Dissertation zur Erlangung des Doktorgrades

der Fakultät für Chemie und Pharmazie

der Ludwig-Maximilians-Universität München

De Novo Synthesis of Arenes and Heteroarenes

von

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aus Augsburg, Deutschland

2017

Erklärung

Diese Dissertation wurde im Sinn von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Univ.-Prof. Dr. Thomas Magauer betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, den 20. Oktober 2017

…………………………….

Johannes Feierfeil

Dissertation eingereicht am: 02.11.2017

1. Gutachter Univ.-Prof. Dr. Thomas Magauer

2. Gutachter Dr. Dorian Didier

Mündliche Prüfung am: 04.12.2017

To my family,

for all their love and support.

Parts of this thesis have been published in peer-reviewed journals.

"*De Novo Synthesis of Benzannelated Heterocycles*" J. Feierfeil, T. Magauer, *Chem. Eur. J*. **2017**, accepted on November 30th, 2017, DOI: 10.1002/chem.201705662.

"*Ring-opening of Bicyclo[3.1.0]hexan-2-ones: A Versatile Synthetic Platform for the Construction of Substituted Benzoates*" J. Feierfeil, A. Grossmann, T. Magauer, *Angew. Chem. Int. Ed*. **2015**, *54*, 11835–11838.

Parts of this thesis have been presented at scientific conferences.

8th SFB 749 workshop

Ring Expansion for the *De Novo* Synthesis of Indoles and Indazoles (poster presentation). *Kloster Irsee, Germany, Oct. 2017*.

26th International Society of Heterocyclic Chemistry Congress

Ring-opening of Bicyclo[3.1.0]hexan-2-ones: Applications in Heterocyclic Synthesis (poster presentation). *University of Regensburg, Regensburg, Germany, Sept. 2017*.

7th SFB 749 workshop

Ring-opening of Bicyclo[3.1.0]hexan-2-ones: A *De Novo* Synthesis of Substituted Benzoates (poster presentation). *Kloster Irsee, Germany, Mar. 2016*.

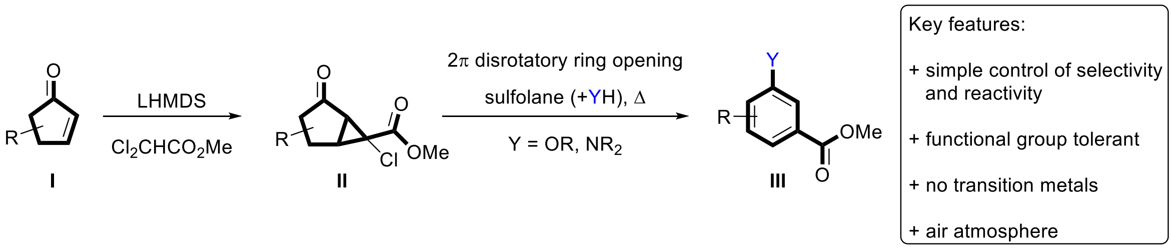
ABSTRACT

This Ph.D. thesis describes the synthesis of polysubstituted arenes and heteroarenes from nonaromatic precursors via a ring-opening aromatization reaction of bicyclo[3.1.0]hexan-2-ones.

CHAPTER I

De Novo Synthesis of Arenes from Nonaromatic Precursors

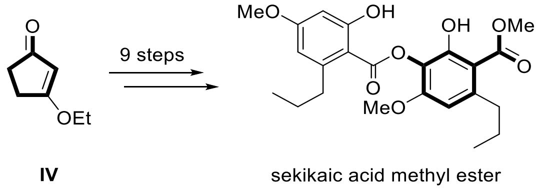
The 3-hydroxybenzoate structural motif constitutes an important building block in organic synthesis and it is also present in various biologically active compounds and pharmaceuticals. The first chapter of this Ph.D. thesis describes the development of an unprecedented methodology for the synthesis of substituted benzoates via a cyclopropanation-ring-opening aromatization sequence. The first step of this sequence is a literature known cyclopropanation reaction starting from the lithium enolate of inexpensive methyl dichloroacetate and a substituted cyclopenten-2-one **I**. The generated substituted bicyclo[3.1.0]hexan-2-one **II** then undergoes an efficient thermal 2π disrotatory ring-opening aromatization sequence to afford a broad array of highly substituted benzoates **III**. This developed methodology enables a simple control of selectivity and reactivity and provides access to various benzoates, bearing alky, alkenyl, alkynyl and phenyl substituents. Moreover, our developed methodology enables the incorporation of heteroaromatic substitutents such as 2-thienyl or 2-furyl and also substrates containing fluoro, chloro, ketones or hydroxyl groups are well tolerated. Additionally, the reaction times are generally short (> 1 h) and no inert atmosphere is required, proving that the methodology is both practical and valuable.



Using secondary amines or alcohols in the ring-opening aromatization step gives access to either anilins, aryl ethers or polycyclic structures without the need of expensive transition

metal catalysts, which are generally required for more traditional approaches to synthesize the ether or aniline motif via Ullmann or Buchwald-Hartwig cross coupling reactions.

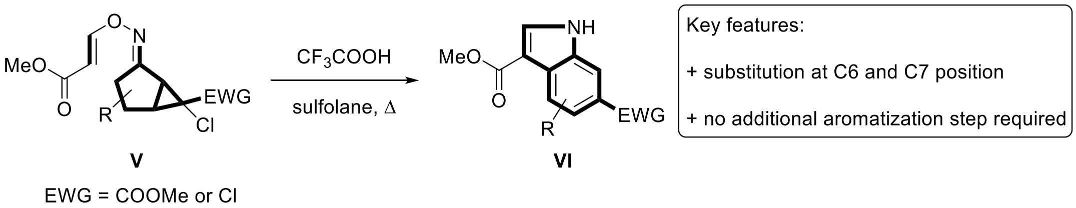
Furthermore, this strategy was applied in a nine-step synthesis of the highly potent GACKIX inhibitor sekikaic acid methyl ester starting from commercially available 3-ethoxycyclopenten-2-one **IV**.



CHAPTER II

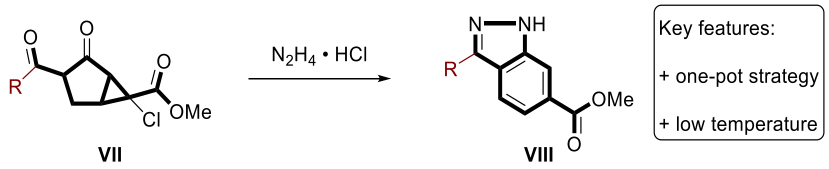
De Novo Synthesis of Heteroarenes from Nonaromatic Precursors

In the second part of this Ph.D. thesis the ring-opening aromatization sequence was applied to the synthesis of benzannelated five-membered heterocycles. Heterocycles such as indoles and indazoles are important structural motifs of natural products and pharmaceuticals. We developed a *de novo* synthesis for substituted indoles from *O*-vinyl oximes **V** which are prepared in two steps from readily available bicyclo[3.1.0]hexan-2-ones. Mechanistically, we propose that **V** first undergoes a thermal 2π-disrotatory ring-opening aromatization reaction to form an aryl-*O*-vinyl-oxime that affords the indole **2** via a facile acid-promoted [3,3]-sigmatropic rearrangement.



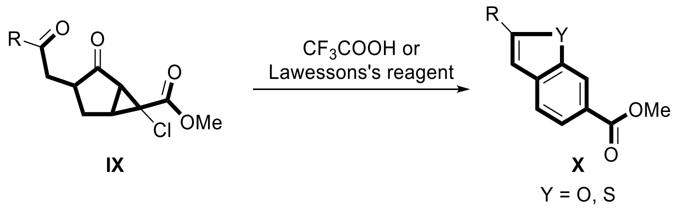
The developed methodology gave access to various indoles **VI**, bearing alky and *ortho*- and *para*-substituted aryl substituents. Moreover, this method worked also well when 1-naphthyl and heteroaromatic substituents such as 2-furyl and 2-thienyl are used.

In addition to our indole synthesis, we have also developed a one-pot strategy for the synthesis of indazoles **VIII** from diketones **VII**. Condensation with hydrazine monohydrochloride and subsequent ring-opening aromatization reaction directly gave the desired indazole.



Using this method, simple variation of the diketone allows us to gain access to a variety of C3-substituted indazoles.

Furthermore, we sought to further exploit our ring-opening aromatization strategy to 1,4-diketones **IX** which gave rise to additional benzannelated five-membered heterocycles. **X**.



Trifluoroacetic acid-promoted Paal-Knorr reaction followed by aromatization reaction provided benzofurans **X**. The use of Lawesson's reagent in the cyclization reaction furnished the corresponding benzothiophenes.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank Univ.-Prof. Dr. Thomas Magauer for giving me the wonderful opportunity to work in his group and providing me these interesting research topics for my Ph.D. studies. I am grateful for all his support, patience and guidance during my work and the freedom to develop my own ideas. It has been a great and very educational time. And I will not forget the Andechs Trail runs and group hikes in the Alps.

Furthermore, I am very thankful to Dr. Dorian Didier for agreeing to be the second reviewer of this thesis and for the helpful discussions during the SFB 749 workshop and the ISHC conference.

I would also like to thank the members of my thesis committee, Prof. Dr. Konstantin Karaghiosoff, Prof. Dr. Klaus Wanner, Prof. Dr. Heinz Langhals and Prof. Dr. Franz Bracher for being on my defense committee.

Special thanks to Prof. Dr. Dirk Trauner for the continuous support of the Magauer group.

I want to thank Dr. Cedric Hugelshofer and Dr. Benjamin Marsh for their proofreading of this thesis and other manuscripts during my Ph.D. and for their helpful suggestions.

Thanks to Dr. Cedric Hugelshofer for the countless laughs during lab time, never-ending motivation and for the discussions about pace, strides and running in general. I hope we can go for one more Nymphenburg run. To Dr. Klaus Speck for getting in shape for the Xletix runs. Thanks to them for their helpful discussions concerning substrate scope, methodology and chemistry in general.

To Raphael Wildermuth for being an incredible lab mate for the last half of my thesis. For all the runs including Andechs, Xletix and Tegernsee. For the parties and for the delicious venison we cooked together. For the funny times in the lab and the discussions about chemistry and daily life.

I would like to thank the rest of the IR lab, Dr. Benjamin Marsh and Sofia Torres Venegas for the enjoyable and good times we had with a lot of laughter and crazy music. For the "snack time" and Leberkäs sessions. For being responsible for the distillation of the solvents, especially hexanes.

I would especially like to thank Tatjana Huber, who worked next to me during master thesis and the first part of my Ph.D. You are one of the most talented people I have ever seen. Special thanks to Adriana Grossmann and Teresa Preuhs for joining the ring expansion team.

I would like to thank my lab mates of the Magauer group for the amazing and unforgettable time. I would like to thank Lara Weisheit, Franz-Lucas Haut, Alexander Rode, Kevin Sokol, Matthias Schmid and Ivica Zamarija for creating an inspiring and motivating atmosphere.

In addition, I would like to thank the whole Trauner group for their friendly acceptance, enjoyable atmosphere and their help.

I would like to acknowledge my intern Andreas Locher, Laura Frey and Lena Mayer who assisted me with my prodejects during their stays.

Additionally, I want to thank, Heike Traub, Aleksandra Sarman Grilc, Dr. Martin Sumser, Carrie Louis, Luis de la Osa de la Rosa and Mariia Palchyk for all their organization that simplifies everyday life in the Trauner group.

For the excellent support from the analytical department of the LMU Munich, I would like to thank Claudia Dubler, Dr. David Stephenson, Petra Keilholz, Sonja Kosak, Dr. Werner Spahl, and especially Dr. Peter Mayer for determination of single crystal X-ray structures. Furthermore, I would like to thank Heidi Buchholz, Hans Eckstaller, Roswitha Reineke, Claudia Brackelmann, Ronald Schürer und Michael Gayer.

Finally, I want to thank the people who mean most to me, I would like to thank my family and friends for their support. My biggest thanks belong to Mom, Dad, Christina and Nadine.

Without their love and support, I would not be where I am now. I want them to know how grateful I truly am for all their patience, love and energy.

LIST OF ABBREVIATIONS

Å	Ångstrom
Ac	acetate
AIBN	2,2’-azobis(2-methylpropionitrile)
Am	amyl (pentyl)
Ar	aryl
ATR	attenuated total reflection (IR spectroscopy)
Bn	benzyl
Boc	tert-butyloxycarbonyl
br	broad (IR spectroscopy)
brs	broad singlet (NMR spectroscopy)
Bu	butyl
calcd	calculated
CAN	ceric ammonium nitrate
conc.	concentrated
CTAB	cetyltrimethylammonium bromide
d	douplet (NMR spectroscopy)
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	tris(dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DHP	3,4-dihydropyran
DIPA	*N*,*N*-diisopropylamine
DIPEA	diisopropylethylamine (Hünig’sbase)
DMAP	4-(dimethylamino)-pyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dppf	1,1´-bis(diphenylphosphino)ferrocene
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	electron impact ionization (mass spectrometry)
equiv	equivalent(s)
ESI	electron spray ionization (mass spectrometry)
Et	ethyl
EtOAc	ethyl acetate
EWG	electron-withdrawing group
F.V.T.	flash vacuum thermolysis
g	gram(s)
gem	geminal
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HRMS	high-resolution mass spectra
Hz	Hertz (frequenzy)
i	*iso* (isomer)
im	imidazole
IR	infrared
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium *N*,*N*-diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
m	medium ((IR spectroscopy)
m	multiplet (NMR spectroscopy)
m.p.	melting point
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MDCA	methyl dichloroacetate
min	minutes
mL	milliliter
MS	molecular sieves
Ms	methanesulfonyl
MW	micro wave
NBS	*N*-bromosuccinimide
NHPI	*N*-hydroxyphthalimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
NMP	*N*-methyl-2-pyrrolidone
Np	naphthyl
o	*ortho*
ODCB	*ortho*-dichlorobenzene
p	*para*
Pd/C	palladium on charcoal
Ph	phenyl
pin	pinacol
PINO	phthalimide *N*-oxy radical
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PPA	polyphosphoric acid
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PTC	phase transfer catalyst
py	pyridine
q	quartet (NMR spectroscopy)
quant.	quantitative
R	undefined substituent
RCM	ring-closing metathesis
R_f	retardation factor (TLC)
s	singlet (NMR spectroscopy)
s	strong (IR spectroscopy)
S_N	nucleophilic substitution
S_EAr	electrophilic aromatic substitution
S_NAr	nucleophilic aromatic substitution
t	triplet (NMR spectroscopy)

t	*tert* (tertiary)
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
tol	tolyl
Ts	tosyl (*para*-toluenesulfonyl)
vs	very strong (IR spectroscopy)
w	weak (IR spectroscopy)

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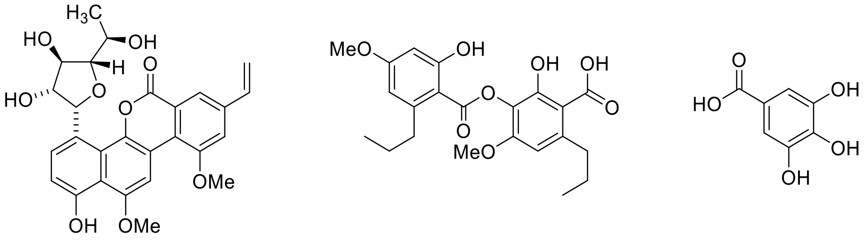
CHAPTER I

De Novo Synthesis of Arenes from Nonaromatic Precursors

1. Introduction

The arene structural motif constitutes an important building block in organic synthesis and it is also present in many biologically active natural compounds, such as gilvocarcin V, sekikaic acid or gallic acid (Figure 1).[1, 2]



gilvocarcin V *(DNA intercalation)* **sekikaic acid** *(CBP/p300 inhibitor)* **gallic acid** *(antioxidant)*

Figure 1: The arene structural motif as a component in natural products.

However, the synthesis of highly substituted arenes from either aromatic or nonaromatic precursors is difficult and previously developed chemistry often suffers from low selectivity or reactivity (Figure 2, methods A−C). Electrophilic aromatic substitution of electron-poor arenes (method A, green) generally requires harsh conditions and shows limited functional-group tolerance. Attempts to functionalize arenes bearing both an electron donating and an electron withdrawing group frequently results in poor regioselectivity due to the competing directing effects in the starting substrate (method B, red). Synthesis of arenes based on a cycloaddition strategy (method C, blue) require symmetrical substrates to access the desired substitution pattern.[3, 4]

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[1] a) T. Hosoya, E. Takashiro, T. Matsumoto, K. Suzuki, *J. Am. Chem. Soc.* **1994**, *116*, 1004–1015; b) C. Y. Majmudar, J.W. Højfeldt, C. J. Arevang, W. C. Pomerantz, J. K. Gagnon, P. J. Schultz, L. C. Cesa, C. H. Doss, S. P. Rowe, V. Vásquez, G. Tamayo-Castillo, T. Cierpicki, C. L. Brooks III, D. H. Sherman, A. K. Mapp, *Angew. Chem. Int. Ed.* **2012**, *51*, 11258–11262; c) S. M. Fiuza, C. Gomes, L. J. Teixeira, M. T. Girão da Cruz, M. N. D. S. Cordeiro, N. Milhazes, F. Borges, M. P. M. Marques, *Bioorg. Med. Chem.* **2004**, *12*, 3581–3589.

[2] a) B. Schäfer, *Naturstoffe der chemischen Industrie*, Elsevier, München, **2007**; b) T. Maki, K. Takeda, *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, **2011**.

[3] a) F. A. Carey, R. A. Sundberg, *Advanced Organic Chemistry*, Springer, Heidelberg, **2007**, pp. 1003–1056; F. Terrier, *Modern Nucleophilic Aromatic Substitution*, Wiley-VCH, Weinheim, **2013**.

[4] For selected examples, see: a) M. G. Weaver, W.-J. Bai, S. K. Jackson, T. R. R. Pettus, *Org. Lett.* **2014**, *16*, 1294–1297; b) S. Valente, Z. Xu, E. Bana, C. Zwergel, A. Mai, C. Jacob, P. Meiser, D. Bagrel, A. M. S. Silva, G. Kirsch, *Eur. J. Org. Chem.* **2013**, 2869–2877; c) S. Giroux, E. J. Corey, *Org. Lett.* **200**8, *10*, 5617–5619; d) A. Axelrod, A. M. Eliasen, M. R. Chin, K. Zlotkowski, D. Siegel, *Angew. Chem. Int. Ed.* **2013**, *52*, 3421–3424; *Angew. Chem.* **2013**, *125*, 3505–3508; e) T. Ziegler, M. Layh, F. Effenberger, *Chem. Ber.* **1987**, *120*, 1347–1355; f) A. Moreno, M. V. Gómez, E. Vázquez, A. de La Hoz, A. Diaz-Ortiz, P. Prieto, J. A. Mayoral, E. Pires, *Synlett* **2004**, 1259–1263; g) J. P. Broom, P. G. Sammes, *Chem. Commun.* **1978**, 162–164.

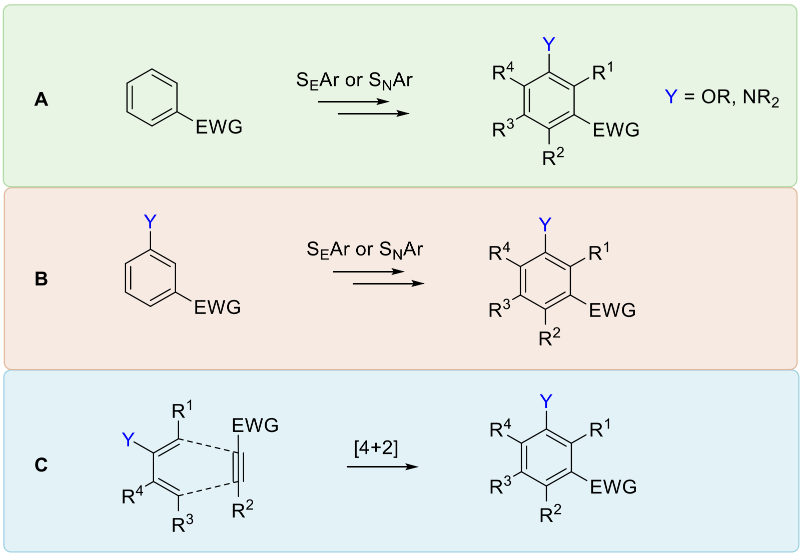

Figure 2: Established methods for the synthesis of polysubstituted arenes.

1.1 Synthesis of Polysubstituted Arenes

1.1.1 Electrophilic Aromatic Substitution

The most common method for the synthesis of polyfunctionalized arenes is the electrophilic aromatic substitution (S_EAr reaction). Classical examples of this reaction are the nitration of toluene or bromination using bromine and iron (III) bromide.[5]

An example for the use of an electrophilic aromatic substitution reaction is depicted in Scheme 1. Empagliflozin (**I.4**) was developed by Boehringer Ingelheim for the treatment of type 2 diabetes. Friedel-Crafts acylation of in situ formed acyl chloride derived from **I.1** and fluorobenzene **I.2** using aluminium (III) chloride as Lewis acid gave benzophenone **I.3** in excellent yield. The latter compound was then converted to empagliflozin **I.4** in six further steps.[6]

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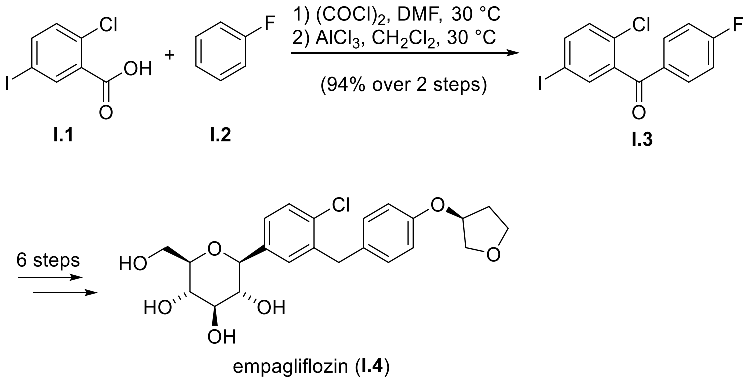
[5] R. Brückner, *Reaktionsmechanismen*, Springer, Heidelberg, **2010**.

[6] D. Weber, S. Renner, T. Fiedler, S. Orlich, **2011**, WO Patent 2011039107A1.

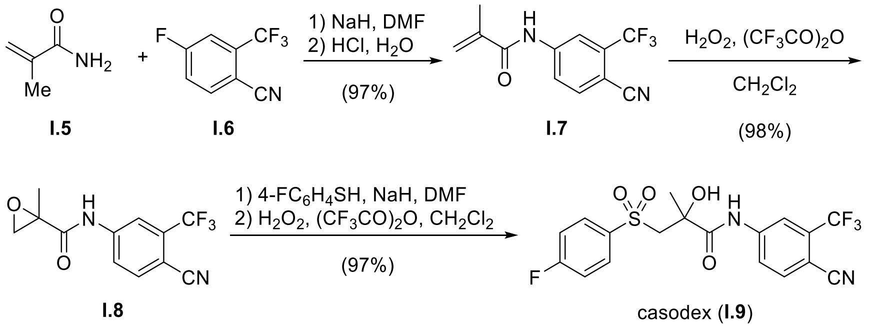


Scheme 1: Synthesis of empagliflozin (**I.4**).

1.1.2 Nucleophilic Aromatic Substitution

The substitution of polysubstituted arenes can also be achieved by nucleophilic aromatic substitution. In general, there are three subclasses of this reaction. The first subclass is the classic S$_N$Ar reaction via an addition-elimination mechanism of a nucleophile to an electron poor arene (the electron withdrawing groups help stabilize the anionic intermediate). Secondly, substitution reactions can occur via diazonium salts, such as in the Sandmeyer-reaction. Furthermore, substitution via benzyne intermediates lead to substituted arenes.

A synthesis of the anticancer drug casodex (**I.9**) by Chen and co-workers from Bristol-Myers Squibb used a nucleophilic aromatic substitution reaction of methacrylamide and fluorobenzene **I.6** to yield aryl amide **I.7** in almost quantitative yield.[7]



Scheme 2: Synthesis of anticancer drug **I.**9 via nucleophilic aromatic substitution.

Epoxidation and opening of the resulting oxirane ring, followed by oxidation of the thioether to sulfone **I.9** completed the synthesis in excellent yields.

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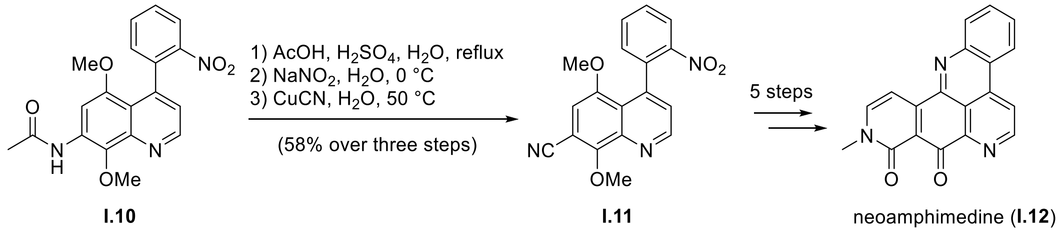
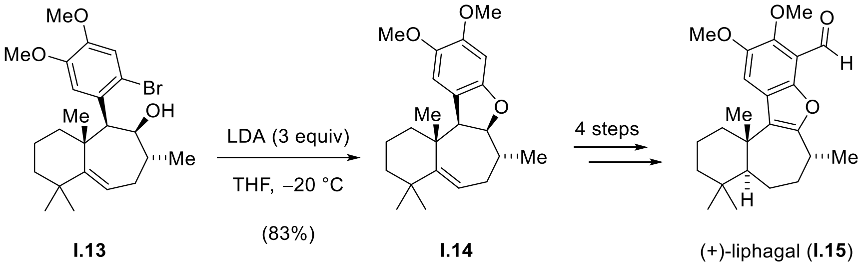
[7] J. C. Barrish, M.E. Salvati, J. E. Sundeen, B. Wang, S. Gove, R. Zhao, B.-C. Chen, *J. Org. Chem*. **2003**, *68*, 10181–10182.

In 2007, Ireland reported a total synthesis of the potent antitumor agent neoamphimedine (**I.12**) using a Sandmeyer reaction.[8] Amide **I.10** was hydrolyzed under acidic conditions followed by diazotation with sodium nitrite and subsequent treatment of the intermediate with cupric cyanide to give nitrile **I.11**. Five additional steps completed the synthesis.



Scheme 3: Total synthesis of antitumor agent neoamphimedine (**I.12**)

An example for the synthesis of polysubstituted arenes via nucleophilic addition to an aryne intermediate is shown in Scheme 4. Based on this method the Stoltz group reported a total synthesis of (+)-liphagal (**I.15**).



Scheme 4: Total synthesis of (+)-liphagal by Stoltz.

Aryl bromide **I.13** was treated with excess of lithium diisopropylamide to give dihydrobenzofurane **I.14** which was further converted to **I.15** in four steps.

1.1.3 Substitution via Organo-Metal Chemistry

Methods for the synthesis of polysubstituted arenes using organometal reactions also constitute a common tool for modern chemists. Transition-metal catalyzed cross coupling reactions are among the most important reactions for C–C bond formation.

The Csp^2–Csp^2 bond formation in the synthesis of the antiviral drug dasabuvir (**I.20**) was accomplished by a Suzuki–Miyaura cross coupling reaction of aryl iodide **I.16** and naphthyl boronic acid **I.17**.[9]

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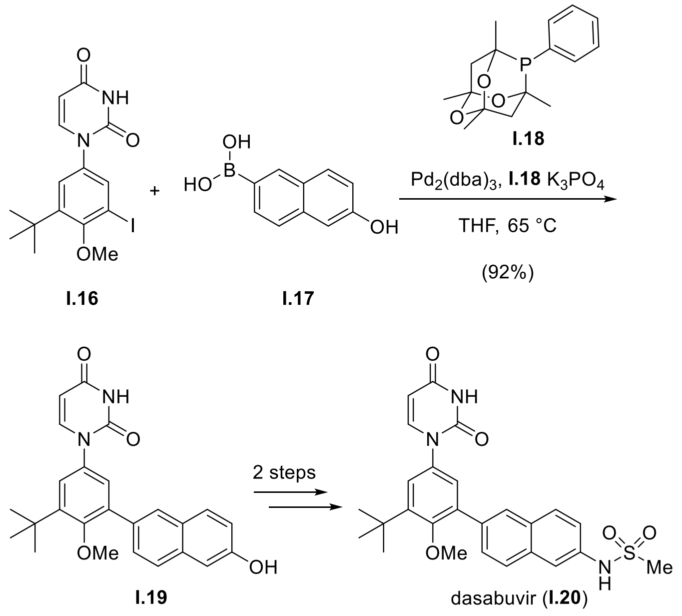
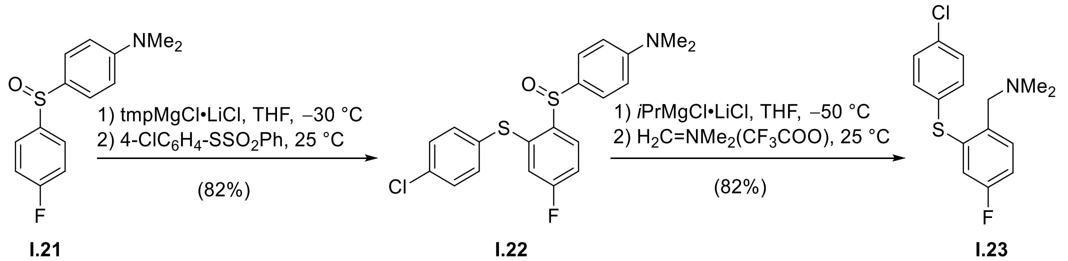
[8] D. V. LaBarbera, T. S. Bugni, C. M. Ireland, *J. Org. Chem*. **2007**, *72*, 8501–8505.

[9] A. C. Flick, H. X. Ding, C. A. Leverett, R. E. Kyne Jr., K. K.-C. Liu, S. J. Fink, C. J. O'Donnell, *Bioorg. Med. Chem*. **2016**, *24*, 1937–1980.



Scheme 5: Synthesis of dasabuvir (**I.20**) via Suzuki-Miyaura cross coupling reaction.

An example for a synthesis employing a key directed metalation reaction is shown in Scheme 6. The group of Knochel described a synthesis of serotonin reuptake inhibitor **I.23** starting from sulfoxide **I.21**.[10]



Scheme 6: Synthesis of serotonin reuptake inhibitor I.23.

The sulfoxide moiety serves as the directing group for the *ortho*-metalation of **I.21** using tmpMgCl·LiCl. Trapping of the magnesiated intermediate with aryl thiosulfonate led to aryl thiol ether **I.22**. Sulfoxide-magnesium exchange, followed by dimethylaminomethylation then gave **I.23** in very good yield.

Substitution of arenes via C–H activation can be achieved by either using directing groups, such as chelating heterocycles attached to the substrate, or by using bulky catalysts which functionalize sterically accessible C–H bonds. Activation of the *ortho*-position is most

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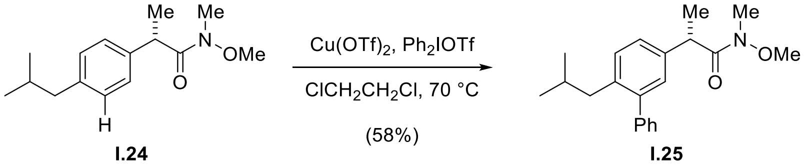
[10] C.B. Rauhut, L. Melzig, P. Knochel, *Org. Lett.* **2008**, *10*, 3891–3894.

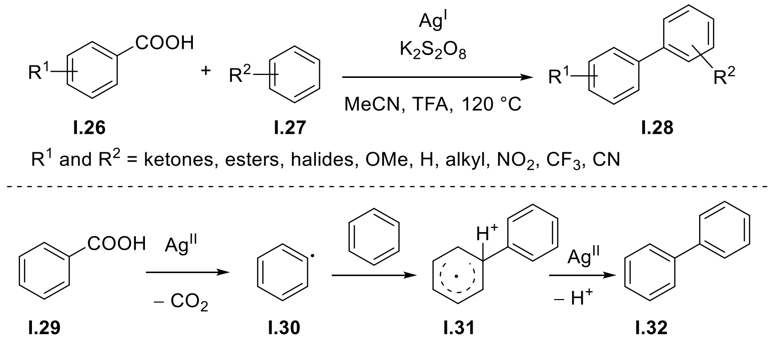
common, however, functionalization of the *meta*-position can be achieved by long-range directing groups.[11] On these grounds, Gaunt described a synthesis of ibuprofen derivative **I.25** via C–H bond activation of arene **I.24** (Scheme 7).[12]



Scheme 7: Synthesis of ibuprofen derivative **I.25** via C–H bond activation.

1.1.4 Minisci-Type Reaction

In 2015, Su and co-workers developed a method for the construction of biaryls **I.28** via silver-catalyzed Minisci-type reaction.[13] They applied aromatic carboxylic acids **I.26** and substituted arenes **I.27** in the presence of silver(I) salts and potassium persulfate. In general, they used various functional groups as substituents including, alkyl, aryl, halides and electron-donating and electron-withdrawing groups.



Scheme 8: Minisci-type reaction for the construction of biaryls.

Mechanistically, the first step is an oxidation of silver (I) to silver (II) by the persulfate anion. Oxidation of the carboxylic acid **I.29** leads to decarboxylation to generate the corresponding aryl radical **I.30** which then adds to benzene to form cyclohexandienyl radical intermediate **I.31**. Aromatization by oxidation with silver (II) gives arylated product **I.32**.[14]

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[11] S. W. Krska, P. Vachal, S. Tyagarajan, K. D. Dykstra, T. Cernak. *Chem. Soc. Rev*. **2016**, *45*, 546–576.

[12] H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps, M. J. Gaunt, *Angew. Chem. Int. Ed*. **2011**, *50*, 463–466.

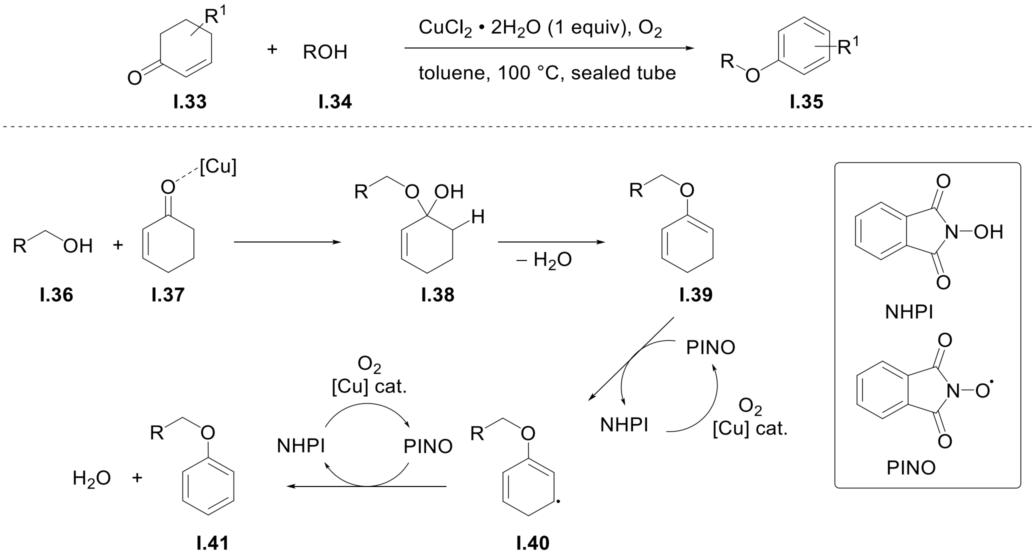
[13] J. Kan, S. Huang, J. Lin, W. Su, *Angew. Chem. Int. Ed*. **2015**, *54*, 2199–2003.

[14] For the synthesis of substituted arenes see: a) F. Sandfort, M. J. O'Neill, J. Cornella, L. Wimmer, P. S. Baran, *Angew. Chem. Int. Ed*. **2017**, *56*, 3319–3323; b) F. Toriyama, J. Cornella, L. Wimmer, T.-G. Chen, D. D. Dixon, G. Creech, P. S. Baran, *J. Am. Chem. Soc*. **2016**, *138*, 11132–11135.

1.2 Synthesis of Arenes from Nonaromatic Precursors

1.2.1 Dehydrogenation Strategies

Synthesis of substituted arenes via dehydrogenation strategies often use cyclohexanone derived precursors. One example was reported by the Li group in 2012, and the concept is presented in Scheme 9.[15] In this strategy, substituted cyclohexenones **I.33** and alcohols **I.34**, such as substituted phenols, β-citronellol or (−)-menthol, react to give substituted aryl ethers **I.35** in the presence of copper(II) chloride.



Scheme 9: Dehydrogenation approach to aryl ethers by Li.

Mechanistically, the reaction proceeds through hemiacetal **I.36**, which is formed by activation of **I.37** by copper (II) chloride. Elimination of water could lead to diene **I.39**. Finally, dehydrogenation with the in situ formed *N*-oxy radical affords aryl ether **I.41**.

Another methodology for the synthesis of polysubstituted arenes was reported by Jiang in 2013.[16] Cyclohexanones **I.42**, bearing a wide range of substituents, such as alkyl, methoxy, ester or aryl groups, reacted with alkyl or aryl *N*-protected thioureates **I.43** to provide 2-aminobenzthiazoles **I.44**. The 2-aminobenzthiazole structural motif can be found in pharmaceuticals such as riluzole (**I.45**) which is used as a treatment against amyotrophic lateral sclerosis.

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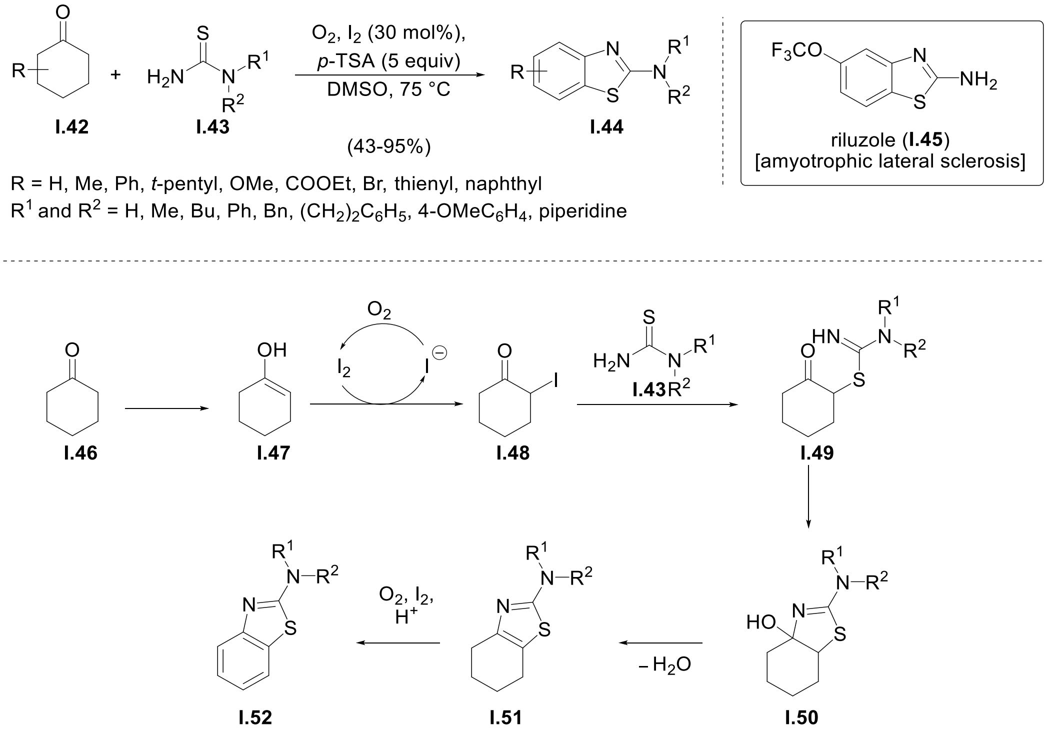
[15] M.-O. Simon, S. A. Girard, C.-J. Li, *Angew. Chem*, **2012**, *124*, 7655–7658.

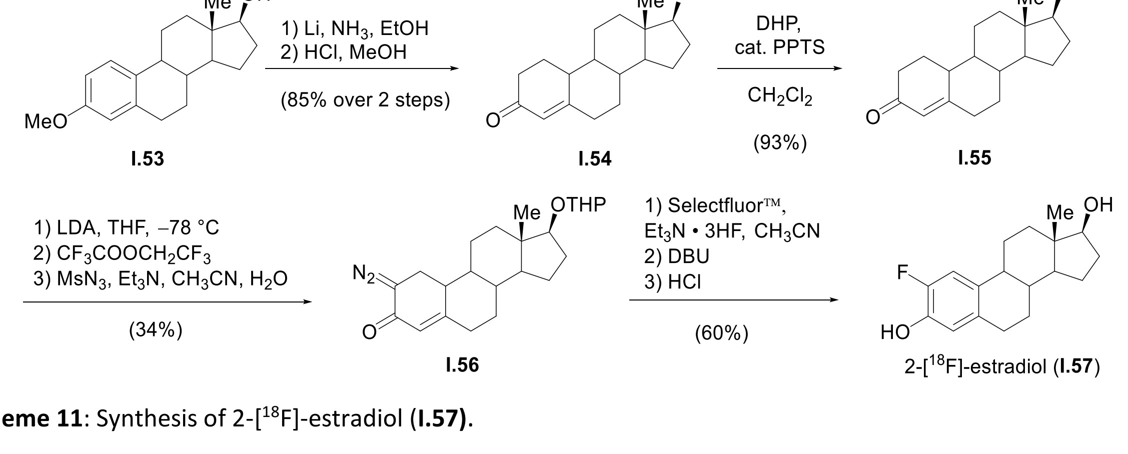
[16] J. Zhao, H. Huang, W. Wu, H. Chen, H. Jiang, *Org. Lett.* **2013**, *15*, 2604–2607.



Scheme 10: Synthesis of 2-aminobenzothiazoles **I.44** by Jiang.

Their proposed mechanism starts with the acid-promoted enolization of cyclohexanone **I.46** followed by α-iodination to generate **I.48**. Nucleophilic substitution with thiourea **I.43** provides **I.49** which further reacts to thiazole **I.51** via a condensation reaction onto the ketone. Subsequent aromatization then yields 2-aminobenzothiazole **I.52**.

In 2015, Katzenellenbogen reported the preparation of 2-[^{18}F]-estradiol (**I.57**), starting their synthesis from methylestradiol **I.53**. First, Birch reduction, followed by hydrolysis and isomerization of the double bond under acidic conditions gave enone **I.54**.[17]



Scheme 11: Synthesis of 2-[^{18}F]-estradiol (**I.57)**.

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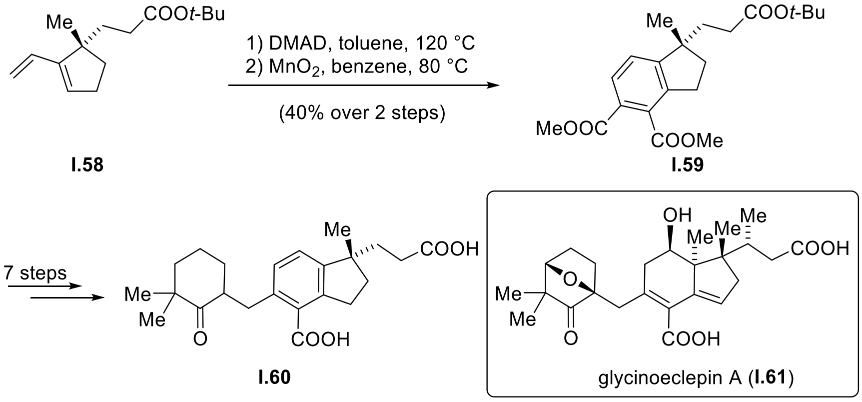
[17] N. Yasui, C. G. Mayne, J. A. Katzenellenbogen, *Org. Lett.* **2015**, *17*, 5540–5543.

Protection of the C-17 hydroxy group as the tetrahydropyran ether **I.55**, followed by *α*-diazotization provided diazoketone **I.56**. α,α-Difluorination with Selectfluor™, elimination using 1,8-diazabicyclo[5.4.0]unde-7-en and deprotection then afforded **I.57** in 60% over three steps.

1.2.2 [4+2] Cycloaddition Reactions

The [4+2] cycloaddition reaction is a powerful tool for the construction of six-membered ring systems. One demonstration of a Diels–Alder reaction in the field of arene-synthesis was reported by E. J. Corey and co-workers. A Diels–Alder reaction of diene **I.58** and dimethyl acetylenedicarboxylate was conducted to obtain the corresponding cycloaddition product.[18]



Scheme 12: [4+2] Cycloaddition reaction of **I.58** and DMAD.

Oxidation of the Diels–Alder product with manganese oxide provided tetrasubstituted benzene derivative **I.59** which was further converted to the analogue **I.60** of the agrochemical glycinoeclepin A (**I.61**).

In 2012, Thomas Hoye described the synthesis of indanones **I.63** via hexadehydro-Diels–Alder reaction of tetrayne **I.62** (Scheme 13).[19] Oxidation of **I.62** with manganese dioxide at room temperature, led to intramolecular [4+2]-cycloaddition to give benzyne **I.65** or its structural isomer **I.64**. The benzyne derivative can then be trapped intra- or intermolecularly using various nucleophiles. Zwitterion **I.66** is formed by intramolecular trapping of **I.65** with a TBS-protected alcohol. Retro-Brook rearrangement then affords indanone **I.65** as the final product.

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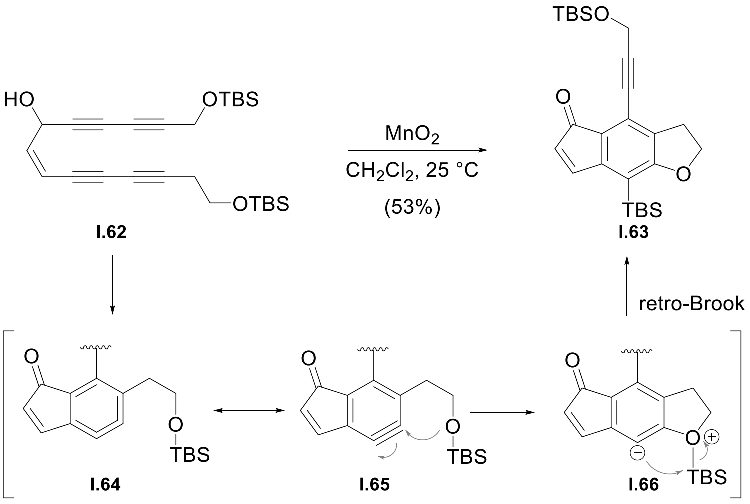
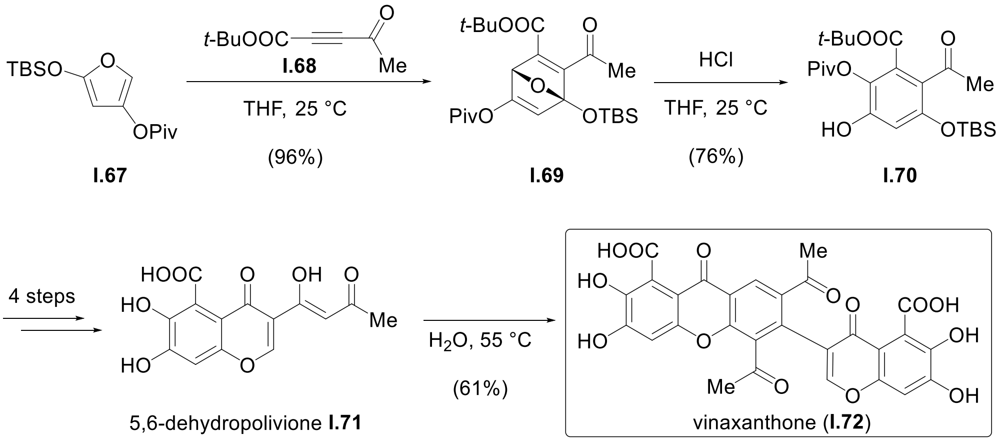
[18] S. Giroux, E. J. Corey, *Org. Lett.* **2008**, *10*, 5617–5619.

[19] B. P. Woods, P. H. Willoughby, D. Niu, B. Baire, T. R. Hoye, *Nature*, **2012**, *490*, 208–212.



Scheme 13: Hexadehydro-Diels–Alder reaction of tetrayne **I.62**.

The Diels–Alder reaction was utilized in the total synthesis of vinaxanthone (**I.72**) by Siegel and co-workers.[20] Regioselective Diels–Alder reaction of furan **I.67** and keto ester **I.68** furnished bicyclic product **I.69**. Aromatization to **I.70** was achieved by treatment with hydrochloric acid in tetrahydrofuran. Interestingly, during the aromatization step migration of the pivaloyl group occured to provide **I.70**.



Scheme 14: Diels–Alder reaction in the total synthesis of vinaxanthone (**I.72**).

Vinaxanthone (**I.72**) was then obtained via a Michael addition-elimination-6π-electrocyclization-cascade of 5,6-dehydropolivione **I.71**.

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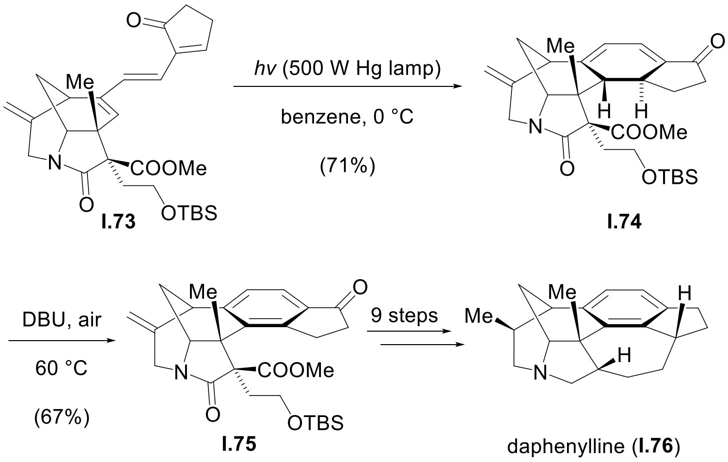
[20] A. Axelrod, A. M. Eliasen, M. R. Chin, K. Zlotkowski, D. Siegel, *Angew. Chem. Int. Ed.* **2013**, *52*, 3421–3424.

1.2.3 6π-Electrocyclization Reactions

In the total synthesis of the *Daphniphyllum* alkaloid daphenylline (**I.76**) the Li group used a 6π-electrocyclization approach to form the aromatic core of the natural product.[21] They first attempted to construct the aromatic core via a thermally induced 6π-electrocyclization, however, triene **I.73** was found to be reluctant to undergo the 6π-electrocyclization under thermal conditions.



Scheme 15: Ang Li’s total synthesis of daphenylline (**I.76**) via 6π-electrocyclization.

It was further found that attempted Lewis acid promoted cyclization led to decomposition. Finally, cyclization product **I.74** was formed by photoirradiation through an isomerization/electrocyclization cascade. To convert the diene **I.74** to the desired benzene derivative **I.75**, various oxidants or dehydrogenation reagents such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, manganese dioxide or palladium, were investigated. However, these conditions only resulted in decomposition. In the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene and air, **I.75** was eventually obtained in 67% yield.

In 2016, the same group achieved the total synthesis of rubriflordilactone B (**I.79**) via a 6π-electrocyclization-aromatization sequence starting from triene-yne **I.77**.[22]

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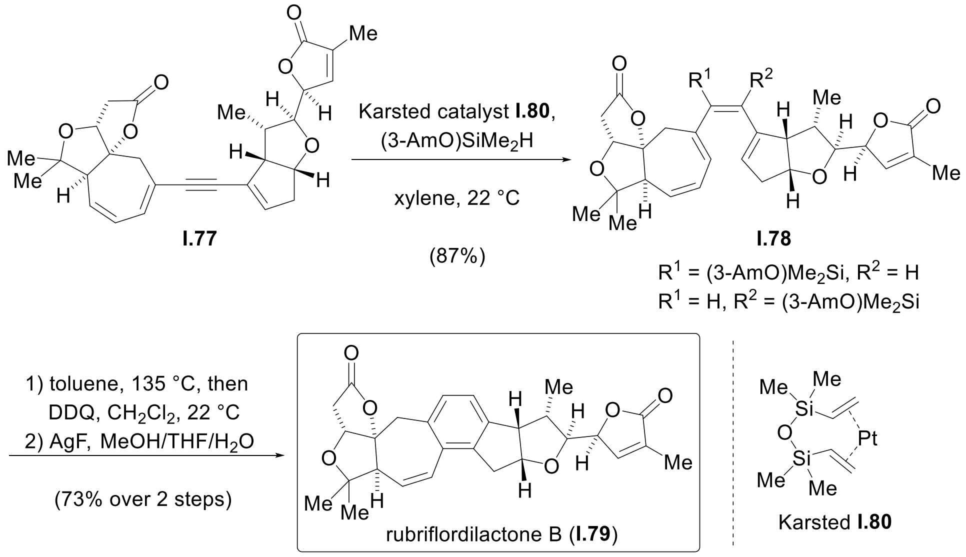
[21] Z. Lu, J. Deng, A. Li, *Nature Chem*. **2012**, *134*, 8078–8081.

[22] P. Yang, M. Yao, J. Li, Y. Li, A. Li, *Angew. Chem. Int. Ed*. **2016**, *55*, 6964–6968.



Scheme 16: Ang Li's aromatization strategy to rubriflordilactone B (**I.79**).

They performed the hydrogenation with Karsted's catalyst and silylation reagent (3-pentylO)$SiMe_2H$ which cleanly delivered triene **I.78** as an inconsequential mixture of regioisomers. Finally, electrocyclization-aromatization with 2,3-dichloro-5,6-*p*-benzoquinone and desilylation afforded rubriflordilactone B (**I.79**).

1.2.4 Transition Metal-Catalyzed Reactions

A demonstration for the use of transition metals in the synthesis of arenes is depicted in Scheme 17. Sorensen and co-workers used a rhodium-catalyzed [2+2+2] cyclotrimerization reaction for the total synthesis of viridin (**I.86**), which is a potent antifungal metabolite of *Gliocladium virens*.[23]

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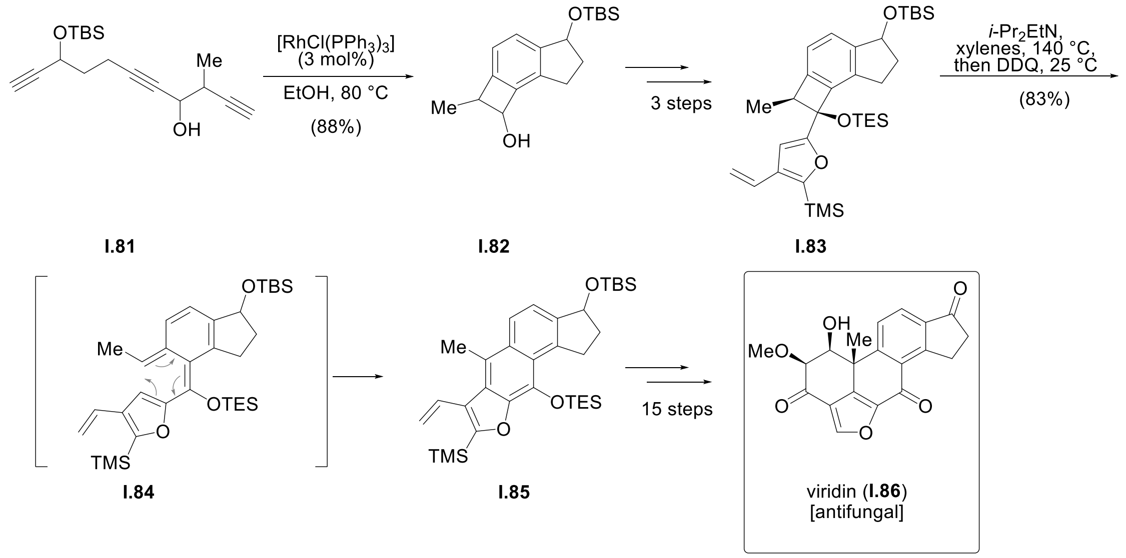
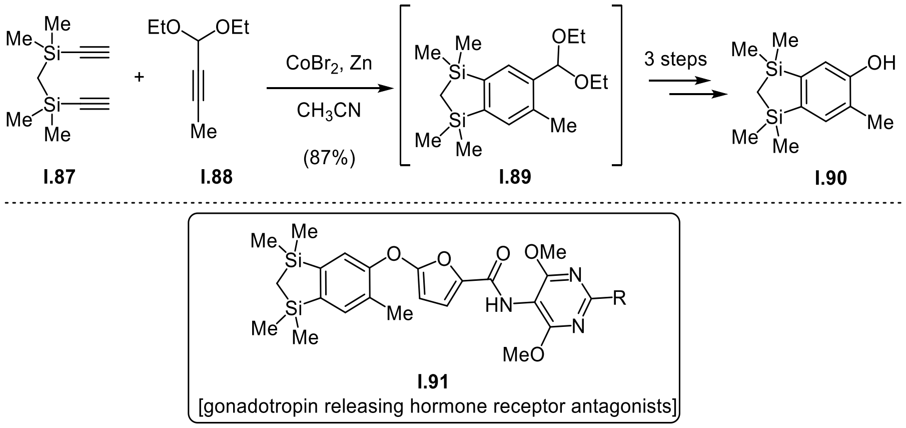
[23] E. A. Anderson, E. J. Alexanian, E. J. Sorensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 1998–2001.



Scheme 17: A [2+2+2] cyclotrimerization reaction in the total synthesis of viridn (**I.86**).

Tetrasubstituted benzene **I.82** was obtained via a Wilkinson's catalyst induced [2+2+2] cyclization of triyne **I.81** in a refluxing solution of ethanol. Tetracycle **I.83** was then formed in three steps from **I.82**. Ring-opening of the cyclobutene structural motif in **I.83**, and 6π-electrocyclization reaction gave naphthol **I.85** which was further converted to viridin (**I.86**) in 15 additional steps.

For a large-scale synthesis of disilaindan-5-ol **I.90**, the Kawamoto group used a cobalt/zinc-catalyzed [2+2+2] cyclotrimerization reaction.[24] Trimerization of **I.87** and alkyne **I.88** provided intermediate **I.89** which was hydrolyzed in situ and further converted to **I.90** via Baeyer-Villiger oxidation and saponification.



Scheme 18: Large-scale synthesis of disilaindan-5-ol **I.90**.

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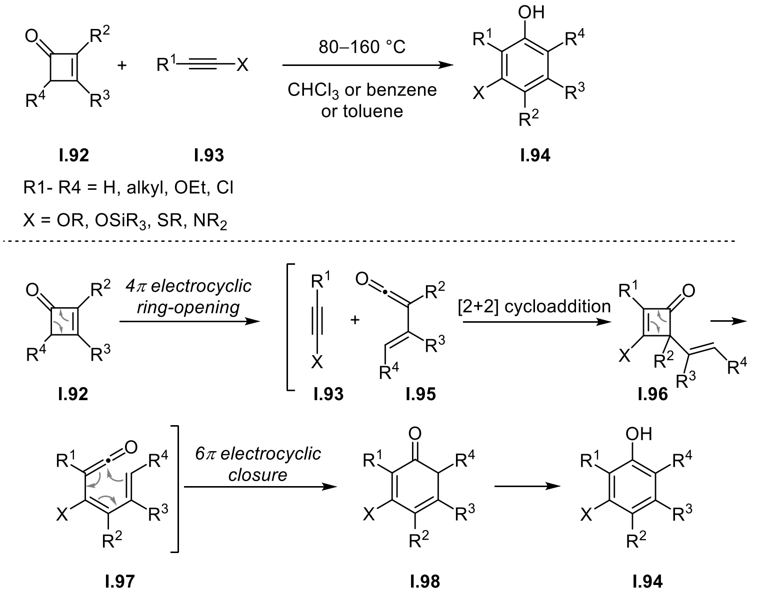
[24] R. Mizojiri, R. Conroy, J. Daiss, E. Kotani, R. Tacke, D. Miller, L. Walsh, T. Kawamoto, *Tetrahedron* **2010**, *66,* 7738–7742.

Disilaindan-5-ol **I.90** can be further transformed to potential gonadotropin releasing hormone receptor antagonists **I.91.**

1.2.5 Ring Expansion Reactions of Cyclobutenones

An example for the construction of highly substituted arenes **I.94** from cyclobutenones **I.92** was described by Danheiser in 1984.[25] The reaction proceeds through a thermally induced 4π-electrocyclic ring-opening of cyclobutenone **I.92** to provide vinyl ketene **I.95**.



Scheme 19: Ring-opening aromatization sequence by Danheiser.

Cycloaddition of **I.95** with silyloxyacetylene **I.93** lead to vinyl cyclobutanone **I.96** which undergoes another 4π-electrocyclic ring-opening and subsequent 6π-electrocyclic ring-closure to afford ketone **I.98** which tautomerizes to phenol **I.94**.

The Kowalski group applied the Danheiser electrocylization strategy in a total synthesis of the minor, physiologically active cannabinoid isomer Δ-6-tetrahydrocannabinol (**I.102**) (Scheme 20).[26]

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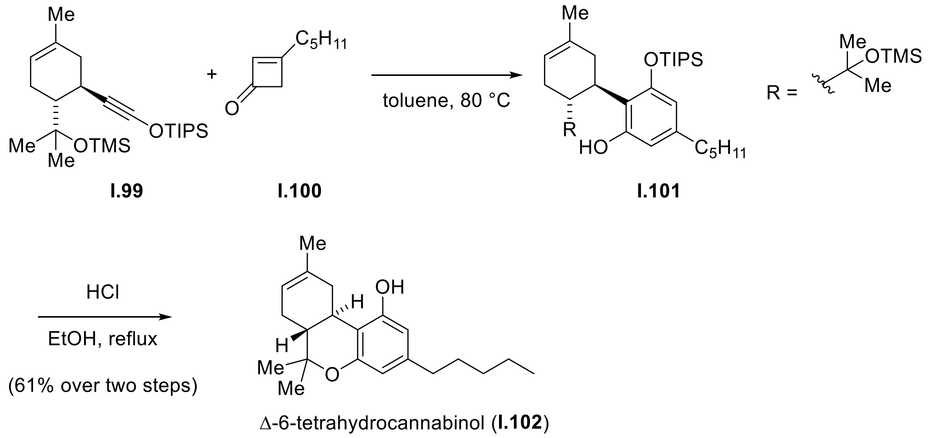
[25] S. K. Gee, R. L. Danheiser, *J. Org. Chem.* **1984**, *49*, 1672–1674.

[26] G. S. Lal, C. J. Kowalski, *J. Am. Chem. Soc.* **1988**, *110*, 3693–3695.



Scheme 20: Total synthesis of **I.102**.

A solution of silyloxyacetylene **I.99** and cyclobutanone **I.100** in toluene was heated to 80 °C and the corresponding resorcinol derivative **I.101** was obtained. Without purification, **I.101** was heated to reflux in acidic ethanol and thus converted to Δ-6-tetrahydrocannabinol (**I.102**) in 61% yield over two steps from **I.99**.

1.2.6 Ring Expansion Reactions of Cyclopropanes[27]

In 1985, Bickelhaupt reported a strategy for the synthesis of halogenated *m*-xylenes **I.107** and **I.110** via a ring-opening aromatization reaction of bicyclo[3.1.0]hexanes **I.106** and **I.109** (Scheme 21).[28] The sequence started with a dichlorocarbene cyclopropanation reaction of diene **I.103**. Thermal induced vinyl cyclopropane rearrangement[29] furnished *gem*-dichlorocyclopentene **I.105** in excellent yields. Cyclopropanation under phase-transfer conditions using cetyltrimethylammonium bromide (CTAB) then gave the corresponding unstable bicyclo[3.1.0]hexanes **I.106**.

The ring-opening aromatization reaction to 5-chloro-*m*-xylenes **I.107** could be achieved by stirring **I.106** and silver perchlorate, 2,6-dimethylpyridine in tetrahydrofuran or using potassium *tert*-butoxide in dimethyl sulfoxide. However, the yield of the aromatization reaction was found to be superior by simply heating the starting material in toluene at 110 °C.

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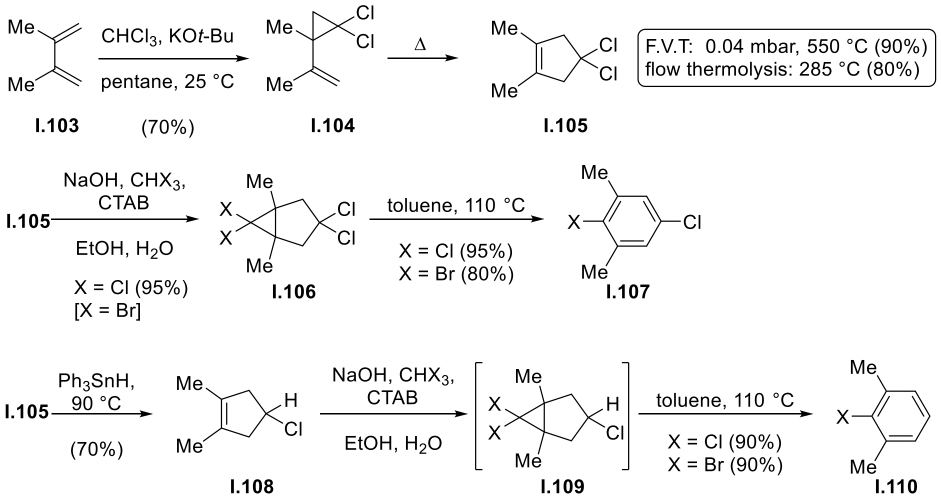
[27] Selected example for the ring opening of bicyclo[4.1.0]heptanes to α-tropolones: R. Kats-Kagan, S. B. Herzon, *Org. Lett.* **2015**, *17*, 2030–2033.

[28] L. W. Jenneskens, W. H. De Wolf, F. Bickelhaupt, *Synthesis*, **1985**, 647–649.

[29] Selected reviews: a) Z. Goldschmidt, B. Crammer, *Chem. Soc. Rev.* **1988**, *17*, 229–267; b) J. W. Reed, T. Hudlicky, *Angew. Chem. Int. Ed.* **2010**, *49*, 4864–4876.



Scheme 21: Ring-opening aromatization reaction of bicyclo[3.1.0]hexanes **I.106** and **I.109** to halogenated *m*-xylenes **I.107** and **I.110**.

For the synthesis of 2-halo-*m*-xylenes **I.110**, *gem*-dichlorocyclopentene **I.105** was hydro dechlorinated using triphenylstannane. Cyclopropanation reaction of **I.108** then directly provided 2-halo-*m*-xylenes **I.110** in high yields.

Another example for the synthesis of substituted arenes via ring expansion of cyclopropanes is shown in Scheme 22. Fukuyama began his investigations with *gem*-dibromobicyclo[3.1.0]hexane **I.112** which was prepared in three steps from methyl ester **I.111**.[30] Electrocyclic ring-opening and concomitant loss of bromide provided allylic cation **I.114**. Deprotonation of **I.115** with 2,6-lutidine and subsequent dehydration gave *para*-substituted bromobenzene **I.113**. In general, alkyl and aryl methyl esters could be employed and the yield for the ring-opening aromatization reaction was excellent.

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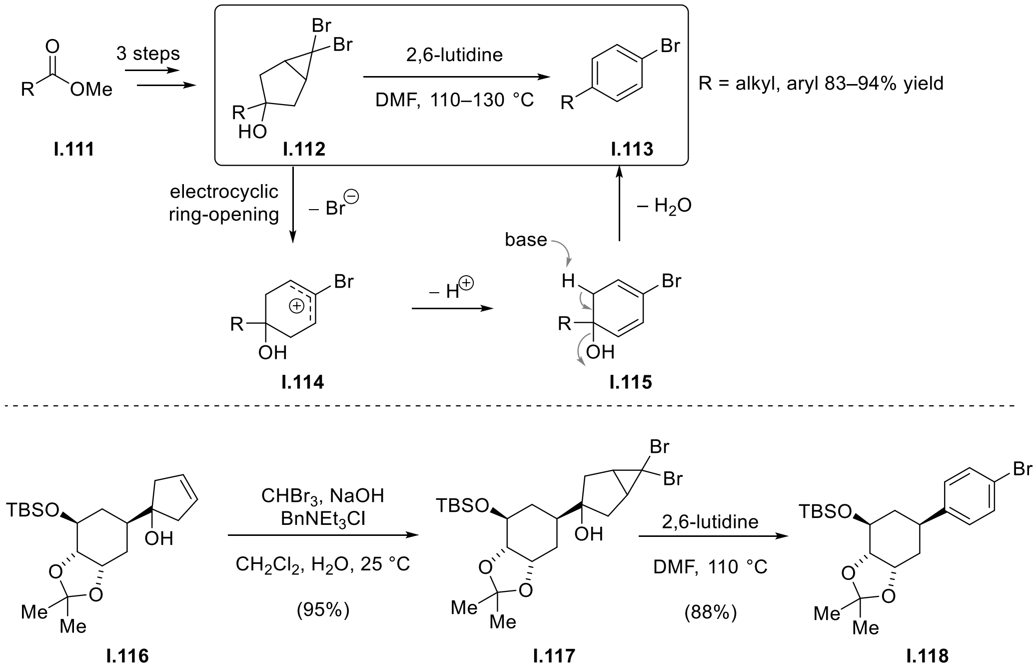
[30] K. Ueda, H. Umihara, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2015**, *17*, 3191–3193.

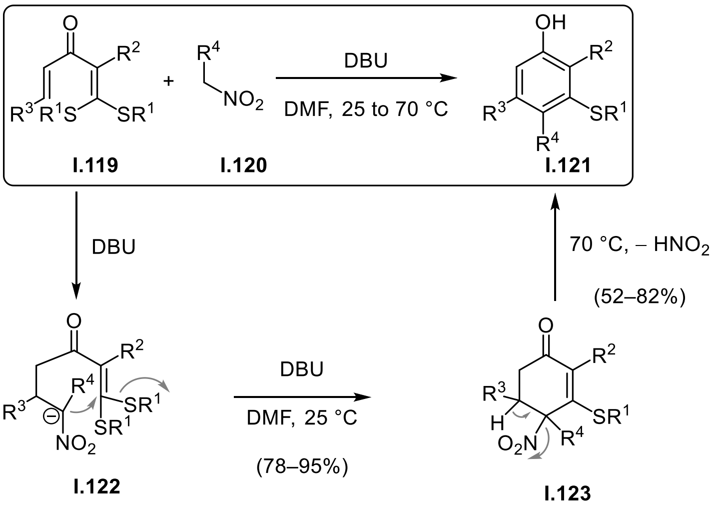


Scheme 22: Fukuyama's approach on the synthesis of arenes via ring-opening of cyclopropanes.

This methodology was applied to cyclopentane **I.116** which was cyclopropanated under phase-transfer conditions in almost quantitative yields. Electrocyclic ring-opening furnished 4-bromobenzene **I.118**.

1.2.7 Miscellaneous Strategies

In 2005, the Dong group reported a strategy for the synthesis of aryl thiol ethers **I.121** via a [5+1] annulation reaction (Scheme 23).[31] In the first step, the anion of nitroalkane **I.120** adds to the Michael acceptor **I.119** to form anionic intermediate **I.122**.



R^1 = Me, Et or *n*-Bu,
R^2 = C_6H_5CO, 4-ClC_6H_4NHCO, 2-MeC_6H_4NHCO,
R^3 = 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 3,4-$O_2CH_2C_6H_3$, 2-thienyl, 2-furyl, $C_6H_4CH{=}CH$
R^4 = Me, Et, COOEt

Scheme 23: [5+1] Annulation strategy for the synthesis of aryl thioethers **I.121**.

Intramolecular cyclization of the anion followed by subsequent elimination of alkyl thiolate led to cyclohexanone **I.123**, which could be isolated. Loss of nitrous acid and tautomerization furnished highly substituted aryl thioether **I.121**.

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[31] X. Bi, D. Dong, Q. Liu, W. Pan, L. Zhao, B. Li, *J. Am. Chem. Soc.* **2005**, *127*, 4578–4579.

2. Results and Discussion

2.1 Ring-opening of Bicyclo[3.1.0]hexan-2-ones: A Versatile Synthetic Platform for the Construction of Substituted Benzoates

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Angewandte Chemie International Edition

Arenes

International Edition: DOI: 10.1002/anie.201506232
German Edition: DOI: 10.1002/ange.201506232

Ring Opening of Bicyclo[3.1.0]hexan-2-ones: A Versatile Synthetic Platform for the Construction of Substituted Benzoates

*Johannes Feierfeil, Adriana Grossmann, and Thomas Magauer**

Abstract: *Described is the development of a highly efficient 2π disrotatory ring-opening aromatization sequence using bicyclo[3.1.0]hexan-2-ones. This unprecedented transformation efficiently proceeds under thermal conditions and allows facile construction of uniquely substituted and polyfunctionalized benzoates. In the presence of either amines or alcohols formation of substituted anilines or ethers, respectively, is achieved. Additionally, the utility of this method was demonstrated in a short synthesis of sekikaic acid methyl ester.*

Substituted benzoic acid derivatives are ubiquitous in nature and they are highly valuable building blocks for organic synthesis.[1] Within this substance class, the 3-hydroxybenzoate structural motif constitutes a prominent subunit that can be found in several biologically active molecules (Figure 1).[2]

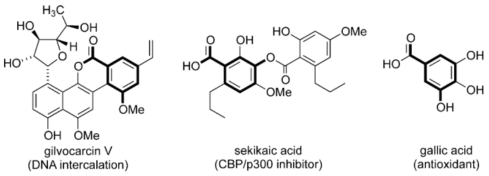


Figure 1. The 3-hydroxybenzoate structural motif as a component of biologically active natural products. LHMDS = lithium hexamethyldisilazane.

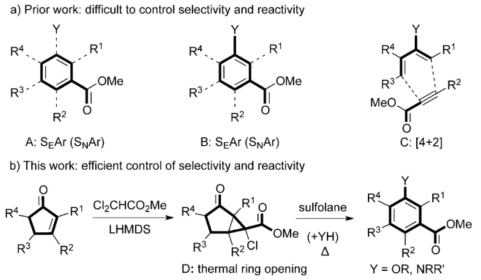
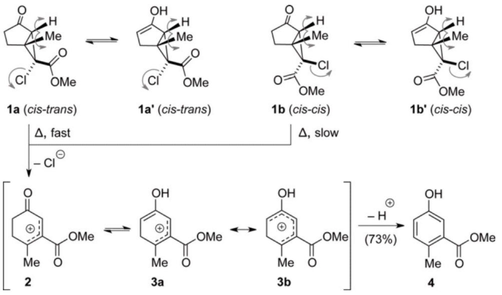


Figure 2. a) Traditional methods for the synthesis of polyfunctionalized benzoates. b) Thermal ring-opening aromatization of bicyclo-[3.1.0]hexan-2-ones.

Conventional syntheses of polysubstituted 3-hydroxybenzoates from either aromatic (linear assembly) or acyclic (convergent assembly) precursors are complicated by difficulties arising from low reactivity and poor selectivity (Figure 2a, methods A–C). The electrophilic aromatic substitution of electron-poor benzoates (method A) requires harsh reaction conditions and shows limited functional-group tolerance.[3] For method B, the directing electronic effects of the ester and electron-donating substituents (Y = OR, NRR′) are mismatched and result in poor regioselectivity. Strategies based on the [4+2] cycloaddition of dienes with alkynoates (method C) usually require symmetrical substrates to allow formation of the desired 1,3-orientation.[4]

As part of our recent efforts to develop new chemical methods for the synthesis of uniquely substituted phenols and naphthols,[5] we discovered that bicyclo[3.1.0]hexan-2-ones undergo an efficient thermal 2π disrotatory ring-opening aromatization sequence to afford a broad array of highly substituted benzoates (Figure 2b). By virtue of its substrate structure, this transformation enables simple control of selectivity and reactivity, and expands the repertoire of retrosynthetic bond disconnections for natural product synthesis. Herein, we report our preliminary results of this unprecedented transformation.[6–8]

We began our investigations with bicyclo[3.1.0]hexan-2-ones **1a/b** (d.r. = 4:1), which are readily available from the reaction of 3-methyl-2-cyclopenten-1-one with the lithium enolate of inexpensive methyl dichloroacetate (Scheme 1).[9]



Scheme 1. 2π Disrotatory ring-opening aromatization of a 4:1 diastereomeric mixture of **1a** and **1b** (sulfolane, 190 °C) to afford **4**.

---

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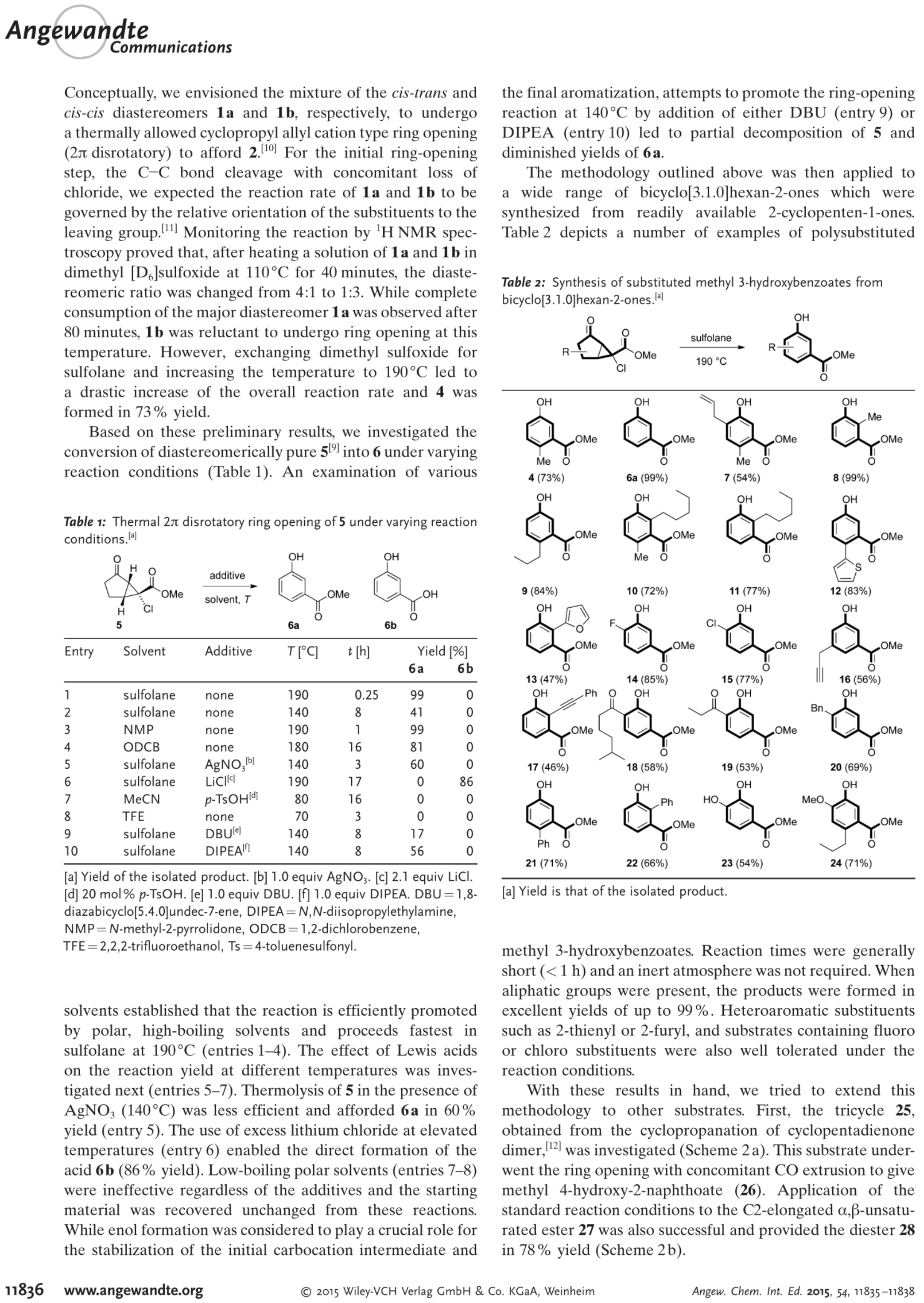
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201506232.



Conceptually, we envisioned the mixture of the *cis-trans* and *cis-cis* diastereomers **1a** and **1b**, respectively, to undergo a thermally allowed cyclopropyl allyl cation type ring opening (2π disrotatory) to afford **2**.[10] For the initial ring-opening step, the C–C bond cleavage with concomitant loss of chloride, we expected the reaction rate of **1a** and **1b** to be governed by the relative orientation of the substituents to the leaving group.[11] Monitoring the reaction by ^{1}H NMR spectroscopy proved that, after heating a solution of **1a** and **1b** in dimethyl [D$_6$]sulfoxide at 110°C for 40 minutes, the diastereomeric ratio was changed from 4:1 to 1:3. While complete consumption of the major diastereomer **1a** was observed after 80 minutes, **1b** was reluctant to undergo ring opening at this temperature. However, exchanging dimethyl sulfoxide for sulfolane and increasing the temperature to 190°C led to a drastic increase of the overall reaction rate and **4** was formed in 73% yield.

Based on these preliminary results, we investigated the conversion of diastereomerically pure **5**[9] into **6** under varying reaction conditions (Table 1). An examination of various solvents established that the reaction is efficiently promoted by polar, high-boiling solvents and proceeds fastest in sulfolane at 190°C (entries 1–4). The effect of Lewis acids on the reaction yield at different temperatures was investigated next (entries 5–7). Thermolysis of **5** in the presence of AgNO$_3$ (140°C) was less efficient and afforded **6a** in 60% yield (entry 5). The use of excess lithium chloride at elevated temperatures (entry 6) enabled the direct formation of the acid **6b** (86% yield). Low-boiling polar solvents (entries 7–8) were ineffective regardless of the additives and the starting material was recovered unchanged from these reactions. While enol formation was considered to play a crucial role for the stabilization of the initial carbocation intermediate and the final aromatization, attempts to promote the ring-opening reaction at 140°C by addition of either DBU (entry 9) or DIPEA (entry 10) led to partial decomposition of **5** and diminished yields of **6a**.

Table 1: Thermal 2π disrotatory ring opening of **5** under varying reaction conditions.[a]

Entry	Solvent	Additive	*T* [°C]	*t* [h]	Yield [%]	
					6a	**6b**
1	sulfolane	none	190	0.25	99	0
2	sulfolane	none	140	8	41	0
3	NMP	none	190	1	99	0
4	ODCB	none	180	16	81	0
5	sulfolane	AgNO$_3$[b]	140	3	60	0
6	sulfolane	LiCl[c]	190	17	0	86
7	MeCN	*p*-TsOH[d]	80	16	0	0
8	TFE	none	70	3	0	0
9	sulfolane	DBU[e]	140	8	17	0
10	sulfolane	DIPEA[f]	140	8	56	0

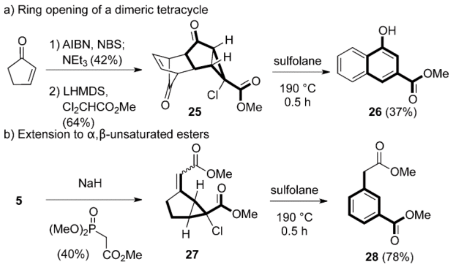
[a] Yield of the isolated product. [b] 1.0 equiv AgNO$_3$. [c] 2.1 equiv LiCl. [d] 20 mol% *p*-TsOH. [e] 1.0 equiv DBU. [f] 1.0 equiv DIPEA. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA = *N*,*N*-diisopropylethylamine, NMP = *N*-methyl-2-pyrrolidone, ODCB = 1,2-dichlorobenzene, TFE = 2,2,2-trifluoroethanol, Ts = 4-toluenesulfonyl.

The methodology outlined above was then applied to a wide range of bicyclo[3.1.0]hexan-2-ones which were synthesized from readily available 2-cyclopenten-1-ones. Table 2 depicts a number of examples of polysubstituted methyl 3-hydroxybenzoates. Reaction times were generally short (< 1 h) and an inert atmosphere was not required. When aliphatic groups were present, the products were formed in excellent yields of up to 99%. Heteroaromatic substituents such as 2-thienyl or 2-furyl, and substrates containing fluoro or chloro substituents were also well tolerated under the reaction conditions.

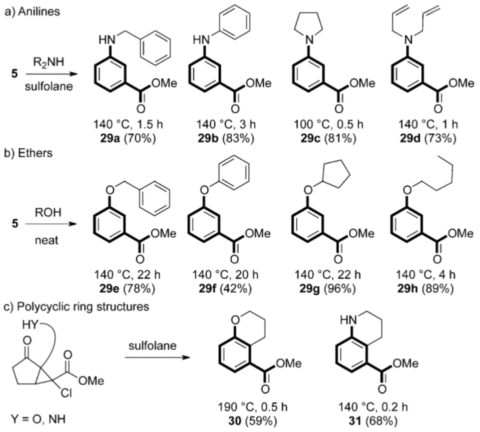
Table 2: Synthesis of substituted methyl 3-hydroxybenzoates from bicyclo[3.1.0]hexan-2-ones.[a]

[a] Yield is that of the isolated product.

With these results in hand, we tried to extend this methodology to other substrates. First, the tricycle **25**, obtained from the cyclopropanation of cyclopentadienone dimer,[12] was investigated (Scheme 2a). This substrate underwent the ring opening with concomitant CO extrusion to give methyl 4-hydroxy-2-naphthoate (**26**). Application of the standard reaction conditions to the C2-elongated α,β-unsaturated ester **27** was also successful and provided the diester **28** in 78% yield (Scheme 2b).



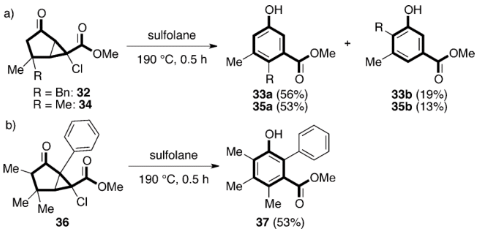
Scheme 2. Extension of the ring-opening reaction. AIBN = 2, 2′-azoisobutyronitrile.



Scheme 3. Synthesis of a) aryl ethers, b) amines, and c) polycyclic ring structures in the presence of O or N nucleophiles.

To further explore the synthetic utility of our methodology, we investigated the in situ condensation of the carbonyl group with simple O and N nucleophiles (Scheme 3). Remarkably, in the presence of an amine (2 equiv) the ring-opening reaction of **5** to the aniline derivatives **29 a–d** proceeded efficiently at temperatures as low as 100 °C. This observation supports our mechanistic hypothesis that enolization (enamine formation) plays a key role for the stabilization of the intermediate carbocation formed during the ring opening.

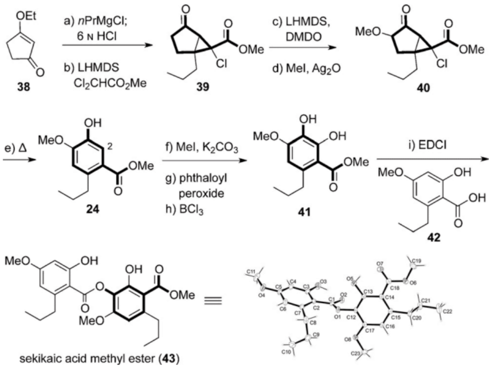
Substitution of sulfolane with high-boiling alcohols such as benzyl alcohol, phenol, cyclopentanol, or 1-pentanol allowed the straightforward synthesis of the protected phenols **29 e–h** in good yield (Scheme 3 b). Lower-boiling alcohols such as hexafluoro-2-propanol, 2,2,2-trifluoroethanol, or 2-methyl-1-butanol resulted in no product formation.[13] To demonstrate that this reaction also enables access to polycyclic ring structures, the nucleophile was tethered to the bicyclo[3.1.0]hexan-2-one framework as shown in Scheme 3 c.



Scheme 4. Thermal ring opening with simultaneous [1,2] shift to give highly substituted methyl 3-hydroxybenzoates.

According to the previously presented mechanistic hypothesis, we envisioned substrates containing a quaternary carbon center to undergo a consecutive ring opening/[1,2] shift (Scheme 4). To determine if this [1,2] shift can be triggered under the standard reaction conditions, we prepared the model substrates **32**, **34**, and **36**. To our delight, thermolysis of **32** and **34** led to the formation of the regioisomeric products **33 a/b** and **35 a/b**, respectively, in good yield, and they were readily separated by column chromatography on silica gel. For **32**, exclusive migration of the benzyl group in preference to the methyl group was observed. Installation of an additional substituent as shown for **36** enabled access to the hexasubstituted benzoate **37** in 53 % yield.

Finally, we set out to apply this methodology to the synthesis of the highly potent GACKIX inhibitor sekikaic acid methyl ester (**43**; Scheme 5).[2d] We began our synthesis with 3-ethoxy-2-cyclopentenone (**38**) which was converted into **39** in two steps. Upon exposure of the lithium enolate of **39** to dimethyldioxirane and treatment of the resulting



Scheme 5. Synthesis and X-ray structure[16] of sekikaic acid methyl ester (**43**). Reagents and conditions: a) *n*PrMgCl, THF, then 6 N HCl, 74 %; b) LHMDS, Cl$_2$CHCO$_2$Me, THF, −78 °C to 23 °C, 23 %; c) LHMDS, DMDO, THF, −78 °C, 60 %; d) MeI, Ag$_2$O, MgSO$_4$, 94 %; e) sulfolane, 190 °C, 20 min, 71 %; f) MeI, K$_2$CO$_3$, DMF, 55 °C, 94 %; g) phthaloyl peroxide, TFE, then MeOH, aq. NaHCO$_3$, 94 %; h) BCl$_3$, CH$_2$Cl$_2$, 0 °C, 59 %; i) EDCI, DMAP, THF, **42**, 80 %. DMAP = 4-(dimethylamino)pyridine, DMDO = dimethyldioxirane, DMF = *N*,*N*-dimethylformamide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, THF = tetrahydrofuran.

α-hydroxy ketone with methyl iodide, clean formation of the α-methoxy product was observed. Ring opening of **40** proceeded smoothly and afforded **24** in 71% yield. After methylation of the free phenol, the phthaloylperoxide-mediated oxidation recently developed by Siegel and co-workers[14] proceeded in high yield with excellent regioselectivity. Selective demethylation gave **41**, which was then coupled with acid **42**[15] to afford **43** in 80% yield. The structure of **43** was confirmed by single-crystal X-ray diffraction and the spectroscopic data were in full agreement with those reported previously.[2d]

In summary, we have developed a highly versatile methodology which converts bicyclo[3.1.0]hexan-2-ones into a broad array of valuable benzoates. In the presence of amines or alcohols, the ring-opening reaction proceeds by the intermediacy of an enamine or enol ether and provides straightforward access to aniline or ether derivatives. A broad application of this method for the synthesis of biologically active molecules is currently underway in our laboratories.

Acknowledgements

We gratefully acknowledge financial support from the FCI (Sachkostenzuschuss to T.M.) and the DFG (SFB 749 and Emmy-Noether Program to T.M.). We thank Dr. David Barber (LMU Munich) and Dr. Kevin Mellem (Revolution Medicines) for helpful discussions during the preparation of this manuscript, and Dr. Peter Mayer (LMU Munich) for X-ray structure analysis.

Keywords: arenes · aromaticity · fused-ring systems · synthetic methods · X-ray diffraction

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 11835–11838
Angew. Chem. **2015**, *127*, 12001–12004

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[4] For selected examples, see: a) M. G. Weaver, W.-J. Bai, S. K. Jackson, T. R. R. Pettus, *Org. Lett.* **2014**, *16*, 1294–1297; b) S. Valente, Z. Xu, E. Bana, C. Zwergel, A. Mai, C. Jacob, P. Meiser, D. Bagrel, A. M. S. Silva, G. Kirsch, *Eur. J. Org. Chem.* **2013**, 2869–2877; c) S. Giroux, E. J. Corey, *Org. Lett.* **2008**, *10*, 5617–5619; d) A. Axelrod, A. M. Eliasen, M. R. Chin, K. Zlotkowski, D. Siegel, *Angew. Chem. Int. Ed.* **2013**, *52*, 3421–3424; *Angew. Chem.* **2013**, *125*, 3505–3508; e) T. Ziegler, M. Layh, F. Effenberger, *Chem. Ber.* **1987**, *120*, 1347–1355; f) A. Moreno, M. V. Gómez, E. Vázquez, A. de La Hoz, A. Díaz-Ortiz, P. Prieto, J. A. Mayoral, E. Pires, *Synlett* **2004**, 1259–1263; g) J. P. Broom, P. G. Sammes, *Chem. Commun.* **1978**, 162–164.

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[6] For the fragmentation of C−C bonds in organic synthesis, see: M. A. Drahl, M. Manpadi, L. J. Williams, *Angew. Chem. Int. Ed.* **2013**, *52*, 11222–11251; *Angew. Chem.* **2013**, *125*, 11430–11461.

[7] For related naphthol syntheses, see: a) E. Hasegawa, H. Tsuchida, M. Tamura, *Chem. Lett.* **2005**, *34*, 1688–1689; b) X. Cai, K. Wu, W. R. Dolbier, Jr., *J. Fluorine Chem.* **2005**, *126*, 479–482; c) H. Tsuchida, E. Hasegawa, *Tetrahedron* **2010**, *66*, 3447–3451; d) D. J. Chang, B. S. Park, *Tetrahedron Lett.* **2001**, *42*, 711–713; e) H. Tsuchida, M. Tamura, E. Hasegawa, *J. Org. Chem.* **2009**, *74*, 2467–2475; f) A. C. Glass, B. B. Morris, L. N. Zakharov, S.-Y. Liu, *Org. Lett.* **2008**, *10*, 4855–4857; g) T. Hamura, T. Suzuki, T. Matsumoto, K. Suzuki, *Angew. Chem. Int. Ed.* **2006**, *45*, 6294–6296; *Angew. Chem.* **2006**, *118*, 6442–6444.

[8] a) Ring opening of bicyclo[4.1.0]heptanes to α-tropolones: R. Kats-Kagan, S. B. Herzon, *Org. Lett.* **2015**, *17*, 2030–2033; b) Conversion of dibromocyclopropanes to 4-bromophenyls: K. Ueda, H. Umihara, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2015**, *17*, 3191–3193.

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[10] a) E. Haselbach, *Helv. Chim. Acta* **1971**, *54*, 2257–2259; b) L. Ghosez, P. Laroche, G. Slinckx, *Tetrahedron Lett.* **1967**, *8*, 2767–2771; c) I. Fleming, E. J. Thomas, *Tetrahedron* **1972**, *28*, 4989–5001.

[11] O. N. Faza, C. S. López, R. Álvarez, A. R. de Lera, *Org. Lett.* **2004**, *6*, 905–908.

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[13] Performing these reactions in a sealed tube (90–135 °C, 3 h) did not lead to product formation either.

[14] C. Yuan, Y. Liang, T. Hernandez, A. Berriochoa, K. N. Houk, D. Siegel, *Nature* **2013**, *499*, 192–196.

[15] For the synthesis of **42**, see the Supporting Information.

[16] CCDC 1410728 (**43**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Received: July 7, 2015

CHAPTER II

De Novo Synthesis of Heteroarenes from Nonaromatic Precursors

3. Introduction

Heterocycles such as indoles and indazoles are important structural motifs of natural products such as monoterpenoid indole alkaloids jerantinine E, aspidophytine or nigellicine.

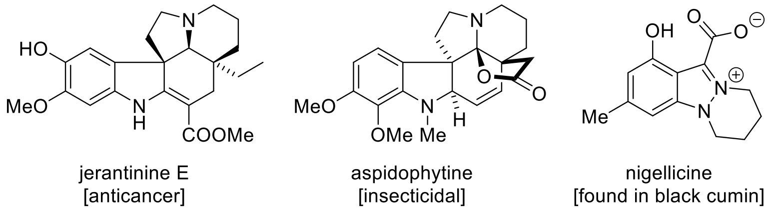

Figure 3: Natural products containing the indole or indazole structural motif.

In medicinal chemistry, indoles and indazoles are of particular interest and can be found various pharmaceuticals such as the anti-HIV drug delavirdin or the tyrosine kinase inhibitor axitinib.

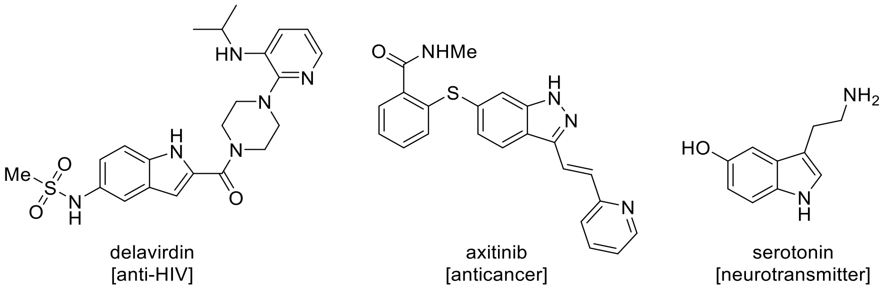

Figure 4: Indoles and indazoles in pharmaceuticals.

The indole structural motif can not only be found in important pharmaceuticals. Serotonin, which is derived from the essential amino acid tryptophan, is a neurotransmitter which is present in the central nervous system of humans.

For the synthesis of these heterocycles, chemists frequently try to functionalize commercially available heterocycles or resort to transformations that make use of benzene derived building blocks.[32]

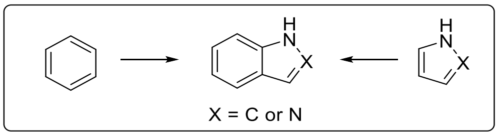

Figure 5: Construction of indoles and indazoles.

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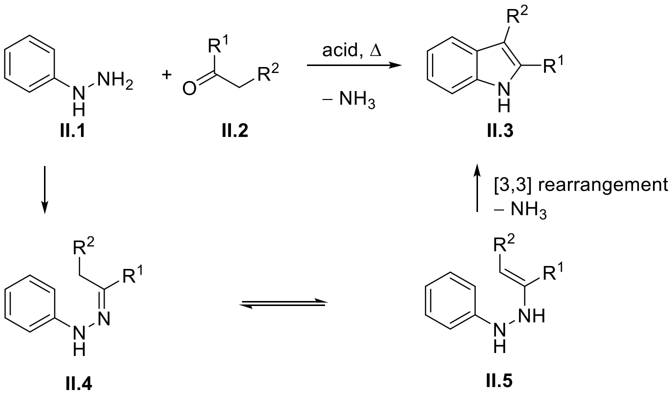
[32] J. A Joule, K. Mills, *Heterocyclic chemistry 5th ed.*, John Wiley & Sons, Chichester **2010**.

3.1 Synthesis of Indoles and Indazoles from Aromatic Precursors

3.1.1 The Fischer Indole Synthesis

The best-known method for the synthesis of indoles is the Fischer indole synthesis which was discovered by E. Fischer in 1883.[33] The first step is a condensation reaction of phenyl hydrazine **II.1** and ketone **II.2** under acidic conditions to form hydrazone **II.4**. Tautomerization of **II.4** to ene-hydrazine **II.5** followed by [3,3]-sigmatropic rearrangement and subsequent loss of ammonia gives indole **II.3**.



Scheme 24: Fischer Indole synthesis.

Common acids employed for this transformation are hydrochloric acid, sulfuric acid, polyphosphoric acid or Lewis acids such as zinc chloride, iron (III) chloride or nickel (II) chloride. While the use of unsymmetrical ketones generally gives two regioisomeric indoles, in certain cases the choice of acid, solvent or temperature can enable good selectivities.

Since the discovery of this reaction, it has been applied in many syntheses of biologically active natural products and pharmaceuticals. Woodward's strychnine synthesis started with a polyphosphoric acid-catalyzed Fischer indole synthesis of phenyl hydrazine **II.1** and acetoveratrone **II.6** to yield veratrylindole **II.7**. Additional 28 steps completed the total synthesis of **II.8**.[34]

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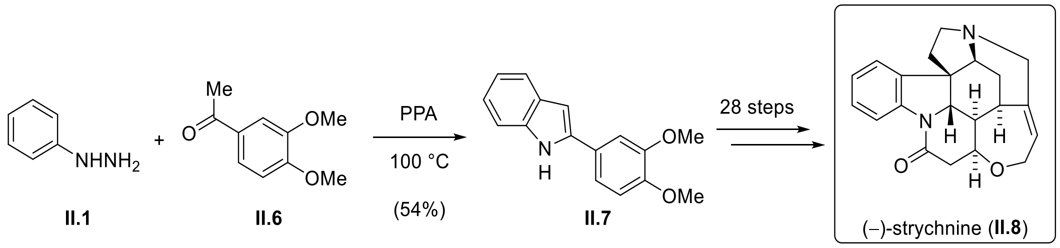
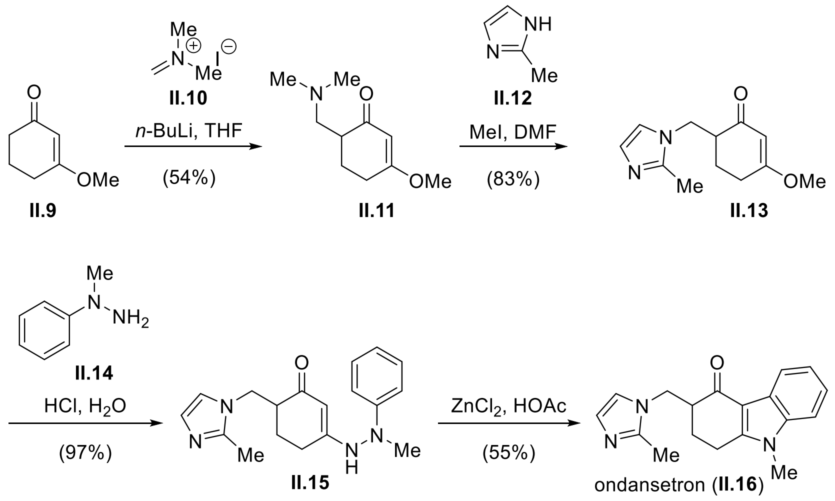
[33] F. Jourdan, E. Fischer, *Ber.* **1883**, *16*, 2241–2245.

[34] K. Schenker, H. U. Daeniker, A. Hunger, W. D. Ollis, M. P. Cava, R. B. Woodward, *J. Am. Chem. Soc.* **1954**, *76*, 4749–4751.



Scheme 25: Indole formation in Woodward's strychnine (**II.8**) synthesis.

Furthermore, the antiemetic drug ondansetron (**II.16**) which was developed by GlaxoSmithKline in the mid-1980s was prepared via Fischer indole synthesis.[35]



Scheme 26: Synthesis of the antiemetic drug ondansetron (**II.16**).

Dimethylaminomethylation of ketone **II.9** with Eschenmoser's salt **II.10**, followed by substitution of the trimethylammonium group with imidazole **II.12** resulted in enol ether **II.13**. Next, condensation reaction with methyl phenyl hydrazine **II.14** under acidic conditions gave ene-hydrazine **II.15**, which underwent Fischer indole reaction to furnish ondansetron (**II.16**) in good yield.

3.1.2 Electrocyclization Reaction

In 2006, the Funk group reported total syntheses of trikentrin A (**II.19**) and B (**II.21**) via 6π-electrocyclization of pyrrole intermediate **II.17**.[36]

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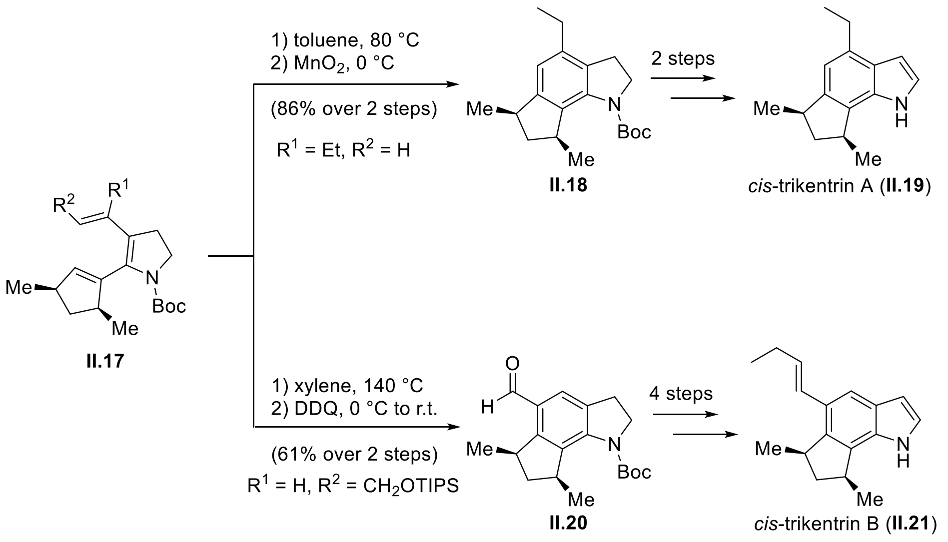
[35] M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, *Beilstein J. Org. Chem.* **2011**, *7*, 442–495.

[36] R. J. Huntley, R. L. Funk, *Org. Lett.* **2006**, *8*, 2643–2645.

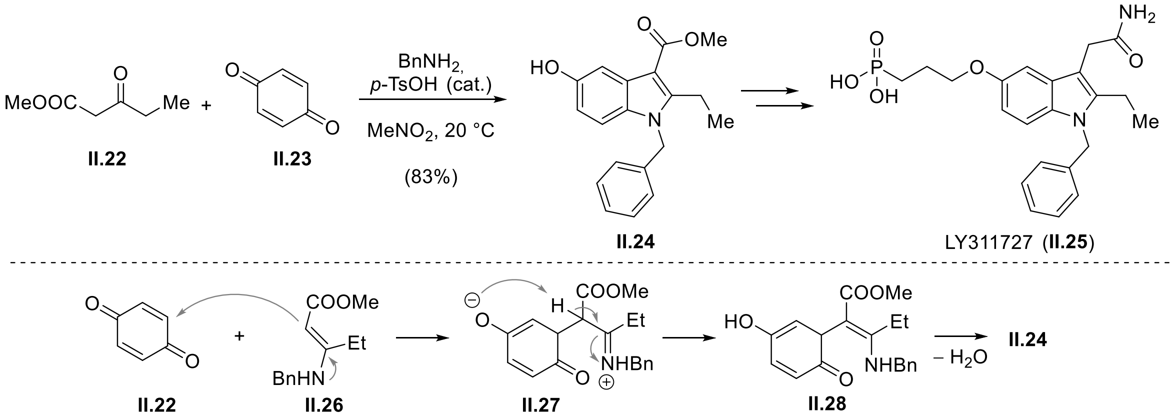


Scheme 27: Total syntheses of trikentrin A (**II.19**) and B (**II.21**).

Electrocyclization of triene **II.17** in toluene or xylene at elevated temperatures, followed by subsequent aromatization using manganese oxide or DDQ gave dihydroindoles **II.18** and **II.20**, which were converted in to the corresponding natural products in few further steps.

3.1.3 The Nenitzescu Reaction

In 1929, Nenitzescu described the synthesis of 5-hydroxyindoles starting from *p*-benzoquinone and aminocrotonate in acetone at 60 °C.[37] Based on this method, Martinelli from Eli Lilly prepared the potent secretory phospolinase A_2 inhibitor LY311727 (**II.25**), which is shown in Scheme 28.[38]



Scheme 28: Synthesis of LY311727 (**II.25**) via Nenitzescu indole synthesis.

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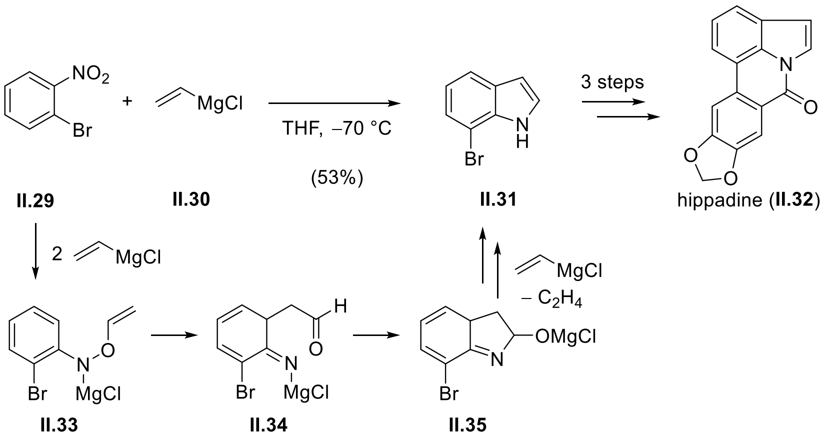
[37] C. D. Nenitzescu, *Bull. Soc. Chim. Romania* **1929**, *11*, 37–43.

[38] J. M. Pawlak, V. V. Khau, D. R. Hutchison, M. J. Martinelli, *J. Org. Chem*. **1996**, *61*, 9055–9059.

Mechanistically, the first step is a Michael addition of enamino ester **II.26** to *p*-benzoquinone **II.22** to give enamine **II.28**. Cyclization and subsequent elimination of water furnished 5-hydroxyindole **II.24** which was further converted to the desired compound **II.25**.

3.1.4 The Bartoli Indole Synthesis

In 1999, the Harrowven group described a short total synthesis of hippadine (**II.32**) via Bartoli indole formation using *ortho*-bromo nitrobenzene **II.29** and excess of vinyl Grignard reagent **II.30**.[39]



Scheme 29: Bartoli indole formation in the synthesis of hippadine (**II.32**).

The first step of the Bartoli indole synthesis is the attack of vinyl Grignard reagent **II.30** to the nitro group of **II.29** which gives the corresponding nitroso intermediate. Addition of an additional equivalent of Grignard reagent, followed by [3,3]-sigmatropic rearrangement furnished **II.34**. Finally, ring-closure and elimination leads to C7-substituted indole **II.31**.

3.1.5 The Larock Indole Synthesis

In the total synthesis of the opioid agonistic indole alkaloid mitrgynine (**II.36**) by Cook and co-workers used a palladium-catalyzed Larock heteroannulation to build the indole core.[40] Mechanistically, the reaction proceeds through oxidative addition of palladium into the aryl iodide, followed by coordination of the transition metal to the alkyne, carbopalladation and subsequent reductive elimination to give the indole **II.35**.

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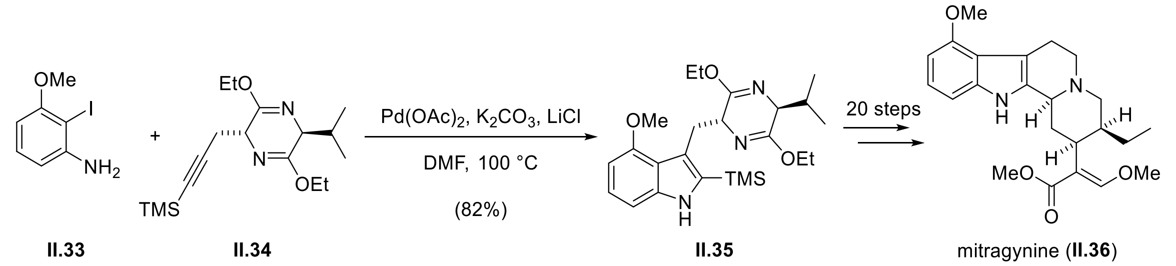
[39] M. C. Lucas, D. Lai, D. C. Harrowven, *Synthesis*, **1999**, *8*, 1300–1302.

[40] J. Ma, W. Yin, H. Zhou, J. M. Cook, *Org. Lett.* **2007**, *9*, 3491–3494.

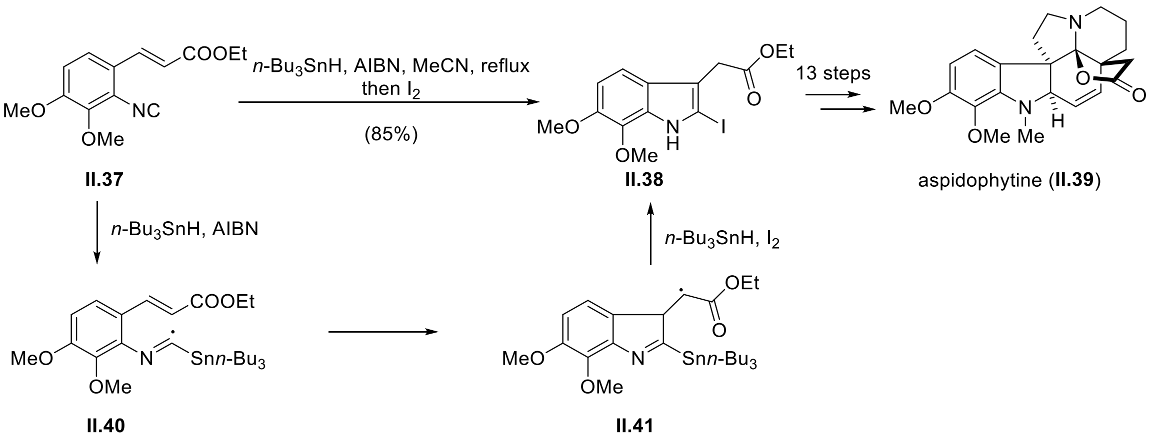


Scheme 30: Total synthesis of mitragynine (**II.36**) via Larock indole synthesis.

They performed the indole formation with 2-iodo aniline **II.33** and silylalkyne **II.34** using palladium acetate as catalyst and potassium carbonate as base. It was found that lithium chloride was necessary to reproduce the yield of the reaction. After twenty additional steps they could isolate the desired compound **II.36**.

3.1.6 The Fukuyama Indole Synthesis

In 1998, Fukuyama described a method for the construction of indoles starting from *ortho*-isocyanostyrenes, tributyltinhydride and azobisisobutyronitrile (AIBN).[41] They applied this method in the total synthesis of aspidophytine (**II.39**) from *ortho*-isocyanostyrene **II.37** .[42]



Scheme 31: Total synthesis of aspidophytine (**II.39**) by Fukuyama indole synthesis.

The first step in the indole formation is the tin-promoted radical cyclization of **II.37** to unstable 2-stannyl indole **II.41** which was directly converted to 2-iodo indole **II.38**.

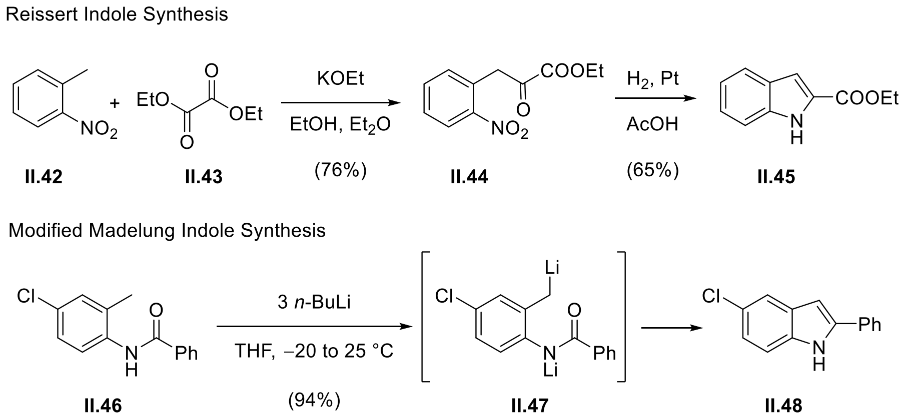
---

[41] Y. Kobayashi, T. Fukuyama, *J. Heterocycl. Chem.* **1998**, *35*, 1043–1056.

[42] S. Sumi, K. Matsumoto, H. Tokuyama, T. Fukuyama, *Org. Lett.* **2003**, *5*, 1891–1893.

3.1.7 The Reissert and Madelung Indole Synthesis

In the Reissert indole synthesis *ortho*-nitrotoluene **II.42** is deprotonated and adds to diethyl oxalate to generate intermediate **II.44**. Reduction of the nitro group and subsequent condensation to the ketone gave 2-substituted indole **II.45**.[43]



Scheme 32: Reissert and Madelung indole syntheses.

A modified Madelung indole synthesis was developed by Houlihan and co-workers from Sandoz.[44] The original Madelung synthesis required harsh reaction conditions such as elevated temperatures and strong bases (sodium amide or potassium *tert*-butoxide). A key feature of the modification by Houlihan is the generation of the organometallic intermediate by the use of *n*-butyllithium at ambient tempertures. Deprotonation of *N*-acylated *ortho*-aminotoluene **II.46** with excess of *n*-butyllithium followed by attack of the lithiated methyl group to the carbonyl group and subsequent elimination-aromatization gave indole **II.48**.

3.1.8 Indoles via C–H Activation

In 2017, the Magauer group described a β-C–H halogenation approach towards the indole alkaloid jerantinine E (**II.53**).[45] Palladium-catalyzed amination of bromo enone **II.49** and aniline **II.50** with SPhos second generation precatalyst gave 3-aminocyclohexanone derivative **II.51**. Subsequent oxidation with palladium and copper acetate furnished indole **II.52**.

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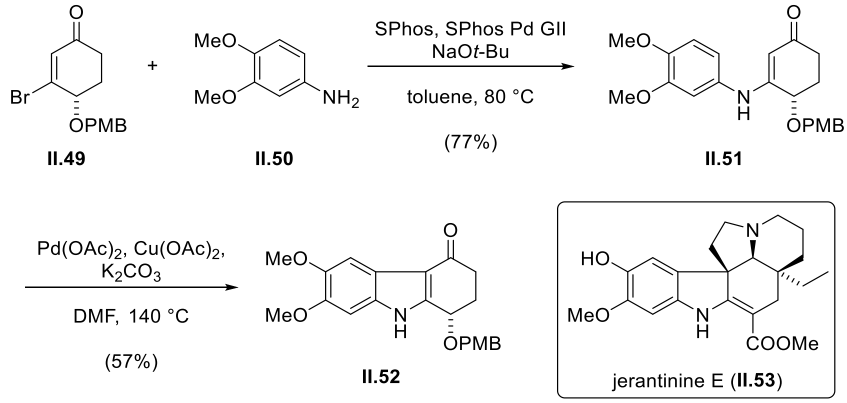
[43] A. Reissert, *Eur. J. Inorg. Chem*. **1897**, *30*, 1030.

[44] Y. Uike, V. A. Parrino, W. J. Houlihan, *J. Org. Chem*. **1981**, *46*, 4511–4515.

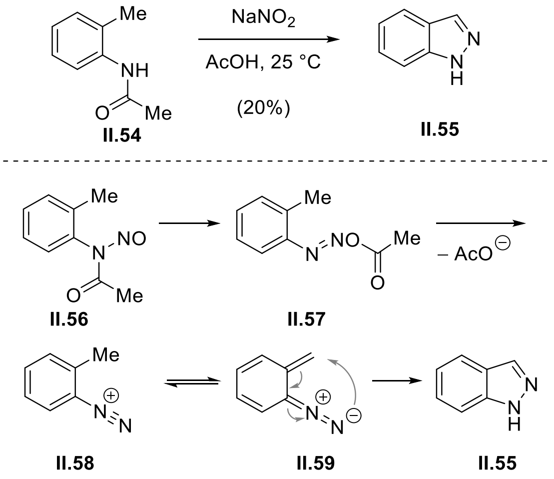
[45] T. Huber, T. A. Preuhs, C. K. G. Gerlinger, T. Magauer, *J. Org. Chem*. **2017**, *82*, 7410–7419.



Scheme 33: Toward synthesis to jerantinine E (**II.53**).

3.1.9 Indazole Syntheses

In 1908, Jacobsen described a synthesis of indazole **II.55** from acylated aniline **II.54** and sodium nitrate under acidic conditions.[46] In 1954, Huisgen and Nakaten proposed the mechanism for this transformation as depicted in Scheme 34.[47]



Scheme 34: Jacobson indazole synthesis and proposed mechanism by Huisgen and Nakaten.

Acetylated nitrosoamine **II.56** reacted to azoester **II.57** which underwent isomerization to the corresponding diazonium salt **II.58**. γ-Deprotonation gave diazo-cyclohexadiene **II.59** and furnished indazole **II.55** after the subsequent 1,5-cyclization.

Another approach toward the synthesis of indazoles is depicted in Scheme 35. Predew[48] reported a microwave-assisted synthesis of the selective estrogen receptor ligand WAY-

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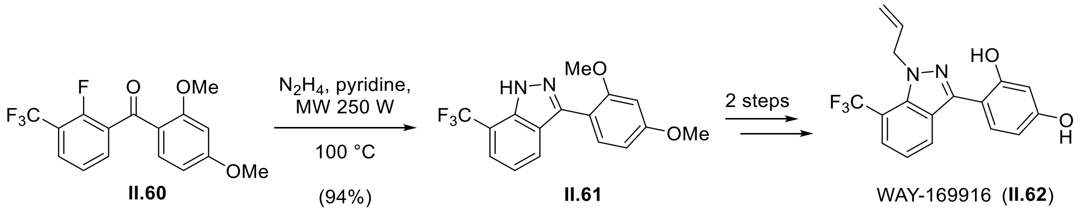
[46] L. Huber, P. Jacobsen, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 660.

[47] H. Nakaten, R. Huisgen, *Liebigs Ann. Chem*. **1954**, *84*, 586.

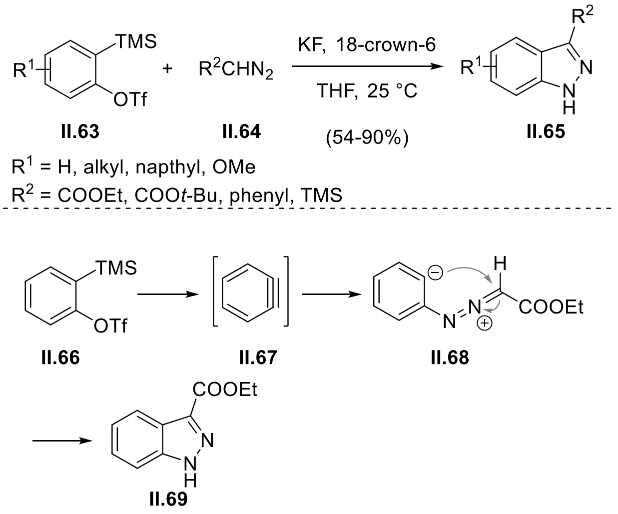
[48] I. A. Murray, G. Krishnegowda, B. C. DiNatale, C. Flaveny, C. Chiaro, J.-M. Lin, A. K. Sharma, S. Amin, G. H. Perdew, *Chem. Res. Toxicol.* **2010**, *23*, 955–966.

169916 (**II.62**) via a condensation reaction of hydrazine and benzylic ketone **II.60** to give **II.61** in almost quantitative yield. Two further steps completed the synthesis of **II.62**.



Scheme 35: Synthesis of WAY-169916 (**II.62**) by Perdew.

In 2007, Yamamoto published a indazole synthesis from benzyne intermediate **II.67** which was prepared from silylphenyl triflate **II.63**, potassium fluoride and 18-crown-6.[49] [3+2]-Cycloaddition of **II.67** and diazomethane derivatives **II.64** occurred under mild reaction conditions and gave substituted indazoles **II.65** in very good yields.



Scheme 36: Indazoles synthesis via benzyne intermediate.

In the same year, Sakamoto accomplished the total synthesis of nigellicine (**II.73**) using a palladium-catalyzed cyclization reaction to construct the indazole core of **II.73**.[50] Condensation reaction of keto-ester **II.70** with *p*-toluenesulfonylhydrazide furnished hydrazone **II.71** as a separable mixture of *E*- and *Z*-isomers. Palladium-catalyzed cyclization reaction in the presence of LHMDS or potassium phosphate then concluded the synthesis of the indazole core **II.72**.

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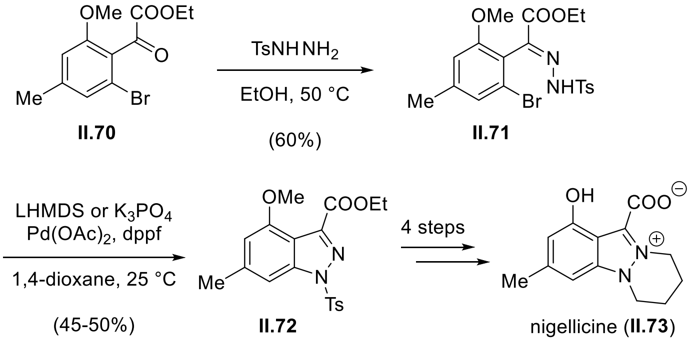
[49] T. Jin, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2007**, *46*, 3323–3325.

[50] K. Inamoto, M. Katsuno, T. Yoshino, Y. Arai, K. Hiroya, T. Sakamoto, *Tetrahedron* **2007**, *63*, 2695–2711.

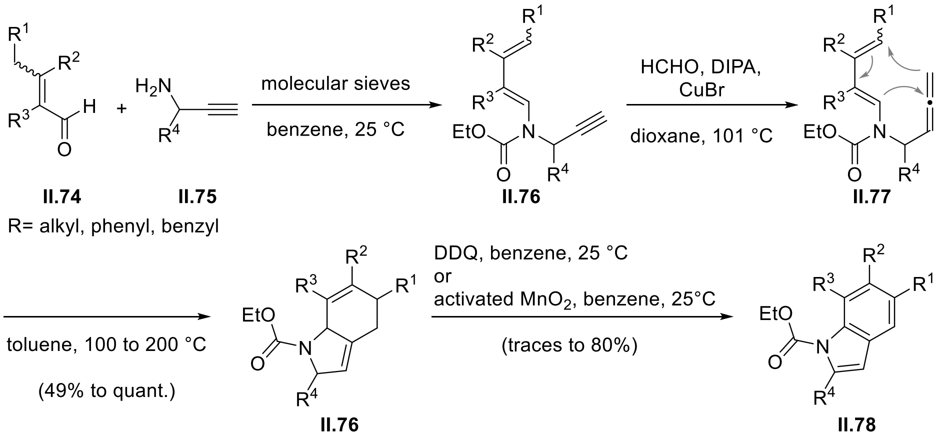


Scheme 37. Total synthesis of nigellicine (**II.73**) by Sakamoto.

3.2 Synthesis of Heteroarenes from Nonaromatic Precursors

3.2.1 Synthesis of Indoles via Electrocyclization Reactions

In 1986, Ken Kanematsu described an efficient indole synthesis via an intramolecular cycloaddition strategy of allenic dienamide **II.76**.[51] The intermediate allene **II.77** was obtained by a condensation reaction of aldehyde **II.74** and propargylic amine **II.75**, followed by homologation to give **II.77**.



Scheme 38: The Kanematsu indole synthesis from allenic dienamide **II.76**.

At elevated temperatures, the intramolecular Diels–Alder reaction furnished bicyclic intermediate **II.78** which was oxidized using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone or activated manganese dioxide to give the corresponding indole **II.79**.

The Danheiser group described an efficient total synthesis of hyellazole (**II.83**) which was isolated from the Hawaiian blue-green alga *Hyella caespitosa*.[52] As depicted in Scheme 39, a

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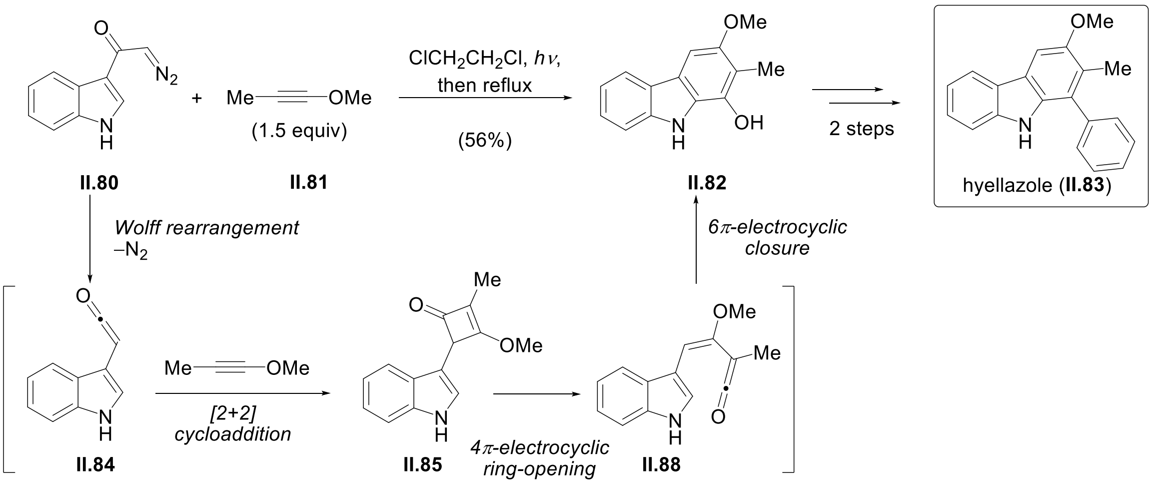
[51] K. Hayakawa, T. Yasukouchi, K. Kanematsu, *Tetrahedron Lett.* **1986**, *27*, 1837–1840.

[52] R. F. Miller, J. J. Kowalczyk, R. G. Brisbois, R. L. Danheiser, *J. Am. Chem. Soc.* **1990**, *112*, 3093–3100.

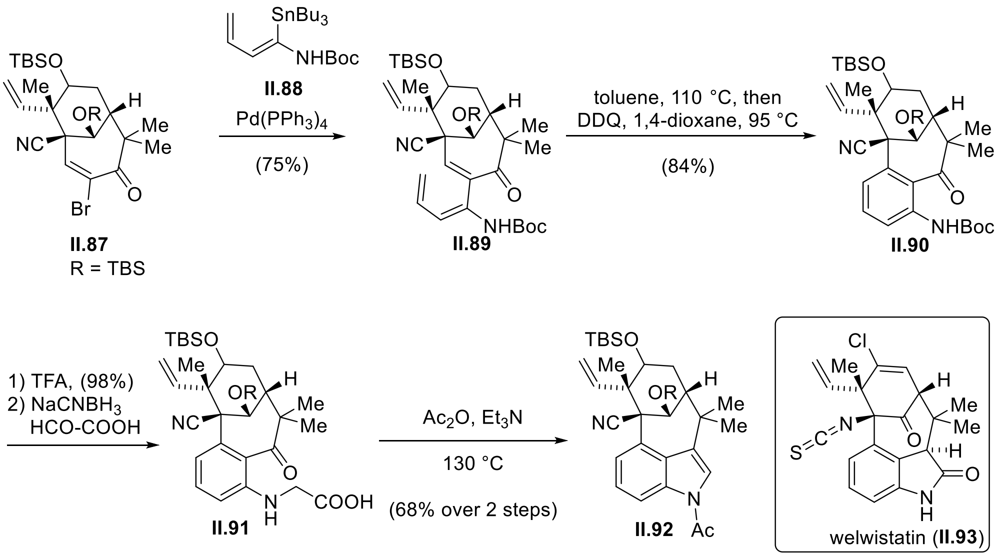
solution of α-diazoketone **II.80** and alkyne **II.81** in 1,2-dichloroethane was irradiated in a Rayonet reactor at 254 nm. Under these conditions, a photochemically induced Wolff rearrangement took place and furnished ketene **II.84**. Heating this solution to 90 °C in a sealed tube gave cyclobutanone intermediate **II.85**, as the product of a [2+2] cycloaddition of **II.84** and alkyne **II.81**.



Scheme 39: Total synthesis of hyellazole (**II.83**) by Danheiser.

Ring-opening of **II.85** and subsequent 6π-electrocyclic closure furnished the expected carbazole derivative **II.82**. Hyellazole (**II.83**) was obtained after triflation of the hydroxy group and Stille cross coupling reaction.

An 6π-electrocyclization approach toward the total synthesis of welwistatin (**II.93**) was reported by the Funk group in 2006.[53] The preparation of the desired electrocyclization precursor started with a Stille cross coupling reaction of bromo enone **II.87** and stannane **II.88**. With **II.89** in hand, they performed the 6π-electrocyclization reaction in toluene at 110 °C.



Scheme 40: Electrocyclization approach toward the total synthesis of welwistatin (**II.93**).

Aromatization was performed in 1,4-dioxane with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone to yield arene **II.90**. Cleavage of the Boc group with trifluoroacetic acid and subsequent reductive amination with glyoxylic acid provided acid **II.916**. Finally, condensation furnished *N*-acetyl indole **II.92** in 68% over two steps.

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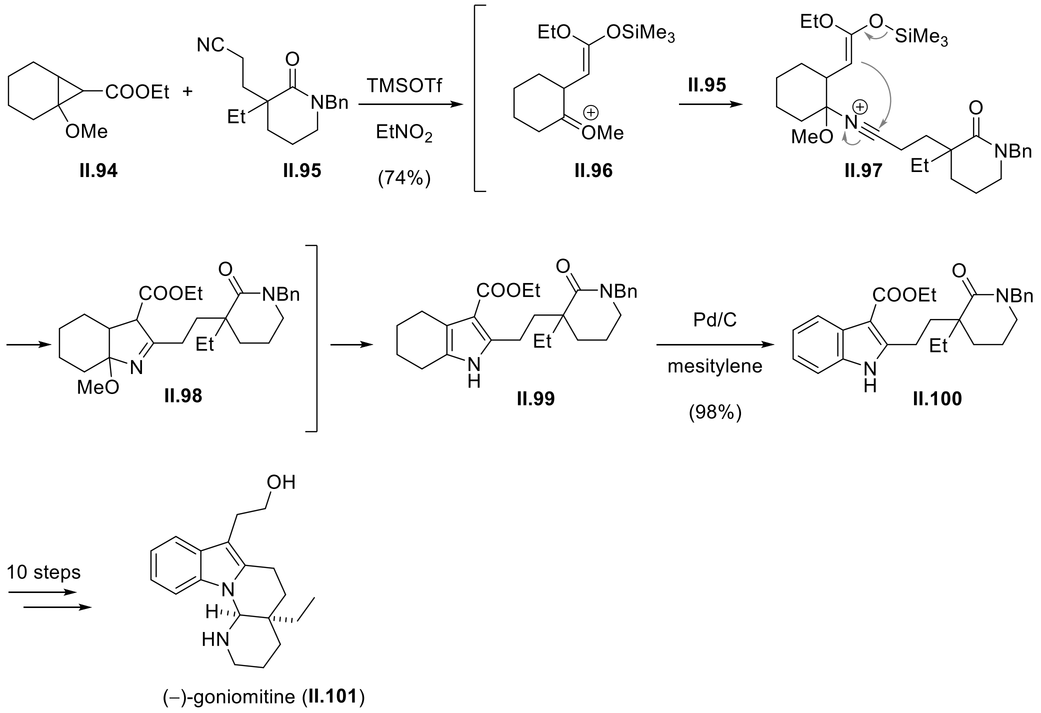
[53] T. J. Greshock, R. L. Funk, *Org. Lett.* **2006**, *8*, 2643–2645.

3.2.2 Ring-opening Reaction to Indoles

In the total synthesis of (−)-goniomitine (**II.101**) by Pagenkopf, the indole core was constructed via a formal nitrile/donor–acceptor cyclopropane [3+2] cycloaddition with bicyclo[4.1.0]heptane **II.94** and nitrile **II.95**.[54]



Scheme 41: Total synthesis of (−)-goniomitine (**II.101**) via [3+2] cycloaddition.

Ring-opening of **II.94** occurred with trimethylsilyltriflate in nitroethane and gave oxonium-ion **II.96** which was trapped in a Ritter-type reaction with nitrile **II.95** to furnish hemiaminal **II.97**. Tautomerization of **II.98** and aromatization using palladium on activated charcoal yielded indole **II.100**. The total synthesis of **II.101** was accomplished after ten additional steps.

3.2.3 Indazoles from Cyclohexanones

An example for the construction of indazoles from nonaromatic precursors is depicted in Scheme 42.[55] The synthesis started with substituted cyclohexanone **II.102** which was converted to the corresponding 1,3-diketone **II.103** via α-acylation.

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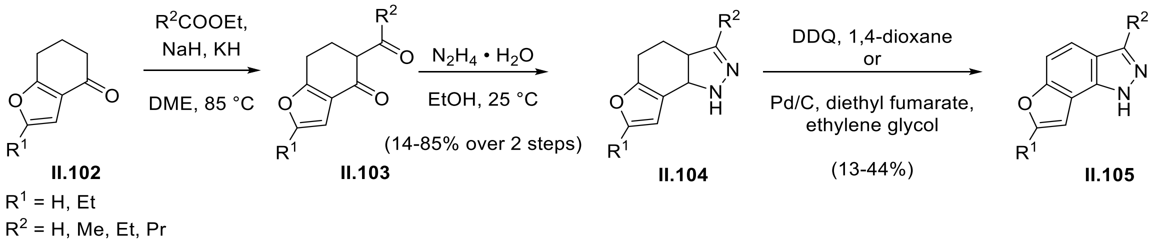
[54] C. L. Morales, B. L. Pagenkopf, *Org. Lett.* **2008**, *10*, 157–159.

[55] S. Tsukamoto, S. Sakamoto, F. Wanibuchi, Y. Naitou, K. Hatanaka, Y. Kimura, T. Kimizuka, H. Kubota, K. Kazuta, K. Maeno, I. Shimada, *Bioorg. Med. Chem.* **2008**, *16*, 1966–1982.

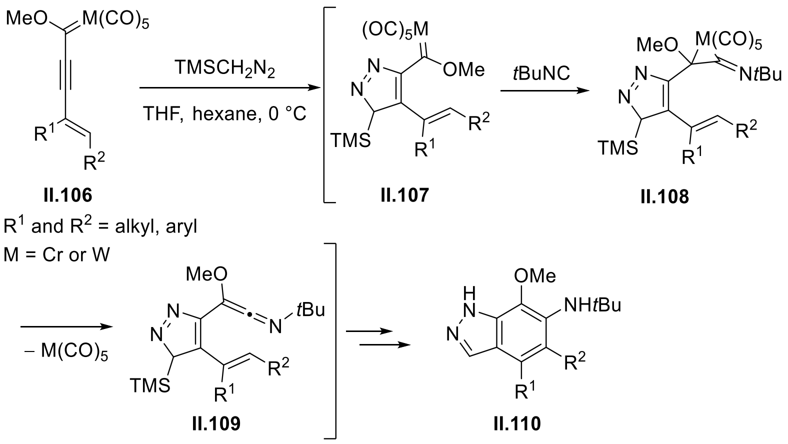


Scheme 42: Shimada's indazole synthesis from substituted cyclohexanone **II.102**.

Addition of hydrazine monohydrate gave 4,5-dihydroindazole **II.104** which underwent dehydrogenation using either 2,3-dichloro-5,6-dicyano-*p*-benzoquinone or palladium on activated charcoal to yield furan-fused indazole **II.105**.

3.2.4 Indazole Synthesis via Dötz Reaction

In 2001, Berluenga described a indazole synthesis utilizing Fischer carbene **II.106** and trimethylsilyl diazomethane dipole.[56] [3+2]-Cycloaddition of trimethylsilyl diazomethane to **II.106** gave metallahexatriene **II.107**. Insertion of *tert*-butylisocyanide to **II.107** followed by ketenimine formation gave intermediate **II.109**. Subsequent electrocyclization-aromatization reaction yielded highly substituted indazole **II.110**.[57]



Scheme 43: Indazole synthesis via Fischer carbene.

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[56] M. A. Palomero, F. Aznar, J. Barluenga, *Chem. Eur. J.* **2001**, *7*, 5318–5324.

[57] R. Aumann, *Angew. Chem.* **1988**, *100*, 1512–1524.

4. Results and Discussion

4.1 *De Novo* Synthesis of Benzannelated Heterocycles

J. Feierfeil, T. Magauer, *Chem. Eur. J.* **2017**, accepted on November 30th, 2017, DOI: 10.1002/chem.201705662.

Chemistry - A European Journal 10.1002/chem.201705662

FULL PAPER WILEY-VCH

De Novo Synthesis of Benzannelated Heterocycles

Johannes Feierfeil and Thomas Magauer*[a]

Dedicated to Professor Dr. Herbert Mayr on the occasion of his 70th birthday

Abstract: Benzannelated heterocycles such as indoles and indazoles are prominent structural motifs found in natural products, pharmaceuticals and agrochemicals. For their synthesis, chemists traditionally either functionalize commercially available heterocycles or resort to transformations that make use of benzene derived building blocks. Here, we report a powerful cascade reaction that enables the *de novo* construction of variously substituted indoles, indazoles, benzofurans and benzothiophenes from readily available bicyclo[3.1.0]hexan-2-ones. The transformation can be conducted under mild, non-anhydrous conditions. For the synthesis of indoles, mechanistic studies revealed that the electrocyclic ring-opening of the bicyclic ring-system and aromatization precedes the 3,3-sigmatropic rearrangement.

Introduction

Five-membered benzannelated heterocycles are ubiquitous in biologically active molecules and are precious building blocks for the chemical industry (Figure 1).[1] Conventional methods for the synthesis of substituted indoles and indazoles typically make use of either pre-functionalized heterocycles or rely on benzene-derived building blocks. Protocols that enable the *de novo* synthesis of these heterocycles are rare and often are associated with unsatisfactory functional group tolerance, efficiency, or practicability (e.g. use of stannanes, high temperatures, expensive transition metals).[2] Examples (Figure 2a) include the Kanematsu indole synthesis, which involves a multistep sequence to access the allene precursor, requires high temperatures, and only tolerates alkyl and phenyl groups,[3] and the Pagenkopf indole synthesis, in which the indole core is constructed via a nitrile/donor-acceptor cyclopropane [3+2] cyclization.[4] The Funk group also reported a 6π-electrocyclization/condensation approach to construct the indole structural motif of the natural product welwistatin.[5

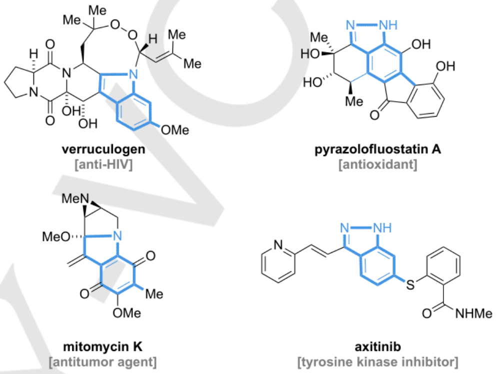

Figure 1. Selected examples of biologically active molecules featuring an C6-functionalized indole or indazole structural motif.

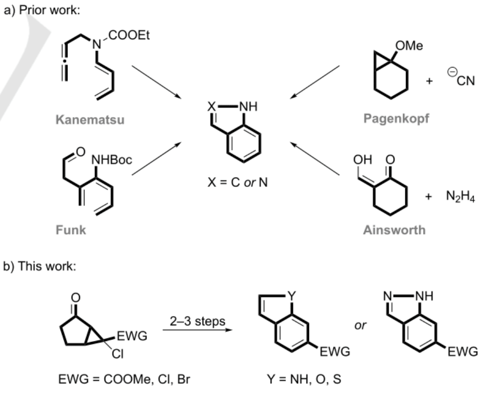

Figure 2. a) Selected methods for the synthesis of indoles and indazoles from non-aromatic precursors. b) *De novo* synthesis of benzannelated heterocycles from bicyclo[3.1.0]hexan-2-ones.

Another rare example for the synthesis of an indazole from a non-aromatic precursor was described by Ainsworth[6] and involves the condensation of hydrazine with a *β*-hydroxyenone. A drawback of these strategies is the need for toxic oxidants such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone or the use of palladium in the final aromatization step.[7]

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Chemistry - A European Journal 10.1002/chem.201705662

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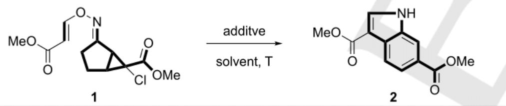
In recent work we demonstrated that bicyclic ring-systems can be efficiently converted to polyfunctionalized 3-hydroxybenzoates[8] and orthogonally functionalized, chlorinated naphthoates.[9] Initial efforts to incorporate heteroatoms in the ring-opening precursor were largely unsuccessful and only trace amounts of the desired heterocycles could be obtained. Here, we report a solution to this problem and show its general applicability to the efficient syntheses of indoles, indazoles, benzofurans and benzothiophenes.

Results and Discussion

We began our investigations with *O*-vinyl oxime **1**, which was prepared in two steps from readily available methyl bicyclo[3.1.0]hexan-2-ones (see Supplementary Information for details).[10] To identify the optimal conditions for the synthesis of indole **2**, *O*-vinyl oxime **1** was subjected to an extensive screen of reaction conditions (Table 1). We found that conducting the reaction in sulfolane (0.2–0.5 M) at 190 °C (entry 1), afforded **2** in only 6% yield. Following this result, the effect of varying reaction temperatures was investigated (70–170 °C, entry 2 and Supplementary Information). While temperatures significantly above 170 °C or below 70 °C only led to trace amounts of **2**, maintaining the reaction temperature at 100 °C improved the yield of **2** to 37%. The presence of zinc chloride or acetic acid (entries 3 and 4), which are common additives in the related Fischer-indole synthesis, was not beneficial.

Table 1: Conversion of **1** to **2** under varying reaction conditions.



Entry	Solvent	Additive	*T* [°C]	*t* [h]	Yield [%][a]
1	sulfolane	None	190	0.5	6
2	sulfolane	None	100	2	37
3	sulfolane	$ZnCl_2$	100	3	traces
4	sulfolane	AcOH	100	5	39
5	HFIP	None	100	3	n.c.
6	Toluene	None	100	3	n.c.
7	toluene	$PPh_3AuCl/AgBF_4$	100	48	traces
8	sulfolane	Amberlyst® 15	100	1.5	63
9	sulfolane	ClCOOEt	100	3	65
10	**sulfolane**	**TFA**[b]	**100**	**1.5**	**65**

[a] Yield of the isolated product. [b] 1.0 equiv TFA. TFA = trifluoroacetic acid, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

A survey of solvents revealed that hexafluoroisopropanol (HFIP) and toluene were ineffective, with only starting material being recovered (entries 5 and 6). In 2010, the Camp group reported a gold(I) catalyzed rearrangement of *O*-vinyl oximes to give substituted pyrroles.[11] Unexpectedly, when **1** was subjected to these conditions, indole **2** was only produced in trace amounts (entry 7). However, significantly improved yields were achieved by employing Amberlyst® 15 as a proton source (63% yield, entry 8). In an attempt to combine the indole formation with an *in situ N*-protection, we heated a mixture of **1** and ethyl chloroformate in dry sulfolane at 100 °C (entry 9). Surprisingly, only formation of unprotected **2** (65%) was observed in this case. An identical yield was obtained when ethyl chloroformate was replaced with trifluoroacetic acid (entry 10). Although the exact role of the acid (or chloroformate) additive is unclear at this point, we believe that it simply increases the rate of imine to enamine tautomerization and thus facilitates initiation of the cascade reaction.

With the optimized conditions in hand, we applied our methodology to a variety of *O*-vinyl oximes, which were prepared in three steps from readily available cyclopenten-2-ones (Figure 3). The reactions could be conducted in an open-flask, with generally short reaction times (< 3 h), and the presence of one equivalent of trifluoracetic acid was found to be optimal in all cases.

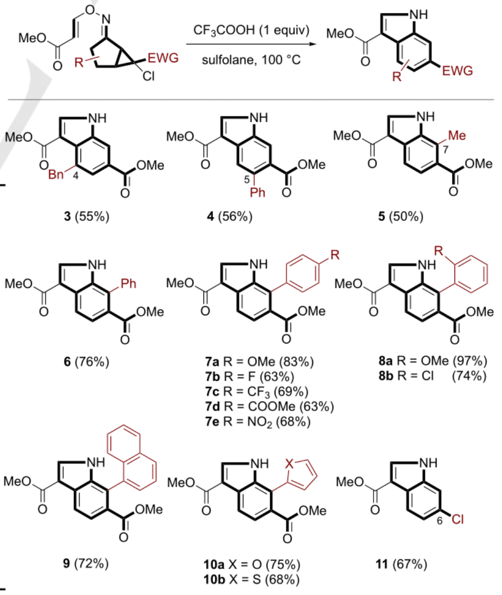
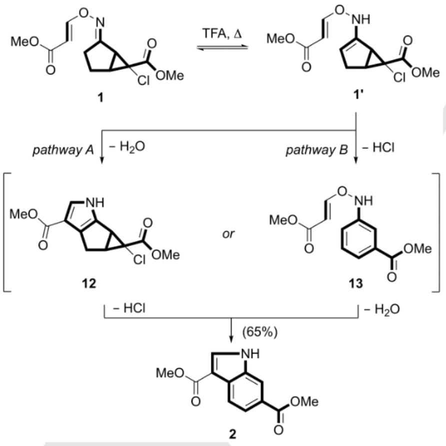


Figure 3. Synthesis of indoles and variation of the substitution pattern at C4–C7.

As demonstrated for **3** and **4**, substituents at the C4 and C5 position of the indole are well tolerated. We could further show that a variety of C7-substituted indoles (**5**–**10**) are accessible and that the transformation is not limited to aryl substituents (**5**). While indoles bearing a *para*-substituted C7-aryl group (compounds **7a**–**7e**) were produced in yields up to 83%, indoles bearing an *ortho*-substituted C7-aryl group (**8a** and **8b**) were isolated in excellent yields up to 97%. The method also worked well for naphthyl-substituted indole **9** and with heteroaromatic substituents such as 2-furyl (**10a**) and 2-thienyl (**10b**). To further vary the substitution pattern of the C6-position of the indole core, we also investigated the *gem*-dichloro cyclopropane derivative of *O*-vinyl oxime **1**. With this substrate, we obtained the 6-chloro indole **11** in 67% yield.

Mechanistically, we envisioned that the enamine tautomer **1'**[11] would follow one of the two pathways illustrated in Scheme 1 to give indole **2**. In pathway A, a [3,3]-rearrangement produces the pyrrol intermediate **12**, which is then converted to **2** via a thermally induced 2π-disrotatory ring-opening-aromatization sequence. In pathway B, the strain-releasing, ring-opening-aromatization reaction takes place first to give the aryl *O*-vinyl oxime **13** which undergoes a sequential [3,3]-rearrangement and condensation to deliver indole **2**.

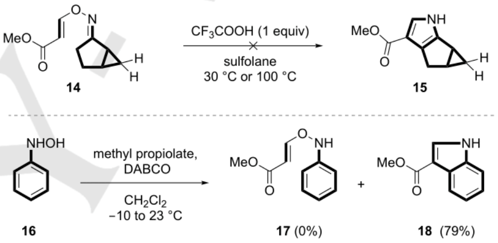
Based on literature precedent,[11,12a] it seemed reasonable that that either of the two pathways could be operational, but it was unclear whether any of the proposed intermediates could be detected by NMR spectroscopy. Interestingly, when a solution of **1** and trifluoroacetic acid (1 equiv) in sulfolane was monitored by ^{1}H NMR spectroscopy and was gradually heated from 30 °C to 100 °C, we observed neither intermediate **12** nor intermediate **13**. After 1 h, heating was discontinued and indole **2** could be isolated as the sole product in 65% yield.



Scheme 1. Mechanistic hypotheses for the indole formation.

Since monitoring of the reaction by ^{1}H NMR spectroscopy did not allow us to differentiate between the two pathways, we next focused our attention on the synthesis of the modified components **14** and **17** (Scheme 2). First, we prepared unsubstituted cyclopropane fragment **14**, lacking the crucial chloride-leaving group for the ring-expansion reaction. Surprisingly, exposure of this substrate to trifluoroacetic acid in sulfolane at 30 °C for 14 h did not afford pyrrole **15**, but left the starting material unreacted. At elevated temperatures (100 °C), complete decomposition of the substrate occurred within 3 h.

Next, we attempted to synthesize the aryl *O*-vinyl oxime 1**7** via 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed 1,4-addition of *N*-aryl hydroxylamine **16** to methyl propiolate at −10 °C. However, using DABCO in the 1,4-addition step, did not afforded **17** but rather directly gave rise to the corresponding indole **18**.[12b] Based on these results, we concluded that the mechanism of the indole formation most likely proceeds via pathway B.



Scheme 2. Mechanistic probes for the indole formation. DABCO = 1,4-diazabicyclo[2.2.2]octane.

Having established a versatile platform for the synthesis of indoles, we turned our attention to the preparation of substituted indazoles. After intensive screening of reaction conditions, we were pleased to find that the condensation reaction of diketone **19** with hydrazine monohydrochloride in a sealed tube directly afforded **20**. Simple variation of diketone **19** gave access to a variety of C3-substituted indazoles, which are depicted in Figure 4. Indazoles bearing an aliphatic (**21** and **22**), phenyl (**23**) or methoxymethyl (**24**) group were obtained in yields up to 77%. Electron-deficient substituents, such as methyl ester (**25a** and **25b**) or trifluoromethyl (**26**) groups, and heteroaromatic substituents, such as 2-pyridinyl (**27**), 2-furyl (**28**) or 2-thienyl (**29**) were also well tolerated. In sharp contrast to the indole synthesis, formation of the related indazoles could also be conducted in a stepwise manner to first form a pyrazole at 23 °C. Upon heating to 100 °C, full conversion to the indazole was observed.

Having developed an efficient strategy for the synthesis of C6-substituted indazoles, we set out to further extend our *de novo* platform for the construction of other benzannelated five-membered heterocycles. Exposure of 1,4-diketone **30** and **32**[13] to trifluoroacetic acid at 190 °C initiated the ring-expansion/aromatization cascade reaction to provide in good yields benzofurans **31** and **33**, respectively. Alternatively, the use of Lawesson's reagent **36** in the cyclization reaction gave access to benzothiophenes **34** and **35**, respectively.

