (54 mg, 0.15 mmol, 3 mol%) in CH_2Cl_2 (25 mL) under a nitrogen atmosphere. The reaction solution was stirred for 24 h at room temperature and then concentrated under reduced pressure. The residue was then dissolved in THF (15 mL) containing 4*N* HCl (10 mL), and the mixture was stirred at room temperature overnight. The reaction solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with diethyl ether (30 mL x 3). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2) by eluting with hexanes and ethyl acetate. The diazo carbon was not detected in the ^{13}C NMR spectra of these compounds.



3a

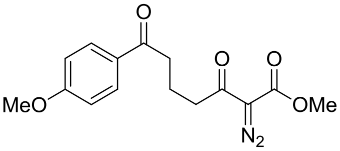
Methyl 2-Diazo-3,7-dioxo-7-phenylheptanoate (3a). Reaction between enone **19a** and enoldiazoacetate **1** gave **3a** as a pale green solid in 80% yield: mp = 40-42 ºC; TLC R_f = 0.25 (3:1 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06-7.44, (comp, 5 H), 3.84 (s, 3 H), 3.08 (t, *J* = 7.2 Hz, 2 H), 2.99 (t, *J* = 7.1 Hz, 2 H), 2.13

(quin, *J* = 7.1 Hz, , 2 H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 199.9, 192.6, 162.1, 137.2, 133.4, 128.9, 128.4, 52.6, 39.8, 38.0, 19.1; IR (neat) 2125, 1720, 1679, 1646 (cm^{-1}); HRMS (ESI) *m/z* 275.100 [$C_{14}H_{15}O_5$ (M+H) requires 275.103].



3b

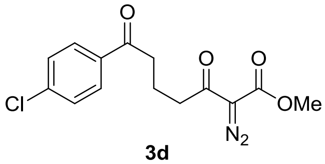
Methyl 2-Diazo-7-(naphth-2-yl)-3,7-dioxoheptanoate (3b). Reaction between enone **19b** and enoldiazoacetate **1** gave **3b** as a pale yellow solid in 83% yield: TLC R$_f$ = 0.25 (3:1 hexane/ EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.52 (s, 1 H), 8.06 (dd, *J* = 8.6, 1.7 Hz, 1 H), 8.00 (d, *J* = 8.0 Hz, 1 H), 7.96-7.53 (comp, 4 H), 3.86 (s, 3 H), 3.23 (t, *J* = 7.2 Hz, 2 H), 3.05 (t, *J* = 7.1 Hz, 2 H), 2.20 (quin, *J* = 7.1 Hz, 2 H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 199.9, 192.7, 162.1, 136.0, 134.6, 133.0, 130.2, 130.0, 128.9, 128.8, 128.2, 127.0, 124.3, 52.7, 39.9, 38.2, 19.3; IR (neat) 2133, 1718, 1678, 1652 cm^{-1}; HRMS (ESI) *m/z* 325.115 [$C_{14}H_{15}O_5$ (M+H) requires 325.118].



3c

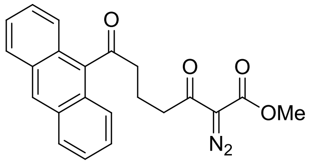
Methyl 2-Diazo-7-(4-methoxyphenyl)-3,7-dioxoheptanoate (3c). Reaction between enone **19c** and enoldiazoacetate **1** gave **3c** as a colorless solid in 92% yield: TLC R$_f$ = 0.25 (2:1 hexane/ EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 (d, *J* = 9.0 Hz, 2 H), 6.95 (d, *J* = 9.0 Hz, 2 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.11-2.90 (comp, 4

H), 2.19-1.98 (comp, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 198.5, 192.6, 163.7, 162.1, 130.7, 130.3, 114.1, 55.9, 52.6, 39.9, 37.6, 19.3; IR (neat) 2133, 1718, 1673, 1653 cm^{-1}; HRMS (ESI) *m/z* 305.112 [$C_{14}H_{15}O_5$ (M+H) requires 305.113].



3d

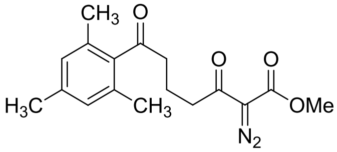
Methyl 7-(4-Chlorophenyl)-2-diazo-3,7-dioxoheptanoate (3d). Reaction between enone **19d** and enoldiazoacetate **1** gave **3d** as a colorless solid in 83% yield: TLC R_f = 0.25 (2:1 hexane/ EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.6 Hz, 2 H), 7.44 (d, *J* = 8.5 Hz, 2 H), 3.84 (s, 3 H), 3.04 (t, *J* = 7.2 Hz, 2 H), 2.98 (t, *J* = 7.0 Hz, 2 H), 2.14-2.05 (comp, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 198.6, 192.5, 162.1, 139.8, 135.5, 129.8, 129.2, 52.6, 39.7, 38.0, 19.0; IR (neat) 2129, 1718, 1679, 1648, 1589 cm^{-1}; HRMS (ESI) *m/z* 309.065 [$C_{14}H_{15}O_5$ (M+H) requires 309.064].



3e

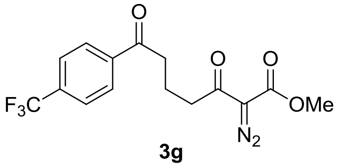
Methyl 7-(Anthracen-9-yl)-2-diazo-3,7-dioxoheptanoate (3e). Reaction between enone **19e** and enoldiazoacetate **1** gave **3e** as an orange solid in 71% yield: TLC R_f = 0.25 (2:1 hexane/ EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 8.03 (dd, *J* = 8.5, 1.2 Hz, 2 H), 7.88-7.73 (m, 2 H), 7.59-7.45 (comp, 4 H), 3.85 (s, 3 H), 3.15 (t, *J* = 7.4 Hz, 2 H), 3.06 (t, *J* = 7.2 Hz, 2 H), 2.34-2.22 (comp, 2 H); ^{13}C NMR (400

MHz, $CDCl_3$) δ 210.1, 192.3, 162.1, 136.8, 131.4, 129.2, 128.5, 127.3, 127.1, 125.8, 124.7, 52.6, 45.7, 39.6, 18.8; IR (neat) 2139, 1722, 1673, 1589, 1573 cm^{-1}; HRMS (ESI) *m/z* 375.130 [$C_{14}H_{15}O_5$ (M+H) requires 375.134].



3f

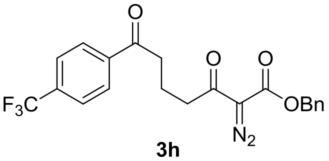
Methyl 2-Diazo-7-mesityl-3,7-dioxoheptanoate (3f). Reaction between enone **19f** and enoldiazoacetate **1** gave **3f** as a colorless solid in 69% yield: mp = 87-89 ºC; TLC R_f = 0.25 (4:1 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 2 H), 3.85 (s, 3 H), 2.97 (t, *J* = 7.2 Hz, 2 H), 2.78 (t, *J* = 7.3 Hz, 2 H), 2.28 (s, 3 H), 2.20 (s, 6 H), 2.06 (quin, *J* = 7.2 Hz, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.4, 192.4, 162.0, 139.9, 138.7, 132.8, 128.8, 52.6, 44.1, 39.6, 21.4, 19.5, 18.4; IR (neat) 2148, 1715, 1694, 1650 cm^{-1}; HRMS (ESI) *m/z* 317.153 [$C_{14}H_{15}O_5$ (M+H) requires 317.1501].



3g

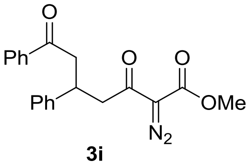
Methyl 2-Diazo-3,7-dioxo-7-[4-(trifluoromethyl)phenyl]heptanoate (3g). Reaction between enone **19g** and enoldiazoacetate **1** gave **3g** as a colorless solid in 81% yield: mp = 42-44 ºC; TLC R_f = 0.25 (2:1 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.6 Hz, 2 H), 7.74 (d, *J* = 8.6 Hz, 2 H), 3.85 (s, 3 H), 3.10 (t, *J* = 7.2 Hz, 2

H), 3.00 (t, *J* = 7.0 Hz, 2 H), 2.22-2.05 (comp, 2 H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 198.9, 192.4, 162.1, 139.8, 134.7 (q, *J* = 37 Hz), 128.8, 126.1 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 274.5 Hz), 52.6, 39.6, 38.3, 18.9; IR (neat) 2134, 1721, 1673, 1654 cm^{-1}; HRMS (ESI) *m/z* 343.093 [$C_{14}H_{15}O_5$ (M+H) requires 343.90].



3h

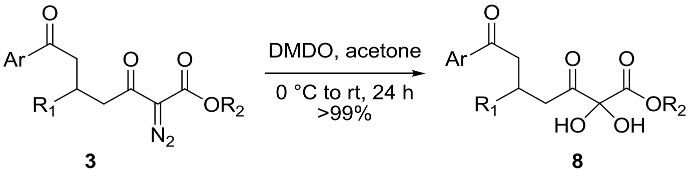
Benzyl 2-Diazo-3,7-dioxo-7-[4-(trifluoromethyl)phenyl]heptanoate (3h). Reaction between enone **19g** and benzyl 3-[(tert-butyldimethylsilyl)oxy]-2-diazobut-3-enoate[12] gave **3h** as a pale green solid in 73% yield: mp = 71-73 ºC; TLC R$_f$ = 0.25 (2:1 hexane/EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.09 (d, *J* = 8.1 Hz, 2 H), 7.75 (d, *J* = 8.3 Hz, 2 H), 7.46-7.33 (comp, 5 H), 5.29 (s, 2 H), 3.09 (t, *J* = 7.2 Hz, 2 H), 3.02 (t, *J* = 7.0 Hz, 2 H), 2.13 (quin, *J* = 7.1 Hz, 2 H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 198.89, 192.42, 161.57, 139.85, 135.49, 134.69 (q, *J* = 33 Hz), 129.16, 129.11, 128.93, 128.79, 126.05 (q, *J* = 4Hz), 124.00 (q, *J* = 277 Hz), 67.42, 39.70, 38.37, 18.91.; IR (neat) 2134, 1716, 1673, 1658 cm^{-1}; HRMS (ESI) *m/z* 419.123 [$C_{14}H_{15}O_5$ (M+H) requires 419.121].



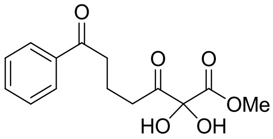
3i

Methyl 2-Diazo-3,7-dioxo-5,7-diphenylheptanoate (3i). Reaction between *trans*-chalcone and enoldiazoacetate **1** gave **3i** as a colorless solid in 89% yield: TLC R_f = 0.25 (2:1 hexane/EtOAc); spectral data were in accord with the literature.[2b]

2.4.3 General Procedure for the Synthesis of Functionalized 2,3,7-Triketoesters

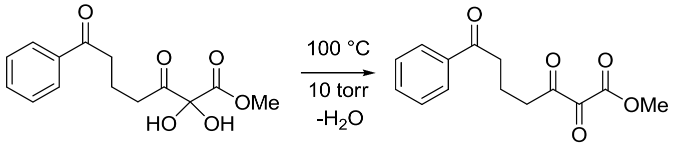


A 0.06 M solution of DMDO (20 mL, 1.3 eq) in acetone was added in one portion to a solution of α-diazo-β-ketoester **3** (0.2 mmol, 1 eq) in acetone (1 mL) under a nitrogen atmosphere at 0 °C. After 15 min, the reaction solution was warmed to room temperature and stirred overnight. This solution was concentrated under reduced pressure to provide **8** as its monohydrate, which was used without further purification.



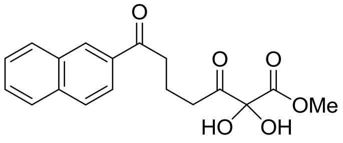
8a

Methyl 2,3,7-Trioxo-7-phenylheptanoate Hydrate (8a). Reaction between **3a** and DMDO gave **8a** as a white amorphous solid in 99 % yield: mp = 55-57 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.48 (comp, 5 H), 4.98 (br, 2 H), 3.83 (s, 3 H), 3.07 (t, *J* = 6.9 Hz, 1 H), 2.79 (t, *J* = 6.9 Hz, 1 H), 2.15 (quin, *J* = 6.9 Hz, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.4, 199.7, 169.8, 137.0, 133.7, 129.1, 128.4, 92.8, 54.3, 37.2, 35.2, 18.2; IR (neat) 3410, 1721, 1719, 1684 cm^{-1}; HRMS (ESI) *m/z* 263.107 [$C_{14}H_{15}O_5$ (M+H) requires 263.109].



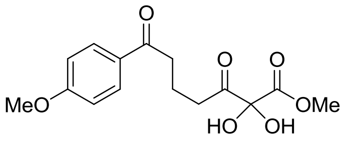
8a (hydrate) **8a**

Methyl 2,3,7-Trioxo-7-phenylheptanoate (8a). Dehydration of **8** was performed by heating hydrate at 100 ºC under high vacuum for 2 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-7.42 (m, 5 H), 3.95 (s, 3 H), 3.10 (t, *J* = 6.9 Hz, 2 H), 2.99 (t, *J* = 7.0 Hz, 2 H), 2.15 (quin, *J* = 7.0 Hz, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.4, 197.7, 182.3, 162.6, 137.0, 133.6, 129.0, 128.4, 53.6, 37.3, 36.6, 17.3.



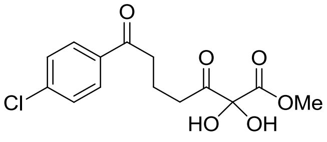
8b

Methyl 7-(Naphthalen-2-yl)-2,3,7-trioxoheptanoate Hydrate (8b). Reaction between **3b** and DMDO gave **8b** as a white amorphous solid in 99 % yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 8.07-7.58 (comp, 6 H), 4.99 (br, 2 H), 3.82 (s, 3 H), 3.19 (t, *J* = 6.9 Hz, 2 H), 2.82 (t, *J* = 6.9 Hz, 2 H), 2.18 (quin, *J* = 6.9 Hz, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.4, 199.6, 169.7, 136.0, 134.3, 132.9, 130.1, 129.9, 129.0, 128.9, 128.2, 127.2, 124.1, 92.7, 54.2, 37.2, 35.3, 18.2; IR (neat) 3431, 1720, 1682, 1626, 1594 cm^{-1}; HRMS (ESI) *m/z* 313.105 [$C_{14}H_{15}O_5$ (M+H) requires 313.107].



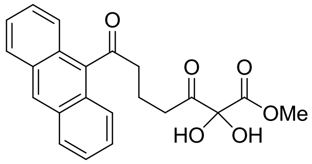
8c

Methyl 7-(4-Methoxyphenyl)-2,3,7-trioxoheptanoate Hydrate (8c). Reaction between **3c** and DMDO provided **8c** as a white solid in 99 % yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 2 H), 6.94 (d, *J* = 8.2 Hz, 2 H), 5.07 (br, 2 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 2.99 (t, *J* = 6.9 Hz, 2 H), 2.76 (t, *J* = 6.9 Hz, 2 H), 2.12 (quin, *J* = 6.9 Hz, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.5, 198.3, 169.7, 163.8, 130.6, 130.0, 114.1, 92.8, 55.8, 54.2, 36.8, 35.3, 18.3; IR (neat) 3354, 1732, 1667, 1596 cm^{-1}; HRMS (ESI) *m/z* 293.102 [$C_{14}H_{15}O_5$ (M+H) requires 293.102].



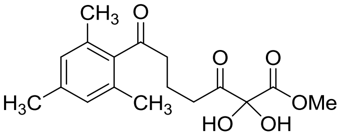
8d

Methyl 7-(4-Chlorophenyl)-2,3,7-trioxoheptanoate Hydrate (8d). Reaction between **3d** and DMDO gave **8d** as a white amorphous solid in 99 % yield: mp = 56-58 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.6 Hz, 2 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 4.97 (br, 2 H), 3.83 (s, 3 H), 3.01 (t, *J* = 6.9 Hz, 2 H), 2.76 (t, *J* = 6.9 Hz, 2 H), 2.14 (quin, *J* = 6.9 Hz, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.9, 198.3, 169.8, 140.0, 135.4, 129.8, 129.3, 92.7, 54.3, 37.2, 35.1, 18.0; IR (neat) 3434, 1739, 1715, 1682 1590 cm^{-1}; HRMS (ESI) *m/z* 297.054 [$C_{14}H_{15}O_5$ (M+H) requires 297.053].



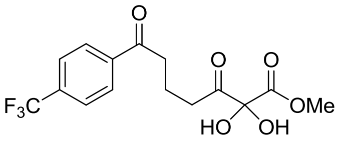
8e

Methyl 7-(Anthracen-9-yl)-2,3,7-trioxoheptanoate Hydrate (8e). Reaction between **3e** and DMDO gave **8e** as a white amorphous solid in 99 % yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1 H), 8.07 (dd, *J* = 8.3, 1.4 Hz, 2 H), 7.77 (dd, *J* = 5.2, 4.5 Hz, 2 H), 7.60-7.49 (comp, 4 H), 4.96 (br, 2 H), 3.88 (s, 3 H), 3.14 (t, *J* = 7.1 Hz, 2 H), 2.91 (t, *J* = 7.0 Hz, 2 H), 2.30 (quin, *J* = 7.0 Hz, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.9, 203.0, 169.7, 136.4, 131.4, 129.2, 128.7, 127.3, 125.9, 124.5, 119.9, 92.7, 54.3, 45.0, 35.1, 17.9; IR (neat) 3431, 1724, 1720, 1676, 1591 cm^{-1}; HRMS (ESI) *m/z* 363.125 [$C_{14}H_{15}O_5$ (M+H) requires 363.123].



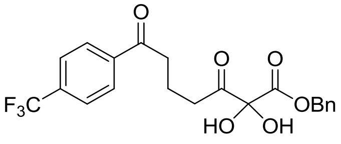
8f

Methyl 2,3,7-Trioxo-7-(2,4,6-trimethylphenyl)heptanoate Hydrate (8f). Reaction between **3f** and DMDO gave **8f** as a white solid in 99 % yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 2 H), 4.94 (br, 2 H), 3.88 (s, 3 H), 2.79-2.74 (comp, 4 H), 2.28 (s, 3 H), 2.18 (s, 6 H), 2.13-2.02 (comp, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.3, 203.2, 169.8, 139.7, 138.8, 132.8, 128.9, 92.7, 54.3, 43.4, 35.9, 21.4, 19.4, 17.6; IR (neat) 3421, 1733, 1693, 1611 cm^{-1}; HRMS (ESI) *m/z* 305.137 [$C_{14}H_{15}O_5$ (M+H) requires 305.138].



8g

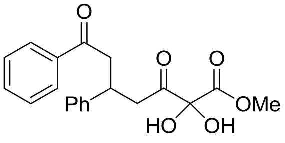
Methyl 2,3,7-Trioxo-7-[4-(trifluoromethyl)phenyl]heptanoate Hydrate (8g). Reaction between **3g** and DMDO gave **8g** as a white amorphous solid in 99 % yield: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.07 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 4.97 (br, 2H), 3.86 (s, 3H), 3.09 (t, *J* = 6.9 Hz, 2H), 2.79 (t, *J* = 6.9 Hz, 2H), 2.16 (quin, *J* = 6.9 Hz, 2H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 203.3, 198.6, 169.7, 139.6, 134.9 (q, *J* = 30 Hz), 128.7, 126.1 (q, *J* = 4 Hz), 123.9 (q, *J* = 270 Hz), 92.7, 54.3, 37.5, 35.0, 18.0; IR (neat) 3456, 3373, 1742, 1715, 1686 cm^{-1}; HRMS (ESI) *m/z* 331.081 [$C_{14}H_{15}O_5$ (M+H) requires 331.079].



8h

Benzyl 2,3,7-Trioxo-7-[4-(trifluoromethyl)phenyl]heptanoate Hydrate (8h). Reaction between **3h** and DMDO gave **8h** as a white amorphous solid in 99 % yield: mp = 59-61°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.39-7.33 (m, 5H), 5.29 (s, 2H), 4.98 (br, 2H), 2.95 (t, *J* = 7.0 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H), 2.09-2.03 (comp, 2H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 203.2, 198.5, 169.3, 139.6,134.9 (q, *J* = 36 Hz) 134.4, 129.3, 129.1, 128.8, 128.7, 126.1 (q, *J* = 4 Hz), 123.9 (q, *J* = 276 Hz), 92.8, 69.1, 37.5, 35.0, 17.9; IR (neat)

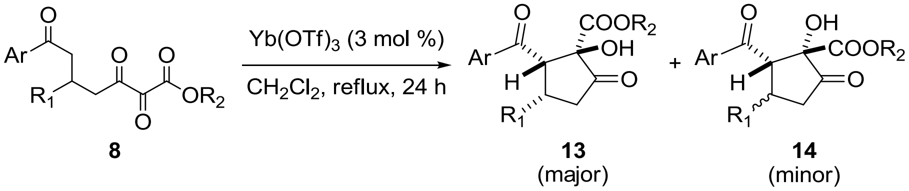
3432, 1730, 1690 cm^{-1}; HRMS (ESI) *m/z* 407.111 [$C_{14}H_{15}O_5$ (M+H) requires 407.110].



8i

Methyl 2,3,7-Trioxo-5,7-diphenylheptanoate Hydrate (8i). Reaction between **3i** and DMDO gave **8i** as a white amorphous solid in 99 % yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.15 (comp, 10 H), 4.96 (d, *J* = 12.1 Hz, 2 H), 4.10-3.94 (m, 1 H), 3.73 (s, 3 H), 3.38 (d, *J* = 7.0 Hz, 2 H), 3.18-3.00 (comp, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 202.2, 198.7, 169.7, 143.5, 137.1, 133.7, 129.0, 129.0, 128.4, 127.7, 127.3, 93.1, 54.2, 44.7, 42.4, 36.5; IR (neat) 3400, 1725, 1665, 1597cm^{-1}; HRMS (ESI) *m/z* 339.121 [$C_{14}H_{15}O_5$ (M+H) requires 339.123].

2.4.4 Method A: General Procedure for the Lewis Acid Catalyzed Synthesis of 1,2-*anti* Cyclopetanones 13



A solution of tricarbonyl compound **8** (0.2 mmol, 1 eq) and $Yb(OTf)_3$ (12 mg, 0.020 mmol, 0.10 eq) in CH_2Cl_2 (1 mL) was refluxed for 24 h under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure; and the residue was purified by flash chromatography (SiO_2), eluting with hexanes/ethyl acetate (ratio indicated below) to provide **13** and **14** as a mixture of diastereomers. The major isomer was purified by recrystallization from CH_2Cl_2/hexanes unless stated otherwise.

Determination of Percent Conversion and Diastereomeric Ratio of Cyclopentanones 13a and 14a. Reaction between **8a** and acid catalysts gave **13a** and **14a** as the only products observed by ^{1}H NMR spectral analysis of the reaction mixture. The methoxy proton of **8a** has a chemical shift of 3.83 ppm and the methoxy protons of *anti*-**13a** and *syn*-**14a** have chemical shift values of 3.85 ppm and 3.86 ppm, respectively. Percent conversion was determined by the relative integration of the methoxy protons of **8a**, **13a,** and **14a**. The diastereomeric ratios were determined by relative integration of the proton alpha to the aryl ketone unit of **13a** and **14a** located at 4.22 ppm and 4.54 ppm, respectively. The diastereomeric ratios of the other substrates were determined analogously to this method.

Interconversion Experiments of 13a and 14a. A solution of **13a** (26 mg, 0.1 mmol) and $Yb(OTf)_3$ (6 mg, 0.01 mmol) in CH_2Cl_2 (1 ml) was refluxed for 24 h. The reaction was cooled to room temperature, and the catalyst was removed by passing the mixture through a short pad of silica and rinsed with ethyl acetate (3 ml). The filtrate and washing were concentrated and the crude residue analyzed by ^{1}H NMR spectroscopy. Only **13a** was observed in the ^{1}H NMR spectrum of the reaction mixture.

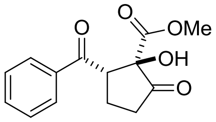
A solution of **13a** (26 mg, 0.1 mmol) and mesitylsulfonic acid dihydrate (7 mg, 0.03 mmol) in CH_2Cl_2 (1 ml) was refluxed for 24 h. The reaction was concentrated, and the residue was analyzed by ^1H NMR spectroscopy. Only **13a** and mesitylsulfonic acid were observed in the ^1H NMR spectrum of the reaction mixture.

A solution of **14a** (26 mg, 0.1 mmol) and $Yb(OTf)_3$ (6 mg, 0.01 mmol) in CH_2Cl_2 (1 ml) was refluxed for 24 h. The reaction was cooled to room temperature, and the catalyst was removed by passing the mixture through a short pad of silica, and rinsed with ethyl acetate (3 ml). The filtrate and washings were concentrated and analyzed by ^1H NMR spectroscopy. Only **14a** was observed based on the ^1H NMR spectrum of the reaction mixture.

A solution of **14a** (26 mg, 0.10 mmol) and mesitylsulfonic acid dihydrate (7 mg, 0.03 mmol) in CH_2Cl_2 (1 ml) was refluxed for 24 h. The reaction was concentrated, and the residue was analyzed by ^1H NMR spectroscopy. Only **14a** and mesitylsulfonic acid were observed in the ^1H NMR spectrum of the reaction mixture.

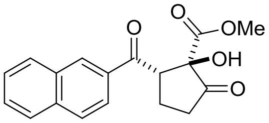
A solution of **13a** (26 mg, 0.1 mmol), mesitylsulfonic acid dihydrate (7 mg, 0.03 mmol) and $CDCl_3$ (0.7 ml) in a NMR tube was heated to 55 ºC in an oil bath for 7 days. Analysis of the reaction mixture by ^1H NMR spectroscopy showed a mixture (67:33) of **13a** and **14a** along with >30% of an unidentified by-product.

A solution of **14a** (26 mg, 0.1 mmol), mesitylsulfonic acid dihydrate (7 mg, 0.03 mmol) and $CDCl_3$ (0.7 ml) in a NMR tube was heated to 55 ºC in an oil bath for 7 days. Analysis of the reaction mixture by ^{1}H NMR spectroscopy showed a mixture (67:33) of **13a** and **14a** along with >30% of an unidentified by-product.



13a

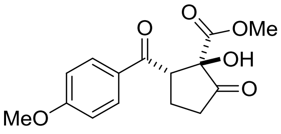
Methyl *anti*-2-Benzoyl-1-hydroxy-5-oxocyclopentane-1-carboxylate (13a). Reaction between **8a** and $Yb(OTf)_3$ gave **13a** (major isomer) and **14a** (minor isomer) as a mixture (95:5) of diastereomers in 98% yield. Pure **13a** was isolated as a colorless crystalline material in 69 % yield after recrystallization from CH_2Cl_2/hexanes (1:1): mp = 159-160 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-7.43 (comp, 5 H), 4.22 (dd, *J* = 12.0, 8.0 Hz, 1H), 4.03 (s, 1 H), 3.85 (s, 3 H), 2.89-2.74 (m, 1 H), 2.70-2.38 (comp, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.0, 197.5, 170.9, 136.1, 134.2, 129.2, 129.0, 82.2, 55.5, 53.9, 35.9, 22.5; IR (neat) 3466, 1764, 1721, 1676, 1596, 1578 cm^{-1}; HRMS (ESI) *m/z* 263.0941 [$C_{14}H_{15}O_5$ (M+H) requires 263.0919].



13b

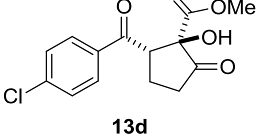
Methyl *anti*-2-(2-Naphthoyl)-1-hydroxy-5-oxocyclopentane-1-carboxylate (13b). Reaction between **8b** and $Yb(OTf)_3$ gave **13b** (major isomer) and **14b** (minor isomer) as a mixture (95:5) of diastereomers in 92 % yield. Pure **13b** was isolated as colorless crystals in 65 % yield by recrystallization from CH_2Cl_2/hexanes (1:1): mp

= 207-211 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1 H), 8.11-7.53 (comp, 6 H), 4.39 (dd, *J* = 11.9, 7.9 Hz, 1 H), 4.07 (s, OH, 1 H), 3.86 (s, 3 H), 2.88-280 (m, 1 H), 2.77-2.41 (comp, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.1, 197.6, 171.0, 136.2, 133.4, 132.8, 131.2, 130.1, 129.3, 129.1, 128.2, 127.4, 124.3, 82.4, 55.5, 53.9, 36.0, 22.6; IR (neat) 3468, 1758, 1723, 1671, 1626, 1596 cm^{-1}; HRMS (ESI) *m/z* 313.1089 [$C_{18}H_{17}O_5$ (M+H) requires 313.1076].



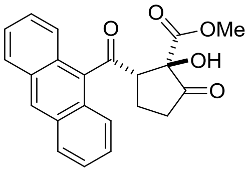
13c

Methyl *anti*-2-(4-Methoxybenzoyl)-1-hydroxy-5-oxocyclopentane-1-carboxyl-ate (13c). Reaction between **8c** and Yb(OTf)$_3$ gave **13c** (major isomer) and **14c** (minor isomer) as a mixture (93:7) of diastereomers in 94 % yield. Pure **13c** was isolated as a colorless crystalline material in 71 % yield by recrystallization from CH_2Cl_2/hexanes (1:1): mp = 155-157 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-7.92 (d, *J* = 8.9 Hz, 2 H), 6.96 (d, *J* = 8.9 Hz, 2 H), 4.17 (dd, *J* = 12.0, 7.7 Hz, 1 H), 4.01 (s, OH, 1 H), 3.89 (s, 3 H), 3.83 (s, 3 H), 2.86 – 2.74 (m, 1 H), 2.33-2.60 (comp, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.3, 195.9, 171.2, 164.5, 131.4, 129.1, 114.4, 82.4, 55.9, 55.2, 53.9, 36.0, 22.5; IR (neat) 3481, 1758, 1715, 1667 cm^{-1}; HRMS (ESI) *m/z* 293.1047 [$C_{15}H_{17}O_6$ (M+H) requires 293.1025].



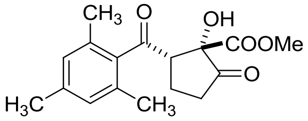
13d

Methyl *anti*-2-(4-Chlorobenzoyl)-1-hydroxy-5-oxocyclopentane-1-carboxylate (13d). Reaction between **8d** and Yb(OTf)$_3$ gave **13d** (major isomer) and **14d** (minor isomer) as a mixture (95:5) of diastereomers in 96% yield. Pure **13d** was isolated in 69 % yield by recrystallization from CH_2Cl_2/hexanes (1:1): mp = 176-178 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.87 (d, *J* = 8.5 Hz, 2 H), 7.54-7.41 (d, *J* = 8.5 Hz, 2 H), 4.15 (dd, *J* = 11.9, 7.7 Hz, 1 H), 4.03 (s, OH, 1 H), 3.82 (s, 3 H), 2.90 – 2.72 (m, 1 H), 2.69 – 2.28 (comp, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.8, 196.5, 170.8, 140.8, 134.4, 130.5, 129.5, 82.2, 55.3, 53.9, 35.8, 22.2; IR (neat) 3478, 1763, 1722, 1680, 1586, 1568 cm^{-1}; HRMS (ESI) *m/z* 297.0557 [$C_{14}H_{14}ClO_5$ (M+H) requires 297.0530].



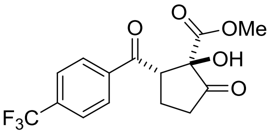
13e

Methyl *anti*-2-(Anthracene-9-carbonyl)-1-hydroxy-5-oxocyclopentane-1-carboxylate (13e). Reaction between **8e** and Yb(OTf)$_3$ gave **13e** (major isomer) and **14e** (minor isomer) as a mixture (57:43) of diastereomers in 70 % yield. Pure **13e** was isolated in 12 % yield by recrystallization from CH_2Cl_2/hexanes (1:1): mp = 189-192 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1 H), 8.15-7.48 (comp, 8 H), 4.30 (s, OH, 1 H), 4.21 (dd, *J* = 12.8, 7.9 Hz, 1 H), 4.08 (s, 3 H), 2.33-2.72 (comp, 3 H), 1.97-1.90 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.9, 206.7, 170.9, 133.8, 131.3, 129.6, 129.3, 127.8, 127.6, 126.0, 124.6, 81.7, 62.4, 54.1, 35.9, 21.9; IR (neat) 3458, 1765, 1736, 1692, 1520 cm^{-1}; HRMS (ESI) *m/z* 363.1263 [$C_{22}H_{19}O_5$ (M+H) requires 363.1232].



14f

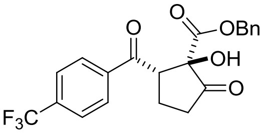
Methyl *syn*-1-Hydroxy-2-oxo-5-(2,4,6-trimethylbenzoyl)cyclopentane-1-carboxylate (14f). Reaction between **8f** and Sc(OTf)$_3$ gave **13f** (minor isomer) and **14f** (major isomer) as a mixture (30:70) of diastereomers determined by ^{1}H NMR spectroscopy from the reaction solution before purification. The major isomer **14f** was isolated by flash chromatography using hexane/ethylacetate (3:1) in 51% yield as a pale green crystalline material: mp = 150-152 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.86 (s, 2 H), 4.00 (dd, *J* = 10.4, 6.9 Hz, 1 H), 3.91 (s, OH, 1 H), 3.70 (s, 3 H), 2.77-2.65 (m, 1 H), 2.55-2.33 (comp, 2 H), 2.30 (s, 3 H), 2.27 (s, 6 H), 2.26-2.21 (m, 1 H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 209.0, 207.3, 170.8, 139.7, 137.3, 134.3, 129.3, 81.2, 57.3, 53.7, 35.5, 21.6, 21.4, 20.0; IR (neat) 3381, 1755, 1733, 1695, 1611, 1572 cm^{-1}; HRMS (ESI) *m/z* 305.1409 [$C_{17}H_{21}O_5$ (M+H) requires 305.1389].



13g

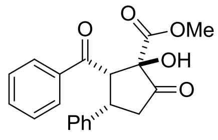
Methyl *anti*-1-Hydroxy-2-oxo-5-(4-(trifluoromethyl)benzoyl)cyclopentane-1-carboxylate (13g). Reaction between **8g** and Yb(OTf)$_3$ gave **13g** (major isomer) and

14g (minor isomer) as a mixture (94:6) of diastereomers in 96 % yield. Pure **13g** was isolated in 60 % yield by recrystallization from CH_2Cl_2/hexanes (1:1): mp = 128-130 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.1 Hz, 2 H), 7.79 (d, *J* = 8.1 Hz, 2 H), 4.21 (dd, *J* = 11.9, 7.6 Hz, 1 H), 4.05 (s, OH, 1H), 3.84 (s, 3 H), 2.91-2.77 (m, 1 H), 2.73-2.33 (comp, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.60, 197.36, 170.83, 139.07, 135.44 (q, *J* = 33 Hz), 129.48, 126.30 (q, *J* = 4 Hz), 123.88 (q, *J* = 268 Hz), 82.27, 55.54, 54.04, 35.80, 22.11. IR (neat) 3461, 1767, 1717, 1692, 1580, 1513 cm^{-1}; HRMS (ESI) *m/z* 331.0811 [$C_{15}H_{14}F_3O_5$ (M+H) requires 331.0793].



13h

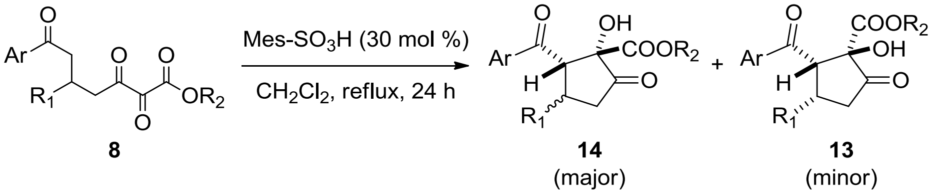
Benzyl *anti*-1-Hydroxy-2-oxo-5-(4-(trifluoromethyl)benzoyl)cyclopentane-1-carboxylate (13h). Reaction between **8h** and $Yb(OTf)_3$ gave **13h** (major isomer) as a colorless crystalline material in 92% isolated yield: mp = 91-93 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.1 Hz, 2 H), 7.76 (d, *J* = 8.1 Hz, 2 H), 7.43-7.30 (comp, 5 H), 5.30-5.19 (m, 2 H), 4.20 (dd, *J* = 12.0, 7.9 Hz, 1 H), 4.08 (s, OH, 1 H), 2.82-2.28 (comp, 4 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.57, 196.88, 170.01, 138.88, 135.37 (q, *J* = 32 Hz), 134.63, 129.46, 129.20, 129.12, 128.91, 126.24 (q, *J* = 4 Hz), 123.97 (q, *J* = 276 Hz), 82.23, 69.25, 55.58, 35.78, 22.09.; IR (neat) 3402, 1759, 1828, 1686, 1582, 1510 cm^{-1}; HRMS (ESI) *m/z* 407.1135 [$C_{21}H_{18}F_3O_5$ (M+H) requires 407.1106].



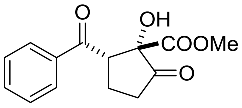
13i

Methyl *anti*-2-Benzoyl-1-hydroxy-5-oxo-3-phenylcyclopentane-1-carboxylate (13i). Reaction between **8i** and Yb(OTf)$_3$ gave **13i** as colorless crystals in 92 % yield as a mixture (93:7) of diastereomers. Pure **13i** was isolated in 49 % yield by recrystallization from CH_2Cl_2/hexanes (1:1): mp = 118-120 ºC. The stereochemistry of 13i was determined by x-ray crystallography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.10 (comp, 10 H), 4.63 (d, *J* = 6.8 Hz, 1 H), 4.38-4.20 (m, 1 H), 4.05 (s, OH, 1 H), 3.63-3.41 (comp, 4 H), 2.93-2.30 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.6, 198.0, 170.0, 137.9, 137.3, 133.1, 128.5, 128.4, 127.8, 127.6, 126.9, 83.2, 57.2, 53.0, 41.9, 39.2; IR (neat) 3496, 1754, 1743, 1676, 1596, 1500 cm^{-1}; HRMS (ESI) *m/z* 339.1254 [$C_{20}H_{19}O_5$ (M+H) requires 339.1232].

2.4.5 Method B: General Brønsted Acid Catalyzed Procedure for the Synthesis of 1,2-*syn* Cyclopetanones 14

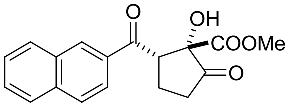


A mixture of 2,3,7-triketoester **8** (0.2 mmol, 1 eq) and mesitylsulfonic acid dihydrate (14 mg, .06 mmol. 0.3 eq) in CH_2Cl_2 (1 mL) was refluxed for 24 h under a nitrogen atmosphere. The reaction was concentrated, and the residue was purified by flash chromatography (SiO_2) eluting with hexanes and ethyl acetate to provide **13** and **14** as an inseparable mixture of diastereomers unless stated otherwise.



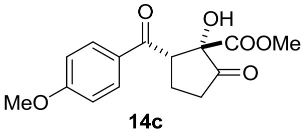
14a

Methyl *syn*-2-Benzoyl-1-hydroxy-5-oxocyclopentane-1-carboxylate (14a). Reaction between **8a** and Mes-SO_3H dihydrate gave **14a** (major isomer) and **13a** (minor isomer) as a mixture (75:25) of diastereomers in 81 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.47 (comp, 5H), 4.54 (t, *J* = 7.1 Hz, 1H), 4.09 (s, OH, 1H), 3.85 (s, 3H), 2.78 (dd, *J* = 9.1, 5.6 Hz, 1H), 2.42-2.65 (comp, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.8, 199.8, 171.0, 137.1, 134.2, 129.2, 128.7, 82.1, 53.8, 50.1, 34.9, 22.6.

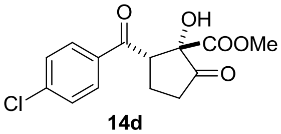


14b

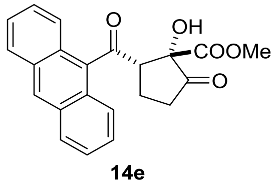
Methyl *syn*-2-(2-Naphthoyl)-1-hydroxy-5-oxocyclopentane-1-carboxylate (14b). Reaction between **8b** and Mes-SO_3H dihydrate gave **14b** (major isomer) and **13b** (minor isomer) as a mixture (61:39) of diastereomers in 80 % yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 7.99 – 7.87 (comp, 4 H), 7.66 – 7.54 (comp, 2 H), 4.68 (t, *J* = 7.1 Hz, 1 H), 4.11 (s, OH, 1 H), 3.83 (s, 3 H), 2.85 – 2.75 (m, 1 H), 2.69 – 2.37 (comp, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.82, 199.78, 171.04, 136.08, 134.33, 132.78, 130.66, 129.99, 129.40, 129.22, 128.33, 127.53, 124.11, 82.11, 53.98, 50.11, 34.94, 22.74.


14c

Methyl *syn*-2-(4-Methoxybenzoyl)-1-hydroxy-5-oxocyclopentane-1-carboxyl-ate (14c). Reaction between **8c** and Mes-SO_3H dihydrate gave **14c** (major isomer) and **13c** (minor isomer) as a mixture (60:40) of diastereomers in 67% isolated yield: ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.0 Hz, 2 H), 6.96 (d, *J* = 9.0 Hz, 2 H), 4.45 (t, *J* = 7.2 Hz, 1 H), 4.34 (s, OH, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 2.80-2.72 (m, 1 H), 2.56-2.40 (comp, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.54, 198.67, 170.98, 164.63, 131.26, 129.68, 114.46, 82.38, 56.00, 53.83, 49.44, 34.93, 23.09.

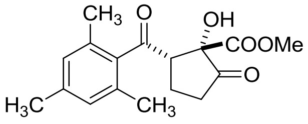

14d

Methyl *syn*-2-(4-Chlorobenzoyl)-1-hydroxy-5-oxocyclopentane-1-carboxylate (14d). Reaction between **8d** and Mes-SO_3H dihydrate gave **14d** (major isomer) and **13d** (minor isomer) as a mixture (75:25) of diastereomers in 75 % isolated yield: ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.6 Hz, 2 H), 7.45 (d, *J* = 8.6 Hz, 2 H), 4.46 (t, *J* = 6.9 Hz, 1 H), 3.90 (s, OH, 1 H), 3.84 (s, 3 H), 2.84 – 2.71 (m, 1 H), 2.68 - 2.31 (comp, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.70, 198.34, 170.72, 140.70, 135.47, 130.13, 129.49, 82.04, 54.01, 49.98, 34.81, 22.35.



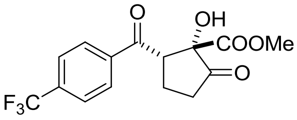
14e

Methyl *syn*-2-(Anthracene-9-carbonyl)-1-hydroxy-5-oxocyclopentane-1-carboxylate (14e). Reaction between **8e** and Mes-SO_3H dihydrate gave **14e** (major isomer) and **13e** (minor isomer) as a mixture (94:6) of diastereomers in 82 % isolated yield together with an inseparable impurity (see ^1H NMR spectrum): ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1 H), 8.05-7.93 (comp,4 H), 7.59 – 7.47 (comp, 4 H), 4.37 (dd, *J* = 10.0, 7.2 Hz, 1 H), 3.80 (s, OH, 1 H), 3.33 (s, 3 H), 2.74 – 2.65 (m, 1 H), 2.55 - 2.40 (m, 2 H), 2.32 – 2.24 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.06, 206.51, 170.38, 134.16, 131.31, 129.91, 129.20, 127.95, 127.43, 126.03, 124.97, 81.20, 58.99, 53.34, 35.55, 21.71.



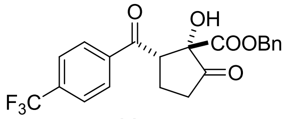
14f

Methyl *syn*-1-Hydroxy-2-oxo-5-(2,4,6-trimethylbenzoyl)cyclopentane-1-carboxylate (14f). Reaction between **8f** and Mes-SO_3H dihydrate gave **14f** as a single isomer in 61 % yield: mp = 150-152 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2 H), 4.00 (dd, *J* = 10.4, 6.9 Hz, 1 H), 3.91 (s, OH, 1 H), 3.70 (s, 3 H), 2.77-2.65 (m, 1 H), 2.55-2.33 (comp, 2 H), 2.30 (s, 3 H), 2.27 (s, 6 H), 2.26-2.21 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.0, 207.3, 170.8, 139.7, 137.3, 134.3, 129.3, 81.2, 57.3, 53.7, 35.5, 21.6, 21.4, 20.0; IR (neat) 3381, 1755, 1733, 1695, 1611, 1572 cm^{-1}; HRMS (ESI) *m/z* 305.1409 [$C_{17}H_{21}O_5$ (M+H) requires 305.1389].



14g

Methyl *syn*-1-Hydroxy-2-oxo-5-(4-(trifluoromethyl)benzoyl)cyclopentane-1-carboxylate (14g). Reaction between **8g** and Mes-SO_3H dihydrate gave **14g** (major isomer) and **13g** (minor isomer) as a mixture (75:25) of diastereomers in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.1 Hz, 2 H), 7.74 (d, *J* = 8.1 Hz, 2 H), 4.51 (t, *J* = 6.7 Hz, 1 H), 3.83 (s, 3 H), 3.79 (s, OH, 1 H), 2.79 – 2.73 (m, 1 H), 2.66 – 2.31 (comp, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.8, 198.5, 170.5, 140.2, 135.2 (*J* = 33 Hz), 128.9, 126.1 (*J* = 4 Hz), 123.9 (*J* = 271 Hz), 81.9, 54.1, 50.4, 34.7, 21.9.

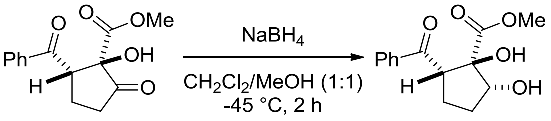


14h

Benzyl *syn*-1-Hydroxy-2-oxo-5-(4-(trifluoromethyl)benzoyl)cyclopentane-1-carboxylate (14h). Reaction between **8h** and Mes-SO_3H dihydrate gave **14h** (major isomer) in 60% yield as a colorless crystalline material and **13h** (minor isomer) 17% yield . These isomers were separated by flash chromatography with hexane/ethyl acetate (1:3) as the eluent: mp = 91-91 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.1 Hz, 2 H), 7.59 (d, *J* = 8.1 Hz, 2 H), 7.45 – 7.29 (m, 5 H), 5.24 (dd, *J* = 38.6, 12.0 Hz, 2 H), 4.47 (t, *J* = 6.9 Hz, 1 H), 3.75 (s, OH, 1 H), 2.78-2.74 (m, 1 H), 2.62 - 2.48

(m, 2 H), 2.37 – 2.23 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.81, 198.07, 170.25, 140.02, 135.00 (q, *J* = 34 Hz), 134.70, 129.45, 129.29, 129.02, 128.89, 126.11(q, *J* = 3.4 Hz), 123.95 (q, *J* = 271 Hz), 81.49, 69.02, 50.39, 35.05, 22.03. IR (neat) 3425, 1763, 1733, 1688 cm^{-1}; HRMS (ESI) *m/z* 407.1123 [$C_{21}H_{18}F_3O_5$ (M+H) requires 407.1106].

2.4.6 Procedure for Selective Reduction to 1,2-Diols

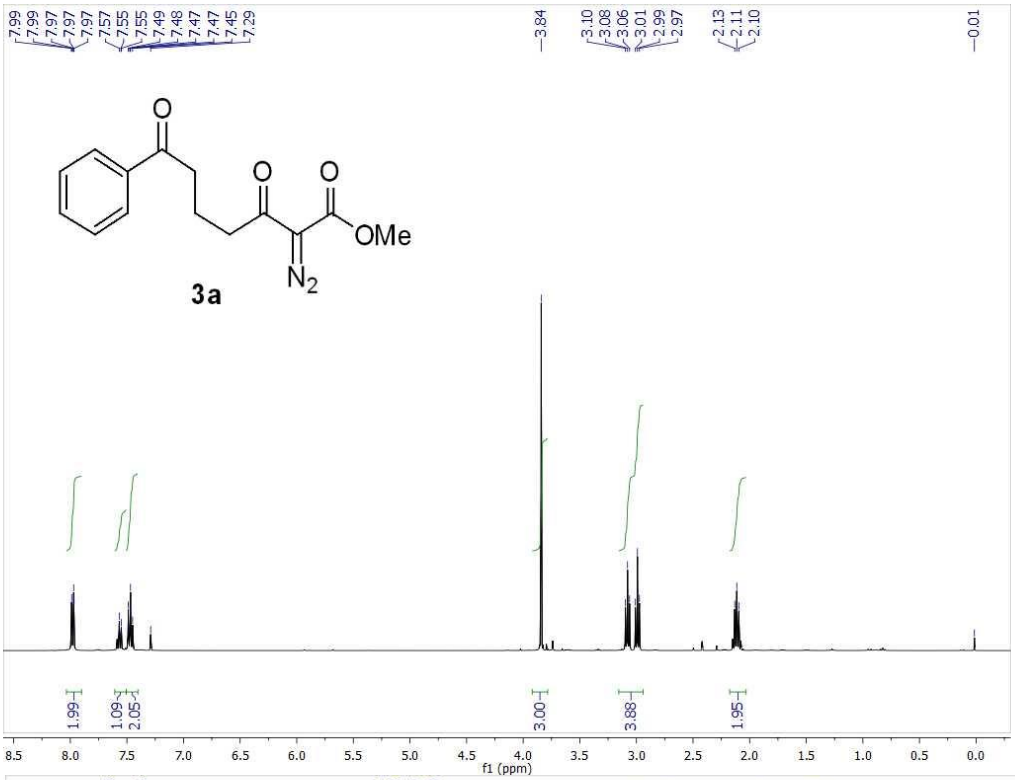


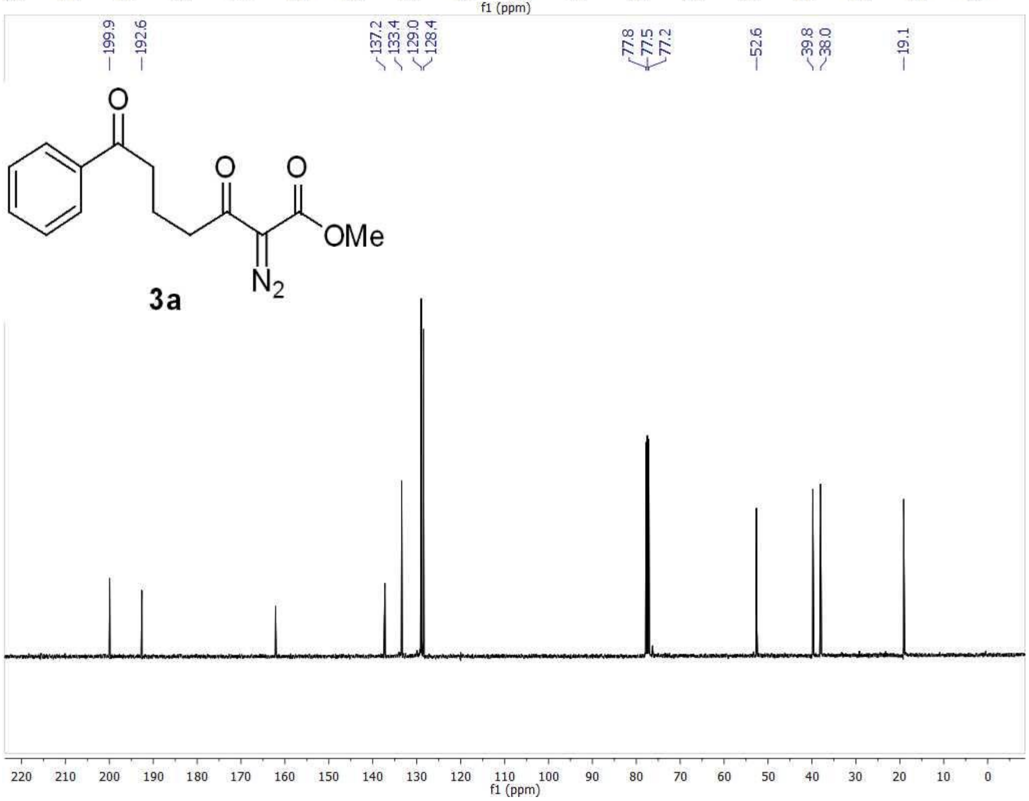
13a **18**

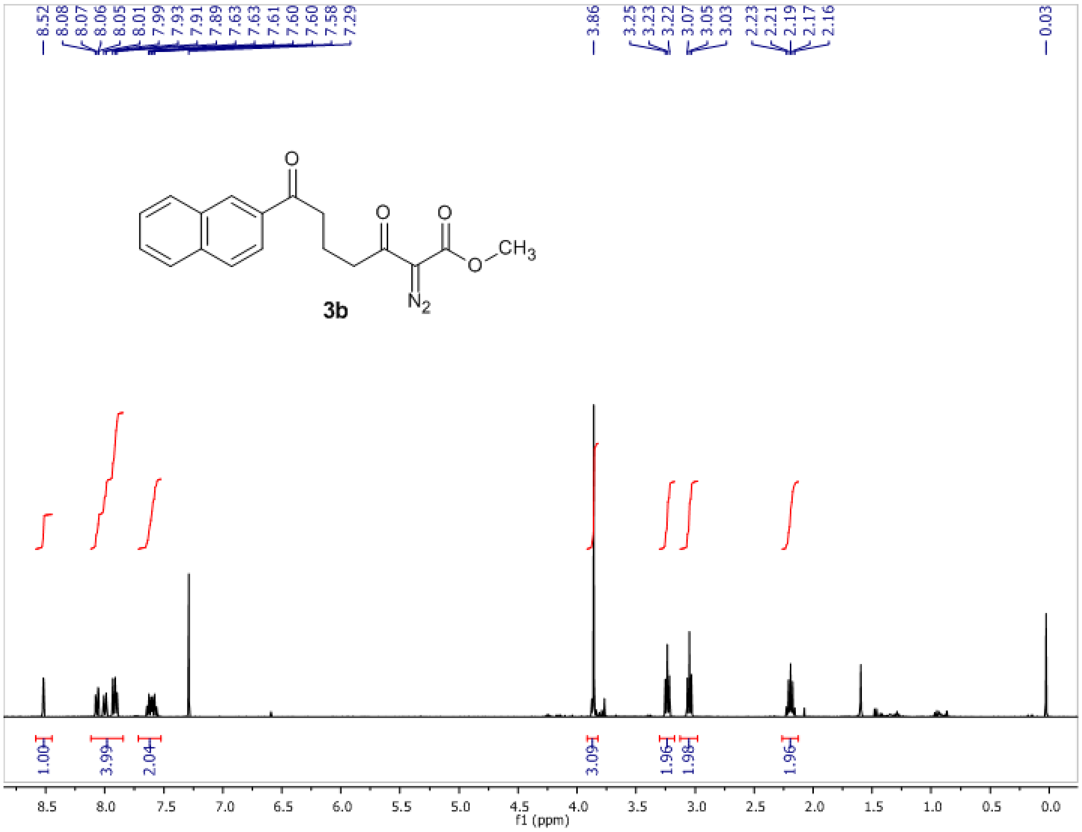
(±)-Methyl (1*R*,2*S*,5*R*)-2-benzoyl-1,5-dihydroxycyclopentane-1-carboxylate (18). A mixture of cyclopentanone **13a** (0.052g, 0.2 mmol) and $NaBH_4$ (0.030 g, 0.80 mmol) in MeOH:CH_2Cl_2 (1.5 mL, 1:1) was stirred for 2 h at -45 ºC. The reaction was quenched with 4 N HCl (2 mL) at -45 ºC, warmed to room temperature, and extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by recrystallization from CH_2Cl_2/hexane (1:1) to provide **18** in 85% yield as a colorless crystal. The stereochemistry of **18** was determined by x-ray crystallography: mp = 134-136 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.42 (comp, 5H), 4.40 - 4.37 (m, 1H), 3.99 (t, *J* = 9.9 Hz, 1H), 3.92 – 3.79 (comp, 4H), 2.48 (br, 1H), 2.29-2.21 (comp, 3H), 2.08 - 2.00 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.3, 174.2, 136.5, 133.7, 129.0, 128.9, 85.5, 80.4, 55.3, 53.3, 29.4, 24.7; IR (neat)

3476, 3412, 2964, 1717, 1684, 1596 cm^{-1}; HRMS (ESI) *m/z* 265.1086 [$C_{14}H_{17}O_5$ (M+H) requires 265.1076].

2.4.7 ^{1}H NMR and ^{13}C NMR Spectra






8.52
8.08
8.07
8.06
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7.93
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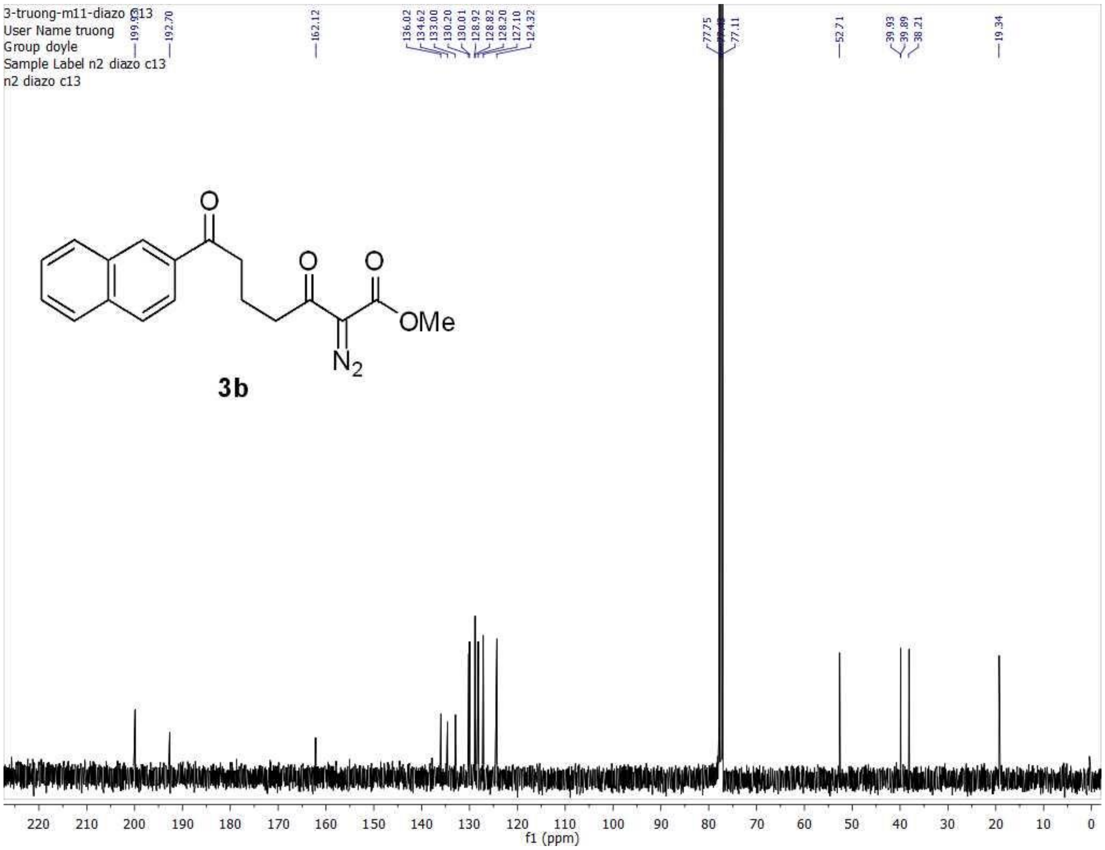
7.60
7.60
7.58
7.29
3.86
3.25
3.23
3.22
3.07
3.05
3.03
2.23
2.21
2.19
2.17
2.16
0.03
O
O
O
O
CH3
N2
3b
1.00
3.99
2.04
3.09
1.96
1.98
1.96
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


3-truong-m11-diazo C13
User Name truong
Group doyle
Sample Label n2 diazo c13
n2 diazo c13
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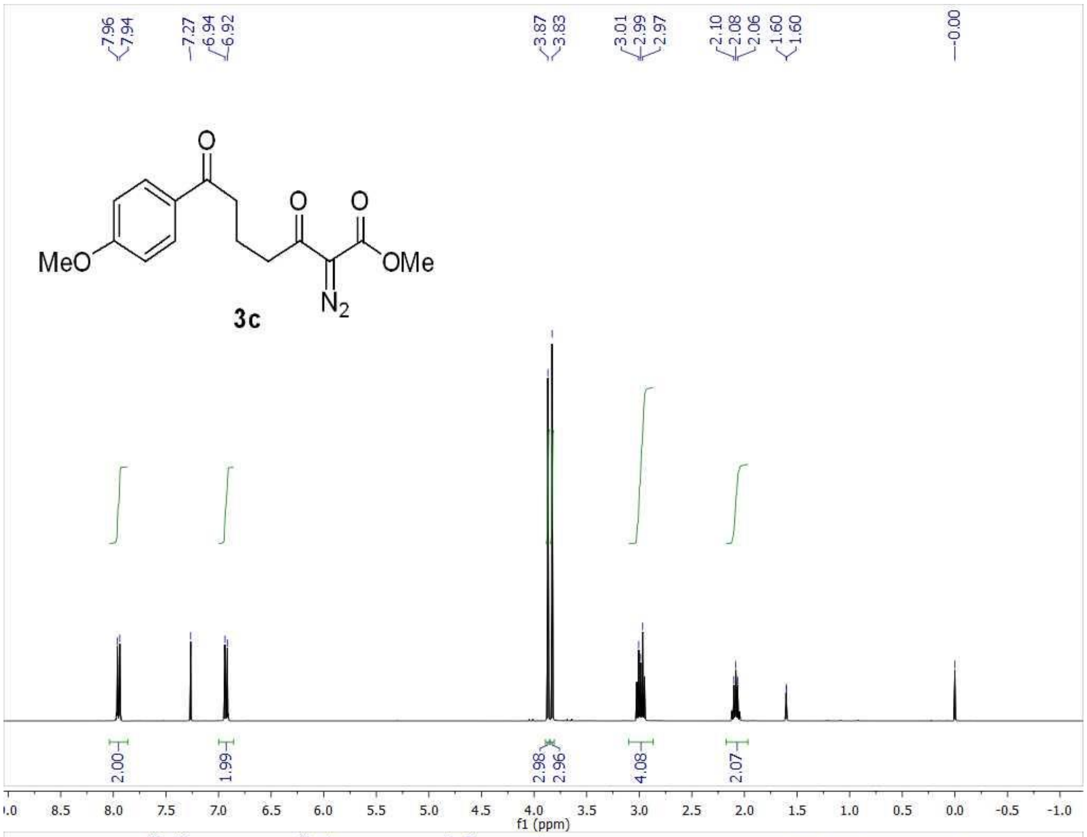
192.70
162.12
136.02
134.62
133.00
130.20
130.01
128.92
128.82
128.20
127.10
124.32
77.75
77.11
52.71
39.93
39.89
38.21
19.34
O
O
O
OMe
N2
3b
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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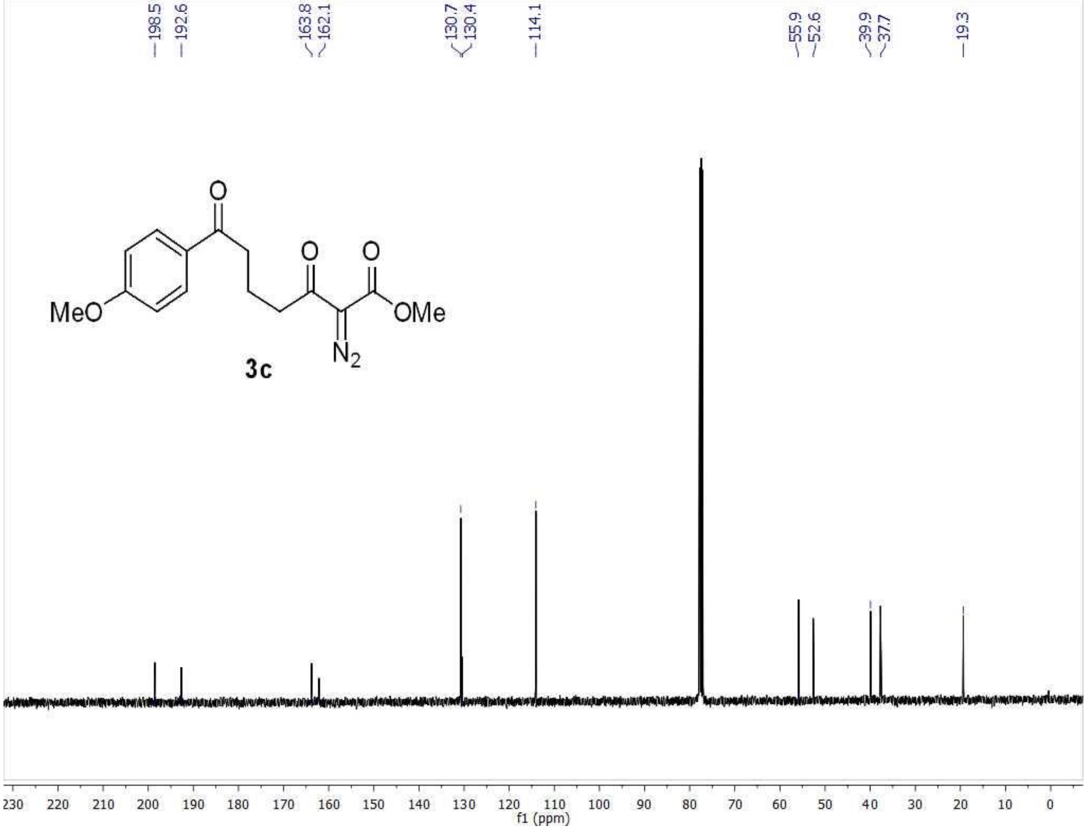
7.94
7.27
6.94
6.92
3.87
3.83
3.01
2.99
2.97
2.10
2.08
2.06
1.60
1.60
0.00
MeO
O
O
O
OMe
N2
3c
2.00
1.99
2.98
2.96
4.08
2.07
f1 (ppm)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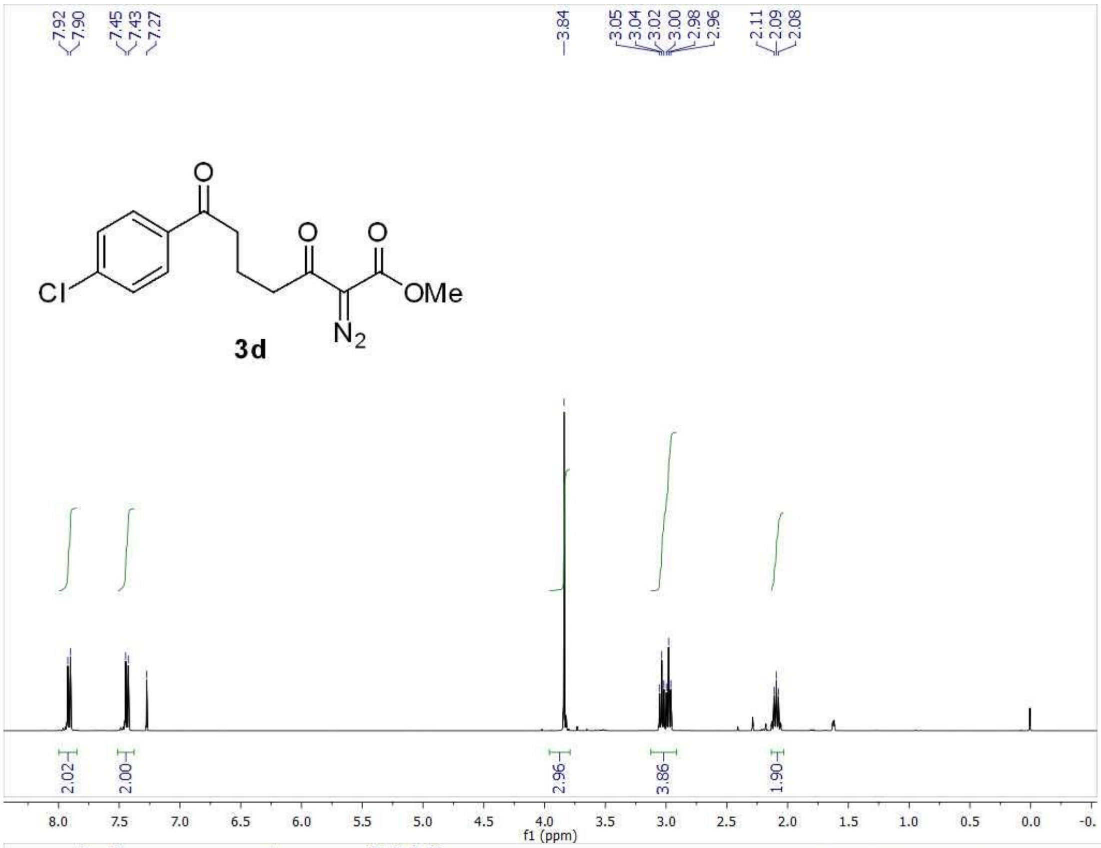
192.6
163.8
162.1
130.7
130.4
114.1
55.9
52.6
39.9
37.7
19.3
MeO
O
O
O
OMe
N2
3c
f1 (ppm)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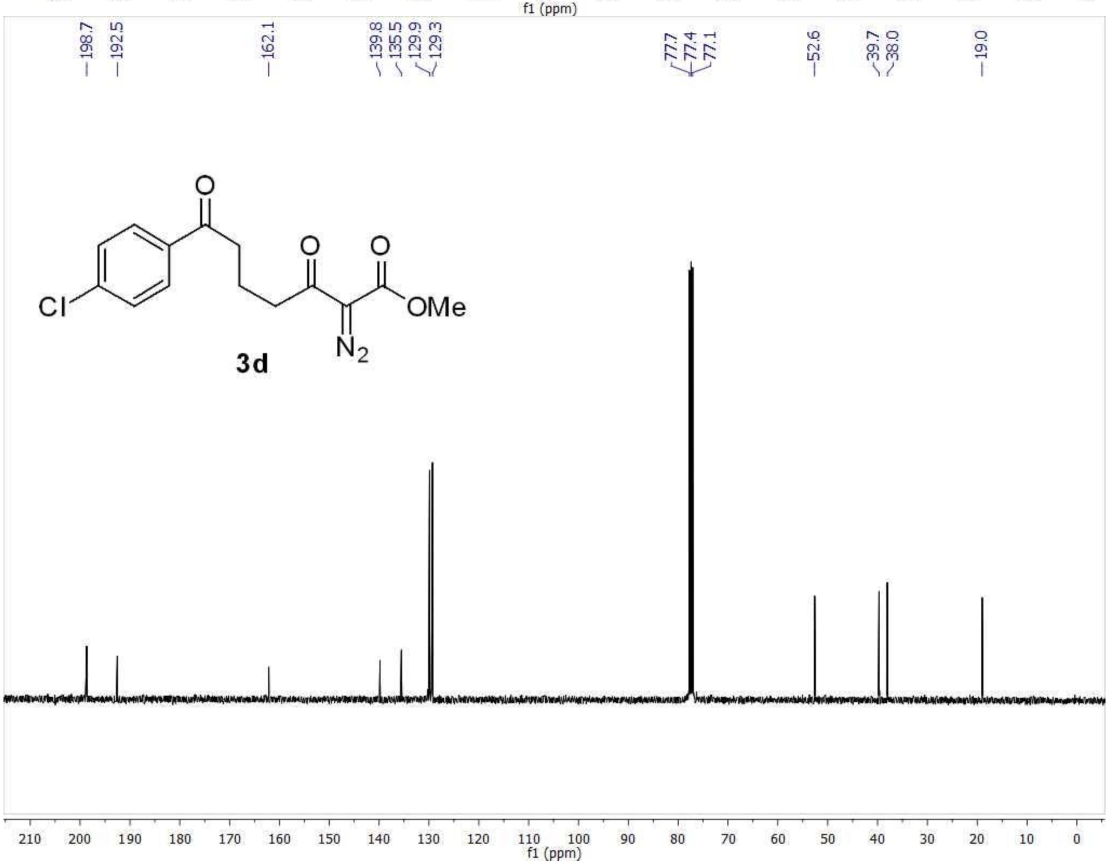
7.90
7.45
7.43
7.27
3.84
3.05
3.04
3.02
3.00
2.98
2.96
2.11
2.09
2.08
O
O
O
Cl
OMe
N2
3d
2.02
2.00
2.96
3.86
1.90
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
f1 (ppm)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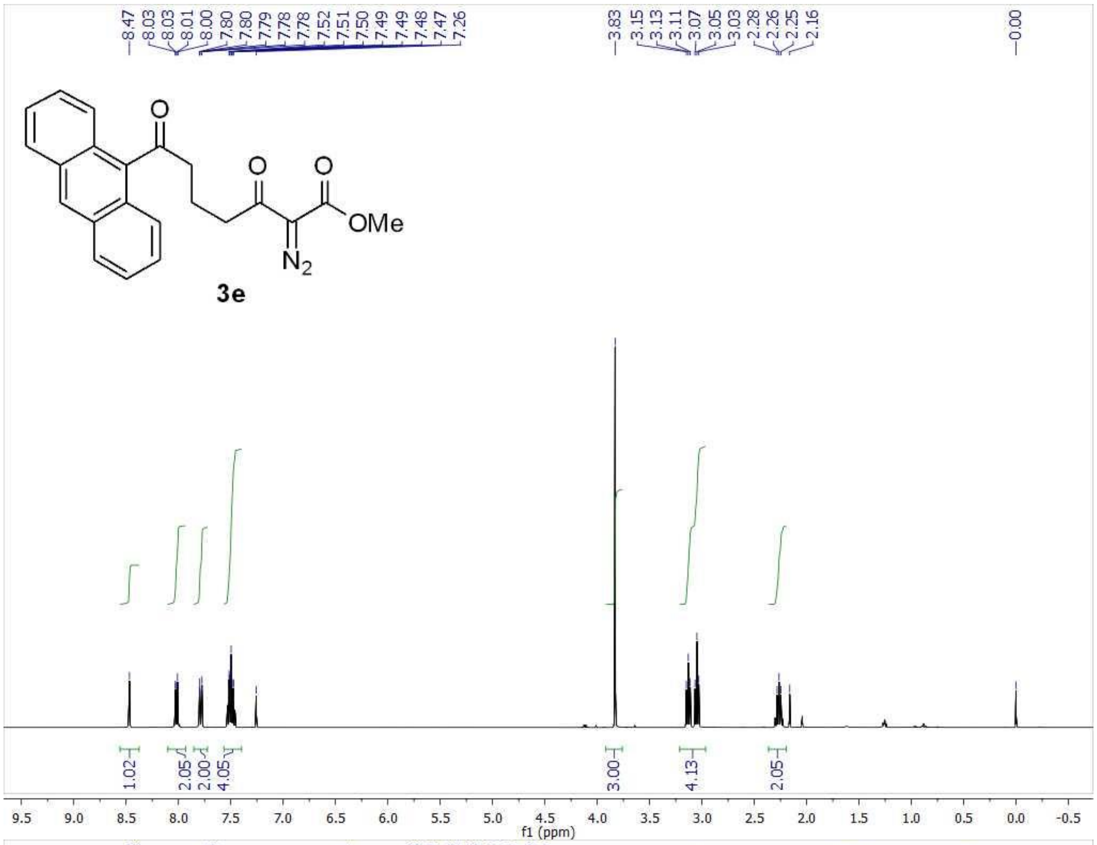
135.5
129.9
129.3
77.7
77.4
77.1
52.6
39.7
38.0
19.0
O
O
O
Cl
OMe
N2
3d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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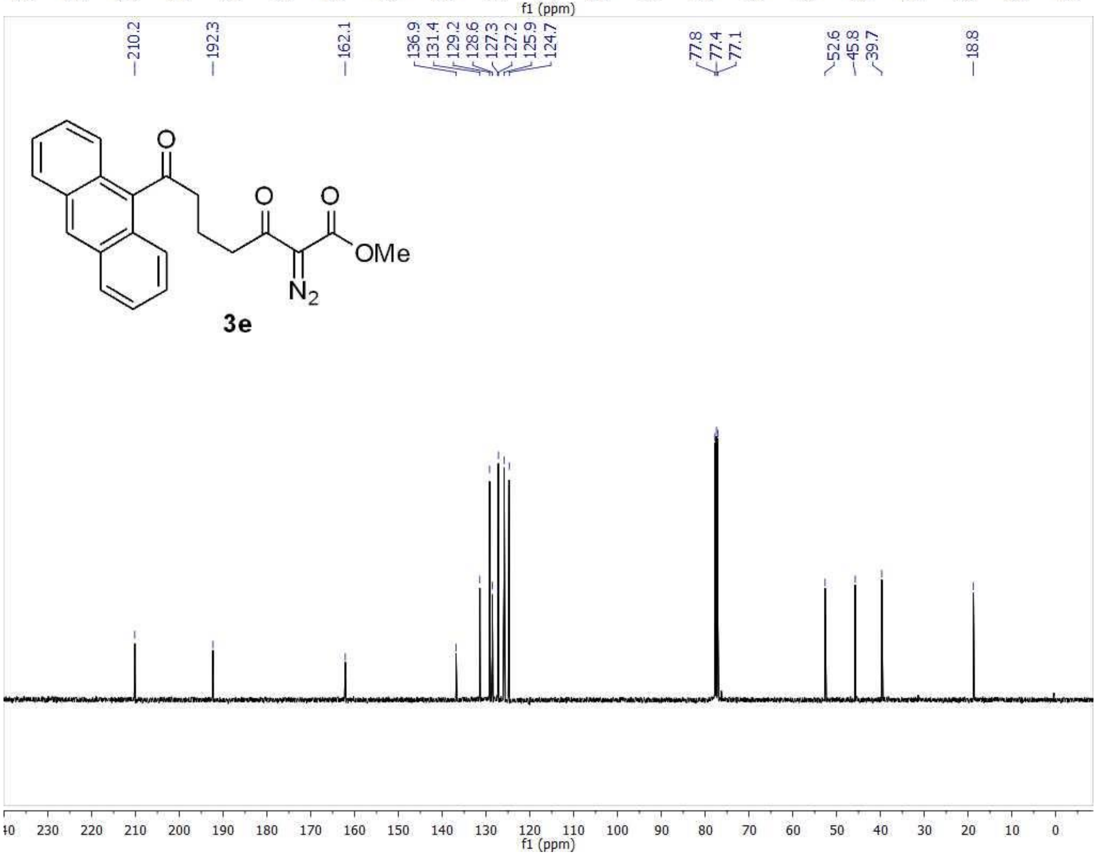
7.80
7.79
7.78
7.78
7.52
7.51
7.50
7.49
7.49
7.48
7.47
7.26
3.83
3.15
3.13
3.11
3.07
3.05
3.03
2.28
2.26
2.25
2.16
0.00
OMe
N_2
3e
1.02
2.05
2.00
4.05
3.00
4.13
2.05
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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192.3
162.1
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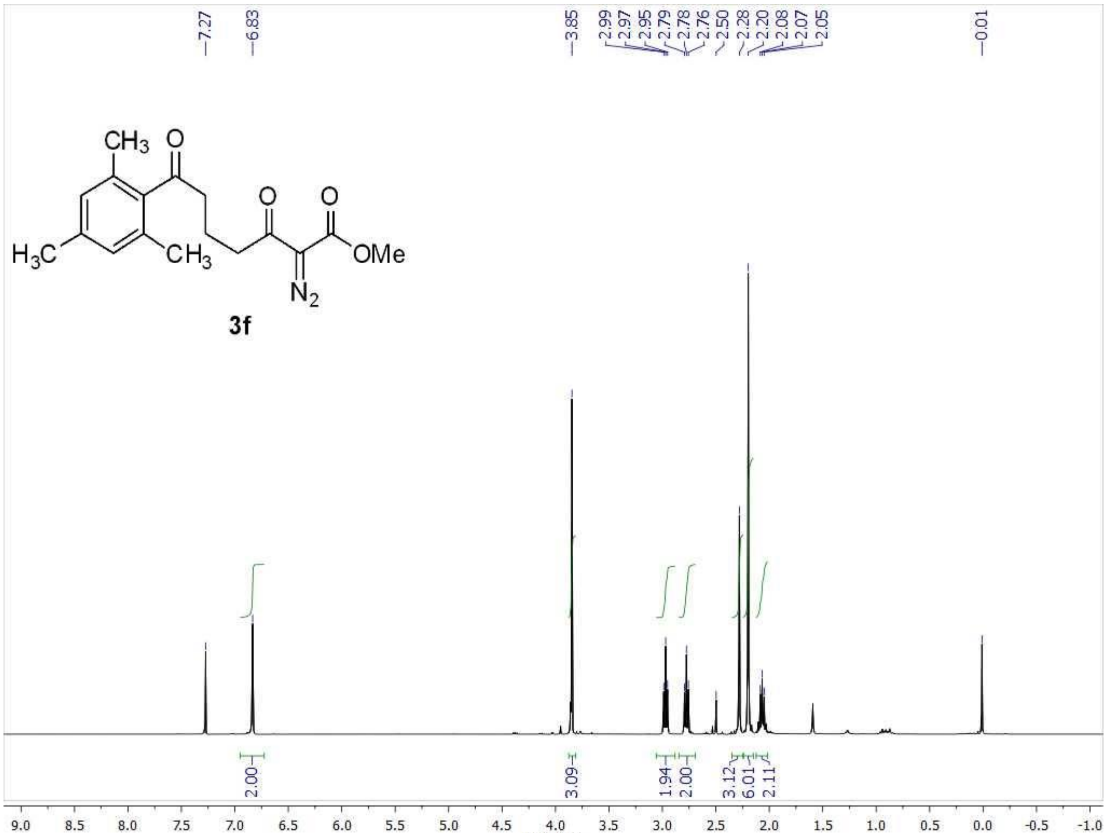
131.4
129.2
128.6
127.3
127.2
125.9
124.7
77.8
77.4
77.1
52.6
45.8
39.7
18.8
OMe
N_2
3e
40
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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6.83
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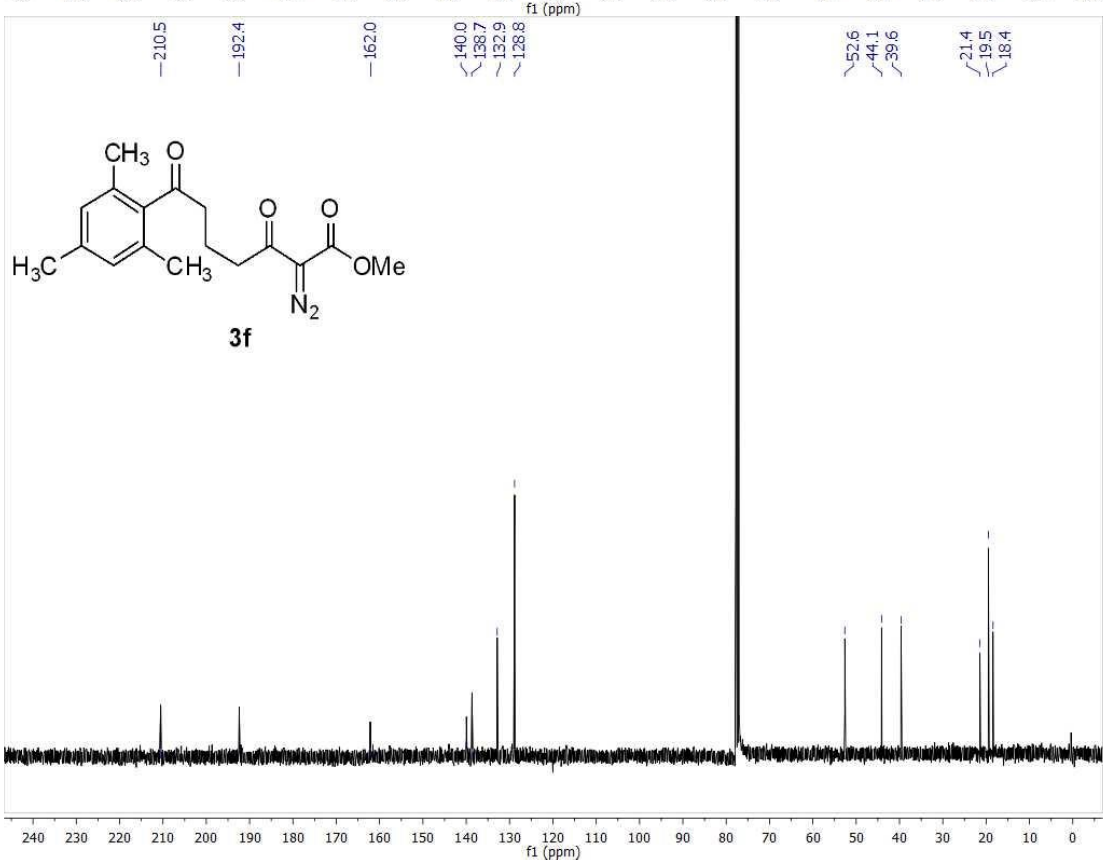
2.99
2.97
2.95
2.79
2.78
2.76
2.50
2.28
2.20
2.08
2.07
2.05
0.01
CH3
O
O
O
H3C
CH3
OMe
N2
3f
2.00
3.09
1.94
2.00
3.12
6.01
2.11
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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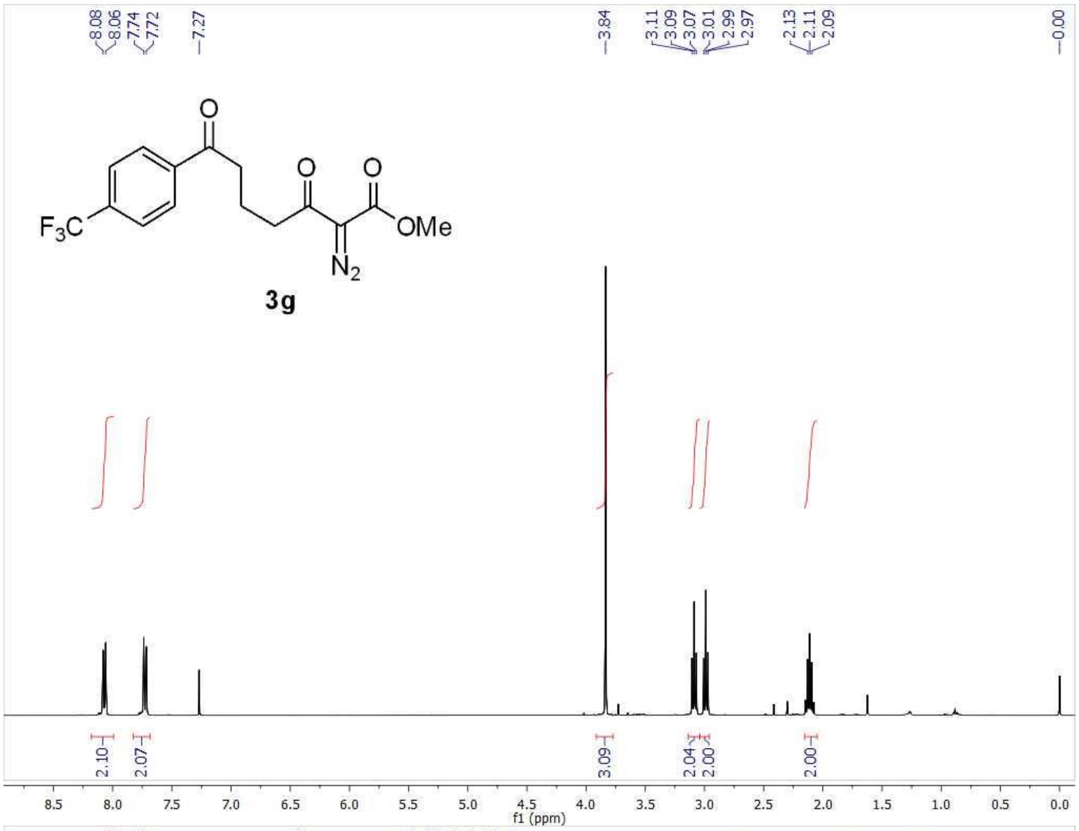
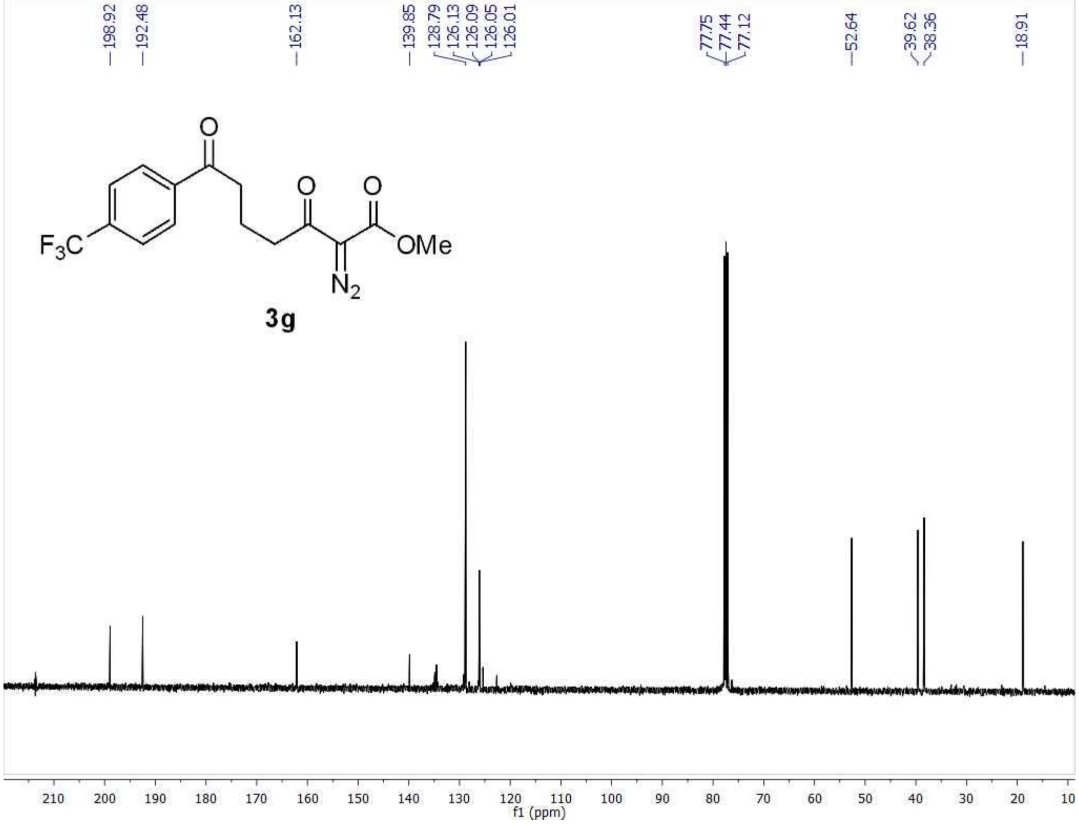
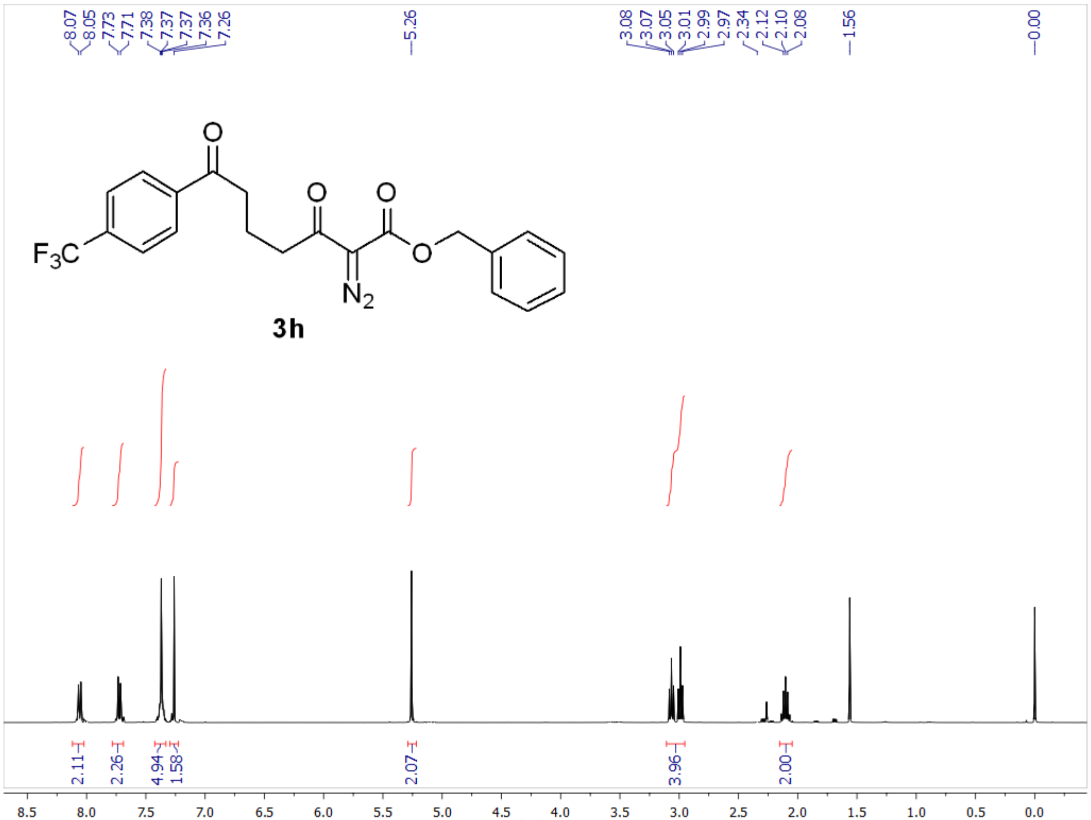
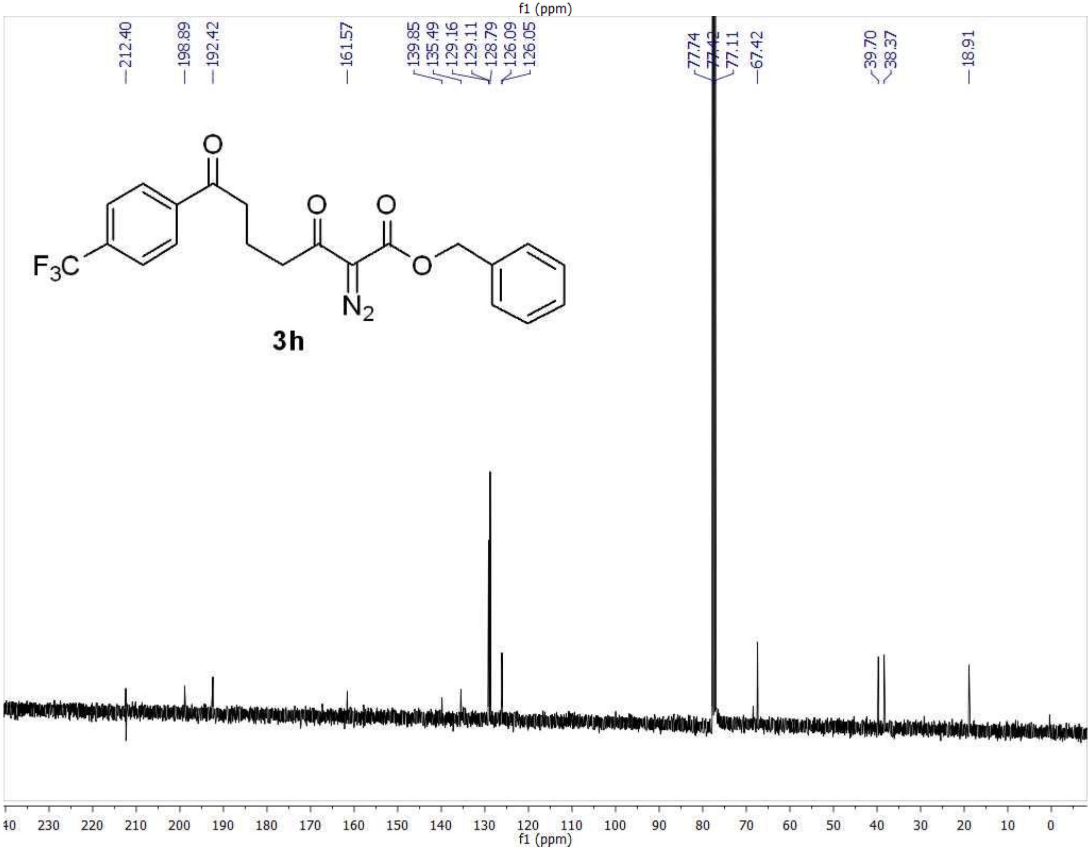
192.4
162.0
140.0
138.7
132.9
128.8
52.6
44.1
39.6
21.4
19.5
18.4
CH3
O
O
O
H3C
CH3
OMe
N2
3f
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.08
8.06
7.74
7.72
7.27
3.84
3.11
3.09
3.07
3.01
2.99
2.97
2.13
2.11
2.09
0.00
O
O
O
F$_3$C
OMe
N$_2$
3g
2.10
2.07
3.09
2.04
2.00
2.00
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
0.5
0.0
f1 (ppm)


198.92
192.48
162.13
139.85
128.79
126.13
126.09
126.05
126.01
77.75
77.44
77.12
52.64
39.62
38.36
18.91
O
O
O
F$_3$C
OMe
N$_2$
3g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


8.07
8.05
7.73
7.71
7.38
7.37
7.37
7.36
7.26
5.26
3.08
3.07
3.05
3.01
2.99
2.97
2.34
2.12
2.10
2.08
1.56
0.00
F3C
O
O
O
O
N2
3h
2.11
2.26
4.94
1.58
2.07
3.96
2.00
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
0.5
0.0
f1 (ppm)


