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Formal homo-Nazarov and other Cyclizations Reactions of Activated Cyclopropanes

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Dedication ((optional))

Abstract: The Nazarov cyclization of divinyl ketones gives access to cyclopentenones. Replacing one of the vinyl groups by a cyclopropane leads to a formal homo-Nazarov process for the synthesis of cyclohexenones. In contrast to the Nazarov reaction, the cyclization of vinyl-cyclopropyl ketones is a stepwise process, often requiring harsh conditions. Herein, we describe two different approaches for further polarization of the three-membered ring of vinyl-cyclopropyl ketones in order to allow the formal homo-Nazarov reaction under mild catalytic conditions. In the first approach, the introduction of an ester group α to the carbonyl on the cyclopropane gave a more than tenfold increase in reaction rate, allowing us to extend the scope of the reaction to non electron-rich aryl donor substituents in β position to the carbonyl on the cyclopropane. In this case, a proof of principle for asymmetric induction could be achieved using chiral Lewis acid catalysts. In the second approach, heteroatoms, especially nitrogen, were introduced β to the carbonyl on the cyclopropane. In this case, the reaction was especially successful when the vinyl group was replaced by an indole heterocycle. With a free indole, the formal homo-Nazarov cyclization on the C3 position of indole was observed using a copper catalyst. In contrast, a new cyclization reaction on the N1 position was observed with Brønsted acid catalysts. Both reactions were applied to the synthesis of natural alkaloids. Preliminary investigations on the rationalization of the observed regioselectivity are also reported.

Keywords: Cyclopropane • Alkaloids • Heterocyclic compd. • Regioselectivity • CATALYSIS

Introduction

The continuing progress in medicinal chemistry and chemical biology requires flexible synthetic approaches for the generation of libraries of active molecules and their analogues. A broad range of biologically active natural and synthetic compounds displays a complex polycyclic heterocyclic scaffold as core structure. Consequently, the search for new cyclization and cycloaddition reactions is a fundamental task in organic chemistry.[1]

Pericyclic reactions involving the concerted rearrangement of bonding electrons have the advantage of low activation barriers, allowing mild reaction conditions. The Nazarov cyclization, discovered by Nazarov in 1941,[2] is an important example of an electrocyclic ring closure – a subclass of pericyclic reactions- in which five-membered rings are generated starting from divinyl (or arylvinyl) ketones (Scheme 1, **A**). After activation of the carbonyl with a Brønsted or a Lewis acid, the intermediate pentadienyl cation **I** undergoes a conrotatory ring closure generating a cyclopentenone after proton transfer. For several decades, the Nazarov cyclization was limited by the necessity to use a stoichiometric amount of a strong Lewis or Brønsted acid.[3] In the last years however, several groups have reported milder catalytic methods.[4-5] Key for success was the introduction of an electron-donating and an electron-withdrawing group in α position to the carbonyl (EDG and R^3 in Scheme 1). In such substrates, one of the vinyl groups becomes nucleophilic, and the other one electrophilic (cross polarization), resulting in an enhanced reactivity of the divinyl ketone. This approach was extensively investigated by Frontier and co-workers.[4k] Since this seminal discovery, several catalytic versions were reported, together with the first examples of asymmetric induction.[5]

Starting from the Nazarov cyclization, a possible approach to access larger ring systems consists in the substitution of a double bond by an activated cyclopropyl group, resulting in a homo-Nazarov process (Scheme 1, **B**). The ring strain of cyclopropanes make them excellent precursors of reactive intermediates in the formation of new carbon-carbon bonds. Furthermore, the Walsh orbital description of the three-membered ring has been used to

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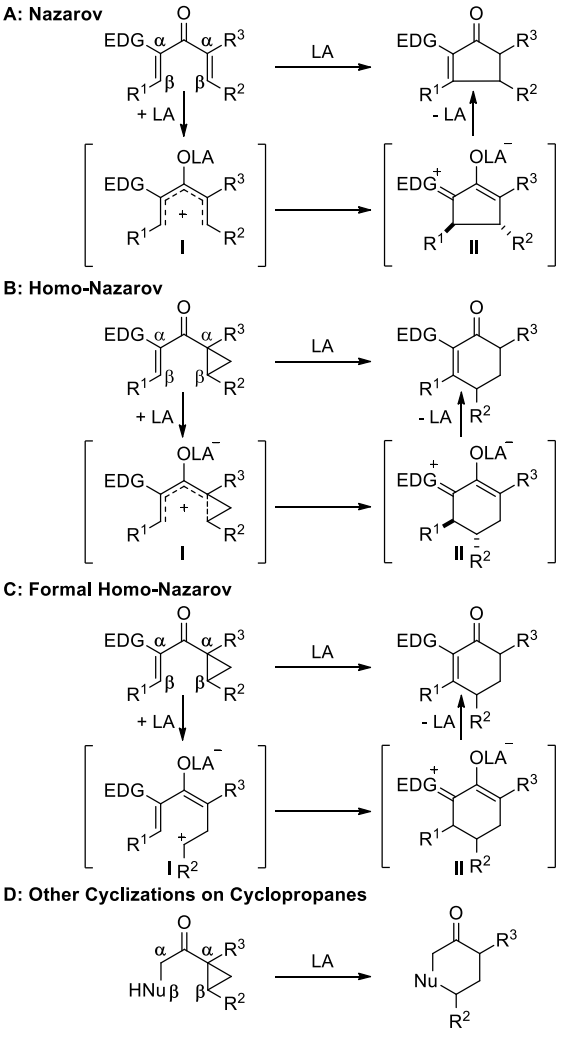
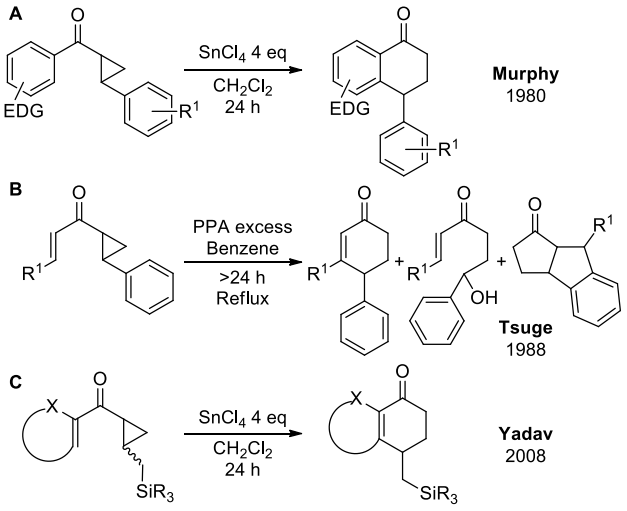
illustrate the partial π-character of C-C bonds in cyclopropanes.[6] They can consequently be considered as homologues of olefins in several annulations and cyclization reactions. Nevertheless, there is strong evidence that all the cyclizations of vinyl-cyclopropyl ketones reported so far are stepwise processes in contrast to the concerted Nazarov reaction (Scheme 1, **C**) and can consequently only formally be compared with an electrocyclic process.[7] An important consequence from the stepwise mechanism is that the reaction is usually not anymore conrotatory. However, as starting materials and products are identical in reactions **B** and **C**, it is useful to keep a "homo-Nazarov" process in mind for retrosynthetic planning. The term formal should never been omitted, as it serves as a strong warning sign to indicate a different mechanism. Finally, further reactions involving intramolecular attack of a nucleophile β to the carbonyl on the cyclopropane, although highly useful, should not be called formal homo-Nazarov reactions, as they lack the pattern of π bonds characteristic for the reaction (Scheme 1, **D**).[7g,8]



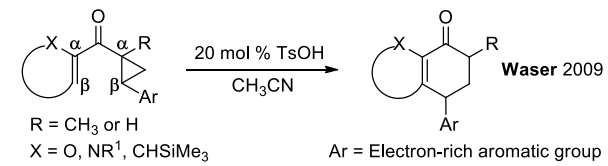
Scheme 1. Nazarov cyclization of divinyl ketones and cyclization reactions of vinylcyclopropyl ketones. (EDG = electron-donating group, LA = Lewis Acid).

To enhance the reactivity of cyclopropanes in order to allow cyclization reactions under mild conditions, it is often required to add further activating groups onto the ring. In particular, zwitterionic intermediates can be generated under mild conditions by tuning the donor-acceptor properties of substituents on the three-membered ring.[9] Despite the groundbreaking works of Stork, Danishefsky, Corey and co-workers during the 1970's,[10] intramolecular cyclizations involving activated cyclopropanes have been only rarely investigated. Until 2008, the formal homo-Nazarov cyclization of vinyl or aryl cyclopropyl ketones to form cyclohexenones was limited in scope and required superstoichiometric amounts of strong Lewis or Brønsted acids (Scheme 2).[7a-e] In 1980, Murphy showed that an excess of $SnCl_4$ allowed the cyclization of aryl-cyclopropyl-ketones for the synthesis of aryltetralones in good yields (Scheme 2, **A**).[7a-c] In 1988, Tsuge reported the first cyclization of vinyl-cyclopropyl ketones using an excess of polyphosphoric acid at 80° C (Scheme 2, **B**).[7d] The reaction was not general and several by-products were obtained. In 2008, Yadav and coworkers reported the cyclization of silylmethylcyclopropyl-ketones using 3 equivalents of $SnCl_4$ at 80° C (Scheme 2, **C**).[7e] In this work, the scope of the reaction could be extended to a broad range of heterocyclic systems, but the utility of the method was limited by the harsh conditions needed.



Scheme 2. Early examples of formal homo-Nazarov cyclizations.

Inspired by the progress in the Nazarov reaction, we decided to develop the first catalytic formal homo-Nazarov cyclization. We speculated that activation via adequate polarization of the cyclopropane ring could also lead to milder catalytic conditions. In our first studies we examined the effect of an electron-donating aromatic group in β position to the carbonyl on the cyclopropane in combination with an enol ether, an electron-rich aromatic ring or an allyl silane as a nucleophilic double bond (Scheme 3).[7f] Using a catalytic amount of *p*-toluenesulfonic acid in polar solvents, we were able to access the desired cyclohexenones under mild conditions. The reaction tolerated variation of the size and nature of the groups attached to the double bond and worked with several electron-rich aromatic groups, but no reaction was observed with a simple phenyl group. Furthermore, no asymmetric induction could be obtained when using chiral Brønsted or Lewis acids.



Scheme 3. Catalytic formal homo-Nazarov cyclization.

In order to overcome these limitations, we decided to apply two strategies (Figure 1): (1) The introduction of an ester group on the cyclopropane at the α position to the ketone. The electron-withdrawing ester group was expected to increase the polarization of the cyclopropane. We examined this approach for the first time in 2009.[11] In 2010, France and co-workers reported the use of the same class of substrates using indium catalysts, which allowed them to extend significantly the scope of the reaction.[7h-i] Apart for enhancing the reactivity, we also thought that this class of substrates will offer unique opportunity for asymmetric induction, as two-points binding with chiral Lewis acids will become possible. (2) The substitution of the aromatic group on the cyclopropane by a heteroatom. The lone pair of the heteroatom would give the electron density required for ring-opening under mild conditions. As heteroatoms are omnipresent in bioactive compounds, the obtained products would furthermore be highly useful for synthetic applications.

Herein we present first our preliminary results on the former strategy, the synthesis and cyclization of β-ketoester cyclopropanes and the first study of this class of substrates in asymmetric cyclizations. Concerning the latter approach, we have reported in 2010 the first example of the formal homo-Nazarov cyclization of aminocyclopropanes and their application in the synthesis of natural alkaloids.[7g] We now present the details of the challenging synthesis of the aminocyclopropanes, the full study of the scope of their cyclization, in particular using ketones derived from electron-rich heterocycles, as well as a comparison with an oxycyclopropane. We also discuss more in details the mechanism of the cyclization reaction based on experimental and computational data.

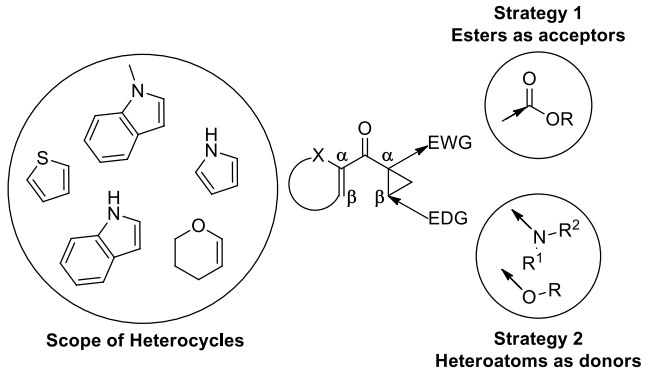


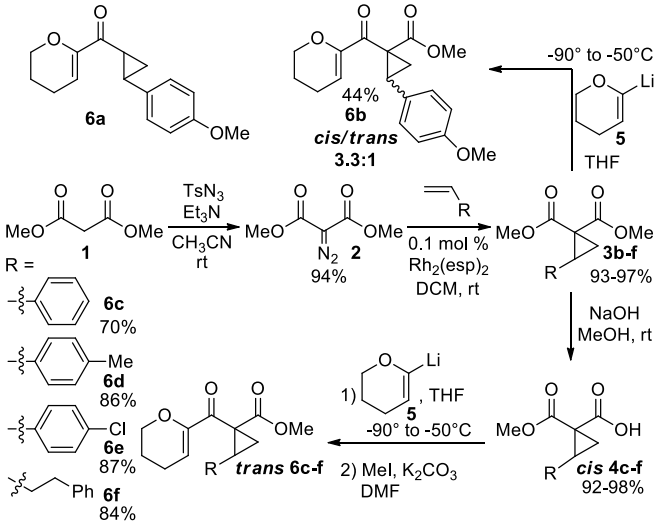
Figure 1. Cyclopropane polarization and heterocycles scope in the formal homo-Nazarov reaction.

Results and Discussion

Activation with an Ester Substituent.

The use of β-ketoester cyclopropanes was expected to lead to more stable enolate intermediates and consequently to allow milder reaction conditions. β-Ketoesters are also known to favor two point-binding interactions with chiral Lewis acid catalysts allowing an easier control of the enantioselectivity. In this context, Trauner[5b-c] proposed in 2004 one of the first examples of a catalytic Nazarov reaction using a scandium PYBOX complex with ketoesters. Aggarwal[5a] and Togni[5d] also reported examples of asymmetric induction for similar substrates using chiral copper and nickel catalysts respectively. More recently, Johnson and co-workers have studied extensively Lewis acid catalyzed [3+2] annulations of polarized 1,1-diester cyclopropanes with aldehydes and they also reported an asymmetric cycloaddition using chiral Mg PYBOX catalysts.[12]

Starting from dimethyl malonate ester (**1**), we first developed a synthetic route towards cyclopropyl β-ketoesters **6b-f** (Scheme 4). The synthesis of cyclopropane **6a** has already been described in our previous work.[7f] A Regitz diazo transfer,[13] followed by Rh-catalyzed cyclopropanation of the required olefins afforded the desired 1,2 cyclopropane diesters **3b-f**.[14] In a first approach, the addition of lithiated dihydropyran **5** on diesters **3b** gave **6b** as a diasteromeric mixture in low yield and with the undesired formation of double addition products. Therefore a more selective synthetic strategy was developed. Hydrolyzing the less sterically hindered of the two esters would give a carboxylic acid, which could be deprotonated and form a stable lithium complex. This will serve two roles: deactivating the acid to solve the regioselectivity problem and stabilize the tetrahedral intermediate obtained after addition of an organometallic reagent in order to prevent double addition. In the event, a selective saponification of the less sterically hindered *trans* ester group in **3c-f** led to the corresponding acids **4c-f** in high yields without further purification.[15] Gratifyingly, treating carboxylic acids **4c-f** with two equivalents of lithiated dihydropyran **5** led to regioselective formation of the corresponding keto acids in high yields. Finally, methylation of the free carboxylate gave access to the desired substrates **6c-f**. Since this strategy afforded the addition products on the more hindered face of the dicarbonyl compounds, it constitutes a new method to obtain selectively the more sterically hindered *trans*-cyclopropane ketoesters.

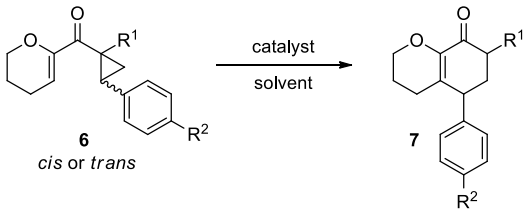


Scheme 4. Synthesis of cyclopropane ketoesters **6a-f**.

In order to have an impression on the reactivity of the ketoester substrates, the reaction in presence of several Brønsted and Lewis acids was first monitored qualitatively by ^{1}H NMR spectroscopy (Table 1). β-Ketoester cyclopropane **6b** was submitted to the catalytic conditions used in our previous work (entry 2).[7f] Gratifyingly, it displayed an enhanced reactivity when compared with ketone cyclopropane **6a** using the standard condition for the formal homo-Nazarov cyclization (20 mol % *p*-toluenesulfonic acid in CH_3CN): With β-ketoesters **6b** complete conversion was observed after only 15 minutes at rt (entry 2), whereas 18 hours were required in absence of the ester group (entry 1). Since phenyl-

substituted cyclopropane **6c** gave no conversion in our previous work,[7f] we decided then to study the activating effect of the ester group for this substrate. However, no conversion was observed with this substrate using *p*-toluenesulfonic acid as catalyst (entry 3). Increasing the strength of the Brønsted acid was unsuccessful (entries 4 and 5). $Cu(OTf)_2$, $Sn(OTf)_2$, and MgI_2 showed a very slow conversion rate at rt while inducing partial decomposition when heated (entries 6-11). On the other hand, stronger Lewis acids such as $SnCl_4$ or $AlCl_3$ gave extensive decomposition in less than one hour (entries 12 and 13). In the search for a milder catalyst, we tested $Ni(ClO_4)_2$•$6H_2O$, which had proven to be an effective Lewis acid for the opening of donor-acceptor cyclopropanes, both as anhydrous [12a,16] or as aquo complex.[15] In our hand, only the aquo complex was active and gave a clean and complete conversion of **6c** after 26 h, with 63% isolated yield of **7c** (entry 14). Surprisingly BF_3•Et_2O, which gave decomposition with **6a** (entry 15), was the catalyst of choice for β-ketoesters cyclopropane **6c** (entry 16), promoting the cyclization in 83% yield and a short reaction time.

Table 1. Preliminary screening of conditions for the homo-Nazarov cyclization for ketoester substrates.

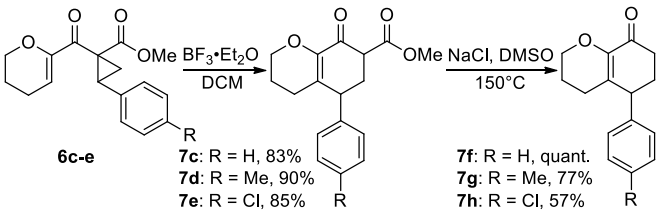


Entry[a]	R^1	R^2	Catalyst (mol %)	Solvent	Time	Conversion[b]
1	H	MeO (**6a**)	TsOH (20)	CH_3CN	18 h	100%
2	CO_2Me	MeO (**6b**)	TsOH (20)	CH_3CN	15 min	100%
3	CO_2Me	H (**6c**)	TsOH (20)	CH_3CN	19 h	0%
4	CO_2Me	H (**6c**)	TfOH (5)	CH_2Cl_2	19 h	0%
5	CO_2Me	H (**6c**)	H_2SO_4 (5)	CH_2Cl_2	19 h	0%
6	CO_2Me	H (**6c**)	$Cu(OTf)_2$ (20)	CH_2Cl_2	36 h	< 20%
7	CO_2Me	H (**6c**)	$Sn(OTf)_2$ (15)	CH_2Cl_2	26 h	< 20%
8	CO_2Me	H (**6c**)	MgI_2 (50)	CH_2Cl_2	18 h	< 20%
9	CO_2Me	H (**6c**)	$Cu(OTf)_2$ (15)	CH_2Cl_2	20 min	dec.[c],[d]
10	CO_2Me	H (**6c**)	$Sn(OTf)_2$ (5)	DCE	15 min	dec.[c],[e]
11	CO_2Me	H (**6c**)	MgI_2 (15)	DCE	1.15 h	dec.[c],[e]
12	CO_2Me	H (**6c**)	$SnCl_4$ (50)	CH_2Cl_2	2.3 h	dec.[c]
13	CO_2Me	H (**6c**)	$AlCl_3$ (50)	CH_2Cl_2	1 h	dec.[c]
14	CO_2Me	H (**6c**)	$Ni(ClO_4)_2$•$6H_2O$ (20)	CH_2Cl_2	26 h	100% (63%)[f]
15	H	MeO (**6a**)	BF_3•Et_2O (50)	CH_2Cl_2	25 min	dec.[c]
16	CO_2Me	H (**6c**)	BF_3•Et_2O (10)	CH_2Cl_2	3 h	100% (83%)[f]

[a] **6a** and **6c** only *trans*, **6b** as a mixture *cis*/*trans* 3.3:1. [b] Reaction run with 50-400 µmol **6** in 0.5-4 mL solvent. Conversion estimated by comparison of integration of peaks of **6** and **7** in the ^1H NMR spectra of the crude reaction mixture. See supporting information for details. [c] Decomposition of the starting material was observed. [d] Reaction run at 110 °C. [e] Reaction run at 55 °C. [f] Isolated yield after column chromatography.

With the optimized conditions in hand, we also examined methyl and chloro substituents on the benzene ring (Scheme 5). Fortunately, the additional reactivity given by the β-ketoesters could compensate even the electron-deficiency of the *p*-chlorophenyl group in **6e**. In order to facilitate characterization, the cyclic compounds were decarboxylated in the presence of NaCl in wet DMSO. In a further experiment, no conversion was observed when the aromatic group was replaced with a 2-phenylethyl substituent in **6f**. This last result underlined the importance of the stabilizing effect of the aromatic group for the reactivity of the cyclopropane.

We also detected a progressive epimerization of the cyclopropane during the homo-Nazarov reaction. Using either *cis* or *trans* phenylcyclopropane **6c**, we isolated the same mixture of *syn* and *anti* cyclic isomers with 1:1.5 diastereoselectivity. This result would be expected if the reaction proceeded via a carbocation or if equilibration of the products was occurring under these conditions.



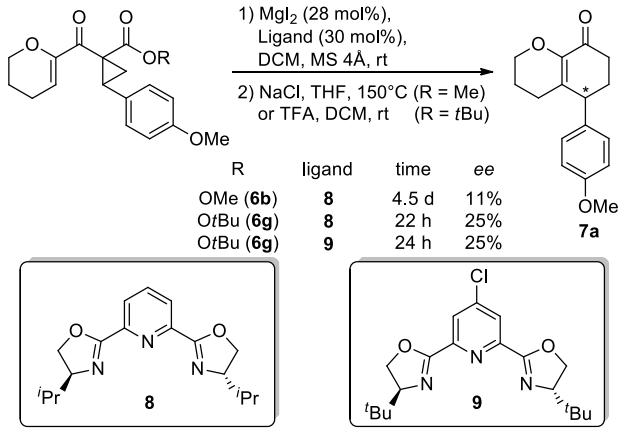
Scheme 5. Effect of the substitution on the aromatic ring on the cyclization reaction on preparative scale.

Inspired by the recent works in asymmetric cyclization with chiral Lewis acids of Johnson,[12] Trauner[5b-c] and Togni,[5d] we then turned to the development of an asymmetric version of the homo-Nazarov cyclization. Preliminary studies were realized with substrate **6b** and **6g**, since the *p*-methoxyphenyl group allowed a rapid ring opening of the cyclopropane, which had been shown to be crucial for the dynamic kinetic asymmetric transformation of racemic cyclopropanes.[12b] The more sterically hindered *tert*-butyl ester **6g** was prepared by addition of lithiated pyran **5** to the corresponding *tert*-butyl-methyl cyclopropane diester.[17] Both methyl (**6b**) and *tert*-butyl (**6g**) esters were then tested in the asymmetric reaction in order to analyze the steric influence of the ester on the stereoselectivity. Basing on the work of Johnson,[12] PYBOX ligands **8** and **9** were tested in association with Mg salts (Scheme 6). As the mixture of diastereoisomers formed during the homo-Nazarov reaction made analysis difficult, the *ee* values were measured on the decarboxylated product **7a**. Only 11% *ee* was observed when using the methyl ester **6b**. A slightly higher value (25%) could be achieved using *tert*-butyl ester **6g**. Although the observed enantioselectivity is still very low, these preliminary results constituted the first example of asymmetric induction in the formal homo-Nazarov reaction. Further screening of chiral catalysts, especially those successful in the Nazarov reaction,[5] in order to increase the selectivity of the reaction will be part of future work.

Introduction of Heteroatoms on the Cyclopropane.

Introduction and Substrates Synthesis: Although new conditions with ketoesters were successfully developed, the necessary presence of an aromatic stabilizing group still constituted a strong limitation in terms of application and scope. Replacing the aromatic group by a heteroatom would give a good stabilization of the formed carbocation and at the same time allow broadening the range of structures accessible. For example, a nitrogen- substituted cyclopropane would generate a zwitterionic species stabilized as an acyliminium intermediate, which could also be considered as the product of a retro-Mannich reaction, a process difficult in the case of acyliminium ions. Moreover, the cyclohexylamines obtained from the aminocyclopropanes are largely represented in the core structure

of several natural alkaloids such as aspidospermidine (**10**), strychnine (**11**), vinblastine (**12**) and vincristine (**13**) (Figure 2).



Scheme 6. Attempts towards an asymmetric homo-Nazarov cyclization.

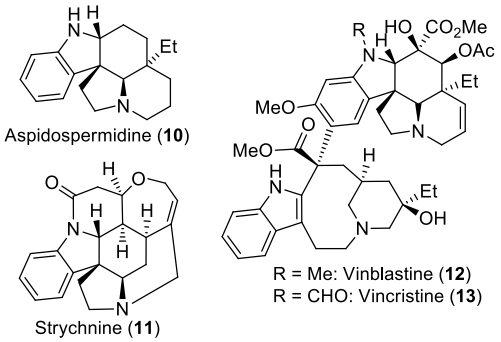


Figure 2. Examples of alkaloid natural products containing a cyclohexylamine ring.

Despite the importance of acyliminium cyclization in alkaloid synthesis, there are only few examples on the use of aminocyclopropanes to generate these intermediates. In the seminal work of Wenkert, aminocyclopropanes were opened under acidic conditions to generate the corresponding lactones, which were used as precursors of acyliminium intermediates in intermolecular addition reactions on indole derivatives.[18] To the best of our knowledge, the only example of intramolecular cyclization of aminocyclopropanes has been reported by Six and co-workers, who studied the intramolecular electrophilic aromatic substitution of simple alkyl cyclopropanes.[19]

Oxycyclopropanes on the other hand were shown to undergo formal homo-Nazarov cyclization in presence of stoichiometric amount of a Lewis acid.[7e] Since the electron-density of oxycyclopropanes could be compared with that of aminocyclopropanes substituted with a carbamate group, similar reactivity in the catalytic formal homo-Nazarov cyclization could be expected. We speculated that the high electron-density of both amino- and oxy- cyclopropanes should allow their use also under catalytic conditions. We consequently decided to examine a range of amino- and oxy- cyclopropanes to assess the potential of the reaction (Figure 3).