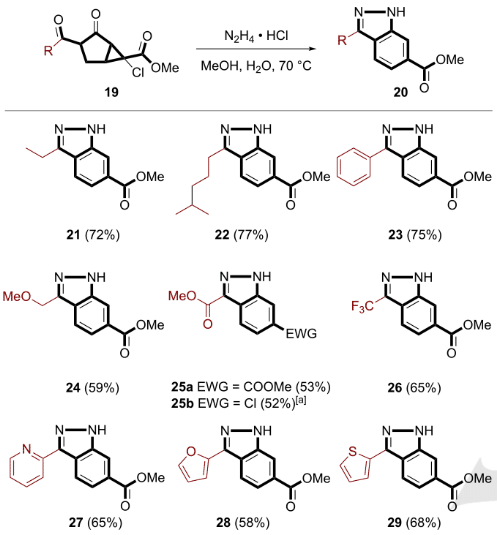
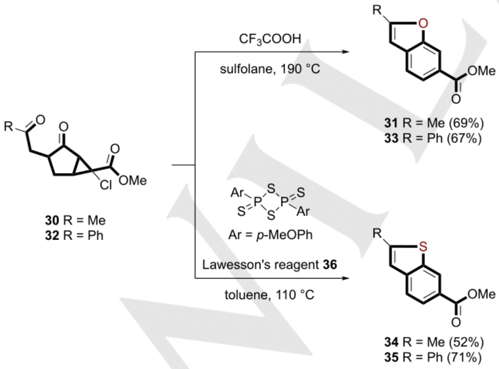


Figure 4. One-Pot Synthesis of substituted indazoles from bicyclo[3.1.0]hexan-2-ones. [a] Yield over two steps after chromatographic purification.



Scheme 3. Synthesis of benzofurans and benzothiopenes.

Conclusions

In conclusion, we have developed a protocol for the *de novo* construction of polysubstituted indoles, indazoles, benzofurans and benzothiophens from non-aromatic precursors. The reaction can be conducted in an open-flask, is operationally simple and does not require expensive reagents or catalysts. Many of the presented heterocycles feature a unique substitution pattern and have never been synthesized before. A broad application of the developed strategy for the synthesis of highly substituted benzannelated heterocycles and its implementation in complex molecule syntheses are currently underway in our laboratory.

Experimental Section

Experimental details and compound characterization data and copies of ^{1}H and ^{13}C NMR spectra, are available in the Supporting Information.

Acknowledgements

We gratefully acknowledge financial support from the German Research Foundation (Emmy Noether Project MA5999/2-1), the European Research Council (ERC StG 714049) and the Funds of the Chemical Industry (Sachkostenzuschuss and Dozentenpreis). We thank Dr. Cedric Hugelshofer (UC Berkeley) and Dr. Kevin Mellem (Revolution Medicines) for helpful discussions during the preparation of this manuscript.

Keywords indoles • indazoles • benzofuran • cyclopropanes • ring-expansion

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[8] J. Feierfeil, A. S. Grossmann, T. Magauer, *Angew. Chem. Int. Ed.* **2015**, *54*, 11835–11838.

[9] T. A. Unzner, A. S. Grossmann, T. Magauer, *Angew. Chem. Int. Ed.* **2016**, *55*, 9763–9767.

[10] *O*-Vinyl oxime **1** was obtained as an inconsequential mixture of double bond isomers. The depicted isomer is the major double bond isomer.

[11] Pyrrol synthesis via gold catalyzed rearrangement of *O*-vinyl oximes: S. Ngwerume, J. E. Camp, *Chem. Commun.* **2011**, *47*, 1857–1859.

[12] a) M. O. Gray, R. J. Lin, H. V. Patel, J. R. Hwu, *J. Org. Chem*, **1994**, *59*, 1577–1582; b) In our hands, conducting the 1,4-addition of *N*-aryl hydroxylamine to methyl propiolate using DMAP did not lead to the corresponding indole. These results are contrary to those reported in the literature, see reference 12a. The use of methyl 3-(hydroxyamino)benzoate led to a mixture of regioisomeric indoles, which could not be fully characterized.

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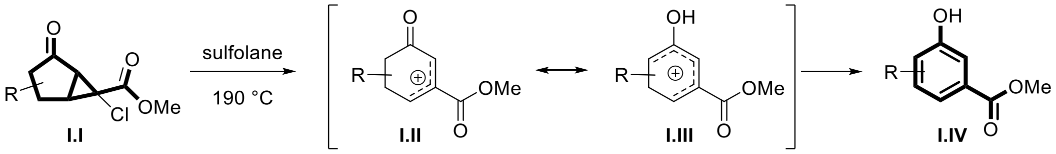
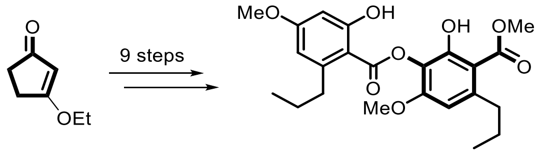
5. Conclusion and Further Directions

In the first part of this Ph.D. thesis we developed an unprecedented methodology for the synthesis of highly substituted 3-hydroxybenzoates **I.IV** via a ring-opening aromatization cascade to form bicyclo[3.1.0]hexan-2-ones **I.I**. Mechanistically, we suggest that the reaction proceeds through a thermally-induced disrotatory 2π-electrocyclic ring-opening and subsequent aromatization reaction to provide the desired benzoates.



Scheme 44: Mechanism of the ring-opening aromatization reaction.

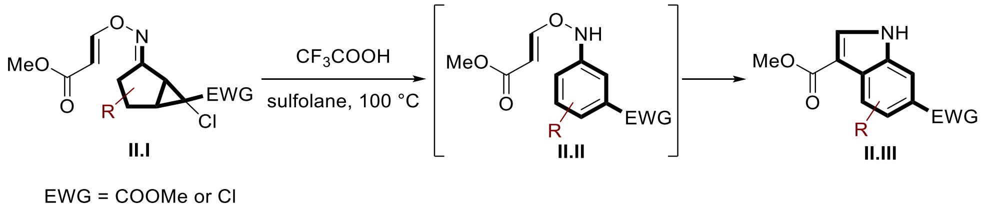
The aromatization precursors were obtained from substituted cyclopentenones which were converted to the corresponding bicyclo[3.1.0]hexan-2-ones via cyclopropanation with the lithium enolate of methyl dichloroacetate. The aromatization reaction was performed in an open flask at elevated temperatures. Various functional groups such as alkyl, alkynyl, phenyl, 2-furyl, halogens, ketones or hydroxy substituents were tolerated. The presence of amines and alcohols in the ring-opening aromatization reaction gave rise to the corresponding aniline or aryl ether derivatives, notably without the need for expensive transition metal catalysts. Moreover, we could successfully synthesize the GACKIX inhibitor sekikaic acid methyl ester from 3-ethoxycyclpentenone **I.V** in nine steps.



I.V sekikaic acid methyl ester

Scheme 45: Total synthesis of sekikaic acid methyl ester.

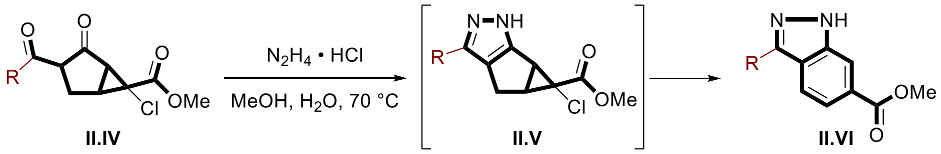
In the second part, we applied this methodology for the construction of five-membered benzannelated heterocycles including indoles, indazoles, benzofurans and benzothiophenes. For the indole synthesis, we started from *O*-vinyl oximes which were prepared in two steps from substituted bicyclo[3.1.0]hexan-2-ones. We hypothesized that the indole formation proceeds first through ring-opening aromatization followed by [3,3]-sigmatropic rearrangement.



Scheme 46: Indole synthesis from *O*-vinyl oximes.

Variation of the substitution pattern gave us a wide range of indoles bearing alkyl, phenyl and *ortho*- and *para*-substituted aryl substituents. Naphthyl and heteroaromatic substituents such as 2-furyl and 2-thienyl were tolerated as well.

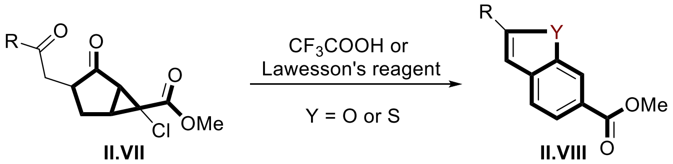
In addition to the indole synthesis, we successfully accomplished a one-pot strategy for the synthesis of indazoles from 1,3-diketones.



Scheme 47: One-pot strategy for the synthesis of indazoles.

A condensation reaction with hydrazine hydrochloride in a mixture of methanol and water at 70 °C directly gave the desired indazoles. Simple variation of the diketone led to a variety of indazoles. Alkyl, phenyl, esters, trifluoromethyl and heteroaromatic groups were well tolerated.

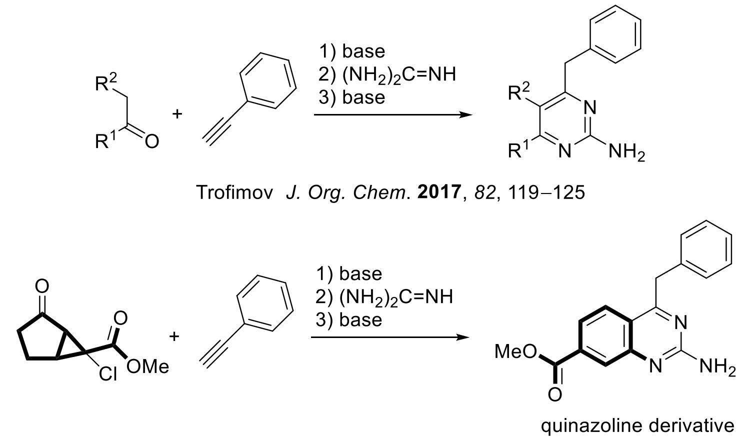
Using 1,4-diketones in the ring-opening aromatization approach C2-substituted benzofurans and benzothiophenes could be readily prepared.



Scheme 48: Synthesis of benzofurans and benzothiophenes.

Acid-promoted ring-opening aromatization reactions yielded benzofurans, whereas using Lawesson’s reagent in the aromatization approach led to benzothiophenes.

Future work will be directed toward the application of the ring-opening aromatization reaction in the synthesis of biologically active natural products such as pyrazolofluostatins or pharmaceuticals such as raloxifene. Furthermore, Trofimov reported a methodology on the preparation of 2-aminopyrimidines. Applying these conditions on our bicyclo[3.1.0]hexan-2-ones may give rise to substituted quinazolines.



Trofimov *J. Org. Chem.* **2017**, *82*, 119–125

quinazoline derivative

Scheme 49: Future work on the ring-opening aromatization reaction to access quinazolines.

CHAPTER III

Experimental Part

6. Experimental Procedures

General Experimental Details

All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless-steel cannula through rubber septa. Solids were added under inert gas counter flow or were dissolved in appropriate solvents. Low temperature-reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (−78 °C), H_2O/ice (0 °C). Reaction temperatures above room temperature were conducted in a heated oil bath. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using aluminium plates precoated with silica gel (0.25 mm, 60 Å pore size, *Merck*) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), were stained by submersion in aqueous potassium permanganate solution ($KMnO_4$) or ceric ammonium molybdate solution (CAM), and were developed by heating with a heat gun. Flash column chromatography was performed as described by Still et al.,[58] employing silica gel (60 Å, 40–63 µm, *Merck KGaA*). The yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) pure material.

Materials

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled under N_2 atmosphere from Na/benzophenone prior to use. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine (DIPA) and Hünig's base (DIPEA) were distilled under nitrogen atmosphere from CaH_2 prior to use. Dimethyl sulfoxide (DMSO), acetonitrile (MeCN), benzene, toluene and methanol (MeOH) were purchased from *Acros Organics* as 'extra dry' reagents and used as received. All other reagents and solvents were purchased from chemical suppliers (*Sigma-Aldrich, Acros Organics, Alfa Aesar, Strem Chemicals, ABCR*) and were used as received. Solvents for extraction, crystallization and flash column chromatography were purchased in technical grade and distilled under reduced pressure prior to use. Lithium chloride was dried at 100 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 150 °C (760 mmHg); the hot, dried solid was flame dried under vacuum (0.1 mmHg) for 4−5 min immediately prior to use. The molarity of *n*-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[59]

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[58] W.C. Still, M.Kahn, A. J. Mitra, *Org. Chem*. **1978**, *43*, 2923.

[59] W. G. Kofron, L. M. Baclawski, *J. Org. Chem.* **1976**, *41*, 1879.

The concentration of freshly prepared dimethyldioxirane solutions[60] was determined by iodometric titration as follows: A 0.02 M aqueous stock solution of sodium thiosulfate pentahydrate (124 mg $Na_2S_2O_3 \times 5H_2O$ in 25 mL H_2O) was prepared in a 25 mL graduated cylinder. A 100 mL flask was charged with water (30 mL), sodium iodide (2.00 g) and glacial acetic acid (1 mL), whereupon the dimethyldioxirane solution (2 mL) was added. The resulting brown mixture was rapidly titrated with the sodium thiosulfate stock solution until disappearance of the yellow iodine colour occurred. The concentration of the dimethyldioxirane solution was calculated according to the following equation:

$$c(DMDO) = \frac{M(titrant) \times V(titrant)}{V(DMDO) \times 2}$$

and was generally in the range of 0.04 M to 0.06 M.

NMR spectroscopy

NMR spectra were measured on a *Bruker* Avance III HD 400 MHz and 800 MHz spectrometer equipped with a CryoProbe^{TM}, *Bruker* AXR300, *Varian* VXR400 S and *Bruker* AMX600 spectrometers operating at 400 MHz, 800 MHz, 300 MHz, 400 MHz and 600 MHz for proton nuclei (100 MHz, 75 MHz, 100 MHz, 150 MHz for carbon nuclei), respectively. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, methanol-d_3: δ 4.78, acetone-d_5: δ 2.05, $CDHCl_2$: δ 5.32, DMSO-d_6: δ 2.50). Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, CD_3OD: δ 49.00, acetone-d_6: δ 29.84, CD_2Cl_2: δ 54.00, DMSO-d6: δ 39.52). ^1H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants *J* (Hz), integration intensity, assigned proton). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. Except for multiplets, the chemical shift of all signals, as well for centrosymmetric multiplets, is reported as the center of the resonance range. Additionally, to ^1H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC) were used to assist signal assignment. Coupling

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[60] Prepared according to: D. F. Taber, P. W. Dematteo, R. A. Hassan, *Org. Synth*. **2013**, *90*, 350.

constants *J* are reported in Hz. All raw fid files were processed and the spectra analyzed using the program *MestReNOVA 9.0* from *Mestrelab Research S. L.*

Mass spectrometry

All mass spectra were measured by the analytic section of the Department of Chemistry, *Ludwig-Maximilians-Universität München*. Mass spectra were recorded on the following spectrometers (ionisation mode in brackets): MAT 95 (EI) and MAT 90 (ESI) from *Thermo Finnigan GmbH*. Mass spectra were recorded in high-resolution. The method used is reported at the relevant section of the experimental section.

IR spectroscopy

IR spectra were recorded on a *PerkinElmer* Spectrum BX II FT-IR system. If required, substances were dissolved in CH_2Cl_2 prior to direct application on the ATR unit. Data are represented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (*vs* = very stong, *s* = strong, *m* = medium, *w* = weak, *br* = broad).

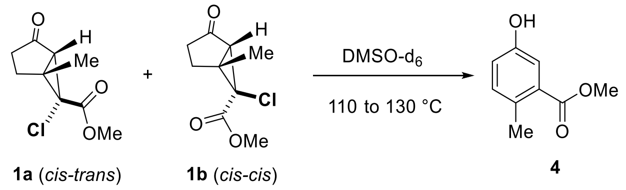
Melting Point

Melting points (mp) were determined with a *Büchi* Melting Point B-540 apparatus and are uncorrected.

6.1 Supporting Information for Chapter I

6.1.1 Experimental Procedures

^{1}H NMR experiment



Monitoring the conversion of 1a and 1b to 4 via ^{1}H NMR spectroscopy.

A solution of a mixture of **1a** and **1b** (71.0 mg, 350 µmol, 1 equiv) in dimethyl sulfoxide-d$_6$ (3.5 mL) was heated at 110 °C. NMR aliquots (200 µL) were taken out every 10 min and were diluted with dimethyl sulfoxide-d$_6$ (400 µL). After 110 min, the solution was heated to 130 °C and a NMR aliquot was taken out after 20 min.

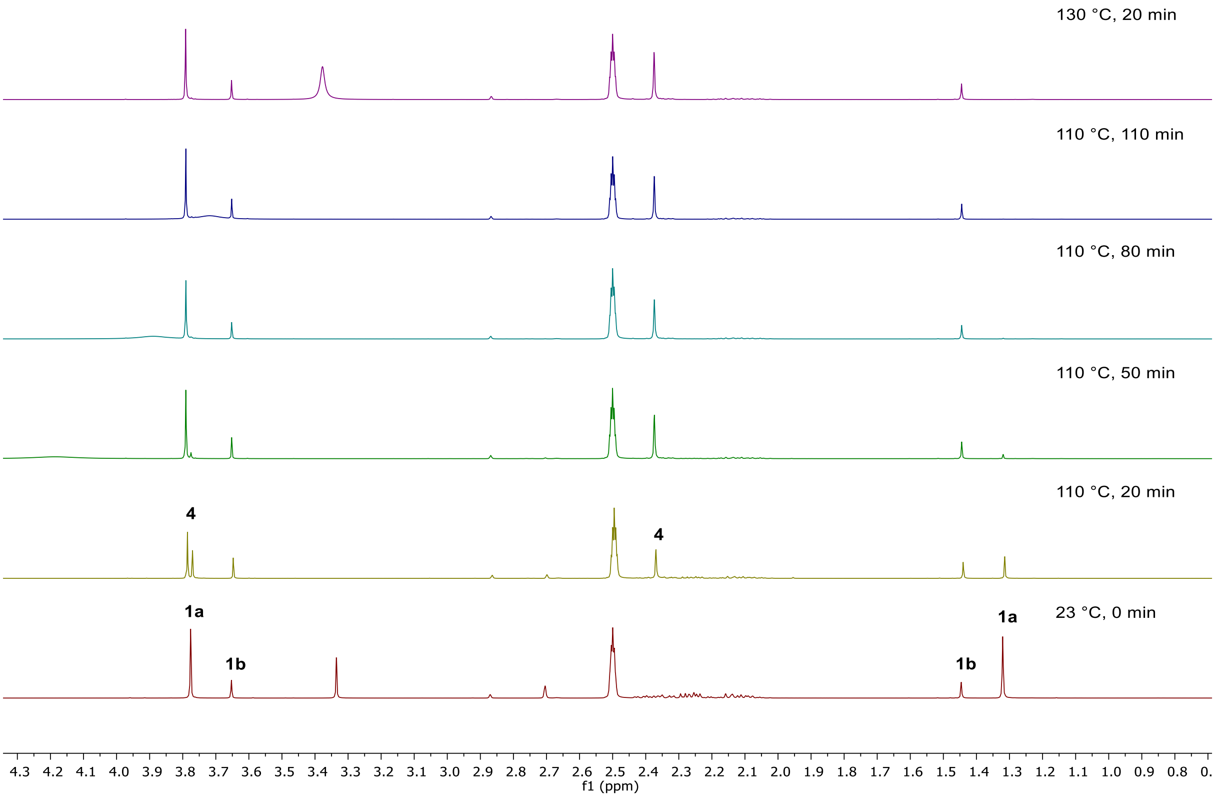
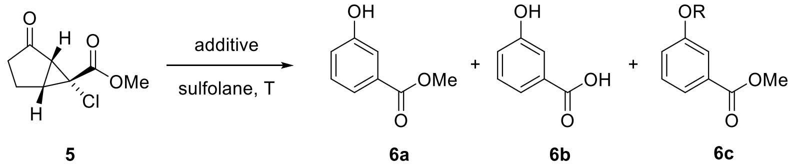


Figure 1: ^{1}H NMR spectra of the conversion of **1a** and **1b** to **4** (400 MHz, DMSO-d$_6$).

Screening of Reaction Conditions

A solution of cyclopropane **5** (1 equiv) and additive in the corresponding solvent was heated at the temperature and time indicated. The reaction mixture was cooled to 23 °C. Water (2 mL) and diethyl ether (2 mL) were added and the layers were separated and the aqueous layer was extracted with diethyl ether (5 × 15 mL). The combined organic extracts were washed sequentially with water (4 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel.

Table 1: Screening of Reaction Conditions**.**



Entry	Solvent	Additive	T (°C)	t (h)	Yield **6a** [%]	Yield **6b** [%]	Yield **6c** [%]
1	**sulfolane**	**none**	**190**	**0.25**	**99**	**0**	**0**
2	sulfolane	none	140	8	41	0	0
3	NMP	none	190	1	99	0	0
4	ODCB	none	180	16	81	0	0
5	sulfolane	$AgNO_3$ 1 equiv	140	3	60	0	0
6	sulfolane	LiCl 2.10 equiv	190	17	0	86	0
7	MeCN	*p*-TsOH 0.20 equiv	80	16	0	0	0
8	TFE[61]	none	70	3	0	0	0
9	sulfolane	DBU 1 equiv	140	8	17	0	0
10	sulfolane	DIPEA 1 equiv	140	8	56	0	0
11	THF	KO*t*-Bu 3 equiv	0–23	4	0	34	0
12	THF	KO*t*-Bu 3 equiv	0–23	28	18	28	0
13	chloroform	$FeCl_3$ 1 equiv	23–100	26	0	0	0
14	nitrobenzene	none	100–140	3	0	0	0
15	HFIP[61]	none	55	3	0	0	0
16	2-methyl-2-butano[61]l	none	100	2	0	0	0
17	2,2-dimethyl-1-propanol	none	110	7	0	0	54

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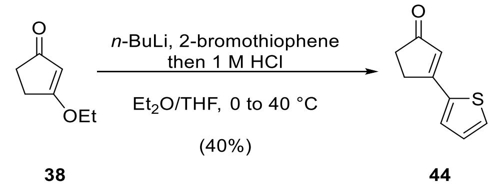
[61] Conducting the reaction in a pressure tube (sealed tube) at 90–130 °C for 3 h did not give any product either.

Syntheses of Precursors

3-(Thiophen-2-yl)cyclopent-2-en-1-one (44)



A solution of 2-bromothiophene (769 mL, 7.93 mmol, 2.00 equiv) in diethyl ether (50 mL) was cooled to −78 °C and a solution of *n*-butyllithium (2.3 M in hexanes, 3.45 mL, 7.93 mmol, 2.00 equiv) was added dropwise. The reaction mixture was warmed to 0 °C. After 2 h, the reaction mixture was transferred dropwise via cannula to a solution of enol ether **38** (500 mg, 3.96 mmol, 1 equiv) in tetrahydrofuran (6 mL). The solution was heated at 40 °C for 1 h. The reaction mixture was cooled to 23 °C and 1 M aqueous hydrochloric acid solution (20 mL) was added. After 1 h, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 40 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (10 mL) and saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **44** (257 mg, 40%) as an orange solid.

TLC (25% ethyl acetate in hexanes): $R_f = 0.27$ (UV, $KMnO_4$)

m.p.: 122–124 °C.

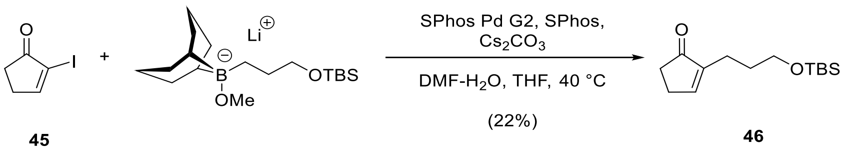
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.56 (dd, J = 5.1, 1.0 Hz, 1H), 7.46 (dd, J = 3.7, 1.0 Hz, 1H), 7.14 (dd, J = 5.1, 3.7 Hz, 1H), 6.31 (t, J = 1.6 Hz, 1H), 3.04–2.99 (m, 2H), 2.52–2.48 (m, 2H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 208.4, 166.9, 139.2, 130.6, 129.0, 128.8, 126.1, 35.5, 29.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3062 (*m*), 1673 (*vs*), 1592 (*vs*), 1420 (*s*), 1237 (*s*), 1183 (*vs*), 853 (*s*), 836 (*s*), 726 (*vs*) cm^{-1}.

HRMS (EI) calcd for C_9H_8OS $[M]^+$: 164.0296; found 164.0288.

2-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)cyclopent-2-en-1-one (46)



To a solution of protected iodopropanol (411 mg, 1.37 mmol, 1.50 equiv) and *B*-methoxy-9-borabicyclo[3.3.1]nonane (1 M in hexanes, 3.20 mL, 3.20 mmol, 3.50 equiv) in degassed tetrahydrofuran (5.5 mL) was cooled to −78 °C. A solution of *tert*-butyllithium (1.7 M in pentane, 2.42 mL, 4.11 mmol, 4.50 equiv) was added dropwise. After 15 min, the solution was warmed to 23 °C and was then transferred via cannula to a mixture of iodocyclopentenone **45** (190 mg, 913 µmol, 1 equiv), 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl (19.0 mg, 46.0 µmol, 5.00 mol%), chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2′-amino-1,1′- phenyl)]palladium(II) (33.0 mg, 46.0 µmol, 5.00 mol%) and cesium carbonate (595 mg, 1.83 mmol, 2.00 equiv) in a degassed mixture of *N,N*-dimethylformamide and water (9 mL, 9:1). The reaction mixture was heated at 40 °C. After 1 h, the reaction mixture was cooled to 23 °C and water (10 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 75 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **46** (50.0 mg, 22%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): $R_f = 0.36$ (UV, $KMnO_4$)

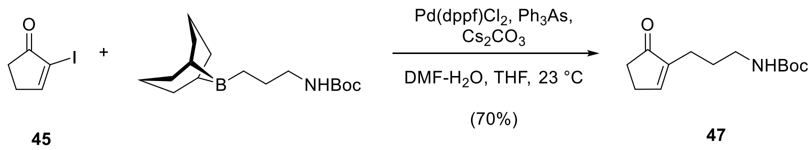
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 (s, 1H), 3.59 (t, *J* = 6.4 Hz, 2H), 2.58–2.49 (m, 2H), 2.40–2.33 (m, 2H), 2.21 (t, *J* = 7.6 Hz, 2H), 1.72–1.65 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.1, 157.7, 146.1, 62.7, 34.7, 30.8, 26.6, 26.1, 21.3, 18.4, −5.20.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953 (*m*), 2928 (*m*), 2894 (*m*), 2856 (*m*), 1702 (*s*), 1471 (*w*), 1252 (*m*), 1101 (*s*), 1003 (*m*), 962 (*m*), 832 (*vs*), 773 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{26}O_2Si$ $[M]^+$: 254.1702; found 254.1696.

***tert*-Butyl (3-(5-oxocyclopent-1-en-1-yl)propyl)carbamate (47)**



To a solution of *N*-Boc allylamine (588 mg, 3.75 mmol) in degassed tetrahydrofuran (7 mL) was added a solution of 9-borabicyclo[3.3.1]nonane (0.5 M in tetrahydrofuran, 10.0 mL). After 16 h, the solution was transferred via cannula to a mixture of iodocyclopentenone **45** (520 mg, 2.50 mmol, 1 equiv), [1,1'-bis(diphenylphosphino)ferrocene]palladiumdichloride (92.0 mg, 125 µmol, 5.00 mol%), triphenylarsine (38.0 mg, 125 µmol, 5.00 mol%) and cesium carbonate (1.22 g, 3.75 mmol, 1.50 equiv) in degassed *N,N*-dimethylformamide (20 mL) and degassed water (1.20 mL). After 1.5 h, the reaction mixture was poured on a saturated aqueous sodium chloride solution (30 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 50 mL). The combined organic extracts were washed with water (6 × 30 mL) and saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to afford **47** (420 mg, 70%) as a colorless oil.

TLC (33% ethyl acetate in hexanes): $R_f = 0.26$ (UV, $KMnO_4$)

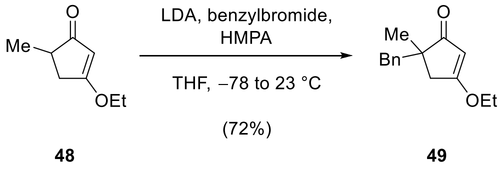
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 (s, 1H), 4.70 (br s, 1H), 3.12–3.07 (m, 2H), 2.59–2.52 (m, 2H), 2.41–2.34 (m, 2H), 2.23–2.15 (m, 2H), 1.66 (app q, *J* = 7.1 Hz, 2H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.1, 158.4, 156.1, 145.6, 79.2, 40.0, 34.7, 28.6, 28.3, 26.7, 22.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3356 (*w*), 2975 (*w*), 2929 (*w*), 1686 (*vs*), 1517 (*s*), 1444 (*m*), 1364 (*s*), 1249 (*s*), 1166 (*vs*), 1001 (*m*), 789 (*m*) cm^{-1}.

HRMS (ESI) calcd for $C_{13}H_{22}NO_3$ $[M+H]^+$: 240.1594; found 240.1596.

5-Benzyl-3-ethoxy-5-methylcyclopent-2-en-1-one (49)



A solution of diisopropylamine (1.16 mL, 8.21 mmol, 1.45 equiv) in tetrahydrofuran (2 mL) was cooled to −78 °C and a solution of *n*-butyllithium (2.3 M in hexanes, 3.43 mL, 7.93 mmol, 1.40 equiv) was added dropwise. After 10 min, the solution was allowed to warm to 0 °C. After 10 min, the solution was cooled to −78 °C and a solution containing enol ether **48**[62] (794 mg, 5.66 mmol, 1 equiv) and hexamethylphosphoramide (985 µL, 5.66 mmol, 1.10 equiv) in tetrahydrofuran (4 mL) was added dropwise. After 20 min, benzylbromide (1.02 mL, 2.68 mmol, 1.50 equiv) was added. The reaction mixture was allowed to warm to 23 °C within 16 h and then saturated aqueous ammonium chloride solution (20 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 40 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford a diastereomeric mixture of **49** (942 mg, 72%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.24$ (UV, $KMnO_4$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.27–7.10 (m, 5H), 5.07 (s, 1H), 3.99–3.86 (m, 2H), 2.92 (d, *J* = 13.3 Hz, 1H), 2.69–2.58 (m, 2H), 2.20 (d, *J* = 17.6 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.16 (s, 3H).

^{13}C NMR (101 MHz CD_2Cl_2) δ = 209.9, 188.1, 138.6, 130.7, 128.5, 126.8, 103.0, 68.0, 48.7, 43.5, 40.8, 25.2, 14.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2981 (*w*), 2925 (*w*), 1690 (*s*), 1587 (*vs*), 1453 (*m*), 1428 (*m*), 1373 (*m*), 1337 (*s*), 1220 (*m*), 1188 (*m*), 702 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{18}O_2$ $[M]^+$: 230.1307; found 230.1299.

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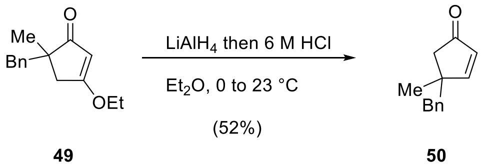
[62] For the synthesis of enol ether **48**, see: D. P. Curran, S.-C. Kuo, *Tetrahedron* **1987**, *43*, 5653–5661.

4-Benzyl-4-methylcyclopent-2-en-1-one (50)



A suspension of lithium aluminium hydride (45.0 mg, 1.19 mmol, 1.10 equiv) in diethyl ether (4 mL) was cooled to 0 °C. A solution of enol ether **49** (250 mg, 1.09 mmol, 1 equiv) in diethyl ether (2 mL) was added dropwise. After 20 min, the reaction mixture was warmed to 23 °C. After 30 min, saturated aqueous ammonium chloride solution (15 mL) was added followed by 6 M aqueous hydrochloric acid solution (10 mL). After 1 h, the layers were separated and the aqueous layer was extracted with diethyl ether (4 × 10 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (10 mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **50** (105 mg, 52%) as a colorless oil. Characterization data for **50** were in full agreement with those reported in the literature.[63]

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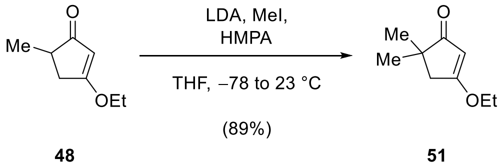
[63] L. Boisvert, F. Beaumier, C. Spino, *Can. J. Chem*. **2006**, *87*, 1290–1293.

3-Ethoxy-5,5-dimethylcyclopent-2-en-1-one (51)



A solution of diisopropylamine (2.12 mL, 15.0 mmol, 1.40 equiv) in tetrahydrofuran (3 mL) was cooled to −78 °C and a solution of *n*-butyllithium (2.3 M in hexanes, 6.05 mL, 13.9 mmol, 1.30 equiv) was added dropwise. After 10 min, the solution was warmed to 0 °C. After 10 min, the solution was cooled to −78 °C and a solution containing enol ether **48**[64] (1.50 g, 10.7 mmol, 1 equiv) and hexamethylphosphoramide (1.86 mL, 10.7 mmol, 1 equiv) in tetrahydrofuran (6 mL) was added dropwise. After 45 min, iodomethane (1.00 mL, 16.1 mmol, 1.50 equiv) was added. After 3 h, wet ethyl acetate (20 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were washed with water (20 mL) and saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to afford **51** (1.47 g, 89%) as a yellow oil.

TLC (33% ethyl acetate in hexanes): $R_f = 0.26$ (UV, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.15 (s, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.13 (s, 6H).

^{13}C NMR (101 MHz $CDCl_3$) δ = 211.2, 187.3, 101.8, 67.6, 44.7, 43.7, 25.4, 25.4, 14.3.
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2961 (*w*), 1692 (*m*), 1589 (*s*), 1375 (*m*), 1338 (*s*), 1224 (*m*), 1134 (*m*), 1027 (*m*), 818 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_9H_{14}O_2$ $[M]^+$: 154.0994; found 154.0997.

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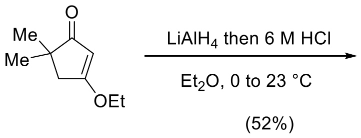
[64] For the synthesis of enol ether **48**, see: D. P. Curran, S.-C. Kuo, *Tetrahedron* **1987**, *43*, 5653–5661.

4,4-Dimethylcyclopent-2-en-1-one (52)



51 **52**

A suspension of lithium aluminium hydride (311 mg, 8.19 mmol, 1.10 equiv) in diethyl ether (6 mL) was cooled to 0 °C. A solution of enol ether **51** (1.15 g, 7.44 mmol, 1 equiv) in diethyl ether (6 mL) was added dropwise. After 20 min, the reaction mixture was warmed to 23 °C. After 30 min, 6 M aqueous hydrochloric acid solution (15 mL) was added. After 1 h, the layers were separated and the aqueous layer was extracted with diethyl ether (4 × 20 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (10 mL) and saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **52** (322 mg, 39%) as a colorless oil. Characterization data for **52** were in full agreement with those reported in the literature.[65]

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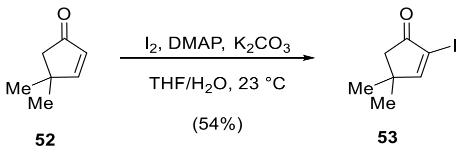
[65] For ^{1}H NMR and ^{13}C NMR spectra see,: K. B. Kingsbury, J. D. Carter, A. Wilde, H. Park, F. Takusagawa, L. McElwee-White, *J. Am. Chem. Soc*. **1993**, *115*, 10056–10065. For IR spectra, see: R. W. Holder, J. P. Daub, W. E. Baker, R. H. Gilbert, N. A. Graf, *J. Org. Chem*. **1982**, *47*, 1445–1451.

2-Iodo-4,4-dimethylcyclopent-2-en-1-one (53):



To a solution of cyclopentenone **52** (322 mg, 2.92 mmol, 1 equiv) in tetrahydrofuran (22.5 mL) and water (22.5 mL) were sequentially added 4-(dimethylamino)-pyridine (71.0 mg, 585 µmol, 0.200 equiv), potassium carbonate (485 mg, 3.51 mmol, 1.20 equiv) and iodine (1.11 g, 4.38 mmol, 1.50 equiv). After 18 h, diethyl ether (30 mL) was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate solution (20 mL) and 0.2 M aqueous hydrochloric acid solution (10 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **53** (375 mg, 54%) as a colorless, light sensitive solid.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.38$ (UV, $KMnO_4$)

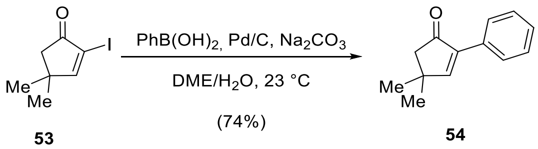
^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.78$ (s, 1H), 2.36 (s, 2H), 1.24 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 203.6, 178.7, 99.9, 47.0, 44.3, 28.1, 28.1$.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3060 (*w*), 2964 (*m*), 2865 (*w*), 1705 (*vs*), 1574 (*s*), 1469 (*m*), 1406 (*w*), 1362 (*w*), 1294 (*s*), 1258 (*m*), 1096 (*w*), 904 (*m*) cm^{-1}.

HRMS (EI) calcd for C_7H_9IO $[M]^+$: 235.9698; found 235.9698.

2-Phenyl-4,4-dimethylcyclopent-2-en-1-one (54):



To a solution of iodide **53** (375 mg, 1.59 mmol, 1.50 equiv) in a mixture of dimethoxyethane (5.1 mL) and water (5.1 mL) were added sodium carbonate (337 mg, 3.18 mmol, 3.00 equiv), phenyl boronic acid (385 mg, 3.18 mmol, 3.00 equiv) and palladium on activated charcoal (254 mg, 239 µmol, 0.150 equiv). After 18 h, water (3 mL) and diethyl ether (30 mL) were added and the reaction mixture was filtered through a short plug of celite. The plug was washed with diethyl ether (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **54** (220 mg, 74%) as a colorless solid.

TLC (12.5% ethyl acetate in hexanes): R_f = 0.55 (UV, $KMnO_4$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.69–7.67 (m, 2H), 7.59 (s, 1H), 7.39–7.30 (m, 3H), 2.44 (s, 2H), 1.29 (s, 6H).

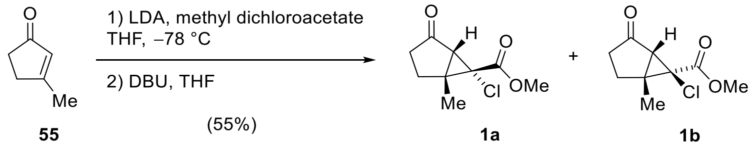
^{13}C NMR (101 MHz, CD_2Cl_2) δ = 207.5, 168.5, 140.5, 132.2, 128.8, 128.8, 127.7, 51.9, 38.7, 28.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2958 (*m*), 2926 (*w*), 1698 (*vs*), 1492 (*m*), 1447 (*m*), 1306 (*m*), 1250 (*m*), 1124 (*m*), 747 (*m*), 693 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{14}O$ $[M]^+$: 186.1045; found 186.1048.

Syntheses of Bicyclo[3.1.0]hexan-2-ones

Methyl 6-chloro-5-methyl-2-oxobicyclo[4.1.0]hexane-6-carboxylate (1a/1b):



A solution of diisopropylamine (0.353 mL, 2.50 mmol, 1.20 equiv) in tetrahydrofuran (2.5 mL) was cooled to –78 °C. A solution of *n*-butyllithium (1.9 M in hexanes, 1.31 mL, 2.50 mmol, 1.20 equiv) was added dropwise. After 5 min, the reaction mixture was warmed to 0 °C. After 10 min, the solution was cooled to –78 °C. A solution of methyl dichloroacetate (0.297 mL, 2.08 mmol, 1 equiv) in tetrahydrofuran (4 mL) was added dropwise. After 10 min, 3-methyl-2-cyclopenten-1-one (**55**) (0.206 mL, 2.08 mmol, 1 equiv) was added dropwise over 7 min. After 4.5 h, saturated aqueous ammonium chloride solution (8 mL) was added at 0 °C. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with 0.5 M aqueous hydrochloric acid solution (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated.

The crude residue (450 mg, 1.88 mmol, 1 equiv) was diluted with tetrahydrofuran (6.66 mL) and 1,8-diazabicyclo[5.4.0]undec-7-en (4.22 mL, 28.2 mmol, 15.0 equiv) was added dropwise at 0 °C. After 3 min, the suspension was warmed to 23 °C. After 40 min, the mixture was cooled to 0 °C and saturated aqueous ammonium chloride solution (8 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic extracts were washed with aqueous 0.5 M hydrochloric acid solution (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to afford a 4:1 diastereomeric mixture of **1a**/**1b** (209 mg, 55%) as a yellow oil. The obtained characterization data were in full agreement with values previously reported.[66]

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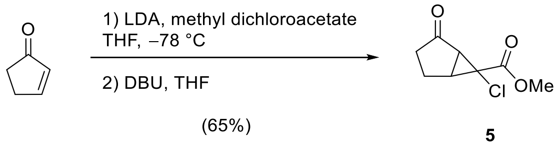
[66] A. Escribano, C. Pedregal, R. González, A. Fernández, K. Burton, G. A. Stephenson, *Tetrahedron* **2001**, *57*, 9423–9427.

Methyl 6-chloro-2-oxobicyclo[3.1.0]hexane-6-carboxylate (5)



5

A solution of diisopropylamine (1.78 mL, 12.6 mmol, 1.20 equiv) in tetrahydrofuran (12.6 mL) was cooled to –78 °C. A solution of *n*-butyllithium (1.9 M in hexanes, 6.63 mL, 12.6 mmol, 1.20 equiv) was added dropwise. After 10 min, the reaction mixture was warmed to 0 °C. After 10 min, the solution was cooled to –78 °C. A solution of methyl dichloroacetate (1.09 mL, 10.5 mmol, 1 equiv) in tetrahydrofuran (21 mL) was added dropwise. After 10 min, 2-cyclopenten-1-one (0.879 mL, 10.5 mmol, 1 equiv) was added dropwise. After 4.5 h, saturated aqueous ammonium chloride solution (24 mL) was added at 0 °C. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 25 mL). The combined organic extracts were washed with 0.5 M aqueous hydrochloric acid solution (2 × 30 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated.

The crude residue (2.26 g, 10.0 mmol, 1 equiv) was diluted with tetrahydrofuran (34 mL) and 1,8-diazabicyclo[5.4.0]undec-7-en (10.0 mL, 66.9 mmol, 6.67 equiv) was added dropwise at 0 °C. After 5 min, the suspension was warmed to 23 °C. After 45 min, the mixture was cooled to 0 °C and saturated aqueous ammonium chloride solution (24 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with aqueous 0.5 M hydrochloric acid solution (2 × 25 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **5** (1.23 g, 65%) as a yellow solid. The obtained analytical data were in full agreement with those reported in the literature.[67]

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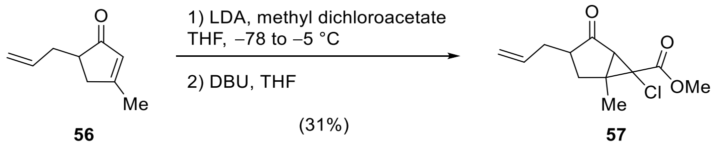
[67] A. Escribano, C. Pedregal, R. González, A. Fernández, K. Burton, G. A. Stephenson, *Tetrahedron* **2001**, *57*, 9423–9427.

Methyl 3-allyl-6-chloro-1-methyl-4-oxobicyclo[3.1.0]hexane-6-carboxylate (57)



A solution of diisopropylamine (0.188 mL, 1.33 mmol, 1.20 equiv) in tetrahydrofuran (1.33 mL) was cooled to –78 °C. A solution of *n*-butyllithium (1.9 M in hexanes, 0.700 mL, 1.33 mmol, 1.20 equiv) was added dropwise. After 5 min, the reaction mixture was warmed to 0 °C. After 10 min, the solution was cooled to –78 °C. A solution of methyl dichloroacetate (0.115 mL, 1.11 mmol, 1 equiv) in tetrahydrofuran (2mL) was added dropwise. After 10 min, 5-allyl-3-methyl-2-cyclopenten-1-one (**56**)[68] (151 mg, 1.11 mmol, 1 equiv) in tetrahydrofuran (0.3 mL) was added dropwise. After 6 h, the mixture was warmed to –5 °C, saturated aqueous ammonium chloride solution (7 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with 0.5 M aqueous hydrochloric acid solution (2 × 10 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated.

The crude residue (184 mg, 659 µmol, 1 equiv) was diluted with tetrahydrofuran (0.8 mL) and 1,8-diazabicyclo[5.4.0]undec-7-en (1.48 mL, 9.89 mmol, 15.0 equiv) was added dropwsie at 0 °C. After 5 min, the suspension was warmed to 23 °C. After 1.5 h, the mixture was cooled to 0 °C and saturated aqueous ammonium chloride solution (7 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with 1 M aqueous hydrochloric acid solution (2 × 10 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes, then 7% ethyl acetate in hexanes) to afford the diastereomeric mixture of **57** (50.0 mg, 31%) as a yellow oil.

TLC (20% ethyl acetate in hexanes), R_f = 0.67 ($KMnO_4$)

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[68] For the synthesis of cyclopentenone **56**, see: C. Tanyeli, D. Özdemirhan, *Tetrahedron* **2005**, *61*, 8212–8217.

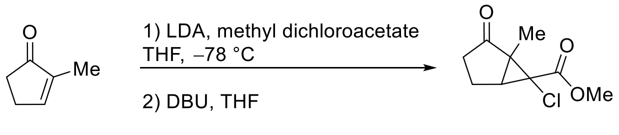
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.77–5.65 (m, 1H), 5.10 (d, *J* = 6.4 Hz, 1H), 5.06 (s, 1H), 3.83 (s, 3H), 2.87 (s, 1H), 2.59 (app dd, *J* = 14.1, 8.5 Hz, 1H), 2.40–2.53 (m, 2H), 2.13 (app dd, *J* = 14.3, 7.4 Hz, 1H), 1.93 (app dd, *J* = 14.1, 6.0 Hz, 1H), 1.38 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 211.2, 167.0, 135.1, 117.5, 53.8, 47.3, 45.3, 40.5, 36.3, 36.1, 17.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2928 (*w*), 1734 (*vs*), 1437 (*w*), 1266 (*m*), 1171 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{15}{}^{35}ClO_3$ $[M]^+$: 242.0710; found: 242.0685.

Methyl 6-chloro-1-methyl-2-oxobicyclo[3.1.0]hexane-6-carboxylate (59)



58 (63%) **59**

A solution of diisopropylamine (0.353 mL, 2.50 mmol, 1.20 equiv) in tetrahydrofuran (2.5 mL) was cooled to –78 °C. A solution of *n*-butyllithium (1.9 M in hexanes, 1.31 mL, 2.50 mmol, 1.20 equiv) was added dropwise. After 5 min, the reaction mixture was warmed to 0 °C. After 10 min, the solution was cooled to –78 °C. A solution of methyl dichloroacetate (0.215 mL, 2.08 mmol, 1 equiv) in tetrahydrofuran (4 mL) was added dropwise. After 10 min, 2-methyl-2-cyclopenten-1-one (**58**) (0.204 mL, 2.08 mmol, 1 equiv) was added dropwise. After 7 h, saturated aqueous ammonium chloride solution (8 mL) was added at 0 °C. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with 0.5 M aqueous hydrochloric acid solution (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated.

The crude residue (500 mg, 2.09 mmol, 1 equiv) was diluted with tetrahydrofuran (7 mL) and 1,8-diazabicyclo[5.4.0]undec-7-en (4.69 mL, 31.4 mmol, 15.0 equiv) was added dropwise at 0 °C. After 5 min, the suspension was warmed to 23 °C. After 3.5 h, the mixture was cooled to 0 °C and saturated aqueous ammonium chloride solution (8 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with aqueous 0.5 M hydrochloric acid solution (2 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **59** (266 mg, 63%) as a colorless solid.

TLC (17% ethyl acetate in hexanes), R_f = 0.56 (UV, $KMnO_4$)

m.p.: 68 °C.

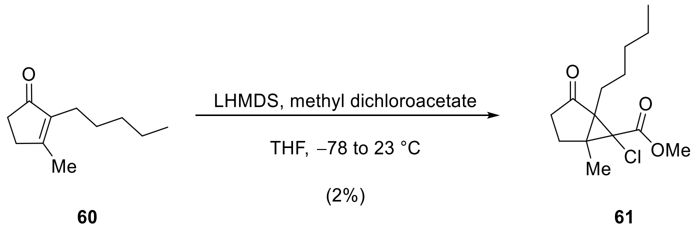
^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.82 (s, 3H), 2.86 (app d, *J* = 5.8 Hz, 1H), 2.40–2.27 (m, 3H), 2.14–2.10 (m, 1H), 1.29 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 211.7, 167.2, 53.7, 51.7, 44.7, 38.7, 36.8, 19.4, 10.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2948 (*w*), 1741 (*s*), 1714 (*vs*), 1438 (*s*), 1280 (*vs*), 1221 (*vs*), 1034 (*s*), 968 (*m*), 8051 (*s*), 747 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_9H_{11}ClO_3$ $[M]^+$: 202.0397; found: 202.0392.

Methyl 6-chloro-2-(pentyl)-3-(methyl)-2-oxobicyclo[3.1.0]hexane-6-carboxylate (61)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.20 mL, 1.20 mmol, 1.20 equiv) was cooled to −78 °C and a solution of methyl dichloroacetate (104 µL, 1.00 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added dropwise. The reaction mixture was stirred at −78 °C. After 45 min, cyclopentenone **60** (182 µL, 1.00 mmol, 1 equiv) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 12 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were washed with aqueous 0.5 M hydrochloric acid solution (2 × 10 mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **61** (6.00 mg, 2%) as a colorless oil.

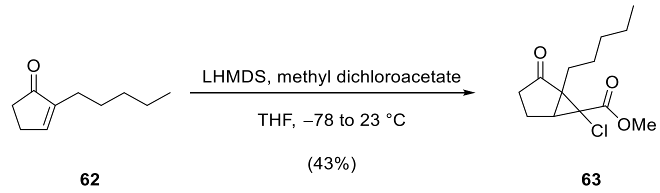
TLC (10% ethyl acetate in hexanes): $R_f = 0.52$ ($KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.79 (s, 3H), 2.34–2.27 (m, 2H), 2.12–2.02 (m, 2H), 1.47 (s, 3H), 1.34–1.19 (m, 8H), 0.86 (t, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 212.2, 166.3, 53.2, 49.9, 41.9, 38.2, 32.3, 29.9, 28.9, 26.7, 24.1, 22.6, 16.0, 14.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953 (*m*), 2929 (*m*), 1735 (*vs*), 1257 (*s*), 1227 (*m*), 1164 (*w*), 1080 (*m*) cm^{-1}.

Methyl 6-chloro-2-(pentyl)-2-oxobicyclo[3.1.0]hexane-6-carboxylate (63)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.20 mL, 1.20 mmol, 1.20 equiv) was cooled to −78 °C and a solution of methyl dichloroacetate (104 µL, 1.00 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 45 min, cyclopentenone **62** (165 µL, 1.00 mmol, 1 equiv) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 4 h, saturated aqueous ammonium chloride solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 10 mL). The combined organic layers were washed with aqueous 0.5 M hydrochloric acid solution (2 × 10 mL) and saturated aqueous sodium chloride solution (30 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes then 10% ethyl acetate in hexanes) to afford **63** (110 mg, 43%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): $R_f = 0.33$ ($KMnO_4$)

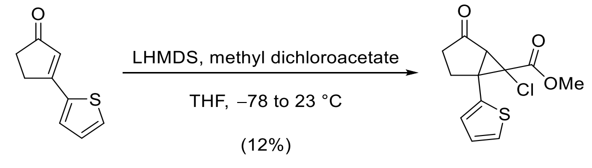
^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.82 (s, 3H), 2.87 (app d, *J* = 5.8 Hz, 1H), 2.39–2.24 (m, 3H), 2.17–2.09 (m, 1H), 2.07–2.00 (m, 1H), 1.43–1.36 (m, 1H), 1.35–1.16 (m, 6H), 0.86 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 211.5, 167.4, 53.8, 51.5, 49.3, 37.6, 37.4, 31.8, 26.9, 24.8, 22.5, 19.4, 14.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2948 (*m*), 2920 (*m*), 1722 (*vs*), 1453 (*m*), 1435 (*m*), 1300 (*m*), 1269 (*s*), 1257 (*s*), 1221 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{19}ClO_3$ $[M]^+$: 258.1023; found: 258.1030.

Methyl 6-chloro-4-oxo-1-(thiophen-2-yl)bicyclo[3.1.0]hexane-6-carboxylate (64)



44 **64**

A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.28 mL, 1.28 mmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (139 µL, 1.34 mmol, 1.10 equiv) was added dropwise. After 30 min, a solution of **44** (200 mg, 1.22 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 45 min, the reaction was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (5 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **64** (38 mg, 12%) as a yellow solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.33$ (UV, $KMnO_4$)

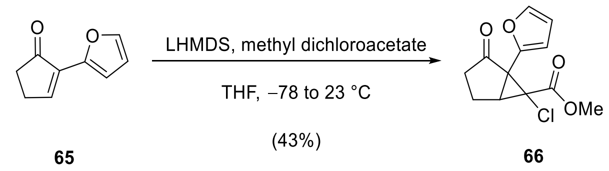
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (d, J = 5.0 Hz, 1H), 7.08 (d, J = 3.3 Hz, 1H), 7.05–7.00 (m, 1H), 3.78 (s, 3H), 3.16 (s, 1H), 2.71–2.49 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 204.2, 167.3, 140.8, 127.3, 127.0, 126.3, 60.7, 53.0, 46.8, 42.7, 35.0, 28.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953 (*w*), 1733 (*vs*), 1436 (*m*), 1282 (*m*), 1206 (*s*), 1169 (*s*), 1013 (*m*), 976 (*m*), 704 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{11}ClO_3S$ $[M]^+$: 270.0117; found 270.0113.

Methyl 6-chloro-1-(furan-2-yl)-2-oxobicyclo[3.1.0]hexane-6-carboxylate (66)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 2.13 mL, 2.13 mmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (231 µL, 2.23 mmol, 1.10 equiv) was added dropwise After 30 min, a solution of **65**[69] (300 mg, 2.02 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 1.5 h, the reaction was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (5 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 25 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **66** (219 mg, 43%) as a yellow solid.

TLC (10% ethyl acetate in hexanes): $R_f = 0.18$ (UV, $KMnO_4$)

m.p.: 104 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.39 (dd, *J* = 3.3, 0.8 Hz, 1H), 6.34 (dd, *J* = 3.3, 1.8 Hz, 1H), 3.59 (s, 3H), 3.46 (app d, *J* = 6.4 Hz, 1H), 2.64–2.53 (m, 1H), 2.52–2.43 (m, 2H), 2.29–2.21 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 206.6, 165.6, 145.1, 142.8, 111.0, 110.9, 53.8, 52.9, 46.3, 37.8, 37.1, 19.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (*w*), 1731 (*vs*), 1436 (*m*), 1268 (*s*), 1226 (*s*), 1134 (*s*), 971 (*m*), 739 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{11}ClO_4$ $[M]^+$: 254.0346; found 254.0324.

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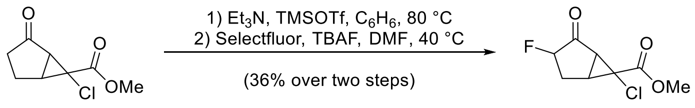
[69] For the synthesis of cyclopentenone **65**, see: D. E. Ebner, J. T. Bagdanoff, E. M. Ferreira, R. M. McFadden, D. D. Caspi, R. M. Trend, B. M. Stoltz, *Chem. Eur. J.* **2009**, *15*, 12978–12992.

Methyl 6-chloro-3-fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylate (67)



5 **67**

To a solution of cyclopropane **5** (208 mg, 1.10 mmol, 1 equiv) in benzene (5 mL) was added triethylamine (368 µL, 2.43 mmol, 2.40 equiv) and trimethylsilyl trifluoromethanesulfonate (440 µL, 2.43 mmol, 2.20 equiv) and the reaction mixture was heated at 80 °C. After 45 min, the solution was cooled to 23 °C and hexanes (5 mL) was added. The solution was washed with saturated aqueous sodium bicarbonate solution (10 mL) and the aqueous layer was extracted with hexanes (30 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated.

To a solution of the crude enol ether in *N,N*-dimethylformamide (5 mL) was added Selectfluor (391 mg, 1.10 mmol, 1 equiv). After 3 h at 23 °C, the reaction mixture was heated to 40 °C. After 18 h, the solution was allowed to cool to 23 °C and a solution of tetrabutylammonium fluoride (1 M in tetrahydrofuran, 1.10 mL, 1.10 mmol, 1 equiv) was added. After 5 min, ice water (5 mL) was added and the reaction was stirred for 4 h. Hexanes (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **67** (81.0 mg, 36%) as an off-white solid.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.25$ (KMnO$_4$)

m.p.: 49 °C.

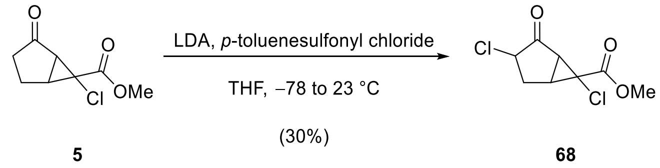
^{1}H NMR (400 MHz, CDCl$_3$) δ = 4.89 (ddd, *J* = 52.0, 7.8, 4.9 Hz, 1H), 3.81 (s, 3H), 2.91 (app t, *J* = 6.4 Hz, 1H), 2.86–2.75 (m, 2H), 2.62–2.43 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ = 202.8 (d, *J* = 15.5 Hz), 167.3, 89.3 (d, *J* = 188.2 Hz), 54.3, 49.5, 39.0, 34.5 (d, *J* = 5.2 Hz), 29.0 (d, *J* = 23.2 Hz).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2959 (*w*), 1749 (*vs*), 1437 (*m*), 1290 (*s*), 1261 (*s*), 1190 (*m*), 1087 (*s*), 910 (*s*), 727 (*vs*) cm^{-1}.

HRMS (EI) calcd for C$_8$H$_8$ClFO$_3$ [M]$^+$: 206.0146; found 206.0154.

Methyl 3,6-dichloro-4-oxo-bicyclo[3.1.0]hexane-6-carboxylate (68)



A solution of diisopropylamine (247 µL, 1.75 mmol, 1.10 equiv) in tetrahydrofuran (1.75 mL) was cooled to −78 °C and a solution of *n*-butyllithium (2.3 M in hexanes, 692 µL, 1.59 mmol, 1 equiv) was added dropwise. After 10 min, the reaction mixture was warmed to 0 °C. After 10 min, the solution was cooled to −78 °C and a solution of cyclopentenone **5** (300 mg, 1.59 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added dropwise. After 45 min, *p*-toluenesulfonyl chloride (303 mg, 1.59 mmol, 1 equiv) was added. After 30 min, the mixture was warmed to 23 °C. After 14 h, the reaction mixture was filtered through a plug of silica gel and the plug was washed with diethyl ether. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **68** (103 mg, 30%) as colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.39$ ($KMnO_4$)

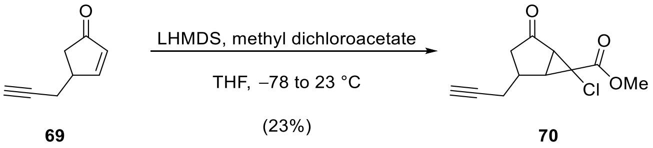
^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.26 (dd, *J* = 8.1, 5.7 Hz, 1H), 3.82 (s, 3H), 2.98–2.83 (m, 3H), 2.68–2.61 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.0, 167.4, 55.8, 54.4, 48.8, 39.5, 34.2, 32.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3071 (*w*), 2955 (*w*), 1749 (*vs*), 1436 (*m*), 1360 (*w*), 1304 (*m*), 1258 (*vs*), 1188 (*m*), 1157 (*m*), 1081 (*m*), 1033 (*w*), 992 (*m*), 878 (*m*), 777 (*m*), 746 (*w*), 694 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_8H_8Cl_2O_3$ $[M]^+$: 221.9850; found: 221.9862.

Methyl 6-chloro-2-oxo-4-(prop-2-yn-1-yl)bicyclo[3.1.0]hexane-6-carboxylate (70)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 655 µL, 655 µmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (71.1 µL, 687 µmol, 1.10 equiv) was added dropwise. After 30 min, a solution of **69**[70] (75.0 mg, 624 µmol, 1 equiv) in tetrahydrofuran (1 mL) was added dropwise. After 30 min, the reaction was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (5 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **70** (33.0 mg, 23%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.37$ ($KMnO_4$)

^{1}H NMR (800 MHz, $CDCl_3$) δ = 3.82 (s, 3H), 2.81 (d, *J* = 6.1 Hz, 1H), 2.74 (d, *J* = 6.1 Hz, 1H), 2.73–2.70 (m, 1H), 2.60–2.57 (m, 1H), 2.56–2.48 (m, 2H), 2.19–2.16 (m, 1H), 2.04 (t, *J* = 2.6 Hz, 1H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 207.8, 168.0, 80.5, 71.2, 54.2, 47.9, 43.5, 42.1, 40.5, 33.3, 25.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3286 (*w*), 2957 (*w*), 1735 (*vs*), 1437 (*m*), 1259 (*vs*), 1188 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{11}ClO_3$ $[M]^+$: 226.0397; found 226.0378.

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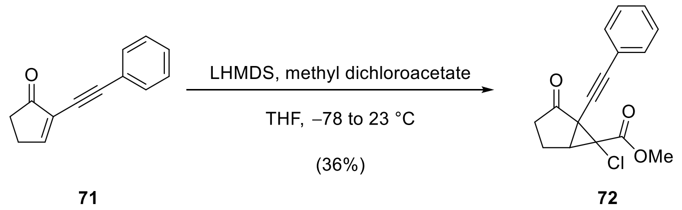
[70] For the synthesis of cyclopentenone **69**, see: Y. Chen, D. M. Ho, C. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 12184–12185.

Methyl 6-chloro-2-(phenylethenyl)-2-oxobicyclo[3.1.0]hexane-6-carboxylate (72)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 864 µL, 864 µmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (93.7 µL, 905 µmol, 1.10 equiv) was added dropwise. After 30 min, a solution of **71**[71] (150 mg, 823 µmol, 1 equiv) in tetrahydrofuran (1.2 mL) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 12 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were washed with aqueous 0.5 M hydrochloric acid solution (2 × 25 mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **72** (85.0 mg, 36%) as a brown solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.45 (UV, $KMnO_4$)

m.p.: 115–119 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.43–7.38 (m, 2H), 7.37–7.28 (m, 3H), 3.84 (s, 3H), 3.40 (app d, *J* = 6.4 Hz, 1H), 2.60–2.50 (m, 1H), 2.49–2.36 (m, 2H), 2.22–2.15 (m, 1H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 205.7, 165.8, 132.3, 129.3, 128.9, 122.6, 85.8, 812, 54.7, 54.2, 41.9, 41.5, 37.0, 19.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3055 (*w*), 2952 (*w*), 1736 (*vs*), 1436 (*m*), 1305 (*w*), 1270 (*s*), 1232 (*m*), 1189 (*m*), 1035 (*m*), 756 (*m*), 691 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{13}ClO_3$ $[M]^+$: 288.0553; found: 288.0546.

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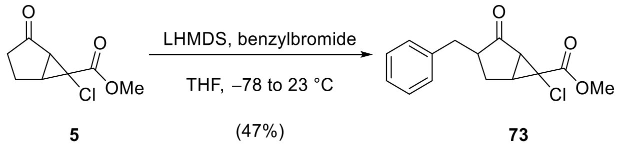
[71] For the synthesis of cyclopentenone **71**, see: T. Yao, X. Zhang, R. C. Larock, *J. Org. Chem*. **2005**, *70*, 7679–7685.

Methyl 6-chloro-4-benzyl-2-oxobicyclo[3.1.0]hexane-6-carboxylate (73)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 278 µL, 278 µmol, 1.05 equiv) was cooled to −78 °C and a solution of **5** (50.0 mg, 265 µmol, 1 equiv) in tetrahydrofuran (1 mL) was added dropwise. After 30 min, benzyl bromide (34.7 µL, 292 µmol, 1.10 equiv) was added and after 30 min, the solution was warmed to 23 °C. After 12 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were washed with aqueous 0.5 M hydrochloric acid solution (2 × 20 mL) and saturated aqueous sodium chloride solution (30 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (11% ethyl acetate in hexanes) to afford **73** (35.0 mg, 47%) as a colorless oil.

TLC (17% ethyl acetate in hexanes): R_f = 0.47 (UV, $KMnO_4$)

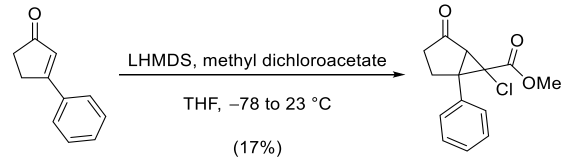
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.32–7.27 (m, 2H), 7.24–7.16 (m, 3H), 3.76 (s, 3H), 3.12 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.75–2.72 (m, 1H), 2.70–2.66 (m, 1H), 2.66–2.59 (m, 1H), 2.53 (dd, *J* = 13.6, 10.3 Hz, 1H), 2.27–2.15 (m, 2H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 210.6, 168.5, 139.5, 129.5, 129.0, 127.0, 54.4, 496, 48.7, 42.4, 38.0, 35.2, 28.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (*w*), 1728 (*vs*), 1600 (*w*), 1302 (*w*), 1259 (*s*), 1191 (*m*), 704 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{15}ClO_3$ $[M]^+$: 278.0710; found: 278.0713.

Methyl 6-chloro-4-oxo-1-phenylbicyclo[3.1.0]hexane-6-carboxylate (75)



74 **75**

A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.66 mL, 1.66 mmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (180 µL, 1.74 mmol, 1.10 equiv) was added dropwise. After 30 min, a solution of 3-phenylcyclopent-2-en-1-one (**74**)[72] (250 mg, 1.58 mmol, 1 equiv) in tetrahydrofuran (1.2 mL) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 12 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were washed with aqueous 0.5 M hydrochloric acid solution (2 × 20 mL) and saturated aqueous sodium chloride solution (30 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **75** (72.0 mg, 17%) as a red oil.

TLC (25% ethyl acetate in hexanes): $R_f = 0.51$ (UV, $KMnO_4$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.46–7.36 (m, 5H), 3.80 (s, 3H), 3.08 (s, 1H), 2.56–2.44 (m, 4H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 205.3, 168.3, 138.5, 129.6, 129.4, 128.9, 59.5, 53.3, 52.0, 42.0, 35.6, 29.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951 (*w*), 1731 (*vs*), 1437 (*m*), 1316 (*m*), 1293 (*m*), 1214 (*s*), 1191 (*s*), 1168 (*s*), 976 (*m*), 761 (*s*), 699 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{13}ClO_3$ $[M]^+$: 264.0553; found: 264.0547.

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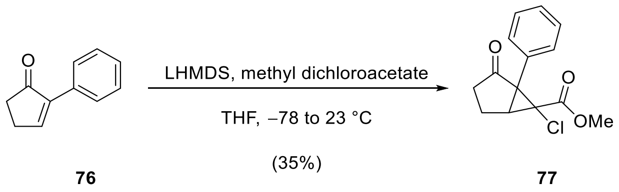
[72] For the synthesis of cyclopentenone **74**, see: V. Jurkauskas, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 2892–2893.

Methyl 6-chloro-2-(phenyl)-2-oxobicyclo[3.1.0]hexane-6-carboxylate (77):



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.26 mL, 1.26 mmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (137 µL, 1.32 mmol, 1.10 equiv) was added dropwise. After 30 min, a solution of **76**[73] (190 mg, 1.20 mmol, 1 equiv) in tetrahydrofuran (1.5 mL) was added dropwise. After 45 min, the solution was warmed to 23 °C. After 3 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 40 mL). The combined organic layers were washed with aqueous 0.5 M hydrochloric acid solution (2 × 20 mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **77** (112 mg, 35%) as a colorless solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.39 (UV, $KMnO_4$)

m.p.: 98 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.27–7.20 (m, 3H), 7.19–7.13 (m, 2H), 3.35 (app d, *J* = 6.4 Hz, 1H), 3.28 (s, 3H), 2.64–2.54 (m, 1H), 2.39–2.35 (m, 2H), 2.20–2.13 (m, 1H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 208.2, 166.0, 131.9, 129.7, 128.5, 128.5, 53.5, 52.9, 37.5, 37.3, 19.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951 (*w*), 1726 (*vs*), 1498 (*w*), 1447 (*m*), 1435 (*m*), 1403 (*w*), 1295 (*w*), 1268 (*s*), 1224 (*s*), 1203 (*m*), 1137 (*m*), 1056 (*m*), 699 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{13}ClO_3$ $[M]^+$: 264.0553; found: 264.0553.

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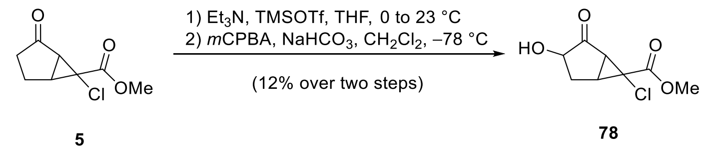
[73] For the synthesis of cyclopentenone **76**, see: F.-.X. Felpin, *J. Org. Chem*. **2005**, *70*, 8575–8575.

Methyl 6-chloro-3-hydroxy-2-oxobicyclo[3.1.0]hexane-6-carboxylate (78):



A solution of cyclopropane **5** (201 mg, 1.07 mmol, 1 equiv) in tetrahydrofuran (5 mL) was cooled to 0 °C. Triethylamine (356 µL, 2.56 mmol, 2.40 equiv) and trimethylsilyl trifluoromethanesulfonate (425 µL, 2.34 mmol, 2.20 equiv) were added and the reaction mixture was warmed to 23 °C. After 45 min, hexane (5 mL) was added and the solution was washed with saturated aqueous sodium bicarbonate solution (10 mL). The layers were separated and the aqueous layer was extracted with hexane (30 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated.

A solution of the crude enol ether in dichloromethane (2 mL) was cooled to −78 °C. Sodium bicarbonate (224 mg, 2.66 mmol, 2.50 equiv) and a suspension of 3-chloroperoxybenzoic acid (70% in water, 294 mg, 1.28 mmol, 1.20 equiv) in dichloromethane (1 mL) were added. After 4 h, saturated aqueous sodium thiosulfate solution (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (4 × 20 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **78** (26.0 mg, 12%) as colorless oil.

TLC (10% ethyl acetate in hexanes): $R_f = 0.10$ ($KMnO_4$)

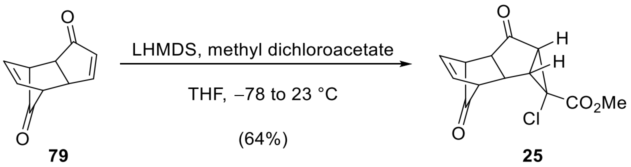
^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.17 (dd, *J* = 7.8, 5.9 Hz, 1H), 3.82 (s, 3H), 2.89–2.76 (m, 2H), 2.71 (dd, *J* = 14.7, 8.0 Hz, 1H), 2.49 (br s, 1H), 2.33 (dt, *J* = 14.7, 5.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.5, 167.8, 71.8, 54.3, 50.0, 39.8, 35.1, 30.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3294 (*m*), 1739 (*s*), 1665 (*vs*), 1602 (*vs*), 1524 (*s*), 1452 (*s*), 1370 (*vs*), 1300 (*vs*), 1263 (*vs*), 1104 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_8H_9ClO_4$ $[M]^+$: 204.0189; found 204.0182.

Cyclopropane 25



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.25 mL, 1.25 mmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (136 µL, 1.31 mmol, 1.10 equiv) was added dropwise. After 30 min, a solution of dicyclopentandienone **79**[74] (191 mg, 1.19 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 45 min, the solution was warmed to 23 °C. After 12 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organic layers were washed with aqueous 0.5 M hydrochloric acid solution (2 × 20 mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to afford **25** (203 mg, 64%) as a colorless solid.

TLC (33% ethyl acetate in hexanes): $R_f = 0.39$ (UV, $KMnO_4$)

m.p.: 141–143 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.57–6.55 (m, 1H), 6.49–6.46 (m, 1H), 3.79 (s, 3H), 3.43–3.30 (m, 2H), 3.18 (dd, *J* = 7.3, 4.5 Hz, 1H), 2.94 (dd, *J* = 7.3, 5.2 Hz, 1H), 2.63 (d, *J* = 6.1 Hz, 1H), 2.52 (d, *J* = 6.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 207.7, 198.5, 167.7, 131.7, 130.6, 54.3, 49.9, 49.1, 48.8, 45.9, 44.8, 37.2, 36.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (*w*), 1776 (*s*), 1730 (*vs*), 1275 (*m*), 1261 (*s*), 1179 (*m*) cm^{-1}.

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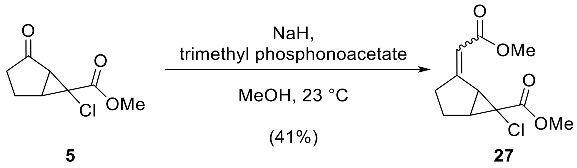
[74] For the synthesis of cyclopentadienone dimer **79**, see: C. H. DePuy, M. Isaks, K. L. Eilers, G. F. Morris, *J. Org. Chem.* **1964**, *29*, 3503–3507.

Methyl 6-chloro-2-(2-methoxy-2-oxoethylidene)bicyclo[3.1.0]hexane-6-carboxylate (27)



To a suspension of sodium hydride (60% dispersion in mineral oil, 76.3 mg, 1.91 mmol, 1.20 equiv) in methanol (2 mL) was added trimethyl phosphonoacetate (230 µL, 1.59 mmol, 1 equiv). After 40 min, a solution of ketone **5** (300 mg, 1.59 mmol, 1 equiv) in methanol (1 mL) was added dropwise. After 20 h, saturated aqueous ammonium chloride solution (5 mL) and ethyl acetate (5 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **27** (161 mg, 41%, mixture of double bond isomers) as a colorless oil.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.37$ (UV, $KMnO_4$)

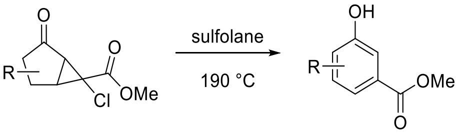
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.93 (app t, J = 2.6 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 3.14–3.04 (m, 1H), 2.87 (d, J = 6.6 Hz, 1H), 2.62–2.52 (m, 2H), (app dt, J = 12.7, 6.4 Hz, 2H), 2.38–2.26 (m, 1H), 2.11–2.01 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.2, 166.6, 163.3, 115.5, 53.7, 51.6, 51.1, 43.3, 36.9, 32.6, 25.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (*w*), 1710 (*vs*), 1651 (*s*), 1435 (s), 1370 (*m*), 1301 (*s*), 1261 (*vs*), 1205 (*vs*), 1137 (*vs*), 1081 (*s*), 1020 (*s*) cm^{-1}.

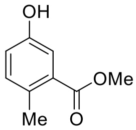
HRMS (EI) calcd for $C_{11}H_{13}ClO_4$ $[M]^+$: 244.0502; found 244.0491.

Syntheses of Benzoates



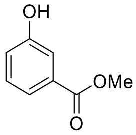
General Procedure: A solution of cyclopropane (1 equiv) in sulfolane (0.2–0.5 M) was stirred for the time and the temperature indicated. After complete consumption of the starting material (as seen by TLC analysis), the reaction mixture was cooled to 23 °C. Water (2 mL) and diethyl ether (2 mL) were added to the reaction mixture, the layers were separated and the aqueous layer was extracted with diethyl ether (5 × 15 mL). The combined organic extracts were washed sequentially with water (4 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel.

Methyl 5-hydroxy-2-methylbenzoate (4)



4 Following the general procedure a solution of cyclopropane **1** (28.6 mg, 141 µmol, 1 equiv) in sulfolane (530 µL) was heated at 190 °C for 15 min. Flash column chromatography (1.5% methanol in dichloromethane) on silica gel afforded **4** (17.0 mg, 73%) as an off-white solid. Characterization data for **4** were in full agreement with those reported in the literature.[75]

Methyl 3-hydroxy-benzoate (6a)



6a Following the general procedure a solution of cyclopropane **5** (50.0 mg, 265 µmol, 1 equiv) in sulfolane (530 µL) was heated at 190 °C for 15 min. Benzoate **6a** (17.0 mg, 99%) was obtained as a

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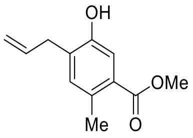
[75] A. G. Schultz, R. E. Harrington, M. Macielag, P. G. Mehta, A. G. Taveras, *J. Org. Chem.* **1987**, *52*, 5482–5484.

colorless solid. Characterization data for **6a** were in full agreement with those reported in the literature.[76]

Methyl 4-allyl-5-hydroxy-2-methylbenzoate (7)



7

Following the general procedure a solution of cyclopropane **57** (16.5 mg, 68.0 µmol, 1 equiv) in sulfolane (170 µL) was heated at 190 °C for 50 min. Preparative thin layer chromatography on silica gel (0.2% methanol in dichloromethane) afforded **7** (7.60 mg, 54%) as a beige solid.

TLC (dichloromethane), R_f = 0.21 (UV, $KMnO_4$)

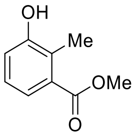
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (s, 1H), 6.91 (s, 1H), 6.05–5.95 (m, 1H), 5.18–5.12 (m, 2H), 4.96 (br s, 1H), 3.80 (s, 3H), 3.33 (d, *J* = 6.3 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.8, 151.8, 135.8, 133.8, 132.8, 130.3, 128.5, 117.8, 117.0, 52.0, 35.0, 21.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3330 (*m*), 2928 (*w*), 1686 (*vs*), 1613 (*m*), 1436 (*vs*), 1248 (*vs*), 1060 (*s*), 908 (*s*), 782 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{14}O_3$ $[M]^+$: 206.0943; found: 206.0942.

Methyl 3-hydroxy-2-methylbenzoate (8)



8

Following the general procedure a solution of cyclopropane **59** (44.6 mg, 22.0 µmol, 1 equiv) in sulfolane (530 µL) was heated at 190 °C for 15 min. Benzoate **8** (36.5 mg, 99%) was obtained as an off-white solid. Characterization data for **8** were in full agreement with those reported in the literature.[77]

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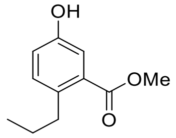
[76] K. W. Anderson, T. Ikawa, R. E. Tundel, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 10694–10695.

[77] H. Takamura, Y. Yamagami, T. Ito, M. Ito, H. Arimoto, I. Kadota, D. Uemura, *Heterocycles*, **2009**, *77*, 351–364.

Methyl 5-hydroxy-2-propylbenzoate (9)



9 Following the general procedure a solution of cyclopropane **39** (70.0 mg, 300 µmol, 1 equiv) in sulfolane (600 µL) was heated at 190 °C for 10 min. Flash column chromatography (12.5% ethyl acetate in hexanes) on silica gel afforded **9** (50.0 mg, 84%) as a colorless solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.34$ (UV, $KMnO_4$)

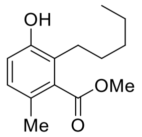
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 (d, *J* = 2.8 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.94 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.31 (br s, 1H), 3.87 (s, 3H), 2.84–2.80 (m, 2H), 1.61–1.52 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.8, 153.7, 136.5, 132.4, 130.1, 119.5, 117.3, 52.3, 35.8, 25.1, 14.2.

IR (Diamond-ATR, neat): 3396 (*w*), 2958 (*w*), 2932 (*w*), 1723 (*m*), 1697 (*s*), 1608 (*m*) 1500 (*m*), 1436 (*s*), 1296 (*vs*), 1276 (*s*), 1218 (*vs*), 1087 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943; found: 194.0935.

Methyl 3-hydroxy-6-methyl-2-pentylbenzoate (10)



10 Following the general procedure a solution of cyclopropane **61** (8.00 mg, 29.0 µmol, 1 equiv) in sulfolane (500 µL) was heated at 190 °C for 10 min. Flash column chromatography (17% ethyl acetate in hexanes) on silica gel afforded **10** (5.00 mg, 72%) as a colorless oil.

TLC (17% ethyl acetate in hexanes): $R_f = 0.51$ (UV, $KMnO_4$)

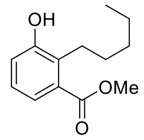
^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.90 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 4.63 (br s, 1H), 3.90 (s, 3H), 2.55–2.51 (m, 2H), 2.21 (s, 3H), 1.59–1.54 (m, 2H), 1.35–1.33 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.5, 151.6, 128.6, 126.9, 126.1, 116.4, 52.1, 32.2, 29.9, 29.8, 28.2, 22.6, 19.0, 14.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3413 (*m*), 2952 (*s*), 2921 (*s*), 2857 (*s*), 1726 (*s*), 1707 (*s*), 1588 (*m*), 1493 (*m*), 1292 (*vs*), 1261 (*s*), 1243 (*s*), 1138 (*m*), 1094 (*s*) cm^{-1}.

HRMS (ESI) calcd for $C_{14}H_{20}O_3$ $[M{-}H]^-$: 235.1333; found: 235.1338.

Methyl 3-hydroxy-2-pentylbenzoate (11)



11 Following the general procedure a solution of cyclopropane **63** (50.0 mg, 193 µmol, 1 equiv) in sulfolane (300 µL) was heated at 190 °C for 30 min. Flash column chromatography (10% ethyl acetate hexanes) on silica gel afforded **11** (35 mg, 77%) as a colorless solid.

TLC (10 % ethyl acetate in hexanes): R_f = 0.35 (UV, $KMnO_4$)

m.p.: 40 °C.

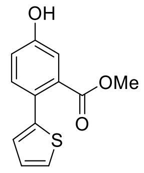
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40–7.36 (m, 1H), 7.13–7.08 (m, 1H), 6.94–6.90 (m, 1H), 4.88 (s, 1H), 3.88 (s, 3H), 2.93–2.86 (m, 2H), 1.65–1.52 (m, 2H), 1.44–1.32 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.6, 154.2, 131.8, 130.4, 126.5, 122.9, 118.8, 52.2, 32.3, 29.9, 26.9, 22.7, 14.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3417 (*w*), 2952 (*m*), 2925 (*m*), 1722 (*m*), 1695 (*s*), 1580 (*m*), 1280 (*vs*), 1233 (*s*), 1189 (*m*), 1165 (*m*), 1140 (*m*), 1094 (*s*), 753 (*vs*) cm^{-1}.

HRMS (ESI) calcd for $C_{13}H_{18}O_3$ $[M-H]^-$: 221.1177; found: 221.1182.

Methyl 5-hydroxy-2-(thiophen-2-yl)benzoate (12)



12 Following the general procedure a solution of cyclopropane **64** (33.6 mg, 124 µmol, 1 equiv) in sulfolane (600 µL) was heated at 190 °C for 10 min. Flash column chromatography (20% ethyl acetate in hexanes) on silica gel afforded **12** (24.0 mg, 83%) as an orange solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.29 (UV, $KMnO_4$)

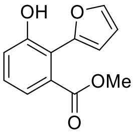
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.35 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 5.1 Hz, 1H), 7.17 (d, *J* = 2.7 Hz, 1H), 7.05–7.02 (m, 1H), 6.98–6.95 (m, 2H), 5.93 (br s, 1H), 3.72 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 169.5, 156.0, 142.4, 133.3, 133.2, 127.7, 126.8, 126.4, 125.9, 118.7, 116.6, 52.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3364 (*m*), 2951 (*w*), 1702 (*s*), 1606 (*s*), 1445 (*s*), 1429 (*s*), 1305 (*vs*), 1218 (*vs*), 1075 (*s*), 824 (*s*), 696 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{10}O_3S$ $[M]^+$: 234.0351; found 234.0346.

Methyl 2-(furan-2-yl)-3-hydroxybenzoate (13)



13 Following the general procedure a solution of cyclopropane **66** (76.0 mg, 298 µmol, 1 equiv) in sulfolane (700 µL) was heated at 190 °C for 10 min. Flash column chromatography (20% ethyl acetate in hexanes) on silica gel afforded **13** (29.0 mg, 47%) as a yellow solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.26$ (UV, $KMnO_4$)

m.p.: 66–68 °C.

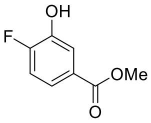
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.58 (d, *J* = 1.7 Hz, 1H), 7.36–7.29 (m, 2H), 7.12 (dd, *J* = 7.0, 2.5 Hz, 1H), 6.61–6.56 (m, 2H), 6.23 (s, 1H), 3.74 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 168.9, 154.4, 147.9, 143.8, 133.0, 130.4, 122.0, 119.5, 116.8, 112.0, 110.7, 52.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3371 (*w*), 2952 (*w*), 1703 (*s*), 1434 (*s*), 1289 (*vs*), 1264 (*s*), 1238 (*s*), 1214 (*s*), 1140 (*s*), 988 (*s*), 904 (*s*), 797 (s), 733 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{10}O_4$ $[M]^+$: 218.0579; found 218.0567.

Methyl 4-fluoro-3-hydroxybenzoate (14)



14 Following the general procedure a solution of cyclopropane **67** (36.0 mg, 174 µmol, 1 equiv) in sulfolane (600 µL) was heated at 190 °C for 20 min. Flash column chromatography (20% ethyl acetate in hexanes) on silica gel afforded **14** (25.3 mg, 85%) as an off-white solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.24$ (UV, $KMnO_4$)

m.p.: 78–86 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.68 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.60–7.56 (m, 1H), 7.14 (dd, *J* = 10.3, 8.6 Hz, 1H), 5.81 (s, 1H), 3.88 (s, 3H).

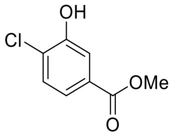
^{13}C NMR (101 MHz, CD_2Cl_2) δ = 166.6, 154.7 (d, *J* = 245.9 Hz), 144.2 (d, *J* = 14.4 Hz), 127.8 (d, *J* = 3.6 Hz), 123.2 (d, *J* = 7.8 Hz), 119.3 (d, *J* = 3.6 Hz), 116.2 (d, *J* = 19.2 Hz), 52.8.

^{19}F NMR (376 MHz, CD_2Cl_2) δ = −133.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3373 (*m*), 2957 (*w*), 1703 (*vs*), 1604 (*s*), 1510 (*s*), 1438 (*vs*), 1302 (*vs*), 1229 (*vs*), 1193 (*s*), 1110 (*s*), 1095 (*s*), 764 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_8H_7FO_3$ $[M]^+$: 170.0379; found 170.0364.

Methyl 4-chloro-3-hydroxybenzoate (15)



15

Following the general procedure a solution of cyclopropane **68** (45.0 mg, 202 µmol, 1 equiv) in sulfolane (800 µL) was heated at 190 °C for 30 min. Flash column chromatography (20% ethyl acetate in hexanes) on silica gel afforded **15** (29.0 mg, 77%) as an off-white solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.40 (UV, $KMnO_4$)

m.p.: 86–98 °C.

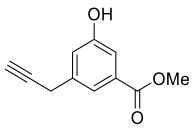
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.66 (d, *J* = 2.0 Hz, 1H), 7.54 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 5.96 (s, 1H), 3.89 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 166.6, 152.1, 131.1, 129.8, 125.5, 122.8, 117.7, 52.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3408 (*m*), 2954 (*w*), 1702 (*vs*), 1593 (*s*), 1434 (*s*), 1416 (*s*), 1296 (*vs*), 1248 (*s*), 1189 (*s*), 1134 (*s*), 1106 (*s*), 1054 (*s*), 756 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_8H_7ClO_3$ $[M]^+$: 186.0084; found: 186.0074.

Methyl 3-hydroxy-5-(prop-2-yn-1-yl)benzoate (16)



16 Following the general procedure a solution of cyclopropane **70** (26.0 mg, 115 µmol, 1 equiv) in sulfolane (600 µL) was heated at 190 °C for 45 min. Flash column chromatography (20% ethyl acetate in hexanes) on silica gel afforded **16** (12.3 mg, 56%) as an off-white solid.

TLC (20% ethyl acetate in hexanes): R$_f$ = 0.29 (UV, $KMnO_4$)

m.p.: 78 °C.

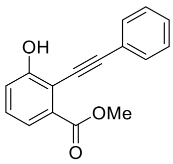
^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.58–7.57 (m, 1H), 7.45–7.44 (m, 1H), 7.11–7.10 (m, 1H), 5.71 (s, 1H), 3.92, (s, 3H), 3.64–3.58 (m, 2H), 2.22 (t, *J* = 2.7 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.2, 156.2, 138.4, 131.7, 121.6, 119.9, 115.0, 81.2, 71.3, 52.5, 24.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\max}$: 3384 (*w*), 2954 (*w*), 1699 (*s*), 1329 (*s*), 1294 (*s*), 1237 (*s*), 906 (*s*), 770 (*s*), 727 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{10}O_3$ $[M]^+$: 190.0630; found: 190.0621.

Methyl 3-hydroxy-2-(phenylethynyl)benzoate (17)



17 Following the general procedure a solution of cyclopropane **72** (25.0 mg, 87.0 µmol, 1 equiv) in sulfolane (500 µL) was heated at 190 °C for 20 min. Flash column chromatography (10% ethyl acetate in hexanes) on silica gel afforded **17** (10.0 mg, 46%) as a colorless solid.

TLC (10% ethyl acetate in hexanes): R$_f$ = 0.58 (UV, $KMnO_4$)

m.p.: 92–94 °C.

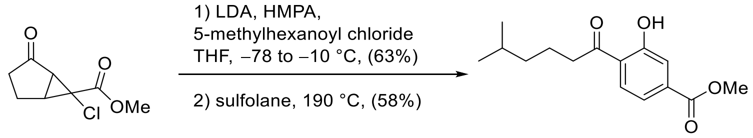
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.97–7.93 (m, 2H), 7.74–7.72 (m, 1 H), 7.67 (d, *J* = 0.9 Hz, 1H), 7.53–7.47 (m, 2H), 7.44–7.39 (m, 1H), 7.38–7.33 (m, 1H), 3.99 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 167.3, 158.3, 155.9, 130.5, 130.4, 129.8, 129.5, 126.0, 125.8, 124.2, 123.1, 116.0, 103.0, 52.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3412 (*w*), 2949 (*w*), 2925 (*w*), 2852 (*w*), 1713 (*vs*), 1284 (*s*), 1263 (*vs*), 1193 (*s*), 1137 (*s*), 1041 (*s*), 750 (*vs*), 688 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{12}O_3$ $[M]^+$: 252.0786; found: 252.0782.

Methyl 3-hydroxy-4-(5-methylhexanoyl)benzoate (18)



5 **18**

In a flame dried flask a solution of diisopropylamine (525 µL, 3.71 mmol, 1.40 equiv) in tetrahydrofuran (1 mL) was cooled to −78 °C and a solution of *n*-butyllithium (2.3 M in hexanes, 1.53 mL, 3.58 mmol, 1.35 equiv) was added dropwise. After 10 min, the solution was warmed to 0 °C. After 10 min, the solution was cooled to −78 °C and a solution of cyclopropane **5** (500 mg, 2.65 mmol, 1 equiv) and hexamethylphosphoramide (461 µL, 2.65 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 30 min, 5-methylhexanoyl chloride (552 mg, 3.71 mmol, 1.40 equiv) was added. After 3 h, saturated aqueous ammonium chloride solution (15 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulfate and the dried solution was filtered and the filtrate was concentrated. The crude product was filtered through a short plug of silica gel to afford the corresponding diketone (500 mg, 63%) as a yellow oil which was used in the next step without further purification.

Following the general procedure a solution of the corresponding diketone (500 mg, 1.66 mmol, 1 equiv) in sulfolane (3 mL) was heated at 190 °C for 10 min. Flash column chromatography (12.5% ethyl acetate in hexanes) on silica gel afforded **18** (255 mg, 58%) as a colorless solid.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.53$ (UV, $KMnO_4$)

m.p.: 61–67 °C.

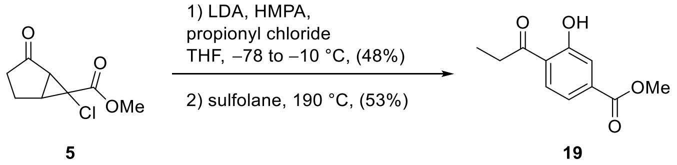
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 12.29 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 1.5 Hz, 1H), 7.52 (dd, *J* = 8.3, 1.5 Hz, 1H), 3.90 (s, 3H), 3.18–2.86 (m, 2H), 1.78–1.70 (m, 2H), 1.66–1.56 (m, 1H), 1.31–1.25 (m, 3H), 0.91 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 207.6, 166.2, 162.6, 137.2, 130.7, 122.5, 120.0, 119.8, 53.0, 39.5, 38.9, 28.4, 22.8, 22.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (*m*), 2906 (*w*), 2870 (*w*), 1723 (*vs*), 1642 (*s*), 1315 (*vs*), 1240 (*m*), 1223 (*s*), 1189 (*vs*), 1096 (*s*), 762 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{20}O_4$ [M]$^+$: 264.1362; found 264.1360.

Methyl 3-hydroxy-4-propionylbenzoate (19)



In a flame dried flask a solution of diisopropylamine (315 µL, 2.23 mmol, 1.40 equiv) in tetrahydrofuran (1 mL) was cooled to −78 °C and a solution of *n*-butyllithium (2.3 M in hexanes, 1.10 mL, 2.15 mmol, 1.35 equiv) was added dropwise. After 10 min, the solution was warmed to 0 °C. After 10 min, the solution was cooled to −78 °C and a solution of cyclopropane **5** (300 mg, 1.59 mmol, 1 equiv) and hexamethylphosphoramide (277 µL, 1.59 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 30 min, propionyl chloride (194 µL, 2.23 mmol, 1.40 equiv) was added. After 4 h, saturated aqueous ammonium chloride solution (15 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulfate and the dried solution was filtered and the filtrate was concentrated. The crude product was filtered through a short plug of silica gel to afford the corresponding diketone (186 mg, 48%) as a colorless oil which was used in the next step without further purification.

Following the general procedure a solution of the corresponding diketone (46.4 mg, 190 µmol, 1 equiv) in sulfolane (600 µL) was heated at 190 °C for 10 min. Flash column chromatography (20% ethyl acetate in hexanes) on silica gel afforded **19** (21.0 mg, 53%) as an off-white solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.62$ (UV, $KMnO_4$)

m.p.: 83 °C.

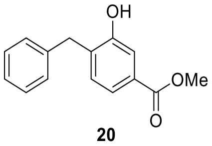
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 12.24 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 1.4 Hz, 1H), 7.52 (dd, *J* = 8.3, 1.4 Hz, 1H), 3.90 (s, 3H), 3.09 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 207.8, 166.2, 162.4, 137.1, 130.6, 122.3, 120.0, 119.8, 53.0, 32.6, 8.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2985 (*w*), 2950 (*m*), 1717 (*vs*), 1646 (*vs*), 1621 (*m*), 1316 (*vs*), 1300 (*s*), 1230 (*s*), 1198 (*vs*), 1100 (*s*), 753 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{12}O_4$ [M]$^+$: 208.0736; found: 208.0726.

Methyl 4-benzyl-3-hydroxybenzoate (20)



20 Following the general procedure a solution of cyclopropane **73** (35.0 mg, 126 µmol, 1 equiv) in sulfolane (500 µL) was heated at 190 °C for 20 min. Flash column chromatography (17% ethyl acetate in hexanes) on silica gel afforded **20** (21.0 mg, 69%) as a colorless solid.

TLC (17% ethyl acetate in hexanes): $R_f = 0.41$ (UV, $KMnO_4$)

m.p.: 128–130 °C.

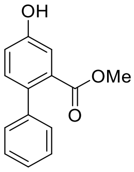
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.55–7.51 (m, 2H), 7.32–7.17 (m, 6H), 5.71 (s, 1H), 4.04 (s, 2H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 167.6, 154.4, 140.2, 133.7, 131.4, 130.2, 129.3, 129.1, 126.9, 122.4, 116.9, 52.7, 36.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3421 (*m*), 3026 (*w*), 2949 (*w*), 1698 (*vs*), 1437 (*s*), 1422 (*s*), 1295 (*vs*), 1227 (*s*), 759 (*s*), 733 (*m*), 695 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{14}O_3$ $[M]^+$: 242.0943; found: 242.0934.

Methyl 4-hydroxy-[1,1'-biphenyl]-2-carboxylate (21)



21 Following the general procedure a solution of cyclopropane **75** (41.0 mg, 155 µmol, 1 equiv) in sulfolane (500 µL) was heated at 190 °C for 15 min. Flash column chromatography (20% ethyl acetate in hexanes) on silica gel afforded **21** (25.0 mg, 71%) as an off-white solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.26$ (UV, $KMnO_4$)

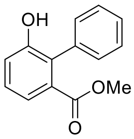
^{1}H NMR (300 MHz, CD_2Cl_2) δ = 7.43–7.25 (m, 7H), 7.02 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.95 (s, 1H), 3.65 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ = 169.6, 155.6, 141.5, 135.3, 132.7, 132.5, 129.0, 128.6, 127.4, 119.0, 116.9, 52.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3376 (*m*), 3028 (w), 2949 (*w*), 1708 (*s*), 1481 (*m*), 1449 (*s*), 1437 (*s*), 1306 (*vs*), 1253 (*s*), 1220 (*s*), 766 (*s*), 699 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{12}O_3$ $[M]^+$: 228.0786; found: 228.0783.

Methyl 6-hydroxy-[1,1'-biphenyl]-2-carboxylate (22)



22 Following the general procedure a solution of cyclopropane **77** (21.2 mg, 80.0 µmol, 1 equiv) in sulfolane (500 µL) was heated at 190 °C for 30 min. Flash column chromatography (20% ethyl acetate in hexanes) on silica gel afforded **22** (12.0 mg, 66%) as a colorless solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.38 (UV, $KMnO_4$)

m.p.: 73–78 °C.

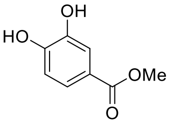
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.52–7.41 (m, 4H), 7.33 (app t, *J* = 7.9 Hz, 1 H), 7.29–7.26 (m, 2H), 7.13 (dd, *J* = 8.1, 1.2 Hz, 1 H), 5.17 (br s, 1H), 3.56 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 168.2, 153.9, 135.4, 132.4, 130.1, 129.6, 129.3, 128.8, 128.7, 122.4, 119.3, 52.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3409 (*w*), 2949 (*w*), 1708 (*s*), 1433 (*m*), 1288 (*vs*), 1139 (*s*), 762 (*s*), 739 (*m*), 700 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{12}O_3$ $[M]^+$: 228.0786; found: 228.0770.

Methyl 3,4-dihydroxybenzoate (23)



23 Following the general procedure a solution of cyclopropane **78** (20.3 mg, 99.2 µmol, 1 equiv) in sulfolane (600 µL) was heated at 190 °C for 20 min. Flash column chromatography (33% ethyl acetate in hexanes) on silica gel afforded **23** (9.00 mg, 54%) as an off-white solid. Characterization data for **23** were in full agreement with those reported in the literature.[78]

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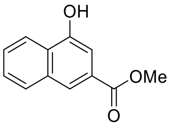
[78] For ^{1}H NNR and ^{13}C NMR spectra, see: H. Chunlin, S. Zuming, Z. Qizhong, L. Shijun, L. Ning, H. Feihe, *J. Org. Chem*. **2008**, *73*, 5872–5880. For IR and MS data, see: B. Reis, M. Martins, B. Barreto, N. Milhazes, E.M. Garrido, P. Silva, J. Garrido, F. Borges, *J. Agric. Food. Chem*. **2010**, *58*, 6986–6993.

Methyl 4-hydroxy-2-naphthoate (26)



26 Following the general procedure a solution of cyclopropane **25** (60.0 mg, 225 µmol, 1 equiv) in sulfolane (700 µL) was heated at 190 °C for 30 min. Flash column chromatography (12.5% ethyl acetate in hexanes) on silica gel afforded **26** (17.0 mg, 37%) as a colorless solid.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.42$ (UV, $KMnO_4$)

m.p.: 159 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (d, *J* = 8.6 Hz, 1H), 8.21 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 1H),

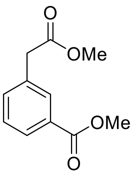
7.64–7.53 (m, 3H), 6.42 (s, 1H), 3.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.8, 152.2, 133.9, 129.3, 127.8, 127.4, 127.3, 127.0, 123.8, 122.2, 107.7, 52.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3408 (*s*), 2950 (*w*), 1693 (*vs*), 1595 (*m*), 1579 (*s*1438 (*s*), 1402 (*vs*), 1363 (*m*), 1309 (*s*), 1266 (*s*), 1246 (*s*), 1075 (*s*), 992 (*m*), 773 (*vs*) cm^{-1}.

HRMS (ESI) calcd for $C_{12}H_{10}O_3$ $[M-H]^-$: 201.0551; found: 201.0555.

Methyl 3-(2-methoxy-2-oxoethyl)benzoate (28):



28 Following the general procedure a solution of cyclopropane **27** (55.8 mg, 228 µmol, 1 equiv) in sulfolane (600 µL) was heated at 190 °C for 20 min. Flash column chromatography (12.5% ethyl acetate in hexanes) on silica gel afforded **28** (36.8 mg, 76%) as an off-white solid. Characterization data for **28** were in full agreement with those reported in the literature.[79]

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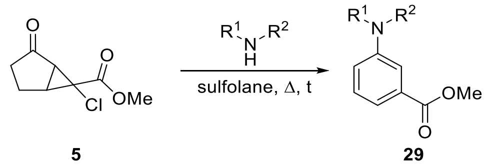
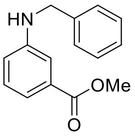
[79] S. Mann, P. M. Concepcion, D. Hawksley, J. F. Leeper, *Org. Biomol. Chem*. **2004**, *2*, 1732–1741.

Synthesis of Anilins



General Procedure: A solution of cyclopropane **5** (1 equiv) and amine (2.00 equiv) in sulfolane (600 µL) was stirred for the time and temperature indicated. After complete consumption of **5** (as seen by TLC analysis), the reaction mixture was cooled to 23 °C. Water (2 mL) and diethyl ether (2 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (4 × 15 mL). The combined organic extracts were sequentially washed with water (4 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel.

Methyl 3-(benzylamino)benzoate (29a)



29a Following the general procedure a solution of cyclopropane **5** (80.7 mg, 428 µmol, 1 equiv) and benzylamine (94.0 µL, 856 µmol, 2.00 equiv) in sulfolane was heated at 100 °C for 1.5 h. Flash column chromatography (12.5% ethyl acetate in hexanes) on silica gel afforded **29a** (72.0 mg, 70%) as a yellow solid. ^{1}H NMR and ^{13}C NMR data for **29b** were in full agreement with those reported in the literature.[80]

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.44$ (UV, $KMnO_4$)

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3389 (*s*), 1709 (*vs*), 1606 (*s*), 1581 (*m*), 1517 (*s*), 1490 (*s*), 1435 (*s*), 1338 (*vs*), 1275 (*vs*), 1235 (*vs*), 1100 (*vs*), 746 (*vs*), 697 (*vs*), 683 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{15}NO_2$ $[M]^+$: 241.1103; found 241.1099.

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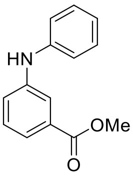
[80] For ^{1}H and ^{13}C NMR spectra, see: C.-T. Yang, Y. Fu, Y.-B. Huang, J. Yi, Q.-X. Guo, L. Liu, *Angew. Chem. Int. Ed.* **2009**, *48*, 7398–7401.

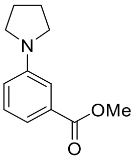
Methyl 3-(phenylamino)benzoate (29b)



29b Following the general procedure a solution of cyclopropane **5** (51.0 mg, 271 µmol, 1 equiv) and aniline (50.0 µL, 542 µmol, 2.00 equiv) in sulfolane was heated at 140 °C for 3 h. Flash column chromatography (10% ethyl acetate in hexanes) on silica gel afforded **29b** (51.0 mg, 83%) as a yellow solid. Characterization data for **29b** were in full agreement with those reported in the literature.[81]

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3365 (*m*), 3035 (*w*), 2950 (*w*), 1708 (*vs*), 1593 (*vs*), 1524 (*m*), 1495 (*vs*), 1319 (*s*), 1291 (*s*), 1216 (*s*), 748 (*vs*) cm^{-1}.

Methyl 3-(pyrrolidin-1-yl)benzoate (29c)



29c Following the general procedure a solution of cyclopropane **5** (54.4 mg, 288 µmol, 1 equiv) and pyrrolidine (47.0 µL, 577 µmol, 2.00 equiv) in sulfolane was heated at 100 °C for 20 min. Flash column chromatography (12.5% ethyl acetate in hexanes) on silica gel afforded **29c** (48.0 mg, 81%) as a yellow oil.

TLC (12.5% ethyl acetate in hexanes): R_f = 0.53 (UV, $KMnO_4$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.25 (d, *J* = 5.0 Hz, 2H), 7.20–7.15 (m, 1H), 6.76–6.70 (m, 1H), 3.86 (s, 3H), 3.32–3.28 (m, 4H), 2.05–1.98 (m, 4H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 168.1, 148.5, 131.4, 129.5, 116.5, 116.3, 112.6, 52.3, 48.2, 26.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2950 (*w*), 2840 (*w*), 1715 (*s*), 1600 (*s*), 1453 (*s*), 1372 (*s*), 1256 (*vs*), 1108 (*s*), 1013 (*s*), 953 (*s*), 750 (*vs*), 708 (*vs*), 680 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{14}NO_2$ $[M-H]^+$: 204.1025; found 204.1020.

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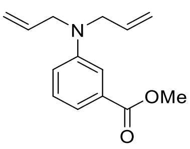
[81] For ^{1}H and ^{13}C NMR spectra, see: C.-T. Yang, Y. Fu, Y.-B. Huang, J. Yi, Q.-X. Guo, L. Liu, *Angew. Chem. Int. Ed.* **2009**, *48*, 7398–7401. For MS data, see: H. Budzikiewicz, J. Rullkötter, H. M. Schiebel, *Organic Mass Spectrometry* **1972**, *6*, 251–264.

Methyl 3-(diallylamino)benzoate (29d)



29d

Following the general procedure a solution of cyclopropane **5** (68.7 mg, 364 µmol, 1 equiv) and diallylamine (90.0 µL, 728 µmol, 2.00 equiv) in sulfolane was heated at 140 °C for 1 h. Flash column chromatography (12.5% ethyl acetate in hexanes) on silica gel afforded **29d** (51.0 mg, 83%) as a yellow oil.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.57$ (UV, $KMnO_4$)

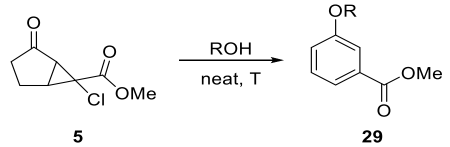
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.36–7.18 (m, 3H), 6.91–6.83 (m, 1H), 5.92–5.83 (m, 2H), 5.22–5.11 (m, 4H), 3.97–3.96 (m, 4H), 3.85 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 168.0, 149.1, 134.2, 134.2, 131.4, 129.5, 117.5, 117.0, 116.3, 113.3, 53.3, 52.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3081 (*w*), 2981 (*w*), 2950 (*w*), 1717 (*vs*), 1600 (*s*), 1494 (*s*), 1271 (*vs*), 1226 (*s*), 1110 (*s*), 1031 (*m*), 988 (*s*), 918 (*s*), 749 (*vs*) cm^{-1}.

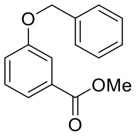
HRMS (EI) calcd for $C_{14}H_{17}NO_2$ $[M]^+$: 231.1259; found 231.1259.

Synthesis of Aryl Ethers



General Procedure: A solution of cyclopropane **5** (1 equiv) in the corresponding alcohol was stirred for the time and temperature indicated. After complete consumption of **5** (as seen by TLC analysis), the reaction mixture was cooled to 23 °C. The reaction mixture was concentrated. The crude product was purified by flash column chromatography on silica gel.

Methyl 3-(benzyloxy)benzoate (29e)



29e Following the general procedure a solution of cyclopropane **5** (100 mg, 530 µmol, 1 equiv) and benzylalcohol (600 µL) was heated at 140 °C for 22 h. Flash column chromatography (0.5% ethyl acetate in hexanes) on silica gel afforded **29e** (100 mg, 78%) as a colorless oil.

TLC (0.5% ethyl acetate in hexanes): $R_f = 0.23$ (UV, $KMnO_4$)

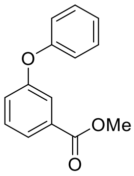
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.65–7.60 (m, 2H), 7.47–7.43 (m, 2H), 7.43–7.33 (m, 4H), 7.20–7.15 (m, 1H), 5.12 (s, 2H), 3.89 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 167.2, 159.4, 137.4, 132.3, 130.1, 129.1, 128.6, 128.1, 122.6, 120.5, 115.7, 70.7, 52.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3033 (*w*), 2951 (*w*), 1721 (*vs*), 1586 (*m*), 1488 (*m*), 1444 (*m*), 1288 (*vs*), 1277 (*vs*), 1219 (*m*), 1100 (*m*), 1026 (*m*), 754 (*s*) cm^{-1}.

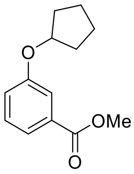
HRMS (EI) calcd for $C_{15}H_{14}O_3$ $[M]^+$: 242.0943; found 242.0946.

Methyl 3-(phenoxy)benzoate (29f)



29f Following the general procedure a solution of cyclopropane **5** (100 mg, 530 µmol, 1 equiv) and phenol (600 µL) was heated at 140 °C for 20 h. Flash column chromatography (0.5% ethyl acetate in hexanes) on silica gel afforded **29f** (51.0 mg, 42%) as a colorless oil. Characterization data for **29f** were in full agreement with those reported in the literature.[82]

Methyl 3-(cyclopentyloxy)benzoate (29g)



29g Following the general procedure a solution of cyclopropane **5** (100 mg, 530 µmol, 1 equiv) and cyclopentanol (600 µL) was heated at 140 °C for 22 h. Flash column chromatography (12.5% ethyl acetate in hexanes) on silica gel afforded **29g** (112 mg, 96%) as a colorless oil.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.76$ (UV, $KMnO_4$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.56 (d, *J* = 7.7 Hz, 1H), 7.50 (s, 1H), 7.33 (app t, *J* = 7.9 Hz, 1H), 7.08–7.05 (m, 1H), 4.84–4.80 (mz, 1H), 3.87 (s, 3H), 2.00–1.54 (m, 8H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 167.3, 158.7, 132.0, 129.9, 121.8, 121.0, 116.4, 80.0, 52.5, 33.2, 33.2, 24.5, 24.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953 (m), 2872 (*w*), 1720 (*vs*), 1582 (*m*), 1486 (*m*), 1443 (*s*), 1273 (*vs*), 1216 (*s*), 1169 (*m*), 1098 (*s*), 1075 (*m*), 1008 (*s*), 890 (*m*), 752 (*vs*), 683 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{16}O_3$ $[M]^+$: 220.1099; found 220.1103.

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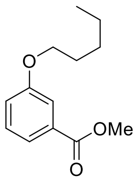
[82] For ^{1}H NMR and ^{13}C NMR spectra, see: Y. Zhu, H. Yan, L. Lu, D. Liu, G. Rong, J. Mao, J. Org. Chem. 2013, 9898–9905. For IR data, see: L. O. Ruzo, R. L. Holmstead, J. E. Casida, *J. Agric. Food. Chem*. **1977**, *25*, 1385–1388.

Methyl 3-(pentyloxy)benzoate (29h)



29h

Following the general procedure a solution of cyclopropane **5** (40.0 mg, 212 µmol, 1 equiv) and 1-pentanol (800 µL) was heated at 140 °C for 4 h. Flash column chromatography (10% ethyl acetate in hexanes) on silica gel afforded **29h** (42.0 mg, 89%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): $R_f = 0.68$ (UV, $KMnO_4$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.59–7.57 (m, 1H), 7.53–7.52 (m, 1H), 7.34 (app t, *J* = 7.9 Hz, 1H), 7.11–7.08 (m, 1H), 4.00 (t, *J* = 6.6 Hz, 2 H), 3.88 (s, 3H), 1.83–1.74 (m, 2H), 1.49–1.34 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H).

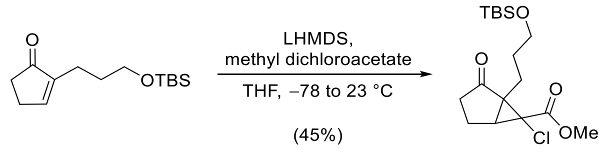
^{13}C NMR (101 MHz, CD_2Cl_2) δ = 167.3, 159.8, 132.1, 129.9, 122.1, 120.2, 115.2, 68.8, 52.6, 29.5, 28.7, 23.0, 14.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (m), 2933 (m), 2871 (w), 1724 (vs), 1585 (m), 1489 (m), 1445 (m), 1288 (vs), 1276 (vs), 1226 (s), 1099 (m), 756 (s) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{18}O_3$ $[M]^+$: 222.1256; found: 222.1245.

Synthesis of Heterocyclic Structures

Methyl 1-(3-((tert-butyldimethylsilyl)oxy)propyl)-6-chloro-2-oxobicyclo[3.1.0]hexane-6-carboxylate (80)



46 **80**

A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 206 µL, 206 µmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (22.4 µL, 216 µmol, 1.10 equiv) was added dropwise. After 45 min, a solution of **46** (50.0 mg, 197 µmol, 1 equiv) in tetrahydrofuran (1 mL) was added dropwise. After 45 min, the reaction was warmed to 23 °C. After 4 h, saturated aqueous ammonium chloride solution (3 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **80** (32.0 mg, 45%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): $R_f = 0.45$ ($KMnO_4$)

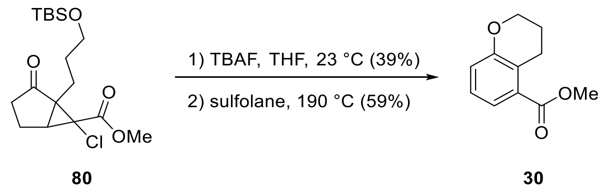
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.80 (s, 3H), 3.53 (t, *J* = 6.1 Hz, 2H), 2.89 (d, *J* = 5.8 Hz, 1H), 2.42–2.21 (m, 3H), 2.18–1.98 (m, 2H), 1.68–1.54 (m, 1H), 1.46–1.37 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 211.3, 167.2, 62.7, 53.8, 51.6, 48.9, 37.6, 37.4, 30.3, 26.1, 21.6, 19.4, 18.5, −5.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953 (*m*), 2929 (*m*), 2857 (*w*), 1728 (*vs*), 1436 (*m*), 1280 (*m*), 1253 (*vs*), 1177 (*m*), 1154 (*m*), 1095 (*s*), 1039 (*m*), 986 (*m*), 833 (*vs*), 775 (*vs*) cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{30}ClO_4Si$ $[M+H]^+$: 361.1597; found 361.1599.

Methyl chromane-5-carboxylate (30)



A solution of protected alcohol **80** (30.0 mg, 83.0 µmol, 1 equiv) in tetrahydrofuran (500 µL) was treated with a solution of tetrabutylammonium fluoride (1 M in tetrahydrofuran, 249 µL, 24.9 µmol, 3.00 equiv). After 1 h, water (2 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (5 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was filtered through a short plug of silica to afford the corresponding alcohol (8.00 mg, 39%) which was used in the next step without further purification.

A solution of the corresponding alcohol (8.00 mg, 32.4 µmol, 1 equiv) in sulfolane (400 µL) was heated at 190 °C. After 30 min, the reaction mixture was cooled to 23 °C and water (2 mL) and diethyl ether (2 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 10 mL). The combined organic extracts were washed with water (4 × 10 mL) and saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford chromane **30** (3.70 mg, 59%) as a colorless oil.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.53$ (UV, $KMnO_4$)

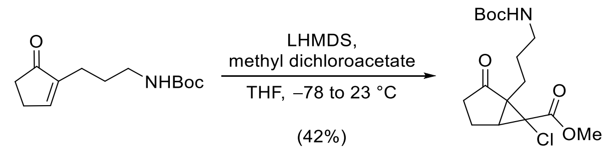
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 (d, *J* = 7.7 Hz, 1H), 7.13 (app t, *J* = 7.9 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 4.21–4.15 (m, 2H), 3.87 (s, 3H), 3.10 (t, *J* = 6.6 Hz, 2H), 2.02–1.97 (m, 2H).

^{13}C NMR (101 MHz $CDCl_3$) δ = 167.9, 155.6, 130.5, 126.7, 124.3, 122.9, 121.2, 66.2, 52.0, 24.0, 22.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951 (*w*), 2872 (*w*), 1720 (*vs*), 1457 (*s*), 1268 (*vs*), 1192 (*m*), 1086 (*m*), 1064 (*m*), 1030 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{12}O_3$ $[M]^+$: 192.0784; found 192.0786.

Methyl 1-(3-((tert-butoxycarbonyl)amino)propyl)-6-chloro-2-oxobicyclo[3.1.0]hexane-6-carboxylate (81)



47 **81**

A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 836 µL, 836 µmol, 2.00 equiv) was cooled to −78 °C and methyl dichloroacetate (91.0 µL, 878 µmol, 2.10 equiv) was added dropwise. After 45 min, a solution of **47** (100 mg, 418 µmol, 1 equiv) in tetrahydrofuran (1.5 mL) was added dropwise. After 45 min, the reaction was warmed to 23 °C. After 4 h, saturated aqueous ammonium chloride solution (5 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **81** (60.0 mg, 42%) as a colorless solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.28$ ($KMnO_4$)

m.p.: 62–65 °C.

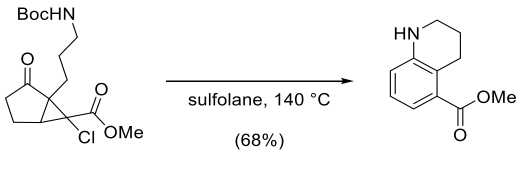
^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.57 (s, 1H), 3.82 (s, 3H), 3.07–3.01 (m, 2H), 2.90 (app d, *J* = 5.9 Hz, 1H), 2.42–2.25 (m, 3H), 2.18–2.08 (m, 1H), 2.07–1.97 (m, 1H), 1.68–1.54 (m, 1H), 1.47–1.37 (m, 11H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 211.4, 167.2, 156.0, 79.3, 53.9, 51.4, 48.8, 40.1, 38.1, 37.3, 28.6, 27.5, 22.2, 19.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3369 (*w*), 2974 (*w*), 2954 (w), 2934 (*w*), 1726 (*vs*), 1515 (*m*), 1452 (*m*), 1365 (*m*), 1252 (*vs*), 1228 (*s*), 1170 (*vs*), 1039 (*m*) cm^{-1}.

HRMS (ESI) calcd for $C_{16}H_{25}ClNO_5$ $[M+H]^+$: 346.1416; found 346.1422.

Methyl 1,2,3,4-tetrahydroquinoline-5-carboxylate (31)



81 **31**

A solution of cyclopropane **81** (40.0 mg, 116 µmol, 1 equiv) in sulfolane (600 µL) was heated at 140 °C. After 10 min, the reaction mixture was cooled to 23 °C and water (2 mL) and diethyl ether (2 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 20 mL). The combined organic extracts were washed with water (4 × 20 mL) and saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford tetrahydroquinoline **31** (15.0 mg, 68%) as a colorless oil.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.30$ (UV; $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.15 (d, *J* = 7.6 Hz, 1H), 6.98 (app t, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 3.85 (s, 3H), 3.31–3.26 (m, 2H), 3.04 (t, *J* = 6.5 Hz, 2H), 1.96–1.88 (m, 2H).

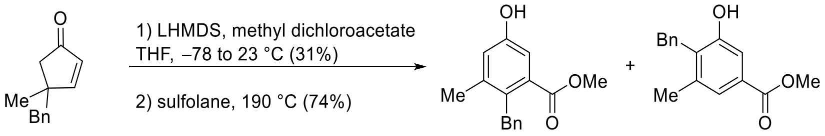
^{13}C NMR (101 MHz $CDCl_3$) δ = 168.8, 145.5, 130.7, 126.3, 122.6, 119.2, 118.0, 51.9, 41.5, 25.5, 22.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3409 (*m*), 2949 (*m*), 2838 (*w*), 1716 (*vs*), 1594 (*s*), 1479 (*m*), 1463 (*s*), 1351 (*m*), 1311 (*s*), 1286 (*vs*), 1248 (*s*), 1196 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{13}NO_2$ $[M]^+$: 191.0946; found 191.0939.

Substrates Containing a Quarternary Carbon Center

Methyl 2-benzyl-5-hydroxy-3-methylbenzoate (33a) and methyl 4-benzyl-5-hydroxy-3-methylbenzoate (33b)



50 **33a** **33b**

A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 547 µL, 547 µmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (59.0 µL, 573 µmol, 1.10 equiv) was added dropwise. After 45 min, a solution of cyclopropane **50** (97.0 mg, 521 µmol, 1 equiv) in tetrahydrofuran (1 mL) was added dropwise. After 45 min, the reaction was warmed to 23 °C. After 4 h, saturated aqueous ammonium chloride solution (5 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, and the dried solution was filtered through a short plug of silica gel. The filtrate was concentrated to afford the corresponding cyclopropane (47.0 mg, 31%) as an off-white solid which was used in the next step without further purification.

The corresponding cyclopropane was dissolved in sulfolane (600 µL) and heated to 190 °C. After 30 min, the reaction mixture was allowed to cool to 23 °C and water (2 mL) and diethyl ether (2 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 10 mL). The combined organic extracts were washed with water (4 × 10 mL) and saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford firstly **33b** (7.5 mg, 19%) as a colorless solid then **33a** (23 mg, 55%,) as a colorless solid.

33a:

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.18$ (UV, $KMnO_4$)

m.p.: 90–93 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.24–7.10 (m, 4H), 7.03–6.99 (m, 2H), 6.86 (d, *J* = 2.6 Hz, 1H), 5.38 (br s, 1H), 4.26 (s, 2H), 3.76 (s, 3H), 2.18 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 169.1, 154.3, 141.4, 141.1, 133.3, 131.8, 128.7, 128.6, 126.08, 121.4, 114.9, 52.6, 35.2, 20.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3397 (*m*), 2951 (*w*), 1720 (*s*), 1698 (*vs*), 1609 (*s*), 1451 (*s*), 1324 (*vs*), 1230 (*vs*), 1117 (*vs*), 728 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{16}O_3$ $[M]^+$: 256.1099; found 256.1094.

33b:

TLC (12.5% ethyl acetate in hexanes): R_f = 0.23 (UV, $KMnO_4$)

m.p.: 148 °C.

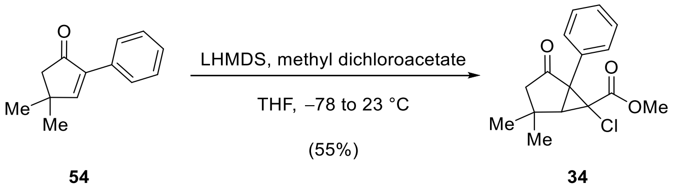
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49–7.45 (m, 1H), 7.35 (d, *J* = 1.2 Hz, 1H), 7.27–7.21 (m, 2H), 7.19–7.12 (m, 3H), 5.28 (br s, 1H), 4.09 (s, 2H), 3.87 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 167.3, 154.5, 139.9, 139.7, 131.6, 129.6, 129.0, 128.7, 126.6, 124.4, 114.5, 52.1, 32.5, 20.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3420 (*m*), 2952 (*w*), 1697 (*vs*), 1586 (*m*), 1438 (*s*), 1328 (*vs*), 1247 (*vs*), 1046 (*m*), 771 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{16}O_3$ $[M]^+$: 256.1099; found 256.1092.

Methyl 6-chloro-4,4-dimethyl-2-oxo-1-phenylbicyclo[3.1.0]hexane-6-carboxylate (34)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 958 µL, 958 µmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (104 µL, 1.00 mmol, 1.10 equiv) was added dropwise. After 45 min, a solution of cyclopropane **54** (170 mg, 913 µmol, 1 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 45 min, the reaction was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (5 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford crude **34** (148 mg, 55%) as a colorless solid.

TLC (10% ethyl acetate in hexanes): R_f = 0.37 (UV, $KMnO_4$)

m.p.: 112–114 °C.

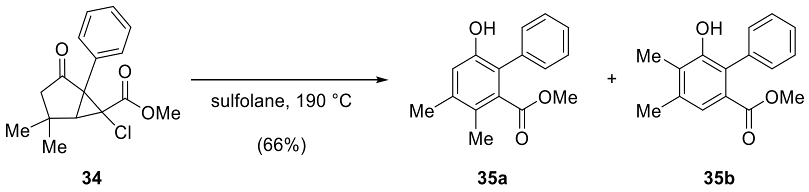
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.36–7.31 (m, 3H), 7.23–7.17 (m, 2H), 3.36 (s, 3H), 3.18 (s, 1H), 2.70 (d, *J* = 19.4 Hz, 1H), 2.19 (d, *J* = 19.4 Hz, 1H), 1.43 (s, 3H), 1.43 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 207.5, 166.4, 131.9, 129.8, 128.7, 55.0, 54.1, 53.8, 50.9, 48.0, 35.6, 32.9, 23.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*w*), 2873 (*w*), 1734 (*vs*), 1274 (*s*), 1219 (*s*), 1147 (*m*), 698 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{17}ClO_3$ $[M]^+$: 292.0866; found 292.0864.

Methyl 6-hydroxy-3,4-dimethyl-[1,1'-biphenyl]-2-carboxylate (35a) and methyl 6-hydroxy-3,5-dimethyl-[1,1'-biphenyl]-2-carboxylate (35b)



A solution of cyclopropane **34** (75.0 mg, 256 µmol, 1 equiv) in sulfolane (600 µL) was heated at 190 °C. After 30 min, the reaction mixture was allowed to cool to 23 °C and water (2 mL) and diethyl ether (2 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 20 mL). The combined organic extracts were washed with water (4 × 20 mL) and saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford firstly **35b** (8.50 mg, 13%) as a solid and then **35a** (34.5 mg, 53%) as an off-white solid.

35a:

TLC (10% ethyl acetate in hexanes): $R_f = 0.16$ (UV, $KMnO_4$)

m.p.: 102 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.49–7.25 (m, 5H), 6.85 (s, 1H), 5.01 (s, 1H), 3.48 (s, 3H), 2.28 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 170.3, 150.8, 139.1, 135.6, 135.1, 130.4, 129.5, 128.7, 125.5, 123.6, 118.3, 52.1, 20.4, 16.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3416 (*m*), 2950 (*m*), 1728 (*vs*), 1706 (*vs*), 1466 (*s*), 1436 (*s*), 1320 (*vs*), 1285 (*vs*), 1242 (*vs*), 1205 (*vs*), 1125 (*vs*), 1034 (*s*), 1020 (*s*), 754 (*s*), 702 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{16}O_3$ $[M]^+$: 256.1099; found 256.1099.

35b:

TLC (10% ethyl acetate in hexanes): $R_f = 0.35$ (UV, $KMnO_4$)

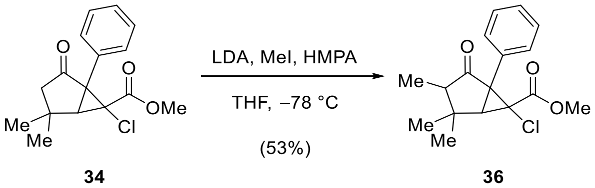
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.51–7.39 (m, 3H), 7.33 (s, 1H), 7.25–7.23 (m, 2H), 5.11 (s, 1H), 3.54 (s, 3H), 2.34 (s, 3H), 2.22 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 168.1, 151.6, 138.1, 136.2, 130.3, 129.6, 128.6, 128.2, 127.9, 126.1, 123.5, 52.0, 20.3, 12.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3531 (*m*), 3025 (*w*), 2949 (*w*), 1725 (*vs*), 1434 (*s*), 1325 (*s*), 1305 (*vs*), 1251 (*vs*), 1200 (*vs*), 1075 (*vs*), 702 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{16}O_3$ $[M]^+$: 256.1099; found 256.1104.

Methyl 6-chloro-3,4,4-trimethyl-2-oxo-1-phenylbicyclo[3.1.0]hexane-6-carboxylate (36)



A solution of diisopropylamine (47.0 µL, 335 µmol, 1.40 equiv) in tetrahydrofuran (0.5 mL) was cooled to −78 °C and a solution of *n*-butyllithium (2.3 M in hexanes, 138 µL, 323 µmol, 1.35 equiv) was added dropwise. After 10 min, the solution was warmed to 0 °C. After 10 min, the solution was cooled to −78 °C and a solution of ketone **34** (70.0 mg, 239 µmol, 1 equiv) in tetrahydrofuran (1.5 mL) was added dropwise. After 30 min, iodomethane (21.0 µL, 335 µmol, 1.40 equiv) and hexamethylphosphoramide (42.0 µL, 239 µmol, 1 equiv) were added. After 4 h, saturated aqueous ammonium chloride solution (5 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **36** (36.0 mg, 53%) as a colorless solid.

TLC (5% ethyl acetate in hexanes): $R_f = 0.36$ (UV, $KMnO_4$)

m.p.: 129–132 °C.

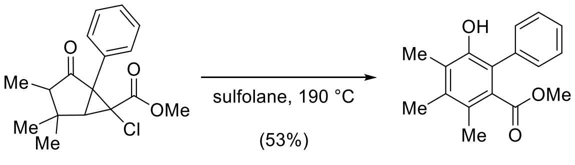
^{1}H NMR (599 MHz, $CDCl_3$) δ = 7.32–7.27 (m, 3H), 7.21–7.19 (m, 2H), 3.37 (s, 3H), 3.17 (s, 1H), 2.87(q, *J* = 7.3 Hz, 1H), 1.42 (s, 3H), 1.23 (s, 3H), 1.01 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz $CDCl_3$) δ = 208.8, 166.3, 131.3, 129.4, 128.3, 55.4, 53.5, 52.3, 50.1, 46.4, 38.6, 27.0, 23.1, 9.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*w*), 2873 (*w*), 1733 (*vs*), 1499 (*w*), 1448 (*w*), 1265 (*m*), 1222 (*m*), 1141 (*m*), 982 (*w*), 754 (*w*), 697 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{17}H_9ClO_3$ $[M]^+$: 306.1023; found 306.1020.

Methyl 6-hydroxy-3,4,5-trimethyl-[1,1'-biphenyl]-2-carboxylate (37)



36 37

A solution of cyclopropane **36** (20.0 mg, 65.0 µmol, 1 equiv) in sulfolane (600 µL) was heated at 190 °C. After 30 min, the reaction mixture was cooled to 23 °C and water (2 mL) and diethyl ether (2 mL) were added. The aqueous layer was extracted with diethyl ether (4 × 20 mL). The combined organic extracts were washed with water (4 × 20 mL) and saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **37** (9.4 mg, 53%) as a colorless solid.

TLC (5% ethyl acetate in hexanes): $R_f = 0.23$ (UV, $KMnO_4$)

m.p.: 54–57 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.50–7.38 (m, 3H), 7.31–7.27 (m, 2H), 4.99 (br s, 1H), 3.45 (s, 3H), 2.24 (s, 6H), 2.17 (s, 3H).

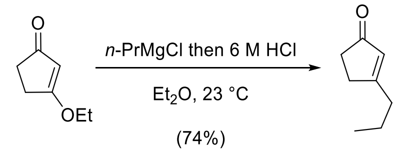
^{13}C NMR (101 MHz, CD_2Cl_2) δ = 170.5, 148.9, 137.5, 135.4, 132.8, 130.5, 129.7, 128.9, 124.9, 124.8, 122.8, 52.0, 17.2, 16.4, 12.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3546 (*w*), 2948 (*w*), 2927 (*w*), 1724 (*vs*), 1434 (*s*), 1335 (*m*), 1299 (*s*), 1204 (*vs*), 1071 (*vs*), 1038 (*vs*), 815 (*m*), 762 (*s*), 732 (*vs*), 700 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{17}H_{18}O_3$ $[M]^+$: 270.1256; found 270.1252.

Synthesis of sekikaic acid methyl ester (43)

3-Propylcyclopent-2-en-1-one (82)



38 **82**

A solution of *n*-propyl magnesium chloride (1.6 M in diethyl ether, 50.0 mL, 80.0 mmol, 2.00 equiv) was cooled to 0 °C and a solution of enol ether **38** (5.00 g, 39.6 mmol, 1 equiv) in tetrahydrofuran (44 mL) was added. After 4.5 h, the reaction mixture was poured on ice water (200 mL) and 6 M aqueous hydrochloric acid (25 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (7 × 100 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (3 × 100 mL) and saturated aqueous sodium chloride solution (2 × 100 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **82** (3.55 g, 74%) as a brown oil.

TLC (20% ethyl acetate in hexanes), $R_f = 0.22$ (UV, $KMnO_4$).

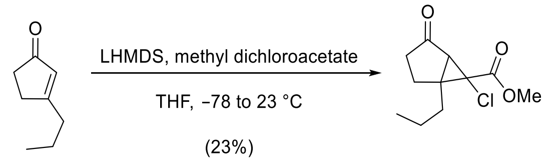
^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 5.94$ (s, 1H), 2.59–2.55 (m, 2H), 2.41–2.36 (m, 4H), 1.68–1.56 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 210.3$, 183.1, 129.7, 35.7, 35.5, 31.7, 20.6, 14.0.

IR (Diamond-ATR, neat): 2961 (*w*), 2932 (*w*), 2874 (*w*), 1706 (*vs*), 1673 (*s*), 1613 (*m*), 1411 (m), 1259 (*m*), 1180 (*m*), 1112 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_8H_{12}O$ $[M]^+$: 124.0888; found: 124.0885.

Methyl 6-chloro-4-oxo-1-propylbicyclo[3.1.0]hexane-6-carboxylate (39)



82 **39**

A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 18.9 mL, 18.9 mmol, 1.05 equiv) was cooled to −78 °C and a solution of methyl dichloroacetate (2.04 mL, 19.8 mmol, 1.10 equiv) in tetrahydrofuran (10 mL) was added dropwise. After 30 min, cyclopentenone **82** (2.23 g, 18.0 mmol, 1 equiv) was added dropwise. After 45 min, the solution was warmed to 23 °C. After 16 h, saturated aqueous ammonium chloride solution (25 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 × 50 mL) and dried over sodium sulfate. The dried solution was filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **39** (946 mg, 23%) as a brown oil.

TLC (20% ethyl acetate in hexanes), $R_f = 0.54$ (UV, $KMnO_4$).

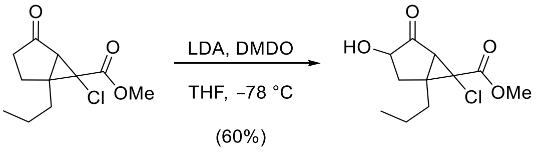
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.82 (s, 3H), 2.85 (s, 1H), 2.42–2.22 (m, 4H), 1.70–1.56 (m, 2H), 1.53–1.31 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.4, 167.0, 53.9, 52.4, 46.3, 44.8, 37.7, 32.7, 27.0, 19.9, 14.0.

IR (Diamond-ATR, neat): 2959 (*w*), 1732 (*vs*), 1453 (*w*), 1436 (*m*), 1262 (*s*), 1242 (*m*), 1194 (*m*), 1166 (*s*), 1099 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{15}ClO_3$ $[M]^+$: 230.0710; found: 230.0676.

Methyl 6-chloro-3-hydroxy-4-oxo-1-propylbicyclo[3.1.0]hexane-6-carboxylate (83)



39 **83**

A solution of diisopropylamine (368 µL, 2.60 mmol, 1.50 equiv) in tetrahydrofuran (0.5 mL) was cooled to −78 °C and a solution of *n*-butyllithium (2.2 M in hexanes, 1.02 mL, 2.25 mmol, 1.30 equiv) was added dropwise. After 10 min, the solution was warmed to 0 °C. After 10 min, the solution was cooled to −78 °C and a solution of cyclopropane **39** (400 mg, 1.73 mmol, 1 equiv) in tetrahydrofuran (5 mL) was added dropwise. After 1 h, the reaction mixture was transferred dropwise via cannula to a solution of freshly prepared dimethyldioxirane (0.05 M in acetone, 55.0 mL, 2.43 mmol, 1.40 equiv) at −78 °C. After 2 h, pH 7 buffer solution (10 mL) was added and the reaction mixture was warmed to 23 °C. Dichloromethane (100 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (4× 75 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **83** (260 mg, 60%) as colorless oil.

TLC (20% ethyl acetate in hexanes), R$_f$ = 0.25 (UV, KMnO$_4$).

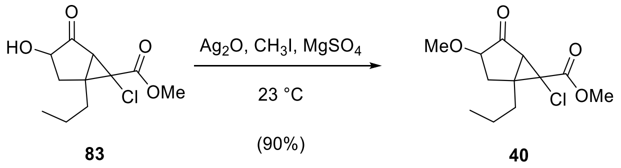
^{1}H NMR (400 MHz, CDCl$_3$) δ = 4.17 (app dd, *J* = 8.2, 5.5 Hz, 1H), 3.83 (s, 3H), 2.93 (s, 1H), 2.83 (app dd, *J* = 14.5, 8.2 Hz, 1H), 2.46 (br s, 1H), 2.14 (app dd, *J* = 14.5, 5.5 Hz, 1H), 1.71–1.54 (m, 2H), 1.53–1.31 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ = 210.0, 166.6, 72.6, 54.1, 54.0, 45.5, 42.8, 36.1, 33.0, 19.7, 13.9.

IR (Diamond-ATR, neat): 3455 (*w*), 2960 (*w*), 2934 (*w*), 2874 (*w*), 1735 (*vs*), 1436 (*m*), 1288 (*m*), 1270 (*s*), 1167 (*s*), 1102 (*s*) cm^{-1}.

HRMS (EI) calcd for C$_{11}$H$_{15}$ClO$_4$ [M]$^+$: 246.0659; found: 246.0575.

Methyl 6-chloro-3-methoxy-4-oxo-1-propylbicyclo[3.1.0]hexane-6-carboxylate (40)



To a solution of **83** (260 mg, 1.05 mmol, 1 equiv) in iodomethane (2.95 mL) in a pressure tube were addded magnesium sulfate (507 mg, 4.22 mmol, 4.00 equiv) and silver(I) oxide (708 mg, 3.06 mmol, 2.90 equiv). After 16 h, the solvent was removed and the residue was suspended in acetone. The suspension was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **40** (246 mg, 90%) as a pale yellow solid.

TLC (20% ethyl acetate in hexanes), $R_f = 0.51$ ($KMnO_4$).

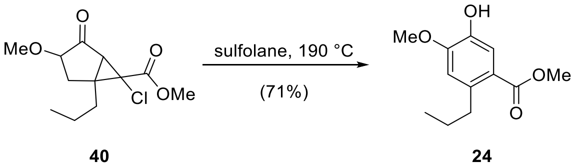
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.82 (s, 1H), 3.75 (dd, *J* = 8.0, 5.1 Hz, 1H), 3.50 (s, 3H), 2.89 (s, 1H), 2.80 (dd, *J* = 14.6, 8.0 Hz, 1H), 2.11 (dd, *J* = 14.6, 5.1 Hz, 1H), 1.71–1.55 (m, 2H), 1.52–1.29 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 207.7, 166.7, 81.0, 58.6, 53.9, 53.7, 44.9, 42.8, 35.3, 32.8, 19.8, 13.9.

IR (Diamond-ATR, neat): 2960 (*w*), 2935 (*w*), 1741 (*vs*), 1436 (*m*), 1298 (*m*), 1273 (*s*), 1242 (*m*), 1195 (*m*), 1165 (*m*), 1107 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{17}ClO_4$ $[M]^+$: 260.0815; found: 260.0806.

Methyl 5-hydroxy-4-methoxy-2-propylbenzoate (24)



A solution of cyclopropane **40** (214 mg, 821 µmol, 1 equiv) in sulfolane (2.00 mL) was heated at 190 °C. After 20 min, the reaction was cooled to 23 °C and water (5 mL) and diethyl ether (5 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 5 mL). The combined organic layers were washed with water (4 × 15 mL) and saturated aqueous sodium chloride solution (2 × 15 mL) and dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **24** (130 mg, 71%) as a pale brown solid.

TLC (20% ethyl acetate in hexanes), $R_f = 0.3$ (UV, $KMnO_4$).

m.p.: 52 °C.

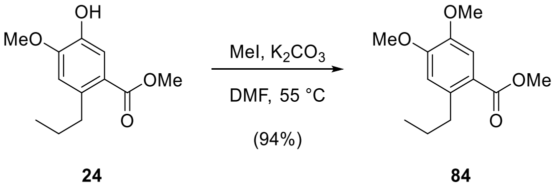
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 (s, 1H), 6.68 (s, 1H), 5.45 (s, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 2.91–2.88 (m, 2H), 1.64–1.55 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.5, 149.4, 143.1, 138.8, 121.6, 116.9, 112.8, 56.0, 51.8, 36.6, 25.3, 14.3.

IR (Diamond-ATR, neat): 2958 (*w*), 2872 (*w*), 1650 (*s*), 1614 (*s*), 1577 (*m*), 1435 (*m*), 1378 (*w*), 1326 (*s*), 1305 (*m*), 1255 (*vs*), 1229 (*m*), 1203 (*s*), 1158 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{16}O_4$ $[M]^+$: 224.1049; found: 224.1044.

Methyl 4,5-dimethoxy-2-propylbenzoate (84)



A solution of phenol **24** (50.0 mg, 223 µmol, 1 equiv), iodomethane (34.0 µL, 557 µmol, 2.50 equiv) and potassium carbonate (77.0 mg, 557 µmol, 2.50 equiv) in *N,N*-dimethylformamide (1 mL) was heated at 55 °C. After 45 min, the reaction mixture was cooled to 23 °C and water (15 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (2 × 15 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **84** (50.0 mg, 94%) as a colorless oil.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.36$ (UV, $KMnO_4$)

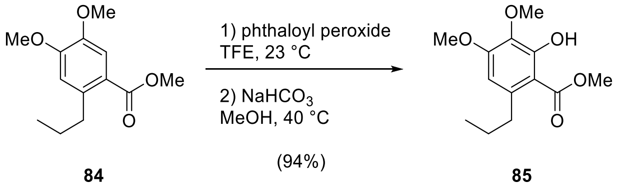
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (s, 1H), 6.70 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 2.96–2.85 (m, 2H), 1.61–1.56 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.6, 151.8, 146.5, 139.8, 120.7, 113.5, 113.5, 56.1, 56.0, 51.9, 36.7, 25.2, 14.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (*w*), 2870 (*w*), 1715 (*s*), 1605 (*m*), 1515 (*m*), 1463 (*m*), 1433 (*m*), 1355 (*m*), 1265 (*s*), 1207 (*s*), 1188 (*m*), 1152 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{18}O_4$ $[M]^+$: 238.1205; found 238.1206.

Methyl 2-hydroxy- 3,4-dimethoxy-6-propylbenzoate (85)



To a solution of benzoate **84** (48.0 mg, 201 µmol, 1 equiv) in trifluoroethanol (1.5 mL) was added freshly prepared phthaloyl peroxide[83] (43.0 mg, 262 µmol, 1.30 equiv). After 4 h, the solvent was evaporated and degassed methanol (2 mL) and saturated aqueous sodium bicarbonate solution (0.4 mL) were added. The reaction mixture was heated at 40 °C. After 6 h, the reaction mixture was diluted with pH 7 buffer solution (5 mL) and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (2 × 15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **85** (48.0 mg, 94%) as a colorless solid.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.30$ (UV, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.41 (s, 1H), 6.31 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 2.87–2.76 (m, 2H), 1.61–1.52 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.0, 157.1, 156.4, 142.3, 134.9, 106.4, 60.8, 56.0, 52.2, 39.2, 25.4, 14.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3398 (*w*), 2958 (*m*), 2933 (*m*), 2871 (*w*), 1727 (*w*), 1654 (*s*), 1407 (*s*), 1303 (*s*), 1278 (*vs*), 1202 (*m*), 1122 (*s*), 1034 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{18}O_5$ $[M]^+$: 254.1154; found 254.1144.

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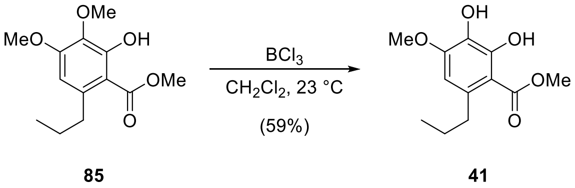
[83] For the synthesis of phthaloyl peroxide, see: C. Yuan, A. Axelrod, M. Varela, L. Danysch, D. Siegel, *Tetrahedron Lett.*, **2011**, *52*, 2540–2542.

Methyl 2,3-dihydroxy-4-methoxy-6-propylbenzoate (41)



A solution of benzoate **85** (25.0 mg, 98.3 µmol, 1 equiv) in dichloromethane (2 mL) was cooled to 0 °C and a solution of boron trichloride (1 M in dichloromethane, 324 µL, 324 µmol, 3.30 equiv) was added dropwise. After 10 min, the solution was warmed to 23 °C. After 6 h, the reaction mixture was diluted with ethyl acetate (2 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **41** (14.0 mg, 59%) as a colorless solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.27 (UV, CAM)

m.p.: 67–29 °C.

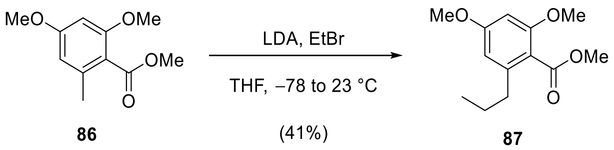
^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.57 (s, 1H), 6.33 (s, 1H), 5.40 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.86–2.79 (m, 2H), 1.60–1.50 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.1, 150.6, 150.1, 137.9, 131.7, 106.4, 105.6, 56.1, 52.2, 38.8, 25.5, 14.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3478 (*m*), 2962 (*w*), 1648 (*s*), 1601 (*m*), 1444 (*m*), 1431 (*s*), 1416 (*s*), 1353 (*w*), 1339 (*w*), 1289 (*vs*), 1203 (*s*), 1174 (*w*), 1100 (*vs*), 1059 (*w*), 1016 (*m*), 808 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{16}O_5$ $[M]^+$: 240.0998; found 240.0997.

Methyl 2,4-dimethoxy-6-propylbenzoate (87)



A solution of diisopropylamine (1.05 mL, 7.62 mmol, 1.60 equiv) in tetrahydrofuran (3 mL) was cooled to −78 °C and a solution of *n*-butyllithium (2.3 M in hexanes, 3.10 mL, 7.14 mmol, 1.50 equiv) was added dropwise. After 15 min, the reaction mixture was warmed to 0 °C. After 20 min, the solution was cooled to −78 °C. A solution of **86**[84] (1.00 g, 4.76 mmol, 1 equiv) in tetrahydrofuran (7 mL) was added dropwise. After 1 h, ethyl bromide (0.640 mL, 7.62 mmol, 1.60 equiv) was added dropwise. After 1 h, the reaction mixture was warmed to to 23 °C. After 3 h, 2 M aqueous hydrochloric acid solution (5 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (5 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (2 × 25 mL) and dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **87** (468 mg, 41%) as a colorless oil.

TLC (12.5% ethyl acetate in hexanes), $R_f = 0.25$ (UV, $KMnO_4$).

^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.33 (d, *J* = 2.2 Hz, 1H), 6.32 (d, *J* = 2.2 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 2.54–2.51 (m, 2H), 1.66–1.55 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.0, 161.5, 158.1, 142.7, 116.5, 106.0, 96.3, 56.0, 55.2, 52.2, 36.1, 24.4, 14.2.

IR (Diamond-ATR, neat): 2959 (*w*), 1726 (*s*), 1604 (*s*), 1585 (*m*), 1458 (*m*), 1430 (*m*), 1326 (*m*), 1269 (*s*), 1215 (*m*), 1200 (*m*), 1158 (*vs*), 1098 (*m*), 1073 (*m*), 1043 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{18}O_4$ $[M]^+$: 238.1205; found: 238.1202.

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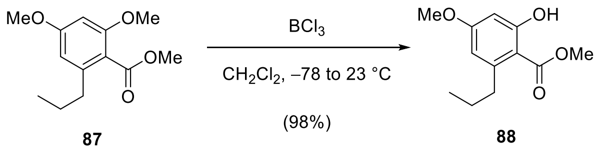
[84] For the synthesis of benzoate **86**, see: A. Hager, D. Mazunin, P. Mayer, D. Trauner, *Org. Lett.* **2011**, *13*, 1386–1389.

Methyl 2-hydroxy-4-methoxy-6-propylbenzoate (88)



A solution of **87** (544 mg, 2.28 mmol, 1 equiv) in dichloromethane (25 mL) was cooled to −78 °C. A solution of boron trichloride (1 M in dichloromethane, 5.00 mL, 5.00 mmol, 2.20 equiv) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 45 min, saturated aqueous ammonium chloride solution (30 mL) was added. The layers were separated and the organic layer was washed with water (2 × 30 mL) and dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **88** (509 mg, 98%) as colorless solid.

TLC (20% ethyl acetate in hexanes), $R_f = 0.46$ (UV, $KMnO_4$).

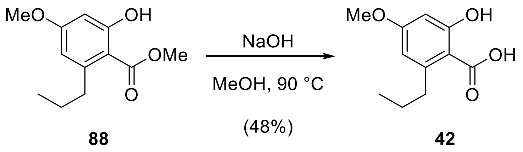
^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.74 (s, 1H), 6.34 (d, *J* = 2.6 Hz, 1H), 6.29 (d, *J* = 2.6 Hz, 1H), 3.92 (s, 3H), 3.80 (s, 3H), 2.85–2.81 (m, 2H), 1.60–1.51 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.1, 165.7, 164.0, 147.9, 110.9, 104.8, 98.9, 55.4, 52.1, 39.1, 25.1, 14.4.

IR (Diamond-ATR, neat): 2958 (*w*), 1650 (*s*), 1614 (*s*), 1577 (*m*), 1435 (*m*), 1378 (*w*), 1326 (*s*), 1305 (*m*), 1255 (*vs*), 1229 (*m*), 1203 (*s*), 1158 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{16}O_4$ $[M]^+$: 224.1049; found: 224.1044.

2-Hydroxy-4-methoxy-6-propylbenzoic acid (42)



To a solution of **88** (220 mg, 980 µmol, 1 equiv) in methanol (5 mL), 10% aqueous sodium hydroxide solution (3.50 mL, 9.77 mmol, 10.0 equiv) was added and the reaction mixture was heated at 50 °C. After 16 h, additional 10% aqueous sodium hydroxide solution (3.50 mL, 9.77 mmol, 10.0 equiv) was added and the reaction mixture was heated at 90 °C. After 18 h, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (1% methanol, 1% acetic acid in dichloromethane) to afford **42** (98.1 mg, 48%) as a colorless solid.

TLC (1% methanol, 1% acetic acid in dichloromethane), R_f = 0.44 (UV, $KMnO_4$).

m.p.: 131–137 °C.

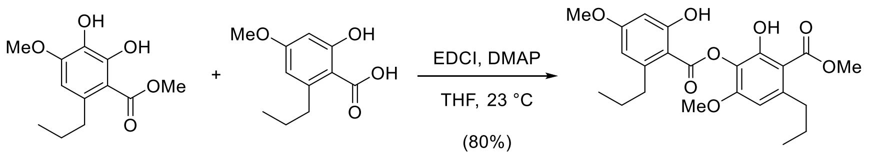
^{1}H NMR (400 MHz, CD_3OD) δ = 6.29–6.27 (m, 2H), 5.15 (br s, 1H), 3.77 (s, 3H), 2.89–2.85 (m, 2H), 1.64–1.51 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, CD_3OD) δ = 175.2, 166.7, 165.2, 149.4, 111.0, 99.7, 55.7, 39.5, 26.2, 20.7, 14.5.

IR (Diamond-ATR, neat): 2962 (*w*), 1712 (*s*), 1613 (*s*), 1448 (*m*), 1434 (*m*), 1415 (*m*), 1359 (*vs*), 1250 (*s*), 1221 (*vs*), 1202 (*vs*), 1160 (*s*), 861 (*s*), 829 (*vs*), 795 (*m*), 743 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{14}O_4$ $[M]^+$: 210.0892; found: 210.0853.

Sekikaic acid methyl ester (43)



41 **42** **43**

A solution of acid **42** (8.00 mg, 38.0 µmol, 1 equiv), phenol **41** (9.00 mg, 38.0 µmol, 1 equiv), 4-(dimethylamino)-pyridine (0.500 mg, 3.80 µmol, 0.100 equiv) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide (6.60 µL, 38.0 µmol, 1 equiv) in tetrahydrofuran (500 µL) was stirred at 23 °C. After 14 h, the solvent was evaporated and the crude product was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to afford **43** (13 mg, 80%) as a colorless solid.

TLC (12.5% ethyl acetate in hexanes): R_f = 0.30 (UV, $KMnO_4$)

m.p.: 112–114 °C.

^{1}H NMR (599 MHz, $CDCl_3$) δ = 11.66 (s, 1H), 11.13 (s, 1H), 6.41 (s, 1H), 6.38 (d, *J* = 0.8 Hz, 2H), 3.95 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.02–2.97 (m, 2H), 2.92–2.88 (m, 2H), 1.78–1.71 (m, 2H), 1.65–1.57 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.7, 169.0, 165.6, 164.5, 156.1, 155.5, 148.9, 145.5, 125.0, 111.0, 106.3, 106.1, 104.7, 99.0, 56.1, 55.5, 52.4, 39.4, 39.0, 25.3, 25.0, 14.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3470 (*w*), 2960 (*m*), 2872 (*m*), 1659 (*vs*), 1617 (*vs*), 1579 (*s*), 1416 (*s*), 1305 (*vs*), 1278 (*vs*), 1250 (*vs*), 1230 (*vs*), 1203 (*vs*), 1158 (*vs*), 1127 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{23}H_{28}O_8$ $[M]^+$: 432.1784; found 432.1782.

6.1.2 X-Ray Crystallographic Data

The data collections were performed either on an *Oxford Diffraction* Xcalibur diffractometer, on a *Bruker* D8Quest diffractometer or on a *Bruker* D8Venture at 100 K or at 173 K using MoKα-radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.3341)[S8] was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97[85] and refined by least-squares methods against *F*2 with SHELXL-97.[86] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in the tables at the different sections.