212.40
198.89
192.42
161.57
139.85
135.49
129.16
129.11
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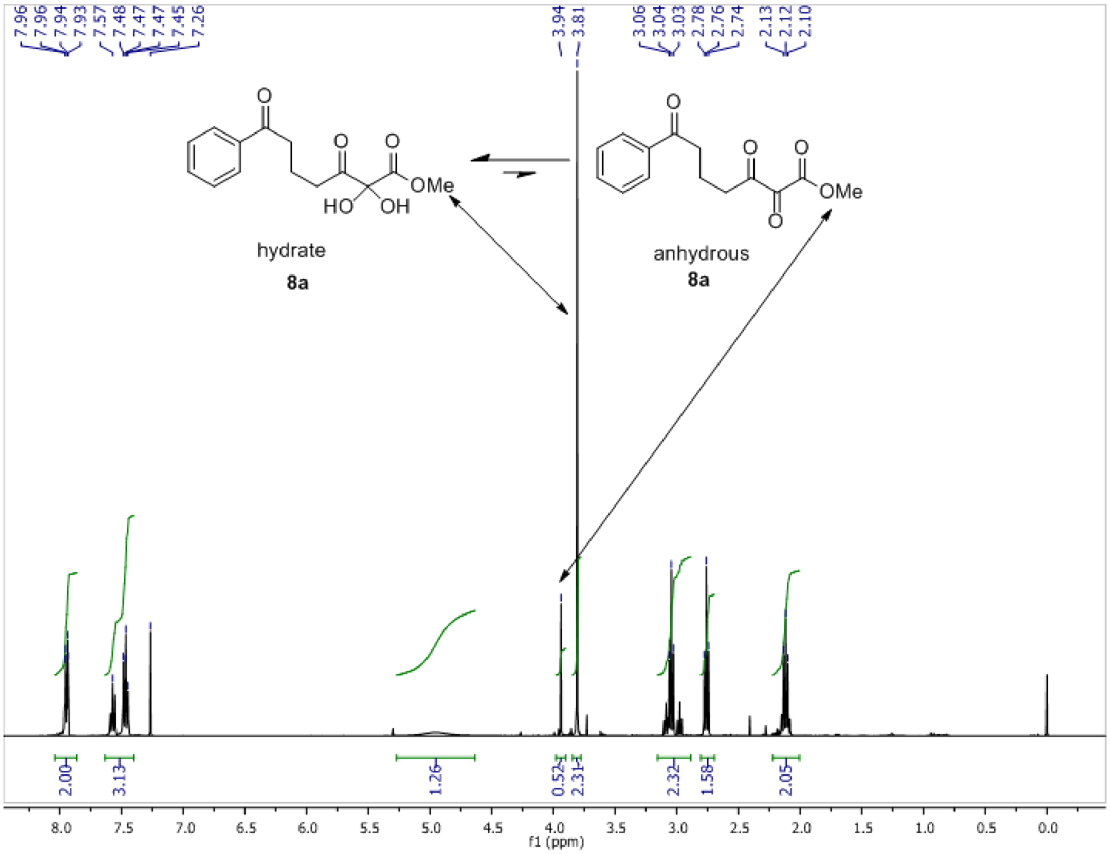
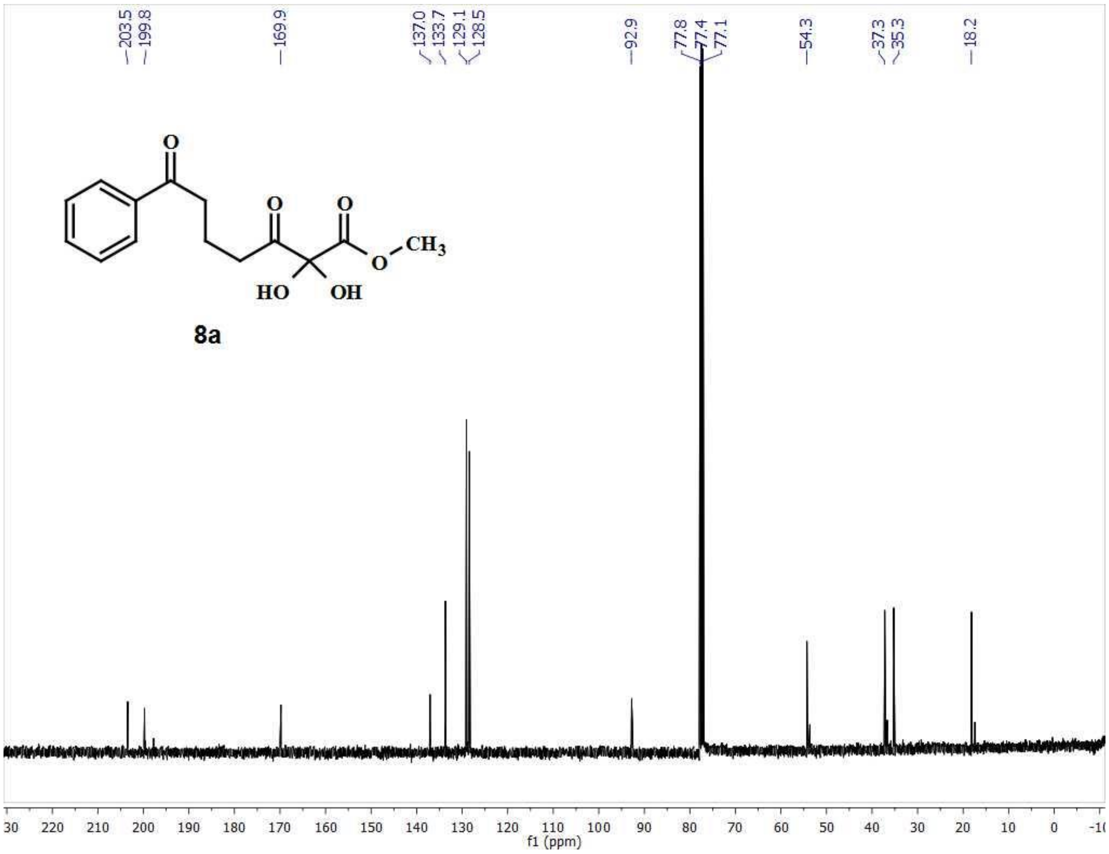
126.09
126.05
77.74
77.42
77.11
67.42
39.70
38.37
18.91
F3C
O
O
O
O
N2
3h
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.96
7.96
7.94
7.93
7.57
7.48
7.47
7.47
7.45
7.26
3.94
3.81
3.06
3.04
3.03
2.78
2.76
2.74
2.13
2.12
2.10
O
O
O
OMe
HO
OH
hydrate
8a
O
O
O
OMe
O
anhydrous
8a
2.00
3.13
1.26
0.52
2.31
2.32
1.58
2.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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199.8
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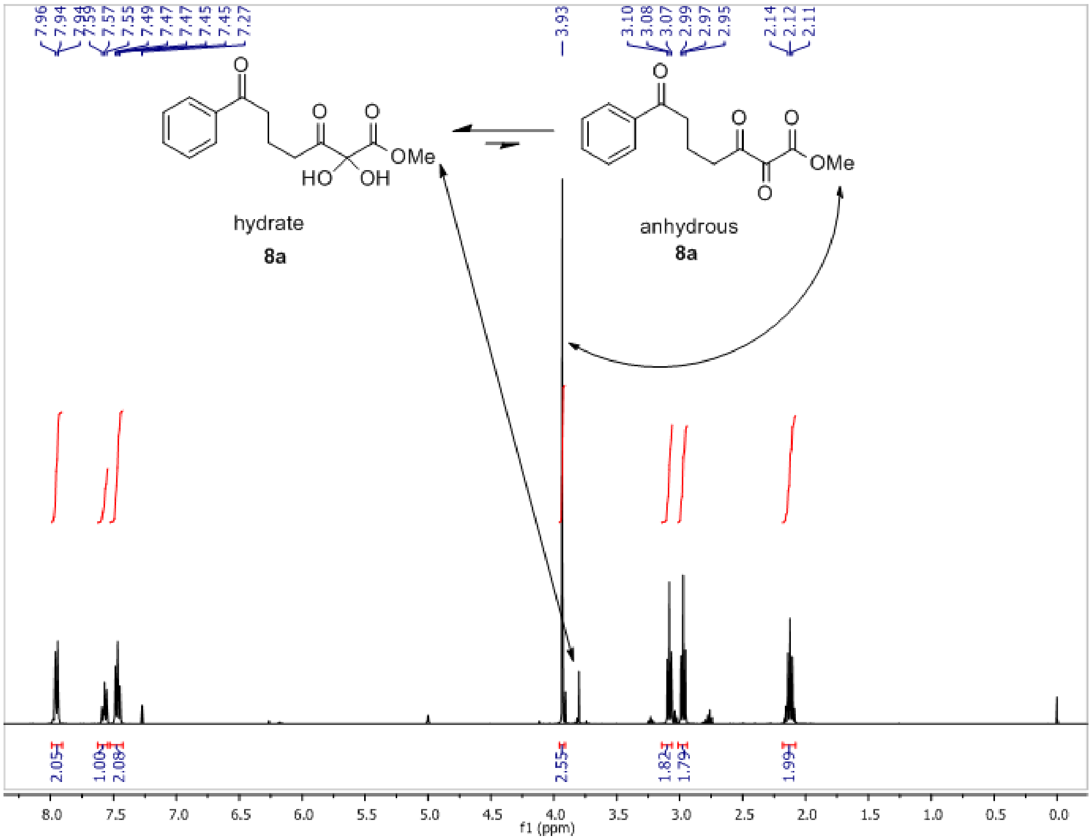
133.7
129.1
128.5
92.9
77.8
77.4
77.1
54.3
37.3
35.3
18.2
O
O
O
O
CH3
HO
OH
8a
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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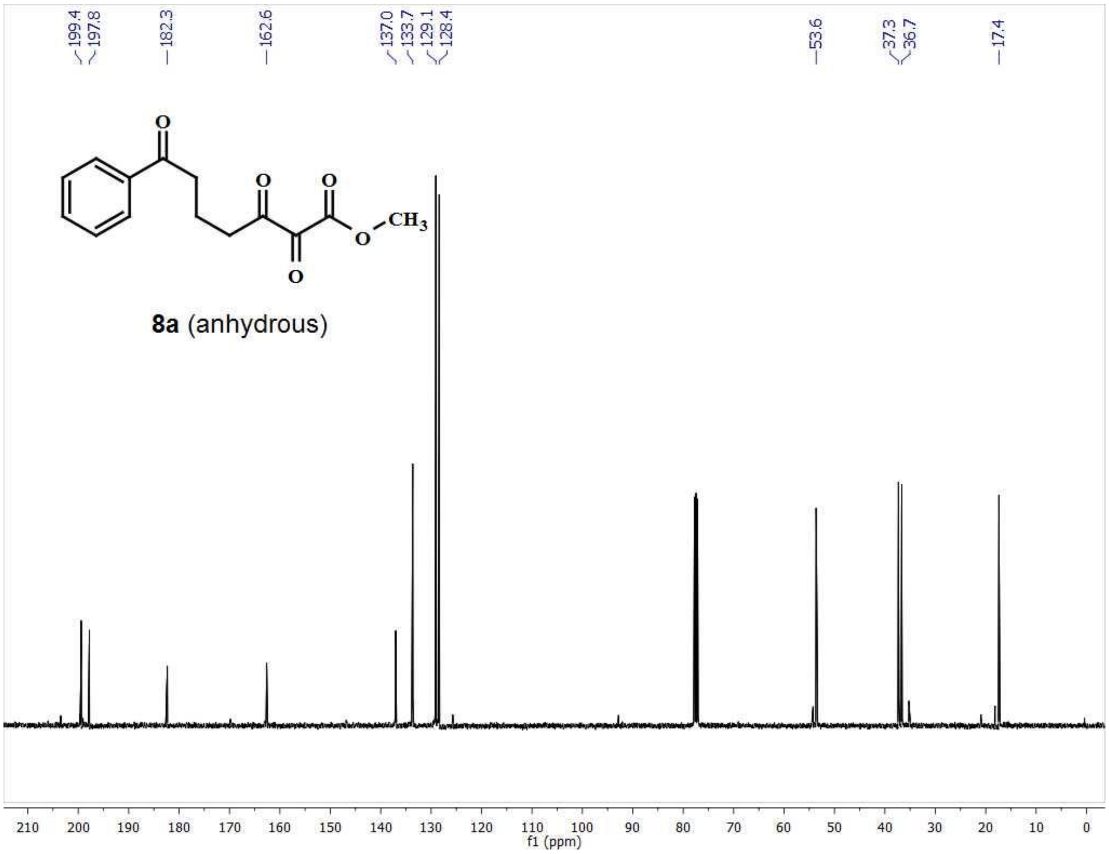
7.94
7.94
7.59
7.57
7.55
7.49
7.47
7.47
7.45
7.45
7.27
3.93
3.10
3.08
3.07
2.99
2.97
2.95
2.14
2.12
2.11
O
O
O
OMe
HO
OH
hydrate
8a
O
O
O
O
OMe
anhydrous
8a
2.05
1.00
2.08
2.55
1.82
1.79
1.99
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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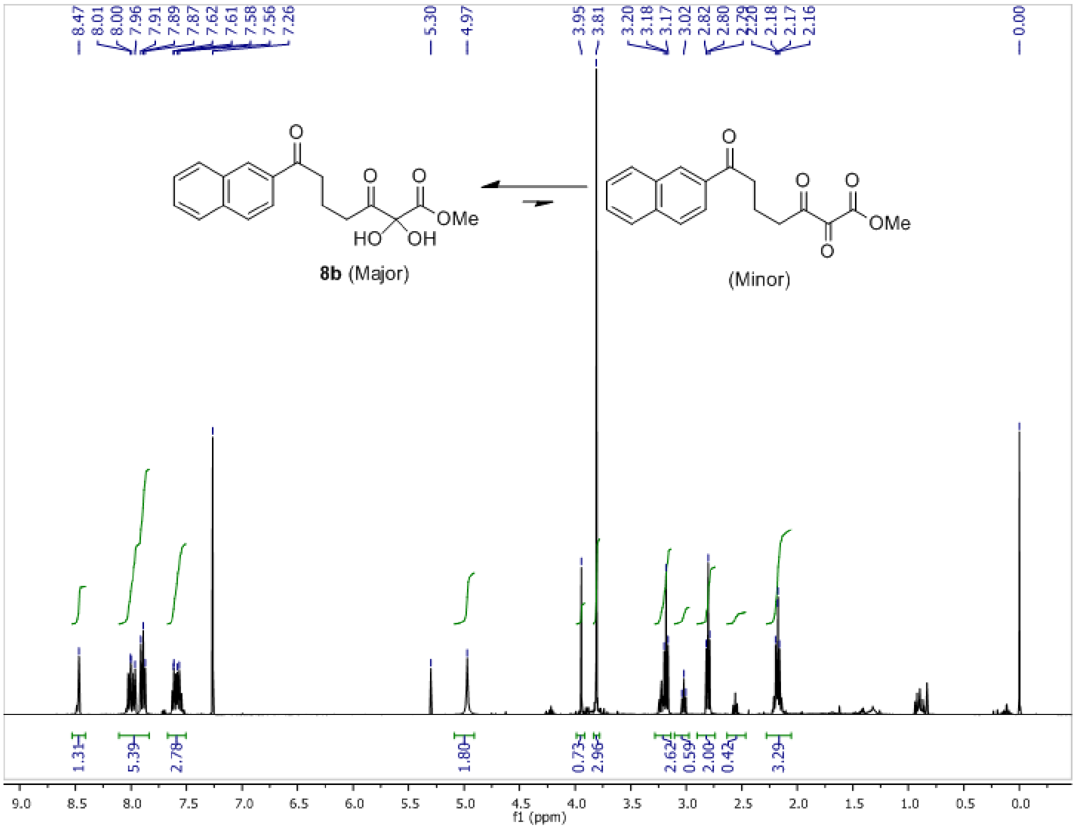
197.8
182.3
162.6
137.0
133.7
129.1
128.4
53.6
37.3
36.7
17.4
O
O
O
O
O
CH3
8a (anhydrous)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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8.00
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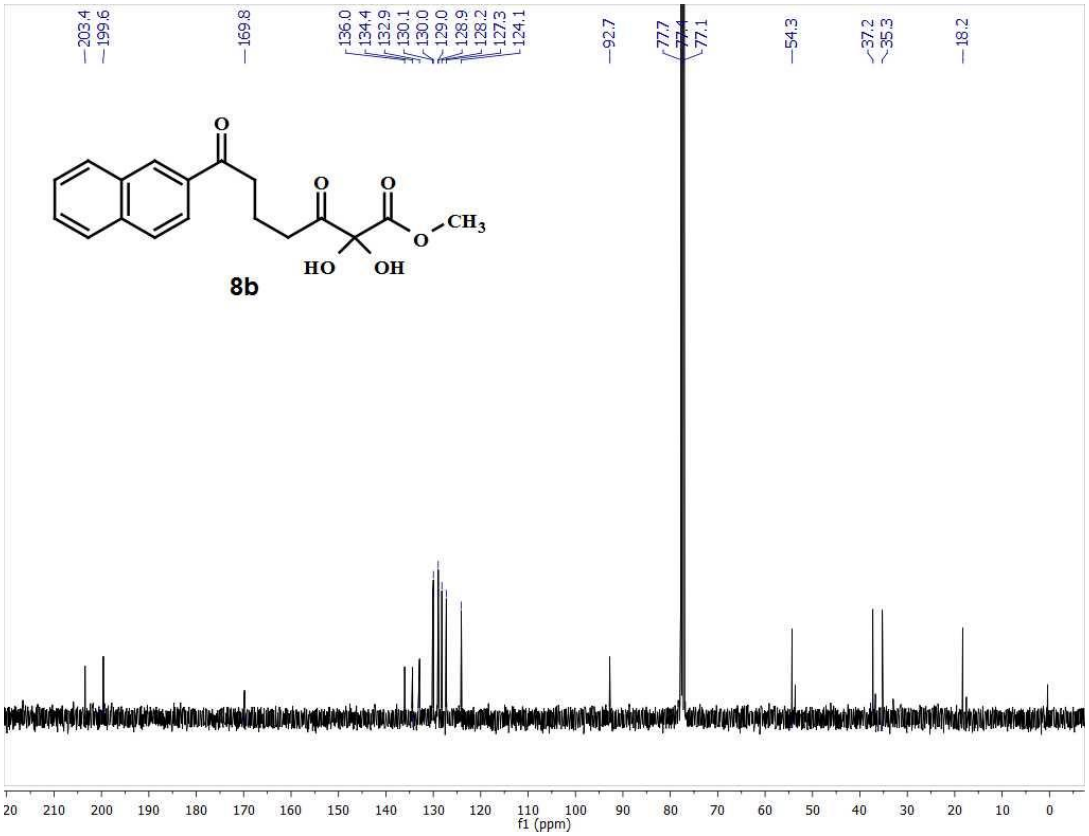
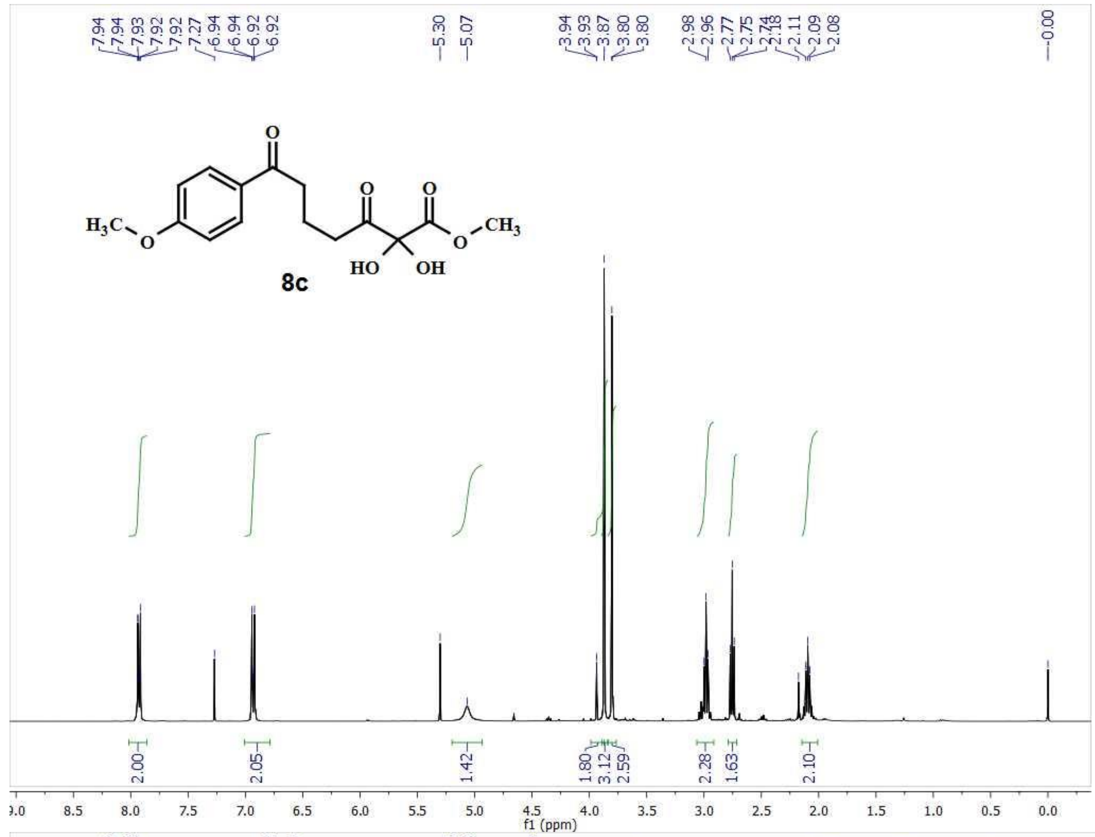
7.91
7.89
7.87
7.62
7.61
7.58
7.56
7.26
5.30
4.97
3.95
3.81
3.20
3.18
3.17
3.02
2.82
2.80
2.79
2.20
2.18
2.17
2.16
0.00
O
O
O
HO
OH
OMe
8b (Major)
O
O
O
O
OMe
(Minor)
1.31
5.39
2.78
1.80
0.73
2.96
2.62
0.59
2.00
0.42
3.29
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


203.4
199.6
169.8
136.0
134.4
132.9
130.1
130.0
129.0
128.9
128.2
127.3
124.1
92.7
77.7
77.4
77.1
54.3
37.2
35.3
18.2
O
O
O
O
CH3
HO
OH
8b
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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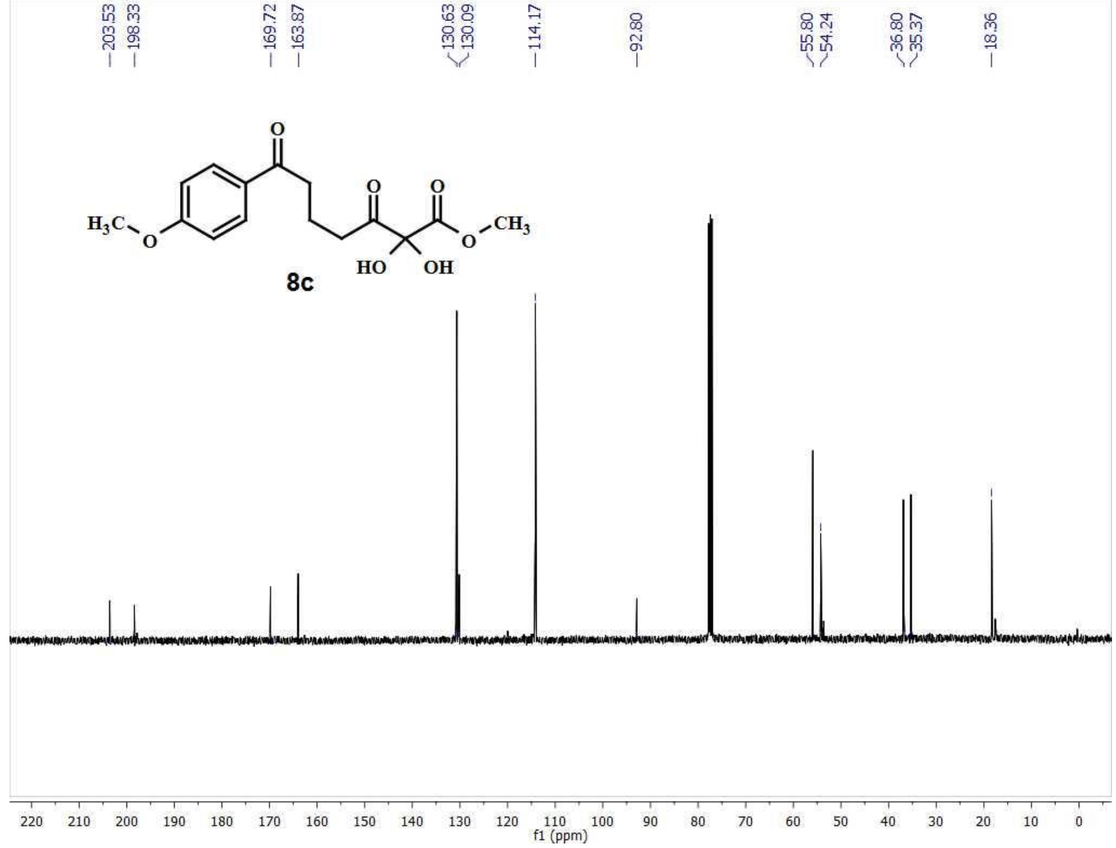
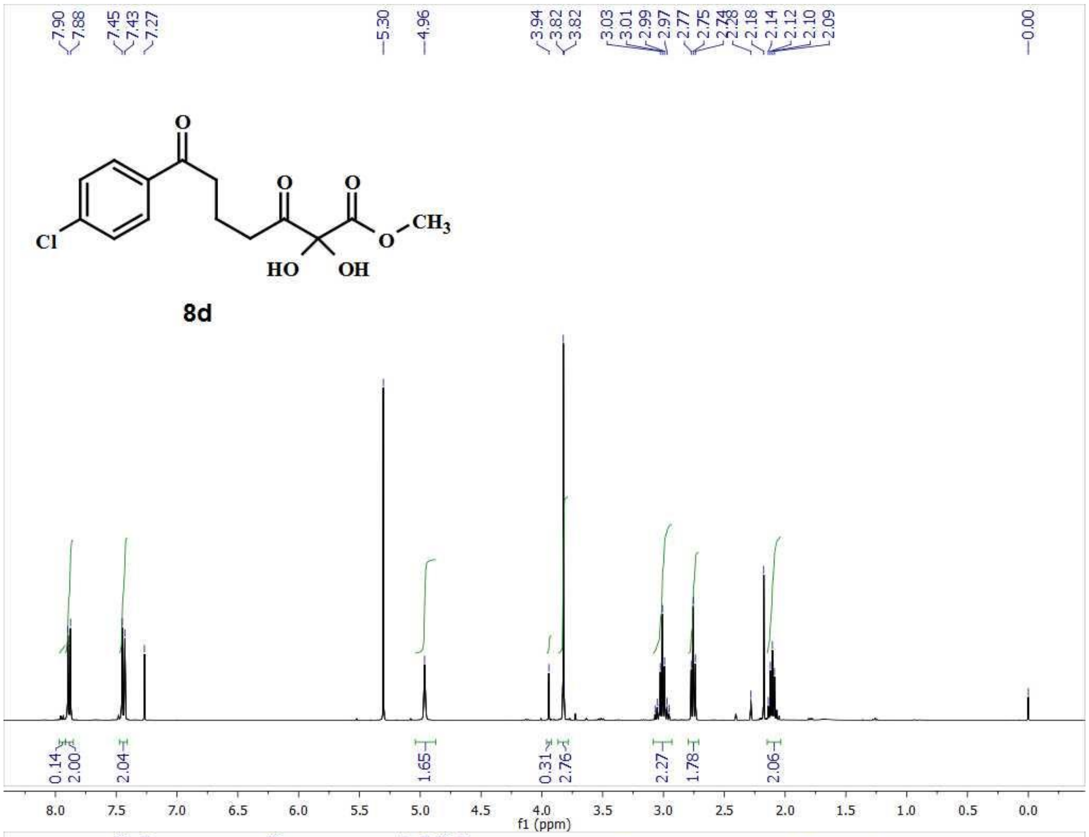
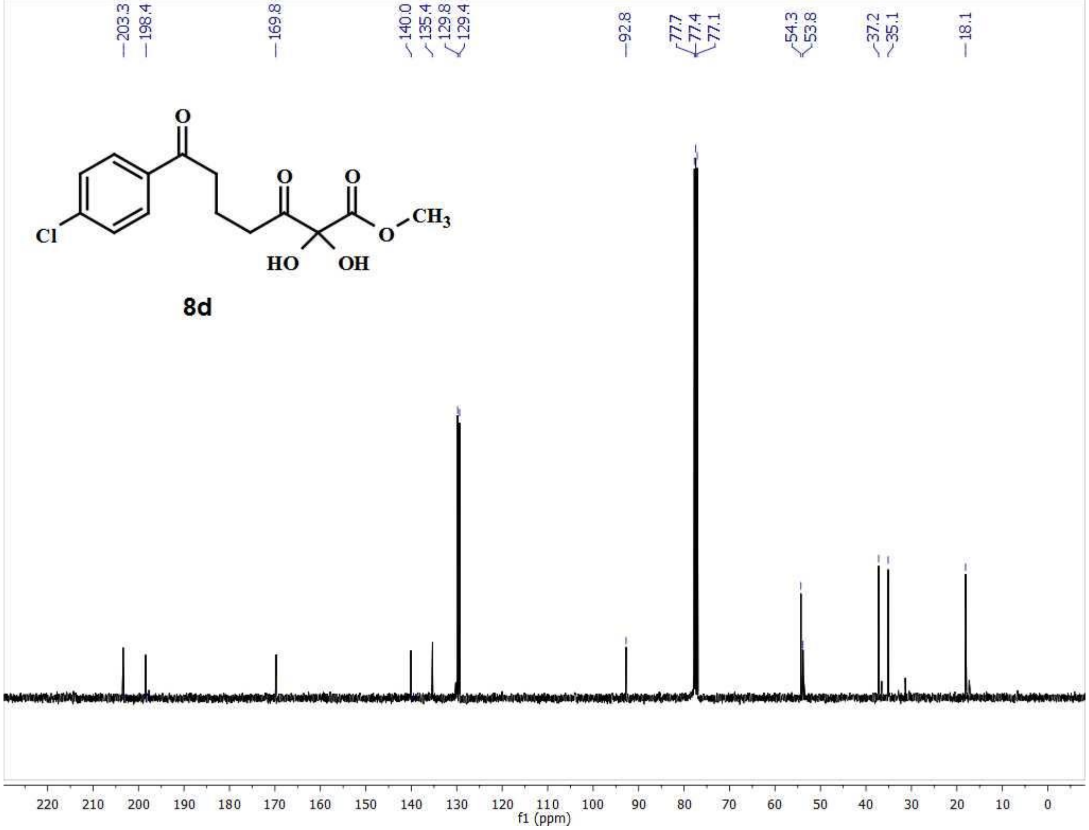
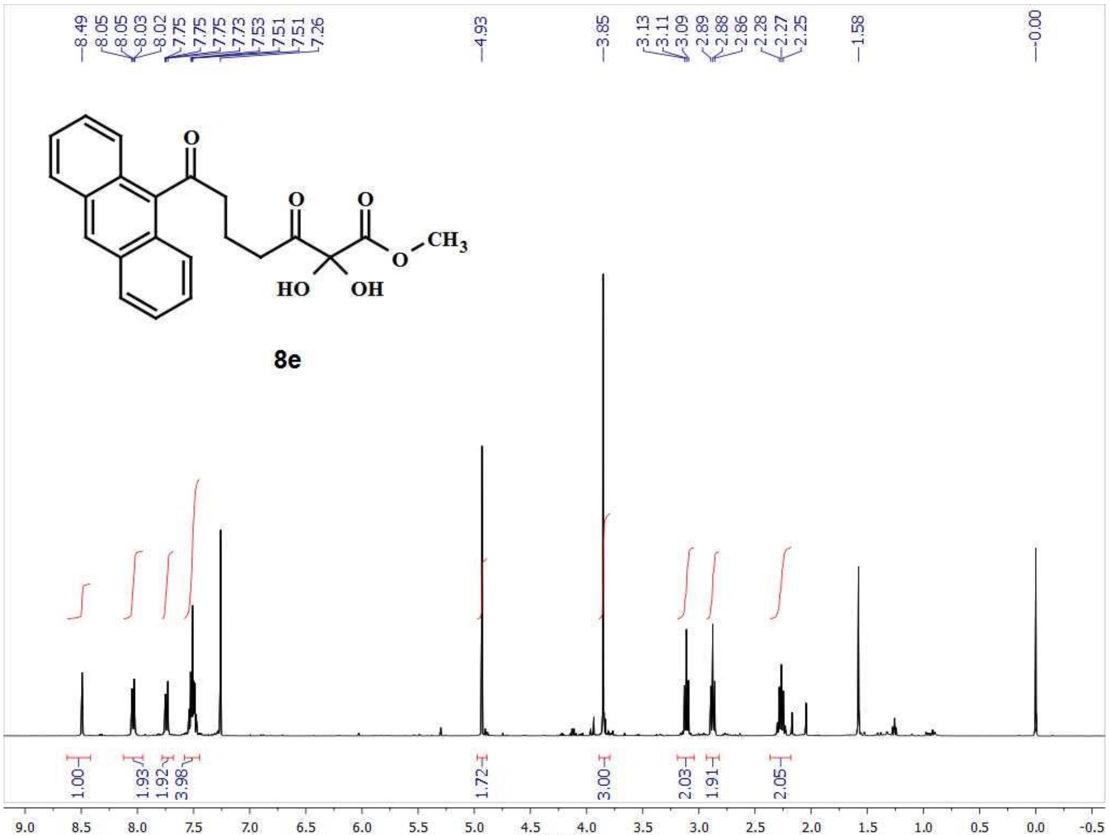
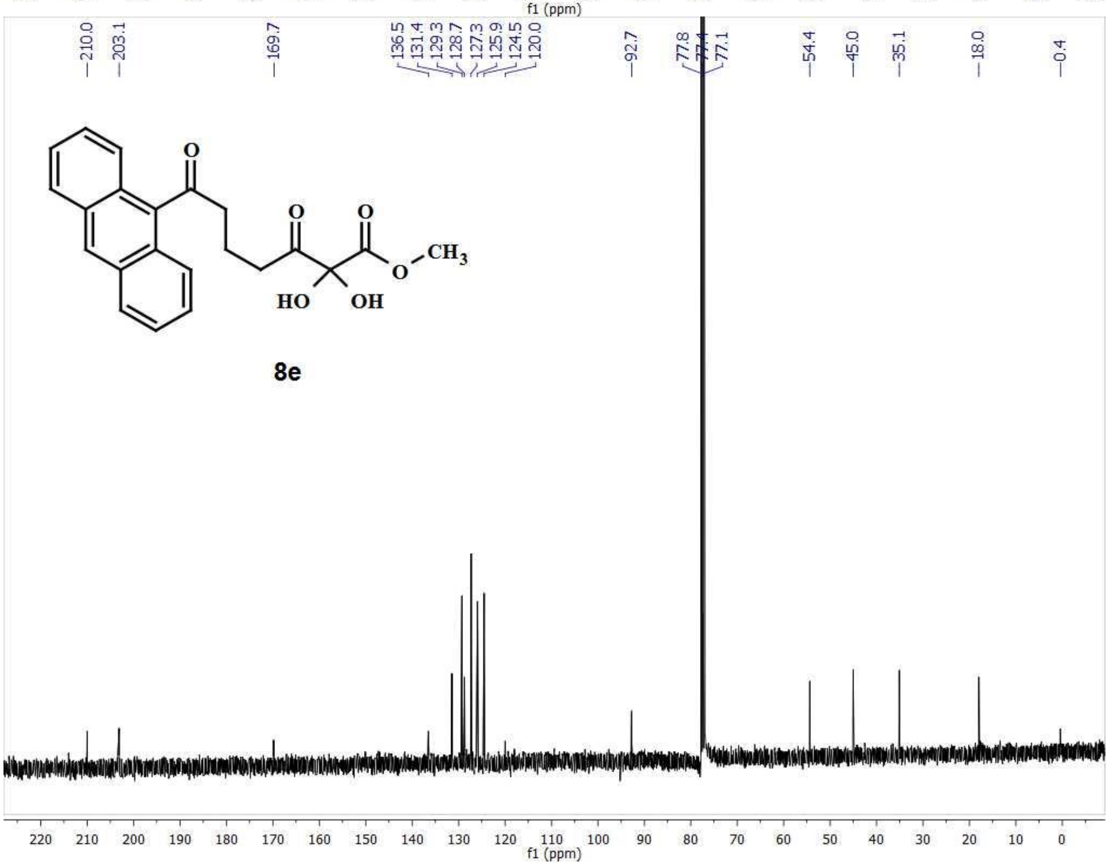
7.94
7.93
7.92
7.92
7.27
6.94
6.94
6.92
6.92
5.30
5.07
3.94
3.93
3.87
3.80
3.80
2.98
2.96
2.77
2.75
2.74
2.18
2.11
2.09
2.08
0.00
H3C
O
O
O
O
O
CH3
HO
OH
8c
2.00
2.05
1.42
1.80
3.12
2.59
2.28
1.63
2.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

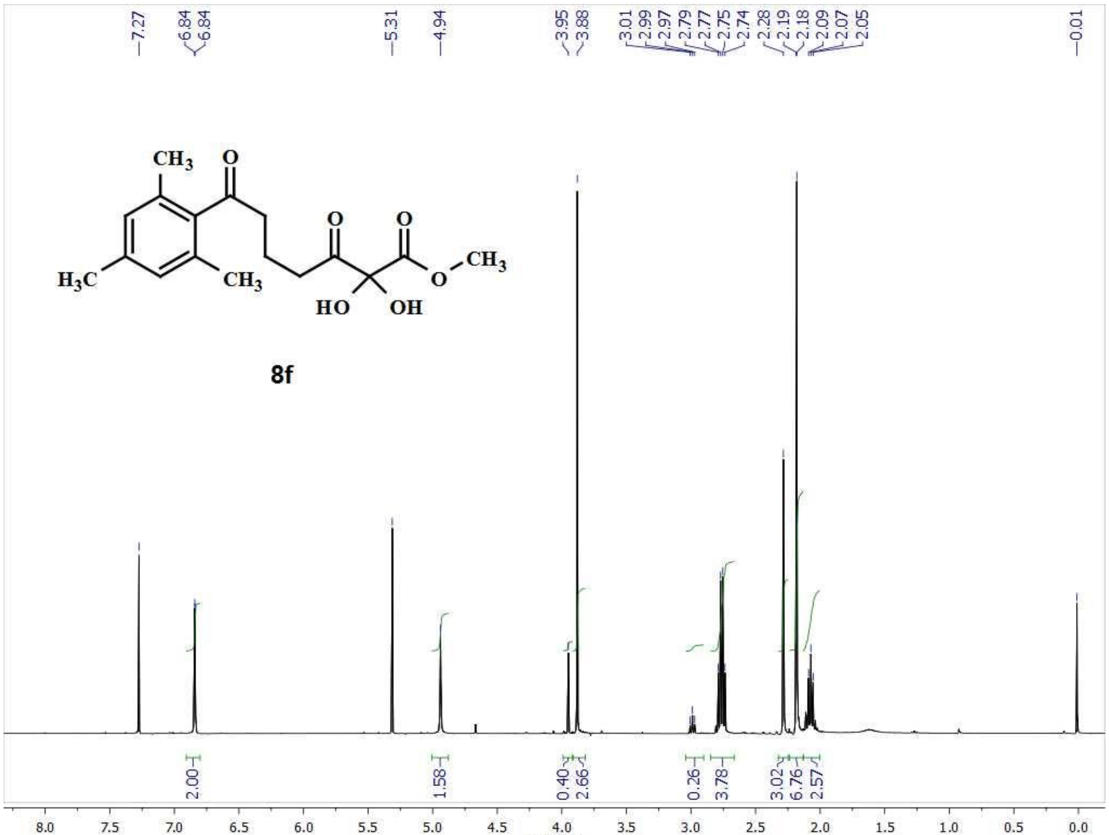

203.53
198.33
169.72
163.87
130.63
130.09
114.17
92.80
55.80
54.24
36.80
35.37
18.36
H3C
O
O
O
O
O
CH3
HO
OH
8c
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

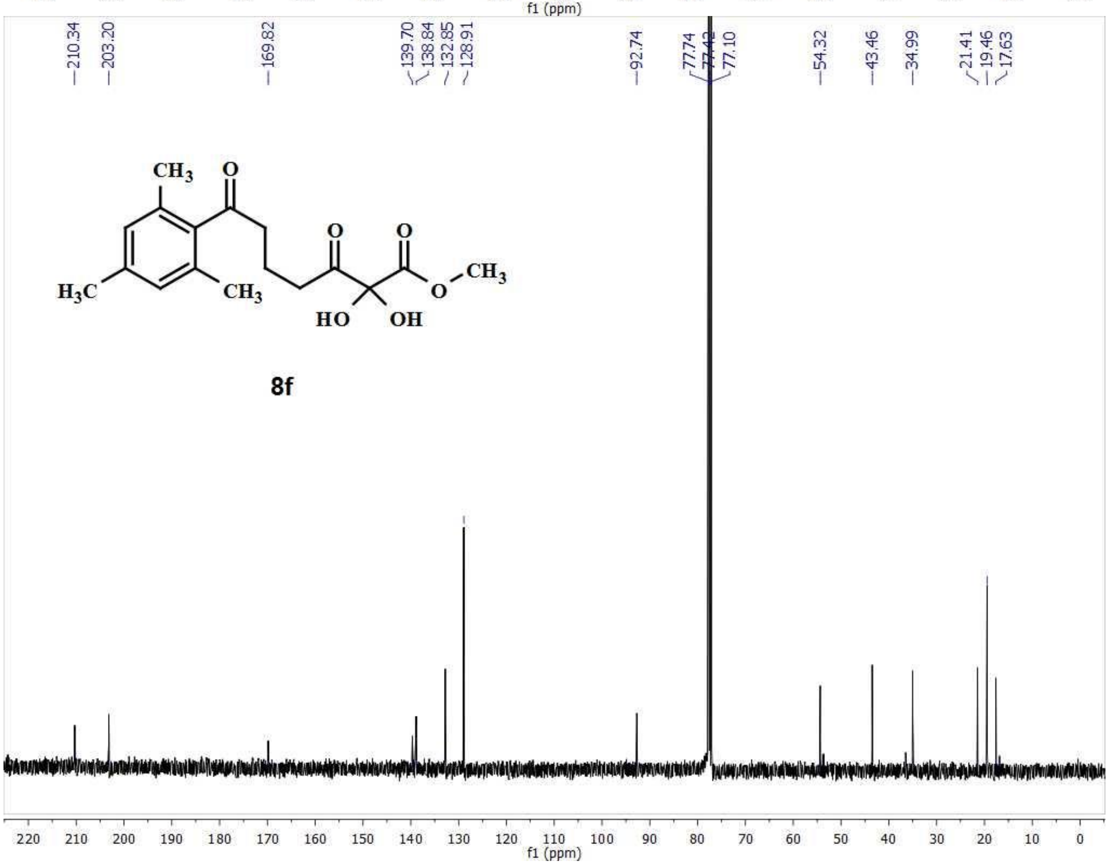

7.90
7.88
7.45
7.43
7.27
5.30
4.96
3.94
3.82
3.82
3.03
3.01
2.99
2.97
2.77
2.75
2.74
2.28
2.18
2.14
2.12
2.10
2.09
0.00
O
O
O
Cl
O
CH3
HO
OH
8d
0.14
2.00
2.04
1.65
0.31
2.76
2.27
1.78
2.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

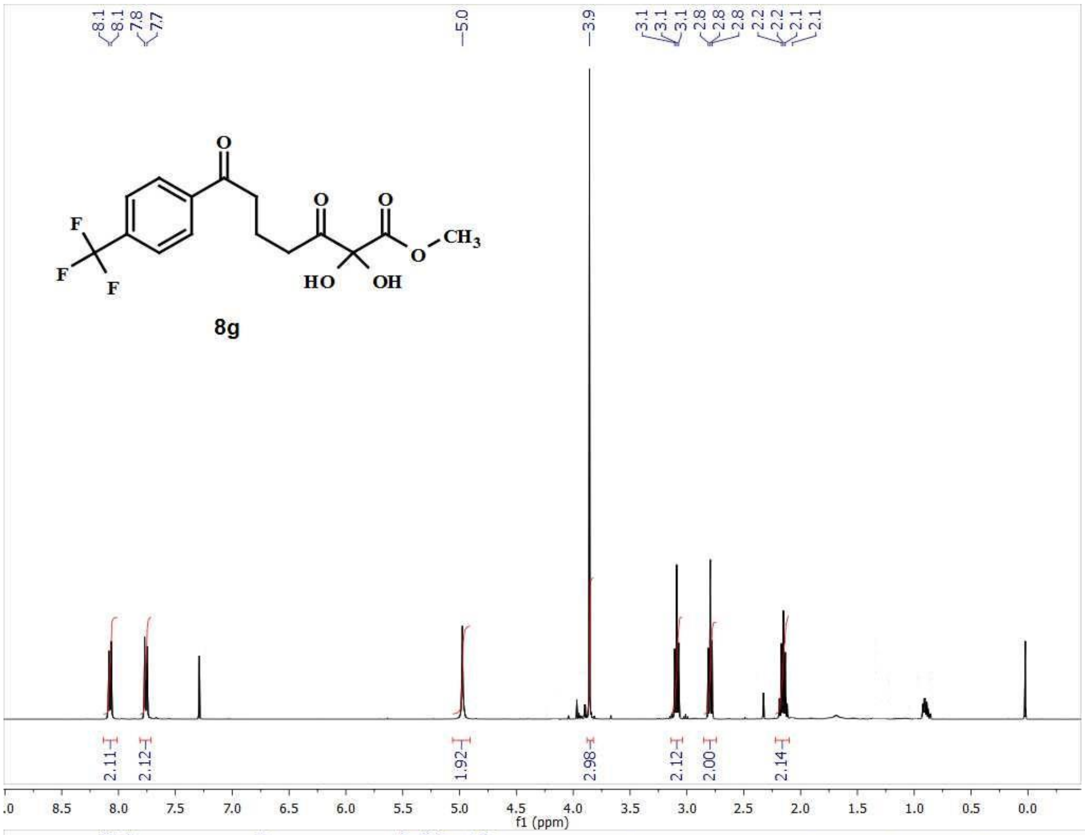

203.3
198.4
169.8
140.0
135.4
129.8
129.4
92.8
77.7
77.4
77.1
54.3
53.8
37.2
35.1
18.1
O
O
O
Cl
O
CH3
HO
OH
8d
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

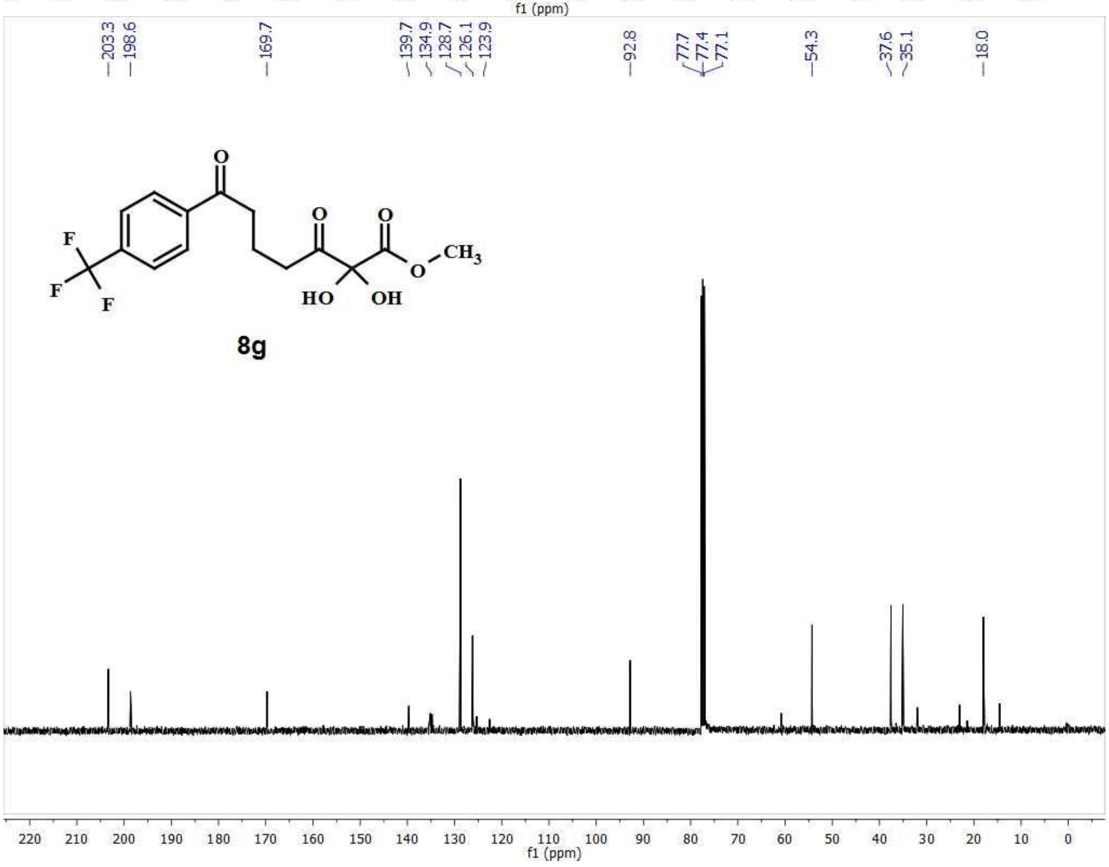

8.49
8.05
8.05
8.03
8.02
7.75
7.75
7.75
7.73
7.53
7.51
7.51
7.26
4.93
3.85
3.13
3.11
3.09
2.89
2.88
2.86
2.28
2.27
2.25
1.58
0.00
O
O
O
O
CH3
HO
OH
8e
1.00
1.93
1.92
3.98
1.72
3.00
2.03
1.91
2.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

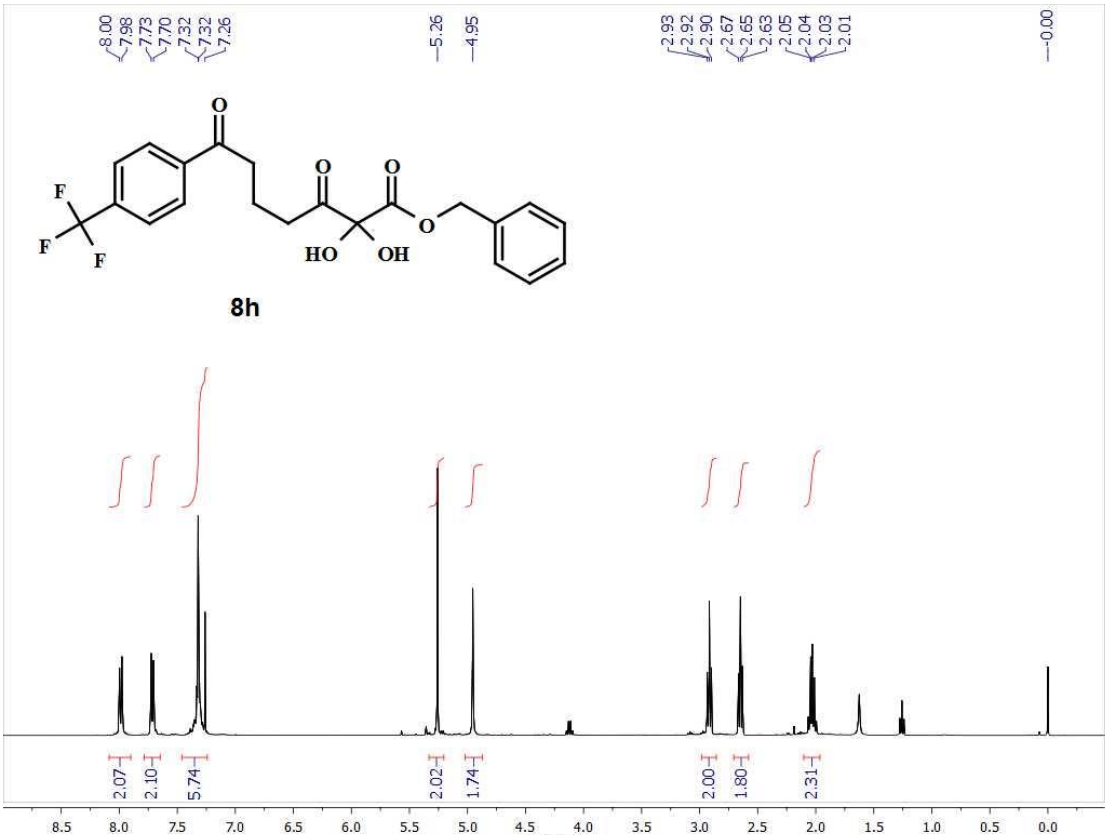

210.0
203.1
169.7
136.5
131.4
129.3
128.7
127.3
125.9
124.5
120.0
92.7
77.8
77.4
77.1
54.4
45.0
35.1
18.0
0.4
O
O
O
O
CH3
HO
OH
8e
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.27
6.84
6.84
5.31
4.94
3.95
3.88
3.01
2.99
2.97
2.79
2.77
2.75
2.74
2.28
2.19
2.18
2.09
2.07
2.05
-0.01
CH3
O
O
O
H3C
CH3
O
CH3
HO
OH
8f
2.00
1.58
0.40
2.66
0.26
3.78
3.02
6.76
2.57
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


210.34
203.20
169.82
139.70
138.84
132.85
128.91
92.74
77.74
77.42
77.10
54.32
43.46
34.99
21.41
19.46
17.63
CH3
O
O
O
H3C
CH3
O
CH3
HO
OH
8f
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

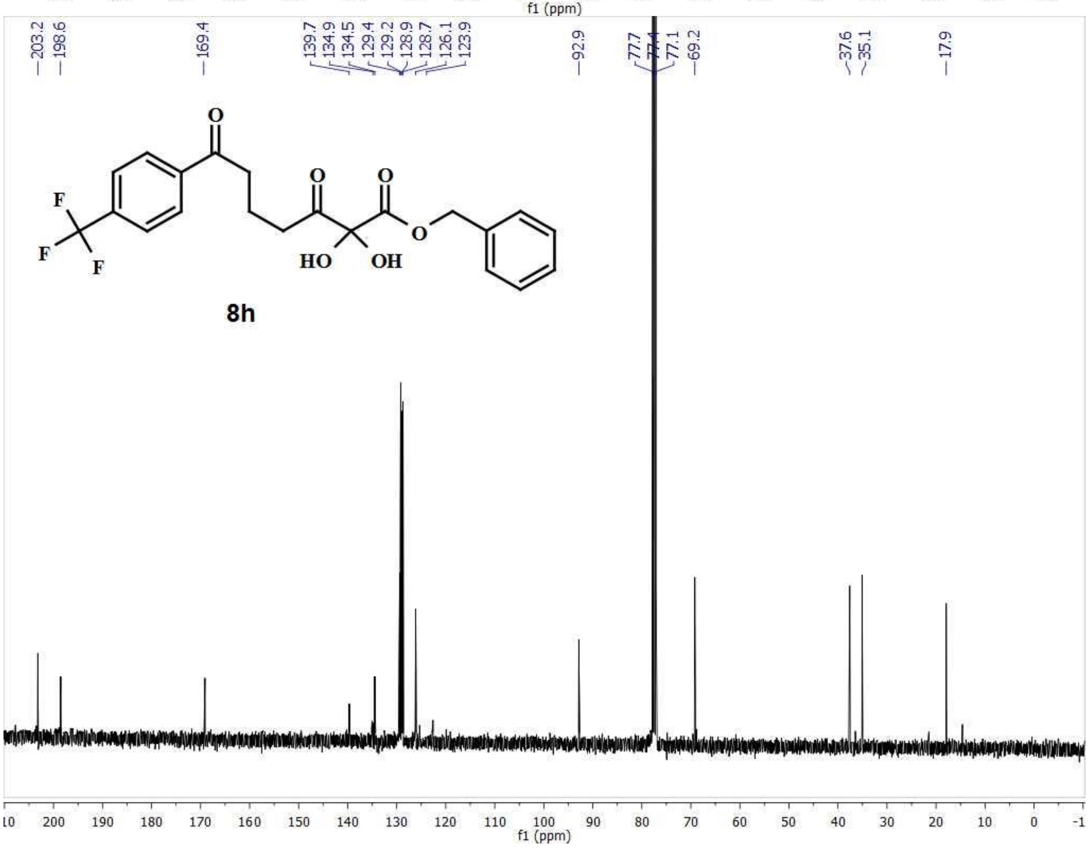

8.1
8.1
7.8
7.7
5.0
3.9
3.1
3.1
3.1
2.8
2.8
2.8
2.2
2.2
2.1
2.1
O
O
O
F
F
F
O
CH3
HO
OH
8g
2.11
2.12
1.92
2.98
2.12
2.00
2.14
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


203.3
198.6
169.7
139.7
134.9
128.7
126.1
123.9
92.8
77.7
77.4
77.1
54.3
37.6
35.1
18.0
O
O
O
F
F
F
O
CH3
HO
OH
8g
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



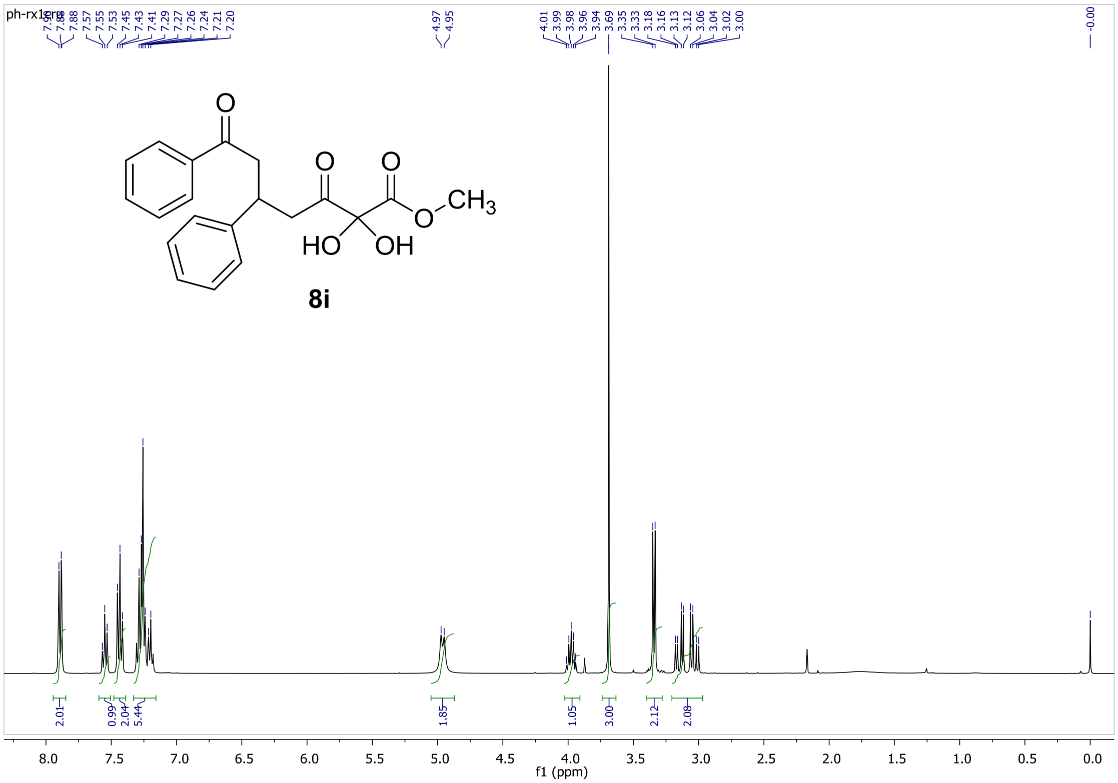
8h

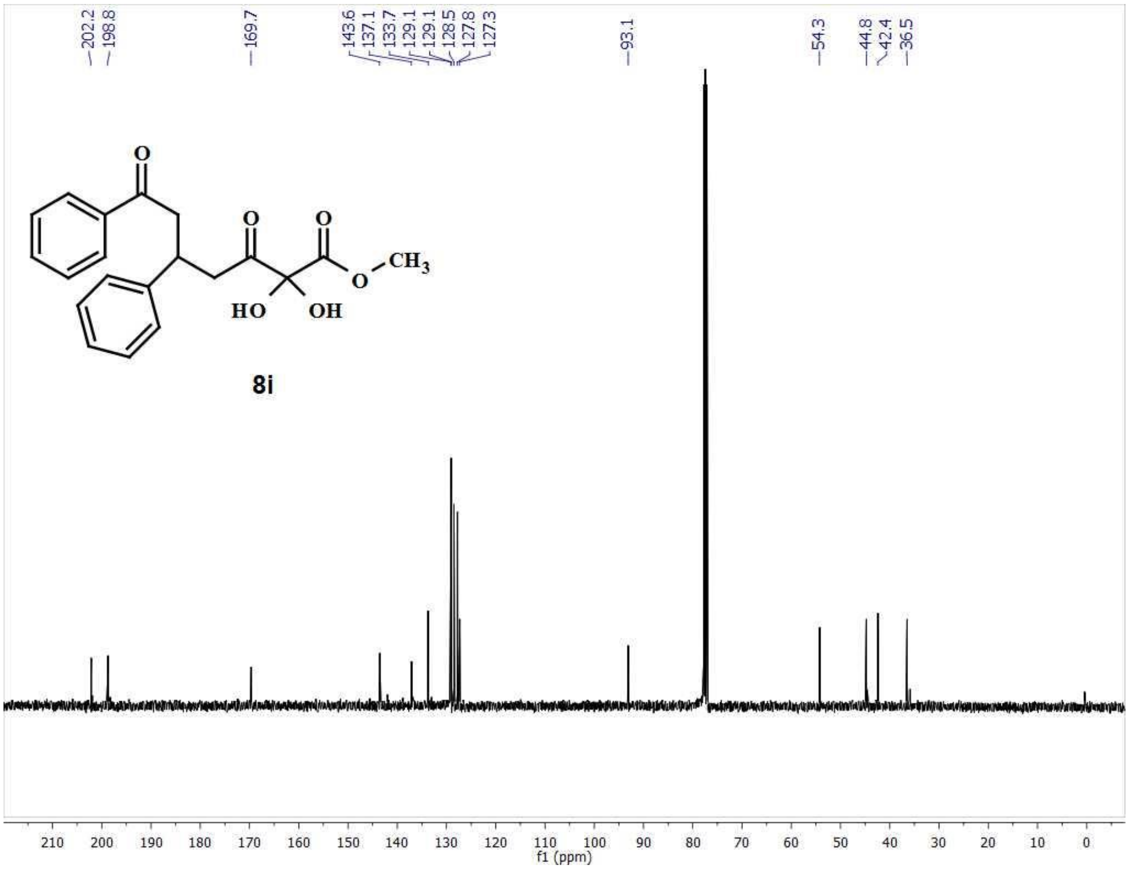
8.00
7.98
7.73
7.70
7.32
7.32
7.26
5.26
4.95
2.93
2.92
2.90
2.67
2.65
2.63
2.05
2.04
2.03
2.01
0.00
2.07
2.10
5.74
2.02
1.74
2.00
1.80
2.31
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
F
F
F
O
O
O
HO
OH
O

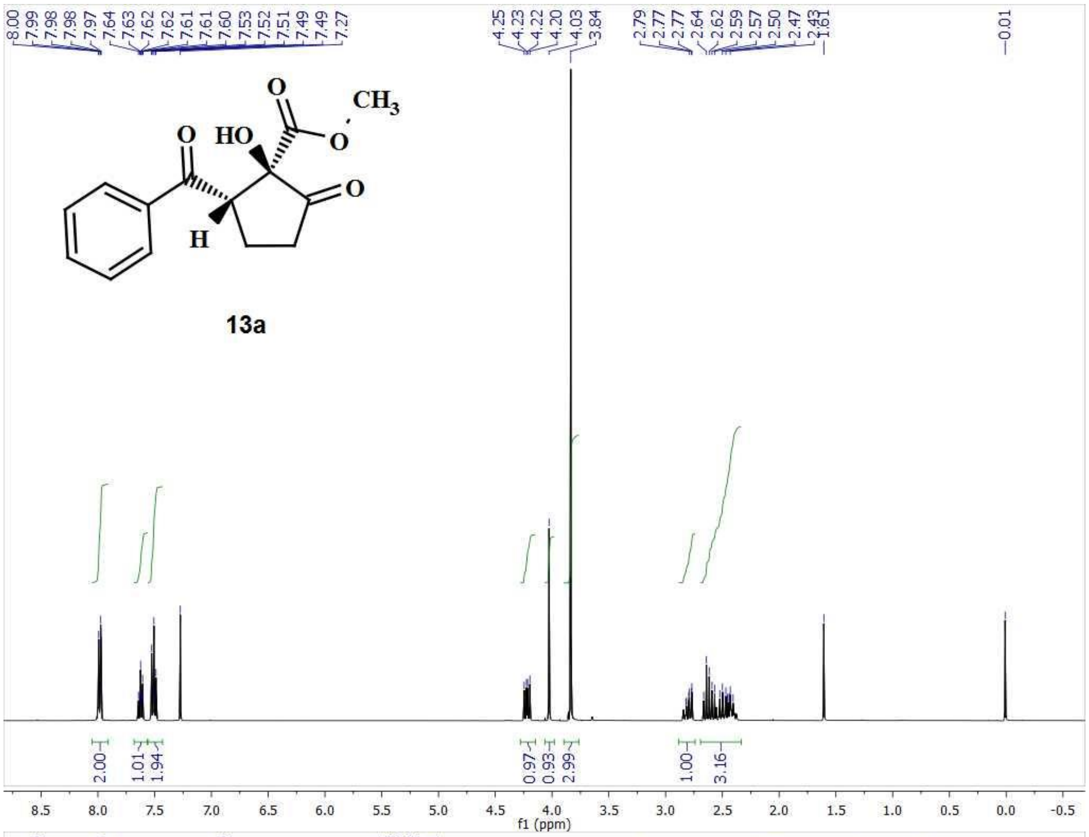


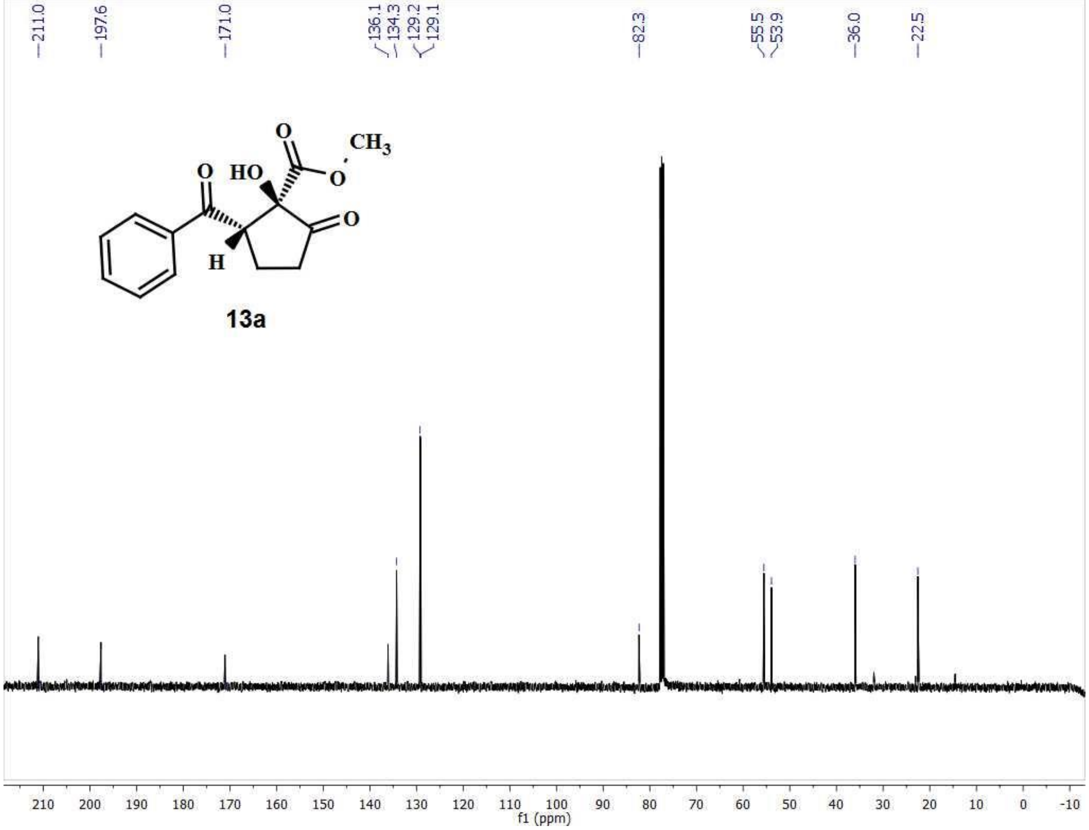
8h

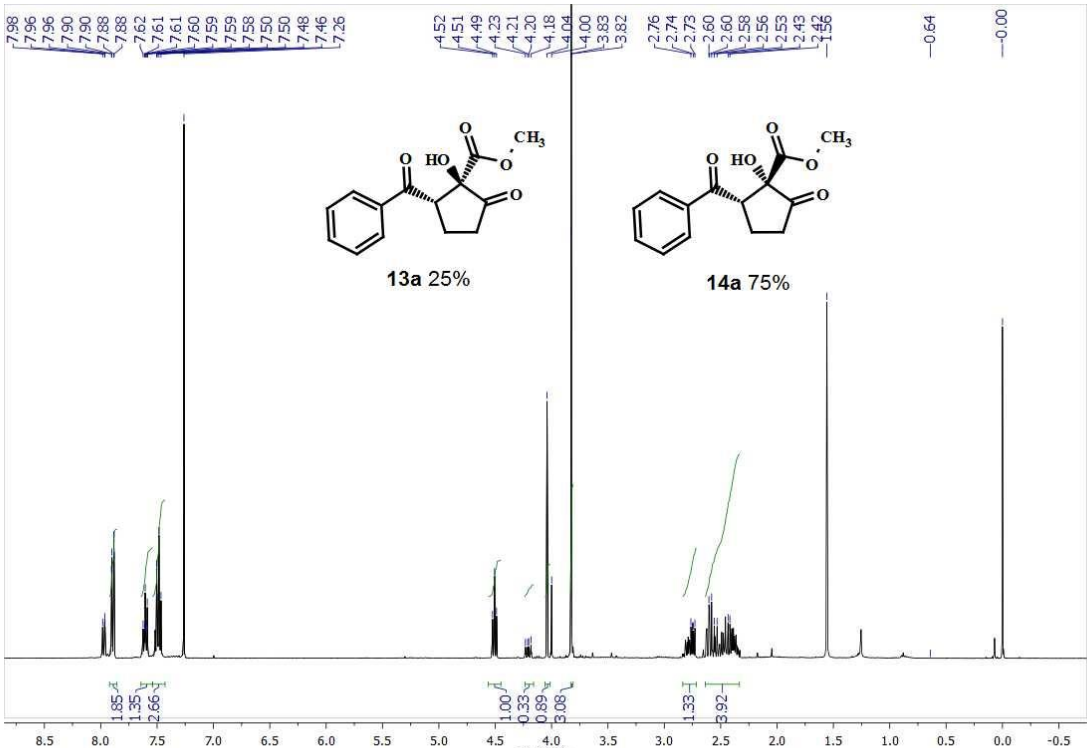
203.2
198.6
169.4
139.7
134.9
134.5
129.4
129.2
128.9
128.7
126.1
123.9
92.9
77.7
77.4
77.1
69.2
37.6
35.1
17.9
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)
F
F
F
O
O
O
HO
OH
O

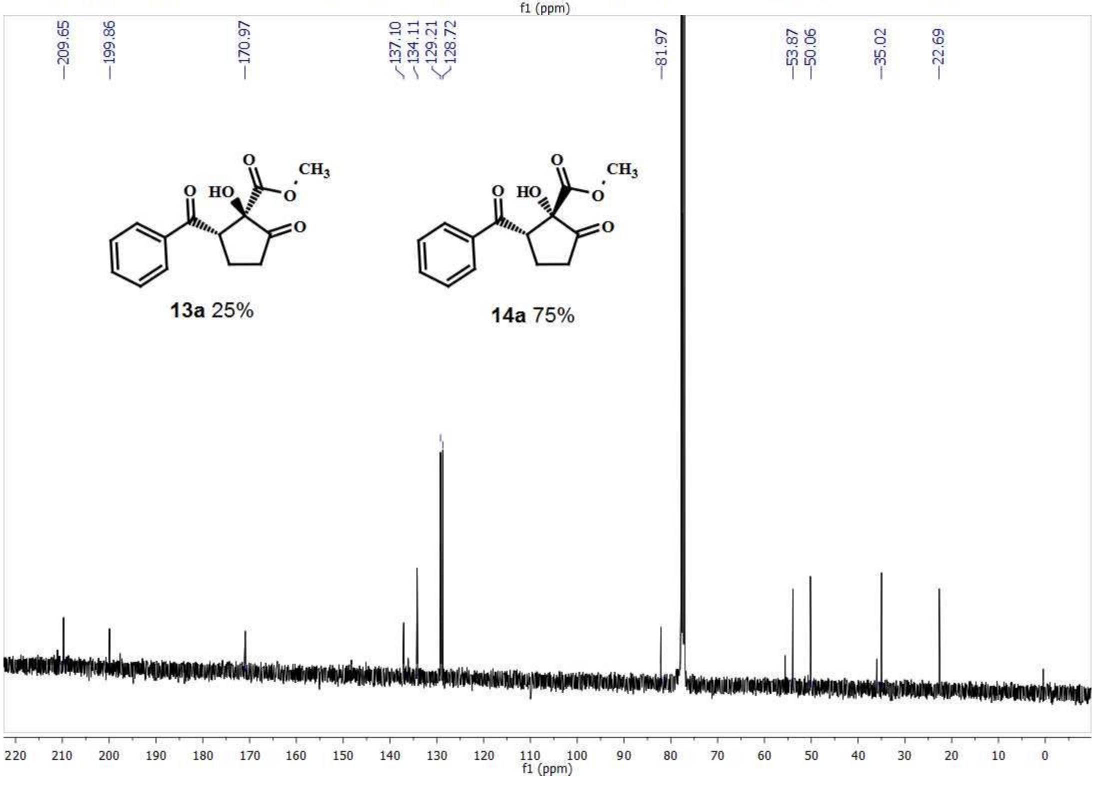

ph-rx1cru
7.90
7.89
7.88
7.57
7.55
7.53
7.45
7.43
7.41
7.29
7.27
7.26
7.24
7.21
7.20
4.97
4.95
4.01
3.99
3.98
3.96
3.94
3.69
3.35
3.33
3.18
3.16
3.13
3.12
3.06
3.04
3.02
3.00
-0.00
O
O
O
CH3
O
HO
OH
8i
2.01
0.99
2.04
5.44
1.85
1.05
3.00
2.12
2.08
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

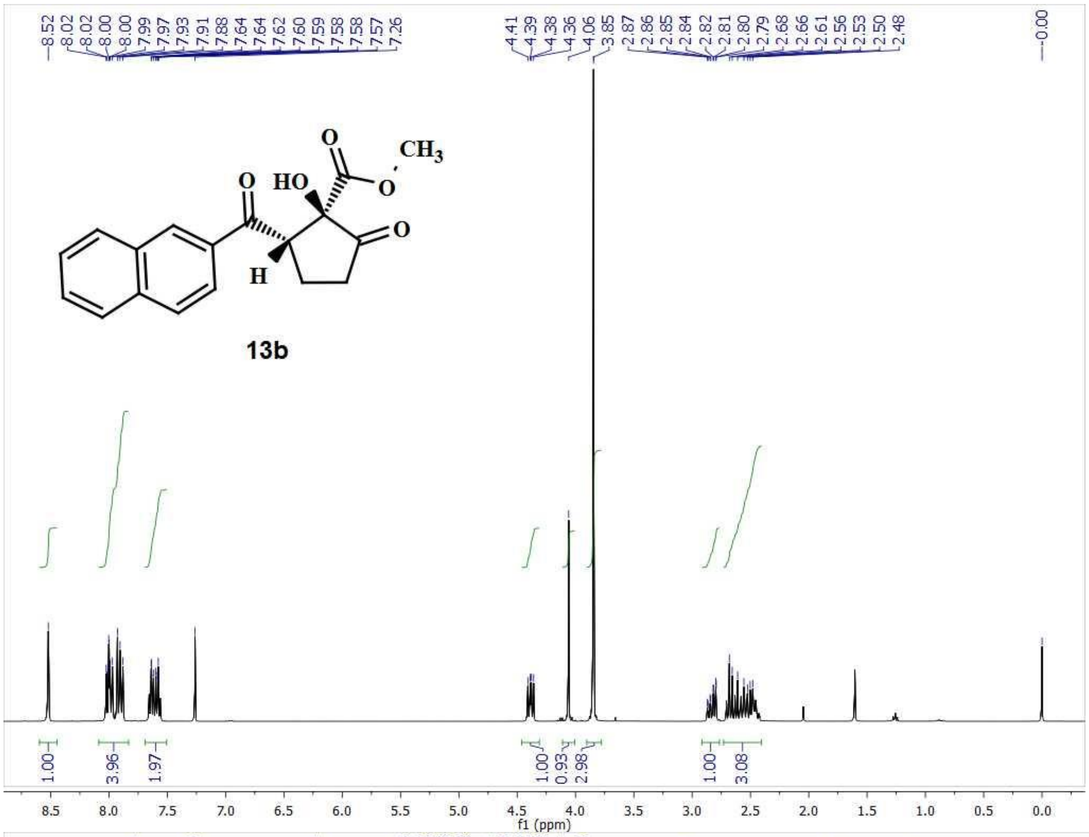

202.2
198.8
169.7
143.6
137.1
133.7
129.1
129.1
128.5
127.8
127.3
93.1
54.3
44.8
42.4
36.5
O
O
O
CH3
O
HO
OH
8i
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

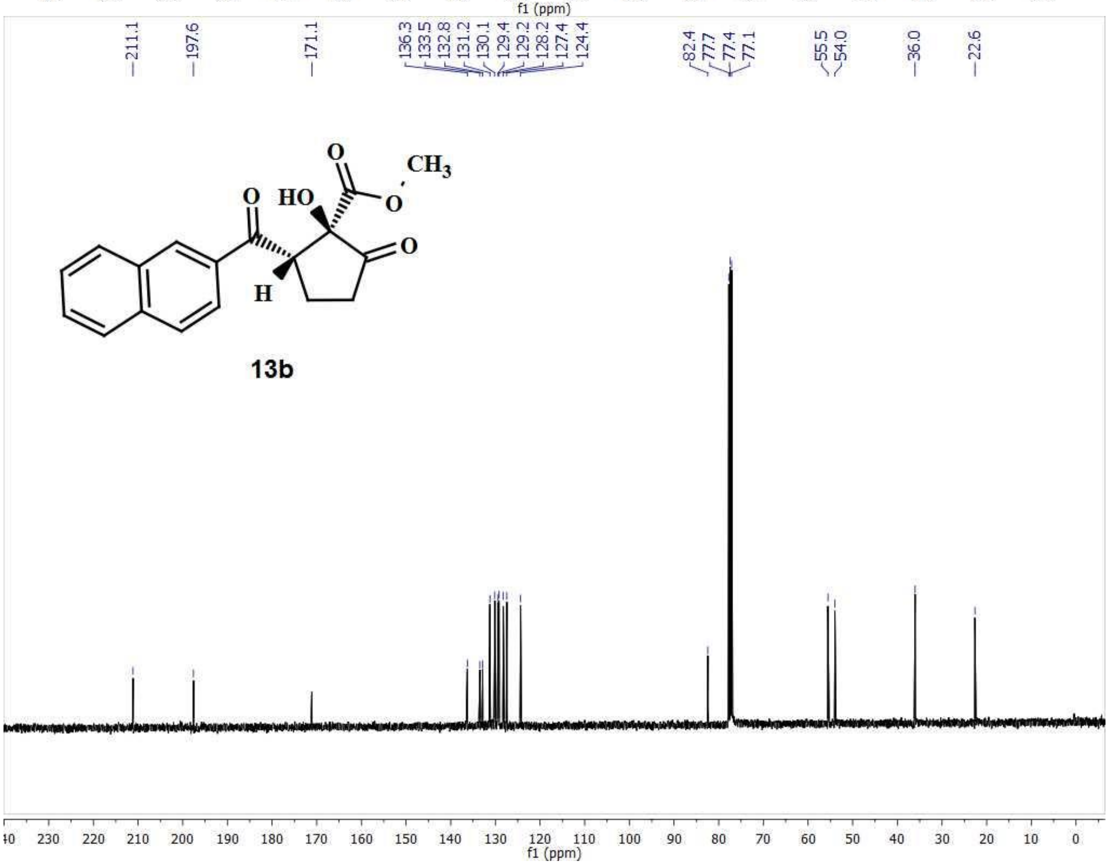

8.00
7.99
7.98
7.98
7.97
7.64
7.63
7.62
7.62
7.61
7.61
7.60
7.53
7.52
7.51
7.49
7.49
7.27
4.25
4.23
4.22
4.20
4.03
3.84
2.79
2.77
2.77
2.64
2.62
2.59
2.57
2.50
2.47
2.43
1.61
-0.01
O
HO
O
CH3
O
O
H
13a
2.00
1.01
1.94
0.97
0.93
2.99
1.00
3.16
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

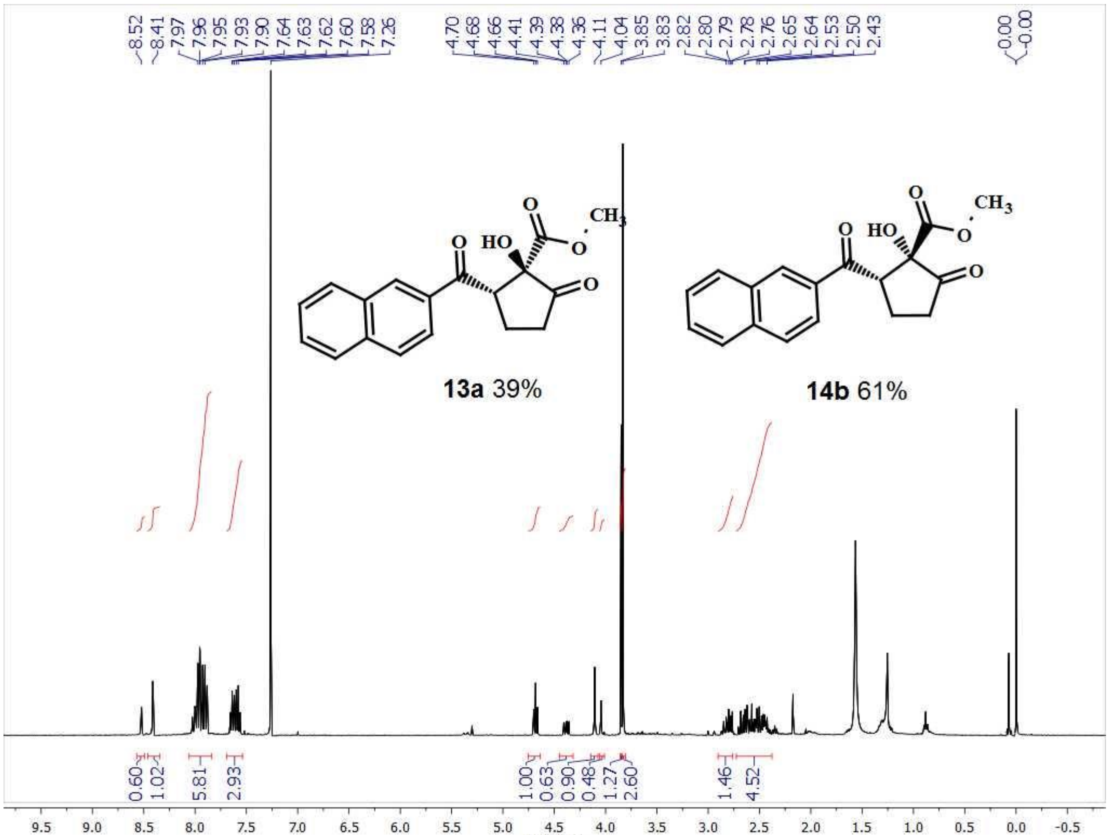

211.0
197.6
171.0
136.1
134.3
129.2
129.1
82.3
55.5
53.9
36.0
22.5
O
HO
O
CH3
O
O
H
13a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

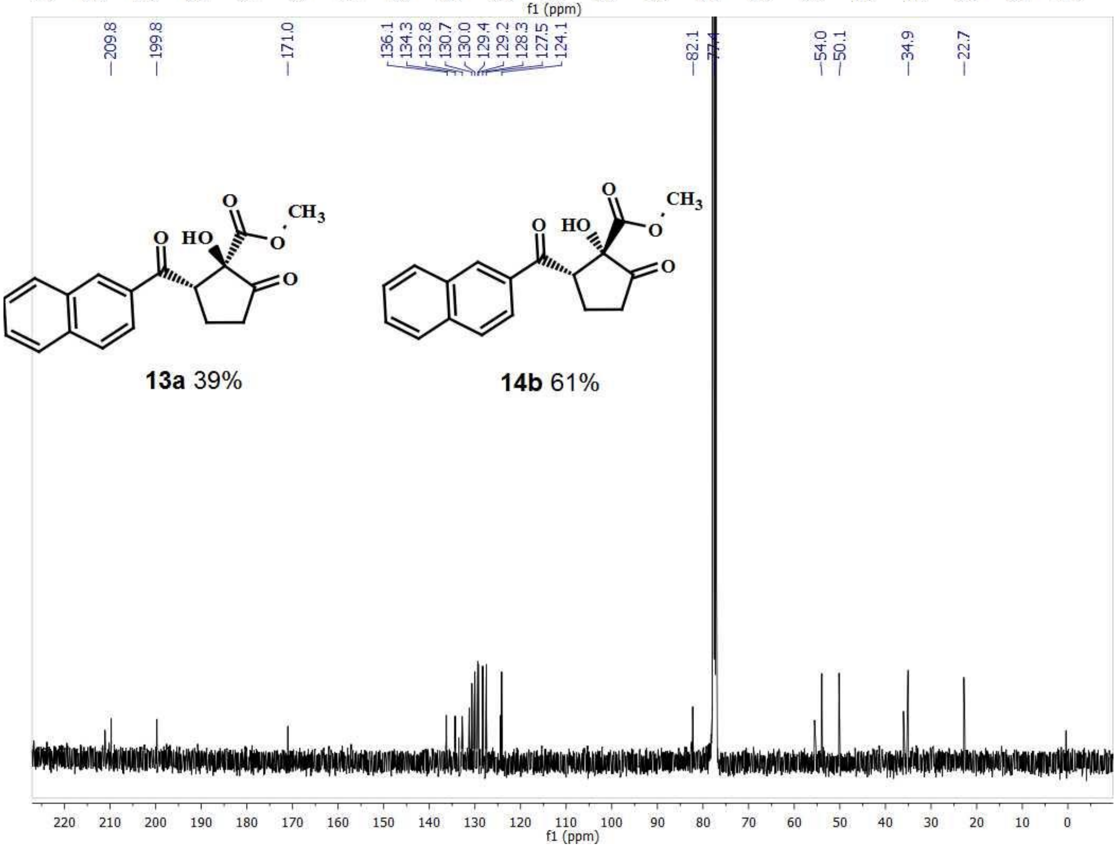

7.98 7.96 7.96 7.90 7.90 7.88 7.88 7.62 7.61 7.61 7.60 7.59 7.59 7.58 7.50 7.50 7.48 7.46 7.26
4.52 4.51 4.49 4.23 4.21 4.20 4.18 4.04 4.00 3.83 3.82
2.76 2.74 2.73 2.60 2.60 2.58 2.56 2.53 2.43 2.42 1.56
0.64
0.00
13a 25%
14a 75%
1.85 1.35 2.66
1.00 0.33 0.89 3.08
1.33 3.92
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

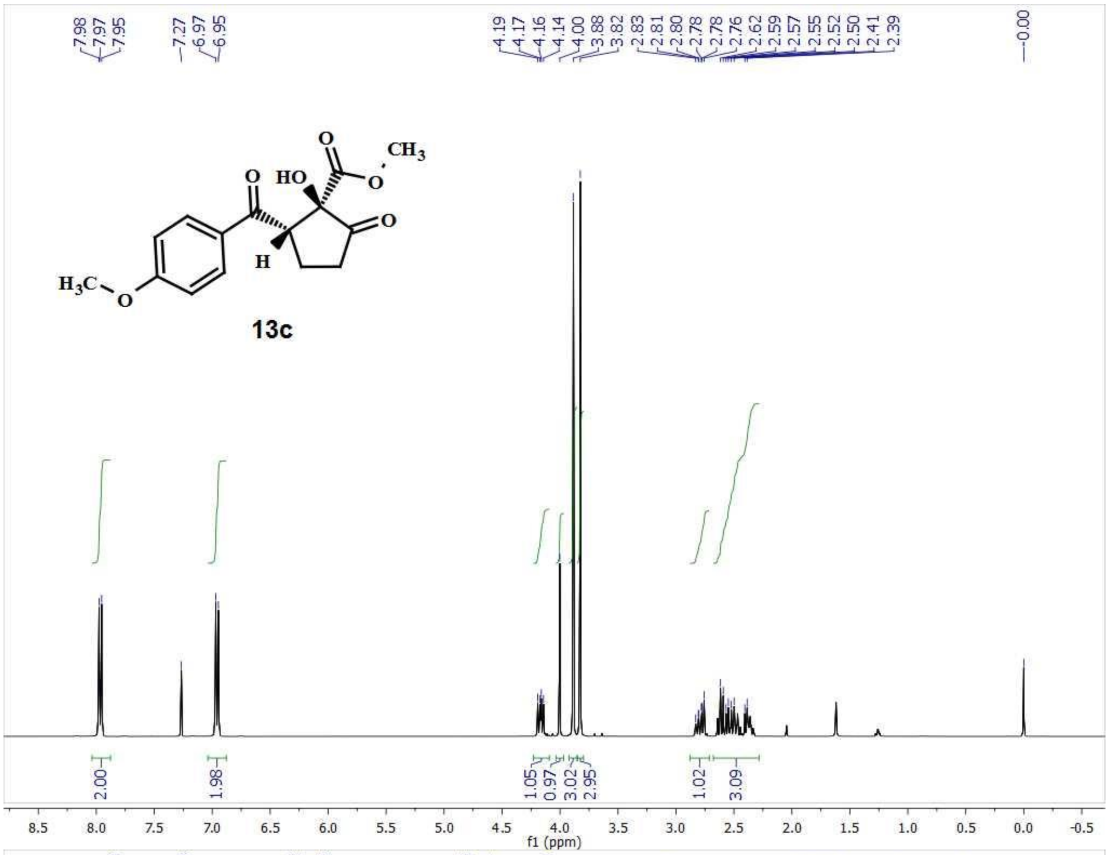

209.65
199.86
170.97
137.10 134.11 129.21 128.72
81.97
53.87 50.06
35.02
22.69
13a 25%
14a 75%
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

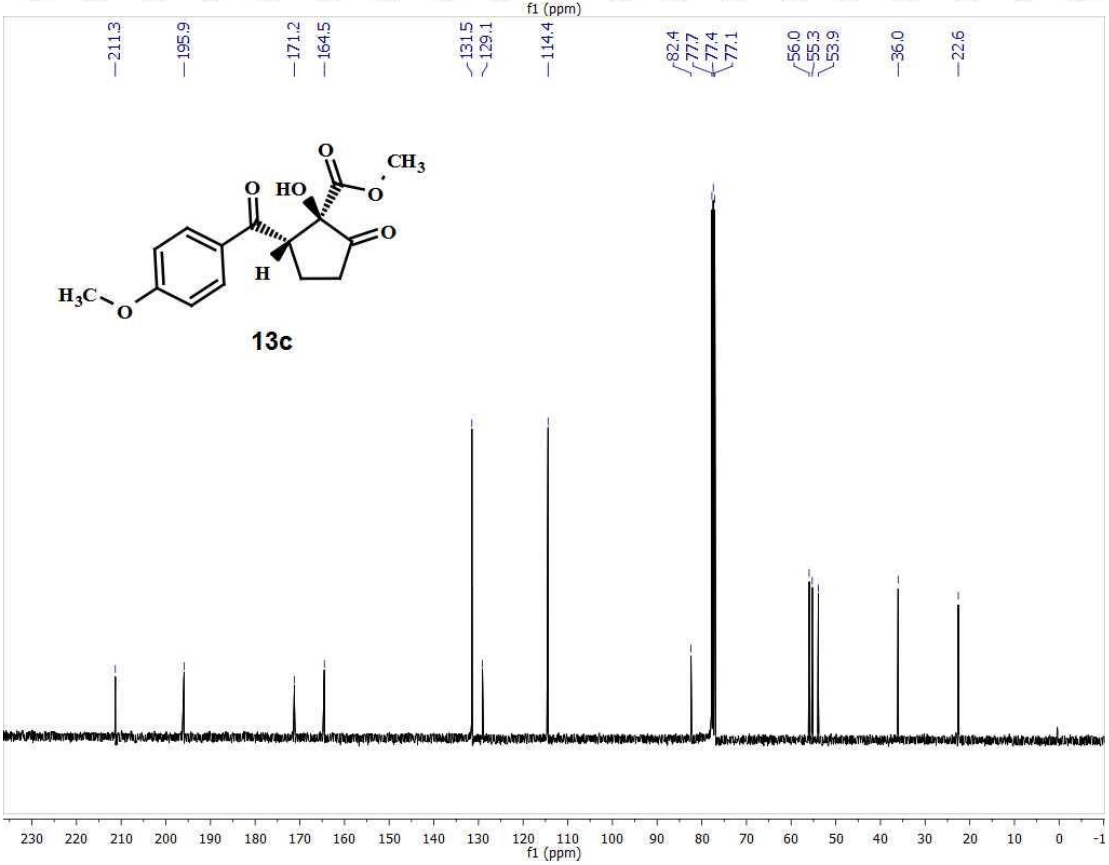

8.52
8.02
8.00
8.00
7.99
7.97
7.93
7.91
7.88
7.64
7.64
7.62
7.60
7.59
7.58
7.58
7.57
7.26
4.41
4.39
4.38
4.36
4.06
3.85
2.87
2.86
2.85
2.84
2.82
2.81
2.80
2.79
2.68
2.66
2.61
2.56
2.53
2.50
2.48
0.00
O
CH3
O
HO
O
O
H
13b
1.00
3.96
1.97
1.00
0.93
2.98
1.00
3.08
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

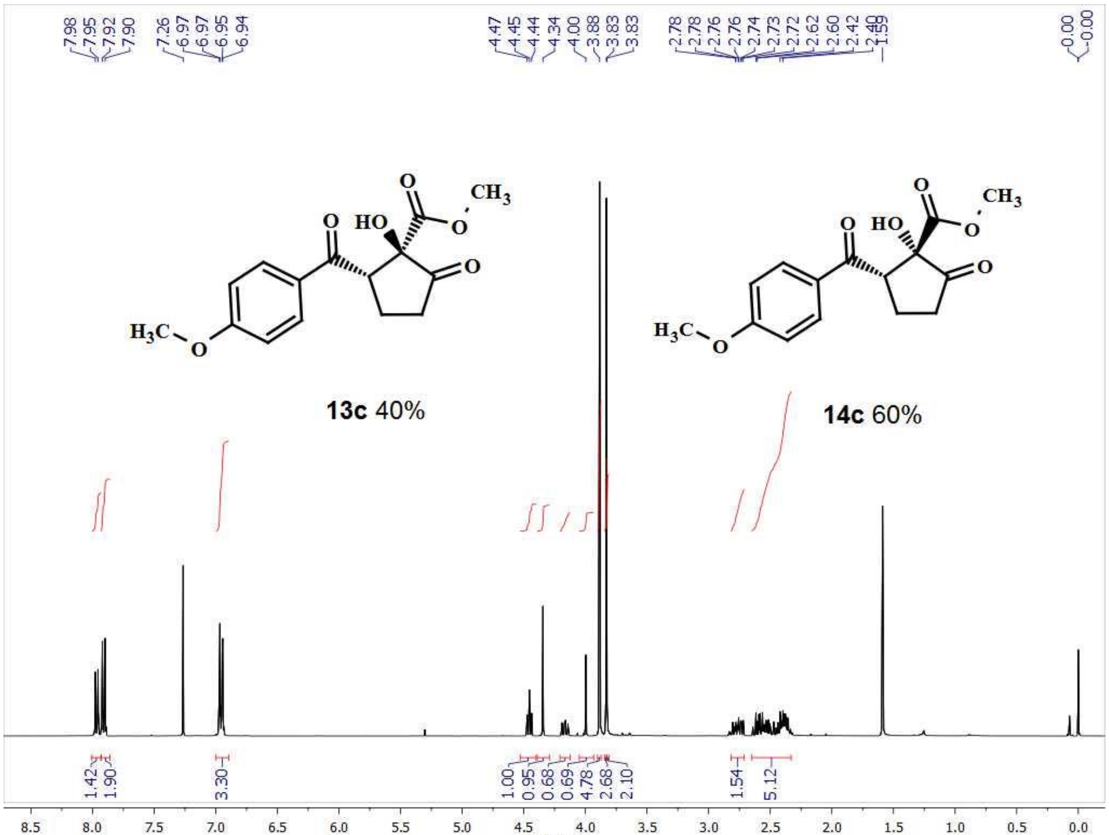

211.1
197.6
171.1
136.3
133.5
132.8
131.2
130.1
129.4
129.2
128.2
127.4
124.4
82.4
77.7
77.4
77.1
55.5
54.0
36.0
22.6
O
CH3
O
HO
O
O
H
13b
40
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

