


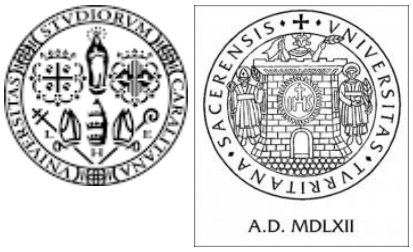

Università degli Studi di Cagliari

DOTTORATO DI RICERCA

Scienze e Tecnologie Chimiche

In convenzione con l'Università degli Studi di Sassari

Ciclo XXX

NEW METHODOLOGIES FOR THE SYNTHESIS OF HIGHLY FUNCTIONALIZED CARBOCYCLES AND HETEROCYCLES

CHIM/06

Presentata da: **Lorenza Ghisu**

Coordinatore Dottorato: **Prof. Stefano Enzo**

Tutor: **Dr. Angelo Frongia**

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ABSTRACT

The main topic of this thesis is the development of new methodologies for the synthesis of highly functionalized carbo- and heterocycles.

The first part (chapter 2) describes an organocatalytic enantioselective synthesis of α-(benzylamino)cyclobutanones. Such products have been achieved by employing a tandem condensation/intramolecular rearrangement/proton transfer reaction and starting from racemic α-hydroxycyclobutanone and a selection of benzylamines. This reaction sequence afforded the products in good to high yields with moderate to high enantioselectivities.

In the second part (chapter 3), a simple and practical protocol for the construction of synthetically important quaternary α-benzyl- and α-allyl-α-methylamino cyclobutanones in good to high yield, via a sequential one pot methylation/Stevens rearrangement, is reported.

Finally, in the third part (chapter 4), a two-step protocol is presented for the preparation of 5-(pyridine-2-ylamino)dihydrofuran-2(3H)-ones from 2-hydroxycyclobutanone and some 2-aminopyridines *via* a catalyst-free synthesis of 2,2-bis(pyridine-2-ylamino)cyclobutanols followed by Dess-Martin periodinane mediated ring expansion.

Keywords – carbocycles, organocatalysis, amines, tryptamines, tandem sequence, rearrangement, ring-expansion, ring-fission

List of publications

I. **Catalytic Enantioselective Synthesis of α-(Benzylamino)cyclobutanones.**

N. Melis, L. Ghisu, R. Guillot, P. Caboni, F. Secci, D. J. Aitken and A. Frongia, **2015**, *European Journal of Organic Chemistry*, *20*, 4358-4366.

II. **Stereoselective aza-Michael addition of anilines to 1-nitro cyclohexene by intramolecular protonation.**

L. Ghisu, N. Melis, F. Secci and A. Frongia., ***2015***, *Tetrahedron Letters*, *56*, 46, 6409-6412.

III. **Synthesis of quaternary α-benzyl- and α-allyl- α-methylamino cyclobutanones.**

L. Ghisu, N. Melis, F. Secci, P. Caboni and A. Frongia, *Tetrahedron*, **2016**, *50*, 8201-8209.

IV. **Synthesis of 2.2-bis(pyridine-2-ylamino)cyclobutanols and their conversion into 5-(pyridine-2-ylamino)dihydrofuran-2(3*H*)-ones.**

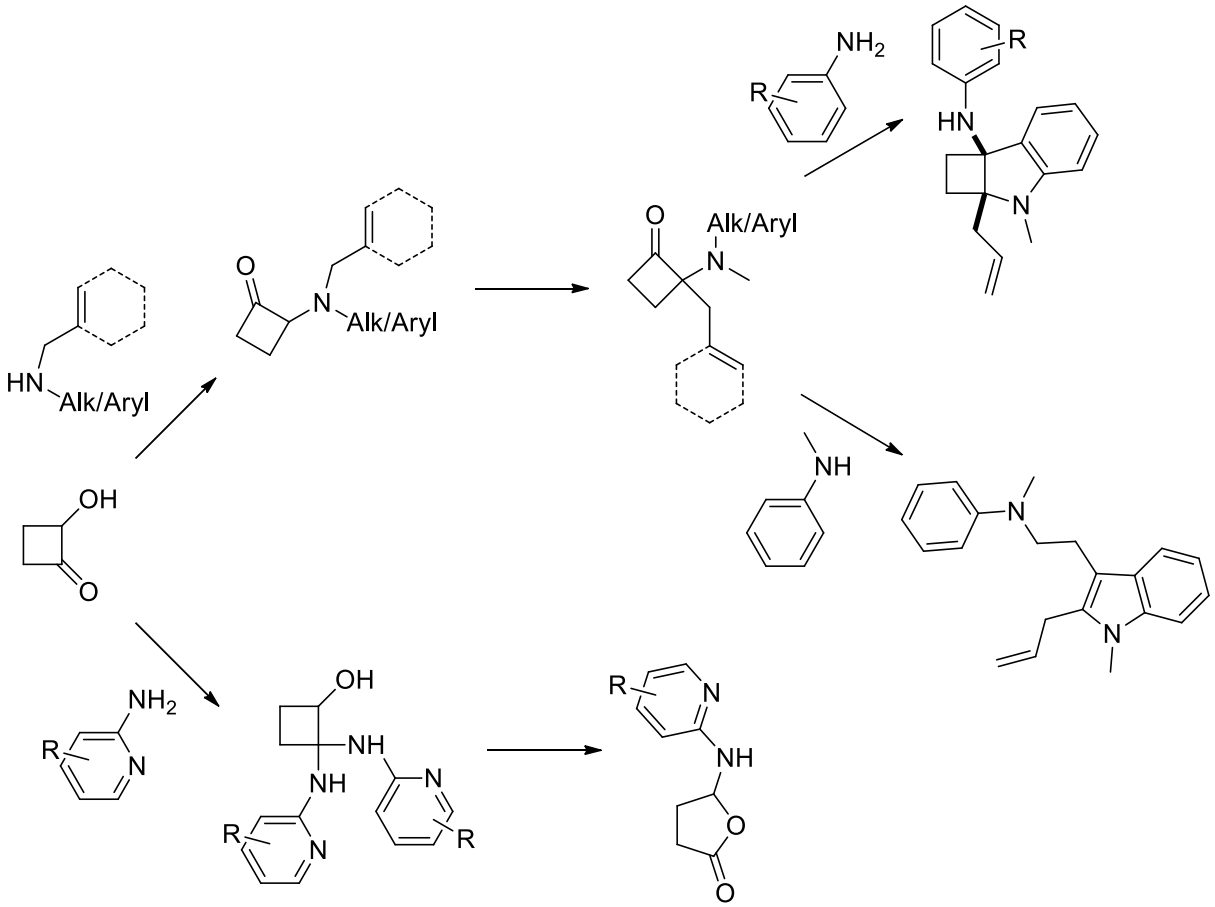
L. Ghisu, N. Melis, F. Secci, P. Caboni, M. Arca, R. Guillot, T. Boddaert, D. J. Aitken and A. Frongia, *Org. Biomol. Chem.,* **2017**, *15*, 9979-9784.

CHAPTER ONE

Introduction and objectives

Among cyclobutane derivatives, 2-hydroxycyclobutanone proved to be extremely appealing due to the presence of two functional groups on a strain four-membered ring and, consequently, undergoes several chemical transformations such as selective aldol reactions[1], nitrogen insertion[2] and amination reactions[3]. These latter reactions led to the formation of 2-arylaminocyclobutanones[4], which are intrinsically intriguing due to their reactivity and to the possibility to act as intermediate themselves. In fact, they can further react with another amine for yielding cyclic heteroaromatic scaffolds such as tryptamines through both two-step[5] and one-pot procedures.

Scheme 1.1 Graphical abstract



At the outset, in order to gain access to new synthetically important molecular functions, we were interested in testing if our recently developed condensation reaction between α-hydroxy cyclobutanone and aromatic amines could be further diversified to include the synthesis of challenging fully aliphatic α-(benzylamino)cyclobutanones and quaternary α-benzyl- and α-allyl-α-methylamino cyclobutanones. The results reported in this thesis provide the first general and

efficient route to assemble these important structural motifs. In addition, the above-mentioned products have been further manipulated, affording new highly functionalized tryptamine derivatives and some valuable cyclobuta-2,3-fused indolines. A big effort has been made in these last years for the development of new synthetic protocols to gain access to cyclopropan-, cyclopentan- and cyclohexan-indolinic C2, C3-fused systems. On the contrary, the analogous term containing a cyclobutanic ring have not received the same attention. Indeed, a synthetic protocol, based on the gold-catalyzed cyclization reaction [2+2] between an indole and an allenamide, was published only in 2015 by Bandini et al.[6] Finally, during our studies we also found that *N*-heteroarylamines reacted differently with the respect to aryl-and alkyl amines and led to the formation of 1-hydroxy-2-diaminocyclobutanone scaffolds that is stabilized by an intramolecular hydrogen bonding. Furthermore, our attempts of obtaining the corresponding 2-diaminocyclobutanone derivative by Dess-Martin periodinane oxidation, surprisingly, led to the unexpected formation of 5-(pyridin-2-ylamino)dihydrofuran-2(3H)-ones, which have not previously been described in the literature, through a new ring expansion process. Dihydrofuran-2(3H)-ones are common skeletons found in several biologically interesting compounds and widely used in organic synthesis.[7] Although the preparation of these heterocycles has attrached broad interest from the synthetic community, it was surprising to find that several structural variants and/or substitution patterns were as yet unknown or relatively little exploited. In this respect, the number of 5-nitrogen-substituted γ-lactones reported was fairly small and moreover, general synthetic strategies for the construction of 5-aza-heteroarylamino γ-lactones have not been described previously.

An introduction is given into the area of the chemistry of cyclobutane derivatives which forms the basis of the literature review within this thesis.

1.1 The application of cyclobutane derivatives in organic synthesis: general introduction

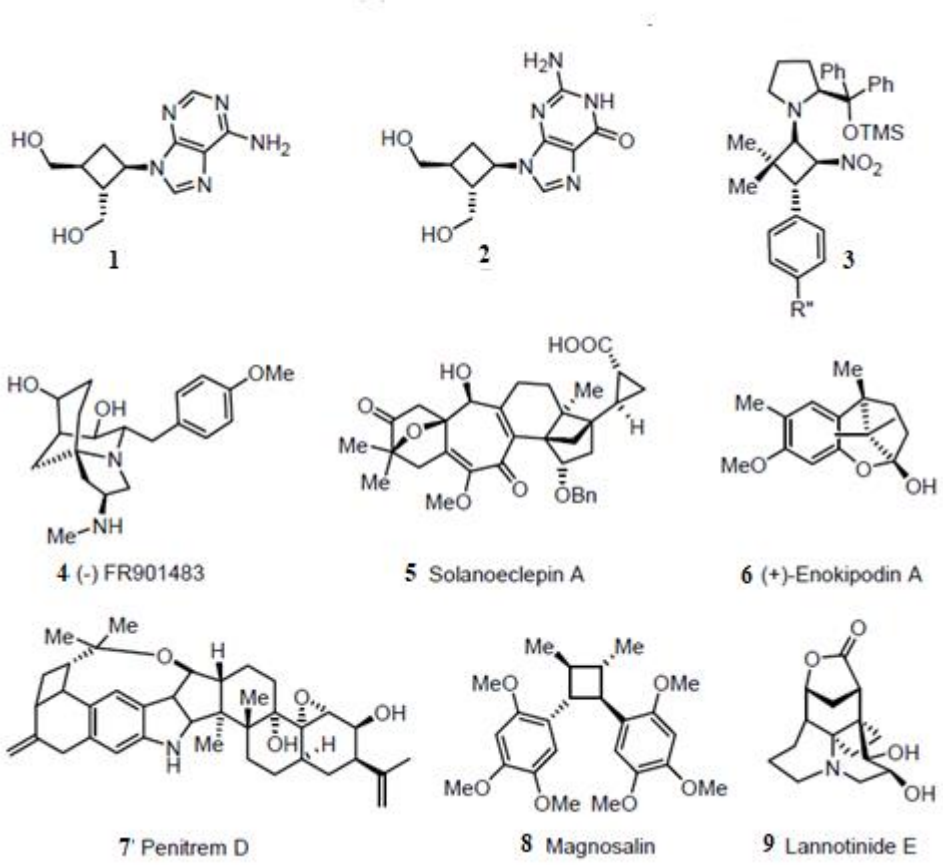
Cyclobutanic rings are very important building blocks of both natural and synthetic molecules. They can be found in a variety of compounds like alkaloids, fatty acids, antifungals, secondary plants metabolites such as compound **9**[8,9] and others. They are also structural motifs of different kinds of bioactive molecules and promising drugs like the antiviral compounds **1** and **2**[10,11,12,13].

A number of carbocycles, heterocycles and open chain products can be obtained by the range of interesting transformations cyclobutanes are able to undergo, including ring opening to acyclic compounds, ring contraction to cyclopropanes, ring expansion and α-functionalization.

Cyclobutane derivatives are important starting materials for a large number of total syntheses, some examples are the syntheses of the compounds **4-8.**[14,15,16,17] A very large number of patents

and papers have been published about the broad synthetic range of applications of cyclobutane chemistry.[18]

Figure 1.1 Cyclobutane containing natural products and synthetic intermediates.



This is the reason why cyclobutanes are considered such useful intermediates for chemical synthesis and, consequently, it explains the importance of syntetic routes that allow to access them and the increase of the interest in this field of synthesis.

Important methods for the synthesis of cyclobutane rings are cycloadditions, the cyclopropylcarbinyl ring expansion and the direct functionalization of precursors.

In the light of the increasing attention towards ecofriendly procedures, both the preparation and the transformation of cyclobutanic compounds have been revisited with particular interest for green strategies and the use of new high-performing organic catalysts.[19]

The properties of these scaffolds are related to their inherent ring strain and their structural rigidity, that induces substituents to assume a well-defined spatial arrangement, and to their angular and torsional effects.[20]

Cyclobutane is interesting because its chemistry is in-between the very reactive (for a hydrocarbon) cyclopropane and other cycloalkanes superior homologues. Its structure also

presents very interesting questions. The presence of a torsional interaction between the two adjacent methylene groups reduces the exact magnitude of the C-C-C angle to 88° instead of 90°, indicating that it adopts a puckered structure. This puckering reduces the torsional strain that would be present in the system if the structure was totally planar, with eclipsed methylene groups and a 90° C-C-C bond angle. The reduction of the C-C-C bond angle causes, at the same time, an increase of the bond strain. The geometry of cyclobutane is the result of a tension between these terms. Another important structural feature of cyclobutanes is that it has been found that the methylene groups in the cycle are rotated inwards. Concerning the strain energy of the molecule, defined as the difference in heat of formation between the compound of interest and that of an "unstrained model", it is very similar to the one reported for the cyclopropane. Their values are, respectively, 26.3 kcal·mol^{-1} and 27.5 kcal·mol^{-1}.[21]

1.2 ***Cyclobutane derivatives synthesis***

Cyclobutane derivatives are accessible by many preparative methods that are known to give good yields, e.g. photochemical methods, ring expansions and direct functionalization of cyclobutanes.

1.2.1 **Cycloaddictions**

Among cycloaddiction reactions, [2 + 2] photocycloaddictions are the most widely used methods to synthetize carbocyclic compounds, other than the Diels-Alder reaction.[22]

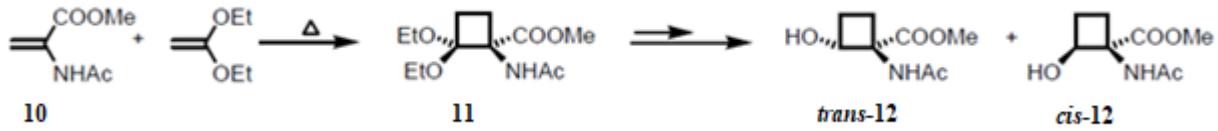
The first examples of [2 + 2] photocycloadditions were conducted using identical olefins and were, as a matter of fact, photodimerizations. The very first compound obtained by [2 + 2] photocycloaddition was the thymoquinone, discovered by Liebermann in 1877.[23]

In the 1960s, different olefines started to be employed, and the possibility to obtain just one among the possible products by using an eccess of one of the two olefins. was demonstrated by Schenck et al.[24]

From 1982 on, the interest in obtaining products with a definite absolute configuration have been increasing. Tolbert and Ali[25] showed that, performing a [2 + 2] photocycloaddition of chiral methyl *l*-bornyl fumarate to trans-stilbene, it was possible to obtain dimethyl μ-truxinate in 90% of enantiomeric eccess.

Peregrina and co-workers[26] published a thermal [2+2] stereoselective cycloaddiction involving 2-acylaminoacrilates **10** to obtain stereoselectively 2-hydroxycyclobutane-(*R*)-amino acid serine analogues (c4Ser) **12**. The procedure includes a Michael-Dieckmann-type reaction followed by deacylation and hydrolysis (Scheme 1.2).

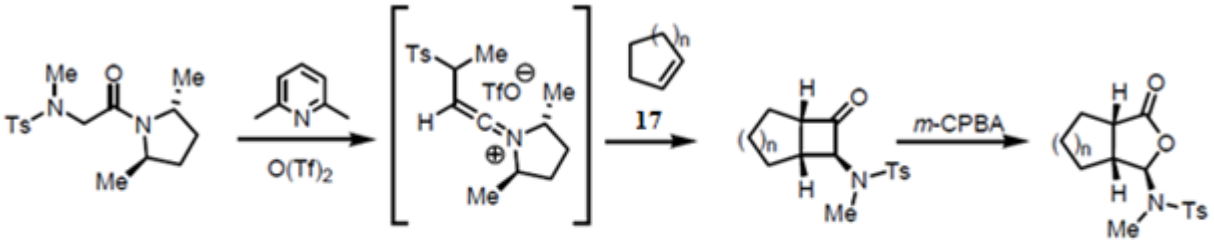
Scheme 1.2. Stereoselective synthesis of (*cis/trans*)-2-hydroxyciclobutane amino acids.



10 11 *trans*-12 *cis*-12

Ghosez and co-workers[27] in 2002 reported a two-step sequence for the synthesis of lactol derivative **16** by asymmetric vicinal acylation of olefins. A transient chiral keteniminium salt **14** obtained from N-tosylsarcosinamide **13** reacted with an olefin **17** by [2+2] cycloaddition affording the *cis*-α-aminocyclobutanones **15**. The good enantioselectivity of this process was retained during the subsequent *m*-CPBA regioselective Baeyer-Villiger oxidation and the products **16** were obtained in good yields (Scheme 1.3).

Scheme 1.3. [2+2] cycloaddiction of chiral keteniminium salts in the synthesis of cyclobutanones.

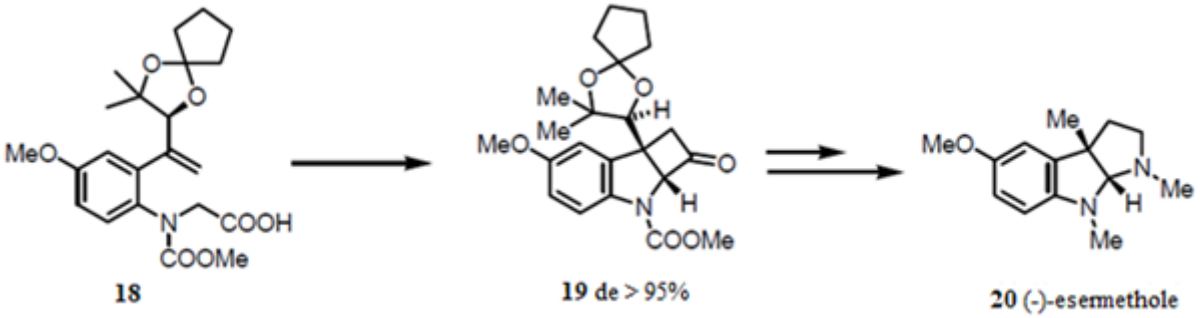


13 14 15 16

68-98 % ee
20-71% yield

In 2013, Shishido and co-workers[28] found the [2+2] intramolecular cycloaddition of the starting material **18** an efficient method to synthetize the (-)-esermethole **20**[29]. In the presence of a dioxolane chiral auxiliary, the scaffold of the tricyclic unit in the compound **19** was obtained in de > 95% (Scheme 1.4).

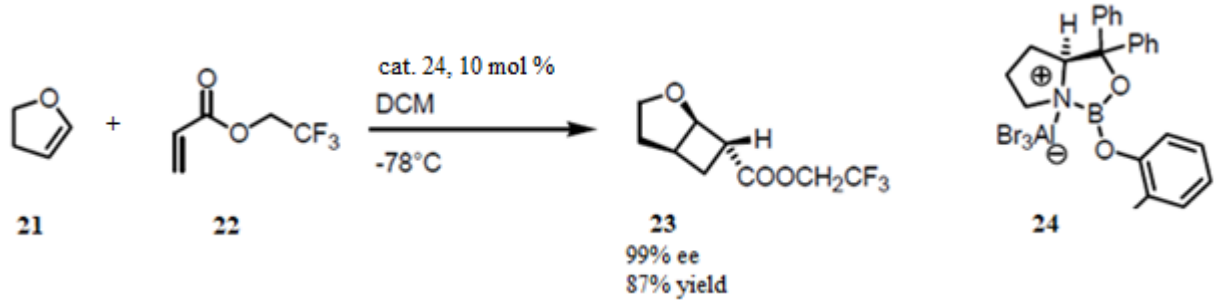
Scheme 1.4. Enantioselective access to pyrrolidinone alkaloids.



18 19 de > 95% 20 (-)-esermethole

Corey et al. showed[30] in 2007 an organocatalyzed [2+2] vinylogous cycloaddition of esters **22** to dihydrofuran **21** in the presence of an *in situ* generated oxazaborolidine-aluminum bromide complex **24**. This methodology led to the formation of the *exo*-[2+2]-cycloadduct **23** in 87% yield and 99% *ee* (Scheme 1.5).

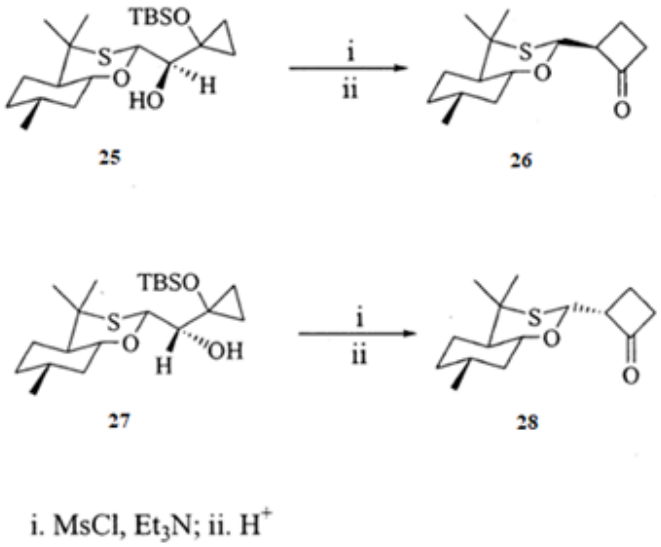
Scheme 1.5. [2+2] enantioselective vinylogous cycloaddition of esters with dihydrofuran.



1.2.2 **Cyclopropylcarbinyl precursors ring expansion**

The ring expansion of cyclopropylcarbinyl precursors to cyclobutanes passes through the formation of a bicyclobutonium ion. The process in itself is not very efficient for the synthesis of cyclobutanes due to the low stereoselectivity. The presence of a chiral auxiliary at C-1 of the cyclopropane ring improves the stereoselectivity of the process.[12]

Scheme 1.6. Enantioselective ring expansion of cyclopropilmethanols to cyclobutanes.



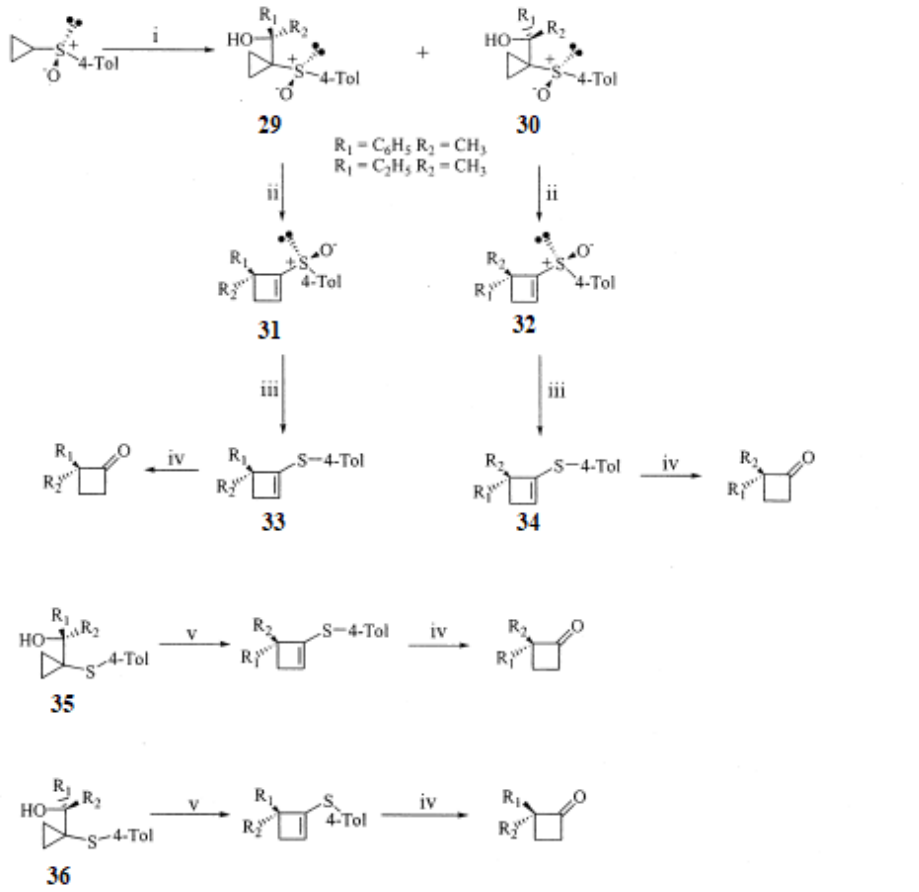
Nemoto et al.[31] obtained the product **28** in an enantiomerically pure form by means of a rearrangement via mesylate under acidic conditions of the oxathianylmethyl-substituted

cyclopropane **25**. The ketone **26** is formed in a stereospecific manner and the epimer **27** reacts in a similar way to afford the compound **28** (Scheme 1.6).

The chiral sulfinyl group is also useful in inducing diastereoselectivity. Hiroi and coworkers[32,33] reported a procedure for the synthesis of the chiral cyclobutanone derivatives **33** and **34** from the cyclopropane methanol diastereomers **29** and **30**. The reagents are converted into the correspondent cyclobutenes **31** and **32**. Subsequently, upon deoxygenation of **31** and **32** the respective thio enol ethers **33** and **34** are generated and, finally, transformed into the correspondent cyclobutanones with good yields between 62% and 88% and *ee*'s of 78-100%.

The rearrangement of the pure enantiomers of sulfanyl cyclopropyl carbinols **35** and **36**, obtained from deoxygenation of **29** and **30**, gave cyclobutenes with retention at the migration terminus (Scheme 1.7).

Scheme 1.7. 1,2-asymmetric rearrangement of chiral sulfinyl cyclopropanes to α,α- disubstituted cyclobutanones.



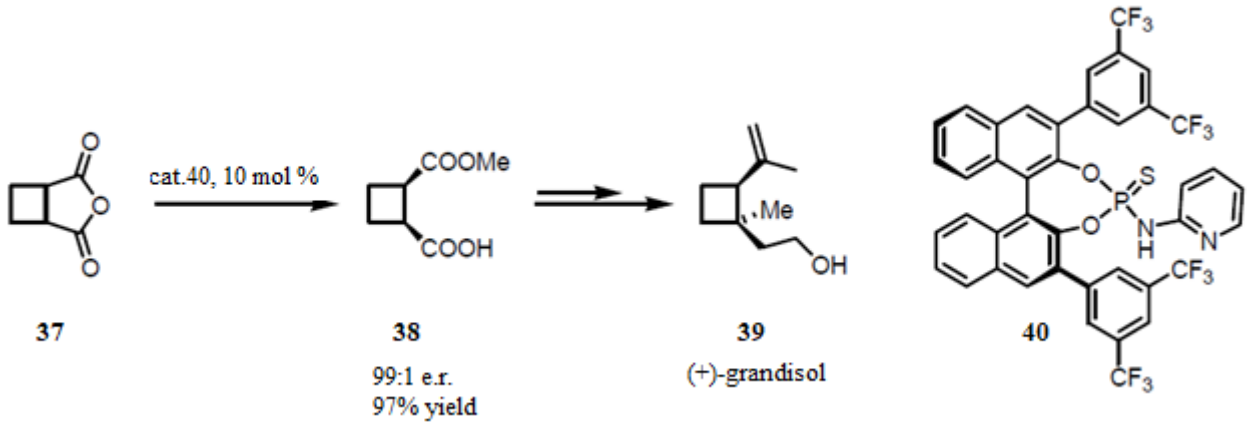
i. BuLi, R_1COR_2; ii. cat. TsOH, C_6H_6 reflux; iii. AcCl, CH_2Cl_2; iv. $TiCl_4$, $Pb(OH)_2$, H_2O; v. MsCl, Et_3N, THF

1.2.3 **Direct functionalization**

The category of direct functionalization methods includes the desymmetrization and the biocatalytic resolution of cyclobutane derivatives.

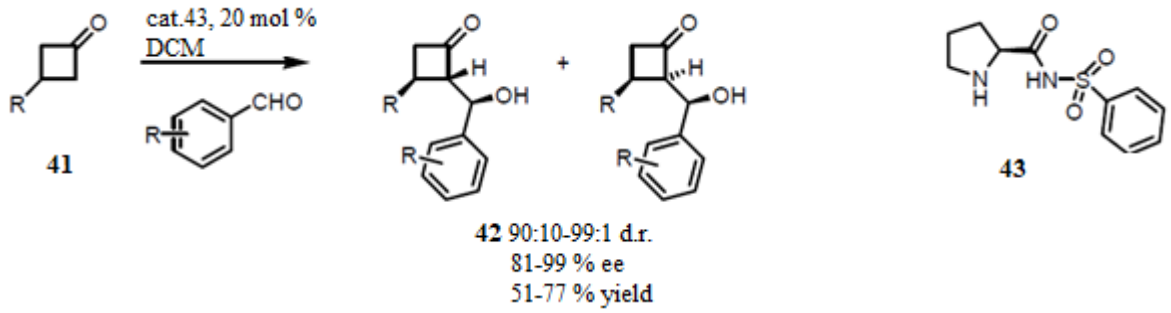
List and co-workers[34] published the synthesis of a new class of chiral binaphtylphosphoric acids-pyridinamides-based catalysts **40** for the enantioselective desymmetrization of *meso* anhydrides. The reaction proceeds through the enantioselective anhydride cleavage and the selective esterification of a carboxylic unit affording compounds like **38** in high yields and *ee*. This reaction protocol was applied for the boll weevils Anthonomous grandis Boheman pheromone (+)-grandisol **39 (**Scheme 1.8).

Scheme 1.8. Bifunctional Brønsted acid based desimmetryzation of meso cyclobutaneanidrides.



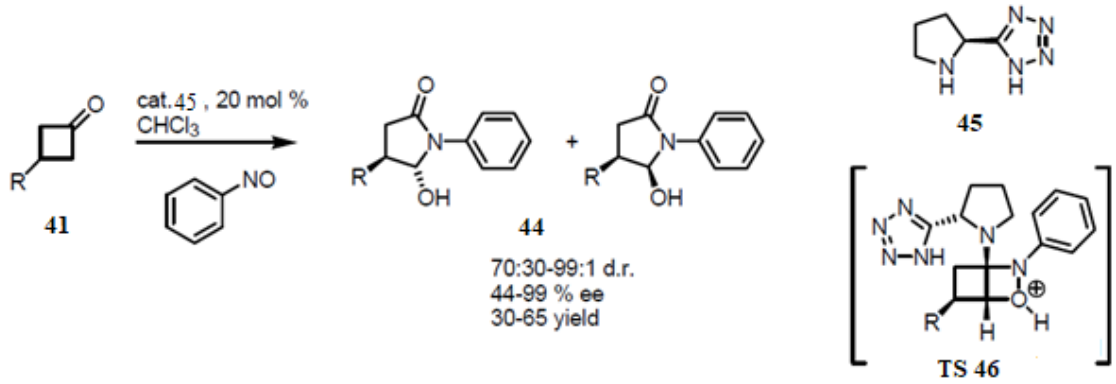
Frongia and Piras[35] reported the enantio- and diastereoselective desymetrization of 3-substituted cyclobutanones **41**. In the presence of *N*-phenylsulfonyl-(*S*)-proline **43** as a catalyst, an aldol reaction took place giving the corresponding functionalized cyclobutanones **42** in good yield and with excellent diastereo- and enantioselectivity (Scheme 1.9).

Scheme 1.9. Desymmetrization of 3-substituted cyclobutanones via organocatalyzed aldol reactions.



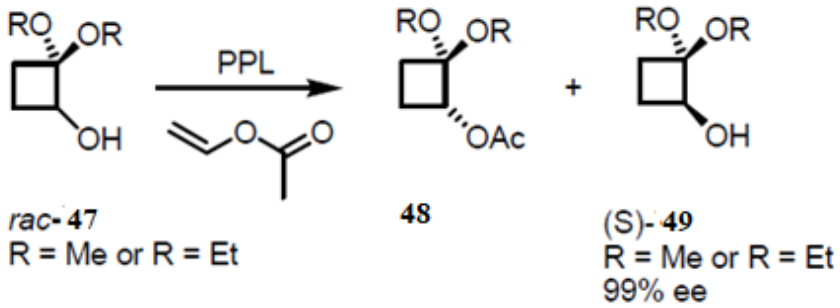
The same research group showed another method for the enantioselective desymmetrization of 3-substituted cyclobutanones **41**[36]. The protocol consists in an *O*-nitrosobenzene alkylation-cyclobutanone ring expansion catalyzed by proline derivatives, and, in particular, by the tetrazole derivative **45,** through the formation of the transition state **46**. The 4-substituted-5-hydroxy-γ-lactams **44**, containing two new stereogenic centers were obtained in good yields and *ee* (Scheme 1.10).[37,38]

Scheme 1.10. Organocatalyzed synthesis of chiral 4-substituted γ-lactams.



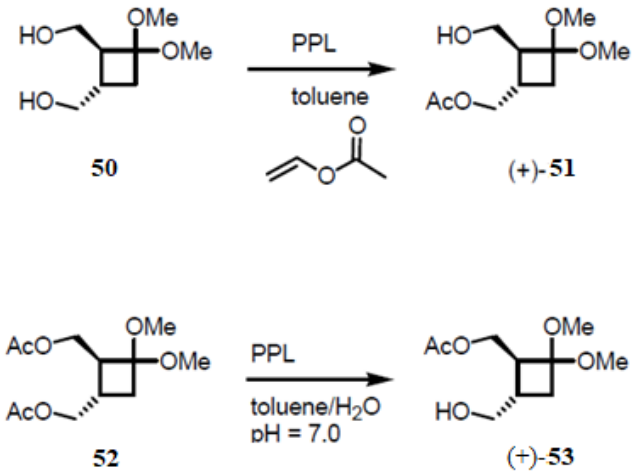
A biocatalytic method for the regio- and enantioselective resolution of cyclobutane derivatives was presented by Fadel et al.[39] The two (±)-alcohols *rac*-**47** were treated with porcine pancreatic lipase PPL, giving the optically pure ester **48** and the cyclobutane alcohol (*S*)-**49** as a pure enantiomer (Scheme 1.11).

Scheme 1.11. Enzymatic transesterification of cyclobutanols.



Another PPL-based protocol was reported by Lee-Ruff.[40] The procedure consists in the resolution of the diol **50** in toluene/vinylacetate to furnish the ester **51** as pure compound. Upon hydrolysis with PPL at pH 7.0 in toluene/water, the cyclobutane diacetate **52** was converted into the monoacetate (+)-**53** in 97% yield. The products were found to be useful key intermediates in the synthesis of chiral cyclobutane nucleosides[11] and aminoacids (Scheme 1.12).[12,41,42,43]

Scheme 1.12. Stereoselective enzymatic esterification and hydrolysis of cyclobutanols.



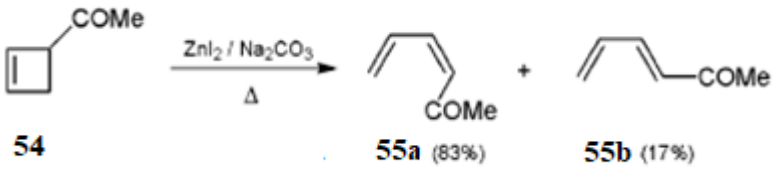
1.3 Reactivity of cyclobutane rings

1.3.1 **Ring opening reactions**

In this kind of reactions, cleavage rate and point depend on the presence of substituents on the ring, the reaction mechanism, the nature of the reagents and the reaction conditions[18].

Houk et al.[44] studied the inward opening reaction reversal to the outward mode of electrocyclization. The process was performed adding the soft Lewis acid zinc iodide during the thermal opening of 3-acetylcyclobutene **54**. Both the *Z* and *E* dienes **55a** and **55b** were obtained in a ratio 83:17 Scheme 1.13).

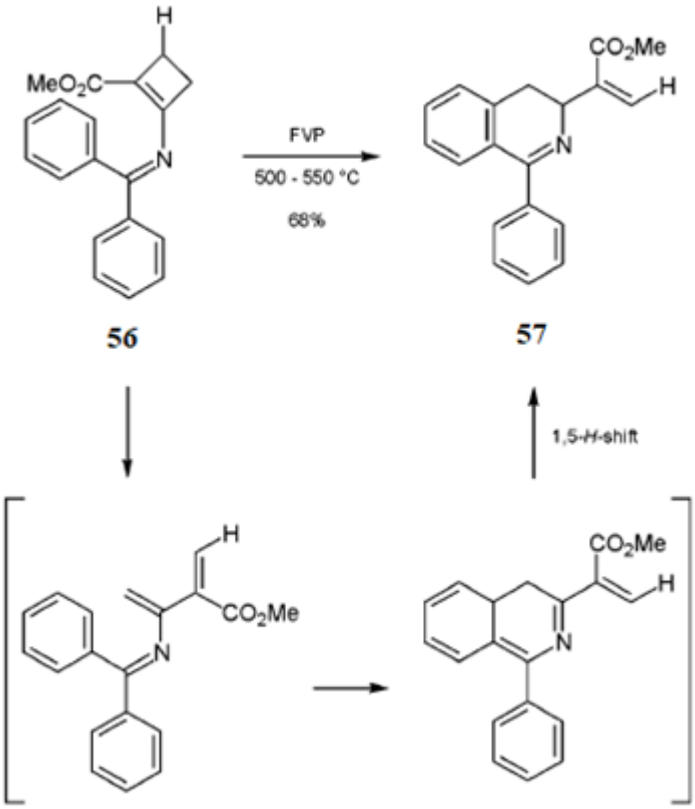
Scheme 1.13. Zinc iodide-mediated thermal opening of 3-acetylcyclobutene.



Cyclobutene ring opening can also be performed, under FVP conditions, for the synthesis of dihydroisoquinolines. De Meijere et al.[45] developed a methodology in which an intermediate azahexatriene underwent a 6π-electrocyclization to give a dearomatized dihydroisoquinoline. After a 1,5-*H* shift, 1,3-disubstituted dihydroisoquinolines were obtained. For example, the product **57** was synthetized from **56** in 68% yield (Scheme 1.14).

Ring opening methodologies can be applied to cyclobutenylcarbene complexes also. For example, by means of electrocyclic ring opening, Wulff et al.[46] obtained the corresponding butadienylcarbenes. A subsequent oxidation with cerium anmmonium nitrate (CAN) led stereoselectively to the dienyl esters. E. g., the conrotatory ring opening of the tungsten complex **58** led to the chelated (dien-2-yl)methoxycarbenetungsten complex **59** in 90% yield (Scheme 1.15).

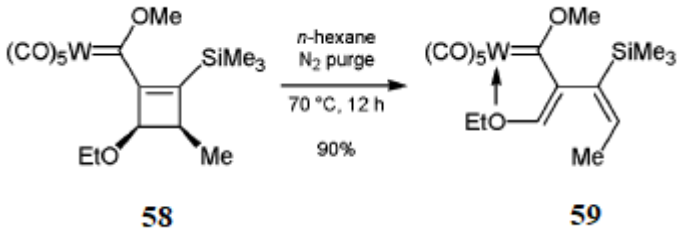
Scheme 1.14. Synthesis of a dearomatized dihidroisoquinoline via FVP conditions 6π-electrocyclization of azahexatriene intermediates.



Snapper[47] et al. used a Grubb catalyst to afford functionalized divinylcycloalkanes from annelated cyclobutene derivatives by ring-opening cross metathesis reaction. For example, the oxatricyclononene **60** reacted with the 5-silyloxypent-1-ene to give the 1,7-dialkenyl-3-oxabicyclo[3.2.0]heptane **61** containing the ω-silyloxyalkyl group in 72% yield as an 8:1 mixture of two regioisomers (Scheme 1.16).

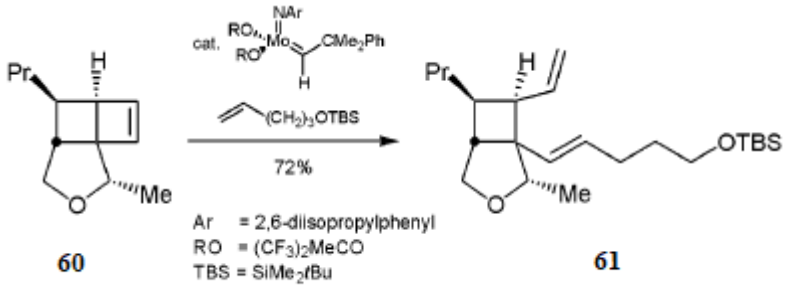
Patra and Ghosh[48] reported the formation of cyclopentanones or γ-lactone-annelated cyclopentanones from tetrahydrofuran-annelated cyclobutyl ethers after a protolytic ring-opening reaction. For example, **62** generated the ring opened monocyclic ketone **63** in 76% yield and **64** formed the bicyclic cyclopentanone **65** (Scheme 1.17).

Scheme 1.15. Stereoselective electrocyclic ring-opening of cyclobutenyl carbene complexes.



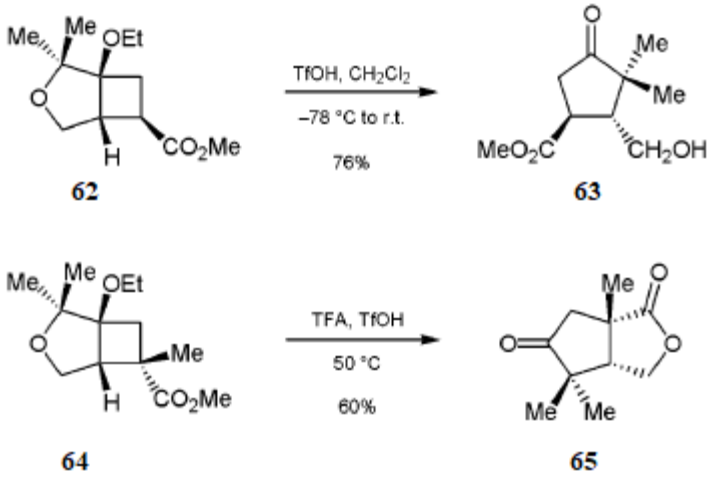
58 **59**

Scheme 1.16. Synthesis of functionalized divinylcycloalkanes by ring-opening cross metathesis reaction of annelated cyclobutene derivatives.



60 **61**

Scheme 1.17. Synthesis of highly substituted cyclopentanones via protolytic ring-opening reaction of tetrahydrofuran-annelated cyclobutyl ethers.

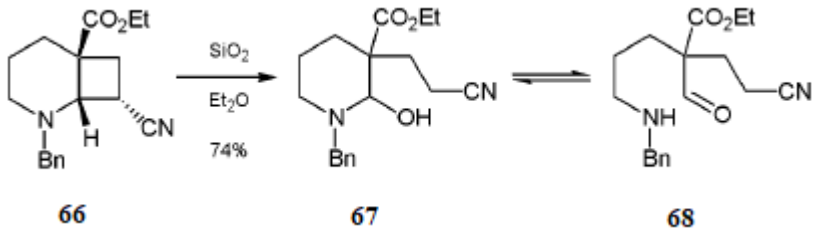


62 **63**

64 **65**

A methodology requiring mild conditions was published by Ponticelli et al.[49] The piperidine derivative **66**, prepared by photochemical [2+2] cycloaddition of acrylonitrile to a tetrahydropyridine, underwent hydrolytic cleavage by wet silica gel in diethyl ether generating the highly substituted 2-hydroxypiperidine **67**, which converted into the open-chain aminoaldehyde **68** (Scheme 1.18).

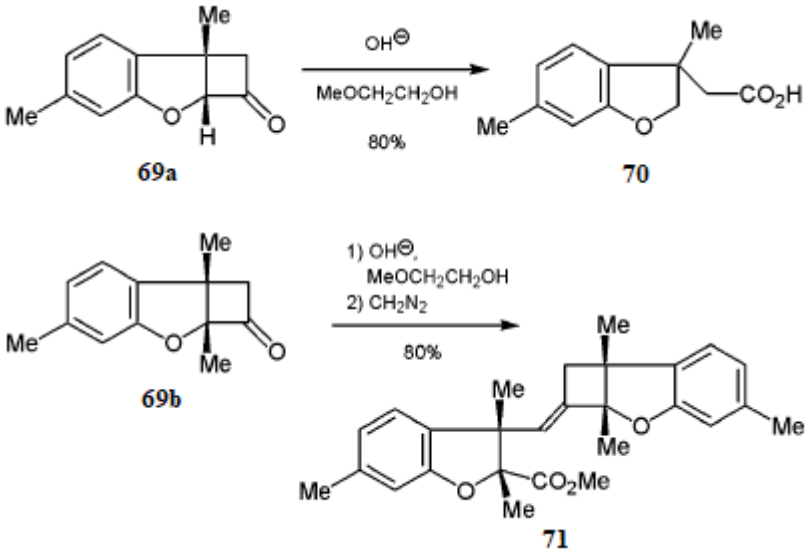
Scheme 1.18. Hydrolytic cleavage of tetrahydropyridines.



66 67 68

Concerning base-induced procedures, Venkateswaran et al.[50] published a Haller-Bauer type cleavage of cyclobutabenzofuranones. The regioselectivity of this process is influenced by the substituents of the cyclobutanone. The cyclobutanone **69a**, holding a furanyl oxygen in the *β*-position to the carbonyl group, underwent ring opening upon treatment with sodium hydroxide to give the oxabicyclic carboxylic acid **70**. When the acidic *α*-position is occupied by a methyl, e.g. in **69b**, the opposite C-C bond adjacent to the carbonyl undergoes regioselective cleavage. The subsequent passage is a coupling with another cyclobutabenzofuranone molecule followed by methylation. The compound **71** was obtained in 80% overall yield (Scheme 1.19).

Scheme 1.19. Haller-Bauer type cleavage of cyclobenzofuranones.

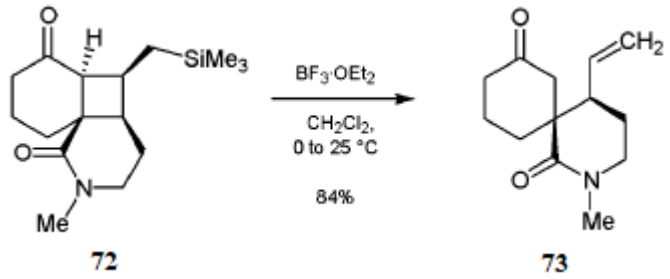


69a 70 69b 71

Lewis acids are also useful reagents for ring cleavage reactions. A ring opening of tricyclic trimethylsilylmethylcyclobutane-annelated six- or seven-membered lactones and lactams upon treatment with boron trifluoride etherate was reported by Piva et al.[51] The *syn*-isomers such as the compound **72** were transformed into the correnspondingvinyl-substituted spiroannelated lactones

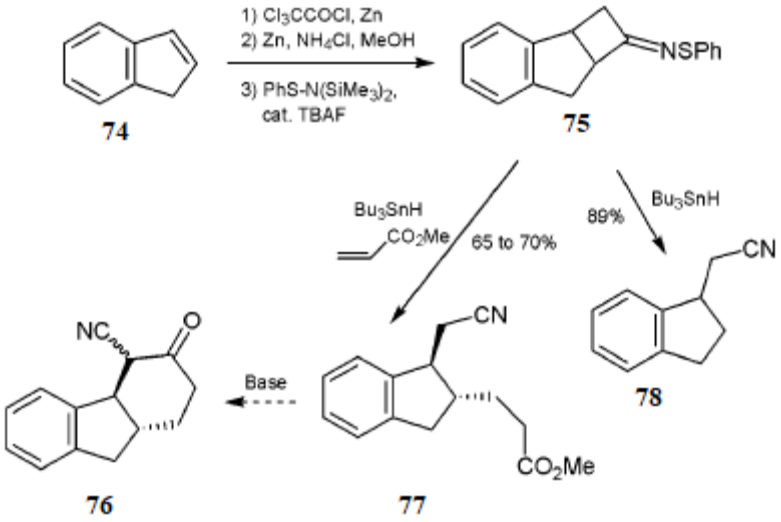
or lactames, while the *anti*-isomers showed a lower reactivity. The lactam **73** was obtained in 84% yield (Scheme 1.20).

Scheme 1.20. Synthesis of spiranic vinyl compounds by Lewis acid-activated cyclobutane ring cleavage.



In the field of radical-triggered reactions, Zard[52,53] showed an example of radical-triggered ring opening of a cyclobutanone sulfenimide, prepared in three steps from 1*H*-indene. After treatment with tributyltin hydride, an iminyl radical was generated that furnished the product **78**. In the presence of methyl acrilate, the cyanoester was generated by *β*-addition. The last passage of this route consists in the formation of the tricyclic *α*-cyanoketone **76** (Scheme 1.21).

Scheme 1.21. Radical-activated ring opening of cyclobutanone sulfenimides.

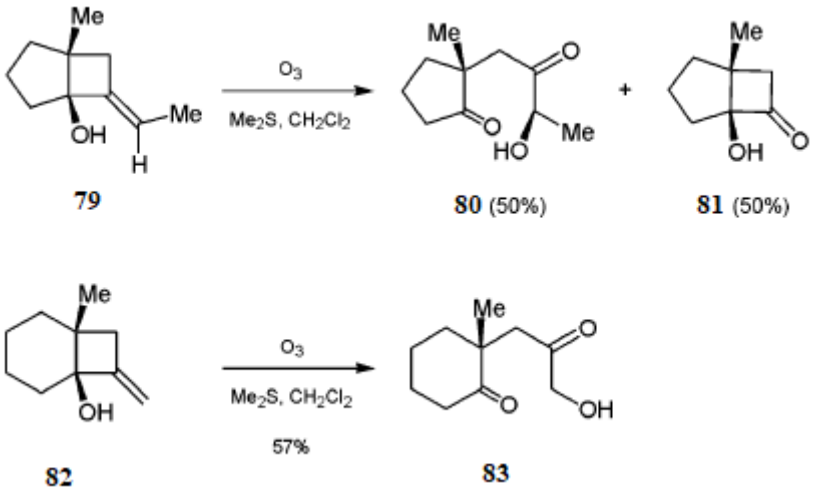


The ozonolysis of the double bond of an α-hydroxymethylenecyclobutane derivatives led Jung and Davidov[54] to obtain an uncommon type of ring-opening product. E. g., the cyclopentane-annelated (*E*)-ethylidenecyclobutanol **79** was treated with ozone and underwent an exo-face attack followed by a Grob-type fragmentation of the ozonide, giving the α-hydroxyketone **81** in

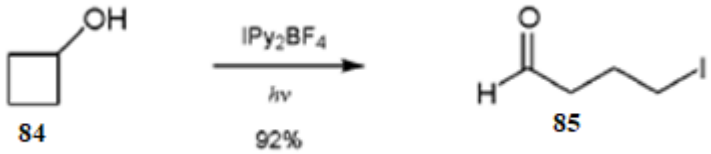
50% yield. The ozonolysis product **80** was also obtained in 50% yield. The cyclohexane-annelated 2-methylenecyclobutanol **82** gave only the uncommon ring-opening product **83** (Scheme 1.22).

An efficient method for the synthesis of ω-iodocarbonyl compounds by oxidative ring cleavage of cycloalkanols was developed by Barluenga et al.[55] For example, γ-iodobutanal **85** was obtained from cyclobutanol **84** in 92% yield after reaction with bis-(pyridine)iodonium(I) tetrafluoroborate under visible light irradiation (Scheme 1.23).

Scheme 1.22. Ozonolysis of methylenecyclobutane derivatives.



Schema 1.23. Oxidative ring cleavage of cycloalkanols.

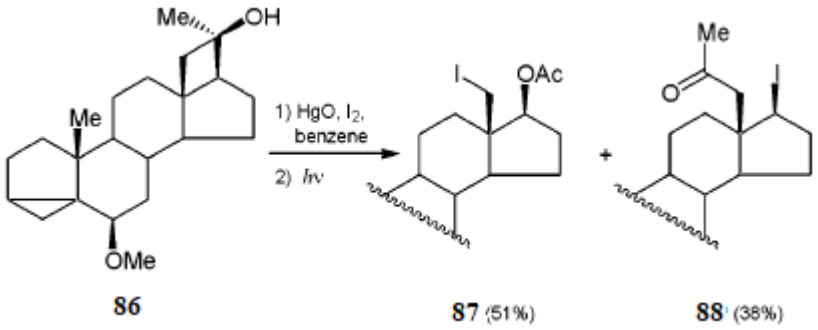


Suginome et al.[56] reported a photoinduced cyclobutane ring opening for the synthesis of bifunctionalized androstanes. For example, pregnan-20-one was photochemically converted into the androstane-related cyclobutanol **86**, which underwent a photolytic β-scission of the cyclobutoxy radical in the presence of HgO/I_2 or NOCl-pyridine and formed the products **87** and **88** in 89% yield and 5:4 ratio (Scheme 1.24).

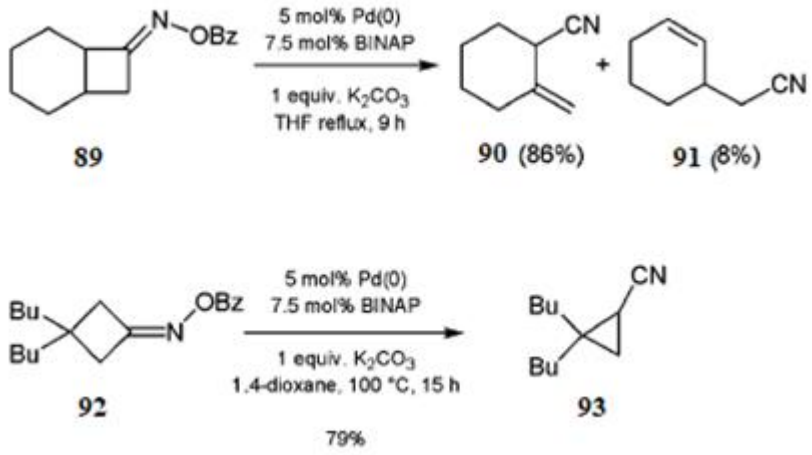
Pd(0) was found to be an useful catalyst for both the ring opening of cyclobutanone oximes and the ring contraction of similar 3,3-disubstituted cyclobutane derivatives to afford the corresponding cyclopropyl cyanides. For example, Nishimura and Uemura[57] obtained the nitriles **90** and **91** via β-carbon elimination from the oxime **89** and, in stronger conditions, the cycropropyl cyanide **93** from the compound **92** in 79% yield. The second reaction is thought to proceed via

formation of a palladacyclobutane followed by a reductive elimination of Pd(0) in the presence of K_2CO_3 (Scheme 1.25).

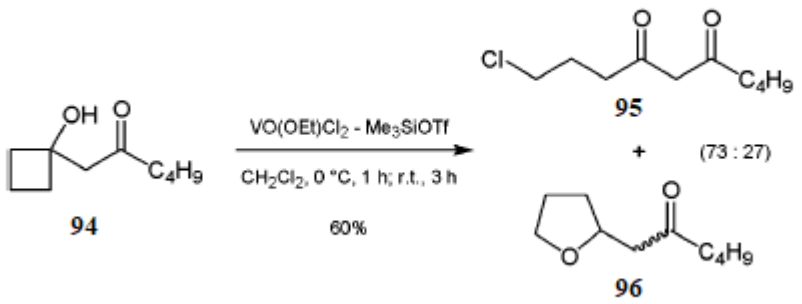
Scheme 1.24. Synthesis of bifunctionalized androstanes by photoinduced cyclobutane ring opening.



Scheme 1.25. Palladium(0)-catalyzed ring cleavage of cyclobutanone oximes.



Scheme 1.26. One-electron oxidation of cyclobutanols by means of oxovanadium(V) derivatives.



Hiroi et al.[58] showed that oxovanadium(V) derivatives can act as one-electron oxidants to form 6-chloro-1,3-diketones and 2-tetrahydrofuranylmethylketones from 1-(2'-oxoalkyl)cyclobutanols.

The published procedure can also be performed as a sequence of a nucleophilic addition of the silyl enol ether followed by an oxidative ring transformation. The cyclobutanol **94** was converted in a mixture of the diketone **95** and the tetrahydrofuran derivative **96** with 60% yield and ratio 73:27 (Scheme 1.26).

1.3.2 **Ring expansion reactions**

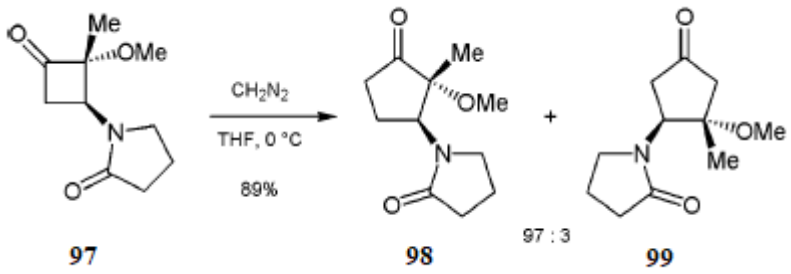
This kind of reaction is used mostly for the synthesis of five- and six- member rings, but larger rings can also be obtained.

Five-membered rings

Diazomethane methodologies have been extensively used for cyclobutanone ring expansion reactions.

Hegedus et al.[59] published a procedure for the regioselective ring expansion of β-substituted α-methyl-α-methoxy-cyclobutanones using diazomethane. For instance, the functionalized cyclobutanone **97** furnished a 97:3 mixture of regioisomeric cyclopentanones **98** and **99** in 89% yield (Scheme 1.27).

Scheme 1.27. Regioselective ring expansion of β-substituted cyclobutanones.

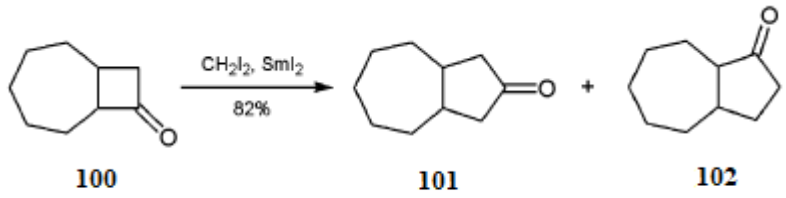


Due to the toxicity of diazomethane, other kinds of procedures have been developed.

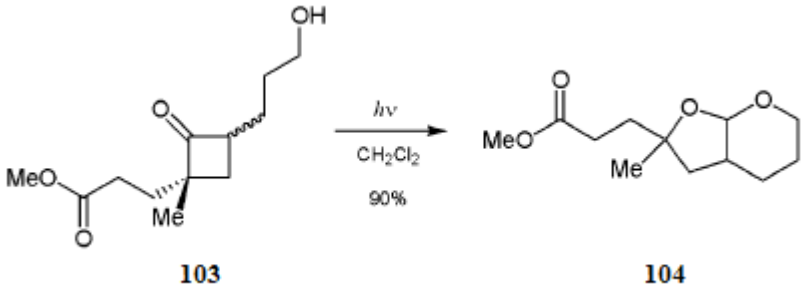
Fukuzawa and Tsuchimoto[60] published a rearrangement of cyclobutanones to cyclopentanones by treatment with CH_2I_2/SmI_2. E. g., the annelated cyclobutanone **100** furnished the octahydroazulenones **101** and **102** in 82% yield and ratio 97:3 (Scheme 1.28).

Pirrung et al.[61,62] developed a methodology for the photochemical ring expansion of cyclobutanes. Intermediate oxacarbenes reacted with primary or secondary alcohols, amines and mercaptans to afford the 2-substituted tetrahydrofurans. The scope of this reaction was extended to synthetize oxabicyclo[*n*.3.0]alcanes in high yields. For example, the propanol-substituted cyclobutanone **103** formed the carbonyl-functionalized dioxabicyclo[4.3.0]nonane **104** in 90% yield (Scheme 1.29).

Scheme 1.28. Iodomethylation and rearrangement of cyclobutanones to cyclopentanones.

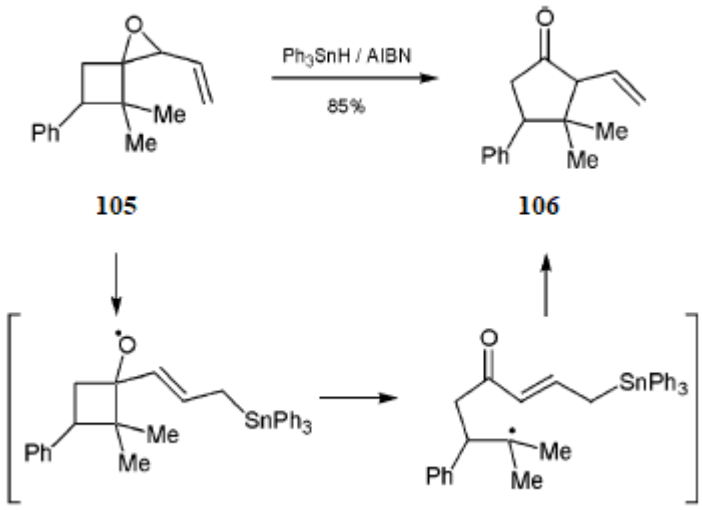


Scheme 1.29. Photochemical ring expansion of cyclobutanes.



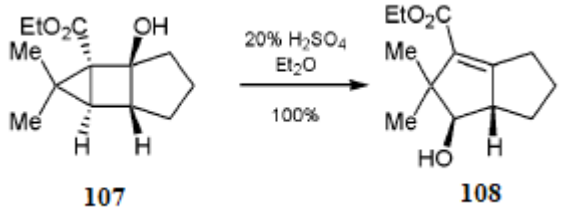
Procedures based on free radical mechanisms were also developed. Kim and Lee[63] used PhSSPh and/or Ph_3SnH as the radical source. The addition of the tin radical induces the opening of the epoxide followed by regioselective *β*-cleavage of the resulting alcoxy radical and ring closure with associated elimination of the tin radical. The ring-expanded vinylcyclopentanone **106** was obtained from the spirocyclobutane-annelated vinyloxirane **105** in 85% yield. Small amounts of another regioisomer (< 2%) and a tin-bearing cyclohexanone (5%) were also obtained (Scheme 1.30).

Scheme 1.30. Free radical mediated expansion of vinyl epoxides.



Franck-Neumann et al.[64] showed the acid-catalyzed rearrangement of cyclopropane-annelated cyclobutanes (bicyclo[2.1.0]pentanes) to cyclopentene derivatives. E.g., the tricyclic hydroxycyclobutanecarboxylate **107** gave the diquinane **108** stereoselectively in quantitative yield (Scheme 1.31).

Scheme 1.31. Acid-catalyzed rearrangement of cyclopropane-annelated cyclobutanes.



107 **108**

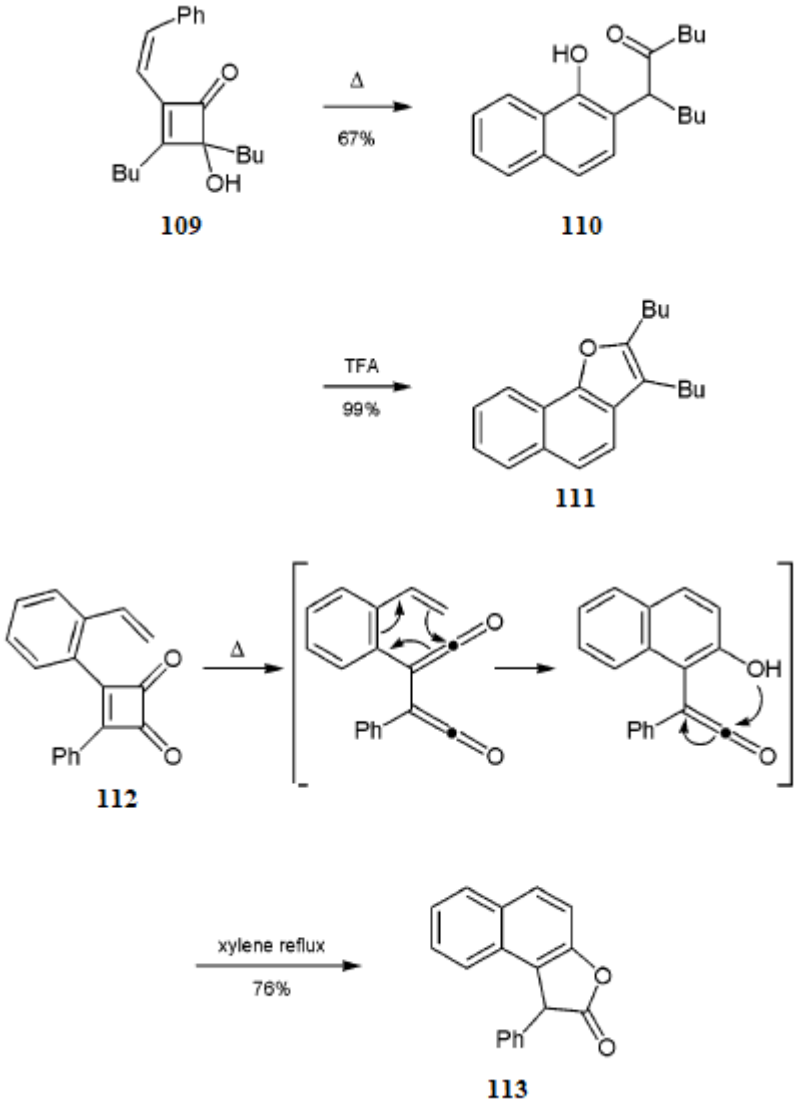
Moore and Liebeskind et al. showed independently that 4-alkenyl/aryl-cyclobutenones can undergo ring expansion to aromatic systems. Moore et al.[65,66] published the synthesis of annelated furans and monocyclic lactones starting from 2-dienyl-4-oxycyclobutenones. For example, the thermal rearrangement of hydroxycyclobutene **109** gave the α-naphtol **110** and, subsequently, the naphthofuran **111** upon treatment with TFA. The reaction of *o*-styryl-substituted cyclobutenediones such as **112** proceeded via intramolecular addition of the intermediate *β*-naphtol to the *ortho*-attached ketene functionality to give naphthofuranones type **113** (Scheme 1.32).

Olah et al.[67] reported a method to transform hydroxymethyl- or carboxyl-substituted cyclic or oligocyclic hydrocarbons into the next higher homologues by reaction with a mixture of sodium borohydride and triflic acid in diethyl ether. Hydroxymethylcyclobutane **114** and cyclobutanecarboxylic acid **115** underwent a formal reductive ring enlargement to cyclopentane **116** in 96% yield (Scheme 1.33).

Takeda et al.[68,69] demonstrated that, by treatment with a suitable Lewis acid, cyclohexene-annelated acetylcyclobutanes give hydrindanone derivatives. For example, the acetylcyclobutane **117** was treated with ethylaluminum dichloride and afforded the annelated cyclopentanone **118** in 93% yield with total *cis*-selectivity (Scheme 1.34).

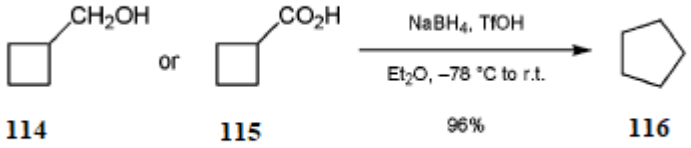
Transition metal-based methods were developed too. Among other rutenium transformations, Ihara et al.[70] published a reaction of 1-allenylcyclobutanols with *α,β*-unsaturated carbonyl compounds to afford cyclopentanone derivatives. The allenylcyclobutanol **119** was converted into the cyclopentanone **268** in 71% yield. Performing the same reaction with the addition of $CeCl_3$ led to the formation of a mixture of **120** and the cyclohemiacetalization product **121** (Scheme 1.35).

Scheme 1.32. Thermal rearrangement of 2-dienylcyclobutenones to annulated furans.

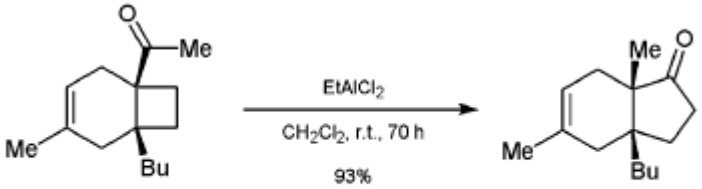


An α-ketol rearrangement of 1-benzoylcyclobutanol **122** by treatment with catalytic amounts (2 mol%) of nickel chloride/TMEDA in methanol at room temperature was published Brunner and Kagan.[71] 2-phenyl-2-hydroxycyclopentanone **123** was obtained in quantitative yield (1.36).

Scheme 1.33. Ring homologation of cyclic and polycyclic hydrocarbons with reducting agents.

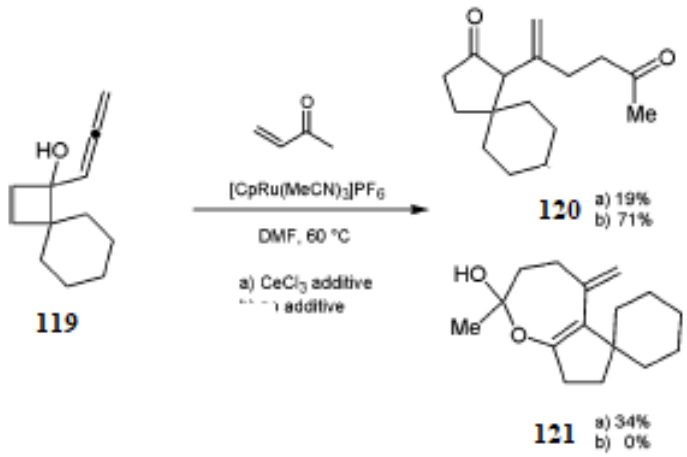


Scheme 1.34. Lewis acid promoted ring enlargement reaction of cyclohexene-annelated cyclobutanes.



117 **118**

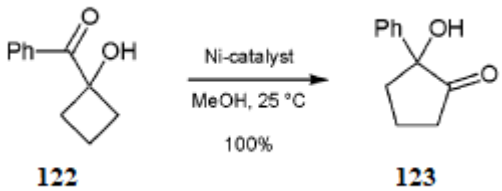
Scheme 1.35. Ruthenium-catalyzed ring expansion reaction of allenylcyclobutanols.



119 **120** a) 19% b) 71% **121** a) 34% b) 0%

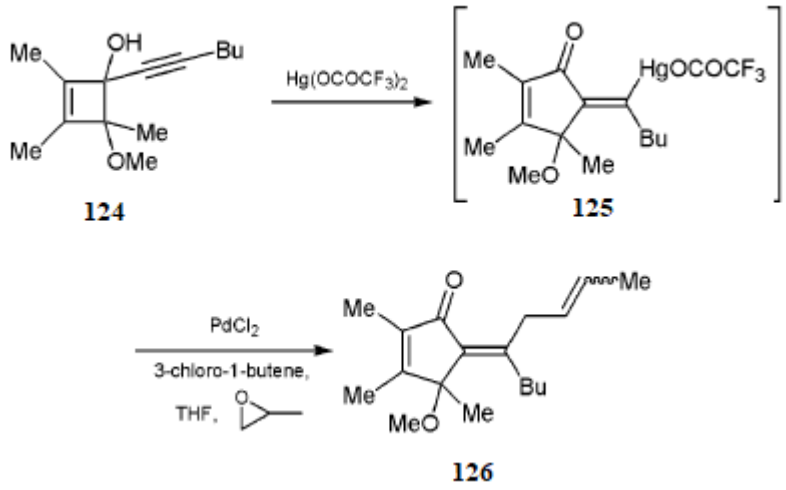
Liebenskind and Bombrun[72] demonstrated that, under the action of a palladium catalyst and a highly electrophilic mercurium salt, a ring expansion followed by a cross-coupling of 1-alkynylcyclobutenols resulted in the formation of 4-methoxy-4-methyl-5-alkylidenecyclopentenones or 5-alkylidene-2-cyclopentene-1,4-diones stereoselectively with yields up to 92%. For example, the 1-alkynylcyclobutenol **124** upon addition of $Hg(OCOCF_3)_2$ gave the alkylidenecyclopentenone **126** in 92% yield via the palladium catalyzed allilation of the intermediate **125** (Scheme 1.37).

Scheme 1.36. Nickel-catalyzed enantioselective α-ketol rearrangement of 1-benzoylcyclobutanol.



122 **123**

Scheme 1.37. Palladium-mercurium cocatalyzed ring expansion-functionalization of 1-alkynylcyclobutenols.



An uncommon thermal ring opening of cyclobutenones was published by Moore and Perri.[73] The inward conrotatory opening of the cyclobutenone **127** was followed by the ring closure of the resulting hydroxyvinylketene **128** to afford a mixture of butenolydes **129** and **130**, with ratio 2:1 and yield 89%. A subsequent treatment with silica gel allowed the complete isomerization of **129** to the *α,β* unsaturated isomer **130** (Scheme 1.38).

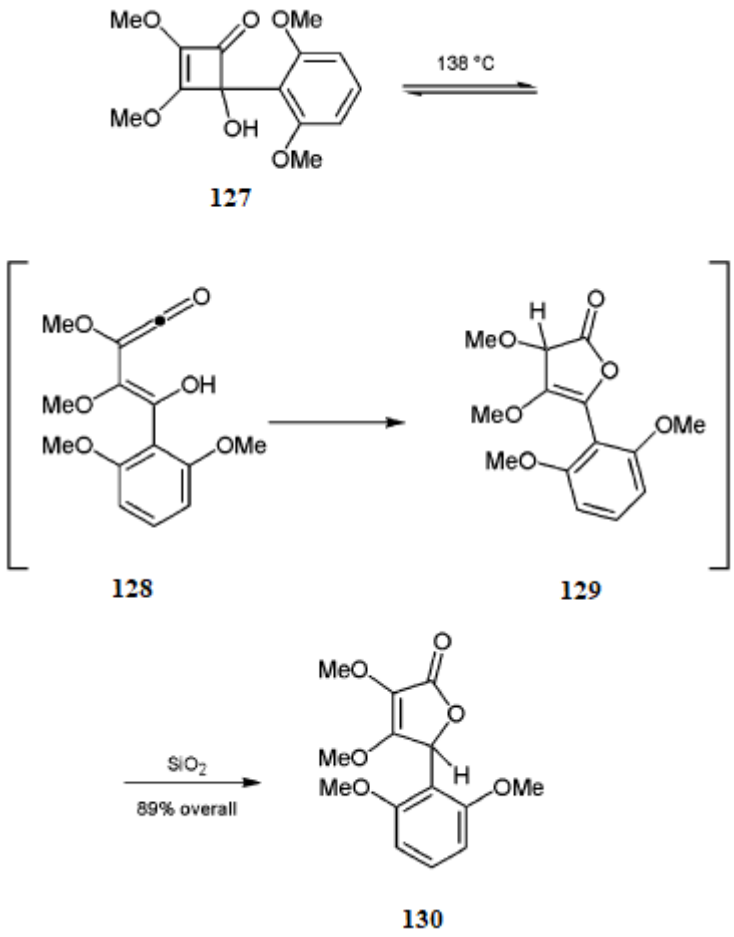
Six-membered rings

Snapper et al.[74] reported the preparation of ring-fused cyclohexadienes by thermal ring-enlargement of annelated bicyclo[2.2.0]hexenes obtained by means of an intramolecular [4+2] cycloaddiction to the linked alkene unit of an *in situ* generated butadiene. For example, the products **132** and **134** were obtained, respectively, from **131** and **133** in 97 and 88% yield (Scheme 1.39).

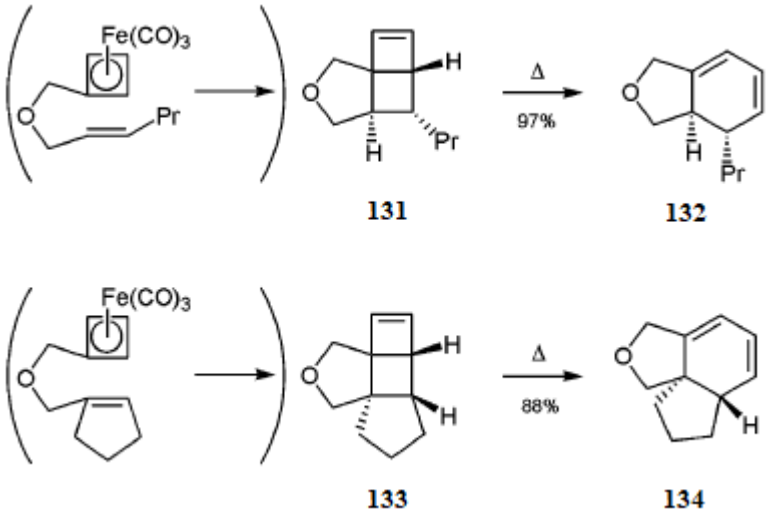
Pattenden and Schulz[75] published a free-radical based ring enlargement of an alkynyl-substituted cyclobutanone oxime benzyl ether to afford a cyclopentane-annelated cyclohexenone oxime benzyl ether. The addition of tris(trimethylsilyl)silane to the starting cyclobutanone oxime benzyl ether **135** generated the β-silyl-substituted vinyl radical **136a**. A subsequent 6-*exo-trig* ring closure led to the bicyclo-[4.2.0]octylaminyl radical **136b**, that underwent a cascade radical rearrangement giving the intermediate bicyclo[3.3.0]octyl ring system **137**. A further ring enlargement and final elimination of the silyl radical generated the cyclopentane-annelated cyclohexenone oxyme benzyl ether **138** in a 70% yield (Scheme 1.40).

Sonoda et al.[76] showed the high-pressure carbonylation of cyclobutanols by oxidative ring cleavage with lead tetraacetate to furnish substituted δ-lactones.

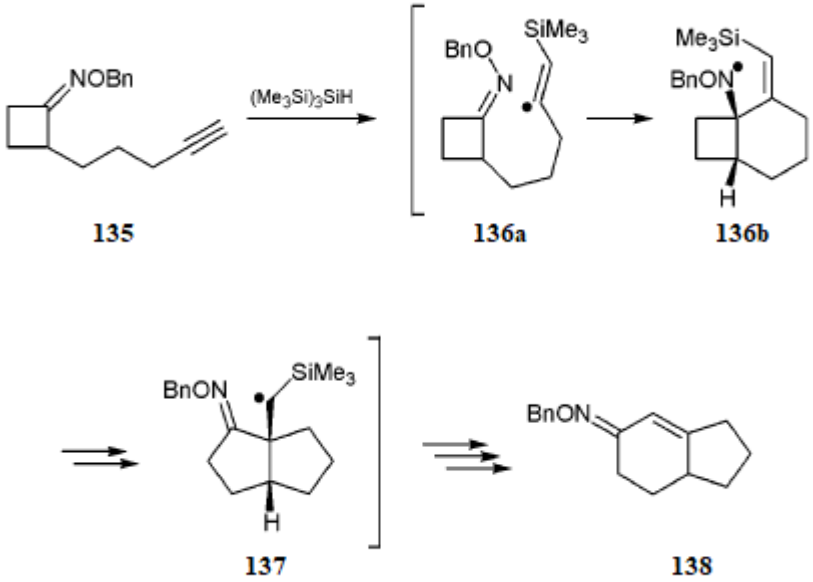
Scheme 1.38. Regiospecific synthesis of annulated quinones by thermal ring opening of cyclobutenones.



Scheme 1.39. Intramolecular cyclobutadiene-olefin [4+2] cycloaddictions.

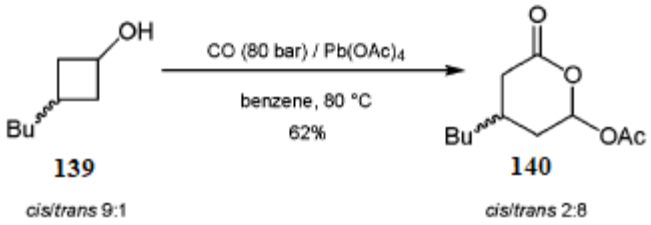


Scheme 1.40. Radical mediated double ring expansion-cyclization of oxime ethers.



The mechanism of this reaction consists in the intramolecular cyclization of an acyl cation previously generated in two one- electron oxidation steps. The cation is then attacked by another cyclobutanol molecule or an acetate anion. The 3-butylcyclobutanol **139** afforded the acetoxy-δ-lactone **140** in 62% yield (Scheme 1.41).

Scheme 1.41. Carbonylation of cyclobutanols by oxidative ring cleavage with LTA.

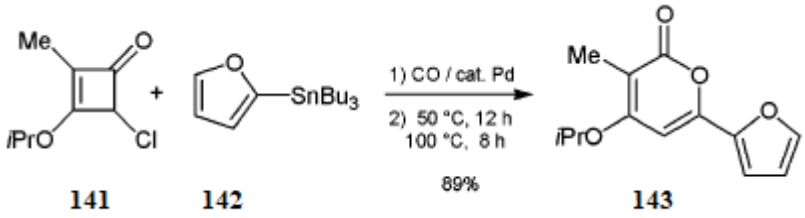


Liebeskind et al.[77] studied a regioselective procedure to synthetize 3,4,6-trisubstituted 2-pyrones starting from cyclobutenones. A Pd-catalyzed carbonilation was followed by cross-coupling with vinyl-, propenyl- or heteroarylstannanes, a thermal ring opening and final ring closing to give the products with yields in the range 60-89%. The coupling of 4-chloro-3-isopropyloxy-2-methylcyclobutenone **141** with the stannylated furan **142** gave the furanylpyranone **143** (Scheme 1.42).

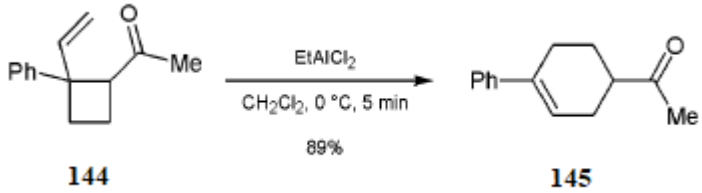
In some cases, the cationic ring expansion of adducts obtained from appropriate cyclobutenyl ketones and alkenylmetals was found to be by Fujiwara and Takeda[68,78] a more efficient method

to obtain cyclohexene derivatives than the Diels-Alder reaction. E.g., the (2-vinylcyclobutyl)methyl ketone **144** afforded the cyclohexenyl ketone **145** in 89% yield after treatment with ethylaluminum dichloride or phenoxyaluminum dichloride (Scheme 1.43).

Scheme 1.42. Carbonilative cross-coupling thermolysis of 4-halocyclobutenones with stannanes.



Scheme 1.43. Ethylaluminium promoted ring enlargement reaction of cyclobutenyl ketones.

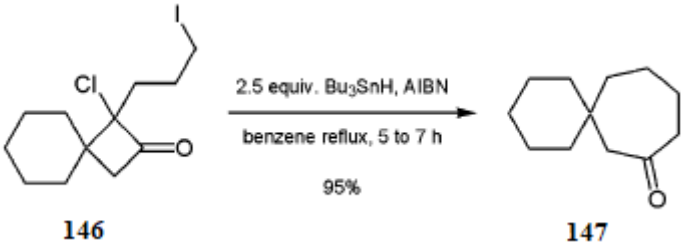


Seven-membered rings

For this kind of reaction, mechanisms based on free radicals are especially important.

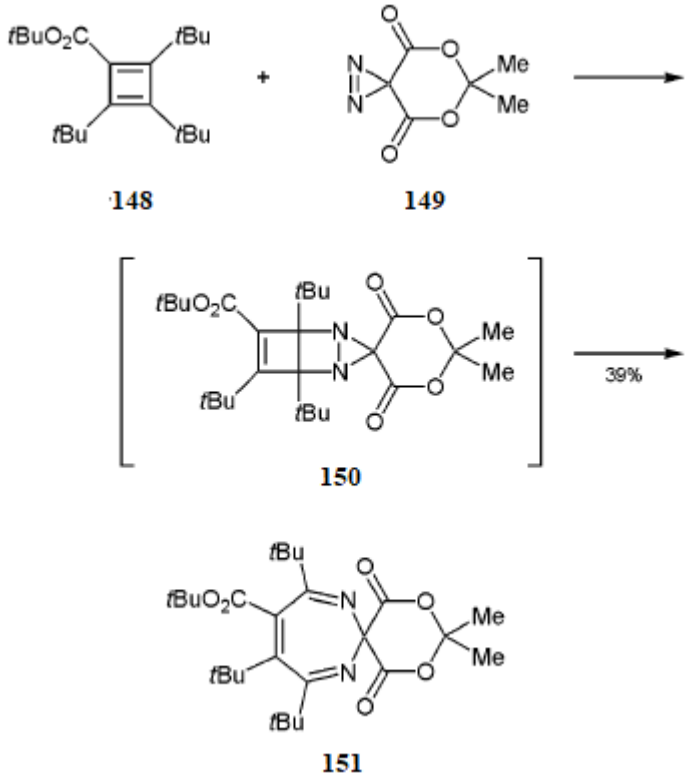
Zhang and Dowd[79] developed a method for the synthesis of seven- and eight-membered systems starting from spiroannelated 2-chloro-2-[ω-iodoalkyl]cyclobutanones. The first step consists in a deiodination with tributyltin hydride followed by a radical attack at the carbonyl group. Depending on the used amount of the tin hydride, it is possible to obtain chlorinated or dechlorinated ketones. The spiro[5.6]dodecan-8-one **147** was obtained in this manner from the 2-chloro-2-iodopropyl cyclobutanone **146** in 95% yield (Scheme 1.44).

Scheme 1.44. Synthesis of spiroannulated ring systems by free radical promoted cyclobutanone ring expansion.



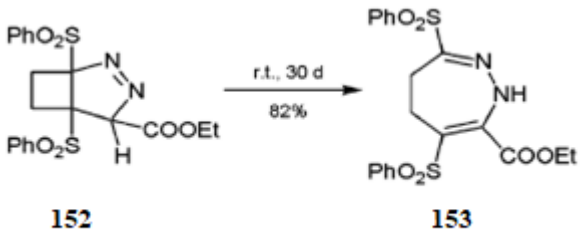
A new methodology for the synthesis of 5*H*-1,3-diazepines was published by Regitz et al.[80] A kinetically stabilized cyclobutadiene reacts with diazirines via [4+2] cycloaddition to give a diazatricyclic intermediate that converts into the final product. For example, the cyclobutadiene **148** undergoes cycloaddiction with the spirocyclic diazirine **149** to afford the dioxospiro-diazepinedioxane **151** in 39% yield via the spirotryciclic intermediate **150** (Scheme 1.45).

Scheme 1.45. [4+2] cycloaddiction between a kinetically stabilized cyclobutadiene and diazirines.



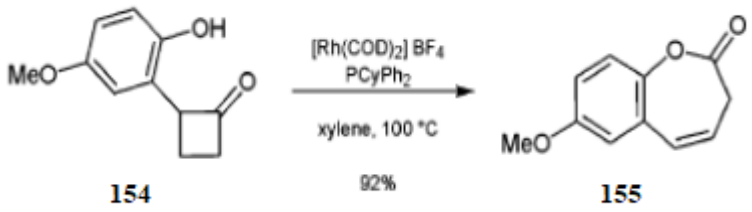
Martin et al. offered[81] a route to afford dihydrodiazepines upon thermal rearrangement of the cyclic adduct of ethyl diazoacetate and a bissulfonyl-activated cyclobutene. For example, ethyl-4,4-dihydro-3,6-bis(phenylsulfonyl)-1-*H*-1,2-diazepine-7-carboxylate **153** was obtained in 82% yield from the 2,3-diazabicyclo[3.2.0]heptene **152** (Scheme 1.46).

Scheme 1.46. Thermal ring enlargement of pyrazolines to dihydrodiazepines.



Murakami and coworkers[82] prepared benzoannelated lactones from cyclobutanones using rhodium catalysts. E.g. a cyclobutanone with an aryl unit at C-2 such as **154** reacts in the presence of $[Rh(COD)_2]BF_4$, and a phosphine ligand under CO atmosphere leading to the unsaturated seven-membered lactone ring **155** in 92% yield (Scheme 1.47).

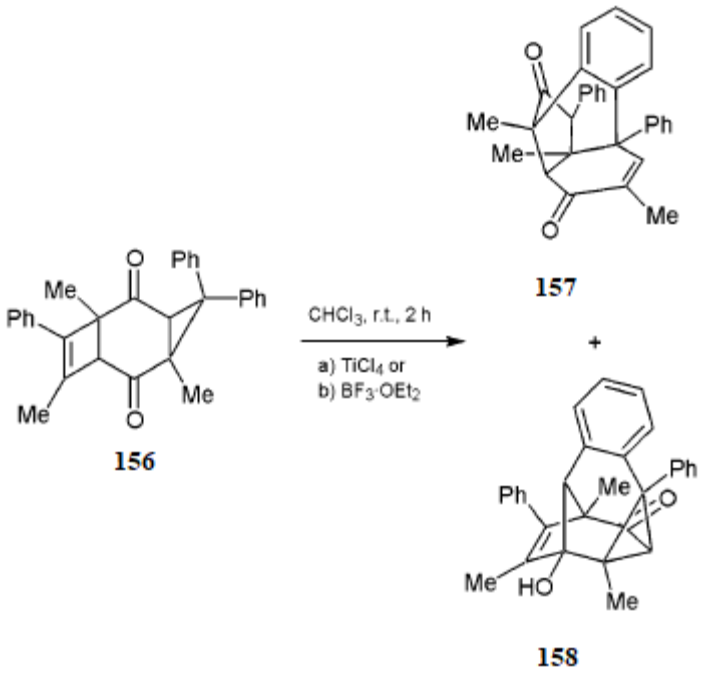
Scheme 1.47. Lactone formation by rhodium-catalyzed C-C bond cleavage of cyclobutanone.



154 **155**

Kokubo et al.[83] reported a Lewis acid-mediated rearrangement of the tricyclic enedione **156** giving bi- to pentacyclic cage-like diketones or keto alcohols depending on the type of Lewis acid used. The main product **157** is formed upon ring cleavage and subsequent new ciclization, whereas the pentacyclic keto alcohol **158** is generated upon vinyl migration and electrophilic attack of an intermediate carbocation (Scheme 1.48).

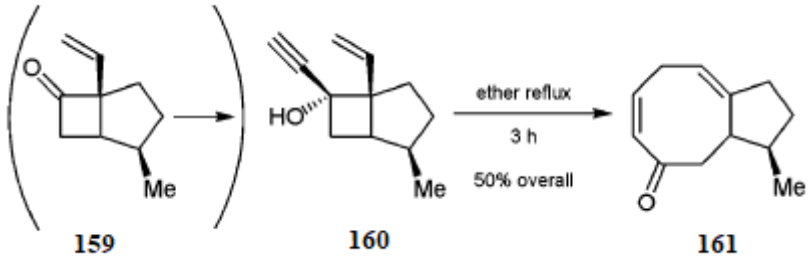
Scheme 1.48. Lewis acid-catalyzed successive skeletal rearrangement of cyclobutene-fused diphenylhomoquinone.



Eight-membered rings

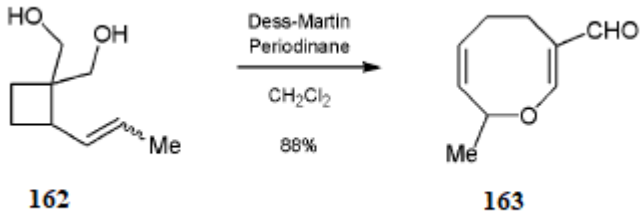
Gadwood et al.[84] published a synthesis of the cyclooctanoid sesquiterpene scaffolding of poitediol, dactylol and precapnelladiene with an Oxy-Cope rearrangement of an intermediate cyclopentane-annelated 1-ethynyl-2-ethenylcyclobutanol as the key step. For example, the bicyclic enyne **160**, obtained by reaction between 2-methyl-5ethenylbicyclo[3.2.0]heptan-6-one **159** and ethynyllithium, afforded the cyclopentacyclooctadienone **161** (Scheme 1.49).

Scheme 1.49. [3,3]-Sigmatropic Rearrangement of Divinylcyclobutanols.



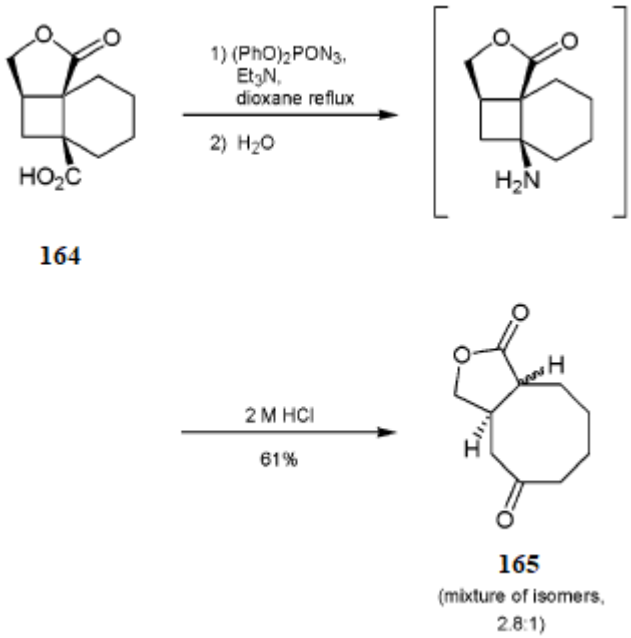
Boeckman et al.[85] described the *retro*-Claisen rearrangement of formylated and alkenyl-substituted strained cycloalkane derivatives.Treating the 1,1-bishydroxymethyl-2-propenylcyclobutane **162** with Dess-Martin periodinane, the 8-methyl-5,8-dihydro-4*H*-oxocine-3-carbaldehyde **163** in 88% yield, via a ring-enlargement of the corresponding bisaldehyde (Scheme 1.50).

Scheme 1.50. Retro-Claisen rearrangement of substituted strained cycloalkane derivatives.



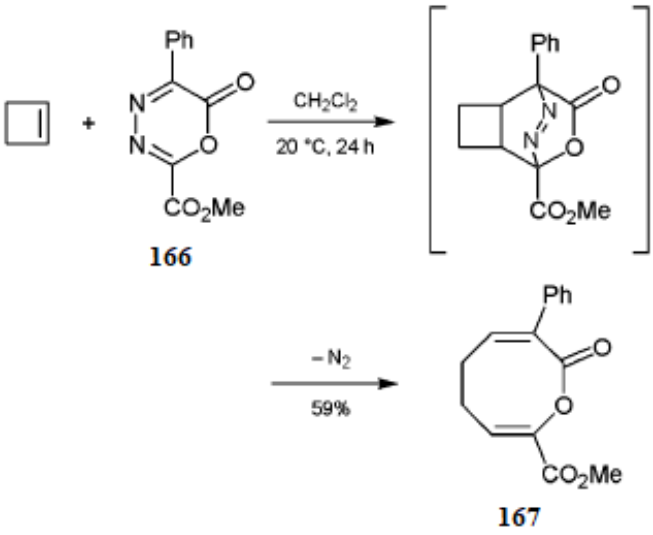
Booker-Milburn et al.[86] published a sequence consisting in a Curtius-type rearrangement of a lactone-annelated tricyclic cyclobutane carboxylic acid **164** in the presence of diphenylphosphoril azide and an aza de Mayo-type fragmentation of the intermediate bisannelated cyclobutylamine in the presence of water to afford the cyclooctanone **165** as a mixture of isomers in ratio *cis:trans* 2,8:1 and 61% yield (Scheme 1.51).

Scheme 1.51. Synthesis of cyclooctenone-lactones by aza de Mayo-Curtius rearrangement of acid lactones.



Christl et al.[87] studied the Diels-Alder reaction between oxadiazinone derivatives containing nitrogen and carbon dioxide with activated cycloalkenes. This is an interesting synthetic route to lactones since it proceeds through selective extrusion of nitrogen. After reaction of the oxadiazinone **166** with cyclobutene, the desired cycloaddiction product 5,8-dihydro-8-oxo-7-phenyl-4*H*-oxocine-2-carboxylic acid methyl ester **167** was obtained in 59% yield (Scheme 1.52).

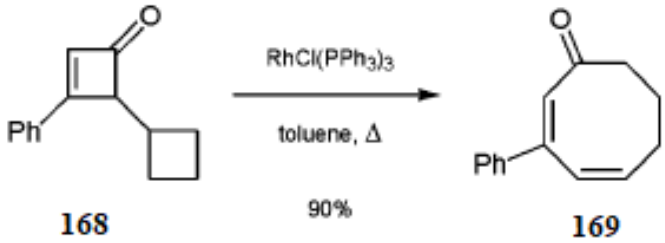
Scheme 1.52. Synthesis of lactones by cicloaddiction between oxadiazinone and activated cycloalkenes.



A procedure for the rhodium(I)-catalyzed ring fusion of a 4-cycloalkylcyclobutenone to afford cyclohepta- or cyclooctadienones was published by Huffman and Liebeskind.[88]

Cyclobutylcyclobutenones react in the presence of triphenylphosphine as the donor ligand for the initial ring opening. The phenyl derivative **168** furnished regioselectively the conjugated 3-phenylcycloocta-2,4-dienone **169** in 90% yield (Scheme 1.53).

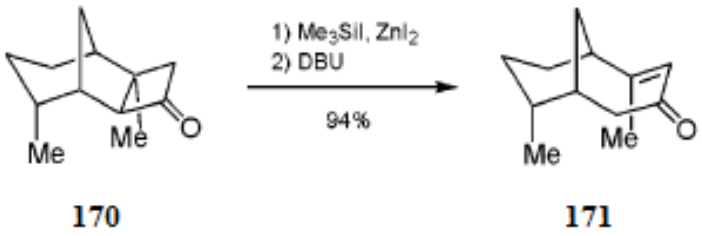
Scheme 1.53. Rhodium(I)-catalyzed intramolecular ring fusion of cyclobutenones.



Nine-membered rings

Dowd et al.[89,90] reported a method for the sinthesis of fused and bridged ring enlarged cyclic ketones from annelated cyclobutanones. The 5,9-dimethyl-bicyclo[4.3.1]dec-4-en-3-one **171** was obtained in 94% yield upon trimethylsilyliodide-promoted ring opening of 5,9-dimethyltricyclo[4.3.1.0[85,86]]decan-3-one **170** (Scheme 1.54).

Scheme 1.54. TMSI-promoted ring-opening of cyclobutanones.



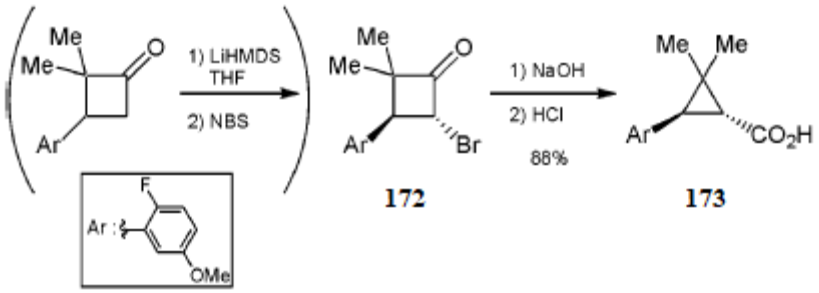
1.3.3 Ring contraction reactions

This kind of reactions has a minor importance, since the easiest way to synthetize a cyclopropanic ring is the use of acyclic precursors.

In 2001, Chen and Ahmad[91] reported a stereoselective procedure for the base-induced ring contraction of an *in situ* formed 2-bromocyclobutanone leading to 2-aryl-3,3-dimethylcyclopropane-1-carboxylic acids. For example, the cyclobutananone derivative **172**

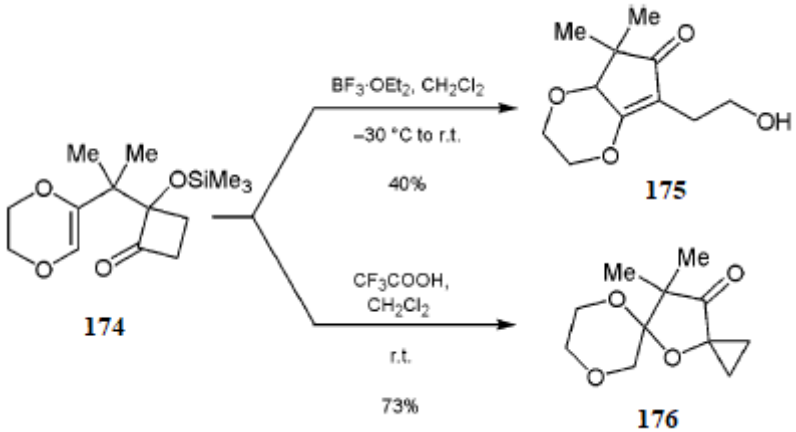
rearranges in the presence of aqueous sodium hydroxide to provide the *trans*-2-arylcyclopropane-carboxylic acid **173** in 88% yield (Scheme 1.55).

Scheme 1.55. Base-induced ring contraction of 2-bromocyclobutanones.



In the course of an acid-catalyzed transformation of a 2-silyloxy-cyclobutanone derivative Hanna and Ricard[92] found that, depending on the reaction conditions, the procedure may lead either to a ring opening followed by a ring closure to a cyclopentenone or to a ring contraction. The reactant **174** was synthetized in 90-95% yield by treating a dioxene-derived allylic alcohol and 1,2-bis-(trimethylsilyloxy)cyclobutene with boron trifluoride-etherate at -30 °C. In the presence of an excess of the Lewis acid at room temperature in methylene chloride, the formation of the 1,4-dioxane-annelated cyclopentenone **175** was reported, whereas using trifluoroacetic acid the ring-contracted tricyclic spiroacetal **176** was obtained (Scheme 1.56).

Scheme 1.56. Acid-catalyzed synthesis of dioxane-annelated cyclopentenones from 2-silyloxy-cyclobutanone derivatives.

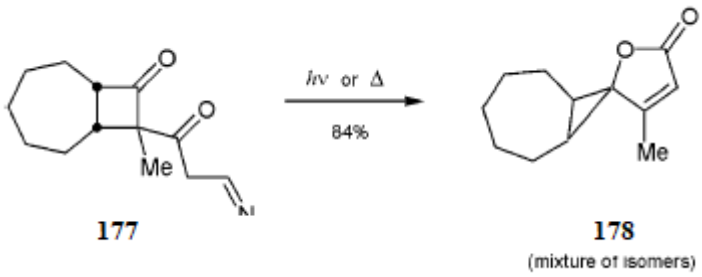


During their studies about palladium(0)-catalyzed ring opening reactions of 3,3-disubstituted cyclobutanone oximes, Nishimura and Uemura[50] found that their methodology led to the formation of the corresponding cyclobutilcyanides in good yields (see Scheme 1.2). Miller et al.[93] published the completely regioselective thermolysis of 2-diazoacetylcyclobutanone derivatives

ring contraction leading to spirocyclopropane-$\Delta^{\alpha,\beta}$-butenolides. ormation of the corresponding cyclobutilcyanides in good yields (see Scheme 1.25).

The reaction proceeds through the formation of α-ketenyl-cyclobutanone intermediates. For example, upon photolysis or thermolysis of the bicyclic diazodiketone in refluxing toluene, the tricyclic spiroannelated butenolide **178** was formed as a mixture of isomers (2.2:1) in 84% yield (Scheme 1.57).

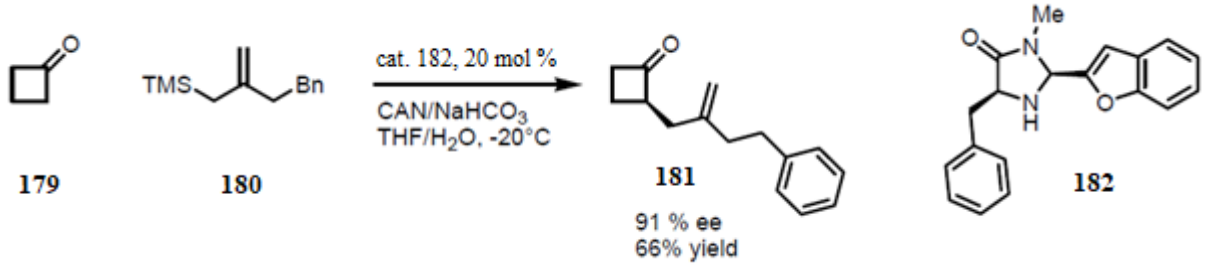
Scheme 1.57. Formation of spiroannelated butanolides by thermal rearrangement of diazoacetylcyclobutanones.



1.3.4 α-functionalization

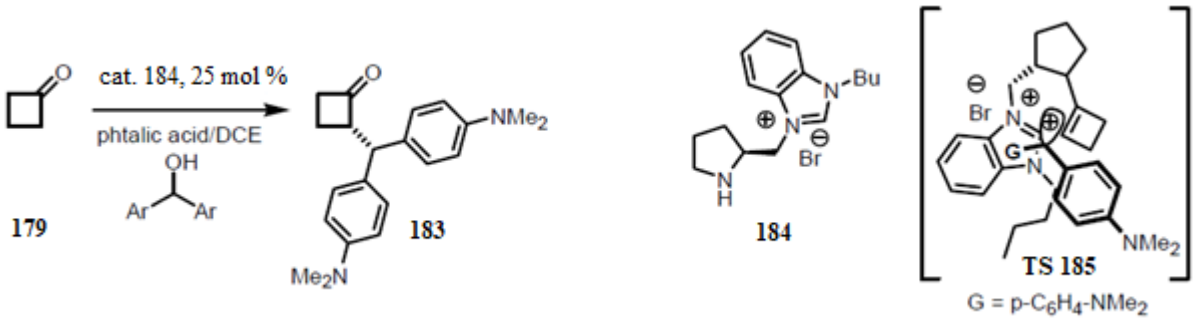
The first enantioselective organocatalytic α-allylation of cyclic ketones[94] via singly occupied molecular orbital catalysis (SOMO)[95,96] was published by Mc Millan et al. The one-electron oxidation of transiently generated enamines leds to the formation of constrained radical cations, that undergo allylic alkylation with a variety of allyl silanes. The α-functionalization of of the cyclobutanone 1**79** was conducted by means of a new oxidatively stable class of imidazolidinone catalysts, such as compound 1**82**, and allylsilane in the presence of CAN and gave the cyclobutanone 1**81** in 66% yield and 91% *ee* (Scheme 1.58).

Scheme 1.58. Enantioselective α-allylation of cyclic ketones via SOMO catalysis.



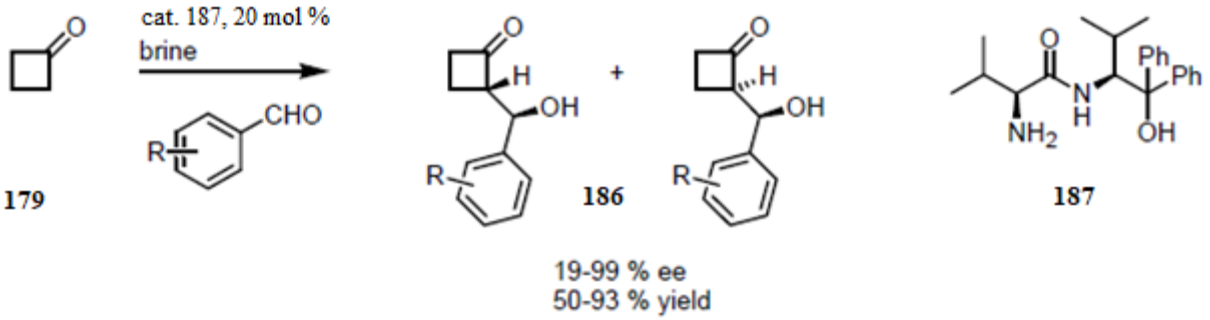
Zhang et al.[97] showed a method for the carbocation alkylation of ketones. The reaction proceeds through the generation of a Brønsted acid *in situ* carbocation formation, employing highly polar and ionic liquids and benzoimidazolium derivatives **184** as catalysts. E.g., cyclobutanone 1**79** by reaction with diphenylmethanol, using phtalic acid as additive generated the α-functionalized cyclobutanone 1**83** in good yields and good *ee*. FCILs are thought to create a favorable catalytic sphere the direct α-alkylation can occur through an asymmetric S_N1 alkylation[98] of ionic intermediates such as **185** (Scheme 1.59).

Scheme 1.59. Asymmetric S_N1 α-alkylation of cyclic ketones catalyzed by chiral ionic liquids.



A procedure for the direct aldol reactions between ketones and aromatic aldehydes using catalytic systems made up of six primary amine organocatalysts such as 1**87**, derived from natural primary amino acids, was achieved by Ma's group.[99] For example, the cyclobutanone **179** reacted with different aromatic aldehydes affording the corresponding aldol adducts **186** with yields in the range 50-93% and *ee* up to 99% (Scheme 1.60).

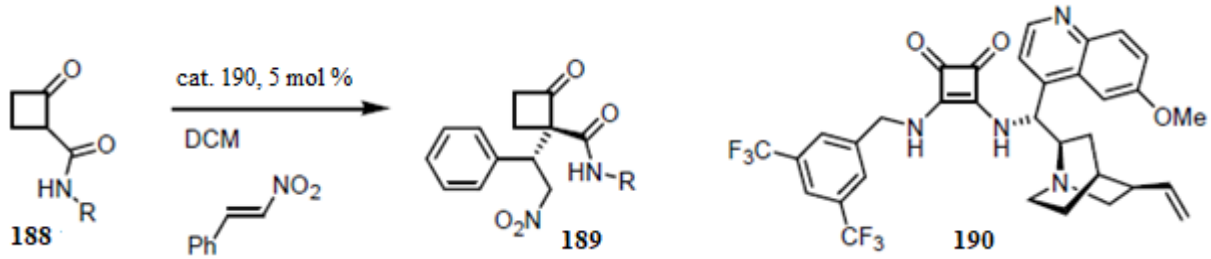
Scheme 1.60. Enantioselective organocatalyzed synthesis of aldol derivatives.



Rodriguez et al.[100] reported a diastereo- and enantioselective organocatalytic Michael addition between 2-substituted cyclobutanone derivatives **188** and nitroalkenes. The approach deals with the use of Brønsted base/hydrogen bonding donor bifunctional organocatalysts **190**, based on cinchona alkaloids, and the stabilization and activation of cyclobutanone with a secondary amide

moiety. The corresponding cyclobutanone derivatives **189** were synthetized in high yields and *ee* with the control of up to three stereogenic centers (Scheme 1.61).

Scheme 1.61. Enantioselective functionalization of 2-substituted cyclobutanones via Michael reaction.



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Schemes 1.2, 1.3, 1.4, 1.5, 1.8, 1.9, 1.10, 1.11, 1.12, 1.58, 1.59, 1.60 and 1.61 reproduced from F. Secci, A. Frongia, P. P. Piras, *Molecules* **2013**, *18*, 15541-15572.

Schemes 1.13, 1.14, 1.15, 1.16, 1.17, 1.18, 1.19, 1.20, 1.21, 1.22, 1.23, 1.24, 1.25, 1.26, 1.27, 1.28, 1.29, 1.30, 1.31, 1.32, 1.33, 1.34, 1.35, 1.36, 1.37, 1.38, 1.39, 1. 40, 1.41, 1.42, 1.43, 1.44, 1.45, 1.46, 1.47, 1.48, 1.49, 1.50, 1.51, 1.52, 1.53, 1.54, 1.55, 1.56 and 1.57 reproduced from J. C. Namsylo, D. E. Kaufmann, *Chem. Rev.* **2003**, *103*, 1485–1537.

Schemes 1.6 and 1.7 reproduced from E. Lee-Ruff, G. Mladenova, *Chem. Rev.* **2003**, *103*, 1449–1484.

Figure 1.1 reproduced from F. Secci, A. Frongia, P. P. Piras, *Molecules* **2013**, *18*, 15541-15572.

CHAPTER TWO

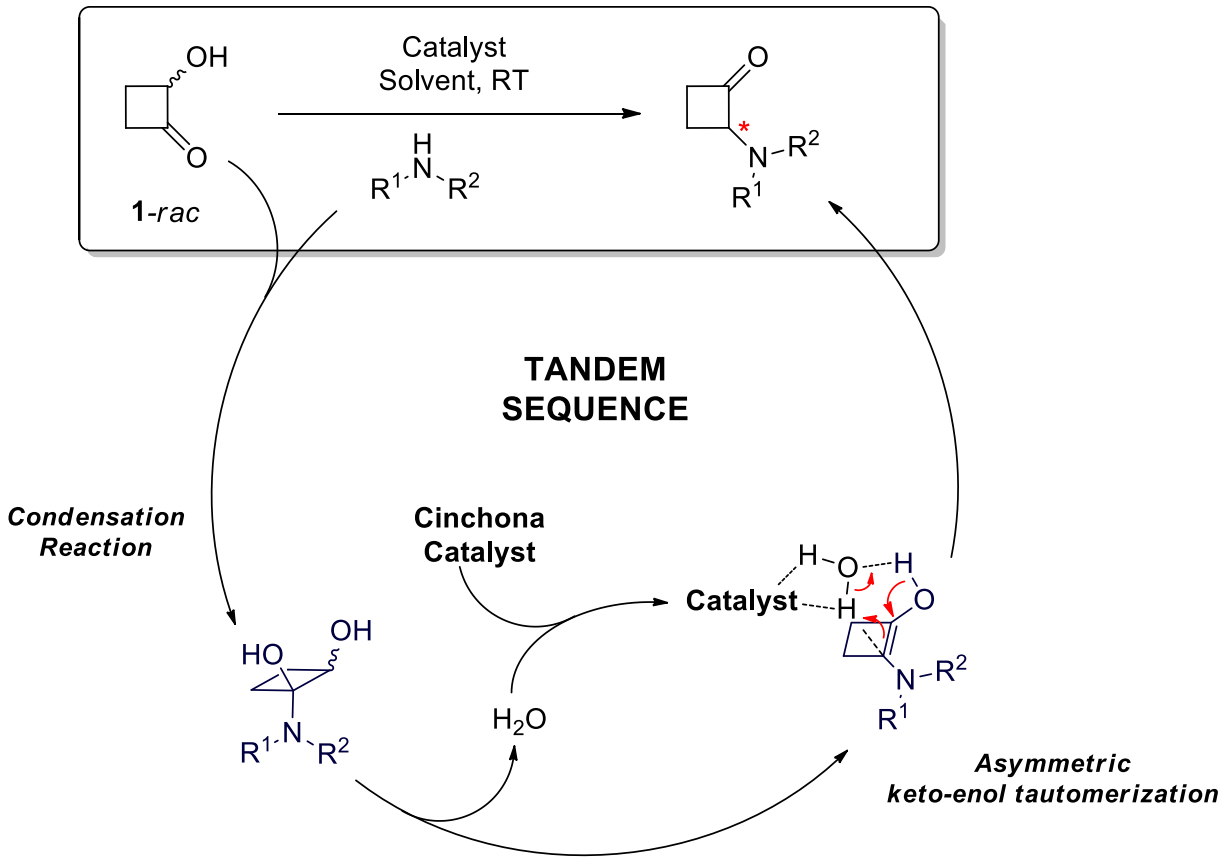
Catalytic enantioselective synthesis of α-(benzylamino)cyclobutanones

2.1 Introduction

Chiral α-aminocyclobutanes[1] are useful intermediates in organic synthesis because of their inherent ring strain and rigidity and have been used for the preparation of a large variety of chemically and biologically interesting synthetic compounds.[2] In addition, the α-aminocyclobutane moiety is found in a number of natural product structures.[3] It is the prevalence of α-aminocyclobutane derivatives that makes the search and design of efficient methods for their preparation of considerable interest. Despite this, only few methods exist that allow for their direct asymmetric synthesis.[4,5]

In this context, we recently developed a new approach for the asymmetric assembly of α-(arylamino)cyclobutanones[6] based on the organocatalytic condensation reaction between racemic 2-hydroxycyclobutanone and arylamines by using commercially available cinchona alkaloids as the catalysts.[7,8] It was found that this method could be successfully applied to the stereoselective synthesis of cyclobutanone α-amino acid ester derivatives.[9] An important aspect of this approach is the unconventional manner in which the nitrogen-containing group is stereoselectively introduced to the carbocyclic ring, which is complementary to an alternative approach based on the asymmetric "electrophilic α-amination" of carbonyl compounds.[10] Our synthetic procedure was achieved by an unprecedented and conceptually new tandem condensation/intramolecular rearrangement/enantioselective proton transfer procedure,[11] resulting in a useful route for the preparation of optically active α-aminocyclobutanones that are beyond the reach of established amination strategies (Scheme 2.1). To further develop our recent discoveries,[6,9] we sought to apply the synthetic methodology to the enantioselective construction of fully aliphatic α-(benzylamino)cyclobutanones. With regard to enantioselective control, benzylamines are challenging partners because of their high reactivity. In contrast with our previous work in which weakly nucleophilic anilines were employed,[6] the enhanced nucleophilicity of the benzylamines makes the noncatalyzed (and thus racemic) reaction a competitive pathway. If this reaction is as fast as the catalyzed one, the asymmetric induction will be compromised.

Scheme 2.1. Key steps in the organocatalytic enantioselective tandem condensation/keto enol tautomerization for the synthesis of optically active α-aminocyclobutanones.

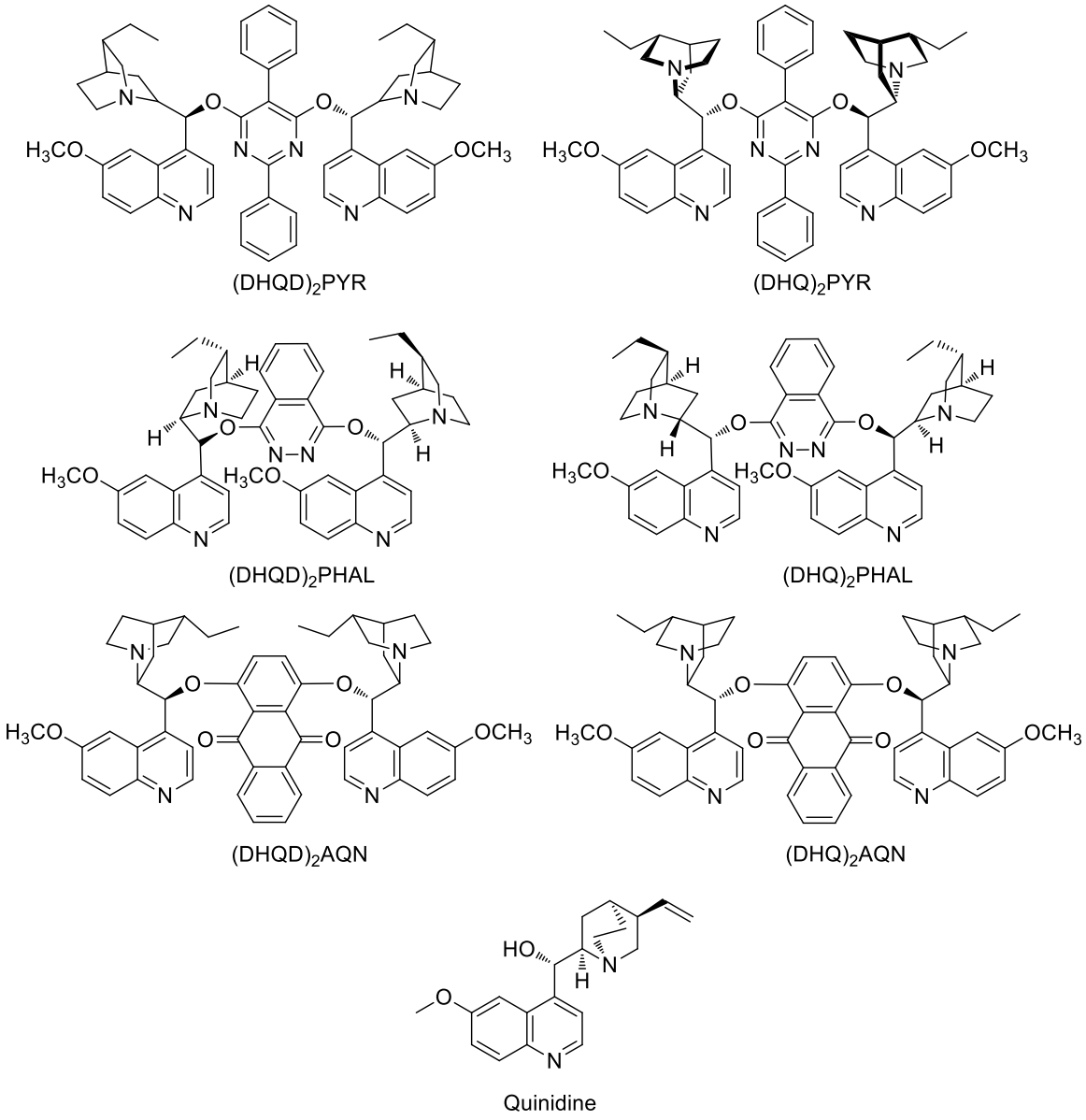


2.2 Results and Discussion

We first examined the model reaction between α-hydroxycyclobutanone (**1**) and dibenzylamine (**2a**) under different conditions to give adduct **3a** (Table 1). In the early stages of this study, as we had suspected, the reaction proceeded with moderate conversion without a catalyst in 1,4-dioxane at room temperature for 3 h (Table 1, Entry 1). Under the same conditions, we used $(DHQD)_2PYR$ as the catalyst and were able isolate the desired product **3a** from the reaction mixture in 81% yield with encouraging enantioselectivity (71:29 *e.r.*; Table 2.1, Entry 2). Moreover, when the pseudoenantiomeric catalyst $(DHQ)_2PYR$ was employed, the reaction afforded the product enriched in the opposite enantiomer with a slightly lower selectivity (Table 2.1, Entry 3). In an effort to improve the enantioselectivity, several other catalysts were evaluated (Table 2.1, Entries 4–8), but they were less rewarding with regard to yield and selectivity than $(DHQD)_2PYR$ and $(DHQ)_2PYR$. By screening different solvents (Table 2.1, Entries 9–11), we discovered that the initial use of 1,4-dioxane had been fortuitous, although the use of ethyl acetate gave almost equally favorable results. Notably, the reaction conditions that had provided good to high

enantioselectivity in our previous study with anilines[6] had no effect on the enantiocontrol of this model reaction (Table 2.1, Entry 12).

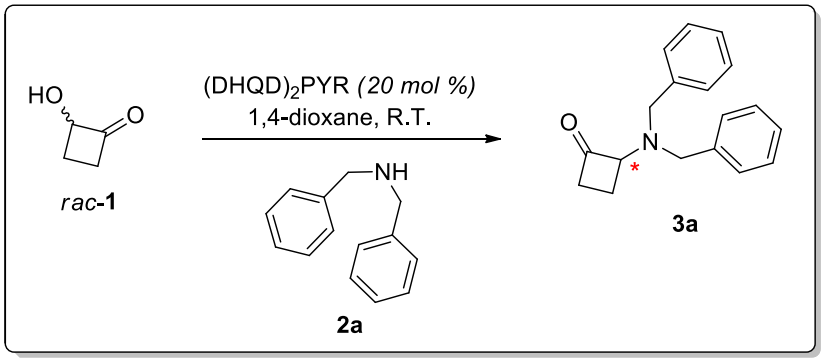
Figure 2.1. Catalyst screening



Having established the appropriate reaction conditions, we next conducted experiments to evaluate the scope of this transformation by varying the ring substituents on the dibenzylamine substrate (Scheme 2.2). Good enantioselectivities were obtained by a series of dibenzylamines with electron-withdrawing groups on the aromatic ring. Dibenzylamines **2b**–**2h**, which contain one electron-withdrawing substituent at the *para* position, gave rise to the desired α-aminocyclobutanones **3b**–**3h** in high yields (up to 94%) with enantioselectivities up to 87:13 *e.r.*

A representative *meta*-substituted dibenzylamine (i.e., **2i**) performed almost equally well (77% yield, 78:22 *e.r.*), whereas *ortho*-substituted dibenzylamine **2j** furnished the desired product **3j** in a diminished 48% yield and with an enantiomeric ratio of only 56:44.

Table 2.1. Optimization of reaction conditions.[a]



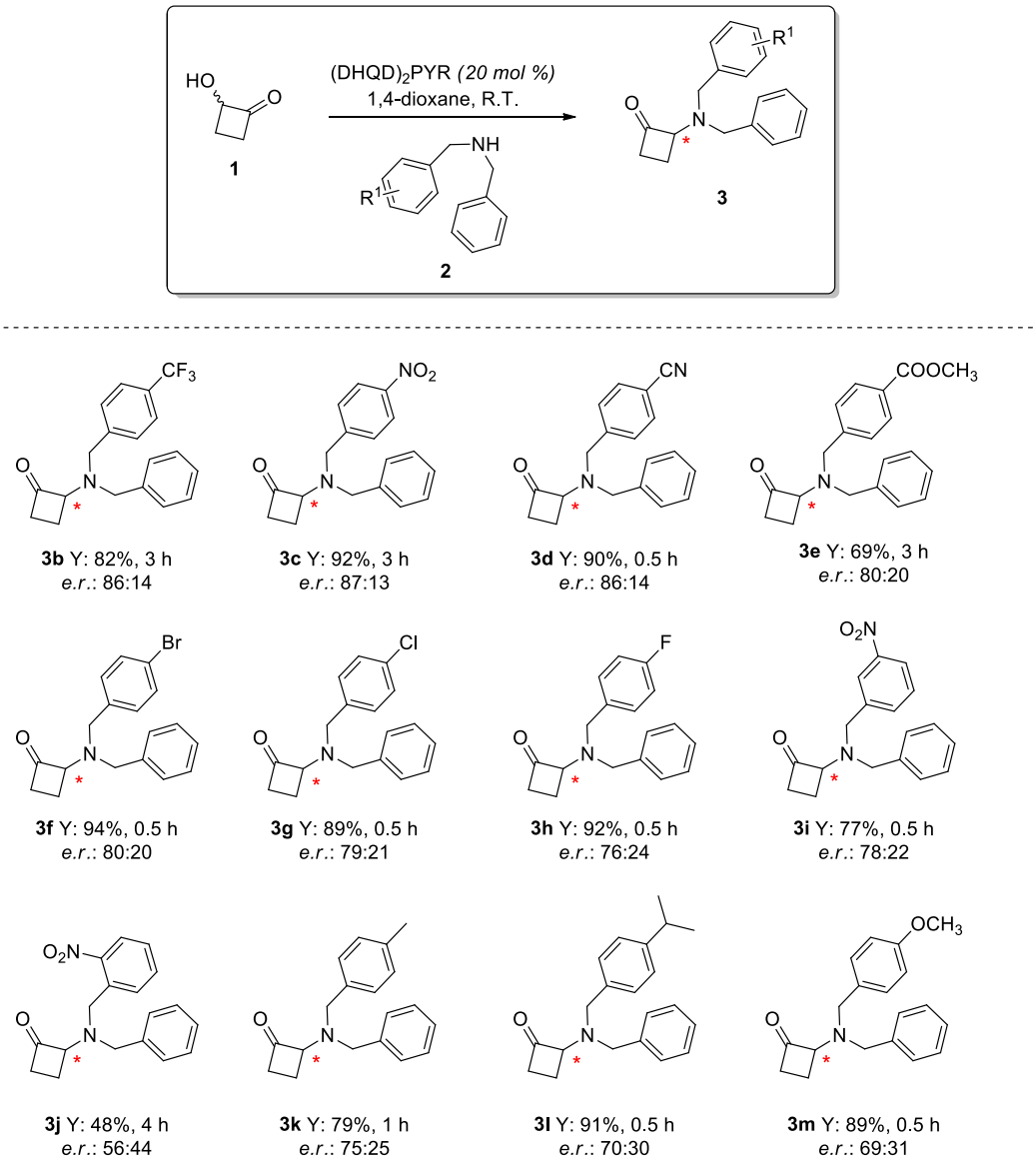
Entry	Catalyst	Solvent	Yield 3a [%][b]	*e.r.*(3a)[c]
1	–	1,4-dioxane	47	–
2	$(DHQD)_2PYR$[d]	1,4-dioxane	81	71:29
3	$(DHQ)_2PYR$[d]	1,4-dioxane	78	32:68
4	$(DHQD)_2PHAL$[d]	1,4-dioxane	66	54:46
5	$(DHQ)_2PHAL$[d]	1,4-dioxane	70	48:52
6	$(DHQD)_2AQN$[d]	1,4-dioxane	54	64:36
7	$(DHQ)_2AQN$[d]	1,4-dioxane	68	44:56
8	quinidine	1,4-dioxane	71	46:54
9	$(DHQD)_2PYR$	toluene	54	59:41
10	$(DHQD)_2PYR$	$CHCl_3$	85	49:51
11	$(DHQD)_2PYR$	CH_3COOEt	77	69:31
12[e]	$(DHQD)_2PHAL$	toluene	80	50:50

[a] Reagents and conditions: **1** (669 µmol), **2** (224 µmol), catalyst (44.8 µmol), solvent (0.5 mL). [b] Isolated yield after chromatography. [c] Enantiomeric ratio (*e.r.*) was determined by HPLC analysis using a chiral stationary phase column. [d] $(DHQD)_2PYR$ = hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQ)_2PYR$ = hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether, $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether, $(DHQD)_2AQN$ = hydroquinidine (anthraquinone-1,4-diyl) diether, $(DHQ)_2AQN$ = hydroquinine (anthraquinone-1,4-diyl) diether. [e] Reagents and conditions: $(DHQD)_2PHAL$ (30 mol-%), toluene (0.5 mL), molecular sieves (4 Å; 0.6 g), 0 °C.

Dibenzylamines **2k**–**2m**, which have one electron-donating substituent at the *para* position, also provided good yields of the corresponding adducts **3k**–**3m** under the designated reaction conditions. These products, however, were obtained with lower enantioselectivities (from 69:31 to 75:25 *e.r.*).

Of particular note, bis(*para*-substituted) dibenzylamines that contain electron-withdrawing groups were tolerated and gave good to high chemical yields with high enantioselectivities.

Scheme 2.2. Substrate scope regarding aromatic ring substituents. Reagents and conditions: **1** (669 μmol), **2** (224 μmol), and $(DHQD)_2PYR$ (44.8 μmol) in 1,4-dioxane (0.5 mL). Yields are given for isolated materials after column chromatography. The *e.r.* values were determined by HPLC analysis using a chiral stationary phase column.



Indeed, by using dibenzylamines **2o**–**2t** as substrates, we obtained the corresponding α-(dibenzylamino)cyclobutanones **3o**–**3t** in yields of 59–85% with up to 91:9 *e.r.* Importantly, by using a dibenzylamine that has an electron-donating substituent on one aryl group and an electron-withdrawing group on the other, compound **2n** provided comparable results in terms of efficiency and stereoselectivity.

The absolute configuration of compound **3o** was unambiguously determined to be (*R*) by single-crystal X-ray diffraction analysis (Figure 2.2), and the configurations of the other products **3a**–**3t** were assumed to be (*R*) by analogy to **3o**.[12]

We also examined *N*-alkylbenzylamines **4a**–**4g** under the standard conditions (Scheme 2.3). Various *N*-alkyl groups such as methyl (i.e., **4a**), ethyl (i.e., **4b**), phenethyl (i.e., **4d**),

(ethoxycarbonyl)ethyl (i.e., **4f**) as well as the sterically more congested isopropyl group (i.e., **4c**) provided products in good to high yields (79–93%).

Scheme 2.3. Substrate scope by using disubstituted dibenzylamines.

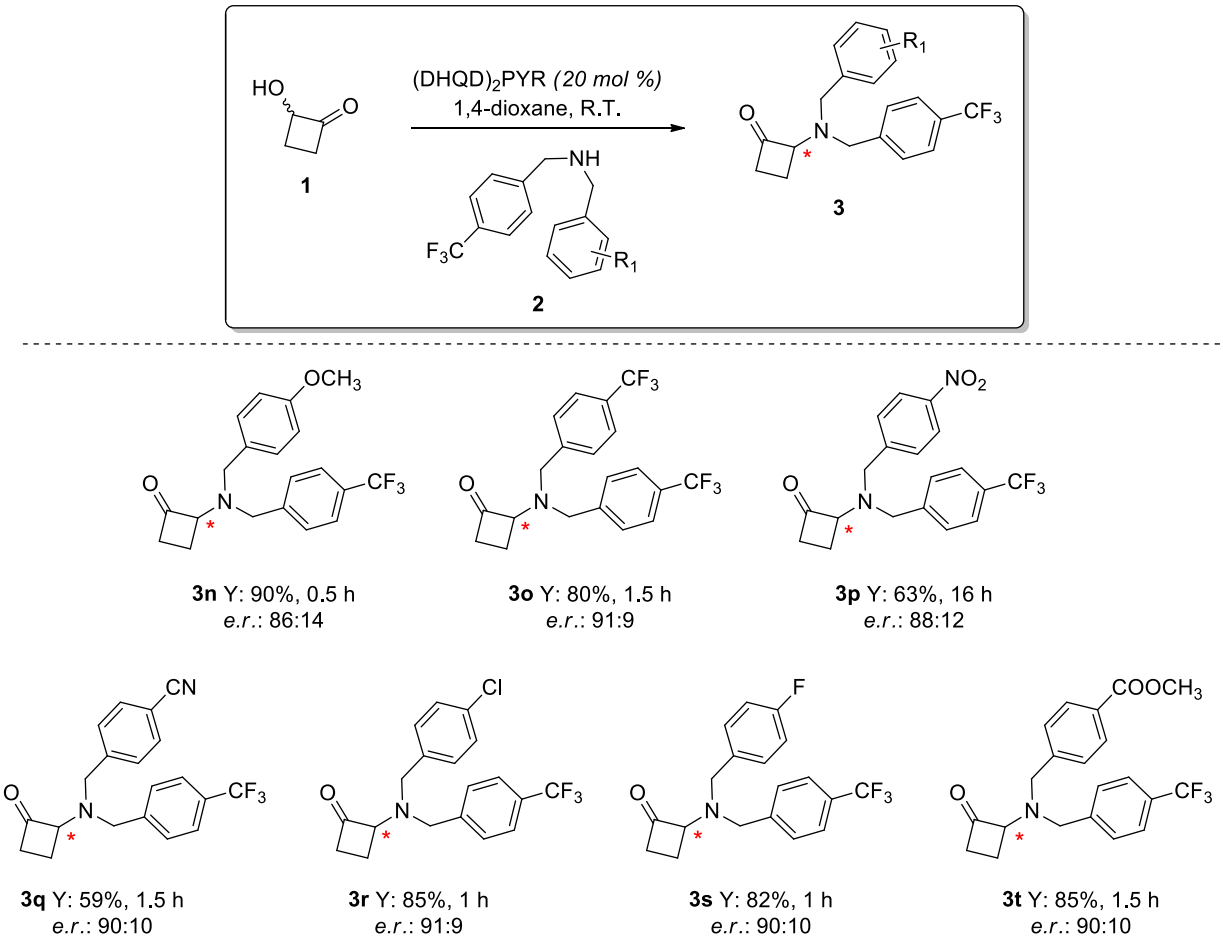
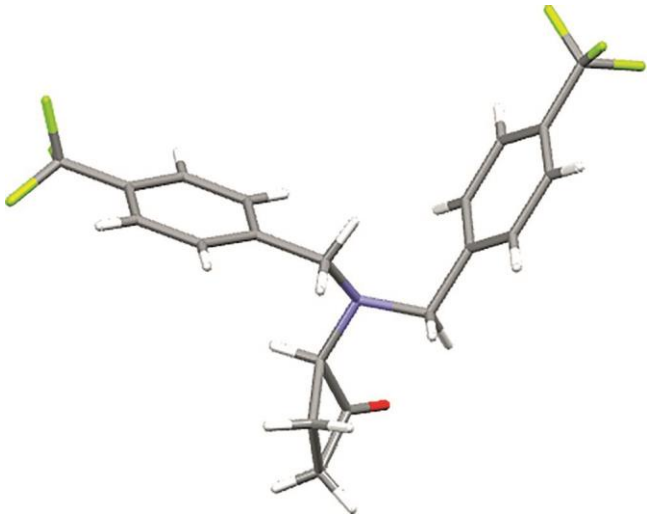
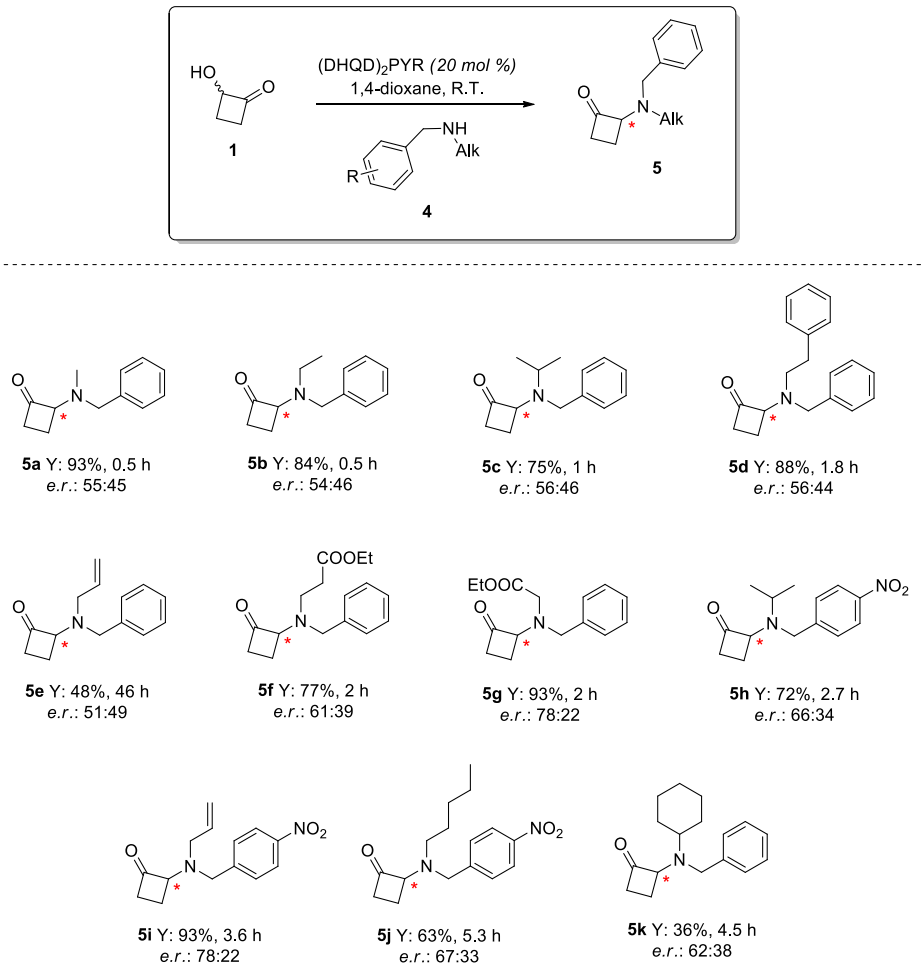


Figure 2.2. X-ray crystallographic structure of compound **3o**.



