



Università degli Studi di Cagliari

DOTTORATO DI RICERCA

Scienze e Tecnologie Chimiche

Ciclo XXIX

SYNTHESIS AND CONSECUTIVE REACTIONS
OF α -AMINOCYCLOBUTANONE DERIVATIVES

CHIM/06

Presentata da:

Nicola Melis

Coordinatore Dottorato

Prof. Stefano Enzo

Tutor

Dr. Angelo Frongia

Esame finale anno accademico 2015 – 2016
Tesi discussa nella sessione d'esame marzo – aprile 2017



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ABSTRACT

This thesis deals with the development and the application of new synthetic methodologies in organic chemistry.

The first part (chapter 3) 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 4) a practical method for the synthesis of optically active cyclobutanones α -aminoacid esters is presented, via an organocatalytic asymmetric condensation reaction between racemic α -hydroxycyclobutanone and chiral *N*-alkyl- α -amino acid ester derivatives.

In chapter 5, an original synthetic protocol for the preparation of highly functionalized tryptamines from α -hydroxycyclobutanone and secondary arylamines via a solvent-free Brønsted acid catalysed two-step reaction sequence is reported.

Finally, chapter 6 reports the synthesis of novel bicyclic oxetanes through Paternò-Büchi reaction and their preliminary evaluation as intermediates for post-functionalization reactions.

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

LIST OF PUBLICATIONS

- I. **Organocatalyzed tandem process involving asymmetric protonations as a stereo-defining step.**
A. Frongia, F. Secci, N. Melis, *Comptes Rendus Chimie*, **2015**, 18, 4, 456-467;
- II. **Catalytic enantioselective synthesis of α -(benzylamino) cyclobutanones**
N. Melis, L. Ghisu, R. Guillot, F. Secci, D. J. Aitken, A. Frongia, *Eur. J. Org. Chem.*, **2015**, 20, 4358-4366;
- III. **Organocatalytic asymmetric condensation/keto-enol tautomerisation tandem reaction: access to cyclobutanone α -amino acid ester derivatives.**
A. Frongia, N. Melis, I. Serra, F. Secci, P. P. Piras, P. Caboni, *Asian J. Org. Chem.* **2014**, 3, 4, 378-381;
- IV. **Synthesis of functionalized tryptamines by Brønsted acid catalysed cascade reactions.**
N. Melis, F. Secci, T. Boddaert, D. J. Aitken, A. Frongia, *Chem. Commun.*, **2015**, 51, 83, 15272-15275;
- V. **Fused bicyclic oxetane scaffold: a versatile intermediate for post-functionalisation reactions.**
N. Melis, A. Luridiana, R. Guillot, F. Secci, A. Frongia, T. Boddaert, D. J. Aitken, A. Frongia, *Manuscript in preparation*.

1 INTRODUCTION

1.1 α -AMINO KETONES

α -Amino ketones have a very common structure, which can be found in a large number of natural products and synthetic drugs. Moreover, due to the fact that their structural motif O-C-C-N is a recurrent sequence in nature, α -amino ketones hold an important role in organic synthesis and have been frequently used as building blocks in the total synthesis of biologically relevant compounds.^[1]

Figure 1.1 shows a selection of representative bioactive both natural and synthetic α -amino ketones. For example, 5-aminolevulinic acid is the first compound in the porphyrin biosynthesis pathway, which lead to the synthesis of *heme* structure in mammals and chlorophyll in plants respectively. This compound was discovered in 1953 by Shemin and its biosynthesis was the first to be described among this class.^[2] Aminoacetone is another important α -amino ketone which have a significant role in the metabolism. In fact it is overproduced in patients with diabetes mellitus and *cri-du-chat* syndrome^[3] and enters in the biosynthesis pathway of Azinomycin B, a natural antitumor agent.^[4]

Gelsemoxonine^[5] and cathinone^[6] are two natural α -amino ketones isolated respectively from *Gelsemium elegans* and the plant *Khat*. Cathinone induce the release of dopamine and acts as an inhibitor of the re-uptake of epinephrine, norepinephrine and serotonin in the central nervous system. Cathine and norephedrine are also found in the plant and they derived from cathinone by means of a diastereoselective bioreduction of the carbonyl group.

It is not surprising that the α -amino ketone scaffold has been chosen as a key intermediate for the development of several synthetic drugs and bioactive molecules. In particular, the general skeleton of cathinone has inspired the design

of a large number of substituted cathinones which can be used as biologically active molecules. Among this class of derivatives, bupropion is used for the treatment of depression and as a smoking cessation aid. It acts as a norepinephrine-dopamine reuptake inhibitor (NDRI) and as nicotine antagonist.

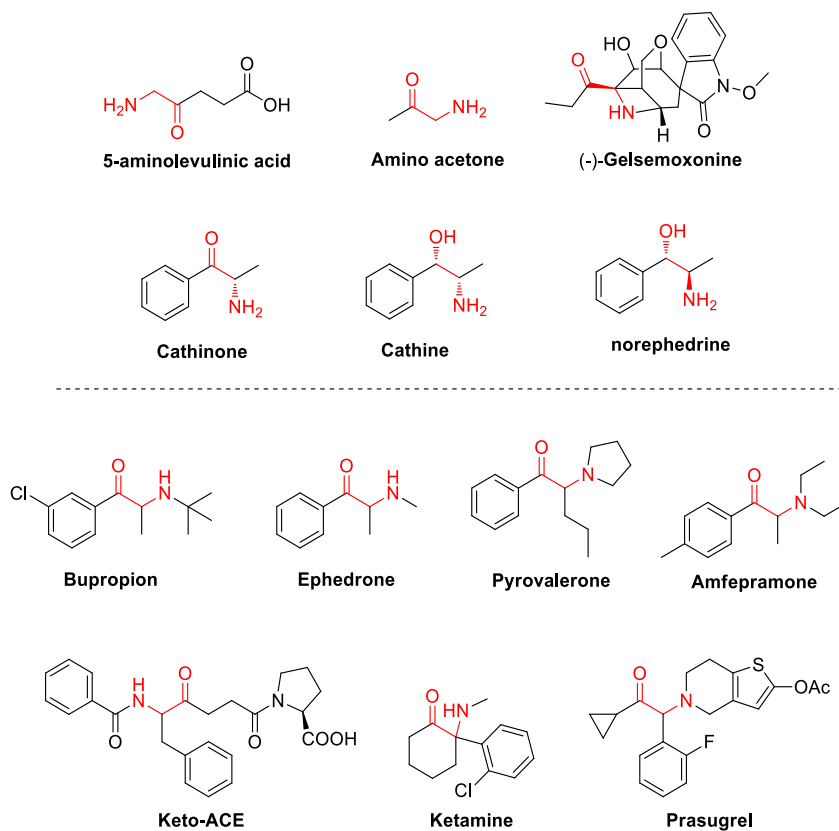


Figure 1.1 – Biologically relevant α -amino ketones.

Ephedrone was commercialised in the '30s as an anti-depressant but nowadays the detention and consumption is illegal or highly regulated worldwide. Pyrovalerone and amfepramone are two others substituted cathinones used as pharmaceuticals for the treatment of chronic fatigue or lethargy and in the management of obesity, respectively. Pharmaceutical drugs containing an α -amino ketone motif include also structure which are different from cathinone unit, such as keto-ACE, an efficient agent for hypertension treatment,^[7] ketamine, which is used as anesthetic,^[8] and prasugrel, used to prevent thrombosis due to its antiaggregant properties in combination with low dose of aspirin. In addition,

some α -amino ketones have been targeted for biological application, such as a probe for the reactivation of the protein p53 in cancer^[9] or as a psychomotor stimulant in rats.^[10]

Moreover, the O-C-C-N structural motif could be found in complex natural products like penicillin, quinine, seretide and Cortisatin A (Figure 1.2), and used as intermediates for the synthesis of drugs and natural nitrogen containing heterocycles, as in the case of the total synthesis of Dragmacidin F developed by the Stoltz's group in 2004.^[11]

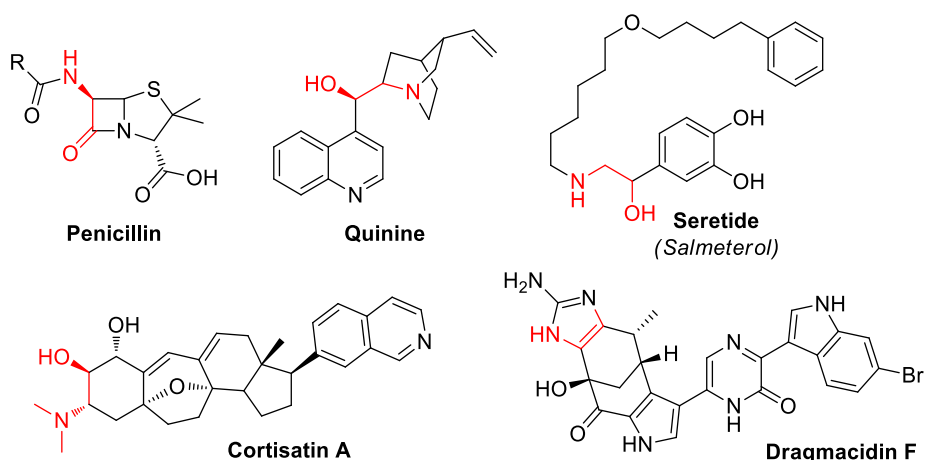
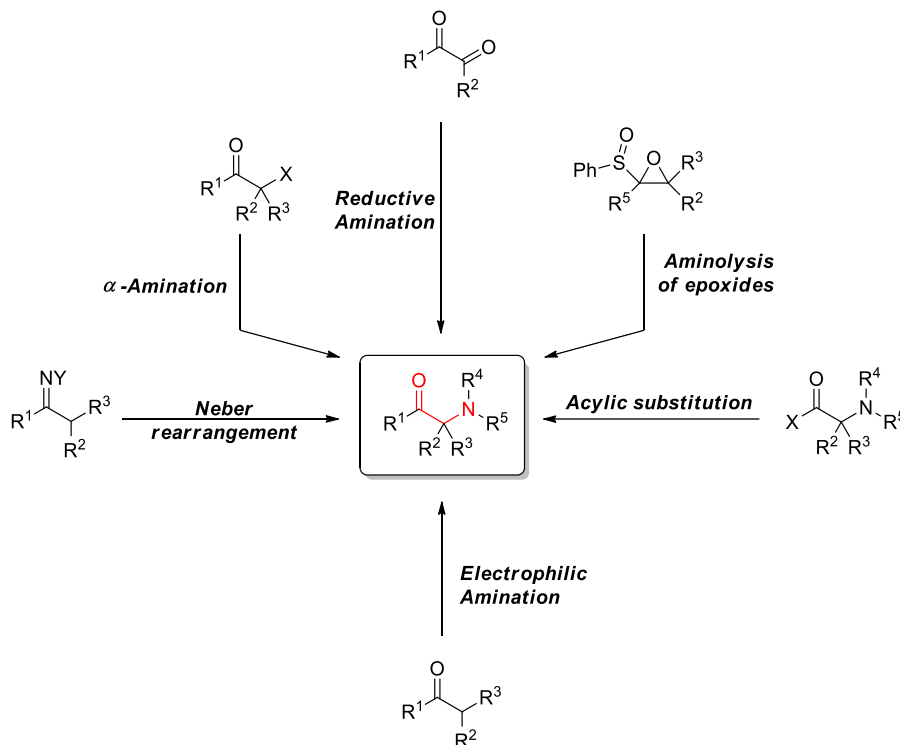


Figure 1.2 – Biologically active molecules which could be related to α -amino ketone precursors.

1.2 SYNTHESIS OF AMINO KETONES

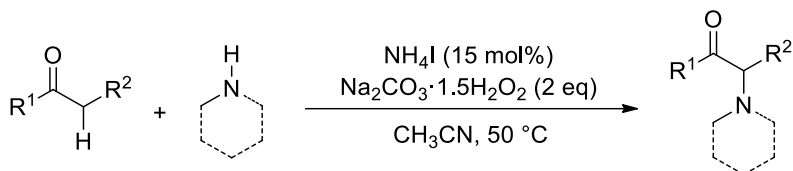
In light of their importance in medicinal and synthetic organic chemistry, the development of robust and general methods for the preparation of this class of substrate is fundamental, especially for what concerns asymmetric approaches. However, it is mandatory to take in consideration the stability and shortcomings in the synthesis of α -aminoketones. For example, during the preparation of such derivatives it is common to observe inter- and intra-molecular self-condensation reactions with unprotected nitrogen and the carbonyl moiety. In fact, self-condensation of α -aminoketones to form substituted pyrazine is one of the oldest reactions still in use in the chemistry of heterocyclic compounds (Staedel-Rugheimer, Gutknecht or Gastaldi pyrazine synthesis).^[12] In addition, the nature

of the nitrogen protecting group play often a significant influence on the reactivity of the carbonyl moiety and the relatively high acidity of the proton in α position make these derivatives prone to be epimerized.



Scheme 1.1 – General synthetic routes to α -amino ketones.

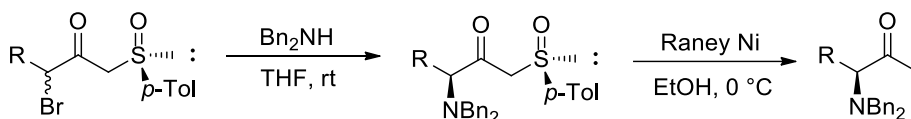
Scheme 1.1 reports the main methodologies developed for the synthesis of α -amino ketones. One of the most classical methods starts from α -halo ketones which can be easily transformed to the corresponding α -amino derivatives by means of a nucleophilic substitution or metal-mediated couplings. α -Halo ketone derivatives can be obtained by insertion of a bromine in the α position of a ketone moiety using bromine or *N*-bromosuccinimide (NBS) with and without radical initiator,^[13] through hydroxybromination-oxidation of the corresponding alkene^[14] or by hydration of suitable halo alkynes^[15]. In addition, some elegant direct α -amination of ketones have been recently reported by MacMillan *et al.*,^[16] via Cu catalysis, and Guo *et al.*,^[17] using ammonium iodide as catalyst and percarbonate as a co-oxidant (Scheme 1.2).



Scheme 1.2 – Metal-free direct α -amination of ketones.

Both of these examples involve the formation of a transient α -halo ketone as the reactive intermediate but, unfortunately, the use of α -halo ketones as starting materials presents some disadvantages when certain combination of ketone and amine are required by the synthetic protocol.

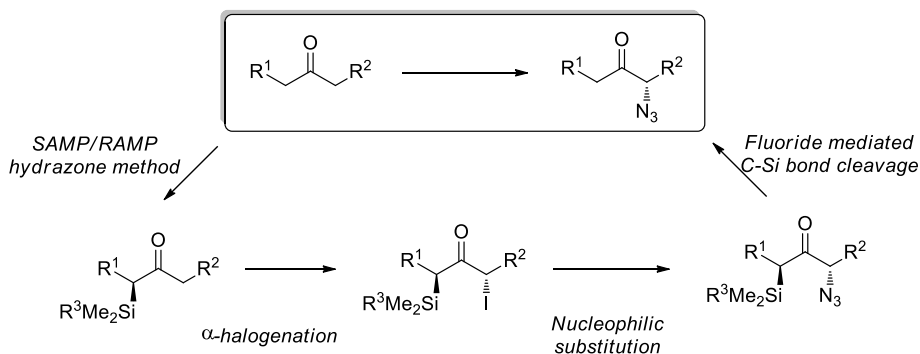
In literature are reported a number of asymmetric approaches involving α -halo ketones. Starting from enantiomerically enriched α -halo ketones, the synthesis of the corresponding amino ketone can be achieved by displacing the halogen atom with an amine. In this case the nucleophilic substitution occurs *via* $\text{S}_{\text{N}}2$ mechanism with complete inversion of stereochemistry. This stereospecific approach was described for the preparation of chiral quaternary stereocenter starting from α -keto esters.^[18] Recently Géant *et al* described the synthesis of chiral 1,2-aminoalcohol containing heterocycles starting from α -bromo- α' -sulfinylketones. In this work, the stereochemical information of the sulfoxide moiety control the chirality of the formed stereocenter during the nucleophilic substitution of bromine with dibenzylamine. The chiral sulfoxide moiety can be easily removed by cleavage of the C-S bond after the 1,4-stereoiduction in order to obtain the corresponding enantiopure α -amino ketone (Scheme 1.3).^[19]



Scheme 1.3 – Asymmetric synthesis of α -aminoketones starting from chiral α -bromo- α' -sulfinylketones.

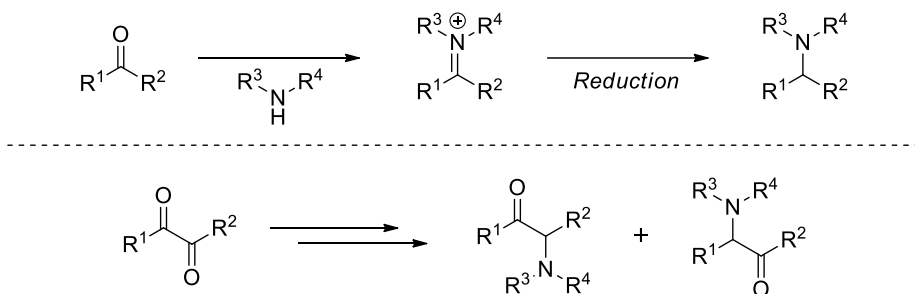
Enantioselective synthesis of α -azido ketones has been reported starting from ketones in four synthetic steps (Scheme 1.4). This approach is based on the synthesis of diastereomerically pure α -silyl- α' -iodo ketones and the subsequent nucleophilic substitution of the halogen with an azide. A fluoride-mediated

cleavage of the silicon-carbon bond lead to the α -azido ketone without racemisation.^[20] Reduction of the azide functionality lead to the desired α -aminoketone.



Scheme 1.4 – Synthesis of enantiopure α -azido ketones starting from simple ketones.

Reductive amination of ketones is a common method extensively described in literature for the formation of C-N bond.^[21] As an expansion of this methodology, α -amino ketones can be synthesized from 1,2-diketones through a selective reductive amination of only one of the two carbonyl functions (Scheme 1.5).

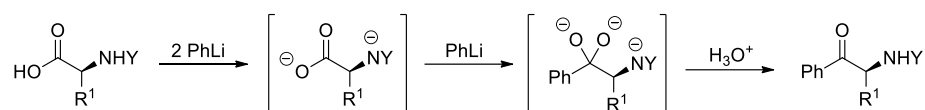


Scheme 1.5 – Reductive amination of ketones and 1,2-diketones.

However, such approach present some disadvantages that are strictly related to the substitution pattern of the starting material. In fact, this type of reaction with non-symmetric diketones typically lead to a mixture of regioisomers. The achieved regioselection is substrate specific and is difficult to predict and control.

Natural α -amino acids and derivatives are perfect starting substrates in the synthesis of α -amino ketones and aldehydes.^[22] As a common rule, this methodology requires the protection of the amine function and the transformation of the carboxylic acid function before the ketonization process.

Another general method for the preparation of optically pure α -amino ketones from α -amino acids is the addition of Grignard or organolithium reagents to *N*-protected amino acid. In this approach, the nature of the protecting group plays a very important role in the preservation of the optical purity of the starting material.^[23]

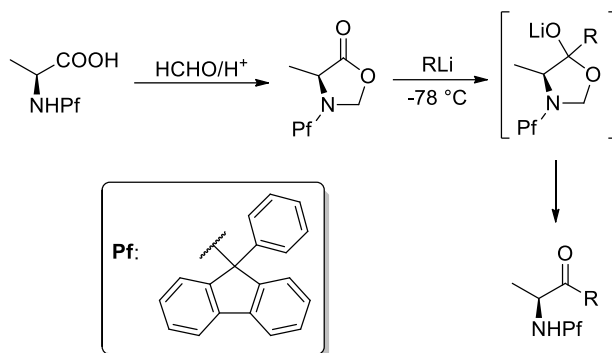


Scheme 1.6 – Mechanistic steps of RLi addition to *N*-protected amino acids.

The good outcome of this procedure depends on the stabilizing effect of both the nitrogen protecting group and the nature of the metallic species of the anionic intermediate. In fact, the formation of a stable transient trianion (Scheme 1.6) prevents the racemisation and/or the over-reaction of the reaction product.

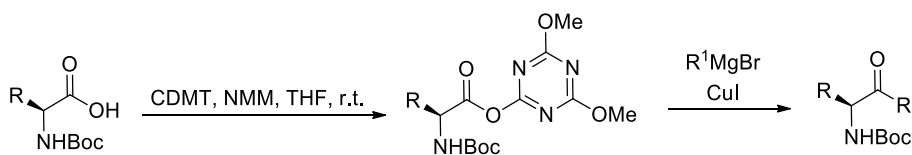
Klix *et al.* developed a multigram-scale methodology based on these findings.^[24] This procedure involves the generation of the carboxylate derivative using lithium hydride followed by the addition of a Grignard reagent to afford the corresponding ketone. Another very similar multigram-scale has been developed by Florjancic *et al.* starting from *N*-Boc protected α -amino acids to prepare the hydrochloride salt of the corresponding *N*-unprotected α -amino ketone.^[25]

Some approaches require derivatization of the carboxylic function before the ketonization reaction and the corresponding esters are probably one of the most used acid derivatives in this regard. For example, *N*-Pf (9-phenyl-9-fluorenyl) protected amino acid in their oxazolidinone forms has been reported to be excellent substrates for organolithium reagent addition (Scheme 1.7), in which the Pf protecting group is able to act as a ligand for the Li⁺ by a cation- π interaction thus stabilising the intermediate.^[26]



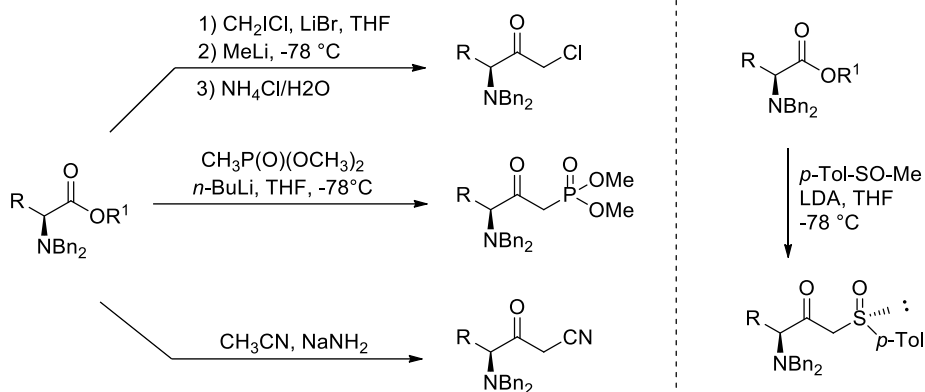
Scheme 1.7 – Synthesis of α -aminoketones from *N*-Pf protected amino acids

More recently, De Luca *et al.* reported another procedure starting from *N*-protected α -amino acids in the presence of 2-chloro-4,6-dimethoxy-[1,3,5]triazine (CDMT), *N*-methylmorpholine (NMM), Grignard reagent and stoichiometric amount of copper iodide. In this two-step approach, the α -amino ketone is formed by reaction of the α -amino acid with the triazine derivative and followed by the addition of the Grignard reagent catalysed by copper (I) iodine (Scheme 1.8).^[27]



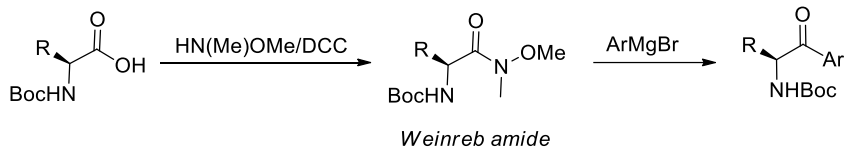
Scheme 1.8 – Two-step synthesis of enantiopure α -amino ketones.

α -Amino acids ester derivatives are substrate of choice also for the synthesis of more functionalised α -amino ketones such as α -amino- α' -chloro ketones through the formation and subsequent acidolysis of the corresponding α' -diazo ketones or by direct functionalization of amino ketones *via* an *in situ* generated chloromethyl lithium.^[28] With the same logic, α -amino- β -ketophosphonates can be obtained by the addition of lithium dimethyl methylphosphonate,^[29] while, the addition of *p*-tolyl sulfoxides^[30] or acetonitrile^[31] led to the corresponding α -amino- β -ketosulfoxides and α -amino keto nitriles respectively (Scheme 1.9).



Scheme 1.9 – Synthesis of α -amino ketone derivatives from α -amino esters.

Also α -amino amides and α -amino chlorides have been used as starting material for the synthesis of α -amino ketone. In this context, Weinreb amides are the most widely used amides because they react with nucleophiles (Grignard reagents, organolithium, LiAlH_4 or other metal-hydride complexes) with little or no overaddition (Scheme 1.10).^[32]

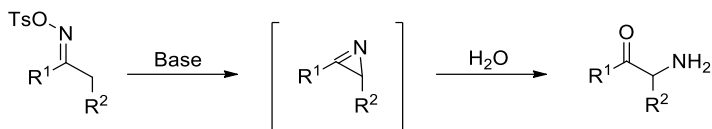


Scheme 1.10 – Synthesis of enantiopure α -amino ketones via Grignard addition to Weinreb amides.

On the other hand, α -amino chlorides have been used as starting material for synthesizing enantiopure α -amino ketones mostly *via* Friedel-Craft acylation reaction.^[23a, 33]

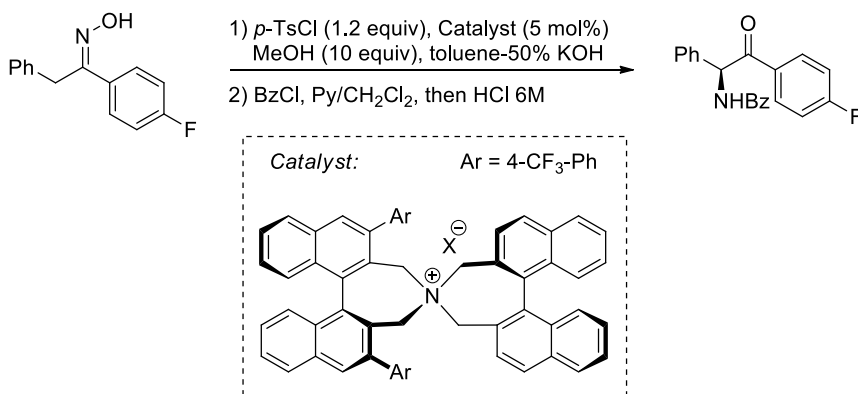
The use of natural amino acids limits the scope of this approach as a consequence of the restricted library of such compound concerning both the substituent pattern and stereochemistry. Therefore, the access to α -amino ketones bearing different substituents or complementary stereochemical information require the *ad hoc* synthesis of the starting material. In these cases, the methodology is often not convenient due to the long and complex procedure for achieving enantiopure unnatural amino acids.

Oxime sulfonates can be converted into α -aminoketones using the Neber rearrangement.^[34] Discovered in 1926, this rearrangement can be utilised for the synthesis of a wide range of α -aminoketones through the intermediate formation of an azirine ring which is converted to the desired product by hydrolysis (Scheme 1.11).



Scheme 1.11 – Neber rearrangement of oxime sulfonates.

However, only few examples of asymmetric Neber rearrangement have been reported in literature using chiral auxiliaries,^[35] cinchona alkaloids^[36] and phase-transfer catalysts.^[37]

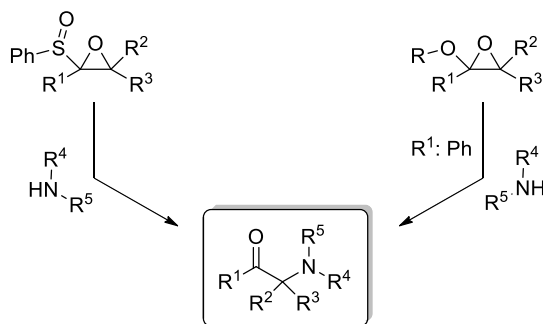


Scheme 1.12 – Asymmetric Neber rearrangement using a C_2 -symmetric phase transfer catalyst.

Interestingly, the use C_2 -symmetric chiral quaternary ammonium bromide as asymmetric phase-transfer catalyst provided important experimental evidences for understanding the mechanism of this transformation (Scheme 1.12). Nevertheless, with this approach it is not possible to access *N*-substituted α -amino ketones and this shortcoming represents a serious limitation of the methodology.

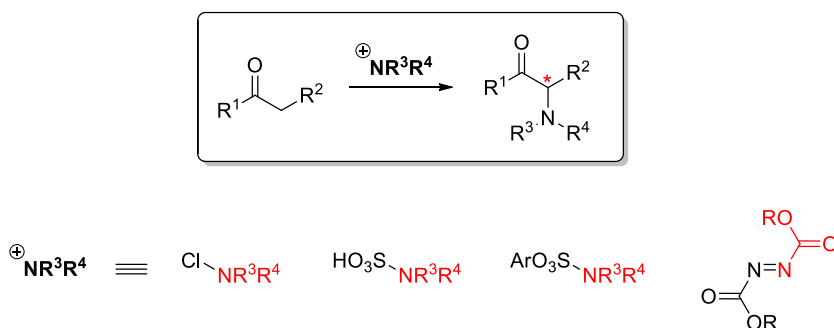
α -Amino ketones can be prepared starting from epoxides through their aminolysis (Scheme 1.13). In this regard, Stevens *et al.* reported the reaction of

phenyl epoxy esters with secondary amines at high temperature, succeeding to prepare a library of phenyl amino ketones in high yields.^[38] In this area, Satoh *et al.* reported the synthesis of α -amino ketones starting from easily accessible α,β -epoxy sulfoxides. Both of these strategies cannot be considered general methodologies for achieving such compounds due to the limited substrate scope and the lack of an asymmetric version.



Scheme 1.13 – Aminolysis of electron poor substituted epoxide derivatives.

Among the numerous methods that have been developed, electrophilic α -amination of carbonyl compounds is the most widely applied enantioselective technology (Scheme 1.14).^[39] The electrophilic aminating agent is a synthetic equivalent of the “ R_2N^+ ” synthon that can react with a carbanion (such as an organometallic species or enolates) or a C-H-activated aromatic derivatives.



Scheme 1.14 – Electrophilic amination of ketones.

Chloramine, O-protected hydroxylamines, sulfonamides and azodicarboxylates are some examples of very commonly used electrophilic

nitrogen source in this type of reaction. In this context, several synthetic strategies have been reported for the generation of C-N bonds.

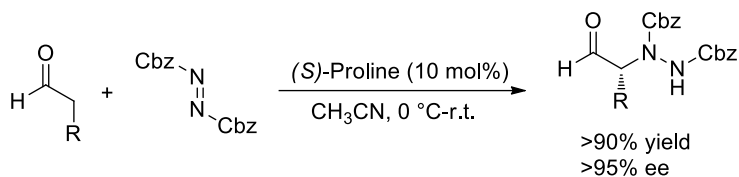
Organometallic species (Grignard reagents, organozinc, zirconium derivatives, etc...) have been successfully employed in such cross-coupling reactions using both transition metal catalysts (Pd, Ni, Cu, Co) and metal-free approaches. Despite the extensive studies accomplished in this field, organoboron derivatives remain the most popular coupling reagents due to their generally high yields and selectivity, mild reaction conditions and substrate scope.^[40]

C-H activation has been principally studied focusing on the formation of C-C connectivities, but also the generation of C-N bonds has been explored.^[41] In fact, this approach has two main advantages: substrates for this type of reaction are typically more readily available than the corresponding halide and a stoichiometric amount of organometallic derivative is no longer required. In this regard, rhodium is the most commonly used metal for activating the C-H bond and its ability has been deeply studied. A large number of aminated products has been successfully prepared using rhodium-based complexes as catalysts, but palladium, ruthenium and copper catalysed amination have also been reported.^[42] Of particular interest is the electrophilic amination of enolates due to the fact that the reaction product can be easily transformed into unnatural α -amino carbonyl derivatives.^[43]

The amination of carbonyl compounds has been extensively studied particularly using azodicarboxylate as aminating agent. This reagent lead to α -hydrazine derivatives which are easily converted to the corresponding amine through deprotection-hydrogenation. This strategy has been also studied in its asymmetric version using enantiopure aminating agents, chiral catalysts and chiral auxiliary such as oxazolidinones.^[44]

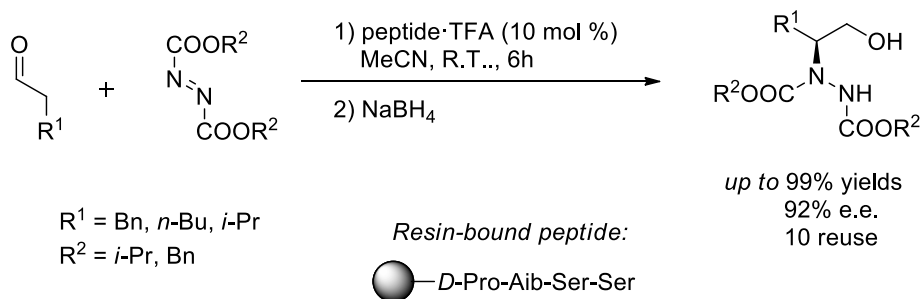
One of the first asymmetric examples has been described by Evans and co-workers using a chiral magnesium complex,^[45] but several enantioselective catalytic variants has been developed and successfully explored. In this context, the organocatalysed process which involves the use of proline and azodicarboxylates represented the first example of an α -amination reaction that

required a non-toxic, inexpensive catalyst which is commercially available in both enantiomeric forms (Scheme 1.15).^[46]



Scheme 1.15 – Proline-catalysed α -amination of aldehydes.

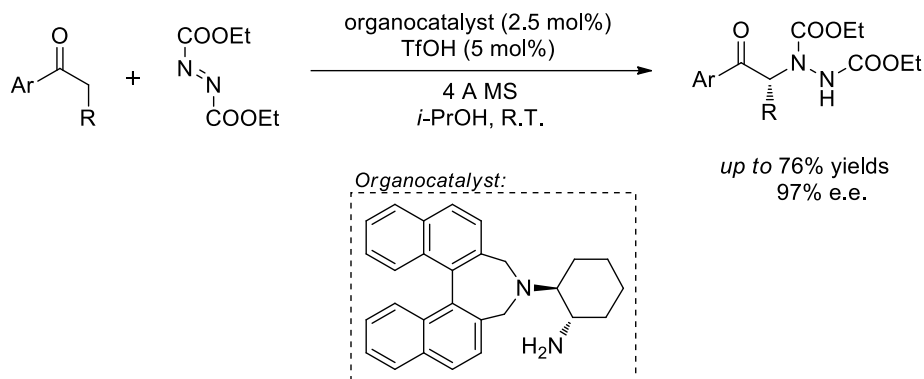
As a result, the use of other organocatalysts extended the methodology to the preparation of a wide variety of α -amino aldehydes and ketones. However, since these synthetic protocols typically demand a high catalyst loading, many efforts are reported in literature to find recoverable or more efficient catalysts.



Scheme 1.16 – Organocatalytic α -amination of aldehyde by means of a catalytic resin-supported peptide.

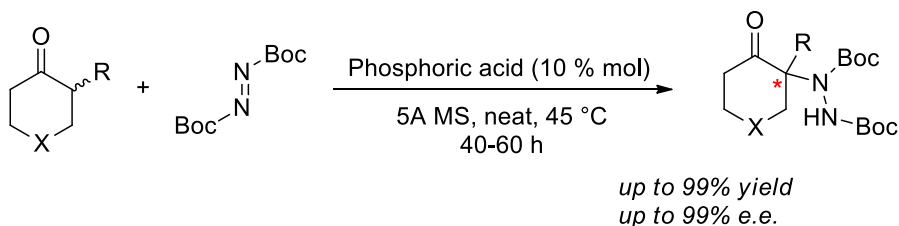
Recently, a resin-supported peptide has been employed by Kudo and Tanaka for the asymmetric organocatalysed α -amination of aldehydes (Scheme 1.16).^[47] The reported catalytic method allowed the preparation of α -amino alcohols in high yields and enantioselectivity. Moreover, the catalyst could be reused up to 10 times without loss of catalytic activity.

Another important advance in this area has been accomplished by Kim and Lim.^[48] In this work, aromatic ketones has been aminated by using a combination of a BINOL-derived organocatalyst and triflic acid in a low catalyst loading (respectively 2.5% and 5%) affording the corresponding products in good yield and enantioselectivity (Scheme 1.17).



Scheme 1.17 – Organocatalytic enantioselective α -amination of aromatic ketones.

Toste research group very recently reported the synthesis of almost enantiopure α -amino- α -alkyl and α -amino- α -aryl cyclic ketones from α -substituted ketones and azodicarboxylate by means of chiral phosphoric acid catalysis (Scheme 1.18).^[49] This procedure represents an elegant and straightforward method for the preparation of such derivatives and showed excellent results in terms of yields and enantioselectivity, other than a wide substrate scope regarding the ketone moiety.

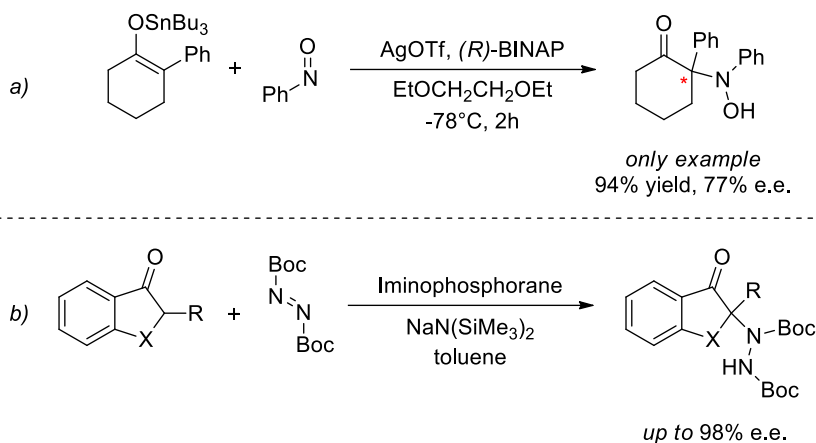


Scheme 1.18 – Synthesis of optically active quaternary α -amino ketones catalysed by phosphoric acid.

Besides that, the majority of this type of chemistry is applied on very reactive carbonyl intermediates such as 1,3-dicarbonyls and α -cyanoacetates.^[43a, 50] Less reactive carbonyl compounds has been used in enamine catalysis^[46, 51] or activated by their conversion to the corresponding silyl enol ethers,^[52] metal enolates^[53] and enamides.^[54]

In addition, this particular synthetic approach represents one of the few examples in which a quaternary stereocenter linked to a nitrogen atom is

generated by means of enantioselective α -amination. Among others, both the works reported by Yamamoto^[53b] *et al* and Terada^[55] *et al* are particularly relevant in this field of research (Scheme 1.19). In the first example, a tin enolate has been aminated with nitrosobenzene *via* silver catalysis affording the optically active α -disubstituted derivative in excellent yield and good enantioselectivity. In the second example, Terada and co-workers reported the use of chiral organosuperbase as catalyst for the α -amination of cyclic aromatic ketones with excellent enantioselection.



Scheme 1.19 – Synthesis of optically active quaternary α -aminoketones reported by Yamamoto (a) and Terada (b).

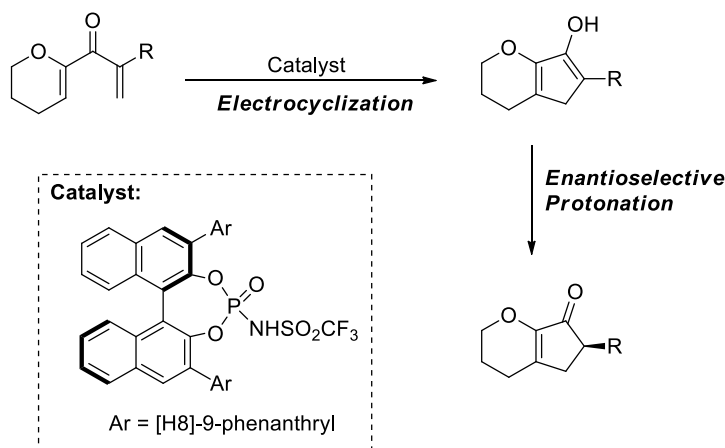
Nevertheless, despite the extensive use, electrophilic α -amination still has some limitations. In fact, the substrate scope has so far remained relatively narrow and, in particular, its application for the asymmetric α -amination of ketones has remained modest.

1.3 α -AMINOCARBONYLS VIA ASYMMETRIC PROTONATION

Asymmetric protonation of a transient prochiral species generated *in situ* from a synthetic operation, in the absence of metal components, are of great value because structurally complex optically active compounds can be obtained with high catalytic efficiency, stereoselectivity and atom economy. The most of these methods are based on protonation of a transient enol or enolate equivalents

prepared through a nucleophilic addition to an α -substituted α,β -unsaturated carbonyl compound or to a ketene derivative, and surprising results have been obtained. In contrast, only a few examples based on process involving intramolecular rearrangement have been reported.

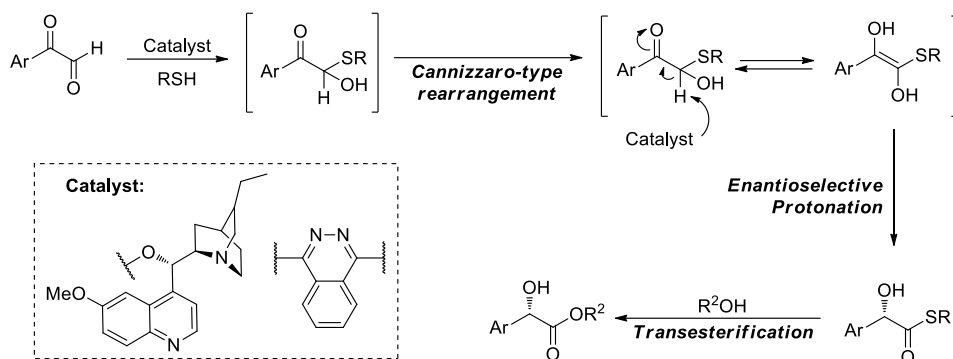
In 2007, Rueping *et al.* developed the first Brønsted acid-catalysed asymmetric tandem cyclization–protonation reaction (Nazarov cyclization), which provides a number of different cyclopentenones in good yields and with high enantioselectivities (67–78% ee) (Scheme 1.20). The proposed mechanism of this transformation involves the formation of a transient enolate by a 4π electrocyclization followed by a chiral phosphoric acid diester-promoted kinetic protonation. In addition, it should be noted that this process employed a low catalyst loading of only 5 mol%.^[56]



Scheme 1.20 – Enantioselective Nazarov cyclization tandem sequence.

In a later report, the same research group showed that acyclic ether derivatives could also be used in organocatalyzed Nazarov cyclizations. This finding resulted in an operationally attractive method for the synthesis of simple cyclopentenone derivatives without any fused tetrahydropyran ring.^[57]

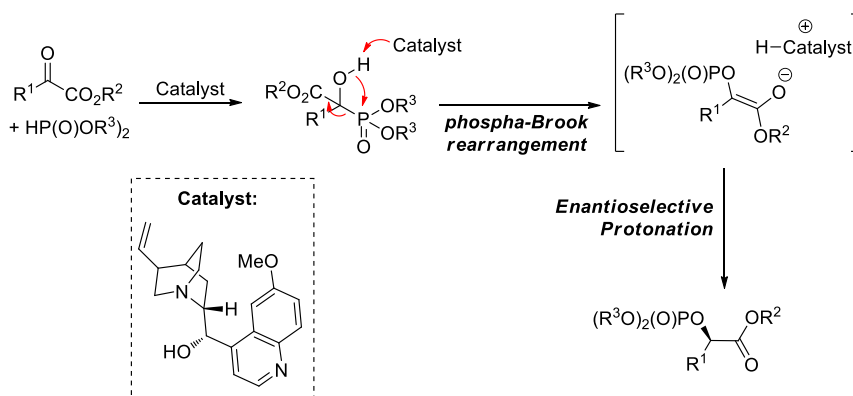
In 2009, Bolm *et al.* developed the enantioselective protonation of a transient enediol prepared by an intramolecular Cannizzaro-type rearrangement of hydrated arylglyoxal yielding optically active mandelic acid methyl ester derivatives with up to 83% ee (Scheme 1.21).^[58]



Scheme 1.21 – Cannizzaro-type rearrangement/protonation tandem sequence.

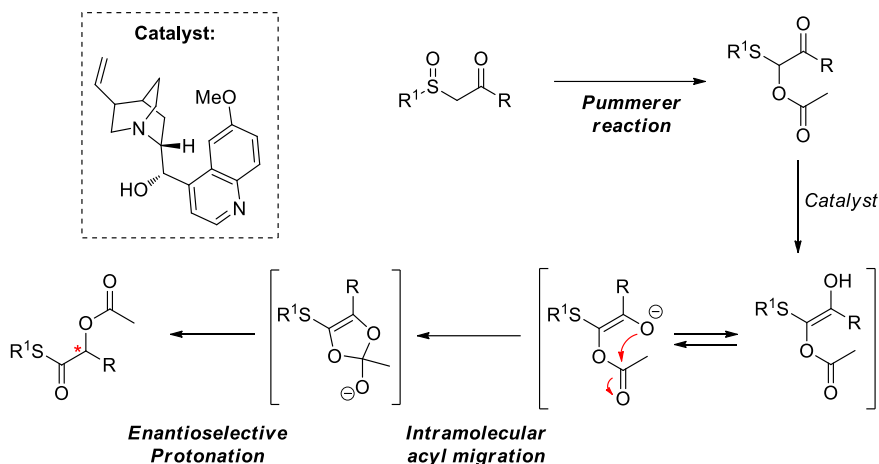
This novel process was catalyzed by a cinchona alkaloid dimer in combination with an achiral thiol. The catalyst could be easily recovered and reused without significant loss of chemical yield or enantioselectivity.

Nakamura and Hayashi reported a highly enantioselective protonation of ester enolates prepared via phospho-Brook rearrangement (Scheme 1.22). In this work, 3.0 equivalent of diphenyl phosphite reacted with an ethyl phenylglyoxalate in the presence of cinchona alkaloids catalyst and a stoichiometric amounts of Na_2CO_3 to afford a transient phosphonyloxy enolate followed by an enantioselective protonation. A series of optically active phosphoric esters having secondary alcohols were achieved with good yield and excellent enantioselectivities using commercially available cinchona alkaloids.^[59]



Scheme 1.22 – Phospha-Brook/Enantioselective protonation tandem sequence.

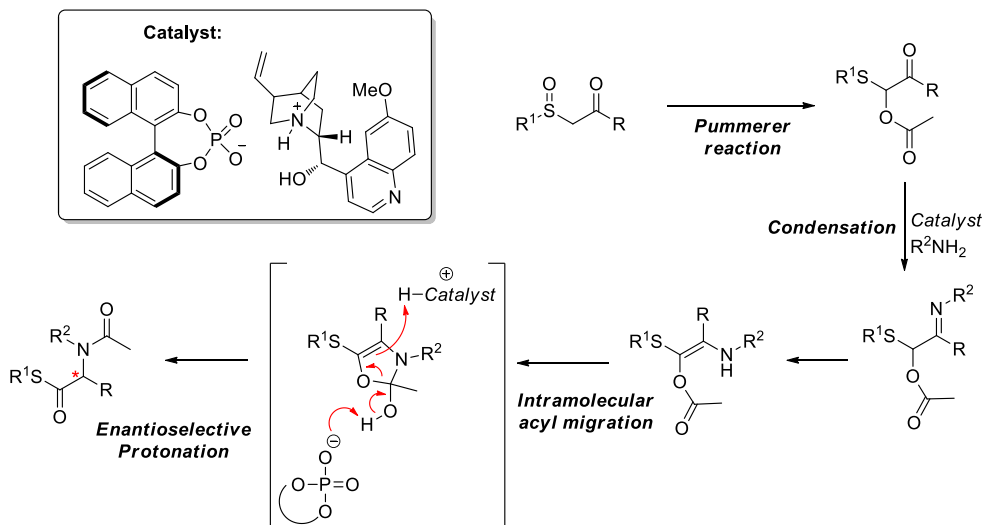
In this context, Frongia's research group investigated the enantioselective organocatalytic rearrangement of α -acyloxy- β -ketosulfides to α -acyloxy thioesters derivatives which involves the generation of a transient enolate though a proton abstraction from a terminal carbon by means of cinchona alkaloids, followed by an in situ enantioselective protonation (Scheme 1.23).^[60]



Scheme 1.23 – Organocatalyzed enantioselective rearrangement of α -acyloxy- β -keto-sulphides to α -acyloxy-thioesters.

Remarkably, high levels of yields and good to high enantioselectivities were observed for the products arising from the reaction of a range of α -acyloxy- β -ketosulfides. It is noteworthy that the Pummerer reaction of β -ketosulfoxides, followed by acyl migration is one of the most useful methods for the preparation of α -acyloxy thioesters which can be easily transformed into sulfur-free biologically active products, such as α -hydroxy acids, amides, esters without racemization.

Then, as a logical extension of the work, they have also demonstrated that the same concept could be applied to the preparation of the corresponding chiral α -amino thioester derivatives in good yield and with moderate enantioselectivities.^[61] The method was based on an unprecedented and conceptually novel chiral Brønsted base/Brønsted acid catalyzed tandem condensation-intramolecular rearrangement-protonation. Although the degree of enantioselectivity observed for this reaction was moderate, these preliminary results formed the basis for further developments (Scheme 1.24).



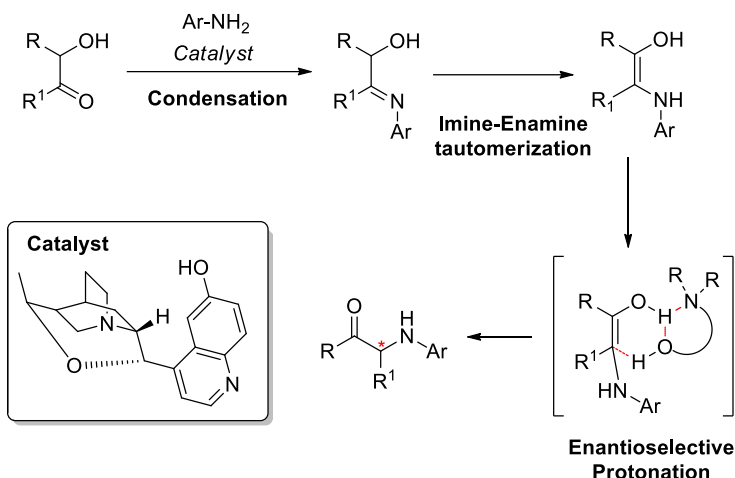
Scheme 1.24 – Organocatalyzed enantioselective rearrangement of α -acyloxy- β -keto-sulphides to α -acylamino-thioesters.

As a matter of fact, in the same context, very recently they have reported the first attempts towards a catalytic and enantioselective Amadori–Heyns type rearrangement and its application for the synthesis of optically active α -amino ketones. The Amadori–Heyns rearrangements, better known in carbohydrate and food chemistry, allows for simple and selective introduction of an amine onto C-1 of an α -hydroxy carbonyl moiety and does not require any protecting group manipulation.^[62]

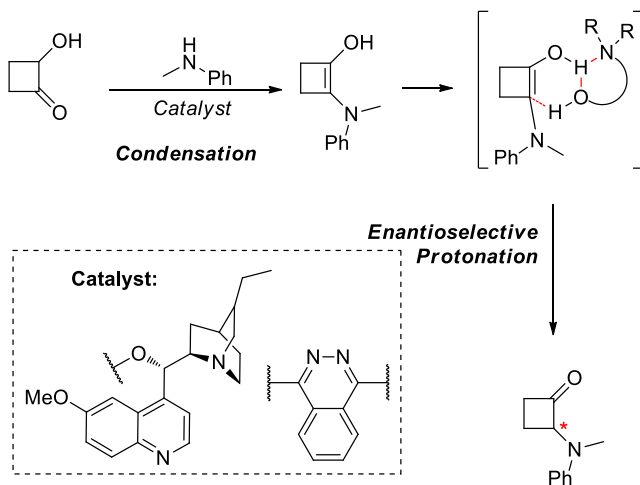
A mechanism involving a tandem condensation-intramolecular rearrangement-proton transfer reaction catalysed by cinchona alkaloids has been proposed. The products have been isolated in good to high yields and up to 81% ee (Scheme 1.25).^[63]

The studied methodology complements among the others, the alternatives recently reported based on the enantioselective “*electrophilic α -amination*” of carbonyl compounds;^[44i, 50b, 64] and result as another example of the more appreciate potential of cinchona scaffolds to induce stereocontrol in organocatalytic reactions. Most notably, the scope of the reaction could be extended to the first catalytic enantioselective synthesis of α -amino cyclobutanones from the readily available α -hydroxy cyclobutanone and *N*-alkyl-

anilines.^[65] Moderate to high enantioselectivities (up to 81% ee) were obtained with a series of *N*-methylanilines with different substitution patterns.



Scheme 1.25 – Enantioselective condensation/protonation tandem sequence for the synthesis of α -aminoketones.



Scheme 1.26 – Enantioselective condensation/protonation tandem sequence for the synthesis of α -arylalkylamino cyclobutanones.

In this case, the reaction could be rationalized by assuming the mechanism shown in Scheme 1.26. The bisquinona alkaloid catalyses the generation of an 1,2-enaminol from the α -hydroxy cyclobutanone and an *N*-alkyl-aniline followed

by an in situ enantioselective enol-keto tautomerisation. Water-mediated proton transfer provides the product and releases the catalyst back into the cycle. It is noteworthy that simple optically active α -amino cyclobutanones are more difficult to access by direct electrophilic α -amination.^[66]

Furthermore, synthetic methods which rely on the use of cyclobutane based structural moiety are of considerable value, because these compounds are key scaffolds of a large number of natural products and versatile building blocks in organic synthesis owing to their inherent ring strain.^[67]

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2 RESEARCH PROJECT

This thesis is the outcome of the project “*Synthesis and consecutive reactions of α -aminocyclobutane derivatives*” which was part of the recent research program of our research group. We have previously dealt with the development of new intramolecular rearrangement/protonation reactions and synthetic methods based on transformation of strained organic compounds.

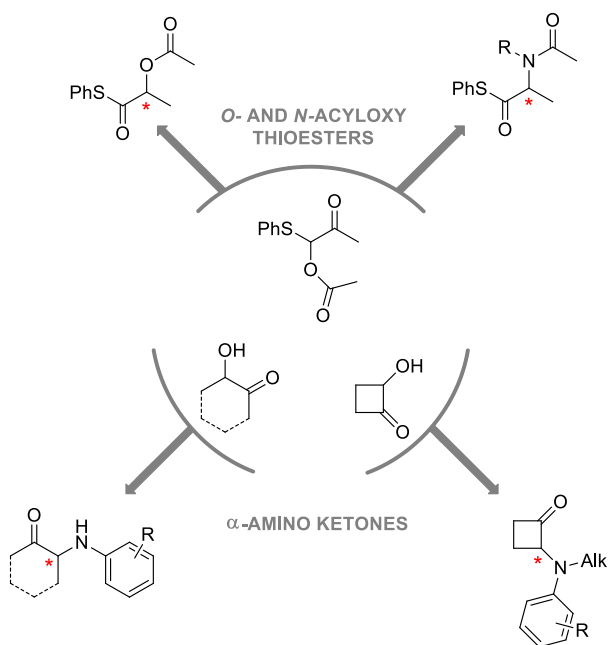
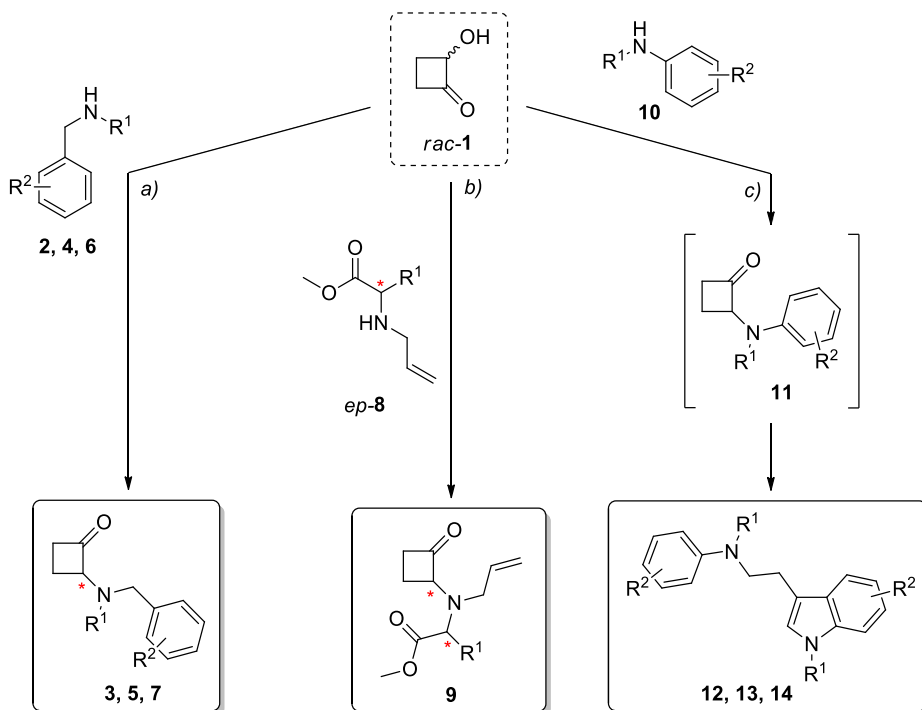


Figure 2.1 – Our previously described examples of condensation/enantioselective protonation tandem sequence strategy for the synthesis of α -hetero atom functionalised carbonyl compounds.

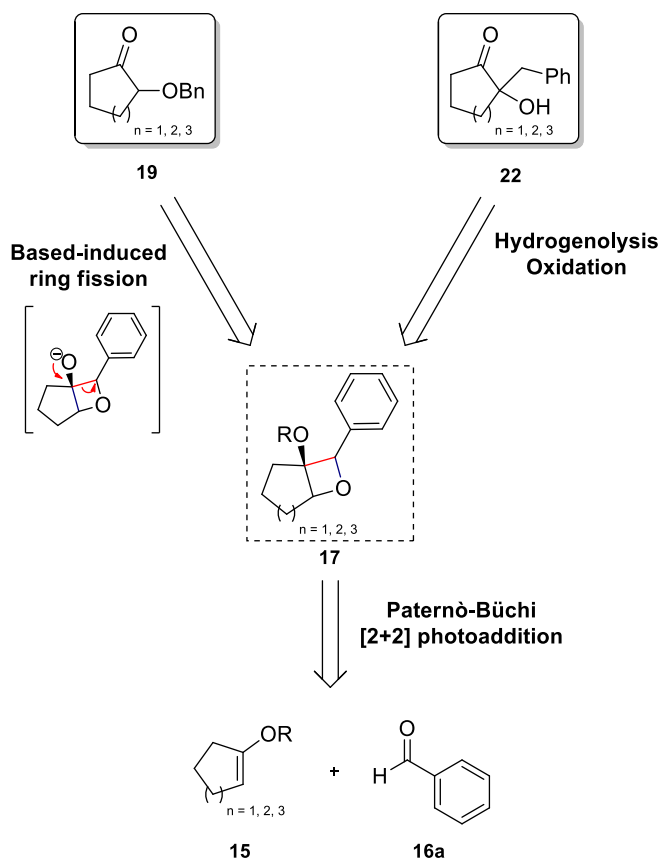
As a matter of fact, in 2010, our group reported an enantioselective organocatalytic rearrangement of α -acyloxy- β -ketosulfides to α -acyloxy thioesters.^[1] The broad lines of these rearrangements involve deprotonation of the

starting materials by a chiral Brønsted base, giving rise to transient enolates that subsequently undergo a tandem intramolecular acyl migration/enantio-selective protonation sequence to furnish the desired enantioenriched α -acyloxythioesters. After this work, we disclosed asymmetric tandem amine condensation/intramolecular acyl migration/protonation reaction sequences with the same α -acyloxy- β -ketosulfides and various primary amines.^[2] In addition, the same strategy has been applied in the synthesis of optically active α -aminoketones starting from α -hydroxyketones by an unprecedented asymmetric Amadori-Heyns-like rearrangement using primary arylamines.^[3] Subsequently, we focused on α -hydroxycyclobutanone as a representative strained cyclic hydroxyketone using *N*-alkylanilines.^[4] It is important to point out that in all the examples previously reported the substrate scope seemed to be limited to weakly nucleophilic aromatic amines.



Scheme 2.1 – Planned reactions starting from racemic α -hydroxycyclobutanone.

Thus, as a continuation of our previous work, we decided to further develop these discoveries applying the methodology to the enantioselective synthesis of more challenging fully aliphatic α -amino cyclobutanones using benzylamines and amino acids. In addition, we then sought to demonstrate the potential of α -amino cyclobutanone derivatives as synthetic precursors of more complex molecules such as biologically important tryptamines exploring new post functionalization reactions.



Scheme 2.2 – Synthesis of cyclic α -hydroxyketones **19** and **22**.

Then, as a further development of this methodology would involve the use of other challenging cyclic α -hydroxyketones in collaboration with the CP³A research group at the *Institut de Chimie Moléculaire et des Matériaux d'Orsay* (ICMMO) of *Université Paris-Sud* (France), under the supervision of Prof. David J. Aitken and Dr. Thomas Boddart, we tried to develop a general approach to such derivatives

based on the Paternò-Buchi [2+2] cycloaddition between cyclic silyl enol ethers and aldehyde under UV irradiation.

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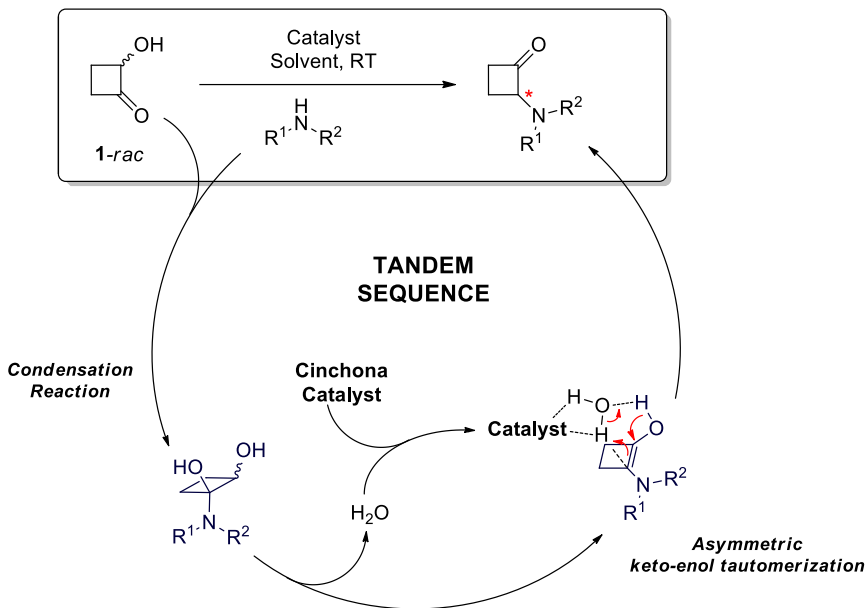
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3 SYNTHESIS OF α -BENZYLAMINO CYCLOBUTANONES

Chiral α -aminocyclobutanes are useful intermediates in organic synthesis because of their inherent ring strain and reactivity.^[1] They 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]

In this context, as mentioned in the introductory chapter, we developed a novel synthetic strategy for the asymmetric assembly of α -(arylamino)-cyclobutanones.^[5] An important aspect of this approach was 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.^[6] This novel procedure was achieved by an unprecedented and conceptually new tandem condensation/intramolecular rearrangement/enantioselective proton transfer procedure,^[7] resulting in a useful route for the preparation of optically active α -aminocyclobutanones that are beyond the reach of established amination strategies (Scheme 3.1).

Therefore, in order to further develop this approach 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.



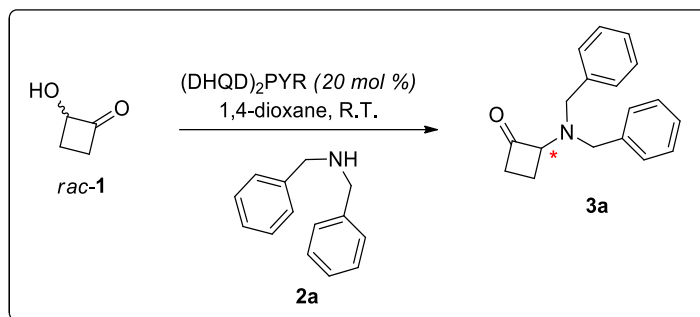
Scheme 3.1 – Key steps in the organocatalytic enantioselective tandem condensation/keto–enol tautomerization for the synthesis of optically active α -aminocyclobutanones.

In contrast with our previous work in which weakly nucleophilic anilines were employed,^[5, 7m] the enhanced nucleophilicity of the benzylamines makes the noncatalyzed (and thus racemic) reaction a competitive pathway. If this reaction is as fast as the catalysed one, the asymmetric induction will be compromised.

The reaction between α -hydroxycyclobutanone (**1**) and dibenzylamine (**2a**) under different conditions to give adduct **3a** (Table 3.1) has been examined as a model. As we suspected, the higher nucleophilic character of benzylamines make the reaction proceed with moderate conversion also in absence of any catalytic species in 1,4-dioxane at room temperature for 3 h (Table 3.1, Entry 1). Under the same conditions, we carried out the reaction with (DHQD)₂PYR as the catalyst and we isolated the desired product **3a** in 81% yield with encouraging enantioselectivity (71:29 *e.r.*; Table 3.1, Entry 2). Moreover, employing the pseudoenantiomeric catalyst (DHQ)₂PYR, the enantiomer of the product has been obtained even with a slightly lower selectivity (Table 3.1, Entry 3). In an effort to improve the enantioselectivity, several other catalysts were evaluated (Table 3.1,

Entries 4–8), but they were less rewarding concerning yield and selectivity than (DHQD)₂PYR and (DHQ)₂PYR.

Table 3.1 – Optimization of reaction conditions.



Entry	Catalyst	Solvent	Yield 3a (%) ^[a]	e.r. 3a ^[b]
1	none	1,4-dioxane	47	-
2	(DHQD) ₂ PYR	1,4-dioxane	81	71:29
3	(DHQ) ₂ PYR	1,4-dioxane	78	32:68
4	(DHQD) ₂ PHAL	1,4-dioxane	66	54:46
5	(DHQ) ₂ PHAL	1,4-dioxane	70	48:52
6	(DHQD) ₂ AQN	1,4-dioxane	54	64:36
7	(DHQ) ₂ AQN	1,4-dioxane	68	44:56
8	quinidine	1,4-dioxane	71	46:54
9	(DHQD) ₂ PYR	Toluene	54	59:41
10	(DHQD) ₂ PYR	CHCl ₃	85	49:51
11	(DHQD) ₂ PYR	CH ₃ COOEt	77	69:31
12 ^[c]	(DHQD) ₂ PHAL	Toluene	80	50:50

[a] Isolated yield after chromatography. [b] Enantiomeric ratio (e.r.) was determined by HPLC analysis using a chiral stationary phase column [c] Reaction carried out with molecular sieves (4 Å; 0.6 g) at 0 °C.

By screening different solvents (Table 3.1, 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 favourable results. It is worth to notice that the reaction conditions that had provided good to high enantioselectivity in the previous study with anilines^[5] had no effect on the enantiocontrol of this model reaction (Table 3.1, Entry 12).

Having established that the appropriate reaction conditions are obtained by employing (DHQD)₂PYR as catalyst and 1,4-dioxane as solvent, we next investigated the scope of this transformation by varying the substituent pattern on the dibenzylamine partner of the tandem sequence (Figure 3.1).

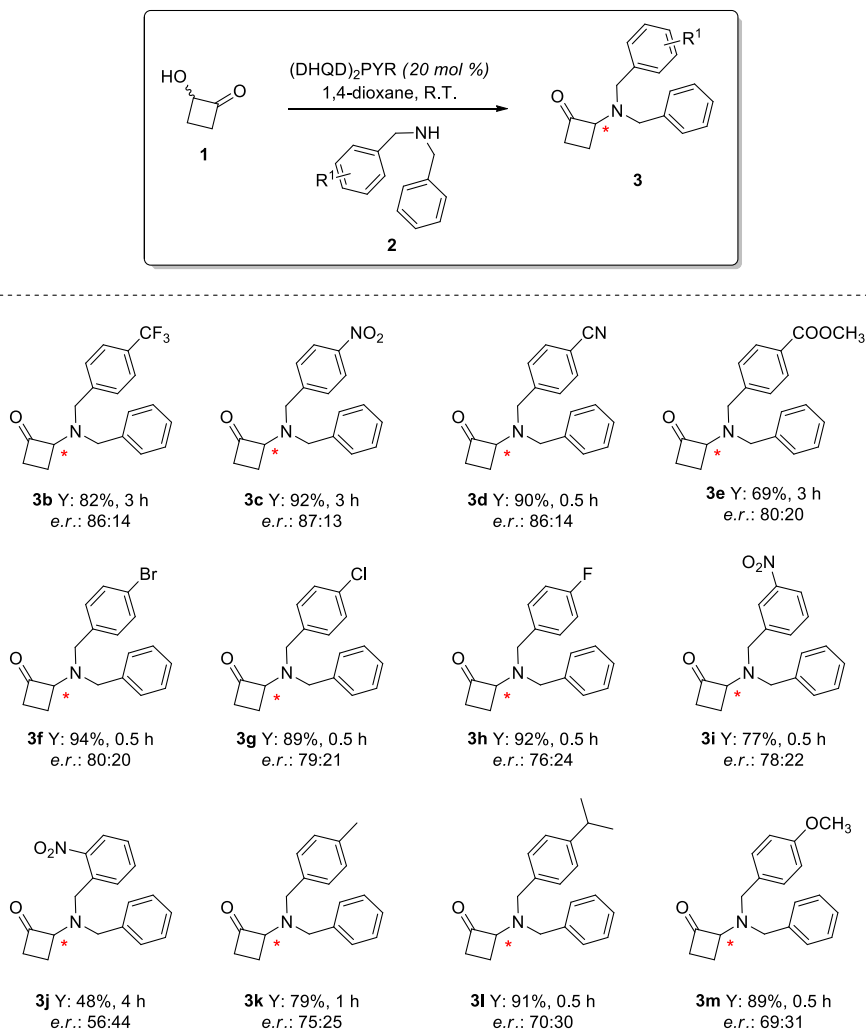


Figure 3.1 – Substrate scope of the tandem sequence by using mono-substituted dibenzylamines.

Good enantioselectivities were obtained by a series of dibenzylamines with electron-withdrawing groups on the aromatic ring. Dibenzylamines **2b–2h**, with electron-withdrawing substituent at the *para* position, afforded the expected α -

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

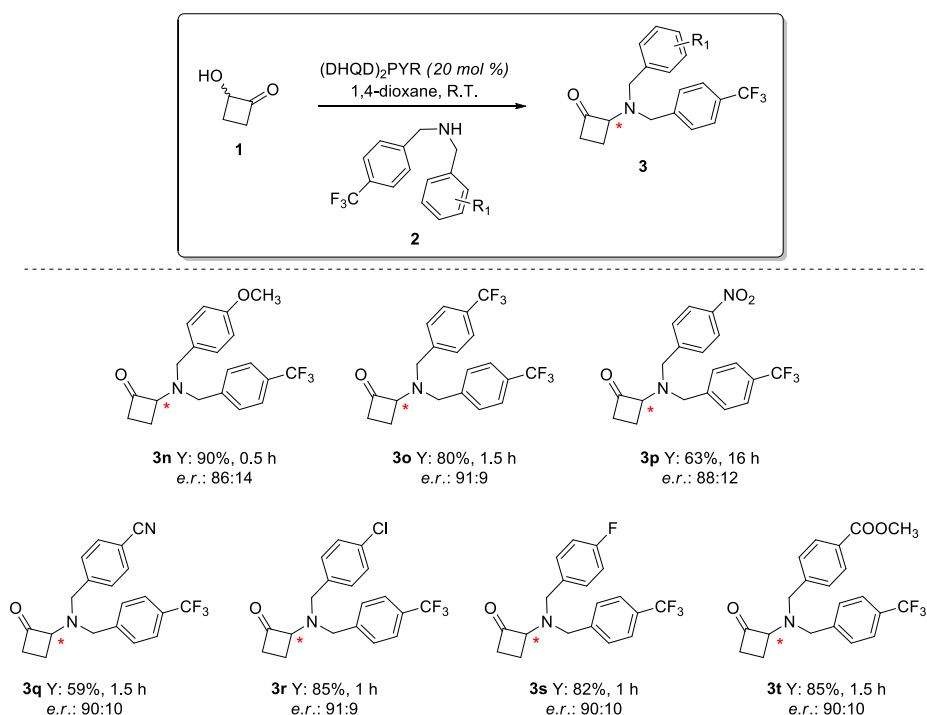


Figure 3.2 – Substrate scope of the tandem sequence by using disubstituted dibenzylamines.

Of particular note, bis(*para*-substituted) dibenzylamines that contain electron-withdrawing groups were tolerated and gave good to high chemical yields with high enantioselectivities (Figure 3.2). Indeed, by using dibenzylamines **2o–2t** as substrates, we obtained the corresponding α -(dibenzylamino)-cyclobutanones **3o–3t** up to 91:9 *e.r.* in 59–85% yields. Importantly, by using a

dibenzylamine with 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 3.3). The absolute configurations of the other products of the series **3a–3t** were assumed to possess (*R*) configuration by analogy to compound **3o**.

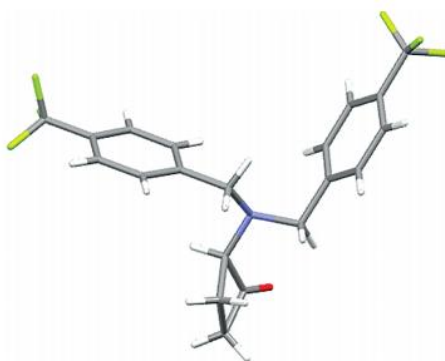


Figure 3.3 – X-ray crystallographic structure of compound **3o** (CCDC-1054222).

To further explore the substrate scope of the reaction with alkyl amines, *N*-alkylbenzylamines **4a–4g** have been examined under the optimised conditions (Figure 3.4). 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 more sterically hindered isopropyl group (i.e., **4c**) provided the corresponding products in good to high yields (79–93%). A lower yield (48%) has been obtained only for the *N*-allyl derivative **4e**, even with prolonged time of reaction (48 h).

Furthermore, since products **5a–5f** were obtained with low selectivity, and this aspect of the reactivity remains a challenge to control. However, we observed that *N*-benzylglycine ester **4g** performed as a more successful partner than its homologue **4f** and afforded the desired product **5g** in high yield (93%) and an improved enantioselection (78:22 *e.r.*). Substrates **4h–4k**, which have an electron-withdrawing group (NO₂) at the para position of the aromatic ring, performed perceptibly better than the non-substituted series **4a–4f** and gave products **5h–5k** with enhanced enantioselection (from 62:38 to 78:22 *e.r.*).

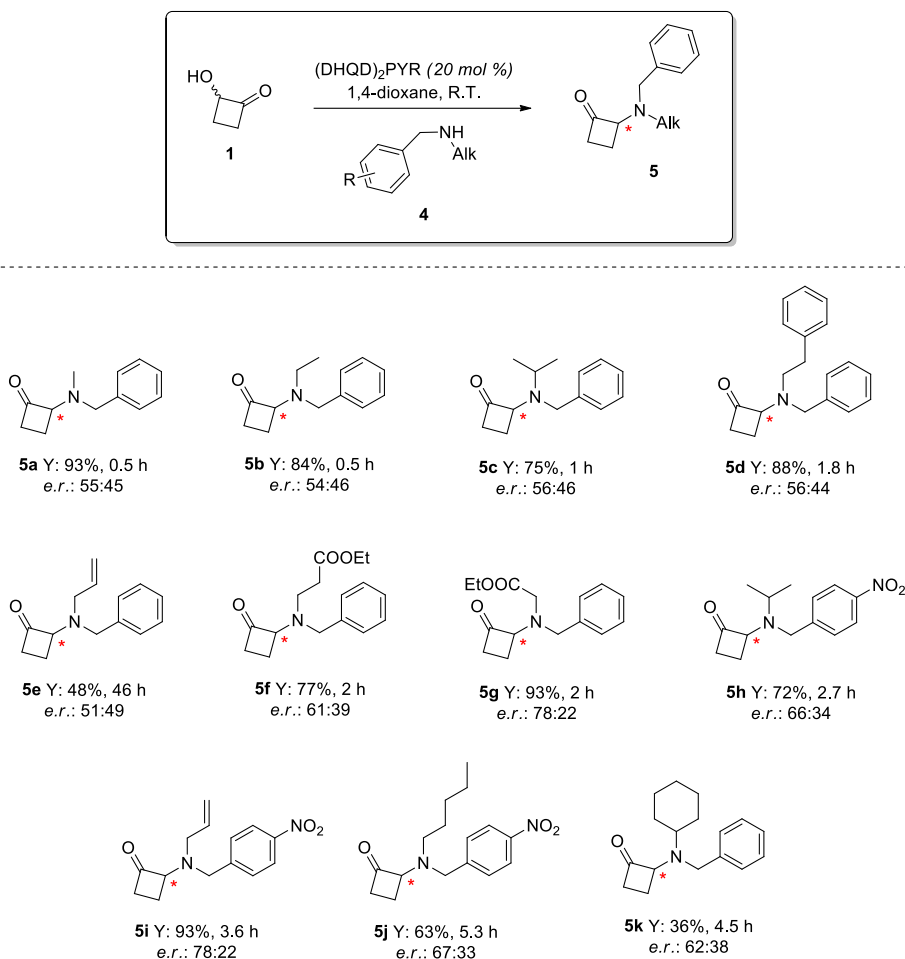
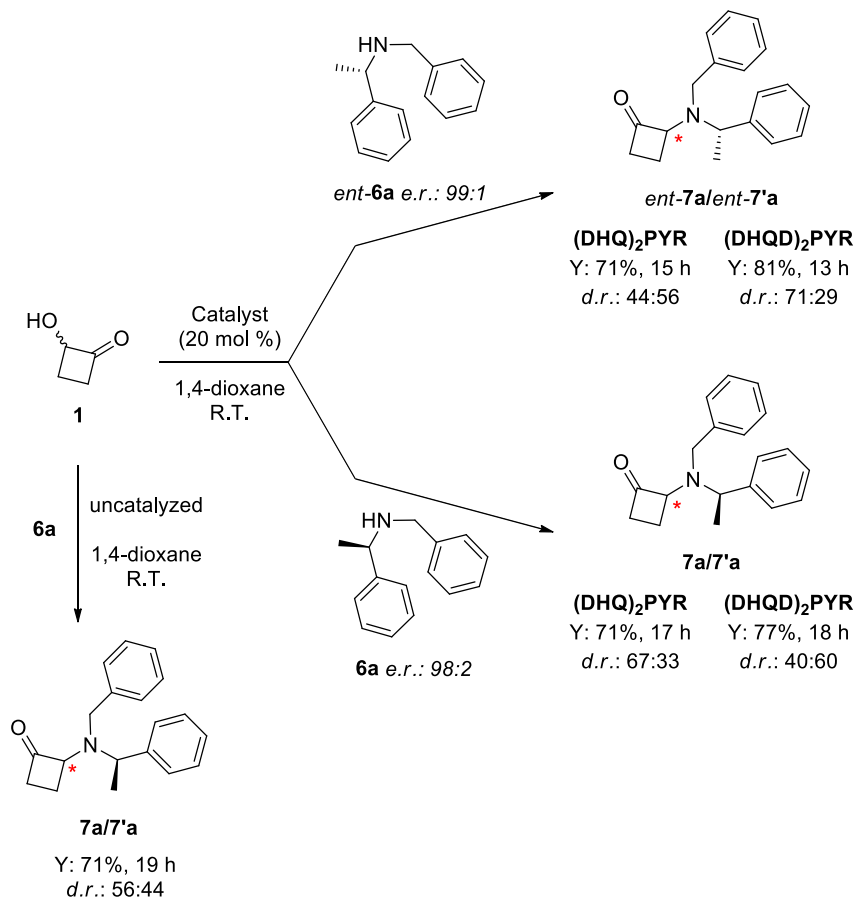


Figure 3.4 – Substrate scope of the tandem sequence by using *N*-alkyl benzylamines.

These results show that steric factors as well as the electronic character of the *N*-alkyl group of the benzylamine partner dramatically affect the stereochemical outcome of the reaction. Moreover, the presence of an electron-withdrawing group at the *para* position of the aromatic ring seems to be required to observe some enantioselection. 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 mechanism might, therefore, be an alternative to the one we suggest in Scheme 3.1.

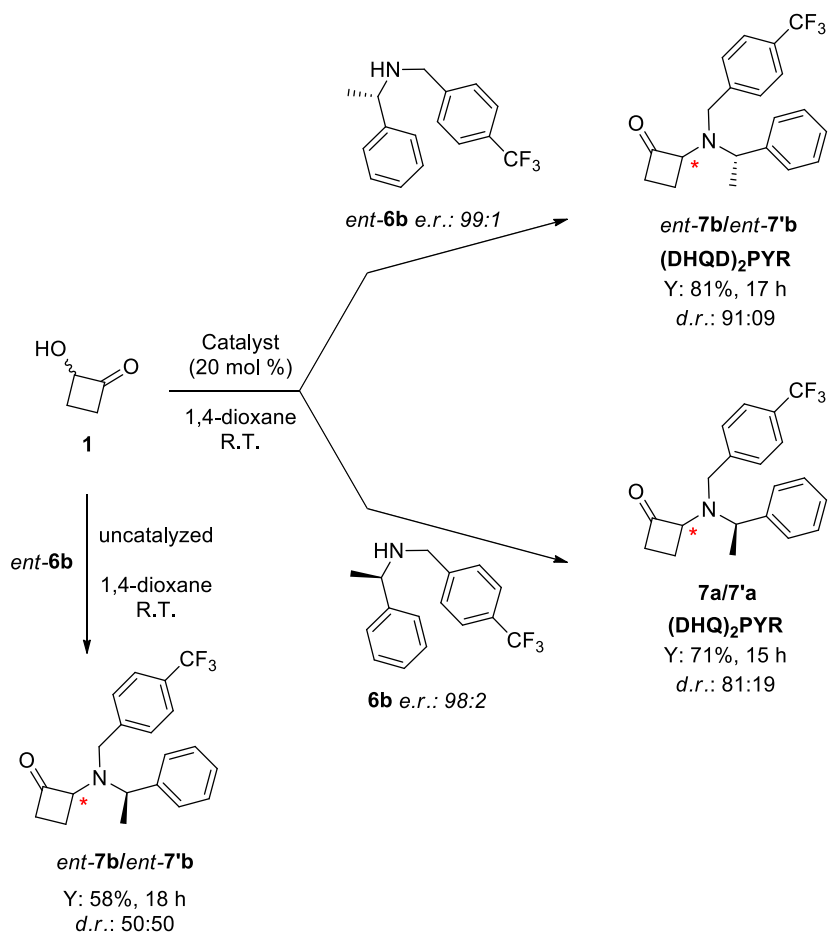
Refocusing to dibenzylamine derivatives, we decided to examine the influence of a pre-existing stereogenic center on the stereochemical outcome of the reaction. In fact, considering the chirality of both the secondary amine and the catalyst *match* and *mismatched* effect can be clearly observed.^[8]



Scheme 3.2 – Diastereomeric approach to the synthesis of α -dibenzylamino cyclobutanones using (S) and (R) optically pure dibenzylamines.

As shown in Scheme 3.2, with optically pure benzylamines **6a** and *ent*-**6a**, a moderate match/mismatch effect between the amine and the catalyst was detected. In both cases, no significant improvement to the stereoselectivity of the catalyzed reaction of dibenzylamine **2a** (Table 3.1, Entry 2) has been observed. However, as already pointed out with series **3** and **5**, the introduction of an electron-withdrawing group (CF₃) at the para position of the aromatic ring (i.e., **6b**

and *ent-6b*, Scheme 3.3) led to a considerable enhancement of the stereoselection respect to non-substituted amines.



Scheme 3.3 – Diastereomeric approach to the synthesis of α -dibenzylamino cyclobutanones using (*S*) and (*R*) optically pure dibenzylamines bearing a *para*-CF₃ substituent in one aromatic ring.

In fact, the desired α -(benzylamino)cyclobutanones **7b/7'b** were afforded in 81:19 diastereomeric ratio (*d.r.*) and *ent-7b/ent-7b* in 91:9 *d.r.*, respectively, by using 30 mol% of (DHQD)₂PYR or (DHQ)₂PYR. It should be also 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 stereoselection.

In conclusion, we described a simple and practical methodology for synthesizing highly functionalized α -(benzylamino)cyclobutanones. Such derivatives has been obtained by using a condensation/intramolecular rearrangement/enantioselective protonation tandem sequence in their optically active form. The reaction sequence started from readily available racemic α -hydroxycyclobutanone and benzylamines and it was catalysed by *cinchona* alkaloid derivatives to afford the products in good to high yields and with moderate to high stereoselectives. Moreover, the reaction proved to be compatible with the employment of substituents and other functional groups. Finally, a preliminary investigation on the effect of a pre-existent element of chirality in the substrate for a diastereoselective approach has been made.

From N. Melis, L. Ghisu, R. Guillot, P. Caboni, F. Secci, D. J. Aitken and A. Frongia, *Catalytic Enantioselective Synthesis of α -(Benzylamino)-cyclobutanones*. *Eur. J. Org. Chem.*, **2015**, 4358–4366.

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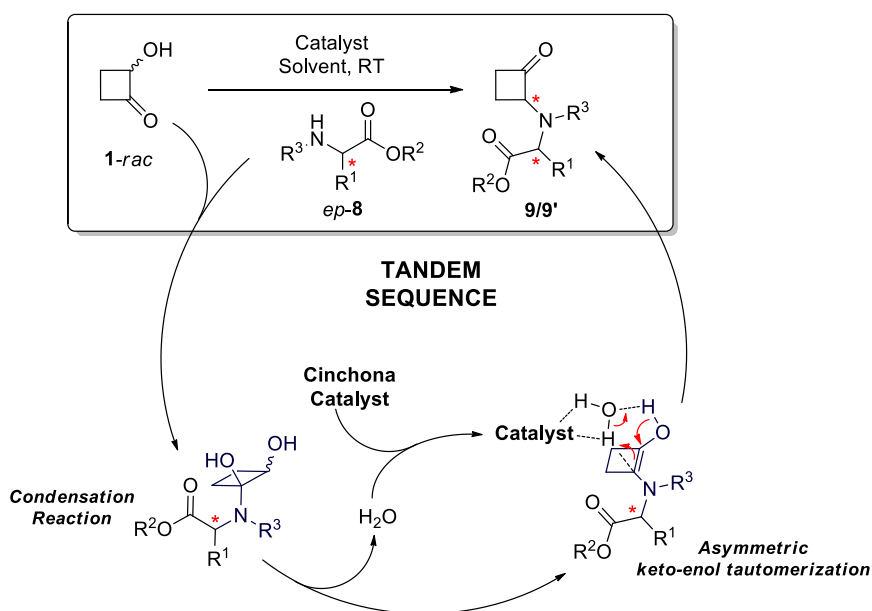
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4 SYNTHESIS OF CYCLOBUTANONE

α -AMINO ACID ESTERS

Despite their importance due to the presence of two contiguous functions on a four-membered carbocyclic ring compound,^[1] α -amino cyclobutanones have been rarely targeted in asymmetric synthesis.^[2] The most common way to synthesize α -aminocyclobutanone derivatives uses the condensation of the requisite amine with α -hydroxycyclobutanone or its *bis*-trimethylsilylated enol ether derivative.^[3] In previous research,^[4] we have observed that α -hydroxycyclobutanone **1** was a substrate of choice in organocatalyzed^[5] condensation reactions with *N*-alkyl-substituted anilines to provide enantioenriched α -arylamino cyclobutanones in the presence of *cinchona* alkaloids as catalysts.



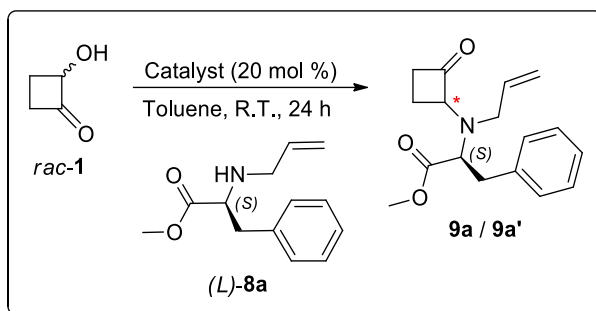
Scheme 4.1 – Key steps in the organocatalytic asymmetric tandem condensation/keto–enol tautomerization sequence for the synthesis of optically active α -aminocyclobutanones.

Thus, in continuation of our work, we envisioned that our method could be applied to an attractive and more challenging stereoselective synthesis of cyclobutanone α -amino acid ester derivatives by the condensation/keto–enol tautomerization tandem reaction between α -hydroxycyclobutanone and a chiral *N*-alkyl- α -amino acid ester derivative (Scheme 4.1).

In addition, as the development of efficient methods for the construction of optically active α -amino ketone derivatives remains a significant task in organic chemistry,^[6] the stereoselective synthesis of α -amino cyclobutanones from fully aliphatic amines, such as α -amino acid esters, was particularly interesting as it would offer the possibility of testing the capacity and limits of our recently reported method in this stimulating and exciting research topic.^[7]

We first chose the reaction of α -hydroxycyclobutanone **1** with *N*-allyl-*L*-phenylalanine methyl ester **8a** as a model reaction for catalyst screening and evaluation. The starting α -amino acid ester derivative **8** was prepared from the corresponding readily available α -amino acid according to literature procedures.^[8] All reactions were carried out at room temperature in a sealed vial in toluene as solvent. It is worth noting that in the absence of catalyst, the reaction took place with moderate conversion and with no diastereoselectivity, which shows clearly that the stereochemical outcome of the reaction does not seem to be affected by the intrinsic chirality of the α -amino acid ester derivative (reagent control, entry 1, Table 4.1).

On the basis of this result, we speculated that a suitable catalyst would be able to control the terminal stereoselective protonation step^[9] of the tandem sequence without suffering match-mismatch processes^[10] due to the simultaneous presence of a stereogenic center previously installed during the initial deracemizing condensation reaction between the α -hydroxycyclobutanone **1** and the corresponding chiral α -amino acid ester derivative **8**. We initially examined the effects of achiral tertiary amine catalysts, such as 4-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), and imidazole, on the reactivity and selectivity of the reaction, and the results are listed in Table 4.1.

Table 4.1 – Initial study: Catalyst screening and evaluation

Entry	Catalyst	Yield (%) ^[a] 9a + 9a'	d.r. ^[b] 9a:9a'
1	none	44	50:50
2	DMAP	84	41:59
3	DABCO	88	58:42
4	Imidazole	60	55:45
5	Quinidine	73	32:68
6	Quinine	56	46:54
7	β -isocupreidine	80	54:46
8	(DHQD) ₂ PHAL	69	31:69
9	(DHQ) ₂ PHAL	68	78:22
10	(DHQD) ₂ AQN	77	30:70
11	(DHQ) ₂ AQN	66	73:27
12	(DHQD) ₂ PYR	73	34:66
13	(DHQ) ₂ PYR	84	81:19
14	Hydroquinidine 4-chlorobenzoate	69	29:71

[a] Isolated total yield after chromatography. [b] The *d.r.* values were determined by ¹H-NMR analysis.

Pleasingly, the expected products **9a/9'a** were formed in high yield (84%), although, with low asymmetric induction (*d.r.*=41:59) when DMAP was used as catalyst (Entry 2, Table 4.1). Interestingly, the reaction with DABCO displayed excellent reactivity giving the desired products with a complementary diastereoisomeric ratio (Entry 3, Table 4.1), whereas the reaction with imidazole provided **9a/9'a** in lower yield and with almost no stereoselectivity (Entry 4, Table 4.1). The catalyst screening was next extended to *cinchona* alkaloids.^[11] To our delight, quinidine (Entry 5, Table 4.1) showed a promising level of asymmetric

induction, whereas quinine (Entry 6, Table 4.1) and β -isocupreidine (Entry 7, Table 4.1) gave somewhat lower diastereoselectivity. Further catalyst evaluation screened a variety of bis-*cinchona* alkaloids under similar reaction conditions (Entries 8-14, Table 4.1).

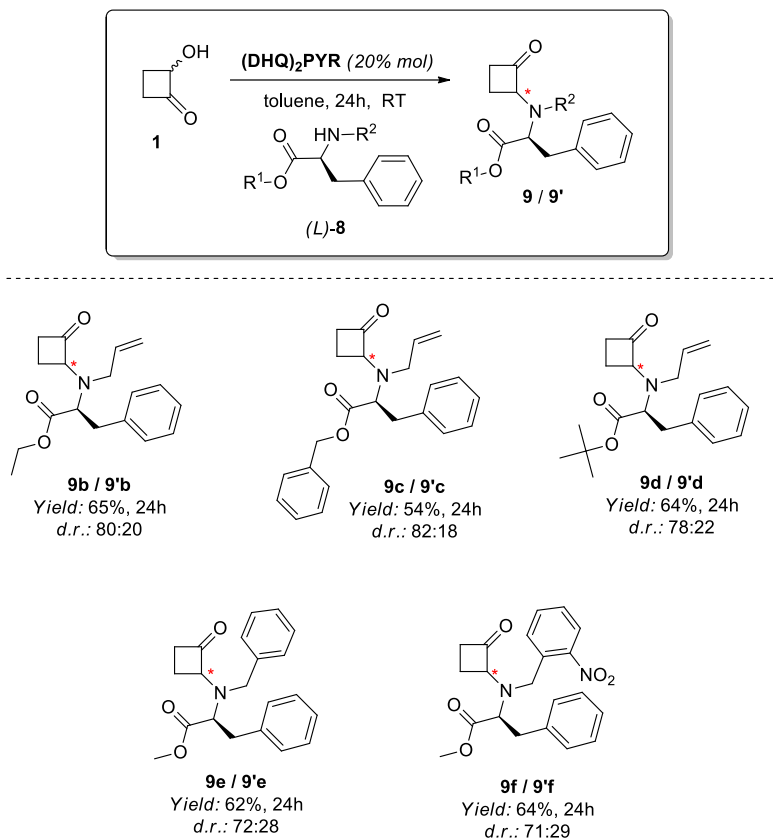


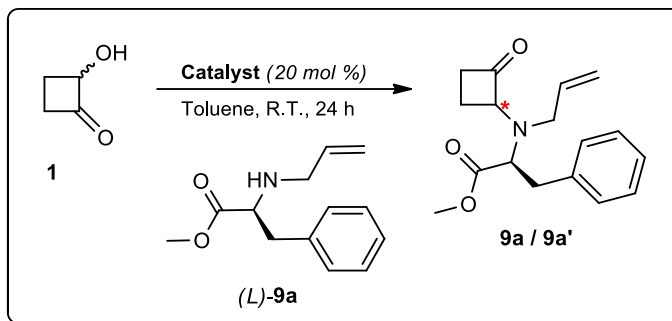
Figure 4.1 – Identification of the optimal R_1 and R_2 . Yields are given for isolated material after column chromatography. The *d.r.* values were determined by $^1\text{H-NMR}$ analysis.

The highest selectivity was obtained with **(DHQ)₂PYR** (Entry 12, Table 4.1), which provided the desired α -amino cyclobutanones **9a/9'a** in 81:19 *d.r.*

Further optimization with variations on the ester moiety of the starting amino acid ester derivative (**8b-d**) does not affect the stereochemical outcome of the reaction (Figure 4.1). Replacing the protecting group on nitrogen with a benzyl (**8f**)

or 2-nitrobenzyl (**8e**) group resulted in a slightly decreased diastereoselectivity (Figure 4.1).

Table 4.2 – Influence of solvent on stereoselectivity



Entry	Solvent	Yield (%) ^[a] 9a + 9a'	d.r. ^[b] 9a:9a'
1	THF	72	86:14
2	CH ₂ Cl ₂	67	83:17
3	MeOH	77	63:37
4	DMF	67	71:29
5	1,4-dioxane	85	93:07
6	Ethyl acetate	85	81:19
7	1,4-dioxane	70	88:12
8	1,4-dioxane	70	85:15
9	1,4-dioxane	66	89:11

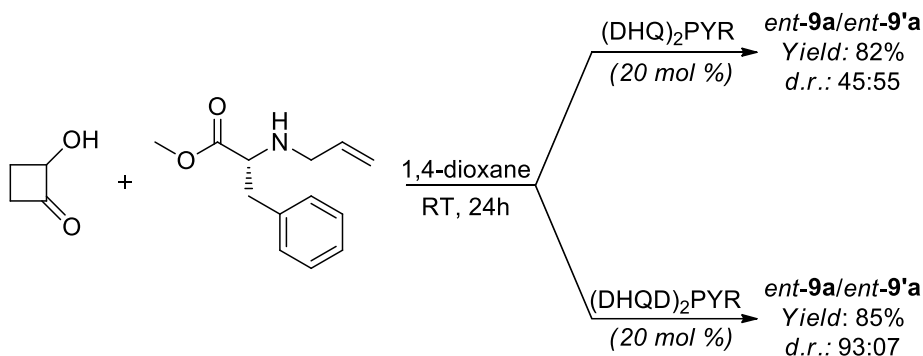
[a] Isolated total yield after chromatography. [b] The *d.r.* values were determined by ¹H-NMR analysis.

Furthermore, we also performed a solvent screening using (DHQ)₂PYR as a catalyst (Table 4.2). The stereoselectivity was slightly enhanced with CH₂Cl₂ and THF (Entries 1-2, Table 4.1), while the use of 1,4-dioxane further increased the *d.r.* to 93:7 (Entry 5, Table 4.2). The use of higher catalyst loadings as well as molecular sieves or different concentrations was not particularly advantageous (Entries 7-9, Table 4.2).

Remarkably, changing the stereochemistry of (*L*)-*N*-allyl phenylalanine methyl ester from (*L*)-**8a** to (*D*)-**8a** (Scheme 4.2) led to a switch in the diastereoselectivity in favour of *ent*-**9'a** with the formation of the corresponding

products in 82% yield and very low *d.r.* (*ent-9a/ent-9'a*=45:55). On the other hand, access to *ent-3a* was achieved also by changing the stereochemistry of both the catalyst and amino acid ester derivative (Scheme 4.2).

Indeed, the reaction of (D)-*N*-allyl phenylalanine methyl ester in combination with (DHQD)₂PYR (the pseudoenantiomer of (DHQ)₂PYR) as the catalyst proceeded in an impressive highly stereoselective complementary fashion (*d.r.*: *ent-9a/ent-9'a*=93:7).^[12]



Scheme 4.2 – Diastereoselective access to *ent-9a/ent-9'a*.

As a matter of fact, because the absolute configuration of the starting amino acid is the opposite, the newly formed stereocenter in the major diastereoisomer has the opposite configuration to that of the major isomer that was obtained from (L)-*N*-allyl phenylalanine methyl ester (**L-8a**) using (DHQ)₂PYR as catalyst. Therefore, interestingly, our method has equally high stereocontrol in favour of **9a** or *ent-9a* with either (L)- and (D)-amino acid ester derivatives simply by tuning the chirality of the catalyst.^[13] Subsequently, the substituent tolerance of α -amino acid ester derivative **8** was preliminary investigated in a series of condensation reactions under the optimized conditions (Figure 4.2). The reactions of **8g**, **8h**, and **8i** proceeded in moderate to high yields and in each case, one diastereoisomer always predominated, with *d.r.* values in the range 84:16–86:14.

To summarize, we have reported an organocatalytic and stereoselective entry to optically active cyclobutanone amino acid ester derivatives, via a tandem condensation/keto-enol tautomerization, that are beyond the reach of established amination methods. Given the potential value of chiral α -amino cyclobutanes as

building blocks in organic synthesis,^[14] studies aimed at further expanding the scope of this approach as well as towards their transformation are currently in progress in our laboratory.

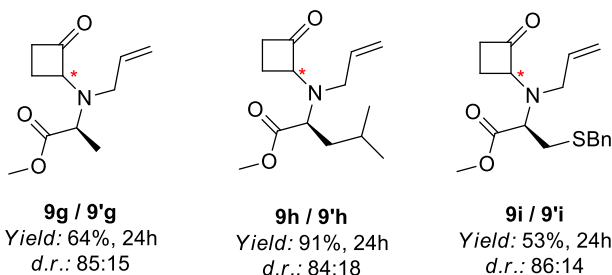
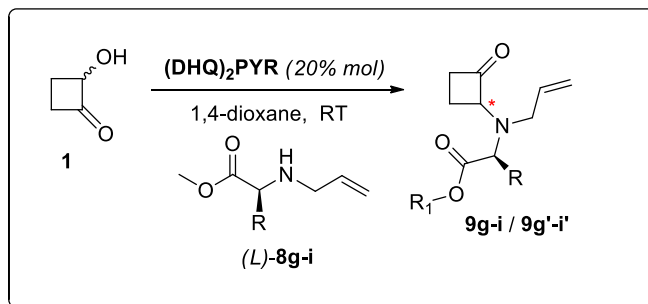


Figure 4.2 – Scope of α -amino acid ester derivatives **8**.

From A. Frongia, N. Melis, I. Serra, F. Secci, P. P. Piras, P. Caboni, *Organocatalytic Asymmetric Condensation/Keto-Enol Tautomerization Tandem Reaction: Access to Cyclobutanone α -Amino Acid Ester Derivatives*, *Asian J. Org. Chem.*, **2014**, 378–381. Copyright © **2015** by John Wiley & Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

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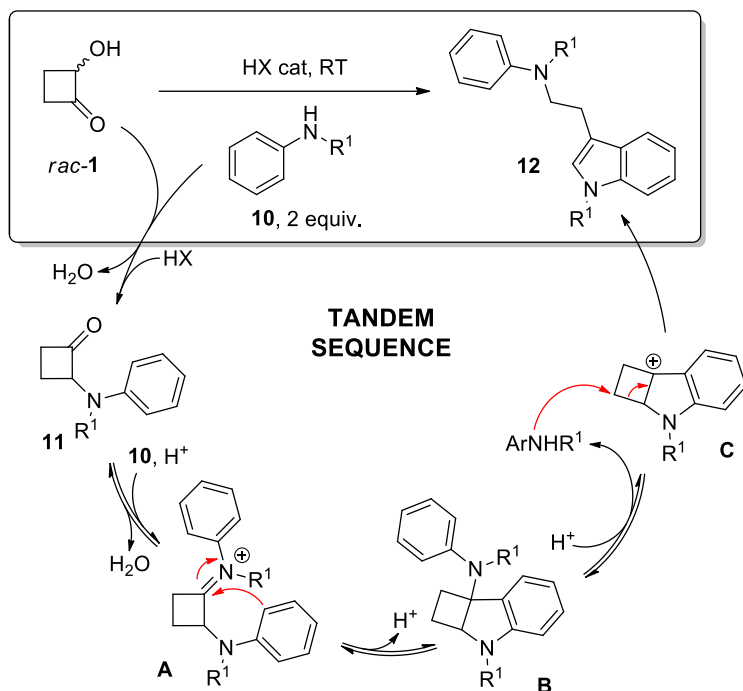
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5 SYNTHESIS OF TRYPTAMINES

Given the ease of its preparation^[1] and the chemical reactivity bestowed by the presence of two adjacent functional groups on a strained four-membered-ring,^[2] α -hydroxycyclobutanone **1** has considerable potential as a building block for organic synthesis. Some notable applications include ring cleavage and methylation to furnish an ester-aldehyde,^[3] one-pot Wittig reaction–acetalization leading to an oxabicyclo[3.2.0]heptane,^[4] preparation of methylenecyclobutane nucleoside analogues^[5] and stereoselective organocatalyzed aldol condensation reactions in the presence of *L*-amino acids.^[6]

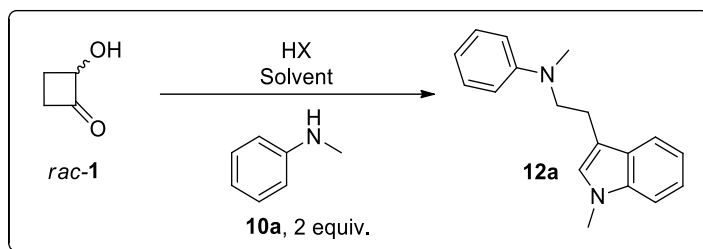
Very recently, our group described that α -hydroxycyclobutanone **1** was a substrate of choice for organocatalyzed condensation reactions with amines, providing access to optically active α -aminocyclobutanones.^[7] Previous studies had reported that the cyclobutanone motif can act as an electrophilic acceptor for intramolecular nucleophilic addition in a ring closure–ring fission process, when a Brønsted acid catalyst is used.^[8] Moreover, this behaviour should be enhanced if a cyclobutyliminium species is involved.^[9] This observation led us to speculate that the reaction of α -hydroxycyclobutanone **1** with two equivalents of a secondary arylamine **10** might deliver a one-pot cascade-reaction^[10] assembly of the tryptamine molecular scaffold. According to our hypothesis (Scheme 5.1), a Brønsted acid catalyst^[11] should promote the formation of the corresponding α -aminocyclobutanone **11** from **1** and one equivalent of **10**. Subsequent acid-mediated condensation with a second equivalent of **10** should furnish the corresponding 2-cyclobutyliminium **A** which undergoes intramolecular ring closure to **B**. Rearrangement by an acid-induced “*depart-and-return*” process^[8b] via **C** should lead to a tryptamine **12**.