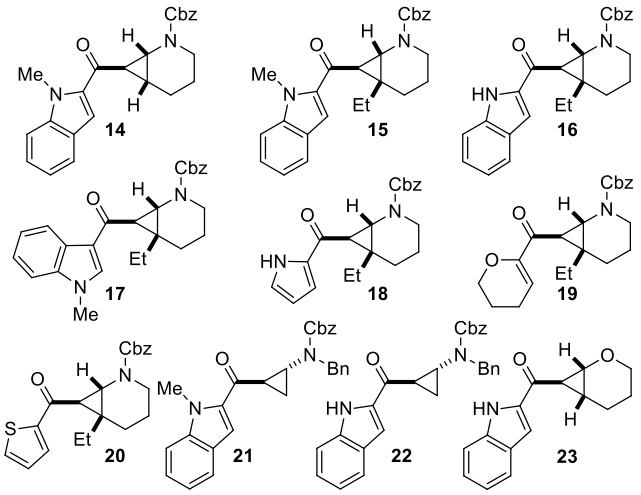
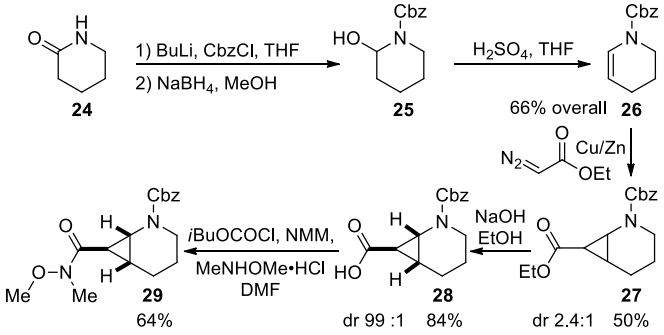


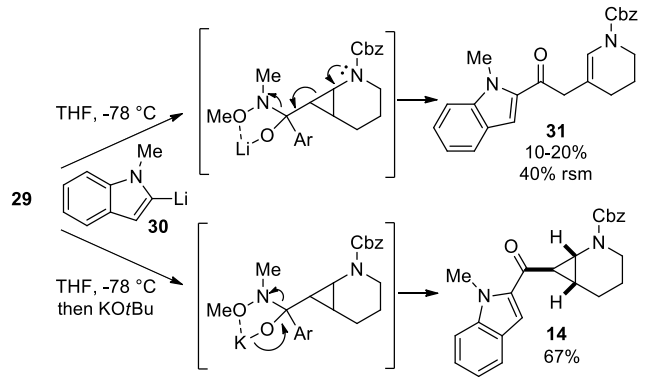
Figure 3. Substrates synthesized for the formal homo-Nazarov cyclization.

As a first attempt, we decided to examine substrate **14**, as it would lead to the tetracyclic scaffold of the *aspidosperma* alkaloid aspidospermidine (**10**). The synthesis of **14** started with δ-valerolactam (**24**), which was protected, reduced and dehydrated to afford enamide **26** (Scheme 7).[20] The non-optimized conditions of cyclopropanation using copper-bronze gave a diastereomeric mixture of esters **27**. A sequence of hydrolysis and amide coupling yielded Weinreb amide **29**. In the hydrolysis step, only the less sterically hindered exo-cyclopropane reacted, allowing the isolation of a single isomer of acid **28**.



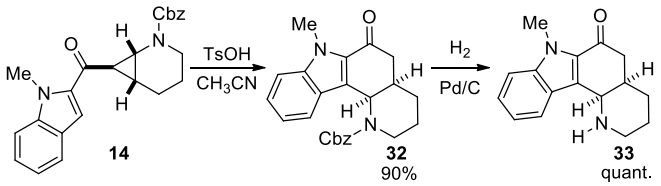
Scheme 7. Synthesis of Weinreb amide **29**.

Optimization of the coupling involving 2-lithiated-*N*-methyl indole (**30**) with the amide **29** was required, as we only observed the formation of enamide **31** derived from cyclopropane ring opening under standard conditions (Scheme 8). We speculated that cyclopropane opening was favored due to the high stability of the *N*,*O*-lithium chelate formed upon addition of the organometallic reagent. The addition of potassium *tert*-butoxide could potentially lead to the exchange of lithium by potassium and form a weaker chelate, which should favor a faster elimination of the hydroxylamine and preserve the cyclopropane integrity. Indeed, we were pleased to obtain the desired product **14** in 67% yield using this approach.



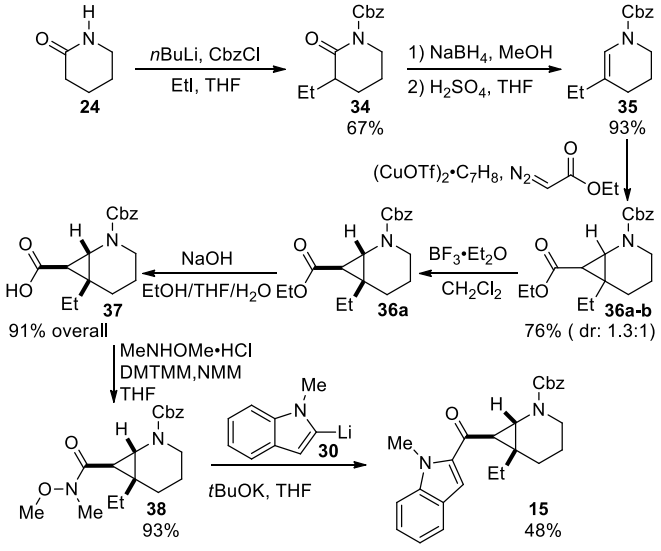
Scheme 8. Coupling of Weinreb amide **29** with lithiated indole **30**.

Using the standard conditions developed for the catalytic homo-Nazarov cyclization, we were delighted to isolate the cyclic compound **32** in 90% yield with high diasteroselectivity for the *cis*-fused product (Scheme 9). As NMR analysis of **32** was difficult due to the presence of carbamate rotamers, it was deprotected prior to complete structure assignment.



Scheme 9. Cyclization of indole aminocyclopropane **14**.

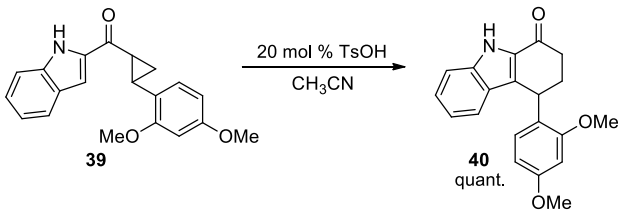
With this successful result in hand we decided to synthesize the ethyl-substituted cyclopropane **15**, as the ethyl group is present in aspidospermidine (**10**) (Scheme 10).



Scheme 10. Synthesis of ethyl-substituted cyclopropane **15**.

Following a modified procedure of Grieco,[20] δ-valerolactam (**24**) was alkylated and protected in one pot. Lactam **34** was then reduced and the resulting half aminal dehydrated to afford enamide **35**. The fine tuning of catalyst and reaction time was crucial for the reproducibility and the yield of the cyclopropanation of **35**. Since the use of Cu/Zn alloy in the cyclopropanation gave no reproducible results, we decided to test several copper and rhodium catalysts. The slow addition of a diluted solution of ethyl diazoacetate was important to avoid extensive polymerization and copper (I) catalysts allowed a better yield when compared to rhodium(II) or copper (II) catalysts. Using copper (I) triflate and syringe-pump addition of an ethyl diazoacetate solution, a diasteromeric mixture (1.3:1 dr) of cyclopropane ethyl esters **36a** and **36b** was obtained in a reproducible 76% of yield. The isomerization of the *endo* ester **36b** into the more stable *exo* form **36a** was possible with catalytic BF_3•OEt_2 in excellent yield.[20] Ester **36a** was then saponified affording the carboxylic acid **37** as a pure diasteroisomer. The use of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) allowed the formation of Weinreb amide **38** in good yield without further purification.[21] The coupling reaction between 2-lithiated-*N*-methylindole (**30**) and Weinreb amide **38** afforded the precursor **15** of the homo-Nazarov reaction.

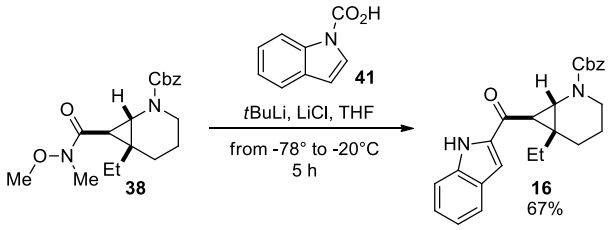
As aspidodermidine contains a free indole nitrogen, cyclization of substrate **16** with an unprotected indole would be more efficient. When using a free indole in the cyclization however, regioselectivity could become a serious issue, as cyclization on the nitrogen could also occur. For this reason cyclopropane **39**, bearing a free indole was first synthesized starting from lithiated *N*-carboxy indole and the corresponding Weinreb amide cyclopropane. We were delighted to find that a catalytic amount of *p*-toluenesulfonic acid in acetonitrile gave exclusive C3 cyclization product **40** in quantitative yield (Scheme 11).



Scheme 11. Cyclization of free indole cyclopropane **39**.

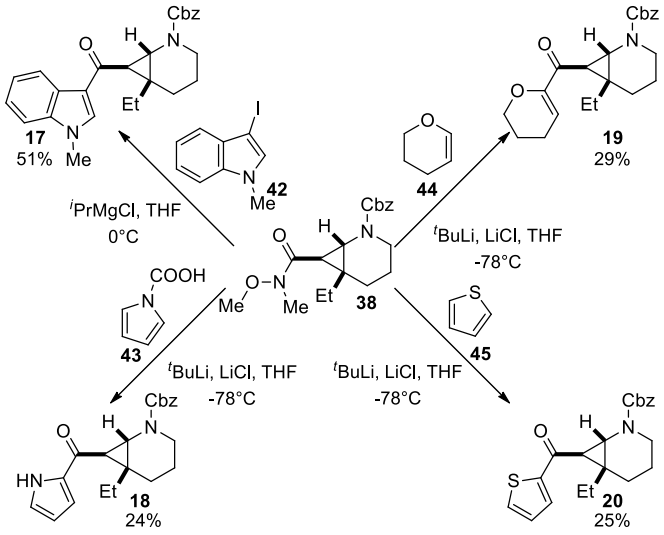
With these promising preliminary results in hand, we move on to the synthesis of indole **16**. The use of indole *N*-carboxylates pioneered by Katritsky[22] presented several advantages for our synthetic strategy: The directing group property of carboxylate favored the selective lithiation on the C-2 position of indole and a protecting group free 2-carbonyl indole is generated after aqueous work up. Nevertheless, this method had been used only with simple substrates in the past. The lithium indole-*N*-carboxylate was initially prepared *in situ* via a sequence of deprotonation/carboxylation/lithiation then added at -78°C into a solution of Weinreb amide **38** affording **16** in low yield. Optimization of additives, temperature, stoichiometry and reaction time and the use of pre-formed and recrystallized indole-*N*-carboxylic acid **41** resulted in an increased yield and reproducible results on a multi-grams scale (Scheme 12). In particular, the use of LiCl as additive and the slow increase of temperature from -78°C to -20°C combined with a reversed quench at 0°C were crucial to prevent side reactions. This implementation of Katritsky method in

complex settings allowed a highly convergent synthesis of indole cyclopropane **16**.



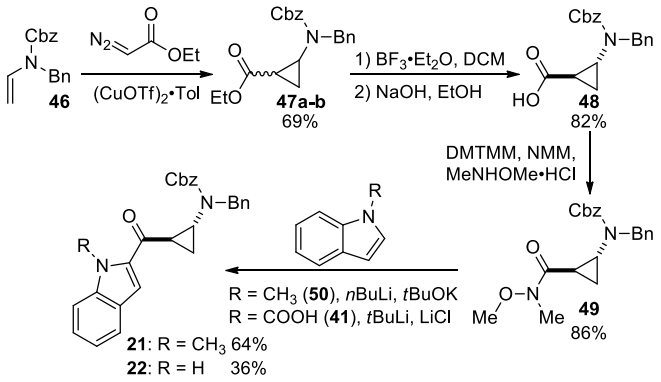
Scheme 12. Synthesis of indole cyclopropane **16**.

In our previous publication we tested successfully the cyclization involving substituted indoles.[7g] Encouraged by these promising results, a further series of substrates was synthesized in order to obtain more information regarding the scope of heterocycles in the cyclization step. For this purpose, a range of heterocycles with decreasing nucleophilicity were targeted as nucleophiles in the cyclization reaction. We focused our studies on the cyclopropanes derived from Weinreb amide **38** since the cyclization products would represent interesting analogues of natural alkaloids. Combining the appropriate metallated heterocycle with Weinreb amide **38**, we generated 3-indole-, pyrrole-, dihydropyran- and thiophene- substituted carbonylcyclopropanes **17**-**20** (Scheme 13). The pyrrole was carboxylated on its free nitrogen prior to lithiation. For these new substrates, no attempt was done to optimize the reaction conditions.



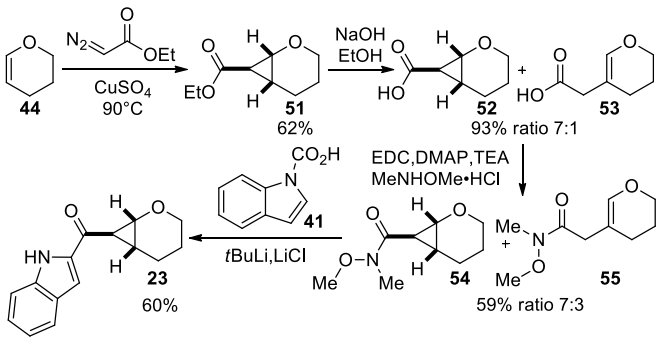
Scheme 13. Coupling of **38** with different heterocycles.

In order to further examine the scope and limitations of the aminocyclopropane cyclization, acyclic carbamates **21** and **22** were then synthesized (Scheme 14). The absence of rigidifying ring makes this class of compounds particularly challenging with regard to the cyclization step. The required enamide **46** was obtained from a Curtius rearrangement of acryloyl chloride followed by benzylation.[23] The optimized cyclopropanation conditions gave a diastereoisomeric mixture (dr 1:1) of aminocyclopropyl ethyl esters **47a** and **47b** in 69% yield. After isomerization with BF_3•OEt_2 and saponification, the resulting acid **48** was converted into Weinreb amide **49**. The right choice of lithiating agent, the fine tuning of reaction conditions and the use of *N*-methylindole **50** or carboxy indole **41** was crucial to give useful yields of cyclopropanes **21** and **22**.[24]



Scheme 14. Synthesis of acyclic cyclopropyl carbamates **21** and **22**.

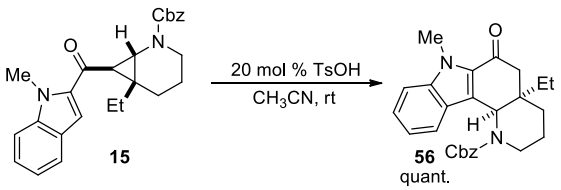
We then synthesized the cyclic ether cyclopropane substrate **23** starting from dihydropyran (**44**) (Scheme 15). A high temperature cyclopropanation with copper catalyst and EDA afforded the desired ester **51** as a single diasteroisomer.[25] Equilibration of the diastereoisomers probably did occur spontaneously through ring opening at high temperature. During saponification to afford the carboxylic acid, the oxycyclopropane ring partially opened, generating a vinylether side product **53**. The mixture of open and closed forms was used directly in a peptide coupling with EDC affording an inseparable mixture of Weinreb amides **54** and **55**. Finally, the separation of the two forms was possible after the reaction with the bis-lithiated carboxyindole obtained from **41** allowing the isolation of pure cyclopropane **23** (Scheme 15).[26]



Scheme 15. Synthesis of oxycyclopropane **23**.

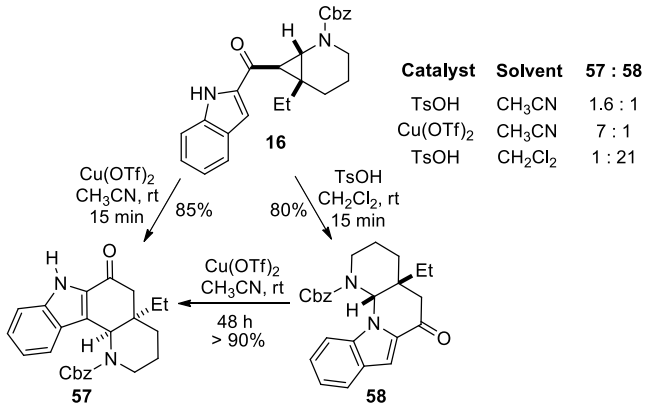
Cyclization: Encouraged by the preliminary results obtained with indole **14** (Scheme 9), we examined the cyclization of ethyl substituted cyclopropane **15** required for the synthesis of aspidospermidine (**10**). The presence of a quaternary carbon and the resulting steric hindrance was expected to be a major challenge for the cyclization process. We were consequently delighted to observe quantitative cyclization with perfect diastereoselectivity under our standard conditions (Scheme 16). The high diastereoselectivity shown by the formal homo-Nazarov cyclization is an important advantage compared to other synthetic strategies proposed for the

synthesis of *aspidosperma* alkaloids using aminocyclopropanes which were based on intermolecular addition and gave low stereoselectivity.[18d]



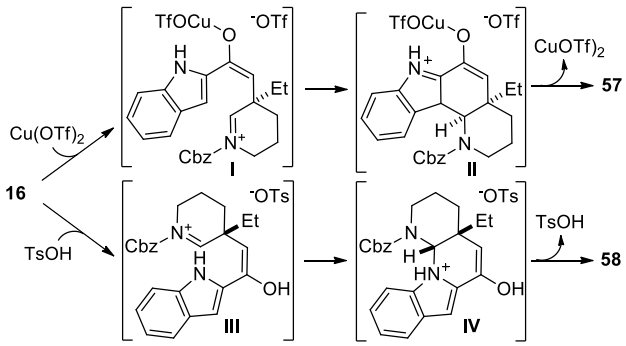
Scheme 16. Cyclization of ethyl-substituted cyclopropane **15**.

In a first cyclization attempt for free indole **16**, using the standard conditions for the homo-Nazarov cyclization, we were surprised to isolate two different compounds. After removal of the protecting group we were able to identify the desired product **57** obtained from the attack at the C3 position of indole and compound **58** derived from the cyclization on the N1 position in a 1.6:1 ratio (Scheme 17). A screening to find the right conditions to control the regioselectivity of the cyclization was carried out. The combination of polar solvent and a soft Lewis acid gave selectively the C-C cyclization compound while a strong Brønsted acid in an apolar solvent favored C-N bond formation (Scheme 17).[27]



Scheme 17. Regio and diastero- selective cyclization of cyclopropane **16**.

One of the potential explanations we had proposed in our previous work[7g] was based on the hard/soft reactivity of the generated charged intermediates (Scheme 18). The use of $Cu(OTf)_2$ would generate a soft copper-bound enolate **I**, which would promote the attack of the iminium on the softer C3 indole position with the higher electron-density in the HOMO orbital. Rearomatization of the cyclization product **II** and proton-transfer would lead to **57** and regenerate the catalyst. Moreover, the stabilizing effect offered by the polar solvent plays a fundamental role in favoring an orbital controlled over a charge-controlled cyclization. On the other hand, when the aminocyclopropane is activated with *p*-toluenesulfonic acid, the formed enol **III** would have a "hard" character, which would favor the attack of the formed acyl iminium at the harder N1 indole position. Using the non-coordinating solvent methylene chloride, a fast charge-controlled reaction on the harder nitrogen is further favored. From the obtained cyclization intermediate **IV**, a simple deprotonation and tautomerization would give **58**.



Scheme 18. Probable intermediates for the cyclization reactions.

The formation of the more stable thermodynamic product over the kinetic product should also be favored under the Cu-catalyzed conditions. In order to support this hypothesis, we examined interconversion of the two cyclization products under the reaction conditions. It was possible to convert the cyclic compound **58** into the regioisomer **57** using copper triflate in acetonitrile (Scheme 17), whereas no interconversion was observed when **57** was submitted to p-toluenesulfonic acid in dichloromethane. These last results suggested that C-N bond formation is under kinetic control, while C-C cyclization is thermodynamically more favored. Nevertheless, the reaction using the Cu catalyst is probably leading directly to the C3 cyclization product, as the reaction time for the conversion of **58** into **57** was much longer than for the direct cyclization.

For a better understanding of the observed cyclization selectivity, geometry optimization calculations were performed on the four possible cyclization products (Figure 4), namely the *cis* and *trans* diastereomers arising from C3 cyclization (**57** and **59** respectively), and the *cis* and *trans* diastereomers deriving from N1 cyclization (**58** and **60** respectively). All geometry optimization calculations[28] were performed at the DFT(B3LYP)/6-31+G* level in redundant internal coordinates[29] using the Gaussian 09 (G09) suite of programs.[30] The nature of all found critical points (geometries are reported in the Supporting Information material) was assessed at the same level of theory and accuracy by means of frequency calculations. In all calculations the solvent (acetonitrile) effect was taken into account at the implicit level using the SCRF-CPM method (G09 defaults were used).[31]

The *cis*-fused ring systems **57** and **58** were found to be substantially lower in energy than their *trans* counterparts **59** ($\Delta E_{57\text{-}59}$=11.45 Kcal/mol) and **60** ($\Delta E_{58\text{-}60}$=9.97 Kcal/mol); this can be easily ascribed to the increased stability of the chair conformation adopted by the piperidine ring in compounds **57** and **58**, compared to the less favorable twist conformation observed in **59** and **60**. Consequently, the high diastereoselectivity observed could either result from the higher stability of the *cis* product, or from the requirement of a twist transition state to form the *trans* product (Fürst-Plattner rule).[32] Furthermore, the higher thermodynamic stability of the C3-cyclization *cis* adduct **57** in respect to the N1-cyclization *cis* adduct **58** ($\Delta E_{57\text{-}58}$=6.59 Kcal/mol) is in agreement with the observed conversion of **58** in **57** *via* copper catalysis, but not *vice-versa.*

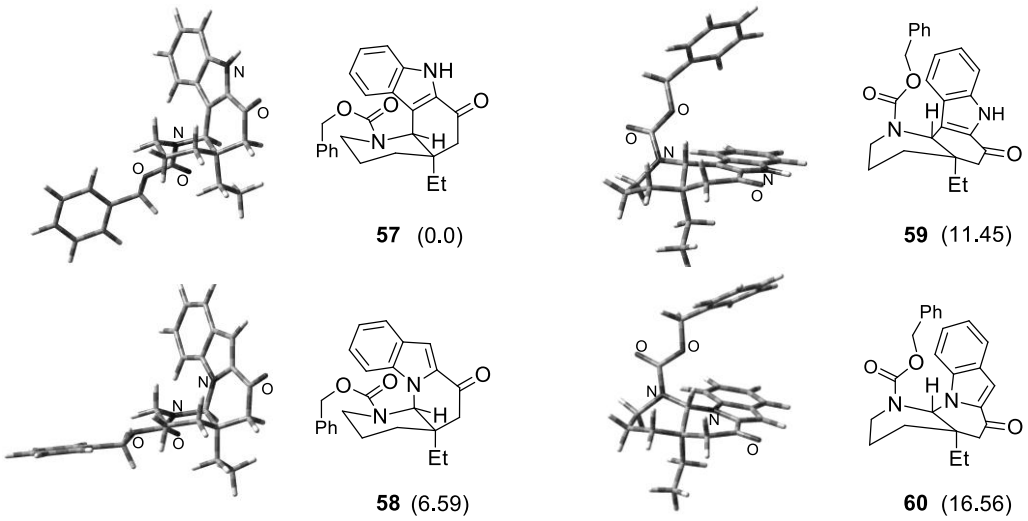
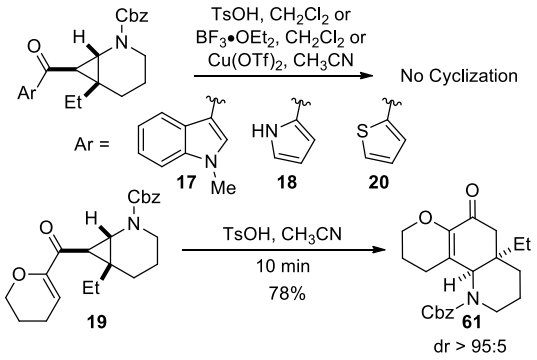


Figure 4. Optimized geometries of the four isomers arising from C3 and N1 cyclization. The energy values [kcal mol^{-1}] reported in parentheses are relative to **57**.

The C-C cyclization product, after deprotection of the amine, led to a formal total synthesis of aspidospermidine (**10**), since the free amine had been used in the total synthesis reported by Wenkert.[18d] On the other hand, the scaffold obtained from the N3 attack, corresponded to the core of the *gonioma* alkaloid goniomitine. Starting from a protected tryptophol derivative, we were able to synthesize goniomitine in 13 linear steps and 11% overall yield using this cyclization strategy.[7g]

Variation of the heterocyclic part was then tested. The synthesized 3-methylindole (**17**), 2-pyrrole (**18**), 2-pyran (**19**) and 2-thiophene (**20**) derivatives were therefore submitted to several cyclization conditions (Scheme 19). All the conditions optimized for the cyclization gave polymerization or α-amidoalcohol side products resulting from the attack of water on the iminium intermediate with 3-methylindole (**17**), 2-pyrrole (**18**), and 2-thiophene (**20**) derivatives. On the other hand, dihydropyran derivative **19** gave the cyclic compound after a brief treatment with catalytic *p*-toluenesulfonic acid in acetonitrile. Again, the cyclization gave only the *cis* diastereoisomer. These results demonstrated that the substitution pattern of the heterocycle is very important for the success of the cyclization reaction with iminium. For future work, it would be important to further modulate the reactivity of the iminium intermediate to extend the scope of the reaction.

When we moved to acyclic carbamate **21**, the standard optimized conditions to obtain C-C cyclization generated an aldehyde side product derived from the opening of the cyclopropane and hydrolysis of the intermediate iminium (Table 2, entry 1). In order to reduce the amount of water, responsible for iminium hydrolysis, we carried out the reaction in presence of molecular sieves (entry 2). After 30 min, the reaction was not complete and we observed the presence of aromatic compound **62** derived from elimination of benzyl-carbamoylbenzylamide. Fortunately, reducing the acid strength (trifluoroacetic acid) and using a more coordinating solvent such as acetonitrile, we could isolate the C-cyclization product after 90 min in 63% isolated yield (89% crude yield by NMR, entry 4). Careful control of the reaction time was also important, since the compound **63** could easily aromatize (entry 5). By using *p*-toluenesulfonic acid in acetonitrile, it was also possible to obtain aromatic compound **62** in 36% yield (entry 6). With longer reaction times, the yield was lower due to decomposition (entries 7-8).



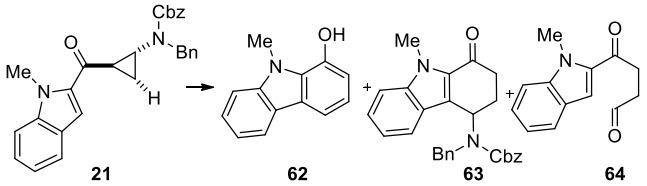
Scheme 19. Influence of the heterocycle structure on the cyclization.

The use of non-protected indole **22** made control over the reaction even more challenging, as formation of the C-N cyclization product was now also possible (Table 3). Nevertheless, we found that the principles discovered in the case of more rigid bicyclic cyclopropanes could also be used in this case. C-Cyclization product **65** was isolated after only 15 minutes in 70 % yield using $Cu(OTf)_2$ in acetonitrile (entry 2), while the combination of p-toluenesulfonic acid and acetonitrile afforded the C-N cyclization product in 75 % yield (entry 3). In the latter case, however, hydrolysis of the formed aminal was observed to give the corresponding half aminal **66**.

Despite the report of Yadav on the cyclization of oxycyclopropane using a large excess of $SnCl_4$,[7e] cyclization of the oxycyclopropane derivatives was not efficient under our conditions. Indeed, all the conditions tested with oxycyclopropane **23** gave side products derived from the water attack on the three-member ring or, in dry conditions, non-defined decomposition, confirming the high sensitivity of this class of compounds observed during the synthesis.