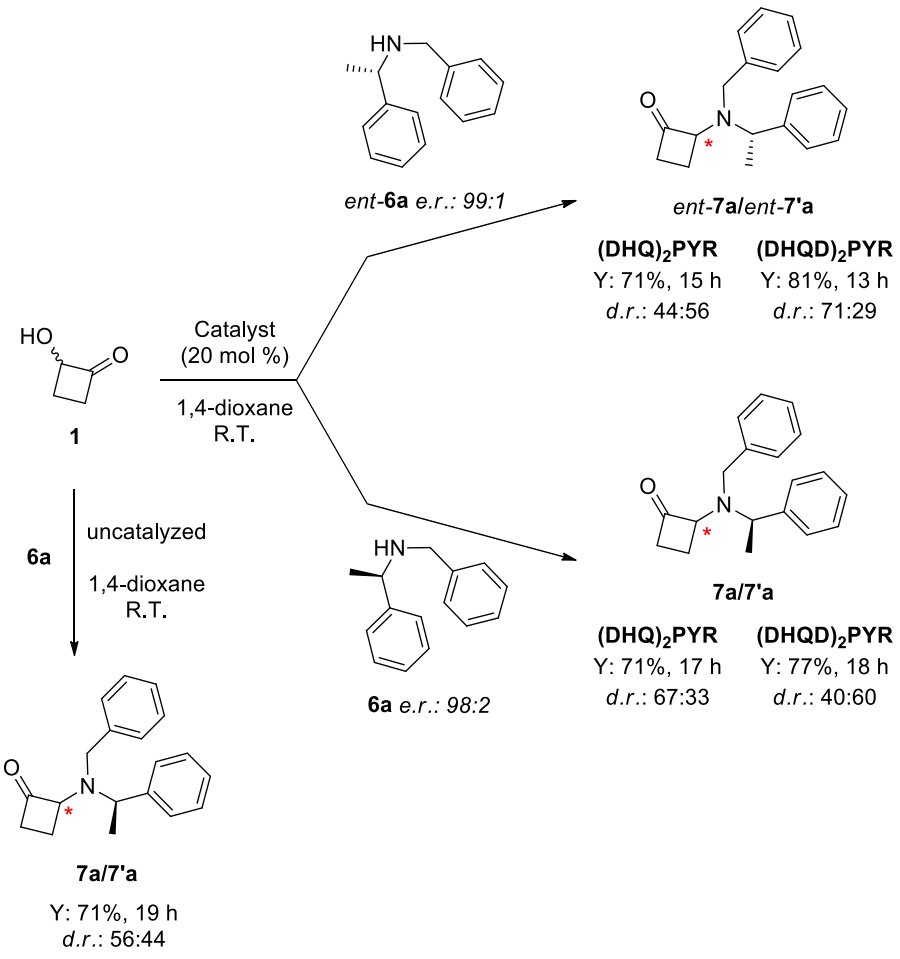
Only *N*-allyl substrate **4e** afforded a disappointing yield, even after a prolonged reaction time (48% yield after 46 h). Furthermore, products **5a**– **5f** were obtained with low selectivity, and this aspect of the reactivity remains a challenge to control. However, as a guide to possible future developments, we found that *N*-benzylglycine ester **4g** was a more successful partner than its homologue **4f** and afforded the desired product **5g** in high yield (93%) with improved enantioselectivity (78:22 *e.r.*). Substrates **4h**–**4k**, which have an electron-withdrawing group (NO_2) at the *para* position of the aromatic ring, performed perceptibly better than the nonsubstituted series **4a**–**4f** and gave products **5h**–**5k** with enantiomeric ratios that ranged from 62:38 to 78:22. These results suggest that steric factors and the electronic character of the *N*-alkyl group of the benzylamine have a dramatic influence on the stereoselectivity of the reaction and that the presence of an electron-withdrawing group at the *para* position of the aromatic ring is required to effect some enantioselectivity.[13]

Scheme 2.4. Substrate scope regarding *N*-alkyl substituents. Reagents and conditions: **1** (669 μmol), **4** (0.224 μmol), and $(DHQD)_2PYR$ (44.8 μmol) in 1,4-dioxane (0.5 mL). Yields are given for isolated materials after column chromatography. The *e.r.* values were determined by HPLC analysis using a chiral stationary phase column.



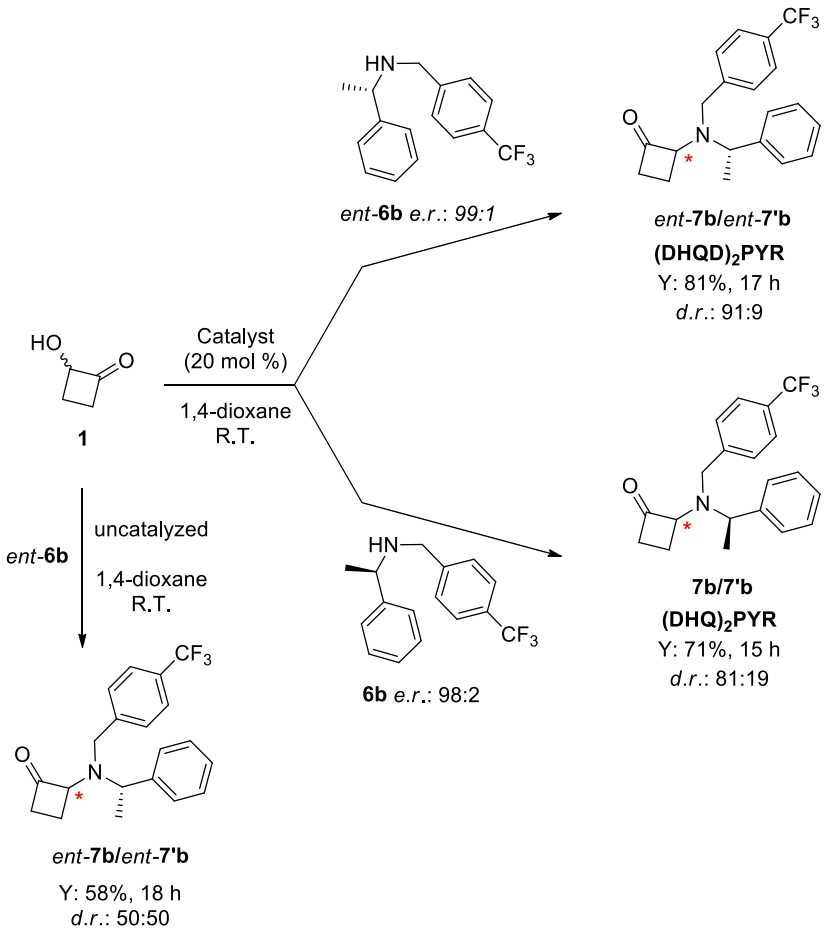
Returning our focus to dibenzylamine substrates, we examined the influence of a pre-existing stereogenic center on the stereochemical outcome of the tandem asymmetric reaction by considering the chirality of both the secondary amine and the catalyst.[14] As revealed in Scheme 2.5, with homochiral benzylamines **6a** and *ent*-**6a**, a moderate match/ mismatch effect between the amine and the catalyst was observed in both cases, without any significant improvement to the stereoselectivity obtained by the catalyzed reaction of dibenzylamine **2a** (Table 2.1, Entry 2). However, as expected, the introduction of an electron-withdrawing group (CF_3) at the *para* position of the aromatic ring (i.e., **6b** and *ent*-**6b**) led to a considerable improvement in the stereoselectivity and afforded the desired α-(benzylamino)cyclobutanones **7b**/**7'b** in 81:19 diastereomeric ratio (*d.r.*) and *ent*-**7b**/*ent*-**7'b** in 91:9 *d.r.*, respectively, by using 30 mol-% of $(DHQD)_2PYR$ or $(DHQ)_2PYR$ (Scheme 2.6). Unfortunately, we could not distinguish the diastereomers by TLC and failed to separate them by silica gel column chromatography.

Scheme 2.5. Diastereomeric approach to α-dibenzylamino cyclobutanones using (S) and (R) optically pure dibenzylamines.



It should be noted that the reaction of either dibenzylamine **6a** or *ent*-**6b** without a catalyst proceeded with almost no intrinsic stereochemical preference, which clearly suggests a catalyst-based control of the stereoselectivity.

Scheme 2.6 – Diastereomeric approach to the synthesis of a-dibenzylamino cyclobutanones using *(S)* and *(R)* optically pure dibenzylamines bearing a *para*-CF_3 substituent in one aromatic ring.



2.3 Conclusions

We have presented a simple and practical method for the synthesis of highly functionalized and optically active α-(benzylamino)cyclobutanones by using a tandem condensation/intramolecular rearrangement/proton transfer reaction. The reaction sequence began from readily available racemic α-hydroxycyclobutanone and benzylamines and was catalyzed by cinchona alkaloid derivatives to afford the products in good to high yields and with moderate to high stereoselectivities.

2.4 Experimental Section

2.4.1 General procedures and experimental data

General procedure for α-benzylamination of α-hydroxycyclobutanones

To a solution of freshly distilled α-hydroxycyclobutanone (0.058 g, 0.669 mmol) and $(DHQD)_2PYR$ (0.0395 g, 0.0448 mmol) in dry 1,4-dioxane (0.5 mL) at room temperature was added the benzylamine (0.224 mmol) dropwise, and the resulting mixture was stirred for 0.5–18 h. The crude reaction mixture was directly loaded onto a silica gel column without aqueous workup, and the pure products were obtained by flash column chromatography (silica gel; hexane/ether, 5:1→1:1). The racemates were synthesized by using 4-(dimethylamino)pyridine (DMAP) as a catalyst.

3a: Yellow oil (48 mg, 81% yield). **IR** (neat): ν̃ = 3087, 3058, 3028, 2930, 2844, 2812, 1778, 1653, 1495, 1453, 1400, 1374, 1069, 1026 cm^{-1}. $\mathbf{[\alpha]^{29}_D}$ = +19.2 (*c* = 2.18, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* = 7.37 (d, *J* = 7.5 Hz, 4 H), 7.31 (t, *J* = 7.5 Hz, 4 H), 7.24 (d, *J* = 7.0 Hz, 1 H), 4.28 (t, *J* = 9.3 Hz, 1 H), 3.76 (d, *J* = 13.6 Hz, 2 H), 3.63 (d, *J* = 13.6 Hz, 2 H), 2.70 (dt, *J* = 19.5, 9.8 Hz, 1 H), 2.59 (ddd, *J* = 14.9, 7.3, 4.6 Hz, 1 H), 2.09–1.95 (m, 2 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* = 209.97, 138.9, 129.0, 128.4, 127.3, 76.6, 55.1, 40.7, 14.9 ppm. **HRMS** (ESI): calcd. for $C_{18}H_{19}NO$ $[M + 1]^+$ 266.1559; found 266.1558. The enantiomeric ratio (71:29) was determined by HPLC (Chiracel OJ column; hexane/*i*PrOH, 90:10; flow rate: 1.0 $mLmin^{-1}$; *λ* = 254 nm): t_R= 17.74 min (major), t_R = 21.83 min (minor).

3b: Yellow oil (61 mg, 82% yield). **IR** (neat): ν̃ = 3031, 2831, 1778, 1617, 1492, 1449, 1420, 1325, 1164, 1124, 1105, 1062, 1019 cm^{-1}. $\mathbf{[\alpha]^{27}_D}$ = +20.1 (*c* = 3.07, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* = 7.56 (d, *J* = 8.2 Hz, 2 H), 7.49 (d, *J* = 8.1 Hz, 2 H), 7.37–7.28 (m, 4 H), 7.25 (dd, *J* = 9.6, 4.3 Hz, 1 H), 4.32–4.21 (m, 1 H), 3.81 (d, *J* = 14.1 Hz, 1 H), 3.73 (dd, *J* = 28.1, 13.8 Hz, 2 H), 3.63 (d, *J* = 13.6 Hz, 1 H), 2.81–2.68 (m, 1 H), 2.67–2.57 (m, 1 H), 2.16–1.94 (m, 2 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* = 209.4, 143.30, 138.4, 129.0, 128.9, 128.5, 127.5, 125.3 (q, *J* = 3.8 Hz), 76.6, 55.3, 54.7, 40.8, 15.0 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{18}F_3NO$ $[M + 1]^+$ 334.1413; found 334.1426. The enantiomeric ratio (86:14) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 98:2; flow rate: 1.0 $mLmin^{-1}$; *λ* = 254 nm): t_R = 11.43 min (major), t_R = 12.32 min (minor).

3c: Yellow oil (64 mg, 92% yield). **IR** (neat): ν̃ = 3022, 2841, 1774, 1604, 1518, 1495, 1456, 1348, 1262, 1105, 1069 cm^{-1}. $[\alpha]^{29}_D$ = +10.9 (*c* = 5.46, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* = 8.16 (d, *J* = 8.7 Hz, 2 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 7.35–7.23 (m, 5 H), 4.27 (dd, *J* = 10.0, 8.4 Hz, 1 H), 3.85 (d, *J* = 14.5 Hz, 1 H), 3.74 (t, *J* = 18.5 Hz, 2 H), 3.64 (d, *J* = 13.6 Hz, 1 H), 2.83–2.70 (m, 1 H), 2.70–2.57 (m, 1 H), 2.12 (qd, *J* = 10.7, 4.5 Hz, 1 H), 2.07–1.96 (m, 1 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* = 209.0, 147.0, 138.0, 129.4, 128.9, 128.5, 127.6, 123.6, 76.6, 55.6, 54.5, 40.8, 15.2 ppm. **HRMS** (ESI): calcd. for $C_{18}H_{18}N_2O_3$ $[M + 1]^+$ 311.139; found 311.1394. The enantiomeric ratio (87:13) was determined by HPLC (Chiracel OJ column; hexane/*i*PrOH, 90:10; flow rate: 1.0 $mLmin^{-1}$; *λ* = 254 nm): t_R = 41.52 min (major), t_R = 36.36 min (minor).

3d: Yellow oil (58 mg, 90% yield). **IR** (neat): ν̃ = 3031, 2831, 2231, 1774, 1610, 1499, 1456, 1371, 1075, 1023 cm^{-1}. $[\alpha]^{27}_D$ = +12.3 (*c* = 5.49, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* = 7.59 (d, *J* = 8.0 Hz, 2 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 4.3 Hz, 5 H), 4.26 (t, *J* = 9.2 Hz, 1 H), 3.80 (d, *J* = 14.4 Hz, 1 H), 3.77–3.67 (m, 2 H), 3.63 (d, *J* = 13.5 Hz, 1 H), 2.80–2.70 (m, 1 H), 2.68–2.58 (m, 1 H), 2.10 (qd, *J* = 10.5, 4.5 Hz, 1 H), 2.06–1.96 (m, 1 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* = 209.1, 144.9, 138.1, 132.2, 129.4, 128.9, 128.5, 127.5, 118.9, 111.1, 76.6, 55.5, 54.7, 40.8, 15.1 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{18}N_2O$ $[M + 1]^+$ 291.1492; found 291.1497. The enantiomeric ratio (86:14) was determined by HPLC (Chiralpak AD-H column; hexane/*i*PrOH, 95:5; flow rate: 1.0 $mLmin^{-1}$; *λ* = 254 nm): t_R = 22.76 min (major), t_R = 26.78 min (minor).

3e: Yellow oil (50 mg, 69% yield). **IR** (neat): ν̃ = 3031, 2956, 2890, 1774, 1722, 1614, 1574, 1492, 1436, 1387, 1282, 1190, 1170, 1111, 1075, 1023 cm^{-1}. $[\alpha]^{20}_D$ = +17.1 (*c* = 4.90, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* = 7.99 (d, *J* = 8.2 Hz, 2 H), 7.45 (d, *J* = 8.2 Hz, 2 H), 7.30 (ddd, *J* = 18.4, 8.7, 5.9 Hz, 5 H), 4.31–4.23 (m, 1 H), 3.90 (s, 3 H), 3.80 (d, *J* = 14.1 Hz, 1 H), 3.72 (dd, *J* = 22.9 13.8 Hz, 2 H), 3.62 (d, *J* = 13.6 Hz, 1 H), 2.72 (ddd, *J* = 19.5, 10.7, 1.9 Hz, 1 H), 2.66–2.55 (m, 1 H), 2.13–1.94 (m, 2 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): *δ* = 209.5, 167.0, 144.4, 138.4, 129.7, 129.2, 128.9, 128.8, 128.4, 127.4, 76.6, 55.3, 54.8, 52.1, 40.7, 15.0 ppm. **HRMS** (ESI): calcd. for $C_{20}H_{21}NO_3$ $[M + 1]^+$ 324.1594; found 324.1602. The enantiomeric ratio (80:20) was determined by HPLC (Chiralpak AS-H column; hexane/*i*PrOH, 99:1; flow rate: 1.0 $mLmin^{-1}$; *λ* = 254 nm): t_R = 25.70 min (major), t_R = 32.21 min (minor).

3f: Pale yellow oil (73 mg, 94% yield). **IR** (neat): ν̃ = 3025, 2844, 1778, 1653, 1591, 1489, 1449, 1403, 1374, 1249, 1164, 1072, 1010 cm^{-1}. $[\alpha]^{27}_D$ = +16.5 (*c* = 6.29, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* = 7.45–7.40 (m, 2 H), 7.35–7.28 (m, 5 H), 7.24 (d, *J* = 7.5 Hz, 2 H), 4.25 (t, *J* = 9.2 Hz,

1 H), 3.76–3.67 (m, 2 H), 3.59 (t, *J* = 12.8 Hz, 2 H), 2.71 (ddd, *J* = 18.3, 10.5, 9.3 Hz, 1 H), 2.65–2.55 (m, 1 H), 2.10–1.94 (m, 1 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 209.5, 138.5, 138.0, 131.5, 130.6, 128.9, 128.4, 127.4, 121.0, 76.5, 55.1, 54.4, 40.7, 15.0 ppm. **HRMS** (ESI): calcd. for $C_{18}H_{18}BrNO$ $[M + 1]^+$ 344.0644; found 344.0651. The enantiomeric ratio (80:20) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 98:2; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 20.28 min (major), t_R = 21.62 min (minor).

3g: Pale yellow oil (59 mg, 89% yield). **IR** (neat): $\tilde{\nu}$ = 3025, 2838, 2812, 1774, 1597, 1492, 1449, 1400, 1371, 1259, 1164, 1095, 1075, 1016 cm^{-1}. **$[\alpha]^{27}_D$** = +19.4 (*c* = 5.46, $CHCl_3$). **^{1}H NMR** (400 MHz): δ = 7.36–7.22 (m, 9 H), 4.30–4.21 (m, 1 H), 3.73 (dd, *J* = 13.7, 6.8 Hz, 2 H), 3.60 (dd, *J* = 13.7, 3.6 Hz, 2 H), 2.78–2.66 (m, 1 H), 2.66–2.55 (m, 1 H), 2.11–1.94 (m, 2 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 209.6, 138.5, 137.4, 133.0, 130.2, 128.9, 128.5, 128.49, 127.4, 76.5, 55.1, 54.4, 40.7, 14.9 ppm. **HRMS** (ESI): calcd. for $C_{18}H_{18}ClNO$ $[M + 1]^+$ 300.115; found 300.115. The enantiomeric ratio (79:21) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 99:1; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 8.99 min (major), t_R = 9.45 min (minor).

3h: Pale yellow oil (58 mg, 92% yield). **IR** (neat): $\tilde{\nu}$ = 3064, 2841, 1778, 1604, 1509, 1449, 1374, 1220, 1157, 1092, 1072 cm^{-1}. **$[\alpha]^{24}_D$** = +14.7 (*c* = 5.16, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.32 (dt, *J* = 17.8, 7.5 Hz, 7 H), 6.99 (t, *J* = 8.7 Hz, 2 H), 4.26 (t, *J* = 9.2 Hz, 1 H), 3.72 (m, 2 H), 3.60 (dd, *J* = 13.6, 5.6 Hz, 2 H), 2.71 (ddd, *J* = 19.5, 10.8, 2.0 Hz, 1 H), 2.65–2.55 (m, 1 H), 2.11–1.93 (m, 2 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 209.7, 163.1, 161.2, 138.7, 134.5 (d, *J* = 3.2 Hz), 130.4, 130.4, 128.9, 128.4, 127.3, 115.3, 115.1, 76.5, 55.1, 54.3, 40.7, 14.9 ppm. **HRMS** (ESI): calcd. for $C_{18}H_{18}FNO$ $[M + 1]^+$ 284.1445; found 284.1452. The enantiomeric ratio (76:24) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/ *i*PrOH, 99:1; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 10.36 min (major), t_R = 10.96 min (minor).

3i: Yellow oil (53 mg, 77% yield). **IR** (neat): $\tilde{\nu}$ = 3071, 3025, 2838, 1778, 1528, 1449, 1351, 1075, 1023 cm^{-1}. **$[\alpha]^{25}_D$** = +8.4 (*c* = 4.98, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 8.09 (d, *J* = 8.2 Hz, 1 H), 7.73 (d, *J* = 7.7 Hz, 1 H), 7.49 (d, *J* = 7.9 Hz, 1 H), 7.33 (t, *J* = 6.3 Hz, 5 H), 4.28 (t, *J* = 9.2 Hz, 1 H), 3.85 (d, *J* = 14.2 Hz, 1 H), 3.76 (d, *J* = 14.5 Hz, 2 H), 3.65 (d, *J* = 13.6 Hz, 1 H), 2.82–2.71 (m, 1 H), 2.70–2.60 (m, 1 H), 2.13 (qd, *J* = 10.7, 4.6 Hz, 1 H), 2.08–1.98 (m, 1 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 209.0, 148.4, 141.4, 138.0, 134.9, 129.3, 129.0, 128.6, 127.6, 123.5, 122.4, 76.6, 55.5, 54.4, 40.8, 15.3 ppm. **HRMS** (ESI): calcd. for $C_{18}H_{18}N_2O_3$ $[M + 1]^+$ 311.139; found 311.1399. The enantiomeric ratio (78:22) was determined

by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 95:5; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 16.11 min (major), t_R = 17.18 min (minor).

3j: Yellow oil (33 mg, 48% yield). **IR** (neat): $\tilde{\nu}$ = 3064, 3025, 1778, 1528, 1495, 1456, 1354, 1200, 1179, 1065 cm^{-1}. **[α]$^{27}_D$** = –13.1 (*c* = 2.28, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.2 Hz, 2 H), 7.55 (dd, *J* = 11.9, 4.3 Hz, 1 H), 7.37 (t, *J* = 7.7 Hz, 1 H), 7.30–7.26 (m, 5 H), 4.27–4.20 (m, 1 H), 4.15 (d, *J* = 15.3 Hz, 1 H), 3.97 (d, *J* = 15.3 Hz, 1 H), 3.77 (d, *J* = 13.5 Hz, 1 H), 3.64 (d, J = 13.5 Hz,1H), 2.76–2.66 (m, 1 H), 2.65–2.56 (m, 1 H), 2.06 (ddd, *J* = 18.4, 13.1, 7.1 Hz, 2 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 209.3, 149.8, 138.0, 134.4, 132.8, 131.2, 128.9, 128.5, 128.0, 127.5, 124.4, 76.7, 56.3, 51.8, 40.7, 15.0 ppm. **HRMS** (ESI): calcd. for $C_{18}H_{18}N_2O_3$ $[M + 1]^+$ 311.139; found 311.1396. The enantiomeric ratio (56:44) was determined by HPLC (Chiralpak AD-H column; hexane/*i*PrOH, 98:2; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 22.66 min (major), t_R = 26.86 min (minor).

3k: Yellow oil (51 mg, 79% yield). **IR** (neat): $\tilde{\nu}$ = 3028, 2982, 2926, 2812, 1778, 1515, 1492, 1449, 1371, 1253, 1200, 1170, 1115, 1075, 1026 cm^{-1}. **[α]$^{24}_D$** = +17.7 (*c* = 5.31, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 7.0 Hz, 2 H), 7.30 (t, *J* = 7.4 Hz, 2 H), 7.24 (dd, *J* = 8.1, 4.7 Hz, 3 H), 7.11 (d, *J* = 7.8 Hz, 2 H), 4.27 (ddd, *J* = 9.4, 4.5, 2.2 Hz, 1 H), 3.73 (t, *J* = 14.0 Hz, 2 H), 3.65–3.55 (m, 2 H), 2.73–2.63 (m, 1 H), 2.58 (dddd, *J* = 9.2, 7.9, 5.4, 2.4 Hz, 1 H), 2.32 (s, 3 H), 2.05–1.98 (m, 2 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 210.0, 138.9, 136.8, 135.7, 129.1, 128.97, 128.96, 128.4, 127.2, 110.1, 76.6, 55.0, 54.8, 40.6, 21.2, 14.9 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{21}NO$ $[M + 1]^+$ 280.1696; found 280.1697. The enantiomeric ratio (75:25) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 98:2; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 9.84 min (major), t_R = 10.69 min (minor).

3l: Yellow oil (62 mg, 91% yield). **IR** (neat): $\tilde{\nu}$ = 3058, 3015, 2959, 1781, 1650, 1518, 1495, 1456, 1371, 1216, 1072 cm^{-1}. **[α]$^{27}_D$** = +14.5 (*c* = 5.90, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.1 Hz, 2 H), 7.29 (dd, *J* = 14.3, 7.6 Hz, 4 H), 7.25–7.20 (m, 1 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 4.33–4.26 (m, 1 H), 3.75 (t, *J* = 14.1 Hz, 2 H), 3.67–3.56 (m, 2 H), 2.88 (dt, *J* = 13.8, 6.9 Hz, 1 H), 2.74–2.64 (m, 1 H), 2.58 (dddd, *J* = 17.3, 9.2, 5.4, 2.5 Hz, 1 H), 2.09– 1.96 (m, 2 H), 1.23 (d, *J* = 6.9 Hz, 6 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 210.0, 147.9, 139.0, 136.1, 128.97, 128.90, 128.4, 127.2, 126.4, 76.6, 55.0, 54.8, 40.6, 33.9, 24.1, 14.8 ppm. **HRMS** (ESI): calcd. for $C_{21}H_{25}NO$ $[M + 1]^+$ 308.2009; found 308.2004. The enantiomeric ratio (70:30) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 99:1; flow rate: 0.8 mLmin^{-1}; λ = 254 nm): t_R = 8.52 min (major), t_R = 8.86 min (minor).

3m: Pale yellow oil (59 mg, 89% yield). **IR** (neat): ν̃ = 2956, 2933, 2838, 1778, 1614, 1512, 1456, 1374, 1302, 1246, 1177, 1108, 1069, 1033 cm^{-1}. **$[\alpha]^{28}_D$** = +14.6 (*c* = 5.19, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 7.0 Hz, 2 H), 7.33–7.20 (m, 5 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 4.36–4.16 (m, 1 H), 3.78 (s, 3 H), 3.77–3.67 (m, 1 H), 3.59 (dd, *J* = 23.4, 13.5 Hz, 1 H), 2.75–2.64 (m, 1 H), 2.59 (dddd, *J* = 17.3, 9.2, 5.3, 2.4 Hz, 1 H), 2.07–1.97 (m, 2 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 210.1 (s), 158.9 (s), 139.0 (s), 130.8 (s), 130.1 (s), 128.9 (s), 128.4 (s), 127.2 (s), 113.8 (s), 76.5 (s), 55.3 (s), 54.9 (s), 54.4 (s), 40.7 (s), 14.9 (s) ppm. **HRMS** (ESI): calcd. for $C_{19}H_{21}NO_2$ $[M + 1]^+$ 296.1645; found 296.1649. The enantiomeric ratio (69:31) was determined by HPLC (Chiracel OJ column; hexane/*i*PrOH, 90:10; flow rate: 1.0 $mLmin^{-1}$; λ = 254 nm): t_R = 17.75 min (major), t_R = 19.74 min (minor).

3n: Pale yellow oil (73 mg, 90% yield). **IR** (neat): ν̃ = 3008, 2844, 1778, 1617, 1591, 1522, 1325, 1249, 1164, 1121, 1108, 1065, 1039, 1019 cm^{-1}. **$[\alpha]^{27}_D$** = +15.0 (*c* = 6.11, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.1 Hz, 2 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 4.27 (t, *J* = 9.2 Hz, 1 H), 3.84–3.77 (m, 4 H), 3.70 (dd, *J* = 13.7, 5.5 Hz, 2 H), 3.58 (d, *J* = 13.4 Hz, 1 H), 2.80–2.69 (m, 1 H), 2.68–2.58 (m, 1 H), 2.14–1.96 (m, 2 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 209.5, 159.1, 143.4, 130.3, 130.1, 129.0, 125.3 (q, *J* = 3.8 Hz), 113.9, 76.5, 55.3, 54.7, 54.5, 40.8, 15.0 ppm. **HRMS** (ESI): calcd. for $C_{20}H_{20}F_3NO_2$ $[M + 1]^+$ 364.1519; found 364.1515. The enantiomeric ratio (86:14) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 97:3; flow rate: 1.0 $mLmin^{-1}$; λ = 254 nm): t_R = 13.79 min (major), t_R = 15.33 min (minor).

3o: White solid (71 mg, 80% yield); m.p. 95–98 °C. **IR** (Nujol): ν̃ = 2975, 2838, 1784, 1621, 1419, 1325, 1162, 1120, 1104, 1068, 1019 cm^{-1}. **$[\alpha]^{21}_D$** = +12.2 (*c* = 7.65, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.1 Hz, 4 H), 7.47 (d, *J* = 8.0 Hz, 4 H), 4.29–4.23 (m, 1 H), 3.81 (d, *J* = 14.1 Hz, 2 H), 3.70 (d, J = 14.0 Hz, 2H), 2.83–2.71 (m, 1 H), 2.70–2.60 (m, 1 H), 2.12 (qd, *J* = 10.7, 4.5 Hz, 1 H), 2.08–1.98 (m, 1 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 208.9, 142.7, 129.9, 129.7, 129.0, 125.4 (q, *J* = 3.8 Hz), 76.6, 54.9, 40.8, 15.2 ppm. **HRMS** (ESI): calcd. for $C_{20}H_{17}F_6NO$ $[M + 1]^+$ 402.1287; found 402.1317. The enantiomeric ratio (91:9) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 99:1; flow rate: 1.0 $mLmin^{-1}$; λ = 254 nm): t_R = 8.48 min (major), t_R = 8.12 min (minor).

3p: Yellow oil (53 mg, 63% yield). **IR** (neat): ν̃ = 2976, 2844, 1774, 1620, 1604, 1525, 1348, 1325, 1157, 1118, 1105, 1062, 1019 cm^{-1}. **$[\alpha]^{21}_D$** = +4.0 (*c* = 4.43, $CHCl_3$). **^{1}H NMR** (500 MHz,

$CDCl_3$): δ =8.17 (d, J = 8.7 Hz, 2 H), 7.58 (d, J = 8.1 Hz, 2 H), 7.54 (d, J = 8.7 Hz, 2 H), 7.46 (d, J = 8.0 Hz, 2 H), 4.25 (dd, J = 10.0, 8.4 Hz, 1 H), 3.79 (tt, J = 16.2, 8.3 Hz, 4 H), 2.85–2.74 (m, 1 H), 2.72–2.63 (m, 1 H), 2.15 (qd, J = 10.7, 4.4 Hz, 1 H), 2.09–1.98 (m, 1 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 208.5, 147.5, 146.4, 142.4, 142.3, 129.4, 129.0, 125.5 (q, J = 3.8 Hz), 123.7, 76.6, 55.1, 54.7, 40.9, 15.3 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{17}F_3N_2O_3$ $[M + 1]^+$ 379.1264; found 379.1276. The enantiomeric ratio (88:12) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 98:2; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 28.71 min (major), t_R = 26.67 min (minor).

3q: Colorless oil (47 mg, 59% yield). **IR** (neat): $\tilde{\nu}$ = 2966, 2844, 2227, 1778, 1620, 1610, 1420, 1325, 1164, 1121, 1102, 1069, 1019 cm^{-1}. **$[\alpha]^{22}_D$** = +3.8 (c = 1.03, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.2 Hz, 2 H), 7.58 (d, J = 8.1 Hz, 2 H), 7.50–7.44 (m, 4 H), 4.29–4.20 (m, 1 H), 3.81 (d, J = 14.5 Hz, 2 H), 3.71 (dd, J = 14.2, 3.1 Hz, 2 H), 2.79 (ddd, J = 19.6, 10.8, 1.9 Hz, 1 H), 2.72–2.61 (m, 1 H), 2.14 (qd, J = 10.6, 4.4 Hz, 1 H), 2.09–1.97 (m, 1 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 208.6, 144.3, 142.48, 142.47, 132.3, 129.3, 129.0, 125.5 (q, J = 3.8 Hz), 118.8, 111.3, 76.5, 55.08, 55.02, 40.8, 15.2 ppm. **HRMS** (ESI): calcd. for $C_{20}H_{17}F_3N_2O$ $[M + 1]^+$ 359.1366; found 359.1361. The enantiomeric ratio (90:10) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 98:2; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 29.10 min (major), t_R = 26.39 min (minor).

3r: Colorless oil (68 mg, 85% yield). **IR** (neat): $\tilde{\nu}$ = 2930, 2838, 1778, 1623, 1492, 1417, 1371, 1325, 1161, 1121, 1105, 1065, 1016 cm^{-1}. **$[\alpha]^{22}_D$** = +13.4 (c = 6.82, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.57 (d, J = 8.1 Hz, 2 H), 7.46 (d, J = 8.0 Hz, 2 H), 7.28 (s, 4 H), 4.28–4.20 (m, 1 H), 3.82–3.56 (m, 4 H), 2.80–2.70 (m, 1 H), 2.68–2.59 (m, 1 H), 2.14–2.04 (m, 1 H), 2.00 (dd, J = 19.7, 9.6 Hz, 1 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 209.1, 142.9, 136.9, 133.2, 130.2, 129.0, 128.7, 125.4 (q, J = 3.8 Hz), 76.5, 54.7, 54.6, 40.8, 15.1 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{17}ClF_3NO$ $[M + 1]^+$ 368.1023; found 368.1031. The enantiomeric ratio (91:9) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 99:1; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 11.61 min (major), t_R = 11.09 min (minor).

3s: Colorless oil (64 mg, 82% yield). **IR** (neat): $\tilde{\nu}$ = 2831, 1778, 1620, 1604, 1509, 1420, 1325, 1226, 1161, 1124, 1105, 1069, 1016 cm^{-1}. **$[\alpha]^{22}_D$** = +16.1 (c = 6.43, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.57 (d, J = 8.1 Hz, 2 H), 7.47 (d, J = 8.0 Hz, 2 H), 7.30 (dd, J = 8.4, 5.6 Hz, 2 H), 7.00 (t, J = 8.7 Hz, 2 H), 4.29–4.20 (m, 1 H), 3.70 (ddd, J = 53.5, 38.2, 13.8 Hz, 4 H), 2.80–2.70 (m, 1 H), 2.68–2.58 (m, 1 H), 2.14–1.96 (m, 2 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 209.2,

163.2, 161.3, 143.1, 134.0 (d, *J* = 3.1 Hz), 130.5, 130.4, 129.0, 125.4 (q, *J* = 3.7 Hz), 115.4, 115.2, 76.5, 54.6, 54.6, 40.8, 15.1 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{17}F_4NO$ $[M + 1]^+$ 352.1319; found 352.1346. The enantiomeric ratio (90:10) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 98:2; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 8.08 min (major), t_R = 7.54 min (minor).

3t: Yellow oil (75 mg, 85% yield). **IR** (neat): $\tilde{\nu}$ = 2953, 2835, 1778, 1722, 1617, 1440, 1417, 1321, 1282, 1164, 1105, 1069, 1019 cm^{-1}. $[\alpha]^{20}_D$ = +10.4 (*c* = 7.49, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.1 Hz, 2 H), 7.45 (dd, *J* = 18.5, 8.0 Hz, 4 H), 4.25 (t, *J* = 9.2 Hz, 1 H), 3.91 (s, 3 H), 3.81 (d, *J* = 14.0 Hz, 2 H), 3.70 (d, J = 14.0 Hz, 2H), 2.76 (ddd, *J* = 19.3, 10.6, 1.5 Hz, 1 H), 2.69–2.58 (m, 1 H), 2.17–1.96 (m, 2 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 209.0, 167.0, 143.9, 142.8, 129.8, 129.4, 129.0, 128.8, 125.4 (d, *J* = 3.1 Hz), 76.6, 55.0, 54.8, 52.1, 40.8, 15.1 ppm. **HRMS** (ESI): calcd. for $C_{21}H_{20}F_3NO_3$ $[M + 1]^+$ 392.1468; found 392.1489. The enantiomeric ratio (90:10) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 98:2; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 21.30 min (major), t_R = 19.73 min (minor).

5a: Yellow oil (39 mg, 93% yield). **IR** (neat): $\tilde{\nu}$ = 3028, 2982, 2792, 1778, 1643, 1495, 1453, 1403, 1075, 1059 cm^{-1}. $[\alpha]^{26}_D$ = +6.5 (*c* = 3.36, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 4.2 Hz, 4 H), 7.26 (dd, *J* = 7.6, 3.8 Hz, 1 H), 4.11 (t, *J* = 9.0 Hz, 1 H), 3.66 (s, 2 H), 2.86–2.75 (m, 1 H), 2.74–2.65 (m, 1 H), 2.29 (s, 3 H), 2.07 (ddd, *J* = 19.1, 12.6, 7.1 Hz, 2 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 208.6, 138.1, 129.2, 128.4, 127.3, 78.9, 59.6, 41.0, 38.5, 14.7 ppm. **HRMS** (ESI): calcd. for $C_{12}H_{15}NO$ $[M + 1]^+$ 190.1226; found 190.1214. The enantiomeric ratio (55:45) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 98:2; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 8.87 min (major), t_R = 10.50 min (minor).

5b: Yellow oil (38 mg, 84% yield). **IR** (neat): $\tilde{\nu}$ = 2969, 1778, 1640, 1499, 1453, 1394, 1377, 1065, 1026 cm^{-1}. $[\alpha]^{27}_D$ = +6.8 (*c* = 2.94, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 2 H), 7.31 (dd, *J* = 10.0, 4.8 Hz, 2 H), 7.26–7.22 (m, 1 H), 4.27 (tt, *J* = 10.8, 2.4 Hz, 1 H), 3.76 (d, *J* = 13.7 Hz, 1 H), 3.66 (d, J = 13.7 Hz,1H), 2.80–2.69 (m, 1 H), 2.69–2.57 (m, 3 H), 2.09 (ddd, *J* = 20.7, 10.7, 4.5 Hz, 1 H), 2.01 (ddd, *J* = 10.8, 9.9, 9.1 Hz, 1 H), 1.07 (t, *J* = 7.1 Hz, 3 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 209.8, 139.1, 128.9, 128.3, 127.1, 77.5, 54.4, 45.1, 40.6, 15.5, 12.6 ppm. **HRMS** (ESI): calcd. for $C_{13}H_{17}NO$ $[M + 1]^+$ 204.1382; found 204.1406. The enantiomeric ratio (54:46) was determined by HPLC (Phenomenex Lux Cellulose-1 column;

hexane/*i*PrOH, 98:2; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 9.26 min (major), t_R = 10.52 min (minor).

5c: Colorless oil (36 mg, 75% yield). **IR** (neat): ν̃ = 2969, 2926, 1781, 1633, 1499, 1459, 1394, 1371, 1279, 1174, 1128, 1059 cm^{-1}. **[α]$^{32}_D$** = +6.8 (*c* = 3.48, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 7.6, 0.6 Hz, 2 H), 7.29 (t, *J* = 7.4 Hz, 2 H), 7.22 (t, *J* = 7.3 Hz, 1 H), 4.41 (td, *J* = 8.6, 2.1 Hz, 1 H), 3.69 (q, *J* = 14.4 Hz, 2 H), 2.88 (dt, *J* = 13.2, 6.6 Hz, 1 H), 2.78–2.66 (m, 1 H), 2.59– 2.50 (m, 1 H), 2.18–2.05 (m, 1 H), 2.03–1.92 (m, 1 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 211.1, 140.5, 128.4, 128.3, 126.9, 74.3, 51.1, 49.6, 40.5, 20.8, 19.8, 17.4 ppm. **HRMS** (ESI): calcd. for $C_{14}H_{19}NO$ $[M + 1]^+$ 218.1539; found 218.1532. The enantiomeric ratio (56:44) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 98:2; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 6.64 min (major), t_R = 7.34 min (minor).

5d: Yellow oil (65 mg, 88% yield). **IR** (neat): ν̃ = 3031, 2976, 1778, 1649, 1607, 1495, 1459, 1157, 1072 cm^{-1}. **[α]$^{29}_D$** = +6.0 (*c* = 3.62, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 4 H), 7.28–7.23 (m, 3 H), 7.21–7.15 (m, 1 H), 7.15–7.10 (m, 2 H), 4.31 (ddt, *J* = 10.7, 8.6, 2.3 Hz, 1 H), 3.84 (d, *J* = 13.7 Hz, 1 H), 3.75 (d, *J* = 13.7 Hz, 1 H), 2.90–2.69 (m, 5 H), 2.60 (dddd, *J* = 17.3, 10.0, 4.5, 2.5 Hz, 1 H), 2.09 (ddd, *J* = 20.8, 10.8, 4.5 Hz, 1 H), 1.97 (ddd, *J* = 10.8, 9.9, 9.0 Hz, 1 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 209.6, 140.1, 138.9, 128.9, 128.8, 128.4, 128.4, 127.3, 126.1, 77.8, 55.2, 53.3, 40.6, 34.4, 15.7 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{21}NO$ $[M + 1]^+$ 280.1696; found 280.1701. enantiomeric ratio (56:44) was determined by HPLC (Chiracel OJ column; hexane/*i*PrOH, 90:10; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 10.50 min (major), t_R = 12.14 min (minor).

5e: Colorless oil (23 mg, 48% yield). **IR** (neat): ν̃ = 2979, 1778, 1640, 1499, 1453, 1420, 1354, 1220, 1170, 1069, 1026 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.29–7.14 (m, 5 H), 5.79 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1 H), 5.22–4.99 (m, 2 H), 4.35–4.14 (m, 1 H), 3.68 (d, *J* = 13.6 Hz, 1 H), 3.58 (d, *J* = 13.6 Hz, 1 H), 3.30–2.95 (m, 2 H), 2.73–2.60 (m, 1 H), 2.53 (dddd, *J* = 17.3, 9.8, 4.7, 2.5 Hz, 1 H), 2.06–1.88 (m, 2 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 209.8, 138.8, 135.6, 129.0, 128.4, 127.2, 118.1, 77.0, 54.8, 54.2, 40.6, 15.3 ppm. **HRMS** (ESI): calcd. for $C_{14}H_{17}NO$ $[M + 1]^+$ 216.1383; found 216.1387. The enantiomeric ratio (51:49) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 98:2; flow rate: 0.5 mLmin^{-1}; λ = 254 nm): t_R = 12.58 min (major), t_R = 12.08 min (minor).

5f: Colorless oil (47 mg, 77% yield). **IR** (neat): ν̃ = 2979, 1781, 1728, 1646, 1495, 1449, 1397, 1374, 1253, 1187, 1075, 1029 cm^{-1}. **[α]$^{29}_{D}$** = +7.1 (*c* = 4.45, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* = 7.35–7.16 (m, 5 H), 4.31–4.20 (m, 1 H), 4.32–4.21 (m, 2 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 3.76 (d, *J* = 13.9 Hz, 1 H), 3.70 (d, *J* = 13.9 Hz, 1 H), 2.93 (t, *J* = 7.2 Hz, 2 H), 2.77–2.65 (m, 1 H), 2.60 (dddd, *J* = 17.3, 10.0, 4.6, 2.5 Hz, 1 H), 2.54–2.41 (m, 2 H), 2.09 (qd, *J* = 10.8, 4.6 Hz, 1 H), 2.05–1.95 (m, 1 H), 1.23 (t, *J* = 7.1 Hz, 3 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* = 209.5, 172.4, 138.6, 128.8, 128.4, 127.3, 77.5, 60.5, 55.1, 47.0, 40.5, 33.3, 15.7, 14.2 ppm. **HRMS** (ESI): calcd. for $C_{16}H_{21}NO_3$ $[M + 1]^+$ 276.1594; found 276.1593. The enantiomeric ratio (61:39) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 98:2; flow rate: 1.0 $mLmin^{-1}$; *λ* = 254 nm): t_R = 13.34 min (major), t_R = 14.42 min (minor).

5g: Colorless oil (54 mg, 93% yield). **IR** (neat): ν̃ = 2982, 1778, 1732, 1659, 1499, 1456, 1377, 1197, 1161, 1079, 1029, 1000 cm^{-1}. **[α]$^{27}_{D}$** = +29.8 (*c* = 4.95, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* = 7.35 (d, *J* = 7.0 Hz, 2 H), 7.31 (dd, *J* = 10.0, 4.6 Hz, 2 H), 7.28– 7.23 (m, 1 H), 4.49–4.40 (m, 1 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 3.92 (d, *J* = 13.5 Hz, 1 H), 3.84 (d, *J* = 13.4 Hz, 1 H), 3.46 (d, *J* = 17.3 Hz, 1 H), 3.35 (d, *J* = 17.2 Hz, 1 H), 2.87–2.73 (m, 1 H), 2.72–2.57 (m, 1 H), 2.20 (qd, *J* = 10.7, 4.3 Hz, 1 H), 2.02 (dt, *J* = 19.4, 9.6 Hz, 1 H), 1.26 (t, *J* = 7.2 Hz, 3 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): *δ* = 207.8, 171.3, 137.9, 129.2, 128.4, 127.5, 77.0, 60.5, 55.3, 51.8, 40.7, 17.1, 14.3 ppm. **HRMS** (ESI): calcd. for $C_{15}H_{19}NO_3$ $[M + 1]^+$ 262.1438; found 262.1442. The enantiomeric ratio (78:22) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 99:1; flow rate: 0.9 $mLmin^{-1}$; *λ* = 254 nm): t_R = 15.25 min (major), t_R = 15.96 min (minor).

5h: Yellow oil (42 mg, 72% yield). **IR** (neat): 2972, 1778, 1600, 1518, 1456, 1394, 1341, 1216, 1190, 1128, 1111, 1062, 1010 cm^{-1}. **[α]$^{22}_{D}$** = +16.7 (*c* = 3.59, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* = 8.24–8.06 (m, 2 H), 7.56 (d, *J* = 8.9 Hz, 2 H), 4.56–4.40 (m, 1 H), 3.88–3.65 (m, 2 H), 2.90–2.68 (m, 2 H), 2.67–2.48 (m, 1 H), 2.18 (qd, *J* = 10.8, 4.3 Hz, 1 H), 2.06–1.87 (m, 1 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 1.04 (d, *J* = 6.7 Hz, 3 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): *δ* = 210.1, 148.9, 147.1, 128.8, 123.6, 74.2, 50.8, 50.5, 40.7, 20.1, 19.6, 17.6 ppm. **HRMS** (ESI): calcd. for $C_{14}H_{18}N_2O_3$ $[M + 1]^+$ 263.139; found 263.1377. The enantiomeric ratio (66:34) was determined by HPLC (Chiralpak AS-H column; hexane/*i*PrOH, 95:5; flow rate: 1.0 $mLmin^{-1}$; *λ* = 254 nm): t_R = 10.69 min (major), t_R = 12.96 min (minor).

5i: Yellow oil (54 mg, 93% yield). **IR** (neat): ν̃ = 3077, 2976, 1778, 1600, 1515, 1341, 1203, 1174, 1111, 1069, 1016 cm^{-1}. **[α]$^{23}_{D}$** = +18.6 (*c* = 5.03, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): *δ*

= 8.17 (d, *J* = 8.8 Hz, 2 H), 7.53 (d, *J* = 8.8 Hz, 2 H), 5.83 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1 H), 5.19 (ddd, *J* = 9.6, 8.5, 3.0 Hz, 2 H), 4.40–4.25 (m, 1 H), 3.81 (q, *J* = 14.6 Hz, 2 H), 3.23 (dd, *J* = 14.2, 6.3 Hz, 1 H), 3.15 (dd, *J* = 14.2, 6.7 Hz, 1 H), 2.87–2.73 (m, 1 H), 2.73–2.58 (m, 1 H), 2.16 (qd, *J* = 10.8, 4.4 Hz, 1 H), 2.09–1.92 (m, 1 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 208.9, 147.1, 134.8, 129.4, 123.6, 118.6, 77.1, 54.6, 54.1, 40.7, 15.7 ppm. **HRMS** (ESI): calcd. for $C_{14}H_{16}N_2O_3$ $[M + 1]^+$ 261.1234; found 261.1239. The enantiomeric ratio (78:22) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 99:1; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 78.49 min (major), t_R = 21.51 min (minor).

5j: Pale yellow oil (43 mg, 63% yield). **IR** (neat): ν̃ = 2963, 2930, 2861, 1778, 1640, 1604, 1522, 1469, 1348, 1177, 1115, 1072, 1013 cm^{-1}. **$[\alpha]^{20}_D$** = +5.9 (*c* = 5.03, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.4 Hz, 2 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 4.28 (t, *J* = 9.2 Hz, 1 H), 3.83 (d, *J* = 14.8 Hz, 1 H), 3.76 (d, *J* = 14.8 Hz, 1 H), 2.87–2.42 (m, 4 H), 2.15 (qd, *J* = 10.6, 4.4 Hz, 1 H), 2.05–1.81 (m, 1 H), 1.54–1.17 (m, 6 H), 0.86 (t, *J* = 6.9 Hz, 3 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 209.2, 147.6, 129.2, 123.6, 112.7, 77.6, 54.7, 51.9, 40.7, 29.4, 27.2, 22.6, 15.6, 14.1 ppm. **HRMS** (ESI): calcd. for $C_{16}H_{22}N_2O_3[M + 1]^+$ 291.1703; found 291.1693. The enantiomeric ratio (67:33) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 99:1; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 13.94 min (major), t_R = 13.17 min (minor).

5k: Yellow oil (29 mg, 36% yield). **IR** (neat): ν̃ = 2933, 2858, 1778, 1604, 1522, 1449, 1394, 1341, 1266, 1203, 1174, 1128, 1108, 1069, 1013 cm^{-1}. **$[\alpha]^{22}_D$** = +14.5 (*c* = 2.47, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.7 Hz, 2 H), 7.56 (d, *J* = 8.8 Hz, 2 H), 4.58–4.41 (m, 1 H), 3.91–3.76 (m, 2 H), 2.88–2.69 (m, 1 H), 2.65– 2.48 (m, 1 H), 2.33 (tt, *J* = 11.4, 3.4 Hz, 1 H), 2.18 (qd, *J* = 10.8, 4.3 Hz, 1 H), 2.18 (qd, *J* = 10.8, 4.3 Hz, 1 H), 2.01–1.88 (m, 1 H), 1.87–1.70 (m, 4 H), 1.58 (d, *J* = 12.6 Hz, 1 H), 1.28–0.96 (m, 5 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 210.3, 149.2, 147.1, 128.7, 123.6, 75.2, 59.9, 50.8, 40.4, 31.1, 30.7, 26.1, 17.8 ppm. **HRMS** (ESI): calcd. for $C_{17}H_{22}N_2O_3$ $[M + 1]^+$ 303.1703; found 303.1700. The enantiomeric ratio (62:38) was determined by HPLC (Chiralpak AS-H column; hexane/*i*PrOH, 98:2; flow rate: 1.0 mLmin^{-1}; λ = 254 nm): t_R = 15.01 min (major), t_R = 19.67 min (minor).

***ent*-7a/*ent*-7a:** Colorless oil (50 mg, 81% yield, inseparable 71:29 mixture of diastereomers). **IR** (neat): ν̃ = 3028, 2972, 1778, 1597, 1495, 1449, 1400, 1377, 1207, 1177, 1128, 1092, 1059, 1029 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.57–7.10 (m, 20 H), 4.36–4.17 (m, 2 H), 3.96–3.71 (m, 6 H), 2.71–2.58 (m, 2 H), 2.58–2.43 (m, 2 H), 2.10 (dd, J = 19.4, 9.6 Hz, 1 H), 2.01 (qd, *J* = 10.6, 4.4 Hz, 1 H), 1.91 (qd, *J* = 10.7, 4.5 Hz, 1 H), 1.82 (quint, *J* = 9.4 Hz, 1 H), 1.43 (d, *J* = 6.8 Hz, 3

H), 1.38 (d, *J* = 6.8 Hz, 3 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 211.3, 210.1, 140.0, 139.99, 139.91, 129.0, 128.7, 128.4, 128.3, 128.2, 127.74, 127.73, 127.23, 127.20, 127.0, 126.9, 74.8, 74.3, 56.6, 56.3, 51.93, 51.90, 41.2, 39.9, 17.4, 16.5, 16.1, 15.0 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{21}NO$ $[M + 1]^+$ 280.1696; found 280.169.

***ent*-7b/*ent*-7b:** Yellow oil (62 mg. 81% yield, inseparable 91:9 mixture of diastereomers). **IR** (neat): $\tilde{\nu}$ = 2976, 1781, 1620, 1495, 1449, 1420, 1381, 1321, 1203, 1164, 1124, 1111, 1065, 1019 cm^{-1}. **$[\alpha]^{26}_D$** = –21.6 (*c* = 3.05, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.61– 7.54 (m, 10 H), 7.38 (d, *J* = 7.6 Hz, 4 H), 7.35–7.27 (m, 3 H), 7.23 (dd, *J* = 13.1, 5.7 Hz, 1 H), 4.32 (dd, *J* = 10.3, 8.7 Hz, 1 H), 4.27 (t, *J* = 9.3 Hz, 1 H), 3.88 (dd, *J* = 13.3, 6.4 Hz, 2 H), 3.80 (q, *J* = 14.3 Hz, 4 H), 2.75–2.63 (m, 2 H), 2.62–2.49 (m, 2 H), 2.05 (dd, *J* = 16.7, 9.6 Hz, 4 H), 1.95 (dd, *J* = 10.7, 4.4 Hz, 1 H), 1.80 (t, *J* = 9.9 Hz, 1 H), 1.43 (d, *J* = 6.8 Hz, 3 H), 1.39 (d, *J* = 6.8 Hz, 3 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 210.5, 209.5, 144.5, 144.47, 144.41, 143.0, 142.8, 129.1, 128.8, 128.45, 128.42, 127.6, 127.25, 127.20, 125.4 (q, *J* = 3.8 Hz), 125.3 (q, *J* = 3.8 Hz), 74.8, 74.4, 57.3, 56.9, 51.6, 51.5, 41.2, 40.1, 17.5, 16.6, 16.6, 15.3 ppm. **HRMS** (ESI): calcd. for $C_{20}H_{20}F_3NO$ $[M + 1]^+$ 348.157; found 348.1583.

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12. CCDC-1054222 (for **3o**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
13. Reactions with benzylamines that have electron-withdrawing groups at the *para* position generally proceed with better enantioselectivity, which might suggest an anionic character to the cyclobutane carbon atom that is being protonated, reminiscent of an asymmetric protonation. Such a mechanism might, therefore, be an alternative to the one we suggest in Scheme 2.1. We thank a reviewer for the useful comments in this regard.
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2.4.2 General methods and experimental data [1]

H NMR spectra were recorded at 500, or 400 MHz spectrometer at ambient temperature with $CDCl_3$ as solvent. Data are reported as follows: chemical shifts (δ), multiplicity, coupling constants and integration. ^{13}C NMR spectra were recorded operating respectively at 126, or 101 MHz at 27°C with $CDCl_3$ as solvent. Infrared spectra were recorded on a FT-IR spectrophotometer. Enantiomeric excesses of α-benzylamino cyclobutanones were determined by HPLC, using a Daicel Chiralpak AD-H, Chiralcel OJ, Phenomenex Lux Cellulose-1 analytical column with *i*-PrOH/hexane as eluent, using authentic racemic samples for reference comparison. High resolution mass spectra (HRMS) was recorded on a spectrometer using Positive Electro Ionization (ESI) mode. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using columns of 230-400 mesh silica gel 60 (0.040-0.063 mm). Yields refer to chromatographically pure materials. Benzylamines **2a**, **2q**, **2s**, **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **4g**, **6a,** *ent*-**6a** were purchased and used without further purification. Benzylamines **2b**,[1] **2c**,[2] **2d**,[2] **2e**,[3] **2f**[3] **2g**,[4] **2h**,[5] **2i**,[6] **2j**,[7] **2k**,[2] **2l**,[5] **2m**,[2] **2n**,[8] **2o**,[8] **2r**,[9] **2s**,[9] **2t**,[10] **4h**,[11] **4i**,[12] **4j**,[13] **4k**,[14] **6b**,[15] *ent*-**6b**,[15] were prepared according to literature procedures. The spectroscopic data are in accordance with those presented in literature. Dibenzylamine **2p** was synthesized by reductive amination:[16] *p*-Nitrobenzaldehyde (1 mmol, 0.151 g) and *p*-trifluoro methylbenzylamine (1.06 mmol, 0.185g)

were mixed in MeOH (5 mL) at room temperature. The mixture was stirred at room temperature for 4 h, until the aldimine formation was completed. The aldimine in MeOH was carefully treated with solid $NaBH_4$ (0.06 g, 1.6 mmol). The reaction mixture was stirred for 60 min and quenched with 1 M NaOH. The product was extracted with ether. The ether extract was washed with saturated aqueous NaCl and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography (silica gel, mixture of hexane/ethyl acetate, 3:1→1:1). Yield 71%, yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (t, *J* = 7.9 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 3.92 (s, 2H), 3.88 (s, 2H), 1.85 (brs, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.8, 147.2, 144.0, 128.7, 128.4, 127.0, 125.5 (q, *J* = 3.2 Hz), 123.7, 52.8, 52.4. **MS** *m/z*: 309 (M^+-1 (42)), 291 (15), 174 (41), 159 (100), 136 (29), 109 (20), 91 (19).

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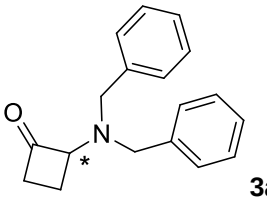
2.4.3 Copies of NMR spectra



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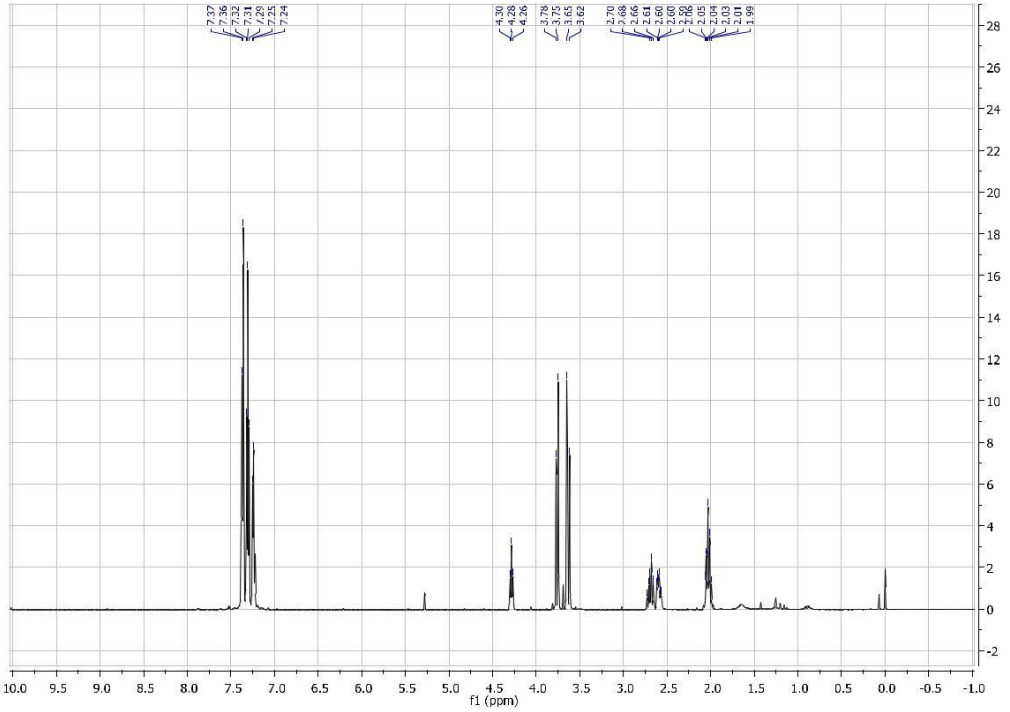

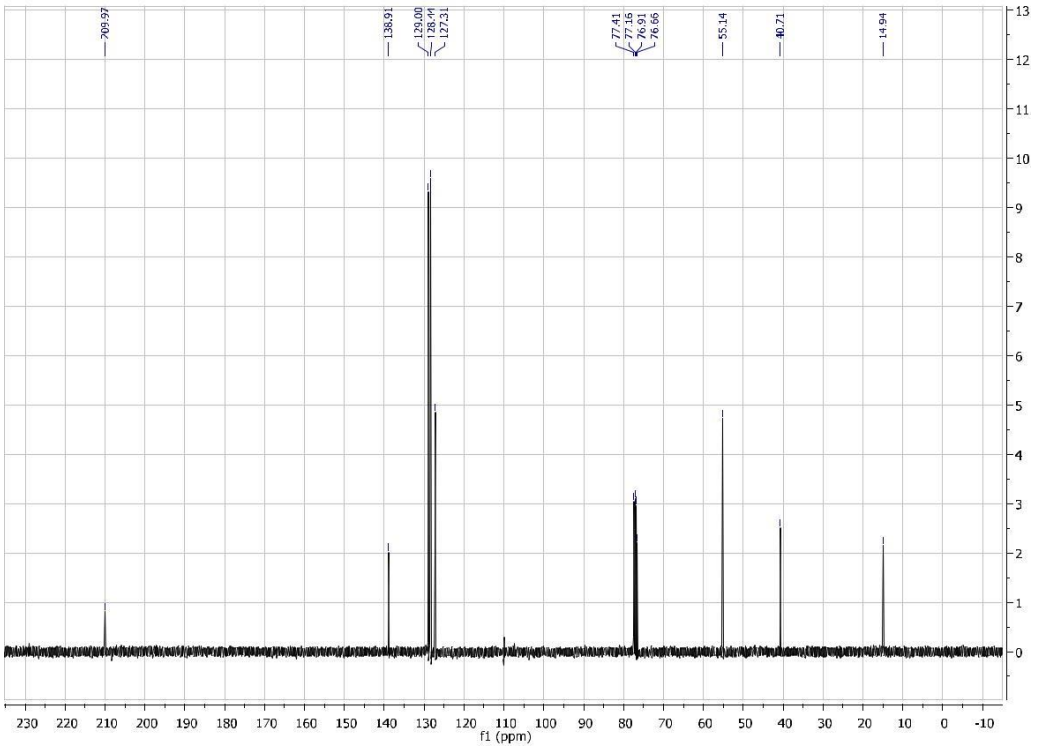

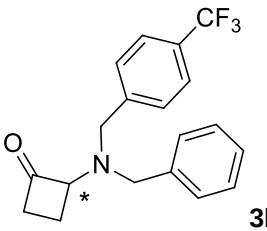
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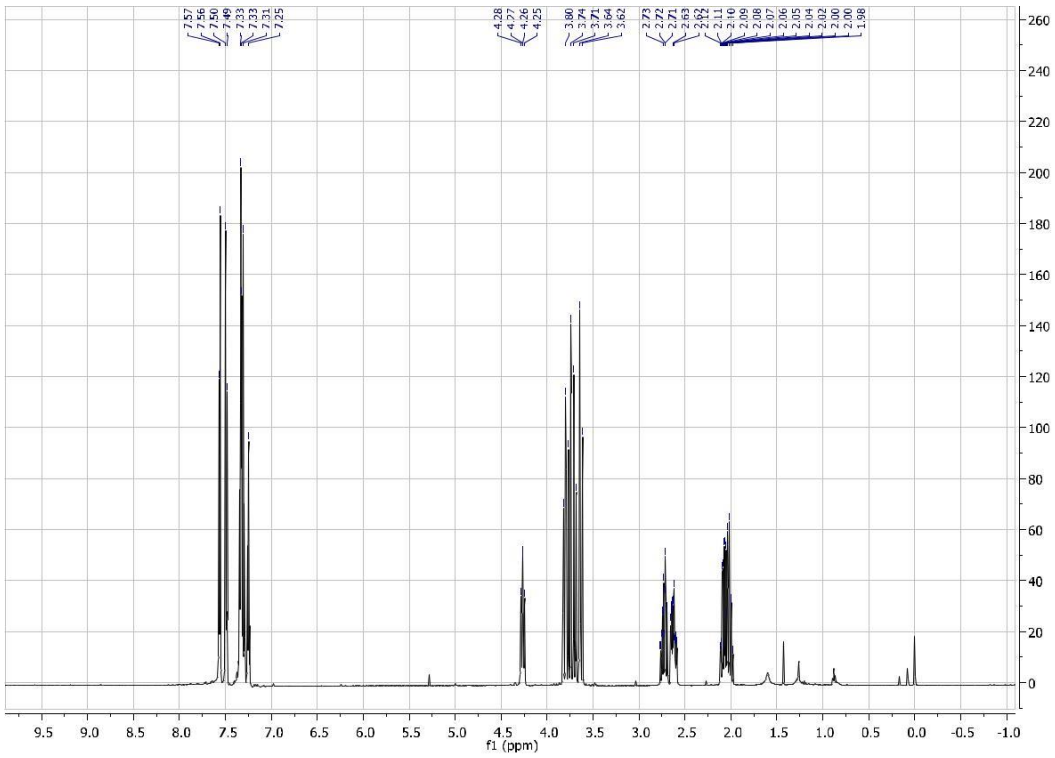
3b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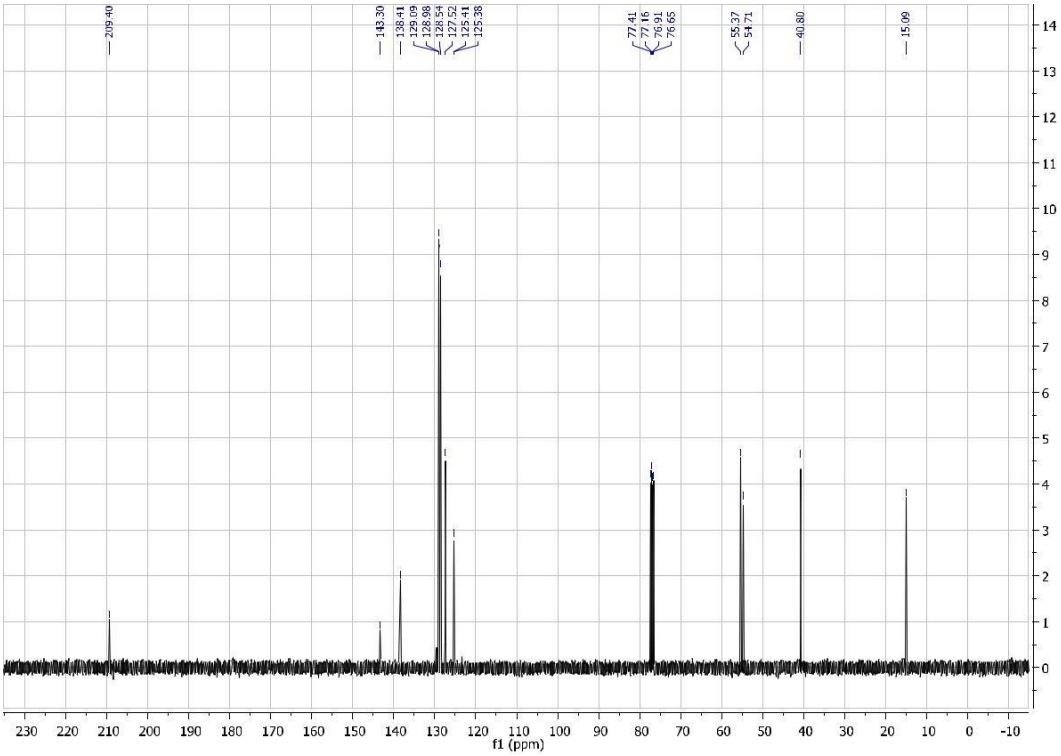
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76.91
76.65
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40.80
15.09
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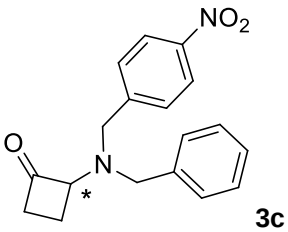
NO2
O
N
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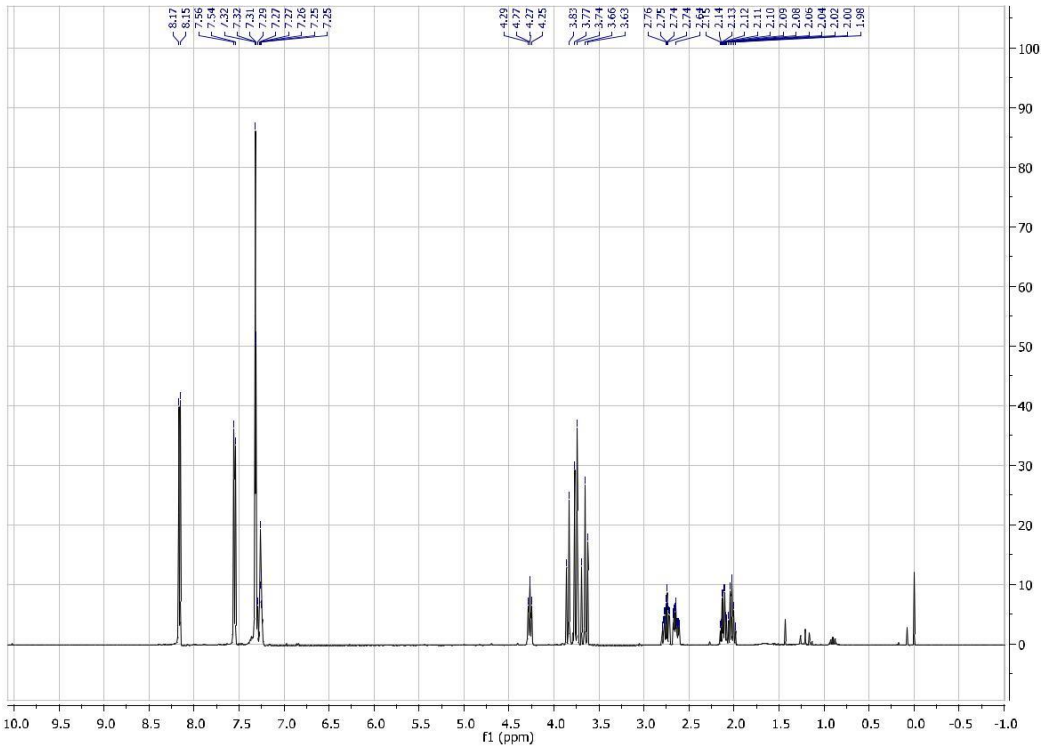
3c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4.25
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3.74
3.66
3.63
2.76
2.75
2.74
2.14
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2.09
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2.06
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2.02
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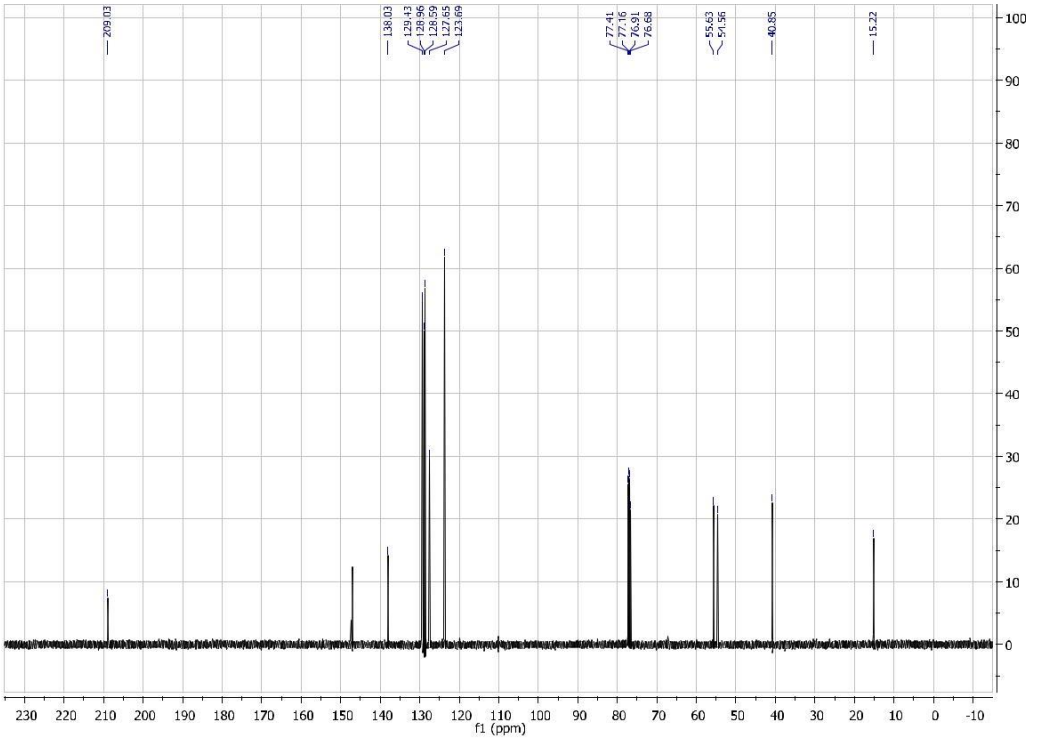
f1 (ppm)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77.41
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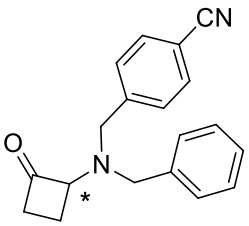
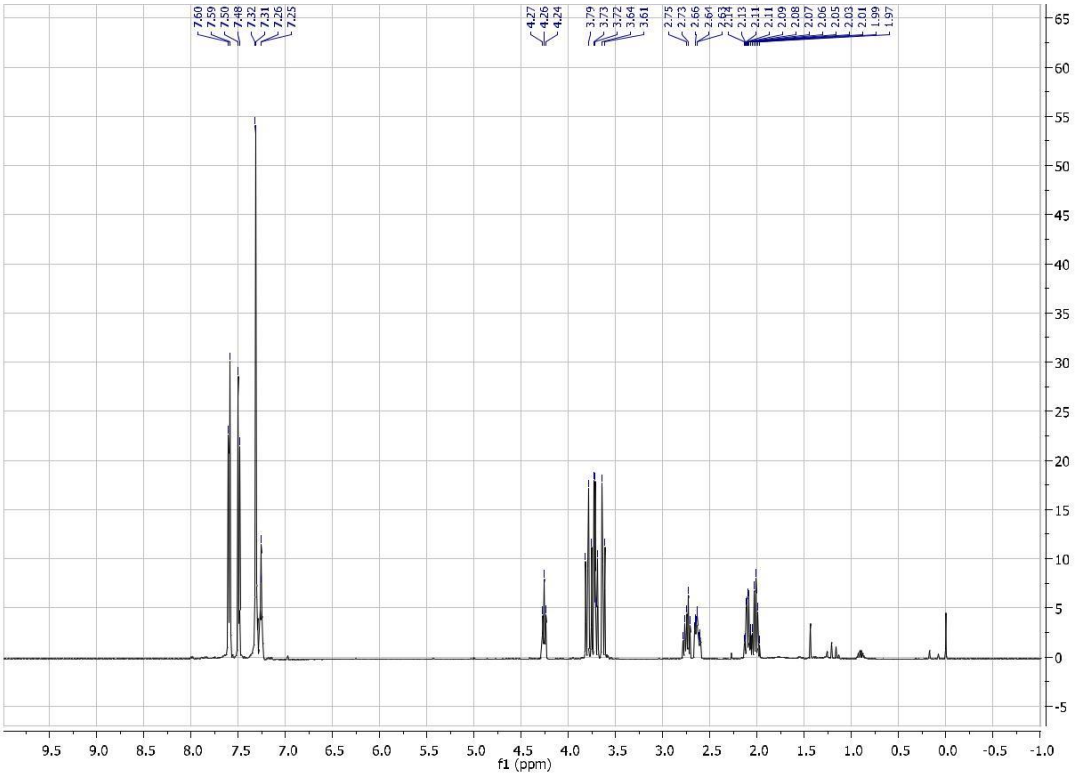
76.91
76.68
55.63
51.56
40.85
15.22
f1 (ppm)


CN
O
N
*

3d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4.24
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3.64
3.61
2.75
2.73
2.66
2.64
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2.06
2.05
2.03
2.01
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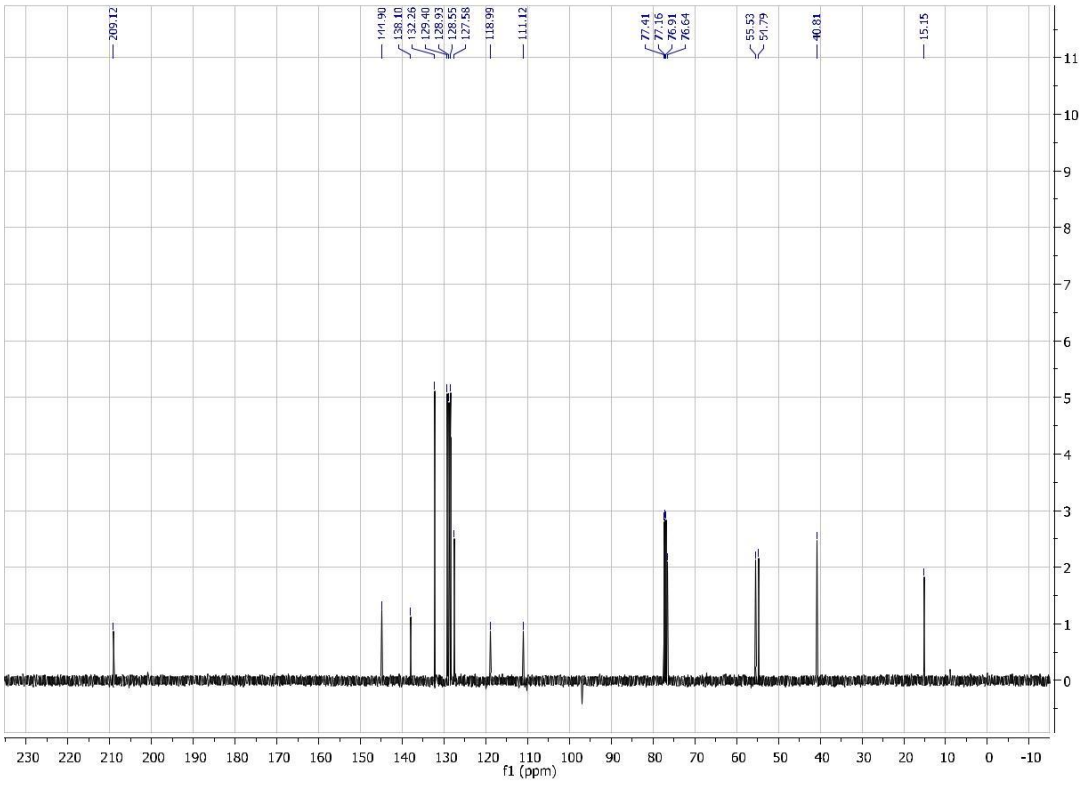
1.97
f1 (ppm)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128.93
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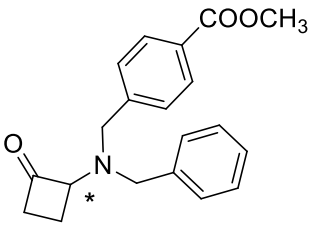
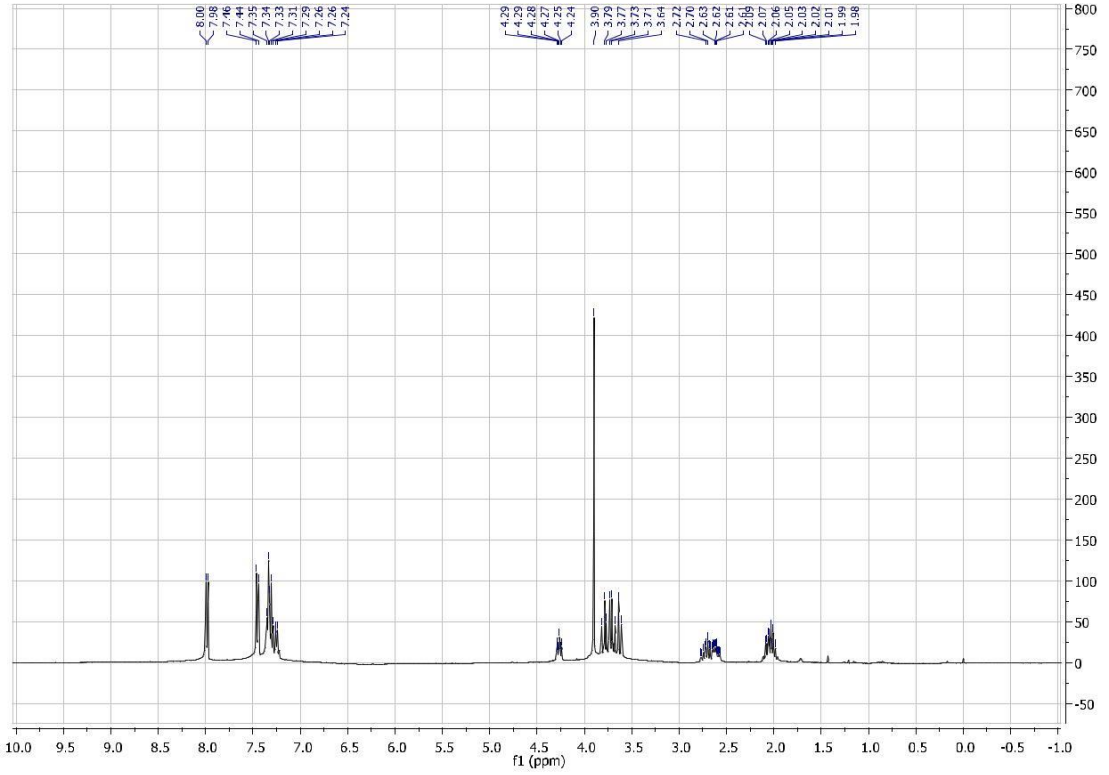
76.91
76.64
55.53
54.79
40.81
15.15
f1 (ppm)


COOCH3
O
N
*

3e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4.29
4.28
4.27
4.25
4.24
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3.77
3.73
3.71
3.64
2.72
2.70
2.63
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2.61
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2.05
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2.02
2.01
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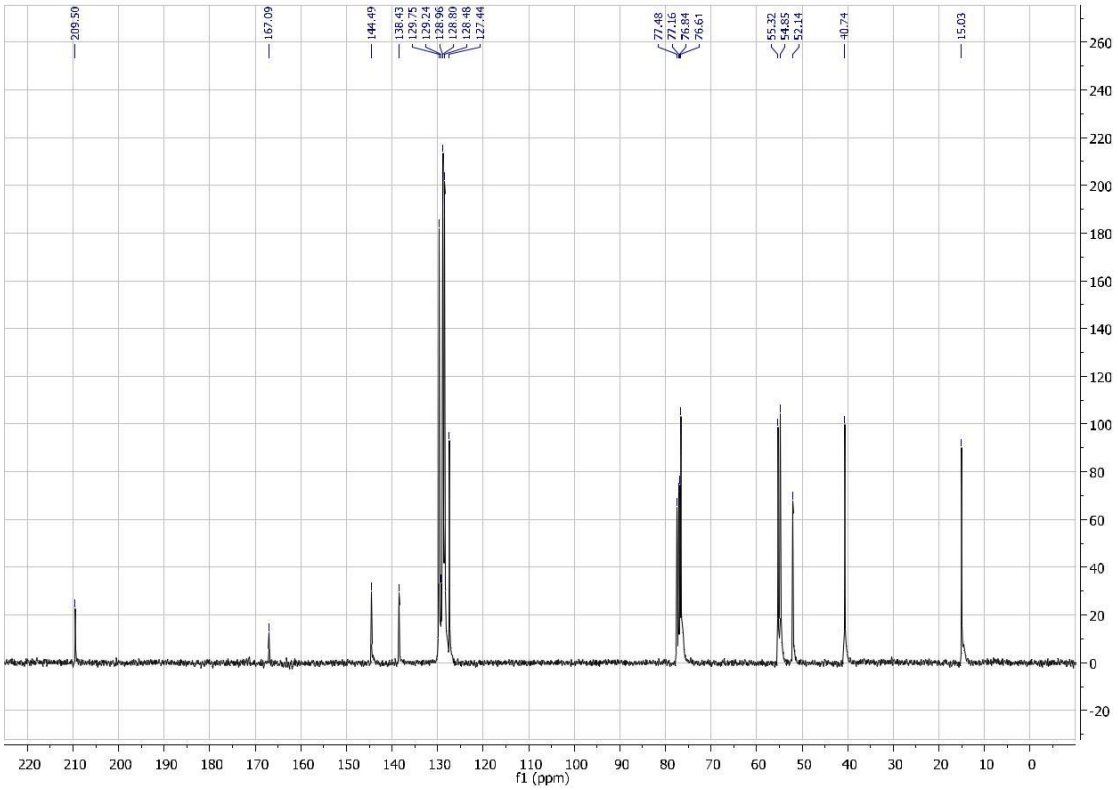
1.98
f1 (ppm)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128.96
128.80
128.48
127.44
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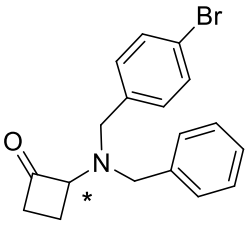
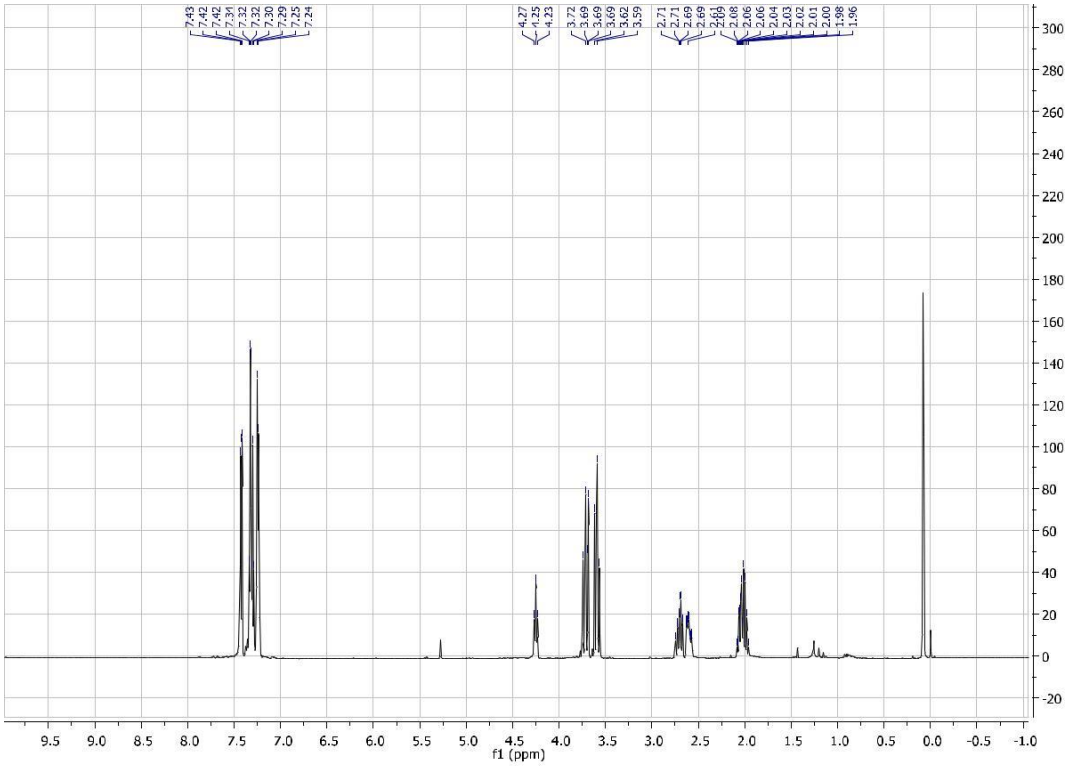
54.85
52.14
40.74
15.03
f1 (ppm)


Br
O
N
*

3f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7.30
7.29
7.25
7.24
4.27
4.25
4.23
3.72
3.69
3.69
3.69
3.62
3.59
2.71
2.71
2.69
2.69
2.61
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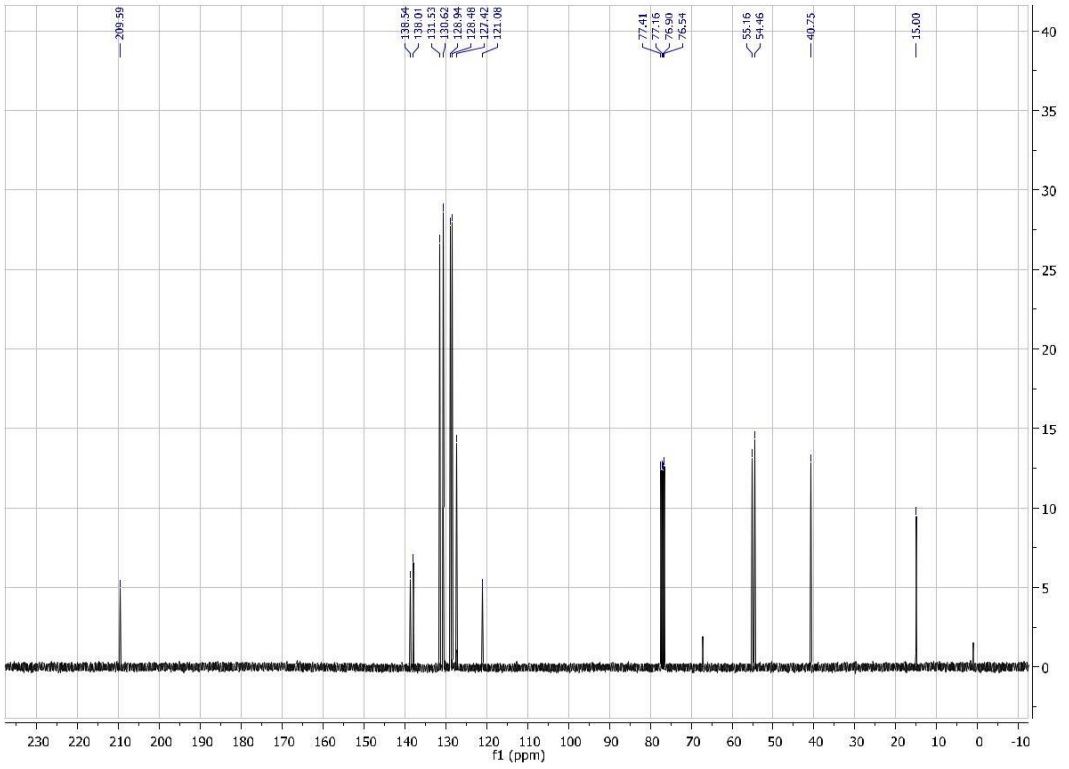
2.08
2.06
2.06
2.04
2.03
2.02
2.01
2.00
1.98
1.96
f1 (ppm)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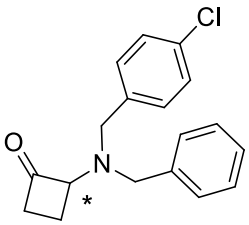
76.54
55.16
54.46
40.75
15.00
f1 (ppm)


Cl
O
N
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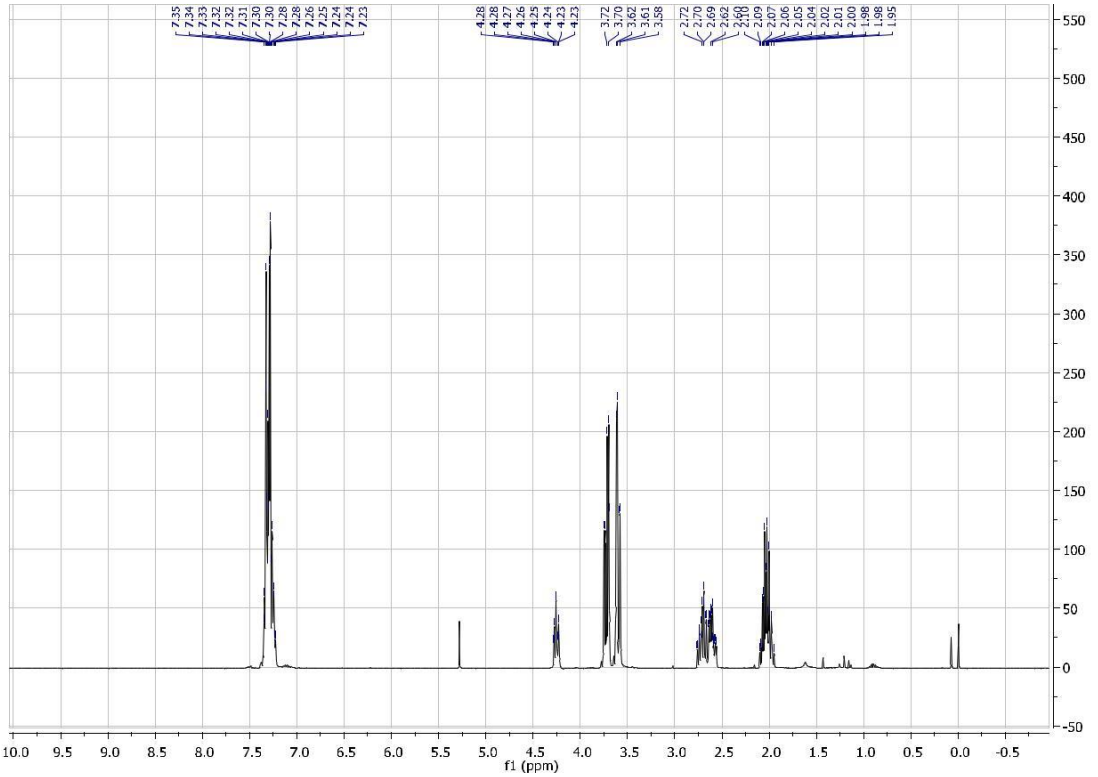
3g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7.32
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7.28
7.26
7.25
7.24
7.24
7.23
4.28
4.28
4.27
4.26
4.25
4.24
4.23
4.23
3.72
3.70
3.62
3.61
3.58
2.72
2.70
2.69
2.62
2.60
2.10
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2.00
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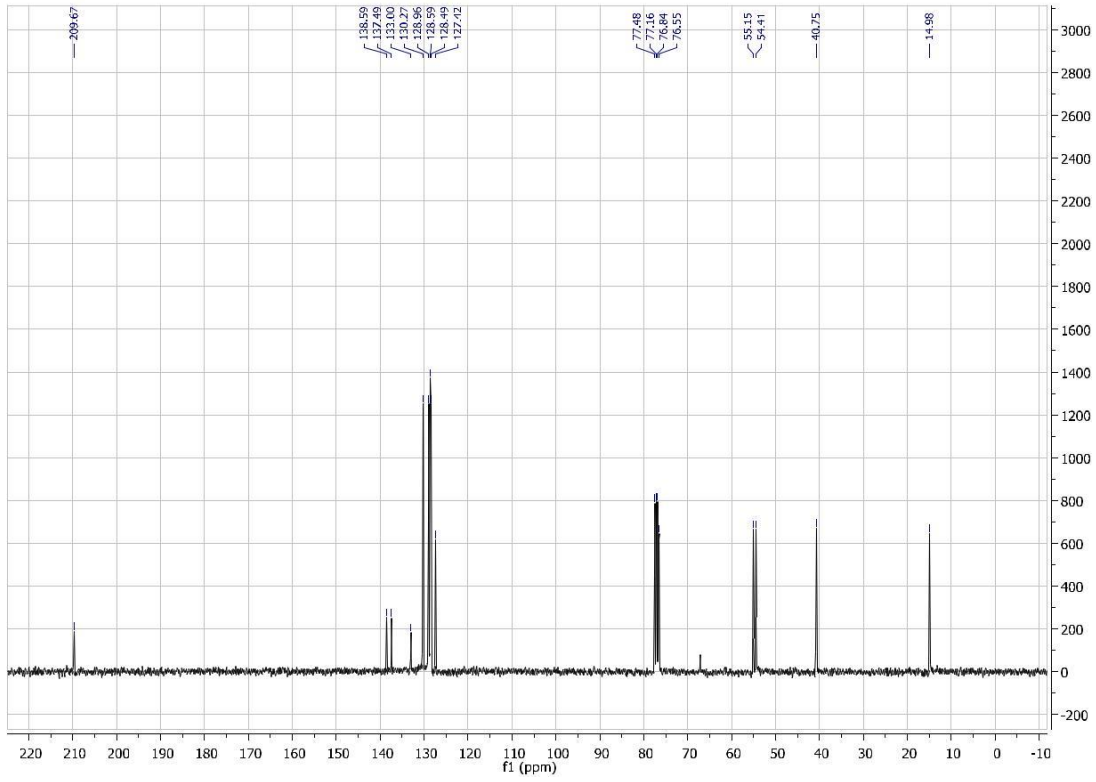
1.98
1.95
f1 (ppm)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128.96
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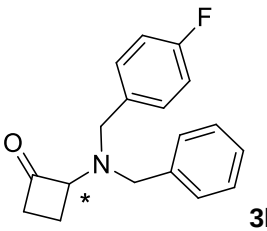
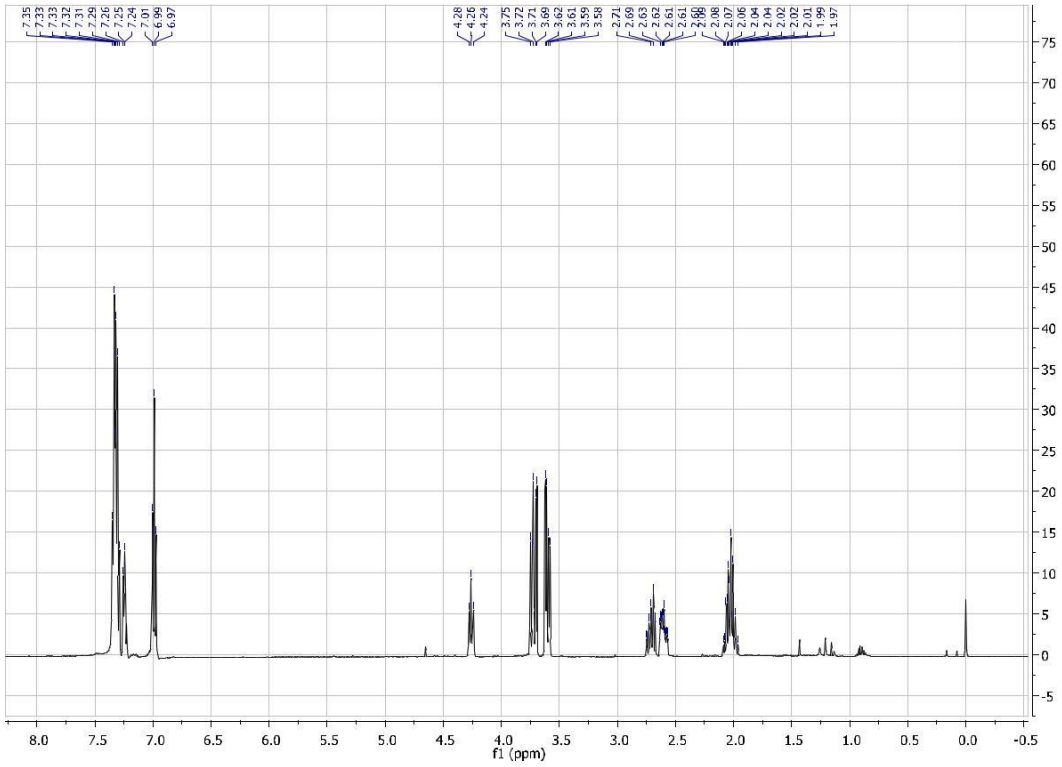
77.16
76.84
76.55
55.15
54.41
40.75
14.98
f1 (ppm)


F
O
N
*

3h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7.26
7.25
7.24
7.01
6.99
6.97
4.28
4.26
4.24
3.75
3.72
3.71
3.69
3.62
3.61
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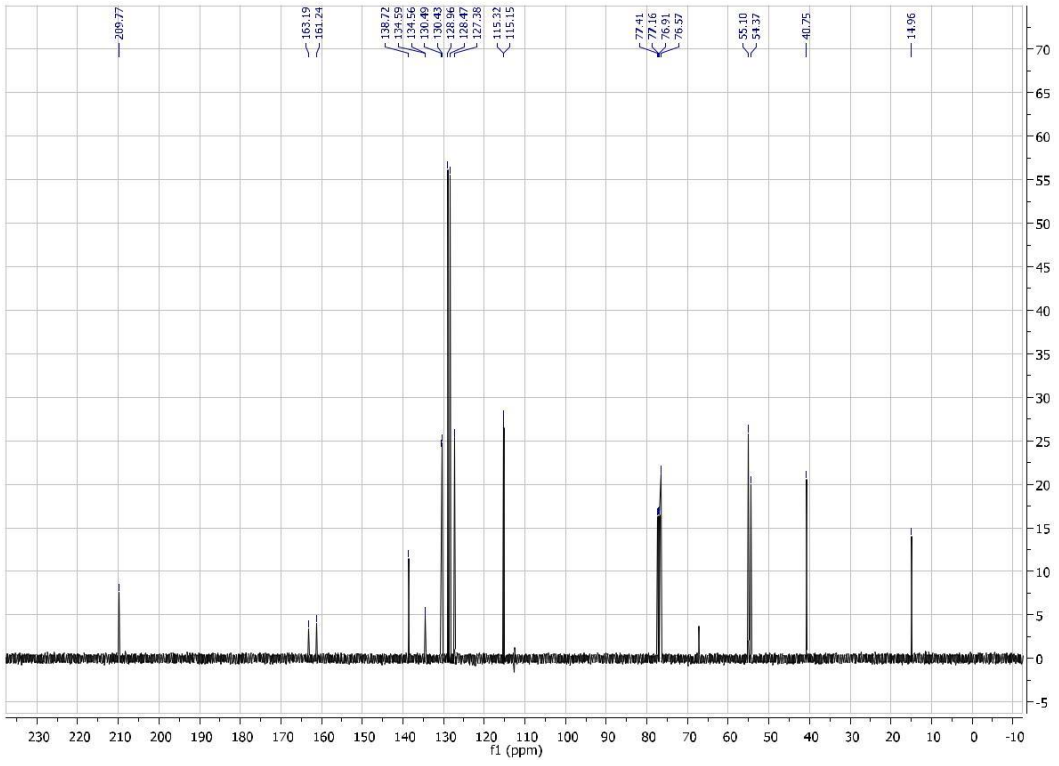
2.69
2.63
2.62
2.61
2.61
2.08
2.07
2.06
2.04
2.04
2.02
2.02
2.01
1.99
1.97
f1 (ppm)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128.47
127.38
115.32
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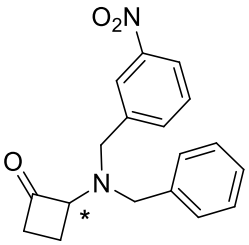
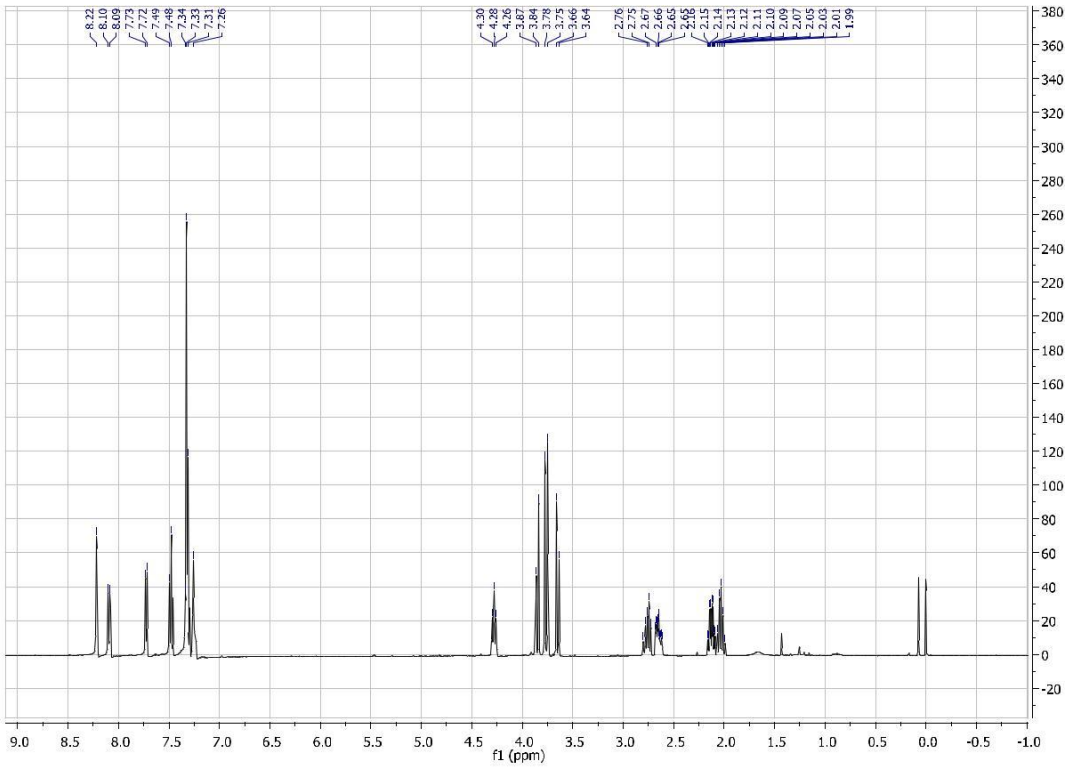
76.57
55.10
54.37
40.75
14.96
f1 (ppm)


O2N
O
N
*

3i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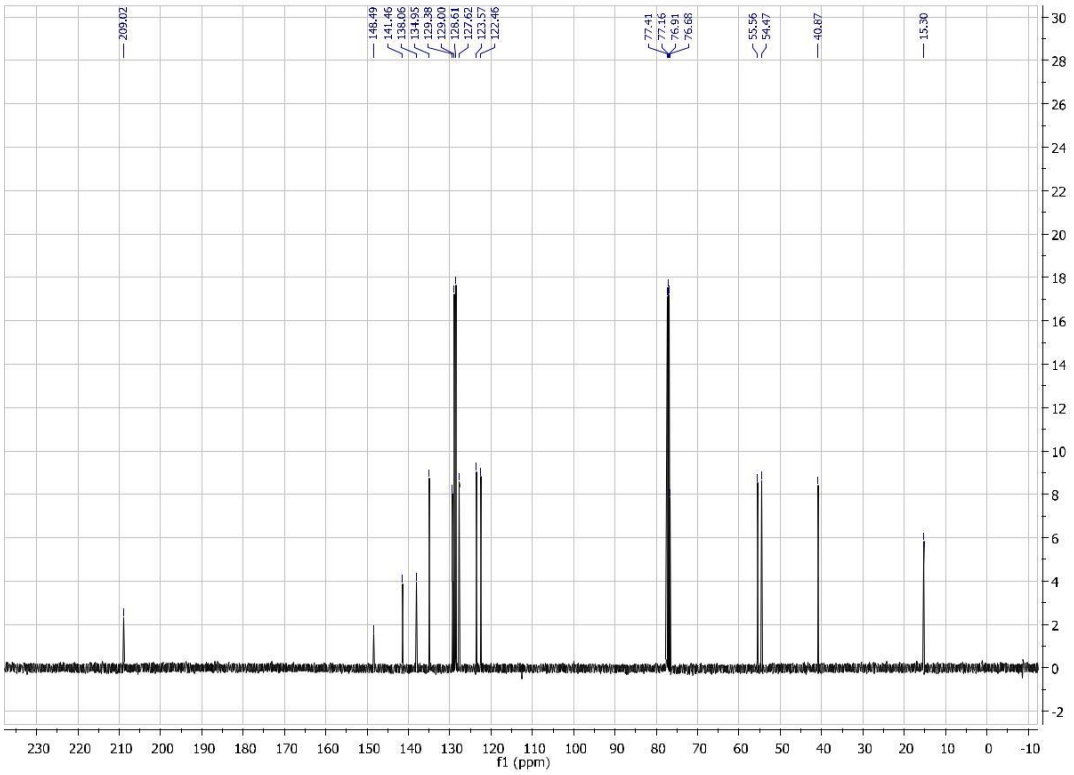
7.48
7.34
7.33
7.31
7.26
4.30
4.28
4.26
3.87
3.84
3.78
3.75
3.66
3.64
2.76
2.75
2.67
2.66
2.65
2.16
2.15
2.14
2.13
2.12
2.11
2.10
2.09
2.07
2.05
2.03
2.01
1.99
f1 (ppm)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76.68
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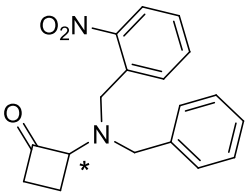
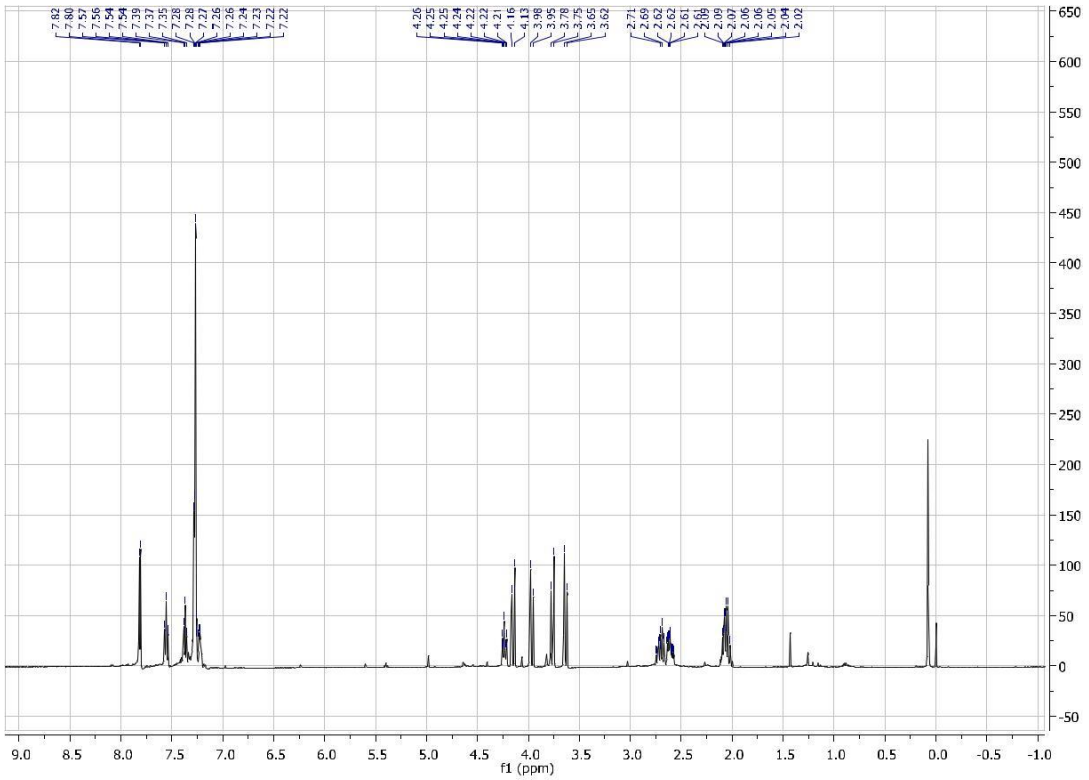
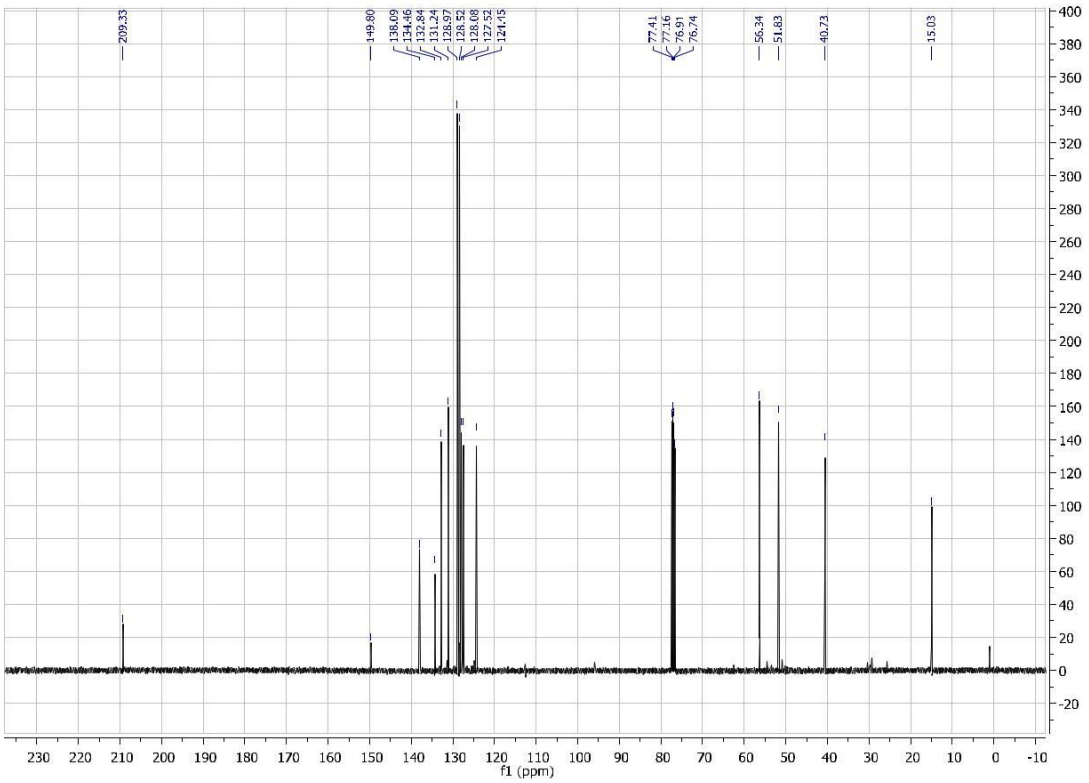
54.47
40.87
15.30
f1 (ppm)


O2N
O
N
*

3j


f1 (ppm)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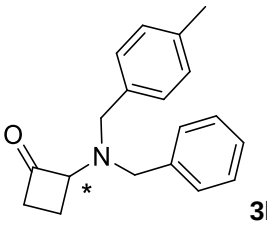
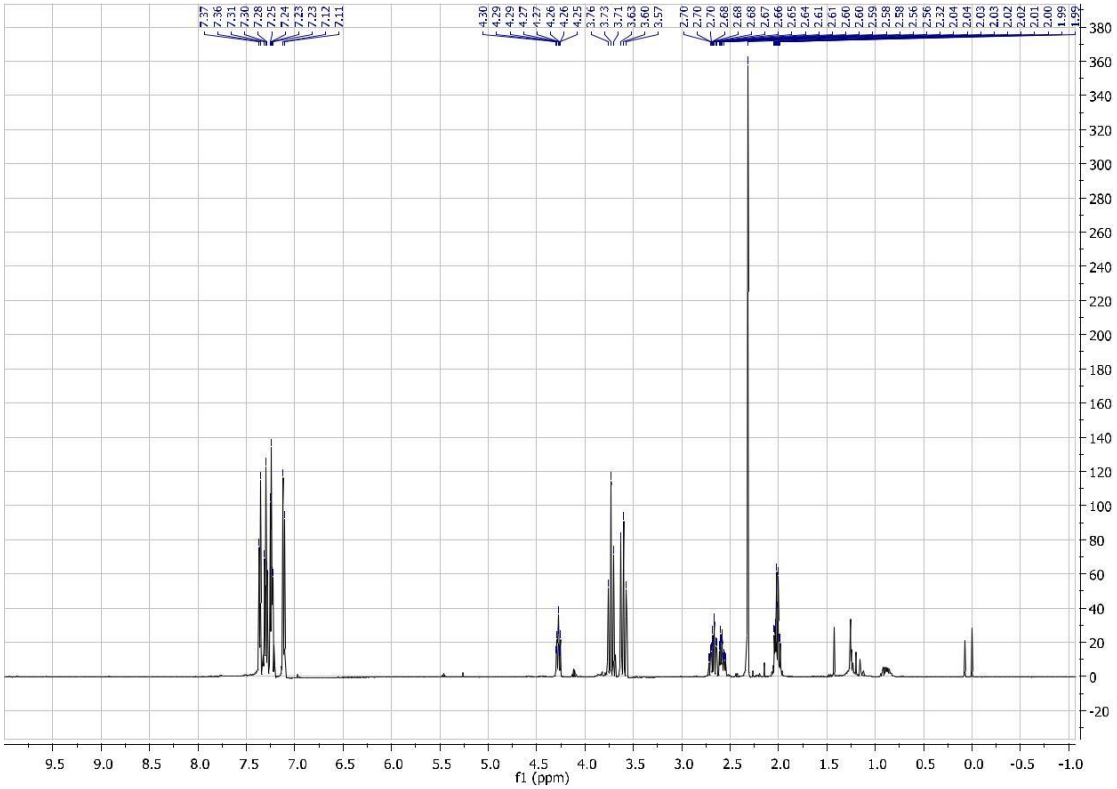
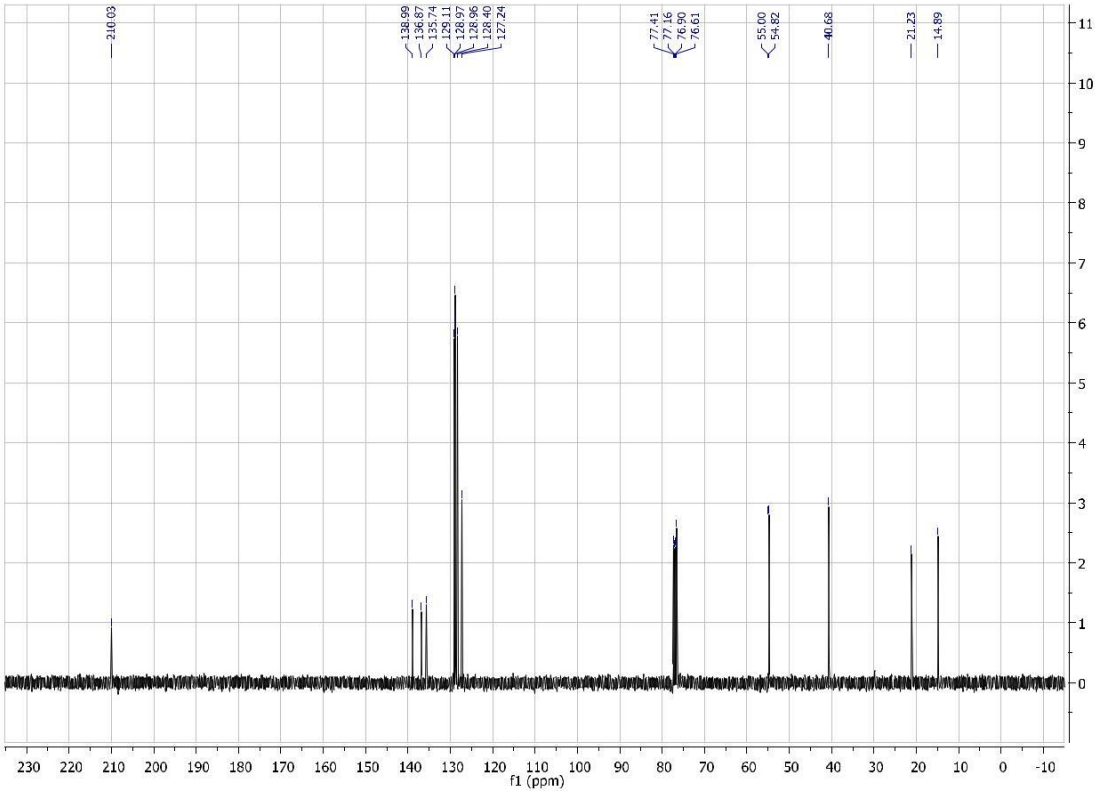
76.91
76.74
56.34
51.83
40.73
15.03
f1 (ppm)


O
N
*

3k


f1 (ppm)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127.24
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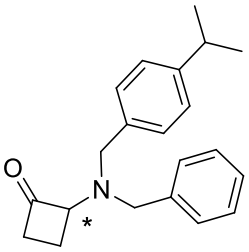
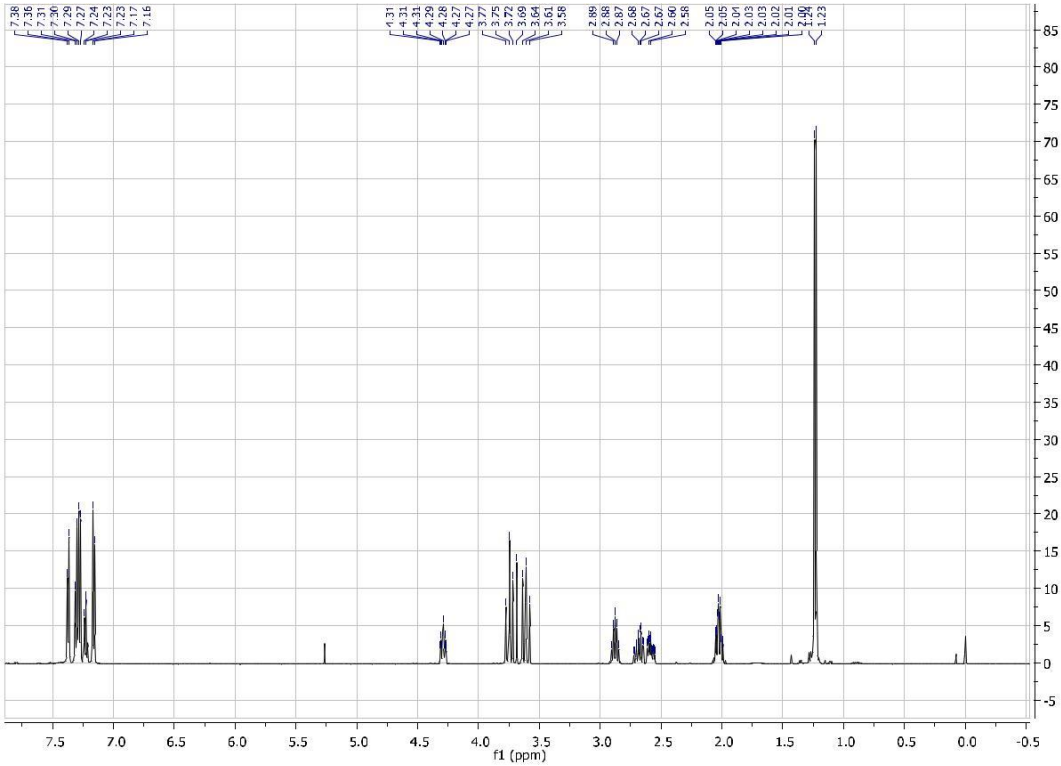
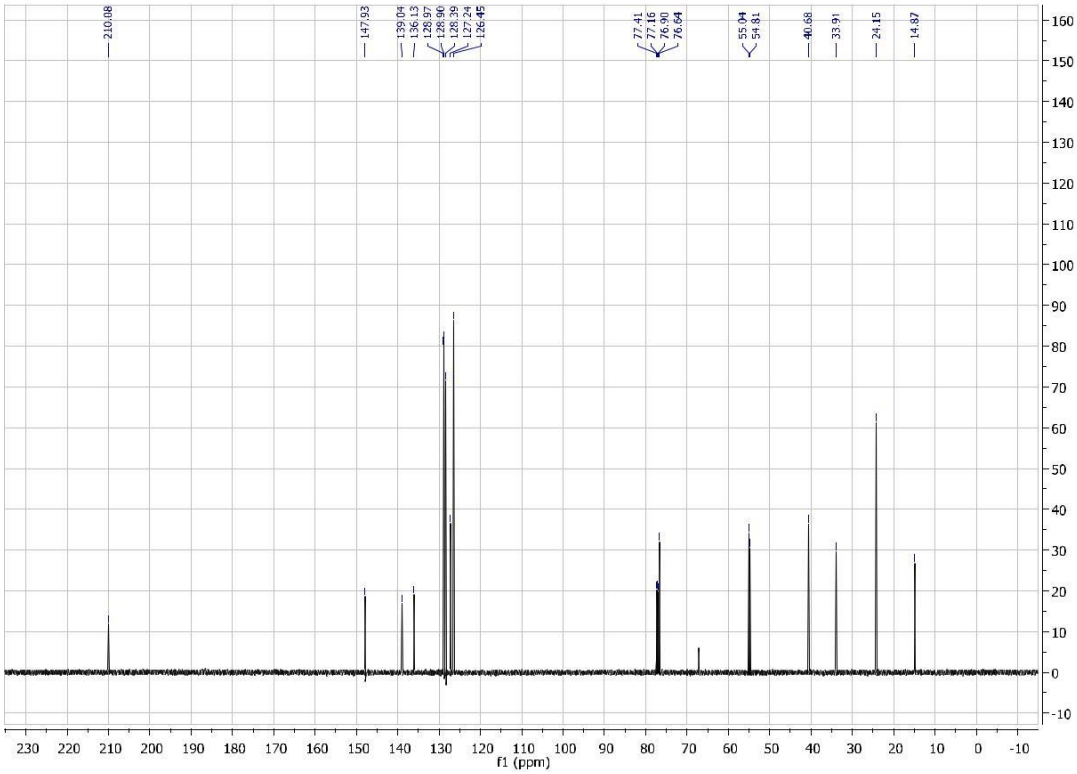
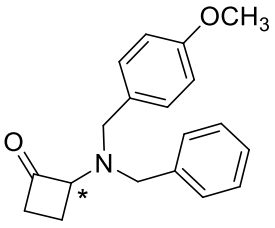
54.82
40.68
21.23
14.89
f1 (ppm)



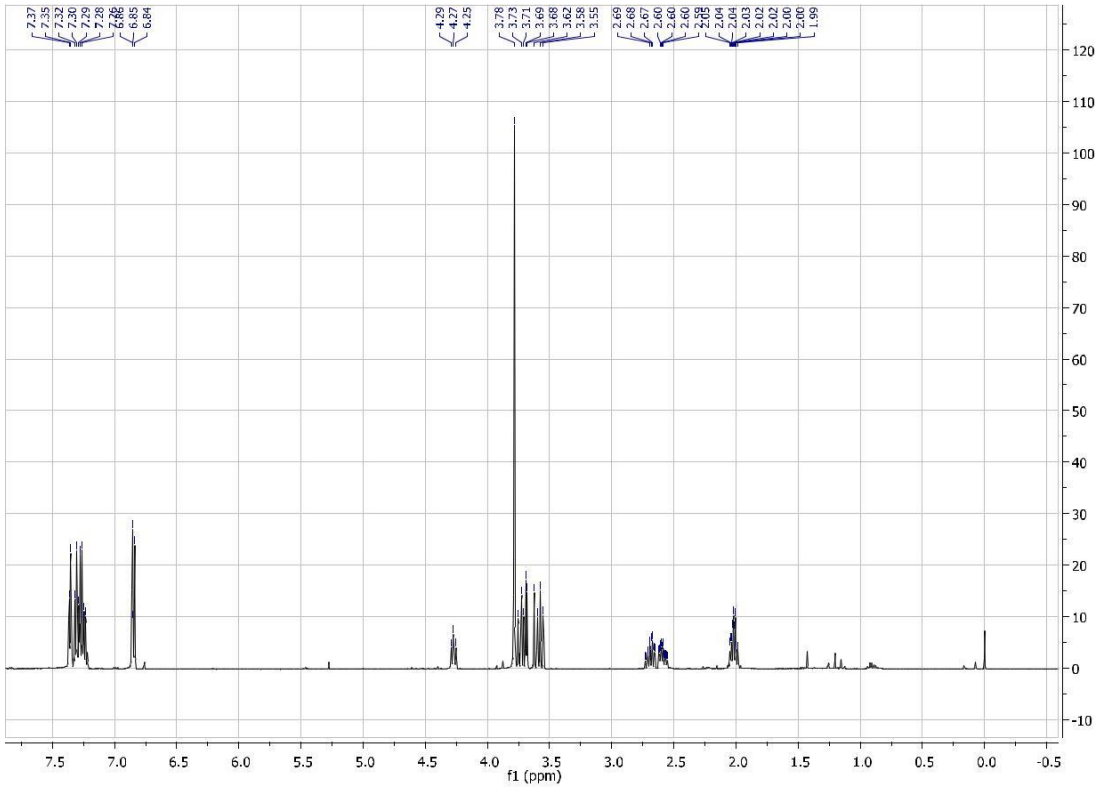
3l






OCH3
O
N
*

3m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3.62
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2.68
2.67
2.60
2.60
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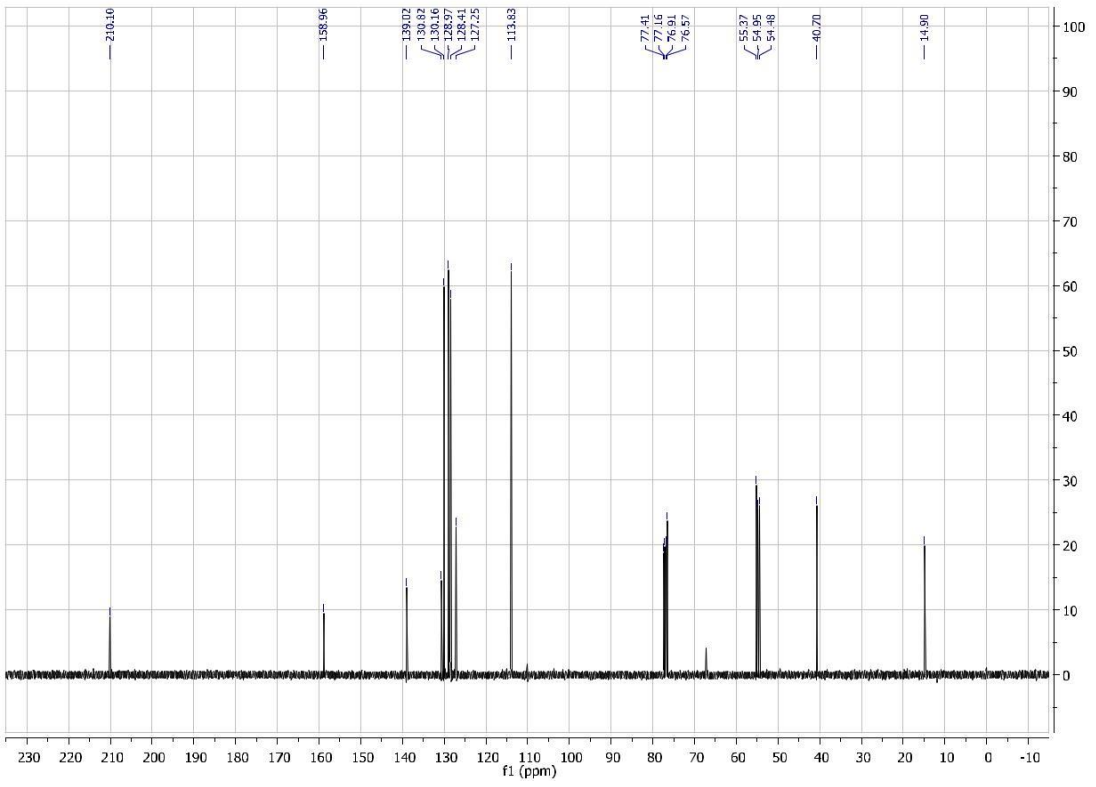
1.99
f1 (ppm)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128.41
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113.83
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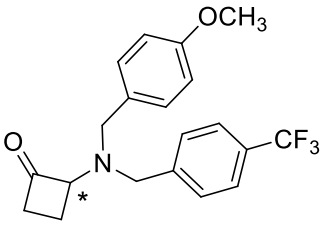
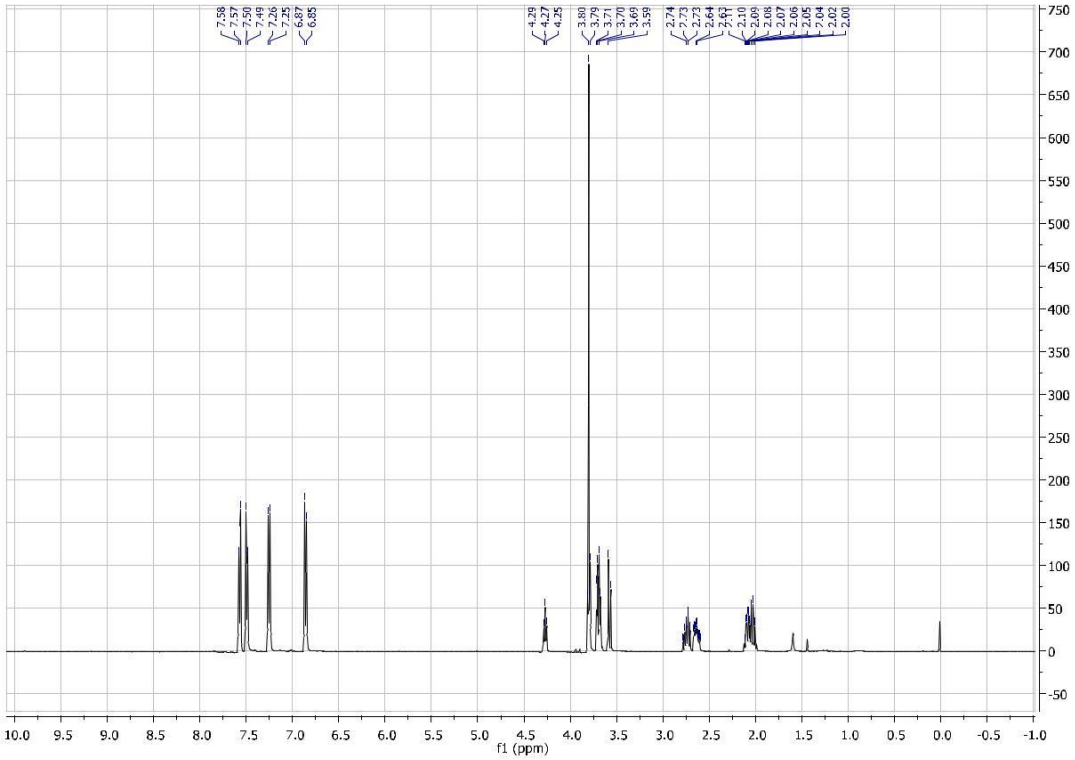
77.16
76.91
76.57
55.37
54.95
54.48
40.70
14.90
f1 (ppm)