Sekikaic Acid Methyl Ester (43)

CCDC 1410728 contains the supplementary crystallographic data for sekikaic acid methyl ester (**43**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Crystallographic data for sekikaic acid methyl ester (**43**).

net formula	$C_{23}H_{28}O_8$
M_r/g mol^{-1}	432.45
crystal size/mm	0.100 × 0.080 × 0.030
T/K	173(2)
radiation	MoKα
diffractometer	'Bruker D8Quest'
crystal system	triclinic
space group	'P -1'
a/Å	8.7231(7)
b/Å	8.7894(9)
c/Å	15.2790(15)
α/°	97.596(3)
β/°	96.994(3)

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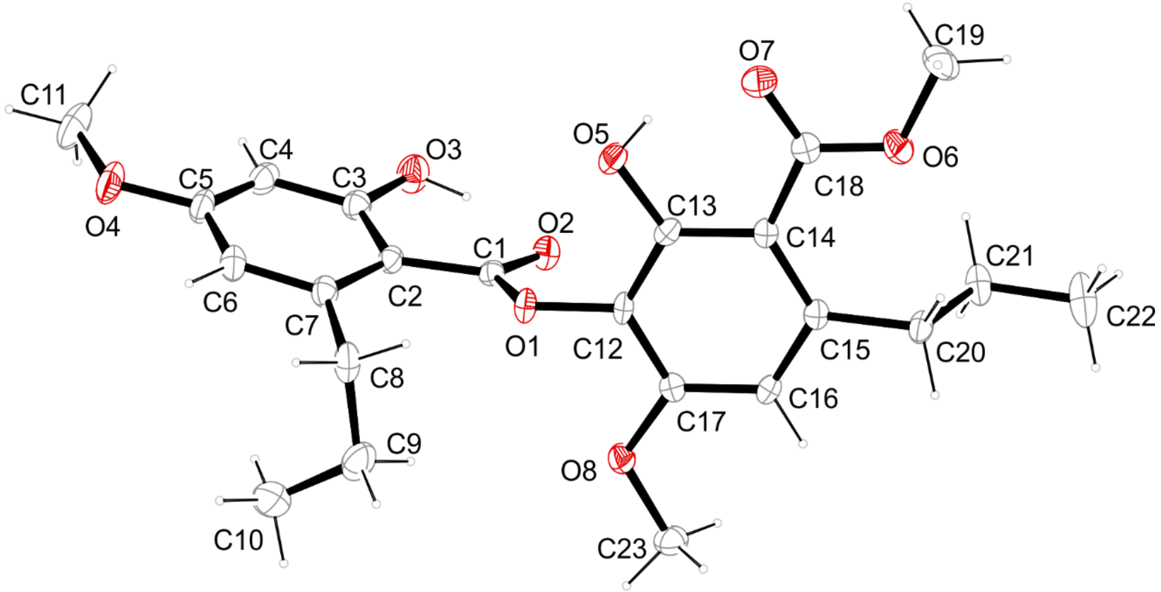
[85] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115.

[86] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112.

γ/°	106.394(3)
V/Å^3	1098.27(18)
Z	2
calc. density/g cm^{-3}	1.308
μ/mm^{-1}	0.099
absorption correction	multi-scan
transmission factor range	0.9053–0.9579
refls. measured	18122
R_{int}	0.0583
mean $\sigma(I)/I$	0.0468
θ range	2.453–25.06
observed refls.	2603
x, y (weighting scheme)	0.0511, 0.2968
hydrogen refinement	mixed
refls in refinement	3814
parameters	291
restraints	2
$R(F_{\text{obs}})$	0.0490
$R_{\text{w}}(F^2)$	0.1175
S	1.063
shift/error$_{\text{max}}$	0.001
max electron density/e Å^{-3}	0.181
min electron density/e Å^{-3}	−0.261



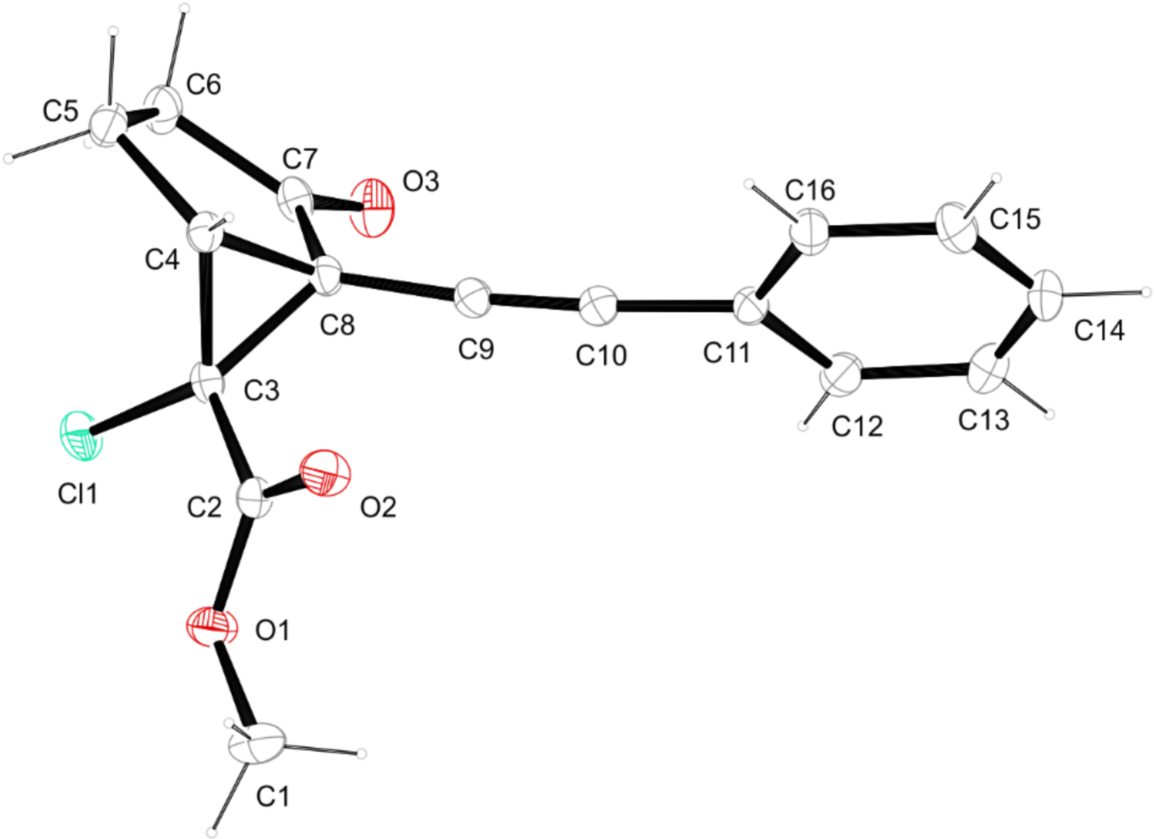
Cyclopropane 72

CCDC 1410734 contains the supplementary crystallographic data for cyclopropane **72**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Crystallographic data for cyclopropane **72**.

net formula	$C_{16}H_{13}ClO_3$
M_r/g mol^{-1}	288.725
crystal size/mm	0.20 × 0.15 × 0.03
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	*Pbca*
a/Å	16.4128(6)
b/Å	8.5431(4)
c/Å	19.8385(6)
α/°	90
β/°	90

γ/°	90
V/Å^3	2781.68(17)
Z	8
calc. density/g cm^{-3}	1.37887(8)
μ/mm^{-1}	0.278
absorption correction	'multi-scan'
transmission factor range	0.90065–1.00000
refls. measured	15424
R_{int}	0.0365
mean $\sigma(I)/I$	0.0272
θ range	4.25–26.37
observed refls.	2306
x, y (weighting scheme)	0.0334, 1.1586
hydrogen refinement	constr
refls in refinement	2839
parameters	182
restraints	0
$R(F_{\mathrm{obs}})$	0.0343
$R_{\mathrm{w}}(F^2)$	0.0846
S	1.032
shift/error$_{\mathrm{max}}$	0.001
max electron density/e Å^{-3}	0.226
min electron density/e Å^{-3}	−0.197



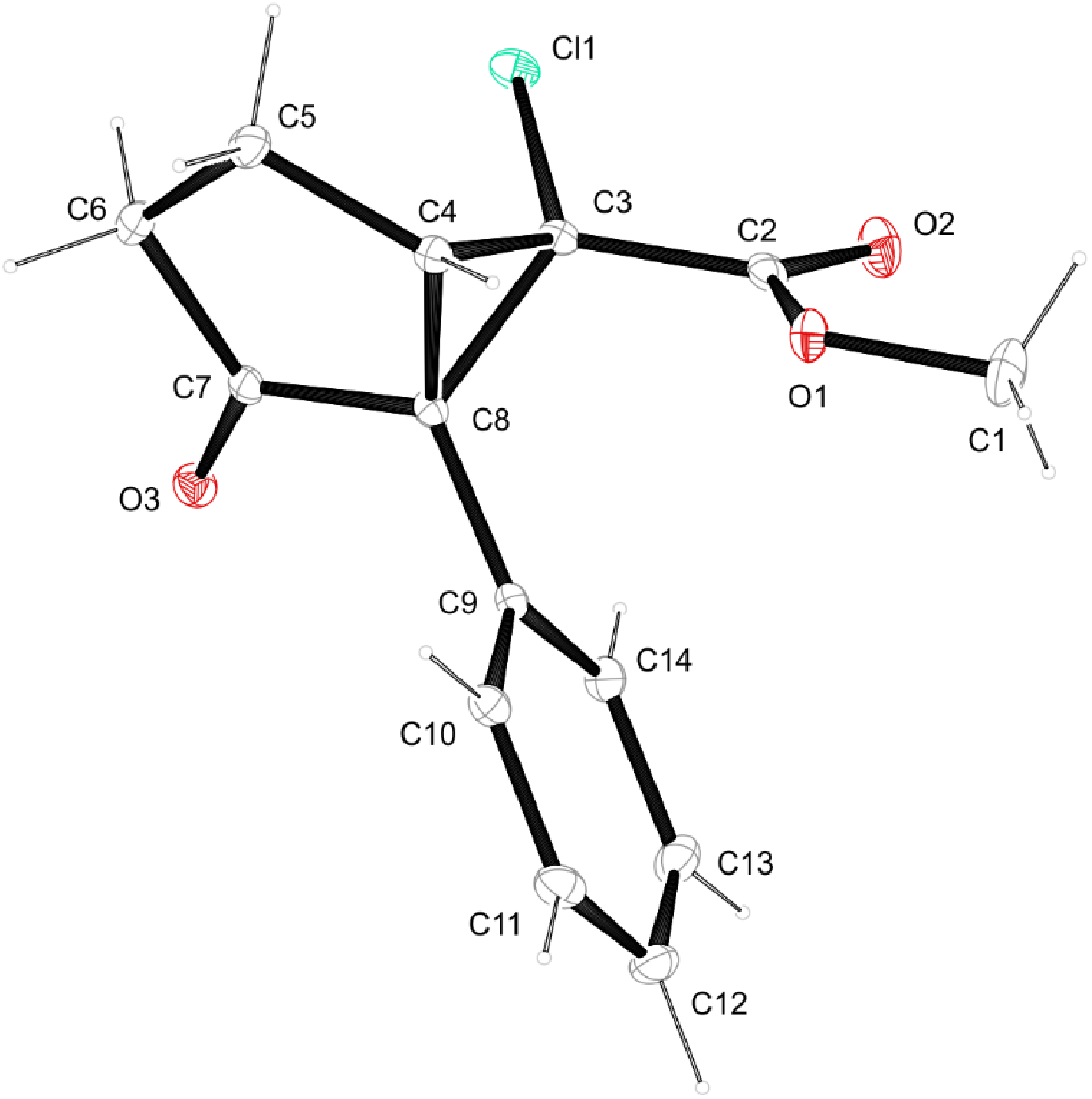
Cyclopropane 77

CCDC 1410735 contains the supplementary crystallographic data for cyclopropane **77**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 3: Crystallographic data for cyclopropane **77**.

net formula	$C_{14}H_{13}ClO_3$
M_r/g mol^{-1}	264.704
crystal size/mm	0.120 × 0.100 × 0.090
T/K	100(2)
radiation	'Mo Kα
diffractometer	'Bruker D8Venture'
crystal system	triclinic
space group	*P*1bar
a/Å	5.5861(4)
b/Å	8.6073(6)

c/Å	13.6232(8)
α/°	75.688(2)
β/°	82.701(2)
γ/°	82.680(2)
V/Å^3	626.40(7)
Z	2
calc. density/g cm^{-3}	1.40344(16)
μ/mm^{-1}	0.302
absorption correction	multi-scan
transmission factor range	0.8207–0.8620
refls. measured	16135
R_{int}	0.0406
mean σ(I)/I	0.0251
θ range	3.20–26.38
observed refls.	2246
x, y (weighting scheme)	0.0304, 0.3763
hydrogen refinement	constr
refls in refinement	2554
parameters	164
restraints	0
$R(F_{\text{obs}})$	0.0305
$R_{\text{w}}(F^2)$	0.0754
S	1.041
shift/error$_{\text{max}}$	0.001
max electron density/e Å^{-3}	0.285
min electron density/e Å^{-3}	−0.217



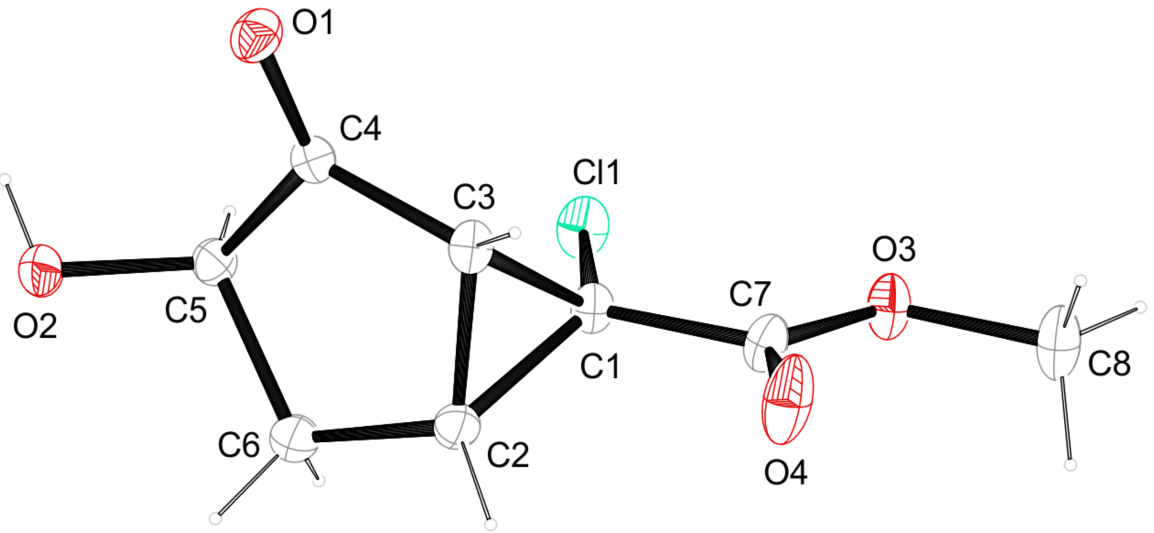
Cyclopropane 78

CCDC 1410729 contains the supplementary crystallographic data for cyclopropane **78**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 4: Crystallographic data for cyclopropane **78**.

net formula	$C_8H_9ClO_4$
M_r/g mol^{-1}	204.607
crystal size/mm	0.354 × 0.269 × 0.162
T/K	173(2)
radiation	MoKα

diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1/c$
a/Å	7.3755(15)
b/Å	7.2731(8)
c/Å	16.455(3)
α/°	90
β/°	90.933(18)
γ/°	90
V/Å^3	882.6(3)
Z	4
calc. density/g cm^{-3}	1.5398(5)
μ/mm^{-1}	0.410
absorption correction	'multi-scan'
transmission factor range	0.88845–1.00000
refls. measured	2978
R_{int}	0.0000
mean $\sigma(I)/I$	0.0272
θ range	4.11–28.32
observed refls.	2443
x, y (weighting scheme)	0.0836, 0.1113
hydrogen refinement	mixed
refls in refinement	2978
parameters	124
restraints	1
$R(F_{\text{obs}})$	0.0435
$R_{\text{w}}(F^2)$	0.1314
S	1.053
shift/error$_{\text{max}}$	0.001
max electron density/e Å^{-3}	0.363
min electron density/e Å^{-3}	−0.325



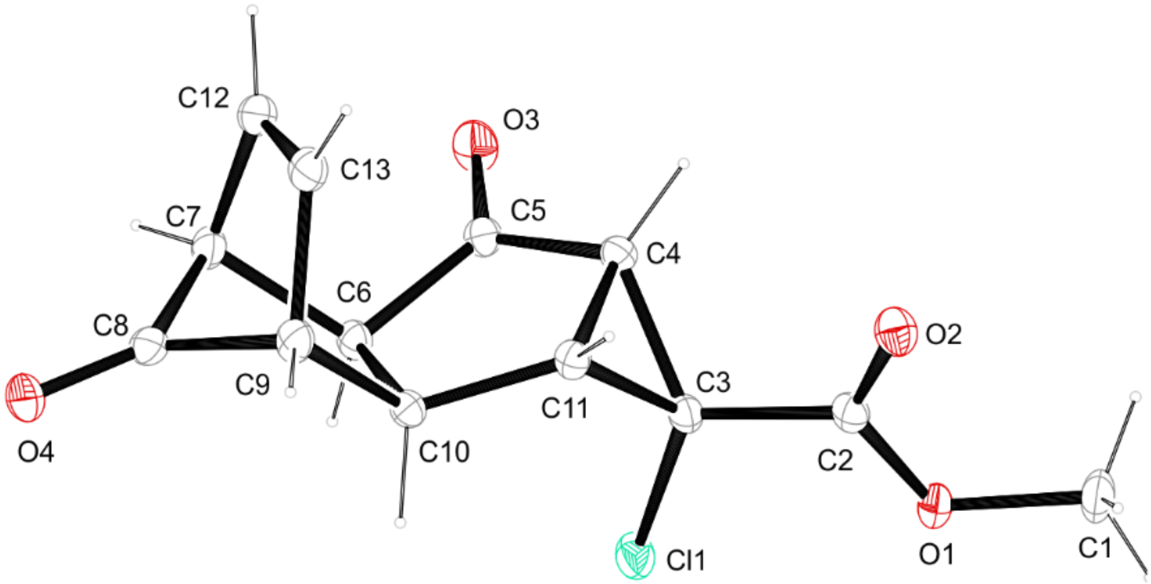
Cyclopropane 25

CCDC 1410732 contains the supplementary crystallographic data for cyclopropane **25**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 5: Crystallographic data for cyclopropane **25**.

net formula	$C_{13}H_{11}ClO_4$
M_r/g mol^{-1}	266.677
crystal size/mm	0.449 × 0.275 × 0.183
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1bar
a/Å	7.4855(6)
b/Å	8.1721(9)
c/Å	10.2108(10)
α/°	76.050(9)
β/°	71.772(9)
γ/°	74.449(9)
V/Å^3	563.06(10)

Z	2
calc. density/g cm^{-3}	1.5730(3)
μ/mm^{-1}	0.343
absorption correction	multi-scan
transmission factor range	0.97739–1.00000
refls. measured	4696
R_{int}	0.0240
mean σ(*I*)/*I*	0.0459
θ range	4.33–28.28
observed refls.	2268
x, *y* (weighting scheme)	0.0317, 0.2604
hydrogen refinement	constr
refls in refinement	2783
parameters	164
restraints	0
$R(F_{\mathrm{obs}})$	0.0414
$R_{\mathrm{w}}(F^2)$	0.0970
S	1.040
shift/error$_{\mathrm{max}}$	0.001
max electron density/e Å^{-3}	0.322
min electron density/e Å^{-3}	−0.236



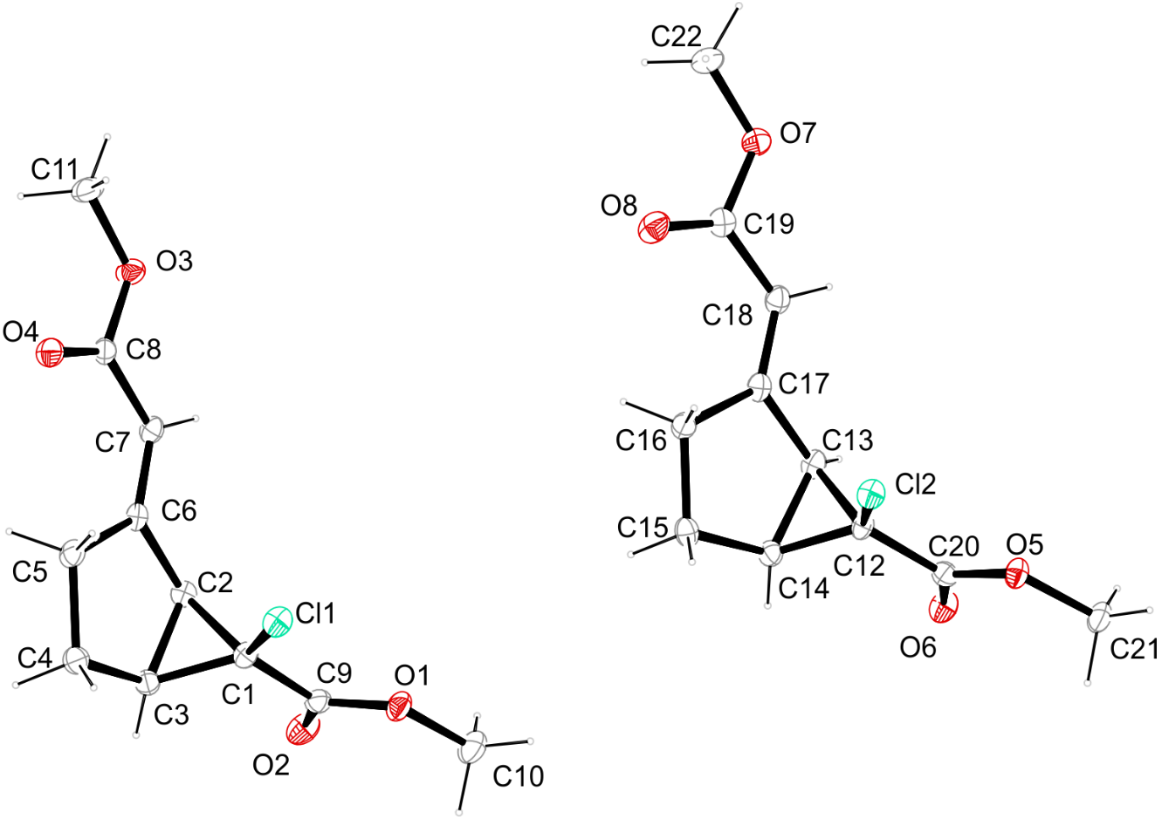
Cyclopropane 27

CCDC 1410731 contains the supplementary crystallographic data for cyclopropane **27**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 6: Crystallographic data for cyclopropane **27**

net formula	$C_{11}H_{13}ClO_4$
M_r/g mol^{-1}	244.671
crystal size/mm	0.378 × 0.169 × 0.049
T/K	123(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	12.8593(5)
b/Å	12.9927(5)
c/Å	13.6141(5)
α/°	90
β/°	90
γ/°	90
V/Å^3	2274.60(15)
Z	8
calc. density/g cm^{-3}	1.42897(9)
μ/mm^{-1}	0.332
absorption correction	'multi-scan'
transmission factor range	0.97195–1.00000
refls. measured	11934
R_{int}	0.0515
mean σ(I)/I	0.0615
θ range	4.34–25.35
observed refls.	3487

x, y (weighting scheme)	0.0322, 0
hydrogen refinement	constr
Flack parameter	0.43(6)
refls in refinement	4155
parameters	294
restraints	0
$R(F_{\mathrm{obs}})$	0.0411
$R_{\mathrm{w}}(F^2)$	0.0852
S	1.025
shift/error$_{\mathrm{max}}$	0.001
max electron density/e Å^{-3}	0.261
min electron density/e Å^{-3}	−0.200



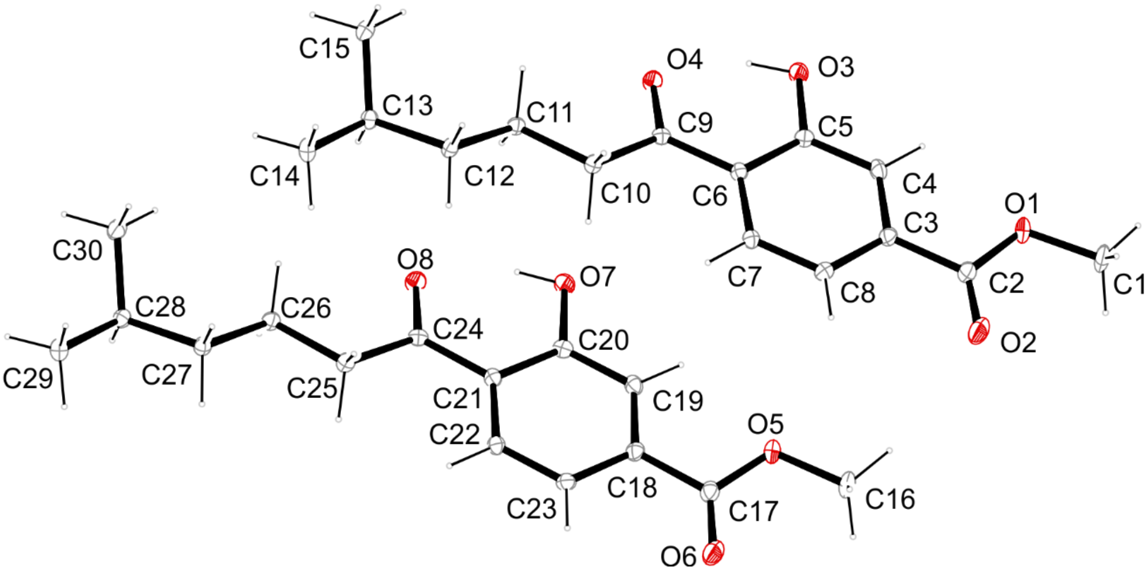
Benzoate 18

CCDC 1410730 contains the supplementary crystallographic data for benzoate **18**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

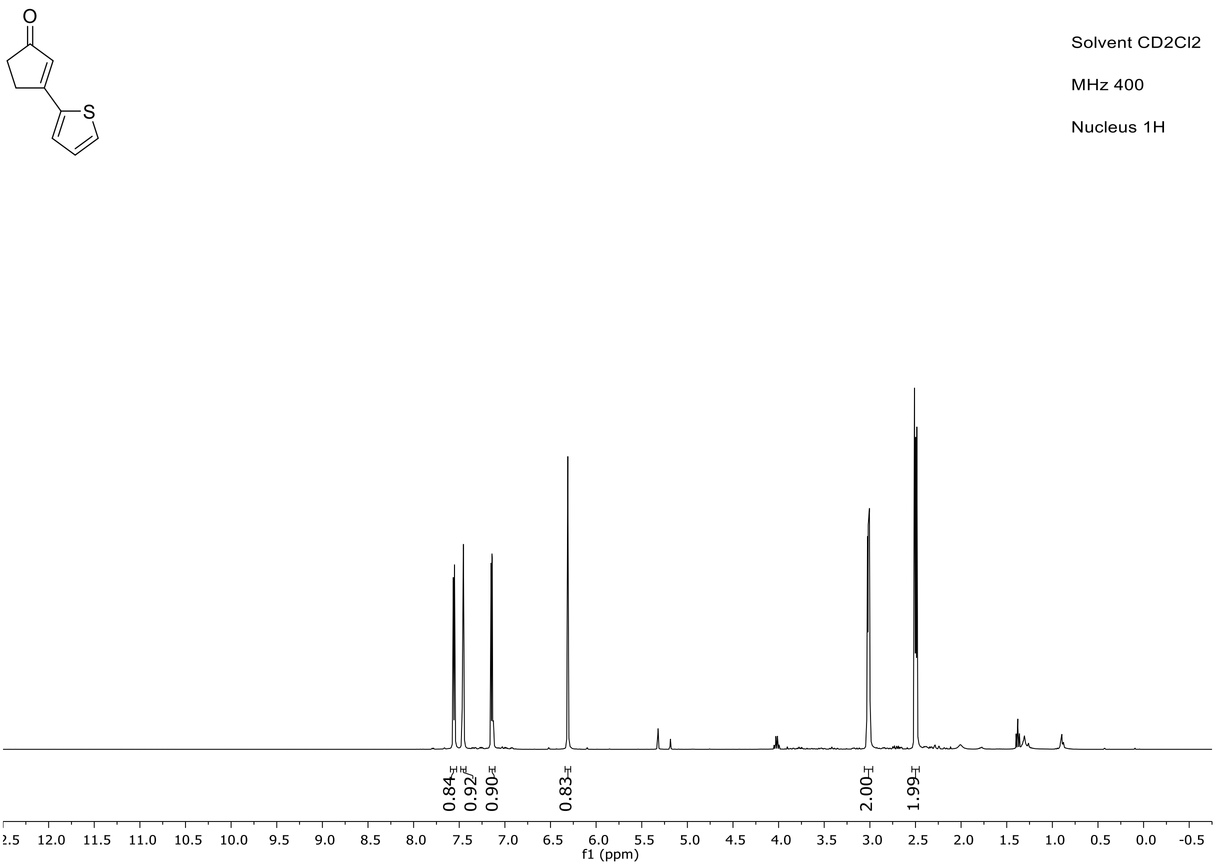
Table 7. Crystallographic data for benzoate **18**.

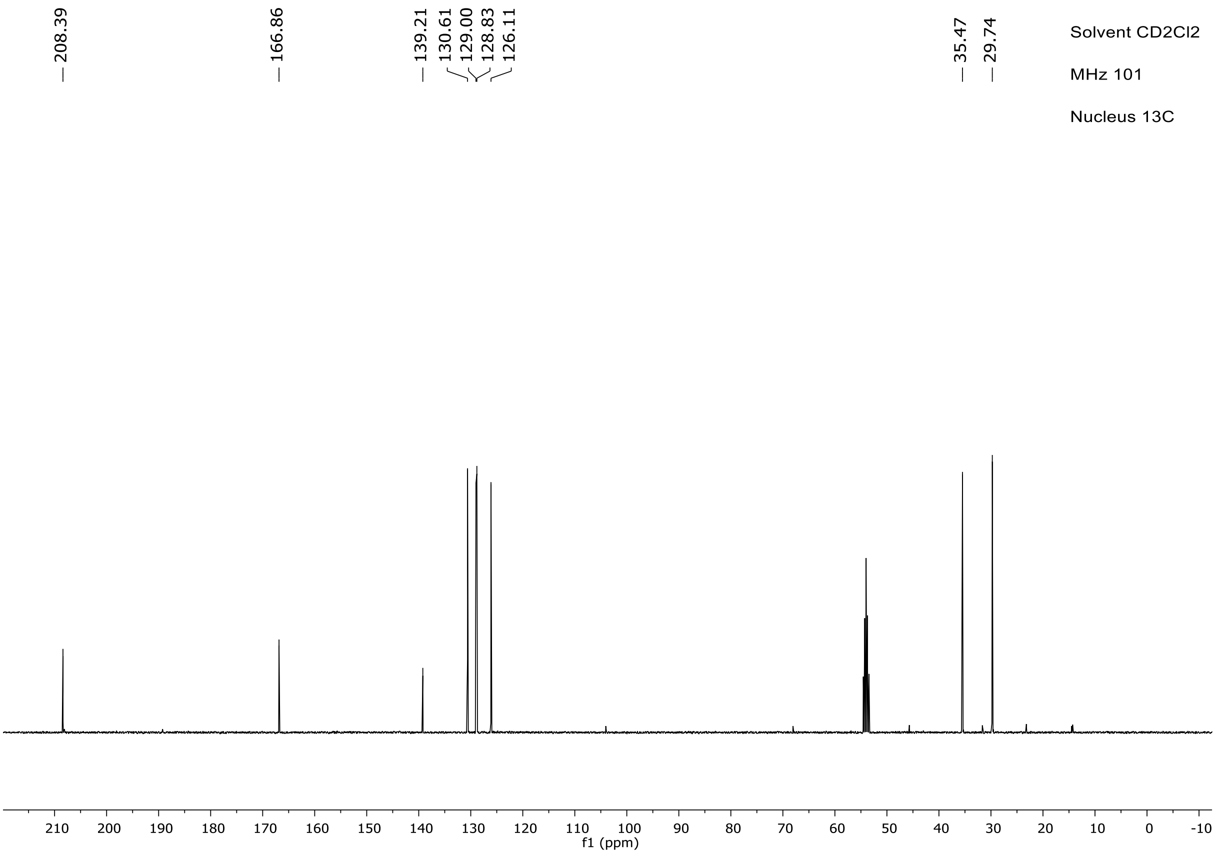
net formula	$C_{15}H_{20}O_4$
M_r/g mol^{-1}	264.317
crystal size/mm	0.060 × 0.040 × 0.020
T/K	100(2)
radiation	'Mo Kα
diffractometer	'Bruker D8Venture'
crystal system	triclinic
space group	*P*1bar
a/Å	4.6714(3)
b/Å	11.2377(7)
c/Å	26.8507(16)
α/°	97.287(2)
β/°	93.2382(18)
γ/°	98.729(2)
V/Å^3	1377.84(15)
Z	4
calc. density/g cm^{-3}	1.27421(14)
μ/mm^{-1}	0.091
absorption correction	multi-scan
transmission factor range	0.8961–0.9580
refls. measured	14065
R_{int}	0.0311
mean σ(I)/I	0.0420
θ range	2.75–25.40
observed refls.	3596

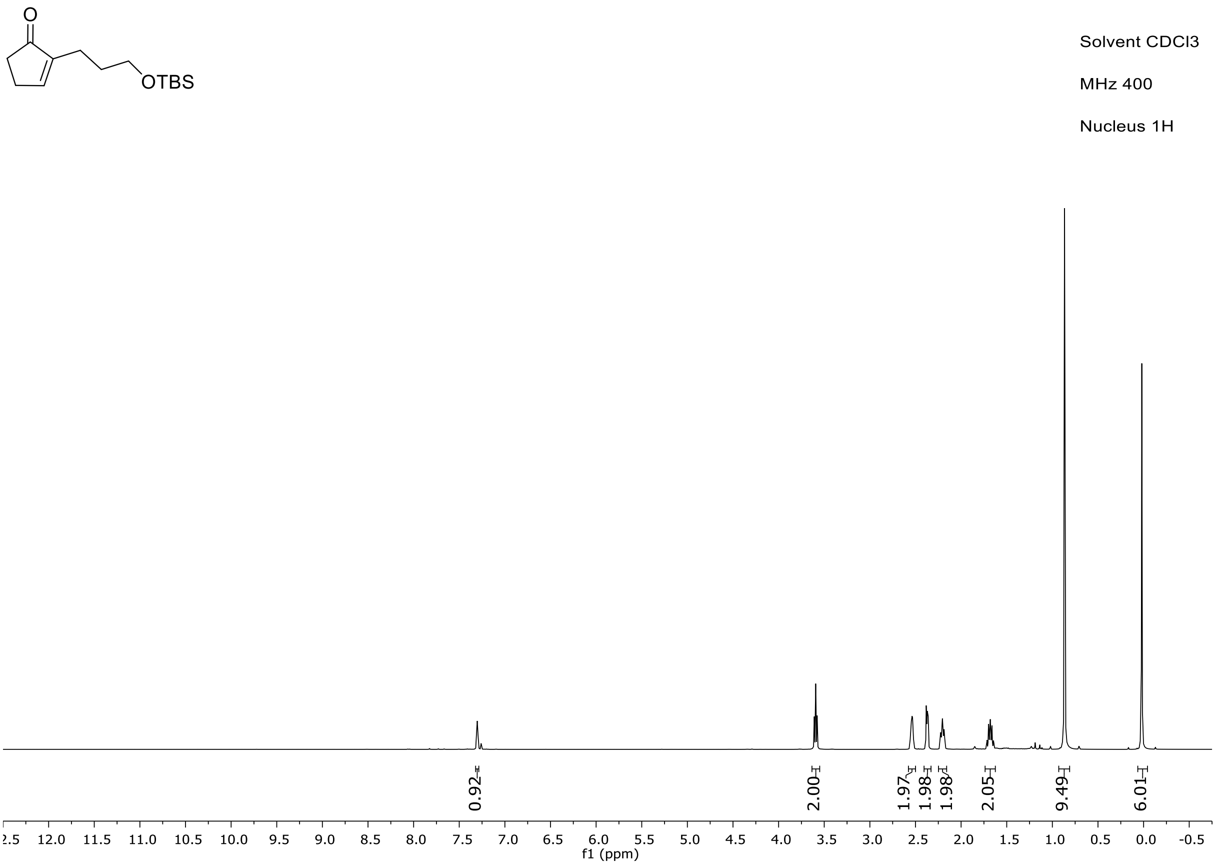
x, y (weighting scheme)	0.0535, 0.3445
hydrogen refinement	mixed
refls in refinement	5033
parameters	357
restraints	0
$R(F_{\text{obs}})$	0.0430
$R_{\text{w}}(F^2)$	0.1158
S	1.039
shift/error$_{\text{max}}$	0.001
max electron density/e Å^{-3}	0.243
min electron density/e Å^{-3}	−0.206

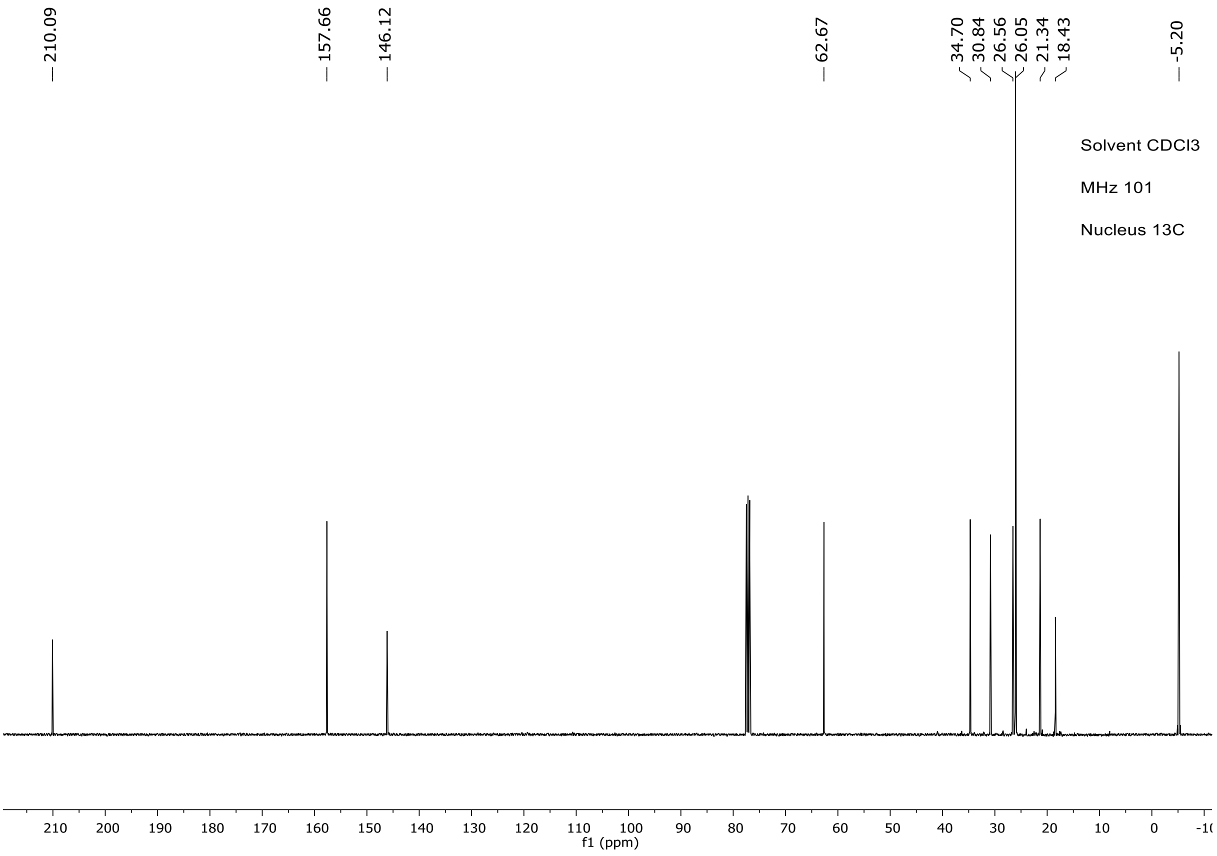


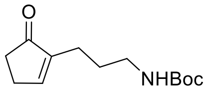
6.1.4 ^{1}H, ^{13}C and ^{19}F NMR Spectra


O
S
Solvent CD2Cl2
MHz 400
Nucleus 1H
0.84
0.92
0.90
0.83
2.00
1.99
f1 (ppm)
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


208.39
166.86
139.21
130.61
129.00
128.83
126.11
35.47
29.74
Solvent CD2Cl2
MHz 101
Nucleus 13C
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


O
OTBS
Solvent CDCl3
MHz 400
Nucleus 1H
0.92
2.00
1.97
1.98
1.98
2.05
9.49
6.01
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

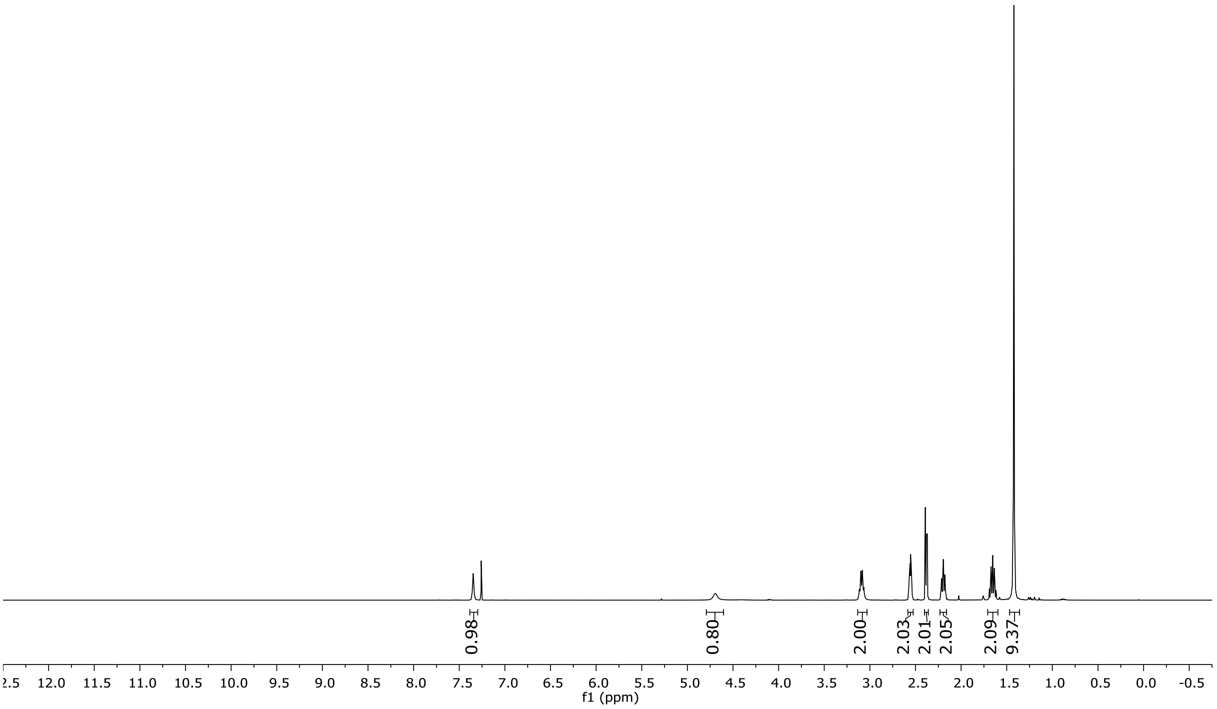

210.09
157.66
146.12
62.67
34.70
30.84
26.56
26.05
21.34
18.43
-5.20
Solvent CDCl3
MHz 101
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



Solvent CDCl3

MHz 400

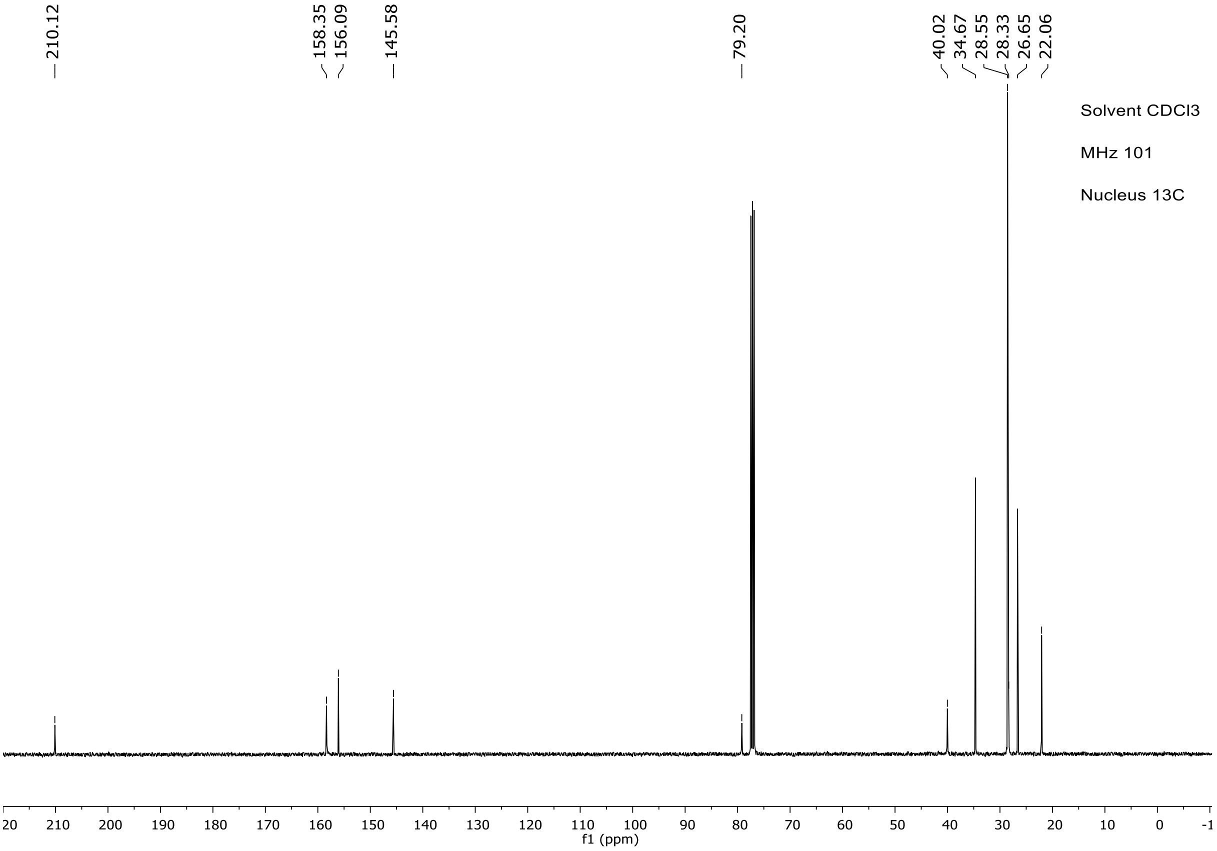
Nucleus 1H

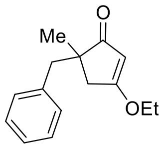


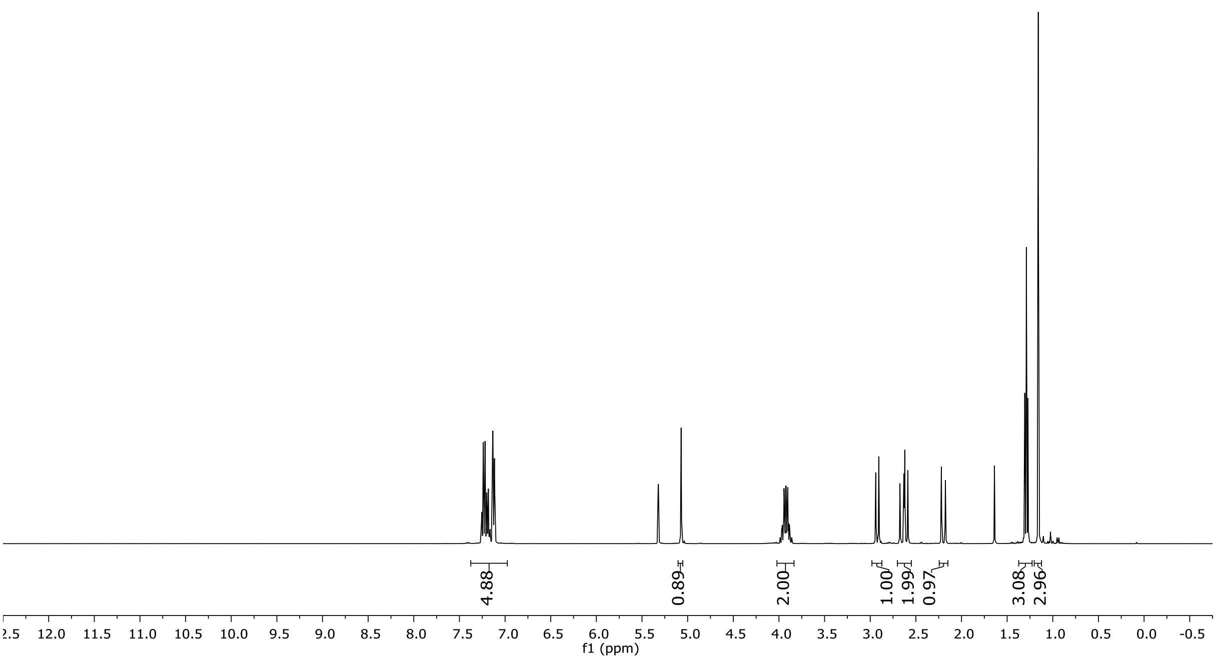
Solvent CDCl3

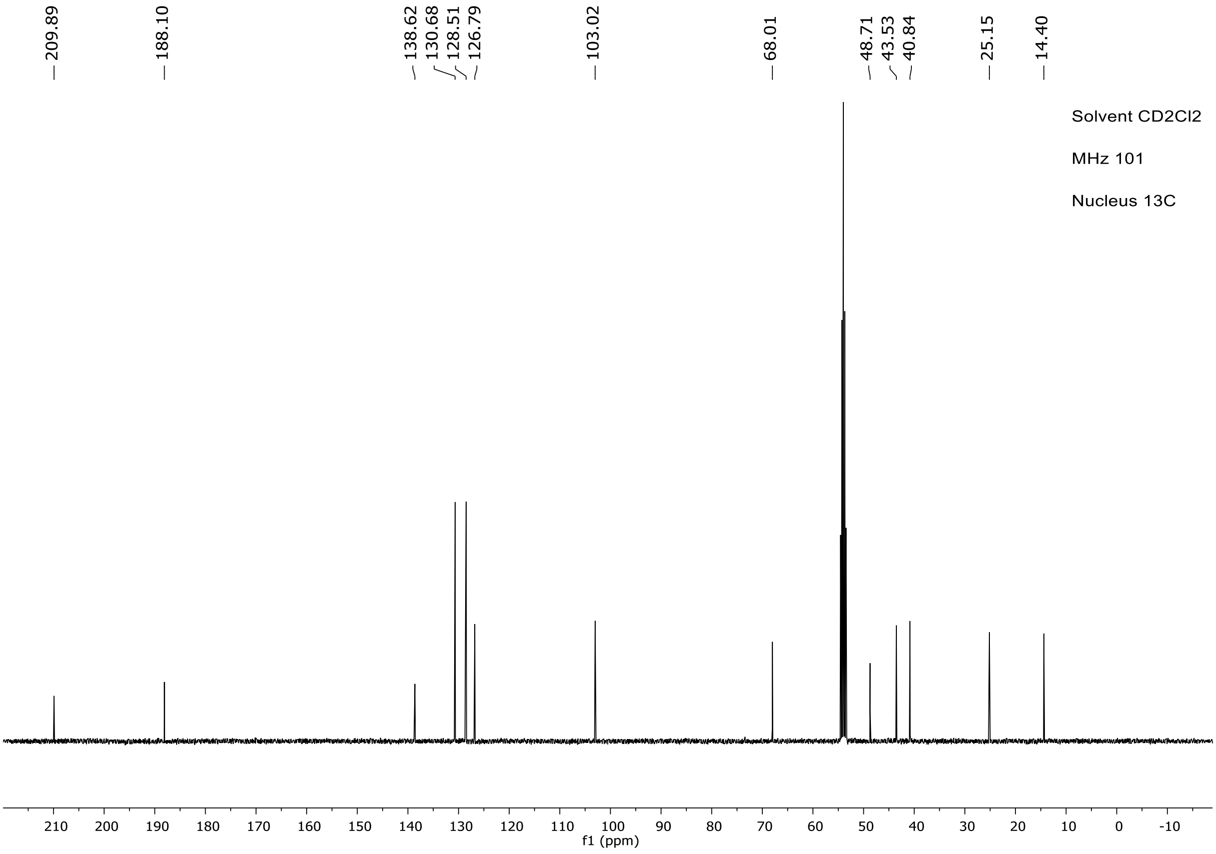
MHz 101

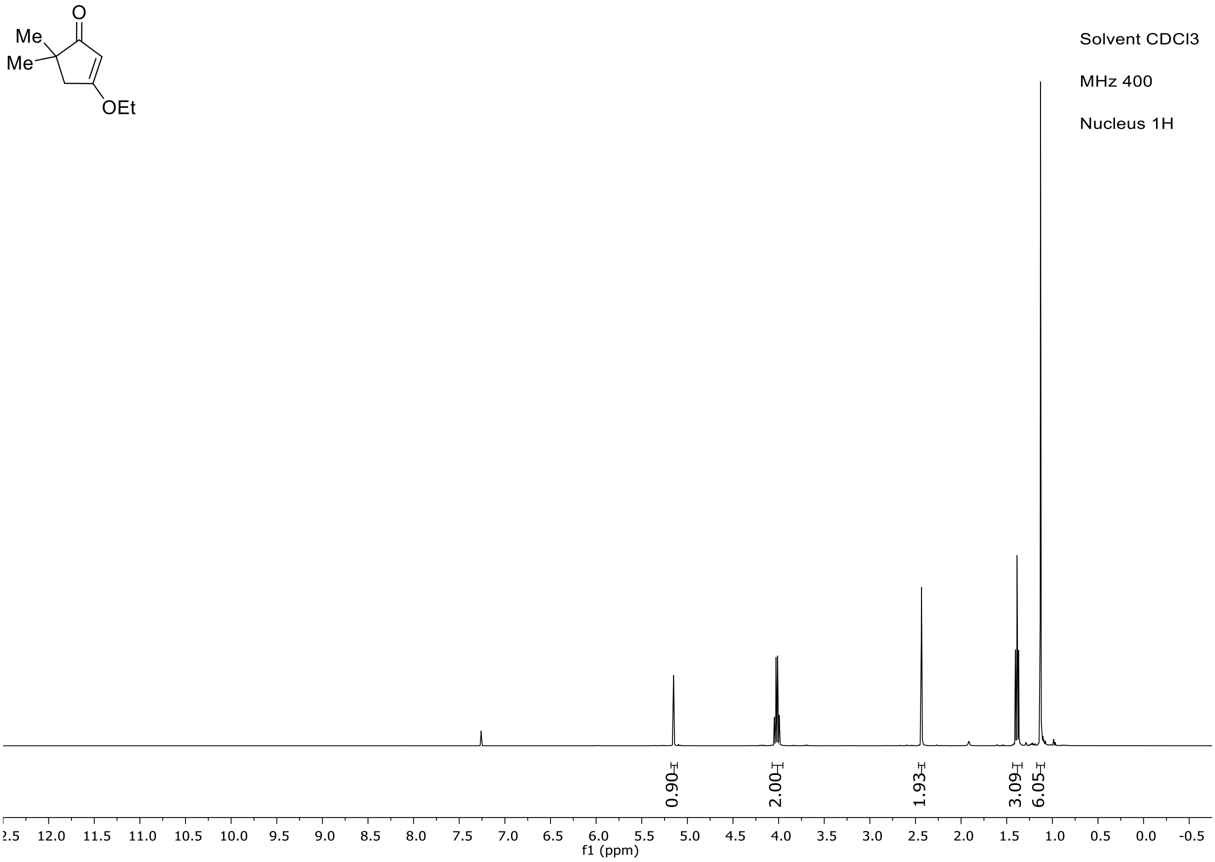
Nucleus 13C

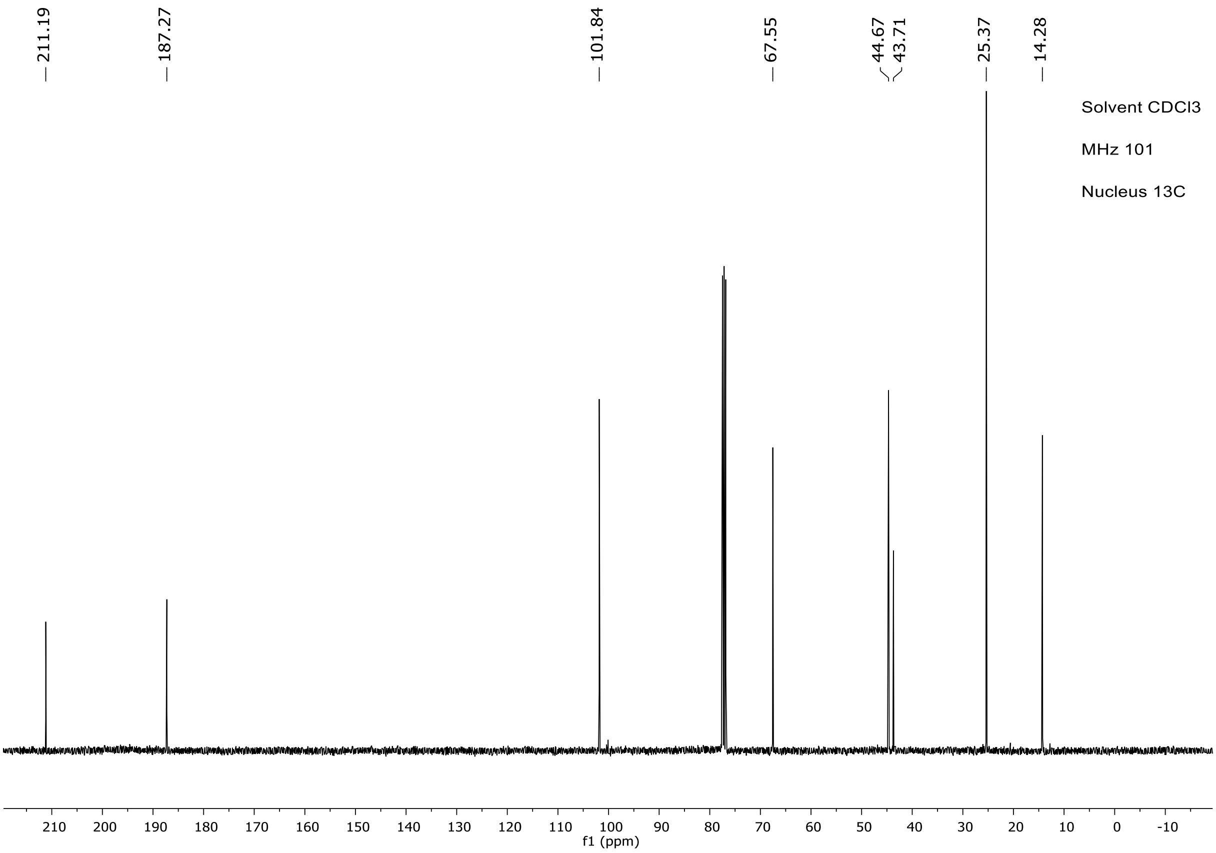


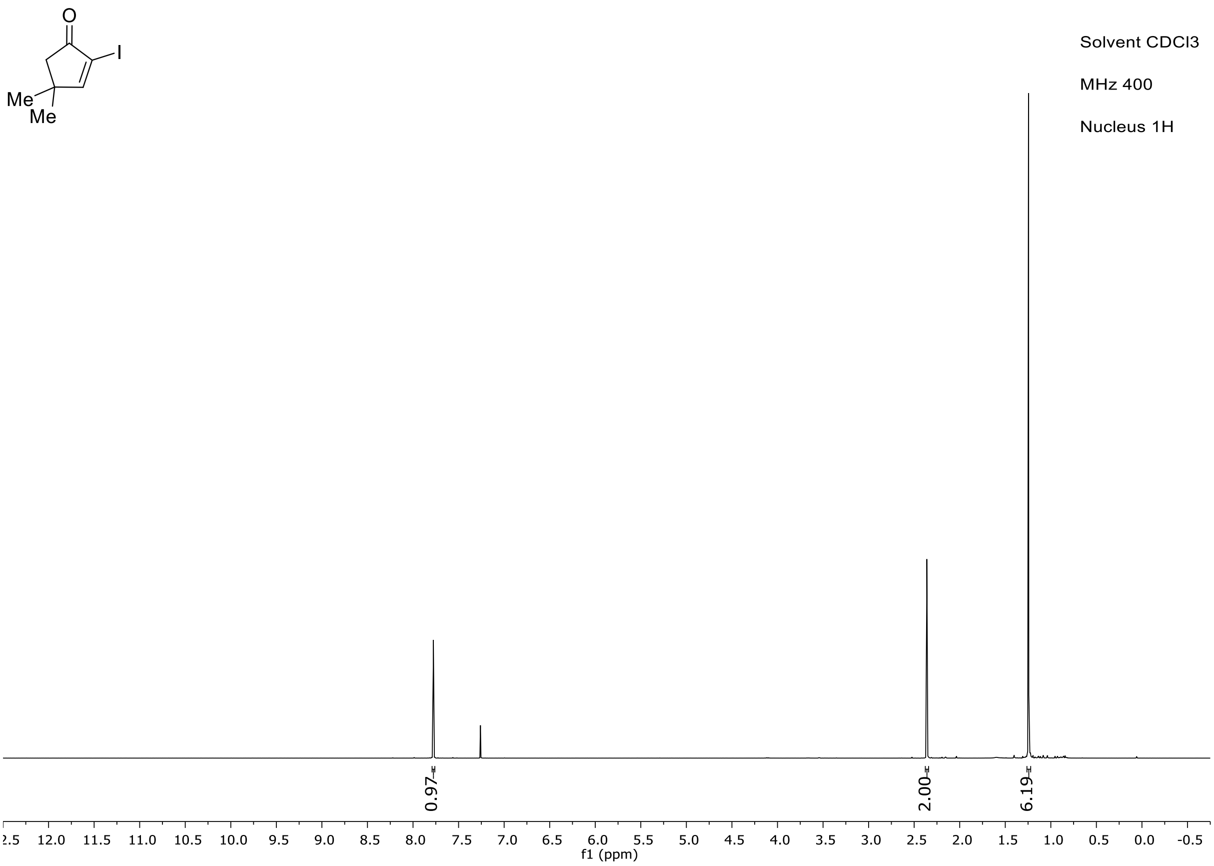

Me
O
OEt

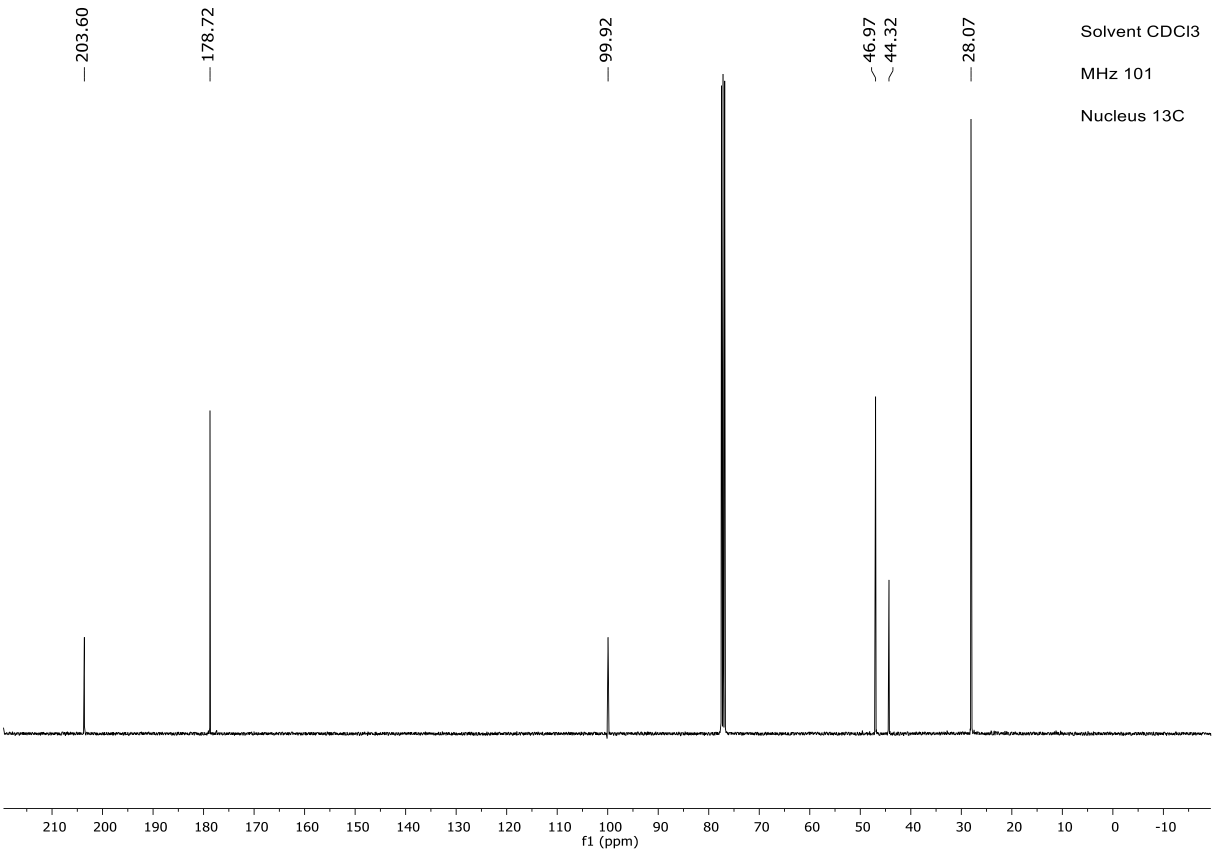

Solvent CD2Cl2
MHz 400
Nucleus 1H
4.88
0.89
2.00
1.00
1.99
0.97
3.08
2.96
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

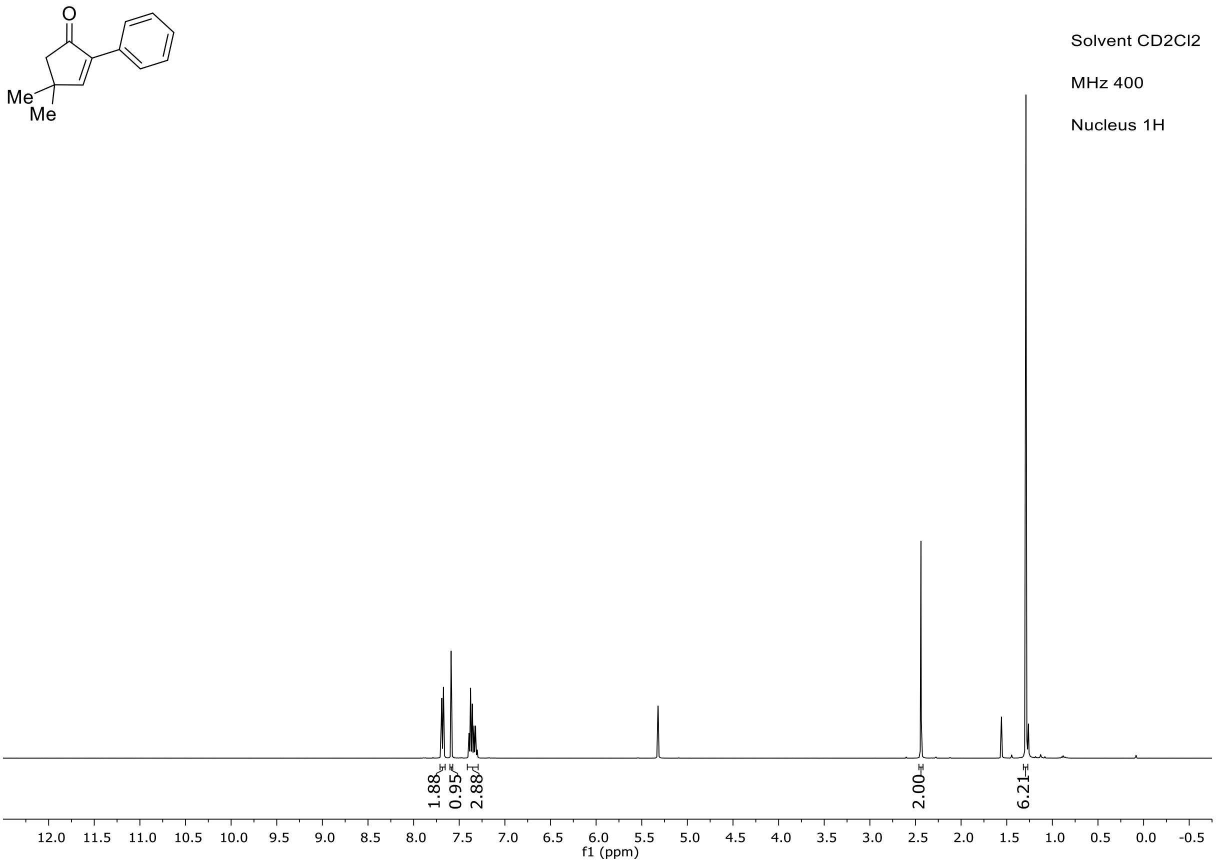

209.89
188.10
138.62
130.68
128.51
126.79
103.02
68.01
48.71
43.53
40.84
25.15
14.40
Solvent CD2Cl2
MHz 101
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

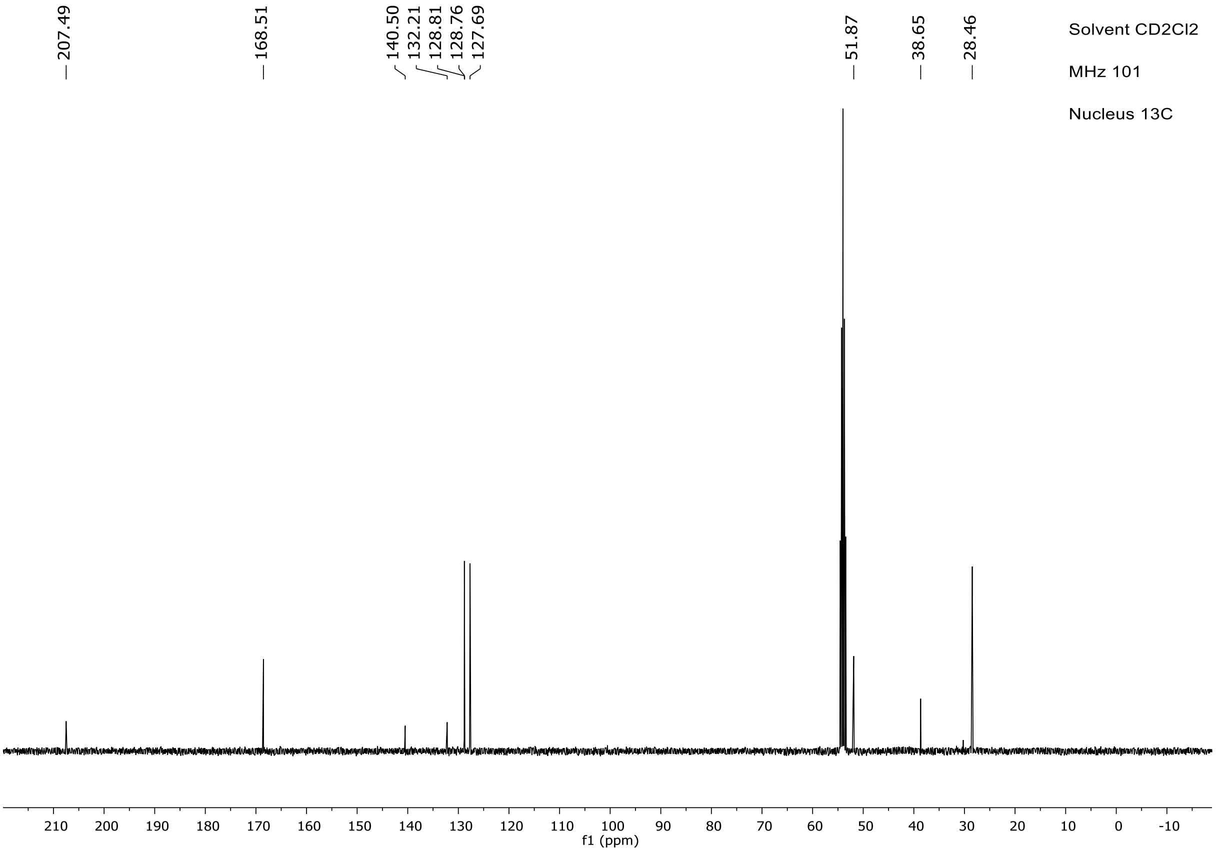

O
Me
Me
OEt
Solvent CDCl3
MHz 400
Nucleus 1H
0.90
2.00
1.93
3.09
6.05
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

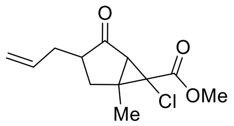

211.19
187.27
101.84
67.55
44.67
43.71
25.37
14.28
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
I
Me
Me
Solvent CDCl3
MHz 400
Nucleus 1H
0.97
2.00
6.19
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


203.60
178.72
99.92
46.97
44.32
28.07
Solvent CDCl3
MHz 101
Nucleus 13C
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)


O
Me
Me
Solvent CD2Cl2
MHz 400
Nucleus 1H
1.88
0.95
2.88
2.00
6.21
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

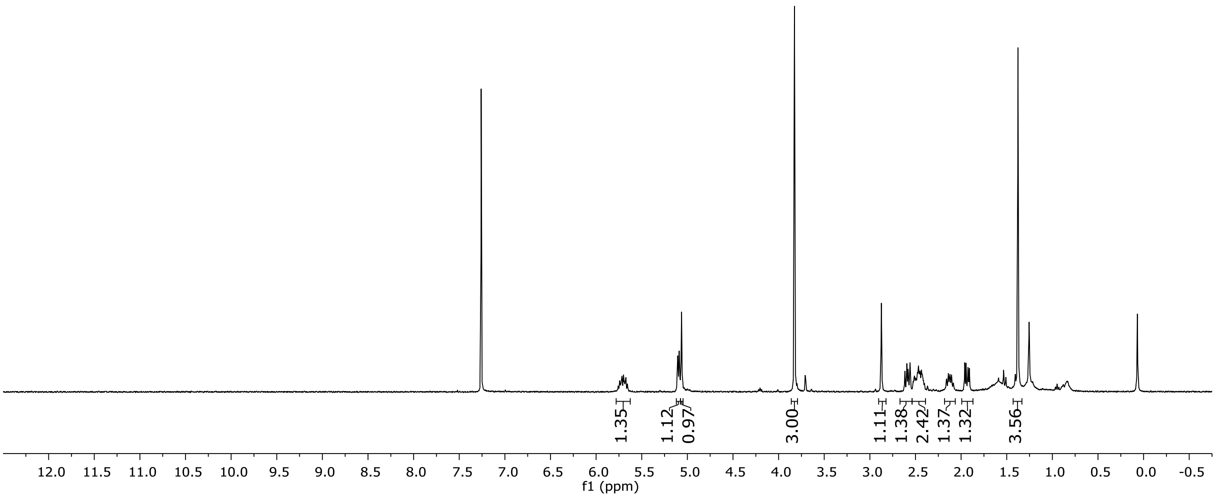

207.49
168.51
140.50
132.21
128.81
128.76
127.69
51.87
38.65
28.46
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

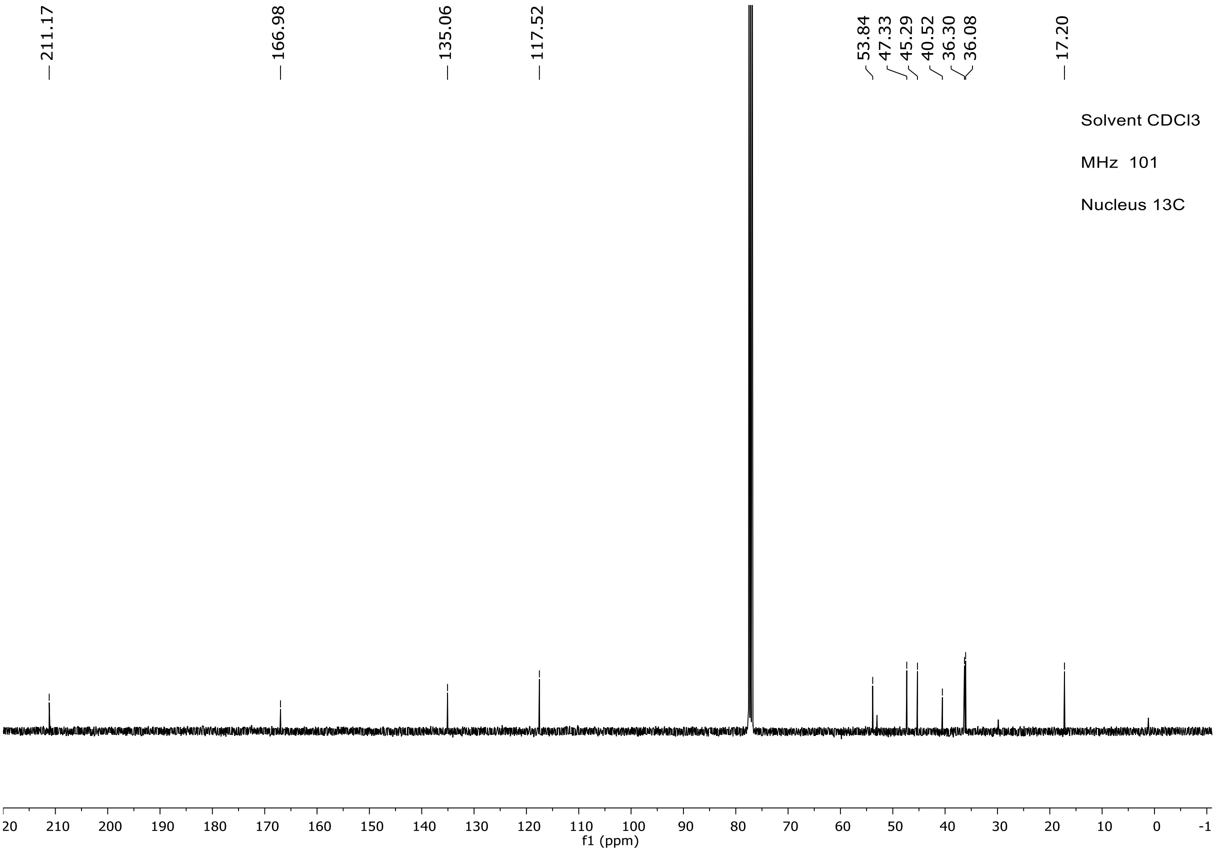


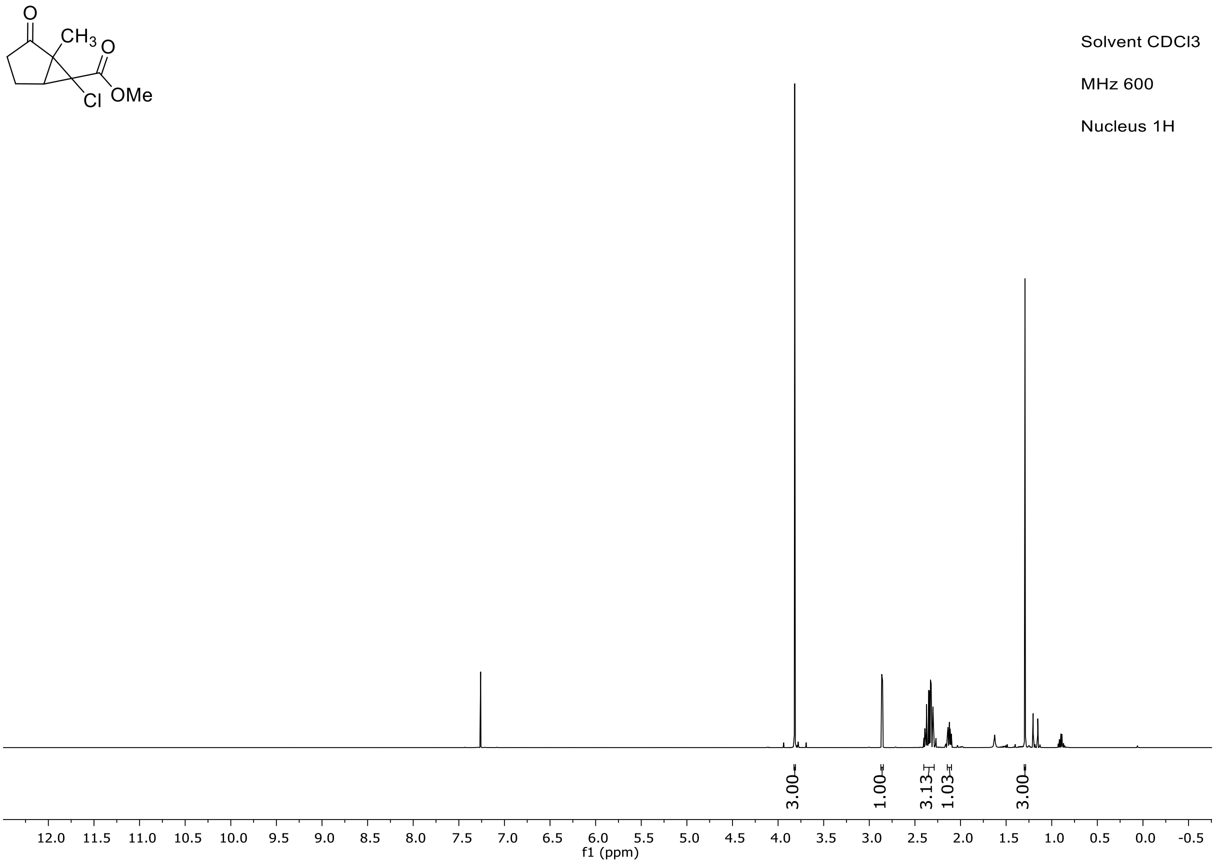
Solvent CDCl3

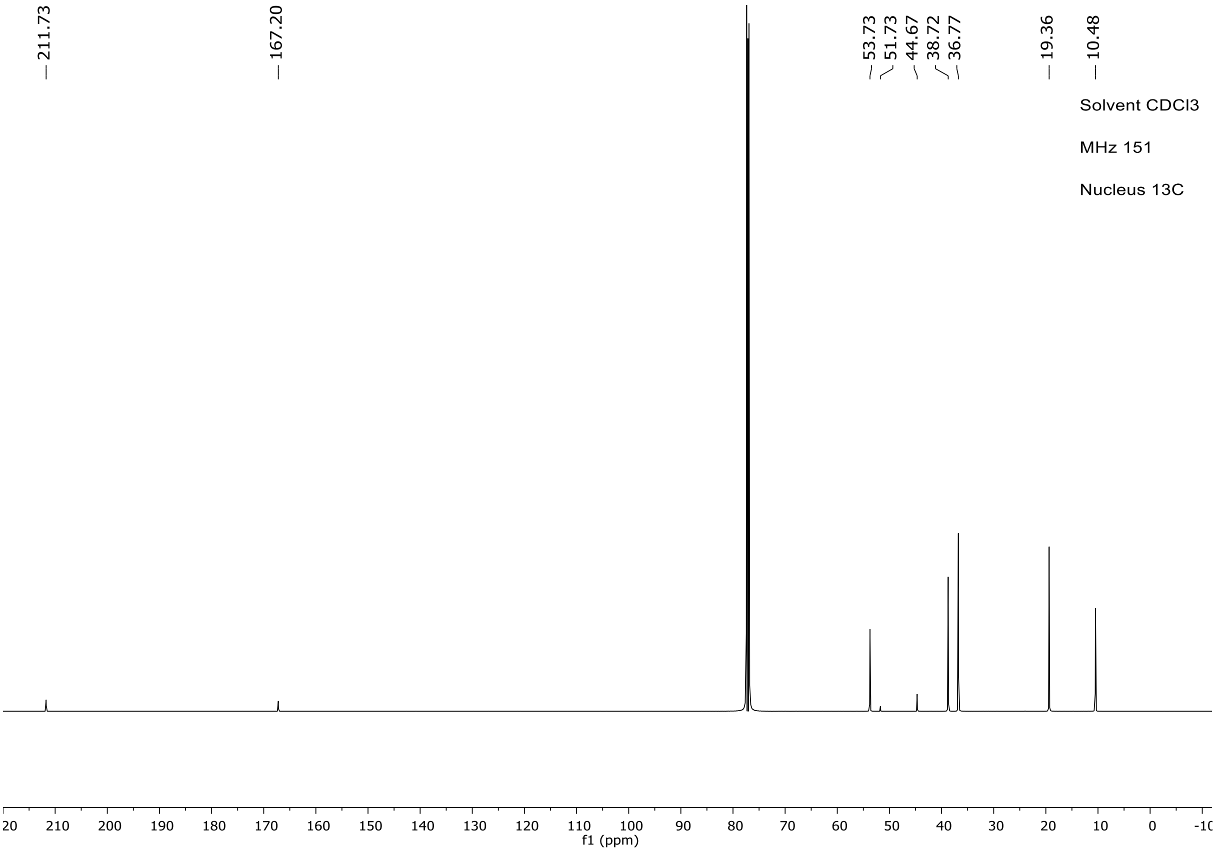
MHz 400

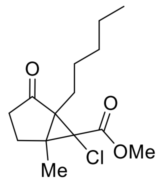
Nucleus 1H

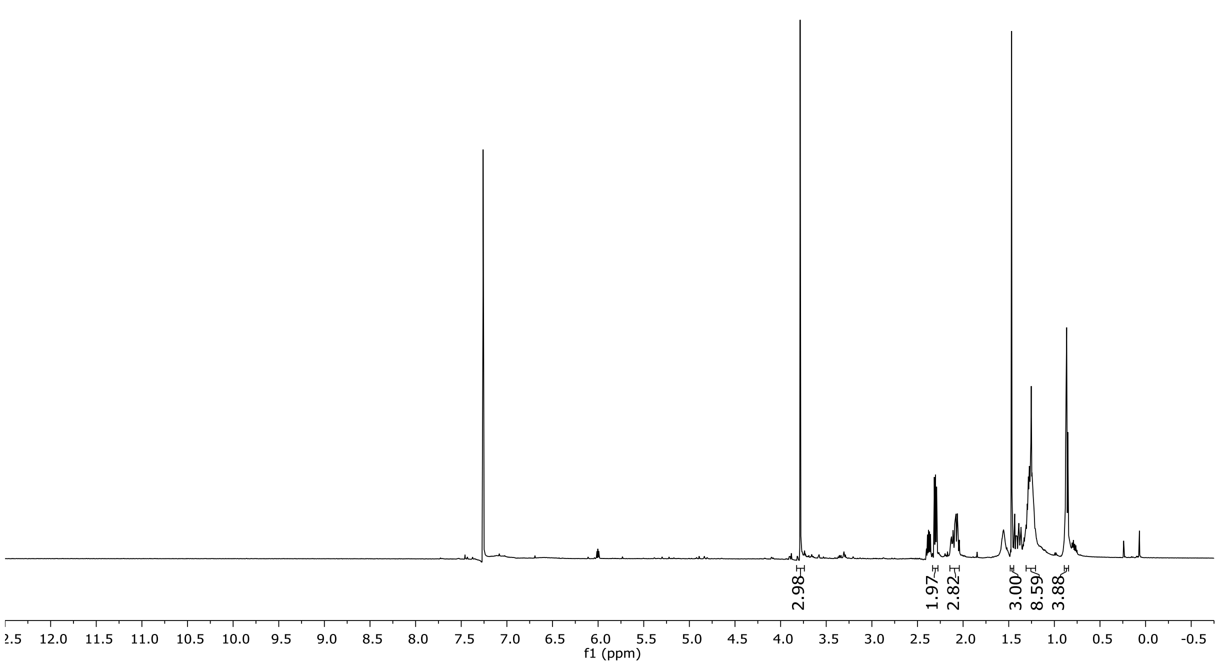


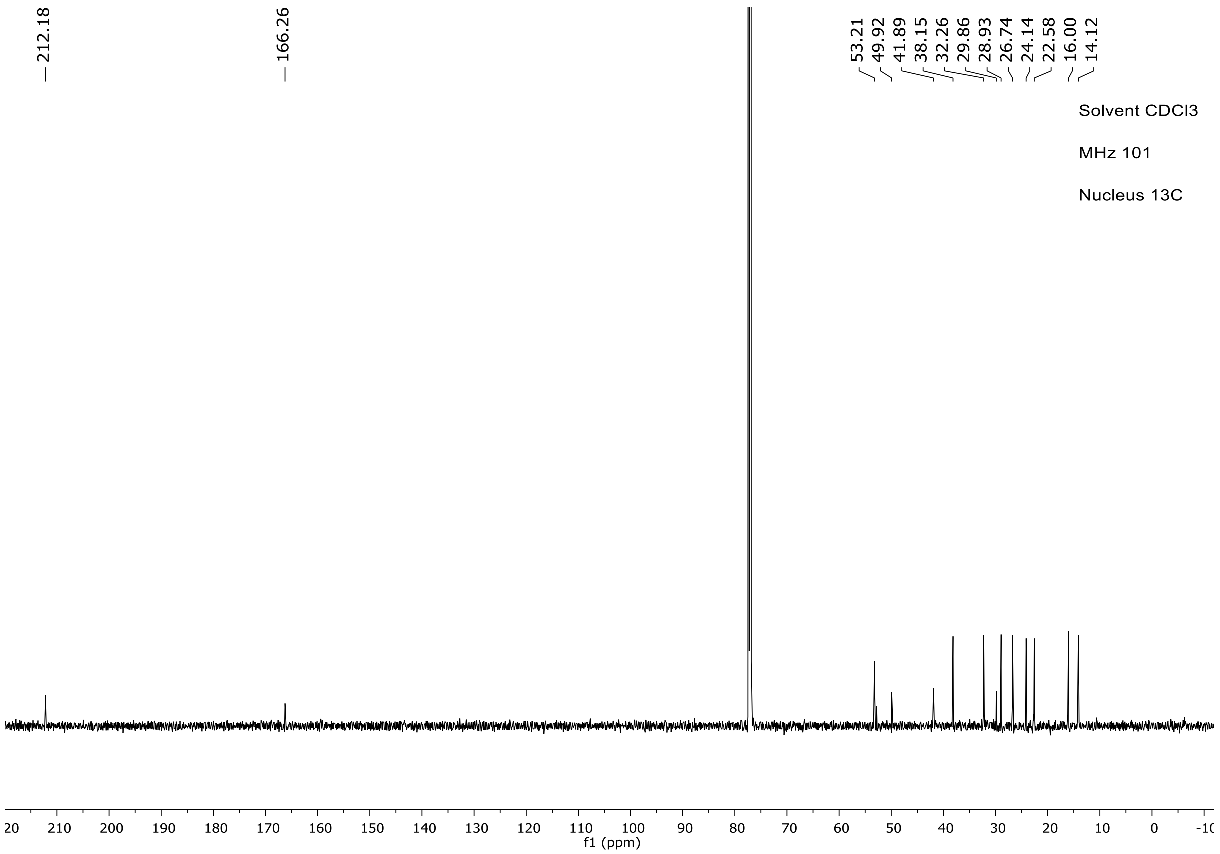


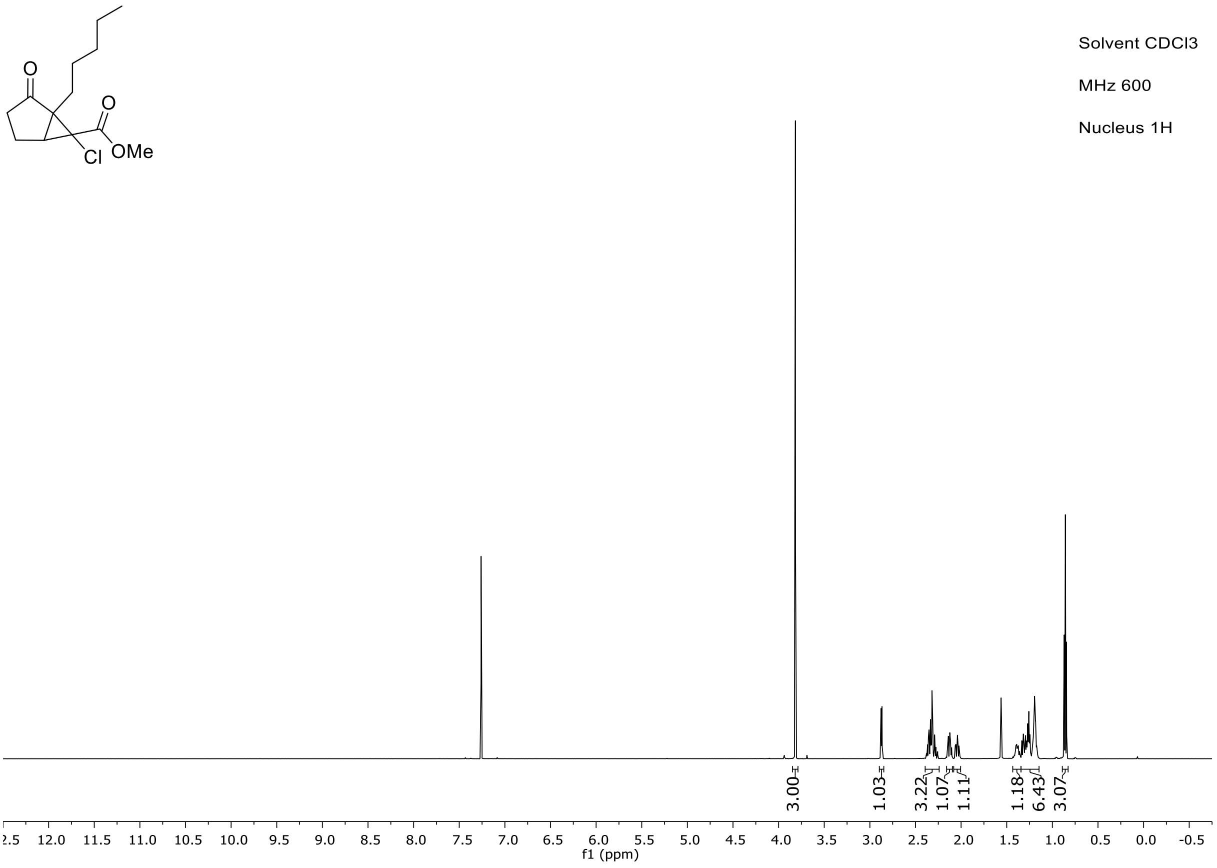

O
CH3
O
OMe
Cl
Solvent CDCl3
MHz 600
Nucleus 1H
3.00
1.00
3.13
1.03
3.00
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

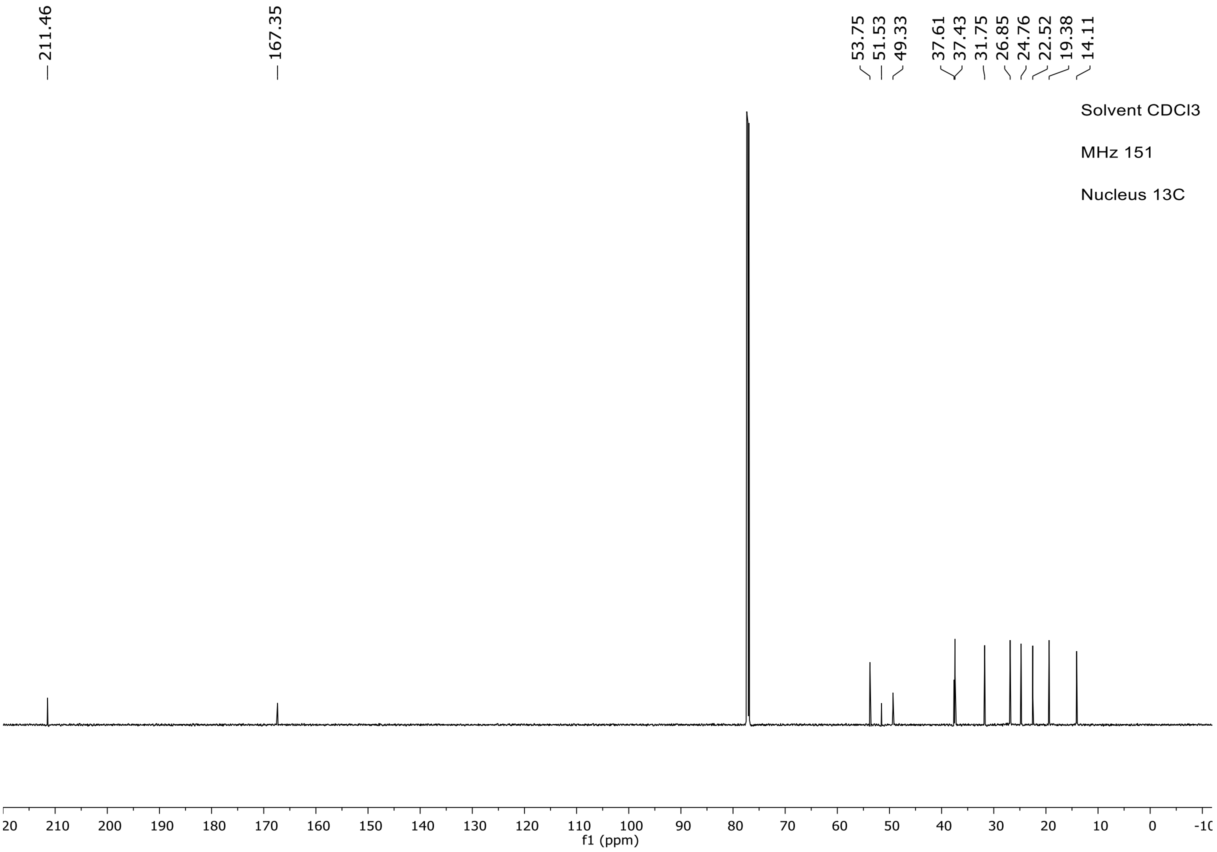

211.73
167.20
53.73
51.73
44.67
38.72
36.77
19.36
10.48
Solvent CDCl3
MHz 151
Nucleus 13C
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1(
f1 (ppm)

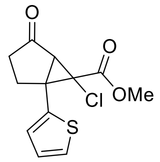

O
O
OMe
Cl
Me


Solvent CDCl3
MHz 400
Nucleus 1H
2.98
1.97
2.82
3.00
8.59
3.88
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


212.18
166.26
53.21
49.92
41.89
38.15
32.26
29.86
28.93
26.74
24.14
22.58
16.00
14.12
Solvent CDCl3
MHz 101
Nucleus 13C
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
Cl
OMe
Solvent CDCl3
MHz 600
Nucleus 1H
3.00
1.03
3.22
1.07
1.11
1.18
6.43
3.07
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

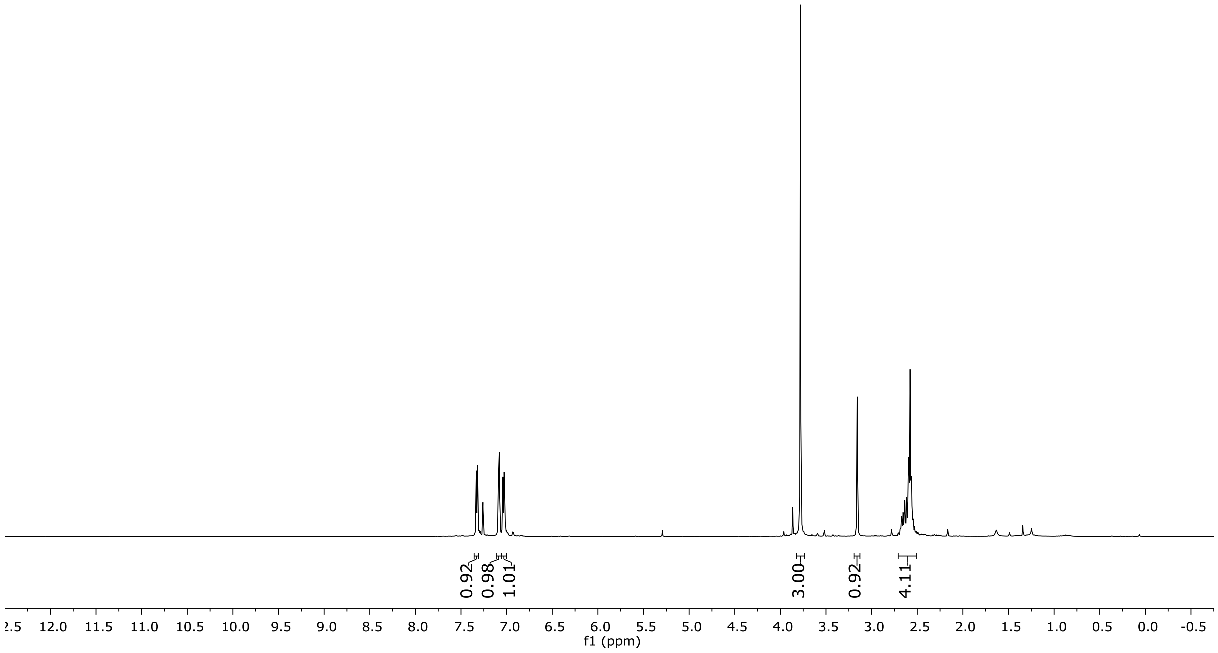

211.46
167.35
53.75
51.53
49.33
37.61
37.43
31.75
26.85
24.76
22.52
19.38
14.11
Solvent CDCl3
MHz 151
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



Solvent CDCl3

MHz 400

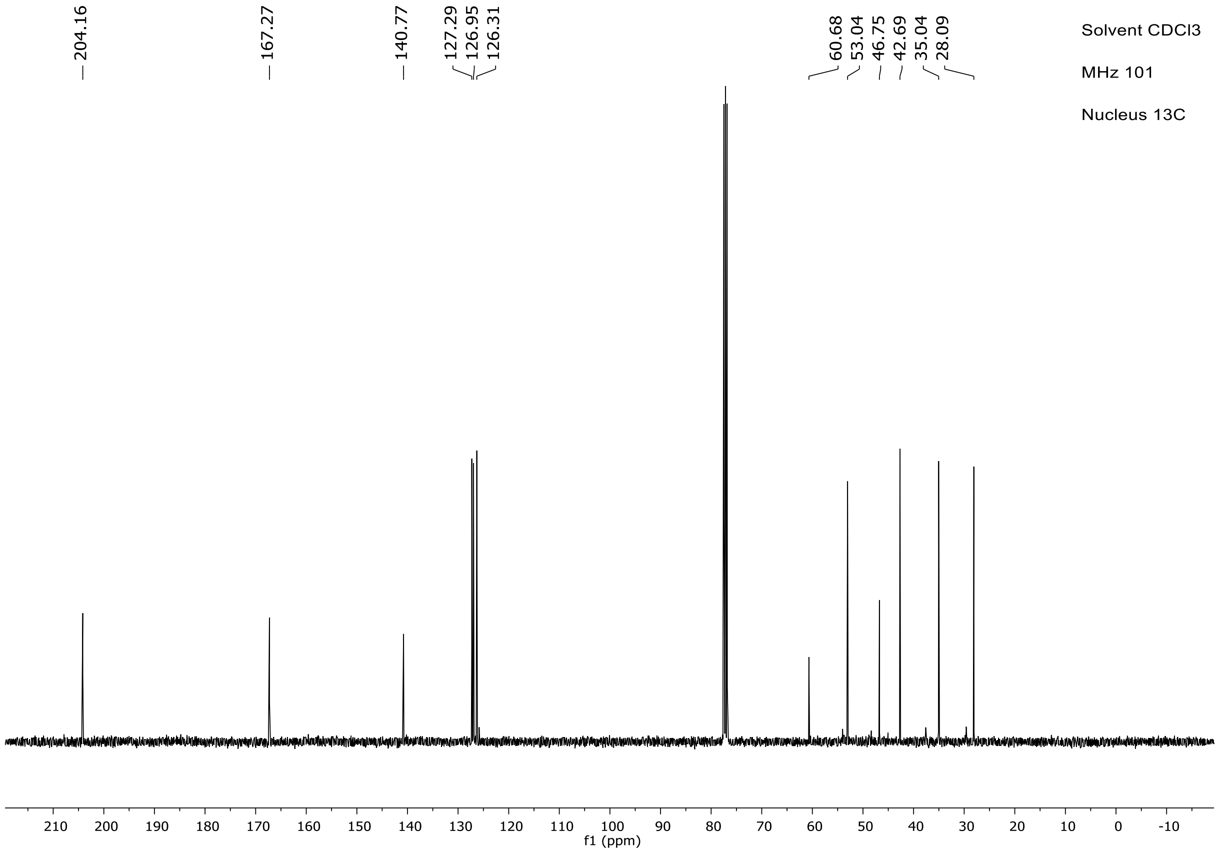
Nucleus 1H

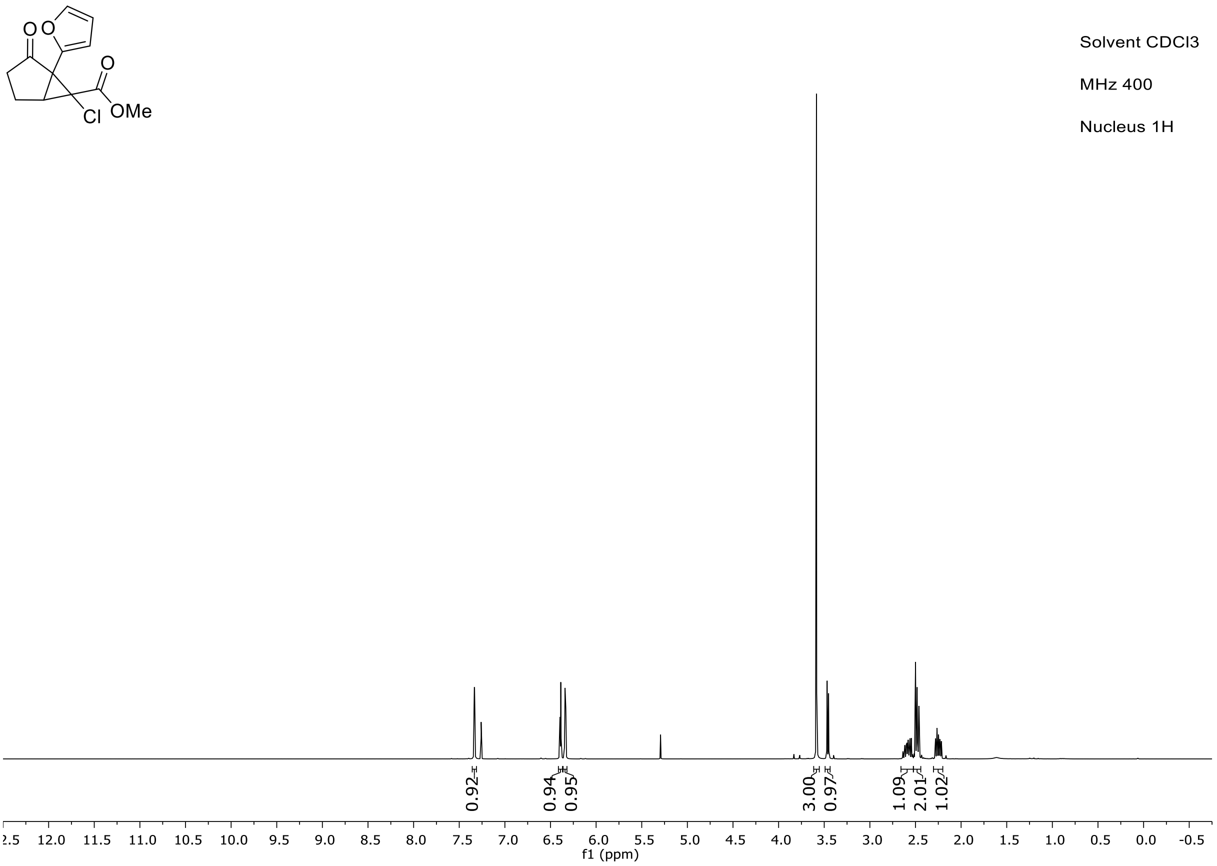


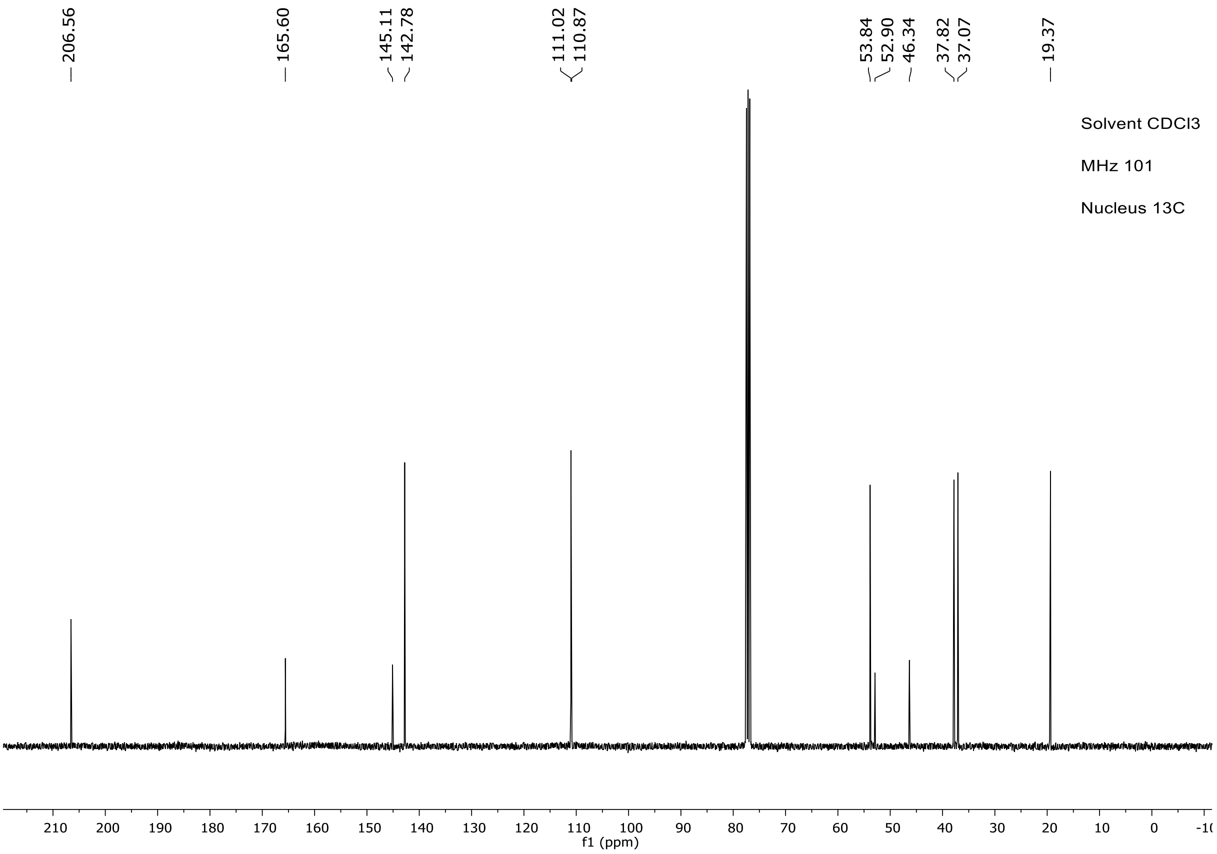
Solvent CDCl3

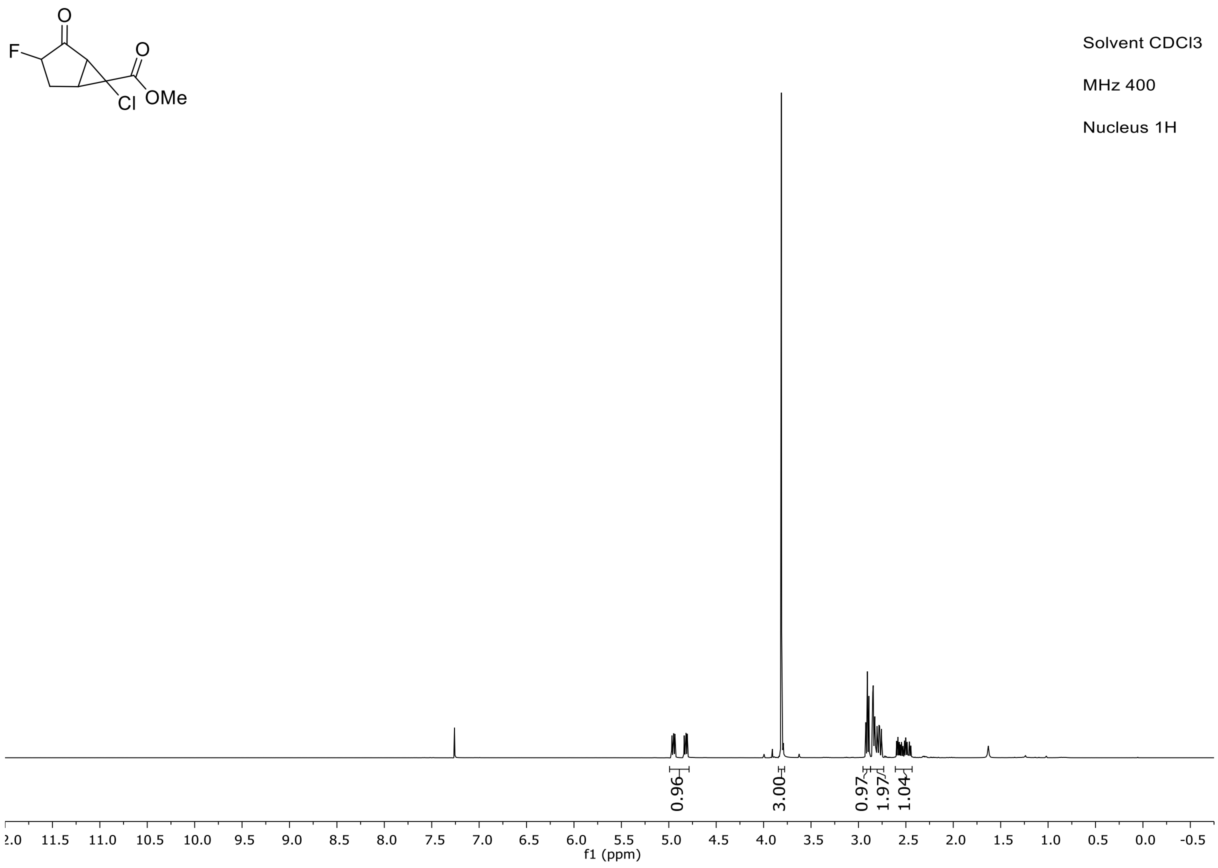
MHz 101

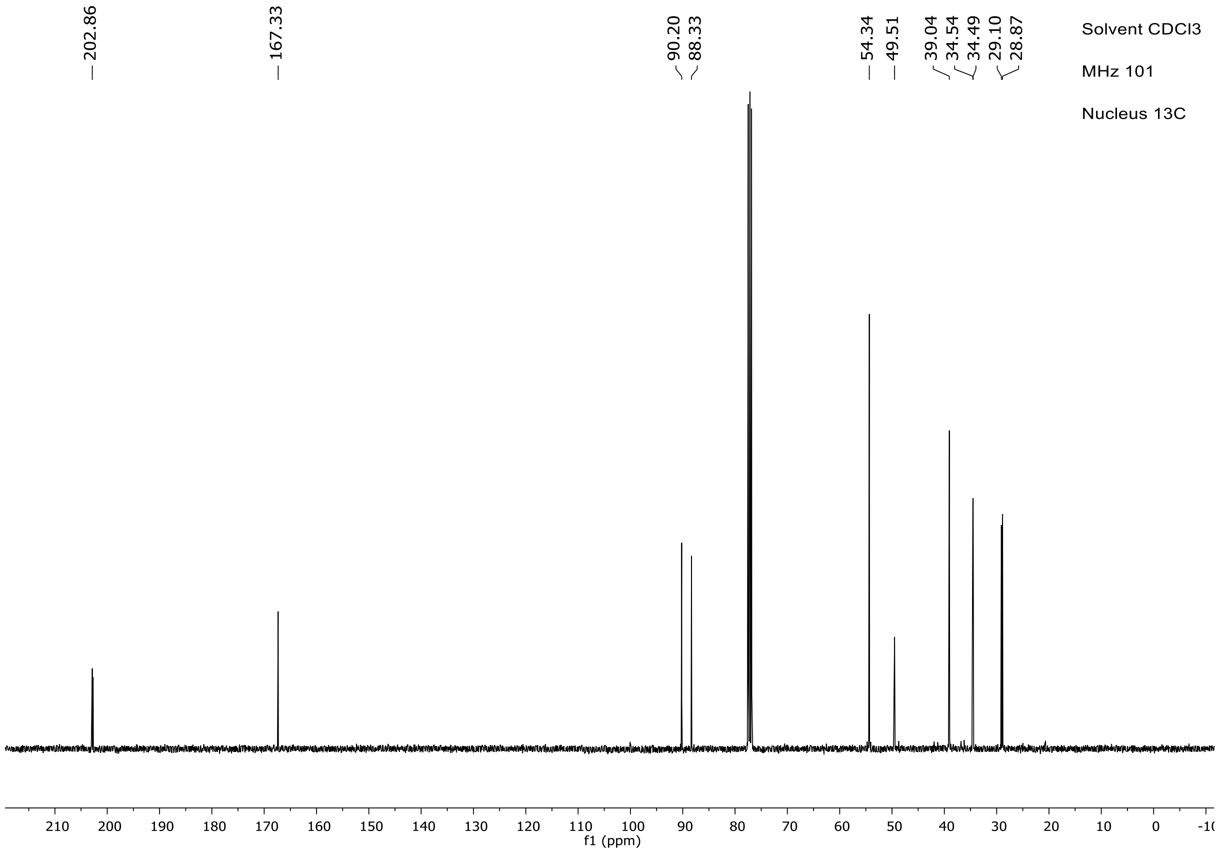
Nucleus 13C

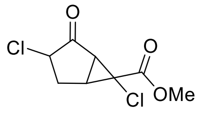



O
O
O
Cl
OMe
Solvent CDCl3
MHz 400
Nucleus 1H
0.92
0.94
0.95
3.00
0.97
1.09
2.01
1.02
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


206.56
165.60
145.11
142.78
111.02
110.87
53.84
52.90
46.34
37.82
37.07
19.37
Solvent CDCl3
MHz 101
Nucleus 13C
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)


O
F
O
Cl
OMe
Solvent CDCl3
MHz 400
Nucleus 1H
0.96
3.00
0.97
1.97
1.04
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

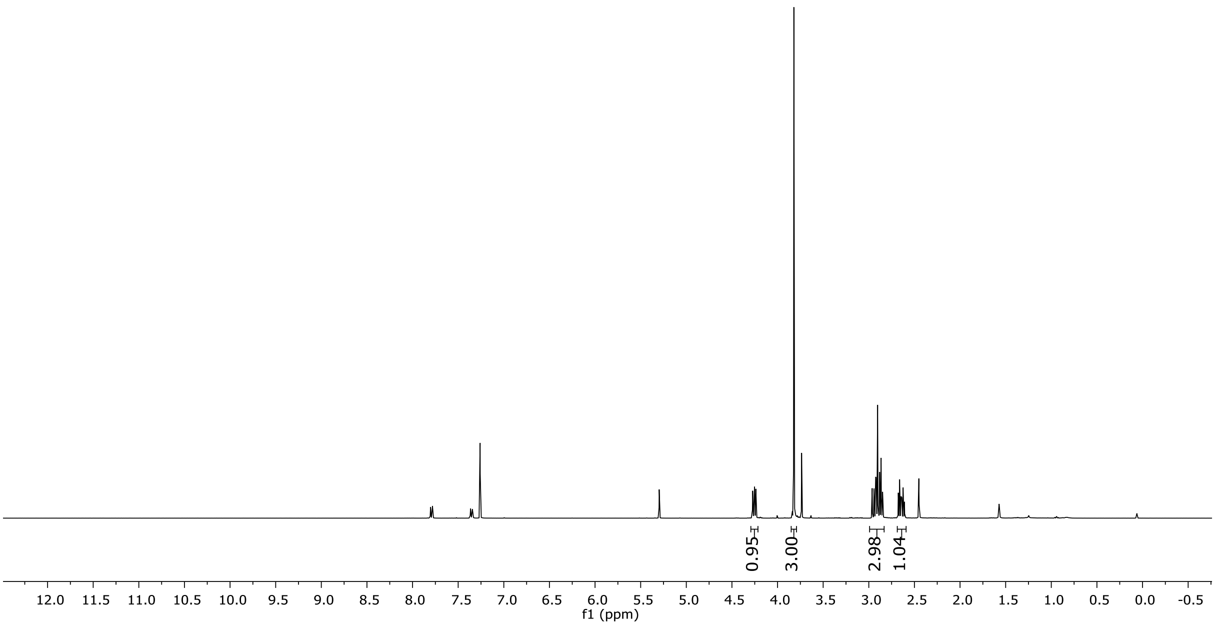

202.86
167.33
90.20
88.33
54.34
49.51
39.04
34.54
34.49
29.10
28.87
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

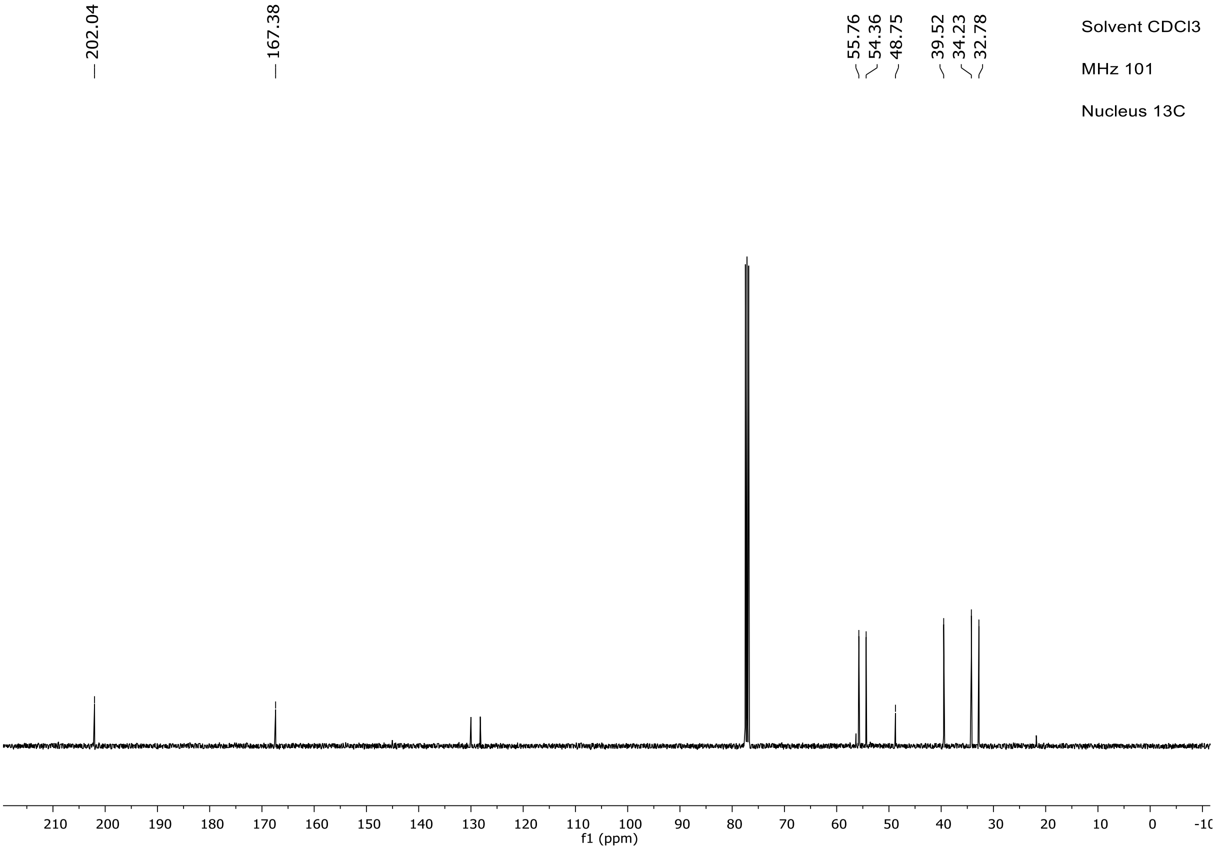


Solvent CDCl3

MHz 400

Nucleus 1H

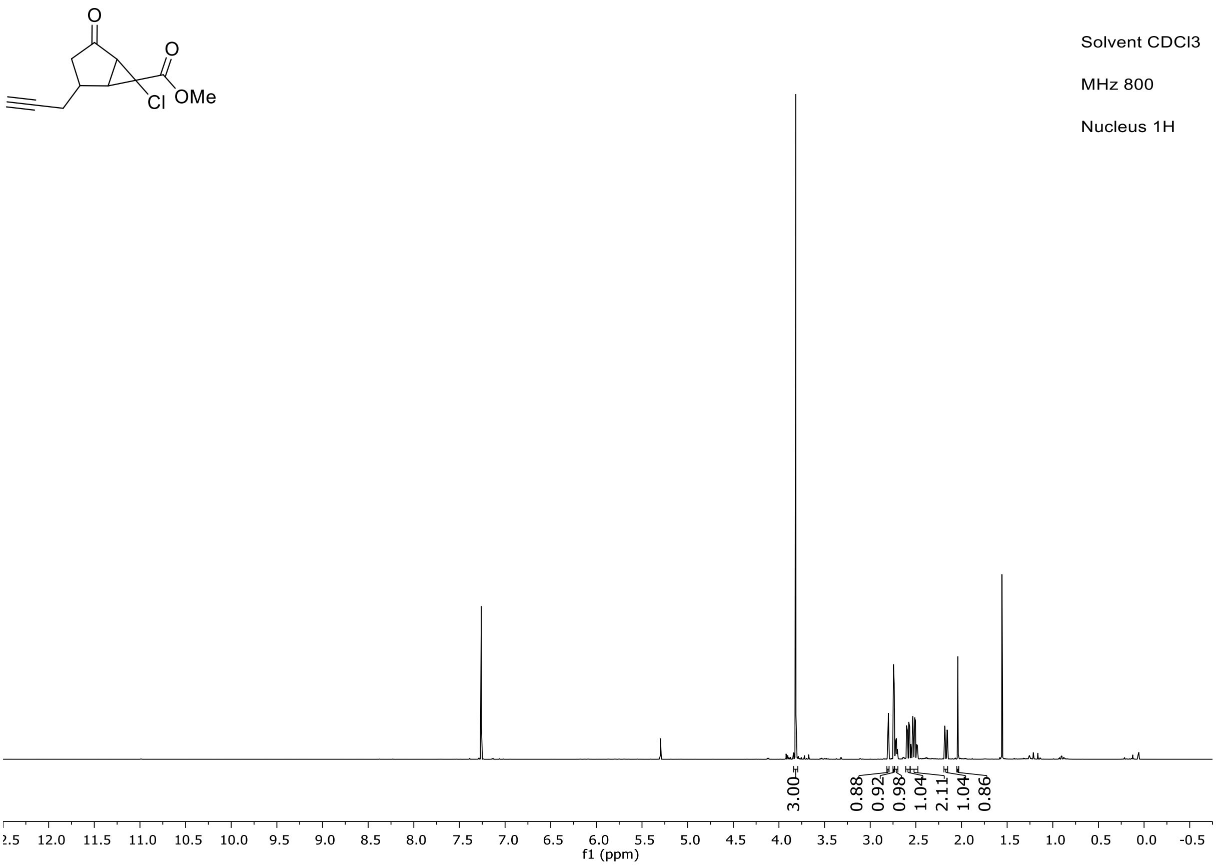


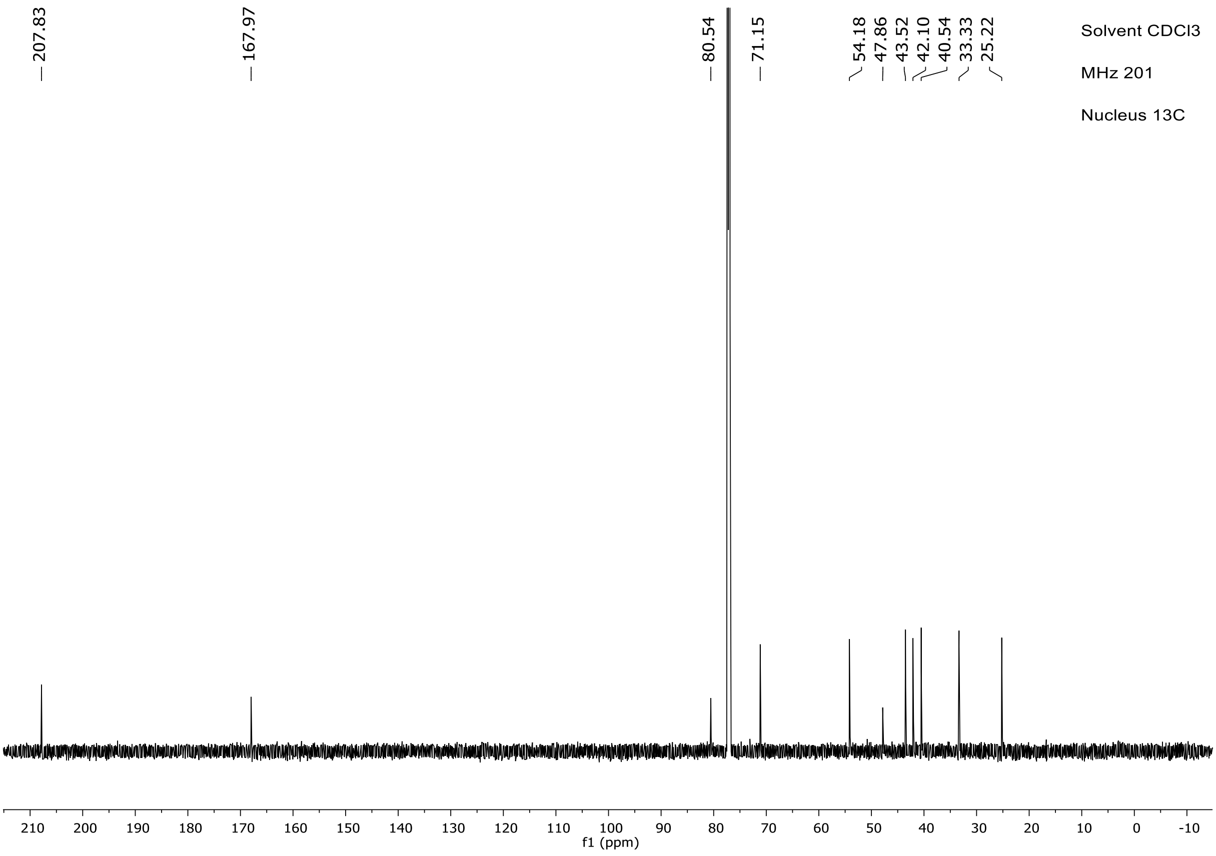


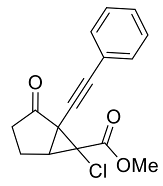
Solvent CDCl3

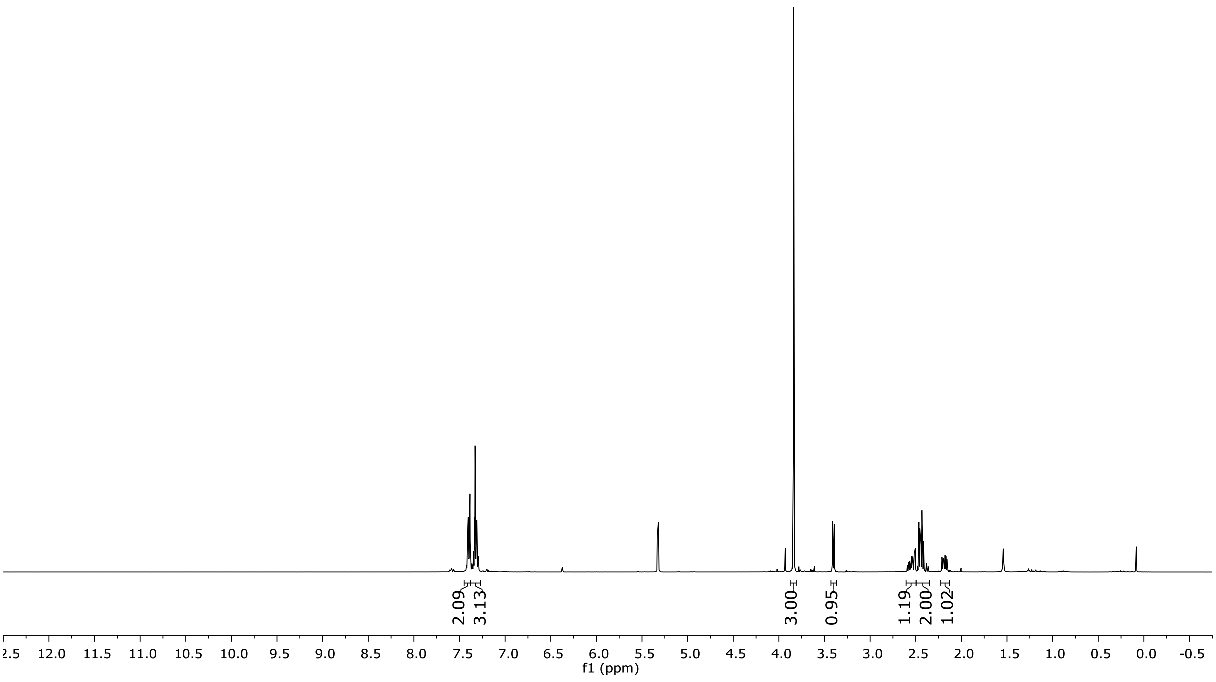
MHz 101

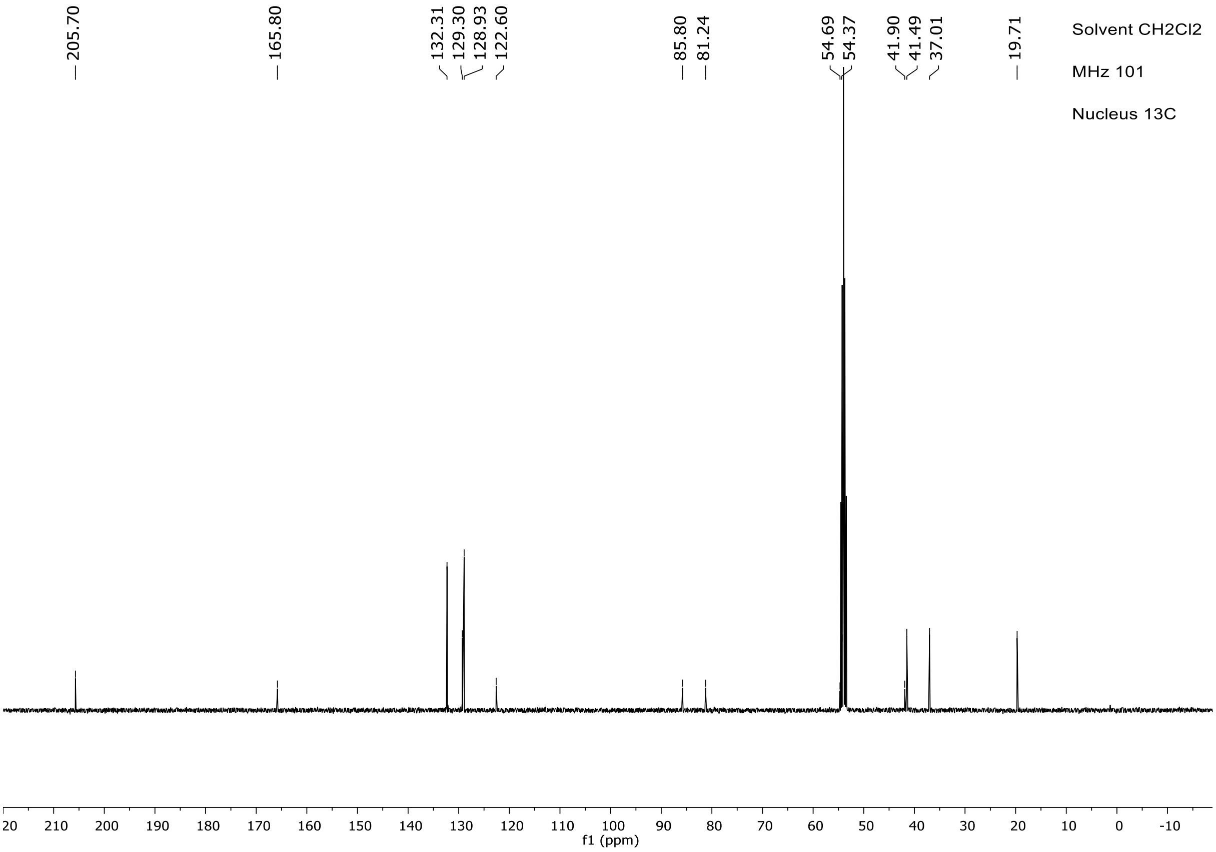
Nucleus 13C

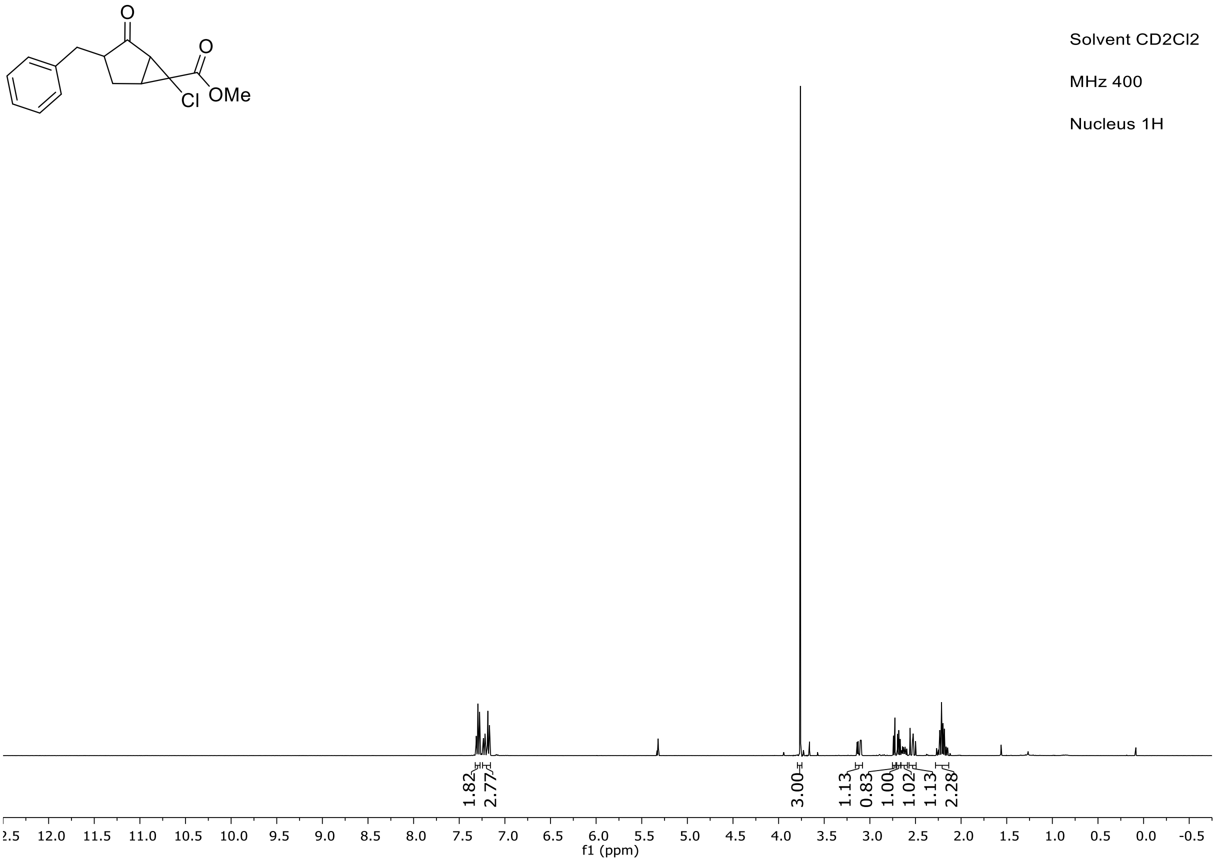

O
O
Cl
OMe
Solvent CDCl3
MHz 800
Nucleus 1H
3.00
0.88
0.92
0.98
1.04
2.11
1.04
0.86
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

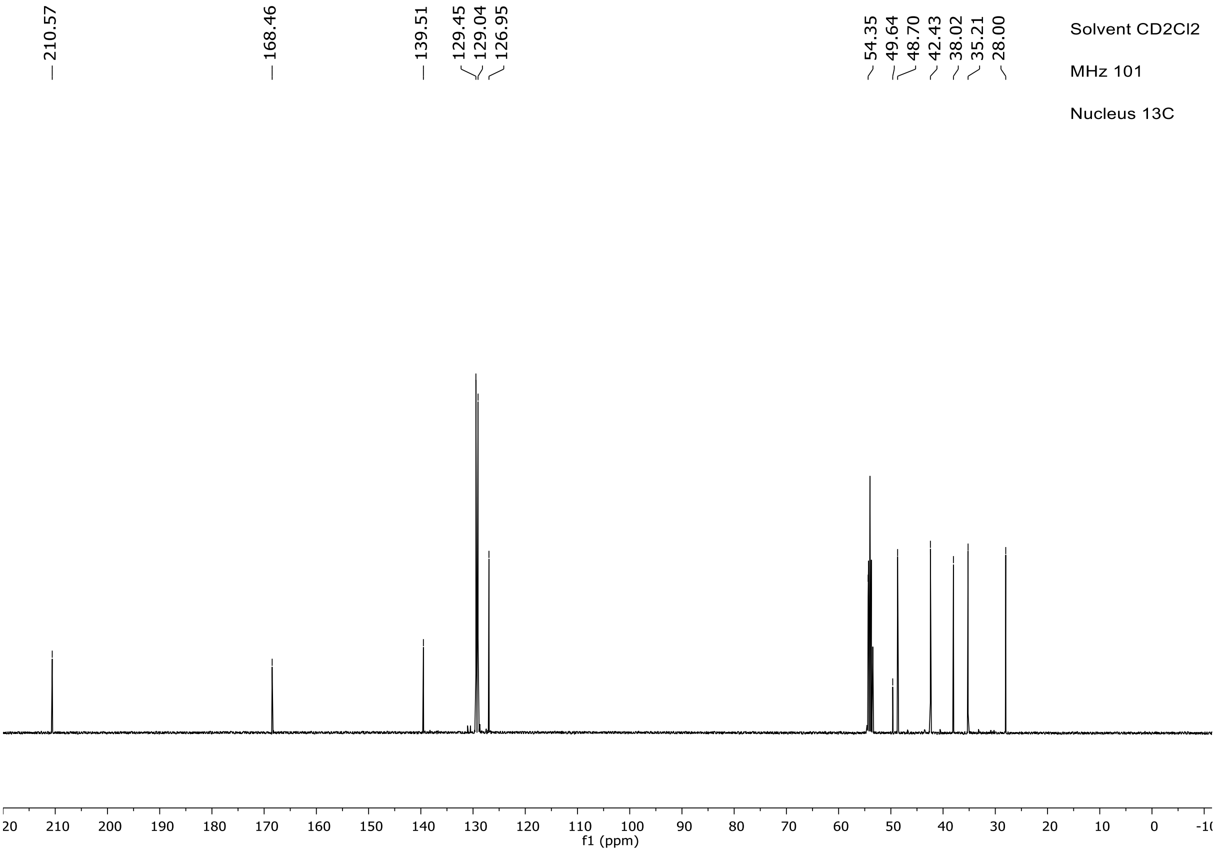

207.83
167.97
80.54
71.15
54.18
47.86
43.52
42.10
40.54
33.33
25.22
Solvent CDCl3
MHz 201
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

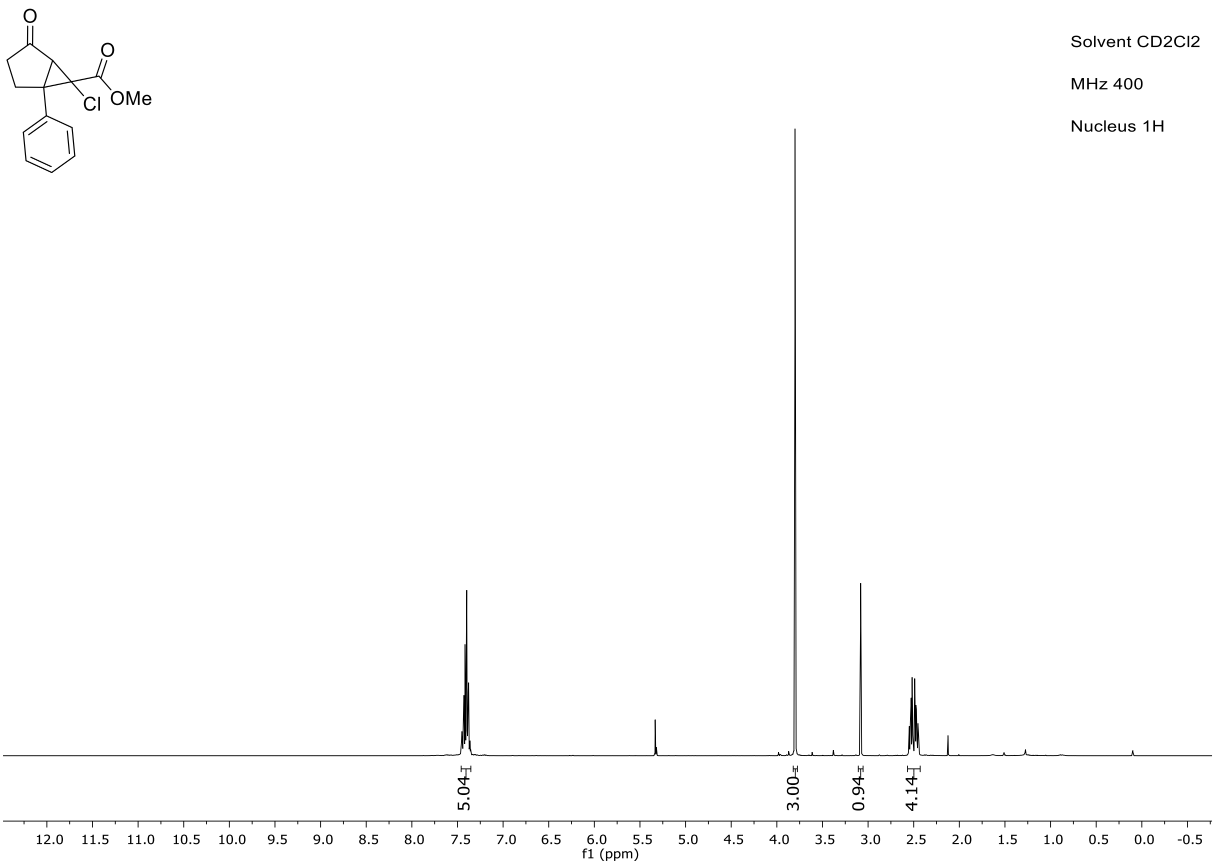

O
O
Cl
OMe

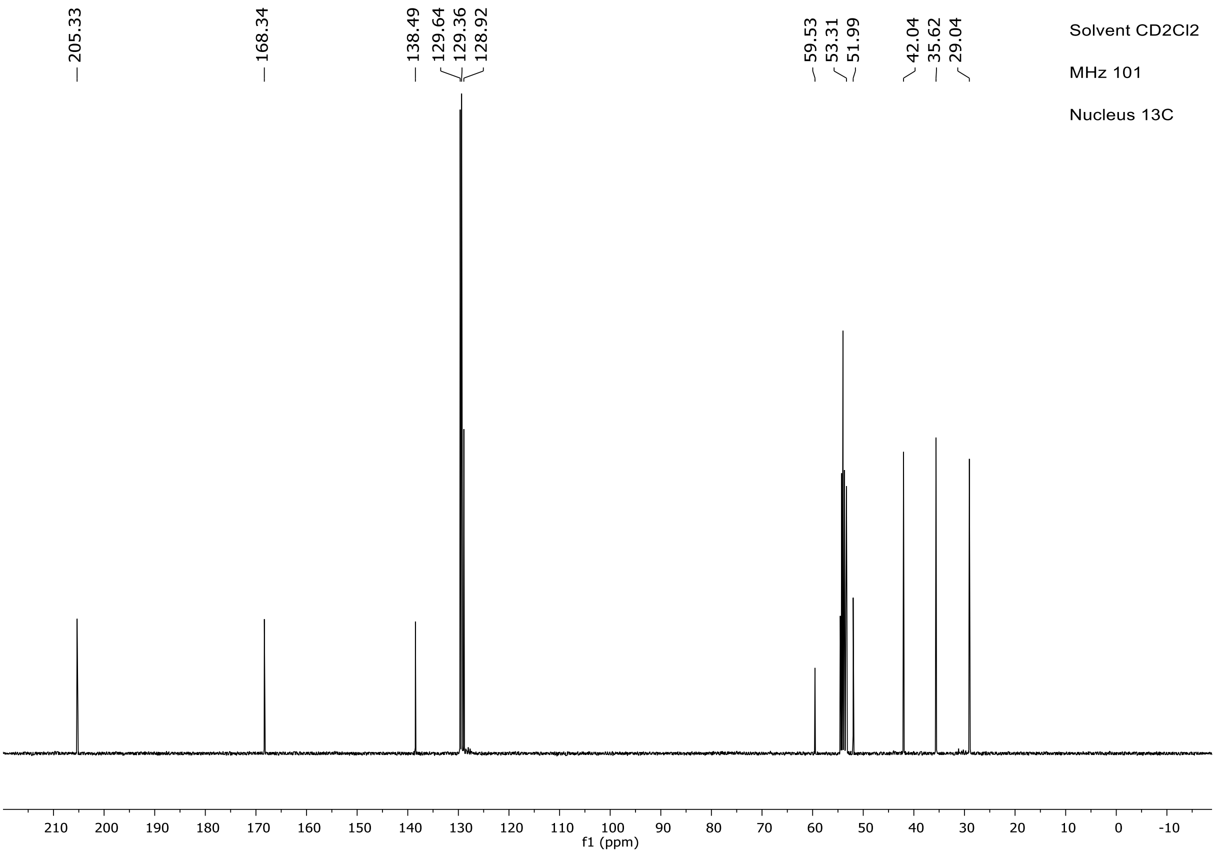

Solvent CD2Cl2
MHz 400
Nucleus 1H
2.09
3.13
3.00
0.95
1.19
2.00
1.02
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

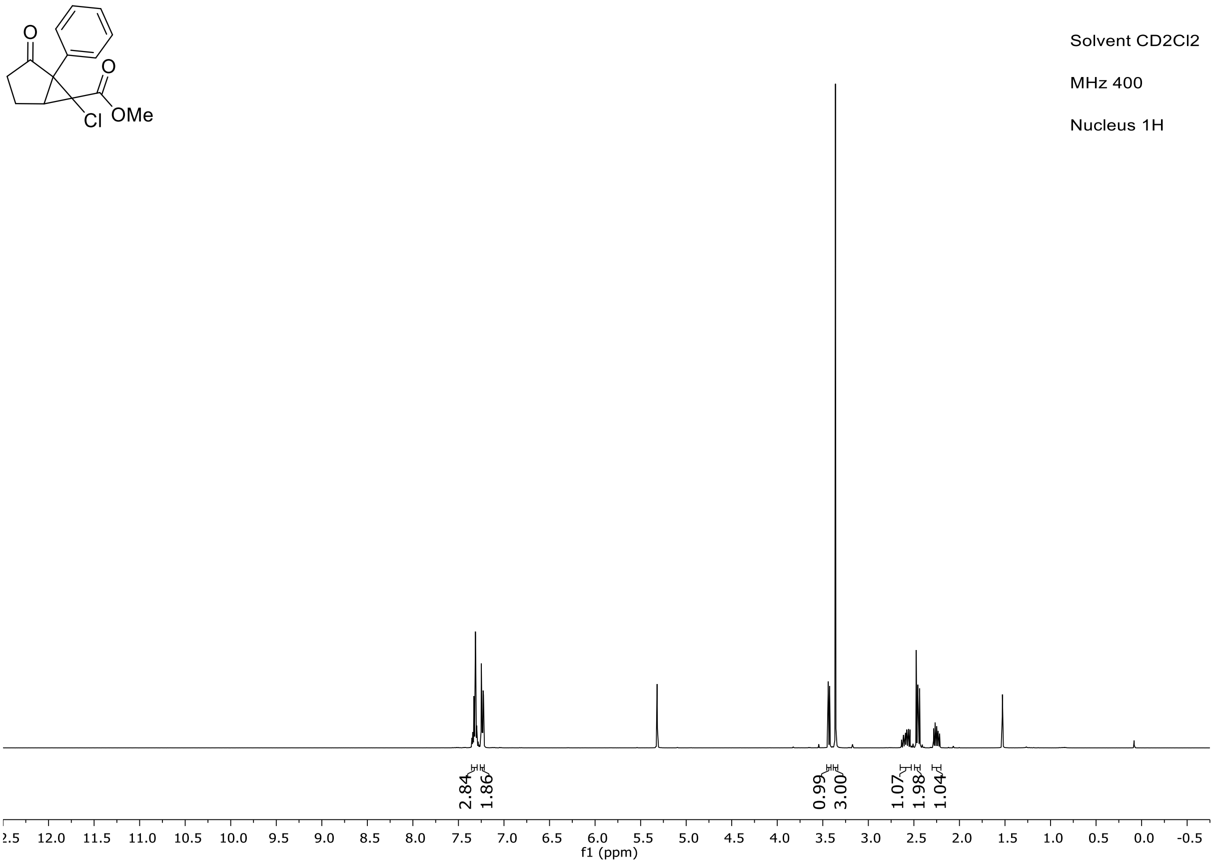

205.70
165.80
132.31
129.30
128.93
122.60
85.80
81.24
54.69
54.37
41.90
41.49
37.01
19.71
Solvent CH2Cl2
MHz 101
Nucleus 13C
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