However, the stoichiometric use of BF_3•Et_2O in combination with a non coordinating solvent gave a useful yield of N-cyclization product **68** (Scheme 20). The fact that oxycyclopropanes preferred reaction with water or cyclization on nitrogen over C-cyclization is in accordance with a potentially harder oxonium intermediate.

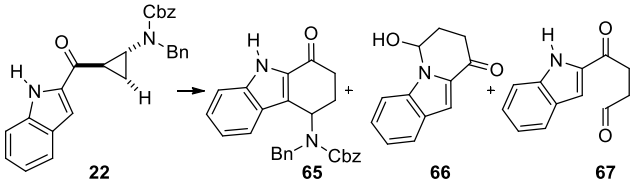
Table 2. Cyclization of acyclic carbamate **21** .



Entry[a]	Catalyst (mol%)	Solvent	Time	Observed Products
1	TsOH (20)	CH_2Cl_2	10 min	**64**
2	TsOH (20)	CH_2Cl_2, MS	30 min	**62**+ **63**
3	TFA (20)	dry CH_3CN	30 min	**21** + **62**
4	TFA (20)	dry CH_3CN	90 min	**63** (89% yield)[b]
5	TFA (20)	dry CH_3CN	12 h	**63** + **62**
6	TsOH (20)	CH_3CN	30 min	**62** (36% yield)[b]
7	TsOH (20)	CH_3CN	3h	**62** (20% yield)[b]
8	TsOH (20)	CH_2Cl_2	3h	**62** + dec.

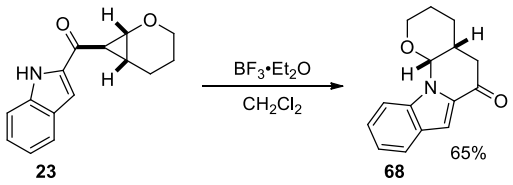
[a] Reaction run with 10-50 mg **21** (20-120 µmol) in 1-5 mL solvent at rt. [b] Yield calculated by NMR, see supporting information for further details.

Table 3. Selective cyclization of acyclic carbamate **22** .



Entry[a]	Catalyst (mol%)	Solvent	Time	Products
1	TsOH	CH_2Cl_2	15min	**65** + **67**
2	$Cu(OTf)_2$	CH_3CN	15 min	**65** (70% yield)[b]
3	TsOH	dry CH_3CN	15 min	**66** (75% yield)[c]

[a] Reaction run with 5-30 mg **22** (12-70 µmol) in 0.5-3 mL solvent, at rt. [b] Calculated by NMR, see supporting information for details. [c] Isolated yield.



Scheme 20. Cyclization of oxocyclopropane **23**

Conclusion

In summary, we have shown a further expansion of the scope of cyclization reactions of activated cyclopropanes, including the formal homo-Nazarov process. We proposed two different strategies to modulate the polarization of the three member ring in order to increase its reactivity under catalytic conditions. In the first approach we introduced an ester group on the cyclopropane, allowing an easy access to six-membered rings bearing not only electron-rich, but also electron-poor aromatic substituents. Moreover, the presence of an additional carbonyl group allowed a first proof of principle for asymmetric control in the cyclization reaction, probably via a two-points binding interaction with the chiral Lewis acid catalyst.

In a second approach, we studied the influence of heteroatoms on the cyclopropane. The use of aminocyclopropanes in particular was key in the application of the methodology in the total synthesis of natural alkaloids. General synthetic strategies were developed for the synthesis of donor-acceptor cyclopropanes with indole-, pyrrole-, pyran- or thiophene- ketones as electron-withdrawing groups and cyclic or acyclic carbamates or ethers as donor groups. This broad range of substrates allowed us to better assess the scope and limitation of the methodology, and led to the following conclusions: (1) Both the nucleophilicity and the substitution pattern of the heterocycle were essential for a successful cyclization. If the fit is not ideal, reaction with water or polymerization became favored. (2) For free indole as a nucleophile, the outcome of the cyclization is dependent of the electrophilic character of the formed carbocationic intermediate. Benzylic cation gave C3 cyclization exclusively, whereas oxonium favored N1 cyclization. For iminium intermediates, it was possible to switch the regioselectivity using a copper catalyst in acetonitrile for C3 cyclization and p-toluenesulfonic acid in dichloromethane for N1 cyclization. Both experiments and calculations showed that C3 cyclization led to the thermodynamic product. (3) Acyclic carbamates could be successfully cyclized, but they are more sensitive substrates. Mild conditions are required to prevent a facile aromatization of the product. This last reaction manifold could have potential for the synthesis of substituted carbazoles, however.

In conclusion we have shown the versatility of the formal homo-Nazarov reaction and other cyclization processes using keto-ester activated cyclopropanes, aminocyclopropanes and oxycyclopropanes. We extended the scope of the reaction and we showed a first preliminary example of asymmetric induction. Currently, our research in this transformation is focusing in new applications in total synthesis, as well as increasing the enantioselectivity by the use of other catalysts.

Acknowledgements

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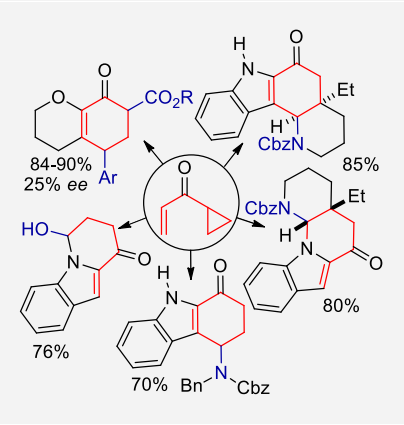
Formal homo-Nazarov and other Cyclizations Reactions of Activated Cyclopropanes



Push and Pull: The extension of the scope of cyclization reactions of donor-acceptor cyclopropanes with particular focus on the catalytic formal homo-Nazarov process is reported. An ester group or a heteroatom was introduced on the cyclopropane to enhance its acceptor or donor-mediated polarization. Control over regio- and diastereo-selectivity could be achieved, and a first proof of principle for asymmetric induction is reported.

Supporting information

Formal homo-Nazarov and other Cyclizations Reactions of Activated Cyclopropanes

*Filippo De Simone, Tanguy Saget, Fides Benfatti, Sofia Almeida and Jérôme Waser**

124 pages

1 General Methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et_2O, CH_3CN, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 10 ppm, *Karl-Fischer* titration). NEt_3 and pyridine were distilled under nitrogen from KOH. All chemicals were purchased from Acros, Aldrich; Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. The deactivation of silica was obtained with a 1% solution of Et_3N in the indicated solvent. TLC was performed on Merck silica gel 60 F_{254} TLC glass plates or aluminium plates and visualized with UV light, permanganate stain, CAN stain or Anisaldehyde stain. Melting points were measured on a calibratedBüchi B-540 melting point apparatus using open glass capillaries. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz and a Brucker AV-500 500 MHz spectrometer in chloroform-d, DMSO-d_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm or the internal methanol signal at 3.30 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration; interpretation).^{13}C-NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz and a Brucker AV-500 125 MHz spectrometer in chloroform-d, DMSO-d_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, br = broad). Gas chromatographic and low resolution mass spectrometric measurements were performed on a Perkin-Elmer Clarus 600 gas chromatographer and mass spectrometer using a Perkin-Elmer Elite fused silica column (length: 30 m, diameter: 0.32 mm) and Helium as carrier gas. High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurement were done on a JASCO HPLC system with an AS2055 Autosampler, a PU 2089 Pump, a UV 2075 detector and a SEDEX 85

(SEDERE) detector using a CHIRALPAK IC column from DAICEL Chemical Industries Ltd. HPLC grade solvents from Sigma-Aldrich were used.

2 General Procedures

General procedure 1 (GP1): cyclopropanation

Following a reported procedure,[1] $Rh_2(esp)_2$ (0.1 mol%) was loaded in a flask in the glovebox. A solution of alkene (1 equiv, 1.2 M in DCM) (freshly filtered over a pad of aluminum oxide) was then added and the reaction mixture was stirred at 0°C. After 5 min, a solution of diazomalonate (1 equiv, 1.2 M in DCM) was added. The resulting mixture was stirred at 0°C for 10 min and then stirred overnight at 23°C. The reaction mixture was then concentrated under reduced pressure and purified directly by column chromatography.

General procedure 2 (GP2): selective saponification

Following a reported procedure,[2] 1,1-cyclopropane diester (1 equiv) was dissolved in MeOH, 1.7 N aqueous NaOH (1.2 equiv) and some drops of THF. The reaction mixture was stirred for 1.5 h and was then diluted with DCM and water. The layers were separated. The pH 14 aqueous solution was washed one more time with DCM, acidified with 1 N HCl to reach pH < 1 and then extracted with DCM (x4). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure to afford the corresponding acid as a white solid which was pure enough to be engaged in the next step without further purification.

General procedure 3 (GP3): coupling

The previously formed acid (1 equiv) was dissolved in THF and cooled to -95°C. Dihydropyran (2.2 equiv) was dissolved in THF and the mixture was cooled to -78°C. ^{t}BuLi (1.6 M solution in pentane, 2.2 equiv) was added dropwise to this solution at the same temperature. The reaction mixture was stirred at 0°C for 30 min, diluted with THF and cooled to -95°C. This solution was then added via cannula to the cooled solution of the acid and the resulting mixture was stirred until the cooling bath reached -50 °C. The reaction mixture was then poured in water and diluted with DCM. The layers were separated and the organic layer was extracted with dilute aqueous solution of NaOH (pH > 13) (x3). The aqueous layers were combined and acidified with 1 N

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HCl to reach pH < 1. The aqueous layer was extracted with DCM (x5). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure to give an oil which was dissolved in DMF. To this solution were added K_2CO_3 (2 equiv) and MeI (5 equiv) and the reaction mixture was stirred for 2 days at 23°C. Then, AcOEt was added. The organic layer was washed with brine (x5), dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (PET/Et_2O 8:1 to 3:1) to afford the desired homo-Nazarov substrate as a single diastereoisomer.

General procedure 4 (GP4): homo-Nazarov cyclization

Toluenesulfonic acid (0.2 equiv) was added to a solution of vinyl cyclopropyl ketone (1 equiv, 0.04 M in anhydrous CH_3CN) at room temperature. The reaction was stirred during the indicated time. The solution was quenched with $NaHCO_3$ and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified as indicated.

General procedure 5 (GP5): hydrogenolysis

Pd/C (0.10 equiv) was added portionswise to a solution (0.02 M in EtOH) of protected amine at room temperature. Hydrogen gas was bubbled into the solution until the conversion of all starting material (controlled by TLC)[3]. The suspension was filtered on celite (pre-washed with DCM), washed with DCM and AcOEt and dried over $MgSO_4$. The organic layer was evaporated on reduced pressure. No further purification was needed.

General procedure 6 (GP6): Carboxylation of indole or pyrrole

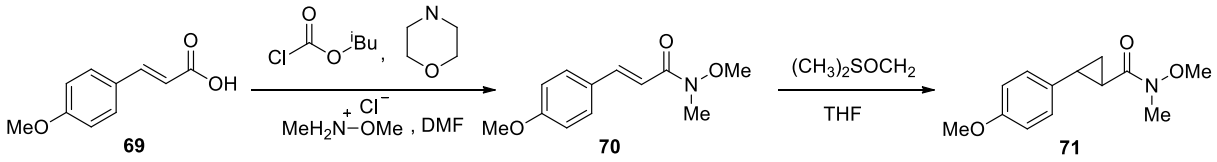
Using a slight modification of a reported procedure,[4] ^{n}BuLi (2.5 M in pentane, 1.2 equiv) was added dropwise to a solution of indole or pyrrole (0.2 M in Et_2O) at 0°C. The reaction was refluxed 2 hours then cooled to 0°C and CO_2 was bubbled in the solution during 30 minutes. The suspension was quenched with water and the organic layer was washed several times with water. The aqueous layer was acidified until pH = 2 and the precipitate was filtered and dried under vacuum.

[3] A batch to batch dependency of the reaction time was observed (15 min to 5 h). It is consequently important to monitor the reaction carefully via TLC.

[4] D. A Shirley, P. A. Roussel, *J. Am. Chem. Soc.* **1953,** *75*, 375.

3 Ketoesters synthesis

(*E*)-*N*-Methoxy-*N*-methyl-3-(4-methoxyphenyl)-acrylamide (69) and *N*-methoxy-*N*-methyl-1-[2-(4-methoxyphenyl)-cyclopropan-1-yl]-formamide (71)



Following the reported procedure[5] *N*-methylmorpholine (1.36 mL, 12.3 mmol, 1.10 equiv) was added to a solution of acid **68** (2.00 g, 11.2 mmol, 1.00 equiv) in DMF (15 mL) at 0 °C. After 25 min, *iso*-butylchloroformate (1.61 mL, 12.3 mmol, 1.10 equiv) was added dropwise at 0 °C. After 10 min, *N,O*-dimethylhydroxylamine hydrochloride (1.20 g, 12.3 mmol, 1.10 equiv) was added, followed by *N*-methylmorpholine (1.61 mL, 14.6 mmol, 1.30 equiv) and the reaction mixture was warmed to 23°C. After 6 h, the reaction was quenched with 0.5 M HCl (20 mL) and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with 0.5 M NaOH (2x20 mL), brine (1x20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. After 30 min in high vacuum, the residues were dissolved in Et_2O (60 mL) and washed with brine (2x30 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the Weinreb amide **70** which was used directly without purification.

A solution of ylide[6] (12.2 mL, 6.58 mmol, 1.20 eq) in anhydrous THF was added dropwise to a solution of amide **70** (1.21 g, 5.47 mmol, 1.00 equiv) in THF (45 mL) at RT under nitrogen. The reaction was stirred at 40°C during 2 h then quenched with $NaHCO_3$ (50 mL) and extracted with Et_2O (3x50 mL). The combined organic layers were washed with brine (2x30 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash column chromatography (PET/AcOEt, 7:3) afforded **71** (824 mg, 3.50 mmol, 64 %) over 2 steps as oil.

R_f 0.35 (PET/AcOEt 7:3, Anisaldehyde).

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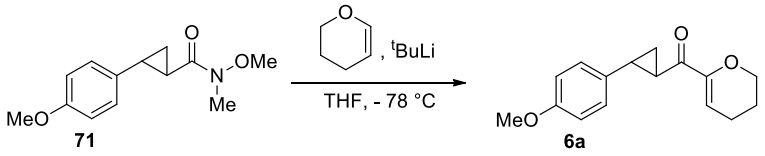
[5] Nagarajan, S. R.; Lu, H. F.; Gasiecki, A. F.; Khanna, I. K.; Parikh, M. D.; Desai, B. N.; Rogers, T. E.; Clare, M.; Chen, B. B.; Russell, M. A.; Keene, J. L.; Duffin, T.; Engleman, V. W.; Finn, M. B.; Freeman, S. K.; Klover, J. A.; Nickols, G. A.; Nickols, M. A.; Shannon, K. E.; Steininger, C. A.; Westlin, W. F.; Westlin, M. M.; Williams, M. L. *Bioorg. Med. Chem.* **2007**, *15*, 3390.

[6] *n*BuLi (2.5 M, 1.0 equiv) was added dropwise to a solution of trimethylsufoxonium iodide (1.1 equiv) in anhydrous THF (0.75 M) at 0°C. The solution was allowed to warm to RT and stirring was continued under nitrogen for 1 hour. A solution 0.54 M of ylide was obtained.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.06 (d, *J* = 8.6 Hz, 2H; ArH), 6.83 (d, *J* = 8.7 Hz, 2H; ArH), 3.78 (s, 3H; OCH_3), 3.69 (s, 3H; OCH_3), 3.23 (s, 3H; NCH_3), 2.50–2.42 (m, 1H; CH), 2.33 (m, 1H; CH), 1.65–1.55 (m, 1H; CH_2), 1.30 – 1.22 (m, 1H; CH_2).

^{1}H NMR spectra corresponded to the literature values.[7]

(*E*)-2-[2-(4-Methoxyphenyl)-1-cyclopropanecarbonyl]-5,6-dihydro-4*H*-pyran (6a)



Following a slight modification of a reported procedure,[7] *t*BuLi (0.85 mL, 1.4 mmol, 2.0 equiv) was added dropwise in a solution of dihydropyran **44** (0.14 mL, 1.5 mmol, 2.2 equiv) in THF (15 mL) at -78°C. The flask was transferred in a bath of ice. After 30 min at 0°C the reaction was cooled to -78°C and a solution of Weinreb amide **71** (0.16 g, 0.68 mmol, 1.0 equiv) in THF (14 mL) was added slowly dropwise. The reaction was stirred at -78°C during 2 h and 15 min then warmed at 0°C and quenched with saturate solution of NH_4Cl (50 mL). The product was extracted with Et_2O (3x50 mL) and washed with brine (2x50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give **6a** (105 mg, 410 μmol, 60%) after purification via flash chromatography (PET/AcOEt, 7:3) as yellow oil.

R_f 0.70 (PET/AcOEt 7:3, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.06 (d, *J* = 8.6 Hz, 2H; ArH), 6.83 (d, *J* = 8.7 Hz, 2H; ArH), 6.01 (t, *J* = 4.2 Hz, 1H; alkeneH), 4.14 – 4.06 (m, 2H; CH_2O), 3.79 (s, 3H; OCH_3), 2.71–2.59 (m, 1H; cyclopropaneH), 2.54 (ddd, *J* = 4.1, 6.6, 10.5 Hz, 1H; cyclopropaneH), 2.22 (dt, *J* = 4.4, 6.3 Hz, 2H; CH_2CH_2), 1.92 – 1.81 (m, 2H; CH_2CH_2), 1.76 – 1.67 (m, 1H; cyclopropaneH), 1.37 (ddd, *J* = 4.0, 6.8, 8.0 Hz, 1H; cyclopropaneH).

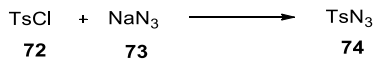
^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.6, 158.2, 151.4, 132.5, 127.2, 113.8, 109.5, 66.3, 55.2, 29.3, 27.30, 21.4, 20.7, 19.2.

[7] Boeckman, R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997.

IR ν (cm^{-1}): 3036 (w), 2950 (w), 2934 (w), 2836 (w), 1681 (m), 1667 (m), 1625 (s), 1516 (s), 1440 (m), 1393 (m), 1331 (m), 1286 (s), 1248 (s), 1237 (m), 1201 (w), 1180 (s), 1091 (m), 1061 (s), 1032 (s), 999 (m), 917 (s), 822 (s), 751 (s).

HRMS(ESI) calcd for $C_{16}H_{18}O_3^+$ (M+H) 259.1329, found 259.1335.

Tosyl azide (74)

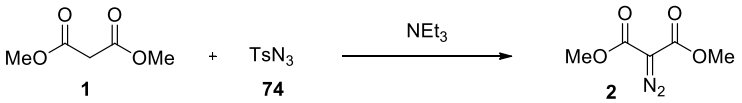


Following a reported procedure,[8] a solution of sodium azide (**73**) (10.3 g, 157 mmol, 1.50 equiv) in water (60 mL) was added dropwise over 1 h to a solution of tosyl chloride (**72**) (20 g, 0.11 mol, 1.0 equiv) in acetone (200 mL) at 0°C. The reaction was allowed to warm up to 23°C and stirred for 16 h. The acetone was removed under reduced pressure at 25 °C and the reaction mixture was extracted with ether (x2). The combined organic layers were washed with water (x2) , 5% Na_2CO_3 (x2) and water (x2), dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford tosyl azide (**74**) (20.7 g, 107 mmol, quantitative) as a colorless oil which solidified under storage at 4°C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, *J* = 8.4 Hz, 2H; ArH), 7.43 (d, *J* = 8.4 Hz, 2H; ArH), 2.51 (s, 3H; CH_3).

The characterization data for **74** corresponded to the reported values.[5]

Dimethyl 2-diazomalonate (2)



Following a reported procedure,[9] dimethylmalonate (**1**) (7.93 mL, 69.7 mmol, 1 equiv), triethylamine (10.6 mL, 76.6 mmol, 1.1 equiv) and tosyl azide (**74**) (15.1 g, 76.6 mmol, 1.1 equiv) were dissolved in acetonitrile (100 mL). The solution was stirred at 23°C for 20 h. The solution was concentrated under reduced pressure and partitioned between DCM and water. The layers were separated and the aqueous layer was extracted with DCM (x1). The organic layers were combined and dried over $MgSO_4$. The crude was first filtered over a plug of silica gel

[8] Serwinski, P. R.; Esat, B.; Lahti, P. M.; Liao, Y.; Walton, R.; Lan, J. *J. Org. Chem.* **2004**, *69*, 5247.
[9] Wyatt, P.; Hudson, A.; Charmant, J.; Orpen, A. G.; Phetmung, H. *Org. Biomol. Chem.* **2006**, *4*, 2218.

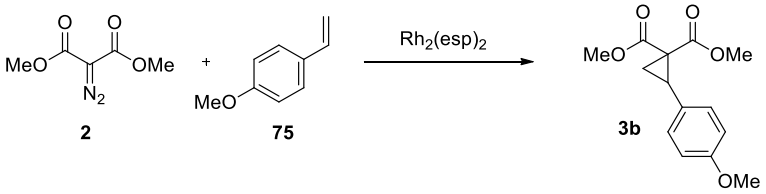
(PET/Et_2O 1/1) to remove most of the tosylamide formed during the reaction. Then, purification by column chromatography (PET/Et_2O 1/1) afforded dimethyl 2-diazomalonate (**2**) (10.4 g, 65.5 mmol, 94%) as a yellow oil which solidified under storage at 4°C.

R_f 0.32 (PET/Et_2O 1:1, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.87 (s, 1H; CH_3).

The characterization data for **2** corresponded to the reported values.[6]

Dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (3b)



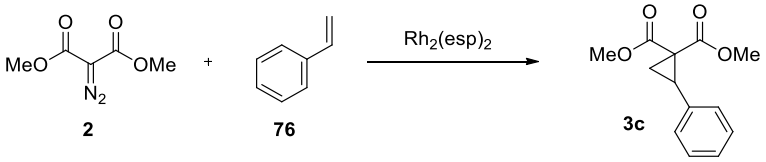
The reaction was performed following **GP1**, using $Rh_2(esp)_2$ (4.8 mg, 6.3 µmol, 0.1 mol%), styrene (**75**) (0.85 mL, 6.3 mmol, 1 equiv) and diazomalonate (**2**) (1.0 g, 6.3 mmol, 1.0 equiv). Purification by column chromatography (PET/Et_2O 5:1 to 3:1) afforded cyclopropane **3b** (1.58 g, 5.98 mmol, 95%).

R_f 0.24 (PET/Et_2O 3:1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17-7.11 (m, 2H; ArH), 6.86-6.79 (m, 2H; ArH), 3.81 (s, 3H; CH_3), 3.80 (s, 3H; CH_3), 3.41 (s, 3H; CH_3), 3.20 (t, J = 8.2 Hz, 1H; CHPh), 2.18 (dd, J = 8.1, 5.2 Hz, 1H; CH_2), 1.74 (dd, J = 9.3, 5.2 Hz, 1H; CH_2).

The characterization data for **3b** corresponded to the reported values.[1]

Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (3c)



The reaction was performed following **GP1**, using $Rh_2(esp)_2$ (4.8 mg, 6.3 µmol, 0.1 mol%), styrene (**76**) (0.73 mL, 6.3 mmol, 1 equiv) and diazomalonate (**2**) (1.0 g, 6.3 mmol, 1.0 equiv).

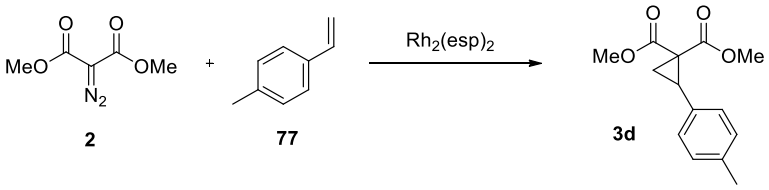
Purification by column chromatography (PET/Et_2O 5:1 to 3:1) afforded cyclopropane **3c** (1.43 g, 6.11 mmol, 97%).

R_f 0.45 (PET/AcOEt 3/1).

^1H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.19 (m, 5H; ArH), 3.82 (s, 3H; CH_3), 3.39 (s, 3H; CH_3), 3.26 (t, *J* = 8.8 Hz, 1H; CHPh), 2.23 (dd, *J* = 7.9, 5.2 Hz, 1H; CH_2), 1.77 (dd, *J* = 9.3, 5.2 Hz, 1H; CH_2).

The characterization data for **3c** corresponded to the reported values.[1]

Dimethyl 2-*p*-tolylcyclopropane-1,1-dicarboxylate (3d)



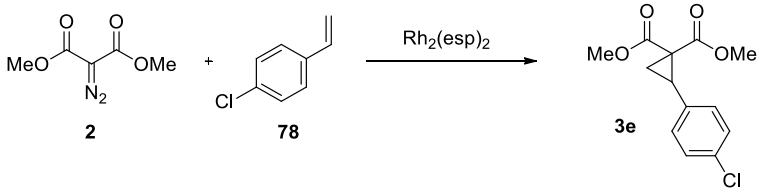
2 77 3d

The reaction was performed following the **GP1**, using $Rh_2(esp)_2$ (4.8 mg, 6.3 μmol, 0.1 mol%), styrene (**77**) (0.83 mL, 6.3 mmol, 1.0 equiv) and diazomalonate (**2**) (1.0 g, 6.3 mmol, 1.0 equiv). Purification by column chromatography (PET/Et_2O 5:1 to 3:1) afforded cyclopropane **3d** (1.53 g, 6.15 mmol, 97%).

R_f 0.63 (PET/AcOEt 3/1).

^1H NMR ($CDCl_3$, 400 MHz) δ 7.10 (m, 4H; ArH), 3.81 (s, 3H; OCH_3), 3.41 (s, 3H; OCH_3), 3.22 (t, *J* = 8.9 Hz, 1H; CHPh), 2.33 (s, 3H; CH_3), 2.20 (dd, *J* = 8.1, 5.2 Hz, 1H; CH_2), 1.75 (dd, *J* = 9.3, 5.2 Hz, 1H; CH_2).

Dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate (3e)



2 78 3e

The reaction was performed following the **GP1**, using $Rh_2(esp)_2$ (4.8 mg, 6.3 μmol, 0.1 mol%), styrene (**78**) (0.76 mL, 6.3 mmol, 1.00 equiv) and diazomalonate (**2**) (1.0 g, 6.3 mmol, 1.0

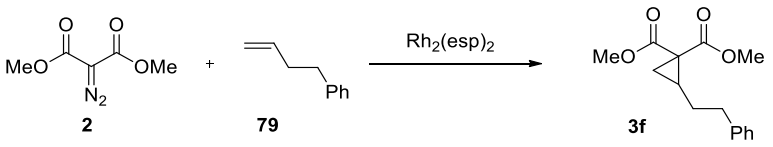
equiv). Purification by column chromatography (PET/Et_2O 5:1 to 3:1) afforded cyclopropane **3e** (1.69 g, 6.27 mmol, 99%).

R_f 0.63 (PET/AcOEt 3:1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (d, *J* = 8.6 Hz, 2H; ArH), 7.15 (d, *J* = 8.4 Hz, 2H; ArH), 3.82 (s, 3H; CH_3), 3.43 (s, 3H; CH_3), 3.21 (t, *J* = 8.6 Hz, 1H; CHPh), 2.18 (dd, *J* = 8.1, 5.3 Hz, 1H; CH_2), 1.77 (dd, *J* = 9.3, 5.3 Hz, 1H; CH_2).