OCH3
O
N
CF3
*

3n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2.73
2.73
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2.06
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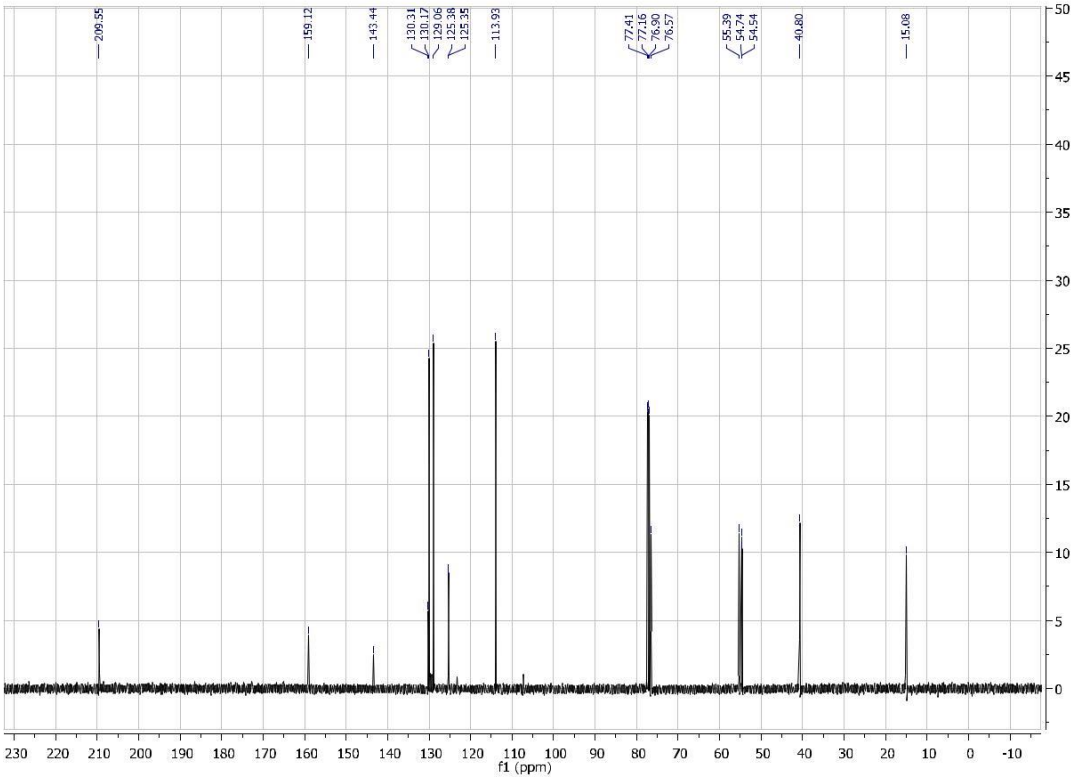
2.04
2.02
2.00
f1 (ppm)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125.35
113.93
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77.16
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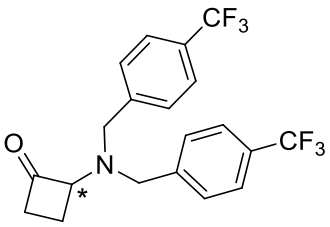
f1 (ppm)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CF3

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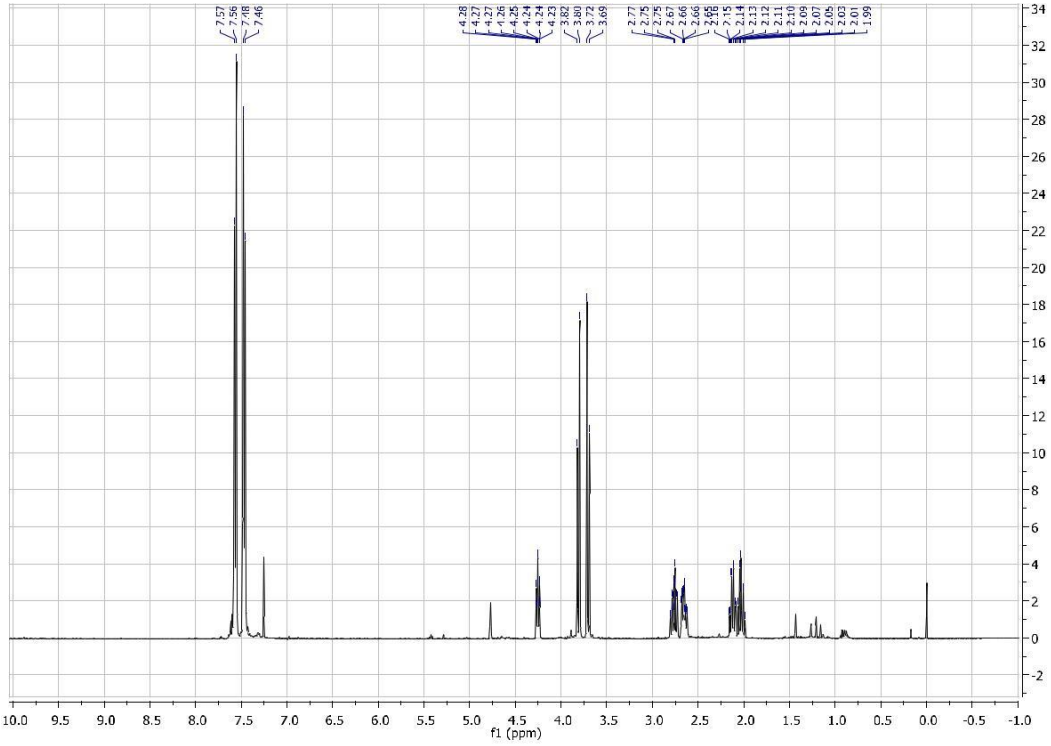
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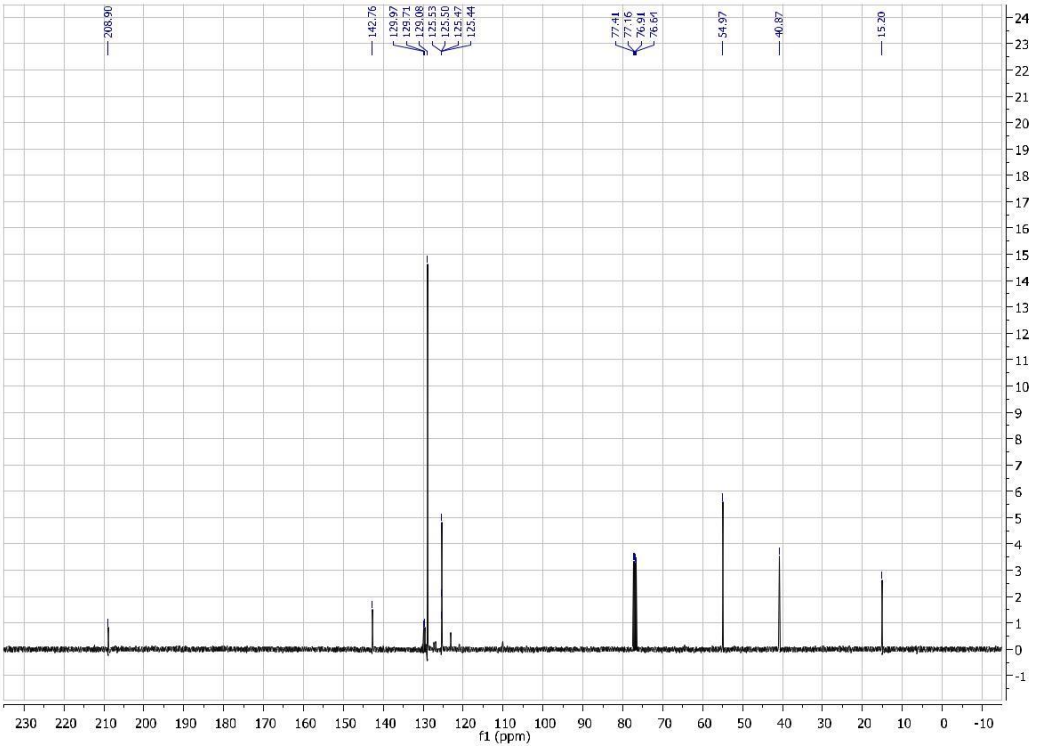
f1 (ppm)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76.61
54.97
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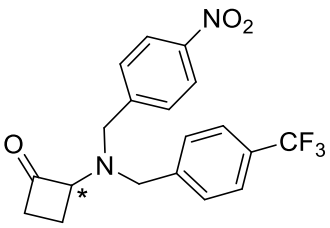
15.20
f1 (ppm)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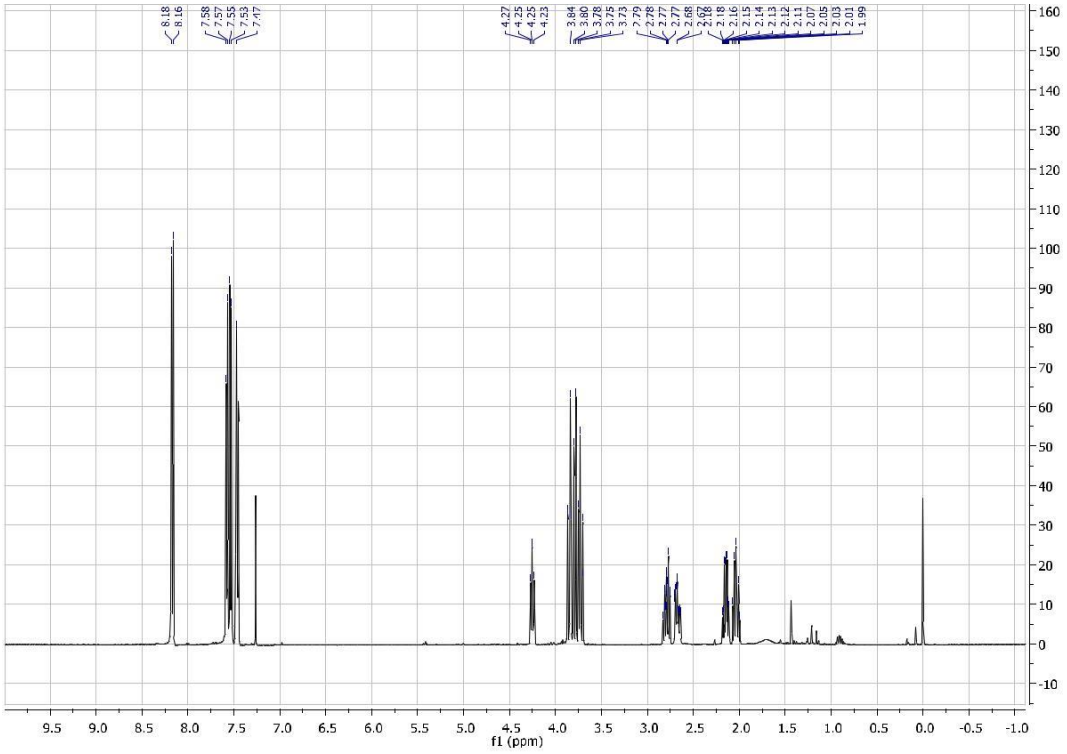
O
N
CF3
*

3p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3.80
3.78
3.75
3.73
7.79
2.78
2.77
2.77
2.68
2.18
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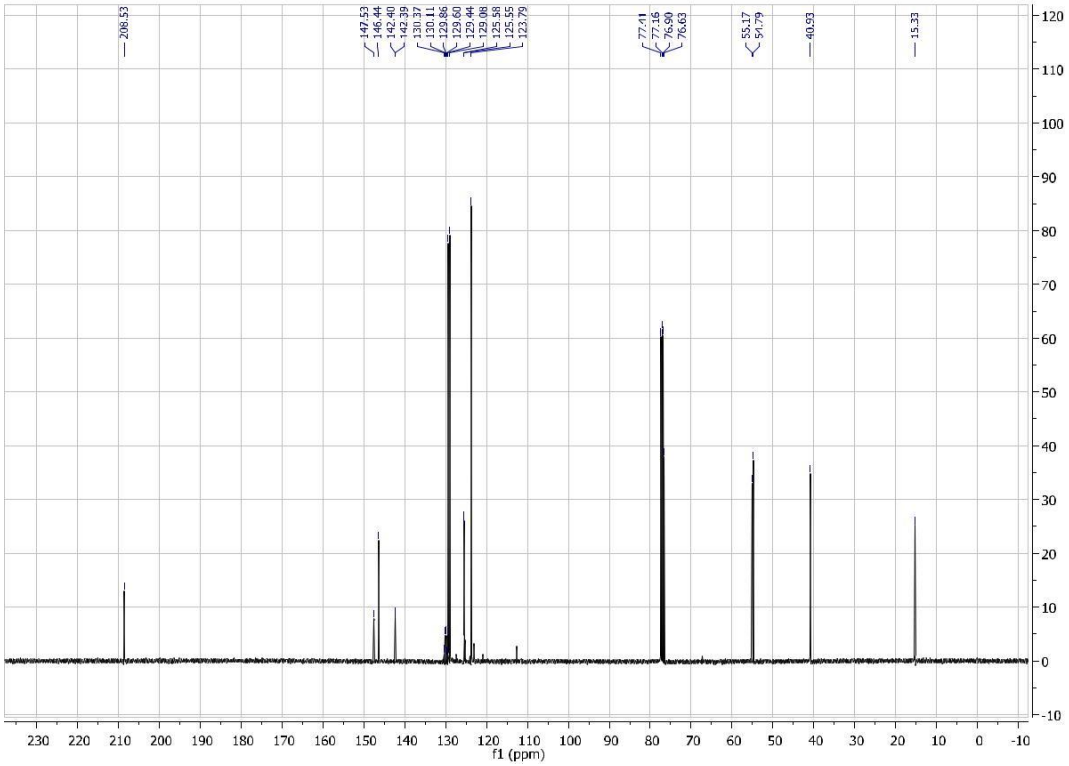
f1 (ppm)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129.08
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54.79
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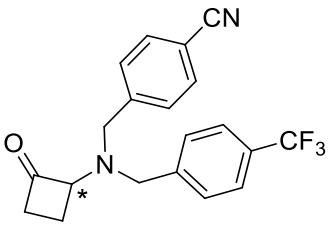
15.33
f1 (ppm)



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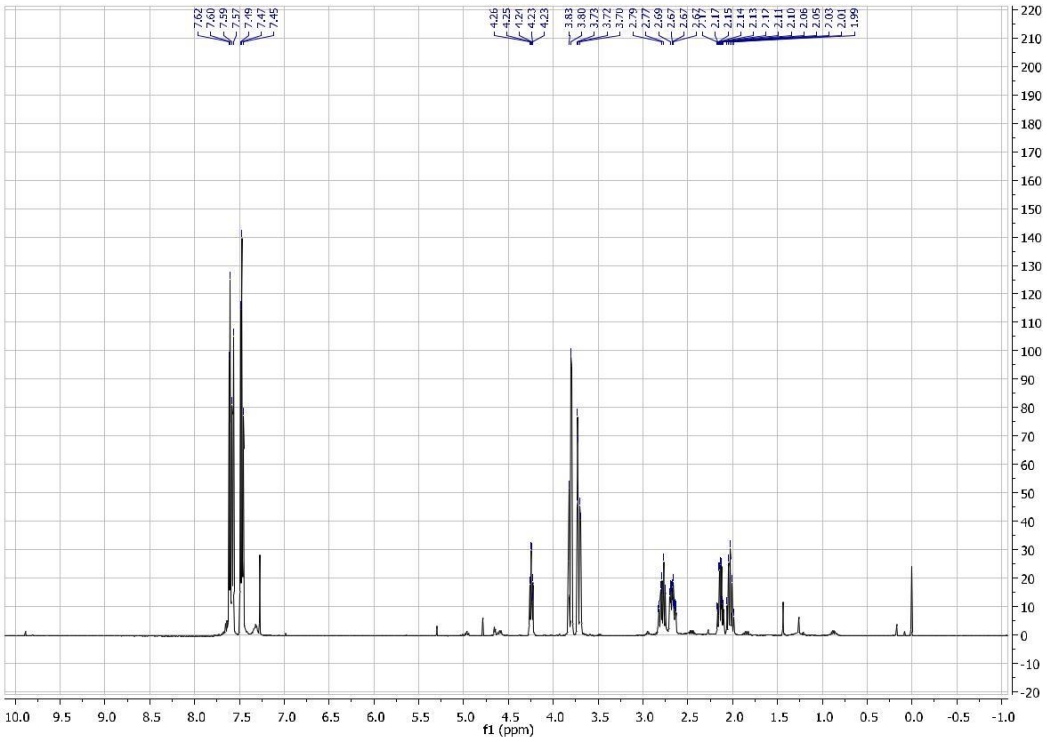

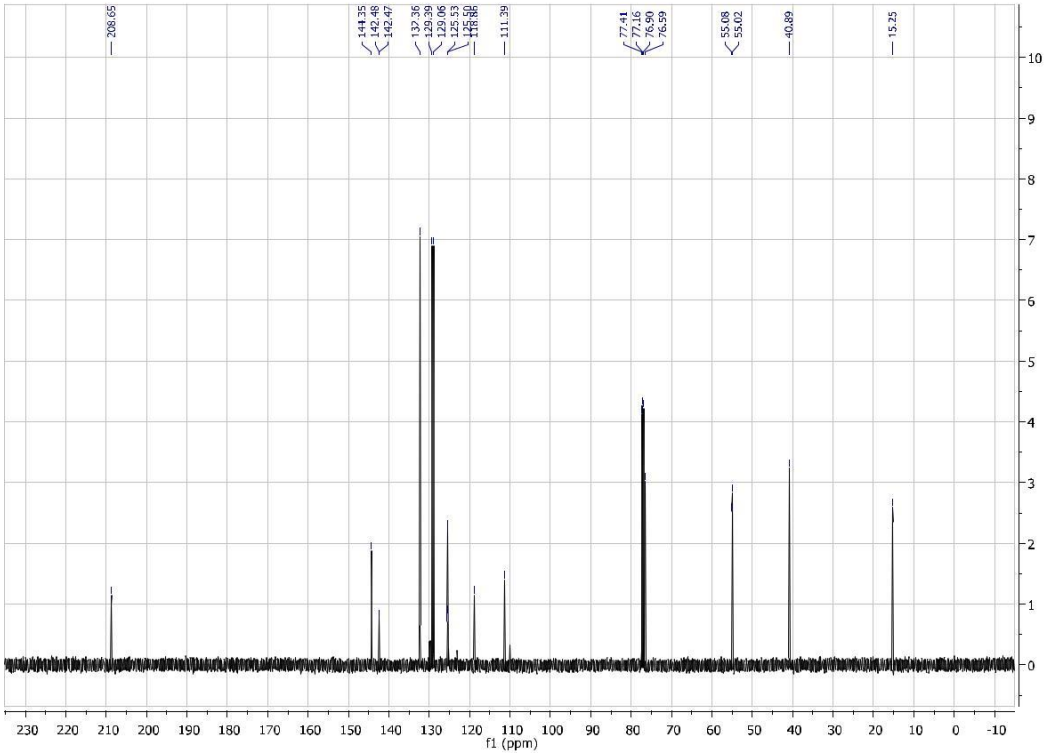

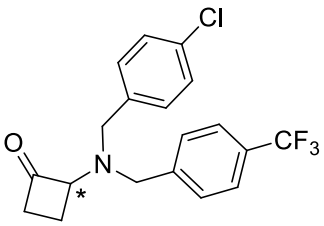
Cl
O
N
*
CF3

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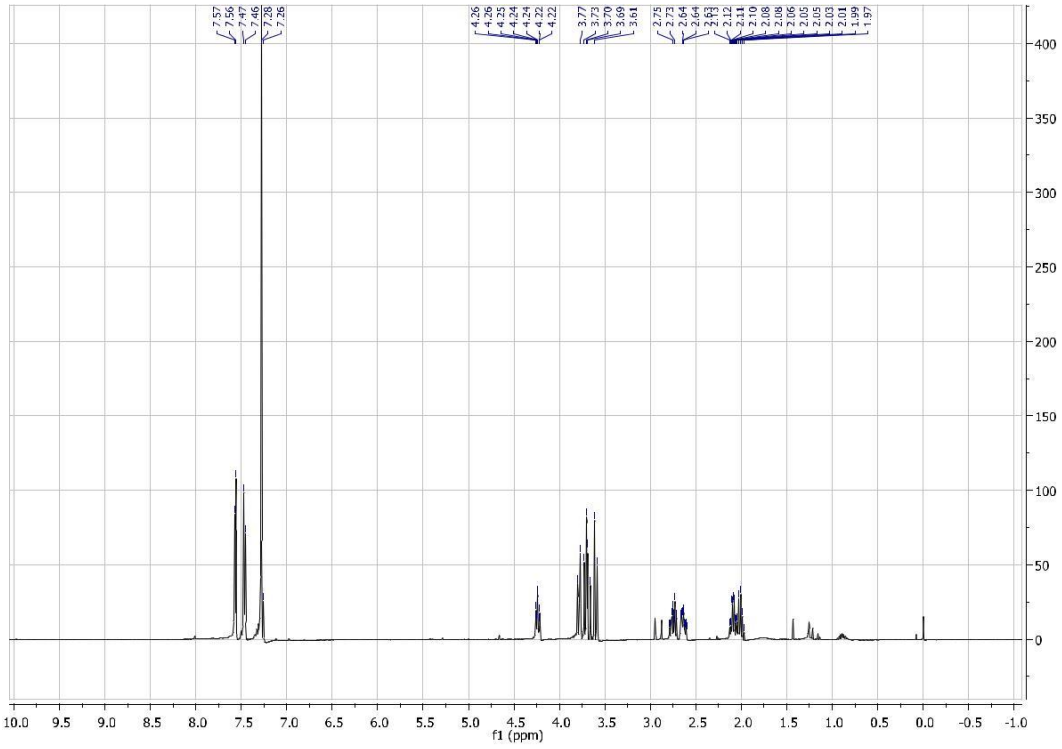
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4.26
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4.22
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3.70
3.69
3.61
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2.64
2.13
2.12
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2.05
2.03
2.01
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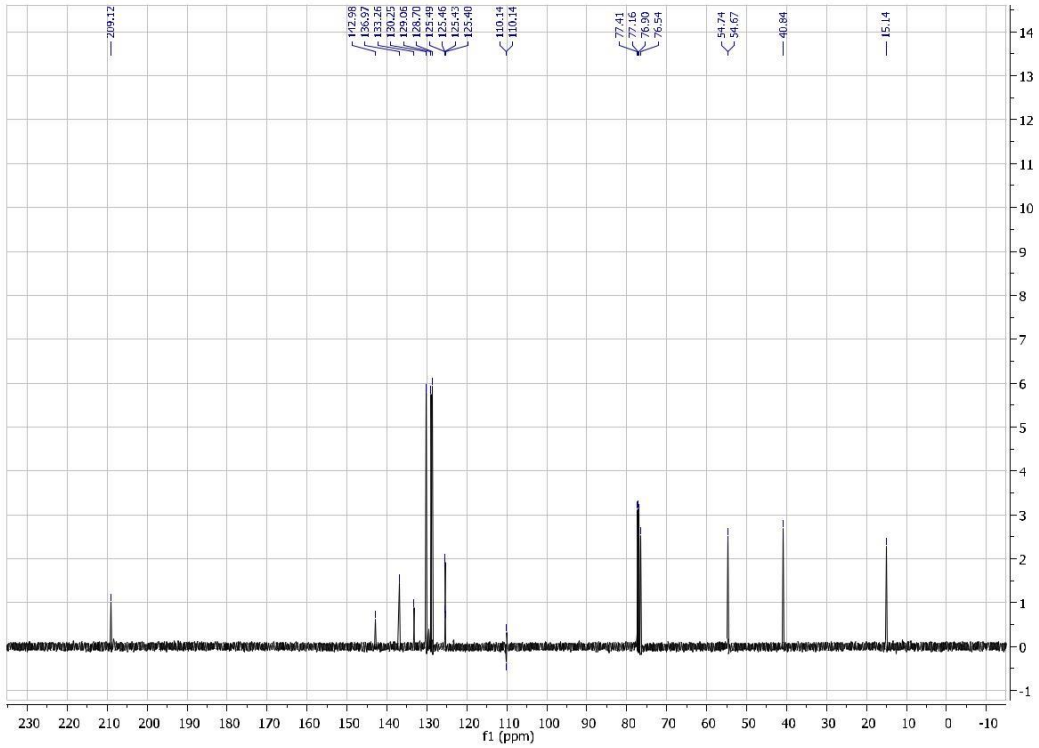
1.97
f1 (ppm)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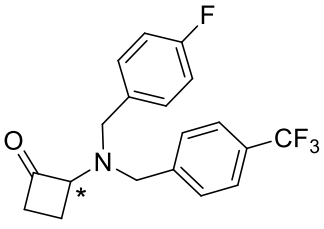
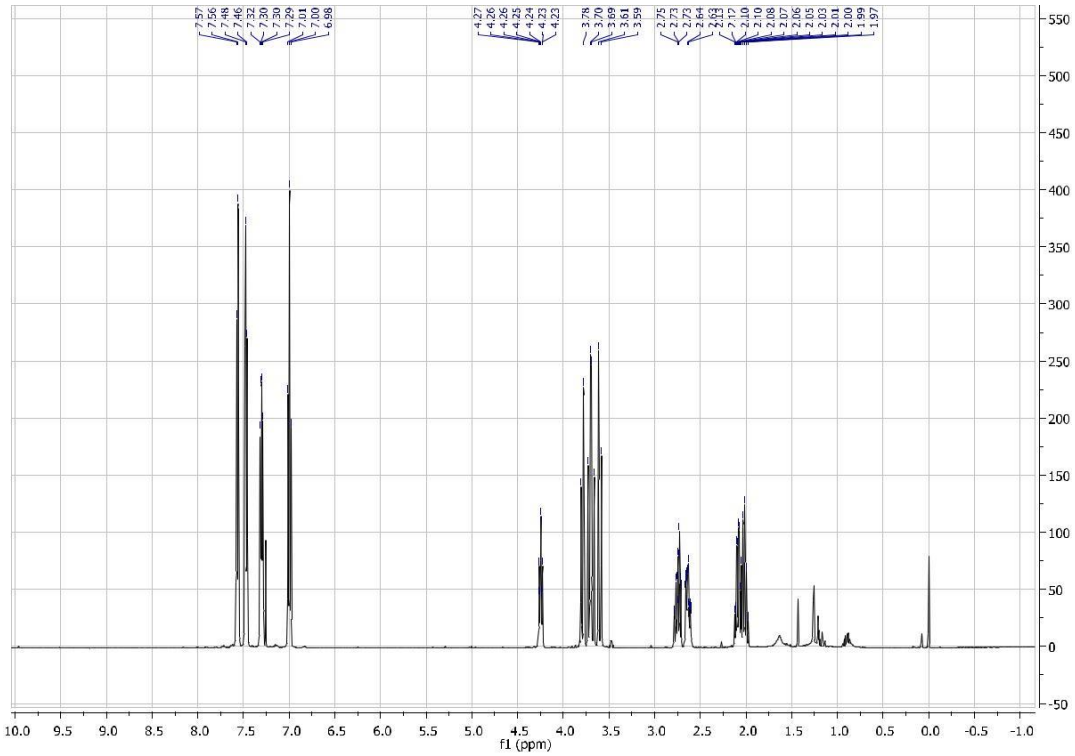
54.74
54.67
40.84
15.14
f1 (ppm)


F
O
N
*
CF3

3s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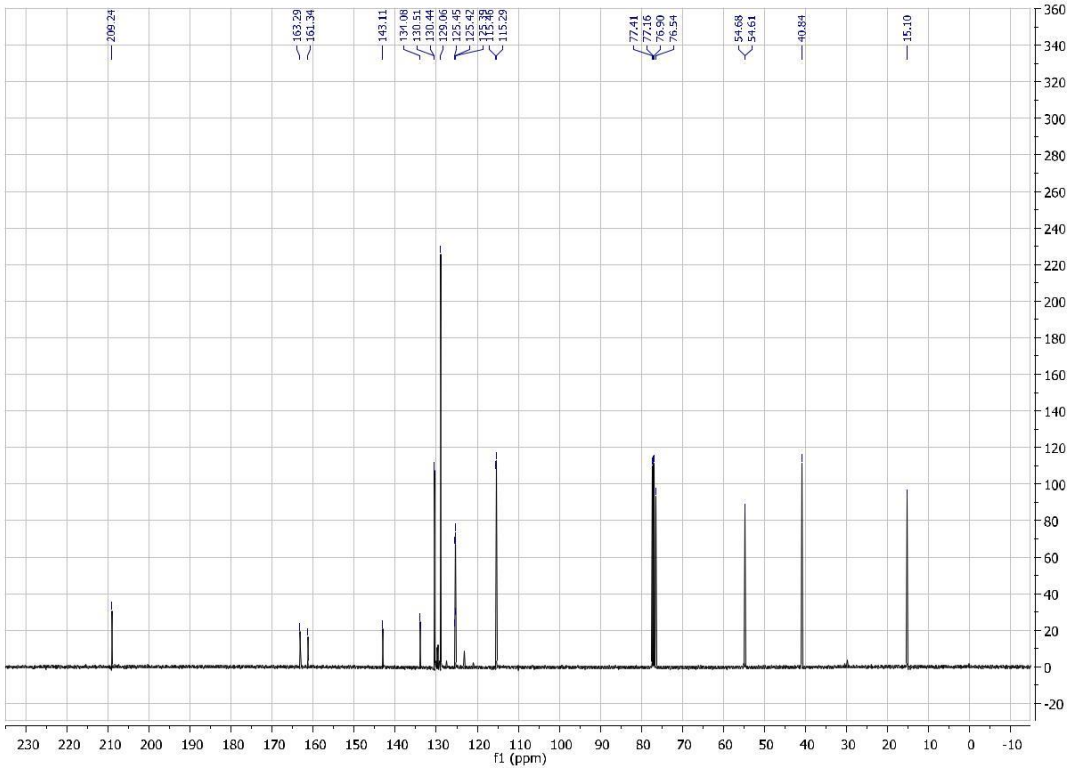
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130.44
129.06
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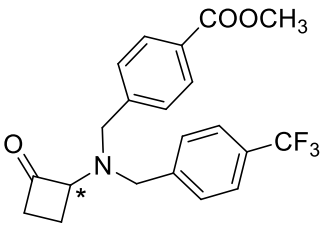
77.16
76.90
76.54
54.68
54.61
40.84
15.10
f1 (ppm)



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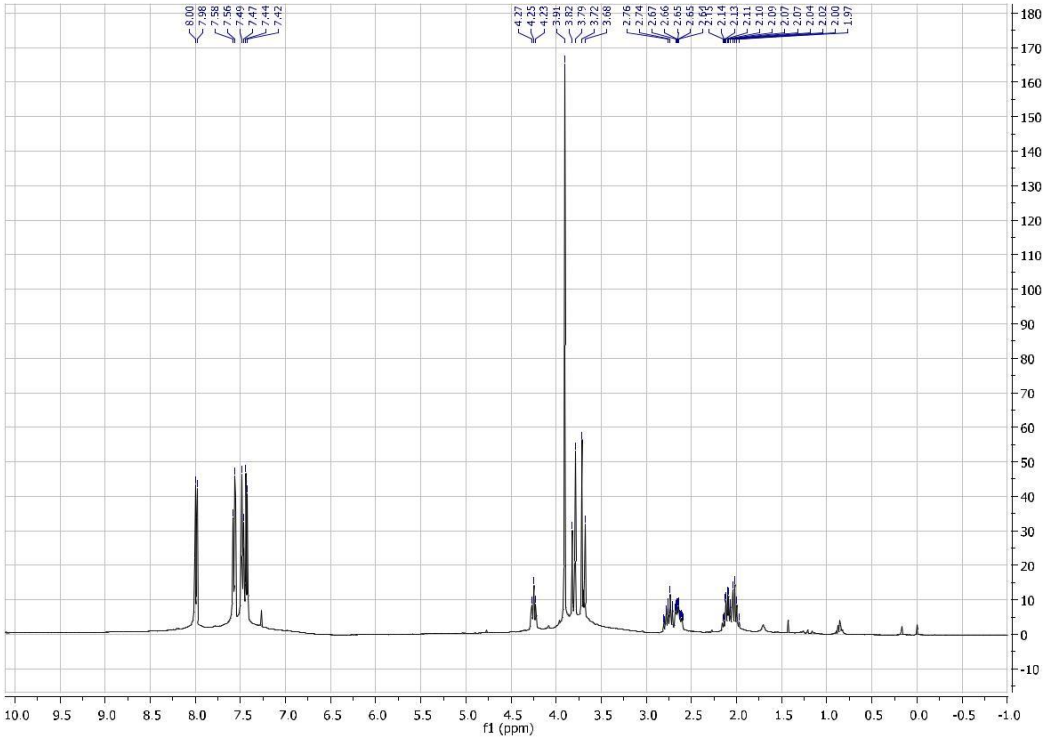

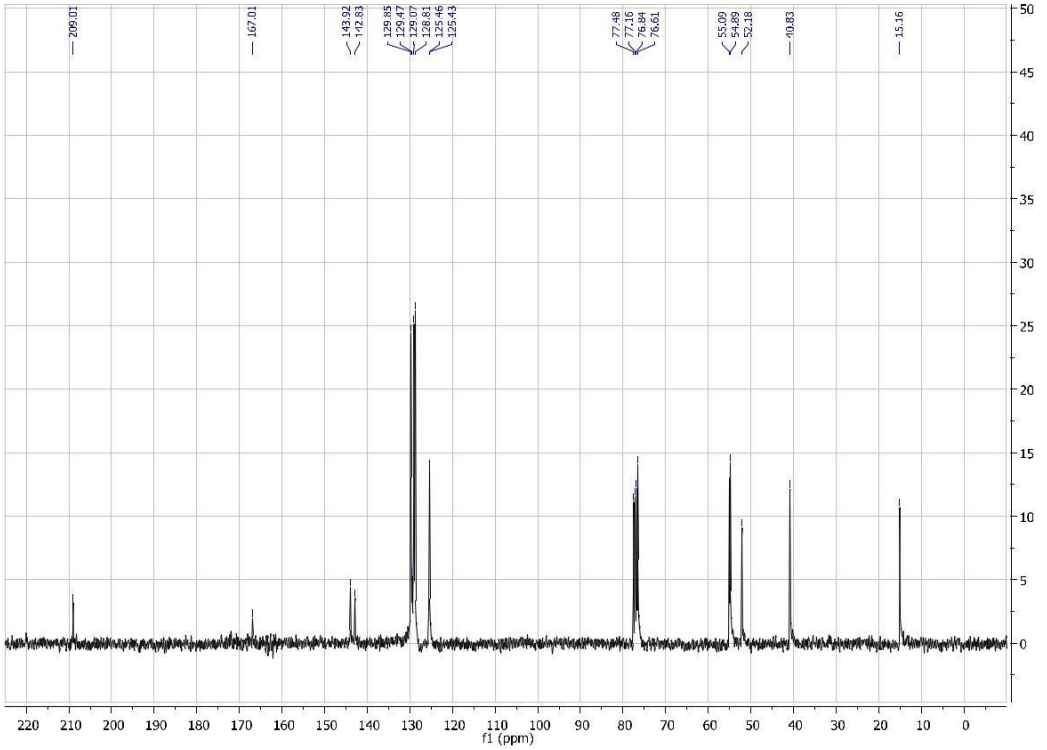

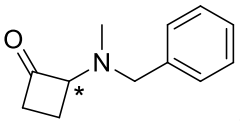

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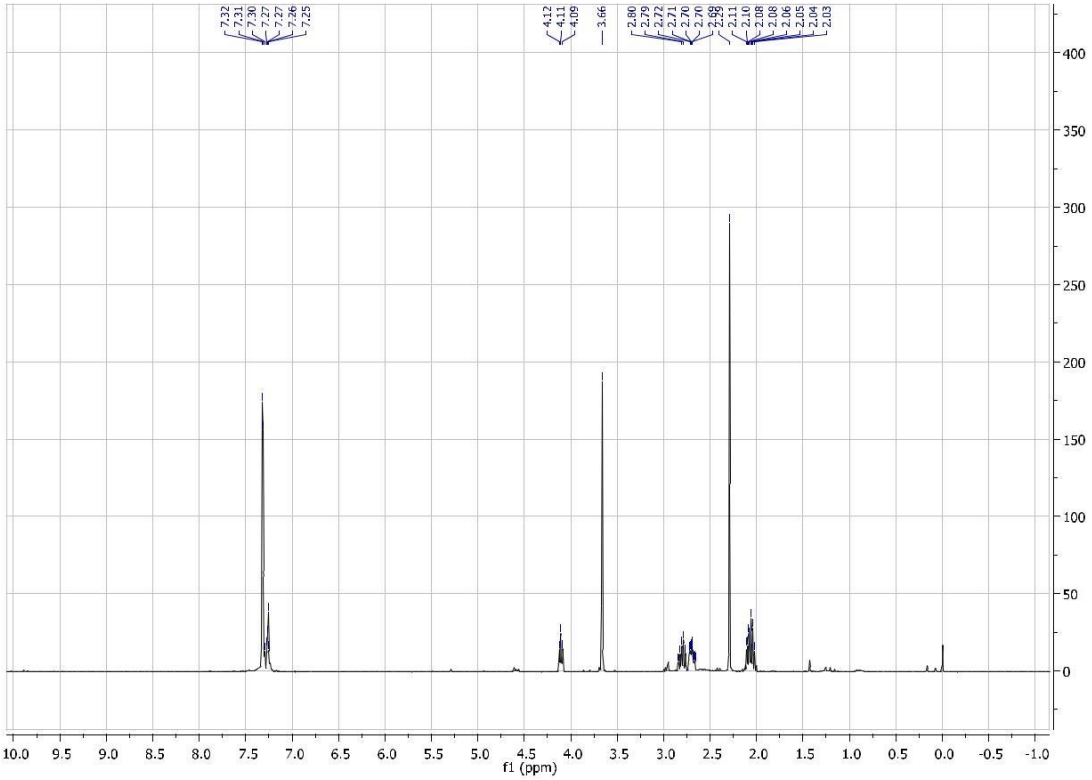
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4.09
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2.79
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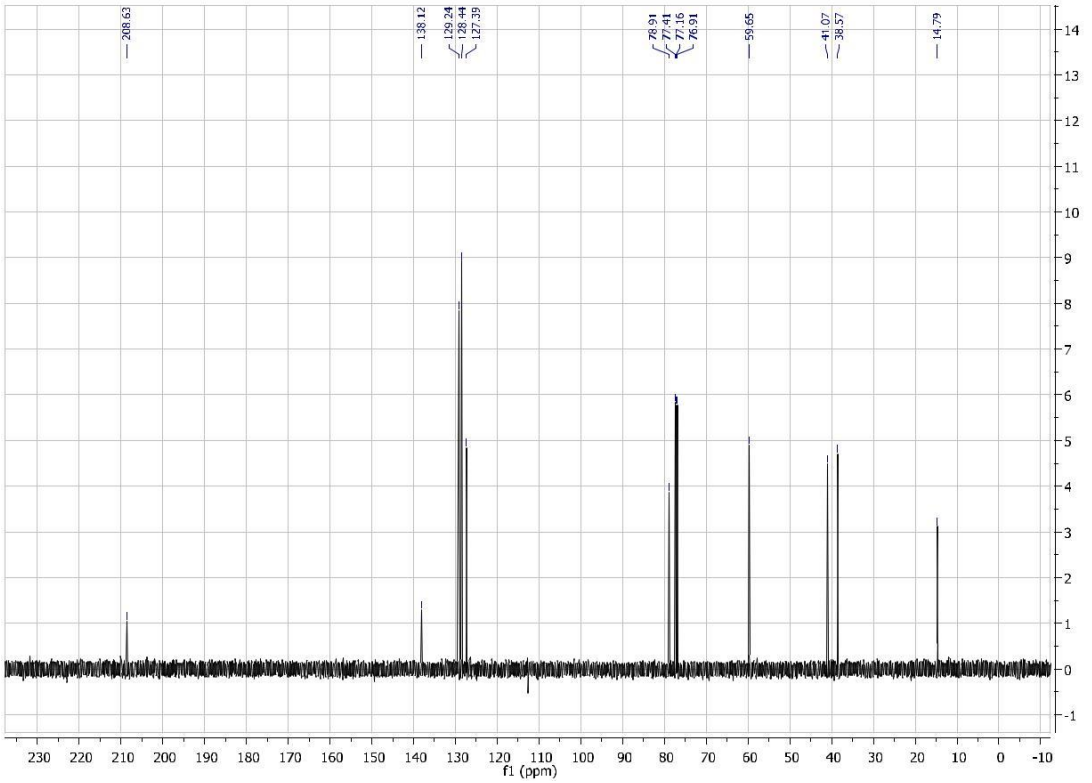
2.06
2.05
2.04
2.03
f1 (ppm)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77.16
76.91
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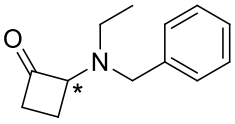
14.79
f1 (ppm)



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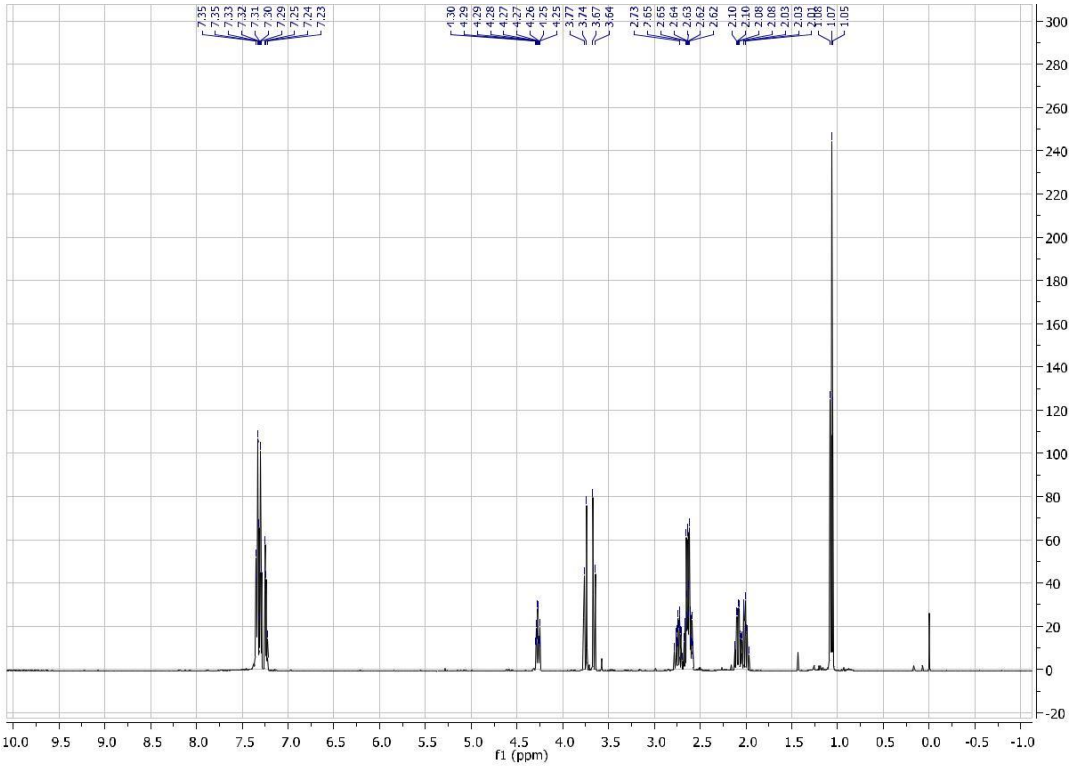
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1.08
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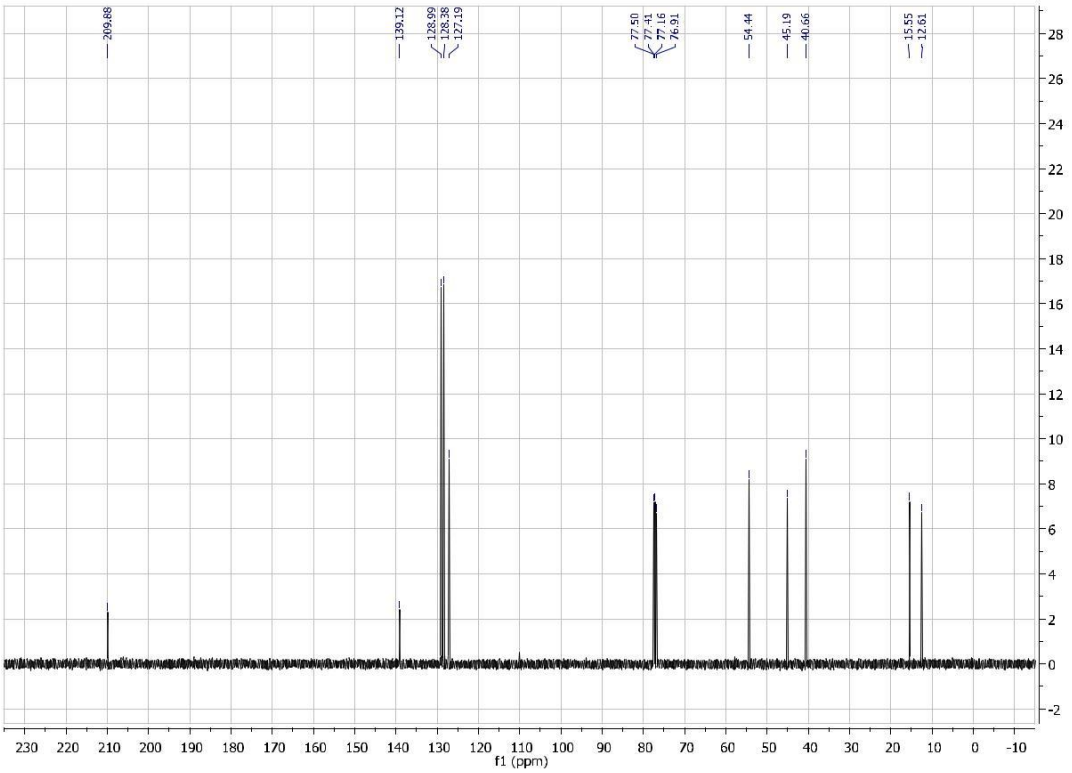
1.05
f1 (ppm)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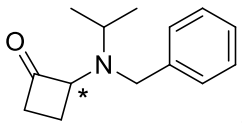
77.16
76.91
54.44
45.19
40.66
15.55
12.61
f1 (ppm)



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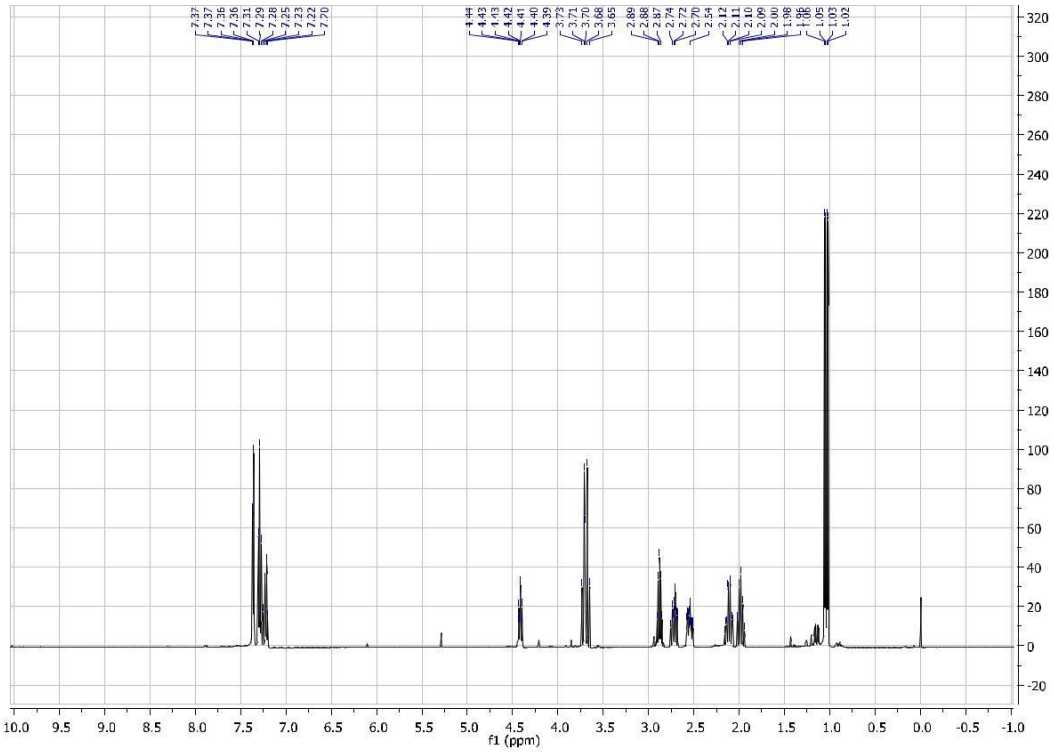

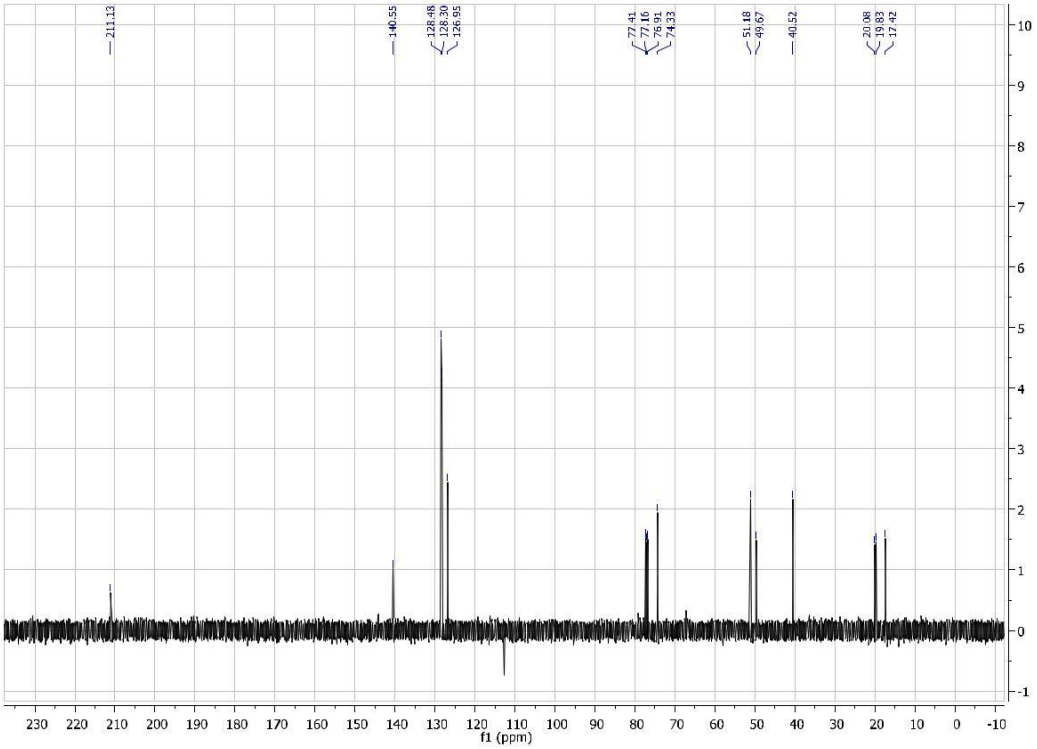

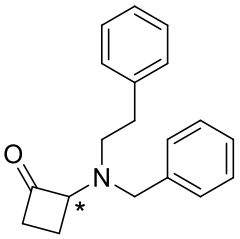
O
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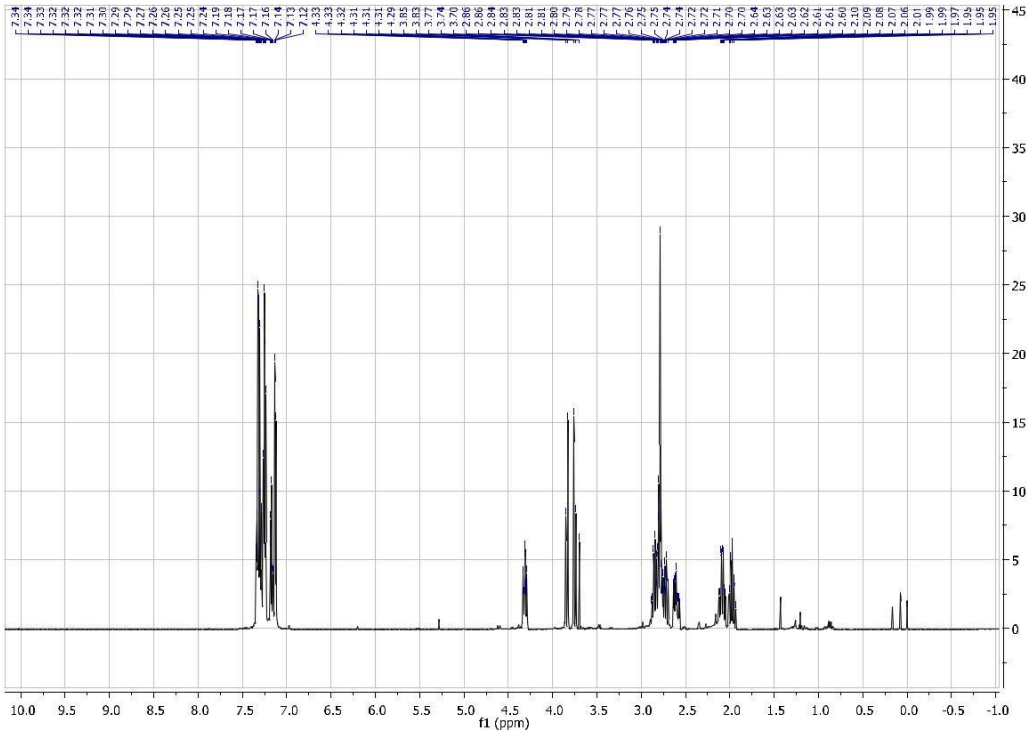
*

5d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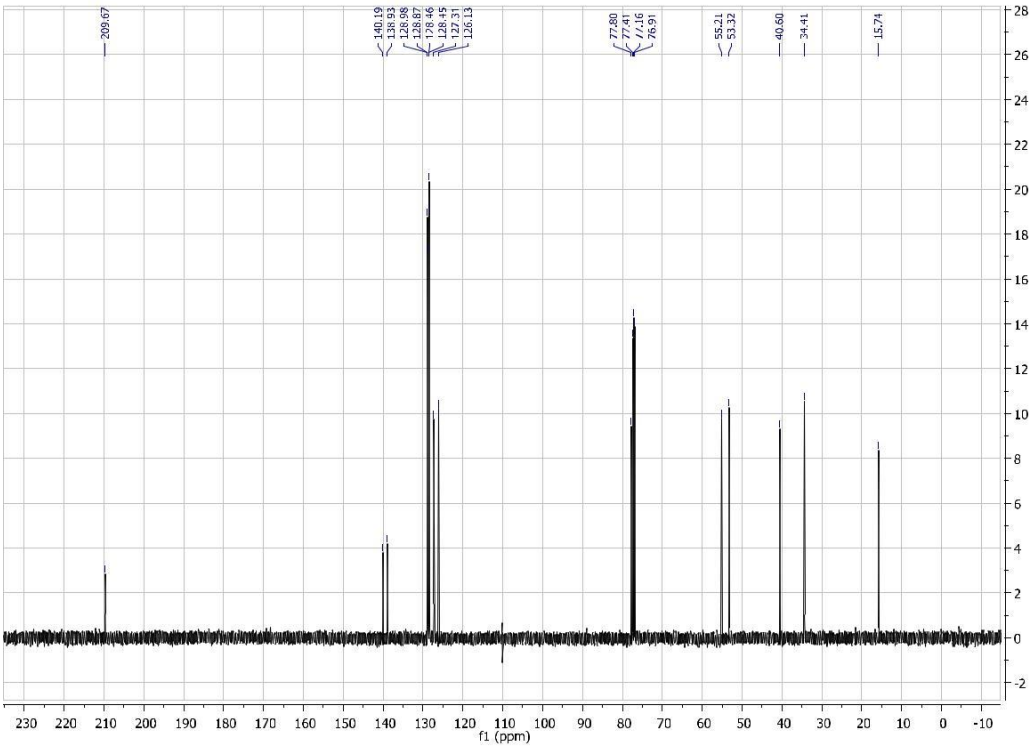
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40.60
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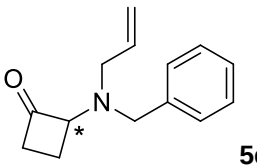
15.74
f1 (ppm)



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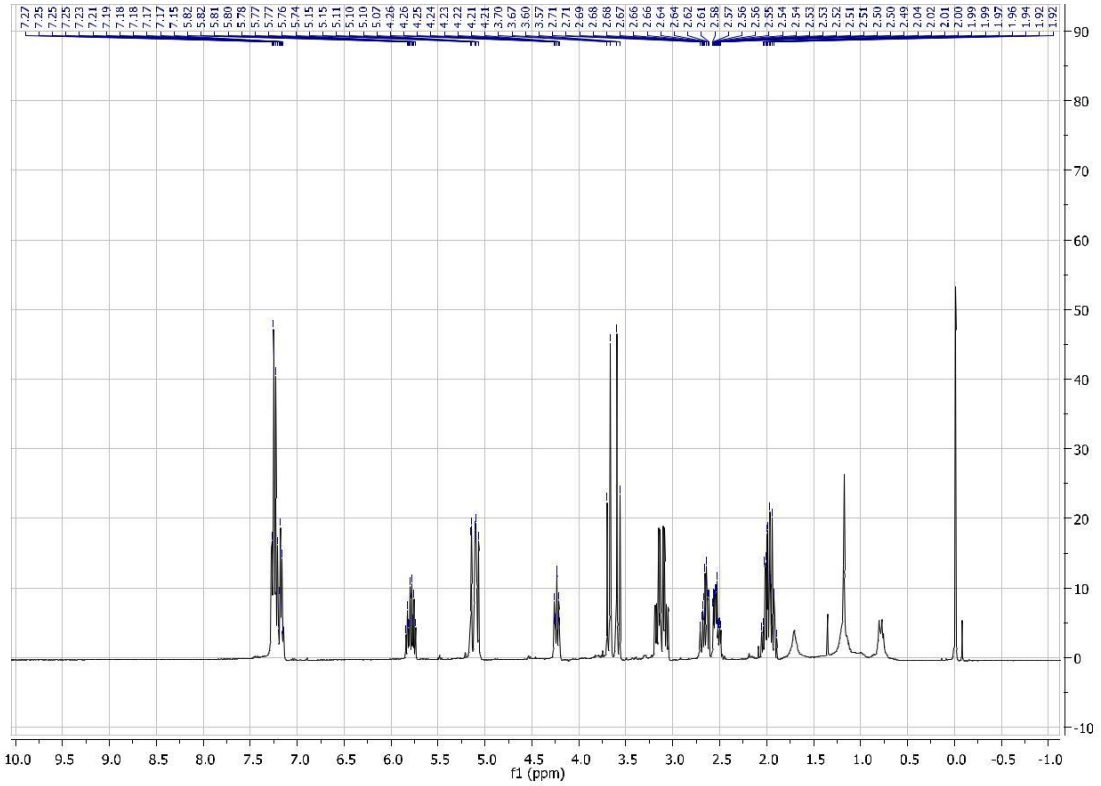
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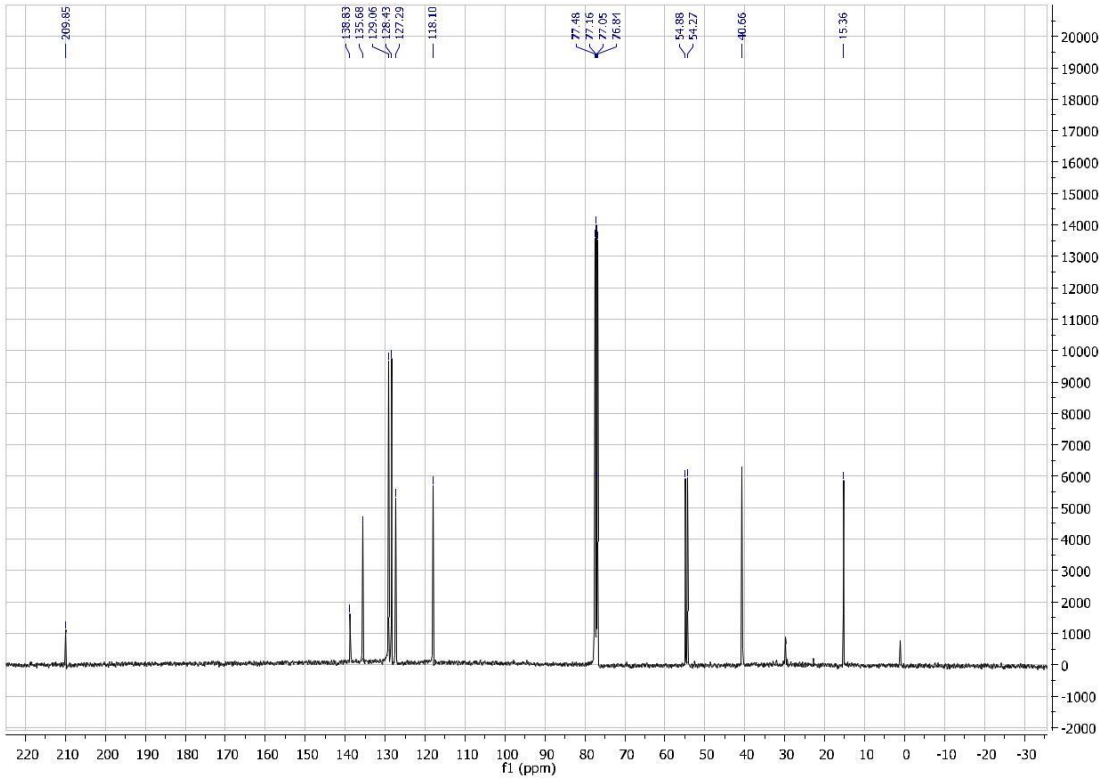
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77.05
76.81
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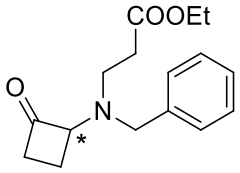
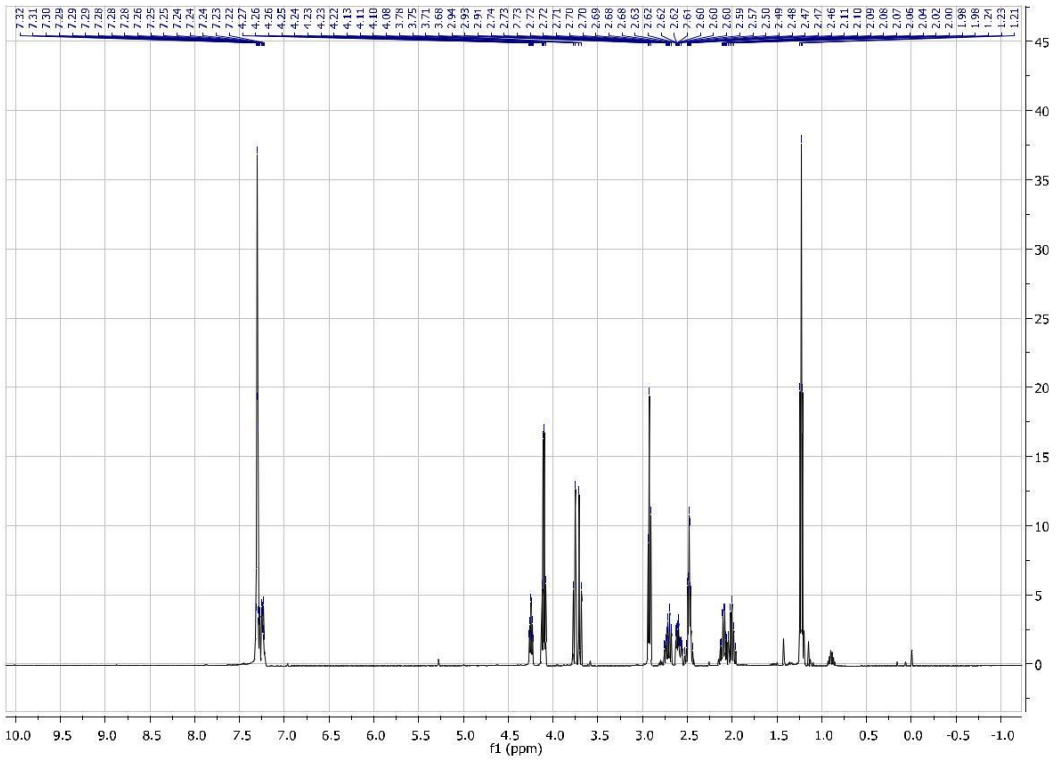
54.27
40.66
15.36
f1 (ppm)


COOEt
O
N
*

5f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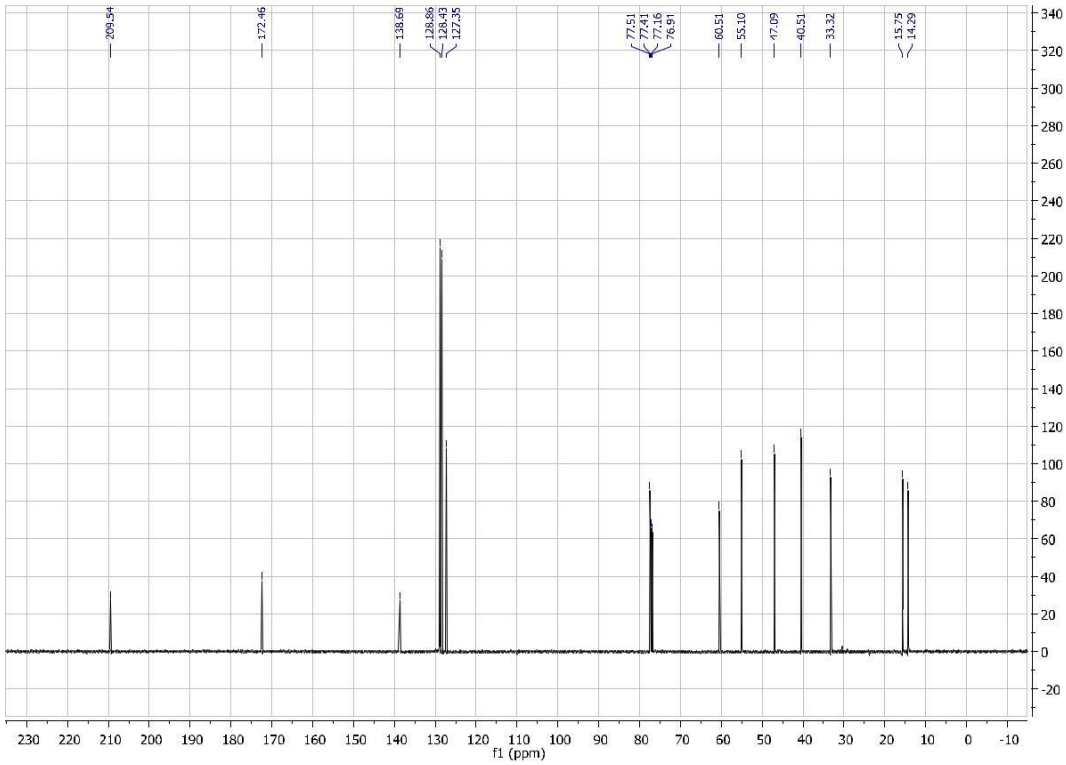
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76.91
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55.10
47.09
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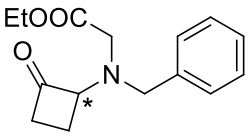
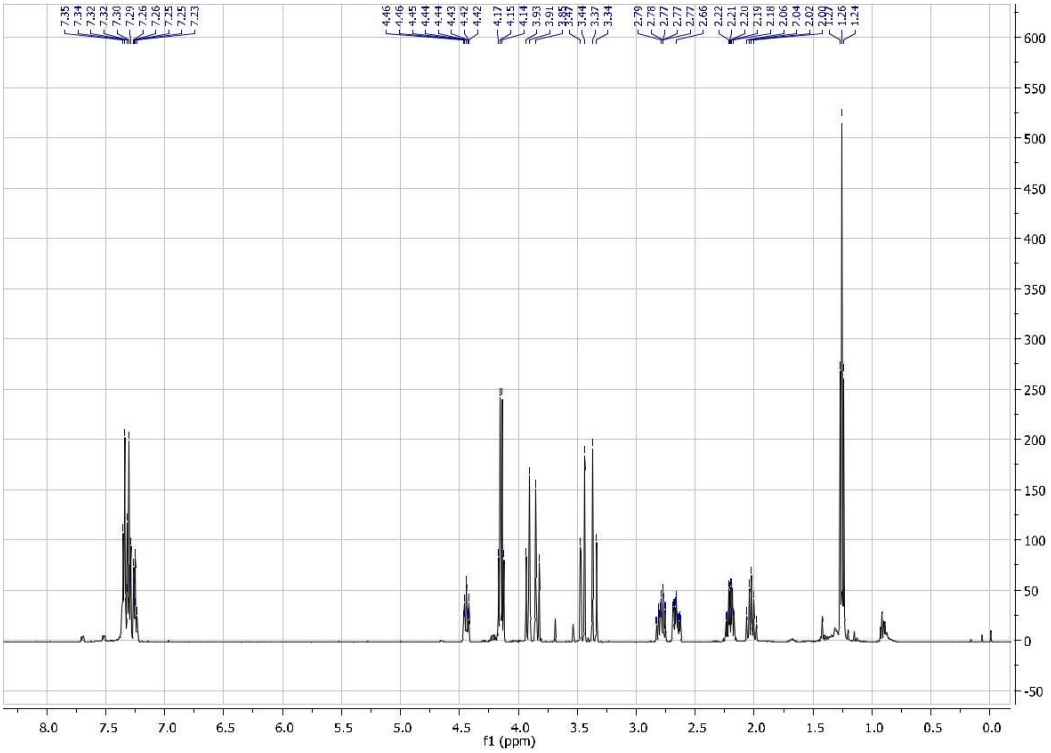
33.32
15.75
14.29
f1 (ppm)


EtOOC
O
N
*

5g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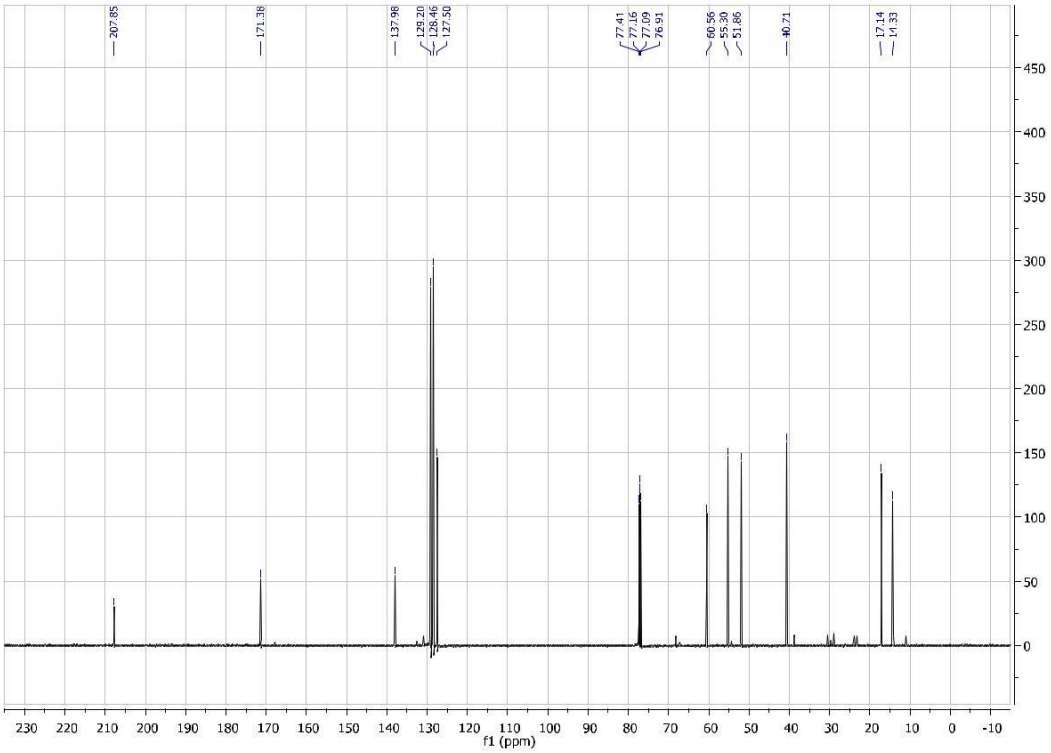
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129.20
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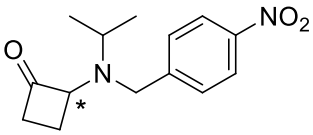
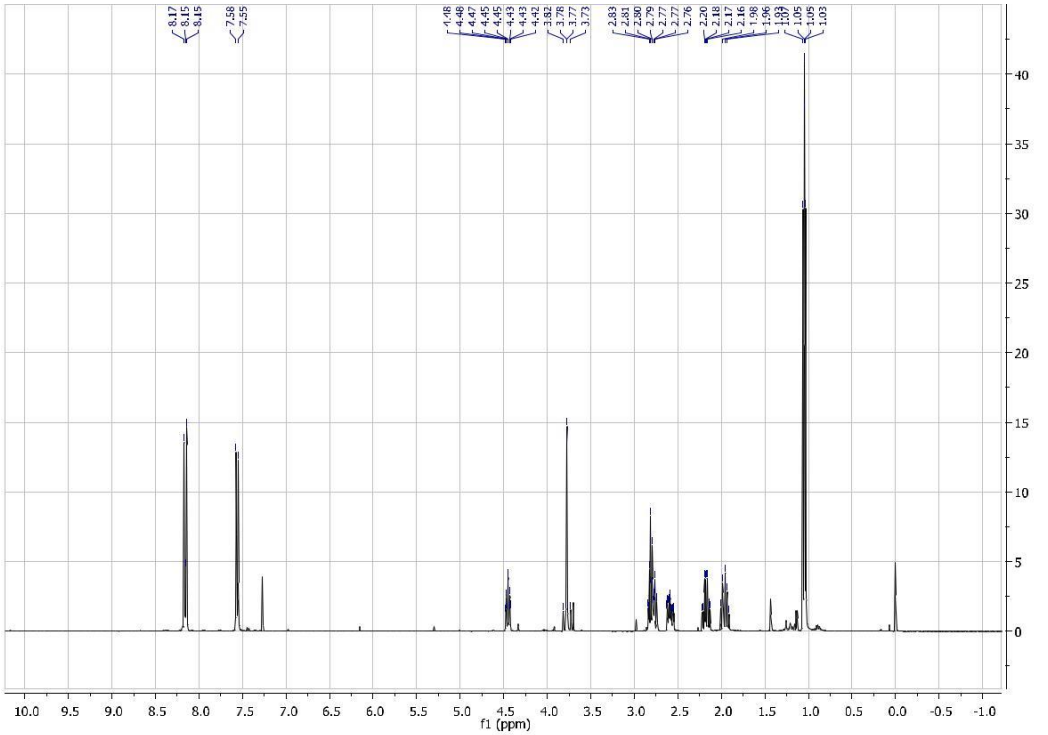
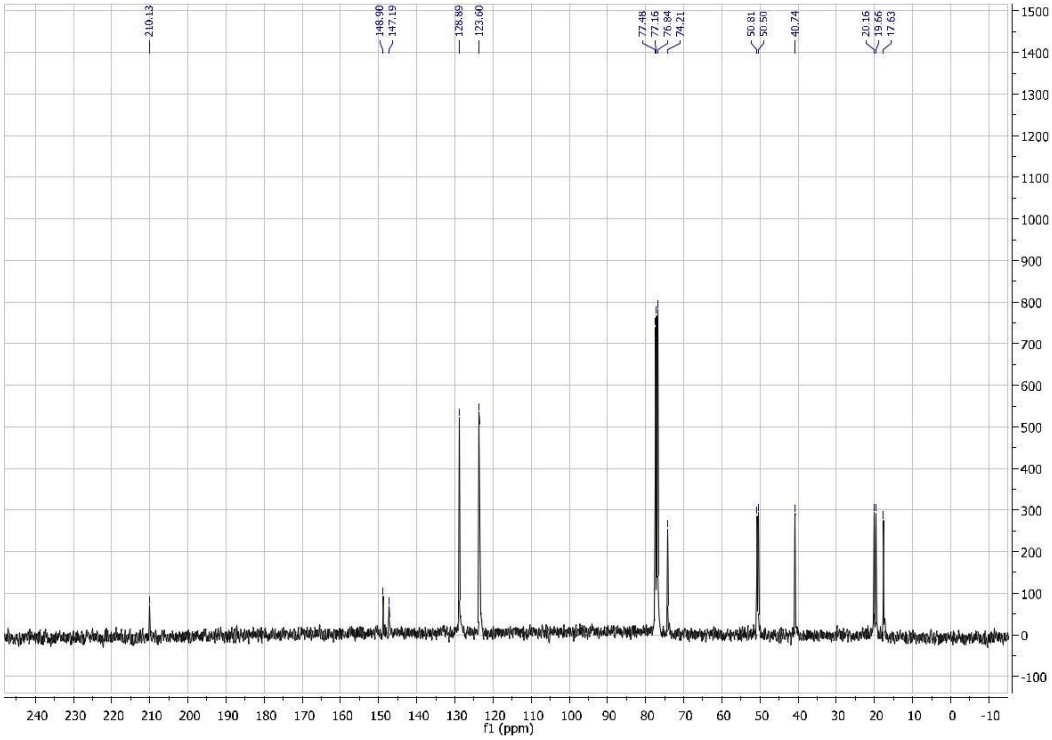
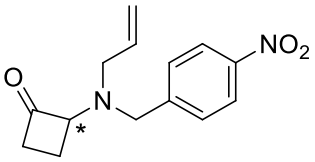
60.56
55.30
51.86
40.71
17.14
14.33
f1 (ppm)



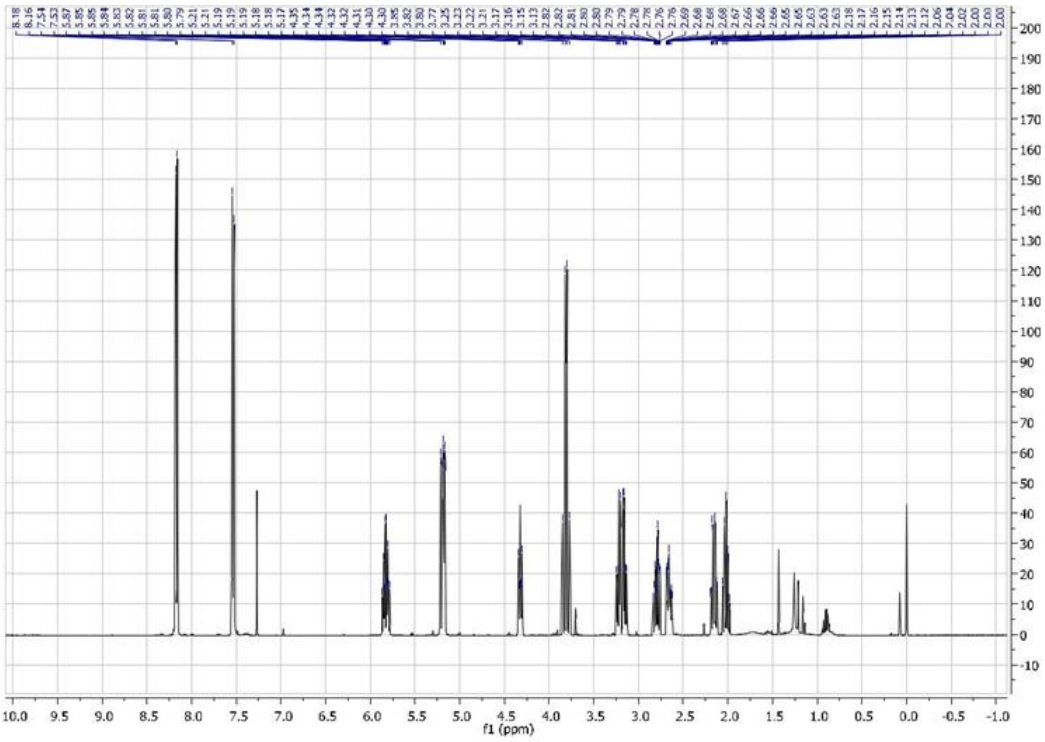
5h

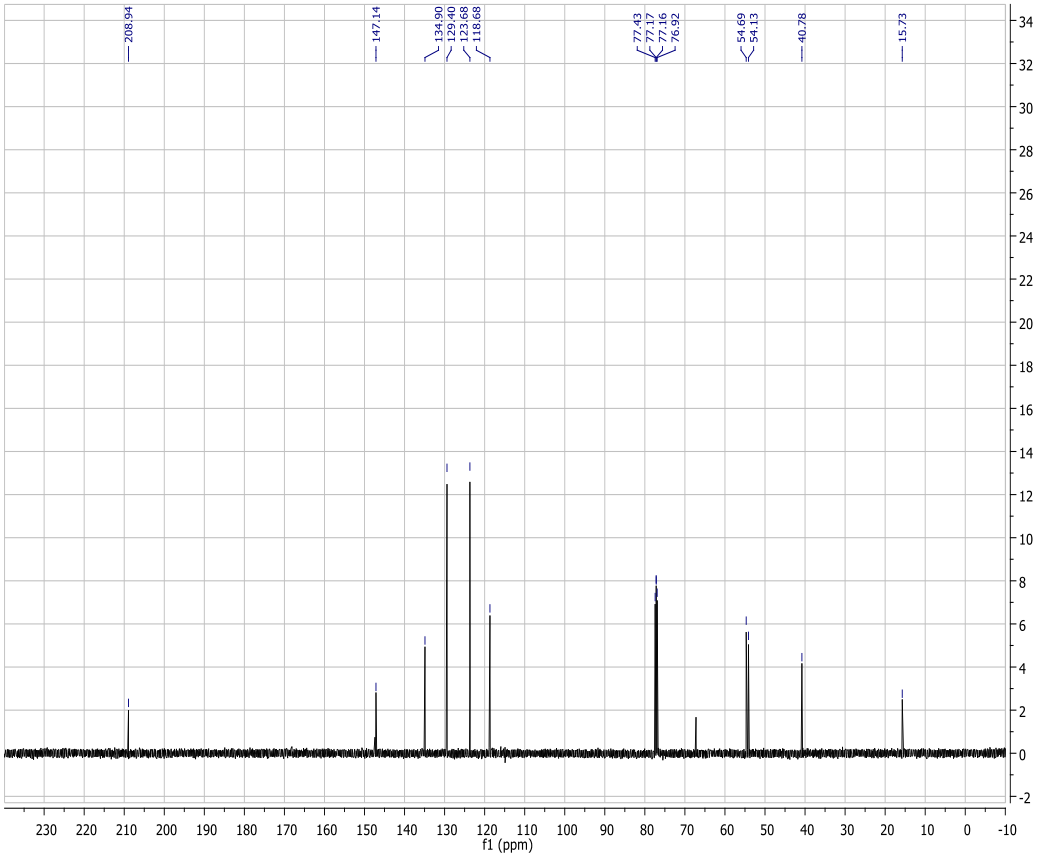


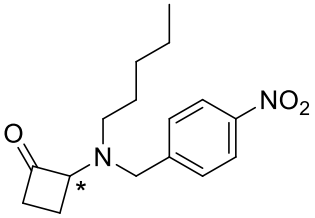



O
N
*
NO2

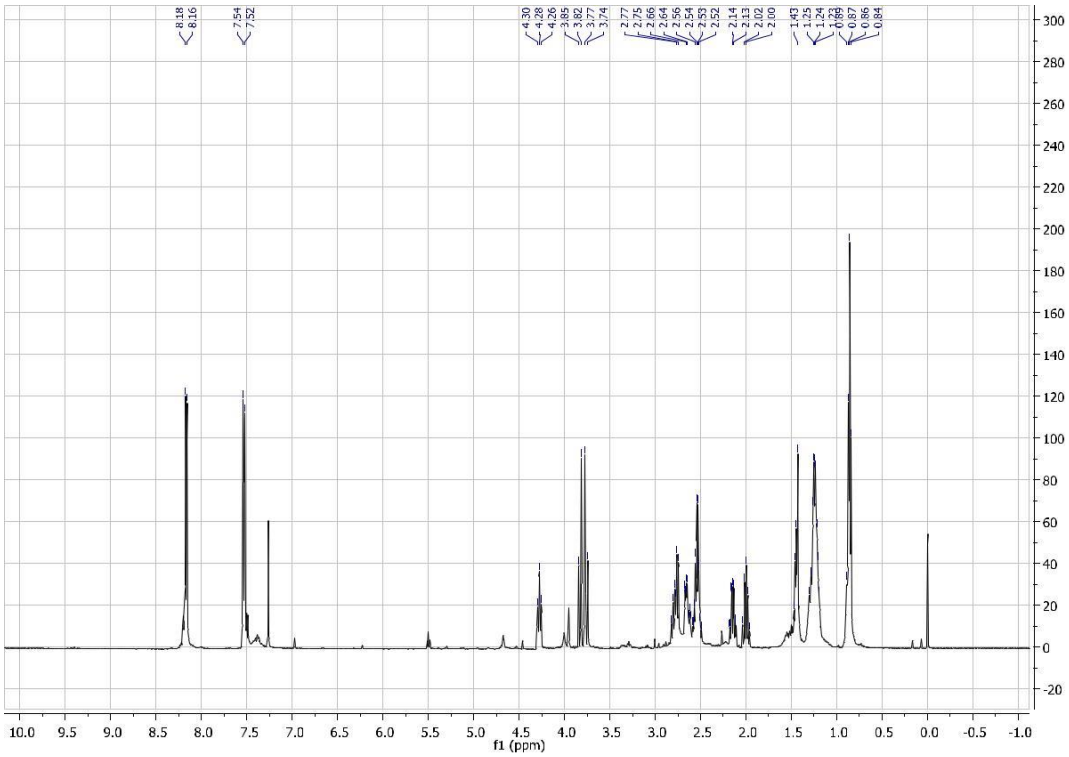
5i

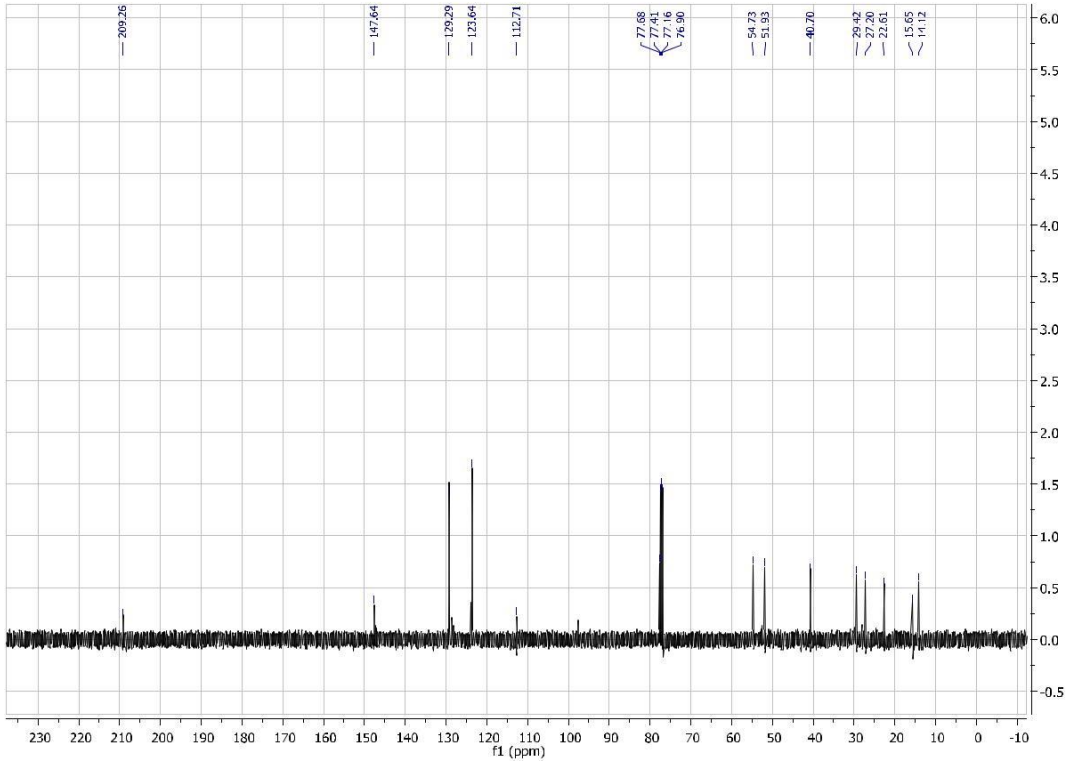

f1 (ppm)

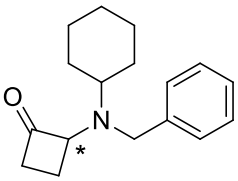

208.94
147.14
134.90
129.40
123.68
118.68
77.43
77.17
77.16
76.92
54.69
54.13
40.78
15.73
f1 (ppm)


O
N
*
NO2

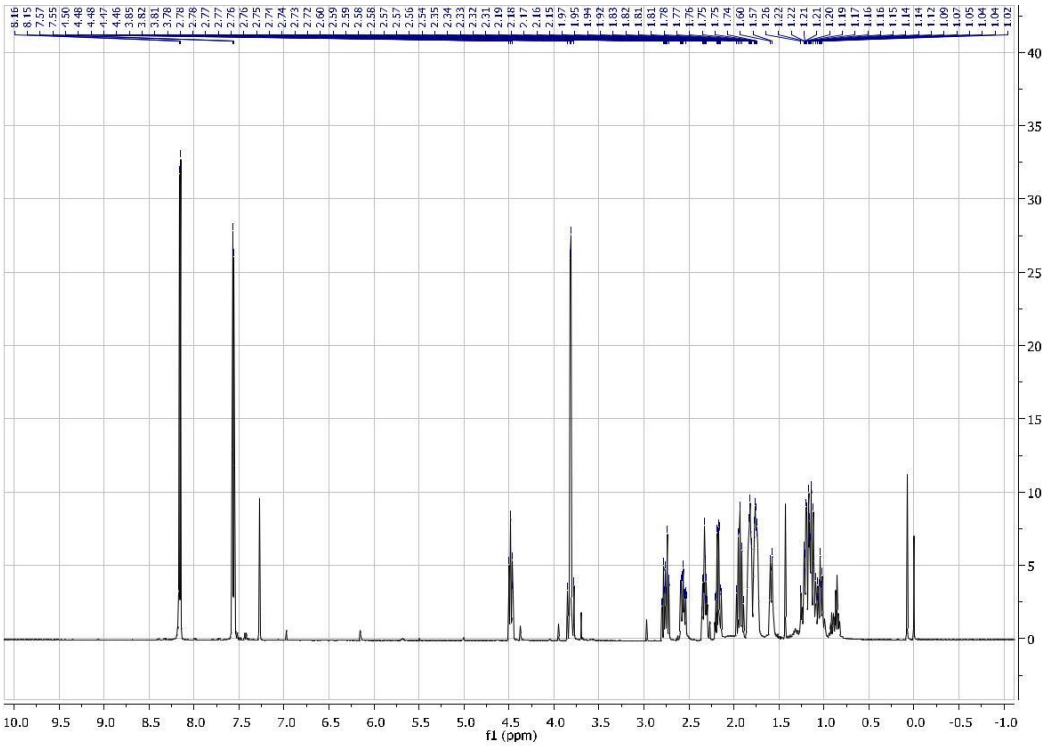
5j

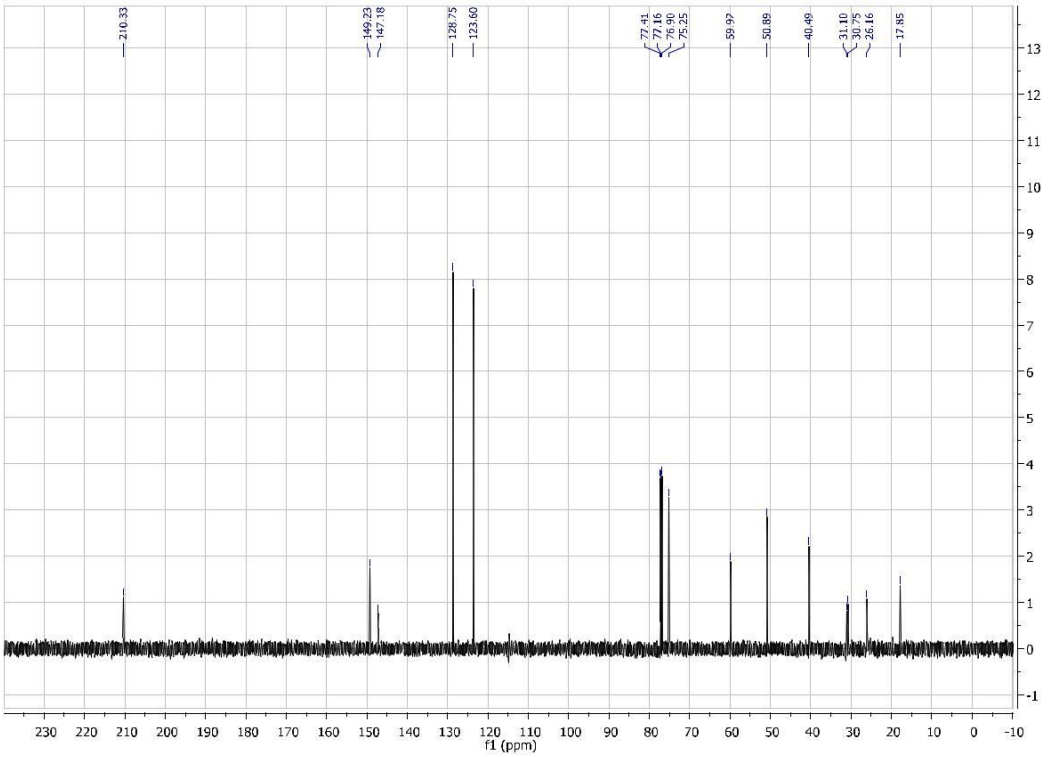

8.18
8.16
7.54
7.52
4.30
4.28
4.26
3.85
3.82
3.77
3.74
2.77
2.75
2.66
2.64
2.56
2.54
2.53
2.52
2.14
2.13
2.02
2.00
1.43
1.25
1.24
0.89
0.87
0.86
0.84
f1 (ppm)

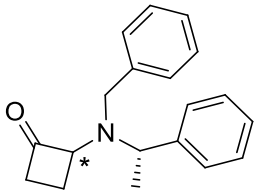

209.26
147.64
129.29
123.64
112.71
77.68
77.41
77.16
76.90
54.73
51.93
40.70
29.42
27.20
22.61
15.65
14.12
f1 (ppm)


O
N
*

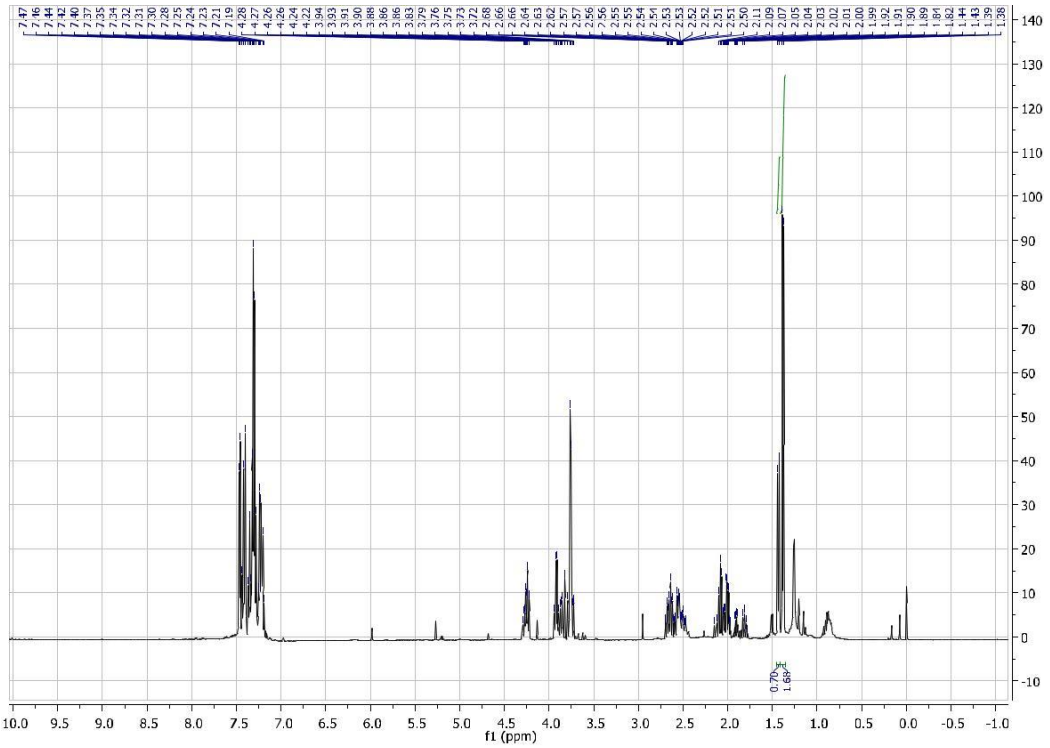
5k

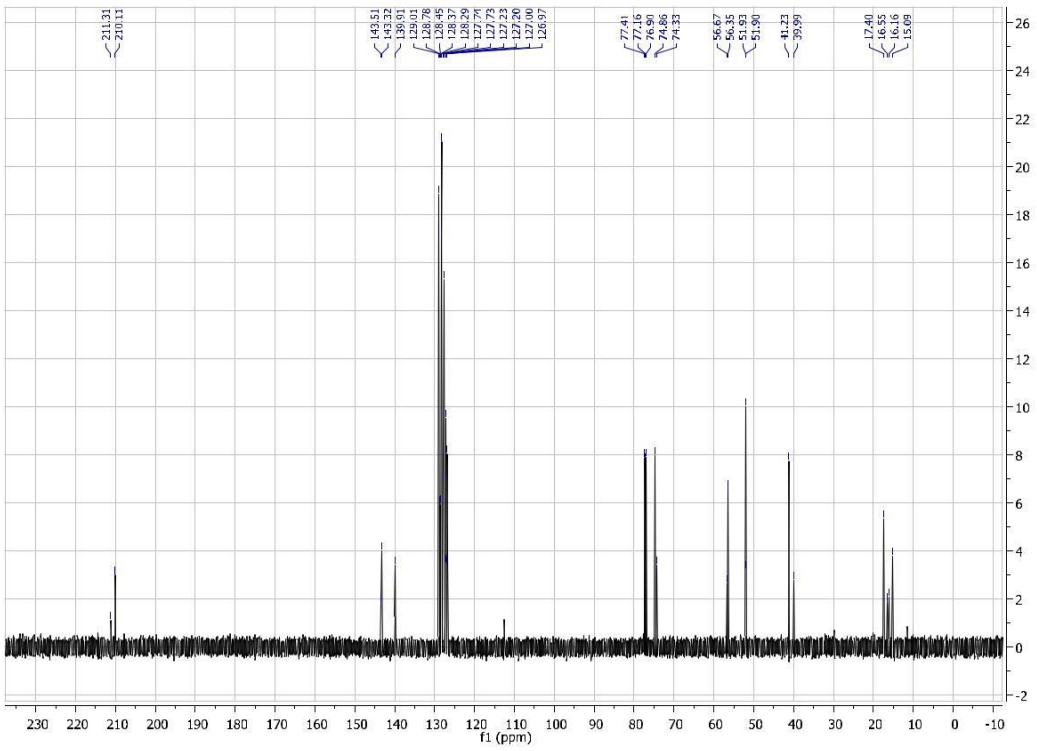

f1 (ppm)

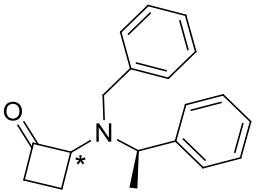

210.33
149.23
147.18
128.75
123.60
77.41
77.16
76.90
75.25
59.97
50.89
40.49
31.10
30.75
26.16
17.85
f1 (ppm)



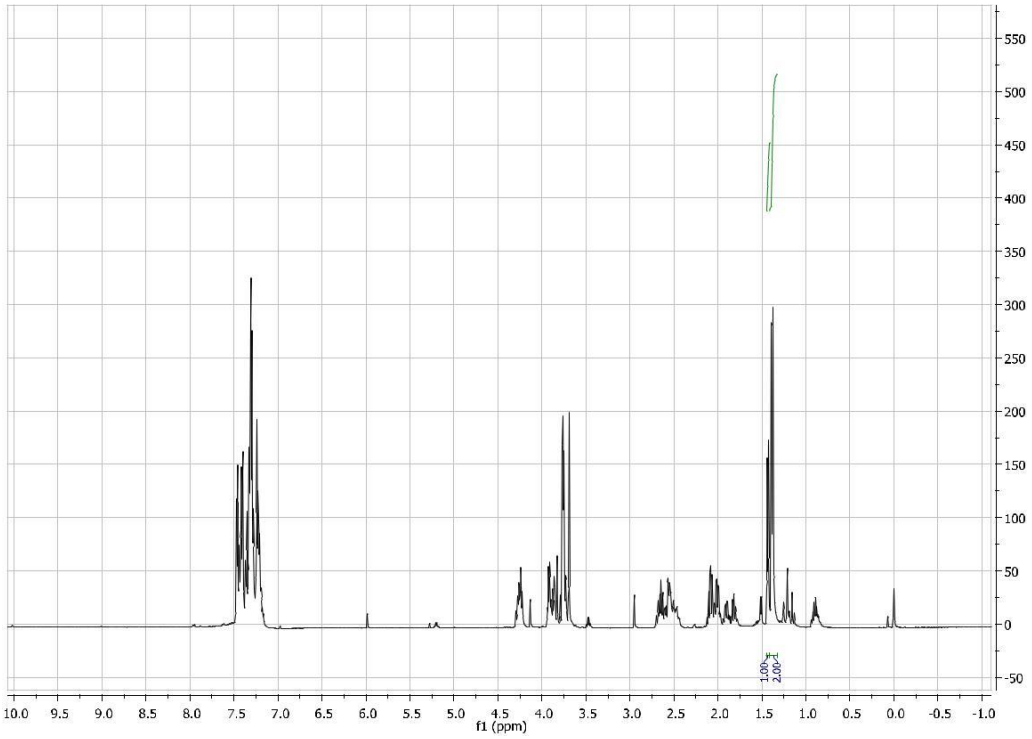
ent-**7a***ent*-**7'a**
d.r.: 71:29

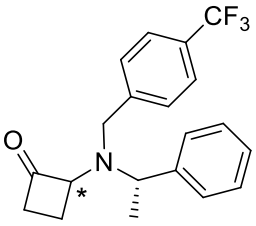




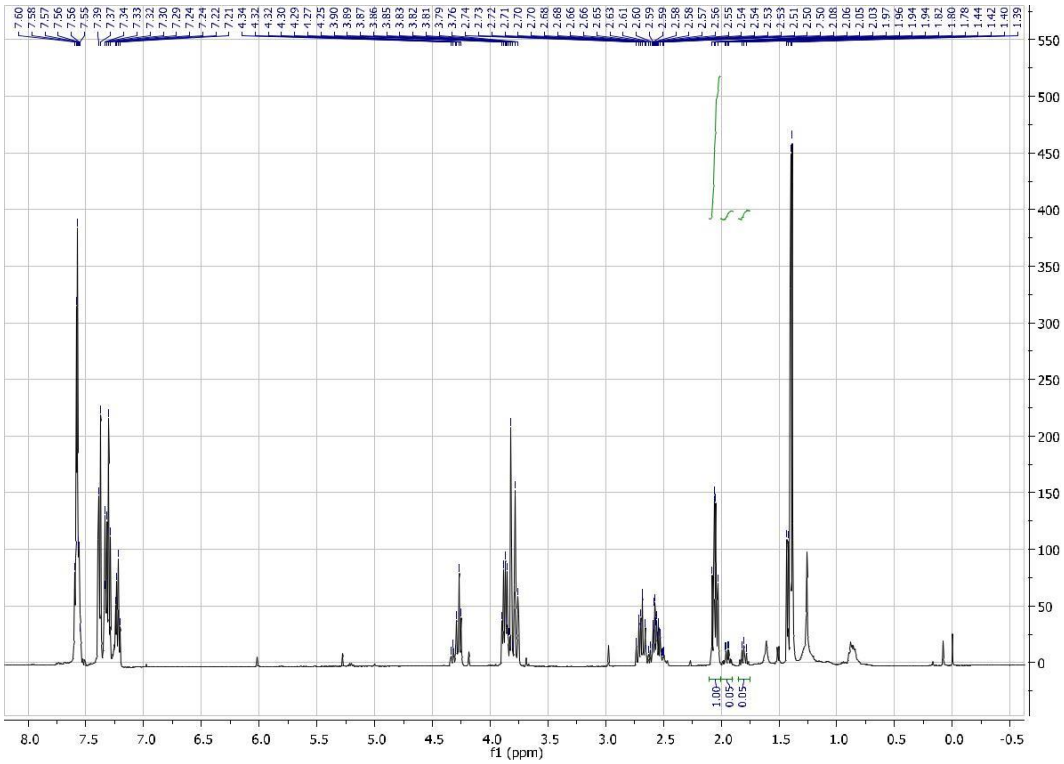

O
N
*

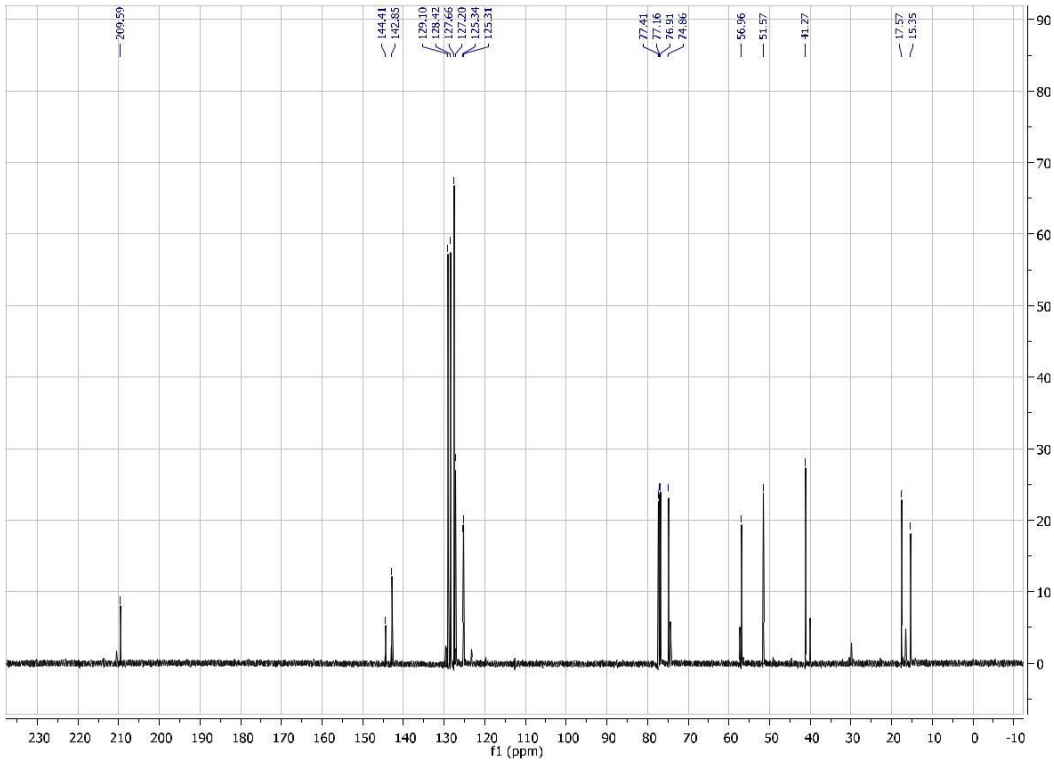
7a/7'a
d.r.: 67:33

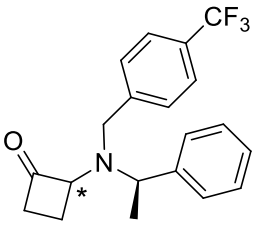

550
500
450
400
350
300
250
200
150
100
50
0
-50
1.00
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)



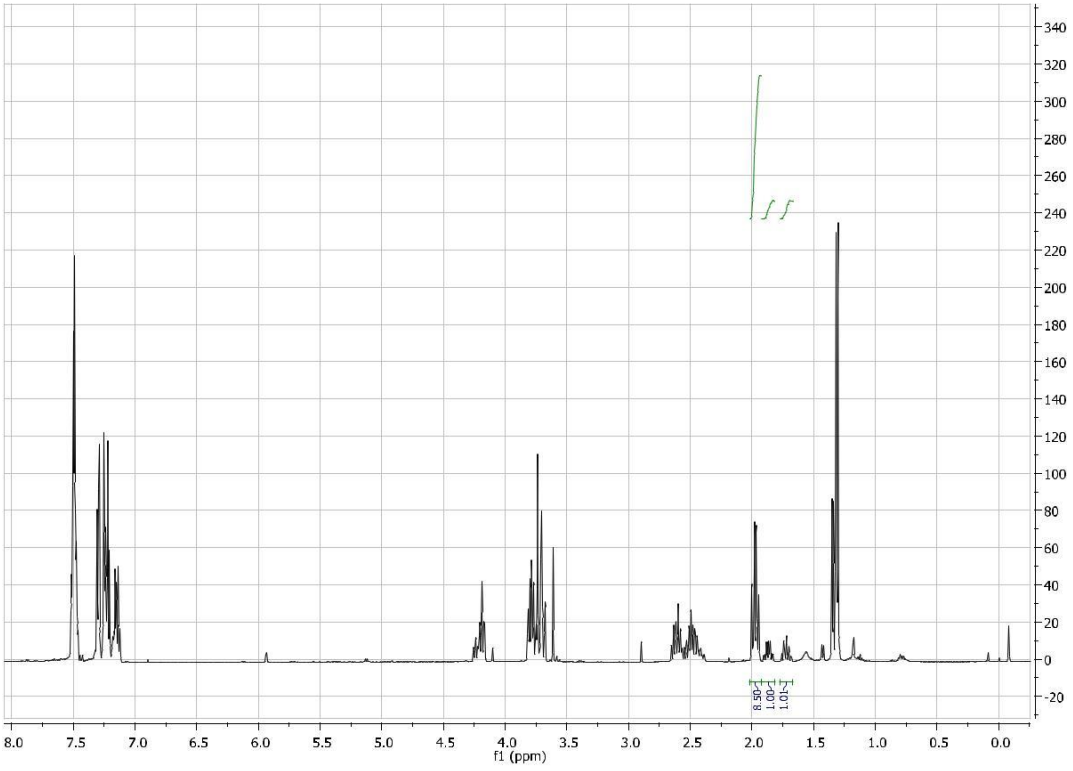
ent-**7b**/*ent*-**7'b**
d.r.: 91:9





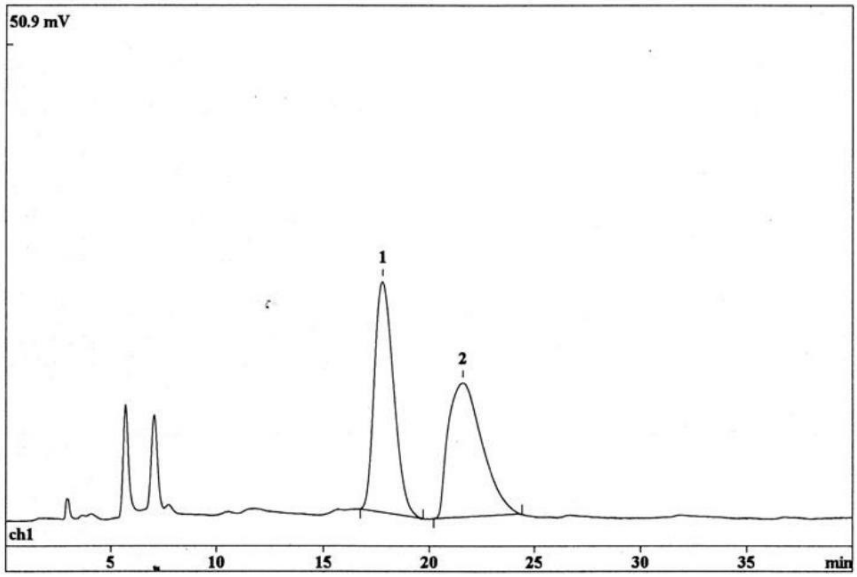


7b/7'b
d.r.: 81:19



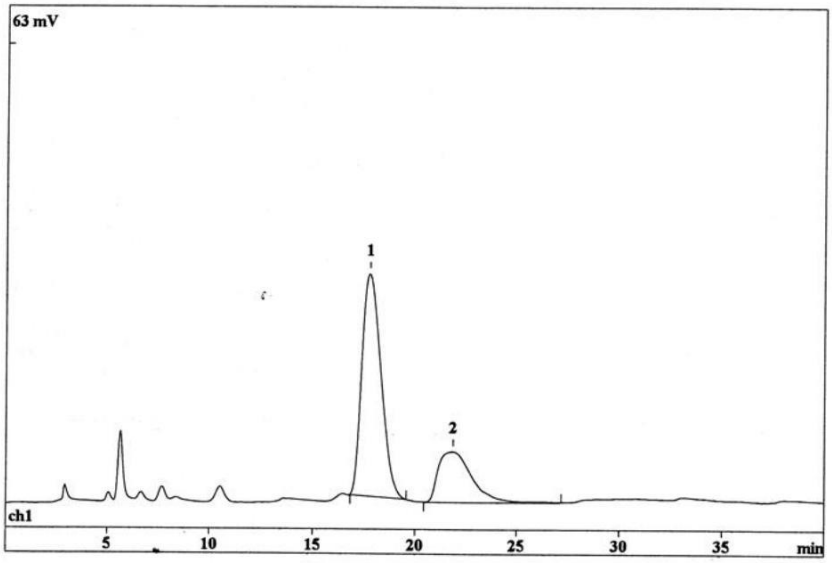
2.4.4 Copies of HPLC chromatograms of racemic/enantioenriched products

3a Chiracel OJ column (hexane/i-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

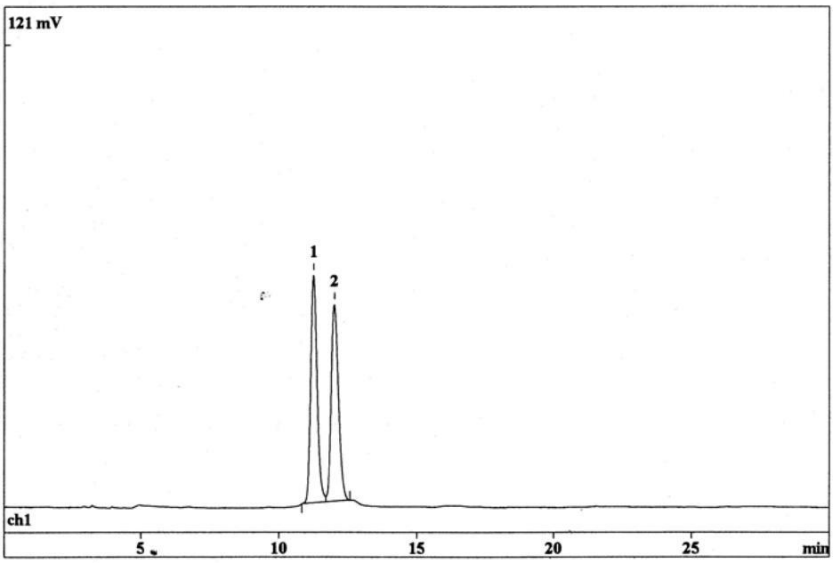
No	Retention min	Area mV*sec	Area %	Name
1	17.78	1480.030	49.26	
2	21.57	1524.664	50.74	
2	40.00	3004.693	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

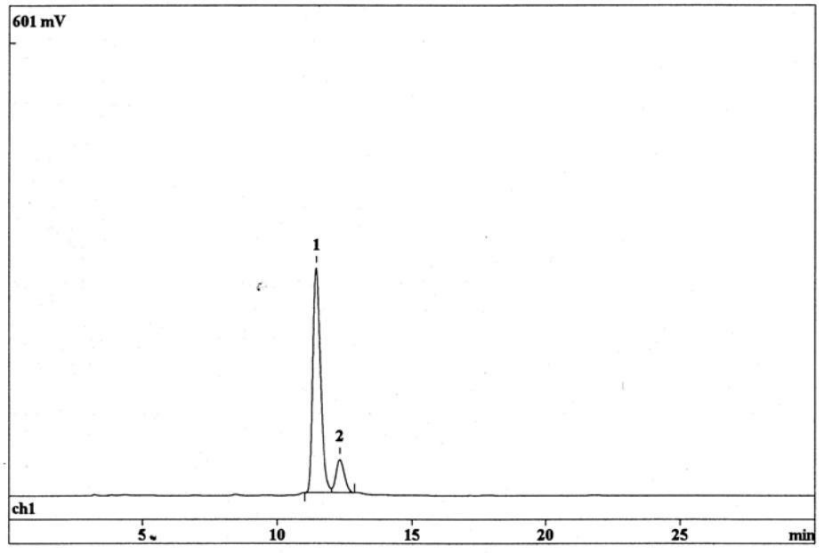
No	Retention min	Area mV*sec	Area %	Name
1	17.74	1874.577	71.26	
2	21.83	756.196	28.74	
2	40.00	2630.772	100.00	

3b Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

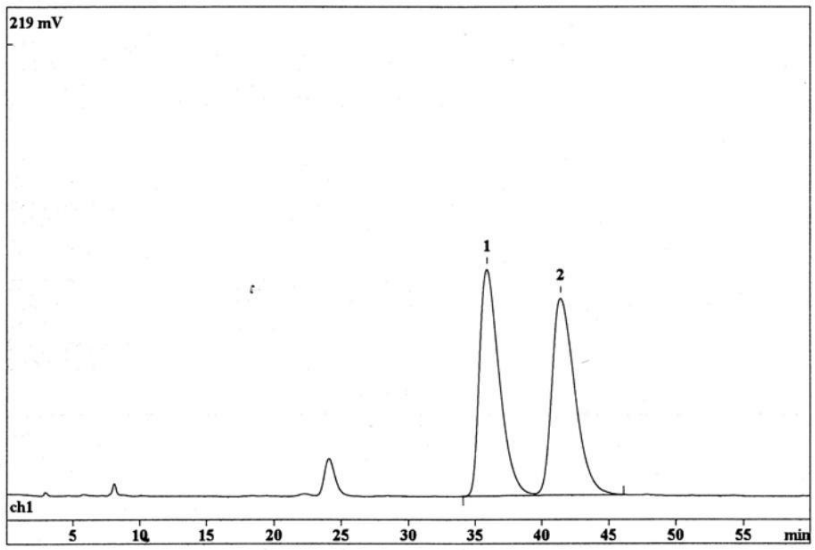
No	Retention min	Area mV*sec	Area %	Name
1	11.25	913.993	50.43	
2	12.01	898.332	49.57	
2	30.00	1812.325	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

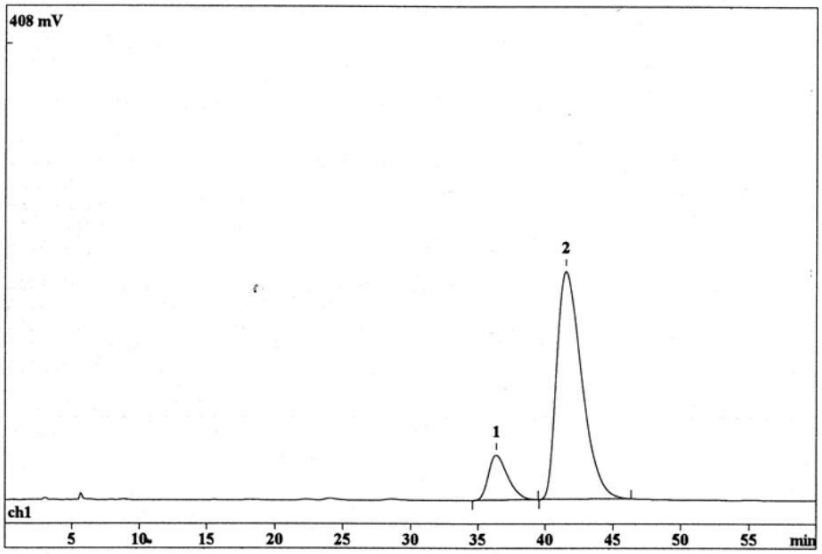
No	Retention min	Area mV*sec	Area %	Name
1	11.43	5646.608	86.37	
2	12.32	891.280	13.63	
2	30.00	6537.888	100.00	

3c Chiracel OJ column (hexane/i-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

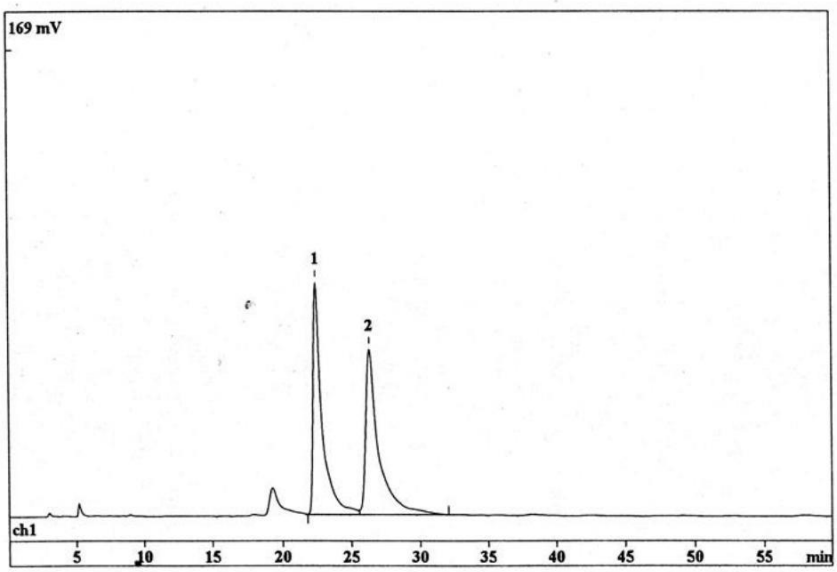
No	Retention min	Area mV*sec	Area %	Name
1	35.88	10838.188	49.91	
2	41.39	10879.324	50.09	
2	60.00	21717.513	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

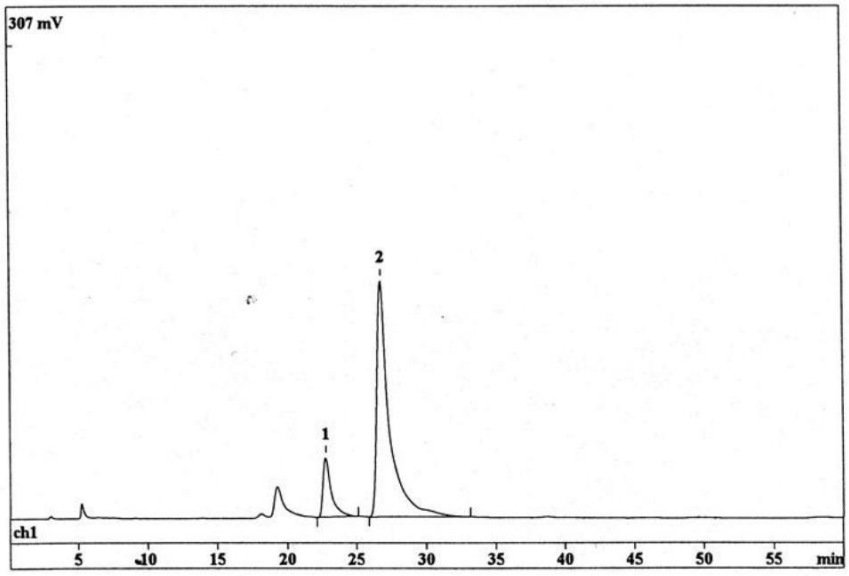
No	Retention min	Area mV*sec	Area %	Name
1	36.36	3849.150	13.33	
2	41.52	25026.714	86.67	
2	60.00	28875.864	100.00	

3d Chiralpak AD-H column (hexane/i-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

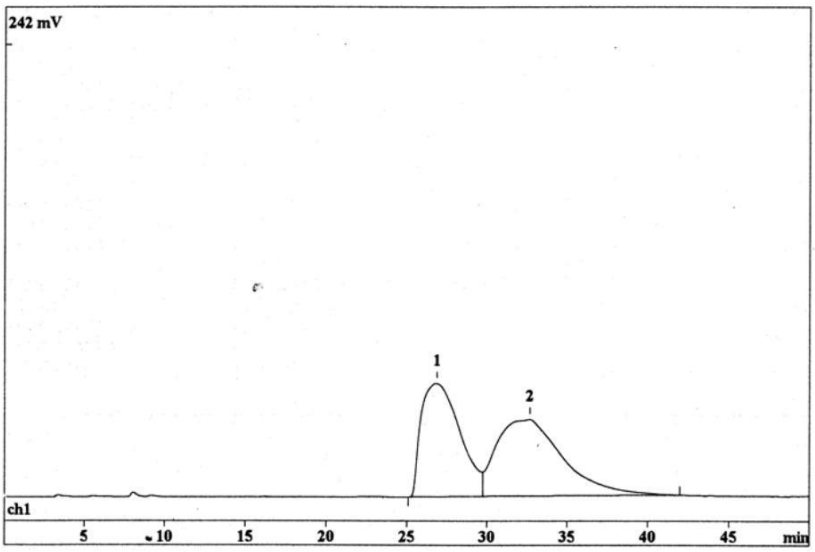
No	Retention min	Area mV*sec	Area %	Name
1	22.44	3679.375	49.74	
2	26.34	3717.960	50.26	
2	60.00	7397.336	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

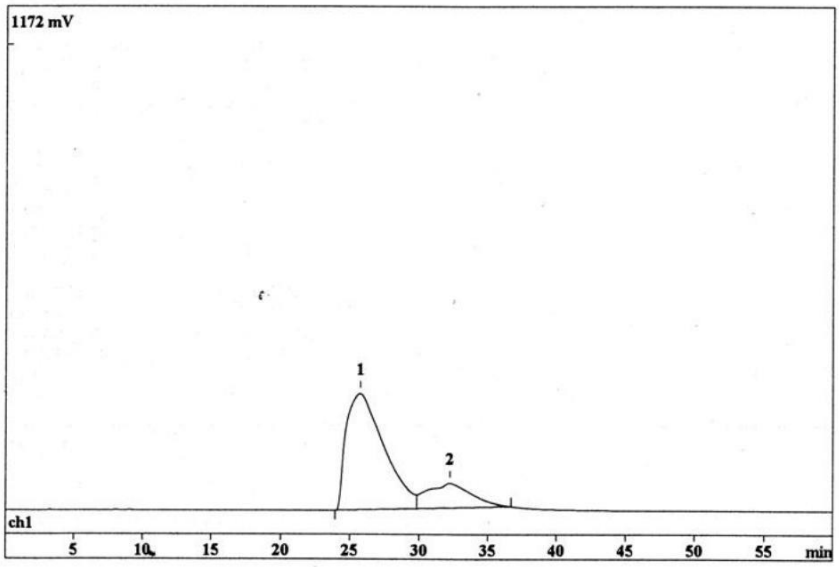
No	Retention min	Area mV*sec	Area %	Name
1	22.76	1526.629	14.33	
2	26.78	9127.052	85.67	
2	60.00	10653.681	100.00	

3e Chiralpak AS-H column (hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

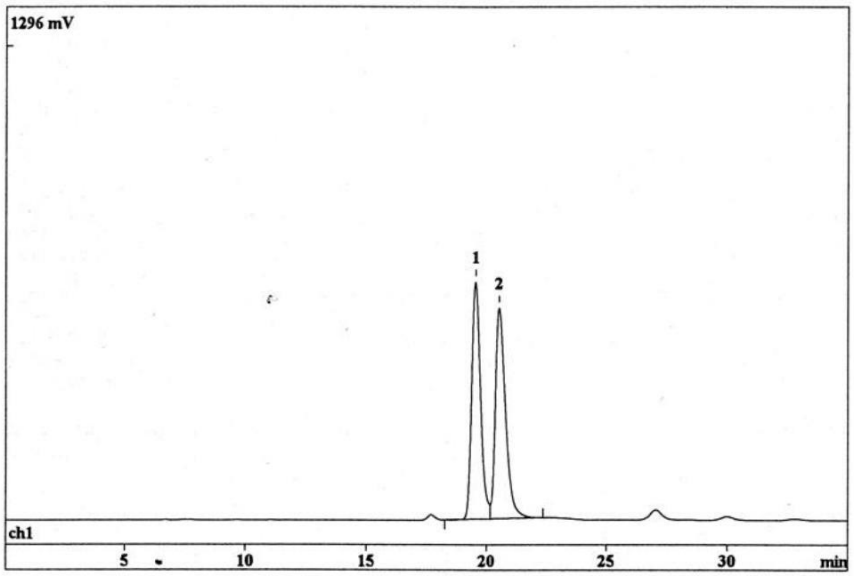
No	Retention min	Area mV*sec	Area %	Name
1	26.84	9661.119	46.16	
2	32.68	11267.904	53.84	
2	50.00	20929.023	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

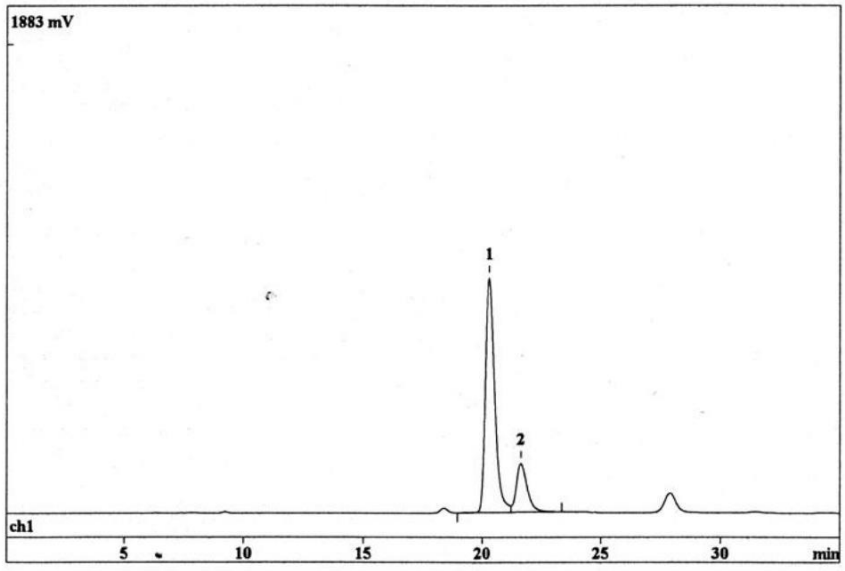
No	Retention min	Area mV*sec	Area %	Name
1	25.70	52823.561	79.65	
2	32.21	13498.480	20.35	
2	60.00	66322.041	100.00	

3f Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

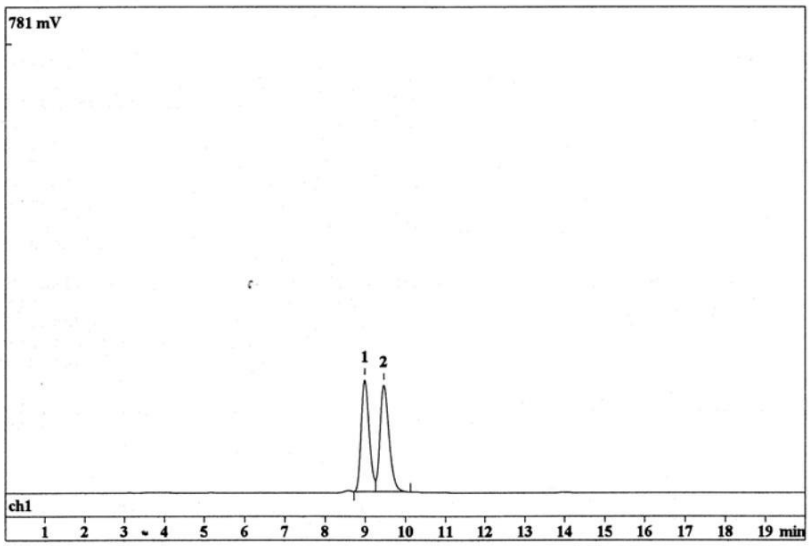
No	Retention min	Area mV*sec	Area %	Name
1	19.52	15884.840	49.42	
2	20.52	16260.020	50.58	
2	35.00	32144.860	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

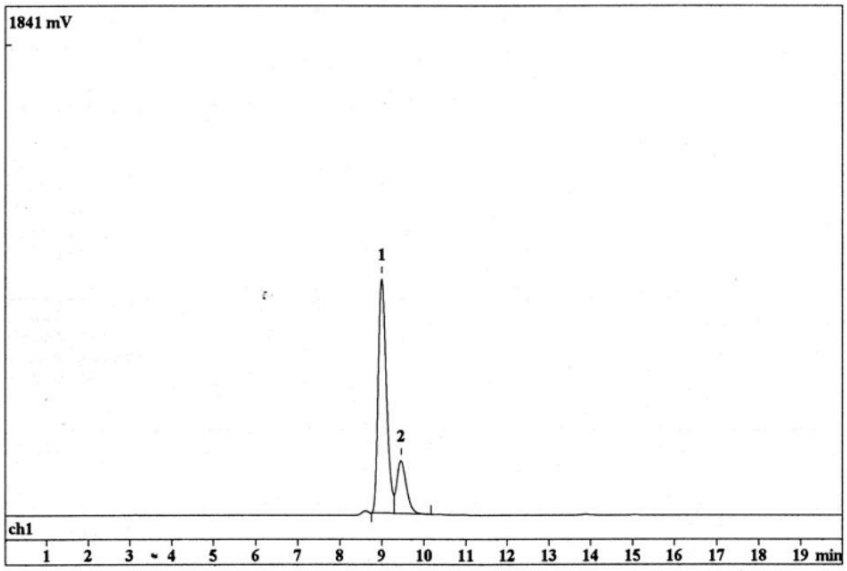
No	Retention min	Area mV*sec	Area %	Name
1	20.28	24939.383	80.47	
2	21.62	6054.238	19.53	
2	35.00	30993.621	100.00	

3g Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

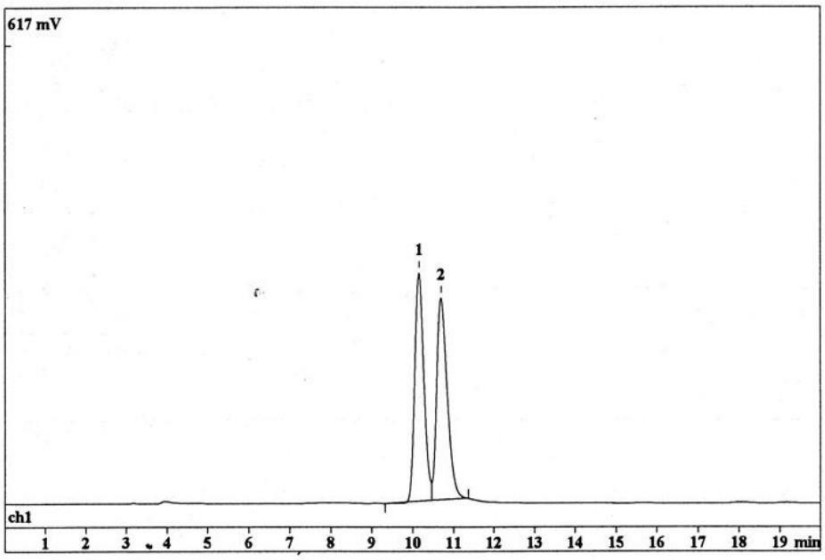
No	Retention min	Area mV*sec	Area %	Name
1	8.98	2563.348	47.97	
2	9.46	2780.398	52.03	
2	20.00	5343.747	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