Scheme 5.1 – Rational design for the synthesis of tryptamines via a Brønsted acid-catalyzed cascade reaction.

To test our hypothesis we first examined the reaction between α -hydroxycyclobutanone **1** and *N*-methyl aniline **10a**, conducted under reflux in toluene using 20 mol% of PTSA as the catalyst. We were delighted to find that the desired tryptamine product **12a** could be isolated from the reaction mixture in 55% yield (Table 5.1, entry 1). Changing the solvent from toluene to 1,4-dioxane, EtOH or EtOAc did not bring any appreciable improvement in the chemical yields (Table 5.1, entries 2-4). However, a higher conversion was observed in solvent-free conditions at room temperature (Table 5.1, entry 5), providing **12a** in 67% yield. Other Brønsted acid catalysts were evaluated in solvent-free conditions: HI (Table 5.1, entry 6) gave a comparable result to that obtained using PTSA, whereas HBr, HCl, MsOH and TFA performed less efficiently (Table 5.1, entries 7-10). Further evaluation of the solvent-free reaction conditions using a higher and lower catalyst loading (Table 5.1, entries 11-12) indicated that the optimum yield of **12a** was obtained in the presence of 20 mol% of PTSA.

Table 5.1 – Optimization of reaction conditions.



Entry	HX (mol %)	Solvent	Temp	Yield (%) ^[a] 12a
1 ^[b]	PTSA (20)	Toluene	Reflux	55
2	PTSA (20)	1,4-dioxane	Reflux	38
3	PTSA (20)	EtOH	Reflux	30
4	PTSA (20)	EtOAc	Reflux	48
5	PTSA (20)	Neat	R.T.	67
6	HI (20)	Neat	R.T.	65
7	HBr (20)	Neat	R.T.	50
8	HCl (20)	Neat	R.T.	42
9	MsOH (20)	Neat	R.T.	36
10	TFA (20)	Neat	R.T.	61
11	PTSA (10)	Neat	R.T.	53
12 ^[c]	PTSA (35)	Neat	R.T.	62

[a] Isolated yield after chromatography. [b] The reaction conducted at room temperature after 7 days gave **12a** in 52% yield associated with a significant amount of the corresponding aminocyclobutanone **11a** (25% yield).

With the optimized reaction conditions in hand, we next examined the reaction scope using a series of secondary arylamines **10**; results are summarized in Figure 5.1. A reasonable substituent tolerance in arylamines **10** emerged, allowing access to a variety of highly functionalized tryptamines **12** with diverse ring-substituent patterns. *N*-Methyl arylamines **10b-g** bearing electron-donating groups at the *para*-position furnished the corresponding tryptamines **12b-g** in 45-60% yield. Similarly, *meta*-substituted aniline **10h** gave a good yield (81%) of the corresponding tryptamine as an inseparable mixture of the two regioisomers **12h+12h'**. In contrast, aniline **10i** bearing a methoxy substituent at the *ortho*-position failed to produce the

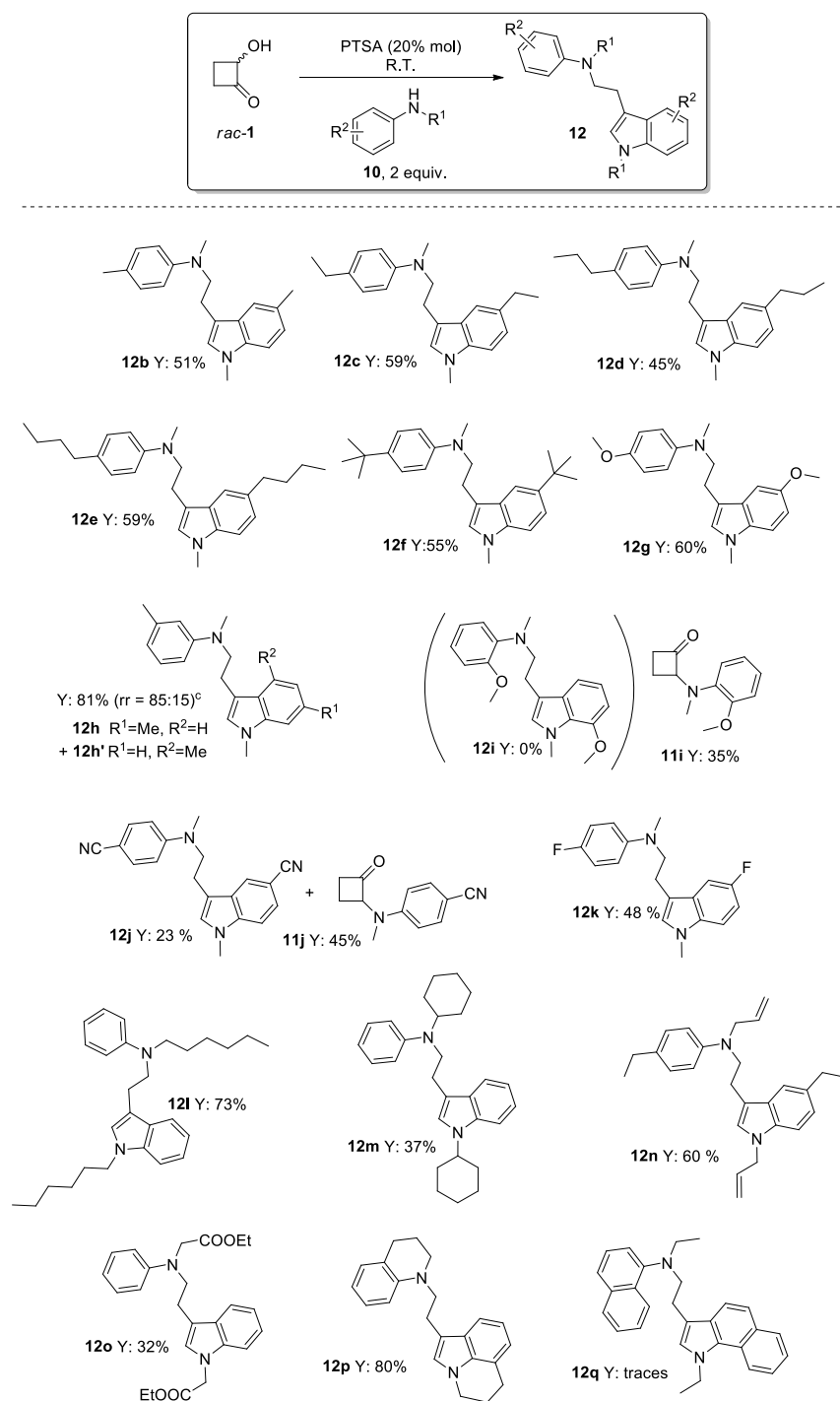
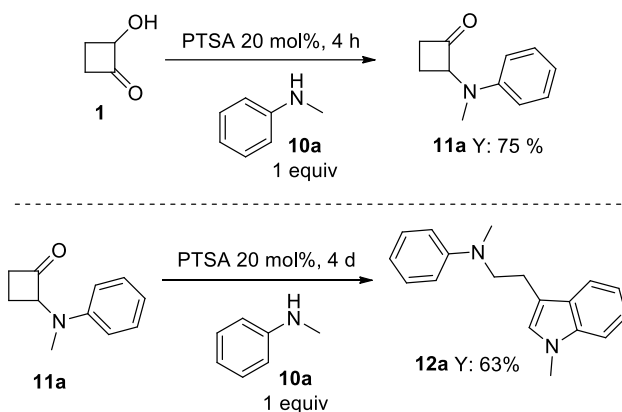


Figure 5.1 – Exploration of substrate scope with a selection of N-alkyl arylamines.

corresponding tryptamine **12i**. In the latter case, the only compound isolated from the reaction was the intermediate α -aminocyclobutanone **11i** with 35% yield.

N-Methyl arylamines **10j** and **10k** (Figure 5.1) bearing electron-withdrawing groups at the *para*-position also underwent the tandem reaction to give tryptamines **12j** (23%) and **12k** (48%). In the former case, the major product was the intermediate α -aminocyclobutanone **11j** (45%). Other *N*-alkyl anilines were examined using the optimized reaction conditions: anilines **10l** and **10n** with primary alkyl and allylic substituents respectively furnished the corresponding tryptamines with good yields (60 and 73%), while an aniline **10m** with a secondary alkyl substituent gave the corresponding tryptamine **12m** with a more moderate yield (37%). The *N*-carboethoxymethyl aniline **10o** gave tryptamine **12o** in 32% yield, showing tolerance of the ester functional group. Interestingly, the best result was obtained using tetrahydroquinoline **10p** which provided the corresponding tryptamine **12p** in 80% yield. *N*-Ethyl-1-naphthylamine **10q** was also examined but tryptamine **12q** was isolated only in trace amounts.



Scheme 5.2 – Control experiments in order to confirm the mechanism and the formation of intermediate **11** in the tandem sequence.

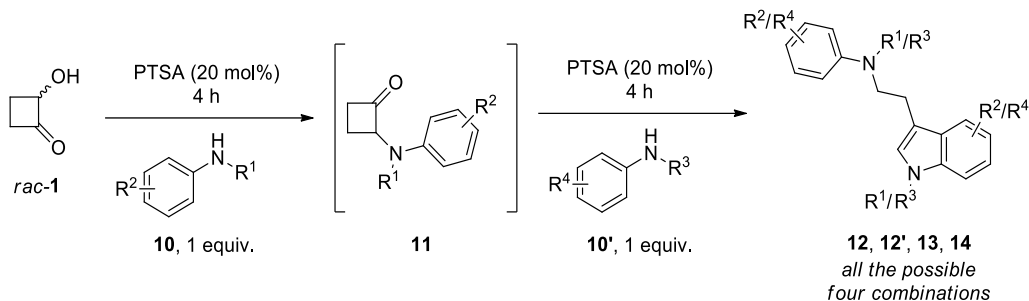
Some control experiments were carried out in order to probe the reaction mechanism (Scheme 5.2). Treatment of α -hydroxycyclobutanone **1** with one equivalent of *N*-methyl aniline **10a** and 20 mol% of PTSA gave α -aminocyclobutanone **11a**, isolated with 75% yield after 4 h reaction time. Subsequently, **11a** was treated with one equivalent of **10a** in the presence of PTSA (20 mol%),

which led smoothly to the expected tryptamine **12a** within 4 days, in 63% isolated yield.

These observations support the working mechanistic hypothesis described in Scheme 5.1. In fact, it can be reasoned that the first step of the sequence involves the formation of the α -aminocyclobutanone intermediate **11** which subsequently undergoes a tandem ring closure–ring fission process to form **12**. The observed formation of **11i** and **11j** during the respective reactions involving **10i** and **10j** is consistent with this proposal.

On the basis of the proposed mechanism, we considered that the reaction process should be tested for the synthesis of tryptamines derived from two different *N*-alkyl anilines **10** and **10'**, by employing one equivalent of each of these reagents sequentially in the one-pot procedure. Thus, in the presence of PTSA (20 mol%), α -hydroxycyclobutanone **1** was treated with one equivalent of an *N*-methylaniline **10** then, after 4 hours, one equivalent of a different *N*-methylaniline **10'** was added and the reaction left to proceed for 4 days. Three such **10/10'** aniline combinations were examined, considering in each case both of the possible sequential order roles.

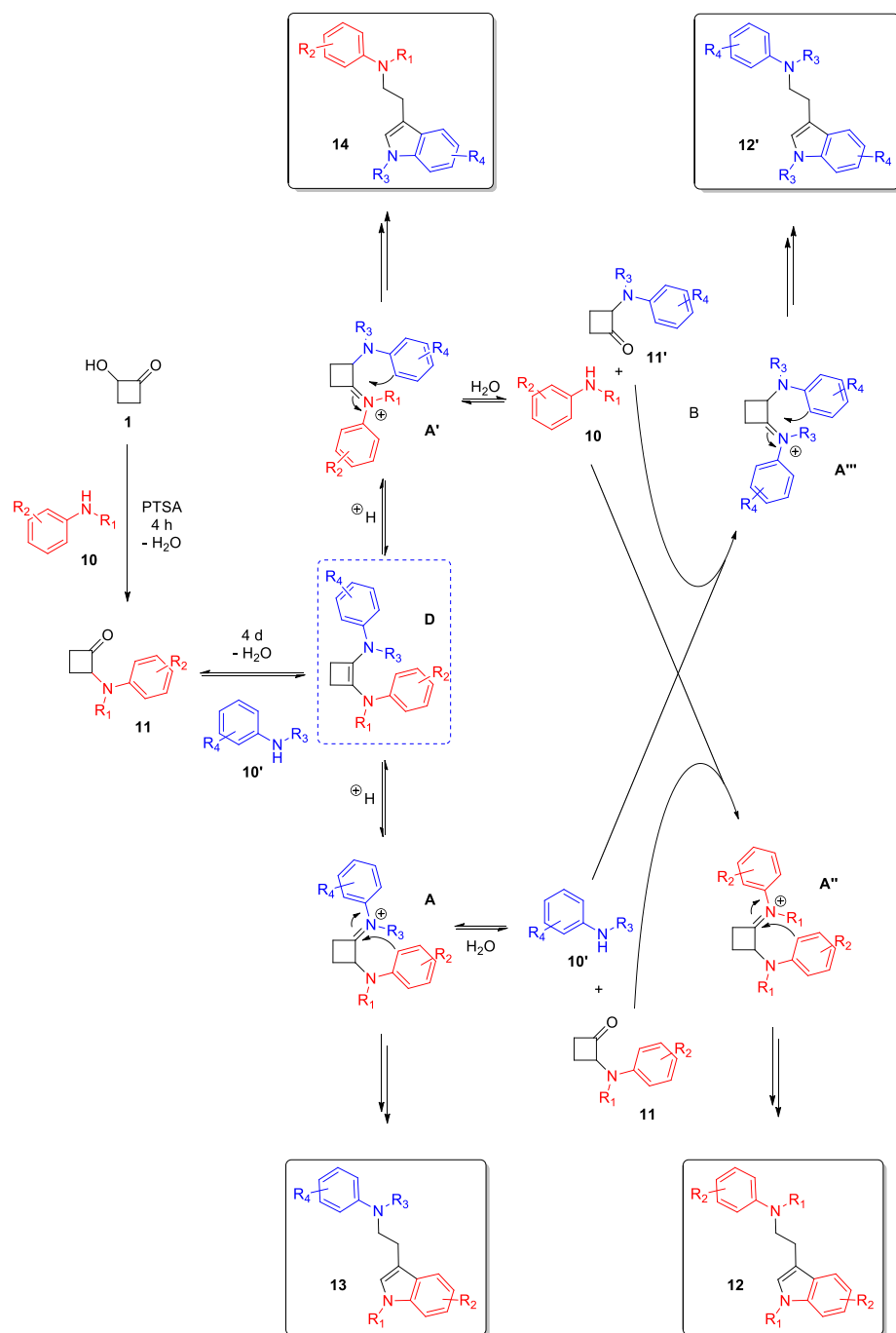
These results are summarized in Scheme 5.3 and Table 5.2. In every case, the anticipated “hetero-assembly” tryptamine product **13**, with the first-added aniline incorporated as the indole core, was indeed obtained (5–44% yield). However, the isomeric tryptamine **14** with the second-added aniline incorporated as the indole core was also obtained (2–18% yield). Furthermore, a significant amount of the “homoassembly” tryptamines **12** and **12'** were formed (12–39%). A plausible explanation is that the condensation of the initially formed α -aminocyclobutanone **11** with the second aniline **10'** might generate cyclobutenediamine **D**, which is the common intermediate in an acid-catalyzed equilibration of two α -aminocyclobutyliminium species **A** and **A'**.

Table 5.2 – Synthesis of tryptamines derived from two different anilines through a sequential one pot procedure.

Entry	10	10'	Tryptamine products (%) ^[a]	Unreacted 10(%) / 10'(%)
1 ^[b]	10a	10b	12a (23)/ 12b (39) 13ab (10)/ 14ab (10)	6/12
2	10b	10a	12a (19)/ 12b (30) 13ab (14)/ 14ab (6)	9/22
3	10a	10l	12a (19)/ 12l (22) 13al (5)/ 14al (12)	7/35
4	10l	10a	12a (19)/ 12l (24) 13al (17)/ 14al (5)	31/4
5	10a	10p	12a (20)/ 12p (13) ^[b] 13ap (8)/ 14ap (18)	11/30
6	10p	10a	12a (12)/ 12p (12) 13ap (44)/ 14ap (2)	17/13

[a] Reaction products were inseparable using standard chromatographic methods; conversions were calculated from analytical GC-MS data. [b] The reaction between **11a** and **10p**, carried out over 4d in the presence of PTSA, exhibits a similar trend: **12a**(19%) / **12p**(17%) / **13ap**(5%) / **14ap**(50%) / **10a** (6%) / **10p** (3%).

Since these cations are in equilibrium with the corresponding cyclobutanones (**11** and **11'**) and free anilines (**10** and **10'**) respectively, any combination of **11** or **11'** with an aniline **10'** or **10** now becomes possible, so that four different intramolecular ring closure–ring fission processes (via **A**, **A'**, **A''** or **A'''**) can be envisaged, leading to tryptamines **13**, **14**, **12** and **12'** respectively. If cation **C** is indeed an intermediate in the “depart-and-return” rearrangement process (Scheme 5.1), it cannot be excluded that any free aniline, **11** or **11'**, could be incorporated in the final tryptamine structure at this late stage. Further mechanistic studies will be required to resolve this issue.



Scheme 5.3 – Synthesis of tryptamines derived from two different anilines through a sequential one pot procedure.

In summary, a new solvent-free Brønsted acid catalysed cascade reaction has been established, allowing access to highly substituted tryptamines from simple starting materials in a one-pot metal-free and solvent-free process under mild conditions. To the best of our knowledge, there are no literature reports of the construction of an indole skeleton using the present strategy.^[12] Therefore, the use of a four-carbon synthon to provide the indole C2, C3 and the two exocyclic centres in a tryptamine synthesis is highly original,^[13] since most synthetic methods involve modifications of other preformed indole derivatives.^[14] It is noteworthy that indoles react with cyclobutanone derivatives in the presence of a Lewis acid in a quite different fashion, to give hydrocarbazoles.^[15] Tryptamines are of great importance due to their wide-ranging biological activities leading to applications in medicinal chemistry and recreational use,^[16] as well as serving as intermediates for the preparation of more complex heterocyclic structures. This concise approach for the assembly of tryptamine derivatives should lend itself to the creation of natural product-inspired molecular-complexity compound collections.^[17]

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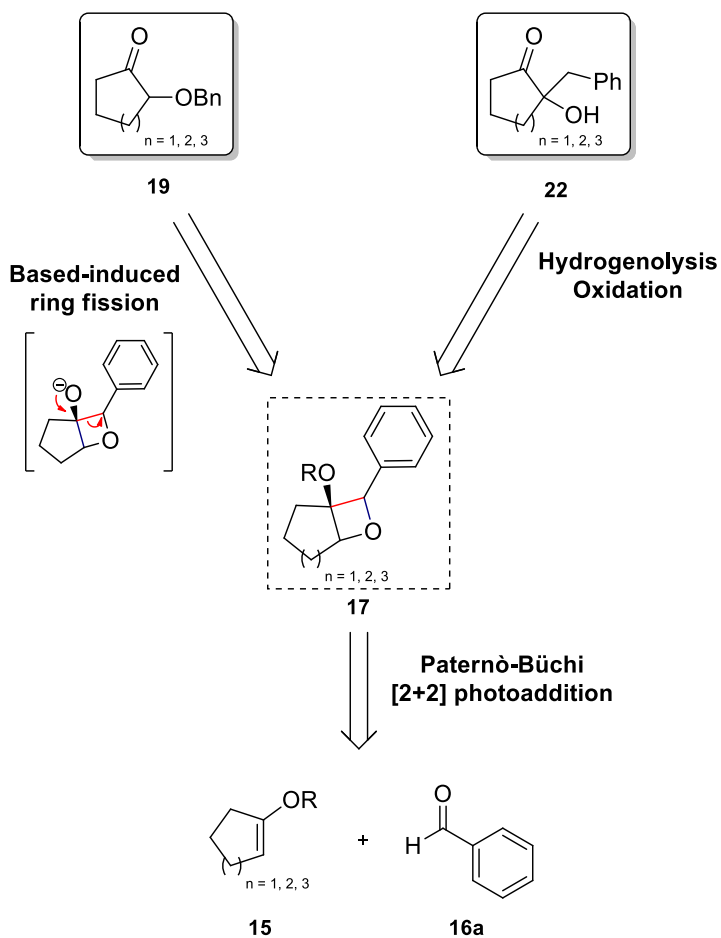
6 SYNTHESIS AND POST-FUNCTIONALISATION OF SILYLATED BICYCLIC OXETANES

The scope of the condensation/asymmetric protonation tandem sequence for the preparation of α -amino ketones has been studied almost exclusively with regards to the substitution pattern of the amine moiety.^[1] On the other hand, only few α -hydroxyketone derivatives has been tested in the methodology. Consequently, with the aim of further study the substrate scope of the tandem sequence focusing on the ketone partner, we looked for a general and straightforward method for the synthesis of cyclic α -hydroxyketones. This part has been conducted in CP³A group of ICMMO (Université Paris-Sud) under the supervision of Prof. David J. Aitken and Dr. Thomas Boddaert and with the help of Alberto Luridiana.

As mentioned in Chapter 2, we identify in the Paternò-Büchi reaction between a cyclic silyl enol ether and benzaldehyde (**16a**) a good strategy to obtain such class of derivatives. In fact, we hypothesized that the bicyclic photoadduct **17** could undergo to a base-induced rearrangement that led to α -benzyloxyketones **19** (Scheme 6.1). Moreover, in order to develop a more general methodology, α -benzyl- α -hydroxyketones **22** could be prepared starting from the same **17** photoadduct through hydrogenolysis and subsequent oxidation.

The Paternò-Büchi reaction is a [2+2]-cycloaddition between an alkene and a carbonyl compound to form the corresponding oxetane.^[2] Woodward-Hoffmann rules on pericyclic reactions classify the formation of the four-membered ring substructure prohibited *via* thermic activation due to the non-conservation of orbital symmetry. Therefore, such transformation can be carried out only under photochemical control through the formation of an excited state. The reaction occurs between a photoexcited carbonyl group and a ground state alkene. In particular, the light-absorbing carbonyl species undergoes n,π^* transition which

involve the excitation of an oxygen non-bonding electron to the first excited singlet state S_1 .



Scheme 6.1 – Retrosynthetic plan for synthesizing α -hydroxyketones **17** and **18** via rearrangement or hydrogenolysis of bicyclic Paternò-Büchi photoadducts.

Transition to the more stable triplet excited state T_1 cannot happen directly from the ground state because it would involve a spin forbidden excitation, but it can occur nonradiatively via intersystem crossing (ISC) from S_1 . Hence, the triplet excited state carbonyl species reacts with the alkene at the ground state to afford the oxetane with the involvement of a 1,4-biradical intermediate (Figure 6.1) and recombination of it.^[3]

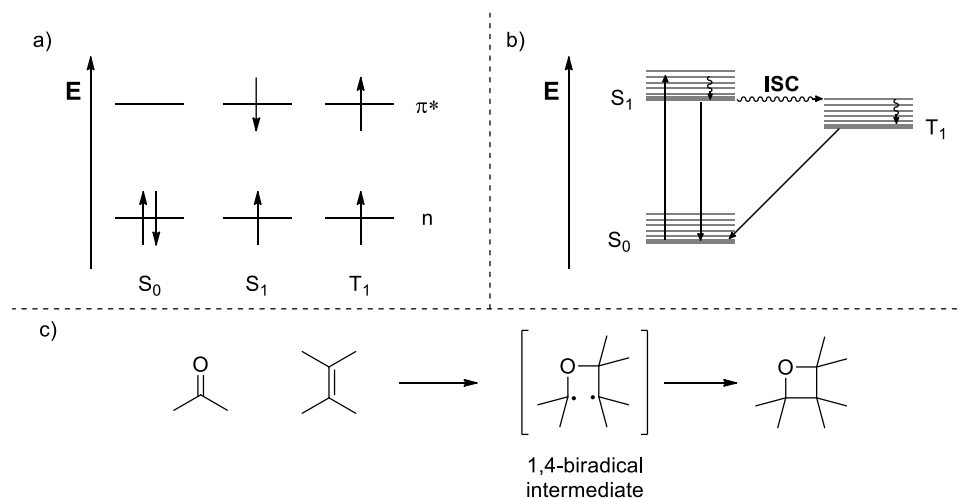
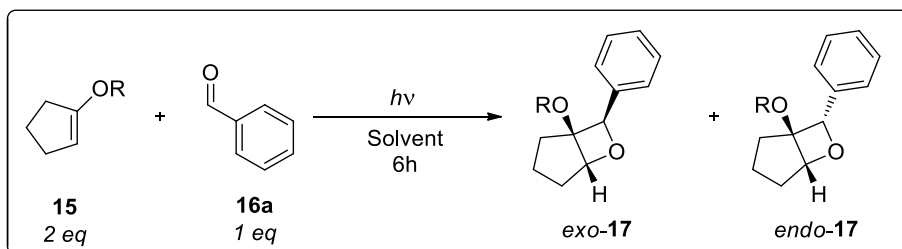


Figure 6.1 – a) Schematic electron occupation diagram for S_0 , S_1 and T_1 . b) Molecular state diagram for excitation of carbonyl compounds. c) General mechanism of Paternò-Büchi reaction.

Despite the applications described on open chain silyl enol ether derivatives in combination with aldehydes and ketones for oxetane synthesis with Paternò-Büchi reaction,^[4] no examples of cyclic silyl enol ethers are reported in literature to the best of our knowledge. For this reason, we started with the optimisation of the reaction condition with such cyclic substrate to synthesize the cyclic photoadduct **17**. The corresponding OTMS silyl enol ether of cyclopentanone **15a** has been chosen as model substrate and we started with a solvent screening. Therefore, Paternò-Büchi reaction between the silyl enol ether **15a** and distilled benzaldehyde **16a** (2:1 ratio) was initially carried out by using the Rayonet RPC-200 photochemical reactor by the Southern New England Ultraviolet Co. with 300 nm lamp. Despite the formation of the expected photoadduct **17**, due to the low reproducibility of results we decided to conduct the reaction between **15** and **16a** has been conducted in a 250 mL pyrex reactor using a 400W Hg-vapor lamp (300-350nm) with a selection of solvents (Table 6.1).

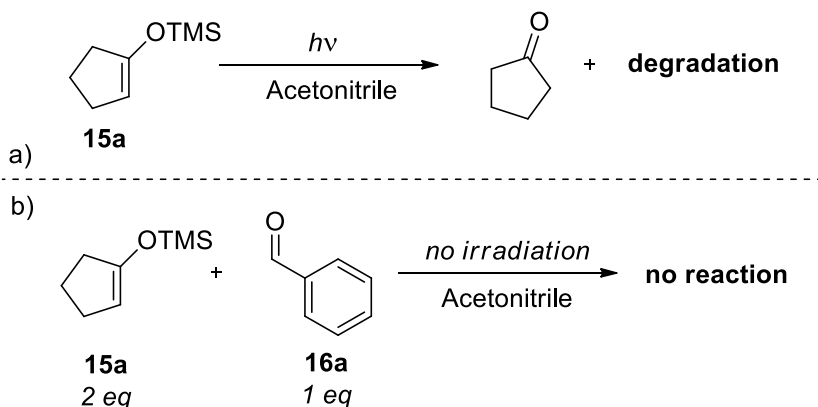
We performed the reaction in acetonitrile, benzene, toluene, trifluorotoluene and cyclohexane (Entries 1-5, Table 6.1) and we isolated the two diastereomeric photoadduct products by column chromatography. Despite the high yields reported for this reaction with open chain silyl enol ethers, we obtain at our best a comprehensive 42% yields of **17** by employing acetonitrile as solvent.^[4a]

Table 6.1 – Paternò-Büchi solvent screening and evaluation.


Entry	R	Solvent	Yield (%)	d.r. ^[a]
			exo-17 + endo-17	exo-17 : endo-17
1	TMS	Acetonitrile	42	65:35
2	TMS	Benzene	27	55:45
3	TMS	Toluene	33	62:38
4	TMS	Trifluorotoluene	27	55:45
5	TMS	Cyclohexane	27	55:45
6	TBS	Acetonitrile	7	55:45
7	TBS	Trifluorotoluene	12	65:35
8 ^[b]	TMS	Acetonitrile	21	65:35

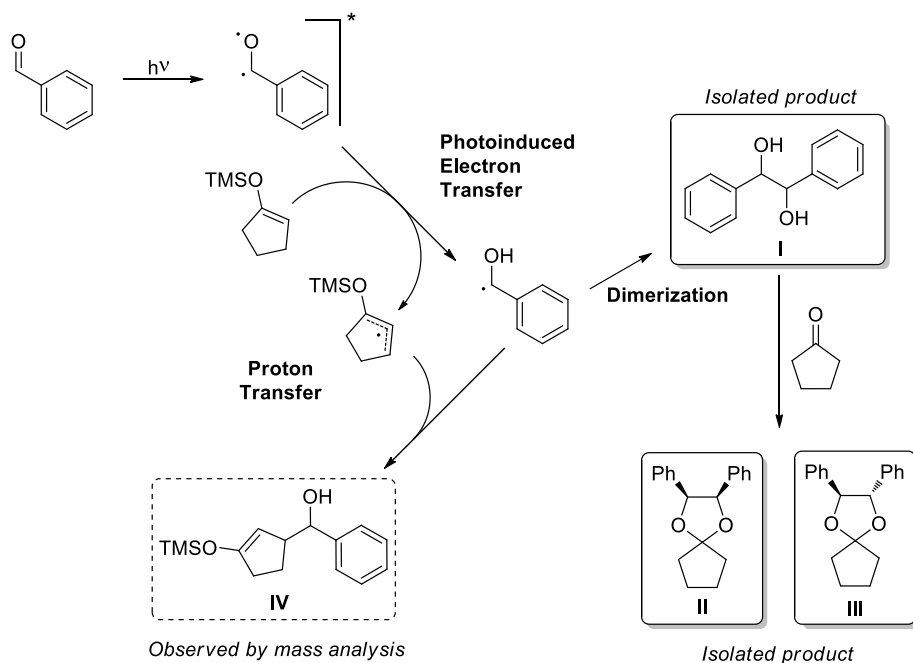
[a] All the *d.r.* are calculated on the ¹H-NMR spectrum of the crude. [b] The reaction has been scaled up in 1 L reactor and conducted for 26h.

Because of the several by-products formed during the reaction, we decided to test the stability of the starting materials, as shown in Figure 6.2.


Figure 6.2 – Stability tests of starting materials **15a** and **16a**.

Degradation of **15a** to cyclopentanone and other derivatives occurred during irradiation under the same experimental conditions of the reaction. Furthermore, **15a** and **16a** do not react without irradiation and no β -hydroxyketone derived from Mukaiyama aldol reaction has been observed. Though, also in the latter case, some cyclopentanone as degradation product of **15a** has been observed.

In addition to the observed instability, benzaldehyde **16a** undergoes to photoinduced electron transfer (PET) under irradiation (Scheme 6.2). In fact, we observed the formation of some products that come from PET mechanism, such as the diol **I** formed by dimerization of benzaldehyde radical and derivatives such as the acetal derivatives **II** and **III**.^[5] Some other products, such as **IV**, has been hypothesized based on high resolution mass analysis. Interestingly, apolar solvents that are supposed to minimize the PET side reaction (e.g. benzene and cyclohexane) performed less efficiently than a polar solvent as acetonitrile.



Scheme 6.2 – Paternò-Büchi side products.

In an effort to improve the efficiency of the reaction by using less sensitive starting material, we performed some tests by using OTBS silyl enol ether **15b** in acetonitrile and trifluorotoluene (Entries 6-7, Table 6.1) with disappointing results

in terms of yields of **17b**. Therefore, keeping acetonitrile as the optimal solvent choice, we scaled up the reaction in 1 L vessel. Working on a larger scale was unfortunately less efficient, probably due to the prolonged reaction time, but provide grams of products **17a** (Entry 8, Table 6.1).

In all our attempts photoadducts **17** has been obtained with a complete regioselectivity and a diastereomeric ratio (*d.r.*) that ranged from 65:35 to 55:45, always in favour of *exo*-**17**. The regioselectivity of the Paternò-Büchi reaction is determined by electronic effects. In fact, the umpolung of the C-O bond of the photoexcited carbonyl compound induces the formation of the new O-C bond between the oxygen atom and the more electron rich Carbon atom of the alkene partner. For this reason, the second regioisomer of the photoadduct **17** is not formed. Concerning the diastereoselectivity of the reaction, the mechanism of the Paternò-Büchi reaction led to the formation of the bicyclic fused ring junction with a *cis* configuration only and the *exo/endo* ratio could be explained by a steric hindrance control. Indeed, as exposed previously by Bach, Abe and Griesbeck in similar studies,^[6] the Paternò-Büchi reaction on electron-rich α,α -disubstituted alkene partners favours the formation of the less congested biradical intermediate.

With the optimised conditions in hands, we started to investigate the substrate scope of the reaction by employing six- and seven-membered ring ketone derivatives (**15c** and **15d** respectively), and two representative ketones (acetone **16e** and benzophenone **16f**). As shown in Figure 6.3, the reaction proved to be extremely substrate dependent. In fact, only **15c** led to the corresponding photoadduct **17c** even with a 5% yield, whereas in the other examples no reaction occurred.

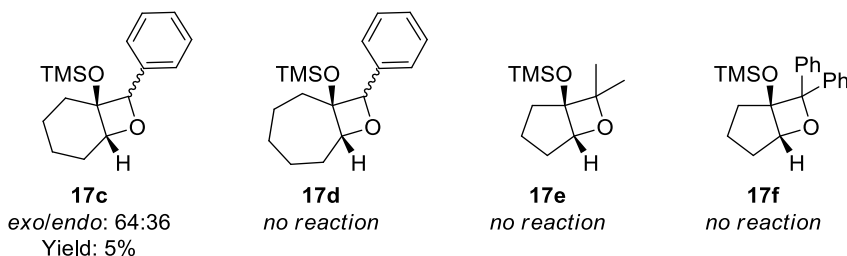
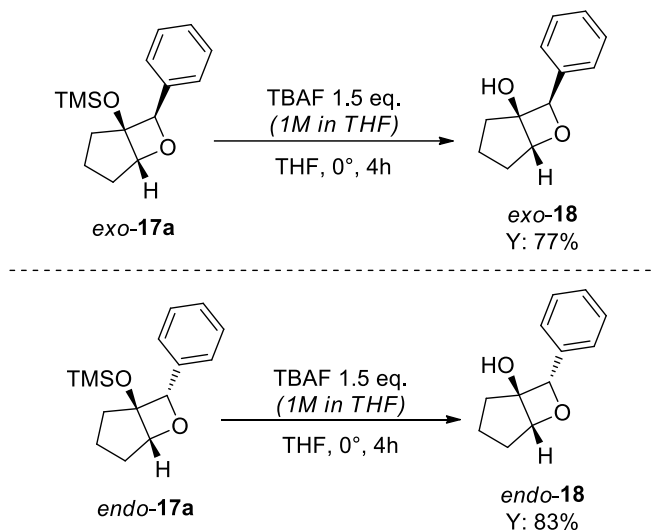


Figure 6.3 – Preliminary investigation on the substrate scope of the reaction.

With pure *exo*- and *endo*- photoadducts **17a** in our hands, we proceeded with the post-functionalization of such derivatives focusing our attention firstly on the desilylation step.



Scheme 6.3 – Deprotection of *exo*-17a and *endo*-17a with TBAF in THF.

Silyl deprotection of both *endo*-17a and *exo*-17a bicyclic photoadducts were carried out under typical tetra-*n*-butylammonium fluoride (TBAF) conditions in THF (Scheme 6.3). It has to be noted that contrary to Bach, treatment of **17** with potassium carbonate in MeOH left it unchanged.^[7] Both substrates led to the corresponding deprotected alcohols *endo*-18 and *exo*-18 with 83% and 77% yield respectively.

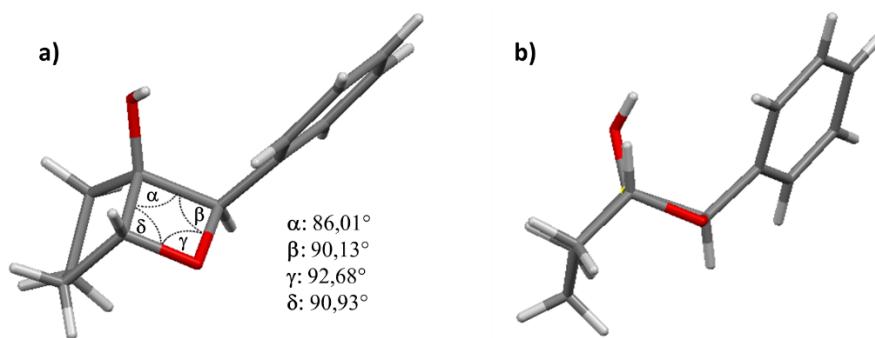


Figure 6.4 – X-ray crystal structure of *exo*-18. In a) angle values are showed while in b) the orientation shows clearly the flat structure of the oxetane moiety.

A crystal sample of both *exo*-**18** and *endo*-**18** were obtained by slow evaporation of chloroform and they were suitable for X-ray analysis (Figure 6.4 and Figure 6.5 respectively) in order to confirm the relative stereochemistry of the derivative.

These substrates crystallize in monoclinic crystal system and the structure shows clearly the configuration of the bicyclic compound and the almost perfectly flat oxetane system. Moreover, it is interesting to notice that the angles of the four-membered ring of the oxetanes have values that ranged from 85,13° to 92,68°. These atypical values for a sp³-hybridized carbon are related to the inherent strain of the oxetane moiety and this can be reflected in the reactivity and stability of such derivatives.

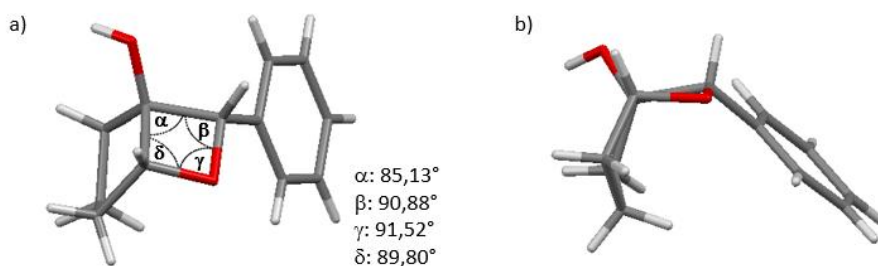


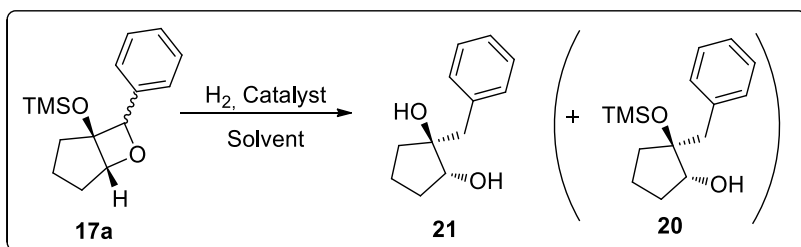
Figure 6.5 – X-ray crystal structure of *endo*-**18** in two different orientations.

Then, we proceeded with the synthesis of diastereochemically pure 1,2-diols *via* palladium-based hydrogenolysis. The hydrogenation step should occur equally on both *exo*- and *endo*- diastereomers because of the breaking of the O-Bn bond, which bears the stereocenter that differentiate them. Hence, since the other two stereocenters have the same relative configuration and they are not affected by the hydrogenolysis process, diastereochemically pure *trans*-1,2-diol **21** can be selectively obtained. Moreover, OTMS protecting group is reported to have a limited stability under classic hydrogenation conditions, such in the case of Bach's studies on oxetanols.^[8] For this reason, hydrogenolysis was performed starting directly from the silylated photoadduct **17**.

Hydrogenation step has been carried out under classic hydrogenolysis condition and the results are reported in Table 6.2. The reaction of *exo*-**17a** in methanol using Pd/C as catalyst led to the expected 1,2-diol **21** in only 59% yield

(Entry 1, Table 6.2). By using ethyl acetate as solvent for carrying out the reaction, diol **20** was afforded with longer time of reaction (26h) but with a cleaner crude and improved yields (Entry 2-3, Table 6.2, respectively 77% for *exo*-**17a** and 97% for *endo*-**17a**).

Table 6.2 – Hydrogenolysis of **17a** to diastereochemically pure 1,2-diols **21**.



Entry	Substrate	Catalyst	Conditions'	Solvent	Yield 20 (%)
1	<i>exo</i> - 17a	Pd/C (8)	RT, 4h	MeOH	59%
2	<i>exo</i> - 17a	Pd/C	RT, 26h	AcOEt	77%
3	<i>endo</i> - 17a	Pd/C	RT, 26h	AcOEt	97%
4	<i>exo</i> - 17a	Pd/C	RT, 2.5h	AcOEt	quant. ^[a]
5	<i>exo</i> - 17a	Pd(OH) ₂ /C	RT, 26h	AcOEt	quant.
6	<i>exo</i> - 18	Pd/C	RT, 4h	AcOEt	quant.

[a] A 50:50 mixture of deprotected and monoprotected diol has been observed by ¹H-NMR analysis of the crude.

By stopping the reaction after 2.5 hours, NMR analysis of the crude showed a 50:50 mixture of deprotected and monoprotected diol (**21** and **20** respectively, entry 4, Table 6.2), which demonstrate clearly that the TMS group is not stable under these conditions and that it is not possible to perform the hydrogenolysis selectively. Even with Pd(OH)₂ instead of Pd(0), the TMS was completely deprotected and the diol **21** was obtained quantitatively after 26h (entry 5, Table 6.2). Pd/C-catalysed hydrogenolysis of *exo*-**18** was performed in ethyl acetate and the corresponding diol **21** was afforded quantitatively in 4h (Entry 6, Table 6.2). Nonetheless, the instability of OTMS functionality under hydrogenolysis conditions and the high efficiency of the reaction make convenient the one-pot procedure directly from **17** rather than a two-step deprotection/hydrogenolysis sequence. Derivative **21** crystallizes in tetragonal crystal system and the X-ray analysis confirms the *trans* relative configuration of the 1,2-diol (Figure 6.6).

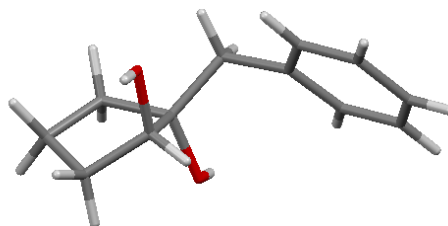
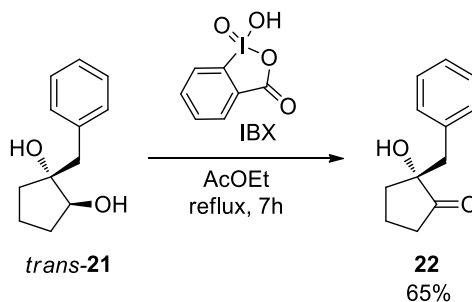


Figure 6.6 – X-Ray crystal structure of *trans*-1,2-diol derivative **21**.

The synthesized 1,2-diol **21** should be easily converted to the corresponding α -benzyl- α -hydroxyketone **22** by means of oxidation of the secondary alcohol. Literature reports some efficient procedures for oxidizing similar vicinal diol derivatives to hydroxyketones.^[9]

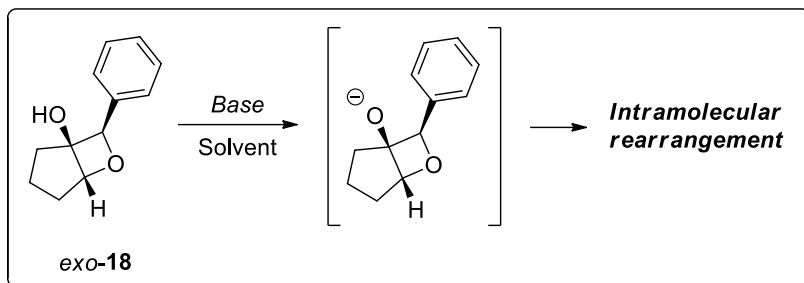


Scheme 6.4 – Oxidation of **21** to α -substituted- α -hydroxyketone **22**.

In our case, we performed the reaction using 2-iodoxybenzoic acid (IBX) as oxidant species^[10] and we were able to afford the corresponding α -hydroxyketone **22** in a non-optimized 65% yield.

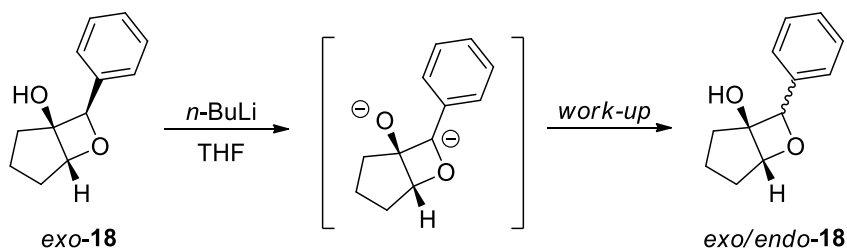
According to our planned strategy, a series of experiments dedicated to induce a base-catalysed rearrangement of **18** were conducted in order to afford our second target ketone: the α -benzyloxycyclopentanone **19**. Consequently, *exo*-**18** was treated under several basic conditions as reported in Table 6.3.

Some experiments with bases and additives were performed with the purpose to make the base or the substrate more reactive. Entry 10 (Table 6.3) refers to the reaction with ^tBuOK in presence of 18-crown-6, which is able to complex K⁺ cation and make the base more reactive.

Table 6.3 – Screening of basic condition for the rearrangement of *exo-18*.

Entry	Base	Solvent	Conditions'	Y (%)
1	K ₂ CO ₃ (1,5 eq)	MeOH	RT, 50 °C, 80 °C	-
2	K ₂ CO ₃ (1,5 eq)	Acetone	RT, 50 °C, 80 °C	-
3	NaOH (1,5 eq)	MeOH	RT, 50 °C, 80 °C	-
4	KOH (1,5 eq)	Toluene	RT, 50 °C, 80 °C	-
5	^t BuOK (1,5 eq)	^t BuOH	RT	-
6	^t BuOK (2,5 eq)	THF	RT, 50 °C, 80 °C	-
7	DIPEA (1,5 eq)	MeOH	RT	-
8	DBU (1,5 eq)	MeOH	RT	-
9	NaH (1,5 eq)	THF	RT, 50 °C	-
10 ^[a]	^t BuOK (1,5 eq)	THF	RT	-
11 ^[b]	NaH (2,5 eq)	THF	RT	26 ^[c]
12 ^[d]	ⁿ BuLi (1; 2 and 4 eq)	THF	0 °C	-

[a] 18-crown-6 has been used for K⁺ complexation. [b] BF₃·Et₂O was added in order to activate the oxetane ring through coordination. [c] The reported yield is referred to product **25** after purification by flash chromatography. [d] Some epimerization of starting material was observed.

**Scheme 6.5** – Hypothesized epimerizing mechanism for *exo-18* with *n*-BuLi

In entry 11 (Table 6.3) the reaction was carried out in presence of NaH and BF_3 diethyl etherate ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) as a coordinating Lewis acid in order to activate the oxetane system by weakening the O-C bond. Among these trials, no reaction has been observed with crown ether but, on the other hand, by using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ the reaction afforded a new product in 26% yield. Surprisingly, the new-formed product is not the expected one but it denotes a different reactivity of the substrate **exo-18**.

This new product has been identified as the derivative **25** by full NMR characterisation and X-ray analysis of a suitable monocystal. Compound **25** crystallizes in monoclinic crystal system by slow evaporation of chloroform and X-ray analysis of the crystal sample allow us to unambiguously determine the correct structure of product **25** as the 2-phenylcyclohex-2-enone (Figure 6.7).

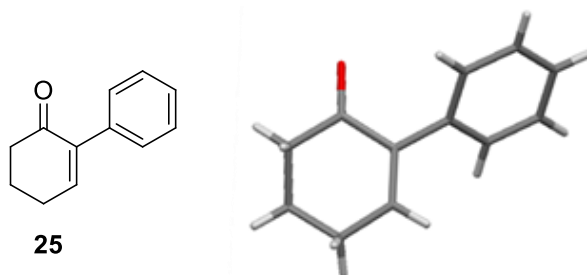


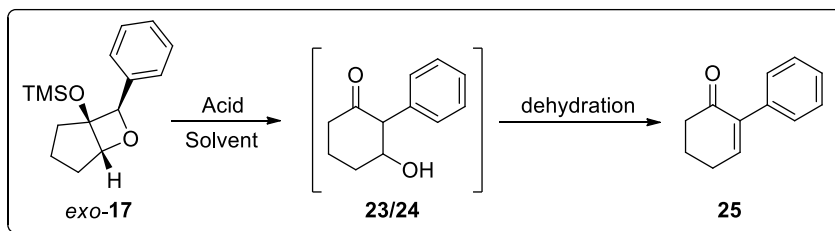
Figure 6.7 – X-ray diffraction structure of derivative **25**.

Since the product was obtained exclusively when a Lewis acid ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) was employed, we speculated that an acid-promoted rearrangement was involved. Such rearrangement product should be an alcohol which can afford **25** through dehydration. According to this hypothesis, **25** is formed *via* a one-pot desilylation/ring fission-ring expansion/dehydration tandem sequence. From a mechanistic point of view, the Lewis acid could bond with both of the oxygen atoms of the bicyclic oxetanol and, between the two, the alcohol function should be a better Lewis base. Despite that, we believe that an equilibrium between the two coordination types is possible and, moreover, only the complexation of the oxetane oxygen make the system evolve further.

We therefore focused our attention on testing acid derivatives in order to enhance the efficiency of the transformation and to prove the presence of

intermediates in the reaction. Table 6.4 summarizes the attempts made in this direction. Due to the instability of OTMS protecting group under acidic condition, we decided to start from the protected photoadduct *exo-17a*. Firstly, we confirmed the formation of **25** by employing $\text{BF}_3 \cdot \text{Et}_2\text{O}$ only and we isolated the product in 23% yield (Entry 1, Table 6.4), similarly to what obtained from *exo-18* with $\text{NaH}/\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Entry 11, Table 6.3). A catalytic amount of TMSCl in MeOH is known to produce HCl *in situ* and remove silyl protecting group. This reaction has been tested and afforded the same compound **25** in 29% yield (Entry 2, Table 6.4). With the aim of a better control of the reaction, these entries were repeated at 0°C and in both cases the product has been isolated in a diminished 20% yield (Entries 3-4, Table 6.4).

Table 6.4 – Screening of acid conditions for the rearrangement of *exo-17*.

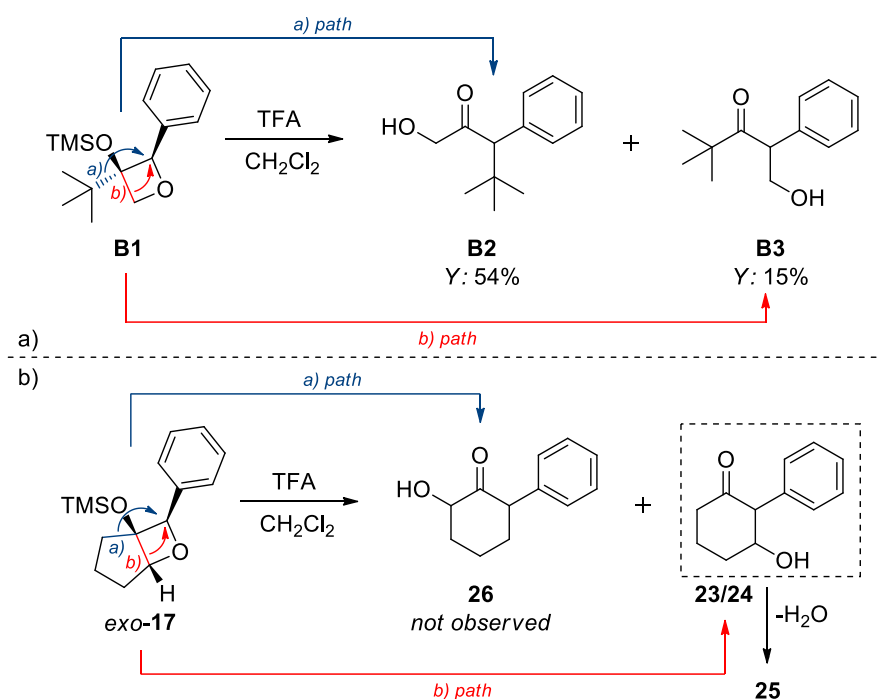


Entry	Substrate	Acid	Solvent	Conditions	Yield
1	<i>exo-17a</i>	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	MeOH	0.024 M, RT, 4h	23%
2	<i>exo-17a</i>	TMSCl (cat)	MeOH	0.024 M, RT, 5h	29%
3	<i>exo-17a</i>	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	MeOH	0.024 M, 0°C , 3h	20%
4	<i>exo-17a</i>	TMSCl (cat)	MeOH	0.024 M, 0°C , 2h	20%
5	<i>exo-17a</i>	TFA (130 eq)	CH_2Cl_2	0.19 M, 0°C , 4h	57%
6	<i>exo-17a</i>	TFA (130 eq)	CH_2Cl_2	0.08 M, 0°C , 26h	78%
7	<i>exo-17b</i>	TFA (130 eq)	CH_2Cl_2	0.19 M, 0°C , 4h	74%
8	<i>exo-18</i>	TFA (130 eq)	CH_2Cl_2	0.08 M, 0°C , 2h	63%
9	<i>endo-17a</i>	TFA (130 eq)	CH_2Cl_2	0.08 M, 0°C , 26h	64%
10	<i>exo-17a</i>	TFA (6.8 eq)	CH_2Cl_2	0.19 M, 0°C , 4h	33%
11	<i>exo-17a</i>	TFA (3 eq)	CH_2Cl_2	0.19 M, 0°C , 5h	24%

We therefore performed the reaction with TFA as Brønsted acid and we were able to isolate enone **25** in 57% yield (Entry 5, Table 6.4). An increased yield

(78%, entry 6, Table 6.4) has been obtained when the reaction was repeated in more diluted conditions. The reaction has been tested starting from OTBS derivative **exo-17b** and the deprotected photoadduct **exo-18** (Entries 7-8, Table 6.4) isolating **25** in 74% and 63% yield respectively.

Same condition has been applied by Bach and his co-workers on non-bicyclic silyloxy oxetanes (Scheme 6.6a).^[11] By using TFA they promoted two different rearrangements involving migration of two different bonds (*a* and *b* in Scheme 6.6a). In fact, the silyloxy oxetane **B1** afforded the product **B2** following path *a*), by migration of *tert*-butyl group to the benzylic position in 54% yield, and the β -hydroxyketone **B3** following the path *b*) by migration of the CH₂-OH group to the benzylic position in 15% yield. Both of these rearrangements implicate the fission of oxetane ring and they are reported to be in competition.



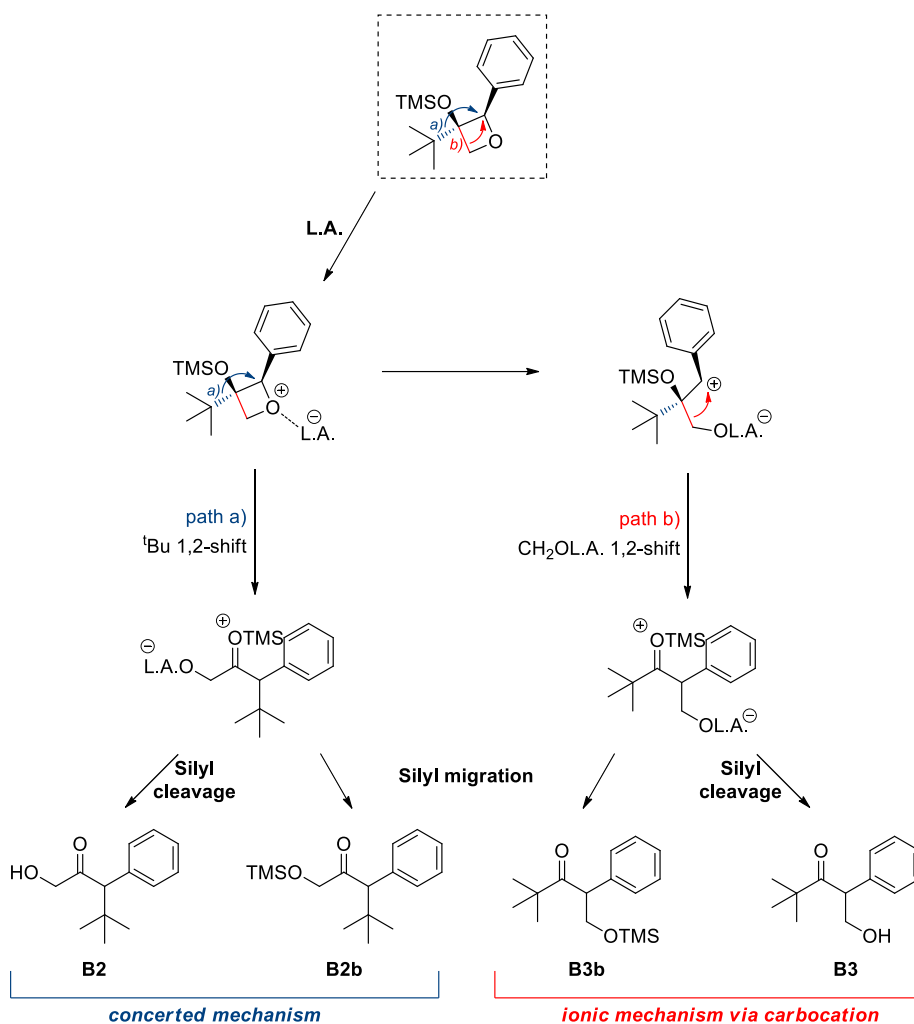
Scheme 6.6 – a) Reactivity of silyloxy oxetanes reported by Bach and co-workers. In presence of TFA, two products derived from two different migration mechanisms have been observed. b) Acid-induced rearrangement products assuming that **exo-17a** shows the same reactivity of **B1** in Bach's work.

Starting from these considerations and assuming the same reactivity of the case described by Bach *et al*, by using the synthesized bicyclic photoadducts **17a** two products should be observed as well, as shown in Scheme 6.6b. Starting from our bicyclic derivatives, the product of such rearrangements have six-membered rings due to the fact that both *a*) and *b*) bonds are part of a second cycle. Interestingly, as already shown in Table 6.4, the only product of the reaction is the enone **25**, which is formed by acid-mediated dehydration of *trans*- or *cis*- alcohol (**23** and **24** respectively). Hence, silyloxy oxetane *exo*-**17a** shows an inverted selectivity and an intrinsic preference towards path *b*) and, more interestingly, no traces of α -hydroxyketone **26** was observed.

Bach's further investigation on this reaction by employing Lewis acids led to a better understanding of the two involved migration processes.^[12] In this work, Bach group pointed out the great influence of the solvent and the Lewis acid species, and they were able to optimise conditions to favour selectively both migration paths. More specifically, a strong Lewis acid such as AlCl₃ promotes the rearrangement through *b*) pathway and shows a selectivity for **B3** derivatives. Whereas a complete selectivity in favour of path *a*) was observed by employing TiCl₄, relatively weaker, in a coordinating polar solvent such as diethyl ether.

Moreover, for each migration process both the free and the silyl protected alcohol were obtained, which derives from silyl migration. The nature of Lewis acid and the solvent was reported to influence the ratio between the products of silyl migration and cleavage competitive reactions. A mechanism based on the reported experimental evidences has been proposed assuming the existence of two competitive pathways (Scheme 6.7).

The Lewis acid (L.A.) activates the oxetane ring by coordination of the oxygen oxetane atom. This adduct can directly react following path *a*) or, in alternative, the opening of the oxetane moiety can occur to form the corresponding benzylic carbocation. In the latter case, the intermediate would yield selectively the migration product formed through path *b*). Previous investigations reported on literature suggest that migration of the alkyl group (path *a*) would be disfavoured *via* carbocation intermediate and, on the other hand, with such intermediate no hydroxymethyl migration (path *b*) would be favoured.



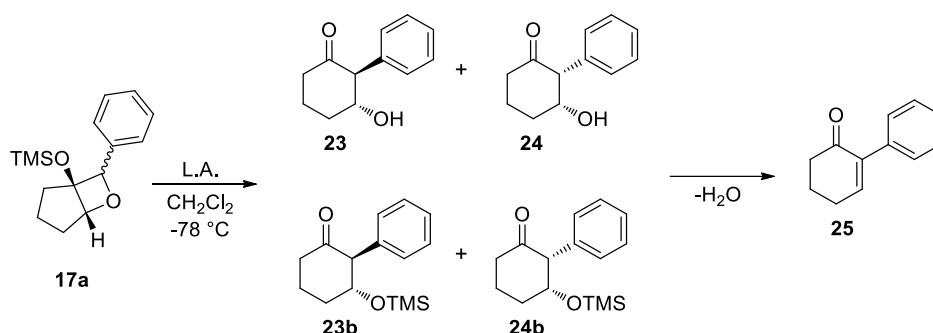
Scheme 6.7 – Mechanistic hypothesis proposed by Bach.

So, with these considerations in mind, we tested Lewis acids on the synthesized bicyclic derivative **17**. AlCl_3 has been chosen as the suitable Lewis acid for this investigation due to the fact that, according to Bach's work, it should favour the observed migration *via* path b). All the tests were carried out at $-78\text{ }^\circ\text{C}$ with the aim of avoiding dehydration with a better control of the transformation and these results are reported in Table 6.5.

Photoadduct *exo*-**17a** reacts easily in presence of AlCl_3 and by NMR analysis of the crude, alcohols **23** and **24** were formed in a 97:3 ratio (Entry 1, Table 6.5) with 60% yield. This attempt shows clearly the complete selectivity towards path

b) migration products and, more interestingly, an excellent diastereoselectivity in favour of the *trans* isomer **23**. A prolonged reaction of *exo*-**17a** under the same conditions led to a less efficient transformation (*d.r.* 85:15) and the major isomer **23** has been isolated in only 27% yield (Entry 2, Table 6.5). By employing a reduced amount of Lewis acid (1.5 eq, entry 3, Table 6.5) we were able to achieve the same level of diastereoselectivity in favour of *trans*-alcohol **23** and to isolate it in 70% yield. The desilylated bicyclic adduct *exo*-**18** showed to be slightly less diastereoselective and *trans*-**23** and *cis*-**24** are formed in 89:11 ¹H-NMR ratio. Both **23** and **24** has been isolated, along with enone **25** as the dehydration product (Entry 4, Table 6.5). It has to be noted that no silylated product was obtained even if we started with *exo*-**17a**.

Table 6.5 – AlCl₃-mediated rearrangement of bicyclic photoadduct **17**.



Entry	Substrate'	L.A. (eq)	Time	Ratio ^[a]	Yield
1	<i>exo</i> - 17a	AlCl ₃ (3)	45min	97:3:0:0	60% (23)
2	<i>exo</i> - 17a	AlCl ₃ (3)	7h	85:15:0:0	27% (23)
3	<i>exo</i> - 17a	AlCl ₃ (1.5)	45min	97:3:0:0	70% (23)
4	<i>exo</i> - 18	AlCl ₃ (1.5)	45min	89:11:0:0	62% (23) 10% (24) 10% (25)
5	<i>endo</i> - 17a	AlCl ₃ (1.5)	1.5h	33:30:0:36	38% (23) 13% (24) 13% (24b)
6	<i>endo</i> - 18	AlCl ₃ (1.5)	45min	32:68:0:0	22% (23) 47% (24) 10% (25)

[a] The ratio has been determined by integration of ¹H-NMR signals on the crude spectrum and is referred to **23:24:23b:24b**.

We therefore tested the reactivity of the *endo-17a* isomer and the corresponding desilylated alcohol *endo-18* (Entries 5-6, Table 6.5). The *endo* isomer exhibit the same complete selectivity towards path *b*) and no product derived from the alkyl migration has been observed. Though, differently from the *exo* isomer, *cis-24* is the major product of the migration showing an inverted diastereoselectivity. Moreover, when the reaction is carried out starting from the silylated *endo-17a*, a 50:50 mixture of *cis-24* and the corresponding TMS-protected derivative *cis-24b* has been observed. Interestingly, the reaction of alcohol *endo-18* led to the same comprehensive ratio 1:2 *trans/cis* of *endo-17a*.

In both cases, *exo-17* and *endo-17*, due to the instability of the rearrangement product, enone **25** has been isolated in 10-13% yield even if the amount of enone in the crude was always lower than 5%.

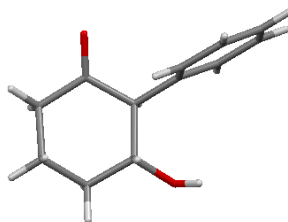


Figure 6.8 – X-ray crystal structure of derivative *trans-23*.

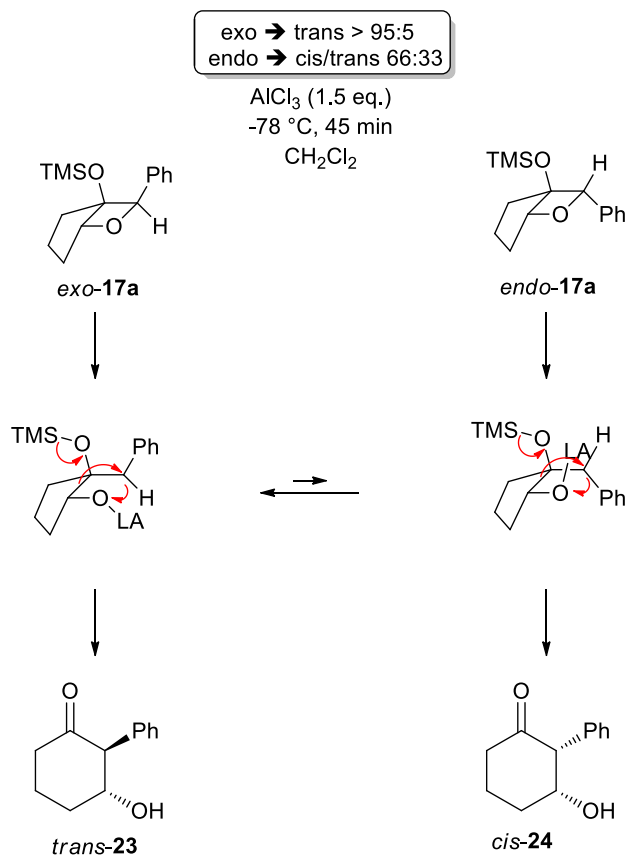
The isolated *trans-23* crystallise in the orthorhombic crystal system and X-ray analysis of a suitable monocrystal gave us the crystal structure of the derivative, as shown in Figure 6.8. Interestingly, this compound *trans-23* crystallise as a conglomerate, which means that the two enantiomers of it crystallise separately. It has to be noted that only 5% of X-ray structure of racemic mixtures are conglomerates.

On the base of these results, some consideration can be made. Since Bach's work already pointed out the involvement of a carbocation intermediate in the observed hydroxymethyl migration, we would expect to observe the same behaviour. Nevertheless, *exo-17a* showed a surprisingly high stereoselectivity for involving a planar intermediate such as a carbocation. On the contrary, a concerted mechanism would imply an equal and inverted selectivity when *endo-17a* is used as starting material. Moreover, the approach of the Lewis acid can

have an important effect on the reactivity. In fact, the *exo* and *endo* lone pairs of the O-atom in both the isomers of **18** are differently accessible due to the presence of the phenyl ring and this difference should be considered in the coordination interaction with the Lewis acid. From a steric point of view, we would expect that an *endo* approach of the Lewis acid is favourite for the *exo*-**18** isomer, while *endo*-**18** favour the coordination from the *exo* lone pair.

By analogy with Bach's proposal, a first hypothetic mechanisms could explain these interesting experimental results via a carbocation intermediate (Scheme 6.8).

First proposal based on a carbocationic mechanism:

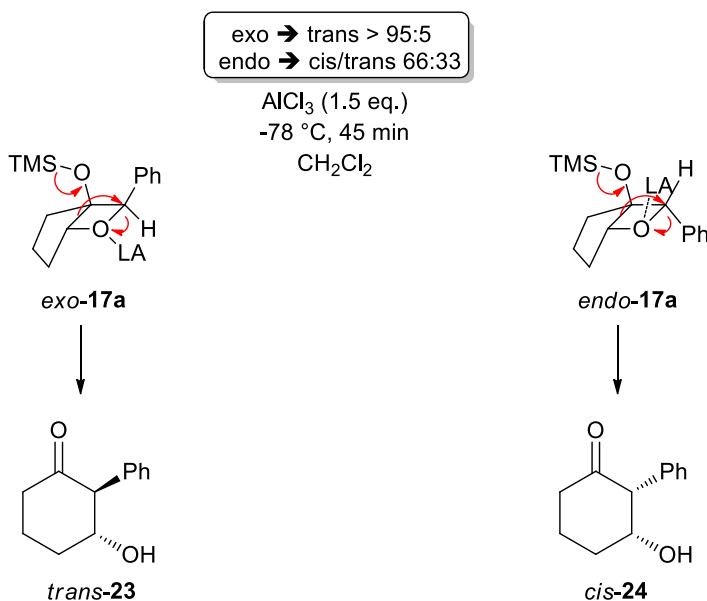


Scheme 6.8 – Limit case hypothesis for a pure carbocationic mechanism.

The proposed mechanism is based on the different relative stability of the *exo*- and *endo*- conformer of the carbocation intermediate. The two conformers can interconvert each other by means of a single bond rotation, which should be slow due to steric hindrance and low temperature effects. Reaction of *exo*-**17a** yields the carbocation intermediate with the most stable conformation and, consequently, it affords **23** with high diastereoselection. On the other hand, opening of *endo*-**17a** forms the less stable conformer of the carbocation intermediate which it starts to convert to its more stable *exo* conformation. When the migration occurs in the less stable conformer, the product of the reaction is *cis*-**24**, otherwise the rotation of the single bond led to the formation of *trans*-**23**. As a consequence of that, reaction of *endo*-**17a** shows a minor selectivity in comparison of the same reaction performed on *exo*-**17a**.

This mechanistic hypothesis should be considered as a limit case for a pure carbocation mechanism in opposition to the corresponding pure concerted limit case mechanism (Scheme 6.9).

Second proposal based on a concerted mechanism:



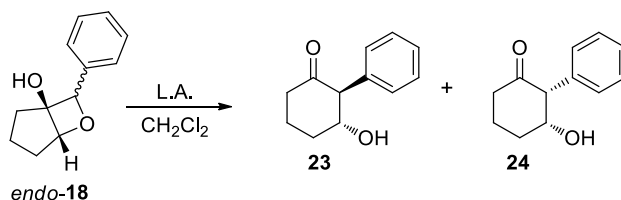
Scheme 6.9 – Limit case hypothesis for a pure concerted mechanism.

In this other case, migration of the bond takes place without ionic intermediates and it induces the opening of the oxetane ring moiety. Moreover, the process should occur in an extremely stereoselective manner that strictly depends on the configuration of the starting material. Therefore, *exo-17* would lead to *trans-23*, whereas *endo-17* to the formation of *cis-24*.

The high diastereoselectivity to *trans-23* observed with *exo-17* could support a pure concerted mechanism. Furthermore, the relatively low selection (2:1 *cis:trans*) observed with *endo-17* can be explained assuming the presence of parasite side mechanisms.

Both of these limit cases fail to explain some experimental results and the mechanism of such transformation is still under investigation. In particular, the carbocationic proposal is in contrast with the high stereoselection observed in the rearrangement of *exo-17*, while a pure concerted mechanism failed to explain the low selectivity of the other isomer.

Table 6.6 – Preliminary tests at different temperatures on *endo-18*.



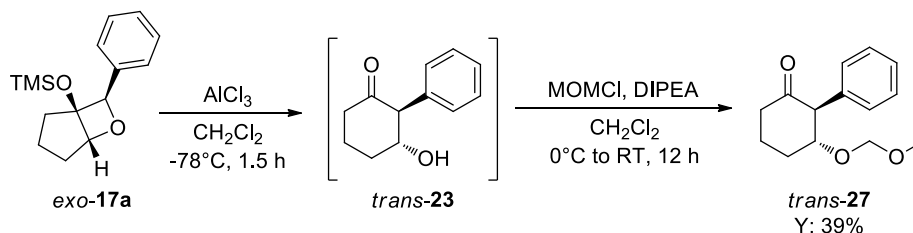
Entry	Substrate'	L.A. (equiv.)	Time	Temperature	Ratio ^[a]
1	<i>endo-18</i>	AlCl ₃ (1.5)	45min	-20 °C	35:65 ^[b]
2	<i>endo-18</i>	AlCl ₃ (1.5)	45min	-78 °C	32:68
3	<i>endo-18</i>	AlCl ₃ (1.5)	2.5h	-90 °C	25:75

[a] The ratio has been determined by integration of NMR signals on the crude spectrum and is referred to **23:24**. [b] Large amount of enone is obtained.

In a preliminary attempt on investigating the mechanism, we performed some tests at different temperatures on *endo-18* in order to see how the *trans/cis* ratio would be affected (Table 6.6). The ratio obtained at -20°C needs to be analysed with caution due to the large amount of enone obtained at -20°C. But we clearly observed a higher selectivity at -90°C in favour of the *cis*-isomer than at -78°C, with only traces of enone. Unfortunately, the enhanced selectivity is compatible

with both limit mechanisms (concerted and *via* carbocation) that could be hypothesized for the reaction. Indeed, a low temperature such as $-90\text{ }^{\circ}\text{C}$ should limit both the bond rotation of a carbocation intermediate and disfavour side mechanisms if the process is concerted. Both cases are compatible with an enhance selectivity towards *cis*-**24**.

In all our attempts to obtain *trans*-**23** (Table 6.5), NMR yields have always been higher than the isolated one after flash column because dehydration occurs during purification to form **25**. For this reasons, we attempted the subsequential MOM protection of *trans*-**23** directly from the crude reaction mixture of *exo*-**17a** and AlCl_3 . MOM-protected *trans* alcohol **27** was isolated in 39% yield in two steps reaction, as shown in Scheme 6.10.



Scheme 6.10 – Synthetic path for *trans*-**27** in two subsequential steps without isolating the alcohol intermediate.

MOM derivative *trans*-**27** crystallizes in triclinic crystal system by slow evaporation of chloroform. X-Ray analysis of the sample confirms the structure of the product and its correct relative stereochemistry (Figure 6.9). Surprisingly this compound *trans*-**27**, closely related to the compound *trans*-**23** did not crystallise as a conglomerate.

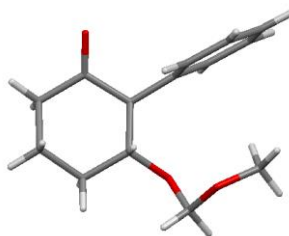


Figure 6.9 – Crystal structure of *trans*-**27**.

Finally, we decided to preliminary investigate the effect of titanium chloride on the outcome of the reaction. Indeed, according to Bach's previous studies, it would favour the migration through path *a* (Scheme 6.6).

The reaction has been performed on both *exo*- and *endo*- isomers. In both cases, the other migration product has not been observed and, among traces of **23** and **24**, only a 50:50 mixture of two chlorinated diastereomers **28** and **29** were observed and isolated as the major products (Figure 6.10).

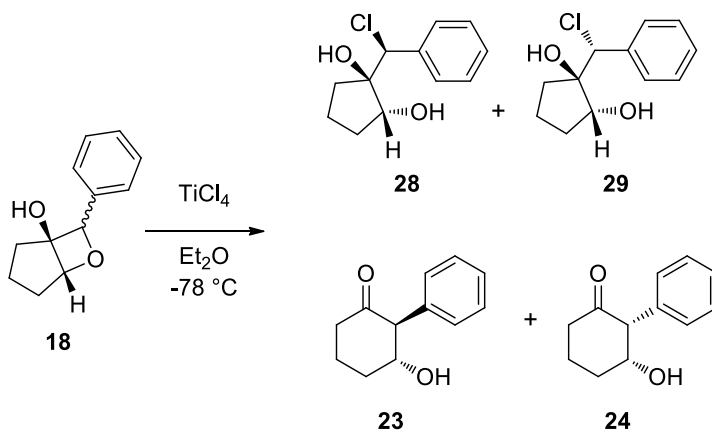


Figure 6.10 – TiCl_4 -induced rearrangement on *exo*- and *endo*- isomers of **18**

Chlorinated diols **28** and **29** are formed through a non-selective ring-fission/chlorination tandem sequence reaction. Derivative **29** crystallize in monoclinic crystal system and the X-Ray structure is reported in Figure 6.11.

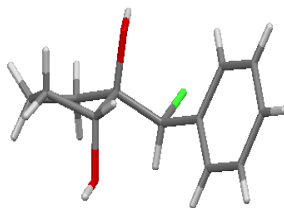
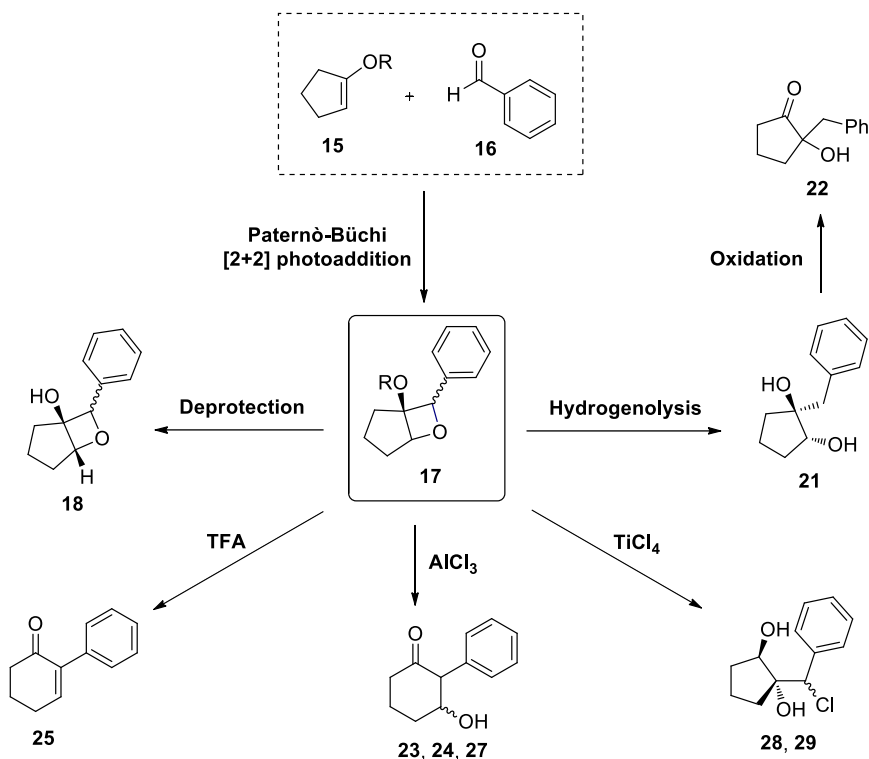


Figure 6.11 – Crystal structure of **29**.

In conclusion, the synthesis of novel bicyclic oxetanes **17** through Paternò-Büchi reaction has been performed and post-functionalization reactions of such intermediates has been evaluated. The desired α -hydroxyketone **22** was

successfully synthesized and, starting from the same intermediate **17**, several scaffolds have been afforded such as bicyclic oxetanols **18**, *trans*-1,2-diols **21**, **28** and **29**, substituted cyclic ketones **23**, **24**, **25** and **27**, proving the importance and versatility of this substrate.



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7 EXPERIMENTAL PART

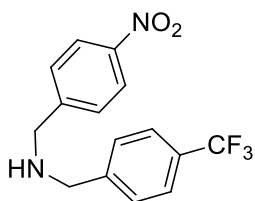
7.1 GENERAL METHODS

All reagents and solvents were of commercial grade and were used without further purification, with the exception of MeCN which was distilled from P₂O₅, CH₂Cl₂ which was dried over activated alumina, and THF which was distilled from sodium/benzophenone. Flash chromatography was performed on columns of silica gel (35–70 μm) or 230-400 mesh silica gel 60 (0.040-0.063 mm). Analytical thin-layer chromatography was carried out on commercial 0.25 mm silica gel plates which were visualized by UV fluorescence at 254 nm then revealed using a phosphomolybdic acid solution (10% in EtOH) or a *p*-anisaldehyde solution. Retention factors (*R*_f) are given for such TLC analyses. Melting points were obtained in open capillary tubes and are uncorrected. Optical rotations were measured using a 10 cm quartz cell; values for $[\alpha]_D^T$ were obtained with the D-line of sodium at the indicated temperature *T*, using solutions of concentration (*c*) in units of g·100 mL⁻¹. Fourier-transform Infrared (IR) spectra were recorded for neat samples using an ATR diamond accessory; maximum absorbances (*v*) are given in cm⁻¹. Nuclear magnetic resonance (NMR) data were acquired on a spectrometer operating at 500/400/360/300/250 MHz for ¹H, and at 121/101/90/75/63 MHz for ¹³C. Chemical shifts (δ) are reported in ppm with respect to tetramethylsilane ($\delta = 0$ ppm). Splitting patterns for ¹H NMR and ¹³C NMR signals are designated as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), broad singlet (br. s) or m (multiplet). Coupling constants (*J*) are reported in Hz. High-resolution mass spectrometry (HRMS) data were recorded using on a spectrometer equipped with an electrospray ionization source either in positive or negative mode as appropriate, with a tandem Q-TOF analyzer. 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.

7.2 EXPERIMENTAL DATA

DIBENZYLAMINES (2)

Benzylamines **2a**, **2q**, **2s** 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] were prepared according to literature procedures. The spectroscopic data are in accordance with those presented in literature.

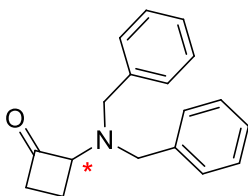


2p was synthesized by reductive amination.^[11] *p*-Nitrobenzaldehyde (1 mmol, 0.151 g) and *p*-trifluoro methylbenzylamine (1.06 mmol, 0.185g) were mixed in MeOH (5 mL) at room temperature. The mixture was stirred at room temperature for 4 h, until the aldimine formation was completed. The aldimine in MeOH was carefully treated with solid NaBH₄ (0.06 g, 1.6 mmol). The reaction mixture was stirred for 60 min and quenched with 1M NaOH. The product was extracted with ether. The ether extract was washed with saturated aqueous NaCl and dried (Na₂SO₄). 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. ¹H-NMR (400 MHz, CDCl₃) 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). ¹³C-NMR (101 MHz, CDCl₃) δ: 147.89, 147.26, 144.00, 128.76, 128.41, 127.09, 125.54 (q, J = 3.2 Hz), 123.79, 52.81, 52.47. **MS** *m/z*: 309 [M⁺-1 (42)], 291 (15), 174 (41), 159 (100), 136 (29), 109 (20), 91 (19).

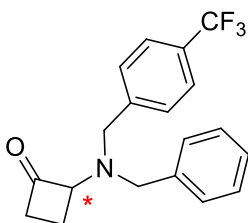
α-DIBENZYLAMINOCYCLOBUTANONES (3)

GENERAL PROCEDURE FOR ORGANOCATALYSED 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 dibenzylamine (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.

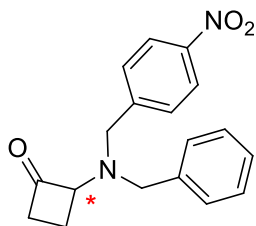


3a – Yellow oil (48 mg, 81% yield). **IR** (*neat*): 3087, 3058, 3028, 2930, 2844, 2812, 1778, 1653, 1495, 1453, 1400, 1374, 1069, 1026 cm^{-1} . $[\alpha]_{\text{D}}^{29} = +19.2$ ($c = 2.18$, CHCl_3). **¹H-NMR** (500 MHz, CDCl_3) δ : 7.37 (d, $J = 7.5$ Hz, 4 H), 7.31 (t, $J = 7.5$ Hz, 4 H), 7.24 (d, $J = 7.0$ 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). **¹³C-NMR** (126 MHz, CDCl_3) δ : 209.97, 138.91, 129.00, 128.44, 127.31, 76.66, 55.14, 40.71, 14.94. **HRMS** (ESI): calcd. for $\text{C}_{18}\text{H}_{19}\text{NO}$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254\text{nm}$): $t_{\text{R}} = 17.74$ min (major), $t_{\text{R}} = 21.83$ min (minor).

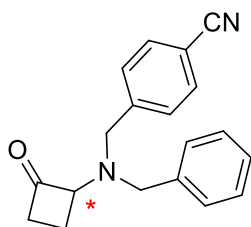


3b – Yellow oil (61 mg, 82% yield). **IR** (*neat*): 3031, 2831, 1778, 1617, 1492, 1449, 1420, 1325, 1164, 1124, 1105, 1062, 1019 cm^{-1} . $[\alpha]_{\text{D}}^{27} = +20.1$ ($c = 3.07$, CHCl_3). **¹H-NMR** (500 MHz, CDCl_3) δ : 7.56 (d, $J = 8.2$ Hz, 2 H), 7.49 (d, $J = 8.1$ Hz, 2 H), 7.37–7.28 (m, 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). $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ : 209.40, 143.30, 138.41, 129.09, 128.98, 128.54, 127.52, 125.39 (q, $J = 3.8$ Hz), 76.65, 55.37, 54.71, 40.80, 15.09. **HRMS** (ES): calcd. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{NO}$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254$ nm): $t_{\text{R}} = 11.43$ min (major), $t_{\text{R}} = 12.32$ min (minor).

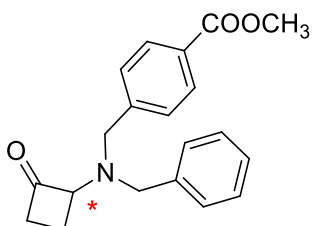


3c – Yellow oil (64 mg, 92% yield). **IR** (*neat*): 3022, 2841, 1774, 1604, 1518, 1495, 1456, 1348, 1262, 1105, 1069 cm^{-1} . $[\alpha]_{\text{D}}^{29} = +10.9$ ($c = 5.46$, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 8.16 (d, $J = 8.7$ Hz, 2 H), 7.55 (d, $J = 8.8$ Hz, 2 H), 7.35–7.23 (m, 5 H), 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). $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ : 209.03, 147.04, 138.03, 129.43, 128.96, 128.59, 127.65, 123.69, 76.68, 55.63, 54.56, 40.85, 15.22. **HRMS** (ES): calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254$ nm): $t_{\text{R}} = 41.52$ min (major), $t_{\text{R}} = 36.36$ min (minor).



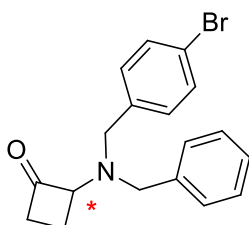
3d – Yellow oil (58 mg, 90% yield). **IR** (*neat*): 3031, 2831, 2231, 1774, 1610, 1499, 1456, 1371, 1075, 1023 cm^{-1} . $[\alpha]_{\text{D}}^{27} = +12.3$ ($c = 5.49$, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 7.59 (d, $J = 8.0$ Hz, 2 H), 7.49 (d, $J = 8.0$ Hz, 2 H), 7.31 (d, $J = 4.3$ Hz, 5 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). $^{13}\text{C-NMR}$ (126

MHz, CDCl₃) δ : 209.12, 144.90, 138.10, 132.26, 129.40, 128.93, 128.55, 127.58, 118.99, 111.12, 76.64, 55.53, 54.79, 40.81, 15.15. **HRMS (ESI)**: calcd. for C₁₉H₁₈N₂O [M+1]⁺ 291.1492; found 291.1497. The enantiomeric ratio (86:14) was determined by HPLC (Chiralpak AD-H column; hexane/iPrOH, 95:5; flow rate: 1.0 mL min⁻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*):

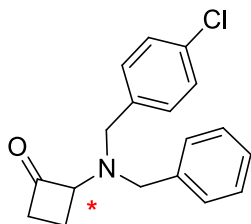
3031, 2956, 2890, 1774, 1722, 1614, 1574, 1492, 1436, 1387, 1282, 1190, 1170, 1111, 1075, 1023 cm⁻¹. $[\alpha]_D^{20}$ = +17.1 (c = 4.90, CHCl₃). **¹H-NMR** (400 MHz, CDCl₃) δ : 7.99 (d, J = 8.2 Hz, 2 H), 7.45 (d, J = 8.2 Hz, 2 H), 7.30 (ddd, J = 18.4, 8.7, 5.9 Hz, 5 H), 4.31–4.23 (m, 1 H), 3.90 (s, 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). **¹³C-NMR** (101 MHz, CDCl₃) δ : 209.50, 167.09, 144.49, 138.43, 129.75, 129.24, 128.96, 128.80, 128.48, 127.44, 76.61, 55.32, 54.85, 52.14, 40.74, 15.03. **HRMS (ESI)**: calcd. for C₂₀H₂₁NO₃ [M+1]⁺ 324.1594; found 324.1602. The enantiomeric ratio (80:20) was determined by HPLC (Chiralpak AS-H column; hexane/iPrOH, 99:1; flow rate: 1.0 mL min⁻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*):

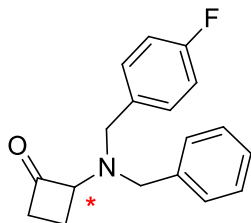
3025, 2844, 1778, 1653, 1591, 1489, 1449, 1403, 1374, 1249, 1164, 1072, 1010 cm⁻¹. $[\alpha]_D^{27}$ = +16.5 (c = 6.29, CHCl₃). **¹H-NMR** (500 MHz, CDCl₃) δ : 7.45–7.40 (m, 2 H), 7.35–7.28 (m, 5 H), 7.24 (d, J = 7.5 Hz, 2 H), 4.25 (t, J = 9.2 Hz, 1 H), 3.76–3.67 (m, 2 H), 3.59 (t, J = 12.8 Hz, 2 H), 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). **¹³C-NMR** (126 MHz, CDCl₃) δ : 209.59,

138.55, 138.01, 131.53, 130.62, 128.94, 128.48, 127.42, 121.08, 76.55, 55.16, 54.46, 40.75, 15.01. **HRMS** (ES): 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/iPrOH, 98:2; flow rate: 1.0 mL min^{-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*):

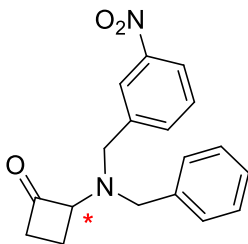
3025, 2838, 2812, 1774, 1597, 1492, 1449, 1400, 1371, 1259, 1164, 1095, 1075, 1016 cm^{-1} . $[\alpha]_D^{27}$ = +19.4 (c = 5.46, $CHCl_3$). **1H -NMR** (400 MHz, $CHCl_3$) δ : 7.36–7.22 (m, 9 H), 4.30–4.21 (m, 1 H), 3.73 (dd, J = 13.7, 6.8 Hz, 2 H), 3.60 (dd, J = 13.7, 3.6 Hz, 2 H), 2.78–2.66 (m, 1 H), 2.66–2.55 (m, 1 H), 2.11–1.94 (m, 2 H). **^{13}C -NMR** (101 MHz, $CDCl_3$) δ : 209.67, 138.59, 137.49, 133.00, 130.27, 128.96, 128.59, 128.49, 127.42, 76.55, 55.15, 54.41, 40.75, 14.98. **HRMS** (ES): 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/iPrOH, 99:1; flow rate: 1.0 mL min^{-1} ; λ = 254 nm): t_R = 8.99 min (major), t_R = 9.45 min (minor).



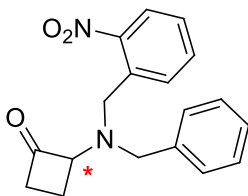
3h – Pale yellow oil (58 mg, 92% yield). **IR** (*neat*):

3064, 2841, 1778, 1604, 1509, 1449, 1374, 1220, 1157, 1092, 1072 cm^{-1} . $[\alpha]_D^{24}$ = +14.7 (c = 5.16, $CHCl_3$). **1H -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). **^{13}C -NMR** (126 MHz, $CDCl_3$) δ : 209.77, 163.19, 161.24, 138.72, 134.58 (d, J = 3.2 Hz), 130.49, 130.43, 128.96, 128.47, 127.38, 115.32,

115.15, 76.57, 55.10, 54.37, 40.75, 14.96. **HRMS (ES)**: 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 mL min^{-1} ; $\lambda = 254$ nm): $t_R = 10.36$ min (major), $t_R = 10.96$ min (minor).

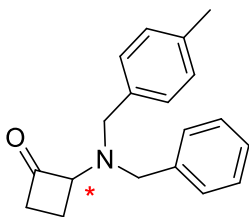


3i – Yellow oil (53 mg, 77% yield). **IR** (neat): 3071, 3025, 2838, 1778, 1528, 1449, 1351, 1075, 1023 cm^{-1} . $[\alpha]_D^{25} = +8.4$ ($c = 4.98$, $CHCl_3$). **1H -NMR** (500 MHz, $CDCl_3$) δ : 8.22 (s, 1 H), 8.09 (d, $J = 8.2$ Hz, 1 H), 7.73 (d, $J = 7.7$ Hz, 1 H), 7.49 (d, $J = 7.9$ Hz, 1 H), 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). **^{13}C -NMR** (126 MHz, $CDCl_3$) δ : 209.02, 148.49, 141.46, 138.06, 134.95, 129.38, 129.00, 128.61, 127.62, 123.57, 122.46, 76.68, 55.56, 54.47, 40.87, 15.30. **HRMS (ES)**: 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 mL min^{-1} ; $\lambda = 254$ nm): $t_R = 16.11$ min (major), $t_R = 17.18$ min (minor).

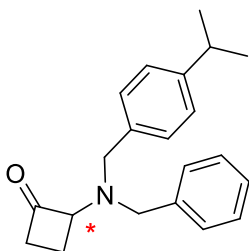


3j – Yellow oil (33 mg, 48% yield). **IR** (neat): 3064, 3025, 1778, 1528, 1495, 1456, 1354, 1200, 1179, 1065 cm^{-1} . $[\alpha]_D^{27} = -13.1$ ($c = 2.28$, $CHCl_3$). **1H -NMR** (500 MHz, $CDCl_3$) δ : 7.81 (d, $J = 8.2$ Hz, 2 H), 7.55 (dd, $J = 11.9, 4.3$ Hz, 1 H), 7.37 (t, $J = 7.7$ Hz, 1 H), 7.30–7.26 (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, 1 H), 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). **^{13}C -NMR** (126 MHz, $CDCl_3$): 209.33, 149.80, 138.09,

134.46, 132.84, 131.24, 128.97, 128.52, 128.08, 127.52, 124.45, 76.74, 56.34, 51.83, 40.73, 15.03. **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 mL min⁻¹; λ = 254 nm): t_R = 22.66 min (major), t_R = 26.86 min (minor).

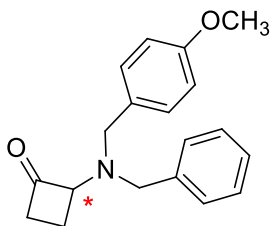


3k – Yellow oil (51 mg, 79% yield). **IR** (*neat*): 3028, 2982, 2926, 2812, 1778, 1515, 1492, 1449, 1371, 1253, 1200, 1170, 1115, 1075, 1026 cm⁻¹. $[\alpha]_D^{24}$ = +17.7 (*c* = 5.31, CHCl₃). **¹H-NMR** (500 MHz, CDCl₃) δ : 7.36 (d, *J* = 7.0 Hz, 2 H), 7.30 (t, *J* = 7.4 Hz, 2 H), 7.24 (dd, *J* = 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). **¹³C-NMR** (126 MHz, CDCl₃) δ : 210.04, 138.99, 136.87, 135.74, 129.11, 128.97, 128.96, 128.40, 127.24, 110.11, 76.61, 55.00, 54.82, 40.68, 21.23, 14.90. **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 mL min⁻¹; λ = 254 nm): t_R = 9.84 min (major), t_R = 10.69 min (minor).



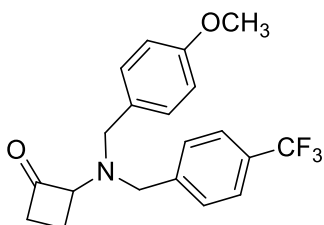
3l – Yellow oil (62 mg, 91% yield). **IR** (*neat*): 3058, 3015, 2959, 1781, 1650, 1518, 1495, 1456, 1371, 1216, 1072 cm⁻¹. $[\alpha]_D^{27}$ = +14.5 (*c* = 5.90, CHCl₃). **¹H-NMR** (500 MHz, CDCl₃) δ : 7.37 (d, *J* = 7.1 Hz, 2 H), 7.29 (dd, *J* = 14.3, 7.6 Hz, 4 H), 7.25–7.20 (m, 1 H), 7.16 (d, *J* = 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). $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ : 210.08, 147.93, 139.04, 136.14, 128.97, 128.90, 128.40, 127.24, 126.45, 76.64, 55.05, 54.81, 40.68, 33.91, 24.15, 14.87. **HRMS** (ESI): calcd. for $\text{C}_{21}\text{H}_{25}\text{NO}$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254$ nm): $t_{\text{R}} = 8.52$ min (major), $t_{\text{R}} = 8.86$ min (minor).



3m – Pale yellow oil (59 mg, 89% yield). **IR** (*neat*):

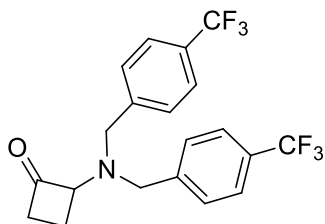
2956, 2933, 2838, 1778, 1614, 1512, 1456, 1374, 1302, 1246, 1177, 1108, 1069, 1033 cm^{-1} . $[\alpha]_{\text{D}}^{28} = +14.6$ ($c = 5.19$, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 7.36 (d, $J = 7.0$ Hz, 2 H), 7.33–7.20 (m, 5 H), 6.85 (d, $J = 8.7$ Hz, 2 H), 4.36–4.16 (m, 1 H), 3.78 (s, 3 H), 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). $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ : 210.10, 158.96, 139.02, 130.82, 130.16, 128.97, 128.41, 127.25, 113.83, 76.57, 55.37, 54.95, 54.48, 40.70, 14.90. **HRMS** (ESI): calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_2$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254$ nm): $t_{\text{R}} = 17.75$ min (major), $t_{\text{R}} = 19.74$ min (minor).



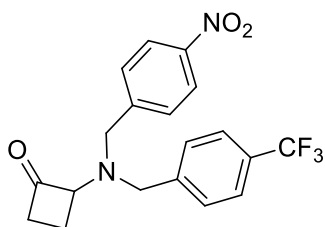
3n – Pale yellow oil (73 mg, 90% yield). **IR**

(*neat*): 3008, 2844, 1778, 1617, 1591, 1522, 1325, 1249, 1164, 1121, 1108, 1065, 1039, 1019 cm^{-1} . $[\alpha]_{\text{D}}^{27} = +15.0$ ($c = 6.11$, CHCl_3). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ : 209.55, 159.12, 143.44, 130.31, 130.17, 129.06, 125.36 (q, $J = 3.8$ Hz), 113.93, 76.57, 55.39, 54.74, 54.54, 40.80, 15.08. **HRMS** (ESI): calcd. for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{NO}_2$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254$ nm): $t_{\text{R}} = 13.79$ min (major), $t_{\text{R}} = 15.33$ min (minor).

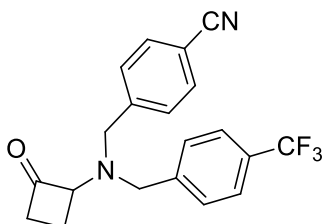


3o – White solid (71 mg, 80% yield); **m.p.** 95–98 °C. **IR** (*Nujol*): 2975, 2838, 1784, 1621, 1419, 1325, 1162, 1120, 1104, 1068, 1019 cm^{-1} . $[\alpha]_{\text{D}}^{21} = +12.2$ ($c = 7.65$, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 7.57 (d, $J = 8.1$ Hz, 4 H), 7.47 (d, $J = 8.0$ Hz, 4 H), 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). $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ : 208.90, 142.76, 129.97, 129.71, 129.08, 125.48 (q, $J = 3.8$ Hz), 76.64, 54.97, 40.87, 15.20 ppm. **HRMS** (ESI): calcd. for $\text{C}_{20}\text{H}_{17}\text{F}_6\text{NO}$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254$ nm): $t_{\text{R}} = 8.48$ min (major), $t_{\text{R}} = 8.12$ min (minor).



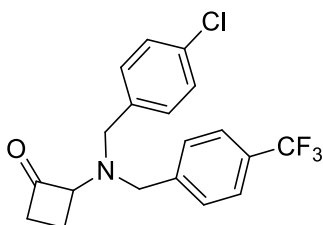
3p – Yellow oil (53 mg, 63% yield). **IR** (*neat*): 2976, 2844, 1774, 1620, 1604, 1525, 1348, 1325, 1157, 1118, 1105, 1062, 1019 cm^{-1} . $[\alpha]_{\text{D}}^{21} = +4.0$ ($c = 4.43$, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 8.17 (d, $J = 8.7$ Hz, 2 H), 7.58 (d, $J = 8.1$ Hz, 2 H), 7.54 (d, $J = 8.7$ 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). **¹³C-NMR** (126 MHz, CDCl₃) δ: 208.53, 147.53, 146.44, 142.40, 142.39, 129.44, 129.08, 125.57 (q, J = 3.8 Hz), 123.79, 76.63, 55.17, 54.79, 40.93, 15.33. **HRMS** (ES): calcd. for C₁₉H₁₇F₃N₂O₃ [M+1]⁺ 379.1264; found 379.1276. The enantiomeric ratio (88:12) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/iPrOH, 98:2; flow rate: 1.0 mL min⁻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):

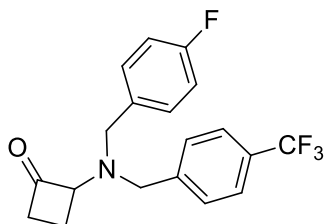
2966, 2844, 2227, 1778, 1620, 1610, 1420, 1325, 1164, 1121, 1102, 1069, 1019 cm⁻¹. [α]_D²² = +3.8 (c = 1.03, CHCl₃). **¹H-NMR** (500 MHz, CDCl₃) δ: 7.61 (d, J = 8.2 Hz, 2 H), 7.58 (d, J = 8.1 Hz, 2 H), 7.50–7.44 (m, 4 H), 4.29–4.20 (m, 1 H), 3.81 (d, J = 14.5 Hz, 2 H), 3.71 (dd, J = 14.2, 3.1 Hz, 2 H), 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). **¹³C-NMR** (126 MHz, CDCl₃) δ: 208.65, 144.35, 142.48, 142.47, 132.36, 129.39, 129.06, 125.52 (q, J = 3.8 Hz), 118.86, 111.39, 76.59, 55.08, 55.02, 40.89, 15.25. **HRMS** (ES): calcd. for C₂₀H₁₇F₃N₂O [M+1]⁺ 359.1366; found 359.1361. The enantiomeric ratio (90:10) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/iPrOH, 98:2; flow rate: 1.0 mL min⁻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):

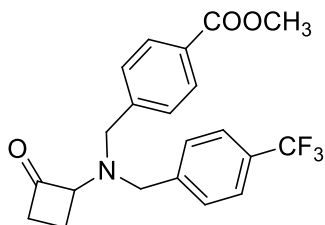
2930, 2838, 1778, 1623, 1492, 1417, 1371, 1325, 1161, 1121, 1105, 1065, 1016 cm⁻¹. [α]_D²² = +13.4 (c = 6.82, CHCl₃). **¹H-NMR** (500 MHz, CDCl₃) δ: 7.57 (d, J = 8.1 Hz, 2 H), 7.46 (d, J = 8.0 Hz, 2 H), 7.28 (s, 4 H), 4.28–4.20 (m, 1 H), 3.82–3.56 (m, 4 H), 2.80–2.70 (m, 1 H), 2.68–2.59 (m, 1 H), 2.14–2.04 (m, 1 H), 2.00 (dd, J = 19.7, 9.6 Hz, 1 H). **¹³C-NMR** (126 MHz, CDCl₃) δ: 209.12, 142.98, 136.97,

133.26, 130.25, 129.06, 128.70, 125.45 (q, $J = 3.8$ Hz), 76.54, 54.74, 54.67, 40.84, 15.14. **HRMS** (*ES*): 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 mL min⁻¹; $\lambda = 254$ nm): $t_R = 11.61$ min (major), $t_R = 11.09$ min (minor).



3s – Colorless oil (64 mg, 82% yield). **IR** (*neat*):

2831, 1778, 1620, 1604, 1509, 1420, 1325, 1226, 1161, 1124, 1105, 1069, 1016 cm⁻¹. $[\alpha]_D^{22} = +16.1$ ($c = 6.43$, $CHCl_3$). **¹H-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). **¹³C-NMR** (126 MHz, $CDCl_3$) δ : 209.24, 163.29, 161.34, 143.11, 134.09 (d, $J = 3.1$ Hz), 130.51, 130.44, 129.06, 125.43 (q, $J = 3.7$ Hz), 115.46, 115.29, 76.54, 54.68, 54.61, 40.84, 15.10. **HRMS** (*ES*): 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 mL min⁻¹; $\lambda = 254$ nm): $t_R = 8.08$ min (major), $t_R = 7.54$ min (minor).