The characterization data for **3e** corresponded to the reported values.[1]

Dimethyl 2-phenethylcyclopropane-1,1-dicarboxylate (3f)



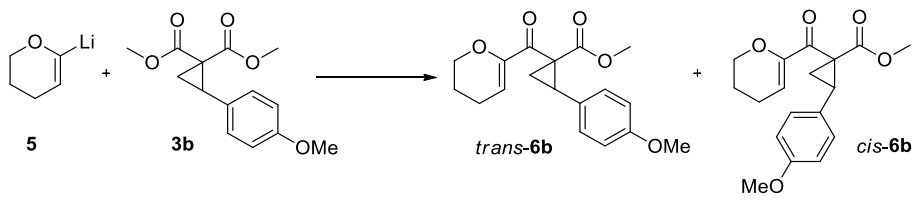
The reaction was performed following the **GP1**, using $Rh_2(esp)_2$ (2.4 mg, 3.1 μmol, 0.1 mol%), 4-phenylbutene (**79**) (0.48 mL, 3.2 mmol, 1.0 equiv) and diazomalonate (**2**) (0.50 g, 3.2 mmol, 1.0 equiv). Purification by column chromatography (PET/Et_2O 5:1 to 3:1) afforded cyclopropane **3f** (0.77 g, 2.9 mmol, 93%).

R_f 0.55 (PET/AcOEt 3:1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.25 (m, 2H; ArH), 7.24-7.13 (m, 3H; ArH), 3.79 (s, 3H; CH_3), 3.75 (s, 3H; CH_3), 2.75 (m, 2H; $PhCH_2$), 1.97 (m, 1H, cyclopropaneH), 1.79 (m, 1H; cyclopropaneH), 1.55 (m, 1H; cyclopropaneH), 1.42 (m, 2H; CH_2CH_2).

The characterization data for **3f** corresponded to the reported values.[1]

Methyl 1-(3,4-dihydro-2H-pyran-6-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (6b) (*trans*/*cis*)



Following a reported procedure,[10] dihydropyran (**44**) (52 µL, 0.57 mmol, 1.0 equiv) was dissolved in THF (0.13 mL) and the mixture was cooled to -78°C. ^{t}BuLi (1.6 M solution in pentane, 0.36 mL, 0.57 mmol, 1 equiv) was added dropwise to this solution at the same temperature. The reaction mixture was stirred at 0°C for 30 min. Then THF (1.5 mL) was added to **5** and the solution was cooled to -95°C. The 1,1-cyclopropane diester **3b** (0.15 g, 0.57 mmol, 1 equiv) dissolved in THF (0.5 mL) was added in one portion to this solution. The reaction mixture was allowed to stir for 2 h until the temperature of the cooling bath was -40°C. Then the reaction mixture was poured in brine and diluted with DCM. The aqueous layer was extracted with DCM (x3). The organic layers were combined, dried over Na_2SO_4 and evaporated under reduced pressure. A 3/1 mixture of trans/cis is detected by ^{1}H NMR of the crude. Purification by column chromatography (PET/Et_2O 5:1 to 3:1) afforded the *trans* isomer of **6b** (52 mg, 0.16 mmol, 29%), a 2.3/1 mixture of *cis*/*trans* isomers of **6b** (27 mg, 85 µmol, 15%) and starting material **3b** (33 mg, 0.12 mmol, 21%).

Trans isomer

R_f 0.41 (PET/AcOEt 3:1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20-7.15 (m, 2H; ArH), 6.85-6.80 (m, 2H; ArH), 6.02 (t, J = 4.1 Hz, 1H; alkeneH), 4.18-4.11 (m, 1H; OCH_2), 3.95-4.01 (m, 1H; OCH_2), 3.80 (s, 3H; OCH_3), 3.43 (s, 3H; OCH_3), 3.40 (t, J = 8.6 Hz, 1H; CHPh), 2.29-2.19 (m, 3H; CH_2), 1.96-1.84 (m, 2H; CH_2), 1.51 (dd, J_1 = 9.3, 4.8 Hz, 1H; CH_2).

^{13}C NMR ($CDCl_3$ 100 MHz) δ 190.8, 168.5, 158.7, 150.8, 130.05, 126.9, 113.5, 109.9, 66.3, 55.2, 52.0, 41.3, 30.0, 21.8, 20.6, 20.6.

IR ν (cm^{-1}): 2951 (w), 2838 (w), 2359 (w), 1741 (m), 1689 (m), 1630 (m), 1517 (s), 1438 (m), 1321 (m), 1291 (s), 1251 (s), 1218 (m), 1175 (m), 1147 (m), 1057 (m), 1036 (m), 921 (m), 838 (m), 749 (s).

HRMS (ESI) calcd for $C_{18}H_{21}O_5^+$ (M+H) 317.1389; found 317.1395.

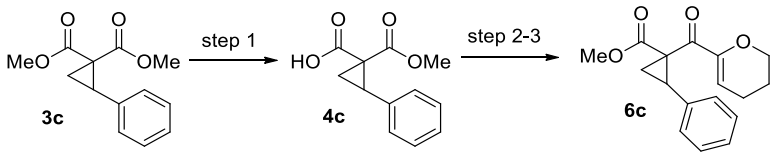
Cis isomer

R_f 0.42 (PET/AcOEt 3/1).

[10] Boeckman, R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10-7.03 (m, 2H; ArH), 6.79-6.74 (m, 2H; ArH), 5.73 (t, *J* = 4.3 Hz, 1H; alkeneH), 3.93 (t, *J* = 5.0 Hz, 2H; OCH_2), 3.77 (s, 3H; OCH_3), 3.76 (s, 3H; OCH_3), 3.34 (t, *J* = 8.4 Hz, 1H; CHPh), 2.26-2.21 (m, 1H; CH_2), 2.08-2.02 (m, 2H; CH_2), 1.77-1.71 (m, 2H; CH_2), 1.57 (dd, *J* = 9.5, 5.3 Hz, 1H; CH_2).

Methyl 1-(3,4-dihydro-2H-pyran-6-carbonyl)-2-phenylcyclopropanecarboxylate (6c)



Following **GP2**, 1,1-cyclopropane diester **3c** (555 mg, 2.37 mmol, 1.00 equiv) was dissolved in MeOH (1.7 mL), 1.7 N aqueous NaOH (1.7 mL, 2.8 mmol, 1.2 equiv) and some drops of THF. The reaction afforded acid **4c** (503 mg, 2.28 mmol, 96%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.01 (brs, 1H; COOH), 7.36-7.19 (m, 5H; ArH), 3.41 (t, *J* = 8.9 Hz, 1H; CHPh), 3.29 (s, 3H; OCH_3), 2.42 (dd, *J* = 8.6, 4.8 Hz, 1H; CH_2), 2.27 (dd, *J* = 9.3, 4.8 Hz, 1H; CH_2).

Following **GP3**, dihydropyran (**44**) (0.46 mL, 5.0 mmol, 2.2 equiv) was dissolved in THF (1 mL) and reacted with ^{t}BuLi (1.6 M solution in pentane, 3.14 mL, 5.02 mmol, 2.20 equiv). The solution was diluted with THF (15 mL) and was added to acid **4c** (503 mg, 2.28 mmol, 1.00 equiv) in THF (6 mL). The obtained oil was dissolved in DMF (21 mL). K_2CO_3 (630 mg, 4.55 mmol, 2.00 equiv) and methyl iodide (710 µl, 11.4 mmol, 5.00 equiv) were added. The crude product was purified by column chromatography (PET/Et_2O 8:1 to 3:1) to afford the desired product **6c** (350 mg, 1.22 mmol, 54% (70% brsm)) as a colourless oil and 1,1-cyclopropane diester **3c** (0.13 g, 0.55 mmol, 23% rsm).

R_f 0.50 (PET/AcOEt 3:1).

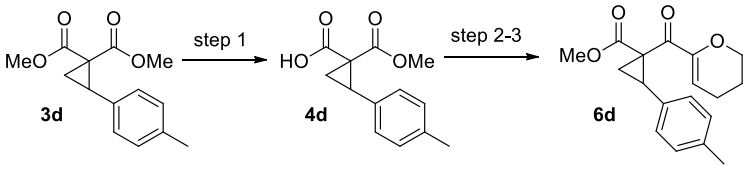
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.12 (m, 5H; ArH), 5.71 (t, *J* = 4.5 Hz, 1H; alkeneH), 3.90 (dt, *J* = 7.0, 4.5 Hz, 2H; OCH_2), 3.77 (s, 3H; OCH_3), 3.37 (t, *J* = 8.5 Hz, 1H; CHPh), 2.27 (dd, *J* = 8.0, 5.0 Hz, 1H; cyclopropaneH), 2.11-1.92 (m, 2H; CH_2CH_2), 1.74-1.64 (m, 2H; CH_2CH_2), 1.61 (dd, *J* = 9.0, 5.0 Hz, 1H; cyclopropaneH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.8, 171.3, 150.7, 134.2, 128.4, 128.0, 127.0, 110.1, 66.1, 52.5, 40.4, 32.7, 21.6, 20.5, 17.2.

IR ν (cm-1): 3333 (w), 2951 (w), 2867 (w), 2147 (w), 1734 (s), 1698 (m), 1631 (s), 1500 (w), 1436 (m), 1320 (m), 1277 (s), 1212 (m), 1150 (s), 1060 (s), 922 (w), 905 (w), 767 (m), 739 (w), 698 (m).

HRMS (ESI) calcd for $C_{17}H_{19}O_4^+$ (M+H) 287.1283; found 287.1285.

Methyl 1-(3,4-dihydro-2H-pyran-6-carbonyl)-2-*p*-tolylcyclopropanecarboxylate (6d)



Following **GP2**, 1,1-cyclopropane diester **3d** (718 mg, 2.89 mmol, 1.00 equiv) was dissolved in MeOH (2.0 mL), 1.7 N aqueous NaOH (2.0 mL, 3.4 mmol, 1.2 equiv) and some drops of THF. The reaction afforded acid **4d** (629 mg, 2.69 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (m, 4H; ArH), 3.40 (t, J = 9.1 Hz, 1H; CHPh), 3.31 (s, 3H; OCH_3), 2.42 (ddd, J = 8.6, 4.6, 1.2 Hz, 1H; CH_2), 2.37-2.31 (m, 1H; CH_2), 2.37 (s, 3H; CH_3).

Following **GP3**, dihydropyran (**44**) (540 μL, 5.92 mmol, 2.20 equiv) was dissolved in THF (1.25 mL) and reacted with ^{t}BuLi (1.6 M solution in pentane, 3.70 mL, 5.92 mmol, 2.20 equiv). The solution was diluted with THF (15 mL) and added to acid **4d** (629 mg, 2.69 mmol, 1.00 equiv) in THF (8 mL). The obtained oil was dissolved in DMF (25 ml). K_2CO_3 (740 mg, 5.36 mmol, 2.00 equiv) and methyl iodide (0.83 mL, 13.4 mmol, 5.00 equiv) were added. The crude product was purified by column chromatography (PET/Et_2O 8:1 to 3:1) to afford the desired product **6d** (562 mg, 1.87 mmol, 70% (86% brsm)) as a colourless oil and the 1,1-cyclopropane diester **3d** (0.13 mg, 0.51 mmol, 0.18 rsm).

R_f 0.50 (PET/AcOEt 3:1).

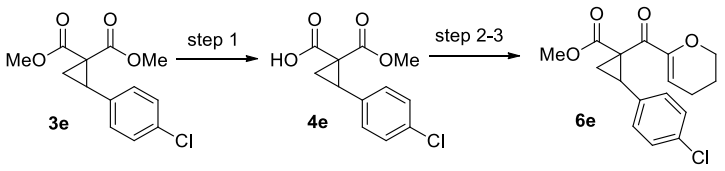
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (m, 4H; ArH), 5.72 (t, J = 4.3 Hz, 1H; alkeneH), 3.92 (t, J = 5.2 Hz, 2H; OCH_2), 3.76 (s, 3H; OCH_3), 3.35 (t, J = 8.6 Hz, 1H; CHPh), 2.29 (s, 3H; CH_3), 2.25 (dd, J = 7.9, 5.0 Hz, 1H; cyclopropaneH), 2.08-1.99 (m, 2H; CH_2CH_2), 1.75-1.67 (m, 2H; CH_2CH_2), 1.58 (dd, J = 9.1,5.2 Hz, 1H; cyclopropaneH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.9, 171.4, 150.8, 136.6, 131.0, 128.7, 128.4, 109.9, 66.1, 52.4, 40.3, 32.6, 21.6, 21.1, 20.5, 17.3.

IR ν (cm^{-1}): 3483 (w), 2953 (w), 1733 (s), 1631 (m), 1519 (m), 1437 (m), 1376 (m), 1320 (m), 1276 (s), 1210 (m), 1150 (s), 1060 (s), 923 (w), 826 (w), 738 (w).

HRMS (ESI) calcd for $C_{18}H_{21}O_4^+$ (M+H) 301.1440; found 301.1450.

Methyl 2-(4-chlorophenyl)-1-(3,4-dihydro-2H-pyran-6-carbonyl)cyclopropanecarboxylate (6e)



Following **GP2**, 1,1-cyclopropane diester **3c** (607 mg, 2.26 mmol, 1.00 equiv) was dissolved in MeOH (1.6 mL), 1.7 N aqueous NaOH (1.6 ml, 2.7 mmol, 1.2 equiv) and some drops of THF. The reaction afforded acid **4e** (527 mg, 2.07 mmol, 92%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (d, *J* = 8.4 Hz, 2H; ArH), 7.20 (d, *J* = 8.4 Hz, 2H; ArH), 3.41-3.33 (m, 4H; CHPh and CH_3), 2.38 (dd, *J* = 8.6, 5.0 Hz, 1H; CH_2), 2.28 (dd, *J* = 9.3, 5.0 Hz, 1H; CH_2).

Following **GP3**, dihydropyran (**44**) (420 μL, 4.55 mmol, 2.20 equiv) was dissolved in THF (1 mL) and reacted with ^{t}BuLi (1.6 M solution in pentane, 2.85 mL, 4.55 mmol, 2.20 equiv). The solution was added to acid **4e** (527 mg, 2.07 mmol, 1.00 equiv) in THF (8 mL). The obtained oil was dissolved in DMF (20 mL). K_2CO_3 (570 mg, 4.14 mmol, 2.00 equiv) and methyl iodide (0.65 mL, 10 mmol, 5.0 equiv) were added. The crude product was purified by column chromatography (PET/Et_2O 8:1 to 3:1) to afford the desired product **6e** (413 mg, 1.29 mmol, 62% (87% brsm) as a colourless oil and the 1,1-cyclopropane diester **3e** (0.16 g, 0.58 mmol, 26% rsm).

R_f 0.50 (PET/AcOEt 3:1).

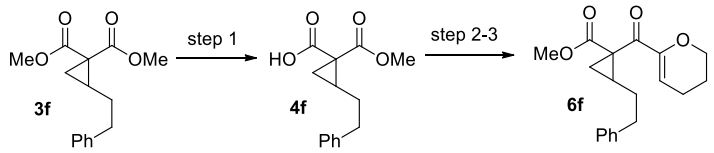
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (d, *J* = 8.4 Hz, 2H; ArH), 7.06 (d, *J* = 8.4 Hz, 2H; ArH), 5.74 (t, *J* = 4.3 Hz, 1H; alkeneH), 3.92 (t, *J* = 5.5 Hz, 2H; OCH_2), 3.77 (s, 3H; OCH_3), 3.33 (t, *J* = 8.4 Hz, 1H; CHPh), 2.23 (dd, *J* = 7.9, 5.2 Hz, 1H; cyclopropaneH), 2.11-2.01 (m, 2H; CH_2CH_2), 1.77-1.68 (m, 2H; CH_2CH_2), 1.59 (dd, *J* = 8.9, 5.2 Hz, 1H; cyclopropaneH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.6, 171.1, 150.7, 132.9, 132.8, 129.9, 128.2, 110.1, 66.2, 52.5, 40.5, 31.0, 21.6, 20.5, 17.2.

IR ν (cm^{-1}): 2956 (w), 1736 (s), 1698 (m), 1630 (s), 1497 (m), 1437 (m), 1285 (s), 1151 (s), 1059 (s), 1017 (m), 922 (m), 836 (m), 718 (m).

HRMS (ESI) calcd for $C_{17}H_{18}ClO_4^+$ (M+H) 321.0894; found 321.0898.

Methyl 1-(3,4-dihydro-2H-pyran-6-carbonyl)-2-phenethylcyclopropanecarboxylate (6f)



Following **GP2**, 1,1-cyclopropane diester **3f** (440 mg, 1.68 mmol, 1.00 equiv) was dissolved in MeOH (1.2 mL), 1.7 N aqueous NaOH (1.2 mL, 2.0 mmol, 1.2 equiv) and some drops of THF. The reaction afforded acid **4f** (409 mg, 1.64 mmol, 98%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.11 (m, 5H; ArH), 3.78 (s, 3H; OCH_3), 2.73 (m, 2H; CH_2Ph), 2.16 (m, 1H; CH_2), 2.07-1.82 (m, 3H; CH_2), 1.69 (dd, *J* = 8.4, 4.3 Hz, 1H; CH).

Following **GP3**, dihydropyran (**44**) (330 μL, 3.57 mmol, 2.20 equiv) was dissolved in THF (0.75 mL) and reacted with ^{t}BuLi (1.6 M solution in pentane, 2.23 mL, 3.57 mmol, 2.20 equiv). The solution was diluted with THF (10 mL) and added to acid **4f** (409 mg, 1.65 mmol, 1.00 equiv) in THF (8 mL). The obtained oil was dissolved in DMF (16 mL). K_2CO_3 (455 mg, 3.30 mmol, 2.00 equiv) and methyl iodide (0.51 mL, 8.3 mmol, 5.0 equiv) were added. The crude product was purified by column chromatography (PET/Et_2O 8:1 to 3:1) to afford of the desired product **6f** (0.29 g, 0.94 mmol, 57% (84% brsm) as a colourless oil and the 1,1-cyclopropane diester **3f** (0.14 mg, 0.53 mmol, 32% rsm).

R_f 0.50 (PET/AcOEt 3/1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.26 (m, 2H; ArH), 7.23-7.14 (m, 3H; ArH), 6.02 (t, *J* = 4.3 Hz, 1H; alkeneH), 4.17-4.10 (m, 1H; OCH_2), 4.04-3.97 (m, 1H; OCH_2), 3.72 (s, 3H; OCH_3), 2.74-2.65 (m, 2H; CH_2Ph), 2.28-2.19 (m, 2H; CH_2), 2.19-2.10 (m, 1H; CH_2), 1.92-1.82 (m, 2H; CH_2), 1.75-1.65 (m, 1H; CH_2), 1.49 (dd, *J* = 7.6, 4.5 Hz, 1H; cyclopropaneH), 1.37-1.28 (m, 1H; CH_2), 1.25 (dd, *J* = 8.8, 4.3 Hz, 1H; cyclopropaneH).

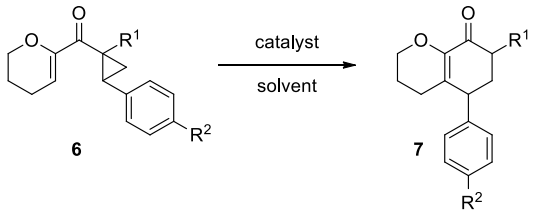
^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.3, 171.9, 151.4, 141.5, 128.5, 128.4, 125.9, 109.9, 66.3, 52.3, 37.3, 35.3, 30.0, 28.7, 21.8, 20.7, 19.5.

IR ν (cm^{-1}): 2950 (w), 1736 (s), 1693 (m), 1630 (s), 1436 (m), 1288 (s), 1205 (m), 1153 (m), 1058 (m), 919 (s), 748 (s), 700 (m).

HRMS (ESI) calcd for $C_{19}H_{23}O_4^+$ (M+H) 315.1596; found 315.1608.

4 Cyclization of ketoesters

Table 1. Optimization of the homo-Nazarov cyclization for ketoester substrates



Cyclopropane **6c** (20 mg, 70 μmol) was dissolved on the indicated solvent (0.05 M). The indicated catalyst was added and the solution was stirred at the indicated temperature during the indicated time. The reaction was quenched with a saturated solution of $NaHCO_3$, extracted with Et_2O (3x), dried over Na_2SO_4 and concentrated on reduced pressure.

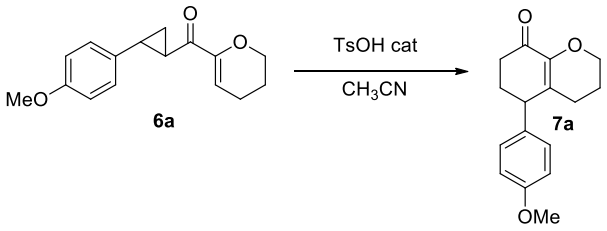
Cyclopropane **6a** and **6b** were used at the following scale and concentration:

Entry 1 (R^1 = H; R^2 = MeO): 6a (103 mg, 0.399 mmol) 0.04 M in CH_3CN.

Entry 2 (R^1 = CO_2Me; R^2 = MeO): 6b (17 mg, 54 μmol) 0.05 M in CH_3CN.

Entry 15 (R^1 = H; R^2 = MeO): 6a (10 mg, 39 μmol) 0.04 M in CH_2Cl_2.

5-(4-Methoxyphenyl)-3,4,6,7-tetrahydro-2*H*-chromen-8(5*H*)-one (7a)



The reaction was performed following **GP4**, starting from cyclopropane **6a** (100 mg, 0.40 mmol, 1.0 equiv) and tosic acid (15 mg, 80 μmol, 0.20 equiv). The reaction was quenched after 18 h. Purification by flash chromatography (PET/AcOEt, 4:1) afforded **7a** (72 mg, 0.28 mmol, 70 %) as yellow oil.

R_f 0.35 (PET/AcOEt 1:1, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (d, *J* = 8.6 Hz, 2H; ArH), 6.88 (d, *J* = 8.6 Hz, 2H; ArH), 4.20 – 3.99 (m, 2H; CH_2O), 3.81 (s, 3H; OCH_3), 3.58 (t, *J* = 5.2 Hz, 1H; CHPh), 2.59 – 2.47 (m, 1H; CH_2), 2.45 – 2.27 (m, 2H; CH_2), 2.03 – 1.90 (m, 3H; CH_2), 1.85 (d, *J* = 6.0 Hz, 2H; CH_2).

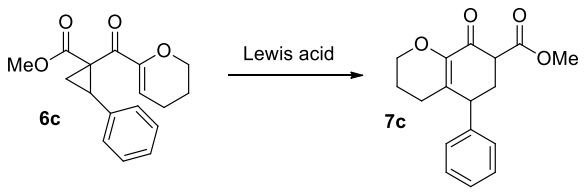
^{1}H NMR (benzene-d^6, 400 MHz) δ 6.83-6.77 (m, 2H; ArH), 6.76-6.70 (m, 2H; ArH), 3.75-3.57 (m, 2H; CH_2O), 3.33 (s, 3H; OCH_3), 3.02 (dd, *J* = 6.0, 5.3 Hz, 1H; CHAr), 2.37 (ddd, *J* = 16.6, 9.6, 4.5 Hz, 1H; CH_2CO), 2.14 (ddd, *J* = 16.6, 8.0, 4.5 Hz, 1H; CH_2CO), 1.85 (tdd, *J* = 13.3, 9.6, 4.6 Hz, 1H; CH_2), 1.62-1.49 (m, 2H; CH_2), 1.45-1.35 (m, 1H; CH_2), 1.32-1.20 (m, 2H; CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.2, 158.5, 146.8, 133.3, 132.1, 128.9, 114.1, 65.8, 55.2, 45.0, 34.9, 30.9, 25.1, 21.8.

IR ν (cm^{-1}): 2934 (m), 2870 (w), 1683 (s), 1612 (w), 1511 (s), 1463 (w), 1385 (w), 1293 (w), 1247 (s), 1180 (m), 1154 (m), 1085 (w), 1035 (m), 986 (w), 926 (w), 833(m).

HRMS(ESI) calcd for $C_{16}H_{18}O_3^+$ (M+H) 259.1329, found 259.1323.

Methyl 8-oxo-5-phenyl-3,4,5,6,7,8-hexahydro-2H-chromene-7-carboxylate (7c)



<u>Lewis acid = $Ni(ClO_4)_2$•$6H_2O$</u>: $Ni(ClO_4)_2$•$6H_2O$ (25.0 mg, 68.3 µmol, 20 mol%) was loaded in a flask. Cyclopropane **6c** (98 mg, 0.34 mmol, 1.0 equiv) diluted in DCM (3.4 mL) was added and the heterogeneous mixture was stirred at 23 °C for 26 h. Then the reaction mixture was quenched with sat. $NaHCO_3$ and diluted with DCM. The aqueous layer was extracted with DCM (x3). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (PET/Et_2O 1:1 then PET/AcOEt 2:1) to afford the homo-Nazarov product **7c** (62 mg, 0.22 mmol, 63 %) as a mixture of anti/syn diastereoisomers and enol isomer.

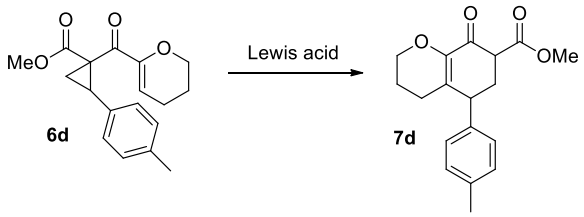
<u>Lewis acid = BF_3•Et_2O</u>: Cyclopropane **6c** (115 mg, 402 µmol, 1.00 equiv) was dissolved in DCM (3.8 mL). A solution of the catalyst was prepared by diluting 500 µL of BF_3•Et_2O in 25 mL of DCM (16 µmol/100 µL) and 250 µL of this solution (40.0 µmol, 10 mol%) were added to

the reaction. The clear solution was stirred at 23°C for 2h45. Then the reaction was quenched by adding sat. $NaHCO_3$ and diluted with DCM. The aqueous layer was extracted with DCM (x3). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (PET/Et_2O 1:1 then PET/AcOEt 2:1) to afford the homo-Nazarov product **7c** (96 mg, 0.34 mmol, 83 %) as a mixture of anti/syn diastereoisomers and enol isomer.

R_f 0.12 (PET/AcOEt 3:1).

^1H NMR ($CDCl_3$, 400 MHz) δ 12.35 (s, 0.02H; OH), 7.39-7.32 (m, 2H; ArH), 7.31-7.27 (m, 1H; ArH), 7.24-7.17 (m, 2H; ArH), 4.27 (m, 0.4H; CH_2O), 4.17-4.07 (m, 1H; CH_2O), 3.85 (m, 0.6H; CH_2O), 3.76 (m, 0.6H; CHCO), 3.72 (s, 1.6H; OCH_3), 3.70 (s, 1.1H; OCH_3), 3.68 (s, 0.3H; OCH_3) 3.62 (dd, *J* = 10.5, 4.9 Hz, 0.4H; CHCO), 3.56 (dd, *J* = 12.8, 5.0 Hz, 0.4H; CHPh), 3.50 (dd, *J* = 10.2, 4.7 Hz, 0.6H; CHPh), 2.75 (m, 0.6H; CH_2), 2.54-2.33 (m, 0.8H; CH_2), 2.16 (dt, *J* = 13.5, 5.0 Hz, 0.6H; CH_2), 2.08-1.73 (m, 4H; CH_2).

Methyl 8-oxo-5-*p*-tolyl-3,4,5,6,7,8-hexahydro-2H-chromene-7-carboxylate (7d)



Lewis acid = $Ni(ClO_4)_2•6H_2O$: $Ni(ClO_4)_2•6H_2O$ (27.9 mg, 76.2 µmol, 20 mol%) was loaded in a flask. Cyclopropane **6d** (115 mg, 383 µmol, 1.00 equiv) diluted in DCM (3.8 mL) was added and the heterogeneous mixture was stirred at 23 °C for 26 h. Then the reaction mixture was quenched with sat. $NaHCO_3$ and diluted with DCM. The aqueous layer was extracted with DCM (x3). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (PET/Et_2O 1:1 then PET/AcOEt 2:1) to afford the homo-Nazarov product **7d** (97 mg, 0.32 mmol, 84 %) as a mixture of anti/syn diastereoisomers and enol isomer.