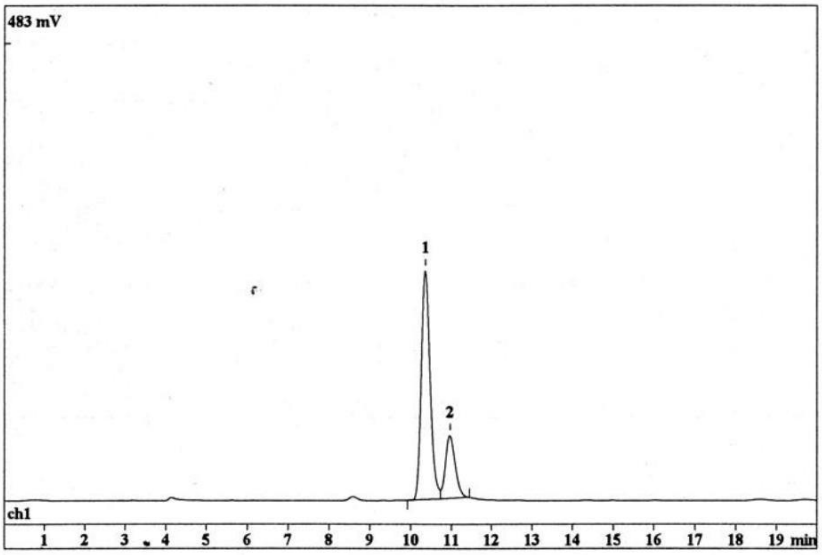
No	Retention min	Area mV*sec	Area %	Name
1	8.99	11923.019	78.92	
2	9.45	3184.687	21.08	
2	20.00	15107.707	100.00	

3h Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

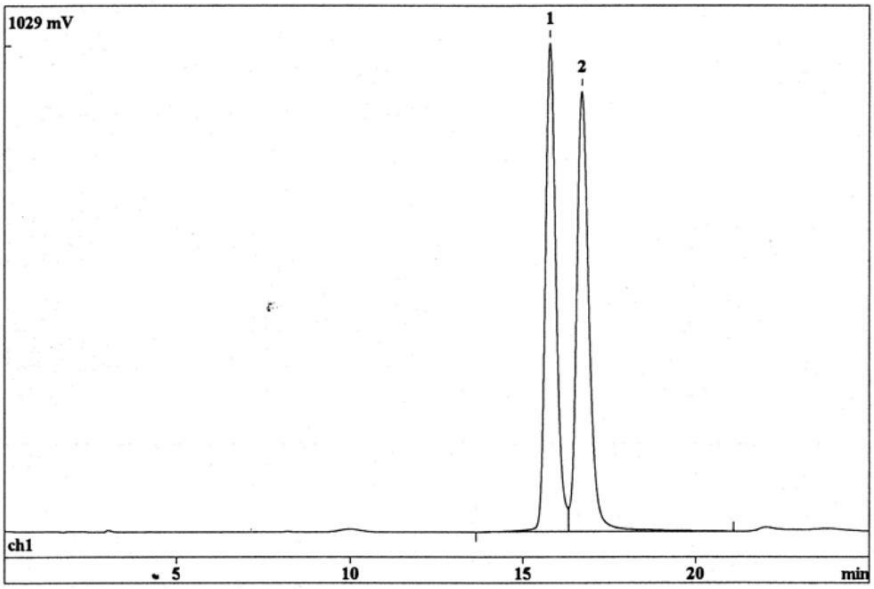
No	Retention min	Area mV*sec	Area %	Name
1	10.15	4535.545	49.21	
2	10.69	4680.663	50.79	
2	20.00	9216.208	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

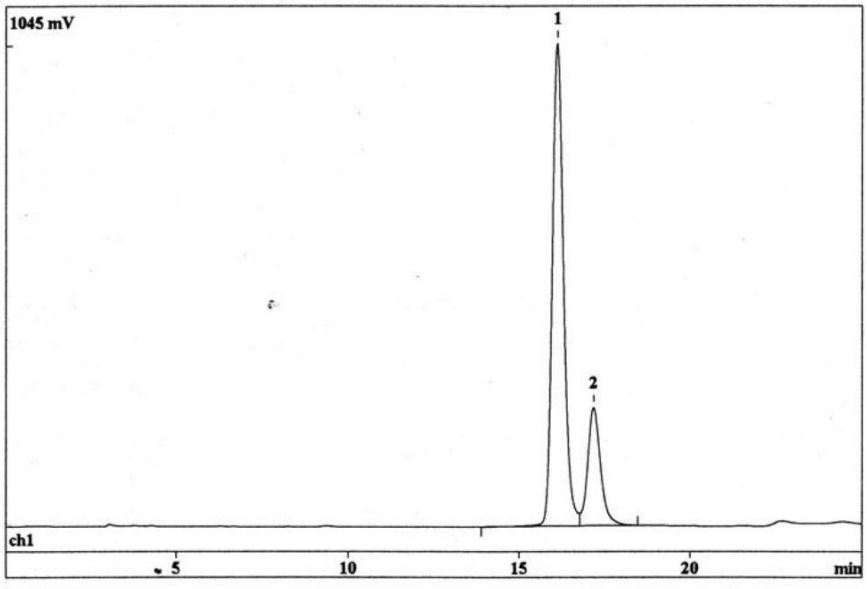
No	Retention min	Area mV*sec	Area %	Name
1	10.36	3482.494	76.44	
2	10.96	1073.095	23.56	
2	20.00	4555.589	100.00	

3i Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

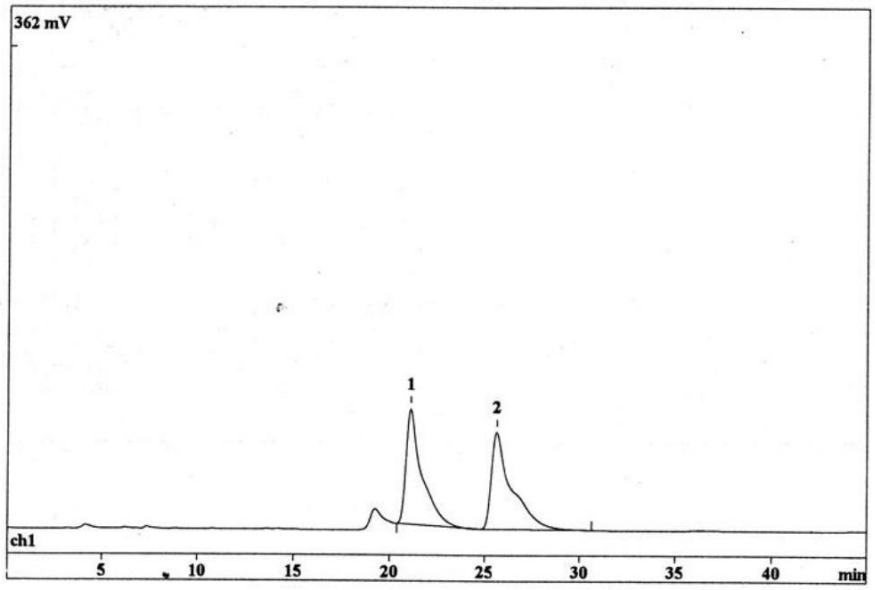
No	Retention min	Area mV*sec	Area %	Name
1	15.79	21269.518	48.84	
2	16.71	22283.514	51.16	
2	25.00	43553.031	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

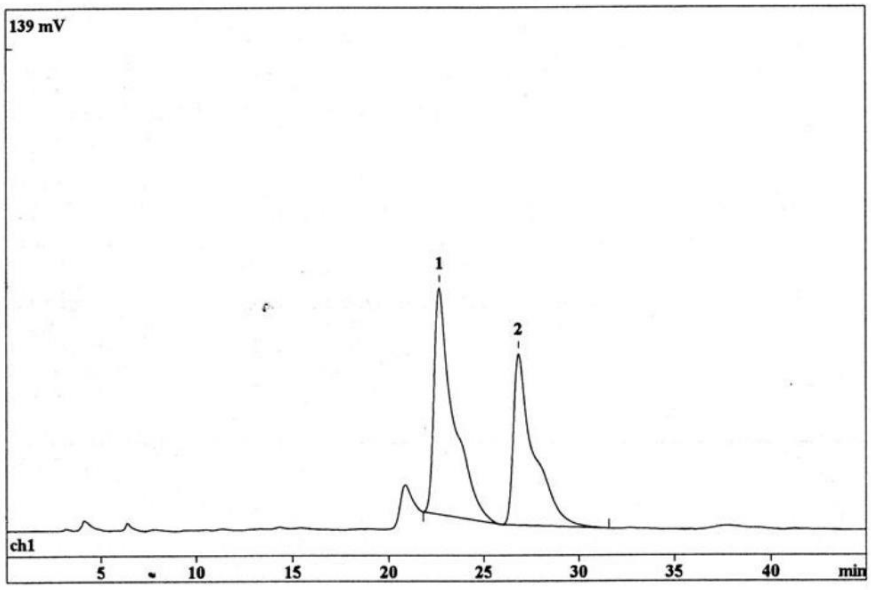
No	Retention min	Area mV*sec	Area %	Name
1	16.11	22947.105	78.00	
2	17.18	6470.962	22.00	
2	25.00	29418.067	100.00	

3j Chiralpak AD-H column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

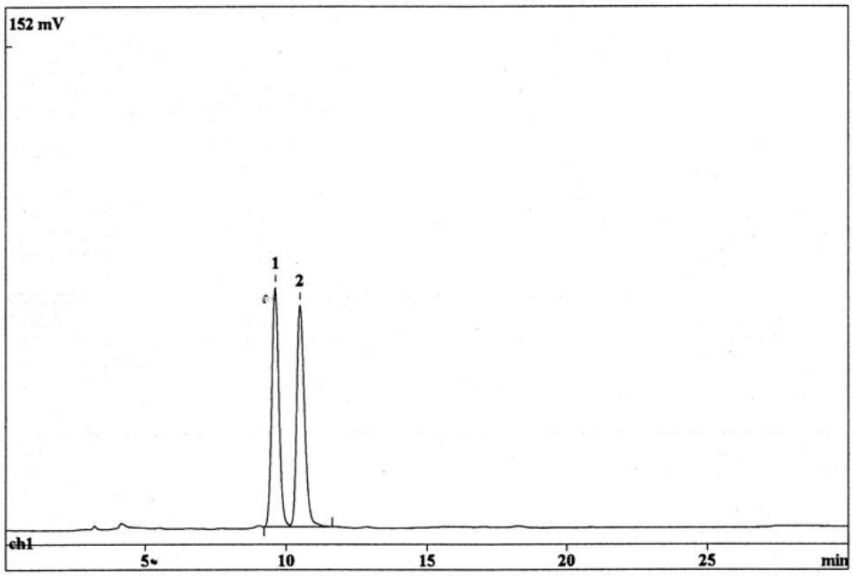
No	Retention min	Area mV*sec	Area %	Name
1	21.09	4780.142	47.71	
2	25.60	5238.868	52.29	
2	45.00	10019.010	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

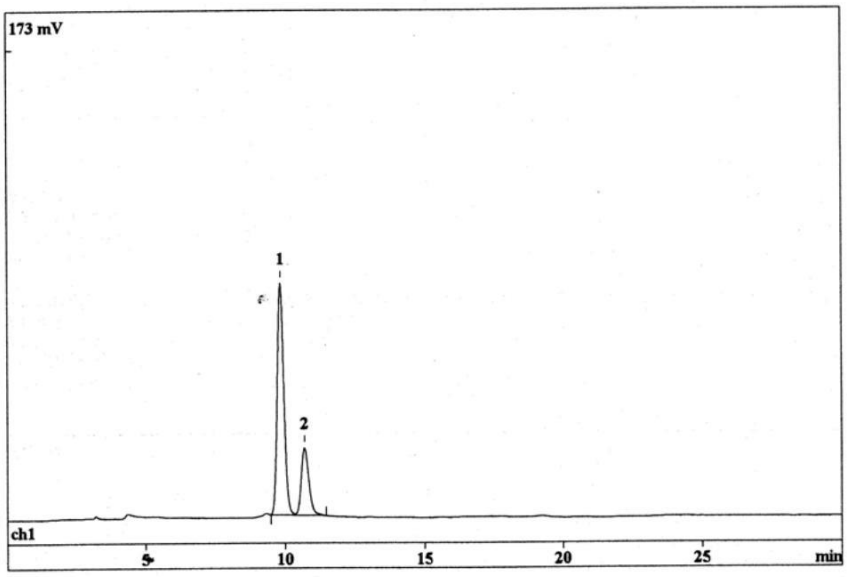
No	Retention min	Area mV*sec	Area %	Name
1	22.66	4369.451	55.67	
2	26.84	3479.647	44.33	
2	45.00	7849.097	100.00	

3k Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

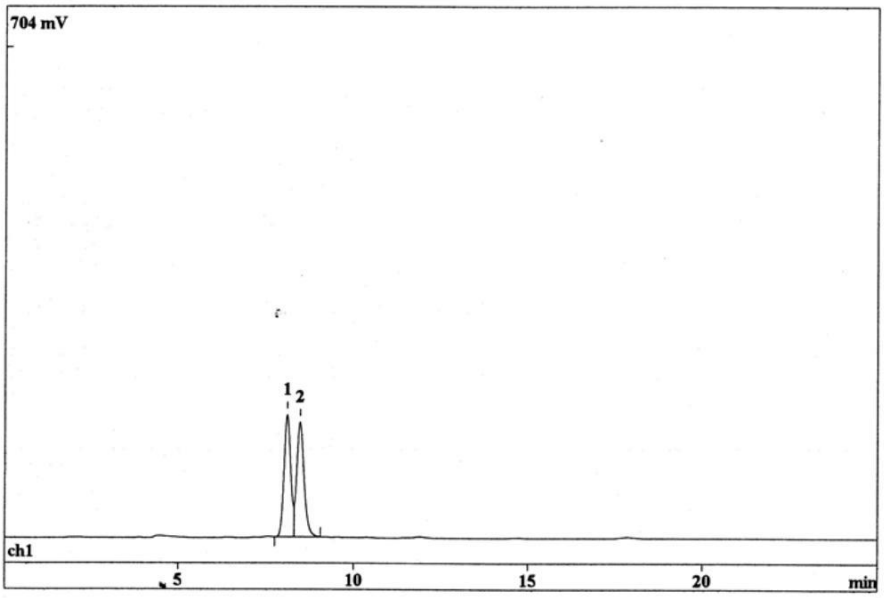
No	Retention min	Area mV*sec	Area %	Name
1	9.62	1272.844	49.72	
2	10.49	1286.978	50.28	
2	30.00	2559.822	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

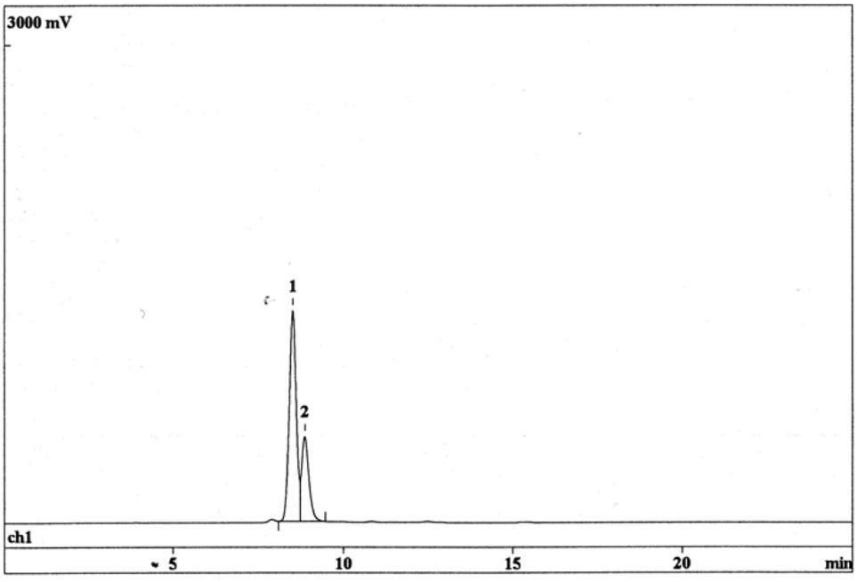
No	Retention min	Area mV*sec	Area %	Name
1	9.84	1330.326	74.90	
2	10.69	445.706	25.10	
2	30.00	1776.032	100.00	

3l Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 99:1, flow rate 0.8 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

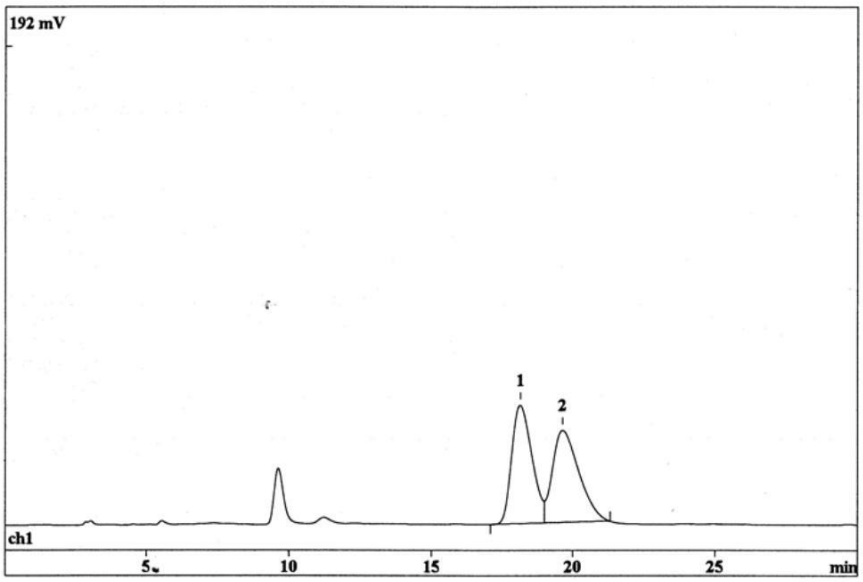
No	Retention min	Area mV*sec	Area %	Name
1	8.11	2190.316	48.62	
2	8.47	2314.376	51.38	
2	25.00	4504.692	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

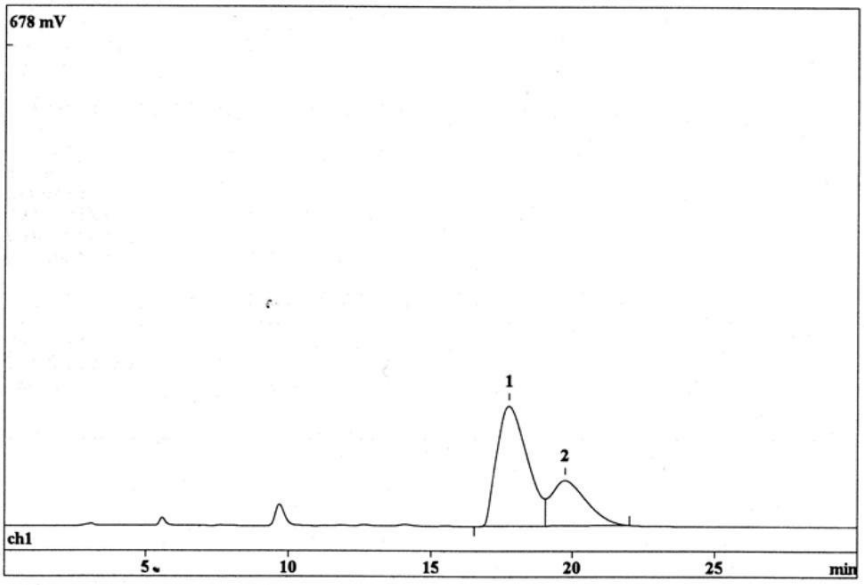
No	Retention min	Area mV*sec	Area %	Name
1	8.52	17851.855	70.40	
2	8.86	7507.122	29.60	
2	25.00	25358.976	100.00	

3m Chiracel OJ column (hexane/i-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

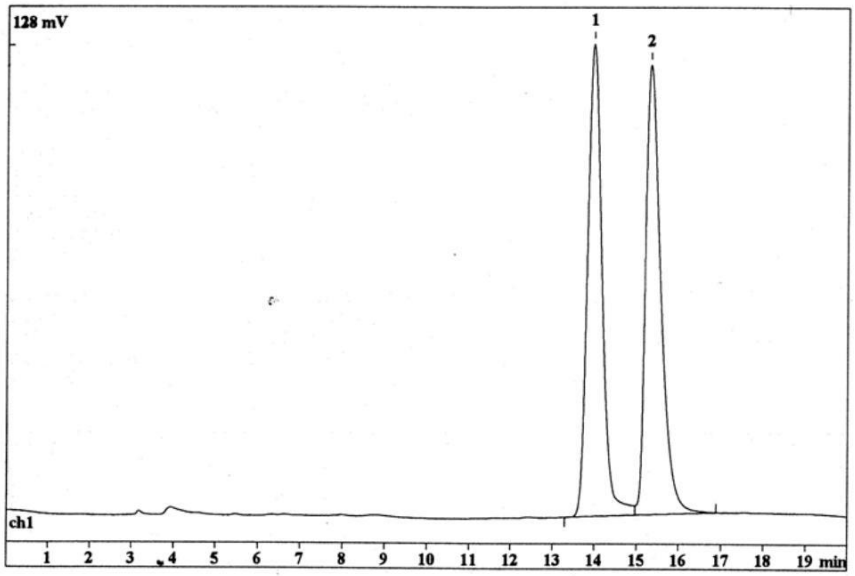
No	Retention min	Area mV*sec	Area %	Name
1	18.14	2251.551	49.56	
2	19.64	2291.519	50.44	
2	30.00	4543.070	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

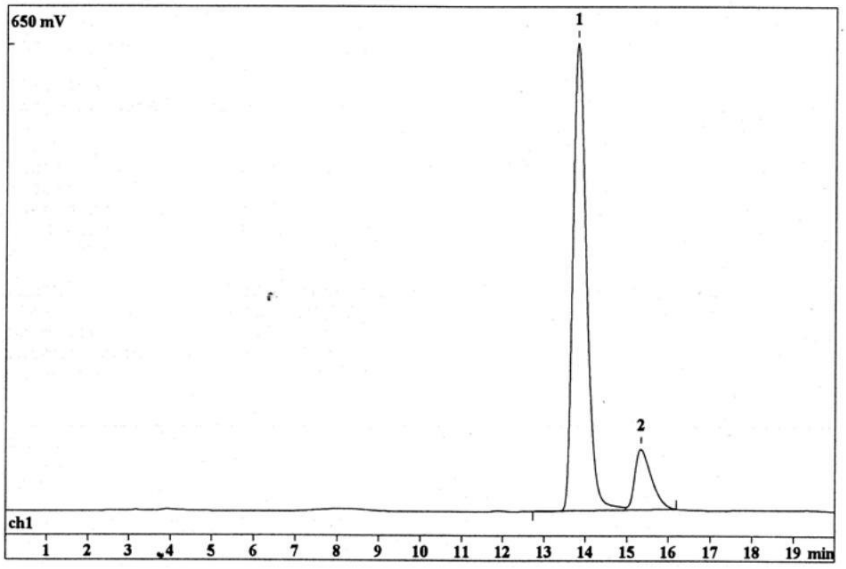
No	Retention min	Area mV*sec	Area %	Name
1	17.75	12172.342	69.43	
2	19.74	5358.391	30.57	
2	30.00	17530.733	100.00	

3n Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 97:3, flow rate 1.0 mL/min, λ = 254



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

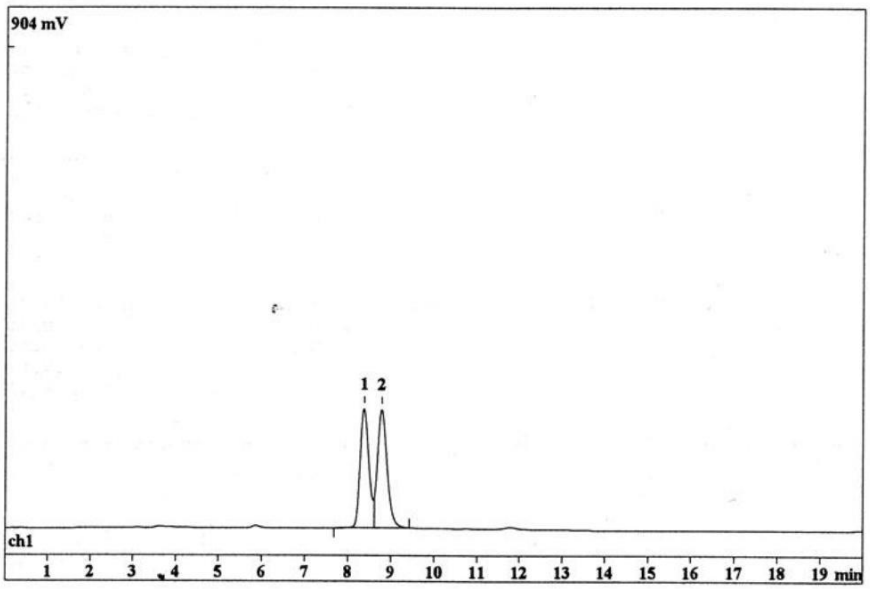
No	Retention min	Area mV*sec	Area %	Name
1	13.96	2922.778	49.86	
2	15.31	2939.151	50.14	
2	20.00	5861.928	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

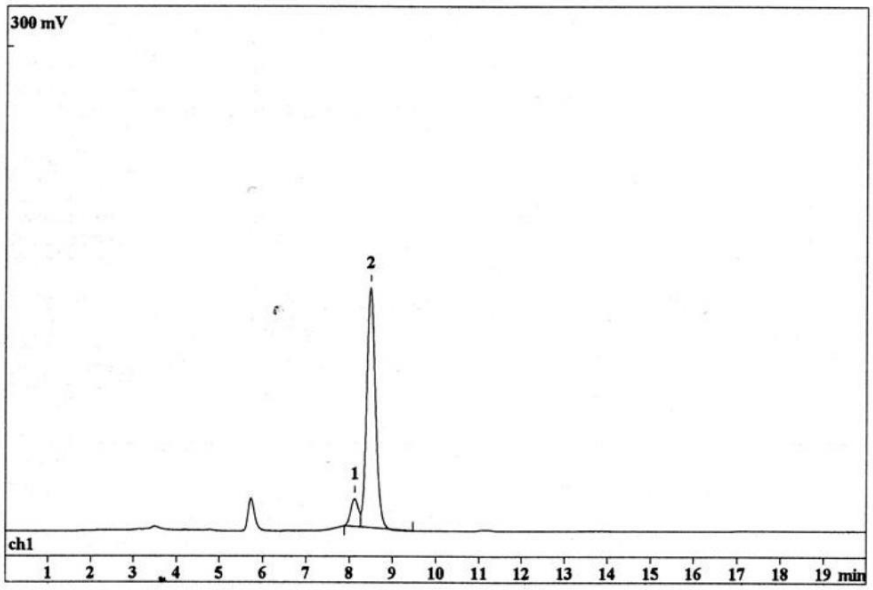
No	Retention min	Area mV*sec	Area %	Name
1	13.79	14167.666	86.23	
2	15.33	2262.218	13.77	
2	20.00	16429.884	100.00	

3o Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

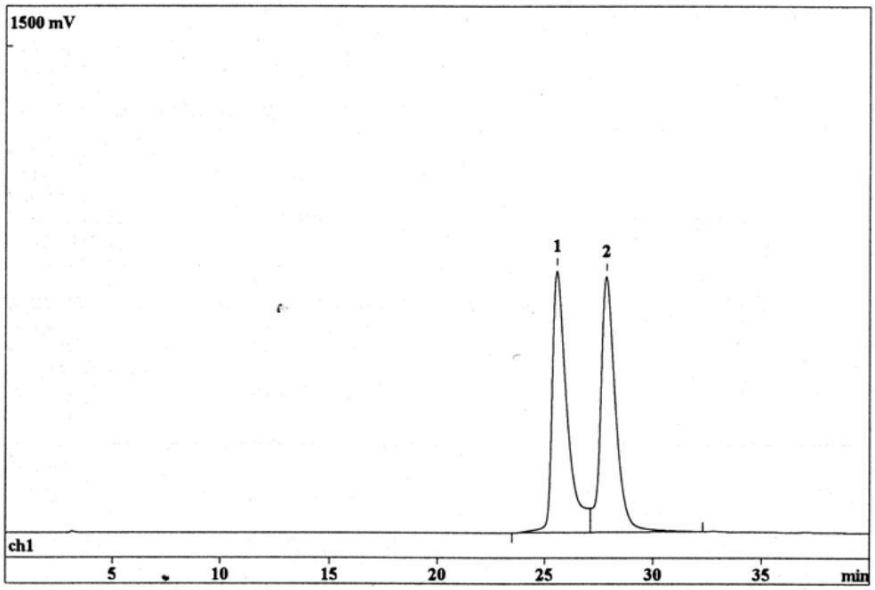
No	Retention min	Area mV*sec	Area %	Name
1	8.36	3040.357	48.26	
2	8.77	3260.144	51.74	
2	20.00	6300.502	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

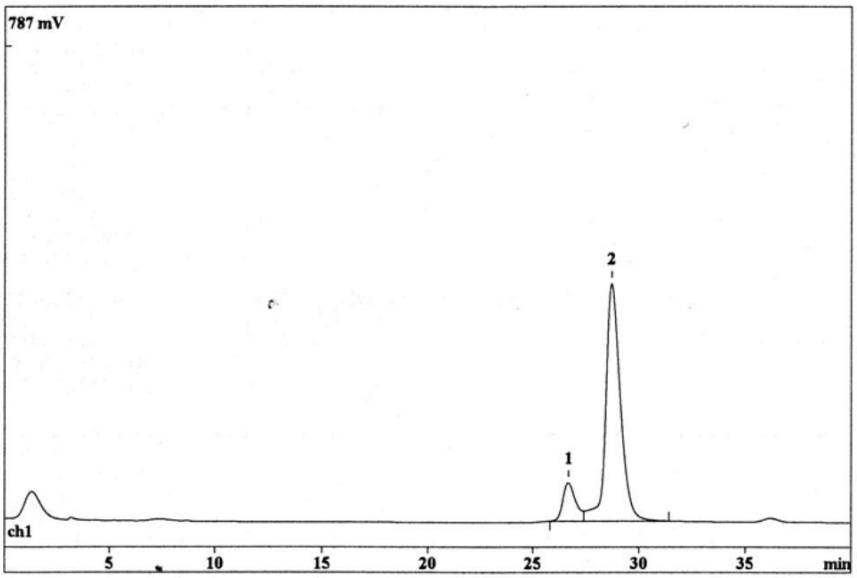
No	Retention min	Area mV*sec	Area %	Name
1	8.12	200.978	9.19	
2	8.48	1986.869	90.81	
2	20.00	2187.846	100.00	

3p Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

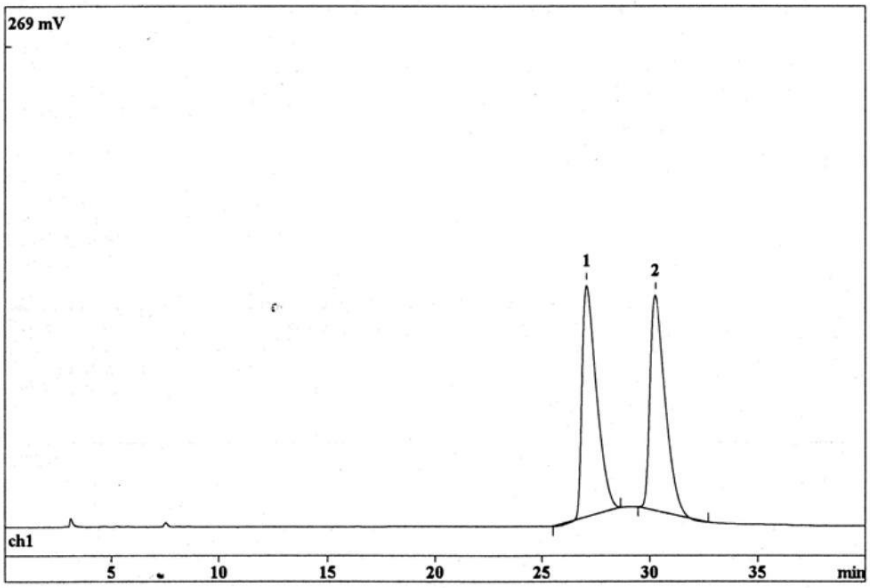
No	Retention min	Area mV*sec	Area %	Name
1	25.55	37049.010	50.67	
2	27.84	36064.611	49.33	
2	40.00	73113.621	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

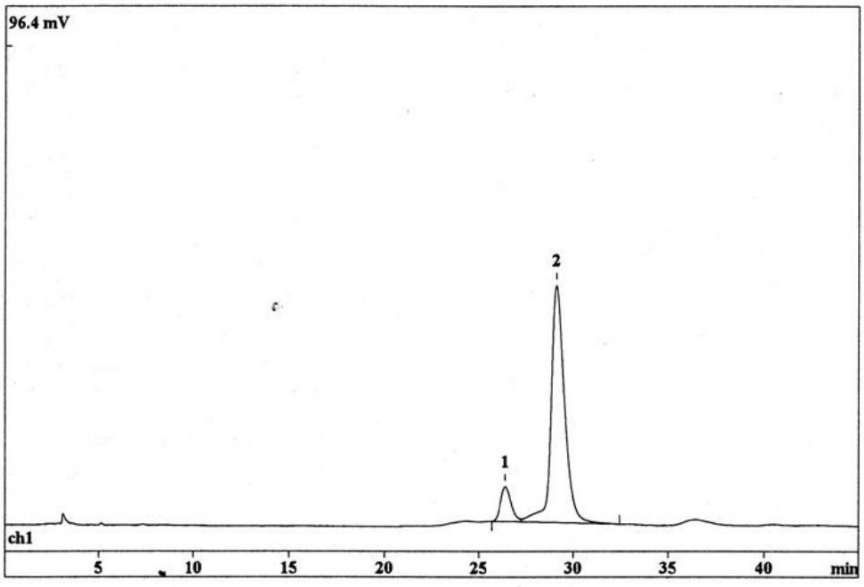
No	Retention min	Area mV*sec	Area %	Name
1	26.67	2535.590	12.38	
2	28.71	17938.440	87.62	
2	40.00	20474.030	100.00	

3q Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

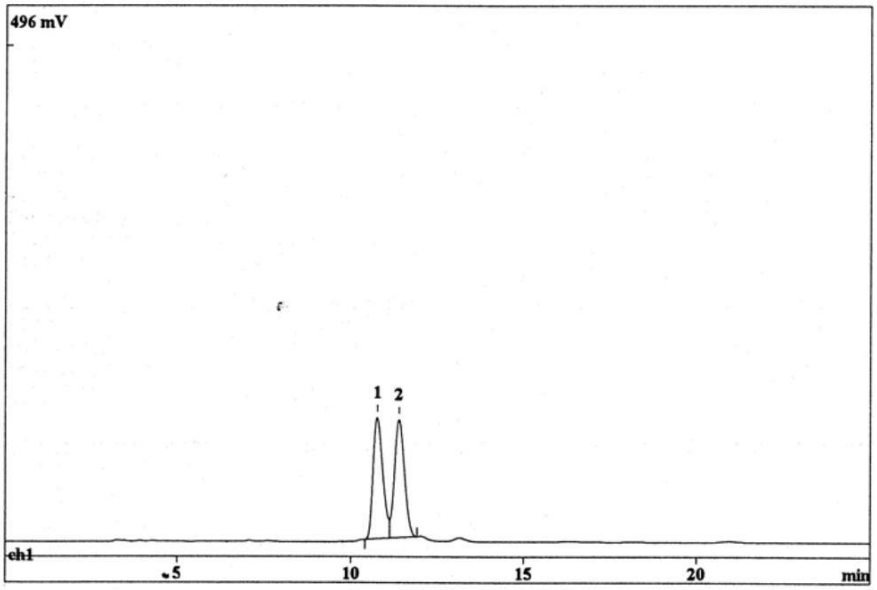
No	Retention min	Area mV*sec	Area %	Name
1	27.07	5693.532	50.36	
2	30.25	5611.176	49.64	
2	40.00	11304.708	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

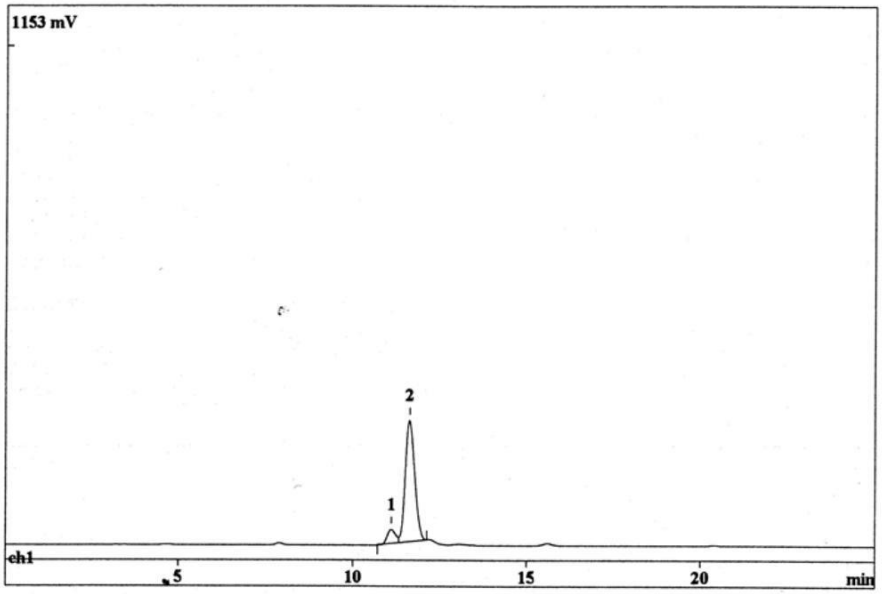
No	Retention min	Area mV*sec	Area %	Name
1	26.39	263.490	10.40	
2	29.10	2271.190	89.60	
2	45.00	2534.680	100.00	

3r Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

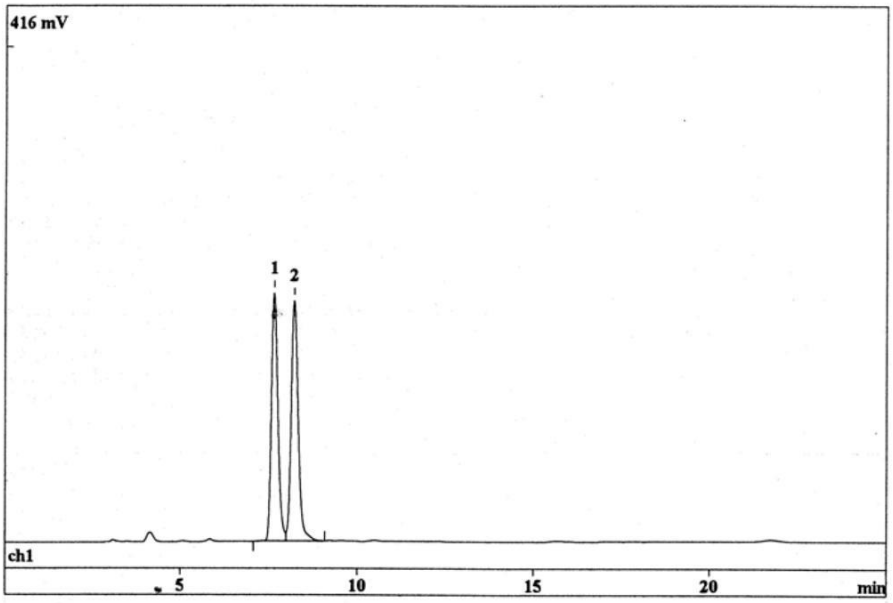
No	Retention min	Area mV*sec	Area %	Name
1	10.75	2281.441	49.67	
2	11.38	2311.383	50.33	
2	25.00	4592.824	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

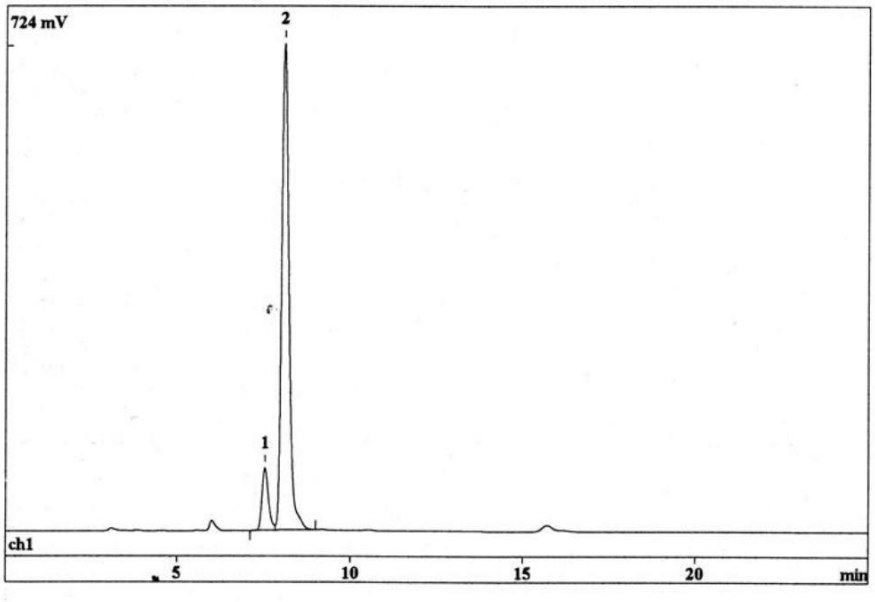
No	Retention min	Area mV*sec	Area %	Name
1	11.09	515.440	9.11	
2	11.61	5140.526	90.89	
2	25.00	5655.966	100.00	

3s Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

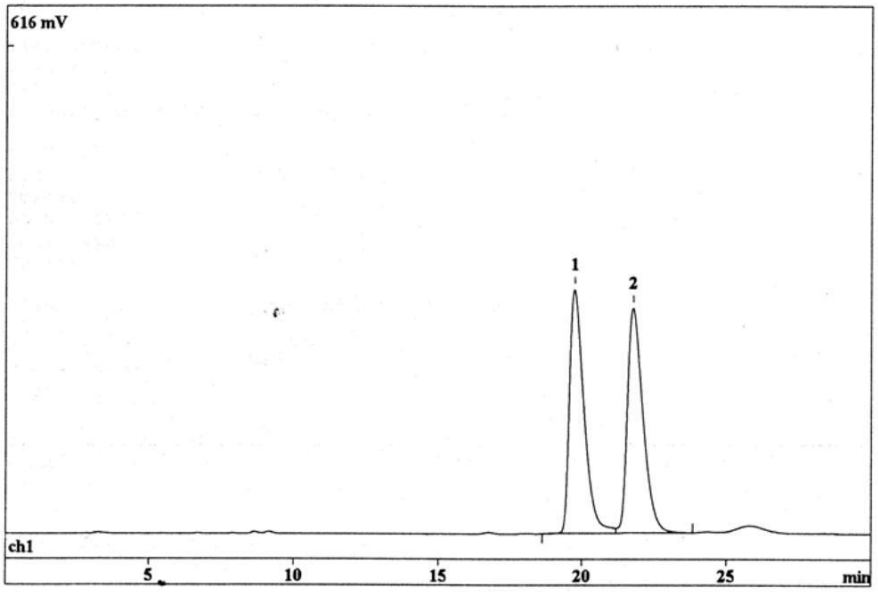
No	Retention min	Area mV*sec	Area %	Name
1	7.65	2511.328	48.86	
2	8.22	2628.302	51.14	
2	25.00	5139.630	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

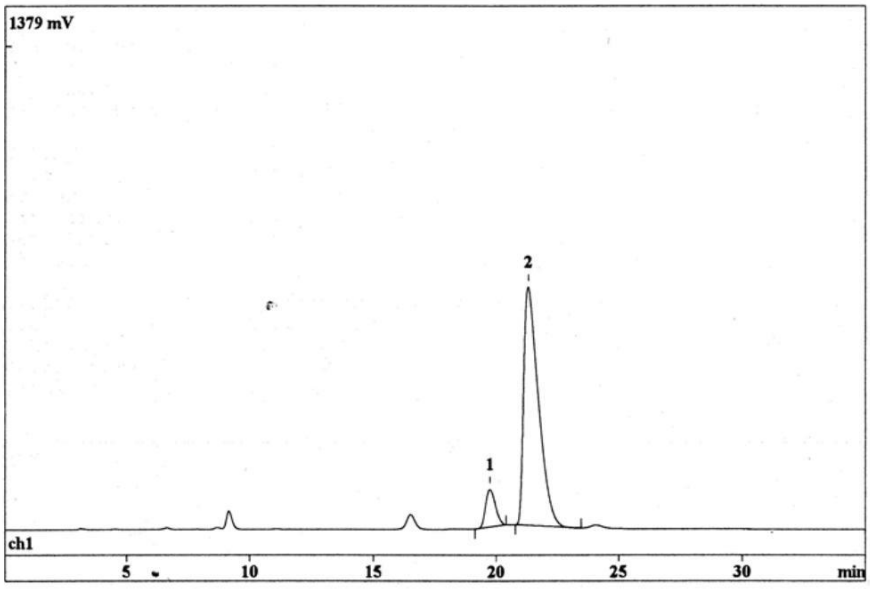
No	Retention min	Area mV*sec	Area %	Name
1	7.54	1142.666	10.24	
2	8.08	10021.491	89.76	
2	25.00	11164.157	100.00	

3t Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

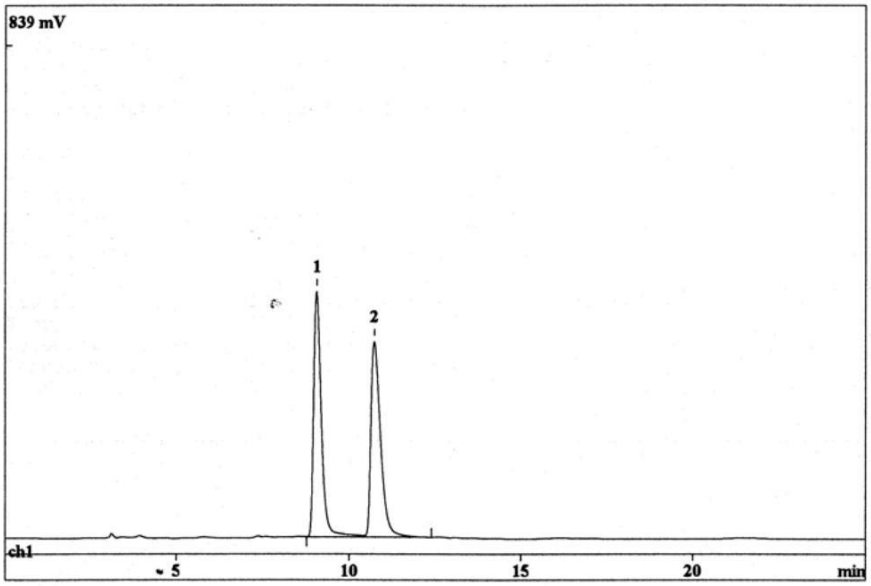
No	Retention min	Area mV*sec	Area %	Name
1	19.73	10383.886	50.38	
2	21.76	10226.798	49.62	
2	30.00	20610.684	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

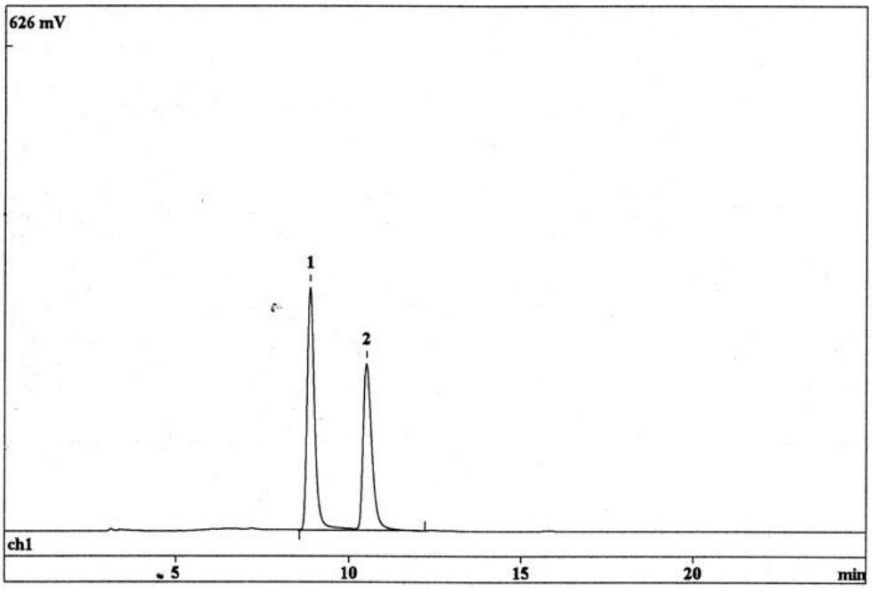
No	Retention min	Area mV*sec	Area %	Name
1	19.73	2901.050	9.71	
2	21.30	26970.880	90.29	
2	35.00	29871.931	100.00	

5a Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

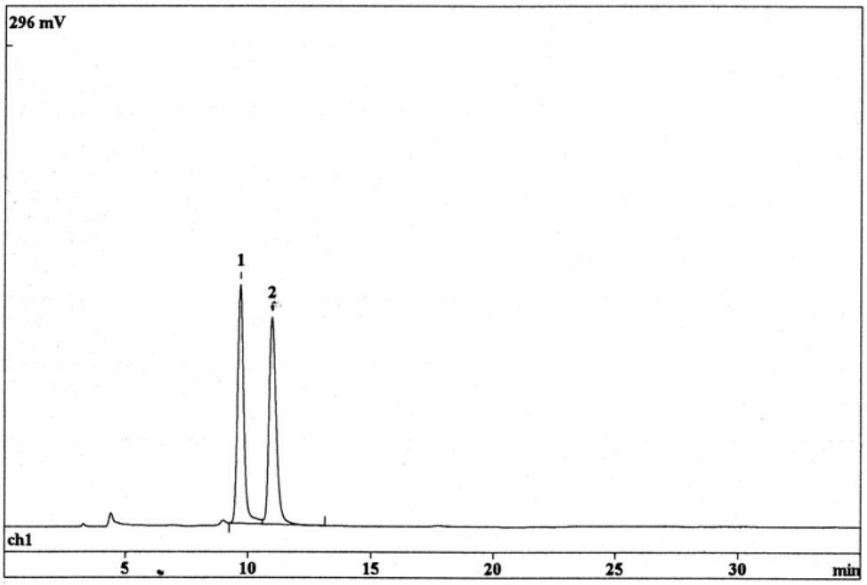
No	Retention min	Area mV*sec	Area %	Name
1	9.06	6248.668	49.98	
2	10.73	6252.756	50.02	
2	25.00	12501.424	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

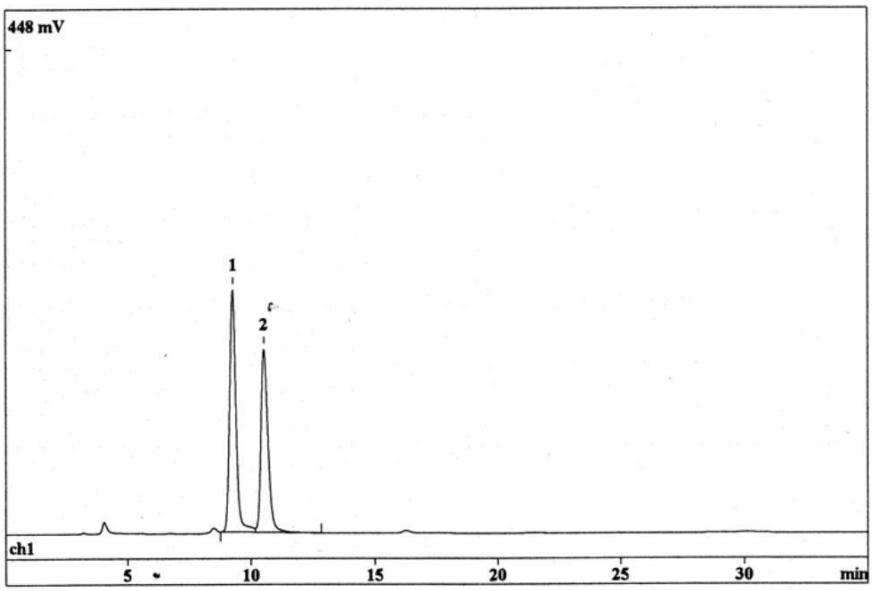
No	Retention min	Area mV*sec	Area %	Name
1	8.87	4463.838	55.33	
2	10.50	3604.106	44.67	
2	25.00	8067.944	100.00	

5b Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

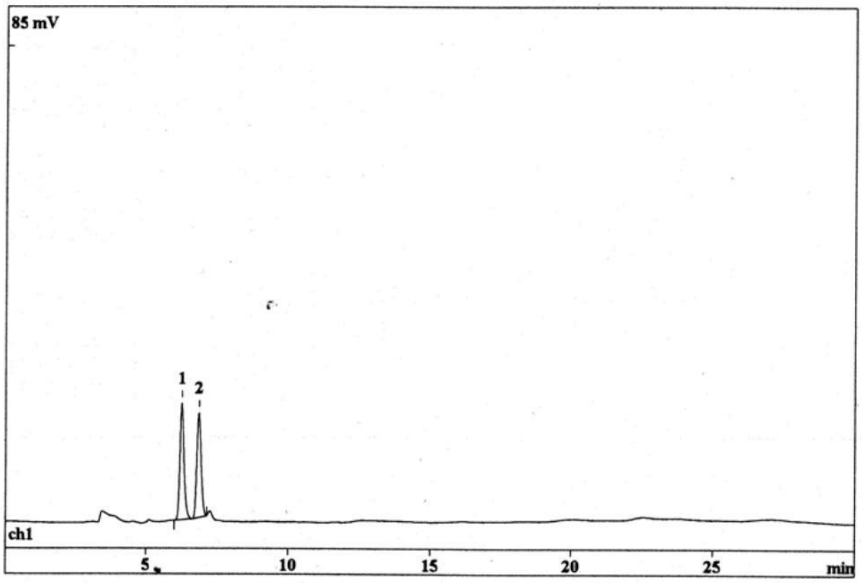
No	Retention min	Area mV*sec	Area %	Name
1	9.68	2448.689	50.01	
2	10.96	2448.121	49.99	
2	35.00	4896.810	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

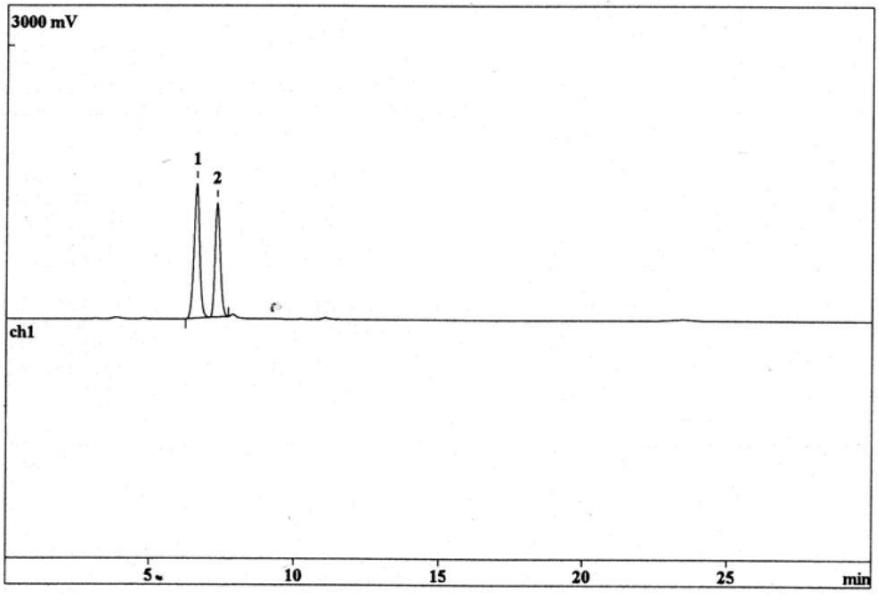
No	Retention min	Area mV*sec	Area %	Name
1	9.26	3791.207	54.37	
2	10.52	3181.133	45.63	
2	35.00	6972.340	100.00	

5c Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

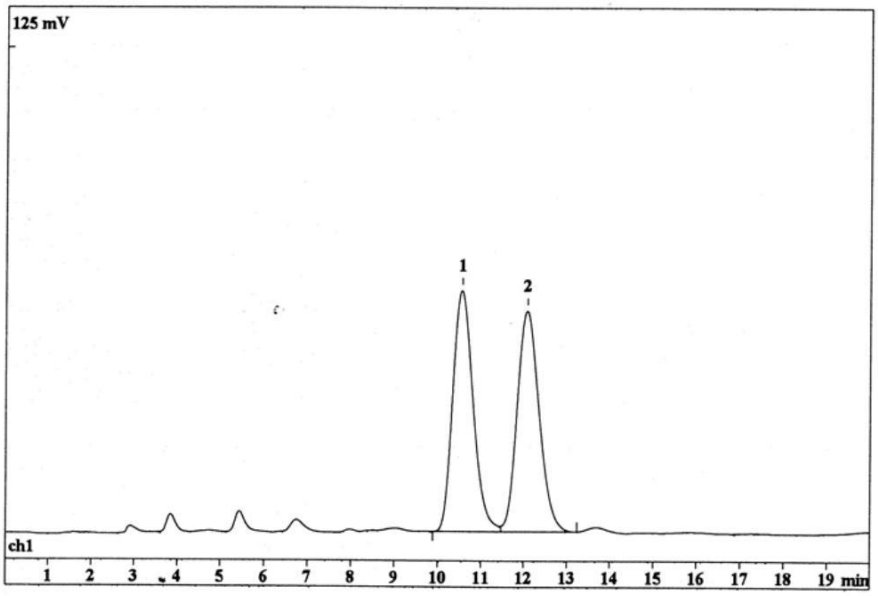
No	Retention min	Area mV*sec	Area %	Name
1	6.26	208.127	52.64	
2	6.87	187.255	47.36	
2	30.00	395.382	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

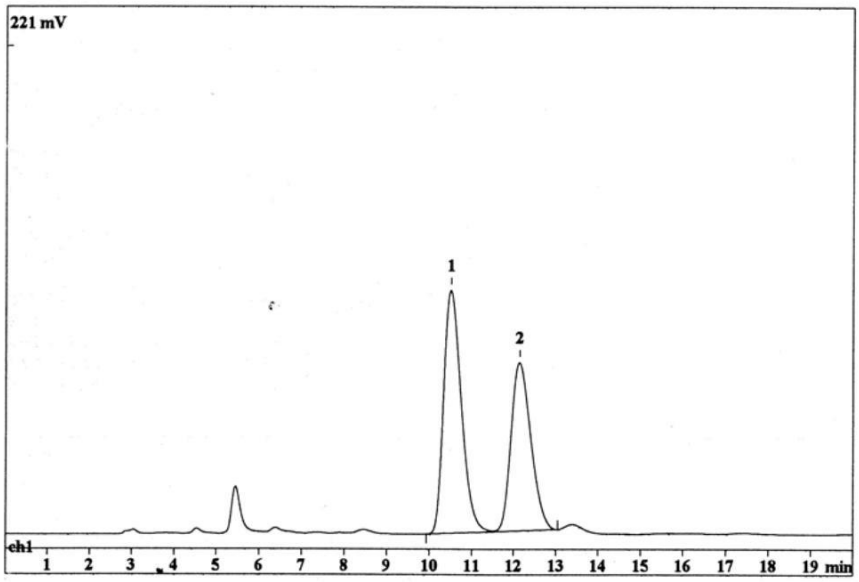
No	Retention min	Area mV*sec	Area %	Name
1	6.64	10672.189	55.82	
2	7.34	8448.441	44.18	
2	30.00	19120.630	100.00	

5d Chiracel OJ column (hexane/i-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

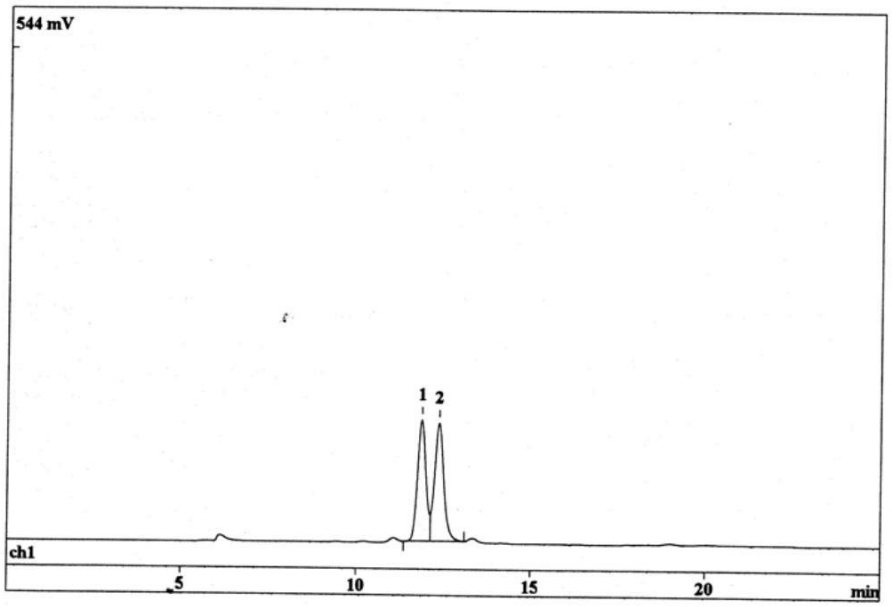
No	Retention min	Area mV*sec	Area %	Name
1	10.54	1945.128	50.28	
2	12.07	1923.552	49.72	
2	20.00	3868.680	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

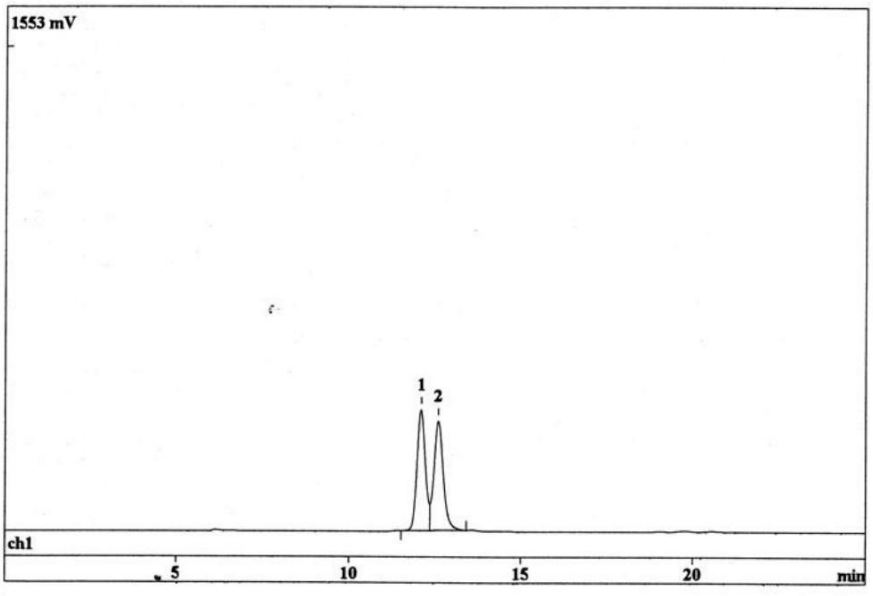
No	Retention min	Area mV*sec	Area %	Name
1	10.50	3130.037	56.27	
2	12.14	2432.306	43.73	
2	20.00	5562.344	100.00	

5e Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 98:2, flow rate 0.5 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

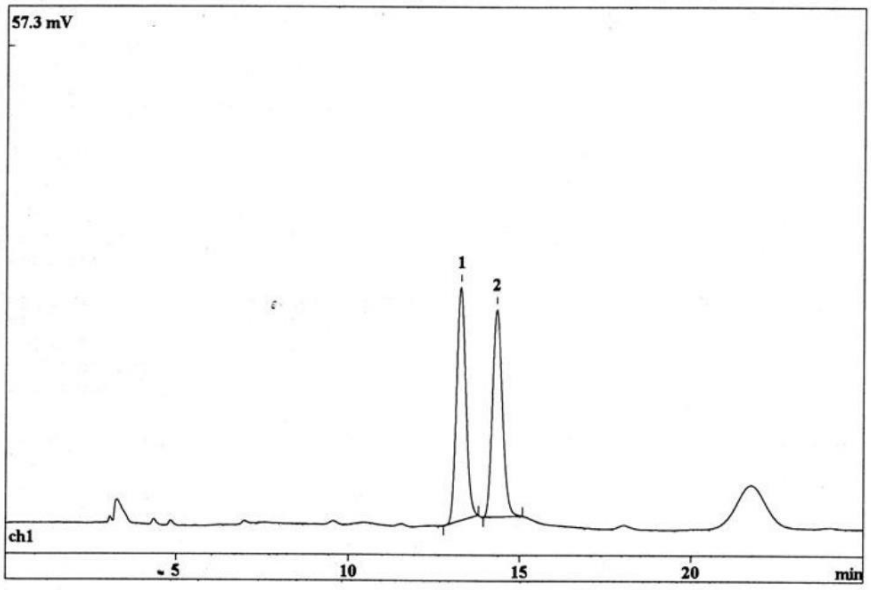
No	Retention min	Area mV*sec	Area %	Name
1	11.85	2120.312	47.88	
2	12.35	2308.403	52.12	
2	25.00	4428.715	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

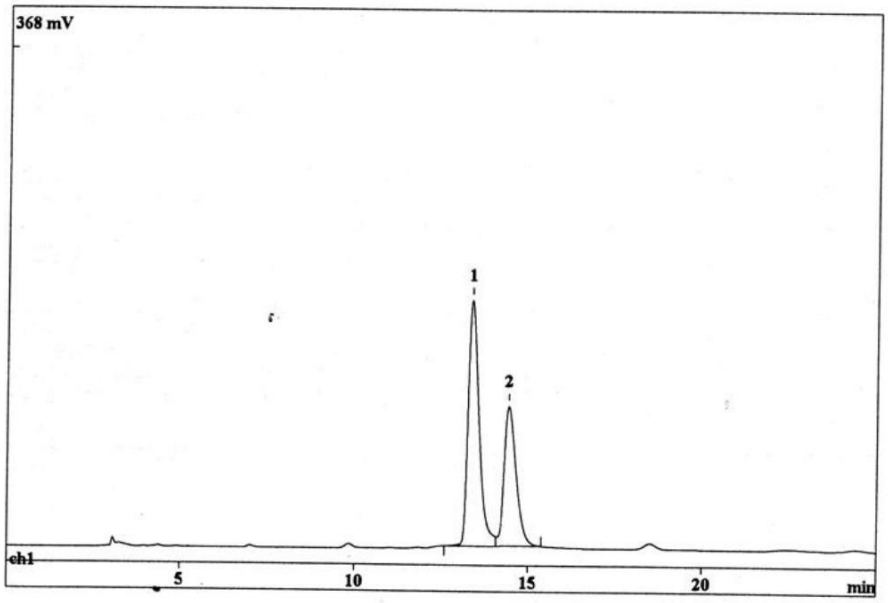
No	Retention min	Area mV*sec	Area %	Name
1	12.08	6229.863	49.45	
2	12.58	6369.607	50.55	
2	25.00	12599.471	100.00	

5f Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

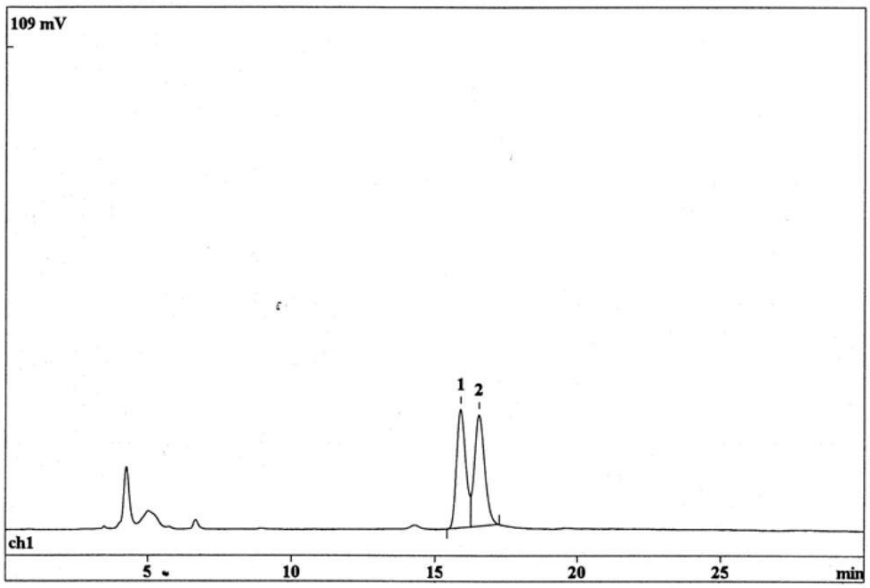
No	Retention min	Area mV*sec	Area %	Name
1	13.25	497.467	50.78	
2	14.31	482.198	49.22	
2	25.00	979.665	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

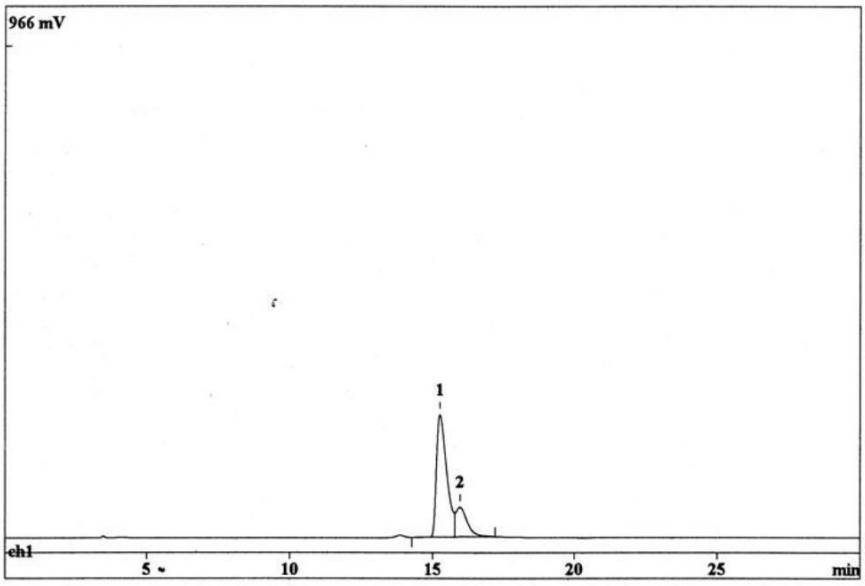
No	Retention min	Area mV*sec	Area %	Name
1	13.34	3868.175	61.21	
2	14.42	2451.523	38.79	
2	25.00	6319.698	100.00	

5g Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 99:1, flow rate 0.9 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

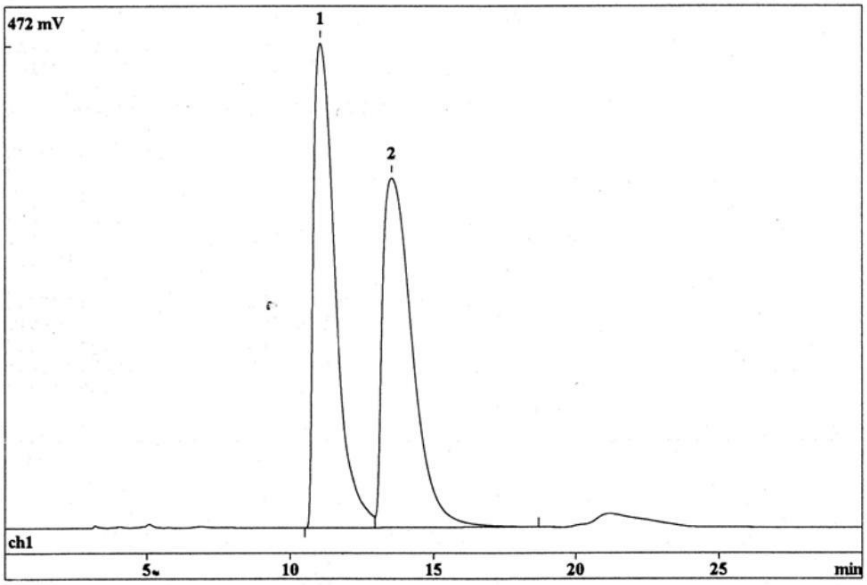
No	Retention min	Area mV*sec	Area %	Name
1	15.89	563.028	48.28	
2	16.54	603.126	51.72	
2	30.00	1166.154	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

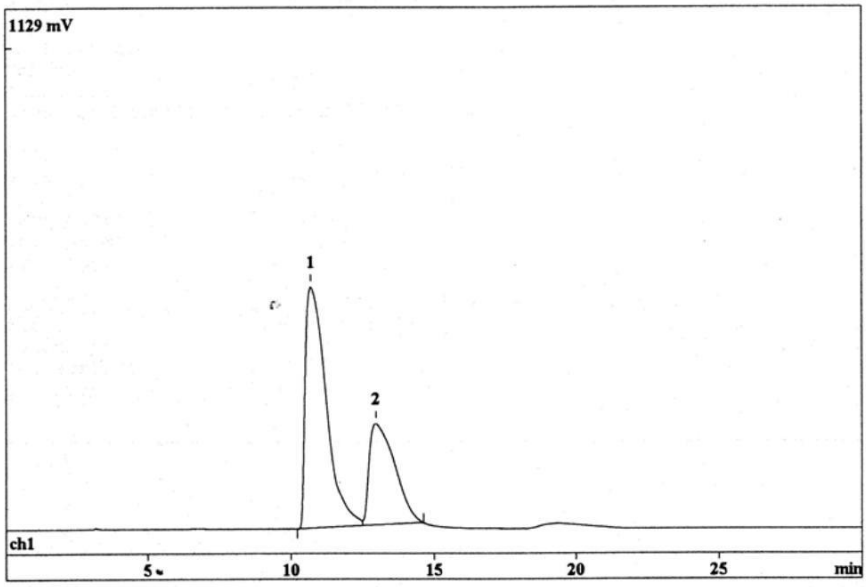
No	Retention min	Area mV*sec	Area %	Name
1	15.25	5823.926	78.24	
2	15.96	1619.973	21.76	
2	30.00	7443.899	100.00	

5h Chiralpak AS-H column (hexane/i-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

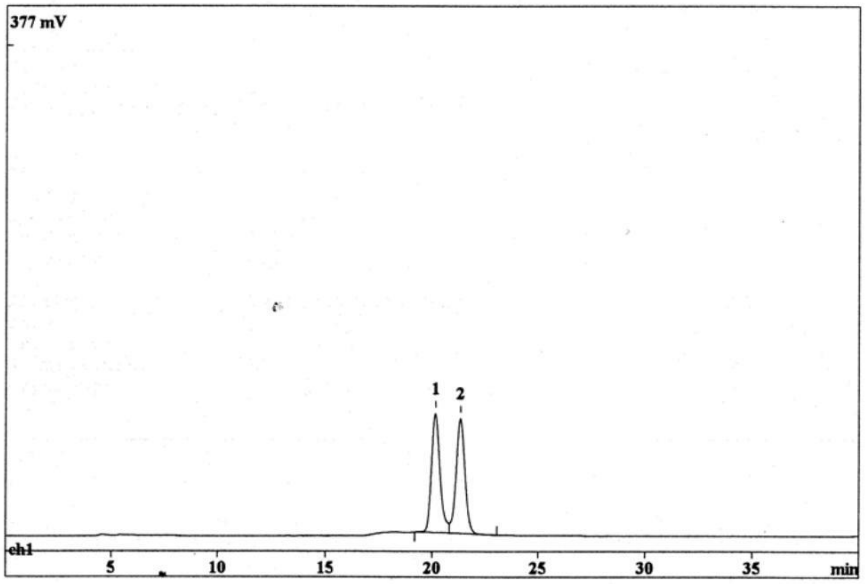
No	Retention min	Area mV*sec	Area %	Name
1	11.04	23638.981	50.07	
2	13.54	23570.854	49.93	
2	30.00	47209.835	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

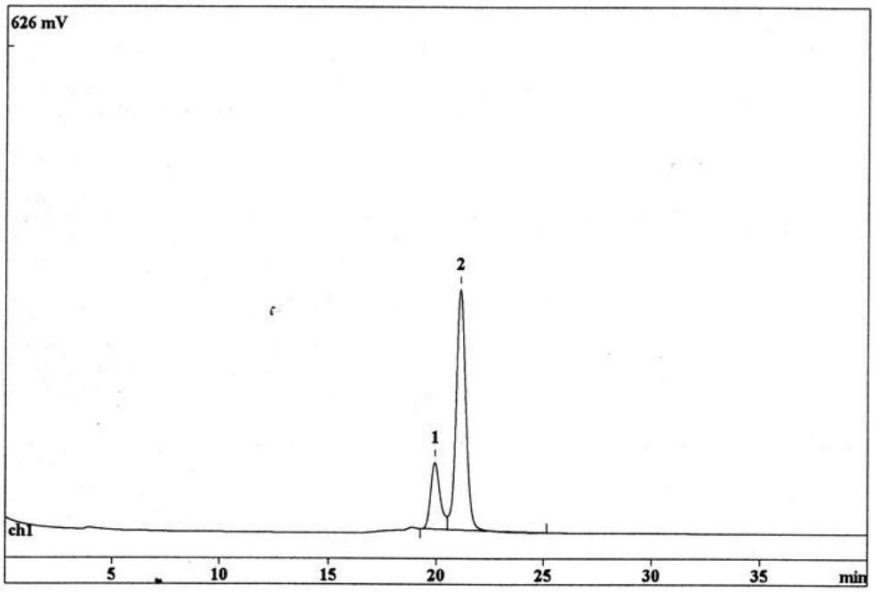
No	Retention min	Area mV*sec	Area %	Name
1	10.69	27186.995	65.95	
2	12.96	14035.027	34.05	
2	30.00	41222.022	100.00	

5i Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

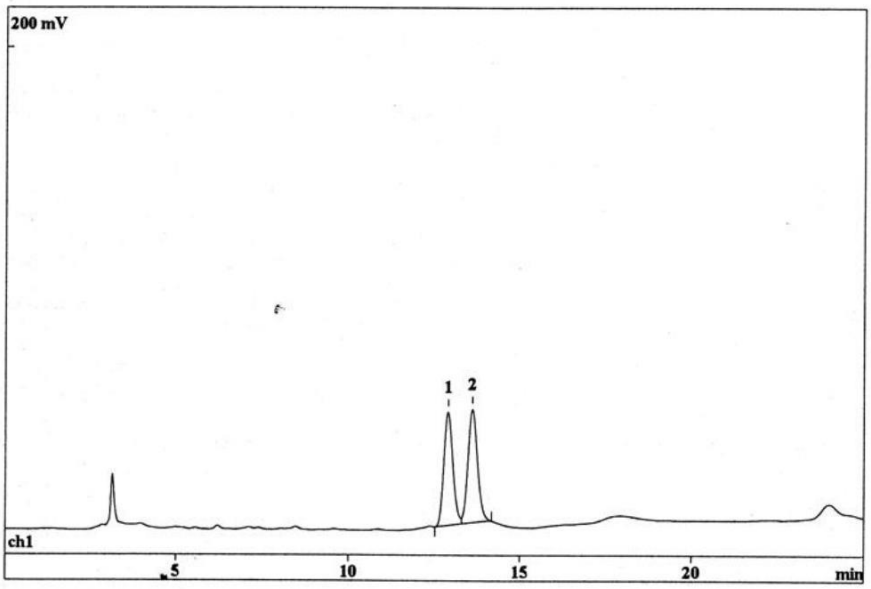
No	Retention min	Area mV*sec	Area %	Name
1	20.14	2522.059	50.16	
2	21.32	2506.382	49.84	
2	40.00	5028.441	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

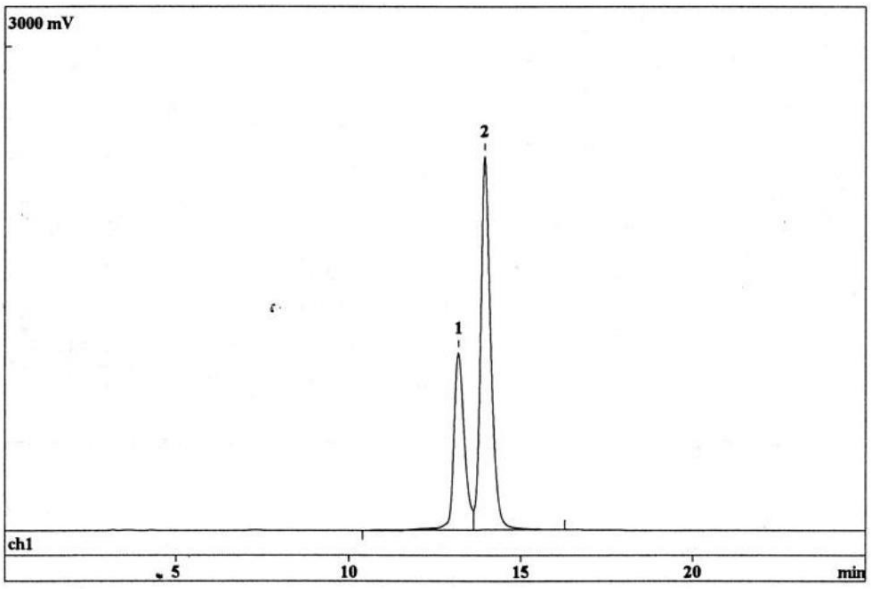
No	Retention min	Area mV*sec	Area %	Name
1	19.92	2519.792	21.51	
2	21.10	9196.004	78.49	
2	40.00	11715.796	100.00	

5j Phenomenex Lux Cellulose-1 column (hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

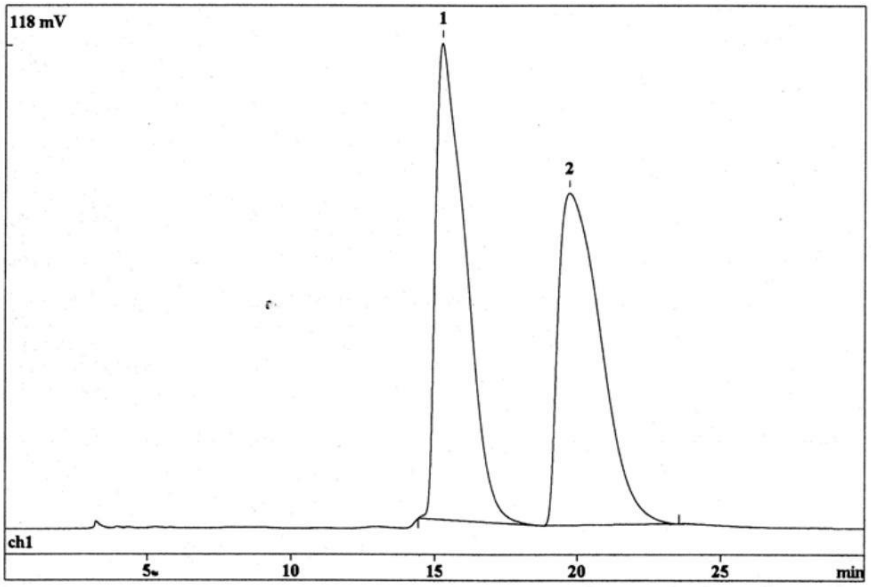
No	Retention min	Area mV*sec	Area %	Name
1	12.89	822.249	48.42	
2	13.60	875.792	51.58	
2	25.00	1698.042	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

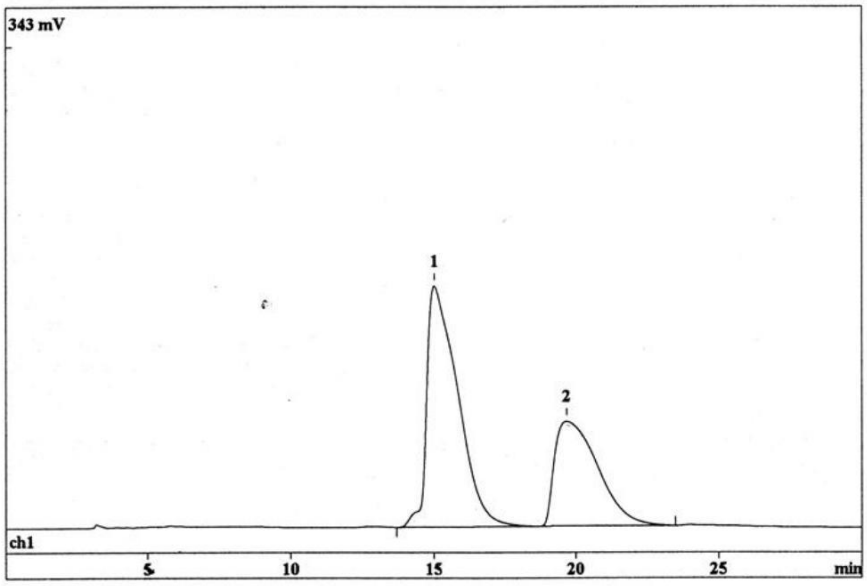
No	Retention min	Area mV*sec	Area %	Name
1	13.17	22690.726	33.20	
2	13.94	45647.209	66.80	
2	25.00	68337.935	100.00	

5k Chiralpak AS-H column (hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm)



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	15.25	8064.143	50.26	
2	19.71	7982.005	49.74	
2	30.00	16046.148	100.00	



Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	15.01	12406.896	62.24	
2	19.67	7527.634	37.76	
2	30.00	19934.530	100.00	

2.4.5 X-Ray Crystallography

X-ray diffraction data of compound **3o** were collected using a Kappa VENTURE PHOTON 100 Bruker diffractometer with IμS microfocus graphite-monochromated $Cu_{K\alpha}$ radiation (λ = 1.54178 Å). The crystal was mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flash-frozen in a nitrogen-gas stream at 100 K. The temperature of the crystal was maintained at the selected value (100 K) by means of a 700 series Cryostream cooling device to within an accuracy of ±1 K. The data were corrected for Lorentz polarization and absorption effects. The structures were solved by direct methods using SIR-97[1] and refined against F^2 by full-matrix least-squares techniques using SHELXL-97[2]with anisotropic displacement parameters for all non-hydrogen atoms. All calculations were performed by using the Crystal Structure crystallographic software package WINGX. [3]

The crystal data collection and refinement parameters are given in Table 2.2.

The absolute configuration was determined by refining the Flack parameter[4] using 1631 quotients [(I+)-(I-)]/[(I+)+(I-)].

CCDC 1054222 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/Community/Requestastructure.

Table 2.2. Crystallographic data and structure refinement details.

Compound	**3o**
Empirical Formula	C_{20} H_{17} F_6 N_1 O_1
M_r	401.35
Crystal size, mm^3	0.21 x 0.19 x 0.17
Crystal system	monoclinic
Space group	*C 2*
a, Å	22.1466(8)
b, Å	5.7422(2)
c, Å	16.4690(6)
α, °	90
β, °	117.0540(10)
γ, °	90
Cell volume, $Å^3$	1865.20(12)
Z	4
T, K	100(1)
F_{000}	824
μ, mm^{-1}	1.131
θ range, °	3.013 – 74.480
Reflection collected	24 100
Reflections unique	3 737
R_{int}	0.0148
GOF	1.067
Refl. obs. ($I>2\sigma(I)$)	3724
Parameters	253
wR_2 (all data)	0.0827
R value ($I>2\sigma(I)$)	0.0319
Largest diff. peak and hole (e-.$Å^{-3}$)	-0.339 ; 0.342

References and notes

1. A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Crystallogr.*, **1999**, *32*, 115.
2. G. M. Sheldrick, *Acta Cryst.*, **2008**, *A64*, 112.
3. L. J. Farrugia, *J. Appl. Crystallogr.*, **1999**, *32*, 837.
4. S. Parsons and H. Flack, *Acta Cryst.*, **2004**, *A60*, s61.

CHAPTER THREE

Synthesis of quaternary α-benzyl- and α-allyl-α-methylamino cyclobutanones

3.1 Introduction

Among cyclobutane derivatives,[1] α-amino cyclobutanes[2] are especially useful as they are widely encountered in a number of natural products and pharmaceutically active compounds.[3] They are also important molecular building blocks which can be easily transformed into more complex organic intermediates owing to their inherent ring strain. Therefore, the development of new methods for synthesizing highly functionalized α-amino cyclobutanes from readily available materials is highly desirable. In this regard, to the best of our knowledge, the synthesis of quaternary α-alkyl-α-amino cyclobutanones has not been explored previously and thus remains a challenge.[4]

As a continuation of our previous work on the synthesis[5] and transformations[6] of cyclobutanones, herein we shall report our recent results on the synthesis of α-benzyl- and α-allyl-α-methylamino cyclobutanones. This approach involves a K_2CO_3-induced sigmatropic rearrangement[7] of an *in situ* generated ammonium salt, prepared by quaternization of nitrogen of the corresponding starting α-amino cyclobutanone derivatives using CF_3SO_3Me as the alkylating reagent (Scheme 3.1).

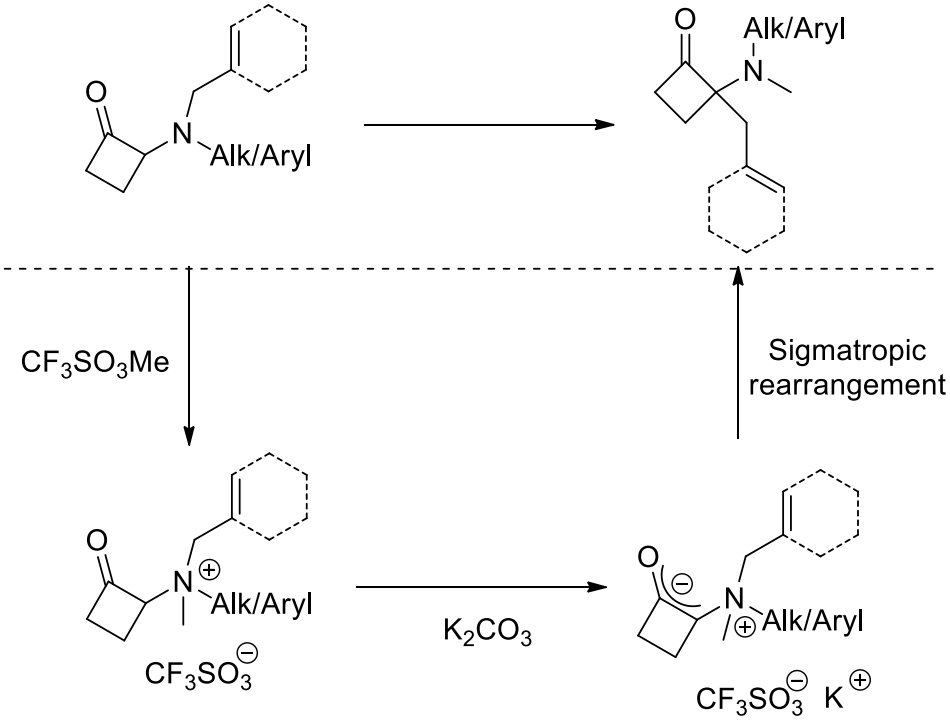
3.2 Results and discussion

Our investigation began with the sequential one pot methylation/[1,2]-rearrangement of the α-dibenzylamino cyclobutanone **1a**, selected as a model substrate.

The representative results are summarized in Table 3.1. A 2:1 molar ratio of methylating reagent to α-benzylamino cyclobutanone **1a** and 2.5 equivalents of base were used in all the experiments (Table 3.1). In the experimental procedure, the methylating reagent was added neat to **1a** at room temperature. After 3 h the solvent and the base were subsequently introduced in one portion, and the mixture heated under reflux for 16 h. The purification of the adduct **2a** was easily carried out by direct application of the crude reaction mixture to the

head of a chromatographic column followed by elution with a mixture of petroleum ether/ether. Among various potential methylating reagents screened in acetonitrile as the solvent, CF_3SO_3Me was identified as the optimal alkylating agent for this reaction. The expected adduct **2a** can be obtained in 66% yield (Table 3.1, entry 3).

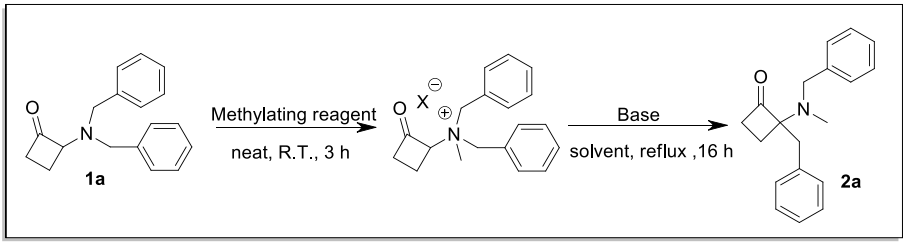
Scheme 3.1. Key steps in the synthesis of quaternary α-alkyl-α-amino cyclobutanones involving a base-induced sigmatropic rearrangement of an *in situ* generated ammonium salt.



By screening different bases (Table 3.1, entries 5-8) it was revealed that the initial use of K_2CO_3 gave the best results. Other bases such as Li_2CO_3, Cs_2CO_3, Na_2CO_3, and *t*-BuOK gave significantly lower yields. A brief solvent screen (Table 3.1, entries 9-13) showed that THF was ideal providing product **2a** in 79% yield (Table 3.1, entry 10). The latter conditions were chosen for further investigation. A survey of the scope of the rearrangement with respect to the presence of ring substituents on the dibenzylamine substrate is presented in Scheme 3.2. Good to high chemical yields of the Stevens rearrangement products **2b, b'-f, f'** were obtained as an inseparable mixture of regioisomers (between 1:1 and 1.6:1 r.r.) with a series of α-dibenzylamino cyclobutanones **1b-f** bearing different electron-donating groups on the aromatic ring. α-dibenzylamino cyclobutanones **1g-i** bearing one electron-withdrawing substituent in the aromatic ring also gave good to high yields of the corresponding adducts **2g,**

g'-i, i' but with higher regioisomeric ratios (between 1.5:1 and 4.5:1 r.r.) under the designated reaction conditions. Interestingly, although the regioselectivity was generally low, in all cases, except for α- dibenzylamino cyclobutanones **1b, c** which gave a 1.0:1.0 regioisomeric mixture and **1d** which exhibited a slight preference for the "opposite" regioisomer, it was the benzyl group with the substituent on the aromatic ring (both electron-donating and electron-withdrawing groups) that was favored during the migration process.

Table 3.1. Evaluation of reaction conditions.[a]

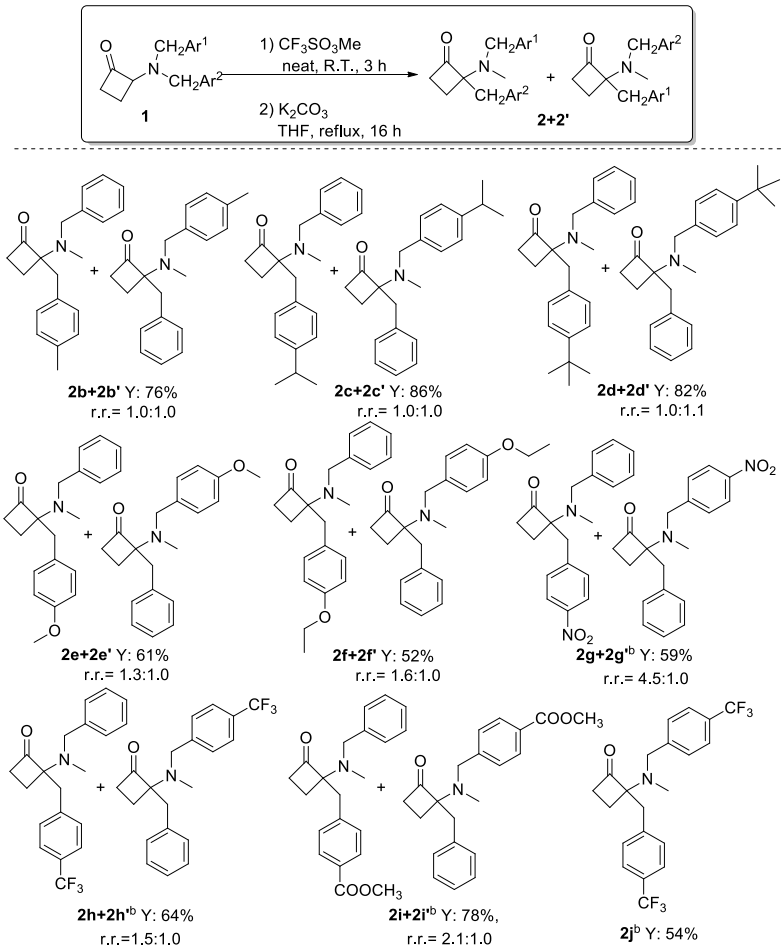


Entry	**Methylating reagent**	**Base**	**Solvent**	**Yield 2a (%)[b]**
1	$Me_3O^+BF_4^-$	K_2CO_3	CH_3CN	36
2	Me_2SO_4	K_2CO_3	CH_3CN	39
3	CF_3SO_3Me	K_2CO_3	CH_3CN	66
4	MeI	K_2CO_3	CH_3CN	8
5	CF_3SO_3Me	Li_2CO_3	CH_3CN	11
6	CF_3SO_3Me	Cs_2CO_3	CH_3CN	45
7	CF_3SO_3Me	Na_2CO_3	CH_3CN	26
8	CF_3SO_3Me	*t*-BuOK	CH_3CN	38
9	CF_3SO_3Me	K_2CO_3	CH_3COOEt	48
10	**CF_3SO_3Me**	**K_2CO_3**	**THF**	**79**
11	CF_3SO_3Me	K_2CO_3	1,4-Dioxane	57
12	CF_3SO_3Me	K_2CO_3	DMF	0[c]
13	CF_3SO_3Me	K_2CO_3	EtOH	0[c]

[a]Conditions: **1a** (380 µmol), methylating reagent (760 µmol), base (950 µmol), solvent (4 mL). [b] Isolated yield after chromatography. [c] Decomposition products were obtained

The preferential migration of the *para*-substituted benzyl group in the dibenzylamine substrates might suggest a radical character of the migrating group[8] and support homolytic cleavage of the carbon-nitrogen bond followed by recombination to provide the products as illustrated in previously reported [1,2]-Stevens-type rearrangements.[9]

Scheme 3.2. Substrate scope regarding aromatic ring substituents.[a]



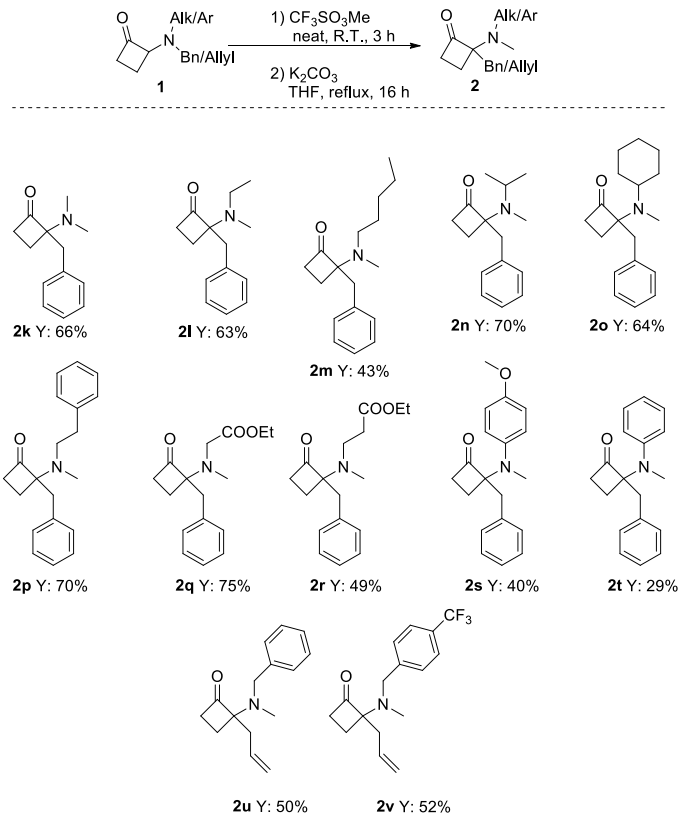
[a] Conditions: **1** (380 µmol), CF_3SO_3Me (760 µmol), K_2CO_3 (950 µmol), THF (4 mL). Yields are given for isolated materials after column chromatography. The r.r. values were based on relative ^{1}HNMR integrations and the assignment of the major regioisomer was based on chemical shifts of the benzyl group protons. [b] The reaction was carried out at room temperature for 120 h; 8 mL of THF were used.

A representative bis-*para*-substituted α-dibenzylamino cyclobutanone with electron-withdrawing groups such as **1j** was tolerated and gave moderate chemical yield. The scope of substrates was further explored as shown in Scheme 3.3. The reactions of several *N*-alkyl benzyl cyclobutanones **1k-r** bearing different *N*-alkyl groups such as methyl (**1k**), ethyl (**1l**),

n-pentyl (**1m**) phenethyl (**1p**), carboethoxymethyl (**1q**), carboethoxyethyl (**1r**) as well as the more sterically congested isopropyl (**1n**) and *c*-hexyl (**1o**) groups, under the standard conditions, were found to afford the corresponding Stevens rearrangement products **2k-r** in moderate to good yields. In addition, the reactions of compounds **1s** and **1t** bearing an aromatic ring on the nitrogen were also successful although the desired products **2s** and **2t** were obtained with lower chemical yield.

On the other hand, the reaction of **1u** and **1v** bearing an allyl substituent on the nitrogen atom occurred preferentially via a [2,3]-rearrangement affording, as the sole product, the corresponding α-allyl-α-benzylamino cyclobutanones **2u** and **2v**.[10]

Scheme 3.3. Substrate scope regarding *N*-alkyl substituents.[a]



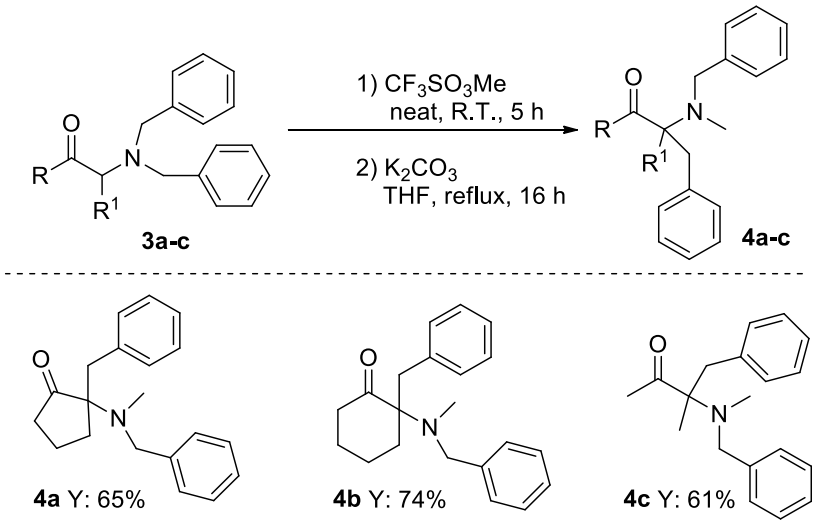
[a] Conditions: **1** (380 µmol), CF_3SO_3Me (760 µmol), K_2CO_3 (950 µmol), THF (4 mL). Yields are given for isolated materials after column chromatography.

As a result, the applicability of the reaction protocol to other cyclic (**3a** and **3b**) as well as acyclic (**3c**) α-amino ketones was then preliminary investigated (Scheme 3.4). Gratifyingly, the reactions of 2-(dibenzylamino)cyclopentanone (**3a**), 2-(dibenzylamino)cyclohexanone

(**3b**) and 3-(dibenzylamino)butan-2-one (**3c**) proceeded with good to high chemical yields in each case thus highlighting the broad generality of this protocol.

Next, the substrate scope was extended to include the synthesis of other structurally related derivatives such as quaternary α-allyl-α-arylamino cyclobutanones (Scheme 3.5). To our delight, parent substrate 5a afforded the product 6a in good yield when the reaction was performed in CH_3COOEt at room temperature for 3 days.

Scheme 3.4. Substrate scope regarding other cyclic and acyclic α-amino ketones.[a]

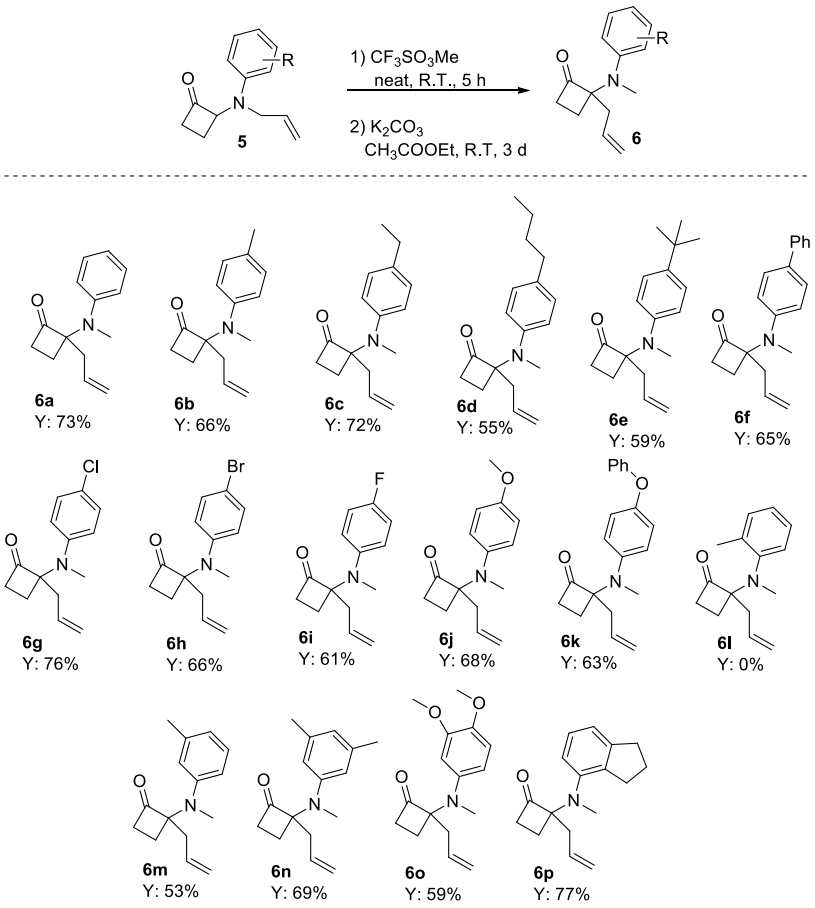


[a] Conditions: **3** (380 µmol), CF_3SO_3Me (760 µmol), K_2CO_3 (950 µmol), THF (4 mL). Yields are given for isolated materials after column chromatography.

Under the same reaction conditions, various α-*N*-allyl-*N*-arylamino cyclobutanones[11] were subjected to the analogous sequential one-pot methylation/[2,3]-rearrangement.[12] With α-*N*-allyl-*N*-arylamino cyclobutanones bearing different electron-donating groups on the *para* position of the aromatic ring such as -Me (**5b**), -Et (**5c**), -OMe (**5j**), -OPh (**5k**) and -Ph (**5f**), the reaction proceeds smoothly to furnish the desired products in moderate to good yields. Interestingly, even substrates with sterically demanding *n*-butyl (**5d**) and *t*-butyl groups (**5e**) on the aromatic ring readily participated in the reaction sequence to generate the corresponding α-allyl-α-arylamino cyclobutanones in moderate to good yields. α-*N*-Allyl-*N*-arylamino cyclobutanones such as **5g-i** bearing one halogen as the substituent in a *para*-position were also found to be good substrates, affording the corresponding products **6g-i** in good yields.

A representative *meta*-substituted arylamino cyclobutanone **5m** performed almost equally well in this reaction (53% yield) whereas the *ortho*-substituted arylamino cyclobutanone **5l** failed to participate in this reaction. Of particular note, disubstituted arylamino cyclobutanones **5n-p** with electron-donating groups were tolerated and gave moderate to good chemical yields.

Scheme 3.5. Substrate scope regarding α-*N*-allyl-*N*-arylamino cyclobutanones.[a]

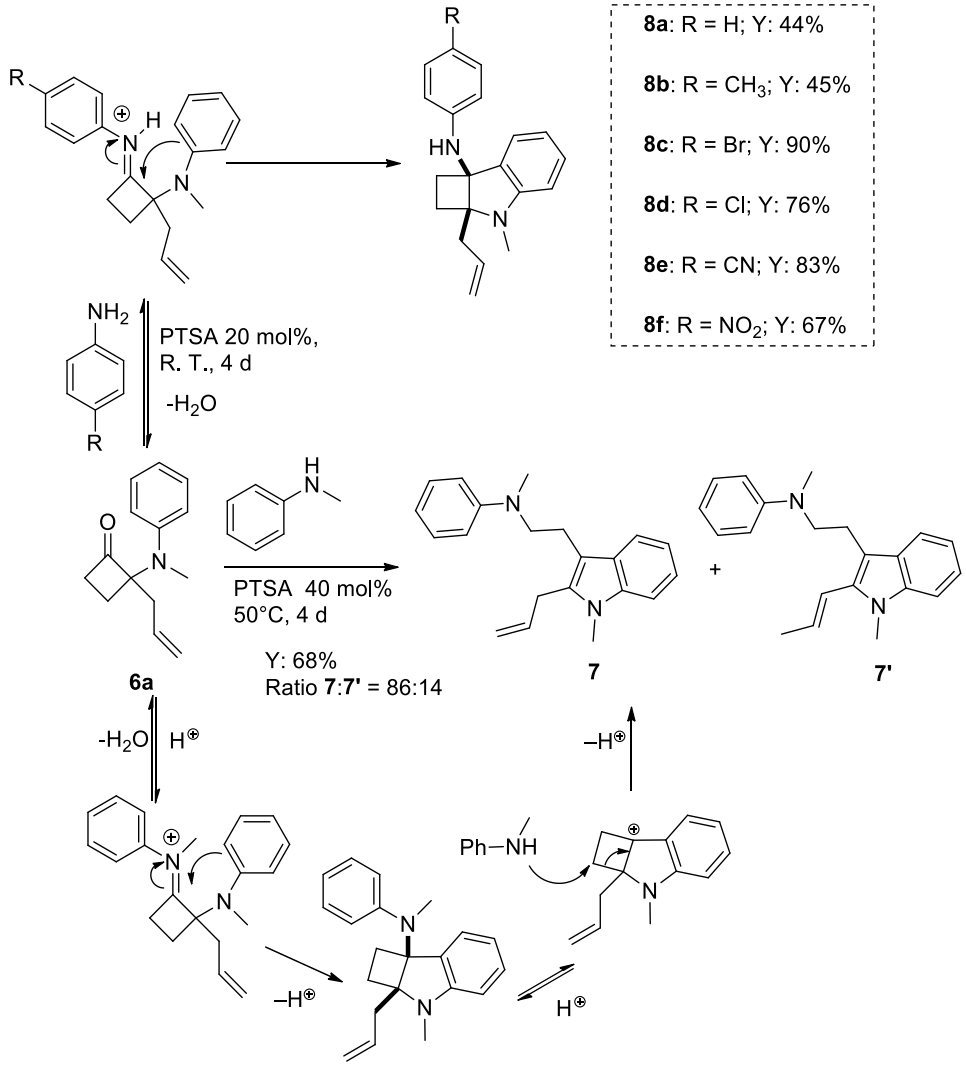


[a]Conditions: **5** (380 µmol), CF_3SO_3Me (760 µmol), K_2CO_3 (950 µmol), CH_3COOEt (4 mL). Yields are given for isolated materials after column chromatography.

We then sought to demonstrate the potential of these products as synthetic precursors of biologically important derivatives (Scheme 3.6). Based on our previous work,[6b] the reaction of **6a** and *N*-methyl aniline was investigated under the catalysis of PTSA. We were happy to find that the corresponding 2-allyl tryptamine[13] **7** along with isomeric derivative **7'** could be obtained in 68% overall yield (ratio **7**:**7'** =86:14) through a solvent-free cascade reaction. The

formation of **7'** may be explained via an acid-mediated isomerization of the terminal double bond of tryptamine **7**. On the other hand, when we carried out the reaction of **6a** with primary anilines the isolated compounds from the reaction were the cyclobuta-2,3-fused indoline derivatives[14] **8a-f** (44-90% yields), and only a trace amount of the corresponding tryptamines, coming from a subsequent acid catalyzed "depart-and-return" process,[6b] were observed. The lower basicity of the less substituted aniline is a potential explanation for the observed difference in reaction outcome.

Scheme 3.6. Application in synthesis: preparation of 2-allyl tryptamine **7** and cyclobuta-fused indolines **8a-f**.



3.3. Conclusions

In conclusion, we have developed a simple and practical method for the synthesis of quaternary highly functionalized α-benzyl- and α-allyl-α-methylamino cyclobutanones using a sequential one pot methylation/sigmatropic rearrangement starting from α-amino cyclobutanones. The method presented in this work provides the first general and efficient route to assemble these important structural motifs. Furthermore, one of the α-alkyl-α-amino cyclobutanones, **6a** was used to prepare a new highly substituted tryptamine derivative and some valuable cyclobuta-2,3-fused indolines. The extension and synthetic application of this reaction are currently under investigation in our laboratories.

3.4. Experimental section

3.4.1 General Methods

^{1}H NMR spectra were recorded on a Varian 500, or Varian 400 MHz spectrometer at ambient temperature with $CDCl_3$ as solvent. Data are reported as follows: chemical shifts (δ), multiplicity, coupling constants and integration. ^{13}C NMR spectra were recorded operating respectively at 126, or 101 MHz at 27 °C with $CDCl_3$ as solvent. Infrared spectra were recorded on a FT-IR spectrophotometer. High resolution mass spectra (HRMS) were recorded on a spectrometer using Positive Electro Ionization (ESI) mode. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using columns of 230-400 mesh silica gel 60 (0.040-0.063 mm). Yields refer to chromatographically pure materials.

3.4.2 General procedures and data

General Procedure for the synthesis of α-benzyl-α-dialkylamino cyclobutanones 2a-f, 2k-v and α-benzyl-α-dialkylaminoketones 4a-c

CF_3SO_3Me (760 µmol, 0.086 mL) was added neat to α-dibenzylamino ketone **1a-f**, **1k-s** or **3a-c** (380 µmol) at room temperature. After 3 h (5 h for **3a-c**), THF (4 mL) and K_2CO_3 (950 µmol, 0.131 g) were subsequently introduced in one portion, and the mixture heated under reflux for 16 h. The crude reaction mixture was directly loaded to a silica gel column without aqueous work-up and pure products were obtained by flash column chromatography (silica gel, mixture of petroleum ether/ether, 10:1→1:1).

2a: Yield 79% (0.084 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.68. **IR** (neat): 3087, 3063, 3030, 2959, 2923, 2847, 2795, 1773, 1604, 1495, 1454, 1063 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 6H), 7.26 – 7.19 (m, 4H), 3.88 (d, *J* = 15.0 Hz, 1H), 3.62 (d, *J* = 15.0 Hz, 1H), 3.22 (d, *J* = 15.0 Hz, 1H), 2.93 – 2.82 (m, 2H), 2.29 (s, 3H), 2.20 – 2.09 (m, 1H), 2.09 – 1.97 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.7, 139.4, 136.9, 130.2, 128.43, 128.40, 128.2, 126.8, 126.4, 86.5, 56.1, 41.9, 35.6, 33.9, 20.9. **HRMS** (ESI) Calcd. for $C_{19}H_{22}NO$ (M+H) m/z 280.1695, found 280.1699.

2b+2b': Spectral data determined from the 1.0:1.0 inseparable mixture of two regioisomers: Yield 76% (0.084 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.69. **IR** (neat): 3025, 2999, 2954, 2919, 2844, 2791, 1772, 1520, 1493, 1458, 1259, 1064 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 – 7.02 (m, 18H), 3.78 (dd, *J* = 19.8, 13.4 Hz, 2H), 3.52 (t, *J* = 13.2 Hz, 2H), 3.12 (t, *J* = 13.2 Hz, 2H), 2.86 – 2.72 (m, 4H), 2.25 (s, 3H), 2.24 (s, 3H), 2.21 (s, 6H), 2.12 – 1.90 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.0, 209.8, 139.5, 136.9, 136.4, 136.3, 135.9, 133.7, 130.2, 130.1, 129.1, 128.9, 128.8, 128.44, 128.40, 128.2, 86.5, 56.1, 55.8, 41.9, 35.6, 35.5, 33.8, 33.4, 21.06, 21.00, 20.9. **HRMS** (ESI) Calcd. for $C_{20}H_{24}NO$ (M+H) m/z 294.1852, found 294.1864.

2c+2c': Spectral data determined from the 1.0:1.0 inseparable mixture of two regioisomers: Yield 86% (0.105 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.74. **IR** (neat): 3030, 2963, 2870, 2795, 1772, 1515, 1493, 1458, 1387, 1365, 1059 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.10 (m, 18H), 3.92 – 3.80 (m, 2H), 3.59 (dd, *J* = 13.3, 8.4 Hz, 2H), 3.20 (t, *J* = 13.3 Hz, 2H), 2.93 – 2.78 (m, 6H), 2.29 (s, 3H), 2.28 (s, 3H), 2.19 – 1.96 (m, 6H), 1.24 (d, *J* = 6.9 Hz, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.0, 209.8, 147.5, 146.9, 139.5, 136.9, 136.7, 134.0, 130.2, 130.1, 128.43, 128.40, 128.1, 126.8, 126.4, 126.3, 126.2, 86.5, 56.1, 55.8, 41.9, 35.6, 33.8, 33.7, 33.6, 33.5, 24.0, 23.9, 20.9. **HRMS** (ESI) Calcd. for $C_{22}H_{28}NO$ (M+H) m/z 322.2165, found 322.2172.

2d+2d': Spectral data determined from the 1.0:1.1 inseparable mixture of two regioisomers: Yield 82% (0.104 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.75. IR (neat): 3034, 2959, 2866, 2791, 1777, 1511, 1493, 1453, 1387, 1360, 1272, 1068 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.11 (m, 18H), 3.85 (t, *J* = 14.2 Hz, 2H), 3.60 (dd, *J* = 13.4, 6.8 Hz, 2H), 3.20 (t, *J* = 13.8 Hz, 2H), 2.85 (ddd, *J* = 12.8, 8.3, 3.7 Hz, 4H), 2.29 (s, 3H), 2.28 (s, 3H), 2.16 – 1.97 (m, 6H), 1.31 (s, 9H), 1.30 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.1, 209.8, 149.7, 149.2, 139.5, 136.9, 136.3, 133.6, 130.2, 129.9, 128.4, 128.3, 128.19, 128.12, 126.8, 126.3, 125.2, 125.1, 86.5, 56.1, 55.7, 41.9, 35.6, 33.8, 33.4, 31.38, 31.34, 20.9. **HRMS** (ESI) Calcd. for $C_{23}H_{30}NO$ (M+H) m/z 336.2321, found 336.2327.

2e+2e': Spectral data determined from the 1.3:1.0 inseparable mixture of two regioisomers: Yield 61% (0.071 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.43. **IR** (neat): 2970, 2932, 2886, 1776, 1610, 1512, 1465, 1379, 1249, 1160, 1127 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 8H), 7.24 – 7.18 (m, 4H), 7.15 – 7.10 (m, 2H), 6.87 – 6.81 (m, 4H), 3.86 (d, *J* = 13.4 Hz, 1H), 3.80 (d, *J* = 13.3 Hz, 1H), 3.78 (s, 3H), 3.78 (s, 3H), 3.60 (d, *J* = 13.4 Hz, 1H), 3.54 (d, *J* = 13.2 Hz, 1H), 3.18 (dd, *J* = 21.5, 13.4 Hz, 2H), 2.91 – 2.78 (m, 4H), 2.27 (s, 3H), 2.26 (s, 3H), 2.21 – 1.92 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.2, 209.9, 158.5, 158.1, 139.4, 136.9, 131.1, 130.2, 129.5, 128.6, 128.4, 128.3, 128.1, 126.8, 126.3, 86.5, 86.4, 56.0, 55.4, 55.19, 55.14, 41.93, 41.90, 35.5, 35.3, 33.8, 33.0, 20.8, 20.7. **HRMS** (ESI) Calcd. for $C_{20}H_{24}NO_2$ (M+H) m/z 310.1801, found 310.1807.

2f+2f': Spectral data determined from the 1.6:1.0 inseparable mixture of two regioisomers: Yield 52% (0.064 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.50. **IR** (neat): 2971, 2930, 2884, 1773, 1511, 1465, 1380, 1300, 1341, 1254, 1160, 1127, 1103, 1049 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 8H), 7.26 – 7.16 (m, 4H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.83 (td, *J* = 7.0, 3.7 Hz, 4H), 4.01 (qd, *J* = 7.0, 2.5 Hz, 4H), 3.86 (d, *J* = 13.5 Hz, 1H), 3.79 (d, *J* = 13.2 Hz, 1H), 3.60 (d, *J* = 13.5 Hz, 1H), 3.55 (d, *J* = 13.2 Hz, 1H), 3.20 (d, *J* = 13.3 Hz, 1H), 3.15 (d, *J* = 13.5 Hz, 1H), 2.91 – 2.77 (m, 4H), 2.27 (s, 3H), 2.27 (s, 3H), 2.21 – 1.95 (m, 6H), 1.40 (td, *J* = 7.0, 1.8 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.2, 209.9, 158.0, 157.5, 139.5, 137.0, 131.2, 130.2, 129.5, 128.6, 128.4, 128.3, 128.2, 126.8, 126.3, 114.4, 114.2, 86.6, 86.5, 63.4, 63.3, 56.1, 55.4, 41.98, 41.95, 35.6, 35.4, 33.9, 33.1, 20.9, 20.8, 14.86, 14.84. **HRMS** (ESI) Calcd. for $C_{21}H_{26}NO_2$ (M+H) m/z 324.1957, found 324.1963.

2k: Yield 66% (0.051 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.2. IR (neat): 2981, 2946, 2866, 2826, 2791, 1777, 1458, 1064 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 – 7.16 (m, 5H), 3.10 (d, *J* = 13.2 Hz, 1H), 2.79 (d, *J* = 13.3 Hz, 1H), 2.71 (ddd, *J* = 15.6, 11.6, 5.8 Hz, 1H), 2.40 (s, 6H), 2.10 – 1.97 (m, 2H), 1.95 – 1.85 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.6, 136.8, 130.2, 128.4, 126.4, 86.2, 41.9, 39.3, 33.8, 19.2. **HRMS** (ESI) Calcd. for $C_{13}H_{18}NO$ (M+H) m/z 204.1382, found 204.1384.

2l: Yield 63% (0.052 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.25. **IR** (neat): 3030, 2972, 2928, 2853, 2791, 1777, 1502, 1453, 1383, 1068 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.15 (m, 5H), 3.10 (d, *J* = 13.2 Hz, 1H), 2.81 – 2.68 (m, 3H), 2.55 (dq, *J* = 14.2, 7.1 Hz, 1H), 2.39 (s, 3H), 2.03 – 1.90 (m, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.4, 137.0, 130.2, 128.3, 126.3, 86.7, 45.8, 41.8, 35.2, 33.8, 20.8, 13.7. **HRMS** (ESI) Calcd. for $C_{14}H_{20}NO$ (M+H) m/z 218.1539, found 218.1547.

2m: Yield 43% (0.042 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.37. **IR** (neat): 2959, 2932, 1774, 1495, 1468, 1454, 1385, 1095 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 – 7.15 (m, 5H), 3.10 (d, *J* = 13.2 Hz, 1H), 2.82 – 2.71 (m, 2H), 2.71 – 2.61 (m, 1H), 2.49 – 2.40 (m, 1H), 2.38 (s, 3H), 2.07 – 1.90 (m, 3H), 1.45 (dd, *J* = 14.6, 7.4 Hz, 2H), 1.40 – 1.21 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.2, 137.1, 130.2, 128.3, 126.2,

86.7, 51.9, 41.8, 35.8, 33.5, 29.4, 28.0, 22.6, 20.8, 14.0. **HRMS** (ESI) Calcd. for $C_{17}H_{26}NO$ (M+H) m/z 260.2008, found 260.2034.

2n: Yield 70% (0.062 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.2. **IR** (neat): 3087, 3065, 3033, 2970, 2929, 2847, 2795, 1779, 1495, 1457, 1388, 1361, 1110, 1050 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 5H), 3.38 (dt, *J* = 13.2, 6.6 Hz, 1H), 3.14 (d, *J* = 13.4 Hz, 1H), 2.88 (d, *J* = 13.4 Hz, 1H), 2.66 (ddd, *J* = 13.3, 10.7, 3.8 Hz, 1H), 2.31 (s, 3H), 2.22 – 2.10 (m, 1H), 2.07 – 1.81 (m, 2H), 1.13 – 0.94 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.4, 136.9, 130.1, 128.2, 126.3, 87.0, 47.6, 41.8, 37.4, 28.3, 20.9, 20.6, 19.6. **HRMS** (ESI) Calcd. for $C_{15}H_{22}NO$ (M+H) m/z 232.1695, found 232.1697.

2o: Yield 64% (0.066 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.32. **IR** (neat): 2975, 2934, 1775, 1381, 1257, 1094 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 – 7.16 (m, 5H), 3.14 (d, *J* = 13.4 Hz, 1H), 2.90 – 2.80 (m, 2H), 2.68 (ddd, *J* = 16.8, 10.7, 5.2 Hz, 1H), 2.37 (s, 3H), 2.20 – 2.07 (m, 1H), 1.97 (dtd, *J* = 16.1, 10.7, 6.4 Hz, 2H), 1.83 – 1.71 (m, 2H), 1.67 – 1.61 (m, 3H), 1.50 – 1.36 (m, 2H), 1.35 – 1.21 (m, 2H), 1.14 – 0.97 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 211.2, 137.0, 130.1, 128.2, 126.3, 87.0, 57.0, 41.8, 37.5, 31.7, 30.8, 29.9, 26.3, 26.2, 26.0, 20.9. **HRMS** (ESI) Calcd. for $C_{18}H_{26}NO$ (M+H) m/z 272.2008, found 272.2008.

2p: Yield 70% (0.078 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.28. **IR** (neat): 3090, 3063, 3027, 2959, 2923, 2850, 2798, 1779, 1604, 1498, 1451, 1063 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.12 (m, 10H), 3.09 (d, *J* = 13.2 Hz, 1H), 3.00 – 2.86 (m, 1H), 2.77 – 2.65 (m, 5H), 2.49 (s, 3H), 2.06 – 1.78 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.8, 140.3, 136.9, 130.2, 128.8, 128.3, 128.2, 126.3, 126.0, 86.5, 54.1, 41.8, 36.0, 35.2, 33.6, 20.8. **HRMS** (ESI) Calcd. for $C_{20}H_{24}NO$ (M+H) m/z 294.1852, found 294.1864.

2q: Yield 75% (0.079 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.15. **IR** (neat): 2985, 1779, 1744, 1496, 1454, 1385, 1265, 1198, 1163, 1102, 1067, 1031 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 – 7.16 (m, 5H), 4.17 (q, *J* = 5.0 Hz, 2H), 3.66 (d, *J* = 15.0 Hz, 1H), 3.34 (d, *J* = 15.0 Hz, 1H), 3.05 (d, *J* = 15.0 Hz, 1H), 2.89 – 2.73 (m, 2H), 2.50 (s, 3H), 2.12 – 1.97 (m, 3H), 1.27 (t, *J* = 10.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.5, 171.2, 136.3, 130.1,

128.3, 126.5, 85.1, 60.5, 53.6, 41.8, 37.0, 34.7, 21.0, 14.1. **HRMS** (ESI) Calcd. for $C_{16}H_{22}NO_3$ (M+H) m/z 276.1593, found 276.1601.

2r: Yield 49% (0.054 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.10. **IR** (neat): 2972, 2930, 2866, 1774, 1725, 1495, 1465, 1381, 1160, 1128, 1099, 1082, 1072 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 – 7.14 (m, 5H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.10 (d, *J* = 13.3 Hz, 1H), 2.93 (dt, *J* = 13.4, 6.8 Hz, 1H), 2.88 – 2.81 (m, 1H), 2.79 – 2.69 (m, 2H), 2.46 (td, *J* = 7.2, 2.9 Hz, 2H), 2.41 (s, 3H), 2.07 – 1.87 (m, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.4, 172.3, 136.8, 130.2, 128.3, 126.3, 86.4, 60.3, 47.6, 41.8, 35.8, 33.8, 33.4, 20.9, 14.1. **HRMS** (ESI) Calcd. for $C_{17}H_{24}NO_3$ (M+H) m/z 290.1750, found 290.1758.

2s: Yield 40% (0.045 g); yellow oil; R_f (petroleum ether/ether, 5:1) 0.46. IR (neat): 2971, 2933, 2884, 1777, 1510, 1422, 1380, 1265, 1075 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.15 (m, 5H), 6.87-6.82 (m, 4H), 3.78 (s, 3H), 3.15 (d, *J* = 13.6 Hz, 1H), 2.98 (d, *J* = 13.6 Hz, 1H), 2.95 (s, 3H), 2.77 – 2.66 (m, 1H), 2.36 – 2.04 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.4, 154.1, 142.1, 136.4, 130.2, 128.3, 126.6, 121.6, 114.1, 84.7, 55.5, 42.3, 37.9, 37.3, 21.9. HRMS (ESI) Calcd. for $C_{19}H_{22}NO_2$ (M+H) m/z 296.1644, found 296.1655.

2t: Yield 29% (0.029 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.65. **IR** (neat): 3206, 2915, 2822, 1776, 1597, 1497 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 5H), 7.17 (d, *J* = 7.2 Hz, 2H), 6.82 (t, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 2H), 3.23 (d, *J* = 13.6 Hz, 1H), 3.10 (d, *J* = 13.6 Hz, 1H), 3.03 (s, 3H), 2.85 – 2.80 (m, 1H), 2.39 – 2.30 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.5, 147.7, 136.4, 130.4, 128.9, 128.6, 126.8, 118.4, 116.5, 83.8, 42.7, 36.7, 36.4, 23.8. **HRMS** (ESI) Calcd. for $C_{18}H_{20}NO$ (M+H) m/z 266.1539, found 266.1541.

2u: Yield 50% (0.044 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.46. **IR** (neat): 2923, 2848, 1776, 905, 729 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 5H), 5.91 – 5.82 (m, 1H), 5.19 – 5.14 (m, 2H), 3.75 (d, *J* = 13.4 Hz, 1H), 3.55 (d, *J* = 13.4 Hz, 1H), 2.99 – 2.97 (m, 1H), 2.85 – 2.83 (m, 1H), 2.62 – 2.60 (m, 1H), 2.48 – 2.46 (m, 1H), 2.20 (s, 3H), 2.18 – 2.14 (m, 1H), 2.00 – 1.93 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.3, 139.5, 133.5, 128.6,

128.3, 127.0, 118.6, 85.8, 56.1, 41.6, 35.8, 34.2, 20.4. **HRMS** (ESI) Calcd. for $C_{15}H_{20}NO$ (M+H) m/z 230.1539, found 230.1543.

2v: Yield 52% (0.059 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.54. **IR** (neat): 2959, 2853, 1777, 1322, 905, 729 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 5.92 – 5.82 (m, 1H), 5.19 – 5.15 (m, 2H), 3.84 (d, *J* = 13.9 Hz, 1H), 3.59 (d, *J* = 13.9 Hz, 1H), 3.00 – 2.97 (m, 1H), 2.88-2.86 (m, 1H), 2.62 (dd, *J* = 14.2, 7.0 Hz, 1H), 2.46 (dd, *J* = 14.2, 7.5 Hz, 1H), 2.20 (s, 3H), 2.18 – 2.12 (m, 1H), 2.03 – 1.95 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.0, 143.8, 133.2, 128.7 (2 C), 125.3 (q, *J* = 3.2 Hz), 118.8, 85.6, 55.8, 41.6, 35.9, 34.2, 20.5. **HRMS** (ESI) Calcd. for $C_{16}H_{19}F_3NO$ (M+H) m/z 298.1413, found 298.1417.

4a: Yield 65% (0.072 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.4. **IR** (neat): 2972, 2932, 2885, 1733, 1492, 1464, 1381 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.08 (m, 10H), 3.90 (d, *J* = 14.0 Hz, 1H), 3.54 (d, *J* = 14.0 Hz, 1H), 3.20 (d, *J* = 13.3 Hz, 1H), 2.84 (d, *J* = 13.3 Hz, 1H), 2.53 – 2.40 (m, 1H), 2.19 (s, 3H), 2.17 – 2.09 (m, 1H), 2.01 – 1.87 (m, 2H), 1.69 – 1.58 (m, 1H), 1.53 – 1.44 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 215.2, 140.3, 138.0, 130.5, 128.25, 128.21, 128.0, 126.7, 126.1, 70.1, 54.2, 36.6, 34.0, 33.0, 31.3, 17.5. **HRMS** (ESI) Calcd. for $C_{20}H_{24}NO$ (M+H) m/z 294.1852, found 294.1875.

4b: Yield 74% (0.087 g); white solid; **m. p.** = 64-66°C; **R_f** (petroleum ether/ether, 5:1) 0.56. IR (neat): 2970, 1710, 1494, 1453, 1422, 1379, 1264, 1159, 1125, 1080, 1029 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.16 (m, 10H), 3.70 (d, *J* = 14.2 Hz, 1H), 3.45 (d, *J* = 14.2 Hz, 1H), 3.41 (d, *J* = 13.4 Hz, 1H), 3.17 (td, *J* = 13.2, 6.4 Hz, 1H), 2.65 (d, *J* = 13.5 Hz, 1H), 2.26 – 2.18 (m, 1H), 2.15 (s, 3H), 2.14 – 2.11 (m, 1H), 2.09 – 1.94 (m, 2H), 1.52 (dt, *J* = 8.9, 7.8 Hz, 1H), 1.45 (d, *J* = 13.3 Hz, 1H), 1.23 – 1.09 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 213.6, 139.6, 138.8, 131.3, 128.3, 128.0, 127.8, 126.8, 125.7, 71.2, 54.3, 38.8, 35.3, 33.4, 32.2, 27.9, 19.9. **HRMS** (ESI) Calcd. for $C_{21}H_{26}NO$ (M+H) m/z 308.2008, found 308.2014.

4c: Yield 61% (0.065 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.43. **IR** (neat): 2973, 2933, 2889, 1708, 1457, 1379, 1255, 1160, 1128, 1095, 1074, 1029 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.18 (m, 10H), 3.60 (d, *J* = 14.2 Hz, 1H), 3.51 (d, *J* = 14.2 Hz, 1H), 3.23 (d,

J = 13.4 Hz, 1H), 2.89 (d, *J* = 13.4 Hz, 1H), 2.30 (s, 3H), 2.20 (s, 3H), 1.18 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.9, 139.7, 137.6, 130.5, 128.3, 128.04, 127.9, 126.8, 126.3, 71.7, 55.9, 39.3, 35.2, 25.5, 16.4. **HRMS** (ESI) Calcd. for $C_{19}H_{24}NO$ (M+H) m/z 282.1852, found 282.1863.

General Procedure for the synthesis of α-benzyl-α-dialkylamino cyclobutanones 2g-j

CF_3SO_3Me (760 µmol, 0.086 mL) was added neat to α-dibenzylamino cyclobutanone **1g-j** (380 µmol) at room temperature. After 3 h, THF (8 mL) and K_2CO_3 (950 µmol, 0.131 g) were subsequently introduced in one portion, and the mixture stirred for 120 h at room temperature.The crude reaction mixture was directly loaded onto a silica gel column without aqueous work-up and pure products were obtained by flash column chromatography (silica gel, mixture of petroleum ether/ether, 10:1→1:1).

2g+2g': Column chromatography afforded pure regioisomer fraction of **2g** and **2g'**. Combined yield 59% (0.073 g); (**2g**): Yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.24. **IR** (neat): 3083, 3065, 3030, 2954, 2848, 2800, 1777, 1604, 1515, 1347, 1117, 860 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 – 8.15 (m, 2H), 7.42 (d, *J* = 5.0 Hz, 2H), 7.32 – 7.24 (m, 5H), 3.83 (d, *J* = 15.0 Hz, 1H), 3.62 (d, *J* = 15.0 Hz, 1H), 3.33 (d, *J* = 15.0 Hz, 1H), 3.02 (dq, *J* = 12.5, 10.0 Hz, 2H), 2.43 – 2.36 (m, 1H), 2.27 (s, 3H), 2.25 – 2.15 (m, 1H), 1.94 – 1.88 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.3, 146.7, 145.0, 138.8, 131.1, 128.3 (2 C), 127.1, 123.5, 86.5, 56.0, 42.1, 35.5, 34.5, 20.6. **HRMS** (ESI) Calcd. for $C_{19}H_{21}N_2O_3$ (M+H) m/z 325.1546, found 325.1551. (**2g'**): Yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.23. **IR** (neat): 2981, 2853, 2795, 1777, 1515, 1347, 1112, 1064, 856 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.31 – 7.20 (m, 5H), 4.07 (d, *J* = 14.5 Hz, 1H), 3.68 (d, *J* = 14.5 Hz, 1H), 3.21 (d, *J* = 13.4 Hz, 1H), 3.07 – 2.74 (m, 2H), 2.29 (s, 3H), 2.27 – 2.16 (m, 1H), 2.09 – 2.04 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.4, 147.5, 147.1, 136.4, 130.2, 128.8, 128.5, 126.6, 123.5, 86.2, 55.7, 42.0, 35.8, 34.2, 21.2. **HRMS** (ESI) Calcd. for $C_{19}H_{21}N_2O_3$ (M+H) m/z 325.1546, found 325.1558.