3t – Yellow oil (75 mg, 85% yield). **IR** (*neat*):

2953, 2835, 1778, 1722, 1617, 1440, 1417, 1321, 1282, 1164, 1105, 1069, 1019 cm⁻¹. $[\alpha]_D^{20} = +10.4$ ($c = 7.49$, $CHCl_3$). **¹H-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, 2 H), 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). **¹³C-NMR** (101 MHz, $CDCl_3$) δ : 209.01, 167.01, 143.92, 142.83, 129.85, 129.47,

129.07, 128.81, 125.45 (d, $J = 3.1$ Hz), 76.61, 55.09, 54.89, 52.18, 40.83, 15.16.

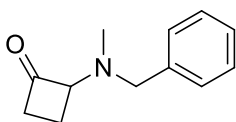
HRMS (ES): calcd. for $C_{21}H_{20}F_3NO_3$ $[M+1]^+$ 392.1468; found 392.1489. The enantiomeric ratio (90:10) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/*i*PrOH, 98:2; flow rate: 1.0 mL min⁻¹; $\lambda = 254$ nm): $t_R = 21.30$ min (major), $t_R = 19.73$ min (minor).

***N*-ALKYL-BENZYLAMINES (4)**

Alkyl-benzylamines **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **4g**, were purchased and used without further purification. Benzylamines **4h**,^[12] **4i**,^[13] **4j**,^[14] **4k**,^[15] were prepared according to literature procedures. The spectroscopic data are in accordance with those presented in literature.

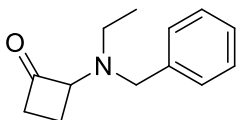
α -*N*-ALKYL-BENZYLAMINO CYCLOBUTANONES (5)

GENERAL PROCEDURE FOR ORGANOCATALYSED 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 alkylbenzylamine (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.

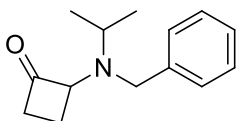


5a – Yellow oil (39 mg, 93% yield). **IR** (*neat*): 3028, 2982, 2792, 1778, 1643, 1495, 1453, 1403, 1075, 1059 cm⁻¹. $[\alpha]_D^{26} = +6.5$ ($c = 3.36$, $CHCl_3$). **¹H-NMR** (500 MHz, $CDCl_3$) δ : 7.32 (d, $J = 4.2$ Hz, 4 H), 7.26 (dd, $J = 7.6, 3.8$ Hz, 1 H), 4.11 (t, $J = 9.0$ Hz, 1 H), 3.66 (s, 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). **¹³C-NMR** (126 MHz, $CDCl_3$) δ : 208.63, 138.12, 129.24, 128.44, 127.39, 78.91, 59.65, 41.07, 38.57, 14.79. **HRMS (ES)**: calcd. for $C_{12}H_{15}NO$ $[M+1]^+$ 190.1226; found 190.1214.

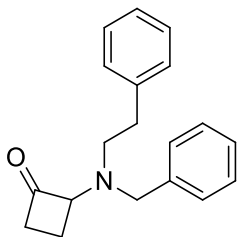
The enantiomeric ratio (55:45) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/iPrOH, 98:2; flow rate: 1.0 mL min⁻¹; λ = 254 nm): t_R = 8.87 min (major), t_R = 10.50 min (minor).



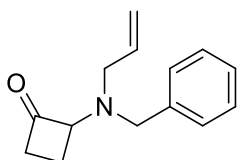
5b – Yellow oil (38 mg, 84% yield). **IR** (*neat*): 2969, 1778, 1640, 1499, 1453, 1394, 1377, 1065, 1026 cm⁻¹. $[\alpha]_D^{27}$ = +6.8 (*c* = 2.94, CHCl₃). **¹H-NMR** (500 MHz, CDCl₃) δ : 7.36–7.32 (m, 2 H), 7.31 (dd, *J* = 10.0, 4.8 Hz, 2 H), 7.26–7.22 (m, 1 H), 4.27 (tt, *J* = 10.8, 2.4 Hz, 1 H), 3.76 (d, *J* = 13.7 Hz, 1 H), 3.66 (d, *J* = 13.7 Hz, 1 H), 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). **¹³C-NMR** (126 MHz, CDCl₃) δ : 209.88, 139.12, 128.99, 128.38, 127.19, 77.50, 54.44, 45.19, 40.66, 15.55, 12.61. **HRMS** (*ESI*): calcd. for C₁₃H₁₇NO [*M*+1]⁺ 204.1382; found 204.1406. The enantiomeric ratio (54:46) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/iPrOH, 98:2; flow rate: 1.0 mL min⁻¹; λ = 254 nm): t_R = 9.26 min (major), t_R = 10.52 min (minor).



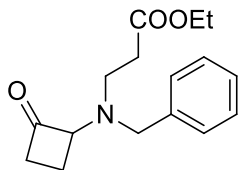
5c: Colourless oil (36 mg, 75% yield). **IR** (*neat*): 2969, 2926, 1781, 1633, 1499, 1459, 1394, 1371, 1279, 1174, 1128, 1059 cm⁻¹. $[\alpha]_D^{32}$ = +6.8 (*c* = 3.48, CHCl₃). **¹H-NMR** (500 MHz, CDCl₃) δ : 7.36 (dd, *J* = 7.6, 0.6 Hz, 2 H), 7.29 (t, *J* = 7.4 Hz, 2 H), 7.22 (t, *J* = 7.3 Hz, 1 H), 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). **¹³C-NMR** (126 MHz, CDCl₃) δ : 211.13, 140.55, 128.48, 128.30, 126.95, 74.33, 51.18, 49.67, 40.52, 20.08, 19.83, 17.42. **HRMS** (*ESI*): calcd. for C₁₄H₁₉NO [*M*+1]⁺ 218.1539; found 218.1532. The enantiomeric ratio (56:44) was determined by HPLC (Phenomenex Lux Cellulose-1 column; hexane/iPrOH, 98:2; flow rate: 1.0 mL min⁻¹; λ = 254 nm): t_R = 6.64 min (major), t_R = 7.34 min (minor).



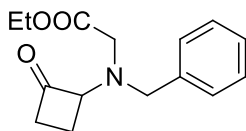
5d – Yellow oil (65 mg, 88% yield). **IR** (*neat*): 3031, 2976, 1778, 1649, 1607, 1495, 1459, 1157, 1072 cm^{-1} . $[\alpha]_{\text{D}}^{29} = +6.0$ ($c = 3.62$, CHCl_3). **$^1\text{H-NMR}$** (500 MHz, CDCl_3) δ : 7.36–7.28 (m, 4 H), 7.28–7.23 (m, 3 H), 7.21–7.15 (m, 1 H), 7.15–7.10 (m, 2 H), 4.31 (ddt, $J = 10.7, 8.6, 2.3$ 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). **$^{13}\text{C-NMR}$** (126 MHz, CDCl_3) δ : 209.67, 140.19, 138.93, 128.98, 128.87, 128.46, 128.45, 127.31, 126.13, 77.80, 55.21, 53.32, 40.60, 34.41, 15.74. **HRMS** (*ES*): calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}$ $[\text{M}+1]^+$ 280.1696; found 280.1701. The enantiomeric ratio (56:44) was determined by HPLC (Chiracel OJ column; hexane/*i*PrOH, 90:10; flow rate: 1.0 mL min^{-1} ; $\lambda = 254$ nm): $t_{\text{R}} = 10.50$ min (major), $t_{\text{R}} = 12.14$ min (minor).



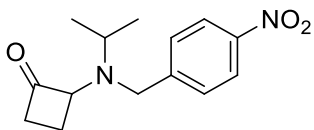
5e – Colourless oil (23 mg, 48% yield). **IR** (*neat*): 2979, 1778, 1640, 1499, 1453, 1420, 1354, 1220, 1170, 1069, 1026 cm^{-1} . **$^1\text{H-NMR}$** (400 MHz, CDCl_3) δ : 7.29–7.14 (m, 5 H), 5.79 (ddt, $J = 16.7, 10.1, 6.5$ Hz, 1 H), 5.22–4.99 (m, 2 H), 4.35–4.14 (m, 1 H), 3.68 (d, $J = 13.6$ Hz, 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). **$^{13}\text{C-NMR}$** (101 MHz, CDCl_3) δ : 209.85, 138.83, 135.68, 129.06, 128.43, 127.29, 118.10, 77.05, 54.88, 54.27, 40.66, 15.36. **HRMS** (*ES*): calcd. for $\text{C}_{14}\text{H}_{17}\text{NO}$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254$ nm): $t_{\text{R}} = 12.58$ min (major), $t_{\text{R}} = 12.08$ min (minor).



5f – Colourless oil (47 mg, 77% yield). **IR** (*neat*): 2979, 1781, 1728, 1646, 1495, 1449, 1397, 1374, 1253, 1187, 1075, 1029 cm^{-1} . $[\alpha]_{\text{D}}^{29} = +7.1$ ($c = 4.45$, CHCl_3). **$^1\text{H-NMR}$** (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). **$^{13}\text{C-NMR}$** (126 MHz, CDCl_3) δ : 209.54, 172.46, 138.69, 128.86, 128.43, 127.35, 77.51, 60.51, 55.10, 47.09, 40.51, 33.32, 15.75, 14.29. **HRMS** (*ES*): calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}_3$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254$ nm): $t_{\text{R}} = 13.34$ min (major), $t_{\text{R}} = 14.42$ min (minor).

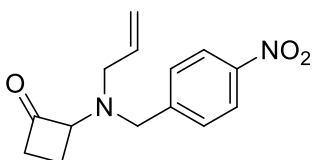


5g – Colourless oil (54 mg, 93% yield). **IR** (*neat*): 2982, 1778, 1732, 1659, 1499, 1456, 1377, 1197, 1161, 1079, 1029, 1000 cm^{-1} . $[\alpha]_{\text{D}}^{27} = +29.8$ ($c = 4.95$, CHCl_3). **$^1\text{H-NMR}$** (500 MHz, CDCl_3) δ : 7.35 (d, $J = 7.0$ Hz, 2 H), 7.31 (dd, $J = 10.0, 4.6$ Hz, 2 H), 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). **$^{13}\text{C-NMR}$** (126 MHz, CDCl_3) δ : 207.85, 171.38, 137.98, 129.20, 128.46, 127.50, 77.09, 60.56, 55.30, 51.86, 40.71, 17.14, 14.33. **HRMS** (*ES*): calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_3$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254$ nm): $t_{\text{R}} = 15.25$ min (major), $t_{\text{R}} = 15.96$ min (minor).



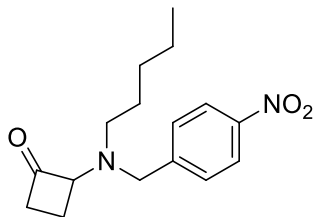
5h – Yellow oil (42 mg, 72% yield). **IR** (*neat*):

2972, 1778, 1600, 1518, 1456, 1394, 1341, 1216, 1190, 1128, 1111, 1062, 1010 cm^{-1} . $[\alpha]_{\text{D}}^{22} = +16.7$ ($c = 3.59$, CHCl_3). **$^1\text{H-NMR}$** (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). **$^{13}\text{C-NMR}$** (101 MHz, CDCl_3) δ : 210.13, 148.90, 147.19, 128.89, 123.60, 74.21, 50.81, 50.50, 40.74, 20.16, 19.66, 17.63. **HRMS** (*ES*): calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_3$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254$ nm): $t_{\text{R}} = 10.69$ min (major), $t_{\text{R}} = 12.96$ min (minor).

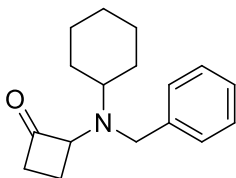


5i – Yellow oil (54 mg, 93% yield). **IR** (*neat*):

3077, 2976, 1778, 1600, 1515, 1341, 1203, 1174, 1111, 1069, 1016 cm^{-1} . $[\alpha]_{\text{D}}^{23} = +18.6$ ($c = 5.03$, CHCl_3). **$^1\text{H-NMR}$** (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). **$^{13}\text{C-NMR}$** (126 MHz, CDCl_3) δ : 208.92, 147.13, 134.89, 129.40, 123.68, 118.67, 54.69, 54.13, 40.78, 15.73. **HRMS** (*ES*): calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254$ nm): $t_{\text{R}} = 78.49$ min (major), $t_{\text{R}} = 21.51$ min (minor).



5j – Pale yellow oil (43 mg, 63% yield). **IR** (*neat*): 2963, 2930, 2861, 1778, 1640, 1604, 1522, 1469, 1348, 1177, 1115, 1072, 1013 cm^{-1} . $[\alpha]_{\text{D}}^{20} = +5.9$ ($c = 5.03$, CHCl_3). **$^1\text{H-NMR}$** (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). **$^{13}\text{C-NMR}$** (126 MHz, CDCl_3) δ : 209.26, 147.64, 129.29, 123.64, 112.71, 77.68, 54.73, 51.93, 40.70, 29.42, 27.20, 22.61, 15.65, 14.12. **HRMS** (*ES*): calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_3$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254 \text{ nm}$): $t_{\text{R}} = 13.94 \text{ min}$ (major), $t_{\text{R}} = 13.17 \text{ min}$ (minor).

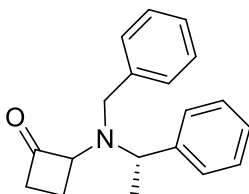


5k – Yellow oil (29 mg, 36% yield). **IR** (*neat*): 2933, 2858, 1778, 1604, 1522, 1449, 1394, 1341, 1266, 1203, 1174, 1128, 1108, 1069, 1013 cm^{-1} . $[\alpha]_{\text{D}}^{22} = +14.5$ ($c = 2.47$, CHCl_3). **$^1\text{H-NMR}$** (500 MHz, CDCl_3) δ : 8.16 (d, $J = 8.7$ Hz, 2 H), 7.56 (d, $J = 8.8$ Hz, 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). **$^{13}\text{C-NMR}$** (126 MHz, CDCl_3) δ : 210.33, 149.23, 147.18, 128.75, 123.60, 75.25, 59.92, 50.89, 40.49, 31.10, 30.75, 26.16, 17.85. **HRMS** (*ES*): calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_3$ $[\text{M}+1]^+$ 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 mL min^{-1} ; $\lambda = 254 \text{ nm}$): $t_{\text{R}} = 15.01 \text{ min}$ (major), $t_{\text{R}} = 19.67 \text{ min}$ (minor).

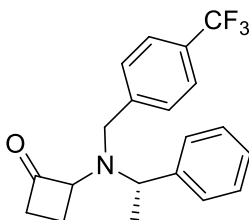
ENANTIOPURE DIBENZYLAMINES (6)

Homochiral dibenzylamines **6a** and *ent*-**6a** were purchased and used without further purification. Enantiopure dibenzylamines **6b**,^[16] *ent*-**6b**,^[16] were prepared according to literature procedures. The spectroscopic data are in accordance with those presented in literature.

DIBENZYLAMINO CYCLOBUTANONES (7)



ent-**7a**/*ent*-**7a**: Colourless oil (50 mg, 81% yield, inseparable 71:29 mixture of diastereomers). **IR** (*neat*): 3028, 2972, 1778, 1597, 1495, 1449, 1400, 1377, 1207, 1177, 1128, 1092, 1059, 1029 cm^{-1} . **¹H-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). **¹³C-NMR** (126 MHz, CDCl_3) δ : 211.31, 210.11, 140.08, 139.99, 139.91, 129.01, 128.78, 128.45, 128.37, 128.29, 127.74, 127.73, 127.23, 127.20, 127.00, 126.97, 74.86, 74.33, 56.67, 56.35, 51.93, 51.90, 41.23, 39.99, 17.40, 16.55, 16.16, 15.09. **HRMS** (*ES*): calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}$ $[\text{M}+1]^+$ 280.1696; found 280.169.

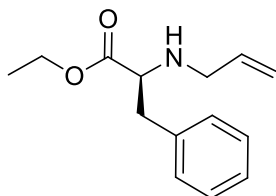


ent-**7b**/*ent*-**7b** – Yellow oil (62 mg, 81% yield, inseparable 91:9 mixture of diastereomers). **IR** (*neat*): 2976, 1781, 1620, 1495, 1449, 1420, 1381, 1321, 1203, 1164, 1124, 1111, 1065, 1019 cm^{-1} . $[\alpha]_{\text{D}}^{26} = -21.6$ ($c = 3.05$, CHCl_3). **¹H-NMR** (500 MHz, CDCl_3) δ : 7.61–7.54 (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,

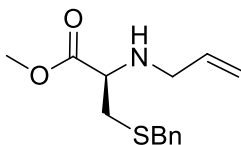
J = 10.3, 8.7 Hz, 1 H), 4.27 (t, J = 9.3 Hz, 1 H), 3.88 (dd, J = 13.3, 6.4 Hz, 2 H), 3.80 (q, J = 14.3 Hz, 4 H), 2.75–2.63 (m, 2 H), 2.62–2.49 (m, 2 H), 2.05 (dd, J = 16.7, 9.6 Hz, 4 H), 1.95 (dd, J = 10.7, 4.4 Hz, 1 H), 1.80 (t, J = 9.9 Hz, 1 H), 1.43 (d, J = 6.8 Hz, 3 H), 1.39 (d, J = 6.8 Hz, 3 H). $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ : 210.59, 209.59, 144.57, 144.47, 144.41, 143.04, 142.85, 129.10, 128.85, 128.45, 128.42, 127.66, 127.25, 127.20, 125.40 (q, J = 3.8 Hz), 125.33 (q, J = 3.8 Hz), 74.86, 74.40, 57.34, 56.96, 51.66, 51.57, 41.27, 40.17, 17.57, 16.66, 16.60, 15.35. **HRMS** (ES): calcd. for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{NO}$ $[\text{M}+1]^+$ 348.157; found 348.1583.

PROTECTED α -AMINO ACIDS (**8**)

The starting α -amino acid ester derivatives **8a**,^[17] **8c**,^[18] **8d**,^[19] **8e**,^[20] **8f**,^[20] **8g**,^[17] **8h**,^[17] were prepared from the corresponding α -amino acid according to literature procedures. The spectroscopic data are in accordance with those presented in literature.



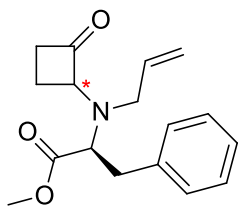
8b was prepared according to the literature procedure.^[17] – Colourless oil (63% yield). **IR** (*neat*): 3330, 3029, 2981, 1731, 1644, 1496, 1455, 1267, 1192, 1029 cm^{-1} . $[\alpha]_{\text{D}}^{23} = +17.7$ (c 2.029, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.10–1.14 (m, 3H), 2.93 (ddd, 2H, J = 6.5 Hz, J = 13.5 Hz), 3.10 (dd, 1H, J = 6.0 Hz, J = 14.0 Hz), 3.25 (dd, 1H, J = 6.0 Hz, J = 14.0 Hz), 3.51 (t, 1H, J = 7.0 Hz), 4.06 (ddd, 2H, J = 2.5 Hz, J = 7.0 Hz, J = 14.0 Hz), 5.04 (d, 1H, J = 10.5 Hz), 5.11 (d, 1H, J = 17.0 Hz), 5.76–5.83 (m, 1H), 7.16–7.19 (m, 3H), 7.23–7.24 (m, 2H). $^{13}\text{C-NMR}$ (124 MHz, CDCl_3) δ : 14.0, 39.7, 50.5, 60.4, 62.0, 116.2, 126.5, 128.2, 129.1, 136.1, 137.2, 174.4. **MS** m/z : 160 $[\text{M}^+-73$ (69)], 142 (100), 114 (18), 91 (47), 68 (26), 41 (43).



8i was prepared according to the literature procedure.^[17] Yellow oil (10% yield). **IR** (*neat*): 3332, 3064, 2953, 2939, 1735, 1642, 1467, 1207 cm^{-1} . $[\alpha]_{\text{D}}^{21} = +7.6$ (c 2.368, CHCl_3). **$^1\text{H-NMR}$** (400 MHz, CDCl_3) δ : 1.80 (br s, 1H), 2.71 (ddd, 2H, $J = 6.0$ Hz, $J = 13.6$ Hz, $J = 19.6$ Hz), 3.12 (dd, 1H, $J = 6.0$ Hz, $J = 13.6$ Hz), 3.26 (dd, 1H, $J = 6.0$ Hz, $J = 14.0$ Hz), 3.43 (t, 1H, $J = 6.4$ Hz), 3.73 (s, 3H), 5.09 (d, 1H, $J = 10.0$ Hz), 5.17 (d, 1H, $J = 17.2$ Hz), 5.83 (ddd, 1H, $J = 6.0$ Hz, $J = 10.8$ Hz, $J = 22.8$ Hz), 7.23-7.26 (m, 1H), 7.30-7.31 (m, 4H). **$^{13}\text{C-NMR}$** (124 MHz, CDCl_3) δ : 34.1, 36.6, 50.4, 51.8, 59.9, 116.5, 127.0, 128.4, 128.8, 135.9, 137.8, 173.9. **MS** m/z : 206 [$\text{M}^+ - 59$ (22)], 174 (4), 128 (100), 91 (70), 68 (24), 41 (34).

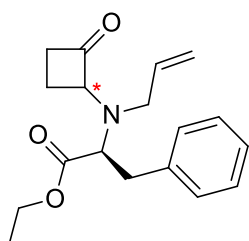
CYCLOBUTANONE α -AMINO ACID DERIVATIVES (9)

General Procedure for α -amination of α -hydroxy cyclobutanones: To a solution of freshly distilled α -hydroxycyclobutanone **1** (0.669 mmol, 0.058 g), $(\text{DHQ})_2\text{PYR}$ (0.0448 mmol, 0.0395 g) in dry 1,4-dioxan (0.5 mL) at room temperature was added the *N*-allyl- α -amino acid ester derivative **8** (0.224 mmol), and the mixture was stirred for 24h. 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 \rightarrow 1:1).

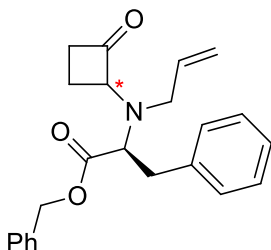


9a – Spectral data worked out from the 93:7 inseparable mixture of two diastereomers **9a/9'a**. Yellow oil (55 mg, 85% yield). **IR** (*neat*): 2952, 1781, 1734, 1644, 1496, 1454, 1196 cm^{-1} . $[\alpha]_{\text{D}}^{22} = -107.8$. (c 2.022, CHCl_3). **$^1\text{H-NMR}$** (500 MHz, CDCl_3) δ : 2.01 (quint., 1H, $J = 9.5$ Hz), 2.14 (ddd, 1H, $J = 4.5$ Hz, $J = 10.5$ Hz, $J = 21.5$ Hz), 2.53-2.59 (m, 1H), 2.67-2.76 (m, 1H), 2.95 (dd, 1H,

$J = 6.0$ Hz, $J = 13.5$ Hz), 3.05 (dd, 1H, $J = 9.0$ Hz, $J = 13.5$ Hz), 3.28 (dd, 1H, $J = 7.0$ Hz, $J = 15.0$ Hz), 3.35 (dd, 1H, $J = 6.0$ Hz, $J = 14.5$ Hz), 3.59-3.63 (m, 1H), 3.61 (s, 3H), 4.64 (t, 1H, $J = 10.0$ Hz), 5.08 (d, 1H, $J = 10.0$ Hz), 5.17 (d, 1H, $J = 17.0$ Hz), 5.62-5.70 (m, 1H), 7.16-7.20 (m, 3H), 7.24-7.27 (m, 2H). **$^{13}\text{C-NMR}$** (124 MHz, CDCl_3) δ : 15.7, 36.2, 40.2, 51.4, 51.9, 63.0, 74.2, 117.9, 126.3, 128.2, 129.1, 129.2, 135.8, 137.7, 173.1, 209.1. **MS** m/z (the same for the two diastereomers): 259 [$\text{M}^+ - 28$ (6)], 228 (21), 200 (33), 168 (73), 131 (21), 91 (94), 41 (100). **HRMS** (ESI) Calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_3$ ($\text{M}+1$) m/z 287.1521, found 288.1594.

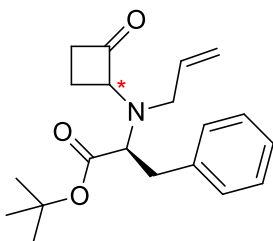


9b – Spectral data worked out from the 80:20 inseparable mixture of two diastereomers **9b/9'b**. Pale yellow oil (44 mg, 65% yield); pale **IR** (*neat*): 3064, 2979, 2932, 1782, 1728, 1603, 1496, 1455, 1163 cm^{-1} . **$^1\text{H-NMR}$** (400 MHz, CDCl_3) δ : 1.17 (t, 3H, $J = 6.8$ Hz), 2.03 (quint., 1H, $J = 9.6$ Hz), 2.16 (ddd, 1H, $J = 4.4$ Hz, $J = 10.4$ Hz, $J = 20.8$ Hz), 2.53-2.59 (m, 1H), 2.66-2.77 (m, 1H), 2.94 (dd, 1H, $J = 6.0$ Hz, $J = 13.6$ Hz), 3.04 (dd, 1H, $J = 9.2$ Hz, $J = 13.6$ Hz), 3.29 (dd, 1H, $J = 6.8$ Hz, $J = 14.0$ Hz), 3.35 (dd, 1H, $J = 5.4$ Hz, $J = 14.0$ Hz), 3.59 (dd, 1H, $J = 6.4$ Hz, $J = 8.4$ Hz), 4.07 (q, 2H, $J = 6.8$ Hz), 4.67 (t, 1H, $J = 9.6$ Hz), 4.09 (d, 1H, $J = 9.6$ Hz), 5.17 (d, 1H, $J = 17.2$ Hz), 4.60-4.73 (m, 1H), 7.17-7.20 (m, 3H), 7.24-7.27 (m, 2H). **$^{13}\text{C-NMR}$** (100 MHz, CDCl_3) δ : 14.0, 15.9, 36.4, 40.2, 51.9, 60.4, 63.1, 74.2, 117.8, 126.3, 128.1, 129.2, 135.9, 137.8, 172.7, 209.2. **MS** m/z (the same for the two diastereomers): 273 [$\text{M}^+ - 28$ (12)], 244 (24), 228 (26), 200 (65), 182 (100), 158 (18), 91 (41), 41 (57). **HRMS** (ESI) Calcd. for $\text{C}_{18}\text{H}_{23}\text{NO}_3$ ($\text{M}+1$) m/z 301.1677, found 302.1750.



9c – Spectral data worked out from the 82:18

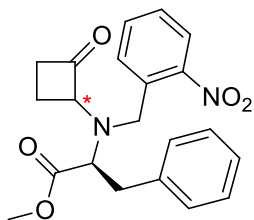
inseparable mixture of two diastereomers **9c/9’c**. Pale yellow oil (44 mg, 54% yield). **IR** (*neat*): 3064, 3030, 2928, 1781, 1731, 1497, 1455, 1159, 1067 cm^{-1} . **$^1\text{H-NMR}$** (400 MHz, CDCl_3) δ : 1.91 (quint., 1H, $J = 9.6$ Hz), 2.04 (ddd, 1H, $J = 4.4$ Hz, $J = 10.8$ Hz, $J = 21.6$ Hz), 2.48-2.54 (m, 1H), 2.63-2.73 (m, 1H), 2.96 (dd, 1H, $J = 6.4$ Hz, $J = 13.6$ Hz), 3.06 (dd, 1H, $J = 9.2$ Hz, $J = 13.6$ Hz), 3.27 (dd, 1H, $J = 7.2$ Hz, $J = 14.4$ Hz), 3.34 (dd, 1H, $J = 5.6$ Hz, $J = 14.4$ Hz), 3.66 (dd, 1H, $J = 6.0$ Hz, $J = 8.8$ Hz), 4.64 (t, 1H, $J = 9.6$ Hz), 5.04 (d, 2H, $J = 3.6$ Hz), 5.09 (d, 1H, $J = 4.8$ Hz), 5.14 (d, 1H, $J = 15.6$ Hz), 5.59-5.71 (m, 1H), 7.12-7.16 (m, 2H), 7.18-7.25 (m, 5H), 7.30-7.34 (m, 3H). **$^{13}\text{C-NMR}$** (100 MHz, CDCl_3) δ : 15.8, 36.3, 40.2, 51.9, 63.1, 66.3, 74.1, 117.9, 126.3, 128.2, 128.40, 128.45, 128.5, 129.2, 135.8, 136.0, 137.6, 172.5, 209.2. **MS** m/z : 204 [$\text{M}^+ - 159$ (54)], 160 (47), 119 (6), 91 (100), 41 (11). **HRMS** (*ES*) Calcd. for $\text{C}_{23}\text{H}_{25}\text{NO}_3$ ($\text{M}+1$) m/z 363.1834, found 364.1909.



9d – Spectral data worked out from the 78:22

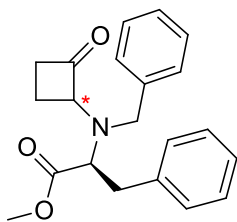
inseparable mixture of two diastereomers **9d/9’d**. Pale yellow oil (47 mg, 64% yield). **IR** (*neat*): 3064, 2977, 2932, 1783, 1722, 1603, 1455, 1393, 1149 cm^{-1} . **$^1\text{H-NMR}$** (400 MHz, CDCl_3) δ : 1.35 (s, 9H), 2.04 (quint., 1H, $J = 9.6$ Hz), 2.18 (ddd, 1H, $J = 4.0$ Hz, $J = 10.4$ Hz, $J = 20.8$ Hz), 2.53-2.59 (m, 1H), 2.70 (dd, 1H, $J = 9.6$ Hz, $J = 11.6$ Hz), 2.90 (dd, 1H, $J = 6.0$ Hz, $J = 13.2$ Hz), 3.01 (dd, 1H, $J = 9.2$ Hz, $J = 13.2$ Hz), 3.33 (t, 1H, $J = 7.2$ Hz), 3.50 (dd, 1H, $J = 6.0$ Hz, $J = 9.2$ Hz), 4.68 (t, 1H, $J = 8.8$ Hz), 5.10 (d, 1H, $J = 10.4$ Hz), 5.18 (d, 1H, $J = 16.8$ Hz), 5.63-5.75 (m, 1H), 7.16-7.19 (m, 3H), 7.23-7.27 (m, 2H). **$^{13}\text{C-NMR}$** (100 MHz, CDCl_3) δ : 16.1, 27.9, 36.5, 40.2, 52.0, 63.5, 74.2, 80.8, 117.7, 126.2, 128.1, 129.3, 136.1, 137.9,

172.1, 209.5. **MS** m/z (the same for the two diastereomers): 301 [M^+ -28 (6)], 244 (36), 228 (38), 200 (100), 154 (88). 91 (34), 41 (48). **HRMS** (*ESI*) Calcd. for $C_{20}H_{27}NO_3$ ($M+1$) m/z 329.1990, found 330.2060.



9e – Spectral data worked out from the 72:28

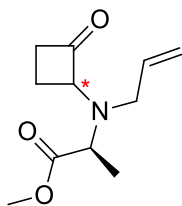
inseparable mixture of two diastereomers **9e/9'e**. Pale yellow oil (53 mg, 62% yield). **IR** (*neat*): 3028, 2951, 1780, 1734, 1525, 1454, 1354, 1165, 1070 cm^{-1} . **1H -NMR** (400 MHz, $CDCl_3$) δ : 2.06 (quint., 1H, $J = 9.6$ Hz), 2.25 (ddd, 1H, $J = 4.0$ Hz, $J = 10.8$ Hz, $J = 21.2$ Hz), 2.50-2.63 (m, 1H), 2.72-2.83 (m, 1H), 2.96 (dd, 1H, $J = 7.6$ Hz, $J = 13.6$ Hz), 3.05 (dd, 1H, $J = 7.6$ Hz, $J = 13.6$ Hz), 3.38 (t, 1H, $J = 7.2$ Hz), 3.65 (s, 1H), 4.0 (ABq, 2H, $J = 19.6$ Hz, $J = 36.0$ Hz), 4.24 (dd, 1H, $J = 8.0$ Hz, $J = 15.6$ Hz), 4.72 (t, 1H, $J = 9.6$ Hz), 7.05 (d, 1H, $J = 6.4$ Hz), 7.19-7.26 (m, 4H), 7.29-7.38 (m, 2H), 7.38-7.44 (m, 2H). **^{13}C -NMR** (100 MHz, $CDCl_3$) δ : 16.2, 35.9, 40.5, 48.9, 51.6, 63.6, 74.1, 124.0, 126.5, 127.7, 128.3, 129.1, 129.2, 130.8, 132.8, 133.8, 137.3, 172.8, 208.0. **MS** m/z (the same for the two diastereomers): 255 [M^+ -127 (36)], 223 (100), 136 (55), 78 (26). **HRMS** (*ESI*) Calcd. for $C_{21}H_{22}N_2O_5$ ($M+1$) m/z 382.1528, found 383.1601.



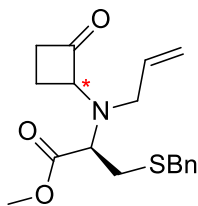
9f: Spectral data worked out from the 71:29 inseparable

mixture of two diastereomers **9f/9'f**. Pale yellow oil (48 mg, 64% yield). **IR** (*neat*): 3028, 2951, 2855, 1781, 1733, 1603, 1496, 1454, 1195 cm^{-1} . **1H -NMR** (500 MHz, $CDCl_3$) δ : 2.06 (quint., 1H, $J = 9.5$ Hz), 2.21 (ddd, 1H, $J = 4.5$ Hz, $J = 11.0$ Hz, $J = 21.0$ Hz), 2.51-2.64 (m, 1H), 2.71-2.82 (m, 1H), 2.95 (dd, 1H, $J = 7.0$ Hz, $J = 13.5$ Hz), 3.06 (dd, 1H, $J = 8.5$ Hz, $J = 13.5$ Hz), 3.51 (t, 1H, $J = 7.0$ Hz), 3.69 (s, 3H), 3.84 (ABq, 2H, $J = 14.0$ Hz, $J = 36.0$ Hz), 4.74 (dd, 1H, $J =$

8.5 Hz, $J = 10.0$ Hz), 7.04-7.05 (m, 2H), 7.19-7.25 (m, 3H). $^{13}\text{C-NMR}$ (124 MHz, CDCl_3) δ : 15.6, 36.1, 40.5, 51.5, 52.5, 62.0, 74.3, 126.2, 127.1, 128.14, 128.18, 128.8, 129.2, 137.4, 138.1, 173.2, 208.8. **MS** m/z (the same for the two diastereomers): 309 [$\text{M}^+ - 28$ (12)], 278 (10), 218 (30), 146 (57), 91 (100). 73 (12), 41 (6). **HRMS** (*ESI*) Calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}_3$ ($\text{M}+1$) m/z 337.1677, found 338.1749.

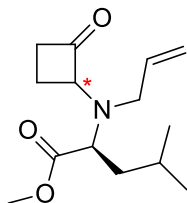


9g – Spectral data worked out from the 85:15 inseparable mixture of two diastereomers **9g/9'g**. Colourless oil (30 mg, 64% yield). **IR** (*neat*): 2980, 2951, 2946, 1782, 1734, 1640, 1458, 1166, 1070 cm^{-1} . $[\alpha]_{\text{D}}^{23} = -120.2$. (c 2.063, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.31 (d, 3H, $J = 7.0$ Hz), 2.06 (quint., 1H, $J = 10.0$ Hz), 2.16 (ddd, 1H, $J = 4.0$ Hz, $J = 10.5$ Hz, $J = 21.0$ Hz), 2.52-2.59 (m, 1H), 2.67-2.75 (m, 1H), 3.30 (t, 2H, $J = 5.5$ Hz), 3.57 (q, 1H, $J = 7.0$ Hz), 3.69 (s, 3H), 3.72 (dd, 1H, $J = 10.0$ Hz, $J = 21.0$ Hz), 4.50 (dd, 1H, $J = 9.0$ Hz, $J = 10.0$ Hz), 5.12 (d, 1H, $J = 9.0$ Hz), 5.21 (dd, 1H, $J = 1.5$ Hz, $J = 17.5$ Hz), 5.77-5.85 (m, 1H). $^{13}\text{C-NMR}$ (124 MHz, CDCl_3) δ : 15.6, 16.1, 40.1, 51.5, 51.7, 56.4, 74.0, 117.1, 136.1, 174.4, 209.6. **MS** m/z (the same for the two diastereomers): 183 [$\text{M}^+ - 28$ (16)], 152 (30), 124 (100), 96 (27), 73 (27). 56 (47), 41 (57). **HRMS** (*ESI*) Calcd. for $\text{C}_{11}\text{H}_{17}\text{NO}_3$ ($\text{M}+1$) m/z 211.1208, found 212.1281.



9h – Spectral data worked out from the 84:16 inseparable mixture of two diastereomers **9h/9'h**. Pale yellow oil (52 mg, 91% yield). **IR** (*neat*): 2959, 2928, 1784, 1734, 1458, 1369, 1164, 1072 cm^{-1} . $[\alpha]_{\text{D}}^{22} = -113.3$. (c 2.24, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 0.89 (t, 6H, $J = 7.0$ Hz), 1.48- 1.61 (m, 3H), 1.70 (ddd, 1H, $J = 6.5$ Hz, $J = 13.0$ Hz), 2.05 (dd, 1H, $J = 9.5$ Hz, $J = 19.0$ Hz), 2.14 (ddd, 1H, $J = 4.5$ Hz, $J = 10.5$ Hz, $J = 21.0$ Hz), 2.51-2.57 (m, 1H), 2.70 (ddd, 1H, $J = 2.0$ Hz, $J = 11.0$ Hz), 3.24 (dd, 1H, $J = 7.0$ Hz, $J = 14.0$ Hz), 3.31 (dd, 1H,

$J = 5.4$ Hz, $J = 14.0$ Hz), 3.45 (t, 1H, $J = 8.0$ Hz), 3.69 (s, 3H), 4.52 (t, 1H, $J = 10.0$ Hz), 5.12 (d, 1H, $J = 10.0$ Hz), 5.20 (d, 1H, $J = 17.0$ Hz), 5.71-5.84 (m, 1H). **$^{13}\text{C-NMR}$** (124 MHz, CDCl_3) δ : 15.8, 21.9, 22.8, 24.3, 38.8, 40.2, 51.3, 52.0, 59.2, 73.9, 117.7, 136.2, 174.4, 209.6. **MS** m/z (the same for the two diastereomers): 225 [$\text{M}^+ - 28$ (7)], 194 (17), 166 (100), 96 (28), 73 (13). 56 (20), 41 (45). **HRMS** (ESI) Calcd. for $\text{C}_{14}\text{H}_{23}\text{NO}_3$ ($\text{M}+1$) m/z 253.1677, found 254.1751.



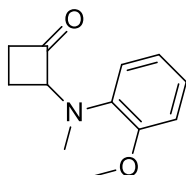
9i – Spectral data worked out from the 86:14 inseparable mixture of two diastereomers **9i/9'i**. Pale yellow oil (39 mg, 53% yield). **IR** (*neat*): 3062, 2951, 1780, 1733, 1641, 1494, 1453, 1198, 1165, 1070 cm^{-1} . $[\alpha]_{\text{D}}^{22} = -50.5$. (c 1.425, CHCl_3). **$^1\text{H-NMR}$** (500 MHz, CDCl_3) δ : 1.96 (quint., 1H, $J = 9.5$ Hz), 2.09 (ddd, 1H, $J = 4.0$ Hz, $J = 10.5$ Hz, $J = 20.5$ Hz), 2.51-2.59 (m, 1H), 2.66 (dd, 1H, $J = 6.0$ Hz, $J = 13.5$ Hz), 2.79 (dd, 1H, $J = 9.0$ Hz, $J = 13.5$ Hz), 3.24-3.26 (m, 2H), 3.53 (dd, 1H, $J = 6.0$ Hz, $J = 9.0$ Hz), 3.72 (s, 3H), 3.70 (dd, 2H, $J = 1.0$ Hz, $J = 13.5$ Hz), 4.46 (dd, 1H, $J = 8.5$ Hz, $J = 10.0$ Hz), 5.14 (dd, 1H, $J = 1.5$ Hz, $J = 10.5$ Hz), 5.21 (dd, 1H, $J = 1.5$ Hz, $J = 17.0$ Hz), 5.74-5.81 (m, 1H), 7.23-7.26 (m, 2H), 7.30-7.31 (m, 3H). **$^{13}\text{C-NMR}$** (124 MHz, CDCl_3) δ : 15.7, 30.8, 36.6, 40.2, 51.7, 61.2, 74.1, 118.1, 127.0, 128.46, 128.48, 128.8, 135.7, 138.0, 172.4, 208.6. **MS** m/z (the same for the two diastereomers): 274 [$\text{M}^+ - 59$ (5)], 246 (5), 214 (16), 168 (29), 91 (100). 65 (16), 41 (25). **HRMS** (ESI) Calcd. for $\text{C}_{18}\text{H}_{23}\text{NO}_3\text{S}$ ($\text{M}+1$) m/z 333.1398, found 334.1461.

N-ALKYLANILINES (10)

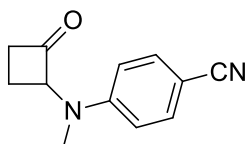
The starting *N*-alkylanilines **10a-q** were purchased and used without further purification for the reaction.

α -ALKYLARYLAMINO CYCLOBUTANONES (11)

The α -alkylaryl amino cyclobutanone **11a** was prepared according to literature procedures. The spectroscopic data are in accordance with those presented in literature.^[21]



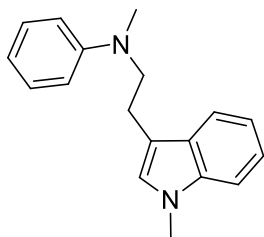
11i – Colourless oil (34 mg, 35% yield). The spectroscopic data are in accordance with those presented in literature.^[21] **¹H-NMR** (400 MHz, CDCl₃) δ : 6.98 (ddd, $J = 15.2, 7.6, 1.7$ Hz, 2H), 6.93 – 6.80 (m, 2H), 4.92 (tt, $J = 10.7, 2.2$ Hz, 1H), 3.84 (s, 3H), 2.83 (s, 3H), 2.81 – 2.71 (m, 1H), 2.65 (dddd, $J = 17.3, 9.9, 4.8, 2.4$ Hz, 1H), 2.29 – 2.09 (m, 2H).



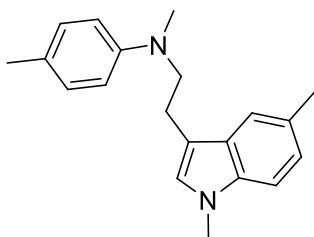
11j – Yellow oil (42 mg, 45% yield). **IR** (*neat*): 3047, 2961, 2928, 2831, 2213, 1785, 1605, 1519, 1399, 1384, 1320, 1179, 1123, 1077 cm⁻¹. **¹H-NMR** (400 MHz, CDCl₃) δ : 7.54 – 7.42 (m, 2H), 6.73 (d, $J = 9.0$ Hz, 2H), 5.14 (dd, $J = 12.8, 5.9$ Hz, 1H), 3.03 – 2.91 (m, 1H), 2.95 (s, 3H), 2.83 (dddd, $J = 17.7, 10.1, 4.6, 2.4$ Hz, 1H), 2.47 (ddd, $J = 14.7, 10.6, 4.4$ Hz, 1H), 2.14 (dt, $J = 19.8, 9.8$ Hz, 1H). **¹³C-NMR** (126 MHz, CDCl₃) δ : 204.98, 151.36, 133.62, 120.12, 112.80, 99.82, 73.06, 41.10, 34.00, 16.89. **HRMS** (*ESI*) Calcd. For C₁₂H₁₂N₂O ($M+Na$) m/z 223.0842, found 223.0839.

TRYPTAMINES (12)

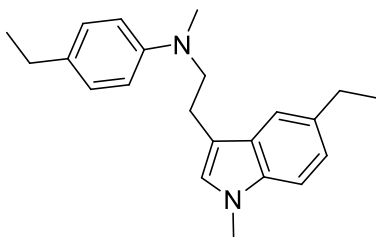
General procedure for the synthesis of tryptamines: A mixture of arylamine **10** (0.930 mmol), freshly distilled α -hydroxycyclobutanone **1** (0.465 mmol), and PTSA (0.093 mmol) was stirred at room temperature for 6 days. The crude reaction mixture was directly loaded on silica gel column without aqueous work-up and pure products were obtained by flash column chromatography (silica gel, mixture of hexane/ether, 10:1→1:1).



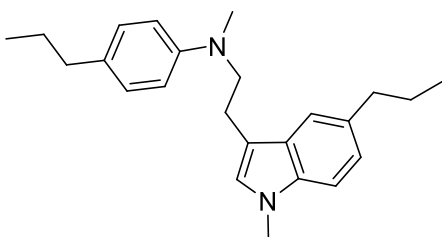
12a – Yellow oil (82 mg, 67% yield). **IR** (*neat*): 3057, 3027, 2937, 2882, 2822, 1601, 1508, 1474, 1377, 1328 cm^{-1} . **$^1\text{H-NMR}$** (500 MHz, CDCl_3) δ : 7.60 (d, $J = 7.9$ Hz, 1H), 7.33 – 7.26 (m, 2H), 7.26 – 7.19 (m, 2H), 7.17 – 7.08 (m, 1H), 6.85 (s, 1H), 6.78 (d, $J = 8.0$ Hz, 2H), 6.70 (t, $J = 7.2$ Hz, 1H), 3.73 (s, 3H), 3.67 – 3.60 (m, 2H), 3.04 – 2.97 (m, 2H), 2.94 (s, 3H). **$^{13}\text{C-NMR}$** (126 MHz, CDCl_3) δ : 149.19, 137.18, 129.38, 128.06, 126.67, 121.73, 118.98, 118.93, 116.16, 112.45, 112.32, 109.37, 53.89, 38.53, 32.71, 22.34. **MS** m/z : 264 [$\text{M}^+(19)$], 144 (11), 120 (100), 105 (3). **HRMS** (*ESI*) Calcd. For $\text{C}_{18}\text{H}_{20}\text{N}_2$ ($\text{M}+1$) m/z 265.1699, found 265.1693.



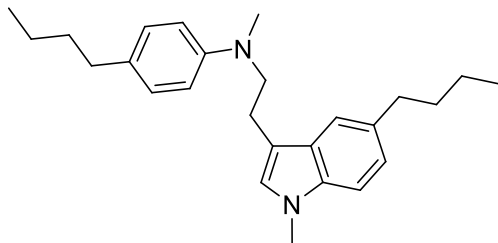
12b – Yellow oil (69 mg, 51% yield). **IR** (*neat*): 3015, 2916, 2863, 1620, 1522, 1494, 1378 cm^{-1} . **$^1\text{H-NMR}$** (400 MHz, CDCl_3) δ : 7.36 (s, 1H), 7.18 (d, $J = 8.4$ Hz, 1H), 7.06 (t, $J = 8.7$ Hz, 3H), 6.81 (s, 1H), 6.72 (d, $J = 8.5$ Hz, 2H), 3.71 (s, 3H), 3.59 (dd, $J = 9.1, 6.6$ Hz, 2H), 2.96 (d, $J = 8.1$ Hz, 2H), 2.93 (s, 3H), 2.47 (s, 3H), 2.27 (s, 3H). **$^{13}\text{C-NMR}$** (101 MHz, CDCl_3) δ : 147.25, 135.62, 129.90, 128.27, 128.08, 126.72, 125.45, 123.32, 118.68, 112.80, 111.97, 109.07, 54.18, 38.72, 32.76, 22.12, 21.66, 20.38. **MS** m/z : 292 [$\text{M}^+(18)$], 158 (9), 134 (100), 119 (5). **HRMS** (*ESI*) Calcd. For $\text{C}_{20}\text{H}_{24}\text{N}_2$ ($\text{M}+1$) m/z 293.2012, found 293.2005.



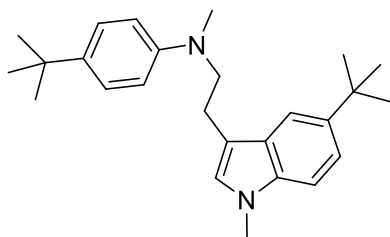
12c – Yellow oil (88 mg, 59% yield). **IR** (*neat*): 3015, 2962, 2926, 2868, 1617, 1522, 1491, 1453, 1377 cm^{-1} . **$^1\text{H-NMR}$** (500 MHz, CDCl_3) δ : 7.39 (d, $J = 0.8$ Hz, 1H), 7.26 – 7.17 (m, 1H), 7.13 – 7.05 (m, 3H), 6.82 (s, 1H), 6.78 – 6.71 (m, 2H), 3.71 (s, 3H), 3.63 – 3.57 (m, 2H), 3.00 – 2.95 (m, 2H), 2.94 (s, 3H), 2.76 (q, $J = 7.6$ Hz, 2H), 2.57 (q, $J = 7.6$ Hz, 2H), 1.30 (t, $J = 7.6$ Hz, 3H), 1.22 (t, $J = 7.6$ Hz, 3H). **$^{13}\text{C-NMR}$** (126 MHz, CDCl_3) δ : 147.45, 135.78, 134.88, 132.05, 128.70, 128.26, 126.69, 122.32, 117.45, 112.71, 112.18, 109.16, 54.14, 38.68, 32.75, 29.21, 27.94, 22.25, 16.71, 16.09. **HRMS** (*ESI*) Calcd. For $\text{C}_{22}\text{H}_{28}\text{N}_2$ ($M+1$) m/z 321.2325, found 321.2317.



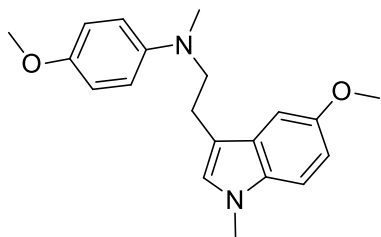
12d – Yellow oil (73 mg, 45% yield). **IR** (*neat*): 2957, 2926, 2868, 1615, 1519, 1491, 1453, 1378 cm^{-1} . **$^1\text{H-NMR}$** (400 MHz, CDCl_3) δ : 7.37 (s, 1H), 7.24 – 7.16 (m, 1H), 7.11 – 7.02 (m, 3H), 6.82 (s, 1H), 6.73 (d, $J = 8.6$ Hz, 2H), 3.71 (s, 3H), 3.67 – 3.54 (m, 2H), 2.97 (dd, $J = 9.0$, 6.7 Hz, 2H), 2.93 (s, 3H), 2.76 – 2.62 (m, 2H), 2.58 – 2.42 (m, 2H), 1.69 (dd, $J = 15.0$, 7.5 Hz, 2H), 1.61 (dd, $J = 15.1$, 7.4 Hz, 2H), 0.97 (t, $J = 5.6$ Hz, 3H), 0.94 (t, $J = 5.6$ Hz, 3H). **$^{13}\text{C-NMR}$** (101 MHz, CDCl_3) δ : 147.42, 135.78, 133.21, 130.46, 129.30, 128.18, 126.63, 122.82, 118.19, 112.58, 112.14, 109.03, 54.13, 38.65, 38.44, 37.21, 32.74, 25.54, 25.03, 22.27, 14.09, 14.05. **HRMS** (*ESI*) Calcd. For $\text{C}_{24}\text{H}_{32}\text{N}_2$ ($M+1$) m/z 349.2638, found 349.2621.



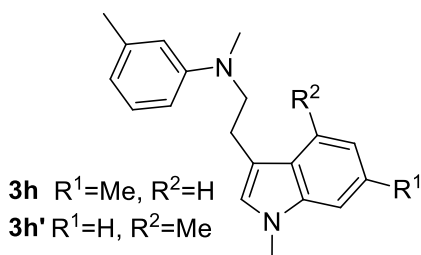
12e – Yellow oil (104 mg, 59% yield). **IR** (*neat*): 3015, 2954, 2924, 2858, 1615, 1522, 1491, 1456, 1373, 1355 cm^{-1} . **$^1\text{H-NMR}$** (500 MHz, CDCl_3) δ : 7.37 (d, $J = 0.8$ Hz, 1H), 7.23 – 7.15 (m, 1H), 7.11 – 7.00 (m, 3H), 6.81 (s, 1H), 6.76 – 6.67 (m, 2H), 3.70 (s, 3H), 3.64 – 3.56 (m, 2H), 3.01 – 2.94 (m, 2H), 2.93 (s, 3H), 2.76 – 2.69 (m, 2H), 2.57 – 2.49 (m, 2H), 1.70 – 1.62 (m, 2H), 1.61 – 1.53 (m, 2H), 1.38 (tq, $J = 14.6, 7.3$ Hz, 4H), 0.95 (t, $J = 5.1$ Hz, 3H), 0.92 (t, $J = 5.1$ Hz, 3H). **$^{13}\text{C-NMR}$** (126 MHz, CDCl_3) δ : 147.41, 135.77, 133.41, 130.65, 129.25, 128.21, 126.62, 122.79, 118.12, 112.61, 112.15, 109.03, 54.14, 38.64, 35.98, 34.74, 34.70, 34.17, 32.73, 22.60, 22.55, 22.29, 14.19, 14.16. **HRMS** (*ESI*) Calcd. For $\text{C}_{26}\text{H}_{36}\text{N}_2$ ($\text{M}+1$) m/z 377.2951, found 377.2935.



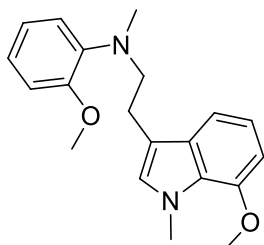
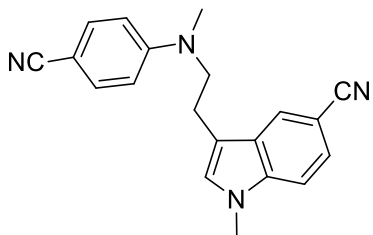
12f – Orange oil (94 mg, 55% yield). **IR** (*neat*): 2954, 2906, 2870, 1615, 1523, 1489, 1362, 1297, 1254 cm^{-1} . **$^1\text{H-NMR}$** (400 MHz, CDCl_3) δ : 7.63 – 7.57 (m, 1H), 7.31 (ddd, $J = 9.0, 7.7, 2.0$ Hz, 3H), 7.23 (d, $J = 8.6$ Hz, 1H), 6.83 (s, 1H), 6.80 – 6.73 (m, 2H), 3.70 (s, 3H), 3.66 – 3.57 (m, 2H), 3.05 – 2.97 (m, 2H), 2.95 (s, 3H), 1.41 (s, 9H), 1.32 (s, 9H). **$^{13}\text{C-NMR}$** (101 MHz, CDCl_3) δ : 147.00, 141.79, 138.80, 135.40, 127.81, 126.54, 126.16, 120.03, 114.72, 112.53, 112.16, 108.88, 54.03, 38.53, 34.72, 33.86, 32.70, 32.13, 31.72, 22.27. **HRMS** (*ESI*) Calcd. For $\text{C}_{26}\text{H}_{36}\text{N}_2$ ($\text{M}+1$) m/z 377.2951, found 377.2942.



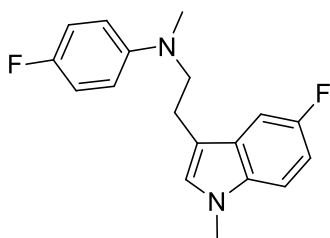
12g – Yellow oil (91 mg, 60% yield). **IR** (*neat*): 2989, 2939, 2904, 2833, 1622, 1575, 1511, 1494, 1459, 1426, 1247, 1226, 1176 cm^{-1} . **¹H-NMR** (400 MHz, CDCl_3) δ : 7.18 (d, $J = 8.8$ Hz, 1H), 7.01 (d, $J = 2.4$ Hz, 1H), 6.93 – 6.81 (m, 4H), 6.77 (d, $J = 9.1$ Hz, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.56 (dd, $J = 8.9, 6.6$ Hz, 2H), 2.97 – 2.91 (m, 2H), 2.90 (s, 3H). **¹³C-NMR** (126 MHz, CDCl_3) δ : 153.88, 151.71, 144.28, 132.61, 128.37, 127.20, 115.05, 114.58, 112.10, 111.89, 110.11, 101.03, 56.15, 56.01, 54.86, 39.21, 32.92, 22.16. **HRMS** (*ESI*) Calcd. For $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$ ($M+1$) m/z 325.1911, found 325.1900.



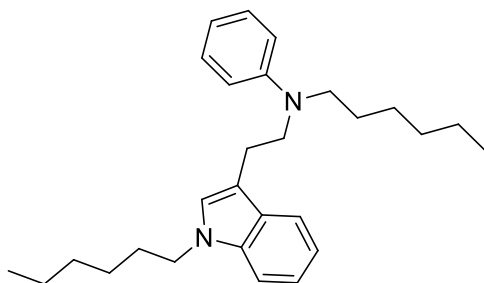
12h+12h': Inseparable 85:15 mixture of two regioisomers. Yellow oil (111 mg, 81% yield). **IR** (*neat*): 3040, 3030, 2914, 2858, 2815, 1602, 1580, 1499, 1475, 1378, 1327, 1247, 1226, 1176 cm^{-1} . **¹H-NMR** (500 MHz, CDCl_3) δ : 7.49 (d, $J = 8.1$ Hz, 1H), 7.26 (s, 1H), 7.17 – 7.10 (m, 3H), 7.08 (dd, $J = 3.0, 2.4$ Hz, 2H), 6.95 (dd, $J = 8.0, 0.9$ Hz, 1H), 6.86 – 6.82 (m, 1H), 6.81 (s, 1H), 6.77 (s, 1H), 6.63 – 6.56 (m, 3H), 6.55 – 6.50 (m, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.65 – 3.57 (m, 4H), 3.15 (dd, $J = 8.7, 6.9$ Hz, 2H), 2.99 – 2.95 (m, 2H), 2.94 (s, 3H), 2.93 (s, 3H), 2.73 (s, 3H), 2.50 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H). **¹³C-NMR** (126 MHz, CDCl_3) δ : 149.36, 149.29, 139.03, 138.98, 137.60, 137.53, 131.55, 130.91, 129.23, 126.94, 126.47, 126.04, 125.96, 121.74, 120.72, 120.68, 118.67, 117.18, 117.12, 113.15, 113.11, 112.36, 109.58, 109.37, 107.45, 107.29, 55.11, 53.92, 38.55, 38.52, 32.79, 32.61, 24.19, 22.44, 22.12, 22.09, 22.00, 20.48. **HRMS** (*ESI*) Calcd. For $\text{C}_{20}\text{H}_{24}\text{N}_2$ ($M+1$) m/z 293.2012, found 293.2007.

**12i** – Yield 0%.**12j** – White solid (33 mg, 23% yield). **MP:**

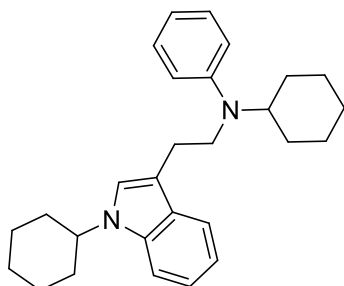
154-158°C. **IR** (*nujol*): 3015, 2934, 2906, 2851, 2218, 1605, 1522, 1486, 1388, 1350, 1174 cm^{-1} . **$^1\text{H-NMR}$** (500 MHz, CDCl_3) δ : 7.87 (d, $J = 0.8$ Hz, 1H), 7.45 (ddd, $J = 5.2, 4.2, 1.8$ Hz, 3H), 7.34 (d, $J = 8.5$ Hz, 1H), 6.95 (s, 1H), 6.62 (d, $J = 9.0$ Hz, 2H), 3.77 (s, 3H), 3.71 – 3.64 (m, 2H), 3.05 – 2.99 (m, 2H), 2.94 (s, 3H). **$^{13}\text{C-NMR}$** (101 MHz, CDCl_3) δ : 151.34, 138.59, 133.68, 129.16, 127.62, 124.83, 124.37, 112.92, 111.44, 110.40, 102.22, 97.60, 53.13, 38.74, 33.03, 22.42. **HRMS** (*ESI*) Calcd. For $\text{C}_{20}\text{H}_{18}\text{N}_4$ ($M+1$) m/z 315.1604, found 315.1593.

**12k** – Yellow oil (59 mg, 48% yield). **IR** (*neat*):

3058, 2939, 2823, 1628, 1612, 1580, 1511, 1489, 1426, 1355, 1179 cm^{-1} . **$^1\text{H-NMR}$** (400 MHz, CDCl_3) δ : 7.21 – 7.13 (m, 2H), 6.95 (ddd, $J = 14.3, 6.8, 2.4$ Hz, 3H), 6.86 (s, 1H), 6.69 – 6.60 (m, 2H), 3.71 (s, 3H), 3.54 (dd, $J = 8.7, 6.6$ Hz, 2H), 2.91 (d, $J = 7.9$ Hz, 2H), 2.88 (s, 3H). **$^{13}\text{C-NMR}$** (101 MHz, CDCl_3) δ : 158.94, 156.60, 154.26, 145.98, 133.81, 128.36, 115.69 (d, $J = 22.0$ Hz), 113.61 (d, $J = 7.1$ Hz), 112.31 (d, $J = 4.5$ Hz), 110.15 (d, $J = 12.3$ Hz), 109.97 (d, $J = 3.7$ Hz), 103.75 (d, $J = 23.2$ Hz), 54.47, 39.02, 32.99, 22.20. **HRMS** (*ESI*) Calcd. For $\text{C}_{18}\text{H}_{18}\text{F}_2\text{N}_2$ ($M+1$) m/z 301.1511, found 301.1506.

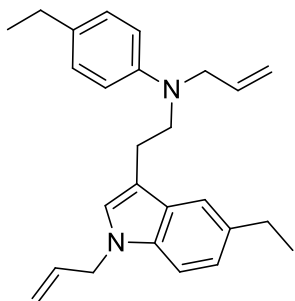


3I – Yellow oil (137 mg, 73% yield). **IR** (*neat*): 3055, 3025, 2954, 2926, 2856, 1597, 1504, 1469, 1368, 1191 cm^{-1} . **$^1\text{H-NMR}$** (400 MHz, CDCl_3) δ : 7.61 (d, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 7.9$ Hz, 1H), 7.27 – 7.19 (m, 3H), 7.11 (t, $J = 7.4$ Hz, 1H), 6.91 (s, 1H), 6.74 (d, $J = 8.6$ Hz, 2H), 6.65 (t, $J = 7.2$ Hz, 1H), 4.05 (t, $J = 7.2$ Hz, 2H), 3.63 – 3.54 (m, 2H), 3.31 – 3.22 (m, 2H), 3.05 – 2.97 (m, 2H), 1.79 (dd, $J = 14.0, 7.0$ Hz, 2H), 1.62 – 1.52 (m, 2H), 1.29 (d, $J = 3.6$ Hz, 12H), 0.88 (dd, $J = 6.7, 4.2$ Hz, 6H). **$^{13}\text{C-NMR}$** (101 MHz, CDCl_3) δ : 148.09, 136.45, 129.44, 128.11, 125.56, 121.54, 119.04, 118.80, 115.41, 112.37, 111.88, 109.57, 52.06, 51.34, 46.36, 31.89, 31.60, 30.44, 27.52, 27.02, 26.86, 23.06, 22.83, 22.69, 14.20, 14.16. **MS** m/z : 404 [$\text{M}^+(11)$], 331 (2), 228 (2), 214 (4), 190 (100), 120 (16), 106 (8). **HRMS** (*ESI*) Calcd. For $\text{C}_{28}\text{H}_{40}\text{N}_2$ ($\text{M}+1$) m/z 405.3264, found 405.3246.



12m – Yellow oil (68 mg, 37% yield). **IR** (*neat*): 3058, 2931, 2856, 1597, 1504, 1461, 1448, 1360, 1343, 1300, 1214, 1156 cm^{-1} . **$^1\text{H-NMR}$** (500 MHz, CDCl_3) δ : 7.63 (d, $J = 7.7$ Hz, 1H), 7.36 (d, $J = 8.3$ Hz, 1H), 7.29 – 7.22 (m, 2H), 7.20 (ddd, $J = 8.2, 7.0, 1.1$ Hz, 1H), 7.11 (ddd, $J = 7.9, 7.0, 0.9$ Hz, 1H), 7.07 (s, 1H), 6.85 (d, $J = 8.1$ Hz, 2H), 6.68 (t, $J = 7.2$ Hz, 1H), 4.20 (tt, $J = 11.9, 3.7$ Hz, 1H), 3.61 (tt, $J = 11.5, 3.4$ Hz, 1H), 3.53 – 3.46 (m, 2H), 3.03 – 2.96 (m, 2H), 2.16 – 2.09 (m, 2H), 1.98 – 1.66 (m, 10H), 1.56 – 1.23 (m, 7H), 1.15 (qt, $J = 12.6, 3.5$ Hz, 1H). **$^{13}\text{C-NMR}$** (101 MHz, CDCl_3) δ : 148.69, 135.96, 129.43, 128.04, 121.62, 121.36, 119.20, 118.89, 115.94, 112.94, 112.73, 109.61,

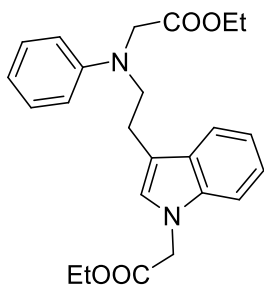
57.60, 55.14, 46.08, 33.73, 31.02, 26.48, 26.17, 25.85, 25.67. **HRMS** (ESI) Calcd. For $C_{28}H_{36}N_2$ (M+1) m/z 401.2951, found 401.2939.



12n – Yellow oil (104 mg, 60% yield). **IR** (neat):

3080, 3012, 2959, 2924, 2868, 1617, 1519, 1486, 1451, 1377, 1189 cm^{-1} .

1H -NMR (400 MHz, $CDCl_3$) δ : 7.40 (s, 1H), 7.24 – 7.17 (m, 1H), 7.07 (t, $J = 6.9$ Hz, 3H), 6.87 (s, 1H), 6.72 (d, $J = 8.6$ Hz, 2H), 5.95 (ddd, $J = 22.4, 10.5, 5.4$ Hz, 1H), 5.85 (ddt, $J = 17.0, 10.1, 5.0$ Hz, 1H), 5.25 – 4.98 (m, 4H), 4.63 (d, $J = 5.4$ Hz, 2H), 3.90 (d, $J = 4.9$ Hz, 2H), 3.68 – 3.53 (m, 2H), 3.02 (dd, $J = 9.2, 6.6$ Hz, 2H), 2.76 (q, $J = 7.6$ Hz, 2H), 2.56 (q, $J = 7.6$ Hz, 2H), 1.30 (t, $J = 7.6$ Hz, 3H), 1.21 (t, $J = 7.6$ Hz, 3H). **^{13}C -NMR** (101 MHz, $CDCl_3$) δ : 146.46, 135.15, 135.01, 134.85, 133.91, 131.84, 128.67, 128.46, 125.58, 122.36, 117.54, 117.19, 115.97, 112.50, 109.52, 53.65, 51.81, 48.85, 29.16, 27.89, 23.16, 16.59, 16.05. **HRMS** (ESI) Calcd. For $C_{26}H_{32}N_2$ (M+1) m/z 373.2638, found 373.2626.

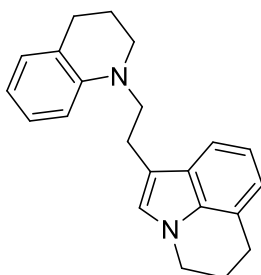


12o – Yellow oil (60 mg, 32% yield). **IR** (neat):

3060, 2979, 2934, 1749, 1602, 1506, 1464, 1368, 1262, 1194, 1027 cm^{-1} .

1H -NMR (500 MHz, $CDCl_3$) δ : 7.60 (d, $J = 7.9$ Hz, 1H), 7.25 – 7.21 (m, 4H), 7.17 – 7.09 (m, 1H), 6.92 (s, 1H), 6.76 – 6.68 (m, 3H), 4.79 (s, 2H), 4.21 (q, $J = 7.1$ Hz, 2H), 4.19 – 4.13 (m, 3H), 3.95 (s, 2H), 3.74 (dd, $J = 8.5, 6.8$ Hz, 2H), 3.15 – 3.05 (m, 2H), 1.26 (dd, $J = 7.8, 5.5$ Hz, 3H), 1.23 (t, $J = 6.7$ Hz, 3H). **^{13}C -NMR** (126 MHz, $CDCl_3$) δ : 171.45, 168.78, 147.85, 137.03, 129.48, 128.30,

126.28, 122.36, 119.66, 119.24, 117.06, 113.70, 112.10, 109.17, 61.79, 61.06, 53.36, 52.93, 47.87, 23.40, 14.37, 14.31. **HRMS** (ESI) Calcd. For $C_{24}H_{28}N_2O_4$ (M+Na) m/z 431.1941, found 431.1926.



12p – Orange oil (118 mg, 80% yield). **IR** (*neat*):

3040, 2931, 2881, 2851, 2841, 1602, 1575, 1504, 1476, 1453, 1345, 1247, 1211, 1194 cm^{-1} . **1H -NMR** (500 MHz, $CDCl_3$) δ : 7.43 (dd, $J = 8.0, 0.7$ Hz, 1H), 7.08 (td, $J = 8.2, 1.7$ Hz, 1H), 7.02 (dd, $J = 7.9, 7.0$ Hz, 1H), 6.98 – 6.93 (m, 1H), 6.90 (dd, $J = 7.1, 0.8$ Hz, 1H), 6.89 (s, 1H), 6.72 (d, $J = 8.1$ Hz, 1H), 6.56 (td, $J = 7.3, 1.0$ Hz, 1H), 4.17 – 3.98 (m, 2H), 3.63 – 3.46 (m, 2H), 3.39 – 3.20 (m, 2H), 3.04 – 2.99 (m, 2H), 2.97 (t, $J = 6.1$ Hz, 2H), 2.75 (t, $J = 6.4$ Hz, 2H), 2.28 – 2.15 (m, 2H), 1.99 – 1.79 (m, 2H). **^{13}C -NMR** (126 MHz, $CDCl_3$) δ : 145.17, 134.68, 129.32, 127.29, 125.52, 123.89, 122.42, 121.86, 119.34, 118.58, 116.57, 115.50, 112.60, 110.66, 77.42, 77.16, 76.91, 52.64, 49.59, 44.00, 28.37, 24.85, 23.07, 22.39, 22.23. **MS** m/z : 316 [M^+ (20)], 170 (9), 146 (100), 130 (4). **HRMS** (ESI) Calcd. For $C_{22}H_{24}N_2$ (M+1) m/z 317.2012, found 317.2006.

SILYL ENOL ETHERS (15)

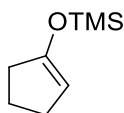
General procedure A for the synthesis of OTMS silylenolether 15^[22]

To a dispersion of anhydrous (dried under high vacuum at 90 °C for 12 h) NaI (1.25 equiv.) in distilled acetonitrile were added the ketone (1 equiv.) followed by Et_3N (1.25 equiv.). Then TMSCl (1.14 equiv.) was added drop wise and the solution was stirred at room temperature for 1 h. Pentane was added and the two layers solution was vigorously stirred for 10 minutes. The two layers were then separated and the acetonitrile phase was extracted with pentane. The combined pentane phase was washed with water and brine, dried over Na_2SO_4 and

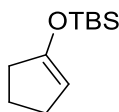
concentrated under reduced pressure to give the crude silyl enol ether **15**, which was used without further purification.

General procedure B for the synthesis of OTBS silylenolether **15**^[23]

To a solution of the ketone (1 equiv.) in distilled acetonitrile were added Et₃N (1.5 equiv.), then TBSCl (1.5 equiv.) and anhydrous (dried under high vacuum at 90 °C for 12 h) NaI (1.5 equiv.). The reaction was stirred overnight at room temperature. Pentane and an aqueous saturated solution of NaHCO₃ were added and the solution was vigorously stirred. The two phases were separated and the acetonitrile/aqueous phase was extracted with petroleum ether. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give the crude mixture, which was purified by flash chromatography on silica gel to afford the requisite silyl enol ether **15**.

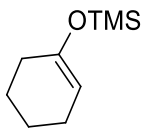


15a - According to the general procedure **A** using NaI (64 mmol, 9.55 g, 1.25 equiv.), cyclopentanone (51 mmol, 4.28 g, 4.50 mL, 1 equiv.), Et₃N (64 mmol, 6.45 g, 8.88 mL, 1.25 equiv.) and TMSCl (58 mmol, 6.31 g, 7.42 mL, 1.14 equiv.) in 80 mL of acetonitrile, the crude product **15a** was obtained as a colourless oil (6.48 g, 81% yield). **¹H-NMR** (250 MHz, CDCl₃) δ: 4.64 – 4.57 (m, 1H), 2.31 – 2.19 (m, 4H), 1.91 – 1.77 (m, 2H), 0.20 (s, J = 1.9 Hz, 9H). **¹³C-NMR** (63 MHz, CDCl₃) δ: 155.16 (C), 102.24 (CH), 33.65 (CH₂), 28.87 (CH₂), 21.46 (CH₂), 0.14 (CH₃). **HRMS** (ESI+/ESI-): unstable.

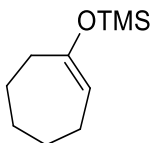


15b - According to the general procedure **B** using NaI (49 mmol, 7.42 g, 1.5 equiv.), cyclopentanone (33 mmol, 2.77 g, 2.91 mL, 1 equiv.), Et₃N (49 mmol, 5.00 g, 6.90 mL, 1.5 equiv.) and TBSCl (49 mmol, 7.46 g, 1.5 equiv.) in 70 mL of acetonitrile, the flash chromatography on silica gel (PE/AcOEt/Pyridine 98:1:1) gave the product **15b** as a colourless oil (4.75g, 73% yield). **R_f** (100% Petroleum ether): 0.70; **IR** (ATR) *cm*⁻¹: 2955, 2857, 1646, 1470, 1342, 1251, 1183,

922, 835, 778. **¹H-NMR** (300 MHz, CDCl₃) δ: 4.65 – 4.58 (m, 1H), 2.29 – 2.21 (m, 4H), 1.91 – 1.79 (m, 2H), 0.92 (s, 9H), 0.15 (s, 6H). **HRMS** (ESI+/ESI-): unstable. No ¹³C NMR was made for this already known and characterised compound.^[24]



15c - According to the general procedure **A** using NaI (64 mmol, 9.55 g, 1.25 equiv.), cyclohexanone (51 mmol, 4.99 g, 5.27 mL, 1 equiv.), Et₃N (64 mmol, 6.45 g, 8.88 mL, 1.25 equiv.) and TMSCl (58 mmol, 6.31 g, 7.42 mL, 1.14 equiv.) in 80 mL of acetonitrile, the crude product **15c** was obtained as a colourless oil (8.00 g, 94% yield). **Rf** (100% Petroleum ether): 0.60; **IR** (ATR) *cm*⁻¹: 2932, 2856, 2839, 1669, 1366, 1250, 1184, 988, 894, 837; **¹H-NMR** (250 MHz, CDCl₃) δ: 4.87 – 4.79 (m, 1H), 2.04 – 1.91 (m, 4H), 1.70 – 1.56 (m, 2H), 1.56 – 1.41 (m, 2H), 0.15 (s, 9H). **¹³C-NMR** (63 MHz, CDCl₃) δ: 150.39 (C), 104.23 (CH), 30.00 (CH₂), 23.91 (CH₂), 23.28 (CH₂), 22.46 (CH₂), 0.38 (CH₃). **HRMS** (ESI+/ESI-): unstable.



15d - According to the general procedure **A** using NaI (64 mmol, 9.55 g, 1.25 equiv.), cycloheptanone (51 mmol, 5.70 g, 1 equiv.), Et₃N (64 mmol, 6.45 g, 8.88 mL, 1.25 equiv.) and TMSCl (58 mmol, 6.31 g, 7.42 mL, 1.14 equiv.) in 80 mL of acetonitrile, the crude product **15d** was obtained as a colourless oil (7.42 g, 79% yield). **Rf** (100% Petroleum ether): 0.50; **IR** (ATR) *cm*⁻¹: 2920, 2842, 1659, 1250, 1228, 1167, 1125, 894, 881, 838, 751; **¹H-NMR** (250 MHz, CDCl₃) δ: 5.01 (t, J = 6.6 Hz, 1H), 2.26 – 2.17 (m, 2H), 2.03 – 1.92 (m, 2H), 1.73 – 1.61 (m, 2H), 1.61 – 1.45 (m, 4H), 0.16 (s, 9H). **¹³C-NMR** (63 MHz, CDCl₃) δ: 156.15 (C), 108.82 (CH), 35.67 (CH₂), 31.70 (CH₂), 27.95 (CH₂), 25.50 (CH₂), 25.38 (CH₂), 0.40 (CH₃). **HRMS** (ESI+/ESI-): unstable.

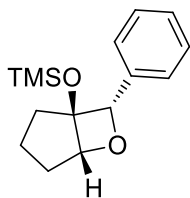
SILYLATED BICYCLIC OXETANES (17)

General procedure C for the Paternò-Büchi Reaction

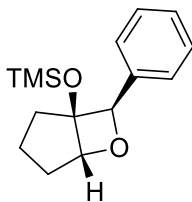
A 60 mM solution of silyl enol ether **15** (2 equiv.) and benzaldehyde **16a** (1 equiv.) in the appropriate degassed solvent (with an argon stream for 30 min) was placed in a cylindrical immersion photochemical reactor. The solution was irradiated for 6 h with a 400 W medium-pressure Hg lamp fitted with a Pyrex® filter and a water-cooling jacket. The reaction was followed by ^1H NMR and the reaction mixture was concentrated under reduced pressure to give the crude mixture, which was purified by flash chromatography on silica gel to afford the requisite photoadducts *endo*-**17** and *exo*-**17**.

Paternò-Büchi Reaction between **15a** and **16a**:

According to the general procedure **C** using the silylenolether **15a** (24 mmol, 3.74 g, 2 equiv.) and benzaldehyde **16a** (12 mmol, 1.22 mL, 1 equiv.) in distilled and degassed acetonitrile (200 mL), the flash chromatography on silica gel (PE/Et₂O 98:2 → 94:6) gave the products *endo*-**17a** as a pale yellow oil (261 mg, 8% yield) and *exo*-**17a** as a pale yellow oil (1.06 g, 34% yield).



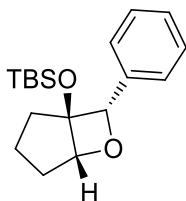
endo-**17a** - R_f (90:10 PE/Et₂O): 0.90; IR (ATR) cm^{-1} : 2954, 2878, 1252, 1200, 1142, 1131, 992, 967, 902, 836, 738, 700. $^1\text{H-NMR}$ (360 MHz, CDCl₃) δ : 7.50 – 7.18 (m, 5H), 5.80 (s, 1H), 5.16 (d, J = 2.7 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.82 – 1.59 (m, 4H), 1.48 – 1.36 (m, 1H), 0.24 (s, 9H). $^{13}\text{C-NMR}$ (63 MHz, CDCl₃) δ : 138.49 (C), 128.14 (CH), 127.13 (CH), 124.73 (CH), 90.63 (CH), 90.49 (CH), 86.14 (C), 34.84 (CH₂), 32.36 (CH₂), 24.04 (CH₂), 2.06 (CH₃). HRMS (ESI+): Calcd. for C₁₅H₂₂NaO₂Si (M + Na⁺), m/z 285.1281, found 285.1270.



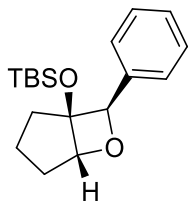
exo-17a - Rf (90:10 PE/Et₂O): 0.7. IR (ATR) cm^{-1} : 2956, 2879, 1335, 1252, 1236, 1201, 968, 927, 898, 837, 748, 696. ¹H-NMR (360 MHz, CDCl₃) δ : 7.50 – 7.19 (m, 5H), 5.30 (s, 1H), 5.12 (d, J = 3.5 Hz, 1H), 2.35 – 2.13 (m, 2H), 2.12 – 1.97 (m, 2H), 1.71 (m, 2H), -0.18 (s, 9H). ¹³C-NMR (91 MHz, CDCl₃) δ : 139.45 (C), 127.87 (CH), 127.85 (CH), 127.81 (CH), 92.62 (CH), 91.96 (CH), 84.83 (C), 39.12 (CH₂), 33.13 (CH₂), 24.16 (CH₂), 1.50 (CH₃). HRMS (ESI⁺): Calcd. for C₁₅H₂₂NaO₂Si (M + Na⁺), m/z 285.1280, found 285.1270.

Paternò-Büchi Reaction between **15b** and **16a**:

According to the general procedure **C** using the silylenolether **15b** (24 mmol, 4.75 g, 2 equiv.) and benzaldehyde **16a** (12 mmol, 1.22 mL, 1 equiv.) in distilled and degassed acetonitrile (200 mL), the flash chromatography on silica gel (PE/Et₂O 98:2 → 94:6) gave the products *endo*-**17b** as a yellow oil (38 mg, 1% yield) and *exo*-**17b** as a yellow oil (203 mg, 6% yield).



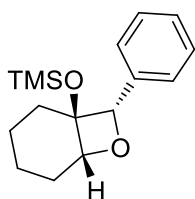
endo-17b - Rf (90:10 PE/Et₂O): 0.60; IR (ATR) cm^{-1} : 2956, 2879, 1251, 1141, 1131, 992, 966, 886, 837, 737, 701. ¹H-NMR (250 MHz, CDCl₃) δ : 7.43 – 7.26 (m, 5H), 5.79 (s, 1H), 5.13 (d, J = 2.6 Hz, 1H), 2.04 – 1.94 (m, 1H), 1.78 – 1.60 (m, 4H), 1.47 – 1.35 (m, 1H), 0.97 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H). ¹³C-NMR (63 MHz, CDCl₃) δ : 138.55 (C), 128.20 (CH), 127.14 (CH), 124.66 (CH), 90.83 (CH), 90.73 (CH), 86.04 (C), 34.79 (CH₂), 32.39 (CH₂), 25.80 (CH₃), 24.03 (CH₂), 18.04 (C), -2.54 (CH₃), -2.57 (CH₃). HRMS (ESI⁺): Calcd. for C₁₈H₂₉O₂Si (M + H⁺), m/z 305.1931, found 305.1922.



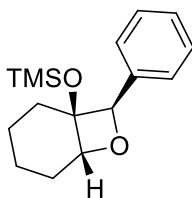
exo-17b - Rf (90:10 PE/Et₂O): 0.47. IR (ATR) cm^{-1} : 2952, 2929, 2856, 1462, 1332, 1237, 1200, 1137, 991, 972, 926, 834, 773, 696. **¹H-NMR** (360 MHz, CDCl₃) δ : 7.40 – 7.34 (m, 4H), 7.28 – 7.22 (m, 1H), 5.34 (s, 1H), 5.04 (d, J = 3.3 Hz, 1H), 2.33 – 2.16 (m, 1H), 2.16 – 1.99 (m, 3H), 1.75 – 1.62 (m, 2H), 0.58 (s, 9H), -0.12 (s, 3H), -0.18 (s, 3H). **¹³C-NMR** (91 MHz, CDCl₃) δ : 139.54 (C), 127.85 (CH), 127.34 (CH), 126.71 (CH), 92.05 (CH), 91.66 (CH), 84.40 (C), 39.06 (CH₂), 33.23 (CH₂), 25.39 (CH₃), 23.76 (CH₂), 17.74 (C), -2.94 (CH₃), -3.04 (CH₃). **HRMS** (ESI+): Calcd. for C₁₈H₂₉O₂Si (M + H⁺), m/z 305.1931, found 305.1922.

Paternò-Büchi Reaction between 15c and 16a:

According to the general procedure **C** using the silylenolether **15c** (24 mmol, 4.08 g, 2 equiv.) and benzaldehyde **16a** (12 mmol, 1.22 mL, 1 equiv.) in distilled and degassed acetonitrile (200 mL), the flash chromatography on silica gel (PE/Et₂O 98:2 → 94:6) gave the products *endo*-**17c** as a pale yellow oil (44 mg, 1% yield) and *exo*-**17c** as a pale yellow oil (117 mg, 4% yield).



endo-17c - Rf (90:10 PE/Et₂O): 0.52. IR (ATR) cm^{-1} : 2937, 2865, 1722, 1451, 1250, 1204, 1130, 1093, 894, 837, 750. **¹H-NMR** (250 MHz, CDCl₃) δ : 7.44 – 7.26 (m, 5H), 5.54 (s, 1H), 4.81 (d, J = 2.8 Hz, 1H), 2.05 – 1.89 (m, 1H), 1.78 – 1.44 (m, 5H), 1.41 – 1.12 (m, 2H), 0.24 (s, 9H). **¹³C-NMR** (63 MHz, CDCl₃) δ : 138.85 (C), 128.17 (CH), 127.34 (CH), 125.48 (CH), 90.50 (CH), 84.07 (CH₂), 76.70 (C), 30.95 (CH₂), 26.74 (CH₂), 20.19 (CH₂), 19.98 (CH₂), 2.39 (CH₃). **HRMS** (ESI+): Calcd. for C₁₂H₁₃O₂ (M + H⁺), m/z 277.1618, found 277.1583.

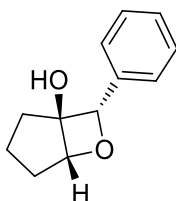


exo-**17c** - Rf (90:10 PE/Et₂O): 0.4. IR (ATR) cm^{-1} : 2952, 2929, 2856, 1462, 1332, 1237, 1200, 1137, 991, 972, 926, 834, 773, 696. ¹H-NMR (250 MHz, CDCl₃) δ : 7.45 – 7.26 (m, 5H), 5.34 (s, 1H), 4.94 (s, 1H), 2.01 – 1.76 (m, 5H), 1.68 – 1.52 (m, 3H), -0.17 (s, 9H). ¹³C-NMR (63 MHz, CDCl₃) δ : 139.16 (C), 127.88 (CH), 127.46 (CH), 127.25 (CH), 90.92 (CH), 87.09 (CH), 74.75 (C), 35.91 (CH₂), 26.42 (CH₂), 19.50 (CH₂), 18.14 (CH₂), 1.79 (CH₃). HRMS (ESI+): Calcd. for C₁₂H₁₃O₂ (M + H⁺), m/z 277.1618, found 277.1609.

DEPROTECTED BICYCLIC OXETANES (**18**)

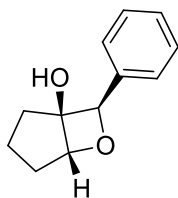
General procedure D for silylated group removal

To a solution of the *endo*-**17a** or *exo*-**17b** (1 equiv.) in anhydrous THF was added a solution of TBAF in THF (1M, 1.5 equiv). The reaction was stirred under argon for 4h at 0°C and then quenched with water. The resulting mixture was diluted with AcOEt and the two phases were separated. The organic phase was washed with water (2 times) and the resulting aqueous phase was extracted with AcOEt (3 times). The combined organic phases were then dried with Na₂SO₄ and concentrated under reduced pressure to give the crude mixture, which was purified by flash chromatography on silica gel to afford the requisite alcohol *endo*-**18** or *exo*-**18**.



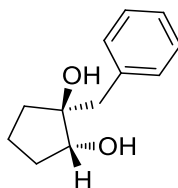
endo-**18** - According to the general procedure **D** using the cycloadduct *endo*-**17a** (1.09 mmol, 284.2 mg, 1 equiv.) and a solution of TBAF (1.64 mL, 1.5 equiv.) in anhydrous THF (11 mL), the flash chromatography on silica gel (PE/Et₂O 80:20 → 50:50) gave the products *endo*-**18** as colourless

crystal (173 mg, 83% yield). **Rf** (50:50 PE/Et₂O): 0.30. **IR** (ATR) cm^{-1} : 3719, 3372, 2952, 1499, 1297, 1109. **MP**: 81-83 °C. **¹H-NMR** (360 MHz, CDCl₃) δ : 7.42 – 7.22 (m, 5H), 5.80 (s, 1H), 5.06 (d, $J = 2.9$ Hz, 1H), 1.98 (dd, $J = 13.1, 5.7$ Hz, 1H), 1.87 – 1.49 (m, 4H), 1.48 – 1.29 (m, 1H). **¹³C-NMR** (91 MHz, CDCl₃) δ : 137.92 (C), 128.33 (CH), 127.37 (CH), 124.45 (CH), 91.75 (CH), 90.34 (CH), 84.97 (CH₂), 33.96 (CH₂), 32.45 (CH₂), 24.41 (CH₂). **HRMS** (ESI⁻): Calcd. for C₁₂H₁₃O₂ (M - H⁺), m/z 189.0911, found 189.0921.



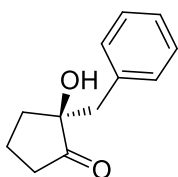
exo-18 - According to the general procedure **D** using the cycloadduct **endo-17a** (0.38 mmol, 100 mg, 1 equiv.) and a solution of TBAF (0.57 mL, 1.2 equiv.) in anhydrous THF (4 mL), the flash chromatography on silica gel (PE/Et₂O 80:20) gave the products **exo-18** as colourless crystal (55 mg, 77% yield). **Rf** (80:20 PE/Et₂O): 0.21. **IR** (ATR) cm^{-1} : 3399, 2958, 1453, 1329, 1231, 1125, 1101, 1073, 957, 922, 750, 696. **MP**: 67-70 °C. **¹H-NMR** (360 MHz, CDCl₃) δ : 7.51 – 7.32 (m, 5H), 5.45 (s, 1H), 4.98 (d, $J = 3.4$ Hz, 1H), 2.24 (ddt, $J = 19.1, 12.8, 6.4$ Hz, 1H), 2.12 – 2.01 (m, 3H), 1.77 – 1.69 (m, 2H). **¹³C-NMR** (75 MHz, CDCl₃) δ : 137.68 (C), 129.04 (CH), 128.52 (CH), 126.25 (CH), 93.65 (CH), 90.81 (CH), 82.75 (CH₂), 37.11 (CH₂), 33.32 (CH₂), 23.73 (CH₂). **HRMS** (ESI⁻): Calcd. for C₁₂H₁₃O₂ (M + H⁺), m/z 189.0921, found 189.0925.

SUBSTITUTED HYDROXPENTANONES PRODUCTS (21, 22)



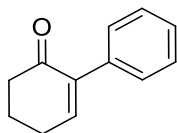
trans-21 - Representative procedure on **exo-17a**: To a solution of **exo-17a** (0.38 mmol, 100 mg, 1 equiv.) in EtOAc (10 mL) under argon was added the Pd/C 10% (50mg). The reaction mixture was stirred under H₂ atmosphere for 26 h and then filtered through a pad of celite® and rinsed with

EtOAc. The solvent was removed under reduced pressure to give the crude mixture, which was purified by flash chromatography on silica gel (90:10 PE/Et₂O → 90:10 DCM/AcOEt) to afford the requisite diol **21** as a colourless crystal (56 mg, 77% yield). **Rf** (50:50 PE/Et₂O): 0.2. **MP**: 71-73 °C. **IR** (ATR) *cm*⁻¹: 3377, 3329, 2922, 2849, 1732, 1490, 1395, 1295, 1079, 979, 702; **¹H-NMR** (250 MHz, CDCl₃) δ: 7.55 – 7.12 (m, 5H), 3.79 (dd, *J* = 5.1, 2.2 Hz, 1H), 3.06, 2.84 (ABq, *J* = 13.5 Hz, 2H), 2.29 – 2.09 (m, 1H), 1.95 – 1.76 (m, 3H), 1.67 – 1.42 (m, 2H). **¹³C-NMR** (63 MHz, CDCl₃) δ: 137.89 (C), 130.49 (CH), 128.56 (CH), 126.67 (CH), 83.62 (C), 78.96 (CH), 40.86 (CH₂), 35.56 (CH₂), 32.88 (CH₂), 20.24 (CH₂). **HRMS** (ESI⁺): Calcd. for C₁₂H₁₆O₂Na (M + Na⁺), *m/z* 215.1043, found 215.1040.



22 - To a solution of diol **21** (0.2 mmol, 40 mg, 1 equiv.) in EtOAc (4 mL) under argon was added the IBX (0.62 mmol, 174 mg, 3 equiv.). The reaction mixture was stirred under reflux for 7 h and then filtered through a pad of celite and rinsed with EtOAc. The solvent was removed under reduced pressure to give the crude mixture, which was purified by flash chromatography on silica gel (50:50 PE/Et₂O) to afford the requisite ketone **22** as a white solid (26 mg, 65% yield). **Rf** (50:50 PE/Et₂O): 0.3. **MP**: 71-72 °C. **IR** (ATR) *cm*⁻¹: 3428, 2921, 1702, 1500, 1310, 1096, 700. **¹H-NMR** (360 MHz, CDCl₃) δ: 7.37 – 7.27 (m, 3H), 7.24 – 7.18 (m, 2H), 2.86 (s, 2H), 2.39 – 2.31 (m, 2H), 2.16 – 2.06 (m, 1H), 2.06 – 1.93 (m, 1H), 1.93 – 1.73 (m, 2H). **¹³C-NMR** (91 MHz, CDCl₃) δ: 219.42 (C), 135.48 (C), 130.41 (C), 130.34 (CH), 128.54 (CH), 128.48 (CH), 127.09 (CH), 79.37 (C), 42.00 (CH₂), 35.06 (CH₂), 34.38 (CH₂), 17.15 (CH₂). **HRMS** (ESI⁺): Calcd. for C₁₂H₁₄O₂Na (M + Na⁺), *m/z* 213.0990, found 213.0892.

BRØNSTED ACID-CATALYSED REARRANGEMENT (25)



25 - Representative procedure on *endo*-**17a**: To a solution of *endo*-**17a** (0.27 mmol, 70 mg, 1 equiv.) in anhydrous dichloromethane (4 mL) at 0 °C, TFA (34.7 mmol, 4.0 g, 2.7 mL, 130 equiv.) was added dropwise and the reaction was stirred at 0 °C for 4 h. The reaction mixture was then concentrated under reduced pressure to give the crude mixture, which was purified by flash chromatography on silica gel (PE/Et₂O 90:10) to afford the requisite enone **25** as a colorless crystal (29 mg, 64% yield). **Rf** (50:50 PE/Et₂O): 0.6. **MP**: 91-93 °C. **IR** (ATR) *cm*⁻¹: 3718, 3372, 2932, 3856, 2839, 1669, 1366, 1264, 1250, 1184, 988, 837. **¹H-NMR** (360 MHz, CDCl₃) δ : 7.39 – 7.30 (m, 5H), 7.06 (t, *J* = 4.2 Hz, 1H), 2.65 – 2.59 (m, 2H), 2.56 (dd, *J* = 10.4, 5.9 Hz, 2H), 2.13 (dt, *J* = 12.5, 6.2 Hz, 2H). **¹³C-NMR** (101 MHz, CDCl₃) δ : 198.06 (C), 148.08 (CH), 140.53 (C), 136.68 (C), 128.74 (CH), 128.10 (CH), 127.67 (CH), 39.18 (CH₂), 26.72 (CH₂), 23.04 (CH₂). **HRMS** (ESI⁺): Calcd. for C₁₂H₁₃O (M + H⁺), *m/z* 173.0961, found 173.0956.

ALCl₃ LEWIS ACID-CATALYSED REARRANGEMENT (**23**, **24**, **24B**)

General procedure E for AlCl₃ Lewis acid-catalysed rearrangement

To a solution of protected or deprotected cycloadduct **17a** or **18** (1 equiv.) in anhydrous dichloromethane was added the AlCl₃ (1.5 or 3 equiv.) at -78 °C. After the appropriate time at -78 °C, the reaction was quenched with water and extracted with dichloromethane (3 times). The combined organic phase was washed with an aqueous saturated solution of NaHCO₃ and brine, dried over Na₂SO₄ and concentrated under reduced pressure to give the crude mixture, which was purified by flash chromatography on silica gel to afford the requisite *trans*- or *cis*-alcohol **23** or **24**.

Rearrangement from *exo*-**17a**:

According to the general procedure **E** using *exo*-**17a** (0,27 mmol, 70 mg, 1 equiv.) and AlCl₃ (0,40 mmol, 53 mg, 1.5 equiv.) in distilled DCM (7 ml) at -78 °C,

the flash chromatography on silica gel (PE/Et₂O 80:20 → 40:60) gave the *trans*-alcohol **23** as a colourless crystal (36 mg, 70% yield).

Rearrangement from *exo*-18:

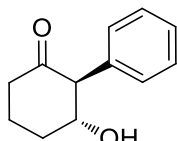
According to the general procedure **E** using *exo*-**18** (0,22 mmol, 42 mg, 1 equiv.) and AlCl₃ (0,33 mmol, 43 mg, 10.5 equiv.) in distilled DCM (5 ml) at -78 °C, the flash chromatography on silica gel (PE/Et₂O 80:20 → 40:60) gave the *trans*-alcohol **23** as a colourless crystal (29 mg, 62% yield), the *cis*-alcohol **24** as a colourless oil (3 mg, 10% yield) and the enone **25** as a colourless crystal (4 mg, 10% yield).

Rearrangement from *endo*-17a:

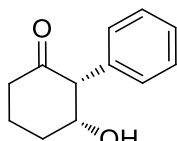
According to the general procedure **E** using *endo*-**17a** (0,25 mmol, 68 mg, 1 equiv.) and AlCl₃ (0,37 mmol, 50 mg, 1.5 equiv.) in distilled DCM (7 ml) at -78 °C, the flash chromatography on silica gel (PE/Et₂O 80:20 → 40:60) gave the *trans*-alcohol **23** as a colourless crystal (19 mg, 38% yield) the *cis*-alcohol **24** as a colourless oil (10 mg, 13% yield) and the protected *cis*-alcohol **24b** as a pale yellow oil (7 mg, 13% yield).

Rearrangement from *endo*-18:

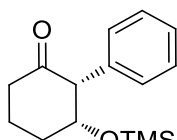
According to the general procedure **E** using *endo*-**18** (0,3 mmol, 57 mg, 1 equiv.) and AlCl₃ (0,45 mmol, 60 mg, 1.5 equiv.) in distilled DCM (6 ml) at -78 °C, the flash chromatography on silica gel (PE/Et₂O 80:20 → 40:60) gave the *trans*-alcohol **23** as a colourless crystal (13 mg, 22% yield), the *cis*-alcohol **24** as a colourless oil (27 mg, 47% yield) and the enone **25** as a colourless crystal (6 mg, 10% yield).



trans-**23** - Rf (50:50 PE/Et₂O): 0.05. **MP**: 93-94 °C; **IR** (ATR) *cm*⁻¹: 3463, 3052, 3030, 2944, 2862, 1698, 1400, 1321, 1022, 750, 735; **¹H-NMR** (360 MHz, CDCl₃) δ: 7.43 – 7.27 (m, 3H), 7.20 – 7.11 (m, 2H), 4.01 (td, J = 10.4, 4.2 Hz, 1H), 3.56 (d, J = 10.3 Hz, 1H), 2.61 – 2.40 (m, 1H), 2.40 – 2.29 (m, 1H), 2.19 – 2.05 (m, 1H), 1.97 – 1.79 (m, 1H), 1.79 – 1.59 (m, 2H). **¹³C-NMR** (91 MHz, CDCl₃) δ: 134.70 (C), 129.92 (CH), 128.96 (CH), 127.95 (CH), 74.96 (CH), 67.15 (CH), 41.05 (CH₂), 33.11 (CH₂), 20.92 (CH₂), the quaternary carbonyl is missing; **HRMS** (ESI⁺): Calcd. for C₁₂H₁₄O₂Na (M + Na⁺), *m/z* 213.0886, found 213.0888.

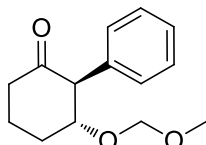


cis-**24** - Rf (50:50 PE/Et₂O): 0.2; **IR** (ATR) *cm*⁻¹: 3437, 3030, 2944, 2870, 1706, 1598, 1122, 698. **¹H-NMR** (360 MHz, CDCl₃) δ: 7.26 (s, 5H), 4.32 (d, J = 2.4 Hz, 1H), 3.74 (d, J = 2.8 Hz, 1H), 2.60 – 2.49 (m, 1H), 2.50 – 2.37 (m, 1H), 2.37 – 2.21 (m, 1H), 2.11 (m, 1H), 2.03 – 1.83 (m, 3H). **¹³C-NMR** (91 MHz, CDCl₃) δ: 208.20 (C), 136.16 (C), 130.01 (CH), 128.61 (CH), 127.45 (CH), 74.51 (CH), 62.13 (CH), 41.85 (CH₂), 32.11 (CH₂), 21.03 (CH₂). **HRMS** (ESI⁺): Calcd. for C₁₂H₁₄O₂ (M + Na⁺), *m/z* 213.0891, found 213.0891.



cis-**24b** - Rf (50:50 PE/Et₂O): 0.65. **¹H-NMR** (250 MHz, CDCl₃) δ: 7.59 – 7.20 (m, 10H), 4.34 (d, J = 3.3 Hz, 1H), 3.62 (d, J = 2.6 Hz, 1H), 2.64 – 2.43 (m, 4H), 2.42 – 2.20 (m, 3H), 2.20 – 1.85 (m, 6H), 1.50 – 0.99 (m, 3H), -0.17 (s, 9H). **HRMS** (ESI⁺): Calcd. for C₁₅H₂₂O₂SiNa (M + Na⁺), *m/z* 285.1287, found 285.1283. The high instability of this compound and the small isolated amount of it did not allow long ¹³C NMR experiment and IR analysis.

ACID-CATALYSED REARRANGEMENT-PROTECTION SEQUENCE (27)

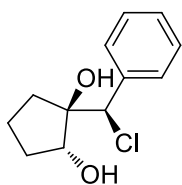


27 - To a solution of *exo*-**17a** (0.19 mmol, 50 mg, 1 equiv.) in anhydrous dichloromethane (3 mL) at -78 °C, AlCl₃ (0.57 mmol, 76.3 mg, 3 equiv.) was added. After 1.5 h, the reaction was quenched with water and extracted with dichloromethane (3 times). The combined organic phase was washed with an aqueous saturated solution of NaHCO₃ and brine, dried over Na₂SO₄ and concentrated under reduced pressure to give the crude mixture, which was directly dissolved in dichloromethane (0.5 mL). Then the reaction mixture was cooled down to 0 °C and the DIPEA (0.38 mmol, 49.1 mg, 0.066 mL, 2 equiv.) and the MOMCl (0.57 mmol, 45.9 mg, 0.043 mL, 3 equiv.) were added. The reaction mixture was stirred at room temperature overnight and then quenched with a 1M aqueous solution of NH₄Cl and extracted with dichloromethane (3 times). The combined organic phases were then dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude mixture, which was purified by flash chromatography on silica gel (PE/Et₂O 90:10 → 80:20) to afford the requisite protected *trans*-alcohol **27** as a colourless crystal (17 mg, 39% yield). **R_f** (50:50 PE/Et₂O): 0.4; **IR** (ATR) *cm*⁻¹: 2944, 2869, 2820, 1707, 1499, 1455, 1264, 1170, 1142, 1091, 1020, 919, 748, 696; **MP**: 49-50 °C; **¹H-NMR** (250 MHz, CDCl₃) δ: 7.48 – 7.28 (m, 3H), 7.26 – 7.07 (m, 2H), 4.60 – 4.47 (m, 1H), 4.35 – 4.19 (m, 1H), 4.03 (td, *J* = 10.0, 4.1 Hz, 1H), 3.65 (d, *J* = 10.0 Hz, 1H), 3.09 – 2.75 (m, 3H), 2.66 – 2.33 (m, 3H), 2.14 (d, *J* = 4.1 Hz, 1H), 1.97 – 1.54 (m, 2H). **¹³C-NMR** (63 MHz, CDCl₃) δ: 207.78 (C), 136.34 (C), 129.67 (CH), 128.43 (CH), 127.21 (CH), 95.11 (CH₂), 79.37 (CH), 64.85 (CH), 55.29 (CH₃), 41.06 (CH₂), 31.39 (CH₂), 20.76 (CH₂). **HRMS** (ESI⁺): Calcd. for C₁₄H₁₈NaO₃ (M + Na⁺), *m/z* 257.1148, found 257.1148.

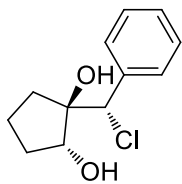
TiCl₄ LEWIS ACID-CATALYSED REARRANGEMENT (28, 29)General procedure F for TiCl₄ Lewis acid-catalyzed rearrangement

To a solution of deprotected cycloadduct **18** (1 equiv.) in anhydrous diethylether was added the TiCl_4 (3 equiv.) at $-78\text{ }^\circ\text{C}$. After 7 h at $-78\text{ }^\circ\text{C}$, the reaction was quenched with water and extracted with dichloromethane (3 times). The combined organic phase was washed with an aqueous saturated solution of NaHCO_3 and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude mixture, which was purified by flash chromatography on silica gel to afford a mixture of products, with a large majority of the compounds **28** and **29** and traces of the alcohol **23** or **24**.

This procedure is non-optimised and the reactions were performed on the endo-**18** and exo-**18** on very small scale, consequently no exploitable yields can be interpreted from these reactions. However, the crucial information of these reactions is the non-formation of the others isomers (path a).