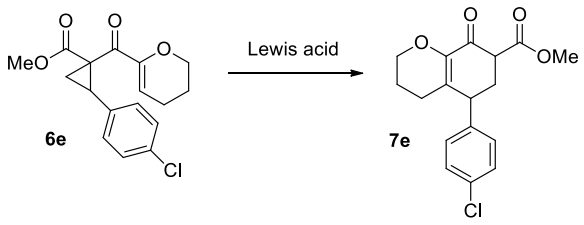
Lewis acid = $BF_3•Et_2O$: Cyclopropane **6d** (121 mg, 403 µmol, 1.00 equiv) was dissolved in DCM (3.8 mL). A solution of the catalyst was prepared by diluting 500 µL of $BF_3•Et_2O$ in 25 ml of DCM (16 µmol/100 µL) and 250 µL of this solution (40.0 µmol, 10 mol%) were added to the reaction. The clear solution was stirred at 23°C for 2h45. Then the reaction was quenched by

adding sat. $NaHCO_3$ and diluted with DCM. The aqueous layer was extracted with DCM (x3). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (PET/Et_2O 1:1 then PET/AcOEt 2:1) to afford the homo-Nazarov product **7d** (109 mg, 363 µmol, 90 %) as a mixture of anti/syn diastereoisomers and enol isomer.

R_f 0.12 (PET/AcOEt 3:1).

^1H NMR ($CDCl_3$, 400 MHz) δ 7.19-7.13 (m, 2H; ArH), 7.13-7.04 (m, 2H; ArH), 4.26 (m, 0.4H; CH_2O), 4.15-4.05 (m, 1H; CH_2O), 3.83 (m, 0.6H; CH_2O), 3.75-3.69 (m, 0.6H; CHCO), 3.72 (s, 1.8H; OCH_3), 3.70 (s, 1.1H; OCH_3), 3.68 (s, 0.1H; OCH_3), 3.62-3.46 (m, 1.4H; CHCO and CHPh), 2.72 (m, 0.6H; CH_2), 2.50-2.31 (m, 0.8H; CH_2), 2.34 (s, 3H; CH_3), 2.13 (dt, *J* = 13.4, 4.9 Hz, 0.6H; CH_2), 2.05-1.73 (m, 4H; CH_2).

Methyl 5-(4-chlorophenyl)-8-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-7-carboxylate (7e)



Lewis acid = $Ni(ClO_4)_2•6H_2O$: $Ni(ClO_4)_2•6H_2O$ (31.5 mg, 86.1 µmol, 20 mol%) was loaded in a flask. Cyclopropane **6e** (138 mg, 430 µmol, 1.00 equiv) diluted in DCM (4.3 mL) was added and the heterogeneous mixture was stirred at 23 °C for 26 h. Then the reaction mixture was quenched with sat. $NaHCO_3$ and diluted with DCM. The aqueous layer was extracted with DCM (x3). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified by column chromatography (PET/Et_2O 1:1 then PET/AcOEt 2:1) to afford the homo-Nazarov product **7e** (90 mg, 0.28 mmol, 65 %) as a mixture of anti/syn diastereoisomers and enol isomer.

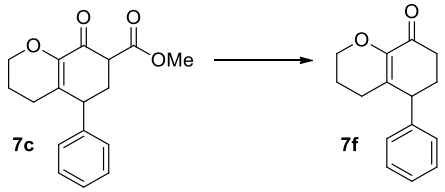
Lewis acid = $BF_3•Et_2O$: Cyclopropane **6e** (140 mg, 436 µmol, 1.00 equiv) was dissolved in DCM (4.1 mL). A solution of the catalyst was prepared by diluting 500 µL of $BF_3•Et_2O$ in 25 mL of DCM (16 µmol/100 µL) and 280 µL of this solution (44.8 µmol, 10 mol%) were added to the reaction. The clear solution was stirred at 23°C for 2h45. Then the reaction was quenched by adding sat. $NaHCO_3$ and diluted with DCM. The aqueous layer was extracted with DCM (x3). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure.

The crude product was purified by column chromatography (PET/Et_2O 1:1 then PET/AcOEt 2:1) to afford the homo-Nazarov product **7e** (119 mg, 371 µmol, 85 %) as a mixture of anti/syn diastereoisomers and enol isomer.

R_f 0.12 (PET/AcOEt 3:1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.28 (m, 2H; ArH), 7.19-7.08 (m, 2H; ArH), 4.27 (m, 0.4H; CH_2O), 4.14-4.07 (m, 1H; CH_2O), 3.84 (m, 0.6H; CH_2O), 3.77-3.58 (m, 0.6H; CHCO), 3.73 (s, 1.7H; OCH_3), 3.70 (s, 1.1H; OCH_3), 3.69 (s, 0.2H; OCH_3), 3.62 (dd, *J* = 10.0, 5.2 Hz, 0.4H; CHCO), 3.55 (dd, *J* = 12.2, 5.5 Hz, 0.4H; CHPh), 3.46 (dd, *J* = 9.9, 4.7 Hz, 0.6H; CHPh), 2.73 (m, 0.6H; CH_2), 2.48-2.30 (m, 0.8H; CH_2), 2.11 (dt, *J* = 13.5, 5.0 Hz, 0.6H; CH_2), 2.07-1.76 (m, 4H; CH_2).

5-Phenyl-3,4,6,7-tetrahydro-2H-chromen-8(5H)-one (7f)



Ketoester **7c** (62 mg, 0.22 mmol, 1.0 equiv) was dissolved in DMSO (1 mL) and water (0.1 mL). NaCl (30 mg, 0.51 mmol, 2.4 equiv) was added and the mixture was heated on microwave at 150°C for 1 h. The reaction mixture was diluted with AcOEt and the organic layer was washed with brine (x5). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (PET/AcOEt 2:1) to afford the decarboxylated product **7f** (49 mg, 0.22 mmol, quantitative).

R_f 0.50 (PET/AcOEt 1:1).

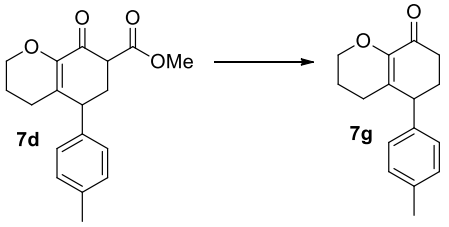
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.33 (m, 2H; ArH), 7.33-7.27 (m, 1H; ArH), 7.26-7.20 (m, 2H; ArH), 4.12 (m, 2H; OCH_2), 3.65 (t, *J* = 5.3 Hz, 1H; CHPh), 2.55 (m, 1H; CH_2), 2.48-2.35 (m, 2H; CH_2), 2.07-1.97 (m, 3H; CH_2), 1.92-1.82 (m, 2H; CH_2).

^{13}C NMR ($CDCl_3$ 100 MHz) δ 193.2, 147.1, 141.4, 131.7, 128.8, 128.1, 127.05, 66.0, 45.9, 35.0, 30.9, 25.2, 21.9.

IR ν (cm-1): 3347 (w), 2945 (w), 2864 (w), 2146 (w), 1682 (s), 1631 (w), 1491 (w), 1453 (w), 1386 (w), 1293 (m), 1154 (s), 1086 (w), 985 (w), 912 (w), 738 (m), 705 (m).

HRMS (ESI) calcd for $C_{15}H_{17}O_2^+$ (M+H) 229.1228; found 229.1231.

5-*p*-Tolyl-3,4,6,7-tetrahydro-2H-chromen-8(5H)-one (7g)



Ketoester **7d** (100 mg, 333 µmol, 1.00 equiv) was dissolved in DMSO (1 mL) and water (0.1 mL). NaCl (50 mg, 0.90 mmol, 2.6 equiv) was added and the mixture was heated on microwave at 150°C for 1h40. The reaction mixture was diluted with AcOEt and the organic layer was washed with brine (x5). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (PET/AcOEt 2:1) to afford the decarboxylated product **7g** (62 mg, 0.26 mmol, 77%).

R_f 0.53 (PET/AcOEt 1:1).

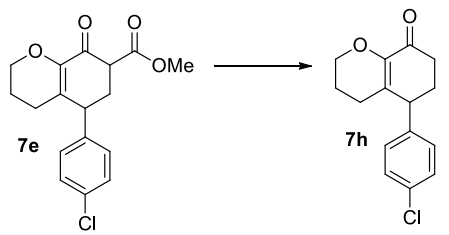
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.18 (d, *J* = 7.7 Hz, 2H; ArH), 7.12 (d, *J* = 8.1 Hz, 2H; ArH), 4.12 (m, 2H; OCH_2), 3.61 (t, *J* = 5.5 Hz, 1H; CHPh), 2.55 (m, 1H; CH_2), 2.47-2.31 (m, 2H; CH_2), 2.37 (s, 3H; CH_3), 2.05-1.94 (m, 3H; CH_2), 1.91-1.81 (m, 2H; CH_2).

^{13}C NMR ($CDCl_3$ 100 MHz) δ 193.3, 147.0, 138.4, 136.7, 132.0, 129.5, 128.0, 66.0, 45.5, 35.0, 30.9, 25.2, 21.9, 21.1.

IR ν (cm-1): 2933 (w), 2867 (w), 2246 (w), 1683 (s), 1628 (w), 1513 (w), 1450 (w), 1384 (w), 1292 (m), 1184 (w), 1151 (s), 1085 (w), 986 (w), 913 (w), 819 (w), 732 (m).

HRMS (ESI) calcd for $C_{16}H_{19}O_2^+$ (M+H) 243.1385; found 243.1397.

5-(4-Chlorophenyl)-3,4,6,7-tetrahydro-2H-chromen-8(5H)-one (7h)



Ketoester **7e** (90 mg, 0.28 mmol, 1.0 equiv) was dissolved in DMSO (2 mL) and water (0.2 mL). NaCl (120 mg, 2.05 mmol, 7.10 equiv) was added and the mixture was heated on microwave at 150°C for 1h30. The reaction mixture was diluted with AcOEt and the organic layer was washed with brine (x5). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified by column chromatography (PET/AcOEt 2:1) to afford the decarboxylated product **7h** (42 mg, 0.16 mmol, 57%).

R_f 0.45 (PET/AcOEt 1:1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, *J* = 8.4 Hz, 2H; ArH), 7.17 (d, *J* = 8.4 Hz, 2H; ArH), 4.12 (m, 2H; OCH_2), 3.63 (t, *J* = 5.5 Hz, 1H; CHPh), 2.59-2.30 (m, 3H; CH_2), 2.05-1.92 (m, 3H; CH_2), 1.92-1.83 (m, 2H; CH_2).

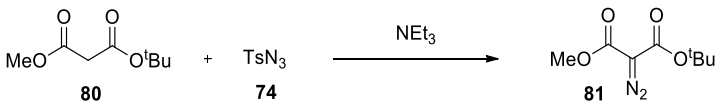
^{13}C NMR ($CDCl_3$ 100 MHz) δ 192.9, 147.19, 140.0, 132.9, 130.9, 129.4, 129.0, 66.0, 45.3, 34.9, 30.8, 25.2, 21.8.

IR ν (cm^{-1}): 2934 (w), 2872 (w), 2249 (w), 1683 (s), 1631 (w), 1489 (w), 1385 (w), 1293 (w), 1155 (m), 1088 (w), 1015 (w), 913 (w), 832 (w), 735 (m).

HRMS (ESI) calcd for $C_{15}H_{16}ClO_2^+$ (M+H) 263.0839; found 263.0844.

5 Asymmetric induction

1-*tert*-Butyl 3-methyl 2-diazomalonate (81)

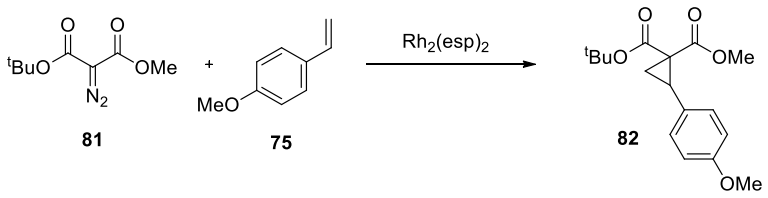


Following the same procedure described precedently,[6] *tert*-butyl methyl malonate diester (**80**) (0.49 mL, 2.9 mmol, 1.0 equiv), triethylamine (0.44 mL, 3.2 mmol, 1.1 equiv) and tosyl azide (**74**) (630 mg, 3.16 mmol, 1.10 equiv) afforded *tert*-butyl-3-methyl-2-diazomalonate (**81**) (460 mg, 2.32 mmol, 81%).

R_f 0.59 (PET/Et_2O 1:1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (s, 1H; OCH_3), 1.54 (s, 9H; CH_3).

1-*tert*-Butyl 1-methyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (82)

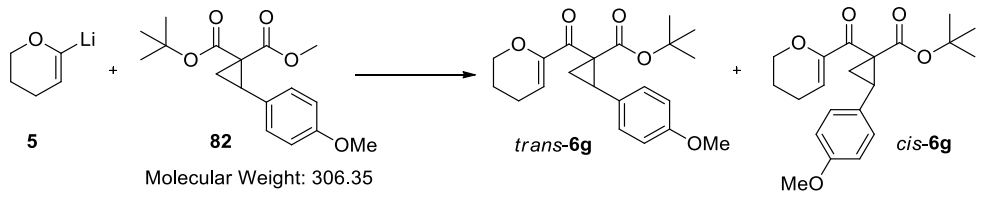


The reaction was performed following the **GP1**, using $Rh_2(esp)_2$ (0.9 mg, 1 μmol, 0.1 mol%), 4-methoxystyrene (**75**) (0.16 mL, 1.2 mmol, 1.00 equiv) and diazomalonate **81** (200 mg, 1.00 mmol, 1.00 equiv). Purification by column chromatography (PET/Et_2O 10:1 to 5:1) afforded cyclopropane **82** (276 mg, 0.90 mmol, 90%).

R_f 0.45 (PET/Et_2O 5:1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.14 (d, *J* = 8.8 Hz, 2H; ArH), 6.82 (d, *J* = 8.8 Hz, 2H; ArH), 3.80 (s, 3H; OCH_3), 3.43 (s, 3H; OCH_3), 3.10 (t, *J* = 8.2 Hz, 1H; CHPh), 2.07 (dd, *J* = 7.7, 5.0 Hz, 1H; CH_2), 1.65 (dd, *J* = 9.3, 5.2 Hz, 1H; CH_2), 1.50 (s, 9H; CH_3).

***t*Butyl-1-(3,4-dihydro-2H-pyran-6-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (6g) (*trans*/*cis*)**



Following a reported procedure,[11] dihydropyran (**44**) (85 μL, 0.93 mmol, 1.0 equiv) was dissolved in THF (0.13 mL) and the mixture was cooled to -78°C. *t*BuLi (1.6 M solution in pentane, 0.56 mL, 0.90 mmol, 1.0 equiv) was added dropwise to this solution at the same temperature. The reaction mixture was stirred at 0°C for 30 min. Then THF (3.0 mL) was added and the solution was cooled to -95°C. The 1,1-cyclopropane diester **82** (270 mg, 0.90 mmol, 1.00 equiv) dissolved in THF (1 mL) was added in one portion to this solution. The reaction mixture was allowed until the temperature of the cooling bath was -40°C (1.30 h). Then the reaction mixture was poured in brine and diluted with DCM. The aqueous layer was extracted with DCM (x3). The organic layers were combined, dried over Na_2SO_4 and evaporated under reduced pressure. A 3/1 mixture of trans/cis is detected by ^{1}H NMR of the crude. Purification by column

[11] Boeckman, R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997.

chromatography (PET/Et_2O 4:1) afforded the *trans* isomer of **6g** (111 mg, 0.31 mmol, 34%), a mixture of *cis*/*trans* isomers of **6g** (34 mg, 11 µmol, 12%) and starting material **82** (71 mg, 0.23 mmol, 25%) as oils.

*Tran*s isomer

R_f 0.41 (PET/AcOEt 4:1).

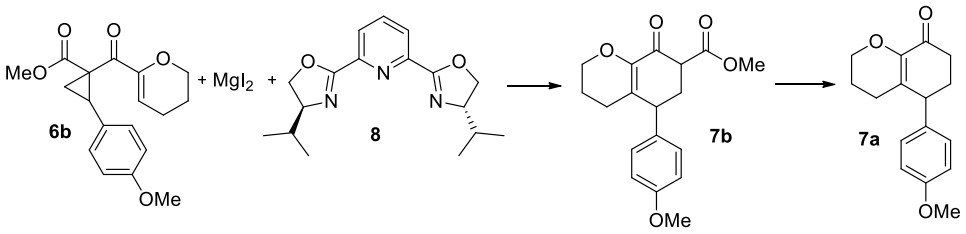
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (d, *J* = 8.6 Hz, 2H; ArH), 6.73 (d, *J* = 8.8 Hz, 2H; ArH), 5.67 (t, *J* = 4.2 Hz, 1H; alkeneH), 3.98 (m, 1H; OCH_2), 3.88 (m, 1H; OCH_2), 3.76 (s, 3H; OCH_3), 3.21 (t, *J* = 8.3 Hz, 1H; CHPh), 2.13 (dd, *J* = 7.9, 5.0 Hz, 1H; CH_2), 2.10-1.96 (m, 2H; CH_2), 1.71 (td, *J* = 6.7, 3.5 Hz, 2H; CH_2), 1.51-1.44 (m, 1H; CH_2), 1.44 (s, 9H; CH_3).

^{13}C NMR ($CDCl_3$ 125 MHz) δ 189.4, 169.8, 158.4, 150.8, 129.5, 126.3, 113.3, 109.2, 101.1, 100.0, 81.6, 66.0, 55.1, 41.3, 31.8, 27.9, 21.6, 20.5, 16.7.

IR ν (cm^{-1}): 2986 (w), 2953 (w), 2936 (w), 1724 (m), 1723 (m), 1697 (w), 1632 (m), 1614 (w), 1517 (s), 1463 (w), 1460 (w), 1459 (w), 1442 (w), 1369 (w), 1339 (w), 1320 (m), 1290 (s), 1251 (s), 1213 (w), 1212 (w), 1176 (m), 1150 (s), 1120 (w), 1062 (w), 1036 (w), 1020 (w), 920 (m), 914 (m), 913 (m), 838 (m), 737 (s).

HRMS (ESI) calcd for $C_{21}H_{27}O_5^+$ (M+H) 359.1853; found 359.1843.

5-(4-Methoxyphenyl)-3,4,6,7-tetrahydro-2*H*-chromen-8(5*H*)-one (7a)

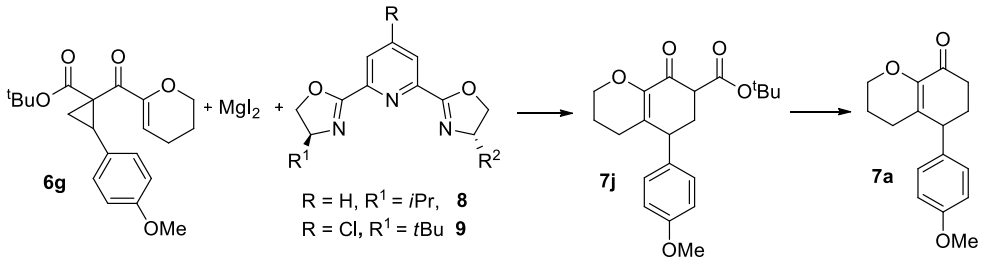


MgI_2 (20.2 mg, 72.6 µmol, 0.28 equiv) and PyBOX ligand **8** (24.1 mg, 80.0 µmol, 0.30 equiv) were stirred in DCM (1 mL) with dried MS 4Å for 45 min at 23°C. Then, cyclopropane **6b** (83 mg, 0.26 mmol, 1 equiv) dissolved in DCM (1.6 mL) was added and the reaction mixture was stirred at 23°C for 4.5 days (complete conversion was achieved). The reaction mixture was filtered over a short column of silica gel (PET/Et_2O 1/1 then PET/AcOEt 1/1). The collected fractions were dissolved in AcOEt and the organic layer was washed with an aqueous solution of $Na_2S_2O_3$ (x2). The organic layer was dried over $MgSO_4$ and concentrated under reduced

pressure. Purification by column chromatography (PE/AcOEt 3/1 to 2/1) afforded **7b** (40 mg, 0.12 mmol, 48 %) as a yellow oil.

Part of **7b** (10 mg, 31.6 µmol, 1 equiv) was dissolved in DMSO (2 mL) and water (0.2 mL). NaCl (100 mg, 1.7 mmol) was added and the reaction mixture was heated in microwave at 150°C for 30 min. The reaction was diluted with AcOEt and the organic layer was washed with brine (x5). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give **7a** (no complete conversion was achieved but the product is detected by ^{1}H NMR).

Optical purity determined by chiral HPLC analysis: 11%.



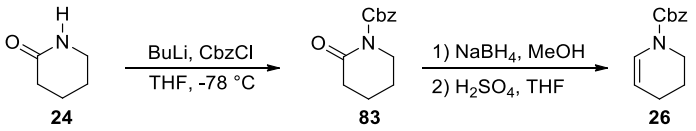
Following a reported procedure,[12] MgI_2 (2.1 mg, 7.6 µmol, 0.14 equiv) and PyBOX ligand **8** (2.6 mg, 8.6 µmol, 0.15 equiv) or **9** (3.1 mg, 8.6 µmol, 0.15 equiv) were stirred in DCM (0.5 mL) for 45 min at 23°C. Then, cyclopropane **6g** (20 mg, 56 µmol, 1 equiv) dissolved in DCM (0.5 mL) was added and the reaction mixture was stirred at 23°C for 22h (no complete conversion was achieved). The reaction was quenched by adding sat. $NaHCO_3$. The aqueous layer was extracted with AcOEt, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (PET/AcOEt 2/1) and the collected fractions were directly engaged in the decarboxylation step. Following a reported procedure,[13] **7j** was dissolved in a mixture DCM/TFA (250 µl/50 µl) and stirred at RT for 20 h. The solution was diluted with DCM and saturated aqueous $NaHCO_3$ was added. After gas evolution had ceased, the layers were separated and the aqueous layer was washed with additional DCM (x2). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give **7a**.

Optical purity determined by chiral HPLC analysis : 25% (with both ligands).

[12] Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122.
[13] Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988.

6 Amino- and oxycyclopropanes synthesis

3,4-Dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (26)



Following a reported procedure,[14] δ-valerolactam **24** (3.00 g, 30.2 mmol, 1.00 equiv) was dissolved in THF (130 mL). The reaction mixture was cooled to -78 °C and ^{n}BuLi (2.5 M in hexane, 12 mL, 30 mmol, 1.0 equiv) was added dropwise to the resulting suspension. After 30 min at -78 °C, a solution of benzylchloroformate (4.3 mL, 30 mmol, 1.0 equiv) in THF (30 mL) was added dropwise. After 4 h at -78 °C, the reaction mixture was quenched with sat. NH_4Cl (40 mL) and warmed to 23 °C. The reaction mixture was extracted with Et_2O (3x50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude Cbz protected lactam **83** (6.95 g, 29.8 mmol, 99%), which was used without further purification.

R_f 0.30 (PET/AcOEt 2:1, Anisaldehyde);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47-7.28 (m, 5H; ArH), 5.28 (s, 2H; OCH_2), 3.74 (m, 2H; CH_2N), 2.54 (m, 2H; CH_2CO), 1.83 (m, 4H; CH_2).

Following a reported procedure,[15] protected lactam **83** (2.82 g, 12.1 mmol, 1.00 equiv) was dissolved in methanol (52 mL) at 0 °C and sodium borohydride (0.46 g, 12 mmol, 1.0 equiv) was added portionswise. After the end of the addition, the reaction mixture was stirred at 0 °C for 15 min and poured onto ice-water (150 mL). The reaction mixture was extracted with AcOEt (3x100 mL). The combined organic layers were washed with brine (50 mL), the combined water layers were extracted with AcOEt (100 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure.

The residues were dried in HV for 15 min and dissolved in THF (25 mL). Conc. sulfuric acid (0.13 mL) was added and the reaction was monitored via TLC (PET/AcOEt 10:1-2:1). After 1 h the reaction mixture was poured onto sat. $NaHCO_3$ (100 mL) and extracted with AcOEt (3x100

[14] A. Giovannini, D. Savoia, A. Umani-Ronchi, *J. Org. Chem.* **1989**, *54*, 228.
[15] Y. Takeuchi, K. Azuma, M. Oshige, H. Abe, H. Nishioka, K. Sasaki, T. Harayama, *Tetrahedron* **2003**, *59*, 1639.

mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 10:1-2:1) to yield enamide **26** (1.76 g, 8.11 mmol, 67%) as a colorless oil.

R_f 0.80 (PET/AcOEt 2:1, Anisaldehyde).

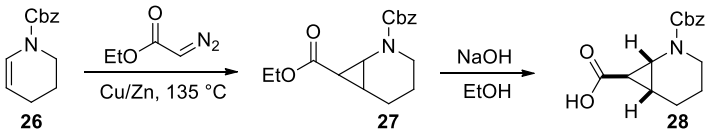
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.27 (m, 5H; ArH), 6.89 (d, *J* = 8.6 Hz, 0.4H; alkeneH), 6.80 (d, *J* = 8.6 Hz, 0.6H; alkeneH), 5.18 (s, 2H; CH_2O), 4.97 (m, 0.4H; alkeneH), 4.86 (m, 0.6H; alkeneH), 3.63 (m, 2H; CH_2N), 2.04 (m, 2H; CH_2), 1.83 (m, 2H; CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 151.7, 136.3, 128.5, 128.5, 128.2, 128.0, 128.0, 125.3, 124.8, 106.7, 106.4, 67.4, 67.3, 42.3, 42.2, 21.6, 21.4, 21.2.

IR ν (cm-1): 2951 (w), 1703 (s), 1653 (m), 1409 (s), 1347 (s), 1256 (s), 1227 (m), 1183 (w), 1108 (s), 1054 (m), 912 (m), 764 (m), 731 (s), 697 (s).

^{1}H NMR corresponded to the literature values.[15]

2-Benzyl 7-ethyl 2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (27) and 2-(benzyloxycarbonyl)-2-azabicyclo[4.1.0]heptane-7-carboxylic acid (28)



Following a reported procedure,[16] a mixture of enamide **26** (1.70 g, 7.82 mmol, 1.00 equiv) and copper/bronze (67 mg, prepared freshly as following: Zinc powder (0.20 g) was added to a solution of $CuSO_4$•$5H_2O$ (1.0 g) in water (2 mL) over 10 min at RT. The resulting suspension was filtered, the solid was washed with water (3x5 mL), ethanol (3x5 mL) and Et_2O (2x5 mL) and dried 1 h in HV) was heated to 135 °C. Ethyl diazoacetate (4.2 mL, 40 mmol, 5.0 equiv) was added via syringe pump over 90 min, and the reaction was stirred for further 30 min before cooling down to RT. The crude product was purified by two successive flash column chromatography (PET/AcOEt 10:1-2:1) to yield cyclopropane **27** (1.18 g, 3.89 mmol, 50%, R_f = 0.30 (PET/AcOEt 3:1), still containing some polymeric impurities) as a colorless oil.

[16] P. A. Grieco, M. D. Kaufman, *J. Org. Chem.* **1999,** *64*, 7586.

The crude ester **27** (1.18 g, 3.89 mmol, 1.00 equiv) was dissolved in ethanol (4 mL) at 0 °C and NaOH (2.2 g, 55 mmol, 14 equiv) was added. The reaction mixture was stirred 1 h at 0 °C and 12 h at RT, diluted with water (10 mL), acidified to pH = 1 with 1 M HCl and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give nearly pure acid **28** (0.89 g, 3.2 mmol, 84%, 42 % from enamide **26**) as a colorless oil.