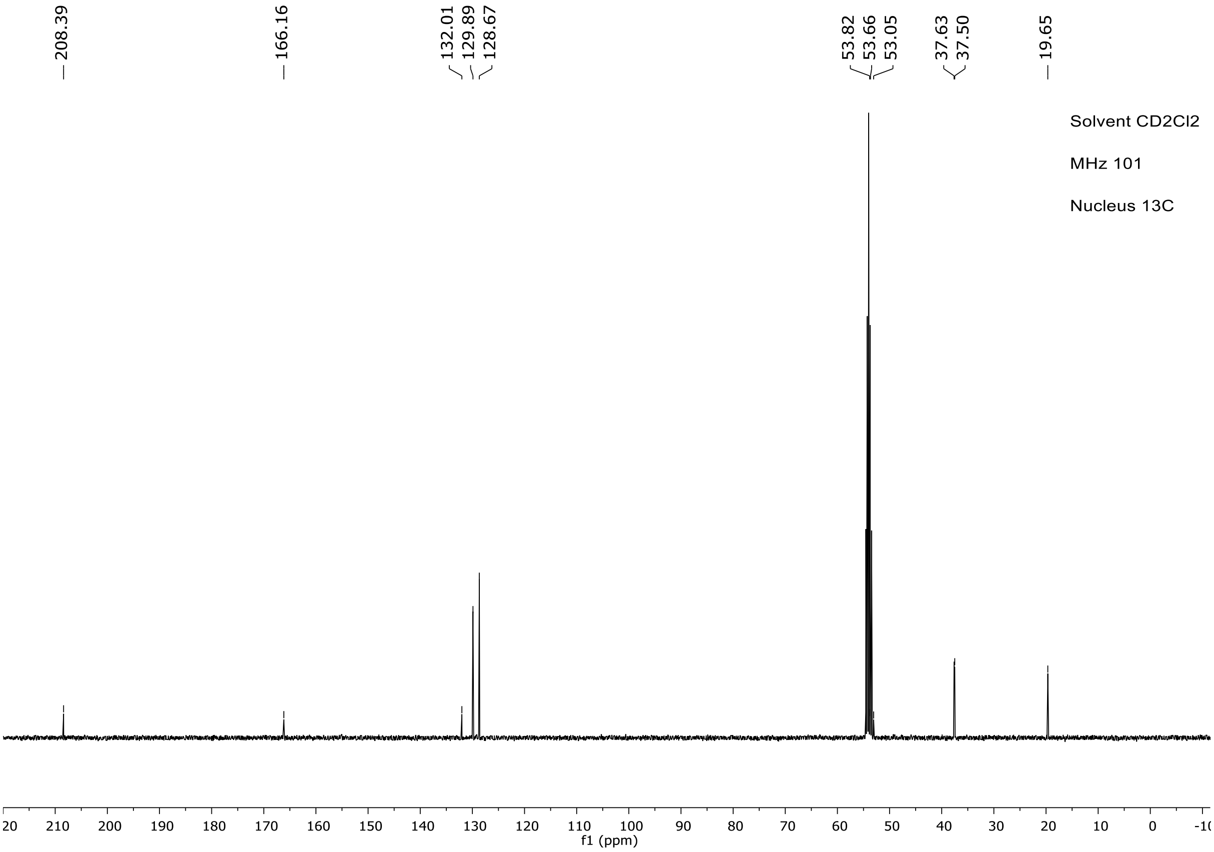

O
O
Cl
OMe
Solvent CD2Cl2
MHz 400
Nucleus 1H
1.82
2.77
3.00
1.13
0.83
1.00
1.02
1.13
2.28
2.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

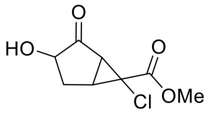

210.57
168.46
139.51
129.45
129.04
126.95
54.35
49.64
48.70
42.43
38.02
35.21
28.00
Solvent CD2Cl2
MHz 101
Nucleus 13C
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1(
f1 (ppm)

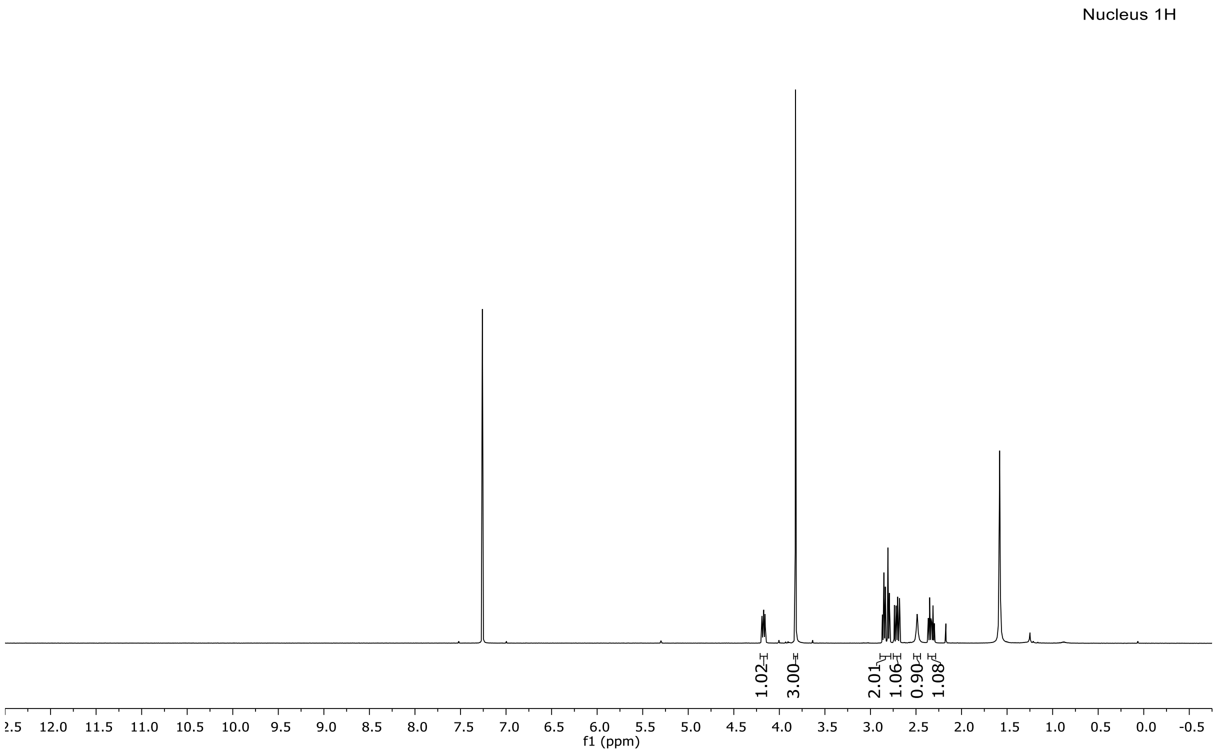

O
O
Cl
OMe
Solvent CD2Cl2
MHz 400
Nucleus 1H
5.04
3.00
0.94
4.14
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

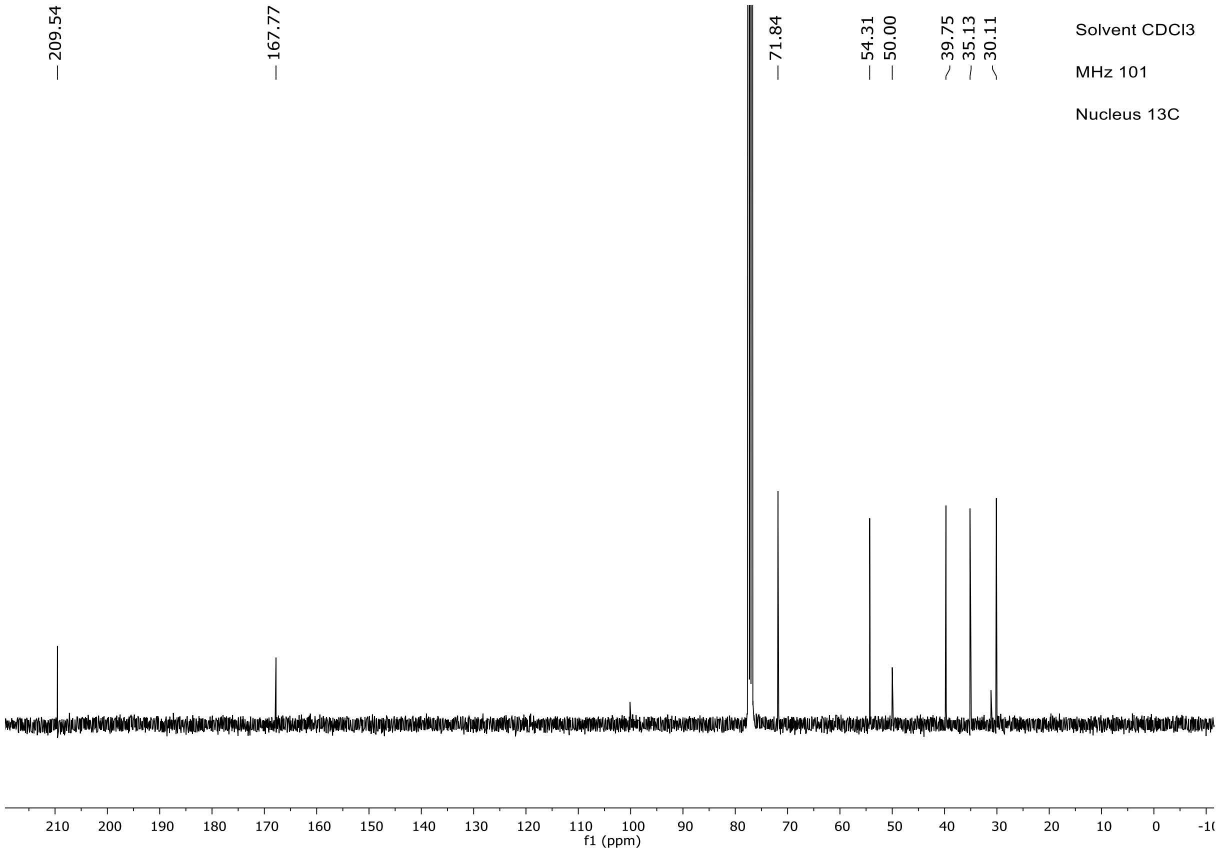

205.33
168.34
138.49
129.64
129.36
128.92
59.53
53.31
51.99
42.04
35.62
29.04
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

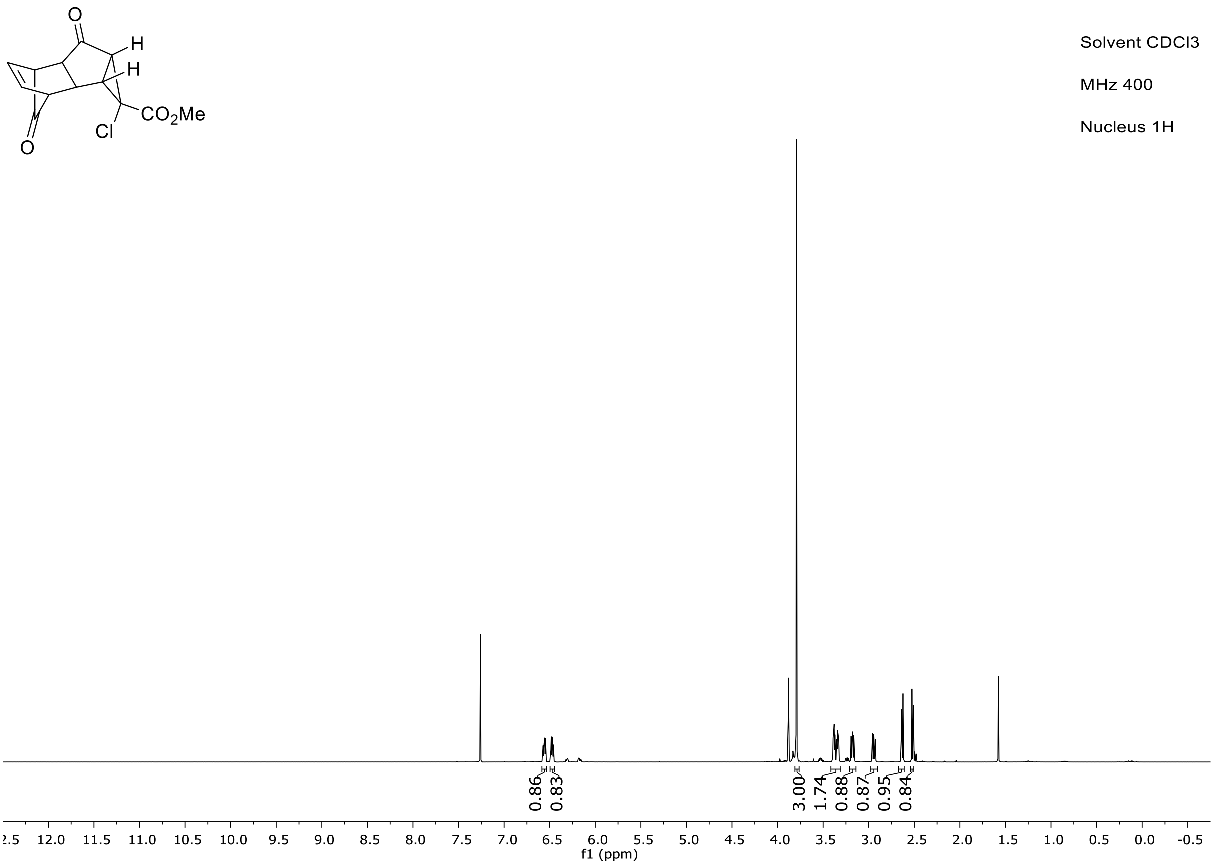

O
O
Cl
OMe
Solvent CD2Cl2
MHz 400
Nucleus 1H
2.84
1.86
0.99
3.00
1.07
1.98
1.04
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

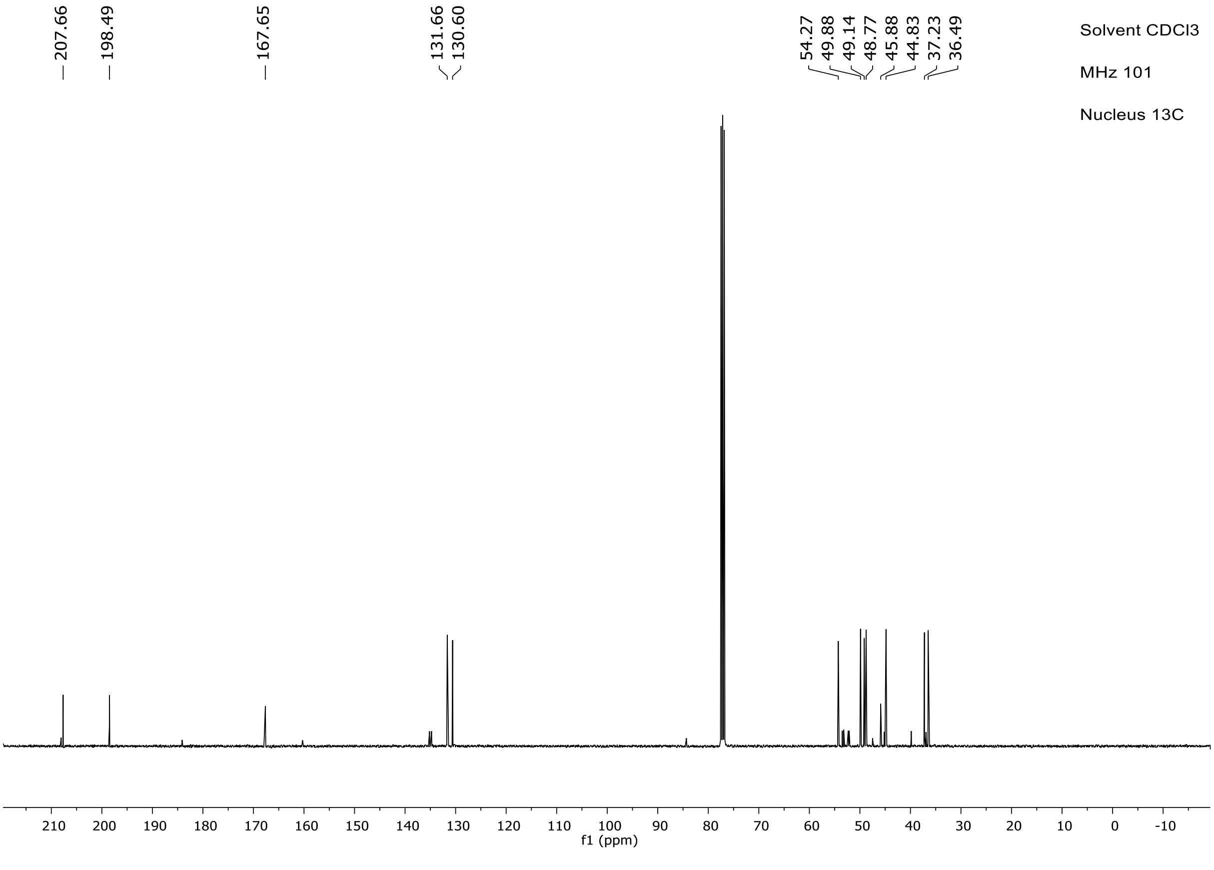

208.39
166.16
132.01
129.89
128.67
53.82
53.66
53.05
37.63
37.50
19.65
Solvent CD2Cl2
MHz 101
Nucleus 13C
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

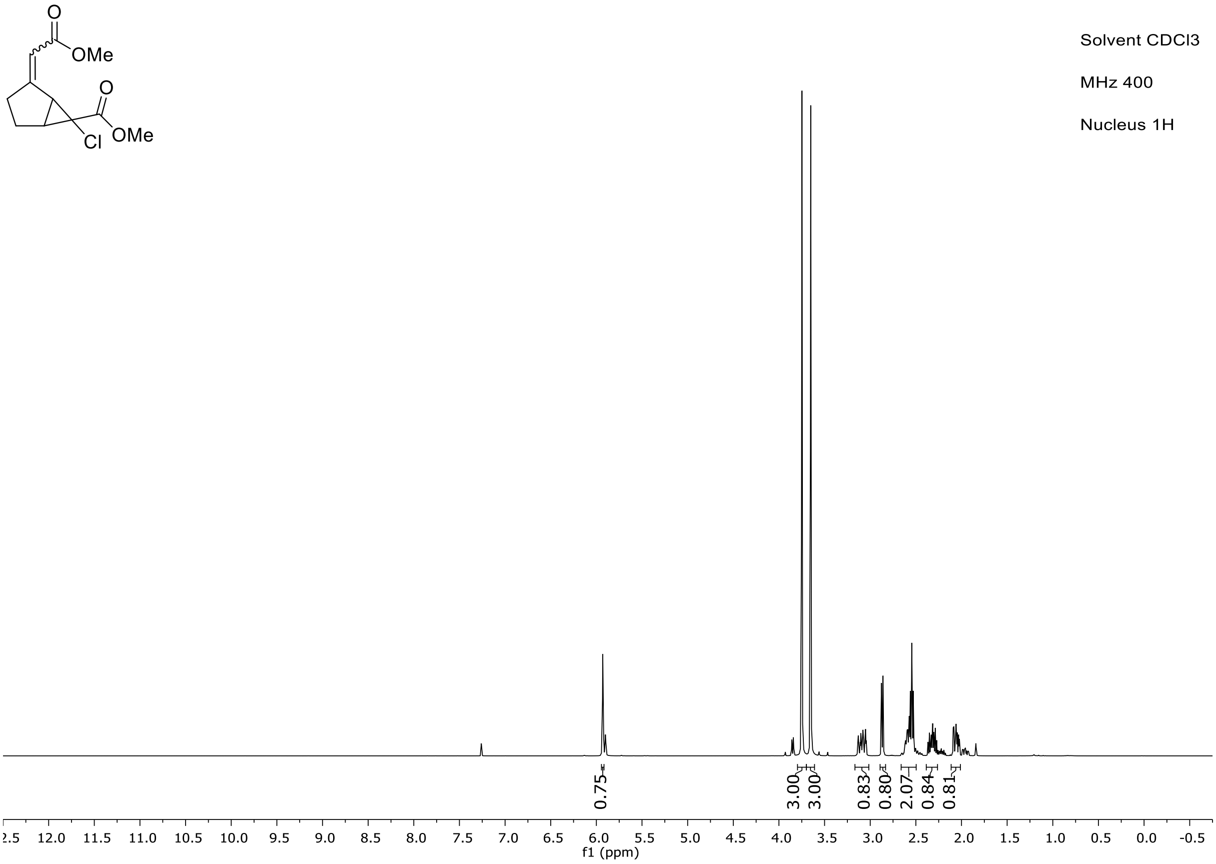

HO
O
O
Cl
OMe

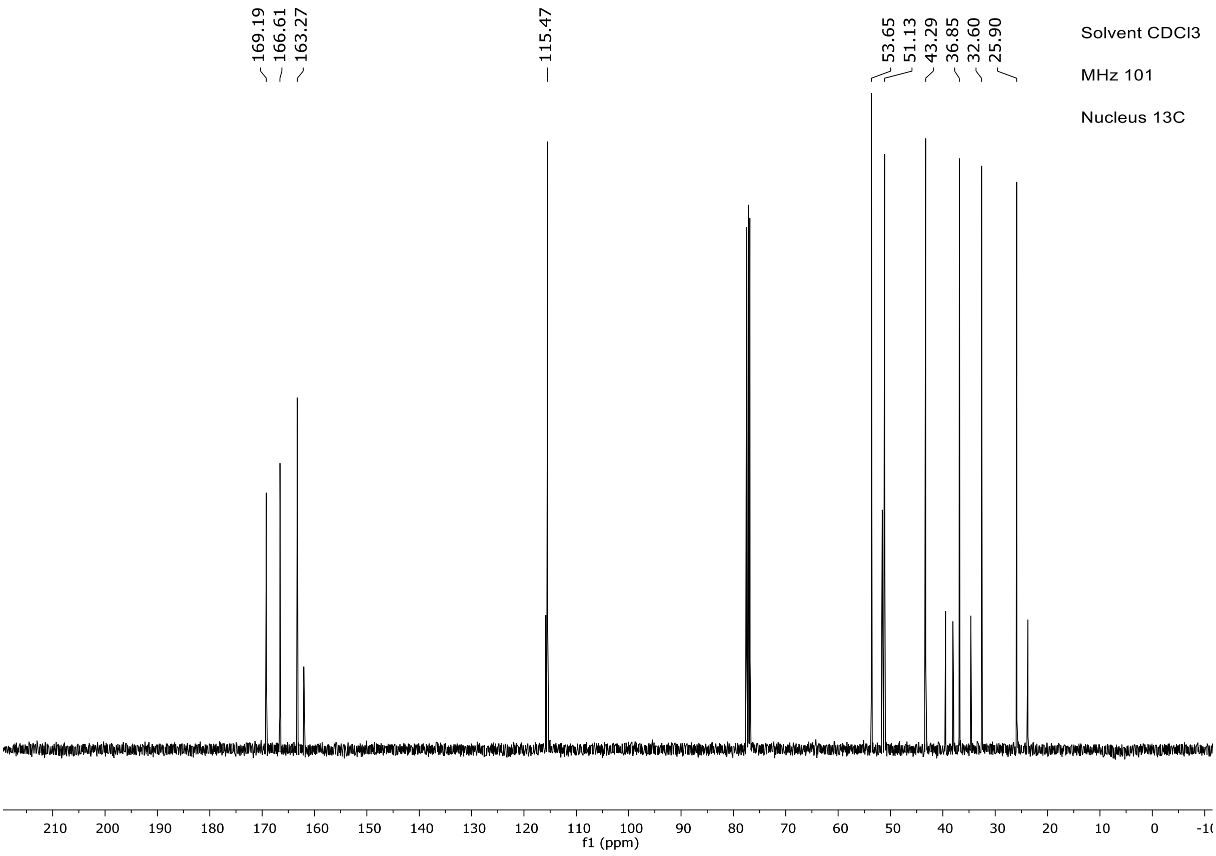

Solvent CDCl3
MHz 400
Nucleus 1H
1.02
3.00
2.01
1.06
0.90
1.08
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

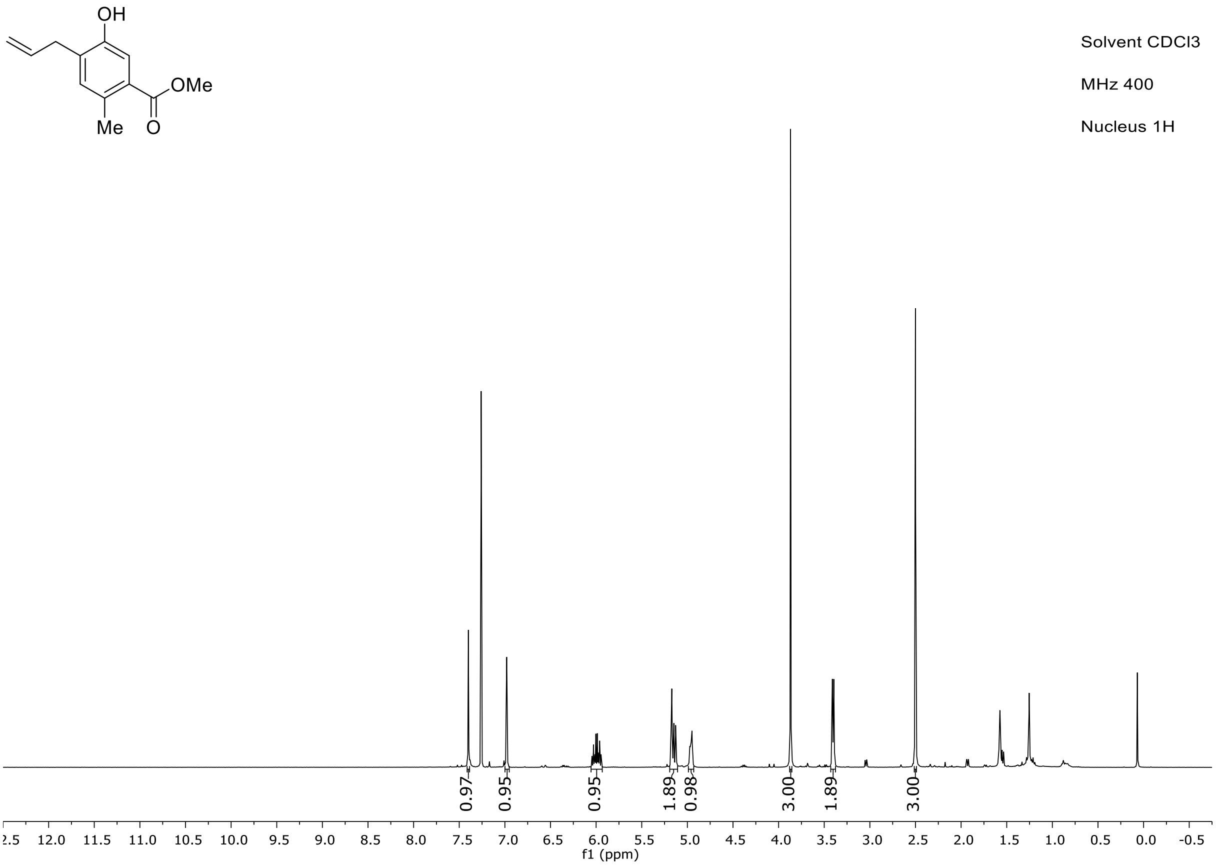

209.54
167.77
71.84
54.31
50.00
39.75
35.13
30.11
Solvent CDCl3
MHz 101
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

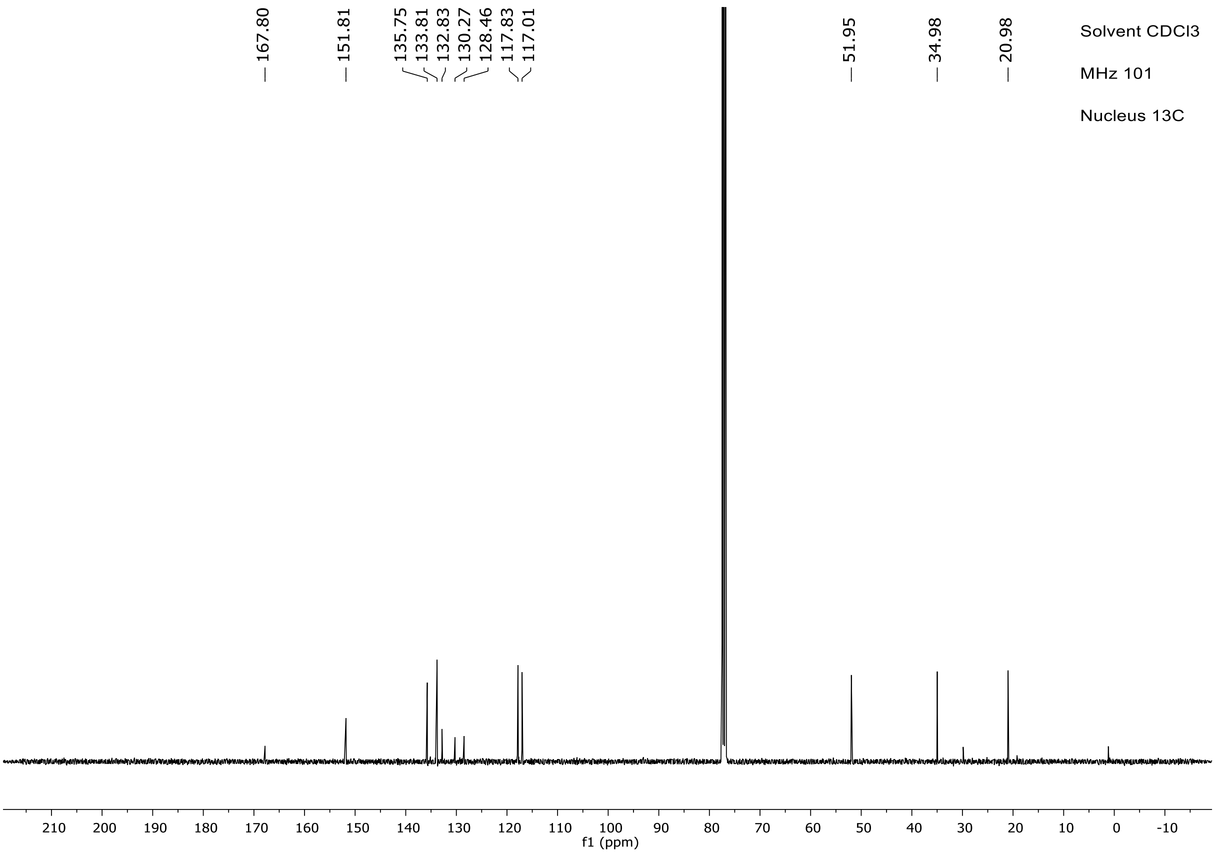

O
H
H
CO_2Me
Cl
O
Solvent CDCl3
MHz 400
Nucleus 1H
0.86
0.83
3.00
1.74
0.88
0.87
0.95
0.84
2.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

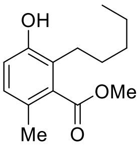

207.66
198.49
167.65
131.66
130.60
54.27
49.88
49.14
48.77
45.88
44.83
37.23
36.49
Solvent CDCl3
MHz 101
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
OMe
O
Cl
OMe
Solvent CDCl3
MHz 400
Nucleus 1H
0.75
3.00
3.00
0.83
0.80
2.07
0.84
0.81
2.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


169.19
166.61
163.27
115.47
53.65
51.13
43.29
36.85
32.60
25.90
Solvent CDCl3
MHz 101
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1(
f1 (ppm)


OH
OMe
Me
O
Solvent CDCl3
MHz 400
Nucleus 1H
0.97
0.95
0.95
1.89
0.98
3.00
1.89
3.00
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

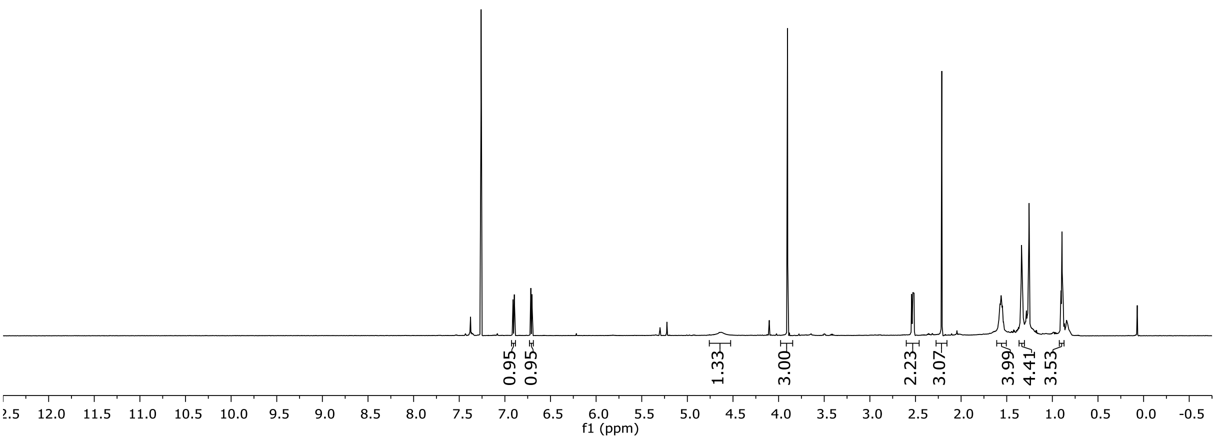

167.80
151.81
135.75
133.81
132.83
130.27
128.46
117.83
117.01
51.95
34.98
20.98
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



Solvent CDCl3

MHz 600

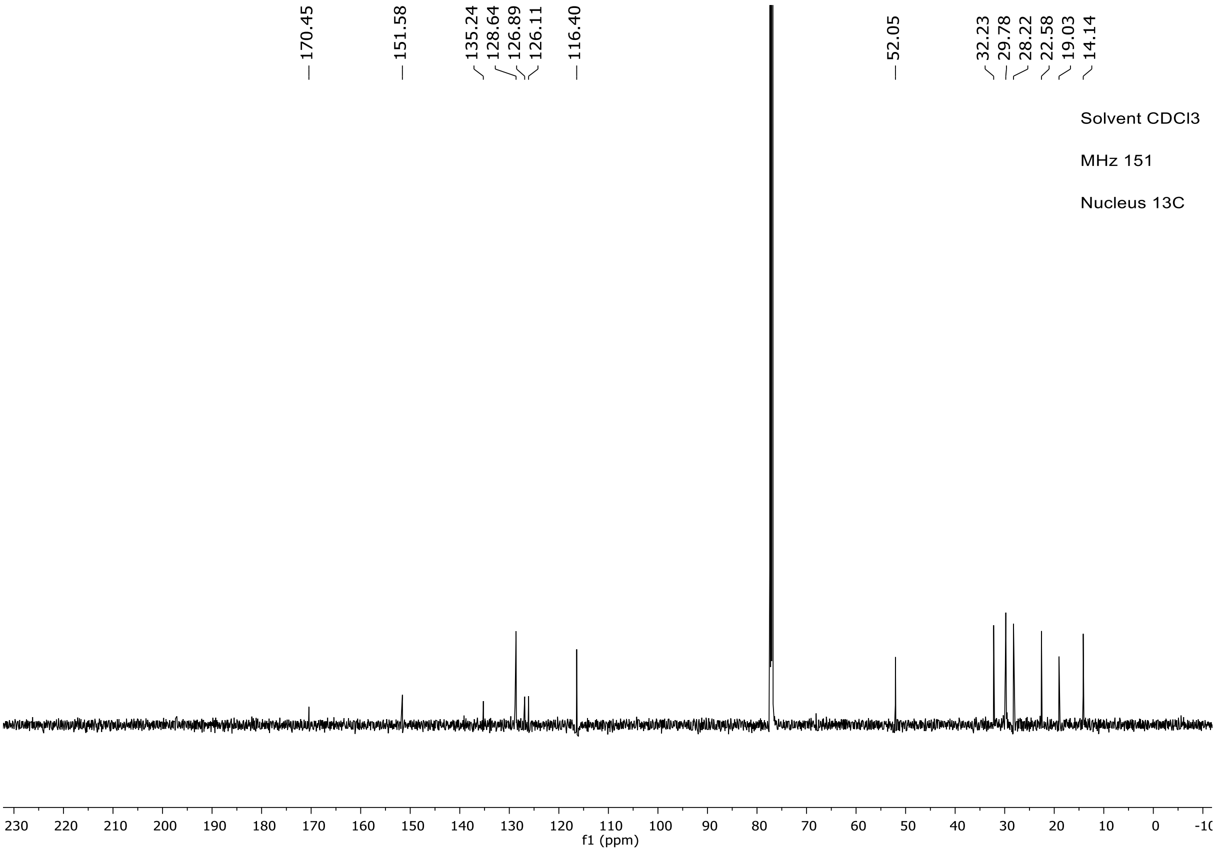
Nucleus 1H

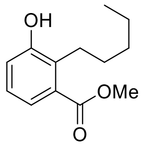


Solvent CDCl3

MHz 151

Nucleus 13C

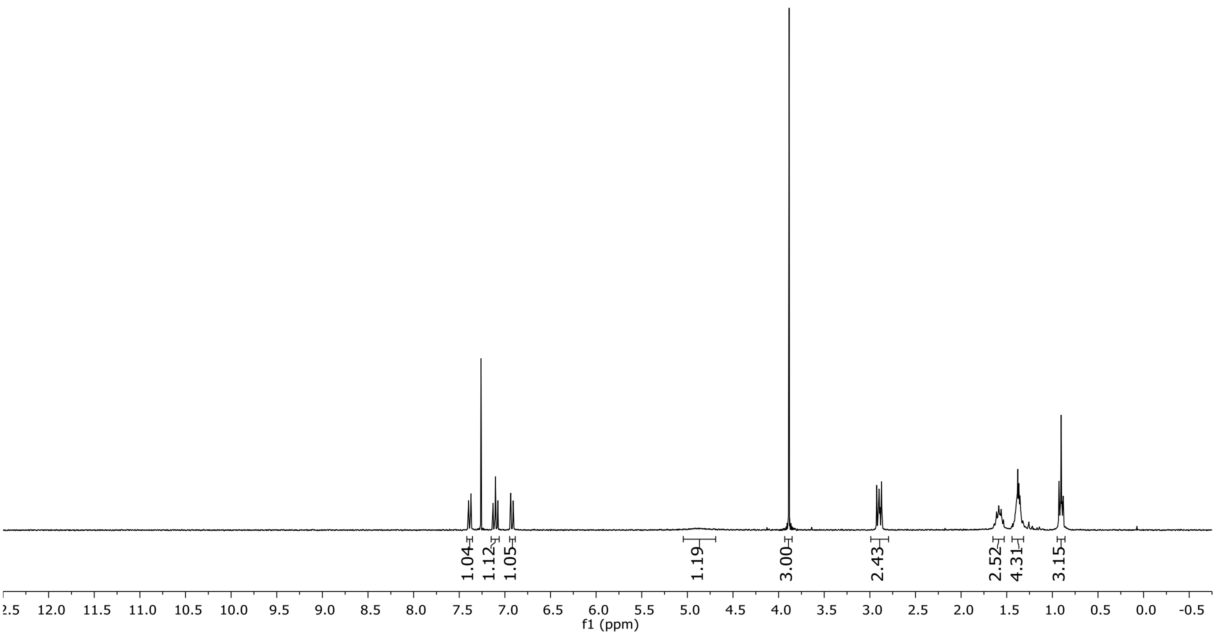


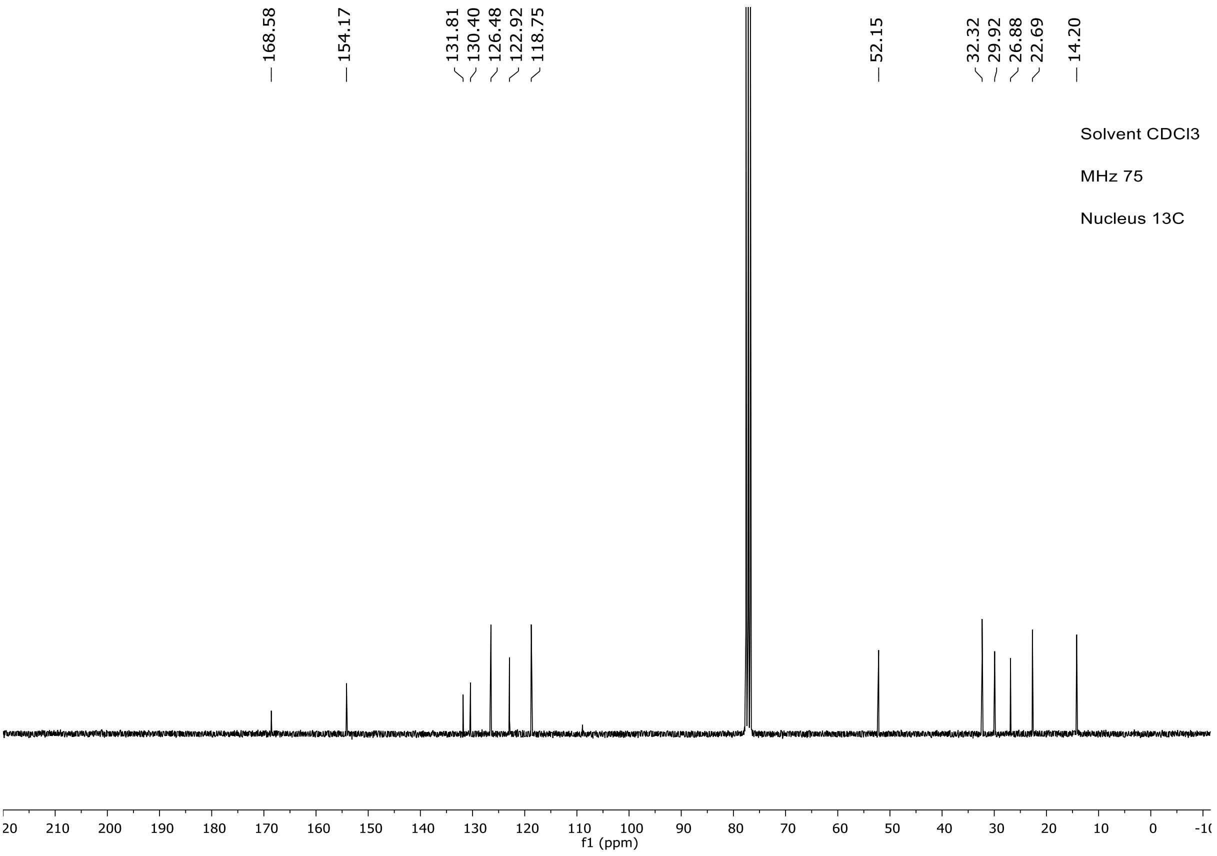


Solvent CDCl3

MHz 300

Nucleus 1H

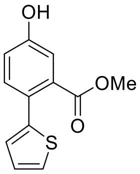




Solvent CDCl3

MHz 75

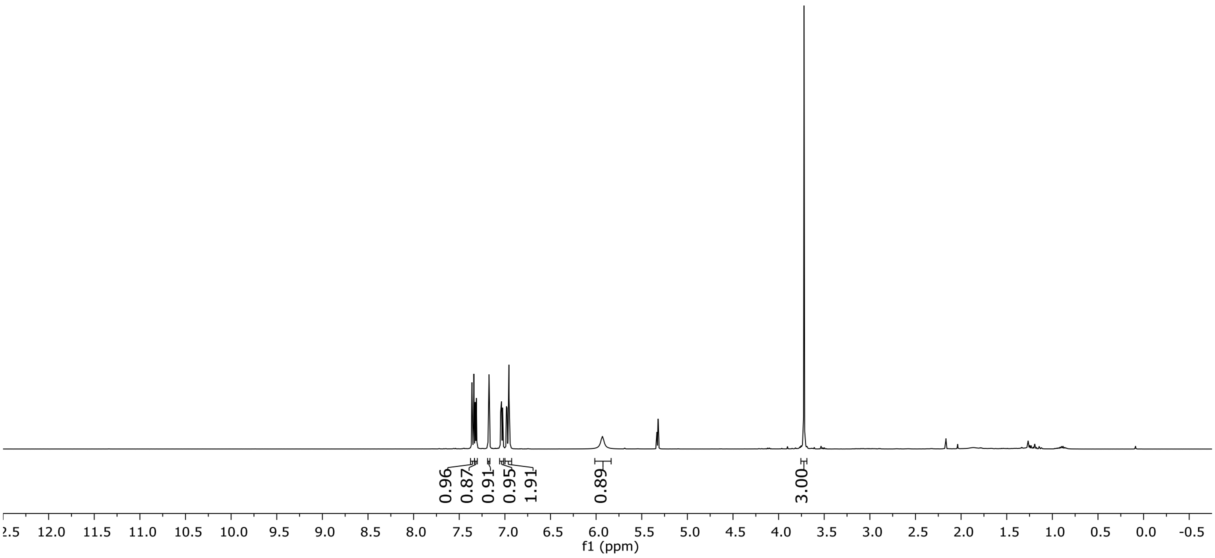
Nucleus 13C



Solvent CD2Cl2

MHz 400

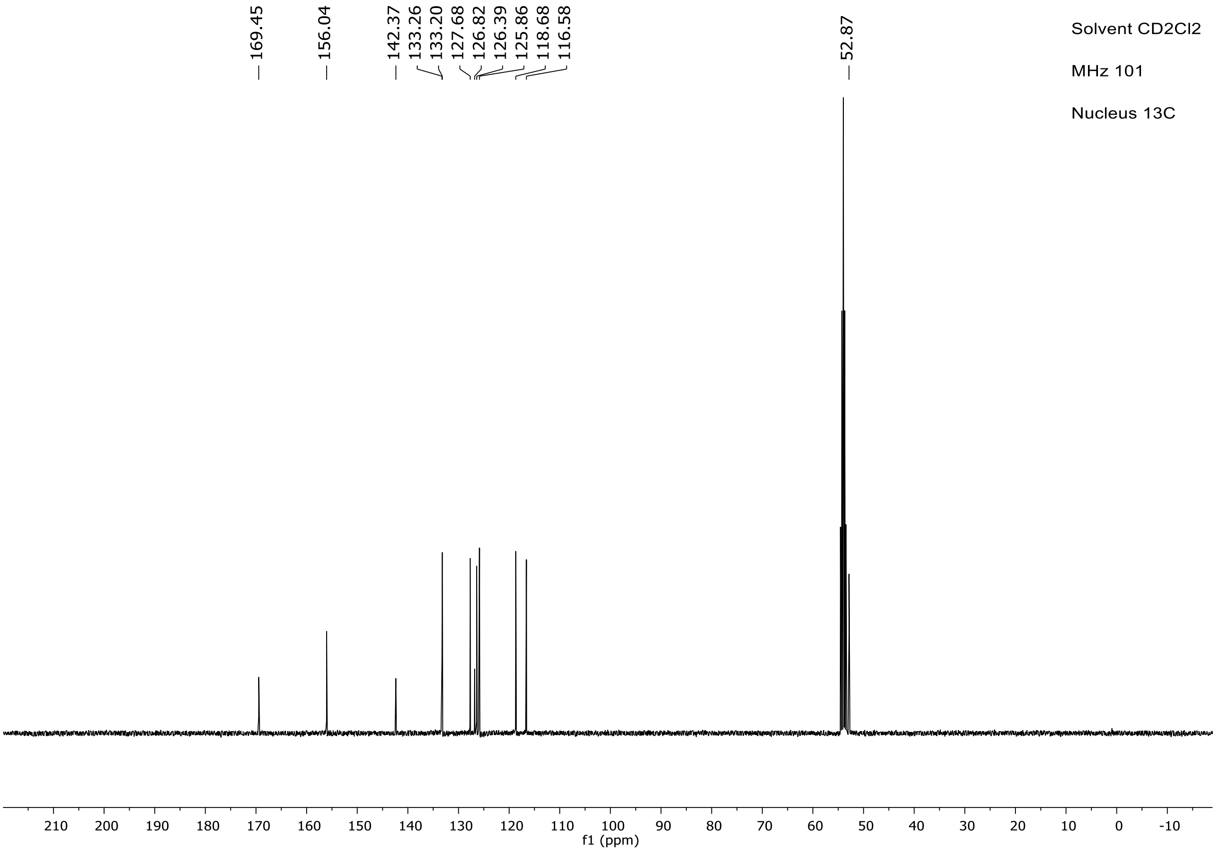
Nucleus 1H

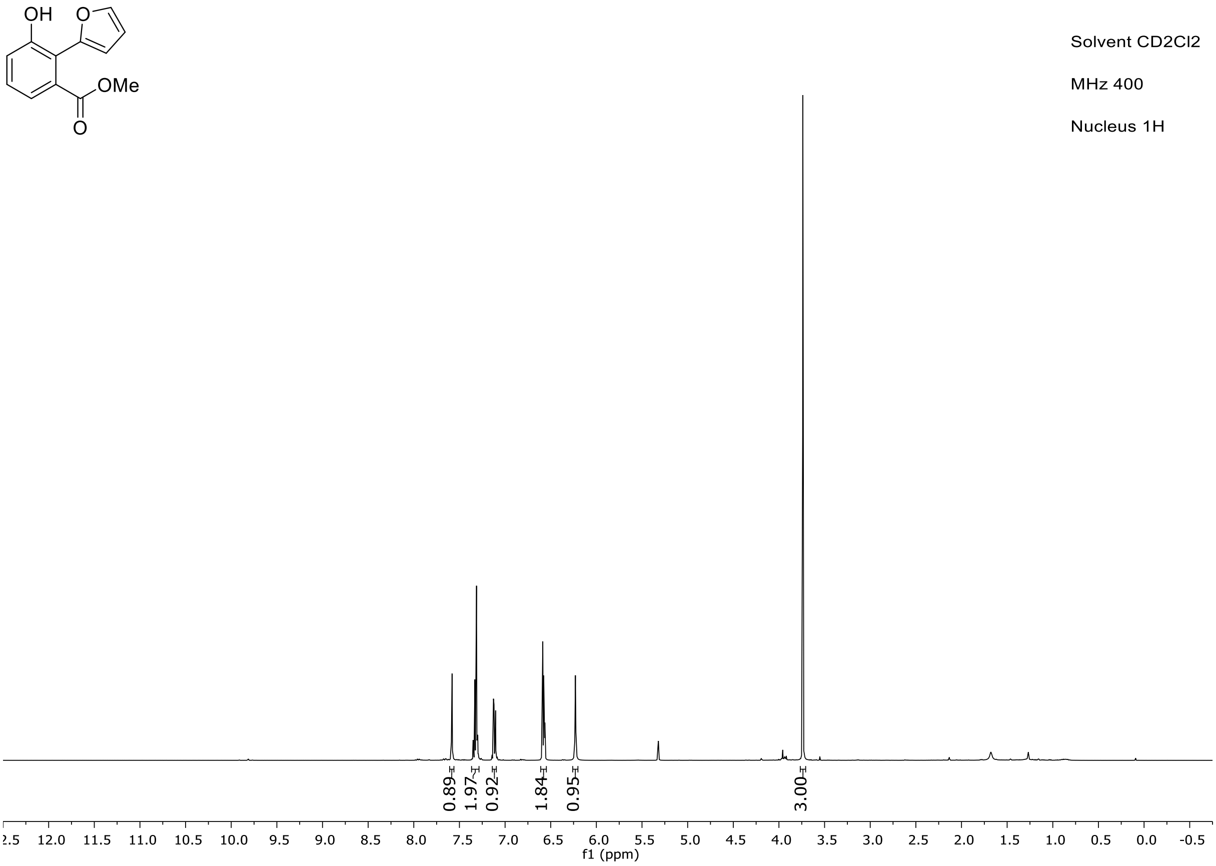


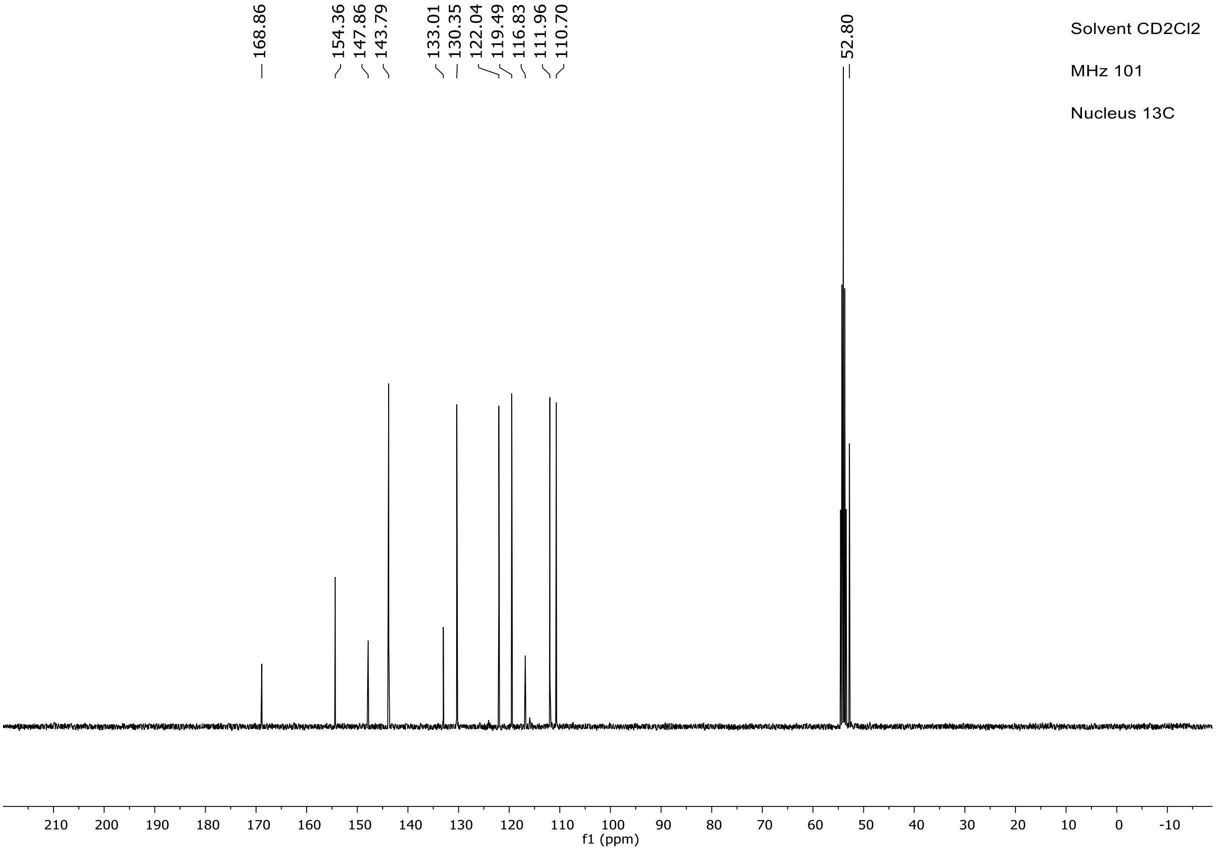
Solvent CD2Cl2

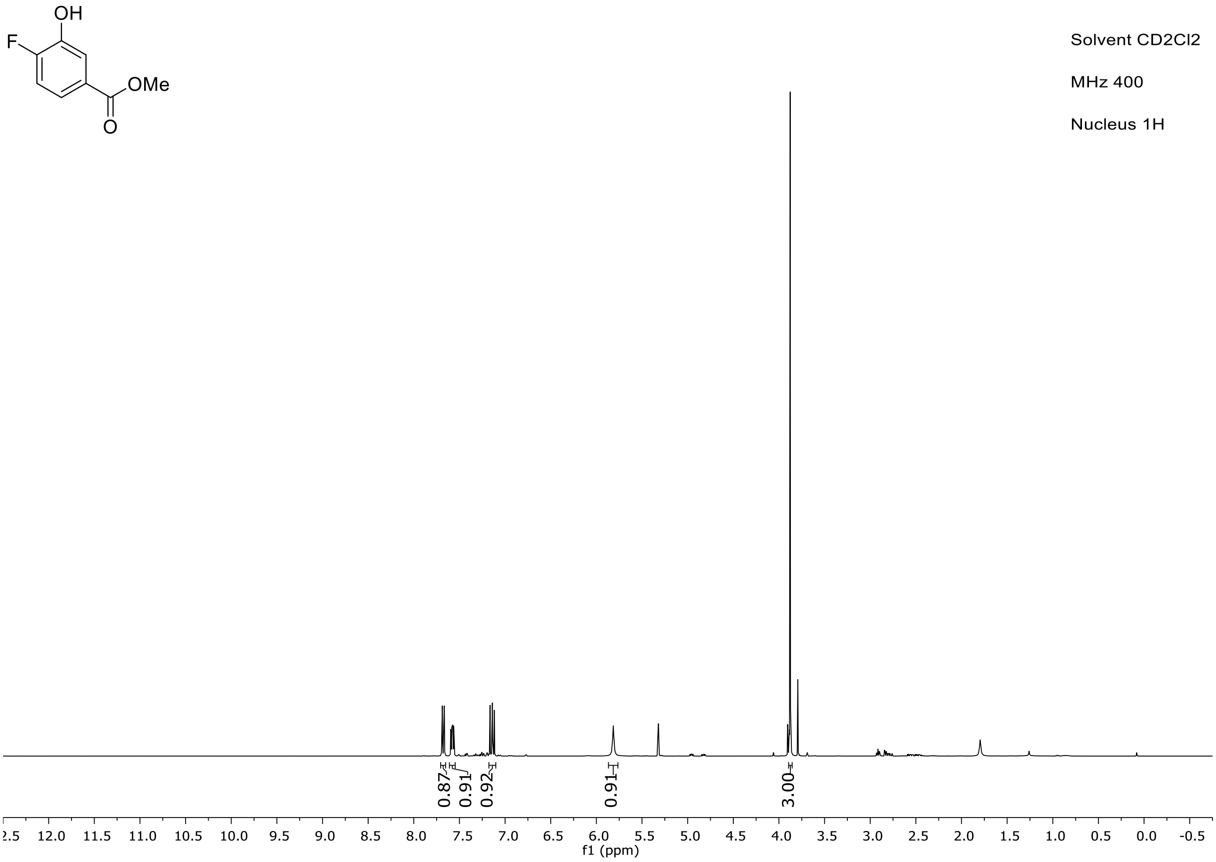
MHz 101

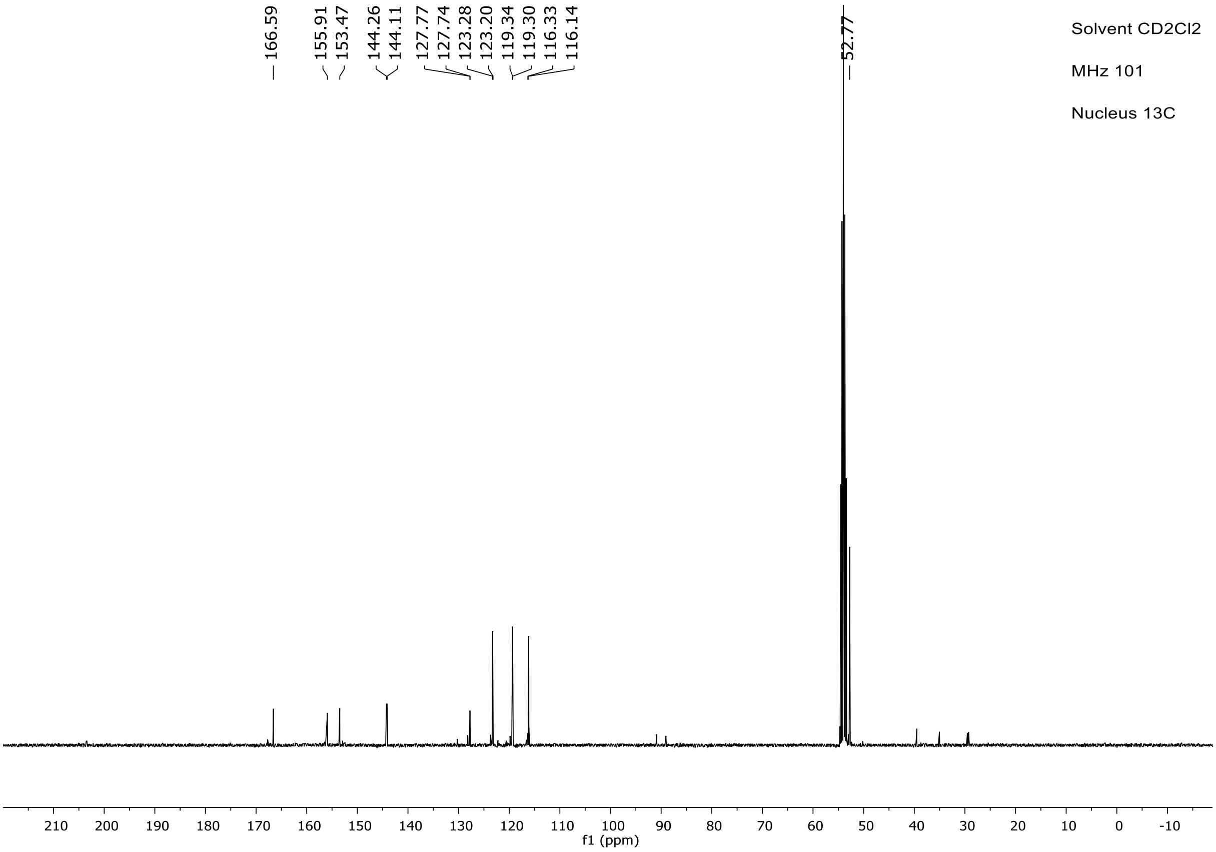
Nucleus 13C

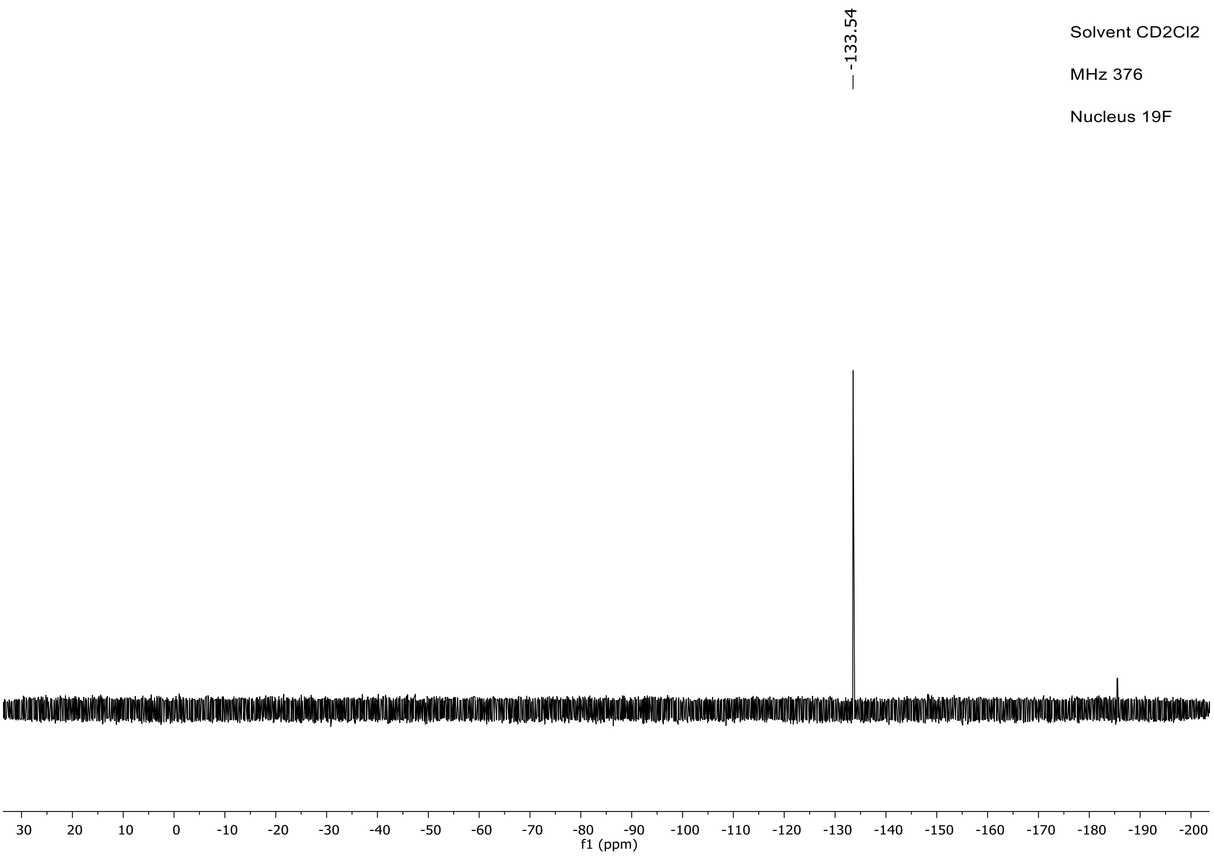


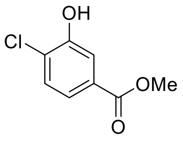

OH
O
OMe
O
Solvent CD2Cl2
MHz 400
Nucleus 1H
0.89
1.97
0.92
1.84
0.95
3.00
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

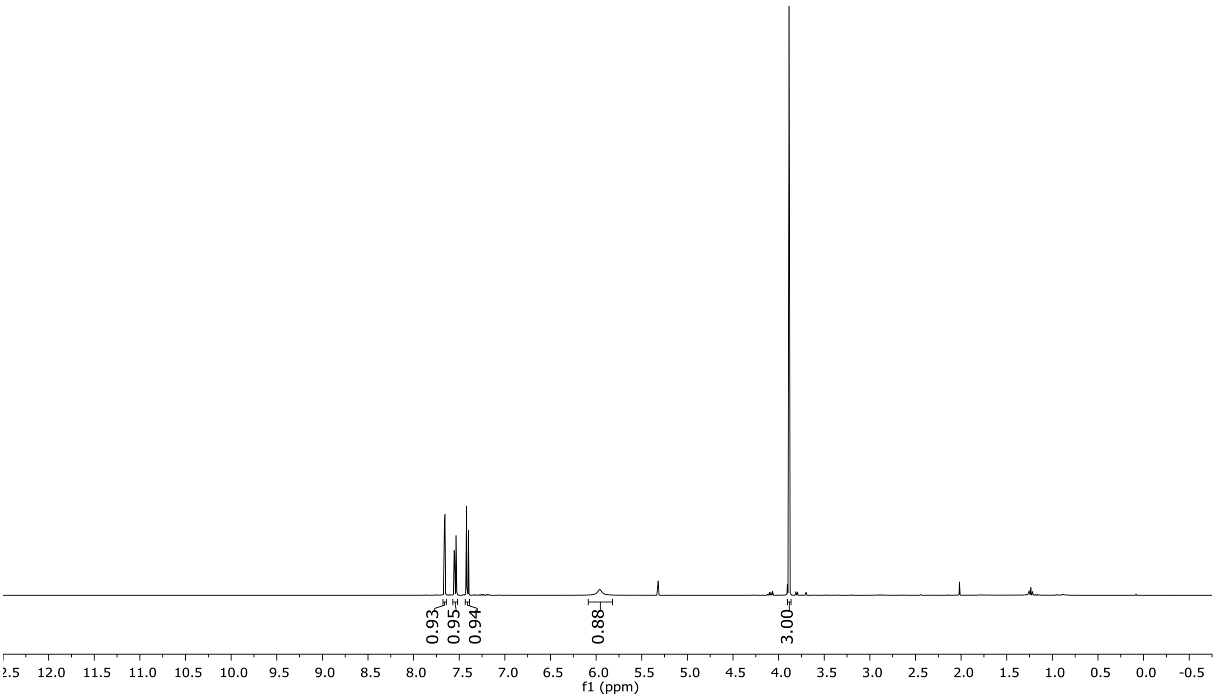

168.86
154.36
147.86
143.79
133.01
130.35
122.04
119.49
116.83
111.96
110.70
52.80
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

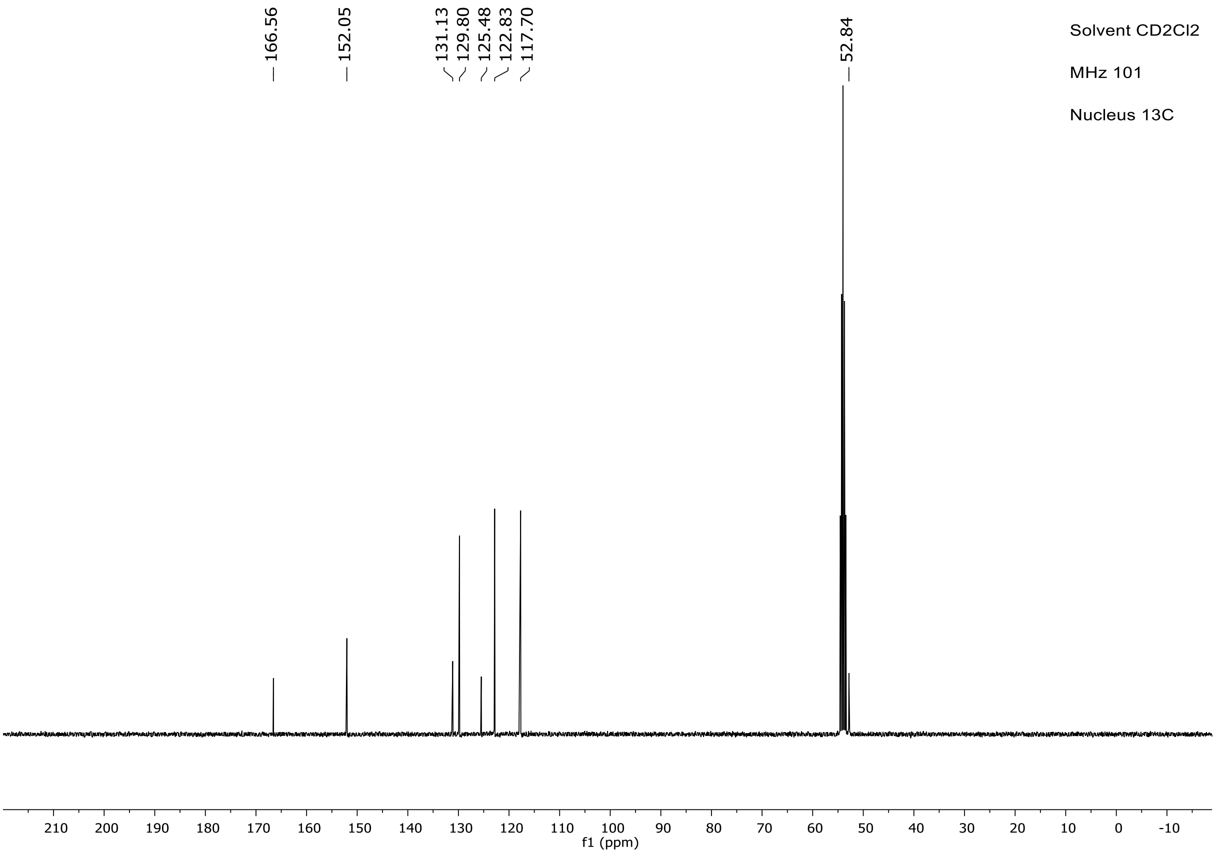

OH
F
OMe
O
Solvent CD2Cl2
MHz 400
Nucleus 1H
0.87
0.91
0.92
0.91
3.00
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

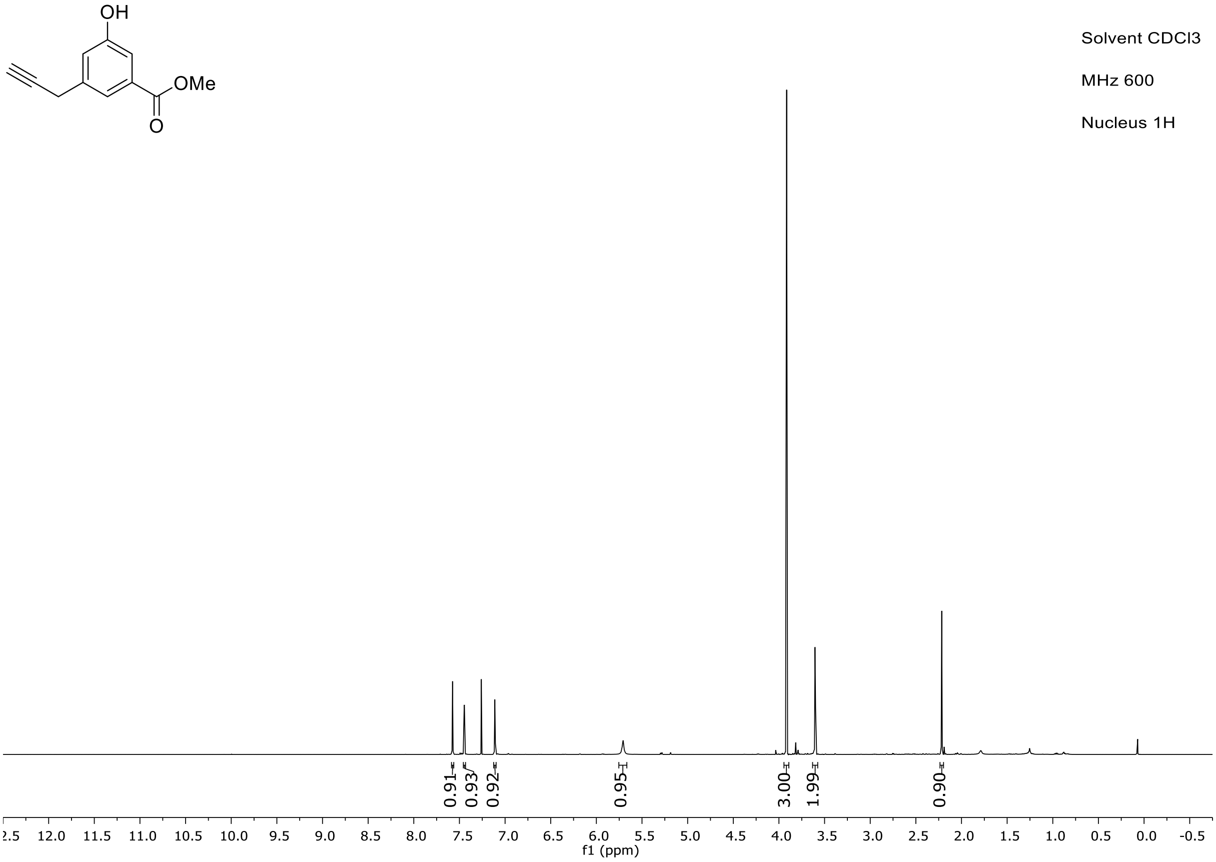

166.59
155.91
153.47
144.26
144.11
127.77
127.74
123.28
123.20
119.34
119.30
116.33
116.14
52.77
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

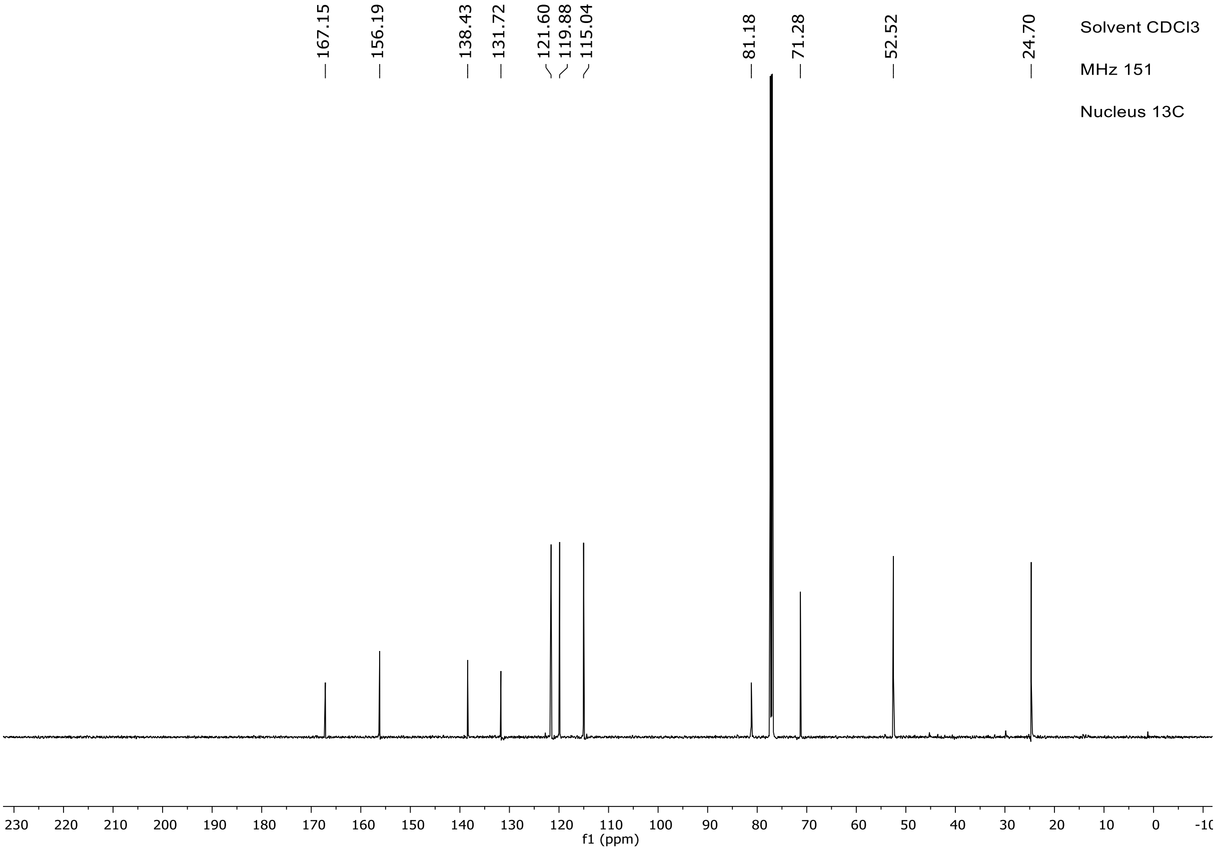

-133.54
Solvent CD2Cl2
MHz 376
Nucleus 19F
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

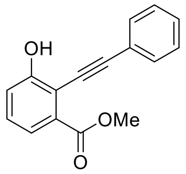

OH
Cl
OMe
O


Solvent CD2Cl2
MHz 400
Nucleus 1H
0.93
0.95
0.94
0.88
3.00
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


Solvent CD2Cl2
MHz 101
Nucleus 13C
166.56
152.05
131.13
129.80
125.48
122.83
117.70
52.84
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)


OH
OMe
O
Solvent CDCl3
MHz 600
Nucleus 1H
0.91
0.93
0.92
0.95
3.00
1.99
0.90
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

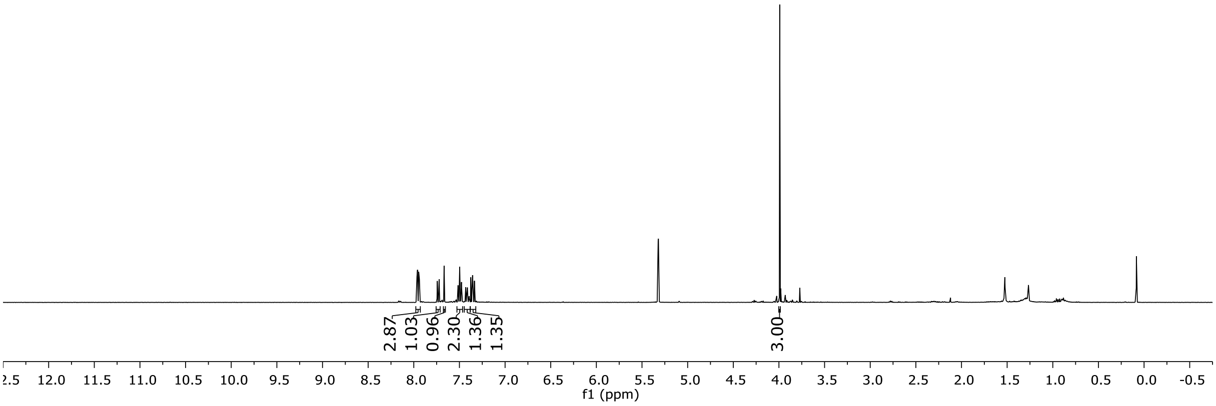

167.15
156.19
138.43
131.72
121.60
119.88
115.04
81.18
71.28
52.52
24.70
Solvent CDCl3
MHz 151
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)



Solvent CD2Cl2

MHz 400

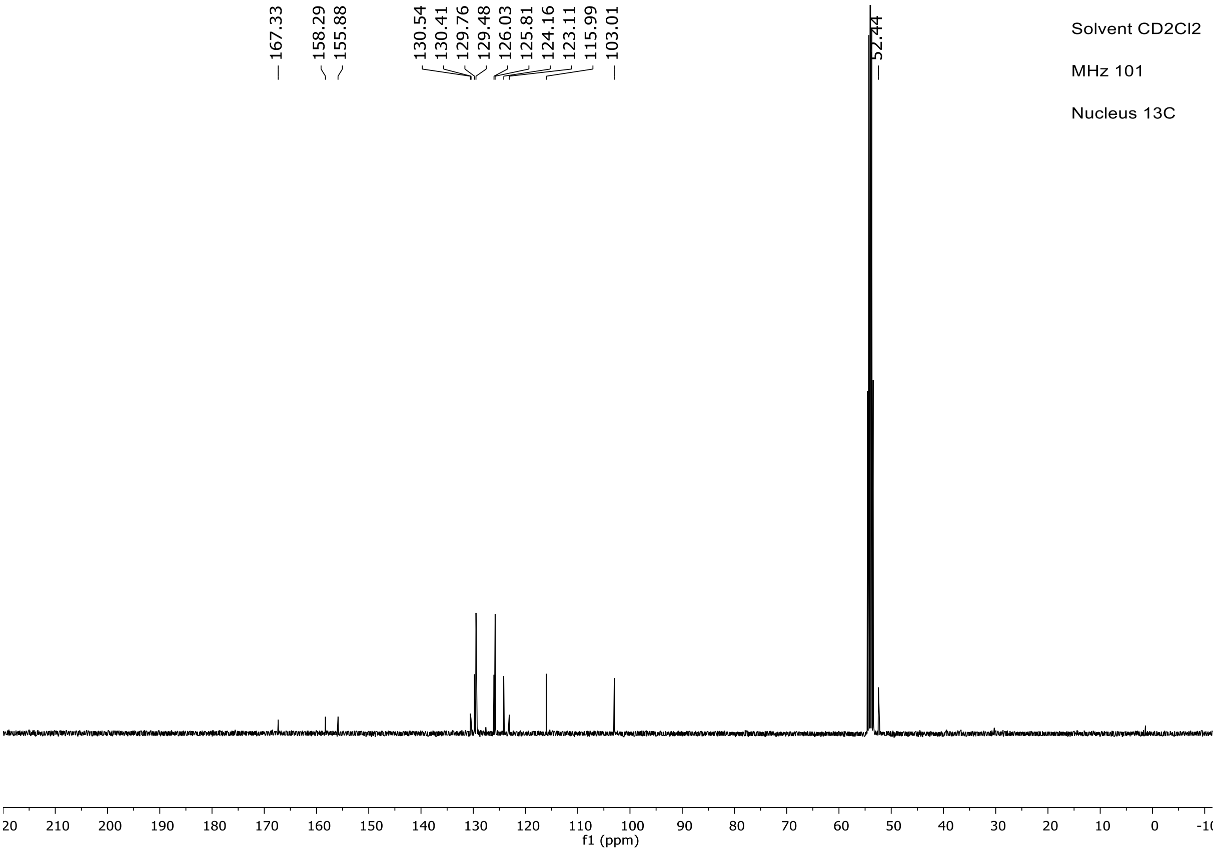
Nucleus 1H

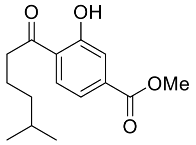


Solvent CD2Cl2

MHz 101

Nucleus 13C

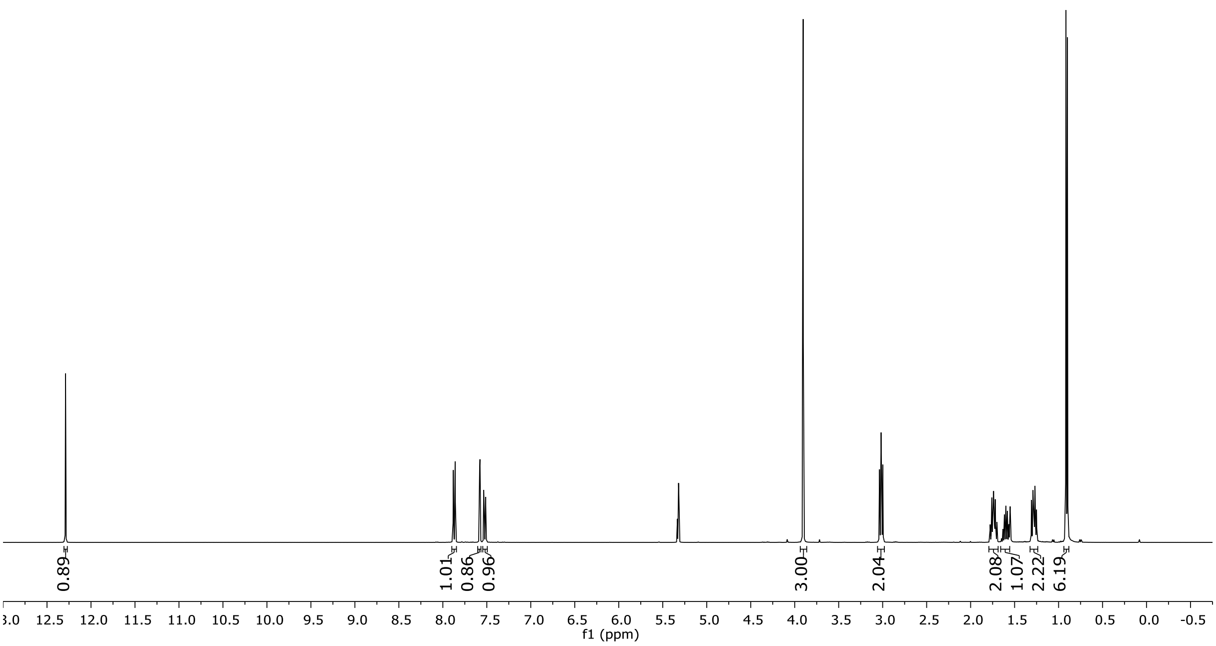


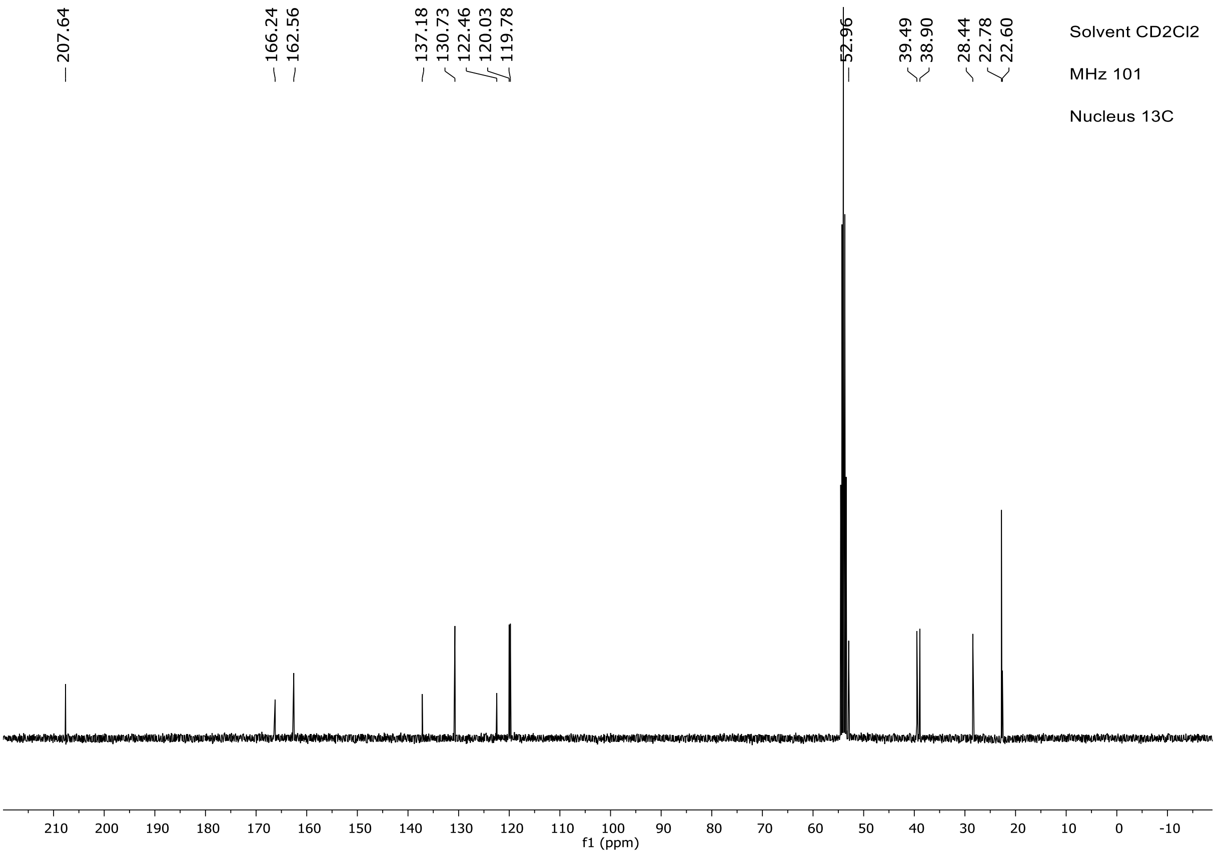


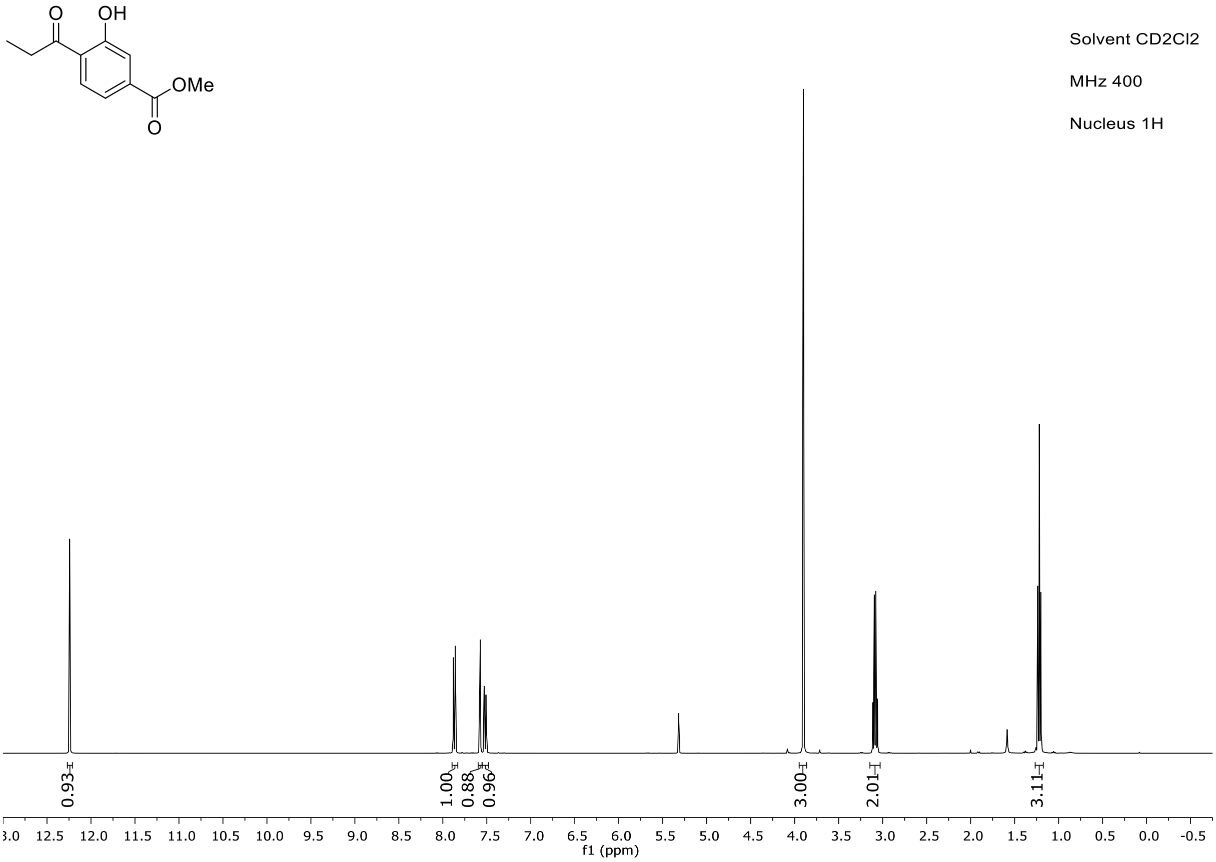
Solvent CD2Cl2

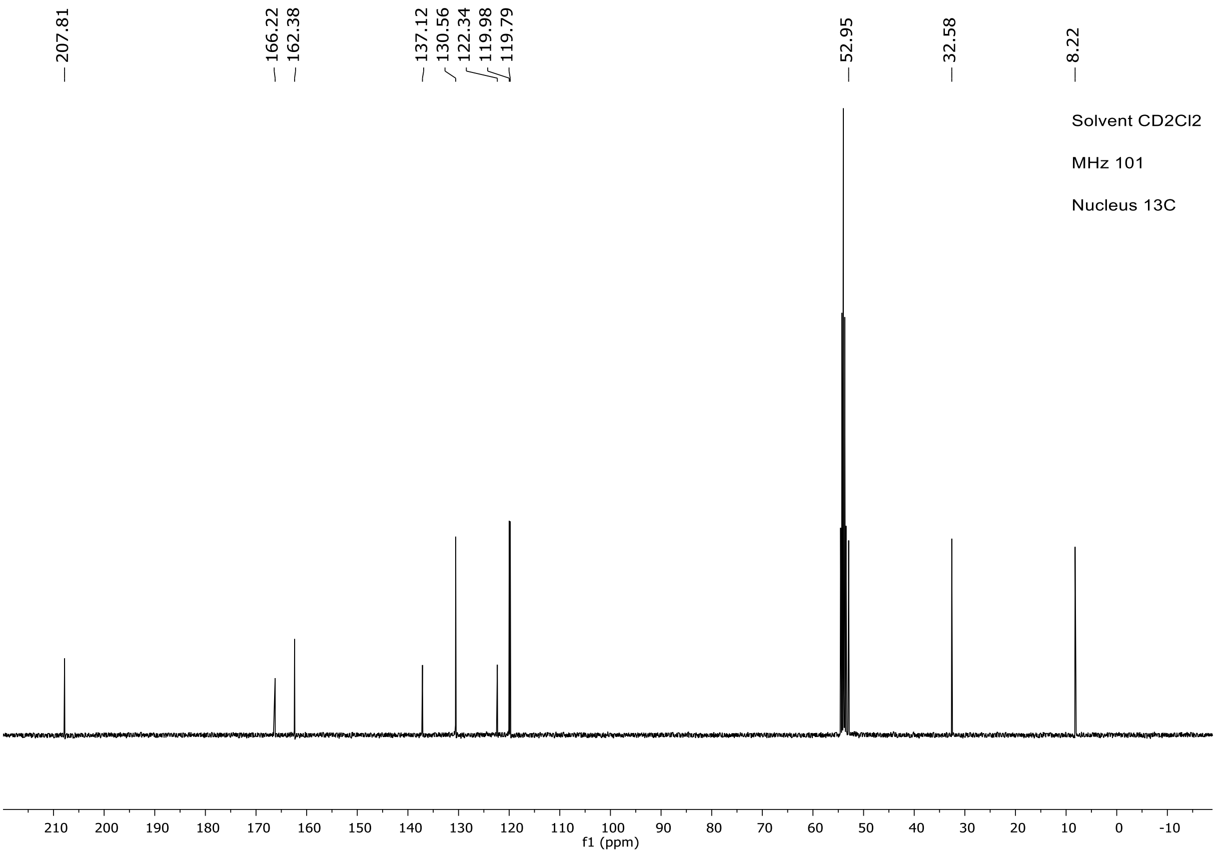
MHz 400

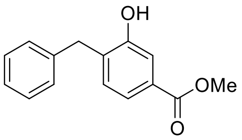
Nucleus 1H

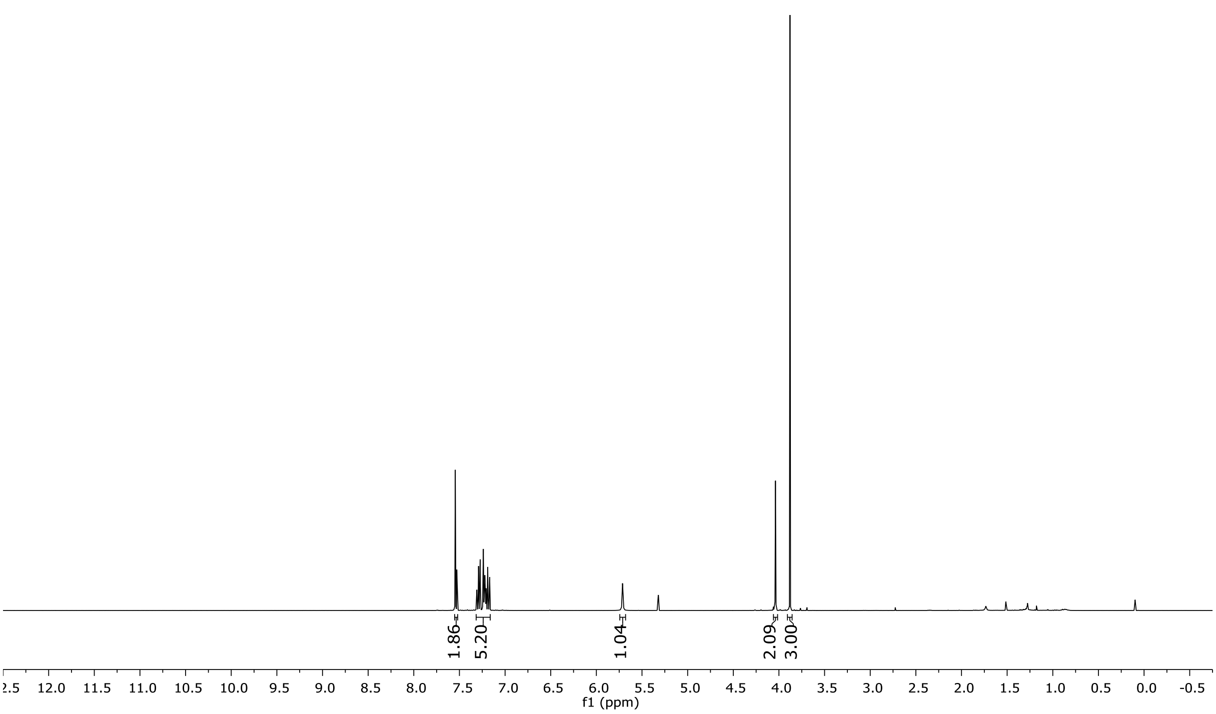


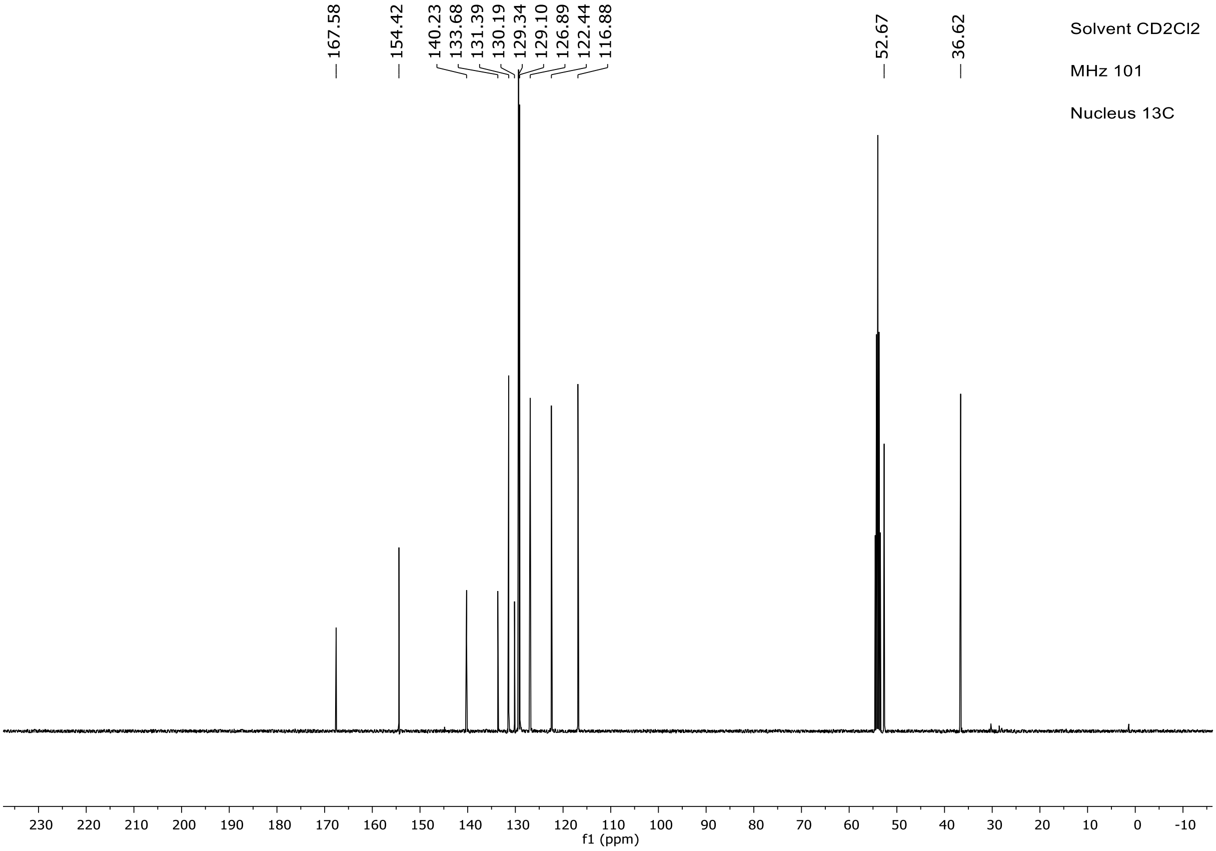


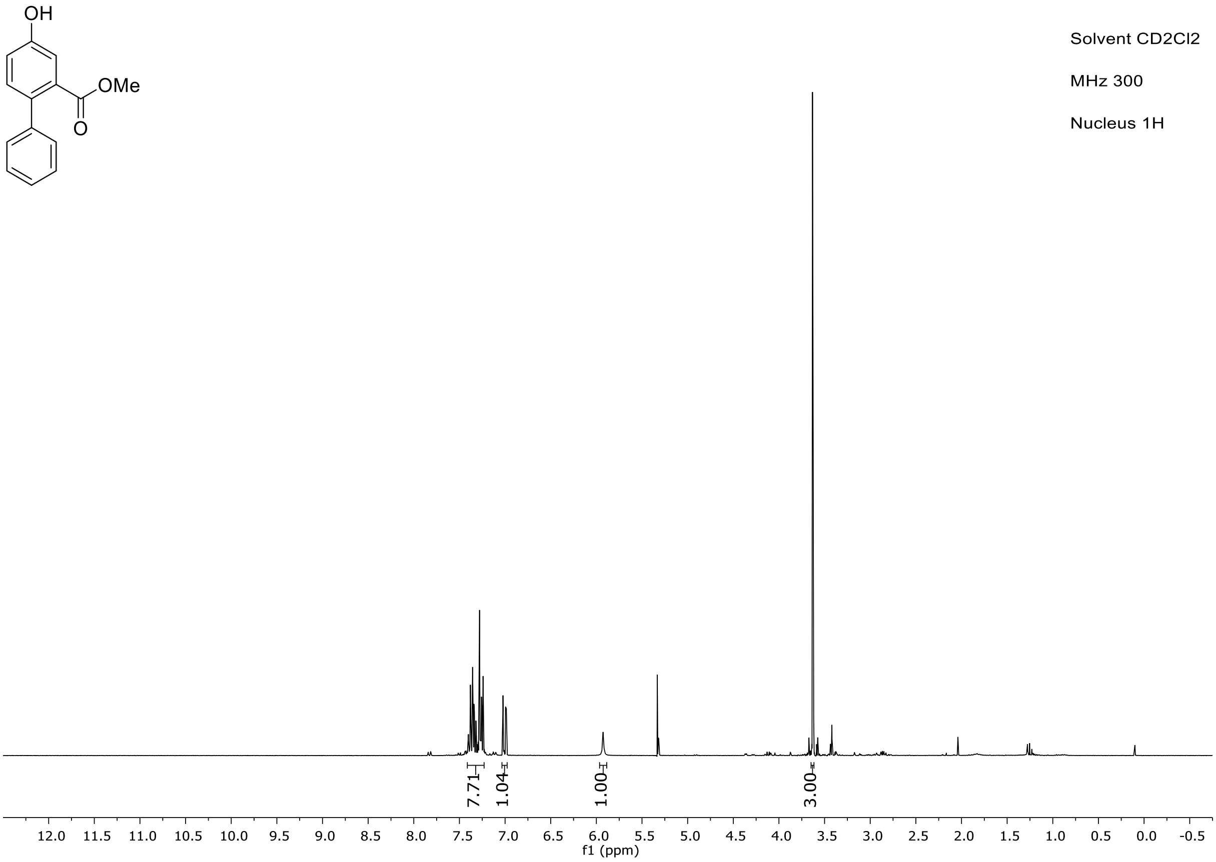

O
OH
OMe
O
Solvent CD2Cl2
MHz 400
Nucleus 1H
0.93
1.00
0.88
0.96
3.00
2.01
3.11
3.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

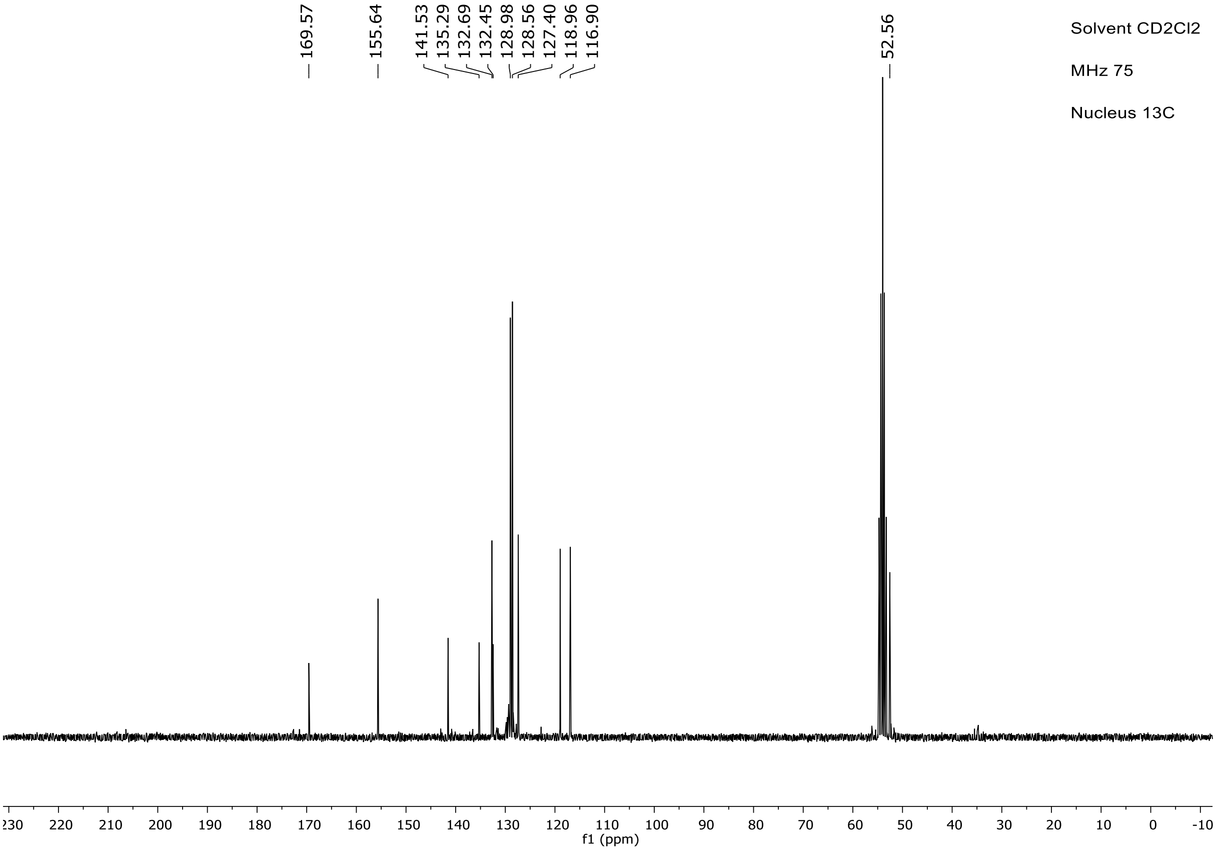

207.81
166.22
162.38
137.12
130.56
122.34
119.98
119.79
52.95
32.58
8.22
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

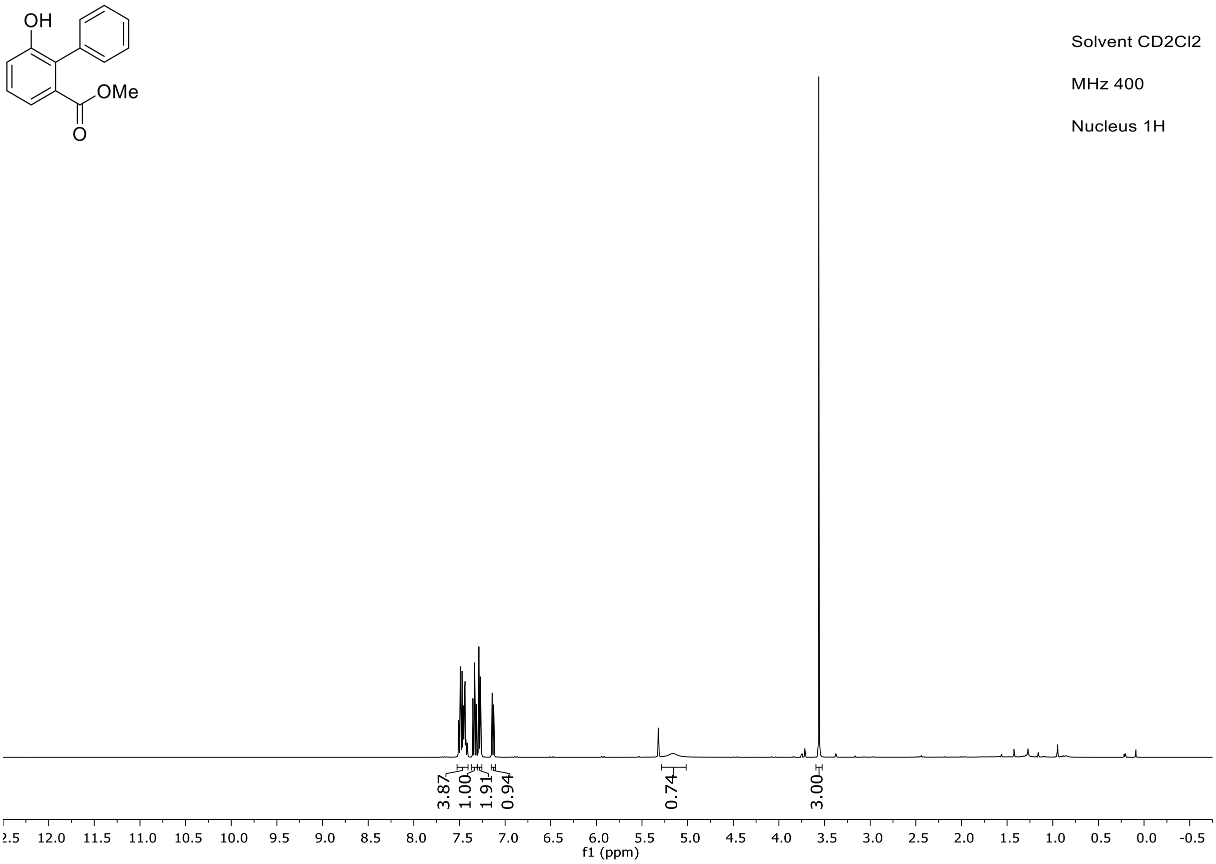

OH
OMe
O

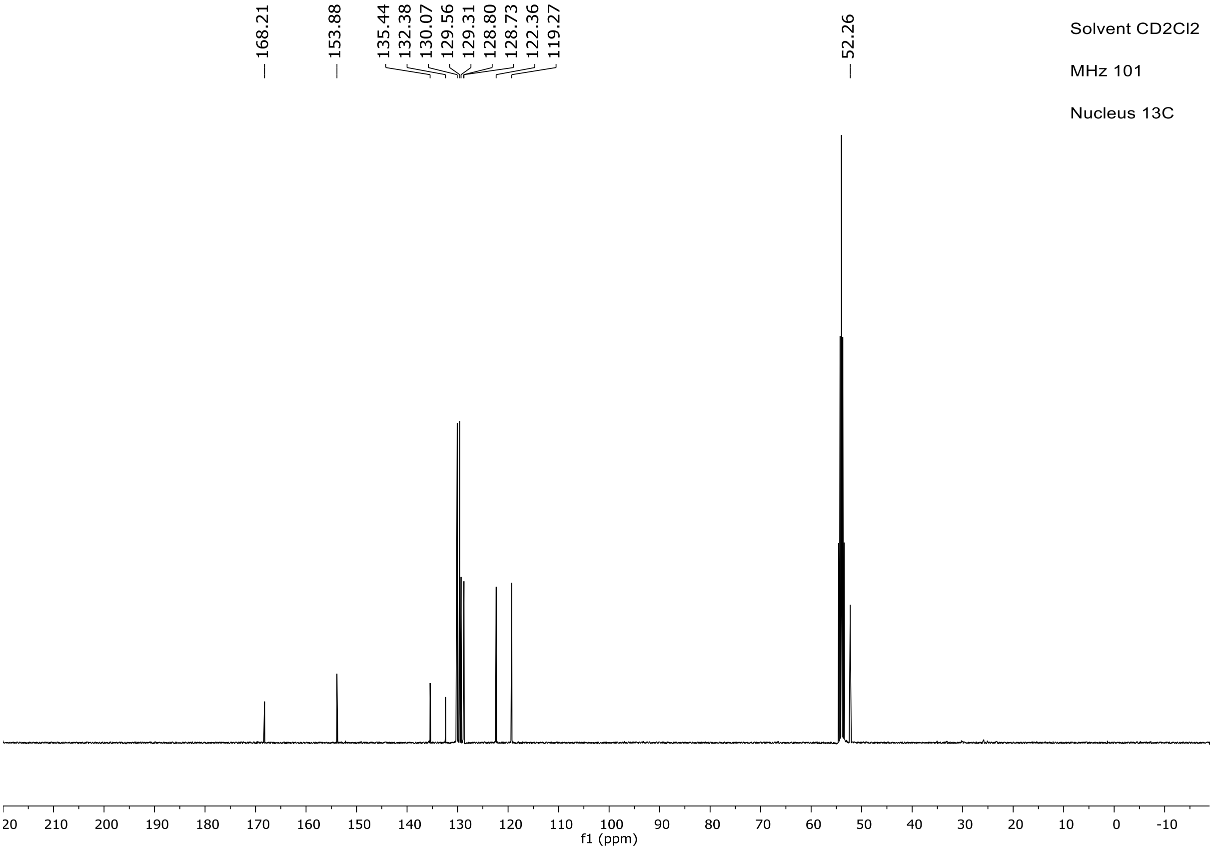

Solvent CD2Cl2
MHz 400
Nucleus 1H
1.86
5.20
1.04
2.09
3.00
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

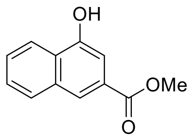

167.58
154.42
140.23
133.68
131.39
130.19
129.34
129.10
126.89
122.44
116.88
52.67
36.62
Solvent CD2Cl2
MHz 101
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
OMe
O
Solvent CD2Cl2
MHz 300
Nucleus 1H
7.71
1.04
1.00
3.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


169.57
155.64
141.53
135.29
132.69
132.45
128.98
128.56
127.40
118.96
116.90
52.56
Solvent CD2Cl2
MHz 75
Nucleus 13C
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)


OH
OMe
O
Solvent CD2Cl2
MHz 400
Nucleus 1H
3.87
1.00
1.91
0.94
0.74
3.00
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

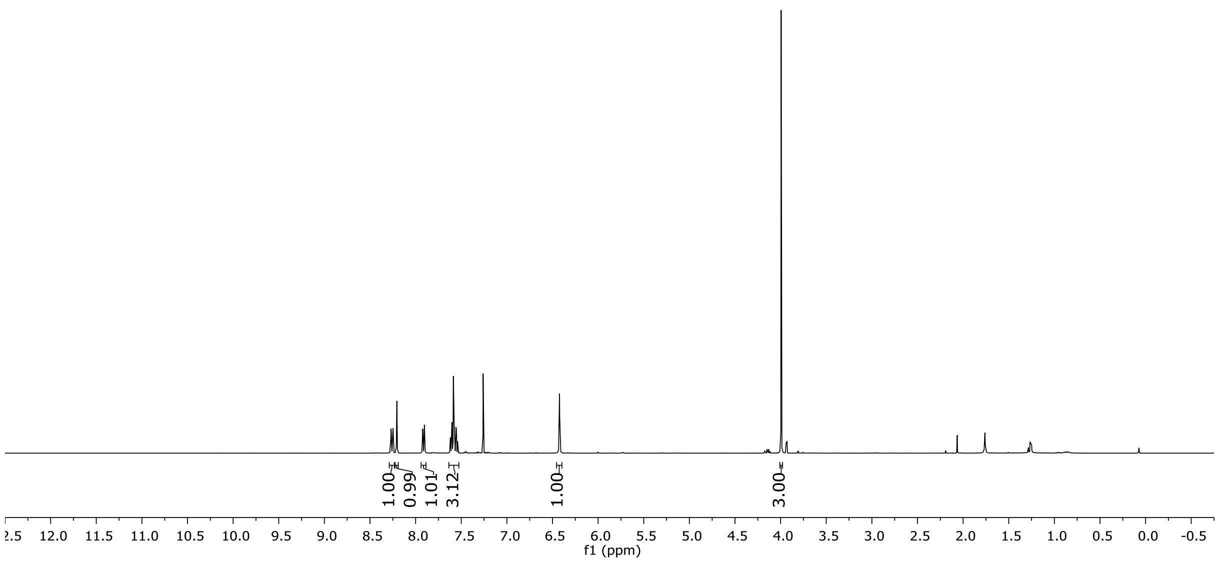

168.21
153.88
135.44
132.38
130.07
129.56
129.31
128.80
128.73
122.36
119.27
52.26
Solvent CD2Cl2
MHz 101
Nucleus 13C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



Solvent CDCl3

MHz 400

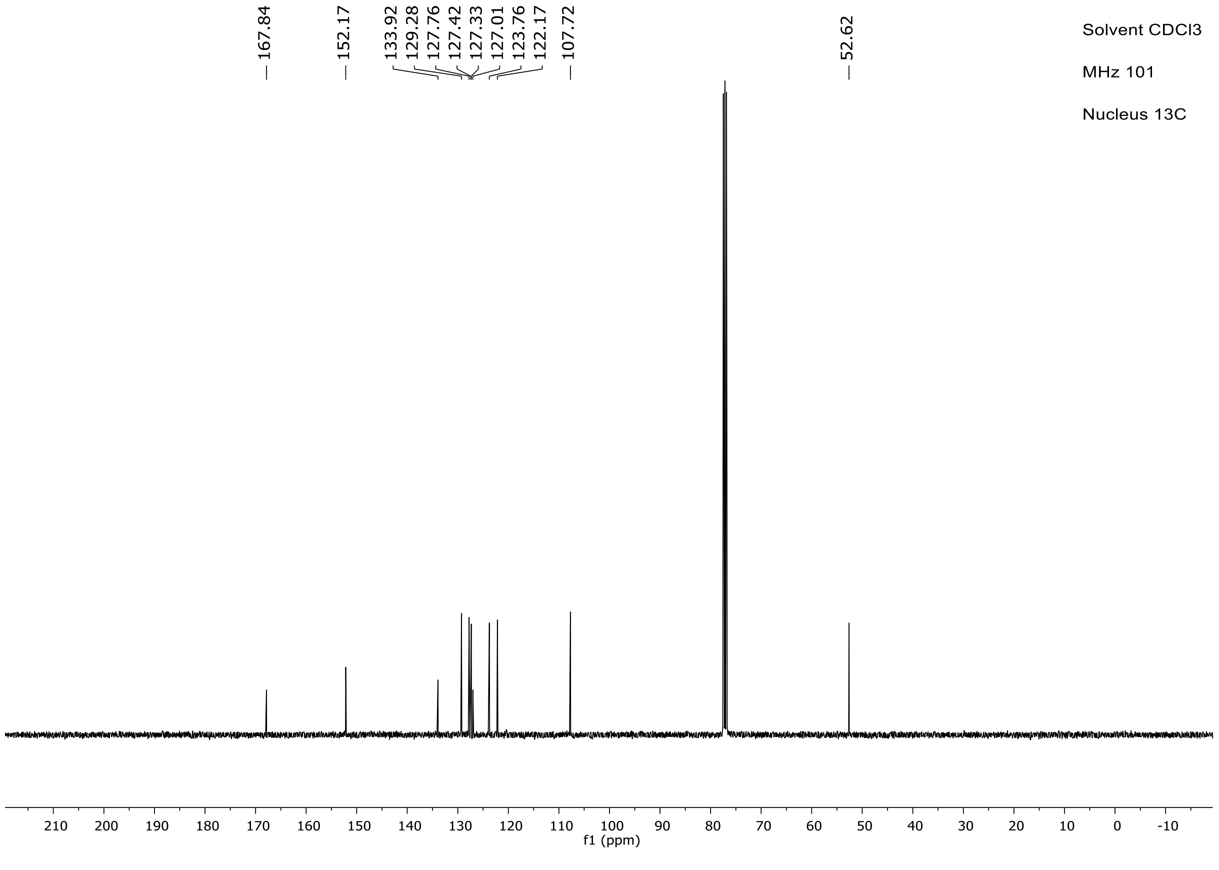
Nucleus 1H

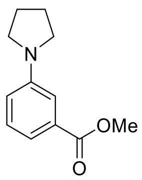


Solvent CDCl3

MHz 101

Nucleus 13C

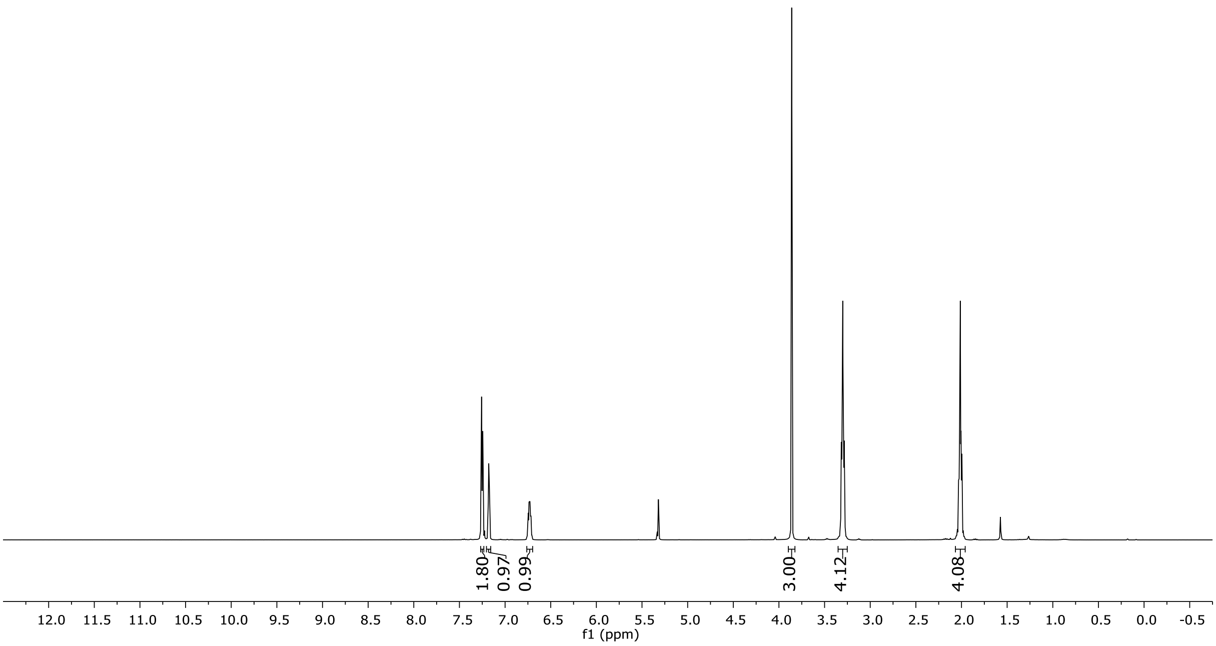


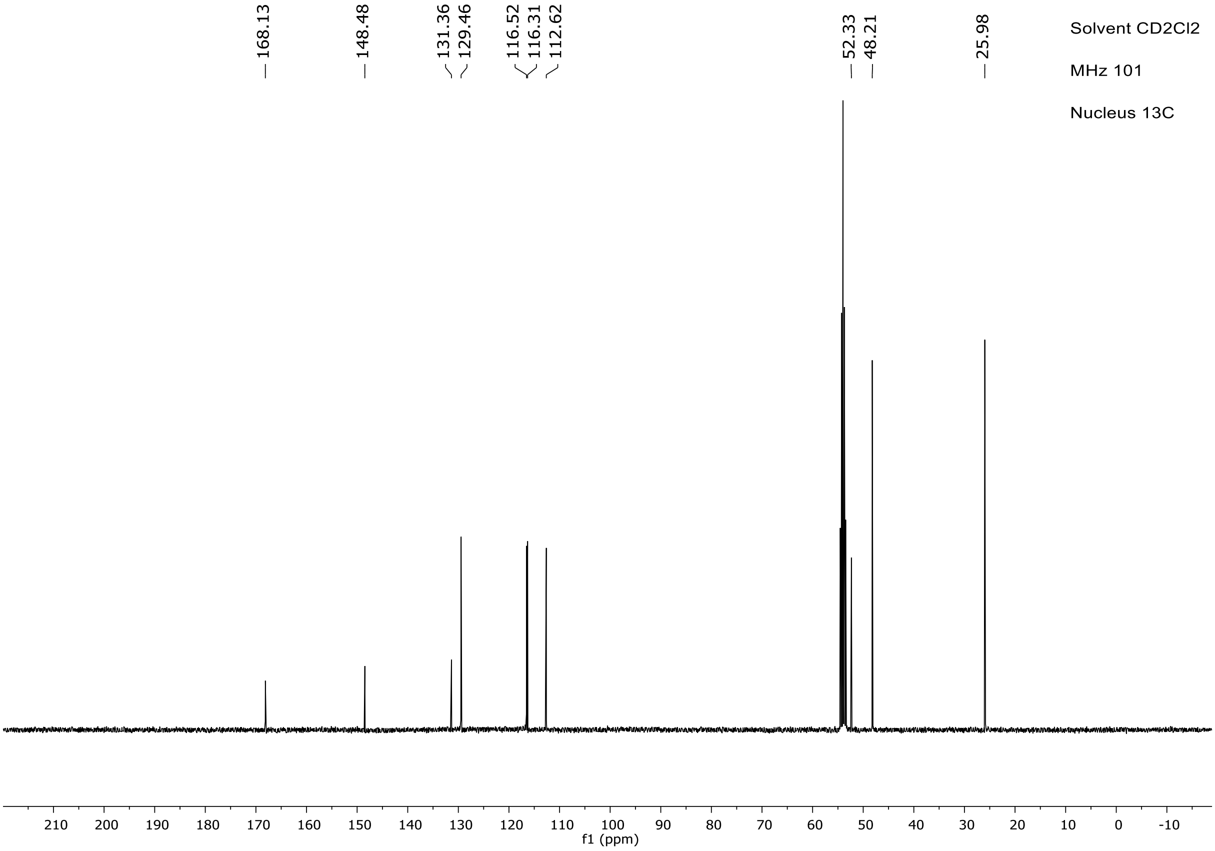


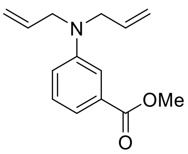
Solvent CD2Cl2

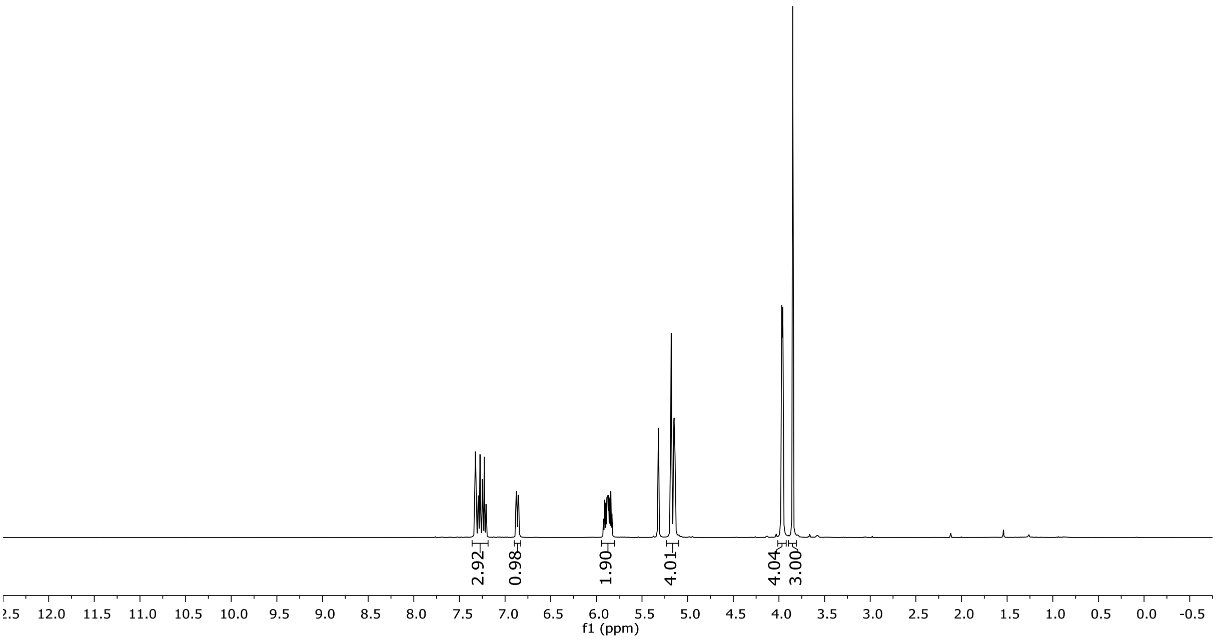
MHz 400

Nucleus 1H





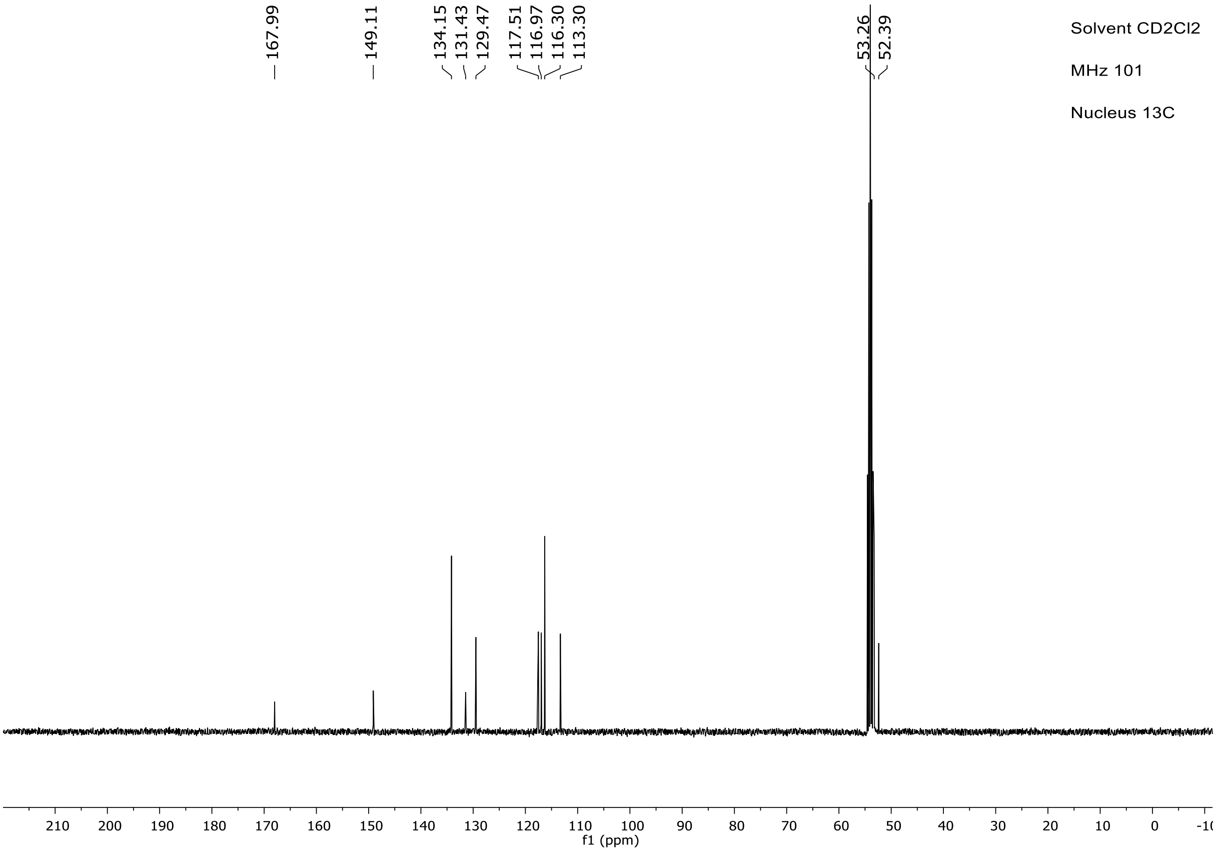




Solvent CD2Cl2

MHz 400

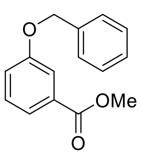
Nucleus 1H



Solvent CD2Cl2

MHz 101

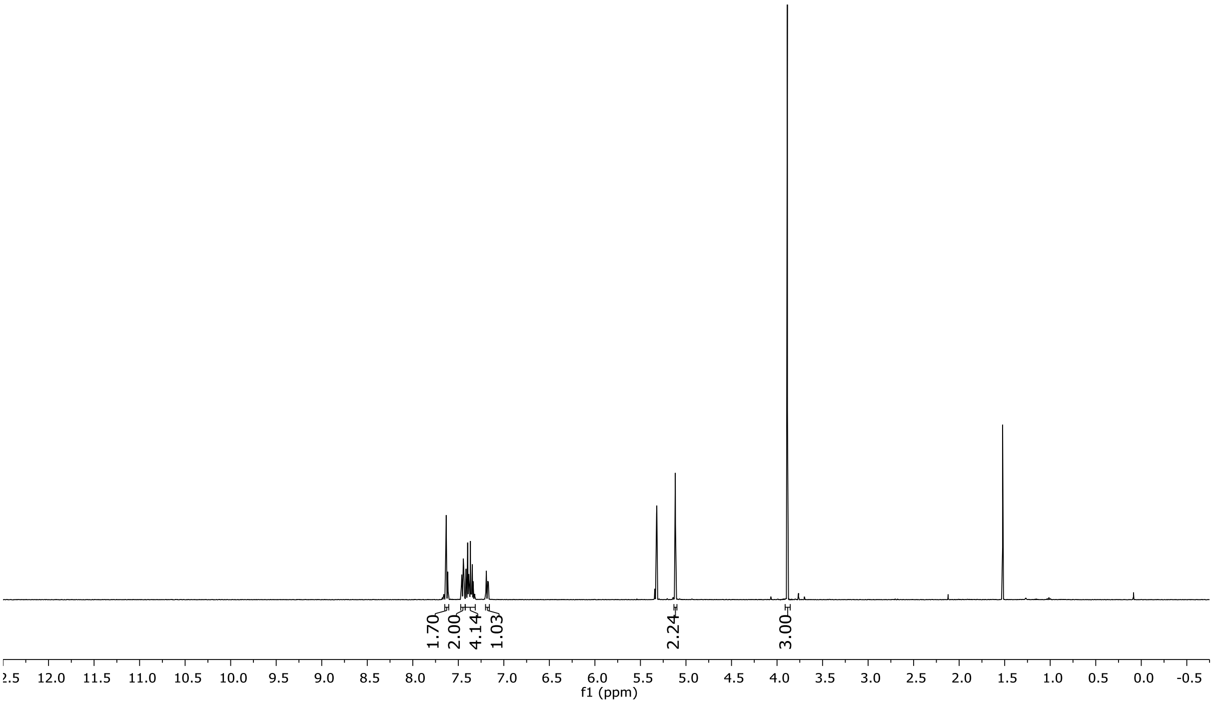
Nucleus 13C



Solvent CD2Cl2

MHz 400

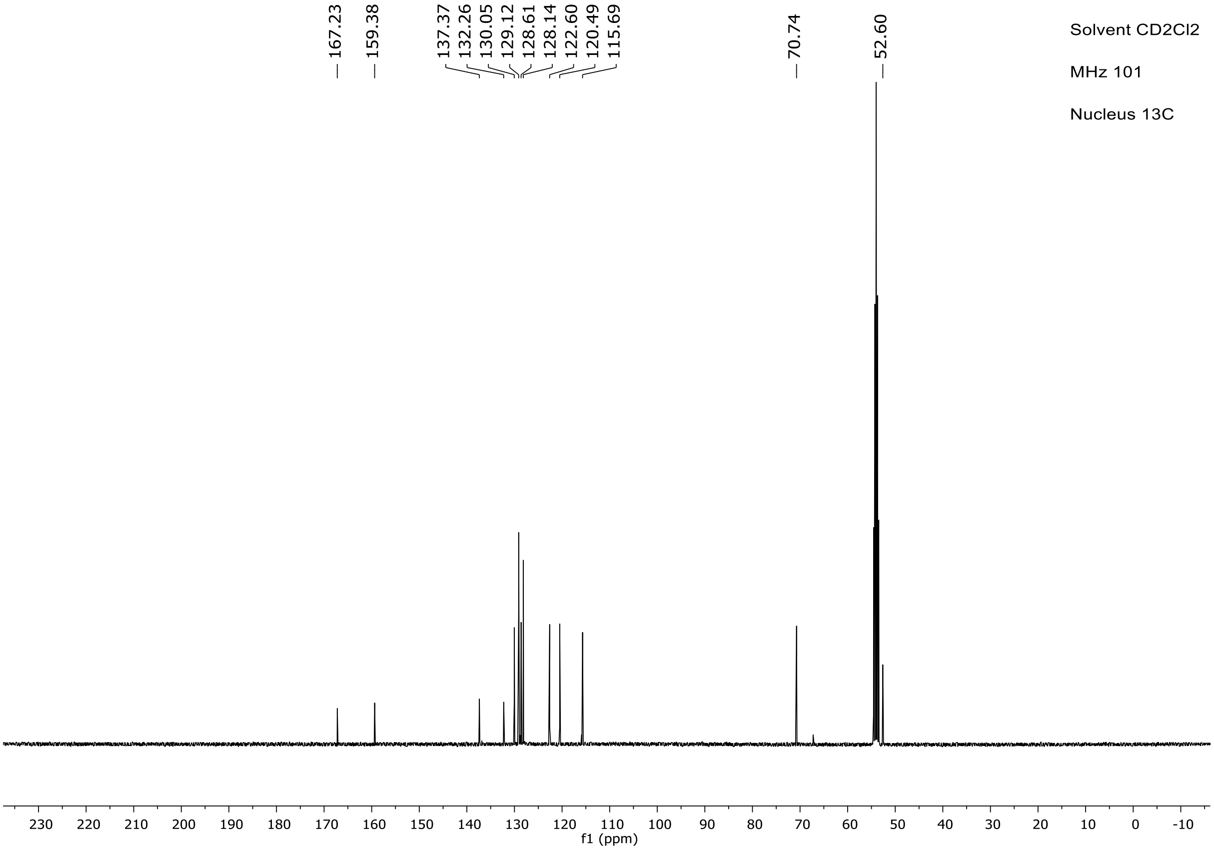
Nucleus 1H

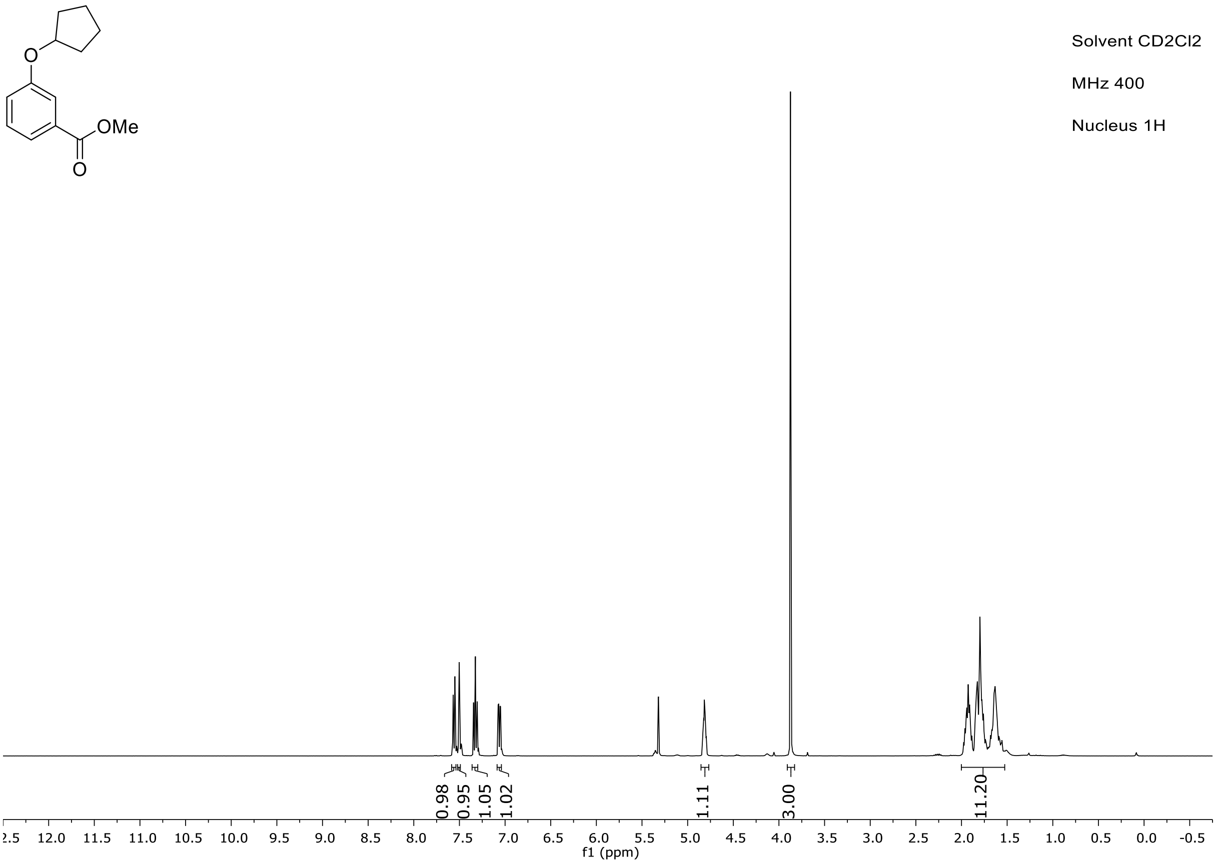


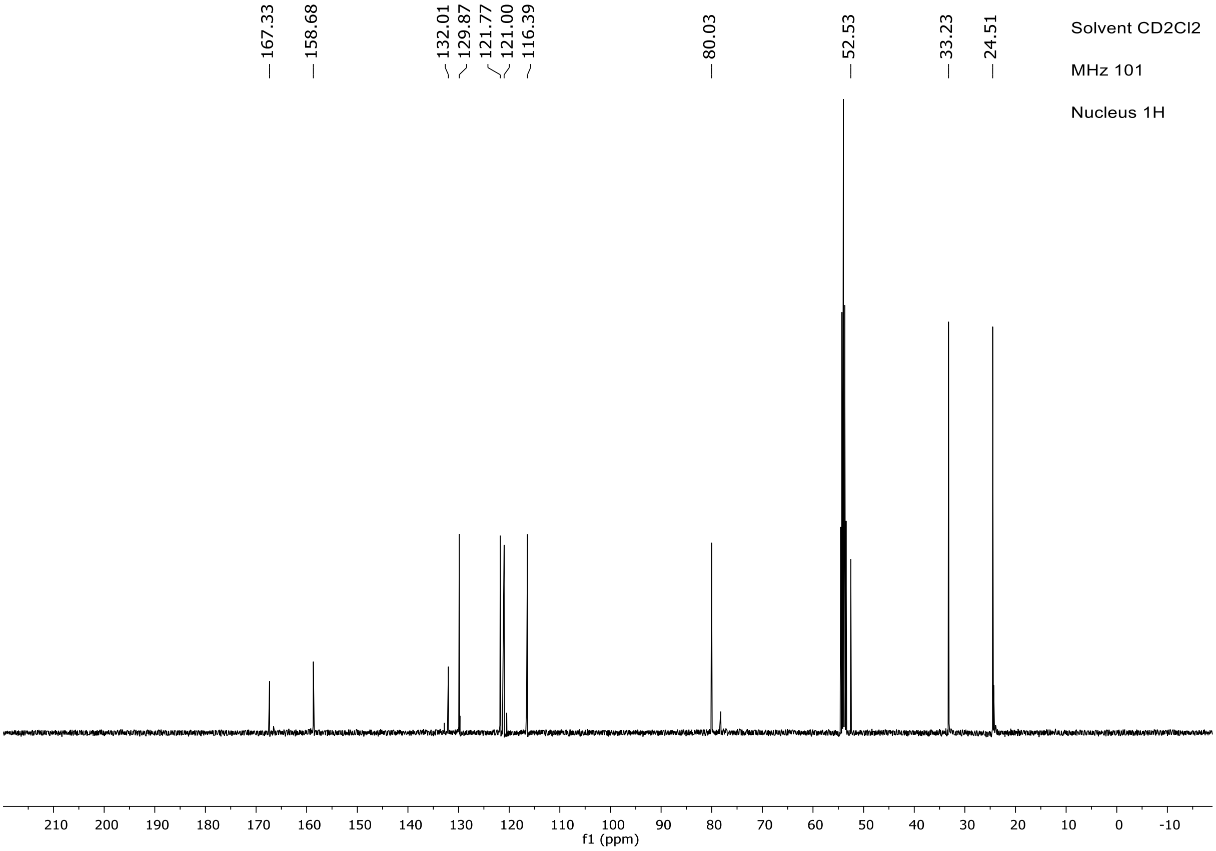
Solvent CD2Cl2

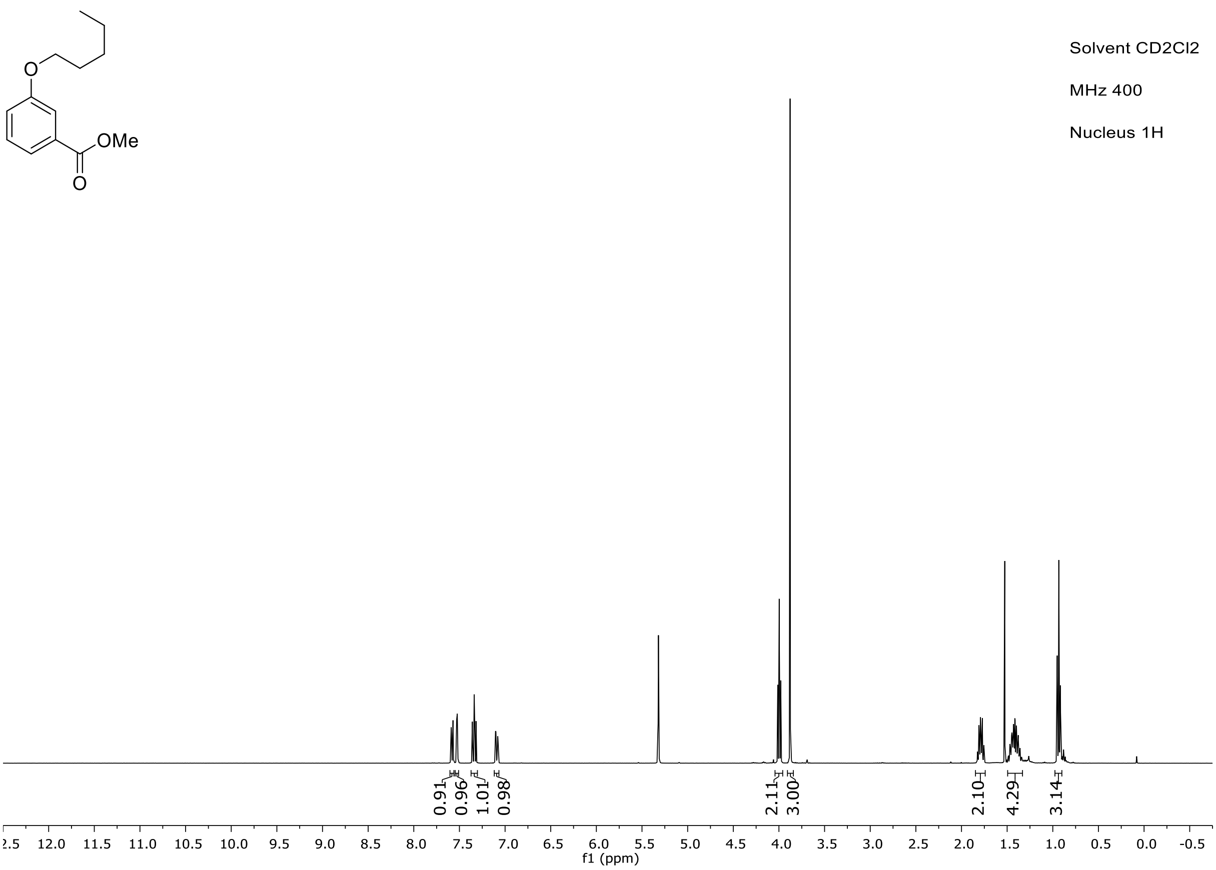
MHz 101

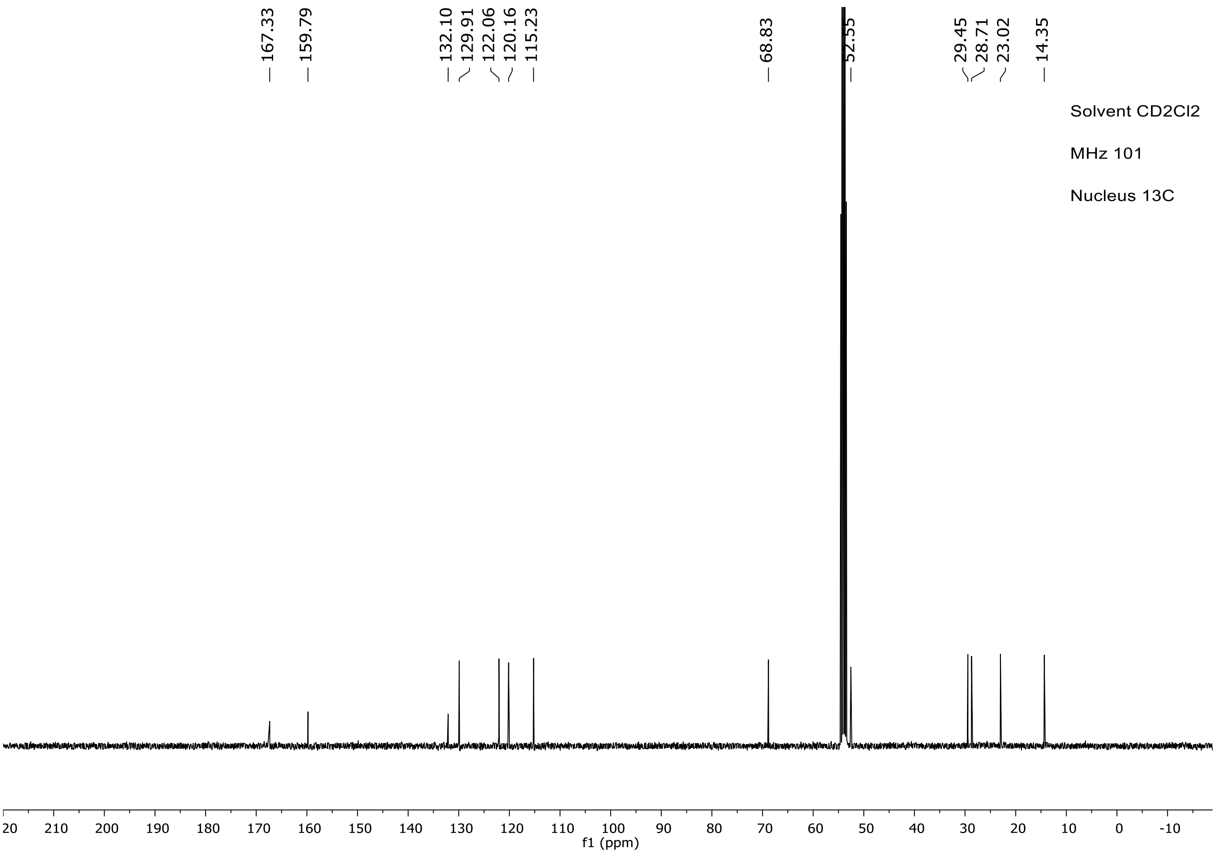
Nucleus 13C

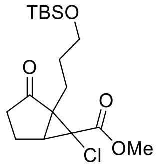


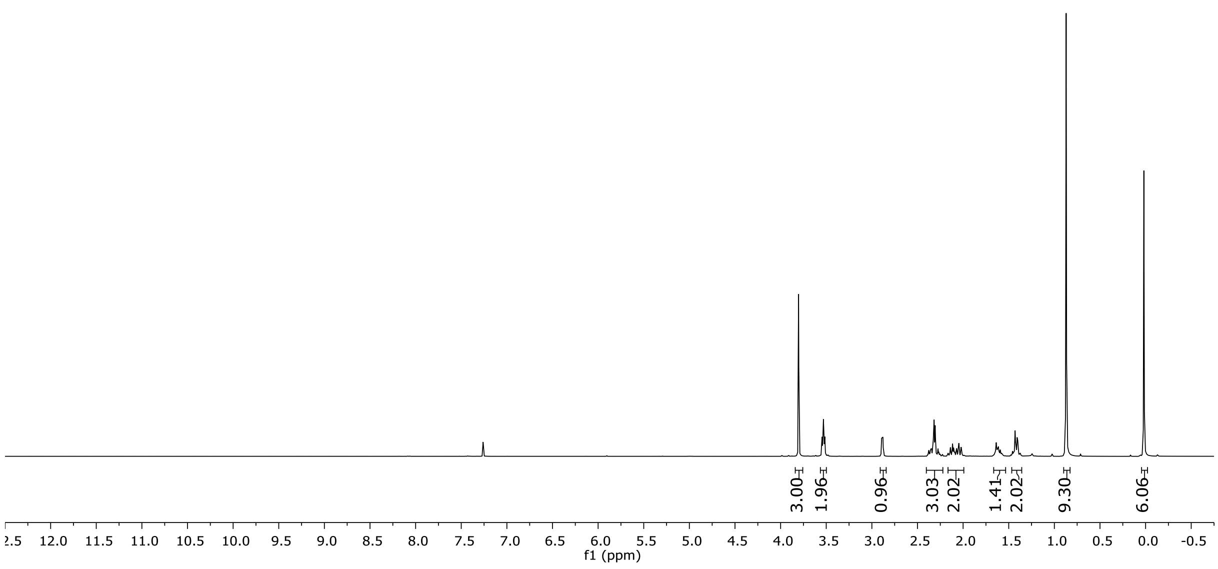

OMe
O
O
Solvent CD2Cl2
MHz 400
Nucleus 1H
0.98
0.95
1.05
1.02
1.11
3.00
11.20
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