28 - Colourless oil. **R_f** (50:50 PE/Et₂O): 0,4. **¹H-NMR** (360 MHz, CDCl_3) δ : 7.67 – 7.57 (m, 2H), 7.42 – 7.29 (m, 3H), 5.33 (s, 1H), 3.49 (t, $J = 5.2\text{ Hz}$, 1H), 2.25 – 2.10 (m, 2H), 1.97-1.84 (m, 3H), 1.62 – 1.51 (m, 1H); **¹³C-NMR** (91 MHz, CDCl_3) δ : 138.85 (C), 128.77 (CH), 128.60 (CH), 128.43 (CH), 86.49 (C), 77.90 (CH), 68.16 (CH), 37.28 (CH_2), 34.10 (CH_2), 20.53 (CH_2); **HRMS**: Unstable.



29 - Colourless crystal; **R_f** (50:50 PE/Et₂O): 0,5. **MP**: 108-109 $^\circ\text{C}$. **¹H-NMR** (360 MHz, CDCl_3) δ : 7.50 (dt, $J = 4.9, 2.8\text{ Hz}$, 2H), 7.42 – 7.29 (m, 3H), 5.36 (s, 1H), 4.10 (d, $J = 5.3\text{ Hz}$, 1H), 2.35 – 2.22 (m, 1H), 1.85 – 1.61 (m, 5H). **¹³C-NMR** (91 MHz, CDCl_3) δ : 128.78 (CH), 128.68 (CH), 128.37 (CH), 79.57 (CH), 66.66 (CH), 34.19 (CH_2), 32.80 (CH_2), 21.84 (CH_2); **HRMS**: Unstable.

7.3 CRYSTAL STRUCTURES

X-ray diffraction data of compound **3o** were collected using a Kappa VENTURE PHOTON 100 Bruker diffractometer with $\text{I}\mu\text{S}$ microfocus graphite-monochromated $\text{CuK}\alpha$ radiation ($= 1.54178 \text{ \AA}$). 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^[25] and refined against F^2 by full-matrix least-squares techniques using SHELXL-97^[26] with anisotropic displacement parameters for all non-hydrogen atoms. All calculations were performed by using the Crystal Structure crystallographic software package WINGX.^[27]

The crystal data collection and refinement parameters are given in Table 7.1). The absolute configuration was determined by refining the Flack parameter^[28] using 1631 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$.

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

Table 7.1

Compound	3o
CCDC dep. number	1054222
Empirical formula	C ₂₀ H ₁₄ F ₆ NO
Formula weight	401.35
Crystal size (mm³)	0.21 x 0.19 x 0.17
Crystal system	Monoclinic
Space group	C 2
Unit cell dimensions	$a = 22.1466(8) \text{ \AA} \quad \alpha = 90^\circ$ $b = 5.7422(2) \text{ \AA} \quad \beta = 117.0540(10)^\circ$ $c = 16.4690(6) \text{ \AA} \quad \gamma = 90^\circ$
Cell volume (Å³)	496.57
Z	4
T (K)	100(1)
F₀₀₀	824
μ (mm⁻¹)	1.131
θ range (°)	3.013 – 74.480
Reflection collected	24100
Reflection unique	3737
R_{int}	0.0148
GOF	1.067
Refl. Obs. (I > 2σ(I))	3724
Parameters	253
wR2 (all data)	0.0827
R value (I > 2σ(I))	0.0319
Largest diff. peak and hole (e- Å³)	-0.339 ; 0.342

Compound	endo-18
CCDC dep. number	-
Empirical formula	C ₁₂ H ₁₄ O ₂
Formula weight	190.23
Wavelength (Å)	0.71073 Å
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>
Unit cell dimensions	<i>a</i> = 9.3250(7) Å $\alpha = 90^\circ$ <i>b</i> = 10.1283(7) Å $\beta = 112.494(2)^\circ$ <i>c</i> = 11.2521(8) Å $\gamma = 90^\circ$
Cell volume (Å ³)	981.87
Z	4
T (K)	100(1)
Index ranges	$-15 \leq h \leq 15$ $-16 \leq k \leq 16$ $-18 \leq l \leq 18$
θ range (°)	2.364 – 35.074
Reflection collected	42955
Data / restraints / parameters	4340 / 0 / 128
Goodness-of-fit on <i>F</i> ²	1.061
Final <i>R</i> indices [<i>F</i> ² > 2 σ (<i>F</i> ²)]	<i>R</i> 1 = 0.0387, <i>wR</i> 2 = 0.1028
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0483, <i>wR</i> 2 = 0.1085

Structure not deposited yet in CCDC.

Compound	exo-18
CCDC dep. number	-
Empirical formula	C ₁₂ H ₁₄ O ₂
Formula weight	190.23
Wavelength (Å)	0.71073 Å
Crystal system	Monoclinic
Space group	<i>Pc</i>
Unit cell dimensions	$a = 9.4521(6)$ Å $\alpha = 90^\circ$ $b = 6.0497(4)$ Å $\beta = 93.299^\circ$ $c = 8.6983(6)$ Å $\gamma = 90^\circ$
Cell volume (Å ³)	496.57(6)
Z	2
T (K)	100(1)
Index ranges	$-13 \leq h \leq 13$ $-8 \leq k \leq 8$ $-12 \leq l \leq 12$
θ range (°)	2.158 – 30.559°
Reflection collected	8514
Data / restraints / parameters	2668 / 2 / 128
Goodness-of-fit on F^2	1.044
Final <i>R</i> indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0400$, $wR2 = 0.0853$
<i>R</i> indices (all data)	$R1 = 0.0511$, $wR2 = 0.0910$

Structure not deposited yet in CCDC.

Compound	<i>trans</i> -21
CCDC dep. number	-
Empirical formula	C ₁₂ H ₁₆ O ₂
Formula weight	192.25
Wavelength (Å)	0.71073 Å
Crystal system	Tetragonal
Space group	<i>P</i> -4 2 ₁ <i>c</i>
Unit cell dimensions	<i>a</i> = 10.5136(6) Å $\alpha = 90^\circ$
	<i>b</i> = 10.5136(6) Å $\beta = 90^\circ$
	<i>c</i> = 18.9071(12) Å $\gamma = 90^\circ$
Cell volume (Å ³)	2089.9
Z	8
T (K)	100(2)
Index ranges	$-15 \leq h \leq 15$
	$-15 \leq k \leq 158$
	$-27 \leq l \leq 27$
θ range (°)	2.154 – 30.626°
Reflection collected	73674
Data / restraints / parameters	3220 / 0 / 131
Goodness-of-fit on <i>F</i> ²	1.079
Final <i>R</i> indices [<i>F</i> ² > 2σ(<i>F</i> ²)]	<i>R</i> 1 = 0.0445, <i>wR</i> 2 = 0.1129
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0650, <i>wR</i> 2 = 0.1263

Structure not deposited yet in CCDC.

Compound	trans-23
CCDC dep. number	-
Empirical formula	C ₁₂ H ₁₄ O ₂
Formula weight	190.23
Wavelength (Å)	0.71073 Å
Crystal system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
Unit cell dimensions	<i>a</i> = 5.3916(3) Å $\alpha = 90^\circ$ <i>b</i> = 9.4754(5) Å $\beta = 90^\circ$ <i>c</i> = 19.0524(11) Å $\gamma = 90^\circ$
Cell volume (Å ³)	973.34
Z	4
T (K)	100(1)
Index ranges	$-5 \leq h \leq 7$ $-8 \leq k \leq 8$ $-27 \leq l \leq 27$
θ range (°)	2.138 – 30.700°
Reflection collected	23795
Data / restraints / parameters	3031 / 0 / 128
Goodness-of-fit on F^2	1.057
Final <i>R</i> indices [$F^2 > 2\sigma(F^2)$]	<i>R</i> 1 = 0.0397, <i>wR</i> 2 = 0.1000
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0485, <i>wR</i> 2 = 0.1057

Structure not deposited yet in CCDC.

Compound	25
CCDC dep. number	-
Empirical formula	C ₁₂ H ₁₂ O
Formula weight	172.22
Wavelength (Å)	0.71073 Å
Crystal system	Tetragonal
Space group	<i>P</i> 2 ₁ <i>C</i>
Unit cell dimensions	<i>a</i> = 6.0341(3) Å $\alpha = 90^\circ$
	<i>b</i> = 12.1361(8) Å $\beta = 101.429^\circ$
	<i>c</i> = 12.5201(8) Å $\gamma = 90^\circ$
Cell volume (Å ³)	898.67
Z	4
T (K)	293(2)
Index ranges	$-8 \leq h \leq 8$
	$-17 \leq k \leq 17$
	$-17 \leq l \leq 17$
θ range (°)	2.360 – 30.696°
Reflection collected	39433
Data / restraints / parameters	2786 / 0 / 118
Goodness-of-fit on <i>F</i> ²	1.079
Final <i>R</i> indices [<i>F</i> ² > 2σ(<i>F</i> ²)]	<i>R</i> 1 = 0.0415, <i>wR</i> 2 = 0.1040
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0642, <i>wR</i> 2 = 0.1111

Structure not deposited yet in CCDC.

Compound	27
CCDC dep. number	-
Empirical formula	C ₁₄ H ₁₈ O ₃
Formula weight	234.28
Wavelength (Å)	0.71073 Å
Crystal system	triclinic
Space group	<i>P</i> -1
Unit cell dimensions	$a = 7.6327(5) \text{ \AA}$ $\alpha = 90.229^\circ$ $b = 8.8953(6) \text{ \AA}$ $\beta = 90.495^\circ$ $c = 9.3689(6) \text{ \AA}$ $\gamma = 104.24^\circ$
Cell volume (Å ³)	616.52
Z	2
T (K)	100(1)
Index ranges	$-10 \leq h \leq 10$ $-11 \leq k \leq 12$ $-11 \leq l \leq 13$
θ range (°)	2.174 – 30.59°
Reflection collected	14291
Data / restraints / parameters	3667 / 0 / 155
Goodness-of-fit on F^2	1.090
Final <i>R</i> indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0385$, $wR2 = 0.1136$
<i>R</i> indices (all data)	$R1 = 0.0440$, $wR2 = 0.1237$

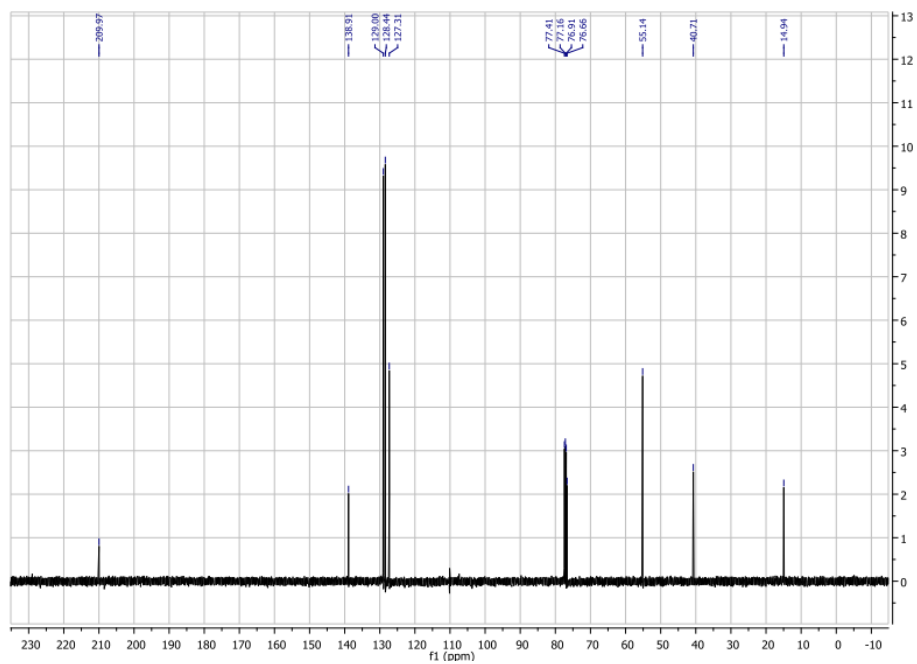
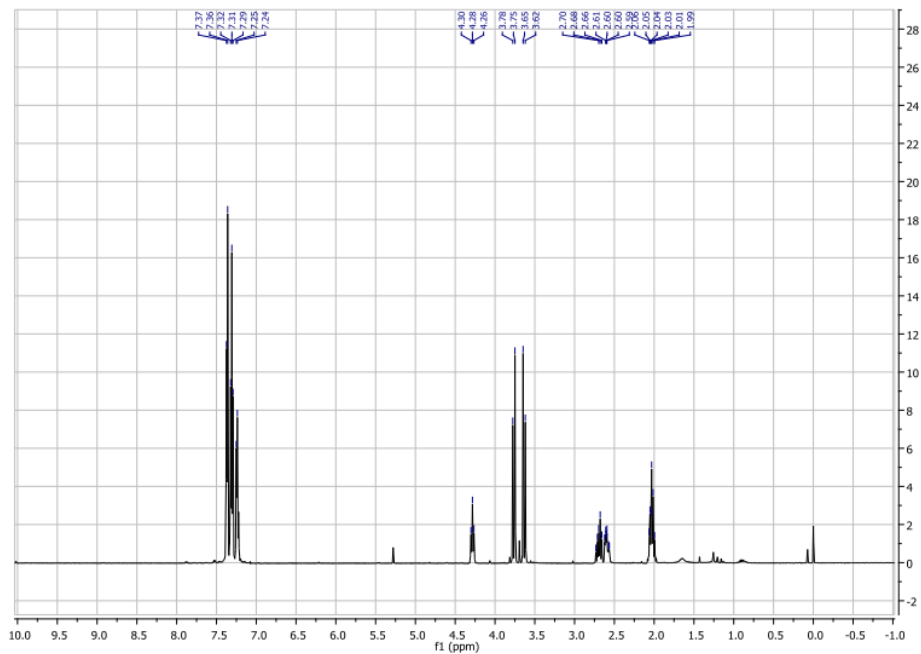
Structure not deposited yet in CCDC.

Compound	29
CCDC dep. number	-
Empirical formula	C ₁₂ H ₁₅ ClO ₂
Formula weight	226.69
Wavelength (Å)	0.71073 Å
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>
Unit cell dimensions	<i>a</i> = 11.0121(8) Å $\alpha = 90^\circ$ <i>b</i> = 18.2457(14) Å $\beta = 108.114^\circ$ <i>c</i> = 11.8328(9) Å $\gamma = 90^\circ$
Cell volume (Å ³)	2259.7
Z	8
T (K)	100(1)
Index ranges	$-15 \leq h \leq 15$ $-26 \leq k \leq 26$ $-16 \leq l \leq 16$
θ range (°)	2.232 – 30.599°
Reflection collected	115796
Data / restraints / parameters	6934 / 0 / 278
Goodness-of-fit on <i>F</i> ²	1.097
Final <i>R</i> indices [<i>F</i> ² > 2σ(<i>F</i> ²)]	<i>R</i> 1 = 0.0713, <i>wR</i> 2 = 0.1422
<i>R</i> indices (all data)	<i>R</i> 1 = 0.1265, <i>wR</i> 2 = 0.1572

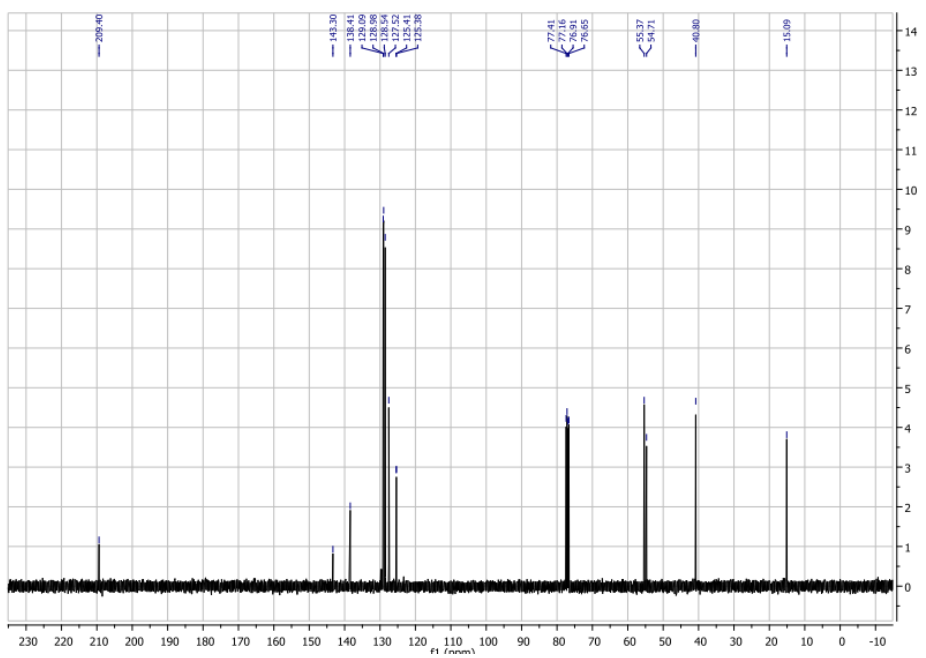
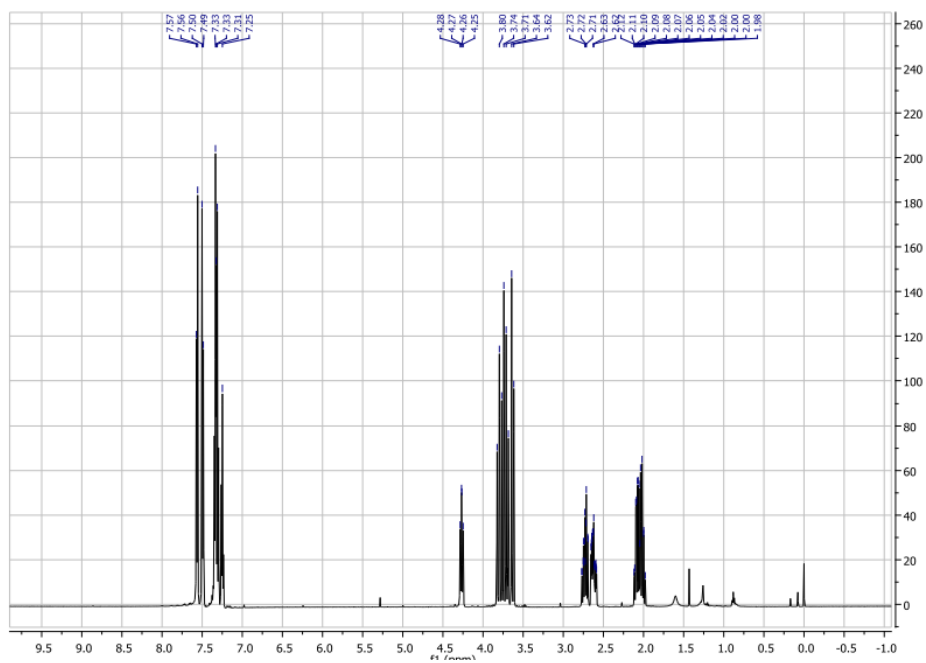
Structure not deposited yet in CCDC.

7.4 NMR SPECTRA

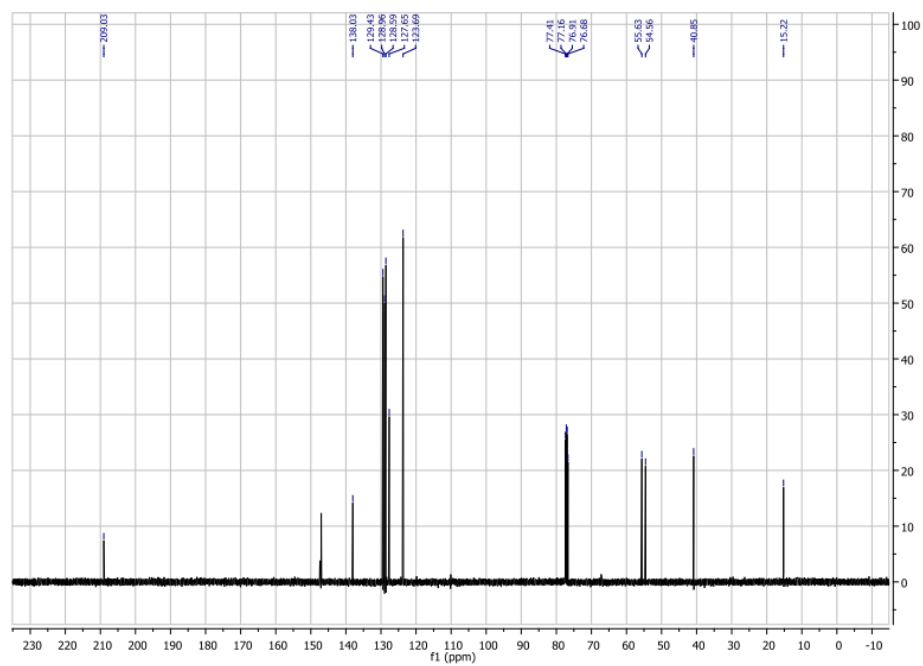
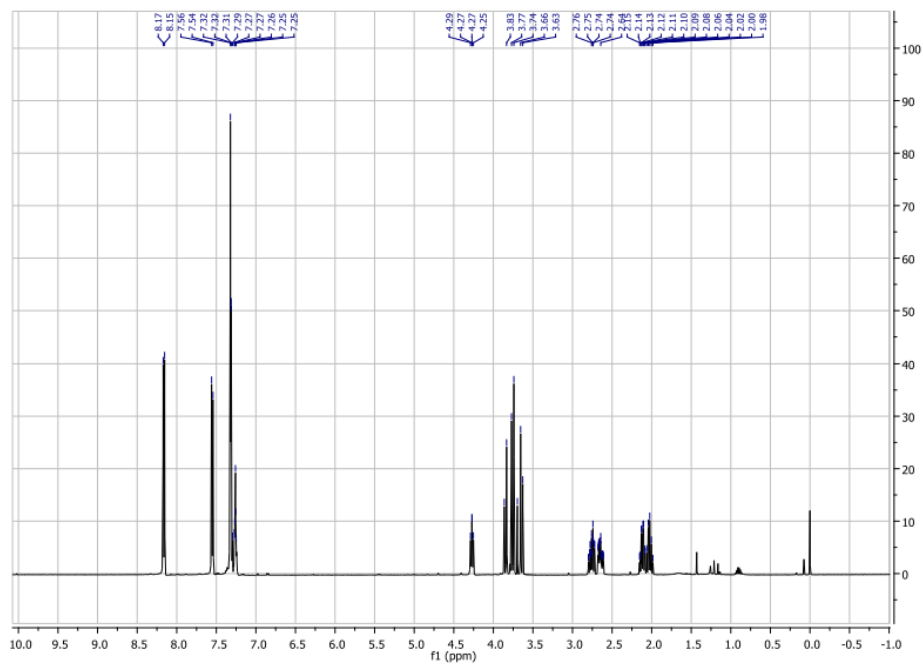
3a



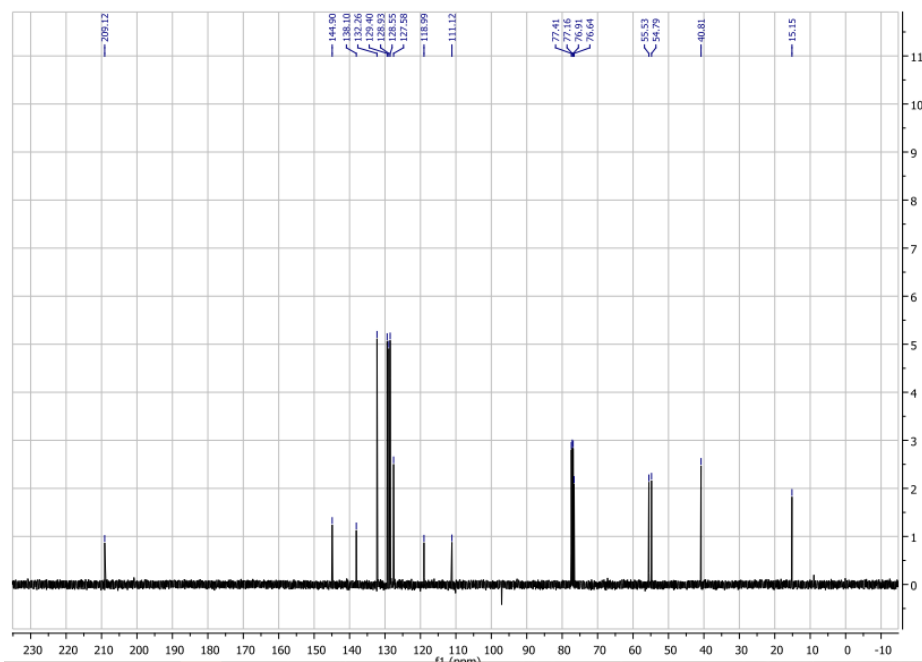
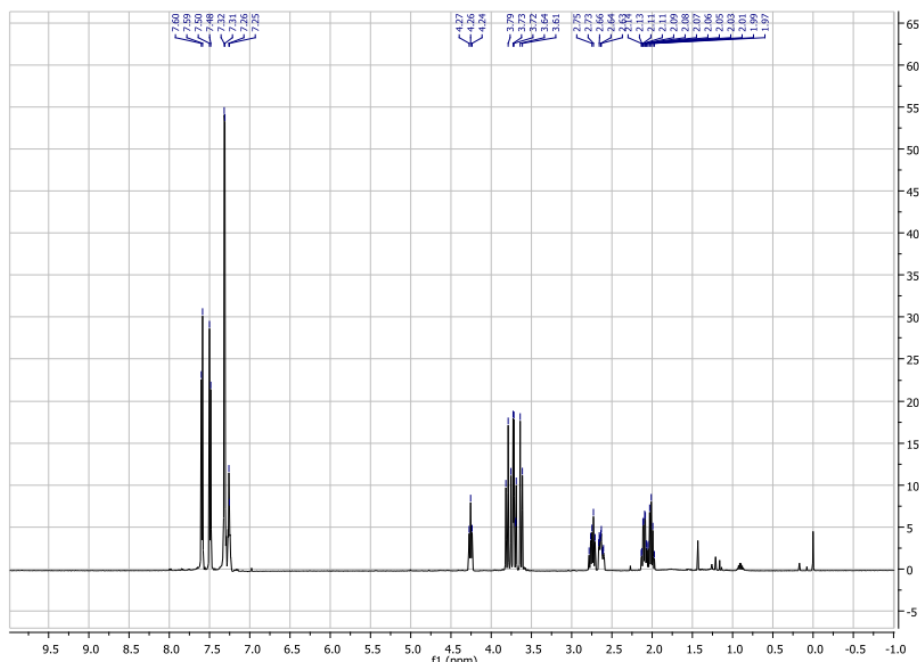
3b



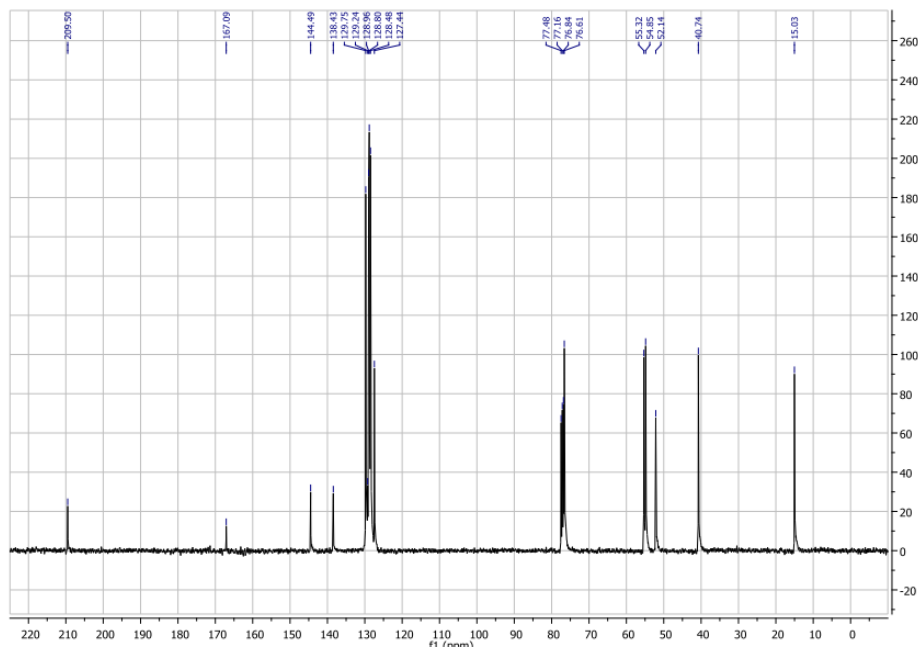
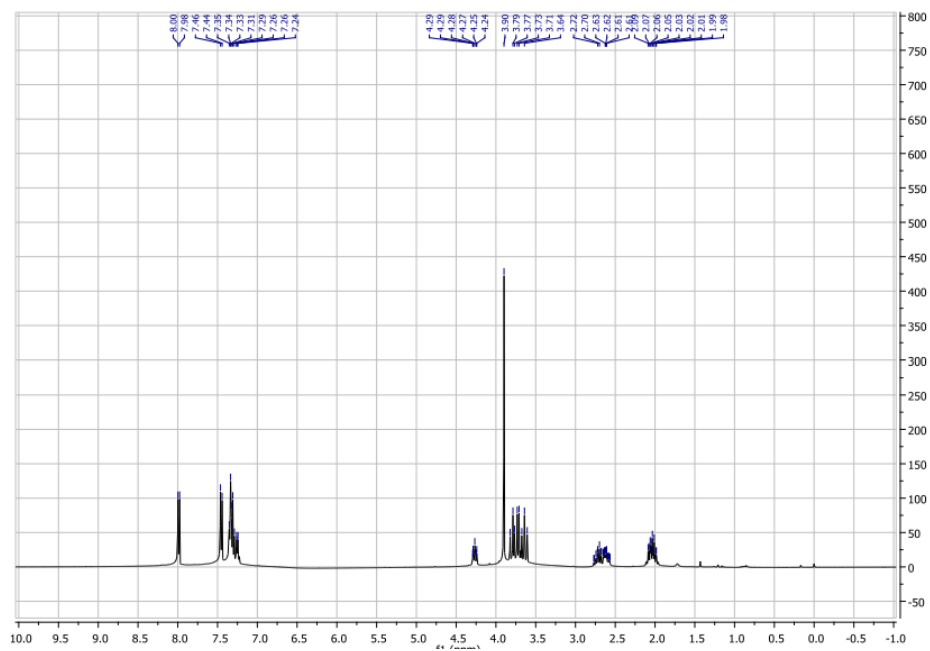
3c



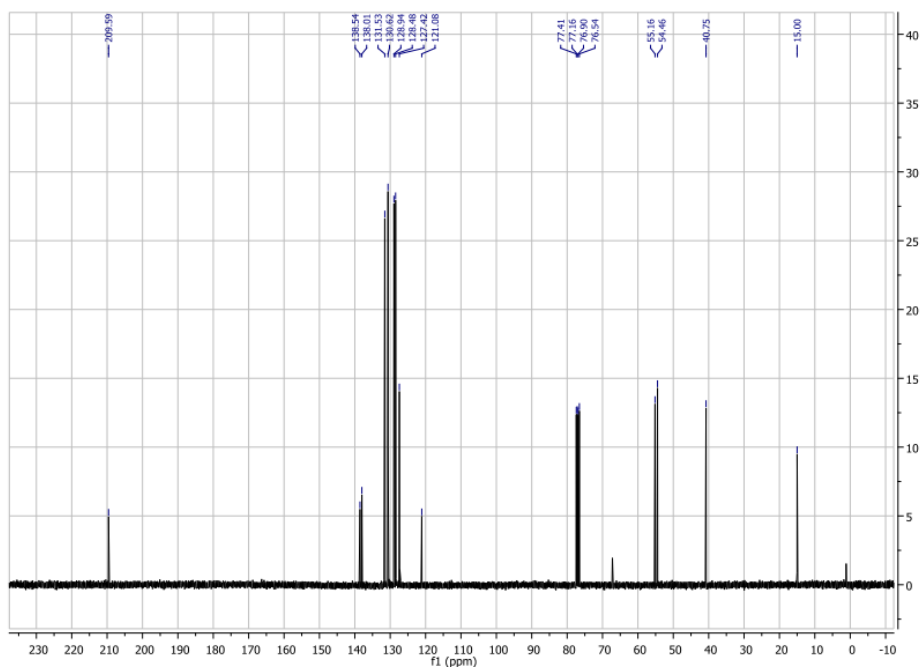
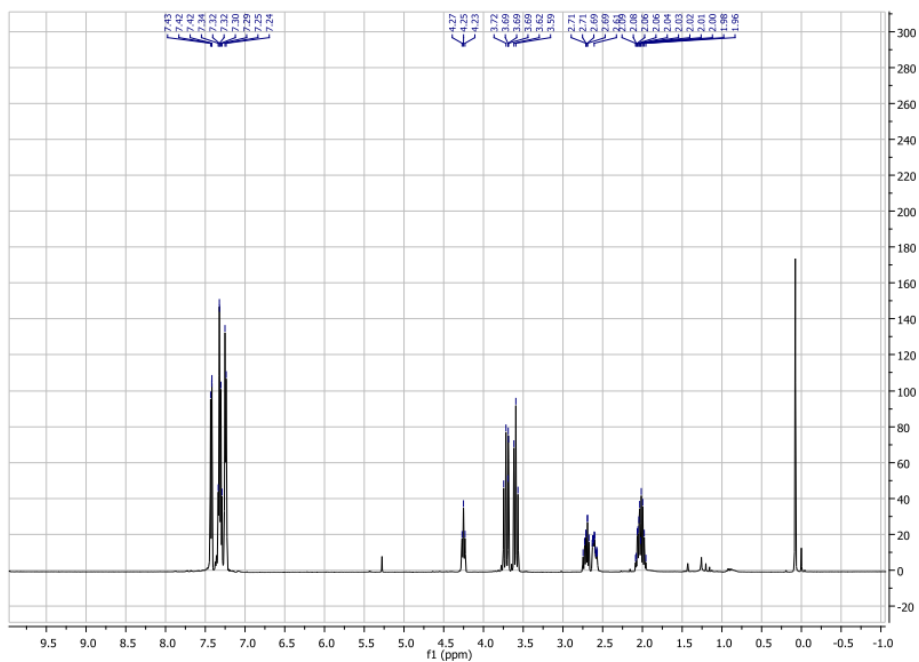
3d



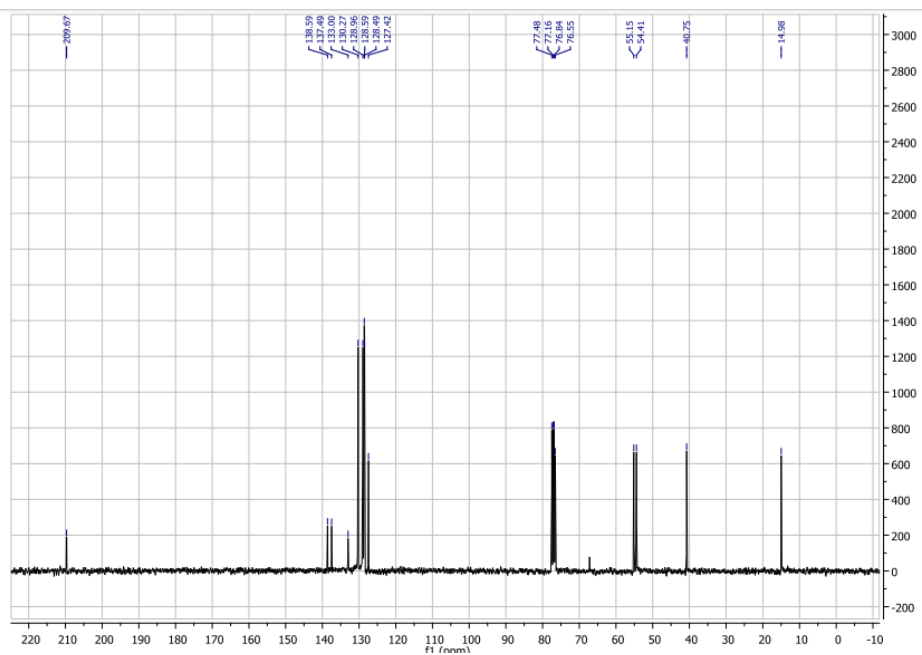
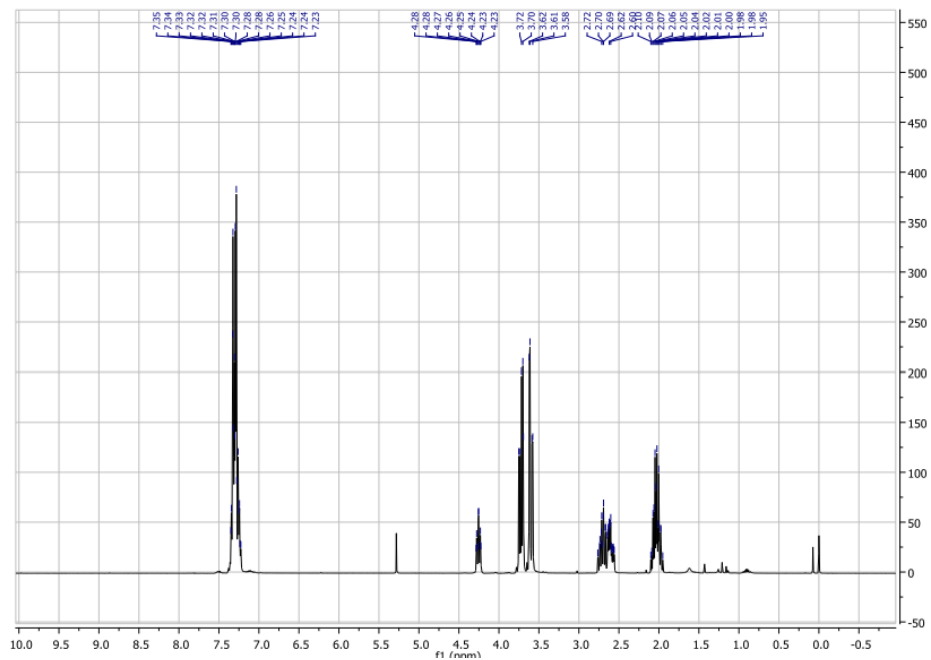
3e



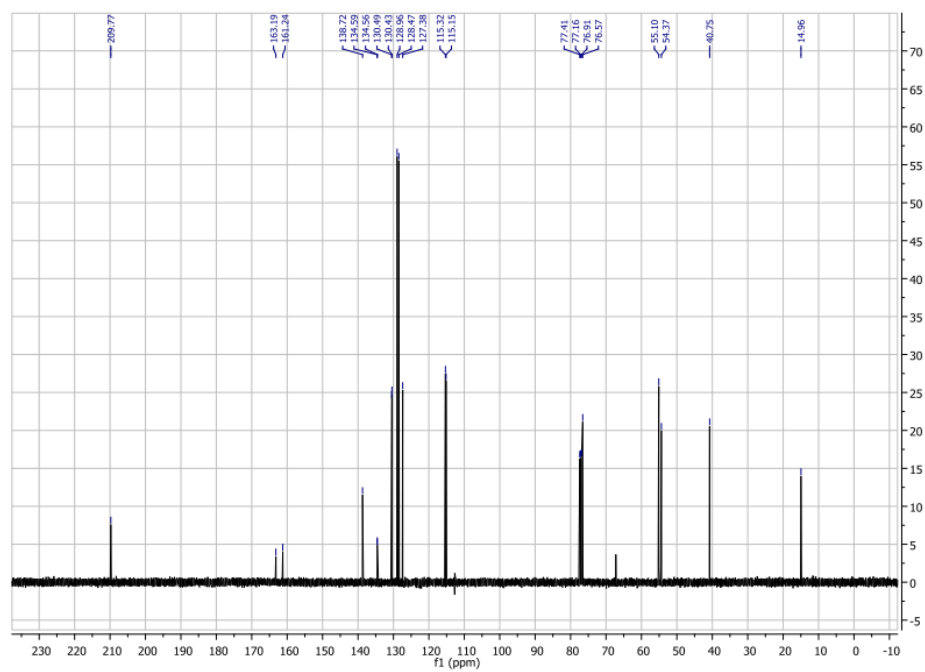
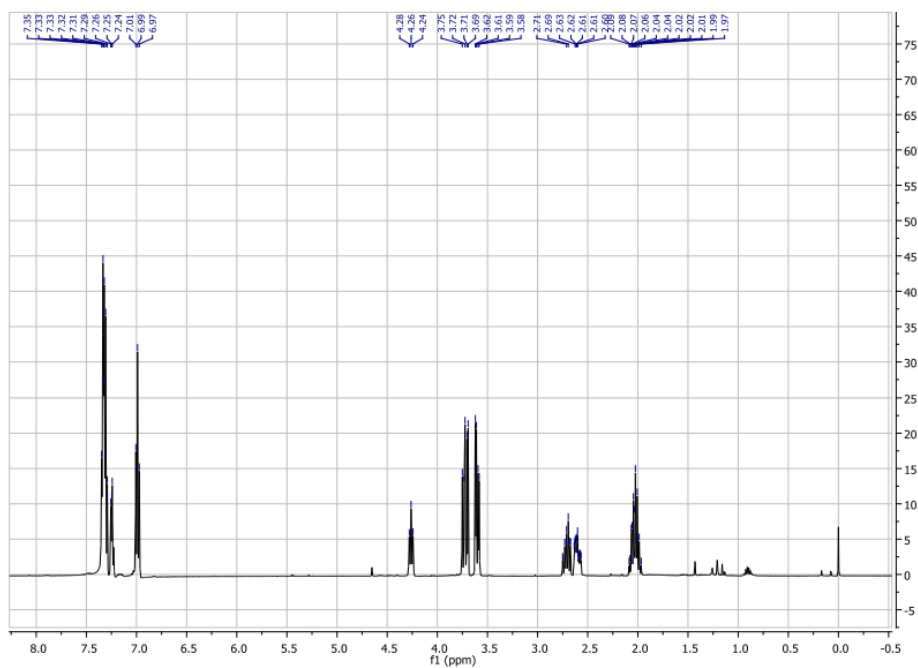
3f



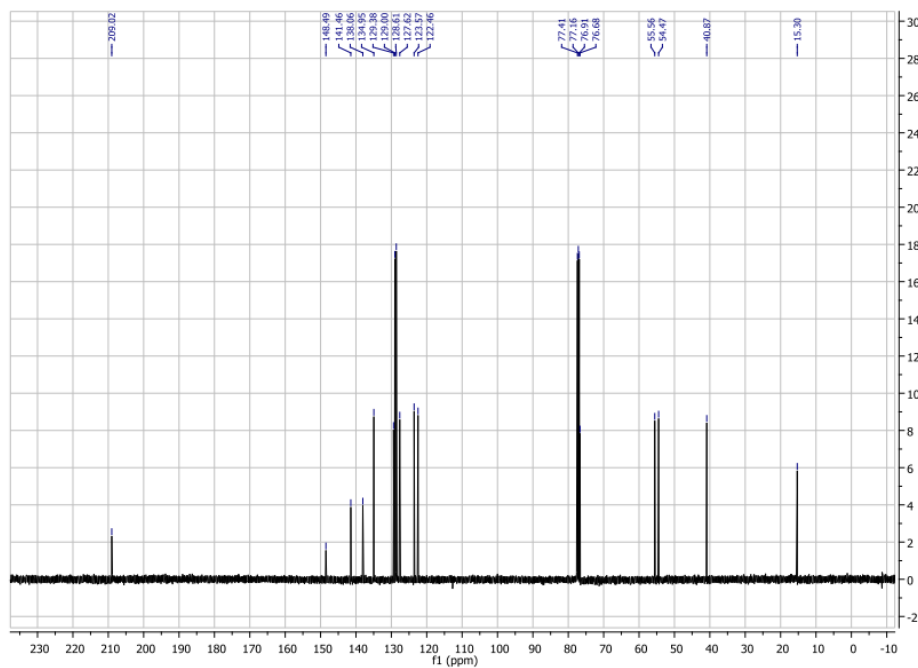
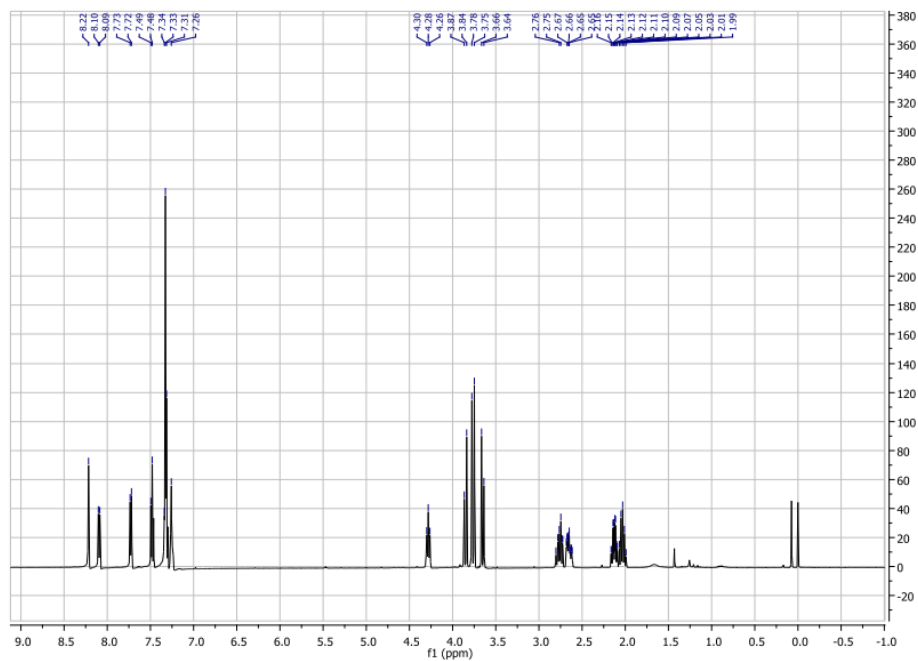
3g



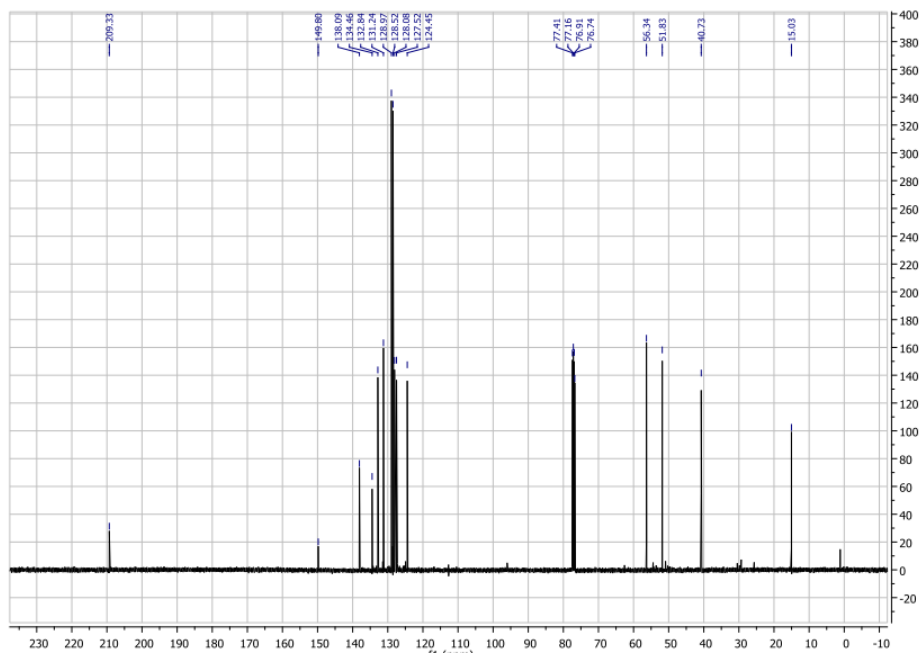
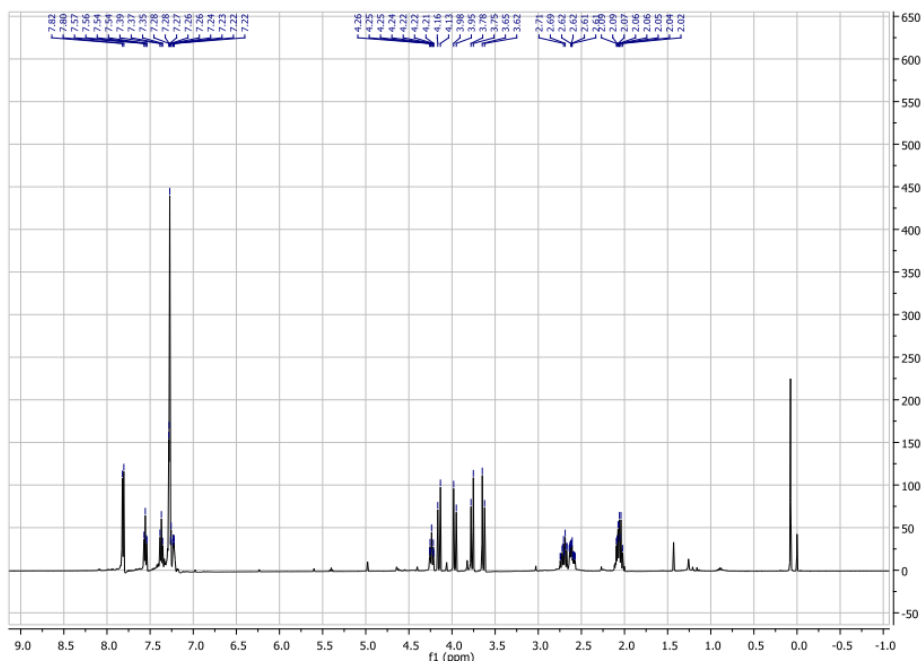
3h



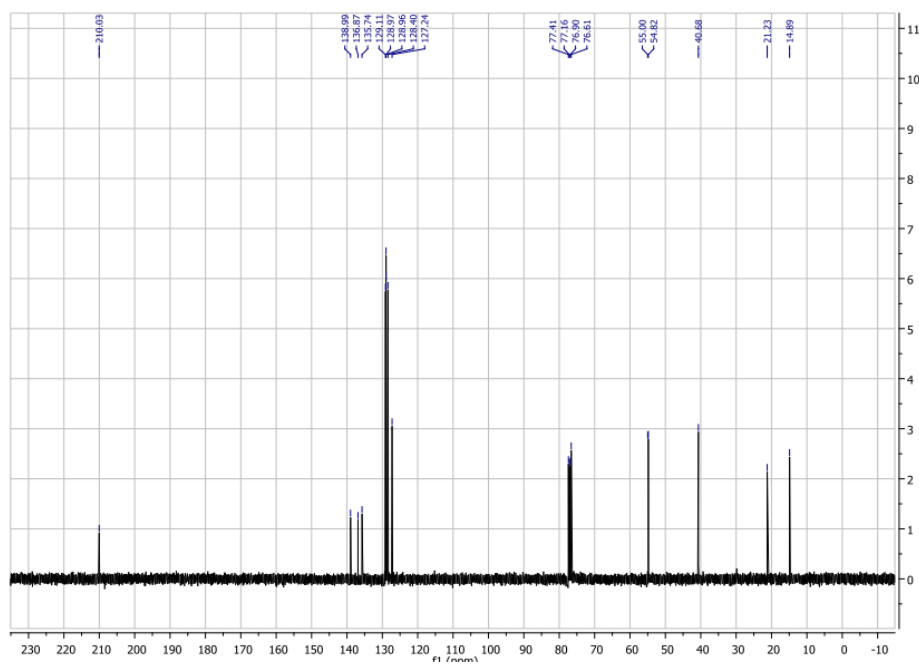
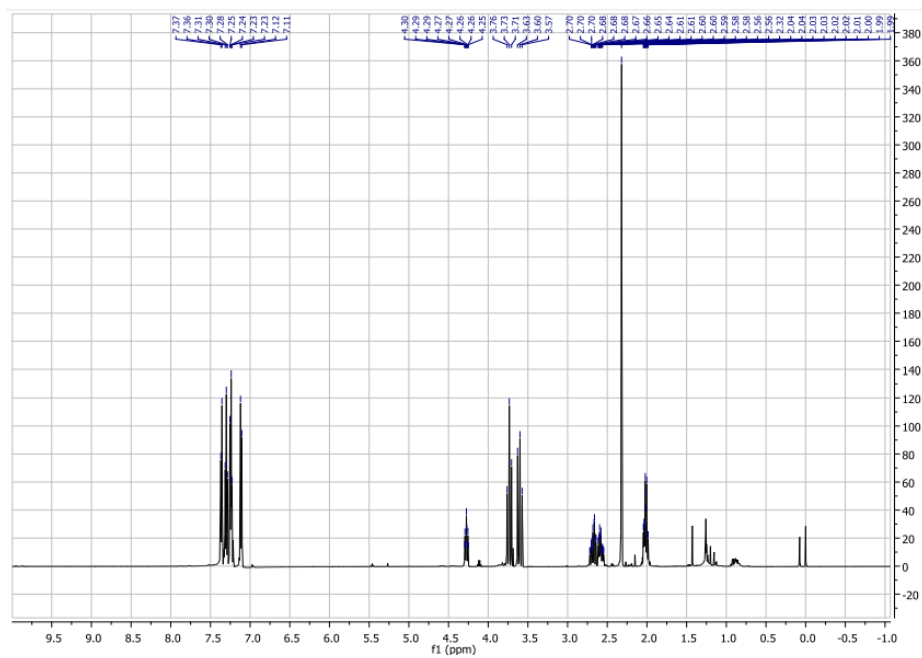
3i



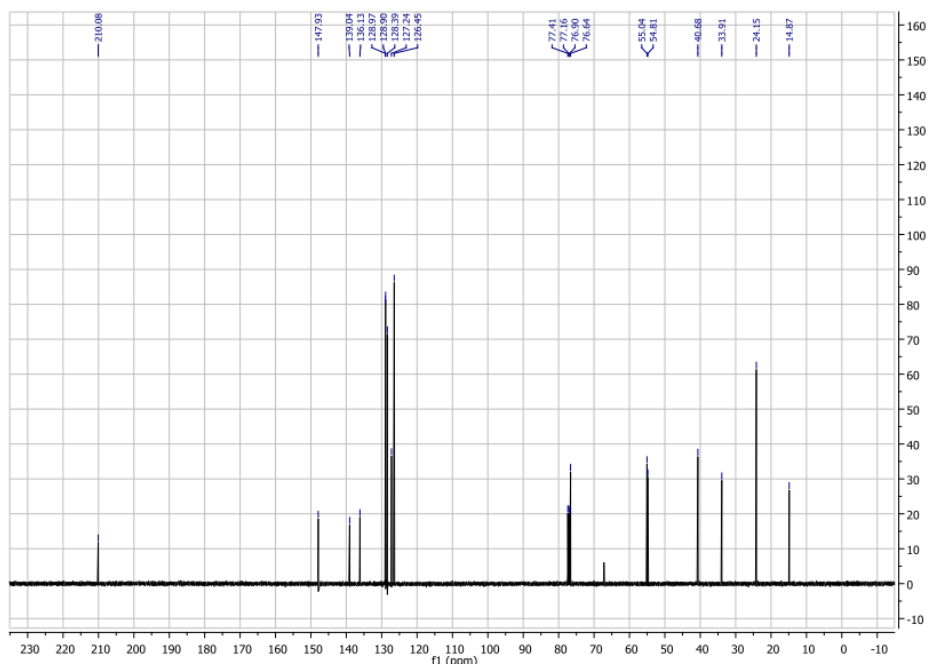
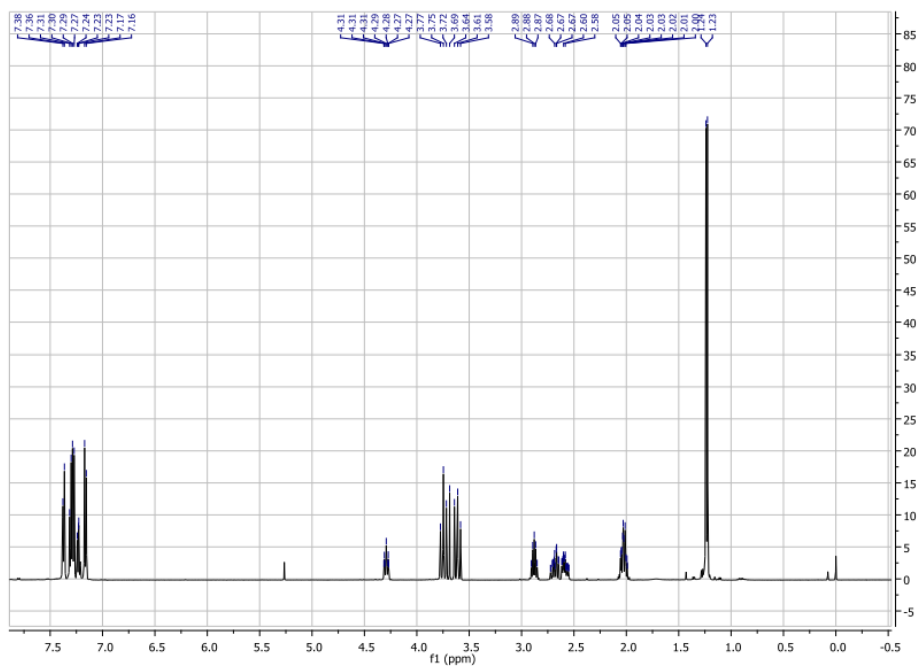
3j



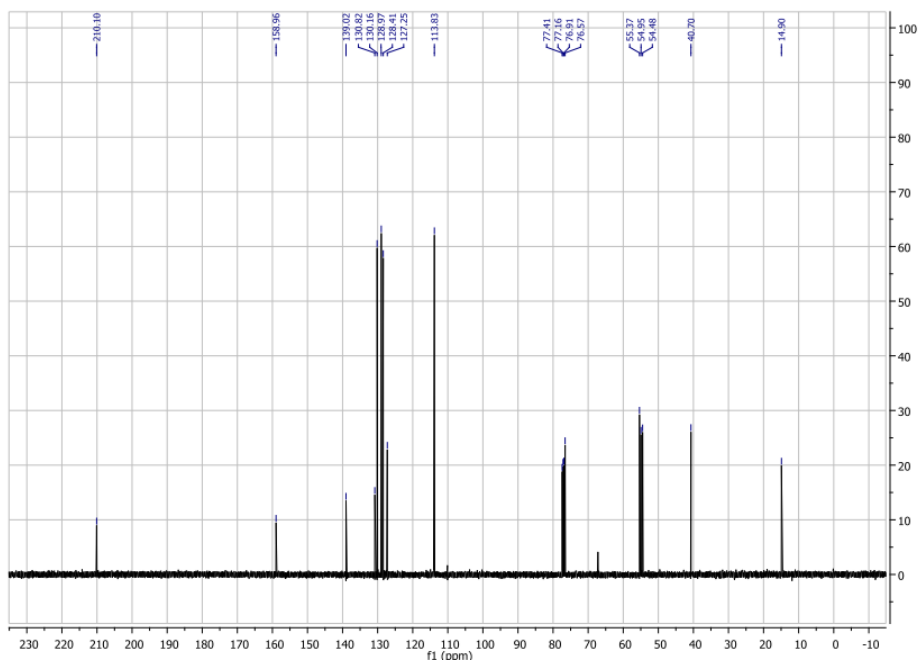
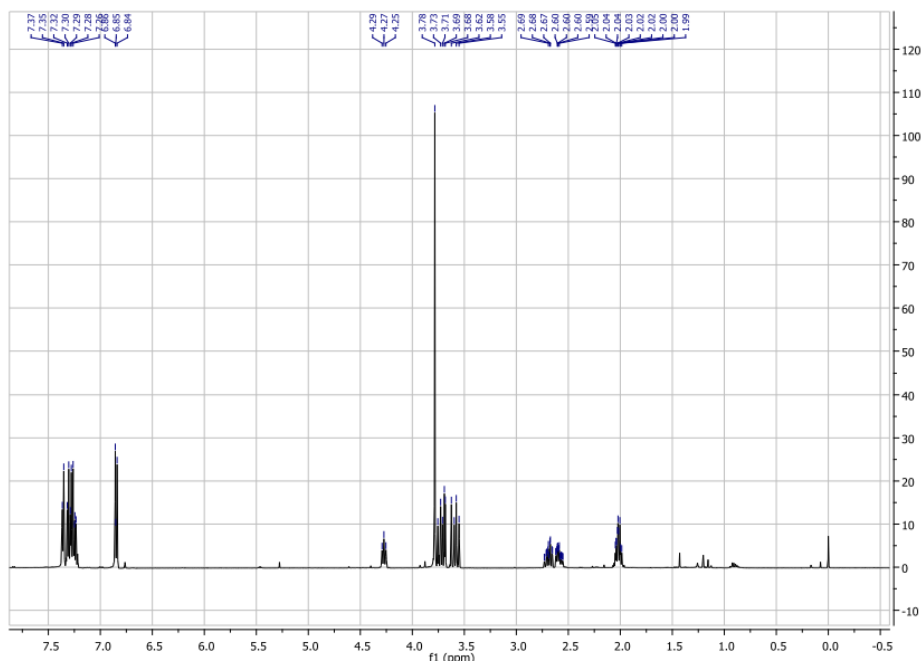
3k



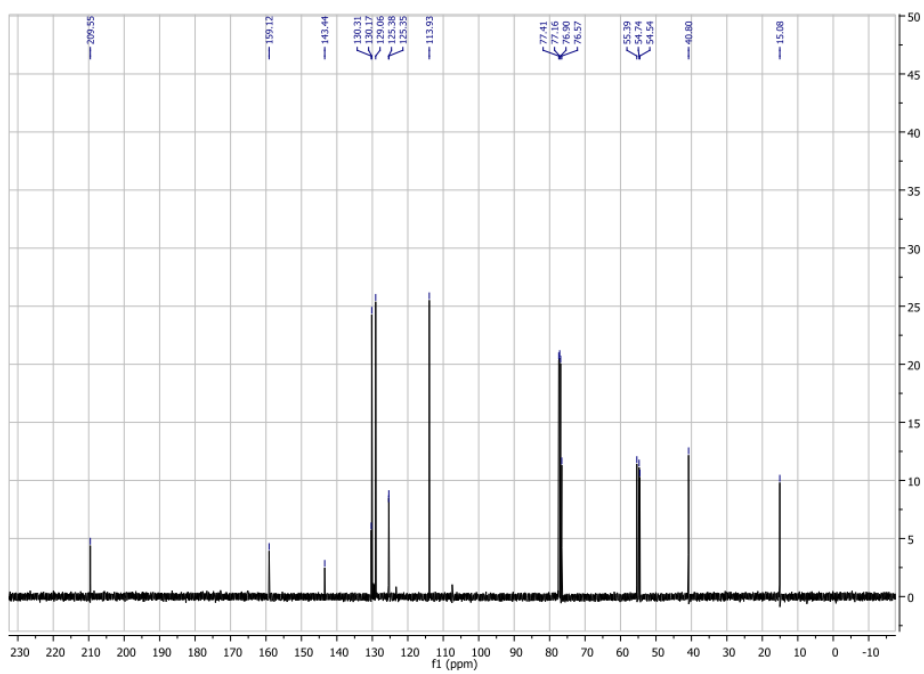
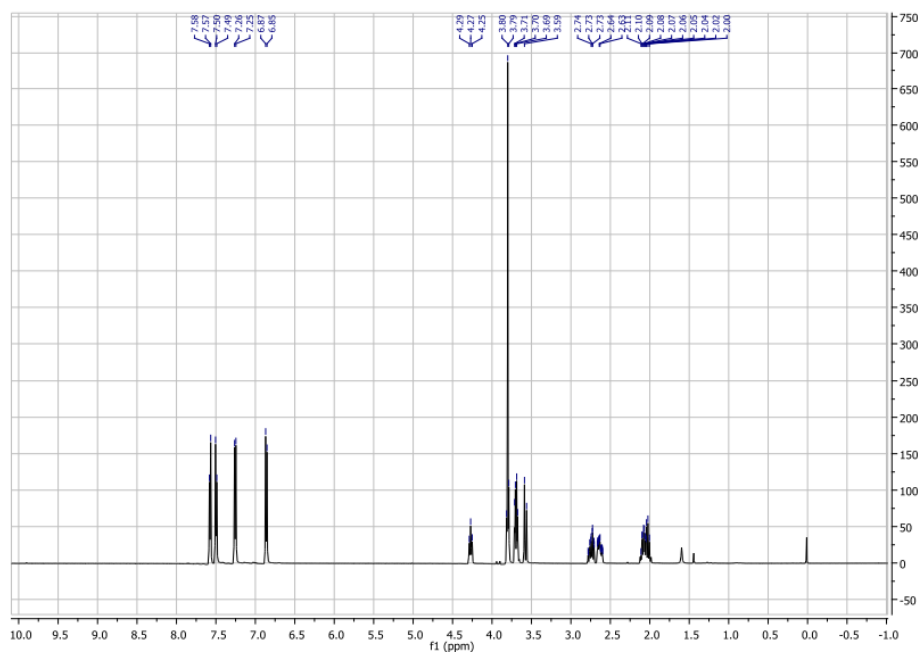
31



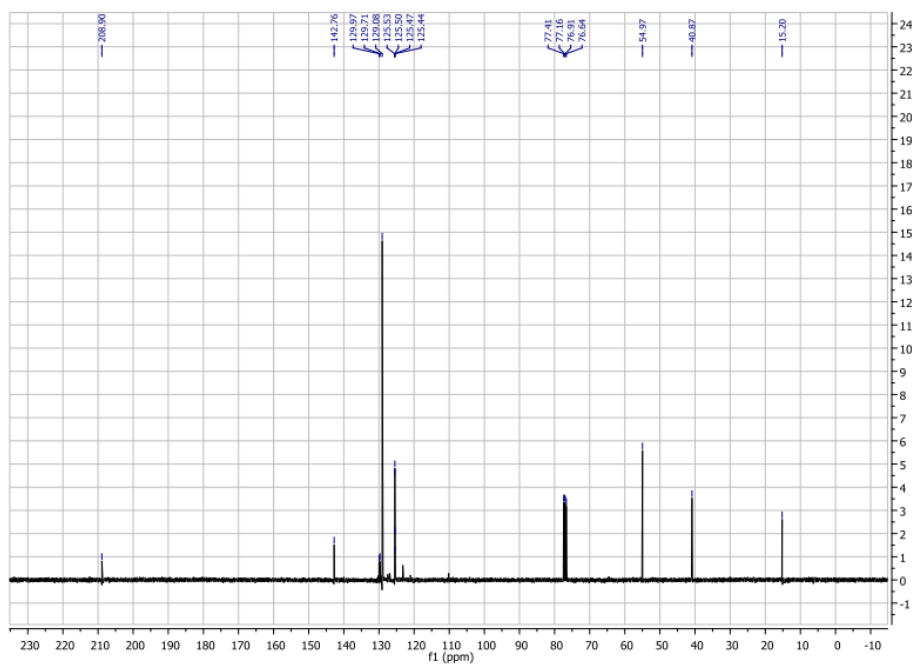
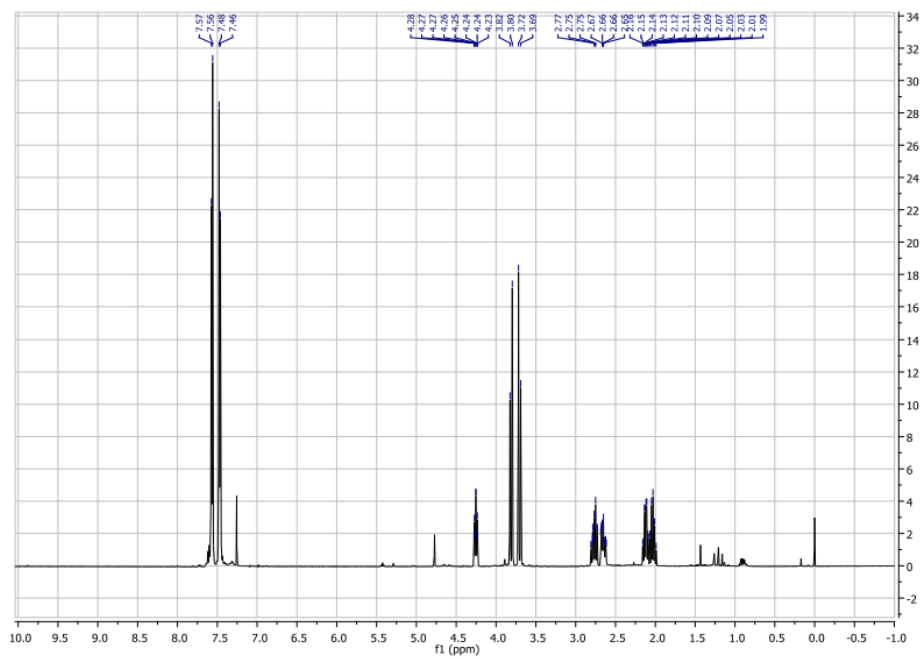
3m



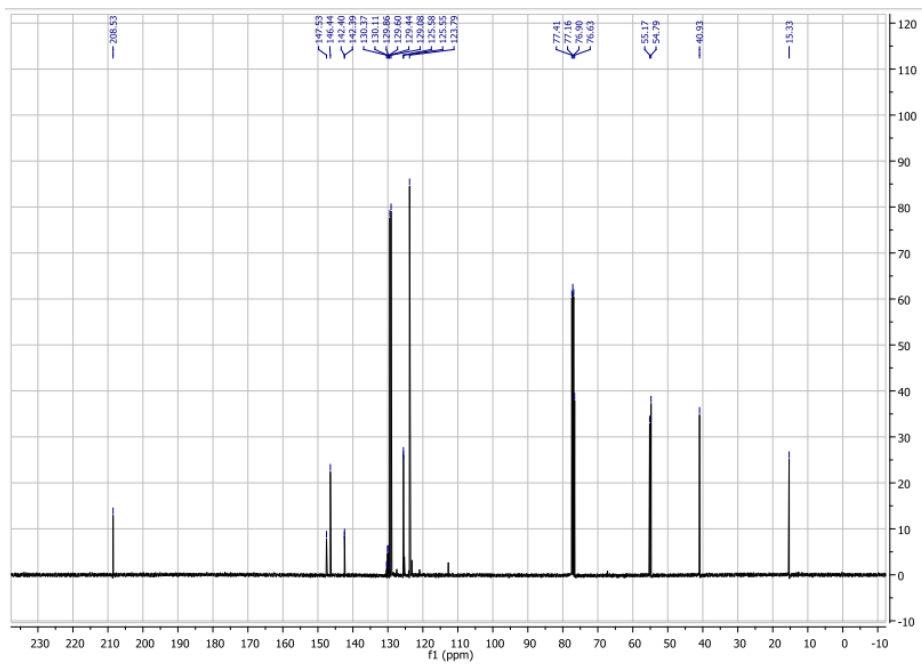
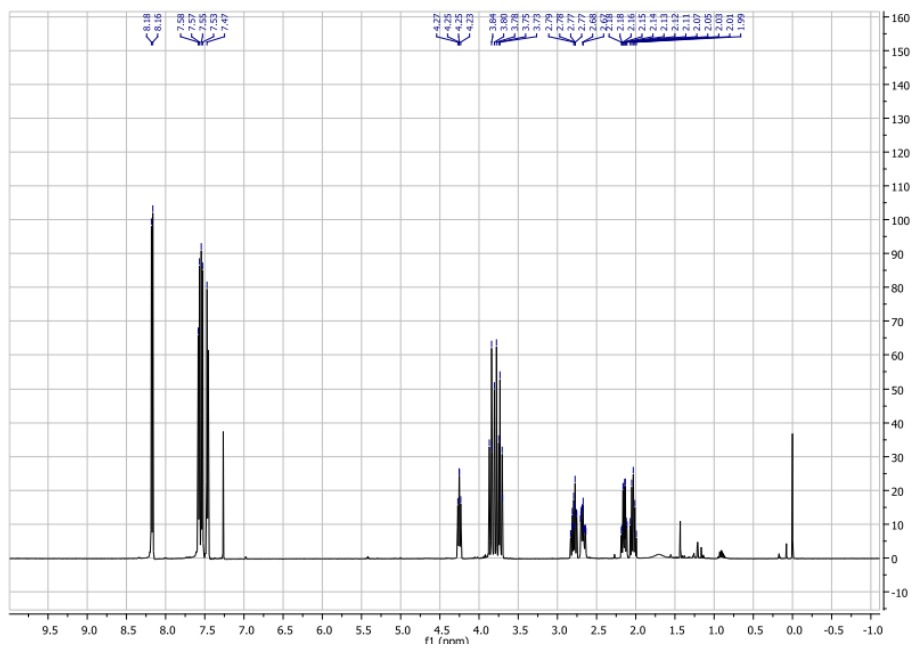
3n



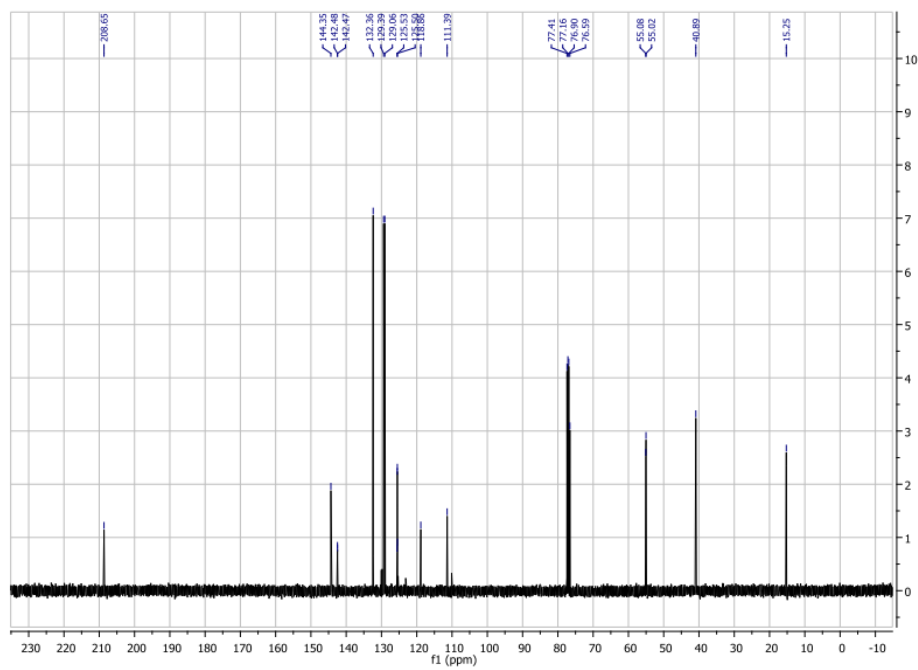
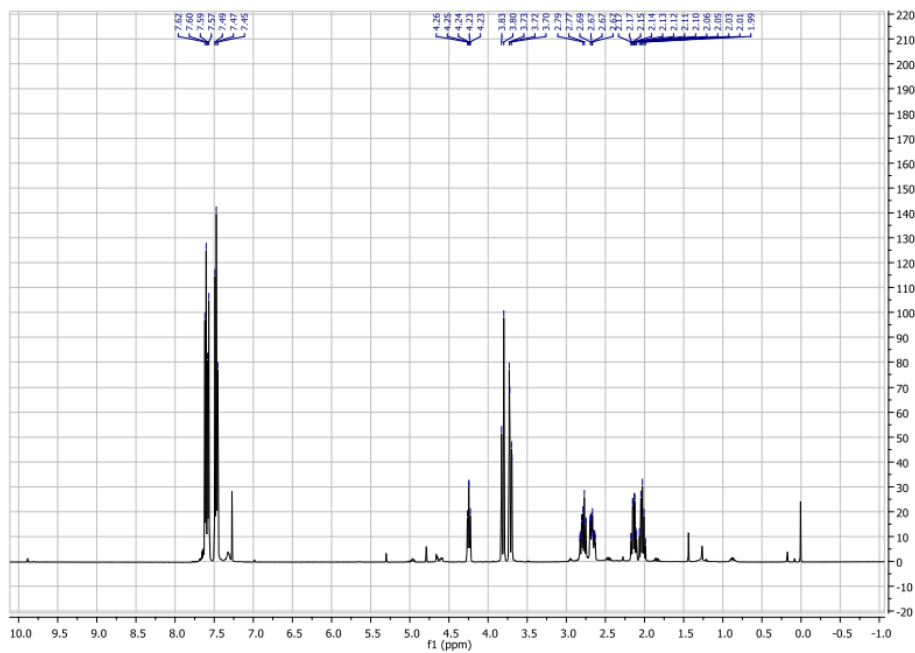
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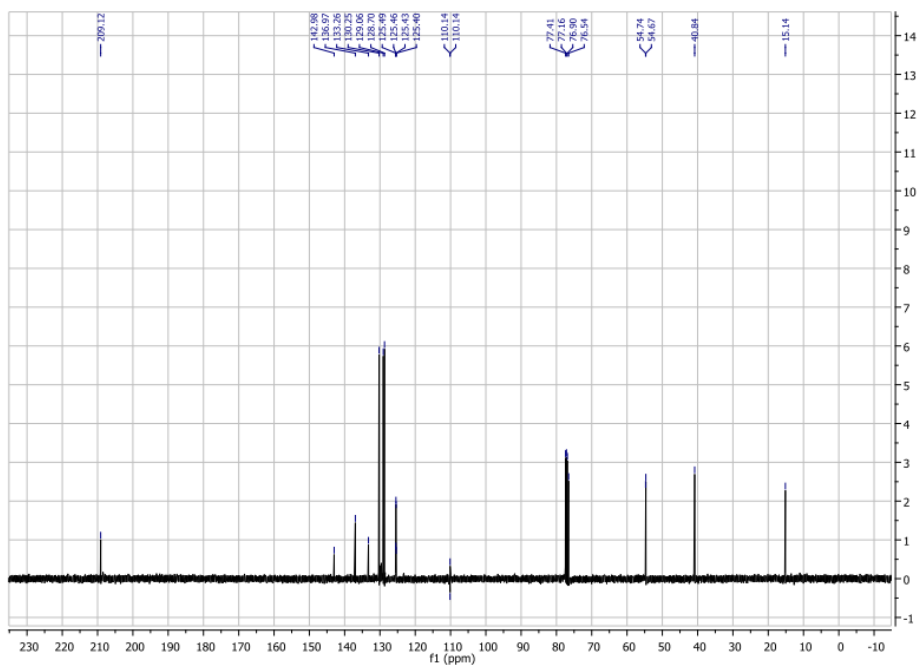
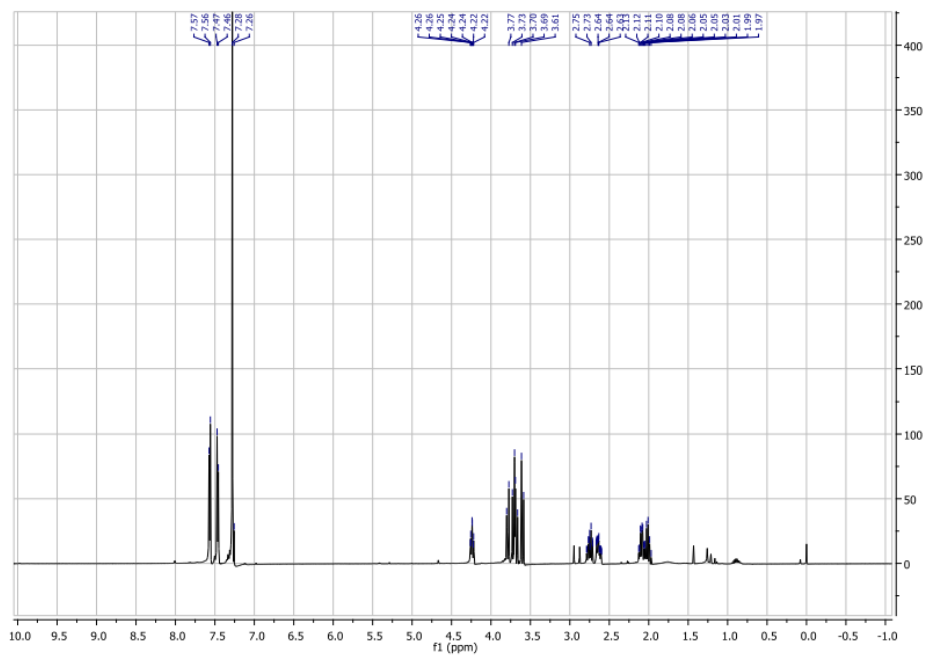
3p



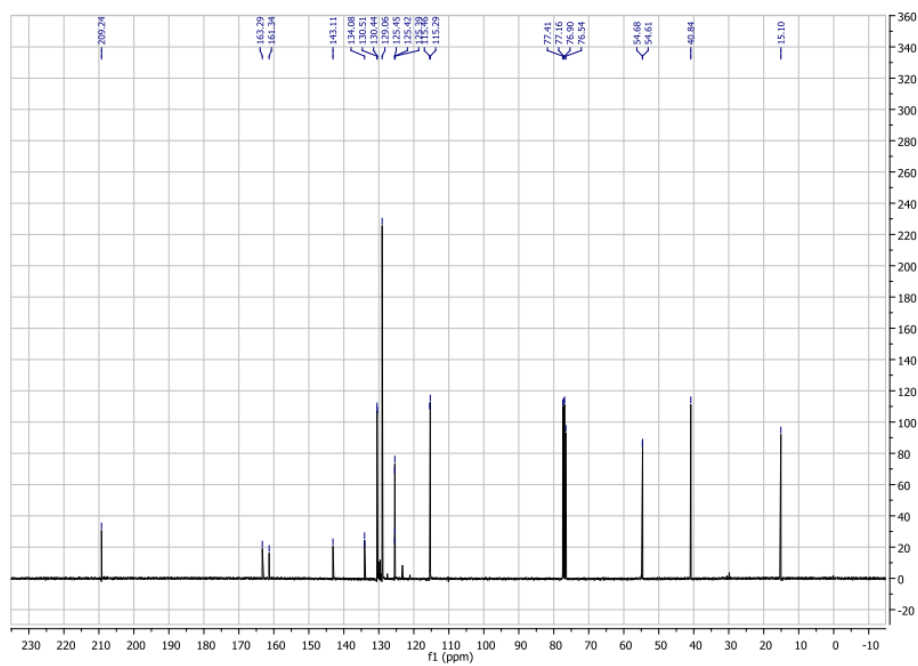
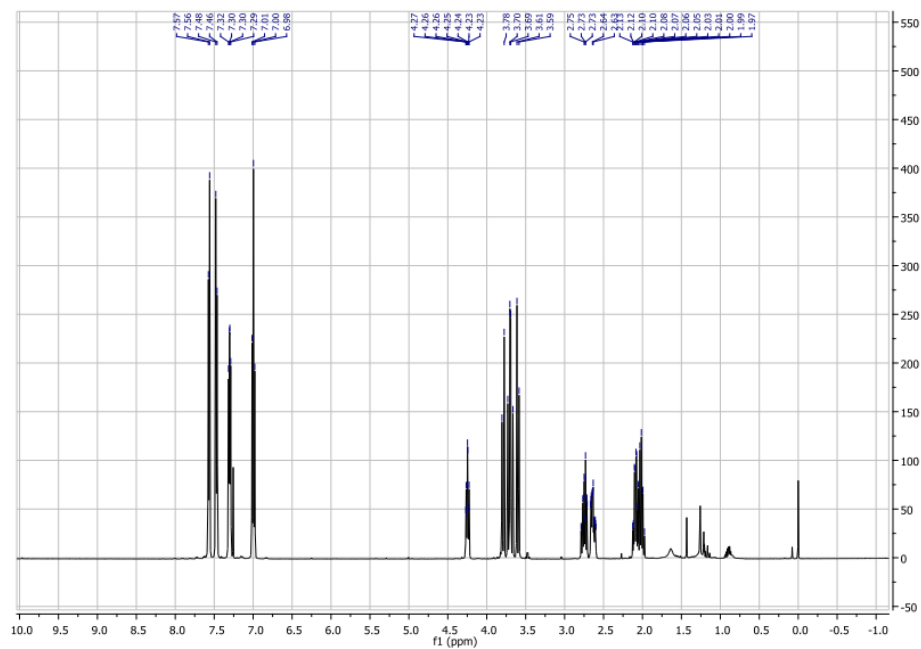
3q



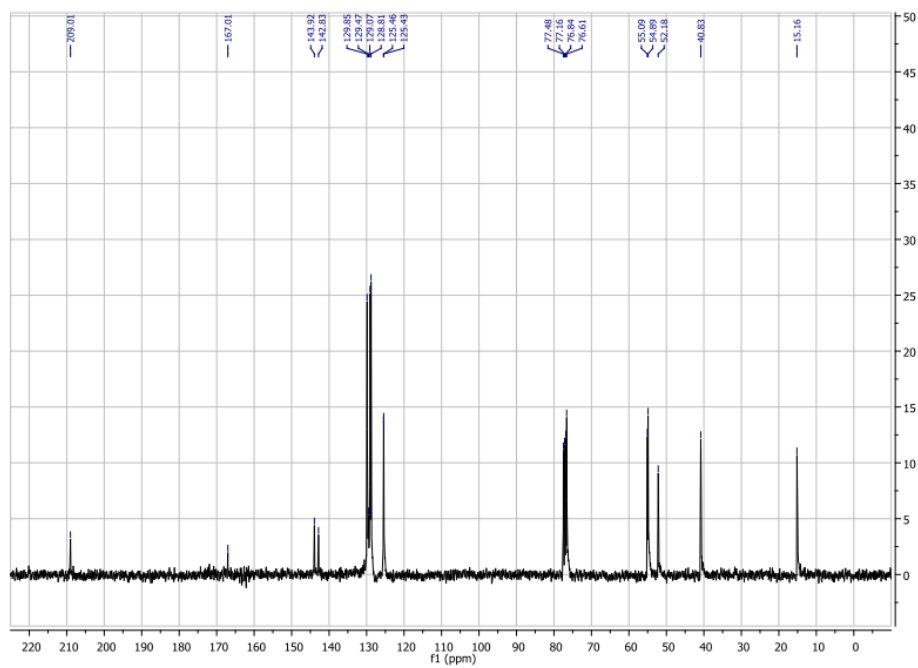
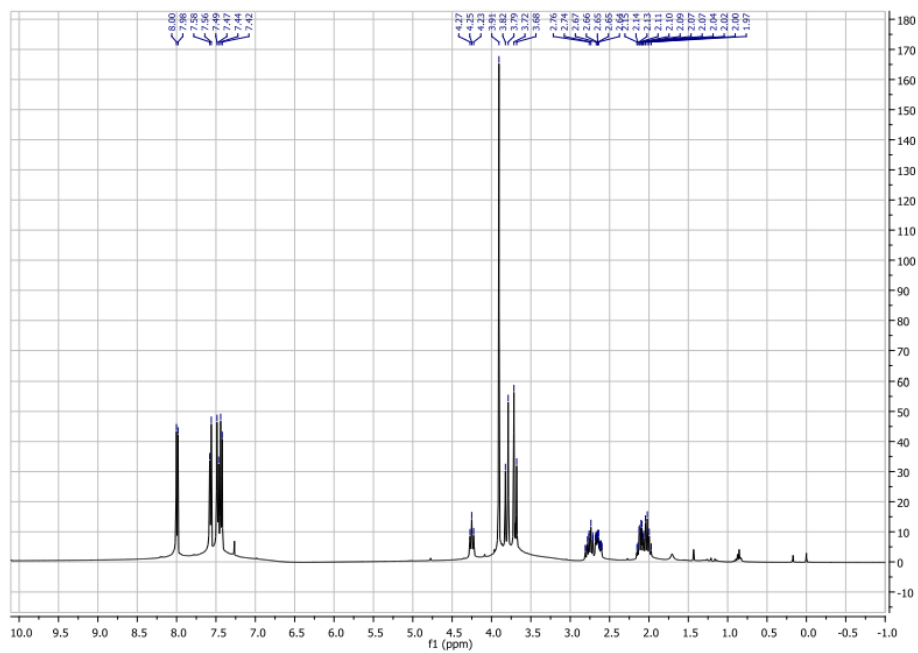
3r



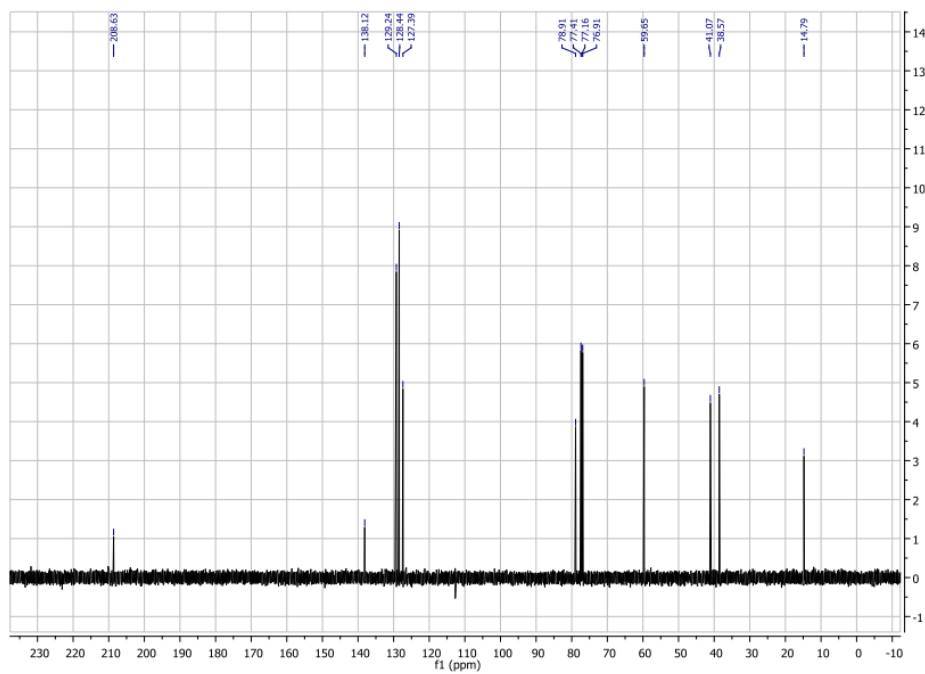
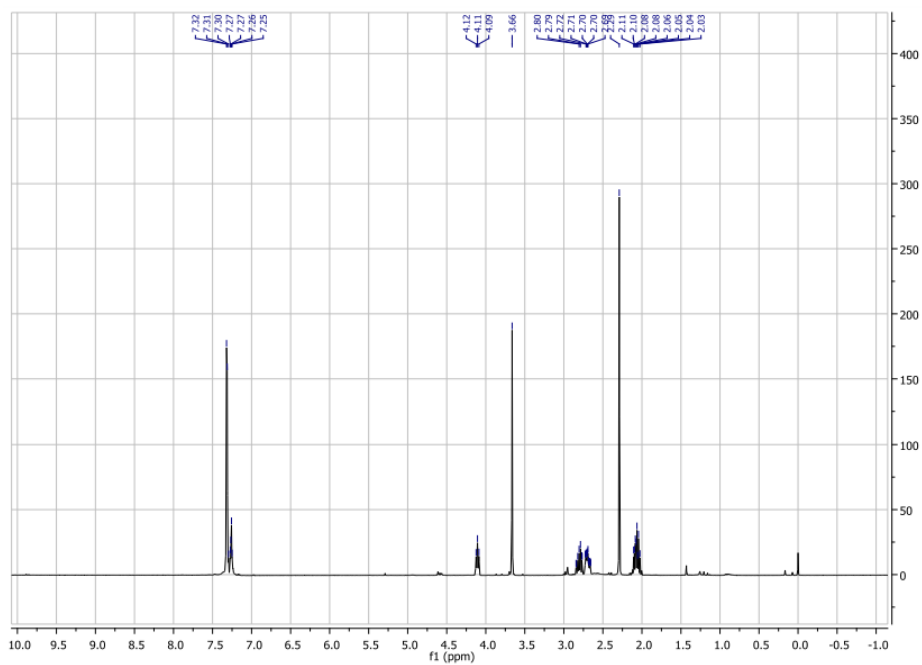
3s



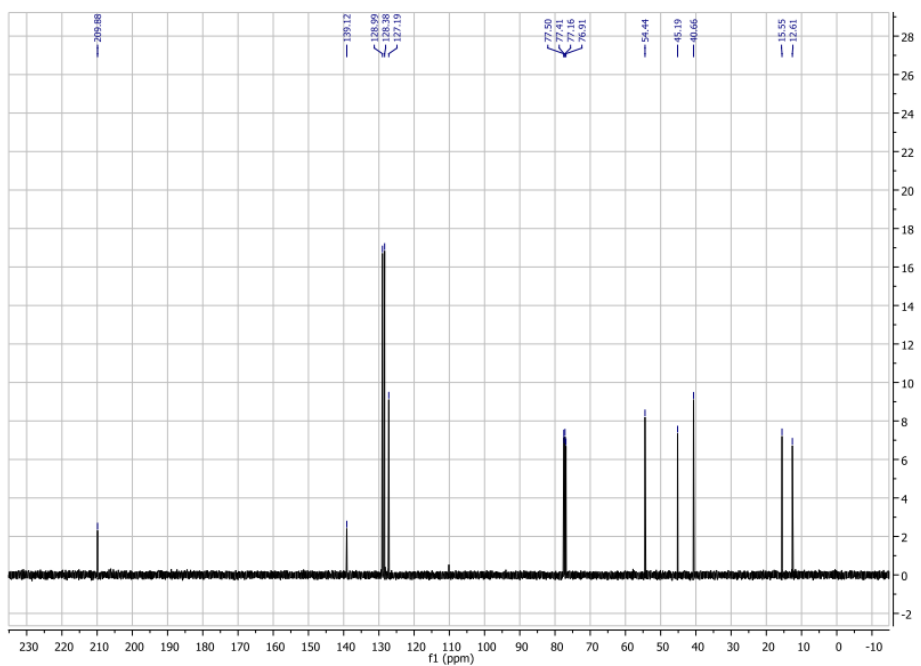
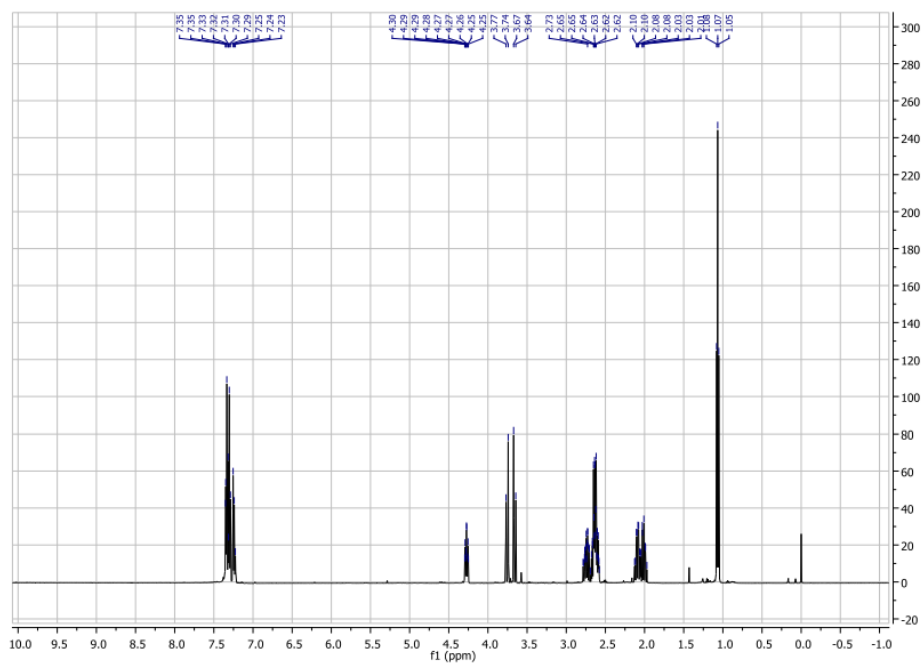
3t



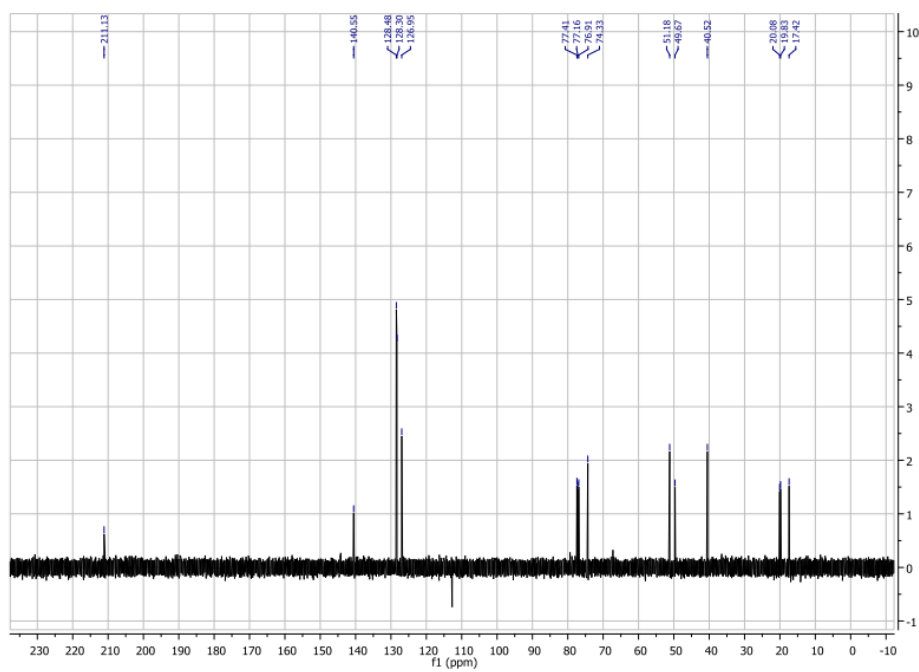
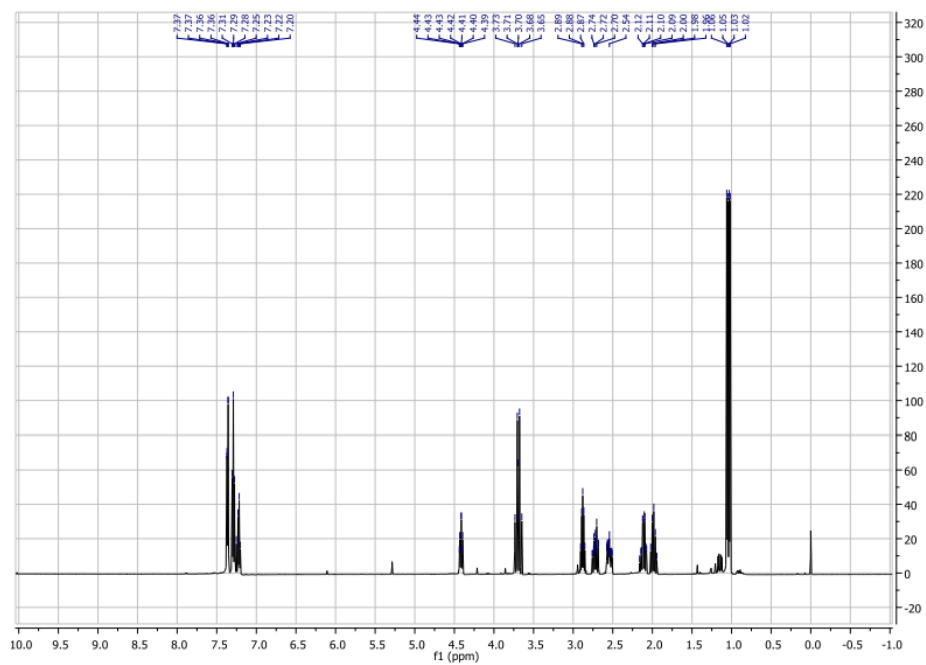
5a



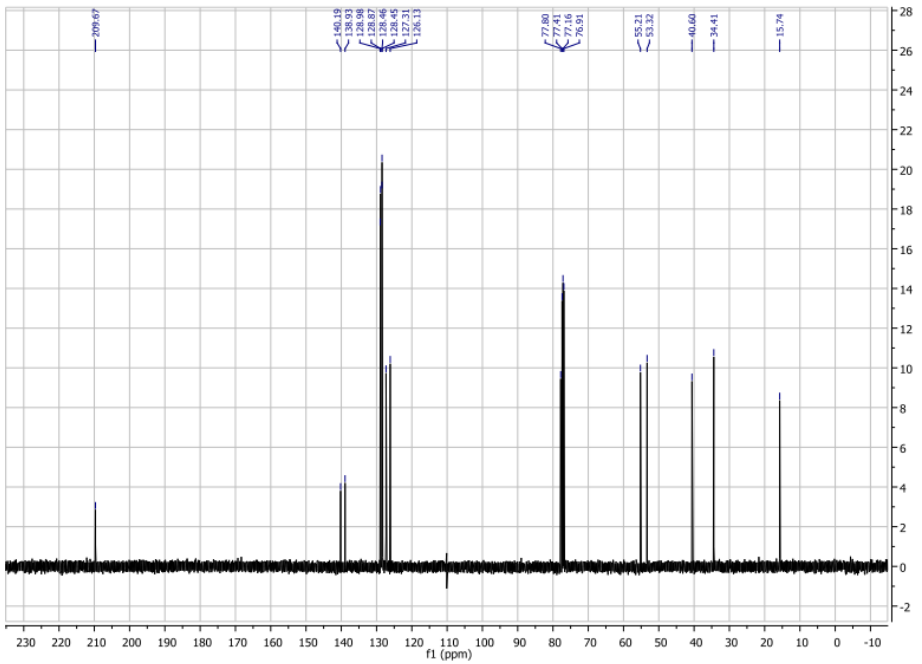
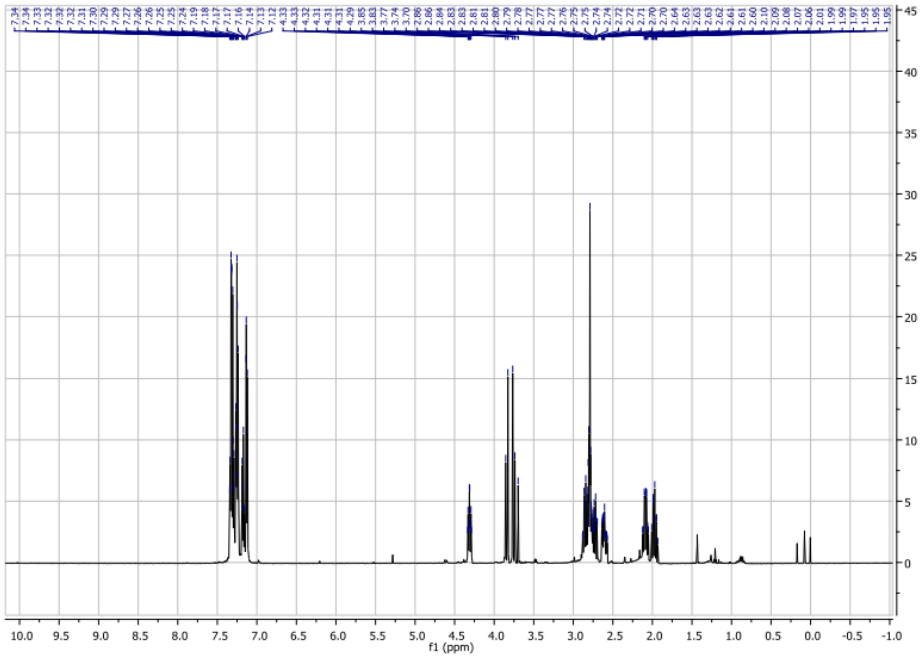
5b