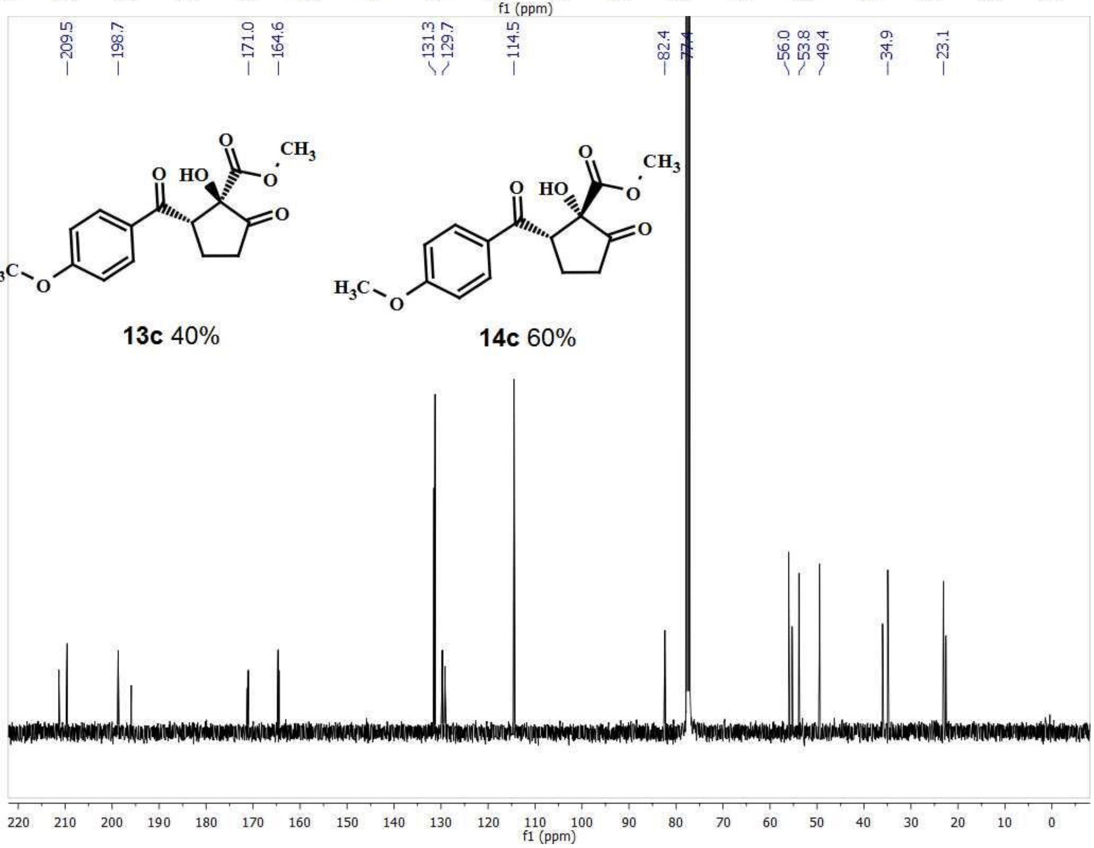

8.52
8.41
7.97
7.96
7.95
7.93
7.90
7.64
7.63
7.62
7.60
7.58
7.26
4.70
4.68
4.66
4.41
4.39
4.38
4.36
4.11
4.04
3.85
3.83
2.82
2.80
2.79
2.78
2.76
2.65
2.64
2.53
2.50
2.43
0.00
-0.00
O
HO
O
CH3
O
O
13a 39%
O
HO
O
CH3
O
O
14b 61%
0.60
1.02
5.81
2.93
1.00
0.63
0.90
0.48
1.27
2.60
1.46
4.52
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

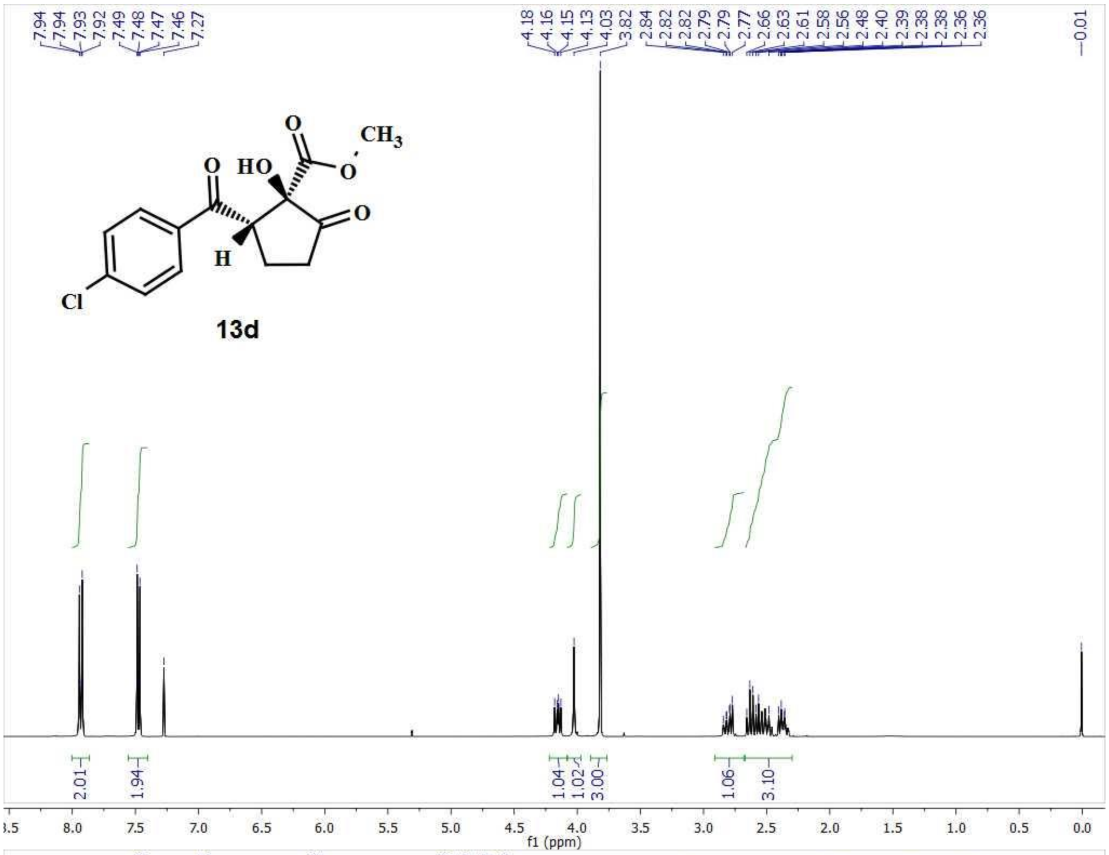

209.8
199.8
171.0
136.1
134.3
132.8
130.7
130.0
129.4
129.2
128.3
127.5
124.1
82.1
77.4
54.0
50.1
34.9
22.7
O
HO
O
CH3
O
O
13a 39%
O
HO
O
CH3
O
O
14b 61%
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

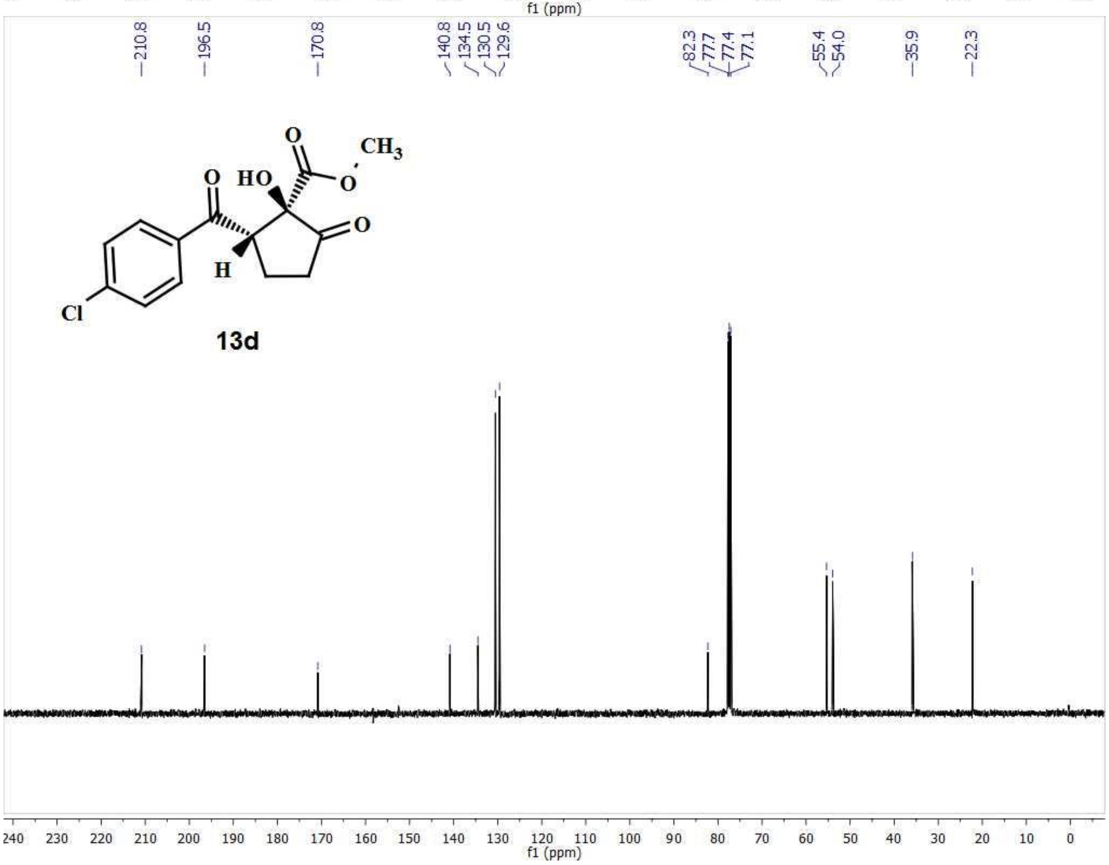

7.98
7.97
7.95
7.27
6.97
6.95
4.19
4.17
4.16
4.14
4.00
3.88
3.82
2.83
2.81
2.80
2.78
2.78
2.76
2.62
2.59
2.57
2.55
2.52
2.50
2.41
2.39
0.00
13c
2.00
1.98
1.05
0.97
3.02
2.95
1.02
3.09
f1 (ppm)

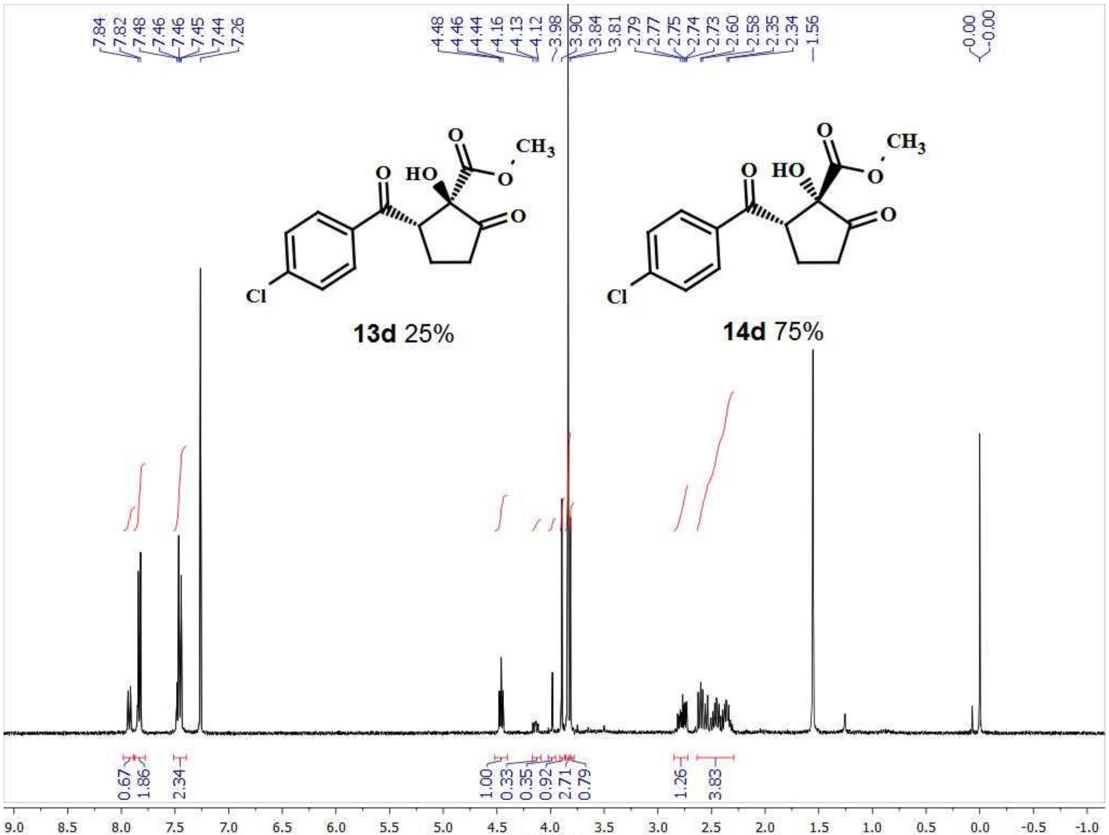

211.3
195.9
171.2
164.5
131.5
129.1
114.4
82.4
77.7
77.4
77.1
56.0
55.3
53.9
36.0
22.6
13c
f1 (ppm)

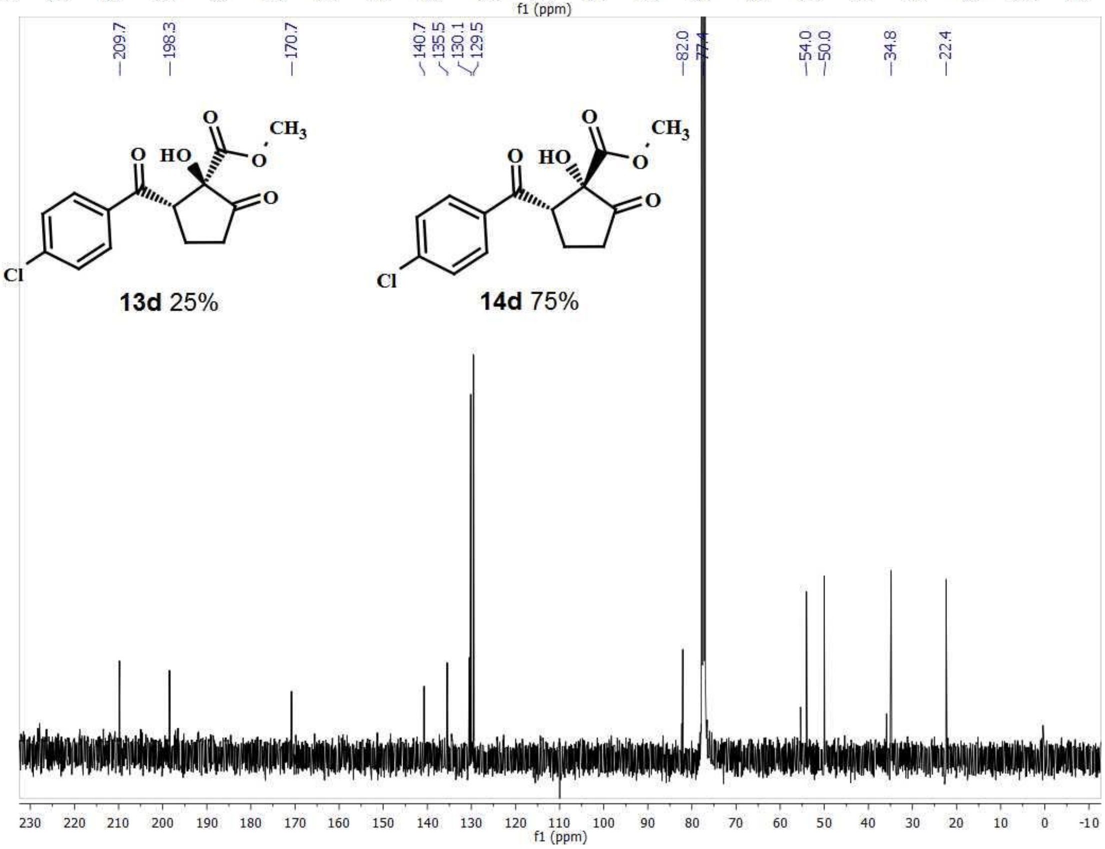

7.98
7.95
7.92
7.90
7.26
6.97
6.97
6.95
6.94
4.47
4.45
4.44
4.34
4.00
3.88
3.83
3.83
2.78
2.78
2.76
2.76
2.74
2.73
2.72
2.62
2.60
2.42
2.40
1.59
0.00
-0.00
HO
O
CH3
H3C
13c 40%
14c 60%
1.42
1.90
3.30
1.00
0.95
0.68
0.69
4.78
2.68
2.10
1.54
5.12
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

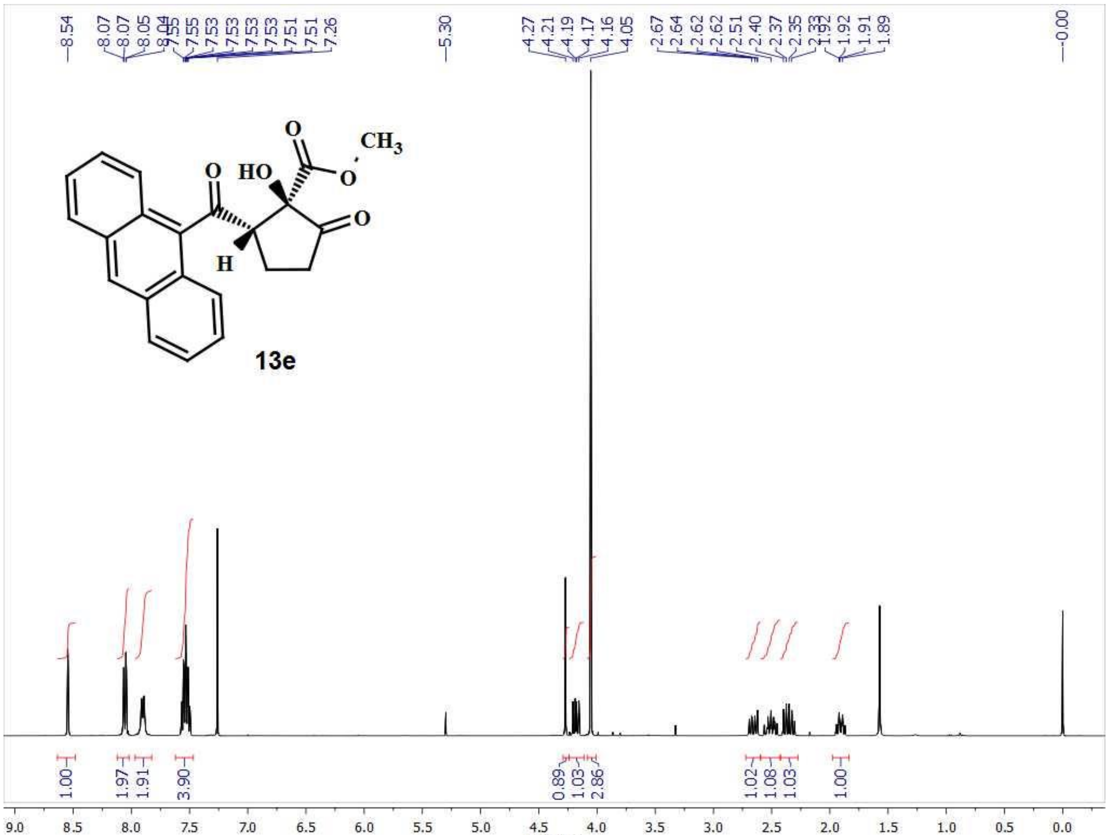

209.5
198.7
171.0
164.6
131.3
129.7
114.5
82.4
77.4
56.0
53.8
49.4
34.9
23.1
HO
O
CH3
H3C
13c 40%
14c 60%
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

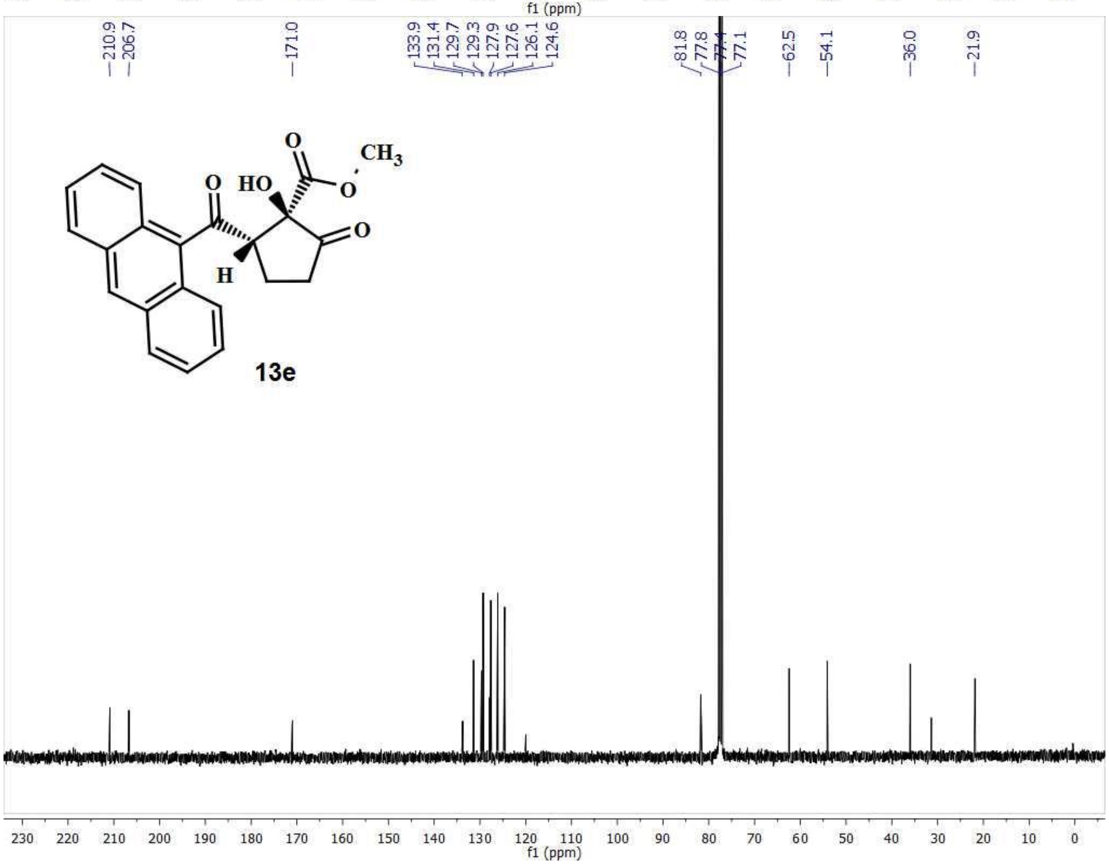

7.94
7.94
7.93
7.92
7.49
7.48
7.47
7.46
7.27
4.18
4.16
4.15
4.13
4.03
3.82
2.84
2.82
2.82
2.79
2.79
2.77
2.66
2.63
2.61
2.58
2.56
2.48
2.40
2.39
2.38
2.38
2.36
2.36
-0.01
O
CH3
O
HO
O
O
H
Cl
13d
2.01
1.94
1.04
1.02
3.00
1.06
3.10
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

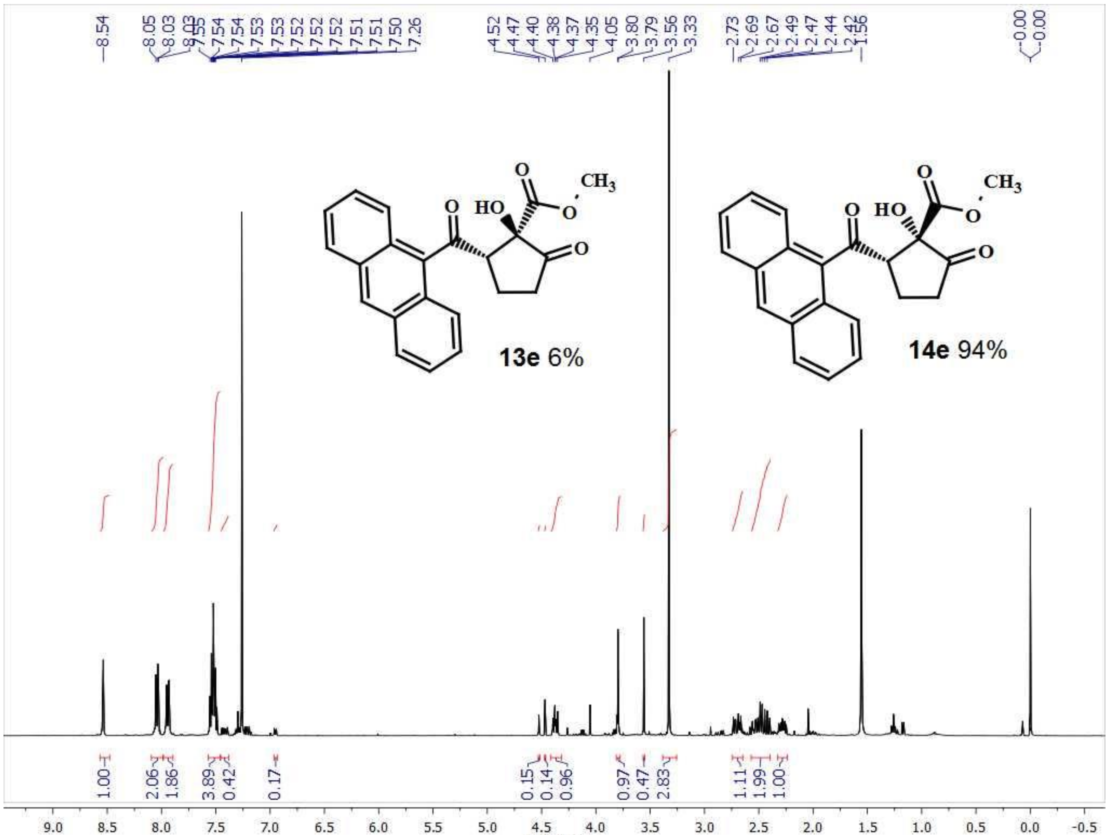

210.8
196.5
170.8
140.8
134.5
130.5
129.6
82.3
77.7
77.4
77.1
55.4
54.0
35.9
22.3
O
CH3
O
HO
O
O
H
Cl
13d
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

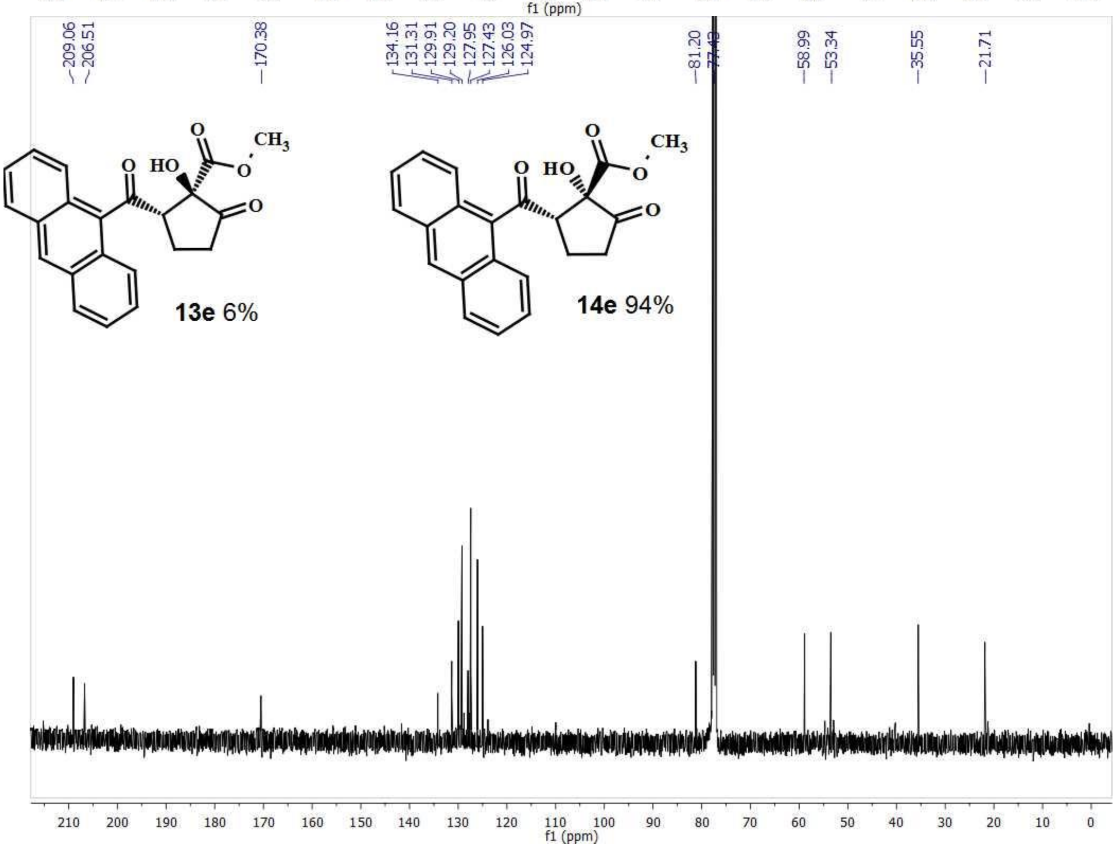

7.84
7.82
7.48
7.46
7.46
7.45
7.44
7.26
4.48
4.46
4.44
4.16
4.13
4.12
3.98
3.90
3.84
3.81
2.79
2.77
2.75
2.74
2.73
2.60
2.58
2.35
2.34
1.56
0.00
-0.00
O
CH3
O
HO
O
O
Cl
13d 25%
O
CH3
O
HO
O
O
Cl
14d 75%
0.67
1.86
2.34
1.00
0.33
0.35
0.92
2.71
0.79
1.26
3.83
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

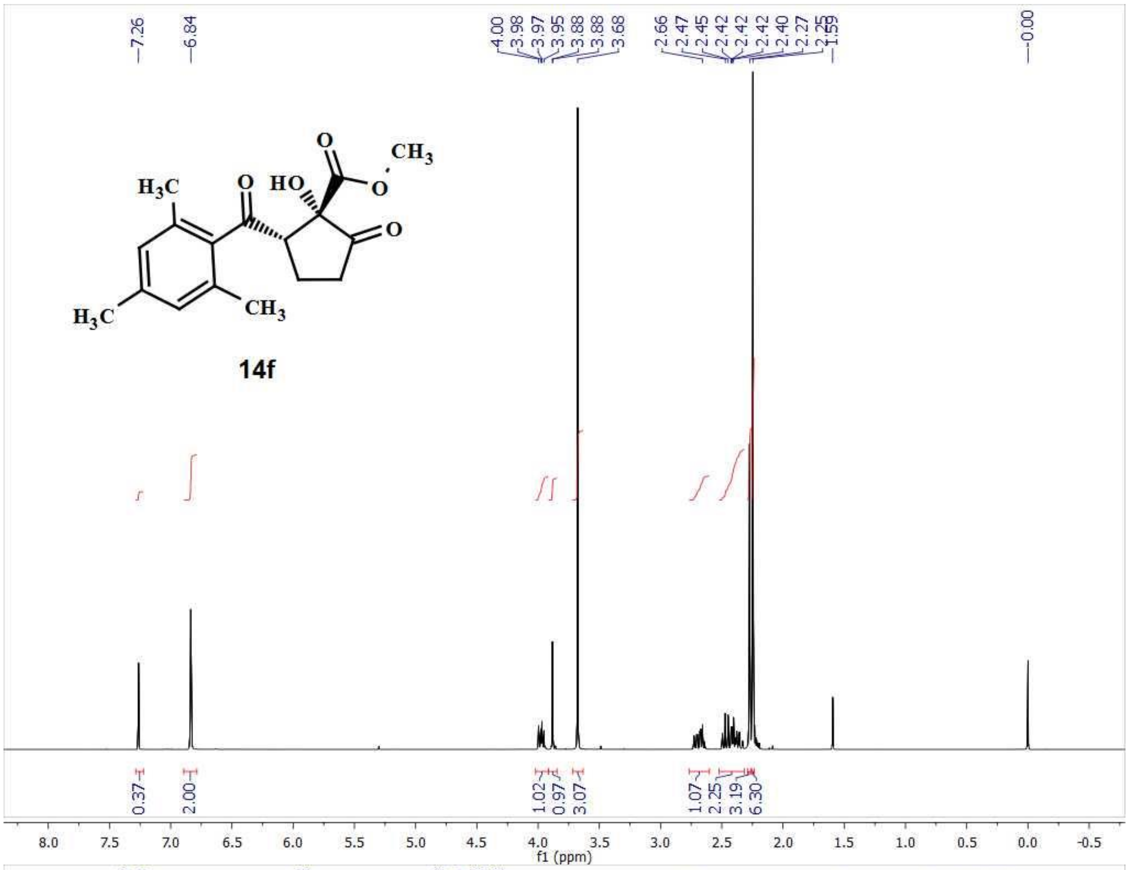

209.7
198.3
170.7
140.7
135.5
130.1
129.5
82.0
77.4
54.0
50.0
34.8
22.4
O
CH3
O
HO
O
O
Cl
13d 25%
O
CH3
O
HO
O
O
Cl
14d 75%
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

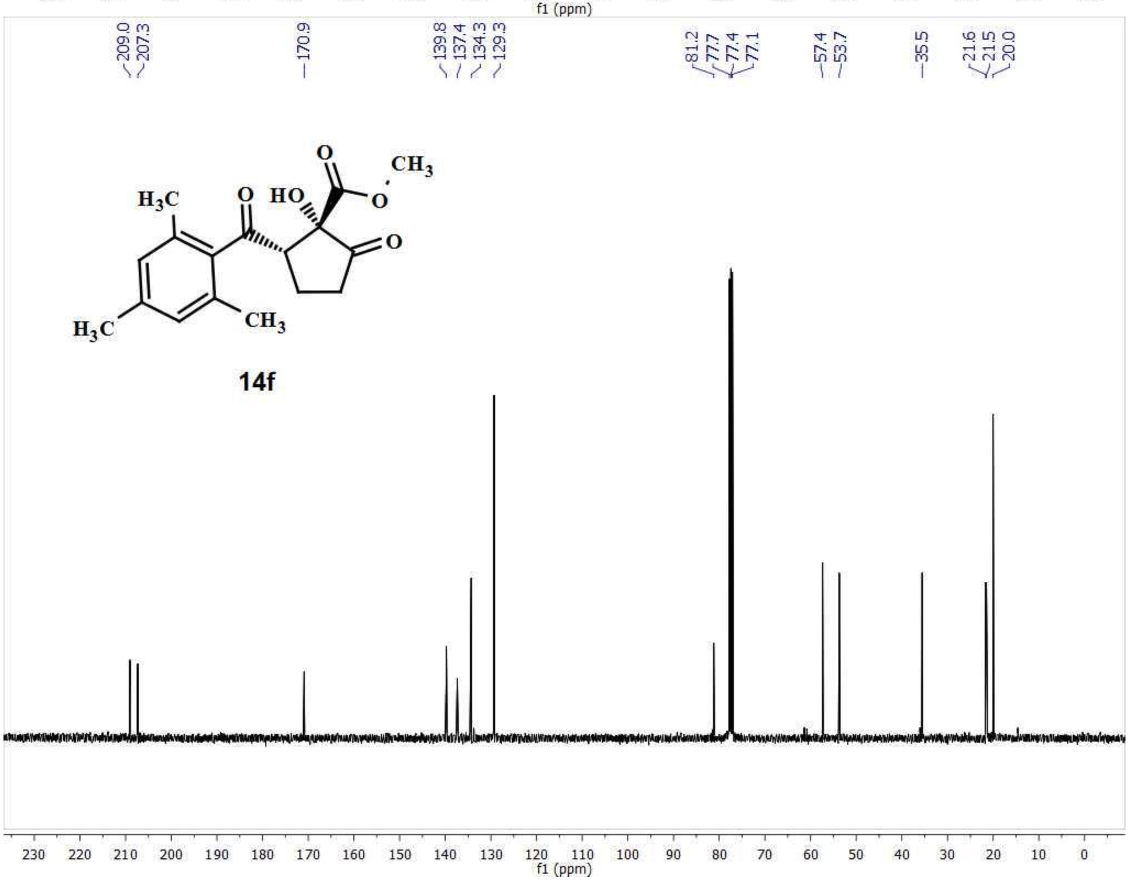

8.54
8.07
8.07
8.05
8.04
7.55
7.55
7.53
7.53
7.53
7.53
7.51
7.51
7.26
5.30
4.27
4.21
4.19
4.17
4.16
4.05
2.67
2.64
2.62
2.62
2.51
2.40
2.37
2.35
2.33
1.92
1.92
1.91
1.89
0.00
O
HO
O
CH3
O
O
H
13e
1.00
1.97
1.91
3.90
0.89
1.03
2.86
1.02
1.08
1.03
1.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


210.9
206.7
171.0
133.9
131.4
129.7
129.3
127.9
127.6
126.1
124.6
81.8
77.8
77.4
77.1
62.5
54.1
36.0
21.9
O
HO
O
CH3
O
O
H
13e
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.54
8.05
8.03
7.93
7.55
7.54
7.54
7.53
7.53
7.52
7.52
7.52
7.51
7.51
7.50
7.26
4.52
4.47
4.40
4.38
4.37
4.35
4.05
3.80
3.79
3.56
3.33
2.73
2.69
2.67
2.49
2.47
2.44
2.42
1.56
0.00
0.00
13e 6%
14e 94%
1.00
2.06
1.86
3.89
0.42
0.17
0.15
0.14
0.96
0.97
0.47
2.83
1.11
1.99
1.00
f1 (ppm)


209.06
206.51
170.38
134.16
131.31
129.91
129.20
127.95
127.43
126.03
124.97
81.20
77.43
58.99
53.34
35.55
21.71
13e 6%
14e 94%
f1 (ppm)


7.26
6.84
4.00
3.98
3.97
3.95
3.88
3.88
3.68
2.66
2.47
2.45
2.42
2.42
2.42
2.40
2.27
2.25
1.59
0.00
O
CH3
H3C
O
HO
O
O
H3C
CH3
14f
0.37
2.00
1.02
0.97
3.07
1.07
2.25
3.19
6.30
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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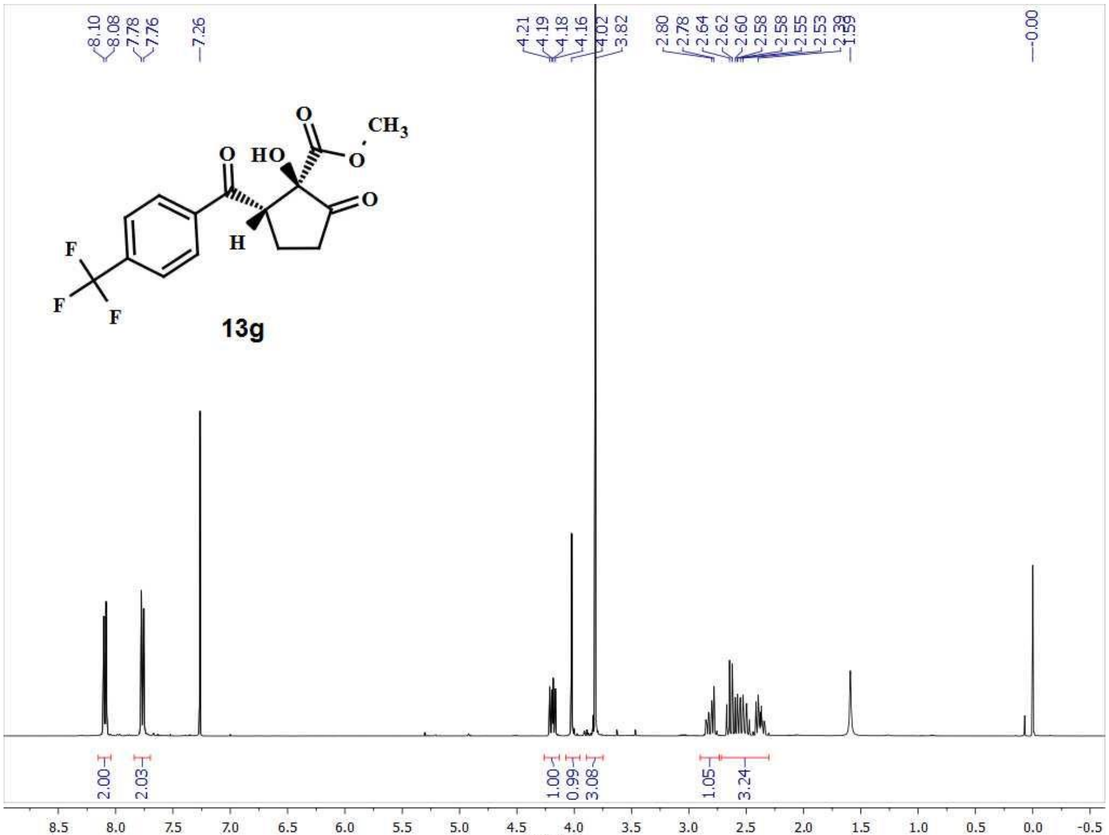
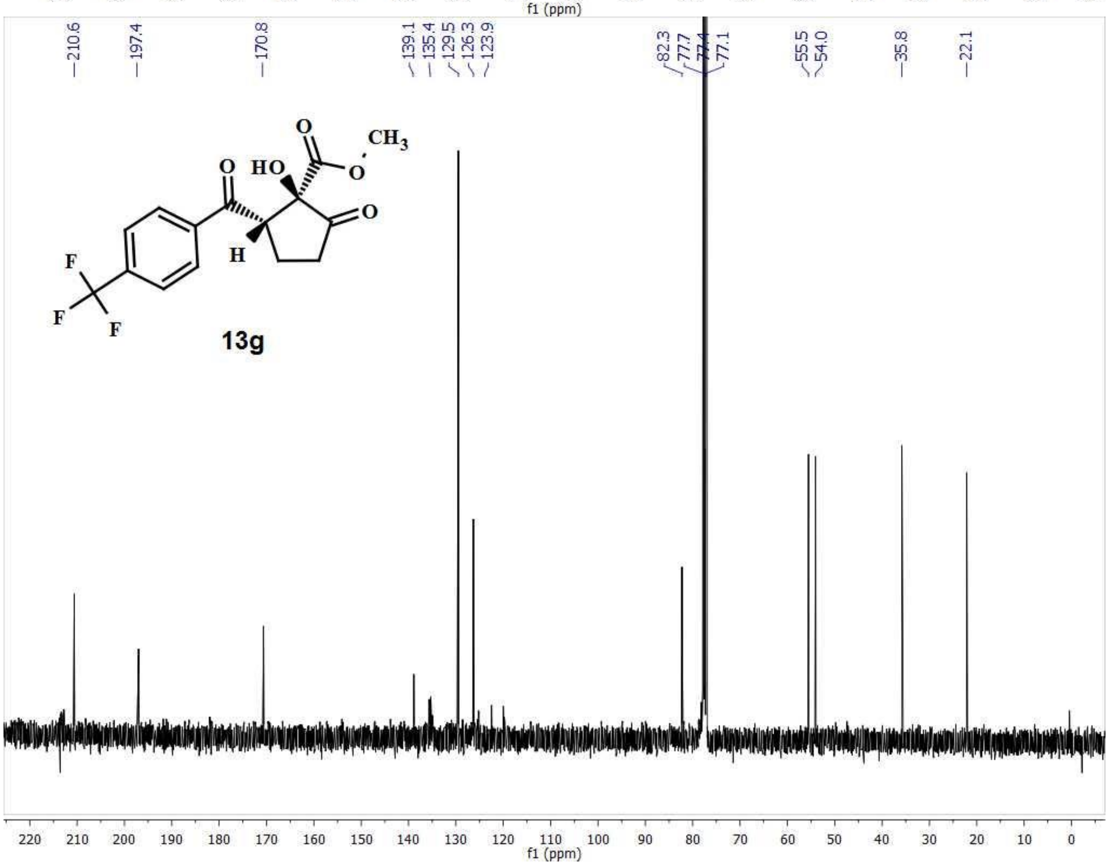
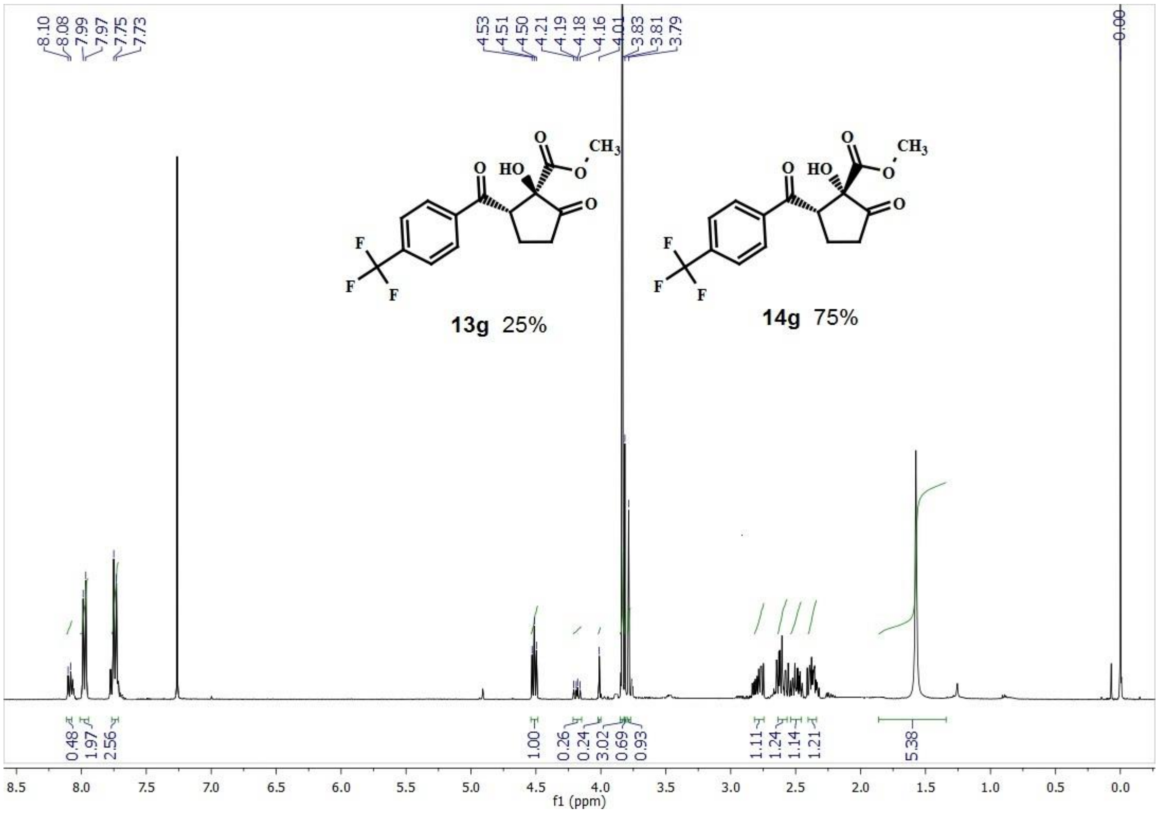
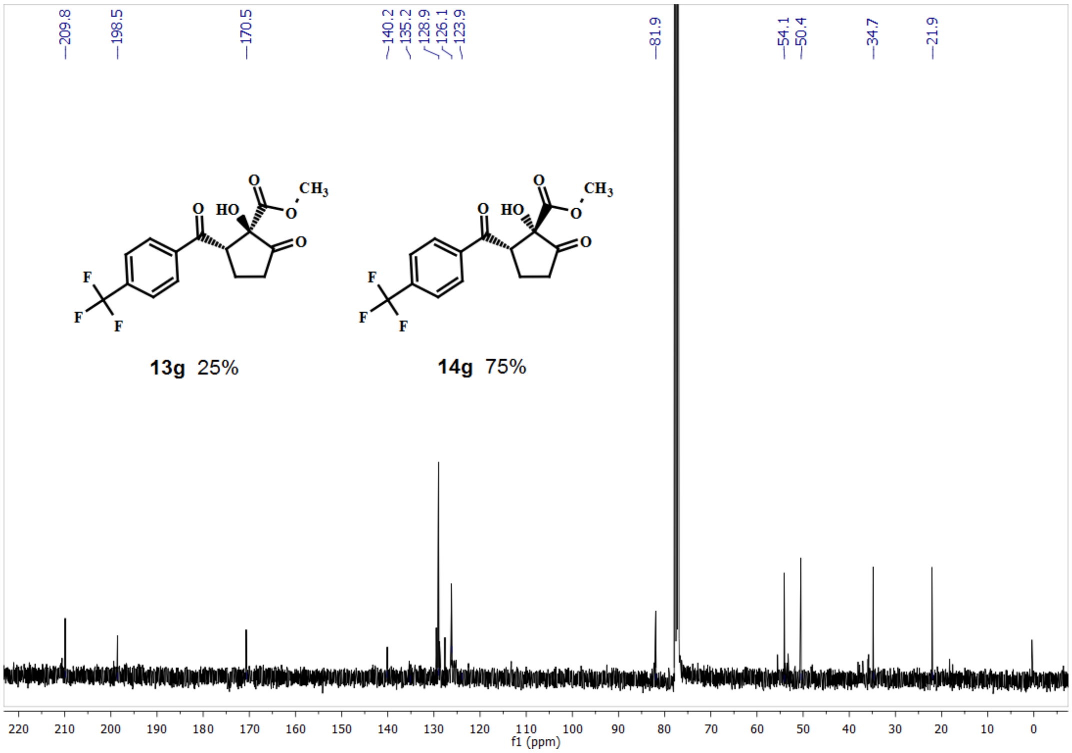
207.3
170.9
139.8
137.4
134.3
129.3
81.2
77.7
77.4
77.1
57.4
53.7
35.5
21.6
21.5
20.0
O
CH3
H3C
O
HO
O
O
H3C
CH3
14f
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.10
8.08
7.78
7.76
7.26
4.21
4.19
4.18
4.16
4.02
3.82
2.80
2.78
2.64
2.62
2.60
2.58
2.58
2.55
2.53
2.39
1.59
0.00
CH3
O
HO
O
O
F
H
F
F
13g
2.00
2.03
1.00
0.99
3.08
1.05
3.24
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

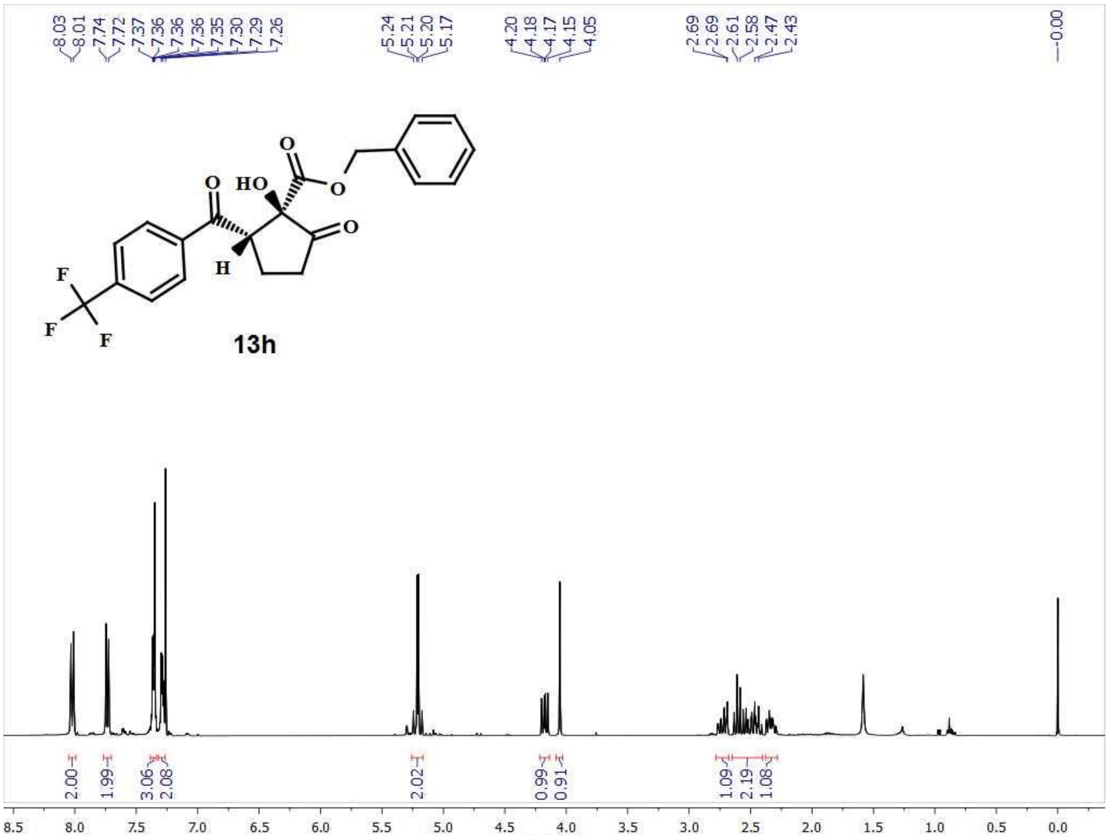

210.6
197.4
170.8
139.1
135.4
129.5
126.3
123.9
82.3
77.7
77.4
77.1
55.5
54.0
35.8
22.1
CH3
O
HO
O
O
F
H
F
F
13g
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

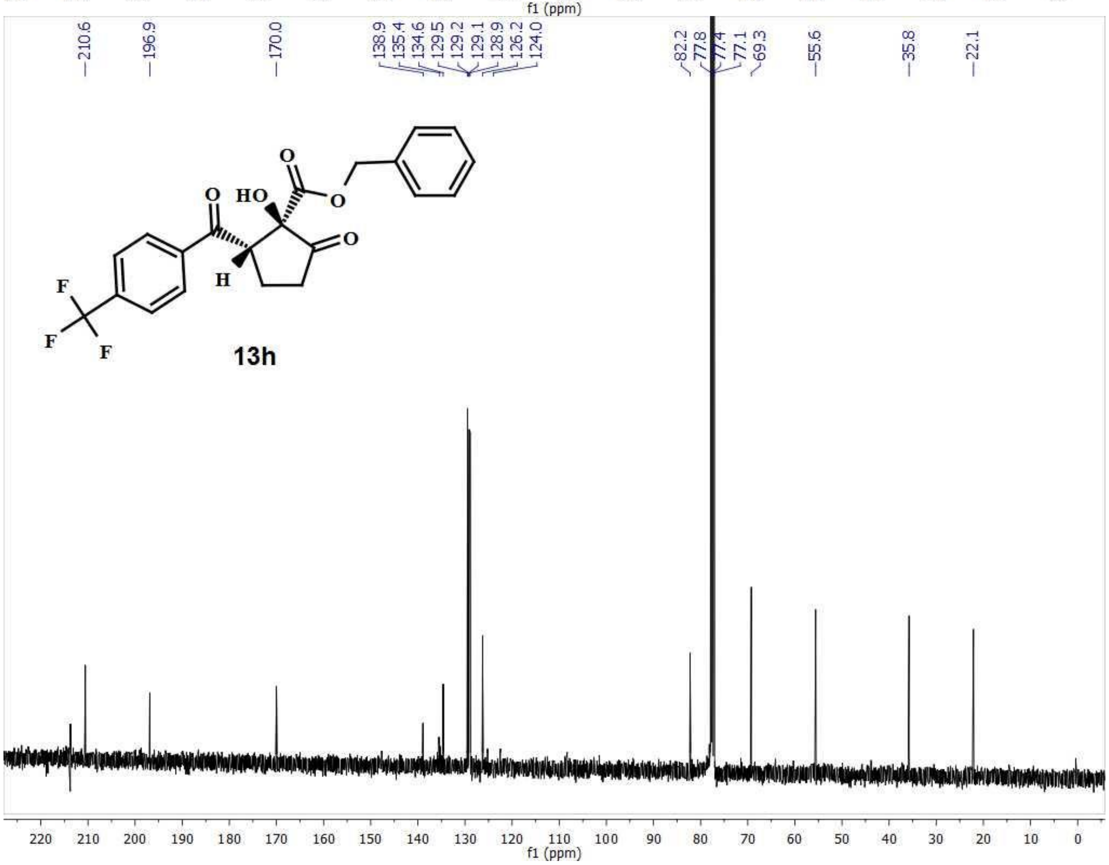


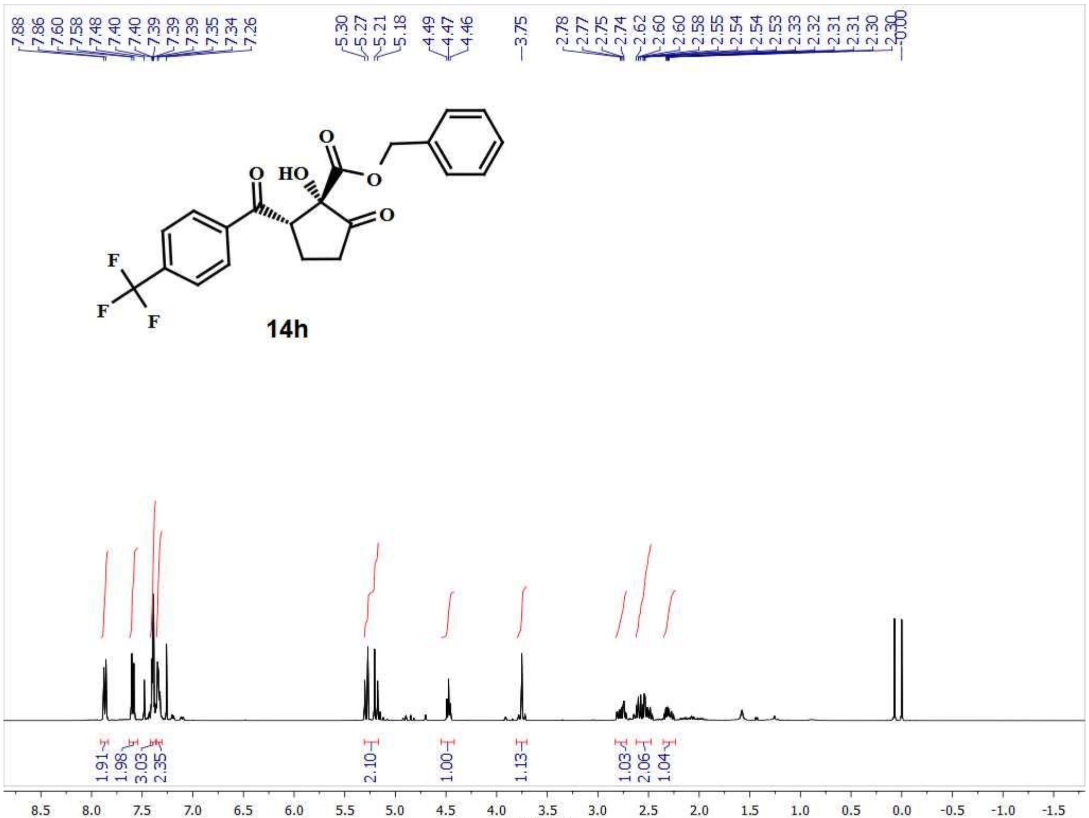
8.10
8.08
7.99
7.97
7.75
7.73
4.53
4.51
4.50
4.21
4.19
4.18
4.16
4.01
3.83
3.81
3.79
0.00
O
HO
O
CH3
O
F
F
F
13g 25%
14g 75%
0.48
1.97
2.56
1.00
0.26
0.24
3.02
0.69
0.93
1.11
1.24
1.14
1.21
5.38
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

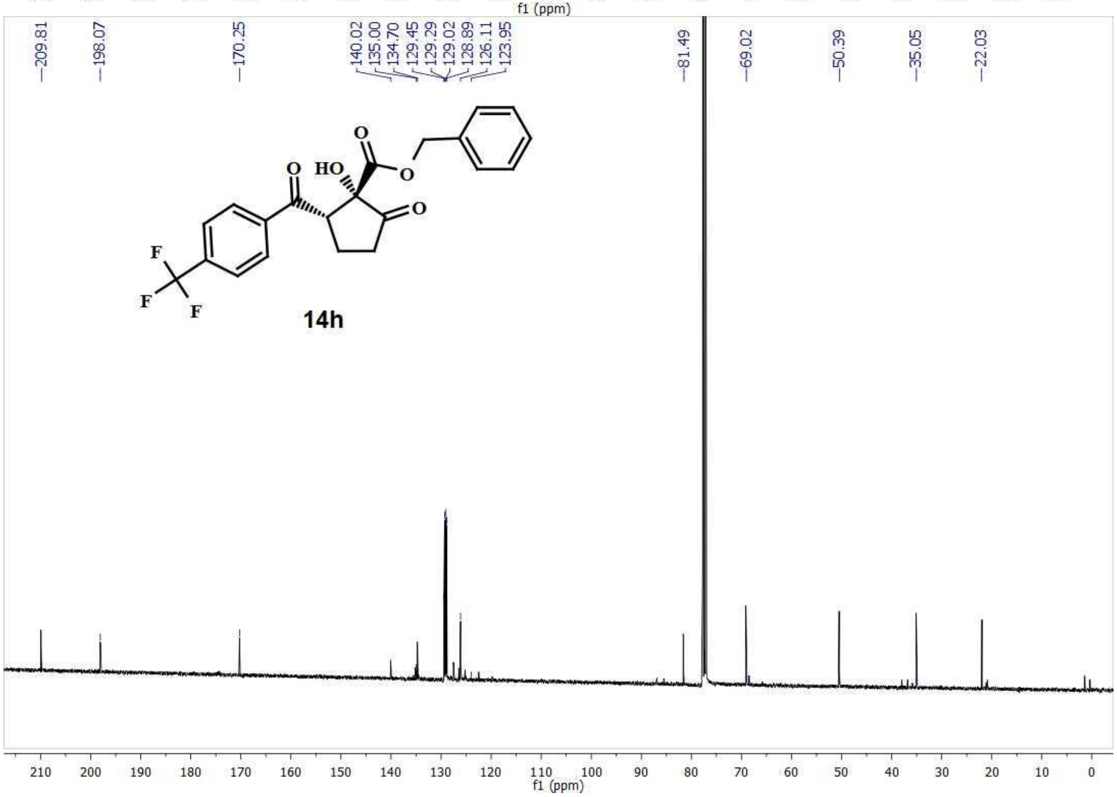


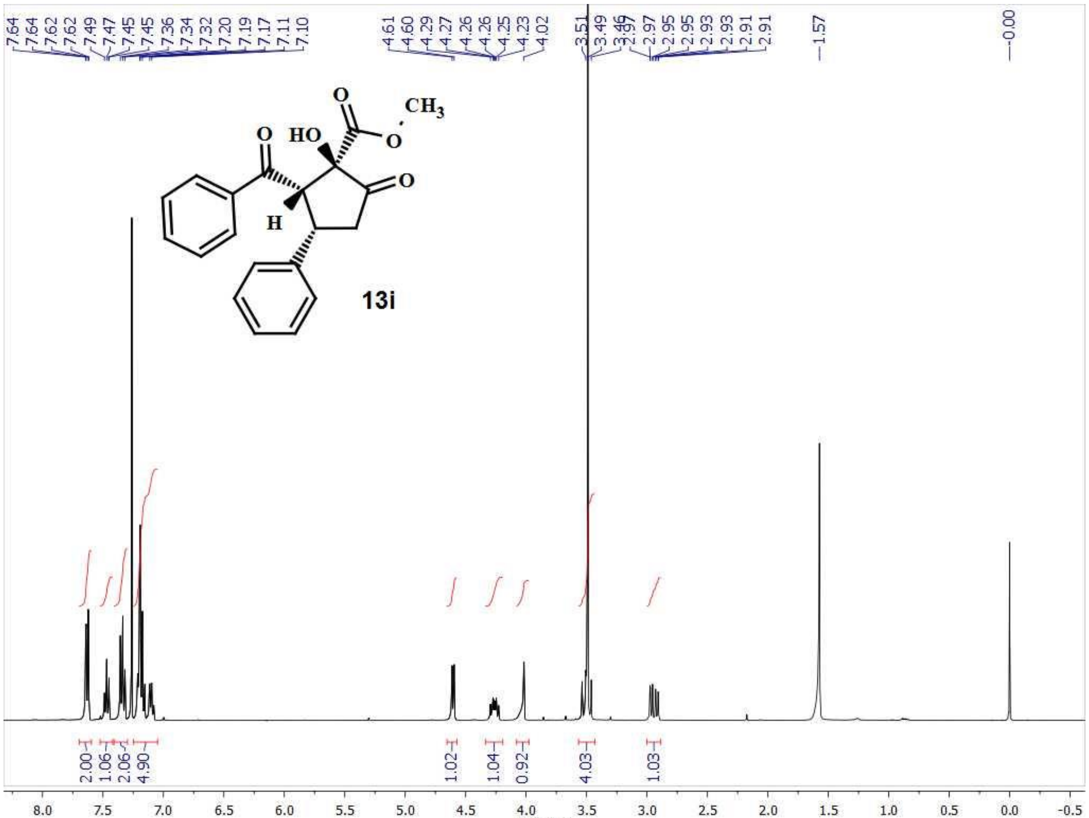
209.8
198.5
170.5
140.2
135.2
128.9
126.1
123.9
81.9
54.1
50.4
34.7
21.9
O
HO
O
CH3
O
F
F
F
13g 25%
14g 75%
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

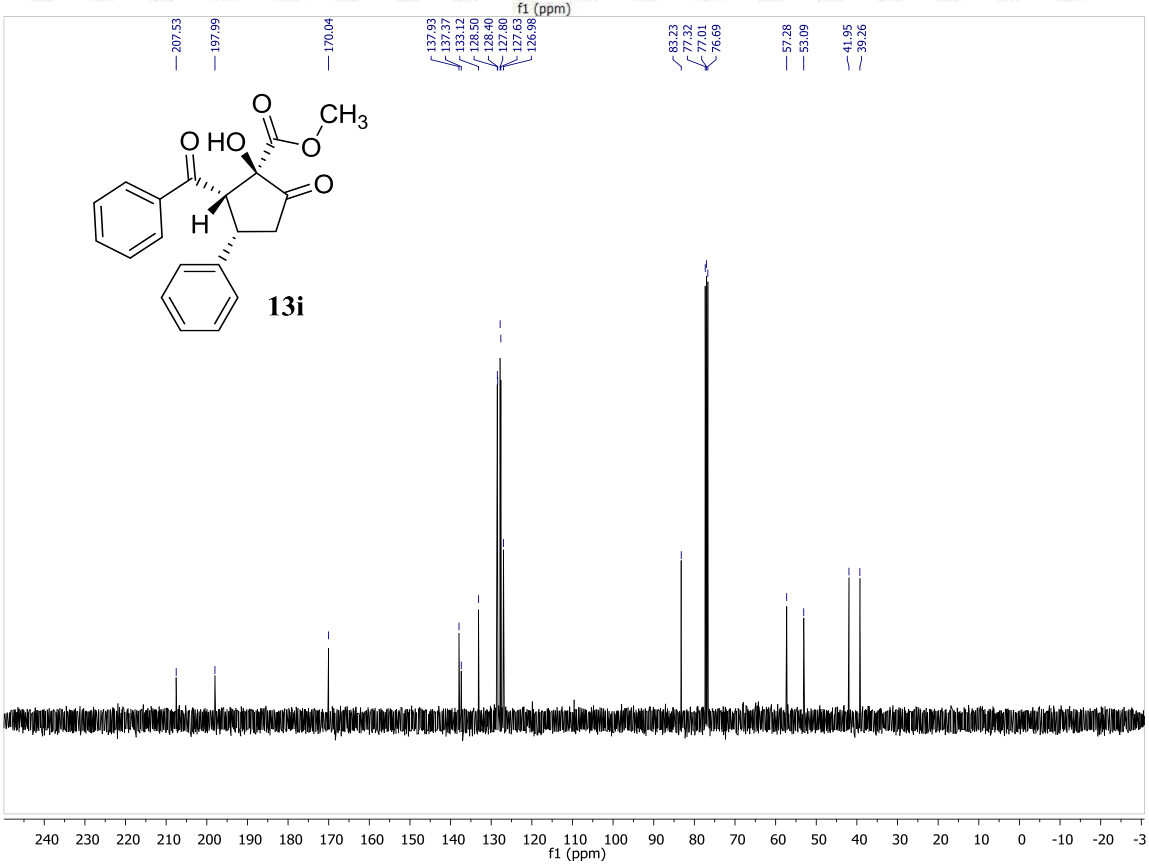

8.03
8.01
7.74
7.72
7.37
7.36
7.36
7.36
7.35
7.30
7.29
7.26
5.24
5.21
5.20
5.17
4.20
4.18
4.17
4.15
4.05
2.69
2.69
2.61
2.58
2.47
2.43
0.00
O
HO
O
O
O
H
F
F
F
13h
2.00
1.99
3.06
2.08
2.02
0.99
0.91
1.09
2.19
1.08
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

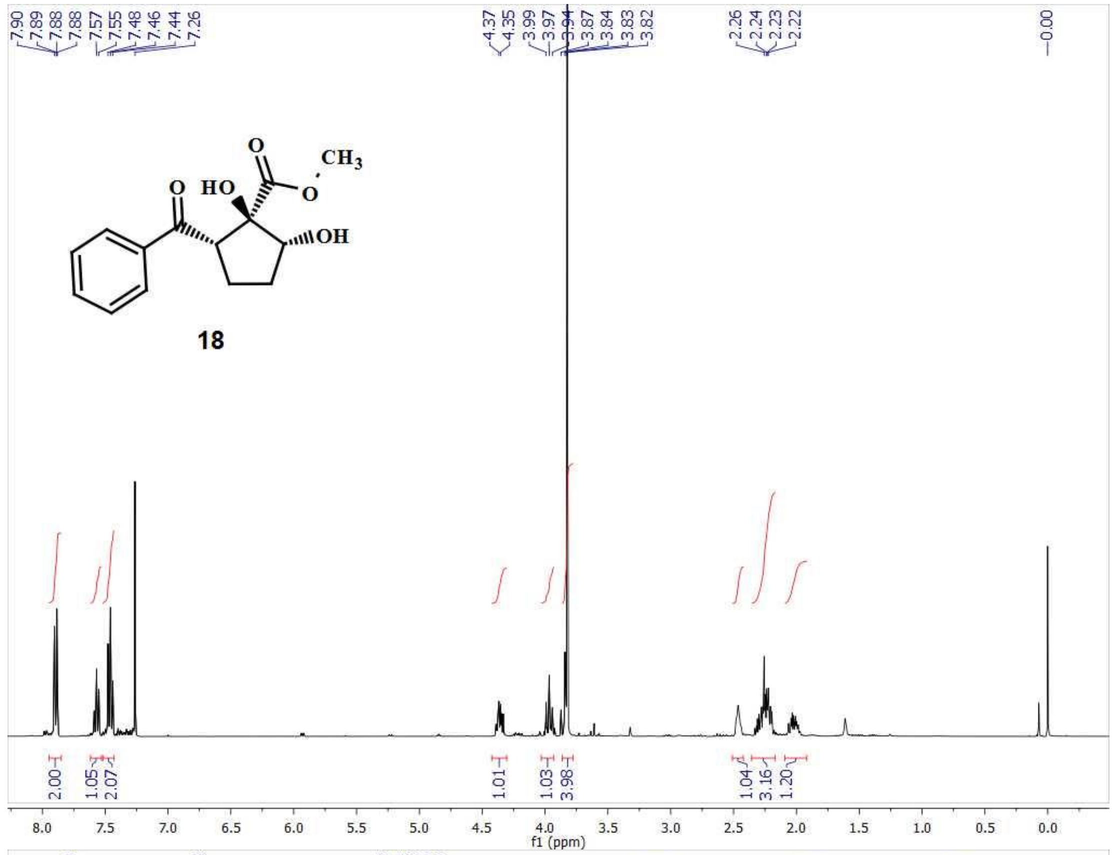

210.6
196.9
170.0
138.9
135.4
134.6
129.5
129.2
129.1
128.9
126.2
124.0
82.2
77.8
77.4
77.1
69.3
55.6
35.8
22.1
O
HO
O
O
O
H
F
F
F
13h
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

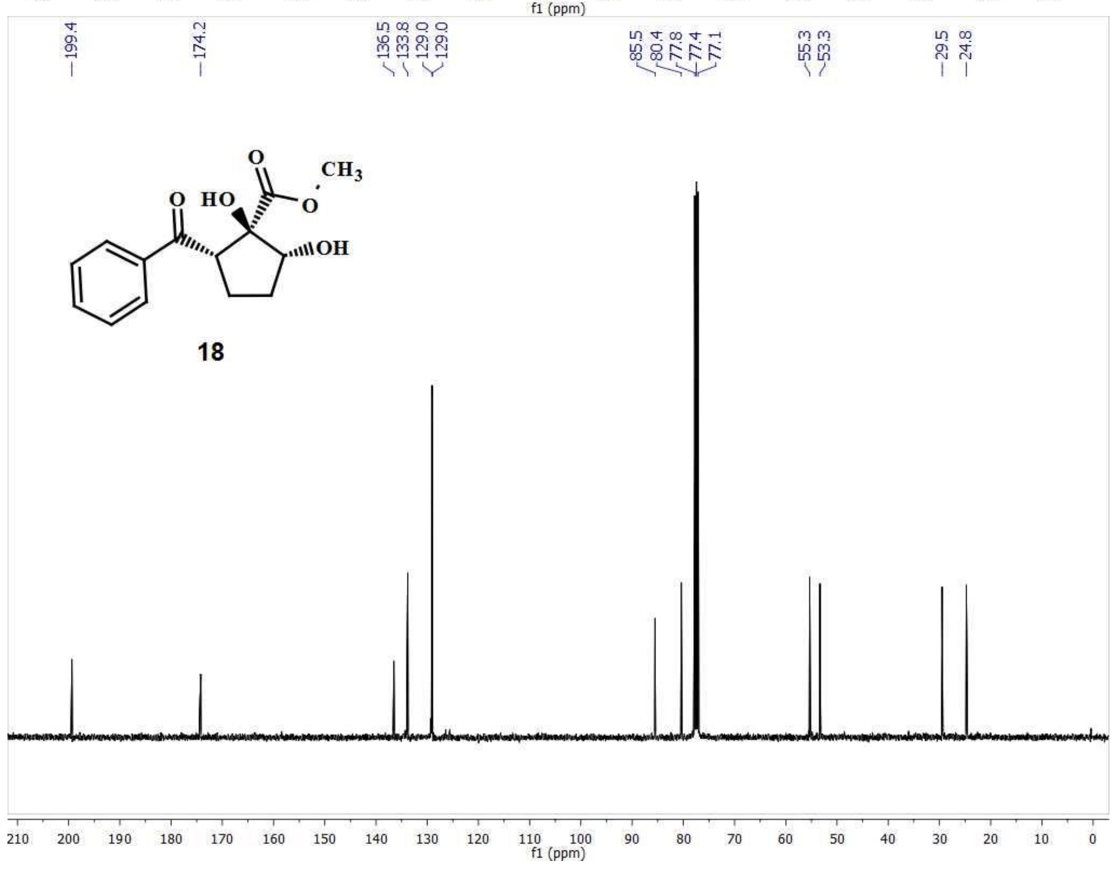

7.88
7.86
7.60
7.58
7.48
7.40
7.40
7.39
7.39
7.39
7.35
7.34
7.26
5.30
5.27
5.21
5.18
4.49
4.47
4.46
3.75
2.78
2.77
2.75
2.74
2.62
2.60
2.60
2.58
2.55
2.54
2.54
2.53
2.33
2.32
2.31
2.31
2.30
2.30
0.00
O
HO
O
O
O
F
F
F
14h
1.91
1.98
3.03
2.35
2.10
1.00
1.13
1.03
2.06
1.04
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
f1 (ppm)


209.81
198.07
170.25
140.02
135.00
134.70
129.45
129.29
129.02
128.89
126.11
123.95
81.49
69.02
50.39
35.05
22.03
O
HO
O
O
O
F
F
F
14h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.64
7.64
7.62
7.62
7.49
7.47
7.45
7.45
7.36
7.34
7.32
7.20
7.19
7.17
7.11
7.10
4.61
4.60
4.29
4.27
4.26
4.26
4.25
4.23
4.02
3.51
3.49
3.46
2.97
2.97
2.95
2.95
2.93
2.93
2.91
2.91
1.57
0.00
O
HO
O
CH3
O
O
H
13i
2.00
1.06
2.06
4.90
1.02
1.04
0.92
4.03
1.03
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

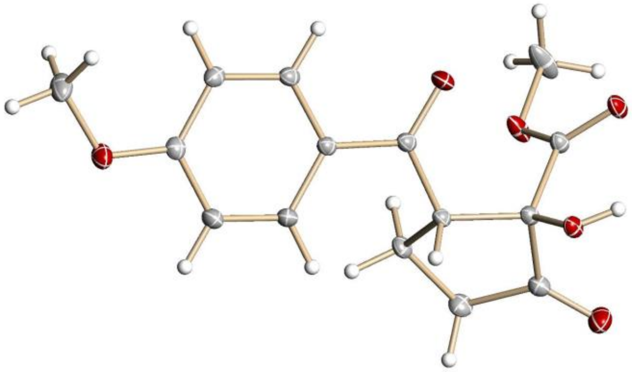

207.53
197.99
170.04
137.93
137.37
133.12
128.50
128.40
127.80
127.63
126.98
83.23
77.32
77.01
76.69
57.28
53.09
41.95
39.26
O
HO
O
CH3
O
O
H
13i
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -3
f1 (ppm)


7.90
7.89
7.88
7.88
7.57
7.55
7.48
7.46
7.44
7.26
4.37
4.35
3.99
3.97
3.94
3.87
3.84
3.83
3.82
2.26
2.24
2.23
2.22
0.00
O
HO
CH3
O
OH
18
2.00
1.05
2.07
1.01
1.03
3.98
1.04
3.16
1.20
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

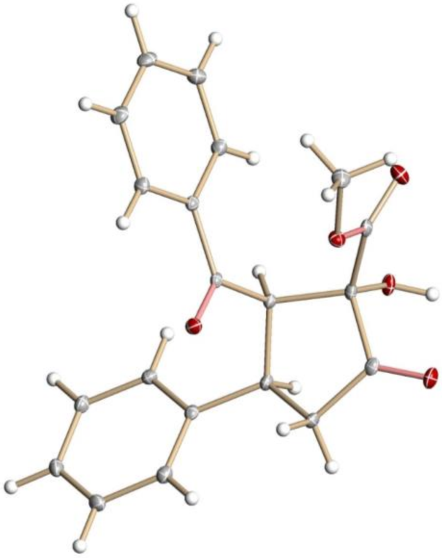

199.4
174.2
136.5
133.8
129.0
129.0
85.5
80.4
77.8
77.4
77.1
55.3
53.3
29.5
24.8
O
HO
CH3
O
OH
18
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

2.4.8 X-ray Crystal Structure Information for 13c.

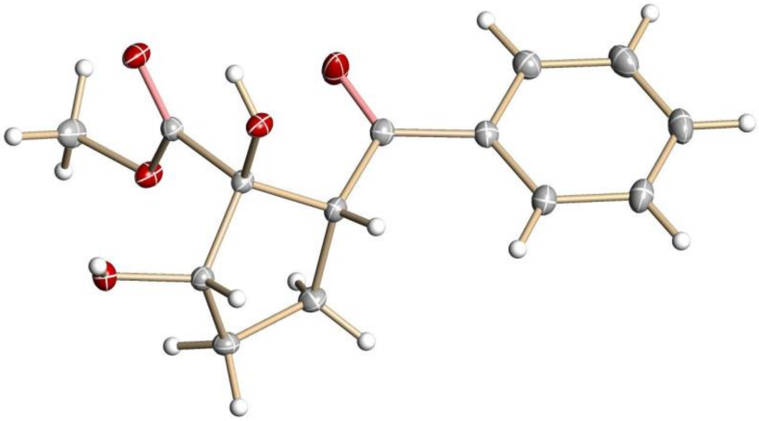
Details X-ray analysis of compounds **13c**, **13i**, and **18** can be found in support information file of our pulished data.[17]



2.4.9 X-ray Crystal Structure Information for 13i



2.4.10 X-ray Crystal Structure Information for 18



‘

2.5 References

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3. (a) Xu, G.; Hou, A.; Zheng, Y.; Zhao, Y.; Li, X.; Peng, L.; Zhao, Q. *Org. Lett.* **2007**, *9*, 291-293. (b) Zheng, J.; Xie, X.; Zhao, C.; He, Y.; Zheng, H.; Yang, Z.; She, X. *Org. Lett*. **2011**, 173-175. (c) Zhu, X.; Xiang, K.; Zhang, F.; Tu, Y. *J. Org. Chem.* **2011**, *76*, 6918-6924.
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6. Typical product mixtures were ~9:1 hydrate:ketone and were used without dehydration for subsequent chemistry. If desired, however, the products can be dehydrated by heating at 100 ºC under high vacuum for 2 h. For other examples see: (a) Rubin, M.B.; Gleiter, R. *Chem. Rev.* **2000**, *100*, 1121-1164. (b) Wasserman, H.H.; Parr, J. *Acc. Chem. Res.* **2004**, *37*, 687-701.
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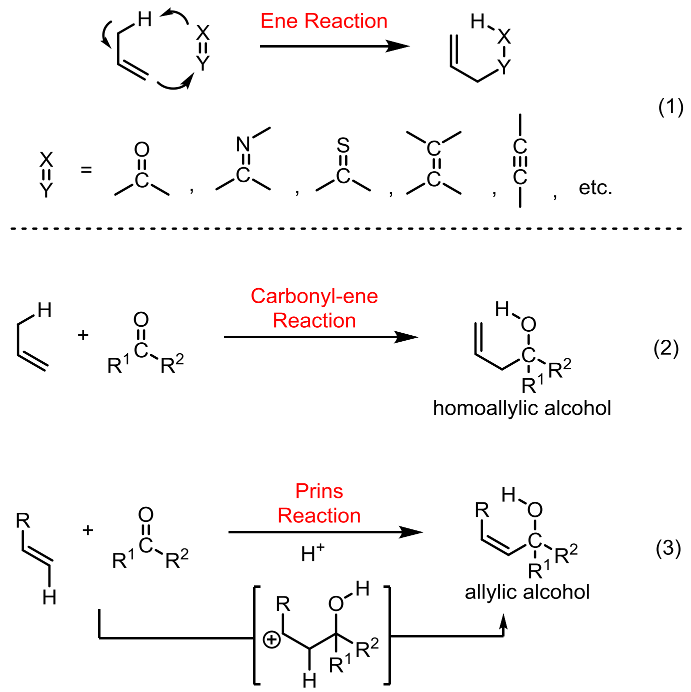
Chapter 3: Highly Enantioselective Carbonyl-Ene Reactions of 2,3-Diketoesters; Efficient and Atom-Economical Process to Functionalized Chiral *α*-Hydroxy-*β*-ketoesters

3.1 Introduction

3.1.1 Asymmetric Carbonyl-ene Reaction

The reaction of an alkene bearing an allylic hydrogen (ene) with a electron-deficient double or triple bond (enophile) that is involved in rearrangement of ene π-bond and 1,5-hydrogen shift can be classified as the ene reaction (Scheme 3.1, eq. 1).[1] When the enophile is a carbonyl group, this process is refered to as the carbonyl-ene reaction (Scheme 3.1, eq. 2).[1] The carbonyl-ene reaction is a versatile, atom-economical process for the construction of carbon-carbon bonds to generate homoallylic alcohols, which are valuable building blocks in organic synthesis. In general, the mechanism of the carbony-ene reaction proceed in a concerted process through a 6-member cyclic transitional state.[1c] However, it can also proceed in a stepwise process through a carbocation intermediate, which refered as the Prins reaction.[1d,1e] In the Prins reaction, the carbocation intermediate can react with nucleophiles or undergo elimination to the allylic alcohol (Scheme 3.1, eq.3).

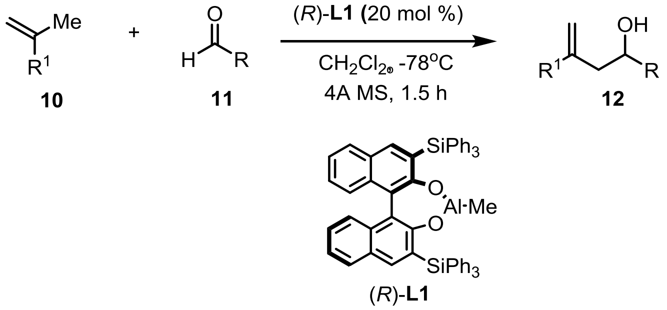
Scheme 3.1 The Ene and Carbonyl-ene Reactions.

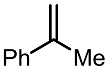
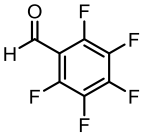
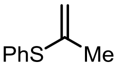
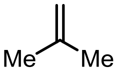
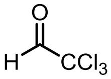
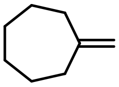
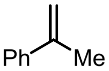
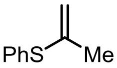
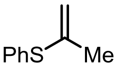
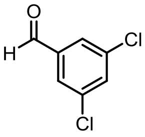


There has been great interest in the development of asymmetric variant of the carbonyl-ene reactions over the last two decades because of the efficiency of this process to access chiral homoallylic alcohols.[1c] As result, numorous catalytic systems including chiral Lewis[2-7] acid and Brønsted[8] acid catalysts have been successfully developed over the years. However, asymmetric catalysis of the carbonyl-ene reactions generally required either a reactive olefin (ene) component or an activated carbonyl group (enophile) or both. Because of these requirements, the carbonyl component has been resticted to mainly glyoxylate and glyoxal derivatives, which limited the substrate scope of this transformation. Therefore, developing an asymmetric carbonyl-ene reaction that can expand the genenally of substrate scope and increase product complexity is a important and challenging task.

Yamamoto and coworkers reported the first example of a catalytic asymmetric carbonyl-ene reaction using the chiral binapthol organo-aliminium (**L1**) catalytic system (Table 3.1). As shown in Table 3.1, the yield and enantiomeric access (ee) of the of homoallylic alcohols **(12)** range from low to moderate even at 20 mol % catalyst loading. Higher yields were obtained in several examples when 1.1 equivalent of catalyst was employed. More importantly, the requirement of activated aldehydes such as (**11a-11c**) has limited the synthetic value of this catalyst system due to its narrow substrate scope.

Table 3.1 First Catalytic Asymmetric Carbonyl-ene Reaction Catalyzed by a Chiral Organoaluminium System.[2]

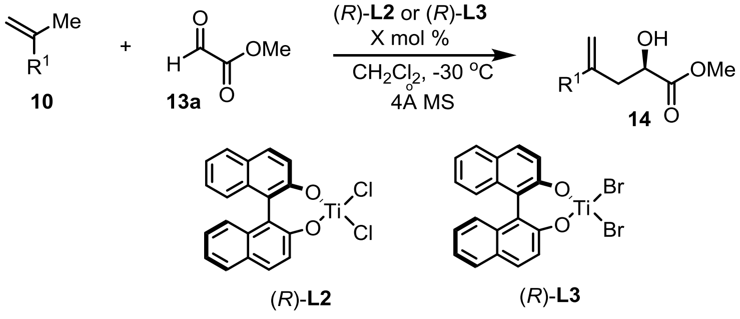

Me
R1
10
+
O
H
R
11
(R)-L1 (20 mol %)
CH2Cl2, -78°C
4A MS, 1.5 h
OH
R1
R
12
SiPh3
O
Al-Me
O
SiPh3
(R)-L1

Entry	Olefin **(10)**	Aldehyde **(11)**	% Yield	% ee
1		 **(11a)**	35	78
2		**(11a)**	88	88
3		 **(11b)**	79	78
4		**(11b)**	38	61
5		**(11b)**	43	73
6		**(11b)**	50	53
7		 **(11c)**	36	49

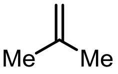
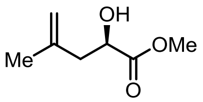
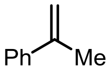
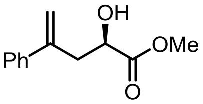
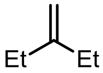
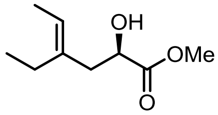
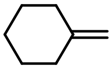
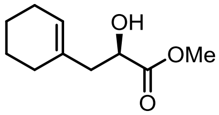
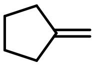
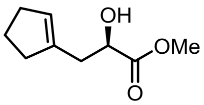
3.1.2 Lewis Acid Catalyzed Asymetric Carbonyl-ene Reactions of Glyoxylate Systems

With a few exceptions,[4,5] the glyoxylate system **(13)** has been the sole substrate class in the development of the asymmetric carbonyl-ene reactions because glyoxylates are highly activated, allow bidentate coordination to the catalyst, and provide access to functionalized chiral α-hydroxyacetates. Following the report of Yamamoto, Mikami and coworkers developed a highly enantioselective carbonyl-ene reaction with methyl glyoxylate **(13a)** catalyzed by chiral BINOL-Ti complex **L2** and **L3**.[3a,3b] Remarkably, reaction proceeded with high yield and excellent enantiocontrol, even at 1 mol % of catalyst loading, to produce enantiomer rich α-hydroxycarboxylate derivatives **(14)** (Table 3.2). However, this catalyst system is restricted to the reactive 1,1-disubstituted alkenes **(10)**, while reaction does not occur with the less reactive mono and 1,2-disubstituted alkenes. .

Table 3.2 Asymmetric Carbonyl-ene of Methyl Glyoxylate by Chiral BINOL-Ti **L2** and **L3** Catalyst.[3a]

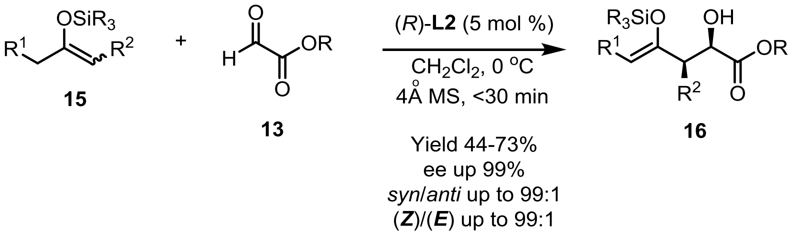


Entry	Alkene **(1)**	Catalyst	Time	Product	% Yield	% ee

		(mol %)	(h)			
1		L2 (10)	8		72	95
2		L2 (1) L3 (1)	8 3		97 98	97 95
3		L3 (5)	3		73	98
4		L2 (10) L3 (5)	8 3		82 89	97 98
5		L2 (10) L3 (5)	8 3		87 92	48 89

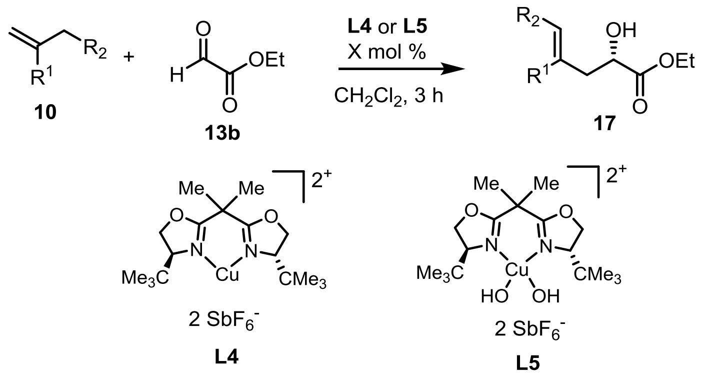
Mikami and Matsukawa extended the asymmetric carbonyl-ene reaction of glyoxylates by replacing alkenes **(10)** with silyl enol ethers **(15)**.[3c] Using 5 mol % of the previously reported BINOL-Ti **L2** catalyst, they were able to generate highly complex chiral α-hydroxyesters **(16)** in moderate yield (Scheme 3.2). Although reaction yields are moderate in most cases, excellent enantioselectivity, diastereoselectivity, and *Z/E* ratio were achieved.

Scheme 3.2 Asymmetric Carbonyl-ene Reaction with Enol Silyl Ether and Glyoxylates.

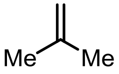
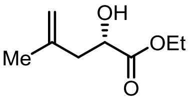
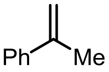
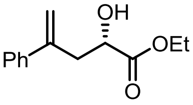
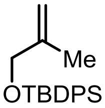
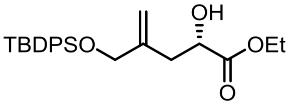
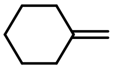
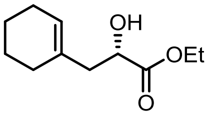


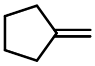
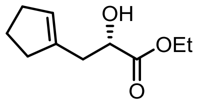
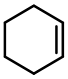
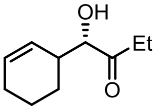
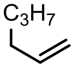
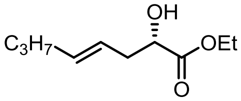
Later, Evans and coworkers reported a highly enantioselective carbonyl-ene reaction with ethyl glyoxylate **(13b)** catalyzed by Cu(II)-*tert*-butyl-bis(oxazoline) (box)complexes **L4** and **L5** to produce chiral α-hydroxyester **(17)** (Table 3.3).[3d] This report also provided the first examples of mono- and 1,2-disubstituted olefins, less reactive alkene substrates, in asymmetric carbonyl-ene reactions (Table 3.3, entries 6 and 7). In addition to mild reaction conditions, impressive yield and enantiocontrol were also accomplished. Subsequently, other chiral Lewis acid catalytic systems were also developed for the glyoxylate system such as the chiral salen-cobalt complex **L6**[3i] and In(III)-pybox complex **L7**[3j] (Scheme 3.3).

Table 3.3 Asymmetric Carbonyl-ene of Glyoxylate with Cu(II)-*tert*-butyl-bis(oxazoline) (box) Complexes **L4** and **L5** Catalysts.[3d]

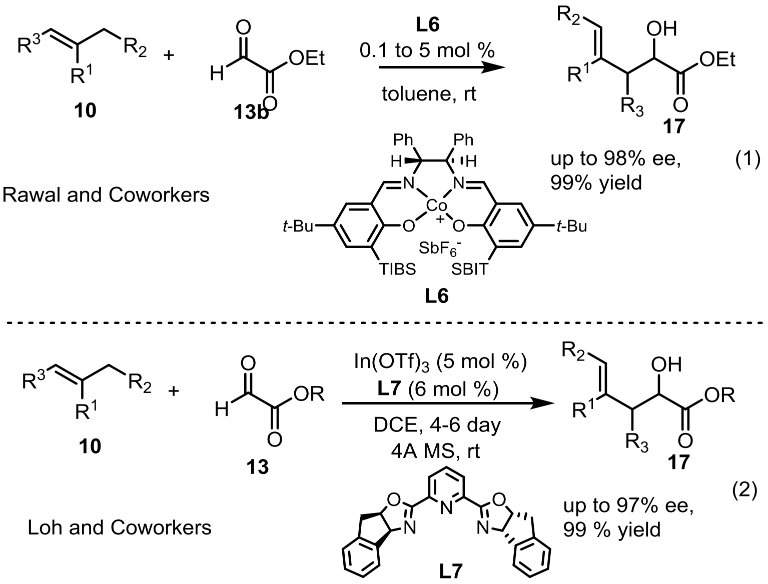


R2
R1
10
+
H
O
OEt
O
13b
L4 or L5
X mol %
CH2Cl2, 3 h
R2
OH
R1
OEt
O
17
Me
Me
2+
O
O
N
N
Cu
Me3C
CMe3
2 SbF6-
L4
Me
Me
2+
O
O
N
N
Cu
Me3C
CMe3
HO
OH
2 SbF6-
L5

Entry	Olefin **(1)**	Catalyst (mol %)	Temp. (C)	Product	% Yield	% ee
1		**L5** (1)	0		83	96
2		**L5** (1)	0		97	93
3		**L5** (1)	25		72	96
4		**L5** (1)	0		90	97

5		**L5** (10)	0		95	96
6		**L4** (10)	0		95	98
7		**L4** (10)	25		96	98

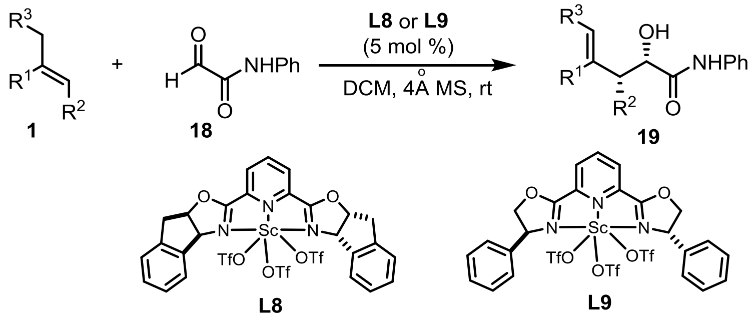
Scheme 3.3 Lewis acid Catalyzed Asymetric Carbonyl-ene Reactions of Glyoxylates.[3i,3j]

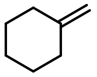
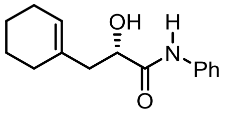
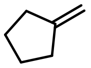
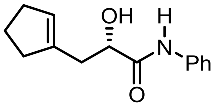
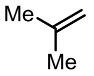
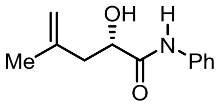
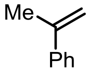
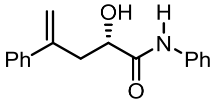
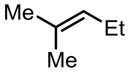
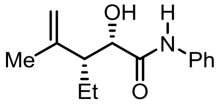
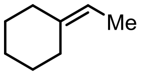
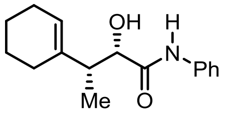
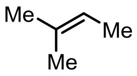
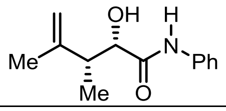

10
13b
L6
0.1 to 5 mol %
toluene, rt
17
up to 98% ee, 99% yield
(1)
Rawal and Coworkers
L6
10
13
In(OTf)3 (5 mol %)
L7 (6 mol %)
DCE, 4-6 day
4A MS, rt
17
up to 97% ee, 99 % yield
(2)
Loh and Coworkers
L7

3.1.3 Sc(III)-pybox Catalyzed Asymmetric Carbonyl-ene Reaction with *N*-Phenyl Glyoxamide

Evans and Wu reported that Sc(III)-pybox **L8** and **L9** complexes are effective catalysts for asymmetric carbonyl-ene reactions of 1,1-disubstituted or trisubstituted olefins with *N*-phenyl glyoxamide **(18)** to generate the chiral α-hydroxycarboxamides **(19)** (Table 3.4).[7e] In addition to high yields and ee's observed for 1,1-disubstituted olefins, entries 1-4, trisubstituted olefins also exhibited high diastereocontrol (Table 3.4, entries 5-7). The *N*-phenylcarboxamides employed in this study may be readily activated for either hydrolysis or transesterification.