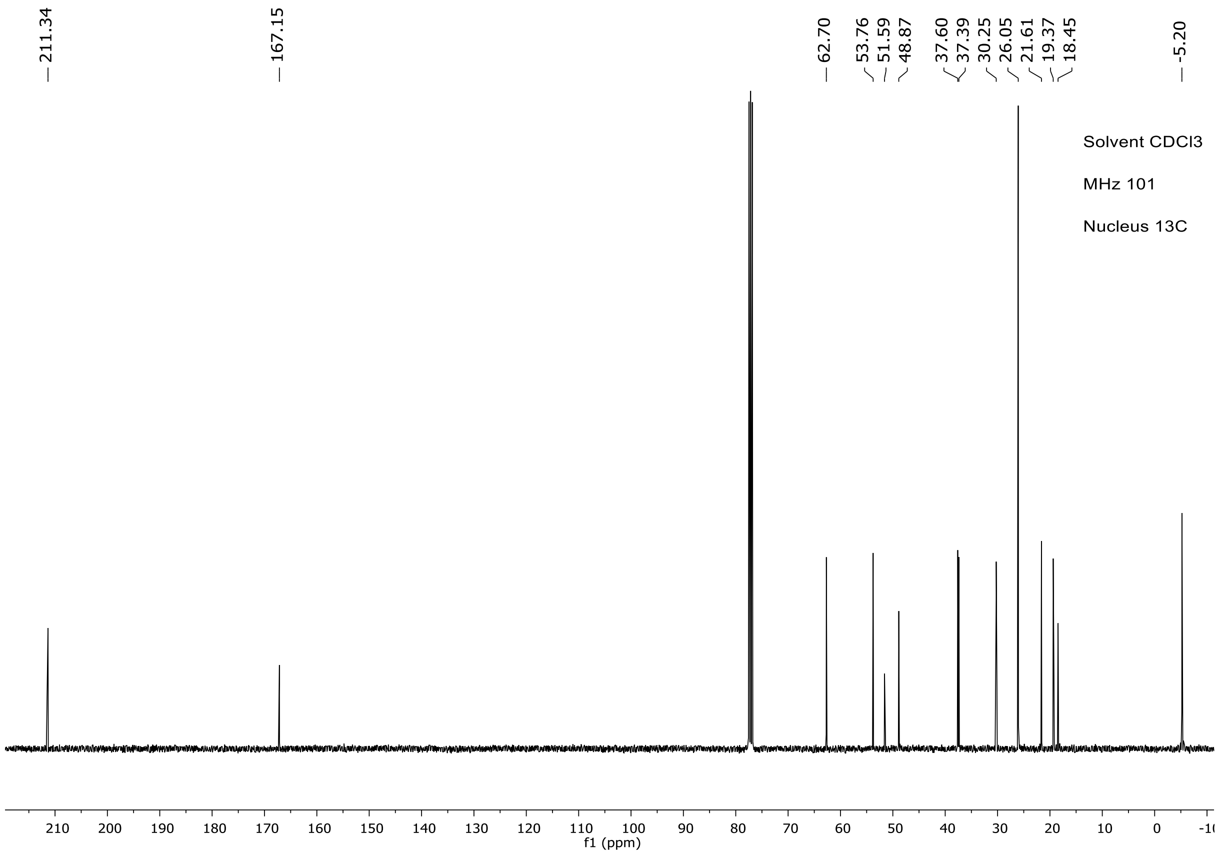

167.33
158.68
132.01
129.87
121.77
121.00
116.39
80.03
52.53
33.23
24.51
Solvent CD2Cl2
MHz 101
Nucleus 1H
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

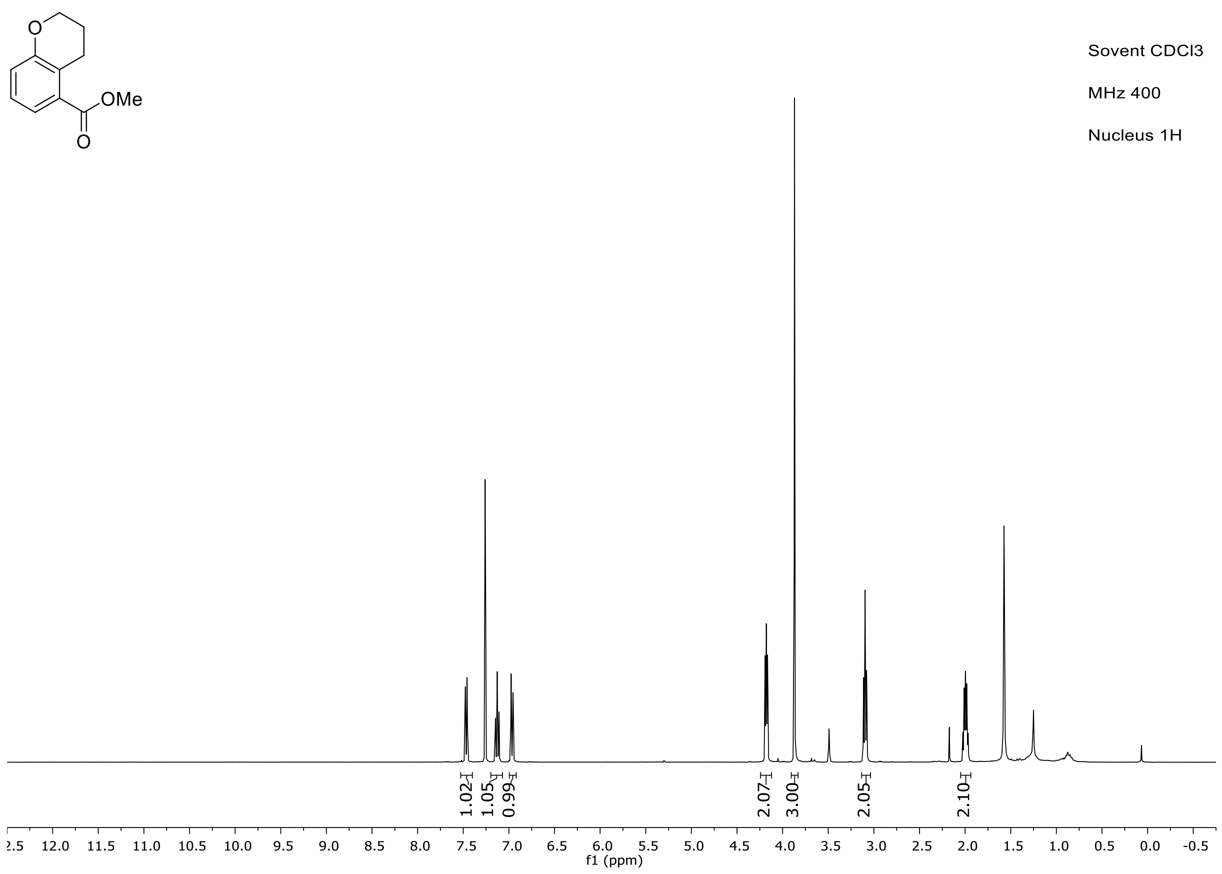

O
OMe
O
Solvent CD2Cl2
MHz 400
Nucleus 1H
0.91
0.96
1.01
0.98
2.11
3.00
2.10
4.29
3.14
2.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

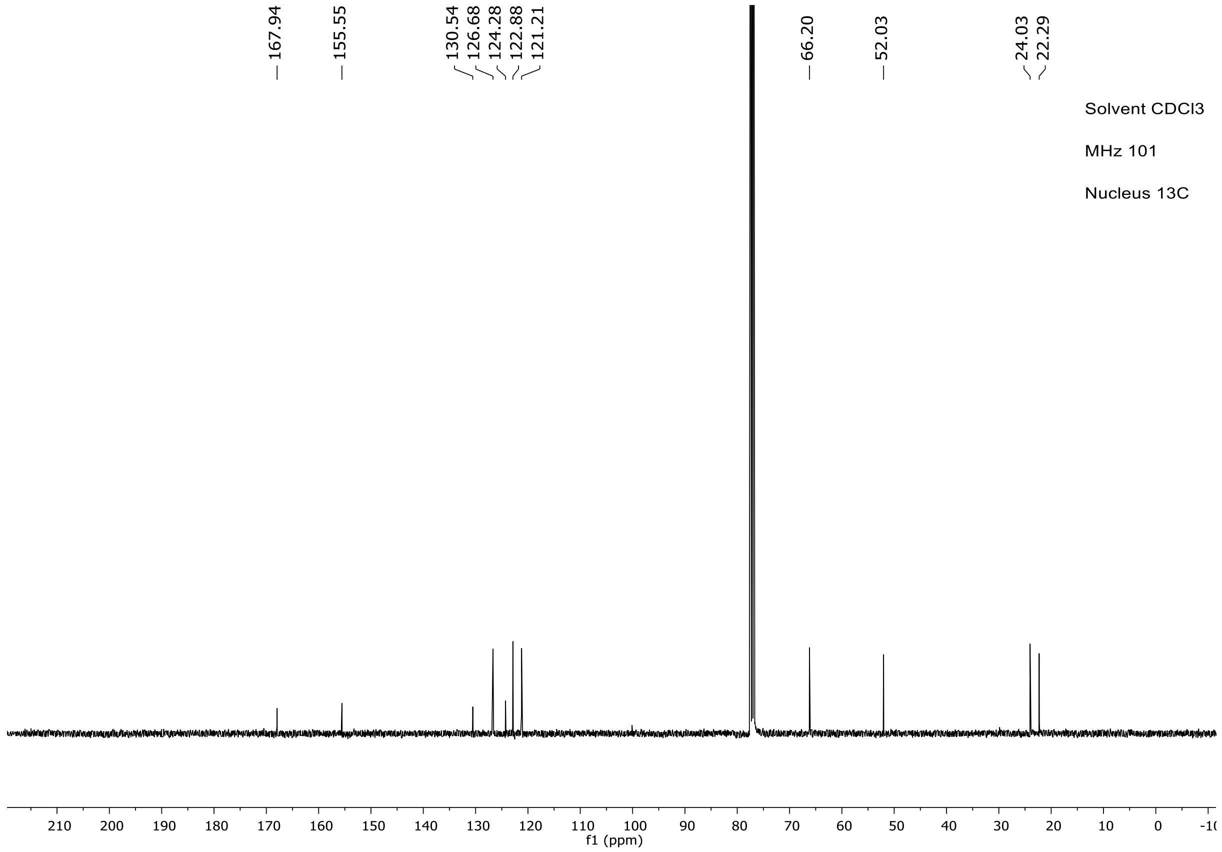

167.33
159.79
132.10
129.91
122.06
120.16
115.23
68.83
52.55
29.45
28.71
23.02
14.35
Solvent CD2Cl2
MHz 101
Nucleus 13C
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

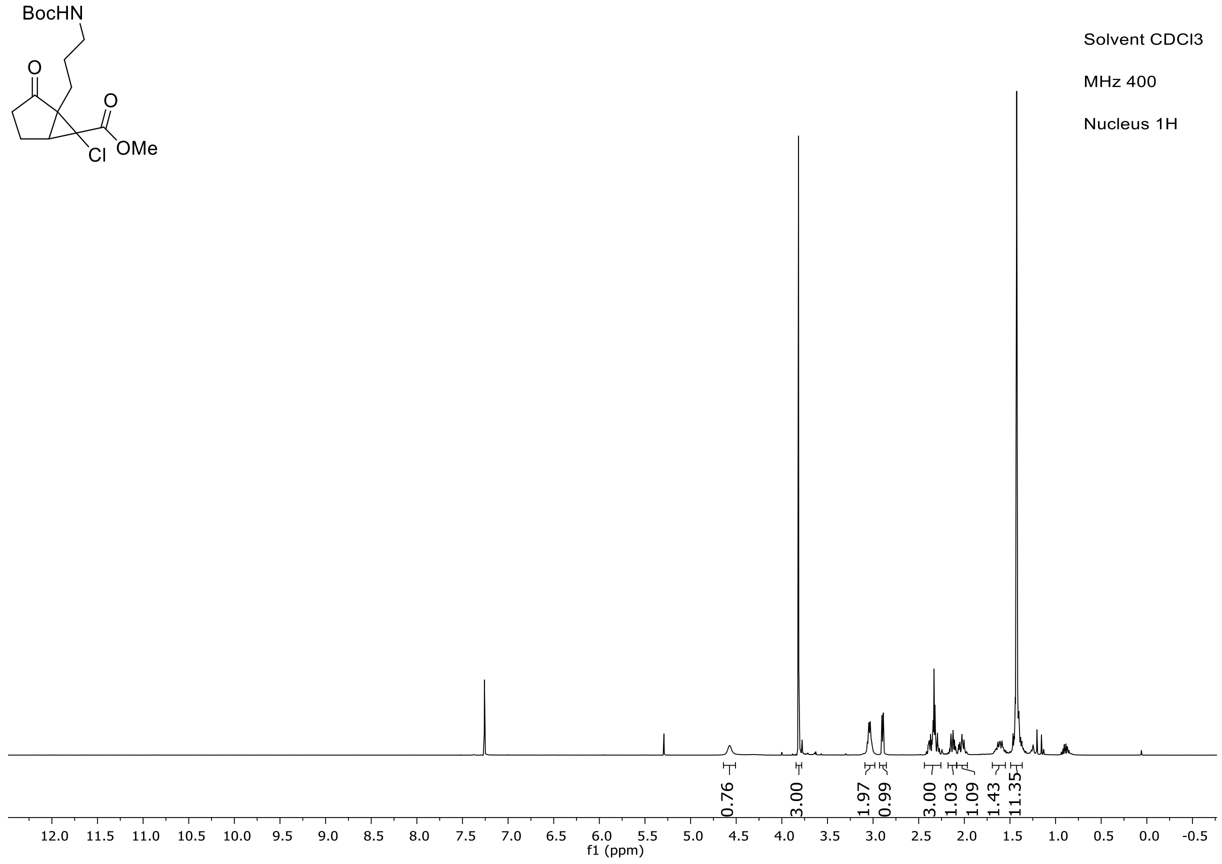

TBSO
O
O
OMe
Cl

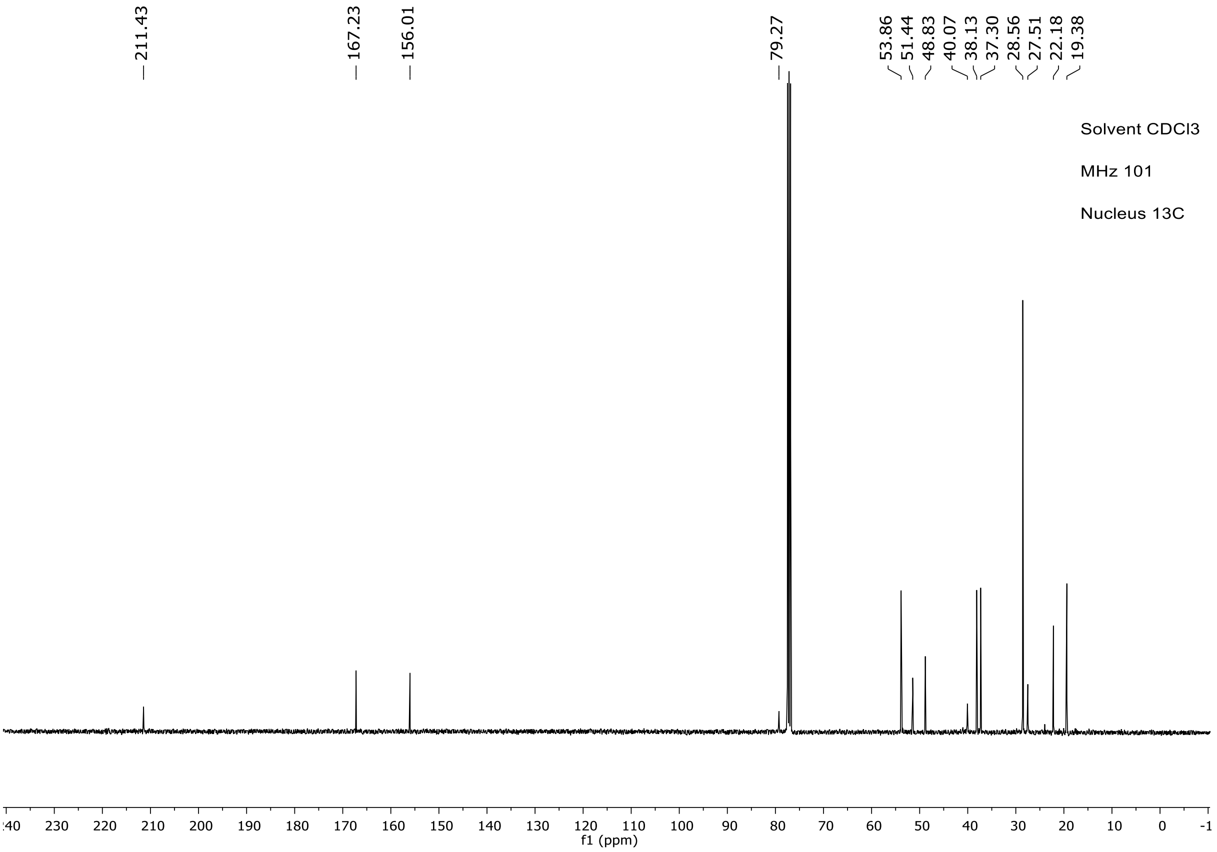

Solvent CDCl3
MHz 400
Nucleus 1H
3.00
1.96
0.96
3.03
2.02
1.41
2.02
9.30
6.06
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

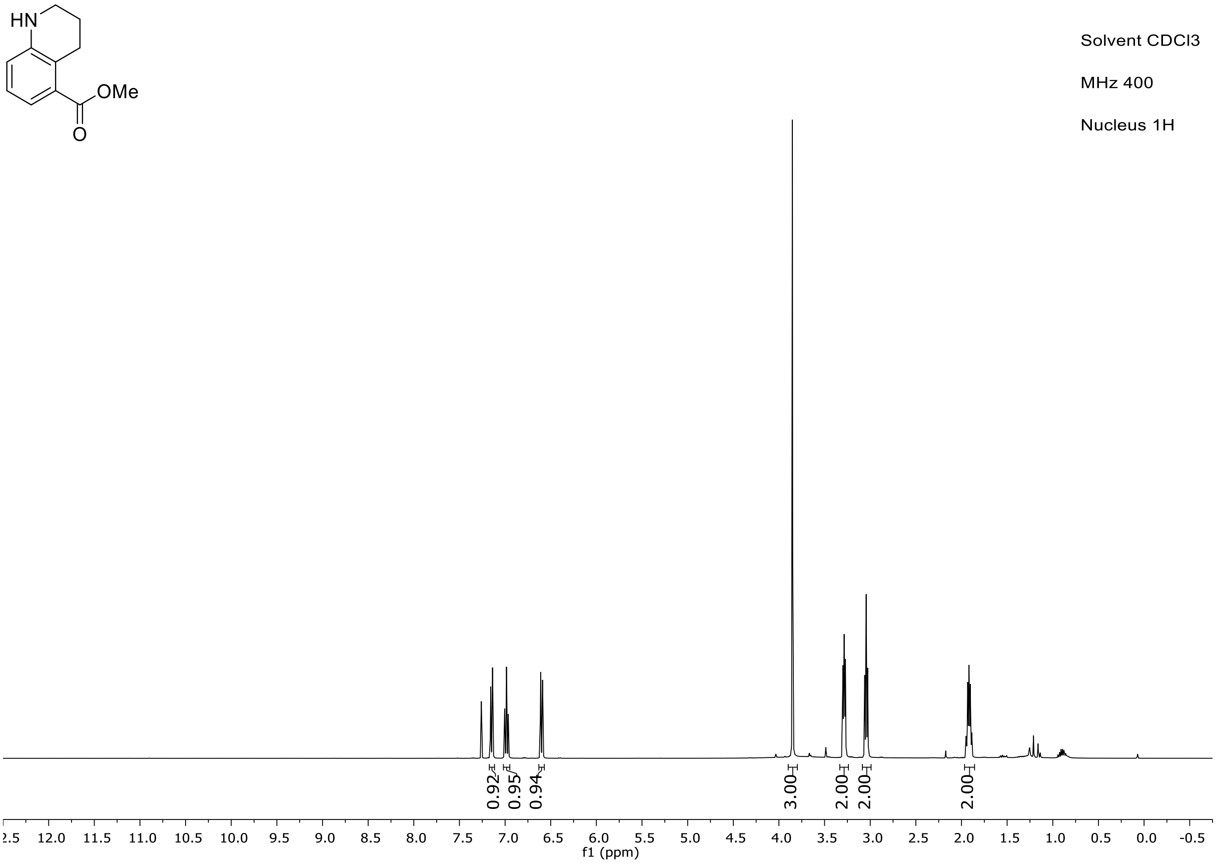

211.34
167.15
62.70
53.76
51.59
48.87
37.60
37.39
30.25
26.05
21.61
19.37
18.45
-5.20
Solvent CDCl3
MHz 101
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

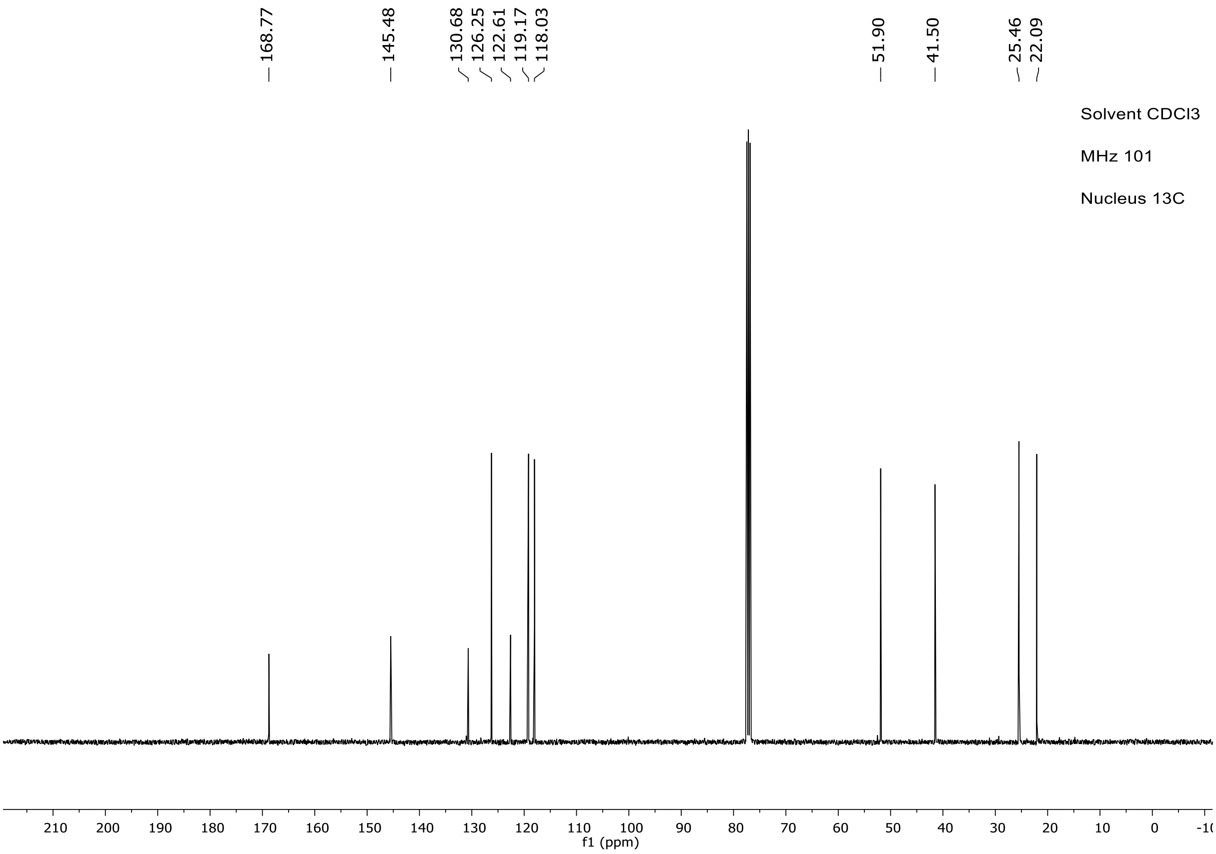

OMe
O
O
Sovent CDCl3
MHz 400
Nucleus 1H
1.02
1.05
0.99
2.07
3.00
2.05
2.10
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

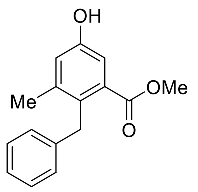

167.94
155.55
130.54
126.68
124.28
122.88
121.21
66.20
52.03
24.03
22.29
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

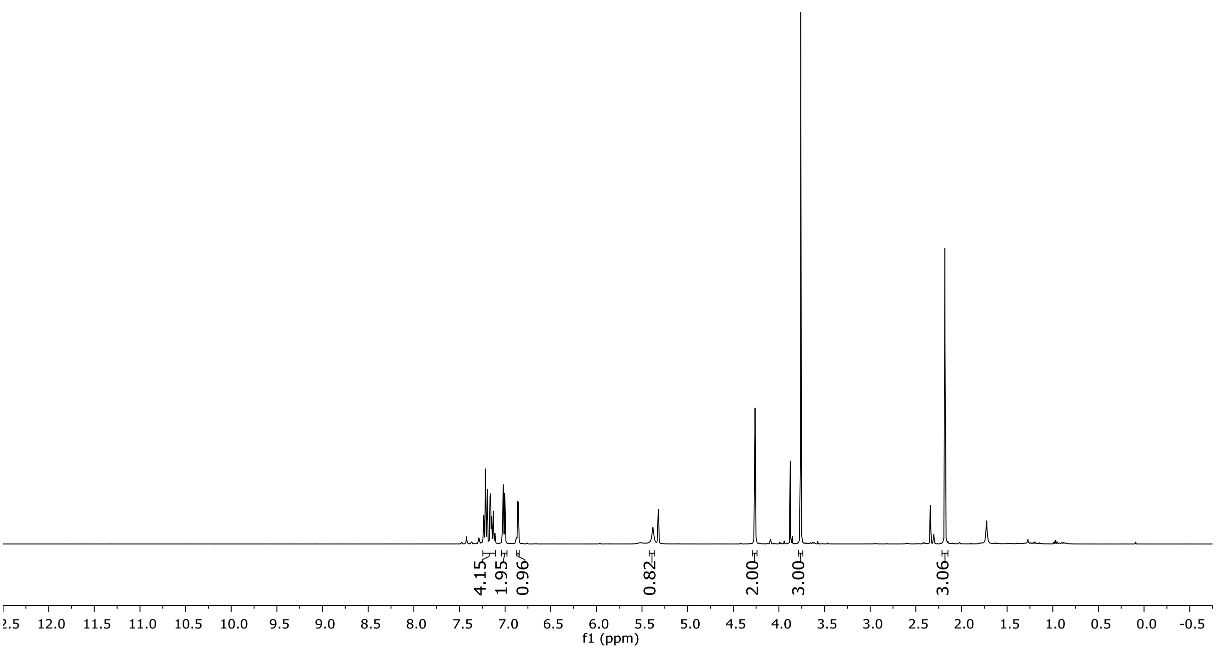

BocHN
O
O
OMe
Cl
Solvent CDCl3
MHz 400
Nucleus 1H
0.76
3.00
1.97
0.99
3.00
1.03
1.09
1.43
11.35
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

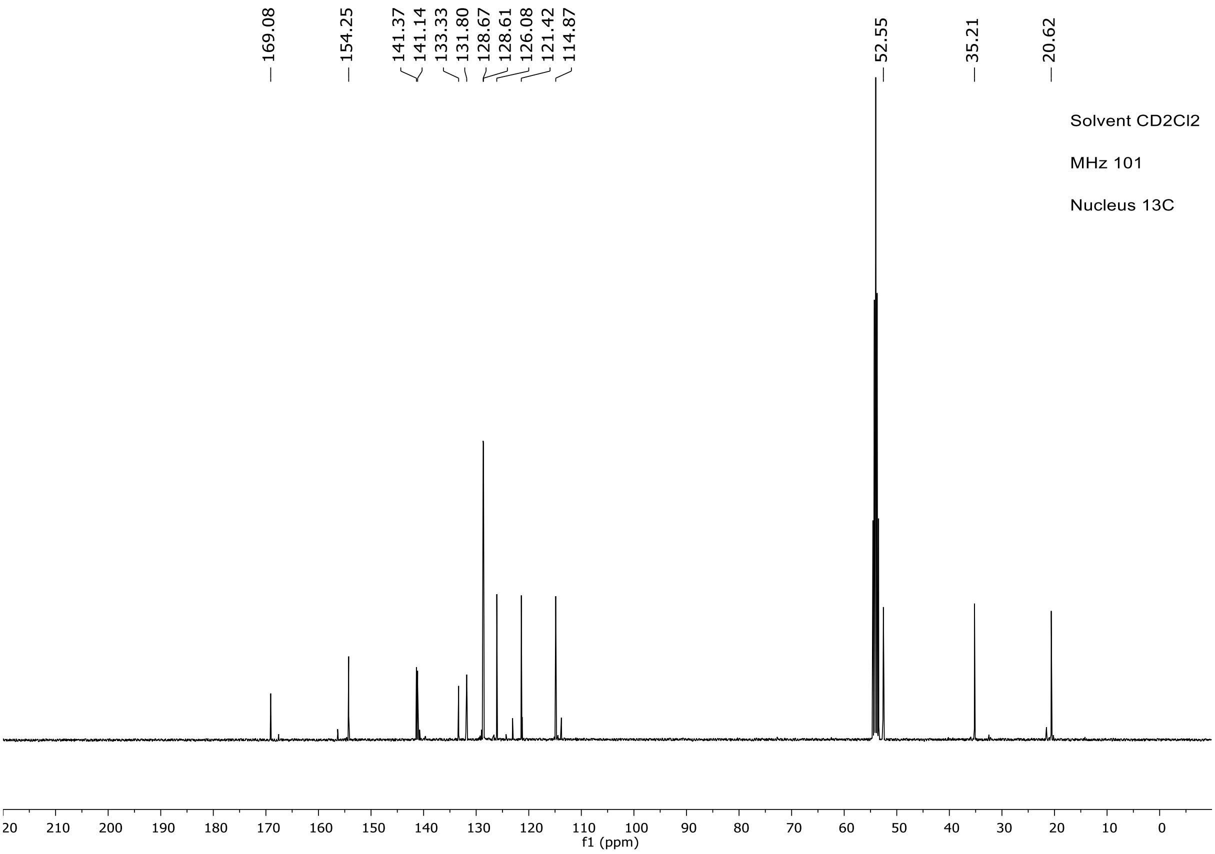

211.43
167.23
156.01
79.27
53.86
51.44
48.83
40.07
38.13
37.30
28.56
27.51
22.18
19.38
Solvent CDCl3
MHz 101
Nucleus 13C
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


HN
OMe
O
Solvent CDCl3
MHz 400
Nucleus 1H
0.92
0.95
0.94
3.00
2.00
2.00
2.00
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


168.77
145.48
130.68
126.25
122.61
119.17
118.03
51.90
41.50
25.46
22.09
Solvent CDCl3
MHz 101
Nucleus 13C
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)


OH
Me
OMe
O


Solvent CD2Cl2
MHz 400
Nucleus 1H
4.15
1.95
0.96
0.82
2.00
3.00
3.06
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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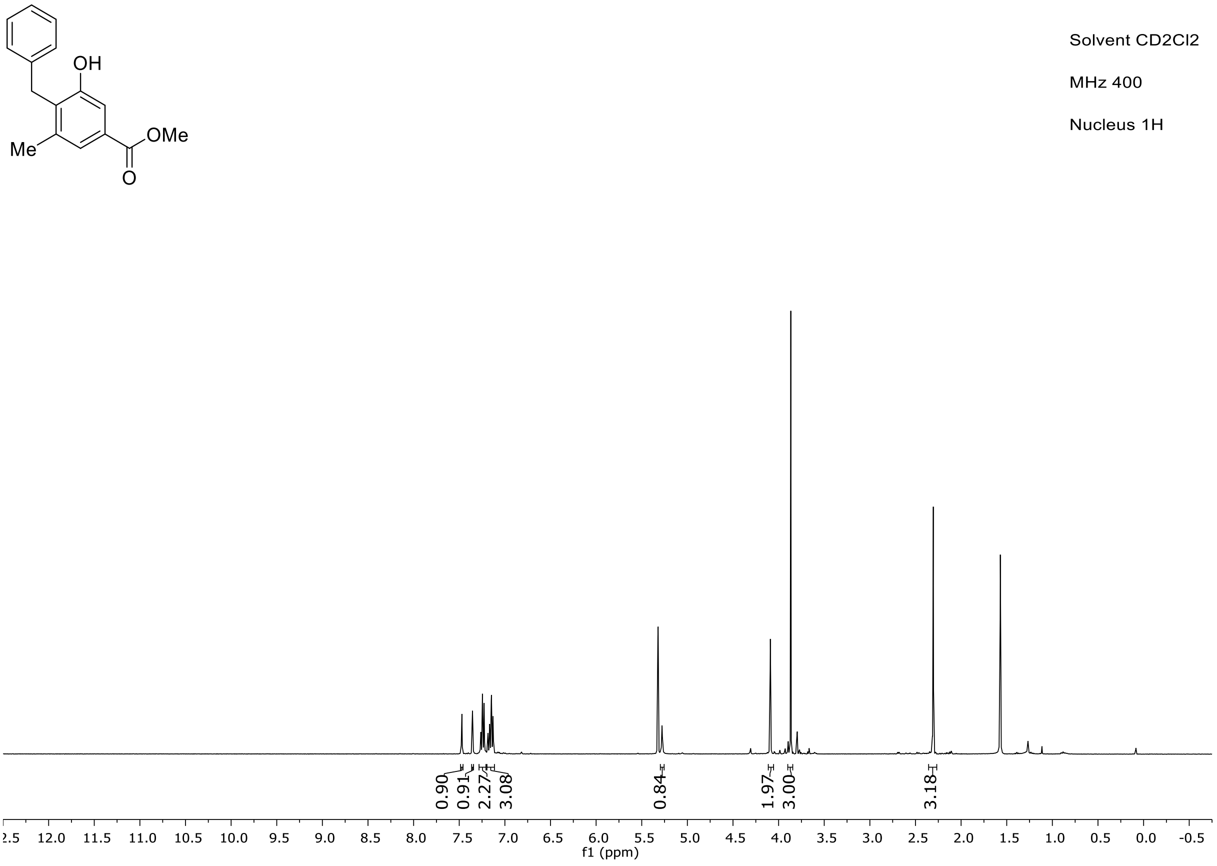
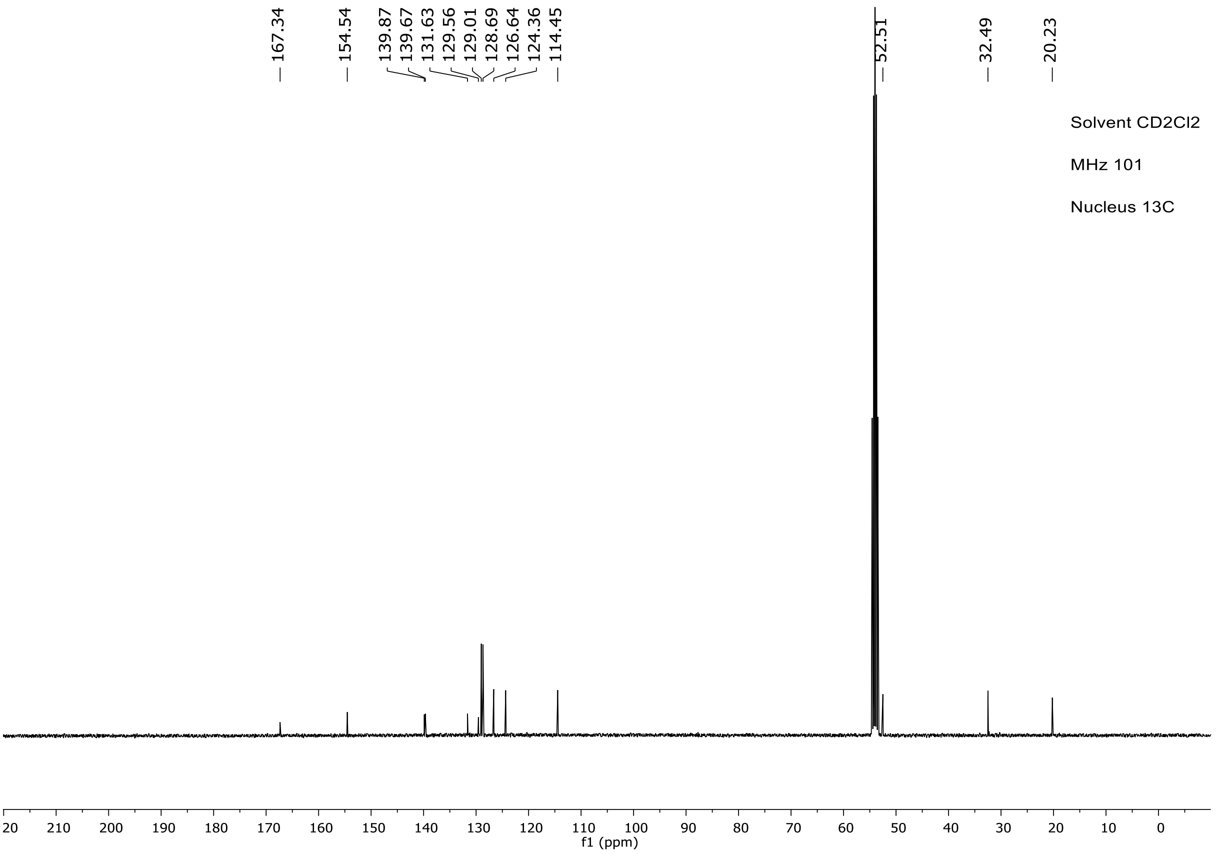
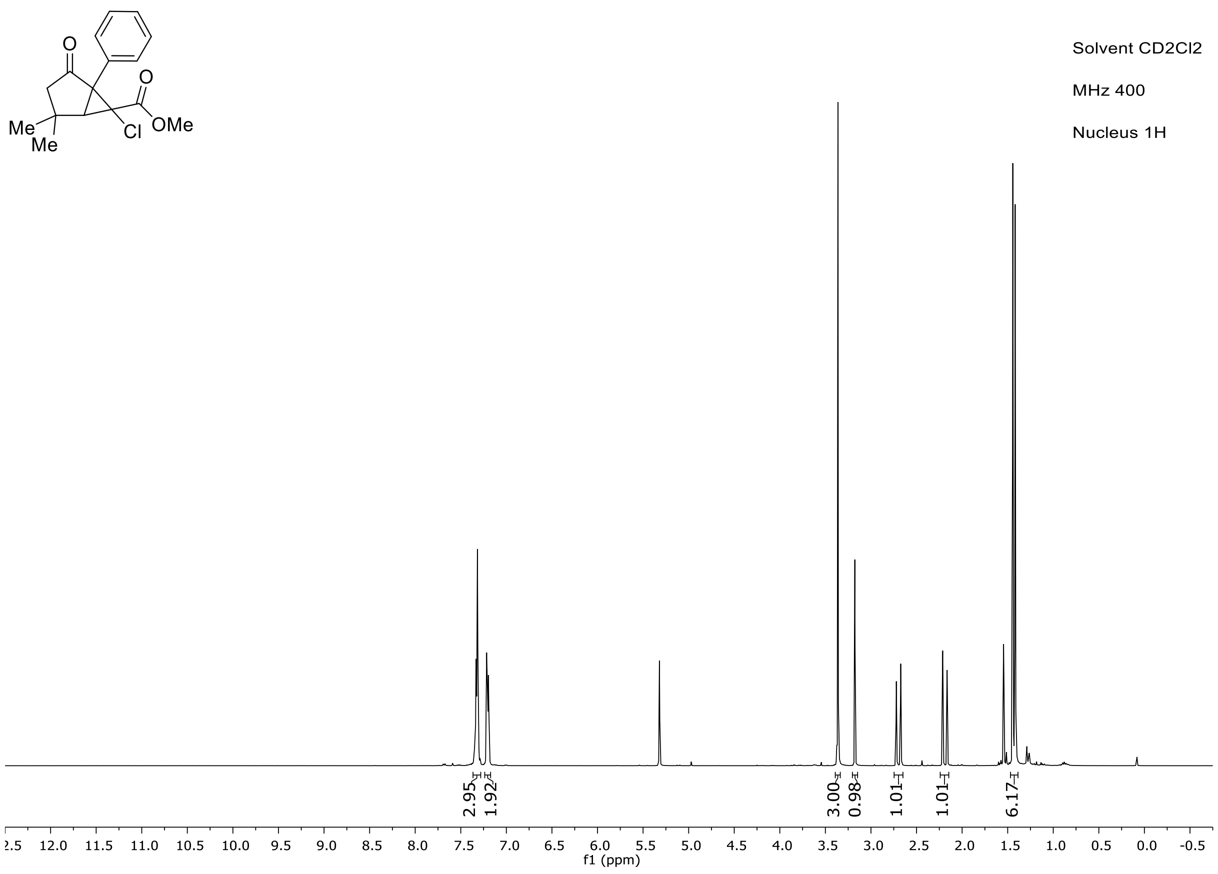
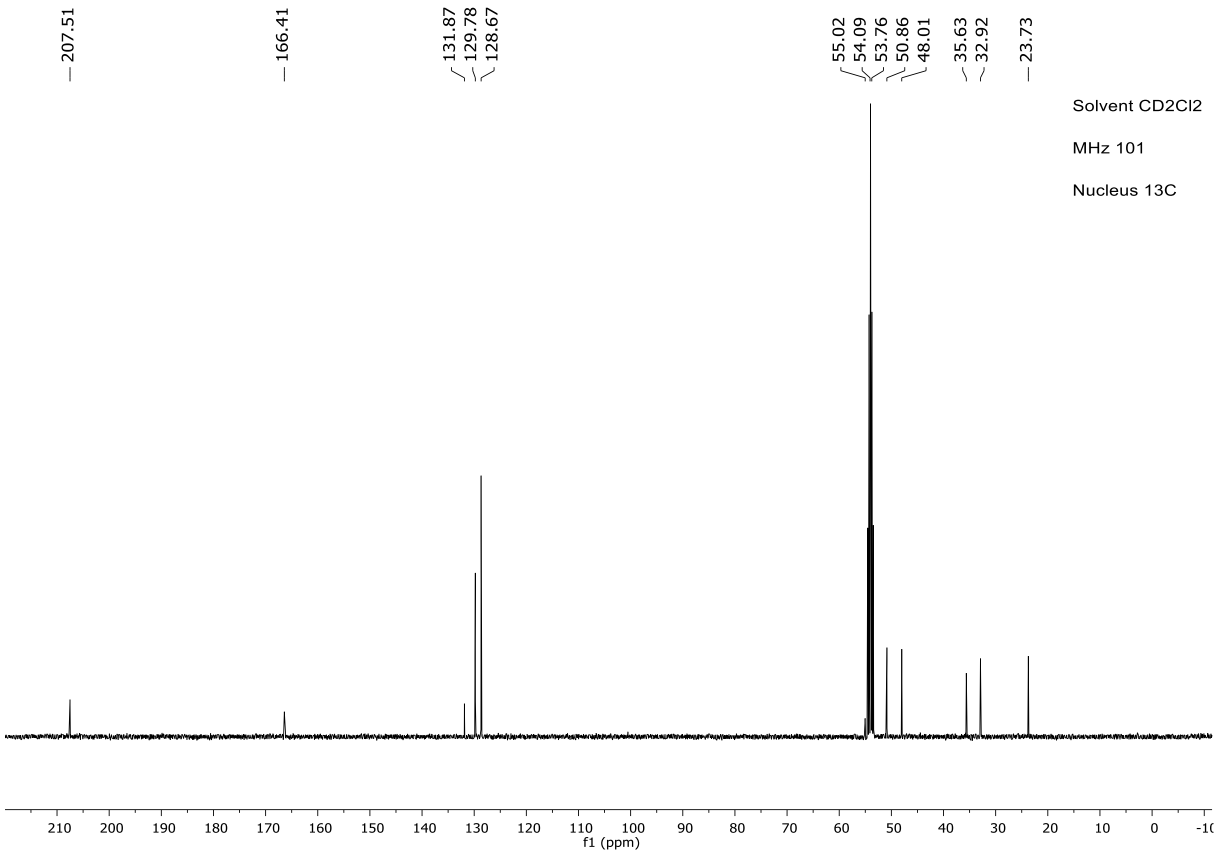
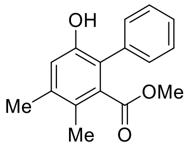
154.25
141.37
141.14
133.33
131.80
128.67
128.61
126.08
121.42
114.87
52.55
35.21
20.62
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

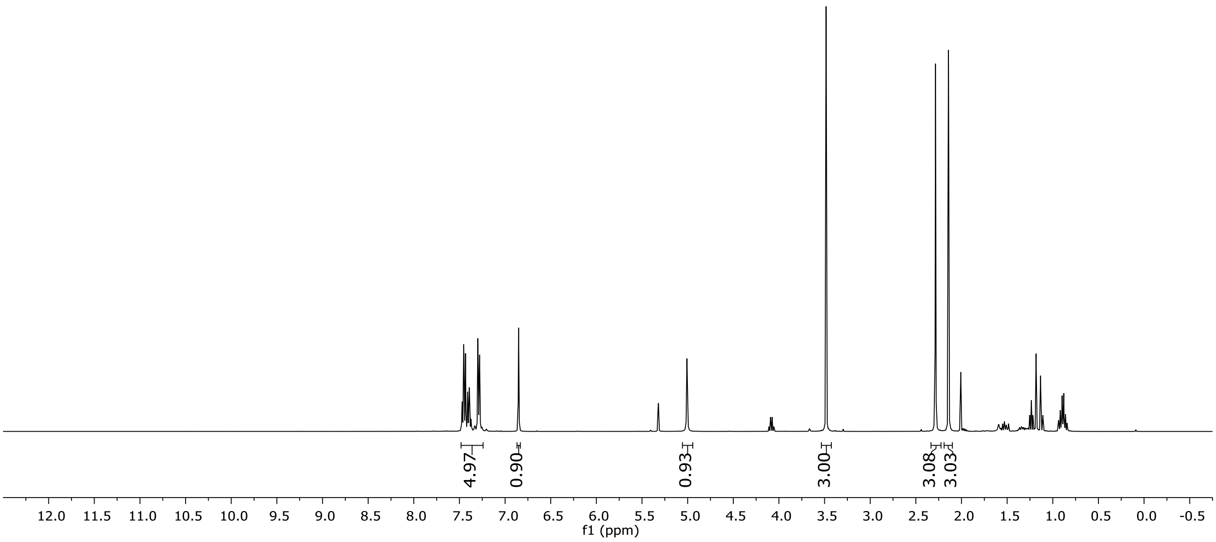

OH
Me
OMe
O
Solvent CD2Cl2
MHz 400
Nucleus 1H
0.90
0.91
2.27
3.08
0.84
1.97
3.00
3.18
2.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

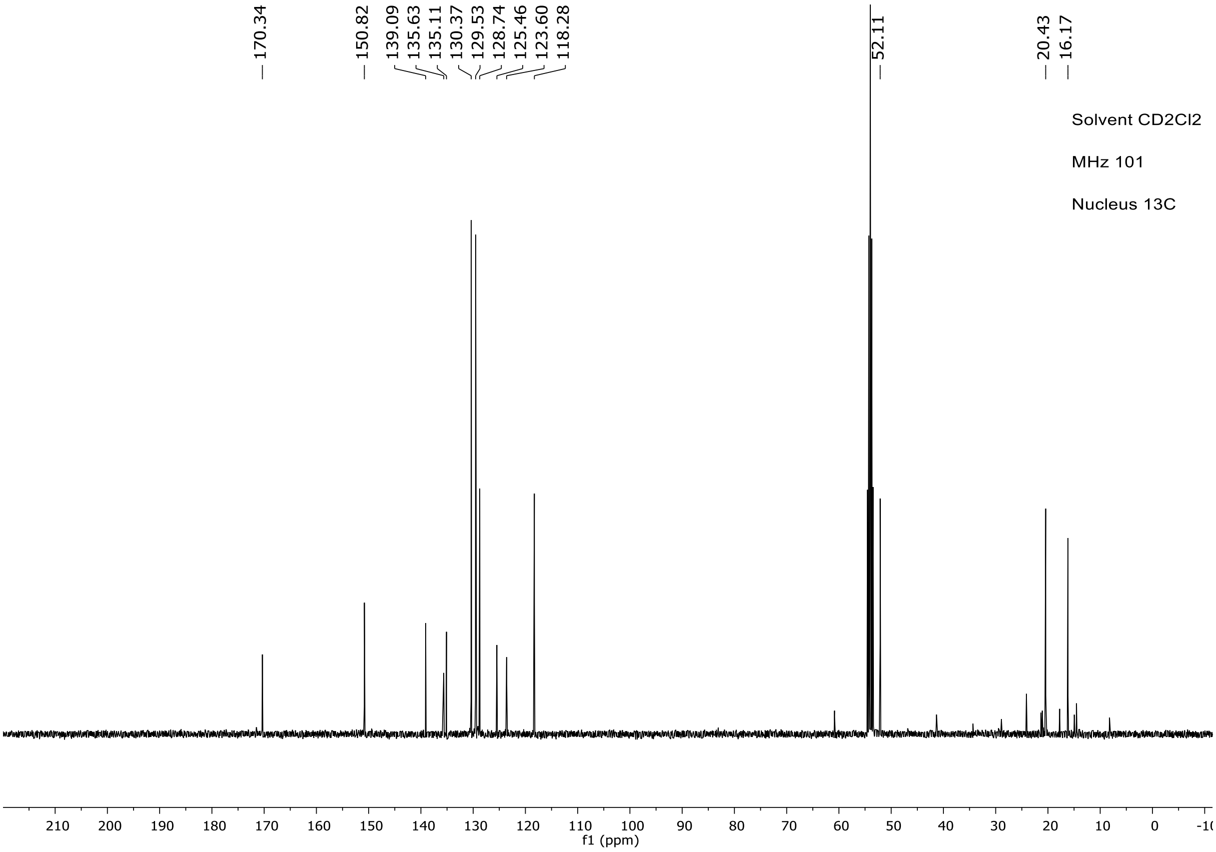

167.34
154.54
139.87
139.67
131.63
129.56
129.01
128.69
126.64
124.36
114.45
52.51
32.49
20.23
Solvent CD2Cl2
MHz 101
Nucleus 13C
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

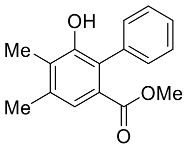

O
O
Me
Me
Cl
OMe
Solvent CD2Cl2
MHz 400
Nucleus 1H
2.95
1.92
3.00
0.98
1.01
1.01
6.17
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

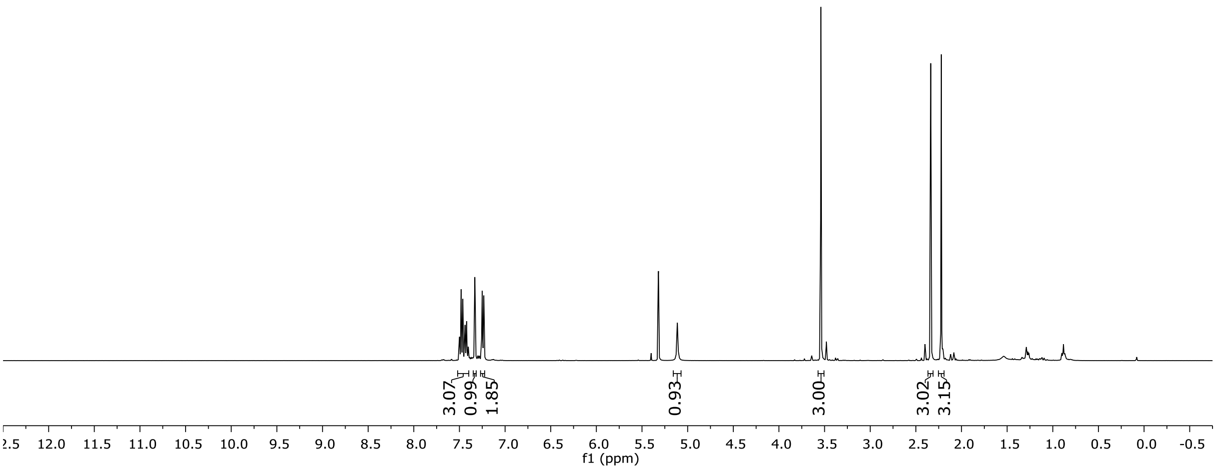

207.51
166.41
131.87
129.78
128.67
55.02
54.09
53.76
50.86
48.01
35.63
32.92
23.73
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

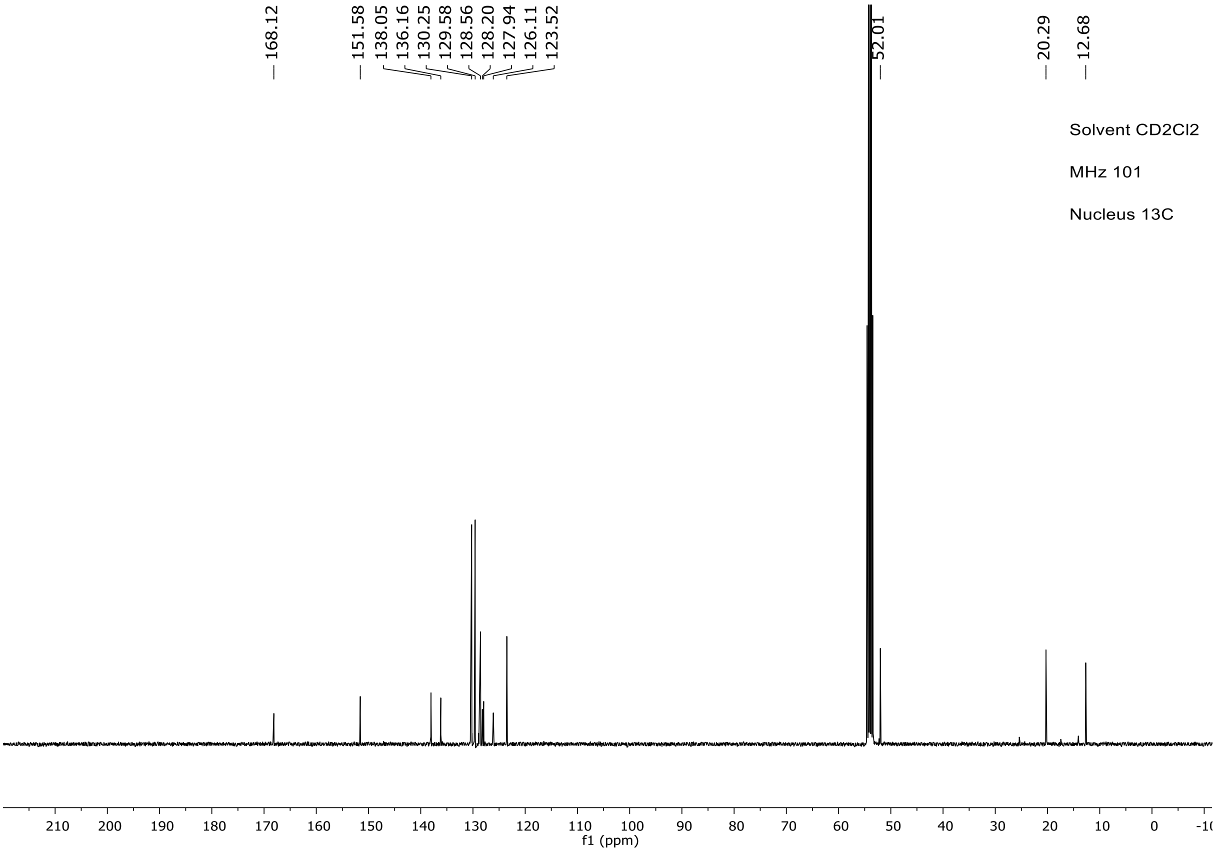

OH
OMe
Me
Me
O

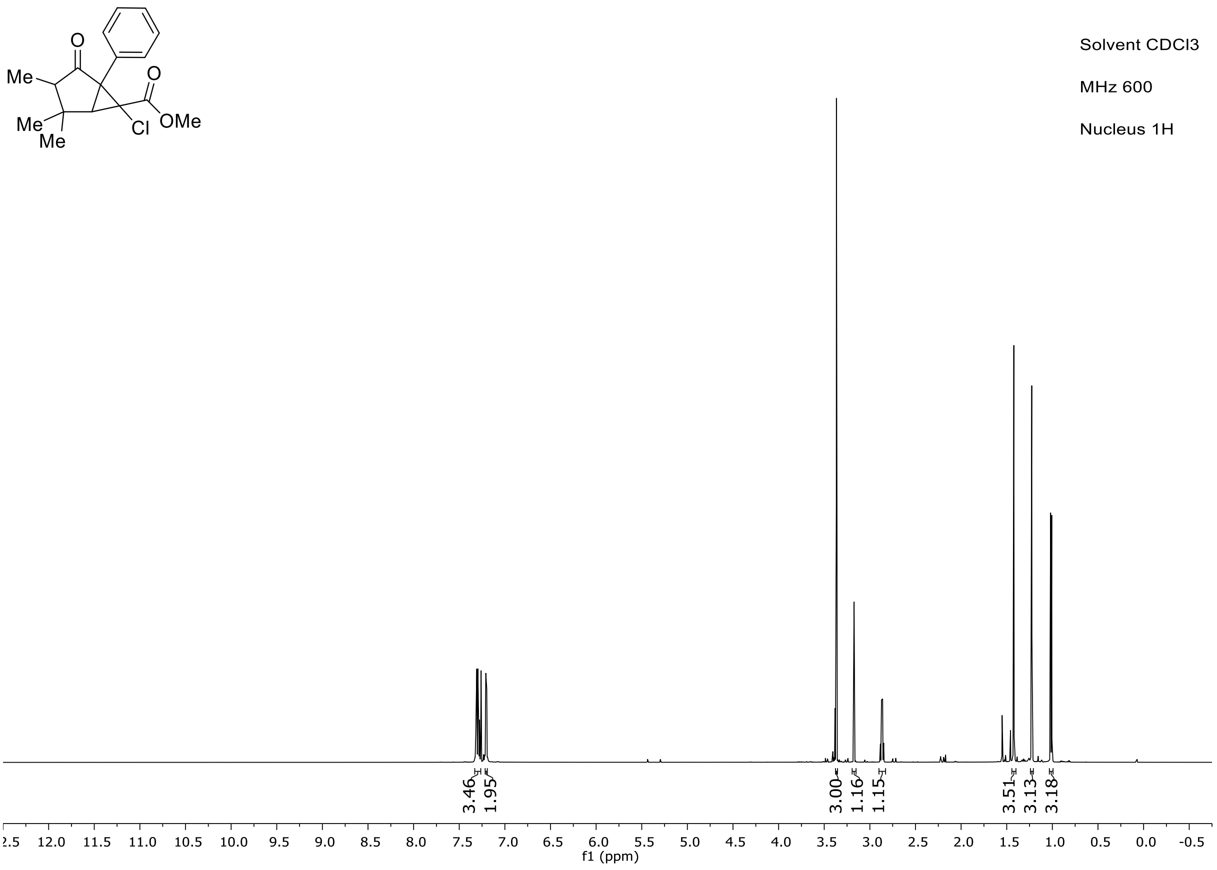

Solvent CD2Cl2
MHz 400
Nucleus 1H
4.97
0.90
0.93
3.00
3.08
3.03
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

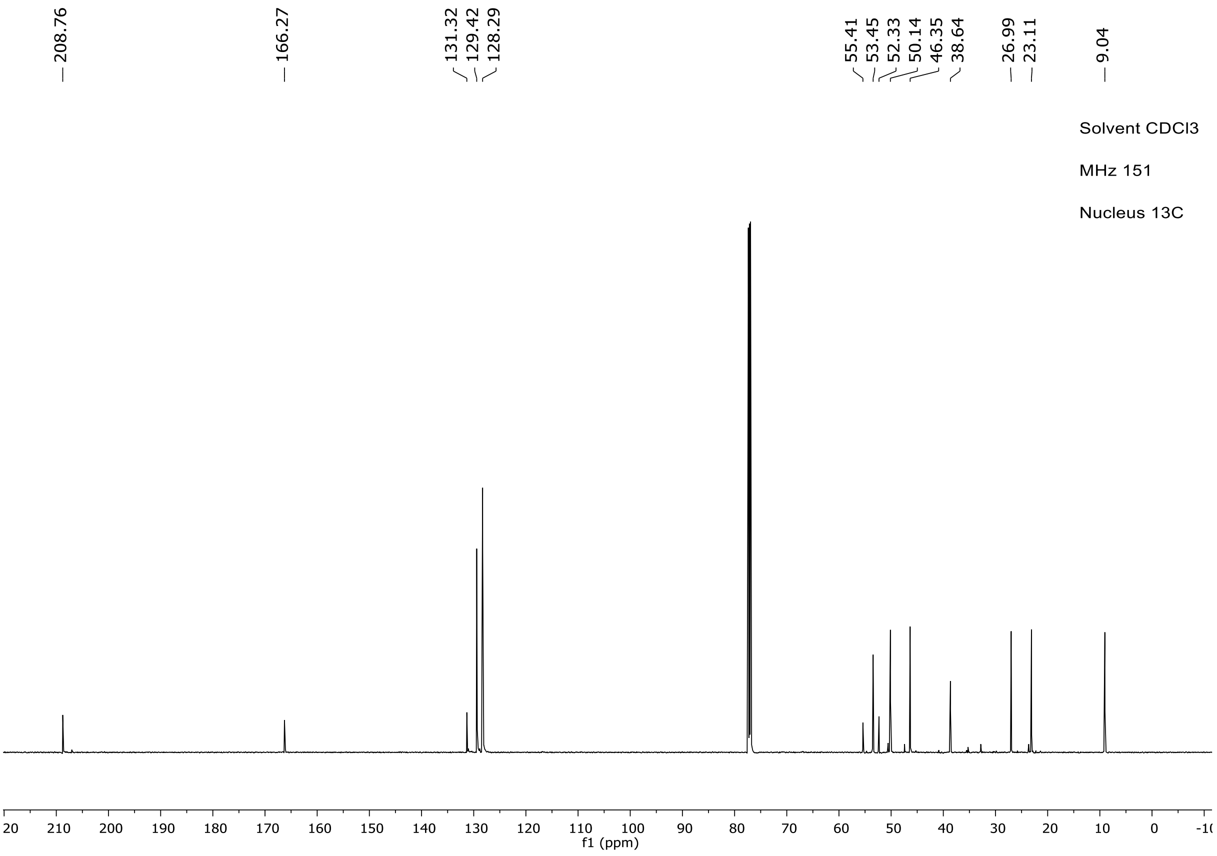

170.34
150.82
139.09
135.63
135.11
130.37
129.53
128.74
125.46
123.60
118.28
52.11
20.43
16.17
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

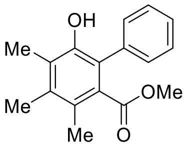

OH
Me
Me
OMe
O

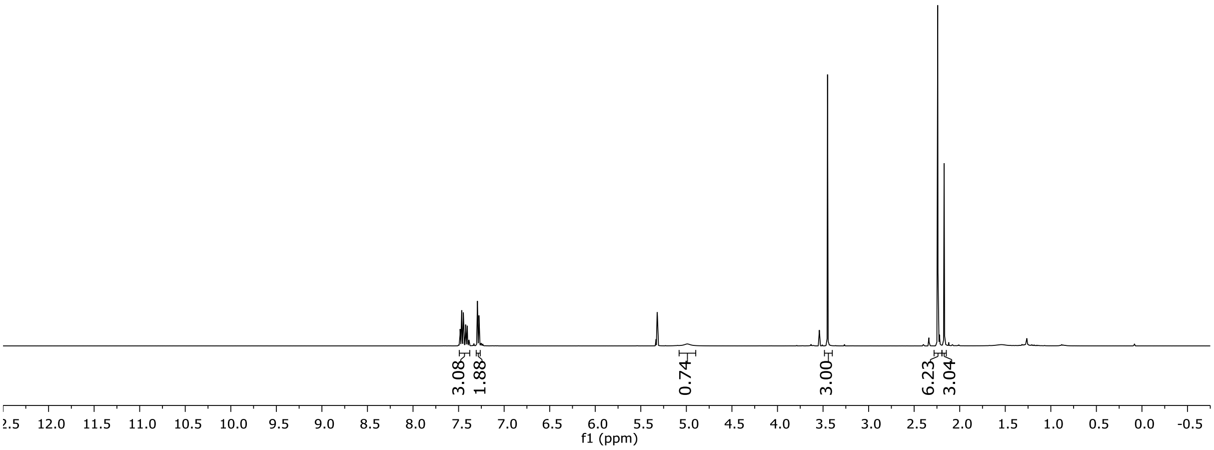

Solvent CD2Cl2
MHz 400
Nucleus 1H
3.07
0.99
1.85
0.93
3.00
3.02
3.15
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

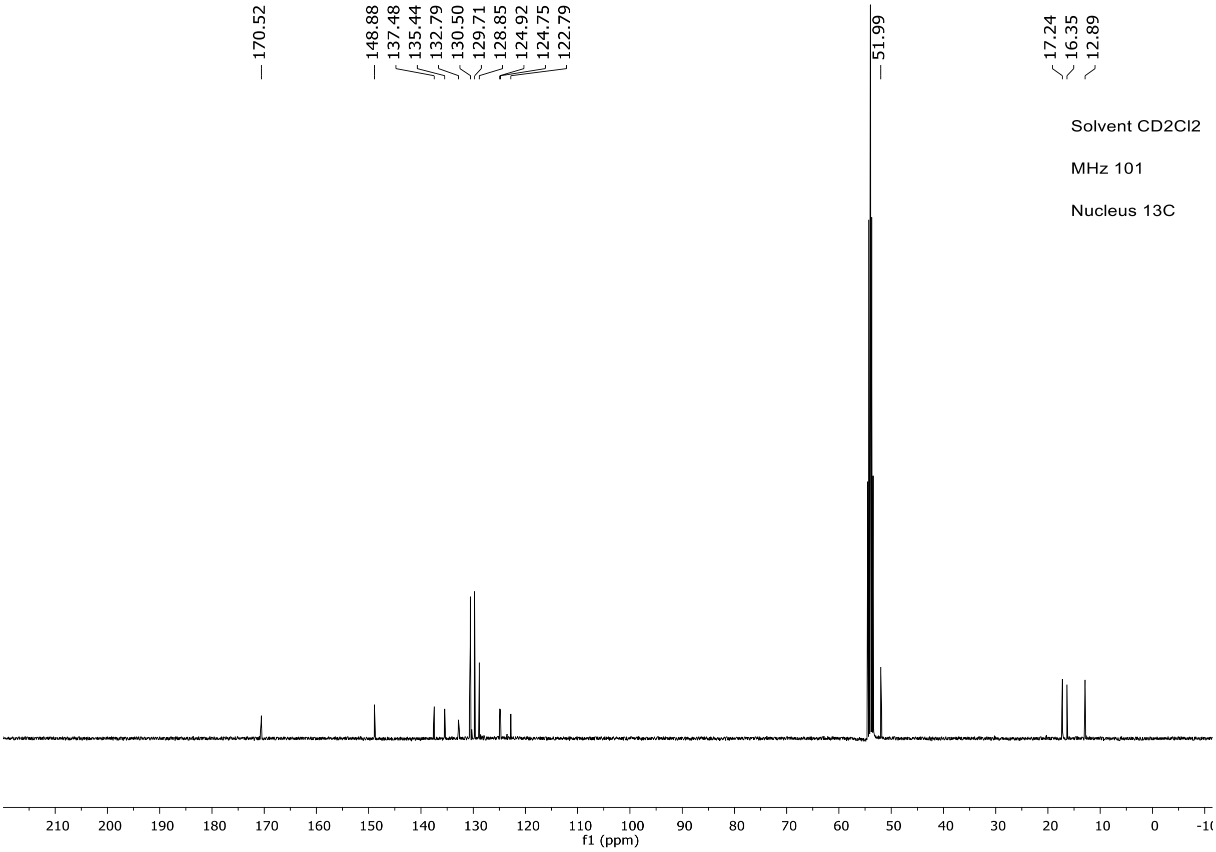

168.12
151.58
138.05
136.16
130.25
129.58
128.56
128.20
127.94
126.11
123.52
52.01
20.29
12.68
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

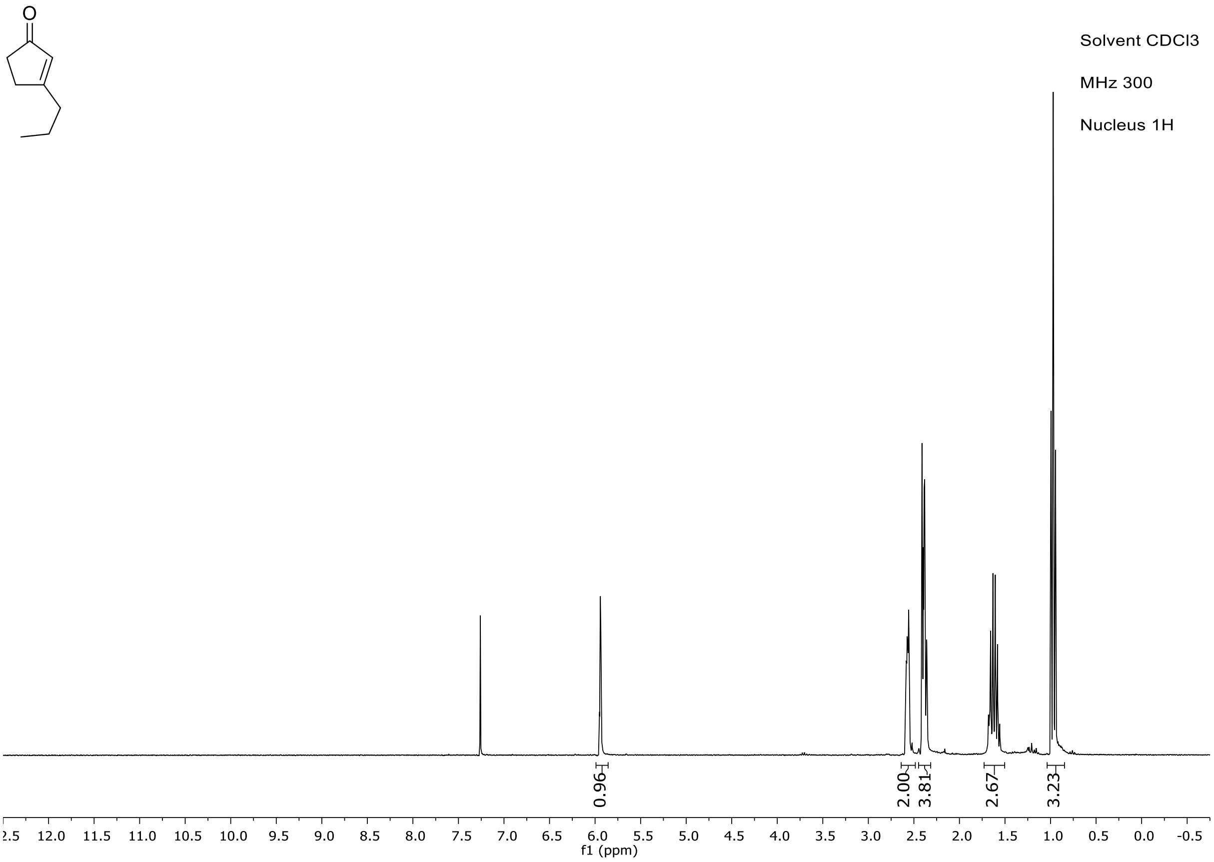

O
O
Me
Me
Me
Cl
OMe
Solvent CDCl3
MHz 600
Nucleus 1H
3.46
1.95
3.00
1.16
1.15
3.51
3.13
3.18
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

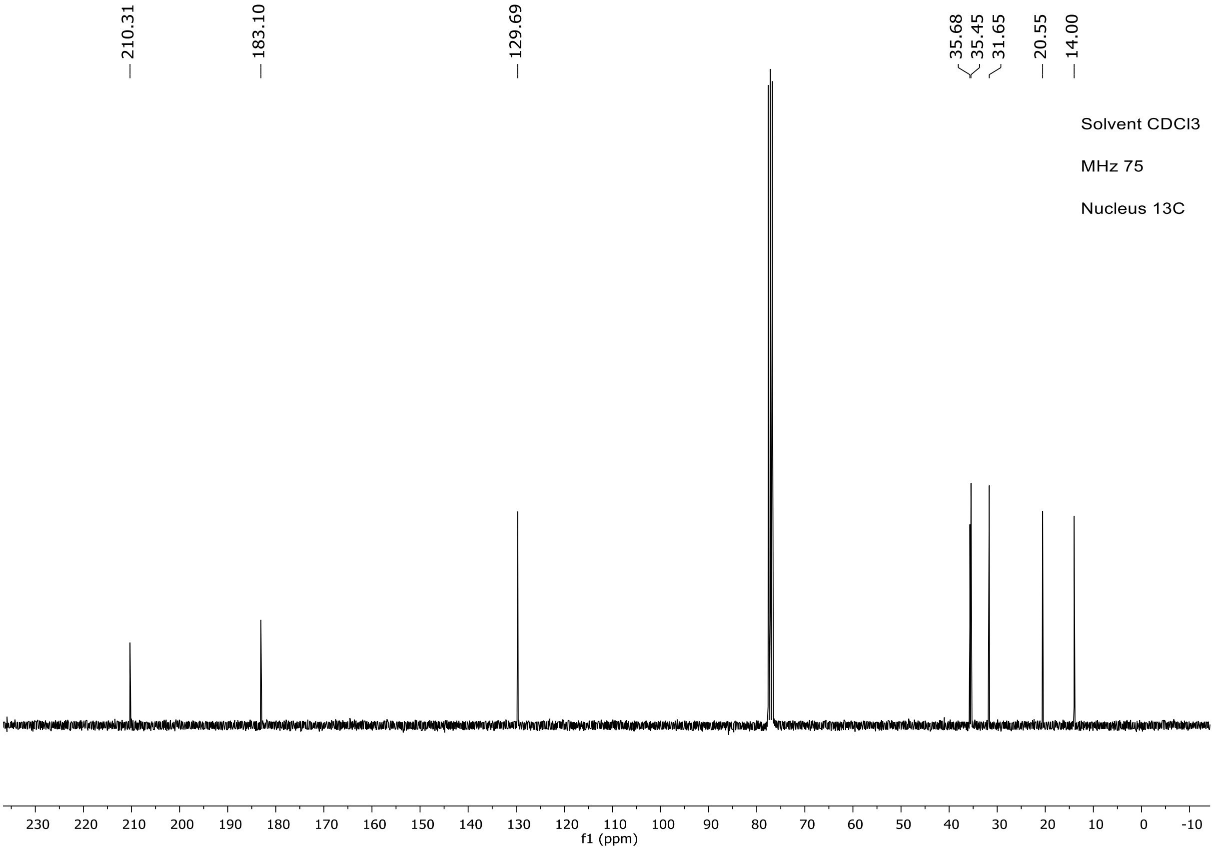

208.76
166.27
131.32
129.42
128.29
55.41
53.45
52.33
50.14
46.35
38.64
26.99
23.11
9.04
Solvent CDCl3
MHz 151
Nucleus 13C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

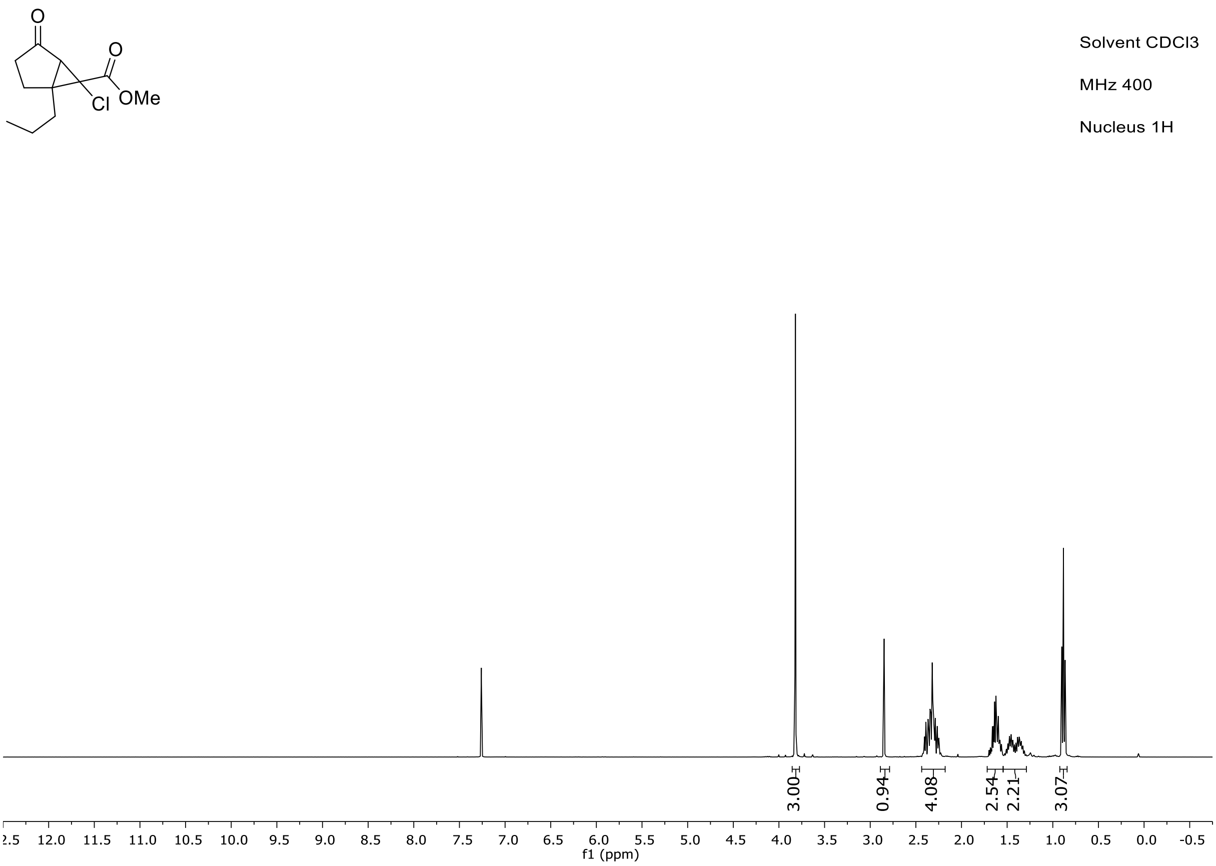

OH
Me
Me
Me
OMe
O

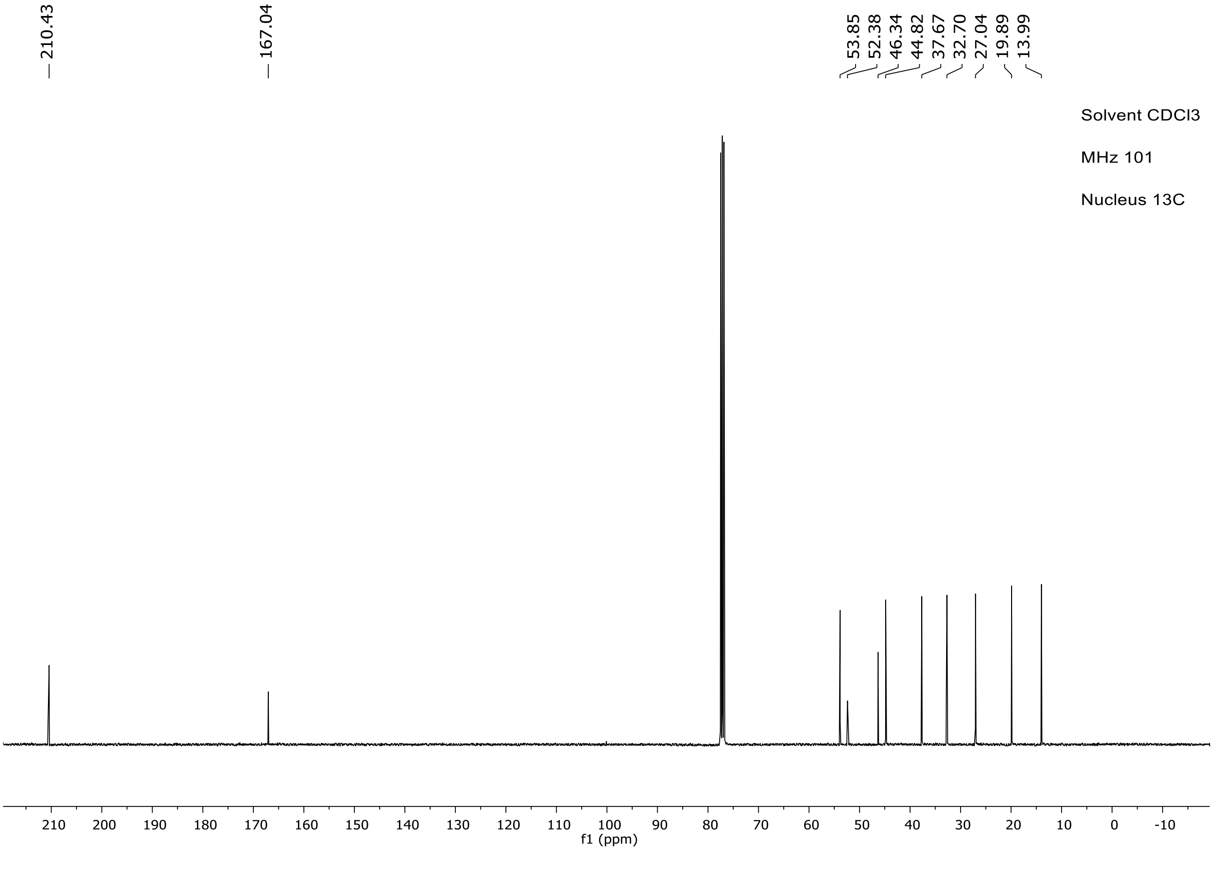

Solvent CD2Cl2
MHz 400
Nucleus 1H
3.08
1.88
0.74
3.00
6.23
3.04
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

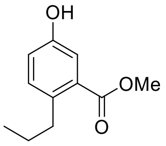

170.52
148.88
137.48
135.44
132.79
130.50
129.71
128.85
124.92
124.75
122.79
51.99
17.24
16.35
12.89
Solvent CD2Cl2
MHz 101
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

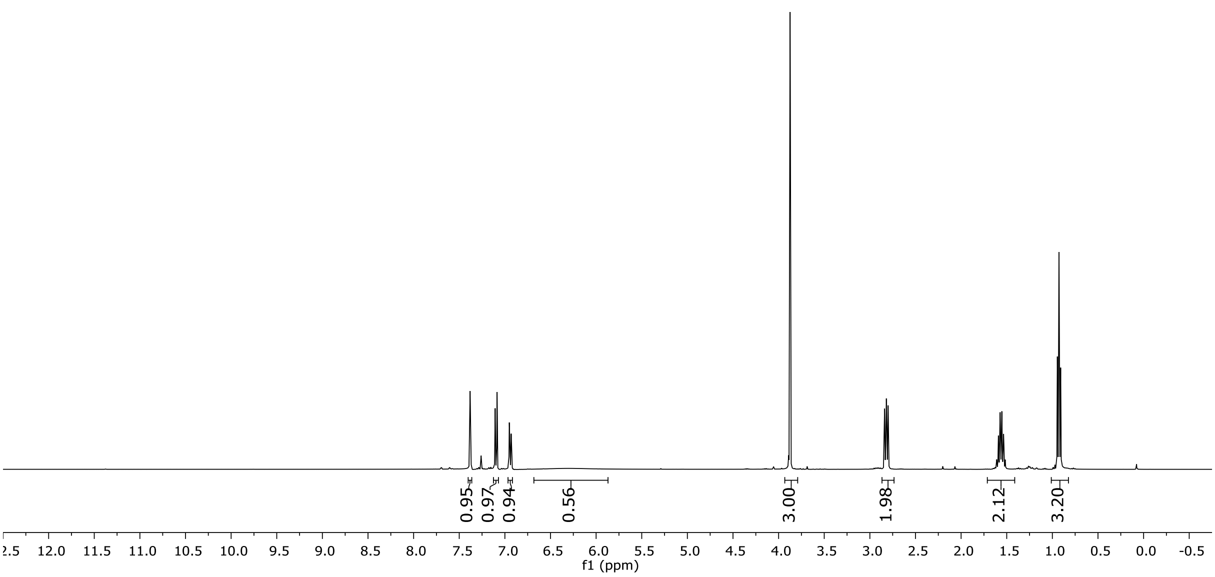

O
Solvent CDCl3
MHz 300
Nucleus 1H
0.96
2.00
3.81
2.67
3.23
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

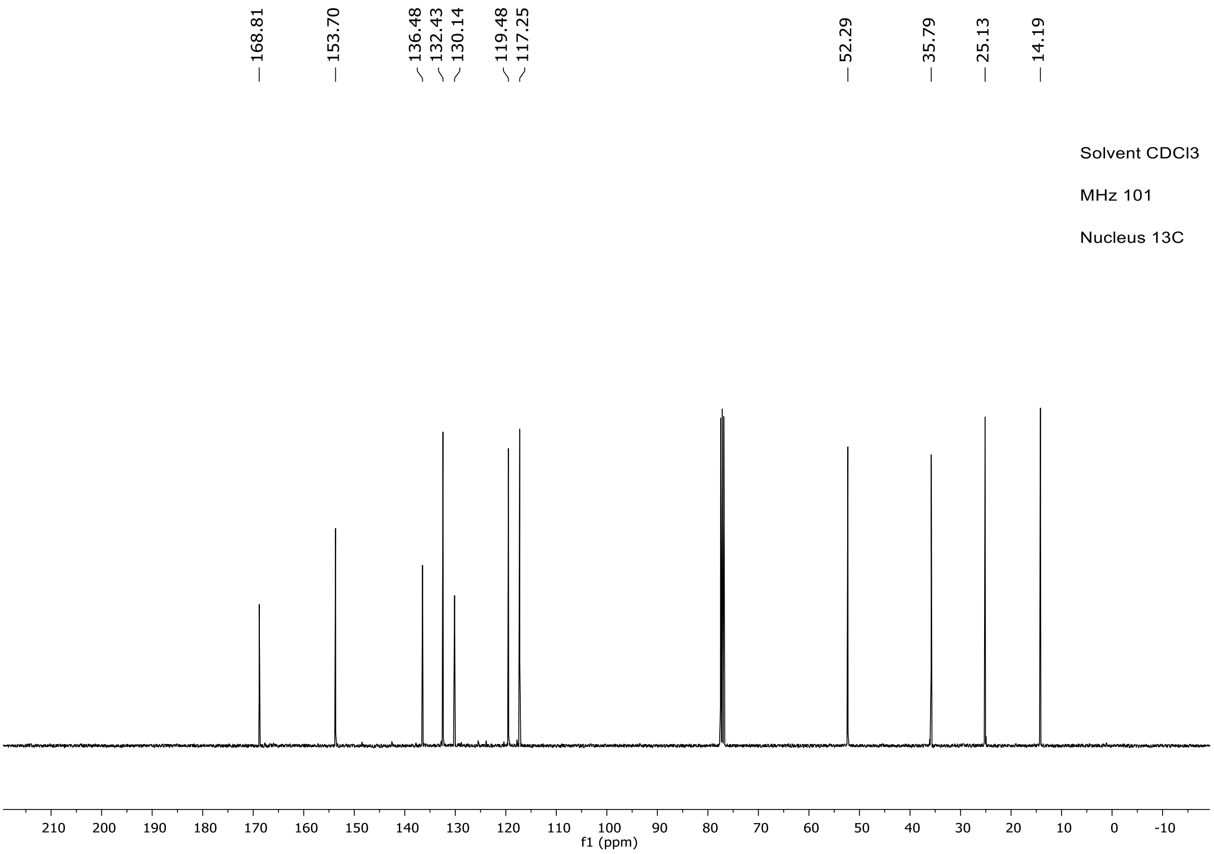

210.31
183.10
129.69
35.68
35.45
31.65
20.55
14.00
Solvent CDCl3
MHz 75
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

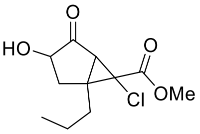

O
O
Cl
OMe
Solvent CDCl3
MHz 400
Nucleus 1H
3.00
0.94
4.08
2.54
2.21
3.07
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


210.43
167.04
53.85
52.38
46.34
44.82
37.67
32.70
27.04
19.89
13.99
Solvent CDCl3
MHz 101
Nucleus 13C
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)


OH
OMe
O


Solvent CDCl3
MHz 400
Nucleus 1H
0.95
0.97
0.94
0.56
3.00
1.98
2.12
3.20
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

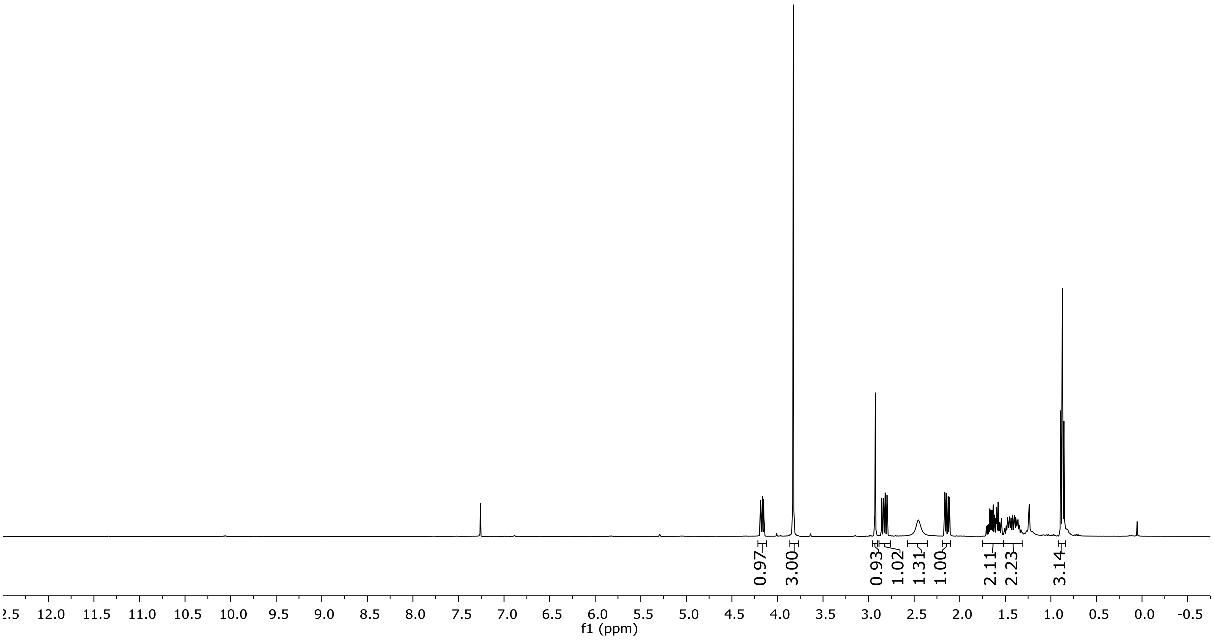

168.81
153.70
136.48
132.43
130.14
119.48
117.25
52.29
35.79
25.13
14.19
Solvent CDCl3
MHz 101
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



Solvent CDCl3

MHz 400

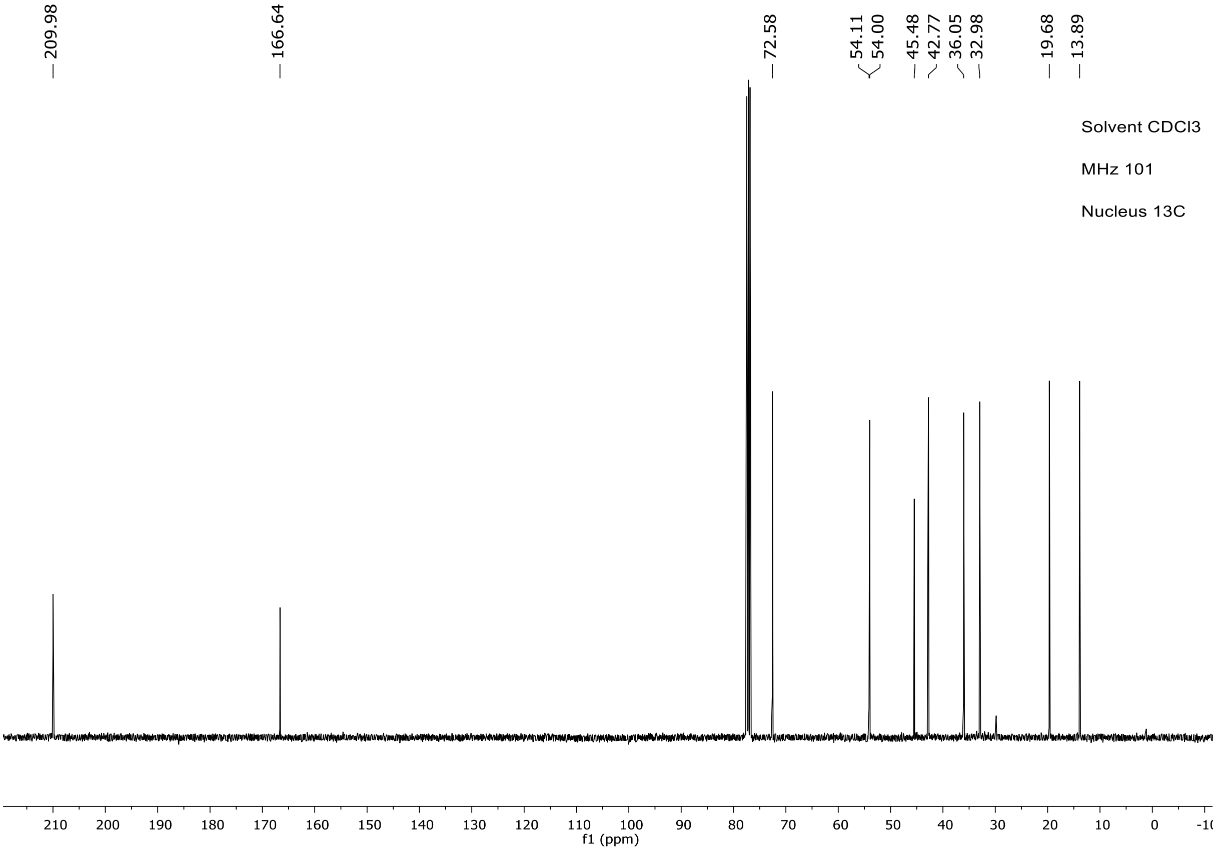
Nucleus 1H

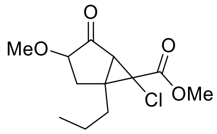


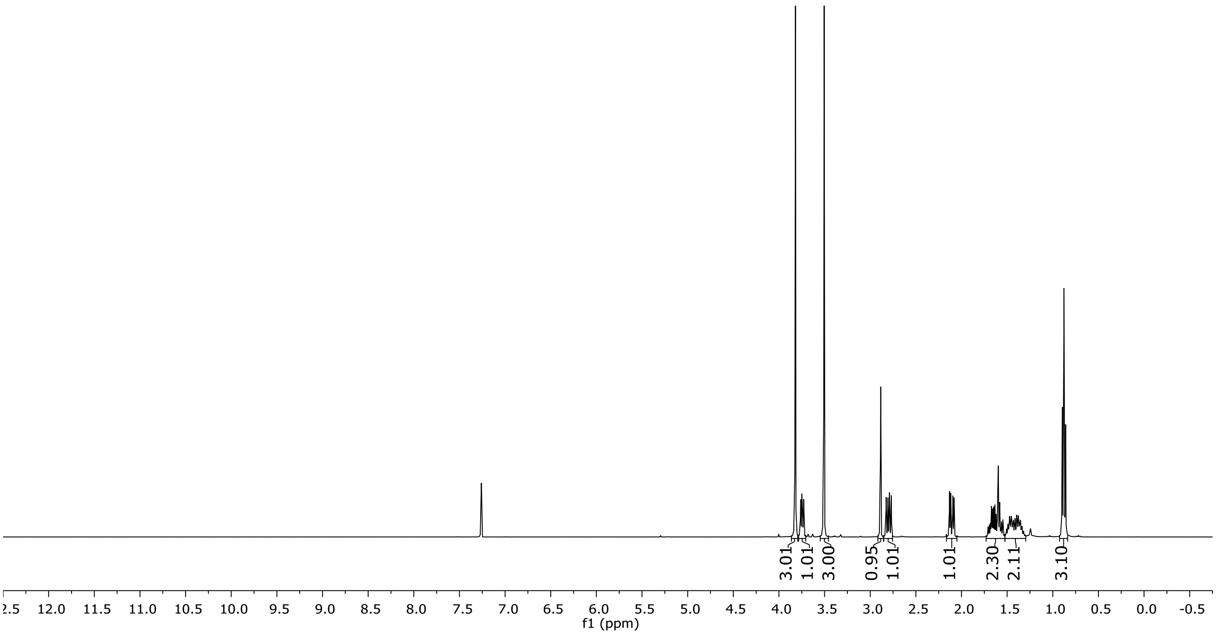
Solvent CDCl3

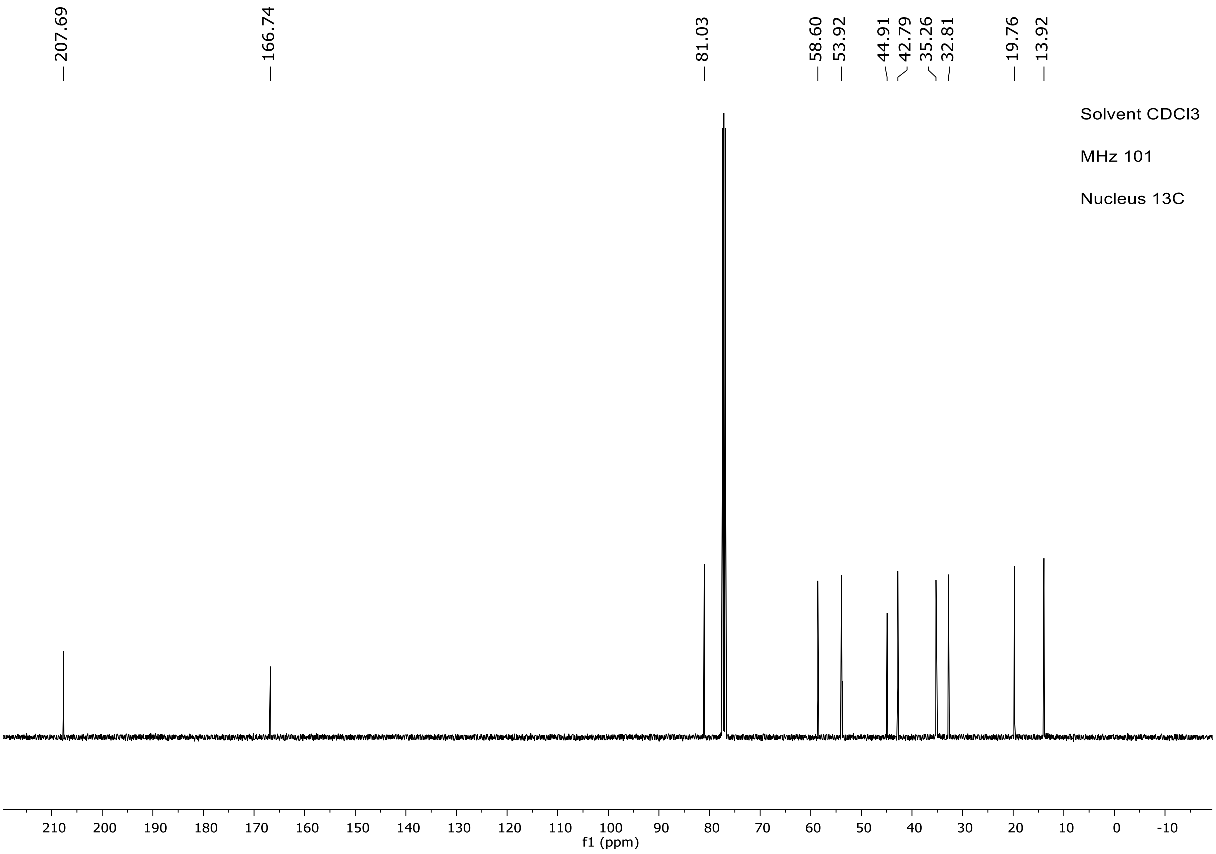
MHz 101

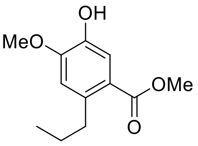
Nucleus 13C

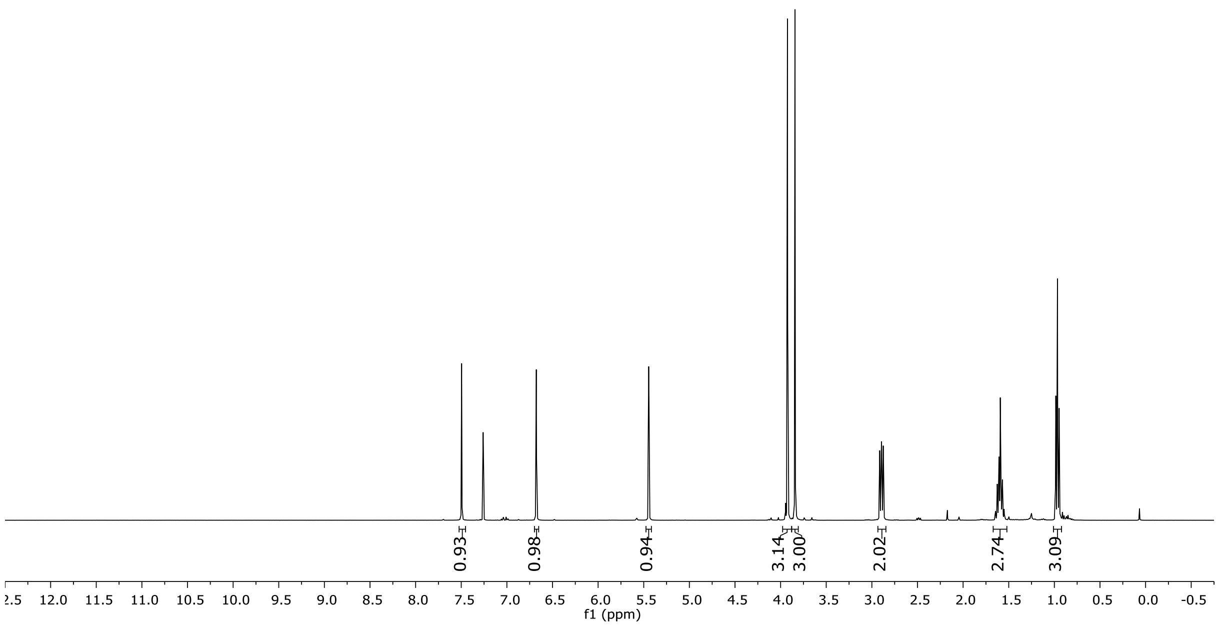


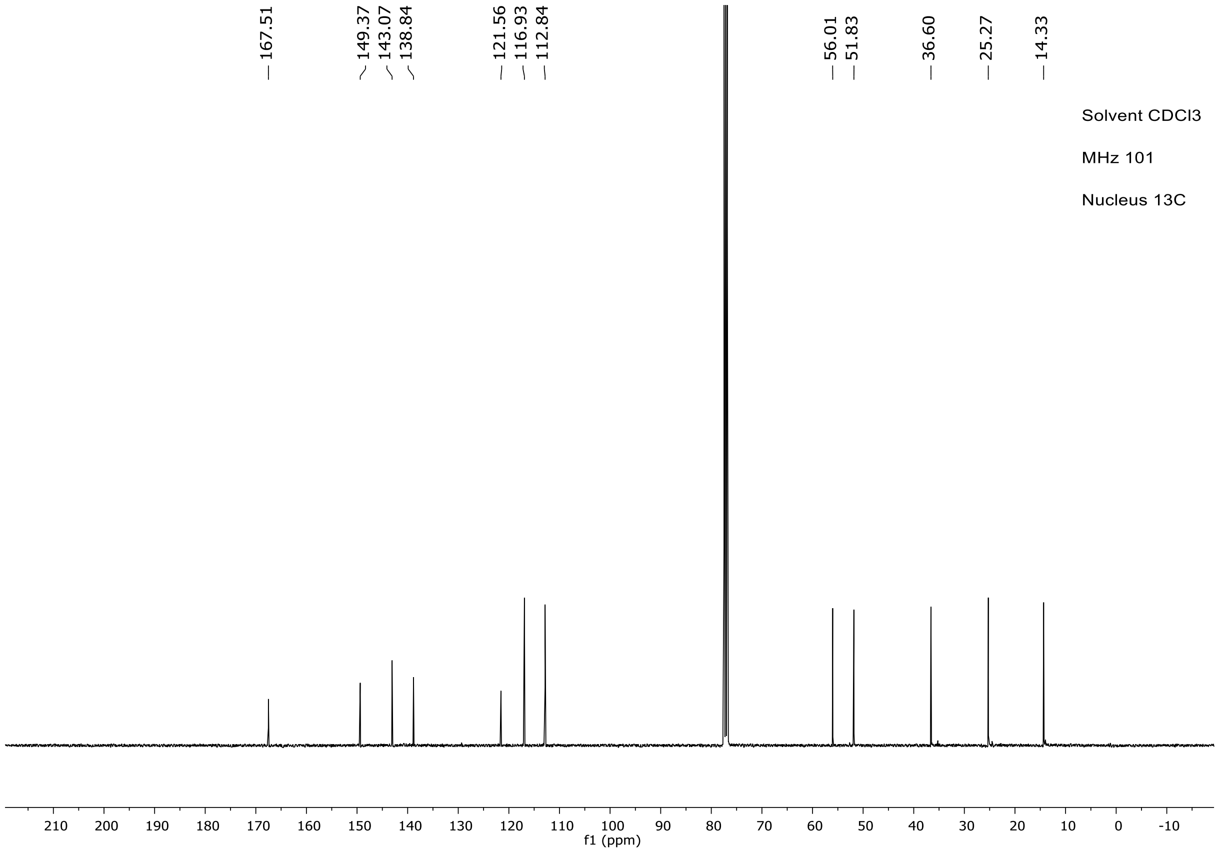

O
MeO
O
Cl
OMe

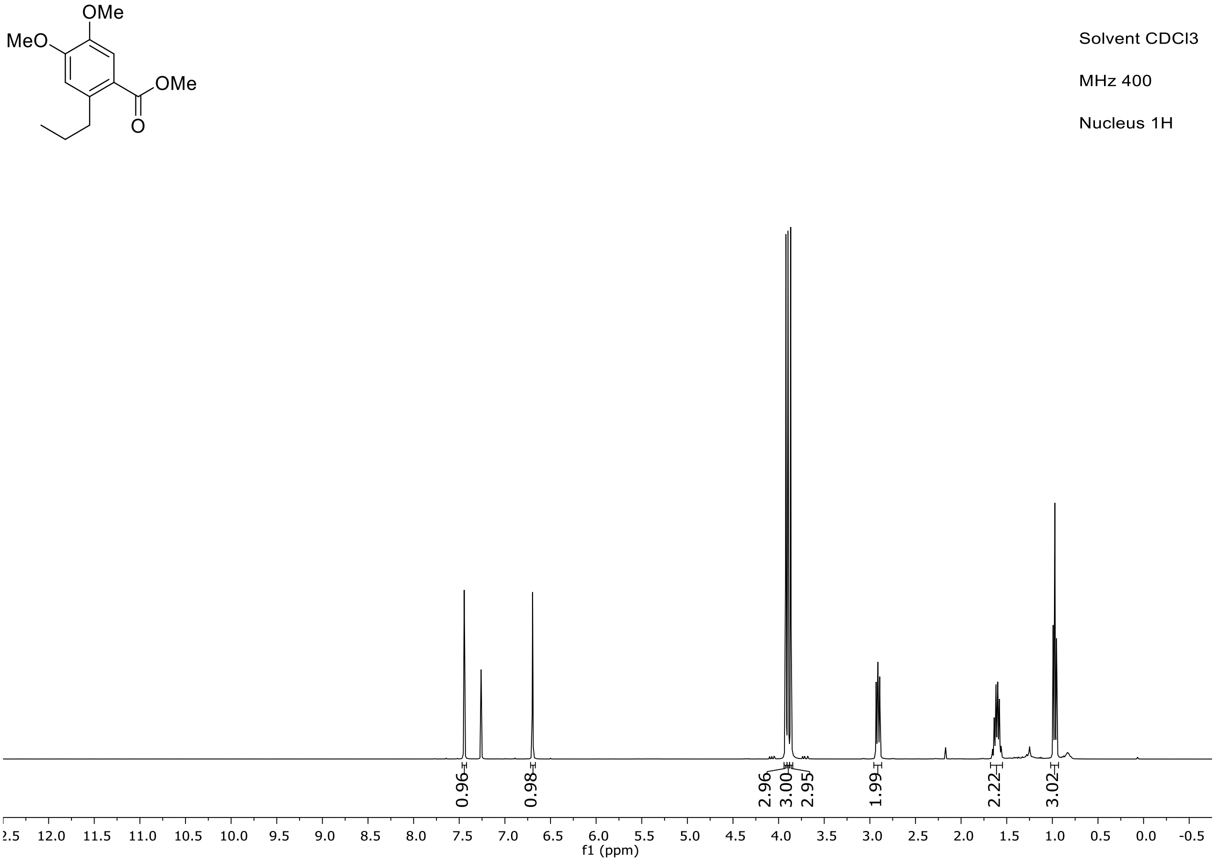

Solvent CDCl3
MHz 400
Nucleus 1H
3.01
1.01
3.00
0.95
1.01
1.01
2.30
2.11
3.10
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

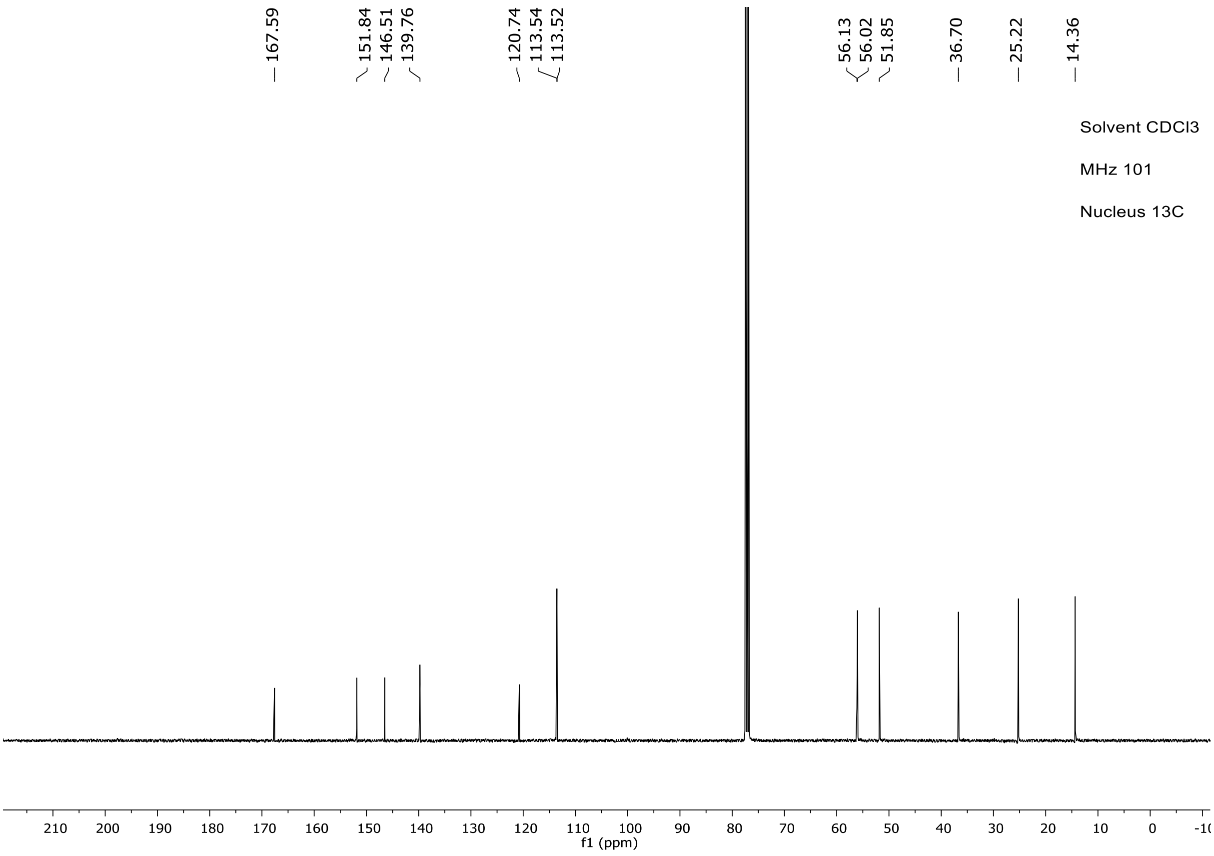

207.69
166.74
81.03
58.60
53.92
44.91
42.79
35.26
32.81
19.76
13.92
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

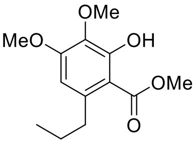

OH
MeO
OMe
O

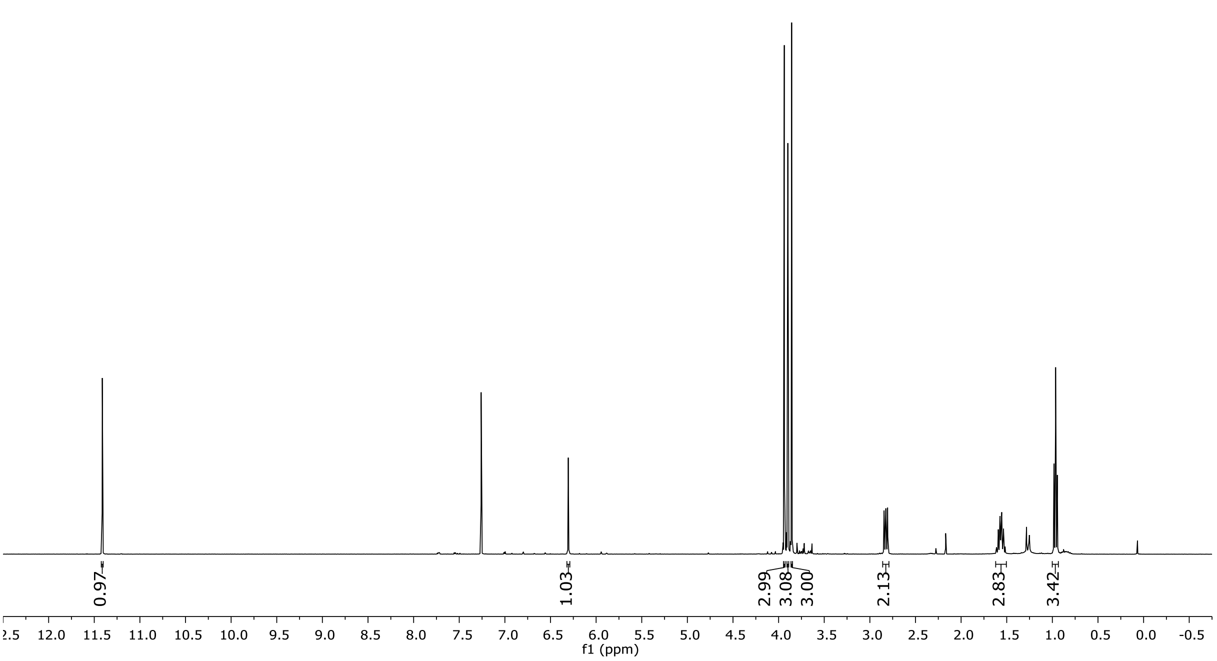

Solvent CDCl3
MHz 400
Nucleus 1H
0.93
0.98
0.94
3.14
3.00
2.02
2.74
3.09
2.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

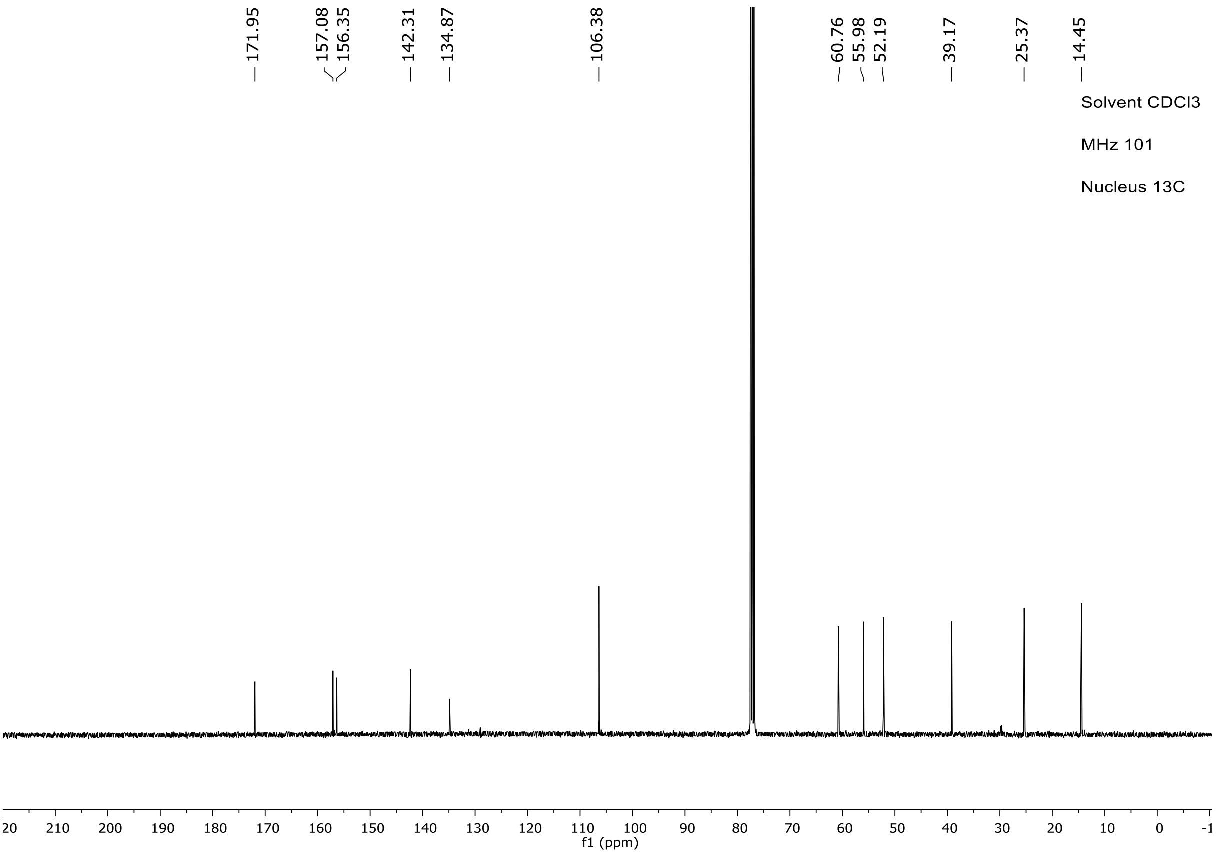

167.51
149.37
143.07
138.84
121.56
116.93
112.84
56.01
51.83
36.60
25.27
14.33
Solvent CDCl3
MHz 101
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

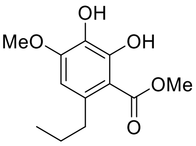

OMe
MeO
OMe
O
Solvent CDCl3
MHz 400
Nucleus 1H
0.96
0.98
2.96
3.00
2.95
1.99
2.22
3.02
2.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

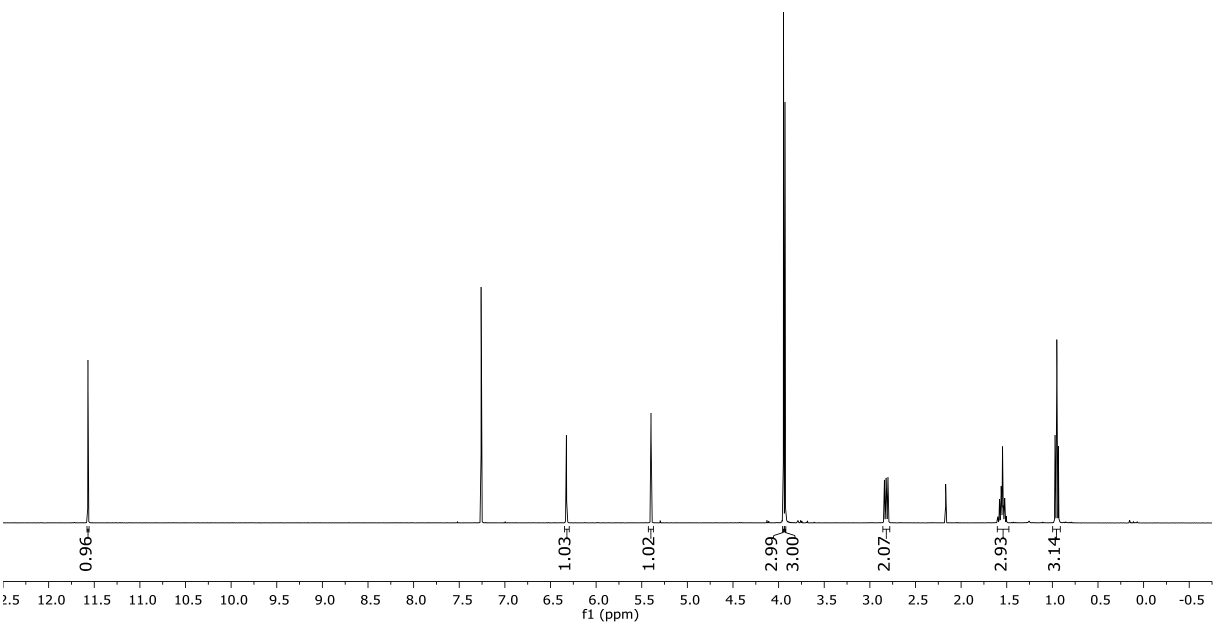

167.59
151.84
146.51
139.76
120.74
113.54
113.52
56.13
56.02
51.85
36.70
25.22
14.36
Solvent CDCl3
MHz 101
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

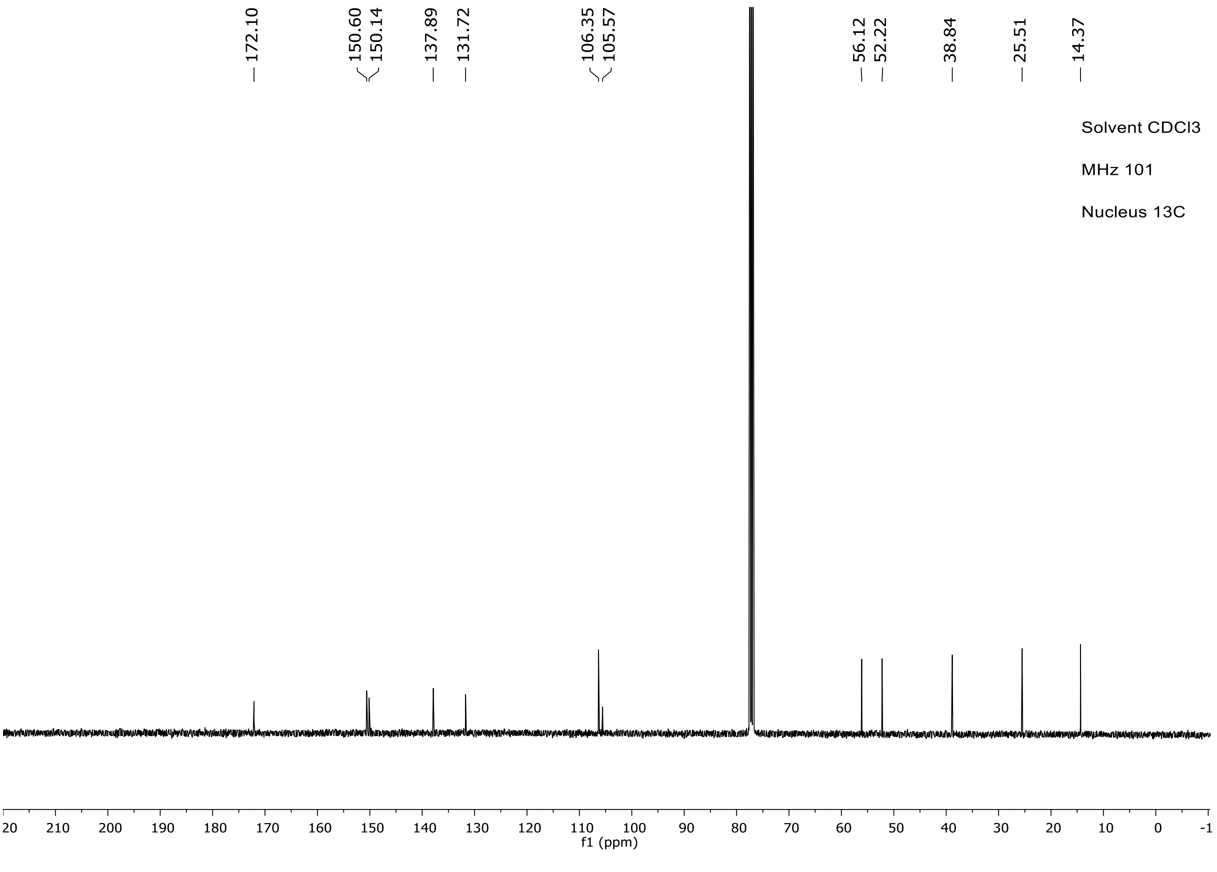

OMe
MeO
OH
OMe
O

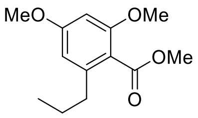

Solvent CDCl3
MHz 400
Nucleus 1H
0.97
1.03
2.99
3.08
3.00
2.13
2.83
3.42
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

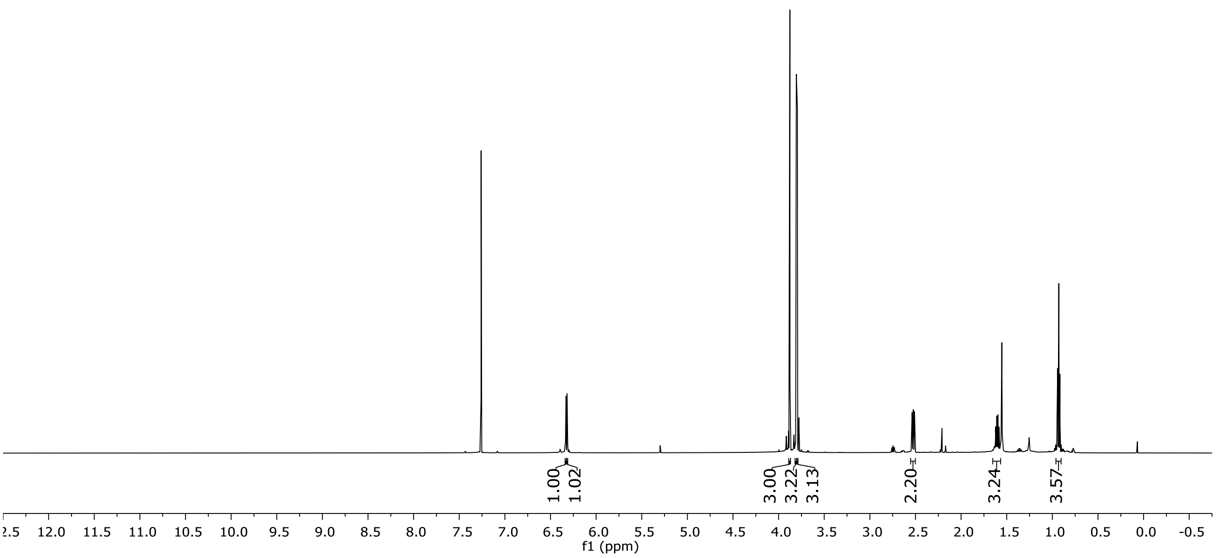

171.95
157.08
156.35
142.31
134.87
106.38
60.76
55.98
52.19
39.17
25.37
14.45
Solvent CDCl3
MHz 101
Nucleus 13C
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

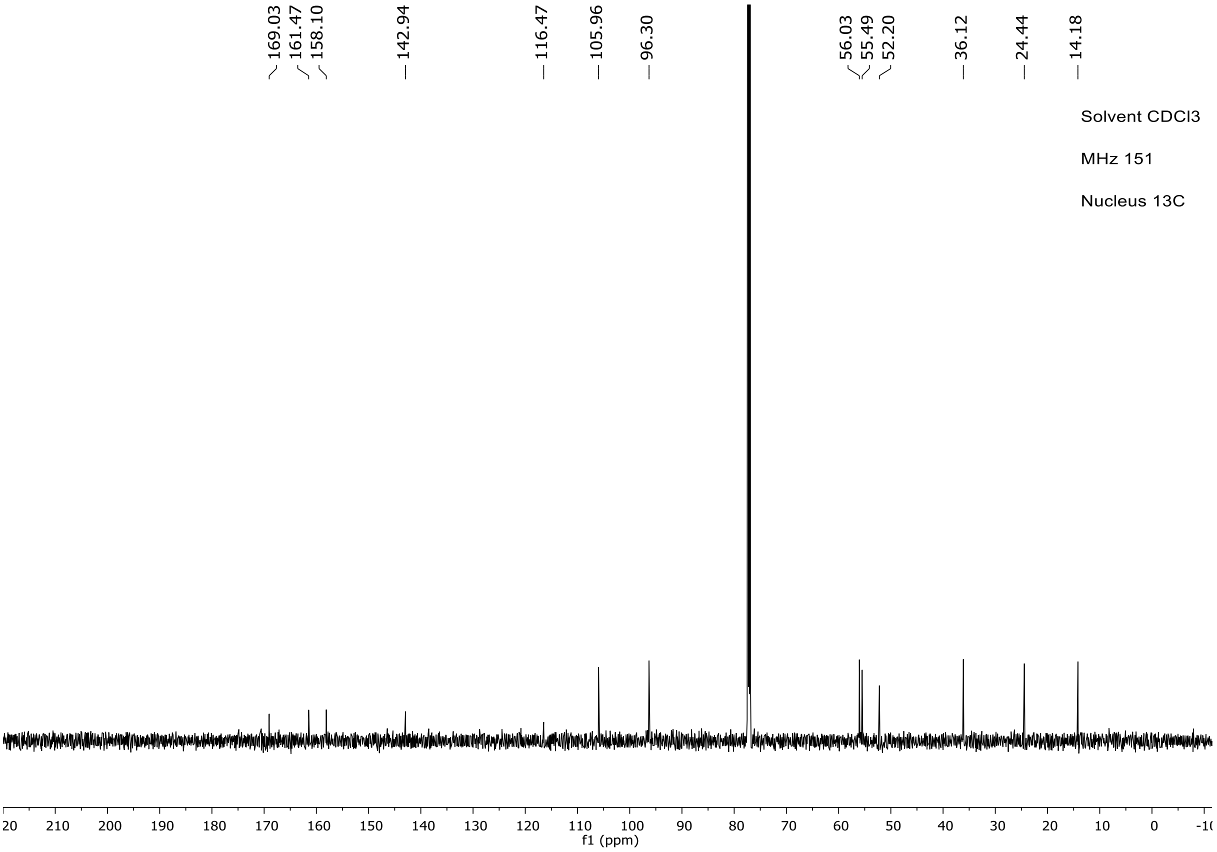

OH
MeO
OH
OMe
O

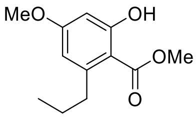

Solvent CDCl3
MHz 400
Nucleus 1H
0.96
1.03
1.02
2.99
3.00
2.07
2.93
3.14
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

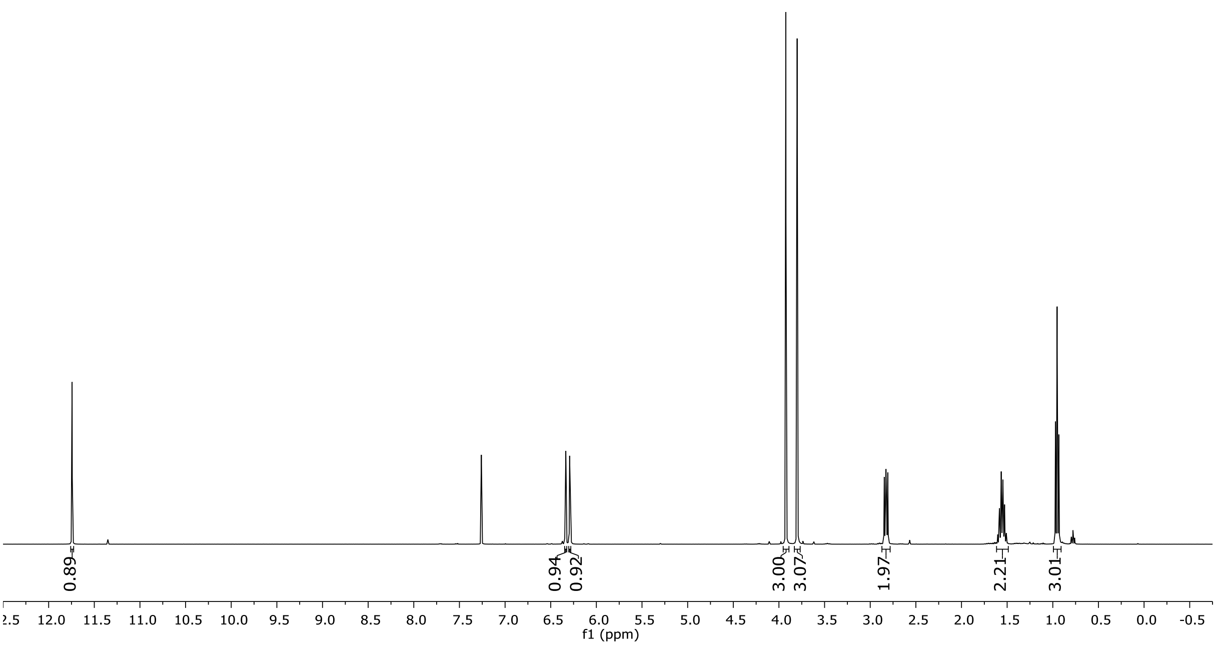

172.10
150.60
150.14
137.89
131.72
106.35
105.57
56.12
52.22
38.84
25.51
14.37
Solvent CDCl3
MHz 101
Nucleus 13C
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

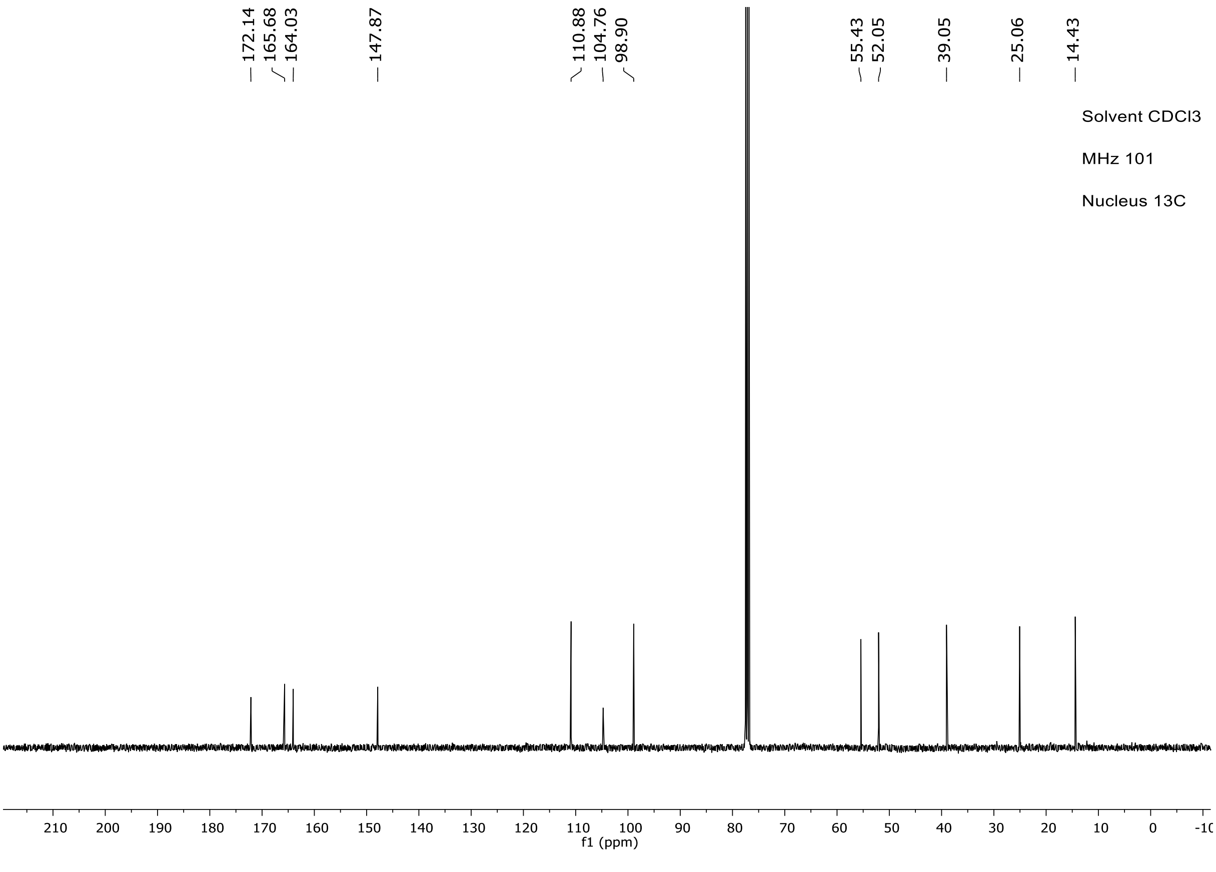

MeO
OMe
OMe
O

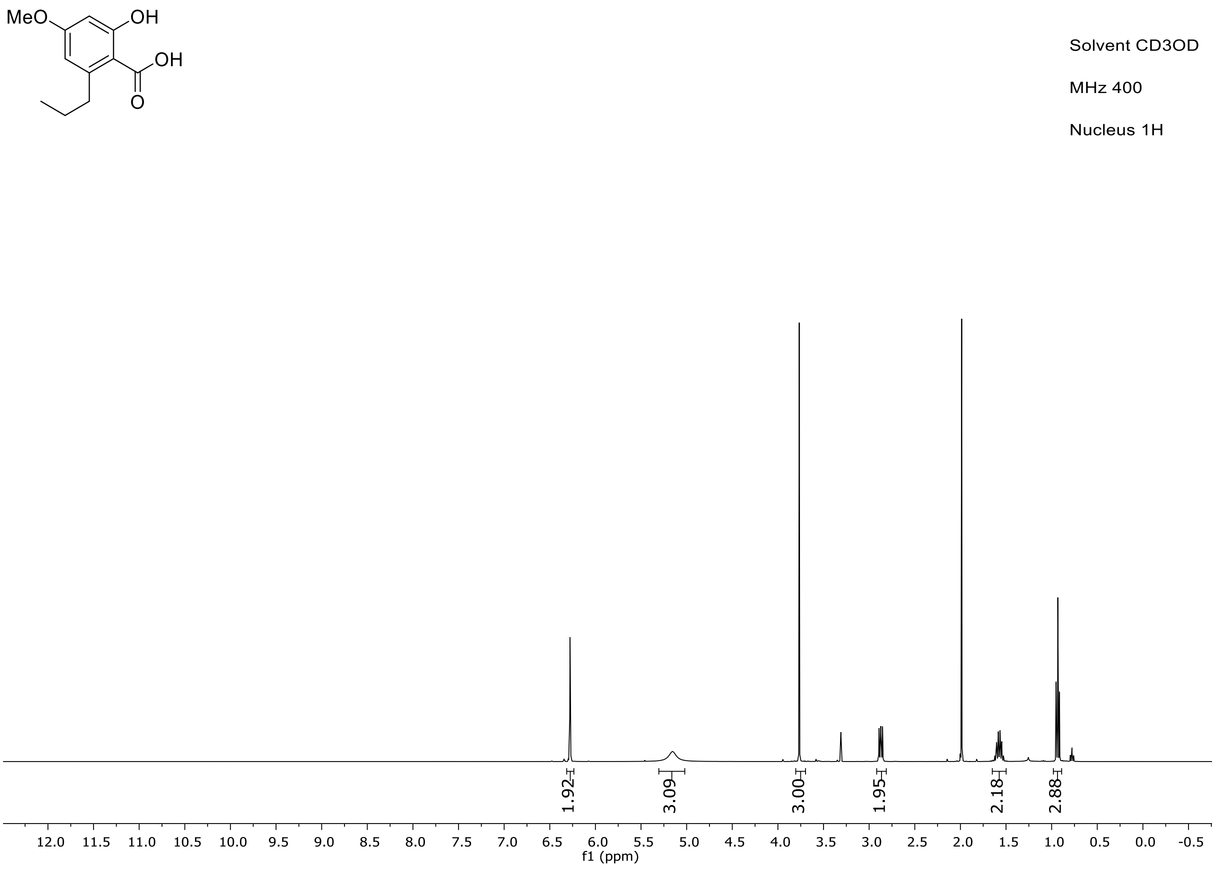

Solvent CDCl3
MHz 600
Nucleus 1H
1.00
1.02
3.00
3.22
3.13
2.20
3.24
3.57
2.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

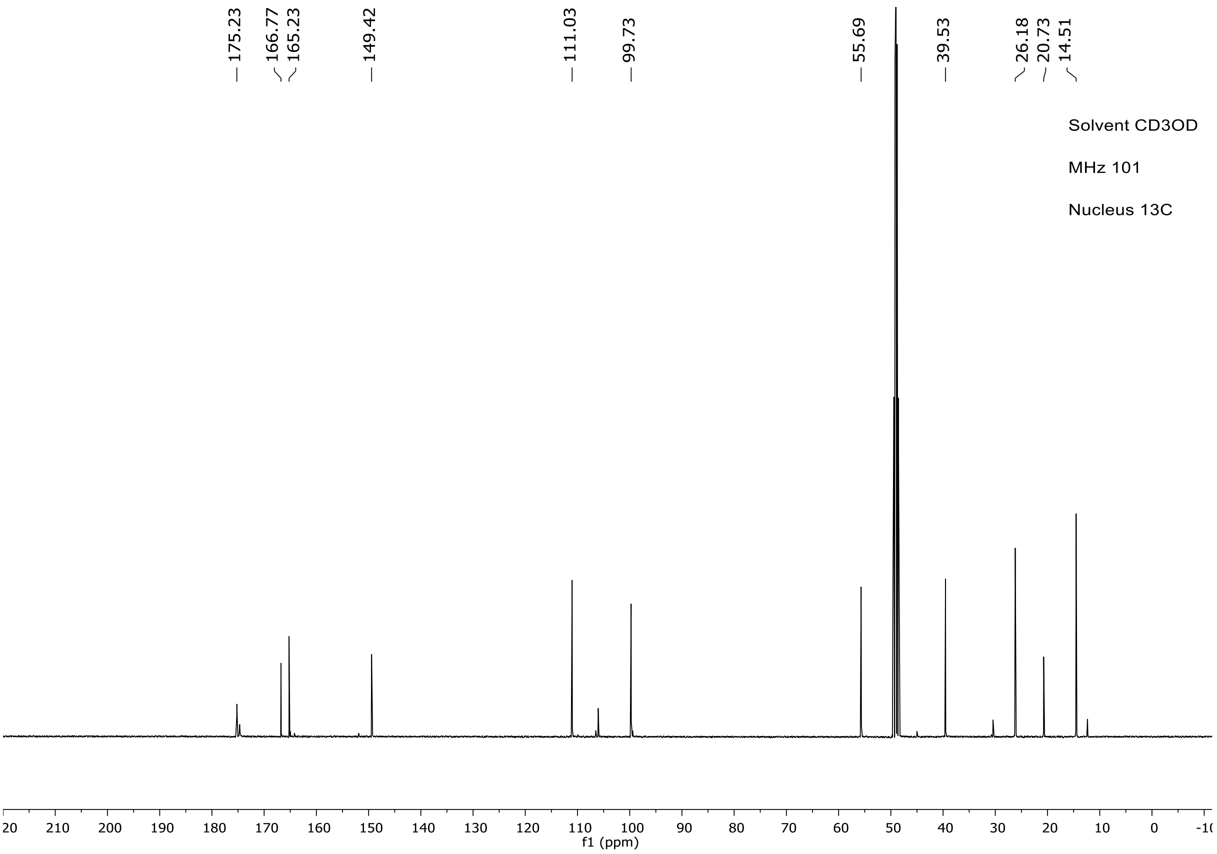

169.03
161.47
158.10
142.94
116.47
105.96
96.30
56.03
55.49
52.20
36.12
24.44
14.18
Solvent CDCl3
MHz 151
Nucleus 13C
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

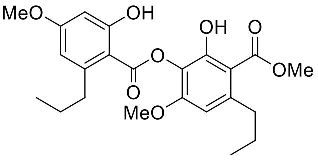

MeO
OH
OMe
O


Solvent CDCl3
MHz 400
Nucleus 1H
0.89
0.94
0.92
3.00
3.07
1.97
2.21
3.01
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


172.14
165.68
164.03
147.87
110.88
104.76
98.90
55.43
52.05
39.05
25.06
14.43
Solvent CDCl3
MHz 101
Nucleus 13C
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)


MeO
OH
OH
O
Solvent CD3OD
MHz 400
Nucleus 1H
1.92
3.09
3.00
1.95
2.18
2.88
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

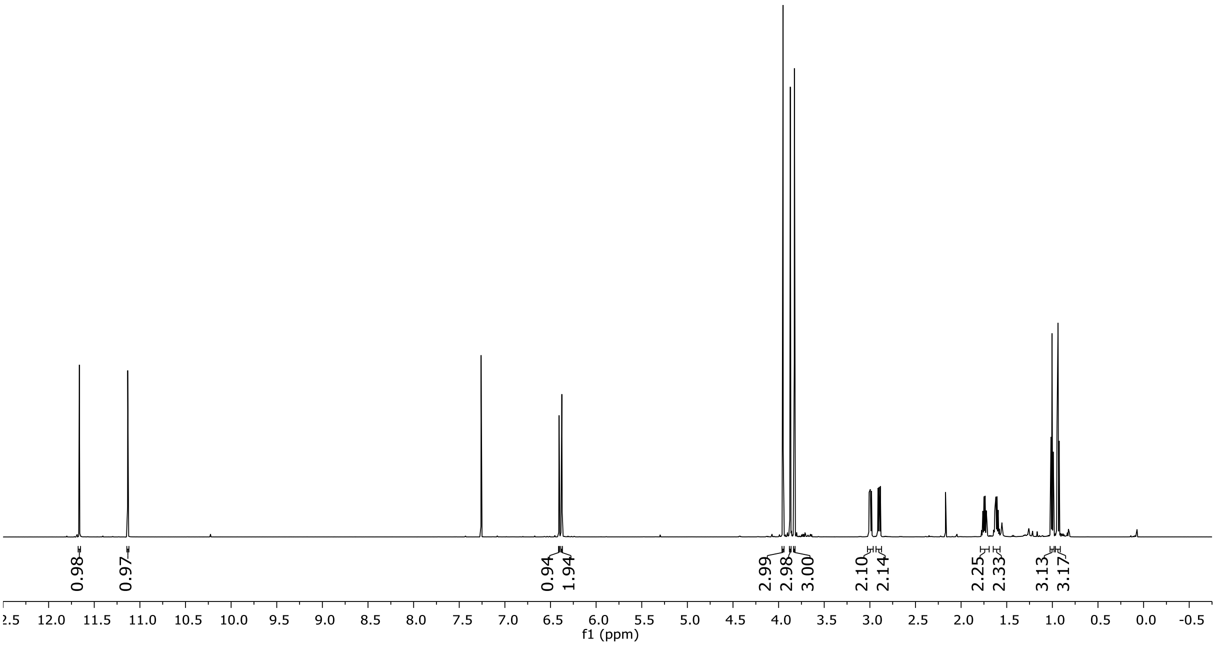

175.23
166.77
165.23
149.42
111.03
99.73
55.69
39.53
26.18
20.73
14.51
Solvent CD3OD
MHz 101
Nucleus 13C
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

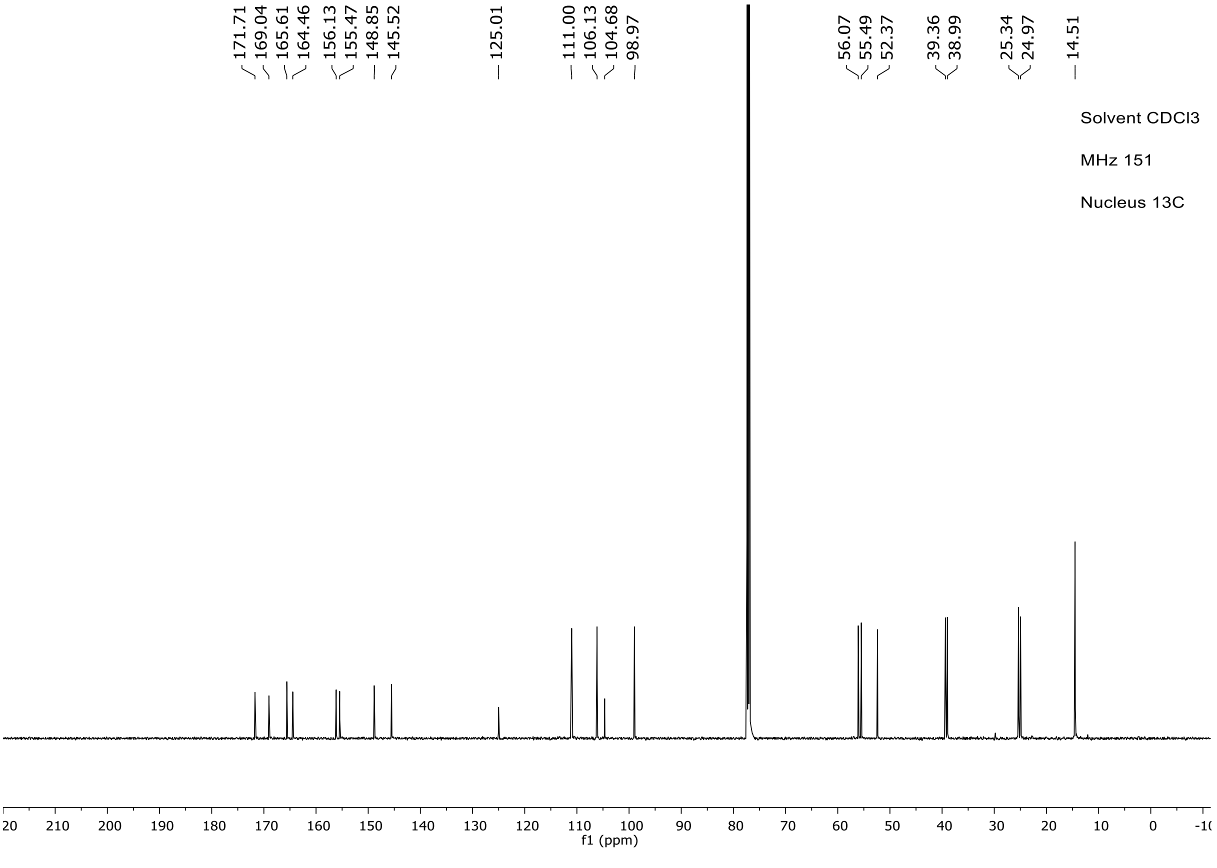


Solvent CDCl3

MHz 600

Nucleus 1H





Solvent CDCl3

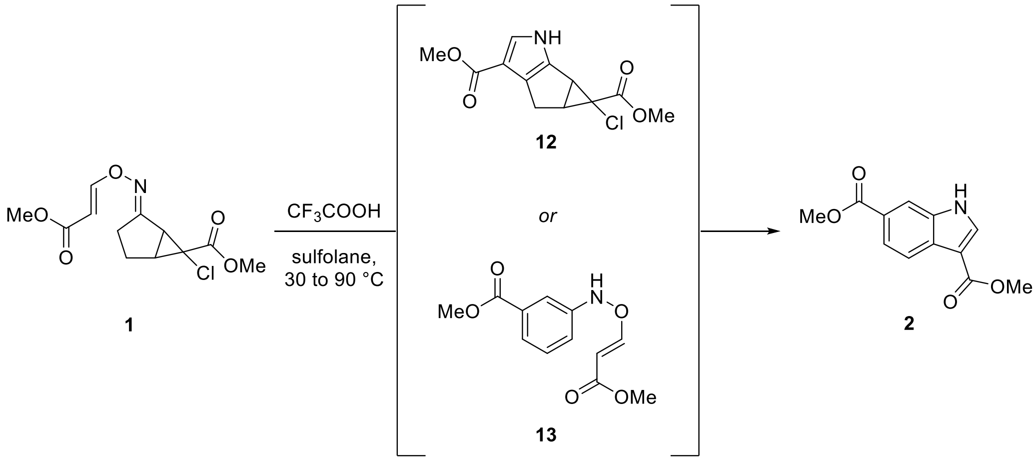
MHz 151

Nucleus 13C

6.2 Supporting Information for Chapter II

6.2.1 Experimental Procedures

^{1}H NMR experiment



Monitoring the conversion of 1 to 2 via ^{1}H NMR spectroscopy.