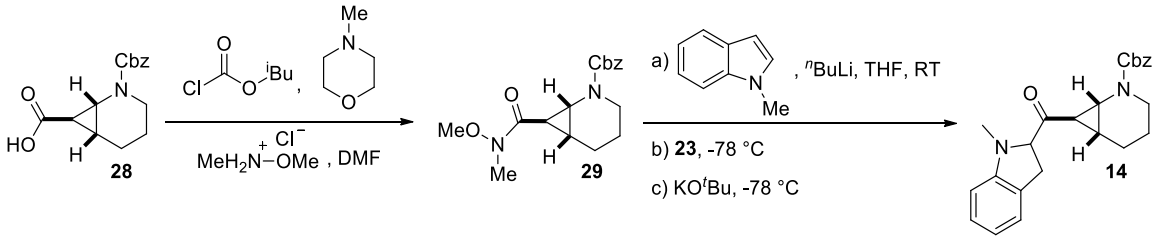
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.26 (m, 5H; ArH), 5.26-5.11 (m, 2H; OCH_2), 3.88 (dt, *J* = 12.5 Hz, 3.2 Hz, 0.7H; NCH_2 or NCH rotamer A), 3.74 (s, 0.3H; NCH_2 or NCH rotamer B), 3.57 (m, 0.3H; NCH_2 or NCH rotamer B), 3.50 (dd, *J* = 8.6 Hz, 2.6 Hz, 0.7H; NCH_2 or NCH rotamer A), 2.77 (dd, *J* = 1.3 Hz, 0.6 Hz, 0.3H; NCH_2 or NCH rotamer B), 2.67 (td, *J* = 12.5 Hz, 2.2 Hz, 0.7H; NCH_2 or NCH rotamer A), 2.08-1.78 (m, 3H; CHCO and CH_2), 1.77-1.58 (m, 2H; CH or CH_2), 1.40-1.20 (m, 1H; CH or CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 178.0, 177.0, 156.4, 136.5, 136.3, 128.8, 128.6, 128.5, 128.3, 127.7, 127.6, 127.5, 127.2, 126.7, 126.4, 68.4, 67.0, 39.8, 39.7, 38.1, 38.0, 26.5, 26.4, 25.5, 25.4, 22.8, 22.6, 19.6, 19.4.

IR ν (cm-1): 3062 (w), 2946 (w), 2870 (w), 1689 (m), 1448 (w), 1423 (m), 1350 (w), 1302 (w), 1266 (m), 1195 (m), 1135 (w), 1098 (w), 1041 (w), 1002 (w), 909 (w), 731 (s), 699 (s).

HRMS(ESI) calcd for $C_{15}H_{18}NO_4^+$ (M+H) 276.1236, found 276.1232.

Benzyl 7-(methoxy(methyl)carbamoyl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (29) and benzyl 7-(1-methyl-*1H*-indole-2-carbonyl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (14)



Following a reported procedure,[17] *N*-methylmorpholine (0.40 mL, 3.6 mmol, 1.1 equiv) was added to a solution of acid **28** (0.90 g, 3.3 mmol, 1.0 equiv) in DMF (3.3 mL) at 0 °C. After 25

[17] S. R. Nagarajan, H. F. Lu, A. F. Gasiecki, I. K. Khanna, M. D. Parikh, B. N. Desai, T. E. Rogers, M. Clare, B. B. Chen, M. A. Russell, J. L. Keene, T. Duffin, V. W. Engleman, M. B. Finn, S. K. Freeman, J. A. Klover, G.

min, *iso*butylchloroformate (0.47 mL, 3.6 mmol, 1.1 equiv) was added dropwise at 0 °C. After 10 min, *N,O*-dimethylhydroxylamine hydrochloride (0.35 g, 3.6 mmol, 1.1 equiv) was added, followed by *N*-methylmorpholine (0.46 mL, 4.2 mmol, 1.3 equiv) and the reaction mixture was warmed to 23 °C. After 12 h, the reaction was quenched with 0.5 M HCl (6 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with 0.5 M NaOH (2x10 mL), brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 4:1-1:1) to yield Weinreb amide **29** (665 g, 2.09 mmol, 64%, R_f = 0.30 (PET/AcOEt 1:1) as a colorless oil, which was used directly in the next step.

N-Methyl indole (0.16 mL, 1.2 mmol, 1.2 equiv) was diluted in THF (4 mL) at 0 °C and ^{n}BuLi (0.47 mL, 1.2 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred 1 h at RT and cooled to -78 °C. Weinreb amide **29** (dried through 3 co-evaporation with toluene, 0.31 g, 0.97 mmol, 1.0 equiv) was added dropwise via cannula as a cooled (-78 °C) solution in THF (2 mL). After further stirring 2 h at -78 °C, a solution of KO*t*Bu (0.22 g, 2.0 mmol, 2.0 equiv) in THF (2 mL) was added. After 2 h, the reaction mixture was warmed to 0 °C, whereas the yellow suspension became an orange solution. After 5 min at 0 °C, the reaction mixture was quenched with sat. $NaHCO_3$ (10 mL) and extracted with Et_2O (3x10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 5:1-3:1) to yield indole **14** (251 mg, 0.646 mmol, 67%) as a colorless solid.

R_f 0.30 (PET/AcOEt 3:1, Anisaldehyde).

Mp 119-121 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, *J* = 8.0 Hz, 1H; ArH), 7.43-7.28 (m, 4H; ArH), 7.22-7.14 (m, 1H; ArH), 7.10-7.02 (m, 2H; ArH), 6.99-6.89 (m, 2H; ArH), 5.16 (d, *J* = 12.5 Hz, 1H; OCH_2), 4.99 (d, *J* = 12.5 Hz, 1H; OCH_2), 4.06 (s, 0.8H; CH_3 rotamer B), 4.00 (s, 2.2H; CH_3 rotamer A), 3.95 (t, *J* = 3.8 Hz, 0.8H; NCH or NCH_2 rotamer A), 3.84 (m, 0.2H; NCH or NCH_2 rotamer B), 3.67 (m, 0.2H; NCH or NCH_2 rotamer B), 3.55 (dd, *J* = 8.3 Hz, 2.2 Hz, 0.8H; NCH or NCH_2 rotamer A), 2.85 (t, *J* = 12.5 Hz, 0.2H; NCH or NCH_2 rotamer B), 2.76 (td, *J* = 12.5 Hz, 2.2 Hz, 0.8H; NCH or NCH_2 rotamer B), 2.63 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H; COCH), 2.28 (m, 1H; CH_2CH), 2.06-1.90 (m, 2H; CH_2), 1.81-1.71 (m, 1H; CH_2), 1.48 (m, 1H; CH_2).

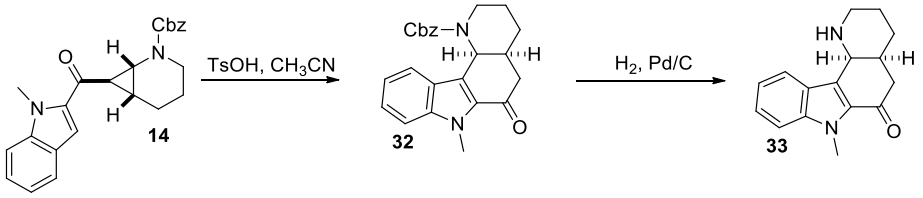
A. Nickols, M. A. Nickols, K. E. Shannon, C. A. Steininger, W. F. Westlin, M. M. Westlin, M. L. Williams, *Bioorg. Med. Chem.* **2007**, *15*, 3390.

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 189.9, 156.4, 140.0, 136.2, 135.4, 128.4, 128.0, 127.5, 127.5, 126.8, 125.9, 125.7, 125.5, 122.8, 122.6, 120.6, 120.3, 111.3, 111.1, 110.2, 67.1, 65.1, 41.6, 41.0, 33.5, 32.8, 32.0, 29.6, 23.8, 21.8, 19.9.

IR ν (cm-1): 2941 (w), 2866 (w), 1702 (s), 1639 (s), 1615 (w), 1513 (m), 1428 (s), 1407 (s), 1347 (s), 1299 (m), 1264 (m), 1195 (s), 1152 (m), 1129 (s), 1095 (m), 1034 (s), 908 (m), 794 (w), 769 (w), 752 (s), 731 (s), 698 (s), 648 (w).

HRMS(ESI) calcd for $C_{24}H_{25}N_2O_3^+$ (M+H) 389.1865, found 389.1854.

Benzyl 7-methyl-6-oxo-2,3,4,4a,5,6,7,11c-octahydro-*1H*-pyrido[3,2-c]carbazole-1-carboxylate (32) and 7-methyl-3,4,4a,5,7,11c-hexahydro-*1H*-pyrido[3,2-c]carbazol-6(*2H*)-one (33)



The reaction was performed following **GP4**, starting from cyclopropane **14** (50 mg, 0.13 mmol, 1.0 equiv) and tosic acid (4.9 mg, 0.030 mmol, 0.20 equiv). The reaction was quenched after 12 h. Purification by flash chromatography (PET/AcOEt, 3:7) afforded **32** (45 mg, 0.12 mmol, 90 %) as yellow oil. R_f 0.60 (PET/AcOEt 7:3, Anisaldehyde). The indole derivative **32** (35 mg, 0.090 mmol, 1.0 equiv) was deprotected following general procedure **GP5**, using Pd/C (10 mg, 10% w/w) in Et_2O (3.5 mL) and a H_2 balloon. The suspension was filtered on celite and washed with DCM to afford **33** as yellow oil in quantitative yield (23 mg, 0.090 mmol, 1.0 equiv).

R_f 0.80 (DCM/MeOH/Et_3N 3:1:2%, Anisaldehyde).

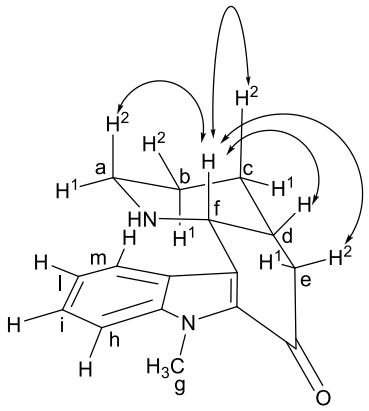
^{1}H NMR ($CDCl_3$, 400 MHz) 7.88 (d, J = 8.1 Hz, 1H; H_m or H_h), 7.43-7.31 (m, 2H; H_m or H_h and H_i or H_l), 7.18 (t, J = 7.4 Hz, 1H; H_i or H_l), 4.35 (d, J = 3.3 Hz, 1H; H_f), 4.06 (s, 3H; $3H_g$), 3.23 (dd, J = 16.5 Hz, 12.0 Hz, 1H; $H^1{}_e$), 2.96 (m, 1H; $H^1{}_a$), 2.83 (m, 1H; $H^2{}_a$), 2.52 (m, 1H; H_d), 2.41 (dd, J = 16.5 Hz, 4.0 Hz, 1H; $H^2{}_e$), 1.87-1.60 (m, 4H; $H^1{}_c$ and/or $H^2{}_c$ and/or $H^1{}_b$ and/or $H^2{}_b$ and NH), 1.57-1.45 (m, 1H; $H^1{}_b$ or $H^2{}_b$ or $H^1{}_c$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.2, 139.7, 130.2, 126.6, 123.9, 121.4 120.7, 110.3, 110.3, 51.4, 45.3, 41.0, 35.9, 31.5, 29.7, 28.5.

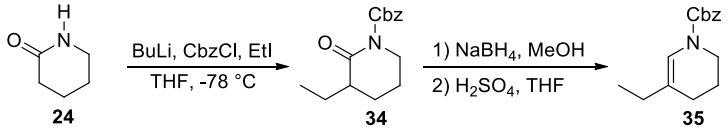
IR ν (cm-1): 3299 (w), 2926 (s), 2855 (m), 2149 (w), 1662 (s), 1616 (w), 1469 (m), 1432 (m), 1419 (w), 1386 (w), 1245 (m), 1062 (w), 758 (s), 746 (s), 732 (w), 655 (m).

HRMS(ESI) calcd for $C_{16}H_{19}N_2O^+$ (M+H) 255.1497, found 255.1490.

Important correlations ROESY: H_f-H_a^2; H_f-H_c^2; H_f-H_d; H_f-H_e^2 (see the 2D spectra in section 6)



3,4-Dihydro-*2H*-3-ethylpyridine-1-carboxylic acid benzyl ester (35)



Following a reported procedure,[16] a 2.5 M solution of *n*BuLi in pentane (88.0 mL, 220 mmol 2.20 equiv) was added dropwise to a solution of δ-valerolactam **24** (10.0 g, 100 mmol, 1.00 equiv) in THF (200 mL) at 0°C. The reaction mixture was stirred during 30 min and distilled ethyl iodide (12.2 mL, 150 mmol, 1.50 equiv) was added. The solution was stirred for additional 20 minutes before benzylchloroformate (14.9 mL, 105 mmol, 1.05 equiv) in THF (50 mL) was added. The reaction was stirred further 20 minutes, diluted with ether (250 mL) and washed with brine (2x50 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 5:1) to yield lactame **34** (17.4 g, 66.5 mmol, 67%) as colorless oil.

R_f 0.25 (PET/AcOEt 5:1, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (m, 2H; ArH), 7.39-7.28 (m, 3H; ArH), 5.27 (s, 2H; OCH_2), 3.81 (m, 1H; NCH_2), 3.69 (m, 1H; NCH_2), 2.35 (m, 1H; CHCO), 2.07-1.73 (m, 4H; CH_2CH_2), 1.58-1.46 (m, 2H; CH_2CH_3), 0.96 (t, J = 7.5 Hz, 3H; CH_3).

Following a reported procedure,[15] sodium borohydride (829 mg, 21.9 mmol, 1.05 equiv) was added portionswise into a solution of lactame **34** (5.45 g, 20.9 mmol, 1.00 equiv) in methanol (100 mL) at 0 °C. After the end of the addition, the reaction mixture was stirred at 0 °C for 15 min and poured onto ice-water (150 mL). The reaction mixture was extracted with AcOEt (3x100 mL). The combined organic layers were washed with brine (50 mL), the combined water layers were extracted with AcOEt (100 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (50 mL) and 0.5 mL of concentrated sulfuric acid was added dropwise. The reaction was stirred at RT for 1 hour then quenched with K_2CO_3 and dried on Na_2SO_4.The suspension was filtered and concentrated to afford **35** (4.75 g, 19.4 mmol, 93% overall) without further purification as a colorless oil.

R_f 0.36 (PET/AcOEt 9:1, Anisaldehyde).

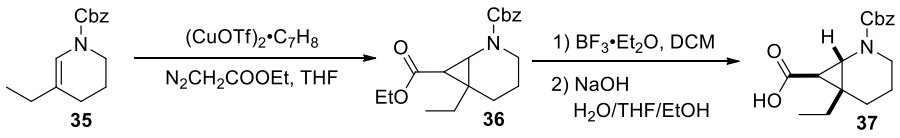
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.28 (m, 5H; ArH), 6.70 (s, 0.45H; alkeneH rotamer A), 6.60 (s, 0.55H; alkeneH rotamer B), 5.19 (s, 1.1H; OCH_2 rotamer B), 5.17 (s, 0.9H; OCH_2 rotamer A), 3.57 (m, 2H; NCH_2), 2.07-1.94 (m, 4H; allylic CH_2), 1.82 (m, 2H; CH_2CH_2), 1.06-0.97 (m, 3H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 153.4, 153.0, 136.5, 136.4, 128.3, 127.9, 127.8, 121.0, 120.6, 119.1, 118.7, 67.1, 67.0, 41.9, 41.8, 28.1, 28.1, 24.8, 24.7, 21.6, 21.6, 12.6, 12.4.

IR ν (cm-1): 2962 (w), 2934 (w), 2880 (w), 1703 (s), 1499 (w), 1409 (s), 1345 (m), 1313 (m), 1258 (s), 1202 (m), 1176 (m), 1111 (m), 1041 (m), 988 (m), 914 (m), 882 (m), 761 (m), 738 (m), 698 (m), 635 (m), 607 (m).

HRMS(ESI) calcd for $C_{15}H_{20}NO_2^+$ (M+H) 246.1494, found 246.1496.

1-Benzyloxycarbonyl-5-ethyl-1-azabicyclo[4.1.0]heptan-7-carboxylic acid ethyl ester (36) 1-Benzyloxycarbonyl-5-ethyl-1-azabicyclo[4.1.0]heptan-7-carboxylic acid (37)



Following a slight modification of a reported procedure,[18] a solution of ethyl diazoacetate (6.2 mL, 59 mmol, 4.0 equiv) in DCM (15 mL) was added to a solution of enamine **35** (3.64 g, 14.9 mmol, 1.00 equiv) and copper triflate (I) toluene complex (192 mg, 0.370 mmol, 0.0200 equiv) in DCM (15mL) over 18 h (1.3 mL/h) via syringe pump. After the addition was complete, the reaction was concentrated and purified by flash column chromatography (PET/AcOEt 15:1 until PET/AcOEt 9:1) to yield **36** (3.74 g, 11.3 mmol, 76%) as colorless oil. Following a reported procedure,[5] the mixture of exo and endo esters (1.50 g, 4.53 mmol, 1.00 equiv) in dichlorometane (20 mL) at -20°C was treated with BF_3•Et_2O (96 mg, 0.68 mmol, 0.15 equiv). The reaction was allowed to warm at 0°C and stirred at the same temperature until the isomerization was finished (from R_f 0.28-0.32 PET/AcOEt 9:1 to R_f 0.30 PET/AcOEt 9:1, Anisaldehyde). Triethylamine (1 mL) was added dropwise to the reaction and the mixture was diluted with Et_2O (50 mL) and washed with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give a pale yellow oil (1.50 g) which was used directly in the next step.

The crude oil (1.50 g, 4.53 mmol, 1.00 equiv) was dissolved in a solution of water/THF/EtOH 1/1/3 (25 mL total) at 0°C and NaOH (1.63 g, 40.3 mmol, 9.00 equiv) was added portionswise. The reaction was heated to 60°C and stirred during 2 hours. The solution was concentrated, then diluted with water (30 mL) and washed with Et_2O (3x20 mL). The aqueous layer was acidified with HCl (1 M aqueous solution) until pH 2 and extracted with DCM (3x20 mL) to give **37** as a colorless oil which turns solid upon storage (1.25 g, 4.12 mmol, 91% overall). No further purification was needed.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.21 (m, 5H; ArH), 5.23-5.09 (m, 2H; OCH_2), 3.86 (dt, *J* = 12.5 Hz, 3.1 Hz, 0.7H; NCH_2 rotamer A), 3.73 (m, 0.3H; NCH_2 rotamer B), 3.55 (d, *J* = 3.5 Hz, 0.3H; NCH rotamer B), 3.49 (d, *J* = 3.6 Hz, 0.7H; NCH rotamer A), 2.77 (dt, *J* = 12.5 Hz, 1.7 Hz, 0.3H; NCH_2 rotamer B), 2.66 (dt, *J* = 12.5 Hz, 3.4 Hz, 0.7H; NCH_2 rotamer A), 2.05 (m, 1H; CHCO), 1.93-1.12 (m, 6H; CH_2), 0.99 (t, *J* = 7.2 Hz, 1H; CH_3 rotamer B), 0.93 (t, *J* = 7.4 Hz, 2H; CH_3 rotamer A).

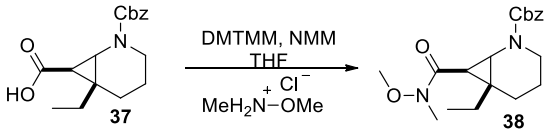
^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 177.2, 176.9, 156.2, 136.5, 128.5, 128.4, 128.1, 127.7, 127.2, 67.1, 67.0, 44.9, 44.8, 41.5, 41.1, 34.7, 34.0, 31.1, 30.6, 25.9, 25.7, 21.5, 21.3, 20.9, 10.3, 9.9.

[18] R. Beumer, C. Bubert, C. Cabrele, O. Vielhauer, M. Pietzsch, O. Reiser, *J. Org. Chem.* **2000,** *65*, 8960.

IR ν (cm-1): 2956 (w), 2939 (w), 2864 (w), 1704 (s), 1584 (w), 1456 (s), 1423 (s), 1348 (m), 1270 (m), 1240 (m), 1214 (s), 1129 (m), 1036 (m), 1017 (w), 948 (w), 909 (m), 883 (m), 752 (m), 736 (s), 698 (m), 676 (m), 668 (m), 635 (m).

HRMS(ESI) calcd for $C_{17}H_{22}NO_4^+$ (M+H) 304.1549, found 304.1548.

_N_-Methoxy-_N_-methylcarbamo-6-yl-5-ethyl-1-azabicyclo[4.1.0]heptanes-1-benzylcarboxylate (38)



Dimethoxytriazin-*N*-methylmorpholinium chloride[19] (DMTMM, 900 mg, 3.24 mmol, 1.50 equiv) was suspended into a solution of acid **37** (655 mg, 2.16 mmol, 1.00 equiv) in THF (7.5 mL) and the reaction mixture was stirred at RT during 60 min. *N,O*-dimethylhydroxylamine hydrochloride (97.5 mg, 2.16 mmol, 1.00 equiv) was added, followed by *N*-methylmorpholine (475 µL, 4.32 mmol, 2.00 equiv) and the reaction mixture was stirred during 36 hours. The reaction was quenched with a 5% aqueous solution of citric acid and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography (AcOEt/PET 3:7) to afford **38** (695 mg, 2.00 mmol, 93%) as colorless oil.

R_f 0.30 (PET/AcOEt 7:3, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.19 (m, 5H; ArH), 5.23 (d, *J* = 12.9 Hz, 0.8H; OCH_2 rotamer A), 5.14 (d, *J* = 12.5 Hz, 0.2H; OCH_2 rotamer B), 5.07 (d, *J* = 13.0 Hz, 1H; OCH_2), 3.84 (dt, *J* = 12.5 Hz, 3.4 Hz, 0.8H; NCH_2 rotamer A), 3.71 (m, 0.2H; NCH_2, rotamer B), 3.64 (s, 0.6H; OCH_3 rotamer B), 3.58-3.52 (m, 2.4H; OCH_3 rotamer A and NCH rotamer B), 3.49 (d, *J* = 3.7 Hz, 0.8H; NCH rotamer A), 3.15 (s, 0.6H; NCH_3 rotamer B), 3.12 (s, 2.4H; NCH_3 rotamer A), 2.73 (t, *J* = 11.7 Hz, 0.2H; NCH_2 rotamer B), 2.64 (dt, *J* = 12.5 Hz, 2.2 Hz, 0.8H; NCH_2 rotamer A), 2.09-1.87 (m, 2H; CHCO and CH_2), 1.77-1.54 (m, 4H; CH_2), 1.36 (m, 1H; CH_2), 0.85 (t, *J* = 7.4 Hz, 3H; CH_3).

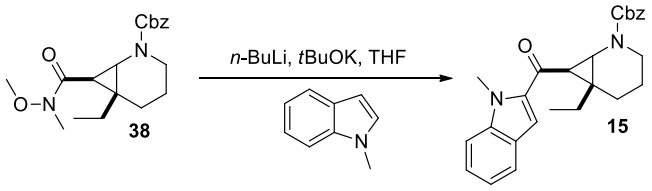
[19] M. Kunishima, C. Kawachi, F. Iwasaki, K. Terao, S. Tani, *Tetrahedron Letters* **1999**, *40*, 5327.

^{13}C NMR ($CDCl_3$, 100 MHz) δ (rotamers!) 171.2, 156.2, 136.8, 128.2, 128.1, 127.8, 127.8, 127.4, 127.0, 66.8, 66.5, 61.2, 42.9, 42.7, 41.5, 41.0, 33.0, 32.4, 29.1, 28.5, 26.0, 25.9, 25.2, 21.6, 10.3.

IR ν (cm-1): 2964 (w), 2937 (w), 2876 (w), 1703 (s), 1651 (s), 1458 (m), 1417 (s), 1384 (m), 1358 (m), 1344 (m) (m), 1295 (m), 1266 (m), 1209 (m), 1180 (m), 1123 (m), 1016 (m), 913 (m), 769 (w), 734 (s), 700 (w).

HRMS(ESI) calcd for $C_{19}H_{27}N_2O_4^+$ (M+H) 347.1971, found 347.1978.

6-(1-Methyl-*1H*-indol-2-carbonyl)-5-ethyl-1-azabicyclo[4.1.0]heptane-1-benzylcarboxylate (15)



A solution of *N*-methylindole (13 μL, 0.10 mmol, 1.3 equiv) in THF (0.5 mL) was stirred at 0° C. Then a solution of *n*BuLi (2.5 M in pentane, 38 μL, 0.10 mmol, 1.2 equiv) diluted in THF (0.2 mL) was added dropwise. The solution was warmed to RT, stirred for 1 hour and then cooled to -78° C. From a separate flask, a solution of Weinreb amide **38** (27 mg, 0.080 mmol, 1.0 equiv) in THF (0.4 mL) was added via cannula into the solution. The mixture was stirred 2 hours at -78° C, then a solution of *t*BuOK in THF (0.3 mL) was added dropwise. The reaction was stirred 2 hours at -78° C and 5 min at 0° C, quenched with $NaHCO_3$ and extracted with Et_2O (5x3 mL). The organic layers were dried over Na_2SO_4, evaporated on reduced pressure and purified on flash chromatography (AcOEt/PET 1:5) to give **15** (16 mg, 0.038 mmol 48%) as a yellow oil.

R_f 0.60 (PET/AcOEt 7:3, Anisaldehyde).

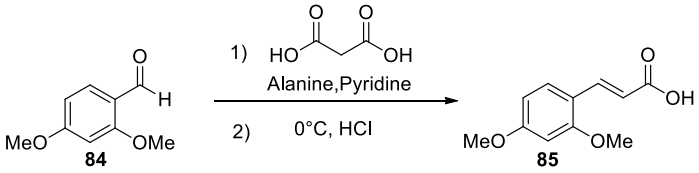
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, *J* = 8.1 Hz, 1H; ArH), 7.45-7.29 (m, 4H; ArH), 7.25-7.00 (m, 5H; ArH), 5.19 (d, *J* = 12.7 Hz, 1H; OCH_2), 5.04 (d, *J* = 12.7 Hz, 1H; OCH_2), 4.08 (s, 0.6H; CH_3 rotamer B), 3.97 (s, 2.4H; CH_3 rotamer A), 3.95 (dt, *J* = 13.2 Hz, 3.4 Hz, 0.8H; NCH_2, rotamer A), 3.88-3.82 (m, 0.2H; NCH_2 rotamer B), 3.77 (d, *J* = 3.4 Hz, 1H; NCH), 2.83 (t, *J* = 11.9 Hz, 0.2H; NCH_2, rotamer B), 2.74 (dt, *J* = 12.0 Hz, 1.9 Hz, 0.8H; NCH_2, rotamer A), 2.68 (d, *J* = 3.1 Hz, 0.2H; COCH; rotamer B), 2.65 (d, *J* = 3.6 Hz, 0.8H; COCH; rotamer A), 2.18 (m, 1H; CH_2), 1.90-1.48 (m, 5H; CH_2), 0.85 (t, *J* = 7.4 Hz, 3H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 190.8, 157.3, 140.9, 137.6, 137.5, 129.4, 129.1, 128.5, 128.2, 126.9, 126.6, 126.3, 123.7, 121.7, 111.7, 111.3, 67.9, 46.2, 45.9, 42.3, 42.6, 39.2, 38.8, 38.4, 33.0, 27.3, 27.0, 26.0, 23.0, 22.8 11.7, 11.5.

IR ν (cm-1): 3064 (w), 3033 (w), 2938 (w), 2876 (w), 1703 (s), 1646 (s), 1614 (w), 1512 (m), 1464 (s), 1428 (s), 1408 (s), 1348 (s), 1268 (m), 1211 (s), 1196 (s), 1163 (m), 1129 (m), 1049 (m), 1027 (m), 910 (m), 769 (m), 737 (s), 698 (m).

HRMS(ESI) calcd for $C_{26}H_{29}N_2O_3^+$ (M+H) 417.2178, found 417.2181.