Table 3.4 Asymmetric Carbonyl-ene Reaction with *N*-Phenyl Glyoxamide.[7e]

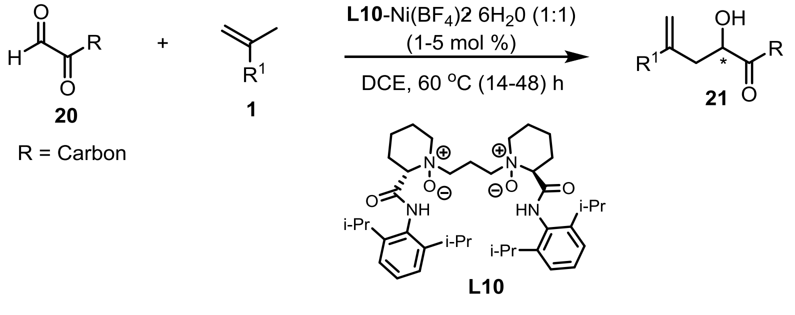

R3
R1
R2
1
+
H
O
NHPh
O
18
L8 or L9
(5 mol %)
DCM, 4Å MS, rt
R3
OH
R1
NHPh
R2
O
19
O
N
Sc
N
N
O
TfO
OTf
OTf
L8
O
N
Sc
N
N
O
TfO
OTf
OTf
L9

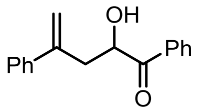
Entry	Olefins	Catalyst	Product	% Yield	% ee	dr
1		**L8**		89	94	-
2		**L8**		99	94	-
3		**L8**		78	94	-
4		**L8**		73	92	-
5		**L9**		58	96	9:1
6		**L9**		78	98	9.3:1
7		**L9**		78	94	13:1

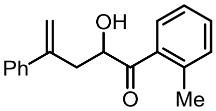
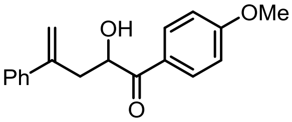
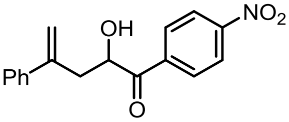
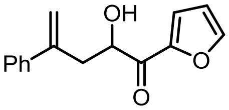
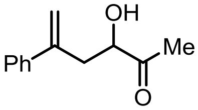
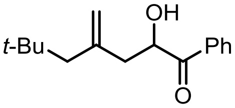
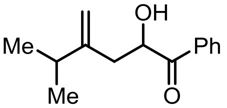
3.1.4 Lewis acid Acid Catalyzed Asymetric Carbonyl-ene Reaction of Glyoxyl Derivatives

The substrate scope is a limiting factor for asymmetric carbonyl-ene reactions mainly because of the requirement of activated aldehydes. The use of glyoxal derivative **(20)** have expand the scope of this transformation, which allows access to chiral *γ,δ*-unsaturated-*α*-hydroxyketones **(21)**. The chiral Lewis acid catalyst systems that have been reported for asymmetric carbonyl-ene reactions with glyoxal derivatives include those of cobalt,[6a] platinum,[6b] and palladium.[6c] Recently, Feng and coworkers have greatly extended the substrate scope of this transformation by utilizing *N,N*'-dioxide-nickel(II) **L10** as the catalyst (Table 3.5).[6d] With 1 to 5 mol % of *N,N*'-dioxide-nickel(II) **L10** at 60 ºC, a variety of glyoxal derivatives **(20)** underwent reactions with olefins to produce entiomerically pure *γ,δ*-unsaturated-*α*-hydroxyketones **(21)** (Table 3.5, entries 1-6).

Table 3.5 Asymmetric Carbonyl-ene Reaction with Glyoxal Derivatives.[6d]



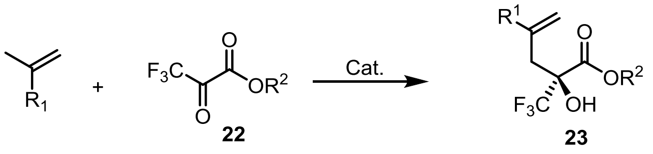
Entry	R	R^1	Product	% Yield	% ee
1	Ph	Ph		98	>99

2	2-MeC$_6$H$_4$	Ph		95	>99
3	4-OMeC$_6$H$_4$	Ph		99	>99
4	4-NO$_2$C$_6$H$_4$	Ph		78	>99
5	2-furyl	Ph		95	>99
6	Me	Ph		75	99
7	Ph	^{t}BuCH$_2$		84	98
8	Ph	^{i}Pr		86	>99

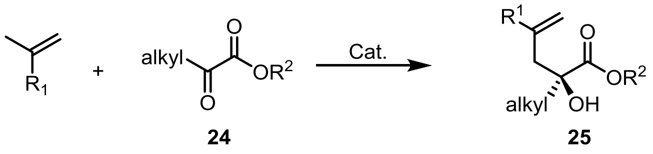
3.1.5 Acid Catalyzed Asymetric Carbonyl-ene Reaction of Pyruvate Derivatives

Intermolecular catalytic asymmetric carbonyl-ene reactions with ketone substrates are rare. Thus far, only the activated ketone system of pyruvate derivatives have been reported (Scheme 3.4).[4,5] The highly activated trifluoropyruvate **(22)** analogues have been key substrates in the ketone-ene reaction for the synthesis of chiral α-CF$_3$-α hydroxyesters **(23)** (Scheme 3.4, Eq. 1).[4,8a-8c] There are also two reports for the less reactive pyruvate system **(24)**, which requires harsh conditions[5a] or more reactive enol silyl ether counterpart.[5b]

Scheme 3.4 Carbonyl-ene Reaction with Pyruvate Derivatives.


F3C
OR2
O
22
Cat.
R1
F3C
OH
23

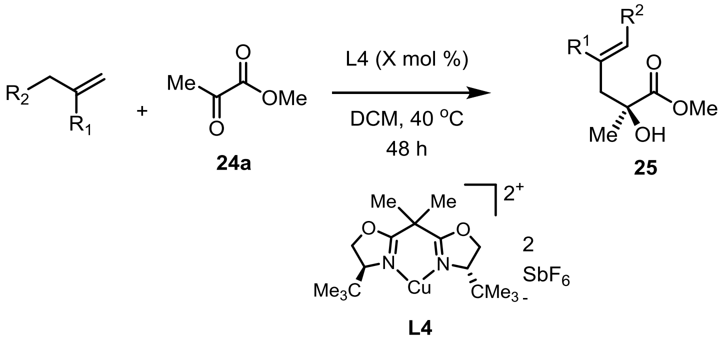
(1)

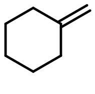
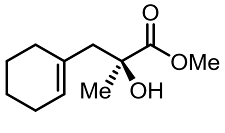

alkyl
OR2
O
24
Cat.
R1
alkyl
OH
25

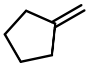
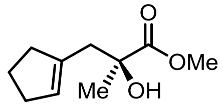
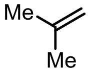
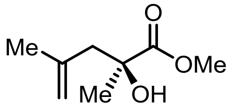
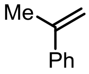
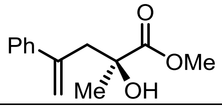
(2)

The first asymmetric intermolecular ketone-ene reaction was reported by Evans and coworkers using methyl pyruvate **(24a)**.[5a] Reactions of 1,1-disubstituted alkenes with methyl pyruvate are difficult compared to glyoxylates[3d] with the same catalyst system. The substrate scope seems to be limited since only four examples were reported (Table 3.6, entries 1-4). Although, high yields and ee's were obtained, however, the reaction conditions required 48 hours at 40 °C and 10-20 mol % of catalyst loading.

Table 3.6 Cu(II) Catalyzed Asymmetric Carbonyl-ene Reaction with Methyl Pyruvate.[5a]

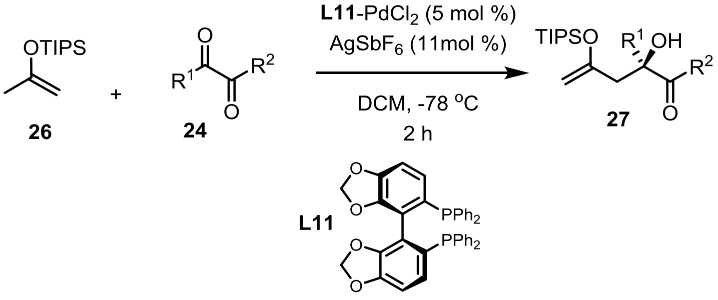

R2
R1
+
Me
OMe
O
24a
L4 (X mol %)
DCM, 40 °C
48 h
R2
R1
OMe
Me
OH
25
Me
Me
2+
O
N
Cu
Me3C
CMe3
2
SbF6 -
L4

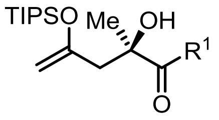
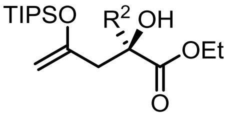
Entry	Olefins	X mol %	Product **(11)**	% Yield	% ee
1		20		84	98

2		5		95	98
3		10		76	98
4		5		94	98

Mikami and coworkers reported reactions of pyruvate derivatives with an activated silyl enol ether **(26)** catalyzed by dicationic palladium(II) complex to generate the chiral silyl enol ether **(27)** (Table 3.7).[5b] The reaction provides high yield and ee in most cases. However, the alkene component seems to be limited to only enol silyl ethers **(26)**.

Table 3.7 Asymmetric Carbonyl-ene Reactions of Methyl Pyruvate Derivatives and Enol Silyl Ethers **(26)**.

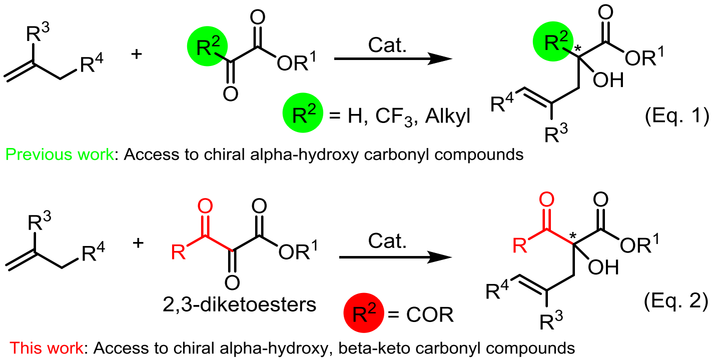

OTIPS
26
+
24
L11-PdCl2 (5 mol %)
AgSbF6 (11mol %)
DCM, -78 °C
2 h
TIPSO
27
L11
PPh2
PPh2

Entry	Product		% Yield	% ee
1		R^1 = OEt	96	93
2		R^1 = OMe	>99	85
3		R^1 = OBn	91	81
4		R^2 = CF_3	70	88
5		R^2 = CH_2CH_2Ph	40	87
6		R^2 = Ph	72	98

3.1.6 Application of 2,3-Diketoesters to Carbonyl-ene Reaction

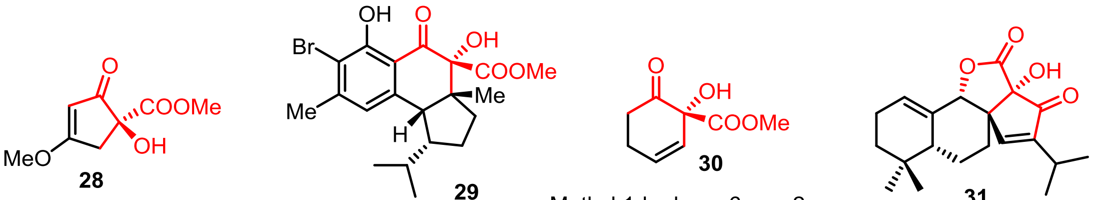
Although, tremendous efforts have been devoted to the asymmetric carbonyl ene reaction for more than two decades, its substrate scope remains a limiting factor due to the need to use reactive substrates such as activated aldehydes, glyoxylates, pyruvate, or reactive ene components (Scheme 3.5, Eq. 1). Because of its multiple coordination sites and the highly reactive electrophilic character of the central carbonyl group, we envisioned that 2,3-diketoesters would be excellent candidates for carbonyl-ene reactions. Herein, we report broadly applicable catalytic asymmetric carbonyl-ene reactions of 2,3-diketoester derivatives that occur in high yield and enantiocontrol (Scheme 3.5, Eq. 2). Although the 2,3-diketoester functional group has been applied over many years to the synthesis of numerous examples of carbocyclic compounds, heterocycles, and natural products,[10] this is the first demonstration of its viability in a catalytic asymmetric transformation.

Scheme 3.5 Asymmetric Carbonyl-ene Reactions.


R3
R4
+
R2
O
OR1
O
Cat.
R2
*
O
OR1
OH
R4
R3
R2 = H, CF3, Alkyl
(Eq. 1)
Previous work: Access to chiral alpha-hydroxy carbonyl compounds
R3
R4
+
O
O
R
OR1
O
2,3-diketoesters
Cat.
R2 = COR
O
O
R
*
OR1
OH
R4
R3
(Eq. 2)
This work: Access to chiral alpha-hydroxy, beta-keto carbonyl compounds

The asymmetric carbonyl-ene reaction of 2,3-diketoesters allows the formation of chiral *α*-functionalized-*α*-hydroxy-*β*-ketoesters, an important structural motif found in many natural product and biological active compounds, such as antibiotic (+)-kjellmanianone (**28**),[11] antiviral hamigeran A (**29**),[12] methyl 1-hydroxy-6-oxo-2-cyclohexenecarboxylate (**30**),[13] and anti HIV-1 (+)-przewalskin B (**31**) **(**Figure 3.1).[14] In addition, this structural framework appears in key intermediates of many natural product synthesis such as, (-)-idesolide **32**,[15] (±)-allosecurinine **34**,[16] (+)-latifolic acid (**36**),[17] (-)-rishirilide B (**38**),[18] leustroducsin B (**40**),[19] (-)-plicatic acid (**42**),[20] alternaric acid (**44**),[21] and (±)-jiadifenin (**46**) (Figure 3.2).[22]

Figure 3.1 Natural Products Contain *α*-Hydroxy-*β*-ketoesters Structural Framework



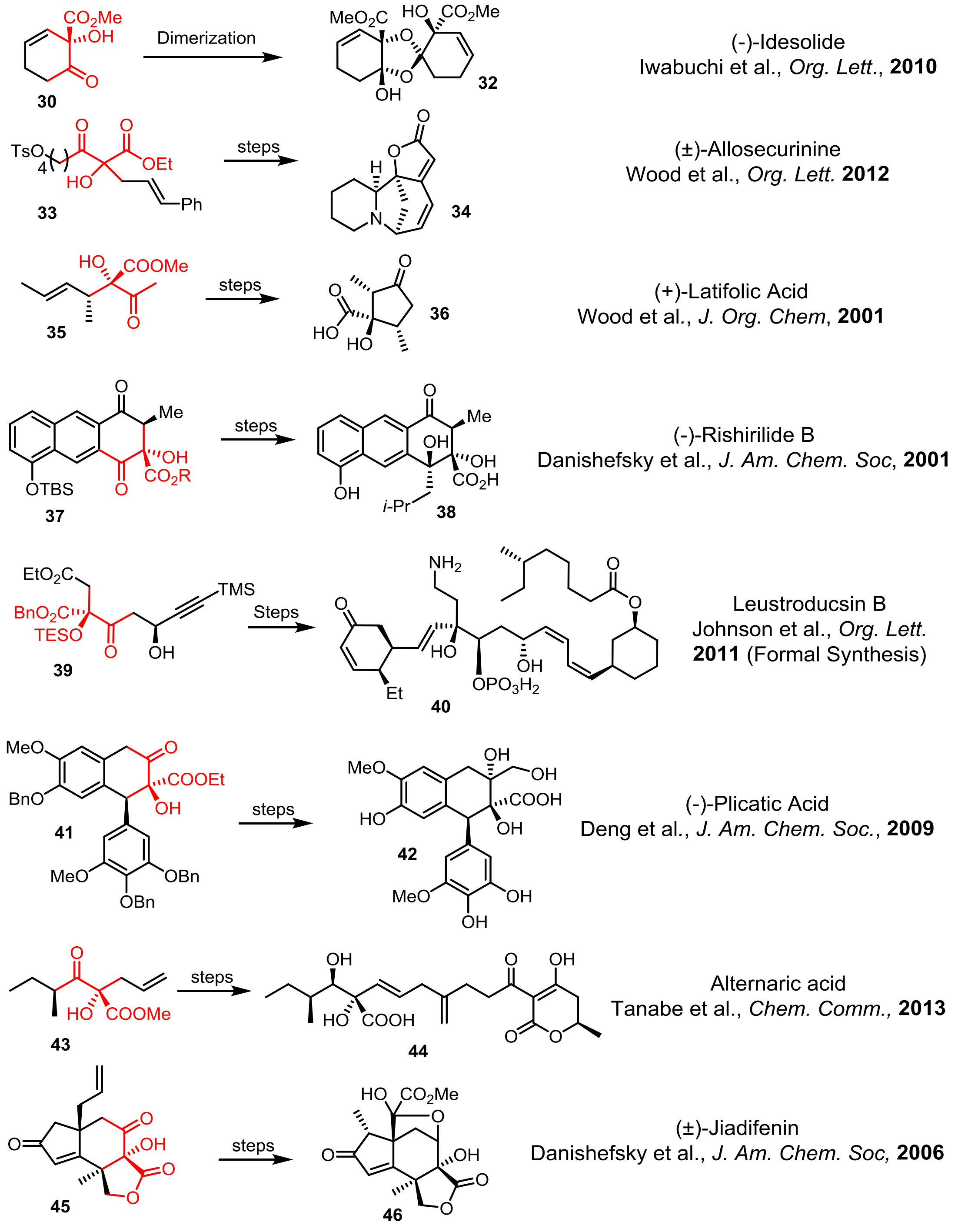
28
(+)-Kjellmanianone

29
Hamigeran A

30
Methyl 1-hydroxy-6-oxo-2-cyclohexenecarboxylate

31
(+)-Przewalskin B

Figure 3.2 *α*-Hydroxy-*β*-ketoester Structural Framework in Natural Product Synthesis.



CO2Me
OH
O
30
Dimerization
MeO2C
HO
CO2Me
O
O
OH
32
TsO
4
O
O
OEt
HO
Ph
33
steps
O
O
H
N
34
HO
COOMe
O
35
steps
O
O
HO
HO
36
O
Me
OH
CO2R
OTBS
O
37
steps
O
Me
OH
OH
CO2H
OH
i-Pr
38
EtO2C
TMS
BnO2C
TESO
O
O
OH
39
Steps
NH2
O
O
O
HO
OH
OPO3H2
Et
40
MeO
O
BnO
COOEt
OH
41
MeO
OBn
OBn
steps
OH
OH
MeO
COOH
HO
OH
42
MeO
OH
OH
O
HO
COOMe
43
steps
OH
O
OH
HO
COOH
O
O
44
O
O
OH
O
O
45
steps
HO
CO2Me
O
O
OH
O
O
46

(-)-Idesolide
Iwabuchi et al., *Org. Lett.*, **2010**

(±)-Allosecurinine
Wood et al., *Org. Lett.* **2012**

(+)-Latifolic Acid
Wood et al., *J. Org. Chem*, **2001**

(-)-Rishirilide B
Danishefsky et al., *J. Am. Chem. Soc*, **2001**

Leustroducsin B
Johnson et al., *Org. Lett.*
2011 (Formal Synthesis)

(-)-Plicatic Acid
Deng et al., *J. Am. Chem. Soc.*, **2009**

Alternaric acid
Tanabe et al., *Chem. Comm.*, **2013**

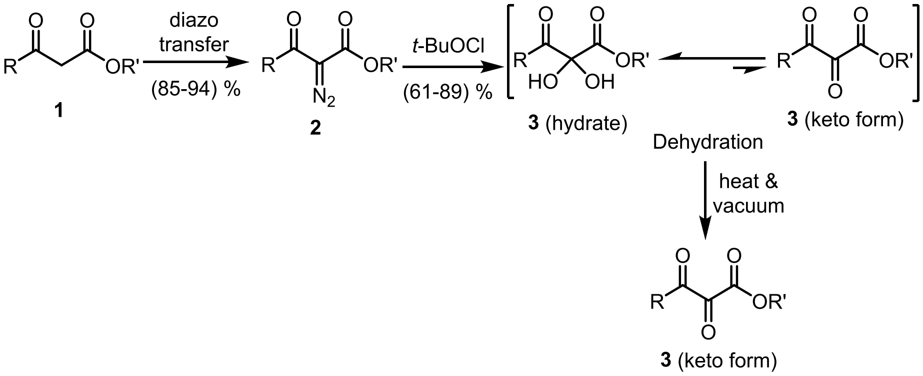
(±)-Jiadifenin
Danishefsky et al., *J. Am. Chem. Soc*, **2006**

3.2 Results and Discussion

3.2.1 Preparation of 2,3-Diketoester Derivatives

The preparation of 2,3-diketoesters **(3)** is achieved by variety of known methods.[10] In our investigations, these derivatives were readily obtained as hydrates in high yield through diazo transfer to 1,3-dicarbonyl compounds, followed by dinitrogen replacement by oxygen using *tert*-butyl hypochlorite (Scheme 3.6).[23] Although oxidation of α-diazo-β-ketoesters to 2,3-diketoesters was achieved in excellent to quantitative yield using dimethyldioxirane,[9] for large scale reactions the commercially available and easily accessable *tert*-butyl hypochlorite[24] oxidant is more practical. 2,3-Diketoesters **3** exist predominantly as the hydrate in equilibrium with the keto-form, but the keto-form was easily obtained (~95%) by heating (90-100 °C) the hydrate under vacuum (~1 mmHg) for 10-15 minutes in a glass vial (Scheme 3.6).

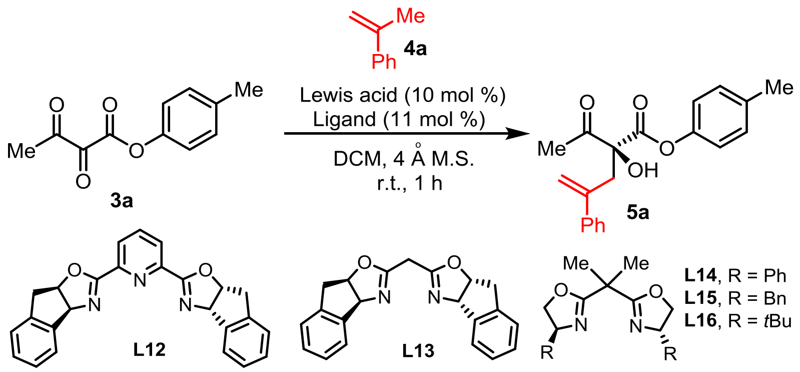
Scheme 3.6 Preparation of 2,3-Diketoester Derivatives.



3.2.2 Catalyst Screening and Optimization

Evans and Wu previously reported that the chiral scandium(III) complex with bis(oxazolinyl)pyridine (pybox) **L12** was an effective catalyst for highly enantioselective carbonyl ene reactions.[7e] As the success of this process was proposed to result from the rigidity of the coordinated substrate due to two-point binding,[7e] we thought this catalyst system would also be suitable for high enantiocontrol in reactions with 2,3-diketoesters. However, reaction of **3a** with α-methylstyrene **4a** catalyzed by scandium(III) [7e] triflate ligated with pybox (**L12**) generated product **5a** with only 18% ee but was complete within 1h at room temperature (Table 3.8, entry 1); this result was surprising in view of prior reports of slow conversions of keto analogues of glyoxylates.[5a] Encouraged by this result, we examined reactions with other Lewis acid/chiral ligand catalysts that have been previously reported for asymmetric carbonyl-ene reactions, and we found that bidentate chiral Cu(II)-bis(oxazoline) [3d,5a] (box) complexes were optimum. The best results were obtained with $Cu(OTf)_2$[3d] (90 % yield and 70 % ee) or $Cu(SbF_6)_2$[5a] (92 % yield and 75 % ee) ligated with **L16** (Table 3.8, entries 2 and 3). With chiral box ligands **L12** – **L15** and $Cu(SbF_6)_2$ comparable activity was found, but the carbonyl-ene product was formed with lower ee (Table 3.8, entries 4-6). Changing the solvent to THF and CH_3CN resulted in only trace amount of product probably due to the interaction of solvent and catalyst, while DCE and toluene provided similar results compared with DCM (Table 3.8, entries 7-10). Since $Cu(SbF_6)_2$ ligated with **L16** provided the highest yield and ee, this catalytic system was selected for further optimization.

Table 3.8 Catalyst Screening and Optimization of Reaction Conditions.[a]


Me
4a
Ph
Lewis acid (10 mol %)
Ligand (11 mol %)
DCM, 4 Å M.S.
r.t., 1 h
Me
O
O
O
Me
O
3a
Me
O
O
OH
O
Me
Ph
5a
L12
L13
Me
Me
R
R
L14, R = Ph
L15, R = Bn
L16, R = *t*Bu

Entry	Lewis acid	Ligand	Solvent	Yield (%)[b]	ee (%)[c]
1	$Sc(OTf)_3$	**L12**	DCM	91	18
2	$Cu(OTf)_2$	**L16**	DCM	90	70
3	$Cu(SbF_6)_2$	**L16**	DCM	92	75
4	$Cu(SbF_6)_2$	**L13**	DCM	68	58
5	$Cu(SbF_6)_2$	**L14**	DCM	84	65
6	$Cu(SbF_6)_2$	**L15**	DCM	89	28
7	$Cu(SbF_6)_2$	**L16**	THF	trace	-
8	$Cu(SbF_6)_2$	**L16**	CH_3CN	trace	-
9	$Cu(SbF_6)_2$	**L16**	DCE	87	74
10	$Cu(SbF_6)_2$	**L16**	Toluene	84	65

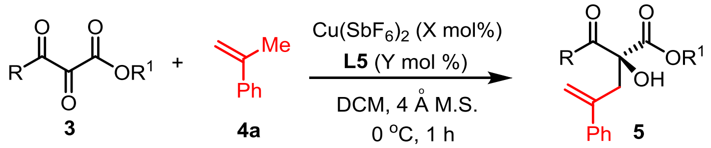
[a] Reactions were carried out on a 0.25 mmol scale of **3a** (keto-form) with 3.0 equiv. of α-methylstyrene **4a** in 2.0 mL of solvent at room temperature. [b] Isolated yield after column chromatography. [c] Determined by chiral stationary phase HPLC analysis.

3.2.3 Screening Reactions with Different 2,3-Diketoesters

A variety of aryl and alkyl ester derivatives **3** were examined to determine the influence of structure on enantioselectivity, but they had only minimal impact (Table 3.9, entries 1-6) although product yields were significantly impacted with R' = Me and *tert*-Bu. However, modification of the 3-keto unit from acetyl (**3c)** to propanoyl

(**3f**) increased enantioselectivity from 82% to 92% (Table 3.9, entry 7) without diminishing product yields. Catalyst loading could be decreased to one mol % using longer reaction times without effecting either yield or enantioselectivity (Table 3.9, entries 8 and 9). Enantioselectivities were further improved to 94% when the reaction was performed at -78 °C then slowly warmed to 0 °C (Table 3.9, entry 10). To test the reproducibility of this process, a gram scale reaction was performed with **3g**, and α-hydroxy-β-ketoester **5g** was obtained in 88% yield with 94% ee (Table 3.9, entry 11). In general, 2,3-diketoesters are isolated as hydrates at the central carbonyl group and exist in equilibrium with the keto form. We were interested to see if the hydrate could be used directly without being converted to the keto form. Remarkably, the readily accessible hydrate form of **3g** could also employed in the catalytic asymmetric carbonyl-ene process, producing **5g** with similar isolated yield and ee after 24 hours of reaction time compared to a 1 h reaction time with the keto-form **3g** (Table 3.9, entry 12 compared with entry 10). The longer reaction time was required probably due to the small fraction of the reactive keto-form available at a given reaction time. Use of the hydrate rather than the keto-form is obviously only a limitation in reaction time.

Table 3.9 Exploring Substituent Effects on Yield and Selectivity with 2,3-Diketoesters.[a]



Entry	**3**	**5**	Catalyst (mol %)[b]	R	R^1	Yield (%)[c]	ee (%)[d]

1	**3a**	**5a**	10	Me	4-MeC_6H_4	92	80
2	**3b**	**5b**	10	Me	4-ClC_6H_4	91	83
3	**3c**	**5c**	10	Me	Ph	90	82
4	**3d**	**5d**	10	Me	Bn	90	82
5	**3e**	**5e**	10	Me	Me	64	85
6	**3f**	**5f**	10	Me	*t*-Bu	58	86
7	**3g**	**5g**	10	Et	Ph	91	92
8	**3g**	**5g**	5	Et	Ph	91	92
9[e]	**3g**	**5g**	1	Et	Ph	90	92
10[f]	**3g**	**5g**	5	Et	Ph	91	94
11[f,g]	**3g**	**5g**	5	Et	Ph	88	94
12[h]	**3g**	**5g**	5	Et	Ph	87	91

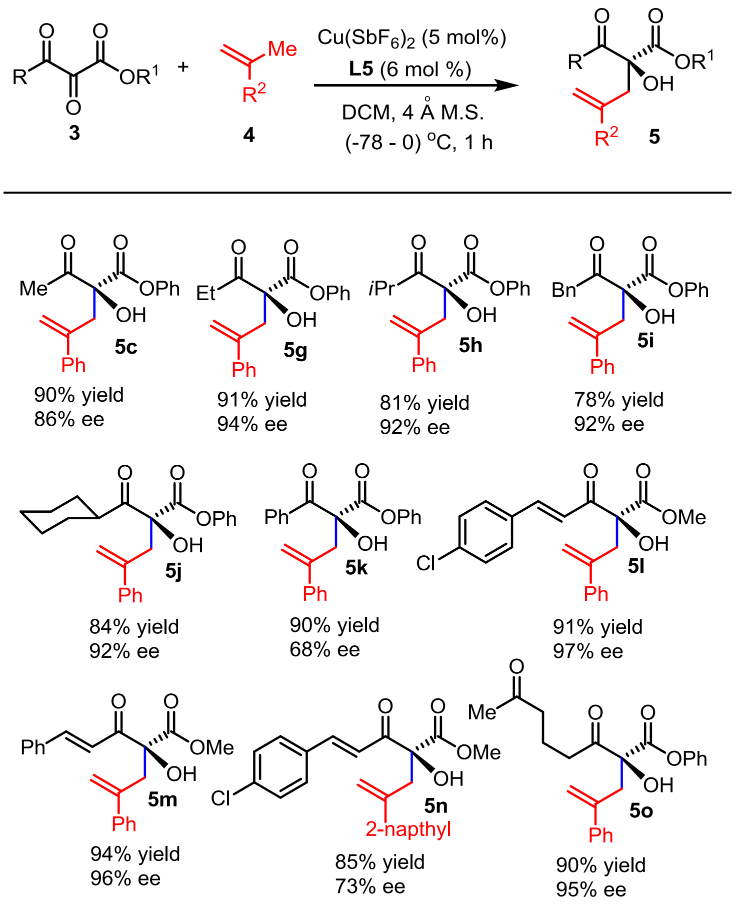
[a] Reactions were carried out on a 0.25 mmol scale of **3** (keto-form) with 3 equiv. of α-methylstyrene **4a** in 2.0 mL of solvent, unless noted otherwise. [b] X mol% as listed; Y = 1.2 times X. [c] Isolated yield after chromatographic purification. [d] Determined by chiral stationary phase HPLC analysis. [e] Reaction was stirred for 3 hours. [f] Reaction was performed at -78 °C then slowly warmed to 0 °C. [g] Reaction was carried out on a 5.0 mmol scale of **3g**. [h] The hydrate form of **3g** was used, and the reaction was run for 24 hours.

3.2.4 The Substrate Scope of Carbonyl-ene Reactions

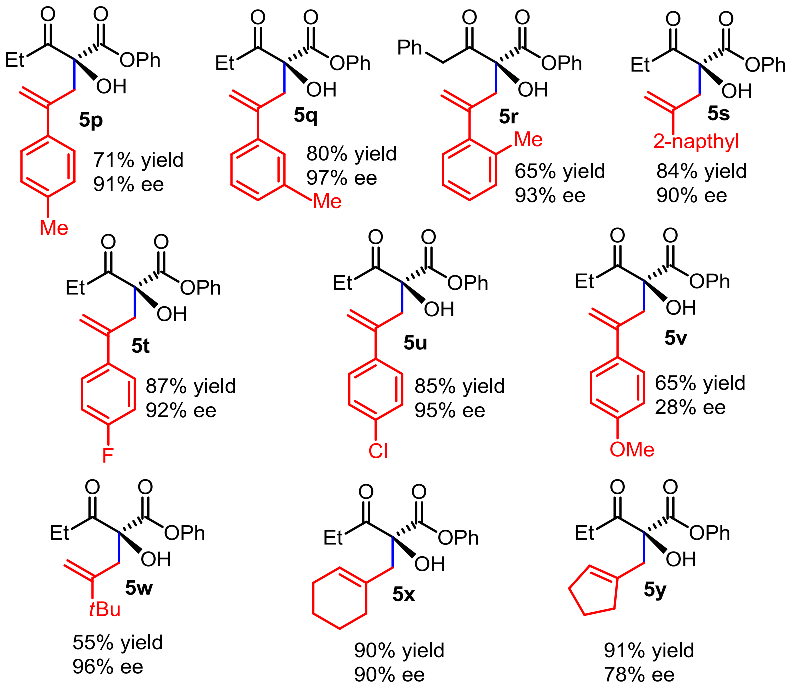
Reactions between structurally diverse 2,3-diketoesters **3** and various alkenes **4** were examined under optimized conditions (Table 3.10). The alkyl (R) substituents of **3,** including methyl, ethyl, isopropyl, benzyl, and cyclohexyl, reacted smoothly with α-methylstyrene to generate **5c, 5g-5j** in high yield and enantioselectivity. However, enantiomeric excess fell to 68% when R = phenyl (**5k)**. To further expand the reaction scope with 2,3-diketoesters **3**, additional functionalities were installed in R. Reactions of **3** (R = styryl derivatives) with α-methylstyrene provided **5l-5m** in excellent yield and enantiomeric access. The successes achieved with these substrates further demonstrated the generality of ene reactions with 2,3-diketoesters and their applicability in forming products that contain the α,β-unsaturated carbonyl functionality which is suitable for further chemical transformations. The carbonyl-ene reaction is also compatible with R = alkyl containing a keto functional group; the product from this reaction (**5o**) was generated in 90% yield with 95% ee. In contrast to the high ee's obtained with α-methylstyrene, however, reaction of **3l** with the naphthyl analogue 2-isopropenylnaphthalene produced **5n** in only 73% ee.

Examination of the reactions of 2,3-diketoester **3** with various alkenes **4** further demonstrated the broad applicability of this methodology. High yields and excellent ee values were obtained for arylalkenes that contain weak electron donating, electron withdrawing, and halogen substituents **5p-5u,** although the *o*-Me substituent **5r** caused a decrease in product yield. However, as seen in the outcome for **5v**, a *p*-methoxy substituent on the reactant α-methylstyrene dramatically decreased both yield and ee. This effect was also previously observed by Loh and coworkers[3j,4d] for carbonyl-ene reactions with glyoxylates. A possible reason might be complexation between the oxygen atom electron lone pair of the methoxy group and the acid catalyst, although electronic effects from the methoxy group on the transition state for product formation may also account for this outcome. A complexation interaction might prevent the catalyst from bidentate coordination to the 2,3-diketoester susbstrate resulting in the loss of enantiocontrol. This might be the reason why other reports of the asymmetric carbonyl-ene reaction did not employ methoxy substituted α-methylstyrene dereivatives in their substrate scope.[4e,5a,6d] Acyclic alkenes and methylenecycloalkanes are also suitable, forming **5w-5x** in high yield and % ee, but there was a slightly lower % ee with methylenecyclopentane **5y** compared to methylenecyclohexane. A limiting factor of this process is the requirement of 1,1-disubstituted alkenes. Mono- and 1,2-disubstituted alkenes such as hexene and cyclohexene do not react with 3g under these conditions.

Table 3.10 Substrate Scope of Carbonyl-ene Reactions with 2,3-Diketoesters.



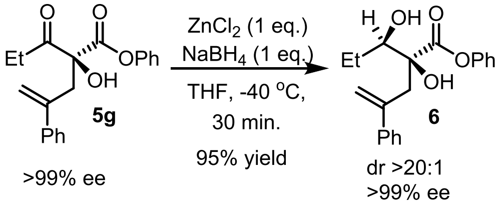
3
4
Cu(SbF6)2 (5 mol%)
L5 (6 mol %)
DCM, 4 Å M.S.
(-78 - 0) °C, 1 h
5
5c
90% yield
86% ee
5g
91% yield
94% ee
5h
81% yield
92% ee
5i
78% yield
92% ee
5j
84% yield
92% ee
5k
90% yield
68% ee
5l
91% yield
97% ee
5m
94% yield
96% ee
5n
2-napthyl
85% yield
73% ee
5o
90% yield
95% ee


5p
71% yield
91% ee
5q
80% yield
97% ee
5r
65% yield
93% ee
5s
2-napthyl
84% yield
90% ee
5t
87% yield
92% ee
5u
85% yield
95% ee
5v
65% yield
28% ee
5w
tBu
55% yield
96% ee
5x
90% yield
90% ee
5y
91% yield
78% ee

3.2.5 Vicinal Diol Formation and Determination of Absolute Sterechemistry

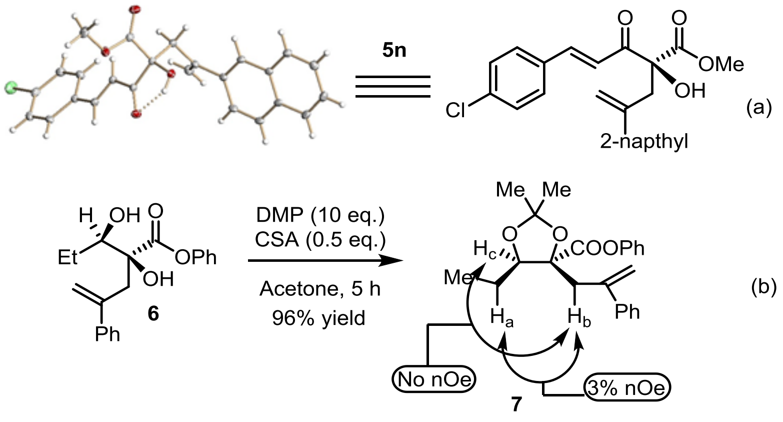
To demonstrate their utility, the keto group was reduced by sodium borohydride in the presence of $ZnCl_2$ at -40 °C in high yield with complete diastereoselectivity, producing the enantiomerically pure (2*S*,3*R*)-vicinal diol **6** bearing a tertiary carbinol (Scheme 3.7). This structural motif has played an essential role in natural products synthesis.[25]

Scheme 3.7 Stereoselective Reduction of *α*-Hydroxy-*β*-ketoester **5g**.


5g
>99% ee
ZnCl2 (1 eq.)
NaBH4 (1 eq.)
THF, -40 °C,
30 min.
95% yield
6
dr >20:1
>99% ee

The absolute configuration of **5** was determined to be *S* through single crystal X-ray analysis of **5n** (Figure 3.3a). The relative stereochemistry of **6** was determined by ^{1}H NMR nOe experiments with the corresponding protected diol **7** (Figure 3.3b).

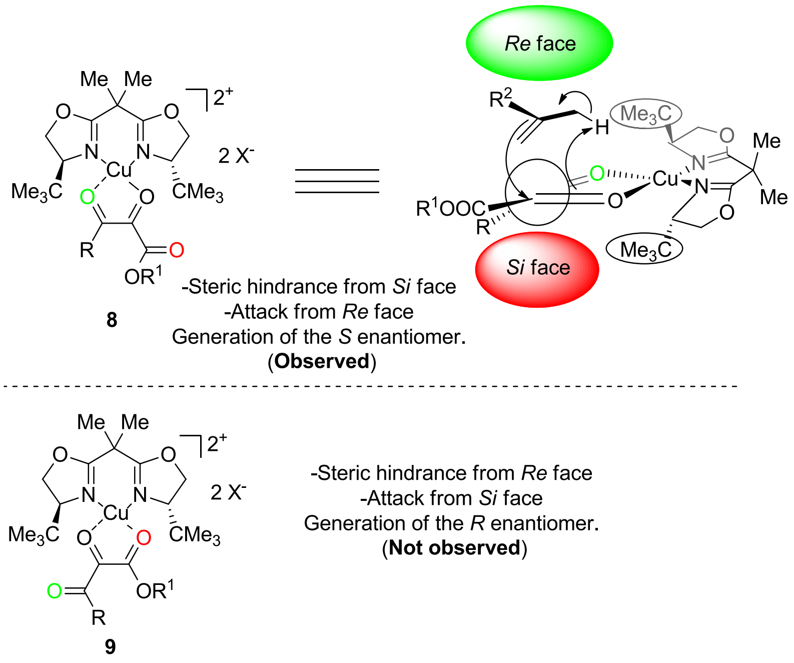
Figure 3.3 X-ray Crystal Structure of **5n** from Asymmetric Carbonyl-ene Reaction and nOe Experiment of Acetonide **7**.



3.2.6 Mechanism Through Coordination Complex Between Catalyst and Substrates

We have previously proposed Lewis acid activation of the central carbonyl of 2,3-diketoesters through a bidentate coordination with the more basic keto group rather than with the carboxylate group, and our current data provide further evidence for this claim. If the [Cu((*S*,*S*)-*tert*-Bu-box)](SbF_6)$_2$ catalyst undergoes bidentate coordination with the 2,3-diketoester **3** in a square-planar complex[26] so that the central carbonyl oxygen and the adjacent keto carbonyl are bound to copper (complex **8**), the approach through the *Si* face is sterically hindered by the *tert*-butyl substituent of the box ligand, thus allowing olefin approach from only the *Re* face which generates the *S* enantiomer (Figure 3.4). On the other hand, if bidentate coordination of the catalyst occurs with the central carbonyl oxygen and the ester carbonyl (complex **9**)**,** olefin attack would come from the less sterically hindered *Si* face to generate the *R* enantiomer. Since, the *S* enantiomers are formed in this carbonyl-ene reaction, the ligated copper catalyst most likely forms bidentate complexes with the two keto carbonyls of the 2,3-diketoesters system (**8**). In addition, the R substituent is in closer proximity to the ligand in complex (**8**) compared to complex (**9**), which also explains the significant impact of the R substituent on enantioselectivity. Complexation of 2,3-diketoester **3g** with [Cu((*S*,*S*)-*tert*-Bu-box)](SbF_6)$_2$ was further verified by the spectral shift in the visible region of the electromagnetic spectrum from the titration experiment of the chiral copper complex with **3g** (Figure 3.5). A well defined isosbestic point at at 592 nm indicated that a new species was formed by the incremental addition of tricarbonyl **3g** to the solution of [Cu((*S*,*S*)-*tert*-Bu-box)](SbF_6)$_2$.

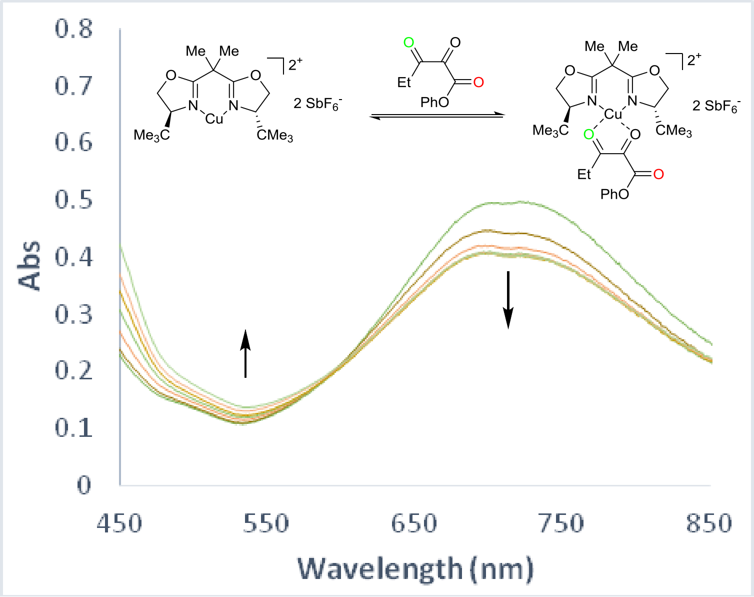
Figure 3.4 Activation of Phenyl 2,3-Diketopropionate by [Cu((*S*,*S*)-*tert*-Bu-box)](SbF_6)$_2$.


Re face
Si face
Me Me
2+
2 X-
Cu
Me3C
CMe3
R
OR1
R2
H
R1OOC
R
8
9

-Steric hindrance from *Si* face
-Attack from *Re* face
Generation of the *S* enantiomer.
(**Observed**)

-Steric hindrance from *Re* face
-Attack from *Si* face
Generation of the *R* enantiomer.
(**Not observed**)

Figure 3.5 Sequential Aliquots of Phenyl 2,3-diketopropionate **3g** (0.1 eq – 2.0 eq) were Added to a Solution of [Cu((*S*,*S*)-*tert*-Bu-box)]$(SbF_6)_2$ (20 x 10^{-3} mmol) 2.5 ml DCM Provided a Well-defined Isosbestic Point at 592 nm with an Incremental Shift of λ_{max} From 750 nm to 680 nm.



3.3 Conclusion

A general, highly enantioselective carbonyl ene reaction using 2,3-diketoester derivatives significantly broadens the scope of this useful transformation and extends access to chiral *α*-substituted-*α*-hydroxy-*β*-ketoesters beyond that currently available.[27] The placement of diverse functional groups at the *α*-position that are suitable for subsequent transformations is of particular value for the construction of enantiomerically enriched synthetic intermediates for natural products.[16,28] Furthermore, the demonstration of their high stereoselectivities in asymmetric ene reactions suggest that 2,3-diketoesters should also be susceptible to other nucleophiles in an asymmetric fashion. Further studies with other nucleophiles are in progress.

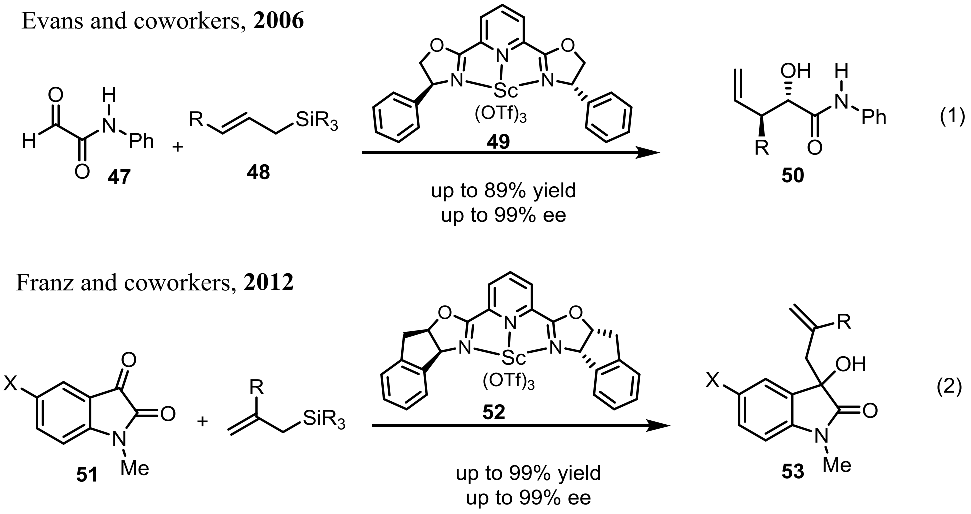
3.4 Future Work

Our research with 2,3-diketoester systems have enable us to develop a new method to access chiral *α*-allyl-*α*-hydroxy-*β*-ketoester derivatives via [Cu((*S*,*S*)-*tert*-Bu-box)]$(SbF_6)_2$ catalyzed carbonyl-ene reaction. We are looking forward to the applications of 2,3-diketoester system with other nucleophiles for further functionalization at the *α*-position. More importantly, demonstration of the synthetic value of this strategy in the area of natural product synthesis such as allosecurinine, latifolic acid, idesolide, and leustroducsin B is a desireable outcome.

3.4.1 Hosomi-Sakurai Addition

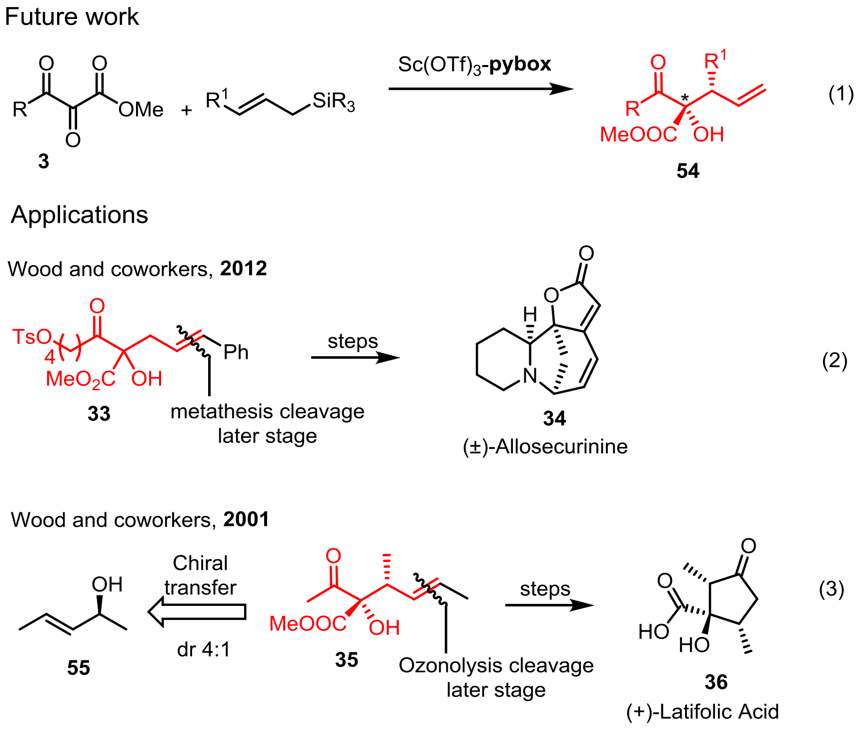
Nucleophilic addition of allylsilanes to aldehydes or ketones is also known as Hosomi-Sakurai reaction.[34] Among others,[35] Evans and coworkers[36] reported the scandium(III)-pybox **49** catalytic system for enantioselective allylation of *N*-phenylglyoxamide **47** (Scheme 3.8, eq. 1). Later, Franz and coworkers[37] reported a similar scandium(III)-pybox **52** catalytic system for reaction of allylsilanes with isatins **51** in the synthesis of chiral 3-allyl-3-hydroxy-oxindoles **53** (Scheme 3.8, eq. 2). The bidentate activation mode of scandium(III)-pybox allylation of glyoxamide and isatins should be applicable to the 2,3-diketoester system.

Scheme 3.8 Background for Enantioselective Hosomi-Sakurai Addition.



Enantioselective addition of allylsilanes to the central carbonyl of the 2,3-diketoester should generate chiral α-allyl-α-hydroxy-β-ketoesters **54** which are similar to the products from the carbonyl-ene reaction (Scheme 3.9, eq. 1). However, the substitution pattern on the α-allyl-substituent in this process would allow possible application to key intermediates in natural product syntheses such as α-allyl-α-hydroxy-β-ketoesters **33**[16] and **35**[17] (Scheme 3.9, eq. 2 and 3). This strategy would provide further improvement to preparation of **34** as the currently available method[16] only produces the racemic form, as well as the chiral intermediate **36**, which was obtain from chirality transfer of the corresponding chiral allylic alcohol **55** starting material with 4:1 dr ratio.[18]

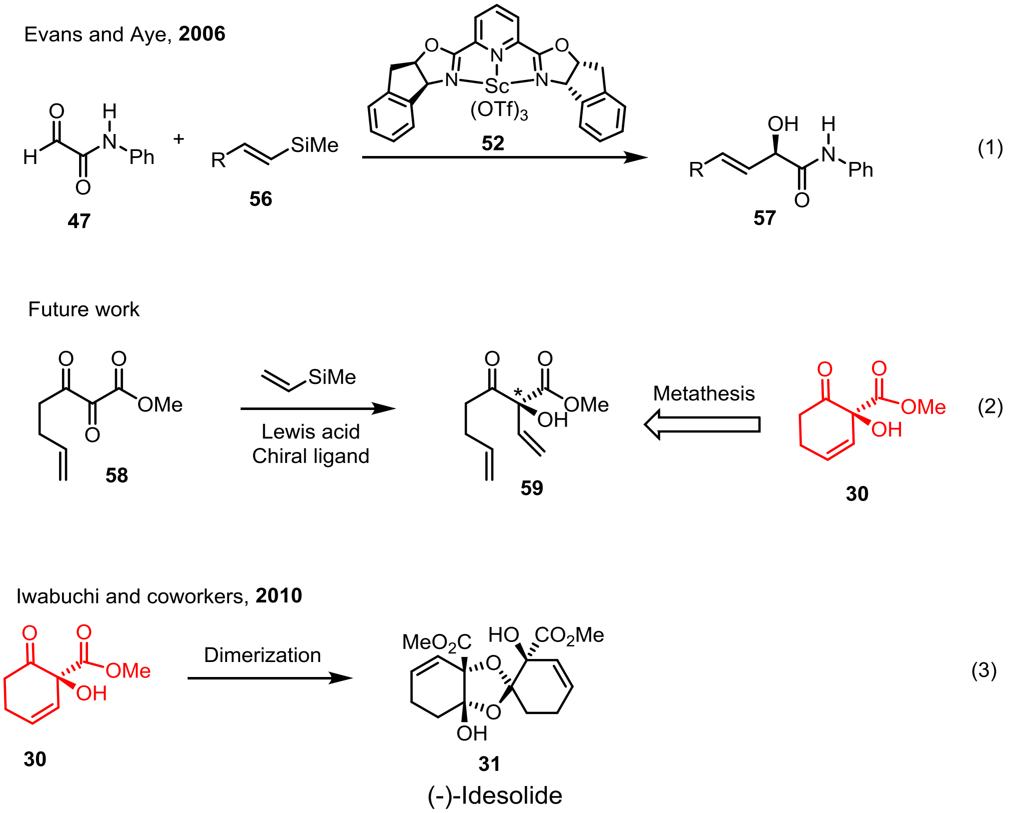
Scheme 3.9 Proposed Future Studies and Its Applications.


Future work
Sc(OTf)$_3$-**pybox**
(1)
3
54
Applications
Wood and coworkers, **2012**
steps
metathesis cleavage
later stage
33
34
(±)-Allosecurinine
(2)
Wood and coworkers, **2001**
Chiral
transfer
dr 4:1
55
35
steps
Ozonolysis cleavage
later stage
36
(+)-Latifolic Acid
(3)

3.4.2 Vinylsilane Addition

Nucleophilic addition of vinylsilanes to a carbonyl group is rare[38] due to the low intrinsic nucleophilicity of these organosilane compounds. Evans and Aye reported the first highly enantioselective Lewis acid catalyzed addition of vinylsilanes to *N*-phenylglyoxamide with scandium(III)-pybox system **52** to generate chiral α-vinyl-α-hydroxy acids **57** (Scheme 3.10, eq. 1).[39] Because of the highly electrophilic property of 2,3-diketoesters, enantioselective acid catalyzed addition of vinylsilanes may be feasible (Scheme 3.10, eq. 2). If 2,3 diketoester **58** is use as starting material, the resulting vinylation product **59** should able to undergo metathesis to form natural product **30.**[13] The structure of **30** might seem to be simple at a first glance, however, it requires a multi-step synthesis.[15] Dimerization[15] of **30** generates (-)-idesolide **15**, an inhibitor of nitric oxide (NO) production in BV2 microglial cell.[40]

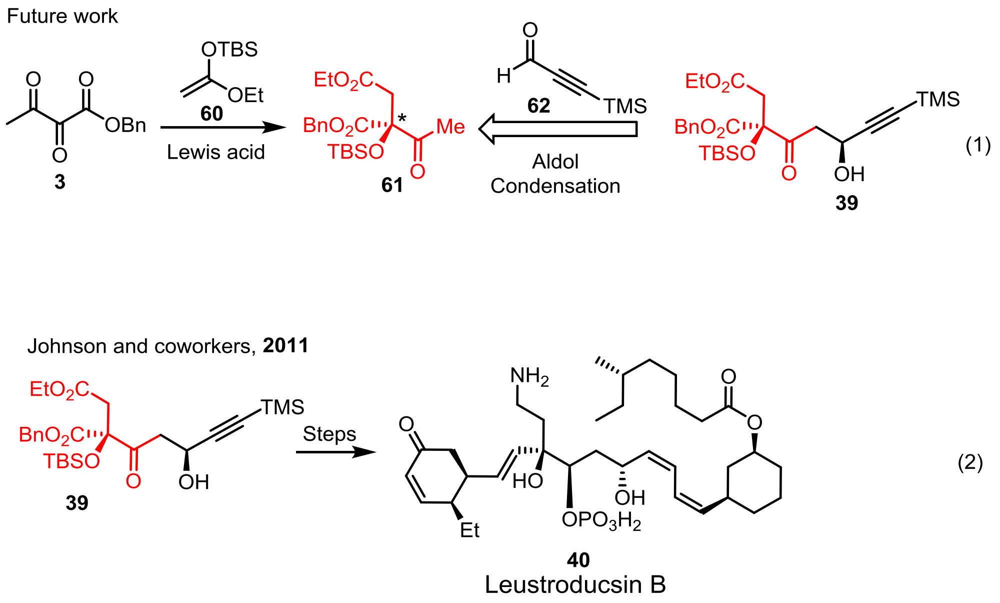
Scheme 3.10 Background, Future Studies, and Potential Applications of Vinylation of 2,3-Diketoesters.


Evans and Aye, 2006
47
56
52
(OTf)3
57
(1)
Future work
58
Lewis acid
Chiral ligand
59
Metathesis
30
(2)
Iwabuchi and coworkers, 2010
30
Dimerization
31
(-)-Idesolide
(3)

3.4.3 Mukaiyama-Aldol Addition

The catalytic enantioselective intermolecular Mukaiyama-aldol reaction is one of the most studied transformations in asymmetric catalysis. A variety of different catalytic systems[41] have been developed for this process which should be applicable to the 2,3-diketoester system for the synthesis of highly complex materials. For example, addition of enolsilyl acetal **60** to the central carbonyl of **3** would generate the densely complex compound **61** (Scheme 3.11, eq. 1). Subsequent aldol condensation between the aceto-group of **61** and aldehyde **62** would generate the key intermediate **39** in the synthesis of Leustroducsin B (Scheme 3.11, eq. 2).[19]

Scheme 3.11 Mukaiyama-aldol Addition and Application to Intermediate **39**.

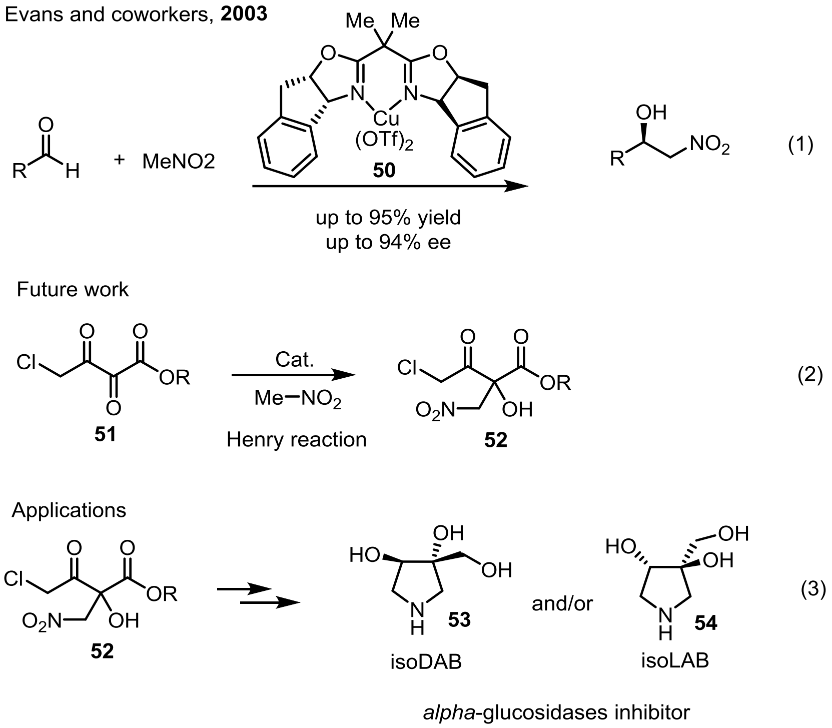

Future work
O
O
O
OBn
3
OTBS
OEt
60
Lewis acid
EtO2C
BnO2C
TBSO
*
Me
O
61
O
H
TMS
62
Aldol
Condensation
EtO2C
BnO2C
TBSO
O
OH
TMS
39
(1)
Johnson and coworkers, 2011
EtO2C
BnO2C
TBSO
O
OH
TMS
39
Steps
O
NH2
HO
OPO3H2
OH
O
O
Et
40
Leustroducsin B
(2)

3.4.4 Henry Reaction

The nitro-aldol reaction, also known as the Henry reaction, is an important transformation in organic synthesis for the construction of a cabon-carbon bond.[44] Numerous asymmetric catalysis systems[45] have been successfully developed including the Cu(II)-box system reported by Evans and coworkers[45d] (Scheme 3.9, eq. 1). We envision asymmetric catalytic reaction of nitro alkane and a 2,3-diketoester such as **51** would generate the highly complex α-hydroxy-β-ketoester **52** (Scheme

3.13, eq, 2). Taking advantage of the nitro-group, compound **52** should be able to undergo standard subsequent transformations converting **52** to isoDAB **53** and/or isoLAB **53**, which are natural products with inhibition activity against α-glucosidases (Scheme 3.12, eq. 3).[46]

Scheme 3.12 Henry Reaction of 2,3-Diketoesters.

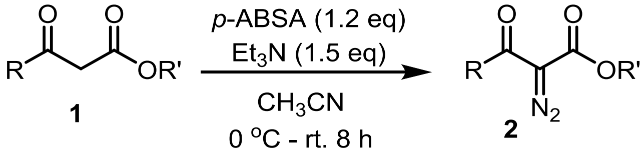

Evans and coworkers, 2003
Me Me
O
N
Cu
(OTf)2
50
O
R H
+ MeNO2
up to 95% yield
up to 94% ee
OH
R NO2
(1)
Future work
Cl
OR
51
Cat.
Me−NO2
Henry reaction
O2N
OH
52
(2)
Applications
52
HO
OH
53
isoDAB
and/or
54
isoLAB
(3)
alpha-glucosidases inhibitor

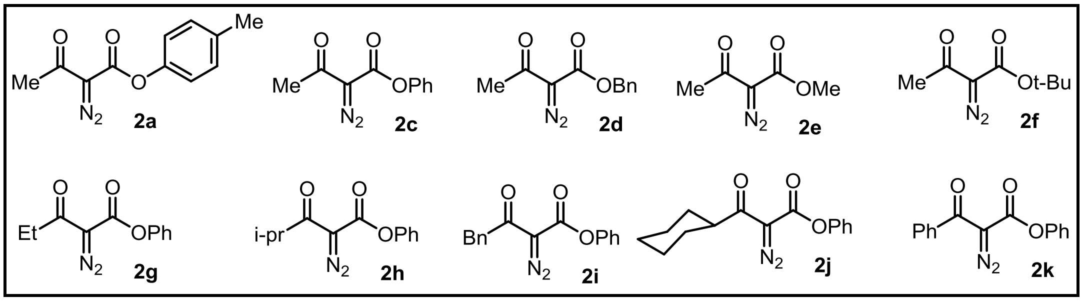
3.5 Experimental

3.5.1 General Information

Dichloromethane (DCM) was distilled and dried over molecular sieves prior to use. Thin layer chromatography (TLC) was carried out using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm), *p*-anisaldehyde (PAA), potassium permanganate ($KMnO_4$) or ceric ammonium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated system on silica gel (230-400 mesh). Metal triflate salts and chiral ligands were purchased from Aldrich and used as received. *tert*-Butyl hypochlorite was prepared according to the literature.[24] *β*-Keto esters **1** were prepared according to the literature.[29,30] ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Advance 400 MHz spectrometer. Chemical shifts are reported in ppm with the solvent signals as reference, and coupling constants (*J*) are given in Hertz. The peak information is described as: br = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, comp = complex multiplet of magnetically inequivalent protons. IR spectra were recorded on a Thermo Nicolet IR200 spectrometer. Melting points were obtained on an Electro Thermo Mel-Temp DLX 104. Enantioselectivity was determined on an Agilent 1200 Series HPLC instrument using Daicel Chiralcel OD-H, AD-H or IC3 columns. High-resolution mass spectra (HRMS) were performed on a JEOL AccuTOF-ESI mass spectrometer using CsI as the standard. UV absorption measurements were performed on a UV-Vis spectrometer with a glass cell of 1.0 cm path length.

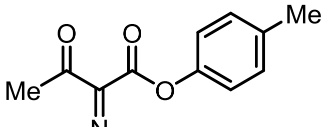
3.5.2 General Procedure for the Preparation of *α*-Diazo-*β*-ketoesters





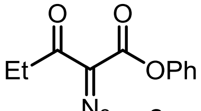
α-Diazo-*β*-ketoesters **2a**, **2c**,[31a] **2d**,[31b] **2e**,[31c] **2f**,[31d] **2g**, **2h**, **2i**, **2j**, and **2k** were prepared by diazo transfer reactions using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) as the diazo transfer reagent.[32]

A solution of *β*-ketoester **1** (10 mmol, 1 eq.) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (2.8 g, 12 mmol, 1.2 eq.) in 75 mL of CH_3CN was added triethylamine (2.1 ml, 1.5 mmol, 1.5 eq.) at 0 °C, and the resulting solution was stirred at room temperature for 8 hours during which time the corresponding sulfonamide precipitated as a white solid. The white precipitate was filtered, and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2), eluting with hexane and ethyl acetate to provide *α*-diazo-*β*-ketoester **2**.



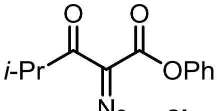
2a

***p*-Tolyl 2-diazo-3-oxobutanoate 2a** was obtained as a yellow liquid in 90% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 2.52 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 189.9, 160.2, 147.3, 136.1, 130.0, 121.1, 28.2, 20.8. ($C=N_2$ signal not observed). IR (neat) 2139, 1727, 1657 cm^{-1}. HRMS (ESI) *m/z* 219.0762 [$C_{11}H_{11}N_2O_3$ (M+H) requires 219.0770]



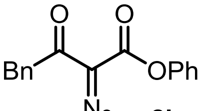
2g

Phenyl 3-keto-2-diazopentanoate 2g was obtained as yellow liquid in 92% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 - 7.39 (comp, 2H), 7.34 – 7.22 (m, 1H), 7.21 – 7.09 (comp, 2H), 2.91 (q, *J* = 7.3 Hz, 2H), 1.17 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 193.1, 159.9, 149.6, 129.5, 126.3, 121.5, 33.8, 8.2. ($C=N_2$ signal not observed). IR (neat) 2133, 1727, 1657 cm^{-1}. HRMS (ESI) *m/z* 219.0765 [$C_{11}H_{11}N_2O_3$ (M+H) requires 219.0770].



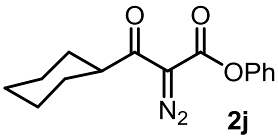
2h

Phenyl 4-methyl-3-keto-2-diazopentanoate 2h was obtained as yellow liquid in 91% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.37 (comp, 2H), 7.28 (t, *J* = 6.9 Hz, 1H), 7.21 – 7.12 (comp, 2H), 3.63 - 3.53 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 196.5, 159.6, 149.6, 129.5, 126.3, 121.5, 36.9, 18.4. ($C=N_2$ signal not observed). IR (neat) 2137, 1729, 1657 cm^{-1}. HRMS (ESI) *m/z* 233.0921 [$C_{12}H_{13}N_2O_3$ (M+H) requires 233.0926].



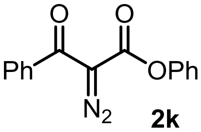
2i

Phenyl 4-phenyl-3-keto-2-diazobutanoate 2i was obtained as yellow liquid in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.40 (comp, 2H), 7.35 – 7.23 (comp, 6H), 7.17 – 7.11 (comp, 2H), 4.22 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 189.8, 159.8, 149.5, 133.6, 129.7, 129.6, 128.5, 127.1, 126.4, 121.5, 45.8. ($C=N_2$ signal not observed). IR (neat) 2138, 1726, 1651 cm^{-1}. HRMS (ESI) *m/z* 281.0920 [$C_{16}H_{13}N_2O_3$ (M+H) requires 281.0926].



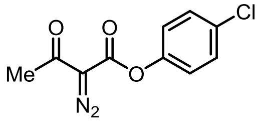
2j

Phenyl 3-cyclohexyl-3-keto-2-diazopropanoate 2j was obtained as yellow liquid in 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.41 (comp, 2H), 7.34 – 7.24 (m, 1H), 7.20 – 7.10 (comp, 2H), 3.39 – 3.24 (m, 1H), 1.92 – 1.17 (m, 4H), 1.52 – 1.16 (comp, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 195.5, 159.8, 149.6, 129.6, 126.3, 121.6, 46.9, 28.7, 25.7, 25.6. ($C=N_2$ signal not observed). IR (neat) 2137, 1729, 1654 cm^{-1}. HRMS (ESI) *m/z* 273.1248 [$C_{15}H_{17}N_2O_3$ (M+H) requires 273.1239].

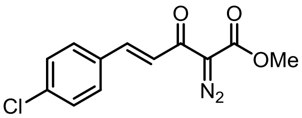


2k

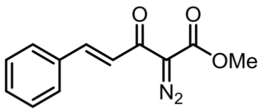
Phenyl 2-diazo-3-oxo-3-phenylpropanoate 2k was obtained as white solid in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.55 – 7.48 (m, 1H), 7.343 - 7.34 (comp, 4H), 7.26 - 7.21 (m, 2H), 7.11 (dd, *J* = 8.6, 1.0 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 186.4, 159.4, 149.6, 136.6, 132.4, 129.4, 128.4, 127.9, 126.2, 121.3. (C=N_2 signal not observed) IR (neat) 2155, 1724, 1637 cm^{-1}. HRMS (ESI) *m/z* 267.0756 [$C_{15}H_{11}N_2O_3$ (M+H) requires 267.0770].



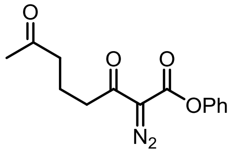
2b



2l

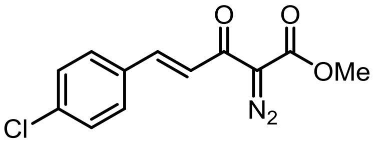


2m



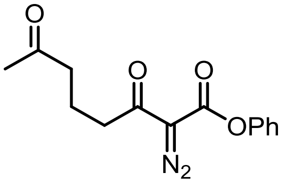
2n

Diazo-compounds **2b**,[4b,4e] **2l**,[4f] **2m**,[4f] and **2n**[4g] were prepared according to their literature procedures. Spectral data for **2b** and **2m** were in agreement with those reported in the literature.



2l

Methyl (E)-5-(4-chlorophenyl)-2-diazo-3-oxopent-4-enoate 2l was obtained as light green solid in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 15.8 Hz, 1H), 7.71 (d, *J* = 15.8 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 181.1, 161.7, 141.4, 136.4, 133.0, 129.8, 129.1, 122.0, 52.3. (C=N_2 signal not observed). IR (neat) 2144, 1719, 1640 cm^{-1}. HRMS (ESI) *m/z* 265.0389 [$C_{12}H_{10}ClN_2O_3$ (M+H) requires 265.0380].

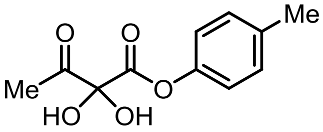


2n

Phenyl 2-diazo-3,7-dioxooctanoate 2n was obtained as a yellow liquid in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.36 (comp, 2H), 7.32 – 7.24 (m, 1H), 7.20 – 7.09 (comp, 2H), 2.91 (t, *J* = 7.2 Hz, 2H), 2.52 (t, *J* = 7.3 Hz, 2H), 2.13 (s, 3H), 2.00 – 1.88 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 208.0, 191.8, 159.9, 149.5, 129.5, 126.4, 121.5, 42.5, 39.3, 29.8, 18.1. ($C=N_2$ signal not observed). HRMS (ESI) *m/z* 275.1021 [$C_{14}H_{15}N_2O_4$ (M+H) requires 275.1032].

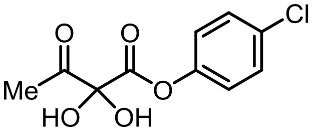
3.5.3 General Procedure for the Synthesis of 2,3-Diketoesters

A solution of α-diazo-β-ketoesters **2** (5.0 mmol, 1.0 eq.) in 20 mL of solvent [CH_3CN:H_2O (9:1)] at 0 °C was added *tert*-butyl hypochlorite (0.61 ml, 5.5 mmol) dropwise over 30 min via syringe pump. The reaction was stirred for an additional 30 min at room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2), eluting with hexane and ethyl acetate to provide compounds **3** as their monohydrates. Dehydration of **3** was performed by heating the hydrate (90–100 °C) under vacuum (~1 mmHg) for 10-15 min. (See example of NMR spectral data for **3d** in anhydrous keto form)



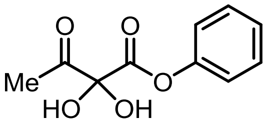
3a

_p_-Tolyl 2,3-Dioxobutanoate Hydrate (3a). Reaction between **2a** and *tert*-BuOCl give **3a** as a white solid in 85% yield; mp = 87-89 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.19 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 5.06 (br, 2H), 2.43 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 200.2, 167.6, 147.6, 136.6, 130.1, 120.2, 92.6, 23.1, 20.8. IR = 3347, 1772, 1725. HRMS (ESI) *m/z* 207.0643 [$C_{11}H_{11}O_4$ (M+H) requires 207.0657]



3b

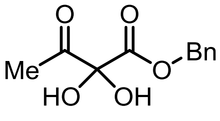
4-Chlorophenyl 2,3-Dioxobutanoate Hydrate (3b). Reaction between **2b** and *tert*-BuOCl give **3b** as a white solid in 77% yield; mp = 63-65 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 (d, *J* = 8.9 Hz, 2H), 7.08 (d, *J* = 8.9 Hz, 2H), 4.99 (br, 2H), 2.43 (s, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 199.9, 167.2, 148.2, 132.3, 129.8, 122.0, 92.6, 23.2. IR (neat) 3346, 1780, 1744. HRMS (ESI) *m/z* 227.0102 [$C_{10}H_8ClO_4$ (M+H) requires 227.0111].



3c

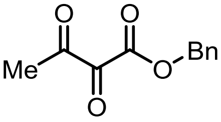
Phenyl 2,3-Dioxobutanoate Hydrate (3c). Reaction between **2c** and *tert*-BuOCl give **3c** as a white solid in 82% yield; mp = 61-63 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 - 7.10 (comp, 5H), 5.11 (br, 2H), 2.44 (s, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ

200.1, 167.4, 149.8, 129.7, 126.8, 120.6, 92.6, 23.2. IR (neat) 3472, 1775, 1719 cm^{-1}. HRMS (ESI) *m/z* 193.0513 [$C_{10}H_9O_4$ (M+H) requires 193.0501].



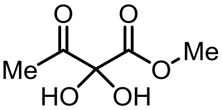
3d

Benzyl 2,3-Dioxobutanoate Hydrate (3d). Reaction between **2d** and *tert*-BuOCl give **3d** in 80% yield. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.27 (comp, 5H), 5.26 (s, 2H), 5.02 (br, 2H), 2.18 (s, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 200.5, 168.7, 134.0, 128.8, 128.7, 128.3, 92.4, 68.6, 22.9. IR (neat) 3329, 1753, 1724 cm^{-1}. HRMS (ESI) *m/z* 207.0648 [$C_{11}H_{11}O_4$ (M+H) requires 207.0657].



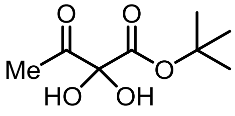
3d

Benzyl 2,3-Dioxobutanoate (3d). Green liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 - 7.35 (comp, 5H), 5.35 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 194.9, 181.4, 161.9, 133.8, 128.9, 128.7, 128.5, 68.3, 24.1.

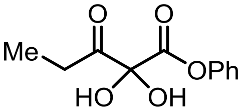


3e

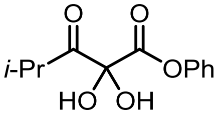
Methyl 2,3-Dioxobutanoate Hydrate (3e). Reaction between **2e** and *tert*-BuOCl give **3e** as a white solid in 61% yield; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.93 (s, 2H), 3.88 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.5, 169.4, 92.3, 53.8, 23.0. HRMS (ESI) *m/z* 131.0340 [$C_5H_7O_4$ (M+H) requires 131.0344].


3f

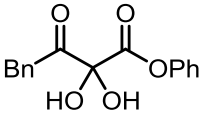
***tert*-Butyl 2,3-Dioxobutanoate Hydrate (3f)**. Reaction between **2f** and *tert*-BuOCl give **3f** as a white solid in 67% yield; mp = 75 – 77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (s, 2H), 2.28 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 201.0, 168.0, 92.4, 85.0, 27.6, 22.9. IR (neat) 3403, 1740, 1720 cm^{-1}. HRMS (ESI) *m/z* 173.0811[$C_8H_{13}O_4$ (M+H) requires 173.0814].


3g

Phenyl 2,3-Dioxopentanoate Hydrate (3g). Reaction between **2g** and *tert*-BuOCl give **3g** as a white solid in 84% yield; mp = 50-53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 2H), 7.31 – 7.24 (m, 1H), 7.14 – 7.08 (m, 2H), 5.11 (s, 1H), 2.78 (q, *J* = 7.3 Hz, 1H), 1.22 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.3, 167.7, 149.8, 129.7, 126.8, 120.6, 92.5, 29.3, 7.5. IR (neat) 3342, 1770, 1741 cm^{-1}. HRMS (ESI) *m/z* 207.0650 [$C_{11}H_{11}O_4$ (M+H) requires 207.0657].

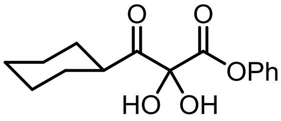

3h

Phenyl 4-Methyl-2,3-dioxopentanoate Hydrate (3h). Reaction between **2h** and *tert*-BuOCl give **3h** as a white solid in 82% yield; mp = 67-69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.05 (comp, 5H), 5.10 (s, 2H), 3.16 - 3.09 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 206.9, 167.8, 149.9, 129.7, 126.8, 120.6, 92.7, 35.5, 19.1, 16.7. IR (neat) 3377, 1762, 1731 cm^{-1}. HRMS (ESI) *m/z* 221.0808 [$C_{12}H_{13}O_4$ (M+H) requires 221.0814].



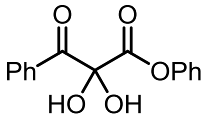
3i

Phenyl 2,3-Dioxo-4-phenylbutanoate Hydrate (3i). Reaction between **2i** and *tert*-BuOCl give **3i** as a white solid in 82% yield; mp = 91 - 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.24 (comp, 8H), 6.96 (dd, *J* = 8.6, 1.1 Hz, 2H), 5.05 (s, 2H), 4.08 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.4, 167.4, 149.8, 131.9, 129.7, 129.6, 128.8, 127.5, 126.7, 120.5, 92.7, 42.6. IR (neat) 3340, 1775, 1745 cm^{-1}. HRMS (ESI) *m/z* 269.0810 [$C_{16}H_{13}O_4$ (M+H) requires 269.0814].



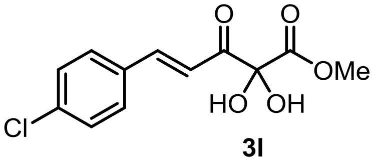
3j

Phenyl 3-Cyclohexyl-2,3-dioxopropanoate Hydrate (3j). Reaction between **2j** and *tert*-BuOCl give **3j** as a white solid in 85% yield;. mp = 82 - 85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.07 (comp, 5H), 5.10 (s, 2H), 2.91 – 2.81 (m, 1H), 1.99 – 1.20 (comp, 10H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 205.6, 167.9, 149.9, 129.7, 126.9, 120.6, 92.7, 45.4, 29.1, 25.3, 25.1. IR (neat) 3377, 1766, 1723 cm^{-1}. HRMS (ESI) *m/z* 261.1121 [$C_{15}H_{17}O_4$ (M+H) requires 261.1127].



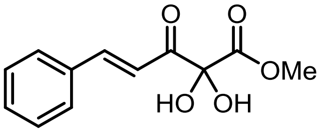
3k

Phenyl 2,3-Dioxo-3-phenylpropanoate Hydrate (3k). Reaction between **2k** and *tert*-BuOCl give **3k** as a white solid in 89% yield; mp = 96 - 98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.16 (m, 2H), 7.68 - 7.19 (comp, 6H), 6.89 – 6.75 (m, 2H), 5.41 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 190.8, 168.5, 149.8, 134.9, 131.3, 130.2, 129.5, 128.9, 126.6, 120.6, 91.7. IR (neat) 3324, 1757, 1704 cm^{-1}. HRMS (ESI) *m/z* 255.06545 [$C_{15}H_{11}O_4$ (M+H) requires 255.0657].



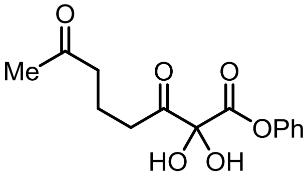
3l

Methyl (*E*)-5-(4-Chlorophenyl)-2,3-dioxopent-4-enoate Hydrate (3l). Reaction between **2l** and *tert*-BuOCl give **3l** as a white solid in 72% yield; mp = 99 - 101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 16.0 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 16.0 Hz, 1H), 5.12 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 190.8, 169.8, 146.6, 137.7, 132.2, 130.1, 129.4, 118.3, 92.3, 53.9. IR (neat) 3415, 1744, 1699, 1617 cm^{-1}. HRMS (ESI) *m/z* 315.0412 [$C_{17}H_{12}ClO_4$ (M+H) requires 315.0424].



3m

Methyl (*E*)-2,3-Dioxo-5-phenylpent-4-enoate Hydrate (3m). Reaction between **2m** and *tert*-BuOCl give **3m** as a white solid in 75% yield. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93 (d, *J* = 16.0 Hz, 1H), 7.66 – 7.36 (comp, 5H), 6.95 (d, *J* = 16.0 Hz, 1H), 5.23 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 190.9, 169.9, 148.1, 133.7, 131.6, 129.0, 129.0, 117.9, 92.3, 53.9. IR (neat) 3420, 1745, 1697, 1607. HRMS (ESI) *m/z* 281.0800 [$C_{17}H_{13}O_4$ (M+H) requires 281.0814].

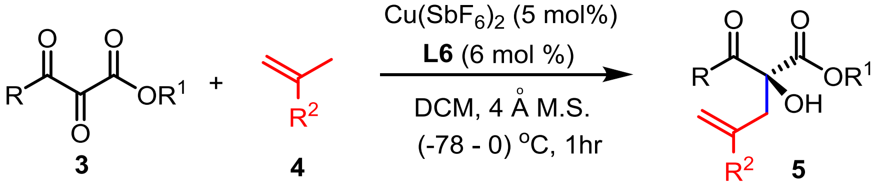


3n

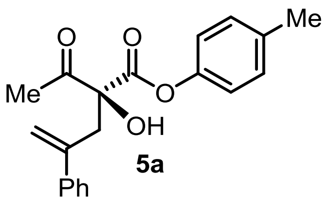
Phenyl 2,3,7-Trioxooctanoate Hydrate (3n). Reaction between **2n** and *tert*-BuOCl give **3n** as a white solid in 81% yield; mp = 66 - 68 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 – 7.10 (comp, 5H), 5.36 (s, 2H), 2.83 (t, *J* = 7.0 Hz, 2H), 2.54 (t, *J* = 7.0 Hz, 2H), 2.12 (s, 3H), 2.03 – 1.94 (m, 2H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 208.5, 202.7, 167.4, 149.8, 129.6, 126.6, 120.6, 92.7, 41.7, 34.7, 29.8, 17.2. IR (neat) 3329, 1773, 1740, 1701 cm^{-1}. . HRMS (ESI) *m/z* 263.0933[$C_{14}H_{15}O_5$ (M+H) requires 263.0919].

3.5.4 General Procedure for the Synthesis of Functionalized *α*-Hydroxy-*β*-ketoesters

Preparation of Chiral Copper Catalyst. A solution of 0.050 M of copper catalyst was prepared in a glove box according to Evans's procedure:[33] A solution of $CuCl_2$ (6.7 mg, 0.050 mmol) and the chiral ligand **L6** (16.2 mg, 0.055 mmol) in 0.50 ml of DCM were stirred for 2 h. Then $Ag(SbF_6)_2$ (34.3mg, 0.1 mmol) in 0.5 ml of DCM was added, and the reaction solution was stirred for two additional hours in the absence of light. The AgCl precipitate was filtered with cotton to provide a green solution of chiral copper catalyst.

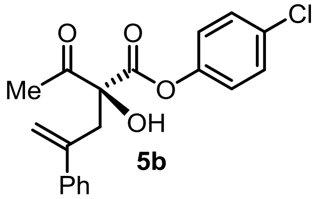


A vial (10 mL) containing the hydrate 2,3-diketoester **3** (0.25 mmol, 1.0 eq.), a magnetic stir bar, and capped with a rubber septum was inserted to a needle that connectsed to a vacuum line (~1 mmHg). The vial was heated in an oil bath (~100 °C) under vacuum for 10-15 minutes. The vacuum line was removed, and then back filled with nitrogen gas. Next, DCM (1.7 mL) and 120 mg of 4Å molecular sieve was added sequentially and cooled to -78 °C. Then 0.25 ml (0.050 M) of the chiral catalyst solution, and alkene **4** (0.75 mmol, 3.0 eq.) were added sequentially. The reaction solution was stirred for 10 min at -78 °C, then transferred to an ice bath and stirred for additional 50 minutes. The reaction mixture was directly subjected to flash column chromatography (SiO_2) eluting with hexane and ethyl acetate to provide pure product **5**. The reported ee values for (**5c-5k, 5n, 5v, 5y**) were obtained from at least 2 independent runs and have an error margin of ±1 %ee for each substrate. The ee values for other substrates (**5l-5u, 5w, 5x**) were obtained from a single run for each substrate. It is crucial to prepare the catalyst solution in the glovebox to obtain reproducible results within ±1 %ee. Generally, a drop of (5-10) % ee was observed when the catalyst prepared outside of the glovebox. This is probably due to the hydroscopic nature of the catalyst, which coordinates with atmospheric water.



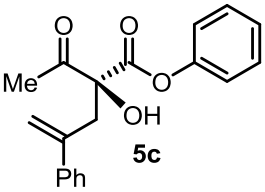
5a

***p*-Tolyl (*S*)-2-Acetyl-2-hydroxy-4-phenylpent-4-enoate (5a)**. Reaction between **3a** and α-methylstyrene gave **5a** in 92% yield as a colorless liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 – 7.29 (comp, 5H), 7.10 (dd, *J* = 8.7, 0.6 Hz, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 4.01 (s, 1H), 3.54 (dd, *J* = 14.6, 0.8 Hz, 1H), 3.20 (dd, *J* = 14.6, 0.9 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 203.1, 169.4, 147.8, 142.6, 141.4, 136.1, 129.9, 128.3, 127.7, 126.8, 120.4, 118.5, 83.4, 40.0, 24.8, 20.8.; enantiomeric excess: 80% (Diacel Chirapak AD-H, hexanes/i-PrOH = 90:10, flow rate 1.0 mL/min, 254 nm, major enantiomer t_r = 11.1 min, minor enantiomer t_r = 13.5 min); HRMS (ESI) *m/z* 325.1431 [$C_{20}H_{21}O_4$ (M+H) requires 325.1440].



5b

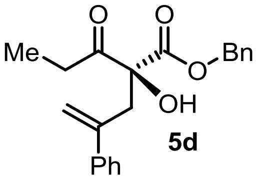
4-Chlorophenyl (*S*)-2-Acetyl-2-hydroxy-4-phenylpent-4-enoate (5b). Reaction between **3b** and α-methylstyrene gave **5b** in 92% yield as a colorless liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 - 7.27 (comp, 7H), 6.70 (d, *J* = 9.0 Hz, 2H), 5.44 (d, *J* = 1.4 Hz, 1H), 5.35 (d, *J* = 1.1 Hz, 1H), 4.03 (s, 1H), 3.59 (dd, *J* = 14.6, 0.7 Hz, 1H), 3.20 (dd, *J* = 14.6, 0.8 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 203.0, 169.0, 148.4, 142.4, 141.2, 131.8, 129.4, 128.4, 127.8, 126.8, 122.2, 118.8, 83.3, 40.2, 24.9.; IR (neat) 3491, 1758, 1723 cm^{-1}.; enantiomeric excess: 83% (Daicel Chiralpak AD-H, hexanes/i-PrOH = 90:10, flow rate 1.0 mL/min, 254 nm, major enantiomer t$_r$ = 10.9 min, minor enantiomer t$_r$ = 13.3 min); HRMS (ESI) *m/z* 345.0884 [$C_{19}H_{18}ClO_4$ (M+H) requires 345.0894].



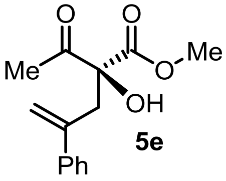
5c

Phenyl (*S*)-2-Acetyl-2-hydroxy-4-phenylpent-4-enoate (5c). Reaction between **3c** and α-methylstyrene gave **5c** in 90% yield as a colorless liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 – 7.12 (comp, 8H), 6.84 – 6.71 (m, 2H), 5.41 (d, *J* = 1.3 Hz, 1H), 5.33 (d, *J* = 1.0 Hz, 1H), 4.02 (s, 1H), 3.56 (dd, *J* = 14.6, 0.5 Hz, 1H), 3.21 (dd, *J* = 14.6, 0.7 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 203.1, 169.3, 150.0, 142.5, 141.3, 129.4, 128.3, 127.7, 126.8, 126.3, 120.7, 118.5, 76.6, 40.0, 24.9.; IR (neat) 3490, 1757, 1722, 1626 cm^{-1}; enantiomeric excess: 86% (Daicel Chiralpak AD-H, hexanes/i-PrOH = 96:4, flow rate 1.0 mL/min, 254 nm, major enantiomer t$_r$ = 16.5

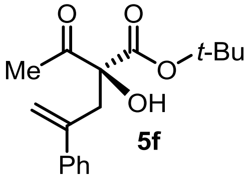
min, minor enantiomer t$_r$ = 18.3 min); (HRMS (ESI) *m/z* 311.1275 [$C_{19}H_{19}O_4$ (M+H) requires 311.1283].


5d

Benzyl (*S*)-2-Hydroxy-4-phenyl-2-propionylpent-4-enoate (5d). Reaction between **3d** and α-methylstyrene gave **5d** in 90% yield as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.17 (comp, 10H), 5.29 (d, *J* = 1.4 Hz, 1H), 5.16 (d, *J* = 1.1 Hz, 1H), 5.00 (d, *J* = 12.2 Hz, 1H), 4.74 (d, *J* = 12.2 Hz, 1H), 3.94 (s, 1H), 3.41 (dd, *J* = 14.6, 0.8 Hz, 1H), 3.07 (dd, *J* = 14.6, 0.8 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.4, 170.3, 142.6, 141.3, 134.5, 128.5, 128.2, 128.1, 127.6, 126.8, 118.2, 83.2, 68.0, 40.1, 24.8.; enantiomeric excess: 82% (Daicel Chiralpak OD-H, hexanes/i-PrOH = 97:3, flow rate 1.0 mL/min, 254 nm, major enantiomer t$_r$= 10.8 min, minor enantiomer t$_r$= 11.8 min); (HRMS (ESI) *m/z* 339.1591 [$C_{21}H_{23}O_4$ (M+H) requires 339.1596].

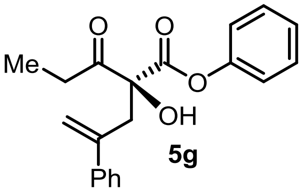

5e

Methyl (*S*)-2-Acetyl-2-hydroxy-4-phenylpent-4-enoate (5e). Reaction between **3e** and α-methylstyrene gave **5e** in 64% yield as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.21 (comp, 5H), 5.36 (d, *J* = 1.5 Hz, 1H), 5.23 (d, *J* = 1.2 Hz, 1H), 3.98 (s, 1H), 3.48 (s, 3H), 3.46 (dd, *J* = 14.5, 1.0 Hz, 1H), 3.05 (dd, *J* = 14.5, 0.8 Hz, 1H), 2.21 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.7, 170.9, 142.6, 141.2, 128.1, 127.6, 126.8, 118.3, 83.1, 53.0, 40.4, 25.0.; enantiomeric excess: 85% (Daicel Chiralpak AD-H, hexanes/i-PrOH = 98:2, flow rate 1.0 mL/min, 254 nm, major enantiomer t_r = 18.0 min, minor enantiomer t_r = 20.1 min); (HRMS (ESI) *m/z* 249.1121 [$C_{14}H_{17}O_4$ (M+H) requires 249.1127].



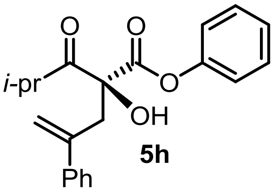
5f

***tert*-Butyl (*S*)-2-Acetyl-2-hydroxy-4-phenylpent-4-enoate (5f)**. Reaction between **3f** and α-methylstyrene gave **5f** in 58% yield as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.22 (comp, 5H), 5.33 (d, *J* = 1.5 Hz, 1H), 5.22 (d, *J* = 1.5 Hz, 1H), 3.90 (s, 1H), 3.32 (d, *J* = 14.7 Hz, 1H), 3.05 (d, *J* = 14.7 Hz, 1H), 2.14 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.8, 169.6, 142.9, 141.8, 128.1, 127.5, 126.7, 117.8, 84.0, 83.3, 39.0, 27.5, 24.6.; enantiomeric excess: 86% (Daicel Chiralpak AD-H, hexanes/i-PrOH = 99:1, flow rate 1.0 mL/min, 254 nm, major enantiomer t_r = 13.4 min, minor enantiomer t_r = 12.6 min); (HRMS (ESI) *m/z* 291.1588 [$C_{17}H_{23}O_4$ (M+H) requires 291.1596].



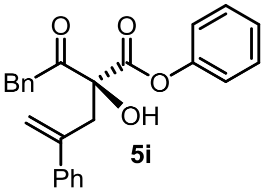
5g

Phenyl (*S*)-2-Hydroxy-4-phenyl-2-propionylpent-4-enoate (5g). Reaction between **3g** and α-methylstyrene gave **5g** in 91% yield as a colorless solid; mp = 58-60 °C; $[\alpha]_D^{21\ °C}$ = + 17.7 (c = 0.9, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.21 (comp, 8H), 6.83 - 6.77 (comp, 2H), 5.44 (d, *J* = 1.4 Hz, 1H), 5.36 (d, *J* = 1.0 Hz, 1H), 4.07 (s, 1H), 3.59 (dd, *J* = 14.6, 0.7 Hz, 1H), 3.28 (dd, *J* = 14.6, 0.8 Hz, 1H), 2.90 – 2.67 (m, 1H), 2.64 - 2.53 (m, 1H), 1.06 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.0, 169.4, 150.0, 142.6, 141.3, 129.4, 128.3, 127.7, 126.8, 126.3, 120.7, 118.5, 83.1, 40.2, 30.7, 7.5; IR (neat) 3433, 1761, 1721, 1589 cm^{-1}. Enantiomeric enantiomeric excess: 94% (Diacel Chirapak AD-H, hexanes/i-PrOH = 98:2, flow rate 0.5 mL/min, 254 nm, major enantiomer t_r = 44.6 min, minor enantiomer t_r = 48.3 min); HRMS (ESI) *m/z* 325.1429 [$C_{20}H_{21}O_4$ (M+H) requires 325.1440].



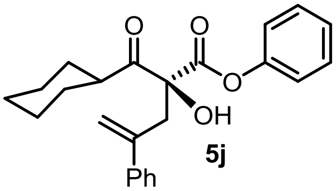
5h

Phenyl (*S*)-2-Hydroxy-2-isobutyryl-4-phenylpent-4-enoate (5h). Reaction between **3h** and α-methylstyrene gave **5h** in 81% yield as a white solid; mp = 103-105 °C; $[\alpha]_D^{21\ °C}$ = + 49.8 (c = 1.0, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.15 (m, 9H), 6.69 (dd, *J* = 8.6, 1.2 Hz, 2H), 5.42 (d, *J* = 1.4 Hz, 1H), 5.33 (d, *J* = 1.2 Hz, 1H), 3.86 (s, 1H), 3.62 (dd, *J* = 14.6, 0.7 Hz, 1H), 3.32 - 3.21 (m, 1H), 3.14 (dd, *J* = 14.6, 0.9 Hz, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.3, 169.7, 150.0, 142.8, 141.4, 129.3, 128.3, 127.7, 126.8, 126.3, 120.7, 118.6, 83.1, 40.3, 35.7, 19.5, 19.2. IR (neat) 3416, 1765, 1717, 1589 cm^{-1}. Enantiomeric excess: 92% (Diacel Chirapak AD-H, hexanes/i-PrOH = 96:4, flow rate 0.7 mL/min, 254 nm, major enantiomer t_r = 17.3 min, minor enantiomer t_r = 19.1 min); HRMS (ESI) *m/z* 339.1588 [$C_{21}H_{23}O_4$ (M+H) requires 339.1596].



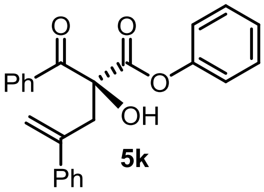
5i

Phenyl (*S*)-2-Hydroxy-4-phenyl-2-(2-phenylacetyl)pent-4-enoate (5i). Reaction between **3i** and α-methylstyrene gave **5i** in 78% yield as a white solid; mp = 79 - 71 °C; $[\alpha]_D^{21\ °C}$ = + 24.1 (c = 1.0, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.07 (comp, 13H), 6.63 – 6.51 (m, 2H), 5.42 (d, *J* = 1.4 Hz, 1H), 5.33 (d, *J* = 1.1 Hz, 1H), 3.98 (d, *J* = 16.1 Hz, 1H), 3.94 (s, 1H), 3.91 (d, *J* = 16.1 Hz, 1H), 3.60 (dd, *J* = 14.6, 0.6 Hz, 1H), 3.24 (dd, *J* = 14.6, 0.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.8, 169.2, 149.9, 142.6, 141.3, 132.9, 129.7, 129.3, 128.6, 128.4, 127.7, 127.1, 126.8, 126.3, 120.7, 118.8, 83.2, 44.0, 40.4. IR (neat) 3415, 1763, 1718, 1589 cm^{-1}. Enantiomeric excess: 92% (Diacel Chirapak IC3, hexanes/i-PrOH = 98:2, flow rate 0.6 mL/min, 254 nm, major enantiomer t_r = 21.8 min, minor enantiomer t_r = 22.3 min); HRMS (ESI) *m/z* 387.1585 [$C_{25}H_{23}O_4$ (M+H) requires 387.1596].