A solution of **1** (67.0 mg, 23.3 µmol, 1 equiv) and trifluoroacetic acid (26.6 mg, 23.3 µmol, 1 equiv) in sulfolane (1 mL) was heated from 30 °C to 90 °C. NMR aliquots (100 µL) were taken out every 10 °C. To this aliquot water (500 µL) and diethyl ether (500 µL) were added and the organic layer was filtered through a short plug of magnesium sulfate. The plug was washed with diethyl ether (1 mL) and the filtrate was concentrated and dried on *high vacuo*.

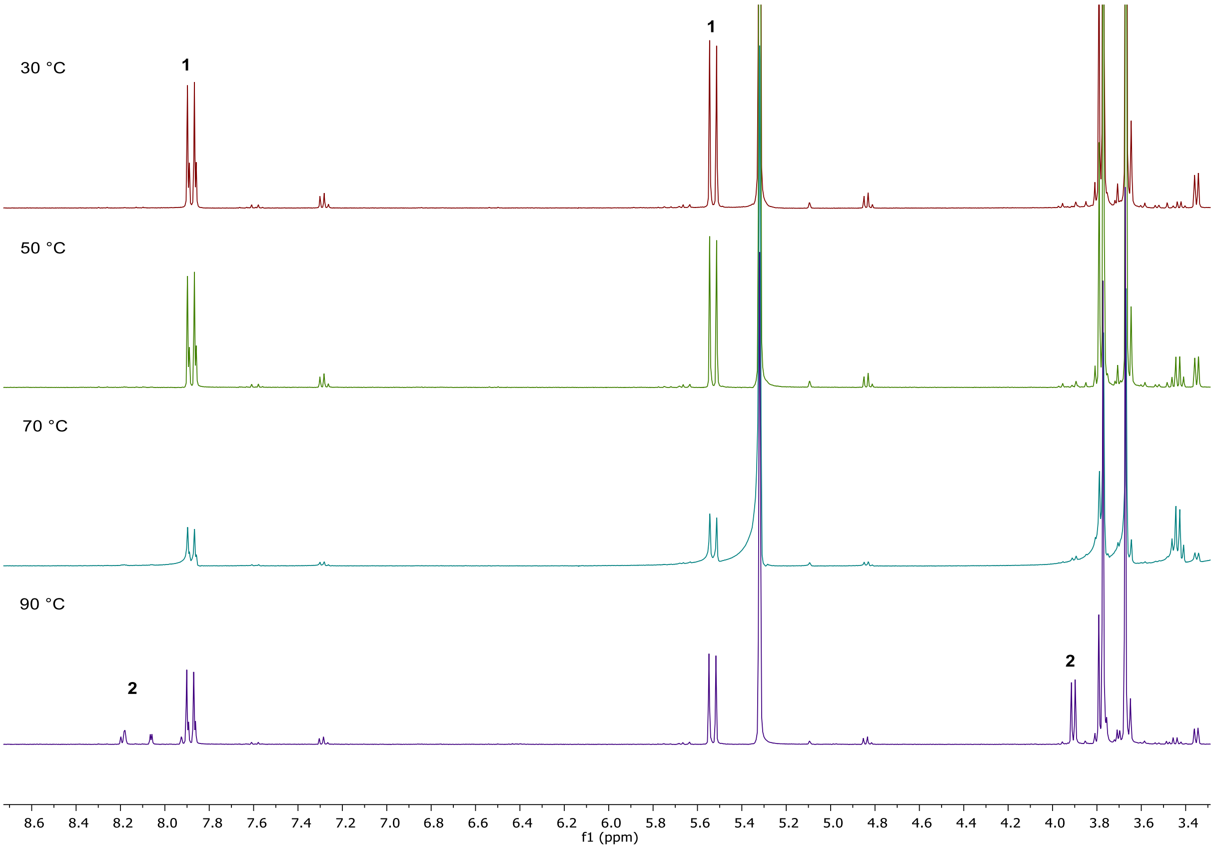
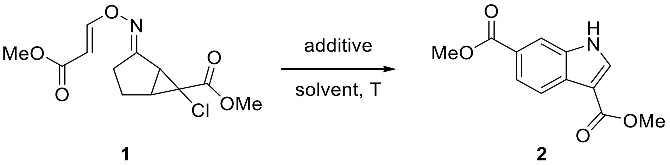


Figure 1: ^{1}H NMR spectra of the conversion of **1** to **2** (400 MHz, CD_2Cl_2).

Screening of Reaction Conditions

A solution of *O*-vinyl oxime **1** (100 µmol, 1 equiv) and additive in the corresponding solvent (0.2–0.5 M) was heated at the temperature and time indicated. The reaction mixture was cooled to 23 °C. Water (2 mL) and diethyl ether (2 mL) were added and the layers were separated. The aqueous layer was extracted with diethyl ether (4 × 10 mL). The combined organic extracts were washed sequentially with water (4 × 10 mL) and saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (33% ethyl acetate in hexanes) on silica gel to afford **2**.

Table 1: Screening of Reaction Conditions.



1 **2**

Entry	Solvent	Additive	T (°C)	t (h)	Yield 2 [%]

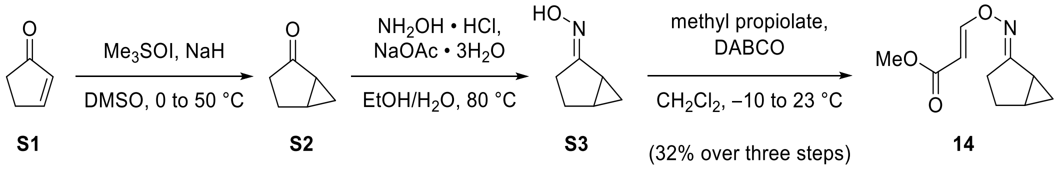
1	**sulfolane**	**CF_3COOH 1 equiv**	**100**	**1.5**	**65**
2	sulfolane	CF_3COOH 0.1 equiv	100	1.5	42
3	sulfolane	CF_3COOH 3 equiv	100	1.5	47
4	sulfolane	none	70	3	n.c.
5	sulfolane	none	100	2	37
6	sulfolane	none	130	0.25	39
7	sulfolane	none	150	0.5	42
8	sulfolane	none	170	0.75	39
9	sulfolane	none	190	0.5	6
10	sulfolane	AcOH	100	5	39
11	sulfolane	$ZnCl_2$	100	3	traces
12	sulfolane	*p*TsOH	100	0.5	16
13	sulfolane	H_3PO_4	100	0.5	53
14	sulfolane	Amberlyst® 15	100	1.5	63
15	sulfolane	CSA	100	1	39
16	sulfolane	4-nitrophenol	100	3	36
17	sulfolane	TfOH	100	1	decompn.
18	sulfolane	bis(trifluoromethanesulfonyl)imide	100	1	decompn.
19	sulfolane	Et_3N	100	3	traces
20	sulfolane	DIPEA	100	2	traces
21	sulfolane	DBU	100	2	decompn.
22	sulfolane	AcCl	100	3	55
23	sulfolane	MeI	100	3	n.c.
24	sulfolane	ClCOOEt	100	3	65
25	sulfolane	ClCOOEt 2 equiv	100	1	67
26	sulfolane	ClCOOEt K_2CO_3 2 equiv	100	2	decompn.
27	DMF	none	100	3	n.c.
28	HFIP	none	100	3	n.c.
29	1,4-dioxane	none	100	3	n.c.
30	toluene	none	100	3	n.c.
31	toluene	none	170	3	decompn.
32	toluene	$PPh_3AuCl/AgBF_4$	100	48	traces
33	CF_3COOH	none	100	1	hydrolysis

34	sulfolane	NCS	100	2	n.c.

n.c.: no conversion; decompn.: decomposition.

Syntheses of *O*-Vinyl Oxime 14

Note: Since the O-vinyl oxime formation yielded an inseparable mixture of four double bond isomers, purified O-vinyl oximes were only characterized by high-resolution mass spectrometry and directly used in the indole formation without further characterization.



A solution of trimethylsulfoxonium iodide (2.95 g, 13.4 mmol, 1.10 equiv) in dimethylsulfoxide (12 mL) was cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 536 mg, 13.4 mmol, 1.10 equiv) was added portion wise. After 10 min, cyclopentenone **S1** (1.02 mL, 12.2 mmol, 1 equiv) was added. After 30 min, the reaction mixture was heated to 50 °C. After 2 h, the reaction mixture was poured on ice-water (50 mL) and diethyl ether (50 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with aqueous lithium chloride solution (10%, 20 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue **S2** (assuming 800 mg) was used without further purification in the next step.

A solution of ketone **S2** (assuming 800 mg, 8.32 mmol, 1 equiv), hydroxylamine hydrochloride (867 mg, 12.5 mmol, 1.50 equiv) and sodium acetate trihydrate (2.27 g, 16.6 mmol, 2.00 equiv) in a mixture of ethanol (9 mL) and water (3 mL) was heated to 80 °C. After 14 h, the reaction mixture was allowed to cool to 23 °C and water (10 mL) and ethyl acetate (20 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude oxime **S3** (assuming 694 mg) was used without further purification in the next step.

In a flame dried flask, a solution of oxime **S2** (assuming 694 mg, 6.24 mmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (70.0 mg, 624 µmol, 0.100 equiv) in dichloromethane (4 mL) was cooled to −10 °C. A solution of methyl propiolate (555 µL, 6.24 mmol, 1 equiv) in dichloromethane (4 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After

2 h, the solvent was evaporated. The residue was purified by lash column chromatography (20% ethyl acetate in hexanes) on silica gel to yield **14** (755 mg, 32% over three steps) as a colorless oil.

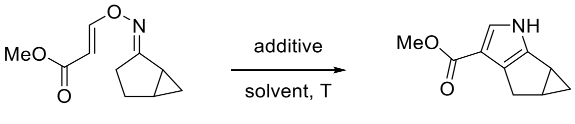
TLC (20% ethyl acetate in hexanes): $R_f = 0.27$ (UV, $KMnO_4$).

HRMS (EI) calcd for $C_{10}H_{12}NO_3$ $[M-H]^+$: 194.0822; found: 194.0810.

Attempted Pyrrol Formation:

A solution of *O*-vinyl oxime **14** (100 µmol, 1 equiv) and trifluoroacetic acid (100 µmol, 1 equiv) in sulfolane (300 µL) was heated at the temperature and time indicated. The reaction mixture was cooled to 23 °C. Water (2 mL) and diethyl ether (2 mL) were added and the layers were separated. The aqueous layer was extracted with diethyl ether (4 × 10 mL). The combined organic extracts were washed sequentially with water (4 × 10 mL) and saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was analyzed via proton NMR spectroscopy.

Table 2: Screening of Reaction Conditions.

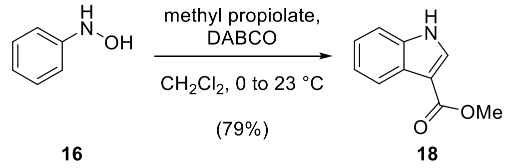


14 **15**

Entry	Solvent	Additive	T (°C)	t (h)	Yield 15 [%]
1	sulfolane	CF_3COOH 1 equiv	30	14	n.c.
2	sulfolane	CF_3COOH 1 equiv	100	4	decompn.

n.c.: no conversion; decompn.: decomposition.

Methyl 1*H*-indole-3-carboxylate (18)

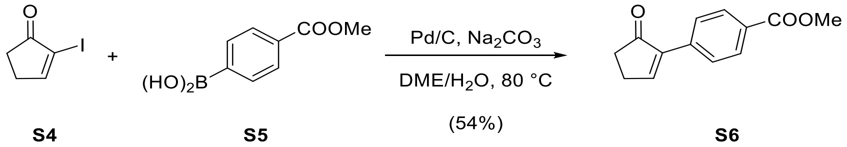


In an oven dried flask a solution of *N*-phenylhydroxylamine (100 mg, 916 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (10.3 mg, 91.6 µmol, 0.100 equiv) in dichloromethane (1 mL) was cooled to 0 °C. A solution of methyl propiolate (81.5 µL, 916 µmol, 1 equiv) in dichloromethane (1 mL) was added dropwise. After 10 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, the reaction mixture was concentrated (rotary evaporater at 40 °C). The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **18** (126 mg, 79%) as a yellow solid. Characterization data of **18** were in full agreement with those reported in literature.[87]

TLC (25% ethyl acetate in hexanes): $R_f = 0.17$ (UV, $KMnO_4$)

Syntheses of Precursors

Methyl 4-(5-oxocyclopent-1-en-1-yl)benzoate (S6)



To a solution of iodide **S4** (250 mg, 1.20 mmol, 1 equiv) in a degassed mixture of dimethoxyethane (2 mL) and water (2 mL) was added sodium carbonate (255 mg, 2.40 mmol, 2.00 equiv), boronic acid **S5** (324 mg, 1.80 mmol, 1.50 equiv) and palladium on activated charcoal (10% Pd basis, 128 mg, 120 µmol, 0.100 equiv). The reaction mixture was then heated to 80 °C. After 1 h, the reaction mixture was allowed to cool to 23 °C and water (3 mL) and diethyl ether (30 mL) were added and the reaction mixture was filtered through a short plug of Celite®. The plug was washed with diethyl ether (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to yield **S6** (140 mg, 54%) as a colorless solid.

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[87] Q.-Q. Yang, M. Marchini, W.-J. Xiao, P. Ceroni, M. Bandini, *Chem. Eur. J.* **2015**, *21*, 18052–18056.

TLC (25% ethyl acetate in hexanes): R_f = 0.20 (UV, $KMnO_4$).

m.p. 104 °C.

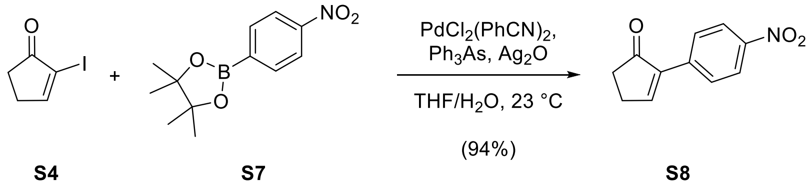
^{1}H NMR (599 MHz, $CDCl_3$) δ = 8.07–8.02 (m, 2H), 7.94 (t, *J* = 3.0 Hz, 1H), 7.81–7.76 (m, 2H), 3.92 (s, 3H), 2.78–2.73 (m, 2H), 2.65–2.60 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 207.2, 167.0, 160.7, 142.8, 136.2, 129.9, 129.8, 127.1, 52.3, 35.9, 26.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (*w*), 1703 (*vs*), 1697 (*vs*), 1320 (*s*), 1282 (*vs*), 1110 (*s*), 854 (*m*), 769 (*vs*), 696 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{12}O_3$ $[M]^+$: 216.0786; found: 216.0780.

2-(4-Nitrophenyl)cyclopent-2-en-1-one (S8)



To a solution of iodide **S4** (292 mg, 1.41 mmol, 1.40 equiv), 4-nitrophenylboronic acid pinacol ester **S7** (250 mg, 1.00 mmol, 1 equiv), silver(I)oxide (698 mg, 3.01 mmol, 3.00 equiv) and triphenylarsine (30.7 mg, 100 µmol, 0.100 equiv) in a degassed mixture of tetrahydrofuran (5.5 mL) and water (0.290 mL) was added bis(benzonitrile)palladium(II)dichloride (19.3 mg, 50.2 µmol, 0.0500 equiv). After 30 min, the reaction mixture was filtered through a short plug of Celite®. The plug was washed with diethyl ether (50 mL). The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to yield **S8** (191 mg, 94%) as an orange solid.

TLC (25% ethyl acetate in hexanes): R_f = 0.10 (UV, $KMnO_4$).

m.p. 120 °C.

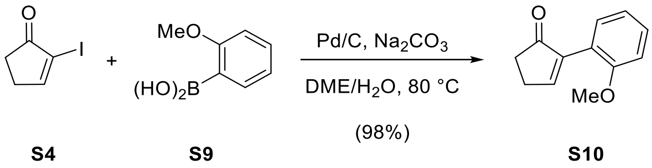
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26–8.21 (m, 2H), 8.02 (t, *J* = 2.9 Hz, 1H), 7.92–7.87 (m, 2H), 2.82–2.77 (m, 2H), 2.68–2.64 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 206.7, 161.9, 147.7, 141.8, 138.1, 127.9, 123.8, 35.9, 26.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2936 (*w*), 2907 (*w*), 1700 (*s*), 1688 (*vs*), 1513 (*vs*), 1344 (*vs*), 1324 (*vs*), 846 (*s*), 694 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_9NO_3$ $[M]^+$: 203.0582; found: 203.0575.

2-(2-Methoxyphenyl)cyclopent-2-en-1-one (S10)



To a solution of iodide **S4** (250 mg, 1.20 mmol, 1 equiv) in a degassed mixture of dimethoxyethane (7 mL) and water (7 mL) was added sodium carbonate (255 mg, 2.40 mmol, 2.00 equiv), boronic acid **S9** (365 mg, 2.40 mmol, 2.00 equiv) and palladium on activated charcoal (10% Pd basis, 128 mg, 120 µmol, 0.100 equiv). The reaction mixture was then heated to 80 °C. After 4 h, the reaction mixture was allowed to cool to 23 °C and water (3 mL) and diethyl ether (30 mL) were added and the reaction mixture was filtered through a short plug of Celite®. The plug was washed with diethyl ether (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to yield **S10** (222 mg, 98%) as a colorless solid.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.14$ (UV, $KMnO_4$).

m.p. 70 °C.

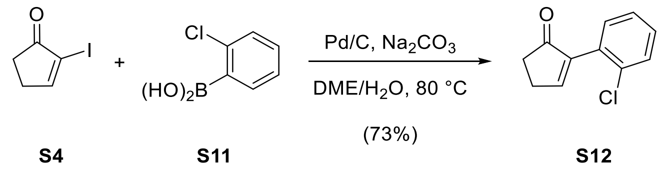
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.96 (t, J = 2.9 Hz, 1H), 7.54 (dd, J = 7.9, 1.7 Hz, 1H), 7.33–7.26 (m, 1H), 7.01–6.94 (m, 2H), 3.81 (s, 3H), 2.75–2.70 (m, 2H), 2.51–2.47 (m, 2H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 208.1, 162.7, 157.8, 140.8, 130.4, 129.7, 121.7, 120.7, 111.5, 56.0, 35.3, 27.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\max}$: 2918 (*w*), 1694 (*vs*), 1594 (*m*), 1492 (*s*), 1434 (*m*), 1318 (*m*), 1243 (*vs*), 1024 (*s*), 752 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{12}O_2$ $[M]^+$: 188.0837; found: 188.0836.

2-(2-Chlorophenyl)cyclopent-2-en-1-one (S12)



To a solution of iodide **S4** (300 mg, 1.44 mmol, 1 equiv) in a degassed mixture of dimethoxyethane (8.5 mL) and water (8.5 mL) was added sodium carbonate (306 mg, 2.88 mmol, 2.00 equiv), boronic acid **S11** (451 mg, 2.88 mmol, 2.00 equiv) and palladium on activated charcoal (10% Pd basis, 153 mg, 144 µmol, 0.100 equiv). The reaction mixture was then heated to 80 °C. After 4 h, the reaction mixture was allowed to cool to 23 °C and water (3 mL) and diethyl ether (30 mL) were added and the reaction mixture was filtered through a short plug of Celite®. The plug was washed with diethyl ether (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to yield **S12** (203 mg, 73%) as a colorless solid.

TLC (12.5% ethyl acetate in hexanes): R_f = 0.22 (UV, $KMnO_4$).

m.p. 97 °C.

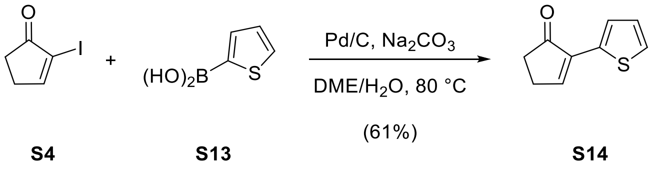
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.84 (t, *J* = 2.8 Hz, 1H), 7.49–7.39 (m, 1H), 7.36–7.24 (m, 3H), 2.82–2.74 (m, 2H), 2.58–2.50 (m, 2H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 206.9, 163.3, 143.5, 133.5, 132.0, 131.4, 130.2, 129.8, 127.1, 35.2, 27.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2927 (*w*), 1694 (*vs*), 1474 (*m*), 1432 (*m*), 937 (*m*), 774 (*vs*), 761 (*vs*), 714 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_9ClO$ $[M]^+$: 192.0342; found: 192.0323.

2-(Thiophen-2-yl)cyclopent-2-en-1-one (S14)



To a solution of iodide **S4** (250 mg, 1.20 mmol, 1 equiv) in a degassed mixture of dimethoxyethane (2 mL) and water (2 mL) was added sodium carbonate (255 mg, 2.40 mmol, 2.00 equiv), boronic acid **S13** (308 mg, 2.40 mmol, 2.00 equiv) and palladium on activated charcoal (10% Pd basis, 128 mg, 120 µmol, 0.100 equiv). The reaction mixture was then heated to 80 °C. After 3 h, the reaction mixture was allowed to cool to 23 °C and water (3 mL) and diethyl ether (30 mL) were added and the reaction mixture was filtered through a short plug of Celite®. The plug was washed with diethyl ether (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **S14** (121 mg, 61%) as a colorless solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.53$ (UV, $KMnO_4$).

m.p. 103 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.78 (t, *J* = 3.1 Hz, 1H), 7.63–7.57 (m, 1H), 7.33 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.06 (dd, *J* = 5.1, 3.1 Hz, 1H), 2.76–2.68 (m, 2H), 2.58–2.51 (m, 2H).

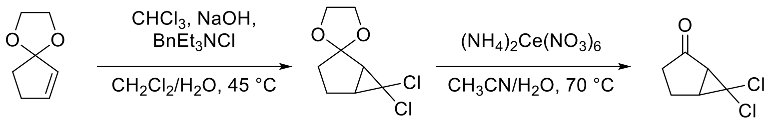
^{13}C NMR (101 MHz, CD_2Cl_2) δ = 206.5, 156.2, 138.0, 133.8, 127.7, 126.4, 126.0, 35.7, 27.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3076 (*m*), 2906 (*w*), 1691 (*vs*), 1430 (*s*), 1320 (*vs*), 1038 (*m*), 778 (*s*), 728 (*vs*) cm^{-1}.

HRMS (EI) calcd for C_9H_8OS $[M]^+$: 164.0296; found: 164.0289.

Syntheses of Bicyclo[3.1.0]hexan-2-ones

6,6-Dichlorobicyclo[3.1.0]hexan-2-one (S17)



S15 **S16** **S17**

In a pressure tube a suspension of cyclopentenone ketal **S15** (1.00 g, 7.93 mmol, 1 equiv), chloroform (7.90 mL, 98.6 mmol, 12.4 equiv) and benzyltriethylammonium chloride (3.97 mg, 17.4 µmol, 0.220 mol%) in dichloromethane (7.9 mL) was treated with aqueous sodium hydroxide solution (50% in water, 7.90 mL, 150 mmol, 18.9 equiv). The reaction mixture was then heated to 45 °C. After 72 h, the reaction mixture was allowed to cool to 23 °C and water (50 mL) and dichloromethane (100 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (4 × 75 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered through a short plug of silica, the plug was washed with dichloromethane and the filtrate was concentrated. To a solution of ketal **S16** (assuming 1.13 g, 5.39 mmol, 1 equiv) in acetonitrile (20 mL) at 70 °C was added a solution of ammonium cerium(IV) nitrate (10.1 g, 18.4 mmol, 2.50 equiv) in water (20 mL). After 10 min, the reaction mixture was allowed to cool to 23 °C and diethyl ether (10 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 30 mL). The combined organic layers were washed saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to yield **S17** (703 mg, 79%) as a colorless oil.

TLC (33% ethyl acetate in hexanes): $R_f = 0.32$ (UV, $KMnO_4$).

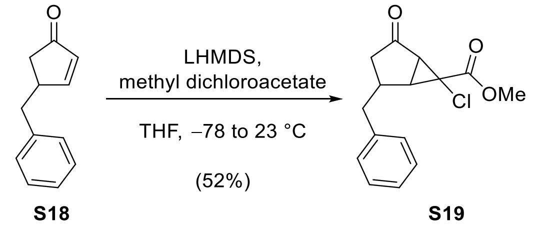
^{1}H NMR (599 MHz, $CDCl_3$) δ = 2.71 (t, *J* = 6.8 Hz, 1H), 2.61 (d, *J* = 6.8 Hz, 1H), 2.45–2.36 (m, 1H), 2.31–2.25 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 208.0, 63.3, 44.9, 39.1, 36.1, 21.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2945 (*w*), 1730 (*vs*), 1452 (*m*), 1405 (*m*), 1266 (*m*), 1183 (*s*), 1061 (*m*), 960 (*m*), 791 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_6H_6Cl_2O$ $[M]^+$: 163.9796; found: 163.9804.

Methyl 2-benzyl-6-chloro-4-oxobicyclo[3.1.0]hexanes-6-carboxylate (S19)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 2.74 mL, 2.74 mmol, 1.10 equiv) was cooled to −78 °C and methyl dichloroacetate (309 µL, 2.99 mmol, 1.20 equiv) was added dropwise. After 30 min, a solution of cyclopentenone **S18**[88] (429 mg, 2.49 mmol, 1 equiv) in tetrahydrofuran (6 mL) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **S19** (363 mg, 52%) as a yellow oil.

TLC (12.5% ethyl acetate in hexanes): R_f = 0.38 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.36–7.30 (m, 2H), 7.27–7.21 (m, 3H), 3.74 (s, 3H), 2.98–2.79 (m, 3H), 2.75–2.72 (m, 1H), 2.64 (d, *J* = 7.8 Hz, 1H), 2.47 (ddd, *J* = 20.0, 7.8, 1.3 Hz, 1H), 2.05 (ddd, *J* = 20.0, 2.9, 1.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.6, 168.1, 138.5, 129.2, 128.9, 126.9, 54.2, 48.4, 44.1, 42.0, 42.0, 40.7, 36.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (*w*), 1731 (*vs*), 1436 (*m*), 1255 (*vs*), 1187 (*s*), 1098 (*m*), 975 (*m*), 745 (*s*), 704 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{15}ClO_3$ $[M]^+$: 278.0704; found: 278.0709.

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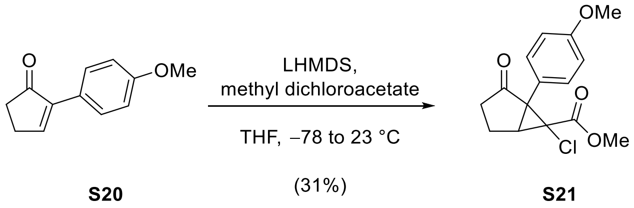
[88] For the synthesis of cyclopentenone **S18** see: M. A. Ciufolini, M.V. Deaton, S. Zhu, M. Chen, *Tetrahedron* **1997**, *53*, 16299–16312.

Methyl 6-chloro-1-(4-methoxyphenyl)-2-oxobicyclo[3.1.0]hexanes-6-carboxylate (S21)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.03 mL, 1.03 mmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (117 µL, 1.13 mmol, 1.10 equiv) was added dropwise. After 45 min, a solution of cyclopentenone **S20**[89] (177 mg, 940 µmol, 1 equiv) in tetrahydrofuran (3 mL) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield **S21** (171 mg, 62%) as a yellow amorphous solid.

TLC (33% ethyl acetate in hexanes): R_f = 0.46 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H), 3.42–3.41 (m, 4H), 2.62–2.51 (m, 1H), 2.51–2.44 (m, 2H), 2.31–2.22 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.3, 165.9, 159.6, 130.6, 123.0, 113.9, 55.4, 53.5, 53.5, 52.0, 37.2, 36.8, 19.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\max}$: 2955 (*w*), 1738 (*vs*), 1436 (*vs*), 1357 (*m*), 1231 (*vs*), 1124 (*s*), 1106 (*s*), 1041 (*m*), 810 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{15}ClO_4$ $[M]^+$: 294.0653; found: 294.0657.

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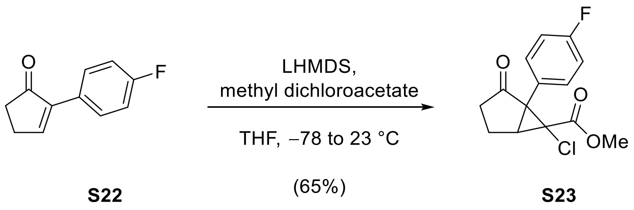
[89] For the synthesis of cyclopentenone **S21** see: J. M. Burns, I. J. S. Fairlamb, A. R. Kapdi, P. Sehnal, T. J. K. Richard, *Org. Lett.* **2007**, *9*, 5397–5400.

Methyl 6-chloro-1-(4-fluorophenyl)-2-oxobicyclo[3.1.0]hexanes-6-carboxylate (S23)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.31 mL, 1.31 mmol, 1.15 equiv) was cooled to −78 °C and methyl dichloroacetate (141 µL, 1.36 mmol, 1.20 equiv) was added dropwise. After 45 min, a solution of cyclopentenone **S22**[90] (200 mg, 1.14 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **S23** (208 mg, 65%) as a yellow amorphous solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.34$ (UV, $KMnO_4$).

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.29–7.19 (m, 2H), 7.08–6.97 (m, 2H), 3.43 (d, J = 5.9 Hz, 1H), 3.39 (s, 3H), 2.65–2.51 (m, 1H), 2.50–2.42 (m, 2H), 2.31–2.19 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 207.8, 165.7, 162.7 (d, J = 247.5 Hz), 131.2 (d, J = 8.3 Hz), 126.8 (d, J = 3.3 Hz), 115.4 (d, J = 21.7 Hz), 53.5, 53.3, 51.8, 37.1, 36.9, 19.2.

^{19}F NMR (377 MHz, $CDCl_3$) δ = −113.27.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (w), 1731 (*vs*), 1512 (*s*), 1269 (*s*), 1221 (*s*), 1138 (*m*), 1057 (*m*), 965 (*w*), 830 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{12}ClFO_3$ $[M]^+$: 282.0454; found: 282.0449.

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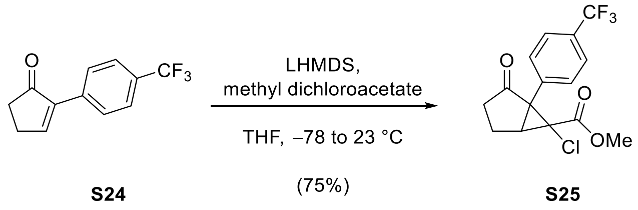
[90] For the synthesis of cyclopentenone **S22** see: R. C. Desai, P. Cicala, L. C. Meurer, P. E. Finke, *Tetrahedron Lett.* **2002**, *43*, 4659–4570.

Methyl 6-chloro-2-oxo-1-(4-(trifluoromethyl)phenyl)bicyclo[3.1.0]hexanes-6-carboxylate (S25)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 597 µL, 597 µmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (67.4 µL, 651 µmol, 1.10 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 45 min, a solution of cyclopentenone **S24**[91] (123 mg, 543 µmol, 1 equiv) in tetrahydrfuran (3 mL) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield **S25** (136 mg, 75%) as a colorless amorphous solid.

TLC (33% ethyl acetate in hexanes): $R_f = 0.64$ (UV, $KMnO_4$).

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 3.50 (app. d, *J* = 6.3 Hz, 1H), 3.42 (s, 3H), 2.64–2.58 (m, 1H), 2.56–2.47 (m, 2H), 2.32–2.29 (m, 1H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 207.1, 165.5, 135.1, 130.6 (q, *J* = 32.6 Hz), 129.9, 125.3 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 272.2 Hz) 53.6, 53.2, 52.2, 37.1, 37.0, 19.3.

^{19}F NMR (377 MHz, $CDCl_3$) δ = −62.71.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*w*), 1732 (*vs*), 1619 (*vs*), 1437 (*vs*), 1409 (*vs*), 1323 (*vs*), 1268 (*s*), 1122 (*s*), 1066 (*s*), 1020 (*s*), cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{12}ClF_3O_3$ $[M]^+$: 332.0422; found: 332.0417.

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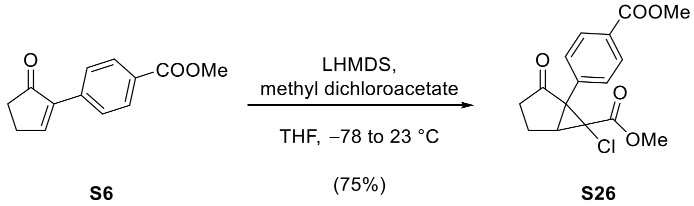
[91] For the synthesis of cyclopentenone **S24** see: S. Chiba, Y.–J. Xu, Y.–F. Wang, *J. Am. Chem. Soc.* **2009**, *131*, 12886–12887.

Methyl 6-chloro-1-(4-(methoxycarbonyl)phenyl)-2-oxobicyclo[3.1.0]hexanes-6-carboxylate (S26)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 691 µL, 691 µmol, 1.15 equiv) was cooled to −78 °C and methyl dichloroacetate (74.7 µL, 721 µmol, 1.20 equiv) was added dropwise. After 45 min, a solution of cyclopentenone **S6** (130 mg, 601 µmol, 1 equiv) in tetrahydrofuran (3 mL) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to yield **S26** (145 mg, 75%) as a colorless oil.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.25$ (UV, $KMnO_4$).

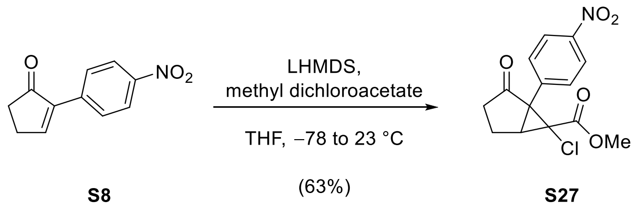
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 3.90 (s, 3H), 3.49 (app. d, *J* = 6.2 Hz, 1H), 3.40 (s, 3H), 2.66–2.55 (m, 1H), 2.54–2.48 (m, 2H), 2.33–2.26 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 207.1, 166.8, 165.5, 136.2, 130.1, 129.6, 129.6, 53.6, 53.3, 52.4, 52.3, 37.2, 37.0, 19.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (*w*), 1730 (v*s*), 1435 (*m*), 1276 (v*s*), 1225 (*m*), 1203 (*m*), 1139 (*m*), 1112 (*m*), 705 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{15}ClO_5$ $[M]^+$: 322.0603; found: 322.0600.

Methyl 6-chloro-1-(4-nitrophenyl)-2-oxobicyclo[3.1.0]hexanes-6-carboxylate (S27)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 996 µL, 996 µmol, 1.15 equiv) was cooled to −78 °C and methyl dichloroacetate (108 µL, 1.04 mmol, 1.20 equiv) was added dropwise. After 30 min, a solution of cyclopentenone **S8** (176 mg, 866 µmol, 1 equiv) in tetrahydrofuran (3 mL) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to yield **S27** (169 mg, 63%) as an orange oil.

TLC (50% ethyl acetate in hexanes): $R_f = 0.64$ (UV, $KMnO_4$).

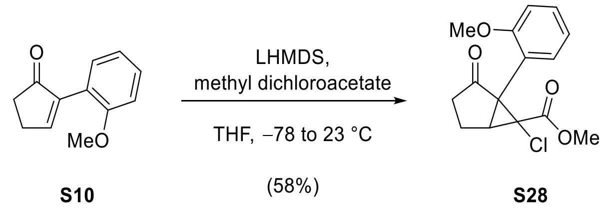
^{1}H NMR (599 MHz, $CDCl_3$) δ = 8.21–8.17 (m, 2H), 7.49–7.45 (m, 2H), 3.52 (app. d, J = 6.0 Hz, 1H), 3.46 (s, 3H), 2.67–2.48 (m, 3H), 2.35–2.30 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 206.4, 165.4, 146.7, 138.4, 130.6, 123.5, 53.8, 53.2, 52.2, 37.3, 37.1, 19.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*w*), 1732 (*m*), 1521 (*m*), 1349 (*s*), 1270 (*m*), 1138 (*m*), 905 (*vs*), 725 (*vs*) cm^{-1}.

HRMS (ESI) calcd for $C_{14}H_{11}ClNO_5$ $[M-H]^-$: 308.03312; found: 308.03328.

Methyl 6-chloro-1-(2-methoxyphenyl)-2-oxobicyclo[3.1.0]hexanes-6-carboxylate (S28)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.30 mL, 1.30 mmol, 1.10 equiv) was cooled to −78 °C and methyl dichloroacetate (147 µL, 1.42 mmol, 1.20 equiv) was added dropwise. After 45 min, a solution of cyclopentenone **S10** (222 mg, 1.18 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to yield **S28** (200 mg, 58%) as a colorless oil.

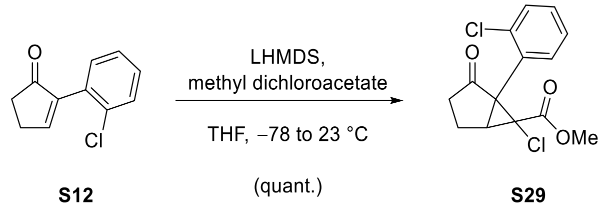
*Note: Since reaction yielded an inseparable mixture of diastereomers, purified bicyclo[3.1.0]hexan-2-one **S28** was directly used in the oxime formation without further characterization except for infrared and high-resolution mass spectrometry.*

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.20$ (UV, $KMnO_4$).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951 (*w*), 1729 (*vs*), 1498 (*m*), 1266 (*s*), 1242 (*s*), 1223 (*s*), 1203 (*s*), 1142 (*s*), 754 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{15}ClO_4$ $[M]^+$: 294.0653; found: 294.0653.

Methyl 6-chloro-1-(2-chlorophenyl)-2-oxobicyclo[3.1.0]hexanes-6-carboxylate (S29)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.05 mL, 1.05 mmol, 1.05 equiv) was cooled to −78 °C and methyl dichloroacetate (114 µL, 1.10 mmol, 1.10 equiv) was added dropwise. After 45 min, a solution of cyclopentenone **S12** (192 mg, 997 µmol, 1 equiv) in tetrahydrofuran (3 mL) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to yield **S29** (298 mg, quant., mixture of diastereomers) as a colorless oil.

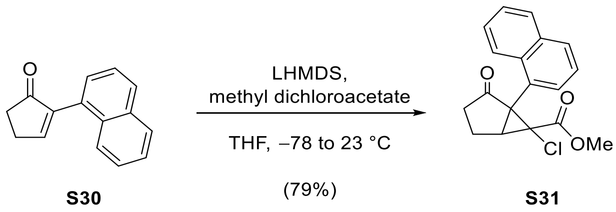
*Note: Since reaction yielded an inseparable mixture of diastereomers, purified bicyclo[3.1.0]hexan-2-one **S29** was directly used in the oxime formation without further characterization except for infrared and high-resolution mass spectrometry.*

TLC (12.5% ethyl acetate in hexanes): R_f = 0.31 (UV, $KMnO_4$).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (*w*), 1730 (*vs*), 1436 (*m*), 1268 (*s*), 1224 (*s*), 1202 (*s*), 1144 (*s*), 1050 (*s*), 963 (*m*), 755 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{12}Cl_2O_3$ $[M]^+$: 298.0158; found: 298.0160.

Methyl 6-chloro-1-(naphthalen-1-yl)-2-oxobicyclo[3.1.0]hexanes-6-carboxylate (S31)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.04 mL, 1.04 mmol, 1.15 equiv) was cooled to −78 °C and methyl dichloroacetate (112 µL, 1.08 mmol, 1.20 equiv) was added dropwise. After 45 min, a solution of cyclopentenone **S30**[92] (188 mg, 903 µmol, 1 equiv) in tetrahydrofuran (3 mL) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to yield **S31** (224 mg, 79%, mixture of diastereomers) as a colorless oil.

*Note: Since reaction yielded an inseparable mixture of diastereomers, purified bicyclo[3.1.0]hexan-2-one **S31** was directly used in the oxime formation without further characterization except for infrared spectroscopy and high-resolution mass spectrometry.*

TLC (12.5% ethyl acetate in hexanes): R_f = 0.29 (UV, $KMnO_4$).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951 (*w*), 1728 (*vs*), 1435 (*m*), 1267 (*vs*), 1227 (*s*), 1198 (*s*), 1147 (*s*), 1042 (*m*), 776 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{15}ClO_3$ [M]$^+$: 314.0704; found: 314.0703.

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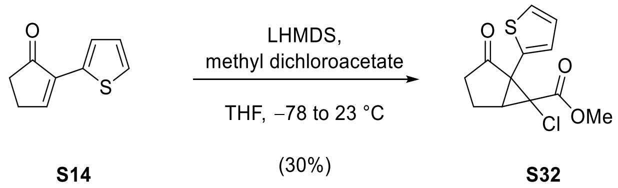
[92] For the synthesis of cyclopentenone **S30** see: J. C. Banks, D. V. Mele, C. G. Frost, *Tetrahedron Lett*. **2006**, *47*,2863–2866.

Methyl 6-chloro-2-oxo-1-(thiophen-2-yl)bicyclo[3.1.0]hexanes-6-carboxylate (S32)



A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 784 µL, 784 µmol, 1.15 equiv) was cooled to −78 °C and methyl dichloroacetate (84.7 µL, 818 µmol, 1.20 equiv) was added dropwise. After 45 min, a solution of cyclopentenone **S14** (112 mg, 682 µmol, 1 equiv) in tetrahydrofuran (3 mL) was added dropwise. After 30 min, the solution was warmed to 23 °C. After 14 h, saturated aqueous ammonium chloride solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to yield **S32** (56 mg, 30%) as an off-white amorphous solid.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.33$ (UV, $KMnO_4$).

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.30 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.91 (dd, *J* = 3.6, 1.2 Hz, 1H), 3.49–3.46 (m, 4H), 2.65–2.52 (m, 1H), 2.50–2.44 (m, 2H), 2.29–2.21 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 206.9, 165.3, 132.4, 128.3, 126.9, 126.6, 54.2, 53.6, 47.8, 38.3, 37.1, 19.3.

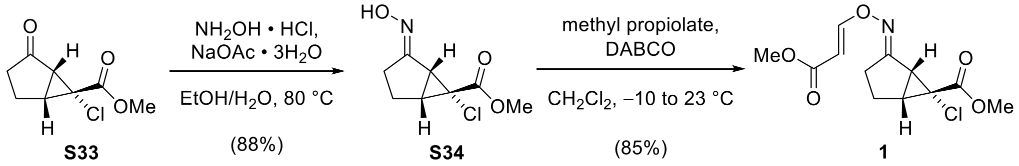
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (*w*), 1731 (*vs*), 1435 (*m*), 1266 (*s*), 1220 (*s*), 1200 (*m*), 1119 (*m*), 1054 (*m*), 705 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{11}ClO_3S$ $[M]^+$: 270.0112; found: 270.0110.

Syntheses of *O*-Vinyl Oximes

Note: Since the O-vinyl oxime formation yielded an inseparable mixture of four double bond isomers, purified O-vinyl oximes were only characterized by high-resolution mass spectrometry and directly used in the indole formation without further characterization. The major double bond isomer is depicted.

O-Vinyl Oxime 1



A solution of ketone **S33**[93] (500 mg, 2.65 mmol, 1 equiv), hydroxylamine hydrochloride (276 mg, 3.98 mmol, 1.50 equiv) and sodium acetate trihydrate (721 mg, 5.30 mmol, 2.00 equiv) in a mixture of ethanol (9 mL) and water (3 mL) was heated to 80 °C. After 2 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield oxime **S34** (442 mg, 88%) as an inseparable mixture of double bond isomers as an off-white solid.

TLC (33% ethyl acetate in hexanes): $R_f = 0.22$ ($KMnO_4$).

In a flame dried flask, a solution of oxime **S34** (355 mg, 1.74 mmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (19.6 mg, 174 µmol, 0.100 equiv) in dichloromethane (3.5 mL) was cooled to −10 °C. A solution of methyl propiolate (155 µL, 1.74 mmol, 1 equiv) in dichloromethane (3.5 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, the solvent was evaporated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) on silica gel yielded **1** (442 mg, 85%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.27$ (UV, $KMnO_4$).

HRMS (ESI) calcd for $C_{12}H_{15}ClNO_5$ $[M+H]^+$: 288.06338; found: 288.06367.

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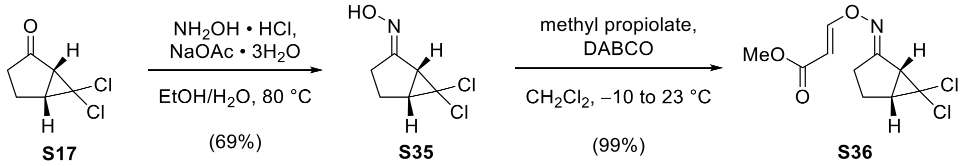
[93] For the synthesis of bicyclo[3.1.0]hexan-2-one **S33** see: A. Escribano, C. Pedregal, R. González, A. Fernández, K. Burton, G. A. Stephenson, *Tetrahedron* **2001**, *57*, 9423–9427.

O-Vinyl Oxime S36



A solution of ketone **S17** (206 mg, 1.25 mmol, 1 equiv), hydroxylamine hydrochloride (130 mg, 1.87 mmol, 1.50 equiv) and sodium acetate trihydrate (340 mg, 2.50 mmol, 2.00 equiv) in a mixture of ethanol (6 mL) and water (2 mL) was heated to 80 °C. After 1 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield oxime **S35** (155 mg, 69%) as an inseparable mixture of double bond isomers as an off-white solid.

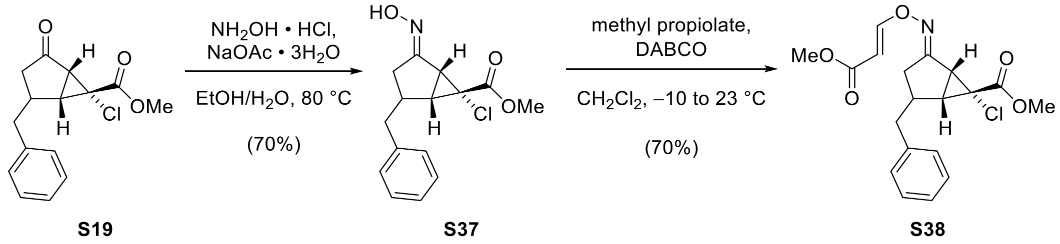
TLC (33% ethyl acetate in hexanes): $R_f = 0.30$ ($KMnO_4$).

In a flame dried flask, a solution of oxime **S35** (120 mg, 667 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (7.48 mg, 66.7 µmol, 0.100 equiv) in dichloromethane (2 mL) was cooled to −10 °C. A solution of methyl propiolate (59.3 µL, 667 µmol, 1 equiv) in dichloromethane (0.5 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, the solvent was evaporated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) on silica gel yielded **S36** (175 mg, 99%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.44$ (UV, $KMnO_4$).

HRMS (ESI) calcd for $C_{10}H_{12}Cl_2NO_3$ $[M+H]^+$: 264.01888; found: 264.01903.

O-Vinyl Oxime S38



A solution of ketone **S19** (324 mg, 1.16 mmol, 1 equiv), hydroxylamine hydrochloride (121 mg, 1.74 mmol, 1.50 equiv) and sodium acetate trihydrate (316 mg, 2.32 mmol, 2.00 equiv) in a mixture of ethanol (6 mL) and water (2 mL) was heated to 80 °C. After 14 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to yield oxime **S37** (240 mg, 70%) as an inseparable mixture of double bond isomers as an off-white solid.

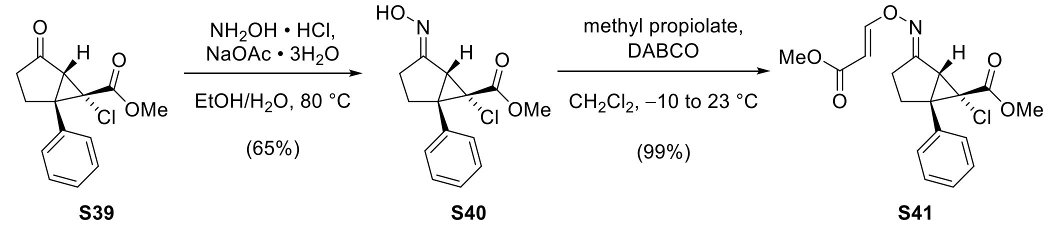
TLC (25% ethyl acetate in hexanes): $R_f = 0.29$ (UV, $KMnO_4$).

In a flame dried flask, a solution of oxime **S37** (211 mg, 718 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (8.06 mg, 71.8 µmol, 0.100 equiv) in dichloromethane (3 mL) was cooled to −10 °C. A solution of methyl propiolate (63.9 µL, 718 µmol, 1 equiv) in dichloromethane (3 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 45 min, the solvent was evaporated. The residue was purified by flash column chromatography (12.5% ethyl acetate in hexanes) on silica gel yielded **S38** (189 mg, 70%) as a colorless oil.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.18$ (UV, $KMnO_4$).

HRMS (ESI) calcd for $C_{19}H_{21}O_5NCl$ $[M+H]^+$: 378.11028; found: 378.11026.

O-Vinyl Oxime S41



A solution of ketone **S39**[94] (83.0 mg, 314 µmol, 1 equiv), hydroxylamine hydrochloride (32.7 mg, 470 µmol, 1.50 equiv) and sodium acetate trihydrate (85.3 mg, 628 µmol, 2.00 equiv) in a mixture of ethanol (3 mL) and water (1 mL) was heated to 80 °C. After 4 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield oxime **S40** (57.0 mg, 65%) as an inseparable mixture of double bond isomers as an off-white solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.26$ (UV, $KMnO_4$).

In a flame dried flask, a solution of oxime **S40** (41.8 mg, 149 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (1.68 mg, 14.9 µmol, 0.100 equiv) in dichloromethane (1 mL) was cooled to −10 °C. A solution of methyl propiolate (13.3 µL, 149 µmol, 1 equiv) in dichloromethane (0.5 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 2.5 h, the solvent was evaporated. The residue was purified by flash column chromatography (dichloromethane) on silica gel yielded **S41** (54.0 mg, 99%) as a colorless oil.

TLC (dichloromethane): $R_f = 0.18$ (UV, $KMnO_4$).

HRMS (ESI) calcd for $C_{18}H_{19}O_5NCl$ $[M+H]^+$: 364.09468; found: 394.09459.

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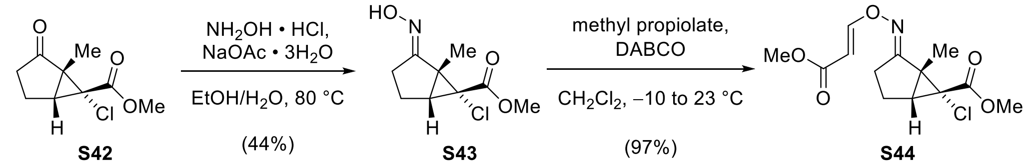
[94] For the synthesis of bicyclo[3.1.0]hexan-2-one **S39** see: J. Feierfeil, A. Grossmann, T. Magauer, *Angew. Chem, Int. Ed*. **2015**, *54*, 11835–11838.

O-Vinyl Oxime S44



A solution of ketone **S42**[95] (260 mg, 1.29 mmol, 1 equiv), hydroxylamine hydrochloride (134 mg, 1.92 mmol, 1.50 equiv) and sodium acetate trihydrate (349 mg, 2.57 mmol, 2.00 equiv) in a mixture of ethanol (6 mL) and water (2 mL) was heated to 80 °C. After 6 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield oxime **S43** (123 mg, 44%) as an inseparable mixture of double bond isomers as an off-white solid.

TLC (33% ethyl acetate in hexanes): $R_f = 0.17$ ($KMnO_4$).

In a flame dried flask, a solution of oxime **S43** (114 mg, 524 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (5.88 mg, 52.4 µmol, 0.100 equiv) in dichloromethane (2 mL) was cooled to −10 °C. A solution of methyl propiolate (46.6 µL, 524 µmol, 1 equiv) in dichloromethane (2 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 30 min, the solvent was evaporated. The residue was purified by flash column chromatography (33% ethyl acetate in hexanes) on silica gel yielded **S44** (154 mg, 97%) as a colorless oil.

TLC (33% ethyl acetate in hexanes): $R_f = 0.26$ (UV, $KMnO_4$).

HRMS (ESI) calcd for $C_{13}H_{17}ClNO_5$ $[M+H]^+$: 302.0790; found: 302.0798.

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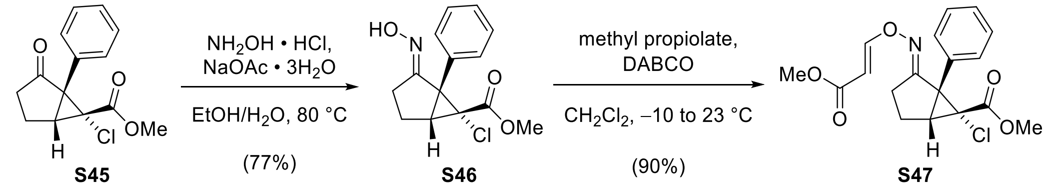
[95] For the synthesis of bicyclo[3.1.0]hexan-2-one **S42** see: J. Feierfeil, A. Grossmann, T. Magauer, *Angew. Chem, Int. Ed.* **2015**, *54*, 11835–11838.

O-Vinyl Oxime S47



A solution of ketone **S45**[96] (200 mg, 756 µmol, 1 equiv), hydroxylamine hydrochloride (78.8 mg, 1.13 mmol, 1.50 equiv) and sodium acetate trihydrate (206 mg, 1.51 mmol, 2.00 equiv) in a mixture of ethanol (6 mL) and water (2 mL) was heated to 80 °C. After 48 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield oxime **S46** (162 mg, 77%) as an inseparable mixture of double bond isomers as an off-white solid.

TLC (33% ethyl acetate in hexanes): $R_f = 0.28$ (UV, $KMnO_4$).

In a flame dried flask, a solution of oxime **S46** (80.0 mg, 286 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (3.21 mg, 28.6 µmol, 0.100 equiv) in dichloromethane (1 mL) was cooled to −10 °C. A solution of methyl propiolate (25.4 µL, 286 µmol, 1 equiv) in dichloromethane (1 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, the solvent was evaporated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) on silica gel yielded **S47** (94.0 mg, 90%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.10$ (UV, $KMnO_4$).

HRMS (EI) calcd for $C_{18}H_{18}ClNO_5$ $[M]^+$: 363.0868; found: 363.0887.

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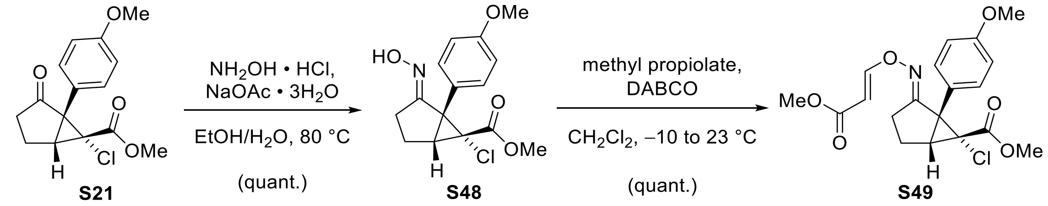
[96] For the synthesis of bicyclo[3.1.0]hexan-2-one **S45** see: J. Feierfeil, A. Grossmann, T. Magauer, *Angew. Chem, Int. Ed.* **2015**, *54*, 11835–11838.

O-Vinyl Oxime S49



A solution of ketone **S21** (156 mg, 528 µmol, 1 equiv), hydroxylamine hydrochloride (55.0 mg, 791 µmol, 1.50 equiv) and sodium acetate trihydrate (144 mg, 1.06 mmol, 2.00 equiv) in a mixture of ethanol (3 mL) and water (1 mL) was heated to 80 °C. After 14 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield oxime **S48** (163 mg, quant.) as an inseparable mixture of double bond isomers as an off-white solid.

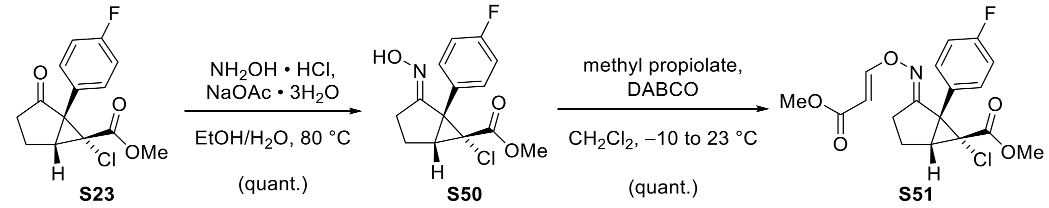
TLC (33% ethyl acetate in hexanes): $R_f = 0.22$ (UV, $KMnO_4$).

In a flame dried flask, a solution of oxime **S48** (81 mg, 262 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (2.93 mg, 26.2 µmol, 0.100 equiv) in dichloromethane (1 mL) was cooled to −10 °C. A solution of methyl propiolate (23.3 µL, 262 µmol, 1 equiv) in dichloromethane (1 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 14 h, the solvent was evaporated. The residue was purifies by flash column chromatography (20% ethyl acetate in hexanes) on silica gel yielded **S49** (102 mg, quant.) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.20$ (UV, $KMnO_4$).

HRMS (ESI) calcd for $C_{19}H_{21}O_6NCl$ $[M+H]^+$: 394.10518; found: 394.10539.

***O*-Vinyl Oxime S51**



A solution of ketone **S23** (201 mg, 711 µmol, 1 equiv), hydroxylamine hydrochloride (74.1 mg, 1.07 mmol, 1.50 equiv) and sodium acetate trihydrate (194 mg, 1.42 mmol, 2.00 equiv) in a mixture of ethanol (3 mL) and water (1 mL) was heated to 80 °C. After 6 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield oxime **S50** (177 mg, quant.) as an inseparable mixture of double bond isomers as an off-white solid.

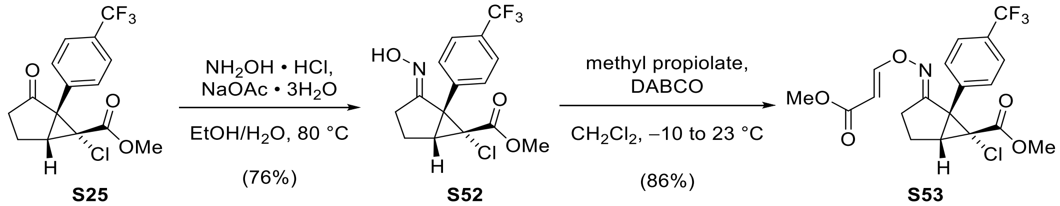
TLC (20% ethyl acetate in hexanes): $R_f = 0.39$ (UV, KMnO$_4$).

In a flame dried flask, a solution of oxime **S50** (177 mg, 595 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (6.67 mg, 59.5 µmol, 0.100 equiv) in dichloromethane (2 mL) was cooled to −10 °C. A solution of methyl propiolate (52.9 µL, 595 µmol, 1 equiv) in dichloromethane (2 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 14 h, the solvent was evaporated. The residue was purified by flash column chromatography (12.5% ethyl acetate in hexanes) on silica gel yielded **S51** (226 mg, quant.) as a colorless oil.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.26$ (UV, KMnO$_4$).

HRMS (ESI) calcd for $C_{18}H_{18}O_5NClF$ $[M+H]^+$: 382.08518; found: 382.08517.

***O*-Vinyl Oxime S53**



A solution of ketone **S25** (105 mg, 316 µmol, 1 equiv), hydroxylamine hydrochloride (33.0 mg, 474 µmol, 1.50 equiv) and sodium acetate trihydrate (86.1 mg, 632 µmol, 2.00 equiv) in a mixture of ethanol (3 mL) and water (1 mL) was heated to 80 °C. After 14 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield oxime **S52** (83.0 mg, 76%) as an inseparable mixture of double bond isomers as an off-white solid.

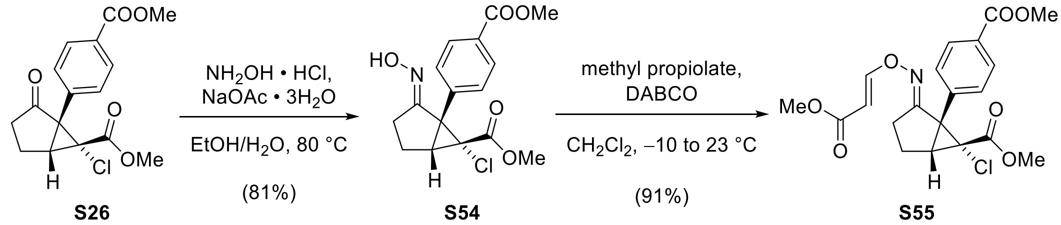
TLC (20% ethyl acetate in hexanes): R_f = 0.13 (UV, $KMnO_4$).

In a flame dried flask, a solution of oxime **S52** (75.0 mg, 216 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (2.42 mg, 21.6 µmol, 0.100 equiv) in dichloromethane (1 mL) was cooled to −10 °C. A solution of methyl propiolate (19.2 µL, 216 µmol, 1 equiv) in dichloromethane (1 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, the solvent was evaporated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) on silica gel yielded **S53** (81.0 mg, 86%) as a colorless solid.

TLC (25% ethyl acetate in hexanes): R_f = 0.39 (UV, $KMnO_4$).

HRMS (EI) calcd for $C_{19}H_{17}ClF_3NO_5$ $[M]^+$: 431.0742; found: 431.0742.

O-Vinyl Oxime S55



A solution of ketone **S26** (130 mg, 403 µmol, 1 equiv), hydroxylamine hydrochloride (42.0 mg, 604 µmol, 1.50 equiv) and sodium acetate trihydrate (110 mg, 806 µmol, 2.00 equiv) in a mixture of ethanol (3 mL) and water (1 mL) was heated to 80 °C. After 72 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield oxime **S54** (110 mg, 81%) as an inseparable mixture of double bond isomers as an off-white solid.

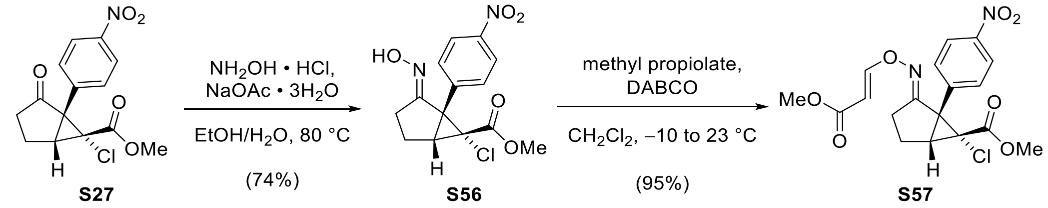
TLC (33% ethyl acetate in hexanes): $R_f = 0.25$ (UV, $KMnO_4$).

In a flame dried flask, a solution of oxime **S54** (110 mg, 326 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (3.65 mg, 32.6 µmol, 0.100 equiv) in dichloromethane (1.5 mL) was cooled to −10 °C. A solution of methyl propiolate (29.0 µL, 326 µmol, 1 equiv) in dichloromethane (1.5 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 45 min, the solvent was evaporated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) on silica gel yielded **S55** (125 mg, 91%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.18$ (UV, $KMnO_4$).

HRMS (ESI) calcd for $C_{20}H_{21}O_7NCl$ $[M+H]^+$: 422.10008; found: 422.09978.

O-Vinyl Oxime S57



A solution of ketone **S27** (149 mg, 481 µmol, 1 equiv), hydroxylamine hydrochloride (50.2 mg, 722 µmol, 1.50 equiv) and sodium acetate trihydrate (131 mg, 963 µmol, 2.00 equiv) in a mixture of ethanol (3 mL) and water (1 mL) was heated to 80 °C. After 16 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield oxime **S56** (116 mg, 74%) as an inseparable mixture of double bond isomers as an off-white solid.

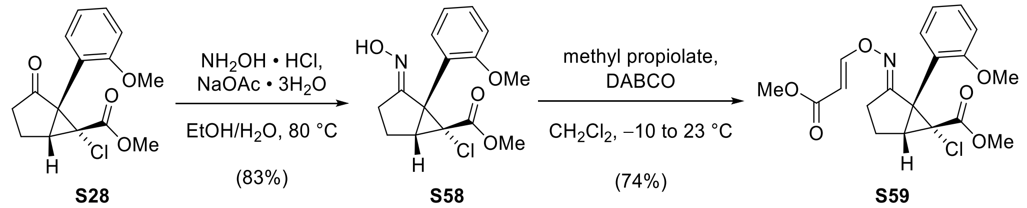
TLC (33% ethyl acetate in hexanes): $R_f = 0.28$ (UV, $KMnO_4$).

In a flame dried flask, a solution of oxime **S56** (116 mg, 357 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (4.01 mg, 35.7 µmol, 0.100 equiv) in dichloromethane (1.5 mL) was cooled to −10 °C. A solution of methyl propiolate (31.8 µL, 357 µmol, 1 equiv) in dichloromethane (1.5 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, the solvent was evaporated. The residue was purified by flash column chromatography (dichloromethane) on silica gel yielded **S57** (138 mg, 95%) as a colorless oil.

TLC (dichloromethane): $R_f = 0.38$ (UV, $KMnO_4$).

HRMS (ESI) calcd for $C_{18}H_{18}O_7N_2Cl$ $[M+H]^+$: 409.07968; found: 409.07951.

***O*-Vinyl Oxime S59**



A solution of ketone **S28** (200 mg, 679 µmol, 1 equiv), hydroxylamine hydrochloride (70.7 mg, 1.02 mmol, 1.50 equiv) and sodium acetate trihydrate (185 mg, 1.36 mmol, 2.00 equiv) in a mixture of ethanol (3 mL) and water (1 mL) was heated to 80 °C. After 14 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield oxime **S58** (175 mg, 83%) as an inseparable mixture of double bond isomers as an off-white solid.

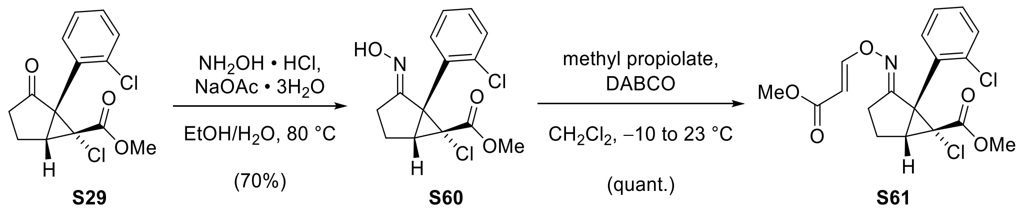
TLC (20% ethyl acetate in hexanes): $R_f = 0.16$ (UV, $KMnO_4$).

In a flame dried flask, a solution of oxime **S58** (158 mg, 510 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (5.72 mg, 51.0 µmol, 0.100 equiv) in dichloromethane (1.5 mL) was cooled to −10 °C. A solution of methyl propiolate (45.4 µL, 510 µmol, 1 equiv) in dichloromethane (1.5 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 1.5 h, the solvent was evaporated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) on silica gel yielded **S59** (149 mg, 74%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.24$ (UV, $KMnO_4$).

HRMS (ESI) calcd for $C_{19}H_{21}O_6NCl$ $[M+H]^+$: 394.10518; found: 394.10535.

O-Vinyl Oxime S61



A solution of ketone **S29** (200 mg, 669 µmol, 1 equiv), hydroxylamine hydrochloride (69.7 mg, 1.00 mmol, 1.50 equiv) and sodium acetate trihydrate (182 mg, 1.34 mmol, 2.00 equiv) in a mixture of ethanol (3 mL) and water (1 mL) was heated to 80 °C. After 14 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield oxime **S60** (147 mg, 70%) as an inseparable mixture of double bond isomers as an off-white solid.

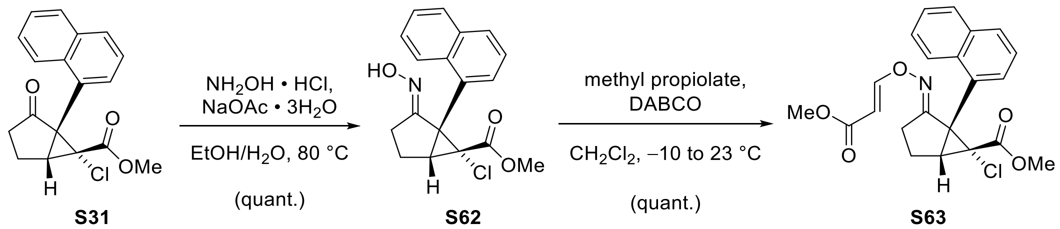
TLC (33% ethyl acetate in hexanes): $R_f = 0.20$ ($KMnO_4$).

In a flame dried flask, a solution of oxime **S60** (147 mg, 468 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (5.25 mg, 46.8 µmol, 0.100 equiv) in dichloromethane (1.5 mL) was cooled to −10 °C. A solution of methyl propiolate (41.6 µL, 468 µmol, 1 equiv) in dichloromethane (1.5 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 14 h, the solvent was evaporated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) on silica gel yielded **S61** (186 mg, quant.) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.35$ (UV, $KMnO_4$).

HRMS (ESI) calcd for $C_{18}H_{18}O_5NCl_2$ $[M+H]^+$: 398.05568; found: 355.05564.

O-Vinyl Oxime S63



A solution of ketone **S31** (220 mg, 699 µmol, 1 equiv), hydroxylamine hydrochloride (72.9 mg, 1.05 mmol, 1.50 equiv) and sodium acetate trihydrate (190 mg, 1.40 mmol, 2.00 equiv) in a mixture of ethanol (3 mL) and water (1 mL) was heated to 80 °C. After 48 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield oxime **S62** (229 mg, quant.) as an inseparable mixture of double bond isomers as an off-white solid.

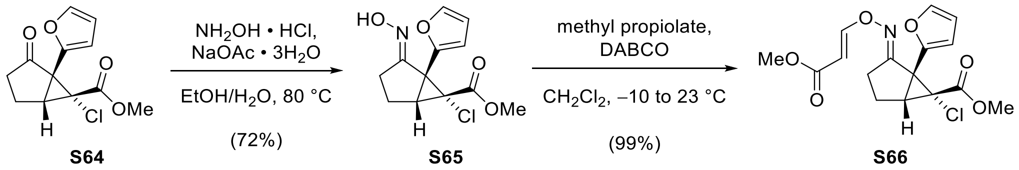
TLC (33% ethyl acetate in hexanes): $R_f = 0.22$ (UV, $KMnO_4$).

In a flame dried flask, a solution of oxime **S62** (203 mg, 616 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (6.90 mg, 61.6 µmol, 0.100 equiv) in dichloromethane (1.5 mL) was cooled to −10 °C. A solution of methyl propiolate (54.8 µL, 616 µmol, 1 equiv) in dichloromethane (1.5 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 14 h, the solvent was evaporated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) on silica gel yielded **S63** (254 mg, quant.) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.25$ (UV, $KMnO_4$).

HRMS (ESI) calcd for $C_{22}H_{21}O_5NCl$ $[M+H]^+$: 414.11028; found: 414.11000.

O-Vinyl Oxime S66



A solution of ketone **S64**[97] (103 mg, 404 µmol, 1 equiv), hydroxylamine hydrochloride (42.2 mg, 607 µmol, 1.50 equiv) and sodium acetate trihydrate (110 mg, 809 µmol, 2.00 equiv) in a mixture of ethanol (3 mL) and water (1 mL) was heated to 80 °C. After 6 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield oxime **S65** (78.0 mg, 72%) as an inseparable mixture of double bond isomers as an off-white solid.

TLC (33% ethyl acetate in hexanes): $R_f = 0.53$ (UV, KMnO$_4$).

In a flame dried flask, a solution of oxime **S65** (68.0 mg, 252 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (2.83 mg, 25.2 µmol, 0.100 equiv) in dichloromethane (1 mL) was cooled to −10 °C. A solution of methyl propiolate (22.4 µL, 252 µmol, 1 equiv) in dichloromethane (0.5 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 30 min, the solvent was evaporated. The residue was purified by flash column chromatography (33% ethyl acetate in hexanes) on silica gel yielded **S66** (89.0 mg, 99%) as colorless oil.

TLC (33% ethyl acetate in hexanes): $R_f = 0.55$ (UV, KMnO$_4$).

HRMS (ESI) calcd for $C_{16}H_{17}ClO_6N$ $[M+H]^+$: 354.0739; found: 354.0749.

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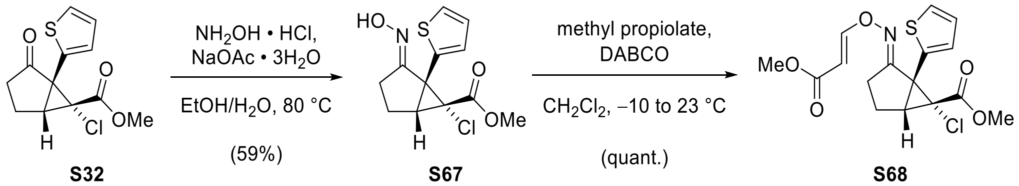
[97] For the synthesis of bicyclo[3.1.0]hexan-2-one **S64** see: J. Feierfeil, A. Grossmann, T. Magauer, *Angew. Chem, Int. Ed.* **2015**, *54*, 11835–11838.

O-Vinyl Oxime S68



S32 **S67** **S68**

A solution of ketone **S32** (51.0 mg, 188 µmol, 1 equiv), hydroxylamine hydrochloride (19.6 mg, 283 µmol, 1.50 equiv) and sodium acetate trihydrate (51.3 mg, 377 µmol, 2.00 equiv) in a mixture of ethanol (1.5 mL) and water (0.5 mL) was heated to 80 °C. After 6 h, the reaction mixture was allowed to cool to 23 °C and saturated aqueous sodium hydrogen carbonate solution (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield oxime **S67** (32.0 mg, 59%) as an inseparable mixture of double bond isomers as an off-white solid.

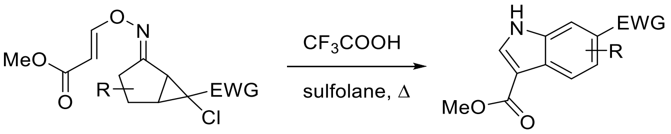
TLC (20% ethyl acetate in hexanes): $R_f = 0.44$ (UV, $KMnO_4$).

In a flame dried flask, a solution of oxime **S67** (32.0 mg, 112 µmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (1.26 mg, 11.2 µmol, 0.100 equiv) in dichloromethane (1 mL) was cooled to −10 °C. A solution of methyl propiolate (10.0 µL, 112 µmol, 1 equiv) in dichloromethane (0.5 mL) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 14 h, the solvent was evaporated. The residue was purified by flash column chromatography (12.5% ethyl acetate in hexanes) on silica gel yielded **S68** (41.3 mg, quant.) as a colorless oil.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.24$ (UV, $KMnO_4$).

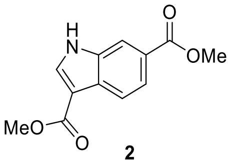
HRMS (ESI) calcd for $C_{16}H_{17}O_5NClS$ $[M+H]^+$: 370.05108; found: 370.05103.

Syntheses of Indoles



General Procedure: A solution of *O*-vinyl oxime (1 equiv) and trifluoroacetic acid (1 equiv) in sulfolane (0.2–0.5 M) was stirred for the time and the temperature indicated. After complete consumption of the starting material (as seen by TLC analysis), the reaction mixture was allowed to cool to 23 °C. Water (2 mL) and diethyl ether (2 mL) were added to the reaction mixture, the layers were separated and the aqueous layer was extracted with diethyl ether (5 × 15 mL). The combined organic extracts were washed sequentially with water (4 × 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel.

Dimethyl 1*H*-indole-3,6-dicarboxylate (2)



2

Following the general procedure, a solution of *O*-vinyl oxime **1** (18.4 mg, 64.0 µmol, 1 equiv) and trifluoroacetic acid (7.29 mg, 64.0 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 90 min. Flash column chromatography (33% ethyl acetate in hexanes) on silica gel yielded **2** (9.70 mg, 65%) as an off-white solid.

TLC (33% ethyl acetate in hexanes): $R_f = 0.21$ (UV, $KMnO_4$).

m.p. 184 °C.

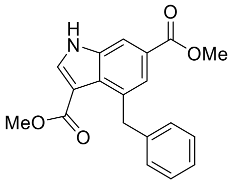
^{1}H NMR (599 MHz, $CDCl_3$) δ = 8.83 (br. s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.19–8.17 (m, 1H), 8.06 (d, *J* = 3.0 Hz, 1H), 7.98–7.93 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.8, 165.2, 135.6, 133.7, 129.5, 125.3, 123.2, 121.4, 113.9, 109.5, 52.3, 51.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3298 (*m*), 2951 (*w*), 2359 (*w*), 1699 (*vs*), 1438 (*s*), 1314 (*s*), 1217 (*vs*), 1084 (*m*), 1050 (*m*), 781 (*m*) cm^{-1}.

HRMS (ESI) calcd for $C_{12}H_{10}O_4N$ $[M-H]^-$: 232.06152; found: 232.06182.

Dimethyl 4-benzyl-1*H*-indole-3,6-dicarboxylate (3)



3

Following the general procedure, a solution of *O*-vinyl oxime **S38** (27.0 mg, 71.5 µmol, 1 equiv) and trifluoroacetic acid (8.15 mg, 71.5 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 2 h. Flash column chromatography (20% ethyl acetate in hexanes) on silica gel yielded **3** (12.6 mg, 55%) as a yellow solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.10$ (UV, $KMnO_4$).

m.p. 190 °C.

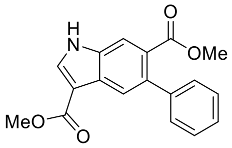
^{1}H NMR (800 MHz, CD_2Cl_2) δ = 9.00 (br. s, 1H), 8.07 (d, *J* = 3.1 Hz, 1H), 8.04 (d, *J* = 1.2 Hz, 1H), 7.68 (s, 1H), 7.25–7.10 (m, 5H), 4.80 (s, 2H), 3.88 (s, 3H), 3.79 (s, 3H).

^{13}C NMR (201 MHz, CD_2Cl_2) δ = 167.8, 165.1, 142.7, 137.3, 135.7, 135.5, 129.3, 128.7, 128.3, 126.2, 125.9, 125.3, 112.6, 110.4, 52.5, 51.8, 40.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3326 (*m*), 2949 (*m*), 1707 (*vs*), 1692 (*vs*), 1353 (*s*), 1241 (*vs*), 1207 (*s*), 1166 (*s*), 1048 (*s*), 770 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{19}H_{17}NO_4$ $[M]^+$: 323.1152; found: 323.1154.

Dimethyl 5-phenyl-1*H*-indole-3,6-dicarboxylate (4)



4

Following the general procedure, a solution of cyclopropane **S41** (23.2 mg, 63.8 µmol, 1 equiv) and trifluoroacetic acid (7.27 mg, 63.8 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 1 h. Flash column chromatography (33% ethyl acetate in hexanes) on silica gel yielded **4** (11.0 mg, 56%) as an off-white solid.

TLC (33% ethyl acetate in hexanes): $R_f = 0.27$ (UV, $KMnO_4$).

m.p. 179 °C.

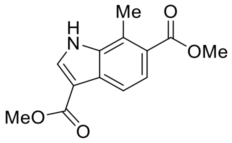
^{1}H NMR (599 MHz, $CDCl_3$) δ = 8.95 (br. s, 1H), 8.15 (s, 1H), 8.05 (d, *J* = 3.0 Hz, 1H), 7.99 (d, *J* = 0.5 Hz, 1H), 7.43–7.32 (m, 5H), 3.91 (s, 3H), 3.63 (s, 3H).

^{13}C NMR (151 MHz, CDCl$_3$) δ = 169.6, 165.2, 142.6, 137.1, 134.7, 134.0, 128.9, 128.1, 128.0, 126.8, 126.1, 123.7, 114.1, 109.5, 52.1, 51.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3306 (*w*), 2950 (*w*), 1704 (*vs*), 1458 (*s*), 1440 (*s*), 1353 (*s*), 1253 (*s*), 1212 (*vs*), 1086 (*s*), 1051 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{15}NO_4$ [M]$^+$: 309.0996; found: 309.0997.

Dimethyl 7-methyl-1*H*-indole-3,6-dicarboxylate (5)



5

Following the general procedure, a solution of *O*-vinyl oxime **S44** (30.0 mg, 99.4 µmol, 1 equiv) and trifluoroacetic acid (11.3 mg, 99.4 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 30 min. Flash column chromatography (33% ethyl acetate in hexanes) on silica gel yielded **5** (12.4 mg, 50%) as an off-white solid.

TLC (33% ethyl acetate in hexanes): R$_f$ = 0.26 (UV, KMnO$_4$).

m.p. 204 °C.

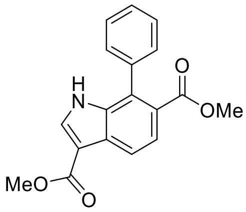
^{1}H NMR (400 MHz, CDCl$_3$) δ = 8.66 (br. s, 1H), 8.06–8.02 (m, 2H), 7.87 (d, *J* = 8.5 Hz, 1H), 3.93 (s, 3H), 3.93 (s, 3H), 2.79 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ = 168.6, 165.3, 136.3, 132.9, 128.3, 124.6, 124.4, 123.9, 118.8, 109.9, 52.0, 51.4, 14.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3339 (*w*), 2358 (*w*), 1692 (vs), 1437 (*w*), 1238 (*s*), 1132 (*m*), 786 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{13}NO_4$ [M]$^+$: 247.0839; found: 247.0833.

Dimethyl 7-phenyl-1*H*-indole-3,6-dicarboxylate (6)



6

Following the general procedure, a solution of *O*-vinyl oxime **S47** (20.0 mg, 55.0 µmol, 1 equiv) and trifluoroacetic acid (6.27 mg, 55.0 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 45 min. Flash column chromatography (33% ethyl acetate in hexanes) on silica gel yielded **6** (13.0 mg, 76%) as a brown solid.

TLC (33% ethyl acetate in hexanes): $R_f = 0.19$ (UV, $KMnO_4$).

m.p. 154 °C.

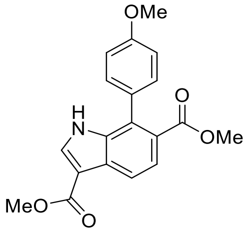
^{1}H NMR (800 MHz, CD_2Cl_2) δ = 8.59 (br. s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.96–7.95 (m, 1H), 7.86 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.47–7.44 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 3.90 (s, 3H), 3.64 (s, 3H).

^{13}C NMR (201 MHz, CD_2Cl_2) δ = 168.6, 165.4, 137.3, 135.9, 133.9, 129.4, 129.2, 128.8, 128.7, 128.4, 124.7, 124.3, 120.6, 109.7, 52.1, 51.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3310 (*w*), 2950 (*w*), 1704 (*vs*), 1531 (*m*), 1440 (*s*), 1312 (*s*), 1239 (*s*), 1133 (*vs*), 1048 (*m*), 702 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{15}NO_4$ $[M]^+$: 309.0996; found: 309.0996.

Dimethyl 7-(4-methoxyphenyl)-1*H*-indole-3,6-dicarboxylate (7a)



7a

Following the general procedure, a solution of *O*-vinyl oxime **S49** (28.0 mg, 71.1 µmol, 1 equiv) and trifluoroacetic acid (8.11 mg, 71.1 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 90 min. Flash column chromatography (25% ethyl acetate in hexanes) on silica gel yielded **7a** (20.0 mg, 83%) as a colorless solid.

TLC (25% ethyl acetate in hexanes): $R_f = 0.17$ (UV, $KMnO_4$).

m.p. 172 °C.

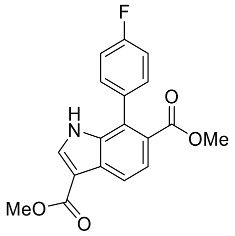
^{1}H NMR (800 MHz, CD_2Cl_2) 8.59 (br. s, 1H), 8.15 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.95 (d, *J* = 3.0 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.30–7.28 (m, 2H), 7.04–7.02 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.66 (s, 3H).

^{13}C NMR (201 MHz, CD_2Cl_2) δ = 168.8, 165.4, 160.0, 136.2, 133.7, 130.6, 129.2, 128.7, 128.4, 124.9, 124.3, 120.4, 114.6, 109.8, 55.9, 52.2, 51.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3307 (*w*), 2950 (*w*), 1703 (*vs*), 1611 (*m*), 1440 (*s*), 1315 (*s*), 1240 (*vs*), 1175 (*s*), 1134 (*vs*), 1047 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{19}H_{17}NO_5$ $[M]^+$: 339.1101; found: 339.1100.

Dimethyl 7-(4-fluorophenyl)-1*H*-indole-3,6-dicarboxylate (7b)



7b

Following the general procedure, a solution of *O*-vinyl oxime **S51** (37.5 mg, 98.2 µmol, 1 equiv) and trifluoroacetic acid (11.2 mg, 98.2 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 60 min. Flash column chromatography (12.5% ethyl acetate in hexanes) on silica gel yielded **7b** (20.1 mg, 63%) as an off-white solid.

TLC (12.5% ethyl acetate in hexanes): R_f = 0.13 (UV, $KMnO_4$).

m.p. 193 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 8.57 (br. s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 3.1 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.38–7.32 (m, 2H), 7.23–7.16 (m, 2H), 3.90 (s, 3H), 3.65 (s, 3H).

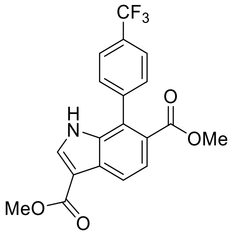
^{13}C NMR (101 MHz, CD_2Cl_2) δ = 168.4, 165.4, 163.1 (d, *J* = 246.4 Hz), 136.0, 134.0, 133.2 (d, *J* = 3.5 Hz), 131.3 (d, *J* = 8.1 Hz), 128.9, 127.6, 124.8, 124.4, 120.9, 116.1 (d, *J* = 21.5 Hz), 109.8, 52.2, 51.6.

^{19}F NMR (377 MHz, CD_2Cl_2) δ = −114.92.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3304 (*w*), 2951 (*w*), 1694 (*vs*), 1516 (*m*), 1441 (*s*), 1313 (*s*), 1238 (*vs*), 1192 (*s*), 1134 (*vs*), 1045 (*s*) cm^{-1}.

HRMS (ESI) calcd for $C_{18}H_{14}FNO_4$ $[M+H]^+$: 328.09798; found: 328.09786.

Dimethyl 7-(4-trifluoromethylphenyl)-1*H*-indole-3,6-dicarboxylate (7c)



7c

Following the general procedure, a solution of *O*-vinyl oxime **S53** (22.4 mg, 51.9 µmol, 1 equiv) and trifluoroacetic acid (5.91 mg, 51.9 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 2.5 h. Flash column chromatography (dichloromethane) on silica gel yielded **7c** (13.4 mg, 69%) as a yellow solid.

TLC (dichloromethane): $R_f = 0.54$ (UV, $KMnO_4$).

m.p. 196 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (br. s, 1H), 8.25 (d, *J* = 8.8 Hz, 1H), 8.00–7.95 (m, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 3.95 (s, 3H), 3.69 (s, 3H).

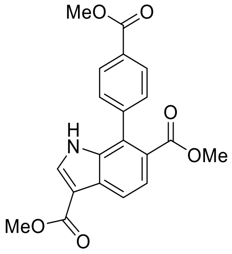
^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.8, 165.1, 140.9, 135.3, 133.6, 130.3 (q, *J* = 32.6 Hz), 129.5, 128.8, 127.0, 125.8 (q, *J* = 3.7 Hz), 124.2 (d, *J* = 272.2 Hz), 124.4, 123.7, 121.2, 109.8, 52.1, 51.5.

^{19}F NMR (377 MHz, $CDCl_3$) δ = −62.54.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3308 (*w*), 2952 (*w*), 1706 (*s*), 1444 (*m*), 1323 (*vs*), 1242 (*m*), 1166 (*m*), 1129 (*s*), 1068 (*m*), 733 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{19}H_{14}F_3NO_4$ $[M]^+$: 377.0869; found: 377.0869.

Dimethyl 7-(4-(methoxycarbonyl)phenyl)-1H-indole-3,6-dicarboxylate (7d)



7d

Following the general procedure, a solution of *O*-vinyl oxime **S55** (28.7 mg, 68.0 µmol, 1 equiv) and trifluoroacetic acid (7.76 mg, 68.0 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 1 h. Flash column chromatography (33% ethyl acetate in hexanes) on silica gel yielded **7d** (15.4 mg, 62%) as a yellow solid.

TLC (33% ethyl acetate in hexanes): R_f = 0.41 (UV, $KMnO_4$).

m.p. 170 °C.

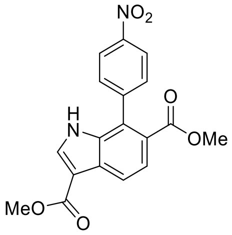
^{1}H NMR (599 MHz, $CDCl_3$) δ = 8.76 (br s, 1H), 8.26–8.21 (m, 1H), 8.12–8.10 (m, 2H), 7.99–7.96 (m, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.46–7.41 (m, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.65 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.9, 166.9, 165.2, 142.1, 135.2, 133.8, 130.1, 129.6, 129.1, 128.8, 127.4, 124.2, 123.6, 121.1, 109.5, 52.4, 52.0, 51.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3298 (*w*), 2951 (*w*), 1705 (*vs*), 1610 (*m*), 1436 (*s*), 1310 (*s*), 1276 (*s*), 1240 (*s*), 1134 (*vs*), 731 (*m*) cm^{-1}.

HRMS (ESI) calcd for $C_{20}H_{16}NO_6$ $[M-H]^-$: 366.09832; found: 366.09836.

Dimethyl 7-(4-nitrophenyl)-1H-indole-3,6-dicarboxylate (7e)



7e

Following the general procedure, a solution of *O*-vinyl oxime **S57** (27.0 mg, 66.0 µmol, 1 equiv) and trifluoroacetic acid (7.53 mg, 66.0 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 2 h. Flash column chromatography (25% ethyl acetate in hexanes) on silica gel yielded **7e** (15.8 mg, 68%) as an off-white solid.

TLC (25% ethyl acetate in hexanes): R_f = 0.29 (UV, $KMnO_4$).

m.p. 210 °C.

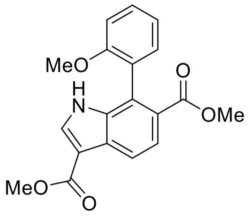
^{1}H NMR (599 MHz, CD_2Cl_2) δ = 8.57 (br. s, 1H), 8.36–8.30 (m, 2H), 8.25 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 3.1 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.58–7.54 (m, 2H), 3.91 (s, 3H), 3.65 (s, 3H).

^{13}C NMR (151 MHz, CD_2Cl_2) δ = 167.9, 165.2, 148.1, 144.8, 135.4, 134.4, 130.7, 129. 4, 126.6, 124.6, 124.3, 124.1, 121.7, 110.0, 52.3, 51.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3210 (*m*), 2948 (*w*), 1708 (*vs*), 1674 (*vs*), 1516 (*vs*), 1452 (*s*), 1342 (*vs*), 1248 (*vs*), 1199 (*s*), 730 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{14}N_2O_6$ $[M]^+$: 354.08462; found: 354.0846.

Dimethyl 7-(2-methoxyphenyl)-1*H*-indole-3,6-dicarboxylate (8a)



8a

Following the general procedure, a solution of *O*-vinyl oxime **S59** (27.0 mg, 68.6 µmol, 1 equiv) and trifluoroacetic acid (7.82 mg, 68.6 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 45 min. Flash column chromatography (33% ethyl acetate in hexanes) on silica gel yielded **8a** (22.5 mg, 97%) as a brown solid.

TLC (33% ethyl acetate in hexanes): $R_f = 0.27$ (UV, $KMnO_4$).

m.p. 170 °C.

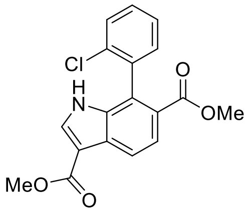
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 8.61 (br. s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 3.1 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.46–7.38 (m, 1H), 7.24 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.12–6.96 (m, 2H), 3.90 (s, 3H), 3.69 (s, 3H), 3.64 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 168.5, 165.4, 157.3, 135.9, 133.7, 130.6, 130.1, 128.9, 125.9, 125.6, 124.9, 124.1, 121.3, 120.5, 111.8, 109.6, 56.1, 52.1, 51.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3296 (*w*), 2949 (*w*), 2838 (*w*), 1704 (*vs*), 1439 (*s*), 1316 (*s*), 1243 (*vs*), 1190 (*s*), 1132 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{19}H_{17}O_5N$ $[M]^+$: 339.1101; found: 339.1097.

Dimethyl 7-(2-chlorophenyl)-1*H*-indole-3,6-dicarboxylate (8b)



8b

Following the general procedure, a solution of *O*-vinyl oxime **S61** (38.0 mg, 95.4 µmol, 1 equiv) and trifluoroacetic acid (10.9 mg, 95.4 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 90 min. Flash column chromatography (33% ethyl acetate in hexanes) on silica gel yielded **8b** (24.2 mg, 74%) as an off-white solid.

TLC (33% ethyl acetate in hexanes): $R_f = 0.35$ (UV, $KMnO_4$).

m.p. 159 °C.

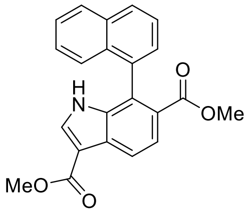
^{1}H NMR (800 MHz, CD_2Cl_2) δ = 8.49 (br. s, 1H), 8.24–8.22 (m, 1H), 7.98–7.96 (m, 2H), 7.56–7.55 (m, 1H), 7.44–7.39 (m, 2H), 7.33–7.31 (m, 1H), 3.91 (s, 3H), 3.66 (s, 3H).

^{13}C NMR (201 MHz, CD_2Cl_2) δ = 167.7, 165.3, 136.3, 135.7, 134.1, 134.0, 131.2, 130.2, 130.0, 129.3, 127.6, 126.0, 124.6, 124.3, 121.3, 109.9, 52.3, 51.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3290 (*w*), 2951 (*w*), 1705 (*vs*), 1436 (*s*), 1315 (*s*), 1246 (*vs*), 1192 (*m*), 1138 (*vs*), 1067 (*s*), 750 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{18}H_{14}ClNO_4$ $[M]^+$: 343.0606; found: 343.0600.

Dimethyl 7-(naphthalen-1-yl)-1*H*-indole-3,6-dicarboxylate (9)



9

Following the general procedure, a solution of *O*-vinyl oxime **S63** (32.0 mg, 77.3 µmol, 1 equiv) and trifluoroacetic acid (8.82 mg, 77.3 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 60 min. Flash column chromatography (25% ethyl acetate in hexanes) on silica gel yielded **9** (20.1 mg, 72%) as an orange solid.

TLC (25% ethyl acetate in hexanes): $R_f = 0.38$ (UV, $KMnO_4$).

m.p. 184 °C.

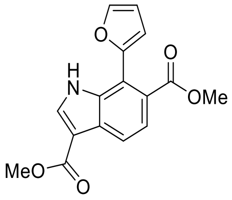
^{1}**H NMR** (400 MHz, CD_2Cl_2) δ = 8.33 (br. s, 1H), 8.27 (dd, *J* = 8.5, 0.6 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.96 (dd, *J* = 8.2, 4.2 Hz, 2H), 7.84 (d, *J* = 3.1 Hz, 1H), 7.59 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.51–7.47 (m, 1H), 7.42 (dd, *J* = 7.0, 1.2 Hz, 1H), 7.34–7.29 (m, 2H), 3.90 (s, 3H), 3.46 (s, 3H).

^{13}**C NMR** (101 MHz, CD_2Cl_2) δ = 167.9, 165.4, 136.6, 135.0, 134.2, 134.0, 132.5, 129.1, 128.9, 128.8, 127.2, 127.1, 126.9, 126.6, 126.1, 125.8, 125.5, 124.5, 121.0, 109.7, 52.1, 51.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3301 (*w*), 2949 (*w*), 2362 (*w*), 1704 (*vs*), 1531 (*m*), 1437 (*s*), 1315 (*s*), 1240 (*s*), 1139 (*s*) cm^{-1}.

HRMS (ESI) calcd for $C_{22}H_{18}NO_4$ [M+H]$^+$: 360.12308; found: 360.12309.

Dimethyl 7-(furan-2-yl)-1*H*-indole-3,6-dicarboxylate (10a)



10a

Following the general procedure, a solution of *O*-vinyl oxime **S66** (20.0 mg, 56.5 µmol, 1 equiv) and trifluoroacetic acid (6.45 mg, 56.5 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 1 h. Flash column chromatography (33% ethyl acetate in hexanes) on silica gel yielded **10a** (12.7 mg, 75%) as a yellow solid.

TLC (33% ethyl acetate in hexanes): R_f = 0.22 (UV, $KMnO_4$).

m.p. 139 °C.

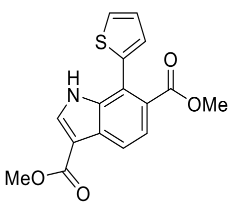
^{1}**H NMR** (599 MHz, CD_2Cl_2) δ = 9.45 (br. s, 1H), 8.18 (dd, *J* = 8.3, 0.7 Hz, 1H), 8.04 (d, *J* = 3.4 Hz, 1H), 7.66 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 6.68 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.63–6.61 (m, 1H), 3.90 (s, 3H), 3.83 (s, 3H).

^{13}**C NMR** (151 MHz, CD_2Cl_2) δ = 169.7, 165.3, 149.8, 143.4, 134.2, 133.7, 129.0, 125.3, 123.6, 121.6, 115.6, 112.3, 110.8, 109.6, 52.8, 51.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3339 (*w*), 2994 (*w*), 2950 (*w*), 1699 (*vs*), 1438 (*s*), 1312 (*s*), 1239 (*vs*), 1157 (*s*), 1130 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{13}NO_5$ [M]$^+$: 299.0788; found: 299.0790.

Dimethyl 7-(thiophen-2-yl)-1*H*-indole-3,6-dicarboxylate (10b)



10b Following the general procedure, a solution of *O*-vinyl oxime **S68** (22.1 mg, 59.4 µmol, 1 equiv) and trifluoroacetic acid (6.78 mg, 59.4 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 2 h. Flash column chromatography (33% ethyl acetate in hexanes) on silica gel yielded **10b** (12.8 mg, 68%) as an orange solid.

TLC (33% ethyl acetate in hexanes): $R_f = 0.39$ (UV, $KMnO_4$).

m.p. 157 °C.

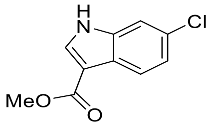
^{1}H NMR (800 MHz, CD_2Cl_2) δ = 8.84 (br. s, 1H), 8.21–8.19 (m, 1H), 7.98 (d, *J* = 3.4 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.52 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.19 (dd, *J* = 5.2, 3.4 Hz, 1H), 7.13 (dd, *J* = 3.4, 1.2 Hz, 1H), 3.90 (s, 3H), 3.71 (s, 3H).

^{13}C NMR (201 MHz, CD_2Cl_2) δ = 168.5, 165.3, 137.1, 136.5, 133.9, 128.7, 128.0, 128.0, 127.4, 126.5, 124.1, 121.6, 120.5, 109.9, 52.4, 51.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3306 (*w*), 2950 (*w*), 1703 (*vs*), 1528 (*m*), 1440 (*s*), 1312 (*s*), 1241 (*s*), 1193 (*m*), 1131 (*vs*) cm^{-1}.

HRMS (ESI) calcd for $C_{16}H_{14}O_4NS$ $[M+H]^+$: 316.06378; found: 316.06371.

Methyl 6-chloro-1*H*-indole-3-carboxylate (11)



11 Following the general procedure, a solution of *O*-vinyl oxime **S36** (25.4 mg, 96.2 µmol, 1 equiv) and trifluoroacetic acid (11.0 mg, 96.2 µmol, 1 equiv) in sulfolane (600 µL) was heated at 100 °C for 90 min. Flash column chromatography (20% ethyl acetate in hexanes) on silica gel yielded **11** (13.5 mg, 67%) as a yellow solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.19$ (UV, $KMnO_4$).

m.p. 198 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.61 (br. s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 2.9 Hz, 1H), 7.48–7.38 (m, 1H), 7.24 (dd, *J* = 8.6, 1.8 Hz, 1H), 3.92 (s, 3H).

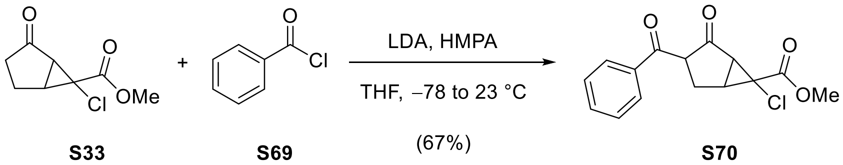
^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.3, 136.5, 131.5, 129.4, 124.5, 123.0, 122.7, 111.6, 109.3, 51.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3227 (*m*), 2358 (*w*), 1674 (*vs*), 1525 (*m*), 1443 (*s*), 1196 (*s*), 1130 (*m*), 1055 (*m*), 803 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{10}H_8ClNO_2$ $[M]^+$: 209.0238; found: 209.0237.

Syntheses of 1,3-Diketones

Methyl 3-benzoyl-6-chloro-2-oxobicyclo[3.1.0]hexanes-6-carboxylate (S70)



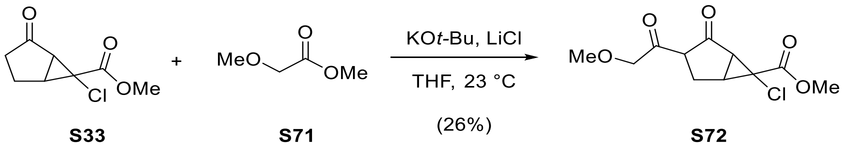
In a flame dried flask, diisopropylamine (180 µL, 1.27 mmol, 1.20 equiv) was dissolved in tetrahydrofuran (1.5 mL) and cooled to −78 °C. A solution of *n*-butyllithium (2.22 M in hexanes, 549 µL, 1.22 mmol, 1.15 equiv) was added dropwise. After 10 min, the reaction mixture was warmed to 0 °C. After 10 min, the reaction mixture was cooled to −78 °C and a solution of ketone **S33** (200 mg, 1.06 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 45 min, benzoyl chloride **S69** (148 µL, 1.27 mmol, 1.20 equiv) and hexamethylphosphoric triamide (184 µL, 1.06 mmol, 1 equiv) were added dropwise. After 4 h, the reaction mixture was allowed to warm to 23 °C. After 14 h, water (2 mL) and ethyl acetate (10 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organic layers were washed with aqueous hydrochloric acid (2 M, 10 mL) and saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **S70** (208 mg, 67%) as a yellow oil.

*Note: Since the reaction yielded an inseparable mixture of keto-enol tautomers, purified 1,3-diketone **S70** was directly used in the indazole formation without further characterization except for infrared spectroscopy and high-resolution mass spectrometry.*

TLC (25% ethyl acetate in hexanes): R_f = 0.26 (UV, $KMnO_4$).
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (*w*), 1746 (*m*), 1728 (*m*), 1626 (*s*), 1595 (*s*), 1436 (*s*), 1370 (*s*), 1250 (*vs*), 1188 (*s*), 1071 (*s*) cm^{-1}.

HRMS (ESI) calcd for $C_{15}H_{12}ClO_4$ $[M-H]^-$: 291.04292; found: 291.04292.

Methyl 6-chloro-3-(2-methoxyacetyl)-2-oxobicyclo[3.1.0]hexanes-6-carboxylate (S72)



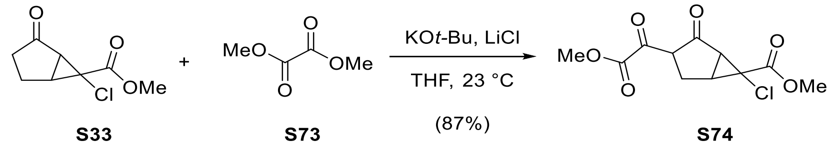
In a flame dried flask, a suspension of anhydrous lithium chloride (112 mg, 2.65 mmol, 2.50 equiv) and potassium *tert*-butoxide (sublimed grade, 178 mg, 1.59 mmol, 1.50 equiv) in tetrahydrofuran (1.5 mL) was heated to 70 °C. After 3 h, the suspension was allowed to cool to 23 °C and a solution of **S33** (200 mg, 1.06 mmol, 1 equiv) and methyl ester **S71** (144 mg, 1.38 mmol, 1.30 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 14 h, aqueous hydrochloric acid (2 M, 2 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (4 × 20 mL). The combined organic layers were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (1% methanol in dichloromethane) to yield **S72** (72 mg, 26%) as a yellow oil.

Note: Since the reaction yielded an inseparable mixture of keto-enol tautomers, purified 1,3-diketone ***S72*** *was directly used in the indazole formation without further characterization except for infrared spectroscopy and high-resolution mass spectrometry.*

TLC (1% methanol in dichloromethane): $R_f = 0.10$ (UV, $KMnO_4$).
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3340 (*w*), 2954 (*w*), 1727 (*vs*), 1663 (*s*), 1627 (*s*), 1438 (*s*), 1278 (*vs*), 1250 (*vs*), 1108 (*s*) cm^{-1}.

HRMS (ESI) calcd for $C_{11}H_{14}ClO_5$ $[M+H]^+$: 261.05248; found: 261.05249.

Methyl 6-chloro-3-(2-methoxy-2-oxoacetyl)-2-oxobicyclo[3.1.0]hexanes-6-carboxylate (S74)



In a flame dried flask, a suspension of anhydrous lithium chloride (281 mg, 6.63 mmol, 2.50 equiv) and potassium *tert*-butoxide (sublimed grade, 446 mg, 3.98 mmol, 1.50 equiv) in tetrahydrofuran (4 mL) was heated to 70 °C. After 3 h, the suspension was allowed to cool to 23 °C and a solution of ketone **S33** (500 mg, 2.65 mmol, 1 equiv) and dimethyl oxalate **S73** (407 mg, 3.45 mmol, 1.30 equiv) in tetrahydrofuran (4 mL) was added dropwise. After 30 h, aqueous hydrochloric acid (2 M, 2 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (4 × 20 mL). The combined organic layers were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (2% methanol in dichloromethane) to yield **S74** (633 mg, 87%) as an orange oil.

TLC (2% methanol in dichloromethane): $R_f = 0.17$ (UV, $KMnO_4$).

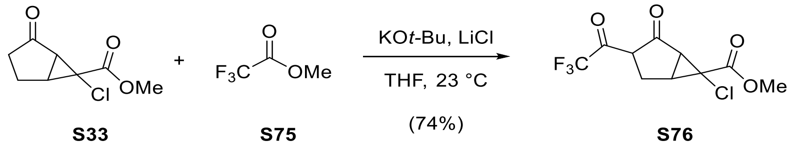
^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.46 (br. s, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.33 (dd, *J* = 18.6, 6.3 Hz, 1H), 3.19 (d, *J* = 18.6 Hz, 1H), 2.97 (d, *J* = 6.3 Hz, 1H), 2.81 (t, *J* = 6.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 203.3, 168.2, 162.9, 152.4, 116.8, 54.2, 53.1, 48.9, 41.6, 32.6, 27.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (*w*), 1731 (*s*), 1673 (*m*), 1437 (*m*), 1244 (*vs*), 1072 (*w*), 878 (*w*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{11}ClO_6$ $[M]^+$: 274.0239; found: 274.0236.

Methyl 6-chloro-2-oxo-3-(2,2,2-trifluoroacetyl)bicyclo[3.1.0]hexanes-6-carboxylate (S76)



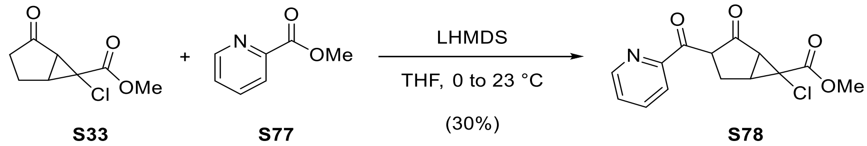
In a flame dried flask, a suspension of anhydrous lithium chloride (112 mg, 2.65 mmol, 2.50 equiv) and potassium *tert*-butoxide (sublimed grade, 178 mg, 1.59 mmol, 1.50 equiv) in tetrahydrofuran (1.5 mL) was heated to 70 °C. After 3 h, the suspension was allowed to cool to 23 °C and a solution of **S33** (200 mg, 1.06 mmol, 1 equiv) and methyl trifluoroacetate **S75** (139 µL, 1.38 mmol, 1.30 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 2 h, aqueous hydrochloric acid (2 M, 2 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (4 × 20 mL). The combined organic layers were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% methanol in dichloromethane) to yield **S76** (224 mg, 74%) as an orange oil.

*Note: Since the reaction yielded an inseparable mixture of keto-enol tautomers, purified 1,3-diketone **S76** was directly used in the indazole formation without further characterization except for infrared spectroscopy and high-resolution mass spectrometry.*

TLC (5% methanol in dichloromethane): $R_f = 0.24$ (UV, $KMnO_4$).
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3480 (*w*), 2954 (*w*), 1729 (*m*), 1639 (*vs*), 1491 (*s*), 1441 (*s*), 1258 (*vs*), 1230 (*vs*), 1137 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{10}H_8ClF_3O_4$ $[M]^+$: 284.0058; found: 284.0058.

Methyl 6-chloro-2-oxo-3-picolinoylbicyclo[3.1.0]hexanes-6-carboxylate (S78)



In a flame dried flask, a solution of ketone **S33** (100 mg, 530 µmol, 1 equiv) in tetrahydrofuran (1.5 mL) was cooled to 0 °C. A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 583 µL, 583 µmol, 1.10 equiv) was added dropwise. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 15 min, a solution of methyl ester **S77** (72.7 mg, 530 µmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added dropwise. After 14 h, saturated aqueous ammonium chloride solution (2 mL), water (2 mL) and ethyl acetate (10 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 x 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield **S78** (46 mg, 30%) as a yellow oil.

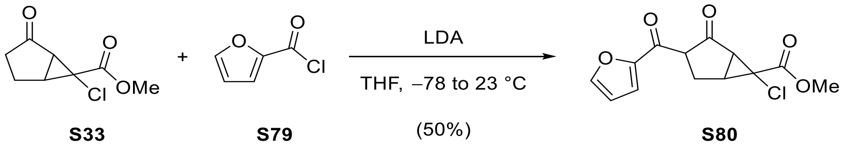
*Note: Since the reaction yielded an inseparable mixture of keto-enol tautomers, purified 1,3-diketone **S78** was directly used in the indazole formation without further characterization except for infrared spectroscopy and high-resolution mass spectrometry.*

TLC (33% ethyl acetate in hexanes): $R_f = 0.10$ (UV, $KMnO_4$).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (*w*), 1748 (*s*), 1726 (*s*), 1610 (*s*), 1578 (*s*), 1566 (*s*), 1434 (*s*), 1262 (*vs*), 1243 (*vs*), 1164 (*s*) cm^{-1}.

HRMS (ESI) calcd for $C_{14}H_{13}ClNO_4$ $[M+H]^+$: 294.05278; found: 294.05285.

Methyl 6-chloro-3-(furan-2-carbonyl)-2-oxobicyclo[3.1.0]hexanes-6-carboxylate (S80)



In a flame dried flask, diisopropylamine (165 µL, 1.17 mmol, 1.10 equiv) was dissolved in tetrahydrofuran (1 mL) and cooled to −78 °C. A solution of *n*-butyllithium (1.6 M in hexanes, 502 µL, 1.17 mmol, 1.05 equiv) was added dropwise. After 10 min, the reaction mixture was warmed to 0 °C. After 10 min, the reaction mixture was cooled to −78 °C and a solution of ketone **S33** (200 mg, 1.06 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added dropwise. After 30 min, 2-furoyl chloride **S79** (115 µL, 1.17 mmol, 1.10 equiv) was added dropwise. After 14 h, water (5 mL) and ethyl acetate (10 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to yield **S80** (150 mg, 50%) as an orange oil.

TLC (25% ethyl acetate in hexanes): $R_f = 0.25$ (UV, $KMnO_4$).

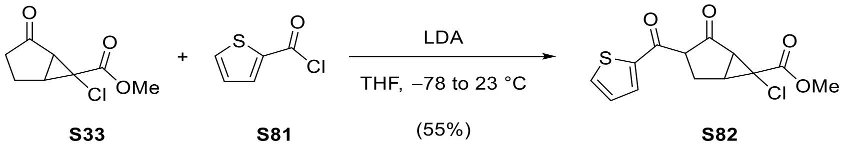
^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.52 (br. s, 1H), 7.72–7.56 (m, 1H), 7.11 (d, *J* = 3.6 Hz, 1H), 6.58 (dd, *J* = 3.6, 1.7 Hz, 1H), 3.82 (s, 3H), 3.29 (dd, *J* = 17.0, 6.7 Hz, 1H), 3.12 (d, *J* = 17.0 Hz, 1H), 2.93 (dd, *J* = 6.7, 1.1 Hz, 1H), 2.76 (t, *J* = 6.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.7, 168.9, 158.7, 148.7, 146.5, 116.5, 112.6, 107.2, 54.0, 48.8, 41.8, 32.3, 27.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*w*), 1746 (*m*), 1727 (*m*), 1612 (*s*), 1404 (*m*), 1361 (*m*), 1257 (*vs*), 1181 (*s*), 1109 (*m*), 751 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{11}O_5Cl$ $[M]^+$: 282.0290; found: 282.0290.

Methyl 6-chloro-2-oxo-3-(thiophene-2-carbonyl)bicyclo[3.1.0]hexanes-6-carboxylate (S82)



In a flame dried flask, a solution of diisopropylamine (165 µL, 1.17 mmol, 1.10 equiv) in tetrahydrofuran (1 mL) was cooled to −78 °C. A solution of *n*-butyllithium (1.6 M in hexanes, 502 µL, 1.11 mmol, 1.05 equiv) was added. After 10 min, the reaction mixture was warmed to 0 °C. After 10 min, the reaction mixture was cooled to −78 °C. A solution of ketone **S33** (200 mg, 1.06 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 30 min, 2-thiophenecarbonyl chloride **S81** (125 µL, 1.17 mmol, 1.10 equiv) was added. After 14 h, saturated aqueous ammonium chloride solution (20 mL) was added. Water (10 mL) and ethyl acetate (30 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to yield **S82** (184 mg, 58%) as a brownish oil.

TLC (25% ethyl acetate in hexanes): $R_f = 0.26$ (UV, $KMnO_4$).

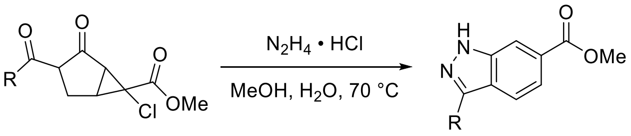
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 14.04 (br. s, 1H), 7.70–7.67 (m, 2H), 7.22 (dd, *J* = 5.0, 3.9 Hz, 1H), 3.80 (s, 3H), 3.24 (dd, *J* = 16.0, 6.6 Hz, 1H), 3.01 (d, *J* = 16.0 Hz, 1H), 2.95 (dd, *J* = 6.6, 1.1 Hz, 1H), 2.80 (t, *J* = 6.6 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 199.1, 168.8, 163.6, 137.5, 132.1, 131.3, 128.5, 107.2, 54.1, 48.9, 41.7, 32.0, 28.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3103 (*w*), 2953 (*w*), 1745 (*m*), 1726 (*s*), 1591 (*s*), 1379 (*s*), 1277 (*s*), 1252 (*vs*), 1218 (*s),* 720 (*s*) cm^{-1}.

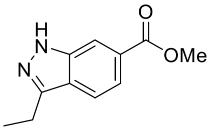
HRMS (EI) calcd for $C_{13}H_{11}O_4ClS$ $[M]^+$: 298.0061; found: 298.0061.

One-Pot Syntheses of Indazoles



General Procedure: A solution of diketone (1 equiv) and hydrazine monohydrochloride (1.10 equiv) in a mixture of methanol (0.5 mL) and water (0.1 mL) was heated to 70 °C. After complete consumption of the starting material (as seen by TLC analysis), the reaction mixture was allowed to cool to 23 °C. Water (2 mL) and ethyl acetate (2 mL) were added to the reaction mixture, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel.

Methyl 3-ethyl-1*H*-indazole-6-carboxylate (21)



21

Following the general procedure, a solution of methyl 6-chloro-2-oxo-3-propionylbicyclo[3.1.0]hexanes-6-carboxylate[98] (30.0 mg, 123 µmol, 1 equiv) and hydrazine monohydrochloride (9.24 mg, 135 µmol, 1.10 equiv) in a mixture of methanol (0.5 mL) and water (0.1 mL) was heated at 70 °C for 14 h. Flash column chromatography (25% ethyl acetate in hexanes) on silica gel yielded **21** (18.1 mg, 72%) as an off-white solid.

TLC (25% ethyl acetate in hexanes): $R_f = 0.35$ (UV, $KMnO_4$).

m.p. 106 °C.

^{1}H NMR (599 MHz, $CDCl_3$) δ = 8.23–8.21 (m, 1H), 7.82 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.76 (dd, *J* = 8.5, 0.8 Hz, 1H), 3.97 (s, 3H), 3.07 (q, *J* = 7.6 Hz, 2H), 1.44 (t, *J* = 7.6 Hz, 3H). N*H* not visible.

^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.4, 148.8, 140.7, 129.0, 124.5, 121.1, 120.4, 112.5, 52.5, 20.5, 13.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3317 (*w*), 3179 (*m*), 2971 (*m*), 1720 (*vs*), 1297 (*s*), 1245 (*s*), 1222 (*vs*), 747 (*m*) cm^{-1}.

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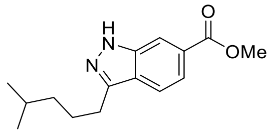
[98] For the synthesis of methyl 6-chloro-2-oxo-3-propionylbicyclo[3.1.0]hexanes-6-carboxylate see: J. Feierfeil, A. Grossmann, T. Magauer, *Angew. Chem, Int. Ed*. **2015**, *54*, 11835–11838.

HRMS (EI) calcd for $C_{11}H_{12}N_2O_2$ $[M]^+$: 204.0893; found: 204.0892.

Methyl 3-(4-methylpentyl)-1*H*-indazole-6-carboxylate (22)



22

Following the general procedure, a solution of methyl 6-chloro-3-(5-methylhexanoyl)-2-oxobicyclo[3.1.0]hexanes-6-carboxylate[99] (29.6 mg, 98.4 µmol, 1 equiv) and hydrazine monohydrochloride (7.42 mg, 108 µmol, 1.10 equiv) in a mixture of methanol (0.5 mL) and water (0.1 mL) was heated at 70 °C for 20 h. Flash column chromatography (25% ethyl acetate in hexanes) on silica gel yielded **22** (19.6 mg, 77%) as an off-white solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.20$ (UV, $KMnO_4$).

m.p. 101 °C.

^{1}H NMR (599 MHz, $CDCl_3$) δ = 8.22–8.21 (m, 1H), 7.81 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.75 (dd, *J* = 8.5, 0.8 Hz, 1H), 3.96 (s, 3H), 3.02–2.97 (m, 2H), 1.89–1.80 (m, 2H), 1.65–1.56 (m, 1H), 1.34–1.28 (m, 2H), 0.89 (s, 3H), 0.88 (s, 3H). N*H* not visible.

^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.5, 147.9, 140.7, 128.8, 124.9, 121.1, 120.4, 112.4, 52.5, 38.9, 28.0, 27.4, 27.1, 22.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3314 (*w*), 3176 (*w*), 2952 (*m*), 1722 (*s*), 1436 (*m*), 1315 (*m*), 1221 (*vs*), 1088 (*m*), 745 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{20}N_2O_2$ $[M]^+$: 260.1519; found: 260.1520.

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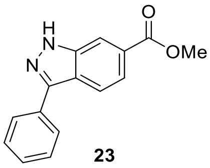
[99] For the synthesis of methyl 6-chloro-3-(5-methylhexanoyl)-2-oxobicyclo[3.1.0]hexanes-6-carboxylate see: J. Feierfeil, A. Grossmann, T. Magauer, *Angew. Chem, Int. Ed*. **2015**, *54*, 11835–11838.

Methyl 3-phenyl-1*H*-indazole-6-carboxylate (23)


23

Following the general procedure, a solution of diketone **S70** (33.7 mg, 115 µmol, 1 equiv) and hydrazine monohydrochloride (8.68 mg, 127 µmol, 1.10 equiv) in a mixture of methanol (0.5 mL) and water (0.1 mL) was heated at 70 °C for 14 h. Flash column chromatography (25% ethyl acetate in hexanes) on silica gel yielded **23** (21.7 mg, 75%) as an off-white solid.

TLC (25% ethyl acetate in hexanes): $R_f = 0.19$ (UV, $KMnO_4$).

m.p. 172 °C.

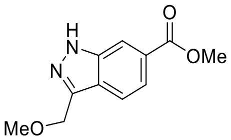
^{1}H NMR (400 MHz, CD_2Cl_2) δ = 10.80 (br. s, 1H), 8.25 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 8.00–7.98 (m, 2H), 7.88 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.56–7.52 (m, 2H), 7.49–7.42 (m, 1H), 3.95 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ = 167.5, 146.1, 141.7, 133.6, 129.4, 129.2, 128.9, 128.0, 123.9, 122.3, 121.5, 113.0, 52.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3172 (*m*), 2950 (*m*), 1720 (*vs*), 1318 (*s*), 1224 (*vs*), 1090 (*s*), 783 (*s*), 743 (*s*), 698 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{12}N_2O_2$ $[M]^+$: 252.0893; found: 252.0895.

Methyl 3-(methoxymethyl)-1*H*-indazole-6-carboxylateylate (24)


24

Following the general procedure, a solution of diketone **S72** (23.4 mg, 89.8 µmol, 1 equiv) and hydrazine monohydrochloride (6.76 mg, 98.7 µmol, 1.10 equiv) in a mixture of methanol (0.5 mL) and water (0.1 mL) was heated at 70 °C for 14 h. Flash column chromatography (20% ethyl acetate in hexanes) on silica gel yielded **24** (11.6 mg, 59%) as a colorless solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.14$ (UV, $KMnO_4$).

m.p. 148 °C.

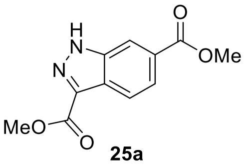
^{1}H NMR (599 MHz, $CDCl_3$) δ = 8.24 (dd, *J* = 1.3, 0.6 Hz, 1H), 7.91–7.88 (m, 1H), 7.85 (dd, *J* = 8.5, 1.3 Hz, 1H), 4.89 (s, 2H), 3.97 (s, 3H), 3.46 (s, 3H). N*H* not visible.

^{13}C NMR (151 MHz, CDCl$_3$) δ = 167.4, 144.1, 140.8, 129.0, 124.8, 121.7, 120.7, 112.5, 67.6, 58.5, 52.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3129 (*m*), 2899 (*m*), 1278 (*vs*), 1239 (*s*), 1221 (*s*), 1088 (*vs*), 985 (*m*), 948 (*m*), 740 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{12}N_2O_3$ [M]$^+$: 220.0842; found: 220.0840.

Dimethyl 1*H*-indazole-3,6-dicarboxylate (25a)



25a

Following the general procedure, a solution of diketone **S74** (29.0 mg, 106 µmol, 1 equiv) and hydrazine monohydrochloride (7.96 mg, 116 µmol, 1.10 equiv) in a mixture of methanol (0.5 mL) and water (0.1 mL) was heated at 70 °C for 14 h. Flash column chromatography (50% ethyl acetate in hexanes) on silica gel yielded **25a** (13.0 mg, 53%) as a colorless solid.

TLC (50% ethyl acetate in hexanes): R_f = 0.29 (UV, KMnO$_4$).

m.p. 216 °C.

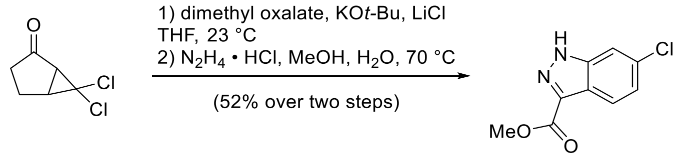
^{1}H NMR (599 MHz, CDCl$_3$) δ = 8.42–8.41 (m, 1H), 8.29 (dd, *J* = 8.6, 0.8 Hz, 1H), 8.01 (dd, *J* = 8.6, 1.3 Hz, 1H), 4.09 (s, 3H), 3.99 (s, 3H). N*H* not visible.

^{13}C NMR (151 MHz, CDCl$_3$) δ = 167.0, 162.9, 140.8, 137.0, 129.6, 125.2, 124.0, 122.1, 113.2, 52.7, 52.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3179 (*w*), 2956 (*w*), 1725 (*vs*), 1469 (*m*), 1220 (*m*), 1157 (*m*), 1091 (*m*), 737 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{10}N_2O_4$ [M]$^+$: 234.0635; found: 234.0634.

Methyl 6-chloro-1*H*-indazole-3-carboxylate (25b)



S17 **25b**

In a flame dried flask, a suspension of anhydrous lithium chloride (128 mg, 3.03 mmol, 2.50 equiv) and potassium *tert*-butoxide (sublimed grade, 204 mg, 1.82 mmol, 1.50 equiv) in tetrahydrofuran (2 mL) was heated to 70 °C. After 3 h, the suspension was allowed to cool to 23 °C and a solution of **S17** (200 mg, 1.21 mmol, 1 equiv) and dimethyl oxalate (186 mg, 1.58 mmol, 1.30 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 45 min, the solvent was removed and the resulting residue was dissolved in a mixture of methanol (1 mL) and water (0.2 mL). Then hydrazine monohydrochloride (141 mg, 2.06 mmol, 1.70 mmol) was added to the solution. The reaction mixture was then heated to 70 °C. After 14 h, the reaction mixture was allowed to cool to 23 °C. Water (2 mL) and ethyl acetate (5 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 x 20 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (33% ethyl acetate in hexanes) on silica gel to yield **25b** (133 mg, 52%) as an off-white solid.

TLC (33% ethyl acetate in hexanes): R_f = 0.27 (UV, $KMnO_4$).

m.p. 225 °C.

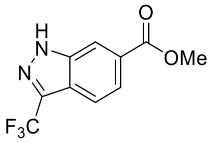
^{1}H NMR (599 MHz, CD_2Cl_2) δ = 12.30 (br. s, 1H), 8.14 (dd, *J* = 8.7, 0.7 Hz, 1H), 7.83 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.33 (dd, *J* = 8.7, 1.7 Hz, 1H), 4.08 (s, 3H).

^{13}C NMR (151 MHz, CD_2Cl_2) δ = 163.6, 142.2, 137.2, 134.2, 124.9, 123.3, 121.5, 111.6, 52.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3177 (*w*), 2364 (*w*), 1733 (*vs*), 1471 (*m*), 1154 (*s*), 1060 (*m*), 825 (*s*), 806 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_9H_7ClN_2O_2$ $[M]^+$: 210.0191; found: 210.0193.

Methyl 3-(trifluoromethyl)-1*H*-indazole-6-carboxylate (26)



26 Following the general procedure, a solution of diketone **S76** (27.8 mg, 97.7 µmol, 1 equiv) and hydrazine monohydrochloride (7.36 mg, 107 µmol, 1.10 equiv) in a mixture of methanol (0.5 mL) and water (0.1 mL) was heated at 70 °C for 4 h. Flash column chromatography (20% ethyl acetate in hexanes) on silica gel yielded **26** (15.5 mg, 65%) as a colorless solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.27$ (UV, $KMnO_4$).

m.p. 171 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.98 (br. s, 1H), 8.37–8.35 (m, 1H), 7.98 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.94–7.91 (m, 1H), 4.00 (s, 3H).

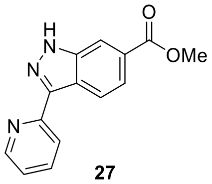
^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.9, 140.6, 136.6 (q, *J* = 38.8 Hz), 130.0, 123.6, 122.2, 121.7 (q, *J* = 269.0 Hz), 120.2, 112.9, 52.8.

^{19}F NMR (377 MHz, $CDCl_3$) δ = −61.10.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3285 (*m*), 2956 (*w*), 1702 (*s*), 1276 (*s*), 1224 (*vs*), 1123 (*vs*), 1093 (*s*), 1018 (*vs*), 748 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{10}H_7F_3N_2O_2$ $[M]^+$: 244.0454; found: 244.0454.

Methyl 3-(pyridin-2-yl)-1*H*-indazole-6-carboxylate (27)



27 Following the general procedure, a solution of diketone **S78** (22.5 mg, 76.6 µmol, 1 equiv) and hydrazine monohydrochloride (5.77 mg, 84.3 µmol, 1.10 equiv) in a mixture of methanol (0.5 mL) and water (0.1 mL) was heated at 70 °C for 14 h. Flash column chromatography (50% ethyl acetate in hexanes) on silica gel yielded **27** (12.6 mg, 65%) as an off-white solid.

TLC (50% ethyl acetate in hexanes): $R_f = 0.20$ (UV, $KMnO_4$).

m.p. 168 °C.

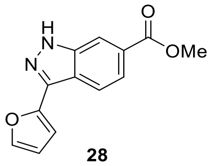
^{1}**H NMR** (400 MHz, CD_2Cl_2) δ = 10.67 (br. s, 1H), 8.78–8.71 (m, 2H), 8.30–8.25 (m, 1H), 8.20 (d, *J* = 8.6 Hz, 1H), 7.91 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.83–7.79 (m, 1H), 7.32–7.29 (m, 1H), 3.96 (s, 3H).

^{13}**C NMR** (101 MHz, CD_2Cl_2) δ = 167.6, 153.6, 149.9, 145.3, 141.9, 137.1, 129.4, 124.7, 124.2, 123.3, 122.7, 121.3, 112.6, 52.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3259 (*m*), 2951 (*w*), 1721 (*vs*), 1592 (*s*), 1315 (*s*), 1222 (*vs*), 1088 (*s*), 1008 (*s*), 786 (*m*), 741 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{11}N_3O_2$ $[M]^+$: 253.0846; found: 253.0847.

Methyl 3-(furan-2-yl)-1*H*-indazole-6-carboxylate (28)



28

Following the general procedure, a solution of diketone **S80** (17.5 mg, 61.9 µmol, 1 equiv) and hydrazine monohydrochloride (4.67 mg, 68.1 µmol, 1.10 equiv) in a mixture of methanol (0.5 mL) and water (0.1 mL) was heated at 70 °C for 20 h. Flash column chromatography (25% ethyl acetate in hexanes) on silica gel yielded **28** (8.70 mg, 58%) as an off-white solid.

TLC (25% ethyl acetate in hexanes): $R_f = 0.11$ (UV, $KMnO_4$).

m.p. 196 °C.

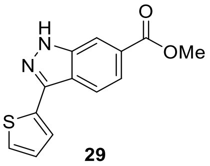
^{1}**H NMR** (599 MHz, $CDCl_3$) δ = 8.27 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.93–7.89 (m, 1H), 7.64 (d, *J* = 1.7 Hz, 1H), 6.99 (d, *J* = 3.3 Hz, 1H), 6.60 (dd, *J* = 3.3, 1.7 Hz, 1H), 3.98 (s, 3H). N*H* not visible.

^{13}**C NMR** (151 MHz, $CDCl_3$) δ = 167.3, 148.4, 142.9, 140.7, 138.2, 129.2, 122.8, 122.3, 121.6, 112.6, 111.7, 107.9, 52.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3169 (*m*), 2953 (*w*), 1725 (*vs*), 1435 (*m*), 1317 (*s*), 1221 (*vs*), 1090 (*m*), 1001 (*s*), 736 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{10}N_2O_3$ $[M]^+$: 242.0686; found: 242.0687.

Methyl 3-(thiophen-2-yl)-1*H*-indazole-6-carboxylate (29)



29

Following the general procedure, a solution of diketone **S82** (37.5 mg, 126 µmol, 1 equiv) and hydrazine monohydrochloride (9.46 mg, 138 µmol, 1.10 equiv) in a mixture of methanol (0.5 mL) and water (0.1 mL) was heated at 70 °C for 14 h. Flash column chromatography (33% ethyl acetate in hexanes) on silica gel yielded **29** (22.0 mg, 68%) as a yellow solid.

TLC (33% ethyl acetate in hexanes): R_f = 0.46 (UV, $KMnO_4$).

m.p. 166 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26–8.22 (m, 1H), 8.09 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.89 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.69 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.42 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.20 (dd, *J* = 5.1, 3.6 Hz, 1H), 3.96 (s, 3H). N*H* not visible.

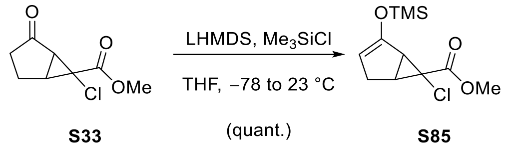
^{13}C NMR (101 MHz, CD_2Cl_2) δ = 167.5, 141.6, 141.3, 135.9, 129.6, 128.3, 126.0, 125.7, 123.3, 122.5, 121.3, 113.1, 52.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3270 (*m*), 2950 (*w*), 1717 (*vs*), 1435 (*m*), 1324 (s), 1313 (*s*), 1298 (*s*), 1263 (*s*), 1223 (*vs*), 1089 (*s*), 744 (*s*), 701 (*s*) cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{10}N_2O_2S$ $[M]^+$: 258.0457; found: 258.0454.

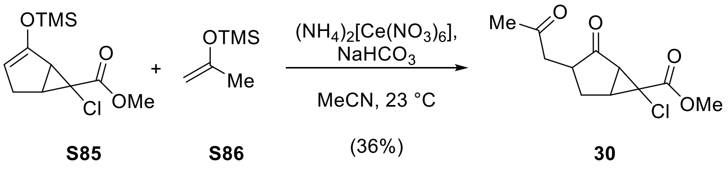
Heterocycles from 1,4-Diketones

Silyl Enol Ether S85



In a flame dried flask, a solution of ketone **S33** (300 mg, 1.59 mmol, 1 equiv) in tetrahydrofuran (5 mL) was cooled to −78 °C. A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.91 mL, 1.91 mmol, 1.20 equiv) was added dropwise. After 30 min, chlorotrimethylsilane (freshly distilled over calcium hydride, 305 µL, 2.39 mmol, 1.50 equiv) was added. After 90 min, hexanes (10 mL) was added and the reaction mixture was filtered through a plug of Celite®. The plug was washed with hexanes (10 mL) and the filtrate was concentrated to yield **S85** (414 mg, quant.) as a colorless oil. Compound **S85** was used in the next step without further purification.

Diketone 30



In an oven-dried flask, to a suspension of anhydrous sodium hydrogen carbonate (351 mg, 4.18 mmol, 4.00 equiv) and ammonium cerium(IV) nitrate (1.15 g, 2.09 mmol, 2.00 equiv) in acetonitrile (4 mL) was added a solution of silyl enol ether **S85** (272 mg, 1.04 mmol, 1 equiv) and acetone trimethyl silyl enol ether **S86** (1.36 g, 10.4 mmol, 10.0 equiv) in acetonitrile (4 mL). After 30 min, water (10 mL) and dichloromethane (10 mL) were added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to yield diketone **30** (91.0 mg, 36%) as a colorless oil.

TLC (25% ethyl acetate in hexanes): $R_f = 0.16$ ($KMnO_4$).

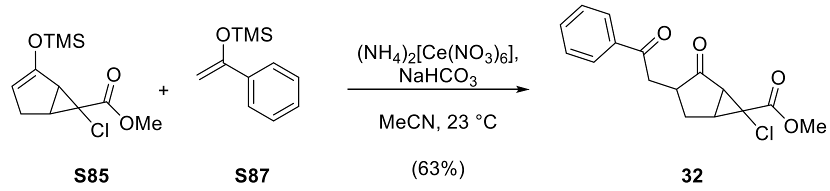
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.80 (s, 3H), 2.96–2.69 (m, 4H), 2.57–2.42 (m, 2H), 2.14 (s, 3H), 2.12–2.04 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.5, 206.0, 168.3, 54.0, 48.9, 46.2, 42.3, 42.1, 35.0, 29.7, 28.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (*w*), 1733 (*vs*), 1714 (*vs*), 1263 (*s*), 1194 (*m*), 1159 (*m*), 1090 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{13}ClO_4$ [M]$^+$: 244.0497; found: 244.0498.

Diketone 32



In an oven-dried flask, to a suspension of anhydrous sodium hydrogen carbonate (249 mg, 2.96 mmol, 4.00 equiv) and ammonium cerium(IV) nitrate (811 mg, 1.48 mmol, 2.00 equiv) in acetonitrile (4 mL) was added a solution of silyl enol ether **S85** (193 mg, 740 µmol, 1 equiv) and acetone trimethyl silyl enol ether **S87** (1.52 mL, 7.40 mmol, 10.0 equiv) in acetonitrile (4 mL). After 30 min, additional ammonium cerium(IV) nitrate (811 mg, 1.48 mmol, 2.00 equiv) was added. After 1 h, water (10 mL) and ethyl acetate (20 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to yield diketone **32** (143 mg, 63%) as an orange oil.

TLC (12.5% ethyl acetate in hexanes): R_f = 0.10 ($KMnO_4$).

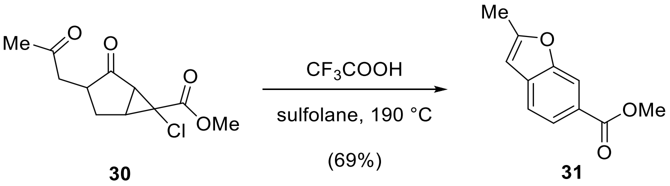
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96–7.91 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 3.82 (s, 3H), 3.59–3.35 (m, 2H), 2.97 (d, *J* = 6.6 Hz, 1H), 2.85 (t, *J* = 6.6 Hz, 1H), 2.74–2.68 (m, 1H), 2.54 (dd, *J* = 14.1, 8.9 Hz, 1H), 2.18 (dt, *J* = 14.1, 6.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.8, 197.4, 168.4, 136.2, 133.7, 128.9, 128.2, 54.1, 49.0, 42.4, 42.3, 41.8, 35.1, 28.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*w*), 1731 (*vs*), 1682 (*s*), 1262 (*s*), 1231 (*s*), 994 (*m*), 754 (*s*), 690 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{15}ClO_4$ [M]$^+$: 306.0653; found: 306.0650.

Methyl 2-methylbenzofuran-6-carboxylate (31)



A solution of 1,4-diketone **30** (12.0 mg, 49.0 µmol, 1 equiv) and trifluoroacetic acid (5.59 mg, 49.0 µmol, 1 equiv) in sulfolane (100 µL) was heated to 190 °C. After 30 min, the reaction mixture was allowed to cool to 23 °C and water (2 mL) and diethyl ether (2 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed sequentially with water (4 × 5 mL) and saturated aqueous sodium chloride solution (5 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield benzofuran **31** (6.40 mg, 69%) as a colorless solid.

TLC (10% ethyl acetate in hexanes): $R_f = 0.55$ (UV, $KMnO_4$).

m.p. 58 °C.

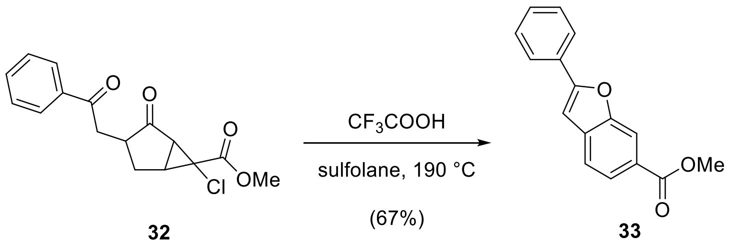
^{1}H NMR (599 MHz, $CDCl_3$) δ = 8.09–8.08 (m, 1H), 7.90 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 6.45–6.41 (m, 1H), 3.93 (s, 3H), 2.49 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.6, 159.1, 154.3, 133.9, 125.2, 124.2, 119.7, 112.4, 103.2, 52.2, 14.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (*w*), 1715 (*vs*), 1600 (*m*), 1434 (*m*), 1283 (*vs*), 1215 (*s*), 1080 (*m*) cm^{-1}.

HRMS (EI) calcd for $C_{11}H_{10}O_3$ $[M]^+$: 190.0624; found: 190.0625.

Methyl 2-phenylbenzofuran-6-carboxylate (33)



A solution of 1,4-diketone **32** (24.6 mg, 80.2 µmol, 1 equiv) and trifluoroacetic acid (9.14 mg, 80.2 µmol, 1 equiv) in sulfolane (300 µL) was heated to 190 °C. After 30 min, the reaction mixture was allowed to cool to 23 °C and water (2 mL) and diethyl ether (2 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed sequentially with water (4 × 5 mL) and saturated aqueous sodium chloride solution (5 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield benzofuran **33** (13.5 mg, 67%) as an off-white solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.57$ (UV, $KMnO_4$).

m.p. 158 °C.

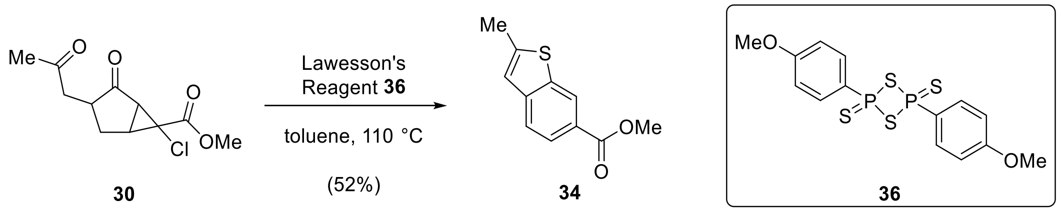
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.22 (s, 1H), 7.96 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.91–7.88 (m, 2H), 7.63–7.59 (m, 1H), 7.51–7.45 (m, 2H), 7.43–7.38 (m, 1H), 7.07 (d, *J* = 0.9 Hz, 1H), 3.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.4, 159.1, 154.5, 133.7, 130.0, 129.5, 129.1, 126.3, 125.5, 124.6, 120.6, 112.9, 101.5, 52.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (*w*), 1712 (*vs*), 1440 (*m*), 1303 (*vs*), 1229 (*s*), 1201 (*m*), 1124 (*m*), 848 (*m*), 770 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{12}O_3$ $[M]^+$: 252.0781; found: 252.0772.

Methyl 2-methylbenzo[*b*]thiophene-6-carboxylate (34)



In a sealed pressure tube a solution of 1,4-diketone **30** (10.6 mg, 43.3 µmol, 1 equiv) and Lawesson's reagent **36** (35.0 mg, 86.6 µmol, 2 equiv) in toluene (500 µL) was heated to 110 °C. After 4 h, the reaction mixture was allowed to cool to 23 °C and the reaction mixture was filtered through a plug of Celite®. The plug was washed with ethyl acetate (10 mL) and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to yield benzothiophene **34** (5.50 mg, 52%) as a yellow oil.

TLC (12.5% ethyl acetate in hexanes): $R_f = 0.62$ (UV, KMnO$_4$).

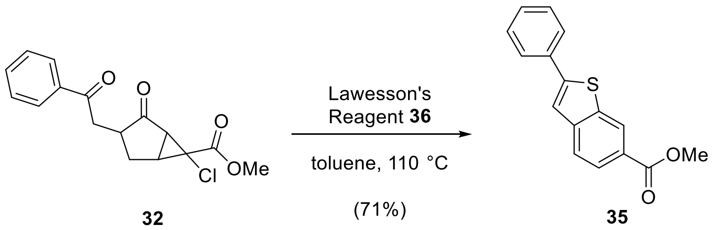
^{1}H NMR (599 MHz, CD$_2$Cl$_2$) δ = 8.46–8.45 (m, 1H), 7.94 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.08–7.06 (m, 1H), 3.91 (s, 3H), 2.63 (s, 3H).

^{13}C NMR (151 MHz, CD$_2$Cl$_2$) δ = 167.6, 146.4, 144.5, 139.9, 125.8, 125.5, 124.5, 122.8, 122.2, 52.5, 16.7

IR (Diamond-ATR, neat) $\tilde{\nu}_{\max}$: 2949 (*w*), 1716 (*vs*), 1598 (*w*), 1433 (*m*), 1280 (*vs*), 1241 (*m*), 1129 (*m*), 1104 (*m*) cm^{-1}.

HRMS (EI) calcd for C$_{11}$H$_{10}$O$_2$S [M]$^+$: 206.0396; found: 206.0393.

Methyl 2-phenylbenzo[*b*]thiophene-6-carboxylate (35)



In a sealed pressure tube a solution of 1,4-diketone **32** (25.0 mg, 81.5 µmol, 1 equiv) and Lawesson's reagent **36** (65.9 mg, 163 µmol, 2 equiv) in toluene (1 mL) was heated to 110 °C. After 8 h, the reaction mixture was allowed to cool to 23 °C and the reaction mixture was filtered through a plug of Celite®. The plug was washed with ethyl acetate (10 mL) and the resulting filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate in hexanes) to yield benzothiophene **35** (15.5 mg, 71%) as an off-white solid.

TLC (12.5% ethyl acetate in hexanes): R_f = 0.52 (UV, $KMnO_4$).

m.p. 197 °C.

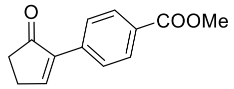
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65–8.45 (m, 1H), 8.02 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.80 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.76–7.71 (m, 2H), 7.58 (d, *J* = 0.7 Hz, 1H), 7.47–7.43 (m, 2H), 7.42–7.35 (m, 1H), 3.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.3, 148.6, 144.2, 139.2, 133.9, 129.2, 129.1, 126.8, 126.1, 125.6, 124.6, 123.4, 119.4, 52.3.

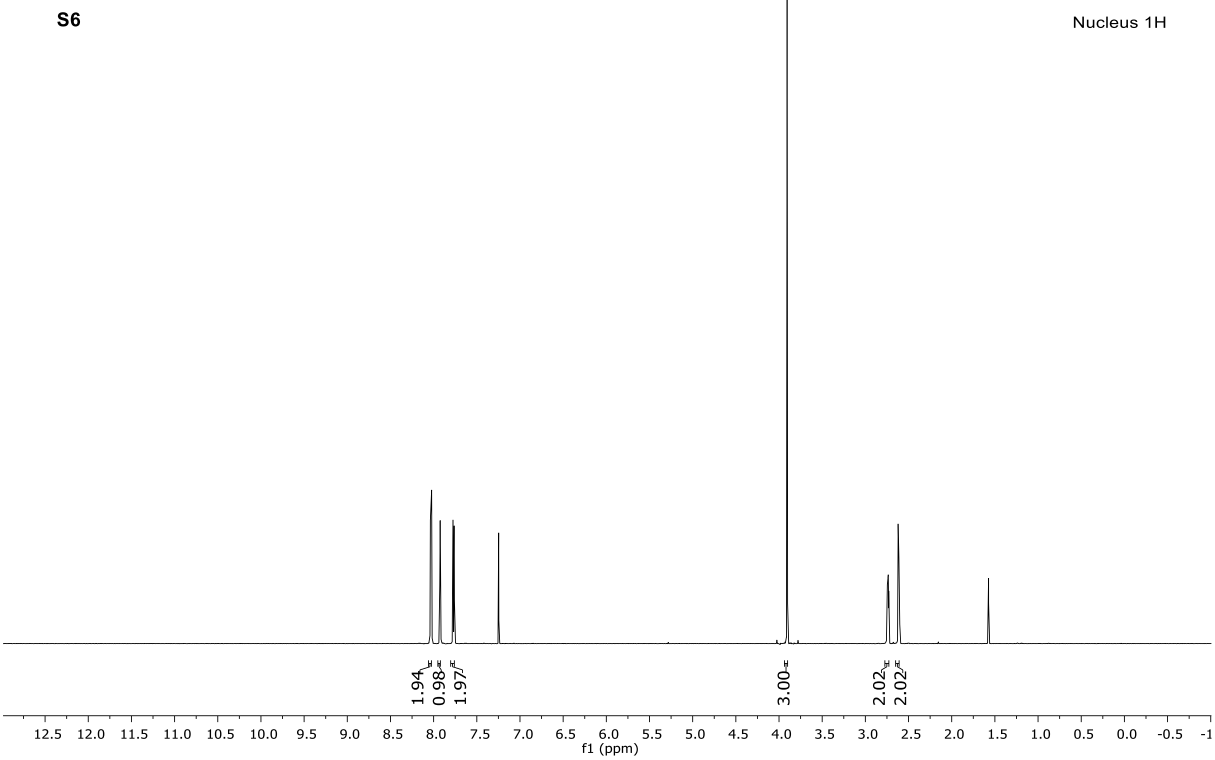
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953 (*w*), 1718 (*vs*), 1447 (*m*), 1288 (*s*), 1249 (*m*), 1116 (*s*), 855 (*m*), 766 (*vs*), 722 (*s*) cm^{-1}.

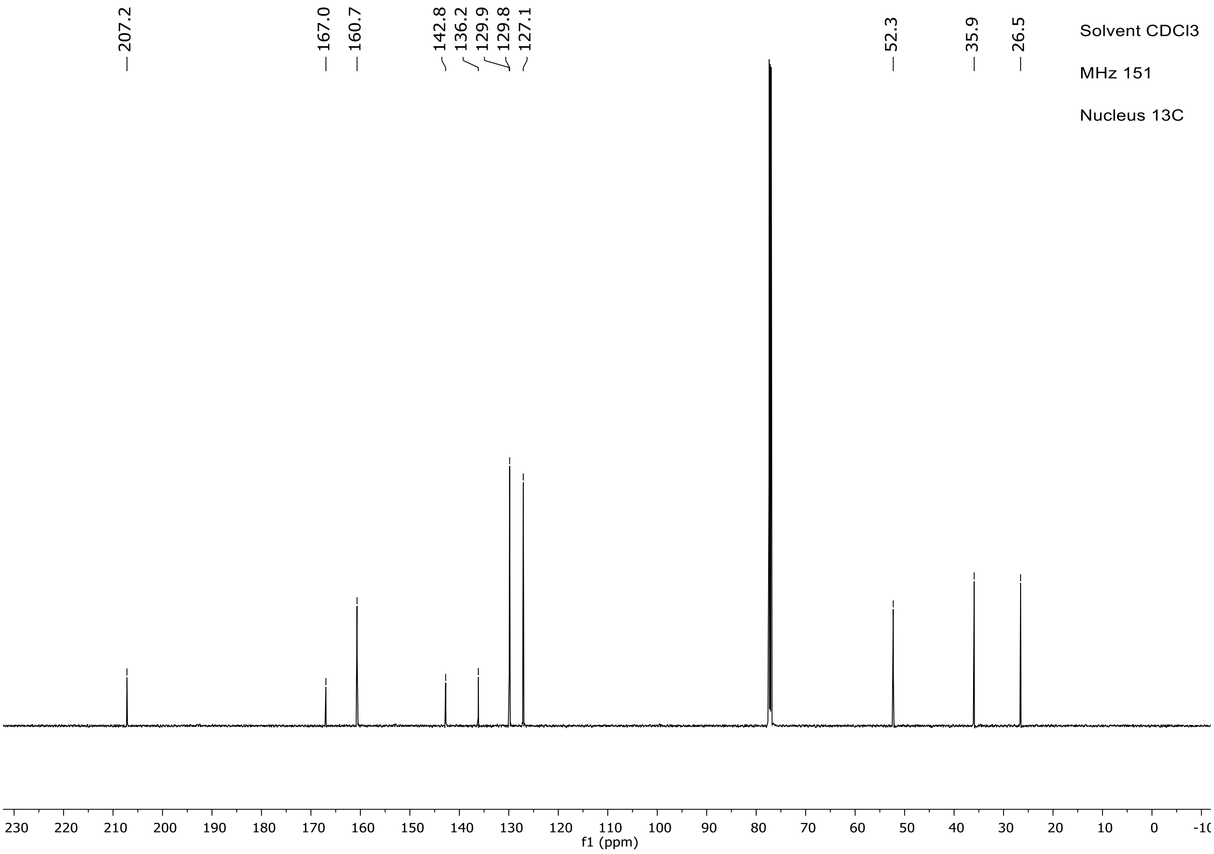
HRMS (EI) calcd for $C_{16}H_{12}O_2S$ $[M]^+$: 268.0553; found: 268.0547.