2h+2h': Column chromatography afforded pure regioisomer fraction of **2h** and **2h'**. Combined yield 64% (0.084 g); (**2h**): Yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.58. IR (neat): 3030, 2892, 2853, 2800, 1777, 1329, 1166, 1126, 1068 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.32 –7.24 (m, 5H), 3.85 (d, *J* = 13.4 Hz, 1H), 3.62 (d, *J* = 13.4 Hz, 1H), 3.28 (d, *J* = 13.5 Hz, 1H), 3.02 – 2.98 (m, 1H), 2.97 – 2.93 (m, 1H), 2.36 – 2.22 (m, 1H), 2.28 (s, 3H), 2.21 – 2.09 (m, 1H), 1.94 (td, *J* = 11.1, 6.4 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.9, 141.3, 139.1, 130.6, 128.3 (2 C), 128.2 (2 C), 127.0, 125.2 (q, *J* = 3.43 Hz), 86.4, 56.0, 42.1, 35.6, 34.0, 20.7. **HRMS** (ESI) Calcd. for $C_{20}H_{21}F_3NO$ (M+H) m/z 348.1569, found 348.1569. (**2h'**): Yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.48. **IR** (neat): 3087, 3063, 3030, 2962, 2923, 2852, 2798, 1779, 1323, 1162, 1123, 1066, 1020 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.28 – 7.19 (m, 3H), 3.99 (d, *J* = 14.0 Hz, 1H), 3.65 (d, *J* = 14.0 Hz, 1H), 3.21 (d, *J* = 13.3 Hz, 1H), 2.92 – 2.83 (m, 2H), 2.28 (s, 3H), 2.19 (dt, *J* = 18.0, 8.0 Hz, 1H), 2.06 (dt, *J* = 10.7, 6.4 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.5, 143.7, 136.6, 130.2, 128.53, 128.50, 126.5, 125.1 (q, *J* = 3.78 Hz), 86.3, 55.8, 42.0, 35.7, 34.1, 21.1. **HRMS** (ESI) Calcd. for $C_{20}H_{21}F_3NO$ (M+H) m/z 348.1569, found 348.1566.

2i+2i': Spectral data determined from the 2.1:1.0 inseparable mixture of two regioisomers: Yield 78% (0.100 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.34. **IR** (neat): 3034, 2954, 2853, 2800, 1772, 1719, 1458, 1436, 1281, 1108 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 4H), 7.41 – 7.17 (m, 14H), 3.97 (d, *J* = 14.0 Hz, 1H), 3.91 (s, 3H), 3.91 (s, 3H), 3.86 (d, *J* = 13.5 Hz, 1H), 3.64 (t, *J* = 13.6 Hz, 2H), 3.27 (d, *J* = 13.3 Hz, 1H), 3.21 (d, *J* = 13.3 Hz, 1H), 3.01 – 2.82 (m, 4H), 2.28 (s, 6H), 2.26 – 1.89 (m, 6H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.5, 208.9, 167.0, 166.9, 145.0, 142.6, 139.2, 136.7, 130.3, 130.2, 129.6, 129.5, 128.46, 128.44, 128.3, 128.26, 128.24, 126.9, 126.5, 86.48, 86.40, 56.0, 55.9, 52.0, 51.9, 42.0, 41.9, 35.7, 35.5, 34.0, 21.0, 20.9. **HRMS** (ESI) Calcd. for $C_{21}H_{24}NO_3$ (M+H) m/z 338.1750, found 338.1752.

2j: Yield 54% (0.085 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.45. **IR** (neat): 2981, 2888, 2852, 2798, 1779, 1325, 1162, 1123, 1068, 1020 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (t, *J* = 5.0 Hz, 4H), 7.38 – 7.26 (m, 4H), 3.96 (d, *J* = 15.0 Hz, 1H), 3.65 (d, *J* = 15.0 Hz,

1H), 3.27 (d, *J* = 15.0 Hz, 1H), 3.05 – 2.90 (m, 2H), 2.35 – 2.29 (m, 1H), 2.27 (s, 3H), 2.16 – 2.00 (m, 1H), 2.03 – 1.93 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.6, 143.4, 141.0, 130.5, 128.4, 125.3 (q, *J* = 3.78 Hz), 125.2 (q, *J* = 3.78 Hz), 86.2, 55.7, 42.1, 35.6, 34.2, 20.8. **HRMS** (ESI) Calcd. for $C_{21}H_{20}F_6NO$ (M+H) m/z 416.1443, found 416.1449.

General procedure for the synthesis of α-allyl-α-methylarylamino cyclobutanones 6a-p

CF_3SO_3Me (760 µmol, 0.086 mL) was added neat to α-allylamino cyclobutanone **5a-p** (380 µmol) at room temperature. After 5 h, CH_3COOEt (8 mL) and K_2CO_3 (950 µmol, 0.131 g) were subsequently introduced in one portion, and the mixture stirred for 72 h at room temperature.The crude reaction mixture was directly loaded onto a silica gel column without aqueous work-up and pure products were obtained by flash column chromatography (silica gel, mixture of petroleum ether/ether, 10:1→1:1).

6a: Yield 73% (0.060 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.36. **IR** (neat): 2969, 1782, 1510, 1229 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 2H), 6.86 – 6.81 (m, 3H), 5.84 – 5.77 (m, 1H), 5.15 – 5.10 (m, 2H), 3.03 (s, 3H), 3.00 – 2.78 (m, 2H), 2.66 – 2.56 (m, 2H), 2.43 – 2.27 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.9, 148.0, 132.8, 128.9, 119.3, 119.2, 117.9, 83.2, 42.4, 36.9, 35.7, 23.3. Calcd. for $C_{14}H_{18}NO$ (M+H) **m/z** 216.1383, found 216.1381.

6b: Yield 66% (0.057 g); yellow oil; R_f (petroleum ether/ether, 5:1) 0.20. **IR** (neat): 2962, 1780, 1515 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.06 – 7.04 (m, 2H), 6.80 – 6.78 (m, 2H), 5.85 – 5.75 (m, 1H), 5.14 – 5.07 (m, 2H), 2.97 (s, 3H), 2.91 – 2.79 (m, 2H), 2.63 – 2.51 (m, 2H), 2.42 – 2.34 (m, 1H), 2.27 (s, 3H), 2.26 – 2.18 (m, 1H). **^{13}C NMR** (101 MHz, CDC_3) δ 208.8, 146.0, 132.9, 129.6, 129.5, 119.6, 119.1, 83.7, 42.3, 37.6, 36.0, 22.6, 20.6. Calcd. for $C_{15}H_{20}NO$ (M+H) **m/z** 230.1539, found 230.1539.

6c: Yield 72% (0.066 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.33. IR (neat): 2963, 1779, 1513 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.09 – 7.07 (m, 2H), 6.81 – 6.79 (m, 2H), 5.84 – 5.75 (m, 1H), 5.14 – 5.08 (m, 2H), 2.98 (s, 3H), 2.92 – 2.83 (m, 2H), 2.61 – 2.55 (m, 4H), 2.40 – 2.37 (m, 1H), 2.27 – 2.23 (m, 1H), 1.21 (td, *J* = 7.6, 2.2 Hz, 3H). **^{13}C NMR** (101

MHz, $CDCl_3$) δ 208.6, 146.1, 135.9, 133.0, 128.2, 119.3, 119.1, 83.7, 42.3, 37.5, 35.9, 28.0, 22.7, 15.8. Calcd. for $C_{16}H_{22}NO$ (M+H) **m/z** 244.1696, found 244.1698.

6d: Yield 55% (0.057 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.22. **IR** (neat): 2961, 1780, 1515 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.07 – 7.05 (m, 2H), 6.80 – 6.78 (m, 2H), 5.84 – 5.75 (m, 1H), 5.14 – 5.08 (m, 2H), 2.98 (s, 3H), 2.92 – 2.84 (m, 2H), 2.61 – 2.48 (m, 4H), 2.41 – 2.35 (m, 1H), 2.27 – 2.22 (m, 1H), 1.59 – 1.55 (m, 2H), 1.36 – 1.32 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.7, 146.1, 134.6, 133.0, 128.8, 119.2, 119.1, 83.7, 42.3, 37.5, 36.0, 34.8, 33.9, 22.7, 22.5, 14.1. Calcd. for $C_{18}H_{26}NO$ (M+H) **m/z** 272.2009, found 272.2008.

6e: Yield 59% (0.061 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.36. **IR** (neat): 2962, 1780, 1515 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 – 7.25 (m, 2H), 6.79 – 6.78 (m, 2H), 5.85 – 5.76 (m, 1H), 5.15 – 5.10 (m, 2H), 3.00 (s, 3H), 2.94 – 2.84 (m, 2H), 2.62 – 2.58 (m, 2H), 2.40 – 2.38 (m, 1H), 2.30 – 2.26 (m, 1H), 1.30 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.4, 145.7, 142.3, 133.0, 125.7, 119.2, 118.1, 83.5, 42.4, 37.2, 35.7, 34.1, 31.6, 22.9. Calcd. for $C_{18}H_{26}NO$ (M+H) **m/z** 272.2009, found 272.2011.

6f: Yield 65% (0.072 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.30. **IR** (neat): 2959, 1779, 1516, 1201 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.38 (m, 6H), 7.42 – 7.25 (m, 1H), 6.87 – 6.85 (m, 2H), 5.86 – 5.78 (m, 1H), 5.18 – 5.13 (m, 2H), 3.09 (s, 3H), 3.03 – 2.85 (m, 2H), 2.70 – 2.61 (m, 2H), 2.47 – 2.35 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.4, 147.2, 141.0, 132.7, 131.6, 128.8, 127.5, 126.5, 126.5, 119.5, 117.5, 83.1, 42.5, 36.7, 35.7, 23.6. Calcd. for $C_{20}H_{22}NO$ (M+H) **m/z** 292.1696, found 292.1700.

6g: Yield 76% (0.072 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.64. **IR** (neat): 2962, 1780, 1503, 1233 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 9.0 Hz, 2H), 6.73 (d, *J* = 9.0 Hz, 2H), 5.81 – 5.73 (m, 1H), 5.16 – 5.09 (m, 2H), 3.01 (s, 3H), 2.99 – 2.88 (m, 2H), 2.65 – 2.53 (m, 2H), 2.36 – 2.25 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.3, 146.6, 132.5, 128.8, 124.2, 119.6, 118.8, 83.1, 42.3, 36.9, 35.8, 23.4. Calcd. for $C_{14}H_{17}{}^{35}ClNO$ (M+H) **m/z** 250.0993, found 250.0995.

6h: Yield 66% (0.073 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.39. **IR** (neat): 2962, 1780, 1503, 1233 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.30 (m, 2H), 6.67 – 6.65 (m,

2H), 5.81 – 5.73 (m, 1H), 5.16 – 5.10 (m, 2H), 3.01 (s, 3H), 2.99 – 2.84 (m, 2H), 2.66 – 2.54 (m, 2H), 2.38 – 2.28 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.0, 146.9, 132.4, 131.6, 119.6, 118.9, 111.2, 82.9, 42.4, 36.7, 35.7, 23.5. Calcd. for $C_{14}H_{17}{}^{79}BrNO$ (M+H) **m/z** 294.0488, found 294.0490.

6i: Yield 61% (0.054 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.61. **IR** (neat): 2959, 1779, 1516, 1201 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.96 – 6.88 (m, 4H), 5.81 – 5.76 (m, 1H), 5.13 – 5.05 (m, 2H), 2.92 (s, 3H), 2.88 – 2.84 (m, 2H), 2.59 – 2.48 (m, 2H), 2.38 – 2.32 (m, 1H), 2.20 – 2.14 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.8, 157.8 (d, *J* = 240.5 Hz), 144.8, 132.7, 122.0 (d, *J* = 7.6 Hz), 119.1, 115.4 (d, *J* = 22.1 Hz), 83.9, 41.9, 38.1, 36.4, 22.2. Calcd. for $C_{14}H_{17}FNO$ (M+H) **m/z** 234.1288, found 234.1291.

6j: Yield 68% (0.059 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.20. **IR** (neat): 2963, 1779, 1496 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.98 – 6.96 (m, 2H), 6.83 – 6.81 (m, 2H), 5.83 – 5.77 (m, 1H), 5.12 – 5.04 (m, 2H), 3.78 (s, 3H), 2.87 (s, 3H), 2.85 – 2.80 (m, 2H), 2.53 – 2.34 (m, 3H), 2.11 – 2.05 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.4, 155.2, 142.5, 133.0, 124.2, 118.8, 114.2, 84.7, 55.6, 41.8, 38.9, 37.0, 21.4. Calcd. for $C_{15}H_{20}NO_2$ (M+H) **m/z** 230.1539, found 230.1538.

6k: Yield 63% (0.074 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.18. **IR** (neat): 2963, 1778, 1597, 1233 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.29 (m, 2H), 7.07 – 7.03 (m, 1H), 6.98 – 6.94 (m, 2H), 6.93 – 6.87 (m, 4H), 5.85 – 5.76 (m, 1H), 5.15 – 5.08 (m, 2H), 2.97 (s, 3H), 2.93 – 2.86 (m, 2H), 2.60 – 2.52 (m, 2H), 2.41 – 2.36 (m, 1H), 2.23 – 2.17 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.8, 158.3, 150.7, 144.5, 132.8, 129.7, 122.7, 121.4, 120.0, 119.2, 118.1, 83.9, 42.1, 38.0, 36.3, 22.4. Calcd. for $C_{20}H_{21}NO_3$ (M+H) **m/z** 308.1645, found 308.1648.

6l: Yield 0%.

6m: Yield 53% (0.046 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.49. **IR** (neat): 2960, 1780, 1516, 1276 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 – 7.10 (m, 1H), 6.68 – 6.62 (m, 3H), 5.84 – 5.76 (m, 1H), 5.16 – 5.10 (m, 2H), 3.02 (s, 3H), 2.99 – 2.81 (m, 2H), 2.64 – 2.56 (m, 2H), 2.43 – 2.33 (m, 1H), 2.32 (s, 3H), 2.30 – 2.26 (m, 1H) **^{13}C NMR** (101 MHz, $CDCl_3$)

δ 208.0, 148.1, 138.7, 132.9, 128.6, 120.2, 119.3, 118.8, 115.2, 83.3, 42.4, 37.0, 35.8, 23.3, 22.0. Calcd. for $C_{15}H_{20}NO$ (M+H) **m/z** 230.1539, found 230.1536.

6n: Yield 69% (0.063 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.50. IR (neat): 2966, 1776, 1587, 1277 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.52 (s, 1H), 6.45 (s, 2H), 5.85 – 5.76 (m, 1H), 5.16 – 5.10 (m, 2H), 3.00 (s, 3H), 2.99 – 2.80 (m, 2H), 2.67 – 2.55 (m, 2H), 2.43 – 2.35 (m, 1H), 2.32 – 2.23 (m, 1H), 2.28 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.1, 148.2, 138.4, 133.0, 121.4, 119.2, 116.1, 83.4, 42.4, 37.1, 35.9, 23.3, 21.8. Calcd. for $C_{16}H_{22}NO$ (M+H) **m/z** 244.1696, found 244.1699.

6o: Yield 59% (0.062 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.15. **IR** (neat): 2961, 1780, 1497, 1233 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.4 Hz, 1H), 6.67 (s, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 5.84 – 5.77 (m, 1H), 5.13 – 5.05 (m, 2H), 3.854 (s, 3H), 3.845 (s, 3H), 2.89 (s, 3H), 2.84 – 2.80 (m, 2H), 2.54 – 2.49 (m, 2H), 2.44 – 2.38 (m, 1H), 2.12 – 2.07 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.3, 149.2, 144.9, 143.0, 133.0, 118.9, 114.3, 111.7, 108.0, 84.7, 56.3, 56.0, 41.7, 38.8, 37.1, 21.5. Calcd. for $C_{16}H_{22}NO_3$ (M+H) **m/z** 276.1594, found 276.1599.

6p: Yield 77% (0.075 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.72. **IR** (neat): 2953, 1776, 1588, 1477 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.09 – 6.89 (m, 3H), 5.80 – 5.70 (m, 1H), 5.04 – 4.89 (m, 2H), 2.92 – 2.76 (m, 6H), 2.74 (s, 3H), 2.58 – 2.39 (m, 3H), 2.07 – 1.98 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.9, 146.1, 145.9, 141.5, 133.1, 126.6, 122.3, 120.6, 118.1, 85.0, 41.6, 38.7, 37.9, 33.5, 31.6, 25.3, 20.8. Calcd. for $C_{17}H_{22}NO$ (M+H) **m/z** 256.1696, found 256.1696.

Procedure for the synthesis of tryptamines 7 and 7'

A mixture of *N*-methyl aniline (0.465 mmol, 0.050 g), α-allyl-α-amino cyclobutanone, **6a** (0.465 mmol, 0.112 g), and PTSA (0.186 mmol, 0.035 g) was stirred at 50°C for 4 days. The crude reaction mixture was directly loaded onto a silica gel column without aqueous work-up and pure products were obtained by flash column chromatography (silica gel, mixture of petroleum ether/ether, 10:1→1:1).

7+7': Yield 68% (0.096 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.57. **IR** (neat): 3056, 1598, 1504, 1469, 745, 691 cm^{-1}. Spectral data determined from the 86:14 inseparable mixture of two isomers; (**7**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.30 – 7.23 (m, 3H), 7.21 – 7.16 (m, 1H), 7.14 – 7.09 (m, 1H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.70 (t, *J* = 7.2 Hz, 1H), 5.99 – 5.88 (m, 1H), 5.09 (dd, *J* = 10.1, 1.6 Hz, 1H), 4.93 (dd, *J* = 17.1, 1.7 Hz, 1H), 3.63 (s, 3H), 3.55 – 3.49 (m, 4H), 2.98 – 2.95 (m, 2H), 2.93 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.0, 137.0, 135.3, 134.5, 129.3, 127.7, 121.1, 119.0, 118.2, 116.4, 116.0, 112.2, 109.5, 108.9, 53.9, 38.5, 29.7, 28.8, 21.6. Calcd. for $C_{21}H_{25}N_2$ (M+H) **m/z** 305.2012, found 305.2015.

Procedure for the synthesis of cyclobuta-fused indolines 8a-f

A mixture of aniline (0.93 mmol), α-allyl-α-amino cyclobutanone, **6a** (0.465 mmol, 0.112 g), and PTSA (0.093 mmol, 0.018 g) was stirred at room temperature for 4 days. The crude reaction mixture was directly loaded onto a silica gel column without aqueous work-up and pure products were obtained by flash column chromatography (silica gel, mixture of petroleum ether/ether, 5:1→1:1).

8a: Yield 44% (0.059 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.73. **IR** (neat): 3056, 2976, 1600, 1505, 1495 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 7.7 Hz, 2H), 6.63 (t, *J* = 7.2 Hz, 1H), 6.57 (t, *J* = 8.7 Hz, 2H), 6.39 (d, *J* = 8.1 Hz, 2H), 6.10 – 6.03 (m, 1H), 5.16 – 5.06 (m, 2H), 4.20 (brs, 1H), 2.74 (s, 3H), 2.60 (d, *J* = 7.2 Hz, 2H), 2.39 – 2.32 (m, 1H), 2.19 (dd, *J* = 20.6, 10.3 Hz, 1H), 1.91 (dt, *J* = 19.4, 9.6 Hz, 1H), 1.81 – 1.74 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.5, 145.7, 134.8, 129.3, 129.1, 128.8, 124.2, 118.6, 117.7, 117.3, 114.5, 108.4, 71.1, 65.2, 36.8, 33.1, 29.8, 21.7. Calcd. for $C_{20}H_{23}N_2$ (M+H) **m/z** 291.1855, found 291.1854.

8b: Yield 45% (0.063 g); yellow oil; **R_f** (petroleum ether/ether, 5:1) 0.75. **IR** (neat): 2923, 2857, 1608, 1516, 1307 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.63 (t, *J* = 7.4 Hz, 1H), 6.55 (d, *J* = 7.9 Hz, 1H), 6.31 (d, *J* = 8.1 Hz, 2H), 6.10 – 6.03 (m, 1H), 5.16-5.06 (m, 2H), 4.11 (brs, 1H), 2.74 (s, 3H), 2.60 (d, *J* = 7.2 Hz, 2H), 2.36 – 2.28 (m, 1H), 2.22 – 2.16 (m, 1H), 2.13 (s, 3H), 1.89 (dd, *J* = 20.5, 10.6 Hz, 1H), 1.77 (td, *J* = 12.0, 2.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.5,

143.3, 134.9, 132.9, 129.4, 129.1, 126.4, 124.2, 118.6, 117.6, 114.6, 108.3, 71.1, 65.4, 36.9, 33.1, 29.8, 21.7, 20.4. Calcd. for $C_{21}H_{25}N_2$ (M+H) **m/z** 305.2012, found 305.2014.

8c: Yield 90% (0.154 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.73. **IR** (neat): 3336, 2973, 2923, 1637, 1596, 1489 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.7 Hz, 1H), 7.05 – 7.01 (m, 3H), 6.65 (t, *J* = 7.4 Hz, 1H), 6.56 (d, *J* = 7.9 Hz, 1H), 6.26 (d, *J* = 8.7 Hz, 2H), 6.06 – 5.98 (m, 1H), 5.15 – 5.06 (m, 2H), 4.25 (brs, 1H), 2.74 (s, 3H), 2.57 (d, *J* = 7.3 Hz, 2H), 2.38 – 2.31 (m, 1H), 2.16 (dd, *J* = 20.8, 10.7 Hz, 1H), 1.94 – 1.86 (m, 1H), 1.80 – 1.74 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.5, 144.7, 134.5, 132.0, 131.5, 129.4, 124.2, 118.7, 117.8, 116.2, 109.2, 108.5, 71.1, 65.1, 36.8, 33.0, 29.8, 21.7. Calcd. for $C_{20}H_{22}{}^{79}BrN_2$ (M+H) **m/z** 368.0888, found 368.0892.

8d: Yield 76% (0.115 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.73. **IR** (neat): 3077, 2976, 1600, 1492, 1311 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 (td, *J* = 7.9, 1.3 Hz, 1H), 7.02 (dd, *J* = 7.3, 0.8 Hz, 1H), 6.92 – 6.88 (m, 2H), 6.65 (td, *J* = 7.4, 0.8 Hz, 1H), 6.56 (d, *J* = 7.9 Hz, 1H), 6.32 – 6.28 (m, 2H), 6.09-5.98 (m, 1H), 5.17 – 5.06 (m, 2H), 4.24 (brs, 1H), 2.74 (s, 3H), 2.58 (d, *J* = 7.3 Hz, 2H), 2.34 (ddd, *J* = 11.3, 9.4, 3.0 Hz, 1H), 2.16 (dd, *J* = 20.7, 10.8 Hz, 1H), 1.90 (dt, *J* = 12.0, 9.5 Hz, 1H), 1.77 (ddd, *J* = 12.2, 10.7, 3.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.5, 144.3, 134.5, 132.1, 129.3, 128.7, 124.2, 122.0, 118.7, 117.8, 115.7, 108.5, 71.1, 65.2, 36.8, 33.0, 29.8, 21.7. Calcd. for $C_{20}H_{22}{}^{35}ClN_2$ (M+H) **m/z** 324.1398, found 324.1398.

8e: Yield 83% (0.121 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.10. **IR** (neat): 2981, 2869, 2214, 1604, 1518 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 – 7.19 (m, 3H), 7.02 (dd, *J* = 7.3, 0.8 Hz, 1H), 6.67 (td, *J* = 7.4, 0.8 Hz, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 6.36 (d, *J* = 8.8 Hz, 2H), 6.03 – 5.97 (m, 1H), 5.13 – 5.06 (m, 2H), 4.74 (s, 1H), 2.75 (s, 3H), 2.56 (t, *J* = 6.9 Hz, 2H), 2.38 (ddd, *J* = 11.4, 9.4, 2.9 Hz, 1H), 2.20 (dd, *J* = 20.8, 10.8 Hz, 1H), 1.93 (dt, *J* = 12.1, 9.5 Hz, 1H), 1.80 (ddd, *J* = 12.3, 10.8, 2.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.4, 149.3, 134.0, 133.3, 131.2, 129.7, 124.0, 120.5, 118.9, 118.2, 114.3, 108.8, 99.2, 71.2, 64.8, 36.7, 32.8, 29.7, 21.8. Calcd. for $C_{21}H_{22}N_3$ (M+H) **m/z** 316.1808, found 316.1807.

8f: Yield 67% (0.105 g); yellow oil; $\mathbf{R_f}$ (petroleum ether/ether, 5:1) 0.10. **IR** (neat): 3374, 2936, 1596, 1472, 1297 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 9.3 Hz, 2H), 7.13 (t,

J = 7.7 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.61 (t, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 6.28 (d, *J* = 9.1 Hz, 2H), 5.95 – 5.90 (m, 1H), 5.06 – 4.93 (m, 2H), 4.93 (s, 1H), 2.69 (s, 3H), 2.55 – 2.45 (m, 2H), 2.36 – 2.31 (m, 1H), 2.16 (q, *J* = 10.6 Hz, 1H), 1.91 – 1.84 (m, 1H), 1.77 – 1.72 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.4, 151.4, 138.5, 133.9, 131.0, 129.9, 125.9, 124.0, 119.0, 118.3, 113.3, 108.9, 71.3, 65.0, 36.7, 32.8, 29.7, 21.9. Calcd. for $C_{20}H_{22}N_3O_2$ (M+H) **m/z** 336.1706, found 336.1708.

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General Procedure for α-benzylamination of α-hydroxy cyclobutanone and α-hydroxy cyclopentanone

To a solution of freshly distilled α-hydroxy cyclobutanone (1.338 mmol, 0.116 g) or α-hydroxy cyclopentanone (1.338 mmol, 0.134 g), DMAP (0.0896 mmol, 0.0109 g) in dry Toluene (1.0 mL) at room temperature was added dropwise the benzylamine (0.448 mmol), and the mixture was stirred for 15 h. The crude reaction mixture was directly loaded on silica gel column without aqueous work-up and pure products were obtained by flash column chromatography (silica gel, mixture of petroleum ether/ether, 5:1→1:1): (**1a**) 90% yield; (**1b**) 86% yield; (**1c**) 68% yield; (**1d**) 62% yield; (**1e**) 77% yield; (**1f**) 71% yield; (**1g**) 89% yield; (**1h**) 63% yield; (**1i**) 75% yield; (**1j**) 67% yield; (**1k**) 71% yield; (**1l**) 73% yield; (**1m**) 85% yield; (**1n**) 93% yield; (**1o**) 51% yield; (**1p**) 74% yield; (**1q**) 81% yield; (**1r**) 88% yield; (**1s**) 71% yield; see Ref. 1.

3a: Yield 91%; yellow oil. **IR** (neat): 2972, 2930, 2883, 1737, 1465, 1381, 1161, 1127, 1103 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 4H), 7.29 (t, *J* = 7.5 Hz, 4H), 7.25 – 7.18 (m, 2H), 3.83 (d, *J* = 13.7 Hz, 2H), 3.59 (d, *J* = 13.7 Hz, 2H), 3.24 (ddd, *J* = 11.9, 8.1, 0.9 Hz, 1H), 2.25 (dd, *J* = 17.9, 7.8 Hz, 1H), 2.12 (ddd, *J* = 10.0, 7.5, 6.3 Hz, 1H), 2.00 (ddt, *J* = 15.9, 9.3, 8.7 Hz, 2H), 1.92

– 1.79 (m, 1H), 1.69 – 1.51 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 219.04, 139.71, 128.63, 128.20, 126.96, 66.65, 55.09, 37.63, 24.61, 18.21. **HRMS** (ESI) Calcd. for $C_{19}H_{21}NO$ (M+1) m/z 280,169575, found 280,1704.

General Procedure for α-dibenzylamination of 2-hydroxycyclohexanone and 3-hydroxybutan-2-one

α-Dibenzylamino ketones **3b,c** were prepared from the corresponding α-hydroxy ketones and dibenzyl amine according to literature procedures.[2]

3b: Yield 62%; white solid; m. p.= 95-97°C. **IR** (neat): 2986, 2942, 2867, 1710, 1494, 1452, 1264, 1065, 1028 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.3 Hz, 4H), 7.28 (t, *J* = 7.5 Hz, 4H), 7.20 (t, *J* = 7.2 Hz, 2H), 3.99 (d, *J* = 14.3 Hz, 2H), 3.75 (d, *J* = 14.3 Hz, 2H), 3.30 (dd, *J* = 12.3, 5.6 Hz, 1H), 2.44 – 2.32 (m, 1H), 2.27 – 2.07 (m, 2H), 2.03 – 1.73 (m, 3H), 1.67 – 1.42 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 211.99, 140.69, 128.45, 128.18, 126.74, 66.55, 54.86, 42.43, 31.64, 27.12, 25.02. **HRMS** (ESI) Calcd. for $C_{20}H_{23}NO$ (M+1) m/z 294,185275, found 294,1871.

3c: Yield 25%; yellow oil. **IR** (neat): 2986, 1710, 1422, 1379, 1264, 1159, 1077 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.38 (m, 4H), 7.34-7.31 (m, 4H), 7.26-7.23 (m, 2H), 3.70 (d, *J* = 13.7 Hz, 2H), 3.46 (d, *J* = 13.7 Hz, 2H), 3.36 (q, *J* = 6.7 Hz, 1H), 2.22 (s, 3H), 1.15 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.80, 139.27, 128.70, 128.38, 127.17, 62.86, 54.58, 27.63, 7.06. **HRMS** (ESI) Calcd. for $C_{18}H_{21}NO$ (M+1) m/z 268,169575, found 268,1707.

General procedure for the synthesis of α-allylamino cyclobutanones 5a-p

To a mixture of freshly distilled α-hydroxy cyclobutanone (1.338 mmol, 0.116 g), DMAP (0.0896 mmol, 0.0109 g) in CH_2Cl_2 (0.25 mL) at room temperature was added the arylallylamine (0.448 mmol), and the mixture was stirred for 24 h. The crude reaction mixture was directly loaded on silica gel column without aqueous work-up and pure products were obtained by flash column chromatography (silica gel, mixture of petroleum ether/ether, 10:1→1:1).

5a: Yield 85%. Spectroscopic data were in accordance with literature reported values; see Ref. 3.

5b: Yield 74%; yellow oil. **IR** (neat): 2961, 1779, 1596, 1501 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H), 5.91-5.84 (m, 1H), 5.23-5.15 (m, 2H), 4.99-4.94 (m, 1H), 3.99 – 3.84 (m, 2H), 2.86-2.81 (m, 1H), 2.75 – 2.73 (m, 1H), 2.42 – 2.30 (m, 1H), 2.24 (s, 3H), 2.23 – 2.08 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.95, 145.70, 135.42, 129.75, 128.17, 116.56, 115.27, 74.40, 51.74, 40.50, 20.42, 17.84.

5c: Yield 77%; yellow oil. **IR** (neat): 2964, 1779, 1506, 1224 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 5.90-5.81 (m, 1H), 5.21 – 5.09 (m, 2H), 4.97 – 4.92 (m, 1H), 3.96 – 3.82 (m, 2H), 2.85 – 2.70 (m, 2H), 2.52 (q, *J* = 7.6 Hz, 2H), 2.36-2.30 (m, 1H), 2.15 – 2.05 (m, 1H), 1.16 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.94, 145.92, 135.51, 134.64, 128.56, 116.52, 115.08, 74.35, 51.71, 40.51, 27.94, 17.89, 15.89.

5d: Yield 39%; yellow oil. **IR** (neat): 2963, 1780, 1598, 1503 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.6 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 2H), 5.94-5.85 (m, 1H), 5.24 – 5.13 (m, 2H), 5.00-4.96 (m, 1H), 4.00 – 3.85 (m, 2H), 2.89 – 2.69 (m, 2H), 2.53 – 2.49 (m, 2H), 2.40-2.36 (m, 1H), 2.18 – 2.09 (m, 1H), 1.58-1.51 (m, 2H), 1.38-1.29 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.01, 135.58, 133.31, 129.14, 116.53, 114.99, 74.36, 51.73, 40.53, 34.75, 33.99, 22.50, 17.92, 14.12.

5e: Yield 64%; yellow oil. **IR** (neat): 2957, 1777, 1512, 1240 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 5.94-5.86 (m 1H), 5.25 – 5.14 (m, 2H), 5.02 – 4.97 (m, 1H), 3.99 – 3.86 (m, 2H), 2.88 – 2.82 (m, 1H), 2.77 – 2.73 (m, 1H), 2.40-2.35 (m, 1H), 2.34-2.14 (m, 1H), 1.28 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.87, 145.55, 141.29, 135.59, 126.03, 116.43, 114.27, 74.14, 51.56, 40.50, 33.96, 31.59, 17.90.

5f: Yield 55%; yellow oil. **IR** (neat): 2917, 1782, 1523, 1044 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.24 (m, 1H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.96-5.88 (m, 1H), 5.27-5.18 (m, 2H), 5.08-5.05 (m, 1H), 4.06-3.93 (m, 2H), 2.91 – 2.87 (m, 1H), 2.80 – 2.78 (m, 1H), 2.48-2.40 (m, 1H), 2.22 – 2.14 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.32, 147.16, 141.01, 135.06, 131.34, 128.80, 127.90, 126.52, 126.43, 116.69, 114.59, 73.86, 51.25, 40.64, 18.05.

5g: Yield 58%; yellow oil. **IR** (neat): 2964, 1779, 1506, 1230 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 9.0 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 5.89 – 5.82 (m, 1H), 5.22 – 5.15 (m, 2H), 4.96 (t, *J* = 9.4 Hz, 1H), 4.00 – 3.85 (m, 2H), 2.89-2.79 (m, 1H), 2.78 – 2.76 (m, 1H), 2.45-2.40 (m, 1H), 2.39 – 2.08 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.07, 146.47, 134.69, 129.06, 123.49, 116.82, 115.75, 73.86, 51.36, 40.64, 17.95.

5h: Yield 72%; yellow oil. **IR** (neat): 2928, 1782, 1492cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9.0 Hz, 1H), 6.62 – 6.60 (m, 2H), 5.89 – 5.81 (m, 1H), 5.21 – 5.15 (m, 2H), 4.98-4.94 (m, 1H), 3.99 – 3.85 (m, 2H), 2.95-2.85 (m, 1H), 2.81-2.72 (m, 1H), 2.46-2.37 (m, 1H), 2.18 – 2.08 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.93, 146.86, 134.59, 131.96, 116.83, 116.10, 110.62, 73.73, 51.22, 40.66, 17.95.

5i: Yield 60%; yellow oil. **IR** (neat): 2962, 1777, 1503, 1236 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.93 – 6.89 (m, 2H), 6.74 – 6.71 (m, 2H), 5.89 – 5.82 (m, 1H), 5.22-5.14 (m, 2H), 4.92-4.89 (m, 1H), 3.96 – 3.83 (m, 2H), 2.89 – 2.83 (m, 1H), 2.77 – 2.70 (m, 1H), 2.41-2.34 (m, 1H), 2.16 – 2.09 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.74, 157.77, 155.88, 144.60, 135.19, 117.07, 117.01, 116.87, 115.73, 115.55, 74.76, 52.34, 40.56, 17.81.

5j: Yield 63%; yellow oil. **IR** (neat): 2961, 1782, 1500, 1261 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.81-6.79 (m, 4H), 5.90-5.83 (m, 1H), 5.23-5.11 (m, 2H), 4.89-4.84 (m, 1H), 3.94 – 3.80 (m, 2H), 3.75 (s, 3H), 2.89 – 2.79 (m, 1H), 2.74 – 2.66 (m, 1H), 2.38-2.30 (m, 1H), 2.15-2.07 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.48, 153.60, 142.31, 135.64, 118.39, 116.81, 114.59, 75.37, 55.74, 52.95, 40.47, 17.62.

5k: Yield 73%; yellow oil. **IR** (neat): 2965, 1779, 1505, 1224 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 2H), 7.03-7.00 (m, 1H), 6.94 – 6.90 (m, 4H), 6.76 – 6.74 (m, 2H), 5.92 – 5.85 (m, 1H), 5.24 – 5.15 (m, 2H), 4.97 – 4.93 (m, 1H), 3.99-3.86 (m, 2H), 2.91 – 2.83 (m, 1H), 2.77 – 2.70 (m, 1H), 2.42-2.35 (m, 1H), 2.16 – 2.12 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.89, 158.70, 149.18, 144.58, 135.35, 129.69, 122.43, 120.70, 117.71, 116.78, 116.58, 74.59, 52.14, 40.58, 17.88.

5l: Yield 48%; yellow oil. **IR** (neat): 2966, 1777, 1507, 1225 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 – 7.12 (m, 3H), 7.03 – 6.99 (m, 1H), 5.83-5.76 (m, 1H), 5.15-5.02 (m, 2H), 4.56-4.51 (m, 1H),

3.84 – 3.69 (m, 2H), 2.77 – 2.69 (m, 1H), 2.65-2.57 (m, 1H), 2.30 (s, 3H), 2.25-2.16 (m, 1H), 2.12 – 2.05 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.83, 148.20, 135.68, 134.92, 131.06, 126.41, 124.66, 124.58, 117.59, 77.47, 54.42, 40.23, 18.36, 16.91.

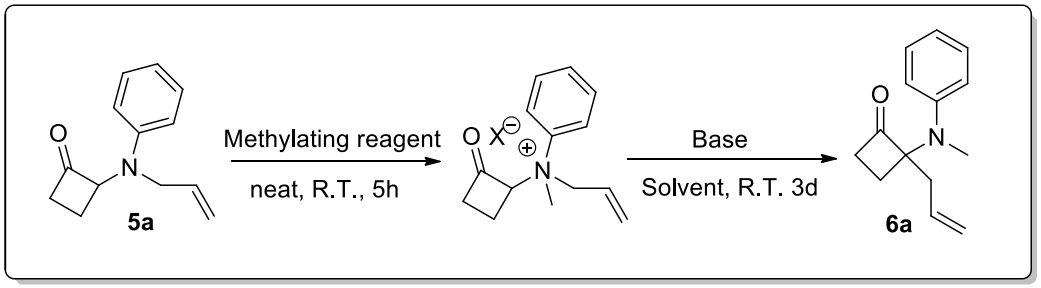
5m: Yield 45%; yellow oil. **IR** (neat): 2963, 1778, 1595, 1069 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12-7.08 (m, 1H), 6.62-6.55 (m, 3H), 5.93 – 5.86 (m, 1H), 5.24 – 5.13 (m, 2H), 5.04 – 4.99 (m, 1H), 4.02 – 3.86 (m, 2H), 2.90 – 2.82 (m, 1H), 2.78 – 2.74 (m, 1H), 2.44-2.35 (m, 1H), 2.29 (s, 3H), 2.18 – 2.11 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.68, 147.97, 138.96, 135.39, 129.08, 119.54, 116.48, 115.28, 111.77, 73.98, 51.25, 40.52, 21.98, 18.02.

5n: Yield 46%; yellow oil. **IR** (neat): 2962, 1780, 1596, 1505 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.45 (s, 1H), 6.39 (s, 2H), 5.93 – 5.86 (m, 1H), 5.24 – 5.14 (m, 2H), 5.05 – 4.99 (m, 1H), 4.01 – 3.85 (m, 2H), 2.89 – 2.82 (m, 1H), 2.78 – 2.69 (m, 1H), 2.44 – 2.39 (m, 1H), 2.25 (s, 6H), 2.18-2.08 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.81, 148.12, 138.84, 135.55, 131.04, 128.96, 120.66, 116.44, 112.55, 74.06, 51.21, 40.51, 21.86, 18.08.

5o: Yield 29%; yellow oil. **IR** (neat): 2965, 1780, 1592, 1496 cm^{-1}. **^{1}H NMR** (500 MHz, CDCl3) δ 6.79 – 6.74 (m, 1H), 6.48 (d, *J* = 2.7 Hz, 1H), 6.36 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.92 – 5.86 (m, 1H), 5.24-5.14 (m, 2H), 4.89 – 4.85 (m, 1H), 3.94 – 3.83 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 2.87-2.81 (m, 1H), 2.73 – 2.67 (m, 1H), 2.37-2.31 (m, 1H), 2.15 – 2.09 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.33, 149.61, 143.20, 142.98, 135.73, 116.79, 112.44, 108.57, 102.86, 75.32, 56.50, 55.91, 52.99, 40.46, 17.59.

5p: Yield 70%; yellow oil. **IR** (neat): 2955, 1780, 1587, 1054 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.05 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.3 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 5.83-5.76 (m, 1H), 5.18-5.04 (m, 2H), 4.73 – 4.68 (m, 1H), 3.94-3.74 (m, 2H), 2.91 – 2.60 (m, 6H), 2.28 – 2.00 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.37, 146.17, 146.12, 137.55, 136.00, 126.82, 119.13, 118.98, 117.24, 76.60, 52.88, 40.19, 33.43, 31.96, 25.70, 17.48.

Table 3.2. Optimization of the conditions for the synthesis of α-allyl-α-methylarylamino cyclobutanone 6a.[a]



Entry	**Methylating reagent**	**Base**	**Solvent**	**Yield 6a** (%)[b]
1	CF_3SO_3Me	K_2CO_3	Diethyl ether	36
2	**CF_3SO_3Me**	**K_2CO_3**	**CH_3COOEt**	**73**
3	CF_3SO_3Me	K_2CO_3	THF	63
4	CF_3SO_3Me	K_2CO_3	1,4-Dioxane	65
5	CF_3SO_3Me	K_2CO_3	Toluene	58
6	CF_3SO_3Me	K_2CO_3	CH_2Cl_2	37
7	CF_3SO_3Me	K_2CO_3	CH_3CN	56
8	CF_3SO_3Me	Li_2CO_3	CH_3COOEt	traces
9	CF_3SO_3Me	Cs_2CO_3	CH_3COOEt	63
10	CF_3SO_3Me	Na_2CO_3	CH_3COOEt	71
11	MeI	K_2CO_3	CH_3COOEt	0
12	Me_2SO_4	K_2CO_3	CH_3COOEt	traces
13	$Me_3O^+BF_4^-$	K_2CO_3	CH_3COOEt	35
14	CF_3SO_3Me	K_2CO_3	CH_3COOEt	55[c]

[a] Conditions: 5a (380 µmol), Methylating reagent (760 µmol), base (950 µmol), solvent (4 mL).

[b] Isolated yield after chromatography.
[c] Reaction carried out under reflux for 16h.

References and notes

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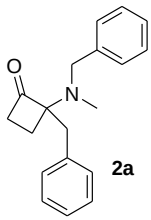
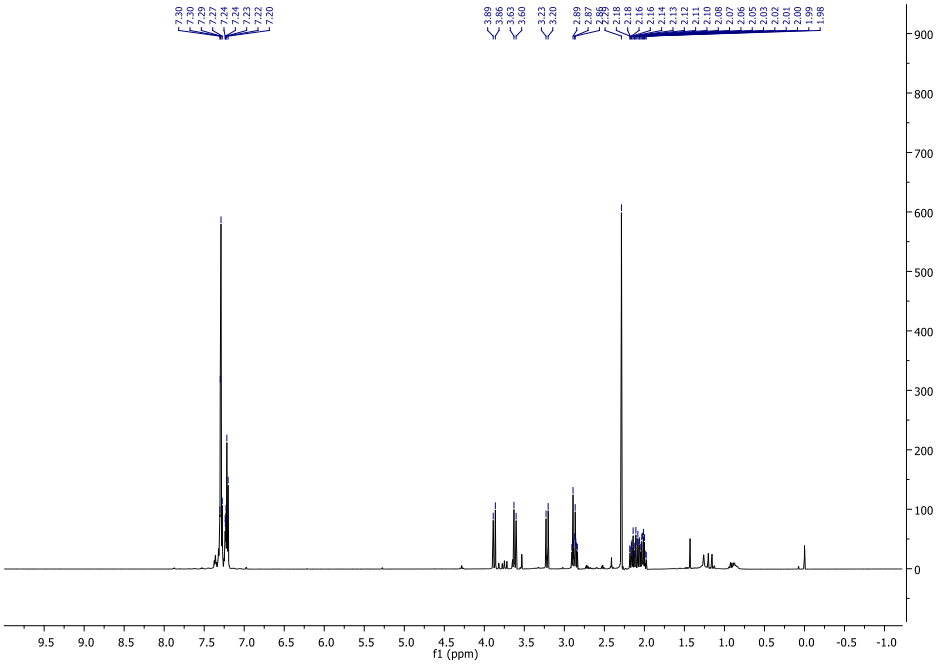
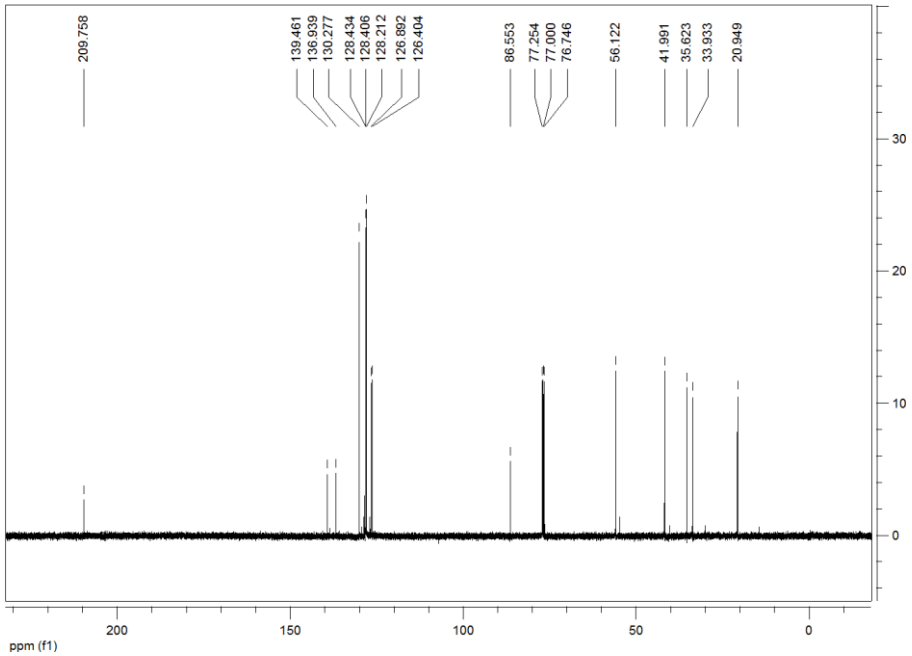
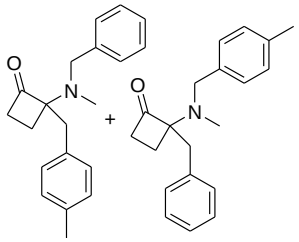
3.4.3 Copies of NMR spectra



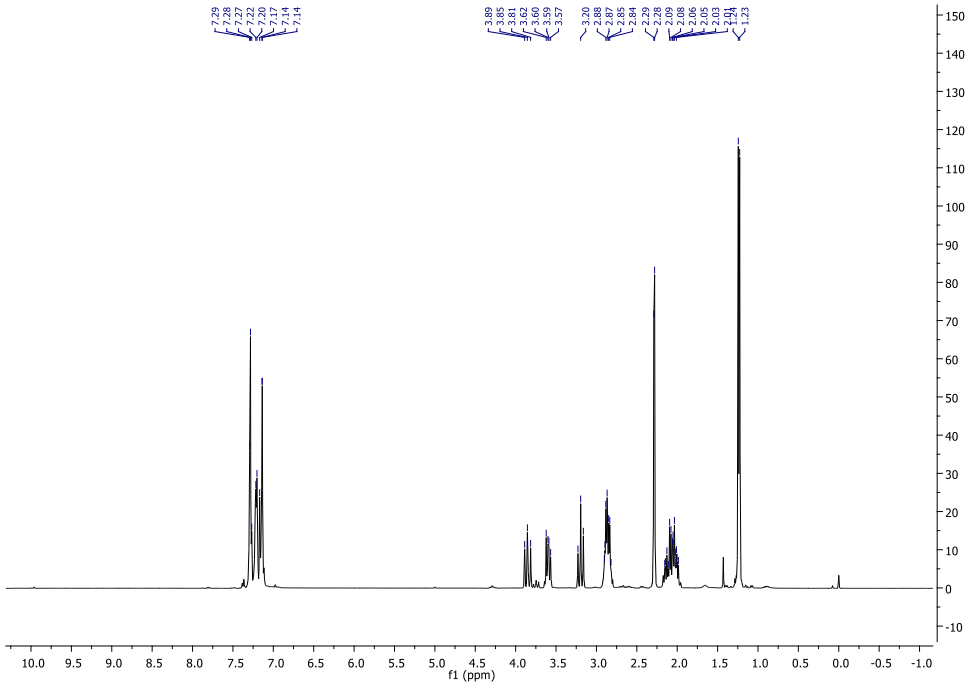
2a







2b+2b'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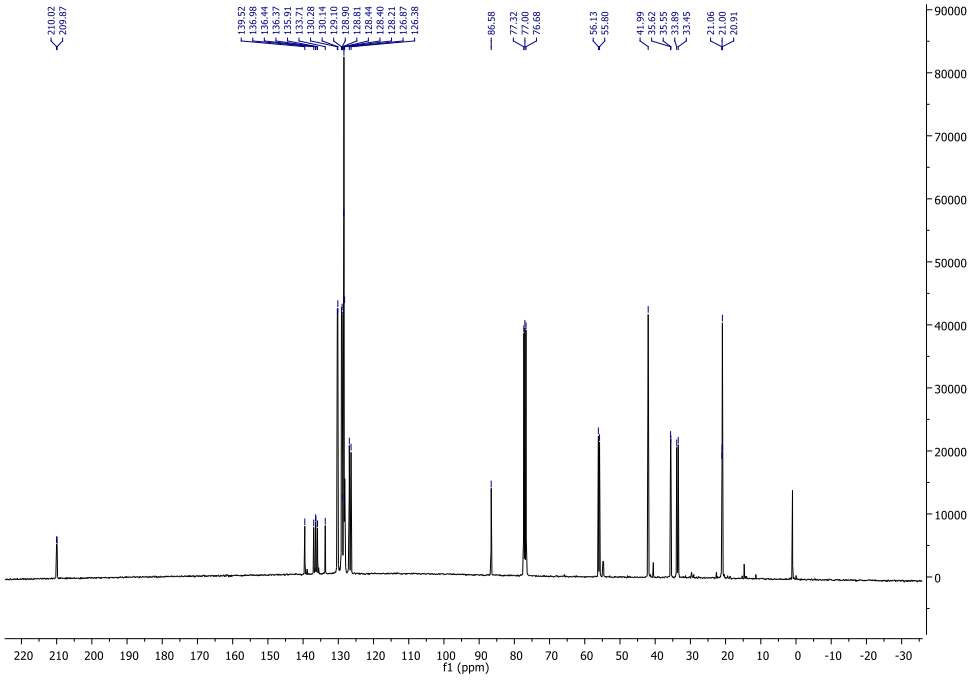
f1 (ppm)


210.02
209.87
139.52
136.98
136.44
136.37
135.91
133.71
130.28
130.14
129.10
128.90
128.81
128.44
128.40
128.21
126.87
126.38
86.58
77.32
77.00
76.68
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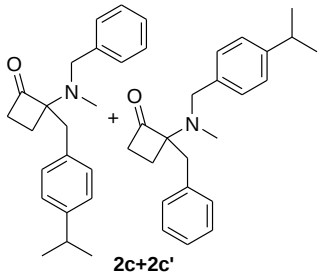
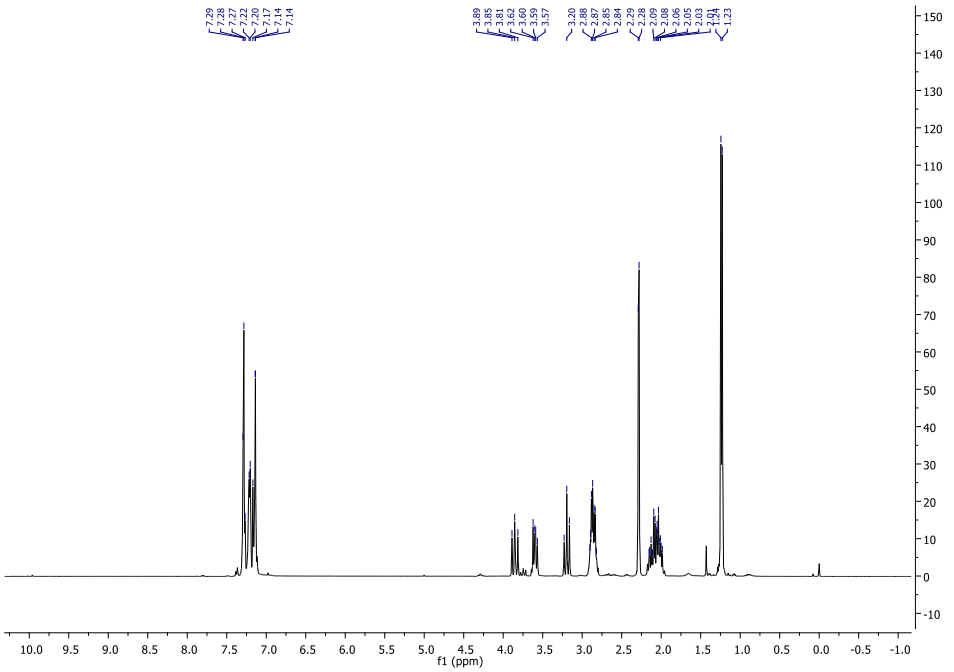
41.99
35.62
35.55
33.89
33.45
21.06
21.00
20.91
f1 (ppm)


O
N
+
O
N

2c+2c'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7.14
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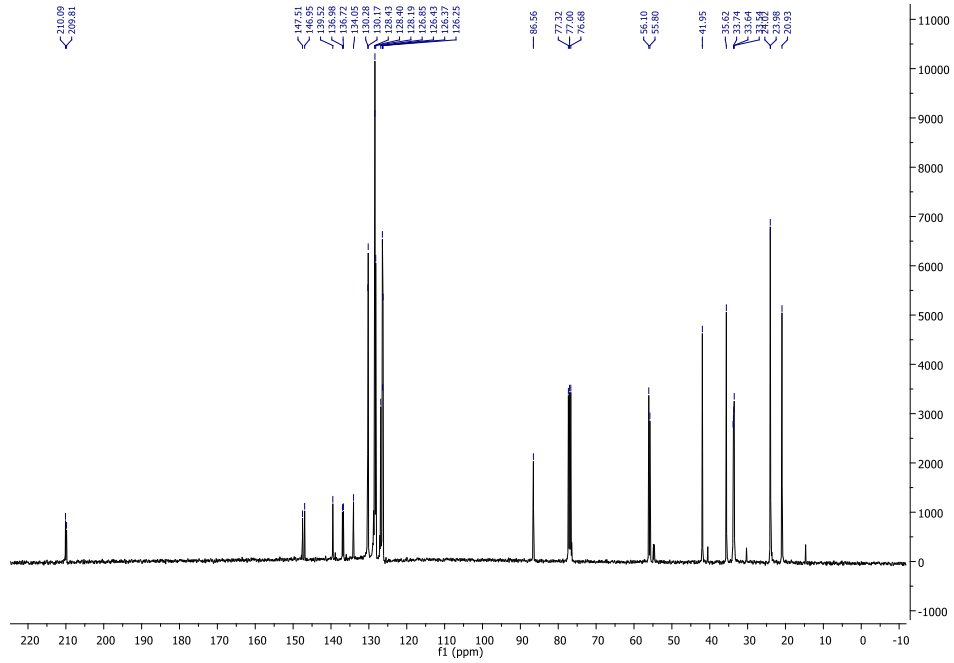
3.85
3.81
3.62
3.60
3.59
3.57
3.20
2.88
2.87
2.85
2.84
2.29
2.28
2.09
2.08
2.06
2.05
2.03
1.24
1.23
f1 (ppm)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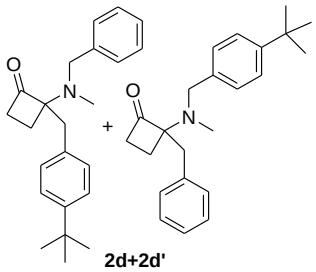
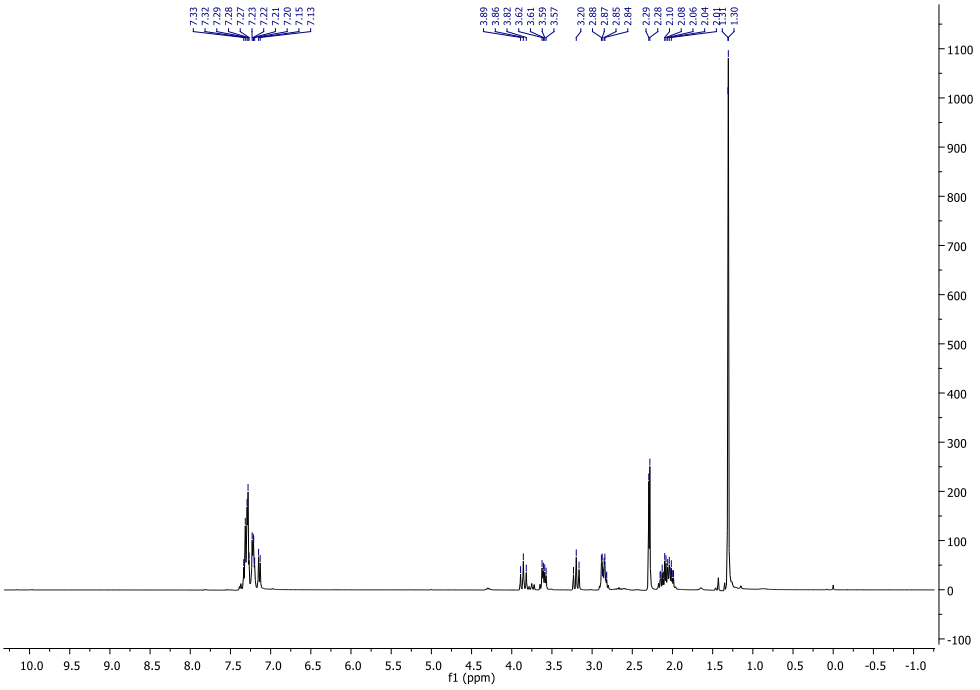
138.98
136.72
134.05
130.28
130.17
129.43
128.40
128.19
126.85
126.43
126.37
126.25
86.56
77.32
77.00
76.68
56.10
55.80
41.95
35.62
33.74
33.64
33.54
33.41
23.98
20.93
f1 (ppm)



2d+2d'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7.22
7.21
7.20
7.15
7.13
3.89
3.86
3.82
3.62
3.61
3.59
3.57
3.20
2.88
2.87
2.85
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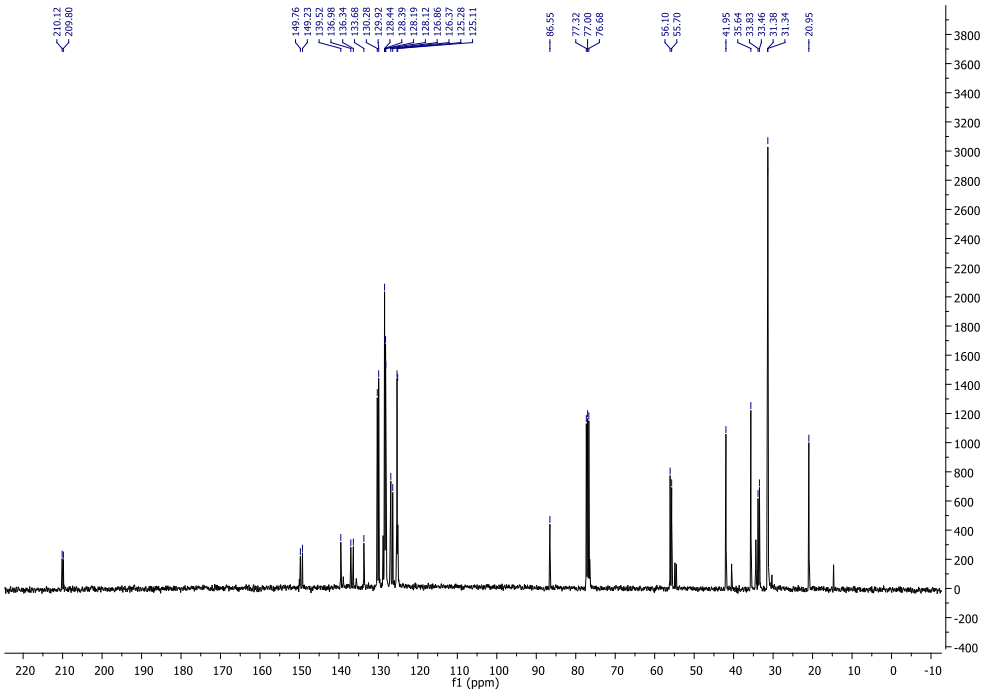
2.29
2.28
2.10
2.08
2.06
2.04
2.01
1.30
f1 (ppm)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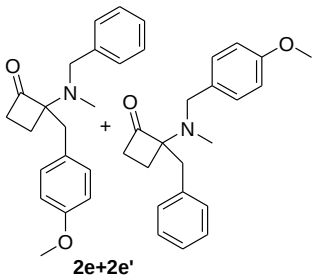
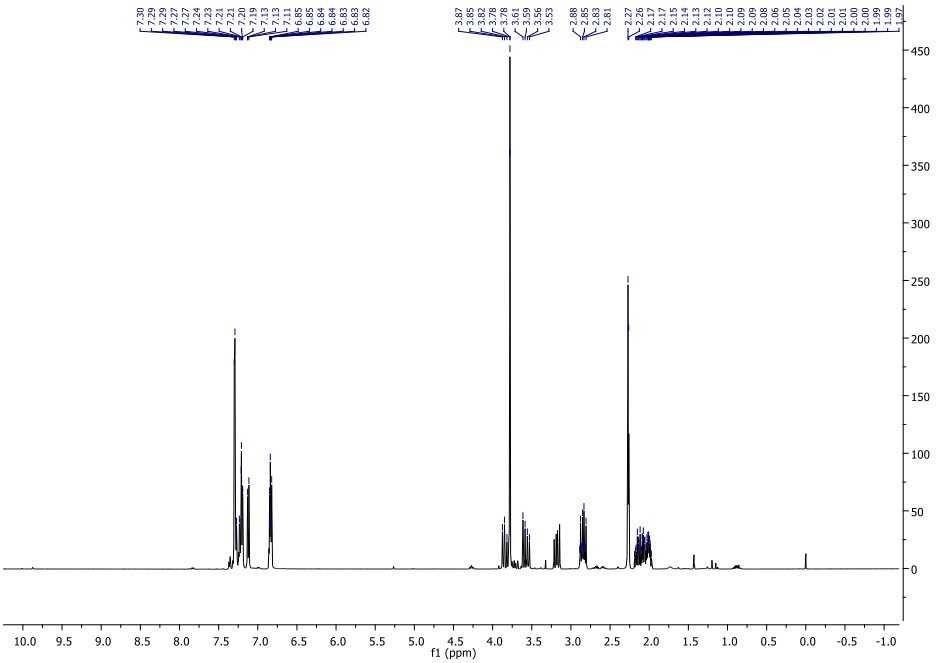
136.34
133.68
130.28
129.92
128.44
128.39
128.19
128.12
126.86
126.37
125.28
125.11
86.55
77.32
77.00
76.68
56.10
55.70
41.95
35.64
33.83
33.46
31.38
31.34
20.95
f1 (ppm)



2e+2e'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7.29
7.27
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7.27
7.24
7.23
7.21
7.21
7.20
7.20
7.19
7.13
7.11
6.85
6.85
6.84
6.84
6.83
6.83
6.82
3.87
3.85
3.82
3.78
3.78
3.61
3.59
3.56
3.53
2.88
2.85
2.83
2.81
2.27
2.26
2.17
2.17
2.15
2.14
2.13
2.12
2.10
2.10
2.09
2.09
2.08
2.06
2.05
2.04
2.03
2.02
2.01
2.01
2.00
2.00
1.99
1.99
1.92
450
400
350
300
250
200
150
100
50
0
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
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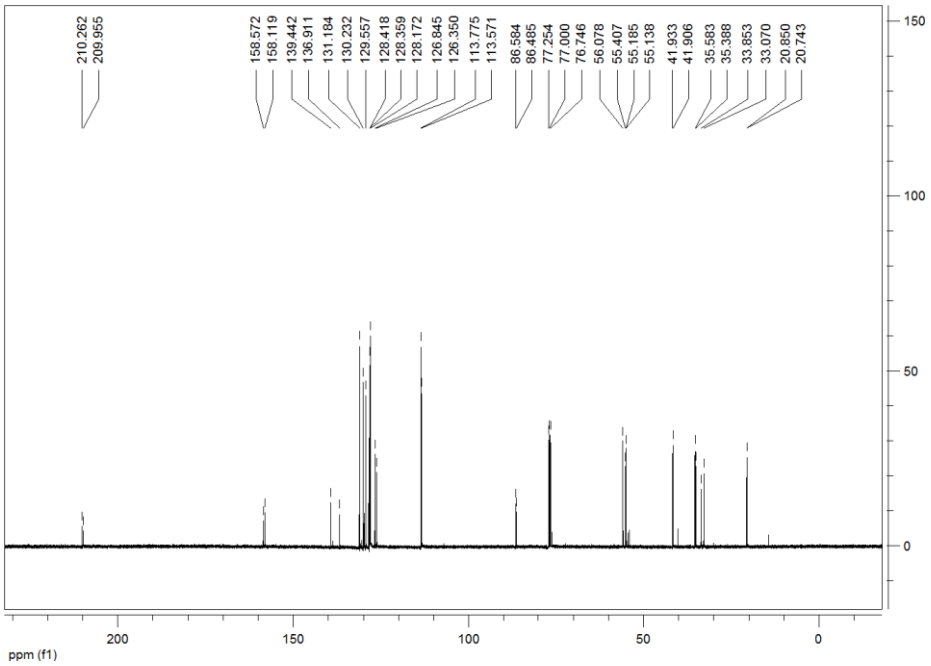
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


210.262
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158.572
158.119
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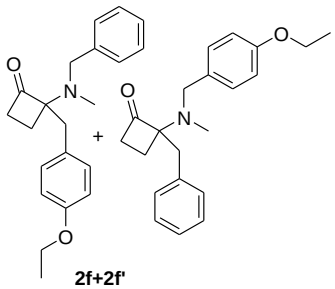
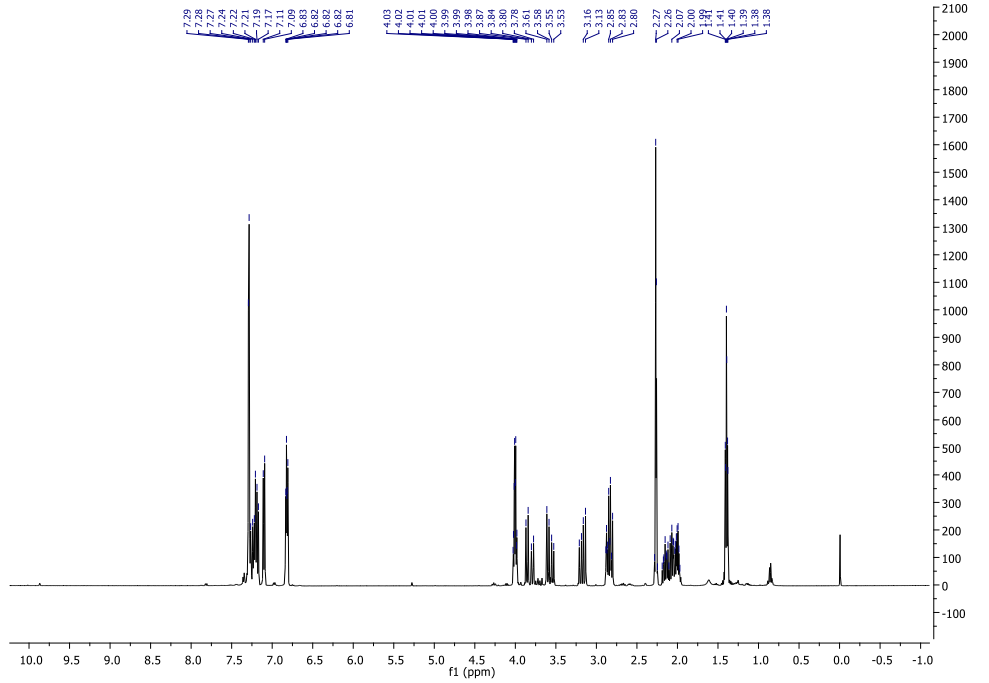
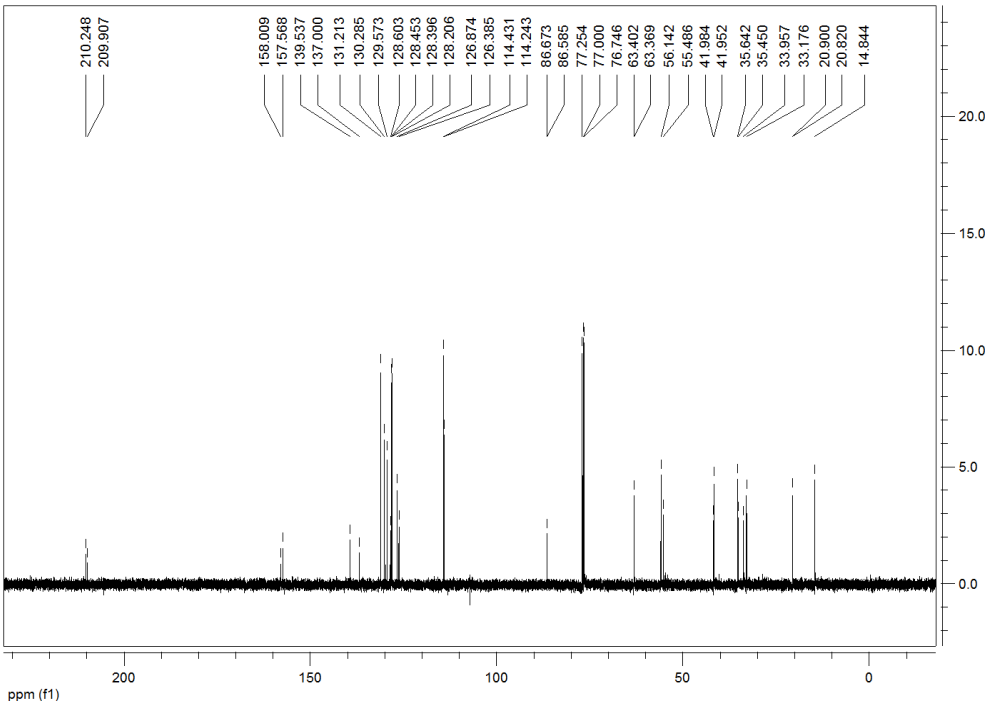
136.911
131.184
130.232
129.557
128.418
128.359
128.172
126.845
126.350
113.775
113.571
86.584
86.485
77.254
77.000
76.746
56.078
55.407
55.185
55.138
41.933
41.906
35.583
35.388
33.853
33.070
20.850
20.743
150
100
50
0
200
150
100
50
0
ppm (f1)



2f+2f'


7.29
7.28
7.27
7.24
7.22
7.21
7.19
7.17
7.11
7.09
6.83
6.82
6.82
6.82
6.81
4.03
4.02
4.01
4.01
4.00
3.99
3.99
3.89
3.87
3.84
3.80
3.78
3.61
3.58
3.55
3.53
3.16
3.13
2.85
2.83
2.80
2.27
2.26
2.07
2.00
1.99
1.41
1.40
1.39
1.38
1.38
f1 (ppm)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137.000
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130.285
129.573
128.603
128.453
128.396
128.206
126.874
126.385
114.431
114.243
86.673
86.585
77.254
77.000
76.746
63.402
63.369
56.142
55.486
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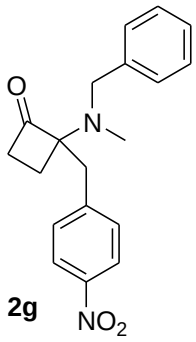
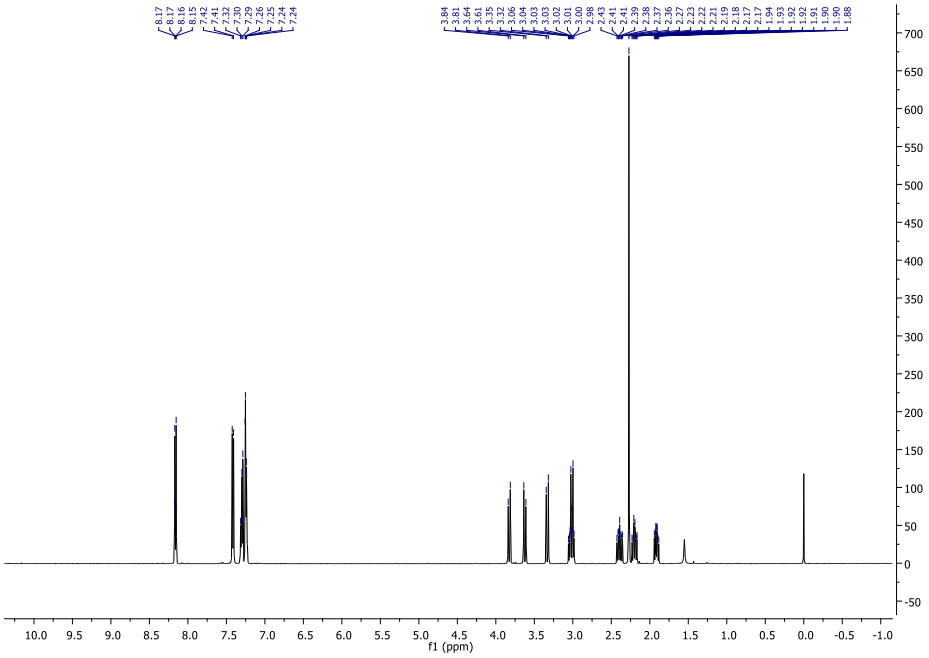
41.952
35.642
35.450
33.957
33.176
20.900
20.820
14.844
ppm (f1)


O
N
NO2

2g


8.17
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7.41
7.32
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7.29
7.26
7.25
7.24
7.24
3.84
3.81
3.64
3.61
3.35
3.32
3.06
3.04
3.03
3.03
3.02
3.01
3.00
2.98
2.43
2.41
2.41
2.39
2.38
2.37
2.36
2.27
2.23
2.22
2.21
2.19
2.18
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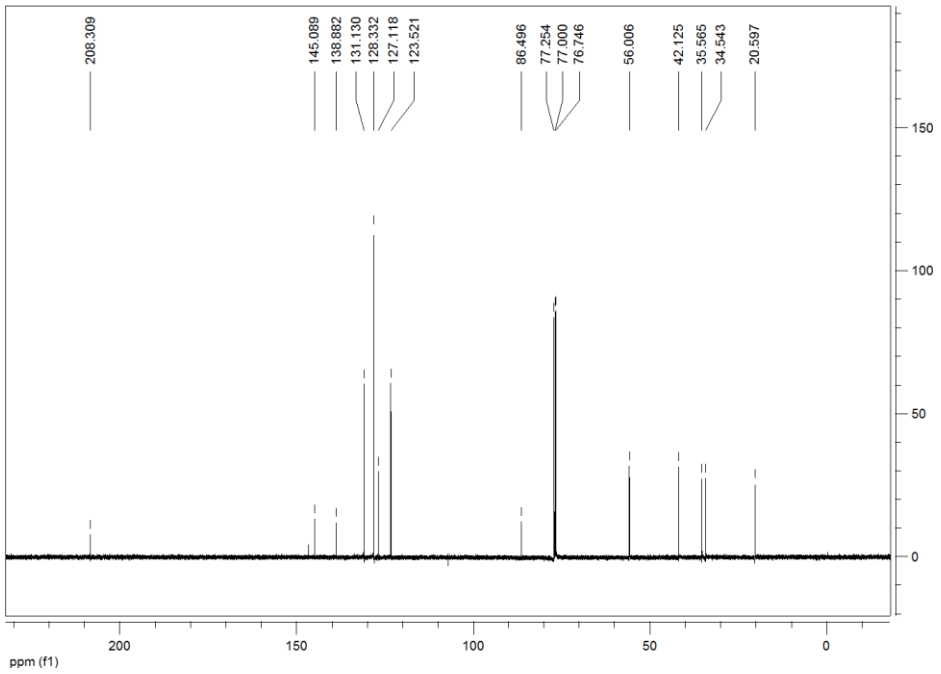
1.94
1.93
1.92
1.92
1.91
1.90
1.90
1.88
f1 (ppm)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138.882
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128.332
127.118
123.521
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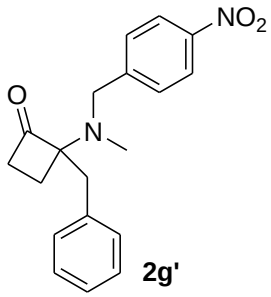
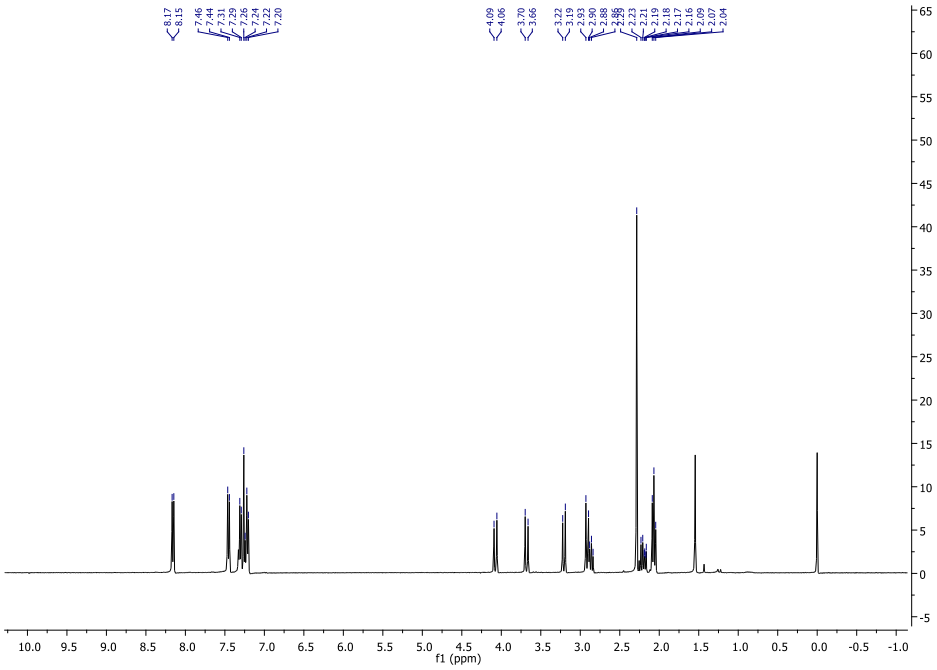
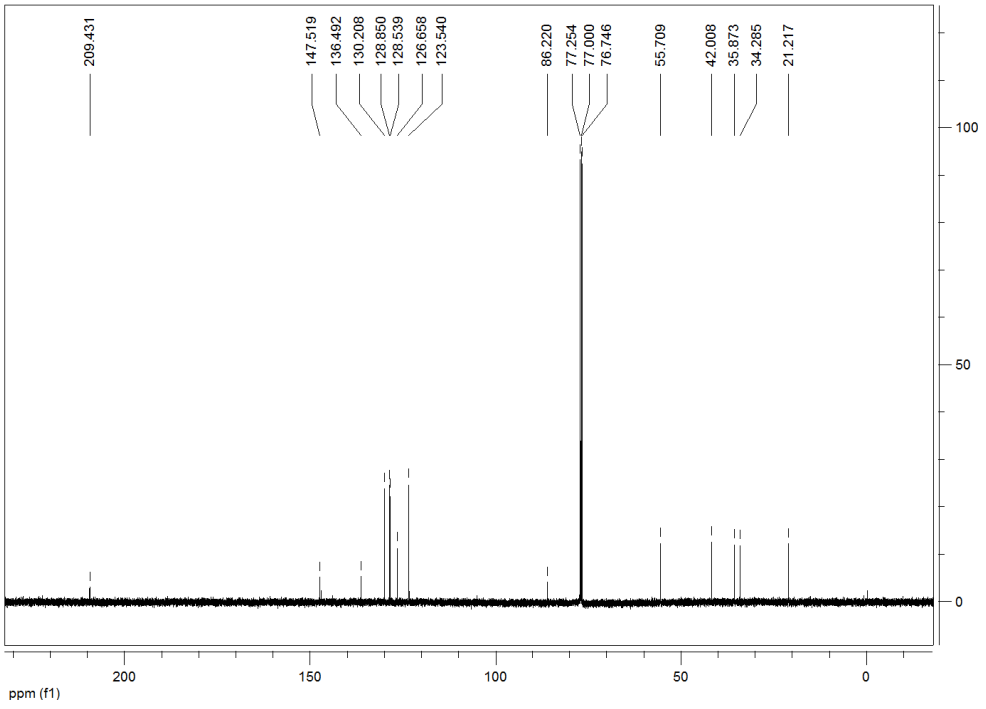
77.254
77.000
76.746
56.006
42.125
35.565
34.543
20.597
ppm (f1)


NO2
O
N

2g'


8.17
8.15
7.46
7.44
7.31
7.29
7.26
7.24
7.22
7.20
4.09
4.06
3.70
3.66
3.22
3.19
3.03
2.90
2.88
2.23
2.21
2.19
2.18
2.17
2.16
2.09
2.07
2.04
f1 (ppm)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136.492
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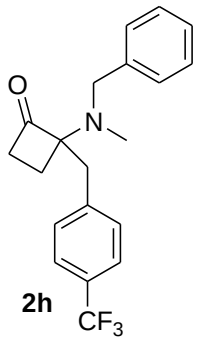
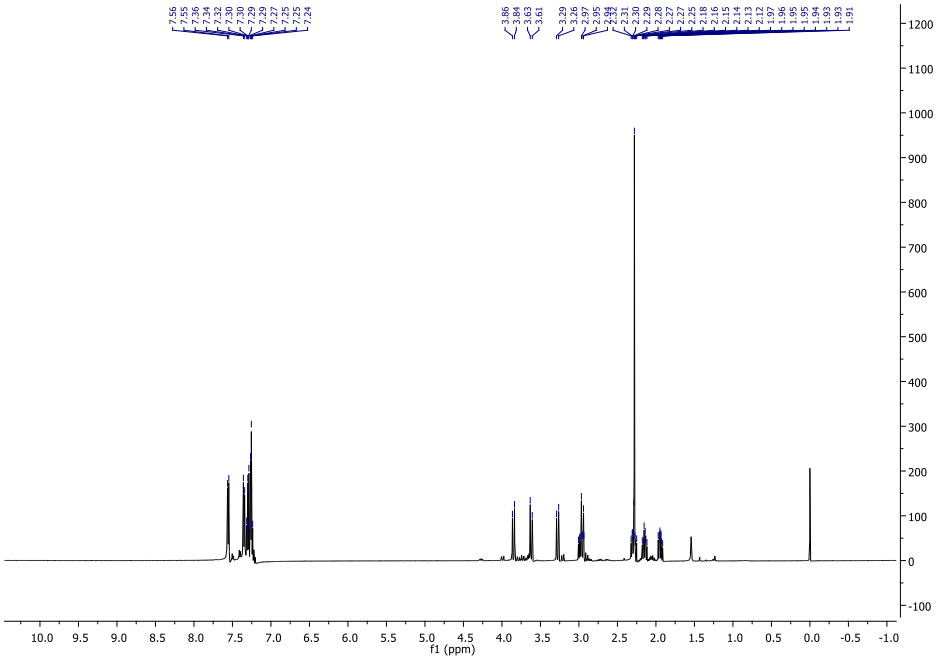
128.850
128.539
126.658
123.540
86.220
77.254
77.000
76.746
55.709
42.008
35.873
34.285
21.217
ppm (f1)


O
N
2h
CF3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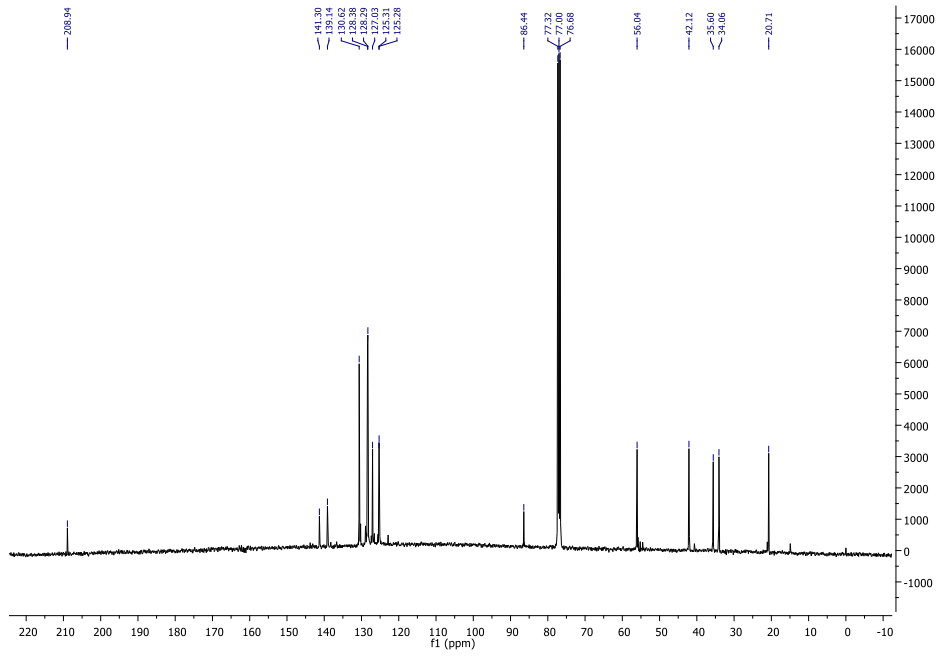
7.30
7.29
7.29
7.27
7.25
7.25
7.24
3.86
3.84
3.63
3.61
3.29
3.26
2.97
2.95
2.34
2.31
2.30
2.29
2.28
2.27
2.27
2.25
2.18
2.16
2.15
2.14
2.13
2.12
1.97
1.96
1.95
1.95
1.94
1.93
1.93
1.91
f1 (ppm)


208.94
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130.02
128.58
128.29
127.03
125.31
125.28
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77.32
77.00
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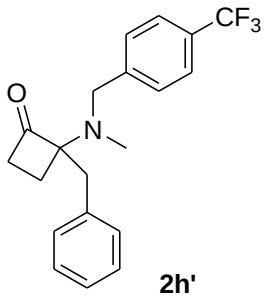
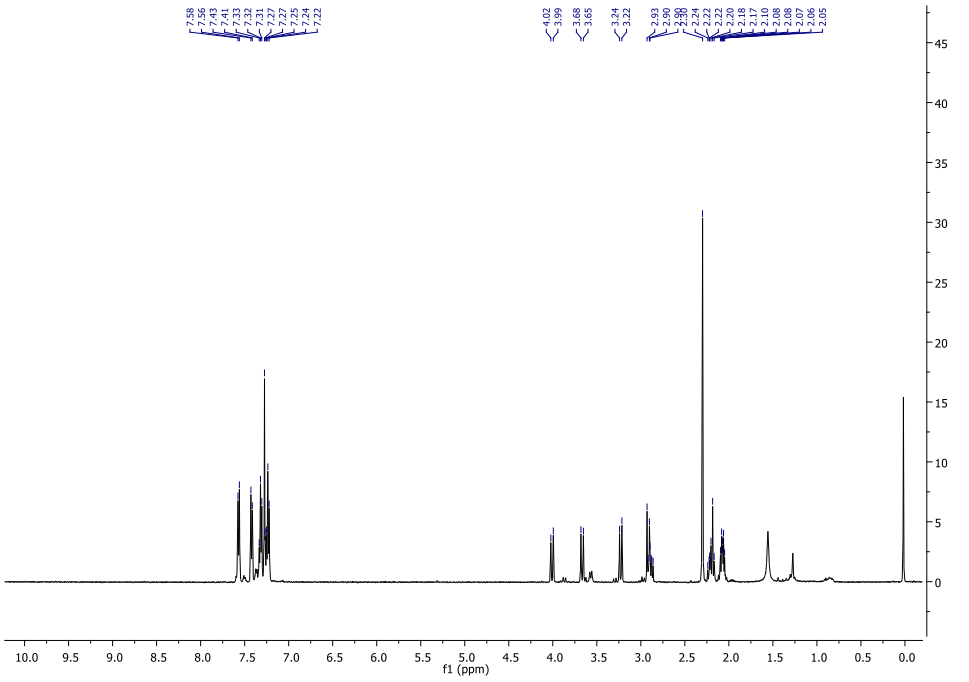
42.12
35.60
34.06
20.71
f1 (ppm)


CF3
O
N

2h'


7.58
7.56
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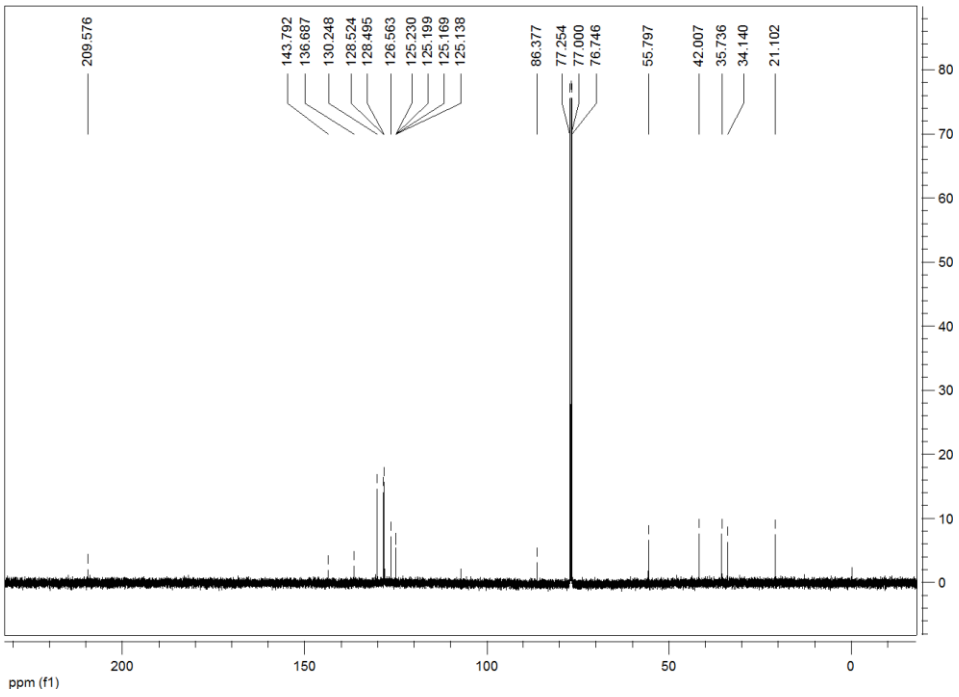
7.41
7.33
7.32
7.31
7.27
7.27
7.25
7.24
7.22
4.02
3.99
3.68
3.65
3.24
3.22
2.93
2.90
2.24
2.22
2.22
2.20
2.18
2.17
2.10
2.08
2.08
2.07
2.06
2.05
f1 (ppm)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128.524
128.495
126.563
125.230
125.199
125.169
125.138
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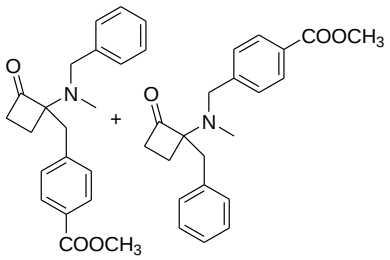
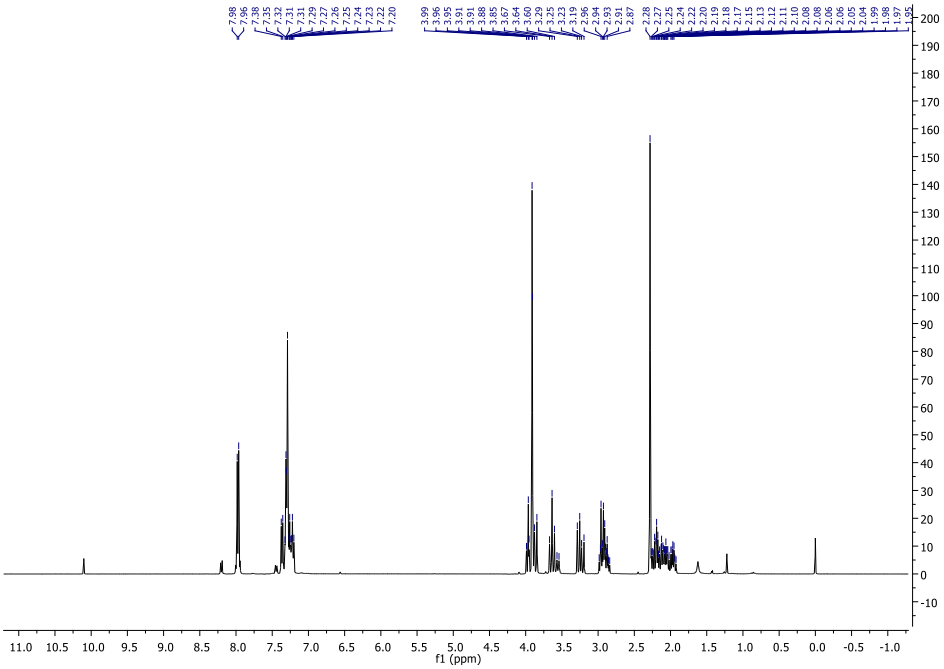
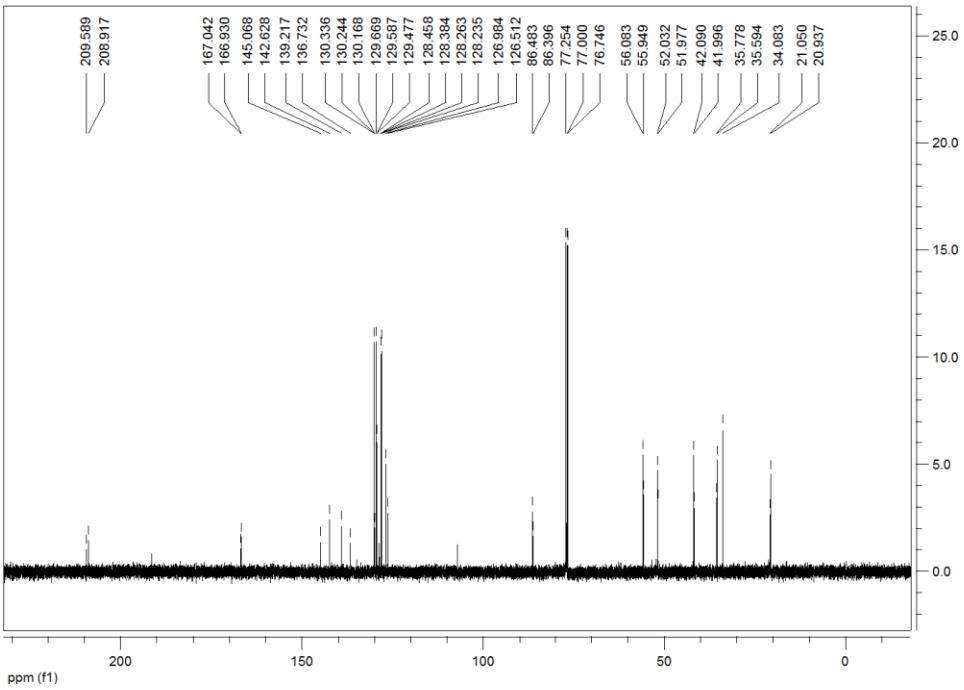
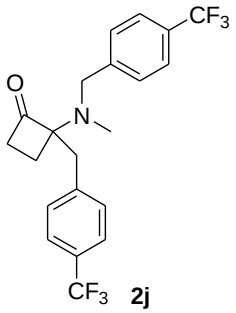
42.007
35.736
34.140
21.102
ppm (f1)



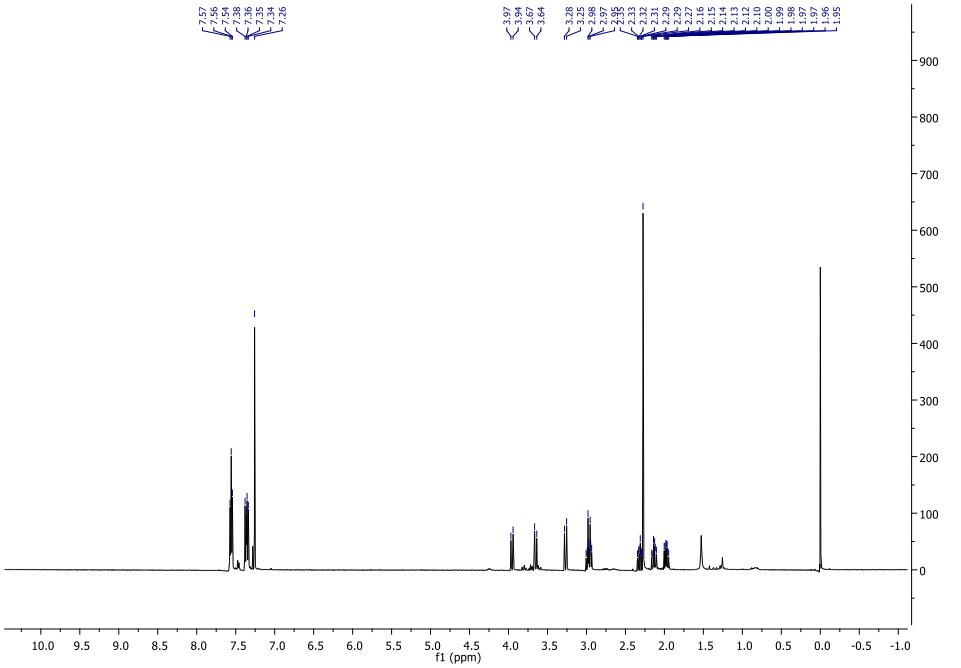
2i+2i'






CF3
O
N
CF3

2j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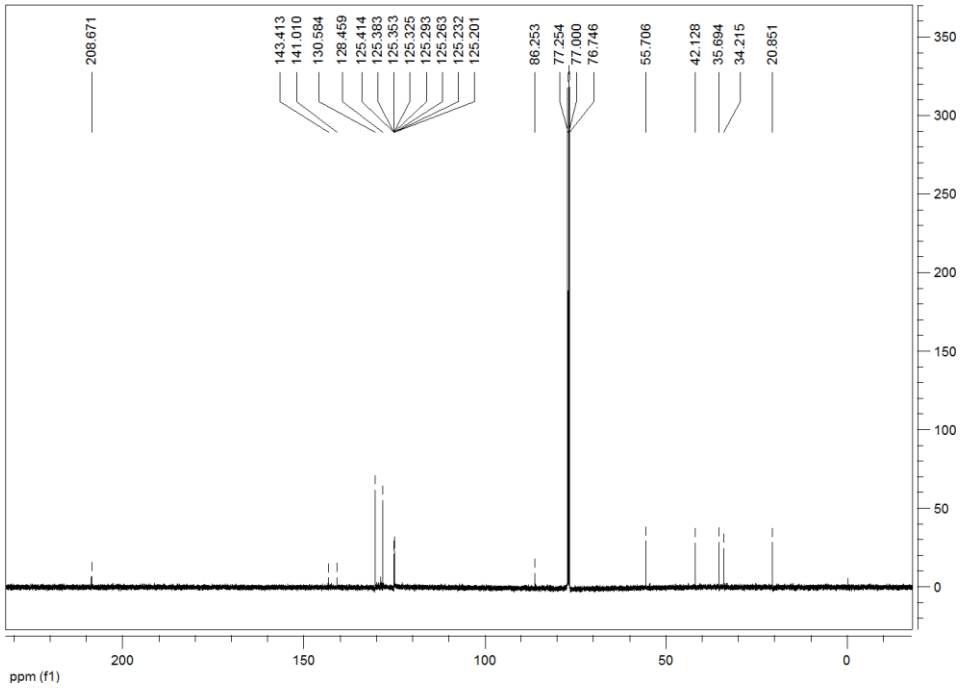
7.34
7.26
3.97
3.94
3.67
3.64
3.28
3.25
2.98
2.97
2.95
2.93
2.33
2.32
2.31
2.29
2.29
2.27
2.16
2.15
2.14
2.13
2.12
2.10
2.00
1.99
1.98
1.97
1.97
1.96
1.95
900
800
700
600
500
400
300
200
100
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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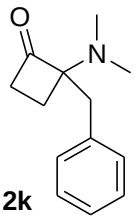
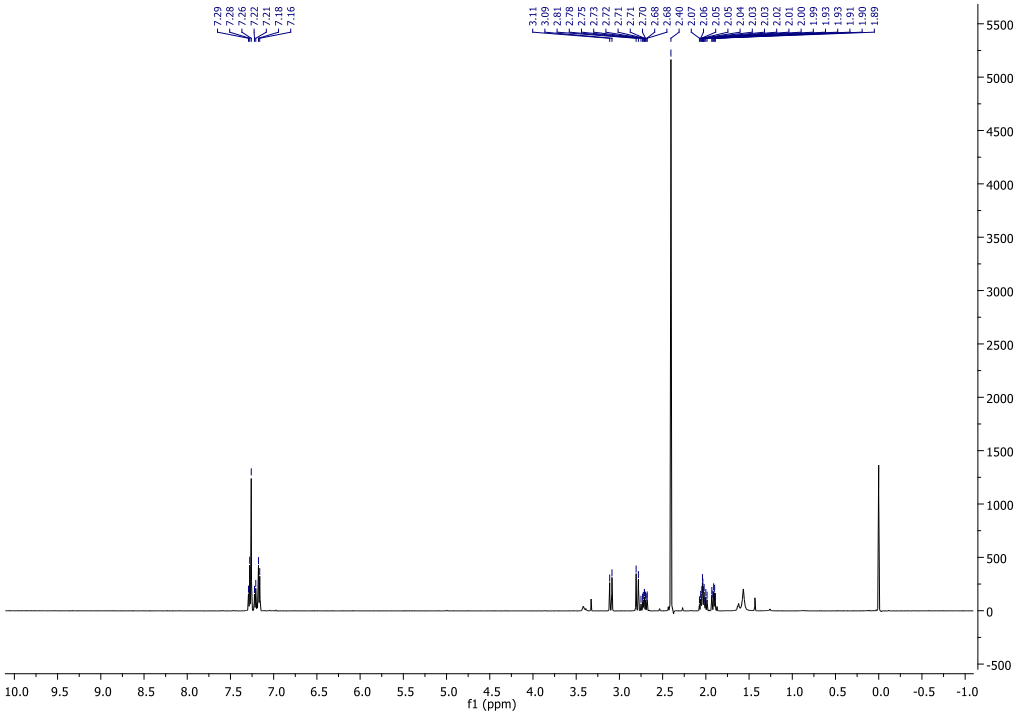
128.459
125.414
125.383
125.353
125.325
125.293
125.263
125.232
125.201
86.253
77.254
77.000
76.746
55.706
42.128
35.694
34.215
20.851
350
300
250
200
150
100
50
0
200
150
100
50
0
ppm (f1)



2k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7.28
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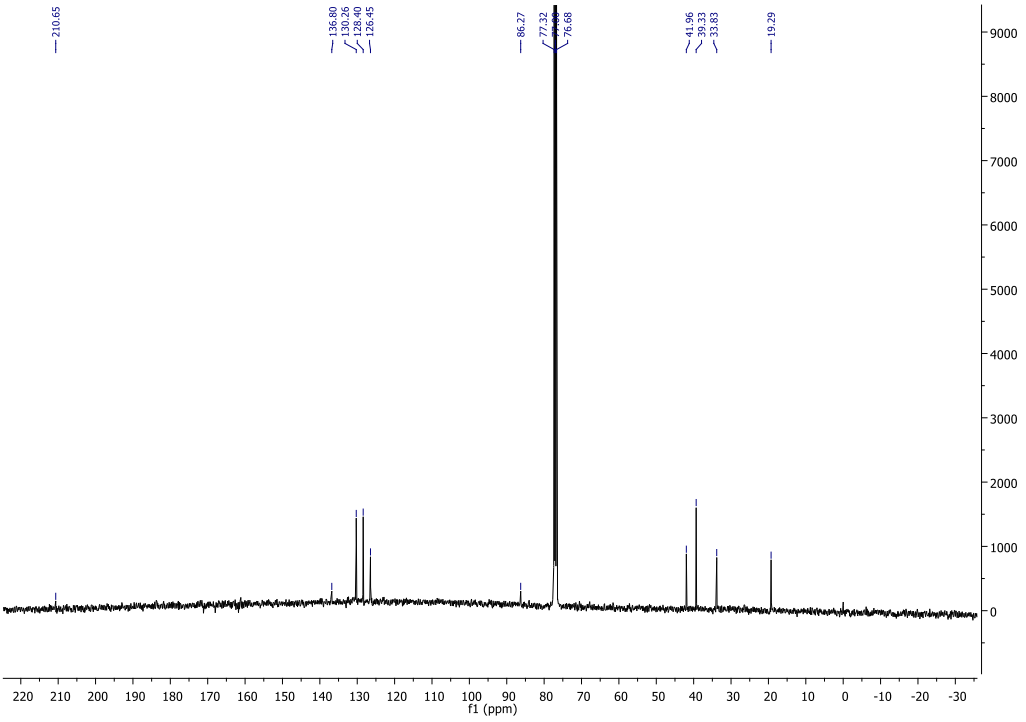
7.16
3.11
3.09
2.81
2.78
2.75
2.73
2.72
2.71
2.71
2.70
2.68
2.68
2.40
2.07
2.06
2.05
2.05
2.04
2.03
2.03
2.02
2.01
2.00
1.99
1.93
1.93
1.91
1.90
1.89
f1 (ppm)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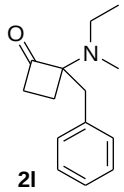
86.27
77.32
77.00
76.68
41.96
39.23
33.83
19.29
f1 (ppm)



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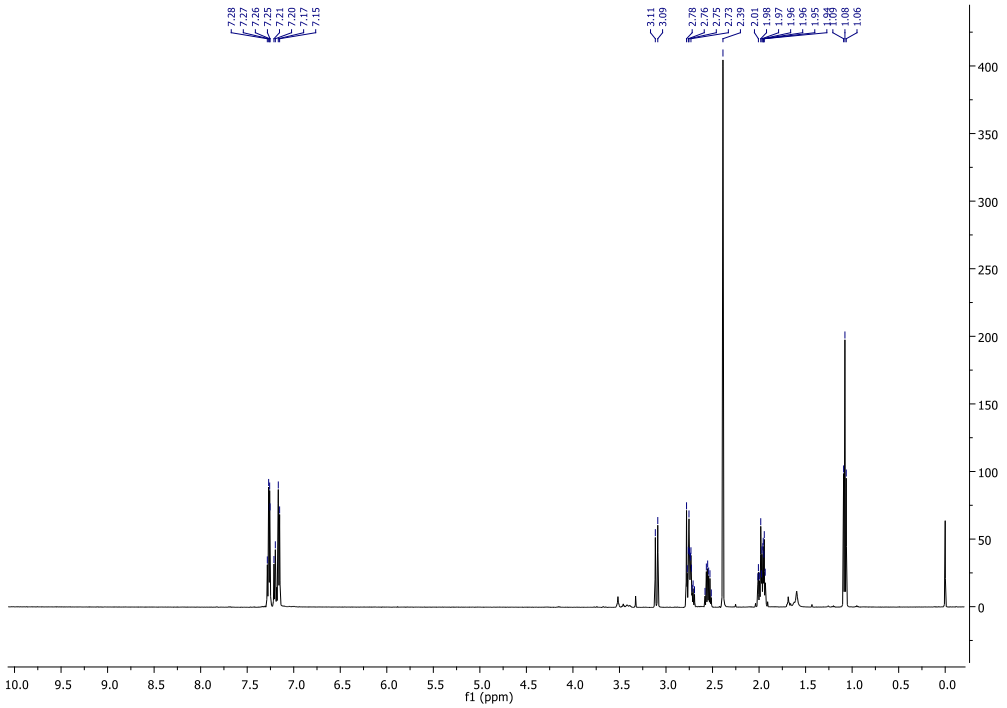
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7.20
7.17
7.15
3.11
3.09
2.78
2.76
2.75
2.73
2.39
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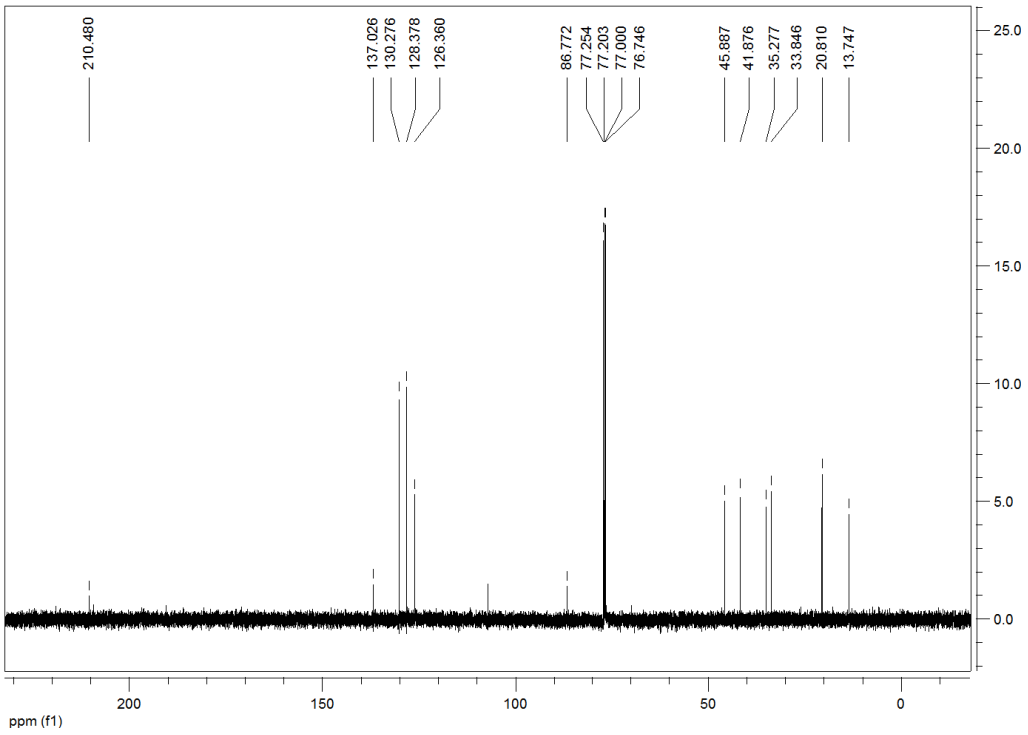
1.97
1.96
1.96
1.95
1.09
1.08
1.06
f1 (ppm)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86.772
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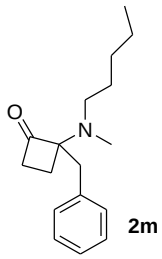
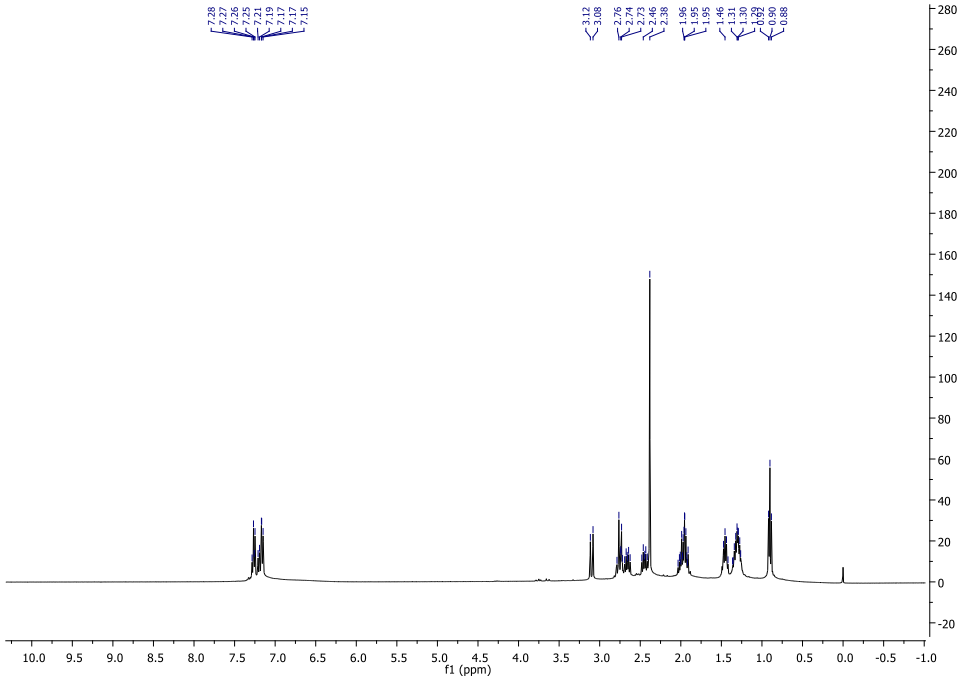
77.000
76.746
45.887
41.876
35.277
33.846
20.810
13.747
ppm (f1)


O
N

2m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7.19
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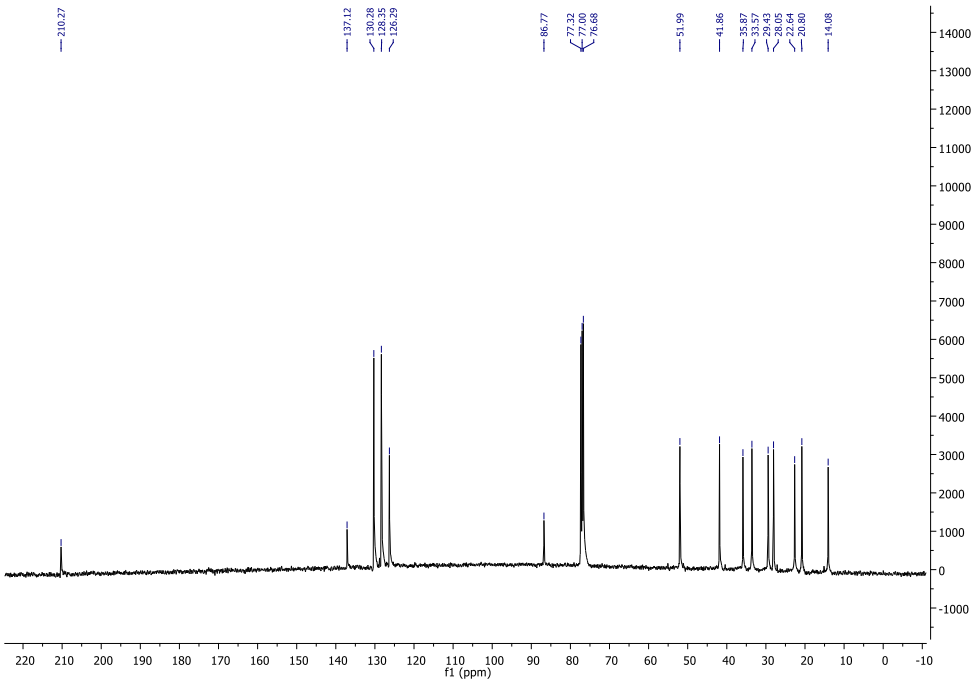
7.17
7.15
3.12
3.08
2.76
2.74
2.73
2.46
2.38
1.96
1.95
1.95
1.46
1.31
1.30
1.29
0.92
0.90
0.88
f1 (ppm)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86.77
77.32
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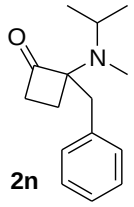
76.68
51.99
41.86
35.87
33.57
29.43
28.05
22.64
20.80
14.08
f1 (ppm)



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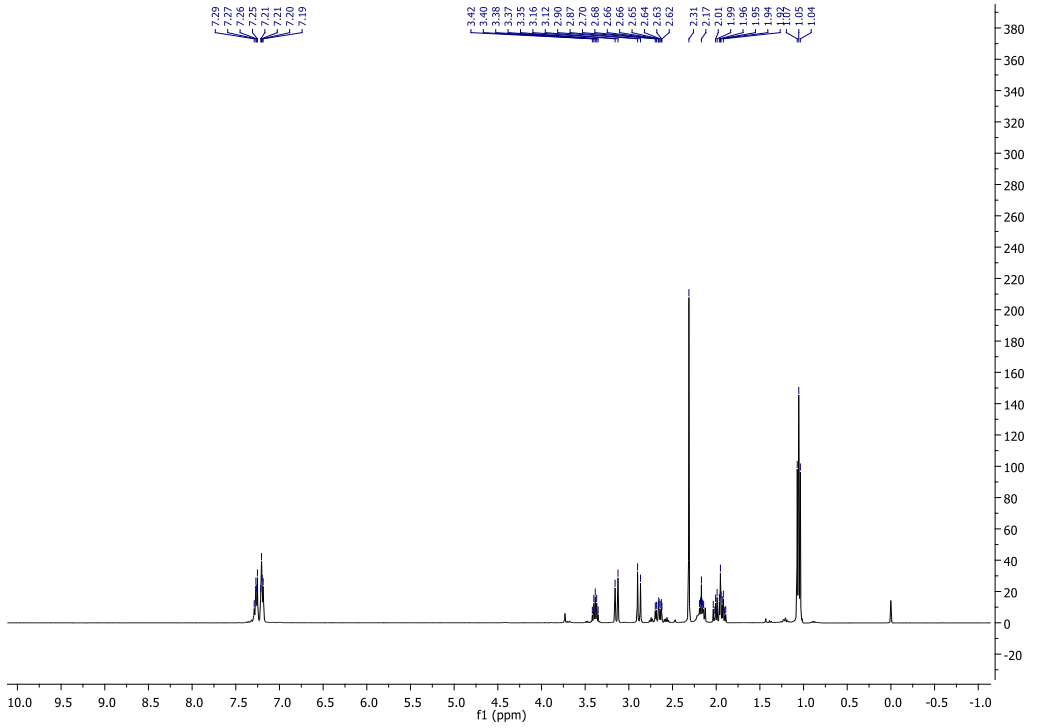
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7.21
7.21
7.20
7.19
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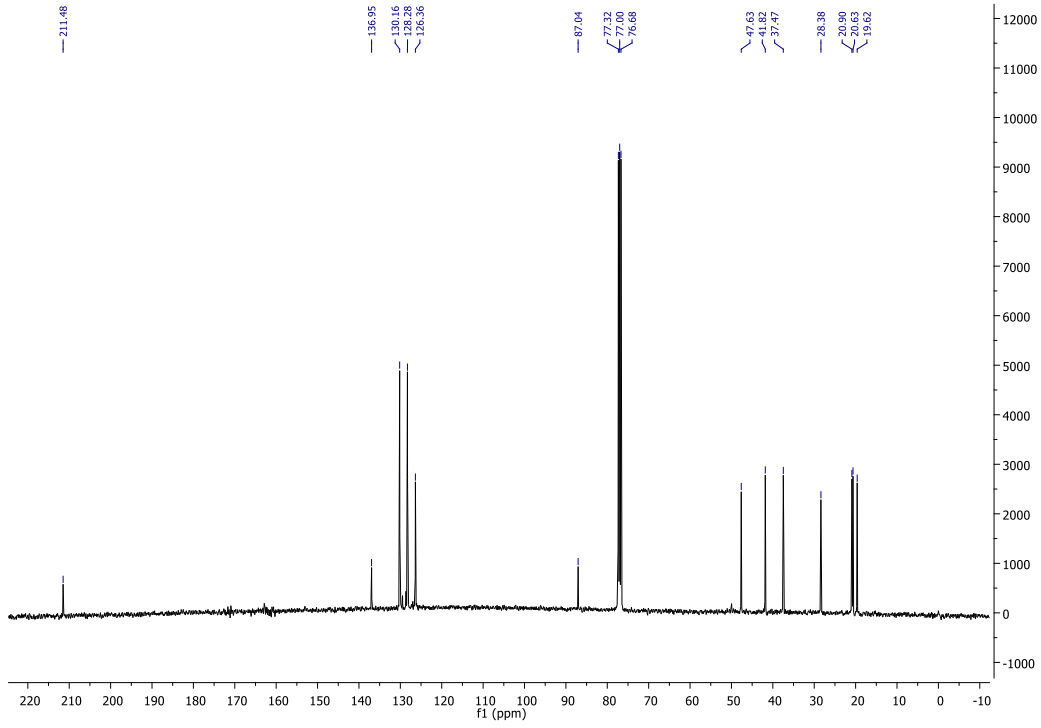
3.40
3.38
3.37
3.35
3.16
3.12
2.90
2.87
2.70
2.68
2.66
2.66
2.65
2.64
2.63
2.62
2.31
2.17
2.01
1.99
1.96
1.95
1.94
1.07
1.05
1.04
f1 (ppm)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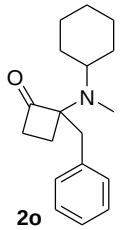
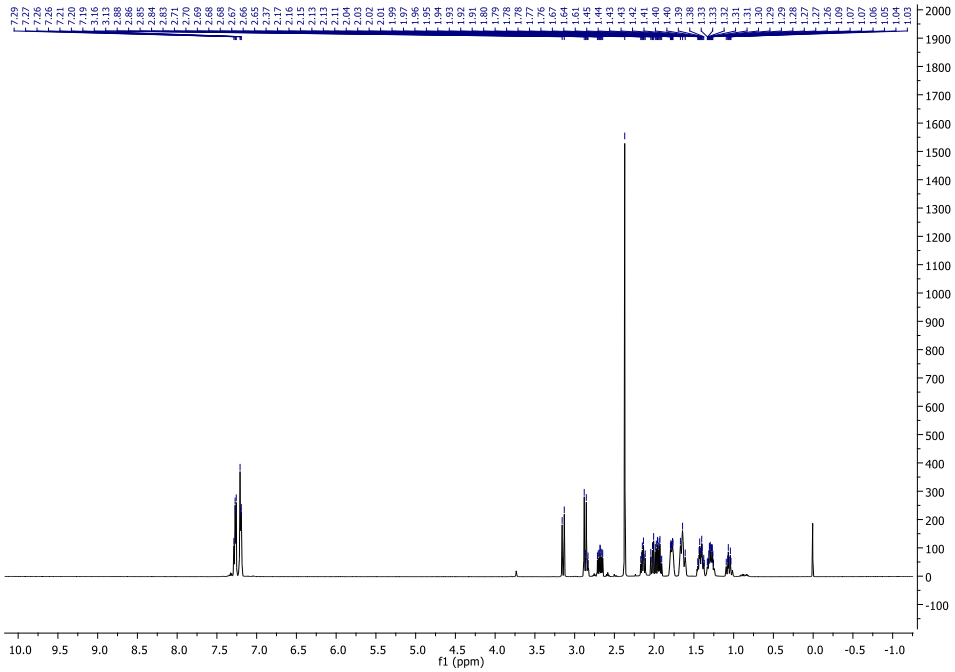
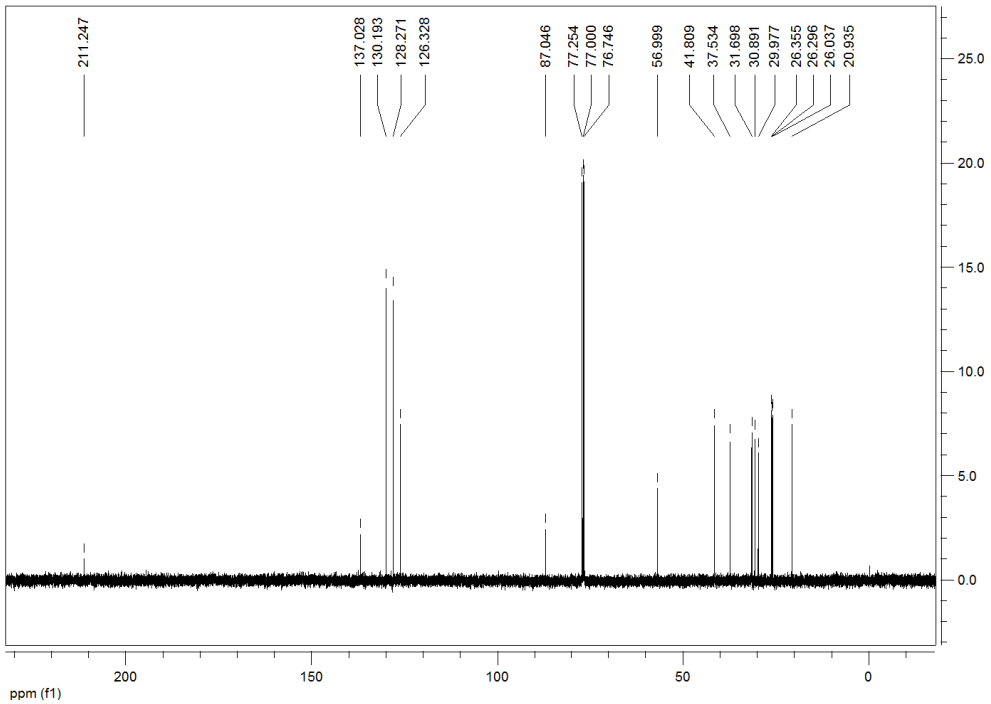
130.16
128.28
126.36
87.04
77.32
77.00
76.68
47.63
41.82
37.47
28.38
20.90
20.63
19.62
f1 (ppm)


O
N

2o


f1 (ppm)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126.328
87.046
77.254
77.000
76.746
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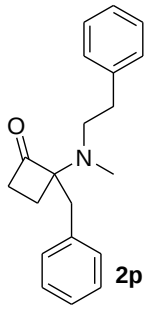
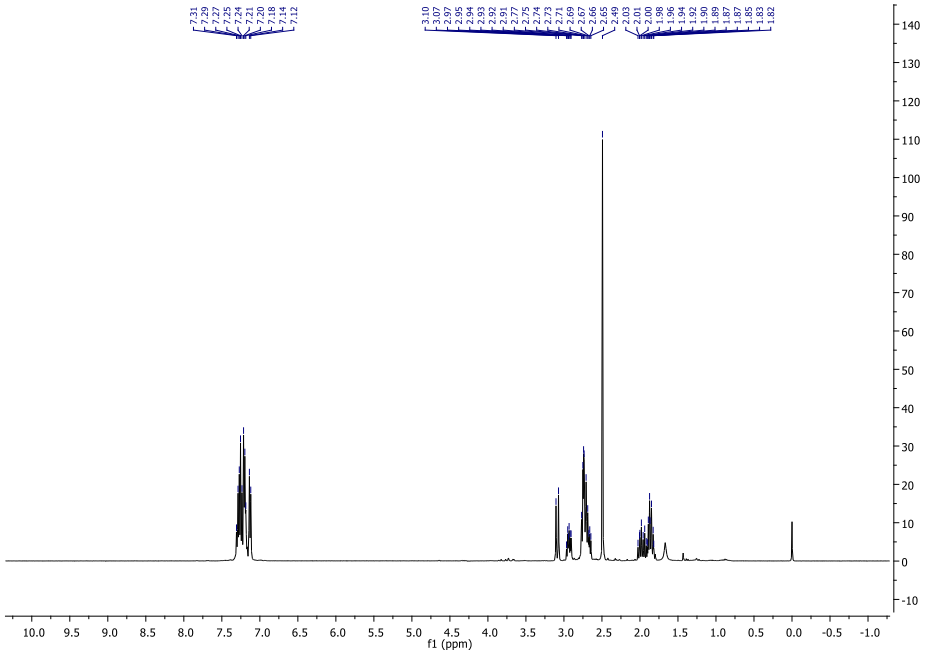
37.534
31.698
30.891
29.977
26.355
26.296
26.037
20.935
ppm (f1)


O
N

2p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7.29
7.27
7.25
7.24
7.21
7.20
7.18
7.14
7.12
3.10
3.07
2.97
2.95
2.94
2.93
2.92
2.91
2.77
2.75
2.74
2.73
2.71
2.69
2.67
2.66
2.65
2.64
2.03
2.01
2.00
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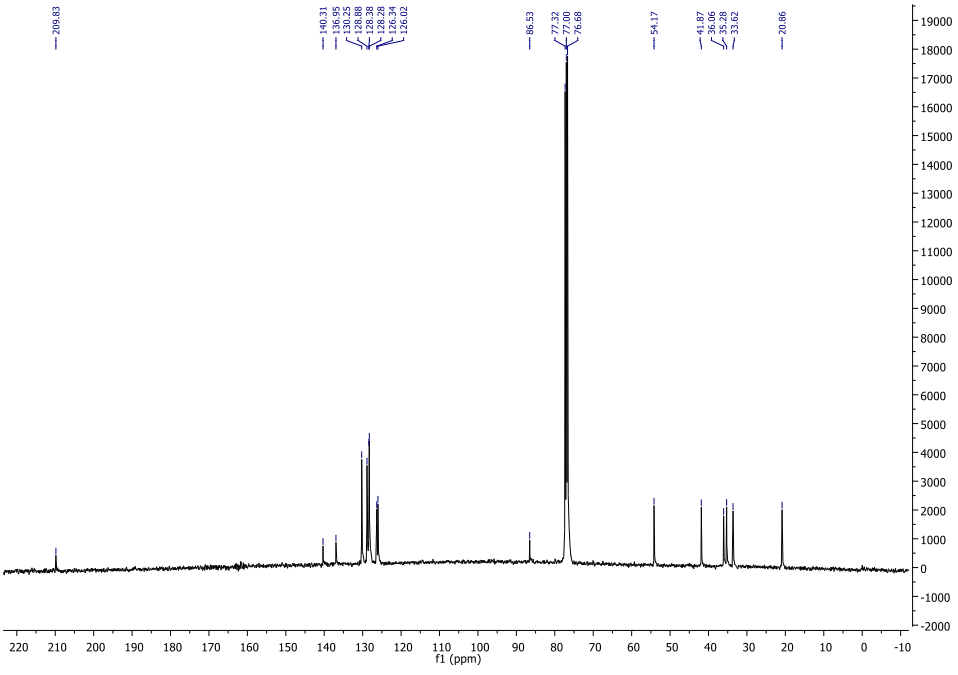
1.87
1.85
1.83
1.82
f1 (ppm)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130.25
128.88
128.38
128.28
126.34
126.02
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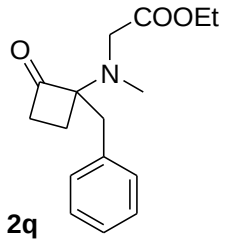
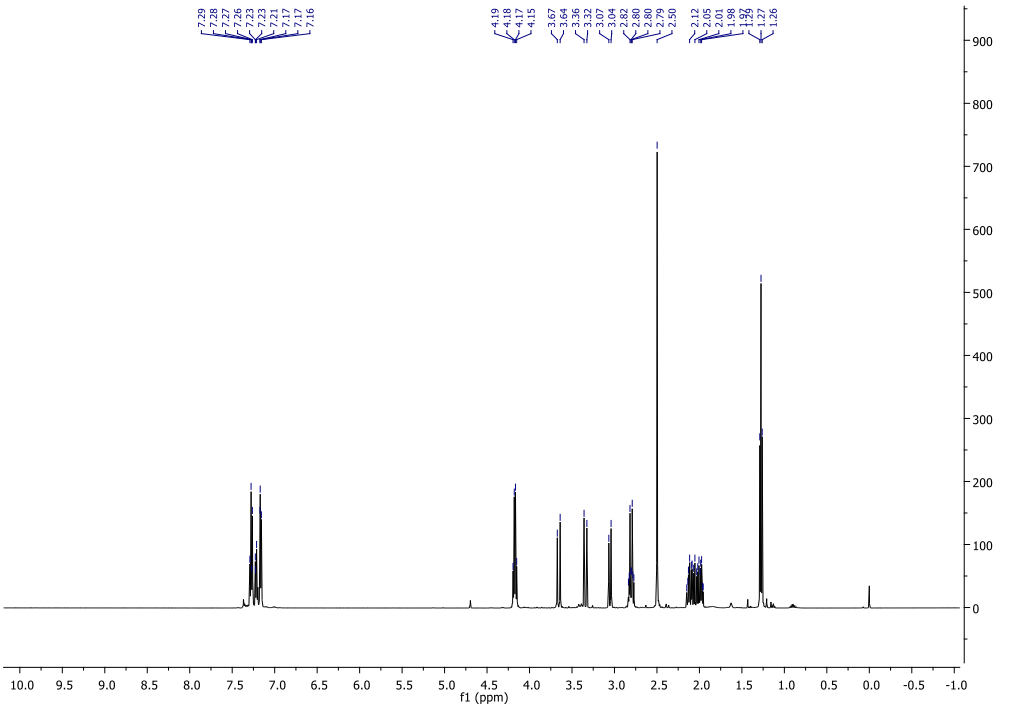
77.00
76.68
54.17
41.87
36.06
35.28
33.62
20.86
f1 (ppm)


COOEt
O
N

2q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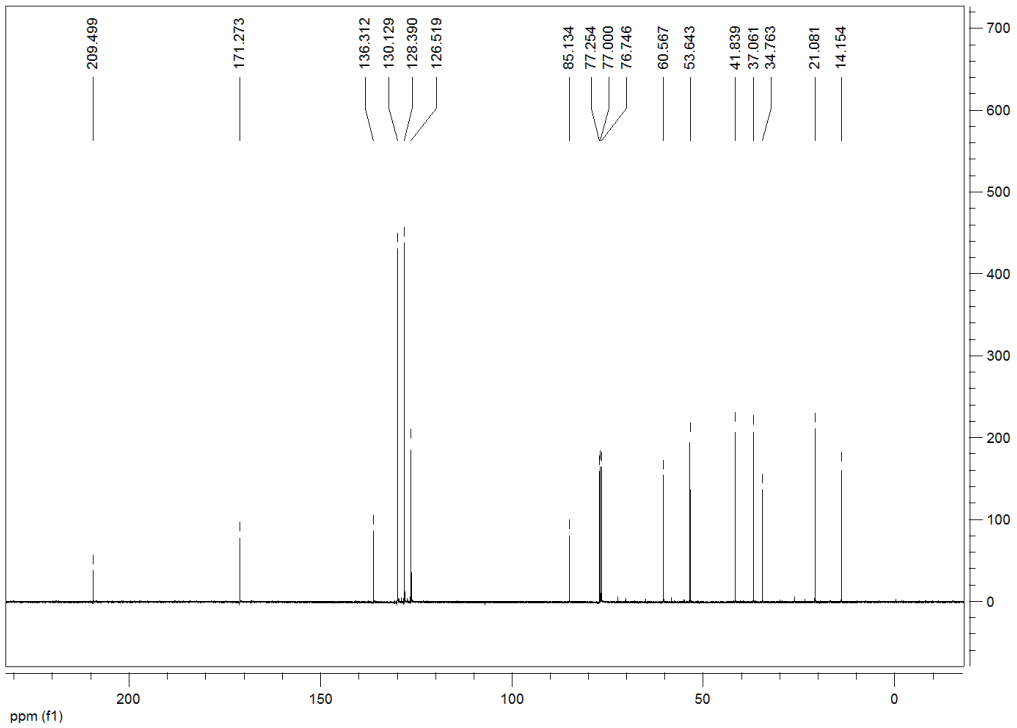
7.28
7.27
7.26
7.23
7.23
7.21
7.17
7.17
7.16
4.19
4.18
4.17
4.15
3.67
3.64
3.36
3.32
3.07
3.04
2.82
2.80
2.80
2.79
2.50
2.12
2.05
2.01
1.98
1.97
1.29
1.27
1.26
f1 (ppm)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128.390
126.519
85.134
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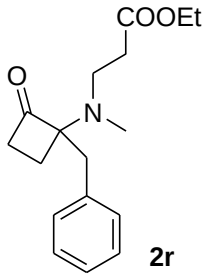
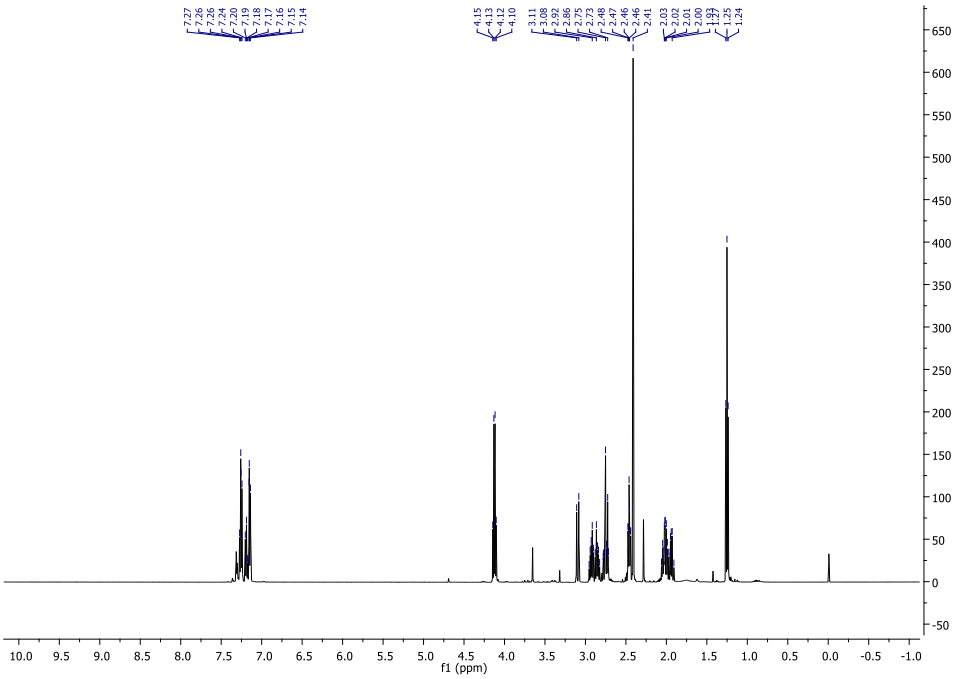
76.746
60.567
53.643
41.839
37.061
34.763
21.081
14.154
ppm (f1)