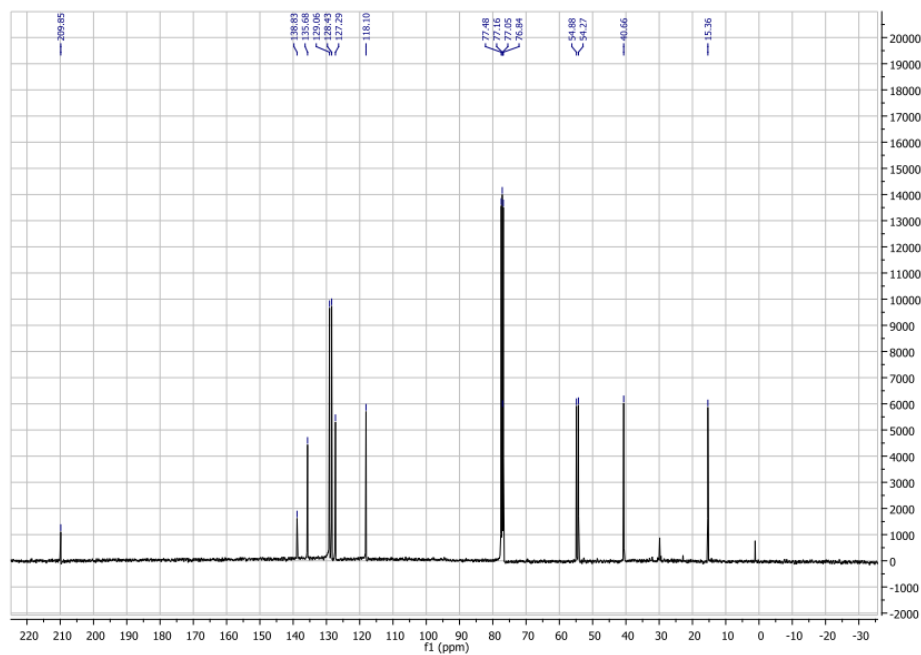
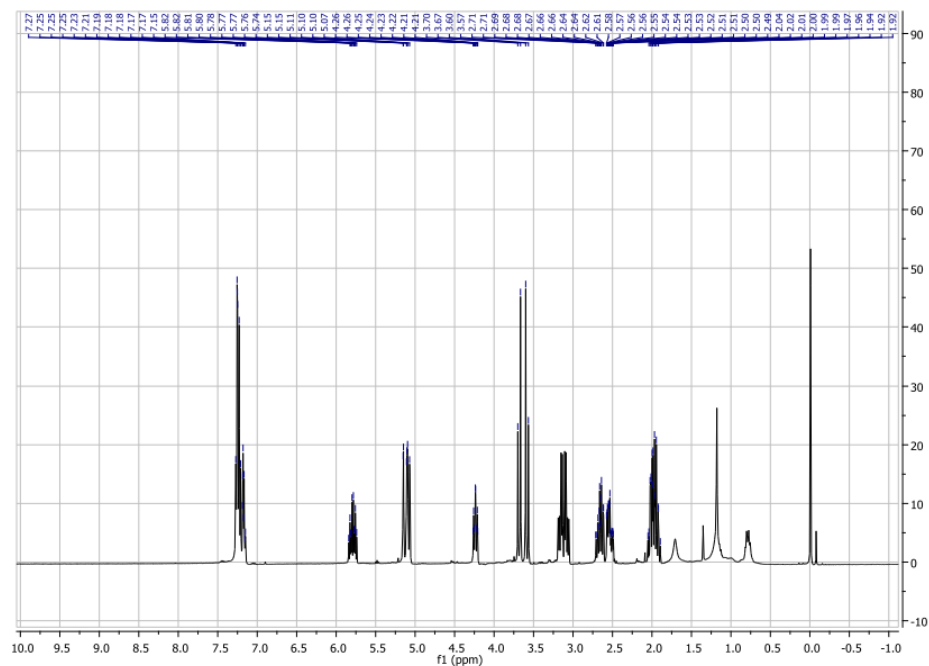
5c



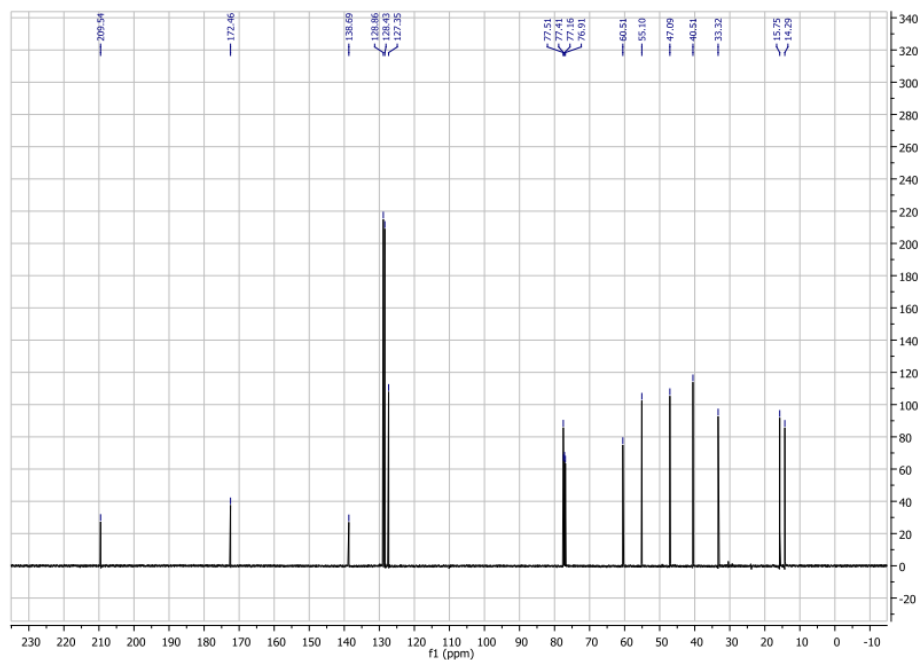
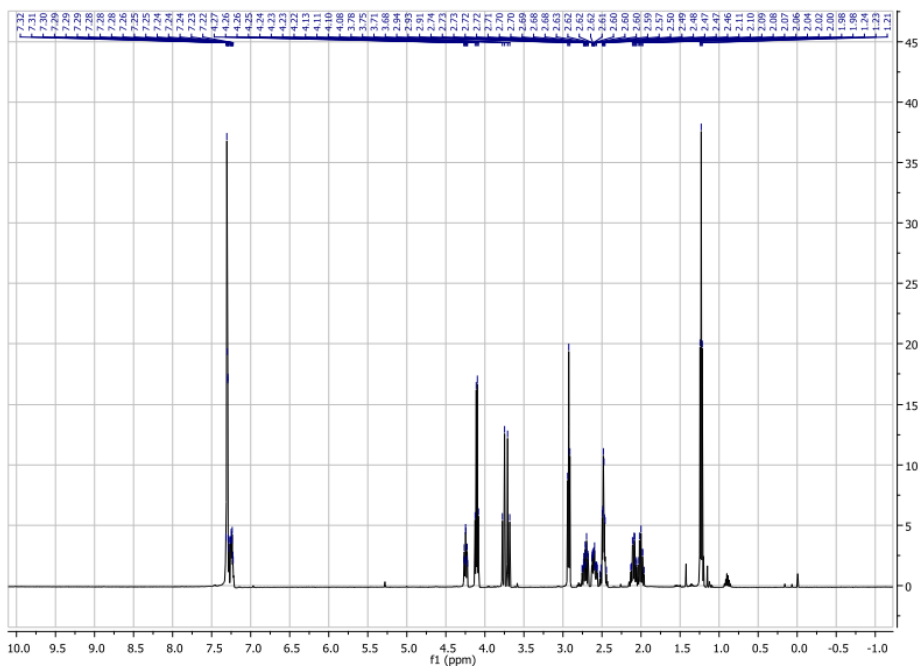
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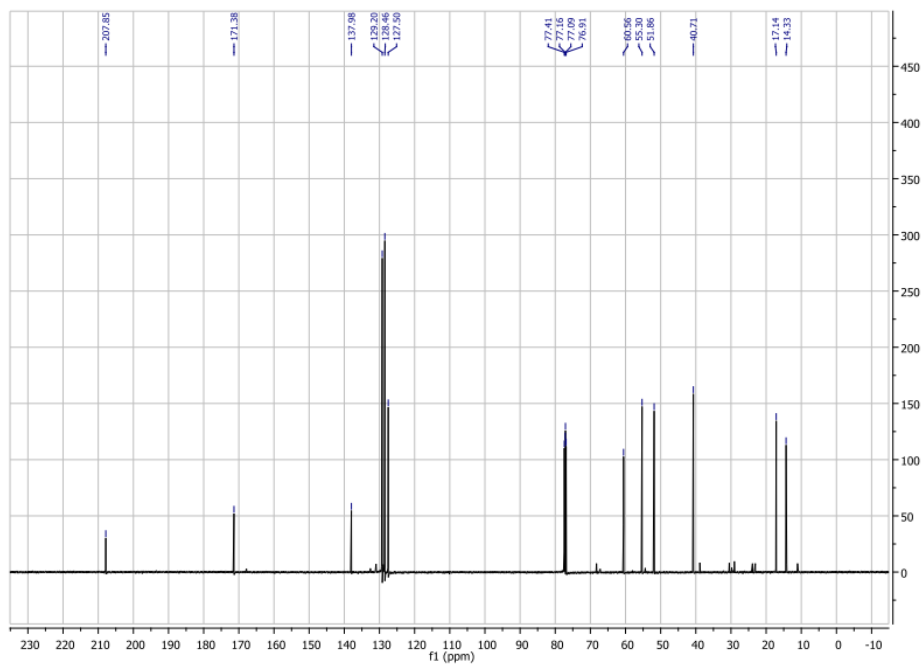
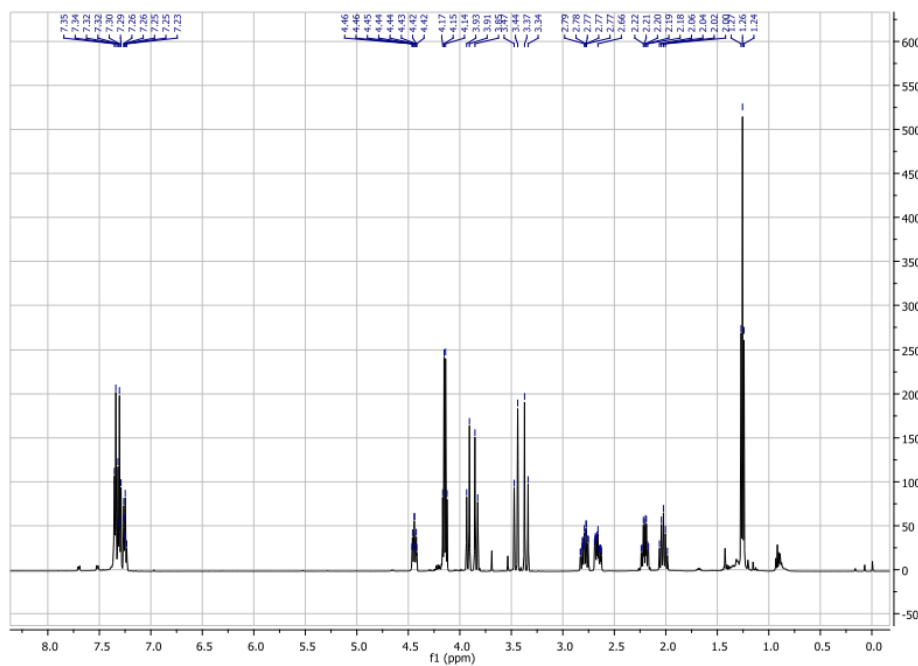
5e



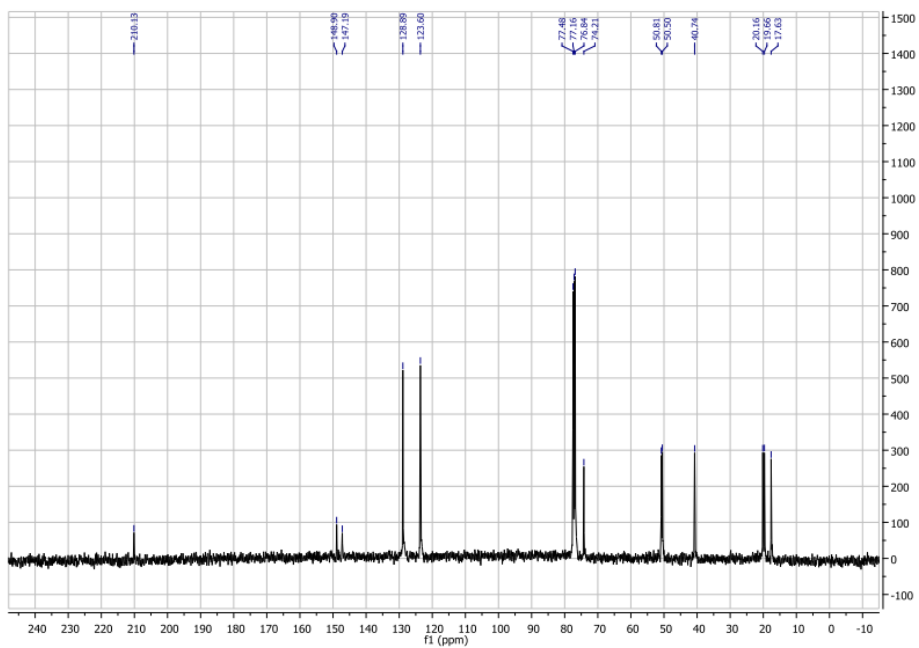
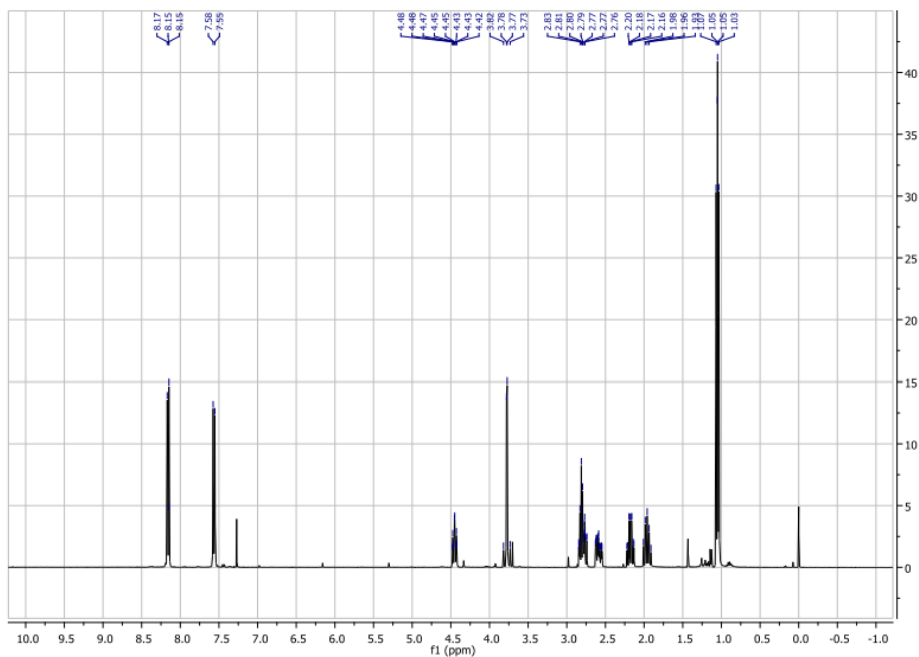
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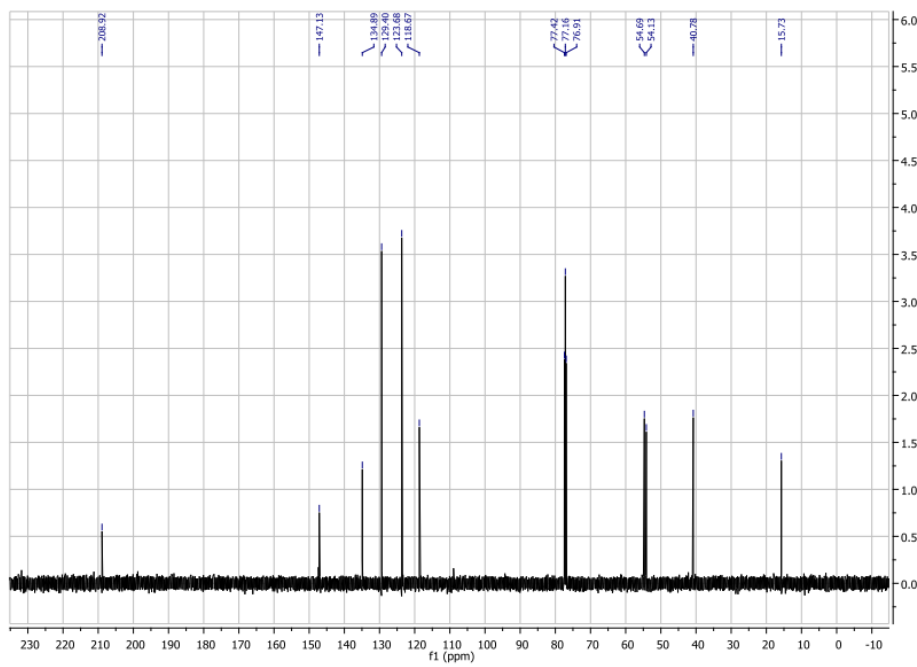
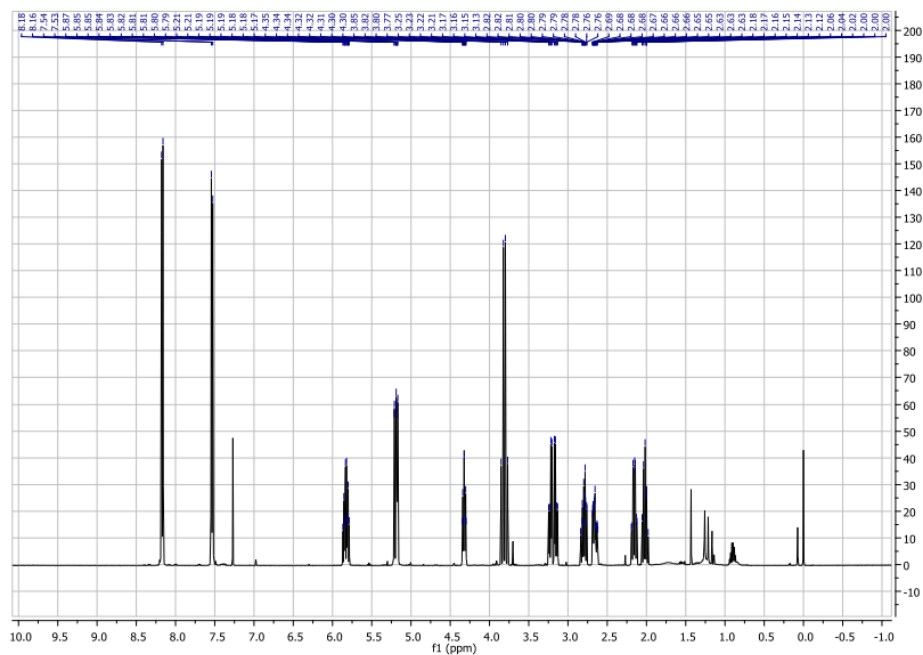
5g



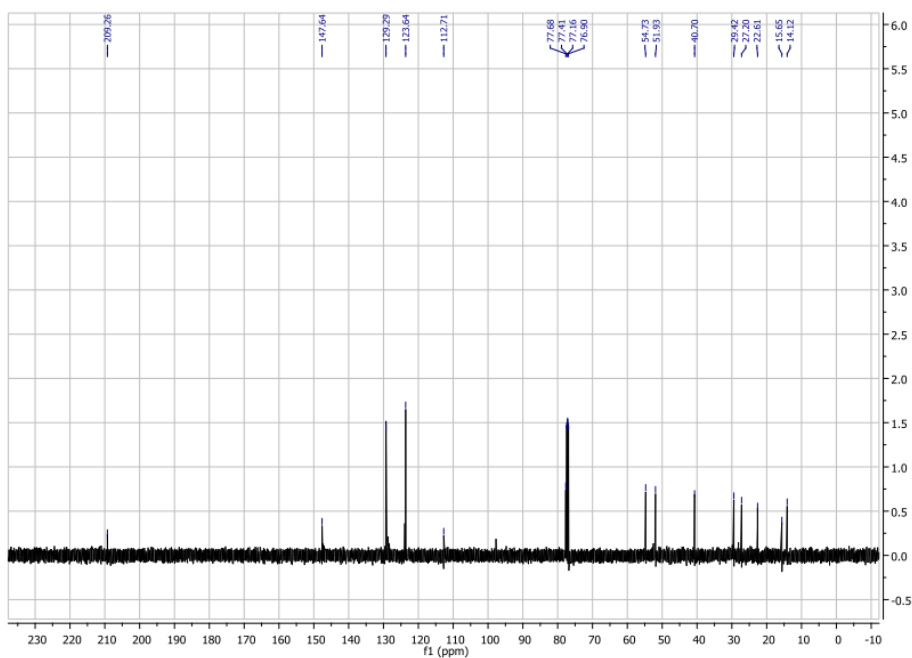
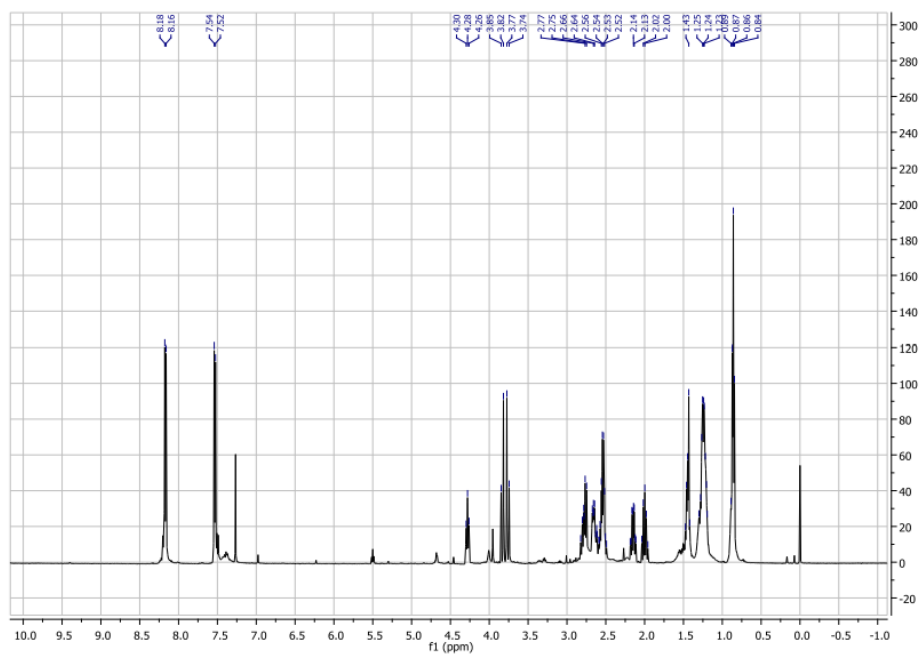
5h



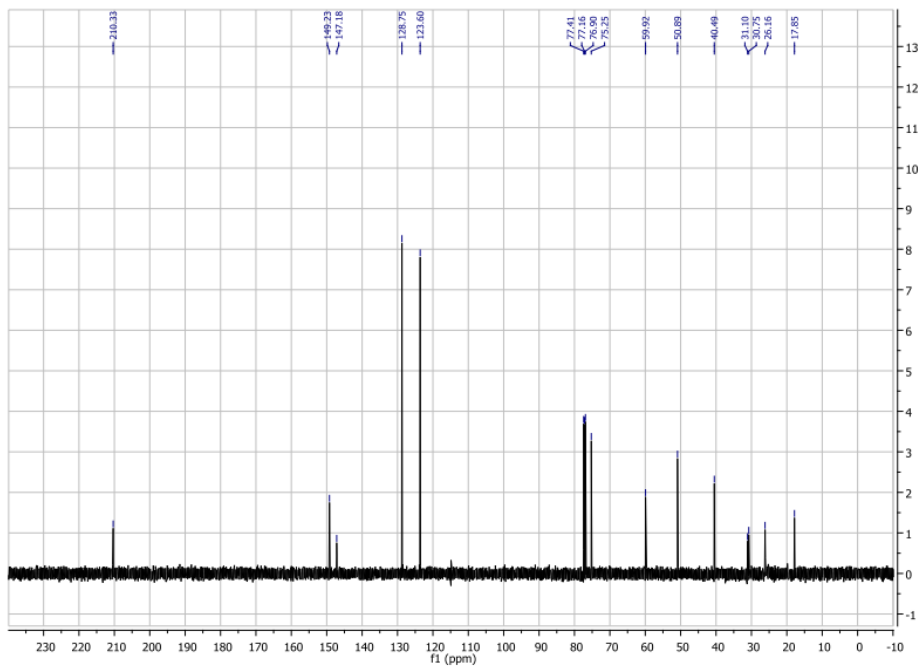
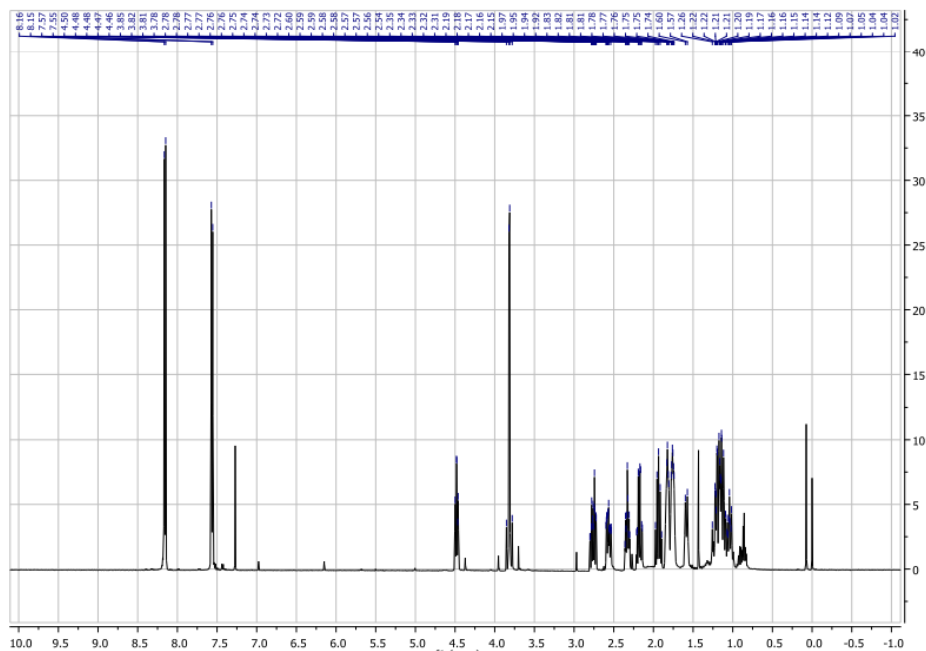
5i

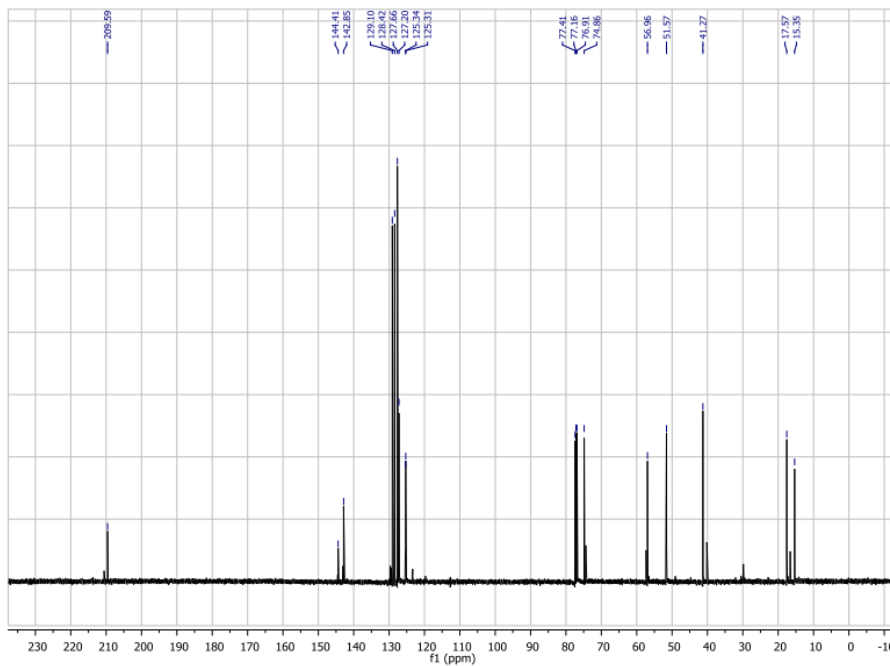
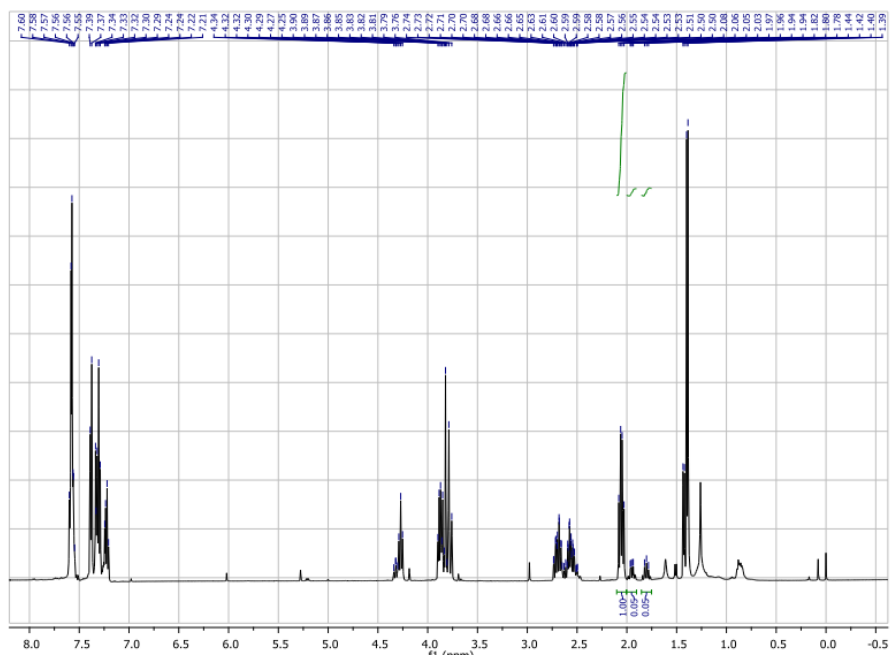


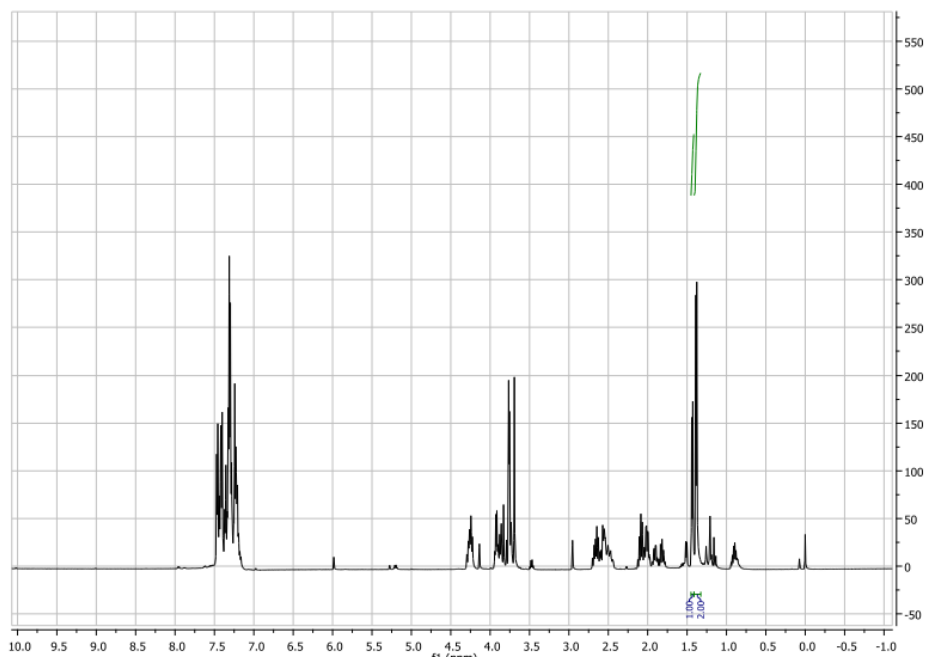
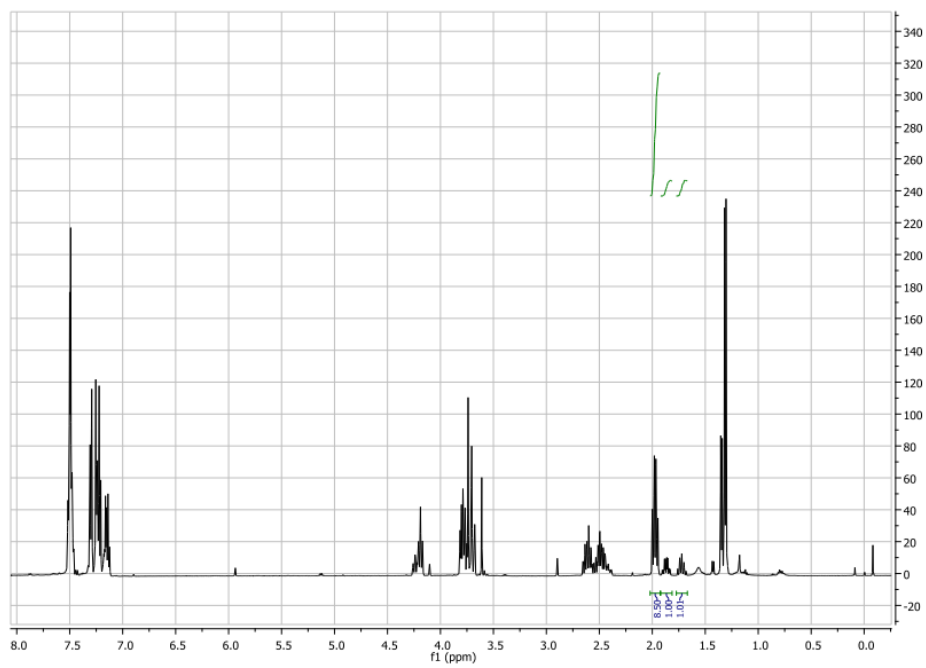
5j



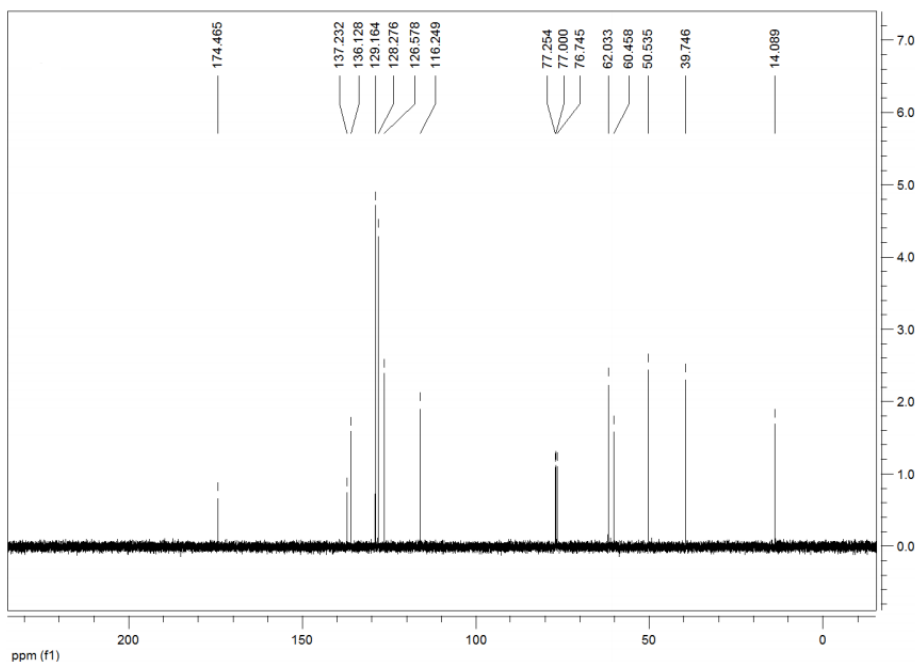
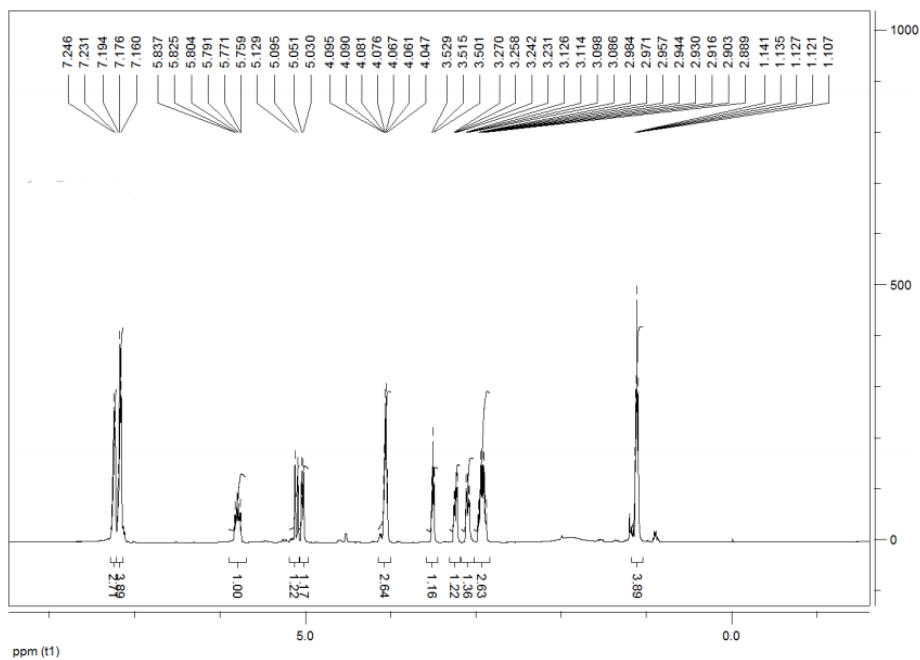
5k



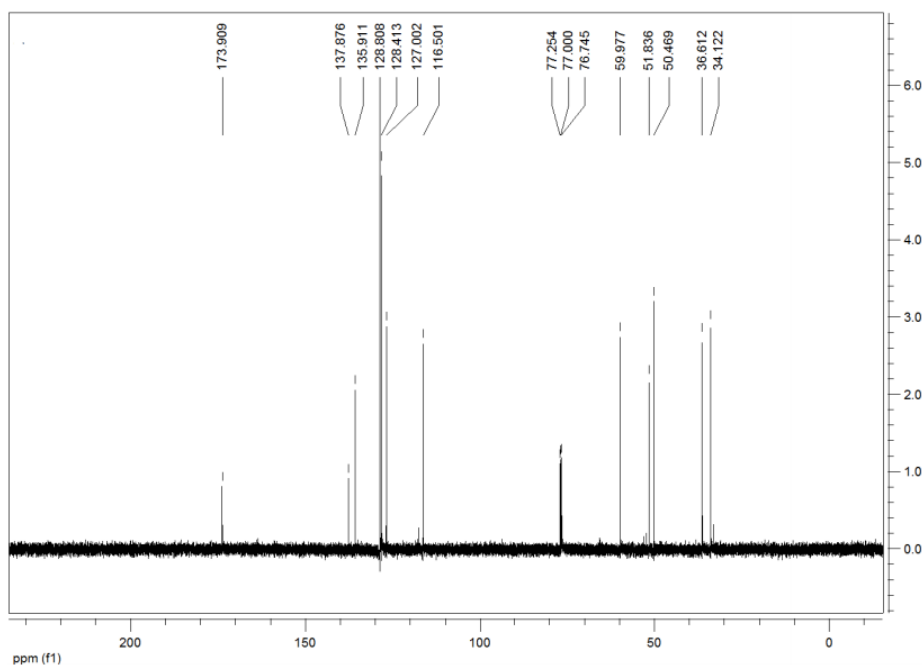
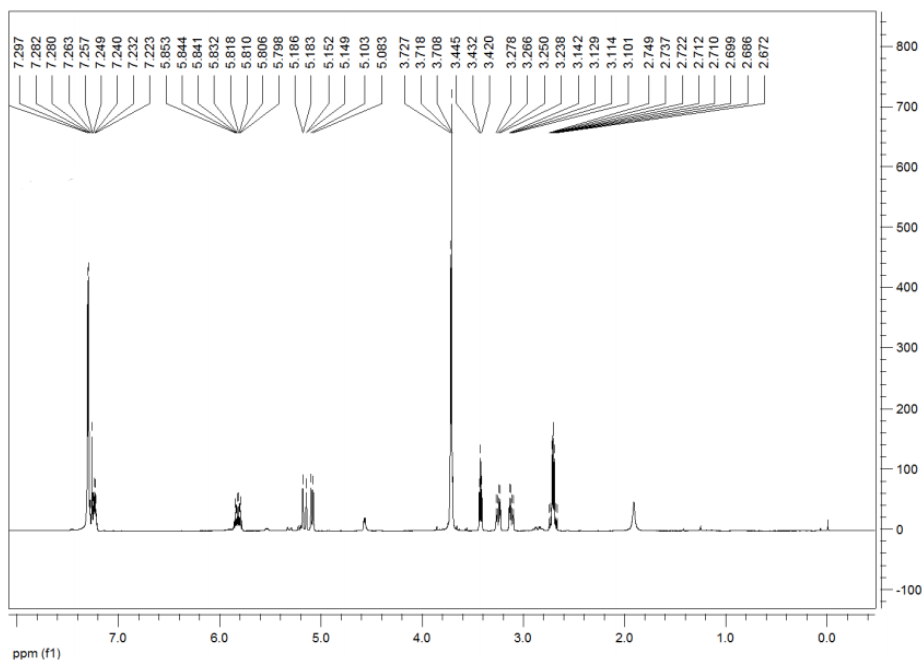
ent-7b/*ent*-7'b (91:9)

7a/7'a (67:33)**7b/7'b (81:19)**

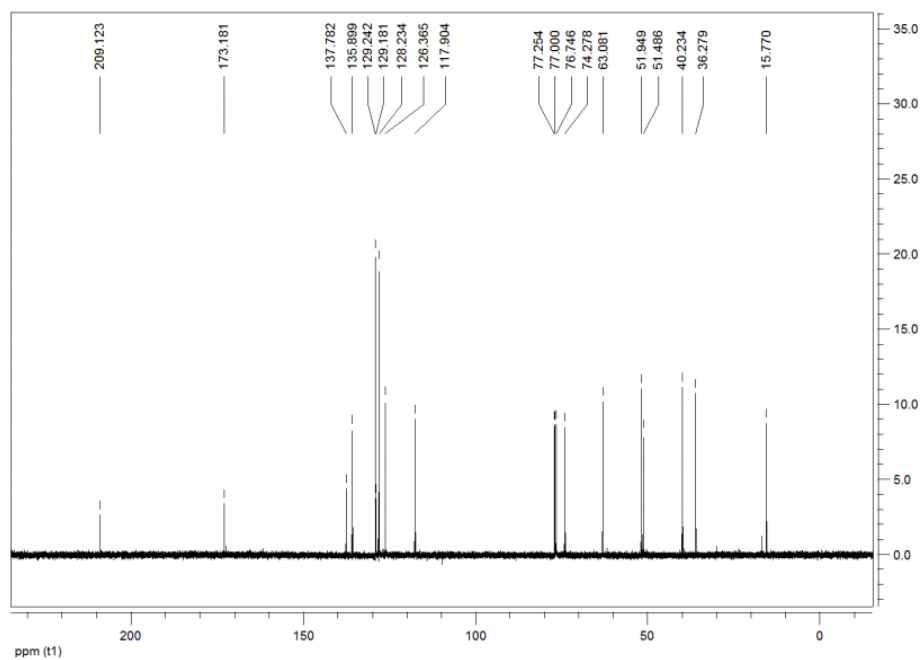
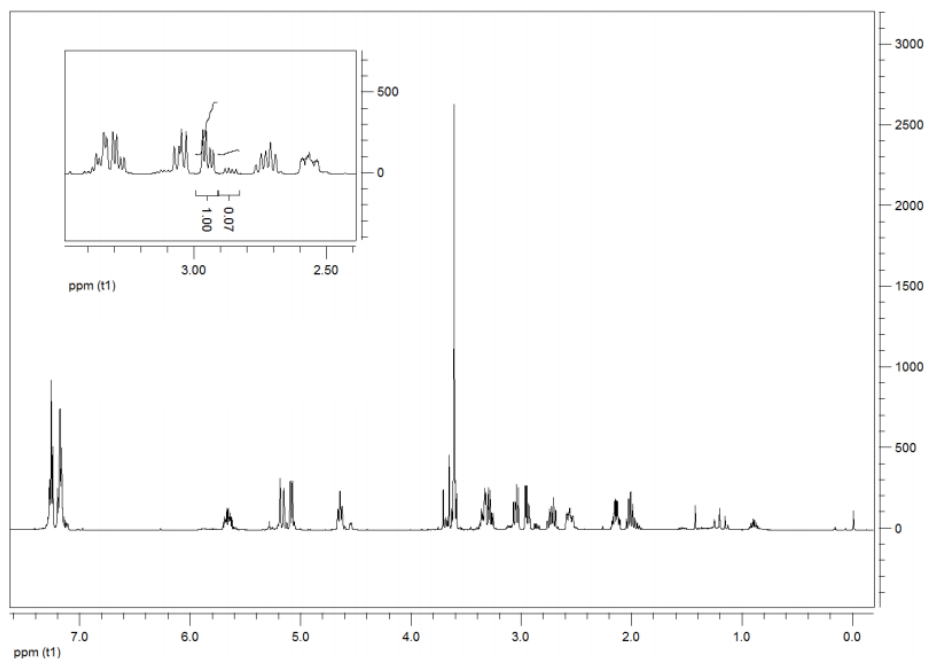
(L)-8b

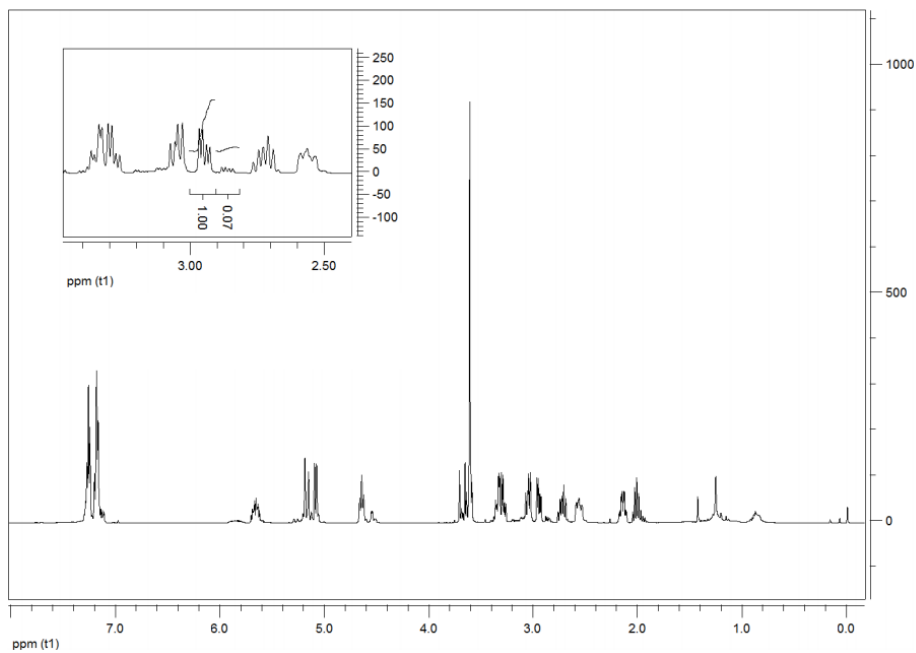


(L)-8i

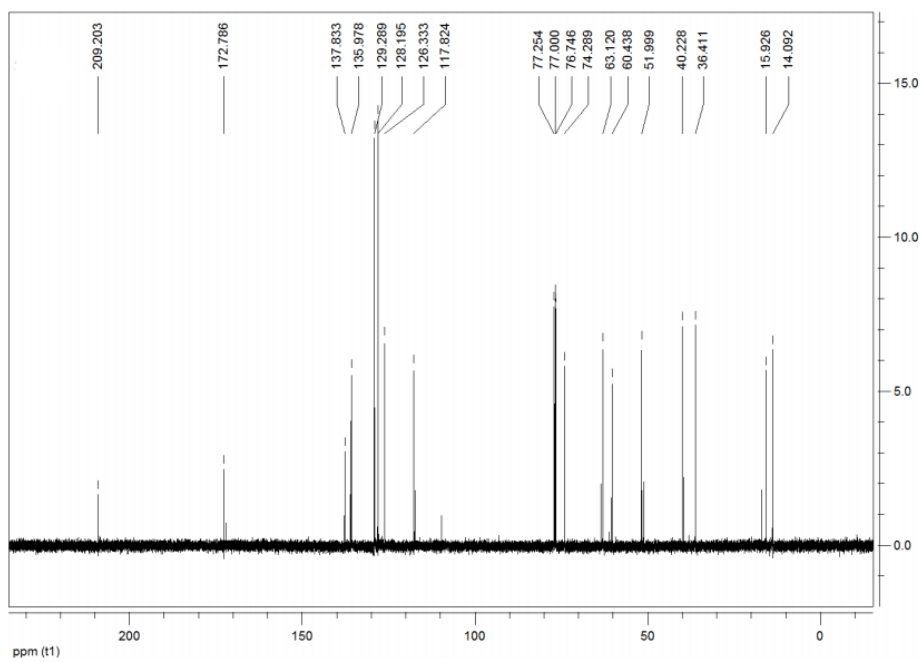
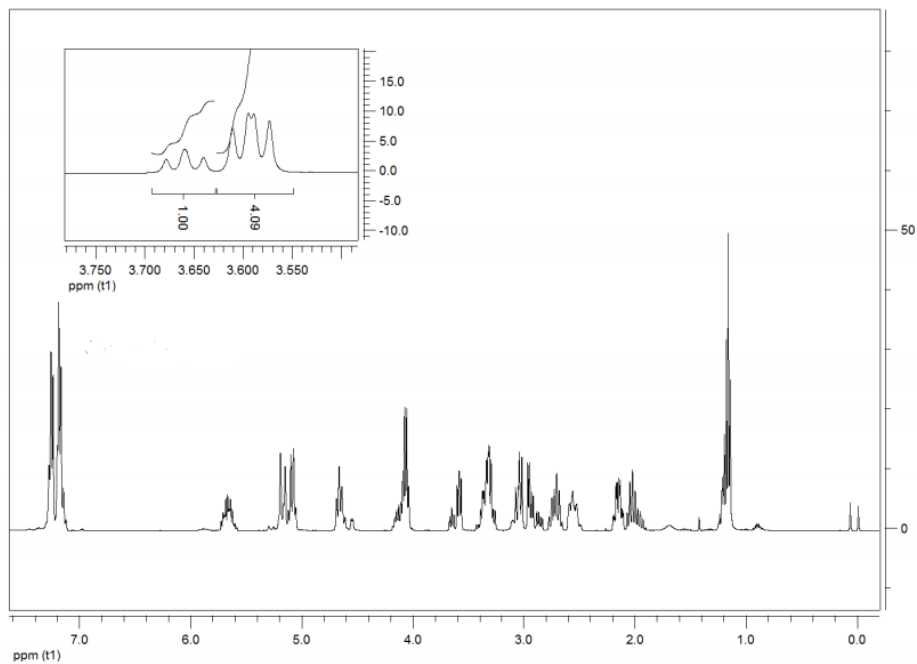


9a/9'a

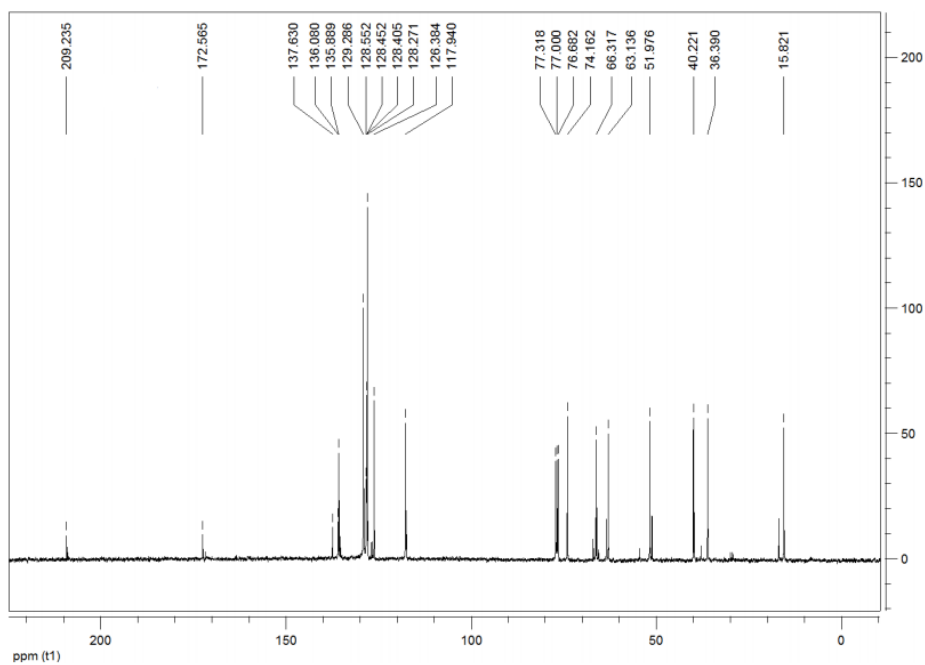
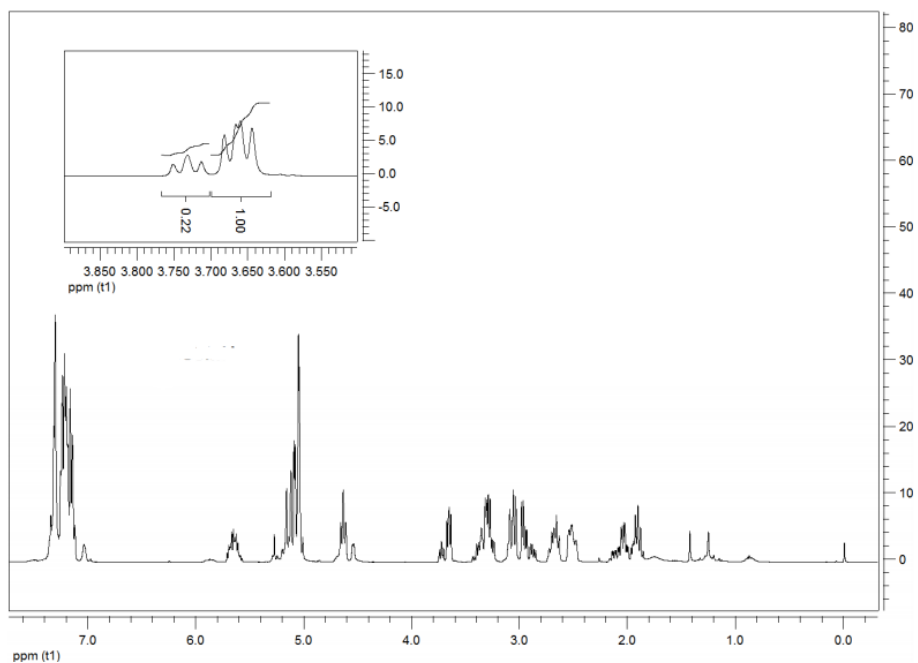


ent-9a/ent-9'a

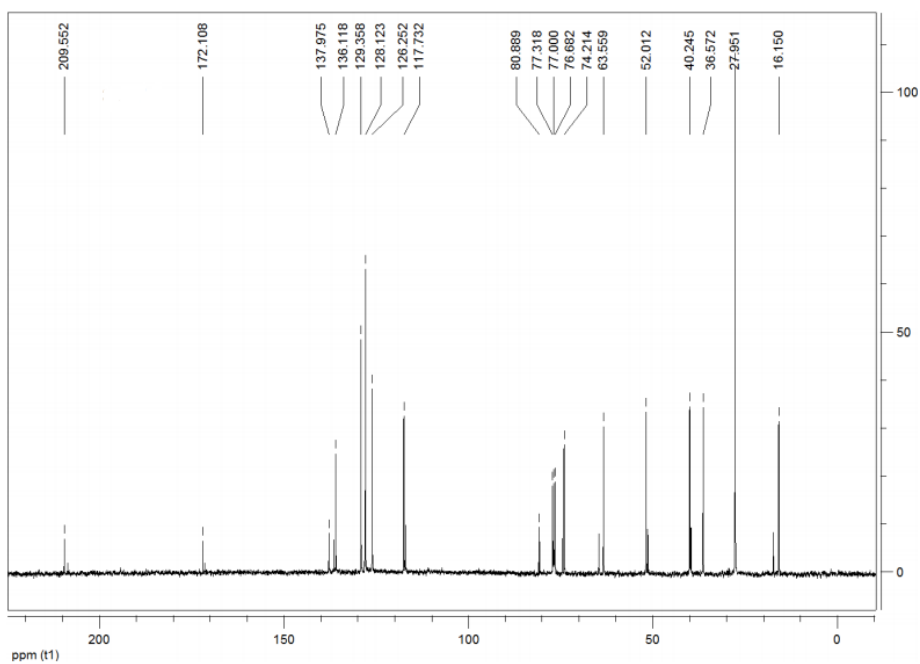
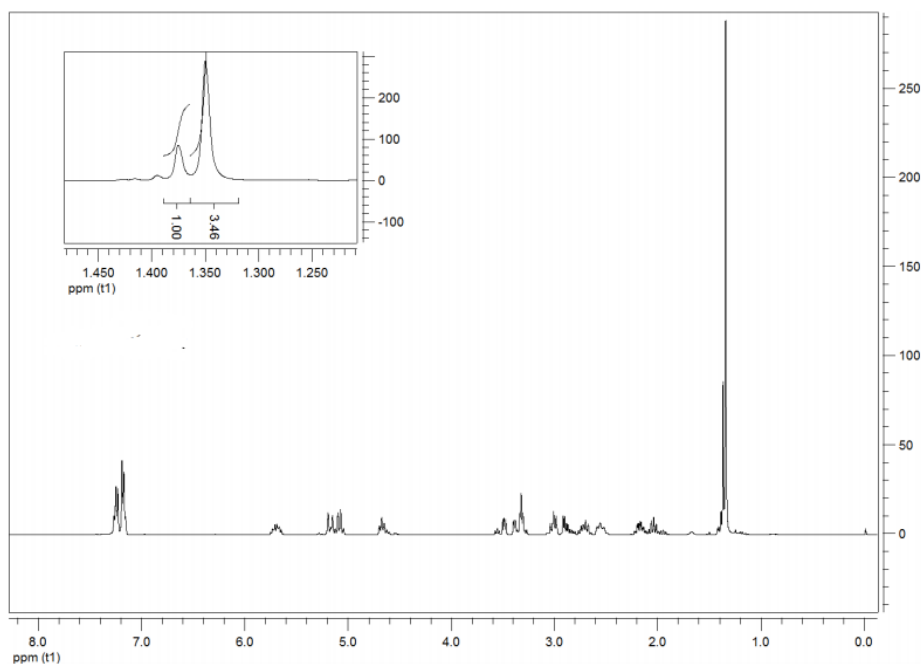
9b/9'b



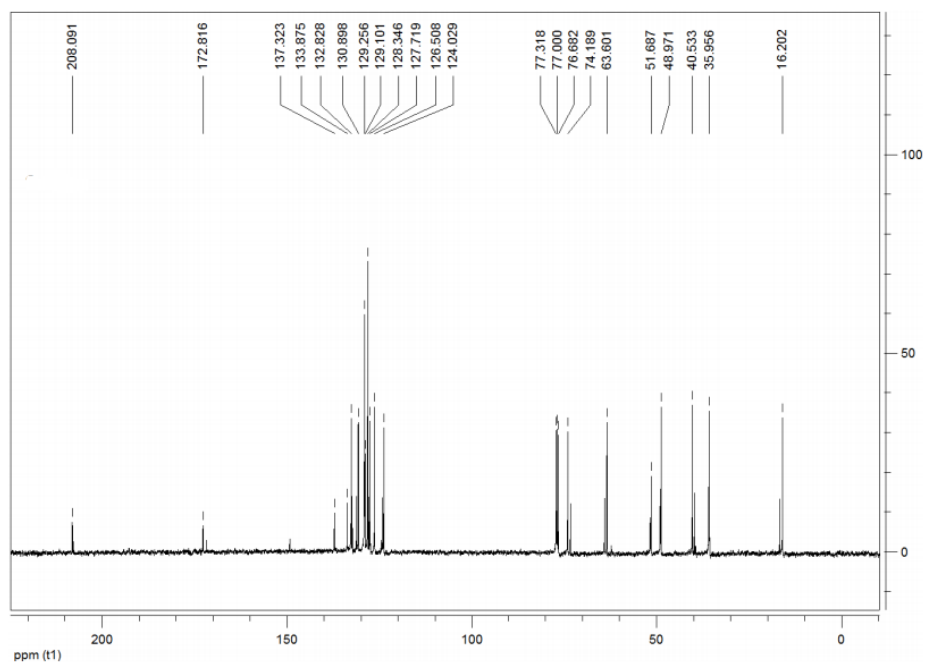
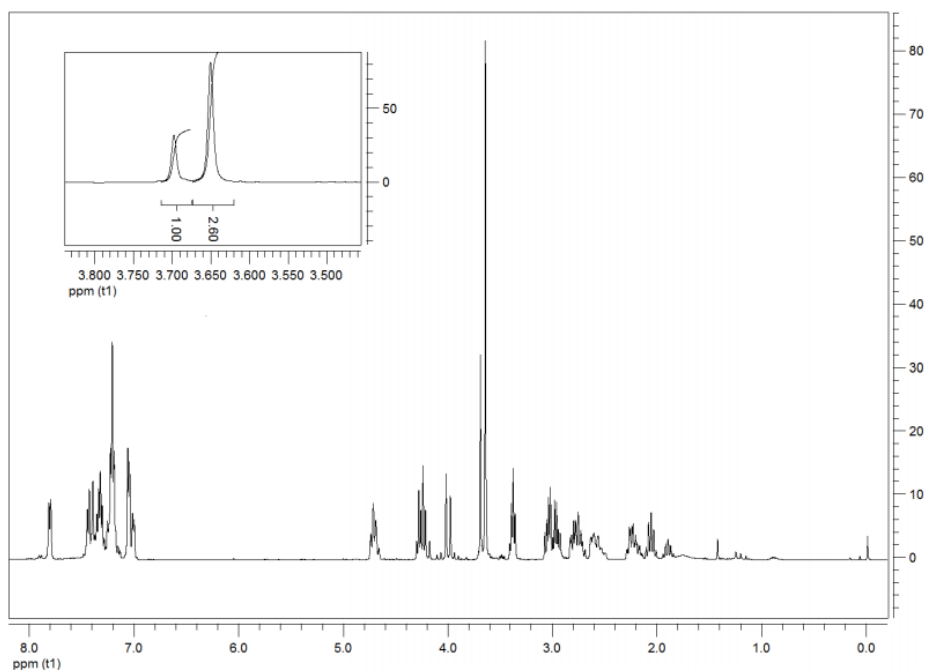
9c/9'c



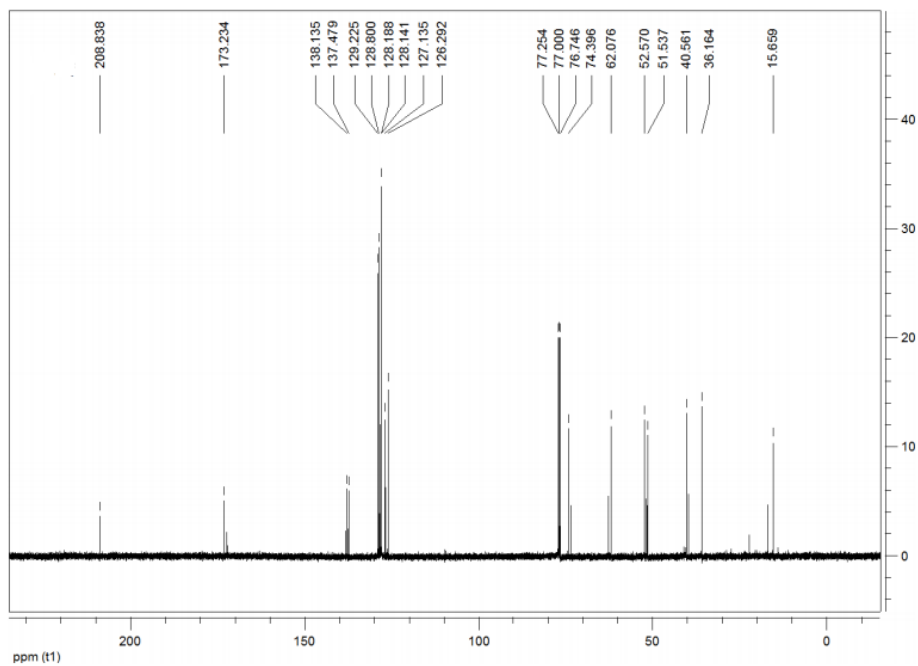
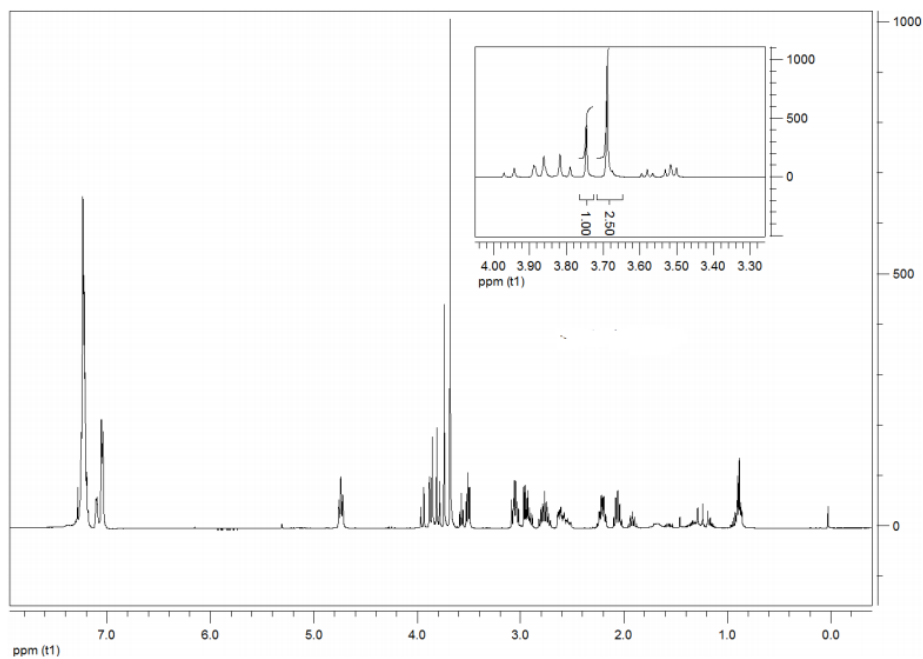
9d/9'd



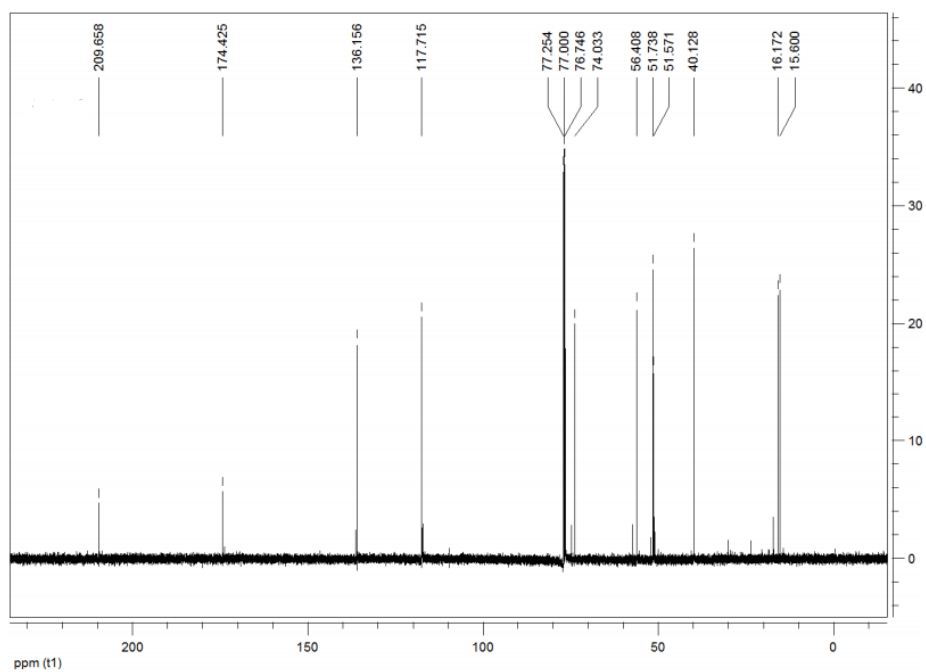
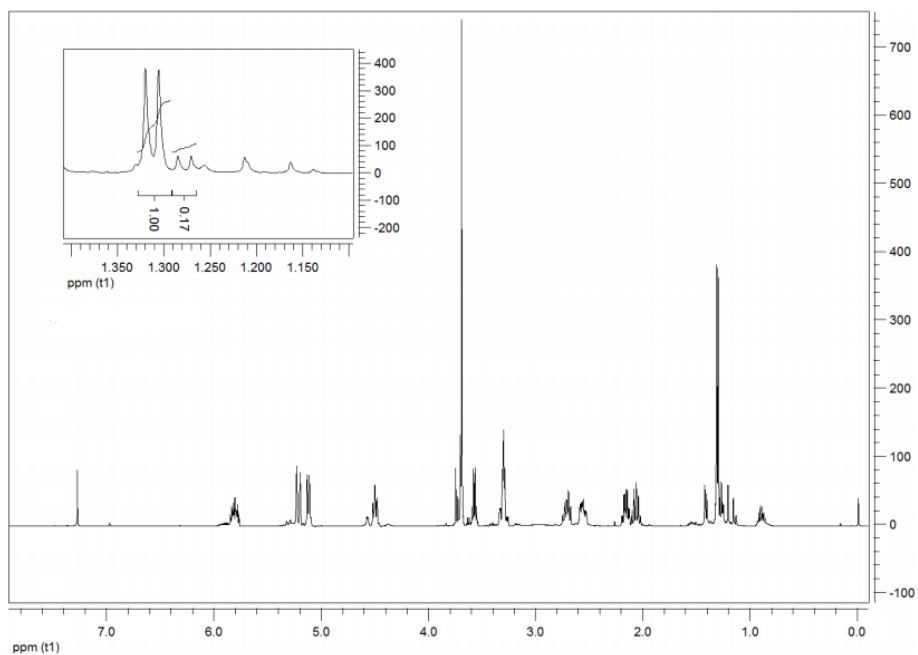
9e/9'e



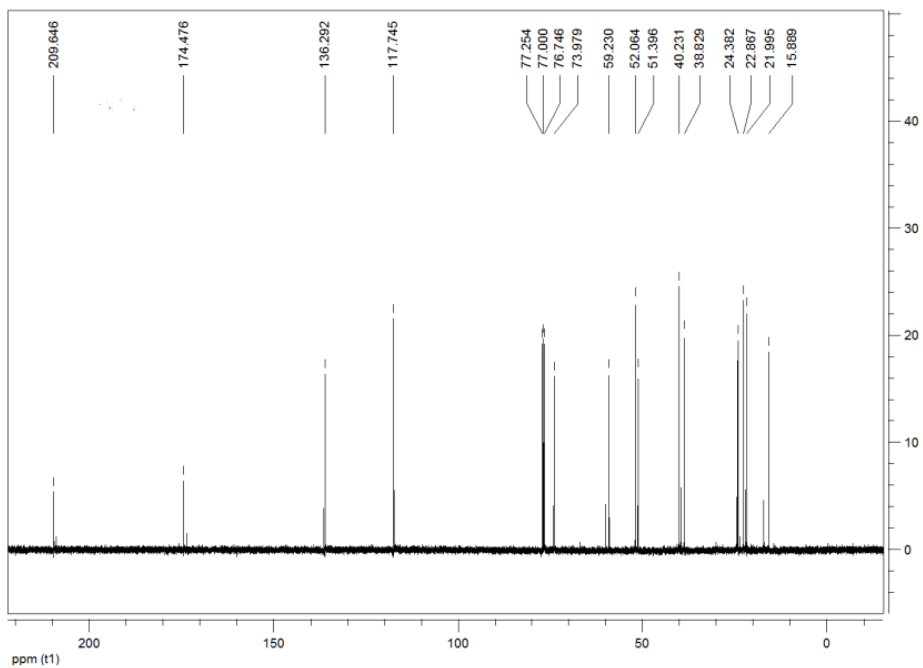
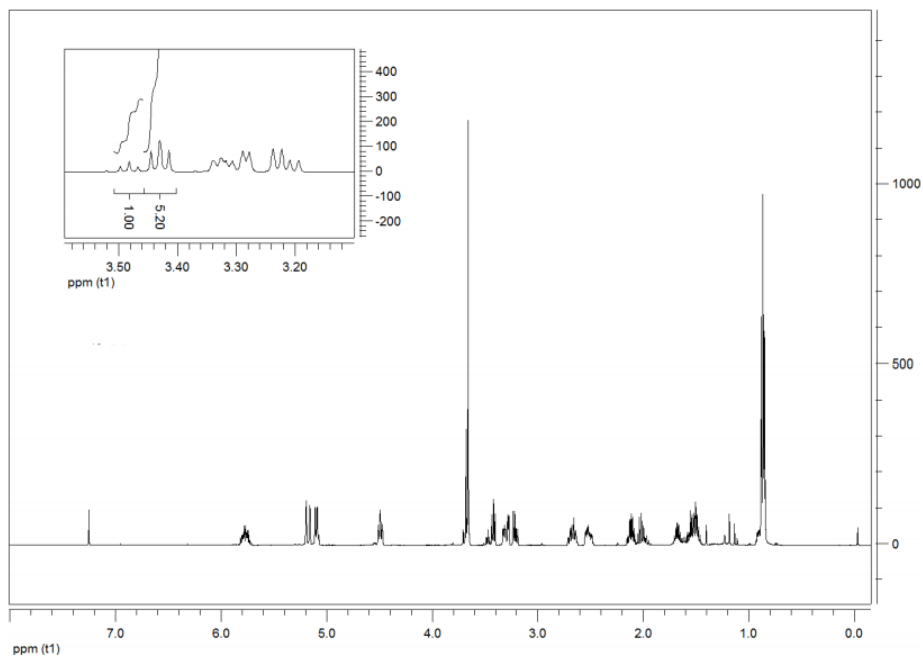
9f/9'f



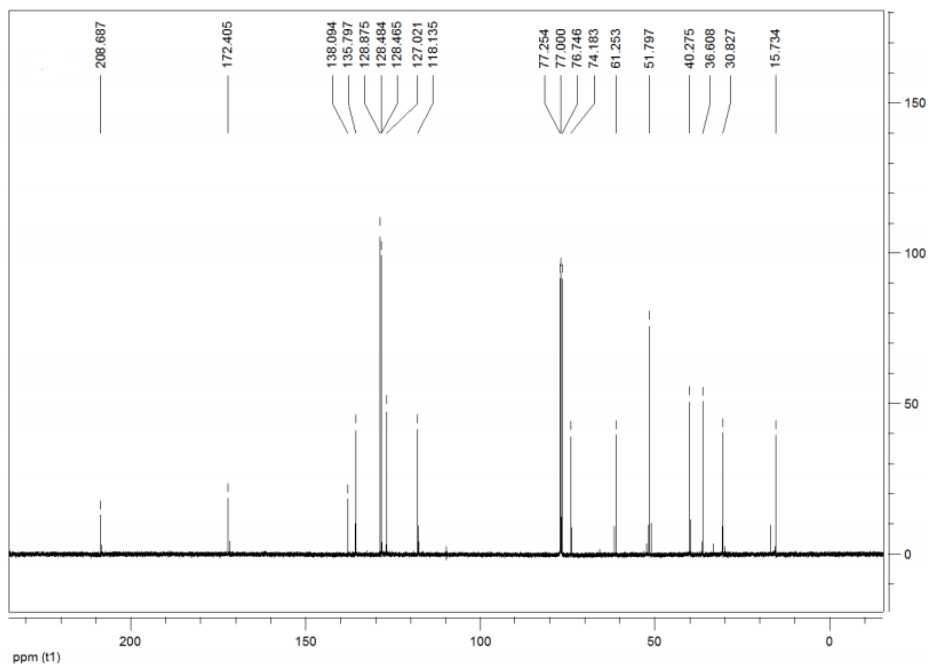
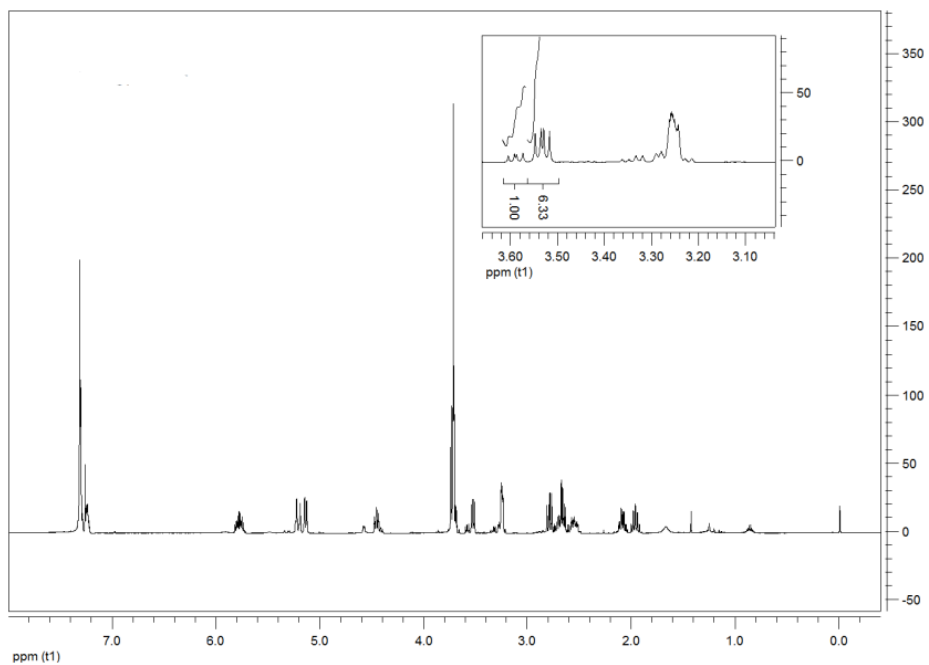
9g/9'g



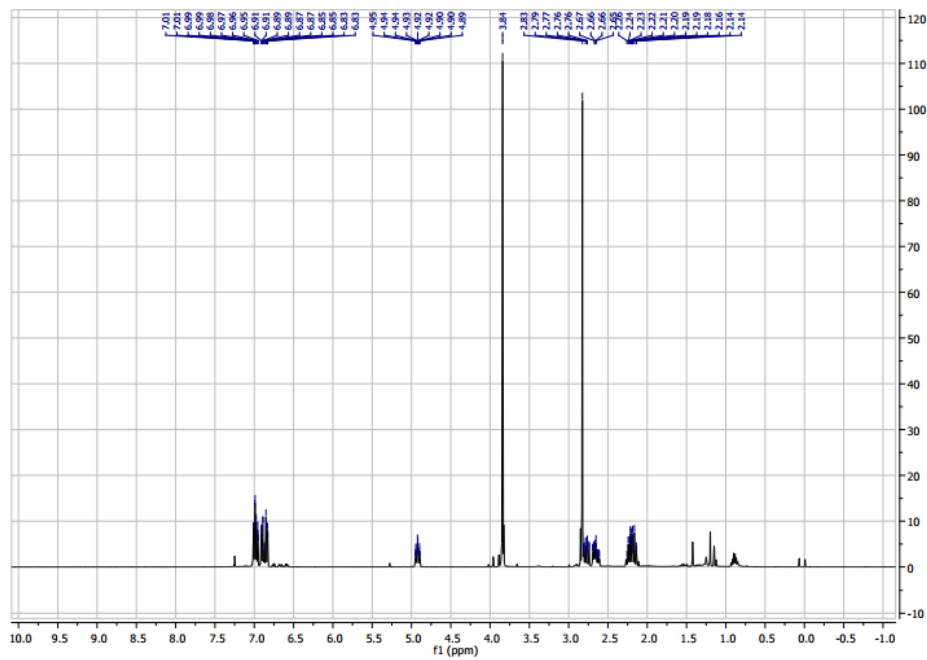
9h/9'h



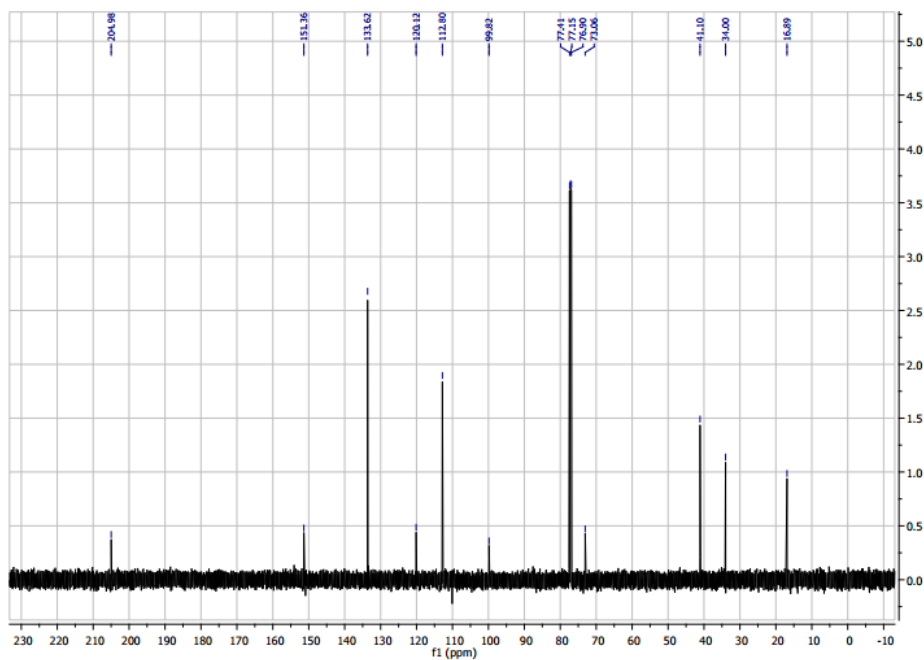
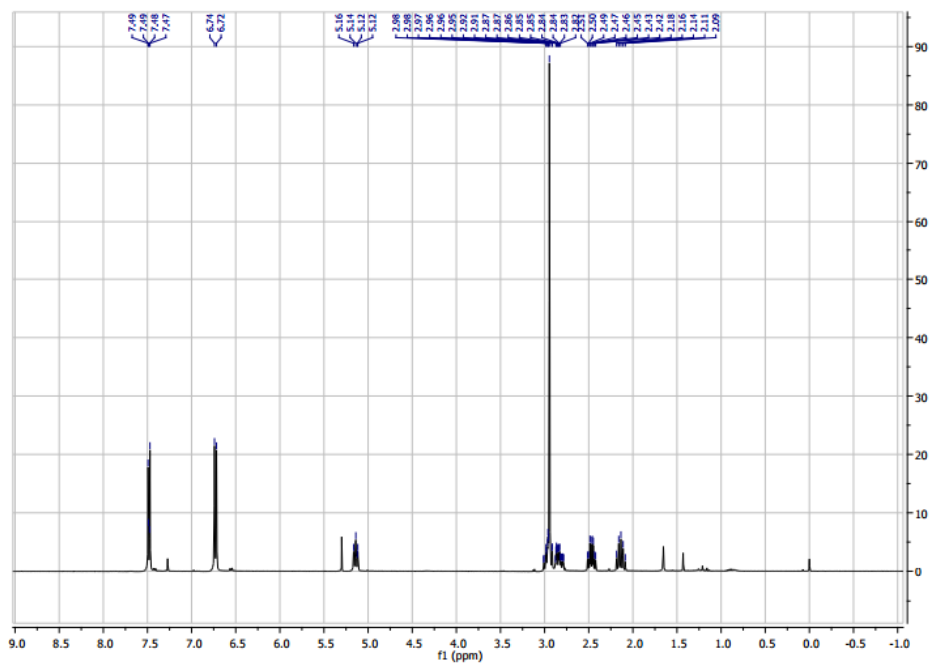
9i/9'i



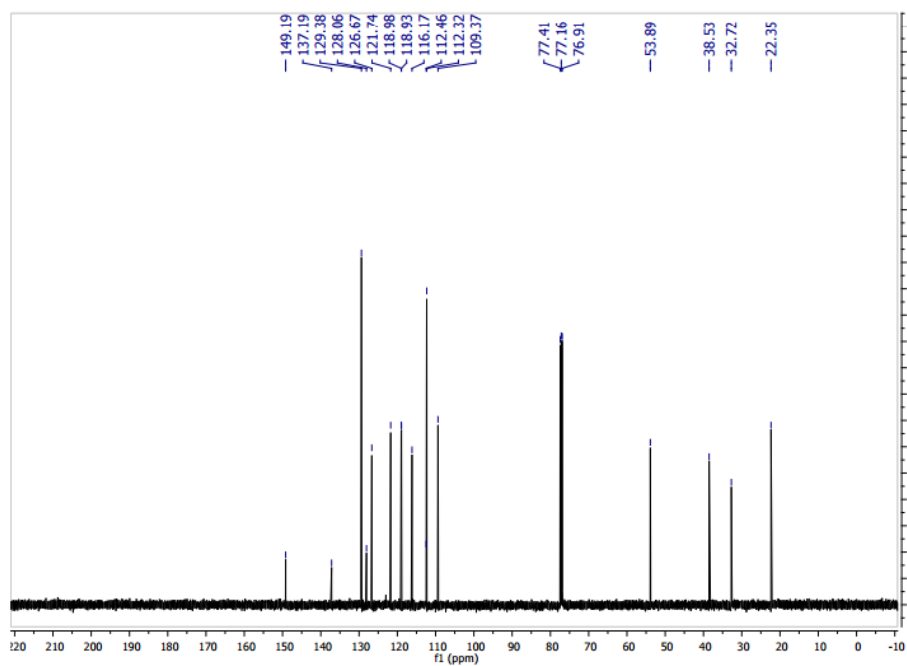
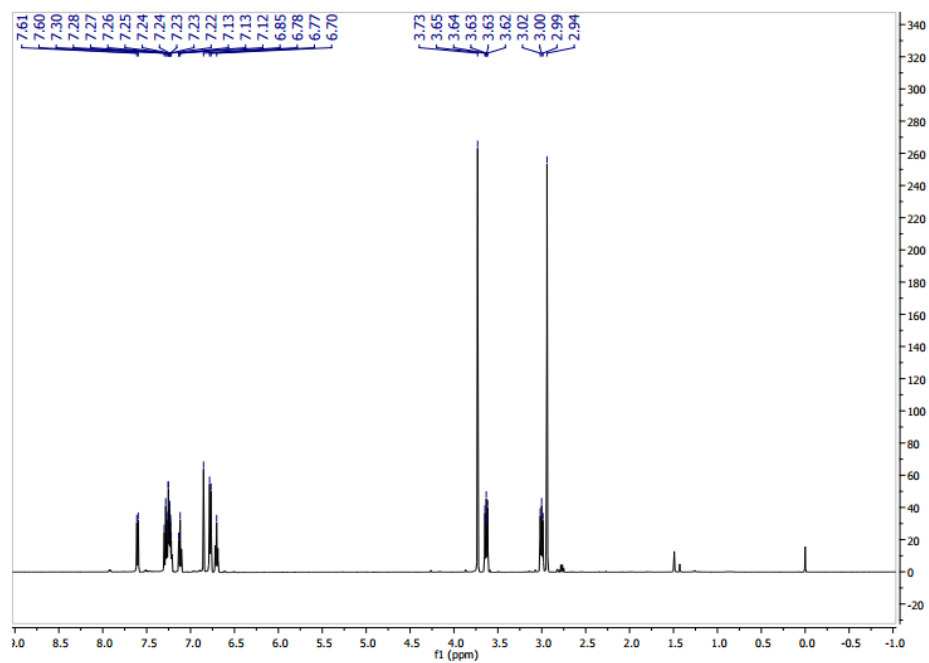
11i



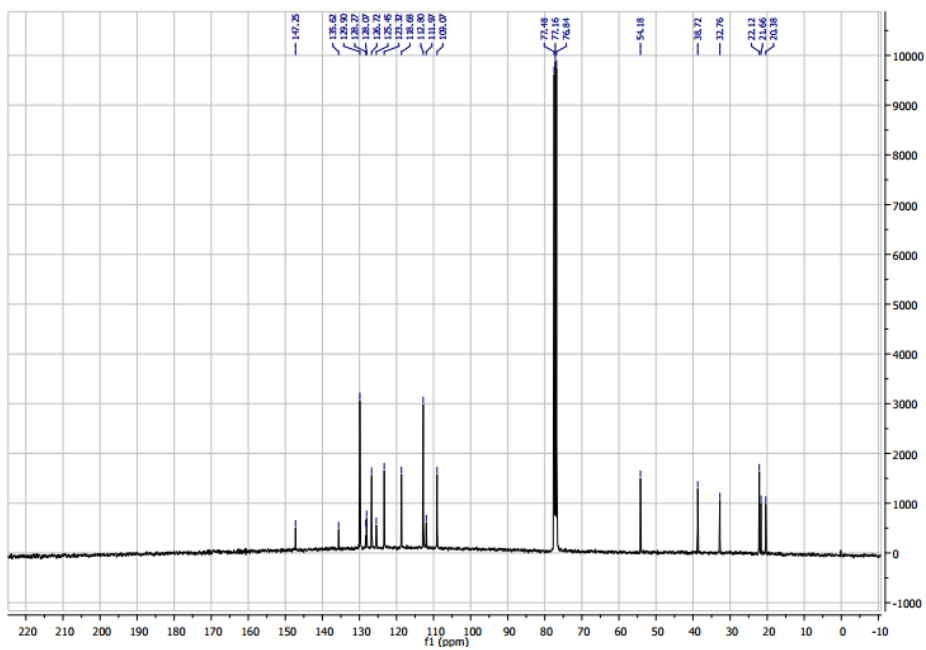
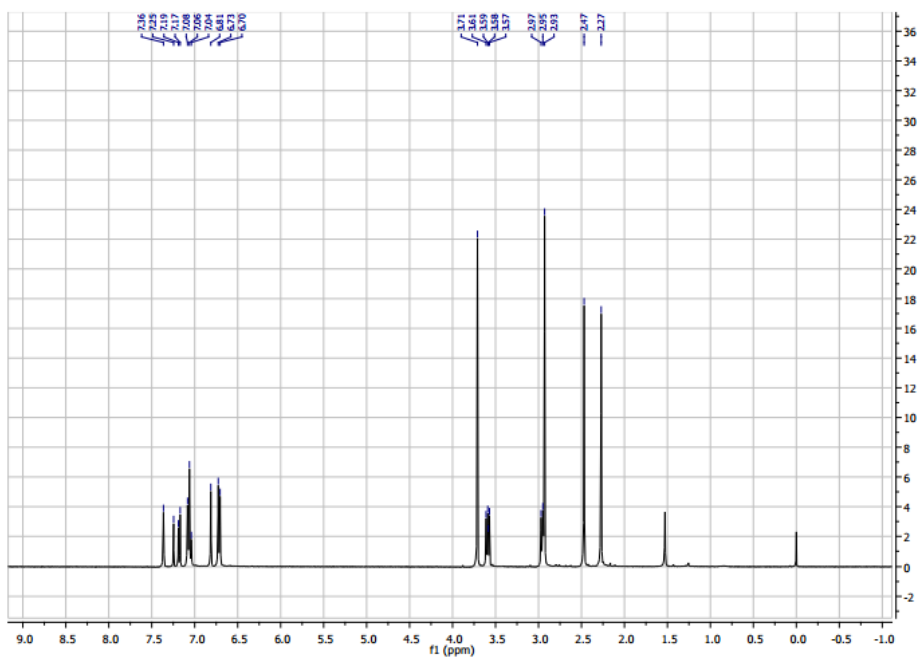
11j



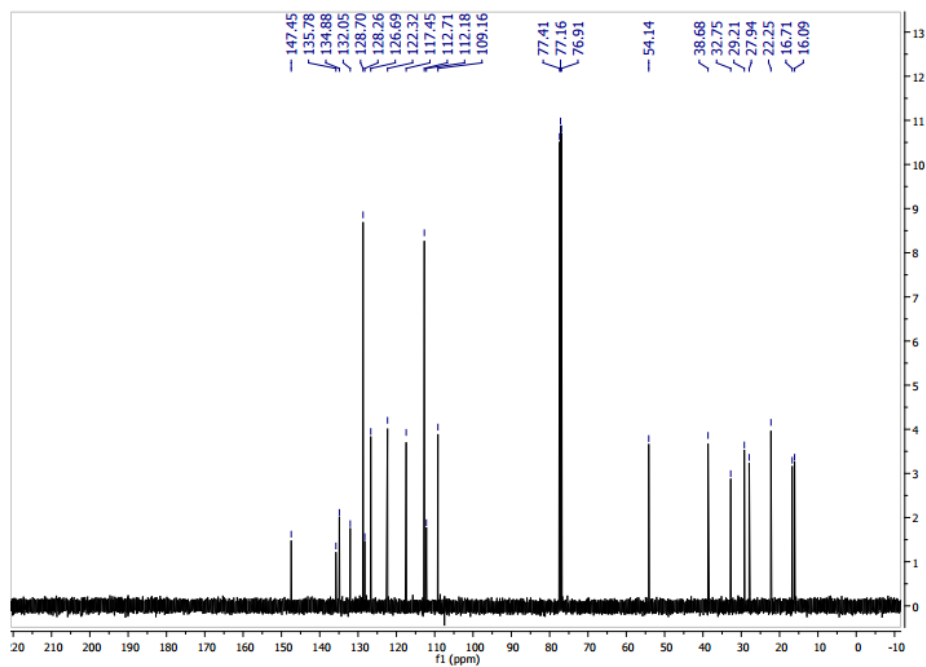
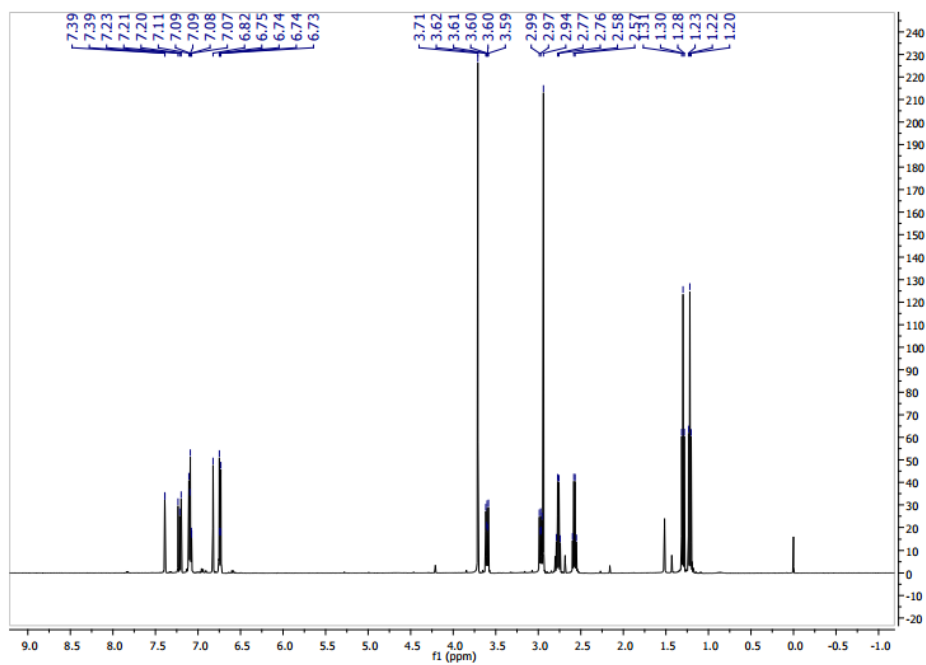
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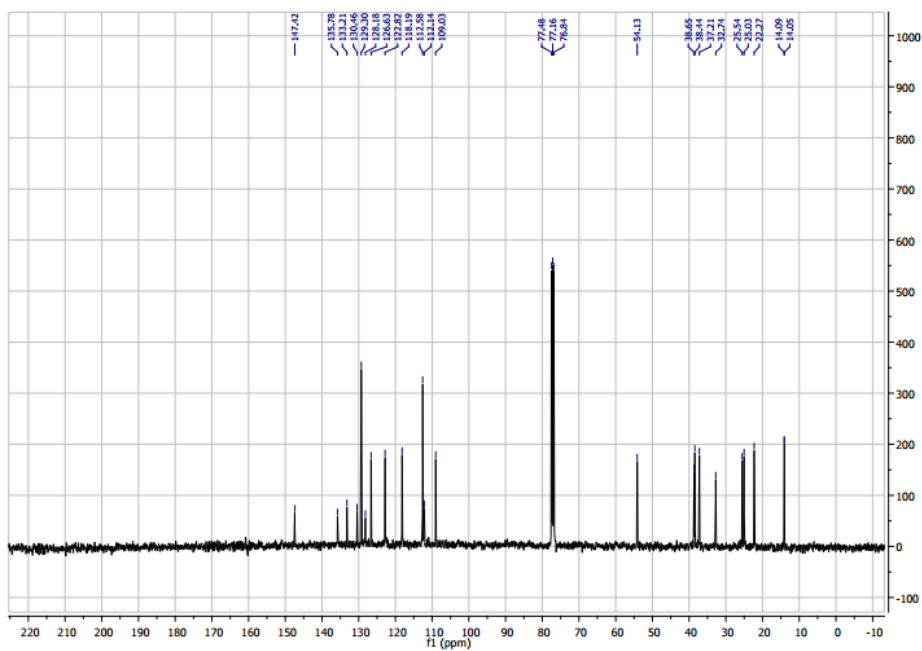
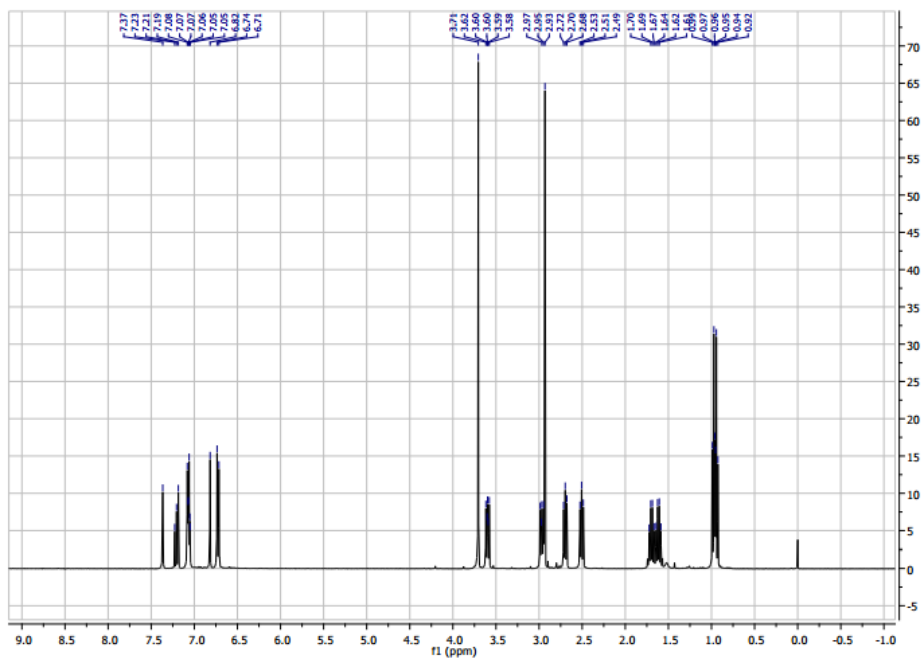
12b



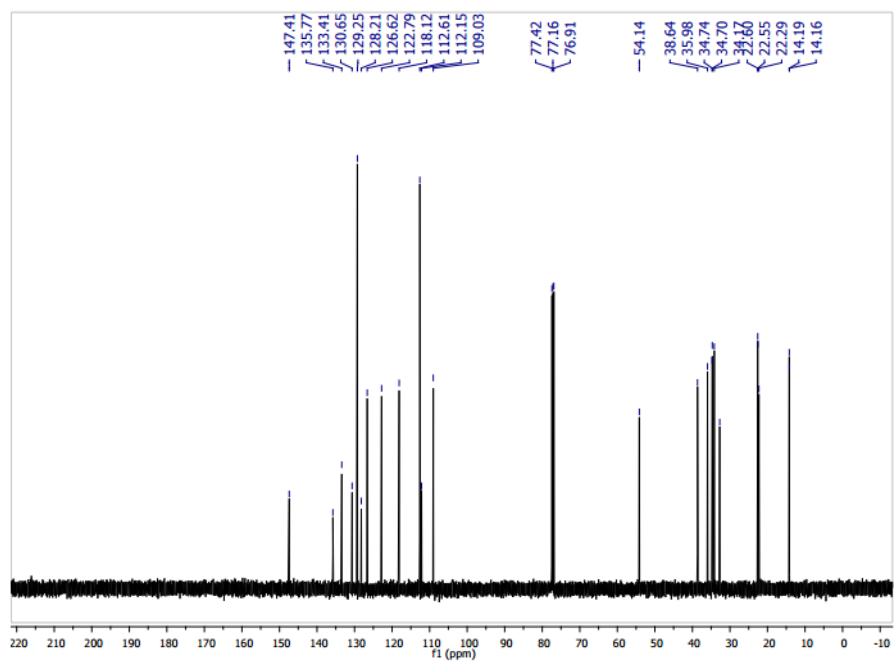
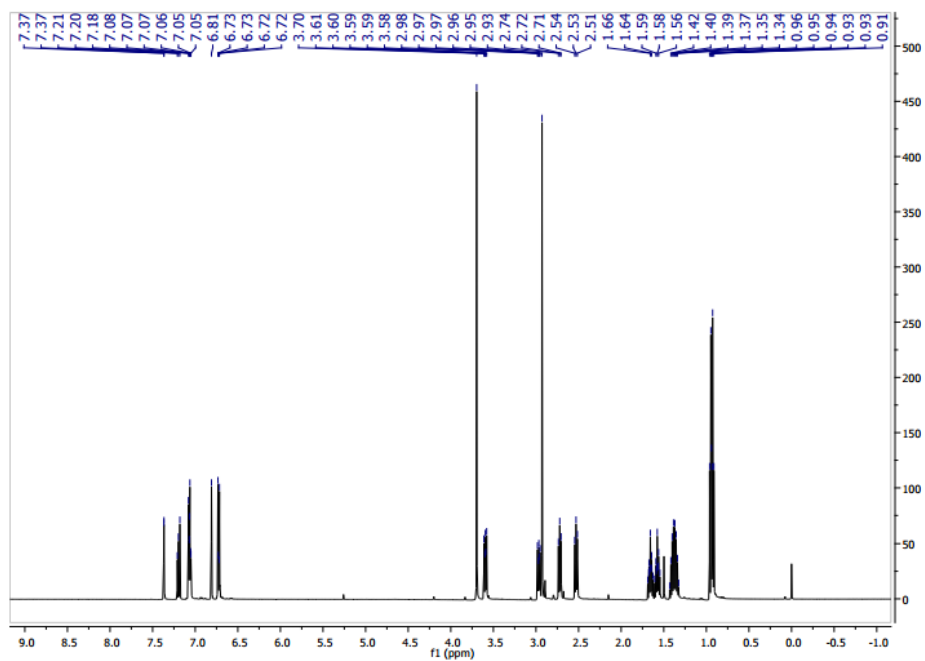
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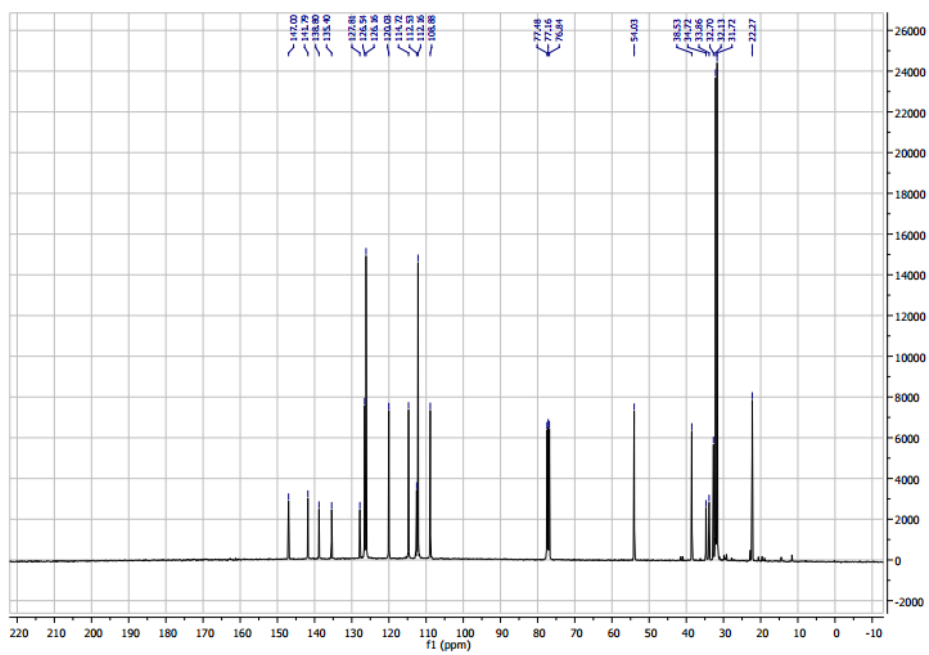
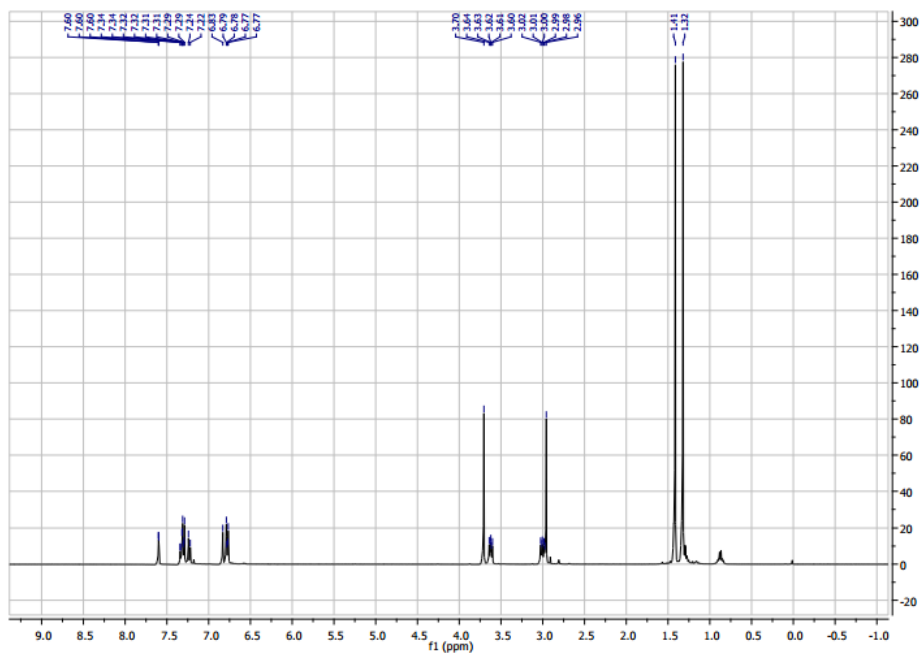
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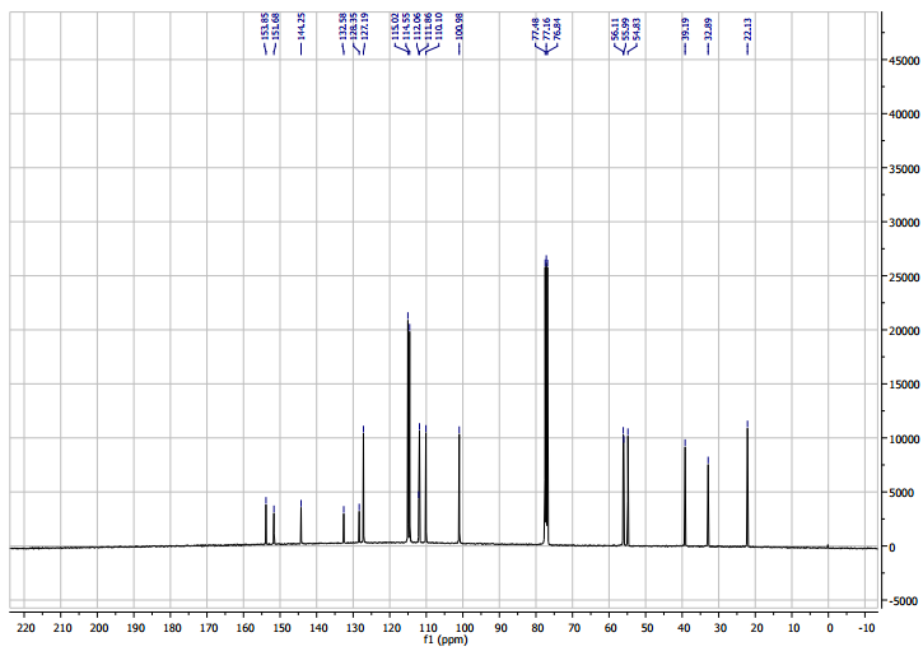
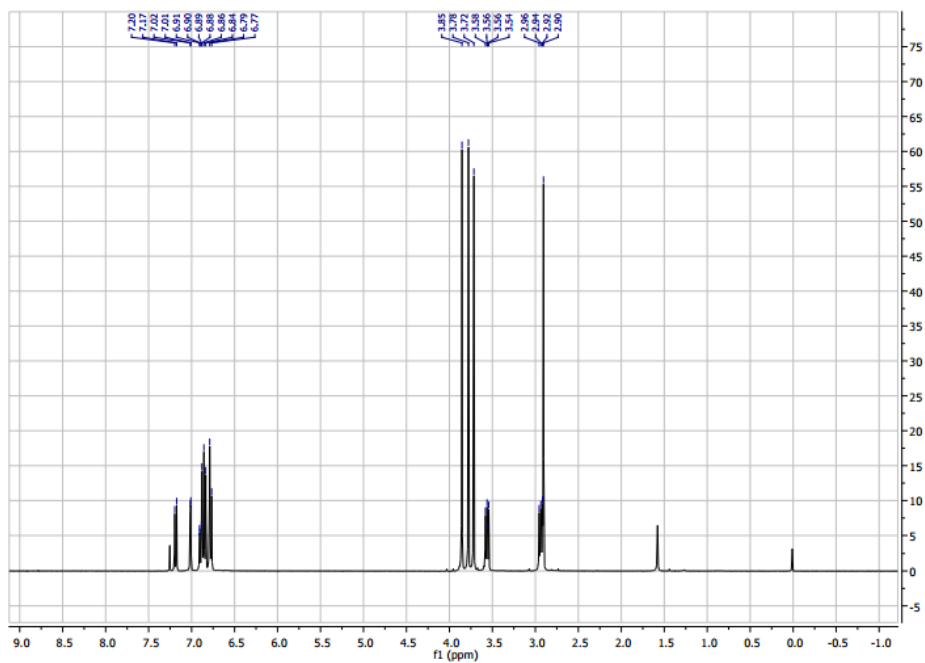
12e