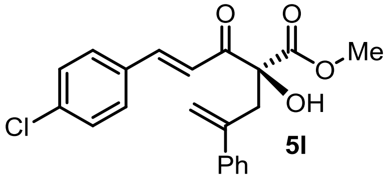
5j

Phenyl (*S*)-2-(Cyclohexanecarbonyl)-2-hydroxy-4-phenylpent-4-enoate (5j). Reaction between **3j** and α-methylstyrene gave **5j** in 90% yield as a white solid; mp = 122 - 124 °C; $[\alpha]_D^{21\,°C}$ = + 31.7 (c = 1.0, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.15 (comp, 8H), 6.69 (dd, *J* = 8.5, 1.1 Hz, 2H), 5.41 (d, *J* = 1.4 Hz, 1H), 5.32 (d, *J* = 1.0 Hz, 1H), 3.61 (dd, *J* = 14.6, 0.5 Hz, 1H), 3.13 (dd, *J* = 14.6, 0.8 Hz, 1H), 3.05 - 3.97 (m, 1H), 1.87 – 1.57 (comp, 5H), 1.50 – 1.10 (comp, 5H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 208.1, 169.7, 150.0, 142.9, 141.4, 129.3, 128.3, 127.6, 126.8, 126.3, 120.7, 118.5, 83.1, 45.7, 40.3, 29.4, 29.2, 25.6, 25.5, 25.4. IR (neat) 3414, 1765, 1717, 1589 cm^{-1}. Enantiomeric excess: 91% (Diacel Chirapak AD-H, hexanes/i-PrOH = 96:4, flow rate 0.7 mL/min, 254 nm, major enantiomer t_r = 16.6 min, minor enantiomer t_r = 25.4 min); HRMS (ESI) *m/z* 379.1901 [$C_{24}H_{27}O_4$ (M+H) requires 379.1909].



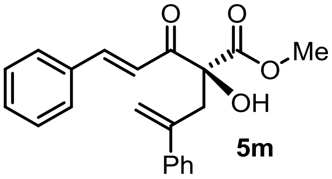
5k

Phenyl (*S*)-2-Benzoyl-2-hydroxy-4-phenylpent-4-enoate (5k). Reaction between **3i** and α-methylstyrene gave **5i** in 90% yield as a white solid; mp = 106 - 108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.65 – 7.51 (m, 1H), 7.46 – 7.10 (comp, 10H), 6.49 (dd, *J* = 8.4, 1.2 Hz, 2H), 5.40 (d, *J* = 1.5 Hz, 1H), 5.25 (d, *J* = 1.2 Hz, 1H), 4.10 (s, 1H), 3.69 (d, *J* = 14.5 Hz, 1H), 3.47 (dd, *J* = 14.5, 0.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 193.5, 170.3, 149.9, 142.6, 141.2, 134.0, 133.6, 129.3, 129.3, 128.6, 128.2, 127.6, 126.9, 126.3, 120.7, 119.1, 81.4, 41.0. IR (neat) 3409, 1762, 1685, 1596 cm^{-1}. Enantiomeric excess: 68% (Diacel Chirapak AD-H, hexanes/i-PrOH = 90:10, flow rate 1.0 mL/min, 254 nm, major enantiomer t_r =11.3 min, minor enantiomer t_r = 12.9 min); HRMS (ESI) *m/z* 373.1452 [$C_{24}H_{21}O_4$ (M+H) requires 373.1440].



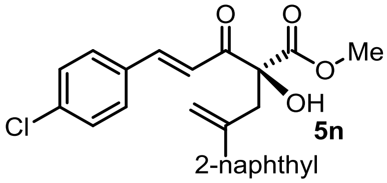
5l

Methyl (*S,E*)-5-(4-Chlorophenyl)-2-hydroxy-3-oxo-2-(2-phenylallyl)pent-4-enoate (5l). Reaction between **3l** and α-methylstyrene gave **5l** in 91% yield as a white solid; mp = 82 - 84 °C; $[\alpha]_D^{21\,°C}$ = - 85.5 (c = 1.7, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 15.8 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.39 – 7.15 (comp, 7H), 7.07 (d, *J* = 15.8 Hz, 1H), 5.34 (d, *J* = 1.5 Hz, 1H), 5.23 (d, *J* = 1.2 Hz, 1H), 4.15 (s, 1H), 3.55 – 3.44 (comp, 4H), 3.17 (dd, *J* = 14.4, 0.7 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 193.6, 171.1, 144.0, 142.6, 141.2, 137.0, 132.6, 129.9, 129.2, 128.0, 127.6, 126.9, 119.4, 118.5, 82.6, 53.1, 41.0. IR (neat) 3439, 1742, 1688, 1607 cm^{-1}. Enantiomeric excess: 97% (Diacel Chirapak IC-3, hexanes/i-PrOH = 85:15, flow rate 1.0 mL/min, 254 nm, major enantiomer t_r = 10.0 min, minor enantiomer t_r = 9.1 min); HRMS (ESI) *m/z* 371.1034 [$C_{21}H_{20}ClO_4$ (M+H) requires 371.1050].



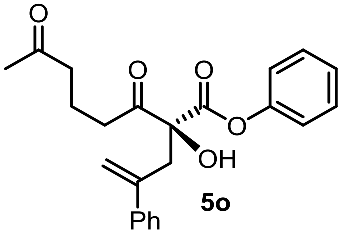
5m

Methyl (*S,E*)-2-Hydroxy-3-oxo-5-phenyl-2-(2-phenylallyl)pent-4-enoate (5m). Reaction between **3m** and α-methylstyrene gave **5m** in 94% yield as a colorless solid; mp = 129 - 130 °C; $[\alpha]_D^{21\ ^\circ C}$ = - 73.5 (c = 0.5, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 15.8 Hz, 1H), 7.53 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.43 – 7.15 (comp, 8H), 7.12 (d, *J* = 15.8 Hz, 1H), 5.34 (d, *J* = 1.5 Hz, 1H), 5.23 (d, *J* = 1.1 Hz, 1H), 3.51 (dd, *J* = 14.4, 0.7 Hz, 1H), 3.48 (s, 3H), 3.18 (dd, *J* = 14.4, 0.7 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 193.7, 171.2, 145.6, 142.7, 141.3, 134.1, 131.0, 128.8, 128.7, 128.0, 127.5, 126.8, 118.9, 118.3, 82.6, 53.1, 40.9. IR (neat) 3394, 1750, 1682, 1604 cm^{-1}. Enantiomeric excess: 96% (Diacel Chirapak IC-3, hexanes/i-PrOH = 97:3, flow rate 0.7 mL/min, 254 nm, major enantiomer t_r = 39.1 min, minor enantiomer t_r = 35.2 min); HRMS (ESI) *m/z* 337.1432 [$C_{21}H_{21}O_4$ (M+H) requires 337.1440].



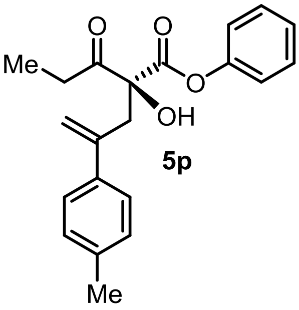
5n

Methyl (*S,E*)-5-(4-Chlorophenyl)-2-hydroxy-2-(2-(naphthalen-2-yl)allyl)-3-oxopent-4-enoate (5n). Reaction between **3l** and 2-(prop-1-en-2-yl)naphthalene gave **5n** in 85% yield as a colorless solid; mp = 140 - 141 °C; Enantiomer excess 73%; The solid was recrystallized in DCM and hexane to provides 97% enantiomer excess. $[\alpha]_D^{21\ ^\circ C}$ = - 115.0 (c = 1.8, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.61 (comp, 4H), 7.52 – 7.22 (comp, 8H), 7.02 (d, *J* = 15.8 Hz, 1H), 5.47 (d, *J* = 1.4 Hz, 1H), 5.33 (d, *J* = 0.9 Hz, 1H), 4.23 (s, 1H), 3.57 (dd, *J* = 14.4, 0.5 Hz, 1H), 3.45 (s, 3H), 3.33 (d, *J* = 14.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 193.6, 171.1, 143.9, 142.4, 138.5, 136.8, 133.0, 132.7, 132.5, 129.7, 129.0, 128.0, 127.6, 127.4, 126.1, 125.9, 125.6, 125.2, 119.3, 119.0, 82.7, 53.2, 41.1. Enantiomeric excess: 97% (Diacel Chirapak IC-3, hexanes/i-PrOH = 85:15, flow rate 1.0 mL/min, 254 nm, major enantiomer t_r = 10.8 min, minor enantiomer t_r = 10.0 min); HRMS (ESI) *m/z* 421.1219 [$C_{25}H_{22}ClO_4$ (M+H) requires 421.1207].



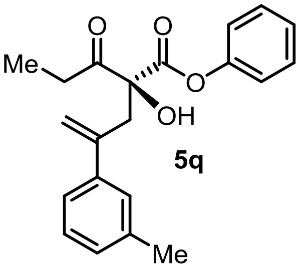
5o

Phenyl (*S*)-2-Hydroxy-3,7-dioxo-2-(2-phenylallyl)octanoate (5o). Reaction between **3n** and α-methylstyrene gave **5o** in 90% yield as a colorless liquid; $[\alpha]_D^{21\,°C}$ = + 13 (c = 1.0, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.14 (comp, 8H), 6.83 – 6.70 (comp, 2H), 5.40 (d, *J* = 1.4 Hz, 1H), 5.31 (d, *J* = 1.1 Hz, 1H), 3.95 (s, 1H), 3.53 (dd, *J* = 14.6, 0.6 Hz, 1H), 3.21 (dd, *J* = 14.6, 0.8 Hz, 1H), 2.83 - 2.75 (m, 1H), 2.60 - 2.52 (m, 1H), 2.41 (t, *J* = 7.1 Hz, 2H), 2.09 (s, 3H), 1.89 - 1.72 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.9, 204.9, 169.3, 150.0, 142.5, 141.3, 129.4, 128.3, 127.7, 126.8, 126.4, 120.7, 118.7, 83.1, 42.1, 40.1, 36.2, 29.8, 17.3. IR (neat) 3469, 1759, 1731 cm^{-1}. Enantiomeric excess: 95% (Diacel Chirapak IC-3, hexanes/i-PrOH = 85:15, flow rate 1.0 mL/min, 254 nm, major enantiomer t_r = 15.5 min, minor enantiomer t_r = 17.1 min); HRMS (ESI) *m/z* 381.1719 [$C_{23}H_{25}O_5$ (M+H) requires 381.1702].



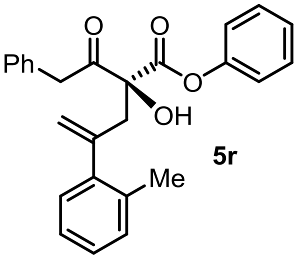
5p

Phenyl (*S*)-2-Hydroxy-2-propionyl-4-(p-tolyl)pent-4-enoate (5p). Reaction between **3g** and 1-methyl-4-(prop-1-en-2-yl)benzene gave **5p** in 71% yield as a white solid; mp = 73 - 74 °C; $[\alpha]_D^{21\ ^\circ C}$ = + 15 (c = 0.5, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.17 (comp, 5H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.82 – 6.73 (m, 2H), 5.37 (d, *J* = 1.4 Hz, 1H), 5.26 (d, *J* = 1.1 Hz, 1H), 3.99 (s, 1H), 3.53 (dd, *J* = 14.6, 0.7 Hz, 1H), 3.20 (dd, *J* = 14.6, 0.8 Hz, 1H), 2.80 - 2.761(m, 1H), 2.61 - 2.48 (m, 1H), 2.33 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 206.1, 169.4, 150.1, 142.4, 138.4, 137.5, 129.3, 129.0, 126.7, 126.3, 120.8, 117.7, 83.2, 40.3, 30.7, 21.0, 7.6. IR (neat) 3428, 1750, 1716 cm^{-1}. Enantiomeric excess: 91% (Diacel Chirapak OJ-H, hexanes/i-PrOH = 70:30, flow rate 1.0 mL/min, 254 nm, major enantiomer t_r = 13.2 min, minor enantiomer t_r = 18.5 min); HRMS (ESI) *m/z* 339.1584 [$C_{21}H_{23}O_4$ (M+H) requires 339.1596].



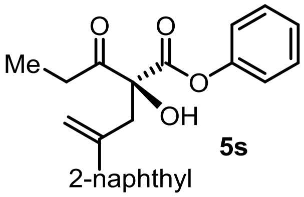
5q

Phenyl (*S*)-2-Hydroxy-2-propionyl-4-(m-tolyl)pent-4-enoate (5q). Reaction between **3g** and 1-methyl-3-(prop-1-en-2-yl)benzene gave **5q** in 80% yield as colorless liquid; $[\alpha]_D^{21\ ^\circ C}$ = + 17 (c = 0.9, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.02 (comp, 7H), 6.86 – 6.73 (comp, 2H), 5.38 (d, *J* = 1.4 Hz, 1H), 5.29 (d, *J* = 1.2 Hz, 1H), 4.00 (s, 1H), 3.53 (dd, *J* = 14.6, 0.8 Hz, 1H), 3.21 (dd, *J* = 14.6, 0.8 Hz, 1H), 2.82 - 2.70 (m, 1H), 2.60 - 2.50 (m, 1H), 2.31 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 206.1, 169.4, 150.1, 142.7, 141.3, 137.9, 129.3, 128.4, 128.2, 127.4, 126.3, 123.9, 120.7, 118.3, 83.2, 40.3, 30.7, 21.3, 7.6. IR (neat) 3426, 1762, 1721 cm^{-1}. Enantiomeric excess: 97% (Diacel Chirapak OJ-H, hexanes/i-PrOH = 75:25, flow rate 0.7 mL/min, 254 nm, major enantiomer t_r = 21.2 min, minor enantiomer t_r = 26.2 min); HRMS (ESI) *m/z* 339.1589 [$C_{21}H_{23}O_4$ (M+H) requires 339.1596].



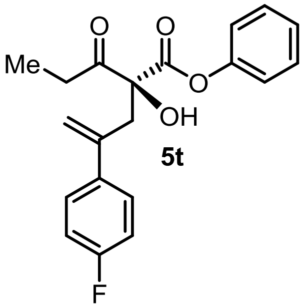
5r

Phenyl (*S*)-2-Hydroxy-2-propionyl-4-(o-tolyl)pent-4-enoate (5r). Reaction between **3i** and 1-methyl-2-(prop-1-en-2-yl)benzene gave **5r** in 65% yield as colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.08 (comp, 12H), 6.62 – 6.47 (comp, 2H), 5.46 (d, J = 1.8 Hz, 1H), 5.15 (d, *J* = 1.8 Hz, 1H), 4.03 (s, 1H), 3.94 (d, *J* = 16.1 Hz, 1H), 3.80 (d, *J* = 16.1 Hz, 1H), 3.50 (d, *J* = 14.6 Hz, 1H), 3.18 (d, *J* = 14.6 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.0, 169.3, 150.0, 143.0, 141.5, 135.2, 132.8, 130.4, 129.7, 129.3, 129.0, 128.6, 127.4, 127.1, 126.3, 125.7, 120.7, 120.7, 83.1, 43.6, 42.5, 20.0. Enantiomeric excess: 93% (Diacel Chirapak AD-H, hexanes/i-PrOH = 95:5, flow rate 1.0 mL/min, 254 nm, major enantiomer t_r = 17.5 min, minor enantiomer t_r = 15.0 min); HRMS (ESI) *m/z* 401.1764 [$C_{24}H_{23}O_4$ (M+H) requires 401.1753].



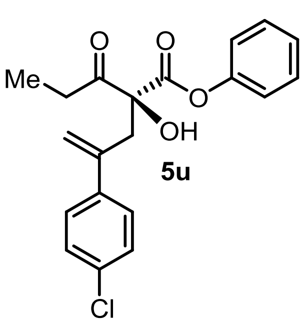
5s

Phenyl (*S*)-2-Hydroxy-4-(naphthalen-2-yl)-2-propionylpent-4-enoate (5s). Reaction between **3g** and 2-(prop-1-en-2-yl)naphthalene gave **5s** in 84% yield as white solid; mp = 74 - 76 °C; $[\alpha]_D^{21\ °C}$ = + 18.3 (c = 0.9, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 - 7.76 (comp, 4H), 7.56 - 7.42 (comp, 3H), 7.23 – 7.10 (comp, 3H), 6.75 – 6.59 (m, 2H), 5.53 (d, *J* = 1.2 Hz, 1H), 5.41 (d, *J* = 0.8 Hz, 1H), 4.03 (s, 1H), 3.67 (d, *J* = 14.7 Hz, 1H), 3.33 (d, *J* = 14.7 Hz, 1H), 2.82 - 2.72 (m, 1H), 2.62 - 2.50 (m, 1H), 1.00 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 206.0, 169.5, 150.0, 142.6, 138.6, 133.2, 132.8, 129.3, 128.1, 127.9, 127.4, 126.2, 126.2, 126.0, 125.5, 125.0, 120.6, 118.9, 83.3, 40.3, 30.7, 7.6. IR (neat) 3441, 1764, 1722 cm^{-1}. Enantiomeric excess: 90% (Diacel Chirapak AD-H, hexanes/i-PrOH = 98:2, flow rate 0.5 mL/min, 254 nm, major enantiomer t_r = 34.0 min, minor enantiomer t_r = 31.7 min); HRMS (ESI) *m/z* 375.1579 [$C_{24}H_{23}O_4$ (M+H) requires 375.1596].



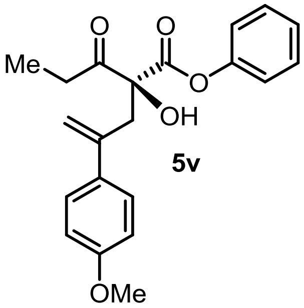
5t

Phenyl (*S*)-4-(4-Fluorophenyl)-2-hydroxy-2-propionylpent-4-enoate (5t). Reaction between **3g** and 1-fluoro-4-(prop-1-en-2-yl)benzene gave **5t** in 87% yield as colorless liquid; $[\alpha]_D^{21\ °C}$ = + 20.3 (c = 0.9, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.30 (comp, 4H), 7.25 - 7.21 (m, 1H), 6.99 (t, *J* = 8.7 Hz, 2H), 6.86 – 6.80 (m, 2H), 5.35 (d, *J* = 1.2 Hz, 1H), 5.29 (d, *J* = 0.9 Hz, 1H), 4.02 (s, 1H), 3.51 (dd, *J* = 14.7, 0.7 Hz, 1H), 3.20 (dd, *J* = 14.7, 0.8 Hz, 1H), 2.82 - 2.72 (m, 1H), 2.60 - 2.50 (m, 1H), 1.04 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.0, 169.4, 162.5 (d, 247.0 Hz), 150.0, 141.7, 137.4 (d, 3.3 Hz), 129.4, 128.5 (d, 8.0 Hz), 126.4, 120.7, 118.4, 115.1 (d, 21.4 Hz), 83.2, 40.3, 30.7, 7.6. IR (neat) 3411, 1757, 1716 cm^{-1}. Enantiomeric excess: 92% (Diacel Chirapak OD-H, hexanes/i-PrOH = 96:4, flow rate 0.5 mL/min, 254 nm, major enantiomer t_r = 20.8 min, minor enantiomer t_r = 19.7 min); HRMS (ESI) *m/z* 343.1329 [$C_{20}H_{20}FO_4$ (M+H) requires 343.1346].



5u

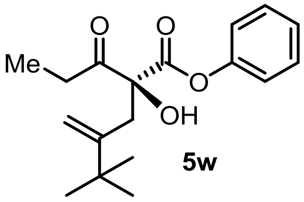
Phenyl (*S*)-4-(4-Chlorophenyl)-2-hydroxy-2-propionylpent-4-enoate (5u). Reaction between **3g** and 1-chloro-4-(prop-1-en-2-yl)benzene gave **5u** in 85% yield as white solid; mp = 66 - 68 °C; $[\alpha]_D^{21\ ^\circ C}$ = + 20.3 (c = 1.4, ethyl acetate); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.16 (comp, 7H), 6.80 (d, *J* = 8.6 Hz, 2H), 5.39 (d, *J* = 1.2 Hz, 1H), 5.32 (d, *J* = 1.0 Hz, 1H), 4.01 (s, 1H), 3.51 (dd, *J* = 14.7, 0.6 Hz, 1H), 3.18 (dd, *J* = 14.7, 0.8 Hz, 1H), 2.18 - 2.72 m, 1H), 2.60 - 2.52 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 205.9, 169.4, 150.0, 141.6, 139.8, 133.6, 129.4, 128.4, 128.1, 126.4, 120.6, 118.9, 83.2, 40.1, 30.7, 7.6. IR (neat) 3440, 1766, 1723 cm^{-1}. Enantiomeric excess: 95% (Diacel Chirapak OD-H, hexanes/i-PrOH = 98:2, flow rate 0.5 mL/min, 254 nm, major enantiomer t$_r$ = 33.6 min, minor enantiomer t$_r$ = 29.4 min); HRMS (ESI) *m/z* 359.1034 [$C_{20}H_{20}ClO_4$ (M+H) requires 359.1050].



5v

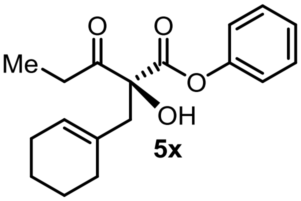
Phenyl (*S*)-2-Hydroxy-4-(4-methoxyphenyl)-2-propionylpent-4-enoate (5v). Reaction between **3g** and 1-methoxy-4-(prop-1-en-2-yl)benzene gave **5v** in 65% yield as light green liquid; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 – 7.12 (comp, 5H), 6.89 – 6.72 (comp, 4H), 5.33 (d, *J* = 1.4 Hz, 1H), 5.22 (d, *J* = 1.1 Hz, 1H), 3.99 (s, 1H), 3.79 (s, 3H), 3.51 (dd, *J* = 14.6, 0.7 Hz, 1H), 3.20 (dd, *J* = 14.6, 0.8 Hz, 1H), 2.88 – 2.70 (m, 1H), 2.66 – 2.46 (m, 1H), 1.03 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ

206.1, 169.4, 159.3, 150.1, 141.9, 133.6, 129.3, 127.9, 126.3, 120.8, 117.1, 113.7, 83.2, 55.2, 40.3, 30.7, 7.6. IR (neat) 3463, 1756, 1722, 1606 cm^{-1}. Enantiomeric excess: 28% (Diacel Chirapak AD-H, hexanes/i-PrOH = 95:5, flow rate 1.0 mL/min, 254 nm, major enantiomer t_r = 21.4 min, minor enantiomer t_r = 23.6 min); HRMS (ESI) *m/z* 355.1540 [$C_{21}H_{23}O_5$ (M+H) requires 355.1545].



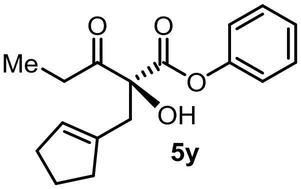
5w

Phenyl (*S*)-2-Hydroxy-5,5-dimethyl-4-methylene-2-propionylhexanoate (5w). Reaction between **3g** and 2,3,3-trimethylbut-1-ene gave **5w** in 55% yield as colorless liquid; $[\alpha]_D^{21\ °C}$ = + 87.3 (c = 0.6, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H), 7.29 – 7.22 (m, 1H), 7.07 – 7.02 (m, 2H), 5.05 (s, 1H), 5.01 (t, *J* = 1.5 Hz, 1H), 4.33 (s, 1H), 3.11 (d, *J* = 17.2 Hz, 1H), 2.92 - 2.82 (comp, 2H), 2.75 - 2.65 (m, 1H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.11 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.4, 170.1, 151.3, 150.4, 129.5, 126.4, 120.9, 108.7, 84.2, 36.5, 35.0, 30.2, 29.1, 7.8. IR (neat) 3463, 1756, 1722, 1606 cm^{-1}. Enantiomeric excess: 96% (Diacel Chirapak AD-H, hexanes/i-PrOH = 96:4, flow rate 0.5 mL/min, 254 nm, major enantiomer t_r = 20.9 min, minor enantiomer t_r = 19.6 min); HRMS (ESI) *m/z* 305.1765 [$C_{18}H_{25}O_4$ (M+H) requires 305.1753].



5x

Phenyl (*S*)-2-(Cyclohex-1-en-1-ylmethyl)-2-hydroxy-3-oxopentanoate (5x). Reaction between **3g** and methylenecyclohexane gave **5x** in 90% yield as colorless liquid; $[\alpha]_D^{21\,°C}$ = + 10.0 (c = 0.7, ethyl acetate); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 - 7.37 (m, 2H), 7.27 - 2.6 (m, 1H), 7.05 (d, *J* = 8.6, 2H), 5.63 (s, 1H), 4.17 (s, 1H), 2.96 (d, *J* = 14.2 Hz, 1H), 2.89 – 2.62 (comp, 3H), 1.95 - 2.15 (comp, *J* = 1.1 Hz, 4H), 1.66 – 1.48 (comp, 4H), 1.14 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 206.9, 169.8, 150.3, 132.1, 129.5, 127.0, 126.3, 120.9, 84.2, 43.4, 30.6, 29.7, 25.4, 22.8, 22.0, 7.7. IR (neat) 3463, 1756, 1722, 1606 cm^{-1}. Enantiomeric excess: 90% (Diacel Chirapak AD-H, hexanes/i-PrOH = 96:4, flow rate 0.7 mL/min, 254 nm, major enantiomer t_r = 17.9 min, minor enantiomer t_r = 21.7min); HRMS (ESI) *m/z* 303.1576 [$C_{18}H_{23}O_4$ (M+H) requires 303.1596].

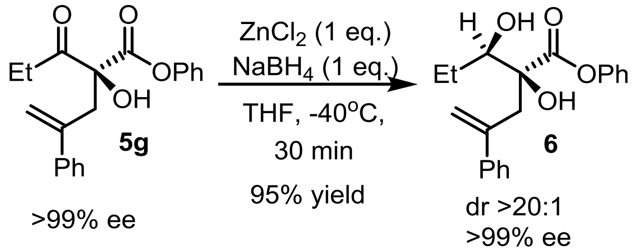


5y

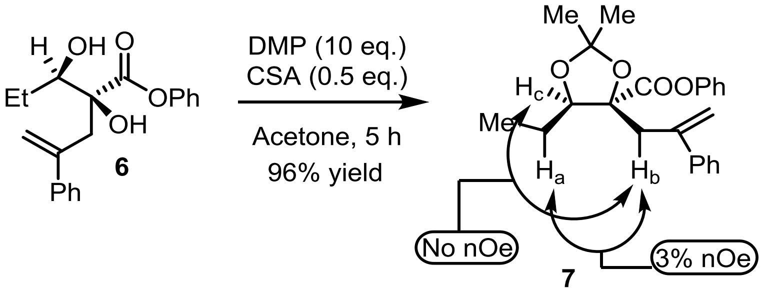
Phenyl (*S*)-2-(Cyclopent-1-en-1-ylmethyl)-2-hydroxy-3-oxopentanoate (5y). Reaction between **3g** and methylenecyclopentane gave **5y** in 91% yield as colorless liquid; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 - 7.35 (m, 2H), 7.27 - 7.23 (m, 1H), 7.07 - 7.04 (comp, 2H), 5.59 (d, *J* = 0.8 Hz, 1H), 4.25 (s, 1H), 3.11 (d, *J* = 14.6 Hz, 1H), 2.89 (d, *J* = 14.7 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.75 - 2.64 (m, 1H), 2.32 (t, *J* = 7.5

Hz, 4H), 1.90 - 1.80 (m, 2H), 1.14 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 206.8, 169.7, 150.3, 137.7, 129.5, 129.4, 126.3, 120.9, 83.8, 36.7, 36.0, 32.4, 30.4, 23.5, 7.7. IR (neat) 3455, 1754, 1720, 1592 cm^{-1}. Enantiomeric excess: 78% (Diacel Chirapak AD-H, hexanes/i-PrOH = 97:3, flow rate 0.7 mL/min, 254 nm, major enantiomer t$_r$ = 21.0 min, minor enantiomer t$_r$ = 23.1 min); HRMS (ESI) *m/z* 289.1427 [C$_{17}$H$_{21}$O$_4$ (M+H) requires 289.1440].

3.5.5 Procedures for the Synthesis of Vicinal Diols and Acetonide



Phenyl (*S*)-2-Hydroxy-2-((*R*)-1-hydroxypropyl)-4-phenylpent-4-enoate (6). A solution of NaBH$_4$ (0.25 mmol, 9.45 mg) in THF (1.0 ml) under nitrogen atmosphere, at -40 °C was added ZnCl$_2$ (1.0 eq., 0.25 mmol, 0.25 ml of 1.0M solution). Then a solution of enantiomerically pure **5g** (1.0 eq, 0.25 mmol, 81 mg,) in 0.5 ml of THF was added to the reaction mixture, and this solution was stirred for 30 min. The reaction was quenched with saturated aqueous NH$_4$Cl (5 mL) then extracted with 10 mL of diethyl ether 3 times. The combined organic layers were dried over anhydrous Na$_2$SO$_4$, concentrated; and the residue was purified by column chromatography (SiO2), eluting with hexane and ethyl acetate to provide **6** (77.4 mg, 95% yield, >99% ee) of a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 – 7.13 (comp, 8H), 6.71 – 6.62 (comp, 2H), 5.41 (d, *J* = 1.5 Hz, 1H), 5.33 (s, 1H), 3.88 (td, *J* = 10.6, 2.3 Hz, 1H), 3.19 (s, 1H), 3.16 (d, *J* = 13.9 Hz, 1H), 2.98 (dd, *J* = 13.9, 0.8 Hz, 1H), 1.96 (d, *J* = 10.7 Hz, 1H), 1.93 – 1.80 (m, 1H), 1.61 – 1.47 (m, 1H), 1.11 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.5, 150.2, 143.3, 141.5, 129.3, 128.3, 127.6, 126.8, 126.1, 121.1, 118.3, 80.4, 40.3, 24.0, 10.4. IR (neat) 3344, 1767, 1590 cm^{-1}. Enantiomeric excess: >99% (Diacel Chirapak AD-H, hexanes/i-PrOH = 90:10, flow rate 1.0 mL/min, 254 nm, major enantiomer t_r = 21.3 min, minor enantiomer t_r = 18.6. min); HRMS (ESI) *m/z* 327.1584 [$C_{20}H_{23}O_4$ (M+H) requires 327.1596].

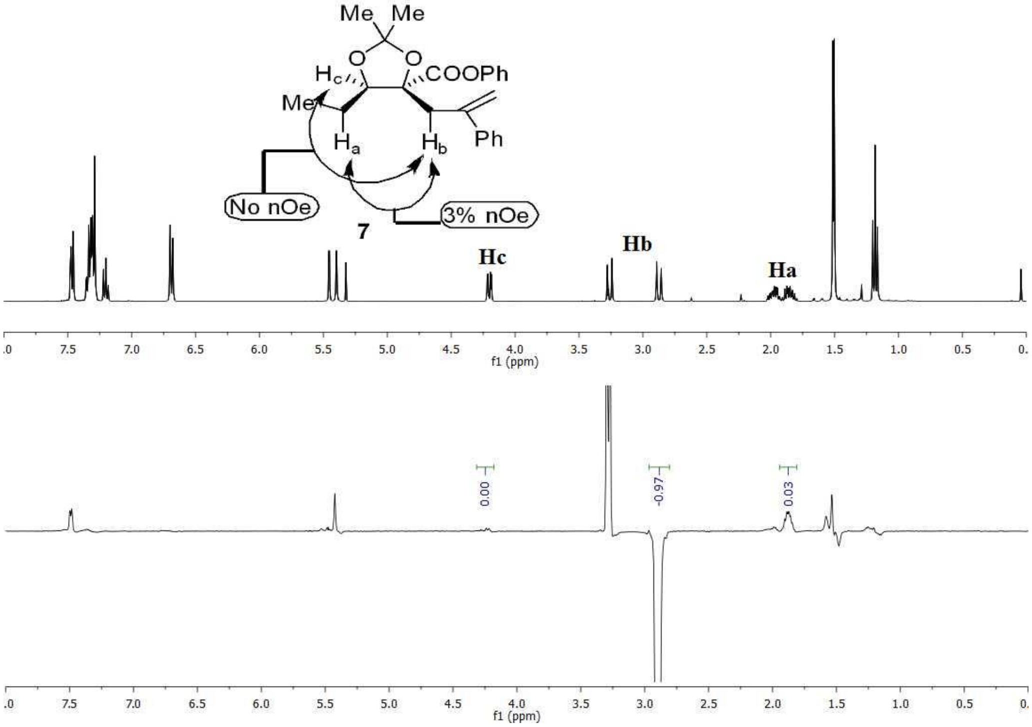


Phenyl (4*S*,5*R*)-5-Ethyl-2,2-dimethyl-4-(2-phenylallyl)-1,3-dioxolane-4-carboxylate (7). A solution of **6** (120 mg, 0.37 mmol) in 5 mL of acetone was added 2,2-dimethoxypropane (DMP) (10 eq., 0.46 ml) and camphorsulfonic acid (CSA) (0.50 eq., 42.9 mg, 0.18 mmol) at room temperature and stirred for 5 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with 15 mL of DCM 3 times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to provide pure **7** (130 mg, 96% yield) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.34 - 7023 (comp, 5H), 7.19 – 7.13 (m, 1H), 6.69 – 6.61 (m, 2H), 5.41 (d, *J* = 1.3 Hz, 1H), 5.36 (d, *J* = 0.9 Hz, 1H), 4.16 (dd, *J* = 9.9, 2.9 Hz, 1H), 3.22 (d, *J* = 14.2 Hz, 1H), 2.83 (d, *J* = 14.2 Hz, 1H), 1.98 - 1.87(m, 1H), 1.87 – 1.76 (m, 1H), 1.47 (s, 3H), 1.46

(s, 3H), 1.14 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 171.0, 150.2, 143.3, 142.1, 129.1, 128.2, 127.3, 126.8, 125.8, 121.1, 117.6, 109.7, 84.7, 83.0, 38.4, 27.8, 25.2, 22.6, 11.6. HRMS (ESI) *m/z* 367.1922 [$C_{23}H_{27}O_4$ (M+H) requires 367.1909].

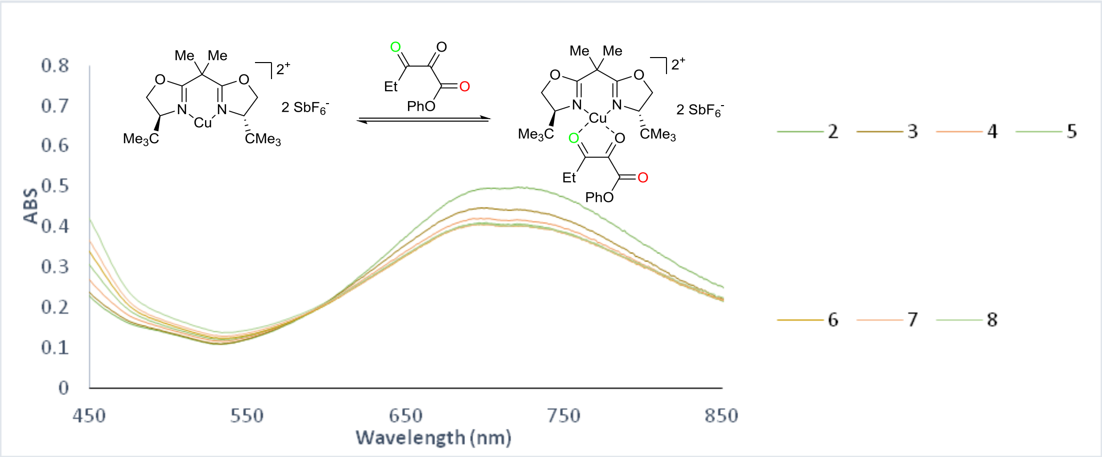
The stereochemistry of the reduced product **6** was confirmed by a nOe experiment of the protected diols **7**. Proton (H_b) was irradiated and 3% nOE correlation to H_a was observed, while no correlation to H_c was detected (Figure 3.6).

Figure 3.6 nOe Experiment of Acetonide 7

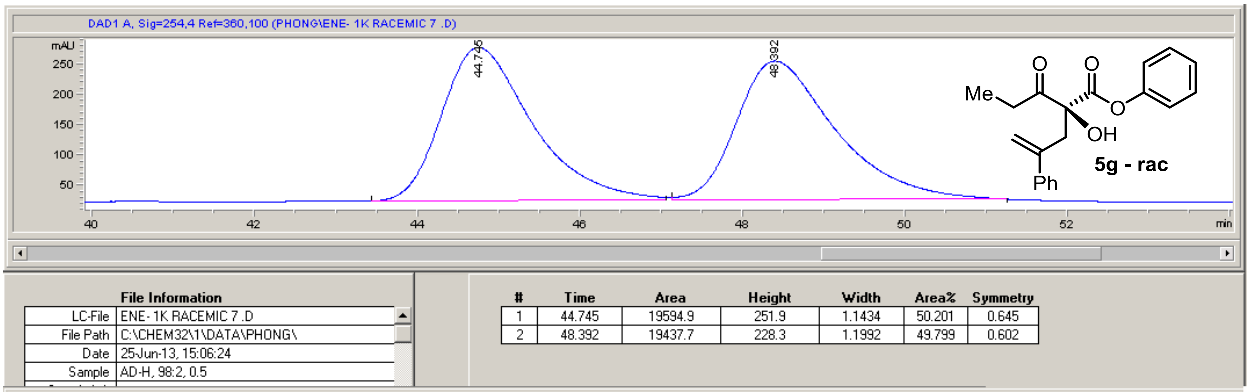


3.5.6 Procedure for UV-Vis Titration Experiment of [Cu((*S*,*S*)-*tert*-Bu-box)](SbF_6)$_2$ with 2,3-Diketoester 3g

A solution of [Cu((*S*,*S*)-*tert*-Bu-box)](SbF_6)$_2$ (20 x 10^{-3} mmol) in 2.5 mL of DCM was prepared in a glove box, and capped with a rubber septum. Prior to the addition of the 2,3-diketoester **3g** solution, the Vis spectrum of (450 nm – 850 nm) [Cu((*S*,*S*)-*tert*-Bu-box)]$(SbF_6)_2$ was recorded. The Vis spectrum (450 nm – 850nm) was recorded after each addition of diketoester **3g** (40 x 10^{-3} mmol in 80µL of DCM) from 0.1 equivalent to 2.0 equivalent to the [Cu((*S*,*S*)-*tert*-Bu-box)]$(SbF_6)_2$ solution. The cell was shook for 1 minute between each addition of **3g** to ensure thorough mixing before the UV-Vis spectrum was recorded at room temperature.



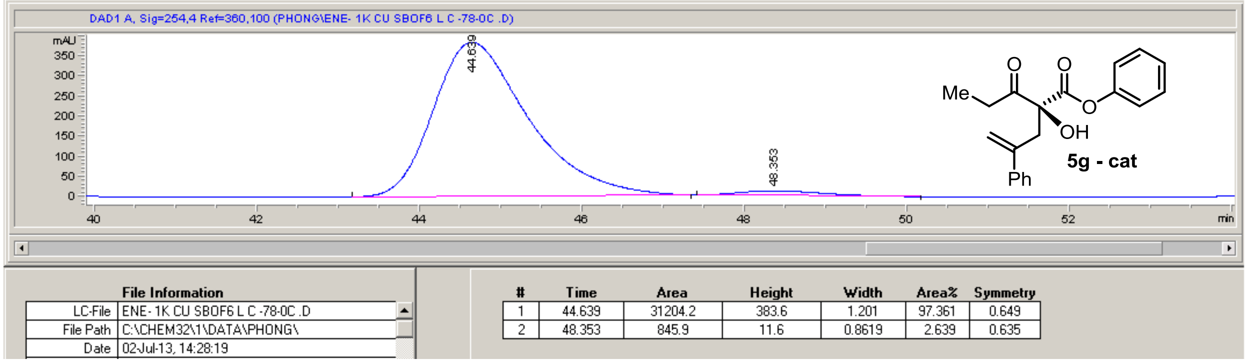
3.5.7 HPLC Spectral Analysis


DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE- 1K RACEMIC 7 .D)
mAU
250
200
150
100
50
44.745
48.392
40
42
44
46
48
50
52
min
Me
O
O
O
OH
Ph
5g - rac

File Information

LC-File	ENE- 1K RACEMIC 7 .D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	25-Jun-13, 15:06:24
Sample	AD-H, 98:2, 0.5

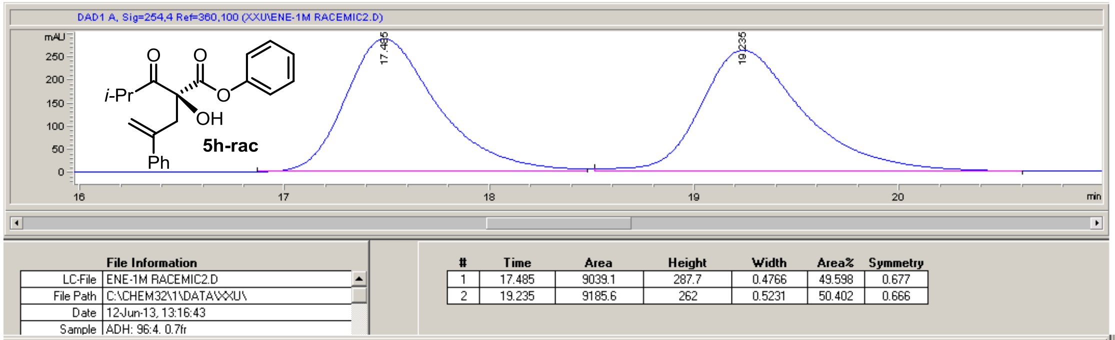
#	Time	Area	Height	Width	Area%	Symmetry
1	44.745	19594.9	251.9	1.1434	50.201	0.645
2	48.392	19437.7	228.3	1.1992	49.799	0.602


DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE- 1K CU SBOF6 L C -78-0C .D)
mAU
350
300
250
200
150
100
50
0
44.639
48.353
40
42
44
46
48
50
52
min
Me
O
O
O
OH
Ph
5g - cat

File Information

LC-File	ENE- 1K CU SBOF6 L C -78-0C .D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	02-Jul-13, 14:28:19

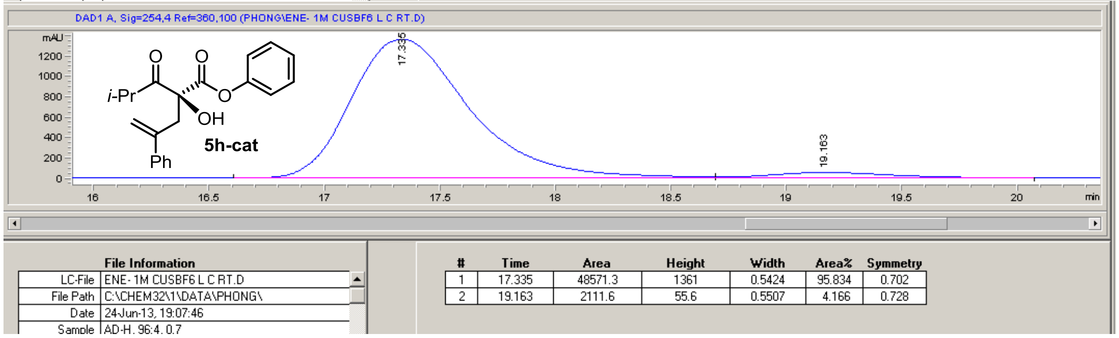
#	Time	Area	Height	Width	Area%	Symmetry
1	44.639	31204.2	383.6	1.201	97.361	0.649
2	48.353	845.9	11.6	0.8619	2.639	0.635


DAD1 A, Sig=254,4 Ref=360,100 (XXU\ENE-1M RACEMIC2.D)
mAU
250
200
150
100
50
0
i-Pr
O
O
O
OH
Ph
5h-rac
17.485
19.235
16
17
18
19
20
min

File Information

LC-File	ENE-1M RACEMIC2.D
File Path	C:\CHEM32\1\DATA\XXU\
Date	12-Jun-13, 13:16:43
Sample	ADH: 96:4. 0.7fr

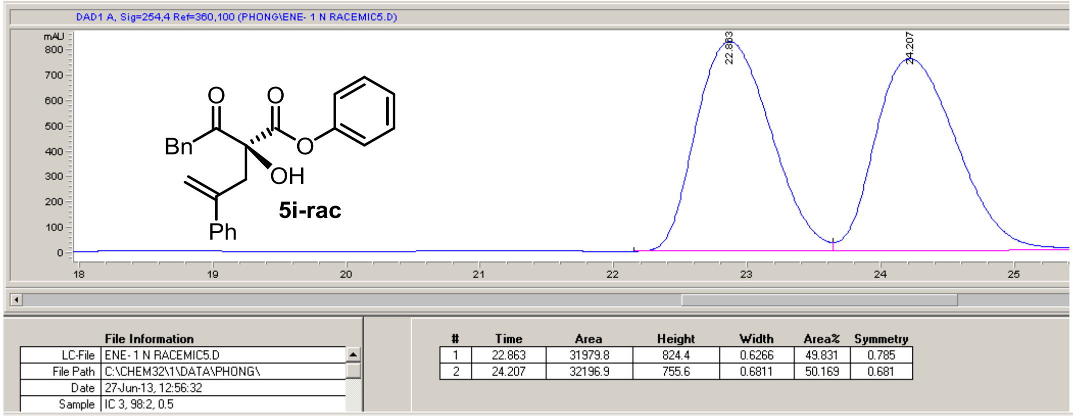
#	Time	Area	Height	Width	Area%	Symmetry
1	17.485	9039.1	287.7	0.4766	49.598	0.677
2	19.235	9185.6	262	0.5231	50.402	0.666


DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE- 1M CUSBF6 L C RT.D)
mAU
1200
1000
800
600
400
200
0
i-Pr
O
O
O
OH
Ph
5h-cat
17.335
19.163
16
16.5
17
17.5
18
18.5
19
19.5
20
min

File Information

LC-File	ENE- 1M CUSBF6 L C RT.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	24-Jun-13, 19:07:46
Sample	AD-H, 96:4, 0.7

#	Time	Area	Height	Width	Area%	Symmetry
1	17.335	48571.3	1361	0.5424	95.834	0.702
2	19.163	2111.6	55.6	0.5507	4.166	0.728



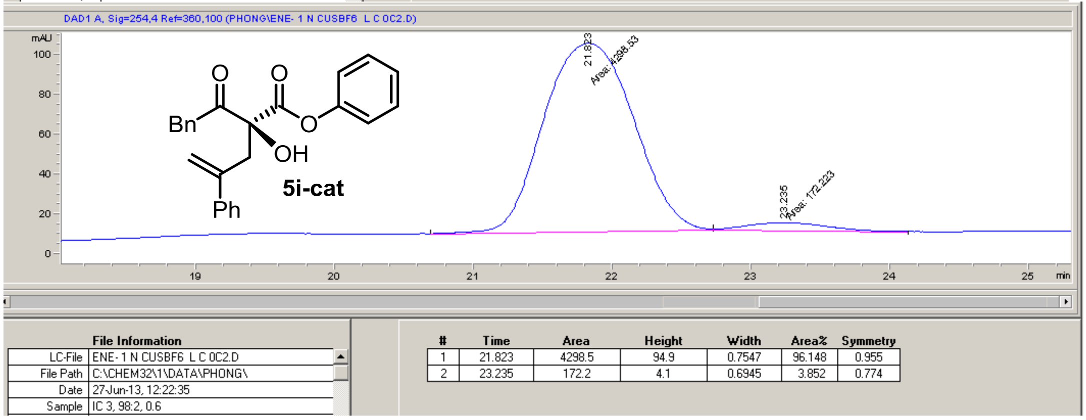
DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE- 1 N RACEMIC5.D)

mAU
800
700
600
500
400
300
200
100
0
18
19
20
21
22
23
24
25
22.863
24.207
O
O
Bn
O
OH
Ph
5i-rac

File Information

LC-File	ENE- 1 N RACEMIC5.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	27-Jun-13, 12:56:32
Sample	IC 3, 98:2, 0.5

#	Time	Area	Height	Width	Area%	Symmetry
1	22.863	31979.8	824.4	0.6266	49.831	0.785
2	24.207	32196.9	755.6	0.6811	50.169	0.681



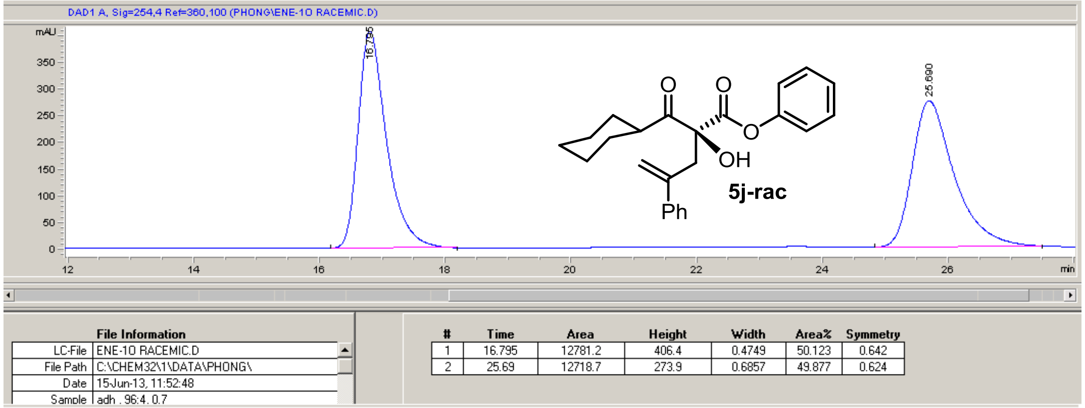
DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE- 1 N CUSBF6 L C 0C2.D)

mAU
100
80
60
40
20
0
19
20
21
22
23
24
25
min
21.823
Area: 4298.53
23.235
Area: 172.223
O
O
Bn
O
OH
Ph
5i-cat

File Information

LC-File	ENE- 1 N CUSBF6 L C 0C2.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	27-Jun-13, 12:22:35
Sample	IC 3, 98:2, 0.6

#	Time	Area	Height	Width	Area%	Symmetry
1	21.823	4298.5	94.9	0.7547	96.148	0.955
2	23.235	172.2	4.1	0.6945	3.852	0.774



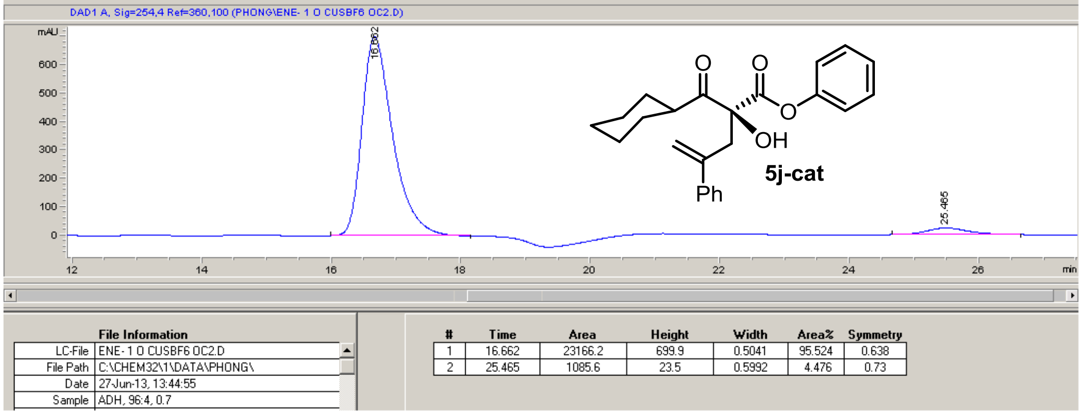
DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE-1O RACEMIC.D)

mAU
350
300
250
200
150
100
50
0
12
14
16
18
20
22
24
26
min
16.795
25.690
O
O
O
OH
Ph
5j-rac

File Information

LC-File	ENE-1O RACEMIC.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	15-Jun-13, 11:52:48
Sample	adh , 96:4, 0.7

#	Time	Area	Height	Width	Area%	Symmetry
1	16.795	12781.2	406.4	0.4749	50.123	0.642
2	25.69	12718.7	273.9	0.6857	49.877	0.624



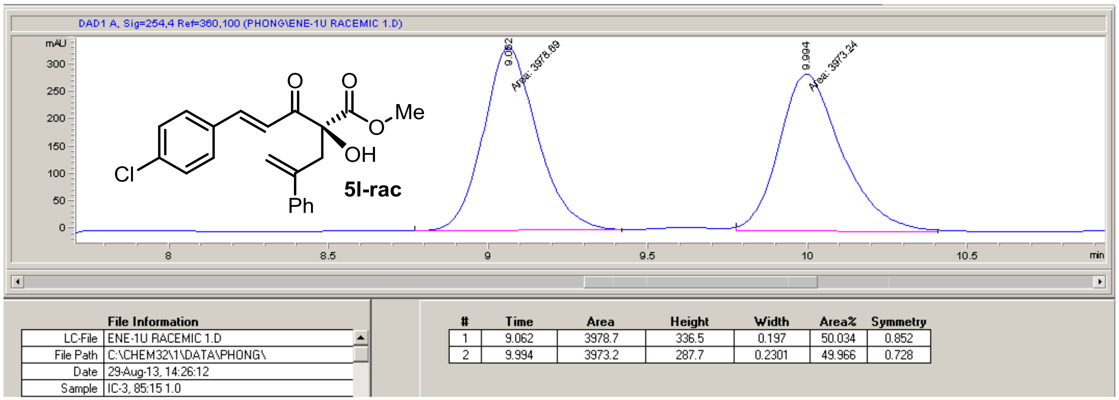
DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE- 1 O CUSBF6 OC2.D)

mAU
600
500
400
300
200
100
0
12
14
16
18
20
22
24
26
min
16.662
25.465
O
O
O
OH
Ph
5j-cat

File Information

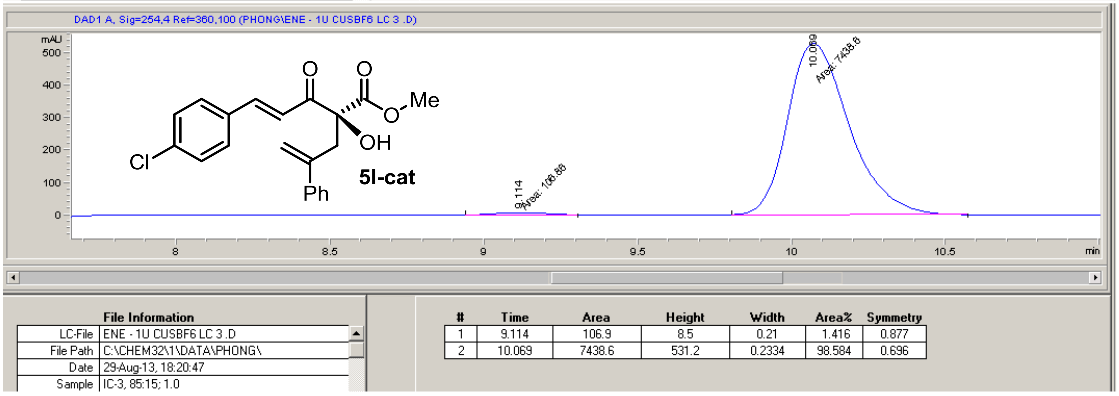
LC-File	ENE- 1 O CUSBF6 OC2.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	27-Jun-13, 13:44:55
Sample	ADH, 96:4, 0.7

#	Time	Area	Height	Width	Area%	Symmetry
1	16.662	23166.2	699.9	0.5041	95.524	0.638
2	25.465	1085.6	23.5	0.5992	4.476	0.73


DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE-1U RACEMIC 1.D)
mAU
300
250
200
150
100
50
0
8
8.5
9
9.5
10
10.5
min
9.062
Area: 3978.69
9.994
Area: 3973.24
O
O
Me
O
OH
Cl
Ph
5l-rac

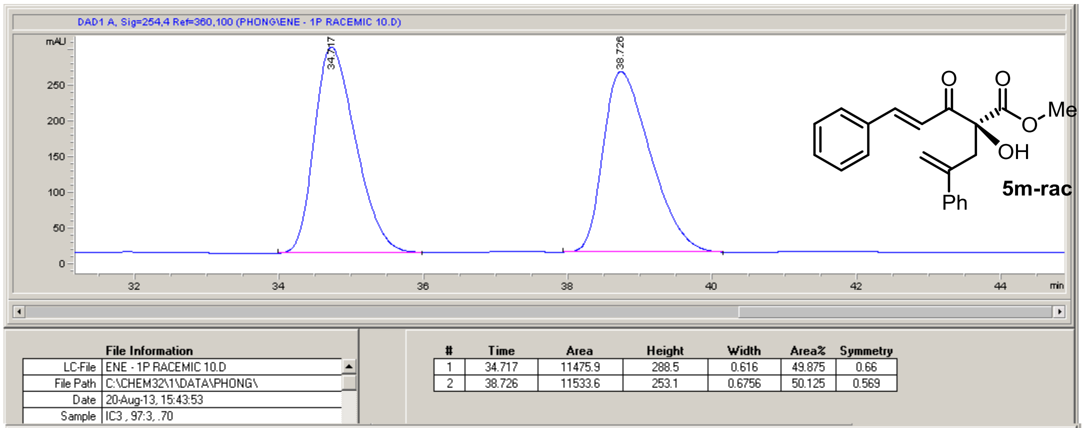
File Information	
LC-File	ENE-1U RACEMIC 1.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	29-Aug-13, 14:26:12
Sample	IC-3, 85:15 1.0

#	Time	Area	Height	Width	Area%	Symmetry
1	9.062	3978.7	336.5	0.197	50.034	0.852
2	9.994	3973.2	287.7	0.2301	49.966	0.728


DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 1U CUSBF6 LC 3 .D)
mAU
500
400
300
200
100
0
8
8.5
9
9.5
10
10.5
min
10.069
Area: 7438.6
9.114
Area: 106.88
O
O
Me
O
OH
Cl
Ph
5l-cat

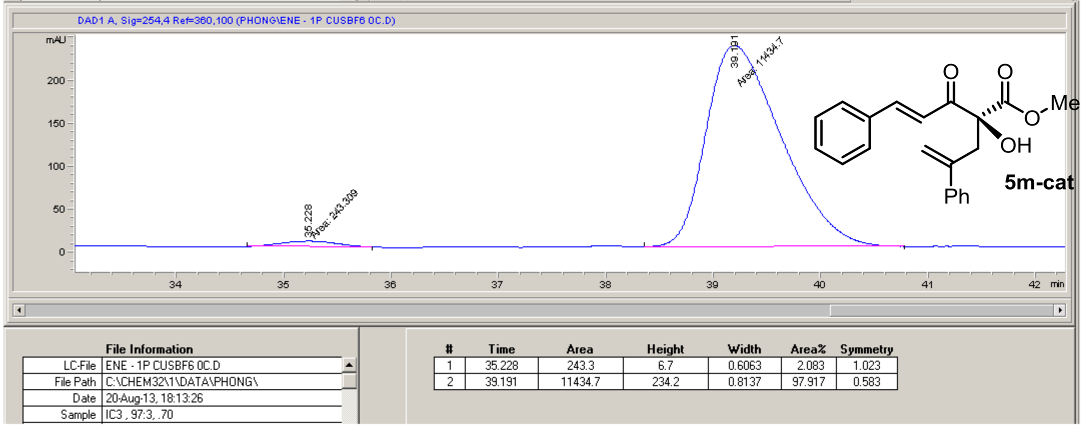
File Information	
LC-File	ENE - 1U CUSBF6 LC 3 .D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	29-Aug-13, 18:20:47
Sample	IC-3, 85:15; 1.0

#	Time	Area	Height	Width	Area%	Symmetry
1	9.114	106.9	8.5	0.21	1.416	0.877
2	10.069	7438.6	531.2	0.2334	98.584	0.696


DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 1P RACEMIC 10.D)
mAU
250
200
150
100
50
0
32
34
36
38
40
42
44
min
34.717
38.726
O
O
Me
O
OH
Ph
5m-rac

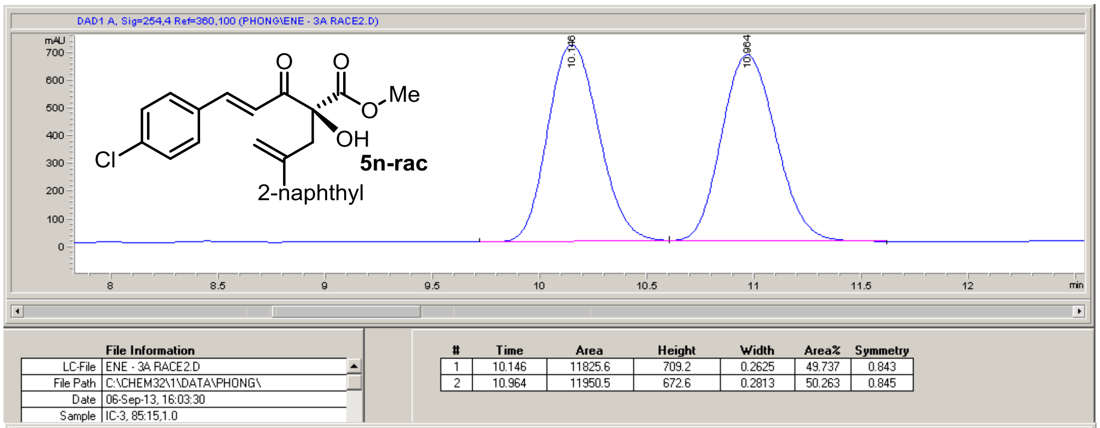
File Information	
LC-File	ENE - 1P RACEMIC 10.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	20-Aug-13, 15:43:53
Sample	IC3 , 97:3, .70

#	Time	Area	Height	Width	Area%	Symmetry
1	34.717	11475.9	288.5	0.616	49.875	0.66
2	38.726	11533.6	253.1	0.6756	50.125	0.569


DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 1P CUSBF6 0C.D)
mAU
200
150
100
50
0
34
35
36
37
38
39
40
41
42
min
39.191
Area: 11434.7
35.228
Area: 243.309
O
O
Me
O
OH
Ph
5m-cat

File Information	
LC-File	ENE - 1P CUSBF6 0C.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	20-Aug-13, 18:13:26
Sample	IC3 , 97:3, .70

#	Time	Area	Height	Width	Area%	Symmetry
1	35.228	243.3	6.7	0.6063	2.083	1.023
2	39.191	11434.7	234.2	0.8137	97.917	0.583



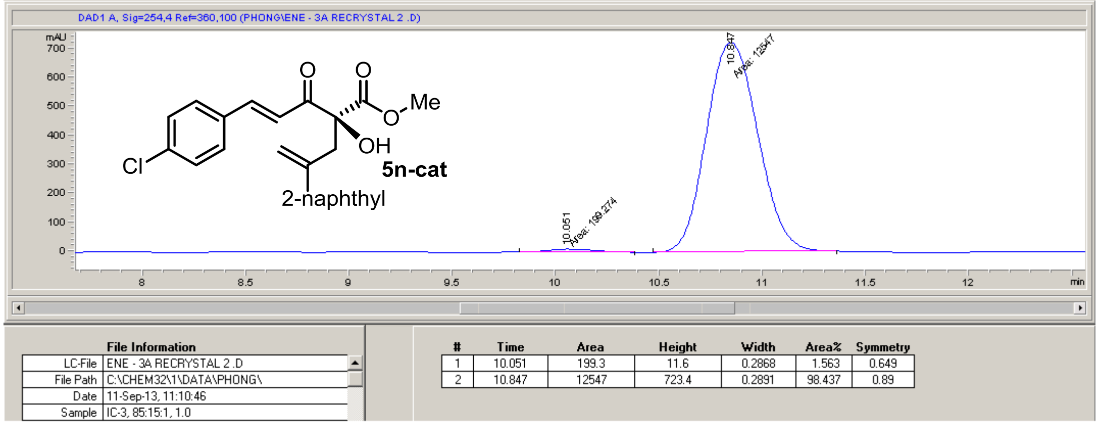
mAU
700
600
500
400
300
200
100
0
8
8.5
9
9.5
10
10.5
11
11.5
12
min
10.146
10.964
O
O
Me
O
OH
Cl
5n-rac
2-naphthyl

DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 3A RACE2.D)

File Information

LC-File	ENE - 3A RACE2.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	06-Sep-13, 16:03:30
Sample	IC-3, 85:15,1.0

#	Time	Area	Height	Width	Area%	Symmetry
1	10.146	11825.6	709.2	0.2625	49.737	0.843
2	10.964	11950.5	672.6	0.2813	50.263	0.845



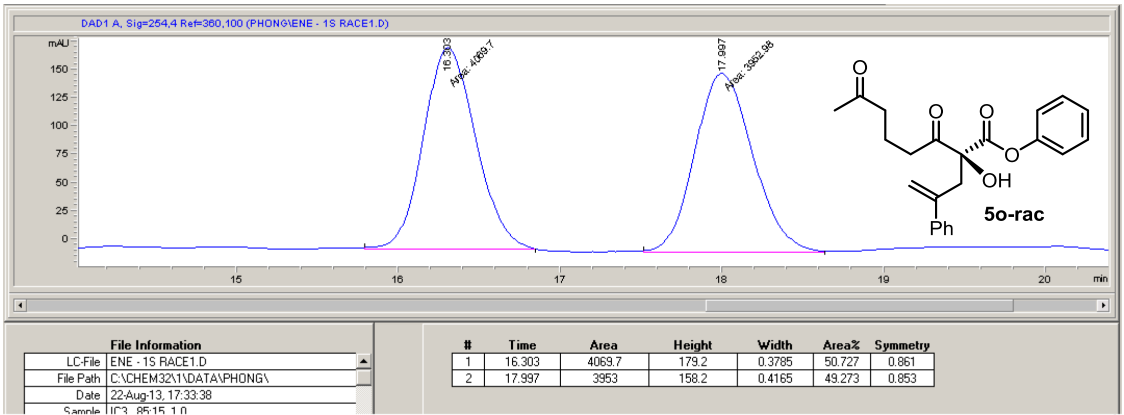
mAU
700
600
500
400
300
200
100
0
8
8.5
9
9.5
10
10.5
11
11.5
12
min
10.051
Area: 199.274
10.847
Area: 12547
O
O
Me
O
OH
Cl
5n-cat
2-naphthyl

DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 3A RECRYSTAL 2 .D)

File Information

LC-File	ENE - 3A RECRYSTAL 2 .D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	11-Sep-13, 11:10:46
Sample	IC-3, 85:15:1, 1.0

#	Time	Area	Height	Width	Area%	Symmetry
1	10.051	199.3	11.6	0.2868	1.563	0.649
2	10.847	12547	723.4	0.2891	98.437	0.89



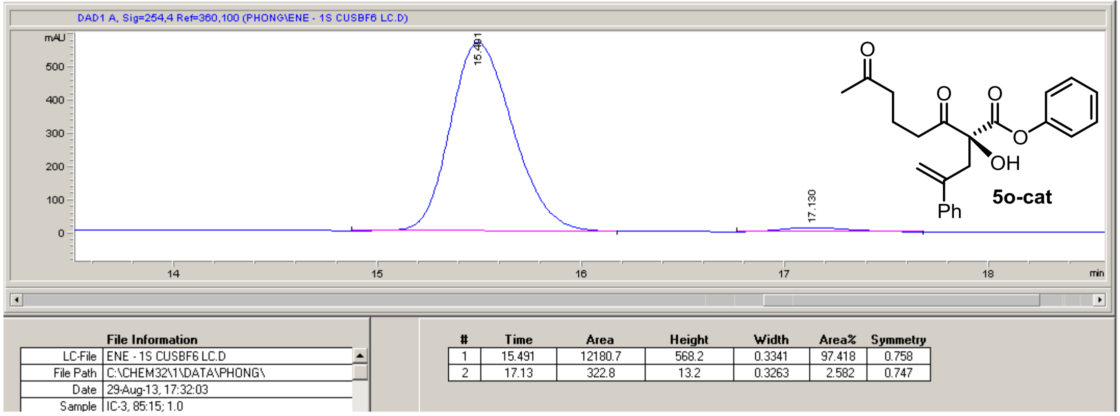
mAU
150
125
100
75
50
25
0
15
16
17
18
19
20
min
16.303
Area: 4069.7
17.997
Area: 3952.98
O
O
O
O
OH
Ph
5o-rac

DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 1S RACE1.D)

File Information

LC-File	ENE - 1S RACE1.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	22-Aug-13, 17:33:38
Sample	IC3, 85:15, 1.0

#	Time	Area	Height	Width	Area%	Symmetry
1	16.303	4069.7	179.2	0.3785	50.727	0.861
2	17.997	3953	158.2	0.4165	49.273	0.853



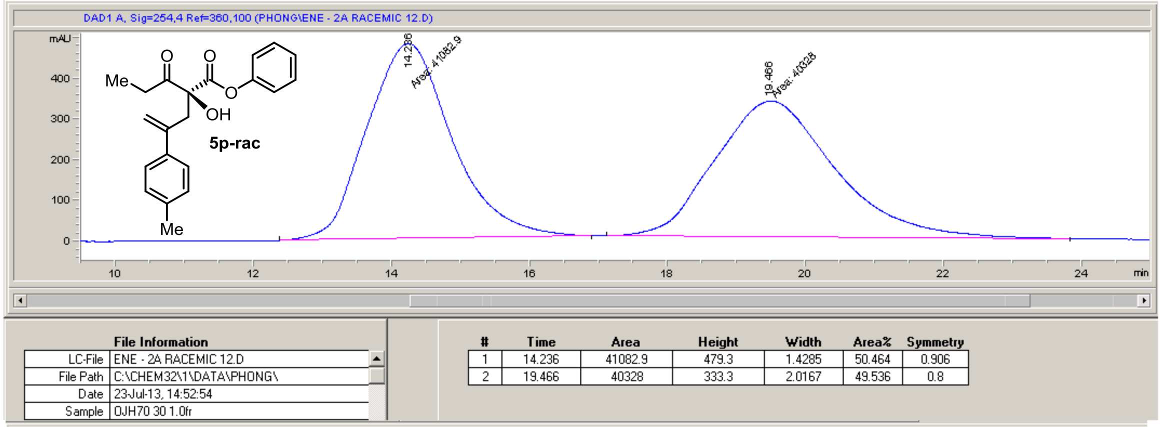
mAU
500
400
300
200
100
0
14
15
16
17
18
min
15.491
17.130
O
O
O
O
OH
Ph
5o-cat

DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 1S CUSBF6 LC.D)

File Information

LC-File	ENE - 1S CUSBF6 LC.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	29-Aug-13, 17:32:03
Sample	IC-3, 85:15; 1.0

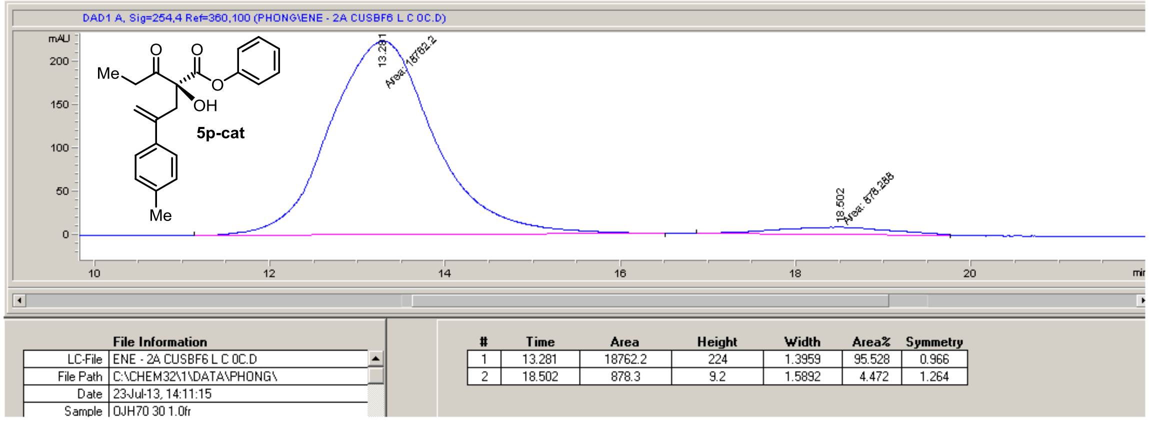
#	Time	Area	Height	Width	Area%	Symmetry
1	15.491	12180.7	568.2	0.3341	97.418	0.758
2	17.13	322.8	13.2	0.3263	2.582	0.747


DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 2A RACEMIC 12.D)
mAU
400
300
200
100
0
10
12
14
16
18
20
22
24
min
14.236
Area: 41082.9
19.466
Area: 40328
Me
O
O
O
OH
Me
5p-rac

File Information

LC-File	ENE - 2A RACEMIC 12.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	23-Jul-13, 14:52:54
Sample	OJH70 30 1.0fr

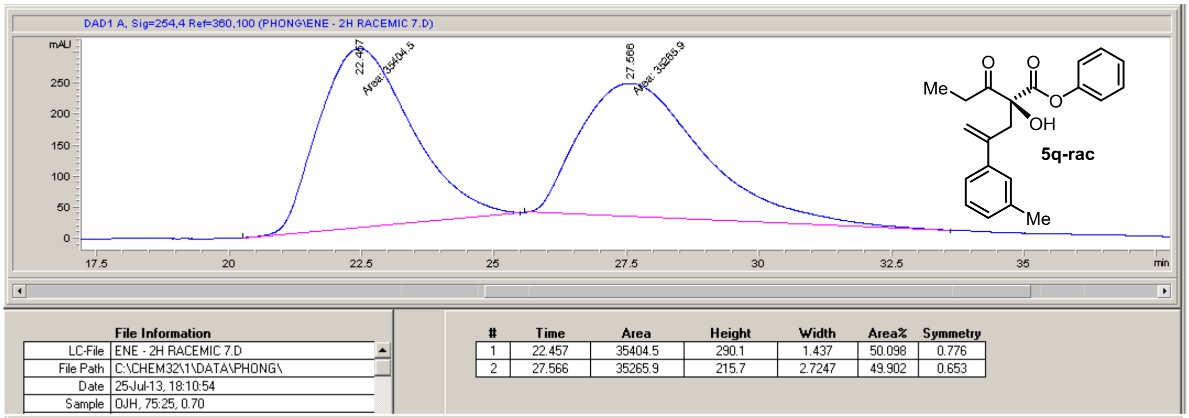
#	Time	Area	Height	Width	Area%	Symmetry
1	14.236	41082.9	479.3	1.4285	50.464	0.906
2	19.466	40328	333.3	2.0167	49.536	0.8


DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 2A CUSBF6 L C 0C.D)
mAU
200
150
100
50
0
10
12
14
16
18
20
min
13.281
Area: 18762.2
18.502
Area: 878.288
Me
O
O
O
OH
Me
5p-cat

File Information

LC-File	ENE - 2A CUSBF6 L C 0C.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	23-Jul-13, 14:11:15
Sample	OJH70 30 1.0fr

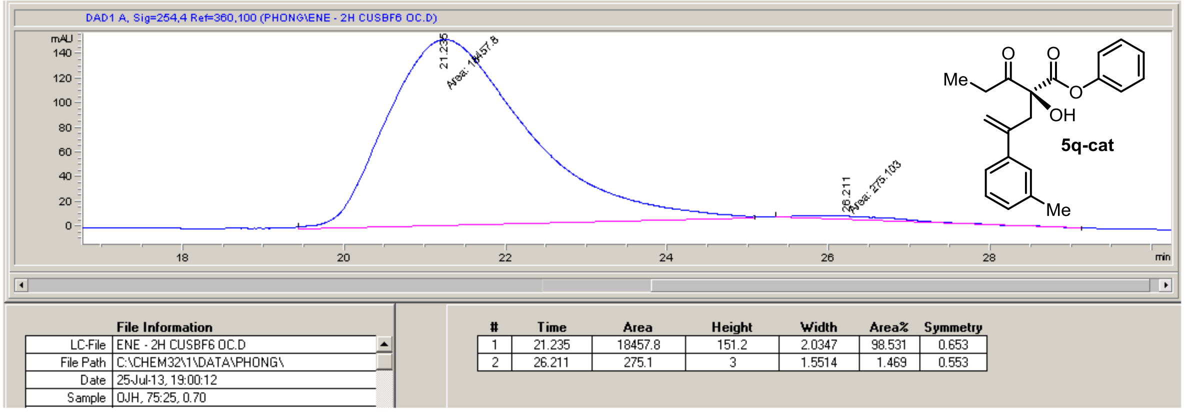
#	Time	Area	Height	Width	Area%	Symmetry
1	13.281	18762.2	224	1.3959	95.528	0.966
2	18.502	878.3	9.2	1.5892	4.472	1.264


DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 2H RACEMIC 7.D)
mAU
250
200
150
100
50
0
17.5
20
22.5
25
27.5
30
32.5
35
min
22.457
Area: 35404.5
27.566
Area: 35265.9
Me
O
O
O
OH
Me
5q-rac

File Information

LC-File	ENE - 2H RACEMIC 7.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	25-Jul-13, 18:10:54
Sample	OJH, 75:25, 0.70

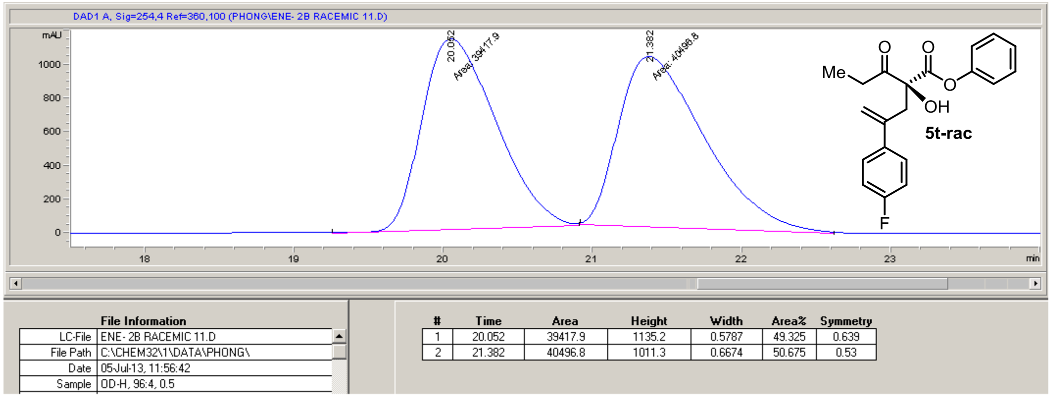
#	Time	Area	Height	Width	Area%	Symmetry
1	22.457	35404.5	290.1	1.437	50.098	0.776
2	27.566	35265.9	215.7	2.7247	49.902	0.653


DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 2H CUSBF6 0C.D)
mAU
140
120
100
80
60
40
20
0
18
20
22
24
26
28
min
21.235
Area: 18457.8
26.211
Area: 275.103
Me
O
O
O
OH
Me
5q-cat

File Information

LC-File	ENE - 2H CUSBF6 0C.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	25-Jul-13, 19:00:12
Sample	OJH, 75:25, 0.70

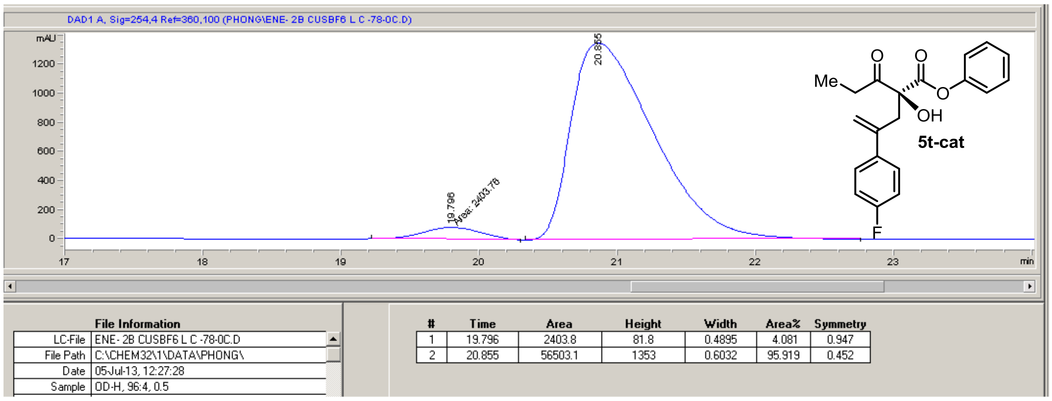
#	Time	Area	Height	Width	Area%	Symmetry
1	21.235	18457.8	151.2	2.0347	98.531	0.653
2	26.211	275.1	3	1.5514	1.469	0.553



File Information

LC-File	ENE- 2B RACEMIC 11.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	05-Jul-13, 11:56:42
Sample	OD-H, 96:4, 0.5

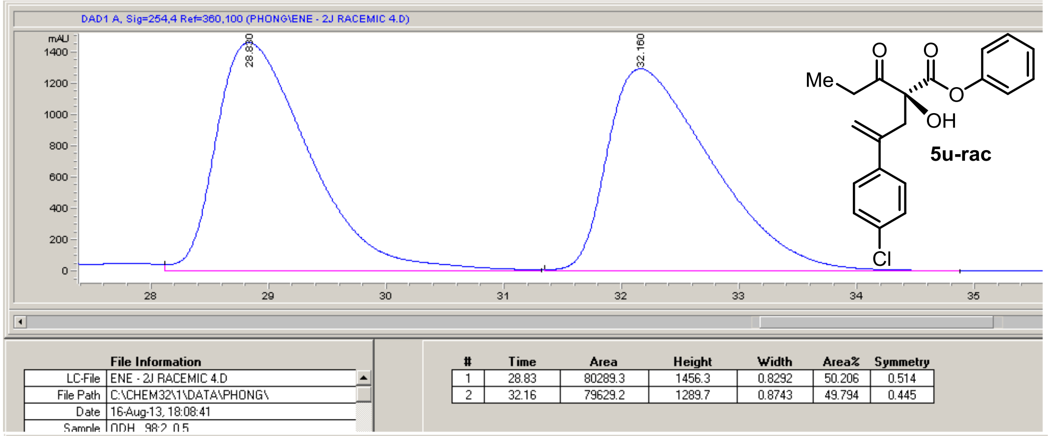
#	Time	Area	Height	Width	Area%	Symmetry
1	20.052	39417.9	1135.2	0.5787	49.325	0.639
2	21.382	40496.8	1011.3	0.6674	50.675	0.53



File Information

LC-File	ENE- 2B CUSBF6 L C -78-0C.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	05-Jul-13, 12:27:28
Sample	OD-H, 96:4, 0.5

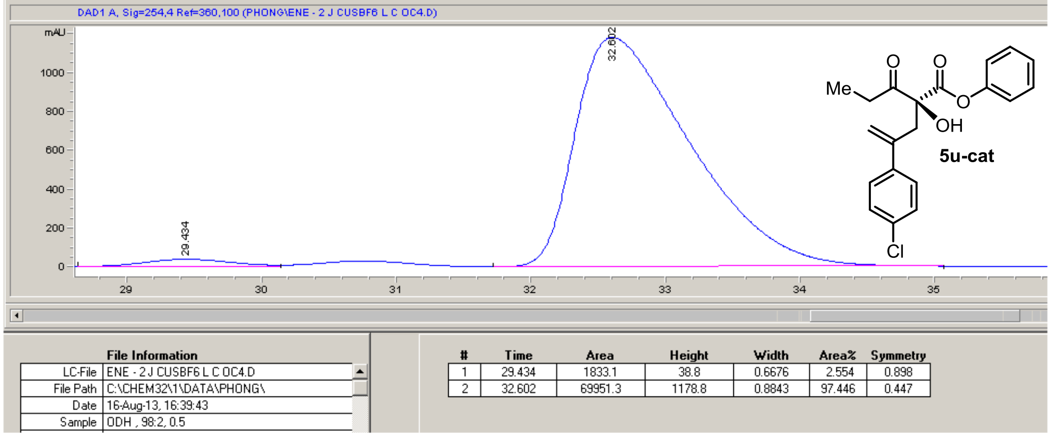
#	Time	Area	Height	Width	Area%	Symmetry
1	19.796	2403.8	81.8	0.4895	4.081	0.947
2	20.855	56503.1	1353	0.6032	95.919	0.452



File Information

LC-File	ENE - 2J RACEMIC 4.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	16-Aug-13, 18:08:41
Sample	ODH , 98:2, 0.5

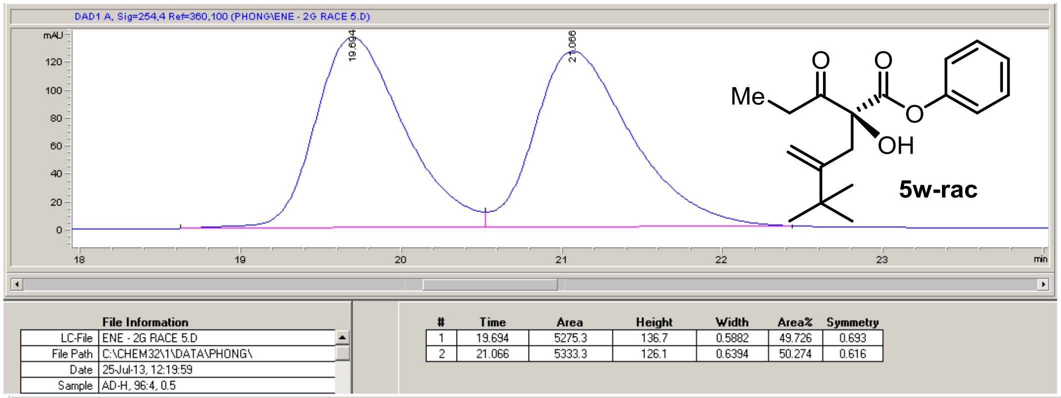
#	Time	Area	Height	Width	Area%	Symmetry
1	28.83	80289.3	1456.3	0.8292	50.206	0.514
2	32.16	79629.2	1289.7	0.8743	49.794	0.445



File Information

LC-File	ENE - 2J CUSBF6 L C OC4.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	16-Aug-13, 16:39:43
Sample	ODH , 98:2, 0.5

#	Time	Area	Height	Width	Area%	Symmetry
1	29.434	1833.1	38.8	0.6676	2.554	0.898
2	32.602	69951.3	1178.8	0.8843	97.446	0.447

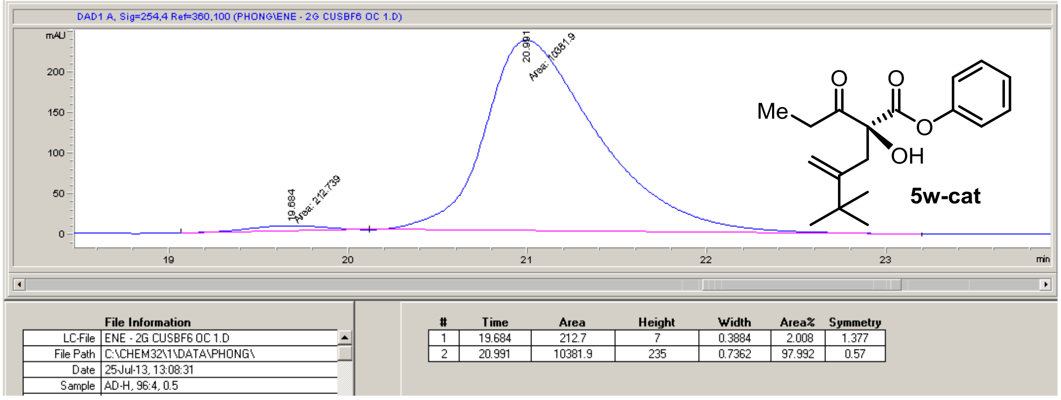

mAU
120
100
80
60
40
20
0
19.694
21.066
18
19
20
21
22
23
min
Me
O
O
O
OH
5w-rac

DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 2G RACE 5.D)

File Information

LC-File	ENE - 2G RACE 5.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	25-Jul-13, 12:19:59
Sample	AD-H, 96:4, 0.5

#	Time	Area	Height	Width	Area%	Symmetry
1	19.694	5275.3	136.7	0.5882	49.726	0.693
2	21.066	5333.3	126.1	0.6394	50.274	0.616

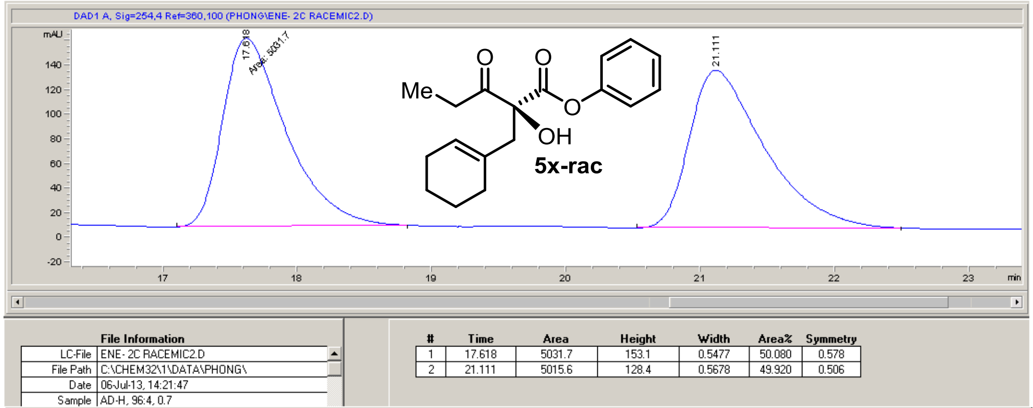

mAU
200
150
100
50
0
20.991
Area: 10381.9
19.684
Area: 212.739
19
20
21
22
23
min
Me
O
O
O
OH
5w-cat

DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE - 2G CUSBF6 0C 1.D)

File Information

LC-File	ENE - 2G CUSBF6 0C 1.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	25-Jul-13, 13:08:31
Sample	AD-H, 96:4, 0.5

#	Time	Area	Height	Width	Area%	Symmetry
1	19.684	212.7	7	0.3884	2.008	1.377
2	20.991	10381.9	235	0.7362	97.992	0.57

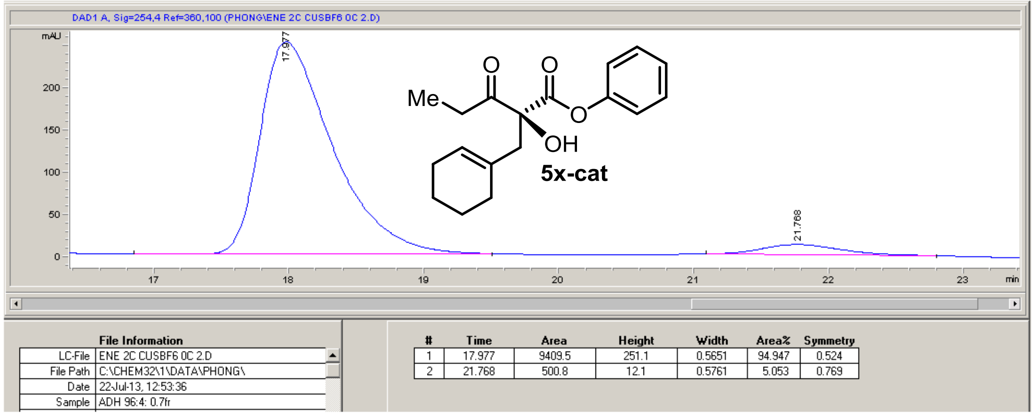

mAU
140
120
100
80
60
40
20
0
-20
17.618
Area: 5031.7
21.111
17
18
19
20
21
22
23
min
Me
O
O
O
OH
5x-rac

DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE- 2C RACEMIC2.D)

File Information

LC-File	ENE- 2C RACEMIC2.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	06-Jul-13, 14:21:47
Sample	AD-H, 96:4, 0.7

#	Time	Area	Height	Width	Area%	Symmetry
1	17.618	5031.7	153.1	0.5477	50.080	0.578
2	21.111	5015.6	128.4	0.5678	49.920	0.506


mAU
200
150
100
50
0
17.977
21.768
17
18
19
20
21
22
23
min
Me
O
O
O
OH
5x-cat

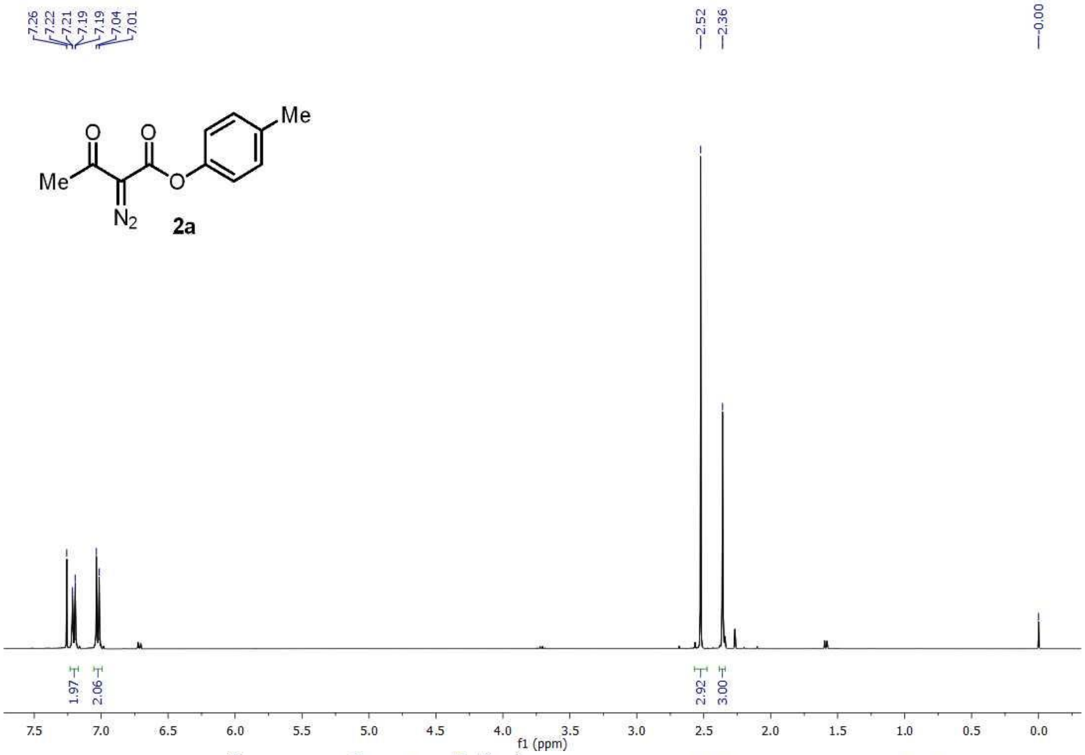
DAD1 A, Sig=254,4 Ref=360,100 (PHONG\ENE 2C CUSBF6 0C 2.D)

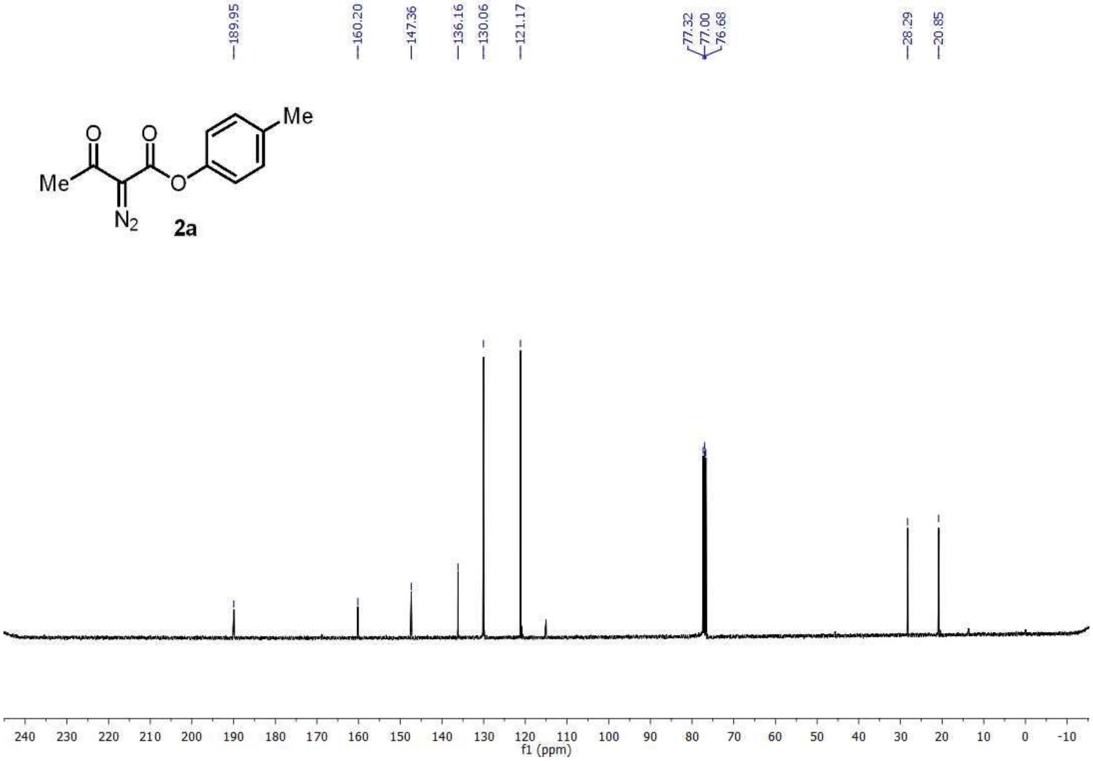
File Information

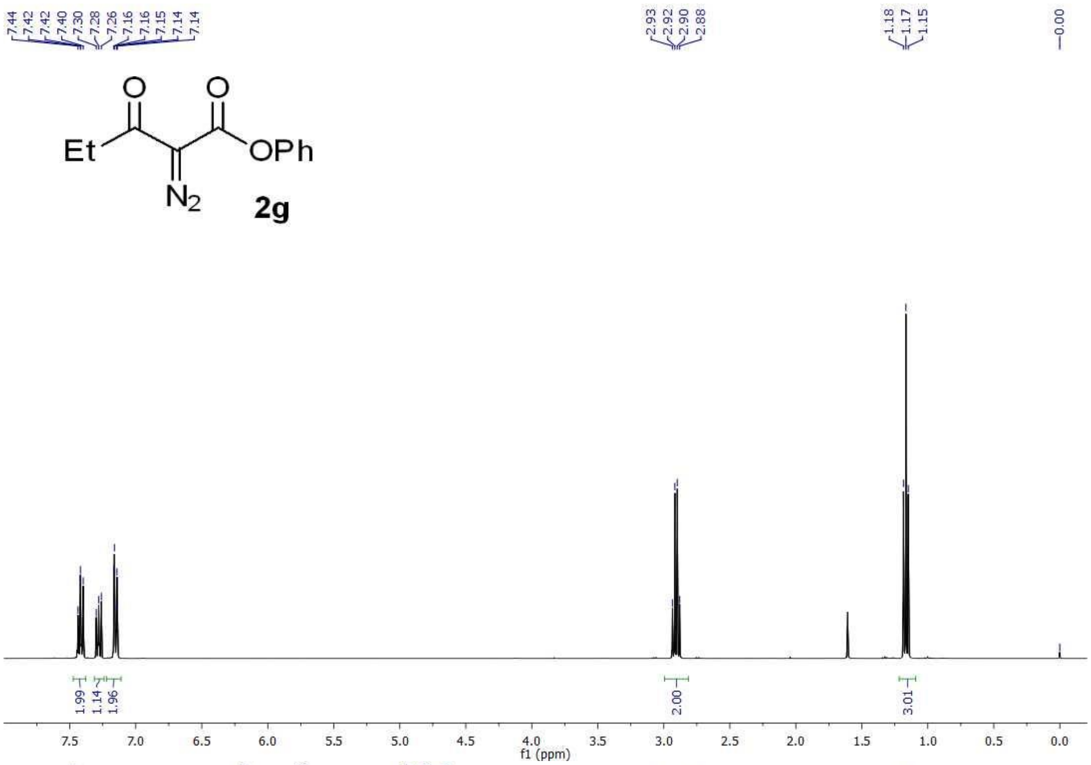
LC-File	ENE 2C CUSBF6 0C 2.D
File Path	C:\CHEM32\1\DATA\PHONG\
Date	22-Jul-13, 12:53:36
Sample	ADH 96:4: 0.7fr