COOEt
O
N

2r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7.25
7.24
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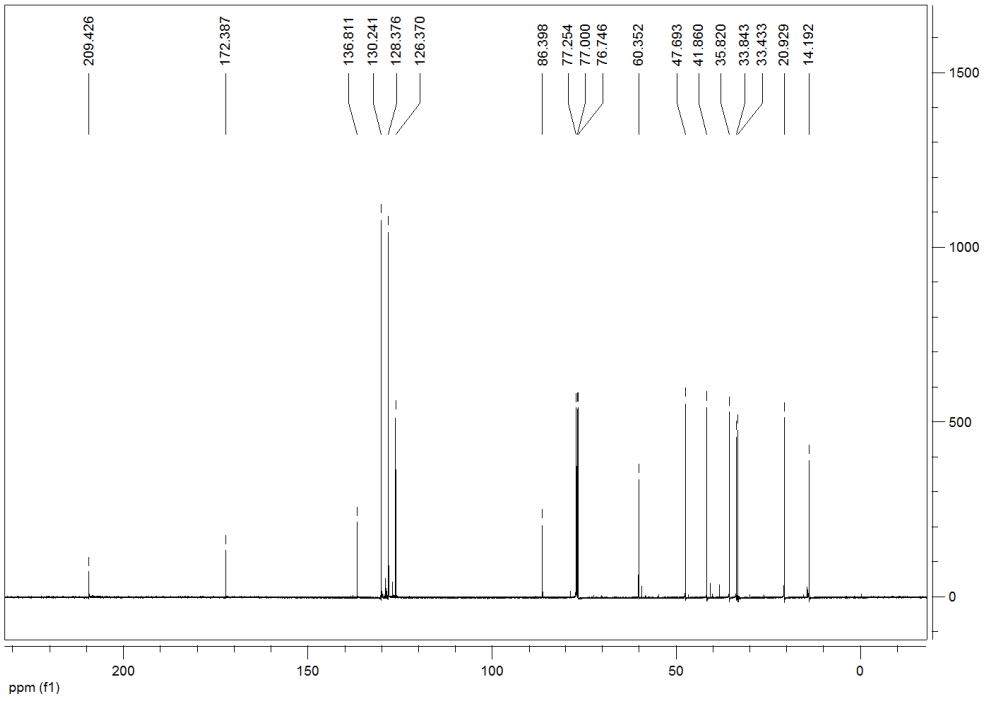
7.19
7.18
7.17
7.16
7.15
7.14
4.15
4.13
4.12
4.10
3.11
3.08
2.92
2.86
2.75
2.73
2.48
2.47
2.46
2.46
2.41
2.03
2.02
2.01
2.00
1.93
1.27
1.25
1.24
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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128.376
126.370
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77.254
77.000
76.746
60.352
47.693
41.860
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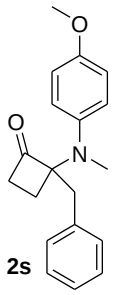
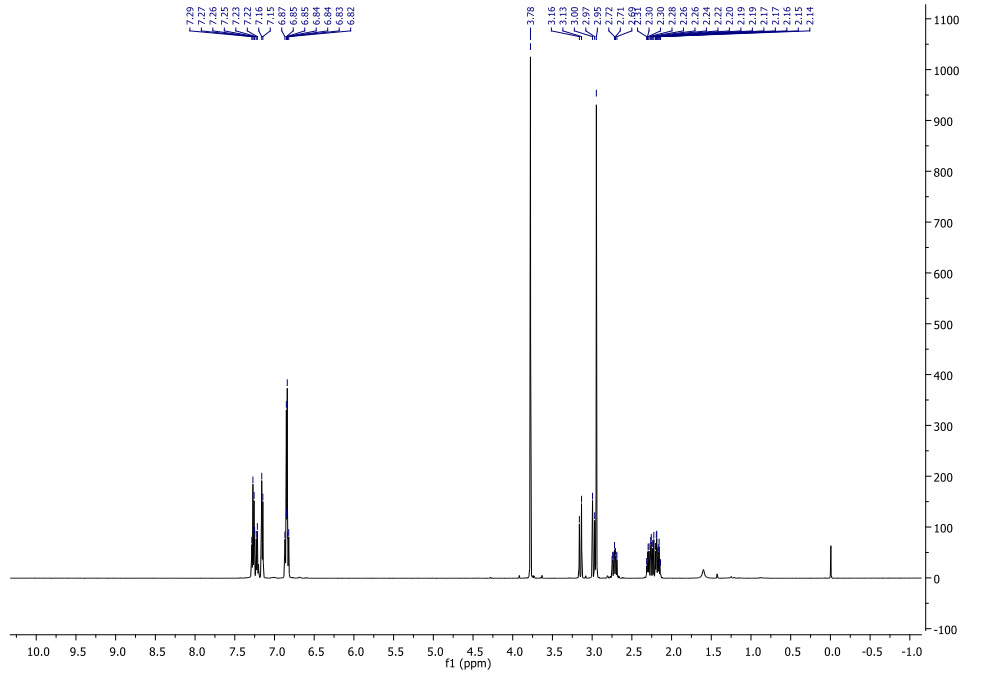
20.929
14.192
1500
1000
500
0
200
150
100
50
0
ppm (f1)


O
O
N

2s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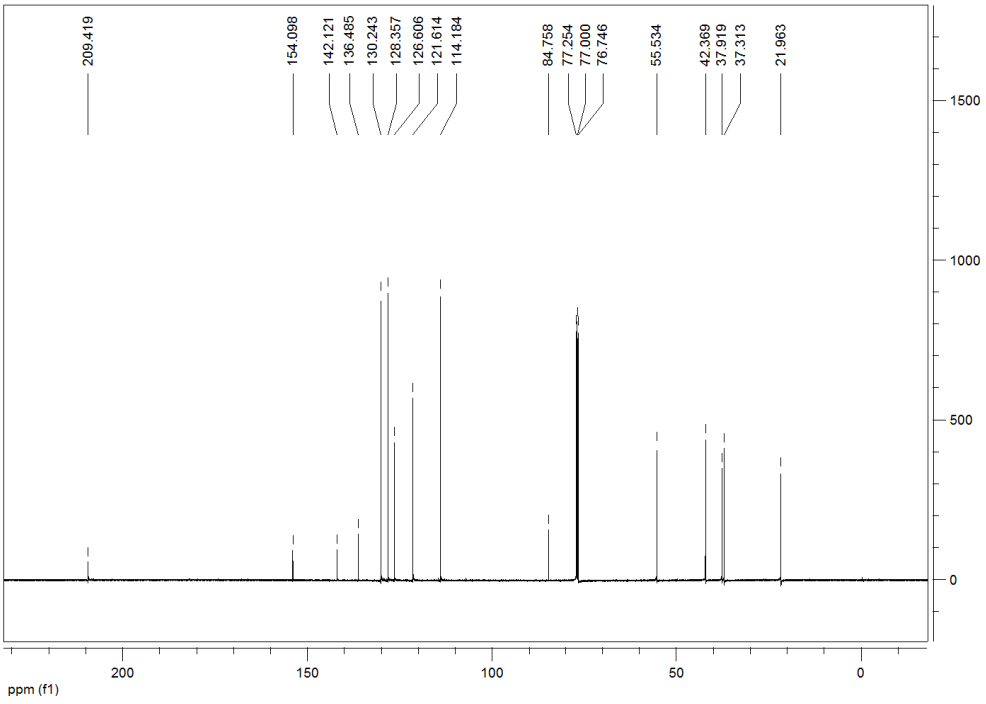
7.16
7.15
6.87
6.85
6.85
6.84
6.84
6.83
6.82
3.78
3.16
3.13
3.00
2.97
2.95
2.72
2.71
2.69
2.31
2.30
2.30
2.28
2.26
2.26
2.24
2.23
2.20
2.19
2.19
2.17
2.17
2.16
2.15
2.14
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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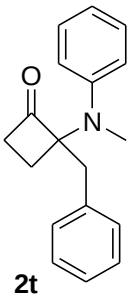
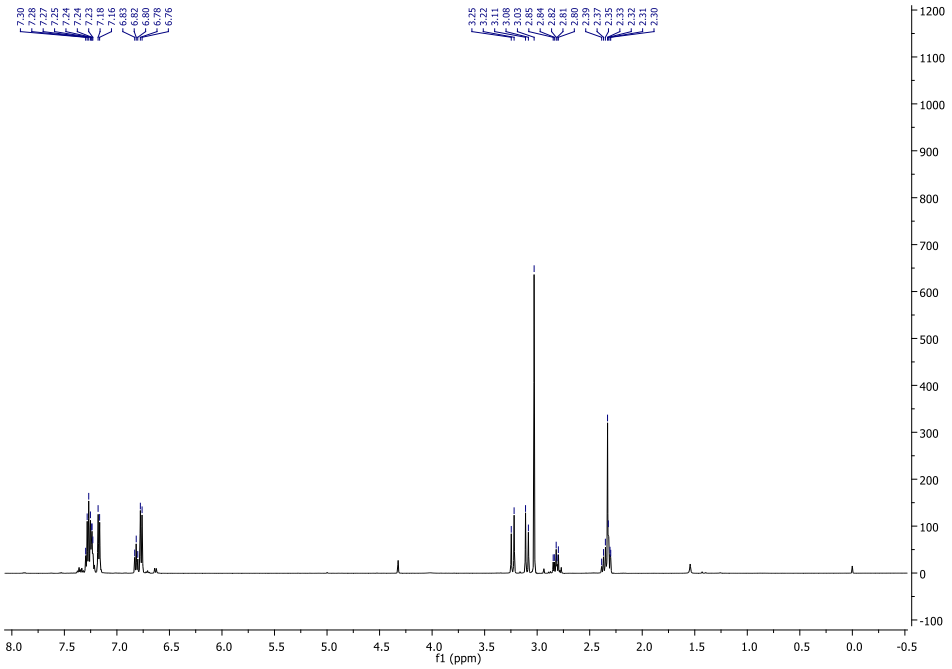
128.357
126.606
121.614
114.184
84.758
77.254
77.000
76.746
55.534
42.369
37.919
37.313
21.963
1500
1000
500
0
200
150
100
50
0
ppm (f1)


O
N

2t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7.27
7.25
7.24
7.24
7.23
7.18
7.16
6.83
6.82
6.80
6.78
6.76
3.25
3.22
3.11
3.08
3.03
2.85
2.84
2.82
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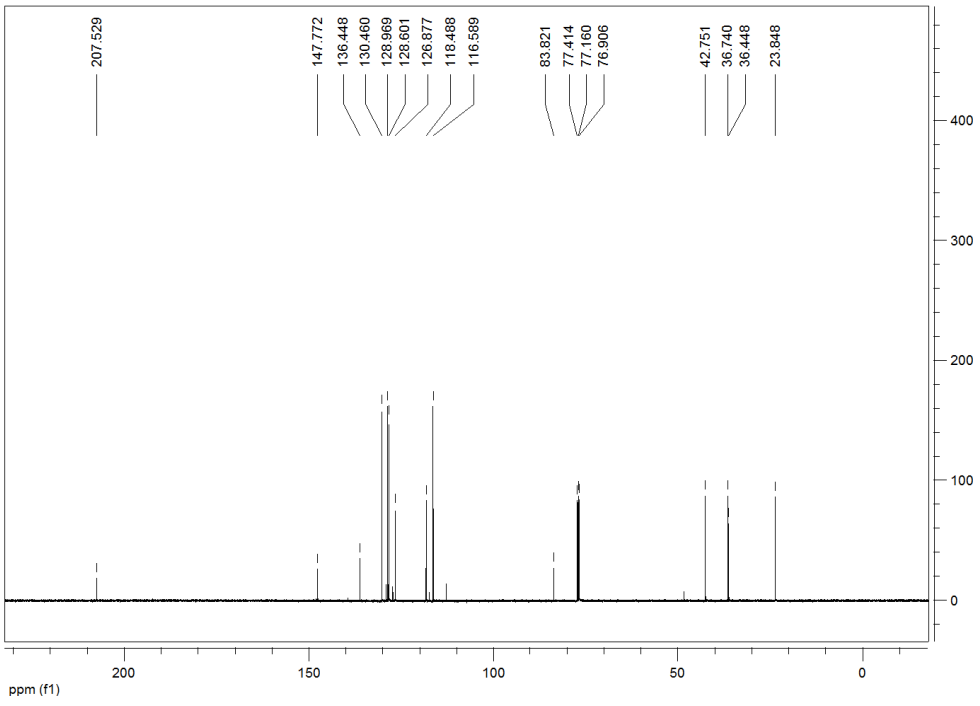
2.80
2.39
2.37
2.35
2.33
2.32
2.31
2.30
f1 (ppm)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77.160
76.906
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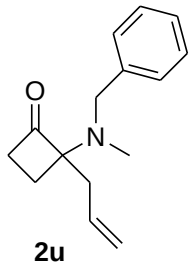
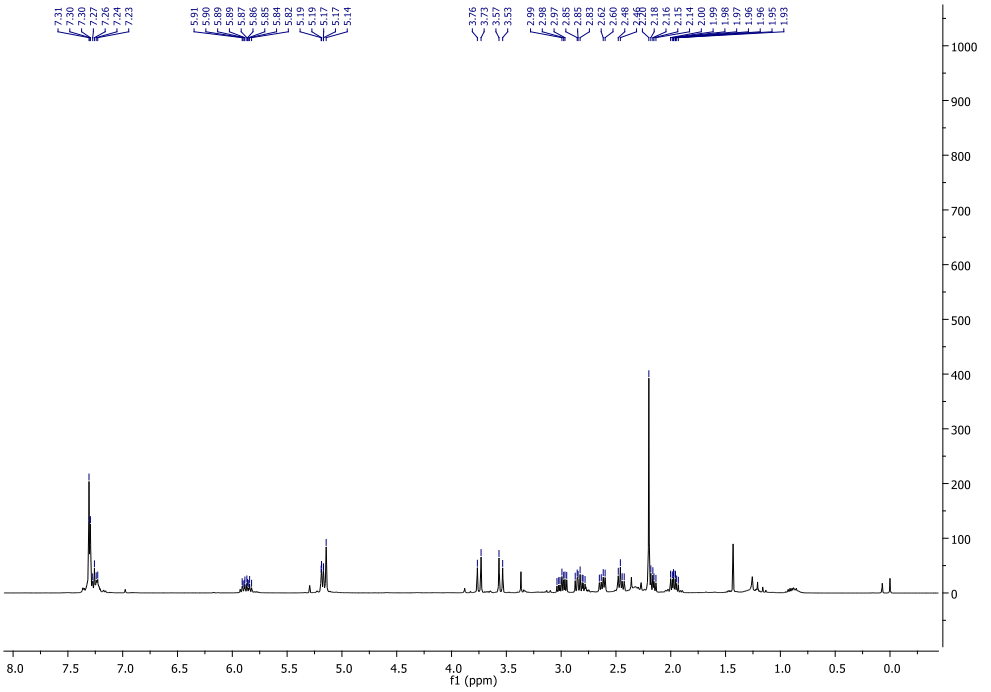
36.740
36.448
23.848
ppm (f1)


O
N

2u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7.30
7.27
7.26
7.24
7.23
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5.90
5.88
5.89
5.87
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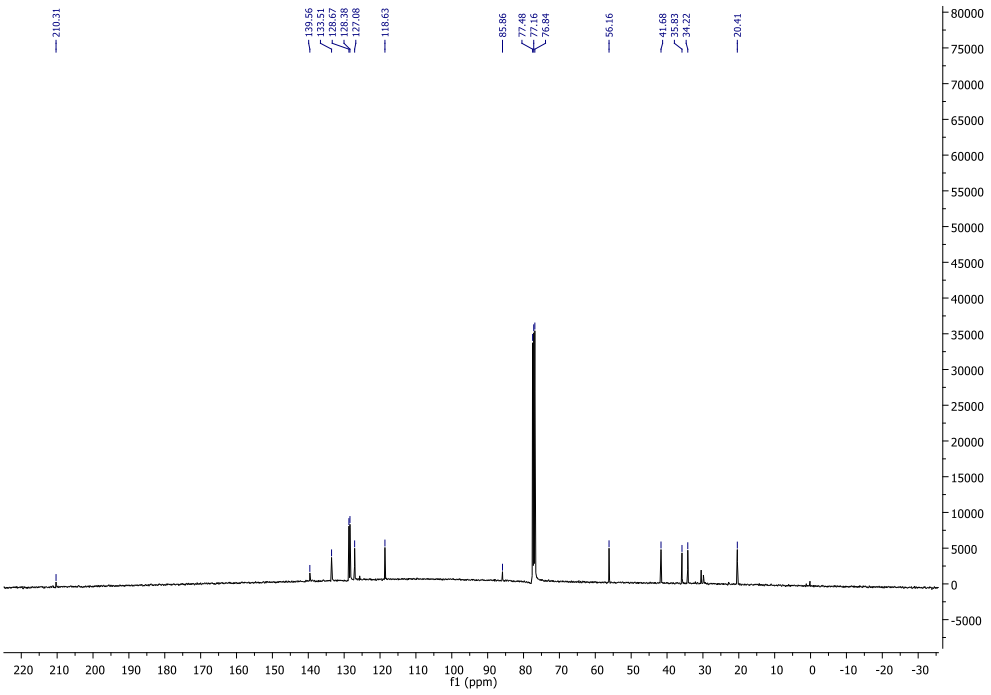
5.85
5.84
5.83
5.19
5.19
5.17
5.17
5.14
3.76
3.73
3.57
3.53
2.99
2.98
2.97
2.85
2.85
2.83
2.62
2.60
2.48
2.46
2.20
2.18
2.16
2.15
2.14
2.00
1.99
1.98
1.97
1.96
1.96
1.95
1.93
1000
900
800
700
600
500
400
300
200
100
0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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128.38
127.08
118.63
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77.48
77.16
76.84
56.16
41.68
35.83
34.22
20.41
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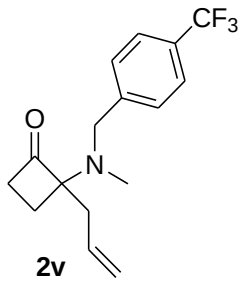
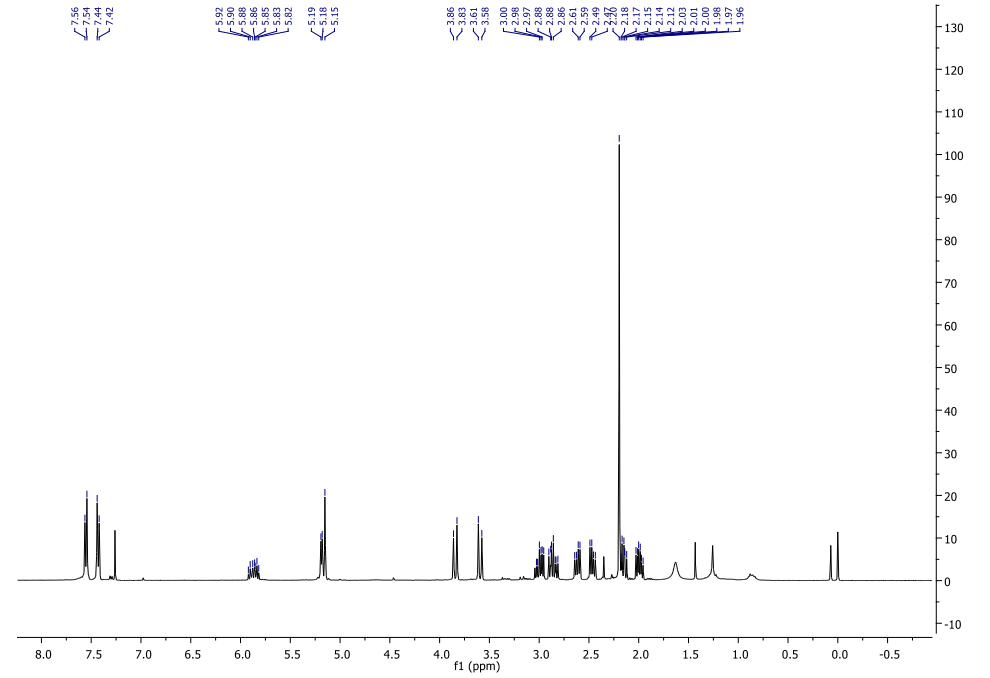
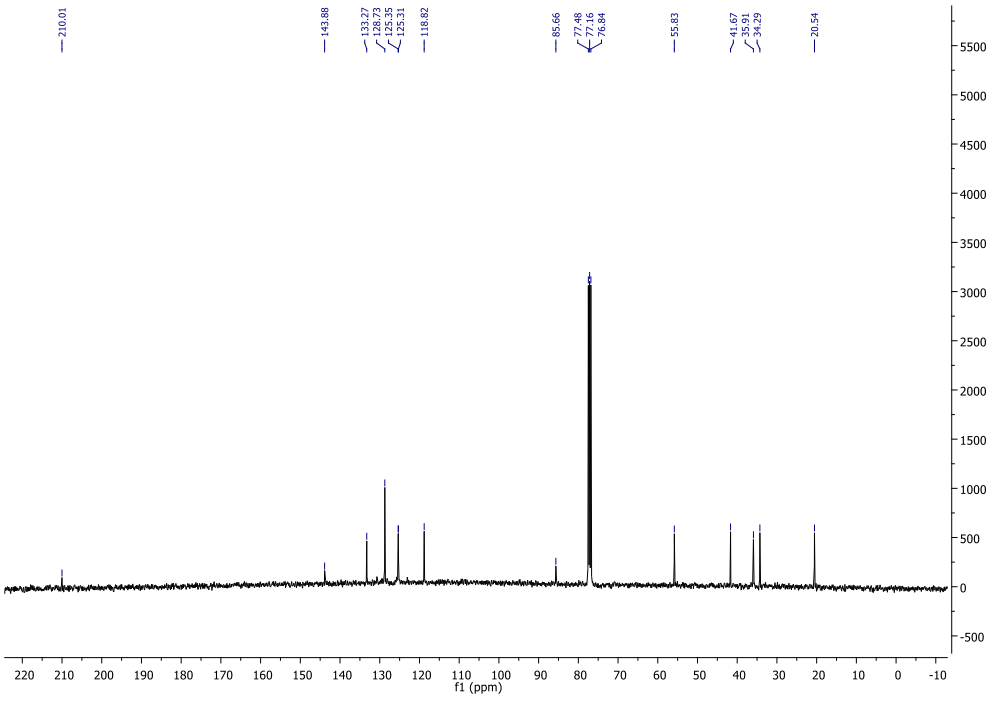
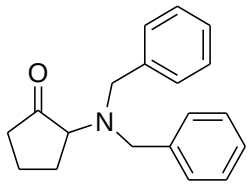
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)


CF3
O
N

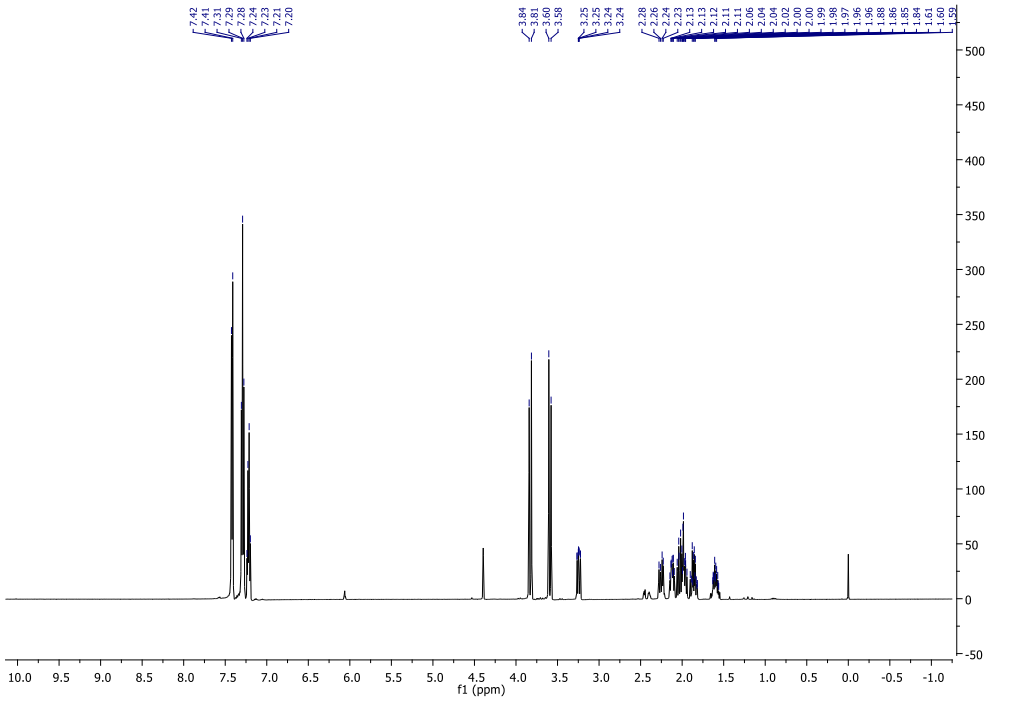
2v

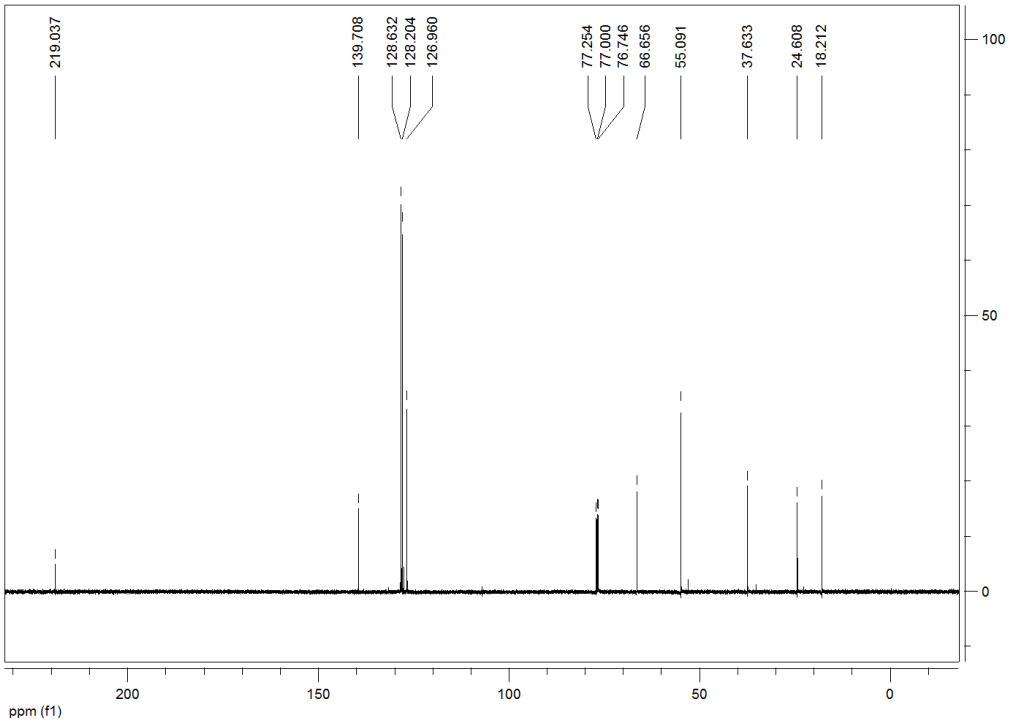

7.56
7.54
7.44
7.42
5.92
5.90
5.88
5.86
5.85
5.83
5.82
5.19
5.18
5.15
3.86
3.83
3.61
3.58
3.00
2.98
2.97
2.88
2.88
2.86
2.61
2.59
2.49
2.47
2.20
2.18
2.17
2.15
2.14
2.13
2.13
2.01
2.01
2.00
1.98
1.97
1.96
f1 (ppm)

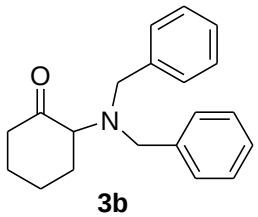

210.01
143.88
133.27
128.73
125.35
125.31
118.82
85.66
77.48
77.16
76.84
55.83
41.67
35.91
34.29
20.54
f1 (ppm)


O
N

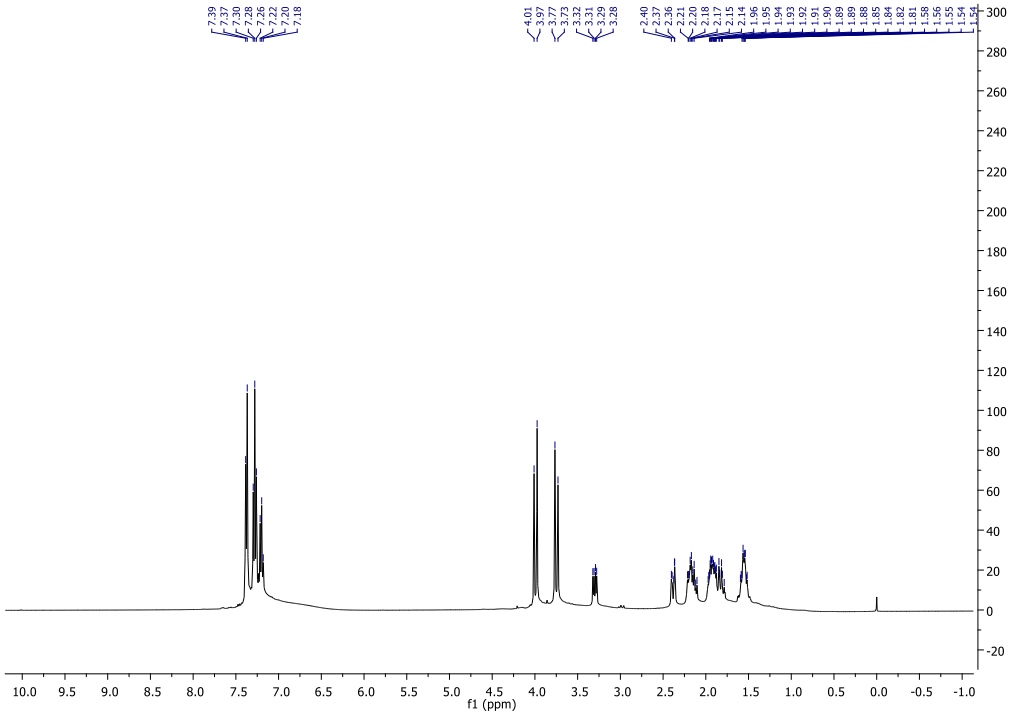
3a


7.42
7.41
7.31
7.29
7.28
7.24
7.23
7.21
7.20
3.84
3.81
3.60
3.58
3.25
3.25
3.24
3.24
2.28
2.26
2.24
2.23
2.13
2.13
2.12
2.11
2.11
2.06
2.04
2.04
2.02
2.00
2.00
1.99
1.98
1.97
1.96
1.96
1.88
1.86
1.85
1.84
1.61
1.60
1.59
500
450
400
350
300
250
200
150
100
50
0
-50
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
f1 (ppm)


219.037
139.708
128.632
128.204
126.960
77.254
77.000
76.746
66.656
55.091
37.633
24.608
18.212
100
50
0
200
150
100
50
0
ppm (f1)


O
N

3b


7.39
7.37
7.30
7.28
7.26
7.22
7.20
7.18
4.01
3.97
3.77
3.73
3.32
3.31
3.29
3.28
2.40
2.37
2.36
2.21
2.20
2.18
2.17
2.15
2.14
1.96
1.95
1.94
1.93
1.92
1.91
1.90
1.89
1.88
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1.82
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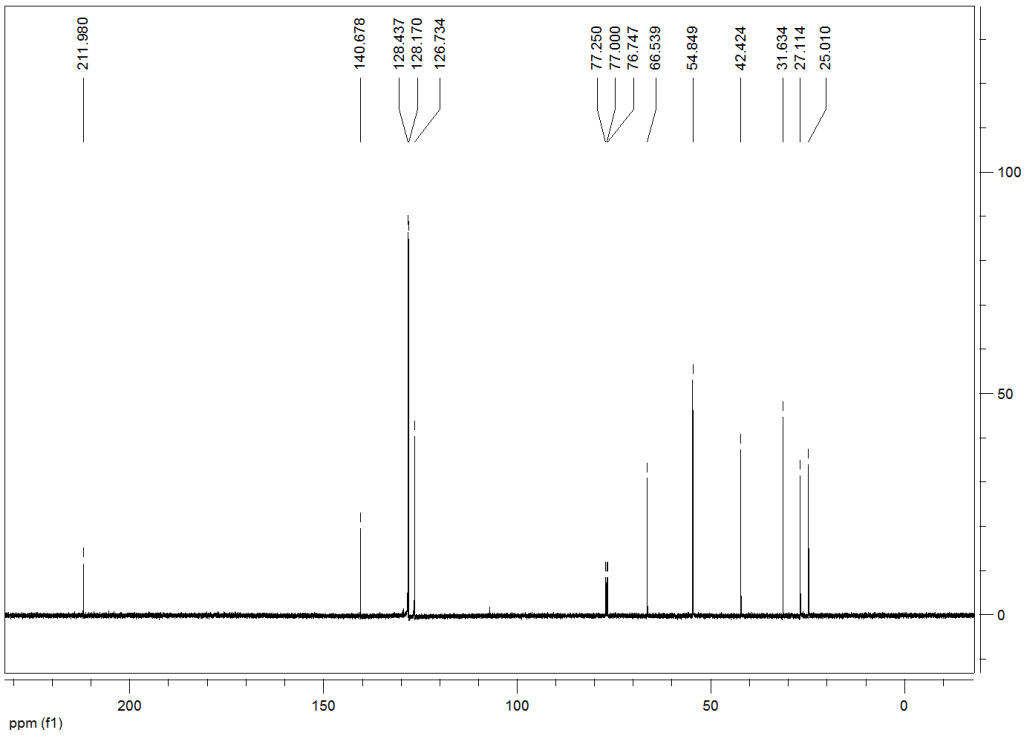
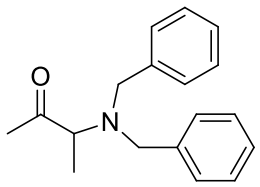
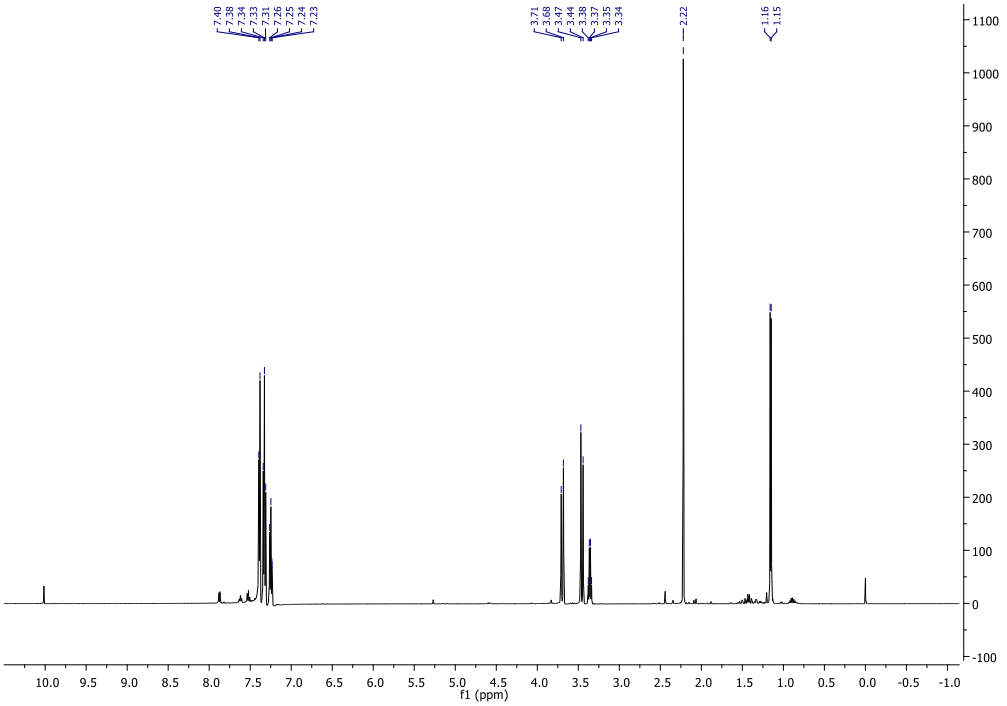
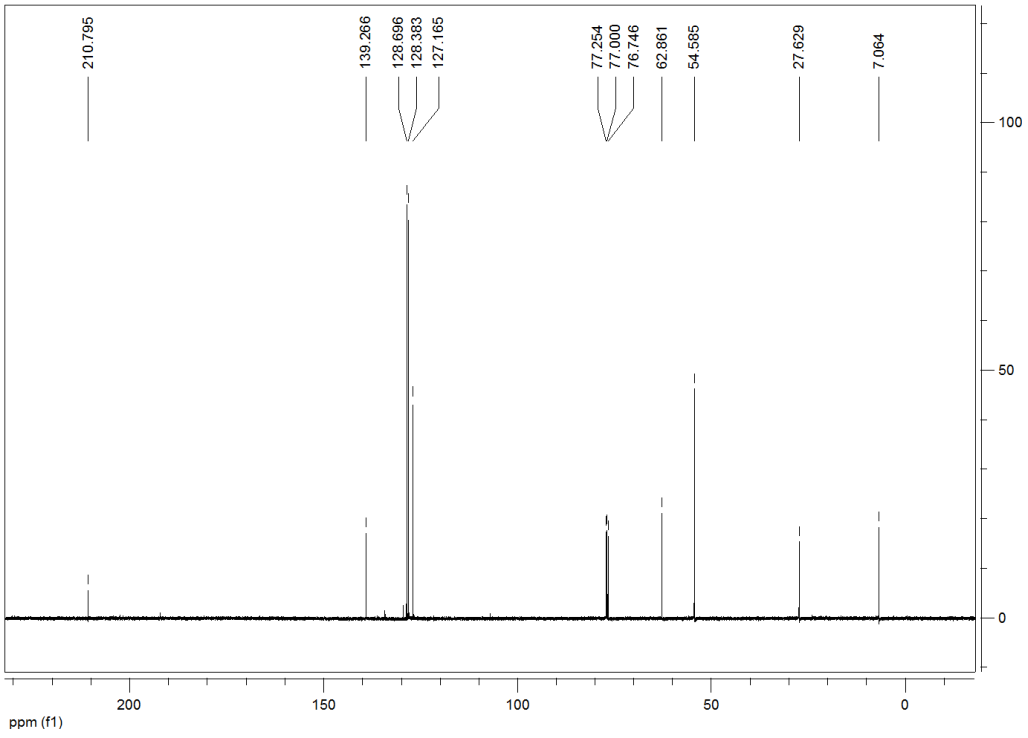
1.56
1.55
1.54
1.54
f1 (ppm)

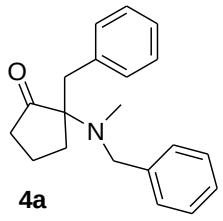

211.980
140.678
128.437
128.170
126.734
77.250
77.000
76.747
66.539
54.849
42.424
31.634
27.114
25.010
ppm (f1)



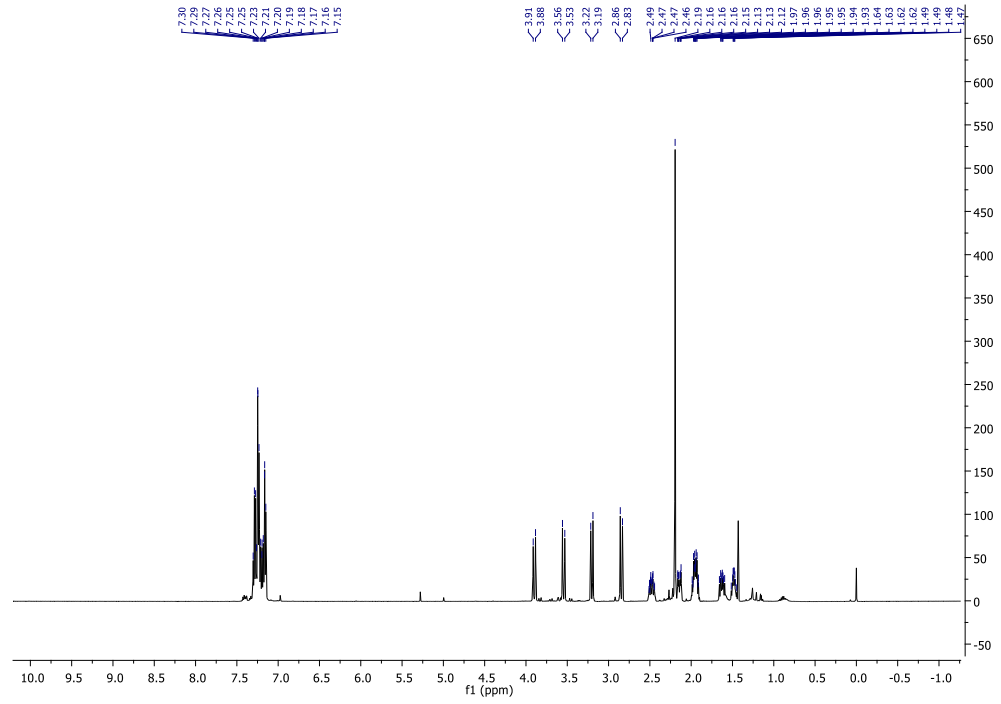
3c

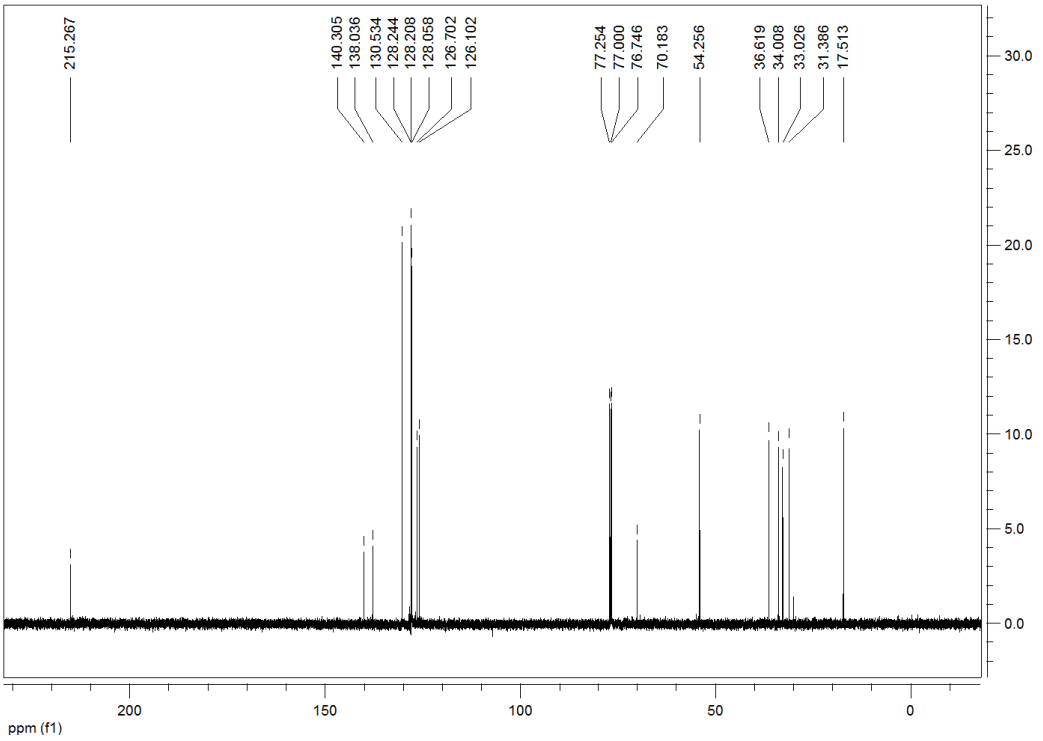

7.40
7.38
7.34
7.33
7.31
7.26
7.25
7.24
7.23
3.71
3.68
3.47
3.44
3.38
3.37
3.35
3.34
2.22
1.16
1.15
f1 (ppm)

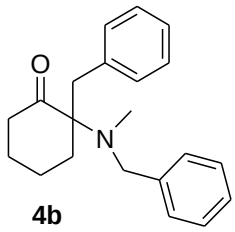

210.795
139.266
128.696
128.383
127.165
77.254
77.000
76.746
62.861
54.585
27.629
7.064
ppm (f1)


O
N

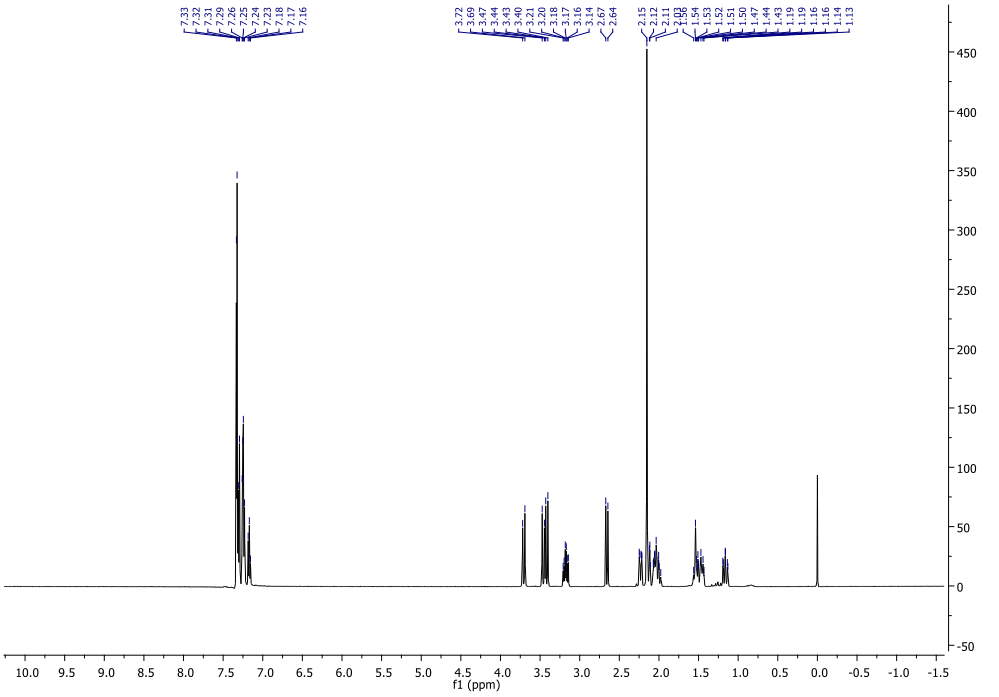
4a

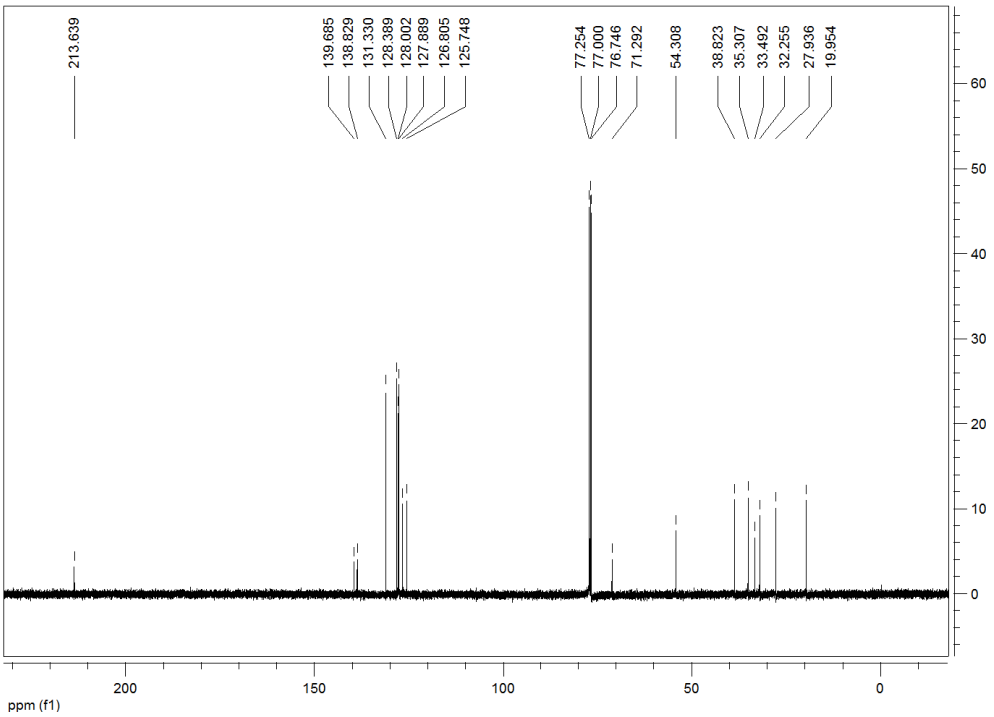

7.30
7.29
7.27
7.26
7.25
7.23
7.21
7.20
7.19
7.18
7.17
7.16
7.15
3.91
3.88
3.56
3.53
3.22
3.19
2.86
2.83
2.49
2.47
2.46
2.19
2.16
2.16
2.15
2.13
2.12
1.97
1.96
1.96
1.95
1.95
1.94
1.93
1.64
1.63
1.62
1.62
1.49
1.49
1.48
1.47
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
10.0 9.5 9.0 8.5 8.0 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
f1 (ppm)

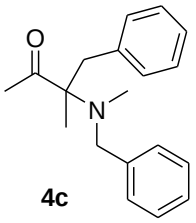

215.267
140.305
138.036
130.534
128.244
128.208
128.058
126.702
126.102
77.254
77.000
76.746
70.183
54.256
36.619
34.008
33.026
31.386
17.513
30.0
25.0
20.0
15.0
10.0
5.0
0.0
200
150
100
50
0
ppm (f1)


O
N

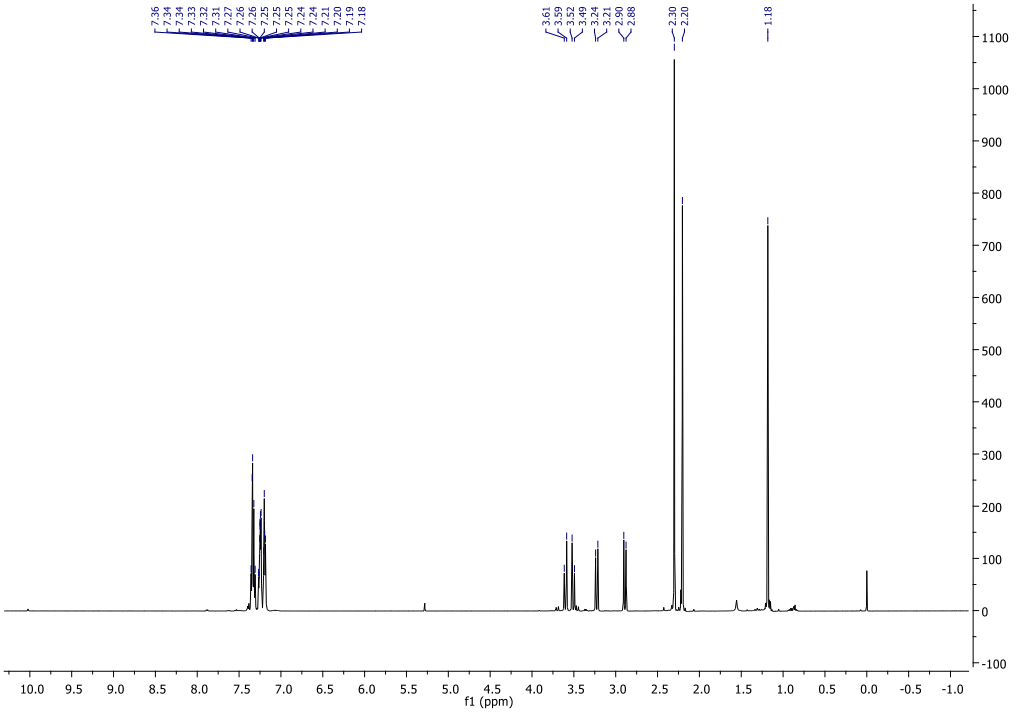
4b

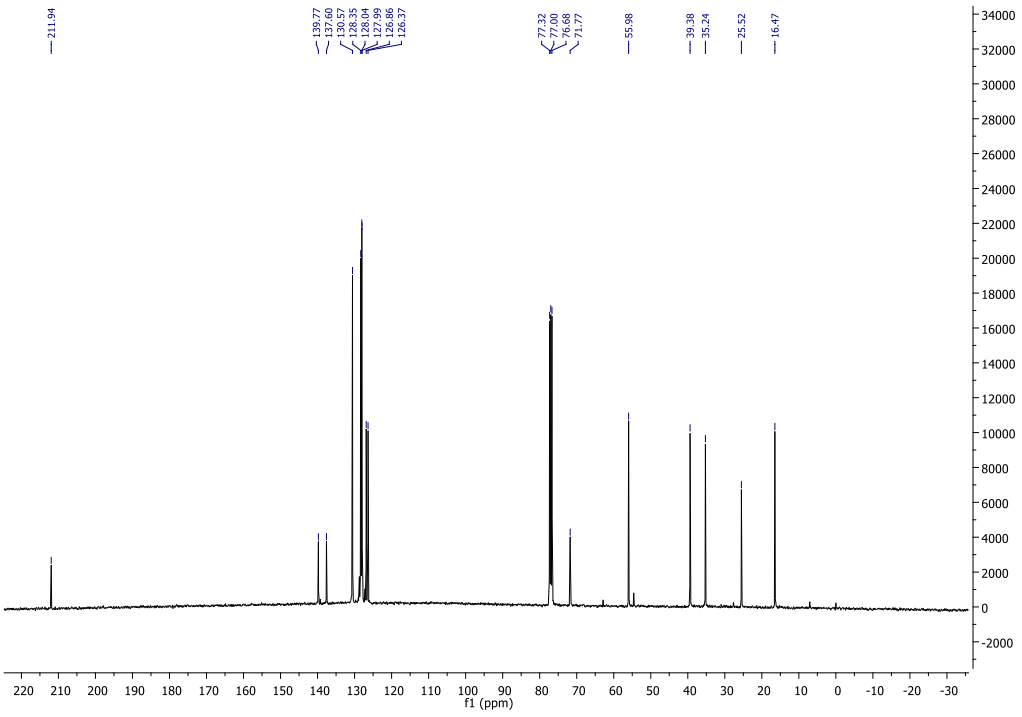

7.33
7.32
7.31
7.29
7.26
7.25
7.24
7.23
7.18
7.17
7.16
3.72
3.69
3.47
3.44
3.43
3.40
3.21
3.20
3.18
3.17
3.16
3.14
2.67
2.64
2.15
2.12
2.11
2.03
1.98
1.54
1.53
1.52
1.51
1.50
1.47
1.44
1.43
1.19
1.16
1.16
1.14
1.13
f1 (ppm)

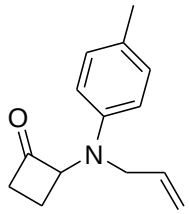

213.639
139.685
138.829
131.330
128.389
128.002
127.889
126.805
125.748
77.254
77.000
76.746
71.292
54.308
38.823
35.307
33.492
32.255
27.936
19.954
ppm (f1)


O
N

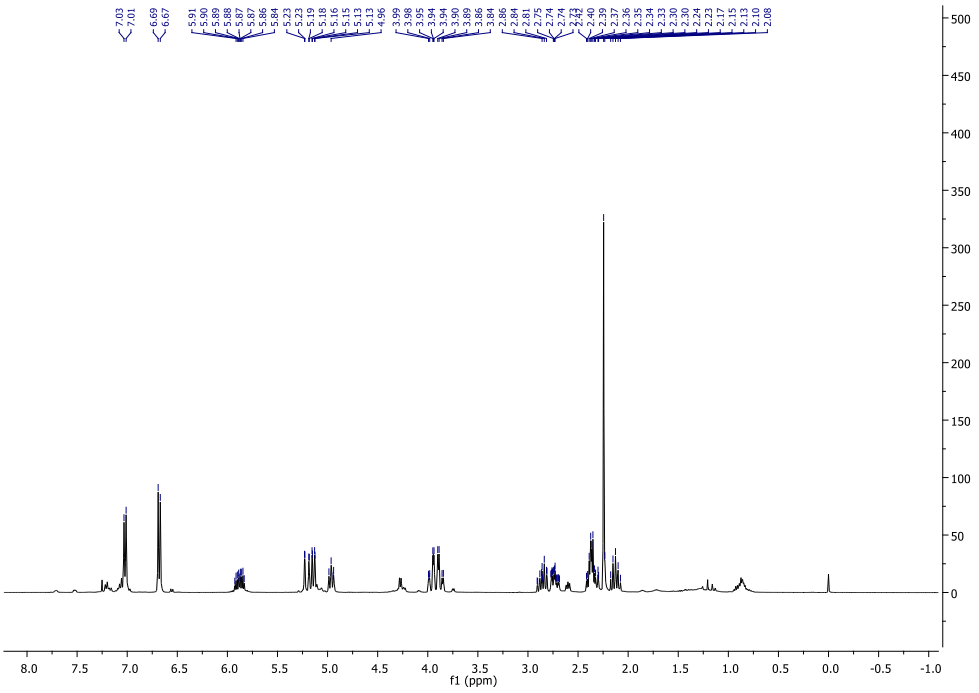
4c

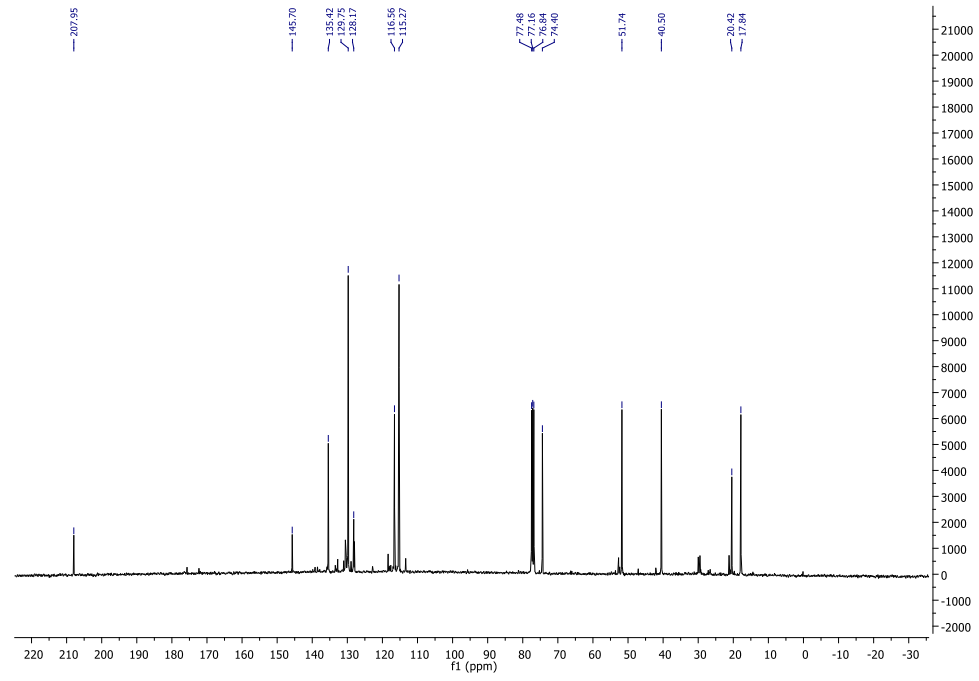

7.36
7.34
7.34
7.33
7.32
7.31
7.27
7.26
7.26
7.25
7.25
7.25
7.24
7.24
7.21
7.20
7.19
7.18
3.61
3.59
3.52
3.49
3.24
3.21
2.90
2.88
2.30
2.20
1.18
f1 (ppm)

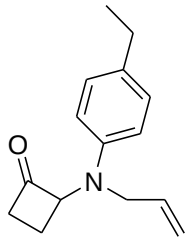

211.94
139.77
137.60
130.57
128.35
128.04
127.99
126.86
126.37
77.32
77.00
76.68
71.77
55.98
39.38
35.24
25.52
16.47
f1 (ppm)


O
N

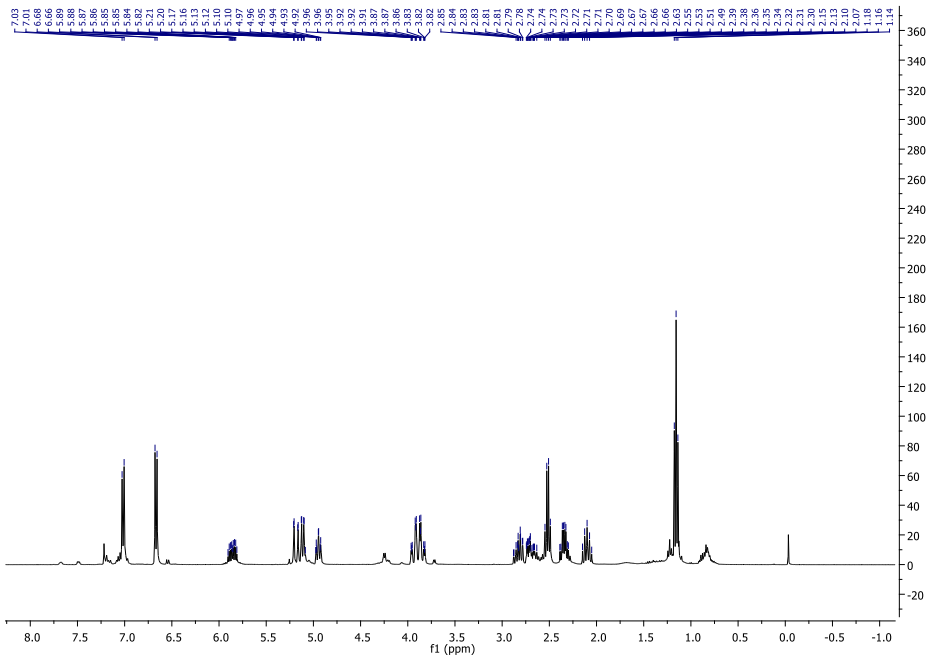
5b

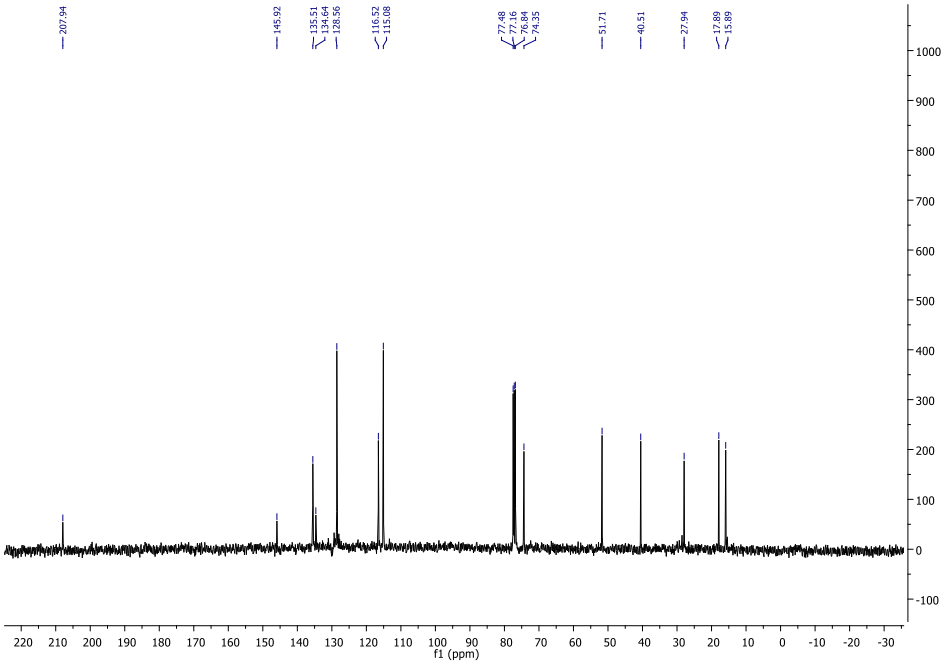

7.03
7.01
6.69
6.67
5.91
5.90
5.89
5.88
5.87
5.87
5.86
5.84
5.23
5.23
5.19
5.18
5.16
5.15
5.15
5.13
4.96
3.99
3.98
3.95
3.94
3.94
3.90
3.89
3.86
3.84
2.86
2.84
2.81
2.75
2.74
2.74
2.42
2.40
2.39
2.37
2.36
2.35
2.34
2.33
2.30
2.30
2.24
2.23
2.17
2.15
2.13
2.10
2.08
f1 (ppm)

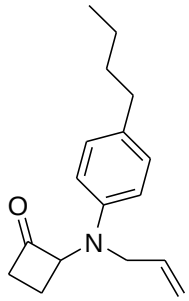

207.95
145.70
135.42
129.75
128.17
116.56
115.27
77.48
77.16
76.84
74.40
51.74
40.50
20.42
17.84
f1 (ppm)


O
N

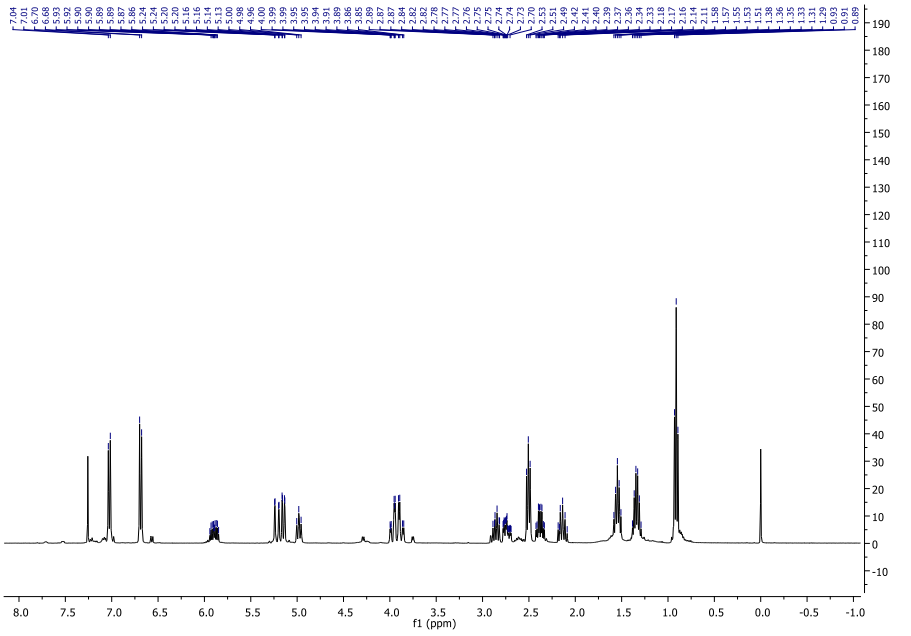
5c

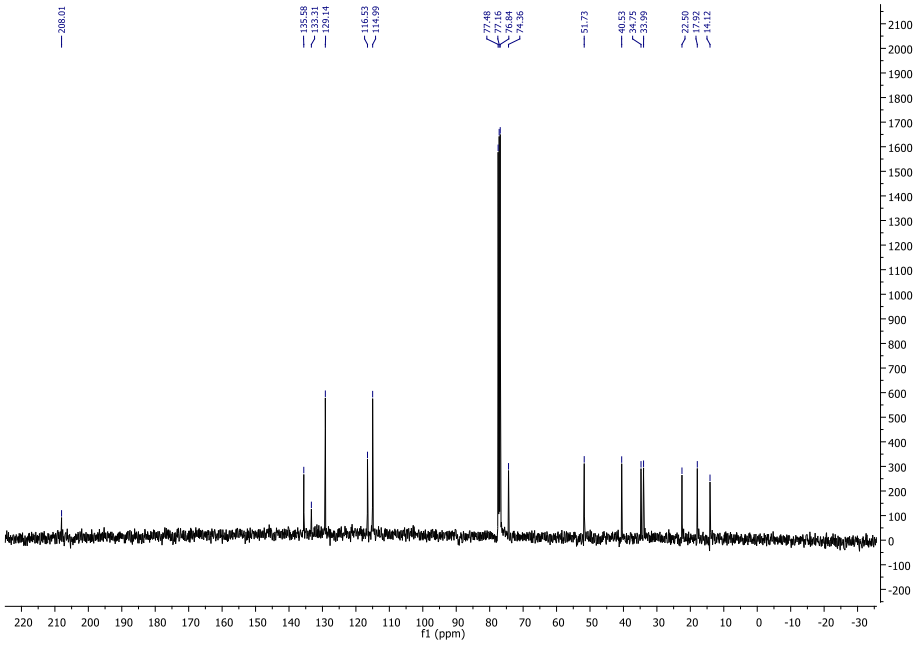

f1 (ppm)

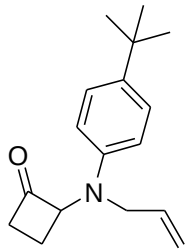

207.94
145.92
135.51
134.64
128.56
116.52
115.08
77.48
77.16
76.84
74.35
51.71
40.51
27.94
17.89
15.89
f1 (ppm)


O
N

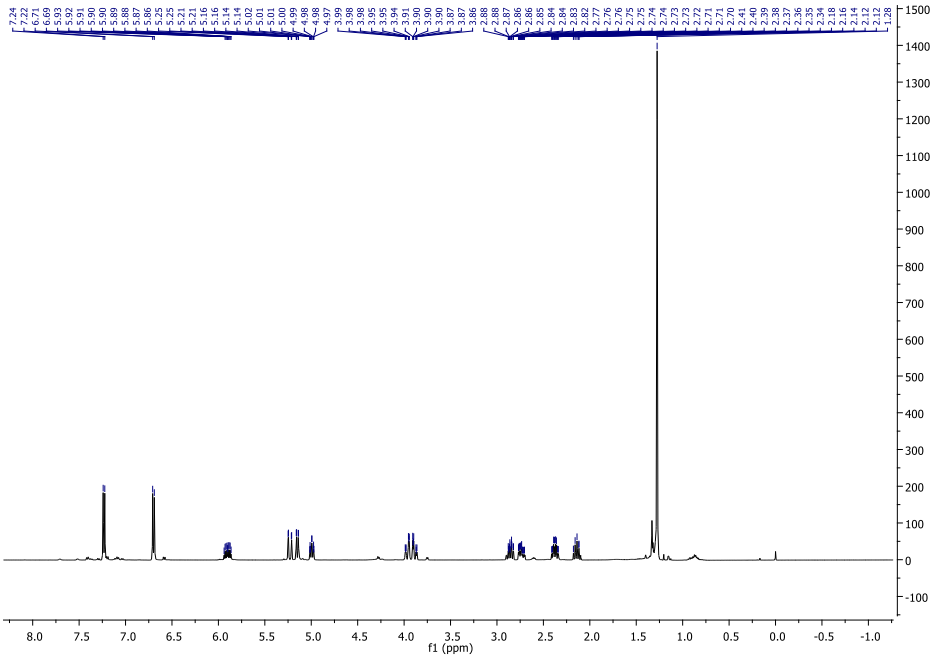
5d

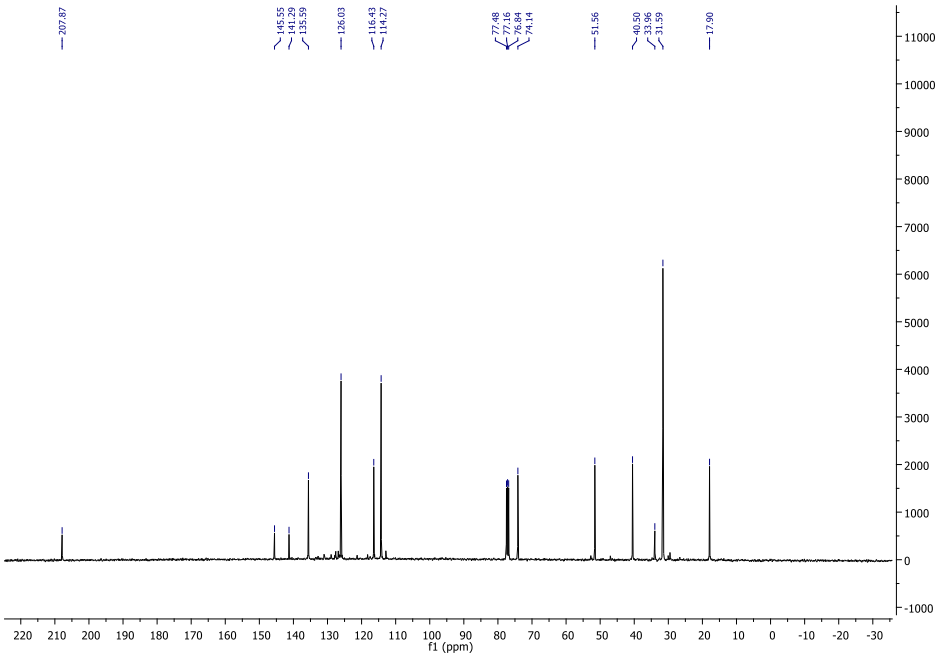

f1 (ppm)

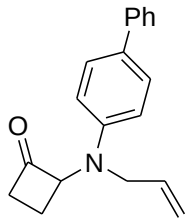

208.01
135.58
133.31
129.14
116.53
114.99
77.48
77.16
76.84
74.36
51.73
40.53
34.75
33.99
22.50
17.92
14.12
f1 (ppm)


O
N

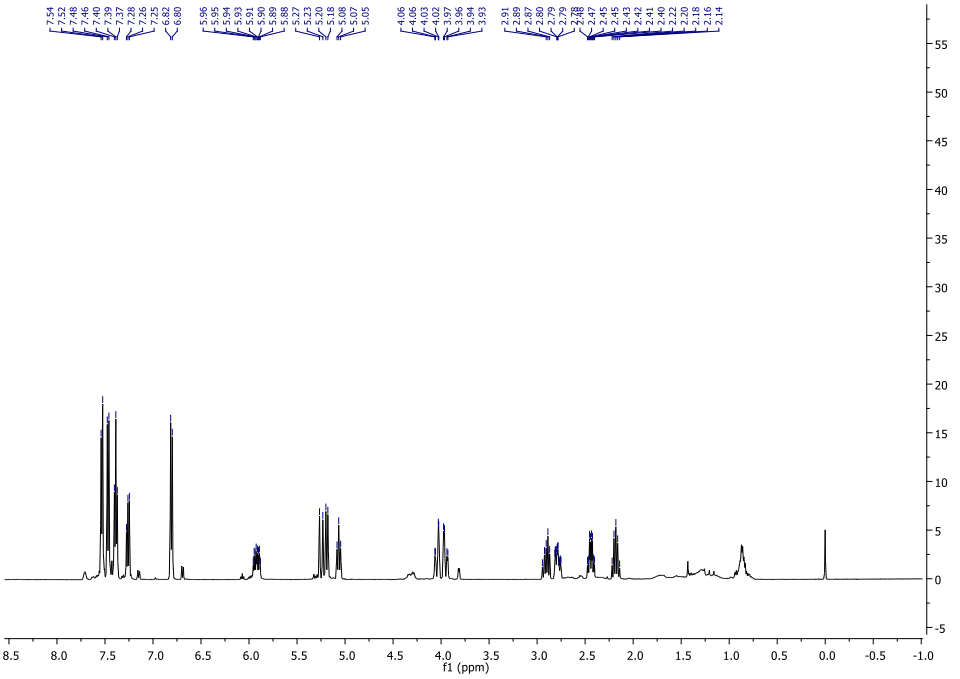
5e


f1 (ppm)


207.87
145.55
141.29
135.59
126.03
116.43
114.27
77.48
77.16
76.84
74.14
51.56
40.50
33.96
31.59
17.90
f1 (ppm)


Ph
O
N

5f


7.54
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6.82
6.80
5.96
5.95
5.94
5.93
5.91
5.90
5.89
5.88
5.77
5.23
5.20
5.18
5.08
5.07
5.05
4.06
4.06
4.03
4.02
3.97
3.96
3.94
3.93
2.91
2.89
2.87
2.80
2.79
2.79
2.48
2.47
2.45
2.45
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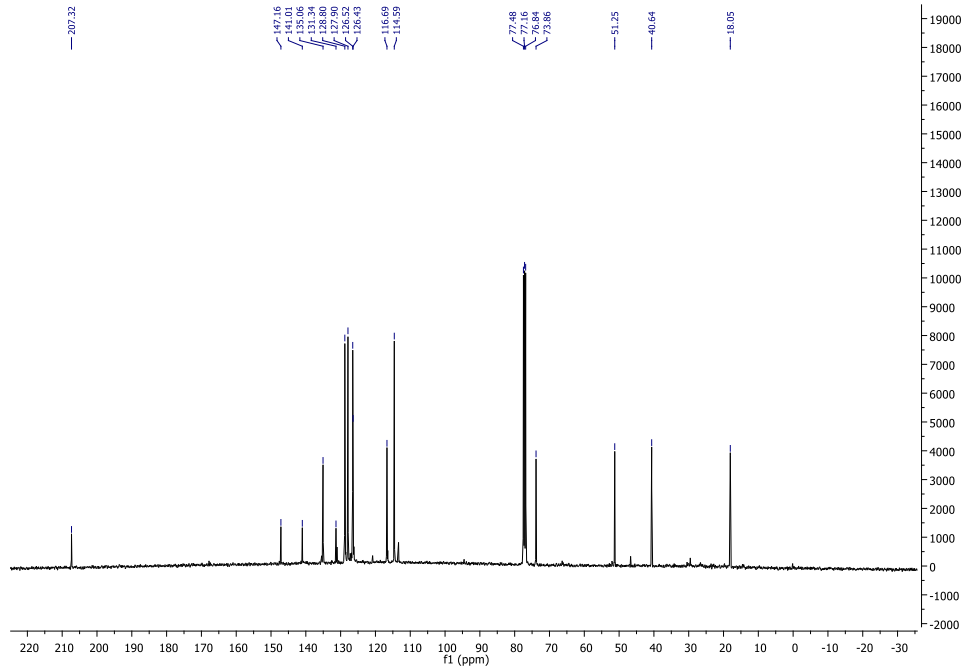
2.42
2.41
2.40
2.22
2.20
2.18
2.16
2.14
f1 (ppm)


207.32
147.16
141.01
135.06
131.34
128.80
127.90
126.52
126.43
116.69
114.59
77.48
77.16
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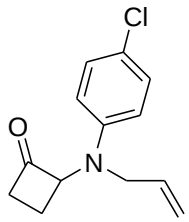
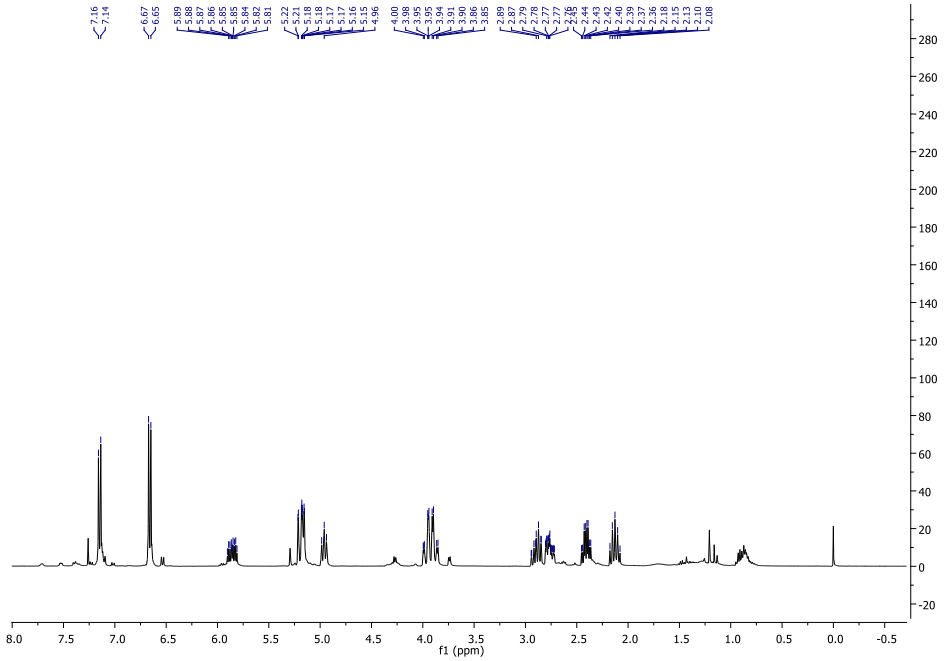
73.86
51.25
40.64
18.05
f1 (ppm)


Cl
O
N

5g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7.14
6.67
6.65
5.89
5.88
5.87
5.86
5.85
5.85
5.84
5.82
5.81
5.22
5.21
5.18
5.18
5.17
5.17
5.16
5.15
4.96
4.00
3.98
3.95
3.95
3.94
3.91
3.90
3.86
3.85
2.89
2.87
2.79
2.78
2.77
2.77
2.76
2.45
2.44
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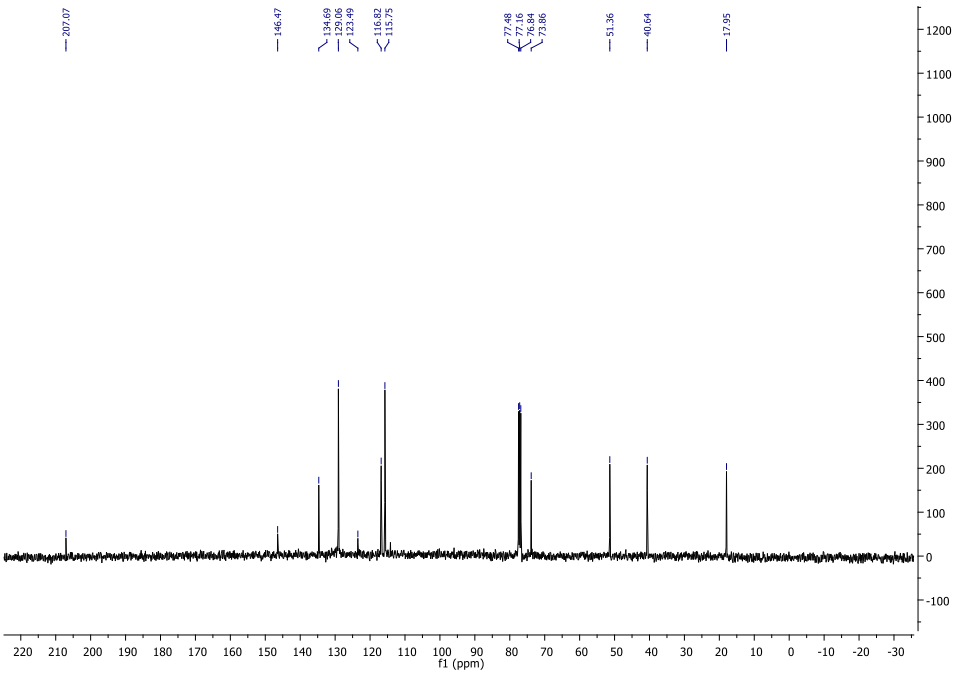
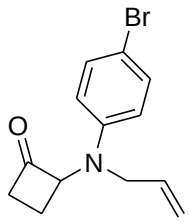
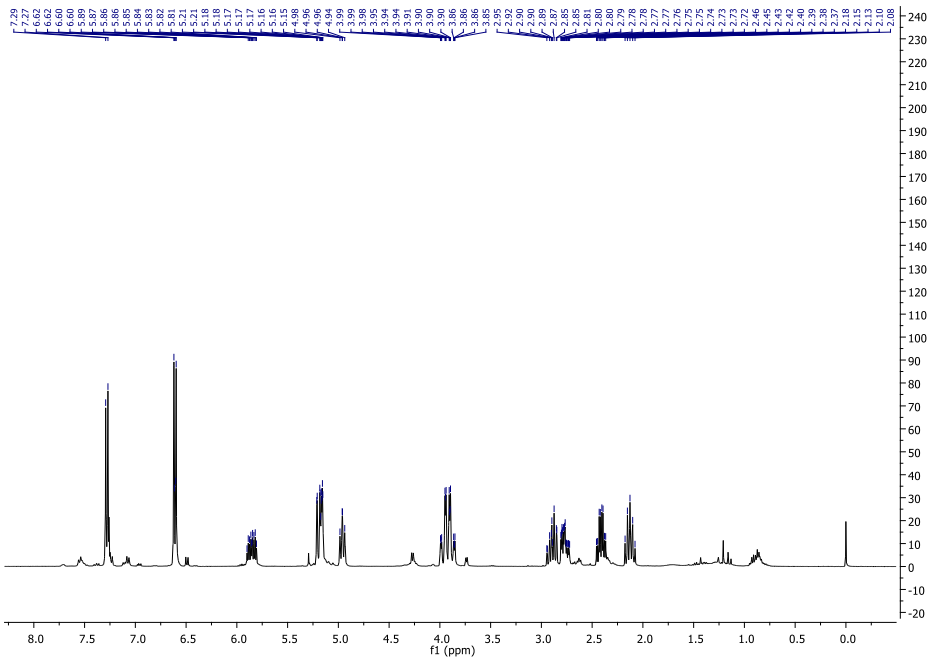
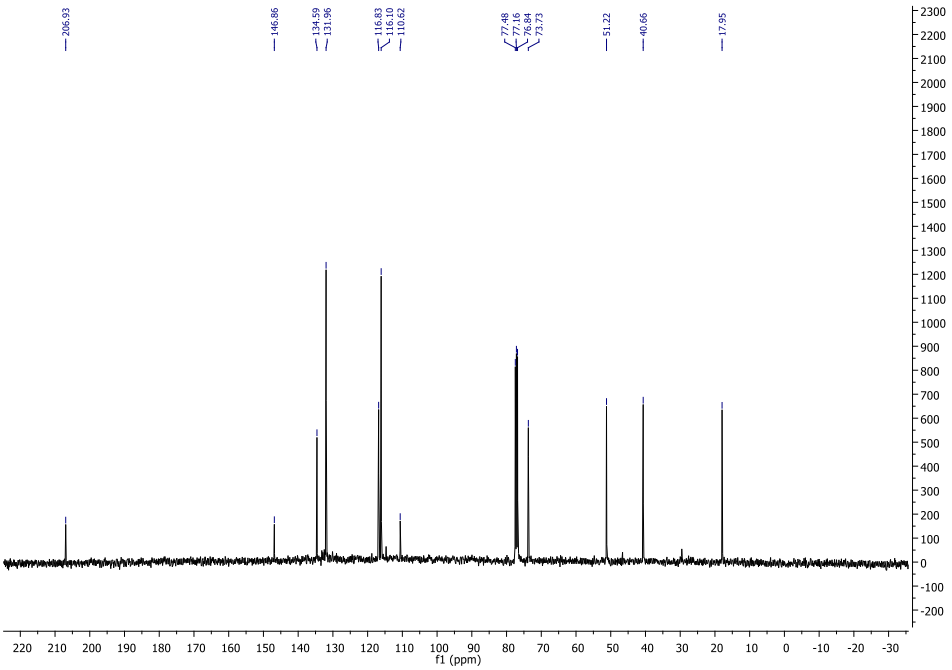
2.39
2.37
2.36
2.18
2.15
2.13
2.10
2.08
f1 (ppm)


207.07
146.47
134.69
129.06
123.49
116.82
115.75
77.48
77.16
76.84
73.86
51.36
40.64
17.95
f1 (ppm)


Br
O
N

5h


f1 (ppm)


206.93
146.86
134.59
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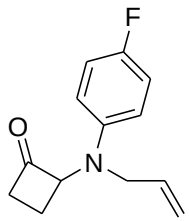
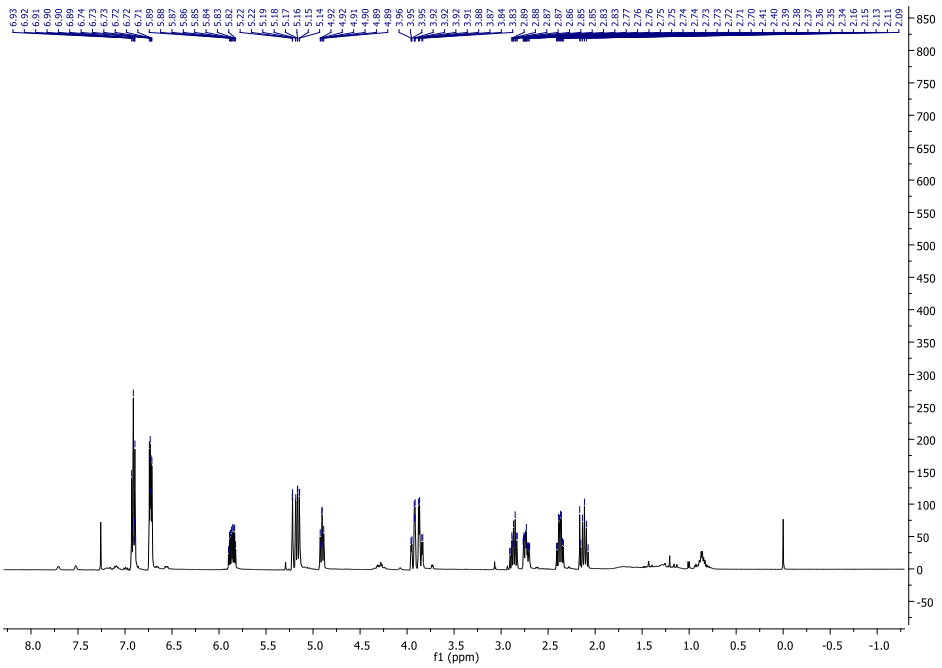
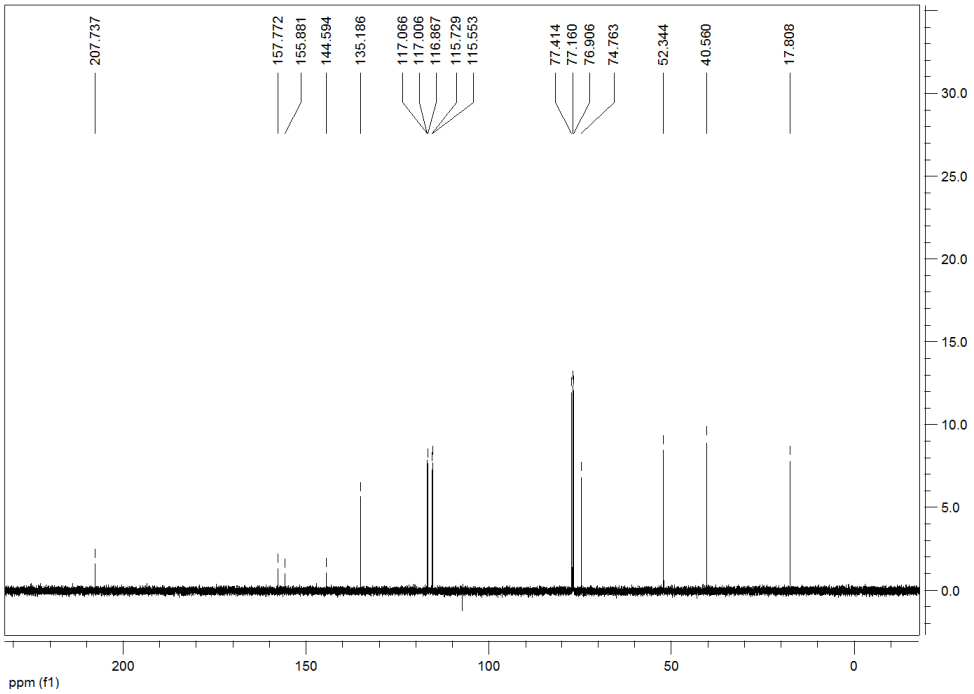
116.83
116.10
110.62
77.48
77.16
76.84
73.73
51.22
40.66
17.95
f1 (ppm)


F
O
N

5i


f1 (ppm)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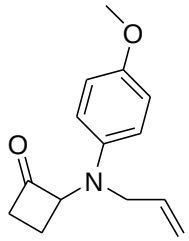
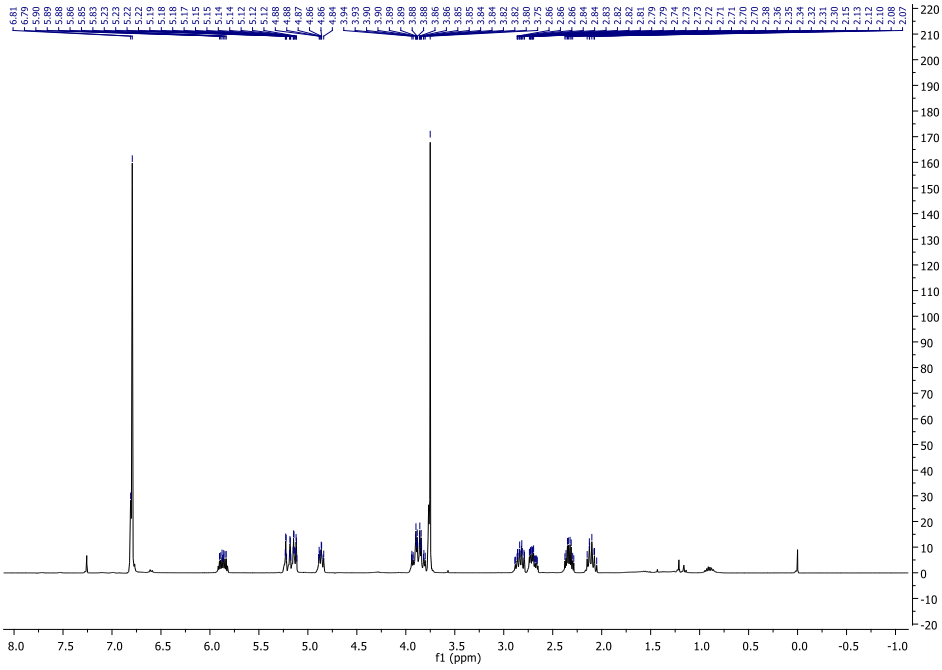
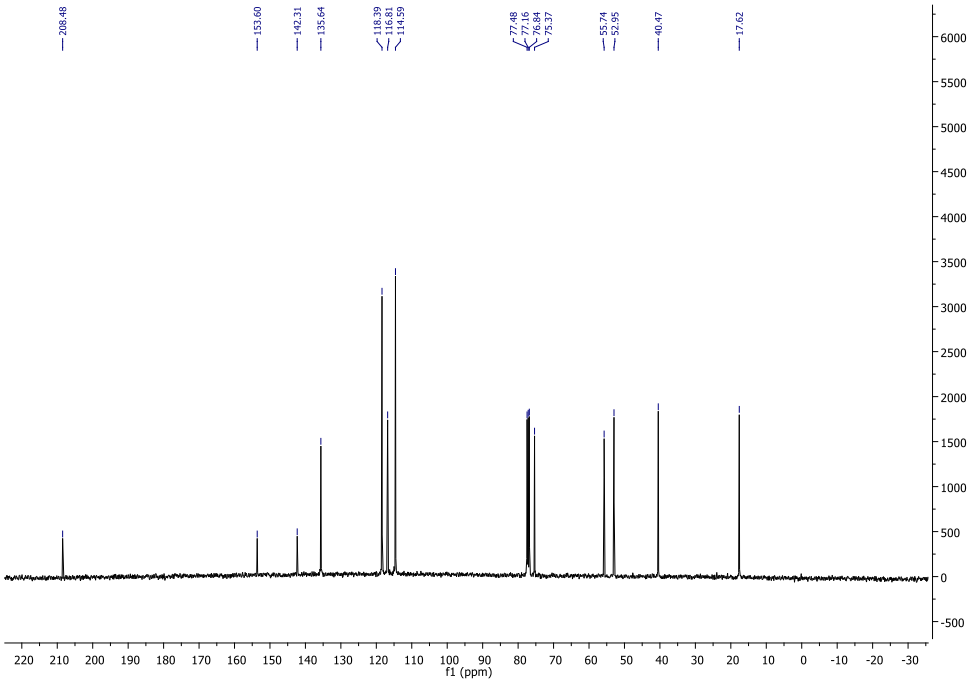
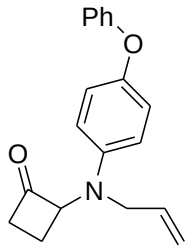
157.772
155.881
144.594
135.186
117.066
117.006
116.867
115.729
115.553
77.414
77.160
76.906
74.763
52.344
40.560
17.808
ppm (f1)


O
O
N

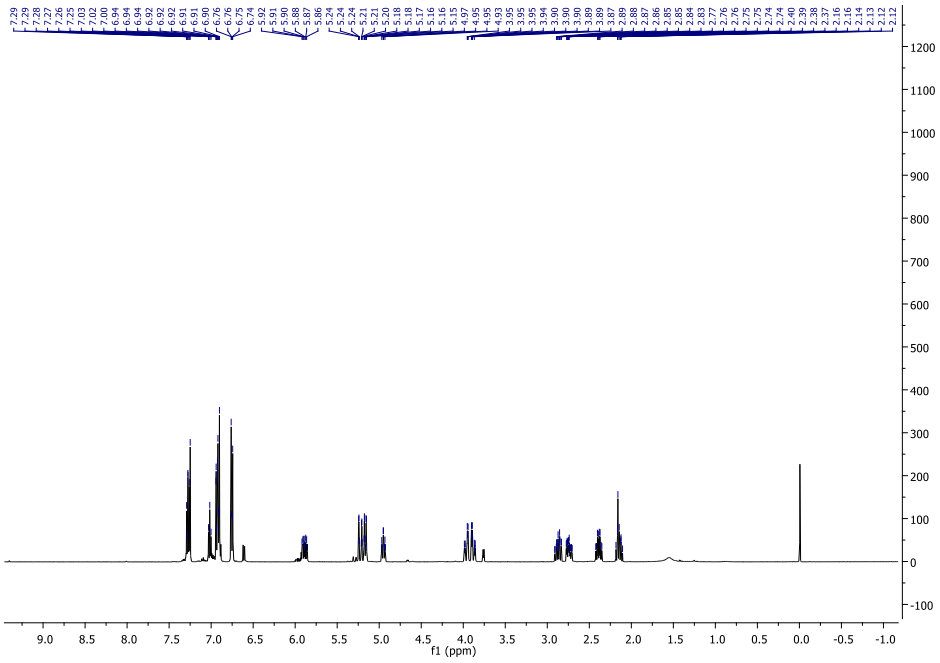
5j

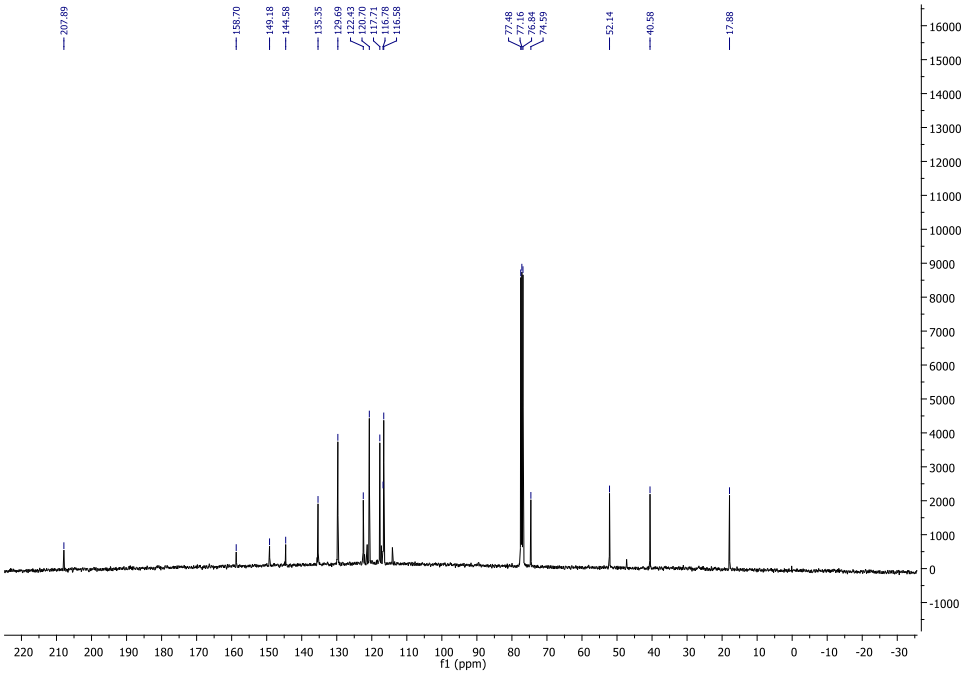

f1 (ppm)


208.48
153.60
142.31
135.64
118.39
116.81
114.59
77.48
77.16
76.84
75.37
55.74
52.95
40.47
17.62
f1 (ppm)


Ph
O
O
N

5k


f1 (ppm)


207.89
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144.58
135.35
129.69
122.43
120.70
117.71
116.78
116.58
77.48
77.16
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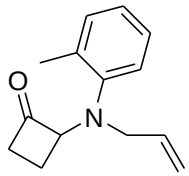
52.14
40.58
17.88
f1 (ppm)



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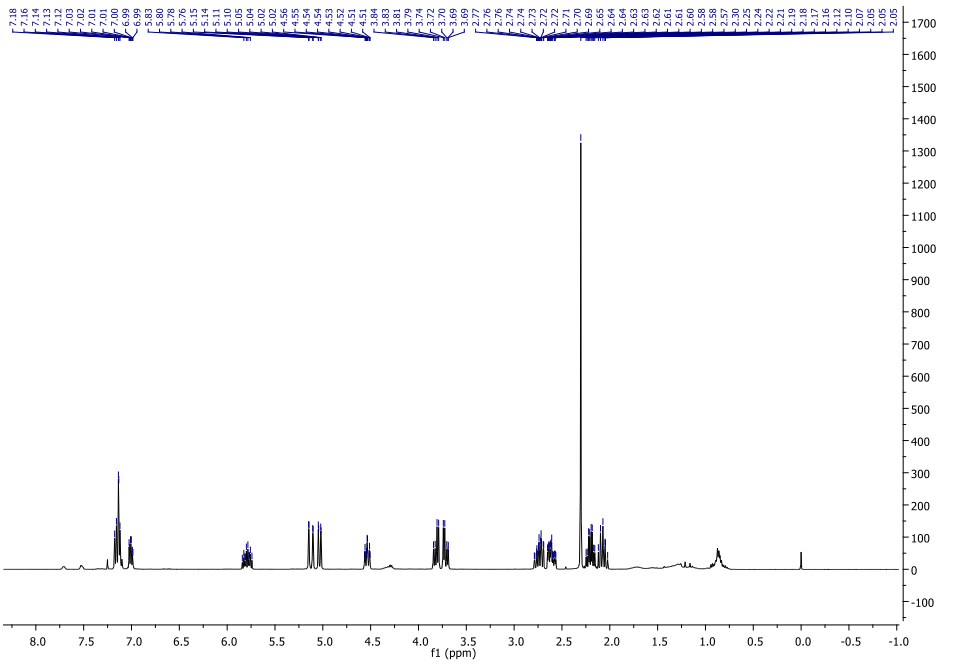
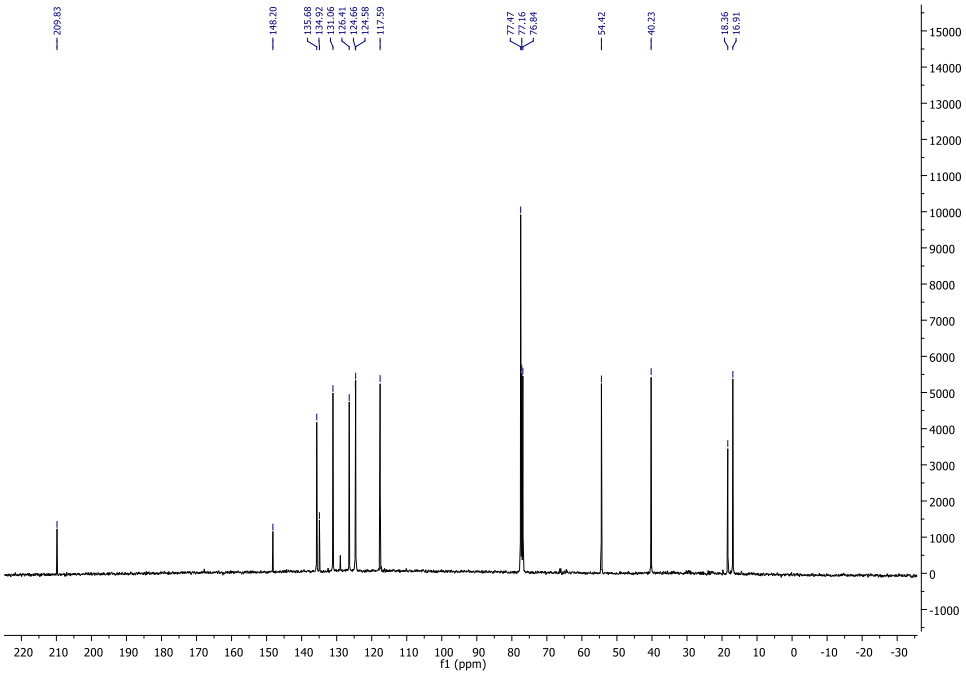
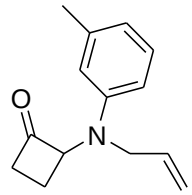
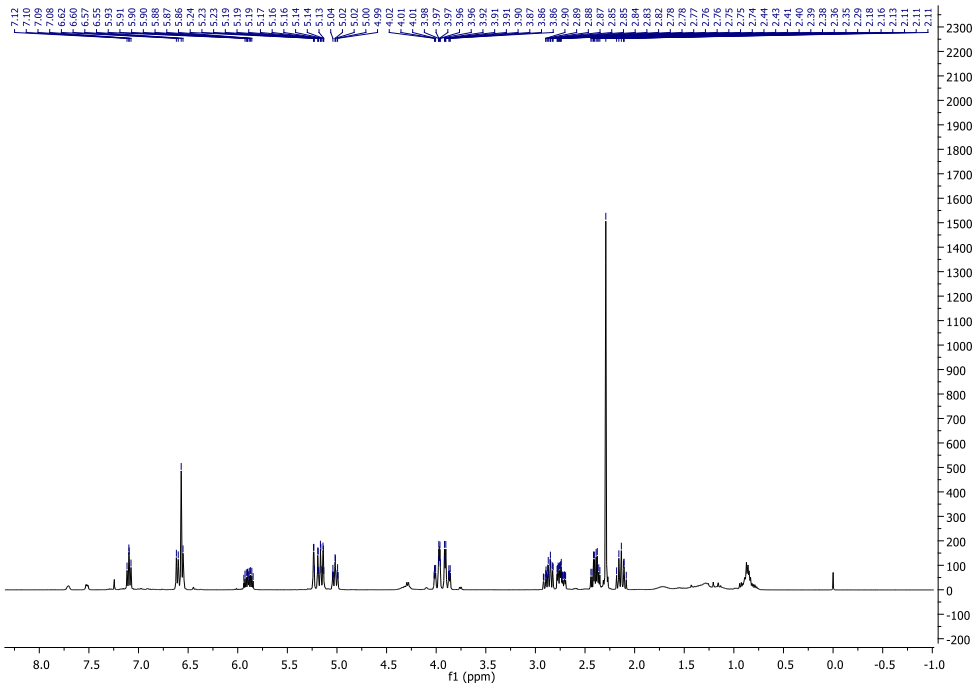
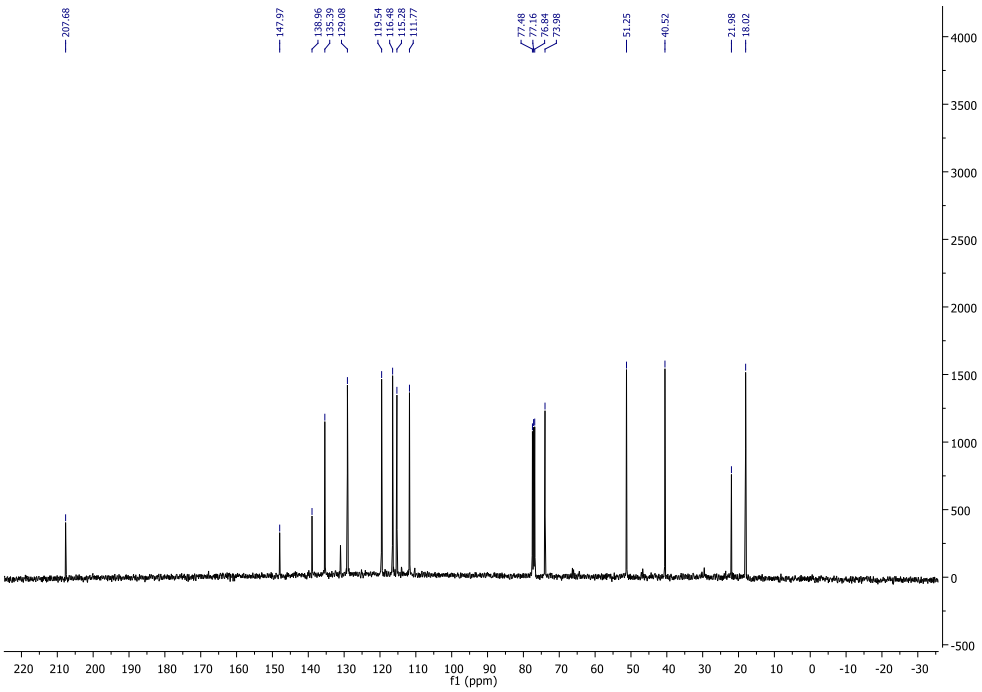





O
N

5m


f1 (ppm)


207.68
147.97
138.96
135.39
129.08
119.54
116.48
115.28
111.77
77.48
77.16
76.84
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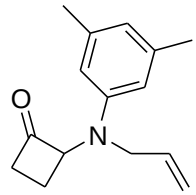
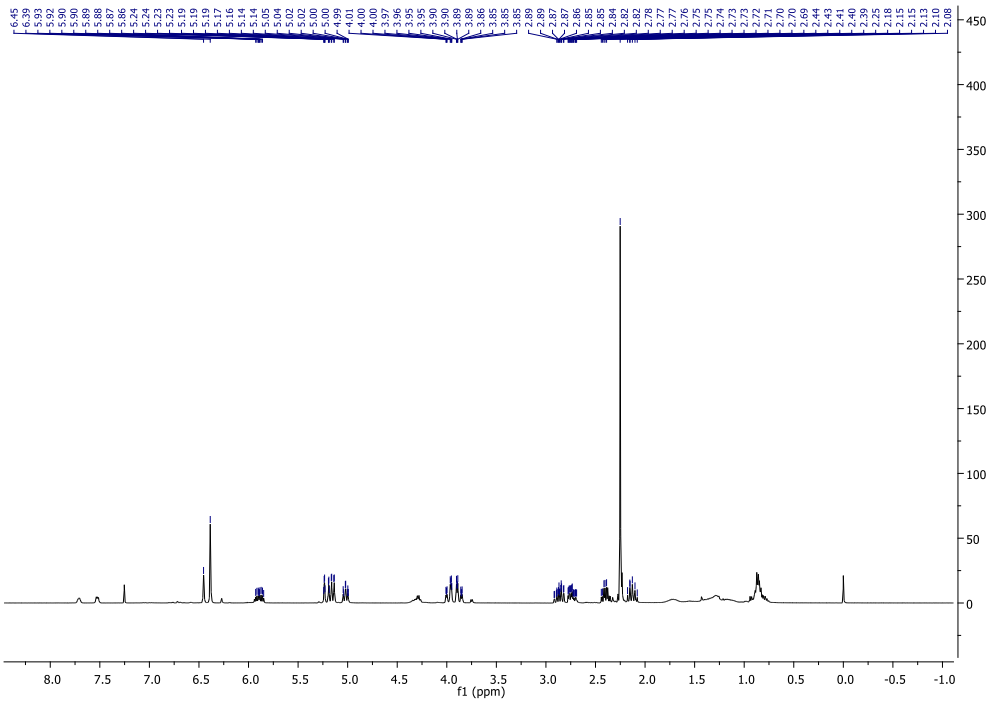
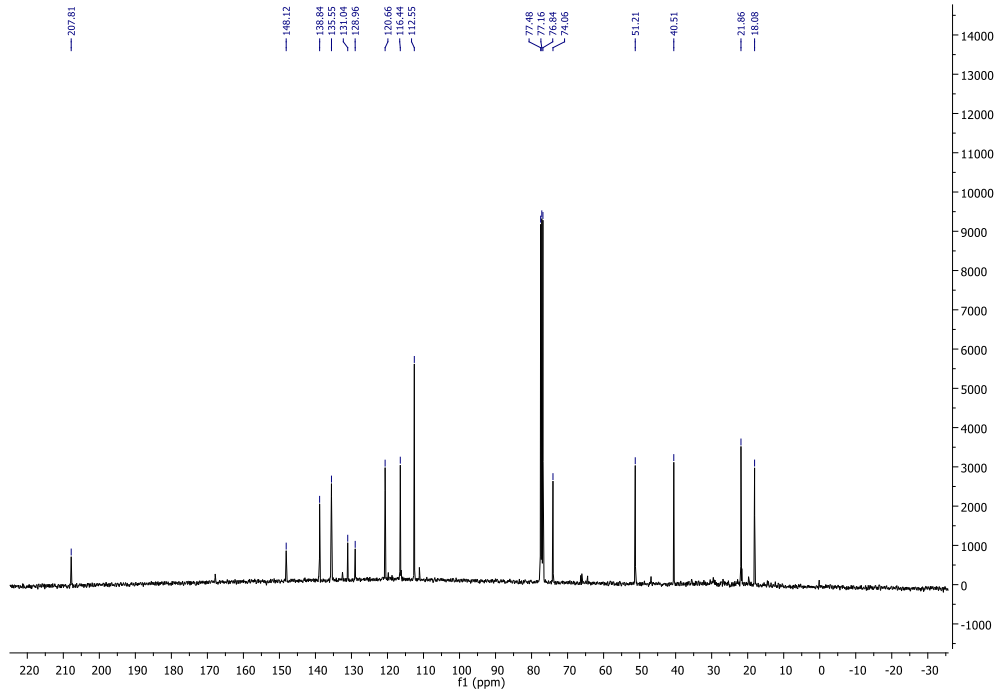
51.25
40.52
21.98
18.02
f1 (ppm)


O
N

5n


f1 (ppm)


207.81
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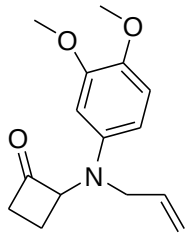
138.84
135.55
131.04
128.96
120.66
116.44
112.55
77.48
77.16
76.84
74.06
51.21
40.51
21.86
18.08
f1 (ppm)



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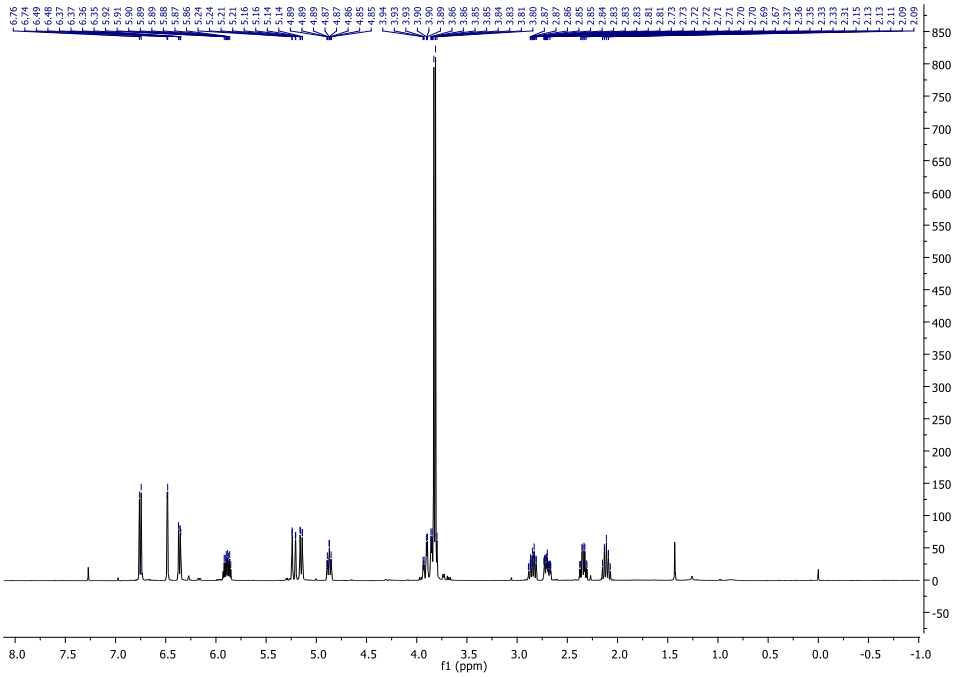
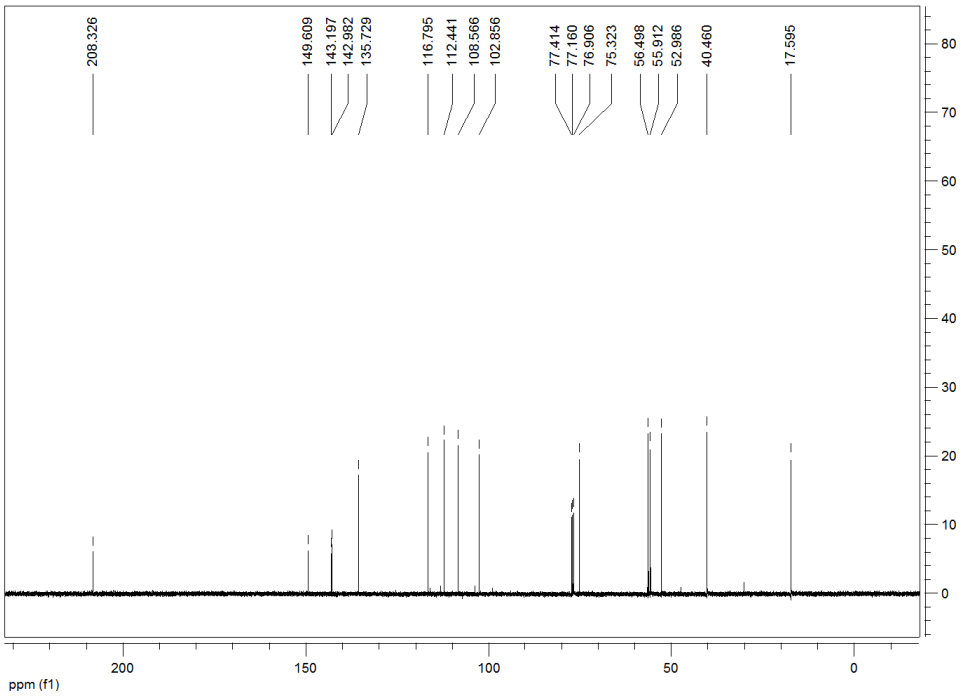
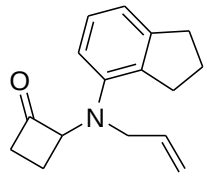
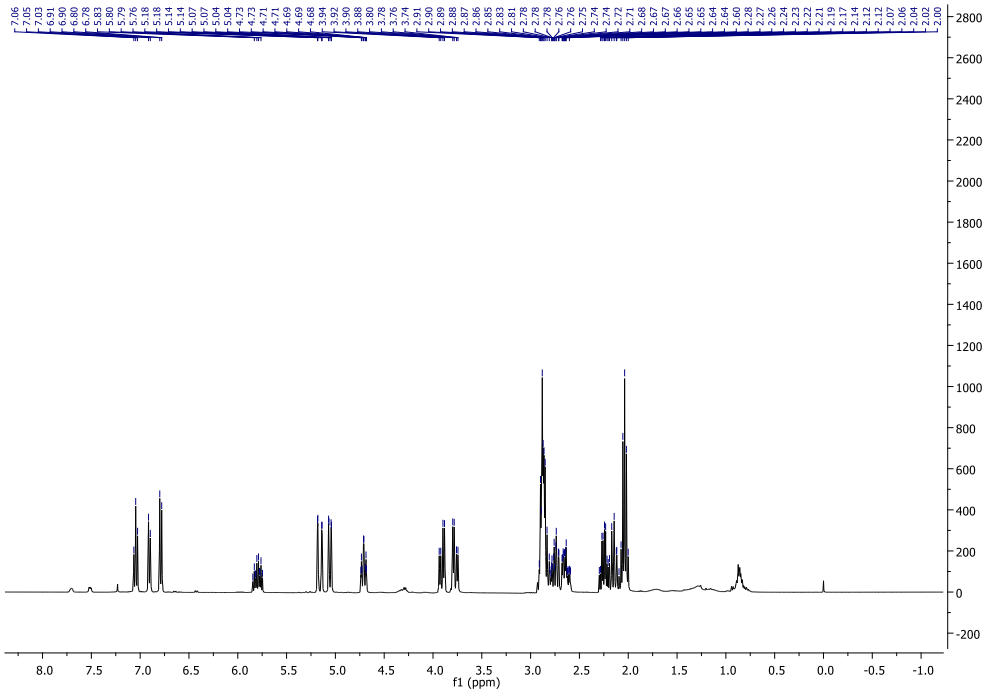
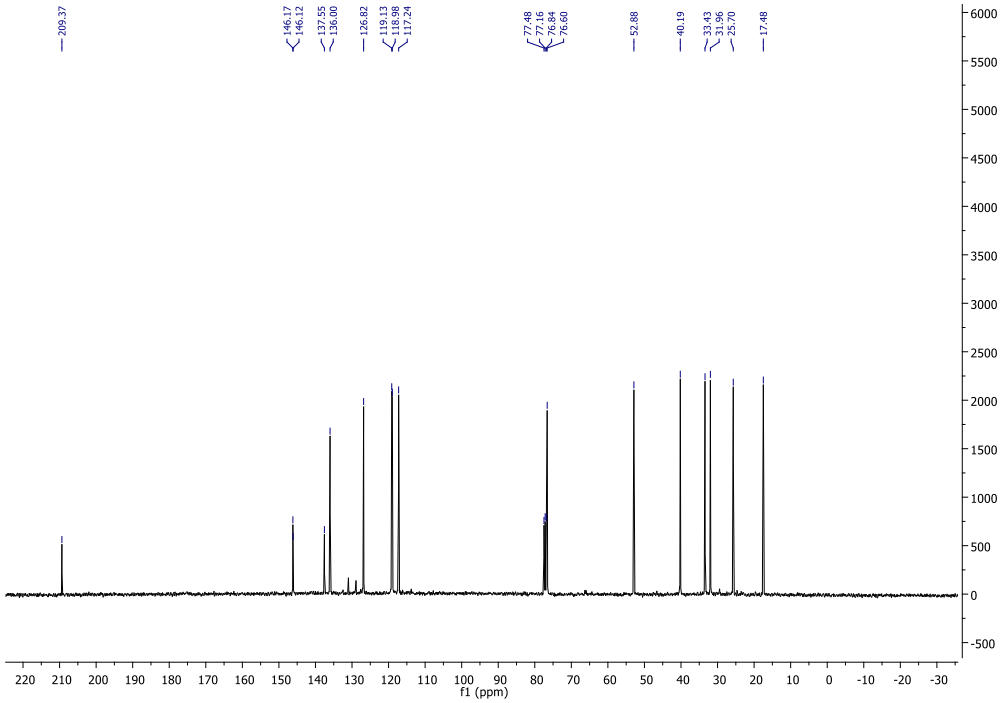





O
N

5p


f1 (ppm)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146.17
146.12
137.55
136.00
126.82
119.13
118.98
117.24
77.48
77.16
76.84
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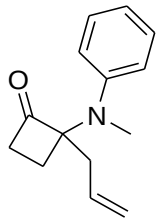
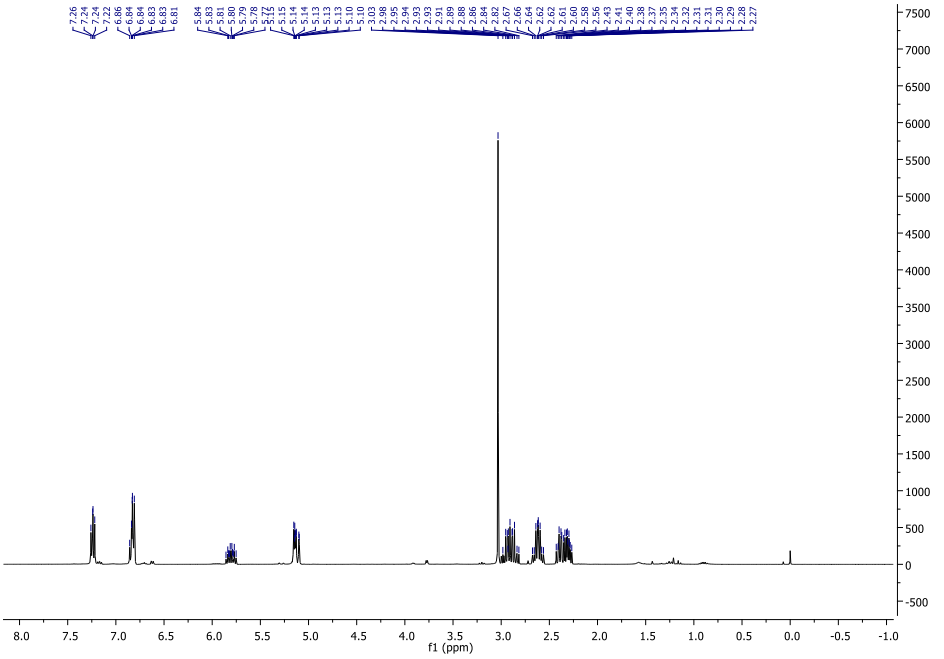
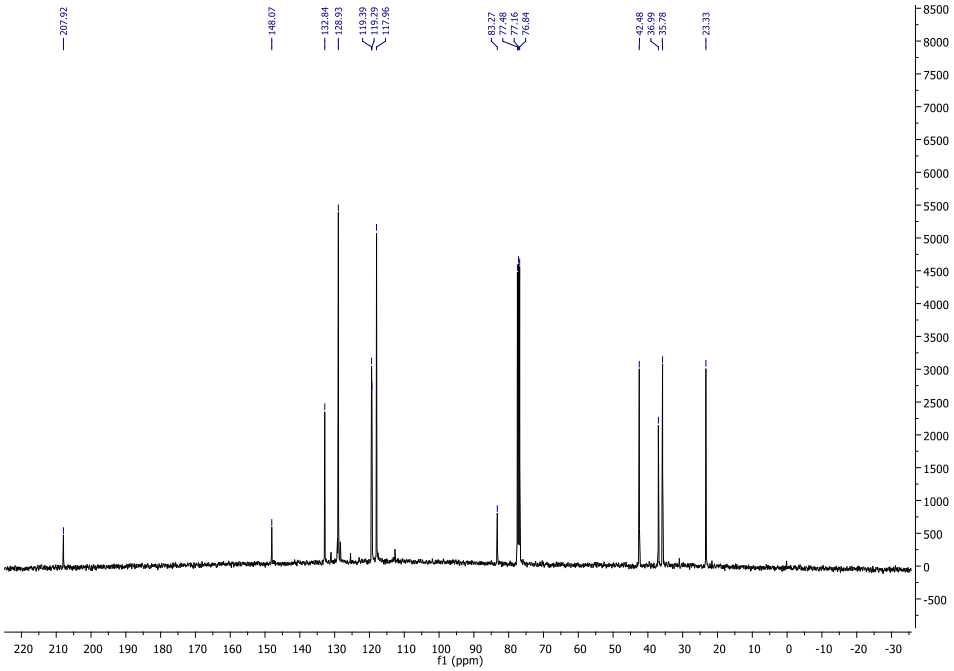
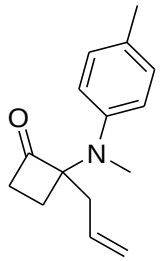
33.43
31.96
25.70
17.48
f1 (ppm)


O
N

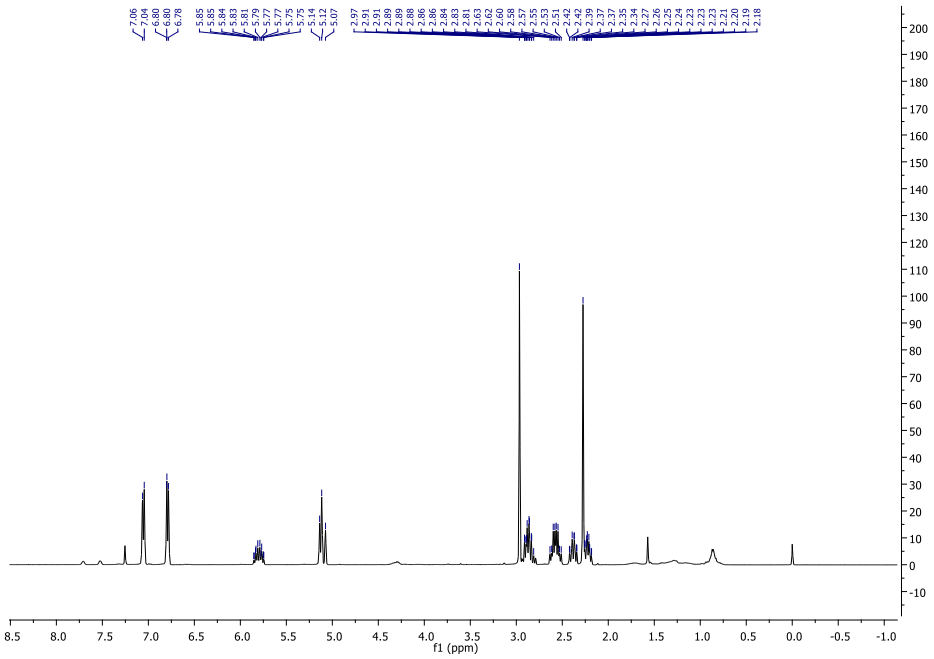
6a


f1 (ppm)


207.92
148.07
132.84
128.93
119.39
119.20
117.96
83.27
77.48
77.16
76.84
42.48
36.99
35.78
23.33
f1 (ppm)


O
N

6b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7.04
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6.80
6.78
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5.85
5.84
5.83
5.81
5.79
5.77
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5.75
5.75
5.74
5.12
5.07
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2.89
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2.84
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2.62
2.60
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2.42
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2.37
2.37
2.35
2.34
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2.20
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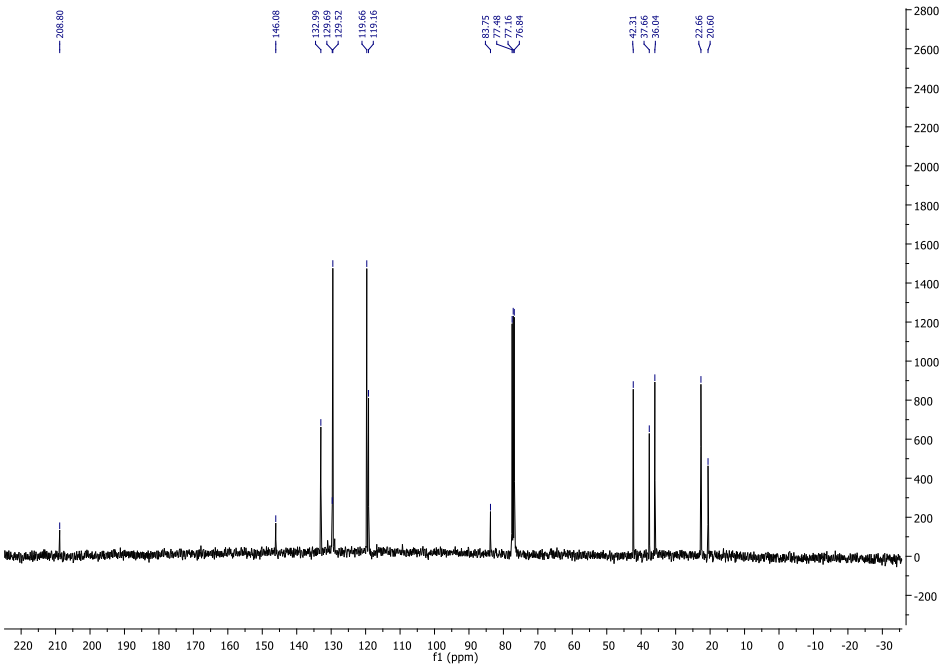
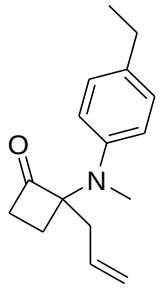
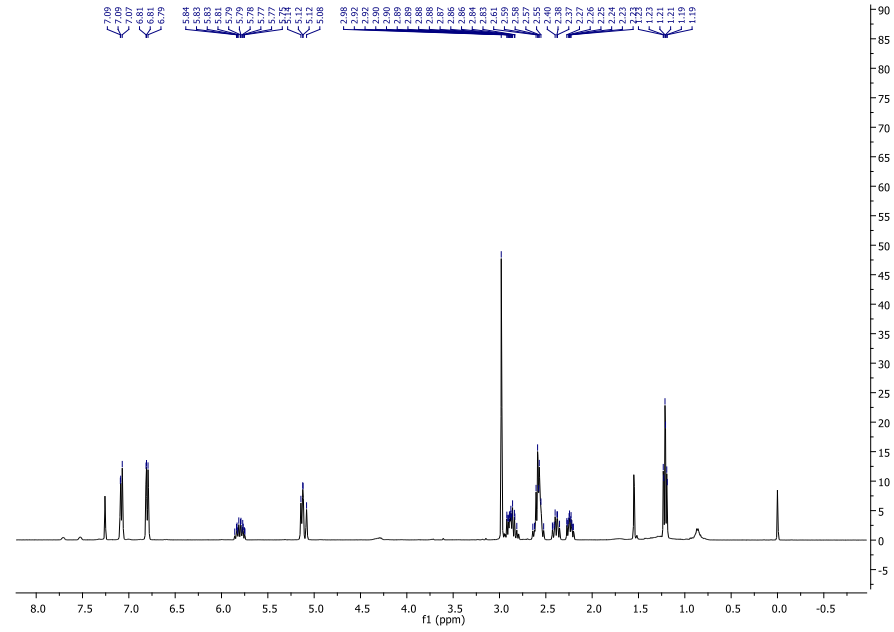
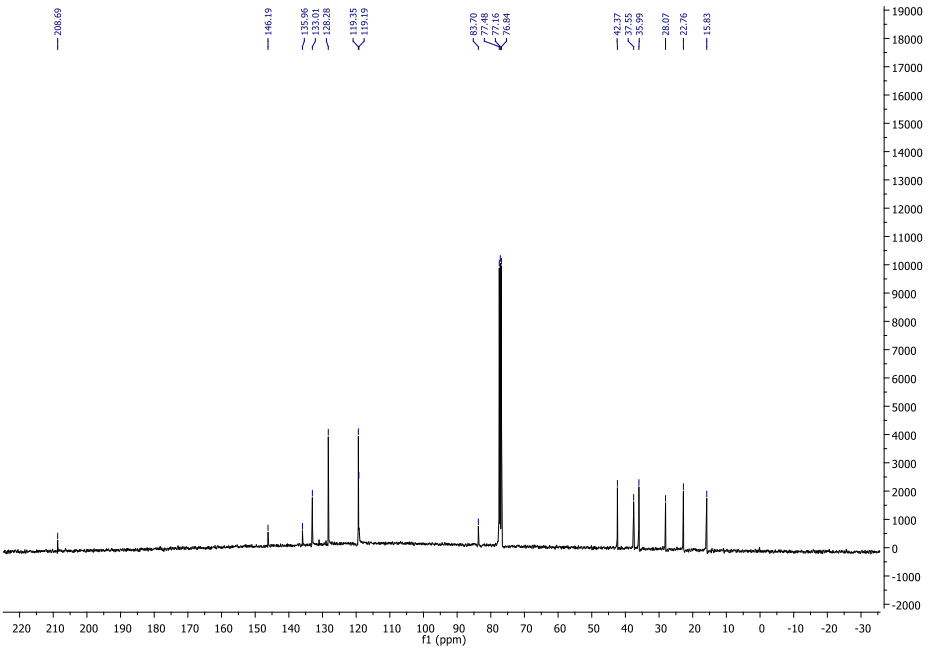
2.18
f1 (ppm)