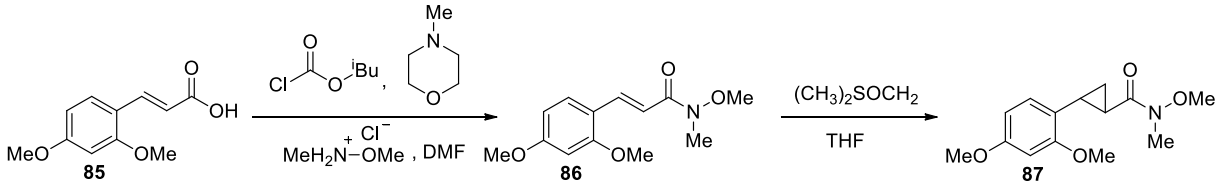
(*E*)-2,4-Dimetoxy-*cis*-cinnamic acid (85)



Following a reported procedure,[20] a solution of aldehyde **84** (11.0 g, 66.7 mmol, 1.00 equiv), malonic acid (17.5 g, 168 mmol, 2.50 equiv) and β-alanine (1.0 g, 89 mmol, 0.20 equiv) in pyridine (3 mL) was stirred under reflux for 90 min. After cooling to RT, the flask was transferred in an ice bath and a concentrated solution of HCl (8 mL) was added dropwise. The precipitate was filtered, washed with cold water (2x10 mL) and dried without further purification to give **85** as light yellow solid (12.5 g, 60.0 mmol, 90%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.11 (s, 1H; OH), 7.75 (d, *J* = 16.1 Hz, 1H; alkeneH), 7.61 (d, *J* = 8.6 Hz, 1H; ArH), 6.64 – 6.54 (m, 2H; ArH), 6.37 (d, *J* = 16.1 Hz, 1H; CHCO), 3.86 (s, 3H; OCH_3), 3.81 (s, 3H; OCH_3). ^{1}H NMR spectra corresponded to the literature values.[21]

(*E*)-*N*-Methoxy-*N*-methyl-3-(2,4-dimethoxyphenyl)-acrylamide (86) and *N*-methoxy-*N*-methyl-1-[2-(2,4-dimethoxyphenyl)-cyclopropan-1-yl]-formamide (87)



[20] Stabile, R. G.; Dicks, A. R. *J. Chem. Educ.* **2004**, *81*, 1488.
[21] Luadthong, C.; Tachaprutinun, A.; Wanichwecharungruang, S. P. *Eur. Polym. J.* **2008**, *44*, 1285.

Following the reported procedure[22] *N*-methylmorpholine (7.23 mL, 65.9 mmol, 1.10 equiv) was added to a solution of acid **85** (12.47 g, 59.89 mmol, 1.000 equiv) in DMF (60 mL) at 0 °C. After 25 min, *iso*-butylchloroformate (8.59 mL, 65.9 mmol 1.10 equiv) was added dropwise at 0 °C. After 10 min, *N,O*-dimethylhydroxylamine hydrochloride (6.43 g, 65.9 mmol 1.10 equiv) was added, followed by *N*-methylmorpholine (8.53 mL, 77.8 mmol, 1.3 equiv) and the reaction mixture was warmed to 23°C. After 6 h, the reaction was quenched with 0.5 M HCl (102 mL) and extracted with CH_2Cl_2 (3x120 mL). The combined organic layers were washed with 0.5 M NaOH (2x120 mL), brine (2x120 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. After 30 min in high vacuum, the residues were dissolved in Et_2O (360 mL) and washed with brine (2x120 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the Weinreb amide **86** which was used directly without purification.

A solution of ylide[23] (53.4 mL, 28.8 mmol, 1.20 eq) in anhydrous THF was added dropwise to a solution of the amide **86** (6.00 g, 23.9 mmol, 1.00 equiv) in THF (240 mL) at RT under nitrogen. The reaction was stirred at RT overnight then quenched with $NaHCO_3$ (240 mL) and extracted with Et_2O (3x240 mL). The combined organic layers were washed with brine (2x240 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash column chromatography (PET/AcOEt, 3:2) gave **87** (3.93 g, 14.8 mmol, 62%) over 2 steps as white solid.

R_f 0.35 (PET/AcOEt 3:2, Anisaldehyde).

Mp 58 -59 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.88 (d, J = 8.3 Hz, 1H; ArH), 6.46 – 6.37 (m, 2H; ArH), 3.80 (s, 3H; OCH_3), 3.79 (s, 3H; OCH_3), 3.70 (s, 3H; OCH_3), 3.24 (s, 3H; NCH_3), 2.64 – 2.51 (m, 1H; CH-CH_2), 2.25 (m, 1H; $CHCH_2$), 1.57 – 1.49 (m, 1H; CH_2CH), 1.30 – 1.20 (m, 1H; CH_2CH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.6, 159.4, 159.2, 126.6, 121.2, 103.7, 98.3, 61.3, 55.2, 55.2, 32.5, 20.7, 19.8, 14.3.

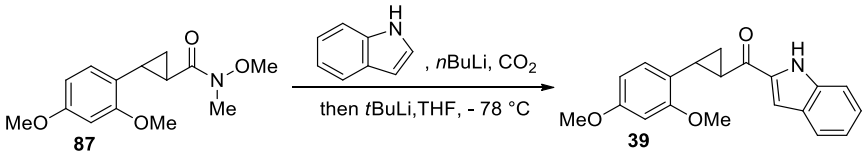
[22] Nagarajan, S. R.; Lu, H. F.; Gasiecki, A. F.; Khanna, I. K.; Parikh, M. D.; Desai, B. N.; Rogers, T. E.; Clare, M.; Chen, B. B.; Russell, M. A.; Keene, J. L.; Duffin, T.; Engleman, V. W.; Finn, M. B.; Freeman, S. K.; Klover, J. A.; Nickols, G. A.; Nickols, M. A.; Shannon, K. E.; Steininger, C. A.; Westlin, W. F.; Westlin, M. M.; Williams, M. L. *Bioorg. Med. Chem.* **2007**, *15*, 3390.

[23] *n*BuLi (2.5 M, 1.0 equiv) was added dropwise to a solution of trimethylsufoxonium iodide (1.1 equiv) in anhydrous THF (0.75 M) at 0°C. The solution was allowed to warm to RT and stirring was continued under nitrogen for 1 hour. A solution 0.54 M of ylide was obtained.

IR ν (cm-1): 3002 (w), 2960 (w), 2938 (w), 2837 (w), 1650 (s), 1614 (m), 1585 (m), 1510 (s), 1461 (s), 1438 (s), 1417 (s), 1394 (m), 1364 (m), 1321 (w), 1289 (s), 1263 (m), 1208 (s), 1176 (s), 1159 (s), 1155 (s), 1127 (s), 1096 (m), 1033 (s), 933 (m), 920 (m), 874 (w), 834 (s), 800 (w), 775 (w), 729 (w).

HRMS(ESI) calcd for $C_{14}H_{20}NO_4^+$ (M+H) 266.1387, found 266.1381.

2-[2-(4-Methoxyphenyl)-1-cyclopropanecarbonyl]-indole (39)



Following a slight modification of a reported procedure[24] indole (66 mg, 0.59 mmol, 1.6 equiv) was diluted in THF (1.5 mL) at -70 °C and *n*BuLi (0.24 mL, 1.59 mmol, 1.6 equiv) was added dropwise. The reaction mixture was stirred at the same temperature for 30 min then CO_2 was bubbled in during 20 min. The solution was left to warm up to rt and the CO_2 was removed in vacuo with a part of solvent. After the addition of freshly distilled THF (0.4 mL) the reaction was cooled down to -78°C. *t*BuLi (1.6 M in pentane, 0.37 mL, 1.59 mmol, 1.6 equiv) was added dropwise during 10 min and the reaction was stirred 2 h at -78°C. Weinreb amide **87** (dried through 3 co-evaporation with toluene, 0.10 g, 0.38 mmol, 1.0 equiv) was added dropwise via cannula as a cooled (-78 °C) solution in THF (0.4 mL). After further stirring 1.5 h at -78 °C, the reaction mixture was transferred via cannula into a saturated aqueous solution of NH_4Cl (20 mL) at 0°C and stirred for 20 minutes before extraction with Et_2O (3x20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 9:1) to yield indole **39** (60 mg, 0.19 mmol, 51%) as a white solid.

R_f 0.25 (PET/AcOEt 9:1, Anisaldehyde).

Mp 177-179 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.78 (s, 1H; NH), 7.71 (dd, *J* = 8.1, 0.9 Hz, 1H; ArH), 7.49 (dd, *J* = 8.4, 0.9 Hz, 1H; ArH), 7.35 (m, 1H; ArH), 7.30 (dd, *J* = 2.1, 0.9 Hz, 1H; ArH), 7.15 (m, 1H; ArH), 7.00 (m, 1H; ArH), 6.47 (m, 2H; ArH), 3.82 (s, 3H; OMe), 3.75 (s, 3H; OMe), 2.89 (ddd,

[24] Katritzky, A. R.; Akutagawa, K., *Tetrahedron Lett.* **1985,** *26*, 5935.

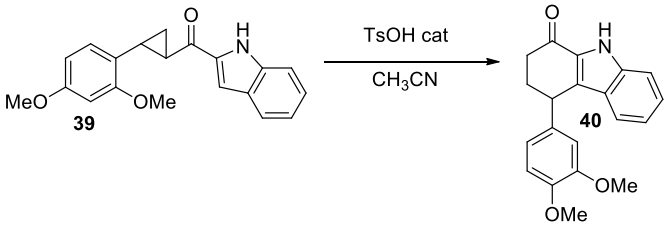
J = 9.0, 7.1, 4.1 Hz, 1H; $CHCH_2$), 2.75 (m, 1H; $CHCH_2$), 1.91 (m, 1H; CH_2CH), 1.59 (m, 1H; CH_2CH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.6, 159.7, 159.5, 137.4, 136.0, 127.7, 127.0, 126.0, 122.9, 121.1, 120.7, 112.3, 109.2, 103.8, 98.4, 55.4, 55.4, 28.1, 24.9, 17.2.

IR ν (cm-1): 3290 (m), 2957 (w), 2923 (w), 2853 (w), 1636 (s), 1617 (m), 1583 (w), 1520 (m), 1509 (m), 1465 (w), 1455 (w), 1437 (w), 1416 (w), 1402 (m), 1346 (w), 1330 (w), 1317 (w), 1289 (w), 1261 (m), 1231 (w), 1208 (s), 1182 (s), 1169 (m), 1160 (s), 1141 (m), 1120 (s), 1068 (m), 1048 (m), 1027 (m), 951 (w), 922 (w), 844 (m), 818 (w), 797 (m), 796 (m), 753 (m), 737 (s), 702 (m), 687 (m), 626 (m).

HRMS(ESI) calcd for $C_{20}H_{20}NO_3^+$ (M+H) 322.1443, found 322.1444.

4-(3,4-Dimethoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (40)



The reaction was performed following **GP4**, starting from cyclopropane **39** (45 mg, 0.14 mmol, 1.0 equiv) and tosic acid (5.4 mg, 30 μmol, 0.2 equiv). The reaction was quenched after 20 min to give **40** (45 mg, 0.14 mmol, quantitative) as yellow solid without further purification.

R_f 0.30 (PET/AcOEt 7:3, Anisaldehyde).

Mp 183-185 °C.

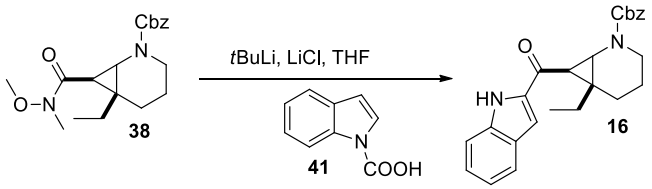
^1H NMR ($CDCl_3$, 400 MHz) δ 8.81 (s, 1H; NH), 7.41 (m, 1H; ArH), 7.31 (m, 1H; ArH), 7.11 (dd, *J* = 8.1, 0.7 Hz, 1H; ArH), 6.96 (m, 1H; ArH), 6.71 (d, *J* = 8.4 Hz, 1H; ArH), 6.56 (d, *J* = 2.4 Hz, 1H; ArH), 6.31 (dd, *J* = 8.4, 2.4 Hz, 1H; ArH), 4.87 (dd, *J* = 6.5, 5.1 Hz, 1H; $CHCH_2$), 3.89 (s, 3H; OMe), 3.78 (s, 3H; OMe), 2.44-2.73 (m, 3H; CH_2), 2.32 (m, 1H; CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.9, 159.6, 157.9, 138.1, 132.0, 131.1, 129.4, 126.8, 125.6, 122.9, 122.3, 120.2, 112.4, 103.8, 98.6, 55.5, 55.3, 36.2, 32.4, 32.1.

IR ν (cm-1): 3287 (w), 3280 (w), 3279 (w), 3274 (w), 2956 (w), 2927 (w), 1650 (s), 1617 (m), 1616 (m), 1588 (w), 1537 (w), 1536 (w), 1505 (m), 1469 (m), 1440 (w), 1418 (w), 1334 (w), 1292 (m), 1257 (w), 1209 (m), 1167 (w), 1158 (w), 1116 (w), 1040 (w), 1040 (w), 912 (m), 834 (w), 826 (w), 735 (s).

HRMS(ESI) calcd for $C_{20}H_{20}NO_3^+$ (M+H) 322.1443, found 322.1440.

6-(*1H*-indol-2-carbonyl)-5-ethyl-1-azabicyclo[4.1.0]heptane-1-benzylcarboxylate (16)



^{t}BuLi (1.6 M in pentane, 38 µL, 0.80 mmol, 2.2 equiv) was added dropwise into a solution of carboxylindole **41** prepared following **GP5** (64 mg, 0.40 mmol, 1.1 equiv) and LiCl[25] (17 mg, 0.40 mmol, 1.1 equiv) in THF (1 mL) at -78° C. The solution was stirred for 3 hours and then transferred via cannula into a solution of amide **38** (125 mg, 360 µmol, 1.00 equiv) in THF (1 mL) at -78°C. The reaction was allowed to warm to -20°C over 5 hours then transferred via cannula into saturated aqueous $NaHCO_3$ solution (10 mL) at 0°C. The aqueous phase was extracted with Et_2O (5x10 mL). The organic layers were dried over Na_2SO_4, evaporated under reduced pressure and purified on flash chromatography with deactivated silica (AcOEt/PET 1:9) to give **16** (97 mg, 24 mmol, 67%) as yellow oil.

R_f 0.70 (PET/AcOEt 7:3, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.39 (d, *J* = 0.4 Hz, 0.2H; NH rotamer B), 9.29 (m, 0.8H; NH rotamer A), 7.72 (d, *J* = 8.0 Hz, 1H; ArH), 7.45 (m, 1H; ArH), 7.36 (m, 2H; ArH), 7.16 (m, 4H; ArH), 7.02 (m, 2H; ArH), 5.21-5.08 (m, 0.4H; OCH_2 rotamer B), 5.15 (d, *J* = 12.7 Hz, 0.8H; OCH_2 rotamer A) 5.02 (d, *J* = 12.7 Hz, 0.8H; OCH_2 rotamer A), 3.93 (m, 1H; NCH_2), 3.81 (d, *J* = 3.3 Hz, 1H; NCH), 2.84 (t, *J* = 12.2 Hz, 0.2H; NCH_2 rotamer B), 2.75 (t, *J* = 12.1 Hz, 0.8H; NCH_2 rotamer A), 2.61 (d, *J* = 3.3 Hz, 1H; COCH), 2.15 (m, 1H; CH_2), 1.77 (m, 4H; CH_2), 1.54 (m, 1H; CH_2), 0.91 (m, 0.6H; CH_3 rotamer B), 0.82 (t, *J* = 7.3 Hz, 2.4H; CH_3 rotamer A).

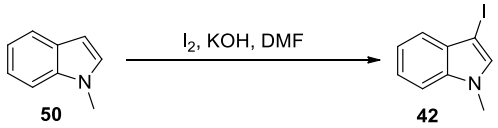
[25] LiCl was dried under HV (< 0.05 Torr), warmed at 600° C (Mp) and stirred. It was then cooled down to RT and dissolved into 1mL of dry THF.

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 188.6, 156.3, 137.1, 136.6, 136.5, 128.5, 128.1, 128.1, 127.7, 127.5, 127.3, 126.1, 122.9, 122.7, 120.9, 120.7, 112.1, 108.6, 108.4, 66.9, 46.0, 45.6, 41.7, 41.3, 38.3, 36.7, 36.0, 26.3, 26.1, 25.0, 21.9, 21.8, 10.7, 10.6.

IR ν (cm-1): 3309 (w), 2960 (w), 2936 (w), 2876 (w), 1700 (s), 1629 (s), 1521 (m), 1446 (m), 1409 (s), 1349 (s), 1313 (w), 1299 (w), 1268 (m), 1232 (w), 1210 (m), 1192 (m), 1164 (m), 1140 (s), 1080 (w), 1034 (w), 1010 (w), 978 (w), 911 (m), 799 (w), 746 (s), 736 (s), 698 (m), 606 (w).

HRMS(ESI) calcd for $C_{25}H_{27}N_2O_3^+$ (M+H) 403.2022, found 403.2034.

3-Iodo-1-methyl-*1H*-indole (42)



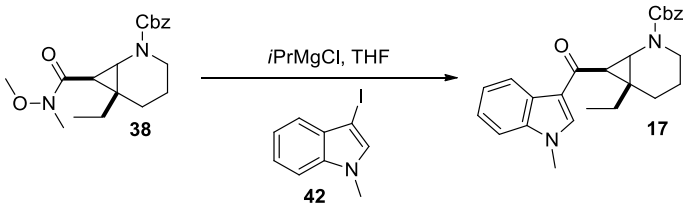
Following a reported procedure,[26] I_2 (3.86 g, 15.2 mmol, 2.00 equiv) was added in one pot to a solution of *N*-methylindole **50** (980 µL, 7.60 mmol, 1.00 equiv) and KOH (1.60 g, 28.5 mmol, 3.75 equiv) in DMF (20 mL) at rt. The reaction was stirred at the same temperature for 10 minutes then poured into a suspension of ice and water (400 mL) containing ammonia (0.5%) and sodium metabisulphite (0.1%). The emulsion was then extracted with a solution of hexane/ethyl acetate 1:1 (5x100 mL). The organic phase was washed with cold water, dried over Na_2SO_4 and evaporated under reduced pressure to afford iodoindole **42** (1.9 g, 74 mmol, 97%). without further purification.

^1H NMR (DMSO-d_6, 400 MHz) δ 7.49 (m, 1H; ArH), 7.44 (d, *J* = 8.2 Hz, 1H; ArH), 7.23 (m, 2H; ArH), 7.13 (m, 1H; ArH), 3.77 (m, 3H; CH_3).

^1H NMR spectra corresponded to the literature values.[26]

6-(1-Methyl-*1H*-indol-3-carbonyl)-5-ethyl-1-azabicyclo[4.1.0]heptane-1-benzylcarboxylate (17)

[26] Bocchi, V.; Palla, G., *Synthesis* **1982,** 1096.



Following a slight modification of a reported procedure, [27] *i*PrMgBr was added dropwise into a solution of iodoindole **42** (165 mg, 64.0 mmol, 3.00 equiv) in THF (2.5 mL) at -20°C. The reaction was stirred 30 min at -20°C then transferred via cannula into a solution of Weinreb amide **38** (74 mg, 0.21 mmol, 1.0 equiv) in THF (2.5 mL) at 0°C. After 1 h at 0 °C, the reaction was transferred via cannula into a saturated aqueous solution of $NaHCO_3$ (10 mL) at 0°C and stirred for 10 minutes before extraction with Et_2O (3x10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 8:2) to yield indole **17** (44 mg, 0.17 mmol, 51%) as a yellow oil.

R_f 0.20 (PET/AcOEt 8:2, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (m, 1H; ArH), 7.63 (s, 1H; ArH), 7.39-7.28 (m, 4H; ArH), 7.20 (m, 2H; ArH), 7.09-6.98 (m, 2H; ArH), 5.17 (d, *J* = 12.8 Hz, 1H; OCH_2), 5.03 (d, *J* = 12.9 Hz, 1H; OCH_2), 3.92 (m, 1H; NCH_2), 3.84 (s, 3H; NCH_3), 3.80 (d, *J* = 3.5 Hz, 1H; NCH), 2.83 (t, *J* = 12.0, 0.1H; NCH_2 rotamer B), 2.74 (t, *J* = 12.4, 0.9H; NCH_2 rotamer A), 2.42 (d, *J* = 3.3 Hz, 0.1H; COCH rotamer B), 2.39 (d, *J* = 3.5 Hz, 0.9H; COCH rotamer A), 2.13 (m, 1H; CH_2), 1.90-1.47 (m, 5H; CH_2), 0.83 (t, *J* = 7.3 Hz, 3H; CH_3).

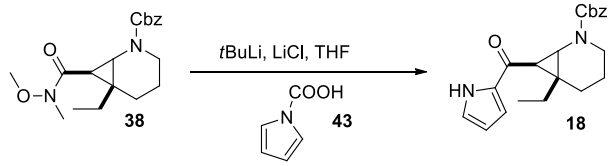
^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 191.0, 156.5, 137.4, 136.7, 134.8, 134.6, 128.4, 128.1, 127.3, 127.1, 126.2, 123.3, 123.0, 122.5, 122.4, 122.2, 118.4, 109.5, 67.0, 66.7, 44.1, 43.9, 41.8, 41.3, 37.5, 37.0, 36.2, 35.1, 33.4, 26.5, 26.2, 25.2, 25.1, 22.1, 10.8.

IR ν (cm-1): 2938 (w), 2873 (w), 1701 (s), 1629 (m), 1531 (s), 1465 (s), 1410 (s), 1374 (m), 1358 (m), 1348 (m), 1297 (w), 1268 (w), 1215 (m), 1193 (w), 1180 (w), 1144 (w), 1127 (m), 1104 (w), 1089 (s), 1052 (w), 1012 (w), 998 (w), 914 (w), 770 (w), 745 (s), 737 (s).

HRMS(ESI) calcd for $C_{26}H_{29}N_2O_3^+$ (M+H) 417.2178, found 417.2181.

[27] Sapountzis, I.; Lin, W. W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P., *Angew. Chem, Int. Ed.* **2005**, *44*, 1654.

Benzyl 6-ethyl-7-(1H-pyrrole-2-carbonyl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (18)



*t*BuLi (0.94 mL, 1.5 mmol, 2.2 equiv) was added dropwise into a solution of *N*-carboxypyrrole **43** prepared following **GP6** (84 mg, 0.75 mmol, 1.1 equiv) and LiCl (32 mg, 0.75 mmol, 1.1 equiv) in THF (3 mL) at -78°C. The reaction mixture was stirred 3 h at -78 °C then added dropwise via cannula into a solution of Weinreb amide **38** (0.24 g, 0.68 mmol, 1.0 equiv) in THF (3 mL) at 0 °C during 20 minutes. The reaction mixture was left to warm up to -20 °C and stirred for additional 20 minutes. After that, the reaction was transferred via cannula into a saturated aqueous solution of $NaHCO_3$ (15 mL) at 0°C and stirred for 20 minutes and extracted with Et_2O (3x10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/PET 2:8 on deactivated silica) to yield pyrrole **18** (58 mg, 0.16 mmol, 24%) as a yellowish oil.

R_f 0.4 (PET/AcOEt 7:3, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.77 (s, 0.3H; NH), 9.56 (s, 0.7H; NH), 7.34 (m, 1.5H; ArH rotamer B), 7.23-7.07 (m, 3.5H; ArH rotamer A), 7.01 (m, 0.7H; pyrroleH rotamer A), 6.97 (m, 0.3H; pyrroleH rotamer B), 6.87 (m, 1H; pyrroleH), 6.29 (m, 0.7H; pyrroleH rotamer A), 6.25 (s, 0.3H; CH-pyrrole rotamer B), 5.17 (d, J = 12.8 Hz, 0.7H; OCH_2 rotamer A), 5.09 (d, J = 12.5 Hz, 0.3H; OCH_2 rotamer B), 5.04 (d, J = 12.8 Hz, 0.7H; OCH_2 rotamer A), 4.98 (d, J = 12.5 Hz, 0.3H; OCH_2 rotamer B), 3.91 (m, 1H; NCH_2), 3.78 (d, J = 3.8 Hz, 0.3H; NCH rotamer B), 3.72 (d, J = 3.6 Hz, 0.8H; NCH rotamer A), 2.80 (m, 0.3H; NCH_2 rotamer B), 2.71 (m, 0.7H; NCH_2 rotamer A), 2.40 (d, J = 3.6 Hz, 1H; COCH), 2.09 (m, 1H; CH_2), 1.86-1.62 (m, 4H; CH_2), 1.50 (m, 1H; CH_2), 0.82 (t, J = 7.4 Hz, 3H; CH_2).

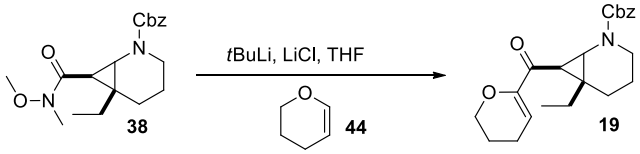
^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 186.3, 156.3, 136.7, 133.4, 128.4, 128.2, 128.1, 128.0, 127.5, 127.1, 123.8, 123.7, 115.4, 115.3, 110.6, 110.4, 67.2, 66.8, 45.1, 44.7, 41.7, 41.2, 37.0, 36.0, 35.4, 26.3, 26.0, 25.2, 25.0, 21.9, 21.8, 19.4, 10.7, 10.6.

IR ν (cm-1): 3276 (w), 3266 (w), 3242 (w), 2962 (w), 2956 (w), 2949 (w), 2936 (w), 2876 (w), 1704 (s), 1619 (m), 1544 (w), 1498 (w), 1457 (m), 1428 (s), 1414 (s), 1351 (m), 1323 (m), 1294

(m), 1267 (m), 1209 (m), 1194 (w), 1193 (w), 1181 (w), 1115 (s), 1061 (m), 1040 (w), 1039 (w), 1029 (w), 1011 (w), 974 (w), 939 (w), 911 (w), 902 (w), 901 (w), 885 (w), 848 (w), 833 (w), 781 (m), 767 (m), 746 (m), 699 (m), 647 (w).

HRMS(ESI) calcd for $C_{21}H_{25}N_2O_3^+$ (M+H) 353.1865, found 353.1861.

Benzyl 7-(3,4-dihydro-2H-pyran-6-carbonyl)-6-ethyl-2 –azabicyclo[4.1.0] heptane -2-carboxylate (19)



A solution of dihydropyran **44** (33 µL, 0.37 mmol, 1.3 equiv) and LiCl (30 mg, 0.58 mmol, 2.0 equiv) in THF (1.5 mL) was stirred at -78° C. Then a solution of *t*BuLi (1.6 M in hexane, 0.22 mL, 0.35 mmol, 1.2 equiv) was added dropwise. The solution was warmed to 0°C and stirred for 40 minutes before cooling down again at -78°C. The lithiated dihydropyran was then added via cannula into the solution of Weinreb amide **38** (0.10 g, 0.29 mmol, 1.0 equiv) in THF (1.5 mL) at 0°C during 20 minutes. The mixture was stirred for additional 20 minutes, transferred via cannula into a saturated aqueous solution of $NaHCO_3$ (5 mL) at 0°C and extracted with Et_2O (5x3 mL). The organic layers were dried over Na_2SO_4, evaporated on reduced pressure and purified on flash chromatography (AcOEt/PET 2:8 on deactivated silica) to give **19** (30 mg, 81 µmol, 29%) as a yellow oil.

R_f 0.6 (PET/AcOEt 7:3, Anisaldehyde).