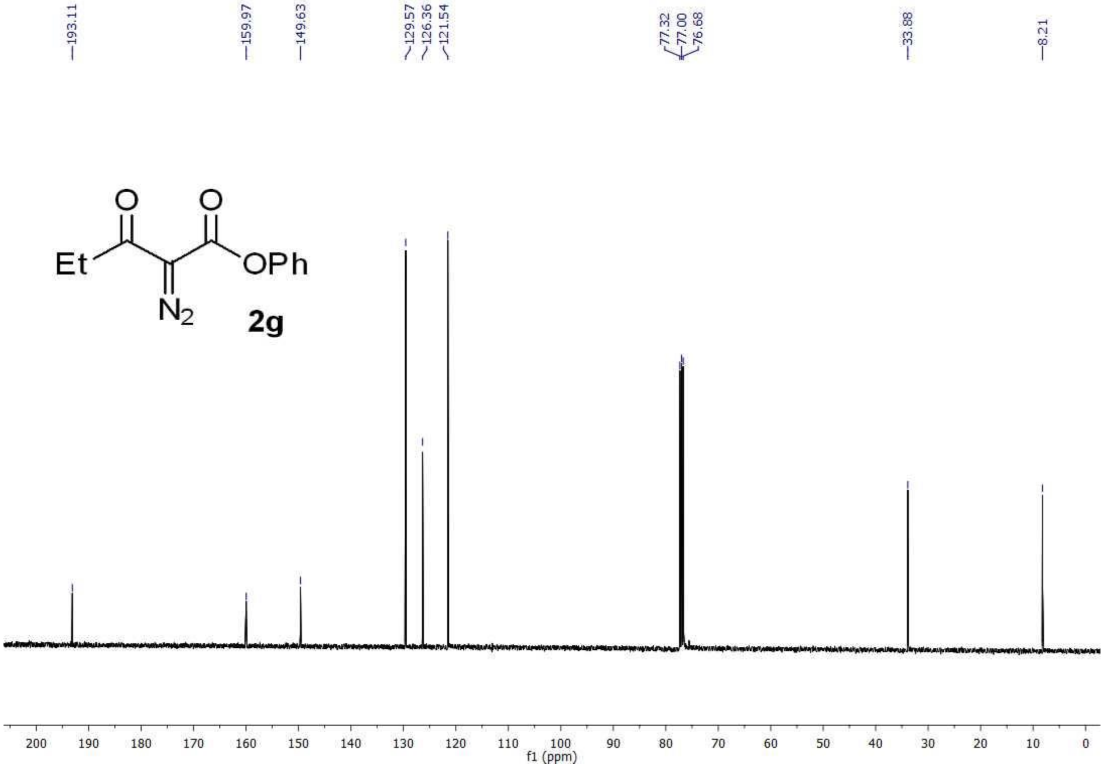
#	Time	Area	Height	Width	Area%	Symmetry
1	17.977	9409.5	251.1	0.5651	94.947	0.524
2	21.768	500.8	12.1	0.5761	5.053	0.769

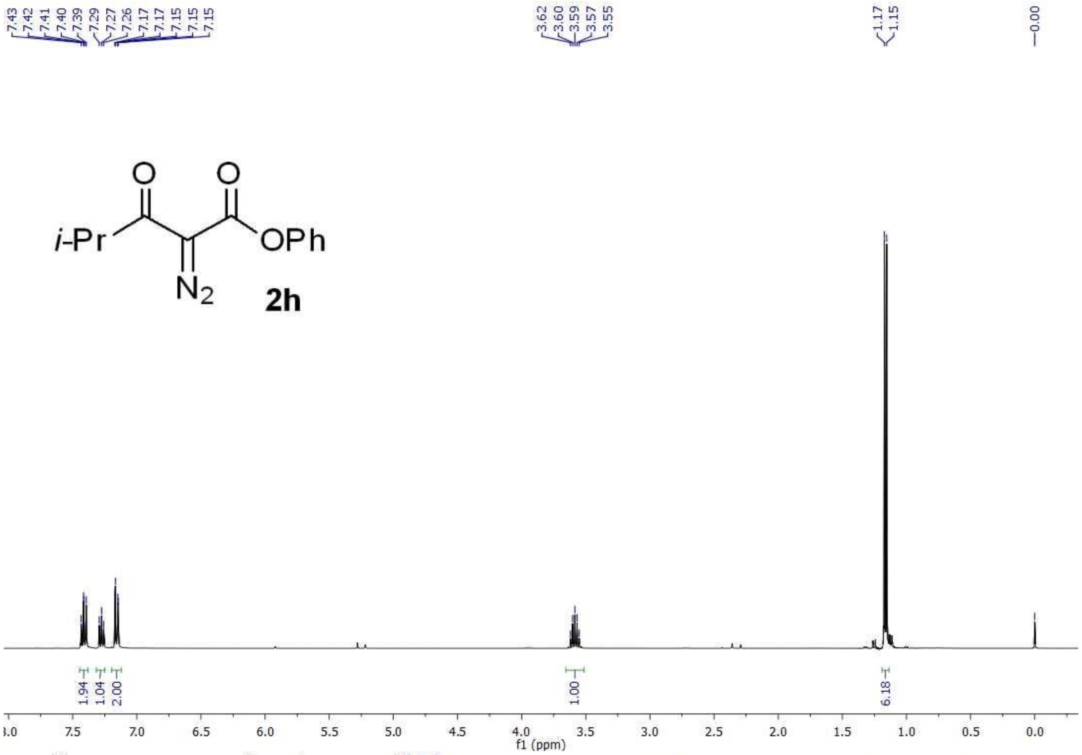
3.5.8 ^{1}H NMR and ^{13}C NMR Spectra

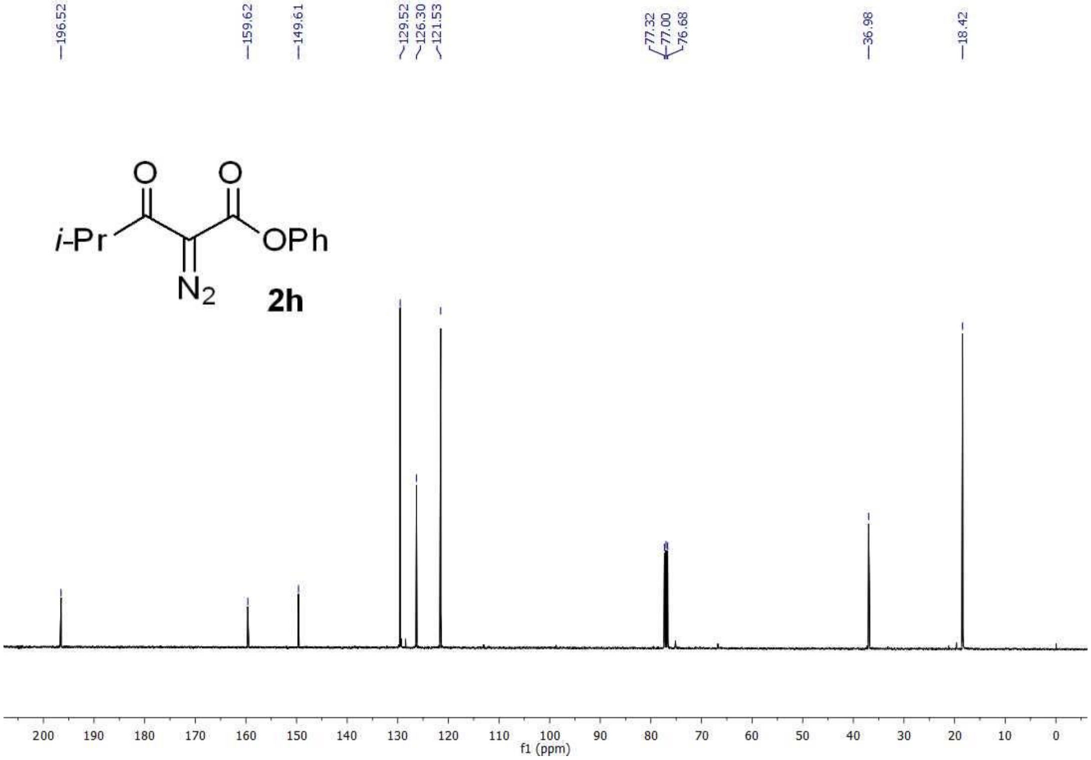


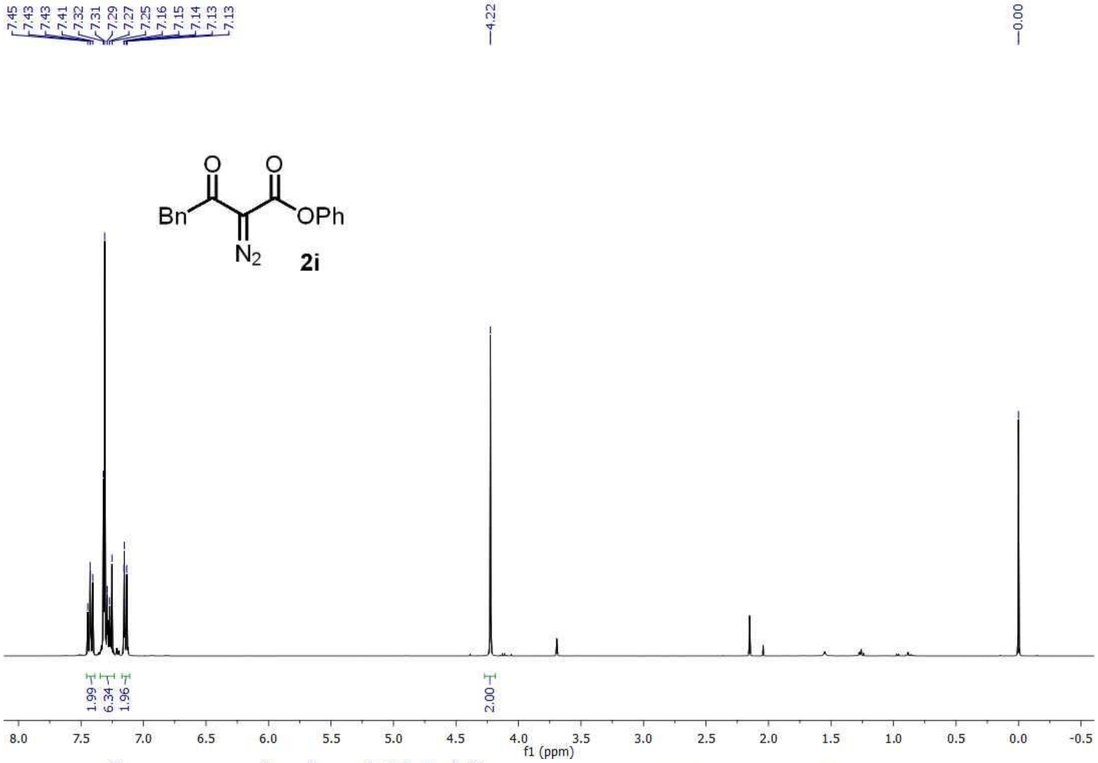


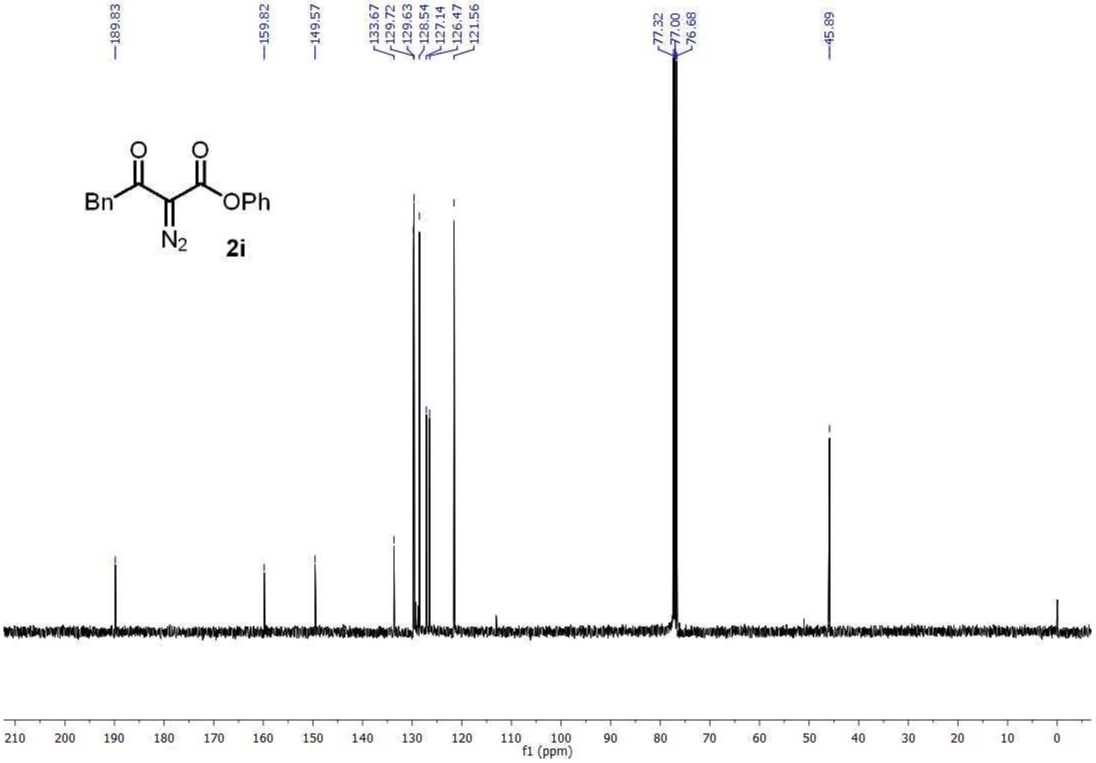

7.44
7.42
7.42
7.40
7.30
7.28
7.26
7.16
7.16
7.15
7.14
7.14
2.93
2.92
2.90
2.88
1.18
1.17
1.15
0.00
Et
O
O
OPh
N2
2g
1.99
1.14
1.96
2.00
3.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

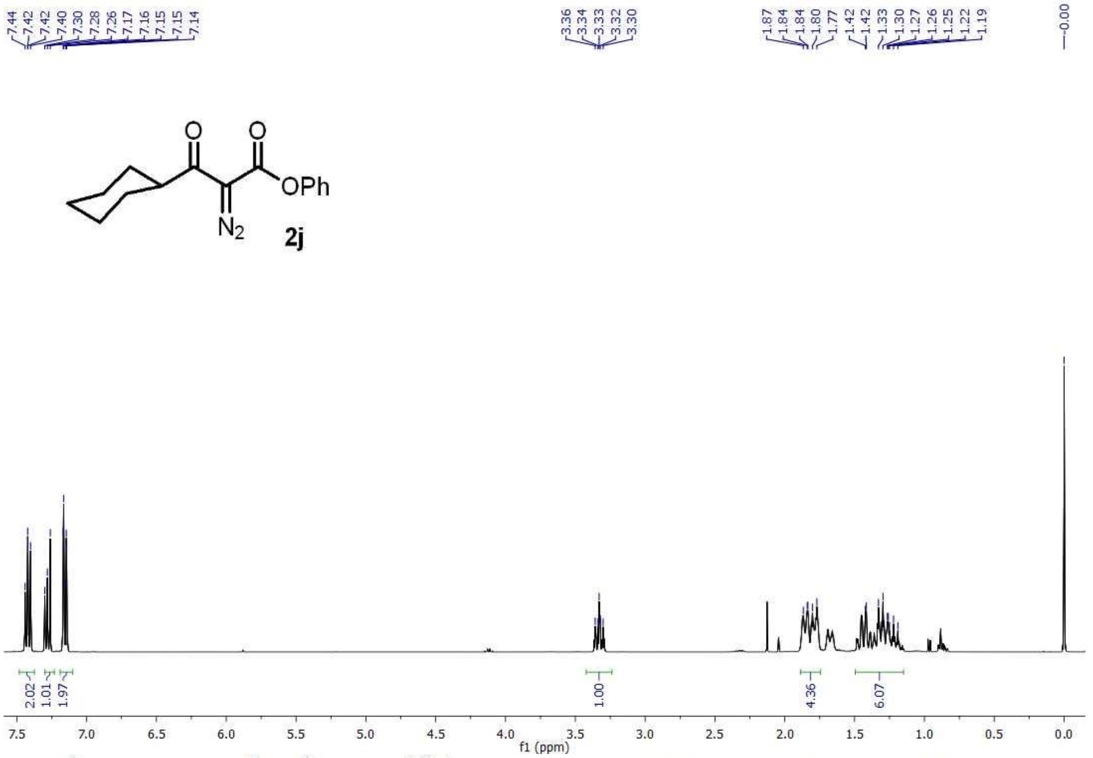

193.11
159.97
149.63
129.57
126.36
121.54
77.32
77.00
76.68
33.88
8.21
Et
O
O
OPh
N2
2g
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

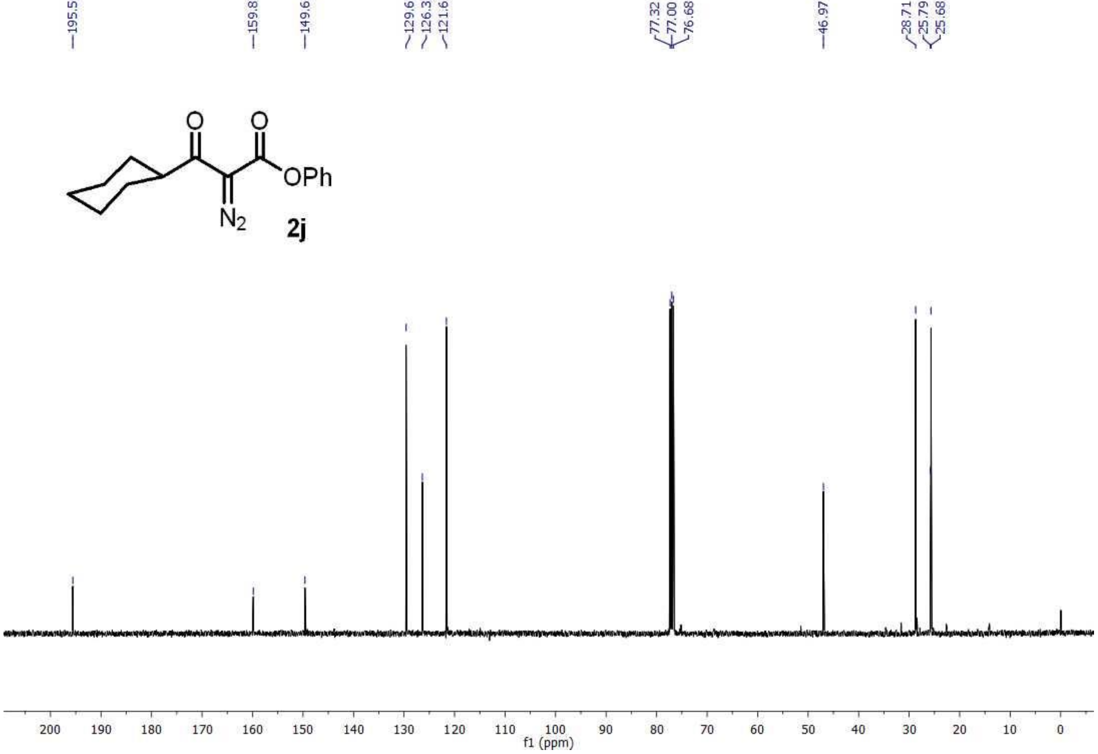

7.43
7.42
7.41
7.40
7.39
7.29
7.27
7.26
7.17
7.17
7.15
7.15
7.15
3.62
3.60
3.59
3.57
3.55
1.17
1.15
0.00
i-Pr
O
O
OPh
N2
2h
1.94
1.04
2.00
1.00
6.18
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

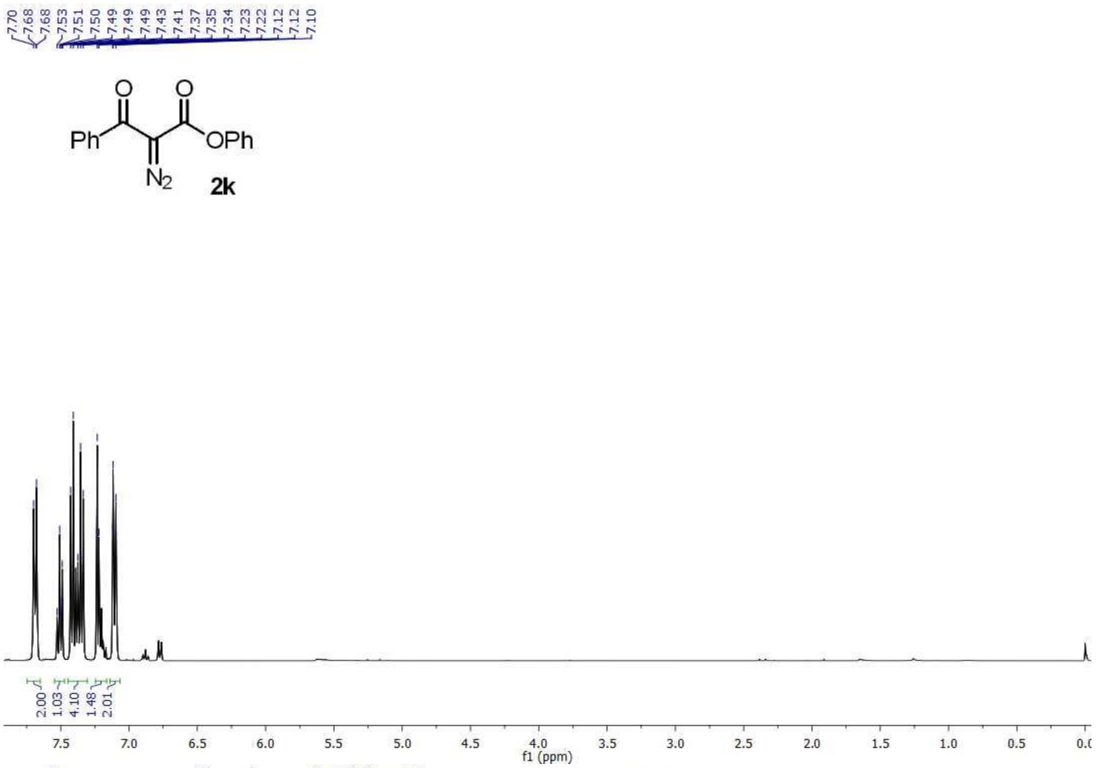

196.52
159.62
149.61
129.52
126.30
121.53
77.32
77.00
76.68
36.98
18.42
i-Pr
O
O
OPh
N2
2h
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.45
7.43
7.43
7.41
7.32
7.31
7.29
7.27
7.25
7.16
7.15
7.14
7.13
7.13
4.22
0.00
Bn
O
O
OPh
N2
2i
1.99
6.34
1.96
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

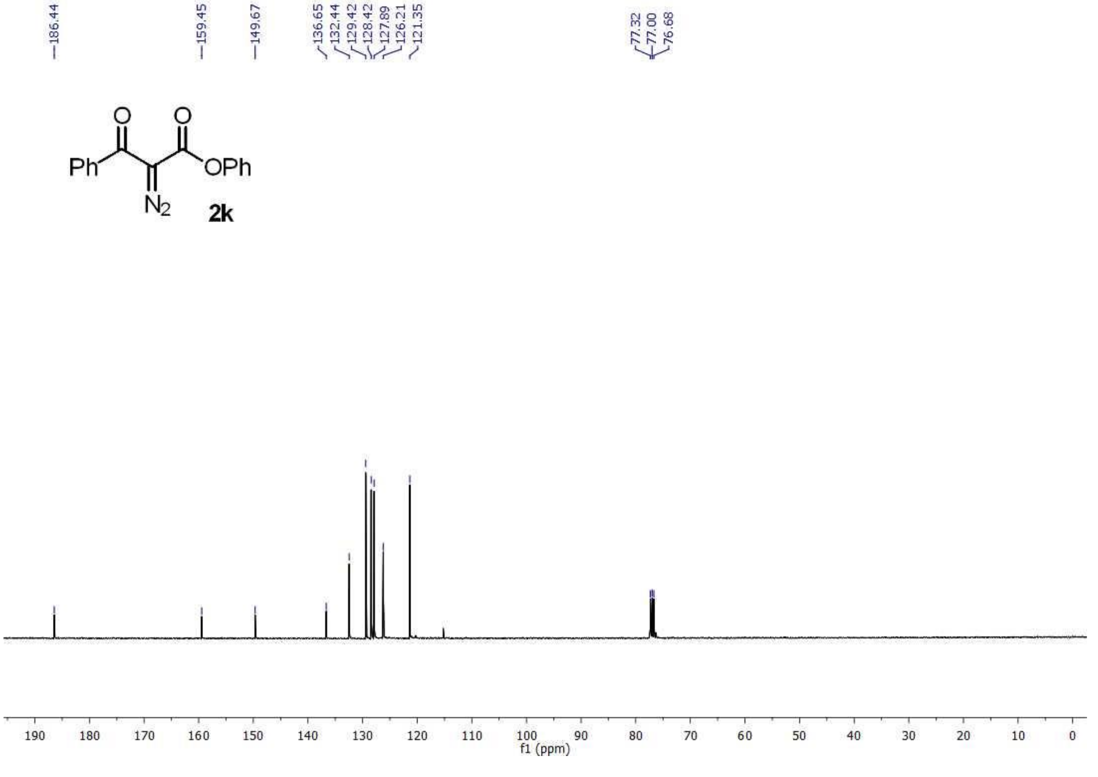

189.83
159.82
149.57
133.67
129.72
129.63
128.54
127.14
126.47
121.56
77.32
77.00
76.68
45.89
Bn
O
O
OPh
N2
2i
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


2j
7.44
7.42
7.42
7.40
7.30
7.28
7.26
7.17
7.16
7.15
7.15
7.14
3.36
3.34
3.33
3.32
3.30
1.87
1.84
1.84
1.80
1.77
1.42
1.42
1.33
1.30
1.27
1.26
1.25
1.22
1.19
0.00
O
O
OPh
N2
2.02
1.01
1.97
1.00
4.36
6.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

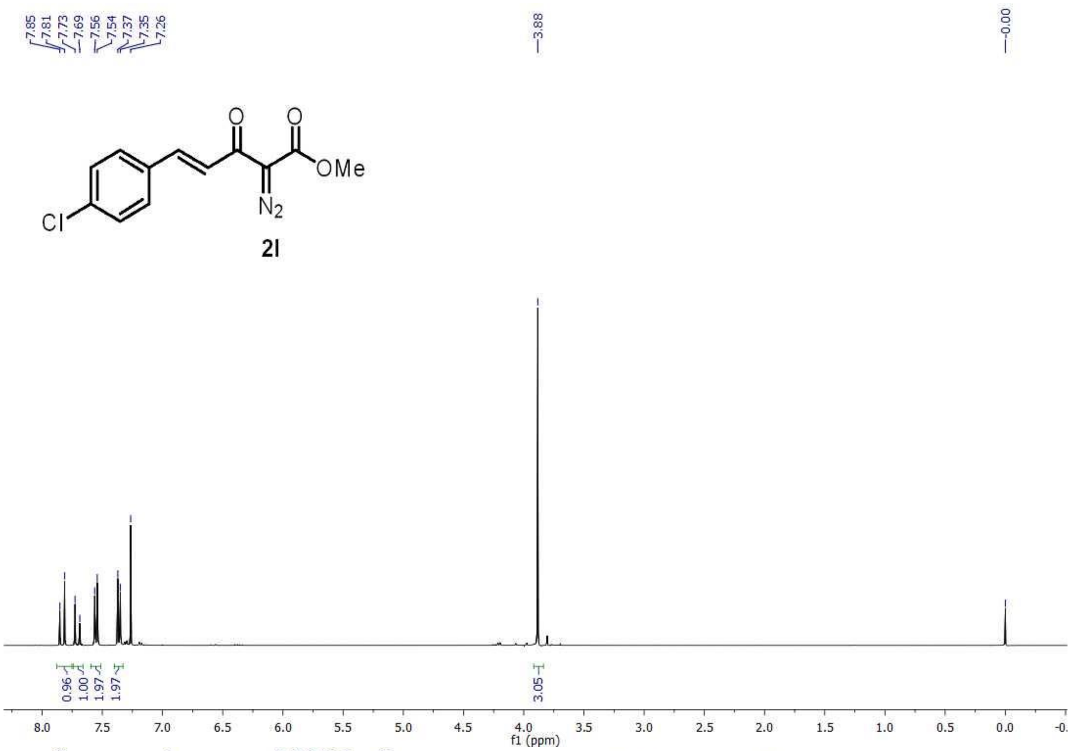

2j
195.58
159.84
149.63
129.60
126.38
121.61
77.32
77.00
76.68
46.97
28.71
25.79
25.68
O
O
OPh
N2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

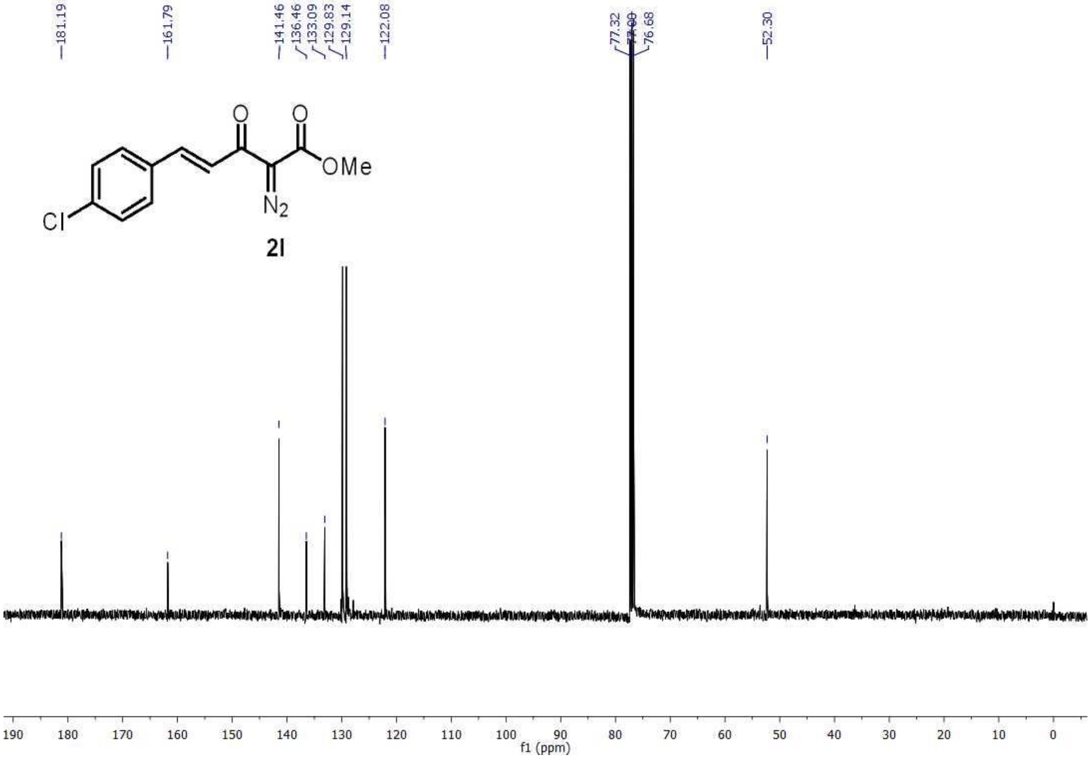

2k

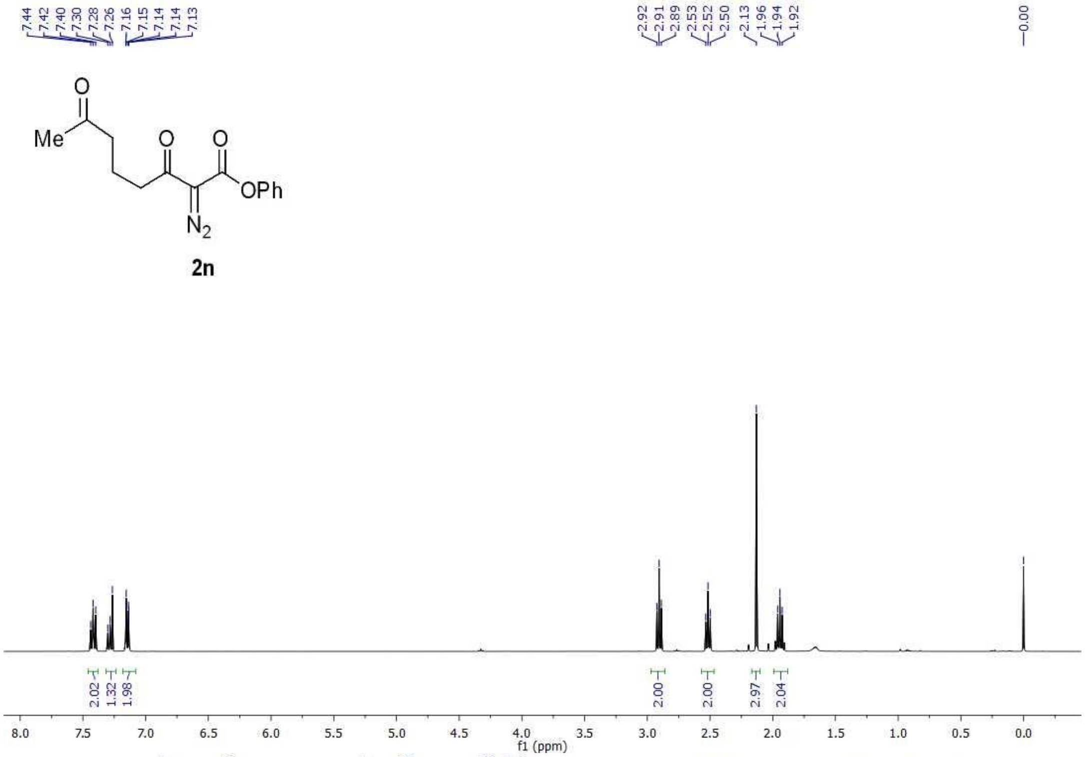
7.70
7.68
7.68
7.53
7.51
7.50
7.49
7.49
7.49
7.43
7.41
7.37
7.35
7.34
7.23
7.22
7.22
7.12
7.12
7.10
Ph
OPh
O
O
N2
2.00
1.03
4.10
1.48
2.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


2k

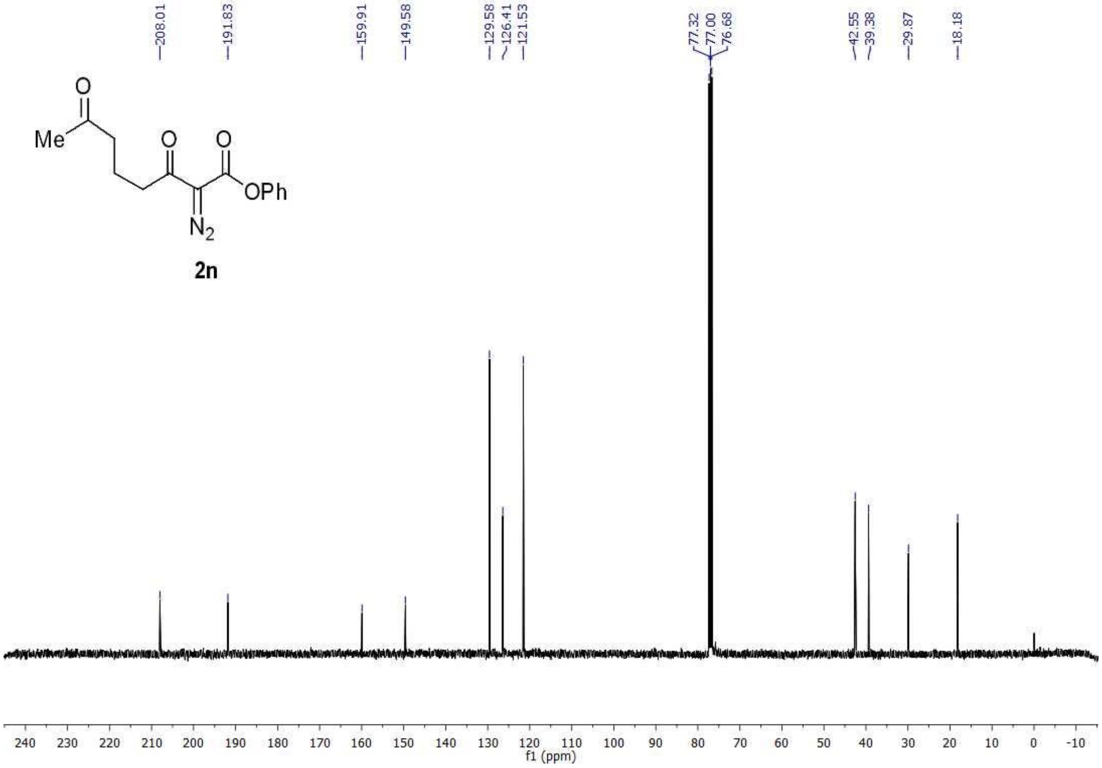
186.44
159.45
149.67
136.65
132.44
129.42
128.42
127.89
126.21
121.35
77.32
77.00
76.68
Ph
OPh
O
O
N2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.85
7.81
7.73
7.69
7.56
7.54
7.37
7.35
7.26
3.88
0.00
O
O
OMe
N2
Cl
2l
0.96
1.00
1.97
1.97
3.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
f1 (ppm)

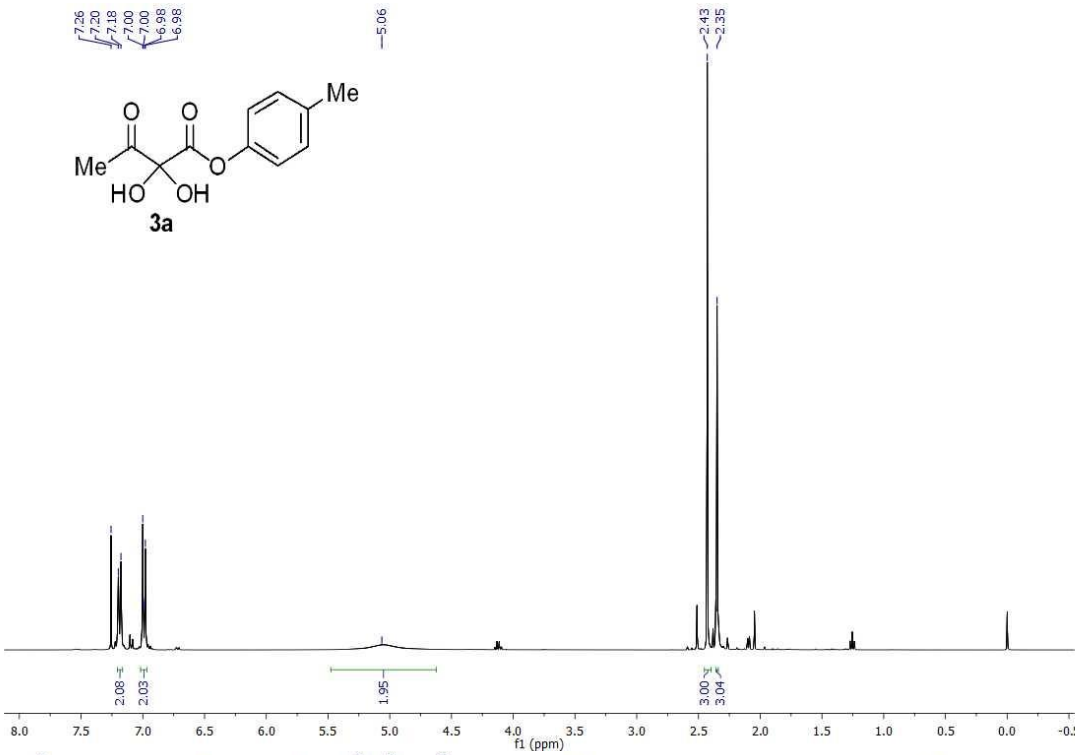

181.19
161.79
141.46
136.46
133.09
129.83
129.14
122.08
77.32
77.00
76.68
52.30
O
O
OMe
N2
Cl
2l
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

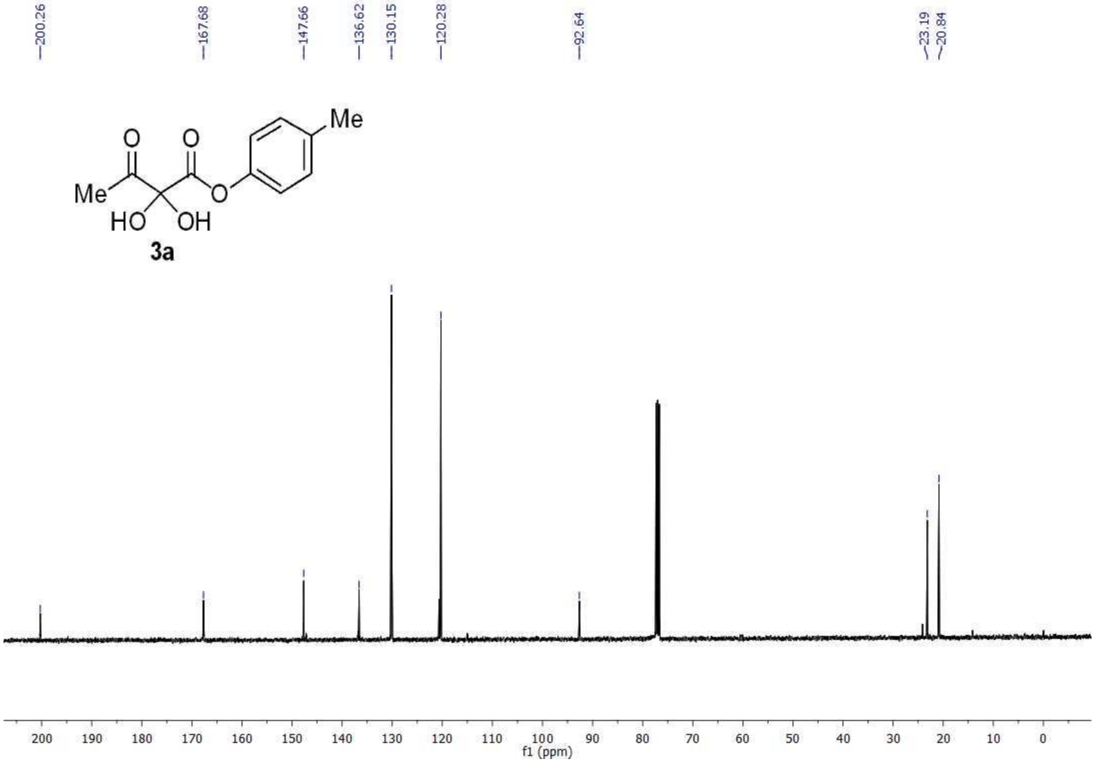

7.44
7.42
7.40
7.30
7.28
7.26
7.16
7.15
7.14
7.14
7.13
2.92
2.91
2.89
2.53
2.52
2.50
2.13
1.96
1.94
1.92
0.00
Me
O
O
O
OPh
N2
2.02
1.32
1.98
2.00
2.00
2.97
2.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

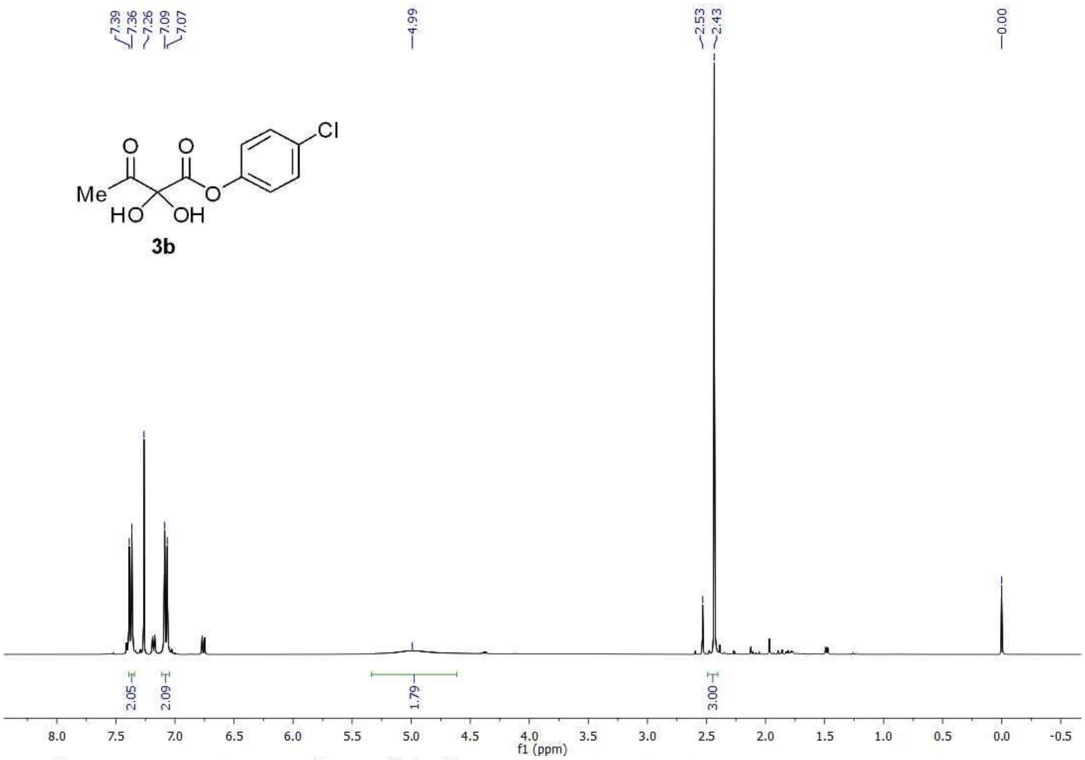
2n

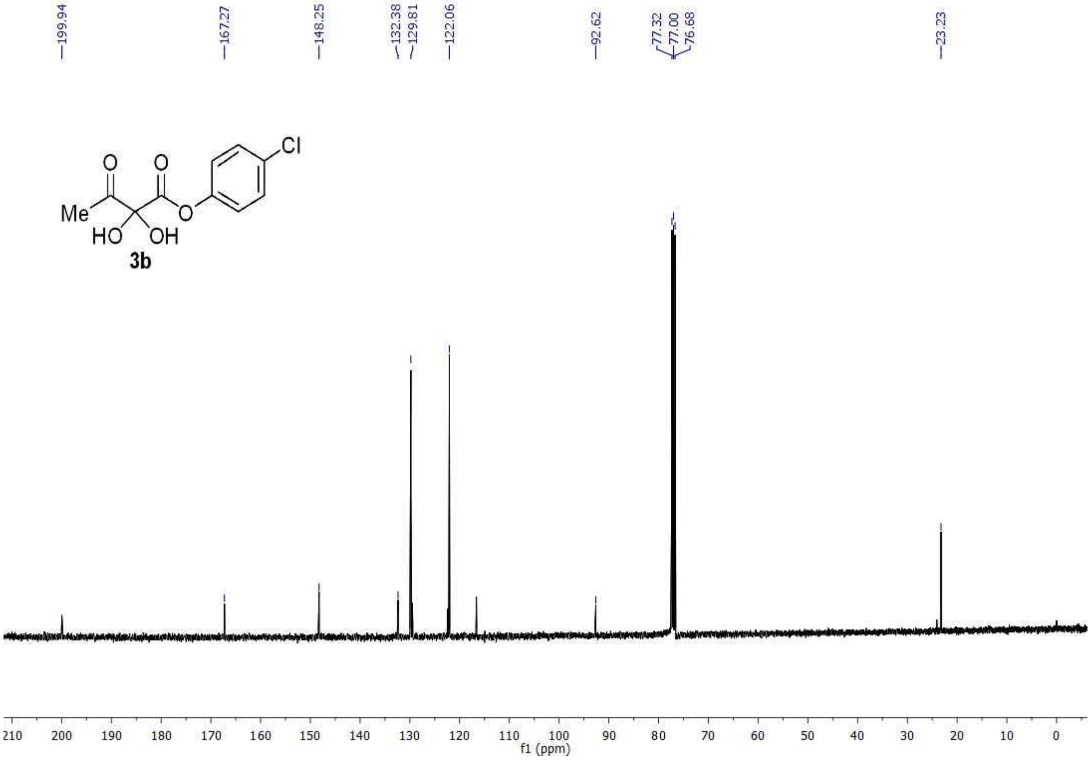

208.01
191.83
159.91
149.58
129.58
126.41
121.53
77.32
77.00
76.68
42.55
39.38
29.87
18.18
Me
O
O
O
OPh
N2
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

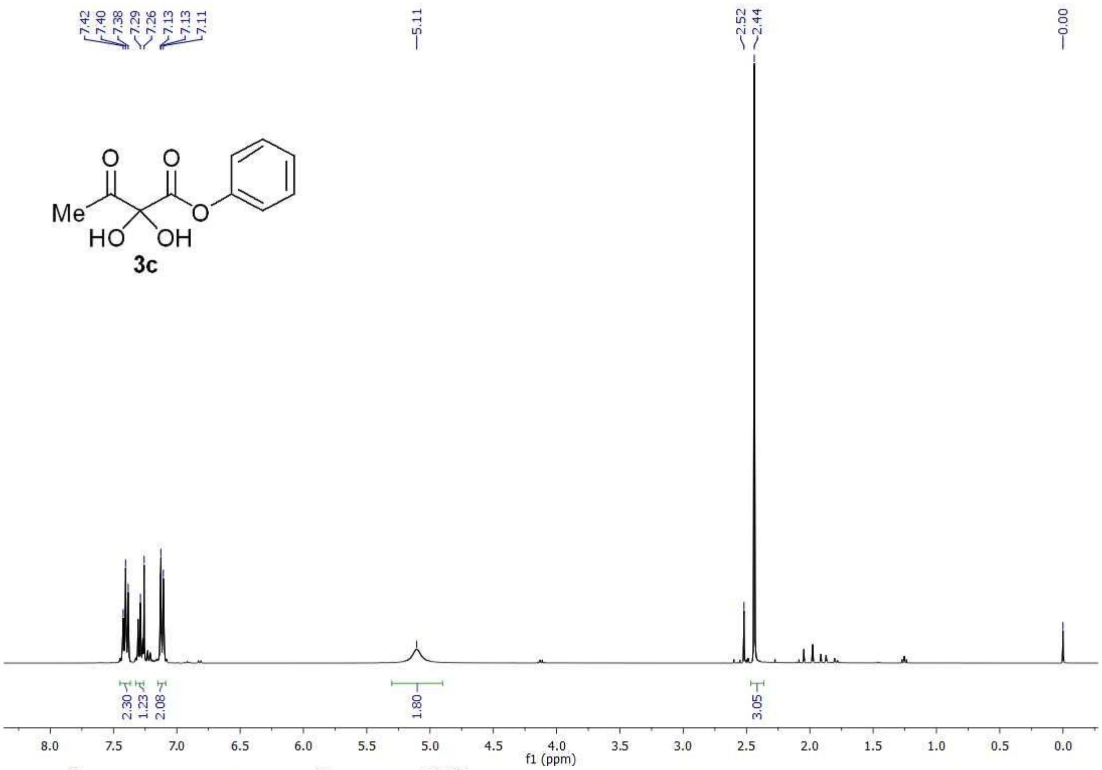
2n


7.26
7.20
7.18
7.00
7.00
6.98
6.98
5.06
2.43
2.35
Me
O
O
Me
O
HO
OH
3a
2.08
2.03
1.95
3.00
3.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

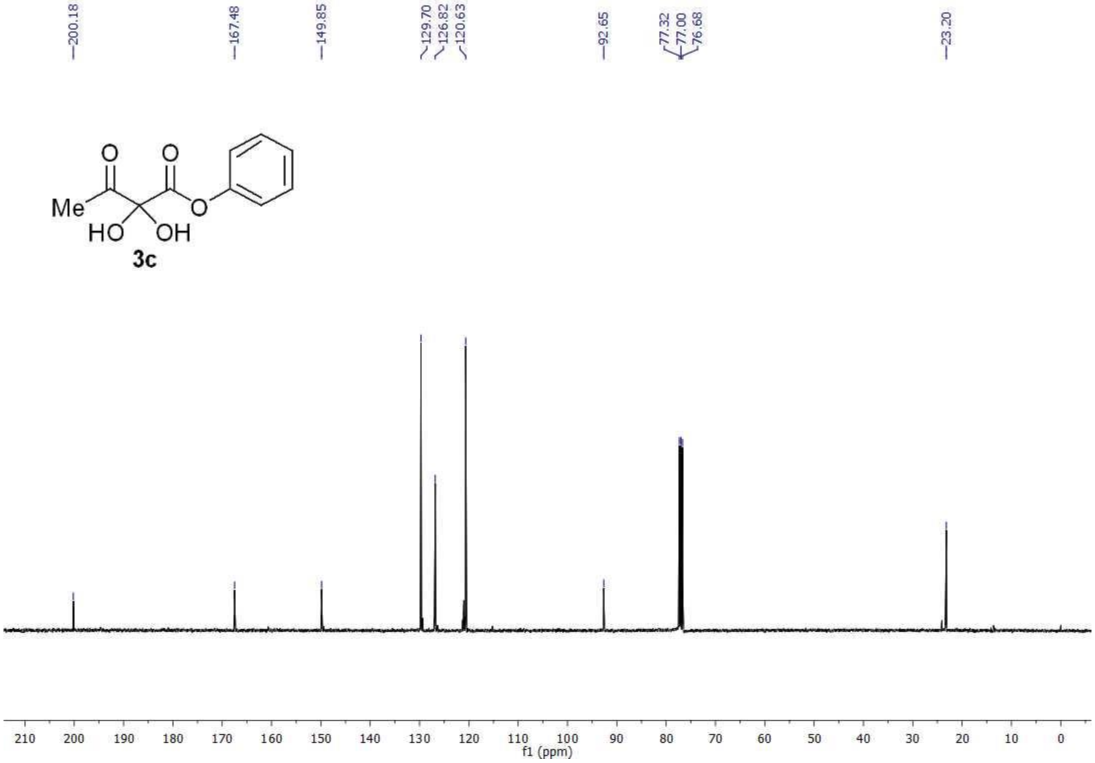

200.26
167.68
147.66
136.62
130.15
120.28
92.64
23.19
20.84
Me
O
O
Me
O
HO
OH
3a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.39
7.36
7.26
7.09
7.07
4.99
2.53
2.43
0.00
Me
O
O
O
Cl
HO
OH
3b
2.05
2.09
1.79
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

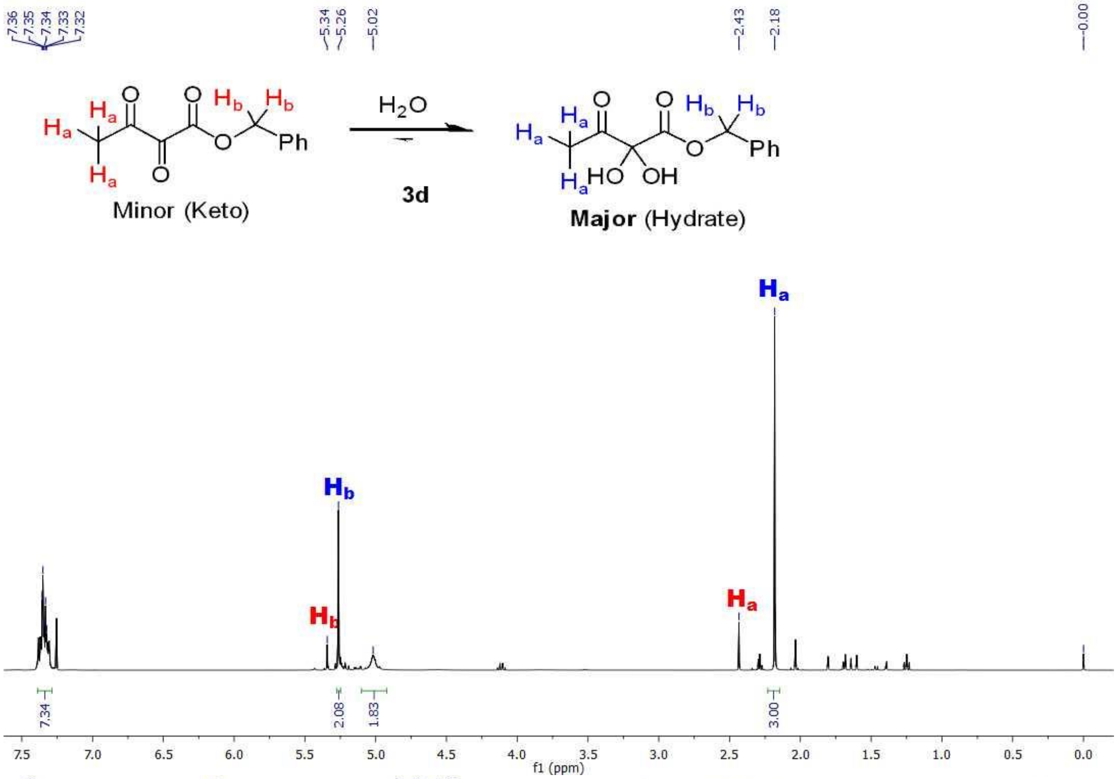

199.94
167.27
148.25
132.38
129.81
122.06
92.62
77.32
77.00
76.68
23.23
Me
O
O
O
Cl
HO
OH
3b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

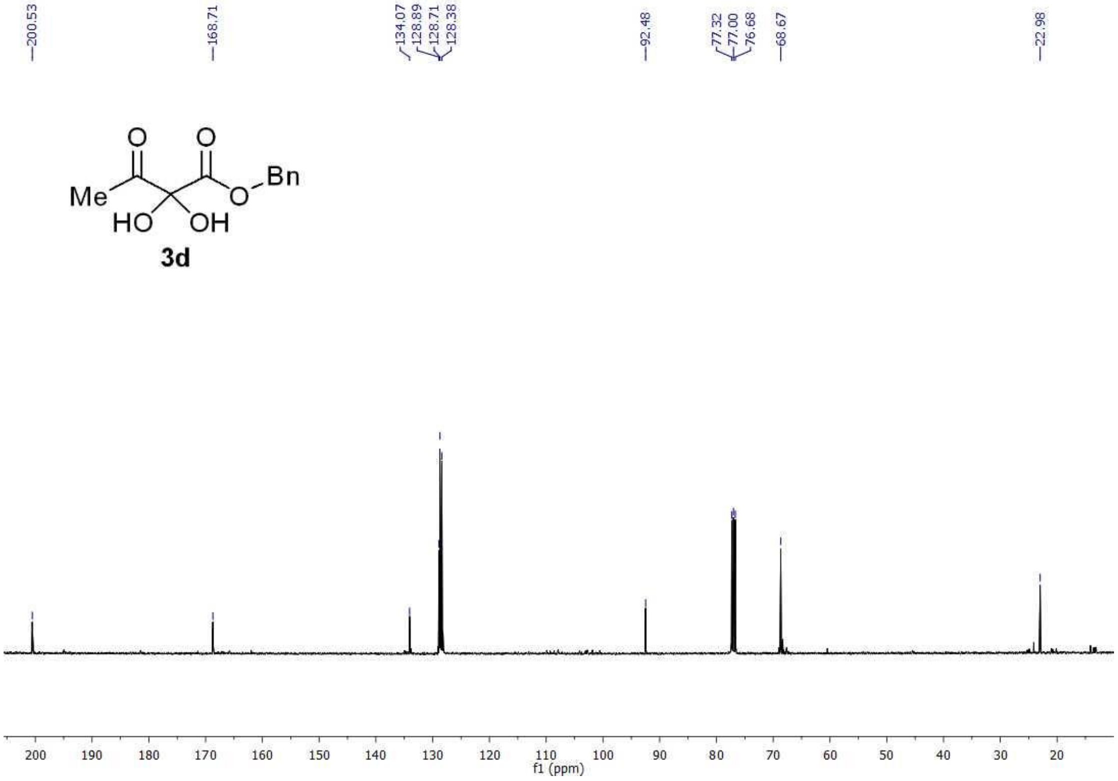


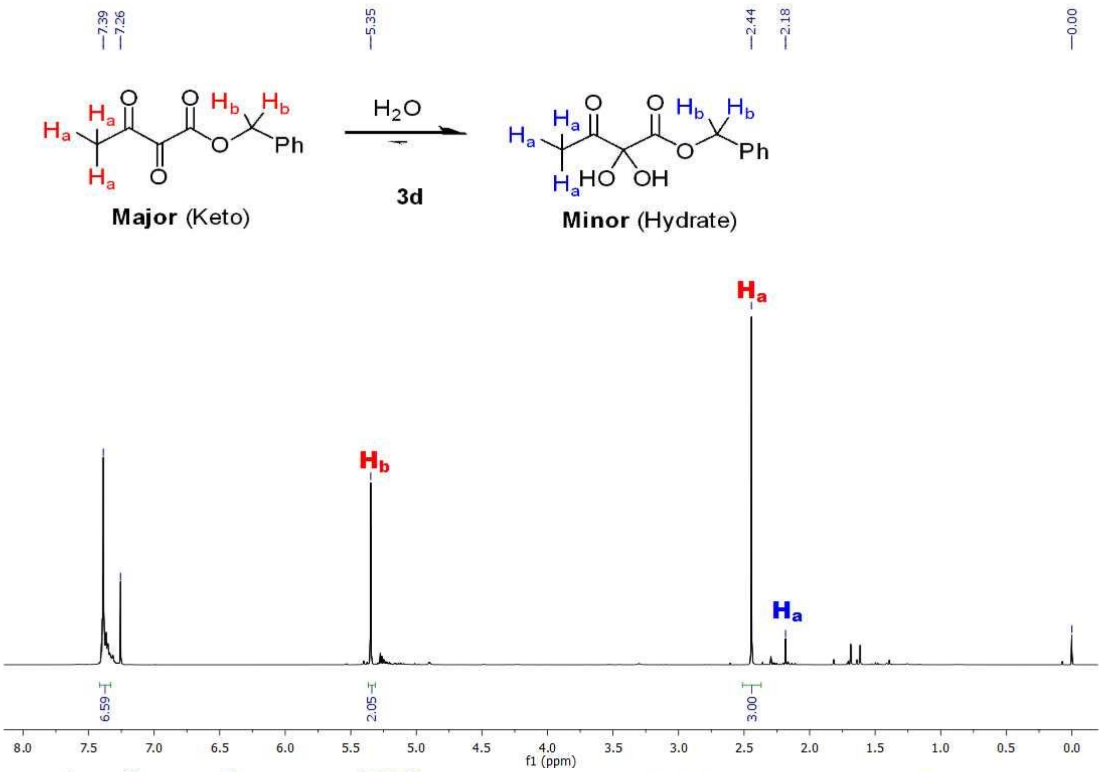
7.42
7.40
7.38
7.29
7.26
7.13
7.13
7.11
5.11
2.52
2.44
0.00
Me
HO
OH
O
O
O
3c
2.30
1.23
2.08
1.80
3.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

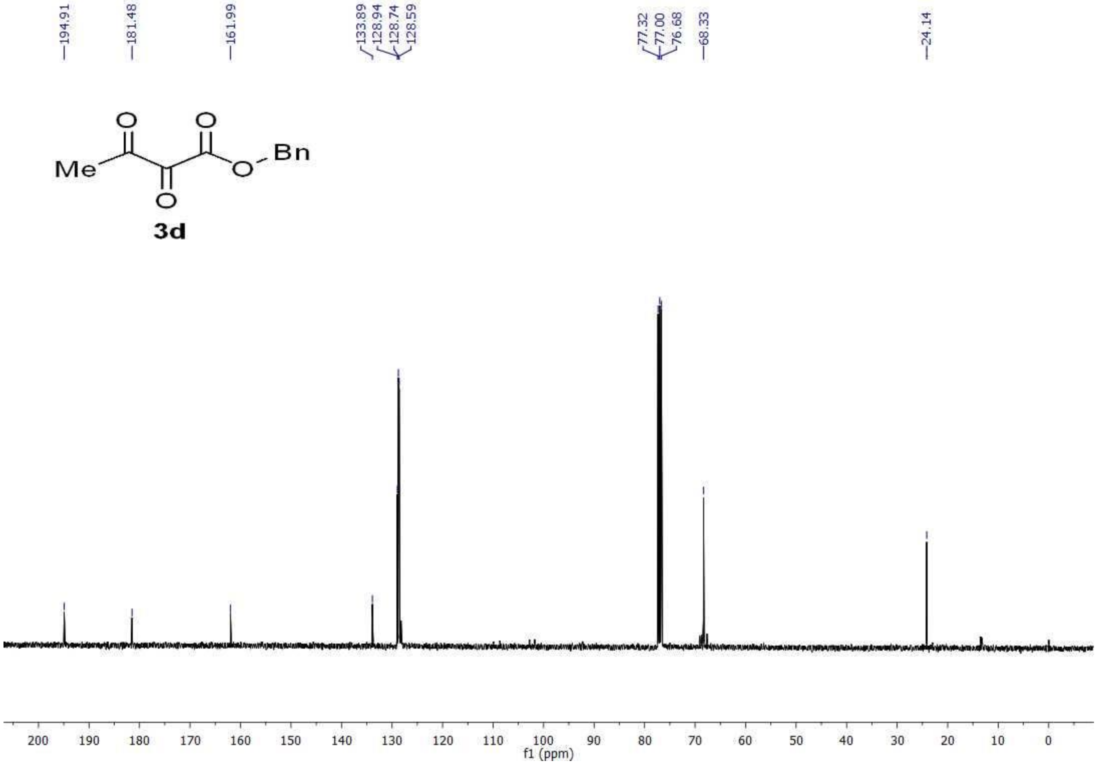


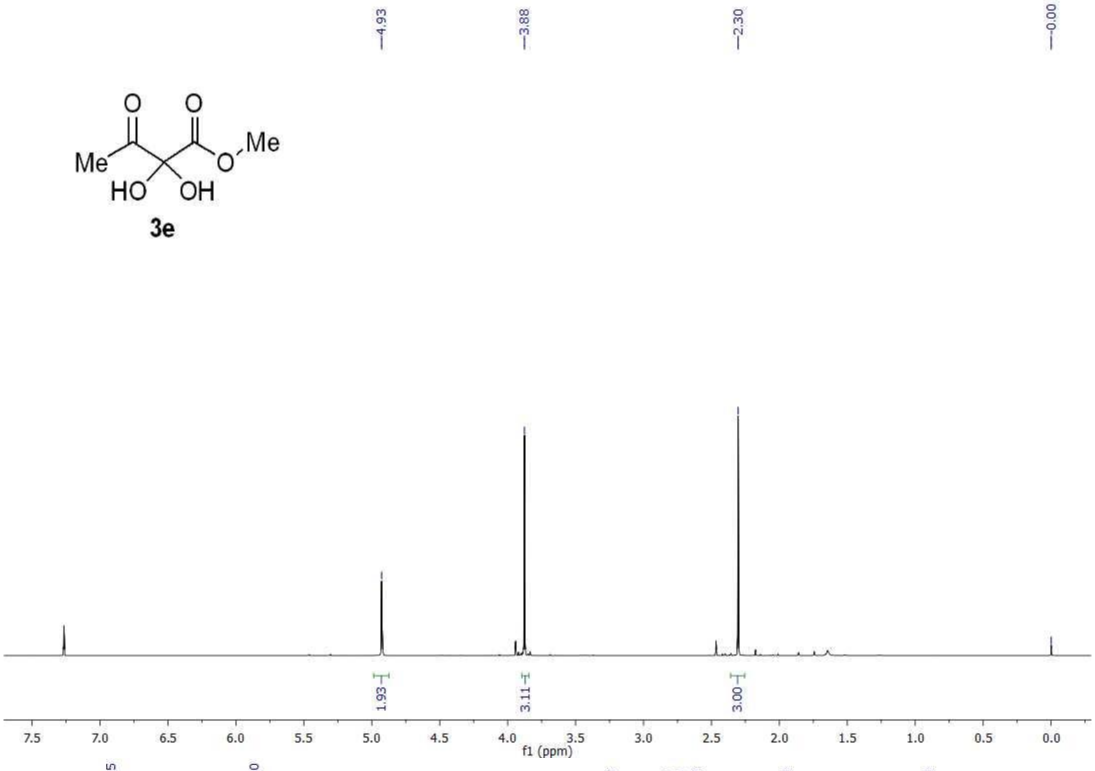
200.18
167.48
149.85
129.70
126.82
120.63
92.65
77.32
77.00
76.68
23.20
Me
HO
OH
O
O
O
3c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

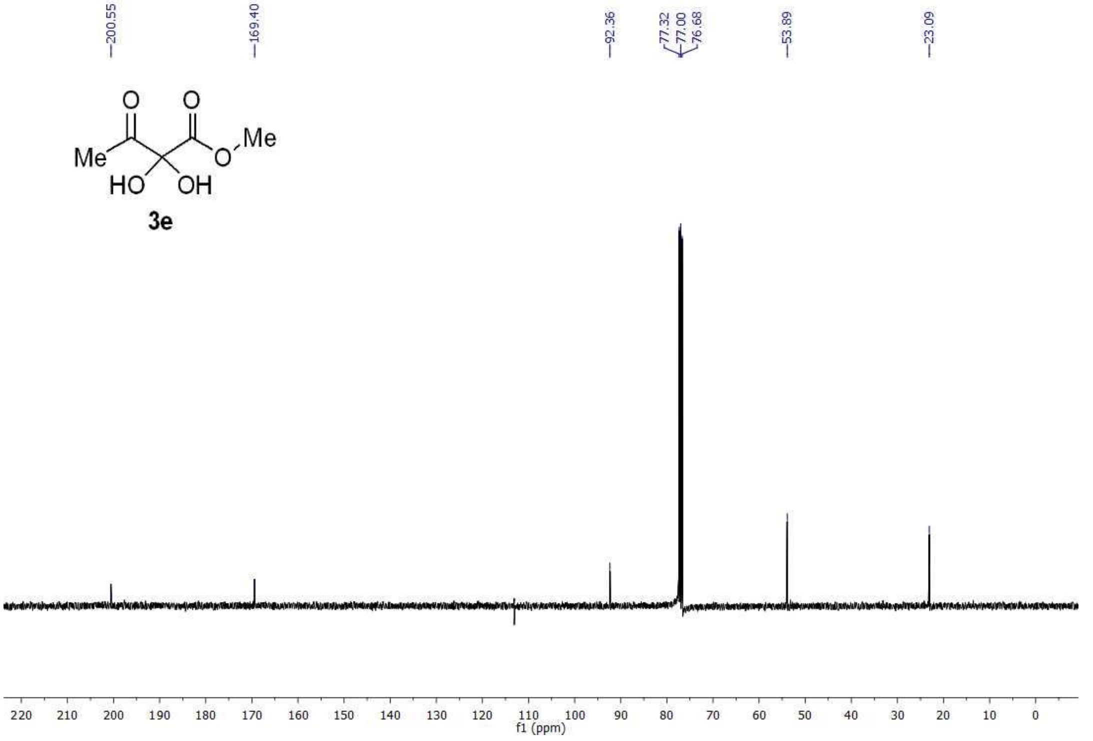

7.36
7.35
7.34
7.33
7.32
5.34
5.26
5.02
2.43
2.18
0.00
Minor (Keto)
H_2O
3d
Major (Hydrate)
H_a
H_b
Ph
HO
OH
7.34
2.08
1.83
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

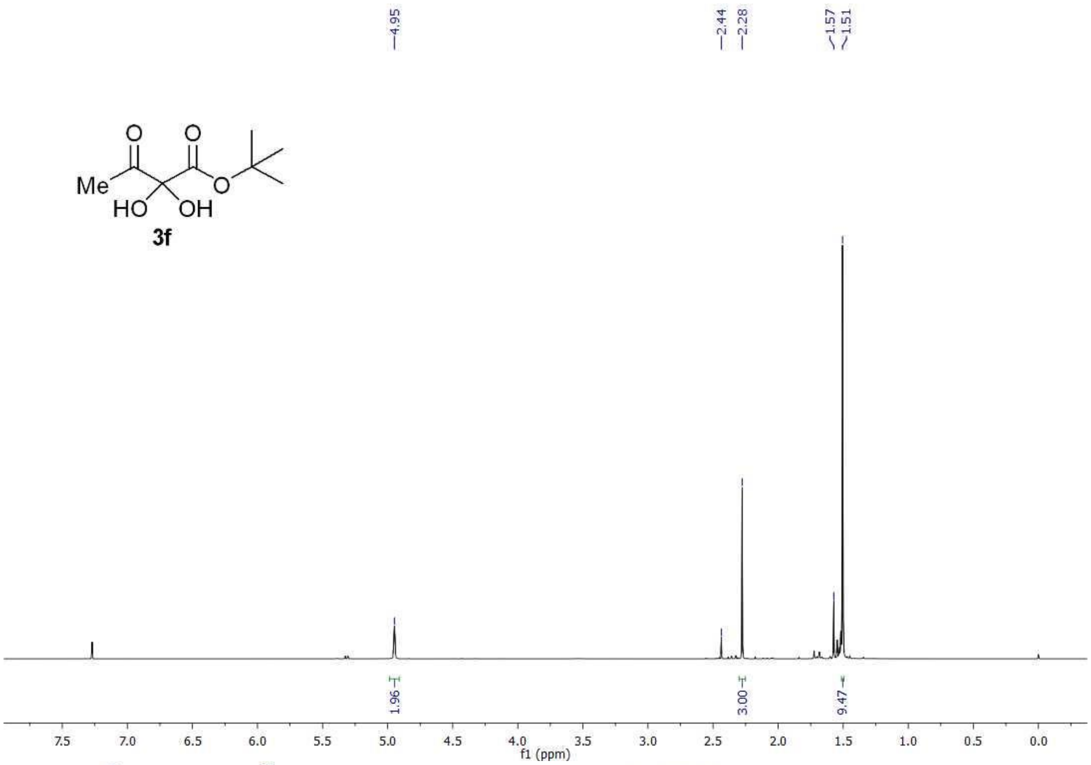

200.53
168.71
134.07
128.89
128.71
128.38
92.48
77.32
77.00
76.68
68.67
22.98
Me
HO
OH
Bn
3d
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

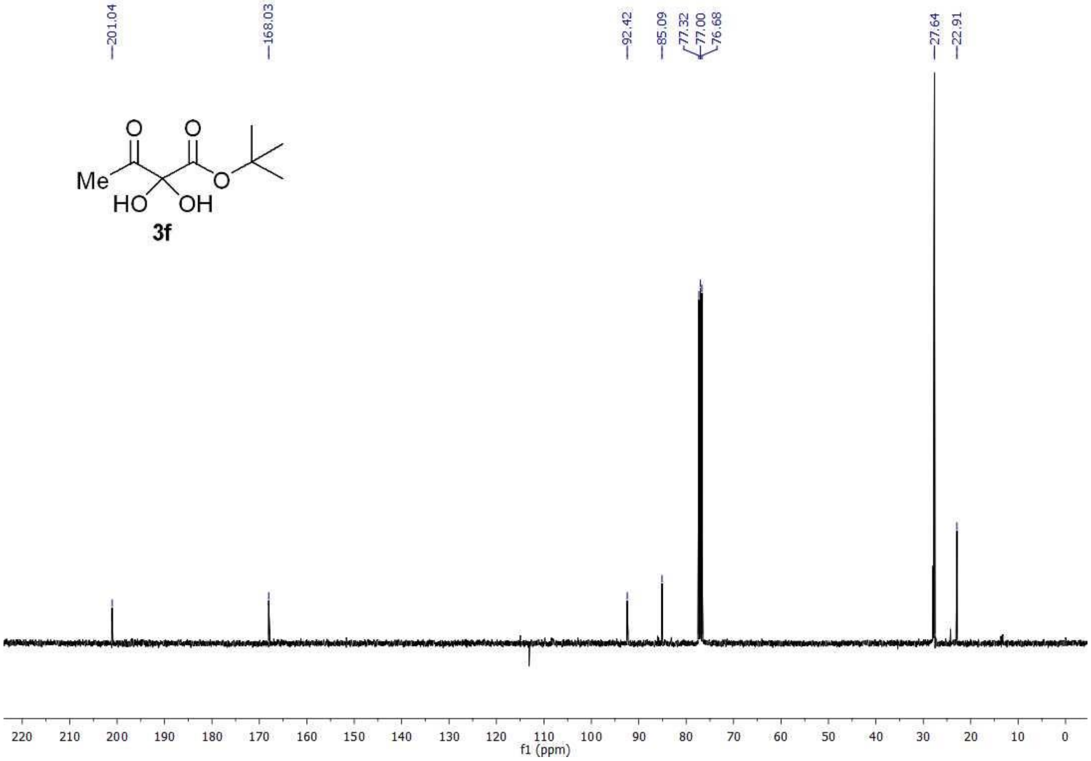

7.39
7.26
5.35
2.44
2.18
0.00
Major (Keto)
H2O
3d
Minor (Hydrate)
Ha
Hb
Ha
6.59
2.05
3.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

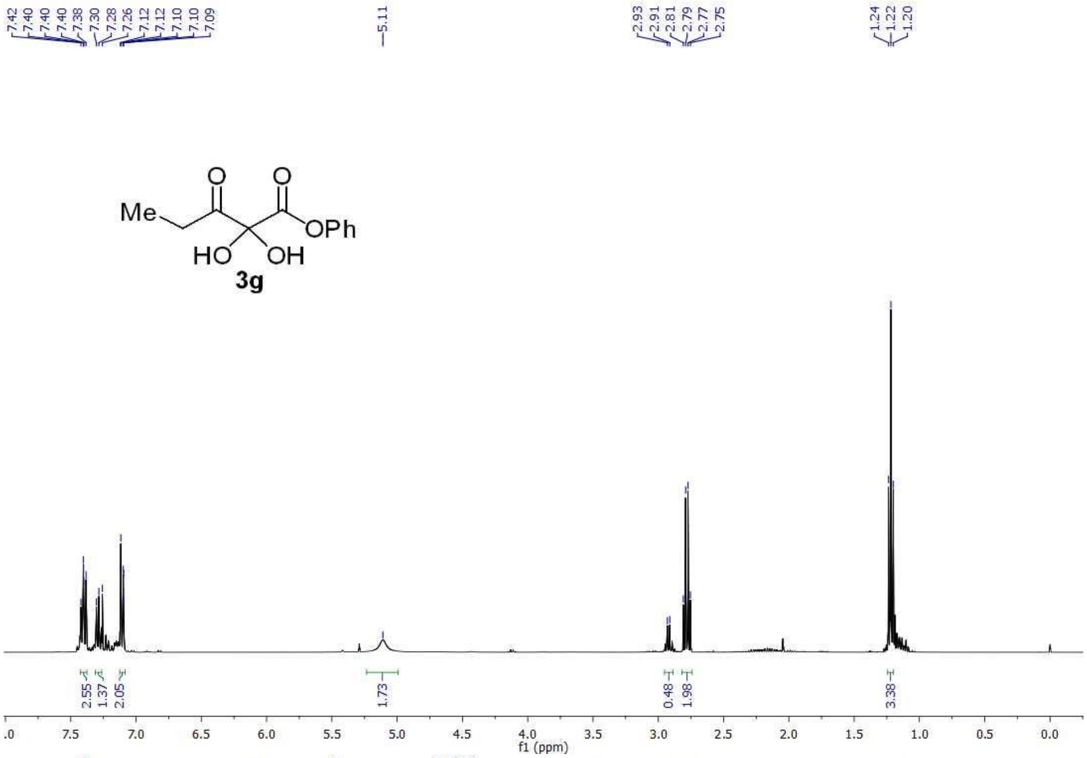

194.91
181.48
161.99
133.89
128.94
128.74
128.59
77.32
77.00
76.68
68.33
24.14
Me
Bn
3d
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

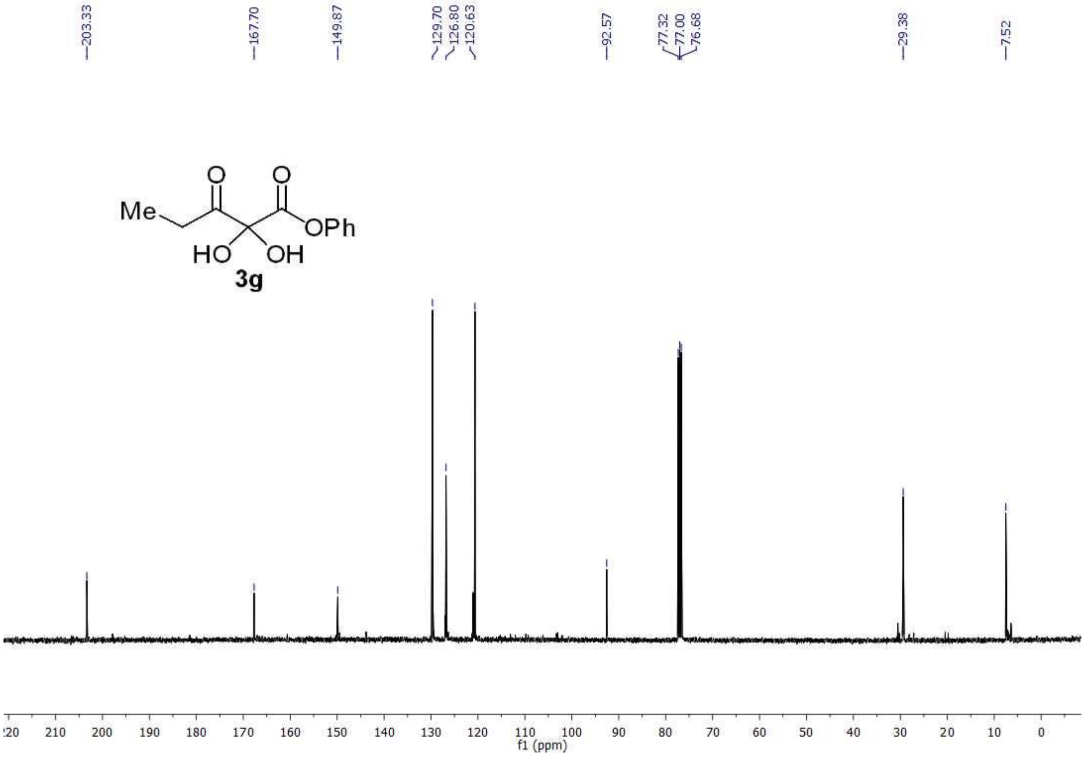

4.93
3.88
2.30
0.00
Me
O
O
O
Me
HO
OH
3e
1.93
3.11
3.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

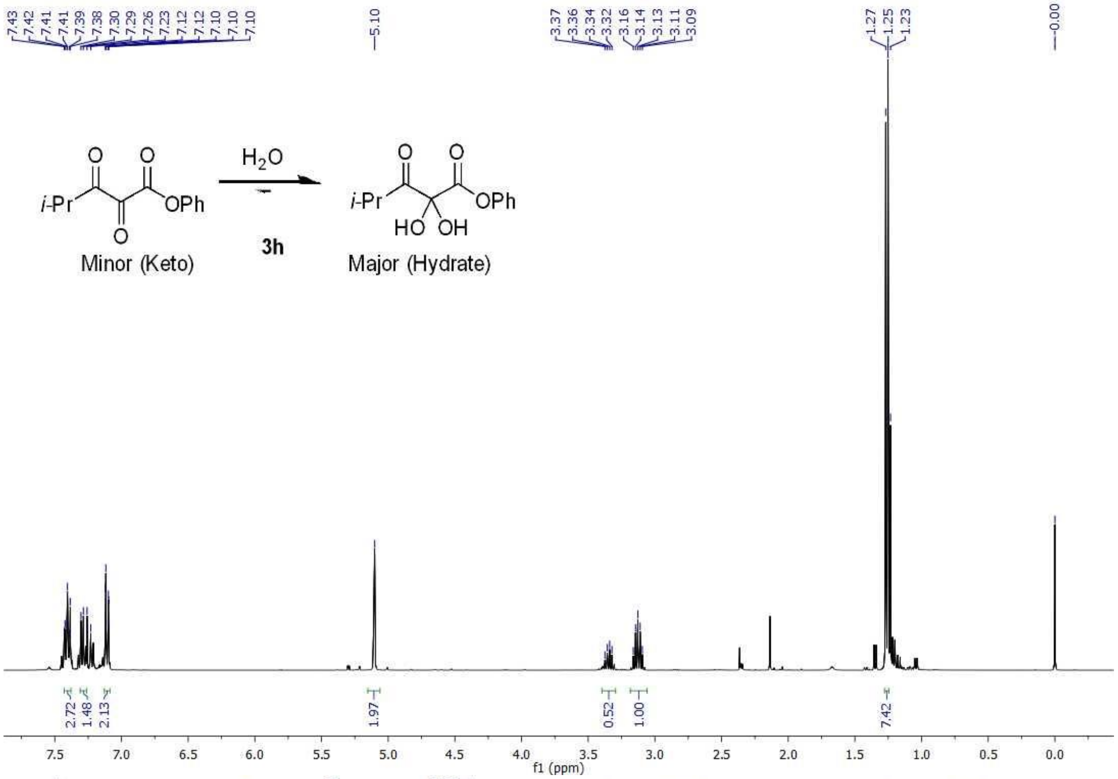

200.55
169.40
92.36
77.32
77.00
76.68
53.89
23.09
Me
O
O
O
Me
HO
OH
3e
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

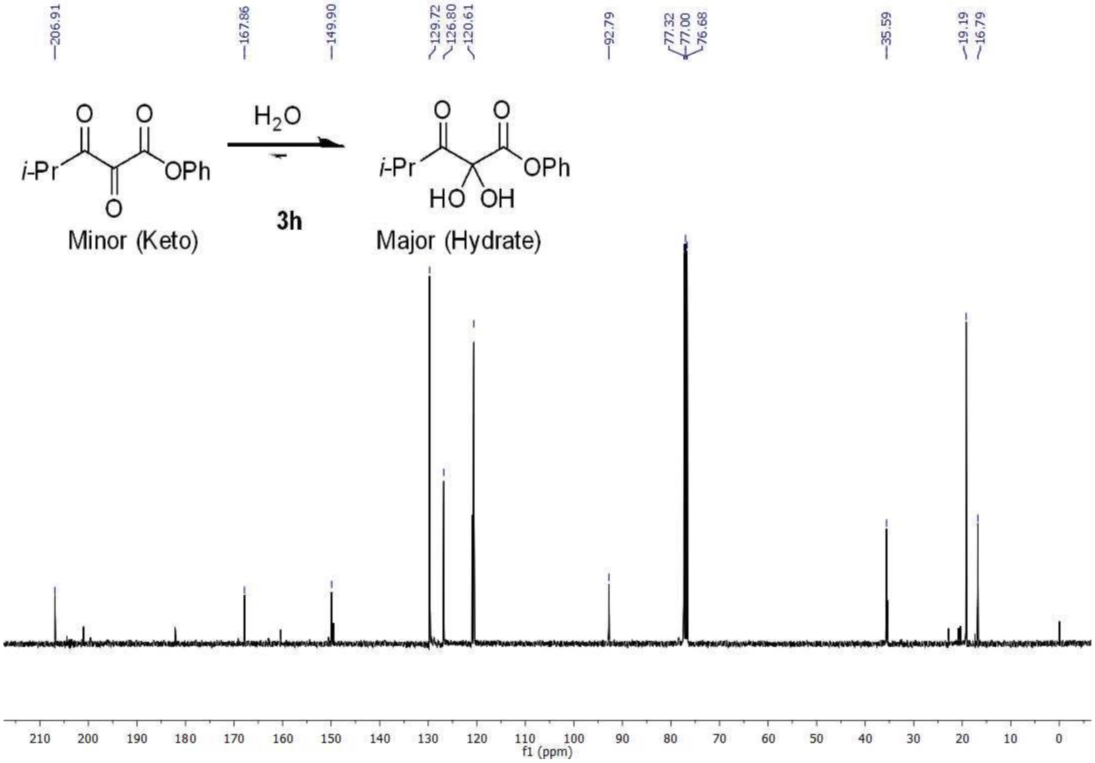

4.95
2.44
2.28
1.57
1.51
Me
O
O
O
HO
OH
3f
1.96
3.00
9.47
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

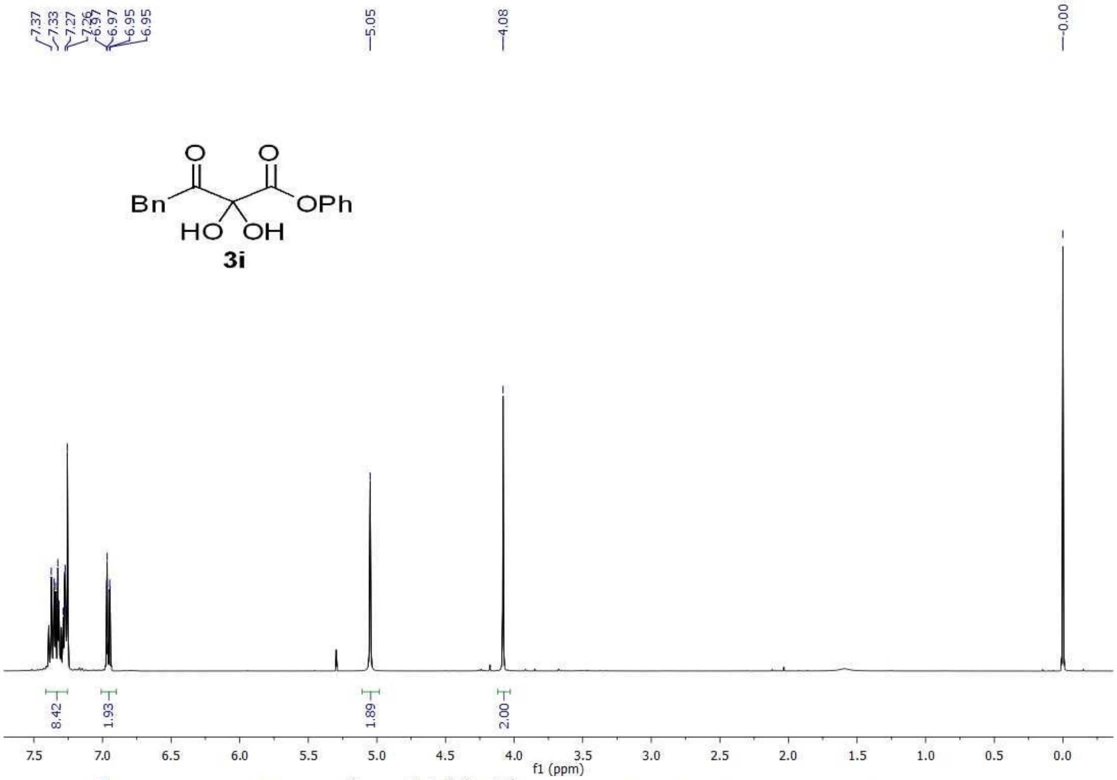

201.04
168.03
92.42
85.09
77.32
77.00
76.68
27.64
22.91
Me
O
O
O
HO
OH
3f
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

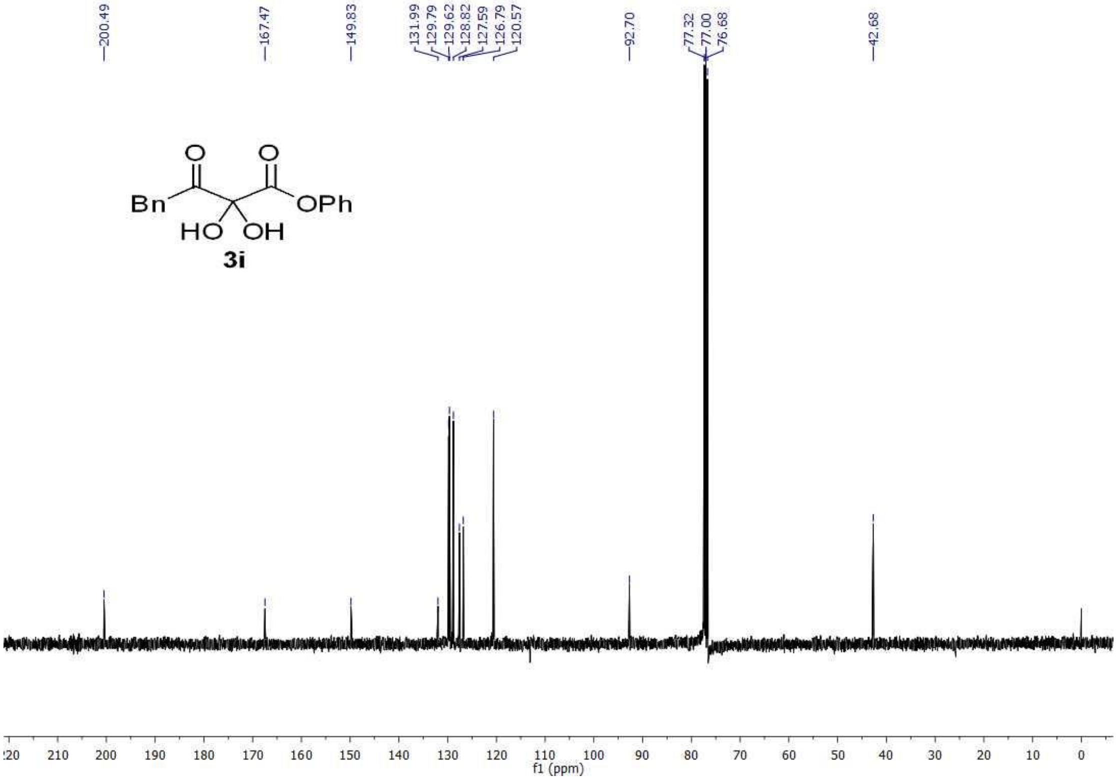

7.42
7.40
7.40
7.40
7.38
7.30
7.28
7.26
7.12
7.12
7.10
7.09
5.11
2.93
2.91
2.81
2.79
2.77
2.75
1.24
1.22
1.20
Me
O
O
OPh
HO
OH
3g
2.55
1.37
2.05
1.73
0.48
1.98
3.38
f1 (ppm)

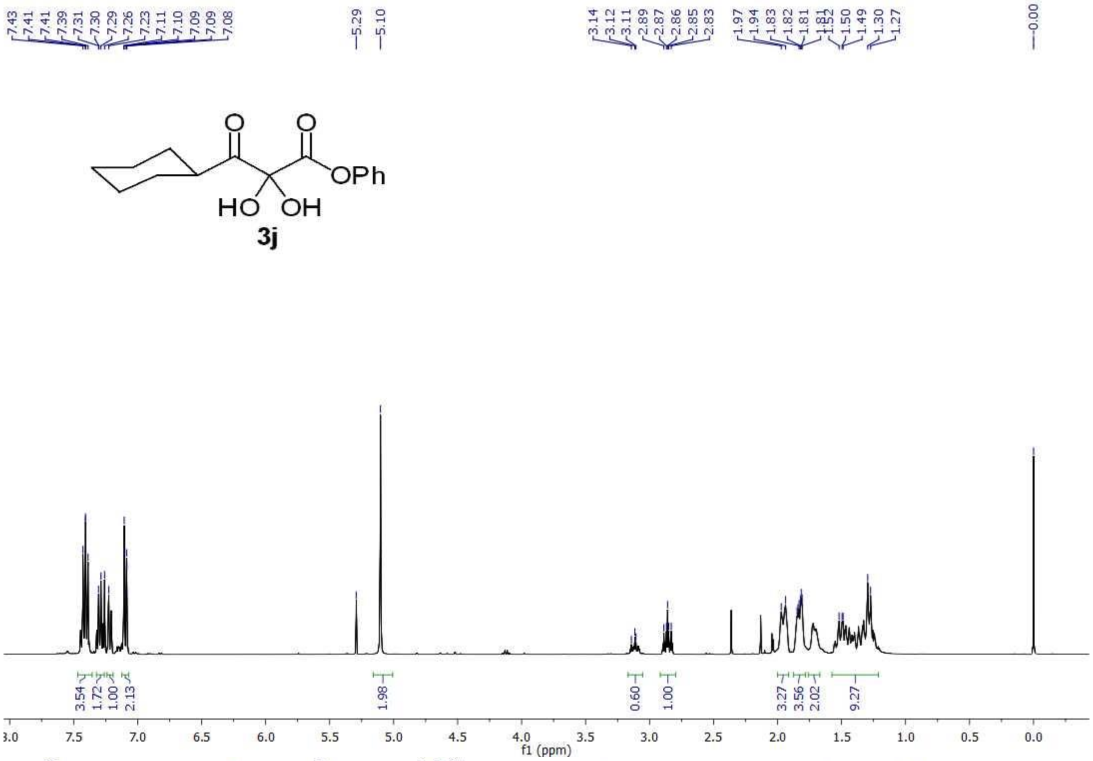

203.33
167.70
149.87
129.70
126.80
120.63
92.57
77.32
77.00
76.68
29.38
7.52
Me
O
O
OPh
HO
OH
3g
f1 (ppm)