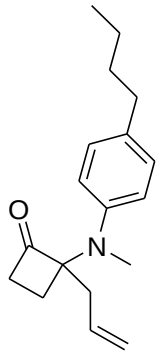

208.80
146.08
132.99
130.69
129.52
119.66
119.16
83.75
77.48
77.16
76.84
42.31
37.66
36.04
22.66
20.60
f1 (ppm)



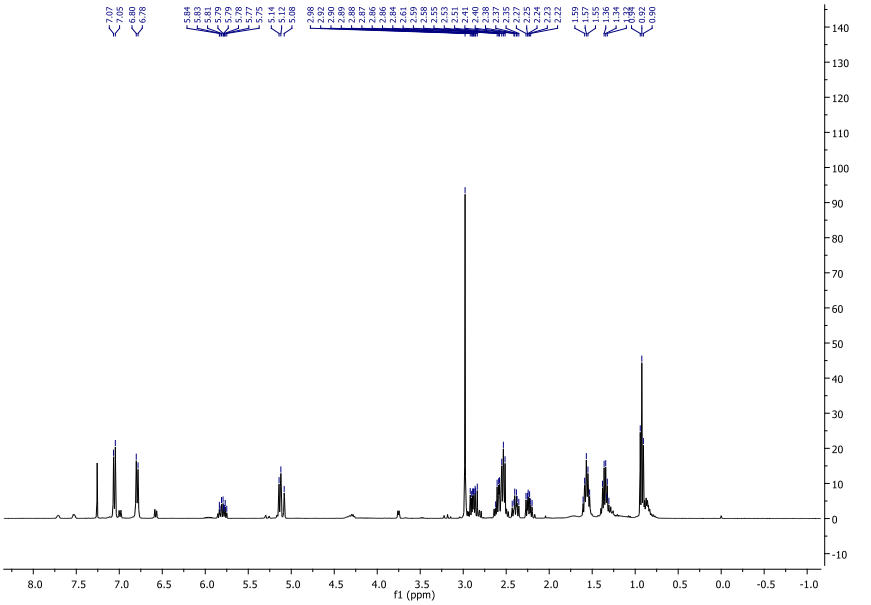
6c

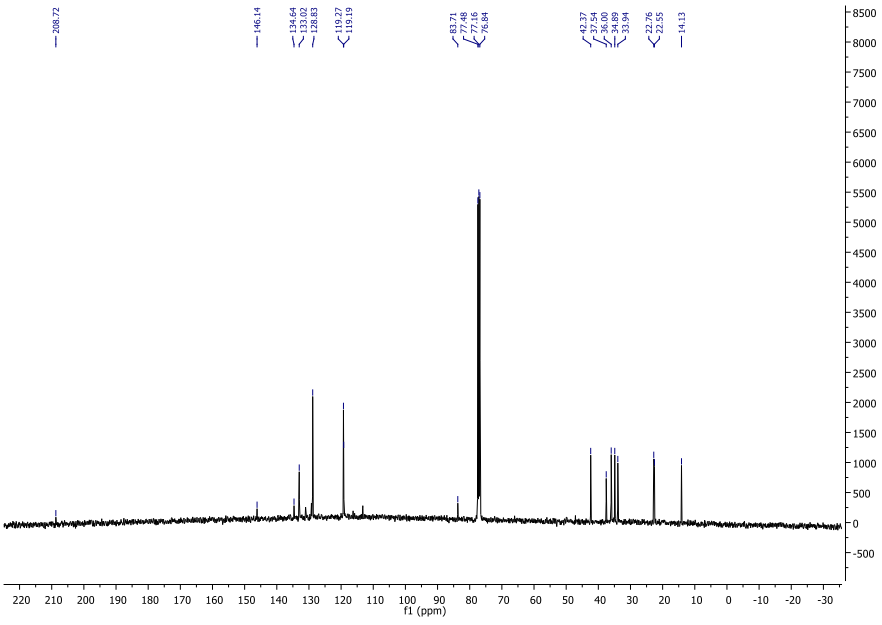


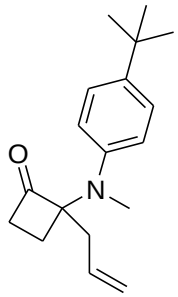



O
N

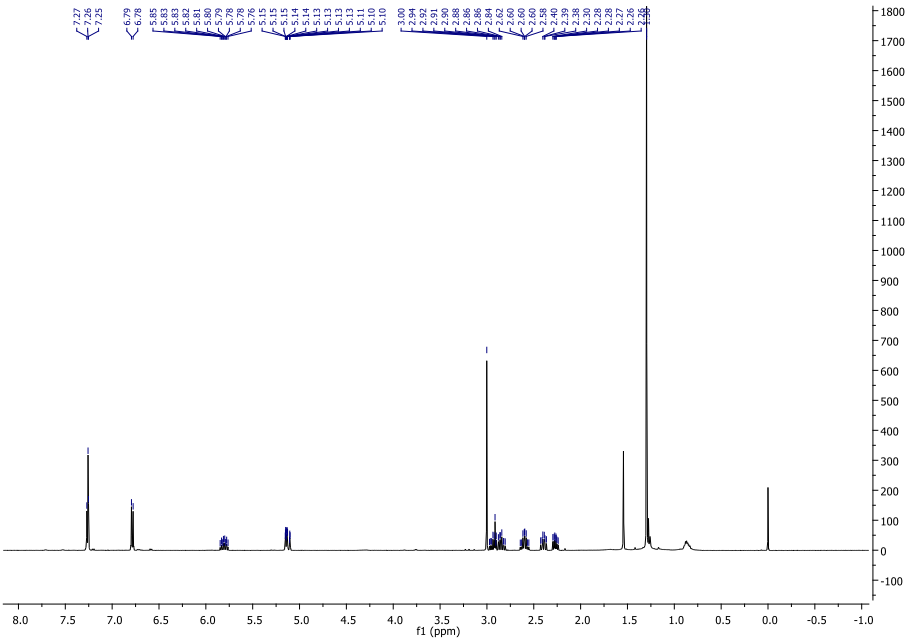
6d


7.07
7.05
6.80
6.78
5.84
5.83
5.81
5.79
5.78
5.77
5.75
5.14
5.12
5.08
2.98
2.92
2.90
2.89
2.88
2.87
2.86
2.84
2.61
2.59
2.58
2.55
2.53
2.51
2.44
2.40
2.38
2.37
2.35
2.27
2.25
2.24
2.23
2.22
1.59
1.57
1.55
1.36
1.34
0.93
0.92
0.90
f1 (ppm)


208.72
146.14
134.64
133.02
128.83
119.27
118.19
83.71
77.48
77.16
76.84
42.37
37.54
36.00
34.88
33.94
22.76
22.55
14.13
f1 (ppm)


O
N

6e


7.27
7.26
7.25
6.79
6.78
5.85
5.83
5.82
5.81
5.80
5.79
5.78
5.76
5.15
5.15
5.15
5.14
5.13
5.13
5.13
5.13
5.11
5.10
3.00
2.94
2.92
2.91
2.90
2.88
2.86
2.84
2.62
2.60
2.60
2.60
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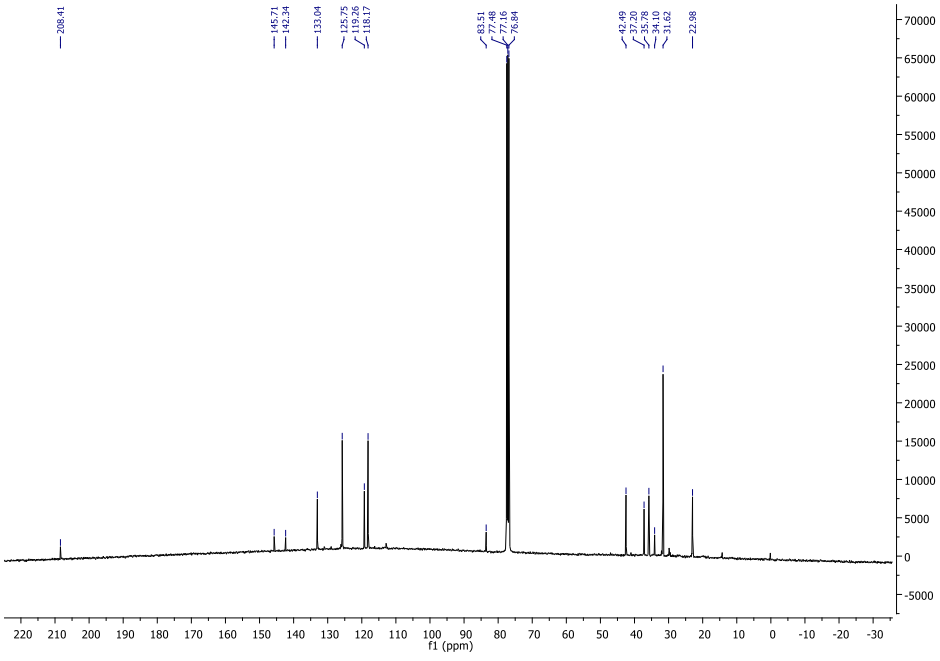
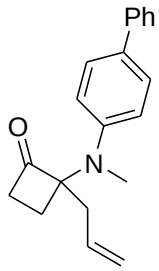
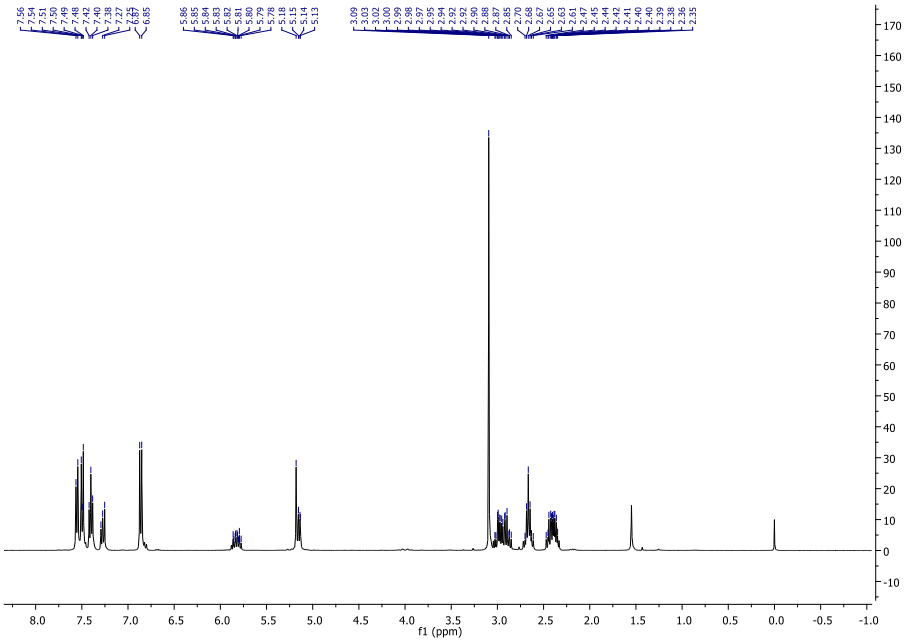
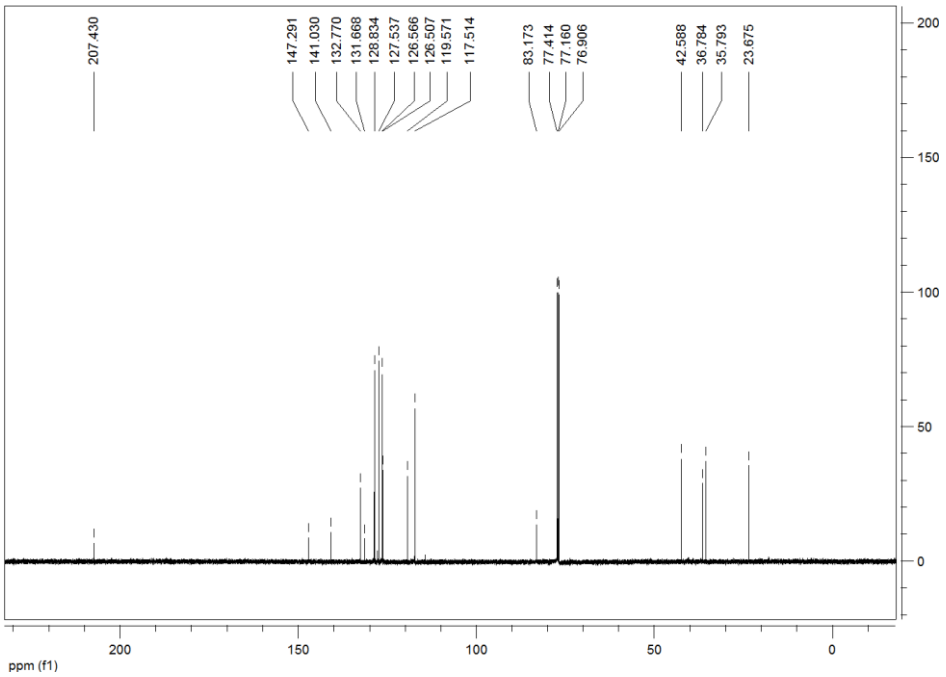
2.28
2.27
2.26
1.30
f1 (ppm)

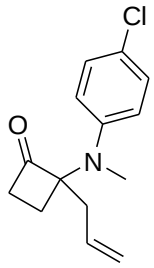

208.41
145.71
142.34
133.04
125.75
119.26
118.17
83.51
77.48
77.16
76.84
42.49
37.20
35.78
34.10
31.62
22.98
f1 (ppm)


Ph
O
N

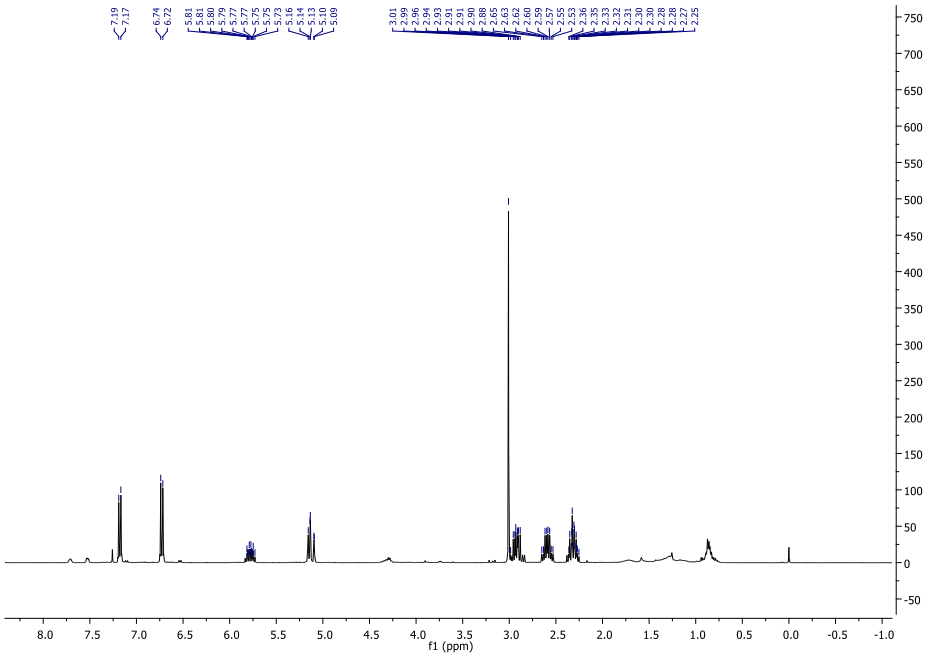
6f

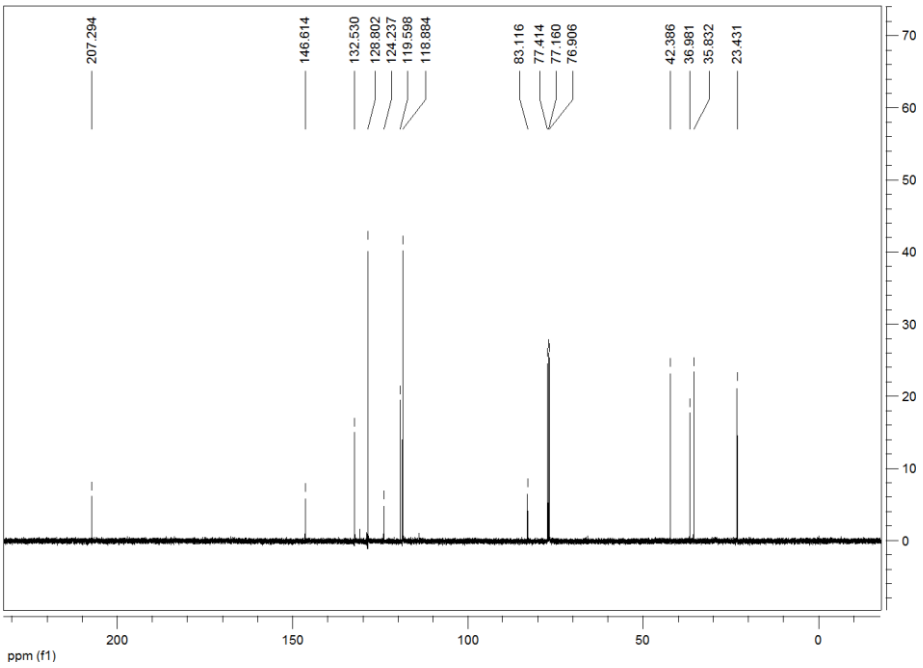

f1 (ppm)

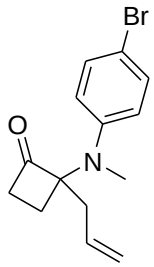

207.430
147.291
141.030
132.770
131.668
128.834
127.537
126.566
126.507
119.571
117.514
83.173
77.414
77.160
76.906
42.588
36.784
35.793
23.675
ppm (f1)


Cl
O
N

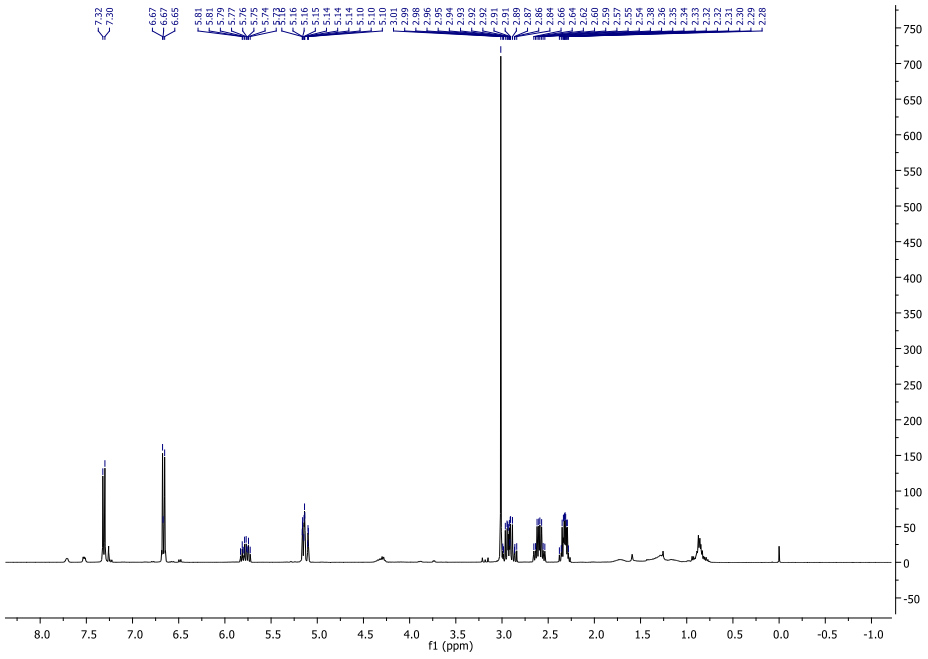
6g

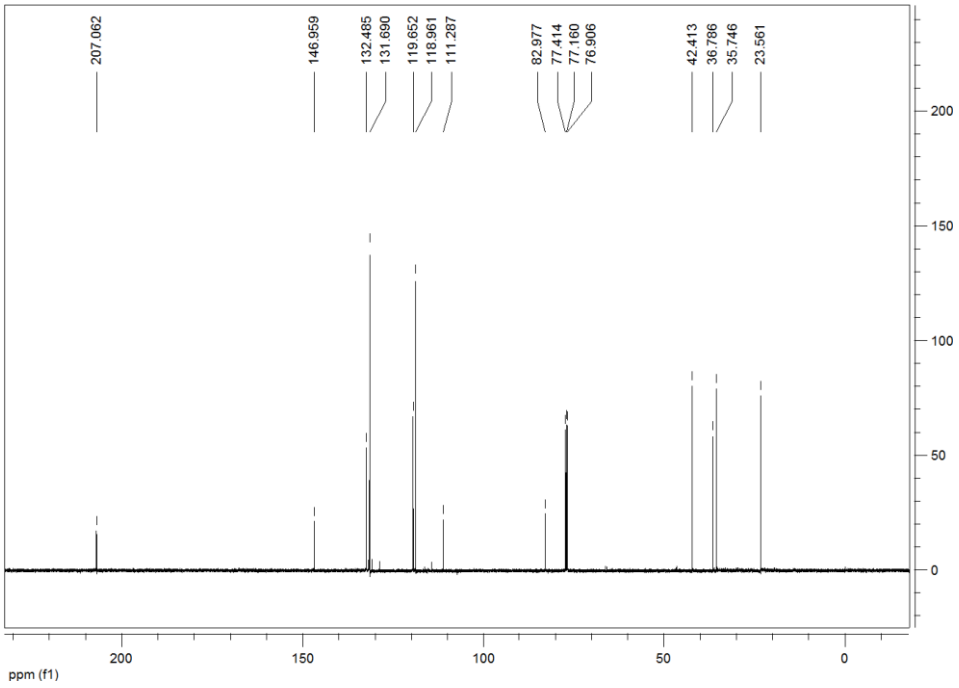

f1 (ppm)

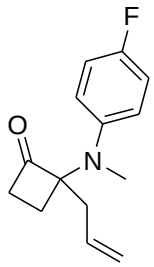

207.294
146.614
132.530
128.802
124.237
119.598
118.884
83.116
77.414
77.160
76.906
42.386
36.981
35.832
23.431
ppm (f1)


Br
O
N

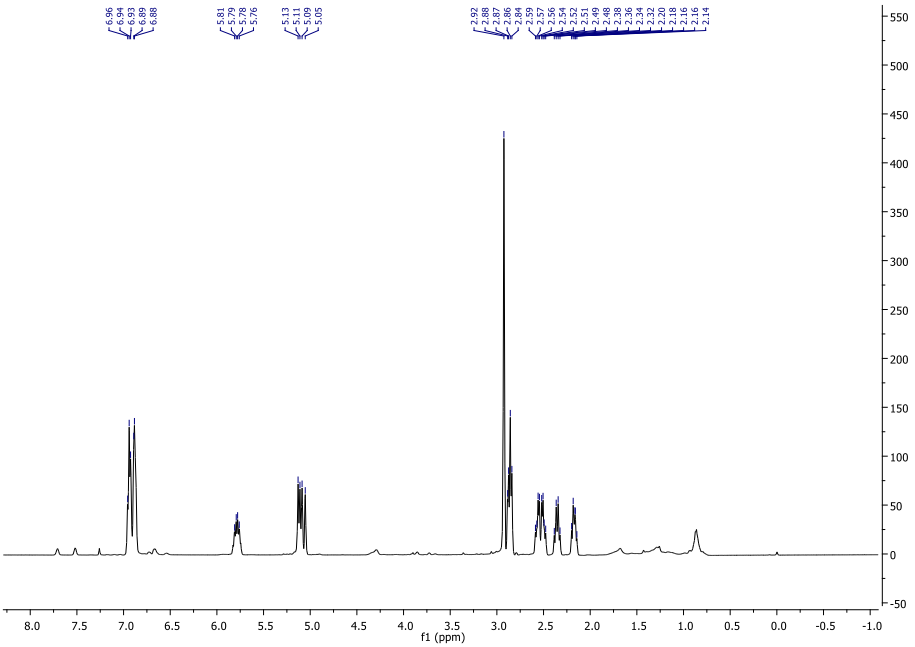
6h

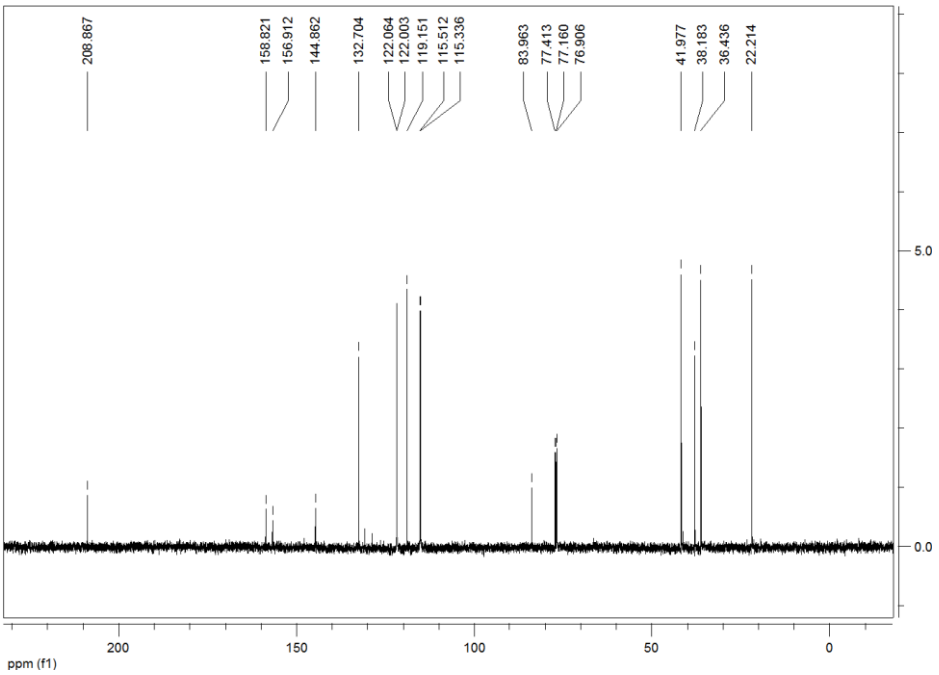

f1 (ppm)

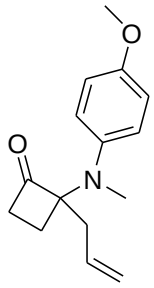

207.062
146.959
132.485
131.690
119.652
118.961
111.287
82.977
77.414
77.160
76.906
42.413
36.786
35.746
23.561
ppm (f1)


F
O
N

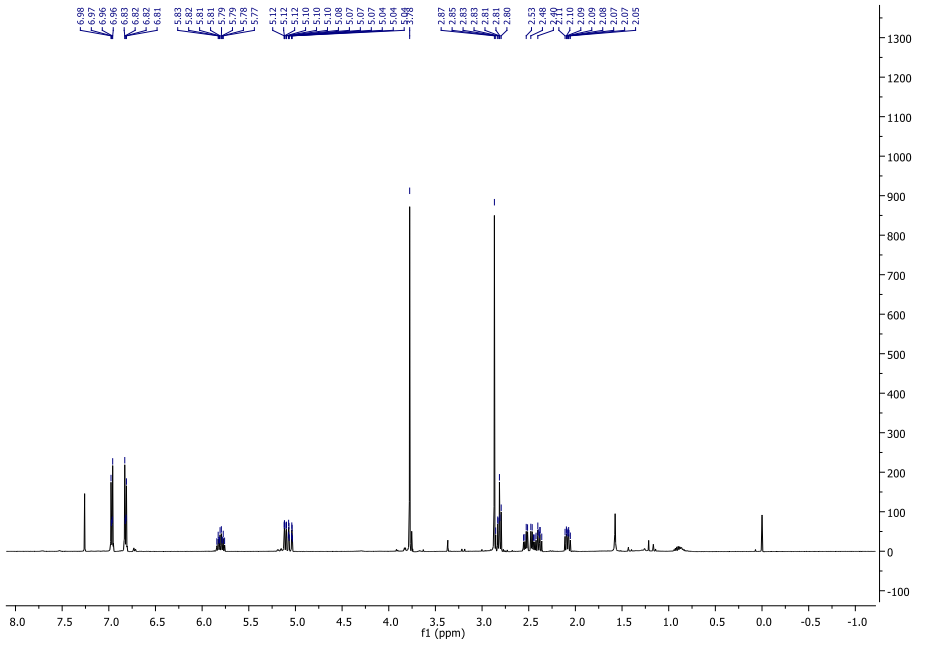
6i

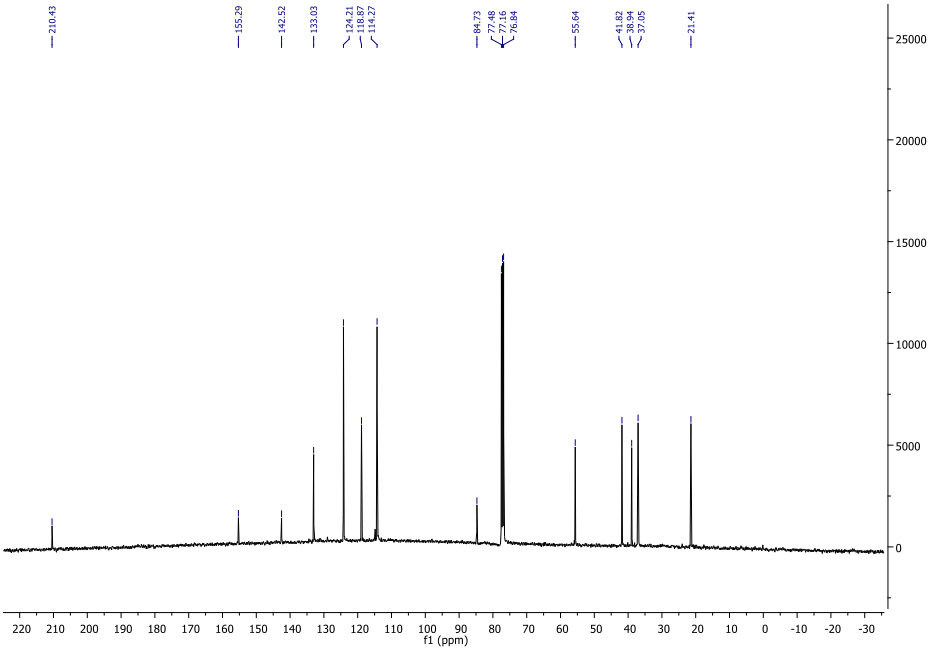

6.96
6.94
6.93
6.89
6.88
5.81
5.79
5.78
5.76
5.13
5.11
5.09
5.05
2.92
2.88
2.87
2.86
2.84
2.59
2.57
2.56
2.54
2.52
2.51
2.49
2.48
2.38
2.36
2.34
2.32
2.20
2.18
2.16
2.16
2.14
f1 (ppm)

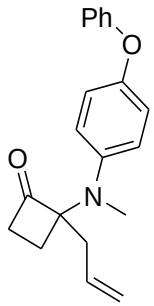

208.867
158.821
156.912
144.862
132.704
122.064
122.003
119.151
115.512
115.336
83.963
77.413
77.160
76.906
41.977
38.183
36.436
22.214
5.0
0.0
ppm (f1)


O
O
N

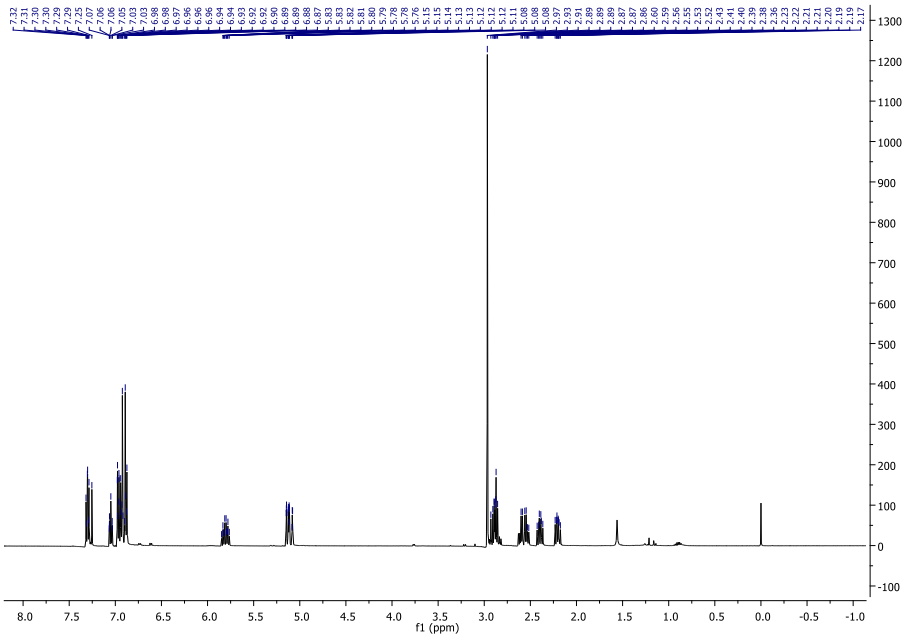
6j

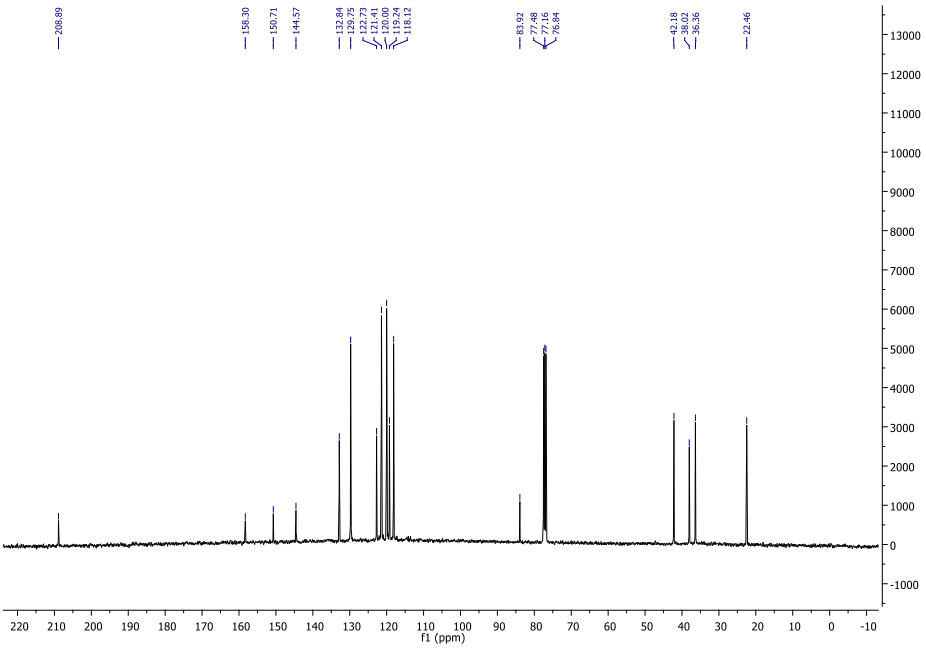

6.98
6.97
6.96
6.96
6.83
6.82
6.82
6.81
5.83
5.82
5.81
5.81
5.79
5.79
5.78
5.77
5.12
5.12
5.12
5.10
5.10
5.10
5.08
5.07
5.07
5.07
5.04
5.04
3.08
2.87
2.85
2.83
2.83
2.81
2.81
2.80
2.53
2.48
2.10
2.10
2.09
2.09
2.08
2.07
2.07
2.05
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

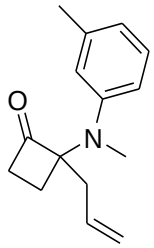

210.43
155.29
142.52
133.03
124.21
118.87
114.27
84.73
77.48
77.16
76.84
55.64
41.82
38.94
37.05
21.41
25000
20000
15000
10000
5000
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)


Ph
O
O
N

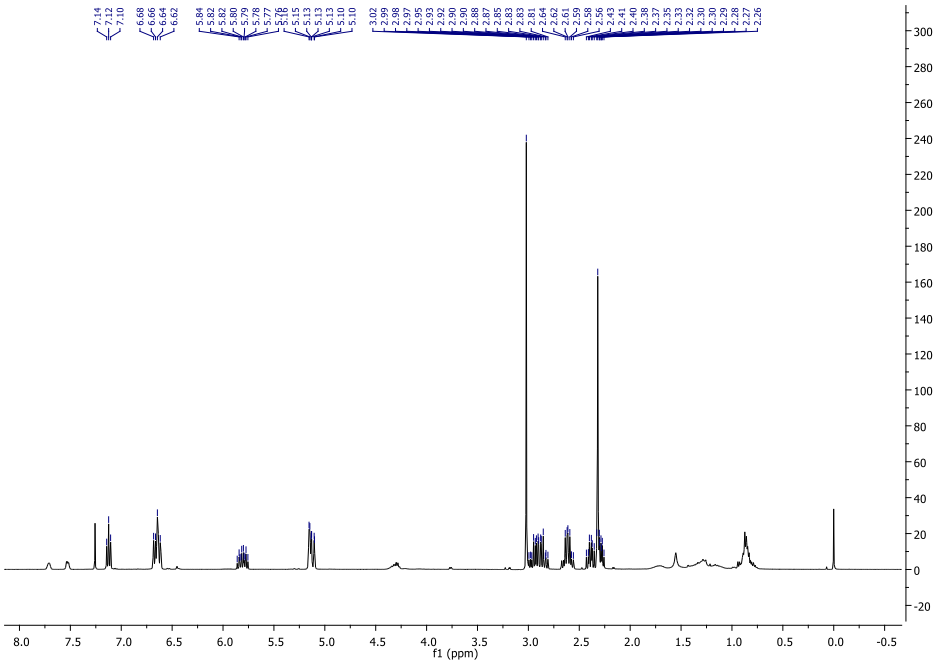
6k

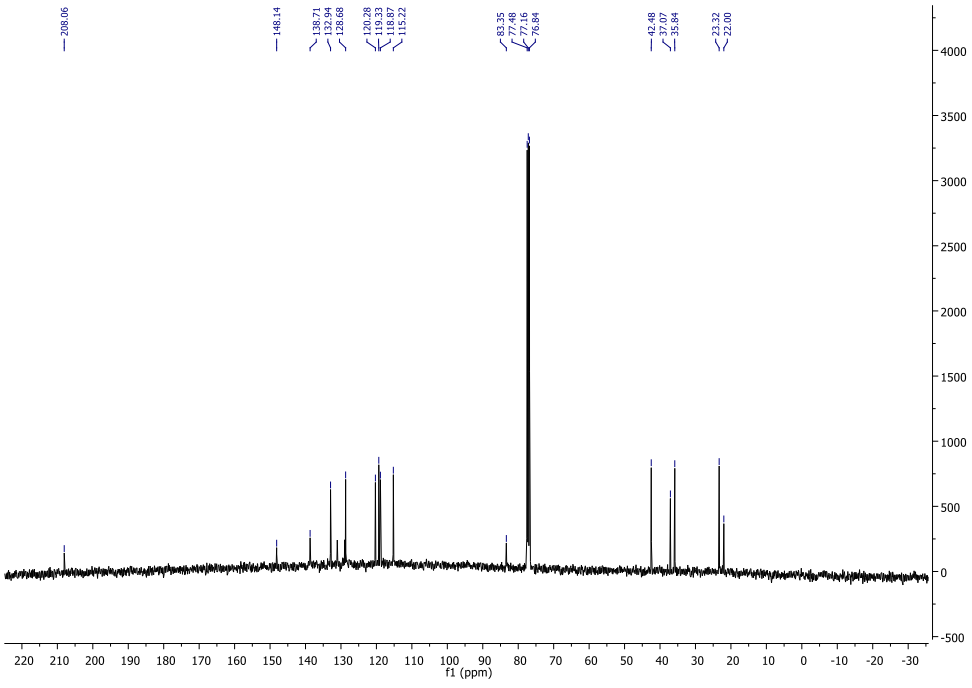

f1 (ppm)

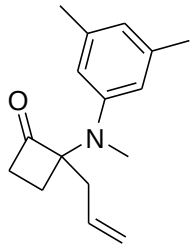

208.89
158.30
150.71
144.57
132.84
129.75
122.73
121.41
120.00
119.24
118.12
83.92
77.48
77.16
76.84
42.18
38.02
36.36
22.46
f1 (ppm)


O
N

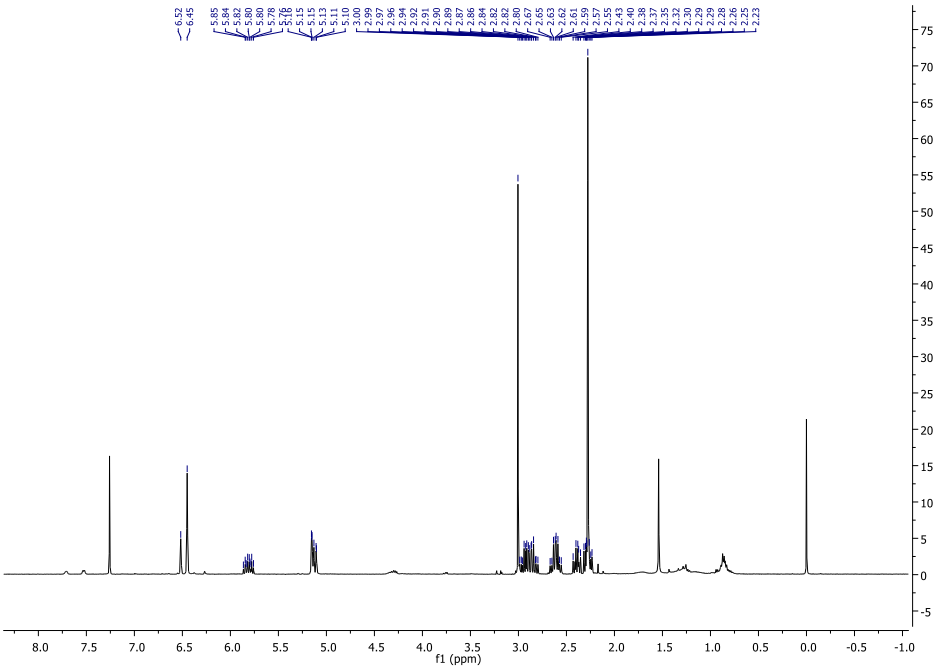
6m

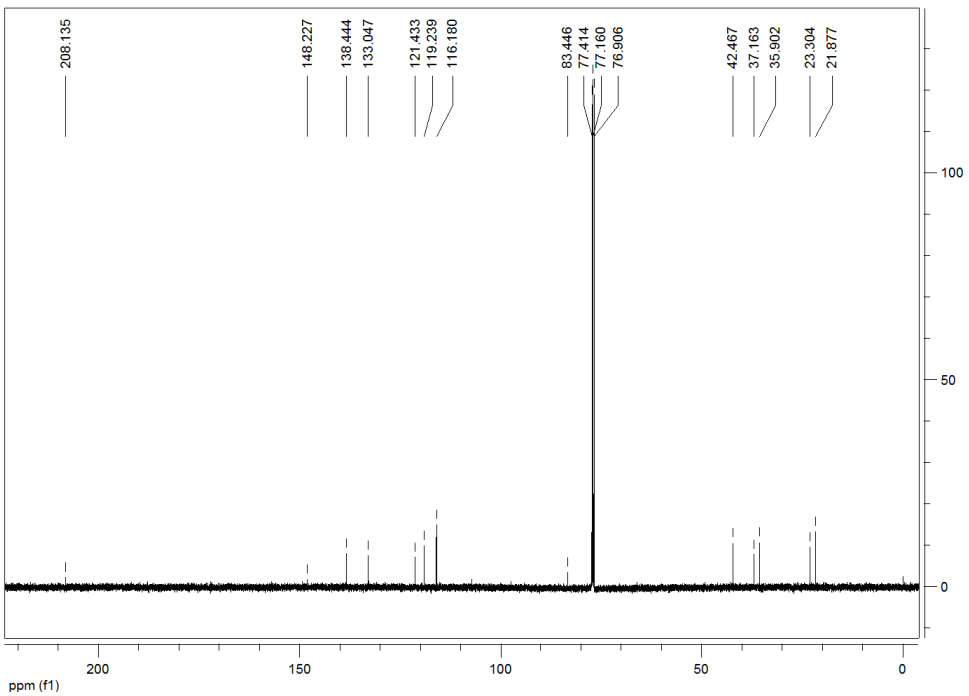

7.14
7.12
7.10
6.68
6.66
6.64
6.62
5.84
5.82
5.80
5.79
5.78
5.77
5.76
5.15
5.13
5.13
5.13
5.10
5.10
3.02
2.99
2.98
2.97
2.95
2.93
2.92
2.90
2.90
2.88
2.87
2.85
2.83
2.83
2.81
2.64
2.62
2.61
2.59
2.58
2.56
2.43
2.41
2.40
2.38
2.37
2.35
2.33
2.32
2.30
2.29
2.28
2.27
2.26
f1 (ppm)

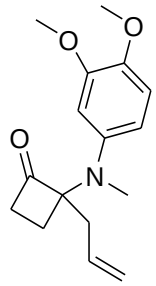

208.06
148.14
138.71
132.94
128.68
120.28
119.33
118.87
115.22
83.35
77.48
77.16
76.84
42.48
37.07
35.84
23.32
22.00
f1 (ppm)


O
N

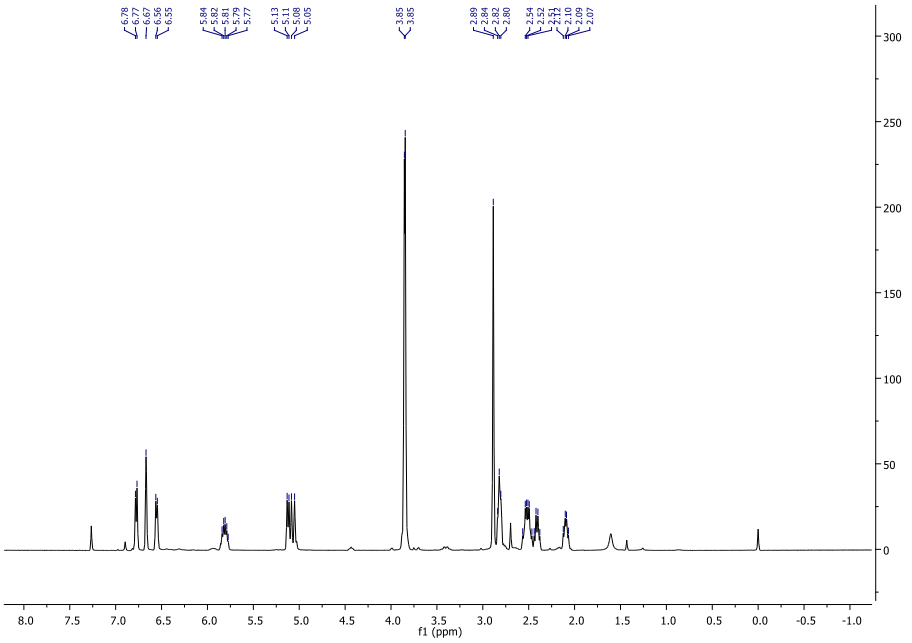
6n

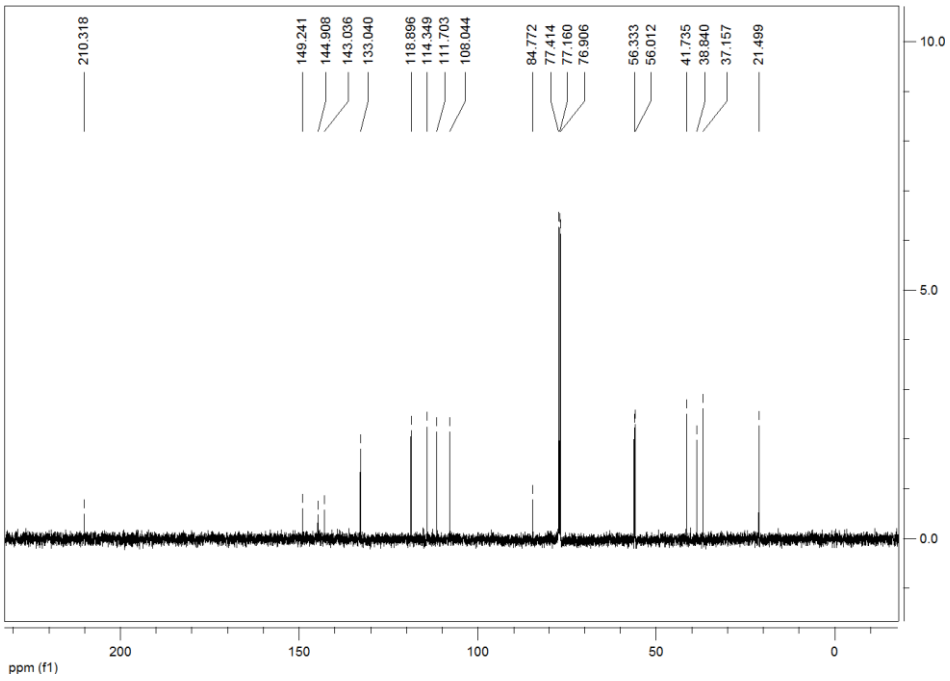

f1 (ppm)


208.135
148.227
138.444
133.047
121.433
119.239
116.180
83.446
77.414
77.160
76.906
42.467
37.163
35.902
23.304
21.877
ppm (f1)

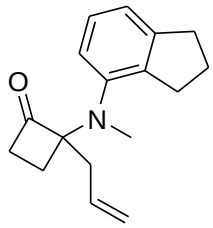


6o

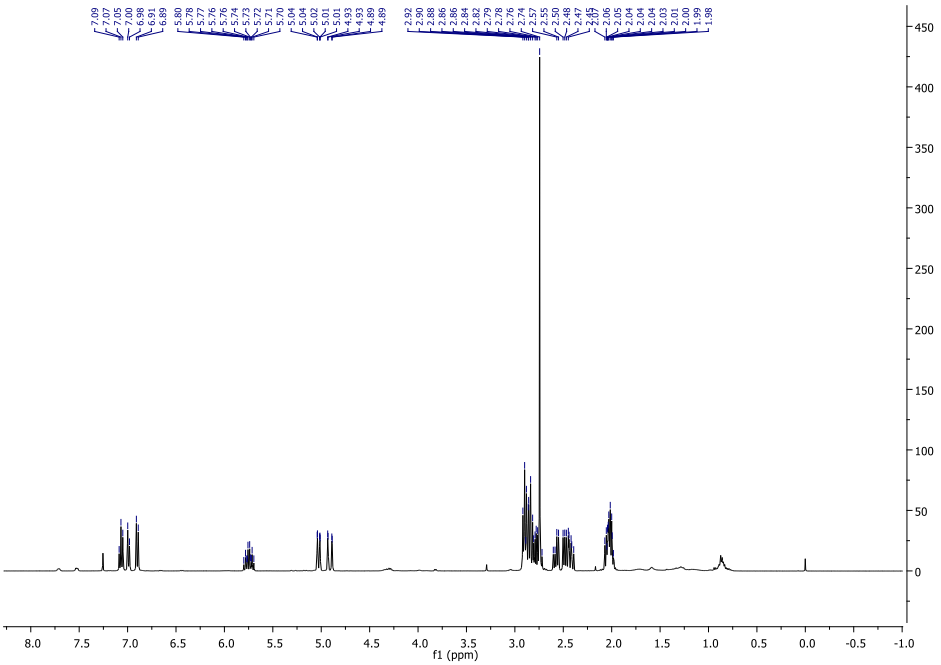

6.78
6.77
6.67
6.56
6.55
5.84
5.82
5.81
5.79
5.77
5.13
5.11
5.08
5.06
3.85
3.85
2.89
2.84
2.82
2.80
2.54
2.52
2.12
2.11
2.10
2.09
2.07
300
250
200
150
100
50
0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


210.318
149.241
144.908
143.036
133.040
118.896
114.349
111.703
108.044
84.772
77.414
77.160
76.906
56.333
56.012
41.735
38.840
37.157
21.499
10.0
5.0
0.0
200
150
100
50
0
ppm (f1)

219


O
N

6p


7.09
7.07
7.05
7.00
6.98
6.91
6.89
5.80
5.78
5.77
5.76
5.76
5.74
5.73
5.72
5.71
5.70
5.04
5.04
5.02
5.01
5.01
4.93
4.93
4.89
4.89
2.92
2.90
2.88
2.86
2.86
2.84
2.82
2.79
2.78
2.76
2.74
2.57
2.55
2.50
2.48
2.47
2.07
2.06
2.05
2.04
2.04
2.04
2.03
2.01
2.00
1.99
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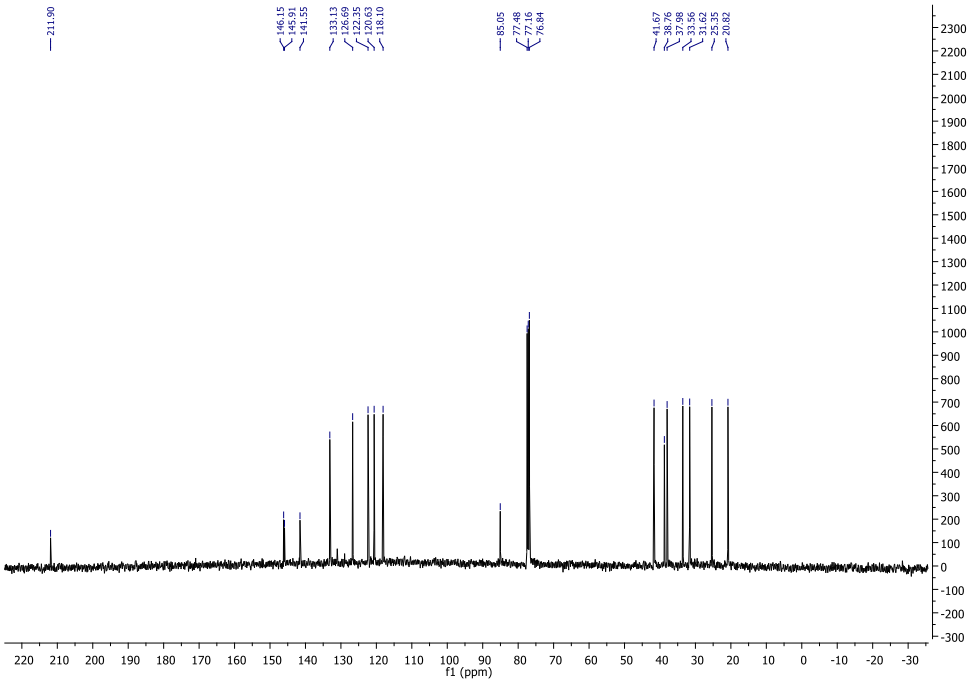
f1 (ppm)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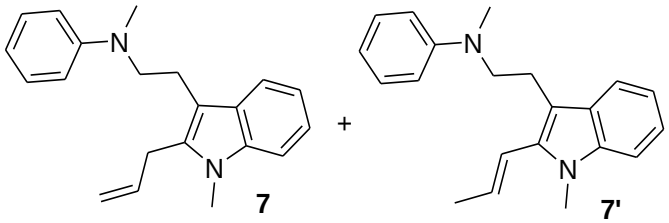
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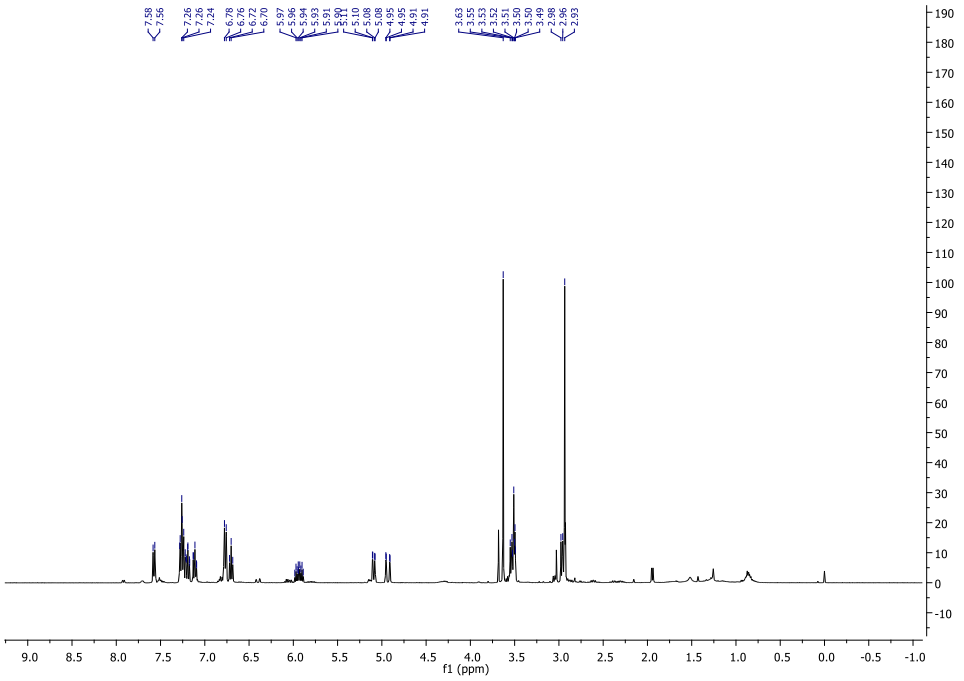
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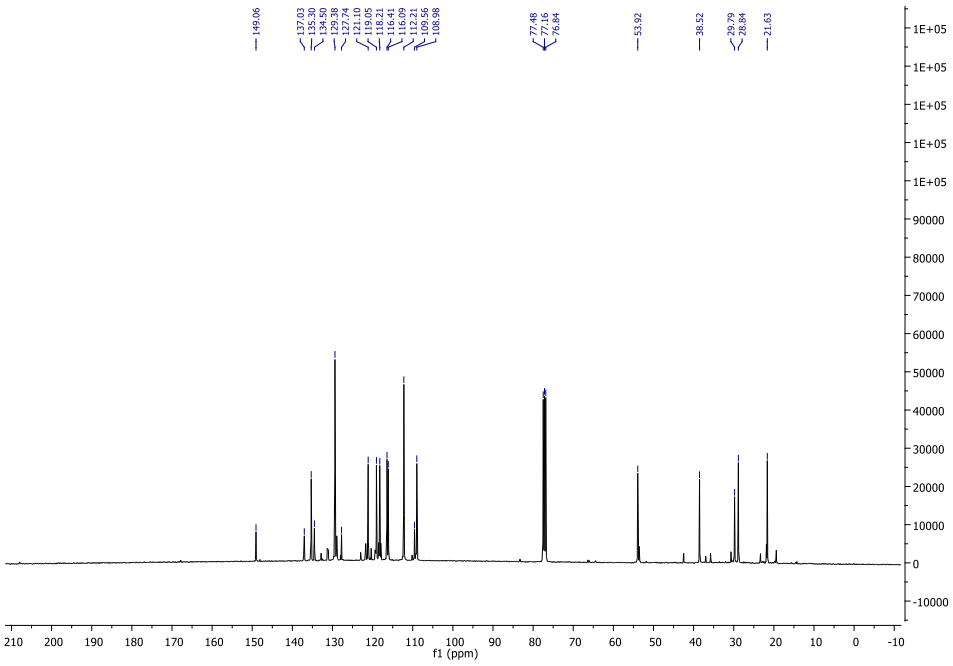
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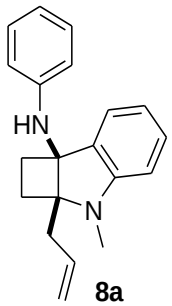
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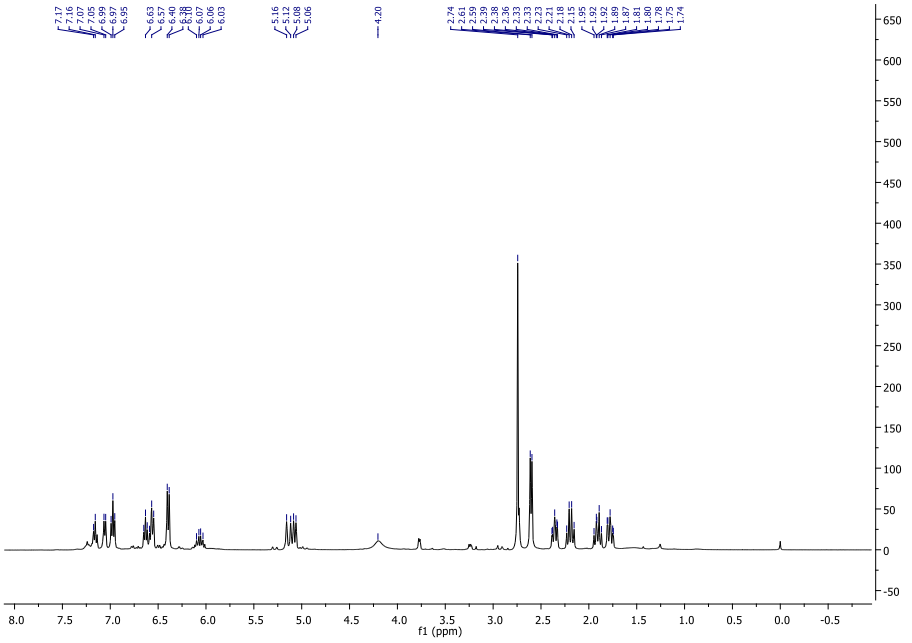
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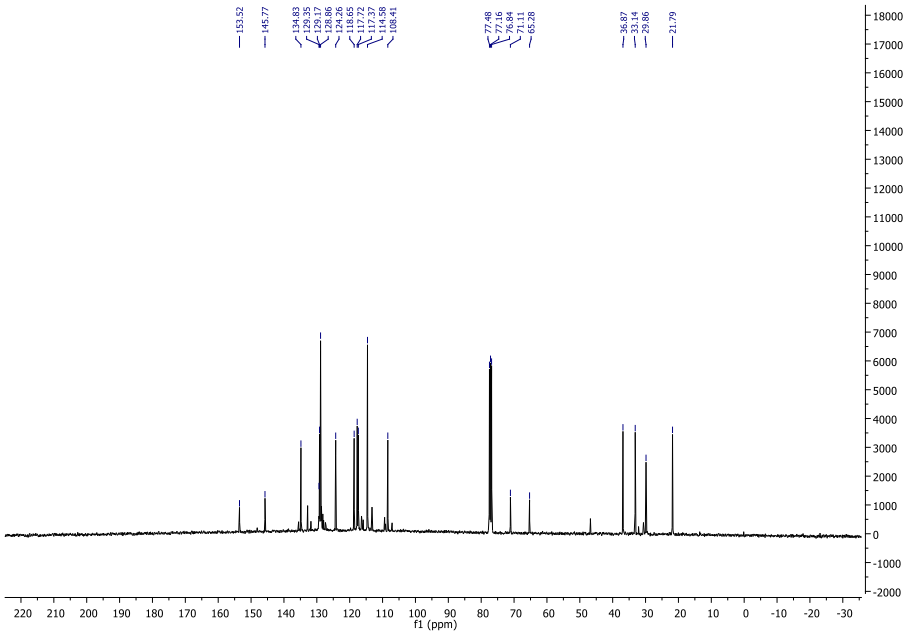
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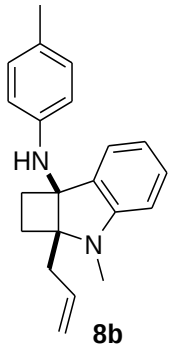
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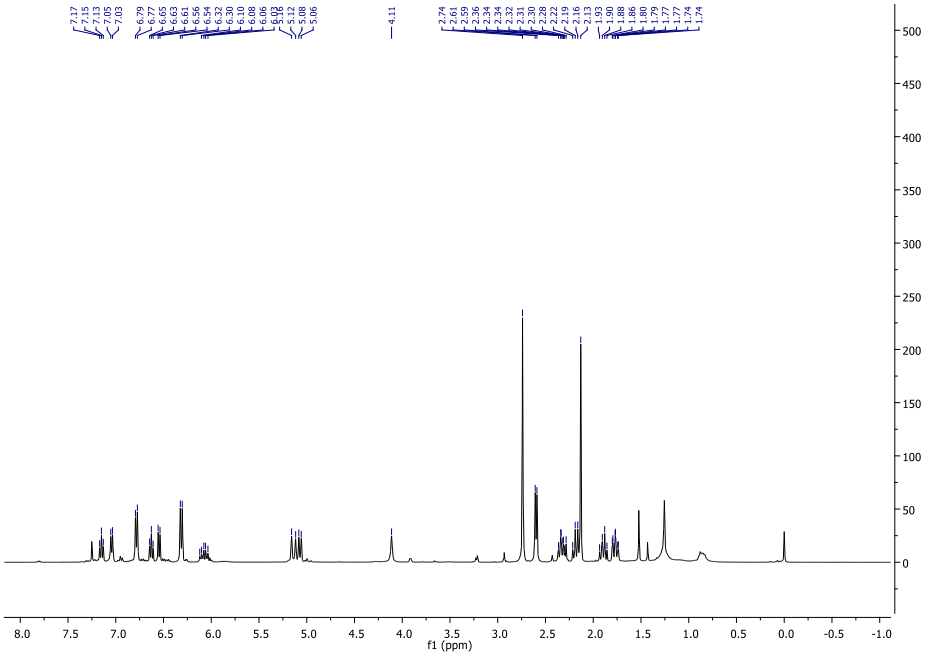
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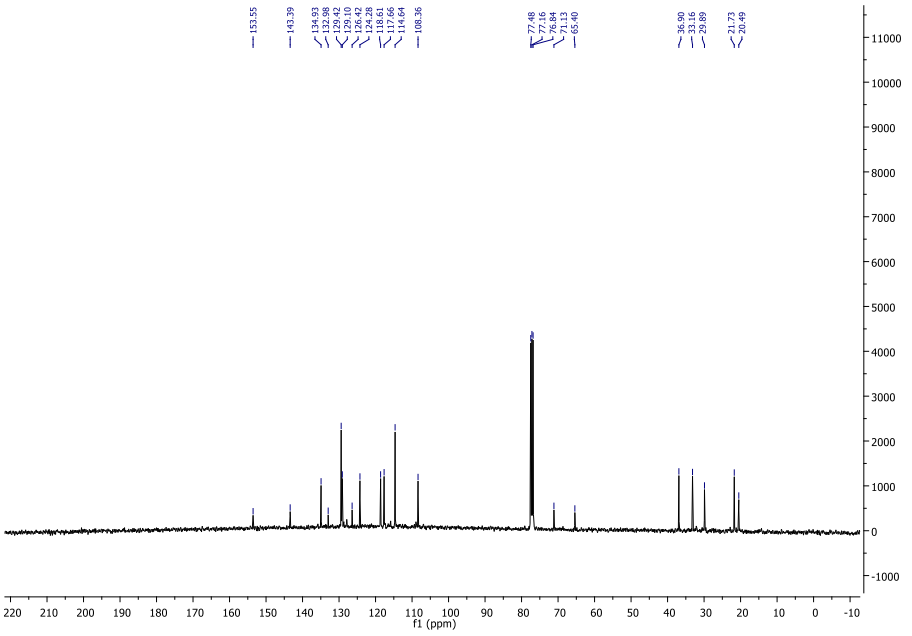
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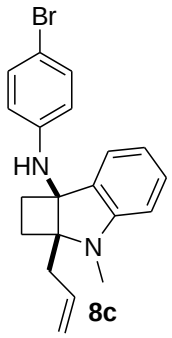
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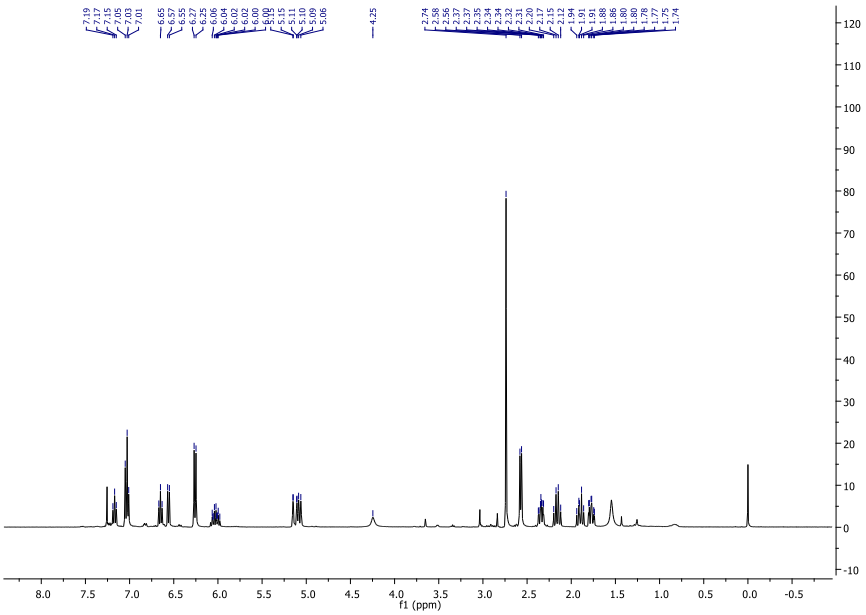
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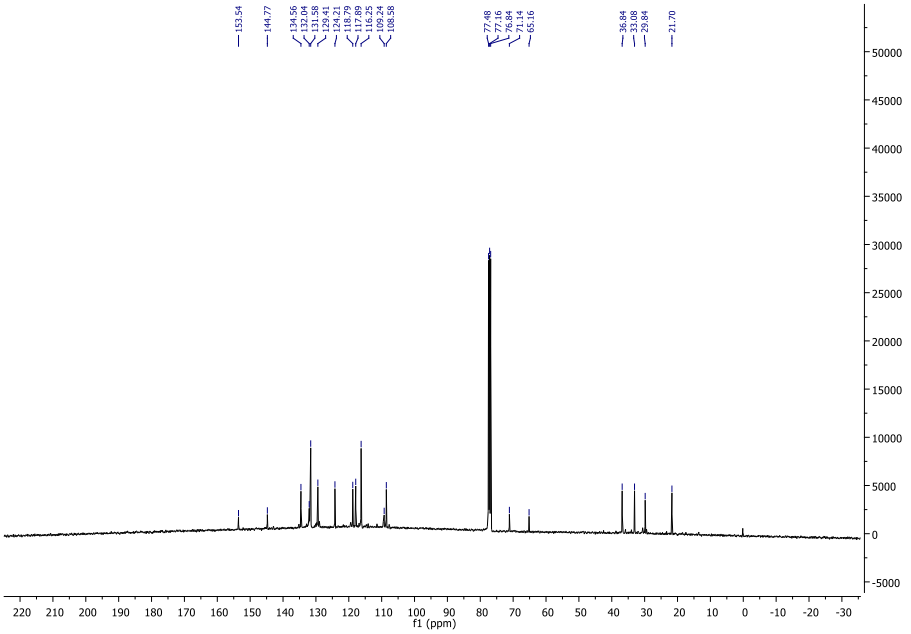
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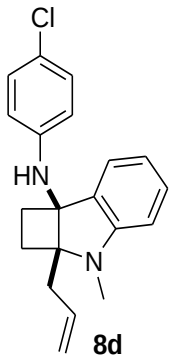
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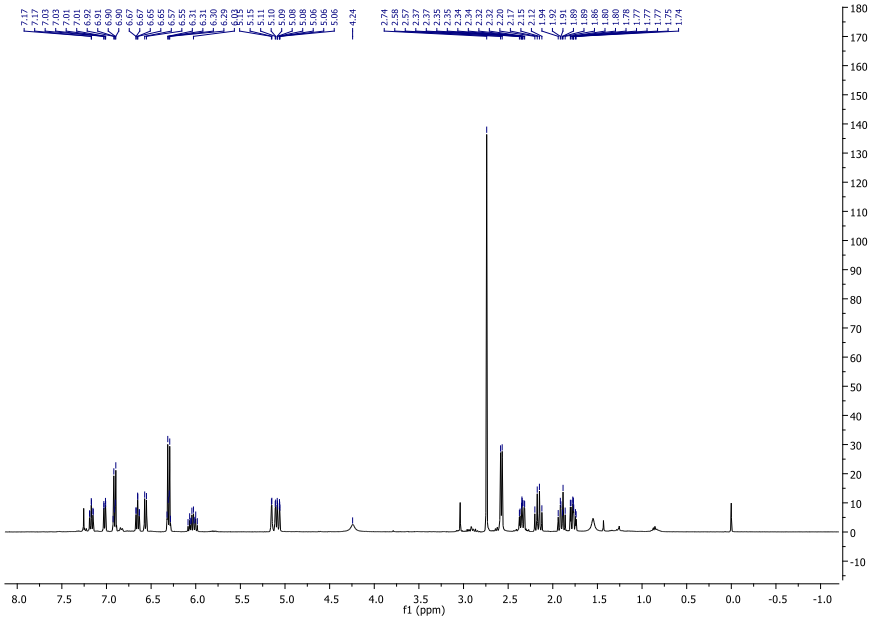
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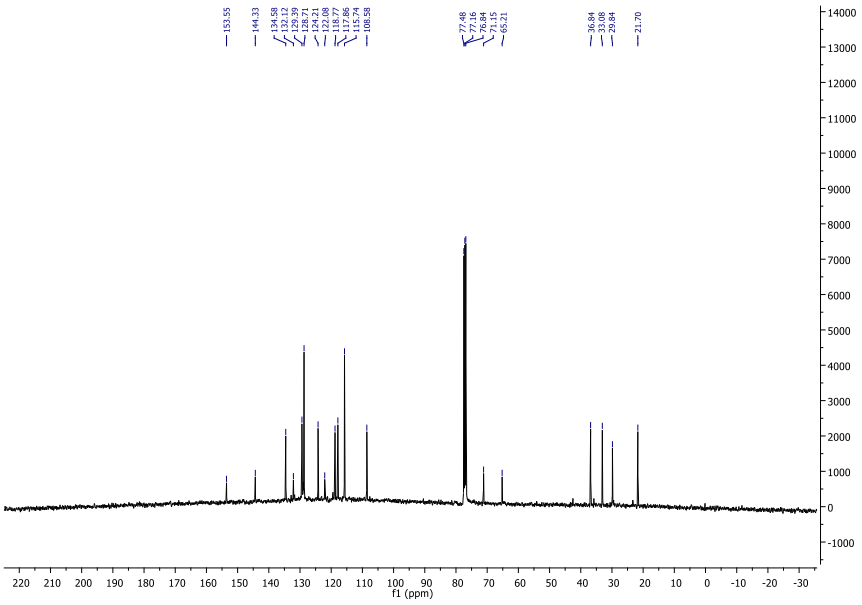
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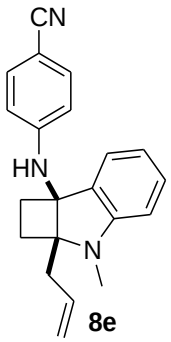
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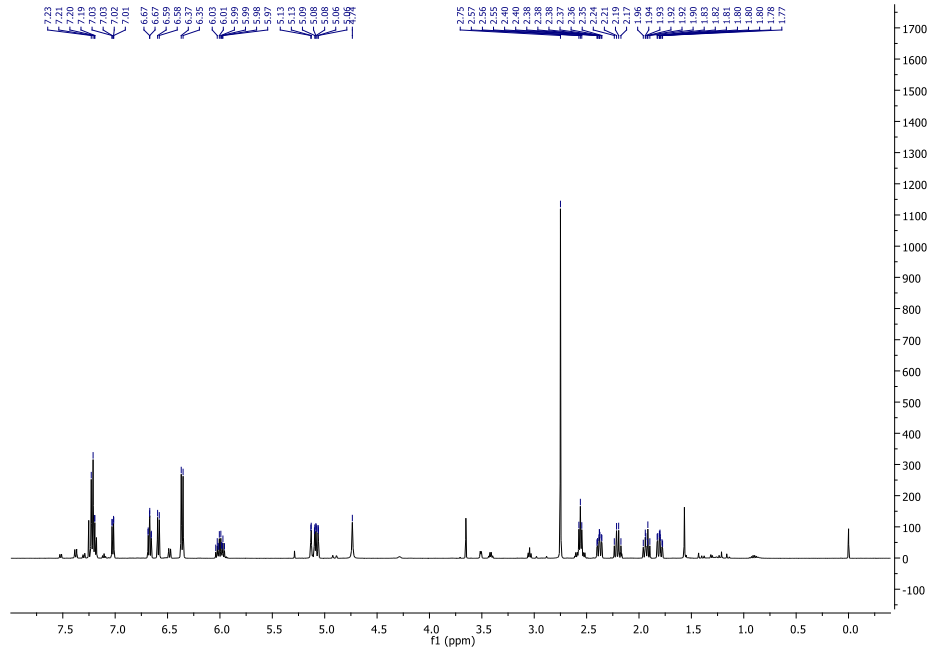
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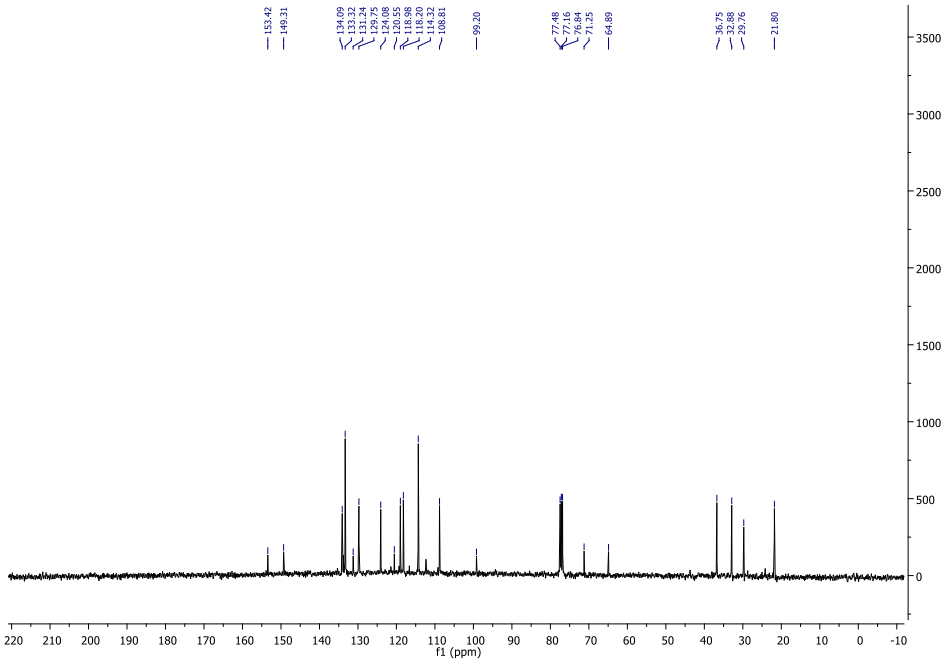
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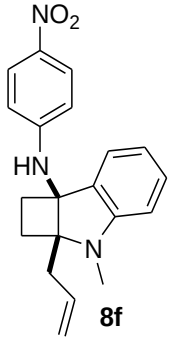
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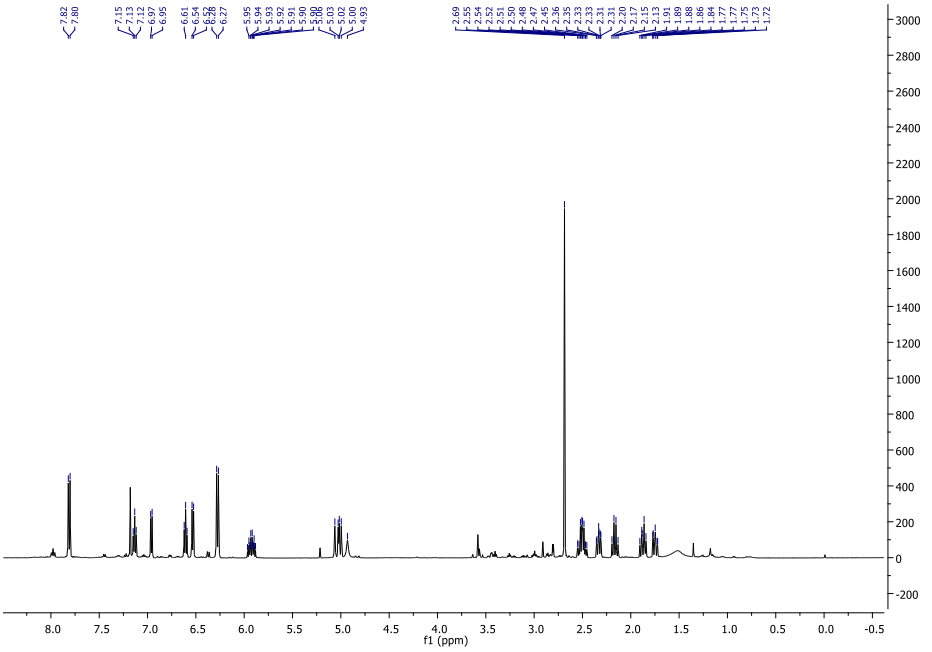
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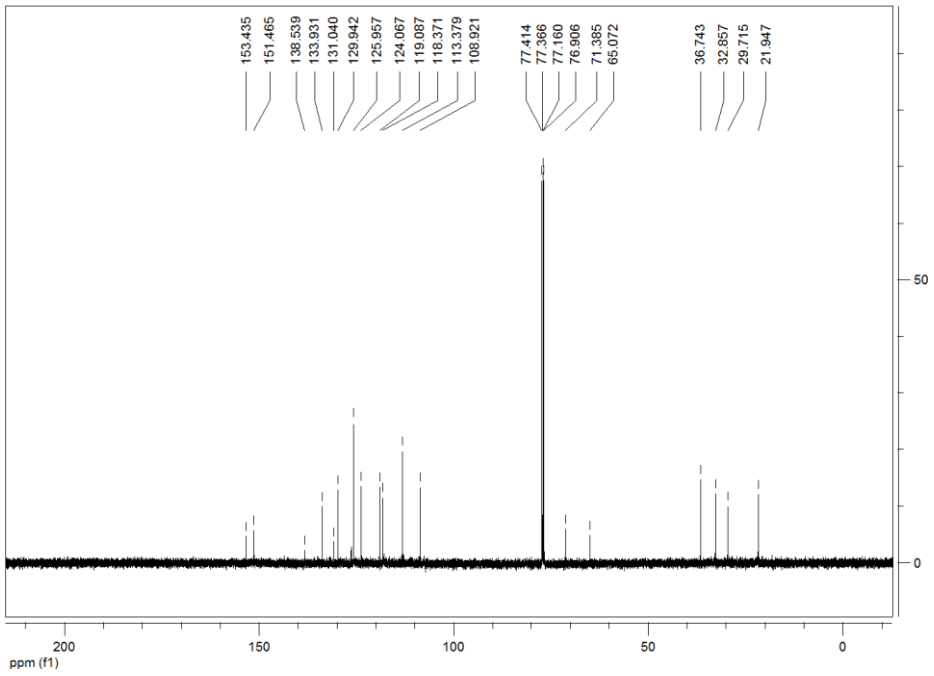
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ppm (f1)

CHAPTER FOUR

Synthesis of 2,2-bis(pyridin-2-yl amino)cyclobutanols and their conversion into 5-(pyridin-2-ylamino)dihydrofuran-2(3*H*)-ones

4.1 Introduction.

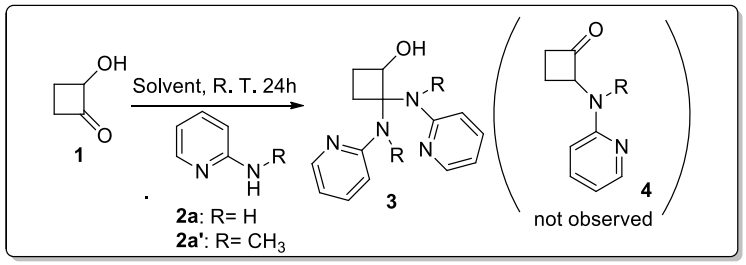
Functionalized cyclobutanes are widely recognised as useful small-molecule building blocks for organic synthesis.[1] One particularly interesting derivative is 2-hydroxycyclobutanone, which undergoes selective aldol,[2] nitrogen insertion,[3] and amination reactions.[4] The 2-aminocyclobutanone adducts obtained in the latter reactions are of notable interest in themselves,[5] and we were interested in further developing the condensation reaction between 2-hydroxycyclobutanone and *N*-heteroarylamines. Here we report on our findings from this study, which has not only provided access to the unexpected aminals, but has led to the discovery of an oxidative ring expansion reaction of these adducts to furnish 5-(pyridin-2-ylamino)dihydrofuran-2(3*H*)-ones.

4.2. Results and discussion

To begin our investigations, we examined the reactivity of 2-hydroxycyclobutanone **1** with 2-(methylamino)pyridine **2a'** under conditions similar to those described for the synthesis of their corresponding 2-(arylamino)cyclobutanones,[4a] employing 20 mol% of catalyst (PTSA or DMAP) with (CH_2Cl_2 or toluene) or without solvent (Table 4.1, entries 1-4). Unfortunately, in all the cases we recovered the starting materials unreacted.

Faced with the lack of reactivity of **2a'**, we examined the unsubstituted parent **2a** as a potential nucleophilic partner in the same reaction. Unexpectedly, when **1** and 2-amino pyridine **2a** were reacted in a 1:1 molar ratio in the presence of 20 mol% DMAP in CH_2Cl_2 at room temperature for 24h, instead of the anticipated cyclobutanone **4**, we obtained 2,2-bis(pyridin-2-ylamino)cyclobutanol **3a**[6] (along with unreacted starting materials) in moderate conversion (43%), as determined by ^{1}H NMR spectroscopy (entry 5).

Table 4.1. Screening of the reaction conditions[a]



Entry	**Solvent**	**Amine**	**Mol. ratio 1:2a/2a'**	**Cat. (20 mol%)**	**Conv.3 (%)[b]**
1	-	**2a'**	1:1	PTSA	0
2	Toluene	**2a'**	1:1	PTSA	0
3	CH_2Cl_2	**2a'**	1:1	PTSA	0
4	-	**2a'**	1:1	DMAP	0
5	CH_2Cl_2	**2a**	1:1	DMAP	43
6	CH_2Cl_2	**2a**	1:2	DMAP	33
7	CH_2Cl_2	**2a**	1:2	PTSA	57
8	CH_2Cl_2	**2a**	1:2	-	58
9	1,4-Dioxane	**2a**	1:2	-	50
10	Toluene	**2a**	1:2	-	82
11	CH_3COOEt	**2a**	1:2	-	37
12	CH_3CN	**2a**	1:2	-	63

[a]Reaction conditions: **1** (419 µmol), **2** (837 µmol), solvent (0.4 mL). [b]Determined by ^{1}H NMR.

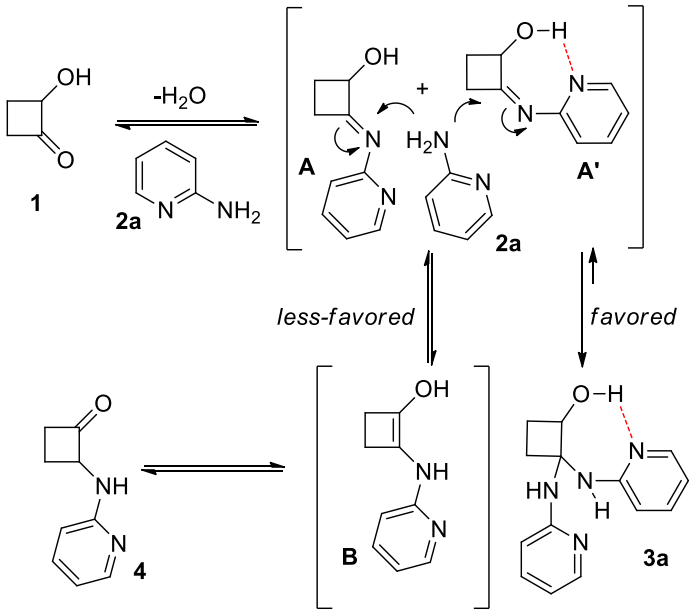
When **1** and **2a** were reacted in a 1:2 molar ratio the yield of **3a** was inferior (33%; entry 6), whereas switching the additive to PTSA had a better effect on the conversion (57%; entry 7).

Significantly, the reaction proceeded in the absence of an additive, giving **3a** in comparable conversion (58%; entry 8).

This result encouraged us to study the effect of solvents in order to further increase conversion. The experimental results revealed that increased solvent polarity (entries 8-12) led to the decrease of reaction efficiency. In fact, among the solvents examined, toluene was found to be the best affording the desired product **3a** in 82% conversion (entry 10). A reasonable explanation for the formation of product **3a** is proposed in Scheme 4.1. The condensation between 2-hydroxycyclobutanone 1 and the exocyclic nitrogen atom of the first equivalent of 2-aminopyridine **2a** gives 2-iminocyclobutanols **A** and **A'** (highly reactive due to the enhanced electrophilicity provided by hydrogen bonding with the vicinal hydroxy group). These intermediates, in contrast to our previous findings,[4] instead of

isomerising, *via* intermediate **B**, to yield the cyclobutanone **4**, undergoes a nucleophilic attack by a second equivalent of 2-aminopyridine **2a** to provide **3a**. In the light of this mechanistic proposal, the inertia observed for **2a'** in this chemical transformation seems to be completely expected.

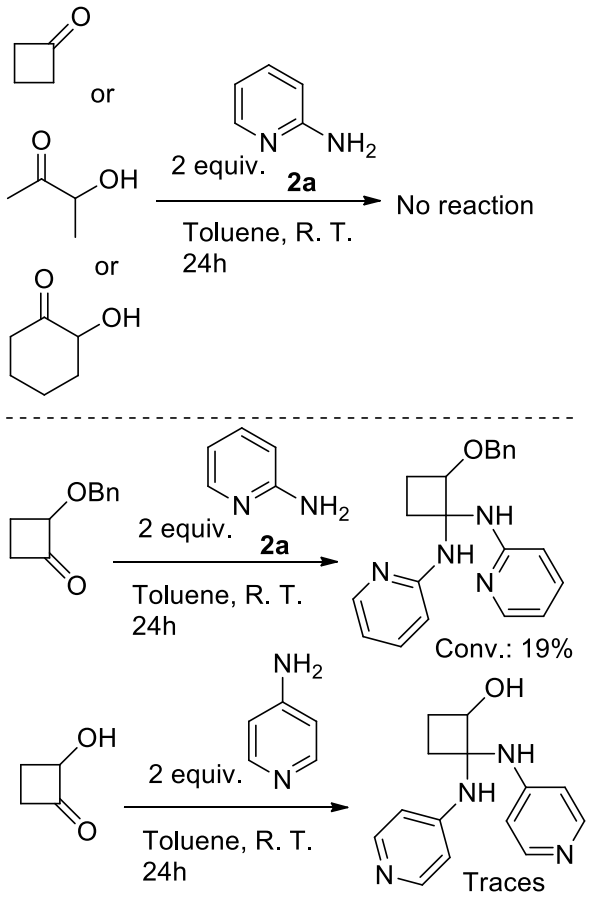
Scheme 4.1. Plausible explanation for the formation of **3a**



Two reasons can be tentatively suggested for this reactivity. First, the intermediate **A'** can be stabilised by an intramolecular hydrogen bond[7,8] involving the hydroxy group and the pyridine nitrogen donor atom. An NBO Second Order Perturbation Theory (SOPT) analysis of Fock Matrix shows that this interaction accounts for 23.3 kcal mol^{-1} and contributes to stabilize the resulting cyclic conformer by about 4.0 kcal mol^{-1} with respect to the non-stabilised one **A**.[7] Second, isomer **B** is calculated to be less stable than **A**,[7] thus favouring the reaction path leading to **3a** as compared to that yielding 4 as the final product. Furthermore, **3a** is stabilised by the strong intramolecular hydrogen bond depicted in Scheme 4.1 (NBO-SOPT analysis evaluates this interaction in 29.0 kcal mol^{-1}). In order to confirm the mechanism proposed for this reaction, some control experiments were carried out (Scheme 4.2). Cyclobutanone itself (lacking the α-hydroxy group) failed to afford the corresponding product as well as other cyclic and acyclic representative α-hydroxy ketones, while α-benzyloxycyclobutanone gave the corresponding aminal in modest conversion (19%). This suggests the requirement of both

a strained cyclobutyl ring and the presence of an α-hydroxy group for the success of this transformation. At the same time, only trace amounts of the corresponding aminal were detected when 4-amino pyridine, bearing the aromatic nitrogen in an "unfavorable spatial orientation" for hydrogen bonding interactions with the hydroxy group, was used. The observed reactivity seems to be thus the result of a synergic effect between these structural features.

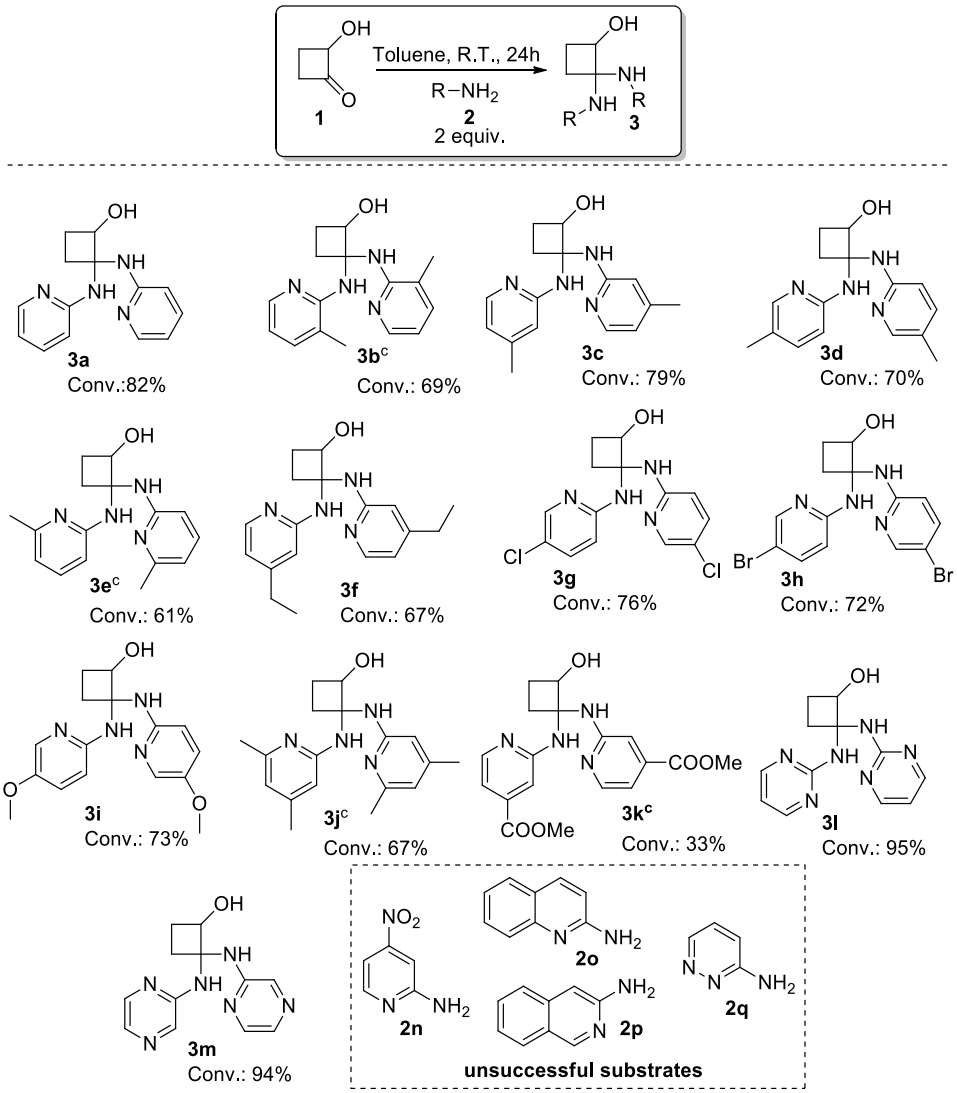
Scheme 4.2. Control experiments



Under the optimum conditions, various substituents that differentiate the stereoelectronic nature of the starting 2-aminopyridines including methyl, ethyl, chloro, bromo, methoxy and methoxycarbonyl could be applied with a general good efficiency of the process (Scheme 4.3; conversions were assessed by analysis of crude ^{1}H NMR spectra). As a matter of fact, all 2-aminopyridines bearing the functional group either at the 3-, 4-, 5- and 6-position on the aromatic ring gave the corresponding products in good to high conversions (54-79%).

Disubstituted 2-aminopyridines such as **2j** could also be accommodated, and the corresponding products were obtained in good conversion (67%). A decreased reaction rate was observed in the case of 2-aminopyridines featuring electron-withdrawing group such as a methyl carboxylate (**2k**) in the aromatic ring (33% conversion).

Scheme 4.3. Substrate scope and limitation of 2,2-bis(aza-heteroaryl amino)cyclobutanols[a,b]

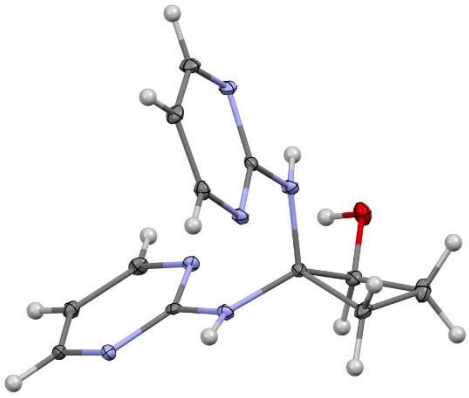


[a]Reaction conditions: **1** (419 µmol), **2** (837 µmol), Toluene (0.4 mL). [b] Products were difficult to purify by column chromatography so conversions were determined by ^{1}H NMR. [c]The reaction was carried out for 72h.

Unfortunately, no reactivity was observed for 2-aminopyridines carrying a stronger electron-withdrawing group such as **2m** and benzo-fused pyridines **2o** and **2p**. In order to further expand the synthetic application of this transformation, the treatment of 2-hydroxy

cyclobutanone with 2-aminopyrimidine **2l** allowed amination reaction to afford **3l** in 95% conversion. Alternatively, 2-amino pyrazine **2m** was proven to be a suitable amine precursor (94% conversion), whereas 3-aminopyridazine **2q** failed to participate in this reaction.

Figure 4.1 ORTEP drawing of product **3l**. Hydrogen atoms are depicted at 30% probability level.



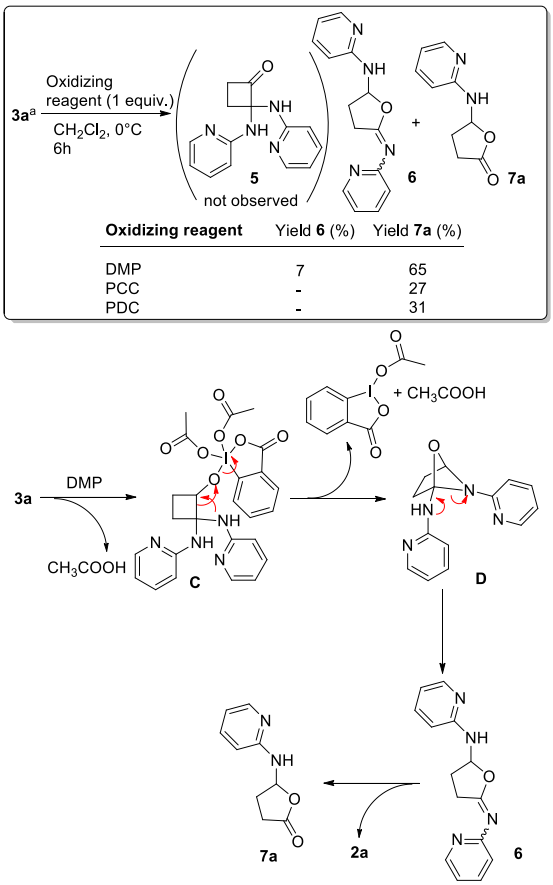
The structure of 2,2-bis(pyridin-2-ylamino)cyclobutanols **3** was further confirmed by an X-ray diffraction analysis carried out on a single crystals obtained by slow evaporation of chloroform solutions of compound **3l** (Figure 4.1; see S. I. for details).[9] During the course of our studies, after the successful achievement of derivatives **3**, we decided to employ them as starting materials for the synthesis of the corresponding 2,2-diaminocyclobutanones **5** by oxidation reaction (Scheme 4.4).[10]

Surprisingly, we found that **3a**, as crude reaction product, in the presence of Dess-Martin periodinane (DMP), in CH_2Cl_2 at 0°C, underwent a ring expansion process,[11] providing the functionalized 5-(pyridin-2-ylamino)dihydrofuran-2(3H)-one **7a** in 65% yield over two steps, along with a small amount of **6** (7% yield). None of the postulated 2,2-diaminocyclobutanone **5** could be observed. Screening of other widely applied oxidant such as PCC and PDC, under similar conditions afforded **7a** in diminished yields (27-31%). The reaction can be rationalized by assuming the mechanism shown in Scheme 4.4, based on a rearrangement reaction resulting in a cyclobutyl ring expansion.

We presume that the hypercoordinated iodine compound[12] acts as a Lewis acid reacting with **3a** to give the intermediate **C** which then undergoes regioselective ring expansion (by migration of the

more substituted terminus) with concomitant intramolecular shift of one of the two α-(pyridinyl)amino groups via intermediate **D** to give **6**.

Scheme 4.4 Oxidation of **3a** and proposed mechanism for the formation of **7a**

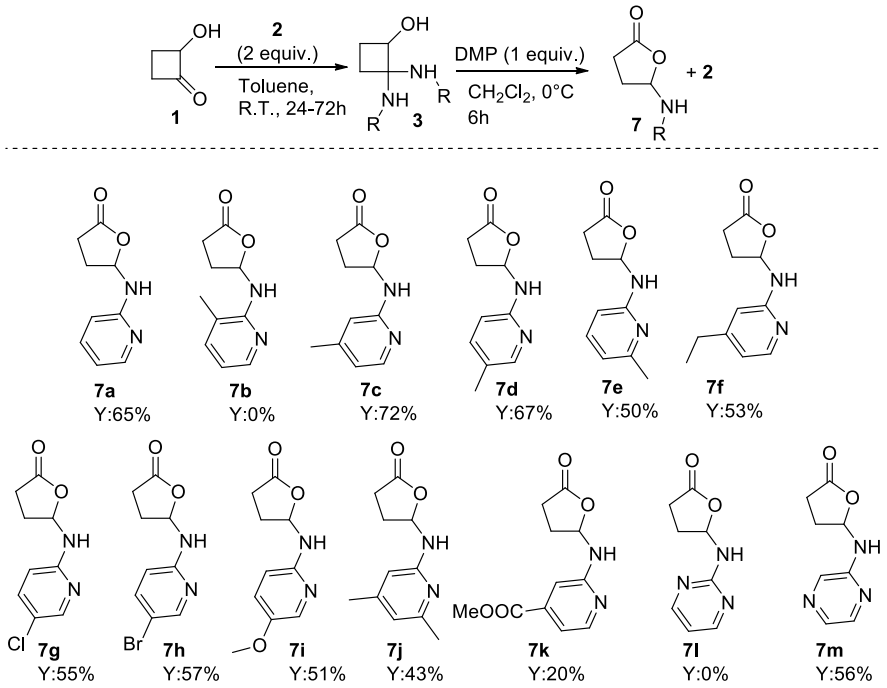


[a]Crude reaction sample containing H_2O released during the aminal formation step.

Finally, product **7a** is generated by hydrolysis of intermediate **6**. The observed formation of **6** during the reaction is consistent with this mechanistic proposal. With a chromium(VI) oxidizing agents, it can be hypothesized that the intermediate chromate ester (in place of **C**) could evolve by an analogous ring expansion during the elimination of $HCrO_3^-$, leading to the same intermediate **D**.

Thus, a two-step reaction sequence was established to synthesize 5-(pyridin-2-ylamino)dihydrofuran-2(3H)-one **7a** in which a mixture of **1** and **2a** (2 equiv.) in toluene was stirred at room temperature for 24h to yield **3a** followed by treatment of the crude reaction product with DMP. The product **7a** was purified by flash column chromatography and the only reaction by-product **2a**, released during the final step of the reaction process, recovered.

Scheme 4.5 A two-step protocol to 5-(heteroarylamino)dihydrofuran-2(3H)-ones **7**.[a]



[a]The yields, after silica gel chromatography, are depicted over two reaction steps.

The developed protocol was subsequently applied to our previously studied functionally different 2-amino pyridines **2b-k** in order to examine the substrate scope and limitation of this unexpected transformation. In general, all of the 2-amino pyridines that were examined (except **2b**) afforded the corresponding γ-lactones **7c-k** in moderate to good yields (20-72% yield) under the two-step reaction sequence. 3-Substituted 2-aminopyridines such as **2b** currently represent a limitation of this method, probably due to steric reasons. Gratifyingly, as for the 5-(pyridin-2-ylamino)dihydrofuran-2(3H)-one system, the pyrazine analogue **7m** was similarly accessible (56% yield) while unfortunately the reaction of pyrimidine **2l** resulted in the recovery of the corresponding intermediate **3l** (Scheme 4.5).

γ-Lactones are commonly found in biologically interesting compounds and are widely used in organic synthesis.[13] Although the preparation of these heterocycles has attracted broad interest from the synthetic community,[14] only a few 5-amino-substituted γ-lactones have been reported to date.[11e,15] Moreover, general synthetic strategies for the construction of 5-(heteroaryl)amino γ-lactones have not been described. The results of the present study should facilitate progress in this area.

4.4.3. Conclusions

We have discovered a novel two-step protocol for the synthesis of 5-(pyridin-2-ylamino)dihydrofuran-2(3H)-one derivatives which have not previously been described in the literature. The reactions proceed under mild conditions and the products can be isolated in moderate to good overall yields.

Reproduced from L. Ghisu, N. Melis, F. Secci, P. Caboni, M. Arca, R. Guillot, T. Boddaert, D. J. Aitken and A. Frongia, *Synthesis of 2.2-bis(pyridine-2-ylamino)cyclobutanols and their conversion into 5-(pyridine-2-ylamino)dihydrofuran-2(3H)-ones, Org. Biomol. Chem.,* **2017**, *15*, 9979-9784 with permission from the Royal Society of Chemistry.

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4.4.Experimental part

4.4.1 General Methods

^{1}H NMR spectra were recorded on a Varian 500 spectrometer at ambient temperature with $CDCl_3$ as solvent. Data are reported as follows: chemical shifts (δ), multiplicity, coupling constants and integration. ^{13}C NMR spectra were recorded operating at 126 MHz at 27 °C with $CDCl_3$ as solvent. Infrared spectra were recorded on a FT-IR spectrophotometer. High resolution mass spectra (HRMS) were recorded on a spectrometer using Positive Electro Ionization (ESI) mode. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using columns of 230-400 mesh silica gel 60 (0.040-0.063 mm).

4.4.2 General procedures and data

General procedure for the two-step preparation of 5-(pyridin-2-ylamino)dihydrofuran-2(3H)-one 7 from 2-hydroxycyclobutanone 1 and 2-amino pyridines 2.

Step 1:

A solution of **1** (419 µmol) and **2** (837 µmol) in Toluene (0.4 mL) was stirred in a sealed tube reactor at room temperature for 24-72h. The resulting reaction mixture was concentrated in a vacuum and controlled by ^{1}H NMR. Conversions (based on **2**) and characteristic spectroscopic data of **3** are reported below. The crude products were used in the following step as obtained by evaporation of the solvent, contaminated with small amount of **1** and **2**.

3a: Conversion 82%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid; **m. p.** = 107–111 °C. **IR** (neat): 3271, 3008, 2955, 2899, 1681, 1601, 1592, 1480, 1407, 1324,

1251, 1179, 1143, 1106, 1065 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.99 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.31 – 7.28 (m, 2H), 6.55 – 6.49 (m, 2H), 6.41 – 6-37 (m, 3H), 6.02 (s, 1H), 4.37 (t, *J* = 8.5 Hz, 1H), 2.47 (t, *J* = 10.2 Hz, 1H), 2.25 – 2.20 (m, 1H), 2.04 (dd, *J* = 19.8, 10.4 Hz, 1H), 1.96 (ddd, *J* = 18.8, 11.9, 7.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.1, 156.9, 147.4, 147.0, 137.6, 137.0, 113.3, 112.7, 110.9, 110.4, 70.7, 70.4, 26.1, 24.6. **HRMS** (ESI) Calcd. for $C_{14}H_{15}N_4$ (MH^+-H_2O) m/z 239.1291, found 239.1304.

3b: Conversion 69%; the crude mixture, diluted with CH_2Cl_2, was purified by filtration through a pad of silica gel to give the title compound as a yellow oil. **IR** (neat): 3429, 3381, 2994, 2951, 1592, 1496, 1469, 1408, 1323, 1251, 1158 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.89 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.15 (dddd, *J* = 5.9, 4.2, 1.6, 0.7 Hz, 2H), 6.48 – 5.51 (m, 3H), 5.91 (s, 1H), 4.43 (t, *J* = 8.4 Hz, 1H), 2.48 (dd, *J* = 14.2, 5.1 Hz, 1H), 2.25 (ddd, *J* = 9.8, 6.4, 4.4 Hz, 1H), 2.10 – 2.04 (m, 2H), 2.03 (s, 3H), 2.01 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.9, 155.5, 144.8, 144.5, 137.5, 137.0, 118.8, 118.2, 113.3, 112.7, 70.6, 70.5, 26.5, 24.7, 17.2, 17.0. **HRMS** (ESI) Calcd. for $C_{16}H_{19}N_4$ (MH^+-H_2O) m/z 267.1604, found 267.1600.

3c: Conversion 79%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid; **m. p.** = 124–128 °C. **IR** (neat): 3408, 3347, 2952, 2864, 1616, 1571, 1501, 1389, 1173, 1141 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 5.3 Hz, 1H), 7.86 (d, *J* = 5.4 Hz, 1H), 6.37 (dd, *J* = 11.0, 5.3 Hz, 2H), 6.28 (s, 1H), 6.22 (s, 1H), 6.19 (s, 1H), 5.89 (s, 1H), 4.34 (t, *J* = 8.5 Hz, 1H), 2.45 (dd, *J* = 14.1, 6.1 Hz, 1H), 2.21 (ddd, *J* = 7.8, 5.9, 3.0 Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H), 2.02 (dd, *J* = 19.8, 10.4 Hz, 1H), 1.99 – 1.90 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.4, 157.2, 148.6, 147.9, 147.2, 146.7, 115.1, 114.4, 111.0, 110.6, 70.7, 70.4, 26.2, 24.6, 21.0 (2C). **HRMS** (ESI) Calcd. for $C_{16}H_{19}N_4$ (MH^+-H_2O) m/z 267.1604, found 267.1596.

3d: Conversion 70%; the crude mixture, diluted with CH_2Cl_2, was purified by filtration through a pad of silica gel to give the title compound as a yellow oil. **IR** (neat): 3404, 3235, 2989, 2952, 2900, 1611, 1566, 1506, 1431, 1320, 1260, 1168 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.82 (s, 1H), 7.15 – 7.12 (m, 2H), 6.33-6.30 (m, 2H), 6.27 (s, 1H), 5.86 (s, 1H), 4.35 (t, *J* = 8.5 Hz, 1H), 2.44 (t, *J* = 10.3 Hz, 1H), 2.24 – 2.20 (m, 1H), 2.12 (s, 3H), 2.11 (s, 3H), 2.02 (dt, *J* = 19.4, 9.8 Hz, 1H), 1.93 (td, *J* = 10.6, 8.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.3, 155.1, 146.9, 146.5, 138.7, 138.1,

122.1, 121.3, 110.5, 110.0, 70.9, 70.6, 26.1, 24.6, 17.48, 17.43. **HRMS** (ESI) Calcd. for $C_{16}H_{19}N_4$ (MH^+-H_2O) m/z 267.1604, found 267.1594.

3e: Conversion 61%; the crude mixture, diluted with CH_2Cl_2, was purified by filtration through a pad of silica gel to give the title compound as an orange oil. **IR** (neat): 3372, 2990, 2954, 1782, 1604, 1588, 1463, 1269, 1234, 1158 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 – 7.19 (m, 2H), 6.42 – 6.38 (m, 2H), 6.33 (br s, 1H), 6.23 – 6.19 (m, 2H), 5.97 (br s, 1H), 4.37 (t, *J* = 8.5 Hz, 1H), 2.48 – 2.44 (m, 1H), 2.37 (s, 3H), 2.36 (s, 3H), 2.22 (dtd, *J* = 9.6, 8.0, 1.6 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.94 – 1.88 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.7, 156.4, 156.3, 155.6, 137.9, 137.3, 112.5, 111.8, 107.7, 106.7, 70.7, 70.6, 26.2, 24.68, 24.67, 24.3. **HRMS** (ESI) Calcd. for $C_{16}H_{19}N_4$ (MH^+-H_2O) m/z 267.1604, found 267.1602.

3f: Conversion 67%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid. **IR** (neat): 3341, 2966, 2936, 2877, 1784, 1612, 1559, 1482, 1439, 1396, 1174 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 5.3 Hz, 1H), 7.88 (d, *J* = 5.6 Hz, 1H), 6.41 (dd, *J* = 5.4, 1.1 Hz, 1H), 6.39 (dd, *J* = 5.3, 1.0 Hz, 1H), 6.37 (s, 1H), 6.25 (s, 1H), 6.21 (s, 1H), 5.94 (s, 1H), 4.35 (t, *J* = 8.5 Hz, 1H), 2.49-2.41 (m, 5H), 2.22 – 2.20 (m, 1H), 2.04-1.97 (m, 1H), 1.95 – 1.91 (m, 1H), 1.17 – 1.12 (m, 6H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.4, 157.2, 154.6, 153.8, 147.1, 146.6, 113.8, 113.2, 109.7, 109.3, 70.7, 70.4, 28.2 (2C), 26.2, 24.6, 14.1, 14.0. **HRMS** (ESI) Calcd. for $C_{18}H_{23}N_4$ (MH^+-H_2O) m/z 295.1917, found 295.1920.

3g: Conversion 76%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid; **m. p.** = 118–122°C. **IR** (neat): 3400, 2986, 2960, 1598, 1562, 1482, 1390, 1370, 1284, 1241, 1135, 1112 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.4 Hz, 1H), 7.97 (d, *J* = 2.5 Hz, 1H), 7.30 – 7.27 (m , 2H), 6.37 (dd, *J* = 8.9, 0.5 Hz, 1H), 6.35 – 6.33 (m, 1H), 6.23 (s, 1H), 5.99 (s, 1H), 4.35 (t, *J* = 8.5 Hz, 1H), 2.43 – 2.39 (m, 1H), 2.23 (ddd, *J* = 8.9, 5.8, 1.6 Hz, 1H), 2.02 – 1.98 (m, 1H), 1.93 (td, *J* = 10.4, 7.7 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.3, 155.1, 145.8, 145.5, 137.8, 137.1, 120.8, 120.1, 111.8, 111.3, 70.6, 70.5, 26.0, 24.5. **HRMS** (ESI) Calcd. for $C_{14}H_{13}Cl_2N_4$ (MH^+-H_2O) m/z 307.0512, found 307.0512.

3h: Conversion 72%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a yellow solid. **IR** (neat): 3387, 3307, 2953, 1625, 1588, 1496, 1476, 1386, 1367, 1300, 1284, 1237 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 2.3 Hz, 1H), 8.06 (d, *J* = 2.4 Hz, 1H), 7.41 (dd, *J* = 5.1, 2.5 Hz, 1H), 7.40 (dd, *J* = 5.1, 2.5 Hz, 1H), 6.34 (d, *J* = 8.8 Hz, 1H), 6.31 (d, *J* = 8.8 Hz, 1H), 6.26 (s, 1H), 6.01 (s, 1H), 4.35 (t, *J* = 8.4 Hz, 1H), 2.41 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.27 – 2.21 (m, 1H), 2.00 (dd, *J* = 19.9, 10.5 Hz, 1H), 1.97 – 1.89 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.5, 155.3, 148.1, 147.8, 140.3, 139.6, 112.4, 111.9, 108.1, 107.6, 70.6, 70.4, 25.9, 24.5. **HRMS** (ESI) Calcd. for $C_{14}H_{13}Br_2N_4$ (MH^+-H_2O) m/z 394.9507, found 394.9516.

3i: Conversion 73%. Orange oil. **IR** (neat): 3364, 2999, 2956, 2837, 1781, 1618, 1579, 1496, 1403, 1257, 1241, 1174, 1035 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 2.9 Hz, 1H), 7.71 (d, *J* = 2.6 Hz, 1H), 7.01 – 6.99 (m, *J* = 9.0, 3.0, 1.0 Hz, 2H), 6.37 – 6.33 (m, 2H), 6.16 (br s, 1H), 5.77 (br s, 1H), 4.35 (t, *J* = 8.5 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.43 – 2.38 (m, 1H), 2.23 – 2.21 (m, 1H), 2.06 – 1.98 (m, 1H), 1.95 – 1.89 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.1, 151.9, 149.0, 148.6, 132.6, 132.0, 126.4, 125.7, 111.5, 111.0, 71.1, 71.0, 56.4, 56.3, 26.2, 24.7. **HRMS** (ESI) Calcd. for $C_{16}H_{19}N_4O_2$ (MH^+-H_2O) m/z 299.1502, found 299.1499.

3j: Conversion 67%; the crude mixture, diluted with CH_2Cl_2, was purified by filtration through a pad of silica gel to give the title compound as an orange oil. **IR** (neat): 3364, 2983, 2953, 1787, 1615, 1572, 1502, 1456, 1267, 1234 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.29 (br s, 1H), 6.26 (s, 1H), 6.24 (s, 1H), 6.05 (s, 1H), 6.01 (s, 1H), 5.88 (br s, 1H), 4.34 (t, *J* = 8.6 Hz, 1H), 2.45 (t, *J* = 10.0 Hz, 1H), 2.32 (s, 6H), 2.21 (dd, *J* = 9.7, 7.5 Hz, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 2.04 – 1.92 (m, 1H), 1.90 – 1.84 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.8, 156.6, 155.3, 155.1, 149.0, 148.2, 114.2, 113.5, 107.0, 106.4, 70.7, 70.6, 26.3, 24.6, 21.06 (2C), 21.00, 20.9. **HRMS** (ESI) Calcd. for $C_{18}H_{23}N_4$ (MH^+-H_2O) m/z 295.1917, found 295.1920.

3k: Conversion 33%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid. **IR** (neat): 3380, 3205, 2983, 2956, 1784, 1724, 1612, 1562, 1502, 1486, 1439, 1390, 1297, 1251, 1112 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 5.2 Hz, 1H), 8.12 (d, *J* = 5.4 Hz, 1H), 7.06 – 7.05 (m, 2H), 7.02 – 6.99 (m, 2H), 6.57 (br s, 1H), 6.26 (br s, 1H), 4.38 (t, *J* = 8.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.49 – 2.44 (m, 1H), 2.26 – 2.23 (m, 1H), 2.06 – 1.98 (m, 2H). **^{13}C NMR**

(126 MHz, $CDCl_3$) δ 166.1, 165.8, 157.3, 157.2, 148.4, 148.0, 138.9, 138.5, 112.1, 111.7, 110.9, 110.3, 70.7, 70.3, 52.5, 52.4, 25.9, 24.5. **HRMS** (ESI) Calcd. for $C_{18}H_{19}N_4O_4$ (MH^+-H_2O) m/z 355.1409, found 355.1398.

3l: Conversion 95%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid; **m. p.** = 174–178 °C. **IR** (neat): 3377, 3231, 2983, 1588, 1562, 1532, 1496, 1453, 1416, 1393, 1277, 1174 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.28 – 8.26 (m, 4H), 6.83 (s, 1H), 6.70 (s, 1H), 6.59 – 6.54 (m, 2H), 4.42 (t, *J* = 8.3 Hz, 1H), 2.51 – 2.47 (m, 1H), 2.28 – 2.23 (m, 1H), 2.10 – 1.97 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.1, 160.9, 158.08, 158.03, 111.4, 111.3, 70.5, 69.2, 26.3, 24.5. **HRMS** (ESI) Calcd. for $C_{12}H_{13}N_6$ (MH^+-H_2O) m/z 241.1196, found 241.1194. A single crystal suitable for X-ray single-crystal structure determination was obtained by slow diffusion of hexane into a solution of **3l** in $CHCl_3$.

3m: Conversion 94%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid; **m. p.** = 144–149°C. **IR** (neat): 3334, 3244, 2983, 2897, 1588, 1519, 1423, 1396, 1290, 1204, 1148 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 – 7.96 (m, 1H), 7.93 (d, *J* = 1.4 Hz, 1H), 7.92 (dd, *J* = 2.8, 1.4 Hz, 1H), 7.90 (d, *J* = 1.3 Hz, 1H), 7.84 (d, *J* = 2.9 Hz, 1H), 7.81 (d, *J* = 2.8 Hz, 1H), 6.34 (s, 1H), 6.19 (s, 1H), 4.39 (t, *J* = 8.4 Hz, 1H), 2.47 – 2.42 (m, 1H), 2.32 – 2.27 (m, 1H), 2.09 – 1.97 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.9, 152.7, 141.3, 140.7, 135.3, 134.7, 133.6, 133.1, 70.3, 70.1, 25.7, 24.5. **HRMS** (ESI) Calcd. for $C_{12}H_{13}N_6$ (MH^+-H_2O) m/z 241.1196, found 241.1210.

Step 2:

To a stirred solution of **3** (crude sample; 419 µmol) in CH_2Cl_2 (2 mL) at 0°C was added Dess-Martin periodinane (419 µmol, 0.178 g) and the reaction mixture was stirred at the same temperature for 6h. The precipitate was filtered and then the mixture was quenched with sat. $NaHCO_3$ aq. and extracted twice with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by flash column chromatography (SiO_2, petroleum ether/ether = 5:1→1:1) to give compound **7**. Yields refer to chromatographically pure materials.

7a: Yield 65% (0.049 g) over two steps; yellow oil. **IR** (neat): 3450, 2974, 1708, 1590, 1573, 1474, 1435, 1394, 1304, 1215 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.32 – 8.31 (m, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.74 (ddd, *J* = 8.4, 7.4, 1.9 Hz, 1H), 7.08 (ddd, *J* = 7.3, 5.0, 0.9 Hz, 1H), 6.06 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.58 – 2.52 (m, 1H), 2.39 – 2.31 (m, 1H), 2.12 (dddd, *J* = 13.5, 9.8, 3.6, 2.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.4, 151.7, 147.2, 138.4, 120.1, 115.3, 83.8, 30.9, 25.4. **HRMS** (ESI) Calcd. for $C_9H_{11}N_2O_2$ $(M+H)^+$ m/z 179,081503, found 179,0815.

7c: Yield 72% (0.058 g) over two steps; yellow oil. **IR** (neat): 3431, 2974, 1704, 1607, 1563, 1479, 1413, 1295, 1217, 1065 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 5.1 Hz, 1H), 8.07 – 8.05 (m, 1H), 6.93 – 6.90 (m, 1H), 6.03 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.88 (ddd, *J* = 17.7, 9.8, 8.7 Hz, 1H), 2.55 (ddd, *J* = 17.6, 9.9, 3.6 Hz, 1H), 2.38 (s, 3H), 2.36 – 2.30 (m, 1H), 2.11 (dddd, *J* = 13.6, 9.8, 3.6, 2.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.4, 151.7, 150.0, 146.8, 121.4, 115.8, 84.0, 31.0, 25.4, 21.5. **HRMS** (ESI) Calcd. for $C_{10}H_{13}N_2O_2$ $(M+H)^+$ m/z 193,097153, found 193,0975.

7d: Yield 67% (0.054 g) over two steps; yellow oil. **IR** (neat): 3429, 2976, 1708, 1604, 1573, 1486, 1382, 1304, 1210 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.12 – 8.11 (m, 2H), 7.57 – 7.54 (m, 1H), 6.02 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.87 (ddd, *J* = 17.6, 9.7, 8.7 Hz, 1H), 2.54 (ddd, *J* = 17.5, 9.9, 3.6 Hz, 1H), 2.38 – 2.30 (m, 1H), 2.31 (s, 3H), 2.13 – 2.07 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.2, 149.6, 147.1, 139.1, 129.5, 114.8, 84.0, 30.9, 25.5, 17.9. **HRMS** (ESI) Calcd. for $C_{10}H_{13}N_2O_2$ $(M+H)^+$ m/z 193,097153, found 193,0976.

7e: Yield 50% (0.041 g) over two steps; yellow oil. **IR** (neat): 3450, 2976, 1708, 1578, 1454, 1389, 1309, 1277, 1159 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 1H), 7.64 – 7.61 (m, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.04 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.87 (ddd, *J* = 17.7, 9.8, 8.7 Hz, 1H), 2.55 (ddd, *J* = 17.5, 9.9, 3.6 Hz, 1H), 2.49 (s, 3H), 2.34 (dddd, *J* = 13.6, 9.9, 8.7, 6.7 Hz, 1H), 2.14 – 2.08 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.3, 156.4, 151.1, 138.8, 119.5, 112.2, 84.0, 31.0, 25.4, 24.4. **HRMS** (ESI) Calcd. for $C_{10}H_{13}N_2O_2$ $(M+H)^+$ m/z 193,097153, found 193,0971.

7f: Yield 53% (0.046 g) over two steps; yellow oil. **IR** (neat): 3441, 2971, 2877, 1711, 1607, 1561, 1483, 1420, 1309, 1217 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 5.1 Hz, 1H), 8.09 (d, *J* = 0.5 Hz, 1H), 6.95 – 6.93 (m, 1H), 6.03 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.91 – 2.84 (m, 1H), 2.68 (q, *J* = 7.6

Hz, 2H), 2.54 (ddd, *J* = 17.5, 9.9, 3.6 Hz, 1H), 2.33 (dddd, *J* = 13.7, 9.8, 8.7, 6.7 Hz, 1H), 2.11 (dddd, *J* = 13.5, 9.8, 3.6, 2.0 Hz, 1H), 1.26 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.3, 156.0, 151.9, 146.9, 120.1, 114.6, 84.0, 31.0, 28.7, 25.4, 14.5. **HRMS** (ESI) Calcd. for $C_{11}H_{15}N_2O_2$ $(M+H)^+$ m/z 207,112803, found 207,1125.

7g: Yield 55% (0.049 g) over two steps; white solid; m. p. = 102–105 °C; **IR** (neat): 3279, 2962, 1684, 1578, 1466, 1372, 1297, 1212, 1108, 1065 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.28 – 8.26 (m, 2H), 7.71 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.04 (dd, *J* = 6.7, 1.9 Hz, 1H), 2.89 (ddd, *J* = 17.9, 9.7, 8.8 Hz, 1H), 2.56 (ddd, *J* = 17.6, 9.9, 3.6 Hz, 1H), 2.35 (dddd, *J* = 13.7, 9.8, 8.8, 6.7 Hz, 1H), 2.13 (dddd, *J* = 13.5, 9.8, 3.5, 2.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.3, 149.9, 146.0, 138.3, 127.5, 116.0, 83.7, 30.9, 25.5. **HRMS** (ESI) Calcd. for $C_9H_{10}ClN_2O_2$ $(M+H)^+$ m/z 213,042531, found 213,0429.

7h: Yield 57% (0.062 g) over two steps; yellow oil. **IR** (neat): 3409, 3061, 2959, 1687, 1575, 1471, 1372, 1300, 1210, 1072 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.38 – 8.36 (m, 1H), 8.22 (dd, *J* = 8.9, 0.5 Hz, 1H), 7.84 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.03 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.92 – 2.85 (m, 1H), 2.55 (ddd, *J* = 17.6, 9.8, 3.6 Hz, 1H), 2.39 – 2.31 (m, 1H), 2.12 (dddd, *J* = 13.6, 9.8, 3.6, 2.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.4, 150.3, 148.2, 141.0, 116.5, 115.4, 83.7, 30.9, 25.5. **HRMS** (ESI) Calcd. for $C_9H_{10}BrN_2O_2$ $(M+H)^+$ m/z 237,086983, found 237,0868.

7i: Yield 51% (0.043 g) over two steps; orange oil. **IR** (neat): 3440, 2950, 2840, 1694, 1575, 1482, 1446, 1396, 1274, 1244, 1241, 1214, 1032, 1012 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.1 Hz, 1H), 7.99 (d, *J* = 2.9 Hz, 1H), 7.31 (dd, *J* = 9.1, 3.1 Hz, 1H), 6.00 (dd, *J* = 6.6, 1.8 Hz, 1H), 3.85 (s, 3H), 2.91 – 2.83 (m, 1 H), 2.54 (ddd, *J* = 17.5, 9.9, 3.5 Hz, 1H), 2.34 (dddd, *J* = 13.7, 9.8, 8.7, 6.7 Hz, 1H), 2.11 (dddd, *J* = 11.7, 9.8, 3.4, 1.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.0, 153.1, 133.7, 124.0, 116.0, 84.1, 56.0, 30.8, 25.6. **HRMS** (ESI) Calcd. For $C_{10}H_{13}N_2O_3$ $(M+H)^+$ m/z 209.0921, found 209.0926.

7j: Yield 43% (0.037 g) over two steps; yellow oil. **IR** (neat): 3448, 2981, 1711, 1612, 1575, 1420, 1387, 1338, 1234, 1164 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 6.78 (s, 1H), 6.00 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.86 (ddd, *J* = 17.6, 9.8, 8.6 Hz, 1H), 2.54 (ddd, *J* = 17.5, 9.9, 3.7 Hz, 1H), 2.43 (s, 3H), 2.36 – 2.27 (m, 1H), 2.33 (s, 3H), 2.10 (dddd, *J* = 15.6, 9.9, 3.6, 2.0 Hz, 1H). **^{13}C NMR** (126

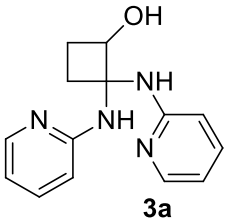
MHz, $CDCl_3$) δ 174.3, 155.9, 151.1, 150.2, 120.7, 112.8, 84.2, 31.0, 25.4, 24.1, 21.4. **HRMS** (ESI) Calcd. for $C_{11}H_{15}N_2O_2$ $(M+H)^+$ m/z 207,112803, found 207,1128.

7k: Yield 20% (0.019 g) over two steps; white solid; **m. p.** = 144-147 °C; **IR** (neat): 3429, 2957, 1730, 1694, 1602, 1563, 1479, 1440, 1406, 1300, 1246, 1212 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 7.65 (dd, *J* = 5.2, 1.4 Hz, 1H), 6.11 – 6.00 (m, 1H), 5.04 (br s, 1H), 3.96 (s, 3H), 2.95 – 2.87 (m, 1H), 2.63 – 2.55 (m, 1H), 2.40 – 2.33 (m, 1H), 2.19 – 2.10 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.4, 165.4, 152.5, 148.0, 140.0, 119.4, 115.0, 83.9, 52.9, 30.9, 25.5. **HRMS** (ESI) Calcd. for $C_{11}H_{13}N_2O_4$ $(M+H)^+$ m/z 237,086983, found 237,0868.

7m: Yield 56% (0.042 g) over two steps; white solid; m. p. = 107–109 °C; IR (neat): 3349, 2976, 1713, 1481, 1416, 1304, 1210, 1065 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (d, *J* = 1.3 Hz, 1H), 8.40 (d, *J* = 2.6 Hz, 1H), 8.29 (dd, *J* = 2.5, 1.5 Hz, 1H), 6.06 (dd, *J* = 6.6, 1.9 Hz, 1H), 2.96 – 2.88 (m, 1H), 2.59 (ddd, *J* = 17.7, 9.8, 3.5 Hz, 1H), 2.44 – 2.36 (m, 1H), 2.18 (dddd, *J* = 13.5, 9.8, 3.4, 1.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 148.2, 141.2, 140.3, 138.3, 83.2, 30.6, 26.0. HRMS (ESI) Calcd. for $C_8H_{10}N_3O_2$ $(M+H)^+$ m/z 180,076752, found 180,0763.

6: Yield 7% (0.007 g); brown resin; **IR** (neat): 3450, 3066, 2953, 1648, 1588, 1559, 1479, 1463, 1433, 1396, 1307, 1218, 1065 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 8.5 Hz, 1H), 8.38 (dd, *J* = 4.9, 1.1 Hz, 1H), 8.37 – 8.29 (m, 1H), 7.70 – 7.69 (m, 1H), 7.61 (td, *J* = 7.9, 1.9 Hz, 1H), 7.02 (ddd, *J* = 7.2, 5.0, 0.8 Hz, 1H), 6.95 (ddd, *J* = 7.3, 5.0, 0.9 Hz, 1H), 6.87 – 6.85 (m, 1H), 6.09 (dd, *J* = 5.6, 2.5 Hz, 1H), 5.43 (br s, 1H), 2.97– 2.90 (m, 1H), 2.86 – 2.79 (m, 1H), 2.29 – 2.20 (m, 1H), 2.09 – 2.03 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.7, 161.4, 153.0, 148.7, 147.0, 138.0, 137.7, 119.0, 118.4, 117.1, 116.4, 85.1, 27.4, 27.1. **HRMS** (ESI) Calcd. for $C_{14}H_{14}N_4O$ $(M+H)^+$ m/z 255,124000, found 255,1249.