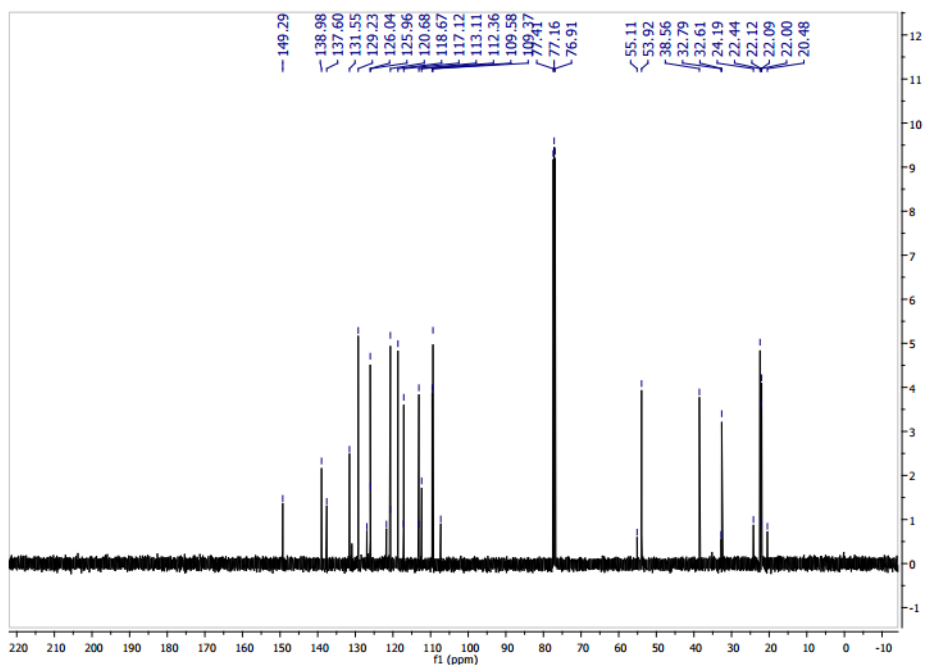
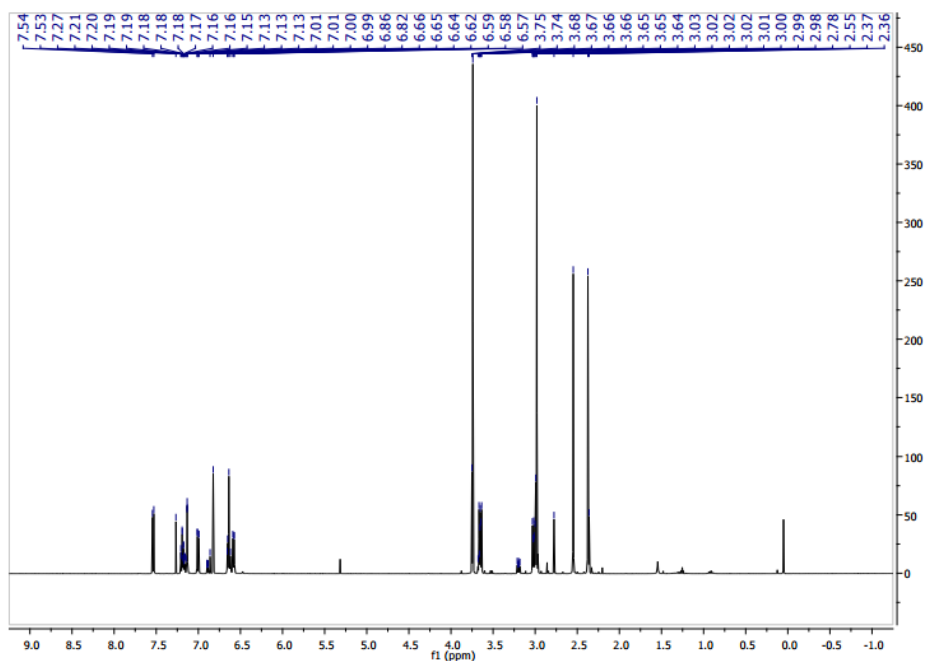
12f



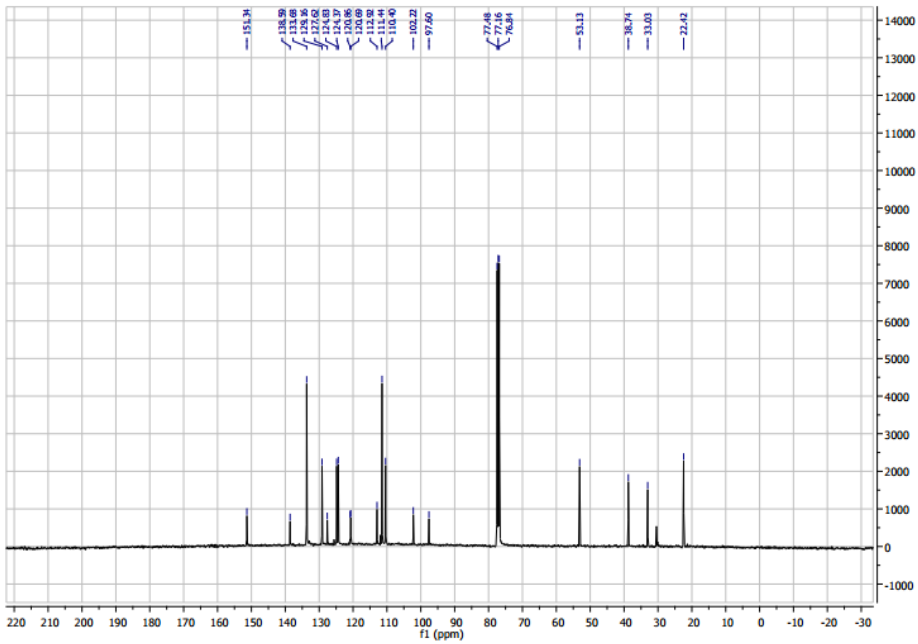
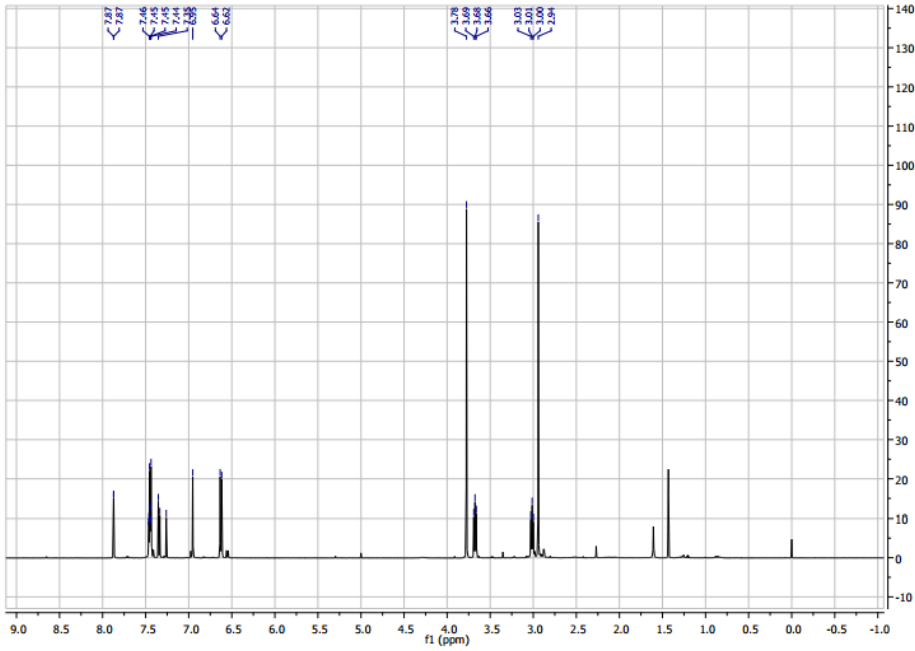
12g



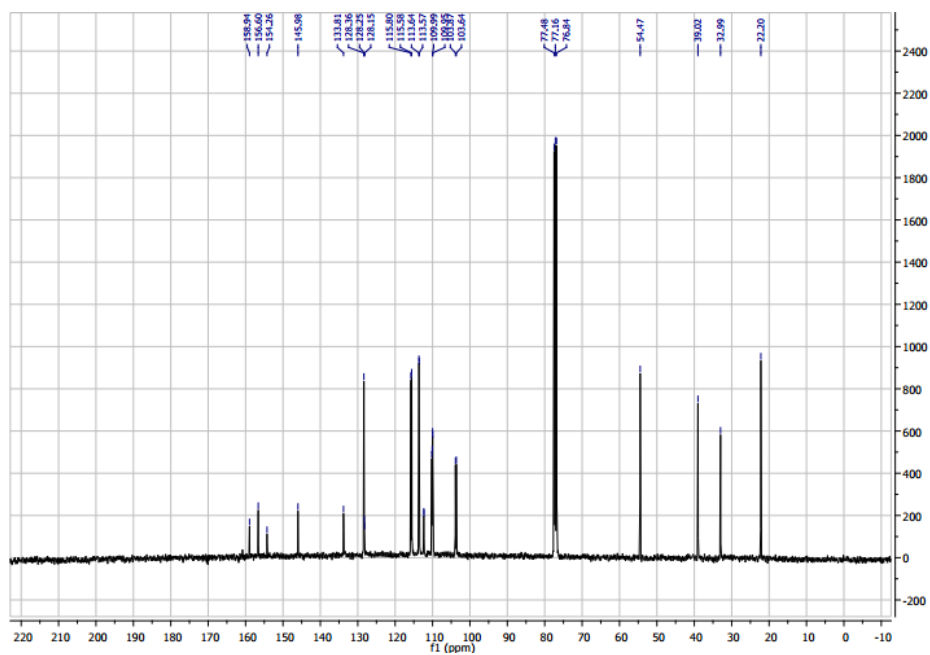
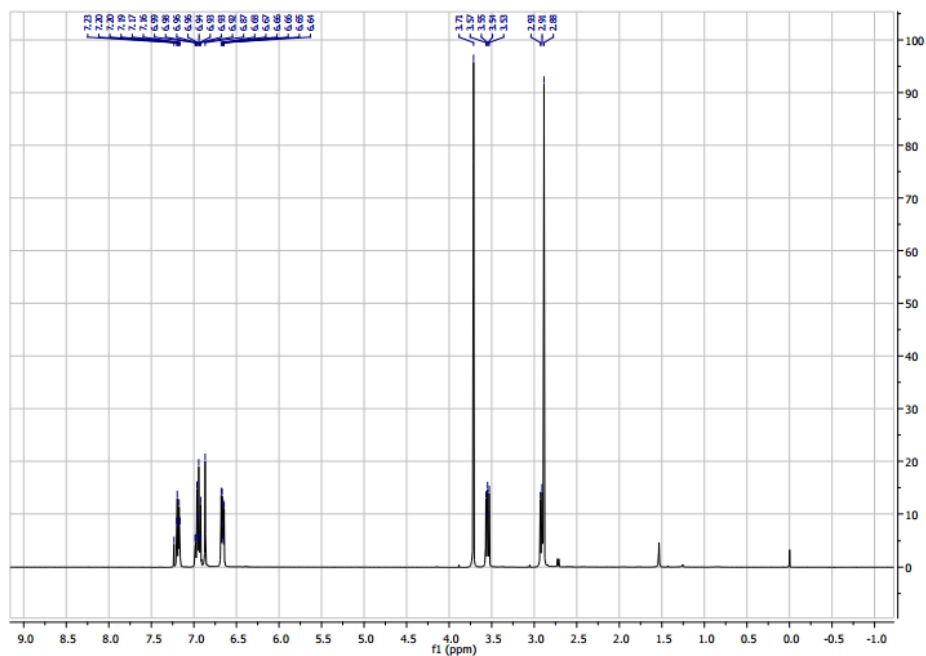
12h+12h'



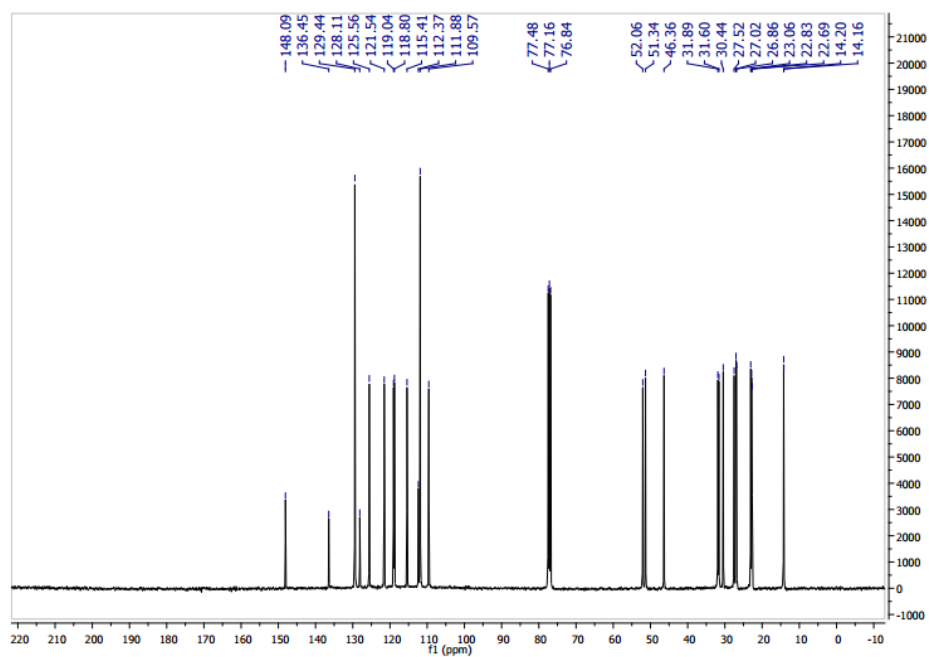
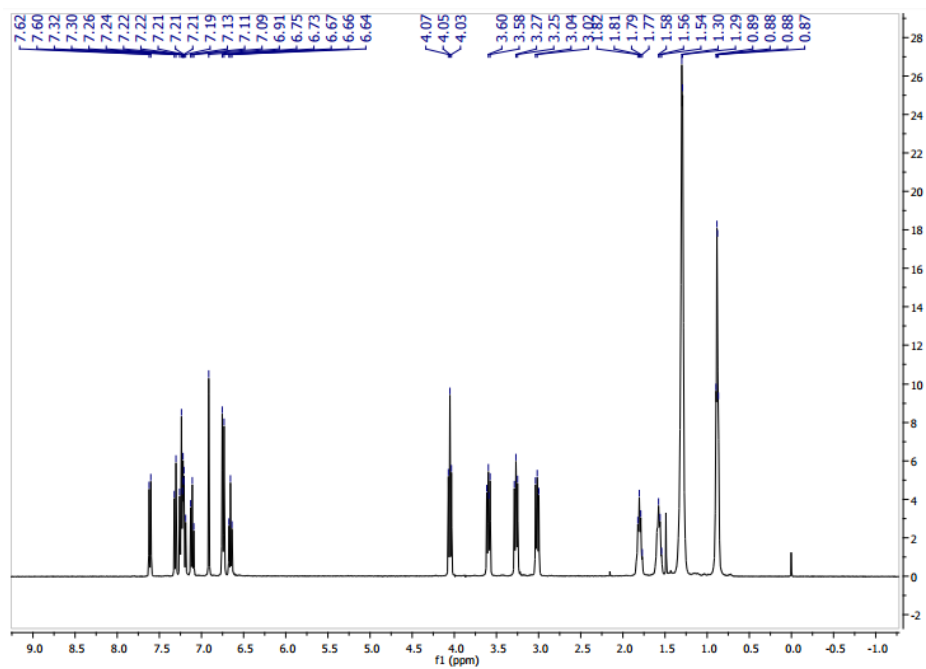
12j



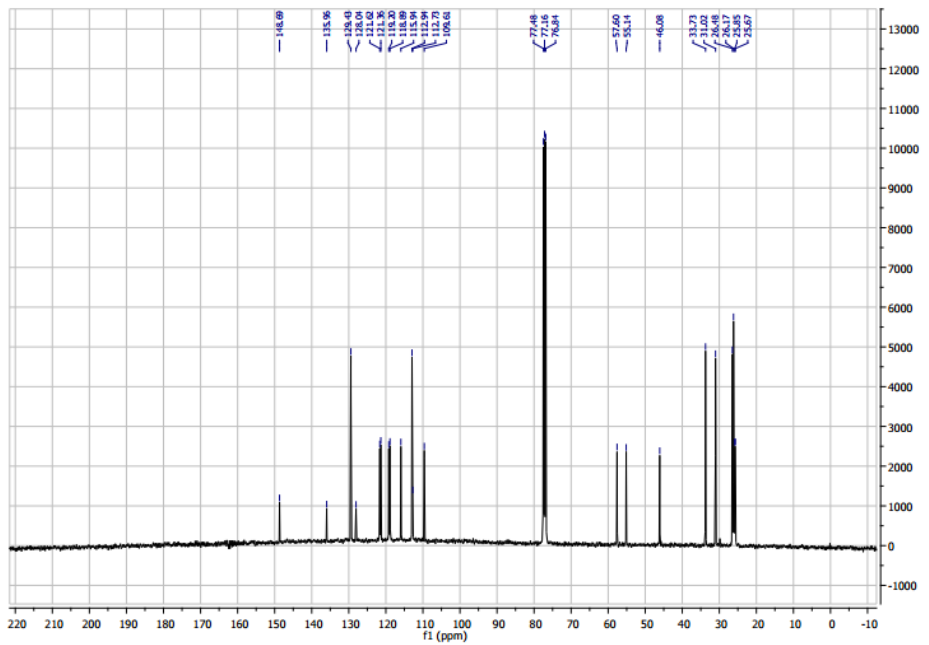
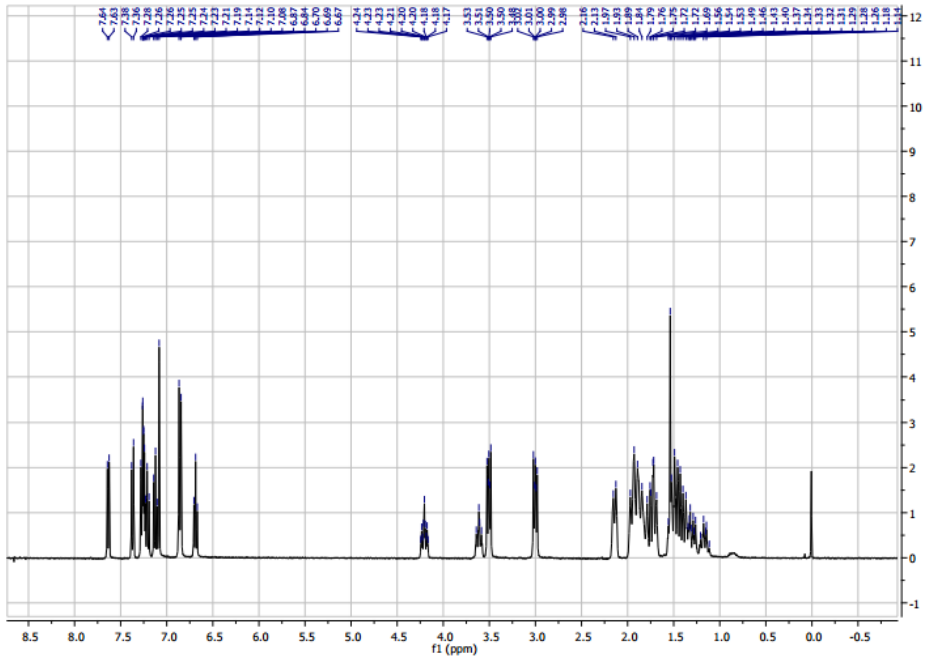
12k



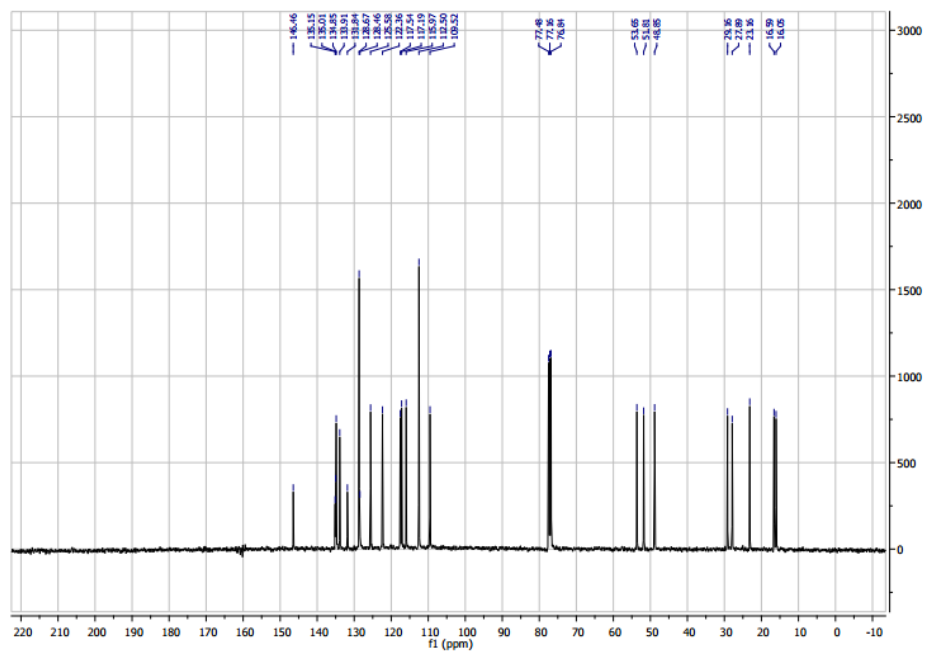
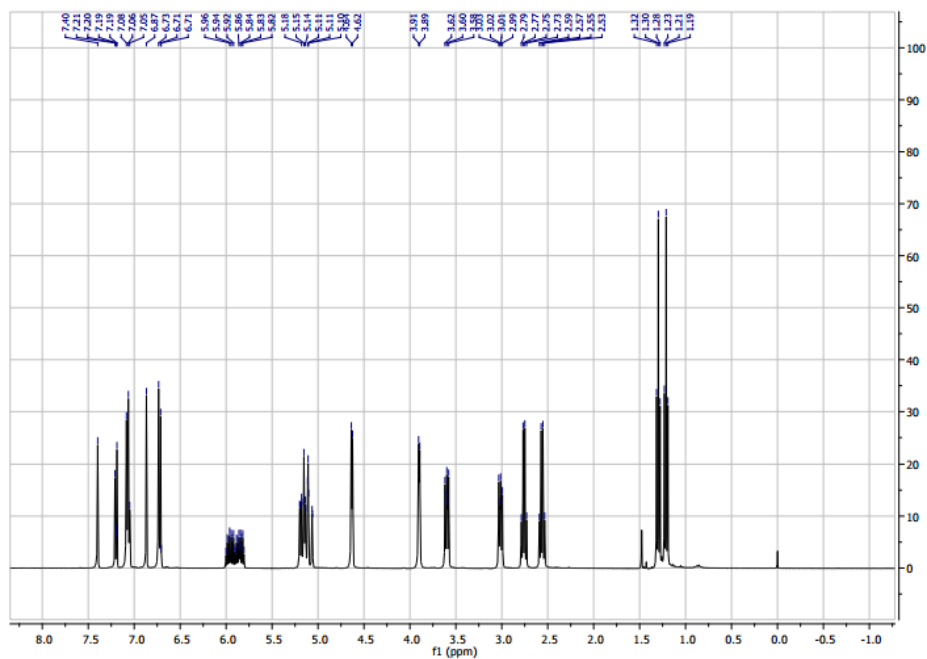
121



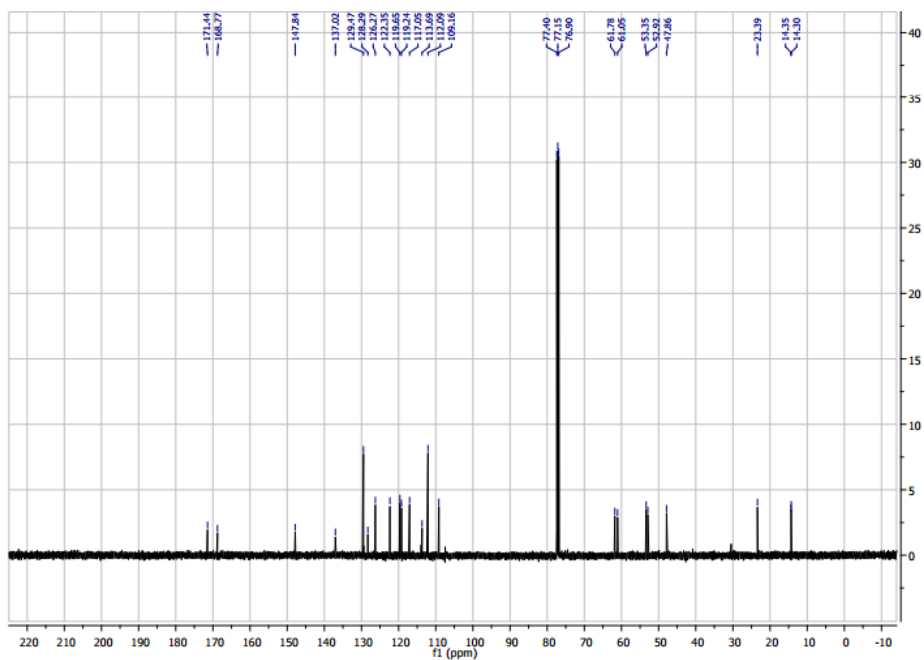
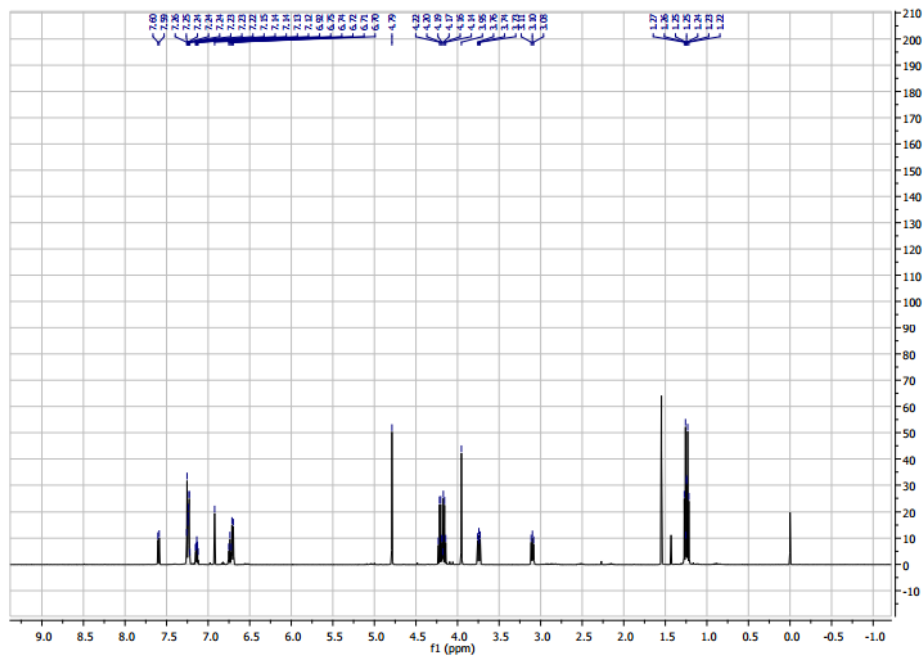
12m



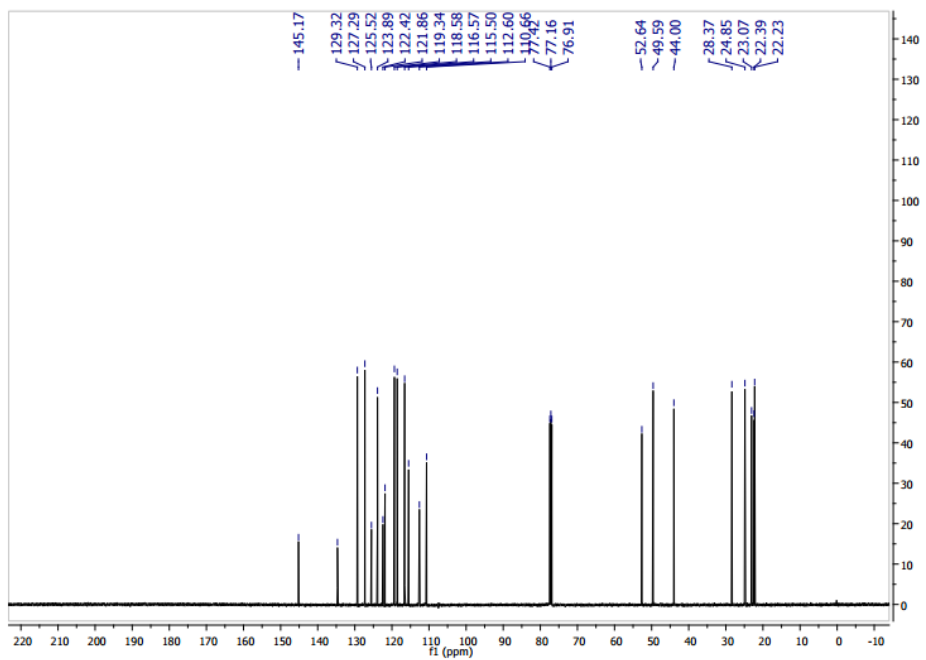
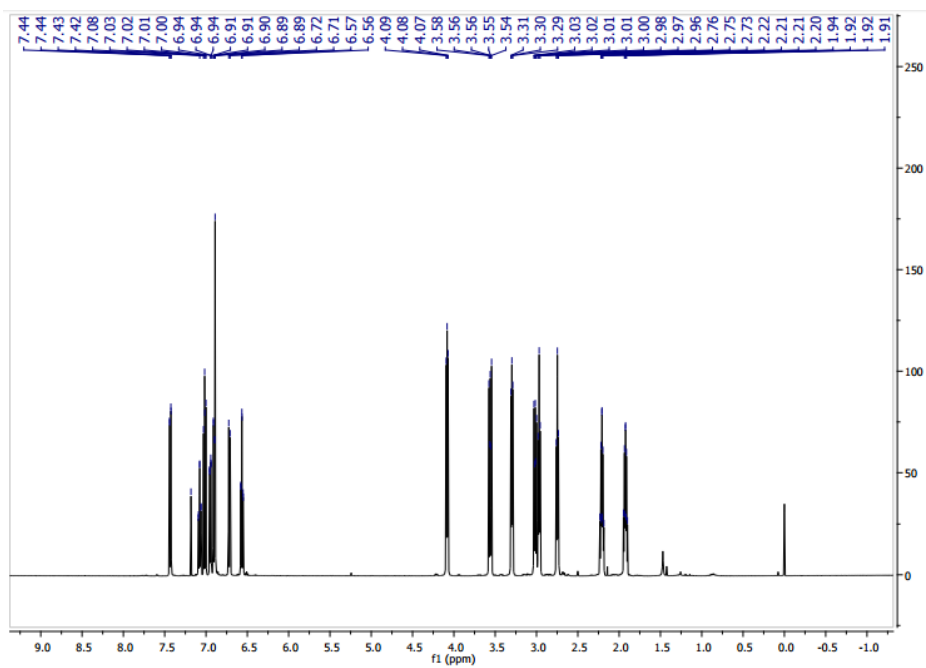
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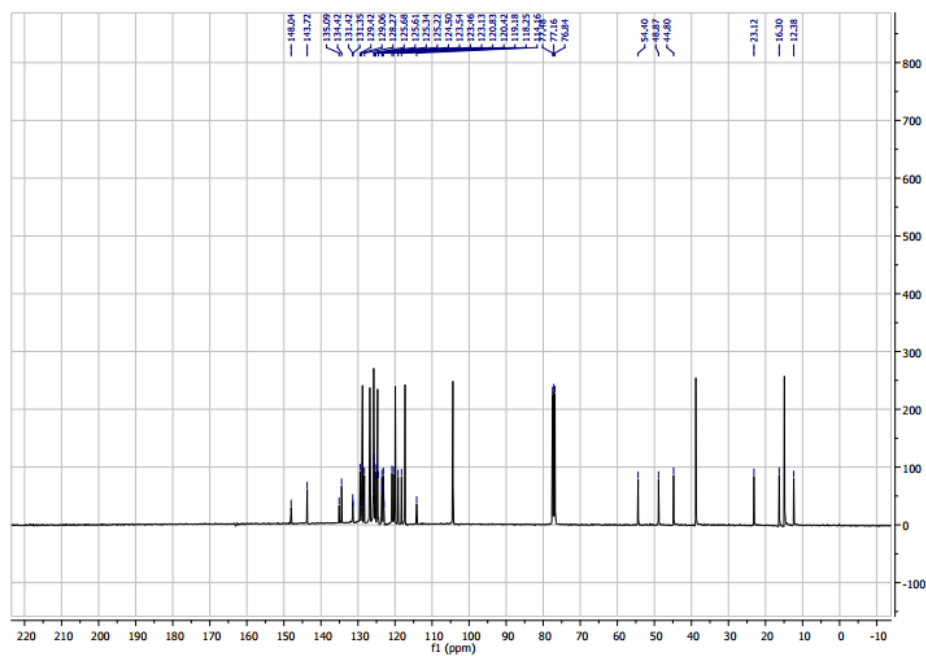
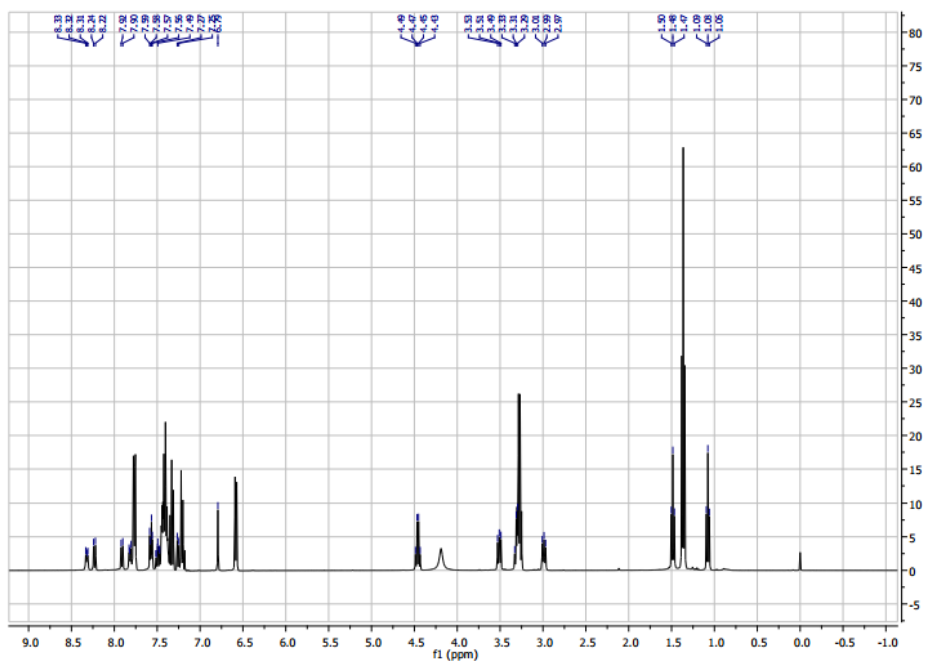
12o

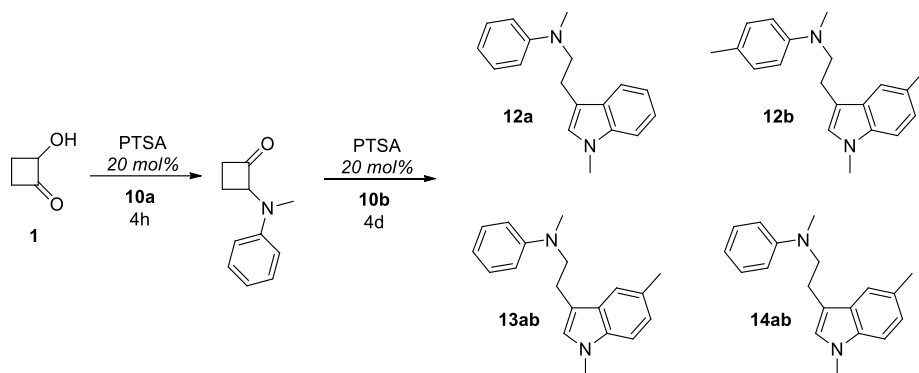


12p

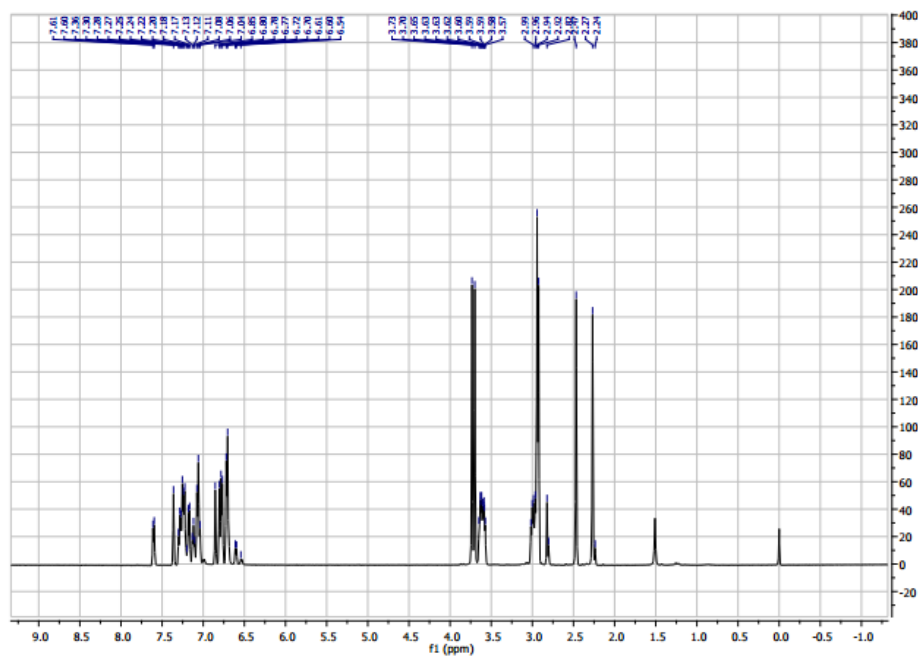


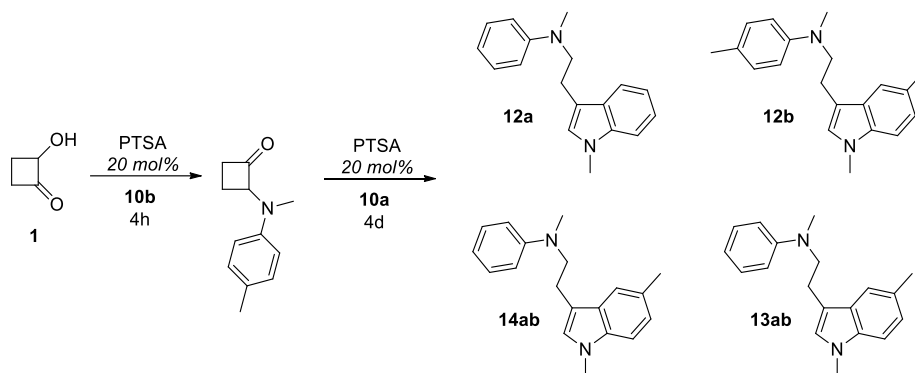
12q



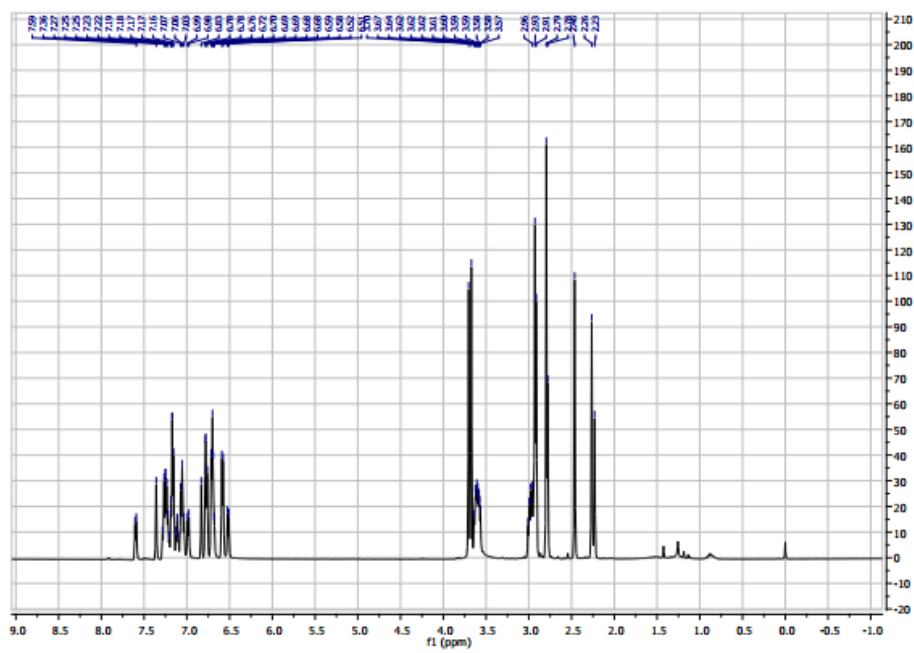


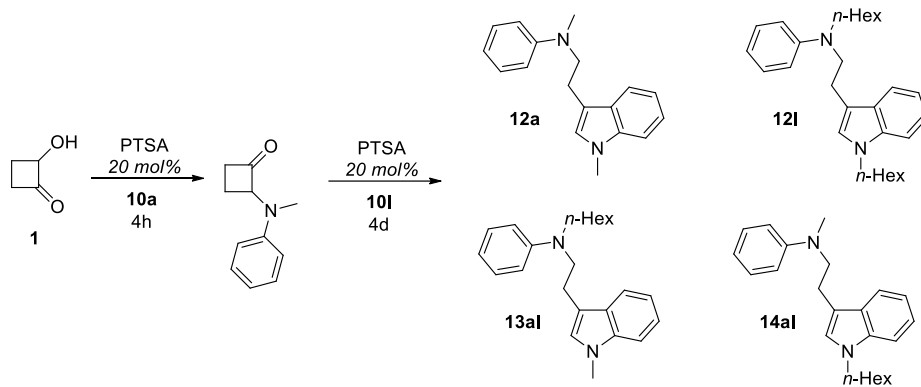
$^1\text{H-NMR}$ of the inseparable reaction products



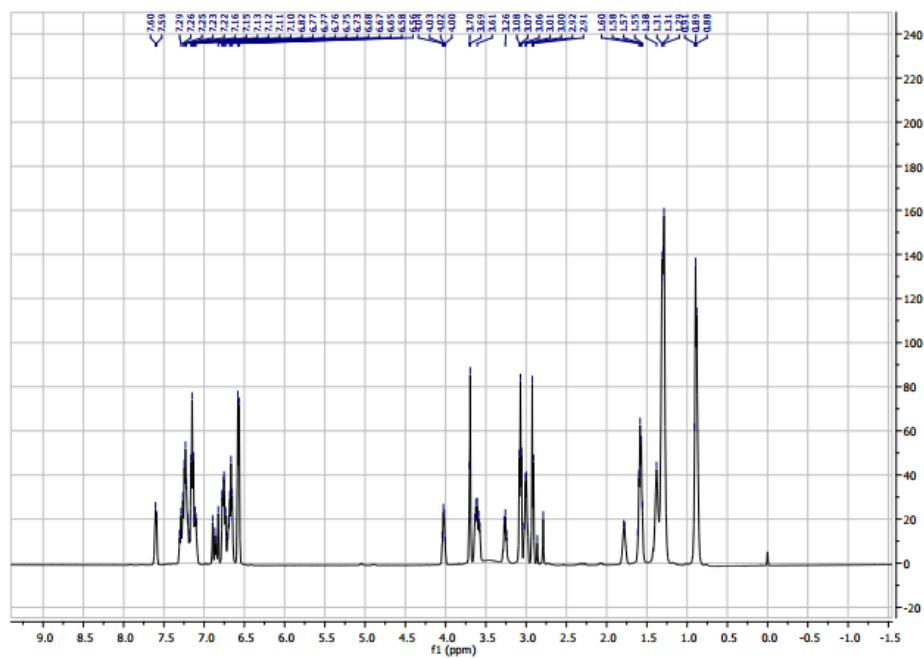


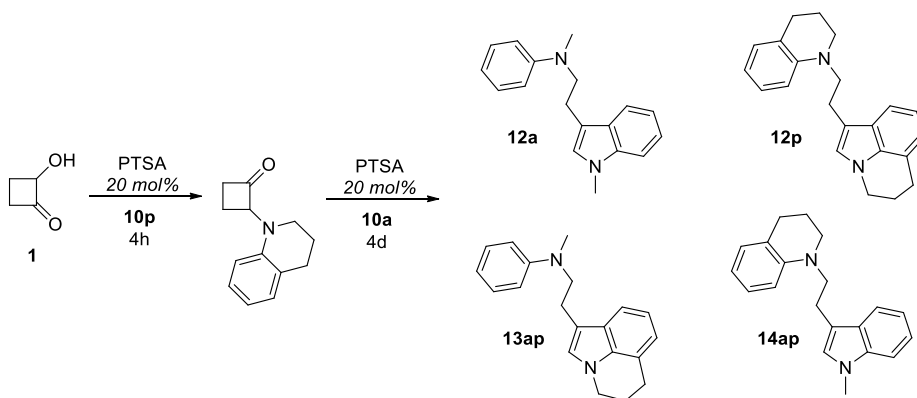
¹H-NMR of the inseparable reaction products



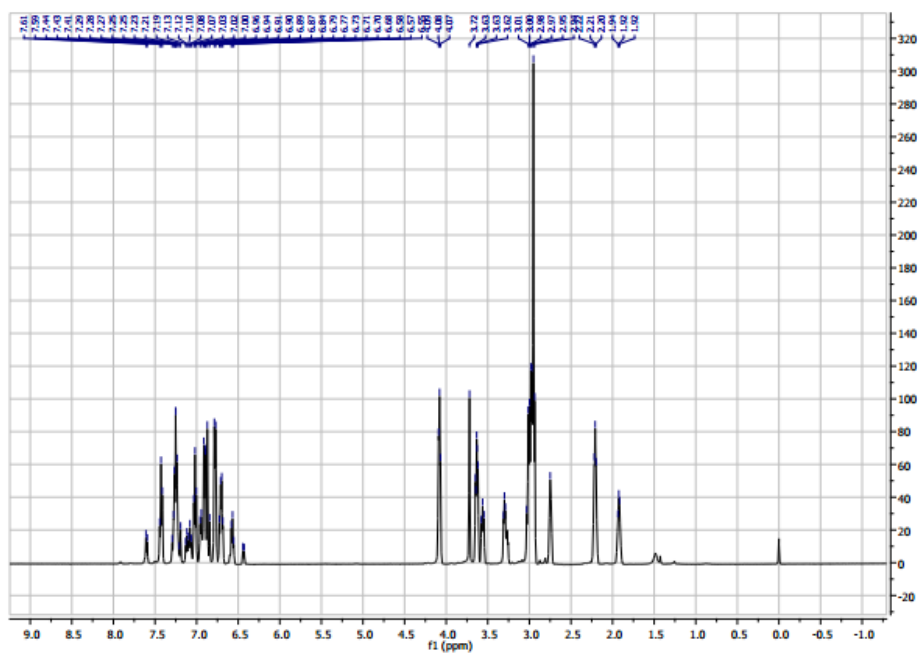


$^1\text{H-NMR}$ of the inseparable reaction products

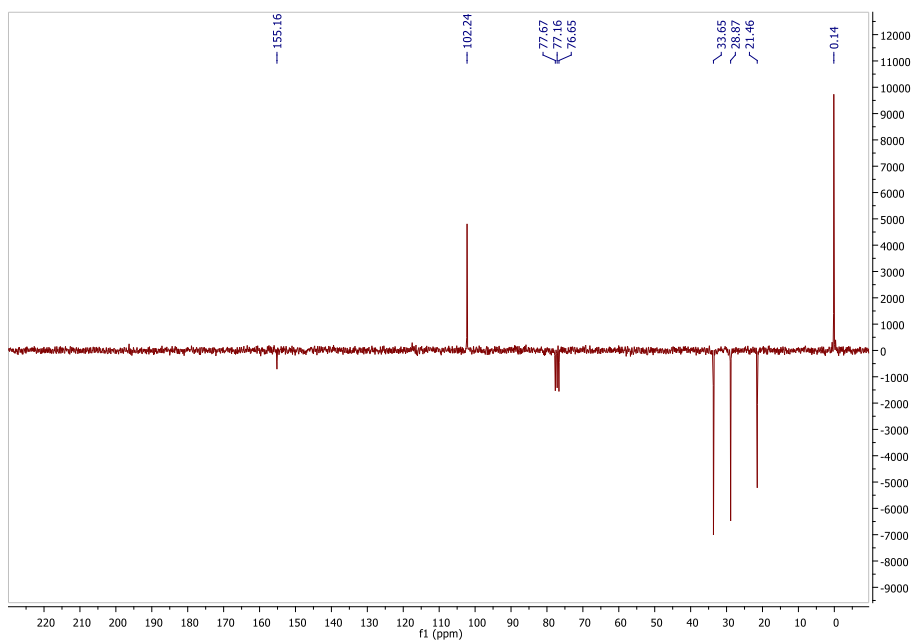
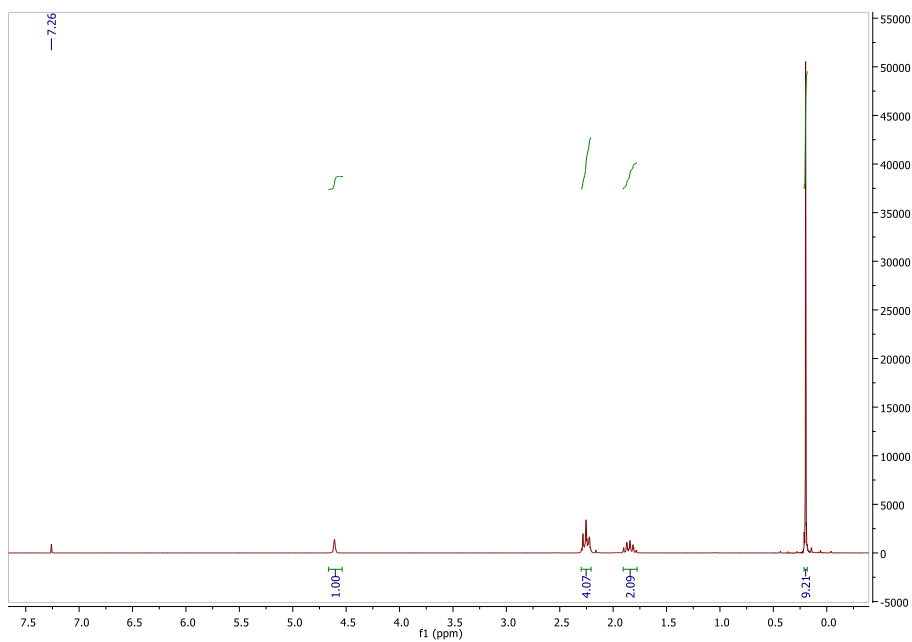




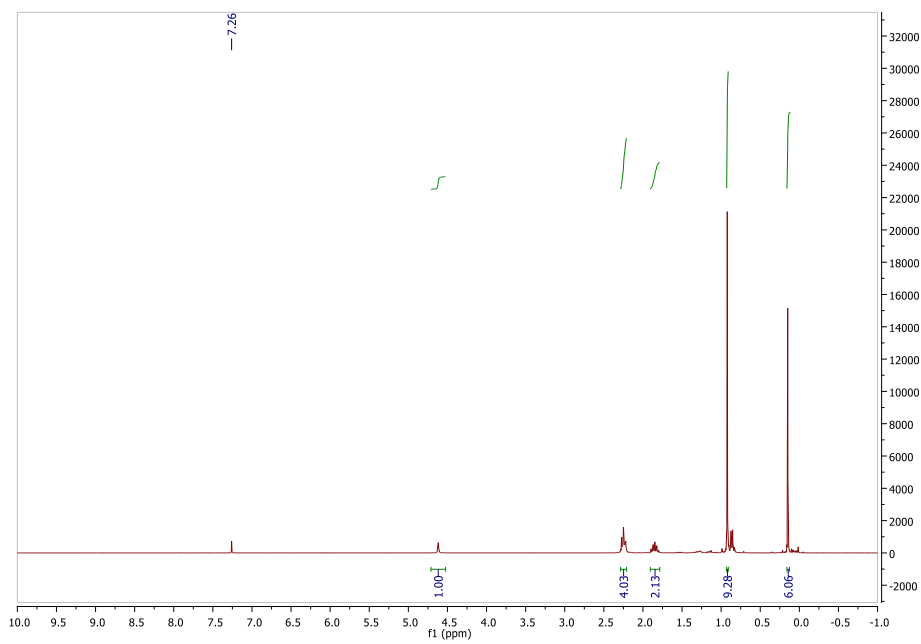
¹H-NMR of the inseparable reaction products



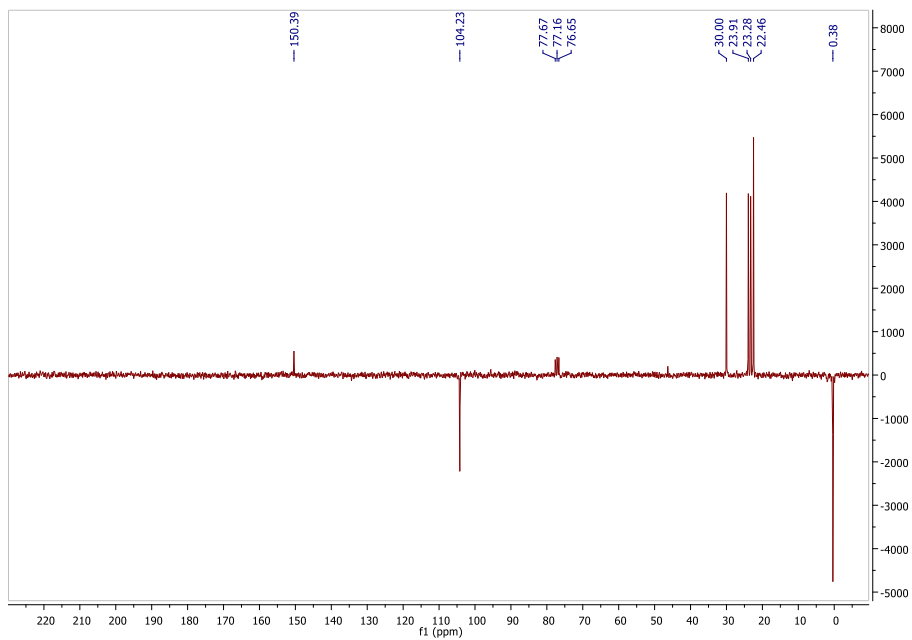
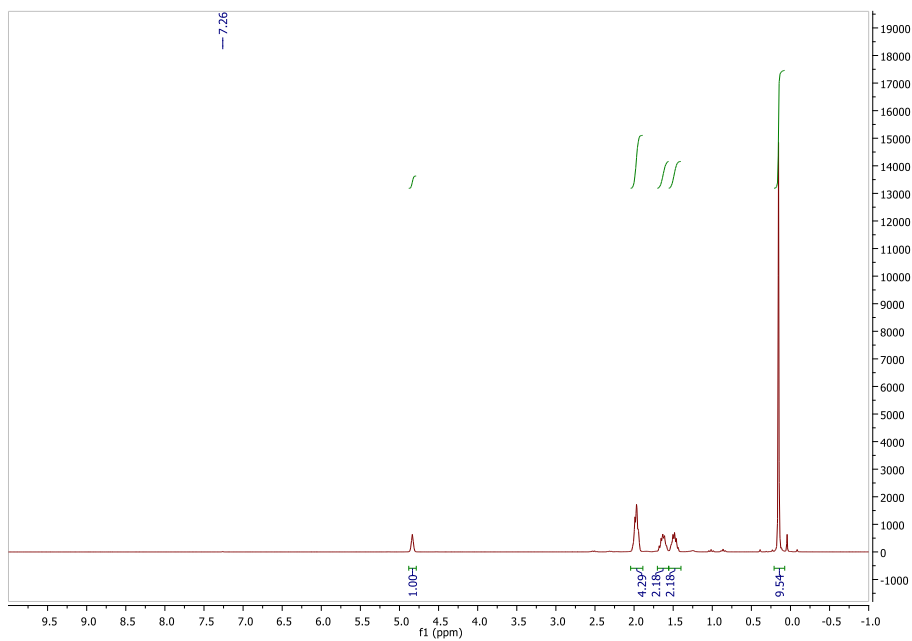
15a



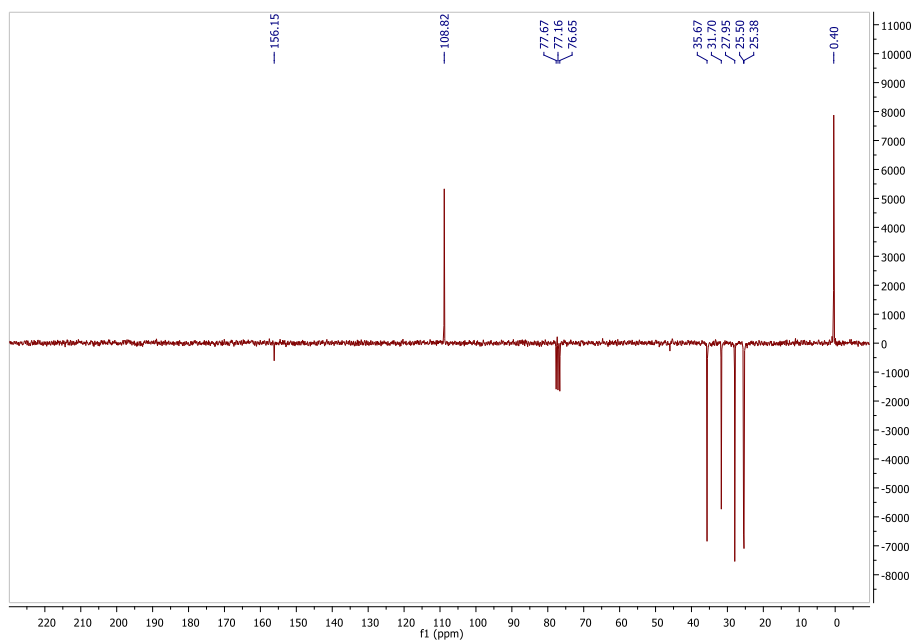
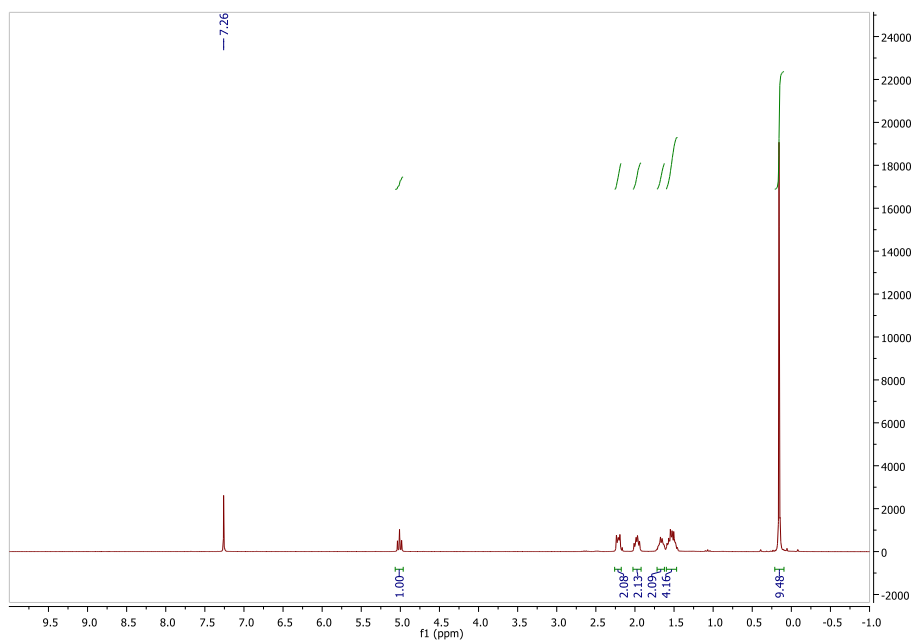
15b

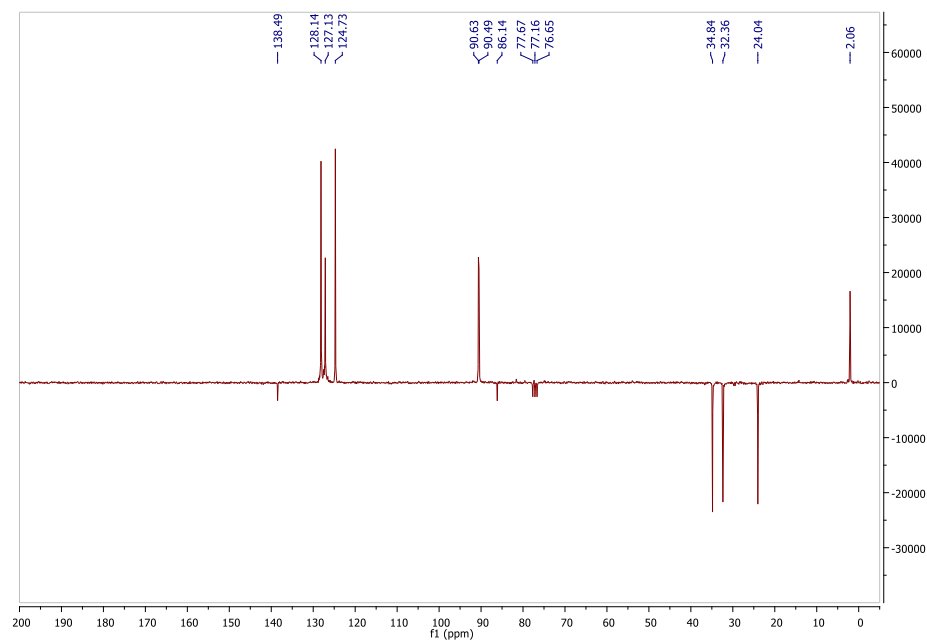
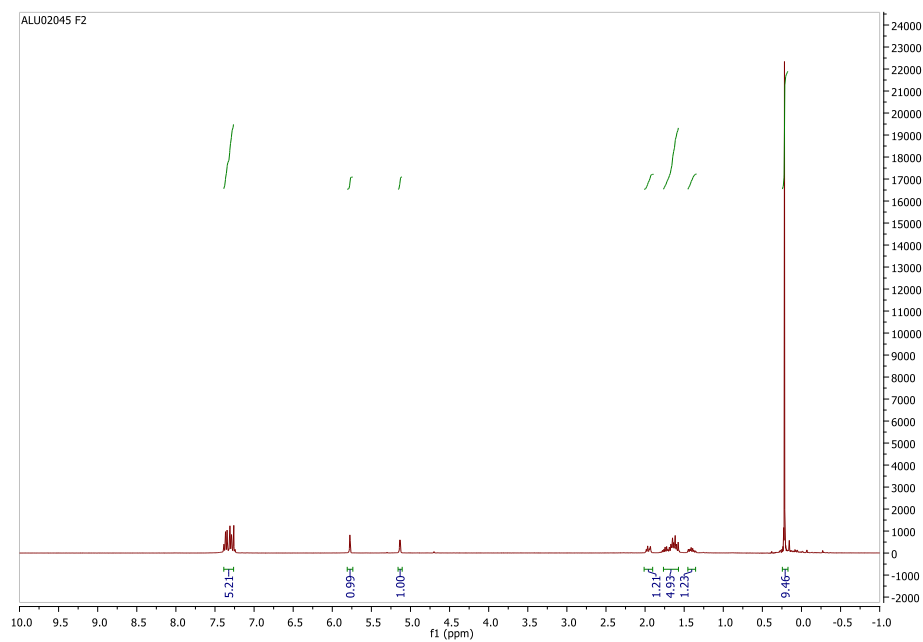


15c

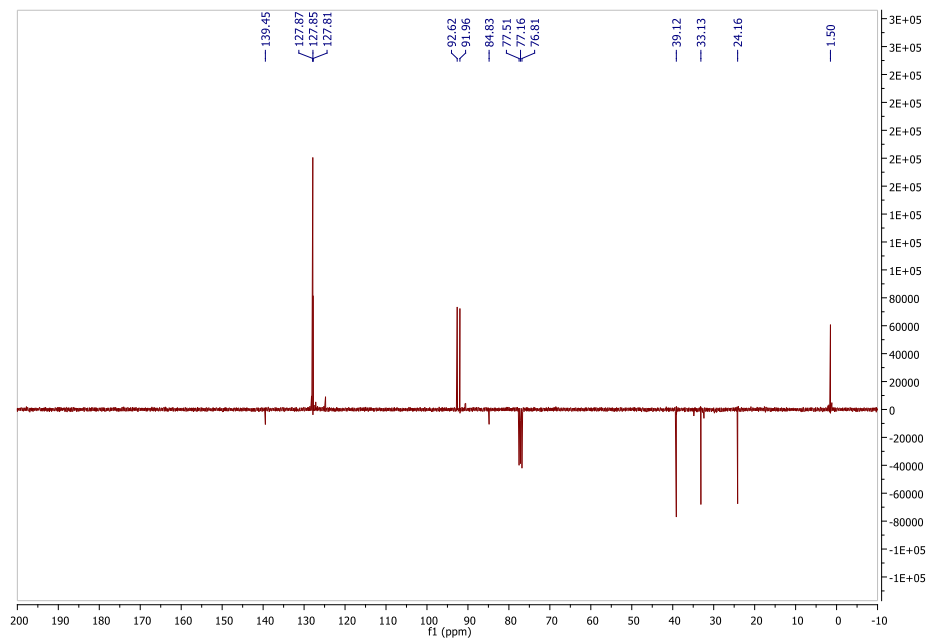
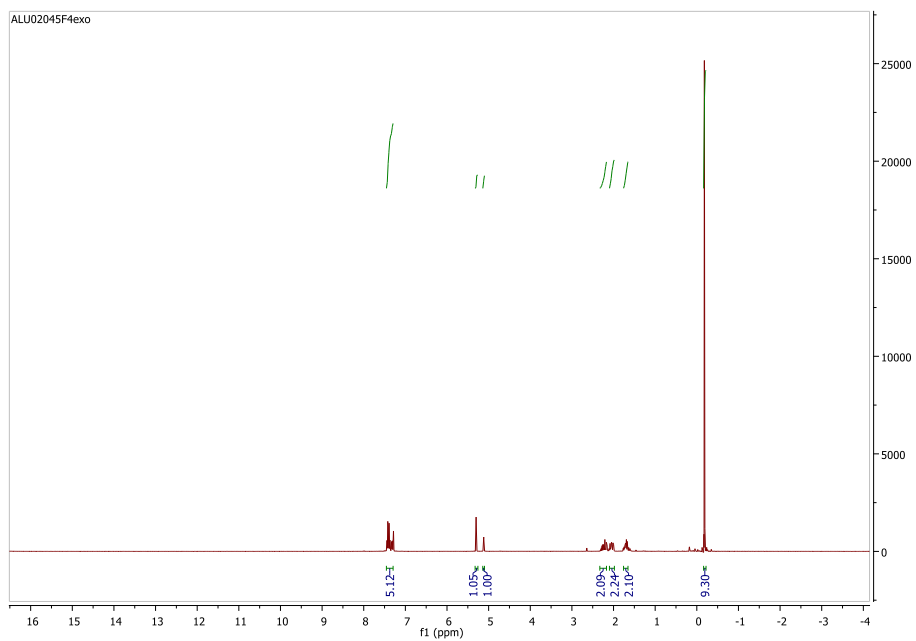


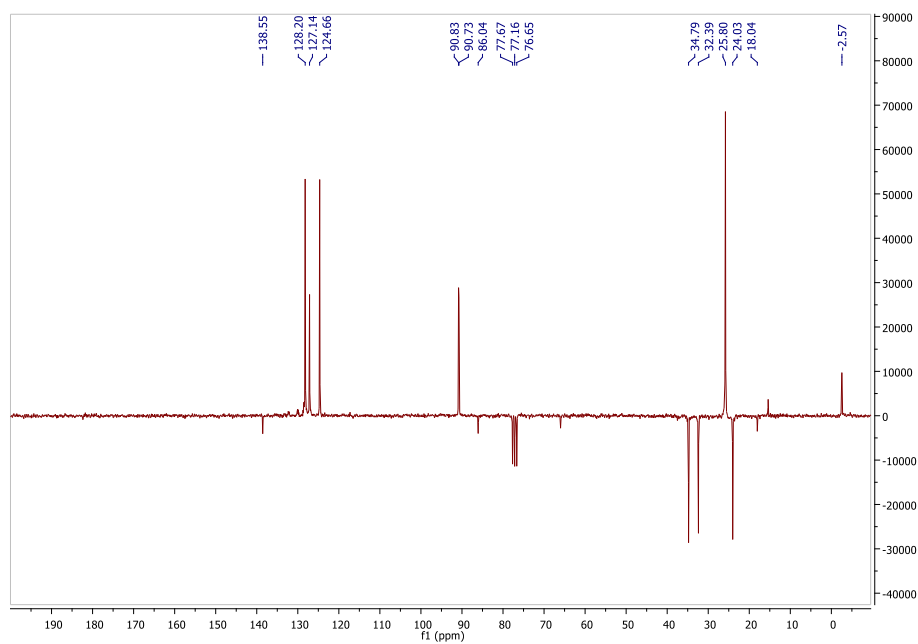
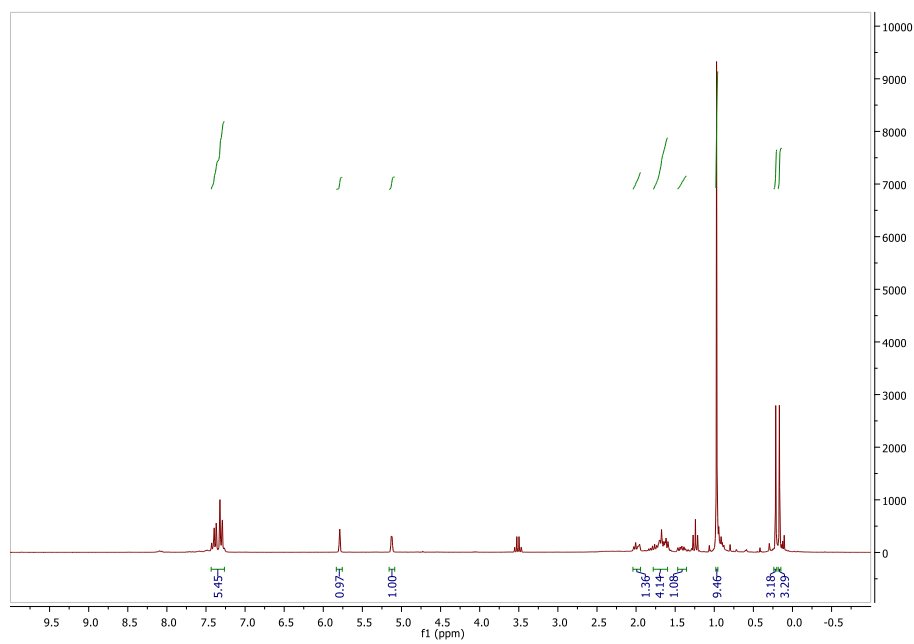
15d



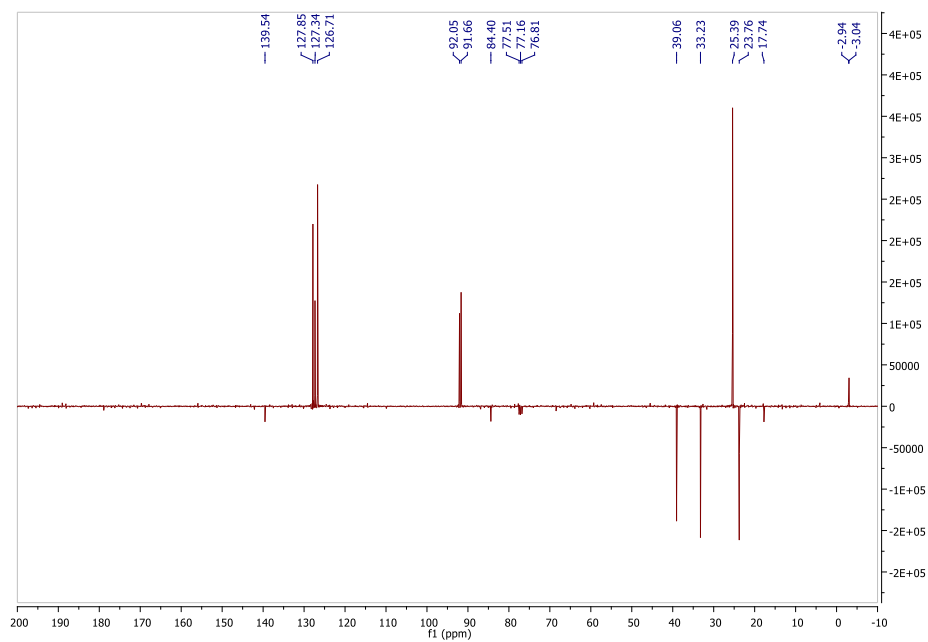
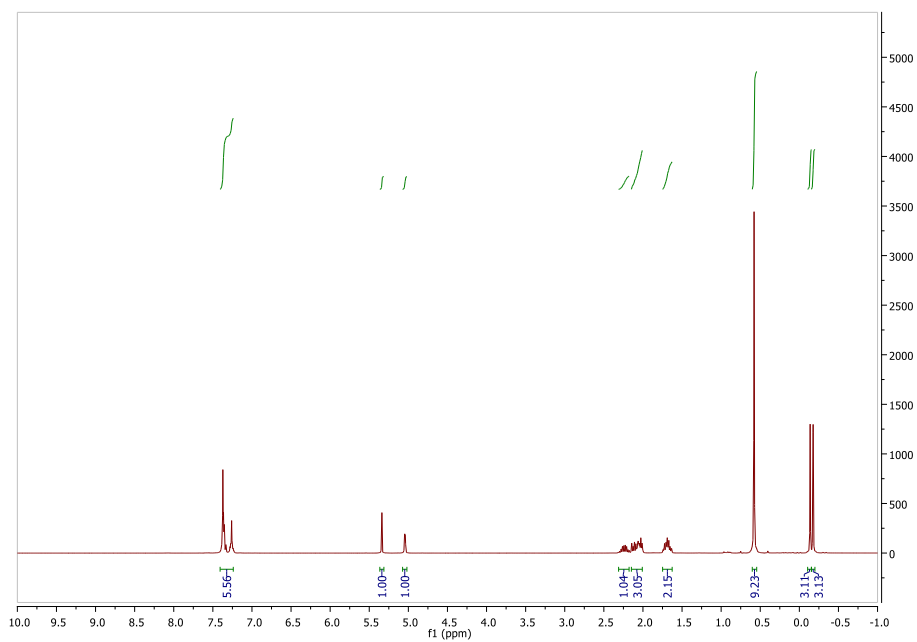
endo-17a

exo-17a

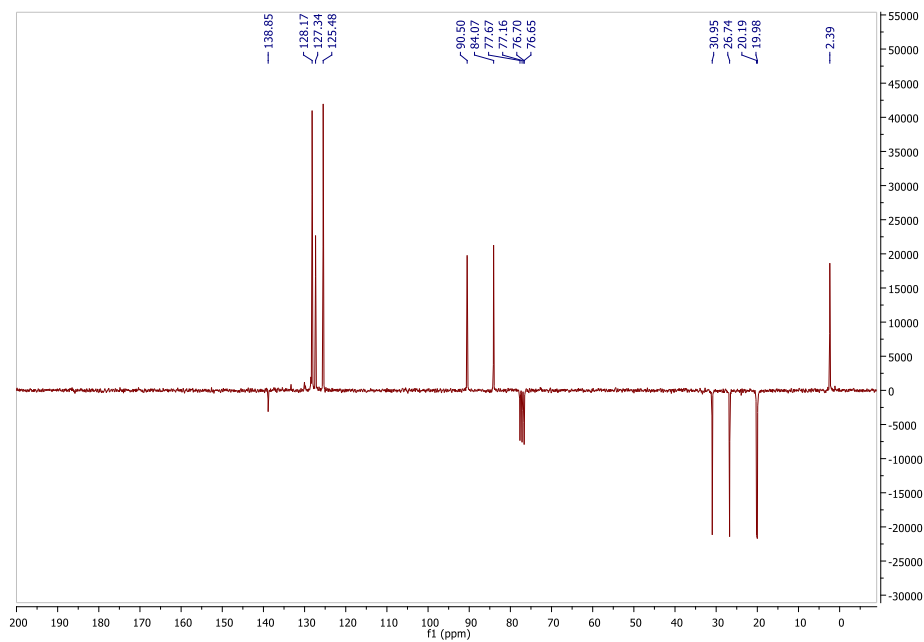
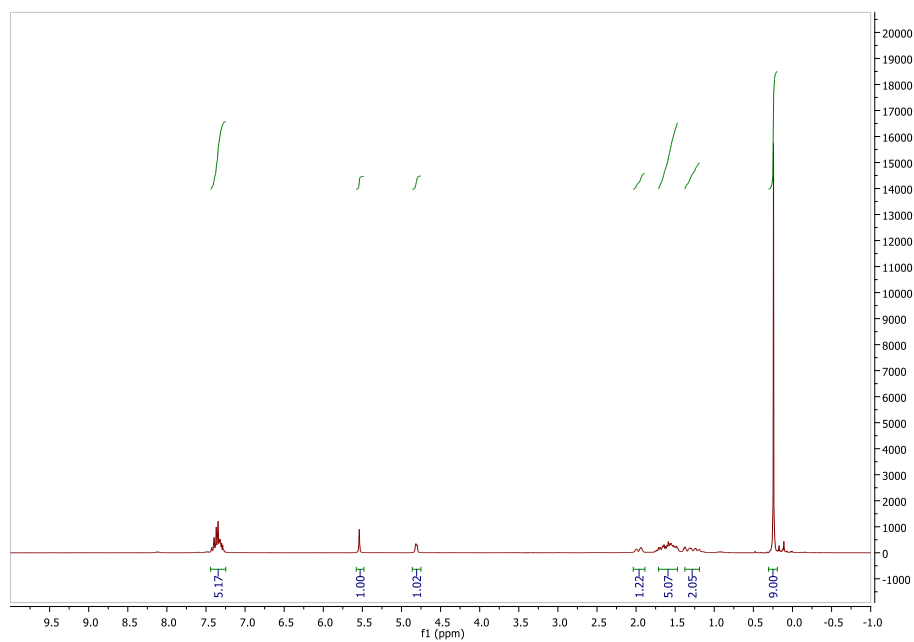


endo-17b

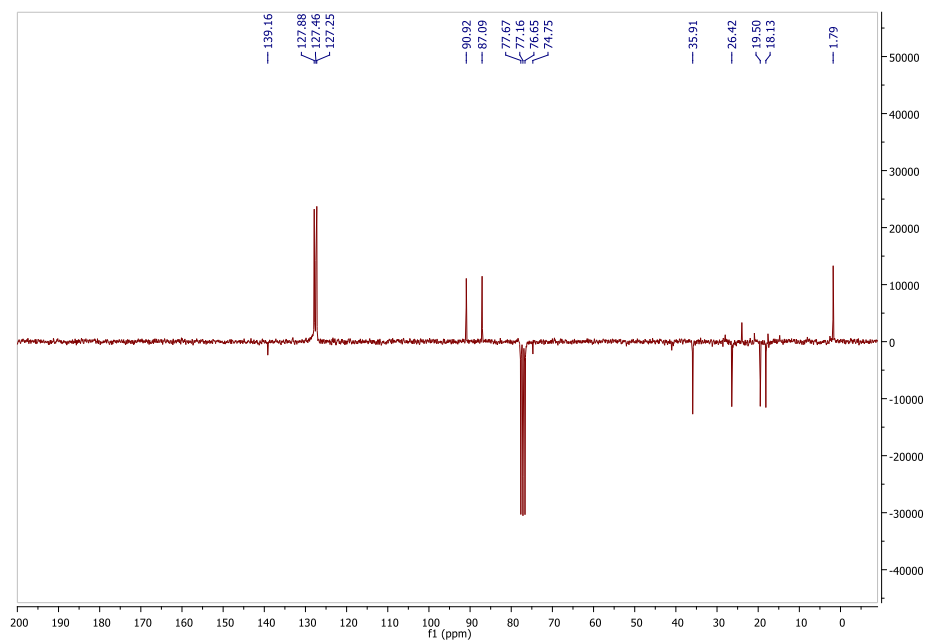
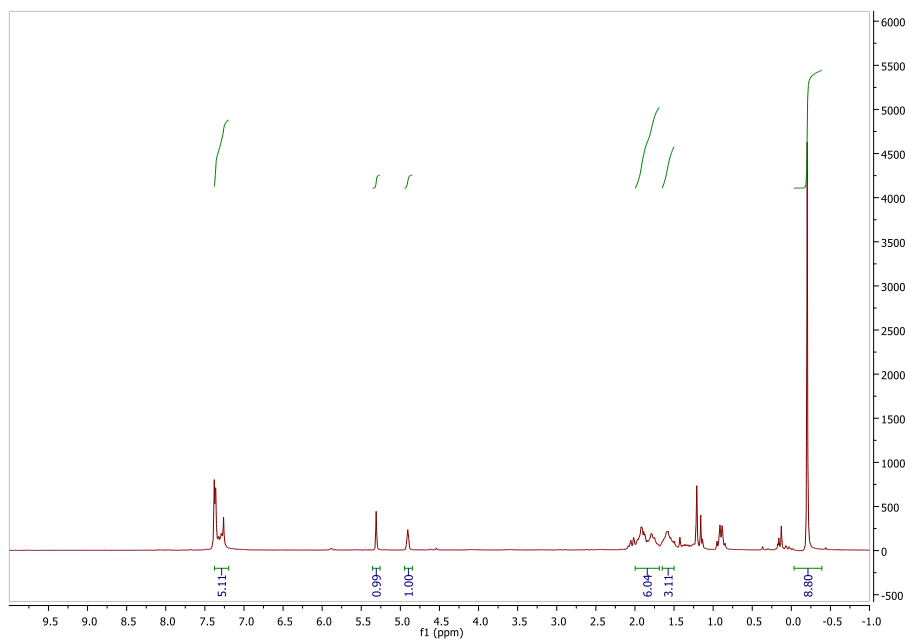
exo-17b



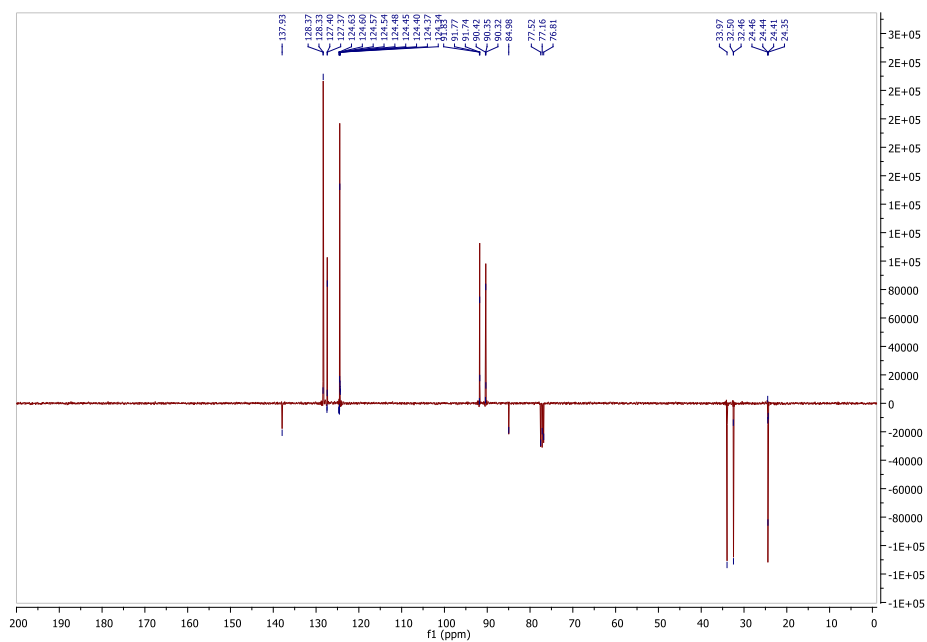
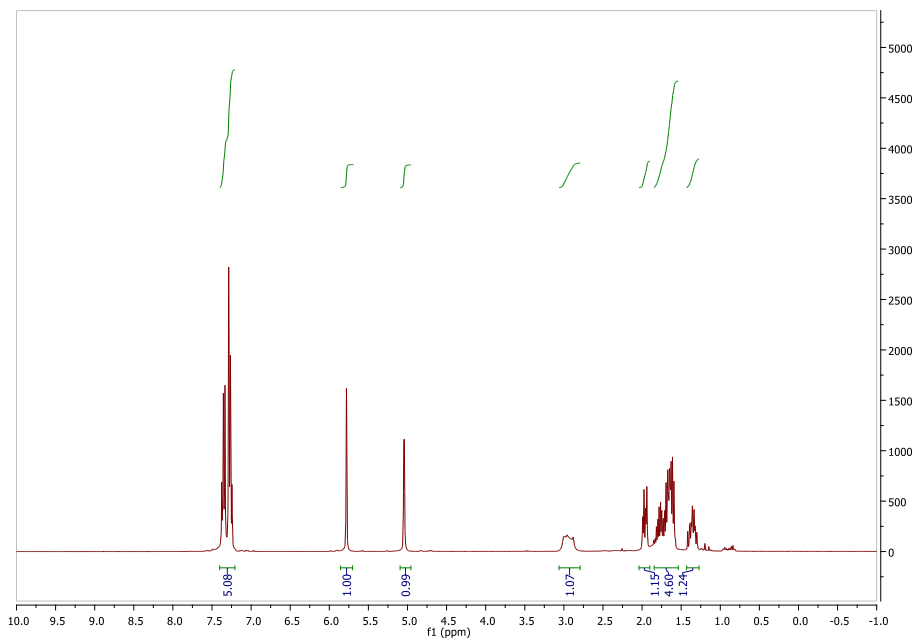
endo-17c



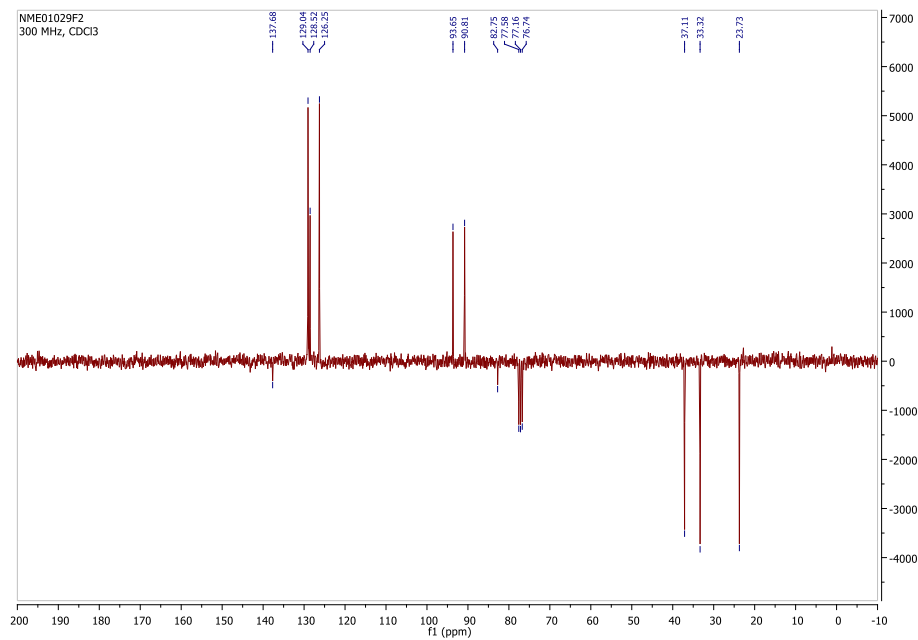
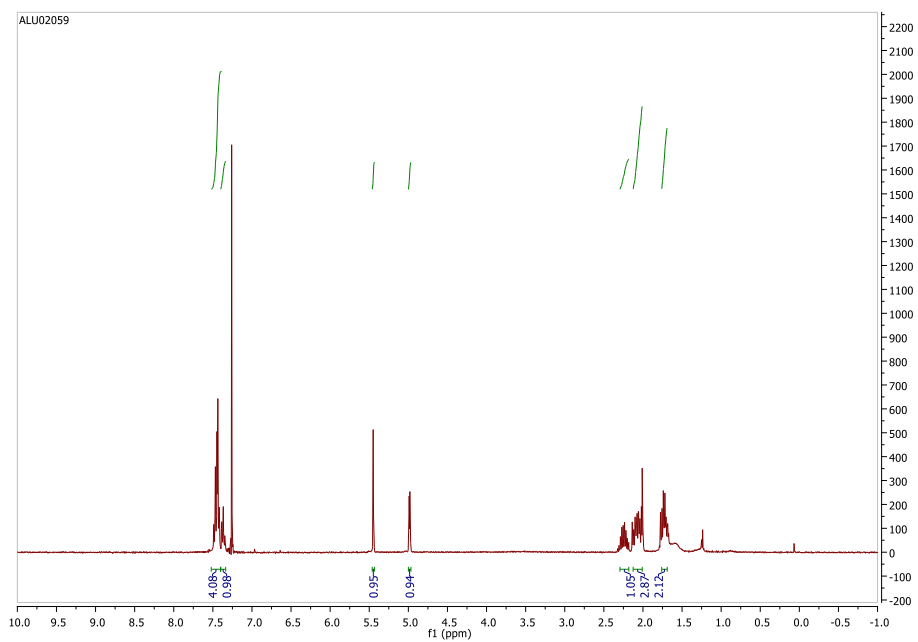
exo-17c

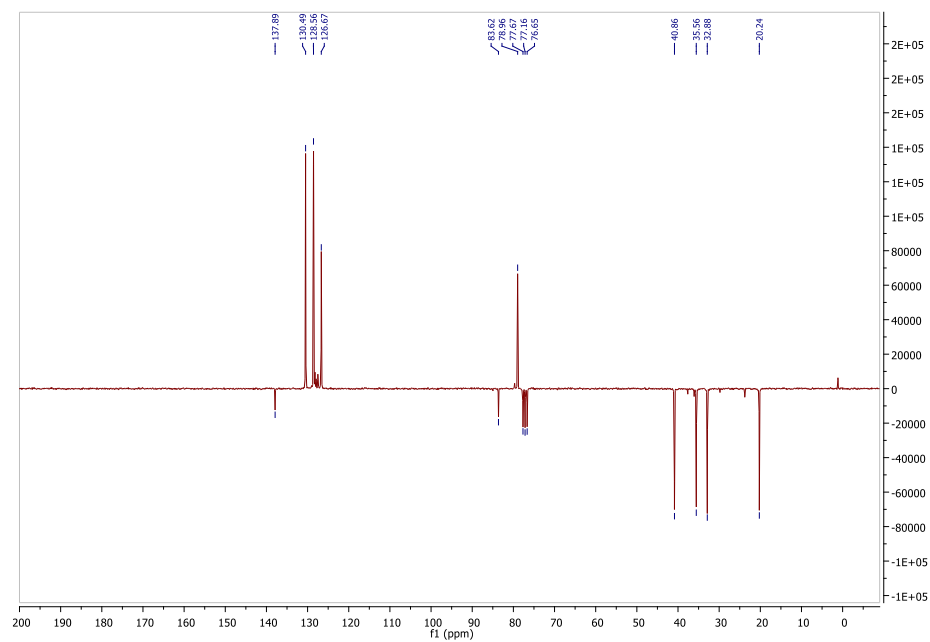
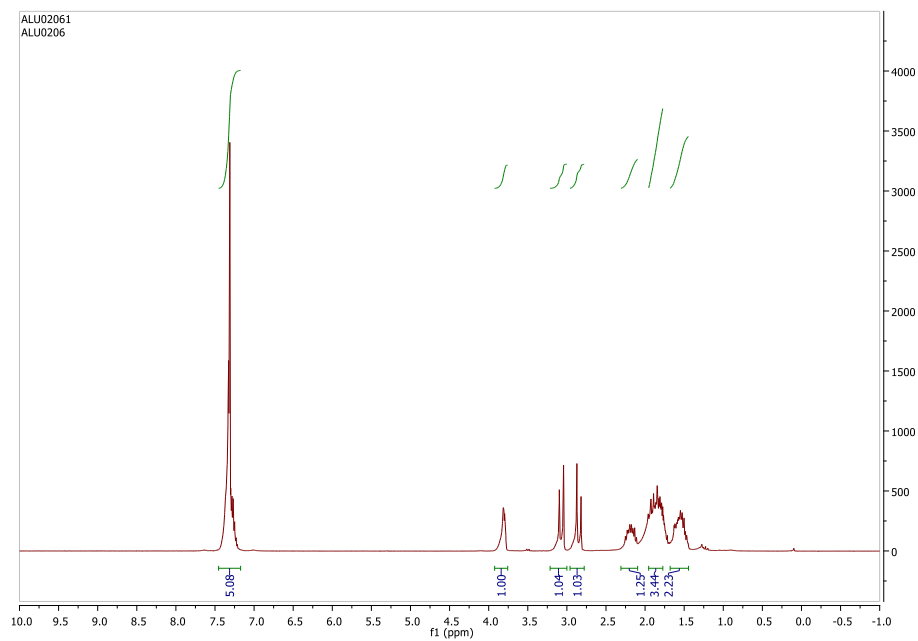


endo-18

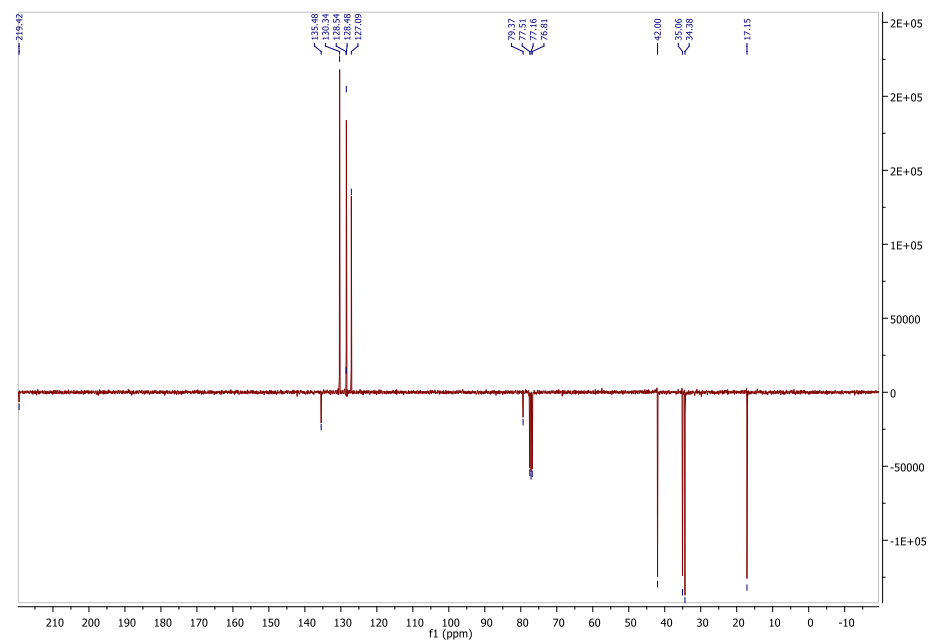
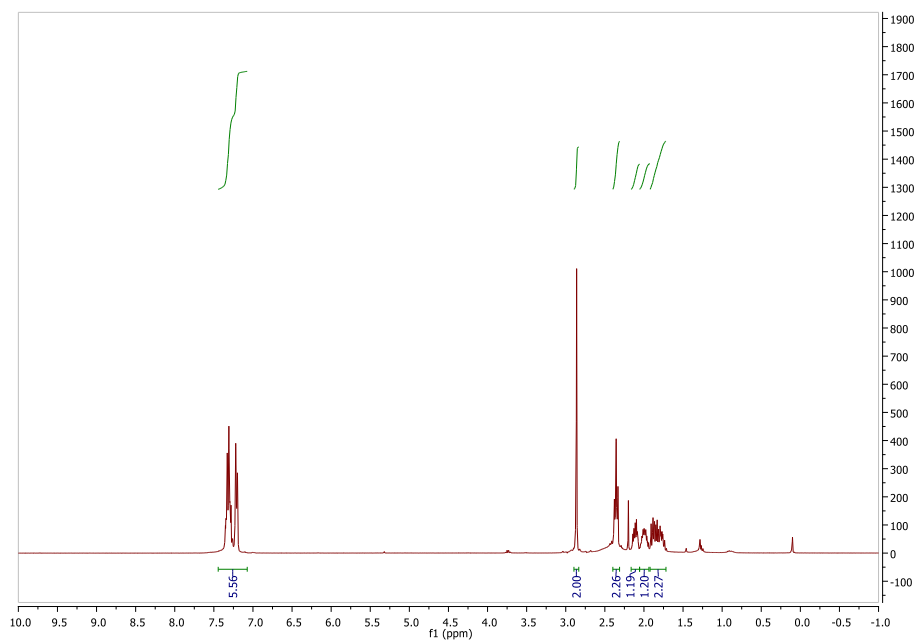


exo-18



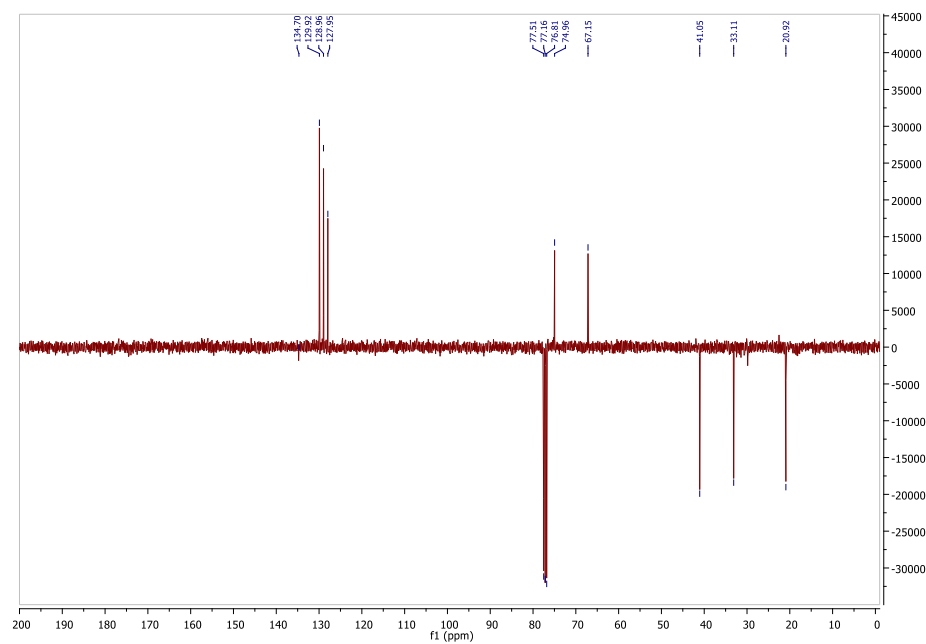
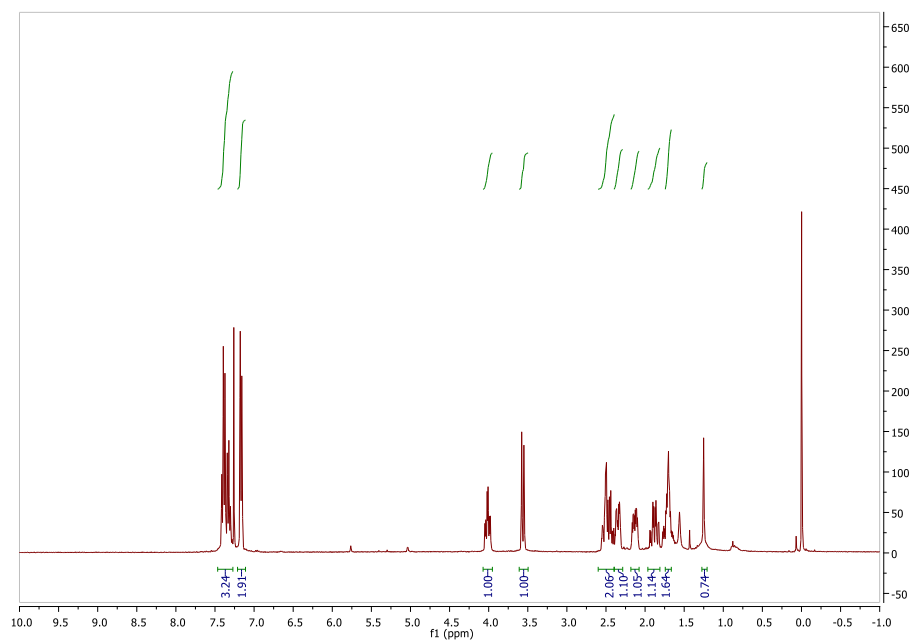