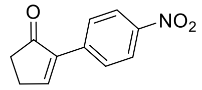
6.2.2 ^{1}H, ^{13}C and ^{19}F NMR Spectra


O
COOMe

S6


Solvent CDCl3
MHz 599
Nucleus 1H
1.94
0.98
1.97
3.00
2.02
2.02
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


207.2
167.0
160.7
142.8
136.2
129.9
129.8
127.1
52.3
35.9
26.5
Solvent CDCl3
MHz 151
Nucleus 13C
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)

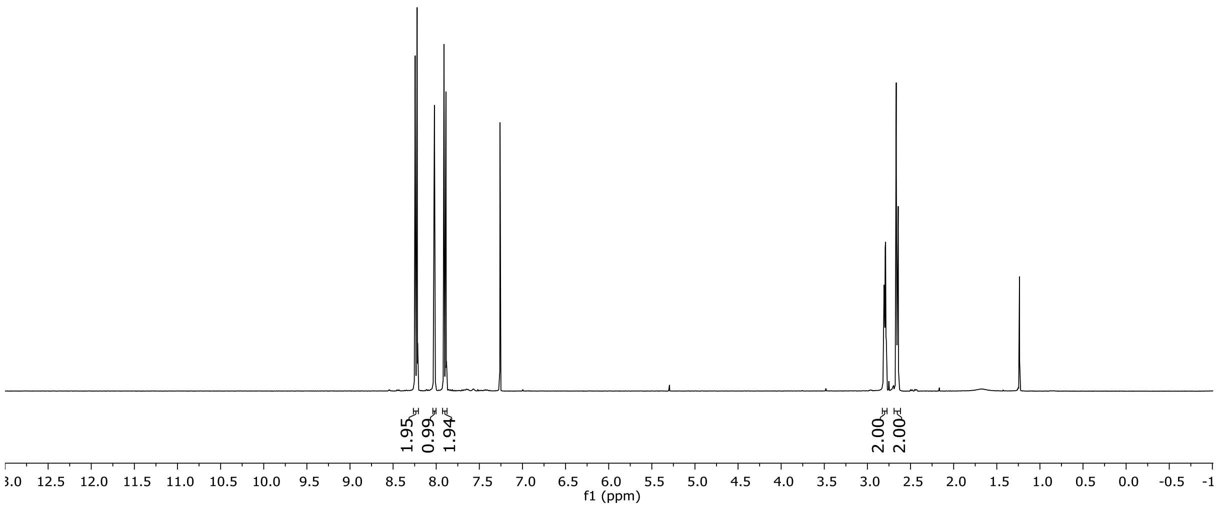


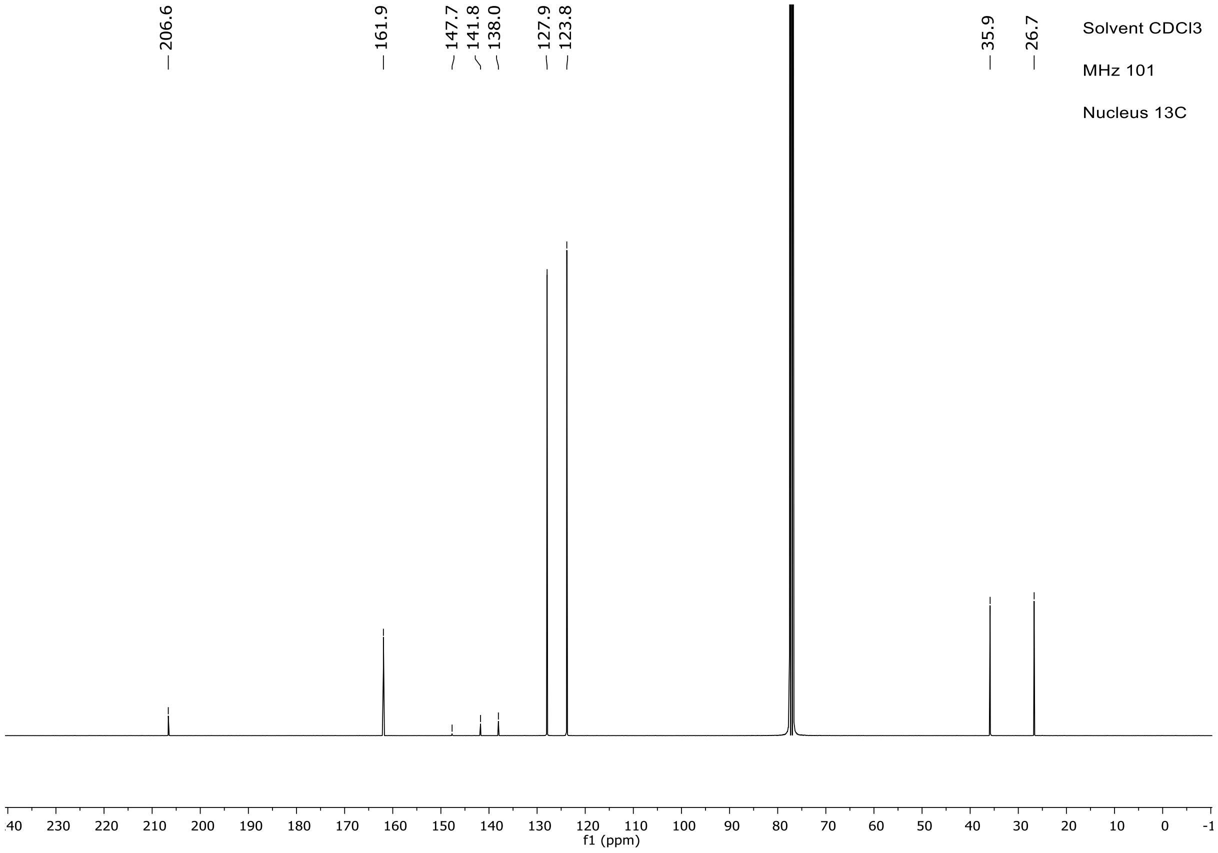
S8

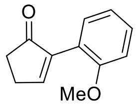
Solvent CDCl3

MHz 400

Nucleus 1H





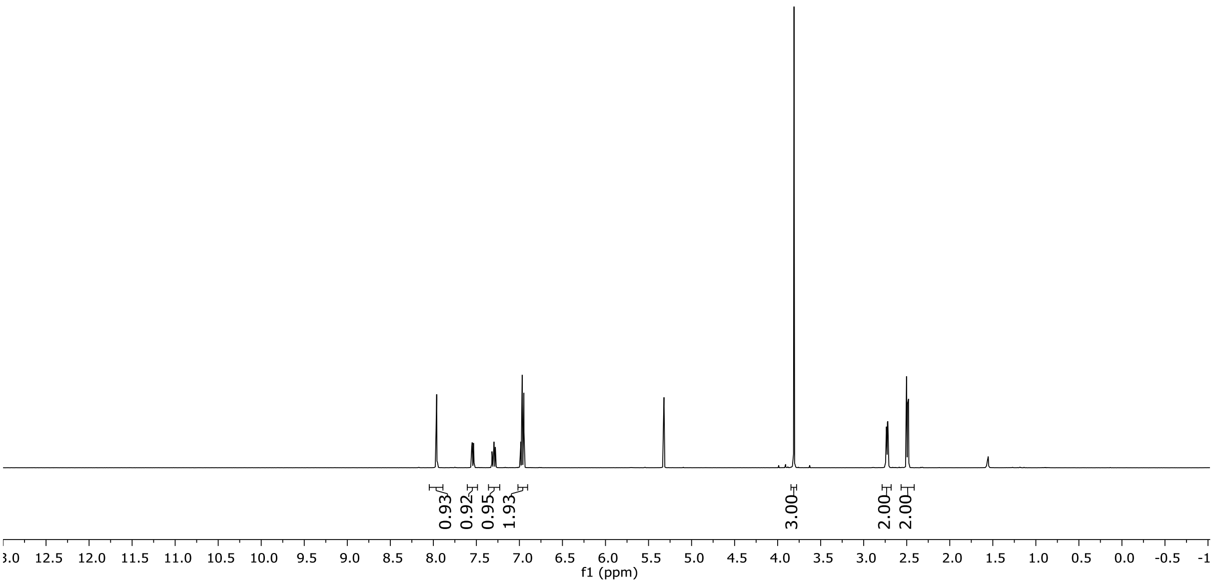


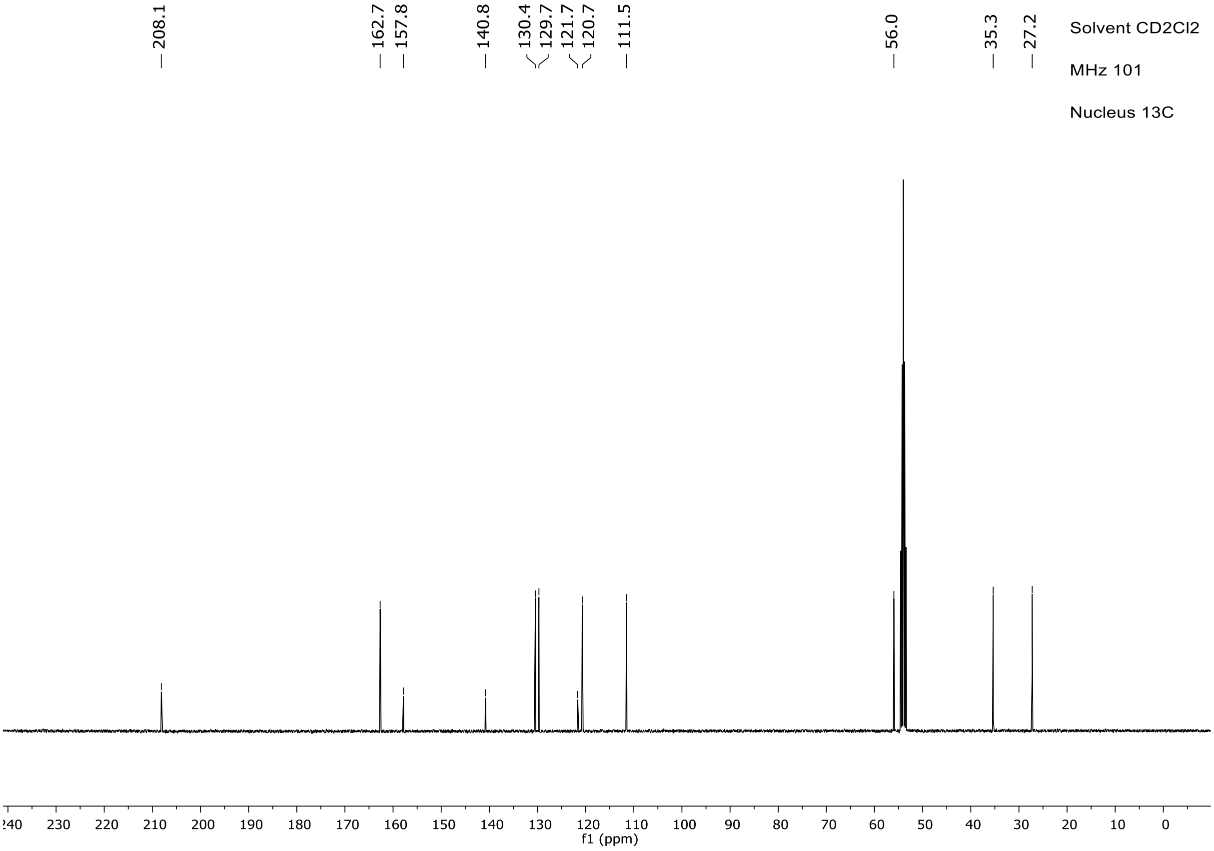
S10

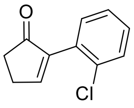
Solvent CD2Cl2

MHz 400

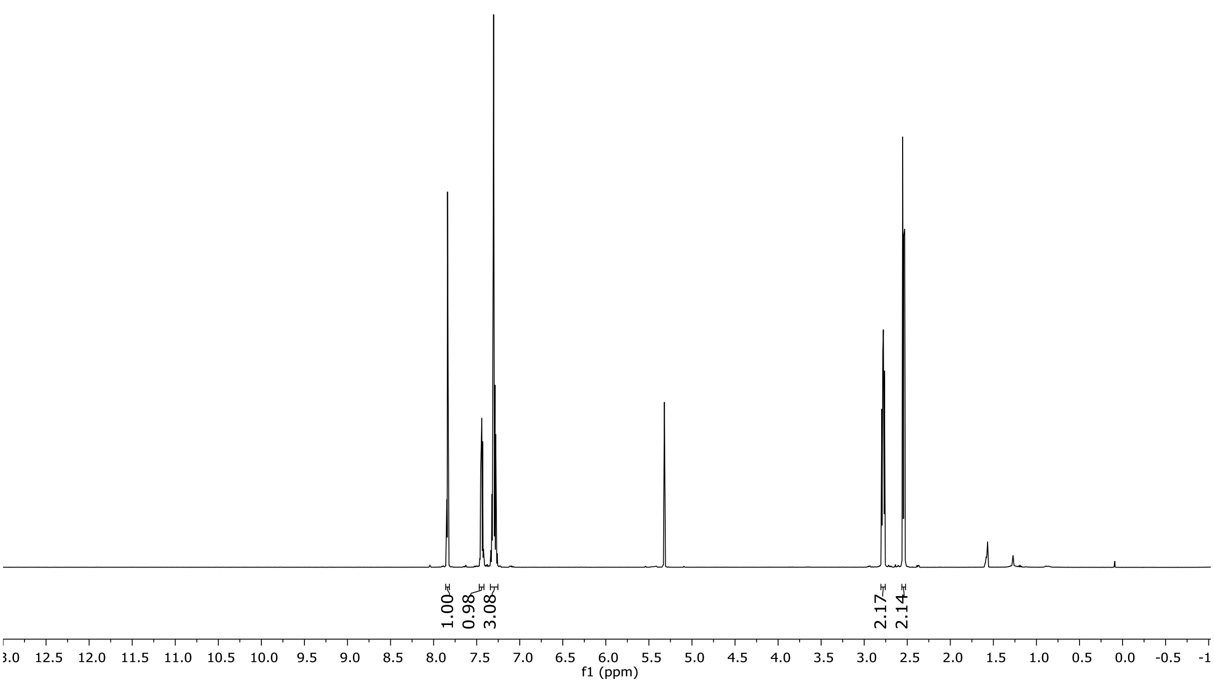
Nucleus 1H

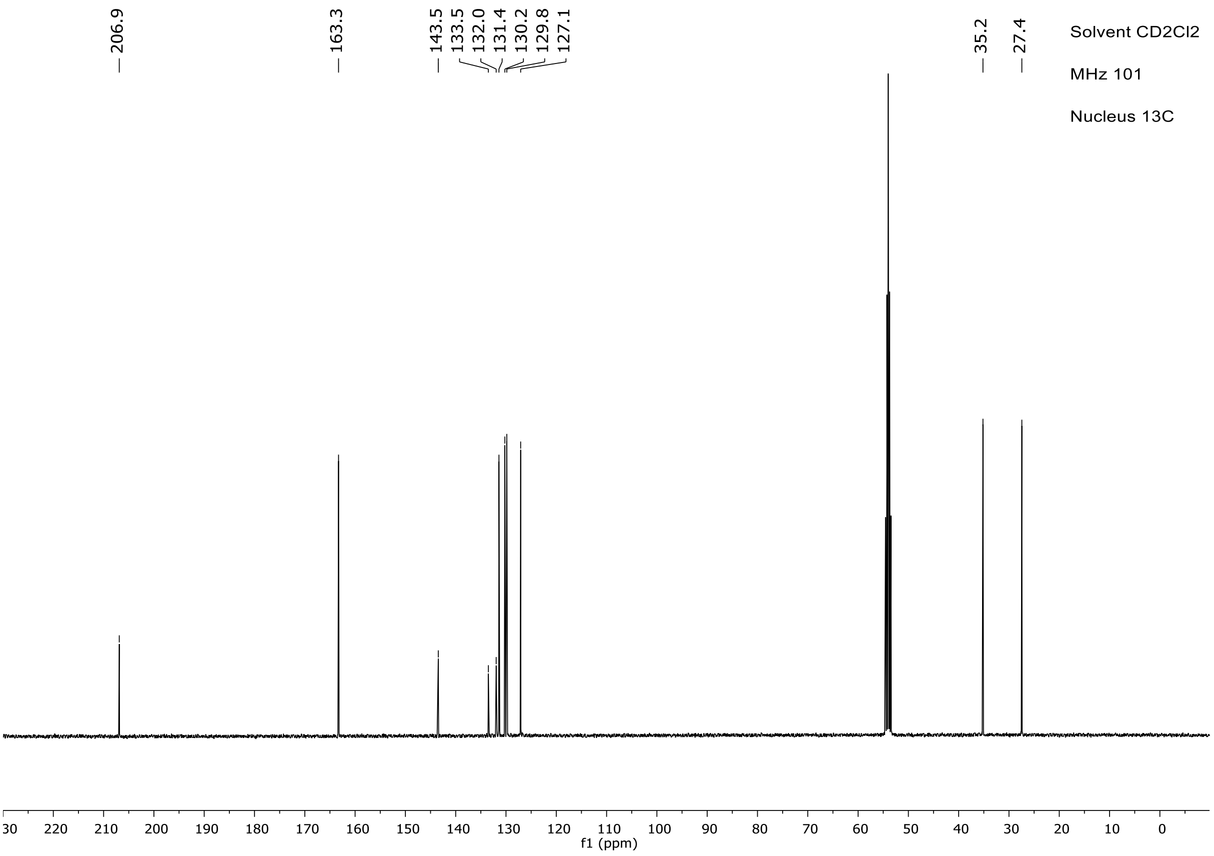


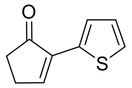



O
Cl

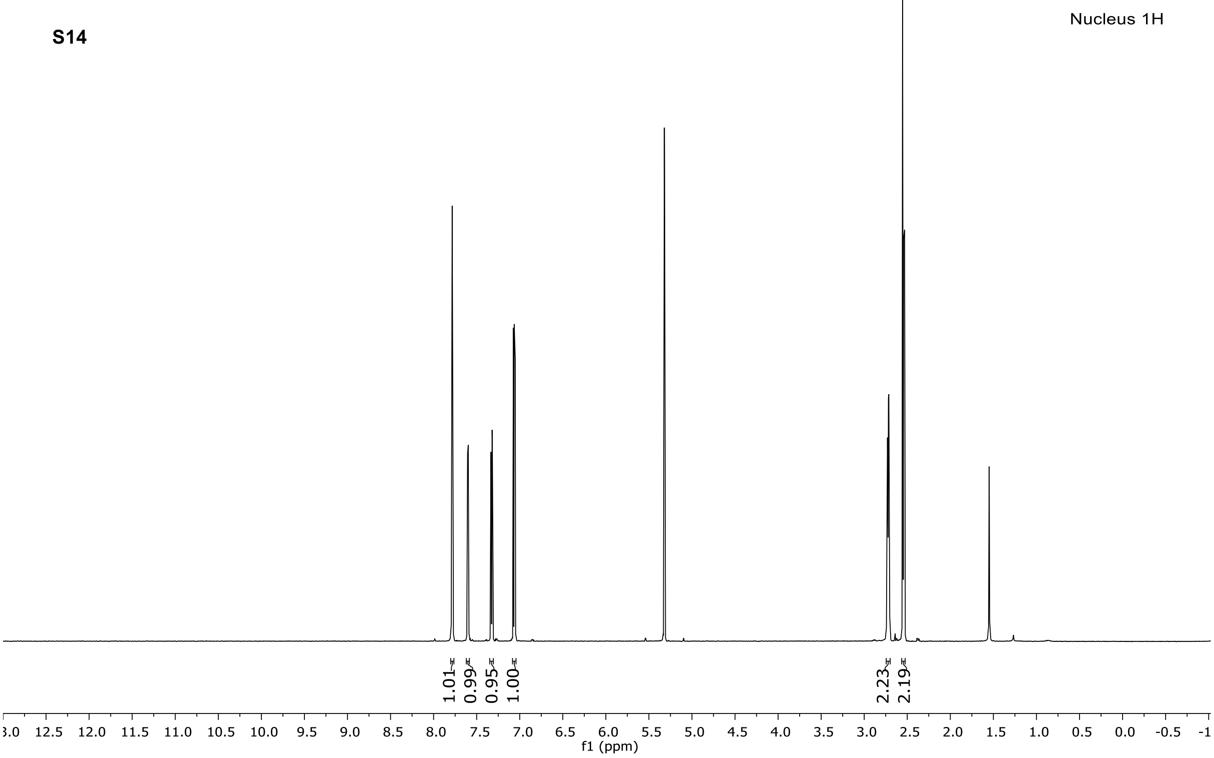
S12

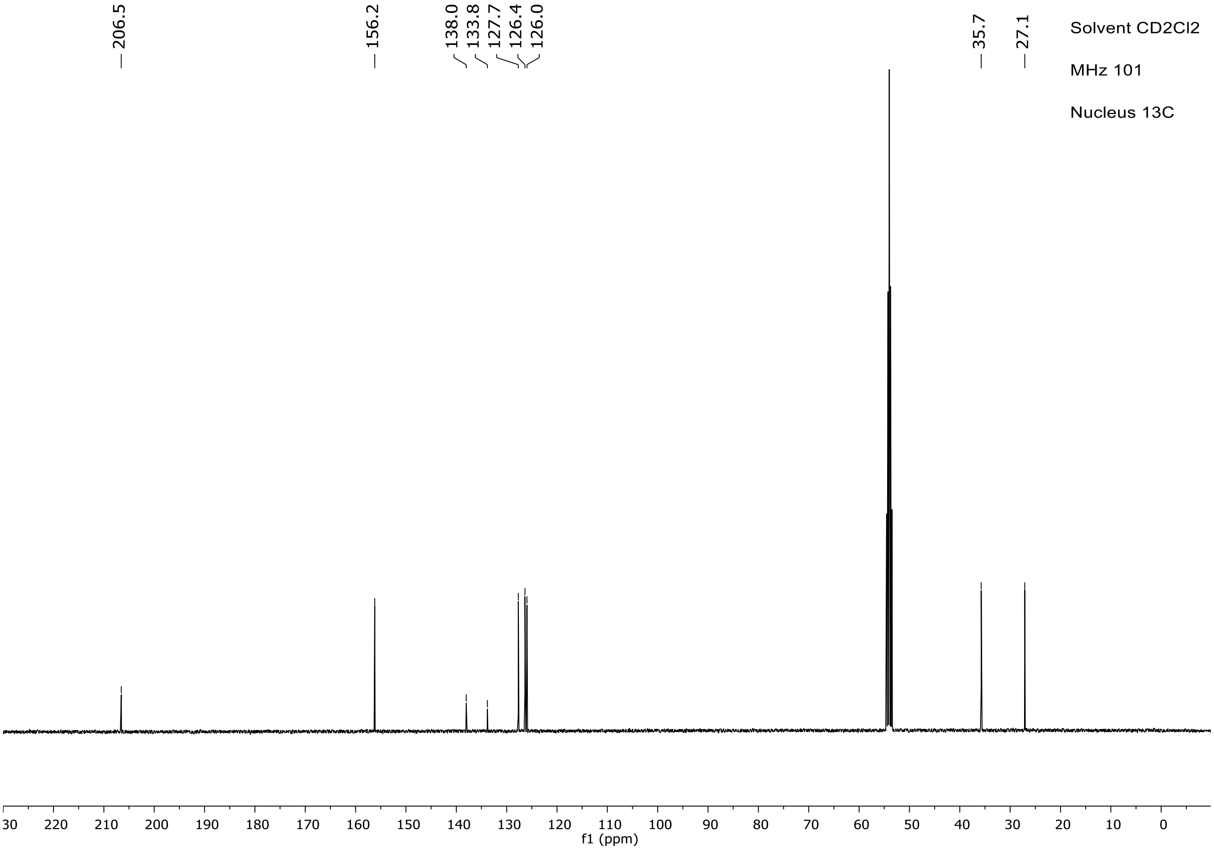

Solvent CD2Cl2
MHz 400
Nucleus 1H
1.00
0.98
3.08
2.17
2.14
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

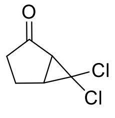

206.9
163.3
143.5
133.5
132.0
131.4
130.2
129.8
127.1
35.2
27.4
Solvent CD2Cl2
MHz 101
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
S

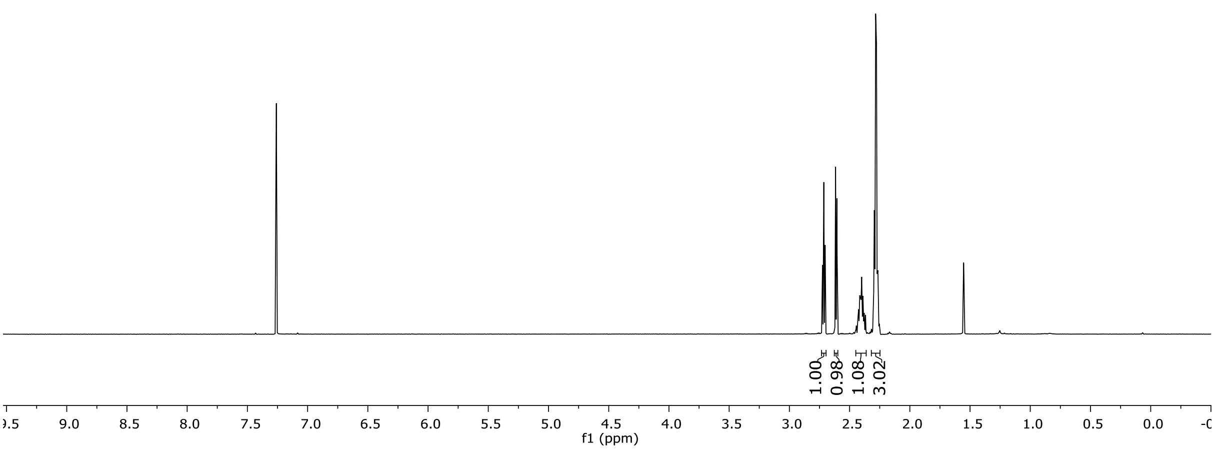
S14

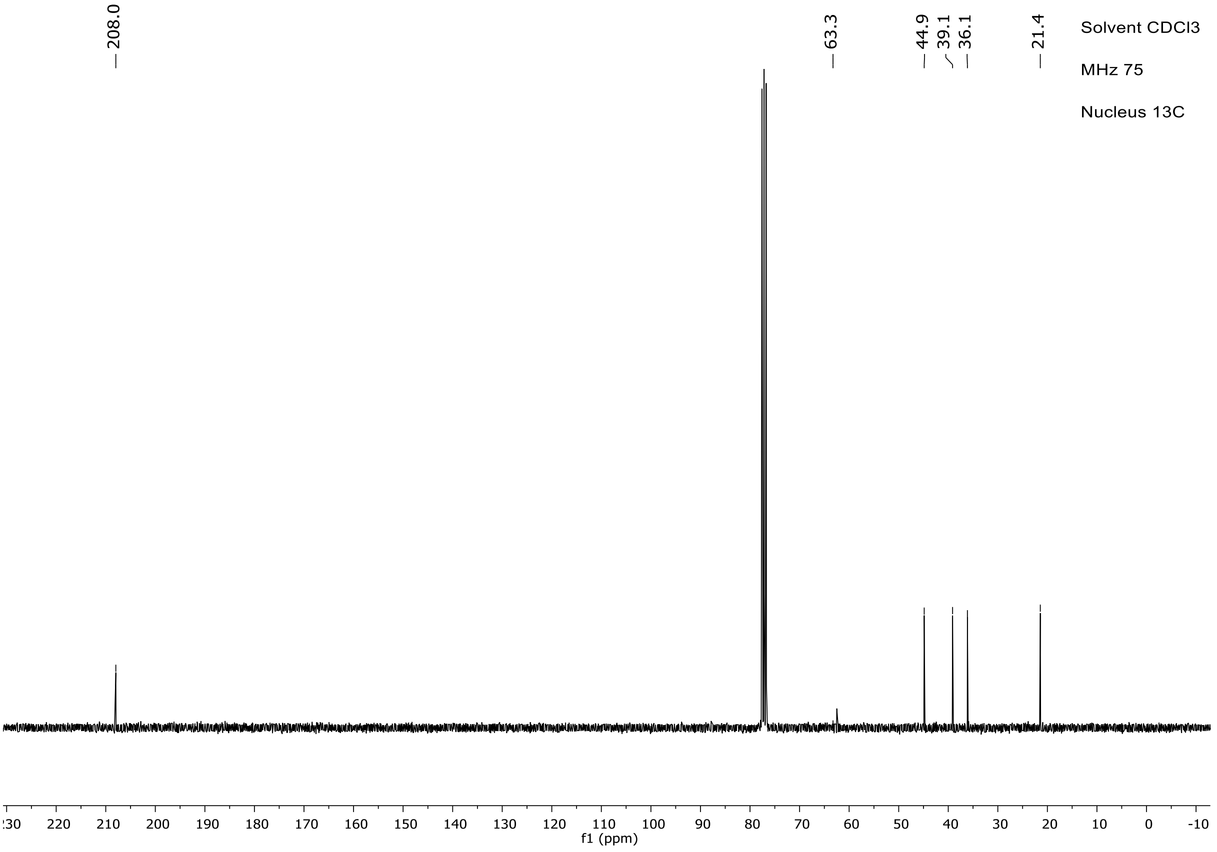

Solvent CD2Cl2
MHz 400
Nucleus 1H
1.01
0.99
0.95
1.00
2.23
2.19
3.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

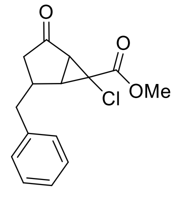

206.5
156.2
138.0
133.8
127.7
126.4
126.0
35.7
27.1
Solvent CD2Cl2
MHz 101
Nucleus 13C
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



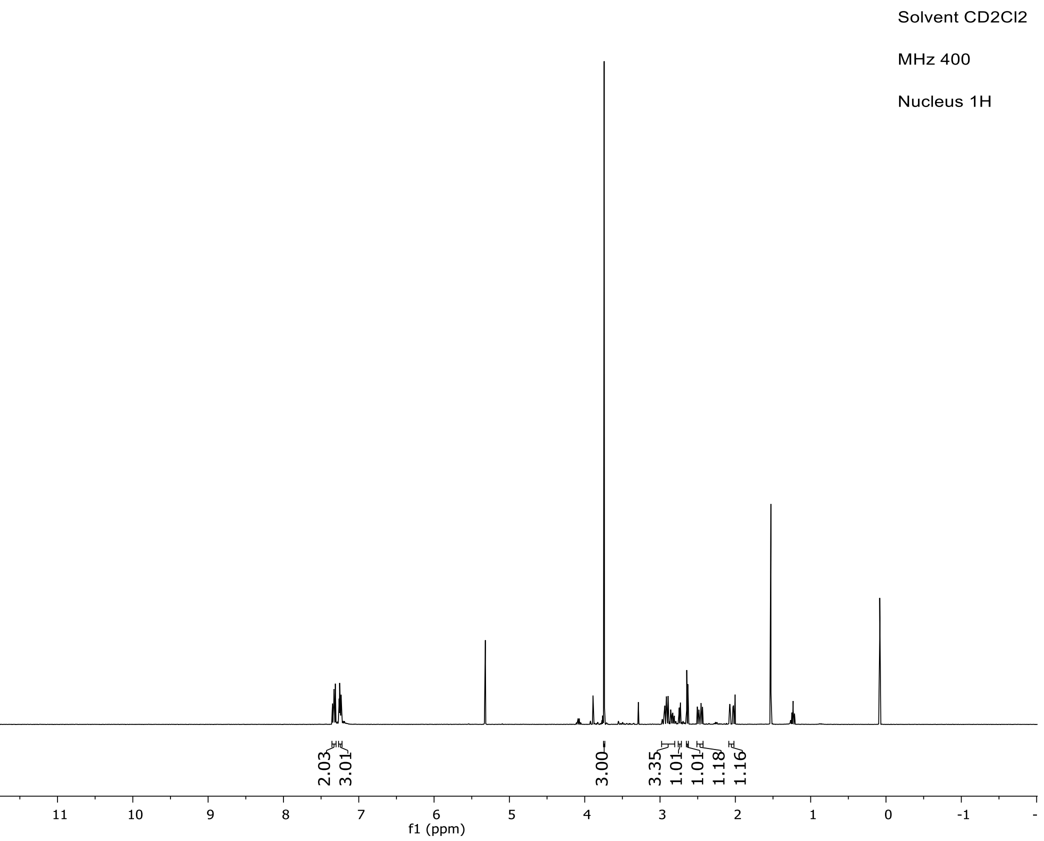
S17

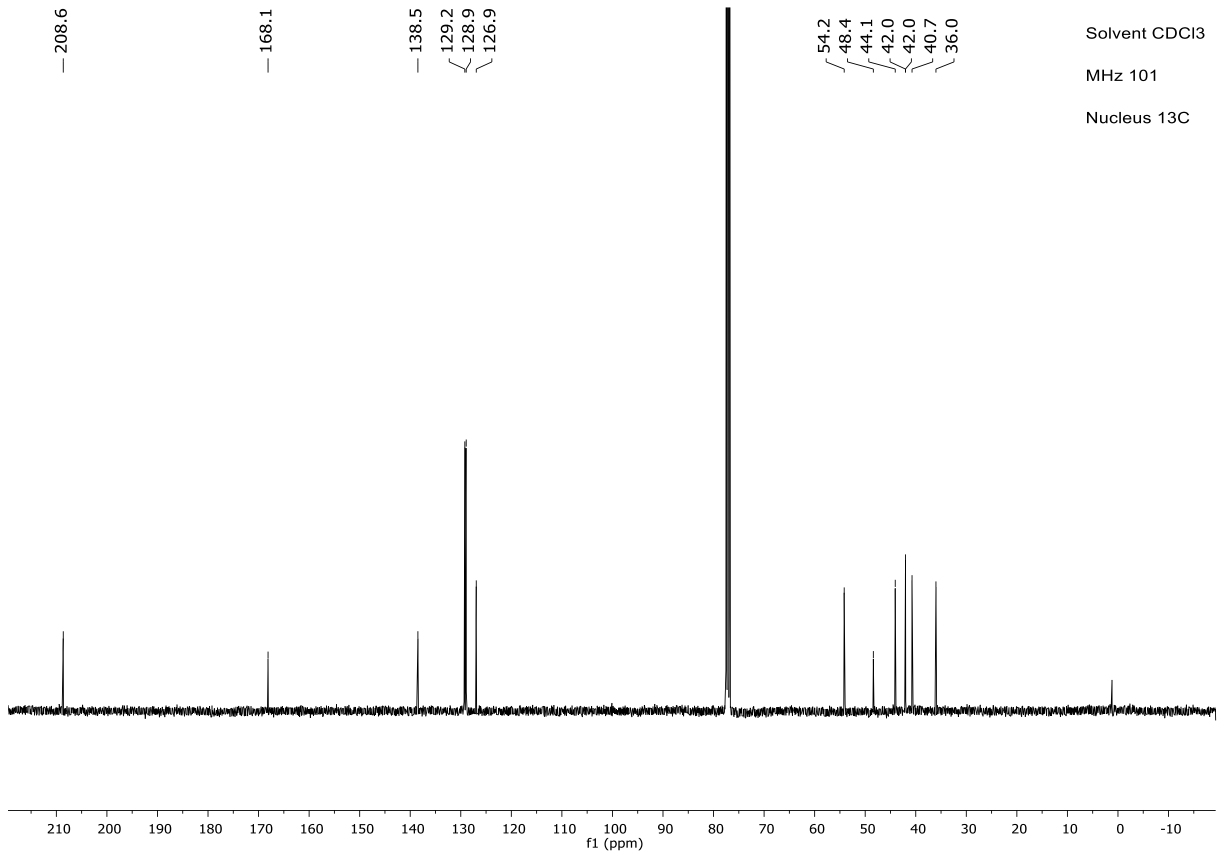

Solvent CDCl3
MHz 599
Nucleus 1H
1.00
0.98
1.08
3.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

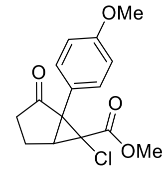

208.0
63.3
44.9
39.1
36.1
21.4
Solvent CDCl3
MHz 75
Nucleus 13C
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
Cl
OMe

S19


Solvent CD2Cl2
MHz 400
Nucleus 1H
2.03
3.01
3.00
3.35
1.01
1.01
1.18
1.16
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


208.6
168.1
138.5
129.2
128.9
126.9
54.2
48.4
44.1
42.0
42.0
40.7
36.0
Solvent CDCl3
MHz 101
Nucleus 13C
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)

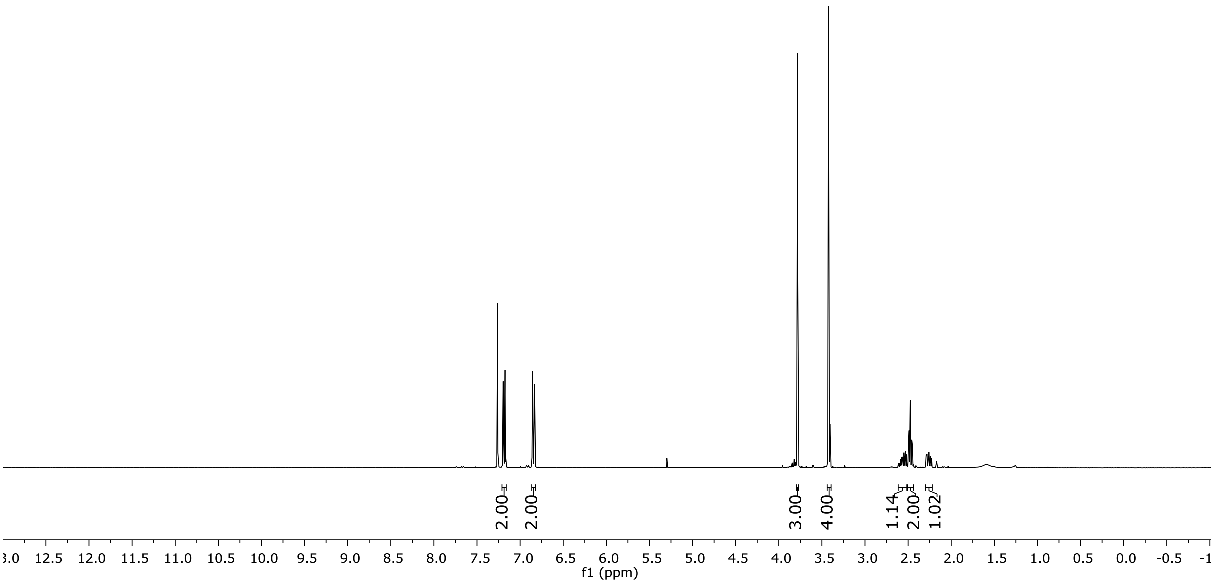


S21

Solvent CDCl3

MHz 400

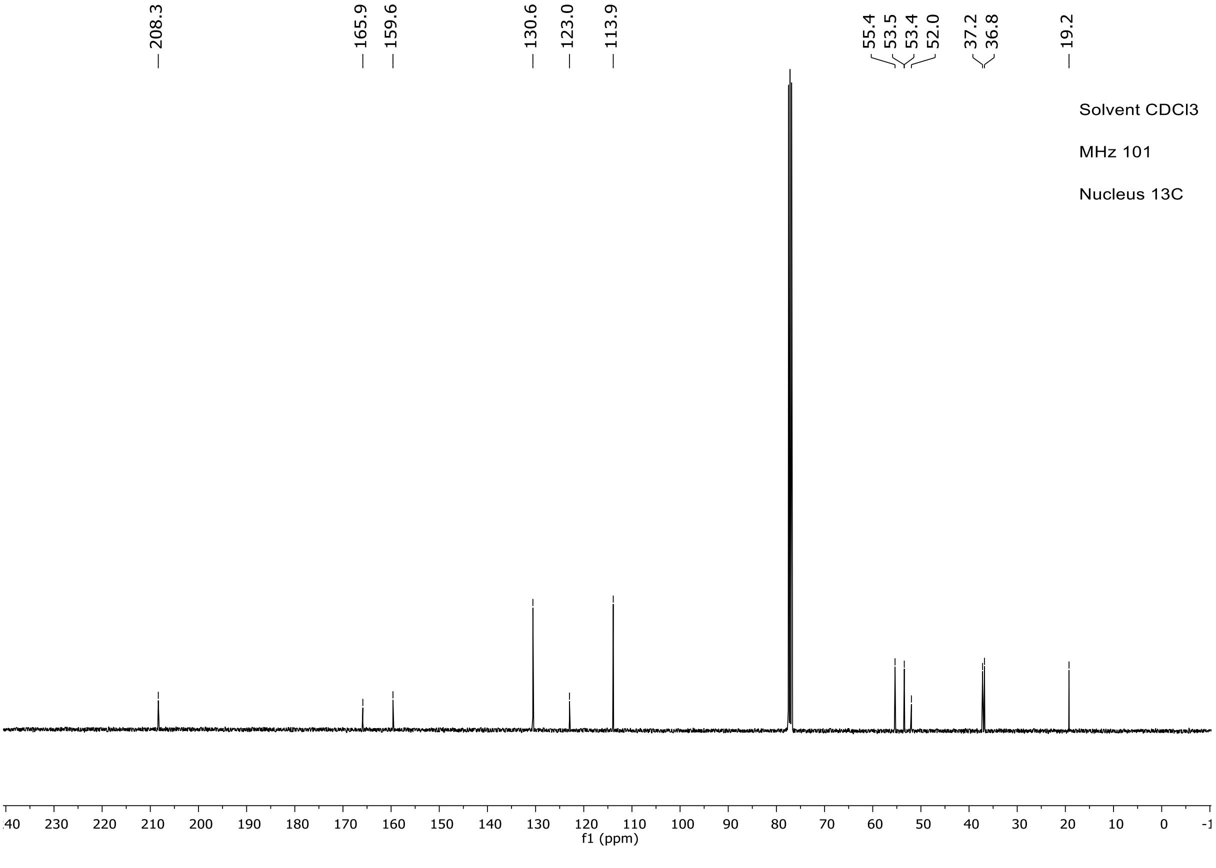
Nucleus 1H

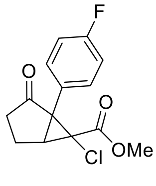


Solvent CDCl3

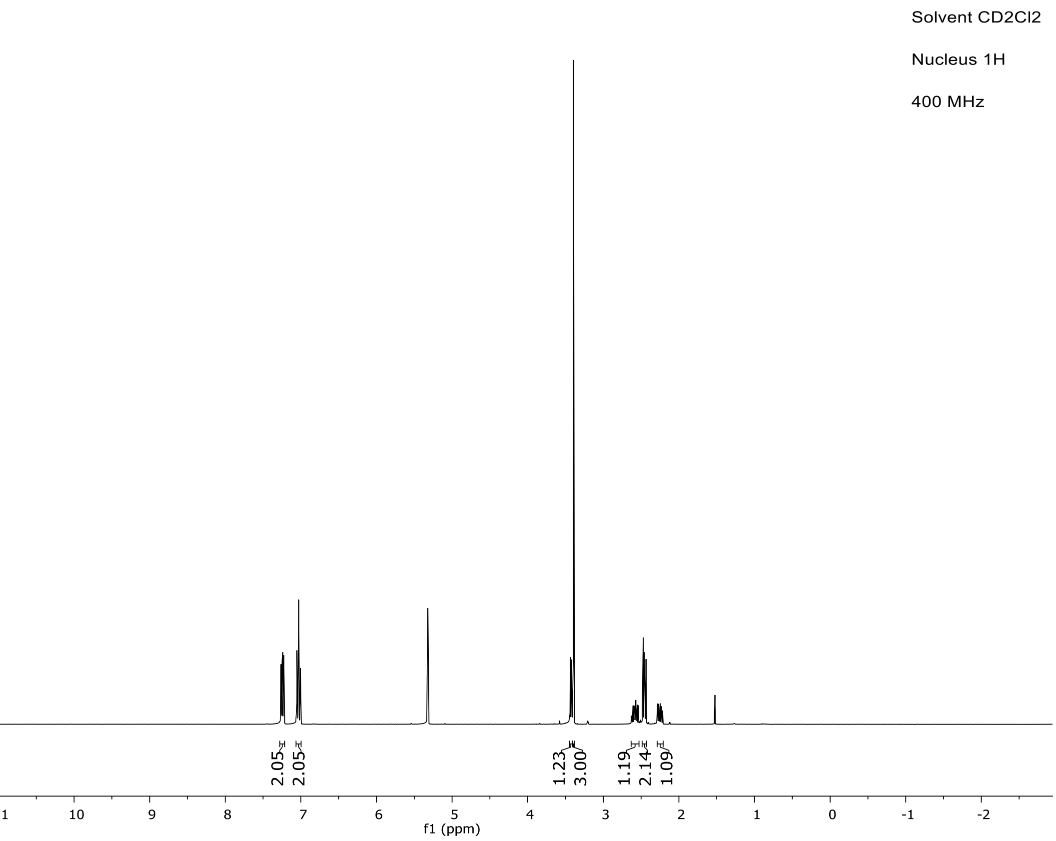
MHz 101

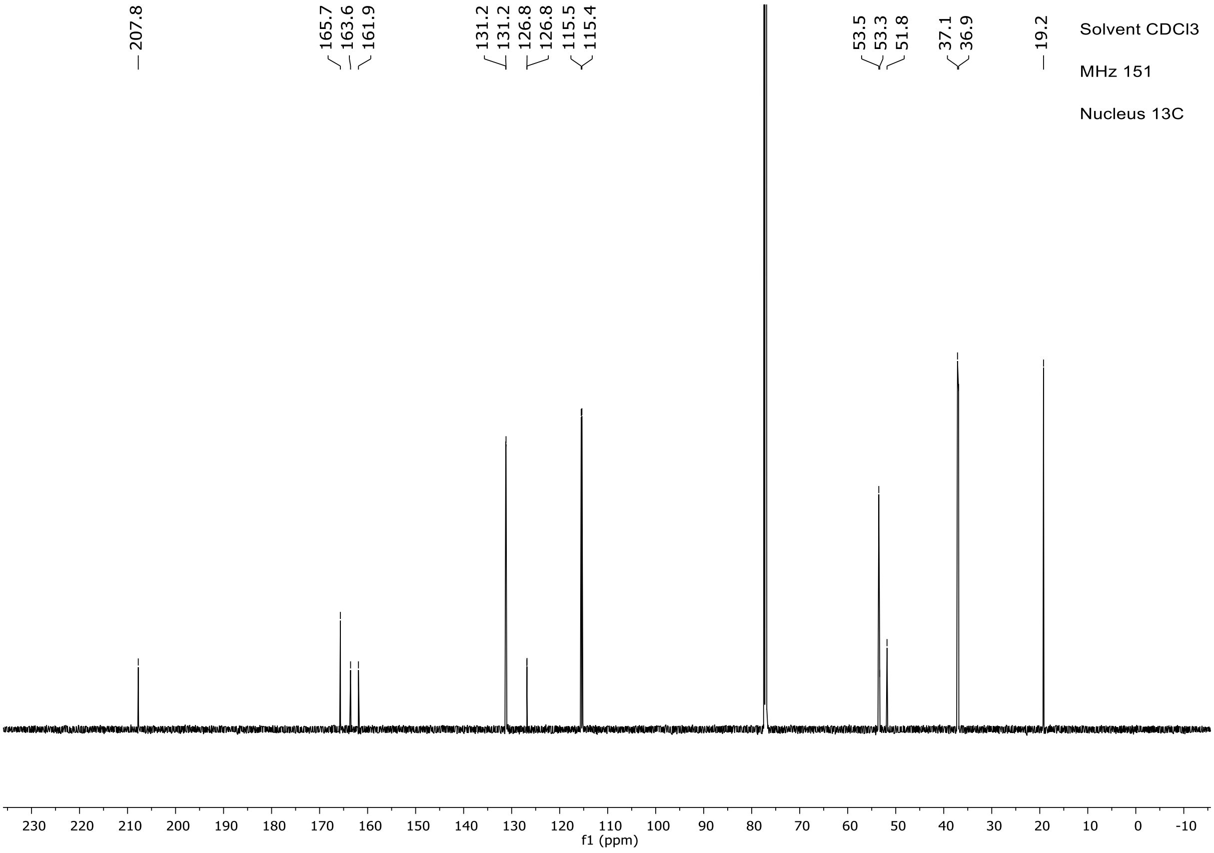
Nucleus 13C

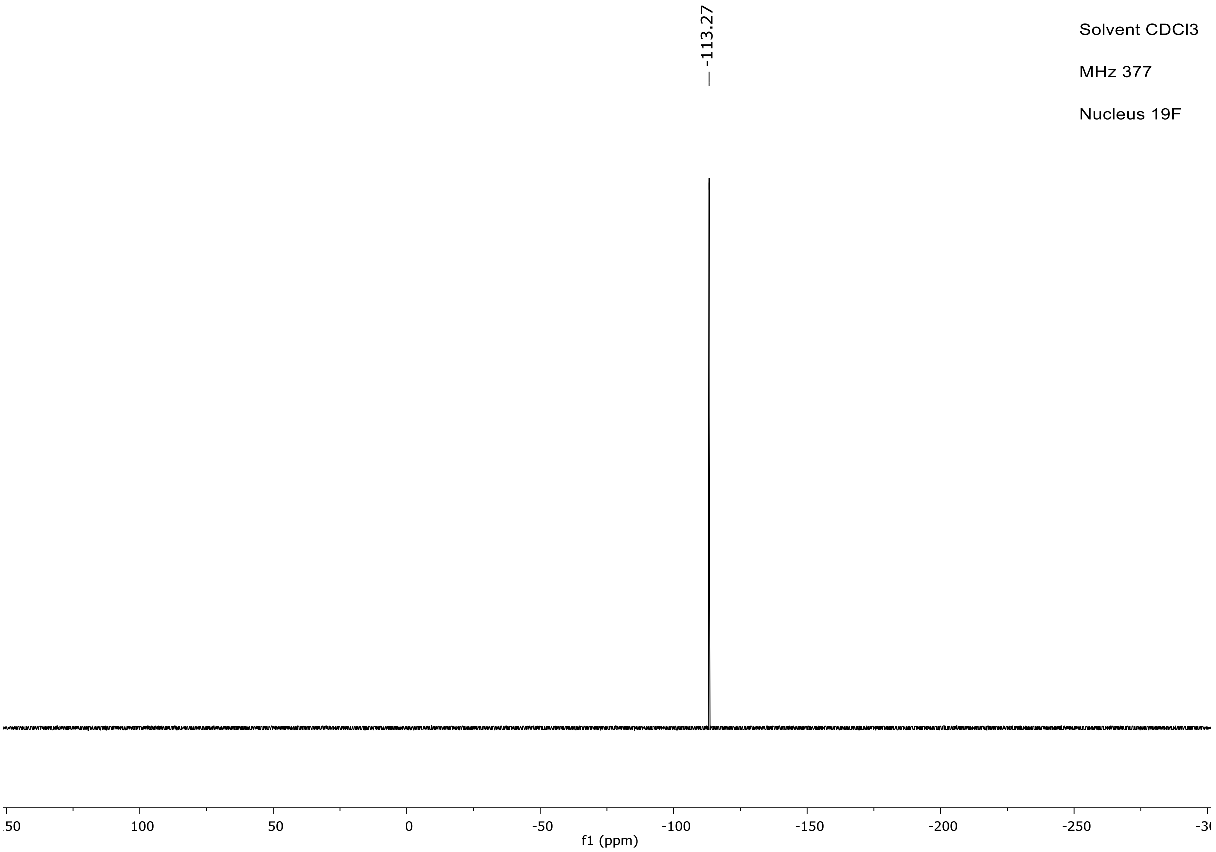


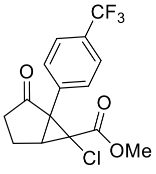


S23


Solvent CD2Cl2
Nucleus 1H
400 MHz
2.05
2.05
1.23
3.00
1.19
2.14
1.09
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


207.8
165.7
163.6
161.9
131.2
131.2
126.8
126.8
115.5
115.4
53.5
53.3
51.8
37.1
36.9
19.2
Solvent CDCl3
MHz 151
Nucleus 13C
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)


-113.27
Solvent CDCl3
MHz 377
Nucleus 19F
.50
100
50
0
-50
-100
-150
-200
-250
-3(
f1 (ppm)

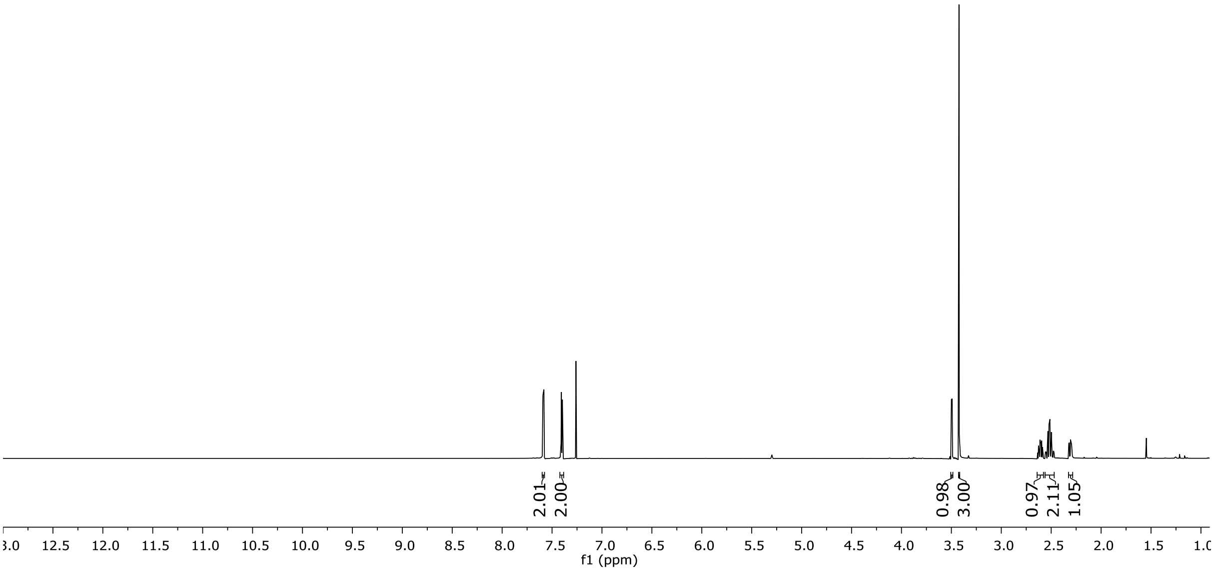


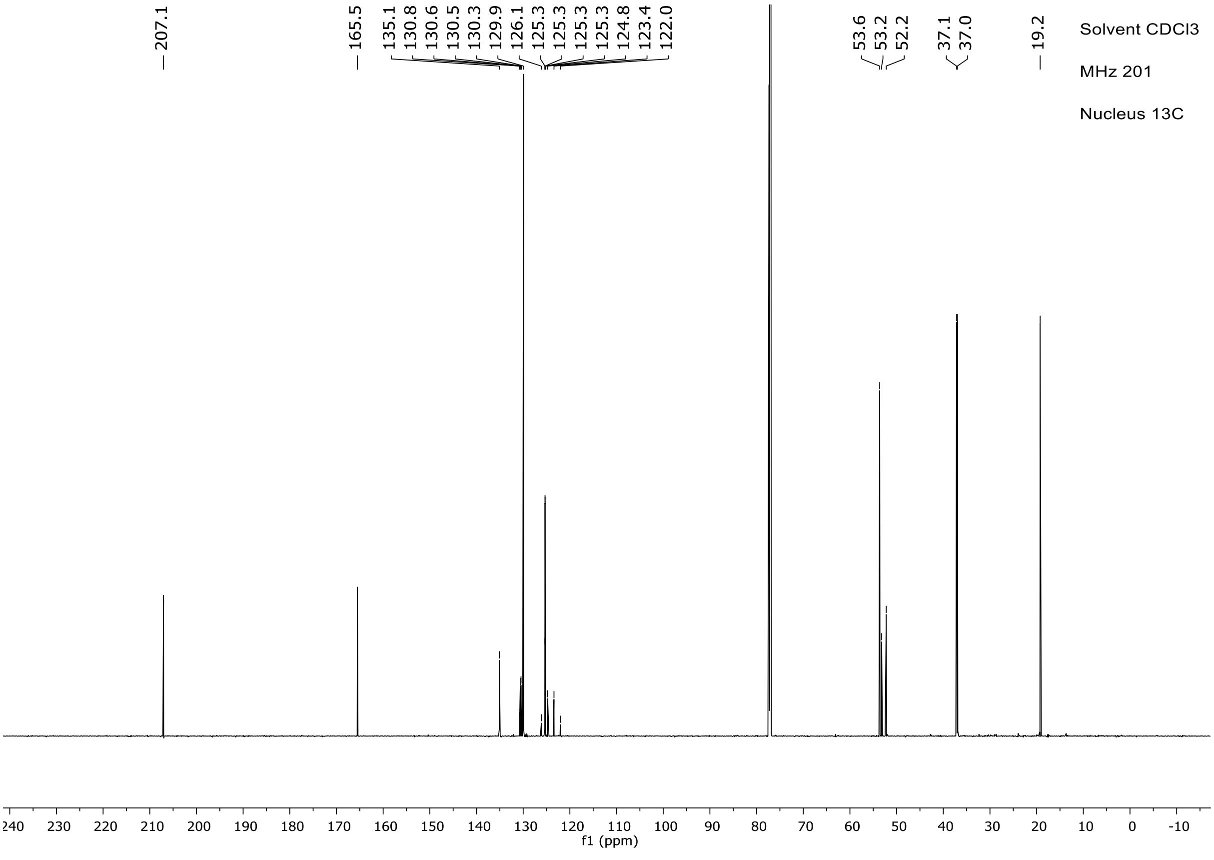
S25

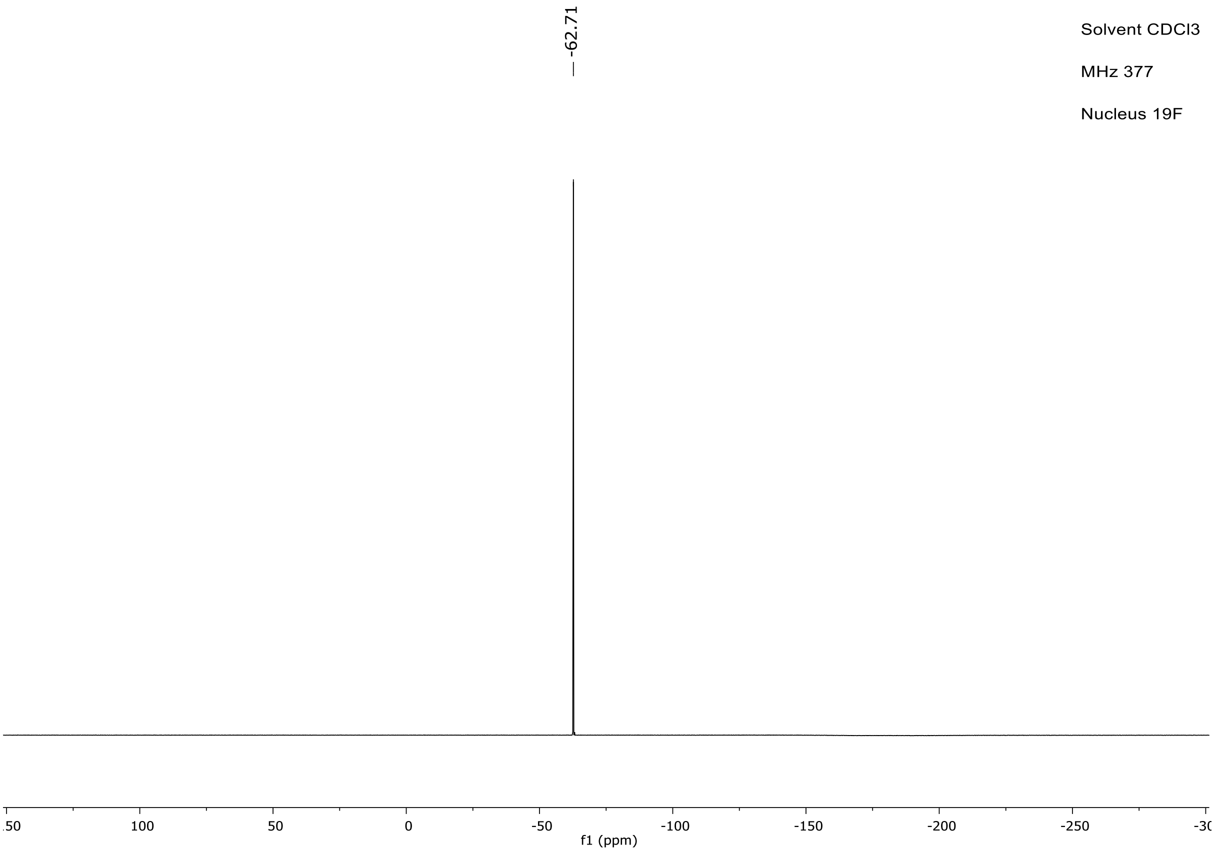
Solvent CDCl3

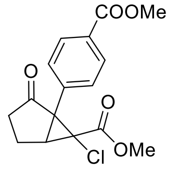
MHz 800

Nucleus 1H

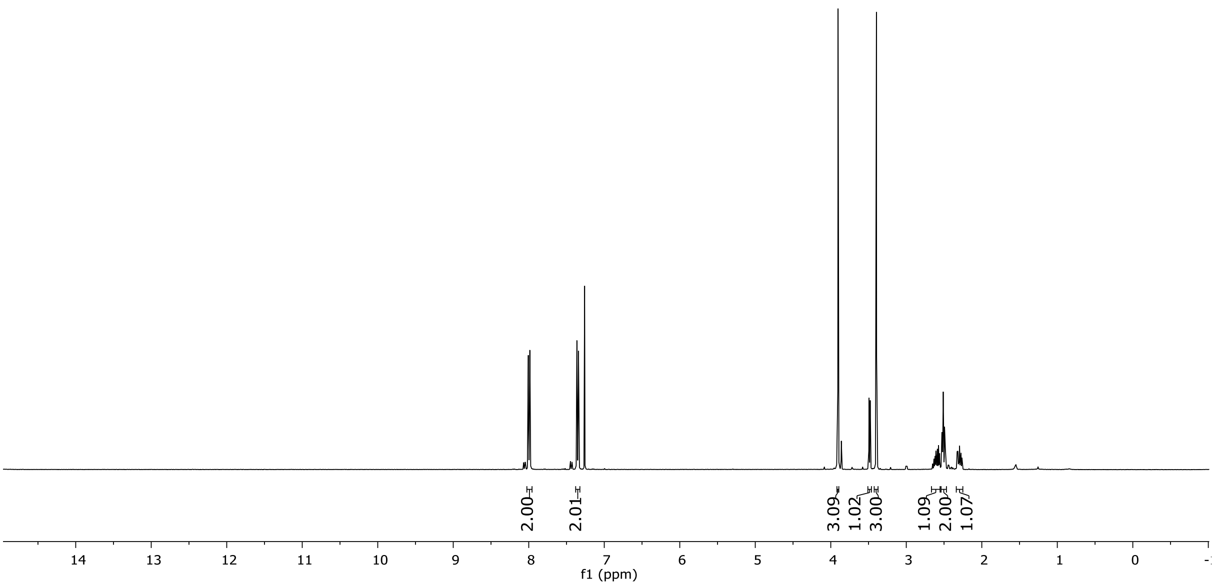


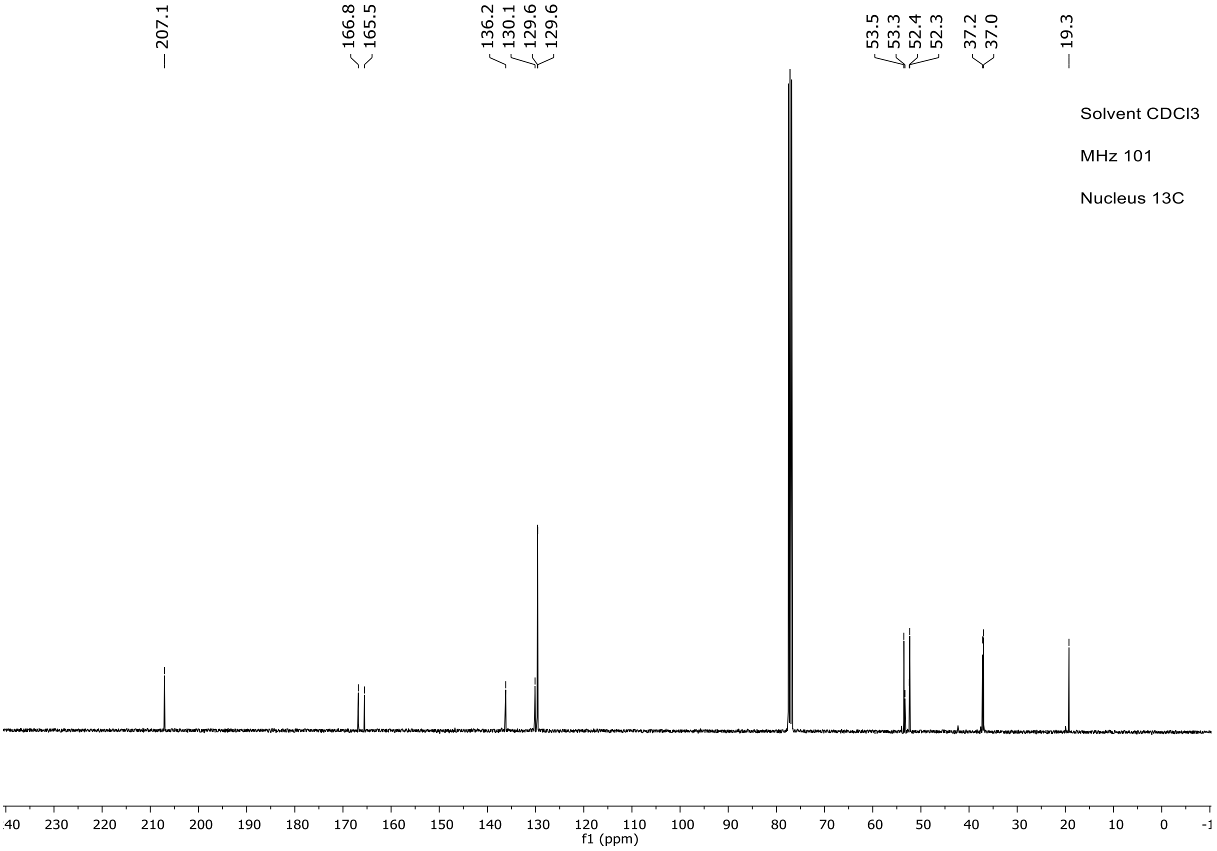


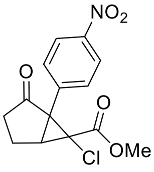

-62.71
Solvent CDCl3
MHz 377
Nucleus 19F
50
100
50
0
-50
-100
-150
-200
-250
-3
f1 (ppm)


COOMe
O
O
Cl
OMe

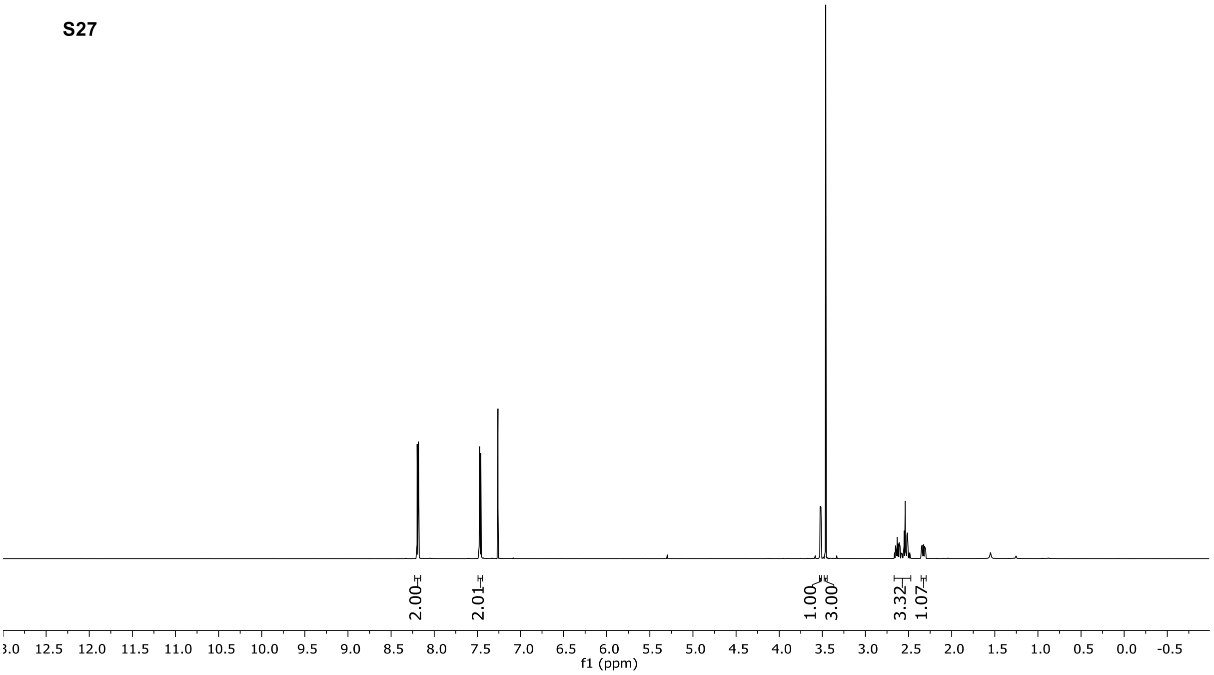
S26

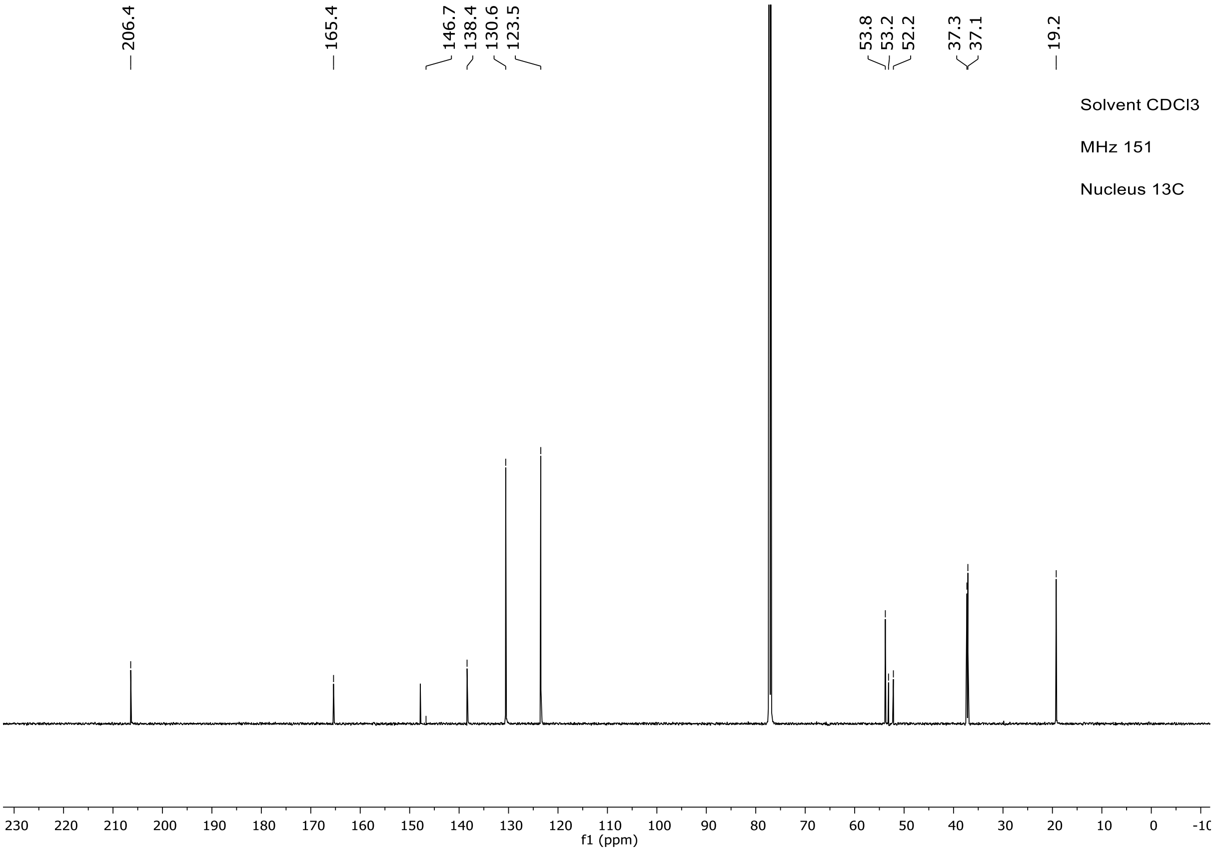

Solvent CDCl3
MHz 400
Nucleus 1H
2.00
2.01
3.09
1.02
3.00
1.09
2.00
1.07
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

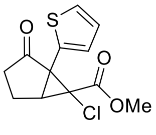

207.1
166.8
165.5
136.2
130.1
129.6
129.6
53.5
53.3
52.4
52.3
37.2
37.0
19.3
Solvent CDCl3
MHz 101
Nucleus 13C
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


NO2
O
O
Cl
OMe

S27


Solvent CDCl3
MHz 599
Nucleus 1H
2.00
2.01
1.00
3.00
3.32
1.07
3.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


206.4
165.4
146.7
138.4
130.6
123.5
53.8
53.2
52.2
37.3
37.1
19.2
Solvent CDCl3
MHz 151
Nucleus 13C
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)

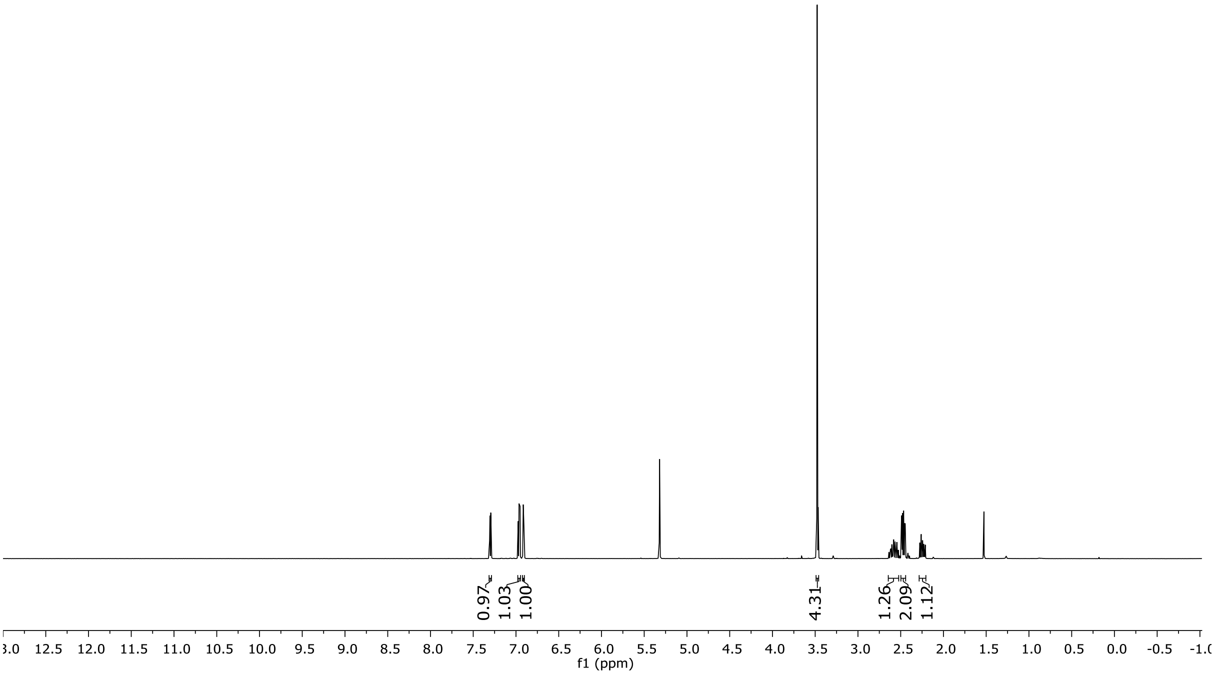


S32

Solvent CD2Cl2

Mhz 400

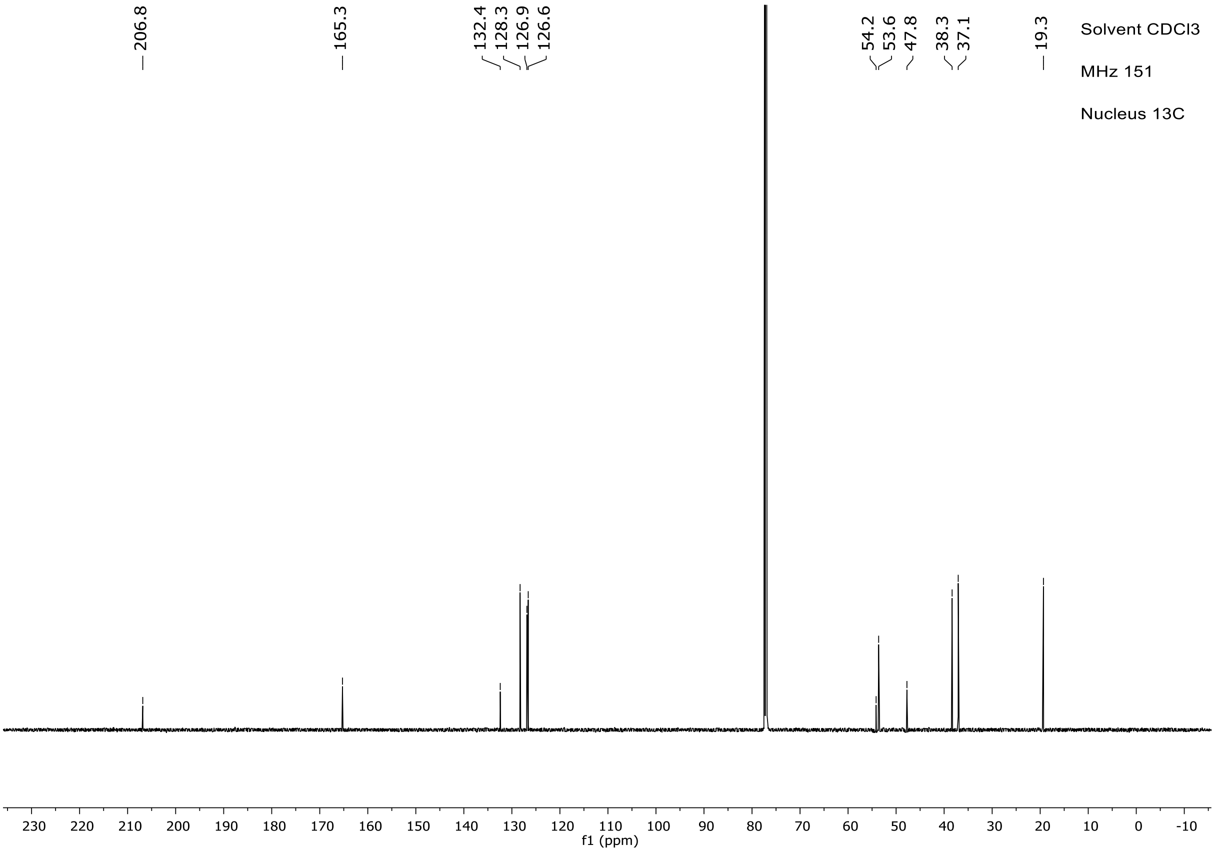
Nucleus 1H

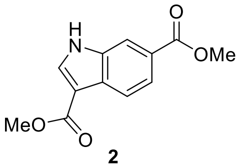


Solvent CDCl3

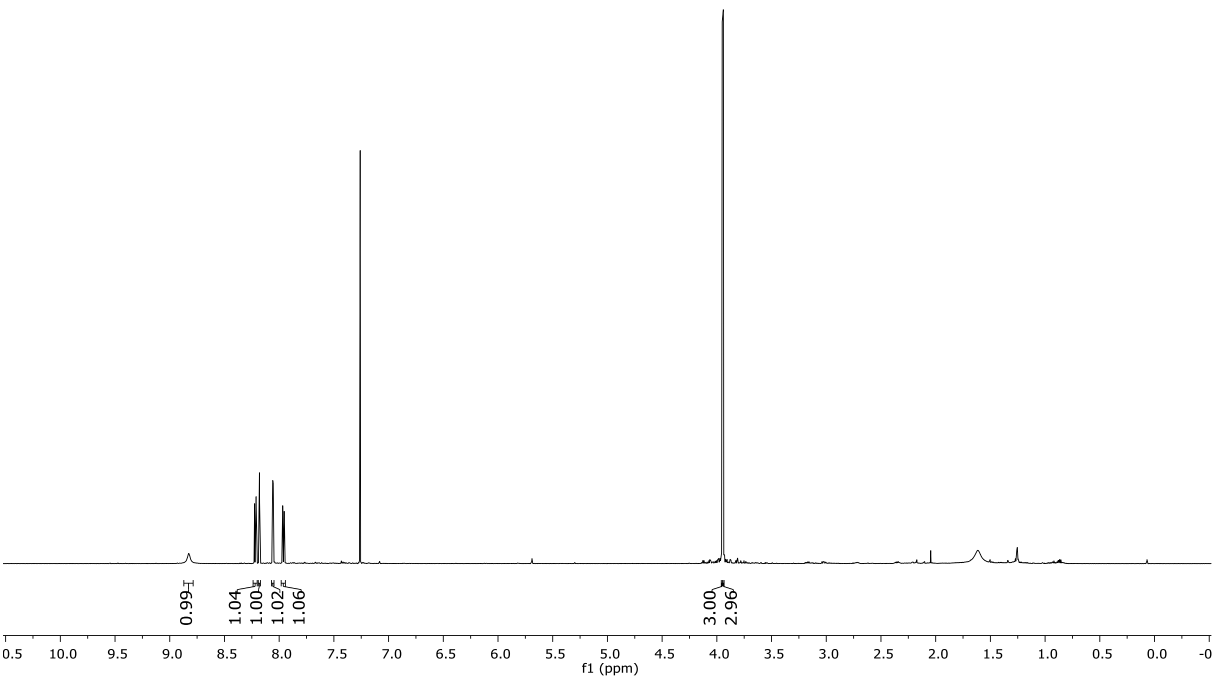
MHz 151

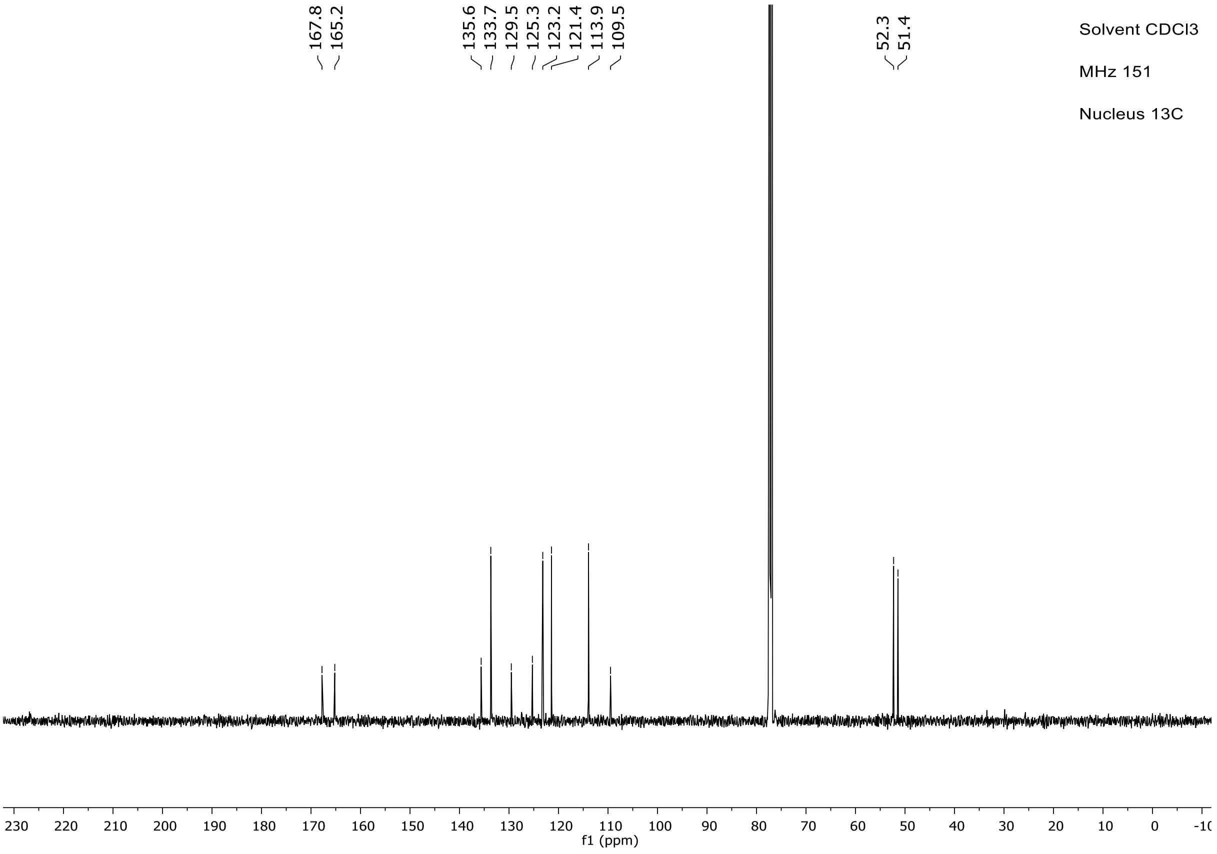
Nucleus 13C

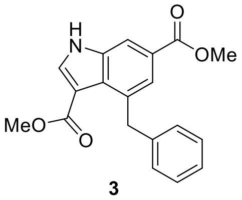




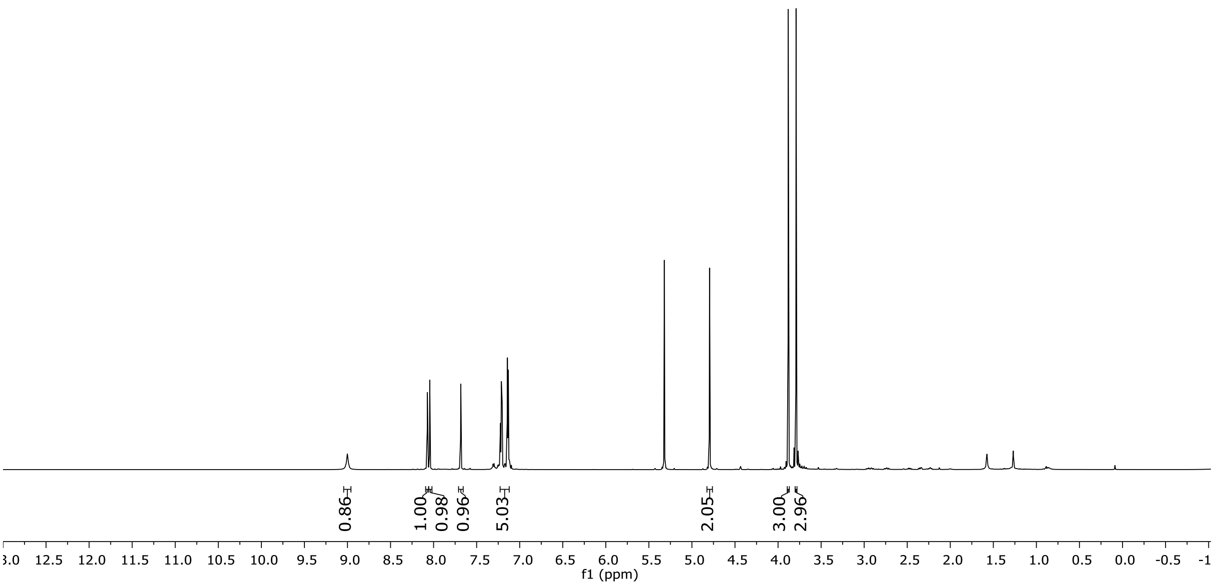
2

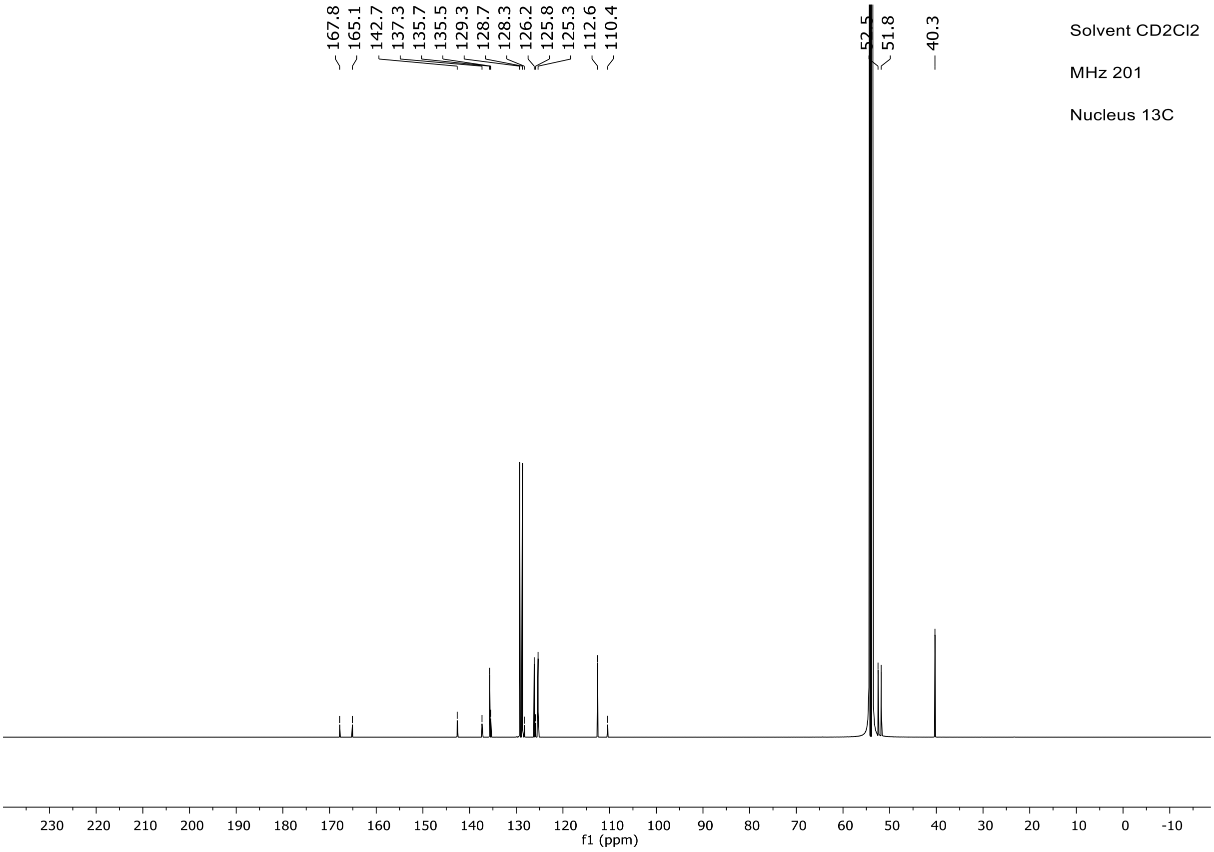

Solvent CDCl3
MHz 599
Nucleus 1H
0.99
1.04
1.00
1.02
1.06
3.00
2.96
0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

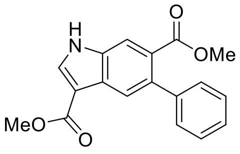

167.8
165.2
135.6
133.7
129.5
125.3
123.2
121.4
113.9
109.5
52.3
51.4
Solvent CDCl3
MHz 151
Nucleus 13C
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


H
N
O
OMe
MeO
O

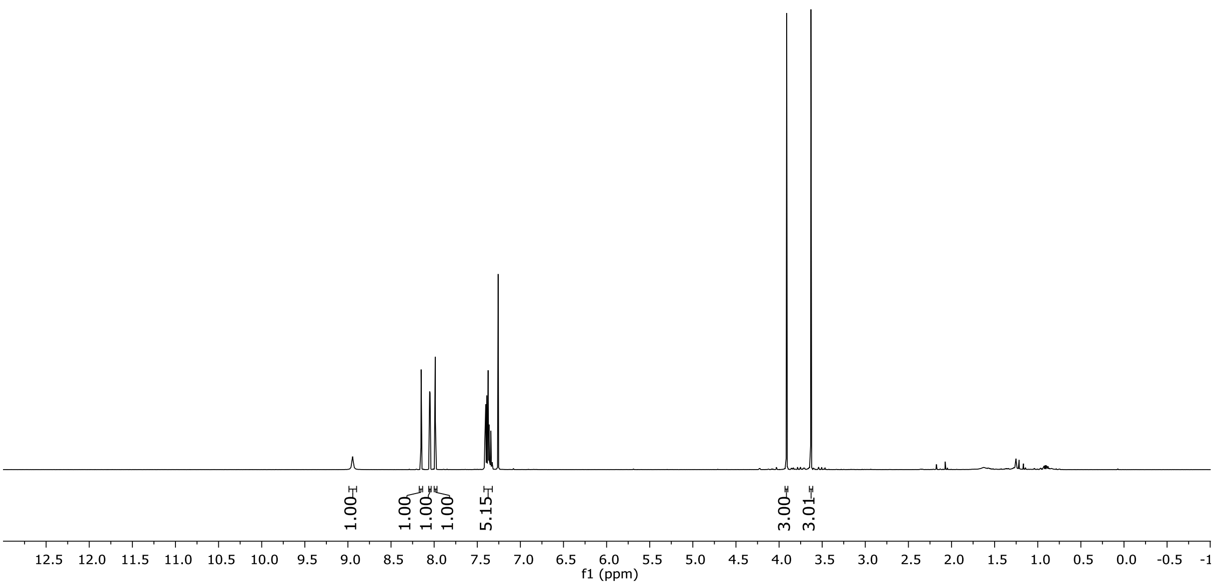
3

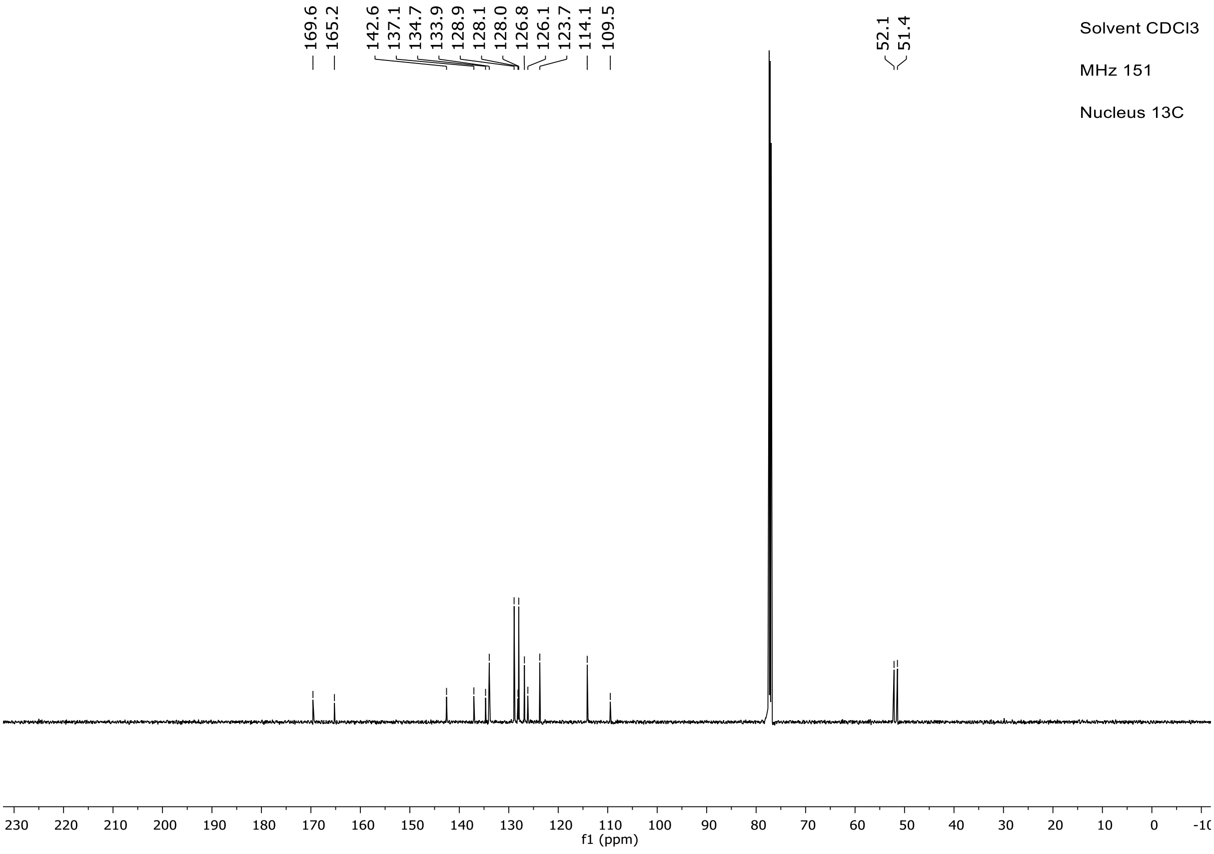

Solvent CD2Cl2
MHz 800
Nucleus 1H
0.86
1.00
0.98
0.96
5.03
2.05
3.00
2.96
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

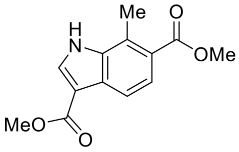

167.8
165.1
142.7
137.3
135.7
135.5
129.3
128.7
128.3
126.2
125.8
125.3
112.6
110.4
52.5
51.8
40.3
Solvent CD2Cl2
MHz 201
Nucleus 13C
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


H
N
O
OMe
MeO
O

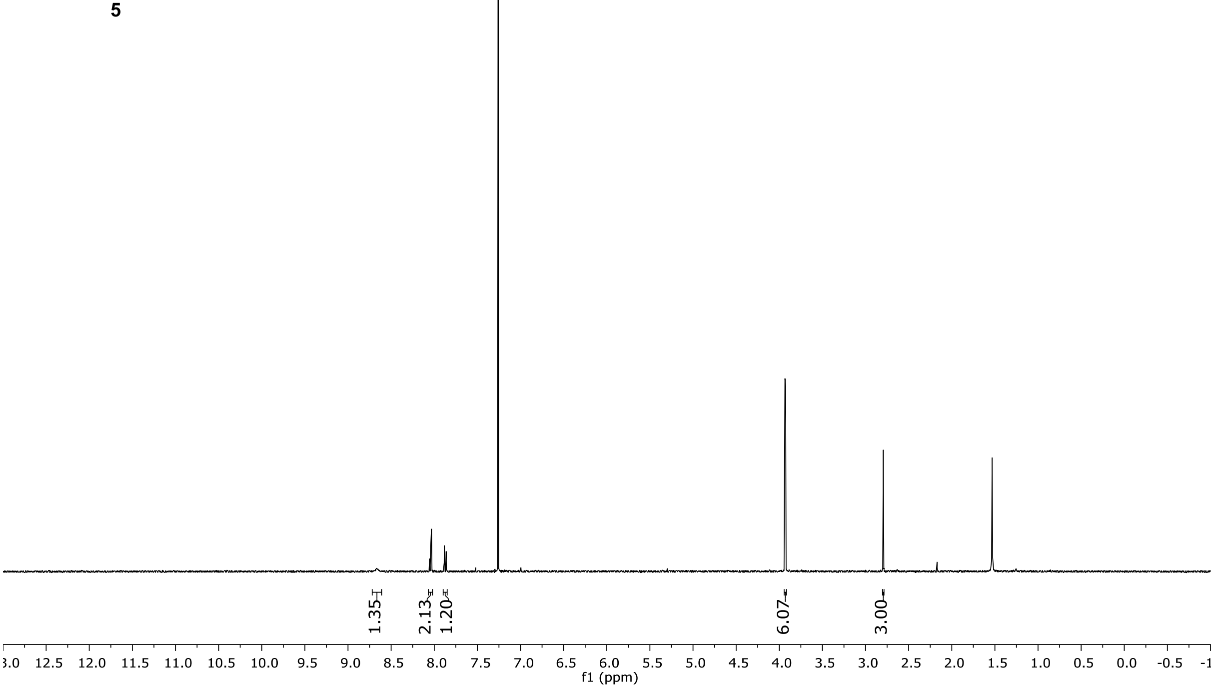
4

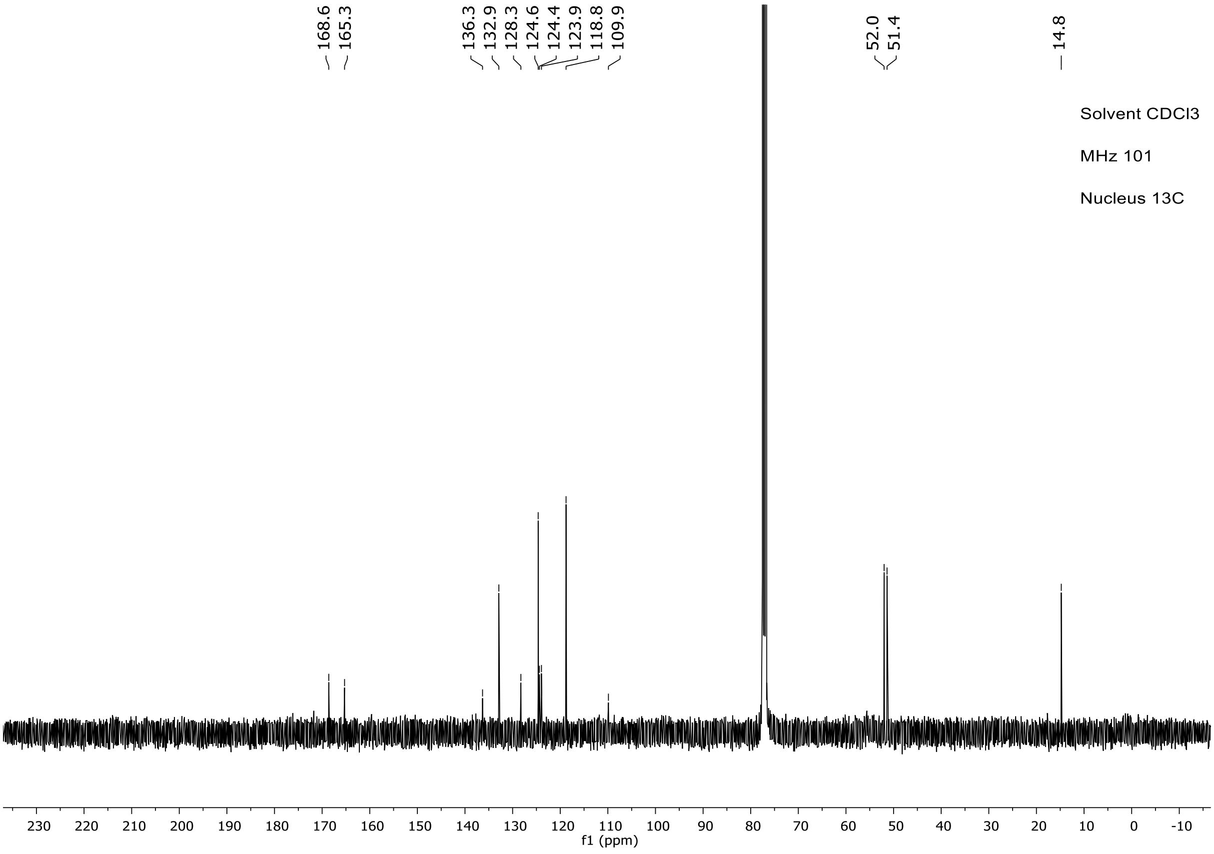

Solvent CDCl3
MHz 599
Nucleus 1H
1.00
1.00
1.00
1.00
5.15
3.00
3.01
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

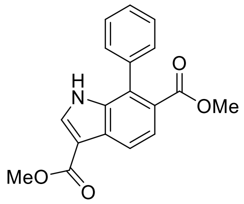

169.6
165.2
142.6
137.1
134.7
133.9
128.9
128.1
128.0
126.8
126.1
123.7
114.1
109.5
52.1
51.4
Solvent CDCl3
MHz 151
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
O
H
N
OMe
MeO
O

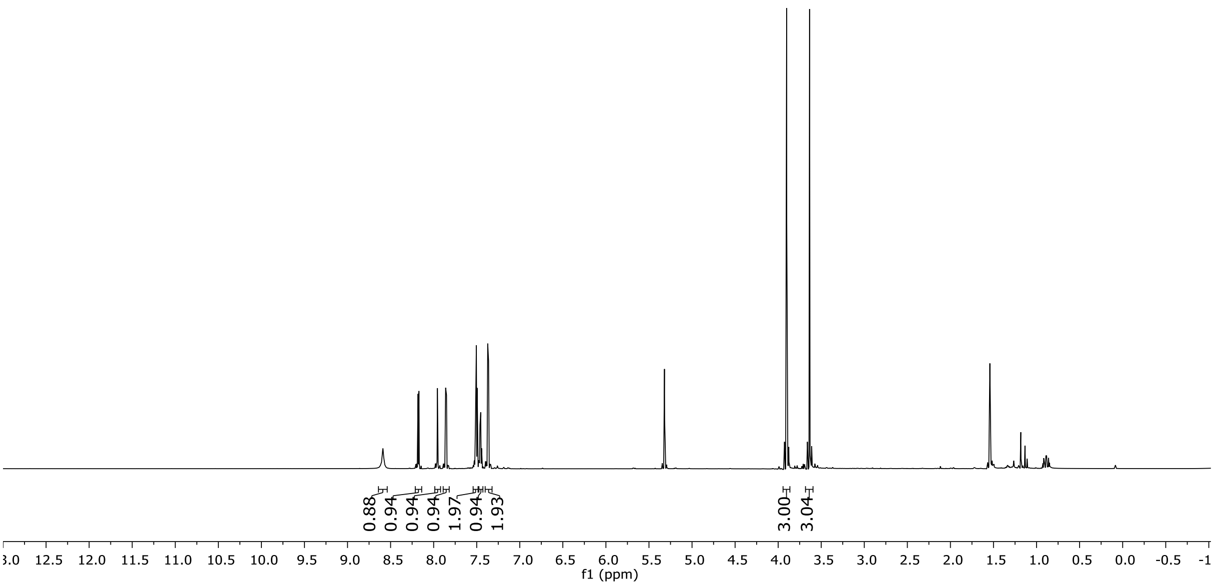
5

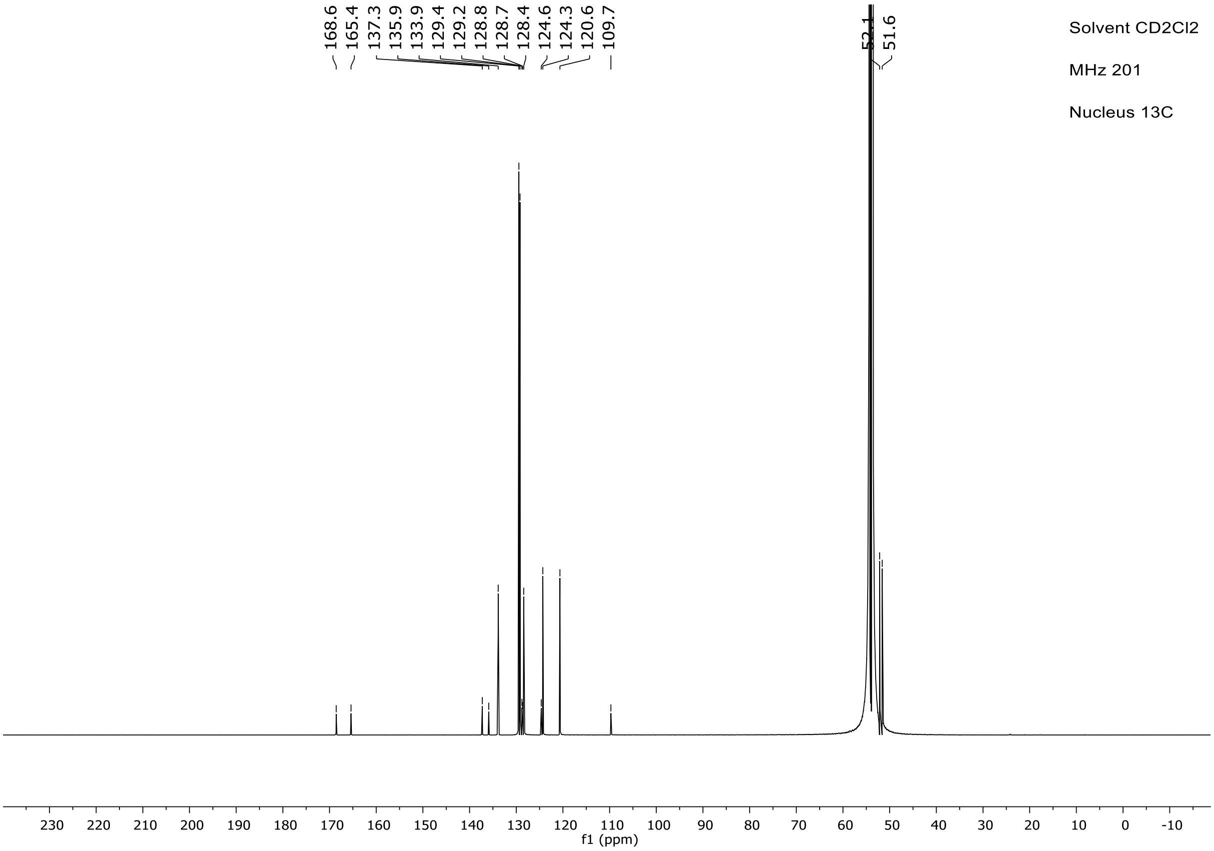

Solvent CDCl3
MHz 400
Nucleus 1H
1.35
2.13
1.20
6.07
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

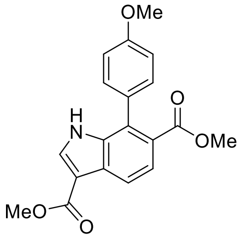

168.6
165.3
136.3
132.9
128.3
124.6
124.4
123.9
118.8
109.9
52.0
51.4
14.8
Solvent CDCl3
MHz 101
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H
N
O
OMe
MeO
O

6


Solvent CD2Cl2
MHz 800
Nucleus 1H
0.88
0.94
0.94
0.94
1.97
0.94
1.93
3.00
3.04
3.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


168.6
165.4
137.3
135.9
133.9
129.4
129.2
128.8
128.7
128.4
124.6
124.3
120.6
109.7
52.1
51.6
Solvent CD2Cl2
MHz 201
Nucleus 13C
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)

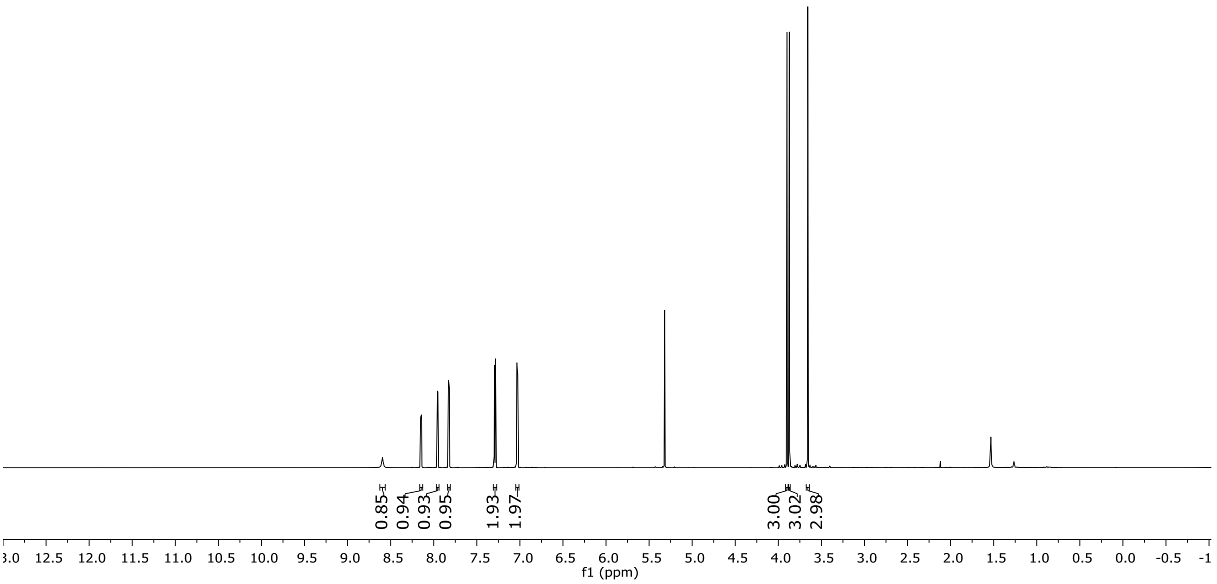


7a

Solvent CD2Cl2

MHz 800

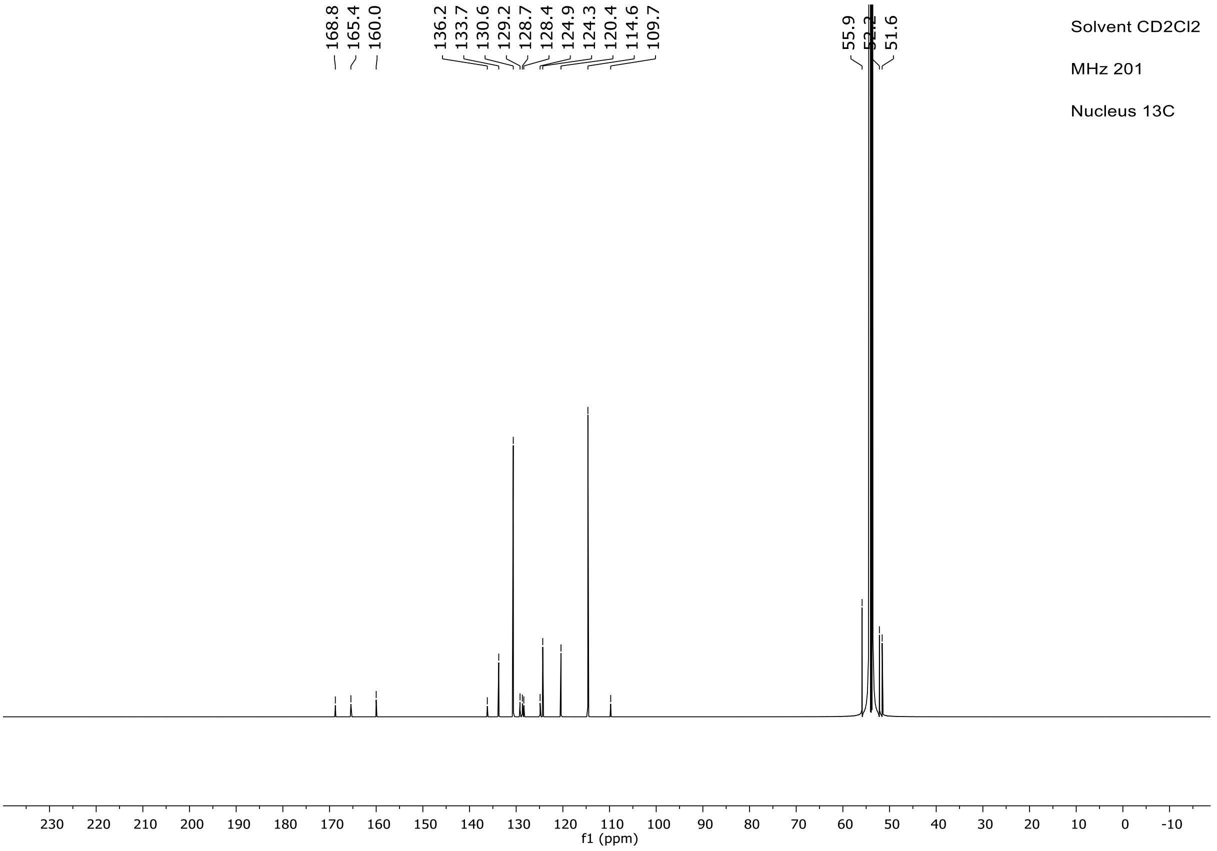
Nucleus 1H

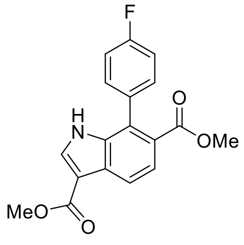


Solvent CD2Cl2

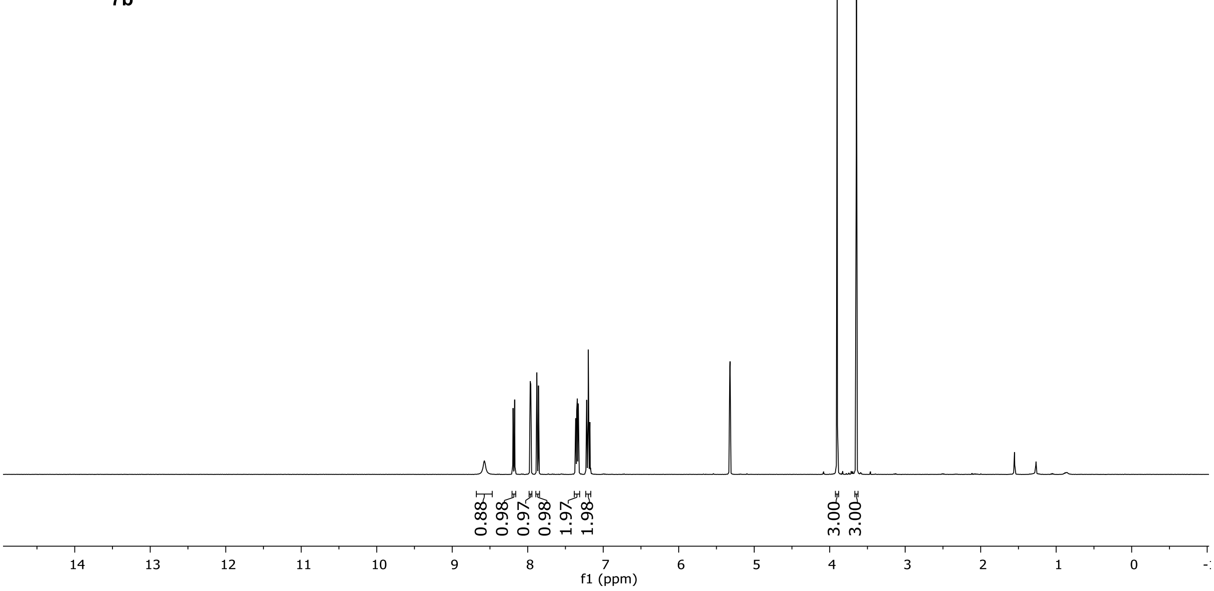
MHz 201

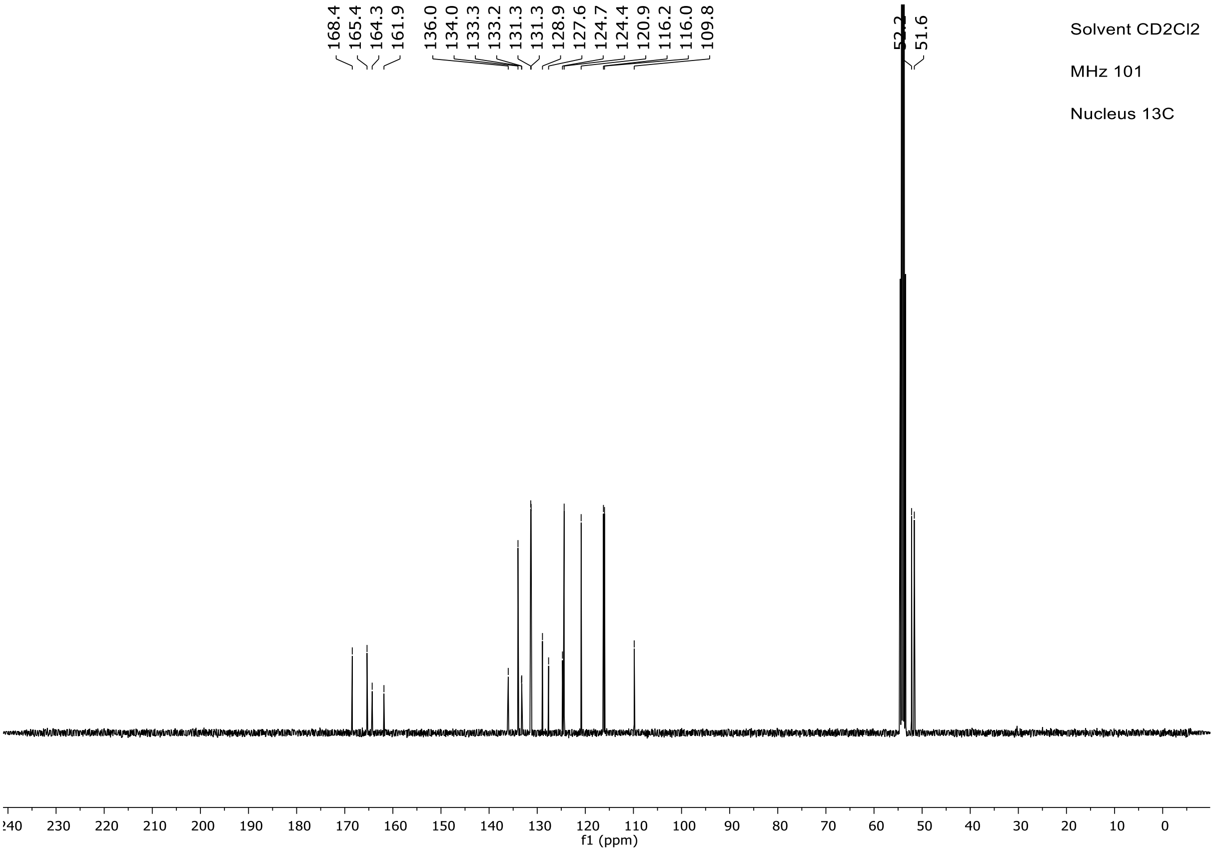
Nucleus 13C

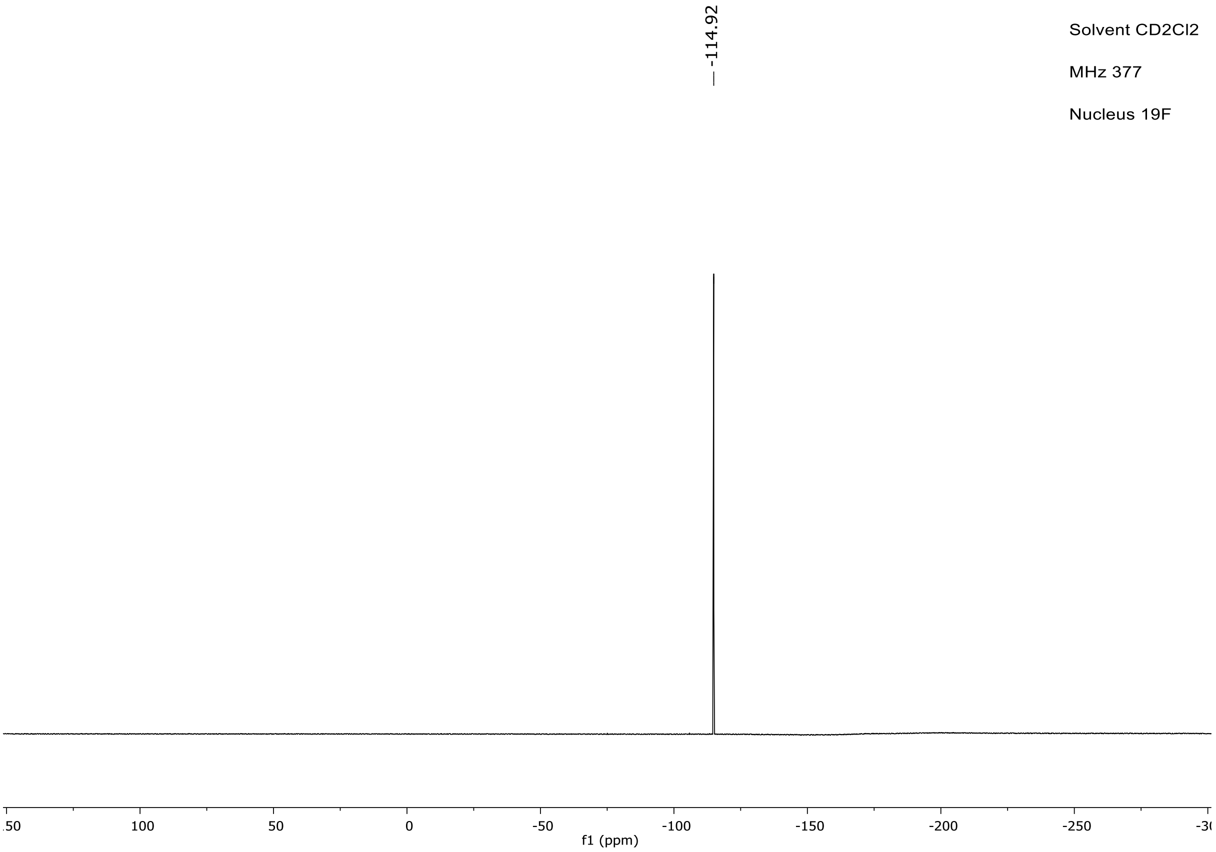


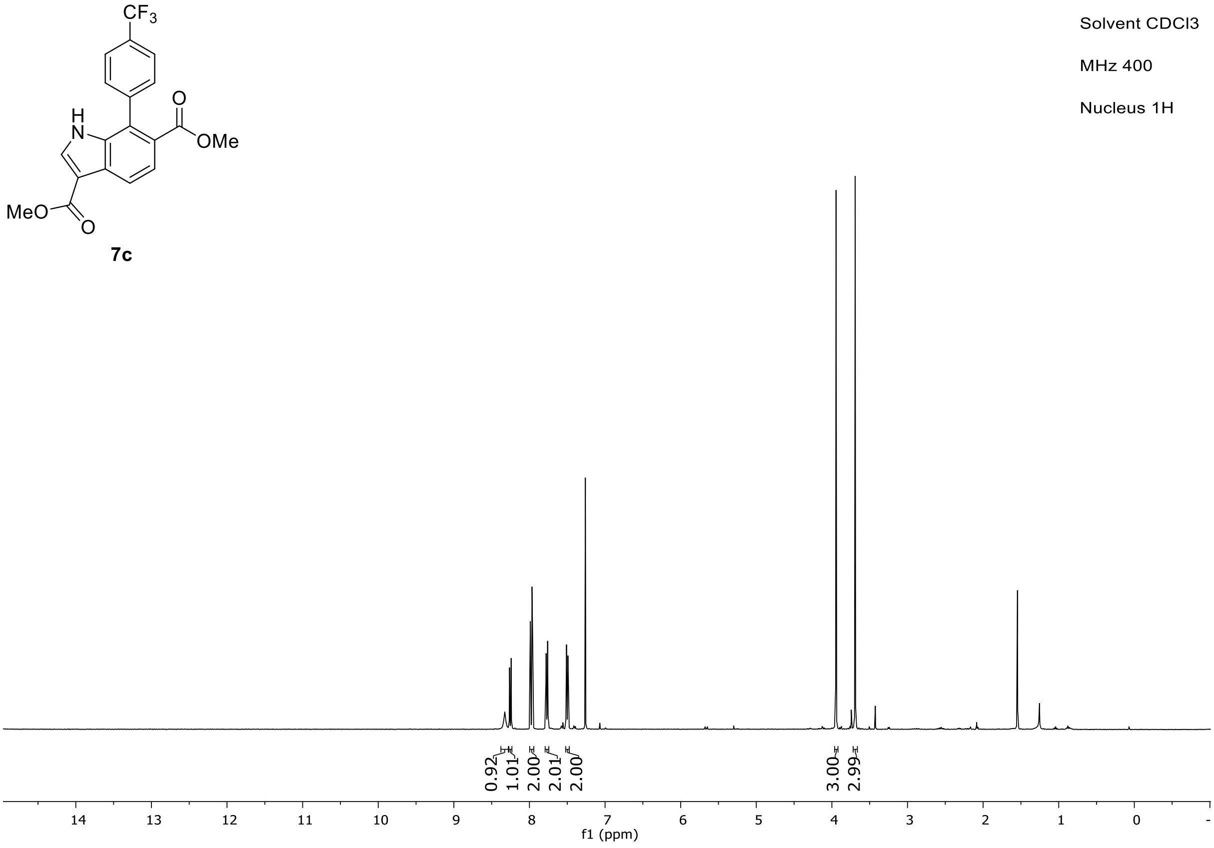

F
H
N
O
OMe
MeO
O

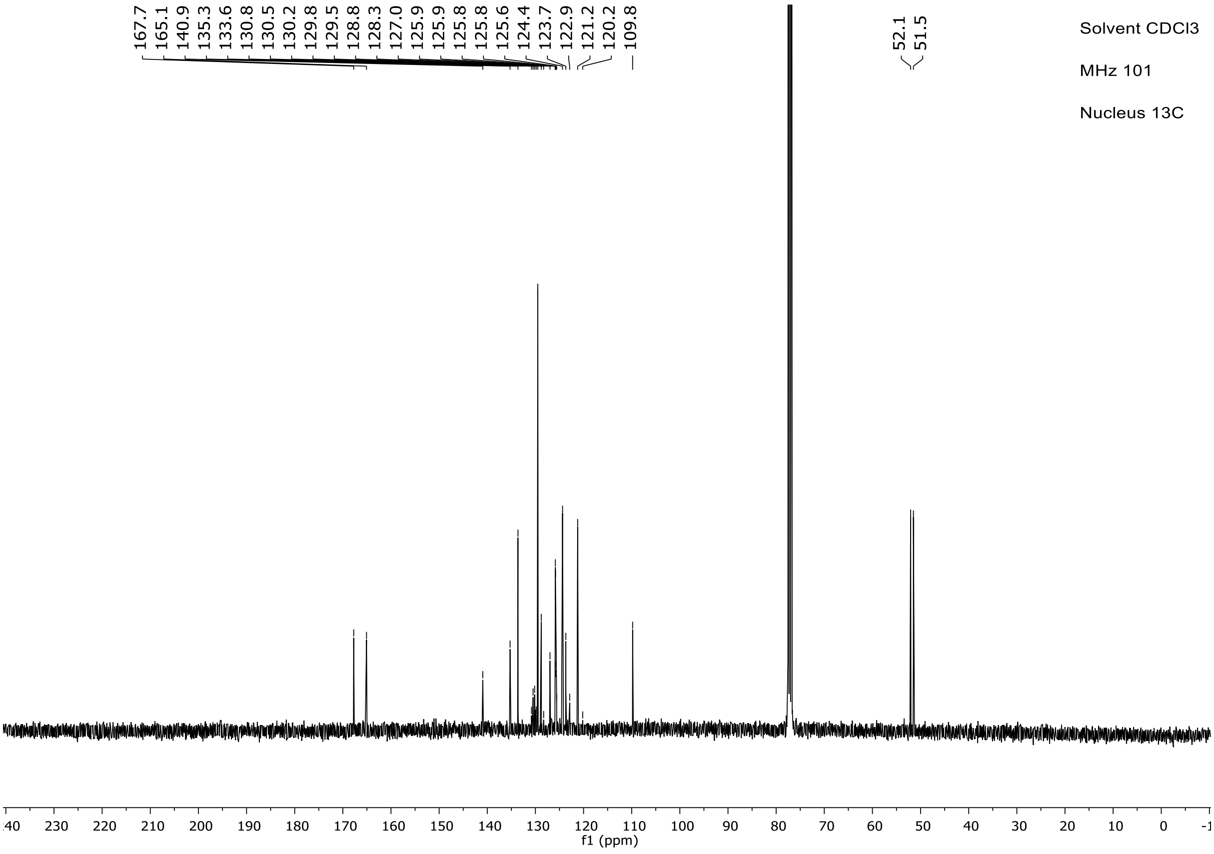
7b

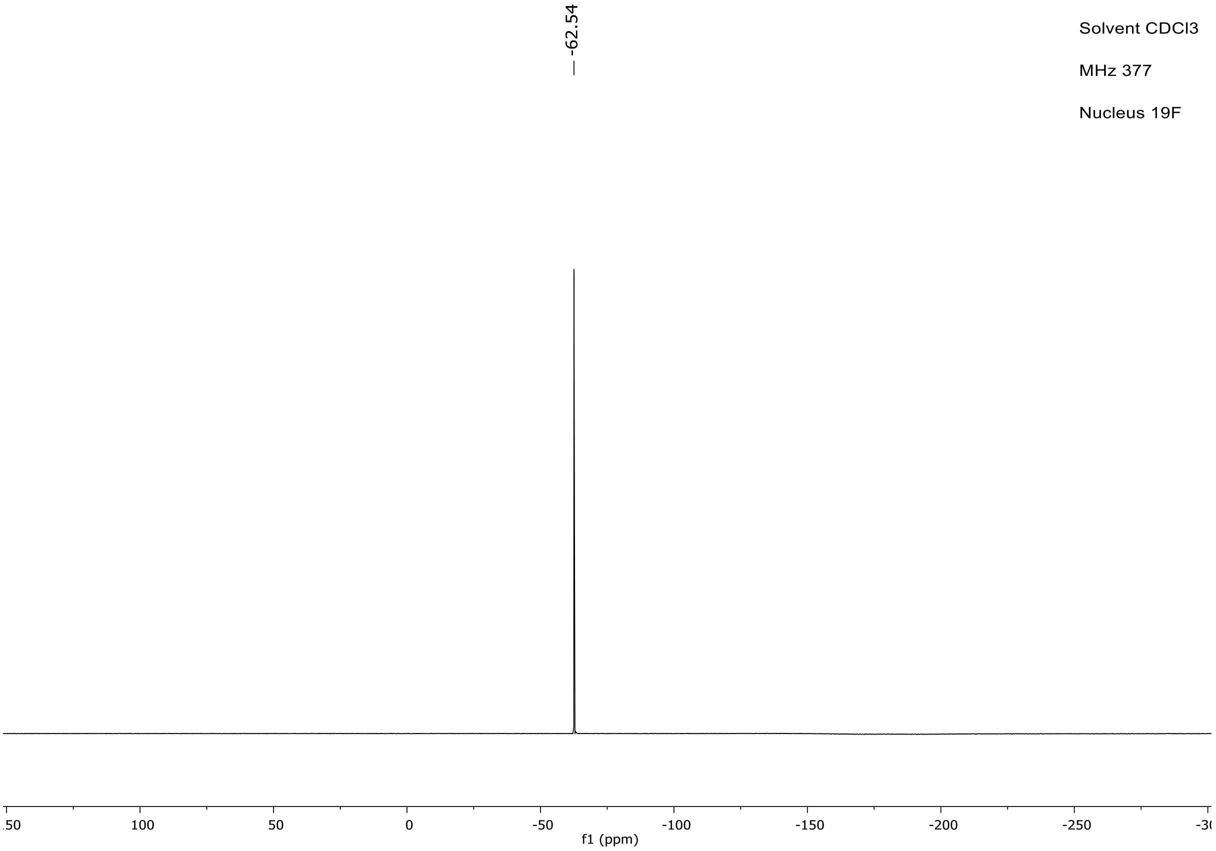

Solvent CD2Cl2
MHz 400
Nucleus 1H
0.88
0.98
0.97
0.98
1.97
1.98
3.00
3.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

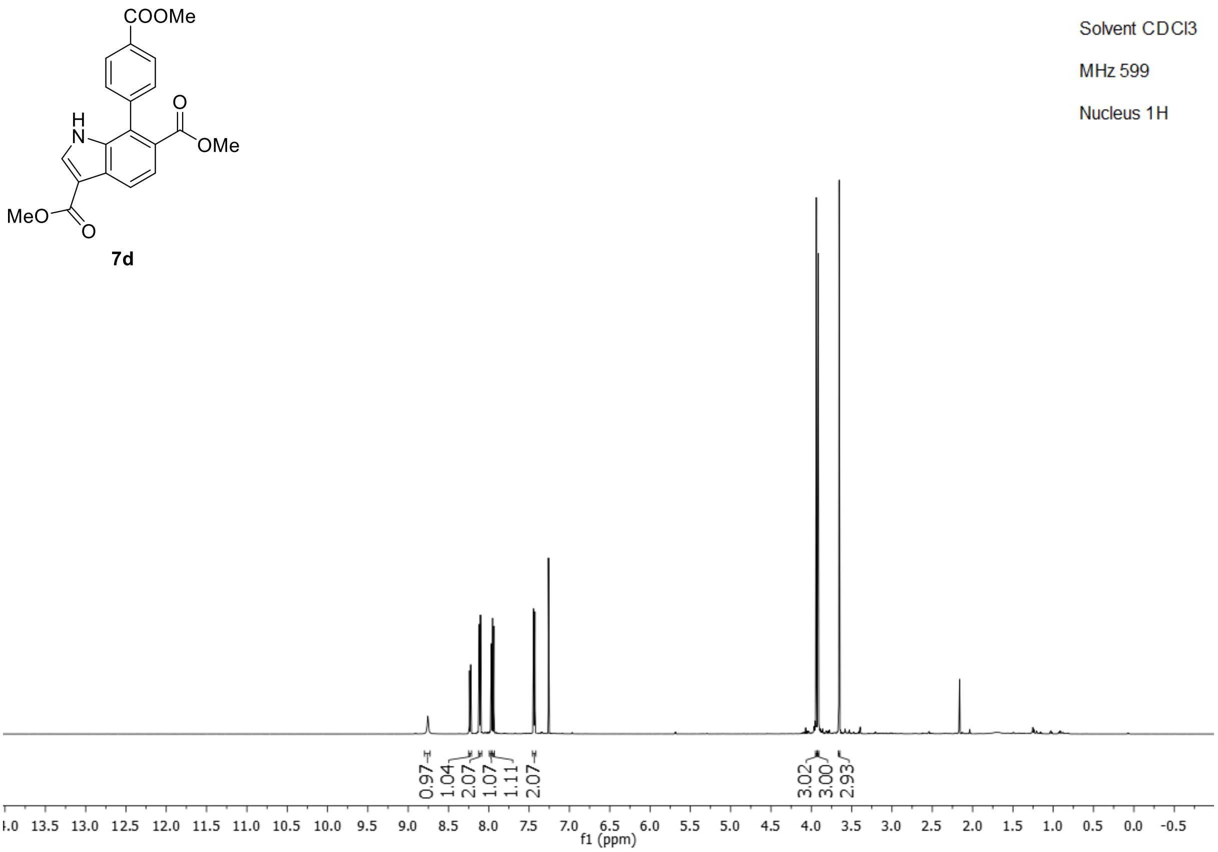

168.4
165.4
164.3
161.9
136.0
134.0
133.3
133.2
131.3
131.3
128.9
127.6
124.7
124.4
120.9
116.2
116.0
109.8
52.2
51.6
Solvent CD2Cl2
MHz 101
Nucleus 13C
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-114.92
Solvent CD2Cl2
MHz 377
Nucleus 19F
50
100
50
0
-50
-100
-150
-200
-250
-3
f1 (ppm)

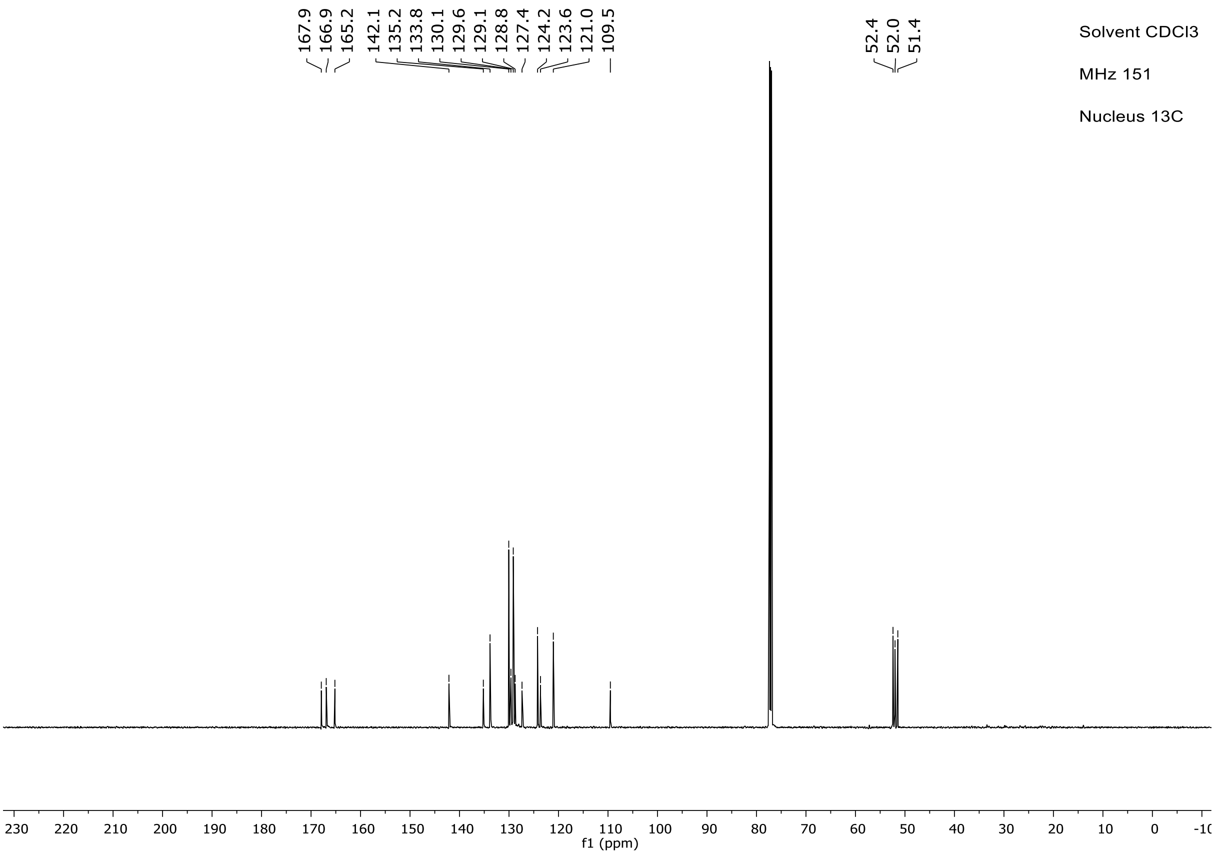

CF3
H
N
O
OMe
MeO
O
7c
Solvent CDCl3
MHz 400
Nucleus 1H
0.92
1.01
2.00
2.01
2.00
3.00
2.99
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

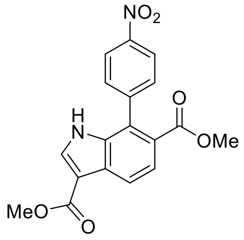

167.7
165.1
140.9
135.3
133.6
130.8
130.5
130.2
129.8
129.5
128.8
128.3
127.0
125.9
125.9
125.8
125.8
125.6
124.4
123.7
122.9
121.2
120.2
109.8
52.1
51.5
Solvent CDCl3
MHz 101
Nucleus 13C
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-62.54
Solvent CDCl3
MHz 377
Nucleus 19F
50
100
50
0
-50
-100
-150
-200
-250
f1 (ppm)

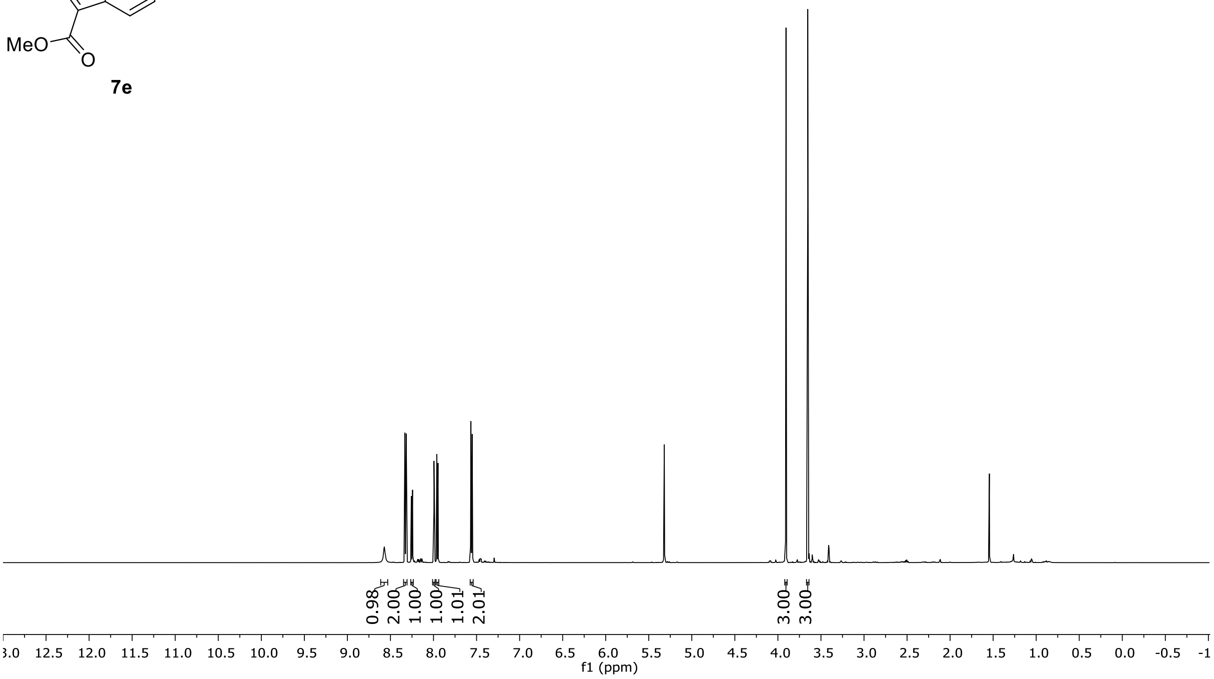

COOMe
H
N
O
OMe
MeO
O
Solvent CDCl3
MHz 599
Nucleus 1H
0.97
1.04
2.07
1.07
1.11
2.07
3.02
3.00
2.93
.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

7d


167.9
166.9
165.2
142.1
135.2
133.8
130.1
129.6
129.1
128.8
127.4
124.2
123.6
121.0
109.5
52.4
52.0
51.4
Solvent CDCl3
MHz 151
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)