4.4.3 Copies of NMR spectra



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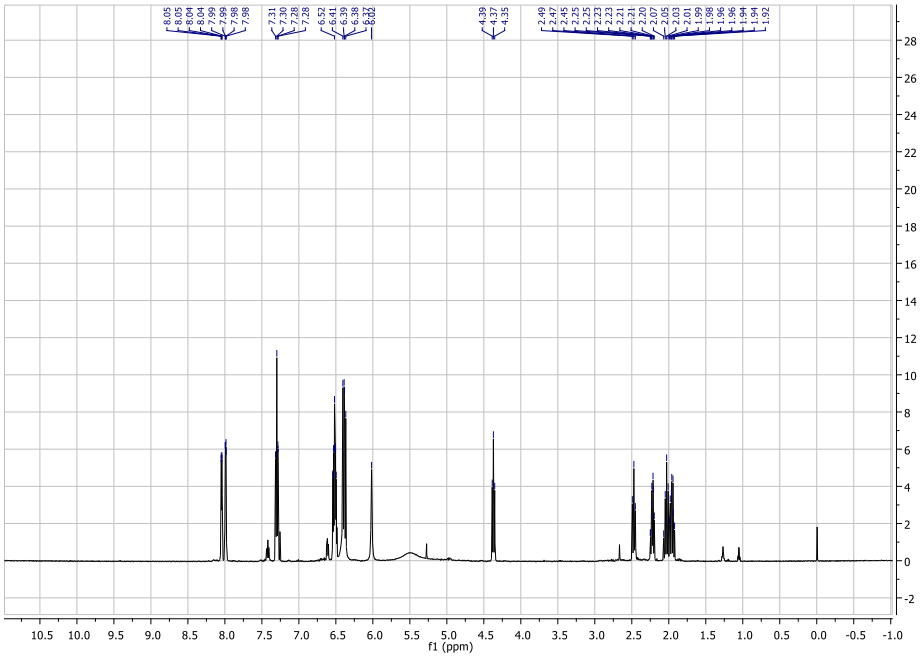

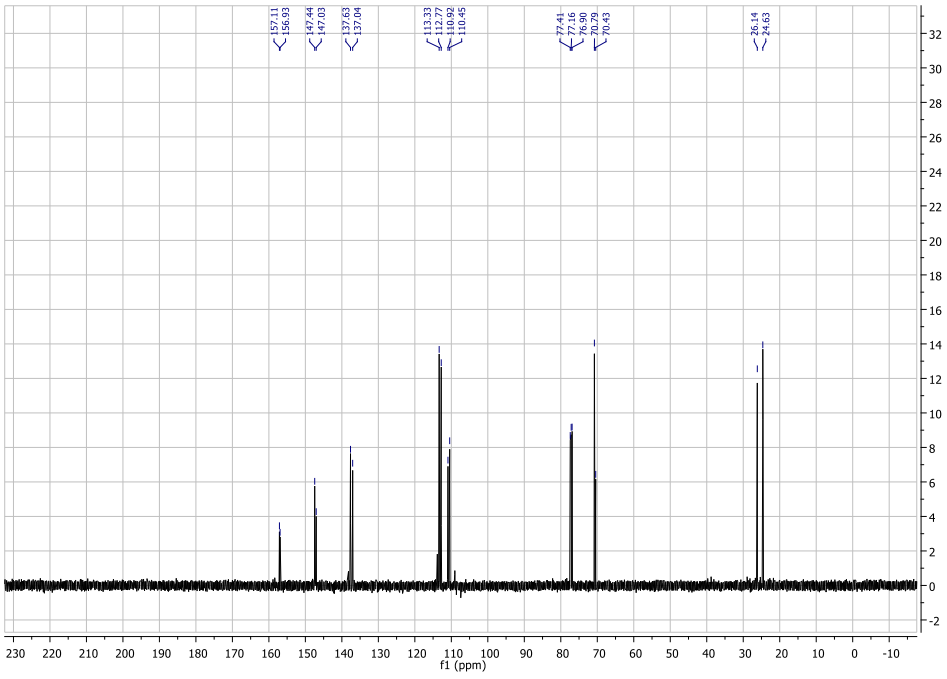

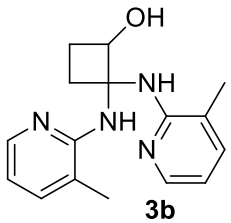
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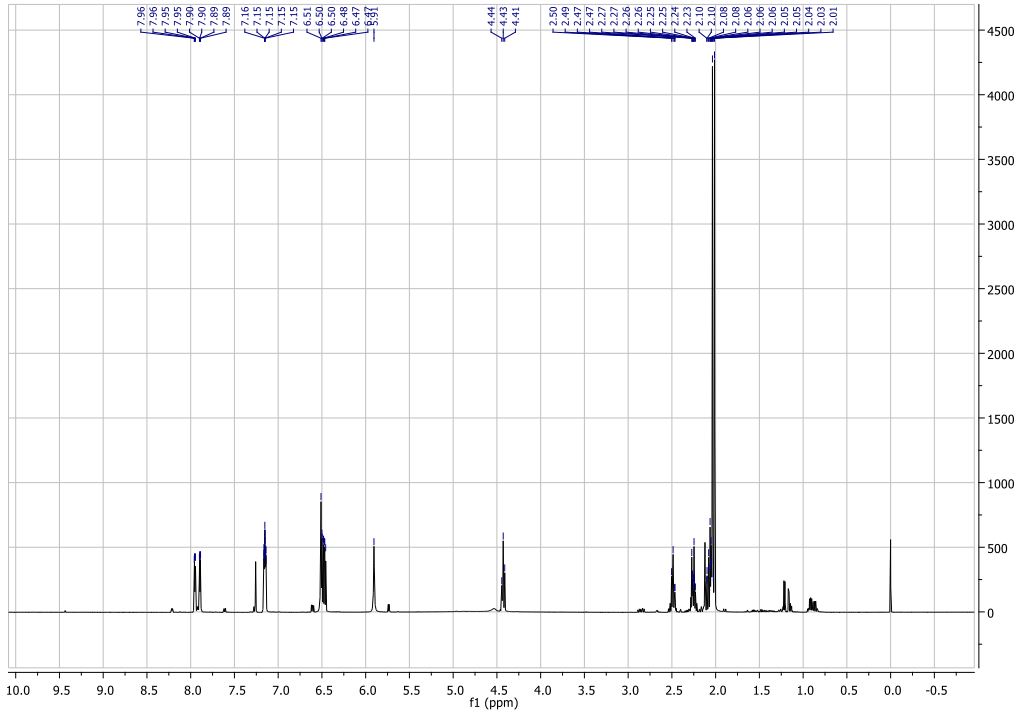
N

3b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2.06
2.06
2.05
2.05
2.04
2.03
2.01
4500
4000
3500
3000
2500
2000
1500
1000
500
0
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
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3.0
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2.0
1.5
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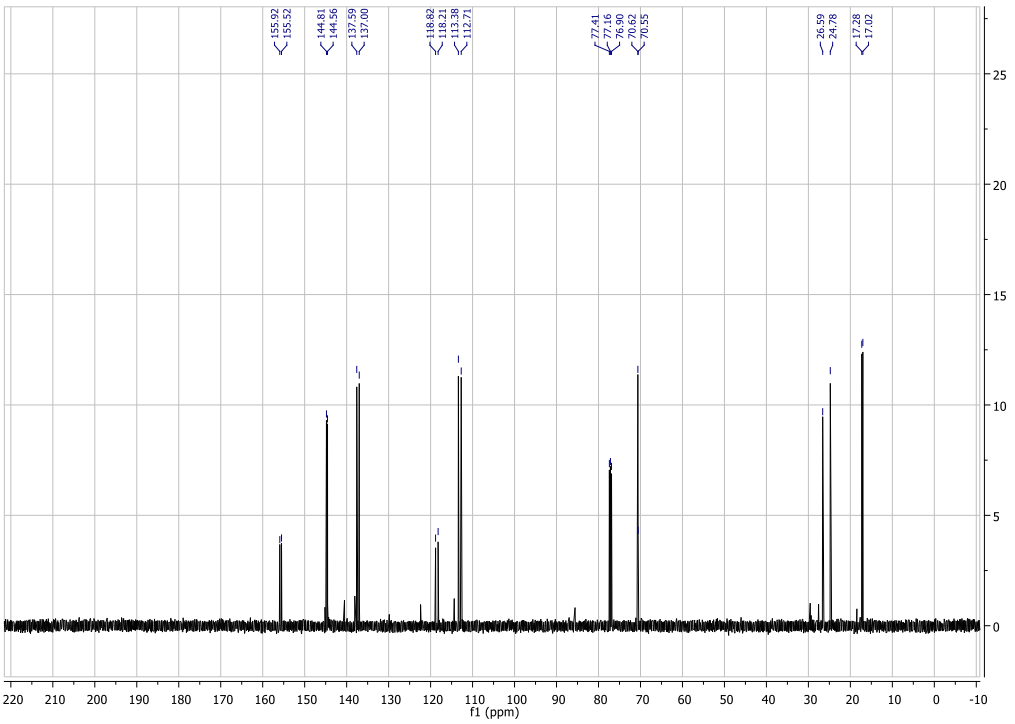
0.5
0.0
-0.5
f1 (ppm)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76.90
70.62
70.55
26.59
24.78
17.28
17.02
25
20
15
10
5
0
220
210
200
190
180
170
160
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120
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100
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80
70
60
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40
30
20
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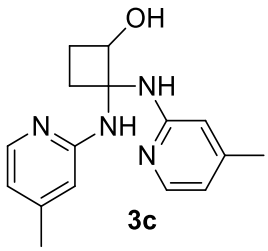
0
-10
f1 (ppm)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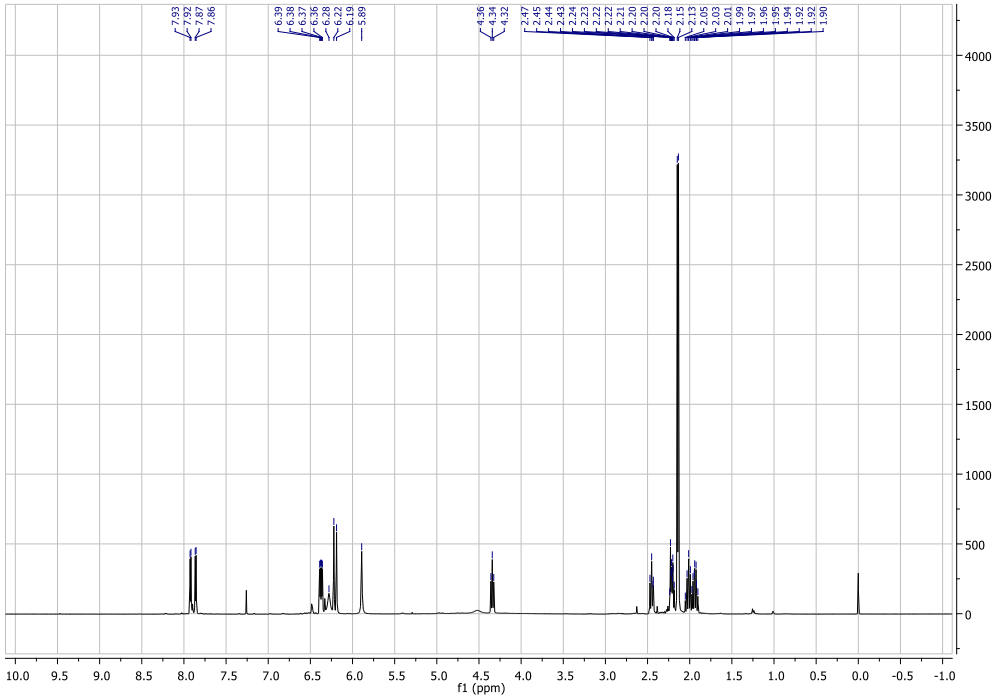
N
NH
N

3c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2.47
2.45
2.44
2.43
2.24
2.23
2.22
2.21
2.20
2.20
2.20
2.18
2.15
2.13
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2.03
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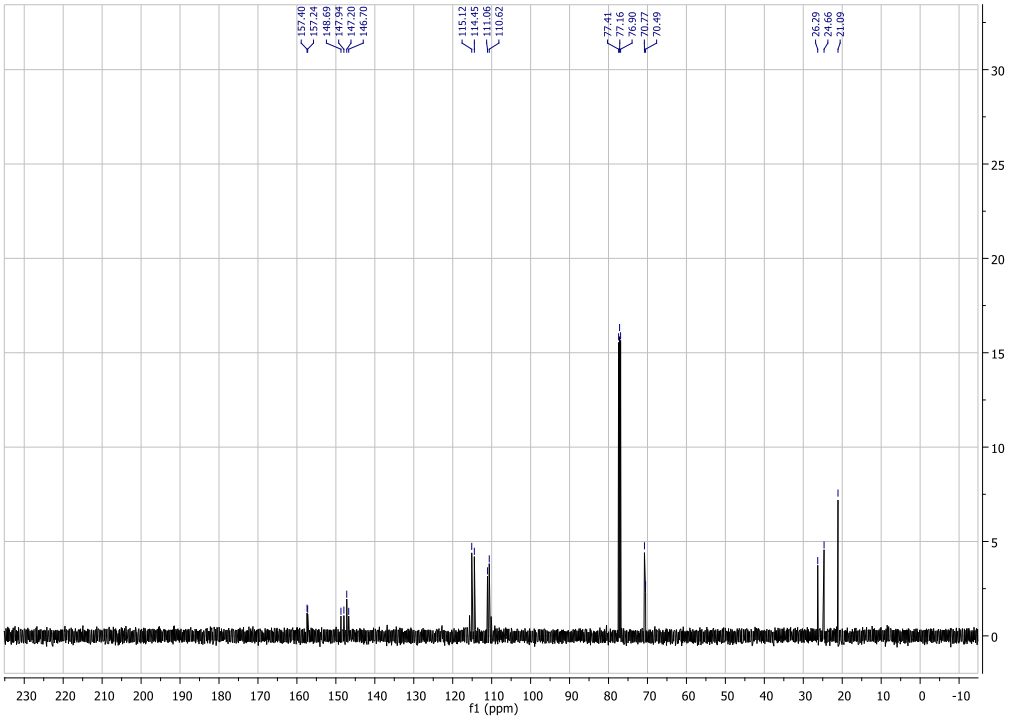
f1 (ppm)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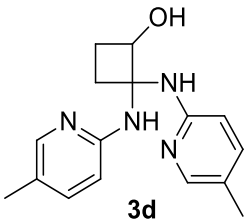
f1 (ppm)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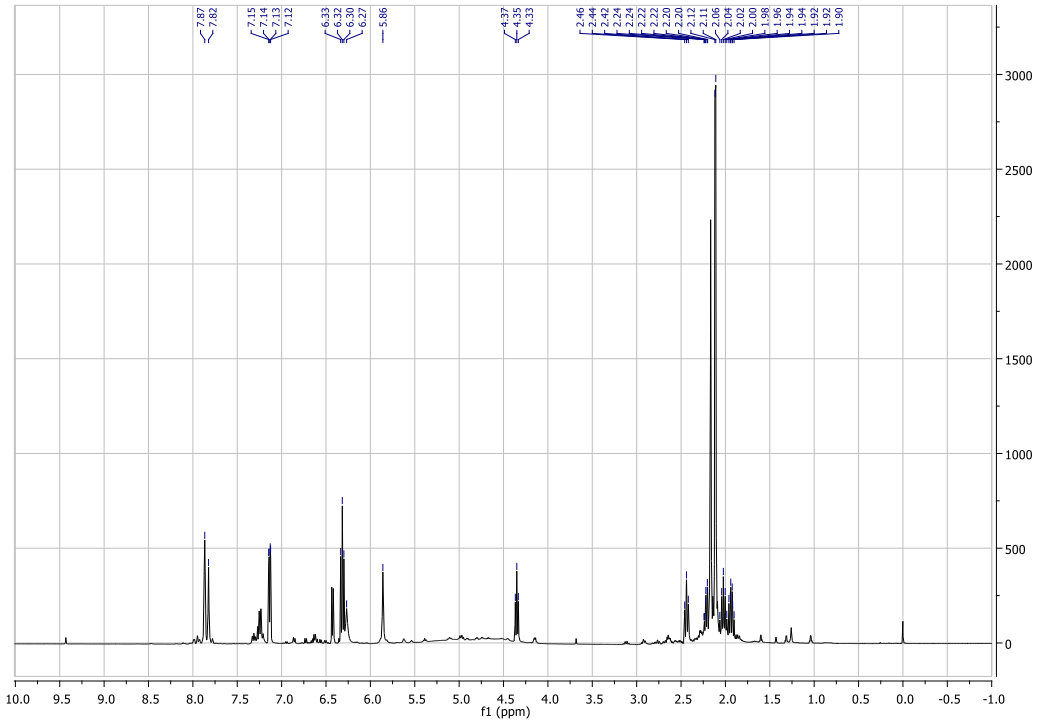
N

3d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4.33
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2.42
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2.24
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2.22
2.20
2.20
2.12
2.11
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1.94
1.92
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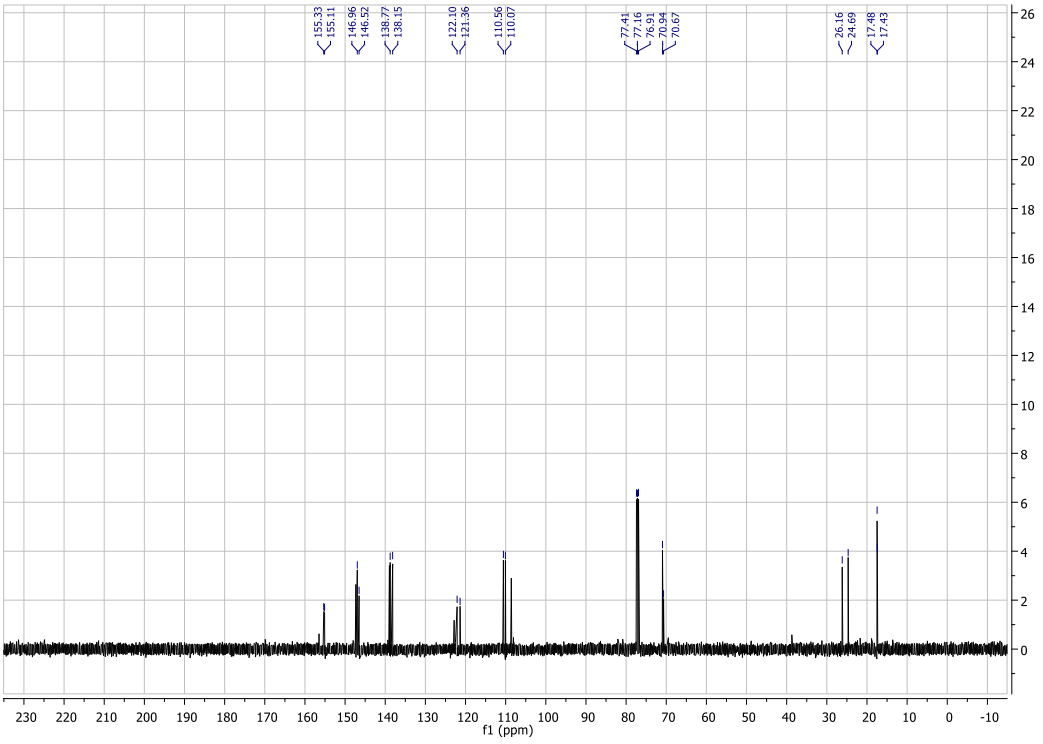
1.90
f1 (ppm)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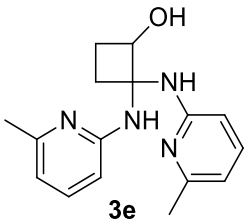
f1 (ppm)



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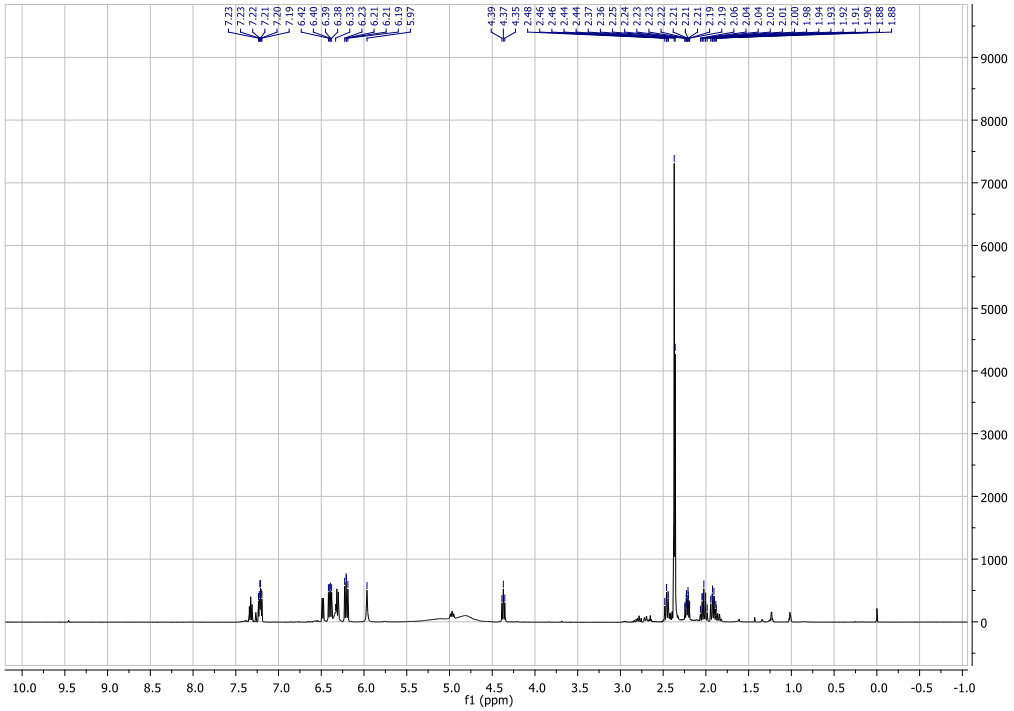

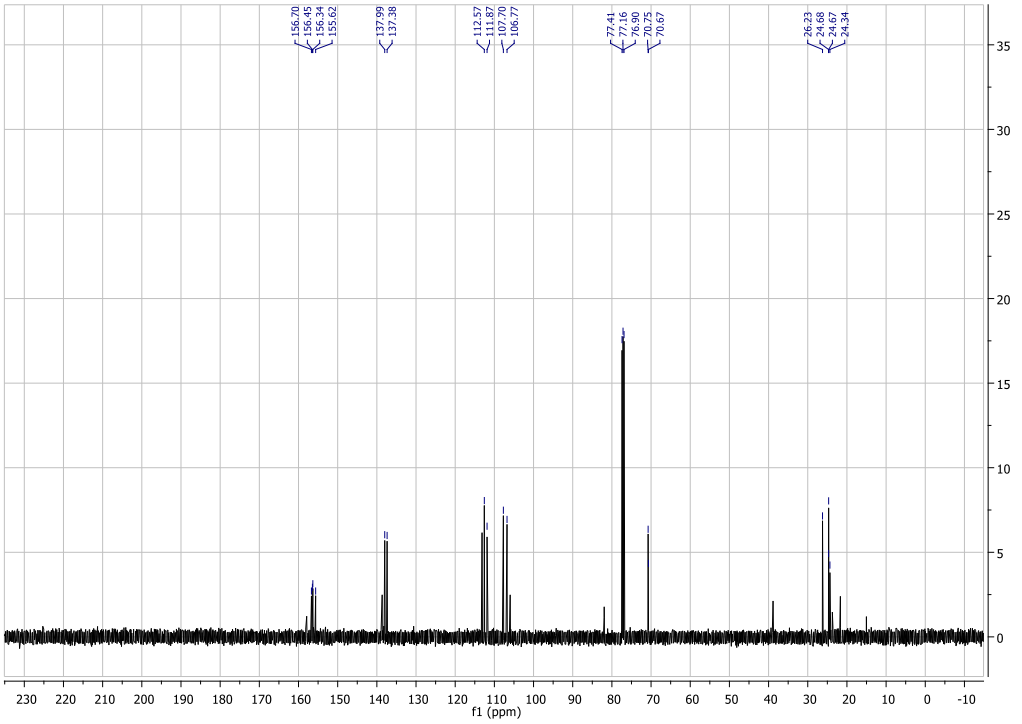

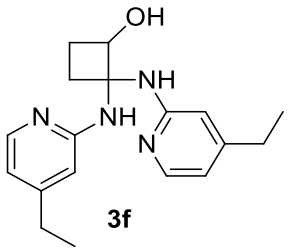
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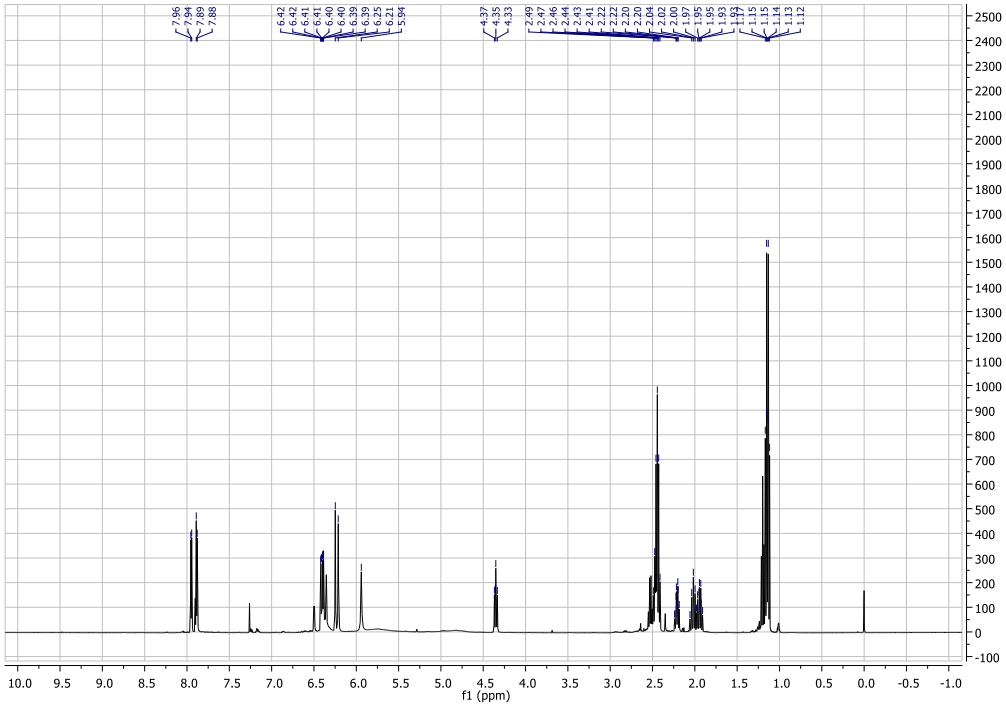
N
NH
N

3f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4.37
4.35
4.33
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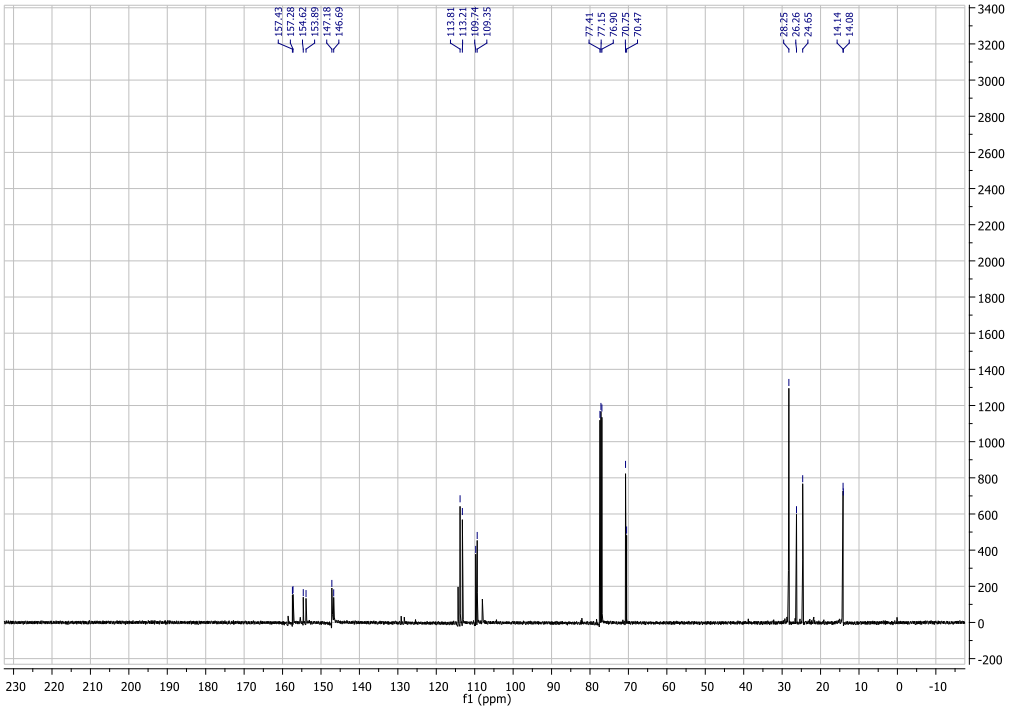
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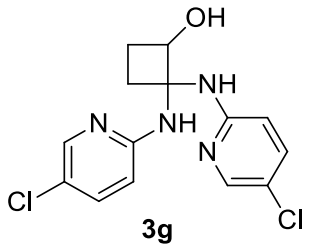
14.08
f1 (ppm)



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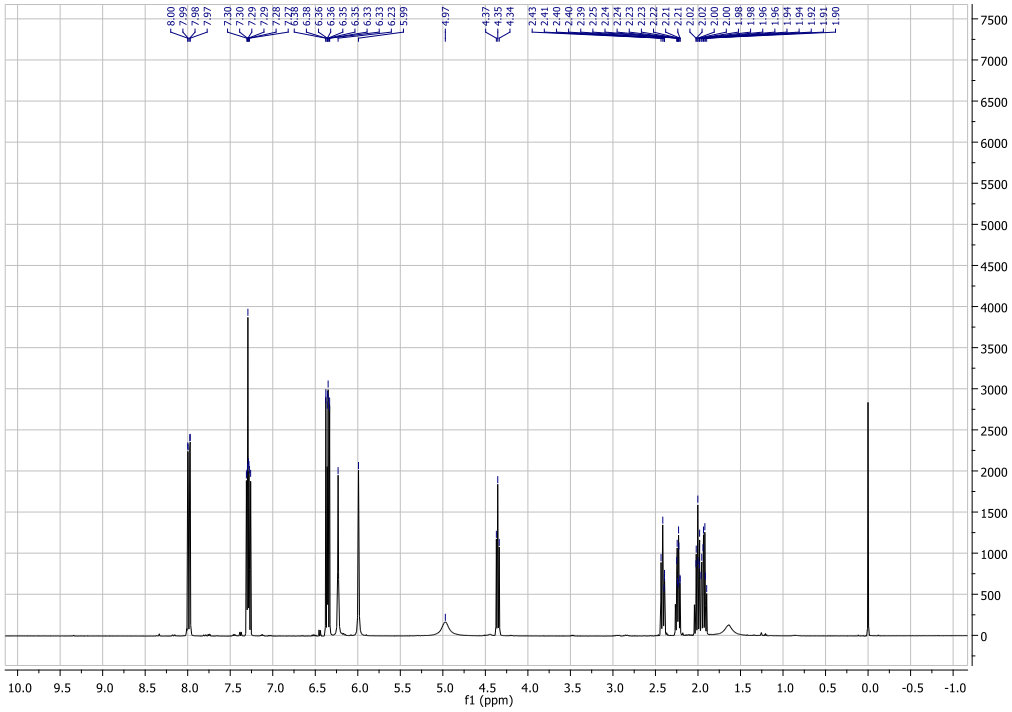

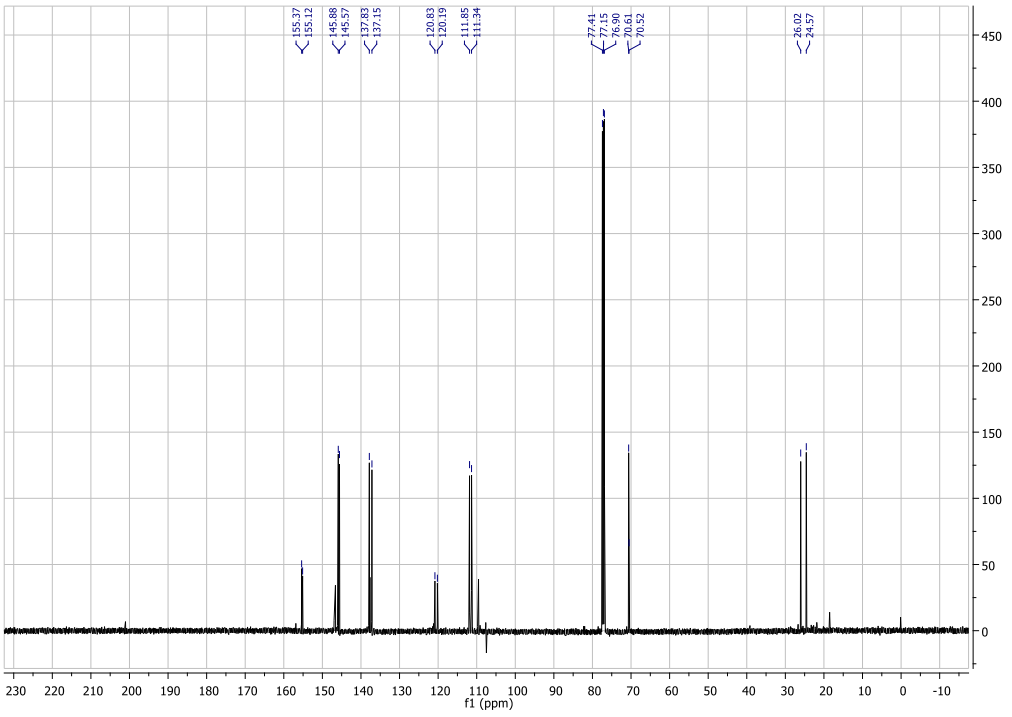

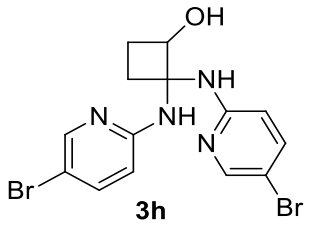
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NH
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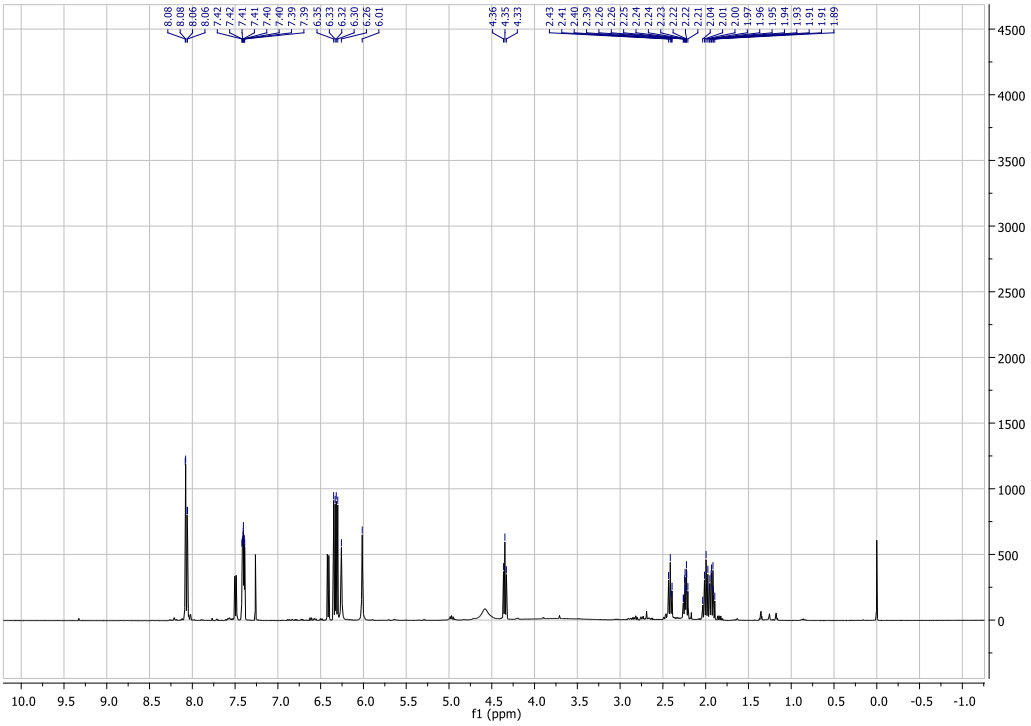
Br
Br

3h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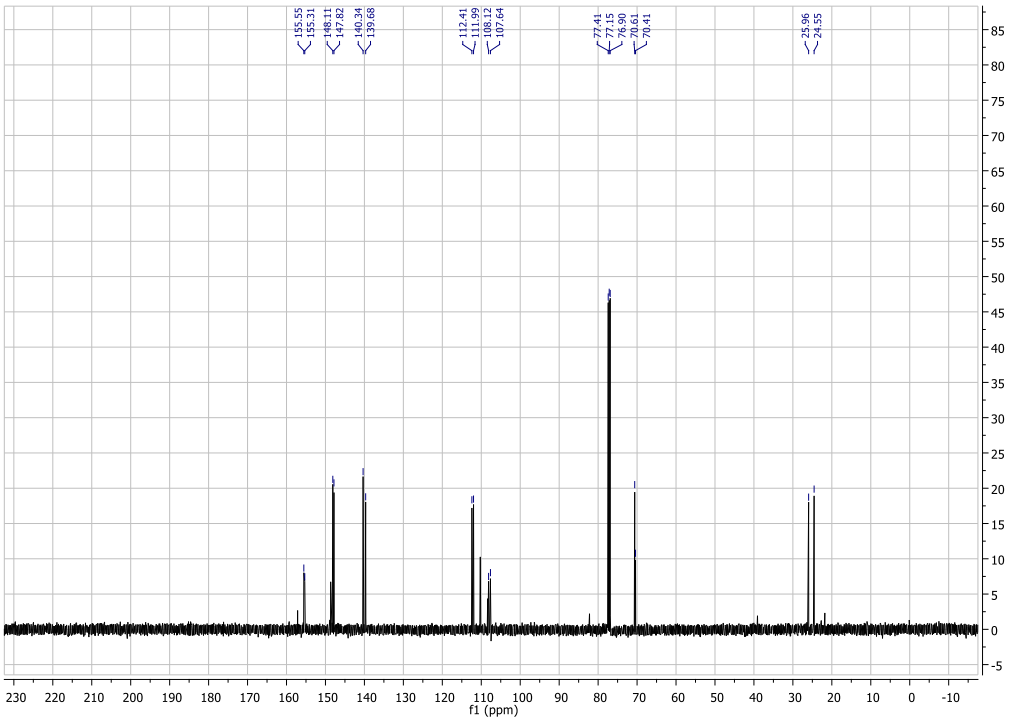
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24.55
85
80
75
70
65
60
55
50
45
40
35
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-5
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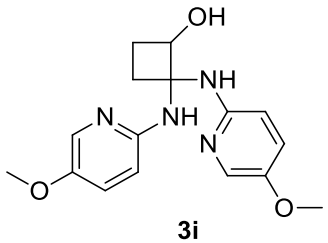
f1 (ppm)



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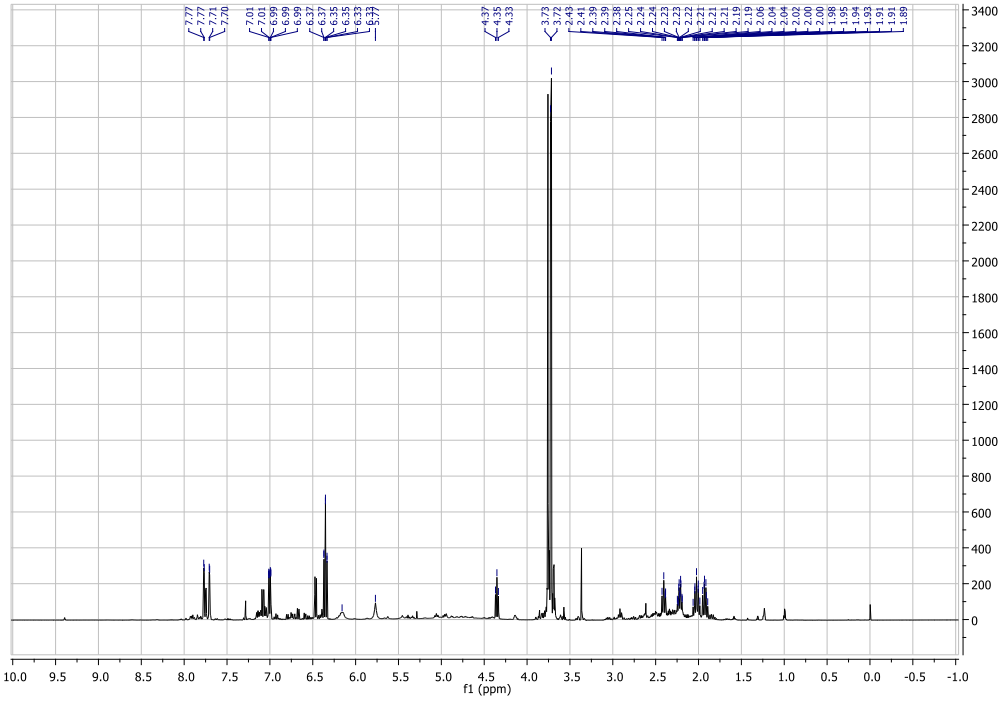

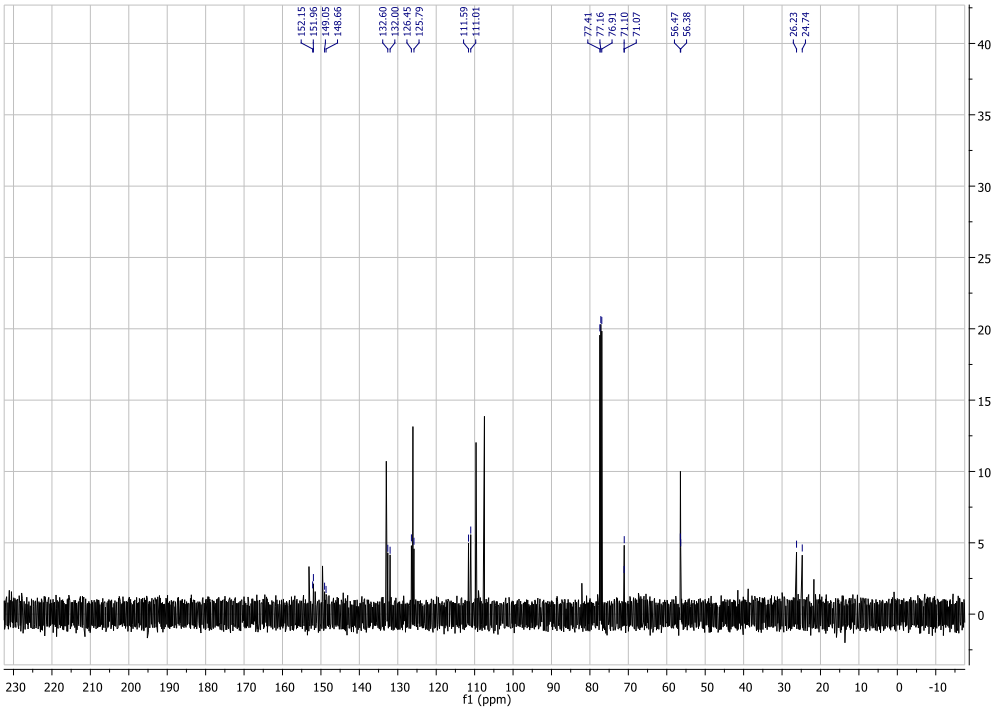

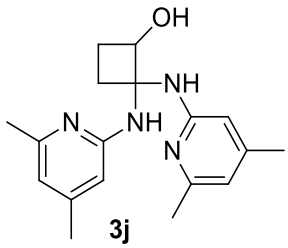
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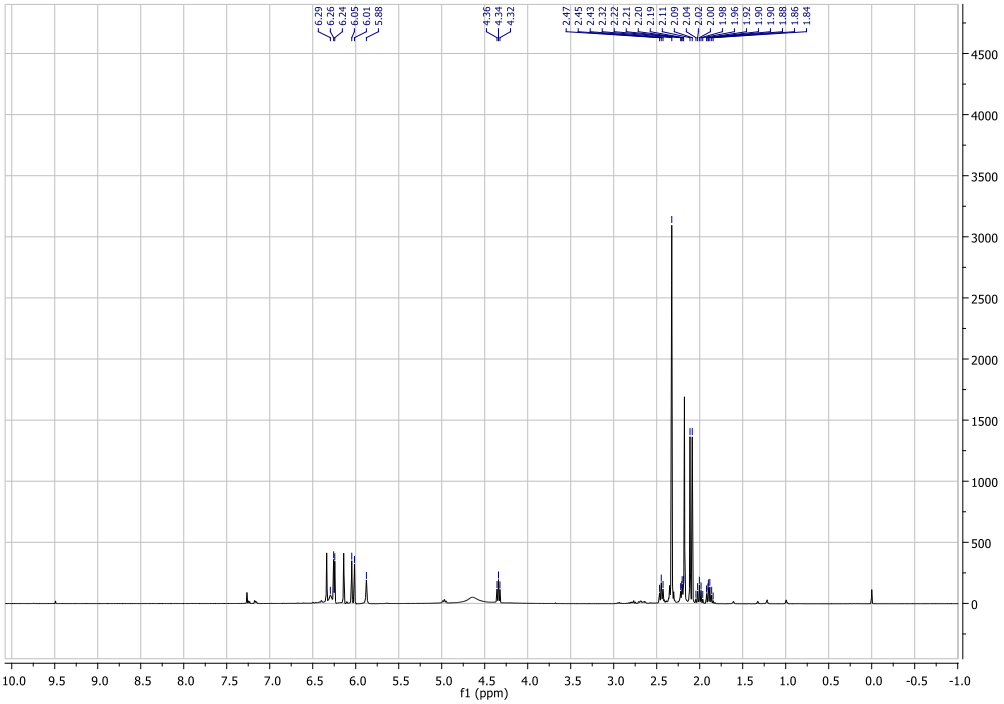
NH
N

3j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2.22
2.21
2.20
2.19
2.11
2.09
2.04
2.02
2.00
1.98
1.96
1.92
1.90
1.90
1.88
1.86
1.84
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3500
3000
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1500
1000
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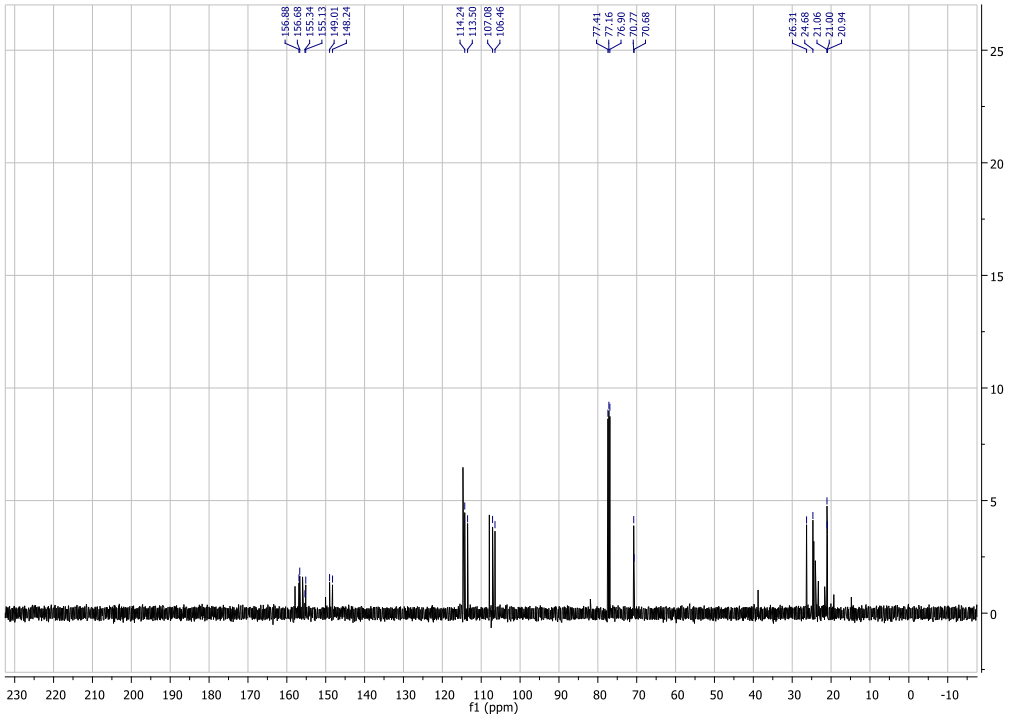
f1 (ppm)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70.77
70.68
26.31
24.68
21.06
21.00
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20
15
10
5
0
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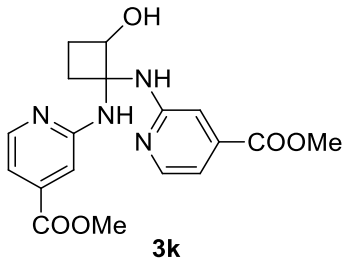
f1 (ppm)


OH
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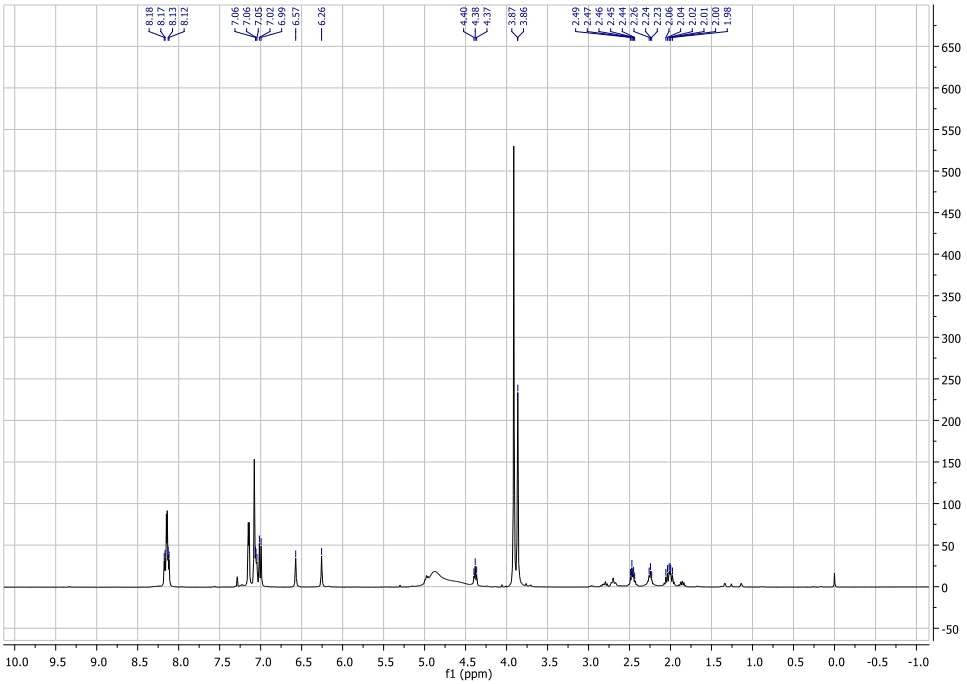
N
NH
N
COOMe
COOMe

3k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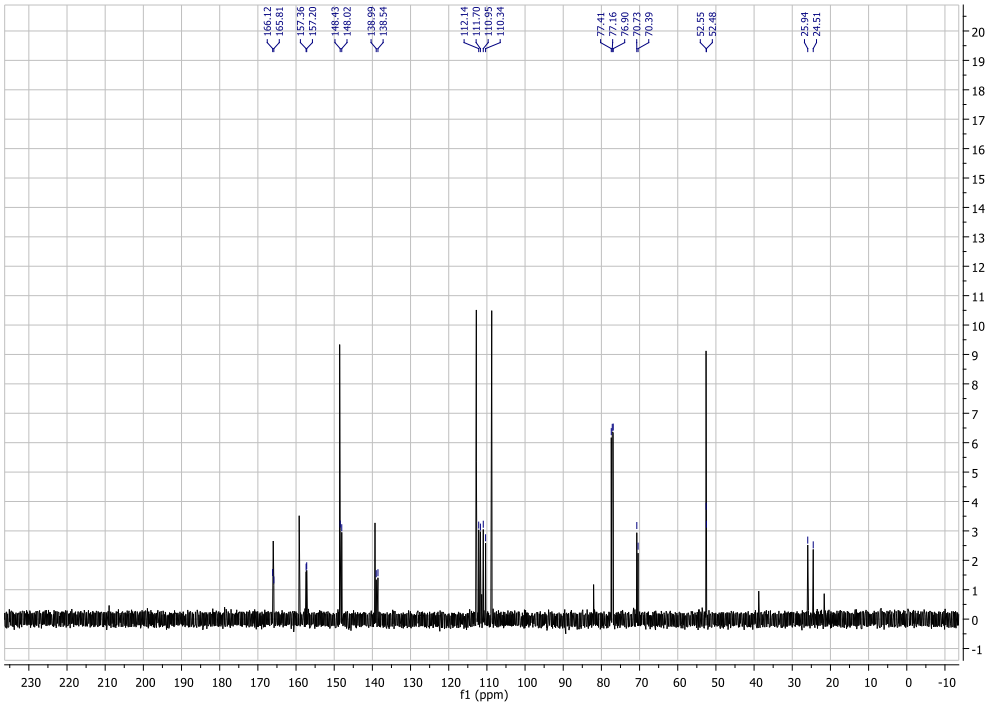
8.17
8.13
8.12
7.06
7.06
7.05
7.03
6.99
6.57
6.26
4.40
4.38
4.37
3.87
3.86
2.49
2.47
2.46
2.45
2.44
2.26
2.24
2.23
2.06
2.04
2.02
2.01
2.00
1.98
f1 (ppm)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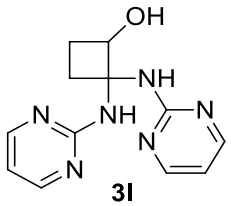
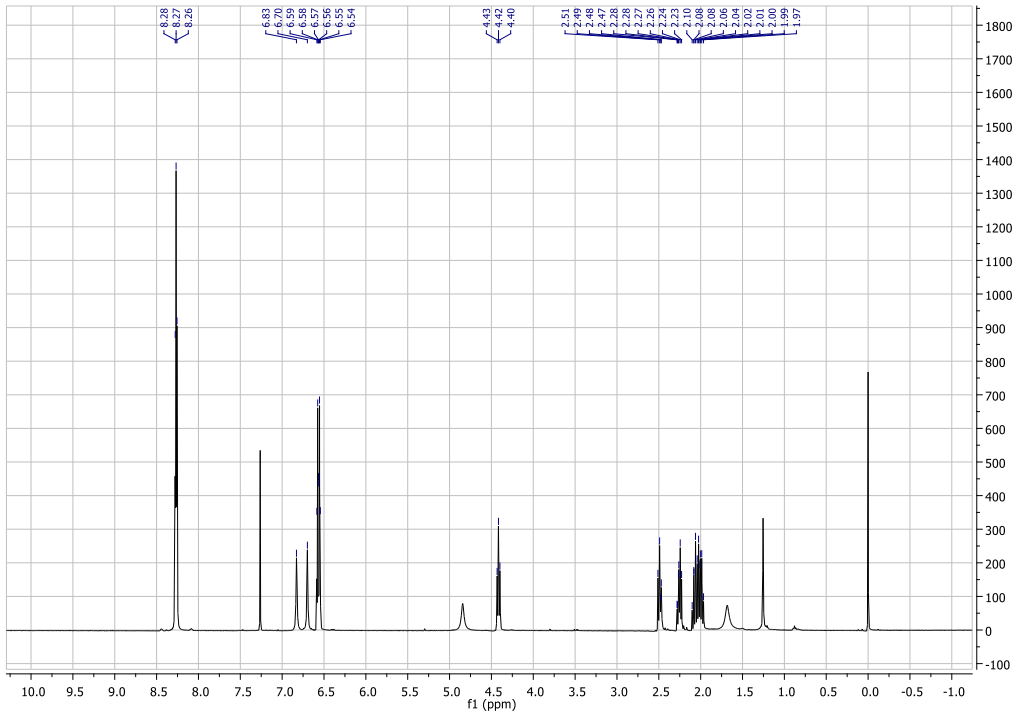
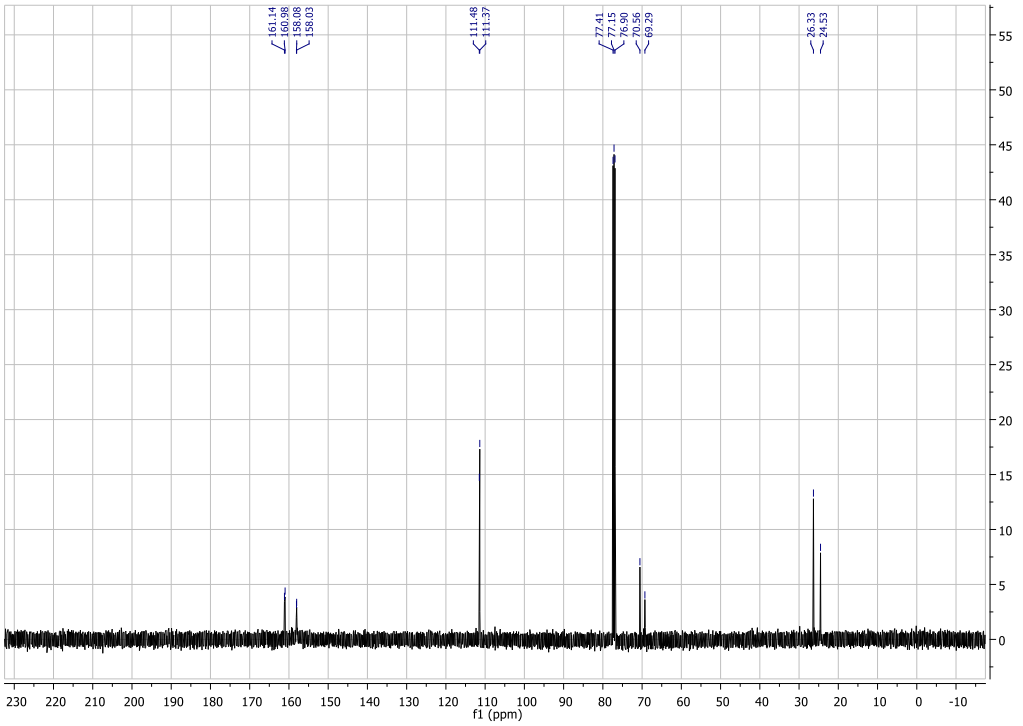
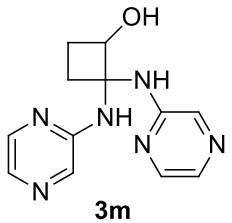
165.81
157.36
157.20
148.43
148.02
138.99
138.94
112.14
111.70
110.95
110.34
77.41
77.16
76.90
70.73
70.39
52.55
52.48
25.94
24.51
f1 (ppm)


OH
NH
NH
N
N
N
N

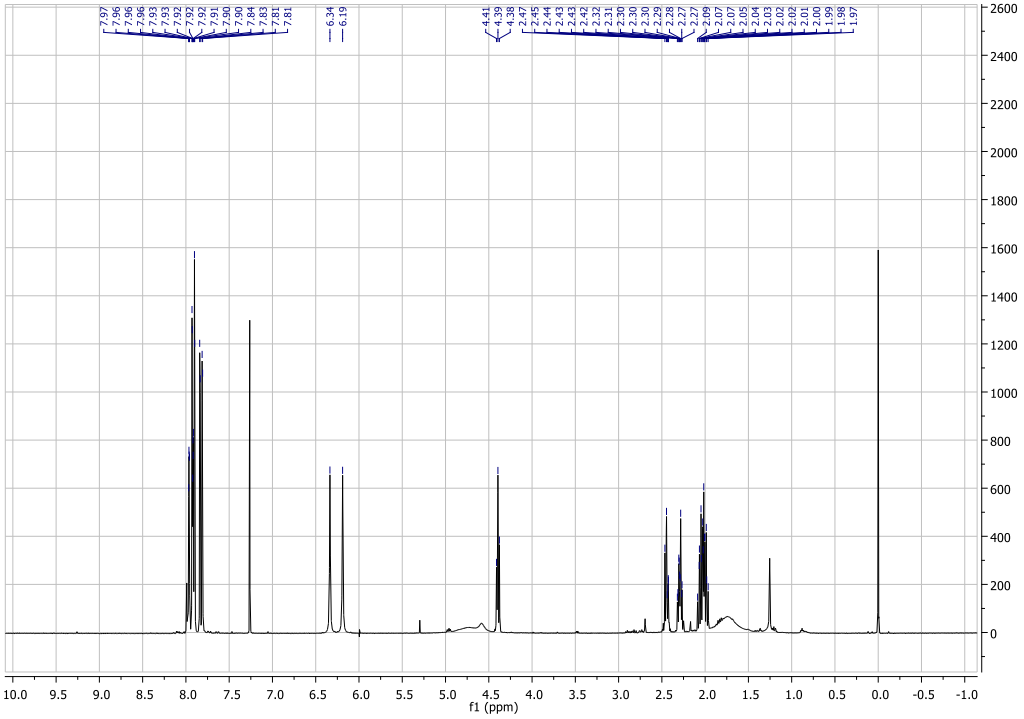
3l

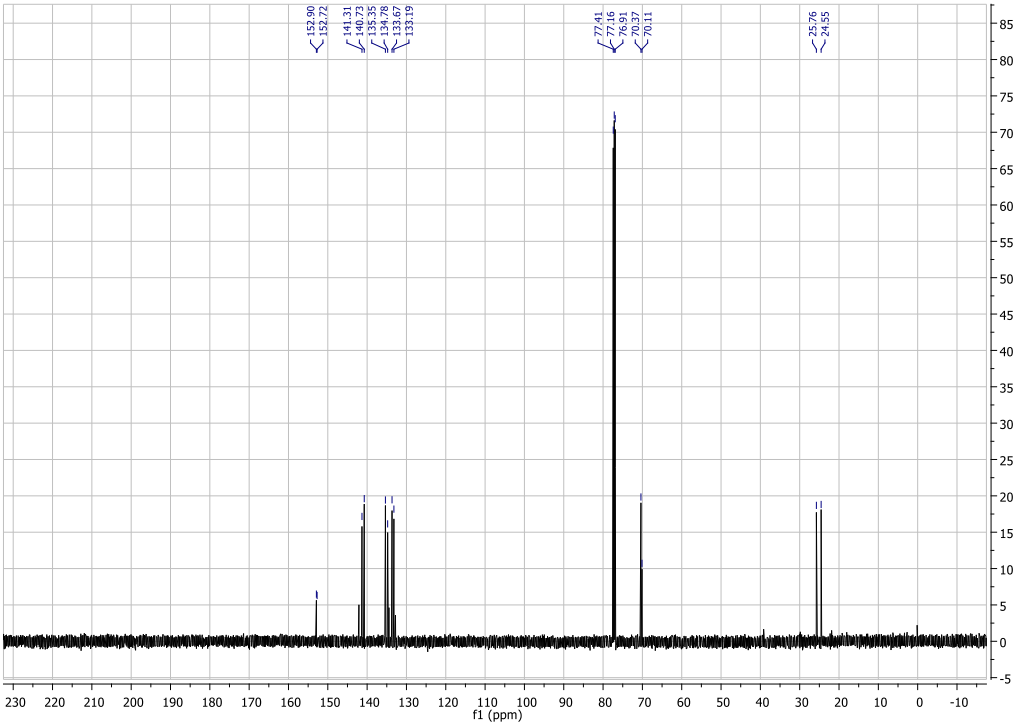

8.28
8.27
8.26
6.83
6.70
6.59
6.58
6.57
6.56
6.55
6.54
4.43
4.42
4.40
2.51
2.49
2.48
2.47
2.28
2.27
2.26
2.24
2.23
2.10
2.08
2.08
2.06
2.04
2.02
2.01
2.00
1.99
1.97
f1 (ppm)

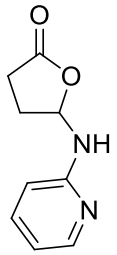

161.14
160.98
158.08
158.03
111.48
111.37
77.41
77.15
76.90
70.56
69.29
26.33
24.53
f1 (ppm)


OH
NH
N
NH
N
N
N

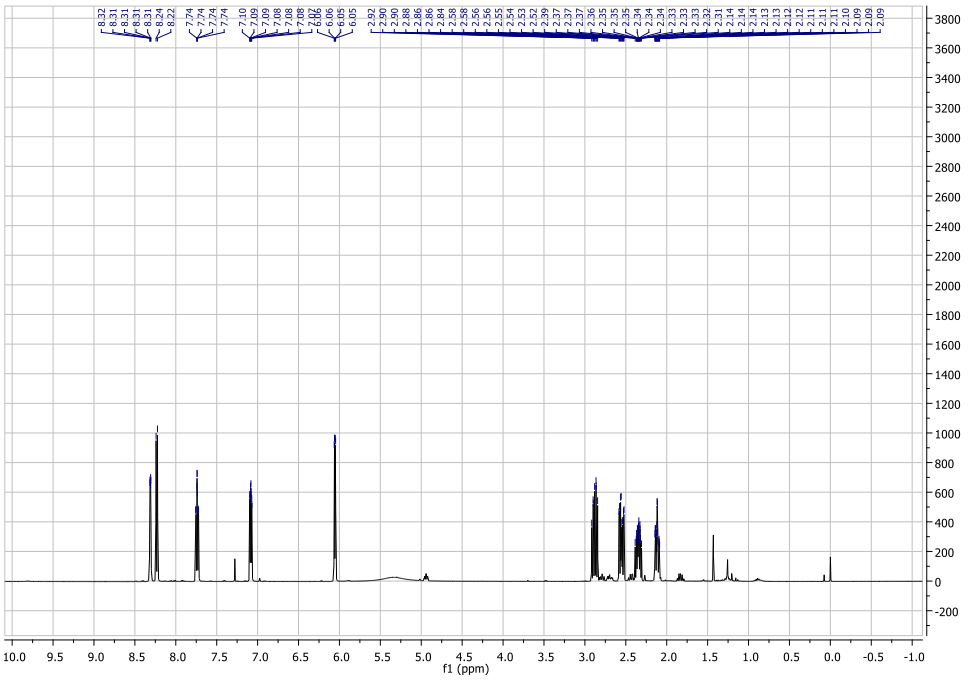
3m

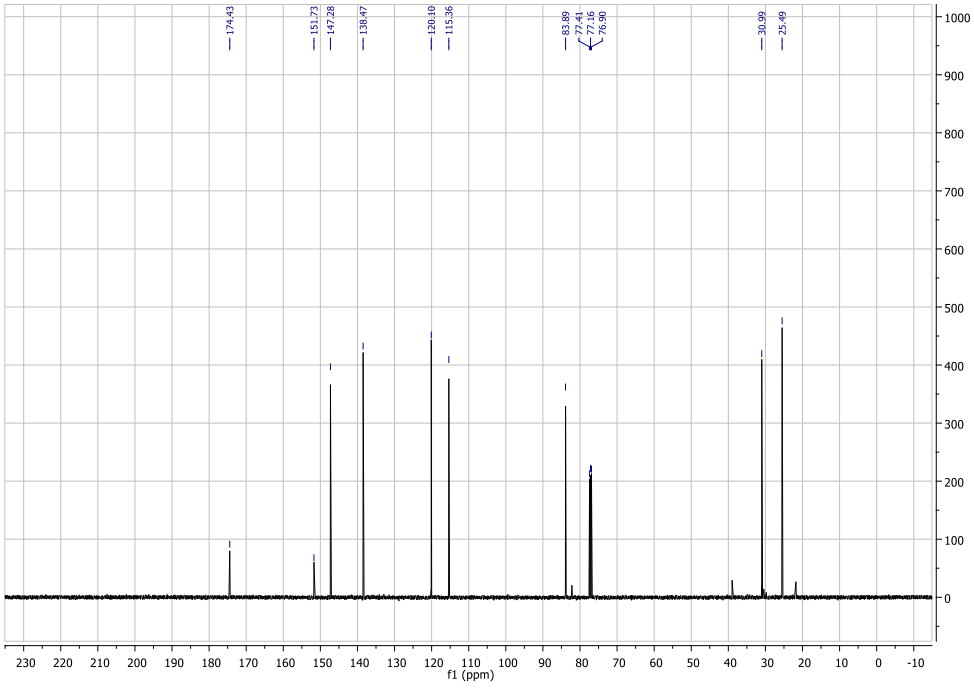

7.97
7.96
7.96
7.96
7.93
7.93
7.92
7.92
7.91
7.90
7.90
7.84
7.83
7.81
7.81
6.34
6.19
4.41
4.39
4.38
2.47
2.45
2.44
2.43
2.43
2.42
2.32
2.31
2.30
2.30
2.30
2.29
2.28
2.27
2.27
2.09
2.07
2.07
2.05
2.04
2.03
2.02
2.02
2.01
2.00
1.98
1.98
1.97
f1 (ppm)

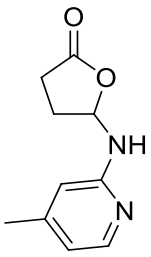

152.90
152.72
141.31
140.73
135.35
134.78
133.67
133.19
77.41
77.16
76.91
70.37
70.11
25.76
24.55
f1 (ppm)


O
O
NH
N

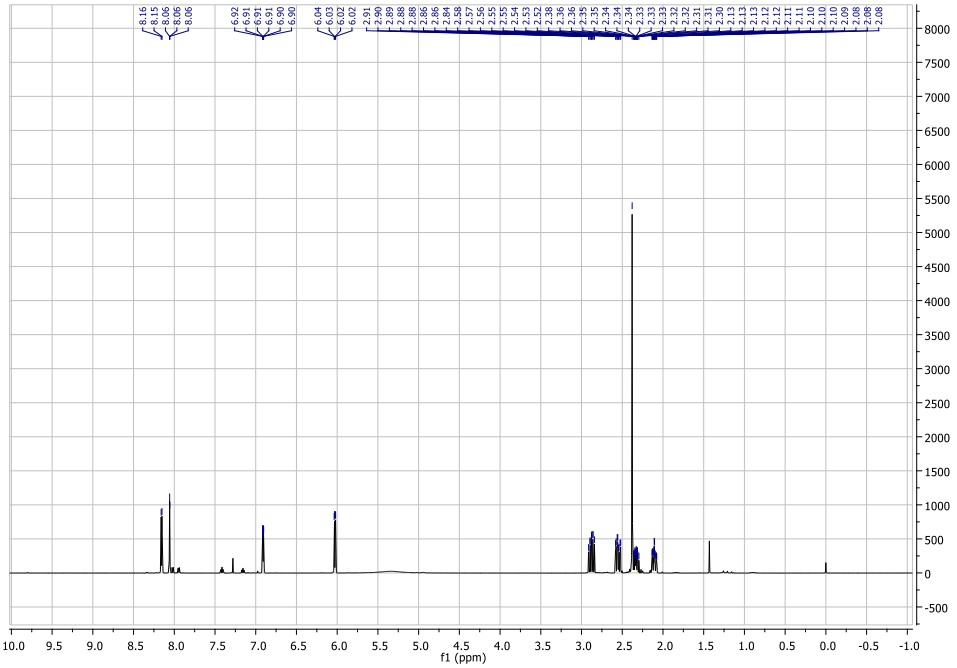
7a


f1 (ppm)


174.43
151.73
147.28
138.47
120.10
115.36
83.89
77.41
77.16
76.90
30.99
25.49
f1 (ppm)


O
O
NH
N

7c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8.15
8.06
8.06
8.06
6.92
6.91
6.91
6.91
6.90
6.90
6.04
6.03
6.02
6.02
2.91
2.90
2.89
2.89
2.88
2.88
2.86
2.86
2.84
2.84
2.58
2.57
2.56
2.55
2.55
2.54
2.53
2.52
2.38
2.36
2.36
2.35
2.34
2.34
2.34
2.33
2.33
2.33
2.32
2.32
2.31
2.31
2.30
2.13
2.13
2.13
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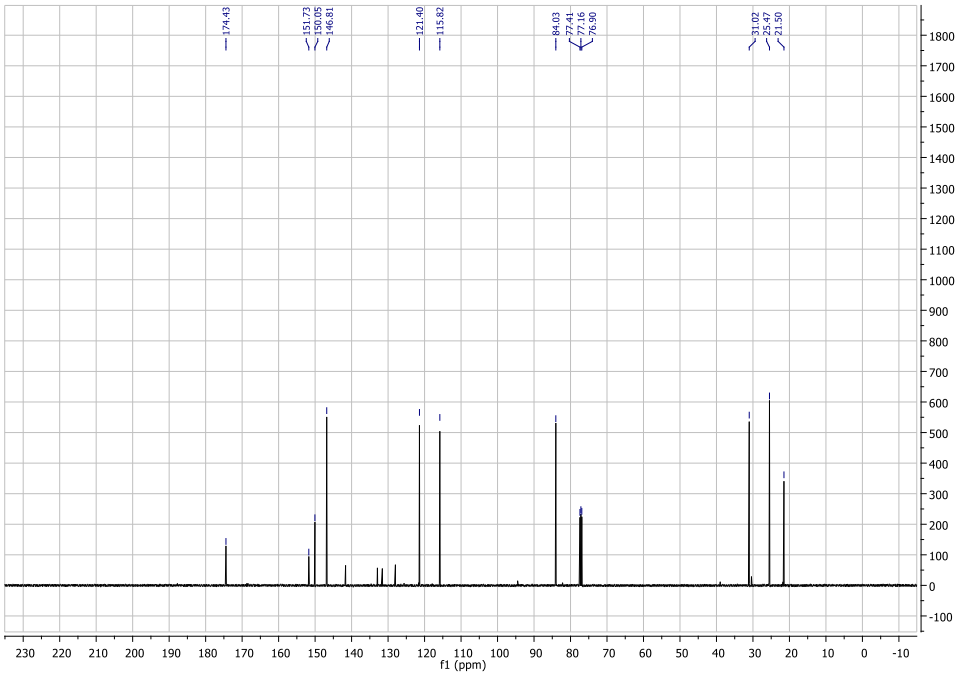
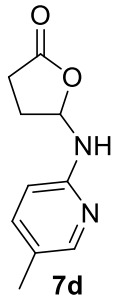
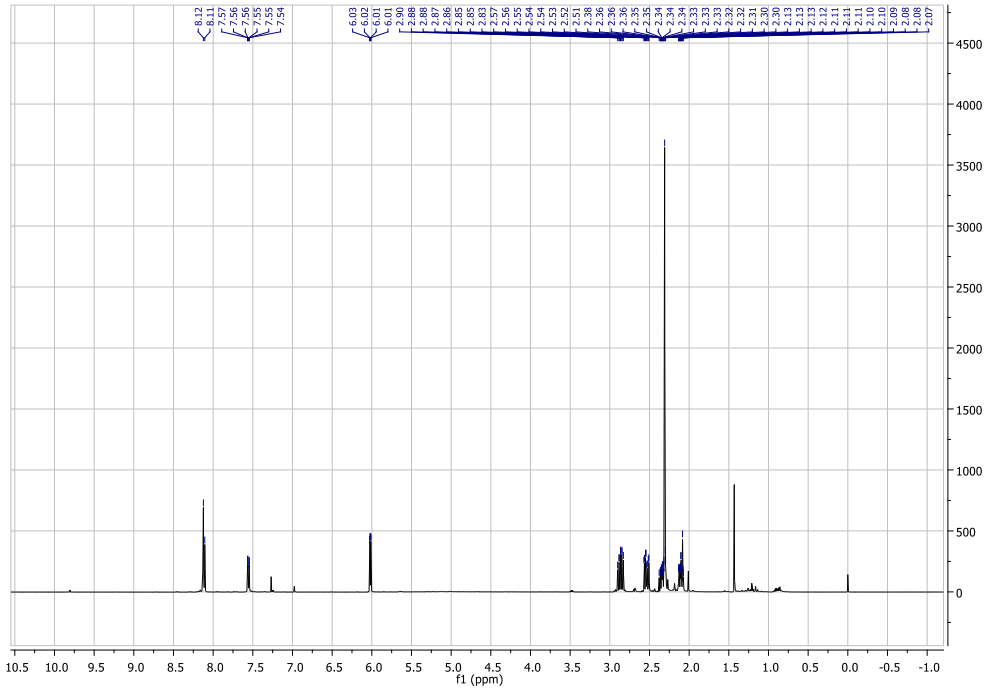
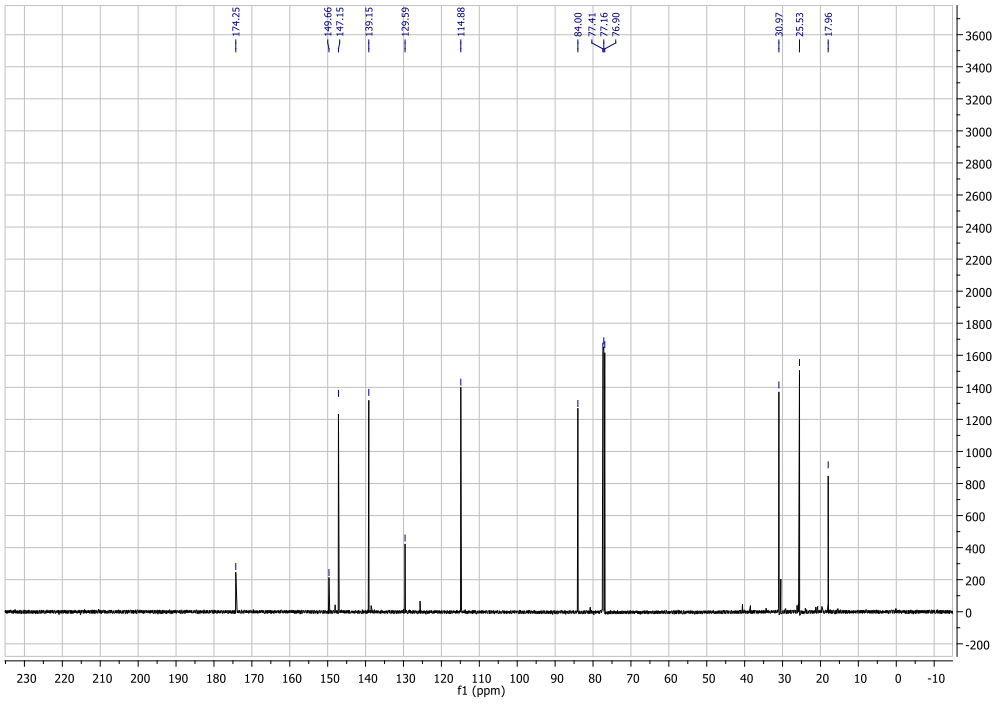
2.09
2.08
2.08
2.08
f1 (ppm)


174.43
151.73
150.05
146.81
121.40
115.82
84.03
77.41
77.16
76.90
31.02
25.47
21.50
f1 (ppm)


O
O
NH
N

7d


8.12
8.11
7.57
7.56
7.56
7.55
7.55
7.54
6.03
6.02
6.01
6.01
2.90
2.88
2.88
2.87
2.86
2.85
2.85
2.83
2.57
2.56
2.55
2.54
2.54
2.53
2.52
2.51
2.38
2.36
2.36
2.36
2.35
2.35
2.34
2.34
2.34
2.33
2.33
2.33
2.32
2.32
2.31
2.30
2.30
2.13
2.13
2.13
2.12
2.11
2.11
2.11
2.10
2.10
2.09
2.08
2.08
2.08
2.07
4500
4000
3500
3000
2500
2000
1500
1000
500
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
f1 (ppm)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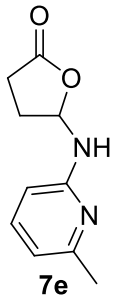
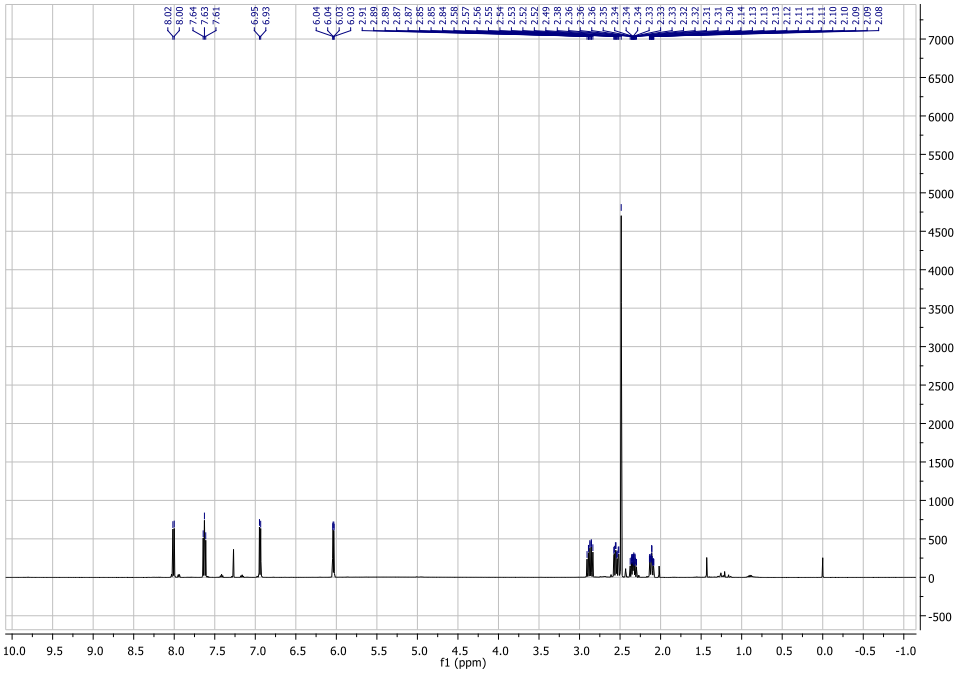
149.66
147.15
139.15
129.59
114.88
84.00
77.41
77.16
76.90
30.97
25.53
17.96
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
NH
N

7e


8.02
8.00
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7.63
7.61
6.95
6.93
6.04
6.04
6.03
6.03
2.91
2.89
2.89
2.87
2.87
2.85
2.85
2.84
2.58
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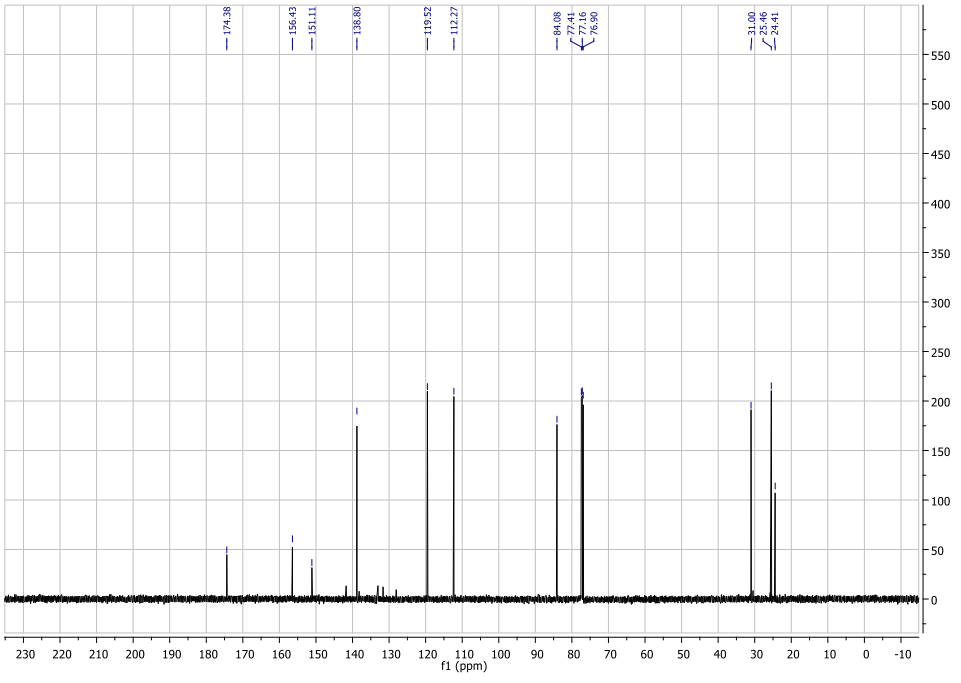
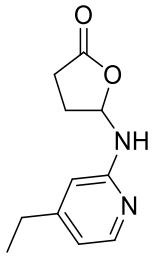
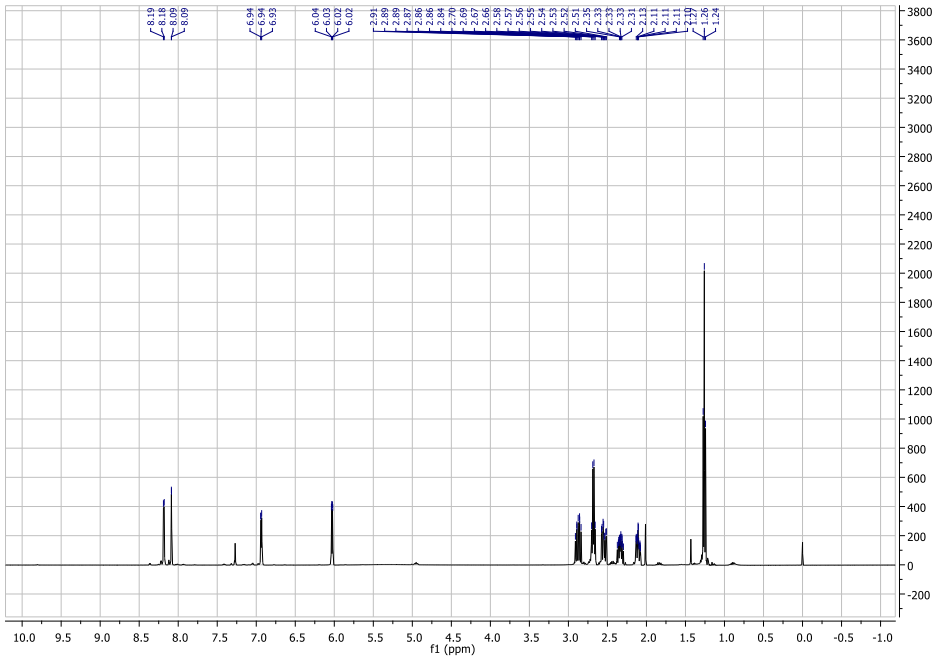
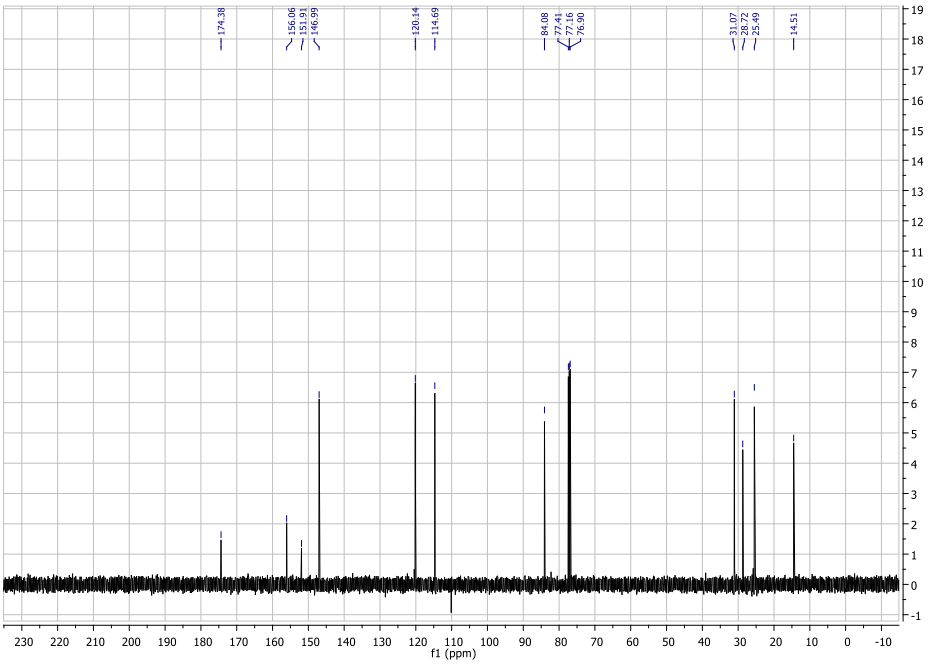
2.56
2.55
2.54
2.53
2.52
2.52
2.49
2.48
2.36
2.36
2.36
2.35
2.34
2.34
2.34
2.33
2.33
2.32
2.32
2.31
2.31
2.30
2.14
2.13
2.13
2.12
2.11
2.11
2.11
2.10
2.10
2.09
2.08
2.08
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

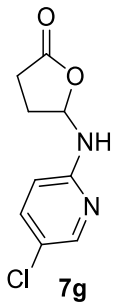

174.38
156.43
151.11
138.80
119.52
112.27
84.08
77.41
77.16
76.90
31.00
25.46
24.41
550
500
450
400
350
300
250
200
150
100
50
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
NH
N

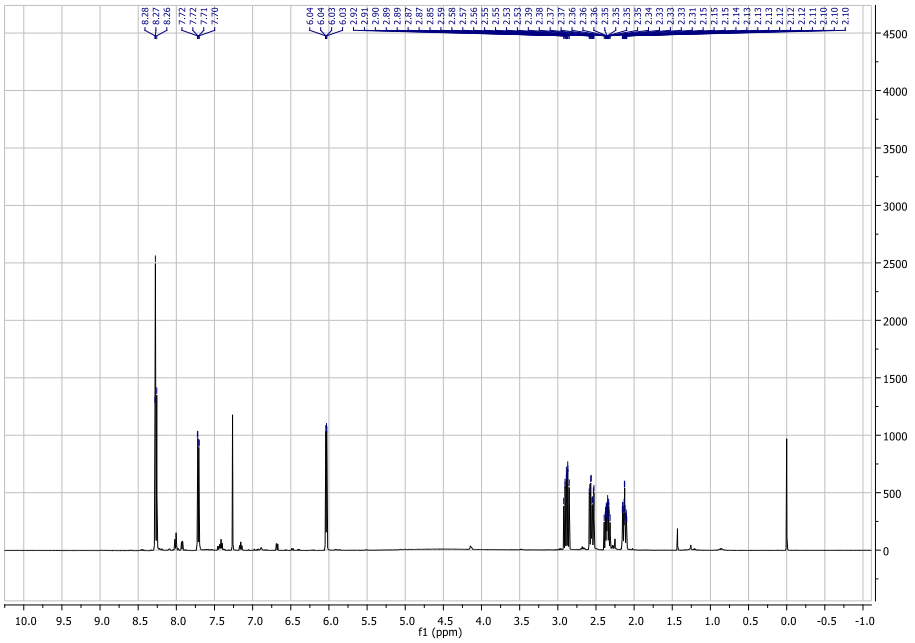
7f


8.19
8.18
8.09
8.09
6.94
6.94
6.93
6.04
6.03
6.03
6.02
2.91
2.89
2.89
2.87
2.86
2.86
2.84
2.70
2.69
2.67
2.66
2.58
2.57
2.56
2.55
2.54
2.53
2.52
2.51
2.35
2.33
2.33
2.31
2.13
2.11
2.11
2.11
1.27
1.26
1.24
f1 (ppm)


174.38
156.06
151.91
146.99
120.14
114.69
84.08
77.41
77.16
76.90
31.07
28.72
25.49
14.51
f1 (ppm)


O
O
NH
N
Cl

7g


8.28
8.27
8.26
7.72
7.72
7.71
7.70
6.04
6.04
6.03
6.03
2.92
2.91
2.90
2.89
2.89
2.88
2.87
2.85
2.59
2.58
2.57
2.56
2.55
2.55
2.53
2.39
2.38
2.37
2.37
2.36
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2.34
2.33
2.33
2.31
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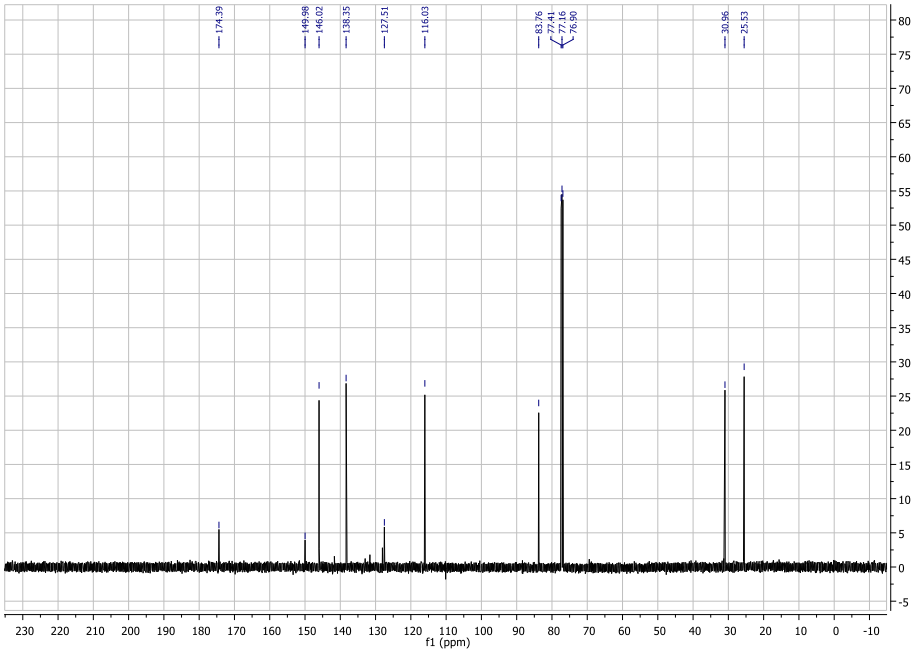
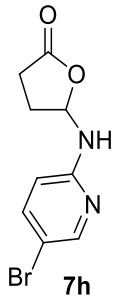
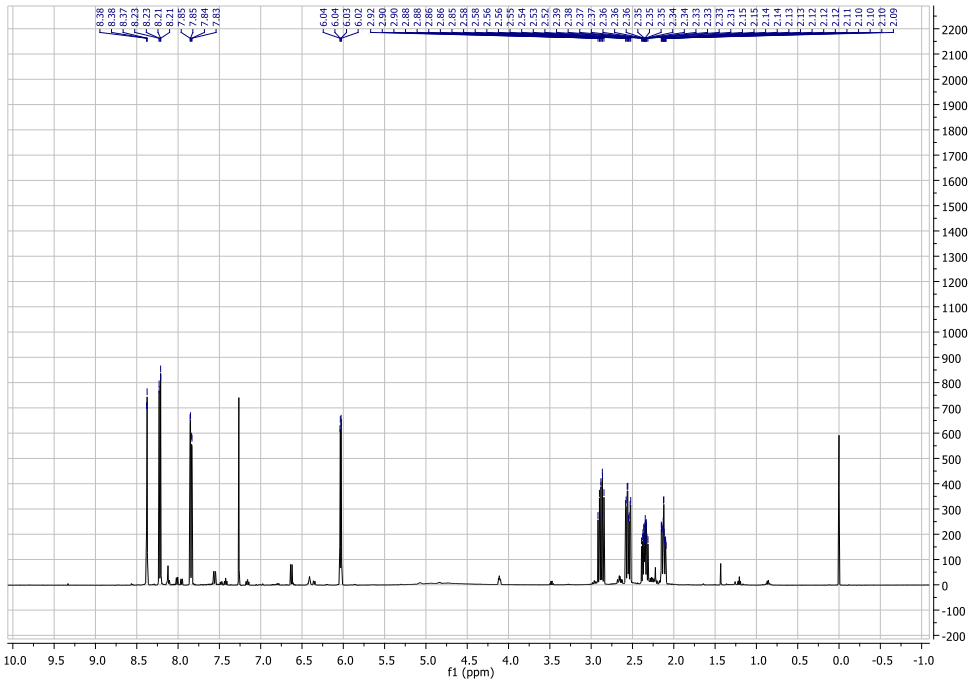
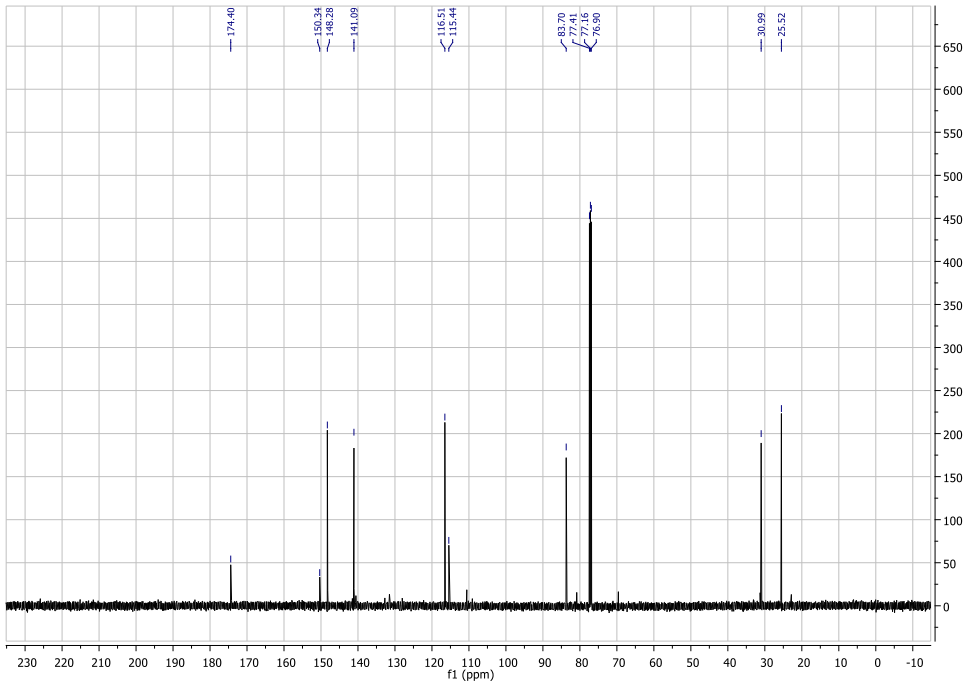
2.15
2.15
2.14
2.13
2.13
2.13
2.12
2.12
2.12
2.11
2.10
2.10
2.10
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

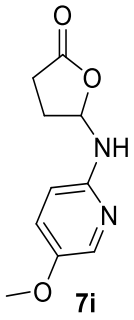

174.39
149.98
146.02
138.35
127.51
116.03
83.76
77.41
77.16
76.90
30.96
25.53
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
NH
N
Br

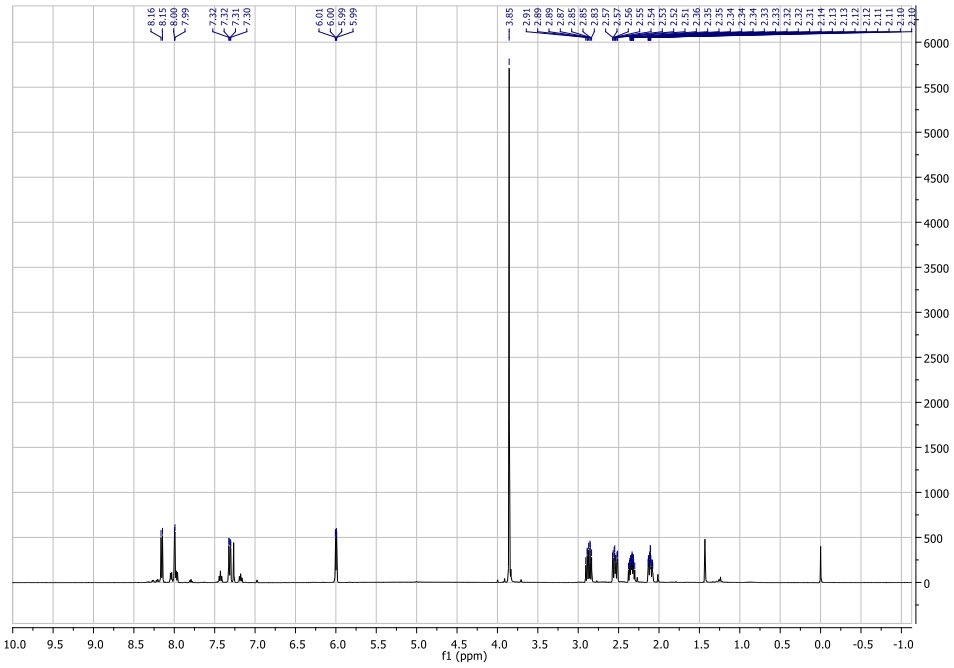
7h


f1 (ppm)


174.40
150.34
148.28
141.09
116.51
115.44
83.70
77.41
77.16
76.90
30.99
25.52
f1 (ppm)


O
O
NH
N
O

7i


8.16
8.15
8.00
7.99
7.32
7.32
7.31
7.30
6.01
6.00
5.99
5.99
3.85
2.91
2.89
2.89
2.87
2.85
2.85
2.83
2.57
2.57
2.56
2.56
2.55
2.54
2.53
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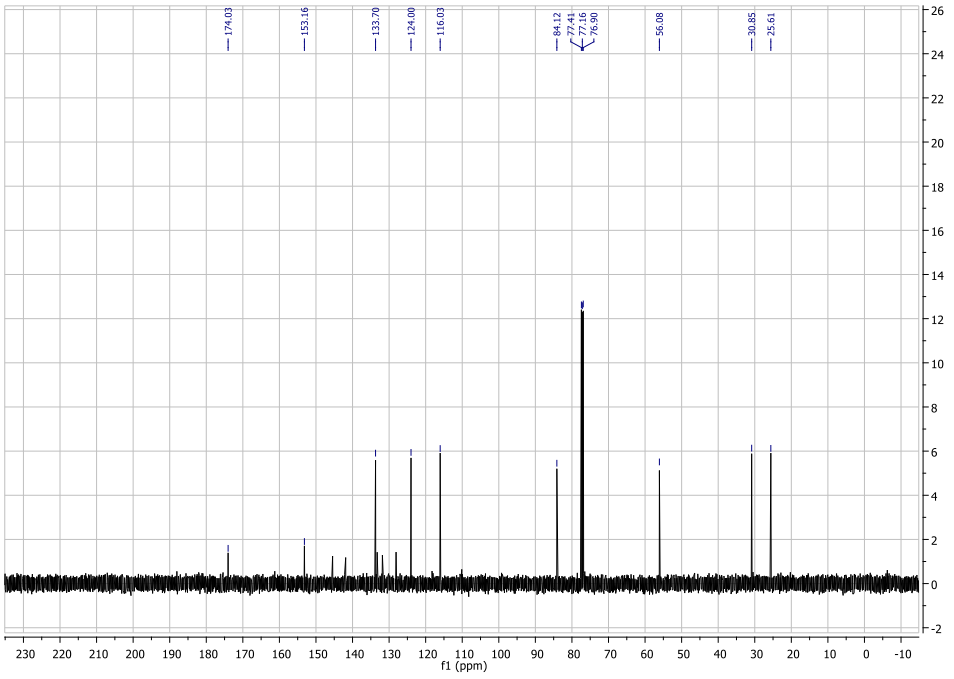
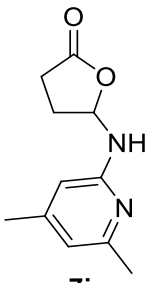
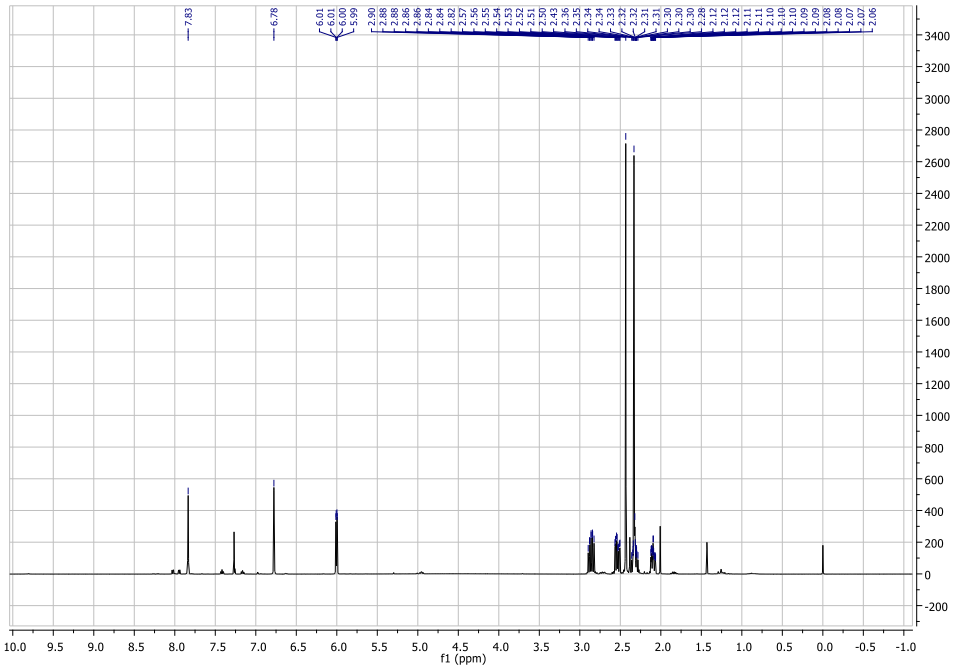
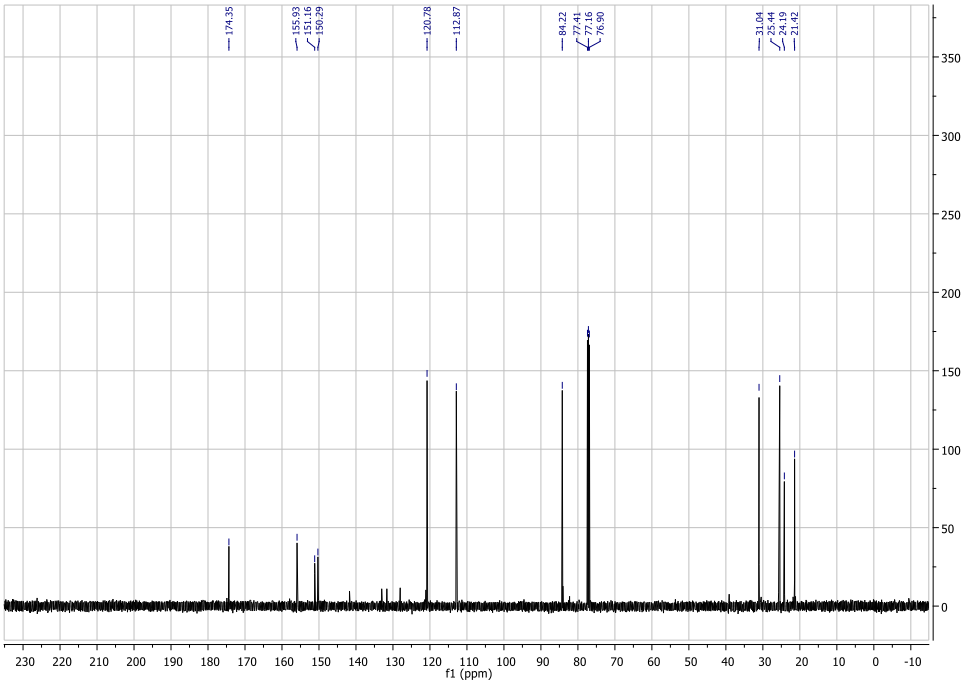
2.36
2.35
2.35
2.34
2.34
2.34
2.33
2.33
2.32
2.32
2.31
2.31
2.14
2.13
2.13
2.12
2.12
2.12
2.11
2.11
2.11
2.10
2.10
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

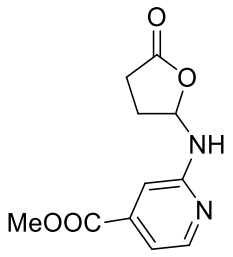

174.03
153.16
133.70
124.00
116.03
84.12
77.41
77.16
76.90
56.08
30.85
25.61
26
24
22
20
18
16
14
12
10
8
6
4
2
0
-2
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
NH
N

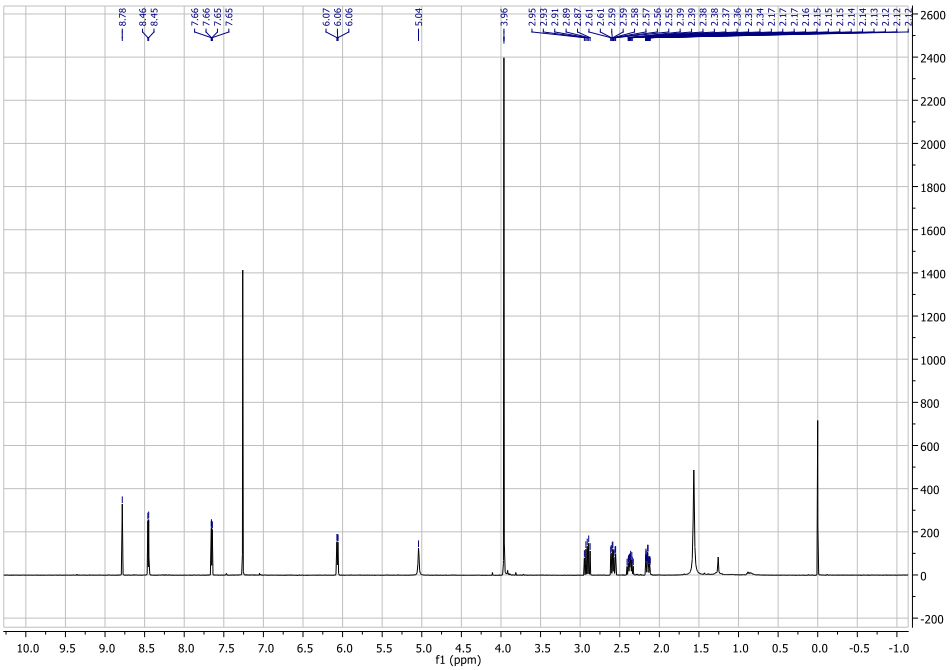
7j

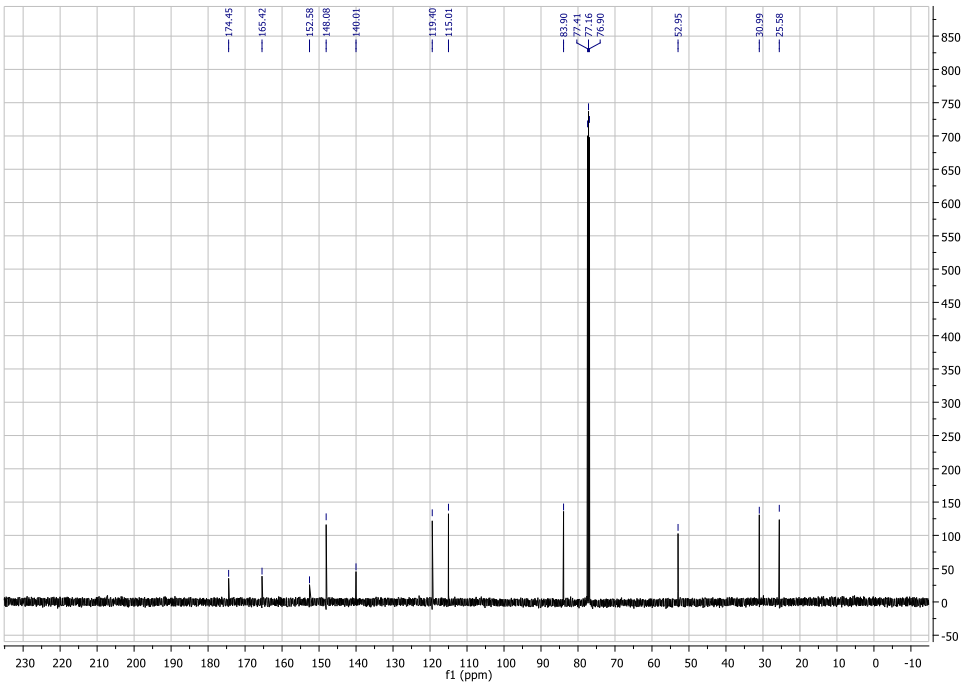

7.83
6.78
6.01
6.01
6.00
5.99
f1 (ppm)

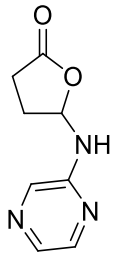

174.35
155.93
151.16
150.29
120.78
112.87
84.22
77.41
77.16
76.90
31.04
25.44
24.19
21.42
f1 (ppm)


O
O
NH
N
MeOOC

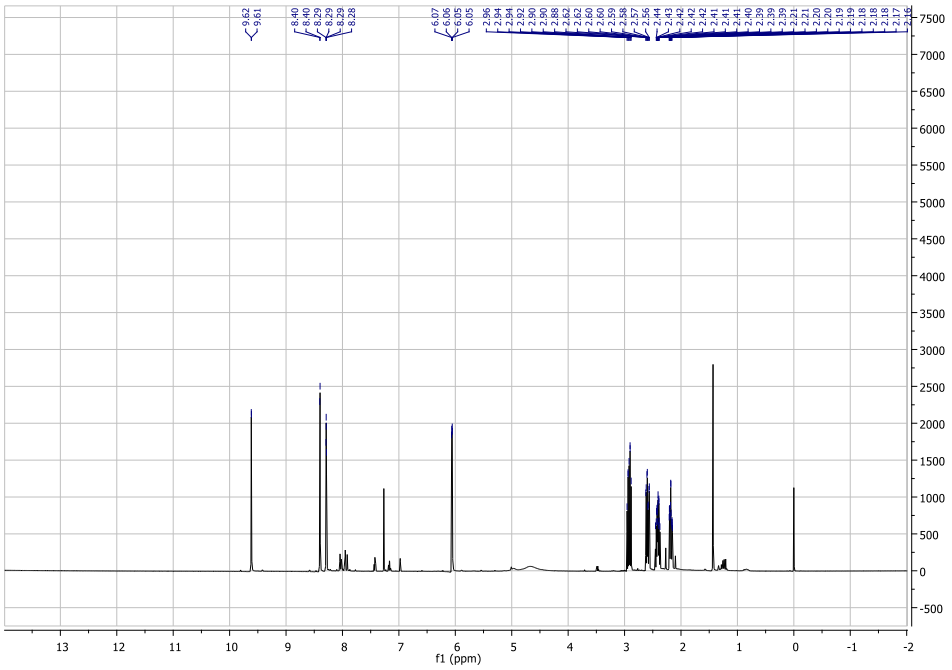
7k

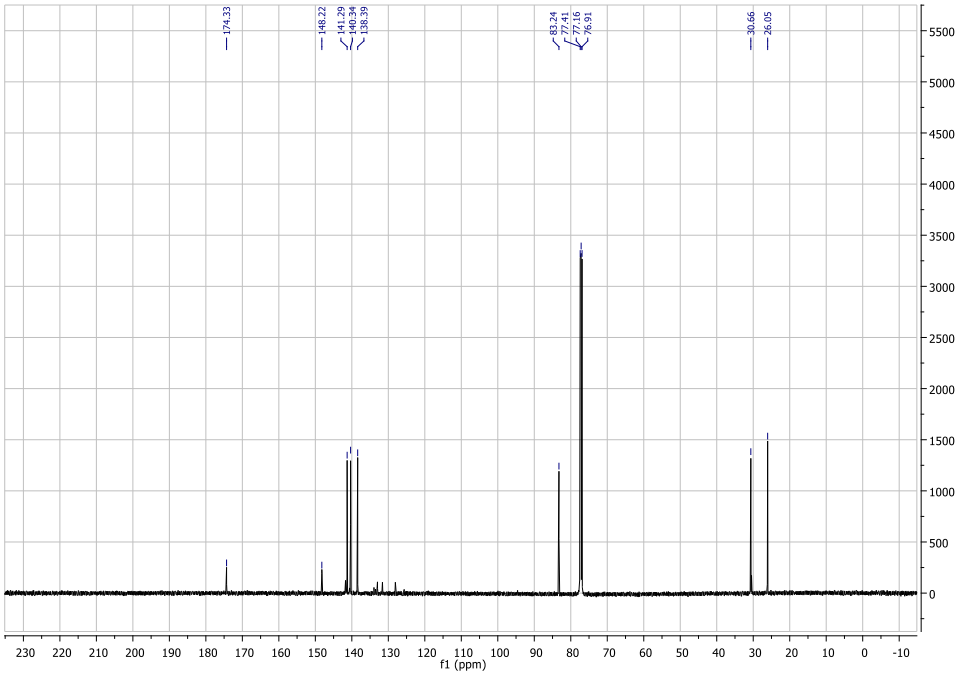

8.78
8.46
8.45
7.66
7.66
7.65
7.65
6.07
6.06
6.06
5.04
3.96
f1 (ppm)

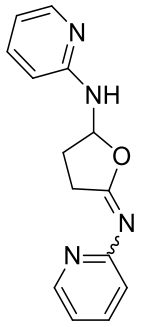

174.45
165.42
152.58
148.08
140.01
119.40
115.01
83.90
77.41
77.16
76.90
52.95
30.99
25.58
f1 (ppm)


O
O
NH
N
N

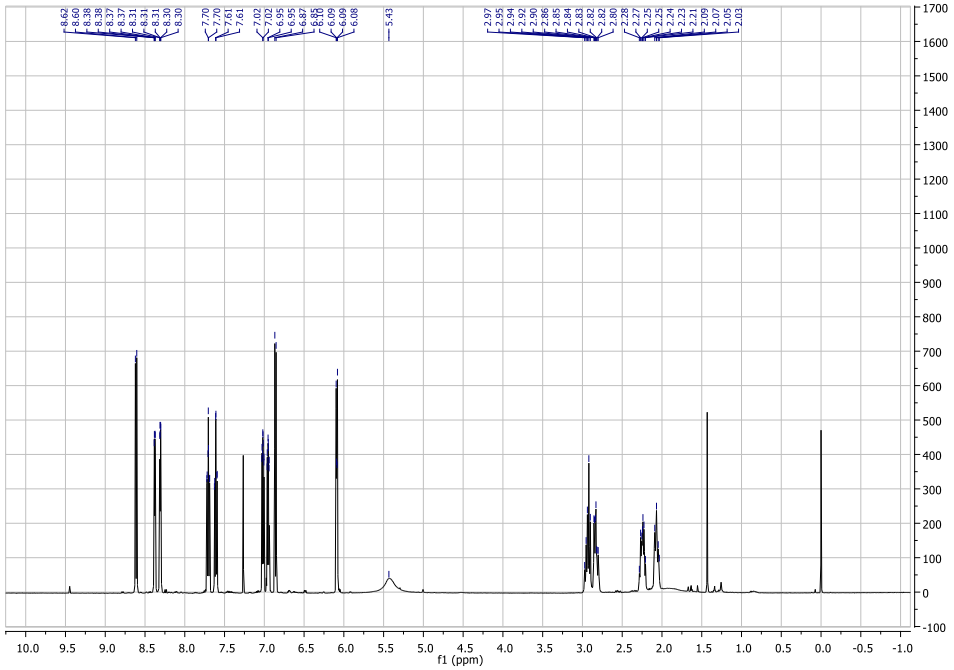
7m

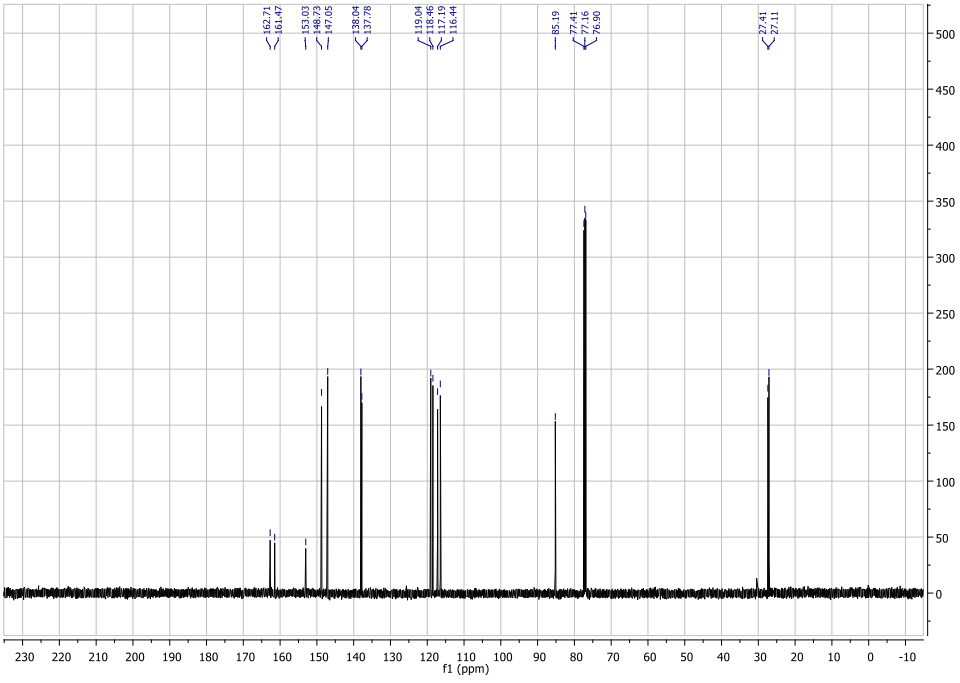

f1 (ppm)


174.33
148.22
141.29
140.34
138.39
83.24
77.41
77.16
76.91
30.66
26.05
f1 (ppm)



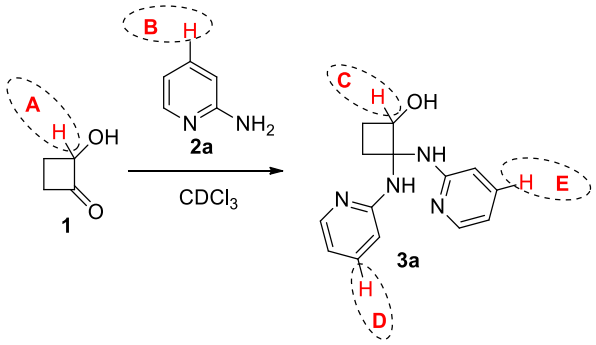
6

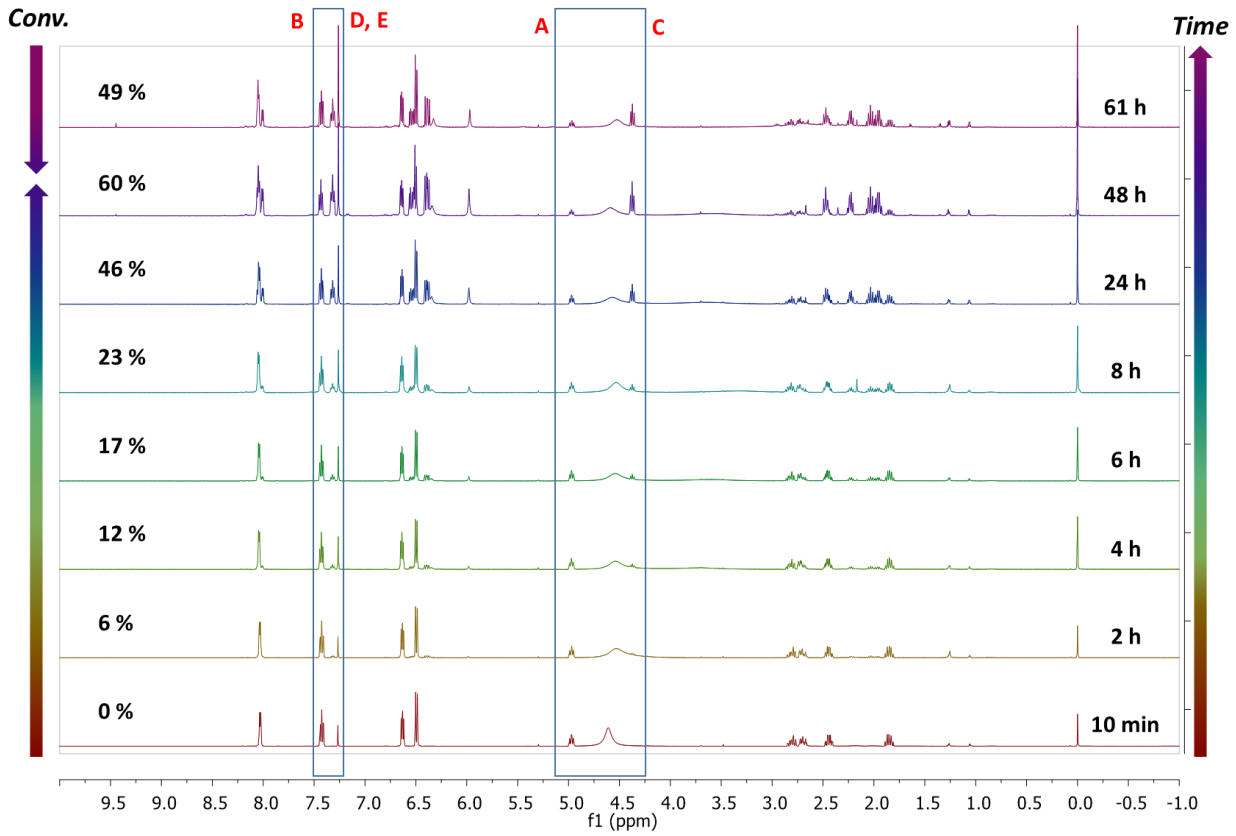

8.62
8.60
8.38
8.38
8.37
8.37
8.31
8.31
8.30
8.30
7.70
7.70
7.61
7.61
7.02
7.02
6.95
6.95
6.88
6.88
6.10
6.09
6.09
6.08
5.43
2.97
2.95
2.94
2.92
2.90
2.86
2.85
2.84
2.83
2.82
2.82
2.80
2.29
2.27
2.25
2.25
2.24
2.23
2.21
2.09
2.07
2.05
2.03
f1 (ppm)


162.71
161.47
153.03
148.73
147.05
138.04
137.78
119.04
118.46
117.19
116.44
85.19
77.41
77.16
76.90
27.41
27.11
f1 (ppm)

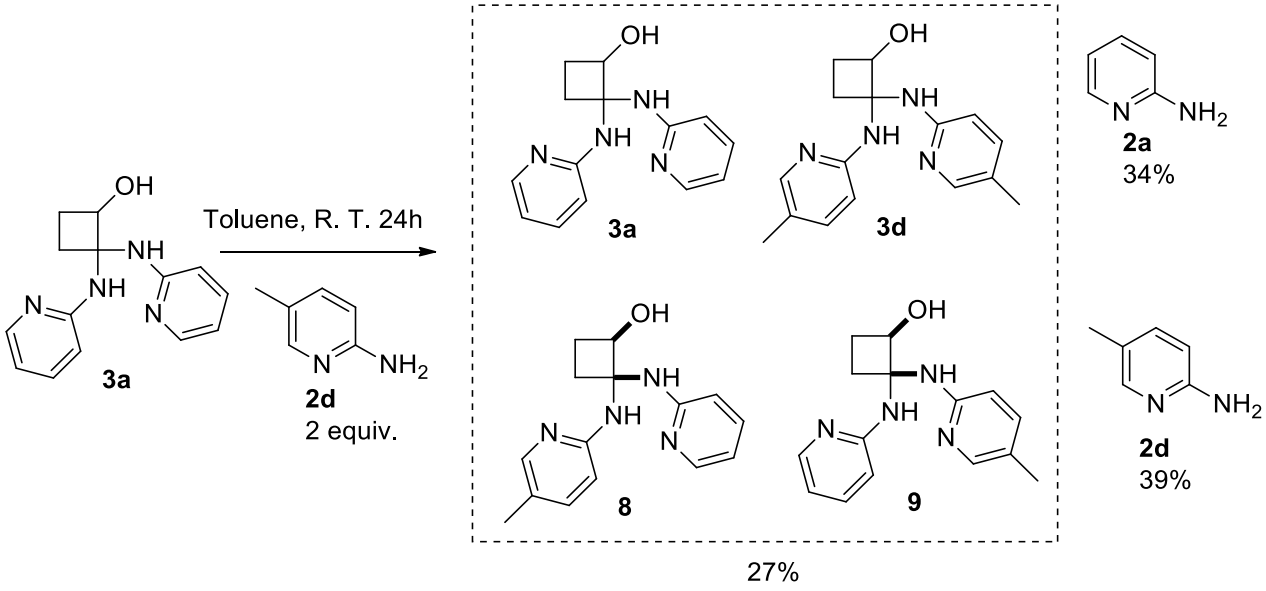
Preliminary characterization of the dynamic covalent reaction for the synthesis of 2,2-bis(aza-heteroaryl amino)cyclobutanols 3.

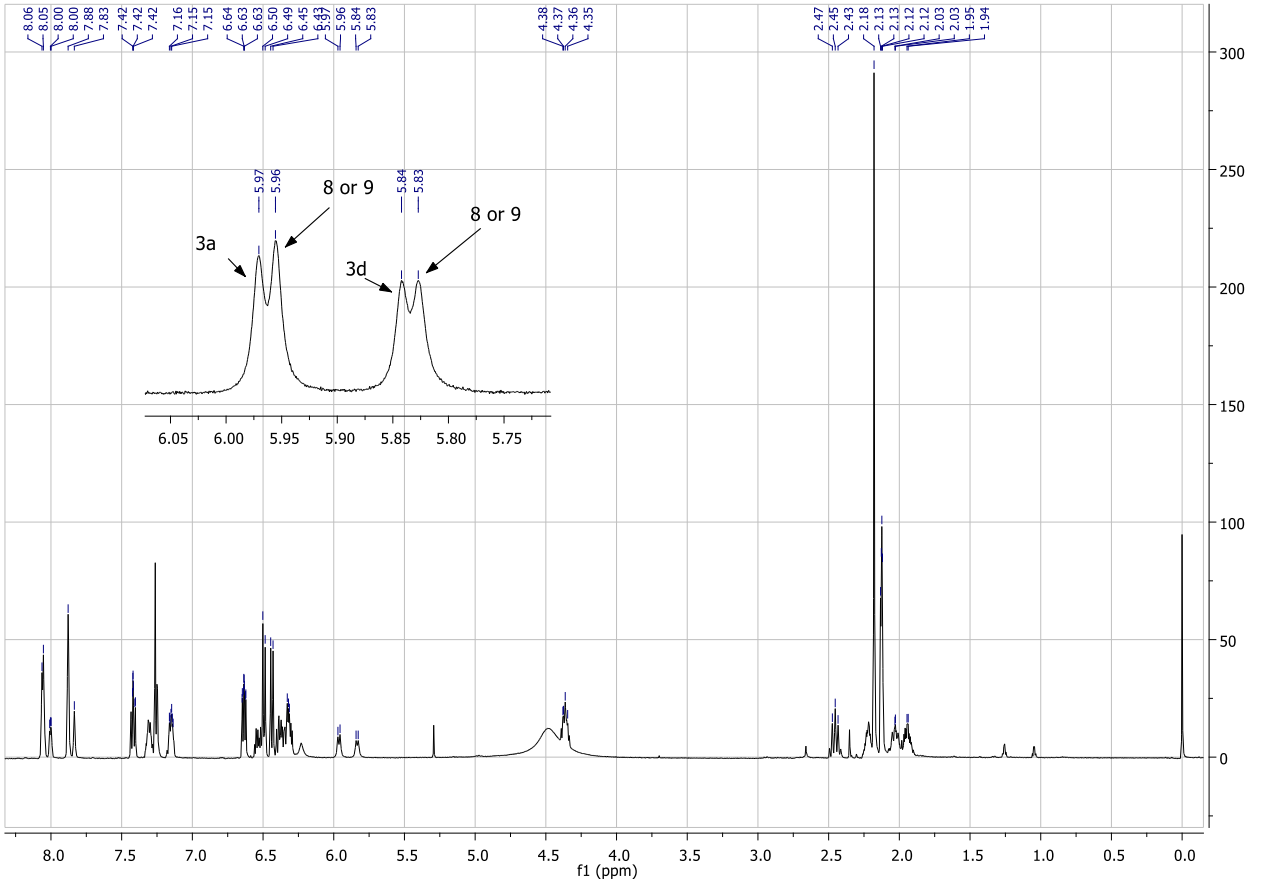
To follow the course of the reaction, the mixture was stirred in $CDCl_3$ and studied by ^1H NMR. The consumption of **1** was monitored by the integration of the peaks at 4.97 ppm with the consumption of **2a** again being monitored by disappearance of the signal at 7.41 ppm. The formation of **3a** was monitored by integration of the signals at 7.31-7.28 ppm and 4.37 ppm. The equilibrium was reached around 48h (~60 % conversion). The ^1H NMR spectrum showed the expected mixture of **1**, **2a** and **3a**; no other products and/or intermediates were detected.





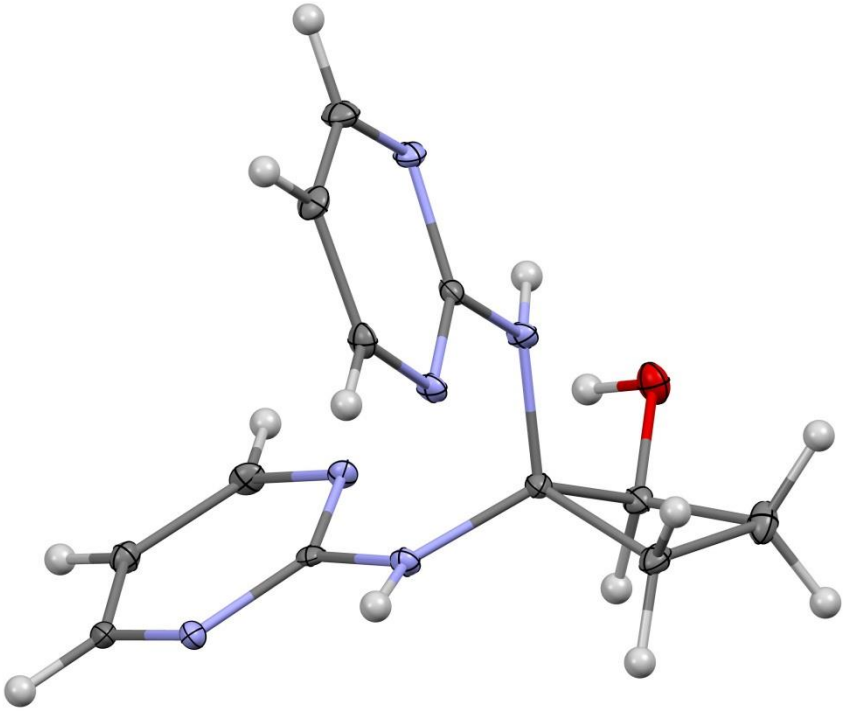
In a strategy of proving the reversibility and to examine the dynamic nature of the system, component exchange was conducted. Aminal **3a**, isolated and purified by reprecipitation was treated with 2 equivalents of **2d** and after 24h, ^{1}H NMR revealed the formation of all the four possible aminals (^{1}H NMR overall yield 27%; aminals ratio = ~26:28:23:23).


OH
NH
NH
N
N
3a
Toluene, R. T. 24h
N
NH2
2d
2 equiv.
3a
3d
8
9
27%
2a
34%
2d
39%


8 or 9
8 or 9
3a
3d
f1 (ppm)

4.4.4 X-ray diffraction data for compound 3l

Fig. 2. ORTEP diagram of compound **3l**, showing 30% probability ellipsoids.



X-ray diffraction data for compound were collected by using a VENTURE PHOTON100 CMOS Bruker diffractometer with Micro-focus IuS source Mo $_{K\square}$ radiation. Crystals were mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flashfrozen in a nitrogen-gas stream at 100 K. For compounds, the temperature of the crystal was maintained at the selected value by means of a 700 series Cryostream cooling device to within an accuracy of ±1 K. The data were corrected for Lorentz polarization, and absorption effects. The structures were solved by direct methods using SHELXS-97[1] and refined against F^2 by full-matrix least-squares techniques using SHELXL-2016[1] with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. All calculations were performed by using the Crystal Structure crystallographic software package WINGX.

The crystal data collection and refinement parameters are given in Table 4.2. [1]

Table 4.2. Crystallographic data and structure refinement details.

Compounds	**3l**
Recrystallization method	slow evaporation of $CHCl_3$
Empirical Formula	C_{12} H_{14} N_6 O
M_r	258.29
Crystal size, mm^3	0.11 x 0.05 x 0.03
Crystal system	triclinic
Space group	*P -1*
a, Å	8.3805(7)
b, Å	8.9419(8)
c, Å	9.0849(7)
α, °	103.317(3)
β, °	107.305(3)
γ, °	98.863(4)
Cell volume, $Å^3$	614.08(9)
Z ; Z’	2 ; 1
T, K	100(1)
Radiation type ; wavelength Å	MoKα ; 0.71073
F_{000}	272
μ, mm^{-1}	0.097
θ range, °	2.411 - 24.997
Reflection collected	13 706
Reflections unique	2 165
R_{int}	0.2330
GOF	0.869
Refl. obs. (I>2σ(I))	2 165
Parameters	182
wR_2 (all data)	0.0770
R value (I>2σ(I))	0.0458
Largest diff. peak and hole (e-.$Å^{-3}$)	0.239 ; -0.277

Details of theoretical calculations

Quantum Mechanics (QM) calculations were carried out at the Density Functional Theory (DFT) level on compounds **1**, **2a**, **A**/**A'**, **B**, and **3a** (Scheme 1). All calculations were performed with the Gaussian 09 commercial suite of computational software.[4] The mPW1PW hybrid functional[5] and the

Def2SVP full-electron split valence basis sets with polarization functions (pVDZ) for all atomic species[6,7] were adopted throughout. For all compounds the geometries were optimized (opt keyword) until a stationary point on the potential surface was found. Analytic gradients were used. The default Berny algorithm was used with a geometry optimization method using an Energy-represented Direct Inversion in the Iterative Subspace algorithm (GEDIIS)[8] in redundant internal coordinates. The converged optimized geometries were verified by a calculation of harmonic frequencies (freq=raman keyword), computed by determining the second derivatives of the electronic energy with respect to the nuclear coordinates. Natural Bonding Orbital (NBO) populations[9-11] and Wiberg bond indices (bndidx keywork in nboread keyword subsection)[12] were calculated at the optimized geometries using the NBO 3.1 module. NPA results were exploited through a Second Order Perturbation Theory Analysis of Fock Matrix in NBO Basis, which allowed defining the donor-acceptor electron transfers between NBOs responsible for the H-bond formation. The results of the calculations were examined with GaussView 5.0.9[13] and Molden 5.3[14] programs. All calculations were carried out on a IBM x3755 server with 4 12-core AMD Opteron processors (48 cores) equipped with 64GB of RAM memory.

References and notes

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Concluding remarks

In conclusion, we have developed a simple and practical method for the synthesis of quaternary highly functionalized α-benzyl- and α-allyl-α-methylamino cyclobutanones using a sequential one pot methylation/sigmatropic rearrangement starting from α-amino cyclobutanones. The method presented in this work provides the first general and efficient route to assemble these important structural motifs. Furthermore, one of the α-alkyl-α-amino cyclobutanones, was used to prepare a new highly substituted tryptamine derivative and some cyclobuta-2,3-fused indolines. In parallel to this study, we address the synthesis of 5-(pyridin-2-ylamino)dihydrofuran-2(3H)-one from 2-hydroxycyclobutanone and some 2-amino pyridines via a catalyst-free preparation of 2,2-bis(pyridin-2-ylamino)cyclobutanols followed by Dess-Martin periodinane mediated ring expansion. We believe that our results provide an advancement in the field of organic synthesis, as the proposed protocol offers the opportunity to further investigate the reactivity of 2-hydroxycyclobutanone with amines and to gain insights on the reaction mechanism. The potential of the novel synthetic strategy is demonstrated by presenting the results on the applicability of the procedure to a wide range of 2-amino pyridines with broad substitution patterns and multiple functionalities for potential elaboration. Moreover, we prospect that the impact of our findings will be beyond the research on strained carbocyclic systems, due to the key role of γ-lactone ring-bearing compounds in bioactive and medicinally relevant molecules. Additional work needs to be undertaken in order to extend the synthetic application and to overcome the current limitations of this chemistry.

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