22

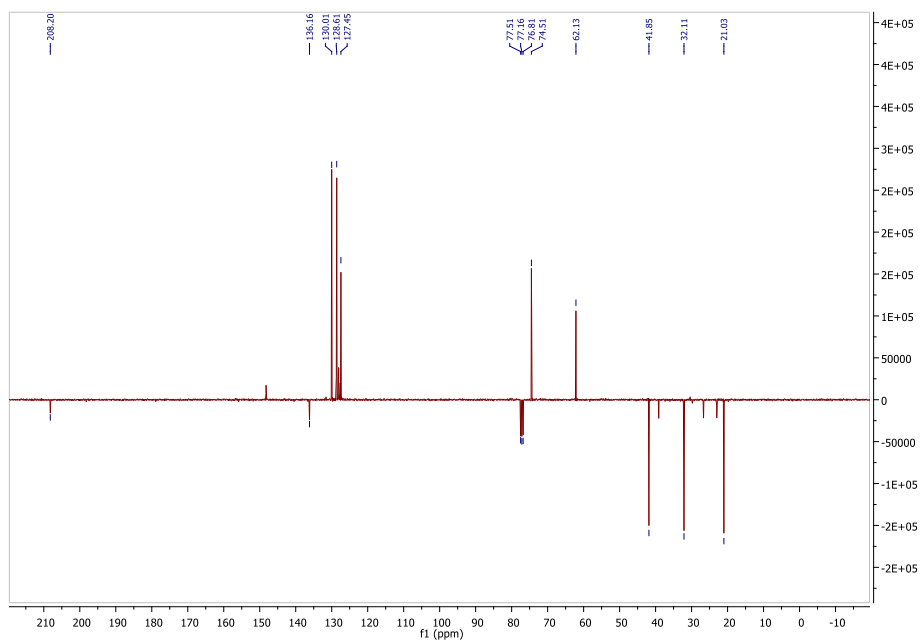
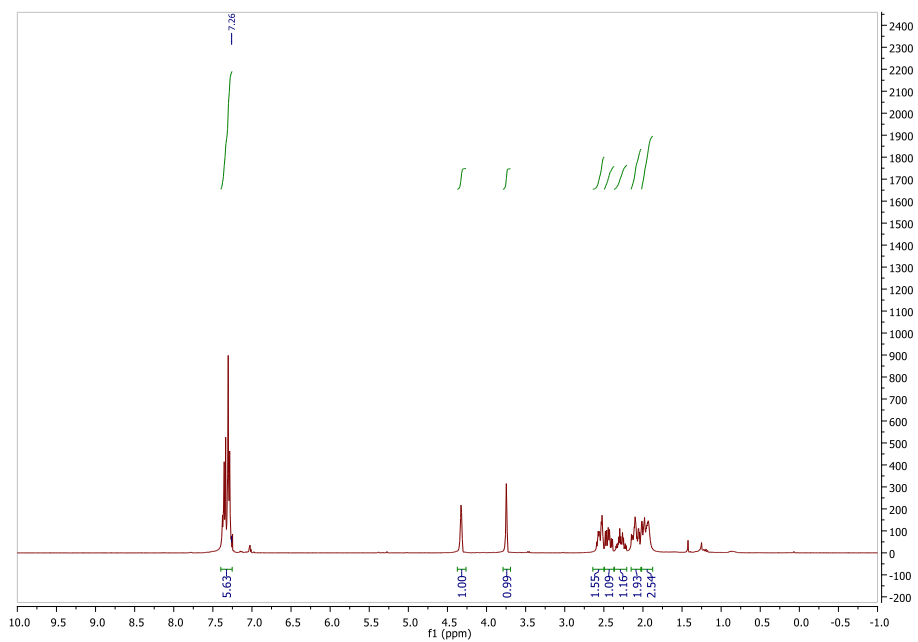


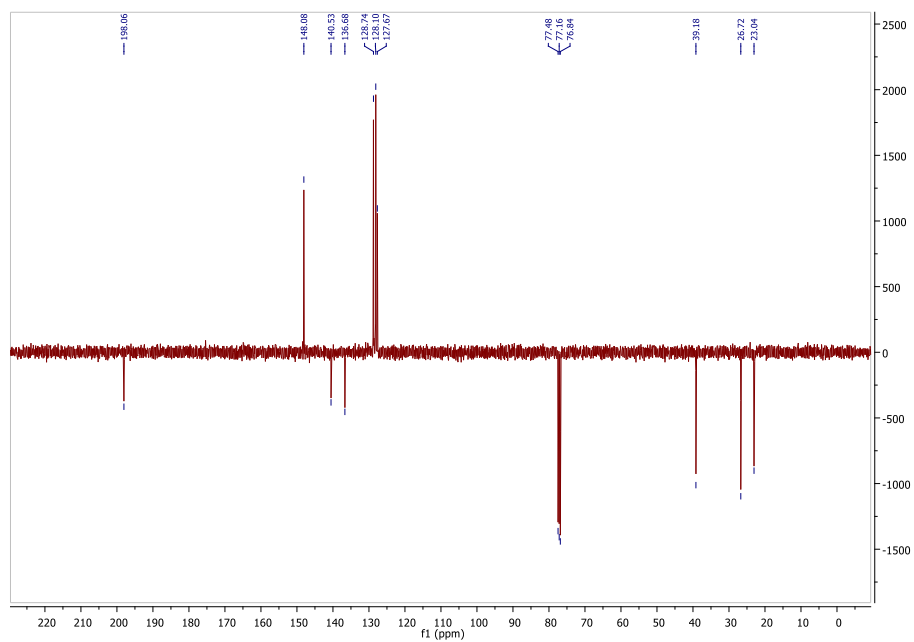
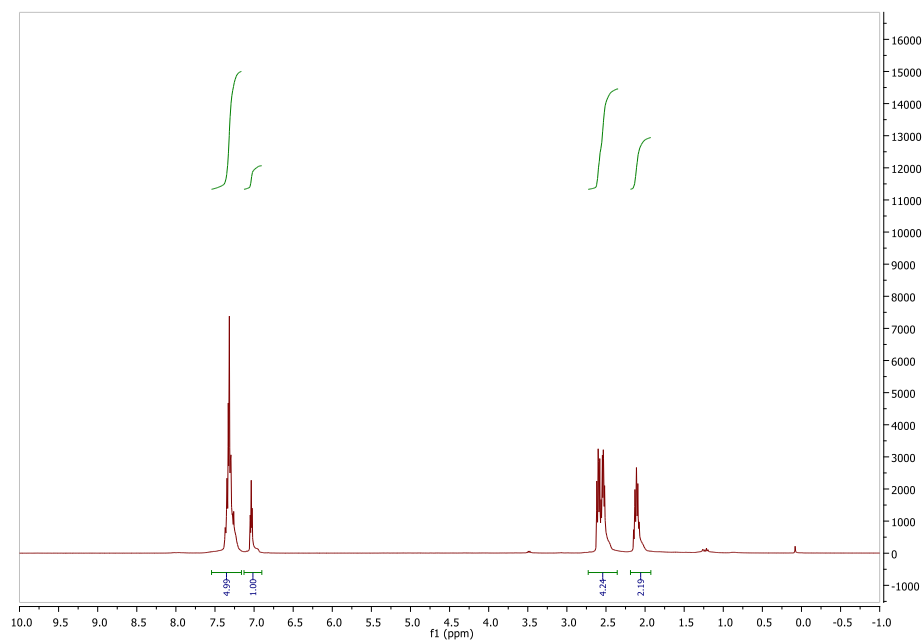
229

trans-23

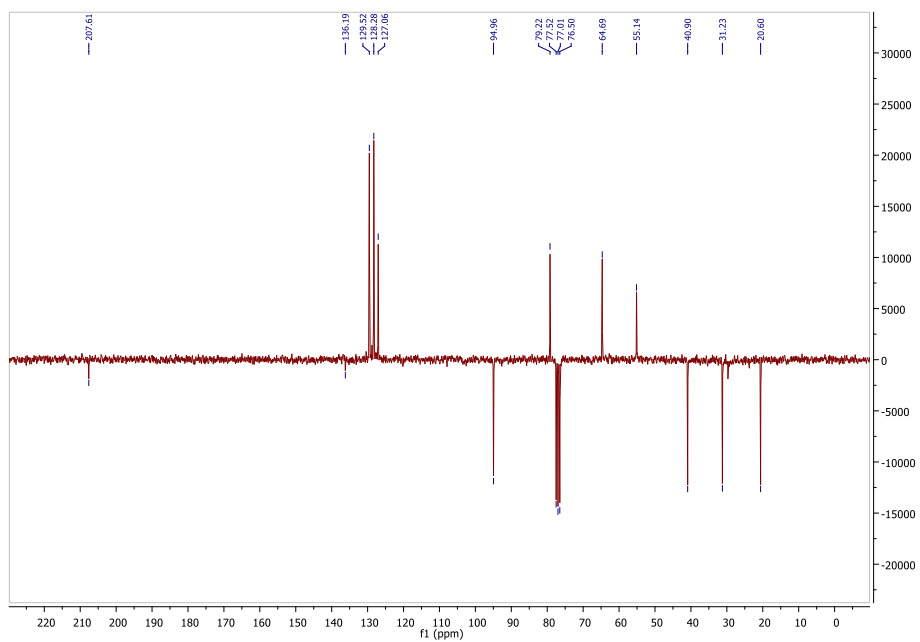
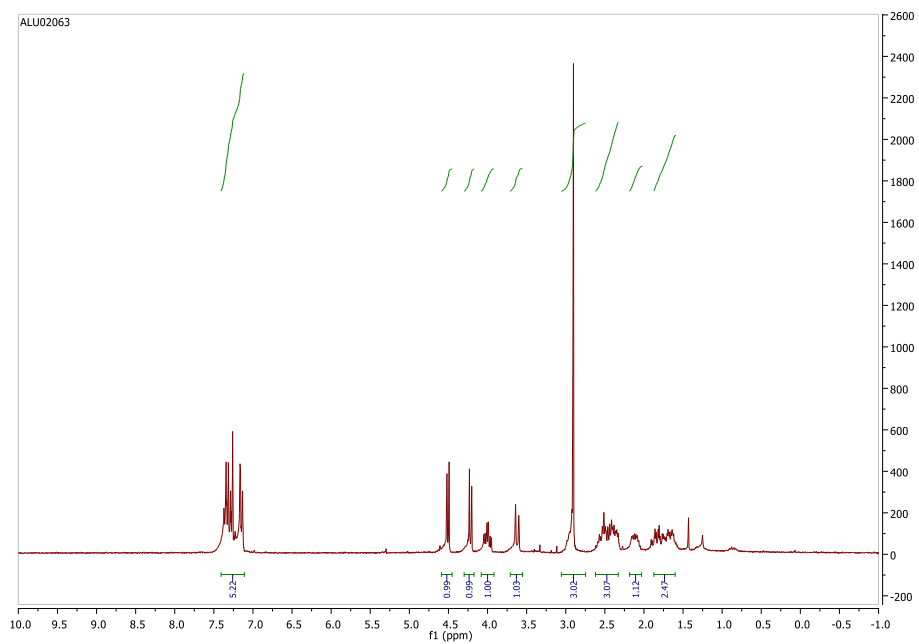


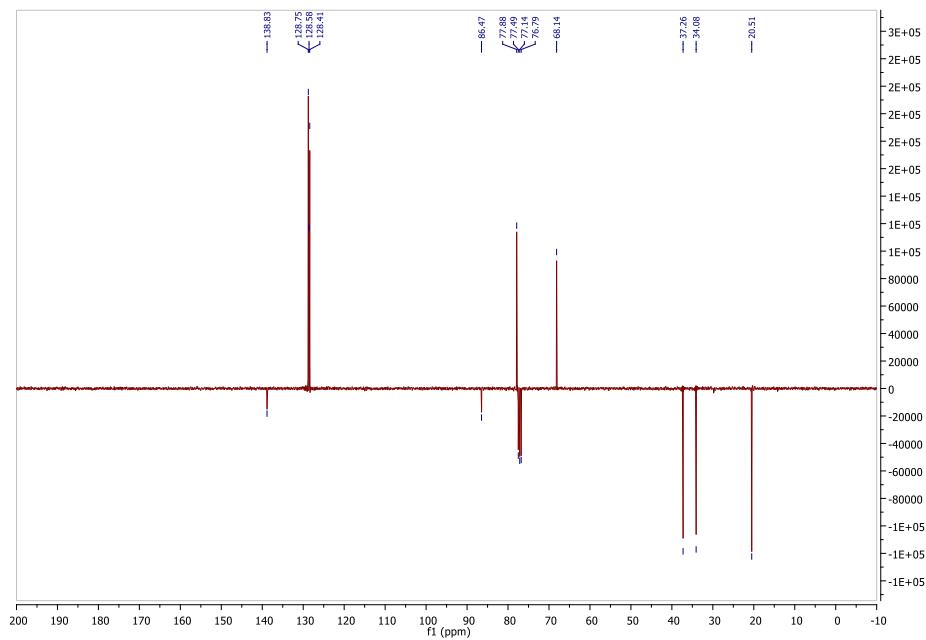
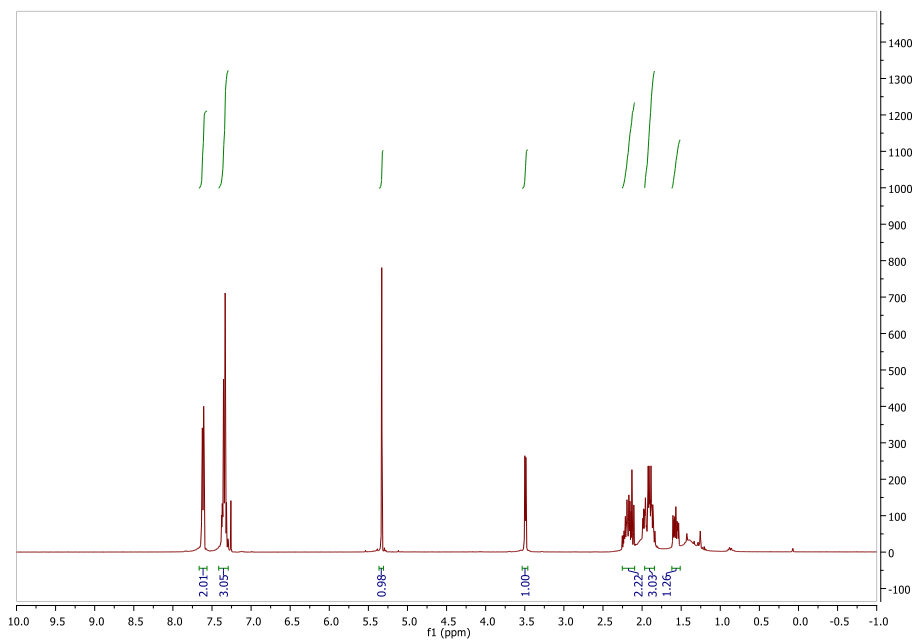
cis-24



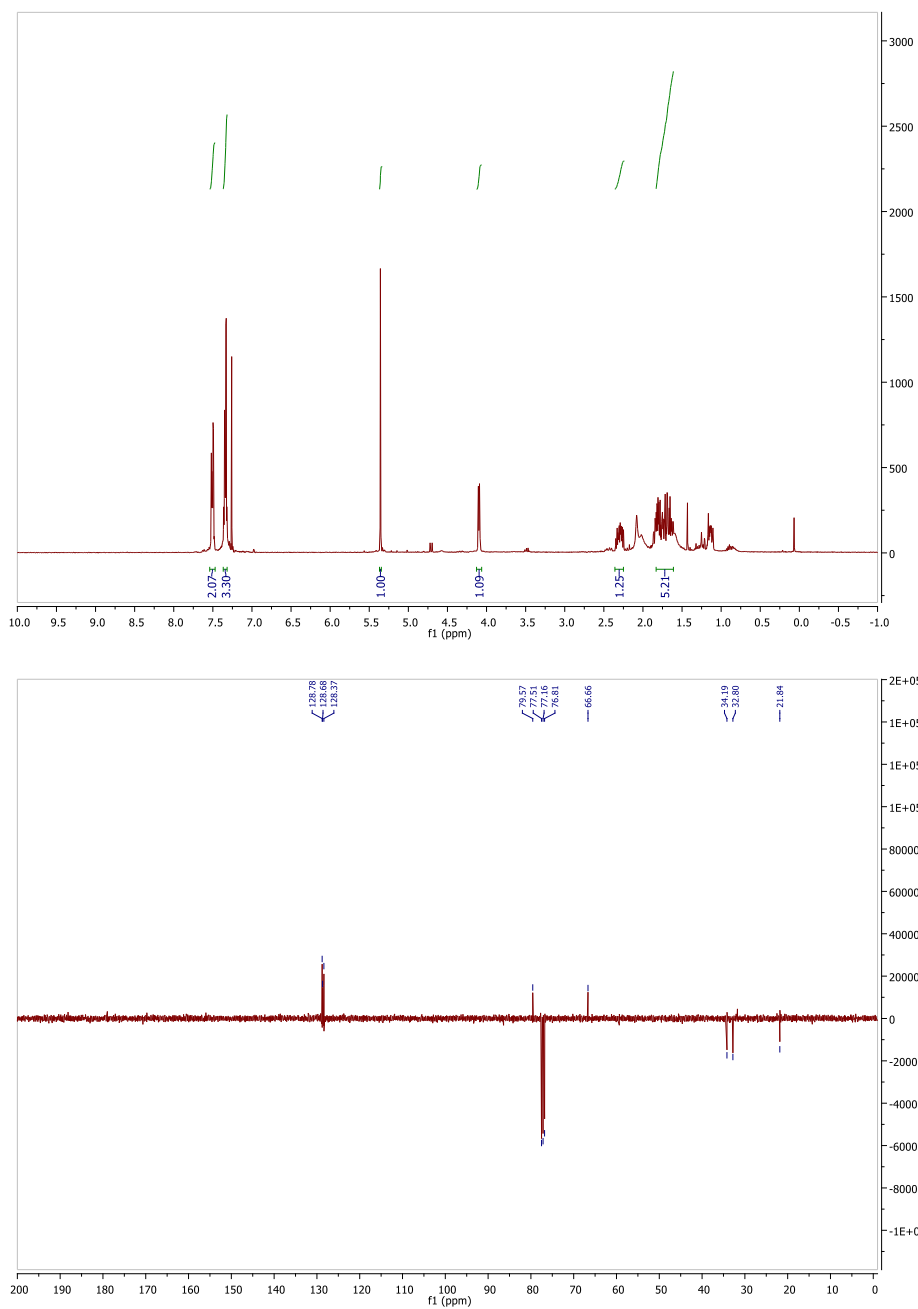


27





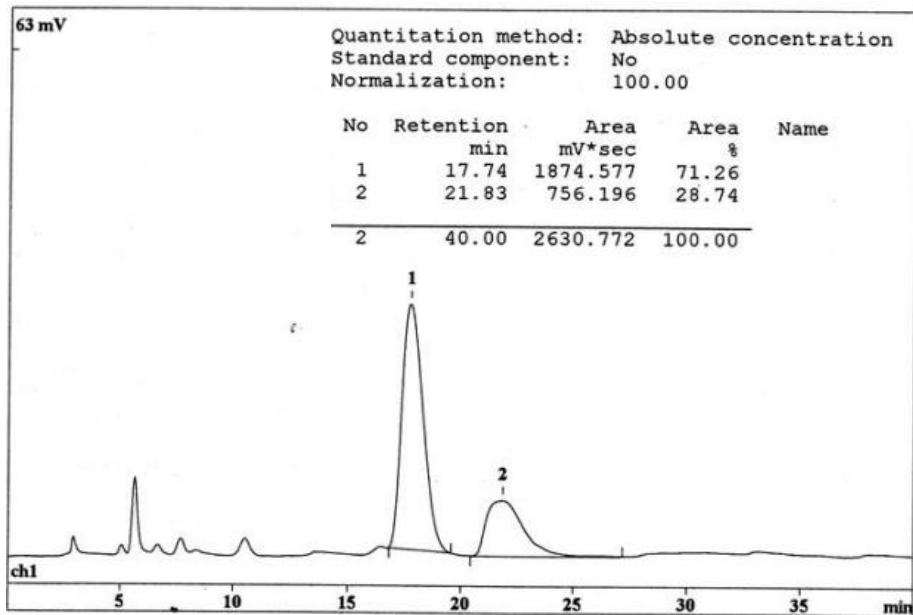
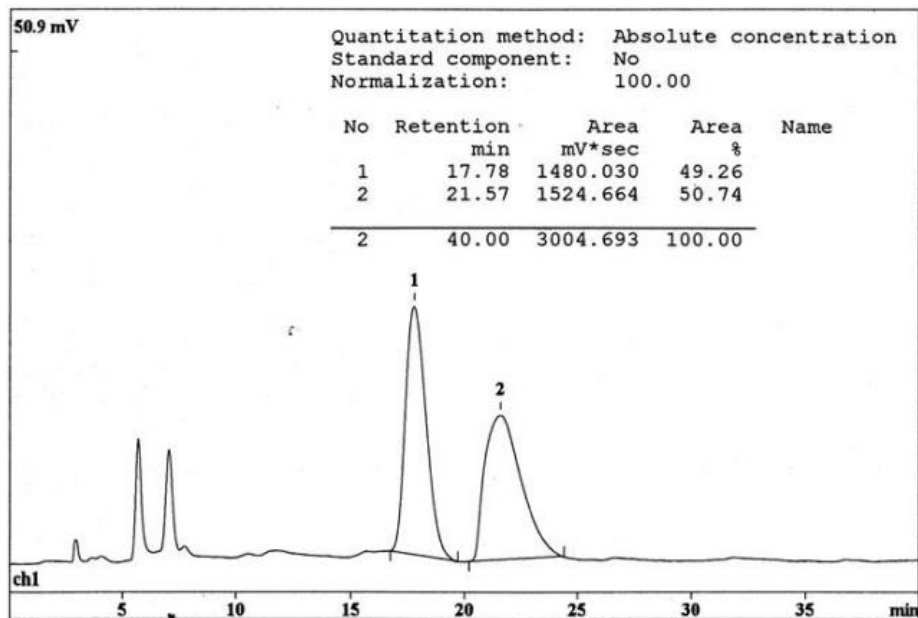
29



7.5 CHIRAL HPLC CHROMATOGRAMS

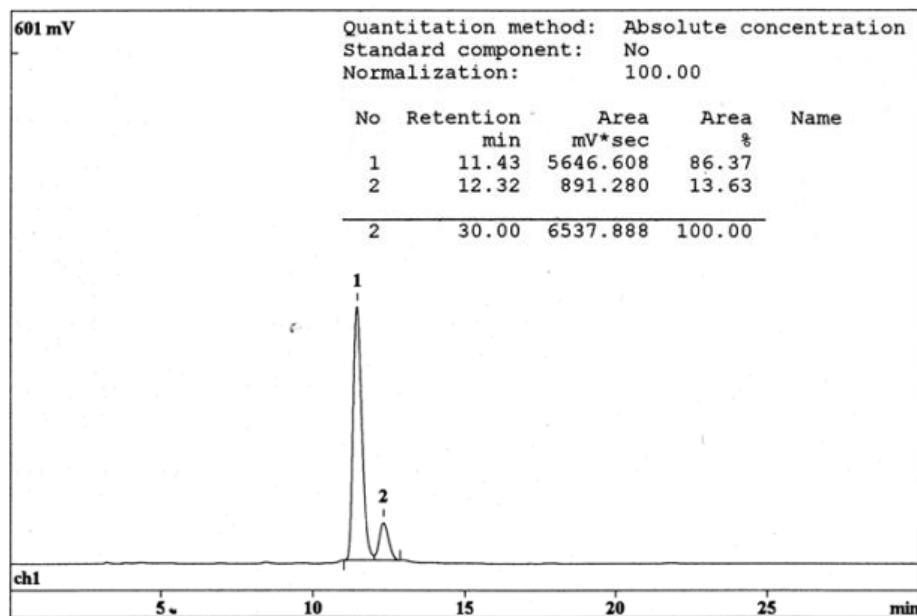
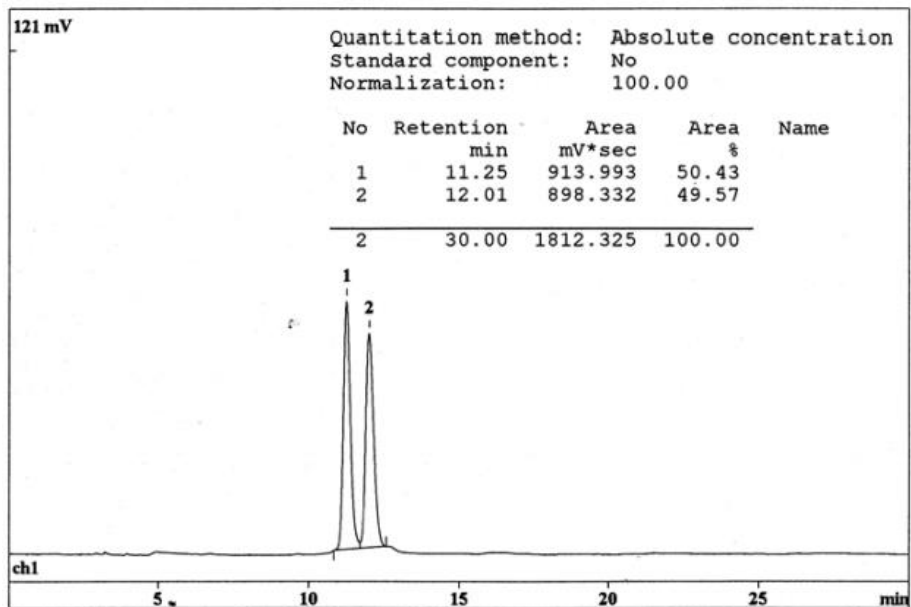
3a

Chiracel OJ column

(hexane/*i*-PrOH: 90:10, flow rate 1.0 mL/min, $\lambda = 254$ nm)

3b

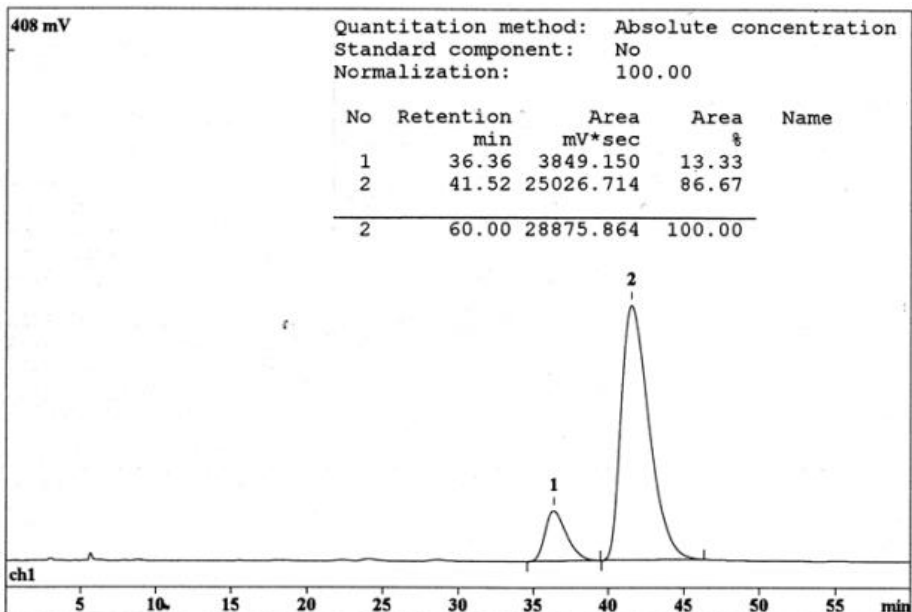
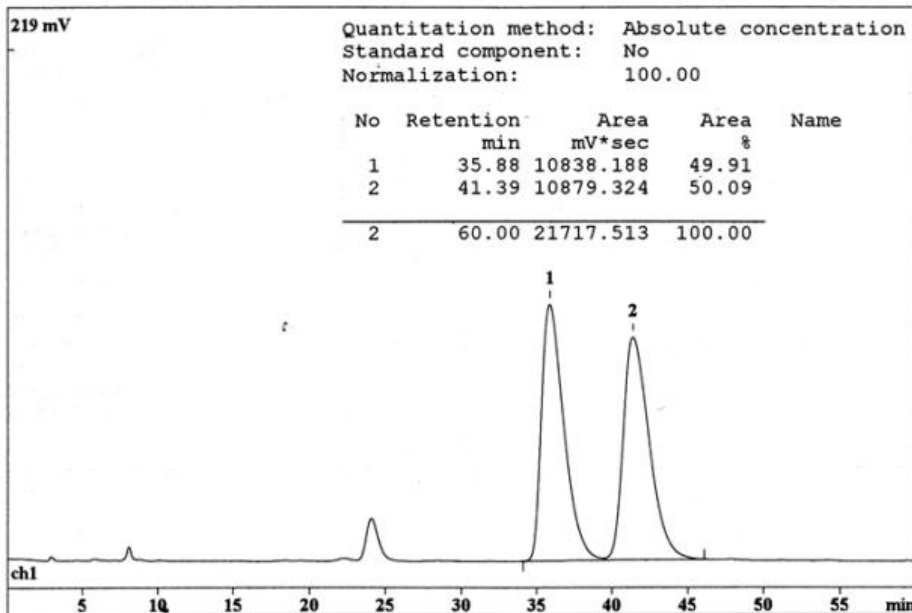
Phenomenex Lux Cellulose-1 column

(hexane/*i*-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm)

3c

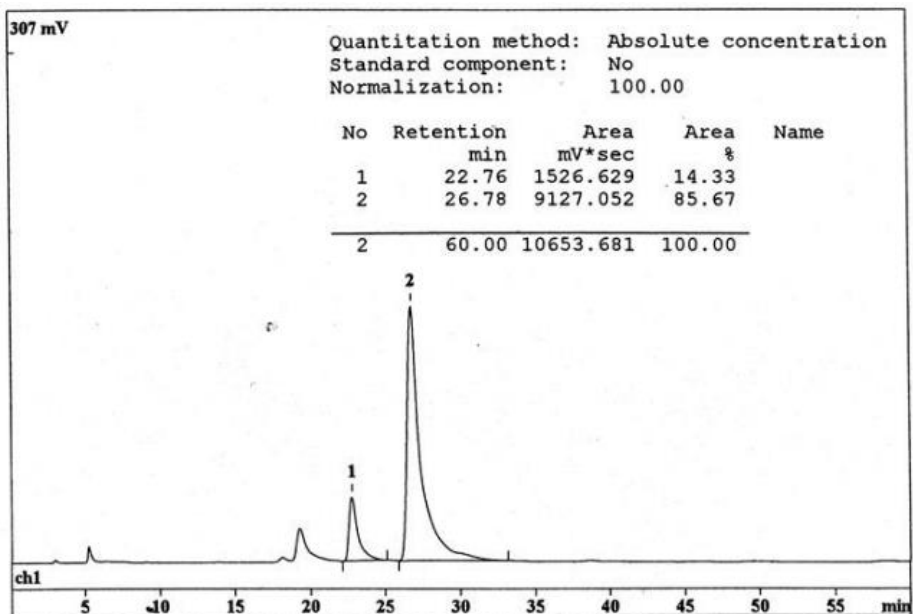
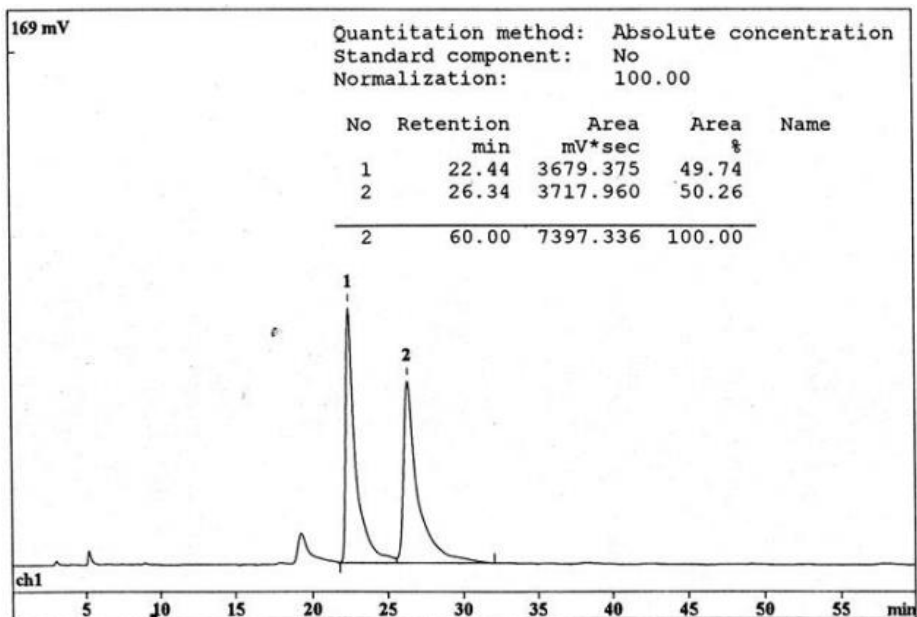
Chiracel OJ column

Hexane/i-PrOH = 90:10, flow rate 1.0 mL/min, $\lambda = 254 \text{ nm}$)



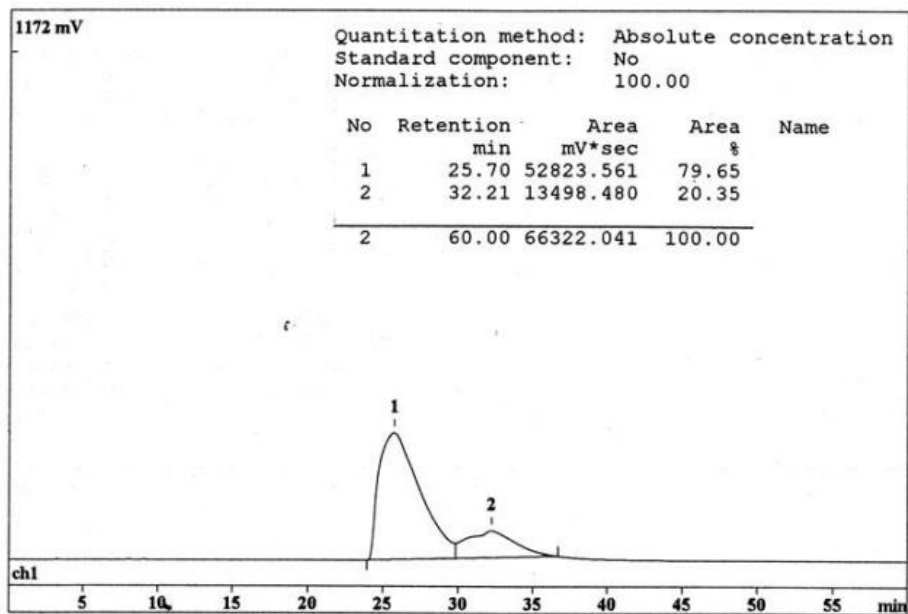
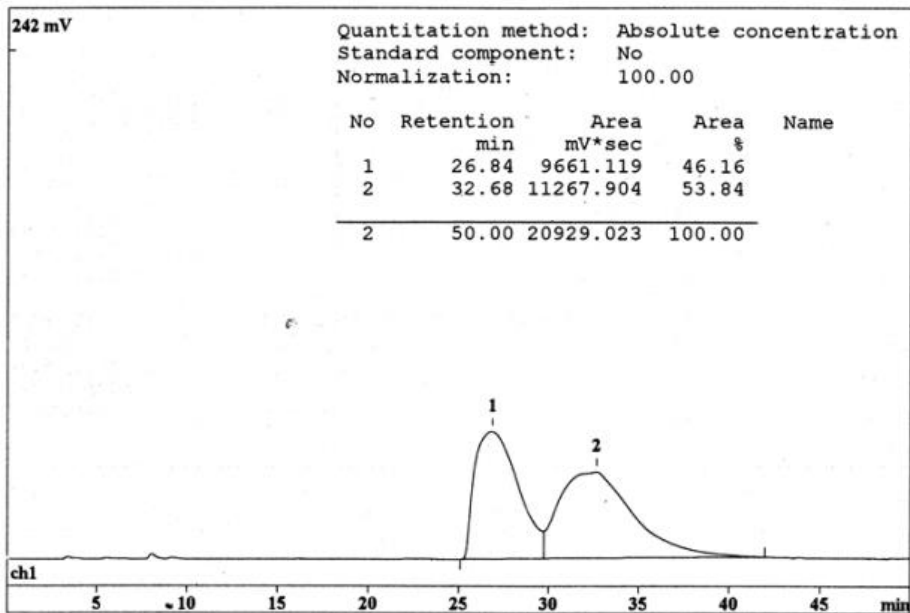
3d

Chiralpak AD-H column

hexane/i-PrOH = 95:5, flow rate 1.0 mL/min, $\lambda = 254$ nm

3e

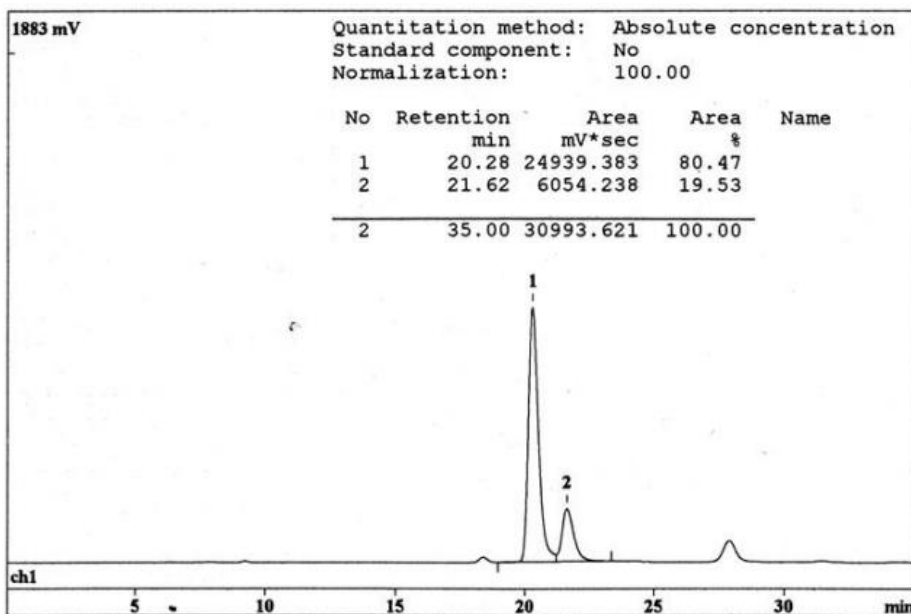
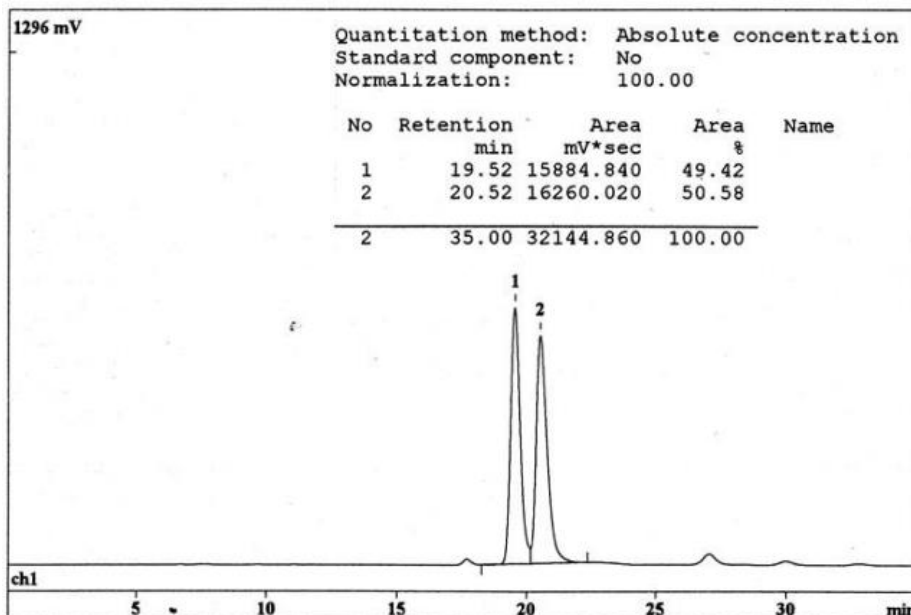
Chiralpak AS-H column

hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, $\lambda = 254$ nm

3f

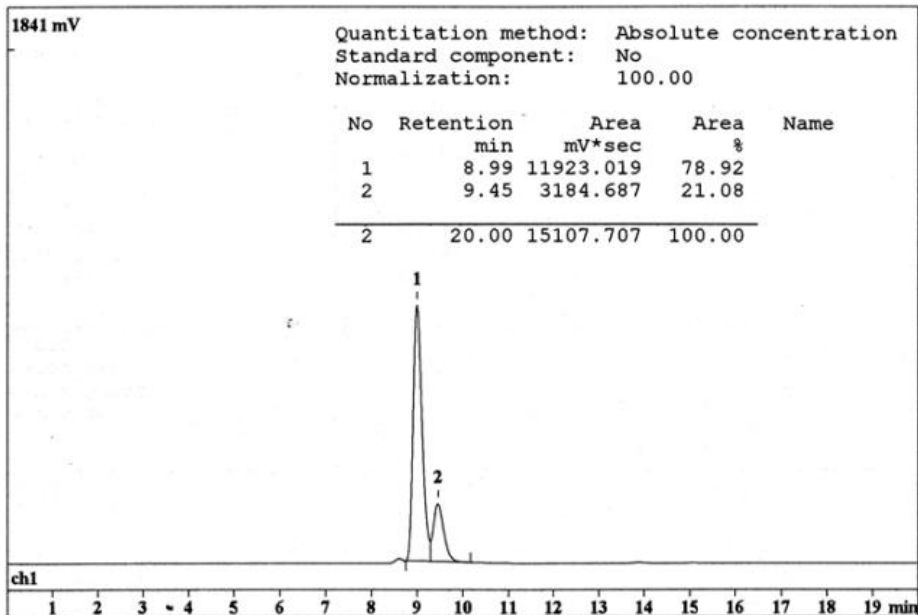
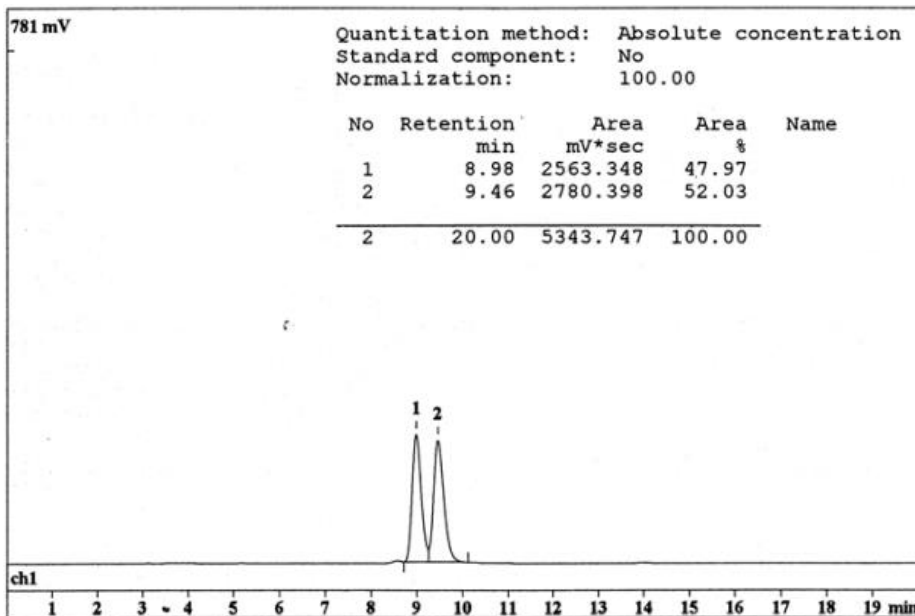
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm



3g

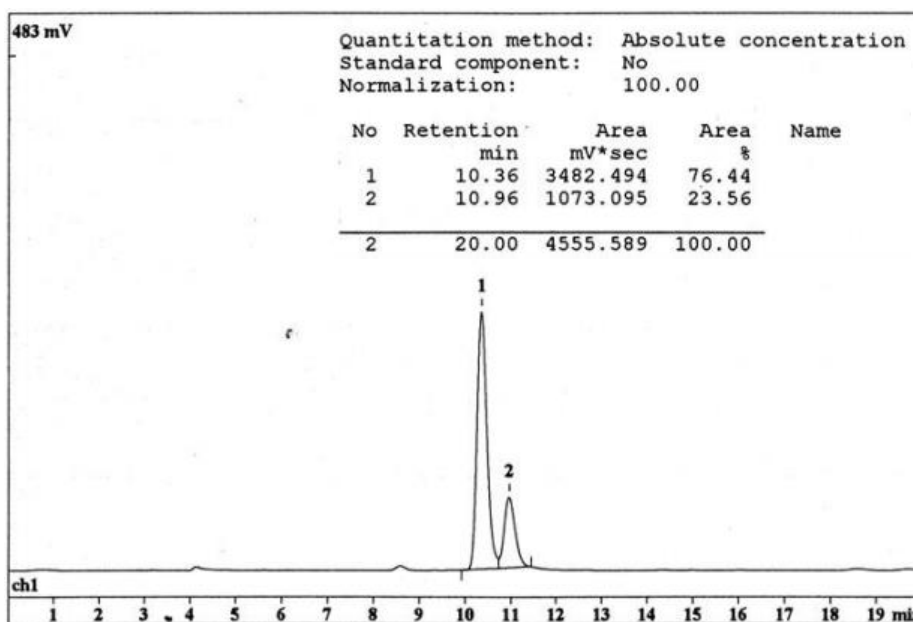
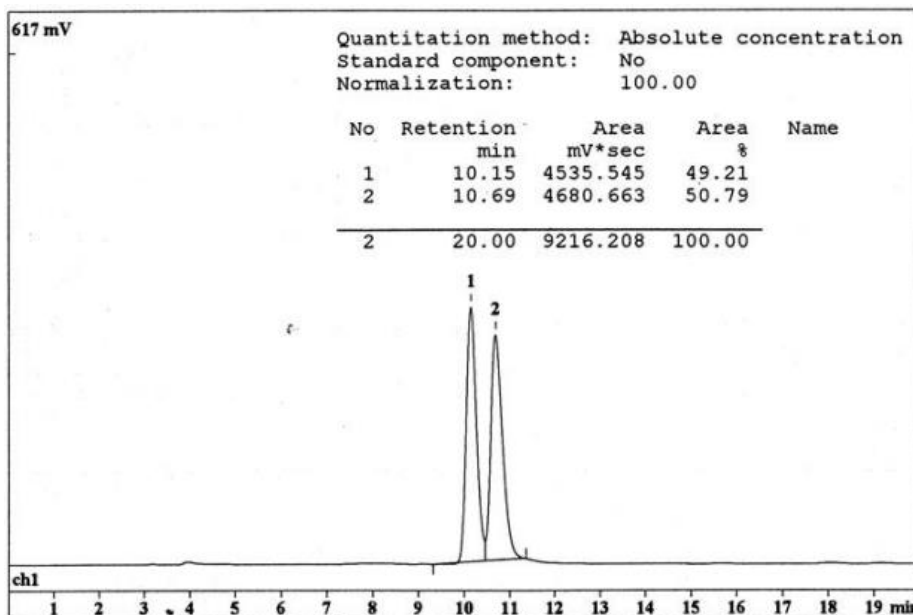
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, $\lambda = 254$ nm

3h

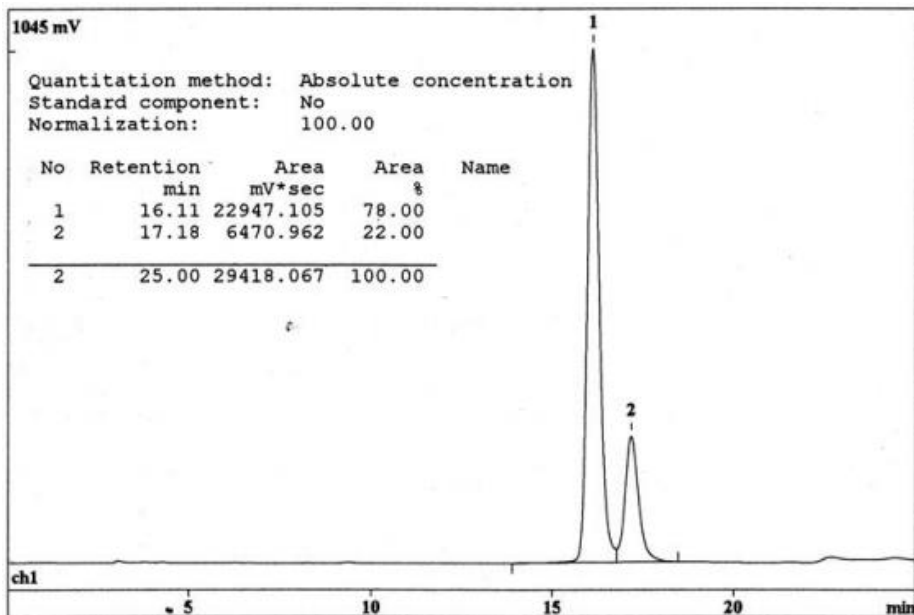
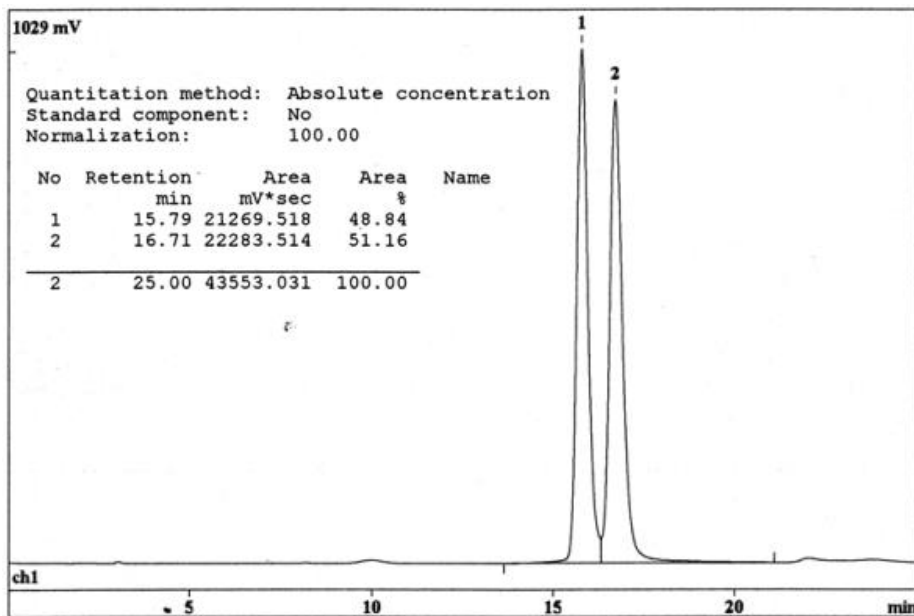
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, $\lambda = 254$ nm



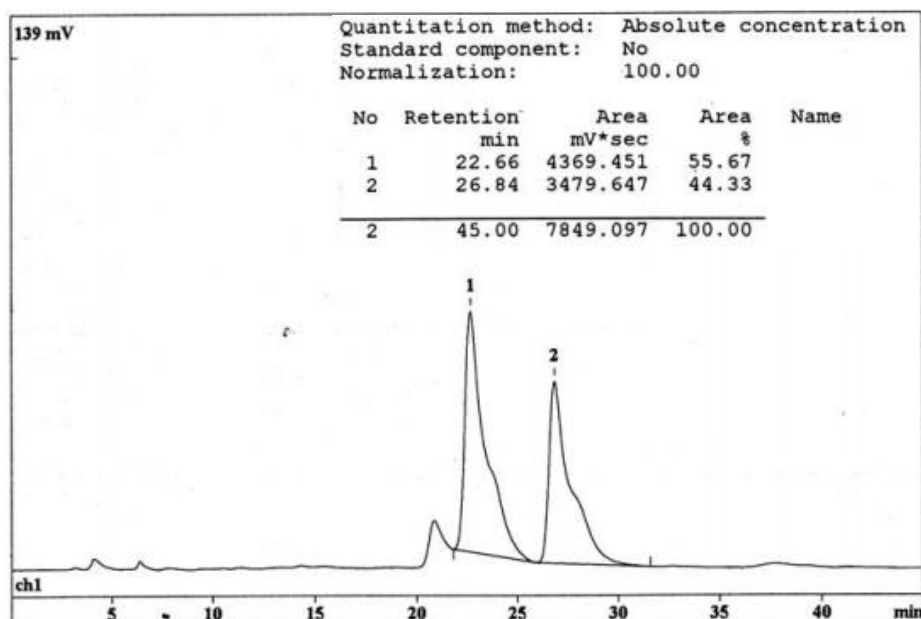
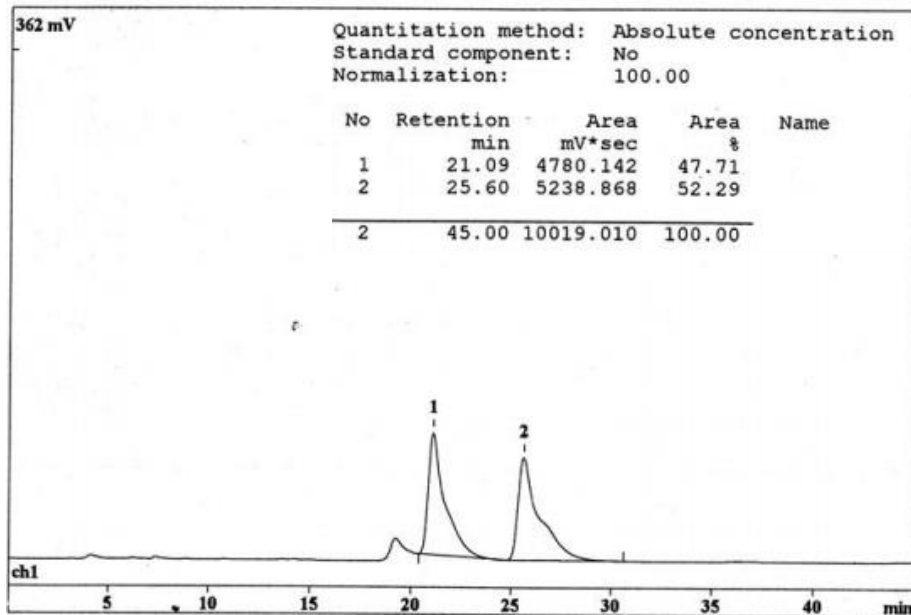
3i

Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 95:5, flow rate 1.0 mL/min, $\lambda = 254$ nm

3j

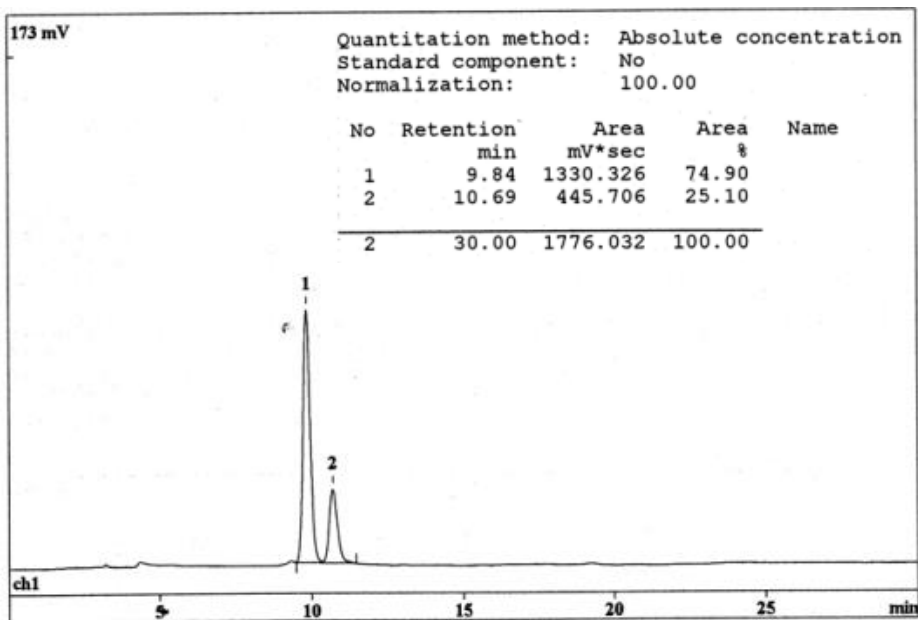
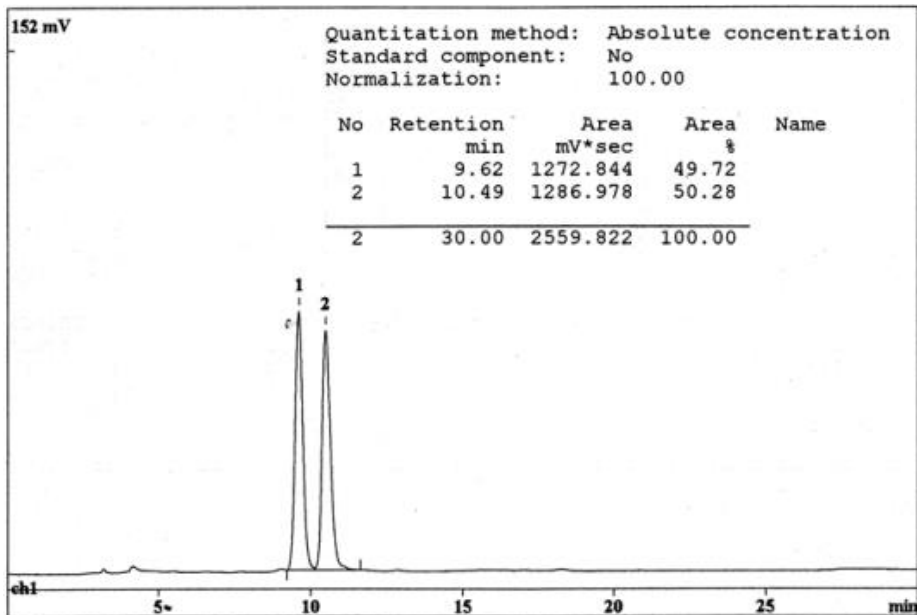
Chiralpak AD-H column

hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm

3k

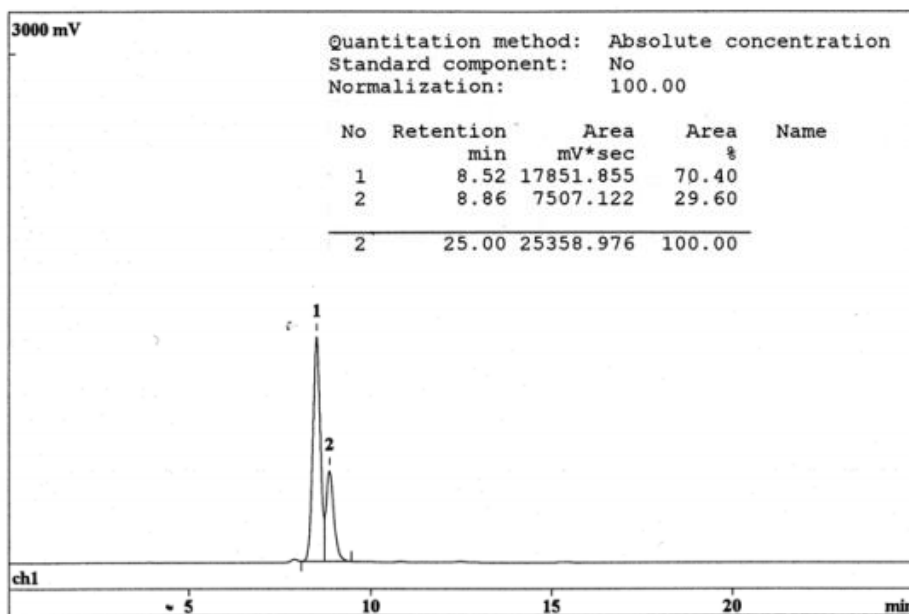
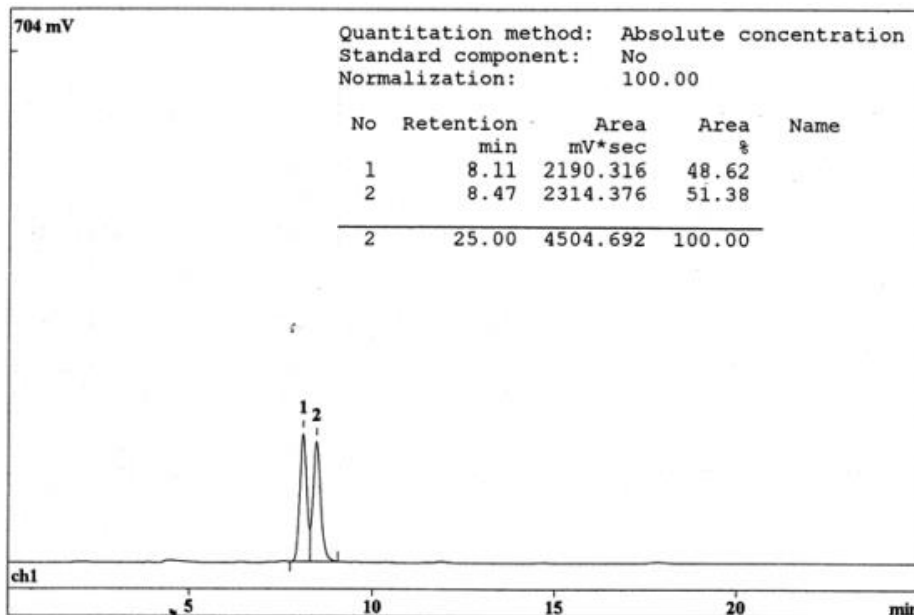
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254 \text{ nm}$



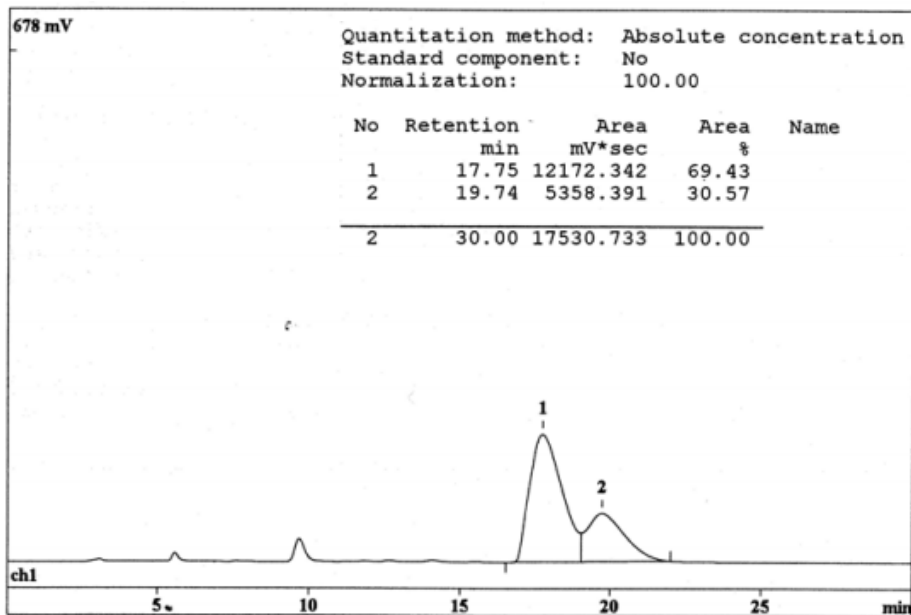
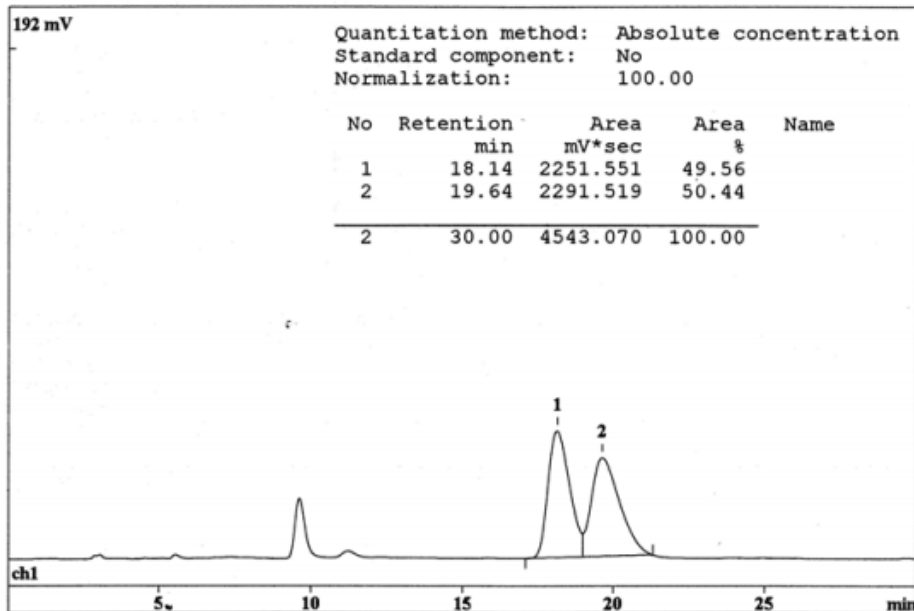
31

Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 99:1, flow rate 0.8 mL/min, $\lambda = 254$ nm

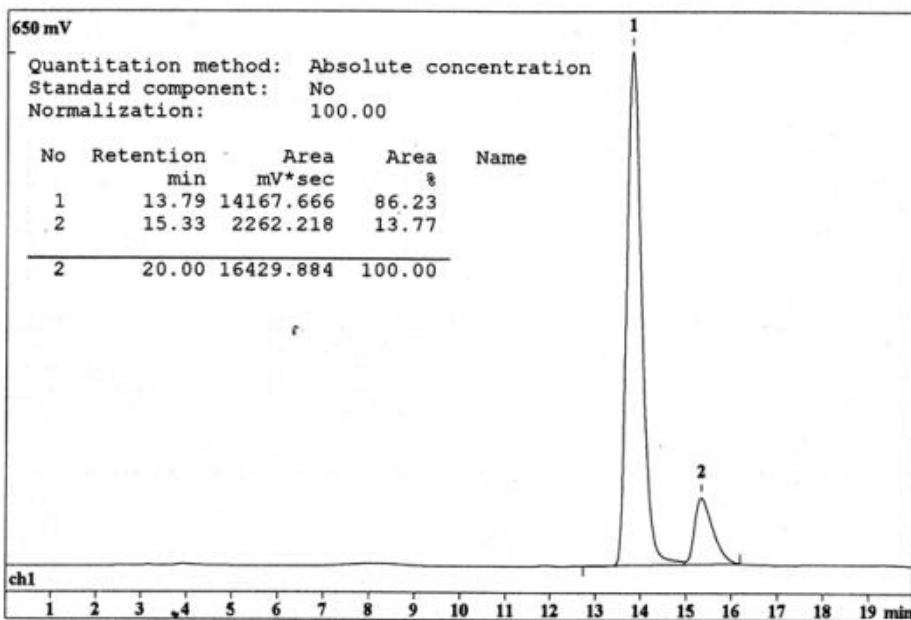
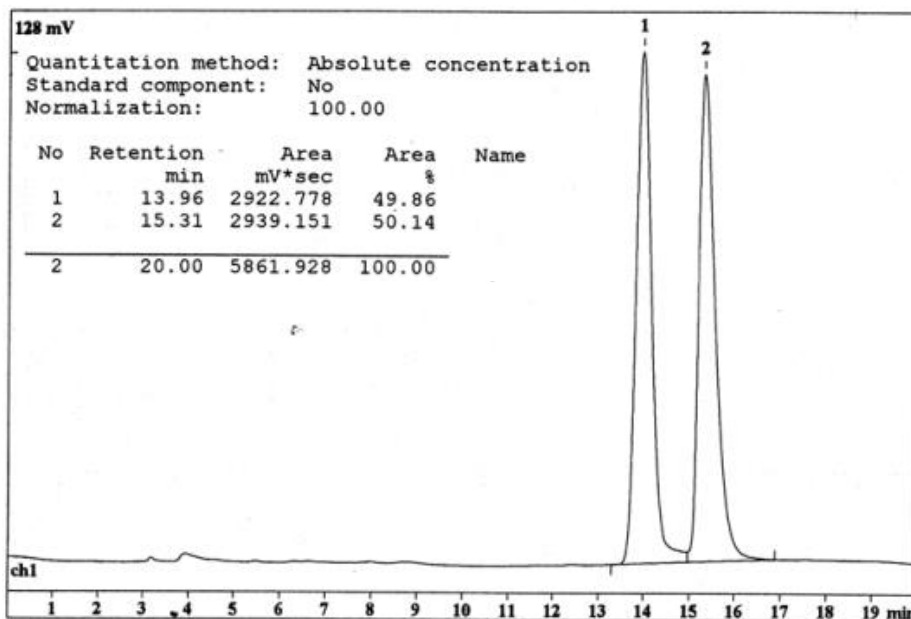
3m

Chiracel OJ column

hexane/i-PrOH = 90:10, flow rate 1.0 mL/min, $\lambda = 254$ nm

3n

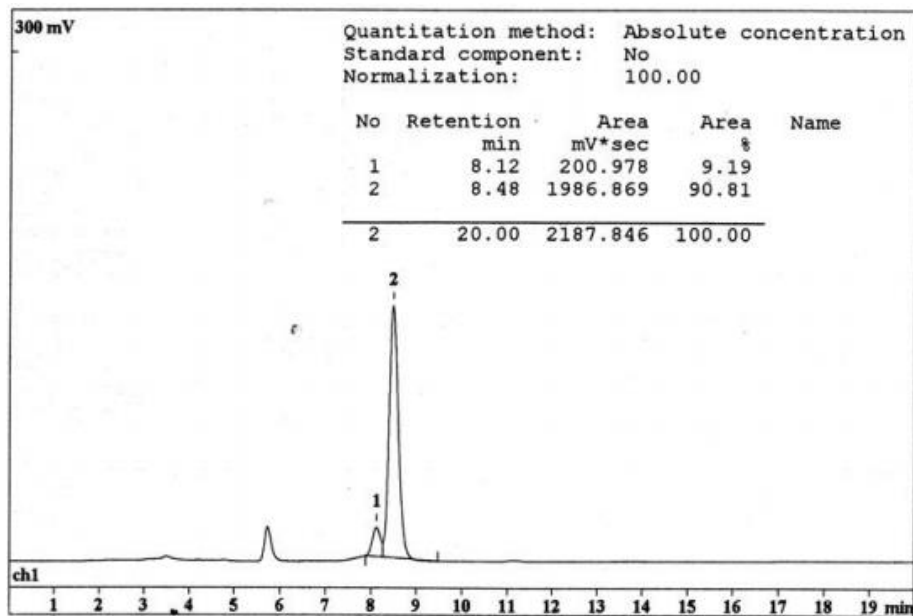
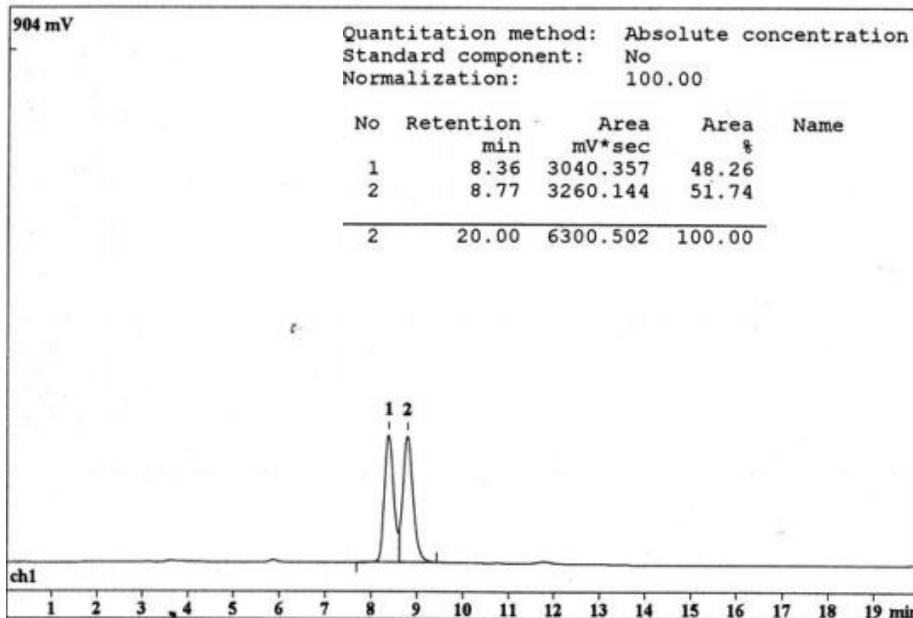
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 97:3, flow rate 1.0 mL/min, $\lambda = 254$ nm

30

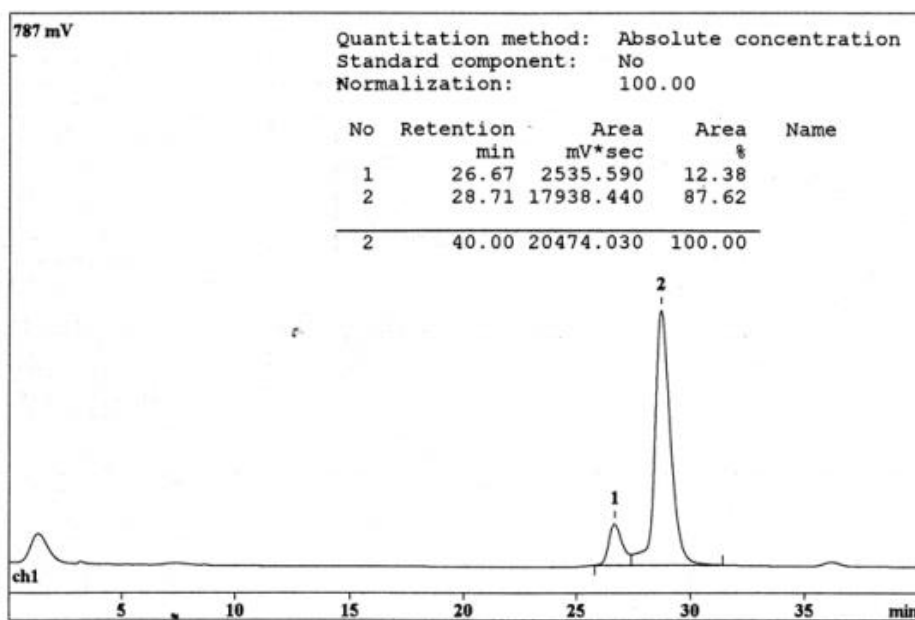
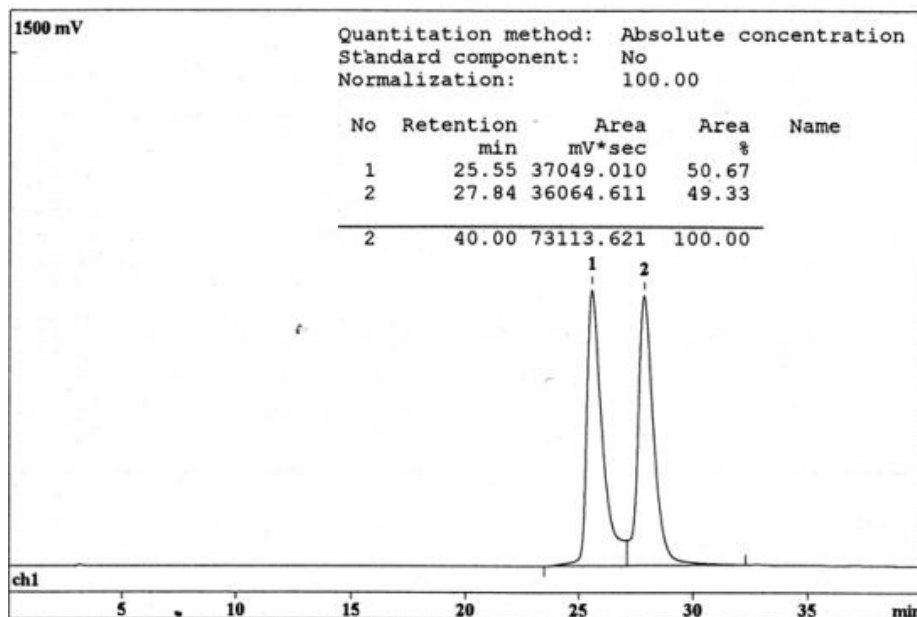
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, $\lambda = 254 \text{ nm}$



3p

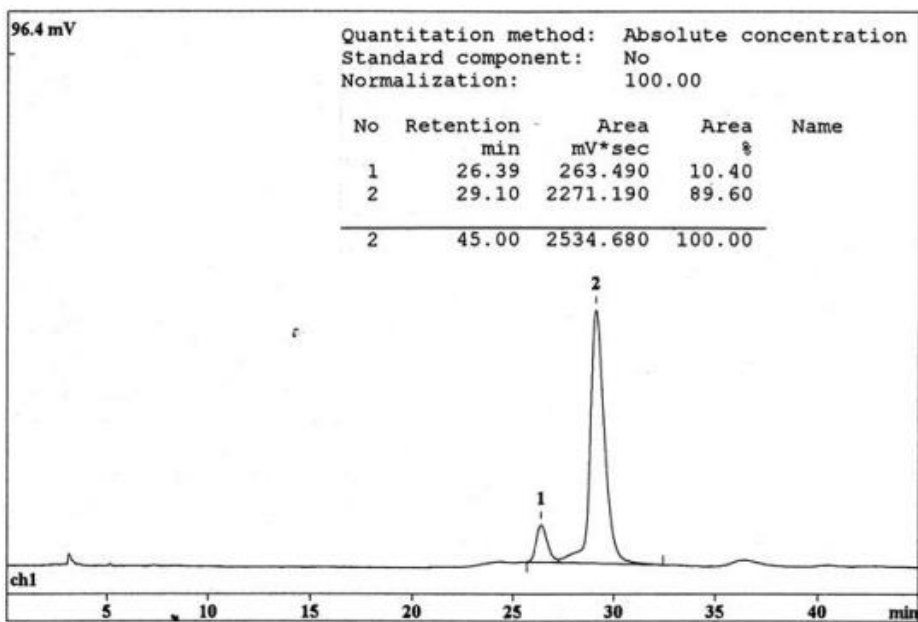
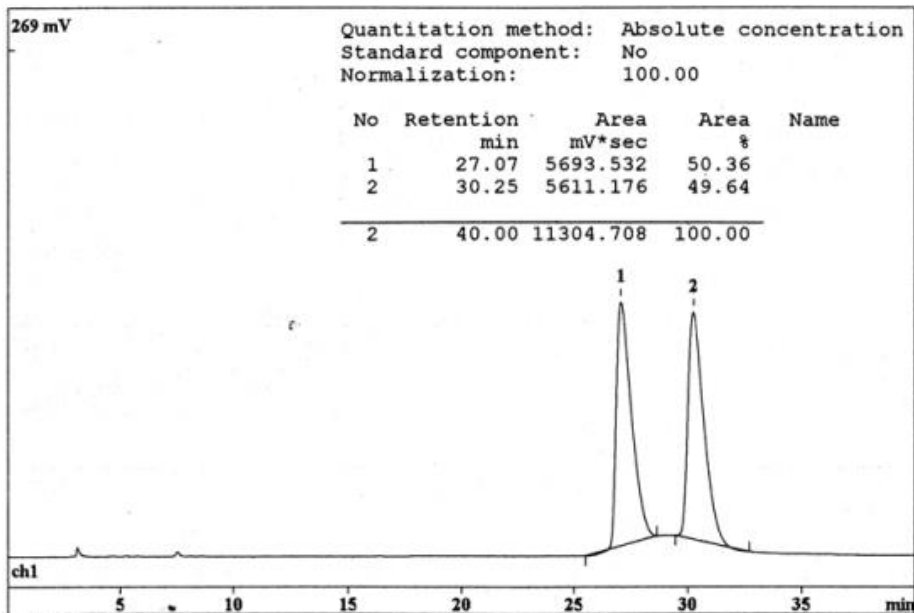
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm

3q

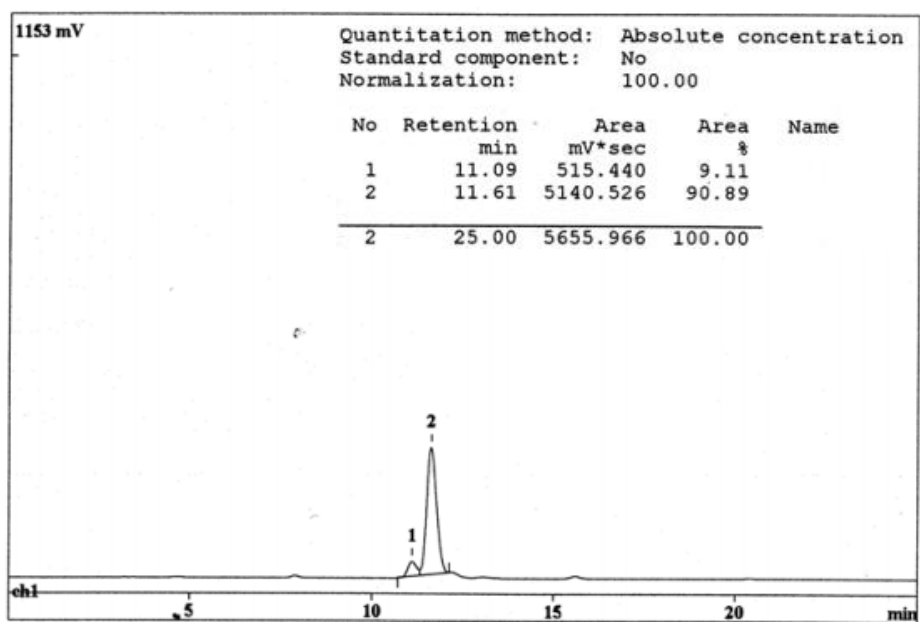
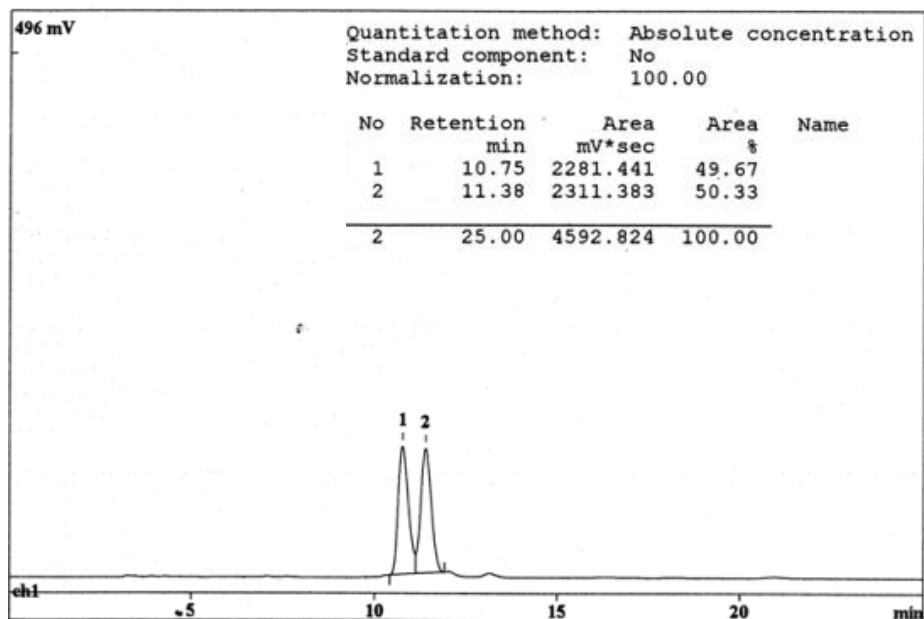
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254 \text{ nm}$



3r

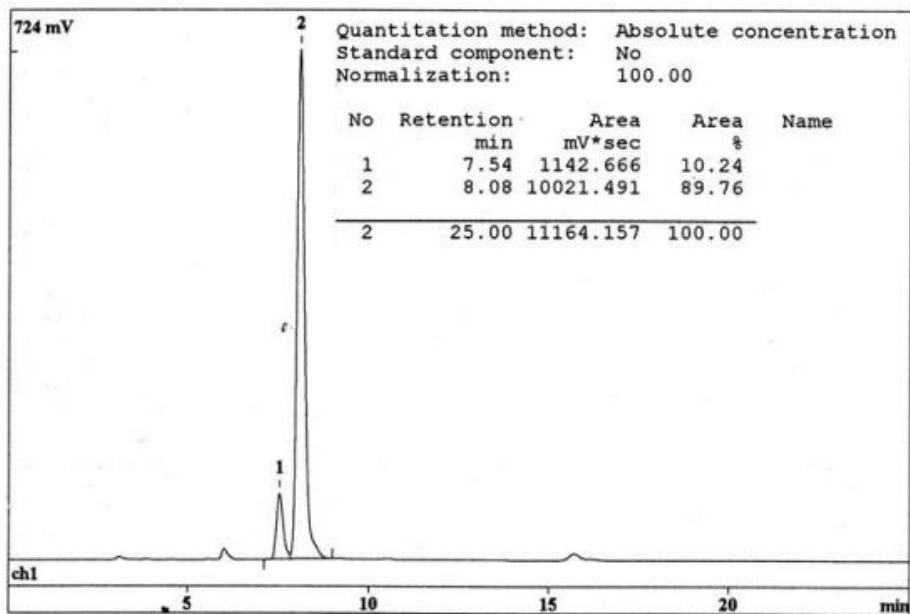
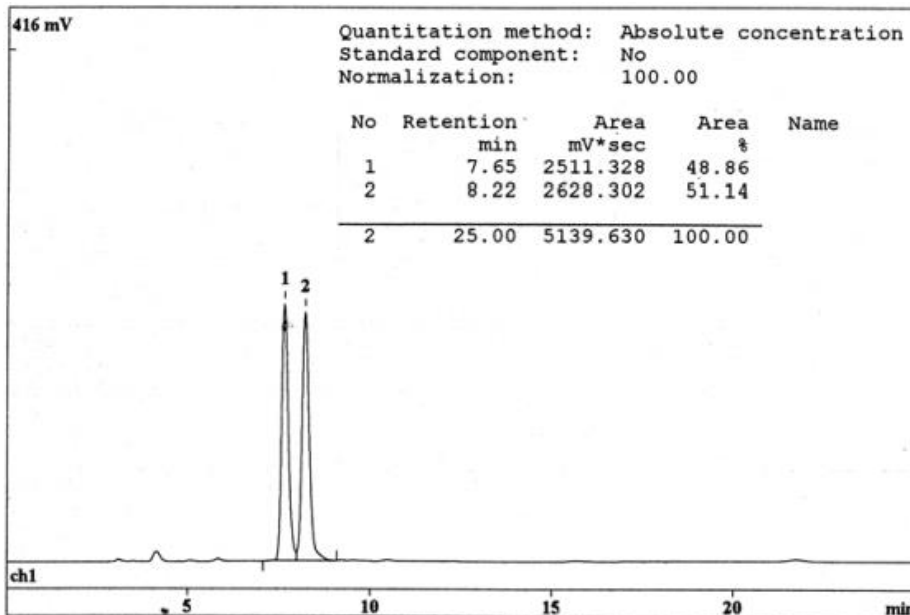
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, $\lambda = 254$ nm

3s

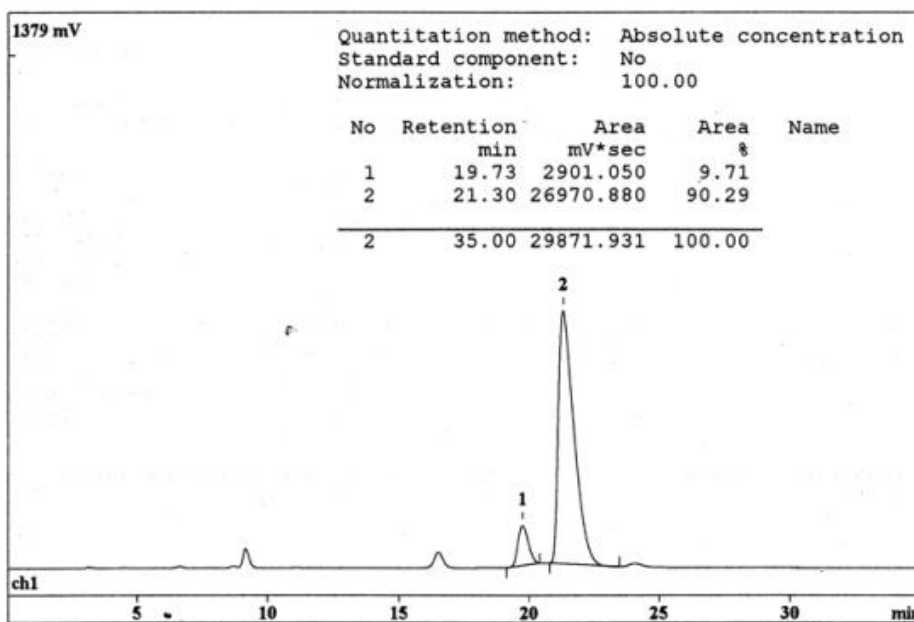
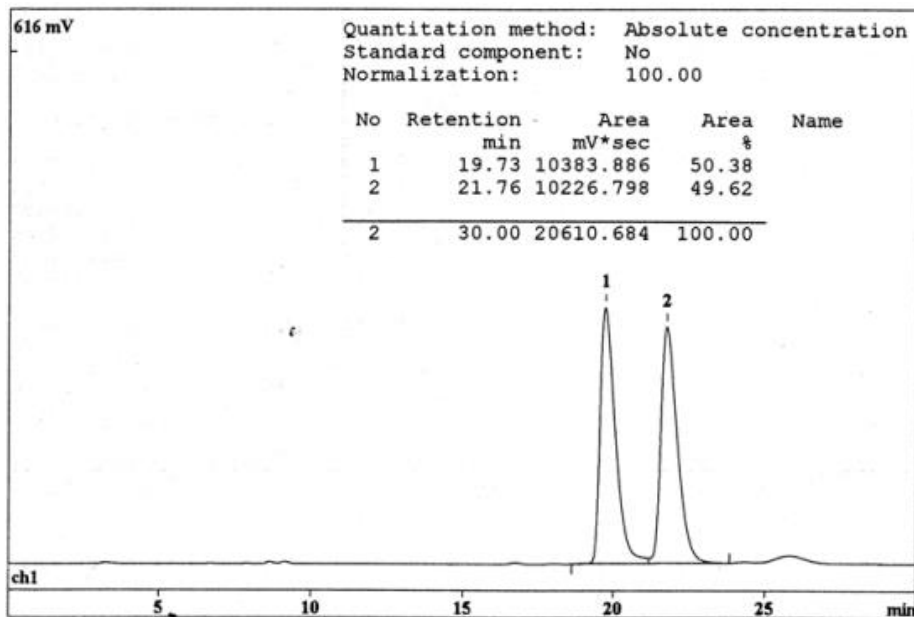
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254 \text{ nm}$



3t

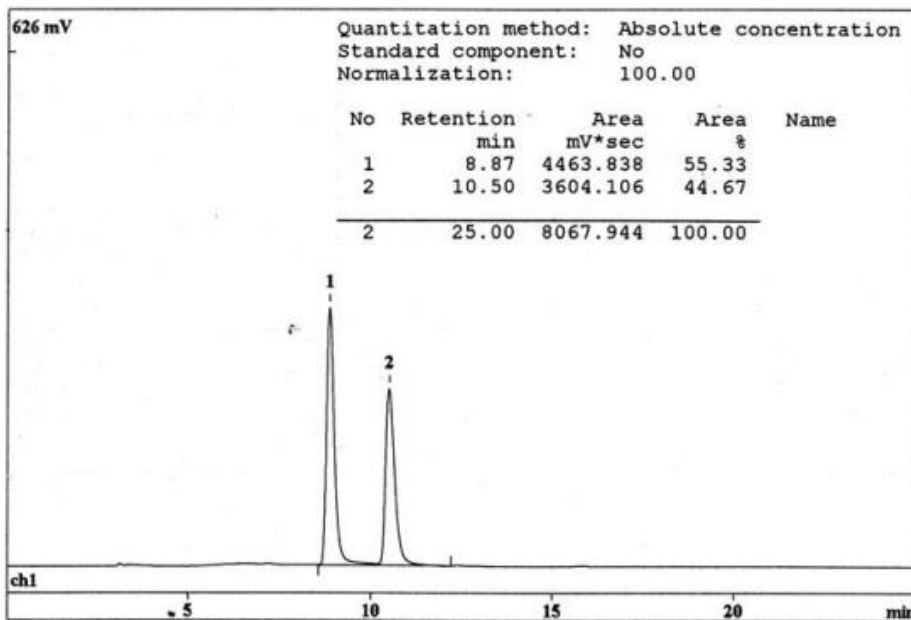
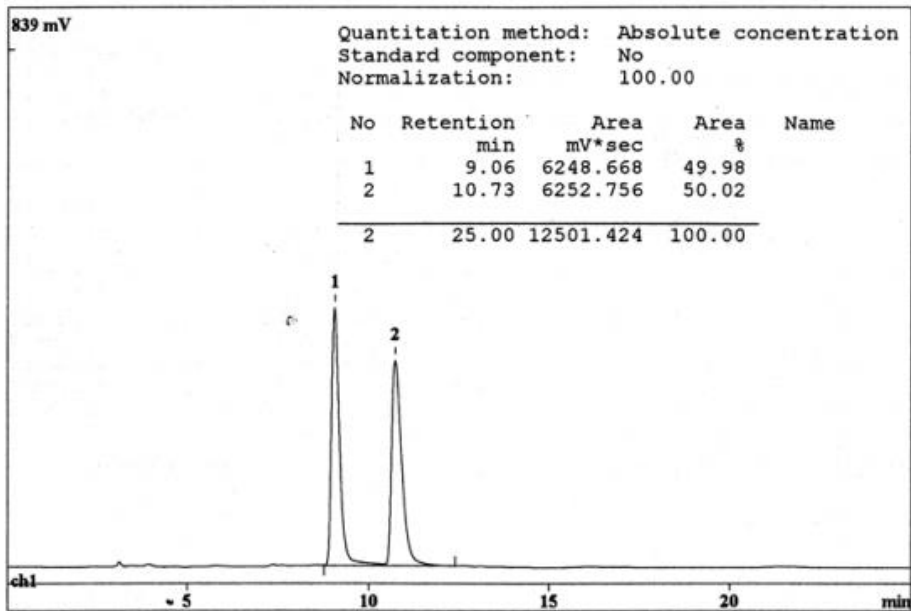
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm

5a

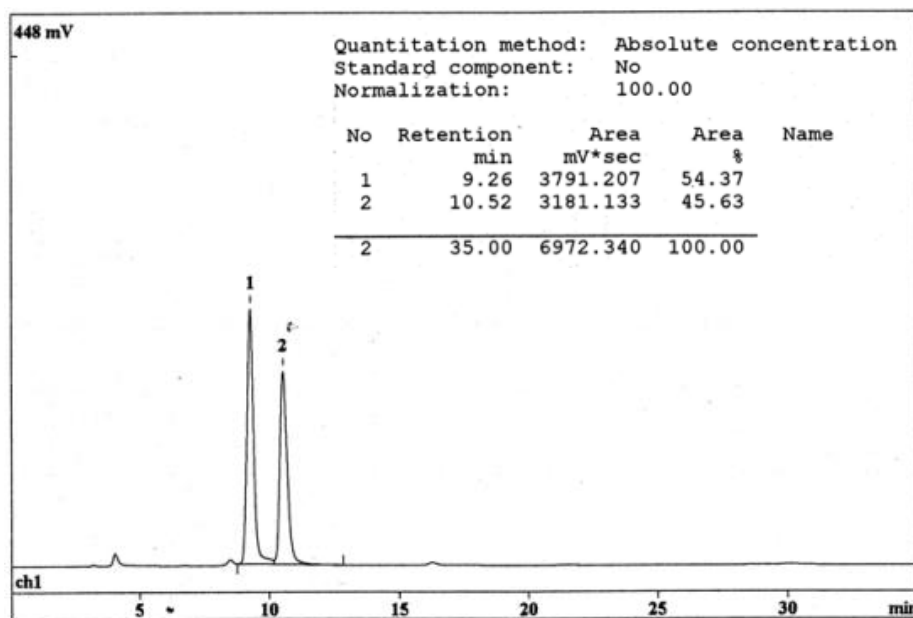
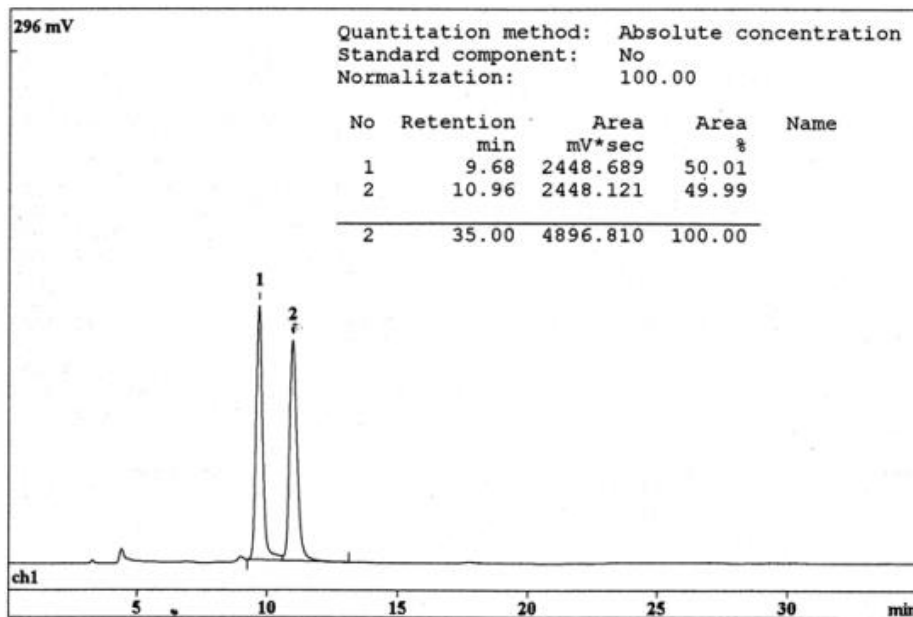
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254 \text{ nm}$)

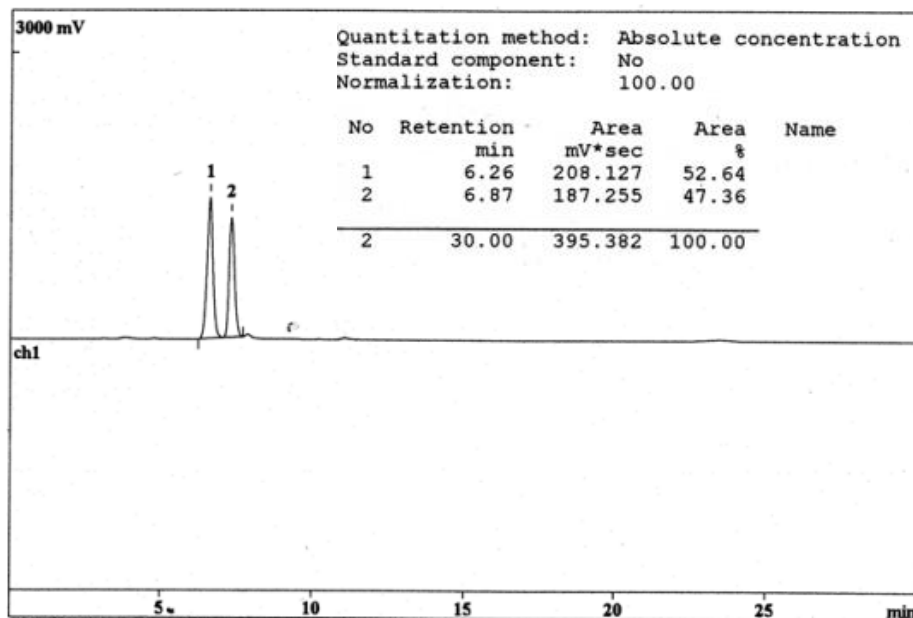
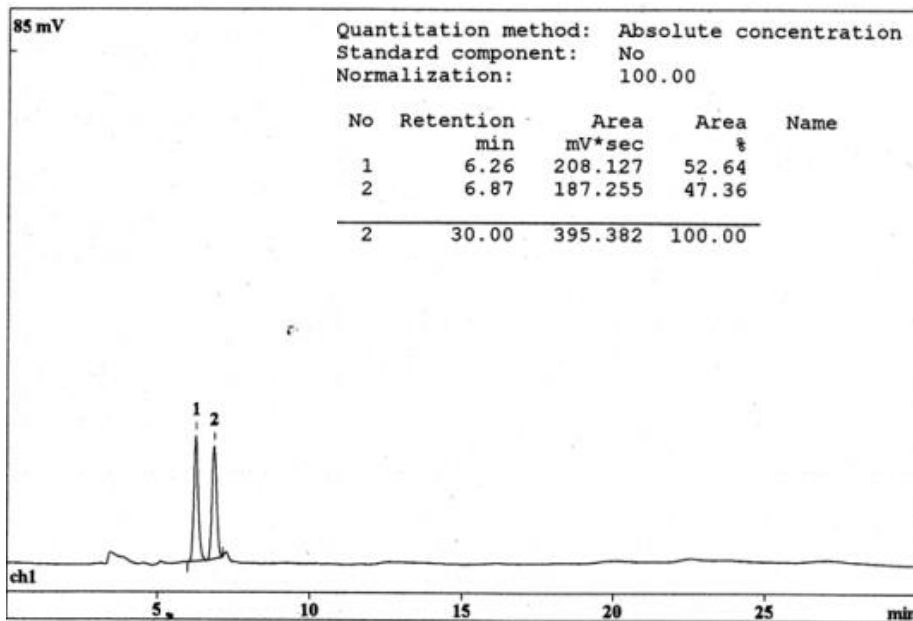


5b

Phenomenex Lux Cellulose-1 column

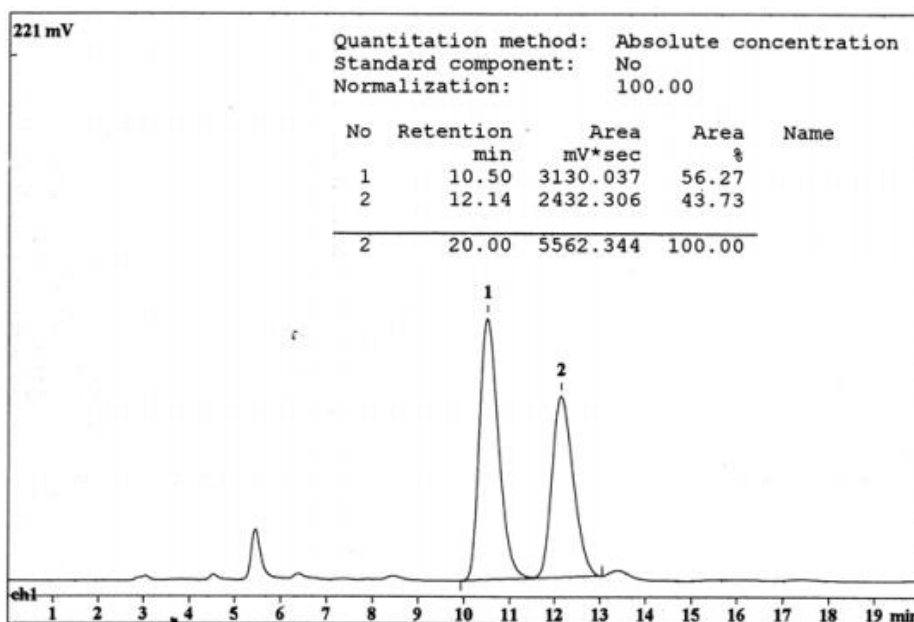
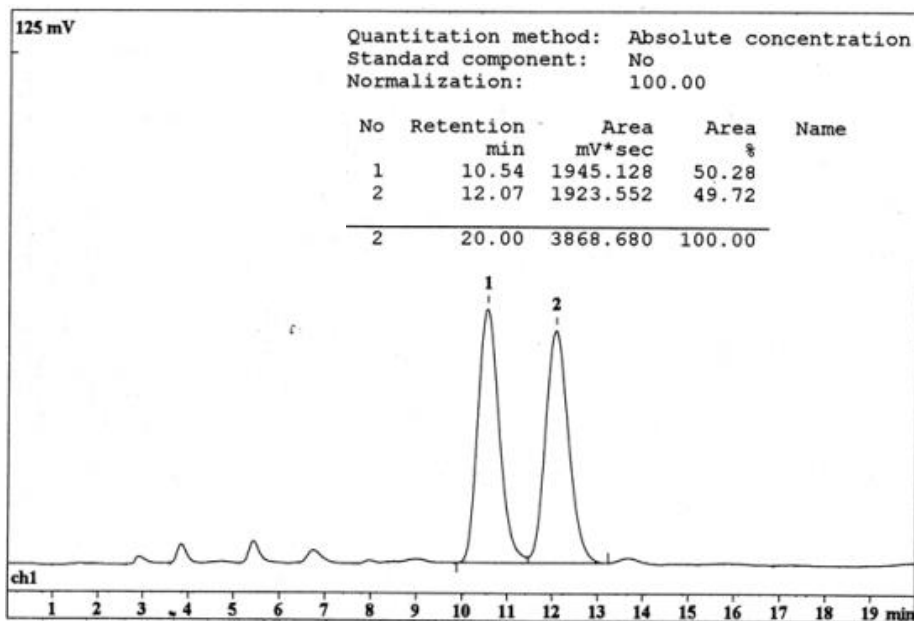
hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm)