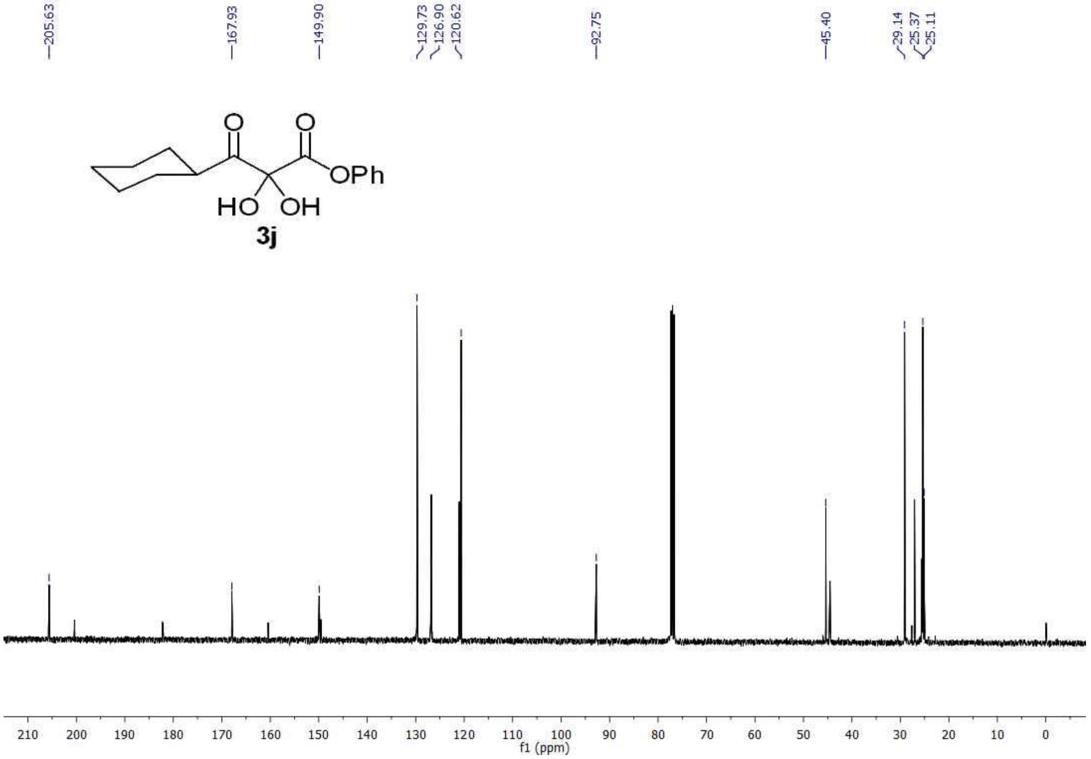

7.43
7.42
7.41
7.39
7.38
7.30
7.29
7.26
7.23
7.12
7.10
7.10
7.10
5.10
3.37
3.36
3.34
3.32
3.16
3.14
3.13
3.11
3.09
1.27
1.25
1.23
0.00
i-Pr
OPh
H2O
3h
HO OH
Minor (Keto)
Major (Hydrate)
2.72
1.48
2.13
1.97
0.52
1.00
7.42
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

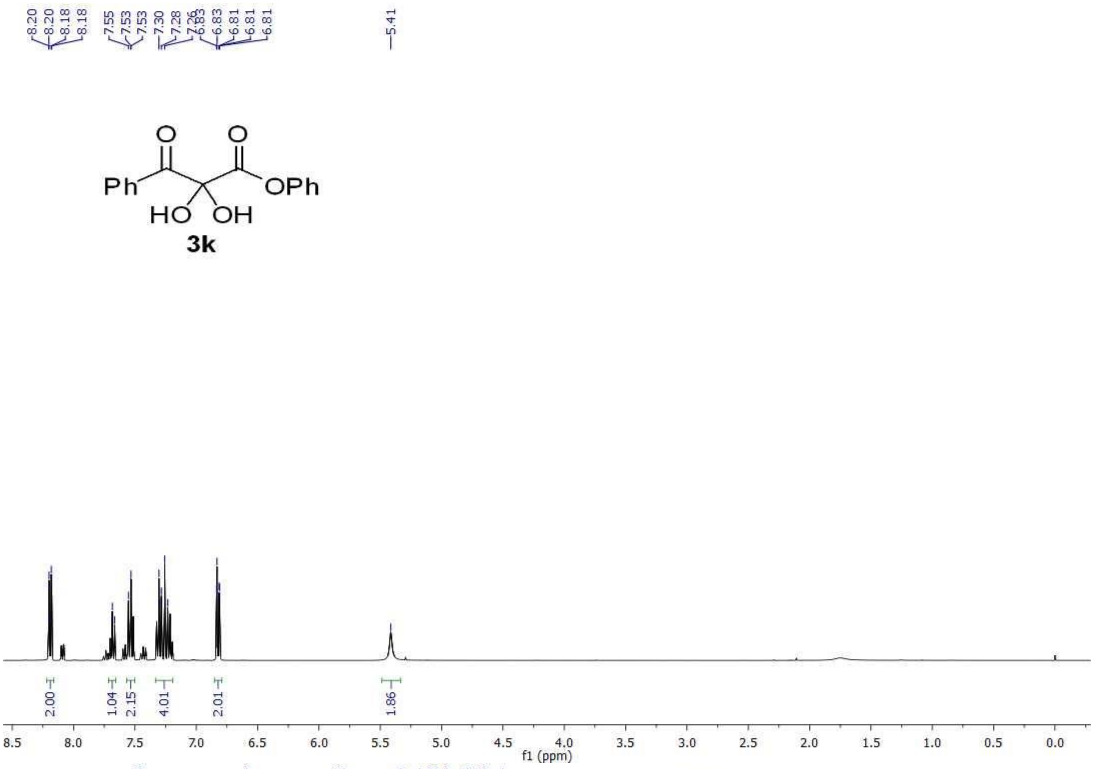

206.91
167.86
149.90
129.72
126.80
120.61
92.79
77.32
77.00
76.68
35.59
19.19
16.79
i-Pr
OPh
H2O
3h
HO OH
Minor (Keto)
Major (Hydrate)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

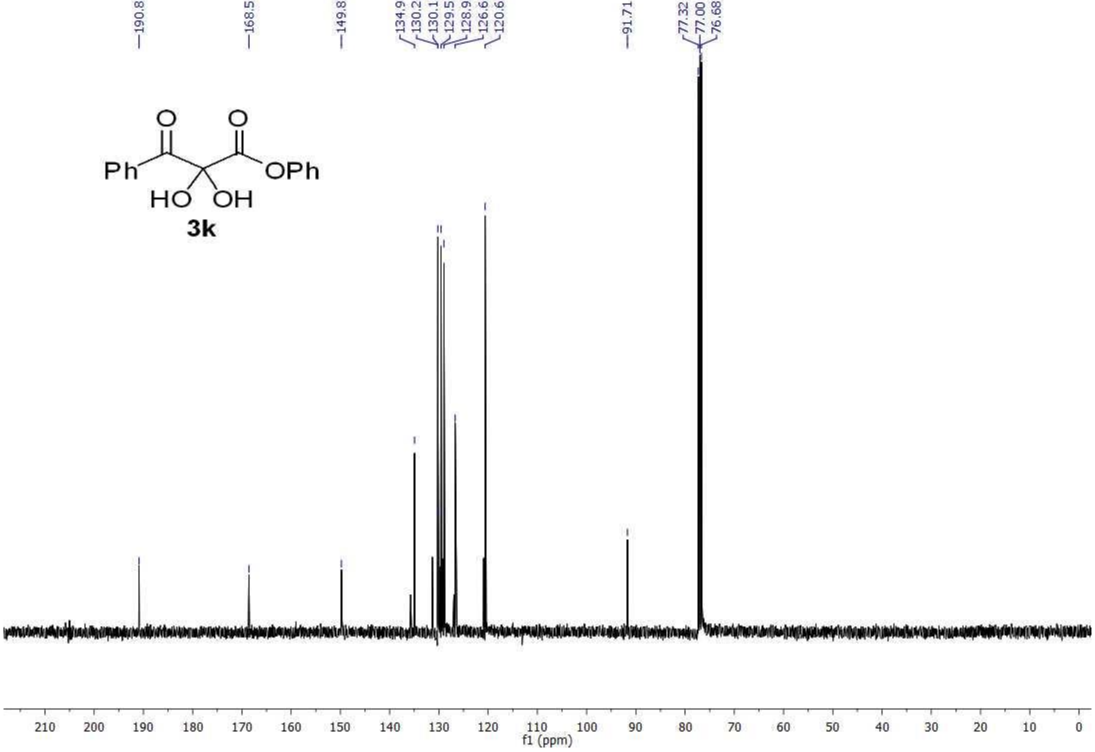

7.37
7.33
7.27
7.26
6.97
6.97
6.95
6.95
5.05
4.08
0.00
Bn
O
O
OPh
HO
OH
3i
8.42
1.93
1.89
2.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

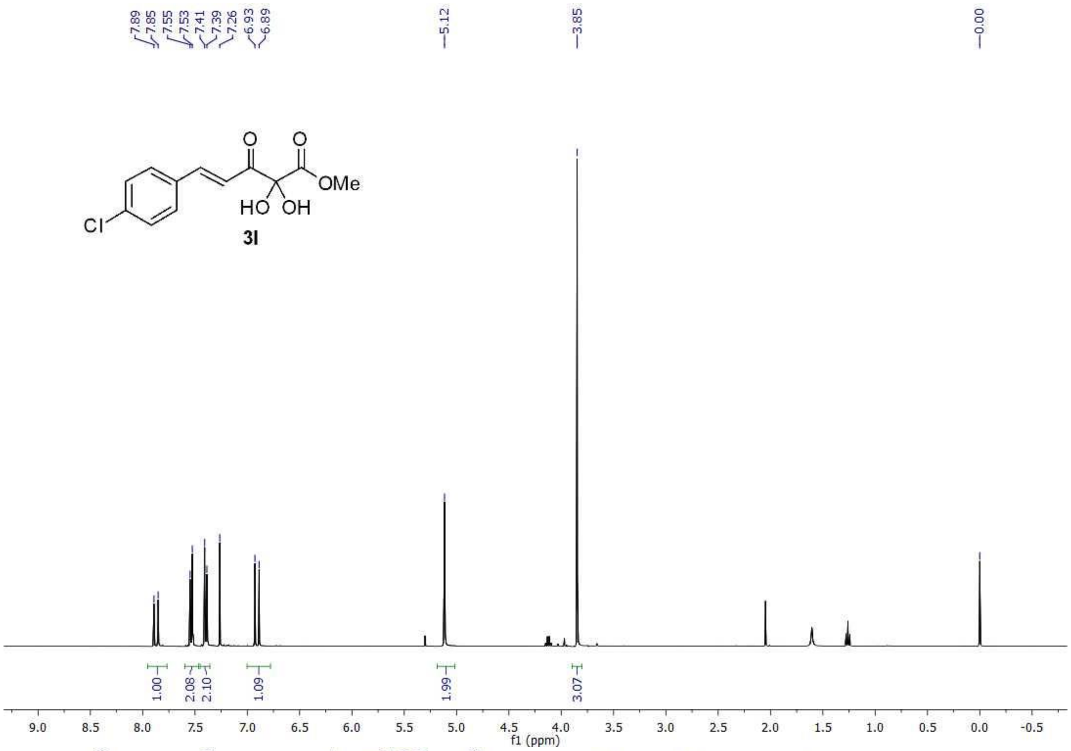

200.49
167.47
149.83
131.99
129.79
129.62
128.82
127.59
126.79
120.57
92.70
77.32
77.00
76.68
42.68
Bn
O
O
OPh
HO
OH
3i
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

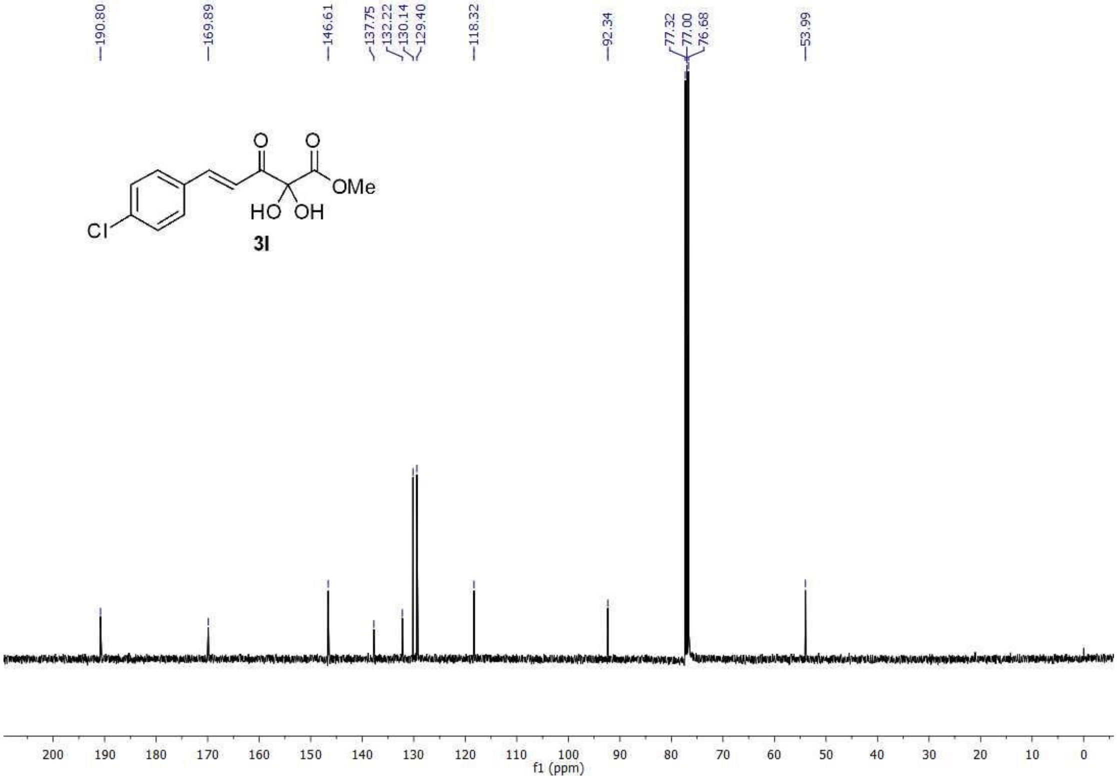

7.43
7.41
7.41
7.39
7.31
7.30
7.29
7.26
7.23
7.11
7.10
7.09
7.09
7.08
5.29
5.10
3.14
3.12
3.11
2.89
2.87
2.86
2.85
2.83
1.97
1.94
1.83
1.82
1.81
1.81
1.52
1.50
1.49
1.30
1.27
0.00
O
O
OPh
HO
OH
3j
3.54
1.72
1.00
2.13
1.98
0.60
1.00
3.27
3.56
2.02
9.27
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

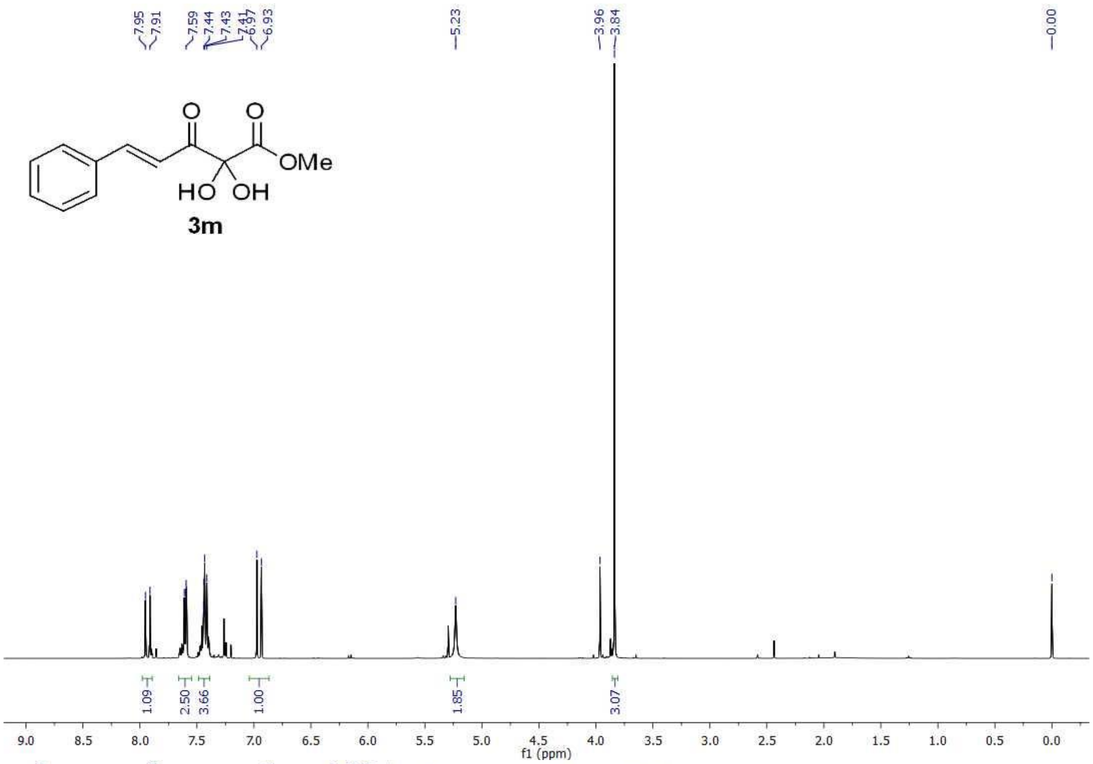

205.63
167.93
149.90
129.73
126.90
120.62
92.75
45.40
29.14
25.37
25.11
O
O
OPh
HO
OH
3j
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

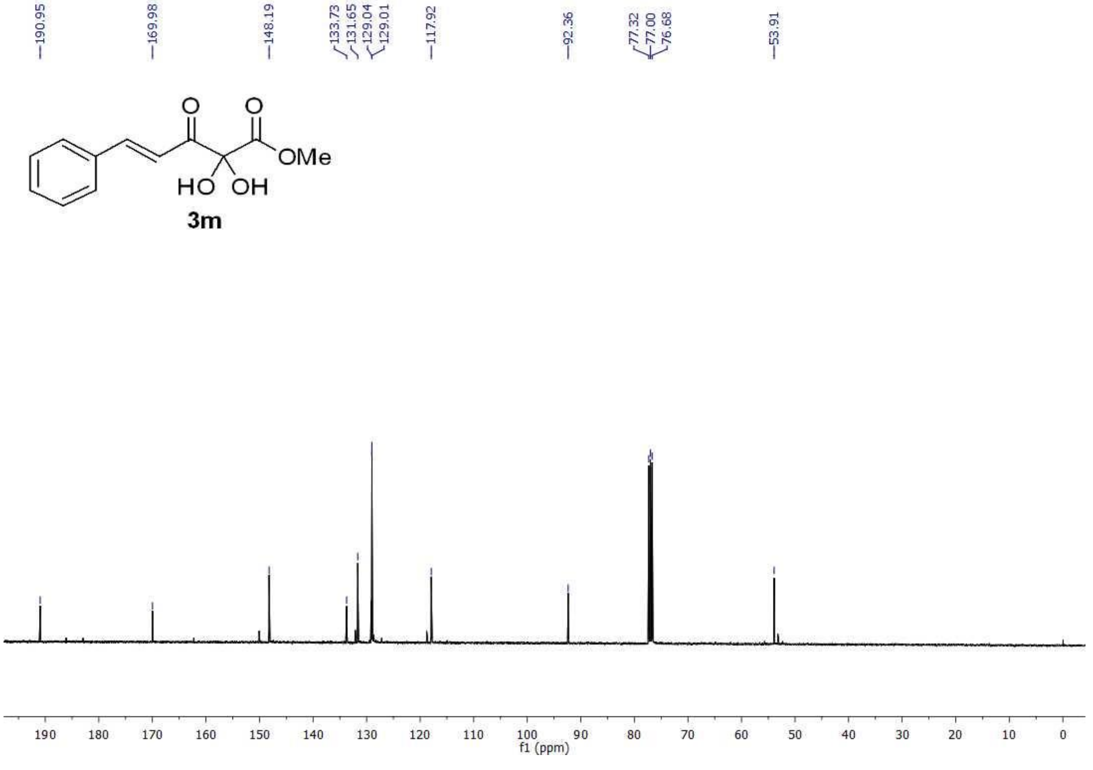

8.20
8.20
8.18
8.18
7.55
7.53
7.53
7.30
7.28
7.26
6.83
6.83
6.81
6.81
6.81
5.41
Ph
OPh
HO
OH
3k
2.00
1.04
2.15
4.01
2.01
1.86
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

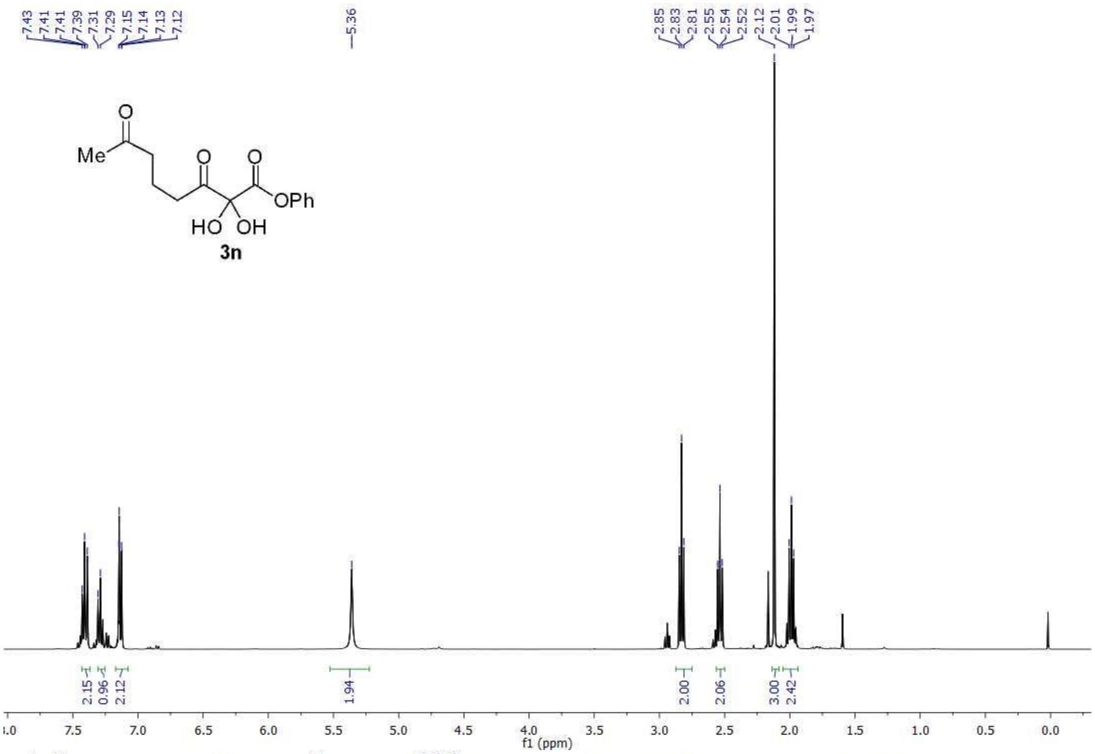

190.89
168.57
149.80
134.94
130.21
130.18
129.57
128.99
126.69
120.61
91.71
77.32
77.00
76.68
Ph
OPh
HO
OH
3k
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.89
7.85
7.55
7.53
7.41
7.39
7.26
6.93
6.89
5.12
3.85
0.00
O
O
OMe
HO
OH
Cl
3l
1.00
2.08
2.10
1.09
1.99
3.07
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

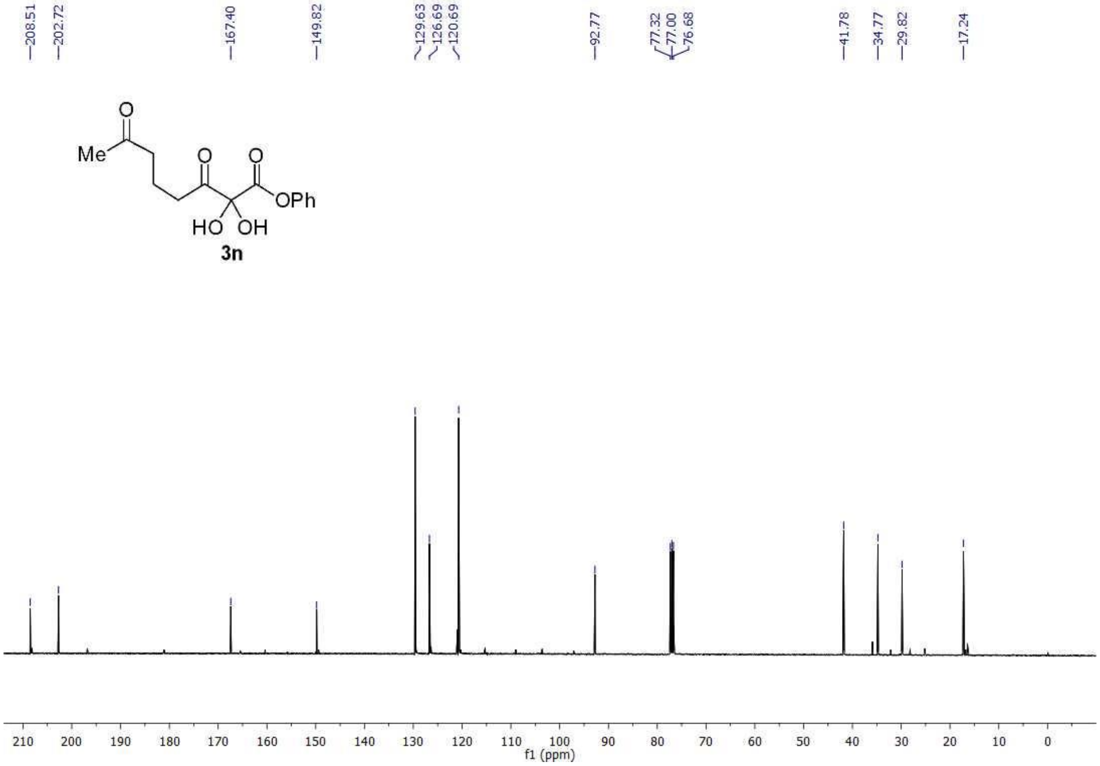

190.80
169.89
146.61
137.75
132.22
130.14
129.40
118.32
92.34
77.32
77.00
76.68
53.99
O
O
OMe
HO
OH
Cl
3l
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.95
7.91
7.59
7.44
7.43
7.41
6.97
6.93
5.23
3.96
3.84
0.00
O
O
OMe
HO
OH
3m
1.09
2.50
3.66
1.00
1.85
3.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190.95
169.98
148.19
133.73
131.65
129.04
129.01
117.92
92.36
77.32
77.00
76.68
53.91
O
O
OMe
HO
OH
3m
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.43
7.41
7.41
7.39
7.31
7.29
7.15
7.14
7.13
7.12
5.36
2.85
2.83
2.81
2.55
2.54
2.52
2.12
2.01
1.99
1.97
Me
O
O
O
OPh
HO
OH
2.15
0.96
2.12
1.94
2.00
2.06
3.00
2.42
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

3n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34.77
29.82
17.24
Me
O
O
O
OPh
HO
OH
210
200
190
180
170
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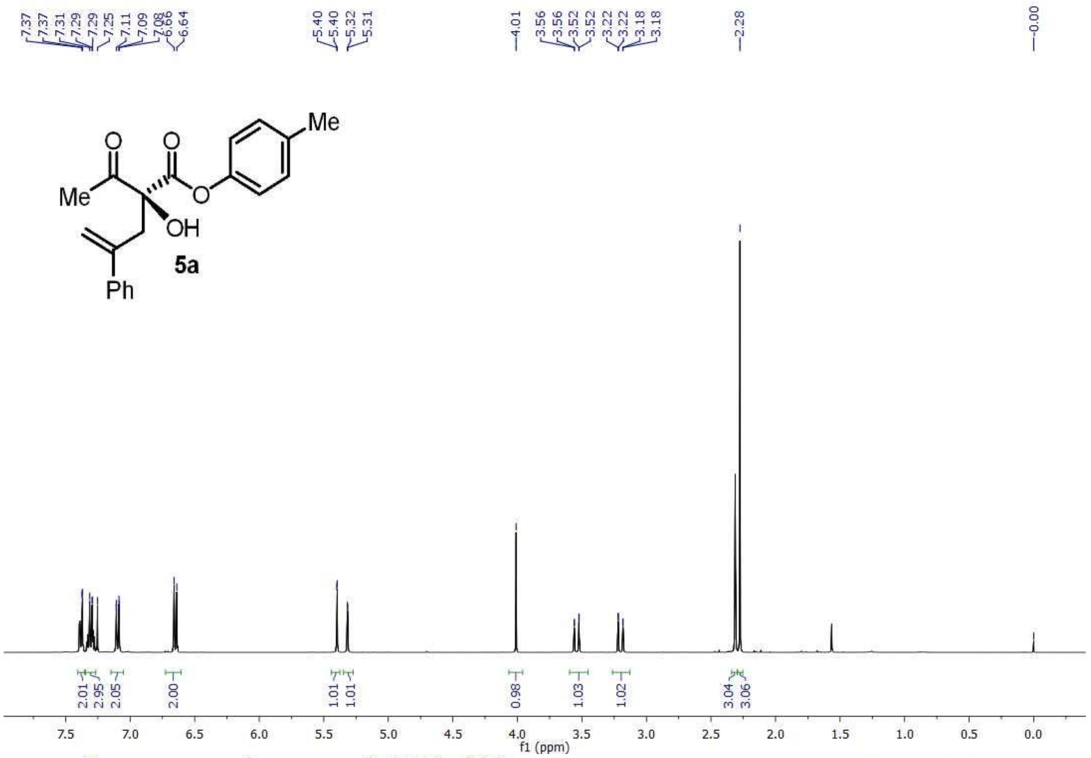
f1 (ppm)

3n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5.40
5.32
5.31
4.01
3.56
3.56
3.52
3.52
3.22
3.22
3.18
3.18
2.28
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O
O
Me
Me
O
OH
Ph
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2.95
2.05
2.00
1.01
1.01
0.98
1.03
1.02
3.04
3.06
7.5
7.0
6.5
6.0
5.5
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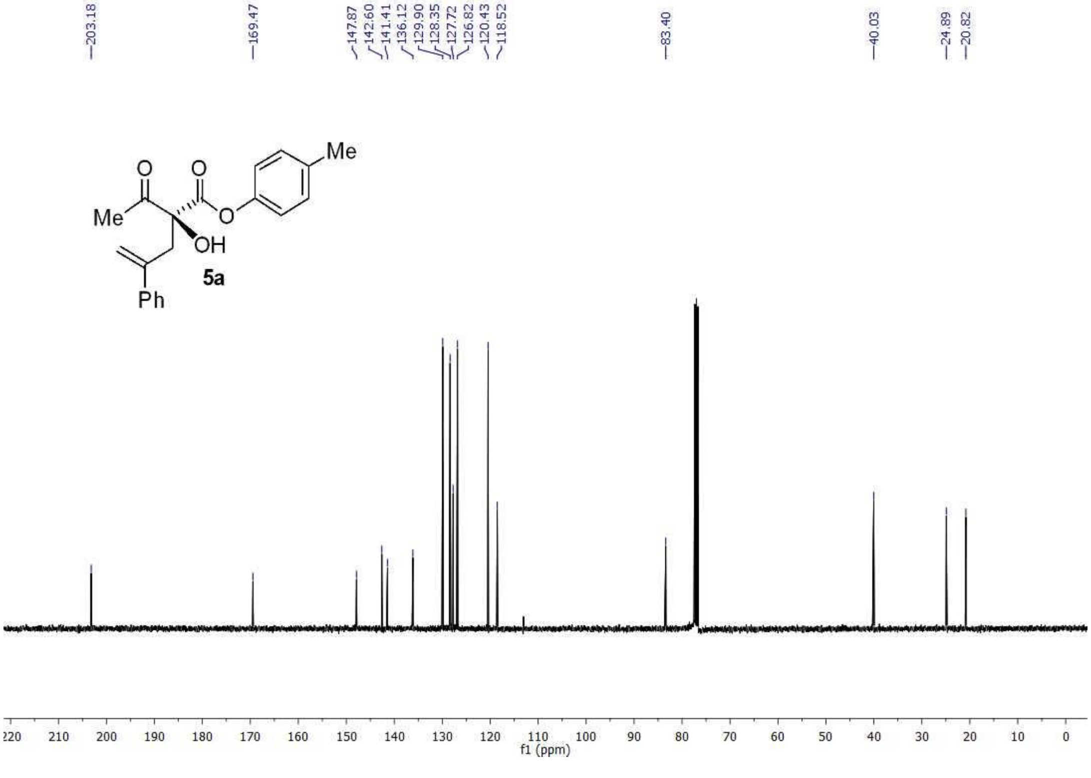
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40.03
24.89
20.82
O
O
Me
Me
O
OH
Ph
5a
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210
200
190
180
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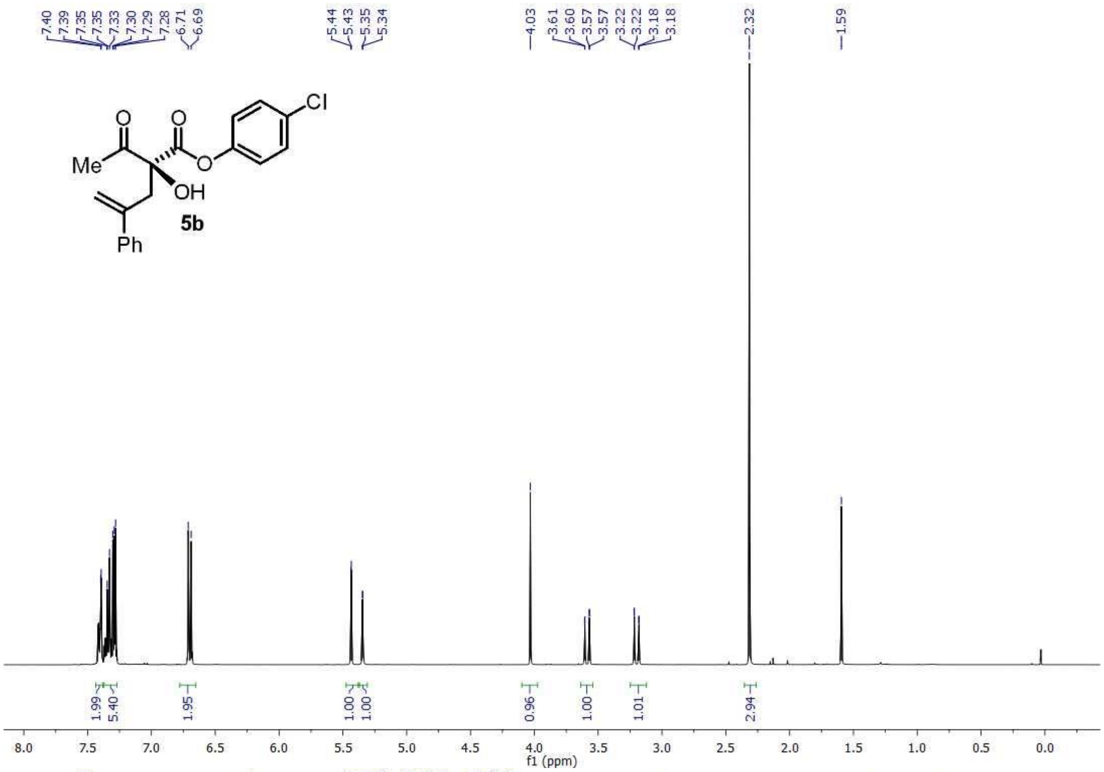
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3.60
3.57
3.57
3.22
3.22
3.18
3.18
2.32
1.59
Me
O
O
O
Cl
OH
Ph
5b
1.99
5.40
1.95
1.00
1.00
0.96
1.00
1.01
2.94
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7.0
6.5
6.0
5.5
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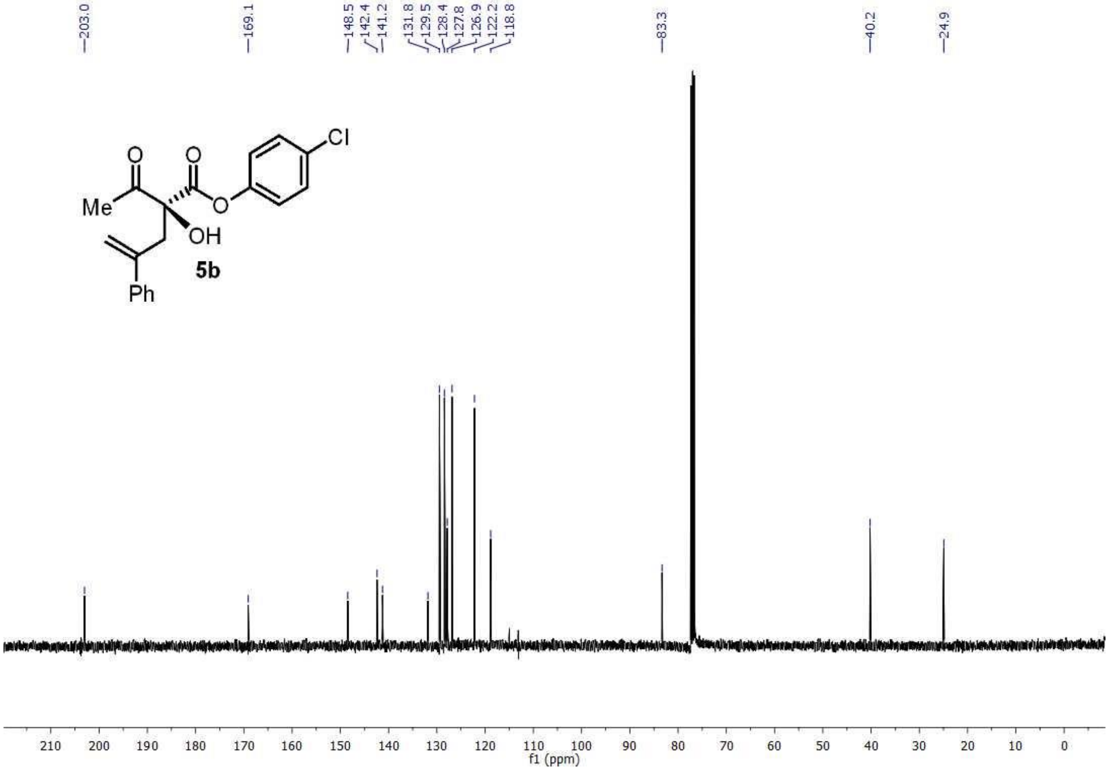
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24.9
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O
O
Cl
OH
Ph
5b
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200
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180
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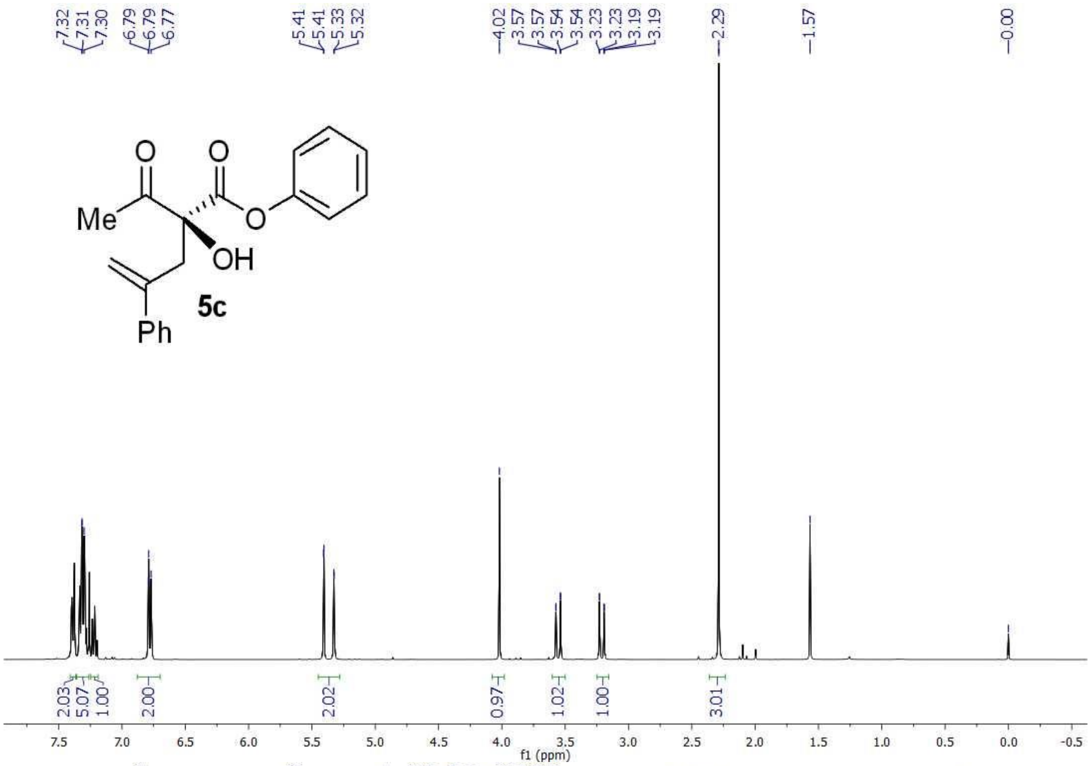
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5.32
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3.54
3.23
3.23
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3.19
2.29
1.57
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O
O
Me
O
OH
Ph
5c
2.03
5.07
1.00
2.00
2.02
0.97
1.02
1.00
3.01
7.5
7.0
6.5
6.0
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5.0
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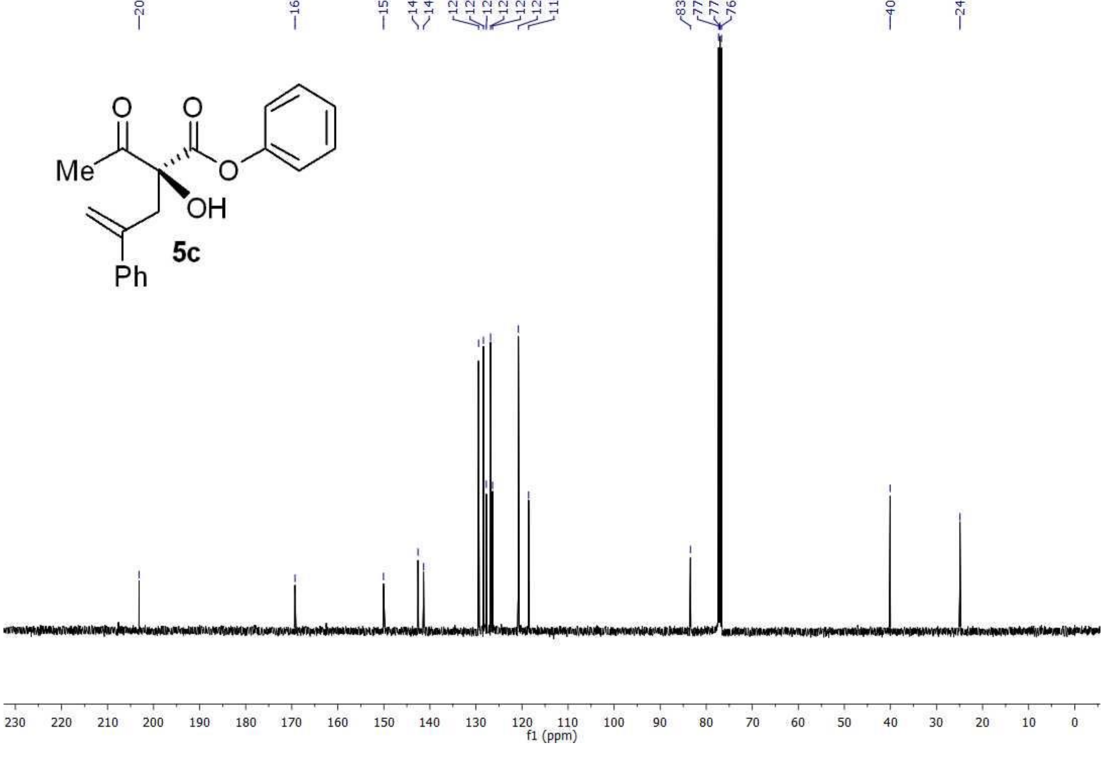
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83.4
77.3
77.0
76.7
40.1
24.9
O
O
Me
O
OH
Ph
5c
230
220
210
200
190
180
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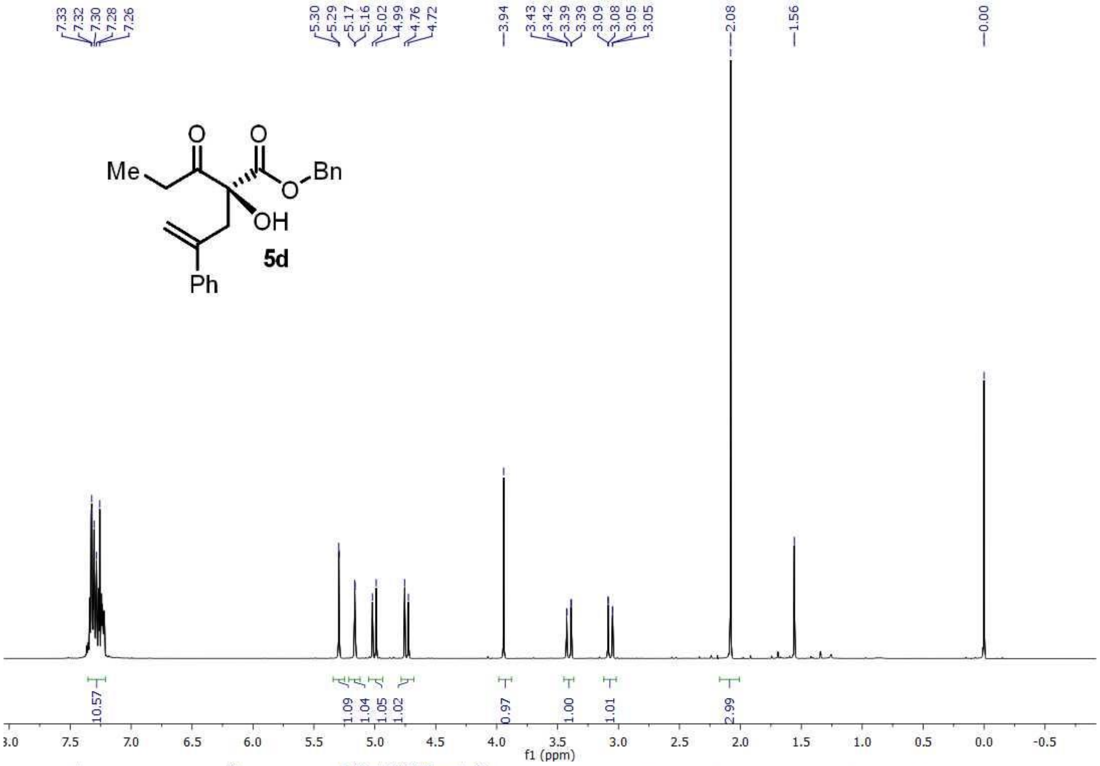
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3.94
3.43
3.42
3.39
3.39
3.09
3.08
3.05
3.05
2.08
1.56
0.00
Me
O
O
O
Bn
OH
Ph
5d
10.57
1.09
1.04
1.05
1.02
0.97
1.00
1.01
2.99
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
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3.0
2.5
2.0
1.5
1.0
0.5
0.0
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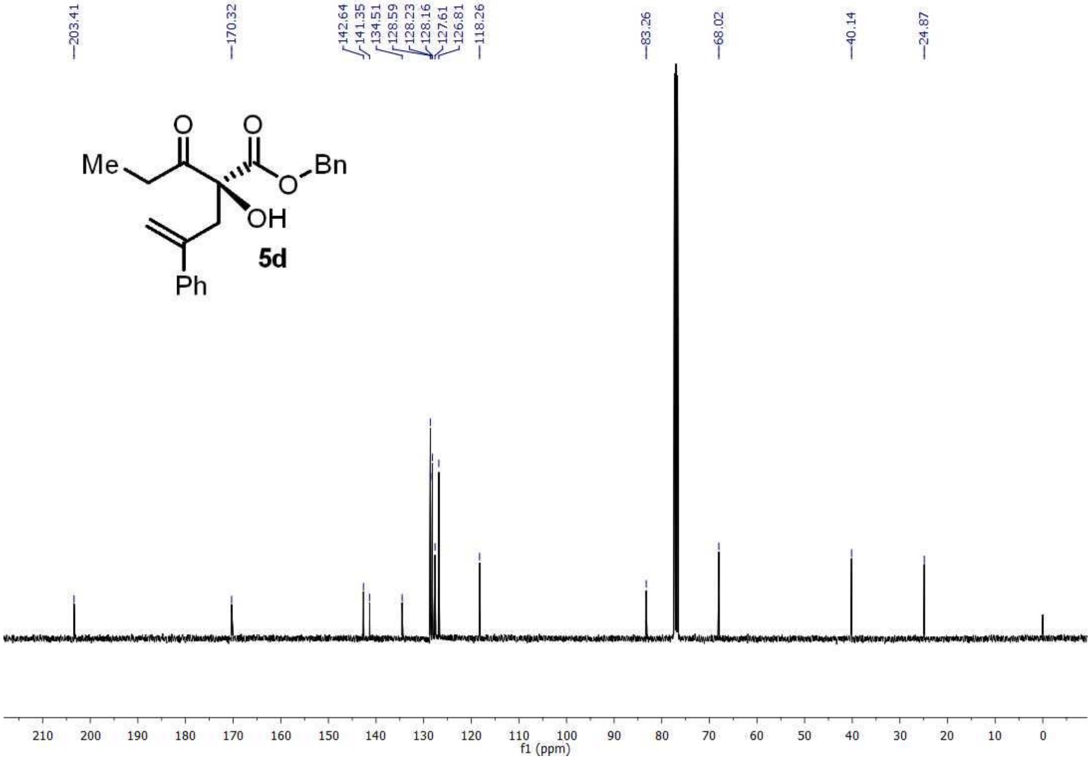
f1 (ppm)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24.87
Me
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O
O
Bn
OH
Ph
5d
210
200
190
180
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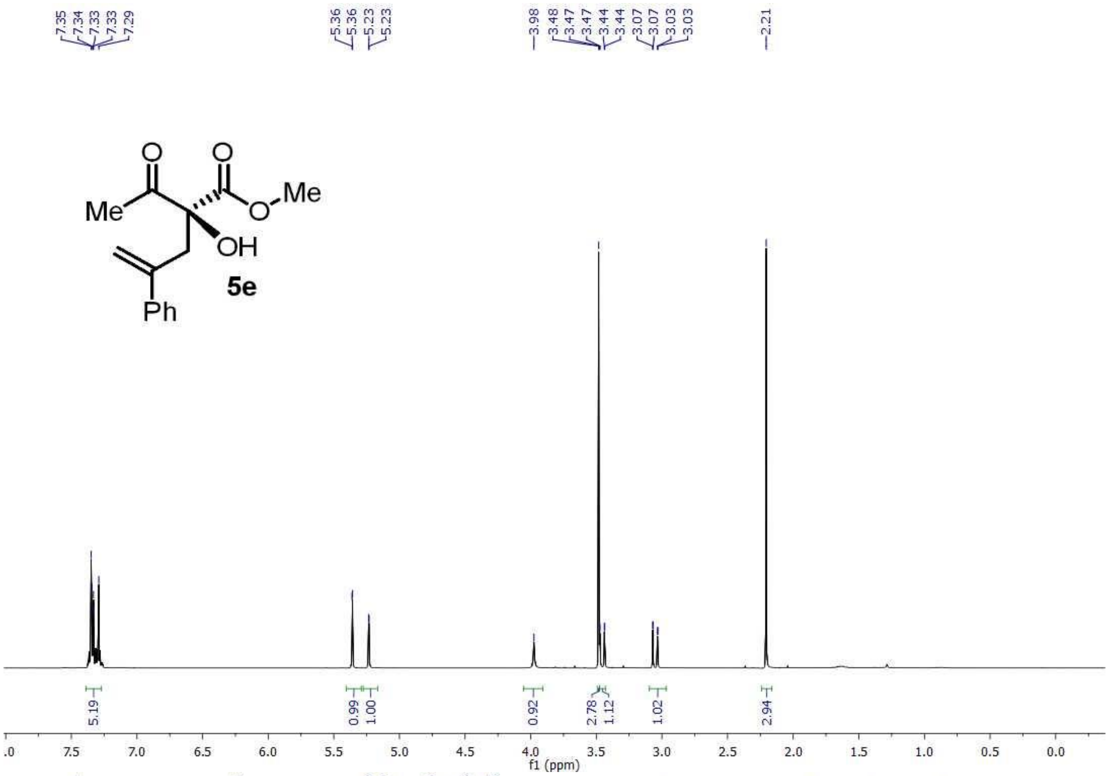
f1 (ppm)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3.44
3.07
3.07
3.03
3.03
2.21
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Me
O
Me
OH
Ph
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1.00
0.92
2.78
1.12
1.02
2.94
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7.0
6.5
6.0
5.5
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1.0
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0.0
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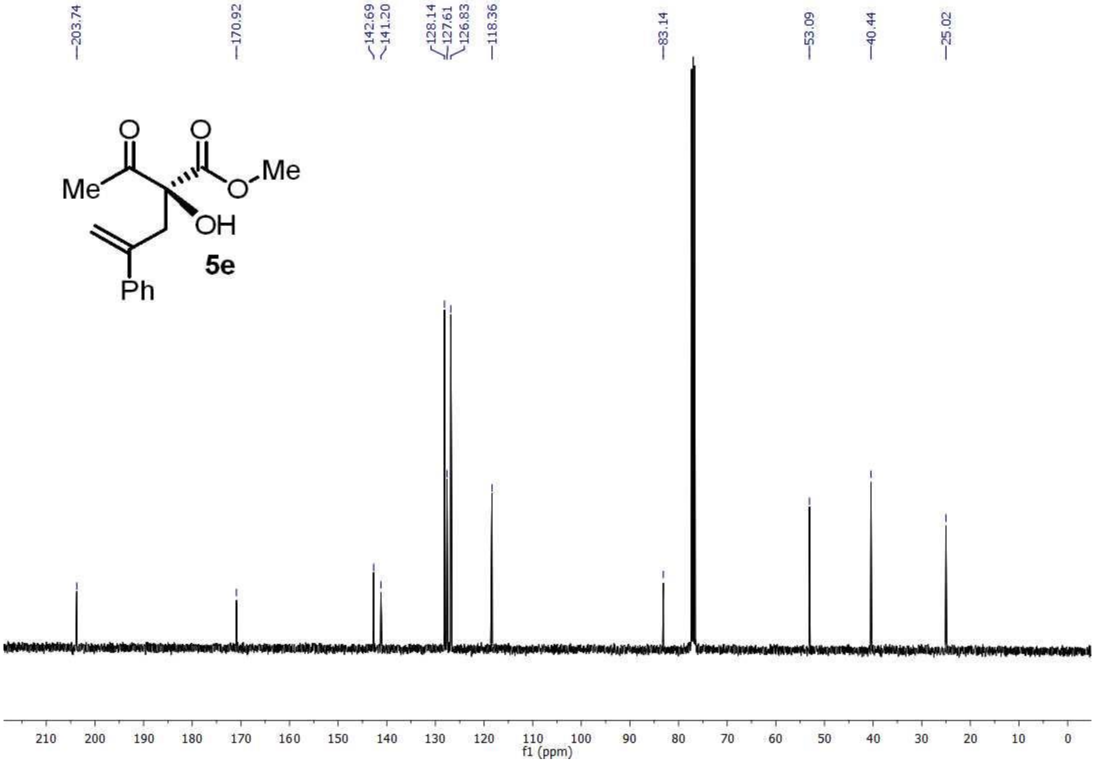
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118.36
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53.09
40.44
25.02
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O
Me
O
Me
OH
Ph
5e
210
200
190
180
170
160
150
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130
120
110
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90
80
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50
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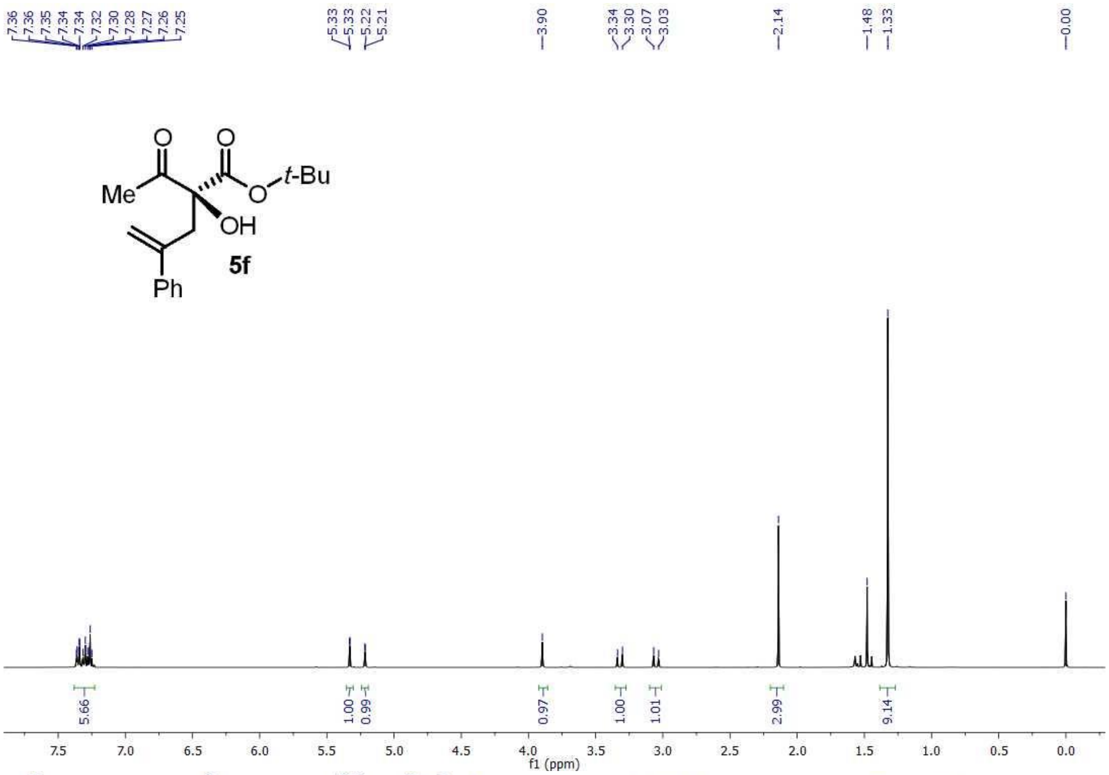
20
10
0
f1 (ppm)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5.33
5.22
5.21
3.90
3.34
3.30
3.07
3.03
2.14
1.48
1.33
0.00
Me
O
O
O
t-Bu
OH
Ph
5f
5.66
1.00
0.99
0.97
1.00
1.01
2.99
9.14
7.5
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6.5
6.0
5.5
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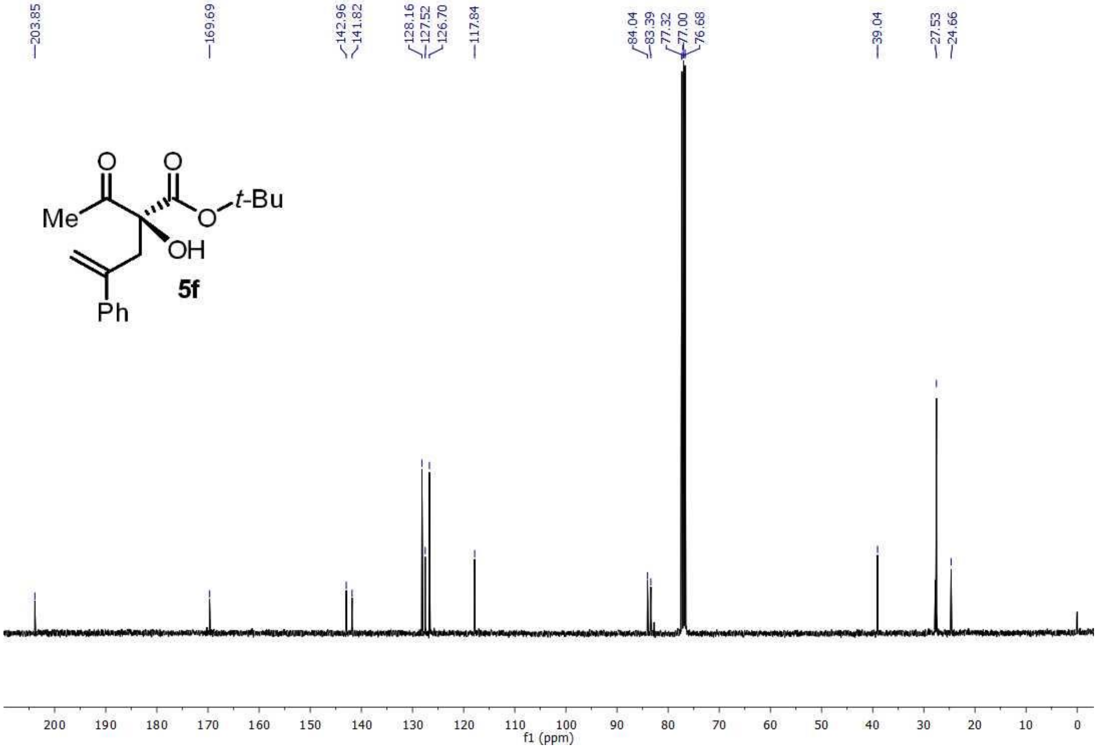
f1 (ppm)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39.04
27.53
24.66
Me
O
O
O
t-Bu
OH
Ph
5f
200
190
180
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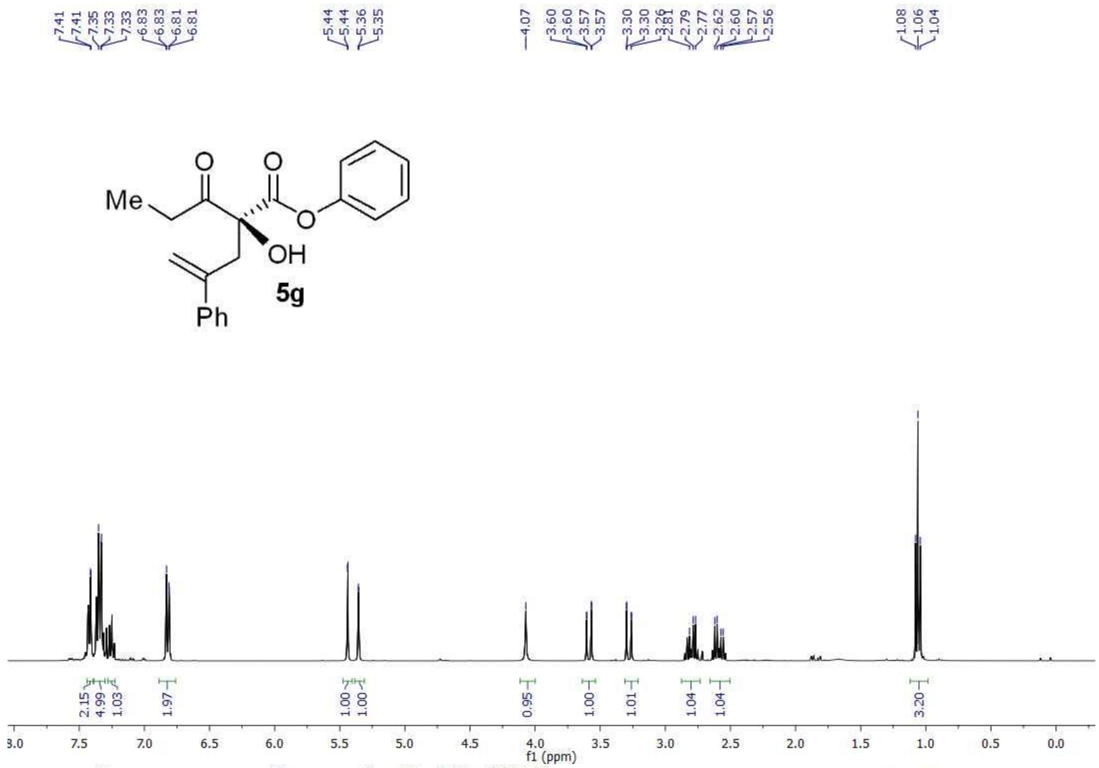
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4.07
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3.60
3.57
3.57
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3.30
3.26
2.81
2.79
2.77
2.62
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1.06
1.04
Me
O
O
O
OH
Ph
5g
2.15
4.99
1.03
1.97
1.00
1.00
0.95
1.00
1.01
1.04
1.04
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6.0
5.5
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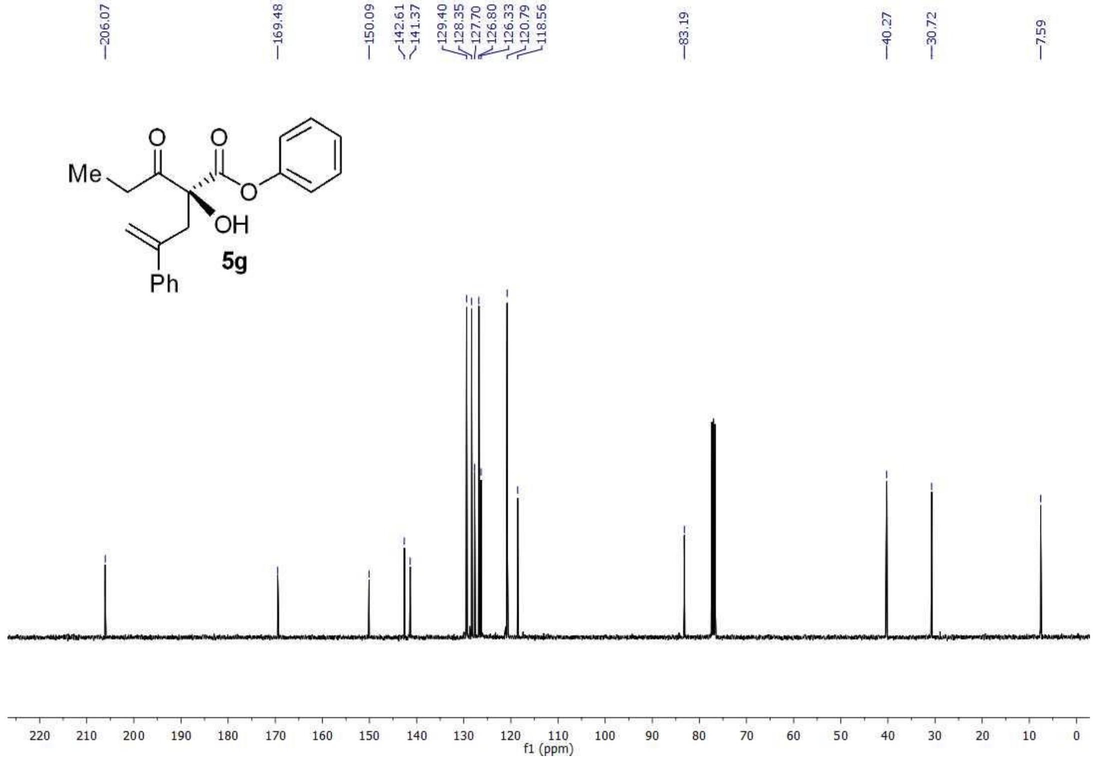
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30.72
7.59
Me
O
O
O
OH
Ph
5g
220
210
200
190
180
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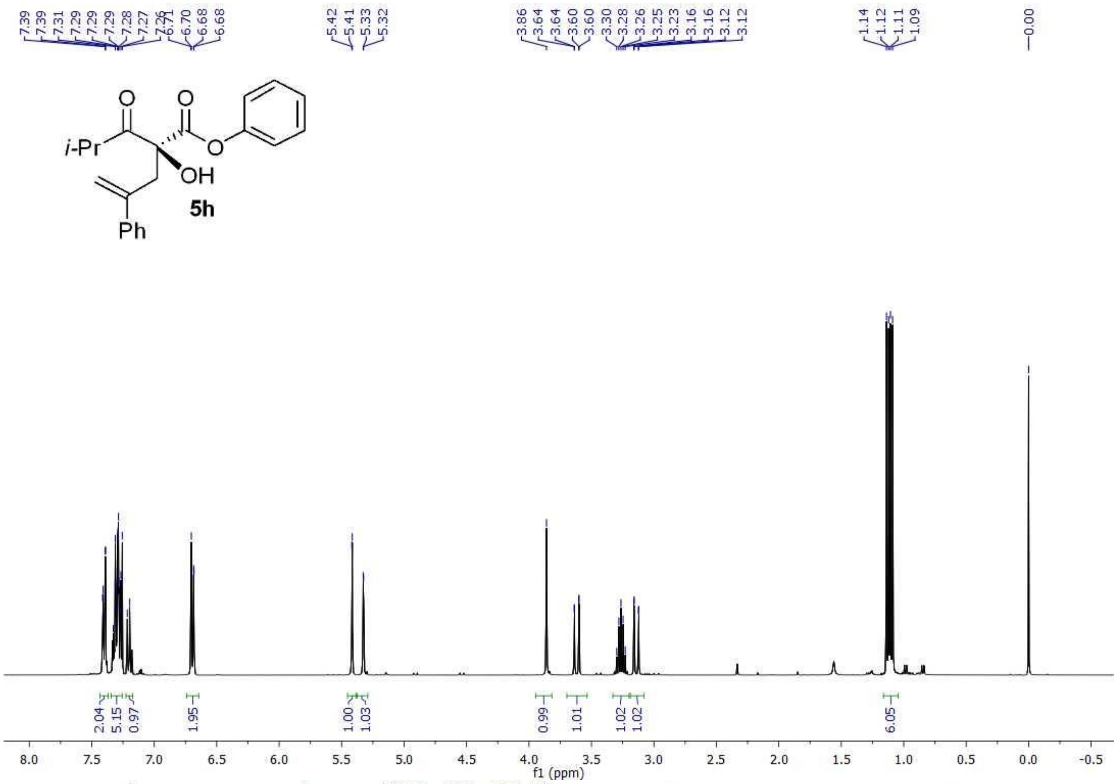
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5.41
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3.25
3.23
3.16
3.12
3.12
1.14
1.12
1.11
1.09
0.00
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O
O
OH
Ph
5h
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1.95
1.00
1.03
0.99
1.01
1.02
1.02
6.05
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7.0
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5.0
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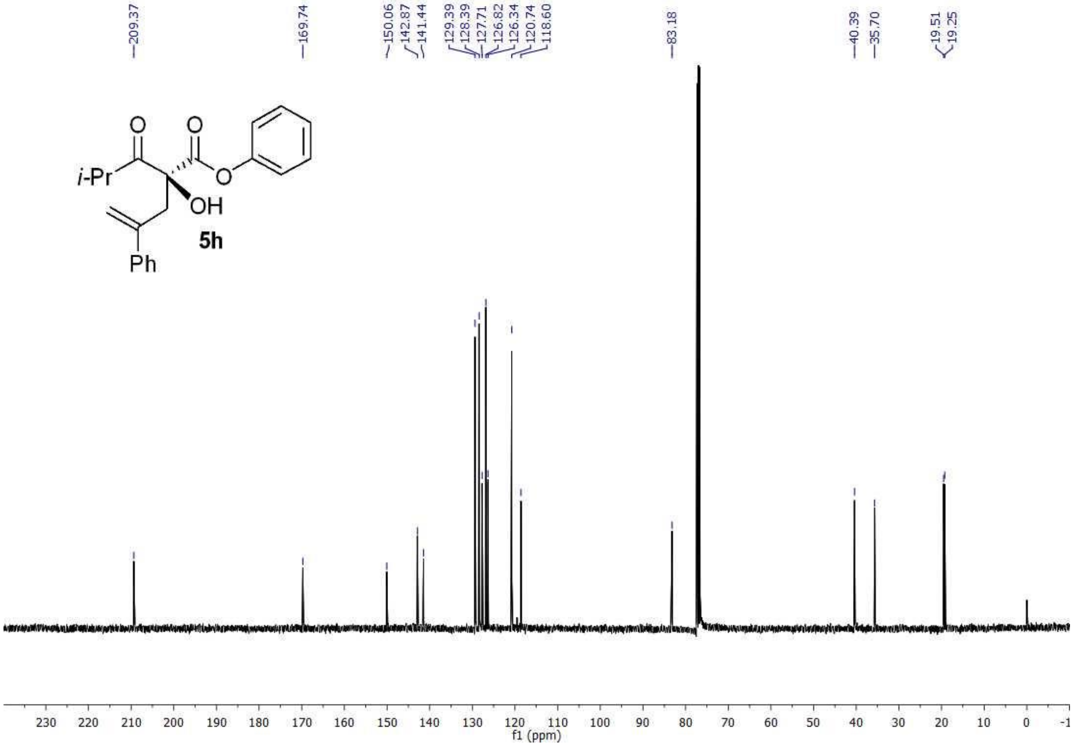
f1 (ppm)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35.70
19.51
19.25
i-Pr
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O
O
OH
Ph
5h
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180
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100
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80
70
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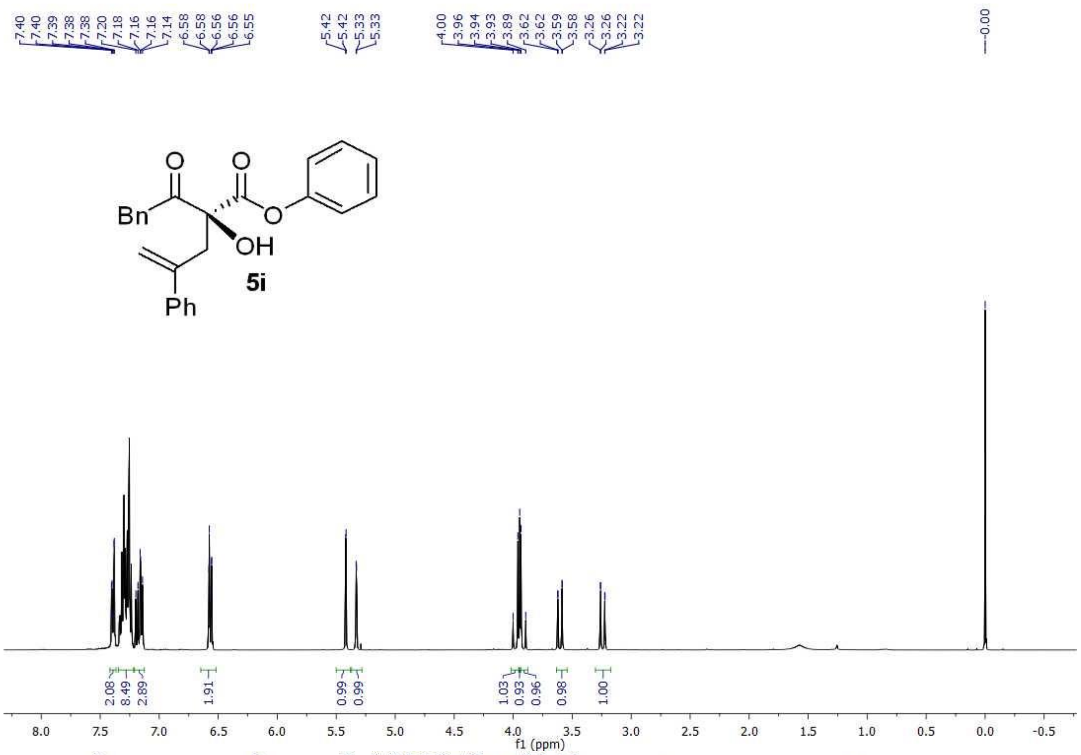
f1 (ppm)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5.42
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3.94
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3.89
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3.62
3.59
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3.26
3.26
3.22
3.22
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O
Bn
O
OH
Ph
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6.0
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5.0
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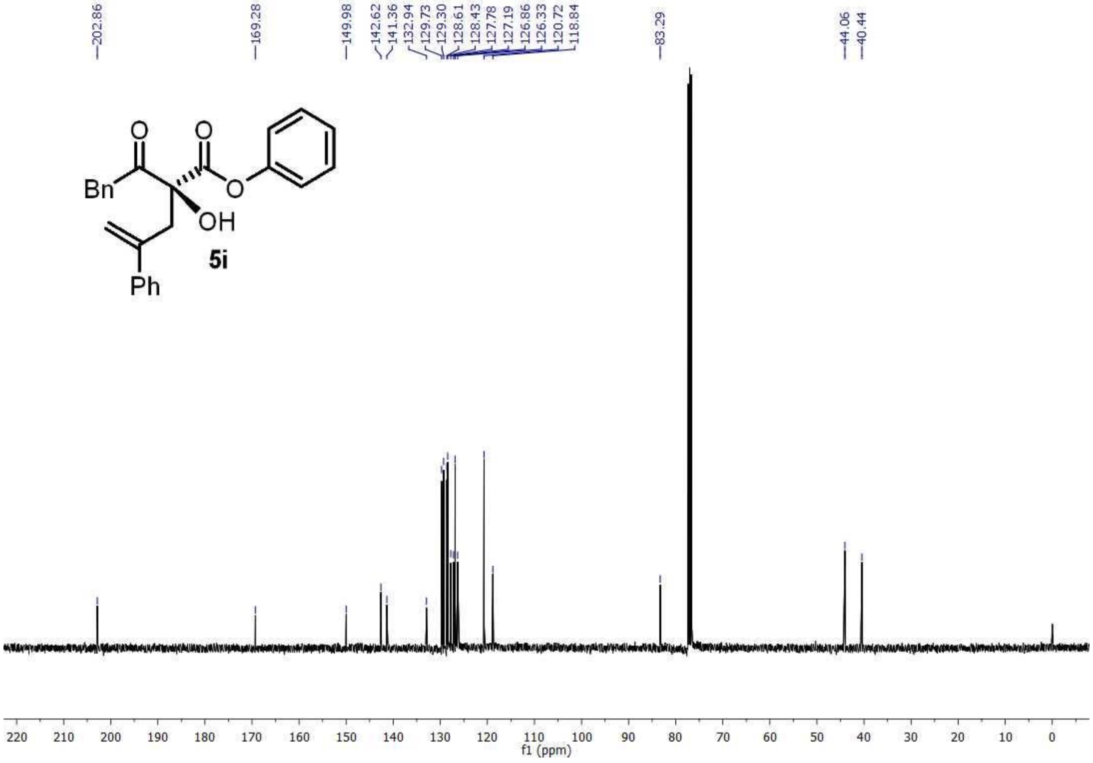
f1 (ppm)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44.06
40.44
O
O
Bn
O
OH
Ph
5i
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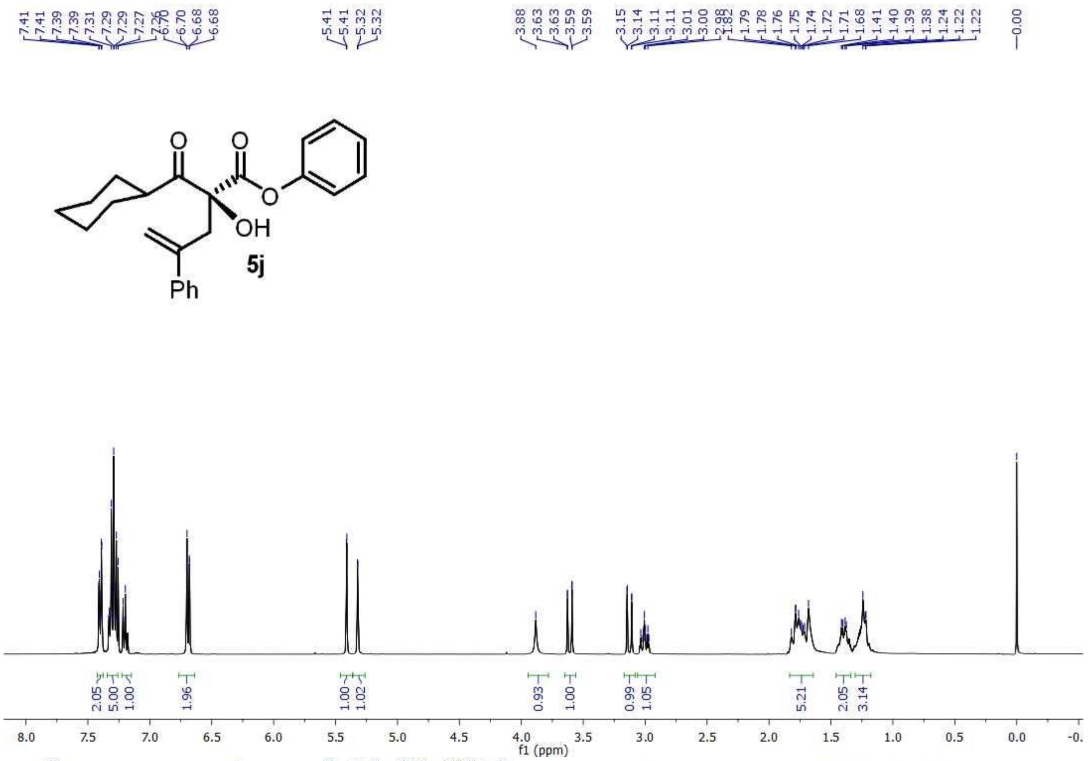
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1.39
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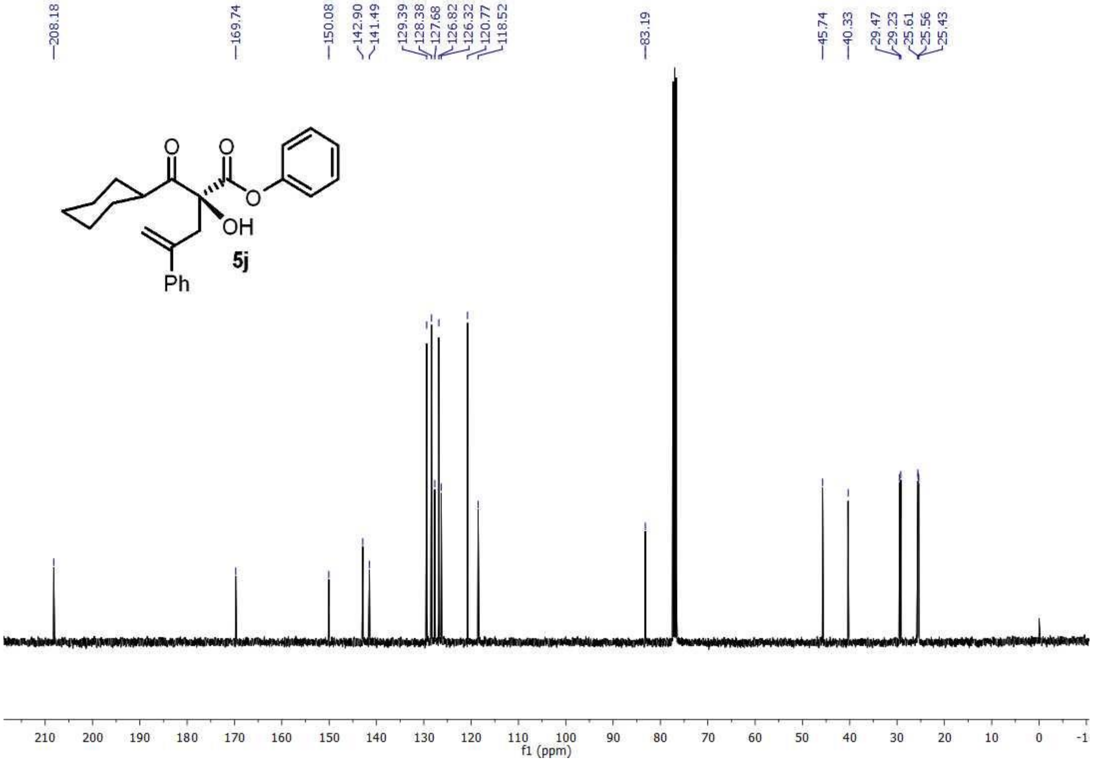
-0.
f1 (ppm)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29.47
29.23
25.61
25.56
25.43
O
O
O
OH
Ph
5j
210
200
190
180
170
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100
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80
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30
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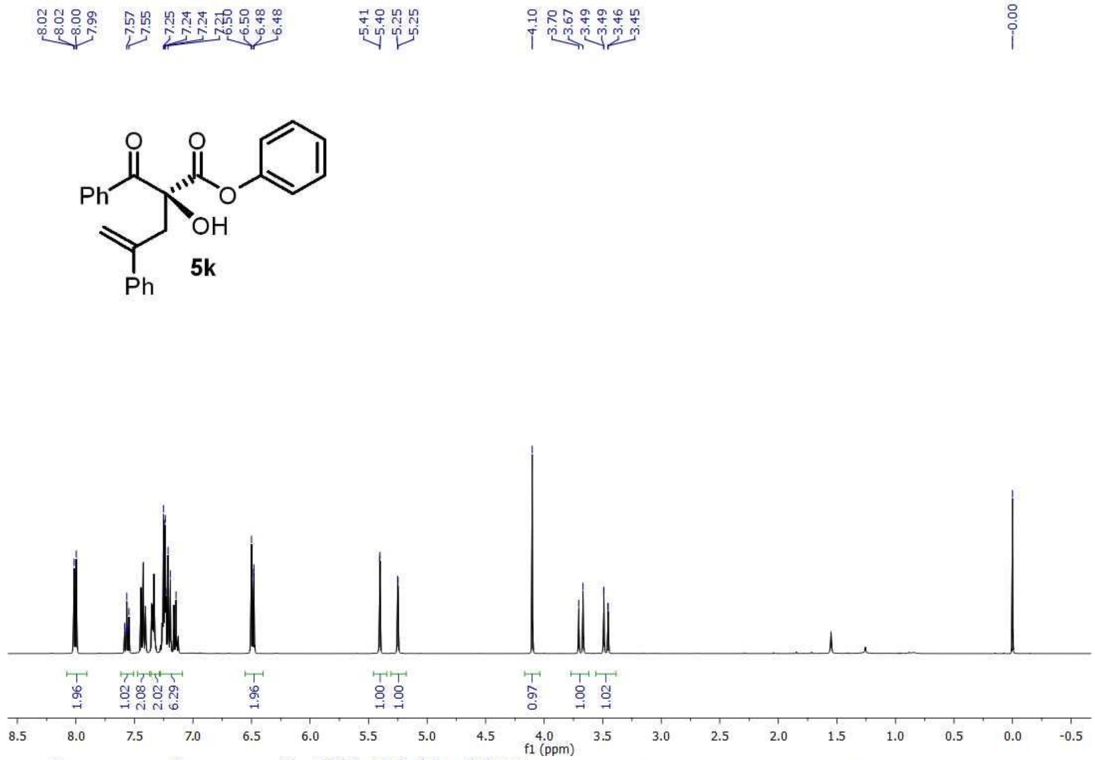
10
0
-1
f1 (ppm)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6.48
5.41
5.40
5.25
5.25
4.10
3.70
3.67
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3.46
3.45
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O
Ph
O
OH
Ph
5k
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1.02
2.08
2.02
6.29
1.96
1.00
1.00
0.97
1.00
1.02
8.5
8.0
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7.0
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6.0
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5.0
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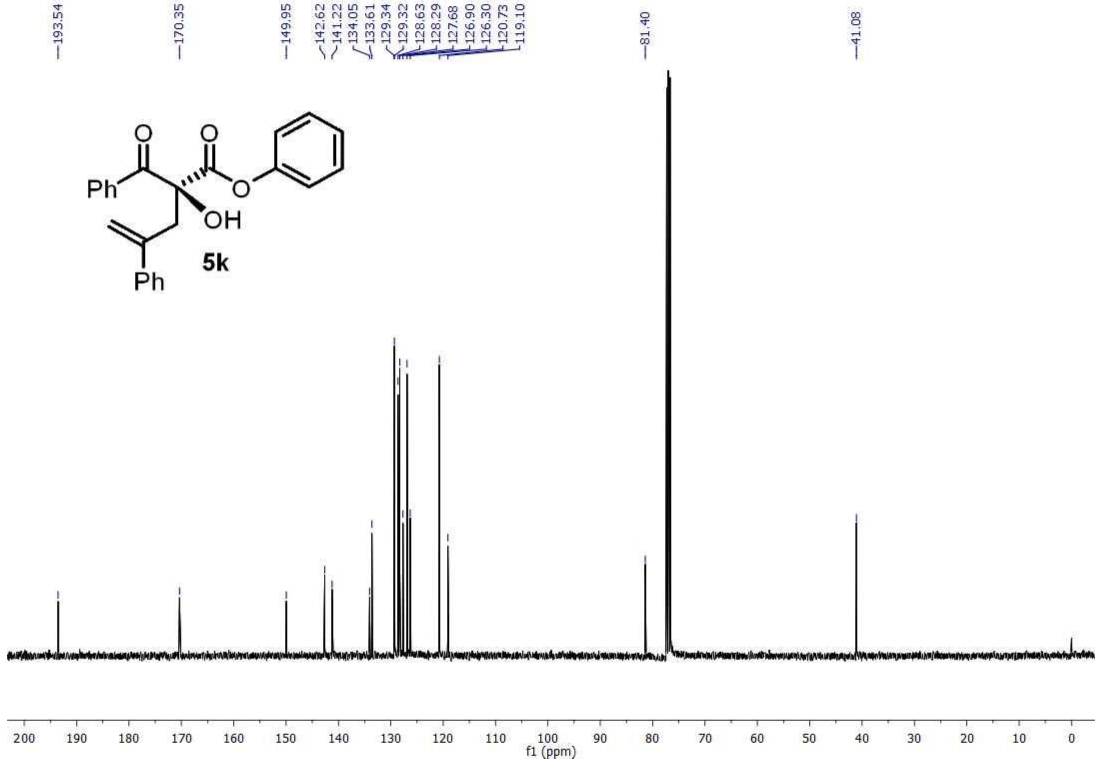
f1 (ppm)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120.73
119.10
81.40
41.08
O
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Ph
O
OH
Ph
5k
200
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180
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0
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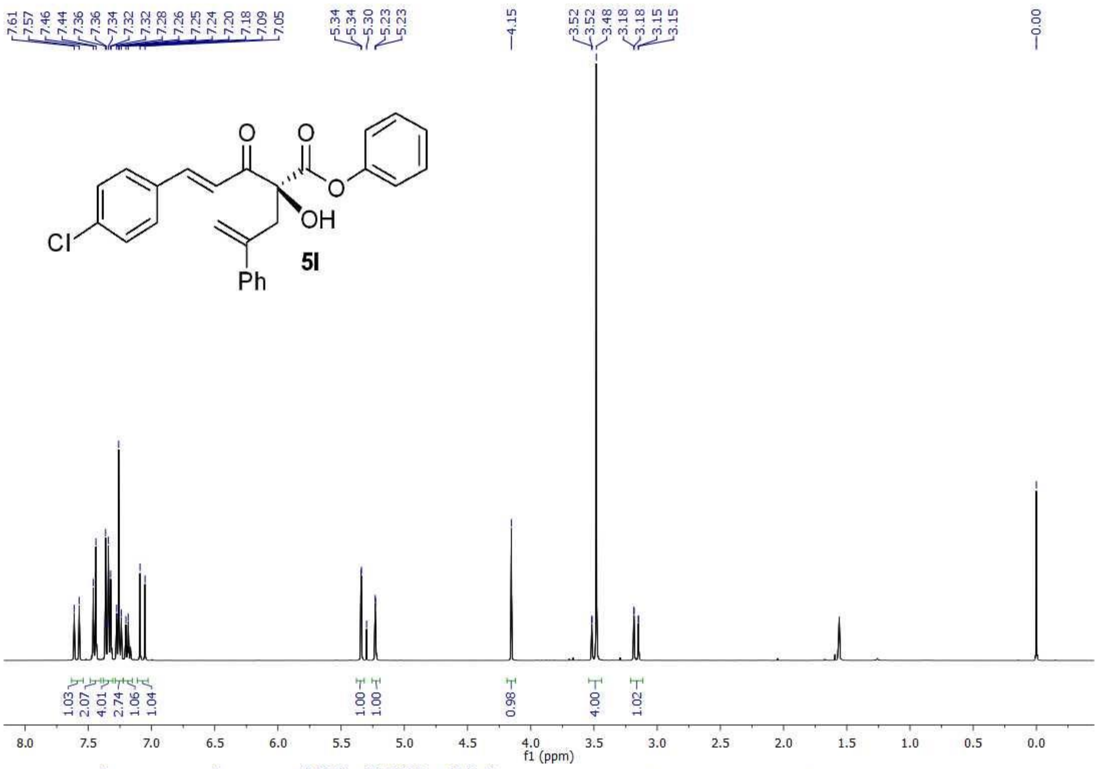
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7.05
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5.34
5.30
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5.23
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3.52
3.52
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3.18
3.15
3.15
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O
OH
Cl
Ph
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2.07
4.01
2.74
1.06
1.04
1.00
1.00
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4.00
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6.0
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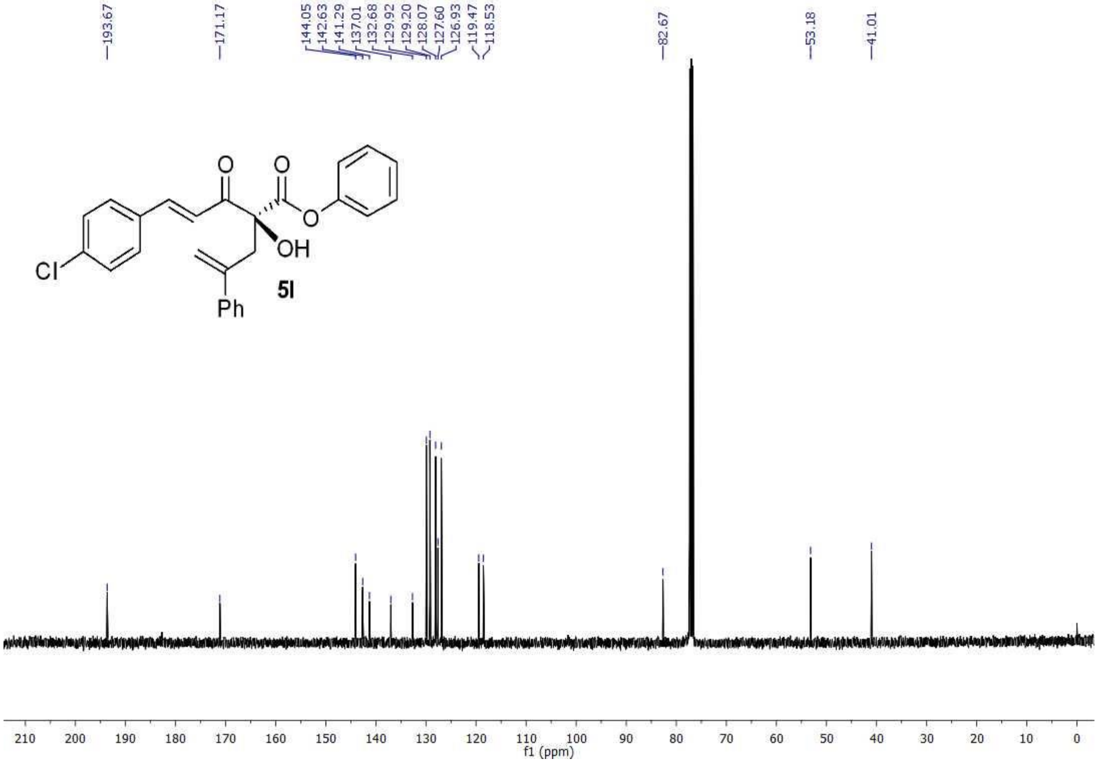
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O
O
OH
Cl
Ph
5l
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180
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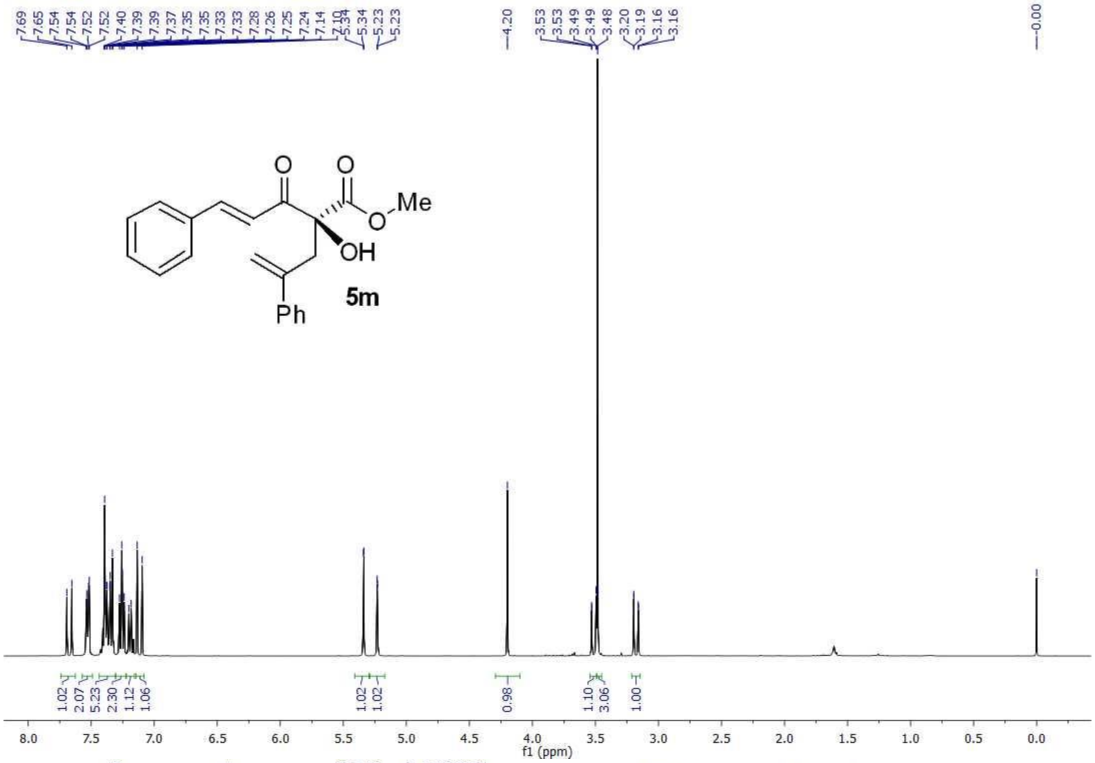
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3.48
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O
Me
OH
Ph
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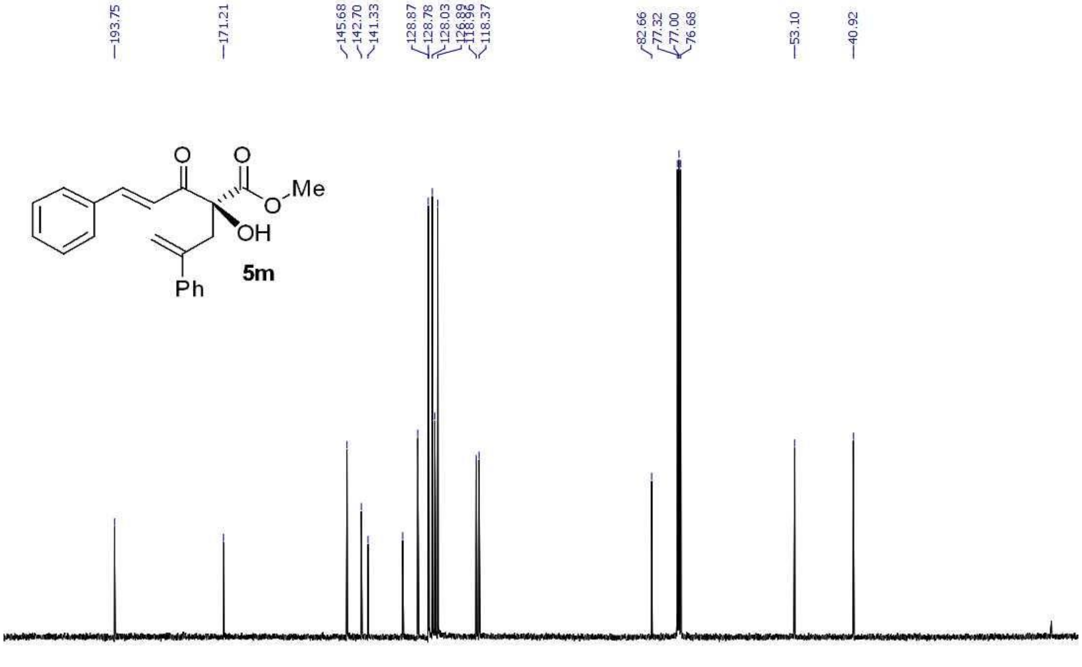
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O
O
Me
OH
Ph
5m
210
200
190
180
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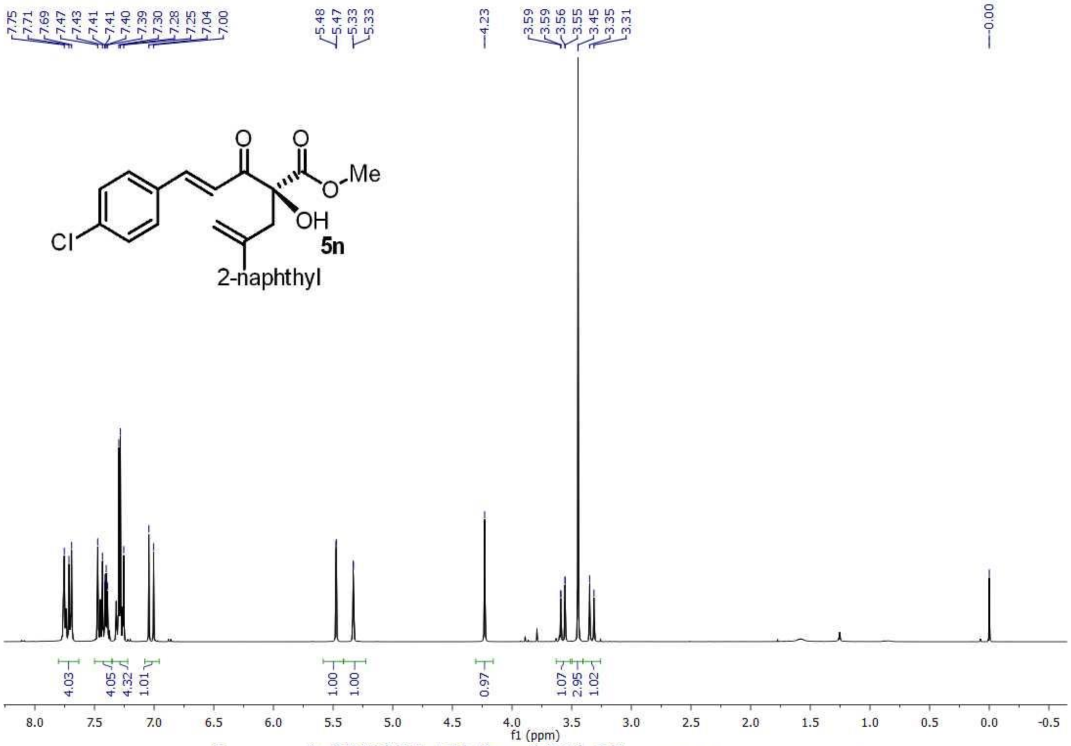
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OH
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1.00
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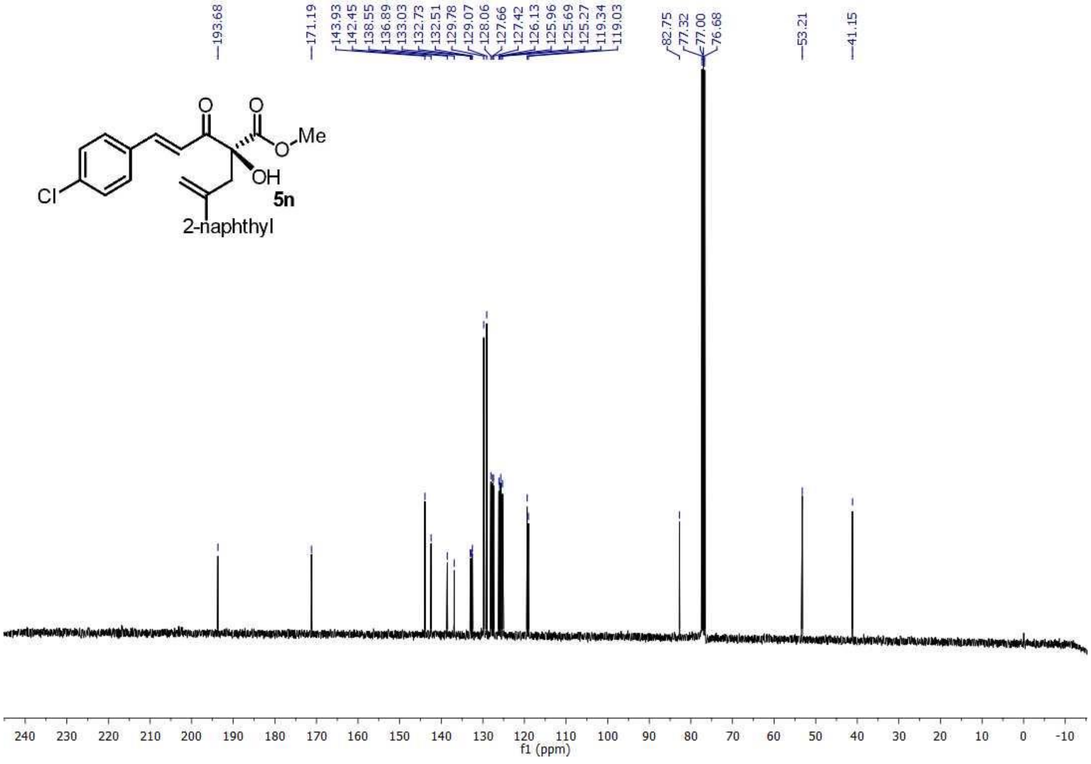
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77.00
76.68
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41.15
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O
O
Me
OH
Cl
5n
2-naphthyl
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180
170
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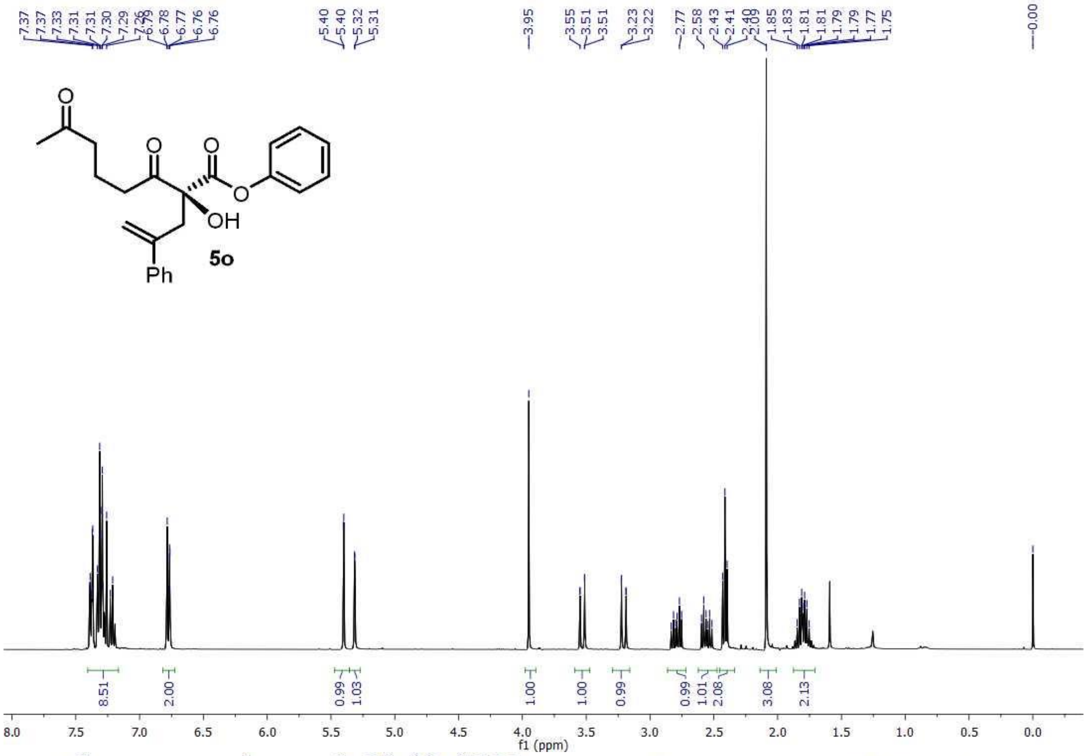
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5.40
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3.23
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1.79
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5o
OH
Ph
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1.00
1.00
0.99
0.99
1.01
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3.08
2.13
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6.0
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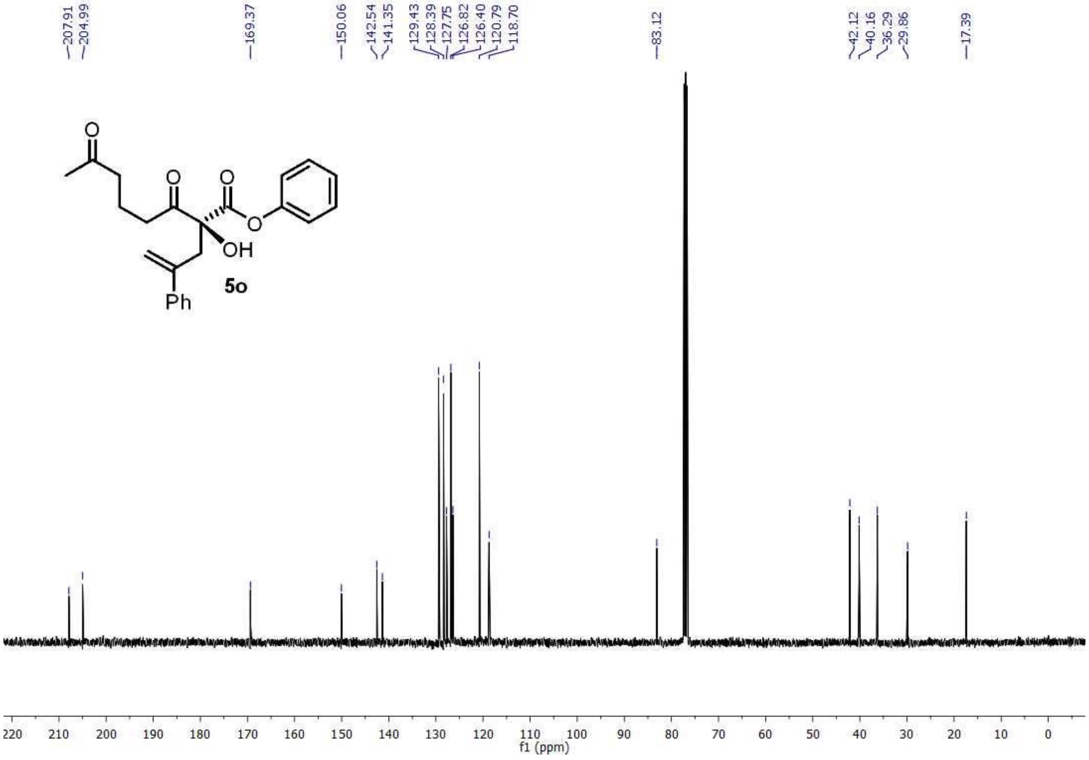
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118.70
83.12
42.12
40.16
36.29
29.86
17.39
5o
OH
Ph
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210
200
190
180
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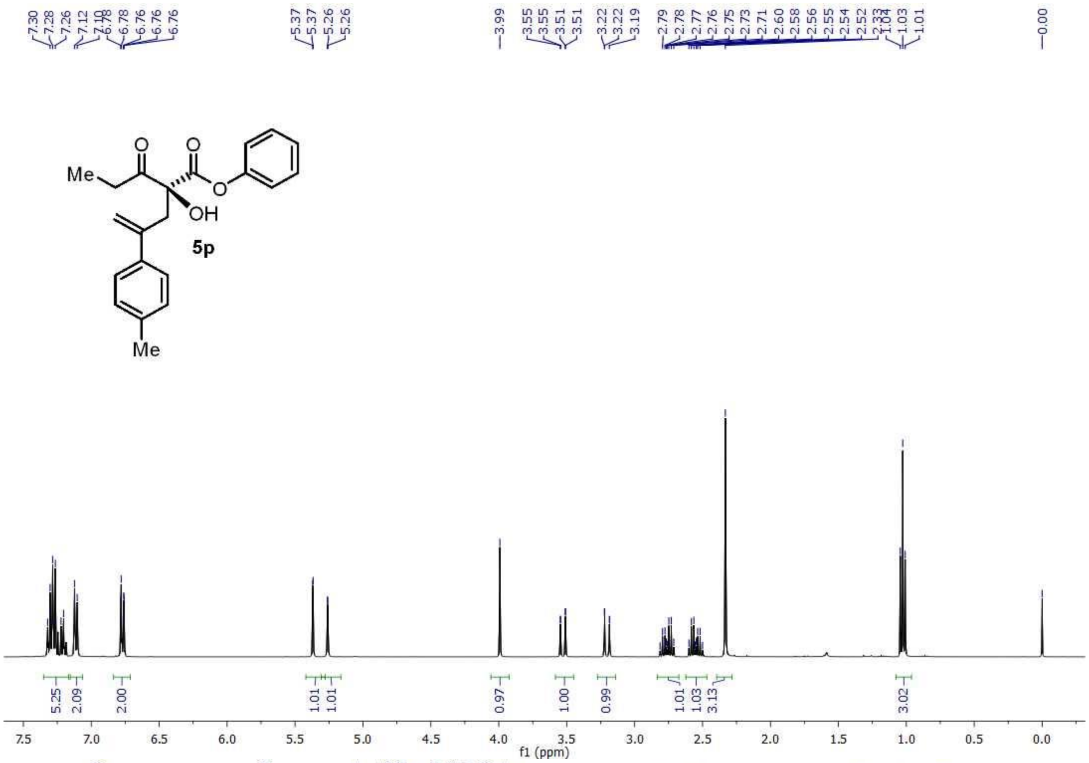
f1 (ppm)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5.37
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5.26
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3.55
3.55
3.51
3.51
3.22
3.22
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2.78
2.77
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2.73
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2.56
2.55
2.54
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O
O
OH
Me
5.25
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1.01
1.01
0.97
1.00
0.99
1.01
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3.02
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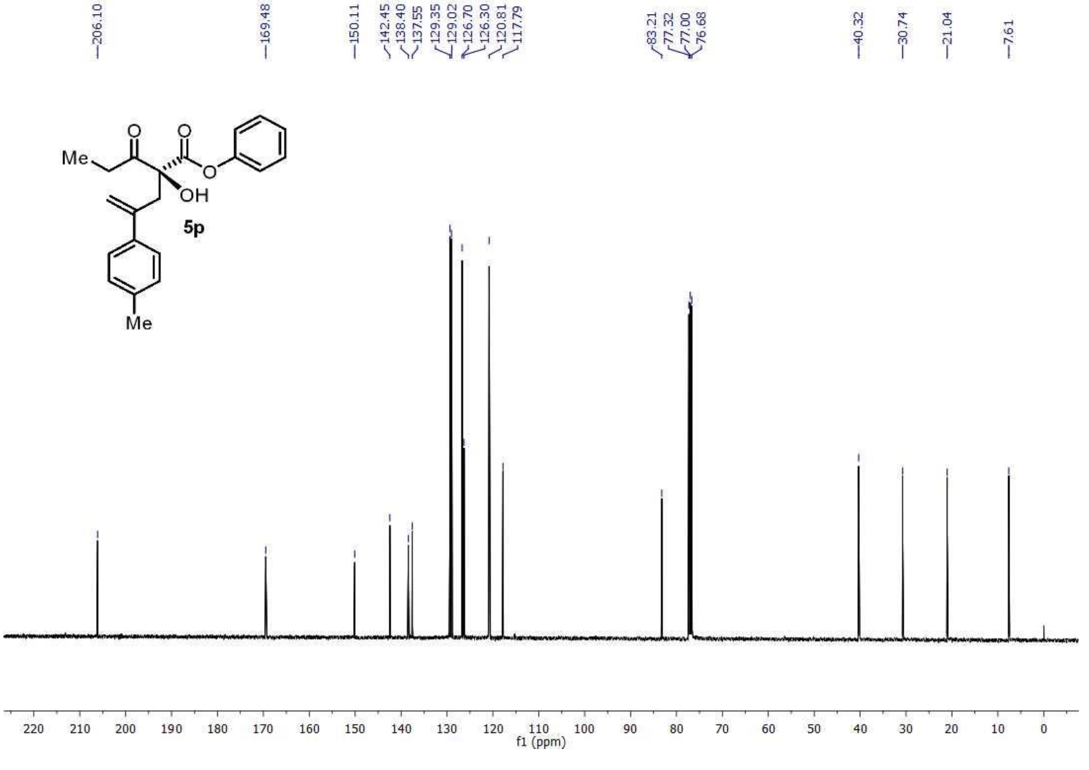
0.0
f1 (ppm)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77.00
76.68
40.32
30.74
21.04
7.61
Me
O
O
O
OH
Me
220
210
200
190
180
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10
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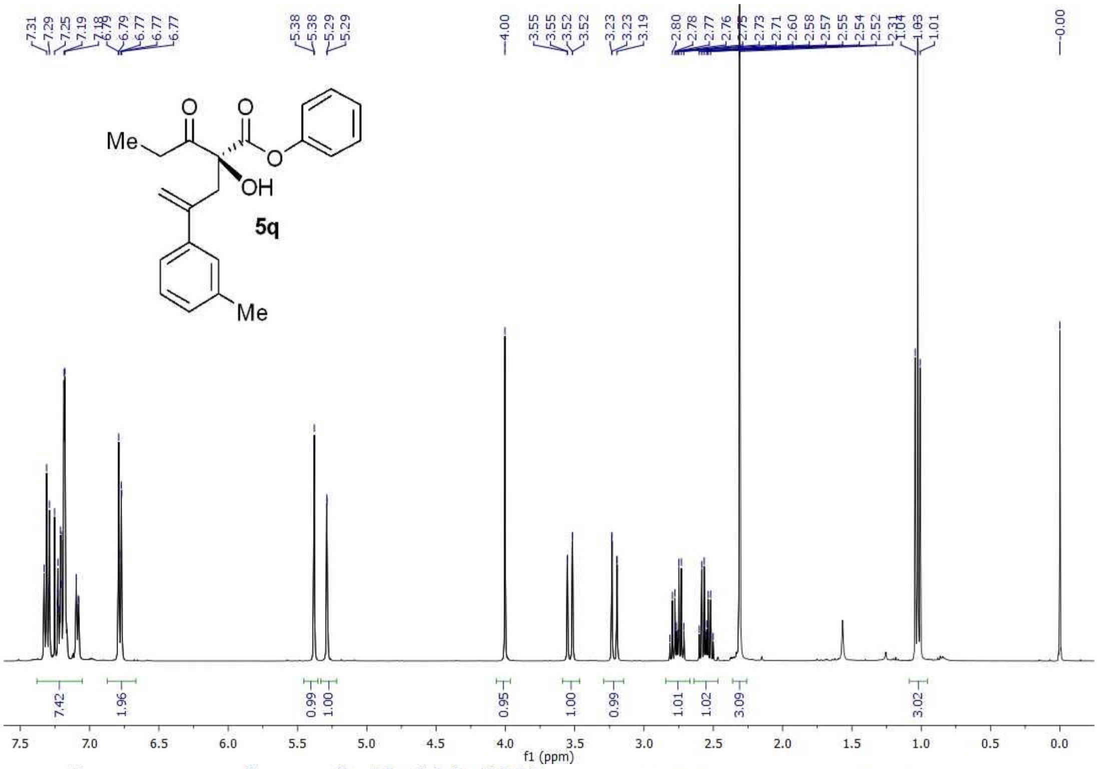
f1 (ppm)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3.55
3.52
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2.73
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2.57
2.55
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OH
Me
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5.5
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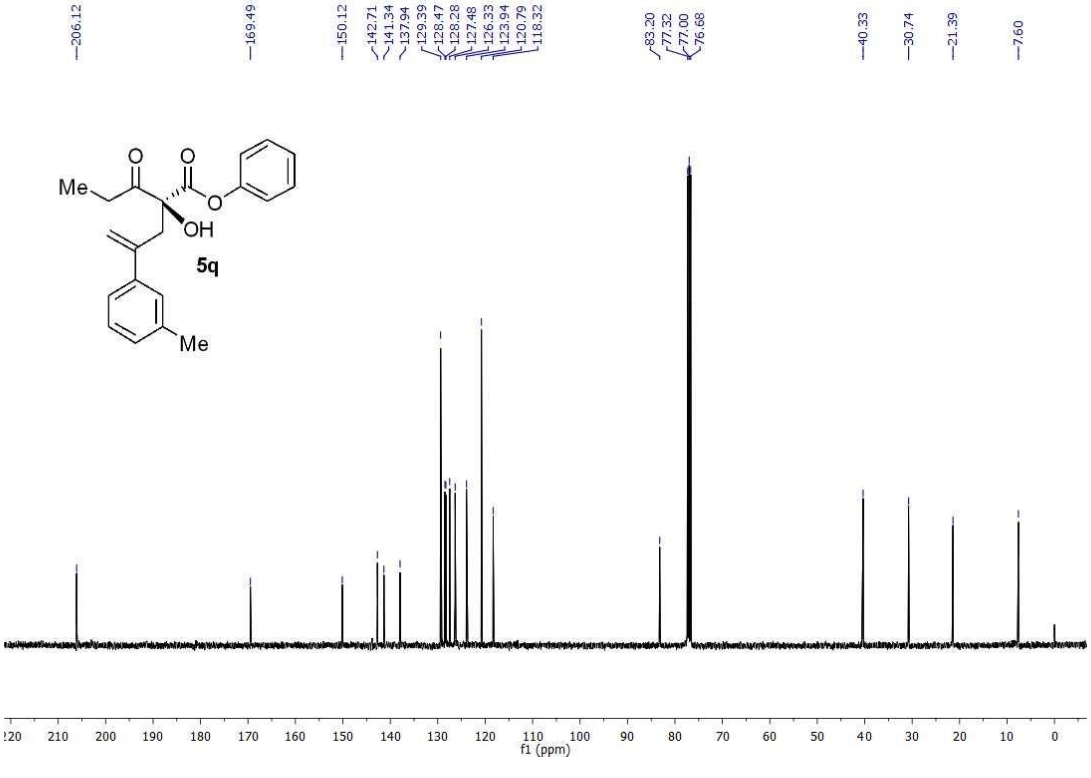
0.0
f1 (ppm)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77.00
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30.74
21.39
7.60
Me
O
O
O
OH
Me
5q
220
210
200
190
180
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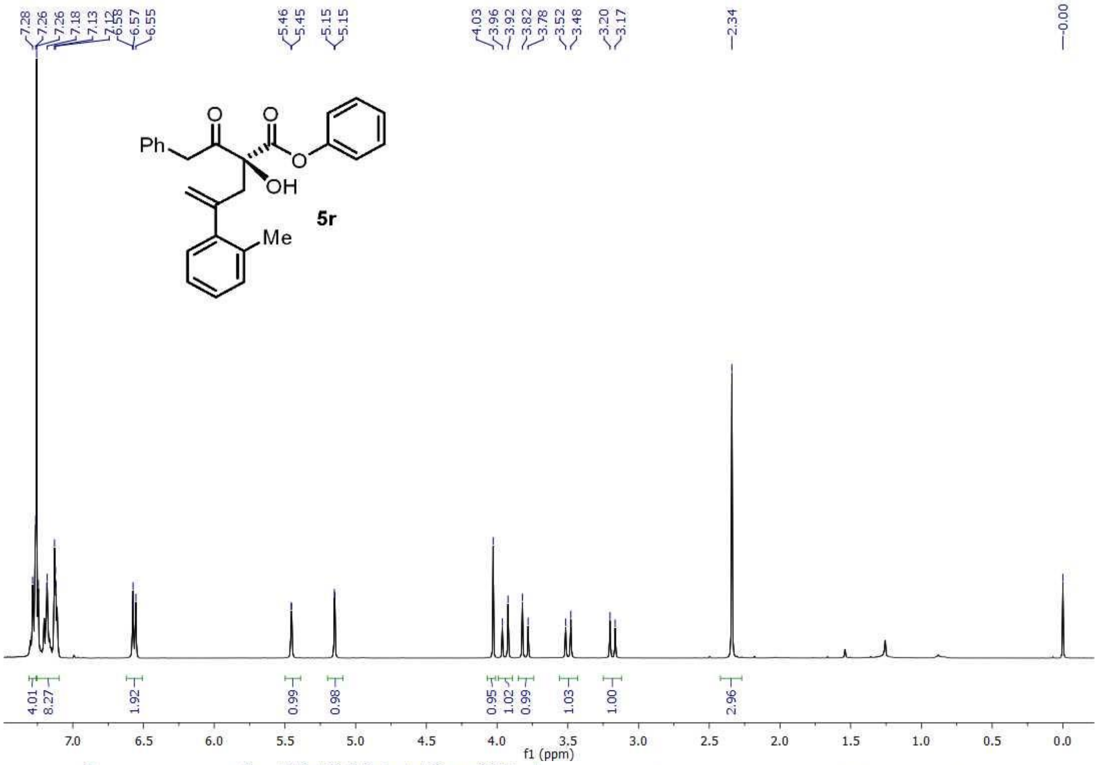
f1 (ppm)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OH
Me
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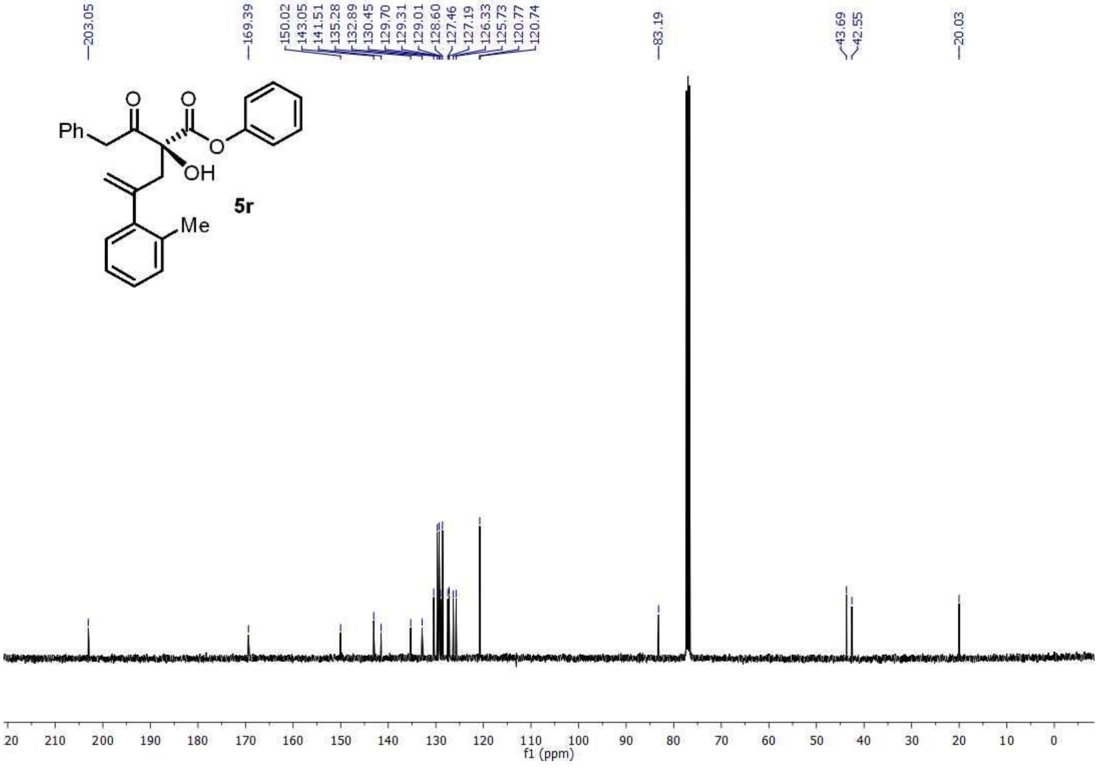
0.0
f1 (ppm)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Ph
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O
O
OH
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5r
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180
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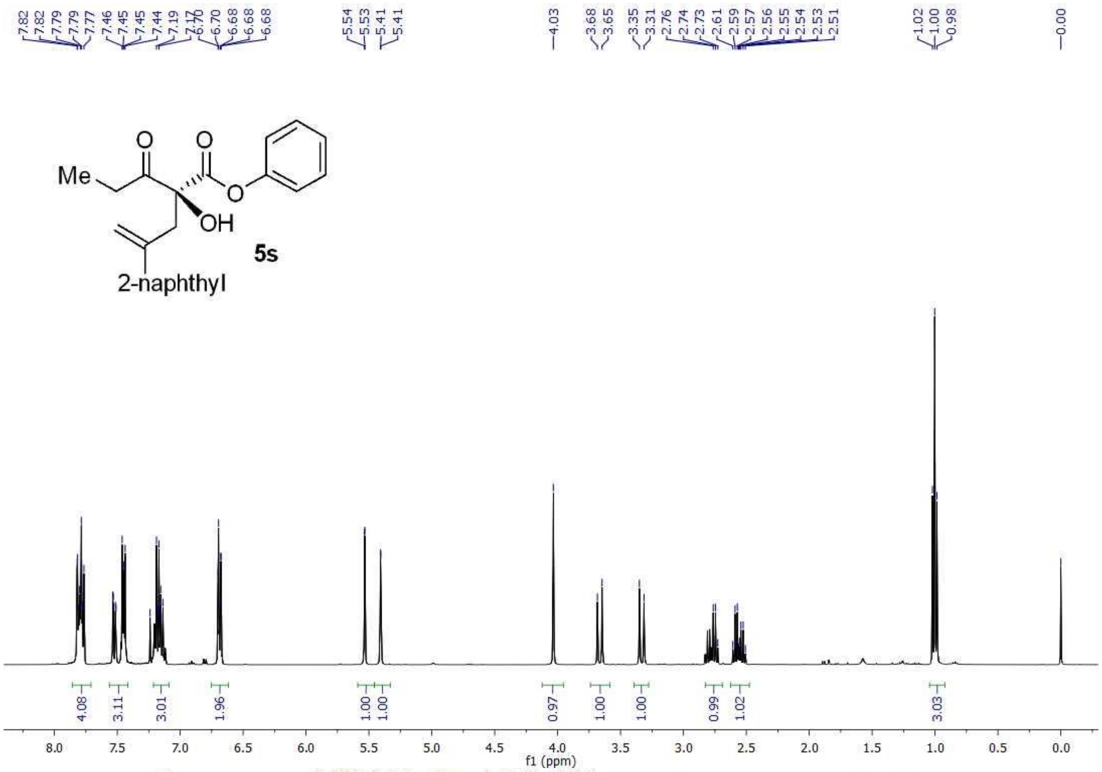
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6.68
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O
O
OH
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1.00
1.00
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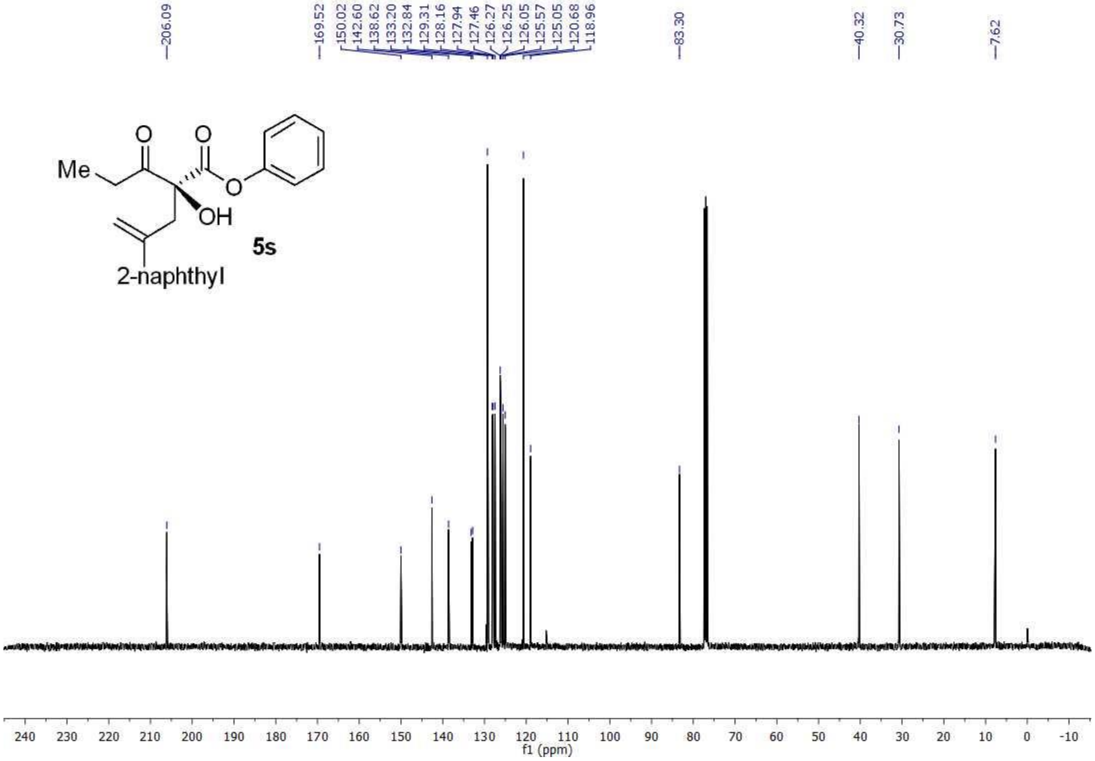
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O
OH
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2-naphthyl
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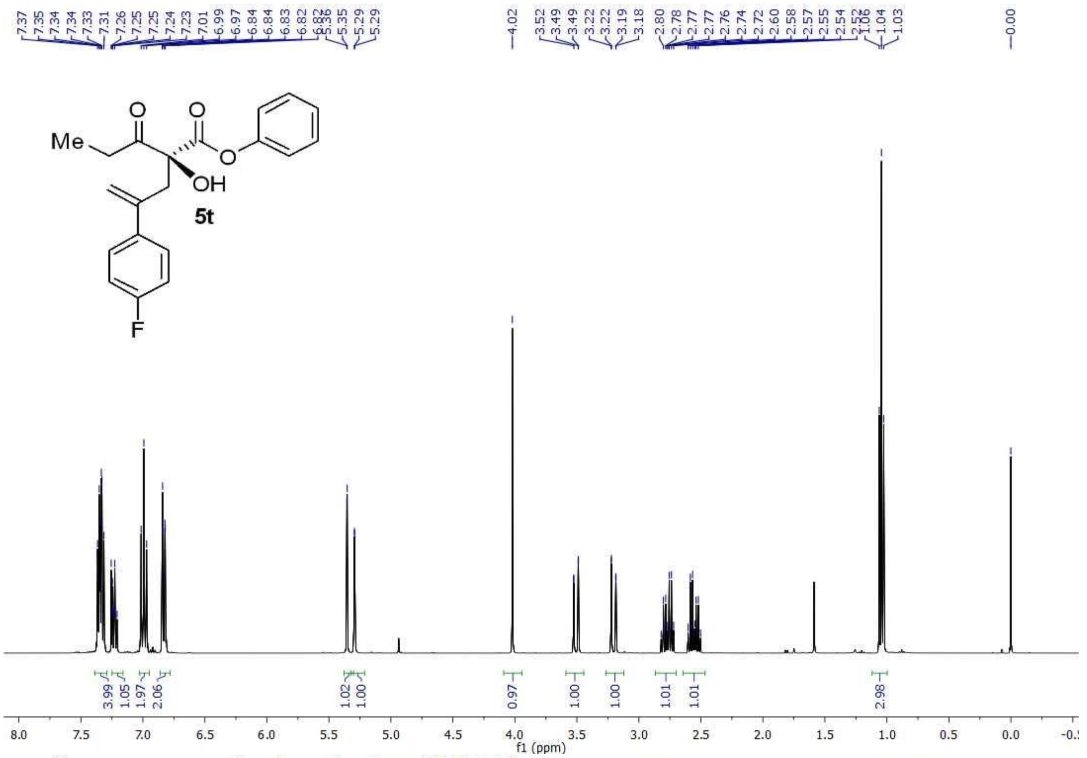
f1 (ppm)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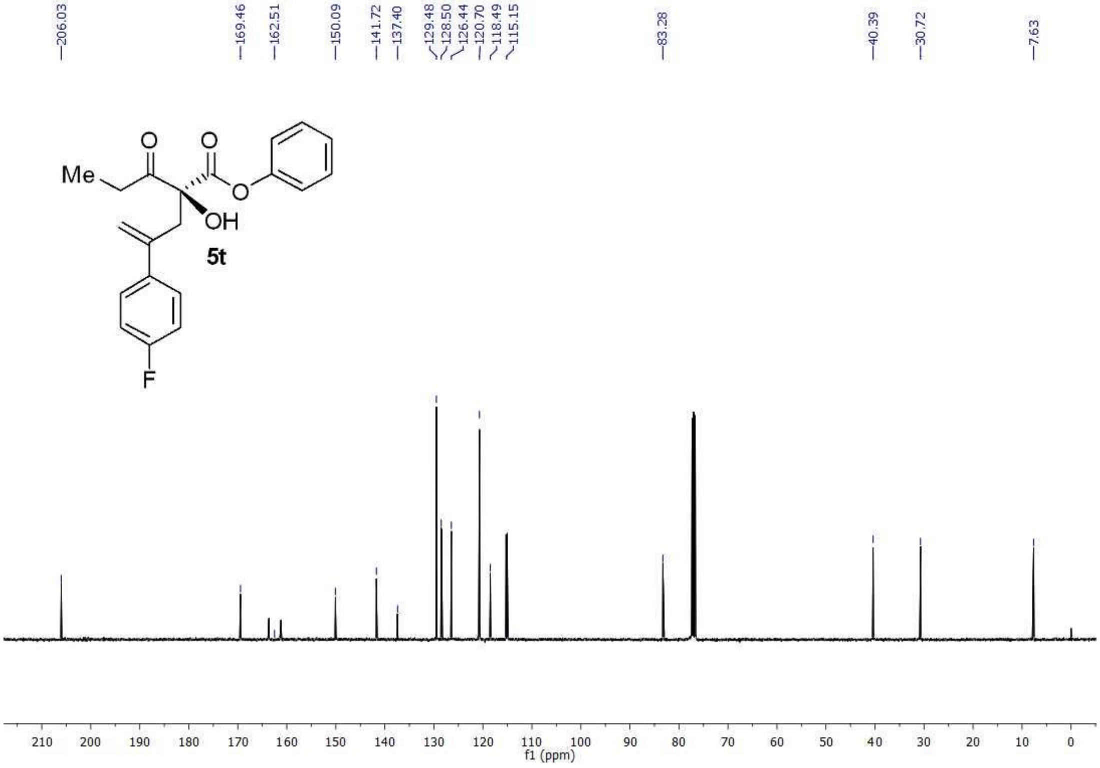
f1 (ppm)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F
5t
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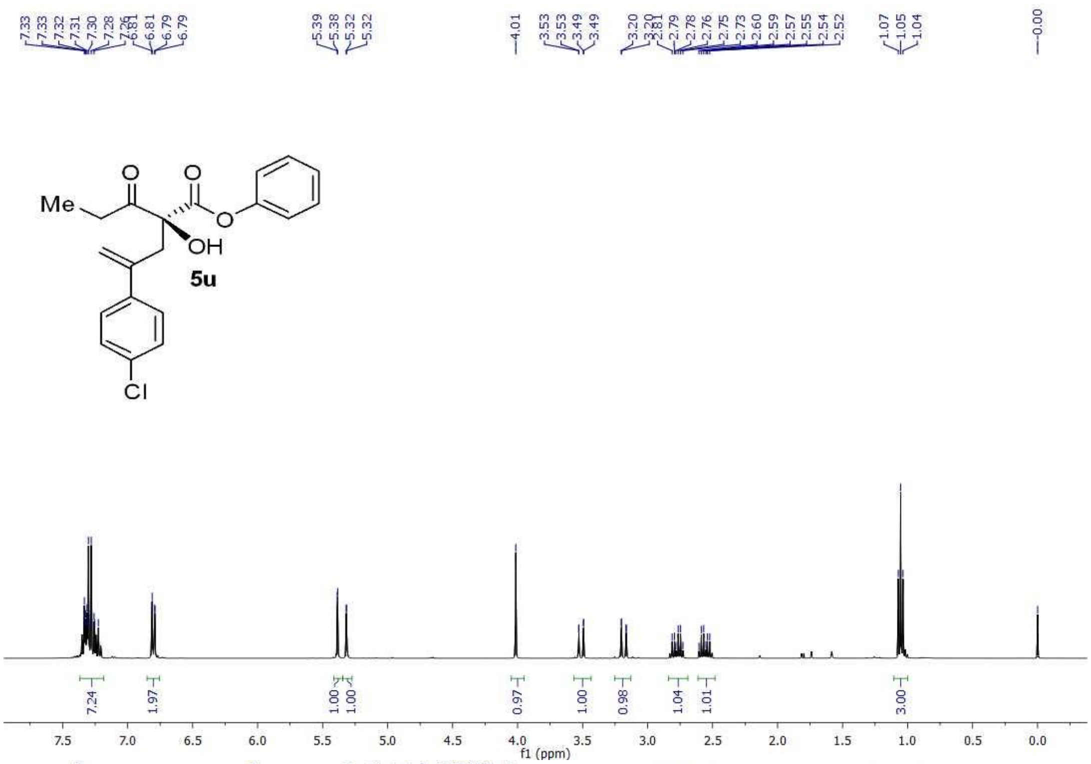
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2.76
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2.57
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O
OH
Cl
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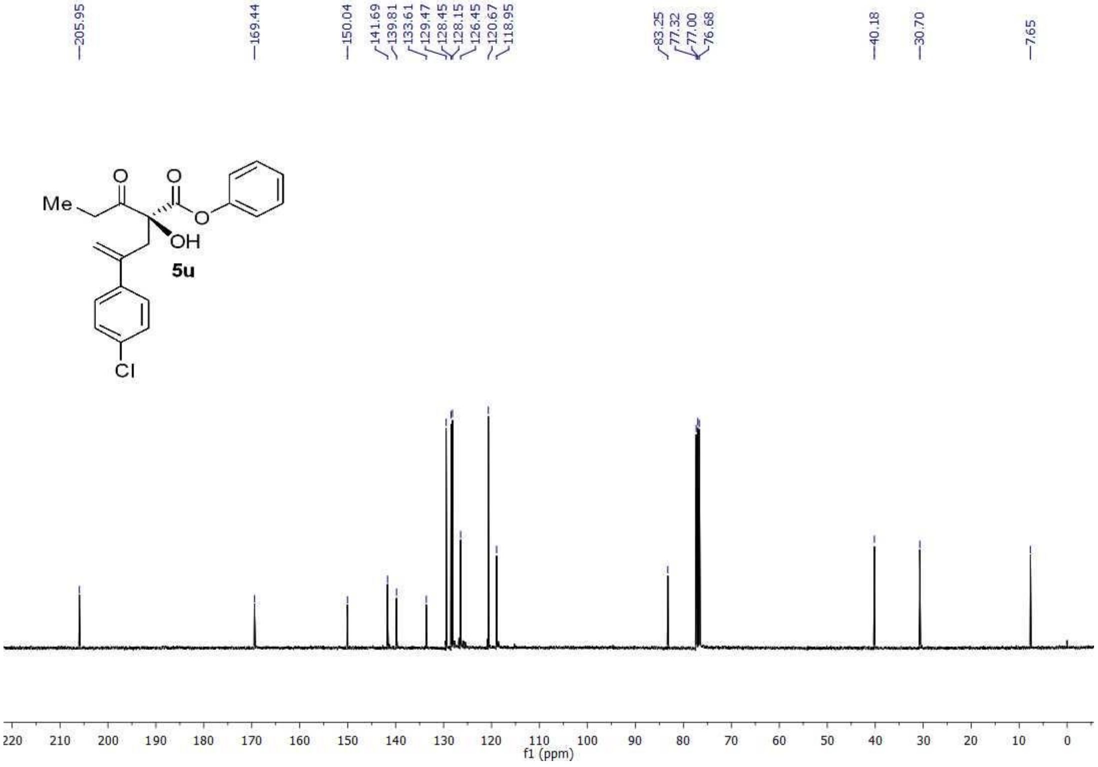
f1 (ppm)