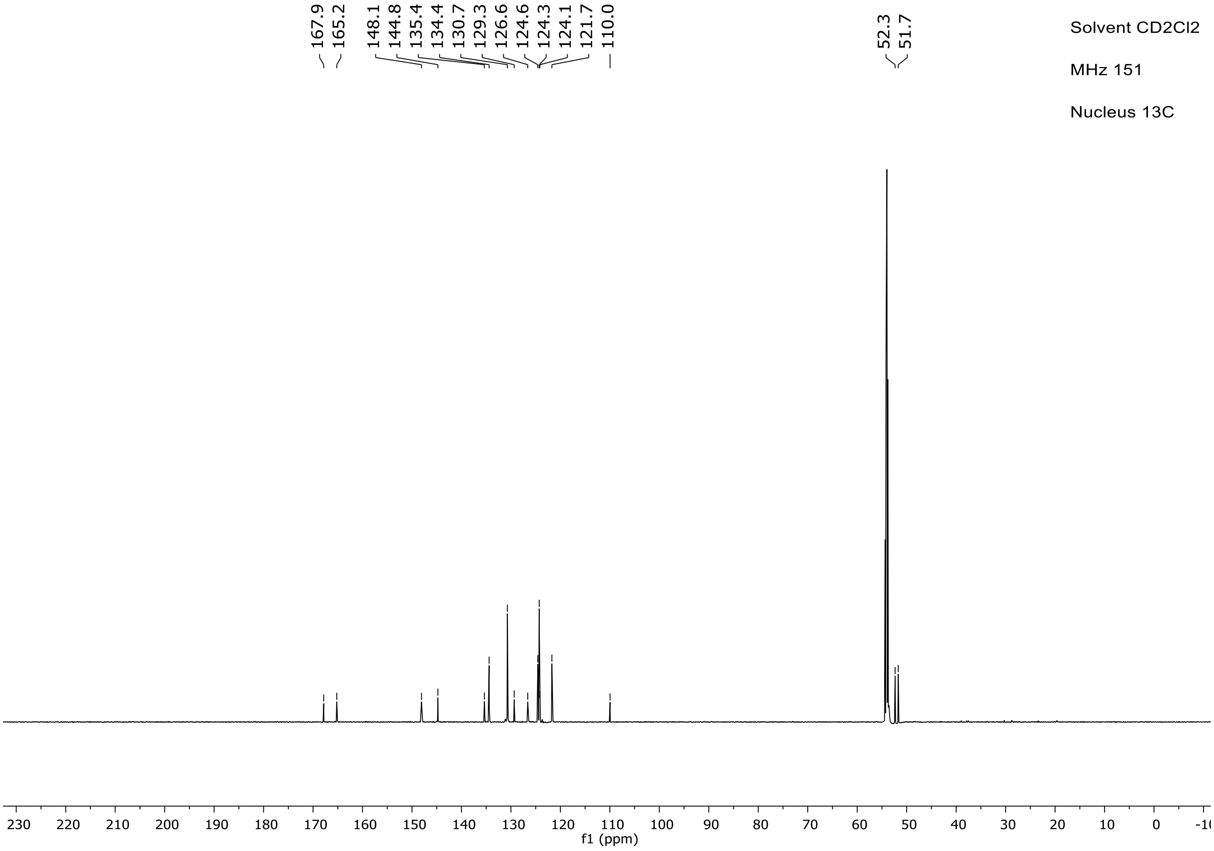
7e



Solvent CD2Cl2

MHz 599

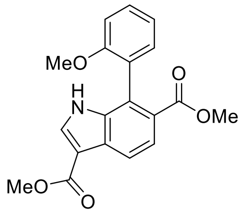
Nucleus 1H



Solvent CD2Cl2

MHz 151

Nucleus 13C

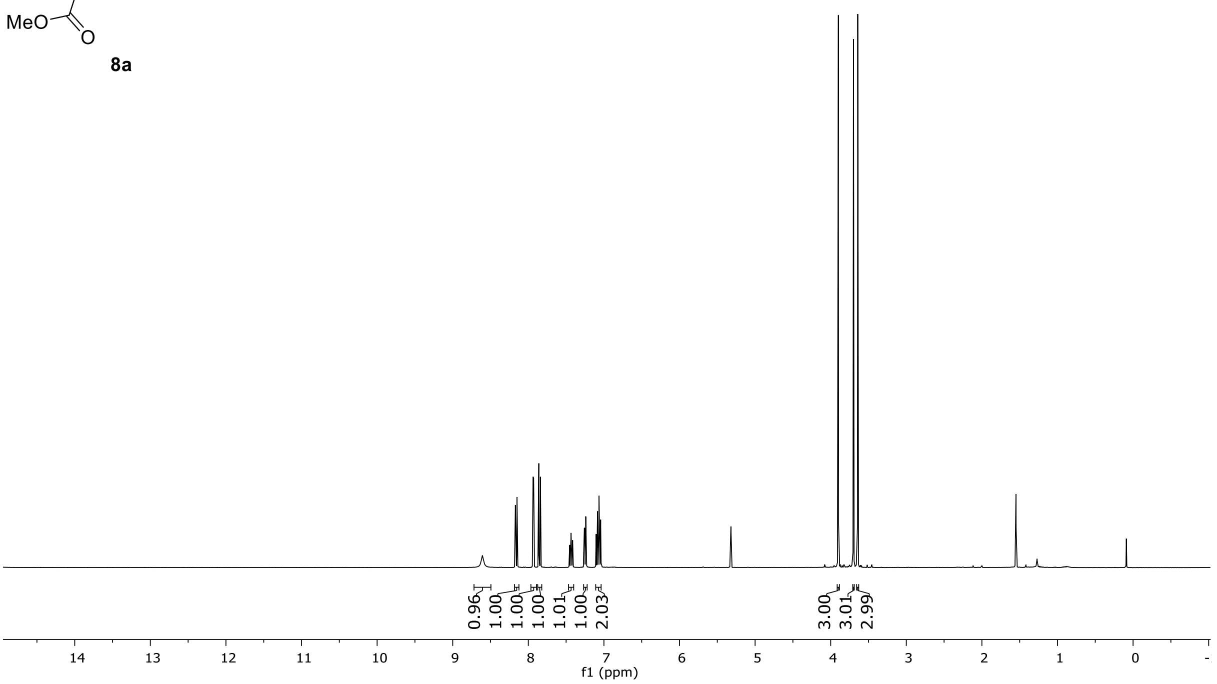


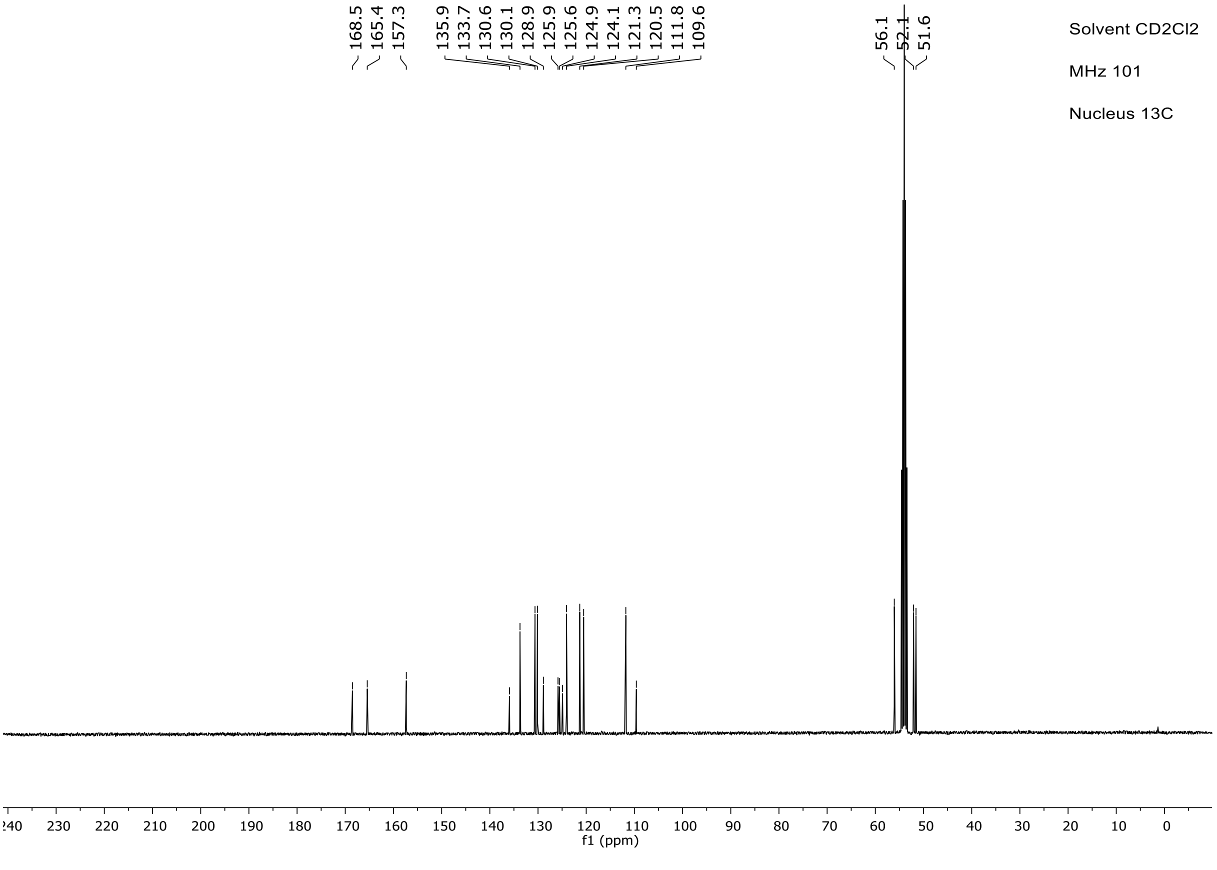
8a

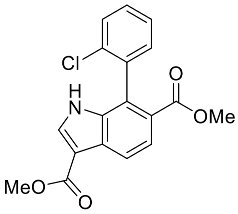
Solvent CD2Cl2

MHz 400

Nucleus 1H

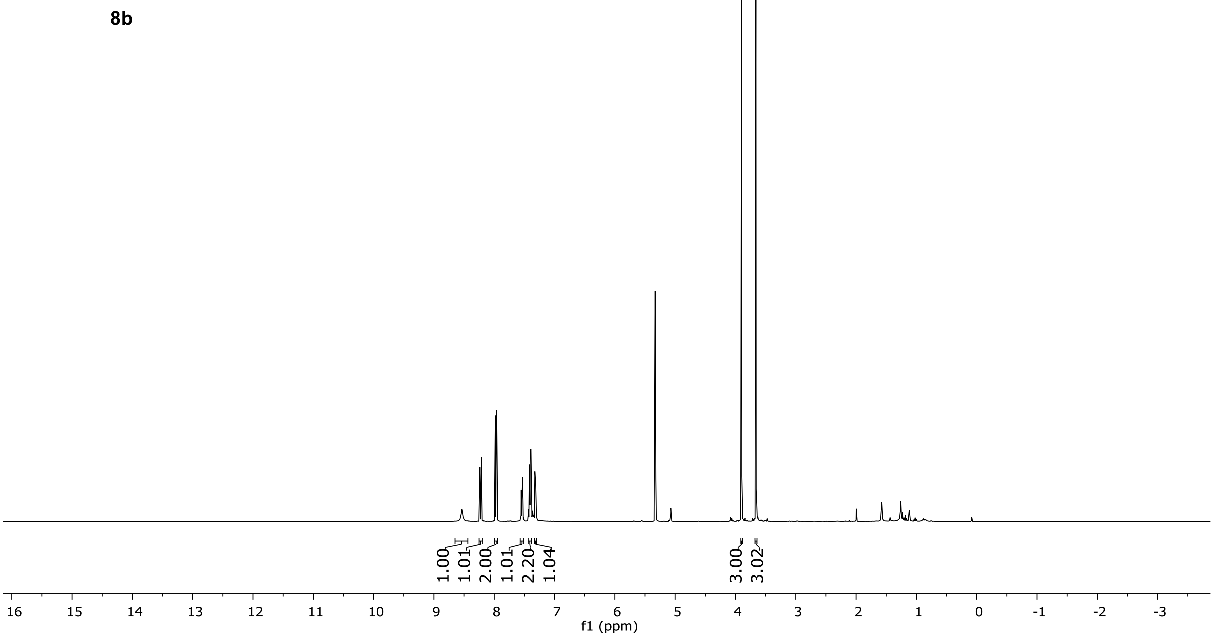


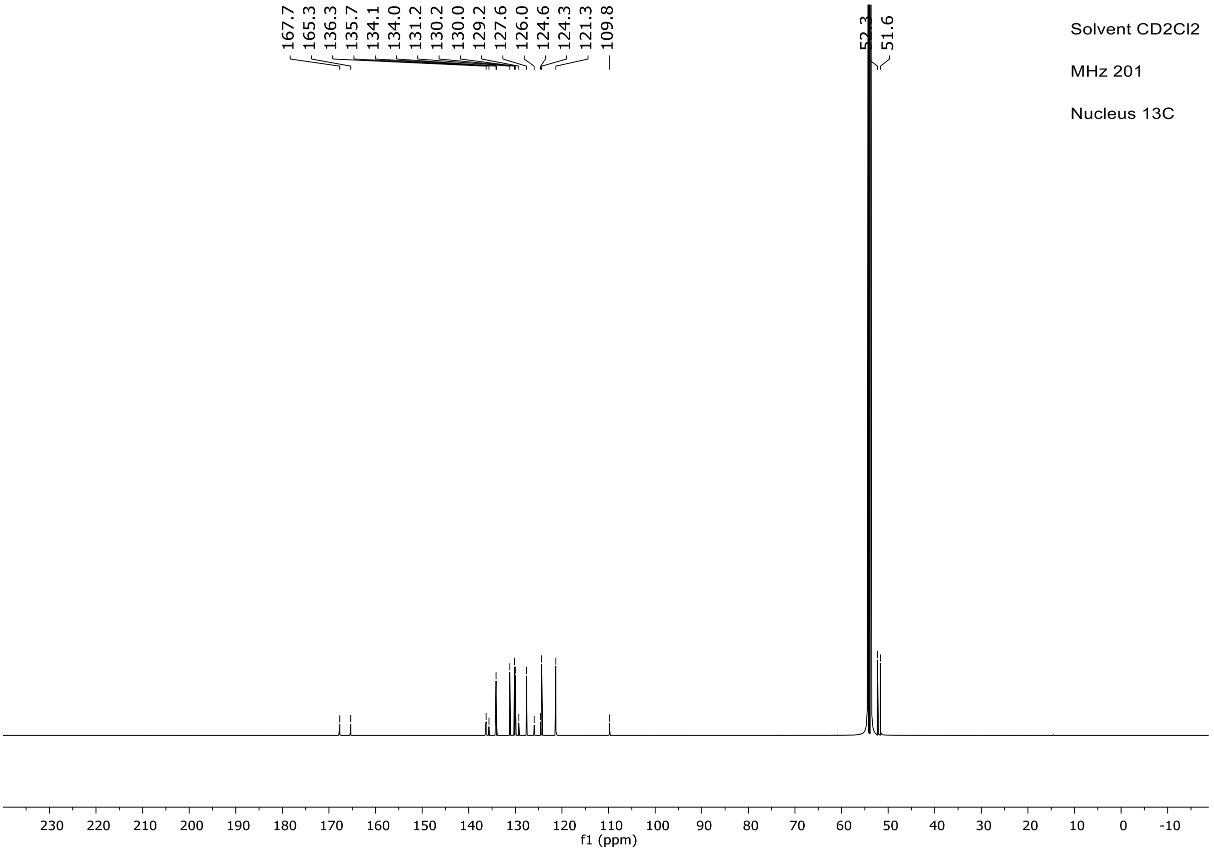


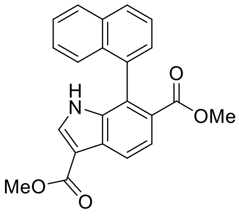

Cl
H
N
O
OMe
MeO
O

8b

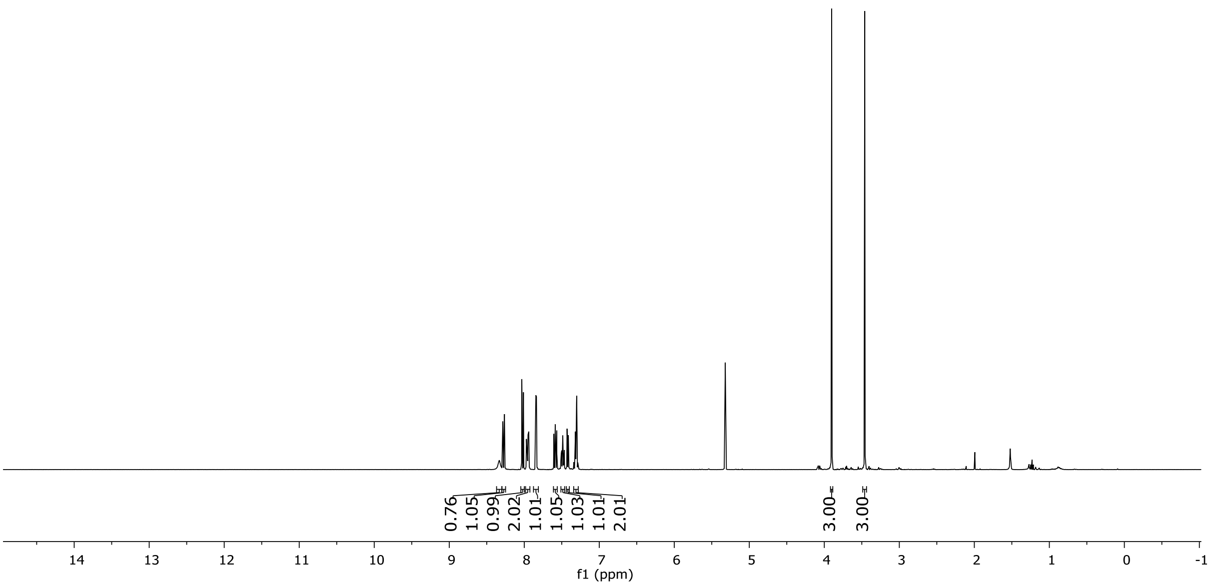
Solvent CD2Cl2
MHz 400
Nucleus 1H

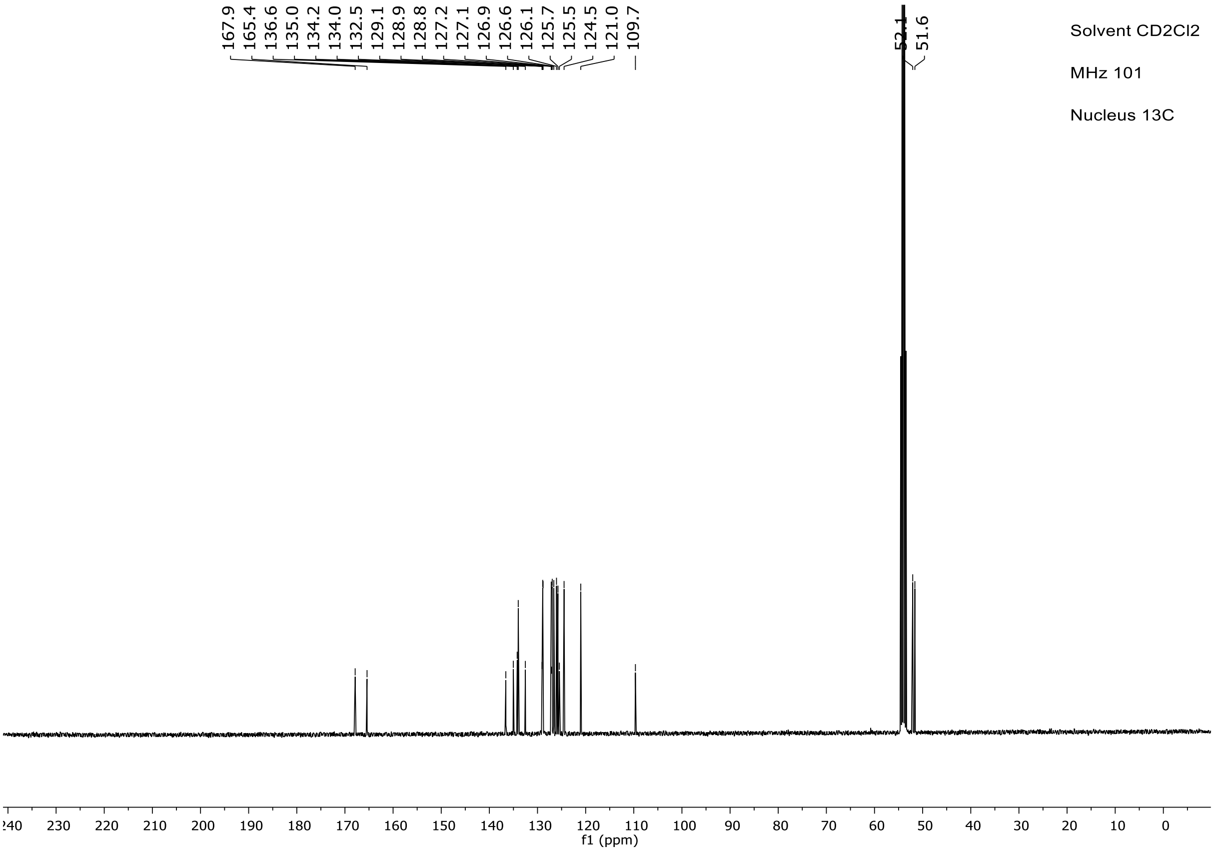

1.00
1.01
2.00
1.01
2.20
1.04
3.00
3.02
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)

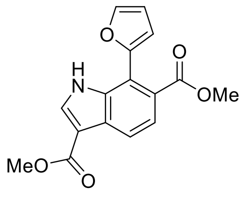

167.7
165.3
136.3
135.7
134.1
134.0
131.2
130.2
130.0
129.2
127.6
126.0
124.6
124.3
121.3
109.8
52.3
51.6
Solvent CD2Cl2
MHz 201
Nucleus 13C
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


H
N
O
OMe
MeO
O

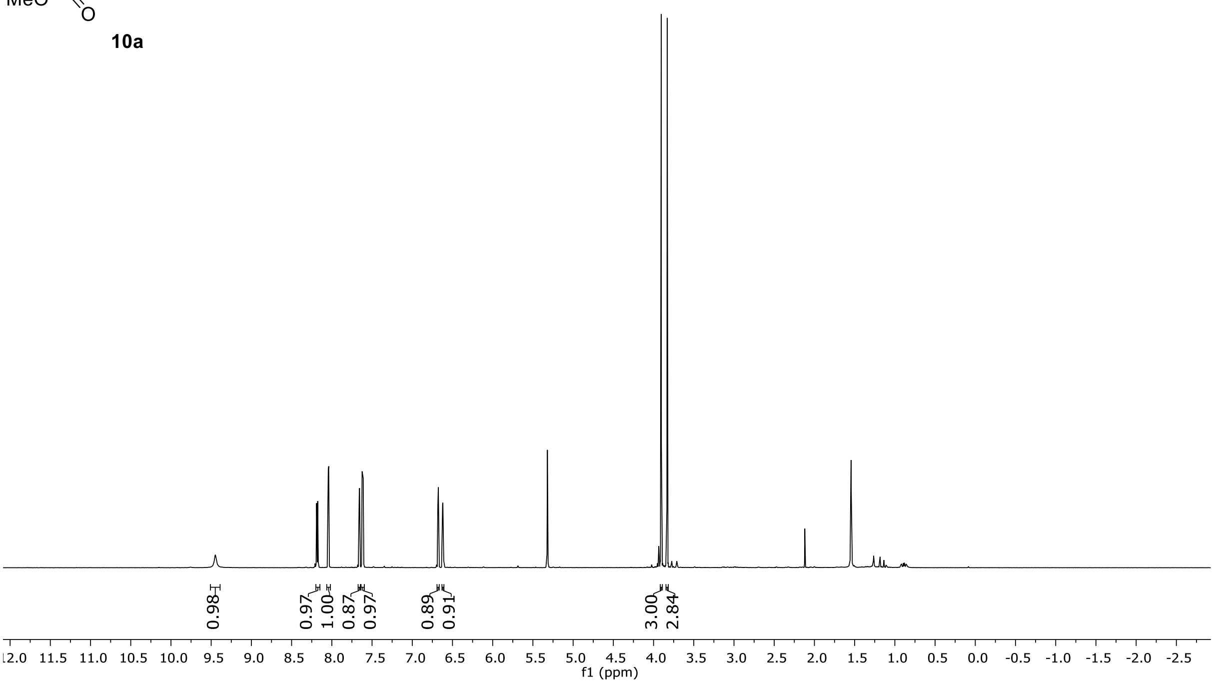
9

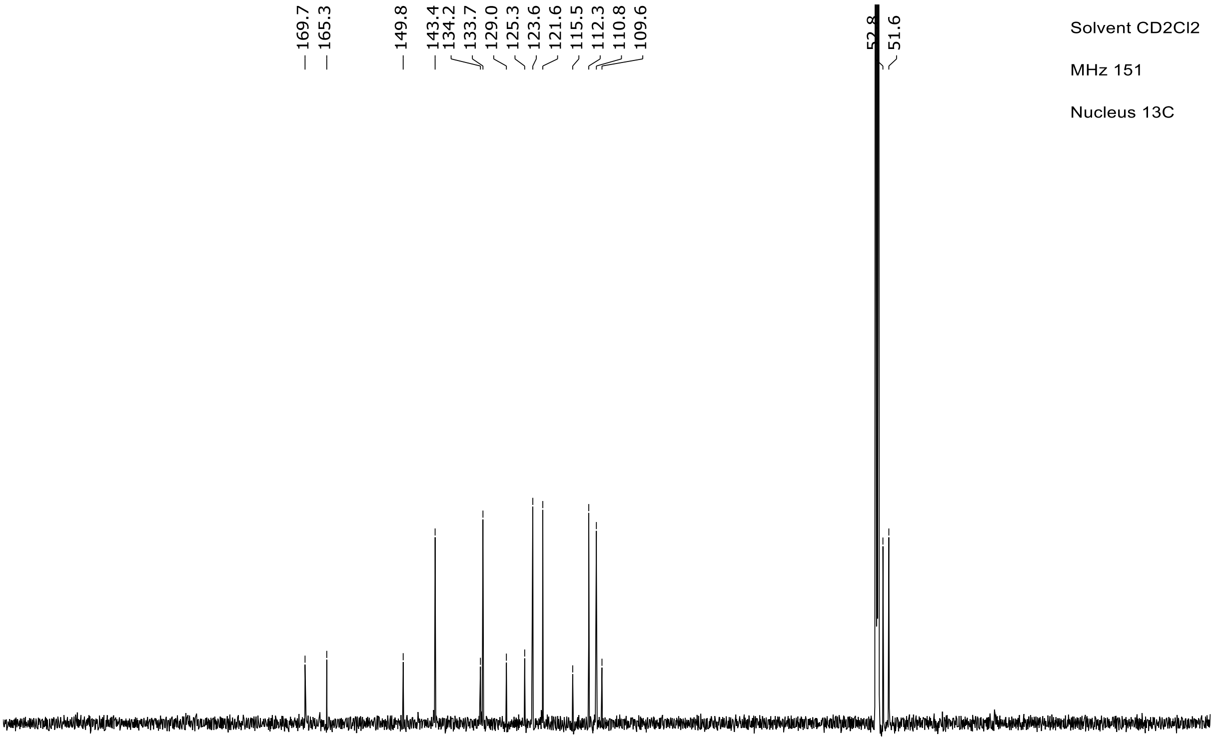

Solvent CD2Cl2
MHz 400
Nucleus 1H
0.76
1.05
0.99
2.02
1.01
1.05
1.03
1.01
2.01
3.00
3.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

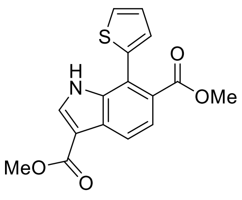

167.9
165.4
136.6
135.0
134.2
134.0
132.5
129.1
128.9
128.8
127.2
127.1
126.9
126.6
126.1
125.7
125.5
124.5
121.0
109.7
52.1
51.6
Solvent CD2Cl2
MHz 101
Nucleus 13C
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



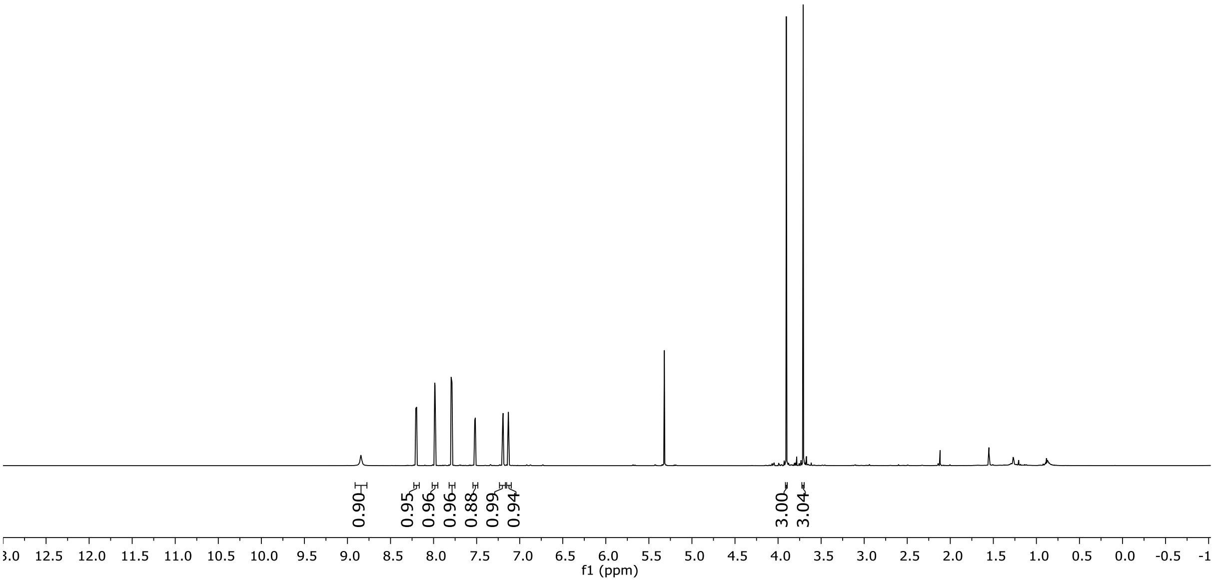
10a


Solvent CD2Cl2
MHz 599
Nucleus 1H
0.98
0.97
1.00
0.87
0.97
0.89
0.91
3.00
2.84
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0 -2.5
f1 (ppm)


169.7
165.3
149.8
143.4
134.2
133.7
129.0
125.3
123.6
121.6
115.5
112.3
110.8
109.6
52.8
51.6
Solvent CD2Cl2
MHz 151
Nucleus 13C
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)



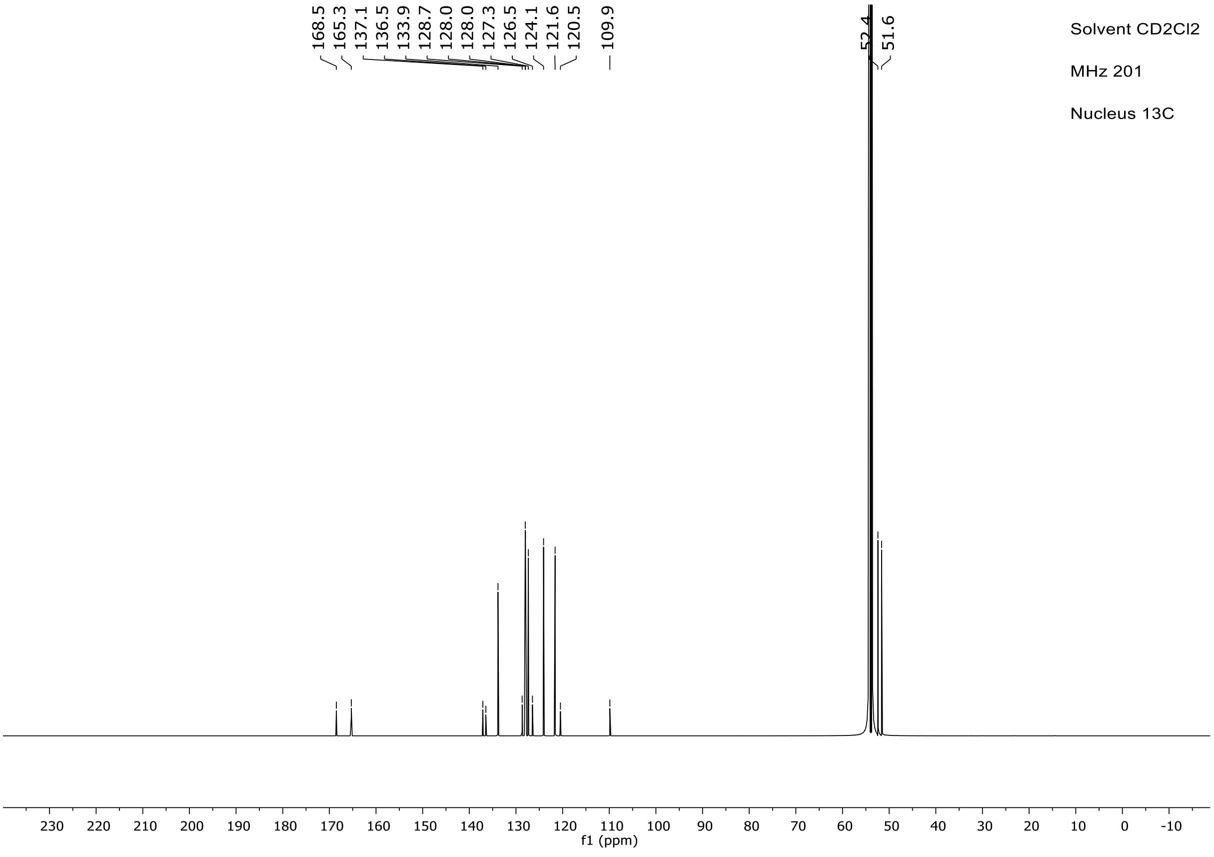
10b



Solvent CD2Cl2

MHz 800

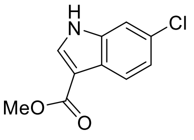
Nucleus 1H



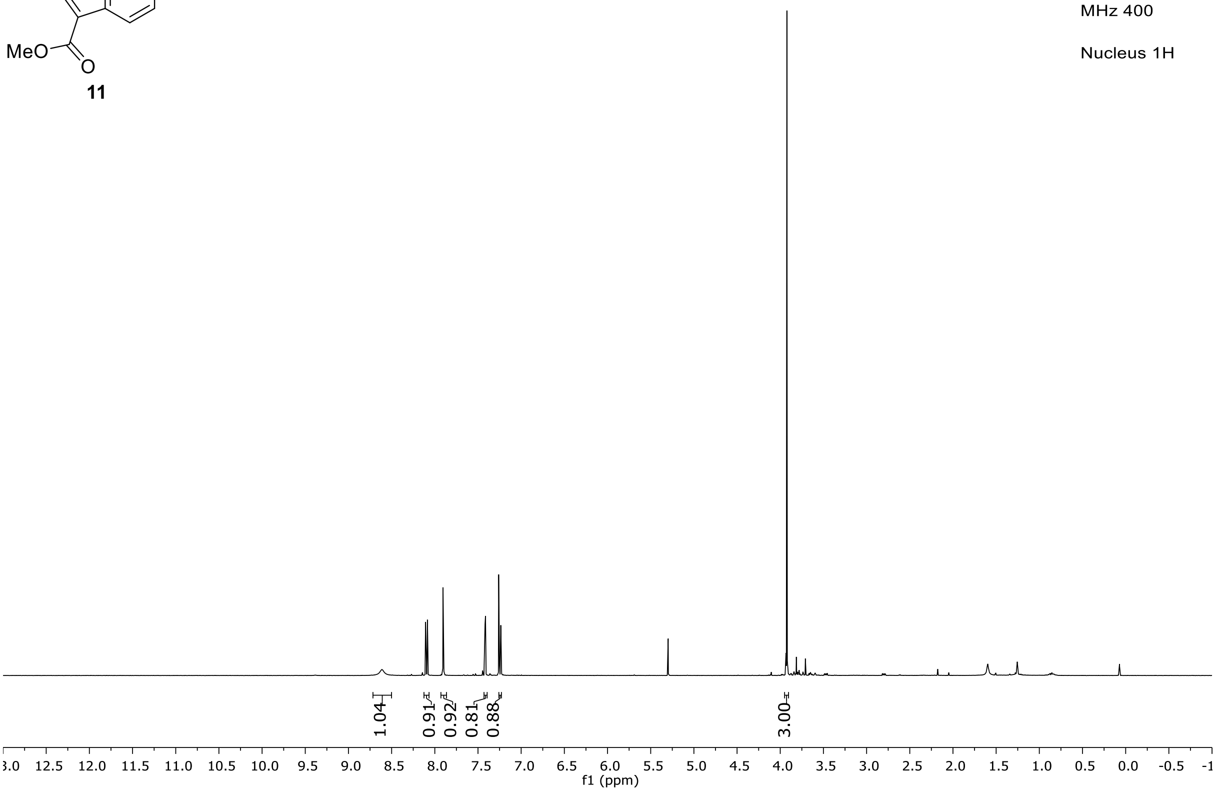
Solvent CD2Cl2

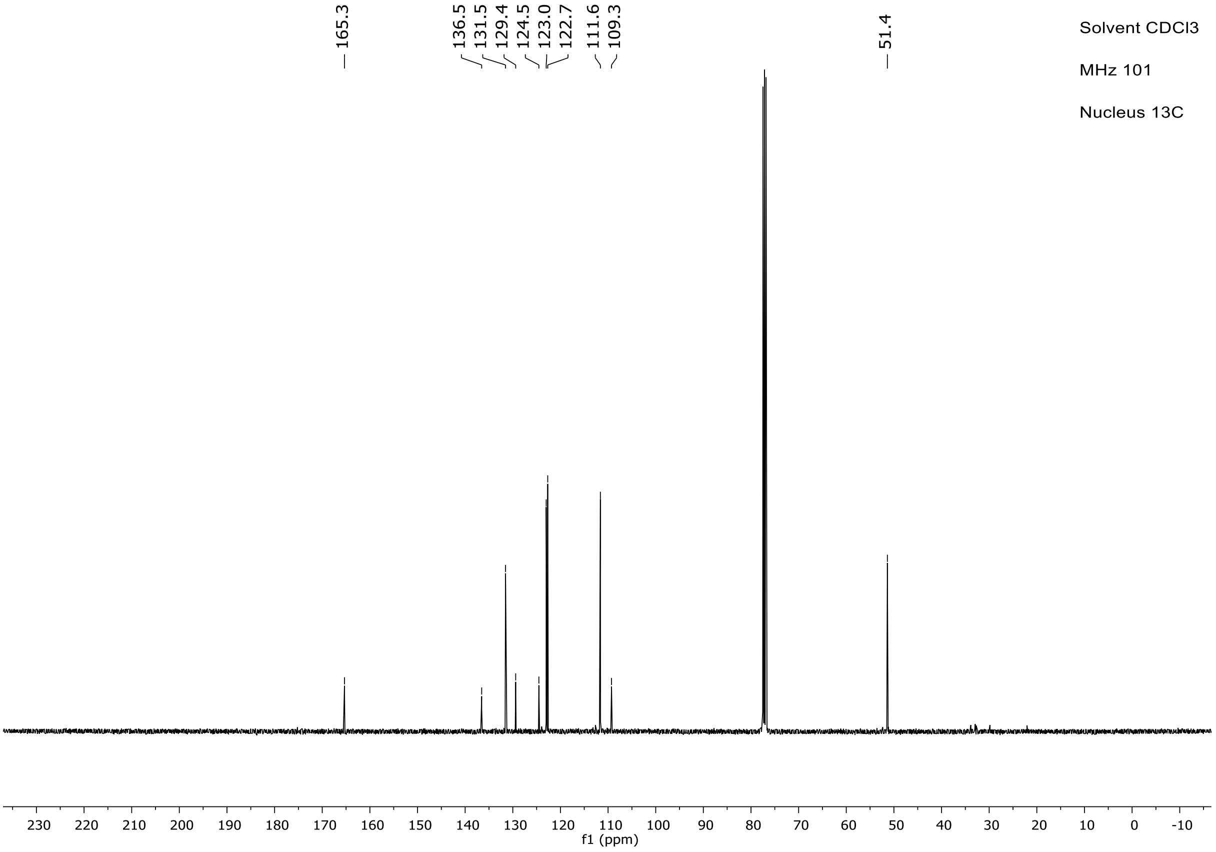
MHz 201

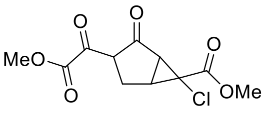
Nucleus 13C


H
N
Cl
MeO
O

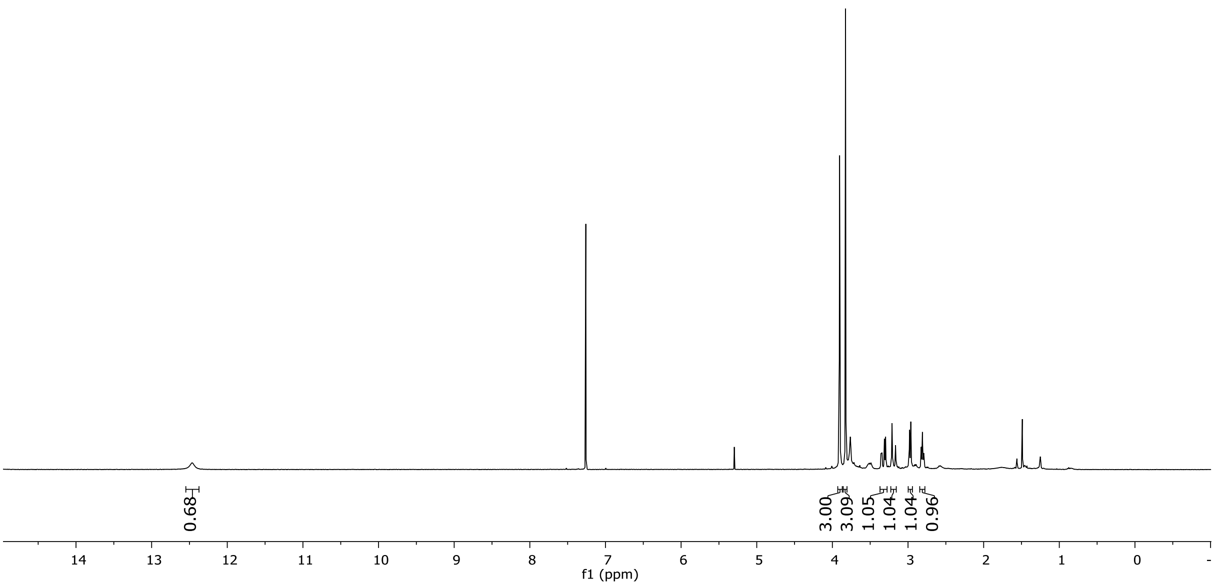
11


Solvent CDCl3
MHz 400
Nucleus 1H
1.04
0.91
0.92
0.81
0.88
3.00
.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


165.3
136.5
131.5
129.4
124.5
123.0
122.7
111.6
109.3
51.4
Solvent CDCl3
MHz 101
Nucleus 13C
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)



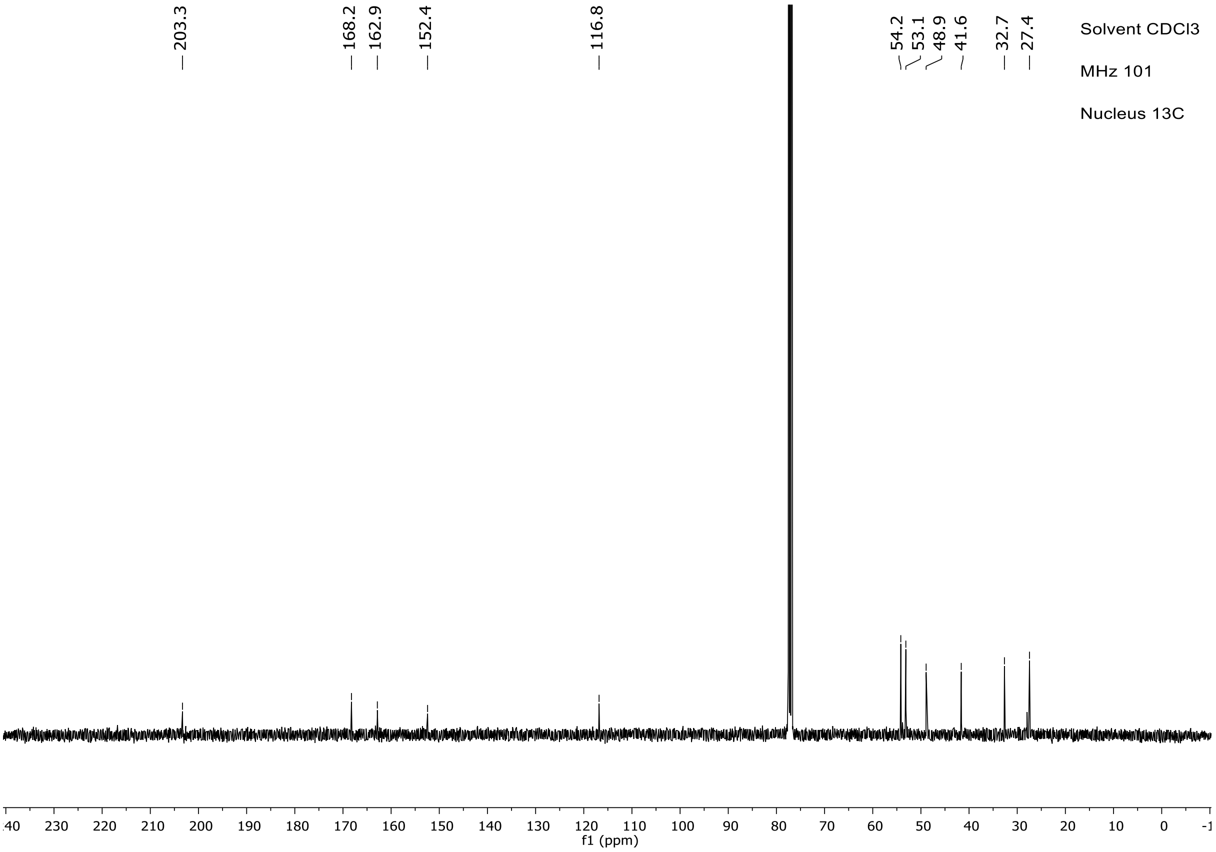
S74



Solvent CDCl3

MHz 400

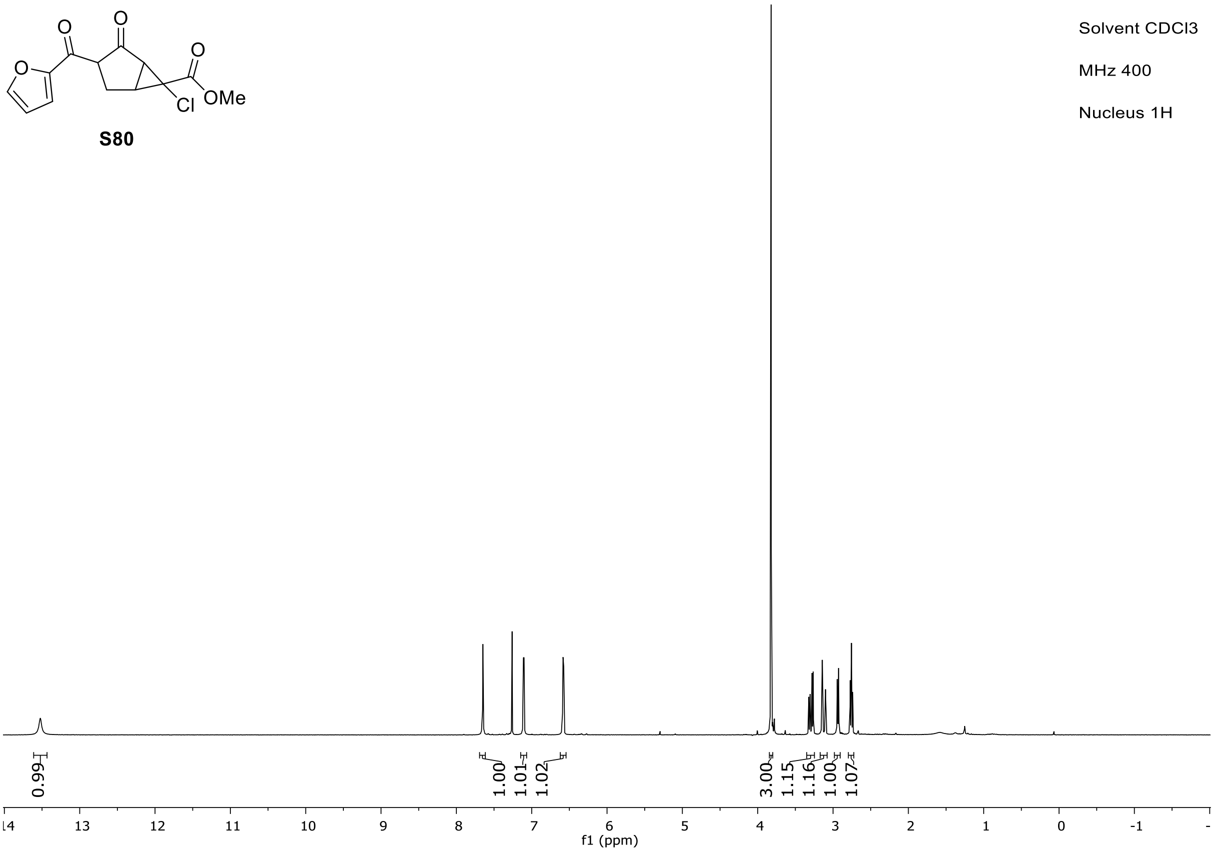
Nucleus 1H



Solvent CDCl3

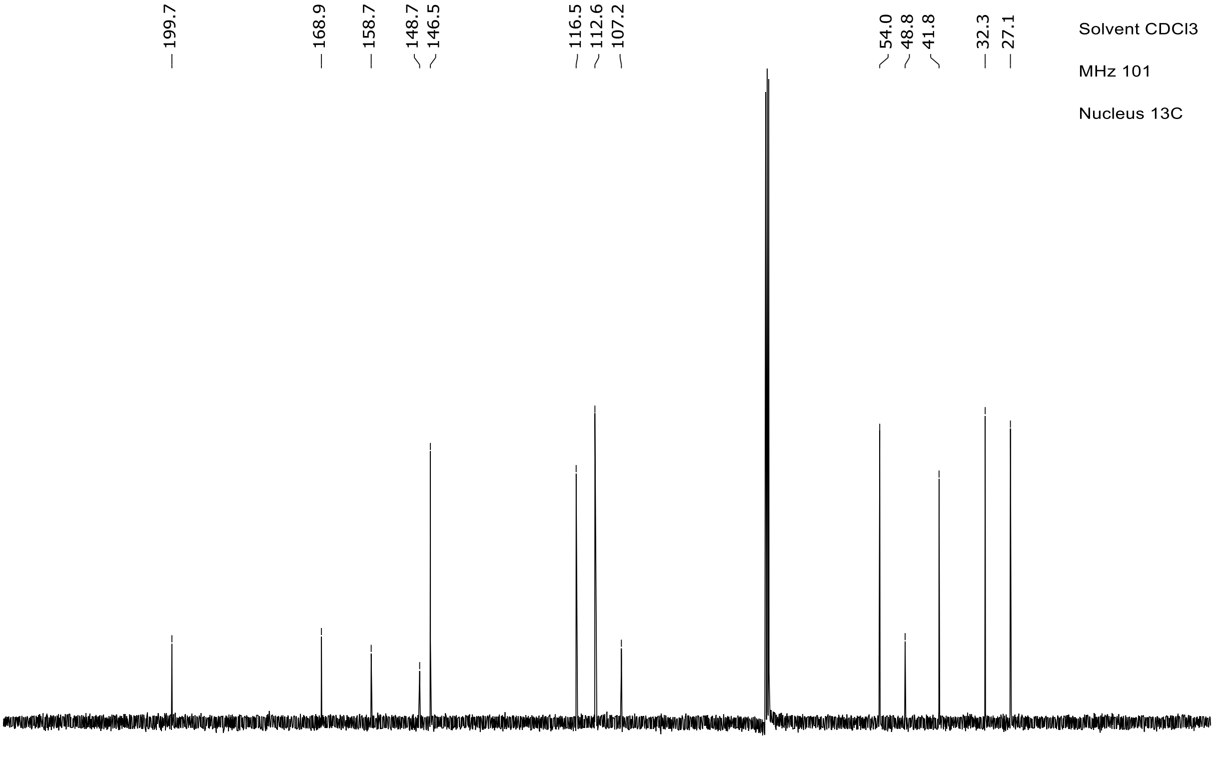
MHz 101

Nucleus 13C

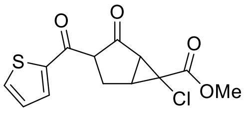


S80

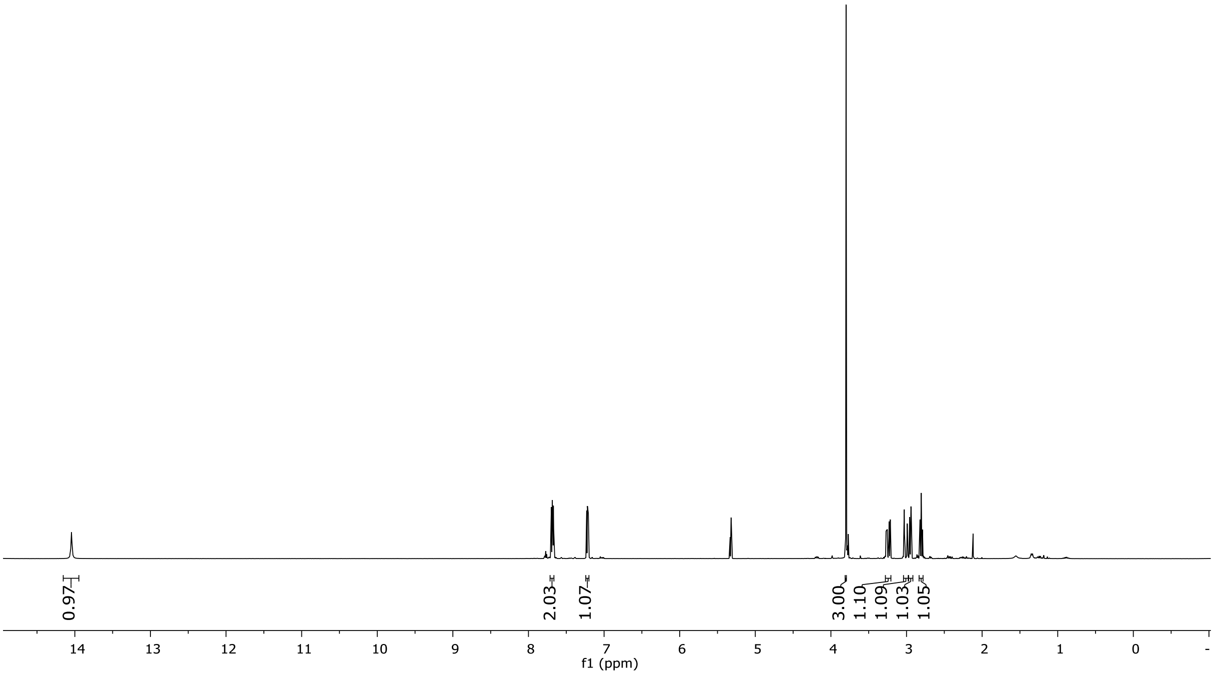
O
O
O
O
OMe
Cl
Solvent CDCl3
MHz 400
Nucleus 1H
0.99
1.00
1.01
1.02
3.00
1.15
1.16
1.00
1.07
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

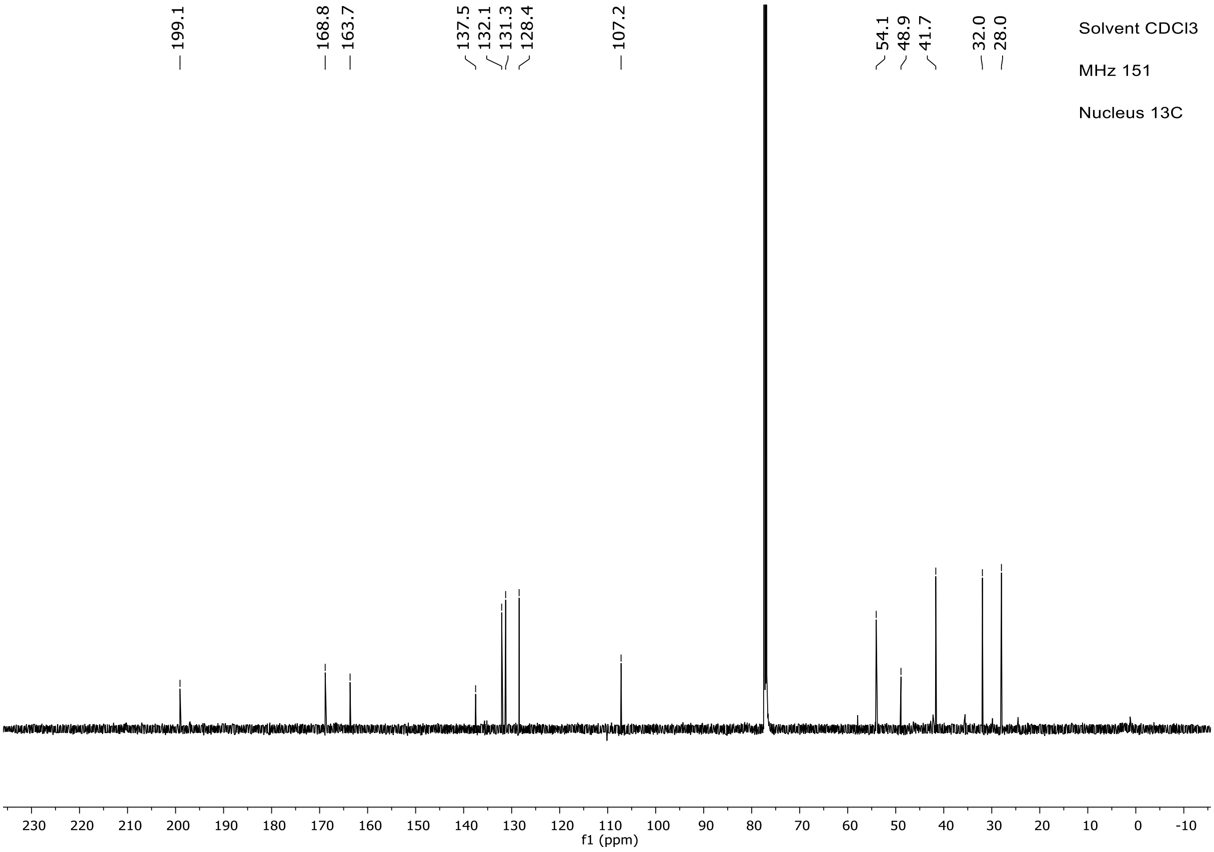


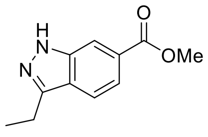
199.7
168.9
158.7
148.7
146.5
116.5
112.6
107.2
54.0
48.8
41.8
32.3
27.1
Solvent CDCl3
MHz 101
Nucleus 13C
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



S82


Solvent CD2Cl2
MHz 400
Nucleus 1H
0.97
2.03
1.07
3.00
1.10
1.09
1.03
1.05
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


199.1
168.8
163.7
137.5
132.1
131.3
128.4
107.2
54.1
48.9
41.7
32.0
28.0
Solvent CDCl3
MHz 151
Nucleus 13C
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)

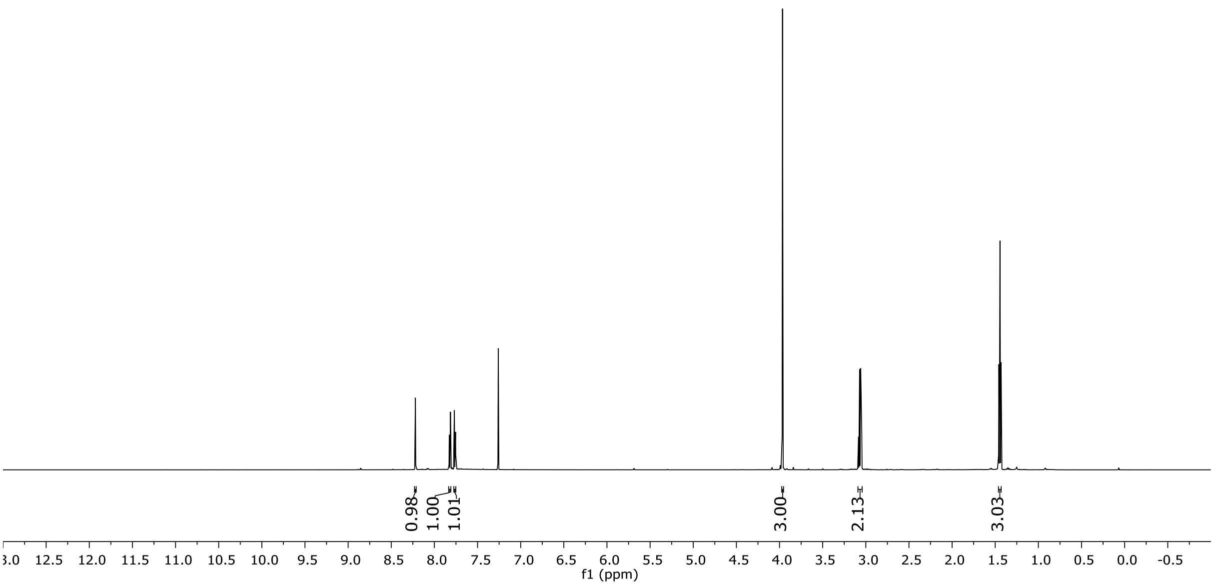


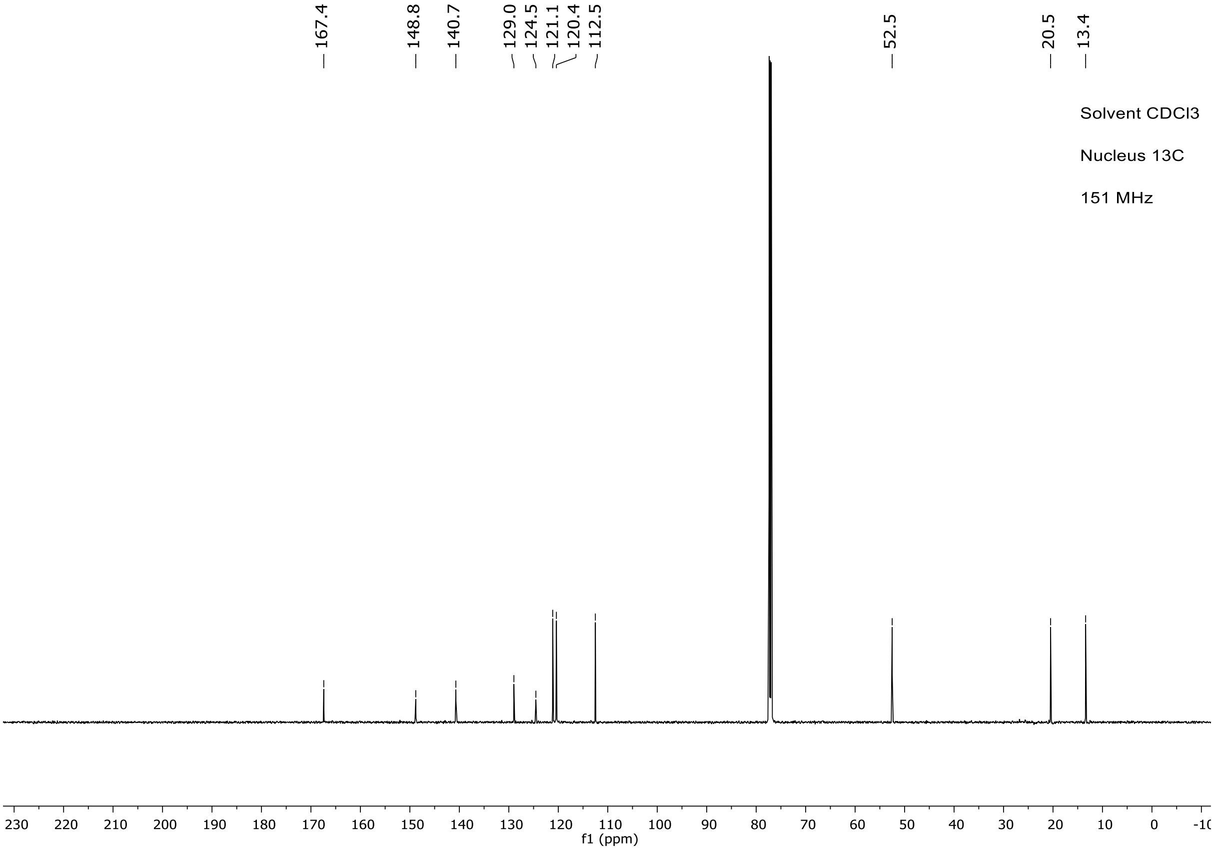
21

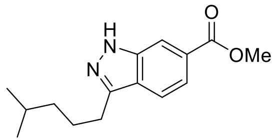
Solvent CDCl3

Nucleus 1H

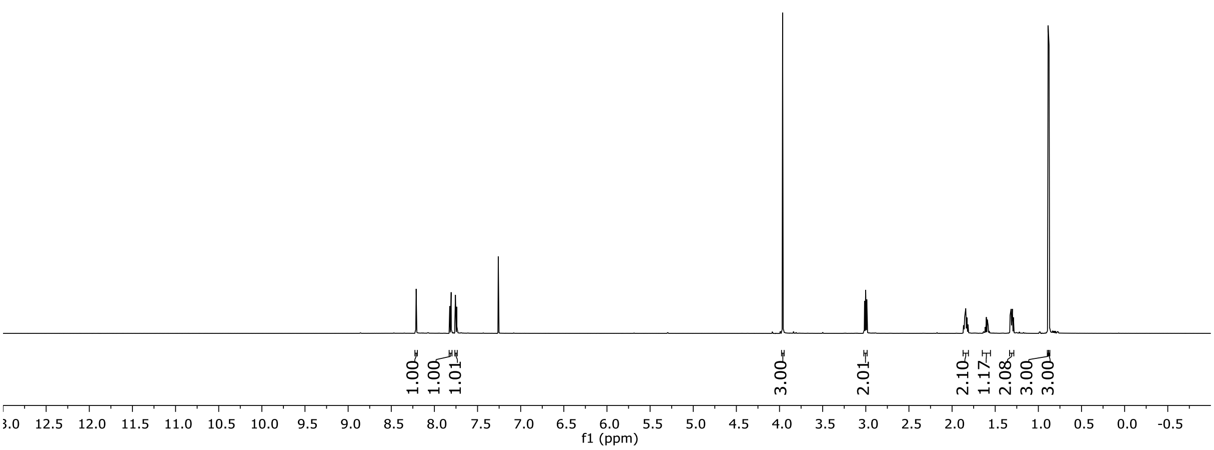
599 MHz

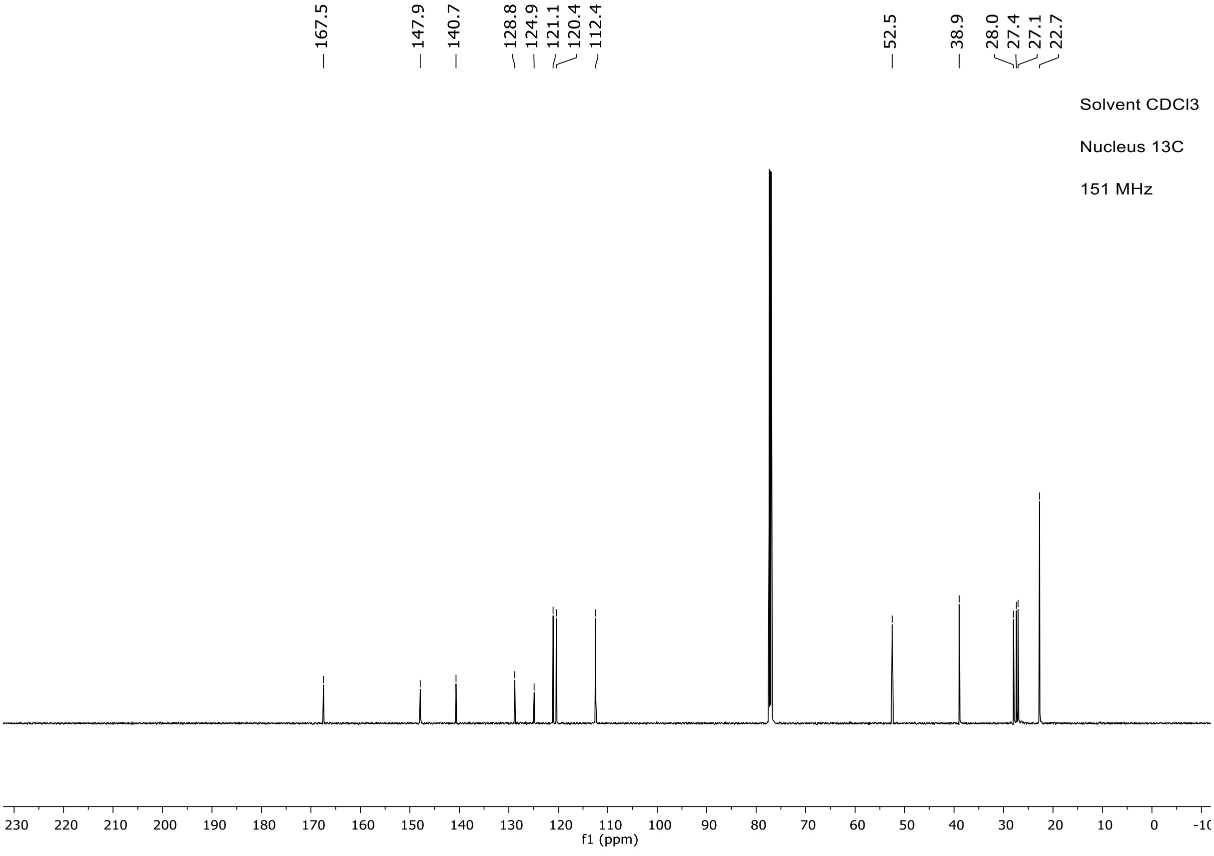


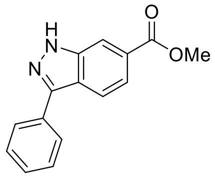



H
N
N
O
OMe

22


Solvent CDCl3
Nucleus 1H
599 MHz
1.00
1.00
1.01
3.00
2.01
2.10
1.17
2.08
3.00
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


167.5
147.9
140.7
128.8
124.9
121.1
120.4
112.4
52.5
38.9
28.0
27.4
27.1
22.7
Solvent CDCl3
Nucleus 13C
151 MHz
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)

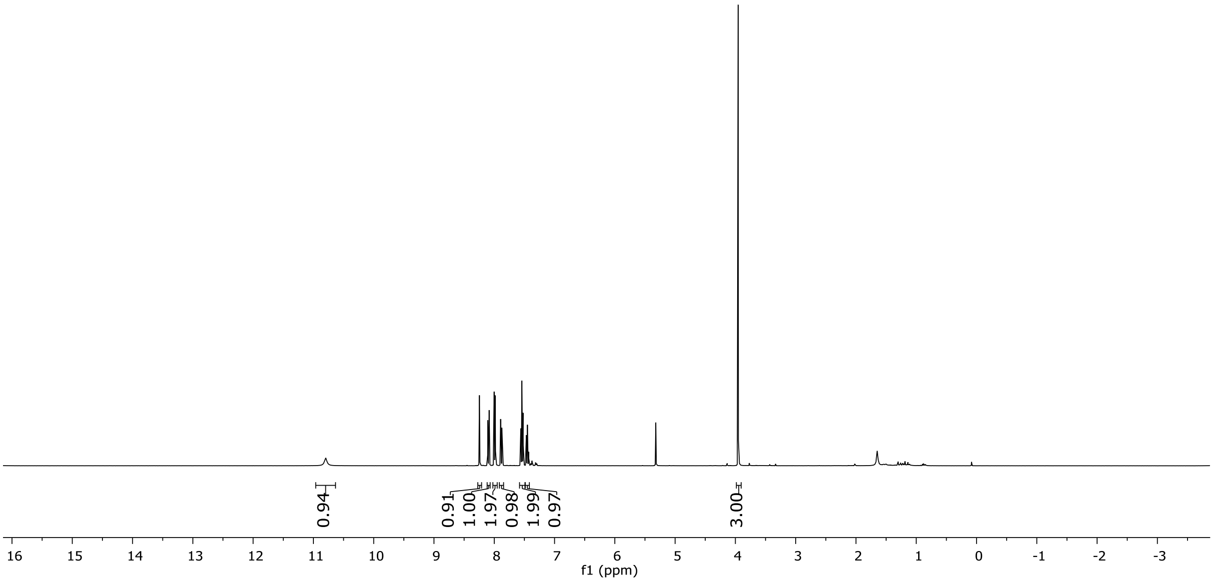


23

Solvent CD2Cl2

MHz 400

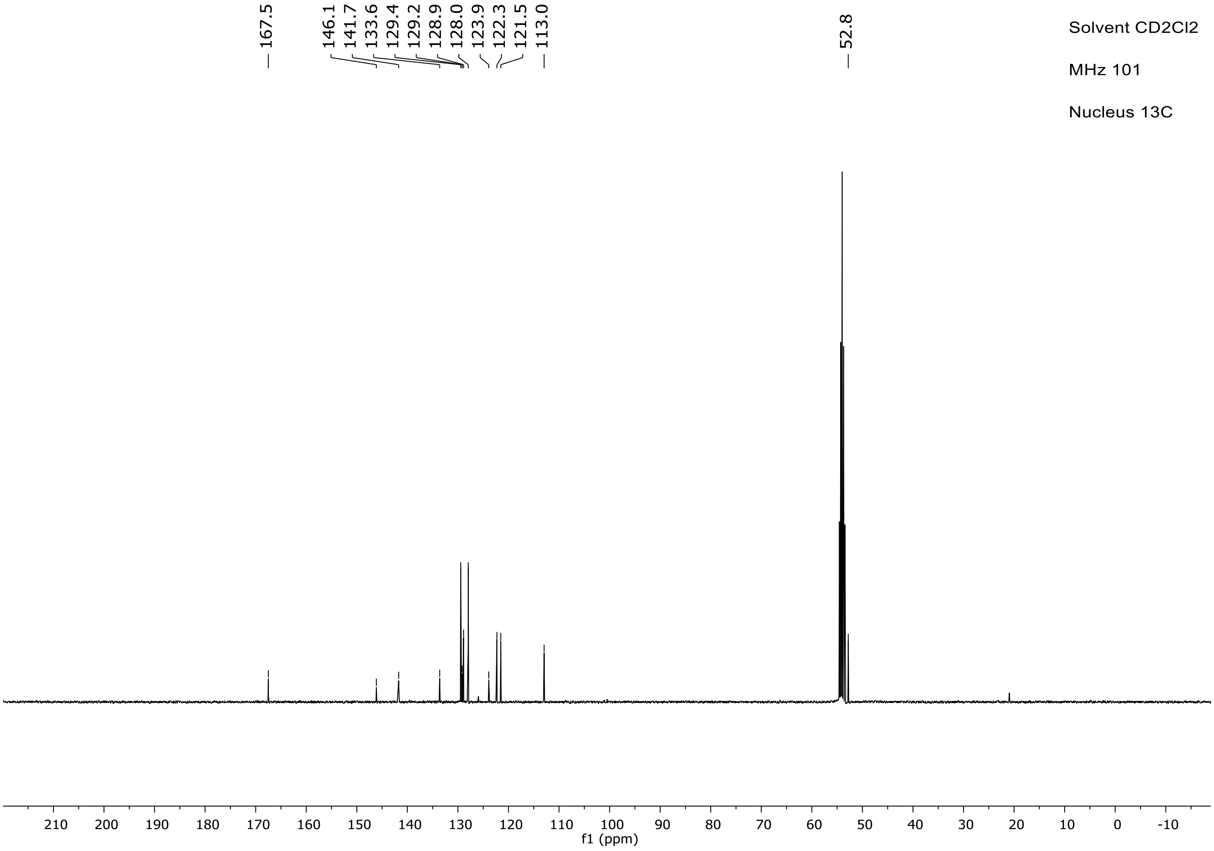
Nucleus 1H

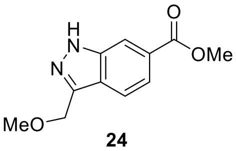


Solvent CD2Cl2

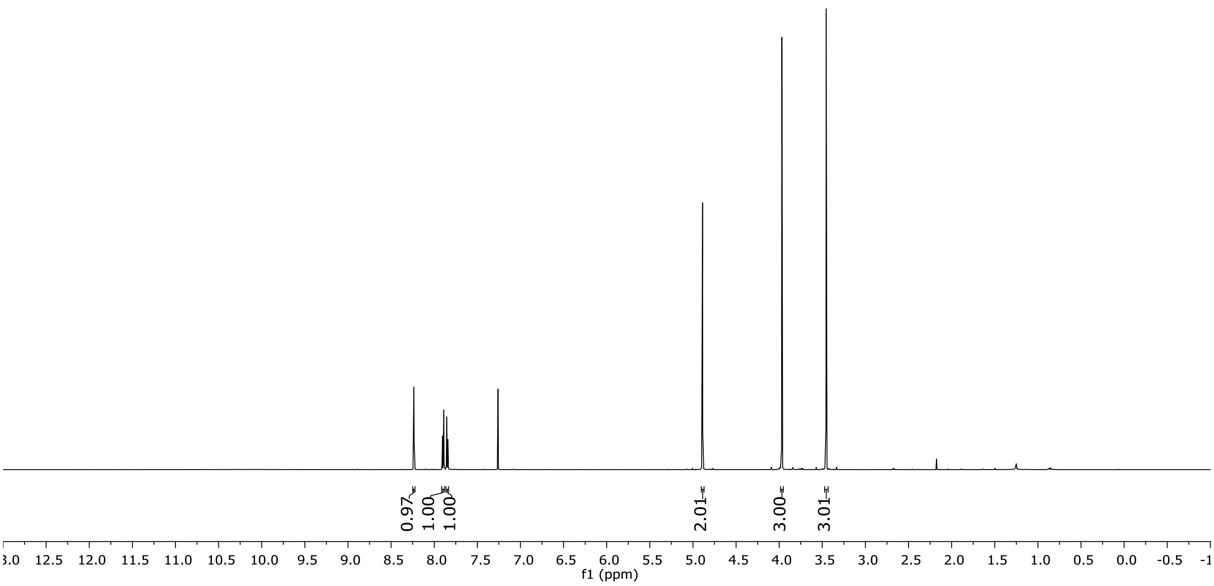
MHz 101

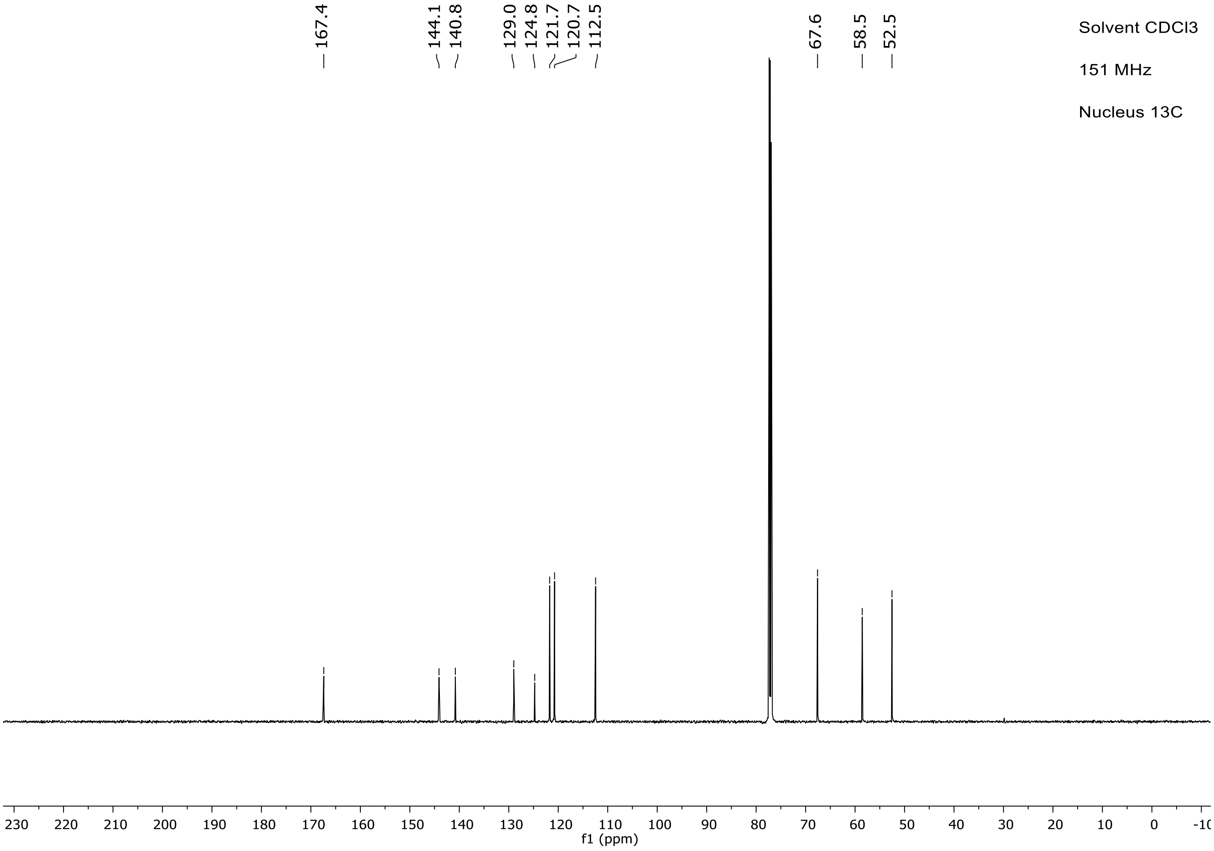
Nucleus 13C

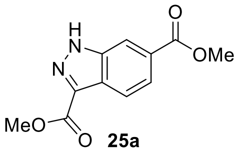



H
N
N
O
OMe
MeO

24

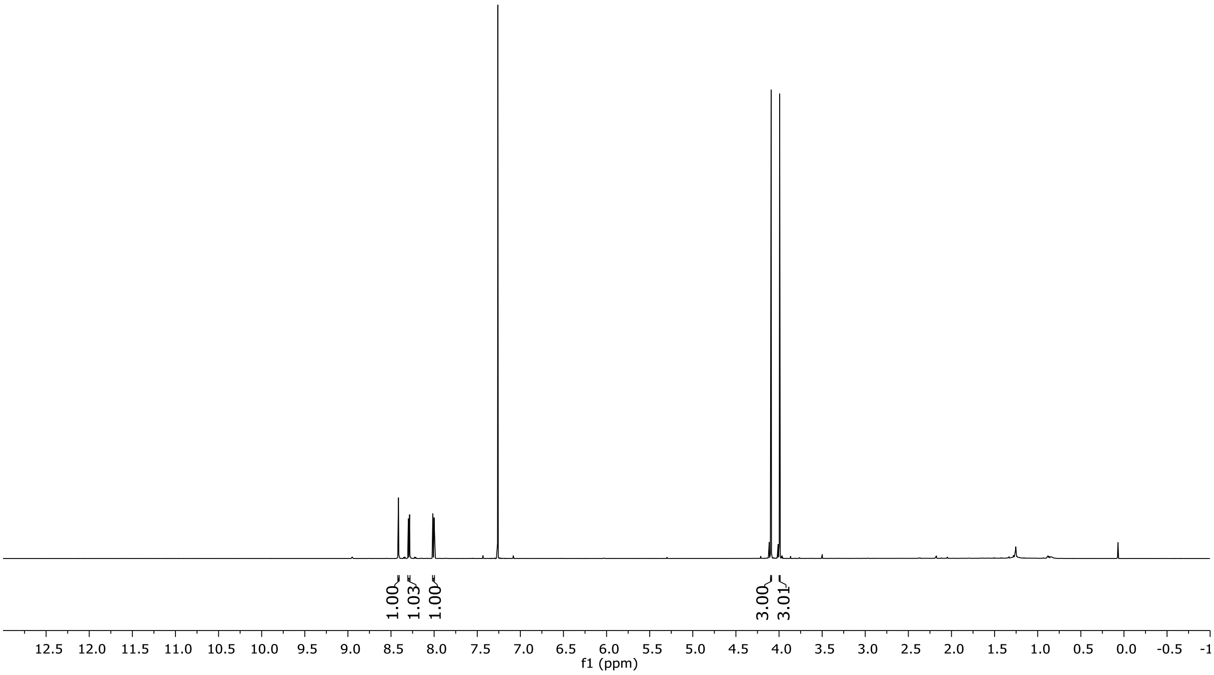

Solvent CDCl3
599 MHz
Nucleus 1H
0.97
1.00
1.00
2.01
3.00
3.01
3.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


167.4
144.1
140.8
129.0
124.8
121.7
120.7
112.5
67.6
58.5
52.5
Solvent CDCl3
151 MHz
Nucleus 13C
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)

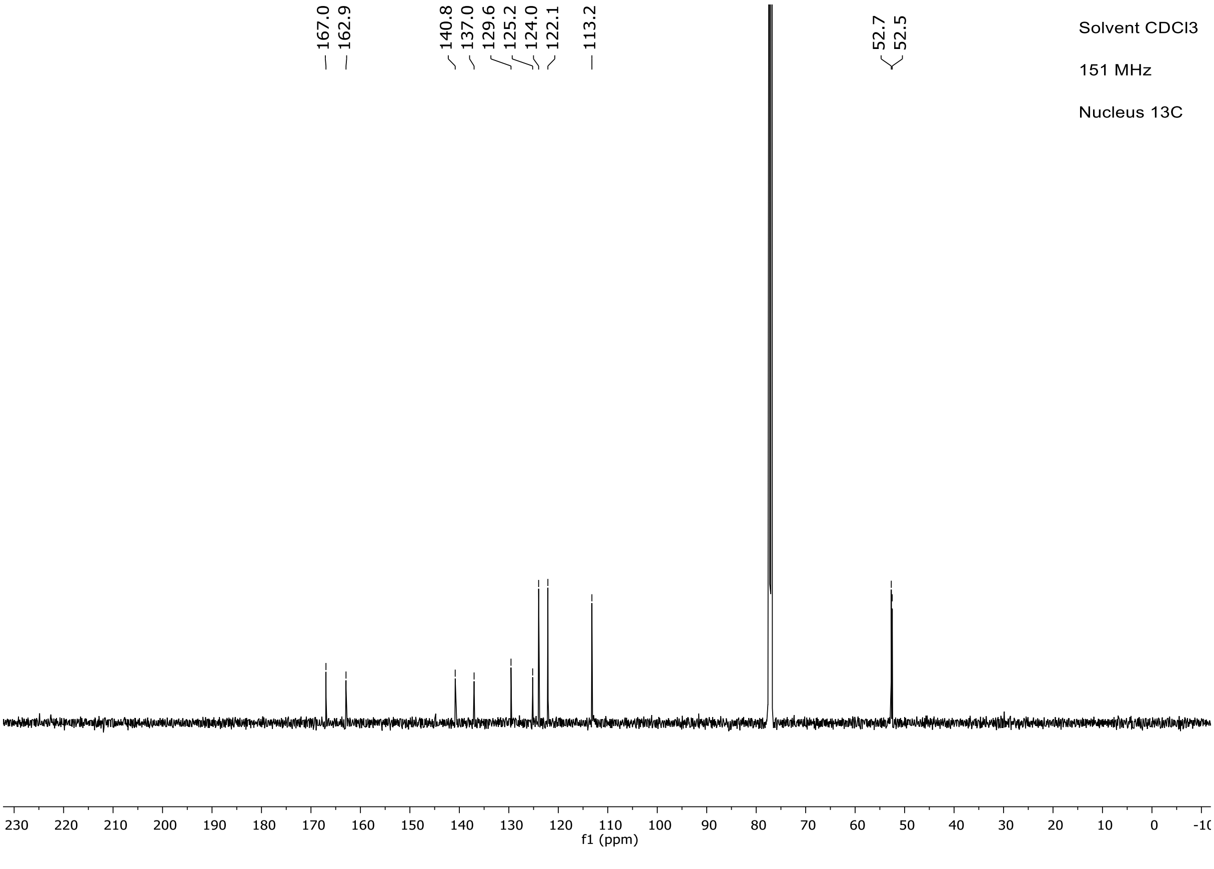


25a

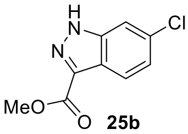
H
N
N
O
OMe
MeO
O



Solvent CDCl3
599 MHz
Nucleus 1H
1.00
1.03
1.00
3.00
3.01
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)



167.0
162.9
140.8
137.0
129.6
125.2
124.0
122.1
113.2
52.7
52.5
Solvent CDCl3
151 MHz
Nucleus 13C
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)

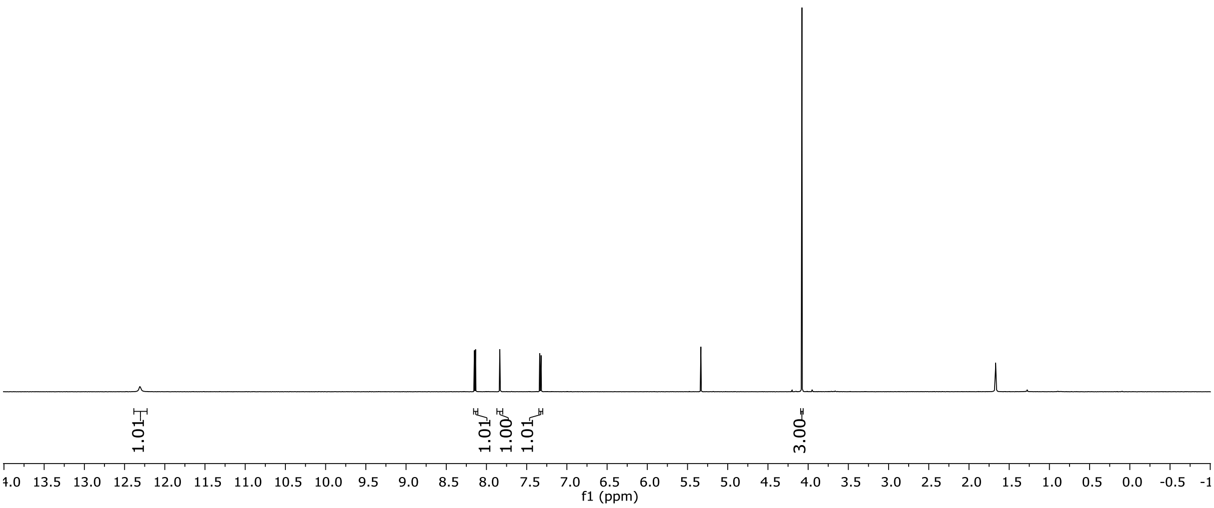


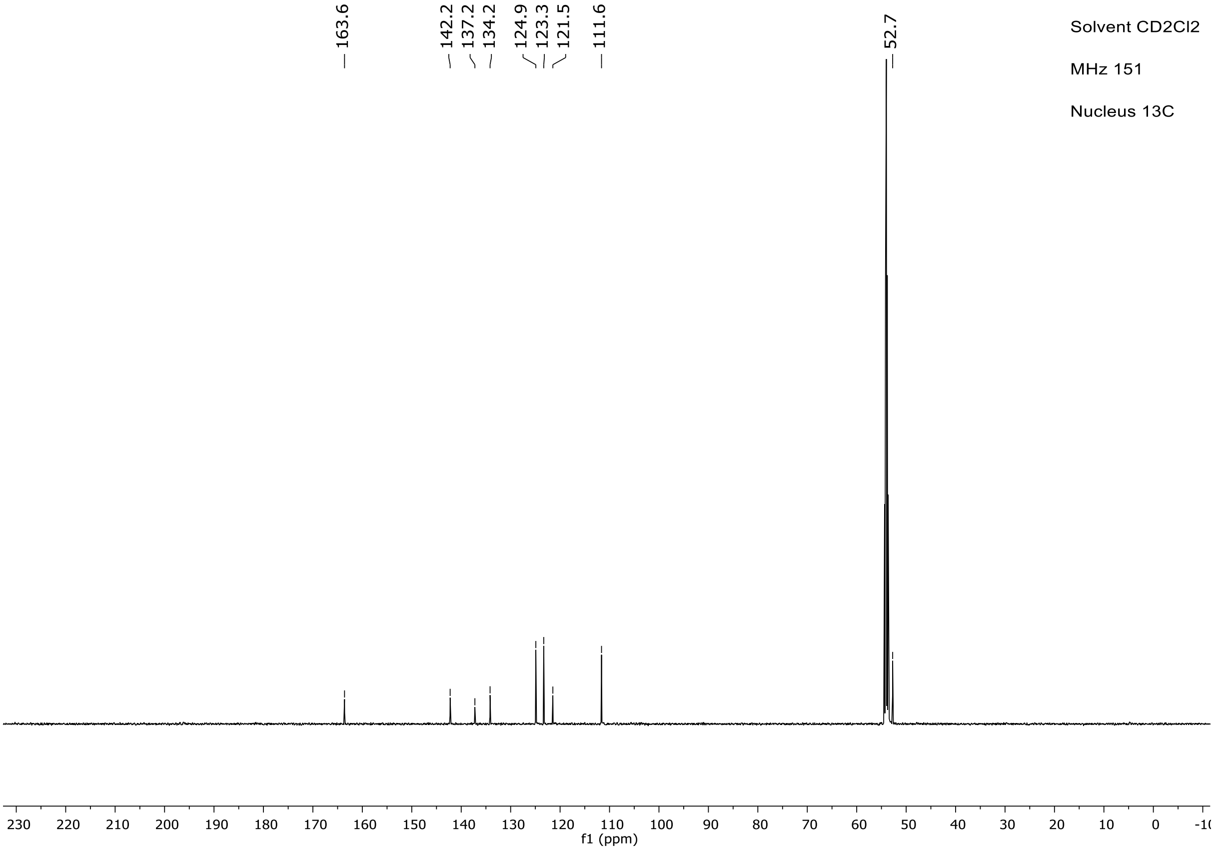
25b

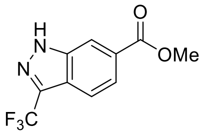
Solvent CD2Cl2

MHz 599

Nucleus 1H







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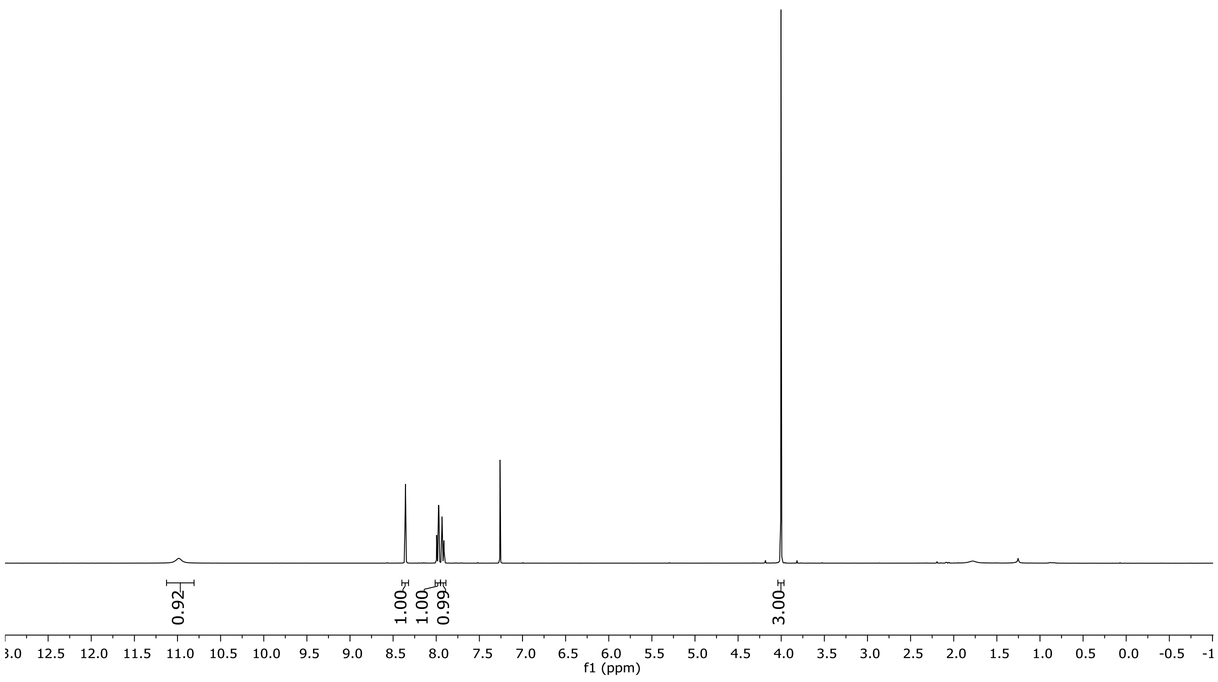
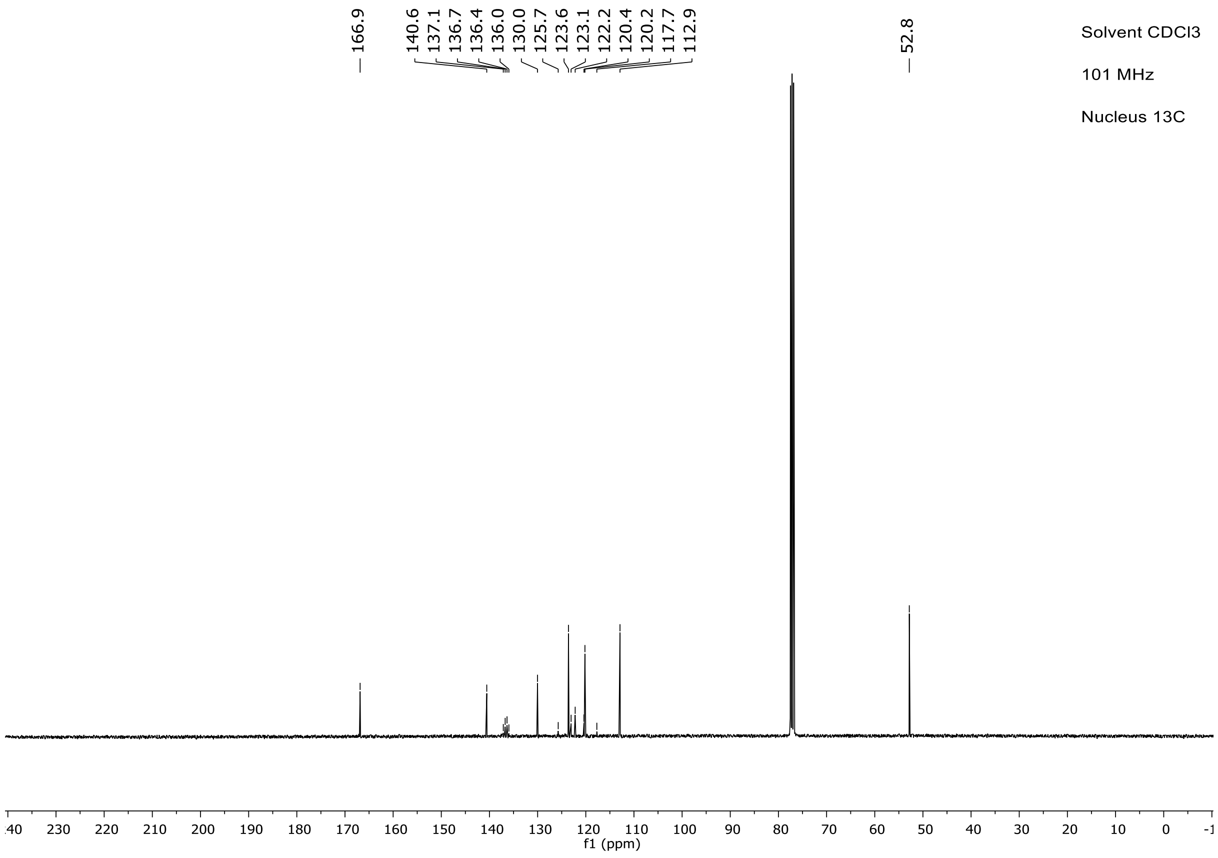
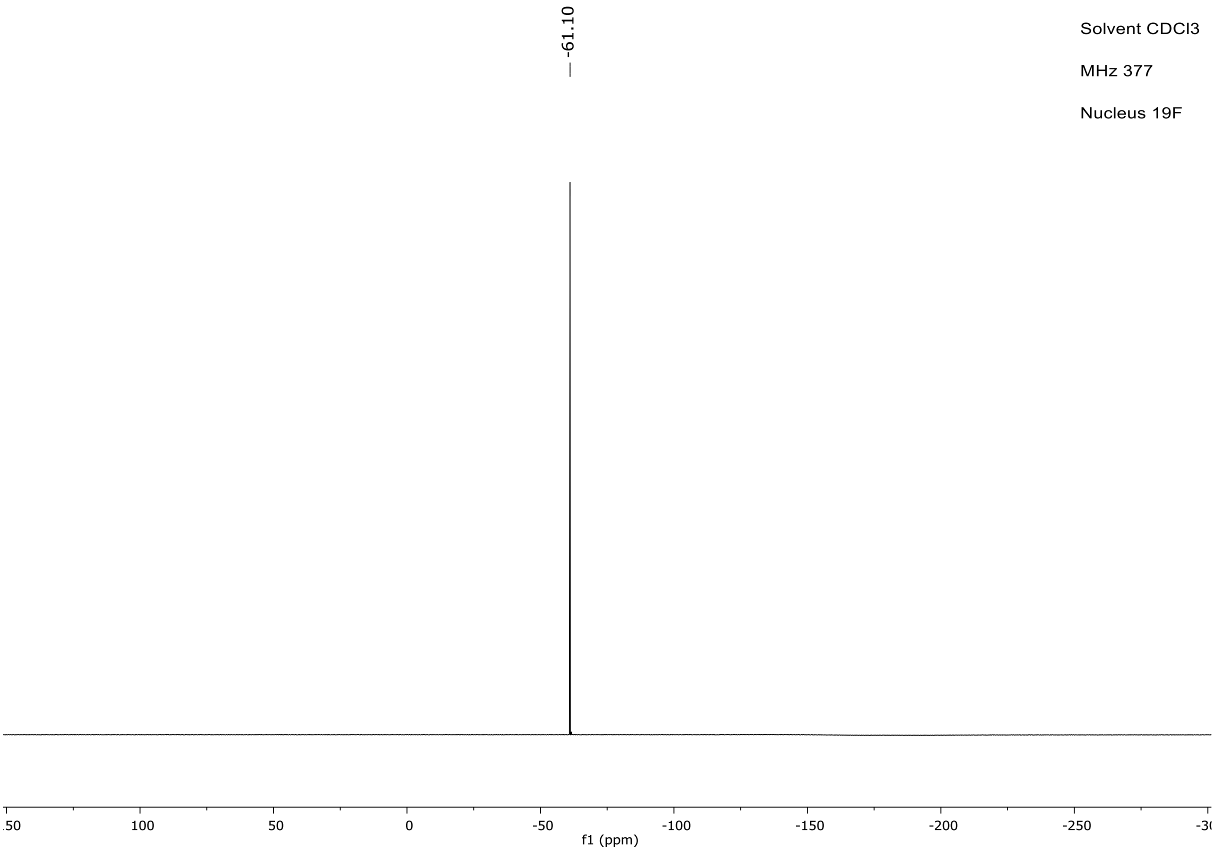
Solvent CDCl3

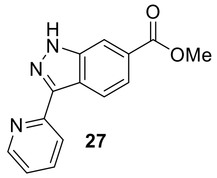
400 MHz

Nucleus 1H

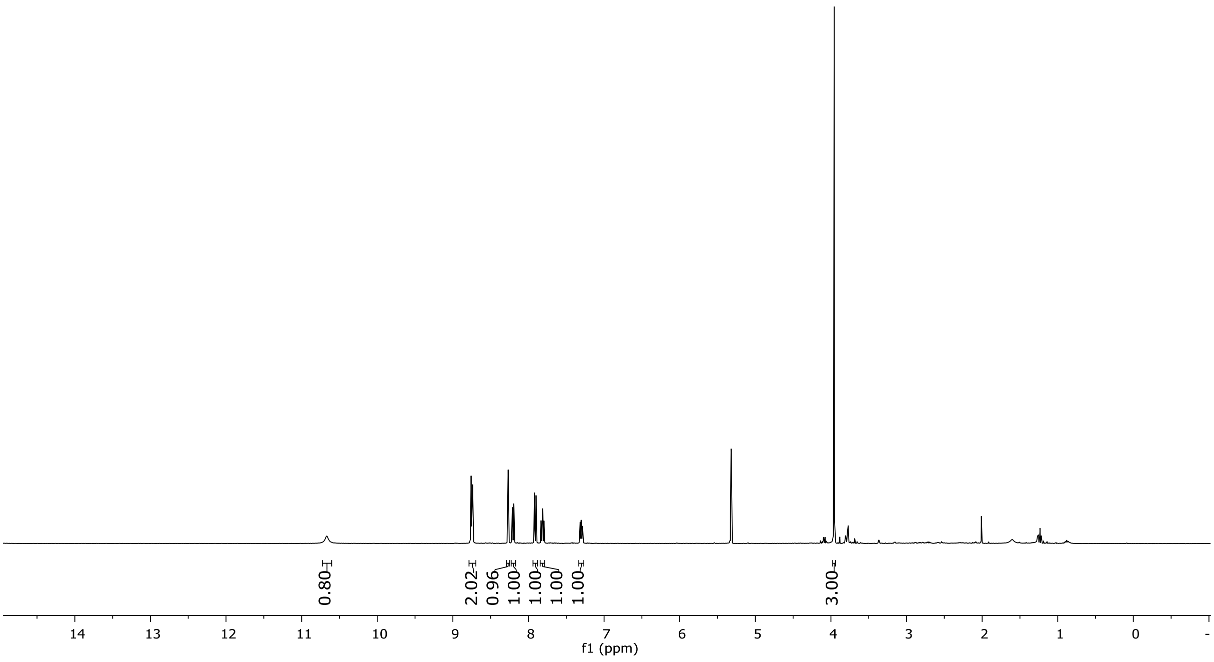


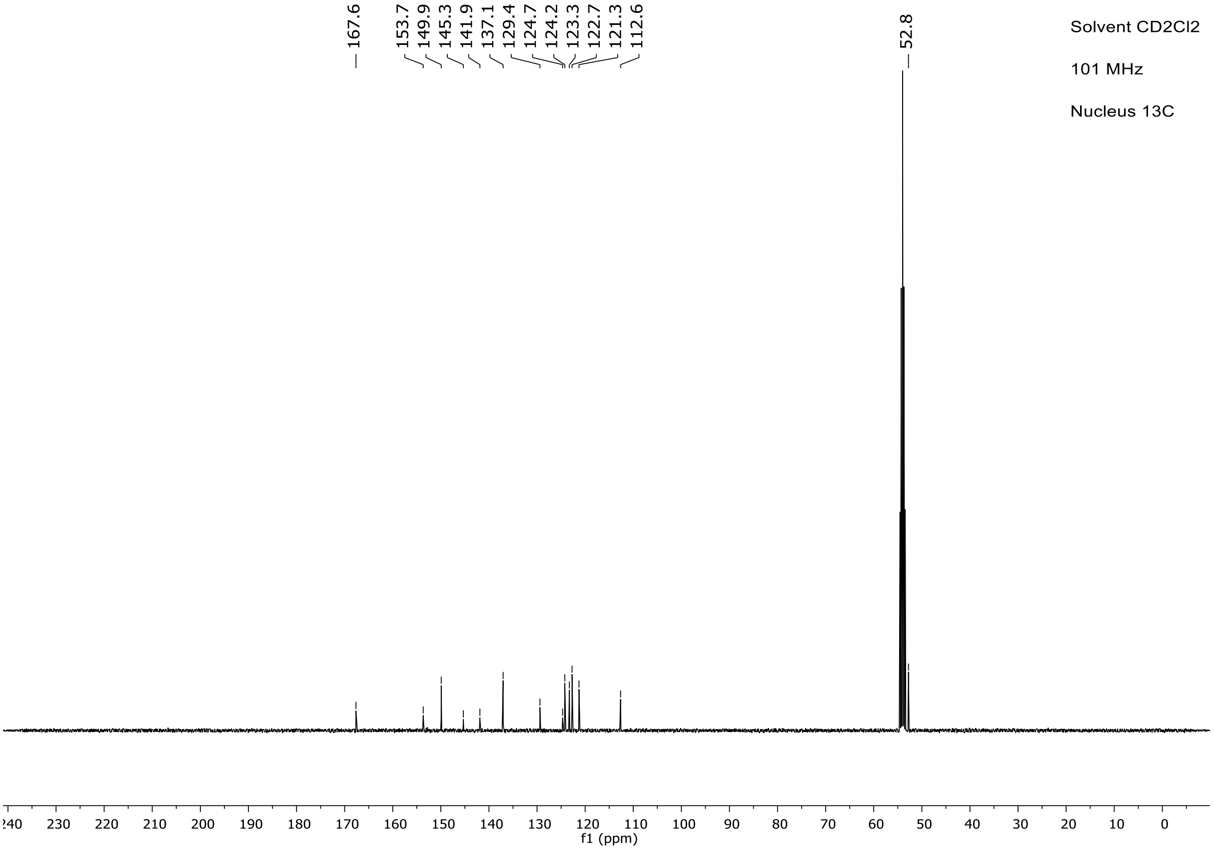


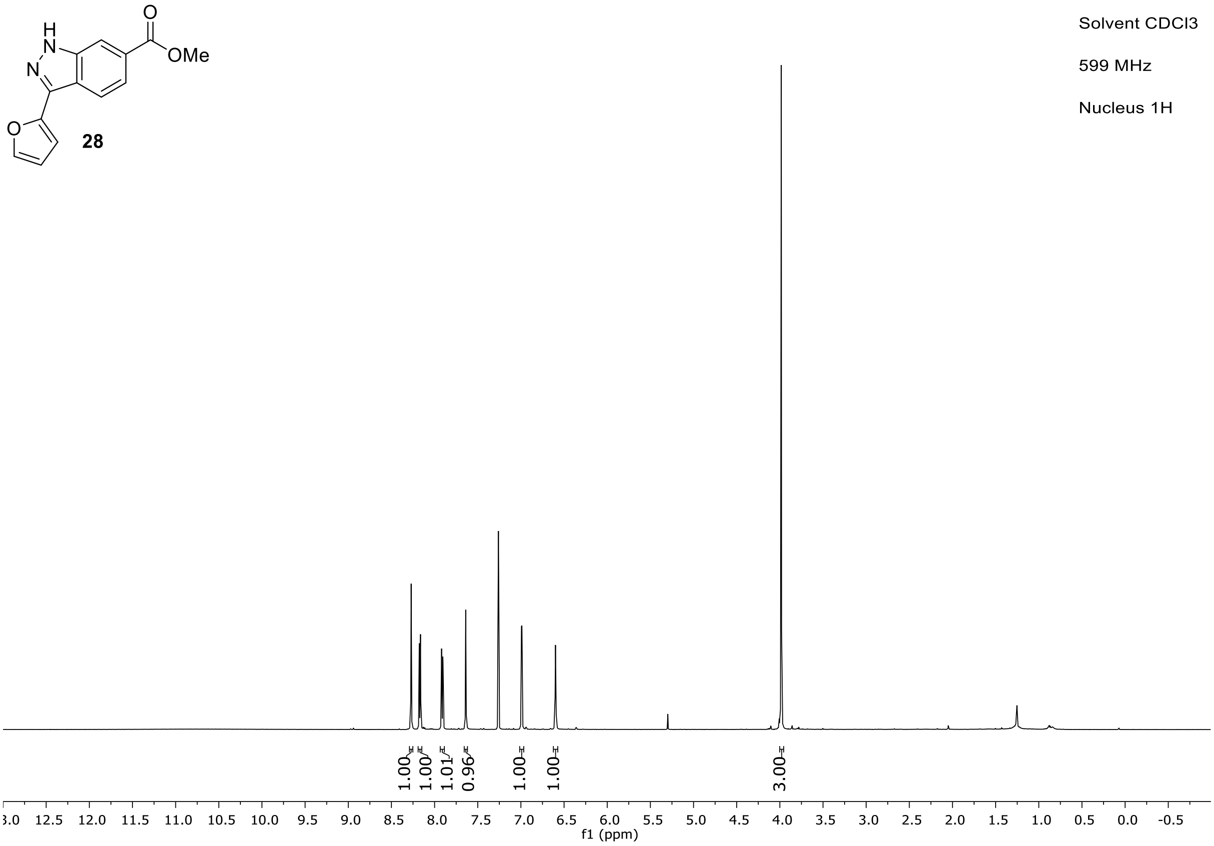

-61.10
Solvent CDCl3
MHz 377
Nucleus 19F
50
100
50
0
-50
-100
-150
-200
-250
-3
f1 (ppm)


H
N
N
O
OMe
N

27

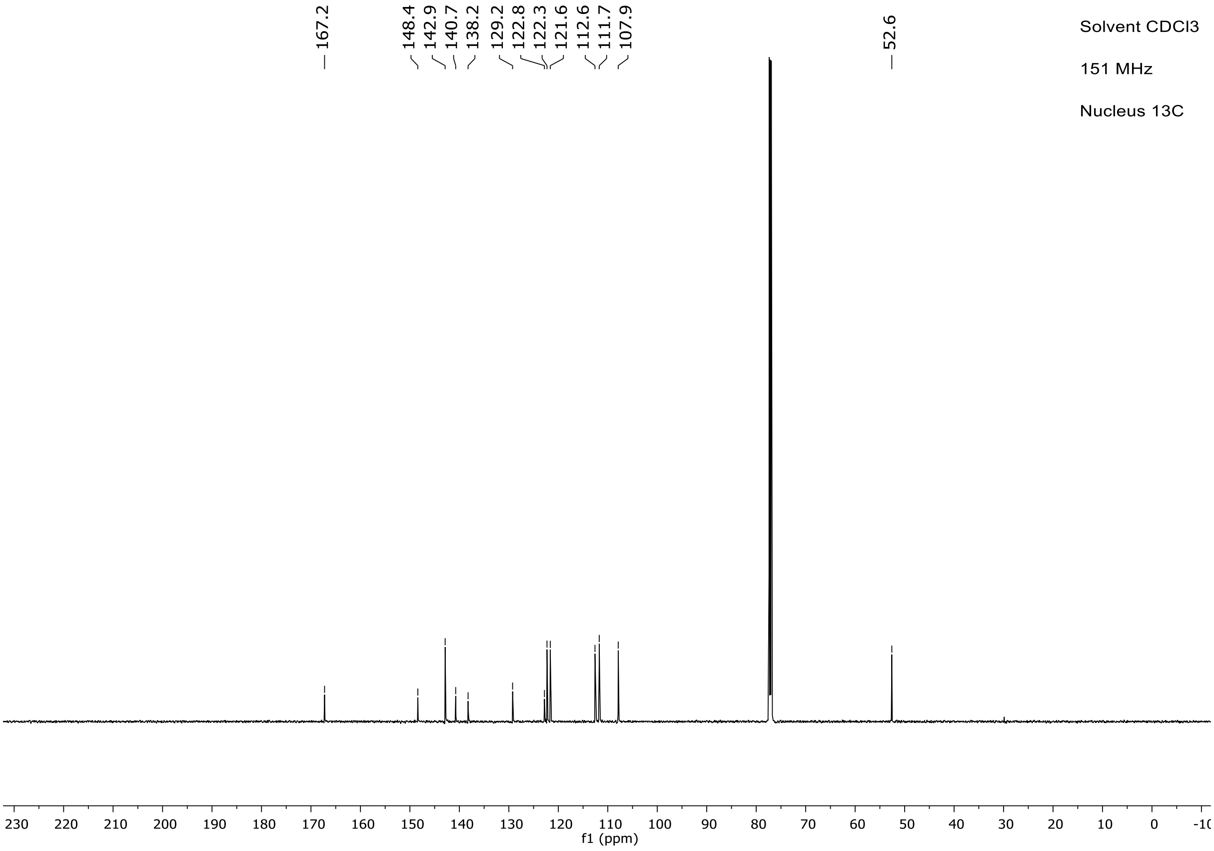

Solvent CD2Cl2
MHz 400
Nucleus 1H
0.80
2.02
0.96
1.00
1.00
1.00
1.00
3.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


Solvent CD2Cl2
101 MHz
Nucleus 13C
167.6
153.7
149.9
145.3
141.9
137.1
129.4
124.7
124.2
123.3
122.7
121.3
112.6
52.8
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)

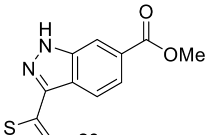


28

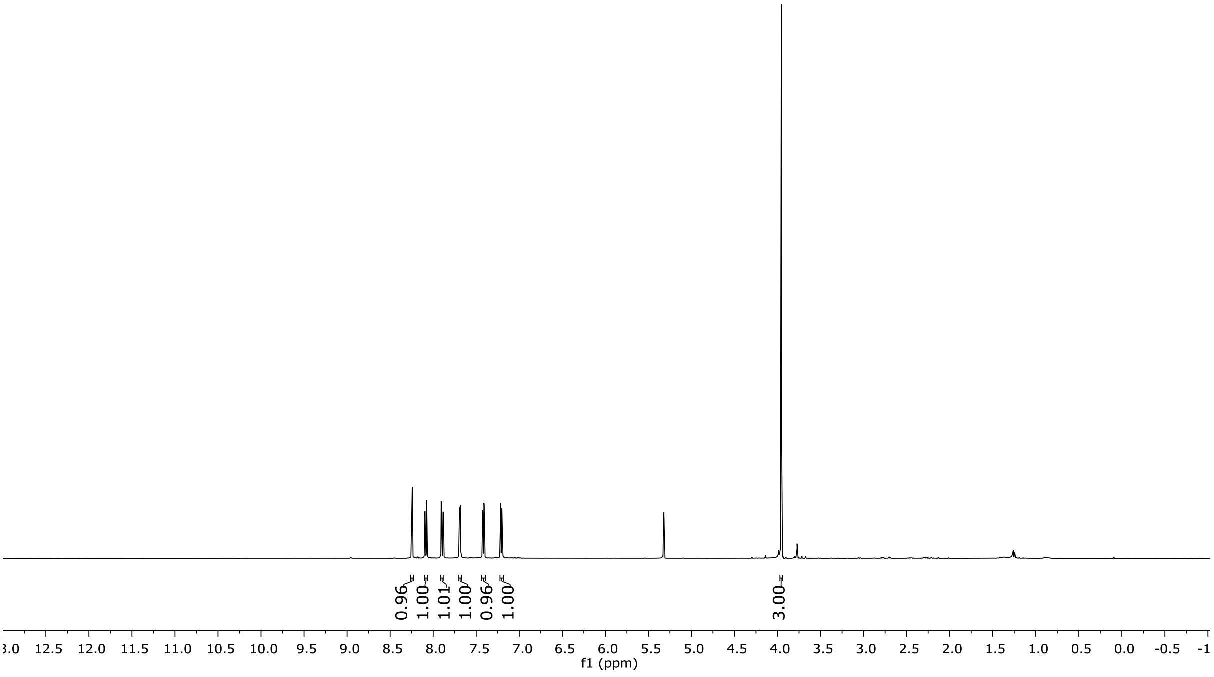
H
N
N
O
OMe
O
Solvent CDCl3
599 MHz
Nucleus 1H
1.00
1.00
1.01
0.96
1.00
1.00
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

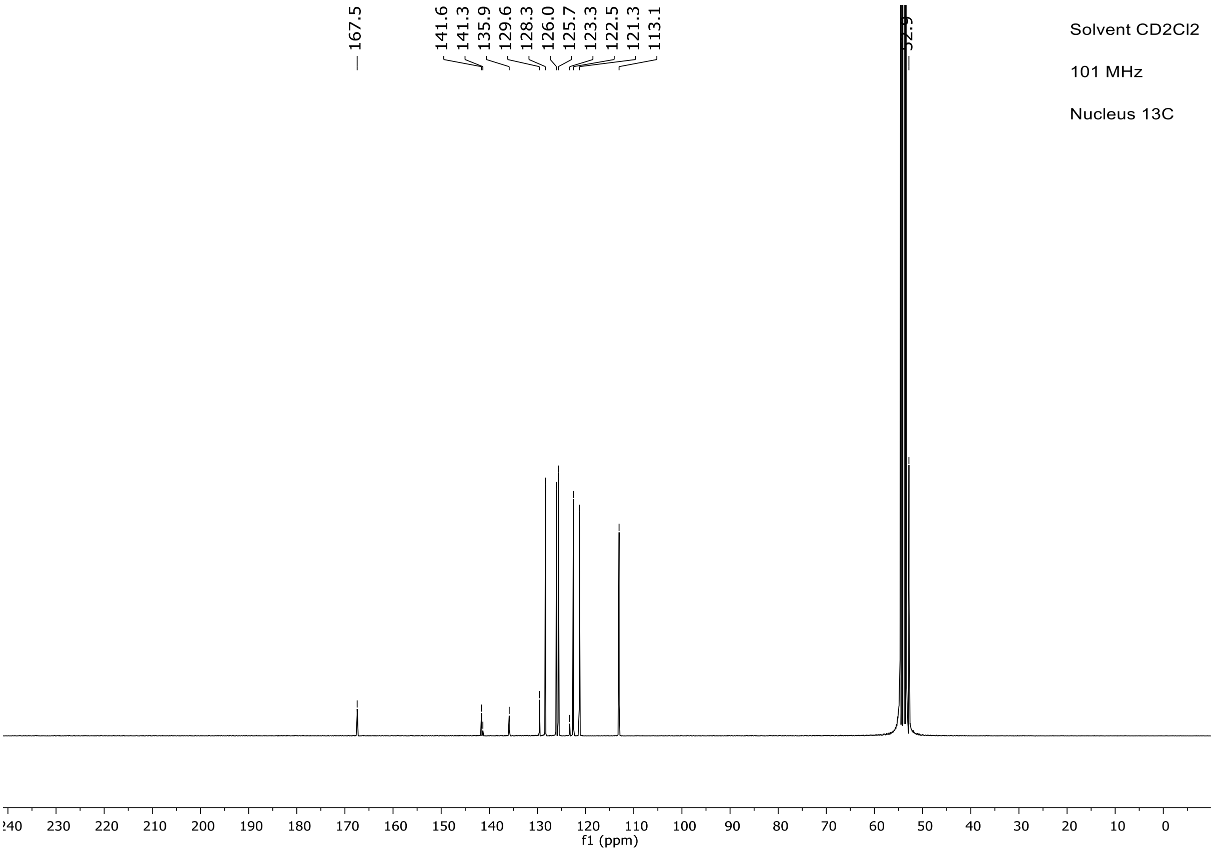


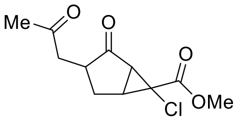
167.2
148.4
142.9
140.7
138.2
129.2
122.8
122.3
121.6
112.6
111.7
107.9
52.6
Solvent CDCl3
151 MHz
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H
N
N
O
OMe
S

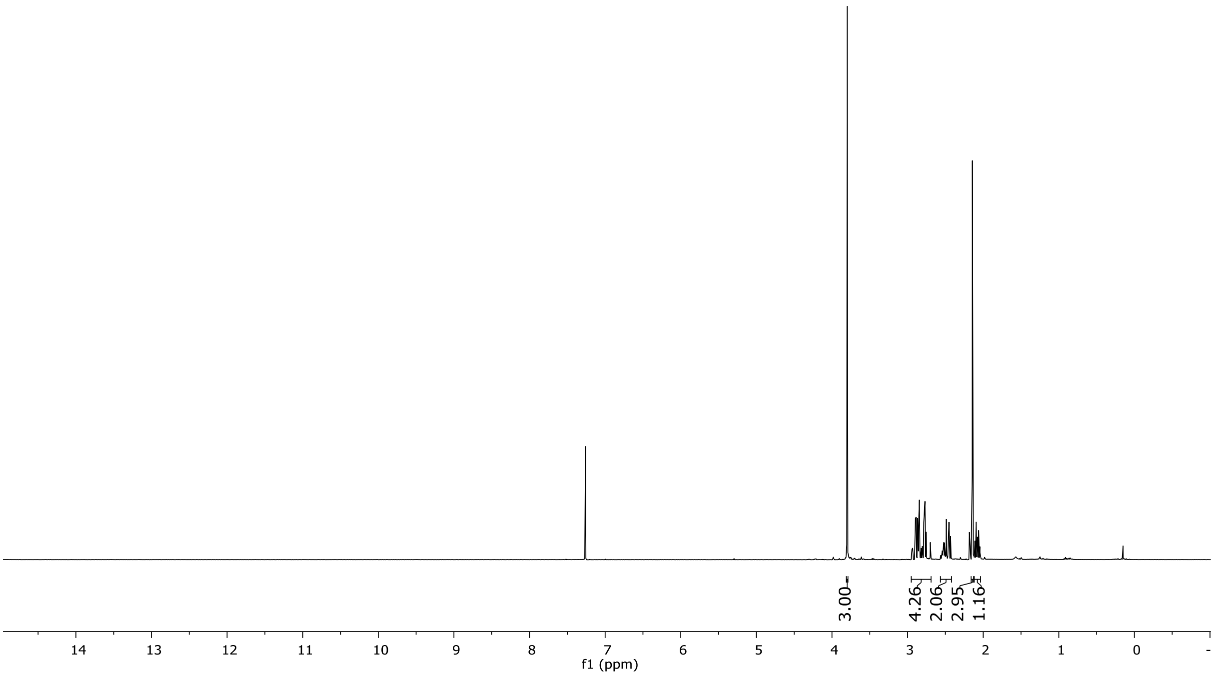
29

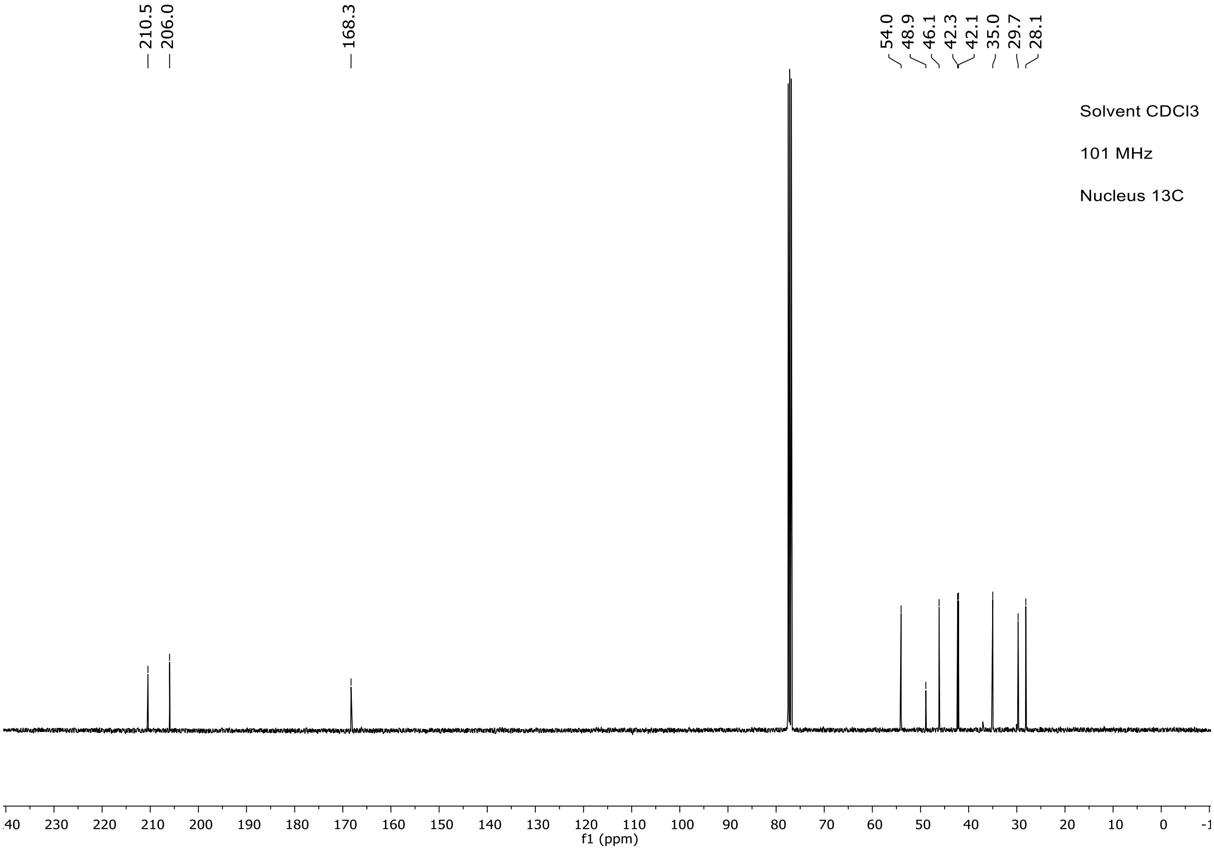

Solvent CD2Cl2
400 MHz
Nucleus 1H
0.96
1.00
1.01
1.00
0.96
1.00
3.00
3.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

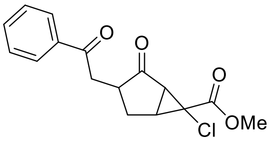

167.5
141.6
141.3
135.9
129.6
128.3
126.0
125.7
123.3
122.5
121.3
113.1
52.9
Solvent CD2Cl2
101 MHz
Nucleus 13C
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
O
O
O
OMe
Cl

30


Solvent CDCl3
MHz 400
Nucleus 1H
3.00
4.26
2.06
2.95
1.16
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


210.5
206.0
168.3
54.0
48.9
46.1
42.3
42.1
35.0
29.7
28.1
Solvent CDCl3
101 MHz
Nucleus 13C
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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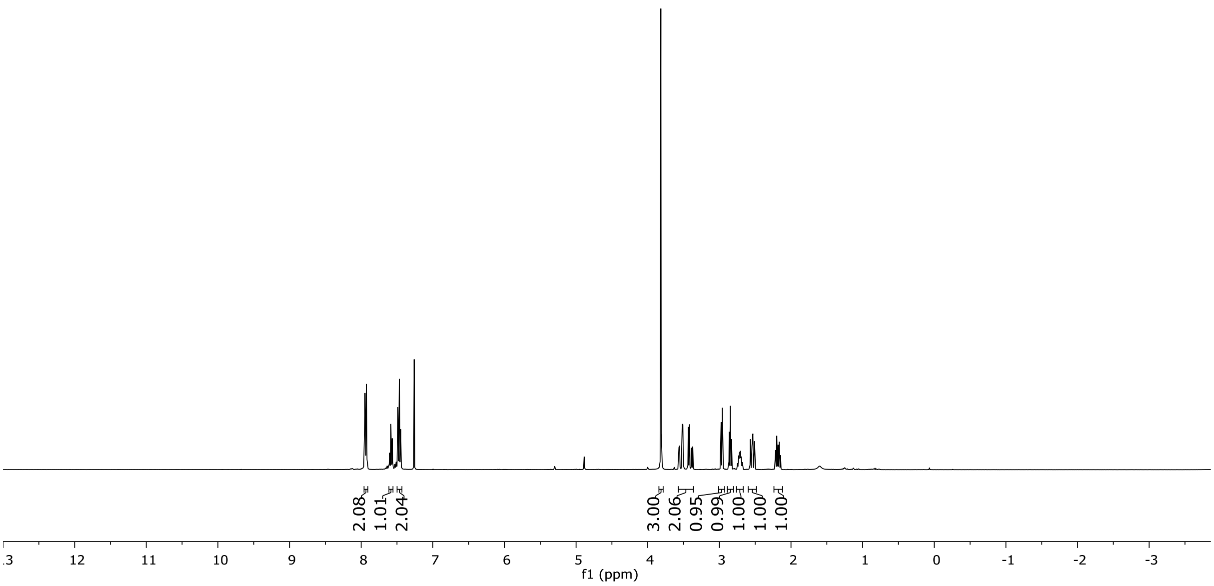
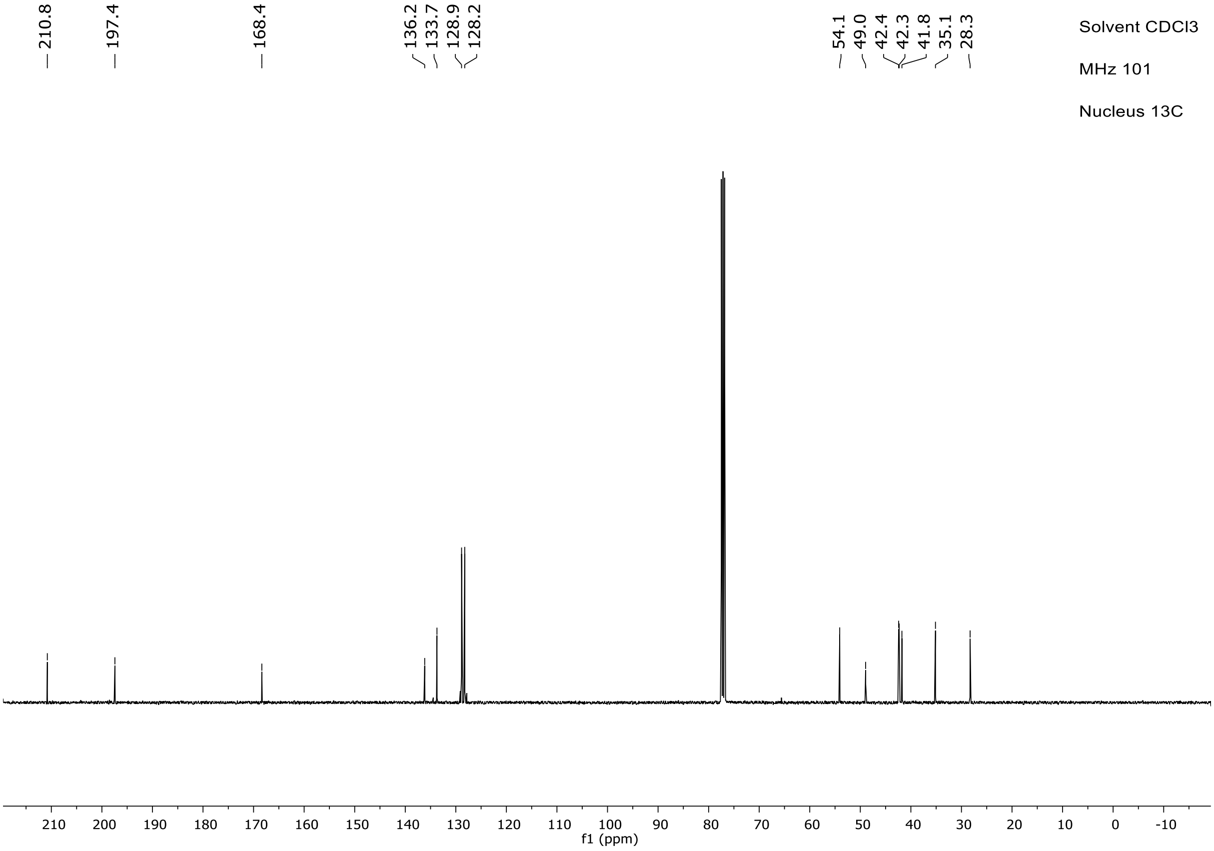
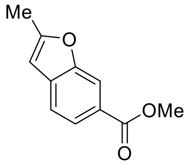
Solvent CDCl3

MHz 400

Nucleus 1H





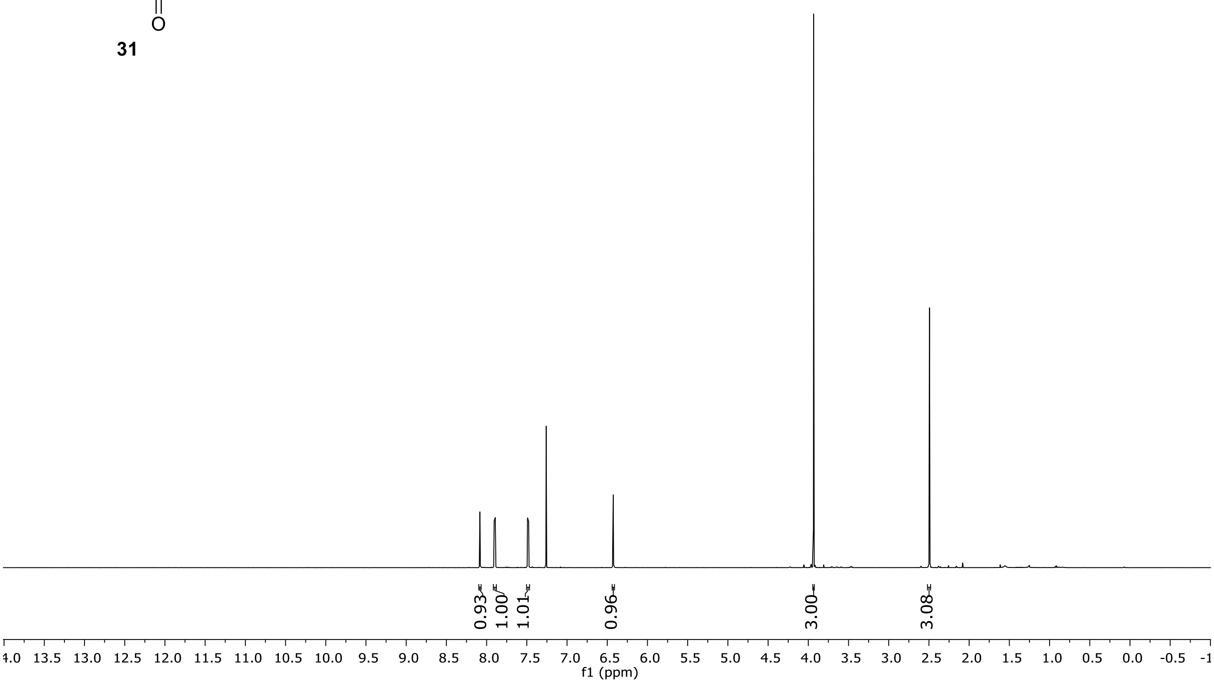


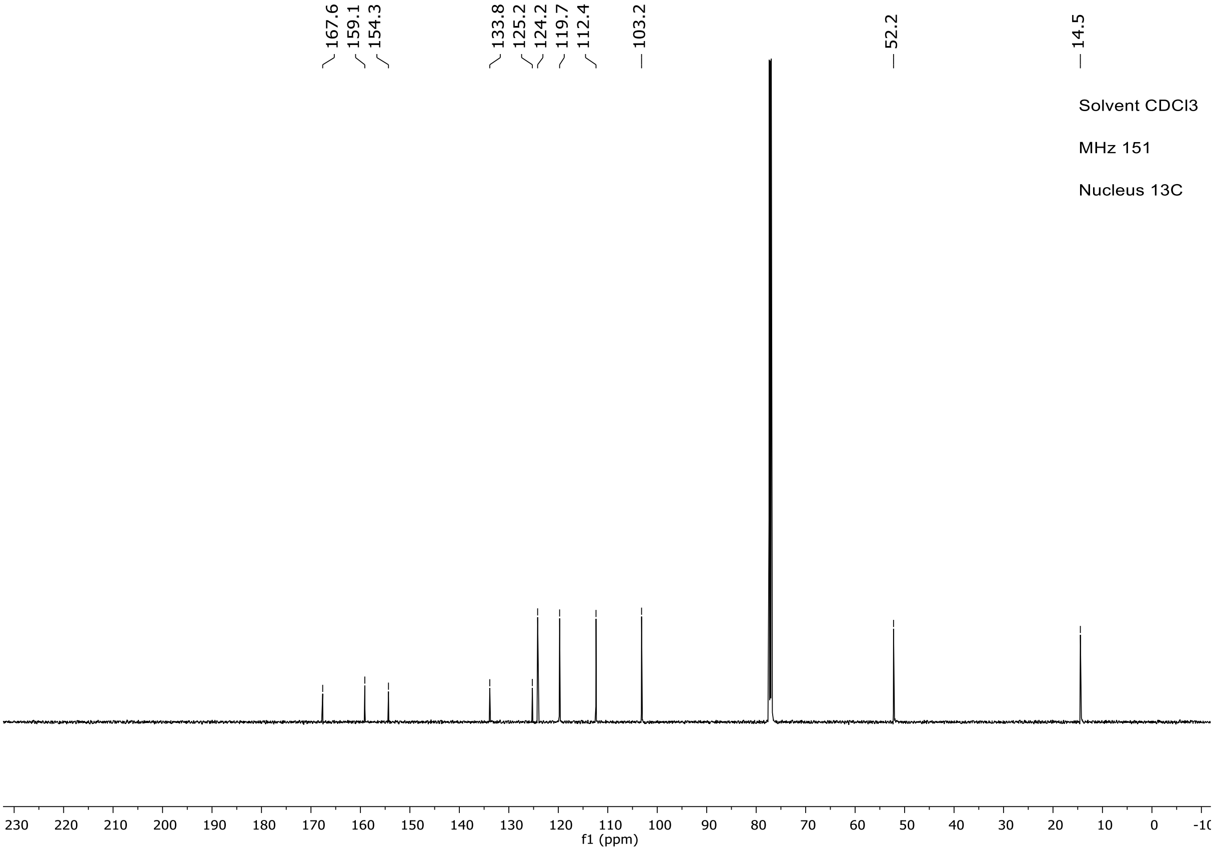
31

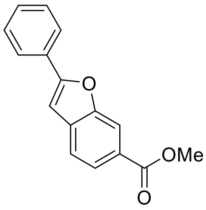
Solvent CDCl3

MHz 599

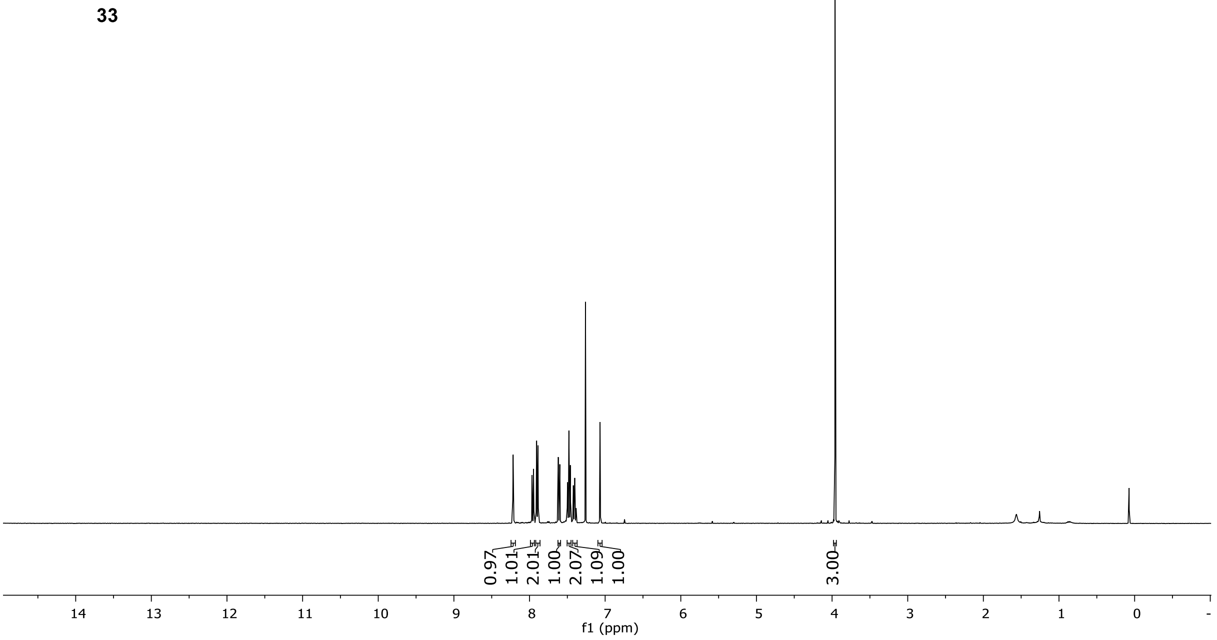
Nucleus 1H

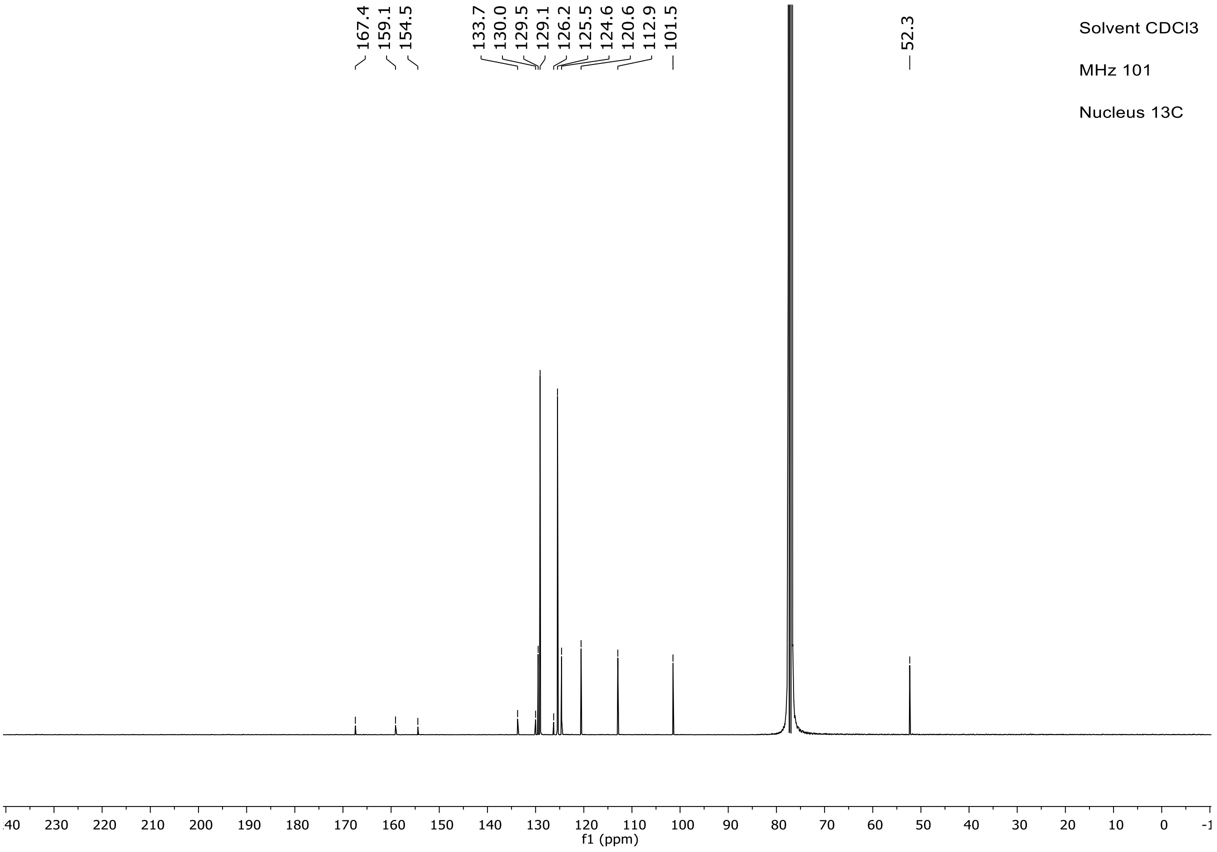


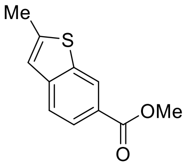



O
OMe
O

33


Solvent CDCl3
MHz 400
Nucleus 1H
0.97
1.01
2.01
1.00
2.07
1.09
1.00
3.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


167.4
159.1
154.5
133.7
130.0
129.5
129.1
126.2
125.5
124.6
120.6
112.9
101.5
52.3
Solvent CDCl3
MHz 101
Nucleus 13C
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)

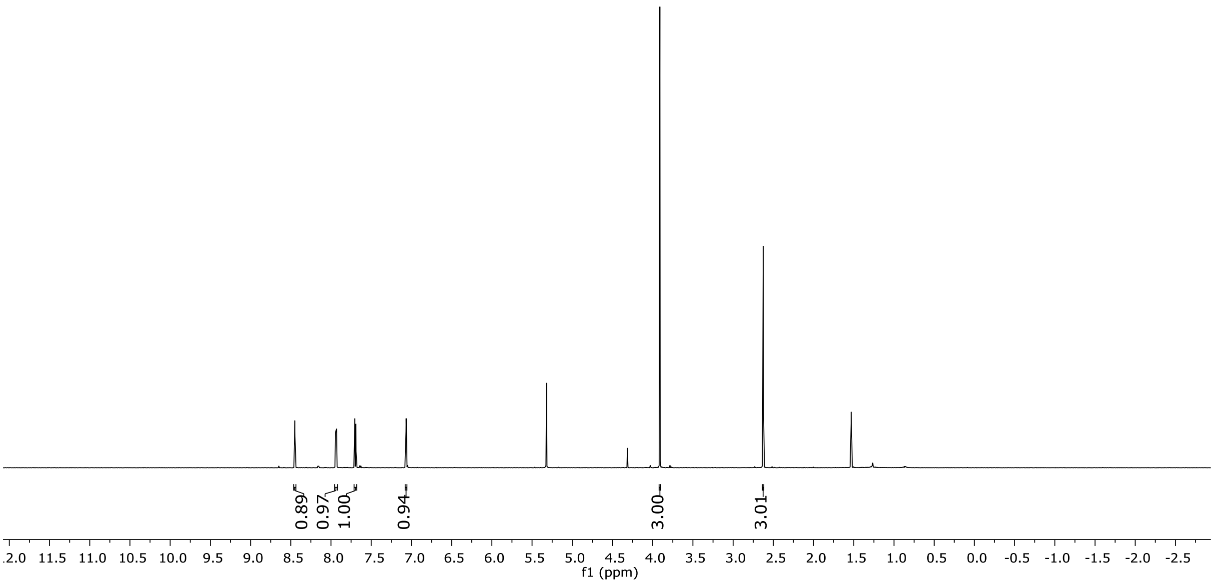


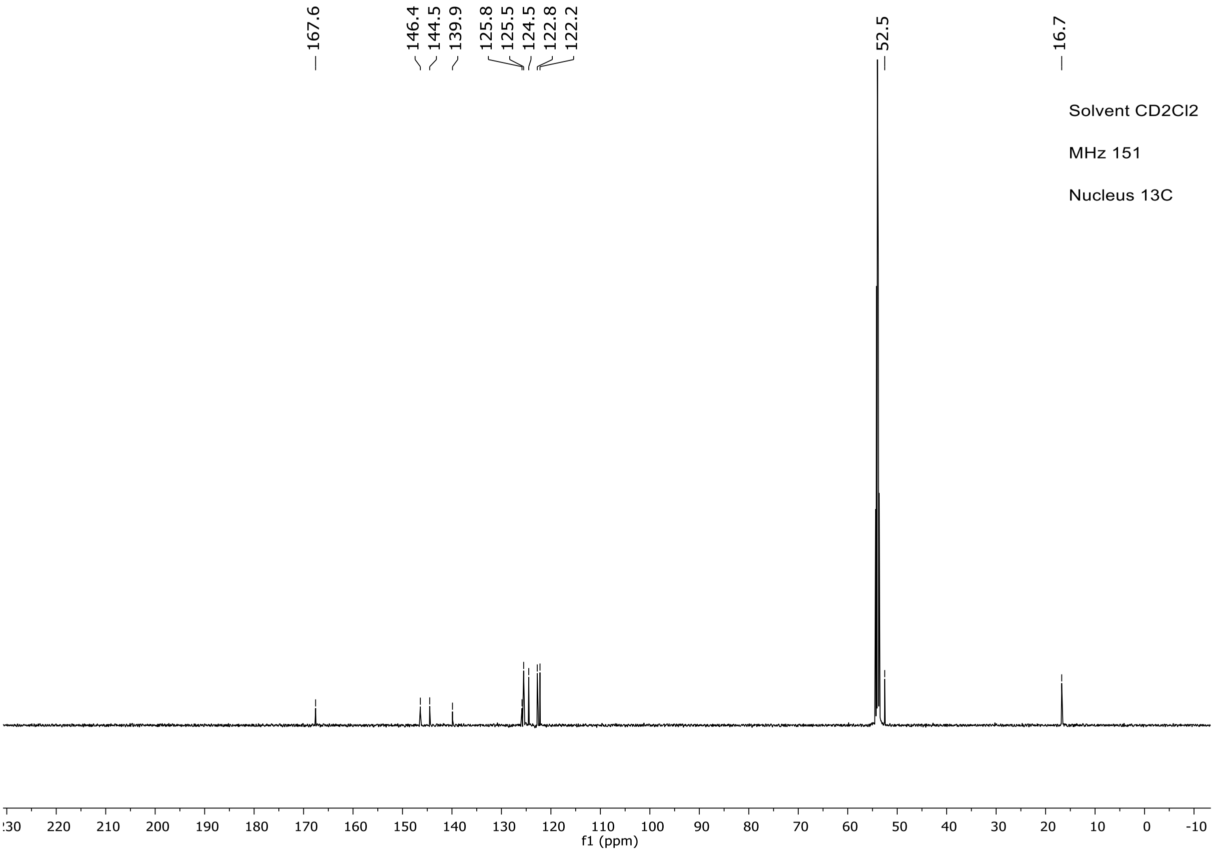
34

Solvent CD2Cl2

MHz 599

Nucleus 1H





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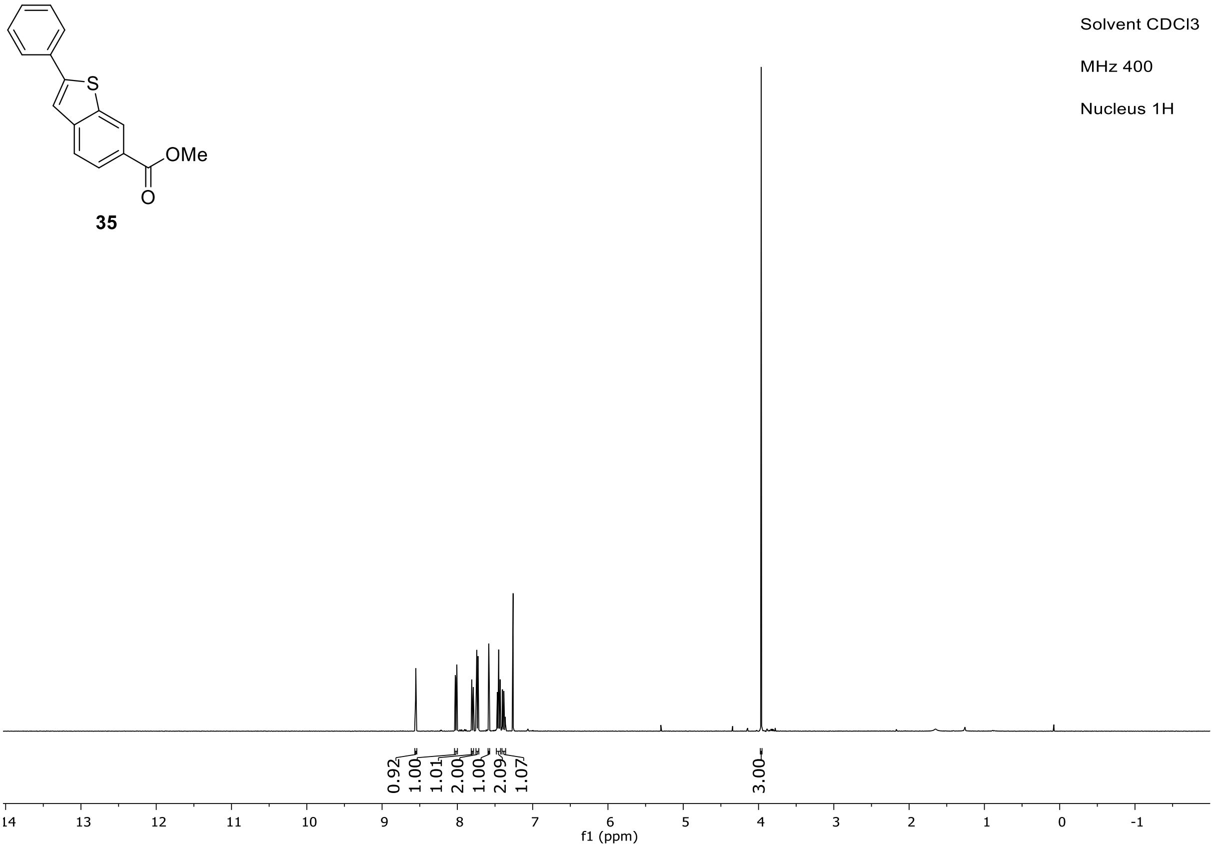
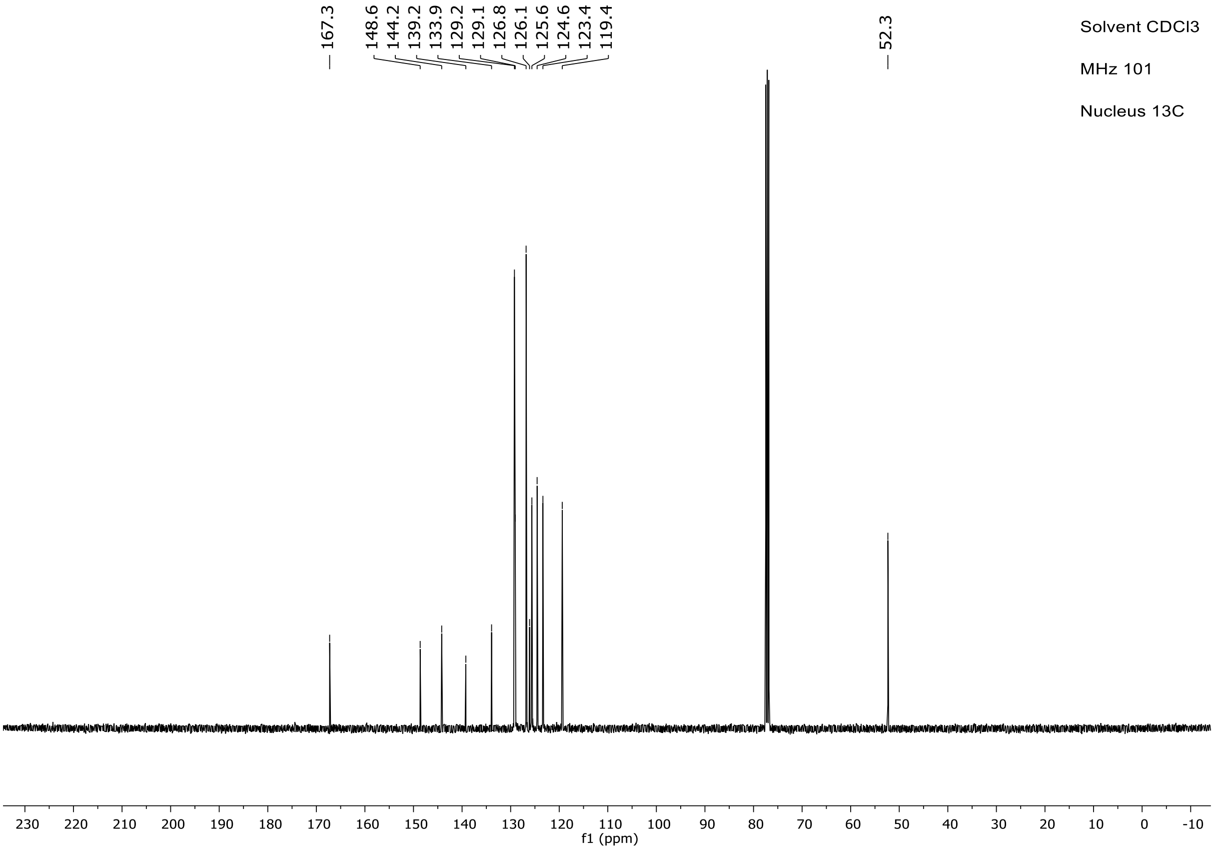

S
OMe
O
Solvent CDCl3
MHz 400
Nucleus 1H
0.92
1.00
1.01
2.00
1.00
2.09
1.07
3.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


167.3
148.6
144.2
139.2
133.9
129.2
129.1
126.8
126.1
125.6
124.6
123.4
119.4
52.3
Solvent CDCl3
MHz 101
Nucleus 13C
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)