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



5d

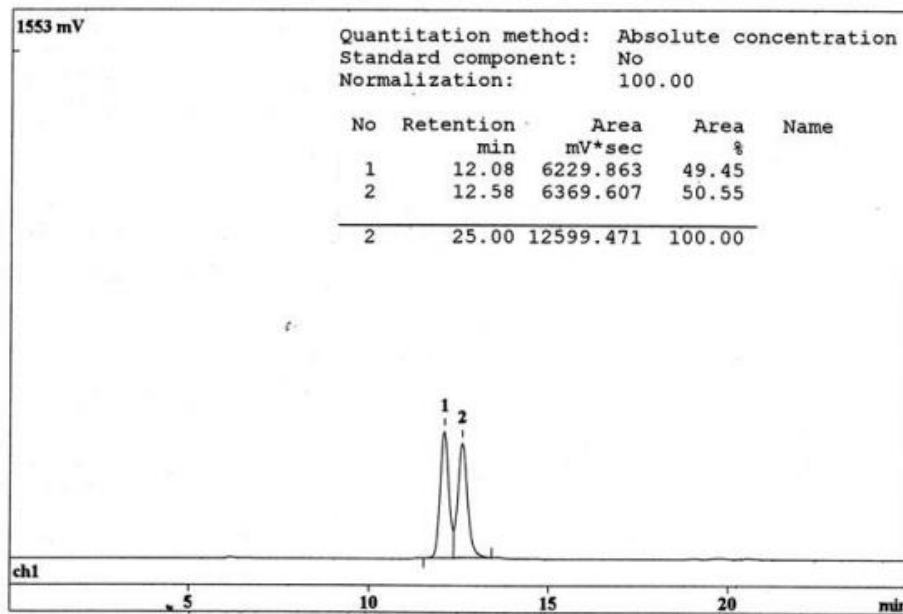
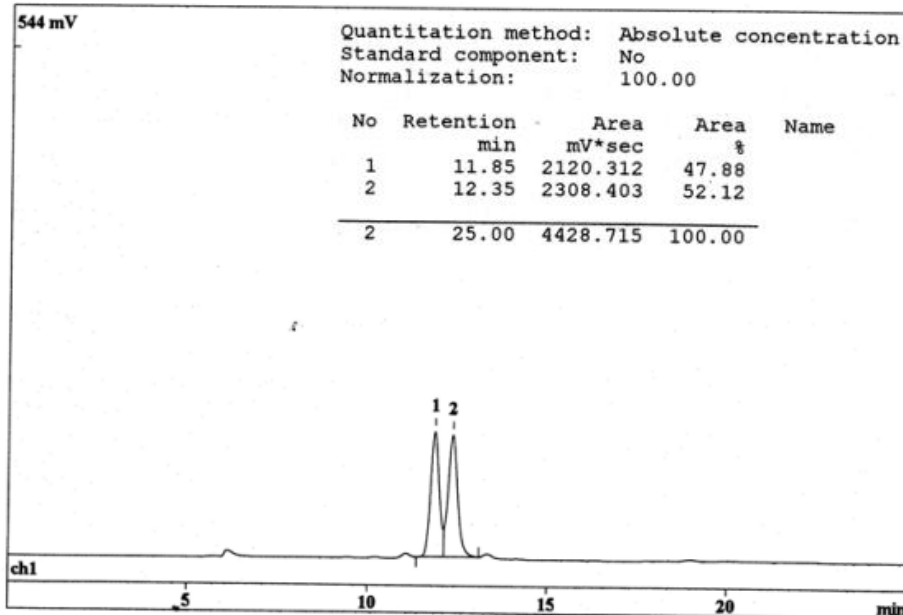
Chiracel OJ column

hexane/i-PrOH = 90:10, flow rate 1.0 mL/min, $\lambda = 254$ nm

5e

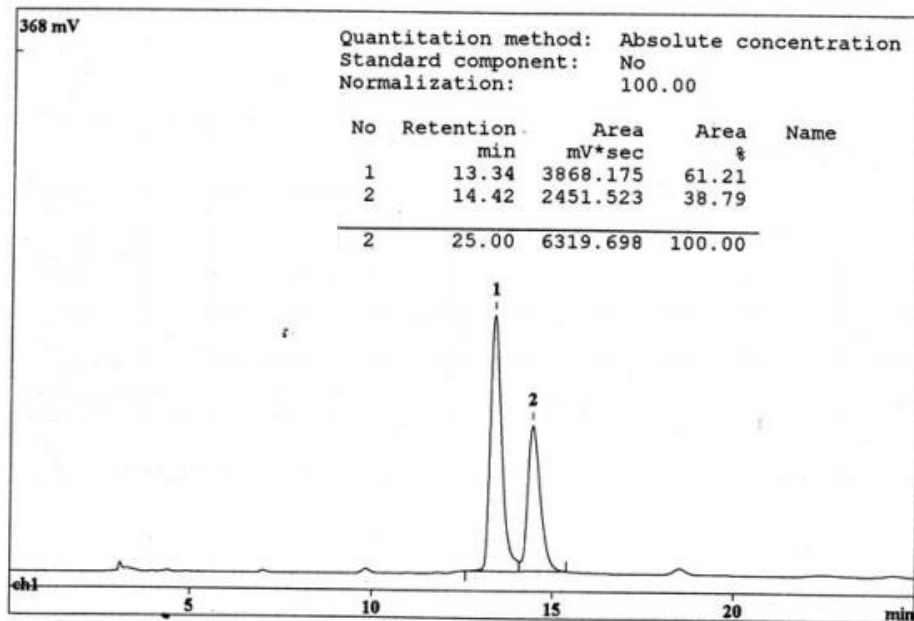
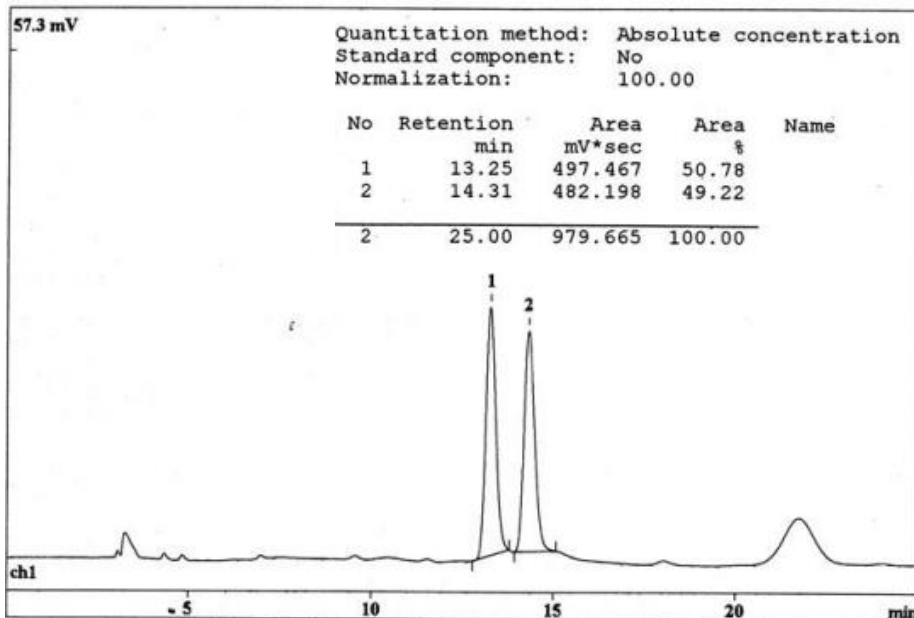
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 98:2, flow rate 0.5 mL/min, $\lambda = 254 \text{ nm}$



5f

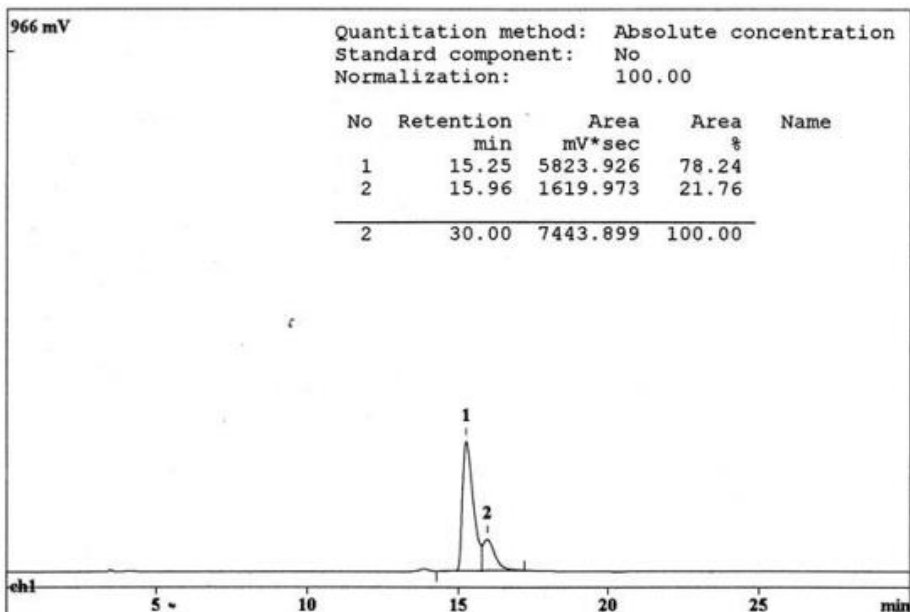
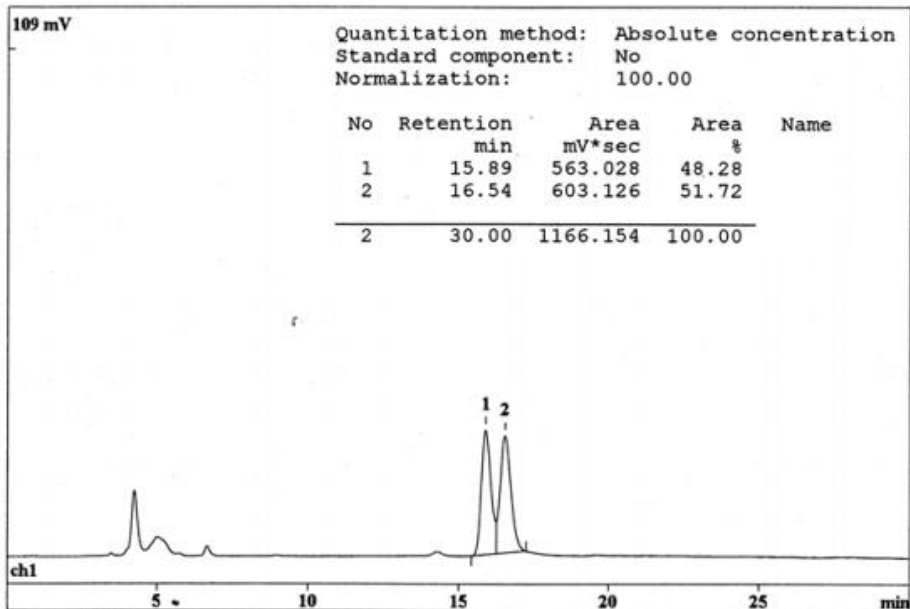
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm

5g

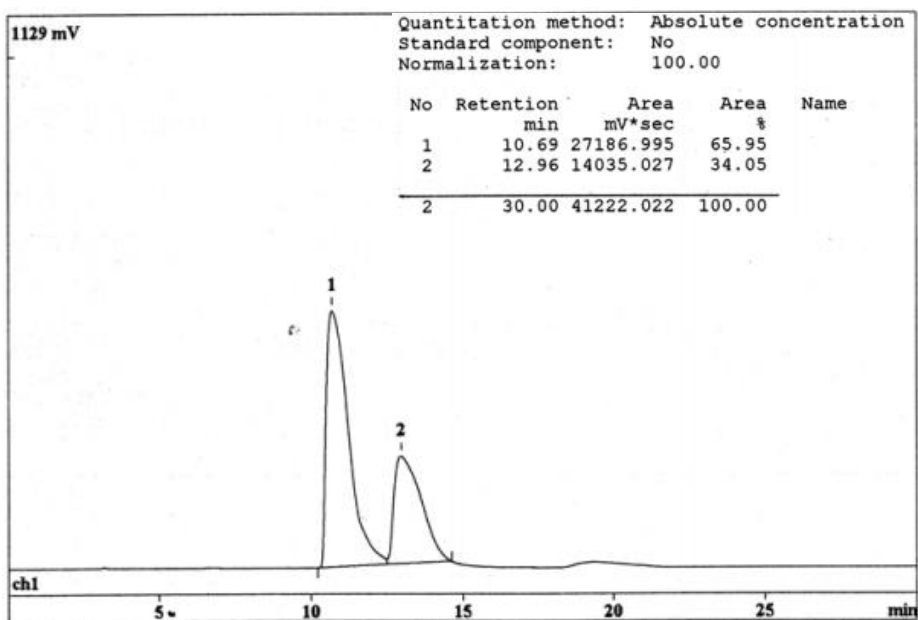
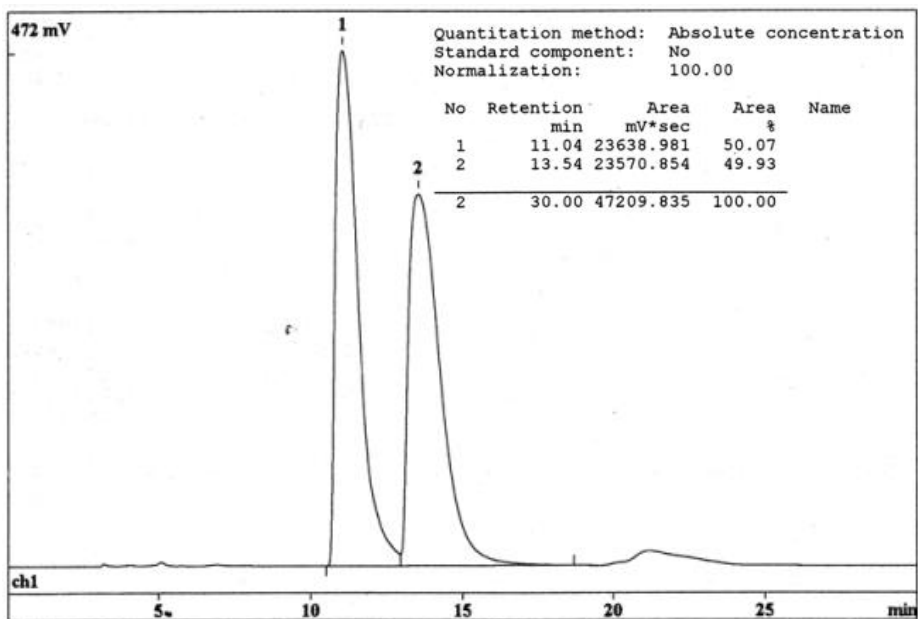
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 99:1, flow rate 0.9 mL/min, $\lambda = 254 \text{ nm}$



5h

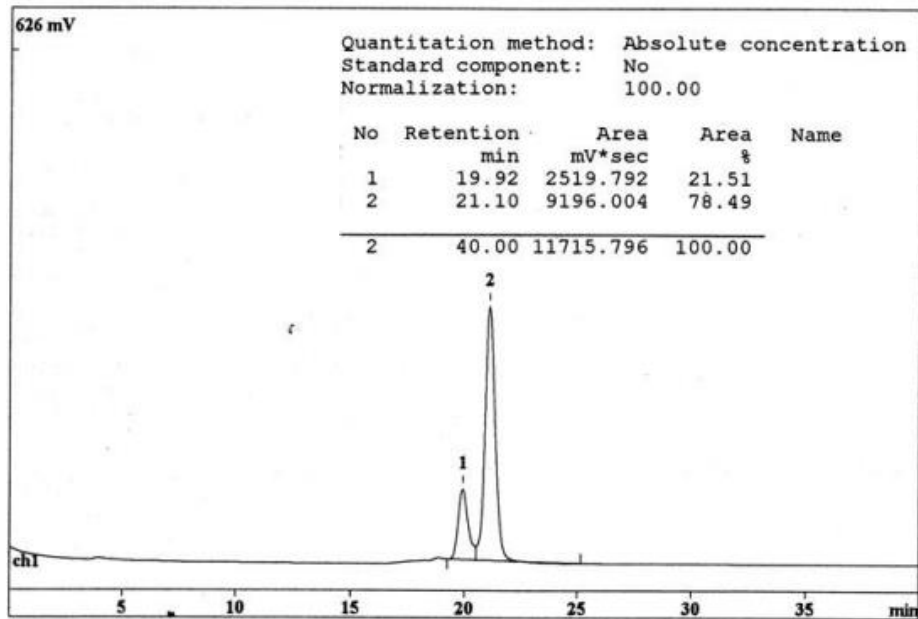
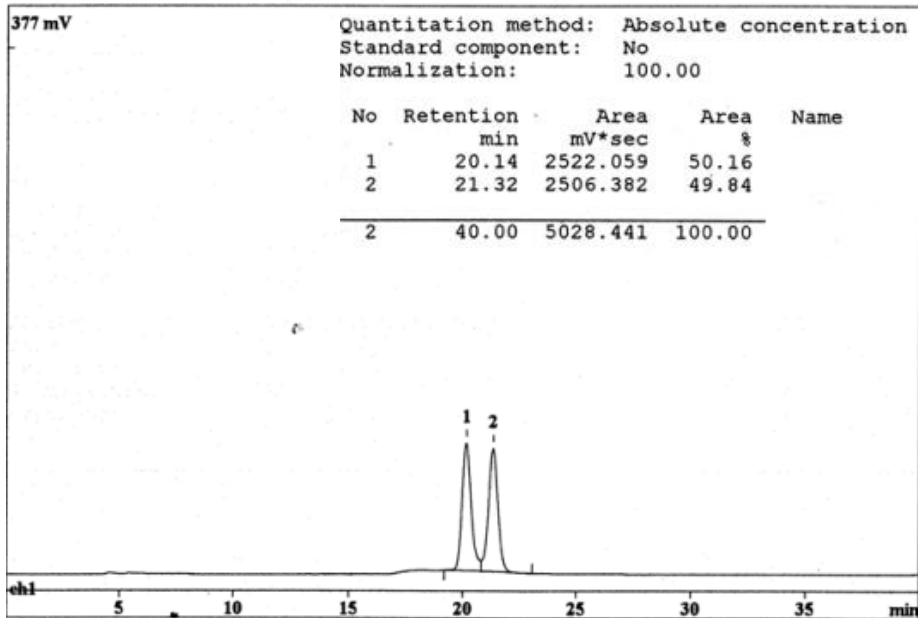
Chiralpak AS-H column

hexane/i-PrOH = 95:5, flow rate 1.0 mL/min, $\lambda = 254$ nm

5i

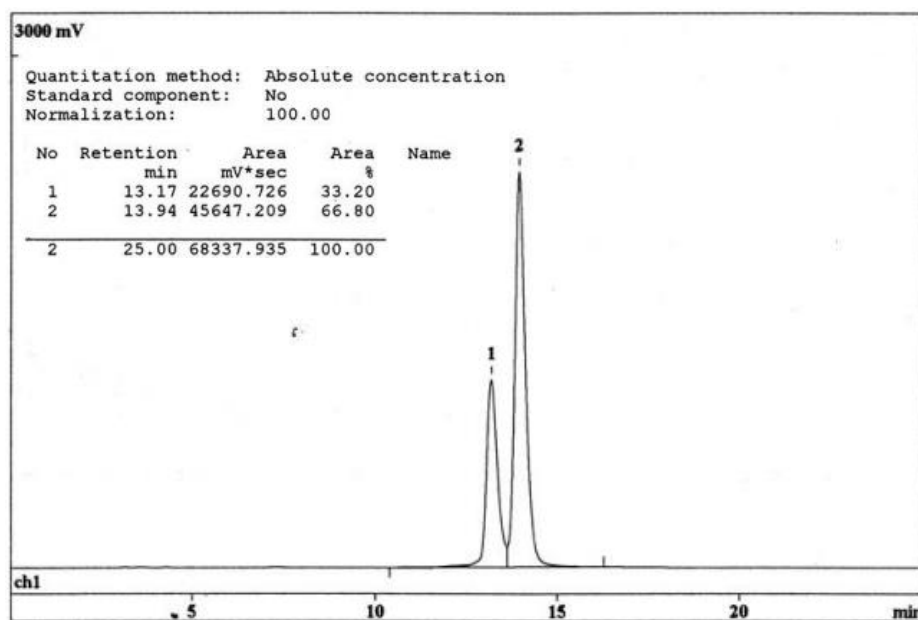
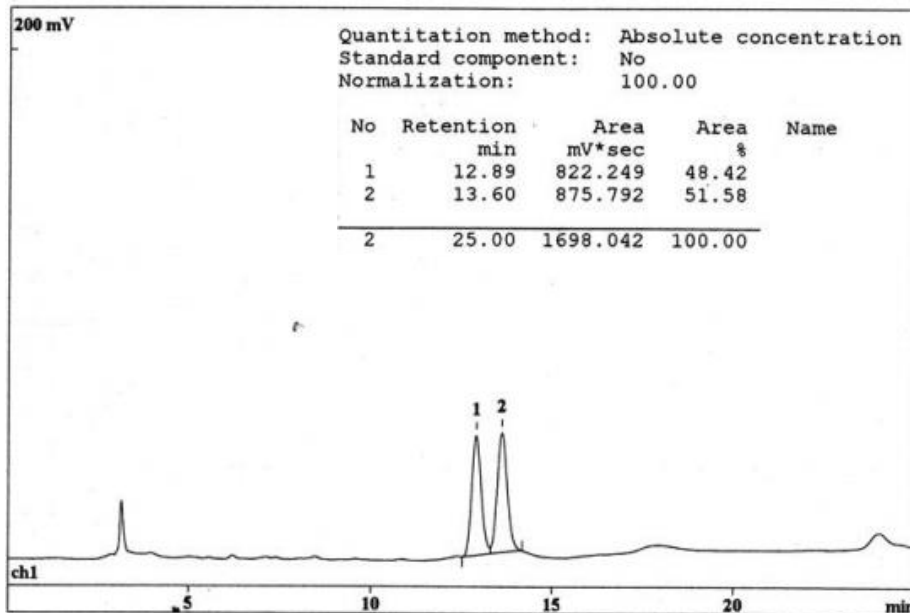
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, $\lambda = 254 \text{ nm}$



5j

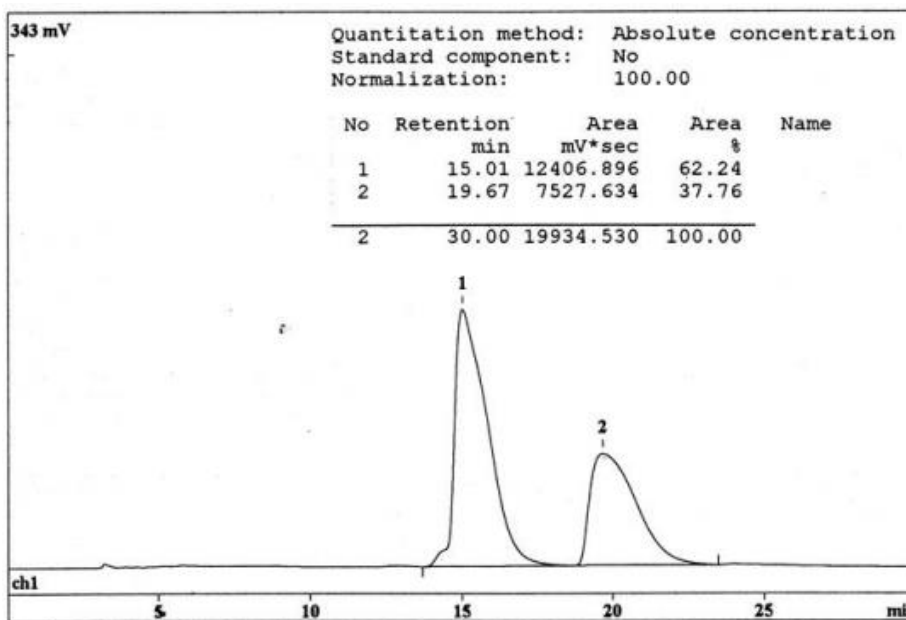
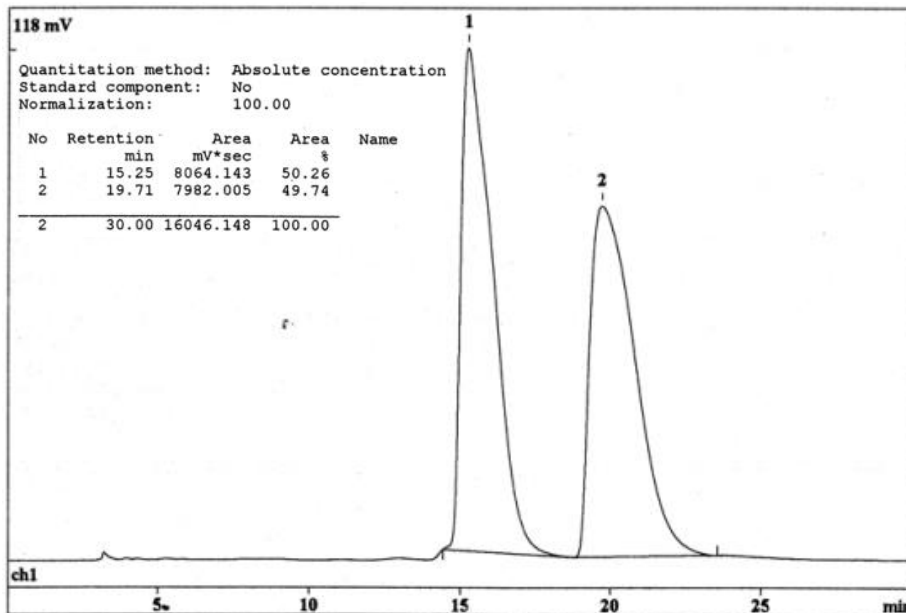
Phenomenex Lux Cellulose-1 column

hexane/i-PrOH = 99:1, flow rate 1.0 mL/min, $\lambda = 254$ nm

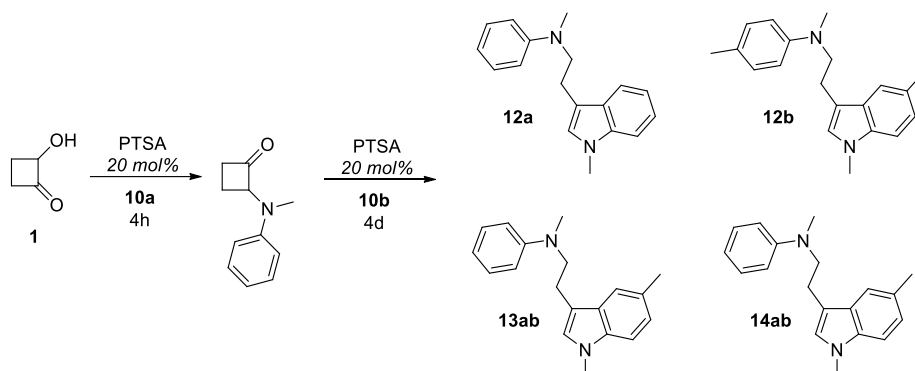
5k

Chiralpak AS-H column

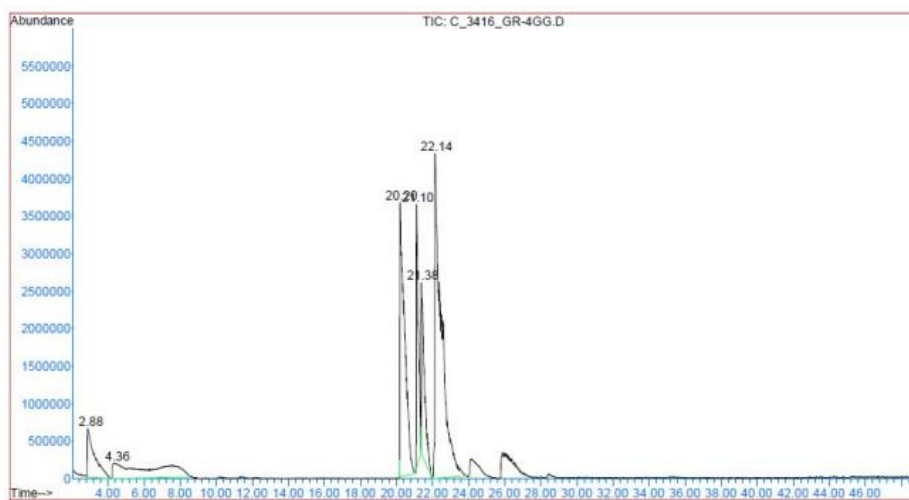
hexane/i-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254 \text{ nm}$



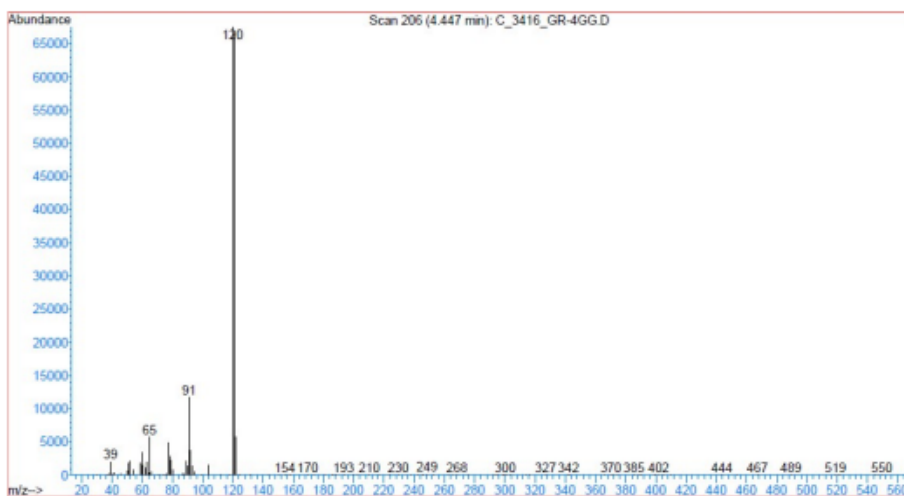
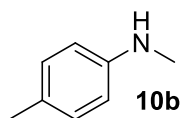
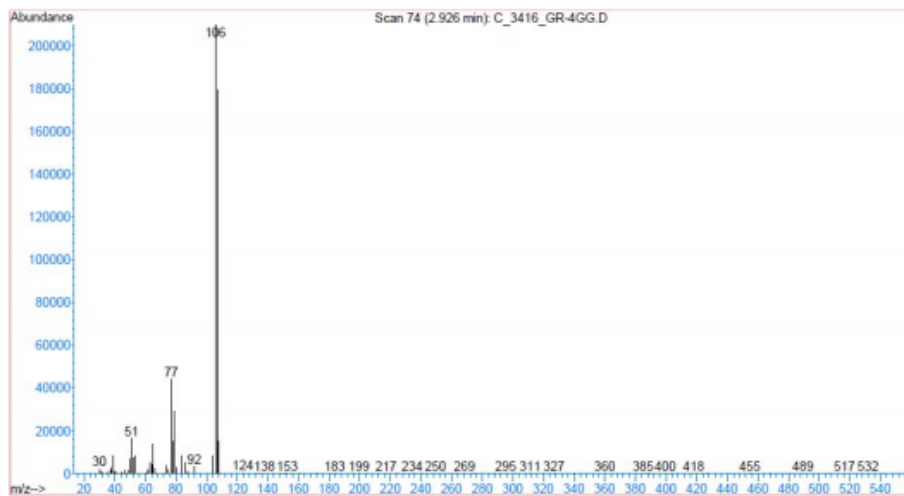
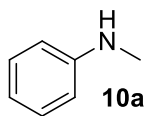
7.6 GC-MS CHROMATOGRAMS

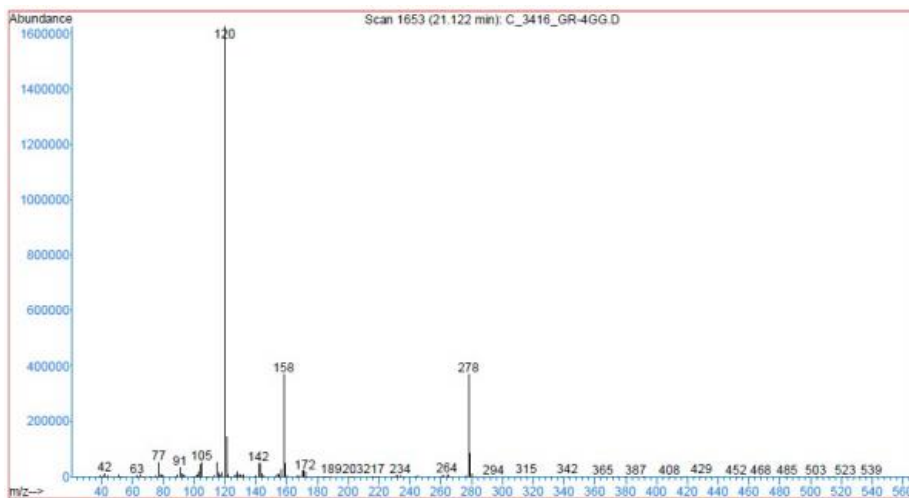
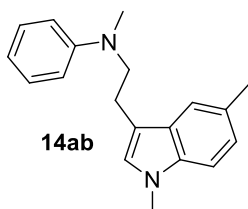
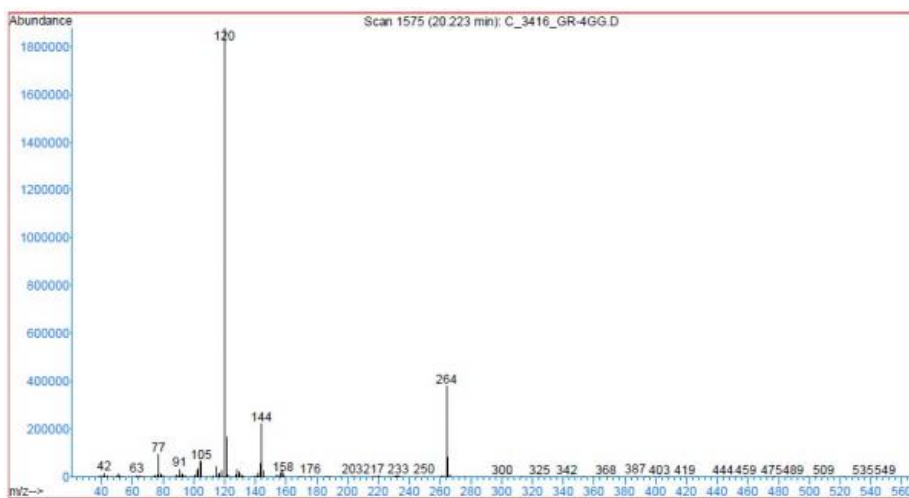
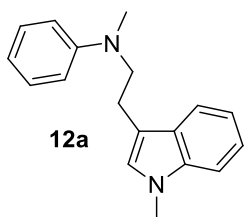


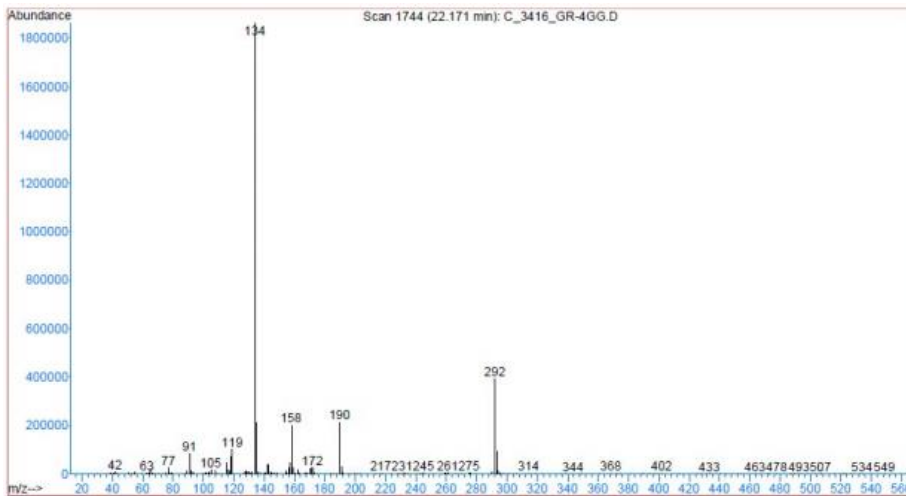
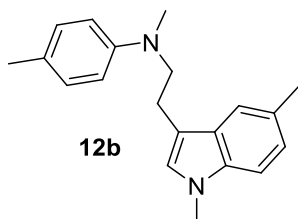
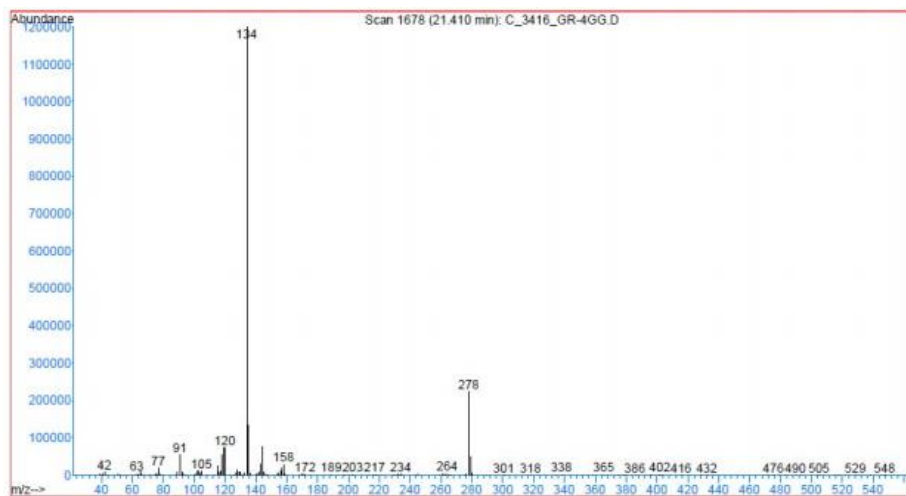
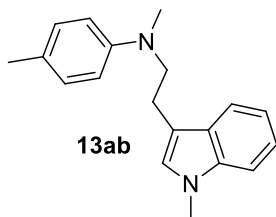
GC-MS analysis of the crude reaction mixture

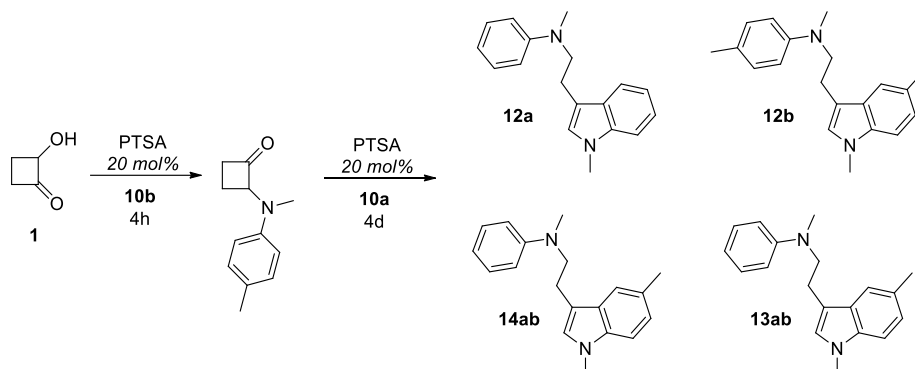


peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	2.880	65	70	185	M3	644722	177467477	16.43%	6.374%
2	4.355	185	198	557	M3	209029	329276190	30.49%	11.826%
3	20.200	1571	1573	1644	M	3698120	642252755	59.46%	23.067%
4	21.099	1644	1651	1674	M	3554848	286058255	26.48%	10.274%
5	21.376	1674	1675	1729	M2	2445472	269151296	24.92%	9.667%
6	22.136	1729	1741	1905	M2	4480440	1080105674	100.00%	38.793%

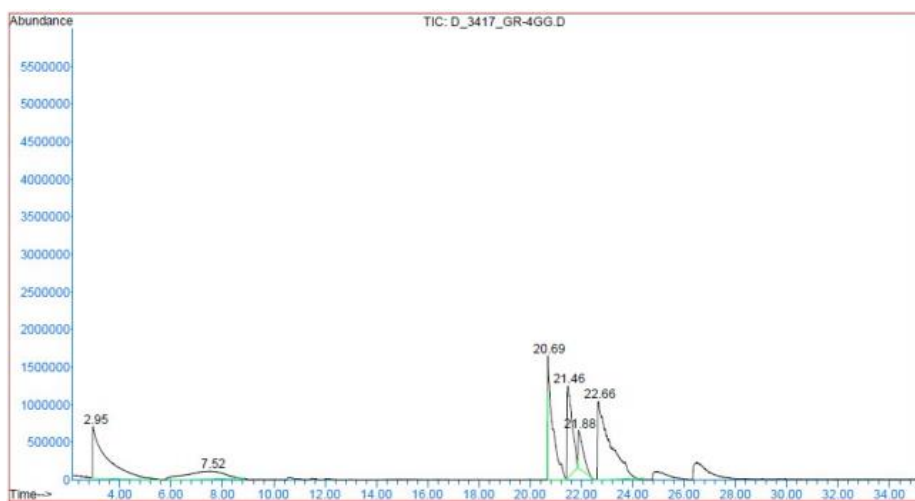




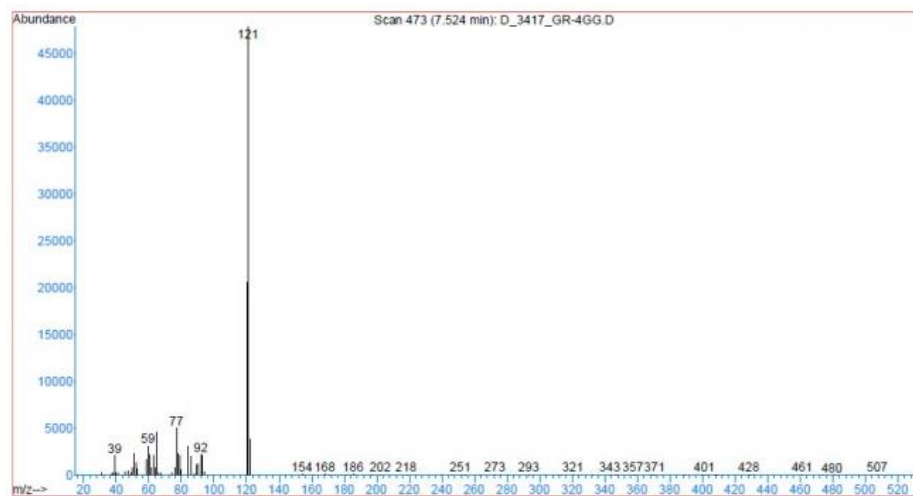
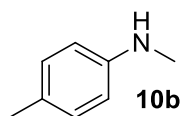
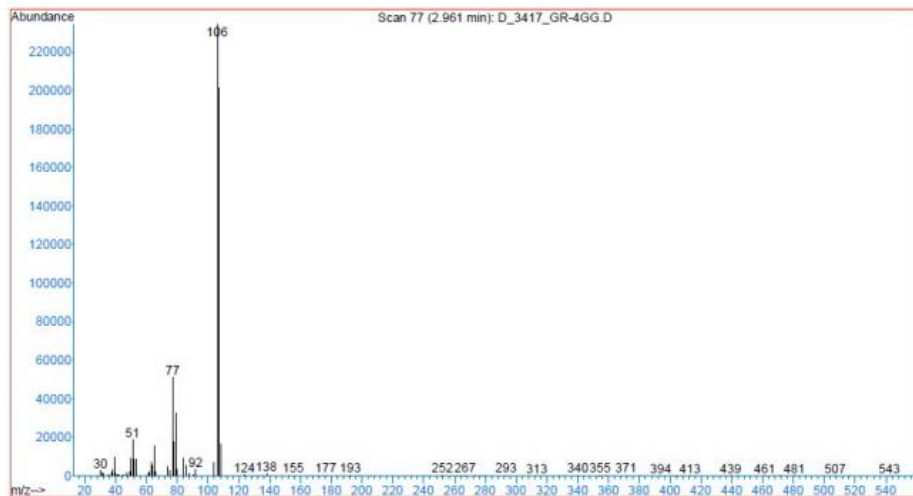
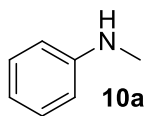


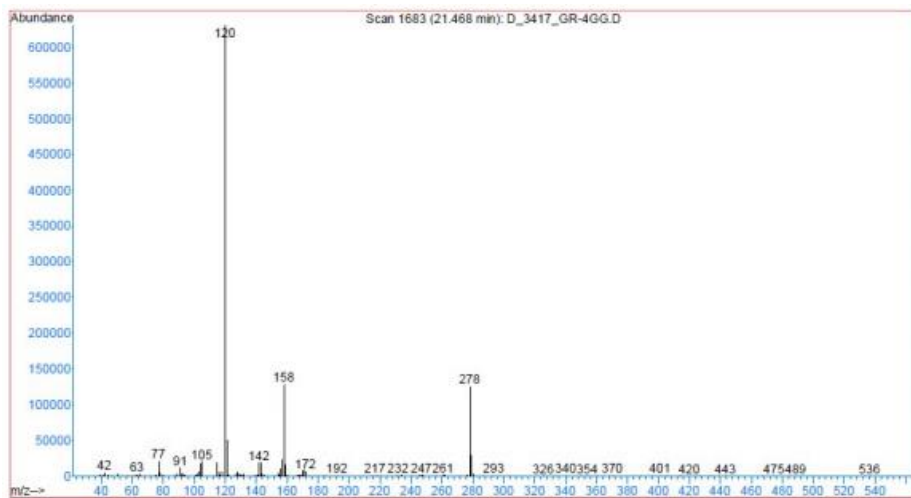
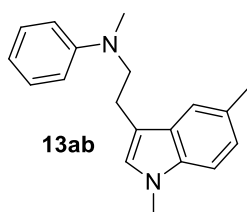
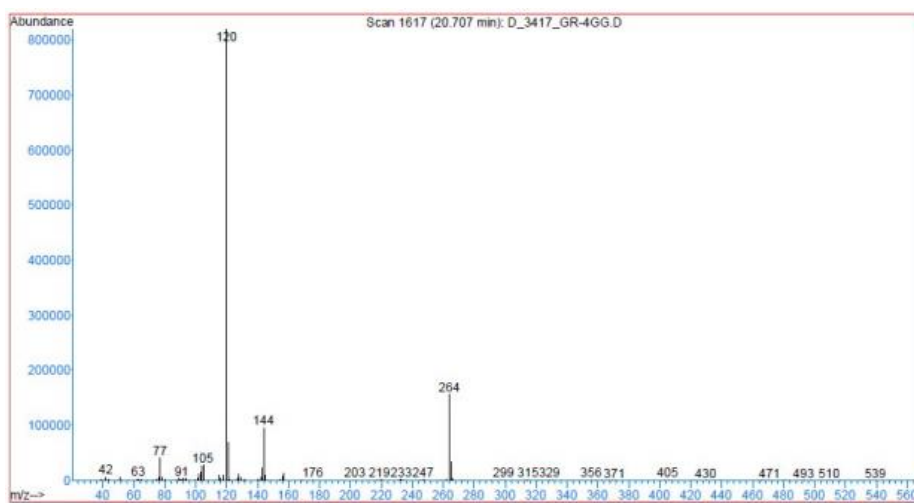
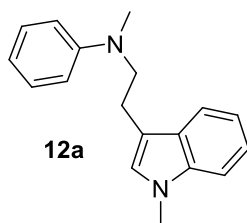


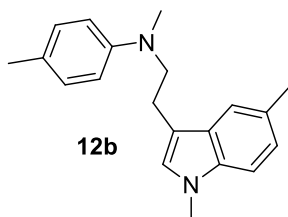
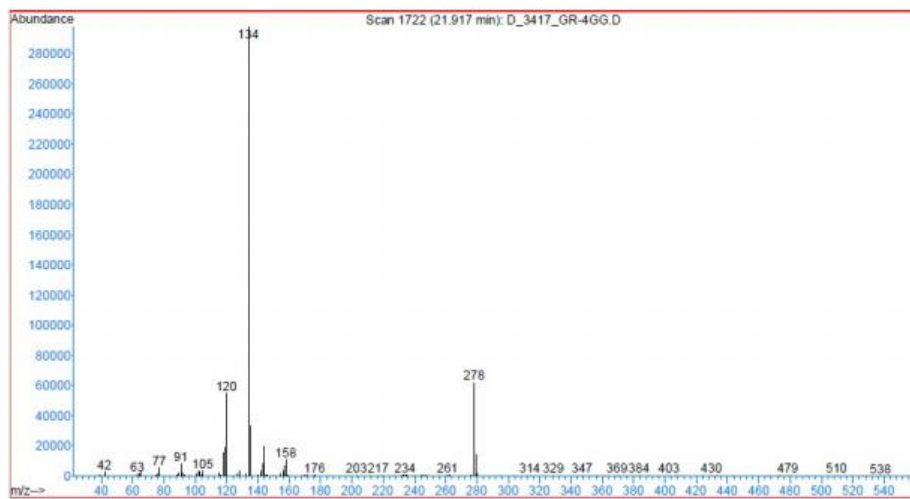
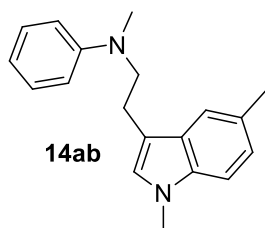
GC-MS analysis of the crude reaction mixture

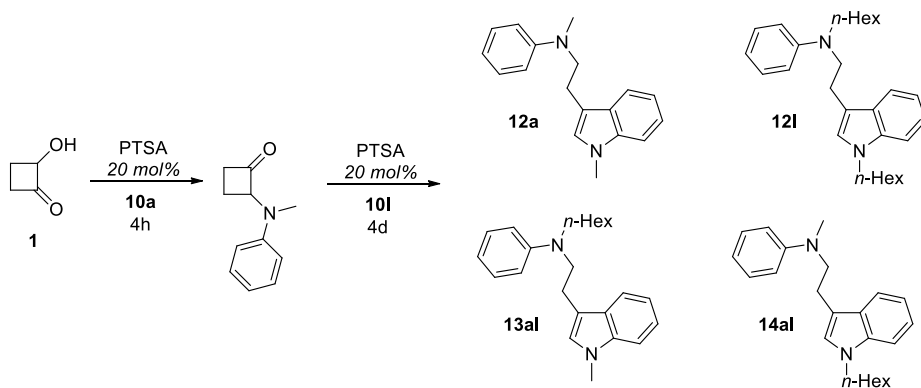
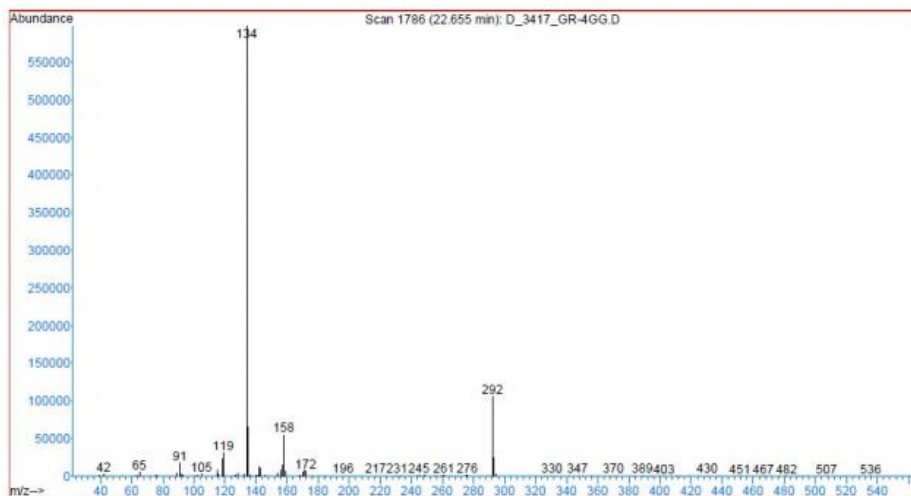


peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	2.949	71	76	304	M2	690395	255621750	72.51%	21.760%
2	7.524	337	473	591	M2	106588	107613422	30.53%	9.161%
3	20.684	1614	1615	1674	M	1654981	224806214	63.77%	19.137%
4	21.468	1674	1683	1716	M	1220175	163956053	46.51%	13.957%
5	21.883	1716	1719	1774	M	503818	70202975	19.92%	5.976%
6	22.655	1777	1786	1937	M2	1048403	352511736	100.00%	30.008%

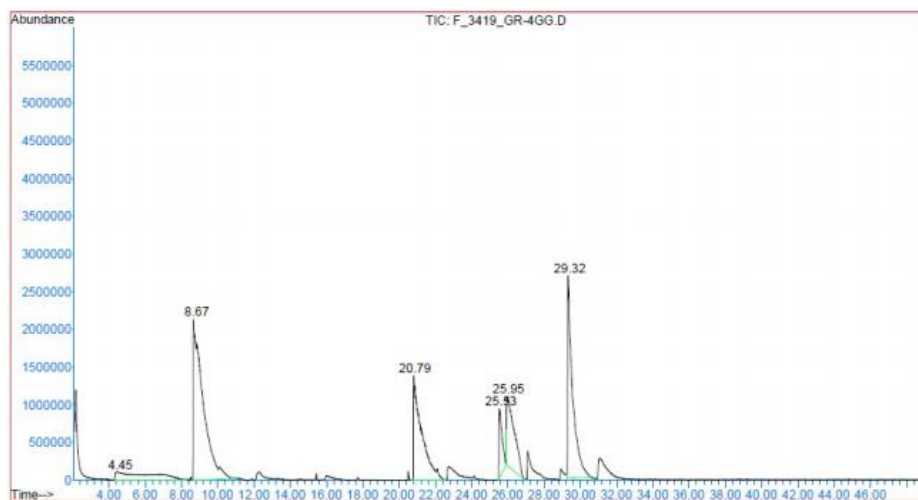




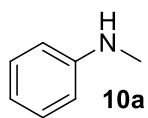


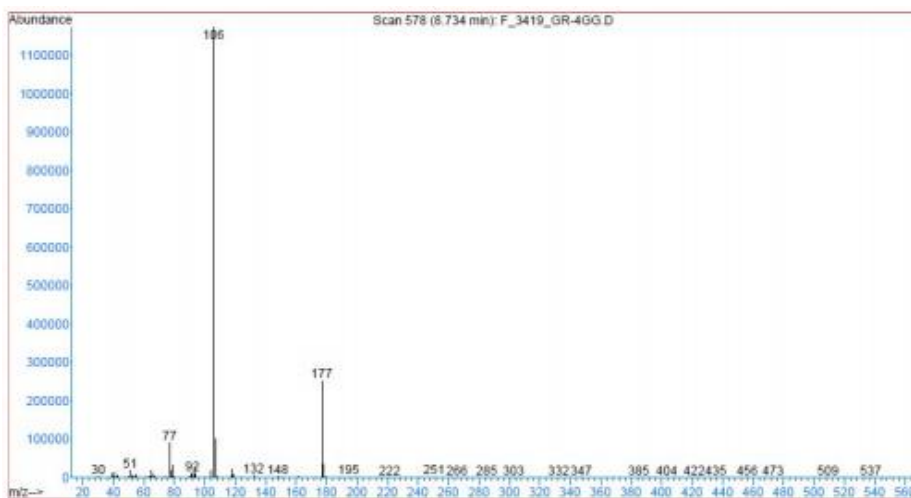
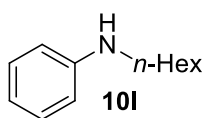
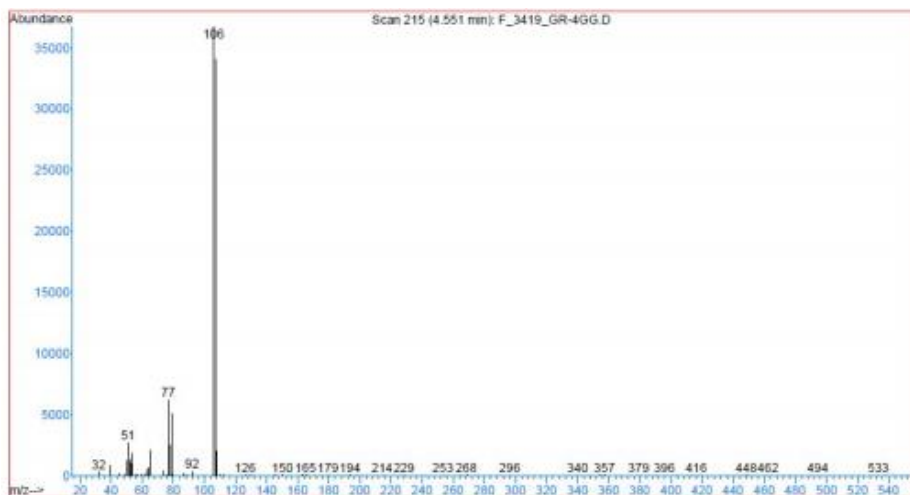


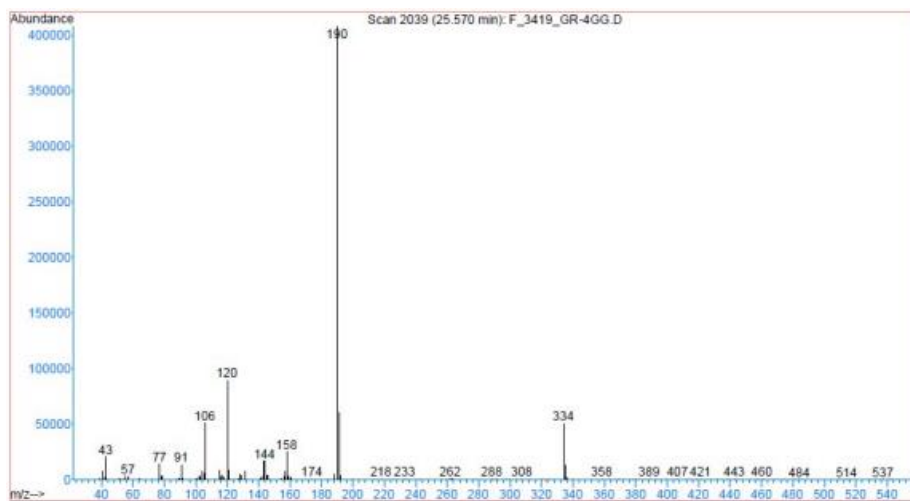
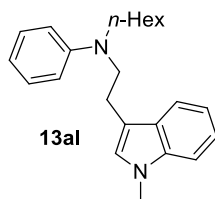
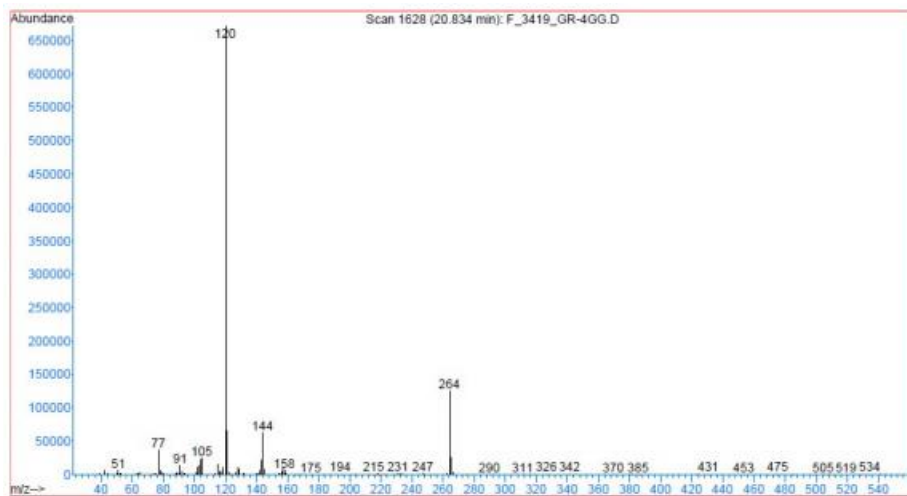
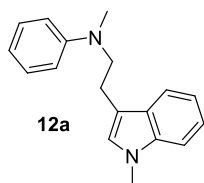
GC-MS analysis of the crude reaction mixture

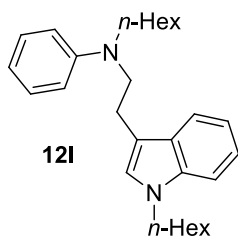
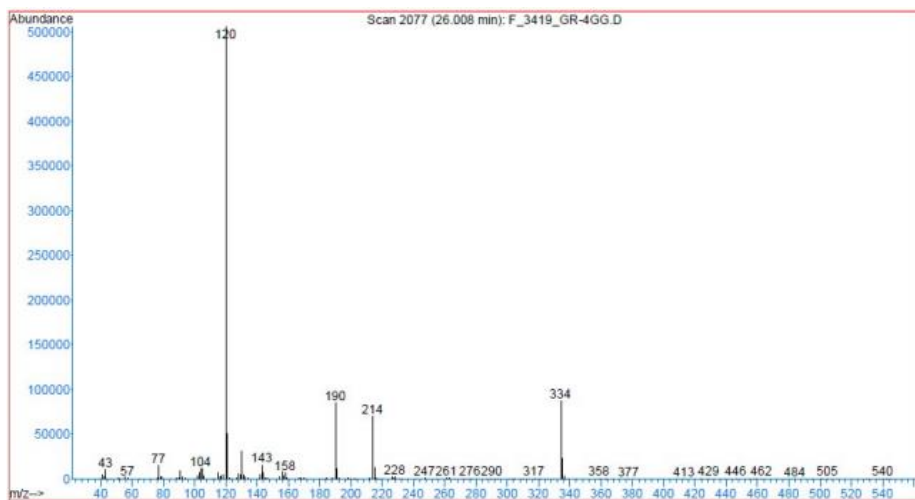
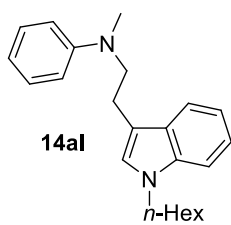


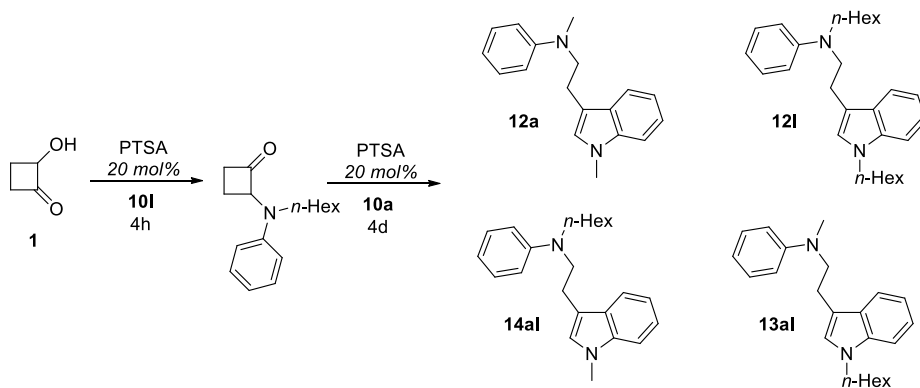
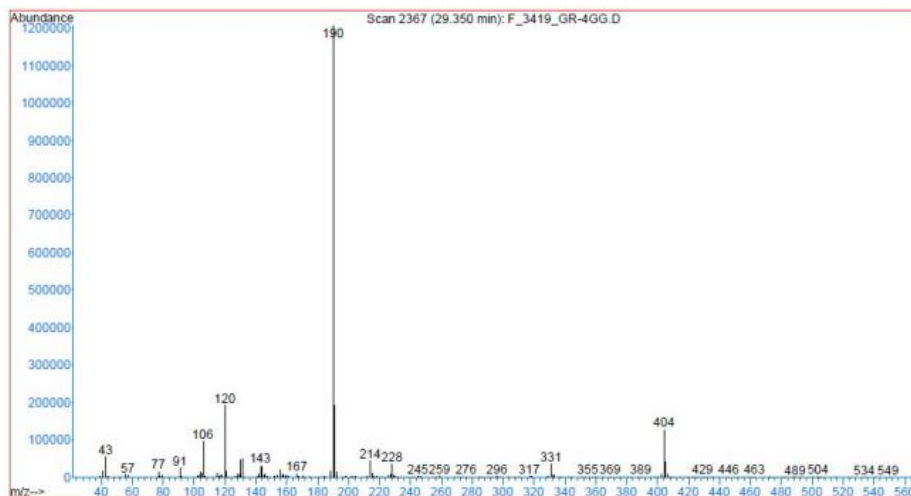
peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	4.447	193	206	539	M4	108428	151724041	19.24%	6.708%
2	8.665	569	572	774	M	2139673	788691545	100.00%	34.869%
3	20.788	1620	1624	1774	M2	1415815	437929147	55.53%	19.361%
4	25.536	2030	2036	2069	M	919366	106436526	13.50%	4.706%
5	25.950	2069	2072	2158	M2	910921	275952017	34.99%	12.200%
6	29.315	2359	2364	2487	M	2706289	501146389	63.54%	22.156%



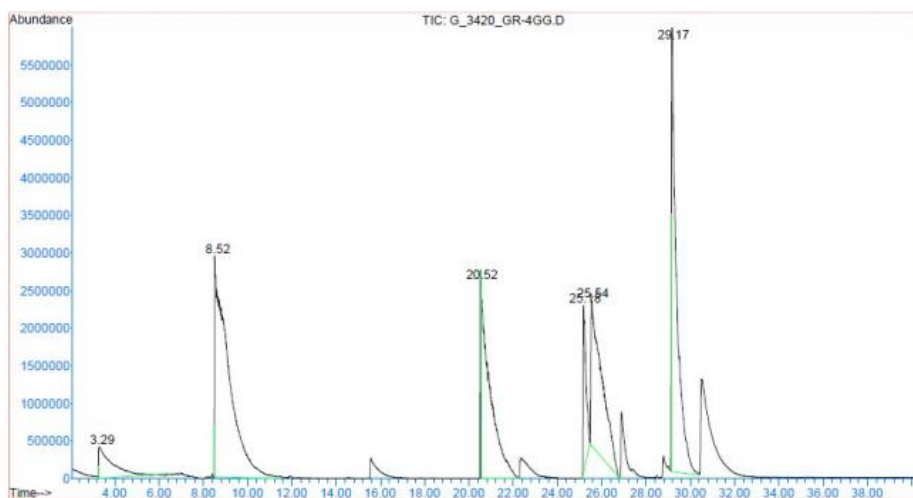




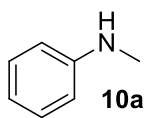


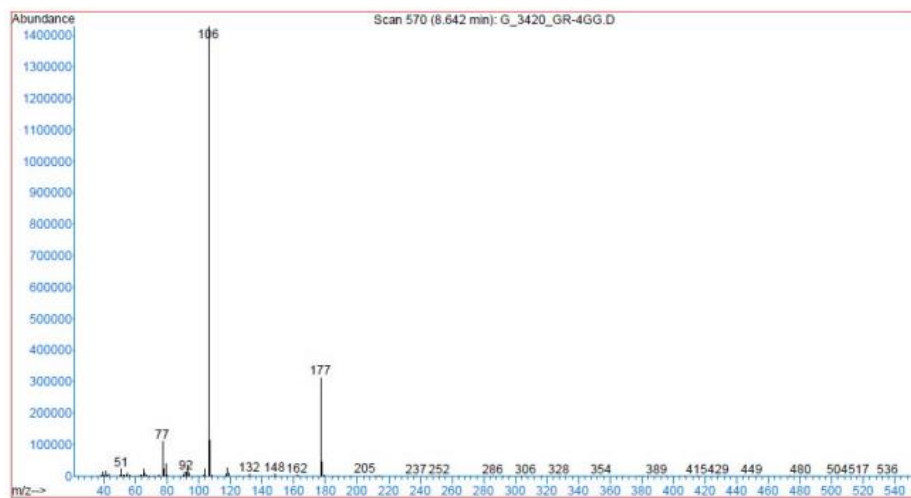
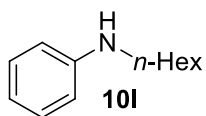
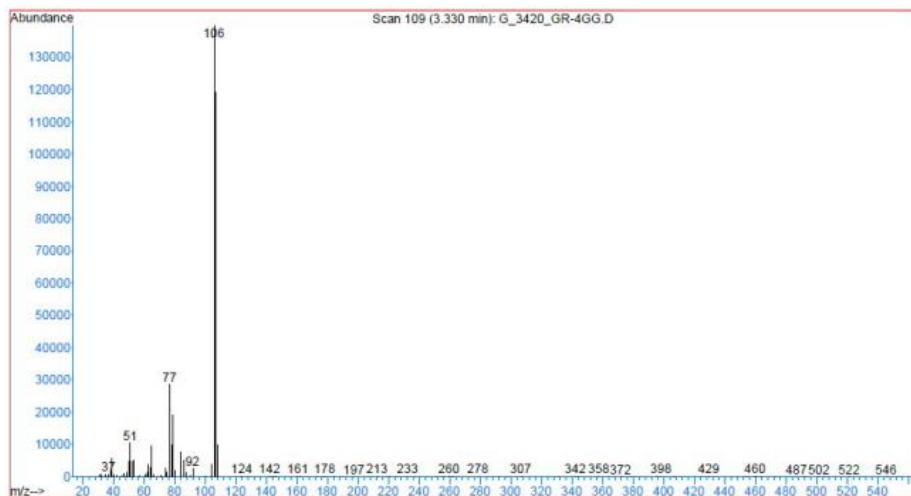


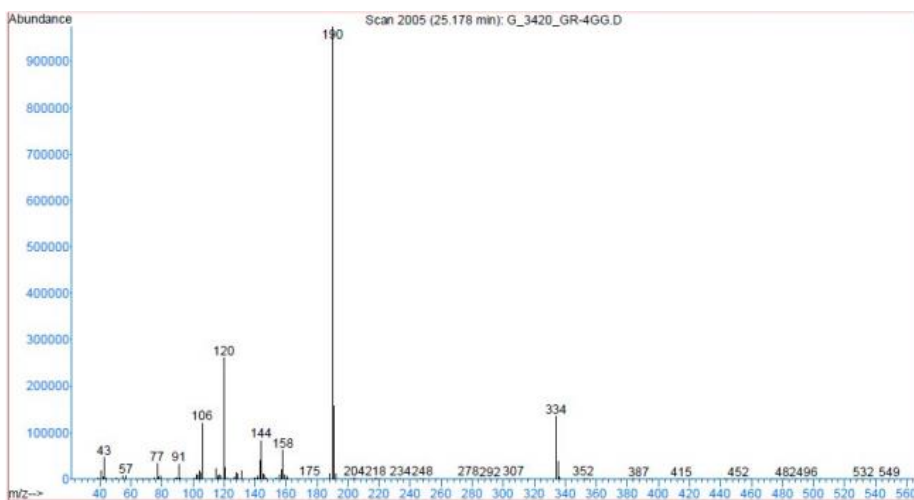
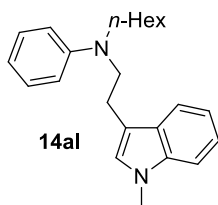
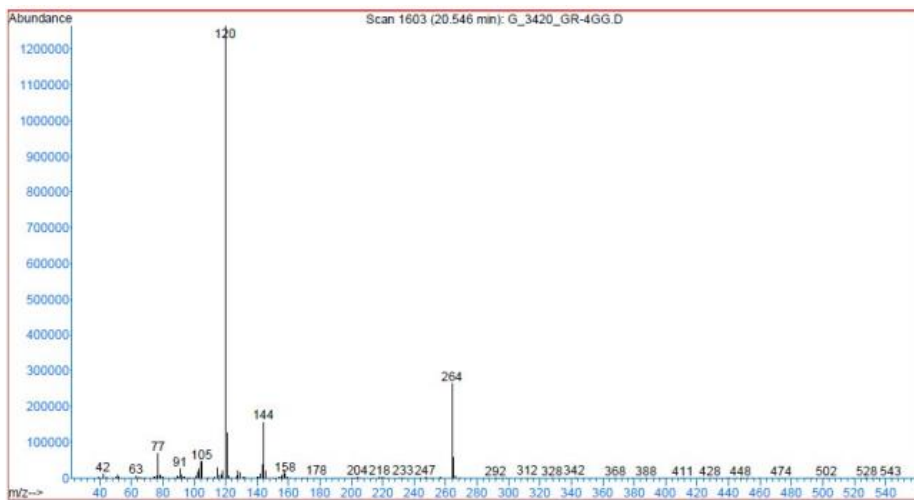
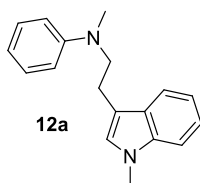
GC-MS analysis of the crude reaction mixture

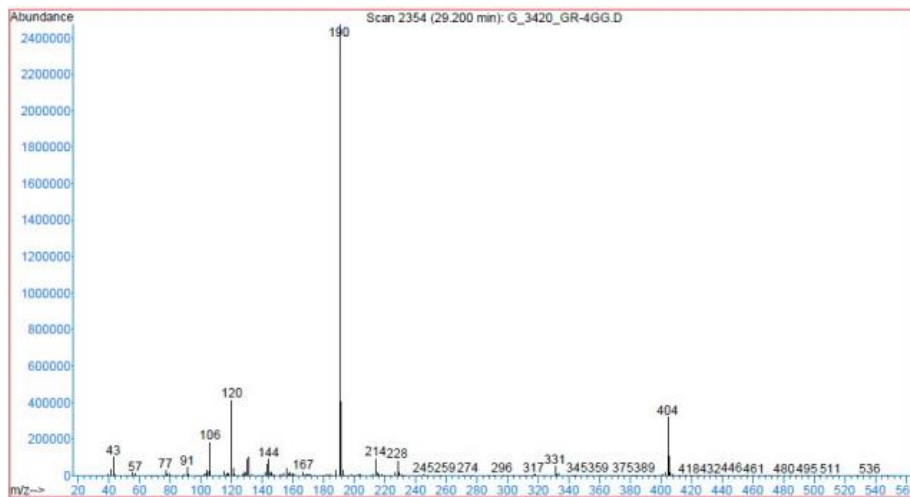
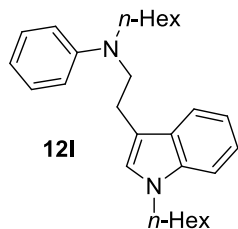
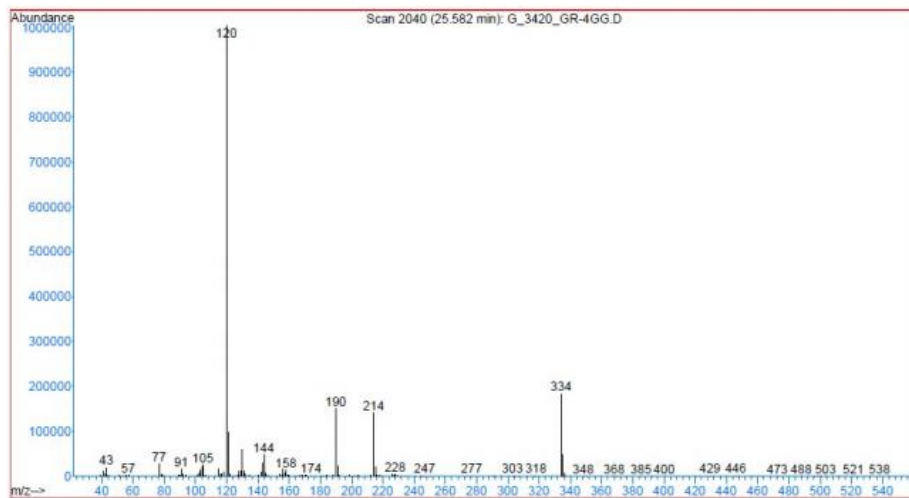
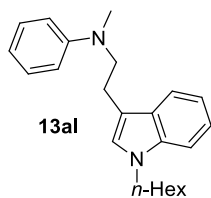


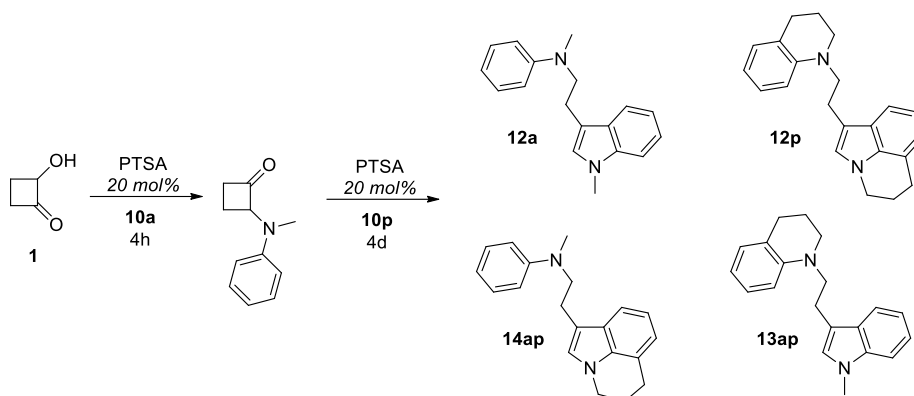
peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	3.295	103	106	376	M3	422761	173983926	14.05%	4.365%
2	8.515	558	559	805	M	2937771	1238217843	100.00%	31.062%
3	20.523	1601	1601	1749	M	2768541	751396797	60.68%	18.850%
4	25.178	1999	2005	2029	M	2226220	195303486	15.77%	4.899%
5	25.535	2029	2036	2147	M	1942798	673479764	54.39%	16.895%
6	29.165	2348	2351	2458	M	5985083	953846271	77.03%	23.929%



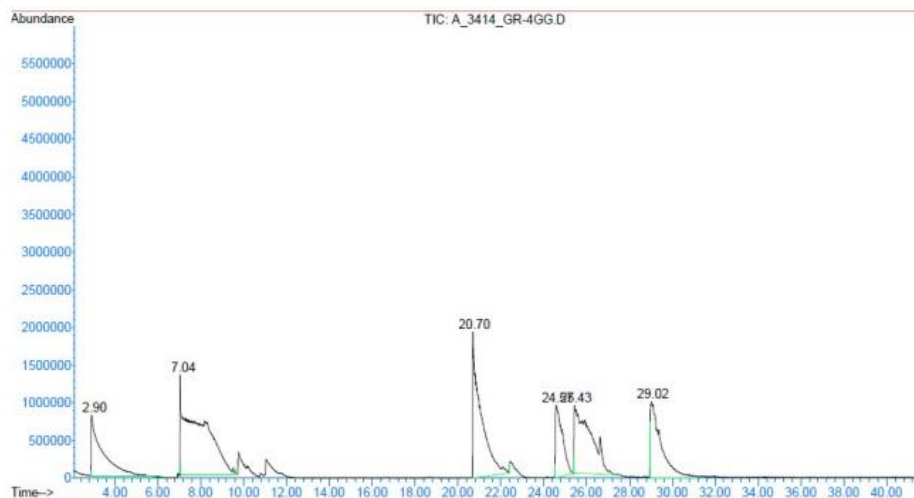




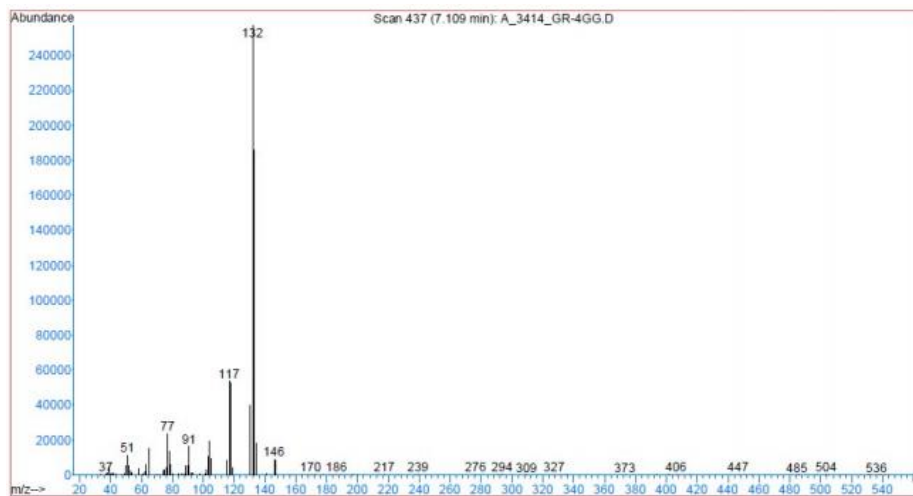
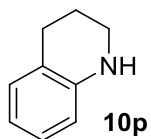
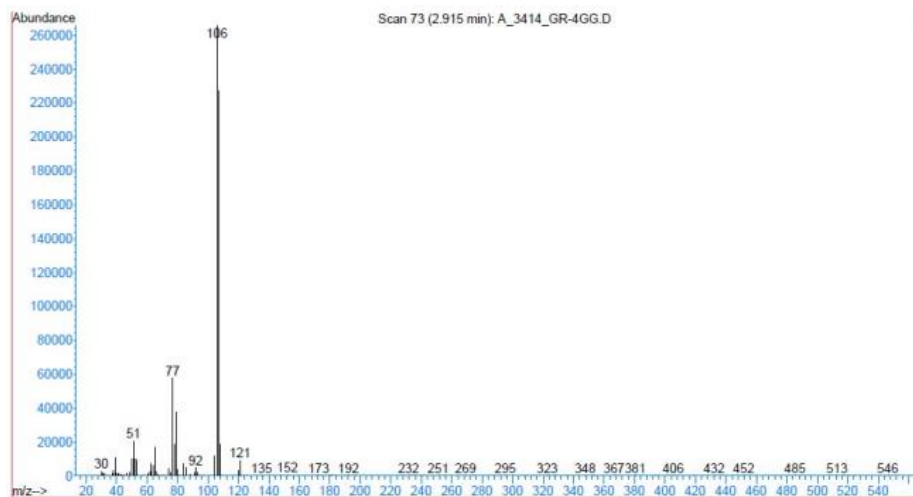
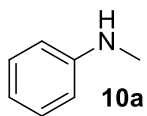


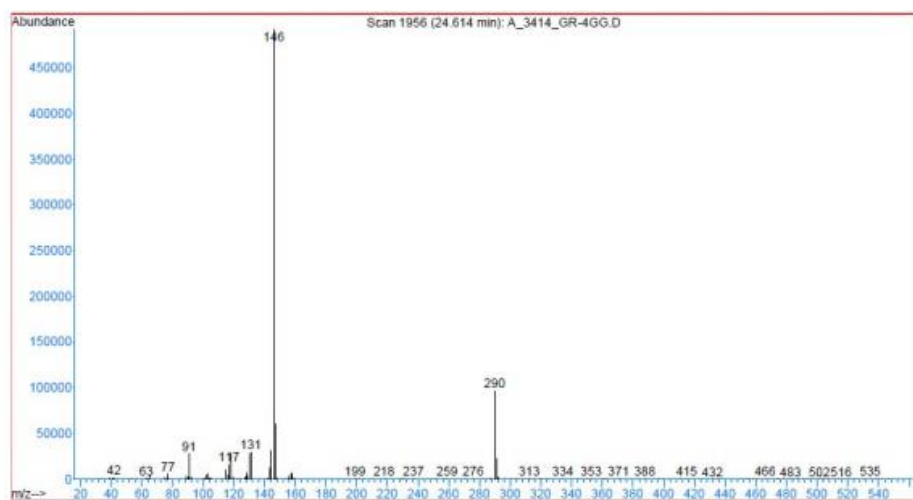
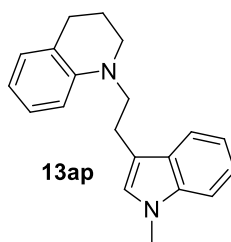
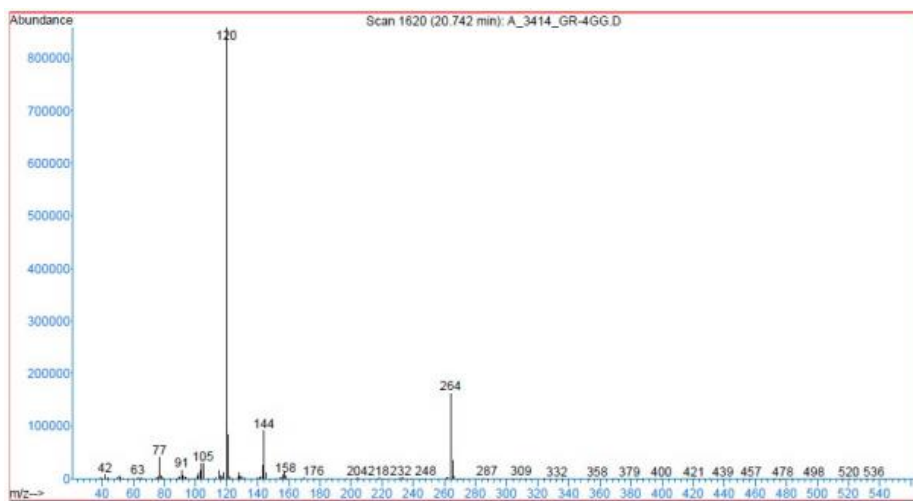
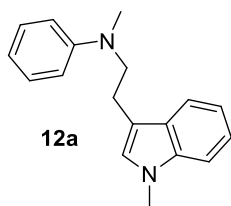


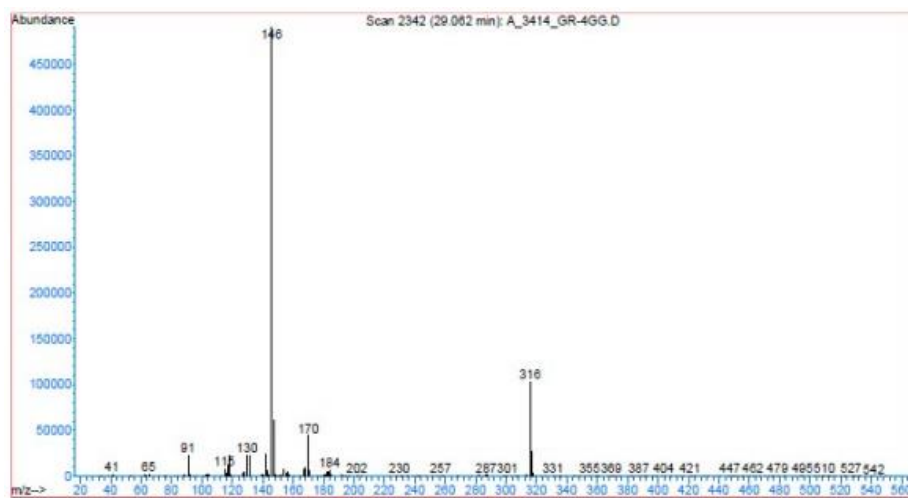
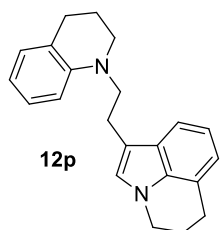
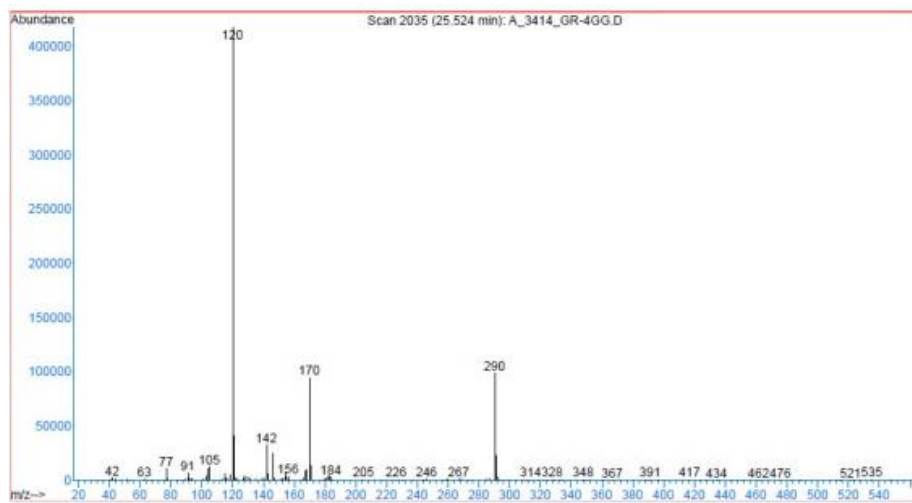
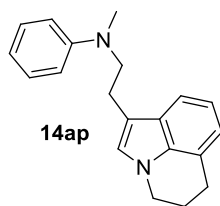
GC-MS analysis of the crude reaction mixture

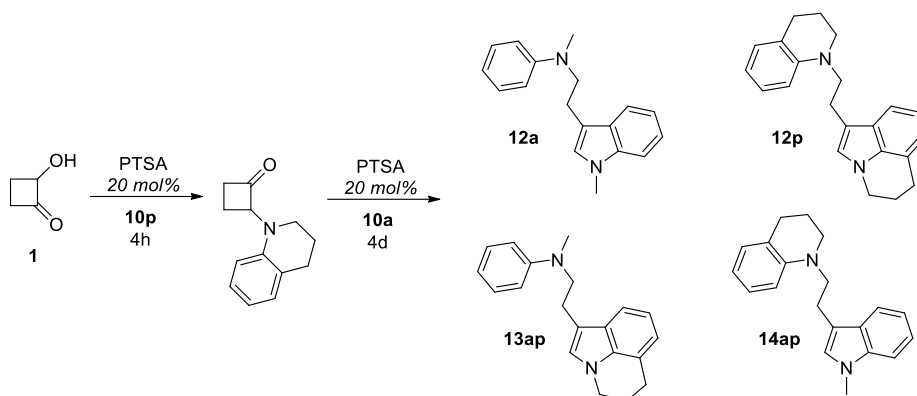


peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	2.903	69	72	307	M2	792365	273333012	35.76%	10.605%
2	7.040	430	431	647	M5	1325940	764335321	100.00%	29.656%
3	20.696	1613	1616	1765	M	1939018	503342442	65.85%	19.529%
4	24.579	1949	1953	2021	M2	970010	217151534	28.41%	8.425%
5	25.432	2024	2027	2208	M2	899382	473278110	61.92%	18.363%
6	29.027	2334	2339	2508	M2	1020174	345934134	45.26%	13.422%

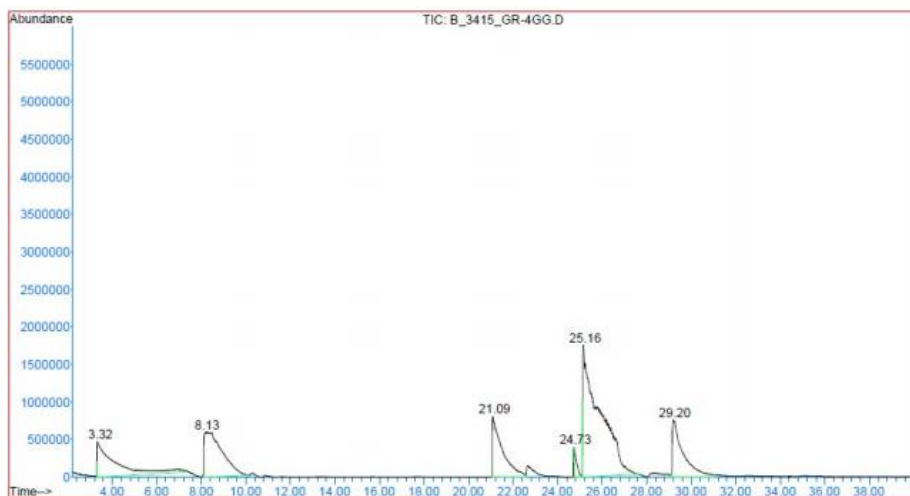




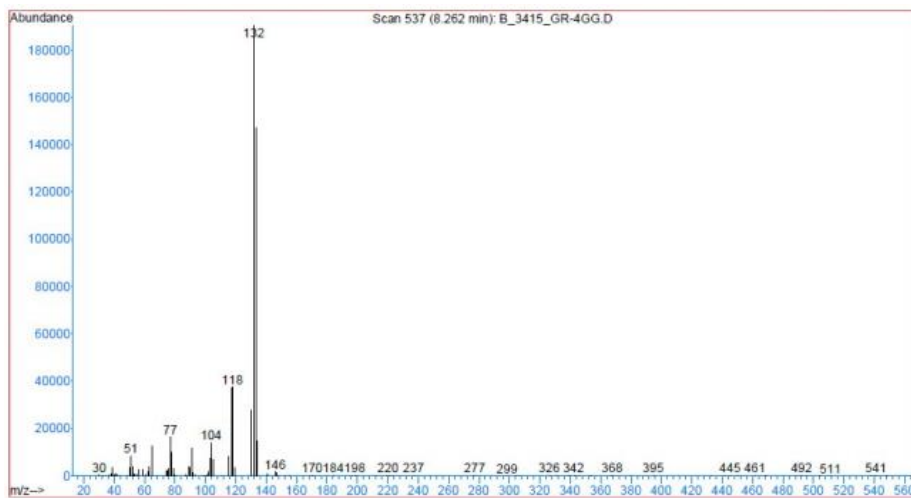
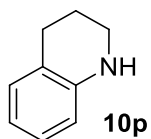
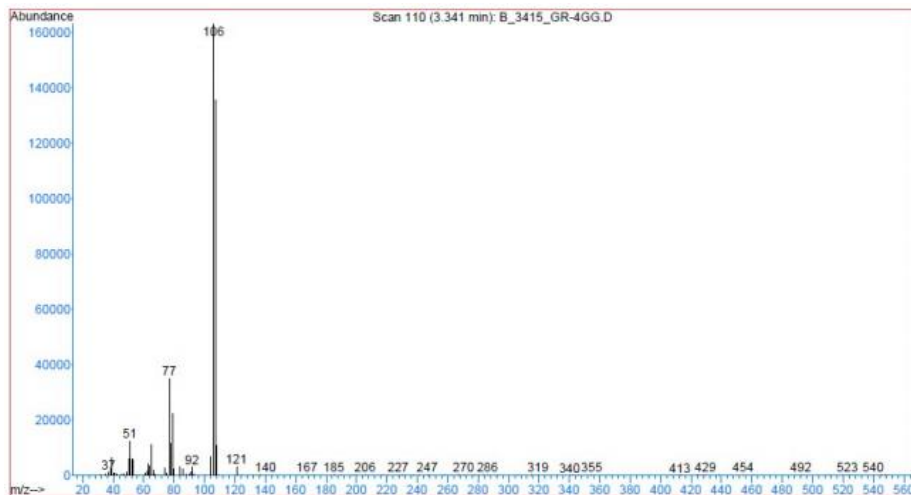
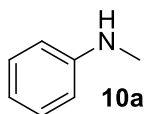


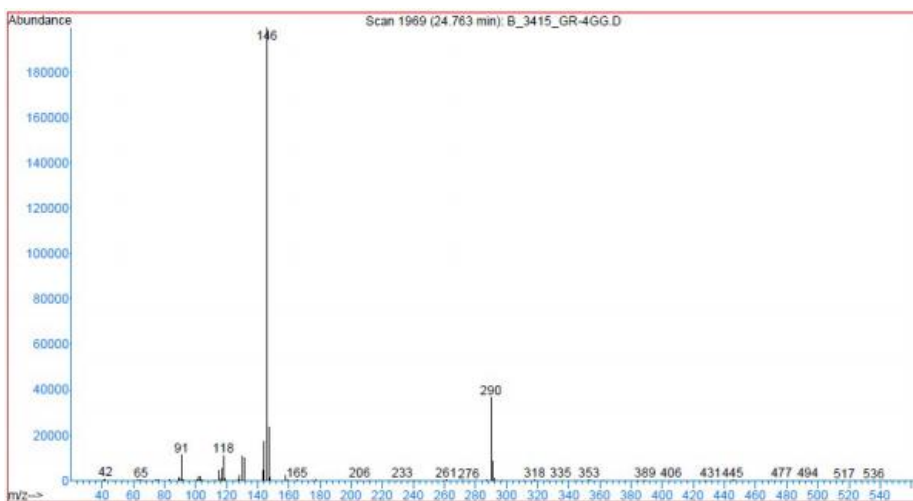
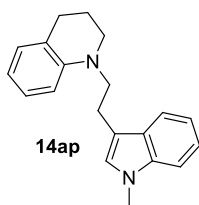
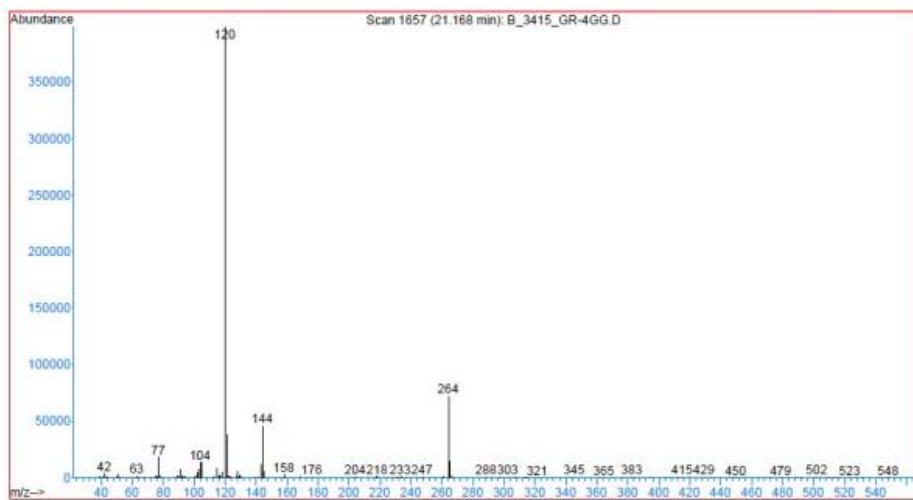
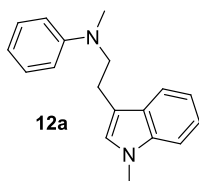


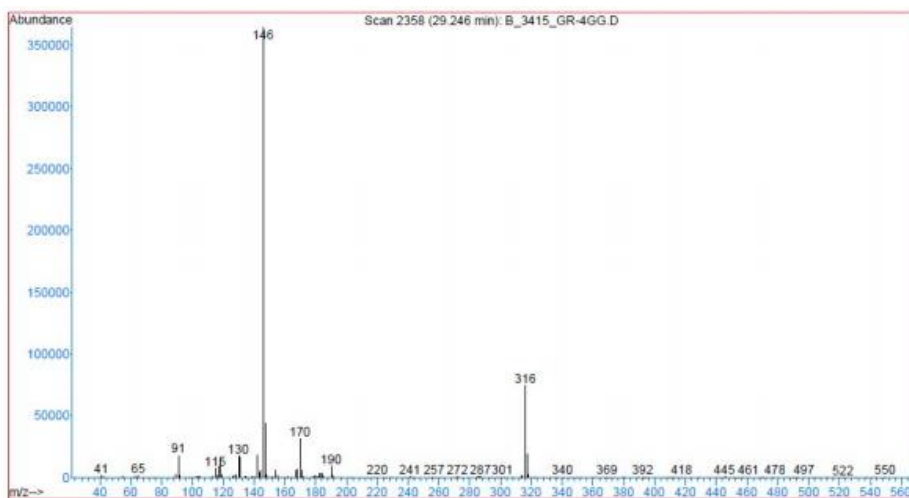
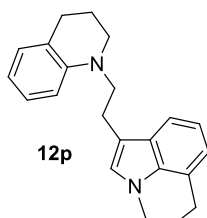
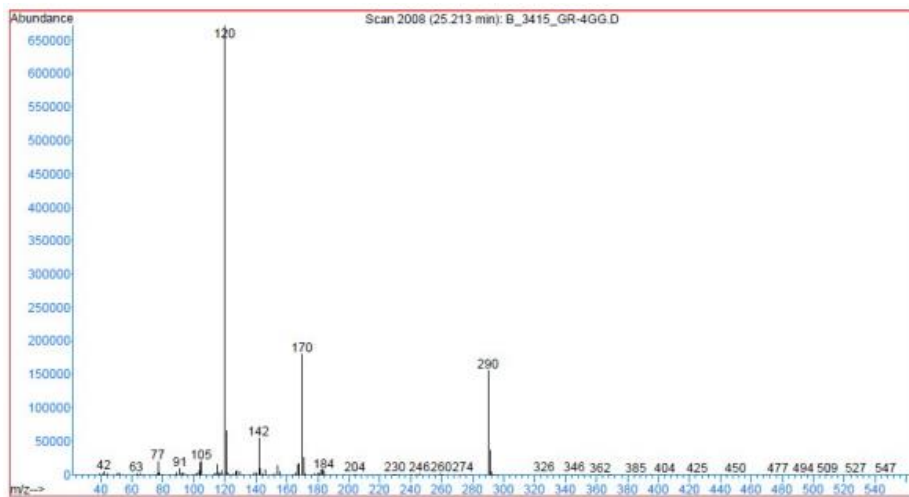
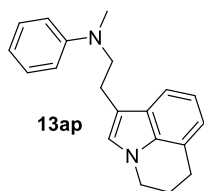
GC-MS analysis of the crude reaction mixture



peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	3.318	107	108	450	M2	486701	263649548	29.51%	12.977%
2	8.123	523	525	696	M6	617000	336696452	37.69%	16.572%
3	21.099	1647	1651	1779	M	814946	249110163	27.89%	12.261%
4	24.729	1966	1966	1997	M4	400517	33792420	3.78%	1.663%
5	25.167	2001	2004	2226	M	1770074	893302144	100.00%	43.969%
6	29.200	2347	2354	2514	M	769010	255132934	28.56%	12.558%







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8 ACKNOWLEDGEMENTS

First of all, my sincere gratitude goes to my supervisor Dr. Angelo Frongia for his guide, support and for the helpful advices he gave me during the three years we spent working together. Thank you very much for your confidence in me your patience and, last but not least, the opportunity of working on these interesting and intriguing subjects.

Likewise, I would like to thank Dr. Francesco Secci, who has been twice my supervisor in my previous academic experiences and gave me the tools for starting this experience. Moreover, thank you for making yourself always at disposal for discussing and giving advices even when you got rid of me.

My sincere gratefulness goes also to Prof. David J. Aitken and to Dr. Thomas Boddart who have hosted me during the ten months I spent in CP³A group of the ICMMO (Université Paris-Sud). I also take the chance to thank all the people I met and worked with. I am really grateful for your welcoming, the discussions we had, the time we spent together and – why not – all your mockeries. I honestly couldn't have wished for more.

In particular, I would like to express my deepest indebtedness to Thomas who has been a marvelous step-supervisor and I really enjoyed to work with. Your enthusiasm, help, motivation and many encouragements played a crucial role during my stay in CP³A group, both professionally and personally. It has been a real pleasure.

I owe a special thanks to Alberto Luridiana, who spent a period in CP³A group and continued working on the project from where I left. Thanks for the late skype calls and discussions, support and for your precious help: your contribution has been essential.

I would like to thank all the PhD students of the ICMMO for allowing me to be part of your group since the beginning and for the nice moments and jokes. A special mention, though, goes to Mathieu for the numerous discussion about chemistry and life in general, for his suggestions, support and all the fun we had. Thank you very much, I'm really grateful to you.

Three years could be really long and exhausting without good colleagues. Thanks to all the current and former PhD students and post-docs for having enriched this experience. In particular, above all, those who started the PhD at the same time as I had. We helped, supported and encouraged each other. It would have been much harder without you. Moreover, I would like to express my appreciation to all the colleagues and students who spent time working in the lab in Cagliari. Thanks for the talks and all the moments we spent together in the lab.

Finally, I would like to thank friends and family for the support, encouragements and, particularly, your immense patience.

The present Ph.D. thesis is based on my three-years research at the University of Cagliari (Italy). It is submitted as a requirement for obtaining the Ph.D. degree with the further certificate of Doctor Europaeus. The whole research has been financed by M.I.U.R. (Ministero dell'Istruzione, dell'Università e della Ricerca), University of Cagliari, Fondazione Banco di Sardegna and Sardinia Regional Government (P.O.R. Sardegna F.S.E. Operational Programme of the Autonomous Region of Sardinia, European Social Fund 2007–2013-Axis IV Human Resources, Objective I.3, Line of Activity I.3.1).