5u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O
O
OH
Cl
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180
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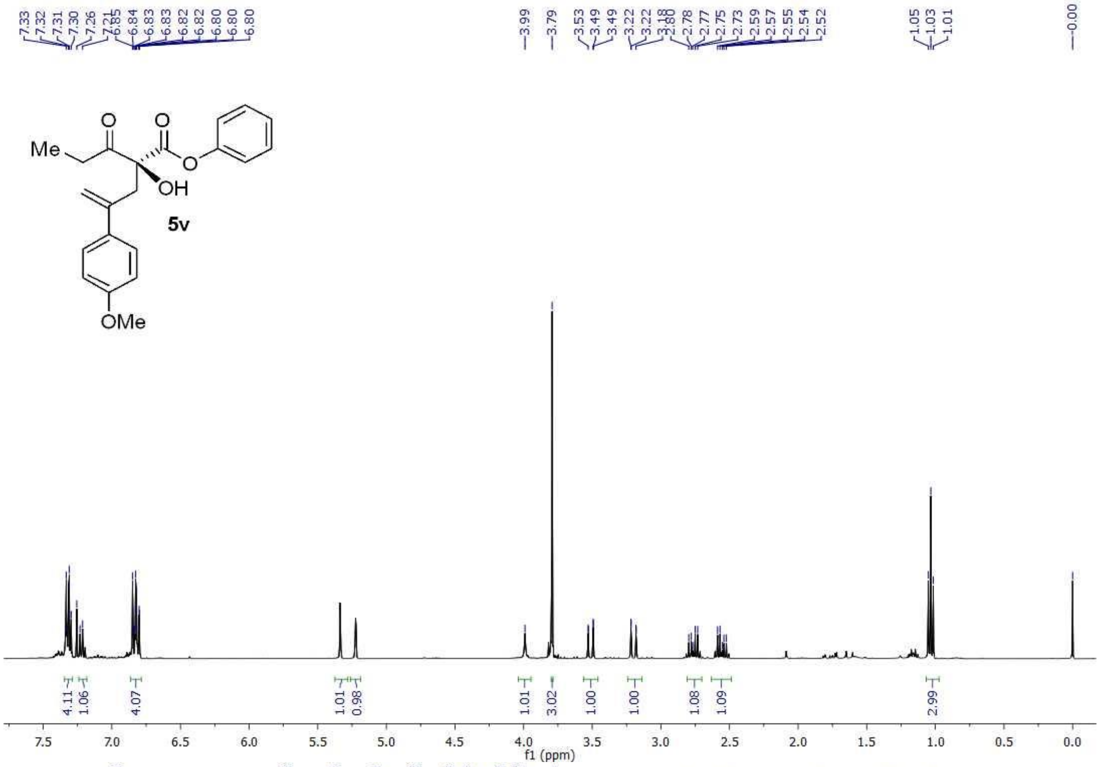
5u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1.01
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OMe
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3.02
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1.09
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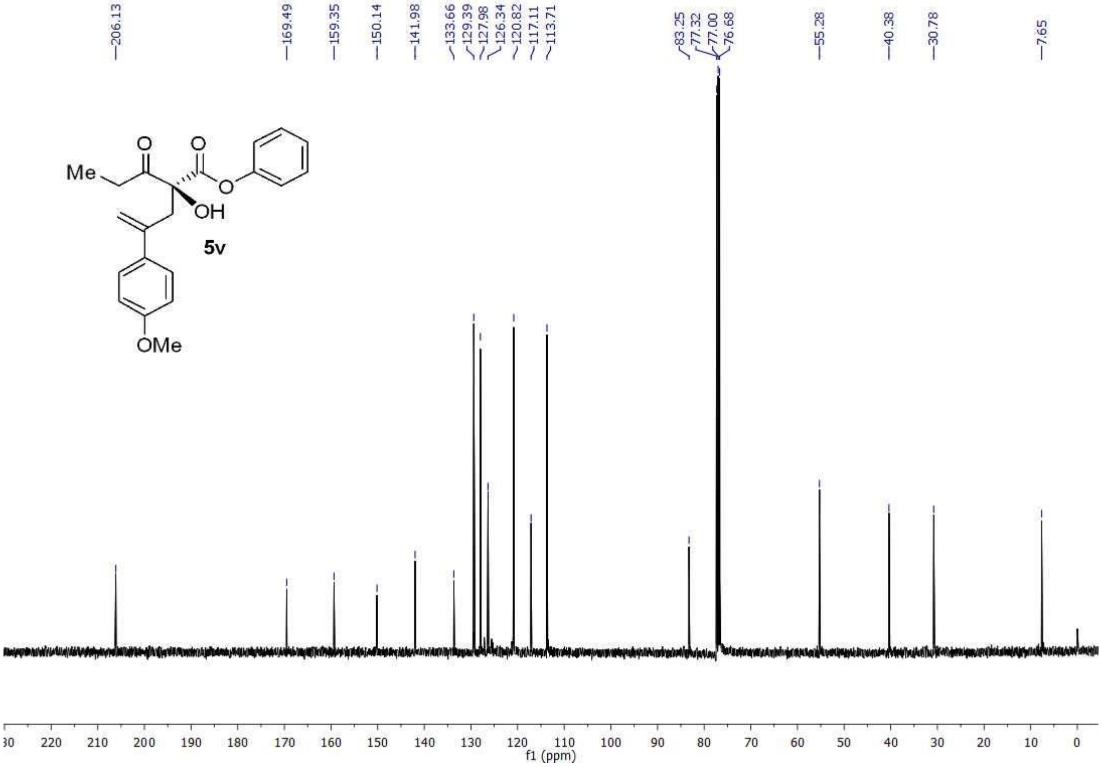
f1 (ppm)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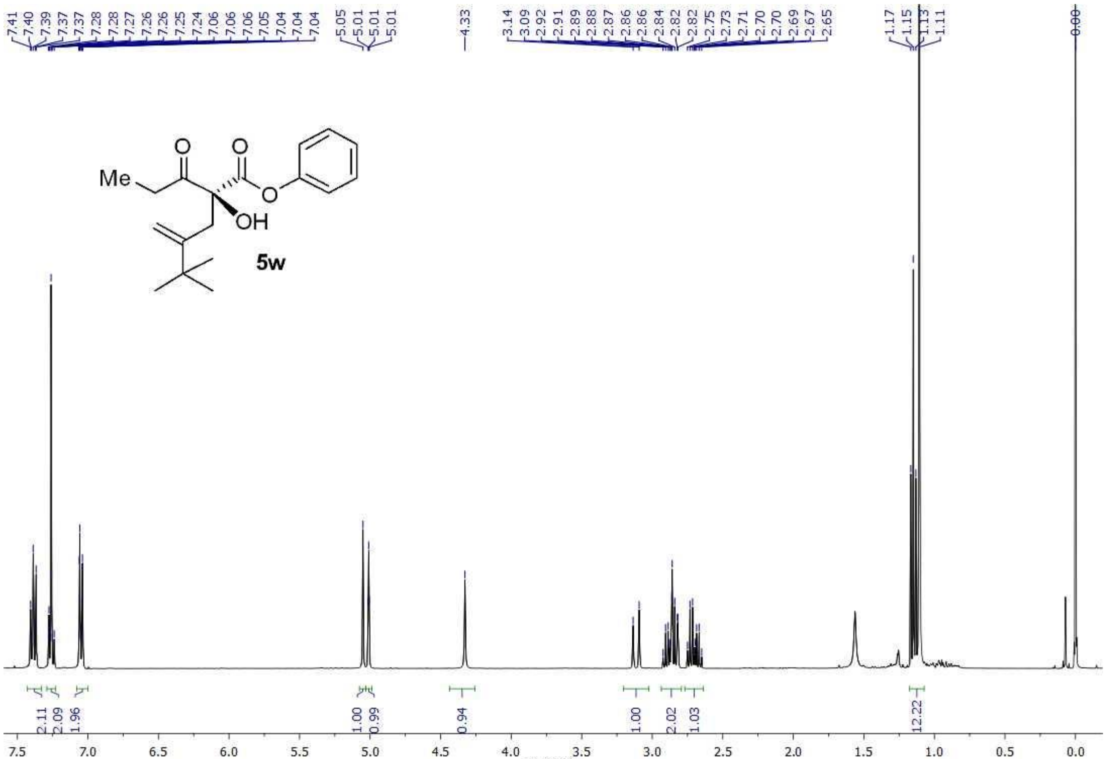
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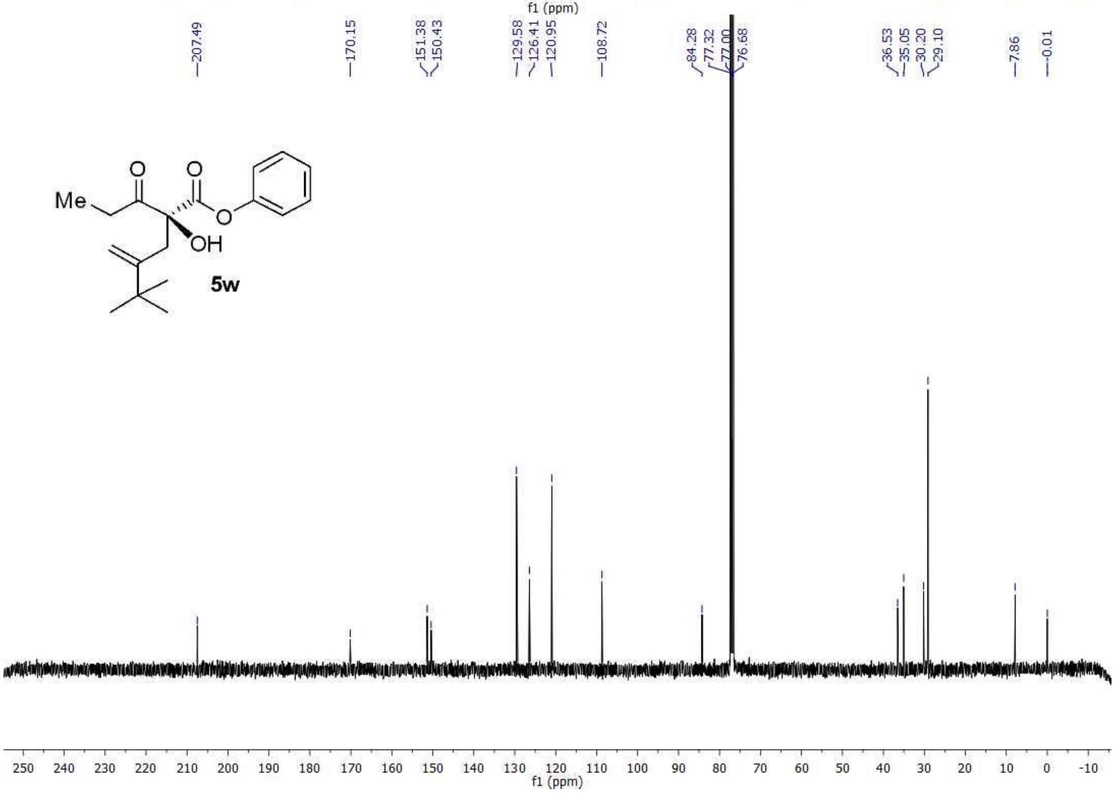
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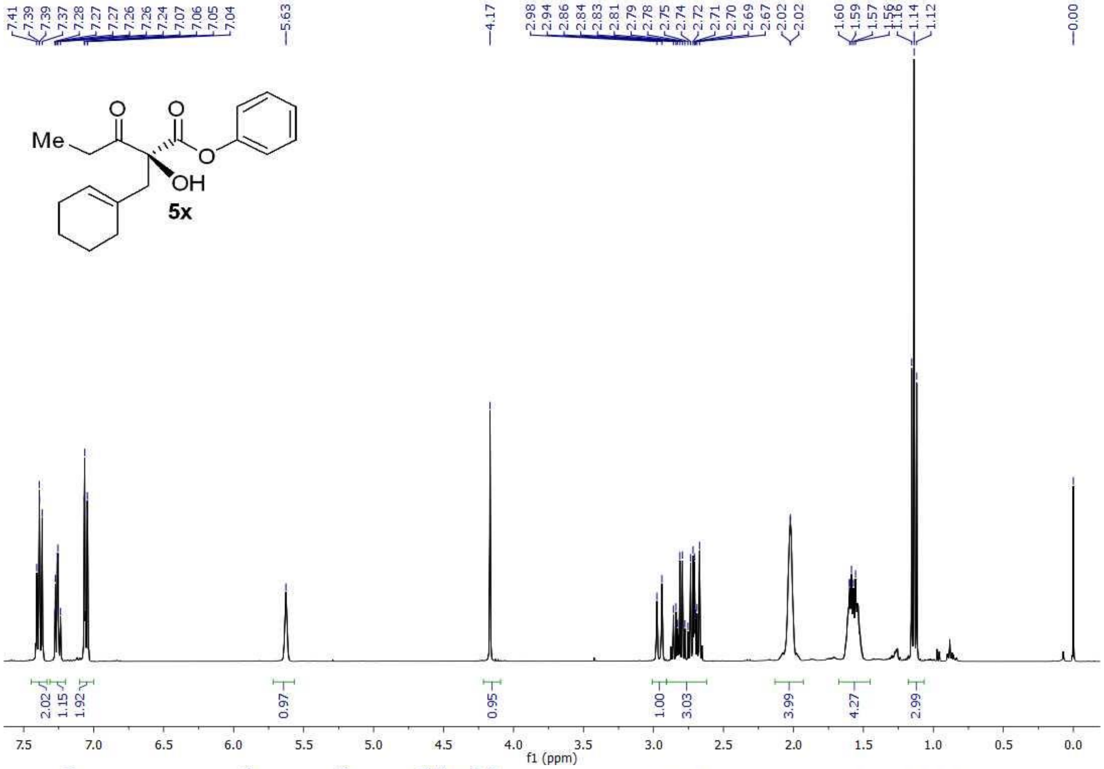
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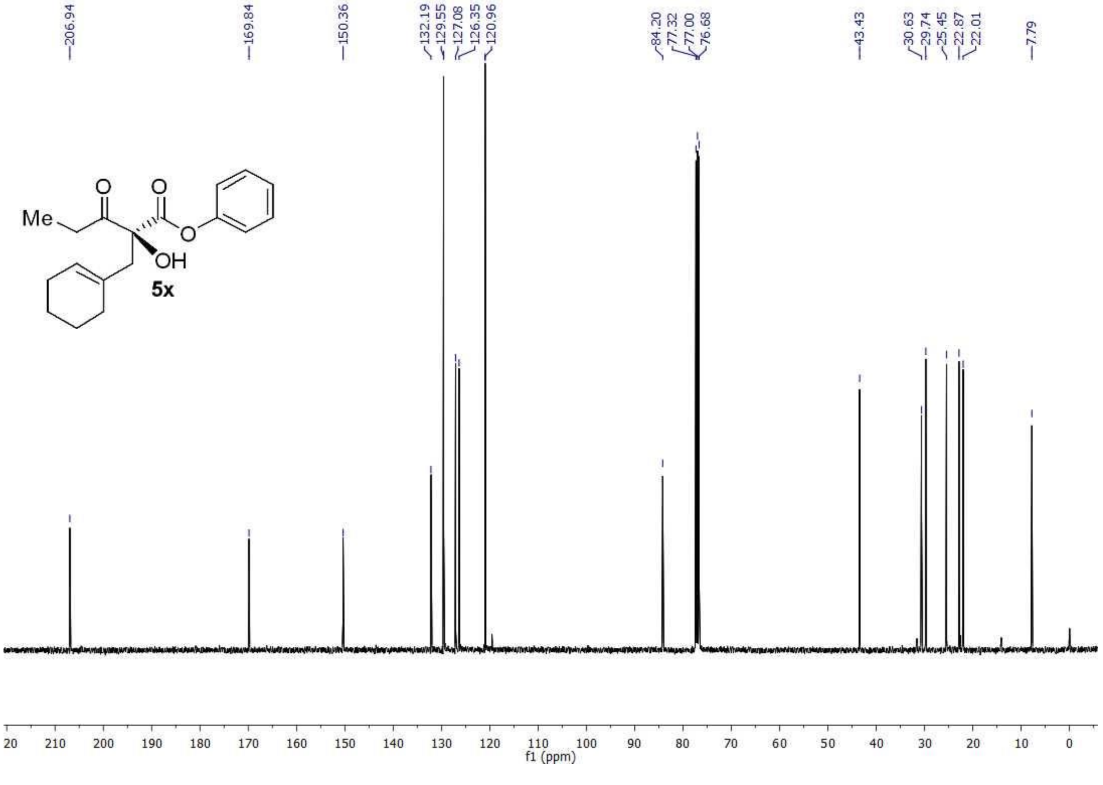
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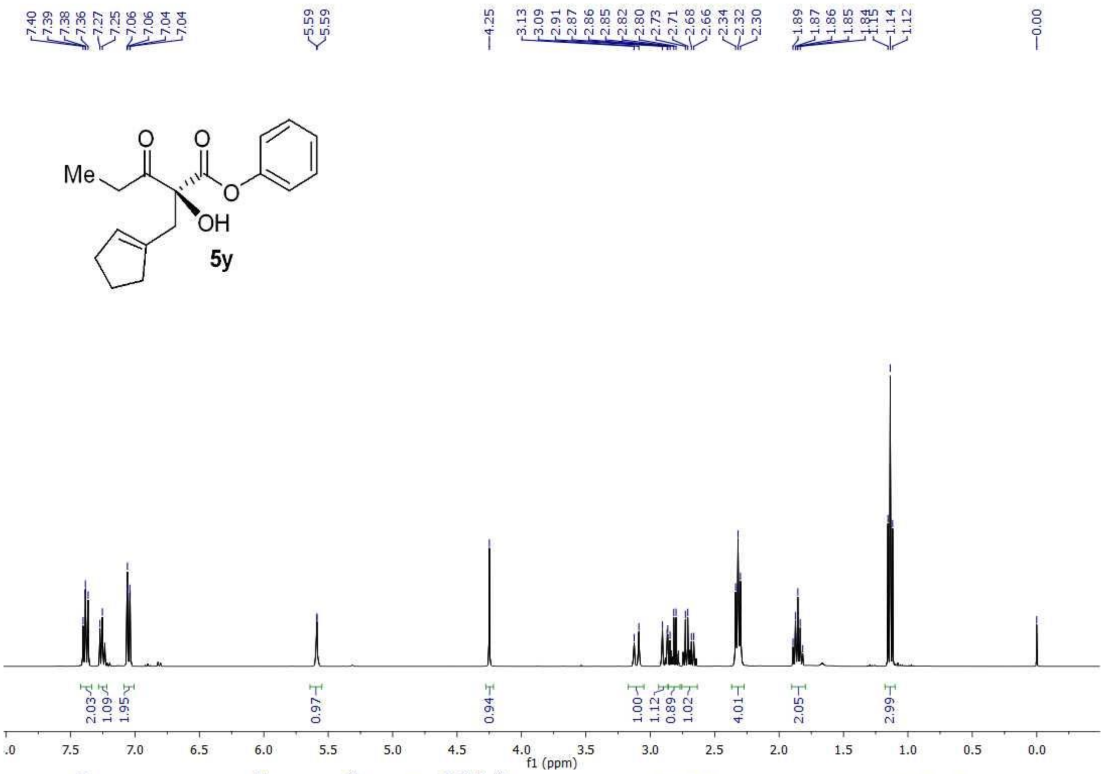
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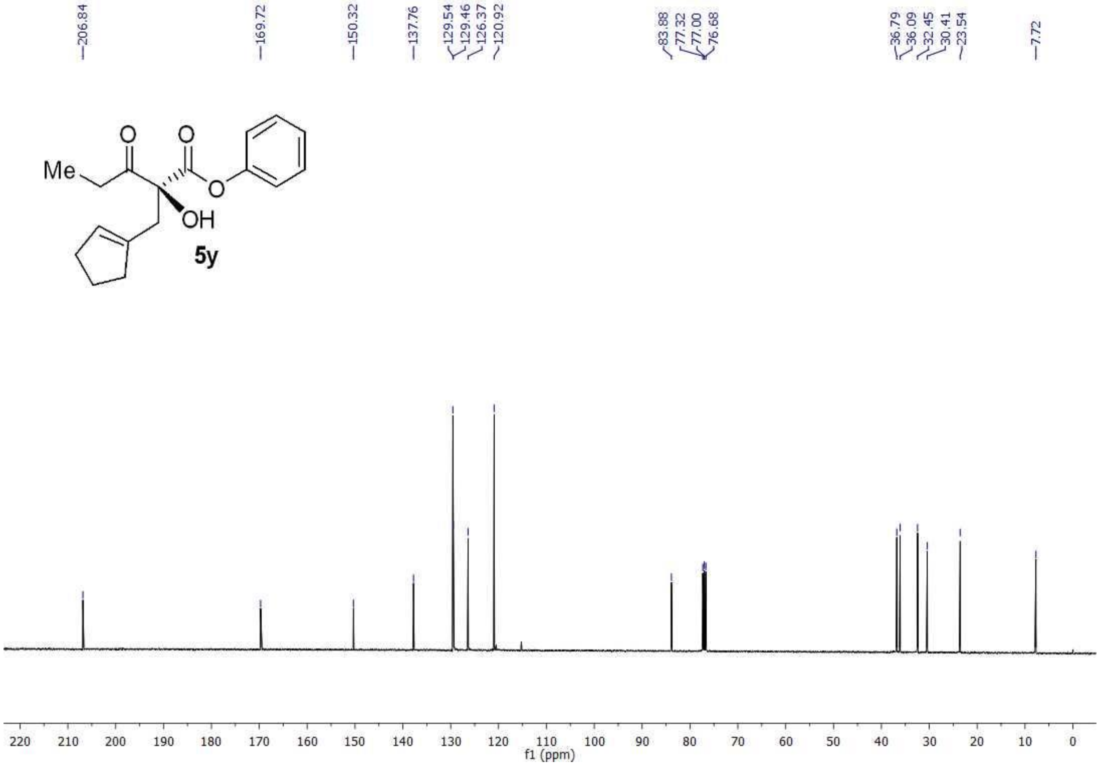
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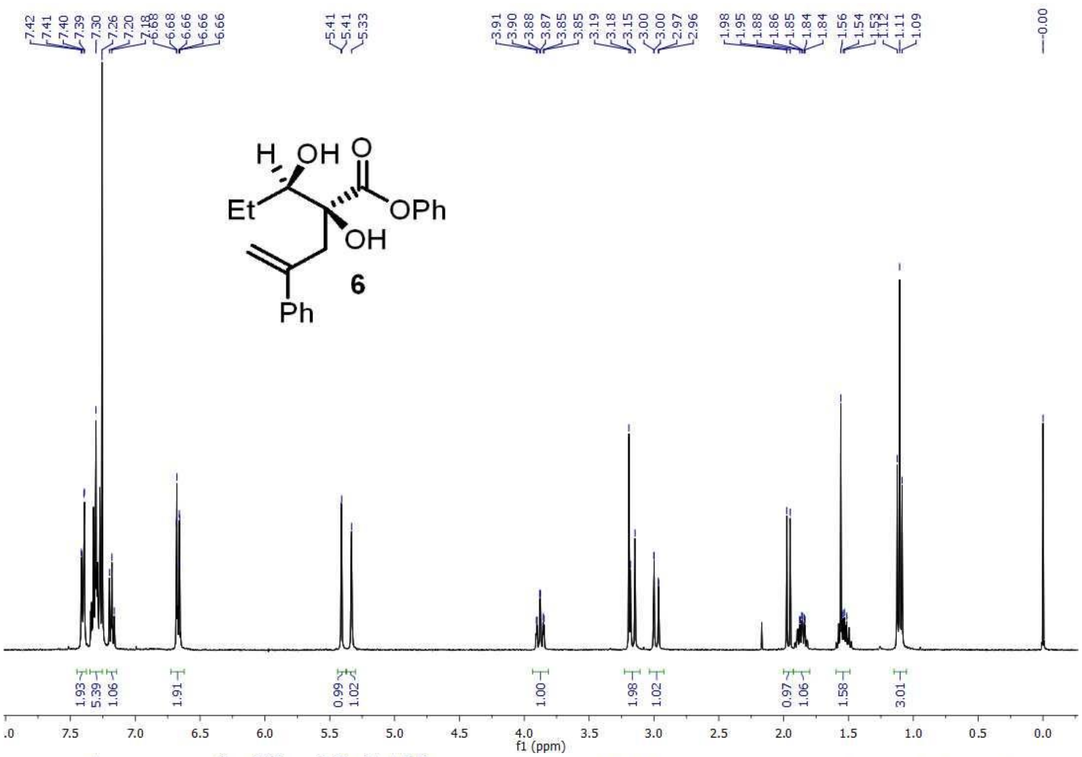
f1 (ppm)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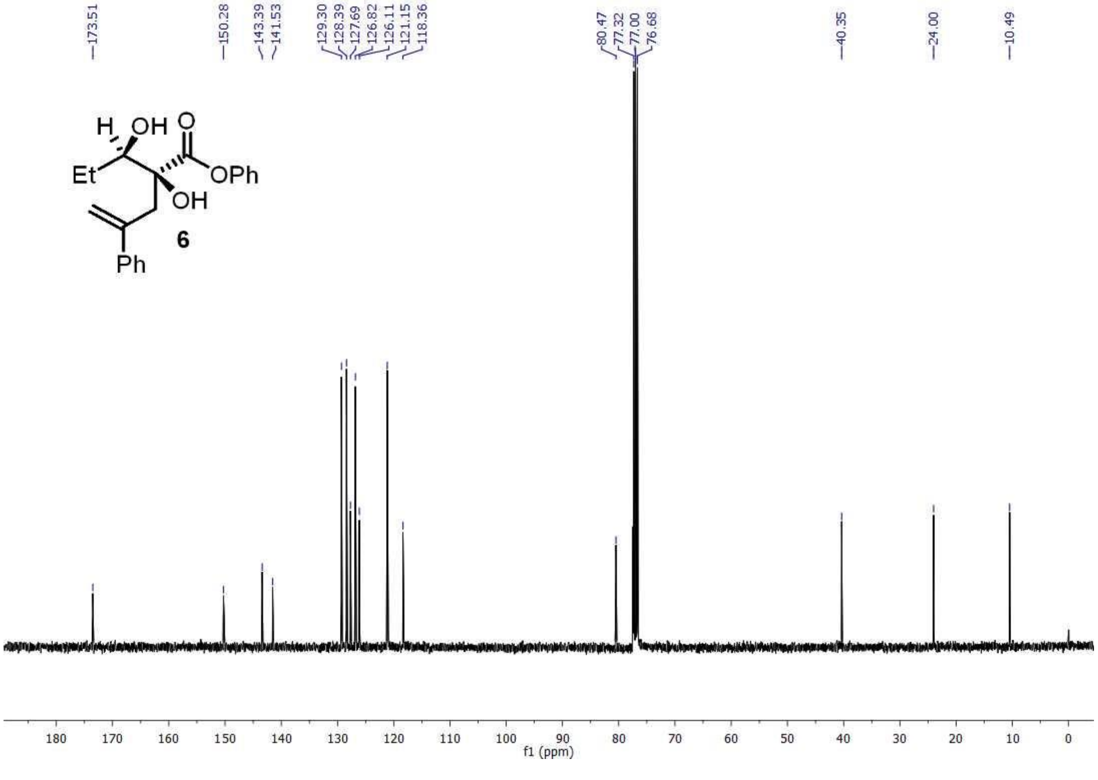
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Ph
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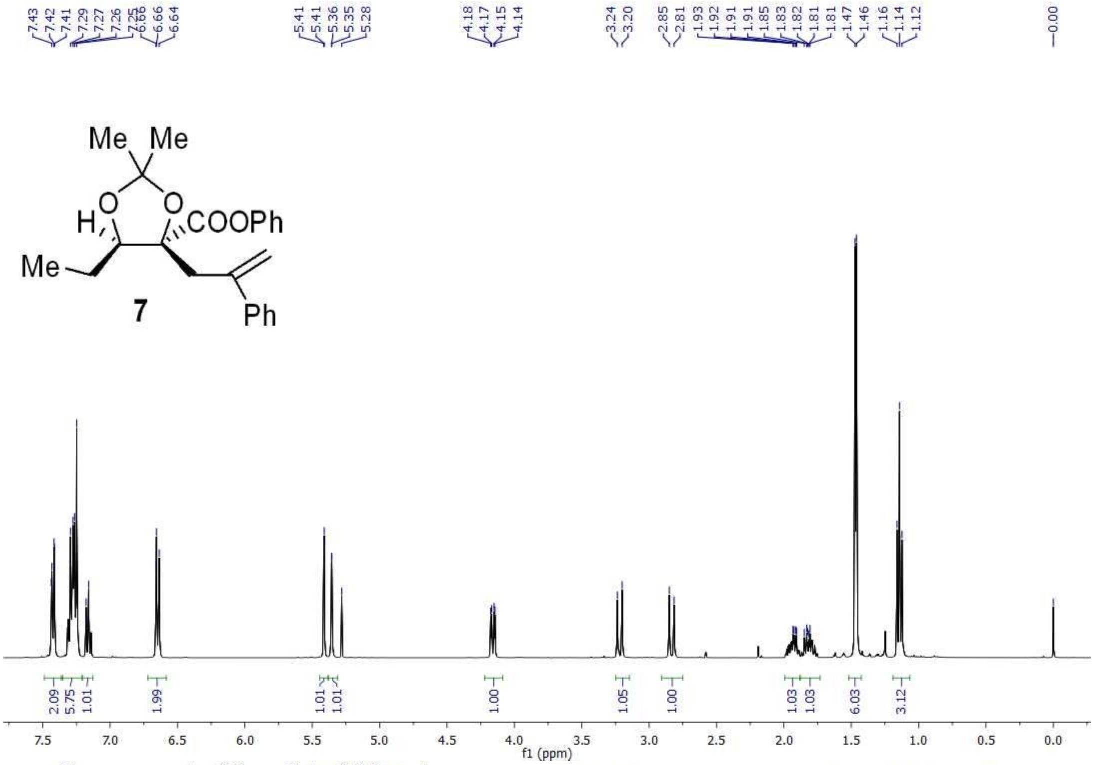
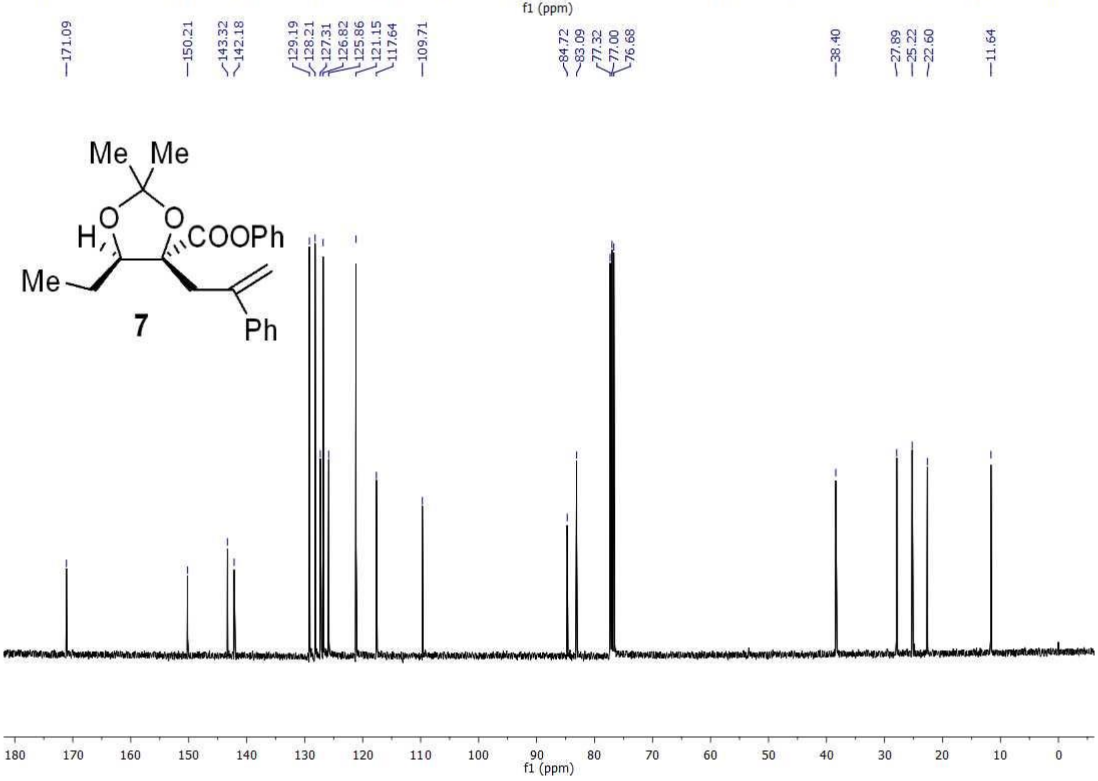
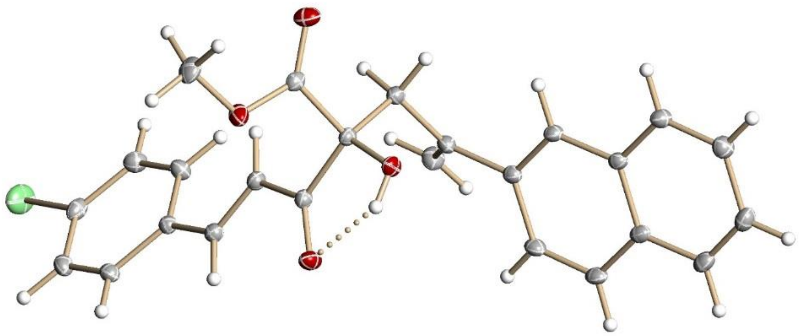




3.5.9 X-ray Crystal Structural Information for 5n



A colorless prism-like specimen of $C_{25}H_{21}ClO_4$, approximate dimensions 0.44 mm × 0.46 mm × 0.51 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a Bruker APEX-II CCD system equipped with a graphite monochromator and a MoKα sealed tube ($\lambda = 0.71073$ Å). Data collection temperature was 150 K.

The total exposure time was 7.58 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 16714 reflections to a maximum θ angle of 30.00° (0.71 Å resolution), of which 5811 were independent (average redundancy 2.876, completeness = 99.9%, R_{int} = 2.89%) and 5727 (98.55%) were greater than $2\sigma(F^2)$. The final cell constants of a = 5.6436(6) Å, b = 11.3076(12) Å, c = 16.2183(17) Å, β = 99.1272(15)°, V = 1021.88(19) Å^3, are based upon the refinement of the XYZ-centroids of 9885 reflections above 20 σ(I) with 5.087° < 2θ < 61.23°. Data were corrected for absorption effects using the multi-scan method (SADABS). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8430 and 0.9090.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_1$, with Z = 2 for the formula unit, $C_{25}H_{21}ClO_4$. The final anisotropic full-matrix least-squares refinement on F^2 with 293 variables converged at R_1 = 3.07%, for the observed data and wR_2 = 6.67% for all data. The goodness-of-fit was 1.000. The largest peak in the final difference electron density synthesis was 0.293 $e^-/Å^3$ and the largest hole was -0.235 $e^-/Å^3$ with an RMS deviation of 0.041 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.368 g/cm^3 and F(000), 440 e^-.

APEX2 Version 2010.11-3 (Bruker AXS Inc.)
SAINT Version 7.68A (Bruker AXS Inc., 2009)
SADABS Version 2008/1 (G. M. Sheldrick, Bruker AXS Inc.)
XPREP Version 2008/2 (G. M. Sheldrick, Bruker AXS Inc.)
XS Version 2008/1 (G. M. Sheldrick, *Acta Cryst.* (2008). A**64**, 112-122)
XL Version 2012/4 (G. M. Sheldrick, (2012) University of Gottingen, Germany)
Platon (A. L. Spek, *Acta Cryst.* (1990). A**46**, C-34)

Table 1. Sample and crystal data for UM2501.

Identification code	2501	
Chemical formula	$C_{25}H_{21}ClO_4$	
Formula weight	420.87	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal size	0.44 × 0.46 × 0.51 mm	
Crystal habit	colorless prism	
Crystal system	monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 5.6436(6) Å	α = 90°
	b = 11.3076(12) Å	β = 99.1272(15)°
	c = 16.2183(17) Å	γ = 90°
Volume	1021.88(19) $Å^3$	
Z	2	
Density (calculated)	1.368 Mg/cm^3	
Absorption coefficient	0.217 mm^{-1}	

F(000)	440

Table 2. Data collection and structure refinement for UM2501.

Diffractometer	Bruker APEX-II CCD	
Radiation source	sealed tube, MoKα	
Theta range for data collection	2.21 to 30.00°	
Index ranges	$-7 \leq h \leq 7$, $-15 \leq k \leq 15$, $-22 \leq l \leq 22$	
Reflections collected	16714	
Independent reflections	5811 [R(int) = 0.0289]	
Coverage of independent reflections	99.9%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9090 and 0.8430	
Structure solution technique	direct methods	
Structure solution program	ShelXS-97 (Sheldrick, 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	ShelXL-2012 (Sheldrick, 2012)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	5811 / 1 / 293	
Goodness-of-fit on F^2	1.000	
Final R indices	5727 data; $I>2\sigma(I)$	$R_1 = 0.0307$, $wR_2 = 0.0662$
	all data	$R_1 = 0.0312$, $wR_2 = 0.0667$
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0100P)^2+0.3253P]$, $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	0.0(1)	
Largest diff. peak and hole	0.293 and -0.235 eÅ^{-3}	
R.M.S. deviation	0.041 eÅ^{-3}	

from mean

$R_{int} = \Sigma|F_o^2 - F_o^2(\text{mean})| / \Sigma[F_o^2]$
$R_1 = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$
$\text{GOOF} = S = \{\Sigma[w(F_o^2 - F_c^2)^2] / (n - p)\}^{1/2}$
$wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$

Table 3. Atomic coordinates and equivalent isotropic atomic displacement parameters ($Å^2$) for UM2501.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
Cl1	0.13979(11)	0.07355(5)	0.53838(4)	0.04903(15)
C1	0.2508(3)	0.97766(16)	0.47007(10)	0.0279(3)
C2	0.4507(3)	0.01027(15)	0.43566(11)	0.0278(3)
C3	0.5378(3)	0.93243(14)	0.38138(10)	0.0239(3)
C4	0.4250(3)	0.82374(14)	0.36063(9)	0.0201(3)
C5	0.2261(3)	0.79323(15)	0.39775(10)	0.0249(3)
C6	0.1390(3)	0.86955(17)	0.45294(11)	0.0283(3)
C7	0.5167(3)	0.74549(14)	0.30097(9)	0.0217(3)
C8	0.3936(3)	0.65873(14)	0.25687(10)	0.0219(3)
C9	0.5164(3)	0.58179(14)	0.20345(9)	0.0210(3)
O10	0.7308(2)	0.58760(12)	0.20191(8)	0.0289(3)
C11	0.3666(3)	0.48832(14)	0.14826(9)	0.0202(3)
C12	0.1827(3)	0.54885(14)	0.08018(9)	0.0221(3)
O13	0.9875(2)	0.50972(13)	0.05370(8)	0.0332(3)
O14	0.2759(2)	0.64573(11)	0.05188(8)	0.0307(3)
C15	0.1307(4)	0.70309(19)	0.98097(12)	0.0371(4)
O16	0.5207(2)	0.42125(11)	0.10543(8)	0.0243(2)
C17	0.2293(3)	0.40588(14)	0.19974(10)	0.0221(3)
C18	0.3879(3)	0.34621(14)	0.27194(10)	0.0227(3)
C19	0.3821(4)	0.38033(17)	0.35029(11)	0.0316(4)
C20	0.5441(3)	0.24680(14)	0.25374(10)	0.0217(3)
C21	0.4660(3)	0.16304(14)	0.19374(10)	0.0219(3)
C22	0.6112(3)	0.06555(14)	0.17855(9)	0.0210(3)
C23	0.5306(3)	0.97821(15)	0.11722(11)	0.0263(3)
C24	0.6762(3)	0.88498(16)	0.10430(11)	0.0298(3)
C25	0.9090(3)	0.87525(17)	0.15134(12)	0.0307(4)

	x/a	y/b	z/c	U(eq)
C26	0.9921(3)	0.95854(16)	0.20979(11)	0.0279(3)
C27	0.8463(3)	0.05538(14)	0.22561(9)	0.0229(3)
C28	0.9250(3)	0.14342(16)	0.28631(10)	0.0262(3)
C29	0.7796(3)	0.23522(16)	0.30021(10)	0.0259(3)

Table 4. Bond lengths (Å) for UM2501.

Cl1-C1	1.7366(17)	C1-C6	1.384(3)
C1-C2	1.385(3)	C2-C3	1.389(2)
C2-H2	0.95	C3-C4	1.400(2)
C3-H3	0.95	C4-C5	1.399(2)
C4-C7	1.465(2)	C5-C6	1.388(2)
C5-H5	0.95	C6-H6	0.95
C7-C8	1.341(2)	C7-H7	0.95
C8-C9	1.476(2)	C8-H8	0.95
C9-O10	1.2162(19)	C9-C11	1.547(2)
C11-O16	1.4161(18)	C11-C17	1.540(2)
C11-C12	1.550(2)	C12-O13	1.201(2)
C12-O14	1.328(2)	O14-C15	1.454(2)
C15-H15A	0.98	C15-H15B	0.98
C15-H15C	0.98	O16-H16	0.82(3)
C17-C18	1.515(2)	C17-H17A	0.99
C17-H17B	0.99	C18-C19	1.333(2)
C18-C20	1.487(2)	C19-H19A	0.95
C19-H19B	0.95	C20-C21	1.379(2)
C20-C29	1.426(2)	C21-C22	1.418(2)
C21-H21	0.95	C22-C23	1.424(2)
C22-C27	1.427(2)	C23-C24	1.373(2)
C23-H23	0.95	C24-C25	1.415(3)
C24-H24	0.95	C25-C26	1.366(3)
C25-H25	0.95	C26-C27	1.417(2)
C26-H26	0.95	C27-C28	1.421(2)
C28-C29	1.364(3)	C28-H28	0.95
C29-H29	0.95		

Table 5. Bond angles (°) for UM2501.

C6-C1-C2	121.93(16)	C6-C1-Cl1	118.72(14)
C2-C1-Cl1	119.34(14)	C1-C2-C3	118.64(16)
C1-C2-H2	120.7	C3-C2-H2	120.7
C2-C3-C4	121.04(15)	C2-C3-H3	119.5
C4-C3-H3	119.5	C5-C4-C3	118.57(15)
C5-C4-C7	121.81(14)	C3-C4-C7	119.63(14)
C6-C5-C4	120.98(16)	C6-C5-H5	119.5
C4-C5-H5	119.5	C1-C6-C5	118.81(16)
C1-C6-H6	120.6	C5-C6-H6	120.6
C8-C7-C4	125.94(14)	C8-C7-H7	117.0
C4-C7-H7	117.0	C7-C8-C9	119.51(14)
C7-C8-H8	120.2	C9-C8-H8	120.2
O10-C9-C8	122.80(15)	O10-C9-C11	118.64(14)
C8-C9-C11	118.56(13)	O16-C11-C17	110.04(12)
O16-C11-C9	109.16(12)	C17-C11-C9	112.07(12)
O16-C11-C12	106.32(12)	C17-C11-C12	108.40(12)
C9-C11-C12	110.69(12)	O13-C12-O14	124.83(15)
O13-C12-C11	124.38(15)	O14-C12-C11	110.68(13)
C12-O14-C15	115.90(14)	O14-C15-H15A	109.5
O14-C15-H15B	109.5	H15A-C15-H15B	109.5
O14-C15-H15C	109.5	H15A-C15-H15C	109.5
H15B-C15-H15C	109.5	C11-O16-H16	108.7(18)
C18-C17-C11	113.72(13)	C18-C17-H17A	108.8
C11-C17-H17A	108.8	C18-C17-H17B	108.8
C11-C17-H17B	108.8	H17A-C17-H17B	107.7
C19-C18-C20	120.86(16)	C19-C18-C17	120.47(16)
C20-C18-C17	118.65(14)	C18-C19-H19A	120.0
C18-C19-H19B	120.0	H19A-C19-H19B	120.0
C21-C20-C29	118.47(15)	C21-C20-C18	121.74(14)
C29-C20-C18	119.78(14)	C20-C21-C22	121.84(13)
C20-C21-H21	119.1	C22-C21-H21	119.1
C21-C22-C23	122.08(13)	C21-C22-C27	118.93(14)
C23-C22-C27	118.99(14)	C24-C23-C22	120.43(15)
C24-C23-H23	119.8	C22-C23-H23	119.8
C23-C24-C25	120.29(17)	C23-C24-H24	119.9
C25-C24-H24	119.9	C26-C25-C24	120.54(17)
C26-C25-H25	119.7	C24-C25-H25	119.7
C25-C26-C27	120.87(16)	C25-C26-H26	119.6

C27-C26-H26	119.6	C26-C27-C28	122.69(14)
C26-C27-C22	118.87(15)	C28-C27-C22	118.44(14)
C29-C28-C27	121.17(14)	C29-C28-H28	119.4
C27-C28-H28	119.4	C28-C29-C20	121.15(15)
C28-C29-H29	119.4	C20-C29-H29	119.4

Table 6. Torsion angles (°) for UM2501.

C6-C1-C2-C3	1.1(3)	Cl1-C1-C2-C3	179.78(12)
C1-C2-C3-C4	0.9(2)	C2-C3-C4-C5	-1.9(2)
C2-C3-C4-C7	177.93(15)	C3-C4-C5-C6	1.1(2)
C7-C4-C5-C6	-178.76(15)	C2-C1-C6-C5	-1.9(3)
Cl1-C1-C6-C5	179.40(13)	C4-C5-C6-C1	0.8(3)
C5-C4-C7-C8	20.8(2)	C3-C4-C7-C8	-159.03(16)
C4-C7-C8-C9	-175.74(14)	C7-C8-C9-O10	5.5(2)
C7-C8-C9-C11	-175.60(14)	O10-C9-C11-O16	1.6(2)
C8-C9-C11-O16	-177.36(13)	O10-C9-C11-C17	123.74(16)
C8-C9-C11-C17	-55.20(18)	O10-C9-C11-C12	-115.12(16)
C8-C9-C11-C12	65.94(17)	O16-C11-C12-O13	94.93(18)
C17-C11-C12-O13	-23.3(2)	C9-C11-C12-O13	-146.63(16)
O16-C11-C12-O14	-81.38(15)	C17-C11-C12-O14	160.35(13)
C9-C11-C12-O14	37.06(17)	O13-C12-O14-C15	-3.1(2)
C11-C12-O14-C15	173.19(14)	O16-C11-C17-C18	67.40(16)
C9-C11-C17-C18	-54.26(17)	C12-C11-C17-C18	-176.71(13)
C11-C17-C18-C19	106.80(18)	C11-C17-C18-C20	-74.99(17)
C19-C18-C20-C21	138.63(18)	C17-C18-C20-C21	-39.6(2)
C19-C18-C20-C29	-40.1(2)	C17-C18-C20-C29	141.73(15)
C29-C20-C21-C22	1.3(2)	C18-C20-C21-C22	-177.46(14)
C20-C21-C22-C23	179.40(15)	C20-C21-C22-C27	-1.3(2)
C21-C22-C23-C24	-179.96(15)	C27-C22-C23-C24	0.7(2)
C22-C23-C24-C25	-0.6(3)	C23-C24-C25-C26	-0.3(3)
C24-C25-C26-C27	1.0(3)	C25-C26-C27-C28	179.48(16)
C25-C26-C27-C22	-0.8(2)	C21-C22-C27-C26	-179.38(14)
C23-C22-C27-C26	0.0(2)	C21-C22-C27-C28	0.3(2)
C23-C22-C27-C28	179.68(15)	C26-C27-C28-C29	-179.71(15)
C22-C27-C28-C29	0.6(2)	C27-C28-C29-C20	-0.6(3)

C21-C20-C29-C28	-0.3(2)	C18-C20-C29-C28	178.44(15)

Table 7. Anisotropic atomic displacement parameters (Å^2) for UM2501.

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1	0.0500(3)	0.0483(3)	0.0504(3)	-0.0237(3)	0.0130(2)	0.0103(2)
C1	0.0295(8)	0.0293(8)	0.0237(7)	-0.0062(6)	0.0006(6)	0.0095(6)
C2	0.0311(8)	0.0223(7)	0.0281(7)	-0.0029(6)	-0.0016(6)	-0.0016(6)
C3	0.0233(7)	0.0235(7)	0.0240(7)	0.0008(6)	0.0014(6)	-0.0034(6)
C4	0.0207(6)	0.0206(7)	0.0187(6)	0.0009(5)	0.0021(5)	0.0005(5)
C5	0.0262(7)	0.0242(7)	0.0253(7)	-0.0026(6)	0.0072(6)	-0.0044(6)
C6	0.0256(8)	0.0343(9)	0.0263(8)	-0.0022(7)	0.0075(6)	0.0001(6)
C7	0.0213(7)	0.0230(7)	0.0209(7)	0.0015(6)	0.0038(5)	0.0008(6)
C8	0.0207(6)	0.0226(7)	0.0227(7)	-0.0005(6)	0.0037(5)	0.0020(5)
C9	0.0220(6)	0.0196(6)	0.0208(6)	-0.0004(6)	0.0022(5)	0.0017(5)
O10	0.0208(5)	0.0312(6)	0.0349(6)	-0.0068(5)	0.0053(4)	0.0001(5)
C11	0.0193(6)	0.0199(6)	0.0212(6)	-0.0018(5)	0.0022(5)	0.0026(5)
C12	0.0234(7)	0.0238(7)	0.0193(6)	-0.0031(5)	0.0036(5)	0.0051(5)
O13	0.0234(6)	0.0458(8)	0.0290(6)	0.0051(6)	0.0002(5)	-0.0020(5)
O14	0.0351(6)	0.0245(6)	0.0288(6)	0.0047(5)	-0.0063(5)	-0.0006(5)
C15	0.0442(10)	0.0351(9)	0.0289(9)	0.0085(8)	-0.0040(7)	0.0087(8)
O16	0.0235(6)	0.0230(5)	0.0276(5)	-0.0048(4)	0.0081(4)	0.0032(4)
C17	0.0202(7)	0.0214(7)	0.0245(7)	-0.0012(6)	0.0027(5)	0.0004(5)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C18	0.0221(7)	0.0201(7)	0.0251(7)	-0.0004(6)	0.0017(5)	-0.0031(6)
C19	0.0358(9)	0.0310(9)	0.0270(8)	-0.0038(7)	0.0023(7)	-0.0001(7)
C20	0.0204(7)	0.0224(7)	0.0218(6)	0.0034(6)	0.0017(5)	-0.0020(5)
C21	0.0176(6)	0.0245(7)	0.0226(7)	0.0015(6)	-0.0002(5)	-0.0003(5)
C22	0.0177(6)	0.0235(7)	0.0218(6)	0.0041(6)	0.0030(5)	-0.0013(5)
C23	0.0221(7)	0.0287(8)	0.0274(7)	-0.0007(6)	0.0021(6)	0.0000(6)
C24	0.0306(8)	0.0286(8)	0.0307(8)	-0.0023(7)	0.0064(7)	0.0005(7)
C25	0.0301(8)	0.0294(8)	0.0339(9)	0.0059(7)	0.0091(7)	0.0084(7)
C26	0.0227(7)	0.0322(8)	0.0287(8)	0.0103(7)	0.0037(6)	0.0050(6)
C27	0.0187(6)	0.0273(8)	0.0227(6)	0.0082(6)	0.0030(5)	-0.0010(6)
C28	0.0196(6)	0.0315(8)	0.0255(7)	0.0063(6)	-0.0029(5)	-0.0030(6)
C29	0.0229(7)	0.0277(8)	0.0249(7)	0.0011(6)	-0.0027(6)	-0.0053(6)

Table 8. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å^2) for UM2501.

	x/a	y/b	z/c	U(eq)
H2	0.5266	1.0844	0.4489	0.040(6)
H3	0.6760	0.9532	0.3580	0.029(5)
H5	0.1494	0.7192	0.3850	0.029(5)
H6	0.0050	0.8479	0.4785	0.030(6)
H7	0.6780	0.7573	0.2928	0.020(5)
H8	0.2286	0.6469	0.2600	0.025(5)
H15A	0.0953	0.6465	-0.0651	0.058(5)
H15B	0.2189	0.7706	-0.0370	0.058(5)
H15C	-0.0198	0.7308	-0.0028	0.058(5)
H16	0.647(5)	0.457(2)	0.1065(16)	0.042(7)
H17A	0.1047	0.4524	0.2219	0.023(4)

	x/a	y/b	z/c	U(eq)
H17B	0.1468	0.3443	0.1624	0.023(4)
H19A	0.4786	0.3410	0.3954	0.036(4)
H19B	0.2815	0.4440	0.3611	0.036(4)
H21	0.3106	0.1709	0.1617	0.032(6)
H23	0.3751	-0.0155	0.0850	0.028(5)
H24	0.6204	-0.1732	0.0636	0.031(6)
H25	1.0082	-0.1898	0.1422	0.039(6)
H26	1.1497	-0.0485	0.2402	0.034(6)
H28	1.0817	0.1383	0.3178	0.041(6)
H29	0.8362	0.2924	0.3416	0.026(5)

Table 9. Hydrogen bond distances (Å) and angles (°) for UM2501.

	Donor-H	Acceptor-H	Donor-Acceptor	Angle
O16-H16···O10	0.82(3)	2.13(3)	2.6086(18)	117.0
O16-H16···O13	0.82(3)	2.30(3)	3.0573(18)	153.0

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