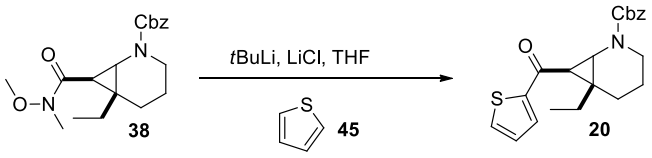
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.23 (m, 5H; ArH), 5.88 (t, *J* = 4.2 Hz, 1H; $CHCH_2$), 5.19 (d, *J* = 12.8 Hz, 1H; $PhCH_2$), 5.08 (d, *J* = 12.8 Hz, 1H; $PhCH_2$), 4.16-3.98 (m, 2H; OCH_2 rotamer A and rotamer B), 3.86 (dt, *J* = 12.9, 3.2 Hz, 0.8H; NCH_2 rotamer A), 3.72 (m, 0.2H; NCH_2 rotamer B), 3.70 (d, *J* = 3.5 Hz, 0.2H; NCH rotamer B), 3.64 (d, *J* = 3.7 Hz, 0.8H; NCH rotamer A), 2.75 (m, 0.2H; NCH_2 rotamer B), 2.67 (m, 0.8H; NCH_2 rotamer A), 2.46 (d, *J* = 3.7 Hz, 1H; COCH), 2.19 (m, 2H; CH_2CH), 2.07 (m, 1H; CH_2), 1.84 (m, 2H; CH_2), 1.78-1.41 (m, 5H; CH_2), 0.81 (t, *J* = 7.3 Hz, 3H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 192.8, 169.6, 151.9, 128.4, 128.3, 128.0, 128.0, 127.5, 127.5, 127.3, 127.2, 127.0, 108.0, 66.8, 66.3, 46.0, 41.2, 38.1, 34.8, 26.2, 24.6, 21.8, 21.6, 20.7, 10.8.

IR ν (cm-1): 2956 (w), 2935 (w), 2876 (w), 1705 (s), 1678 (m), 1626 (m), 1498 (w), 1447 (m), 1429 (m), 1406 (s), 1369 (m), 1349 (m), 1309 (m), 1287 (m), 1268 (m), 1239 (w), 1213 (m), 1198 (m), 1170 (m), 1122 (m), 1092 (m), 1061 (s), 1027 (m), 1011 (m), 981 (w), 973 (w), 918 (m), 901 (w), 873 (w), 768 (m), 739 (m), 699 (m), 630 (w).

HRMS(ESI) calcd for $C_{22}H_{28}NO_4^+$ (M+H) 370.2018, found 370.2033

Benzyl 6-ethyl-7-(thiophene-2-carbonyl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (20)



A solution of thiophene **45** (30 µL, 0.37 mmol, 1.3 equiv) and LiCl (30 mg, 0.58 mmol, 2.0 equiv) in THF (1.5 mL) was stirred at -78° C. Then a solution of *t*BuLi (1.6 M in hexane, 0.22 mL, 0.35 mmol, 1.2 equiv) was added dropwise. The solution was warmed to 0°C and stirred for 40 minutes before cooling down again at -78°C. The lithiated thiophene was then added via cannula into the solution of Weinreb amide **38** (0.10 g, 0.29 mmol, 1.0 equiv) in THF (1.5 mL) at 0°C during 20 minutes. The mixture was stirred for additional 20 minutes, transferred via cannula into a saturated aqueous solution of $NaHCO_3$ (5 mL) at 0°C and extracted with Et_2O (5x3 mL). The organic layers were dried over Na_2SO_4, evaporated under reduced pressure and purified on flash chromatography (AcOEt/PET 2:8 on deactivated silica) to give **20** (27 mg, 73 µmol, 25%) as a yellow oil.

R_f 0.3 (PET/AcOEt 8:2, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, *J* = 0.9 Hz, 0.2H; thiopheneH rotamer B), 7.66 (dd, *J* = 3.5, 0.7 Hz, 0.8H; thiopheneH rotamer A), 7.61 (dd, *J* = 4.8, 0.7 Hz, 0.8H; thiopheneH rotamer A), 7.58 (d, *J* = 0.9 Hz, 0.2H; thiopheneH rotamer B), 7.33 (m, 1H; thiopheneH), 7.23-7.08 (m, 5H; ArH), 5.19 (d, *J* = 12.8 Hz, 0.8H; OCH_2 rotamer A), 5.18 (d, *J* = 12.0 Hz, 0.2H; OCH_2 rotamer B), 5.08 (d, *J* = 12.5 Hz, 0.2H; OCH_2 rotamer B), 5.04 (d, *J* = 12.8 Hz, 0.8H; OCH_2 rotamer A), 3.91 (m, 0.8H; NCH_2 rotamer A), 3.85 (m, 0.2H; NCH_2 rotamer B), 3.78 (d, *J* = 3.5

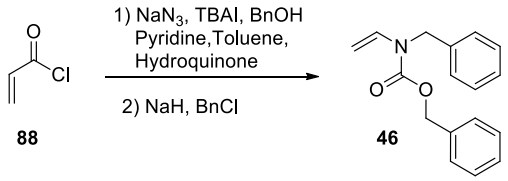
Hz, 1H; NCH), 2.82 (m, 0.2H; NCH_2 rotamer B), 2.72 (m, 0.8H; NCH_2 rotamer B), 2.50 (br s, 0.2H; COCH rotamer B), 2.48 (d, *J* = 3.5 Hz; 0.8H; COCH rotamer A), 2.12 (dd, *J* = 12.3, 4.6 Hz, 1H; CH_2), 1.89-1.64 (m, 4H; CH_2), 1.50 (m, 1H; CH_2), 0.81 (t, *J* = 7.3 Hz, 3H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 188.8, 156.2, 145.9, 136.6, 134.7, 132.9, 132.7, 131.0, 128.4, 128.2, 128.0, 127.8, 127.6, 127.2, 67.2, 66.8, 45.9, 45.7, 41.7, 41.2, 38.1, 37.3, 36.6, 26.3, 26.1, 25.0, 21.9, 10.7

IR ν (cm-1): 2960 (w), 2936 (w), 2875 (w), 1706 (s), 1666 (s), 1665 (s), 1460 (m), 1416 (m), 1356 (w), 1311 (w), 1310 (w), 1267 (w), 1237 (w), 1236 (w), 1202 (w), 1201 (w), 1127 (w), 1107 (w), 1106 (w), 1080 (w), 1079 (w), 1069 (w), 1068 (w), 1062 (w), 1036 (w), 1035 (w), 1019 (w), 752 (m), 740 (s), 731 (s), 709 (m).

HRMS(ESI) calcd for $C_{21}H_{24}NO_3S^+$ (M+H) 370.1471, found 370.1408.

Benzyl-*N*-benzyl-*N*-vinylcarbamate (46)



88 **46**

Following a slight modification of a reported procedure,[28,29] a solution of acryloyl chloride **88** (8.97 mL, 110 mmol, 1.00 equiv) and TBAI (2.04 g, 5.52 mmol, 0.05 equiv) in toluene (100 mL) was added dropwise to a solution of sodium azide (8.60 g, 132 mmol, 1.20 equiv) in H_2O (100 mL) at 0°C. The biphasic reaction was stirred at 0°C for 5 hours then the layers were separated. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was added carefully into a solution of benzyl alcohol (120 g, 1.10 mol, 10 equiv), pyridine (523 mg, 6.63 mmol, 0.06 equiv) and hydroquinone (607 mg, 5.52 mmol, 0.05 equiv) at 85°C. The reaction was stirred for 1 hour at 85°C then distilled under reduced pressure. The crude distillate (140°C, 0.13 mmHg) was recrystallized in cyclohexane to give benzyl-vinylcarbamate as colorless crystals (4.82 g, 27.2 mmol, 25%).

R_f 0.3 (AcOEt/PET 1:9 Anisaldehyde).

[28] Wieber, G. M.; Hegedus, L. S.; Akermark, B.; Michalson, E. T., *J. Org. Chem.* **1989,** *54*, 4649.
[29] Kamatani, A.; Overman, L. E., *J. Org. Chem.* **1999,** *64* (23), 8743.

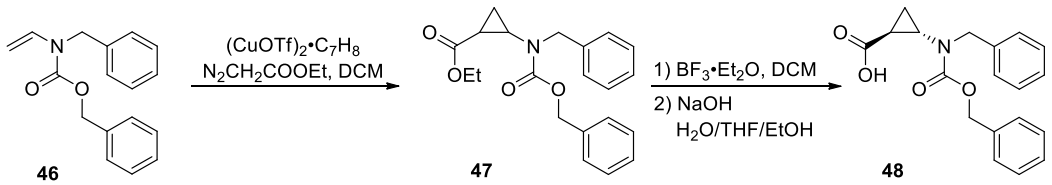
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (m, 5H; ArH), 6.70 (m, 1H; CHN), 6.41 (br s, 1H; NH), 5.15 (s, 2H; CH_2Ar), 4.48 (d, *J* = 15.7 Hz, 1H; vinylH, *cis*), 4.30 (d, *J* = 8.4 Hz, 1H, vinylH, *trans*).

A solution of benzyl-vinylcarbamate (800 mg, 4.52 mmol, 1.00 equiv) in THF (10 mL) was added dropwise into a suspension of NaH (163 mg, 6.80 mmol, 1.5 equiv) in THF (40 mL) at 0°C. The mixture was stirred at 0°C for 1.5 hour then benzyl bromide was added dropwise. The reaction was allowed to warm to rt and stirred overnight before quenching with aqueous $NaHCO_3$ at 0°C. The suspension was extracted with Et_2O (30mL x 3), dried on Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/AcOEt 30:1-9:1) to give the protected enamide **46** (850 mg, 3.18 mmol, 70 %) as a pale yellow oil.

R_f 0.7 (AcOEt/PET 1:9 Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46-7.07 (m, 11H; ArH and CHN), 5.23 (m, 2H; OCH_2Ar), 4.80 (m, 2H; CH_2Ar), 4.44-4.18 (m, 2H; vinylH).

2-(Benzyl((benzyloxy)carbonyl)amino)cyclopropanecarboxylic acid (48)



Following the reported procedure,[30] a solution of ethyl diazoacetate (1.5 mL, 15 mmol, 4.6 equiv) in DCM (8 mL) was added via a syringe pump (0.5 mL/h) into a suspension of vinyl amide **46** (0.85 g, 3.2 mmol, 1.0 equiv) and $(CuOTf)_2$•Tol (47 mg, 92 μmol, 0.030 equiv) in DCM (8 mL). The suspension was then filtered and purified by column chromatography (pentane/AcOEt 9:1) to afford the cyclopropane derivative **47** (0.78 g, 2.2 mmol, 69%) as a diastereomeric mixture.

Following a reported procedure,[31] the diastereomeric mixture of esters **47** (0.49 g, 1.4 mmol, 1.0 equiv) in dichlorometane (9 mL) at -20°C was treated with BF_3•Et_2O (40 mg, 0.38 mmol, 0.20 equiv). The reaction was allowed to warm at 0°C and stirred at the same temperature until the isomerization was finished (from R_f 0.2-0.3 PET/AcOEt 8:2 to R_f 0.3 PET/AcOEt 8:2,

[30] De Simone, F.; Gertsch, J.; Waser, J., *Angew. Chem., Int. Ed.* **2010,** *49*, 5767.
[31] Grieco, P. A.; Kaufman, M. D., *J. Org. Chem.* **1999,** *64*, 7586.

Anisaldehyde). Triethylamine (1 mL) was added dropwise to the reaction and the mixture was diluted with Et_2O (20 mL) and washed with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give a yellow oil (0.49 g) which was used directly in the next step.

The crude oil (0.49 g, 1.4 mmol, 1.0 equiv) was dissolved in a solution of water/THF/EtOH 1/1/3 (7.5 mL total) at 0°C and NaOH (0.56 g, 14 mmol, 10 equiv) was added portionswise. The reaction was stirred at 0°C during one hour then concentrated, diluted with water (20 mL) and washed with Et_2O (3x20 mL). The aqueous layer was acidified with HCl (1 M aqueous solution) until pH 2 and extracted with DCM (3x20 mL) to give **48** as a colorless oil which turns solid upon storage (370 mg, 1.14 mmol, 82% overall). No further purification was needed.

R_f 0.0 (AcOEt/PET 3:7 Anisaldehyde).

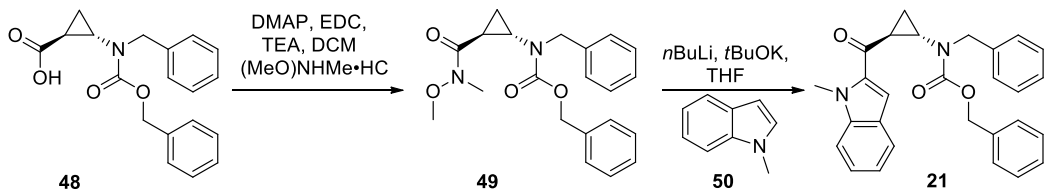
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41-7.17 (m, 10H, ArH), 5.22 (d, J = 12.4 Hz, 1H; OCH_2Ar), 5.16 (d, J = 12.3 Hz, 1H; OCH_2Ar), 4.57 (d, J = 15.4 Hz, 1H; CH_2Ar), 4.42 (d, J = 15.4 Hz, 1H; CH_2Ar), 3.06 (m, 1H; CHNH), 1.87 (m, 1H; CHCO), 1.44 (m, 1H; CH_2), 1.35 (m, 1H; CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.6, 157.7, 137.5, 137.4, 136.2, 128.7, 128.5, 128.5, 128.4, 128.1, 128.0, 127.5, 127.3, 67.7, 51.4, 38.3, 23.4, 17.1. [32]

IR ν (cm-1): 3065 (w), 3035 (w), 2996 (w), 2948 (w), 1700 (s), 1700 (s), 1699 (s), 1699 (s), 1587 (w), 1543 (w), 1498 (w), 1453 (m), 1410 (s), 1410 (s), 1409 (s), 1409 (s), 1356 (m), 1325 (w), 1291 (m), 1290 (m), 1273 (m), 1238 (m), 1237 (m), 1218 (m), 1189 (m), 1178 (m), 1134 (m), 1033 (w), 980 (w), 912 (w), 911 (w), 774 (w), 737 (m), 737 (m), 737 (m), 700 (m), 700 (m), 639 (w), 630 (m), 630 (m), 630 (m), 621 (s), 621 (s), 621 (s).

HRMS(ESI) calcd for $C_{19}H_{20}NO_4^+$ (M+H) 326.1392, found 326.1389.

Benzyl benzyl(2-(1-methyl-1H-indole-2-carbonyl)cyclopropyl)carbamate (21)



[32] Not all the aromatic signals were resolved

Dimethylhydroxylamine hydrochloride (55 mg, 0.57 mmol, 1.5 equiv) was added to a solution of acid **48** (0.12 g, 0.38 mmol, 1.0 equiv) in DCM (3 mL) at rt. The reaction was stirred until complete dissolution then DMAP (9 mg, 7 µmol, 0.2 equiv) and EDC (0.11 g, 0.57 mmol, 1.5 equiv) were added portionwise followed by the dropwise addition of TEA (79 µL, 0.57 mmol, 1.5 equiv). The solution was stirred overnight then quenched with a 1 M solution of HCl (2 mL), diluted in DCM (20 mL), washed with a 1 M solution of HCl (3 x 4 mL) and a saturated aqueous solution of $NaHCO_3$ (2 x 4 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Et_2O/pentane 7:3) to yield the Weinreb amide **49** (0.22 g, 0.33 mmol, 86%, R_f = 0.5 (Et_2O/pentane 8:2) as a colorless oil, which was used directly in the next step.

N-Methyl indole **50** (0.15 g, 1.1 mmol, 1.3 equiv) was diluted in THF (7 mL) at 0 °C and ^{n}BuLi (0.42 mL, 1.0 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred 1 h at rt and cooled to -78 °C. Weinreb amide **49** (dried through 3 co-evaporation with toluene, 0.32 g, 0.87 mmol, 1.0 equiv) was added dropwise via cannula as a cooled (-78 °C) solution in THF (7 mL). After further stirring 2 h at -78 °C, a solution of KO*t*Bu (0.11 g, 1.7 mmol, 2.0 equiv) in THF (1 mL) was added. After 2 h, the reaction mixture was left to warm up to -20 °C and stirred. After 20 min at -20 °C, the reaction mixture was transferred via cannula into a saturated aqueous solution of $NaHCO_3$ (20 mL) at 0°C and stirred for 20 minutes before extraction with Et_2O (3x20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 9:1-8:2) to yield indole **21** (243 mg, 0.554 mmol, 64%) as an orange oil.

R_f 0.6 (AcOEt/PET 3:7 Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, *J* = 8.0 Hz, 1H; ArH), 7.47-7.06 (m, 14H; ArH), 5.20 (d, *J* = 12.2 Hz, 1H; OCH_2Ar), 5.13 (d, *J* = 12.2 Hz, 1H; OCH_2Ar), 4.76 (d, *J* = 15.3 Hz, 1H; CH_2Ar), 4.45 (d, *J* = 15.4 Hz, 1H; CH_2Ar), 3.99 (s, 3 H, NCH_3), 3.20 (m, 1H; CHNH), 2.93 (m, 1H, CHCO), 1.67 (d, *J* = 5.4 Hz, 1H; CH_2), 1.45 (m, 1H; CH_2).

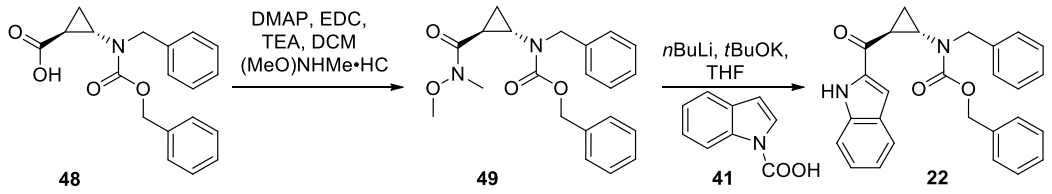
^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.3, 157.2, 140.1, 137.8, 136.0, 135.1, 128.6, 128.2, 128.0, 127.8, 127.5, 127.4, 125.9, 125.9, 122.9, 120.6, 112.0, 110.3, 67.6, 51.5, 40.4, 32.0, 29.3, 18.0.

IR ν (cm-1): 3059 (w), 3031 (w), 3031 (w), 2949 (w), 1706 (s), 1649 (s), 1615 (w), 1514 (m), 1466 (m), 1456 (m), 1430 (m), 1404 (s), 1385 (m), 1353 (m), 1321 (m), 1229 (m), 1228 (m),

1200 (m), 1166 (m), 1152 (m), 1129 (m), 1041 (w), 1005 (m), 936 (w), 771 (m), 744 (s), 700 (s), 640 (m), 631 (m), 605 (m).

HRMS(ESI) calcd for $C_{28}H_{27}N_2O_3^+$ (M+H) 439.2022, found 439.2033.

Benzyl (2-(1H-indole-2-carbonyl)cyclopropyl)(benzyl)carbamate (22)



Dimethylhydroxylamine hydrochloride (55 mg, 0.57 mmol, 1.5 equiv) was added to a solution of acid **48** (0.12 g, 0.38 mmol, 1.0 equiv) in DCM (3 mL) at rt. The reaction was stirred until complete dissolution then DMAP (9 mg, 7 µmol, 0.2 equiv) and EDC (0.11 g, 0.57 mmol, 1.5 equiv) were added portionwise followed by the dropwise addition of TEA (79 µL, 0.57 mmol, 1.5 equiv). The solution was stirred overnight then quenched with a 1 M solution of HCl (2 mL), diluted in DCM (20 mL), washed with a 1 M solution of HCl (3 x 4 mL) and a saturated aqueous solution of $NaHCO_3$ (2 x 4 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Et_2O/pentane 7:3) to yield Weinreb amide **49** (0.22 g, 0.33 mmol, 86%, R_f = 0.5 (Et_2O/pentane 8:2) as a colorless oil, which was used directly in the next step.

*t*BuLi (0.74 mL, 1.2 mmol, 2.2 equiv) was added dropwise into a solution of *N*-carboxylindole prepared following **GP6** (96 mg, 0.59 mmol, 1.1 equiv) and LiCl (25 mg, 0.59 mmol, 1.1 equiv) in THF (1.5 mL) at -78°C. The reaction mixture was stirred 3 h at -78 °C then a solution of Weinreb amide **49** (0.20 g, 0.54 mmol, 1.0 equiv) was added dropwise via cannula as a cooled (-78 °C) solution in THF (1.5 mL). The reaction mixture was left to warm up to -20 °C and stirred. After 20 min at -20 °C, the reaction was transferred via cannula into a saturated aqueous solution of $NaHCO_3$ (10 mL) at 0°C and stirred for 20 minutes before the extraction with Et_2O (3x10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 9:1-8:2) to yield indole **22** (82 mg, 0.19 mmol, 36%) as a yellow oil.

R_f 0.7 (AcOEt/PET 3:7 Anisaldehyde).

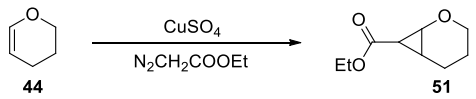
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.78 (br s, 1H; NH), 7.71 (d, *J* = 8.1 Hz, 1H; ArH), 7.45-7.06 (m, 14H; ArH), 5.24 (d, *J* = 12.2 Hz, 1H; OCH_2Ar), 5.14 (br m, 1H; OCH_2Ar), 4.78 (d, *J* = 15.2 Hz, 1H; CH_2Ar), 4.45 (d, *J* = 15.4 Hz, 1H; CH_2Ar), 3.28 (m, 1H; CHN), 2.88 (m, 1H; CHCO), 1.76 (m, 1H; CH_2), 1.50 (m, 1H; CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 189.6, 157.1, 137.6, 137.5, 136.0, 135.3, 128.6, 128.4, 128.2, 127.9, 127.9, 127.5, 127.4, 126.9, 126.5, 126.2, 124.1, 123.0, 121.7, 120.7, 120.6, 119.6, 112.2, 111.0, 110.0, 102.3, 67.6, 65.1, 51.5, 40.5, 28.1, 26.1, 18.2.

IR ν (cm-1): 3308 (w), 3307 (w), 3281 (w), 3063 (w), 3032 (w), 2957 (w), 1699 (s), 1636 (m), 1574 (w), 1523 (m), 1497 (m), 1455 (m), 1436 (m), 1400 (s), 1353 (m), 1344 (m), 1299 (m), 1298 (m), 1265 (m), 1229 (m), 1204 (m), 1165 (m), 1140 (s), 1079 (m), 1068 (m), 1049 (w), 1048 (w), 1029 (m), 982 (w), 982 (w), 960 (w), 910 (m), 805 (m), 771 (m), 736 (s), 736 (s), 699 (s), 619 (m).

HRMS(ESI) calcd for $C_{27}H_{25}N_2O_3^+$ (M+H) 425.1860, found 425.1852.

7-Carbethoxy-2-oxabicyclo[4.1.0]heptane (51)



Following a reported procedure,[33] a solution of ethyl diazoacetate (5.0 mL, 48 mmol, 1.0 equiv) in freshly distilled dihydropyran **44** (9.0 mL) was added via a syringe pump to a refluxing solution of $CuSO_4$ (0.38 mg, 2.4 mmol, 0.050 equiv) in dihydropyran **44** (21 mL) over 2.5 hours. The reaction was refluxed for additional 2h. The excess of dihydropyran was removed under atmospheric pressure and the resulting solution was distilled (90 °C, 3 mmHg) to give cyclopropane **51** (5.0 g, 29 mmol, 62%) as a colorless oil.

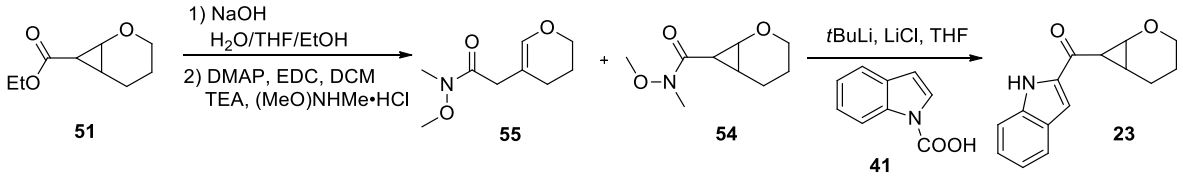
R_f 0.8 (AcOEt/PET 2:8 Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.12 (m, 2H; $COOCH_2$), 3.91 (m, 1H; OCH), 3.60 (dtd, *J* = 10.8, 3.3, 1.0 Hz, 1H; OCH_2), 3.36 (td, *J* = 11.3, 2.2 Hz, 1H; OCH_2), 2.11-1.83 (m, 3H; CHCO, CH

[33] Temme, O.; Taj, S. A.; Andersson, P. G., *J. Org. Chem.* **1998,** *63*, 6007.

and CH_2), 1.75 (m, 1H; CH or CH_2), 1.60-1.40 (m, 2H; CH or CH_2), 1.26 (t, 3H, *J* = 7.2 Hz, CH_3).

2-Oxabicyclo[4.1.0]heptan-7-yl(1H-indol-2-yl)methanone (23)



51 55 54 41 23

The ester **51** (1.50 g, 8.82 mmol, 1.00 equiv) was dissolved in a solution of water/THF/EtOH 1/1/3 (25 mL total) at 0°C and NaOH (2.47 g, 61.8 mmol, 7.00 equiv) was added portionswise. The reaction was stirred during 20 minutes at 0°C then diluted with water (30 mL) and washed with Et_2O (3x20 mL). The aqueous layer was acidified with HCl (1 M aqueous solution) until pH 2 and extracted with DCM (3x20 mL) to give the carboxylic acid **52** (1.16 g, 8.17 mmol, 93%, 7:1 mixture of open and closed form) as a white solid which was used directly in the next step.
Dimethylhydroxylamine hydrochloride (0.54 g, 5.6 mmol, 1.5 equiv) was added to a solution of acid **52** (0.53 g, 3.7 mmol, 1.0 equiv) in DCM (30 mL) at rt. The reaction was stirred until complete dissolution, then DMAP (91 mg, 0.75 mmol, 0.2 equiv) and EDC (1.0 g, 5.6 mmol, 1.5 equiv) were added portionwise followed by the dropwise addition of TEA (0.74 mL, 5.6 mmol, 1.5 equiv). The solution was stirred overnight then quenched with a 1 M solution of HCl (2 mL), diluted in DCM (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/PET 3:7) to yield Weinreb amide **54** (0.41 g, 0.22 mmol, 59%, R_f = 0.3 (AcOEt/PET 3:7) as an inseparable mixture of open and closed form in 2:1 ratio respectively.

*t*BuLi (1.6 M in pentane, 3.6 mL, 5.8 mmol, 2.6 equiv) was added dropwise into a solution of *N*-carboxylindole prepared following **GP6** (0.46 g, 2.9 mmol, 1.3 equiv) and LiCl (0.24 g, 5.8 mmol, 2.6 equiv) in THF (20 mL) at -78°C. The lithiated indole was then added via cannula into the solution of Weinreb amide **54** (as a mixture of open and closed form in 2:1 ratio respectively) (0.41 g, 2.2 mmol, 1.0 equiv) in THF (20 mL) at 0°C during 20 minutes. The mixture was stirred for additional 15 minutes, transferred via cannula into a saturated aqueous solution of $NaHCO_3$ (20 mL) at 0°C and extracted with Et_2O (3x20 mL). The organic layers were dried over Na_2SO_4, evaporated under reduced pressure and purified on flash chromatography (AcOEt/PET 2:8 on deactivated silica) to give **23** (0.22 g, 0.90 mmol, 41%) (60% calculated on purity of starting material) as a yellow oil.

R_f 0.4 (AcOEt/PET 2:8 Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (br s, 1H; NH), 7.73 (d, *J* = 7.8 Hz, 1H; ArH), 7.42 (d, *J* = 8.3 Hz, 1H; ArH), 7.34 (m, 2H; ArH), 7.16 (t, *J* = 7.7 Hz, 1H; ArH) 4.13 (dd, *J* = 7.2, 1.4 Hz, 1H; OCH), 3.72 (dt, *J* = 10.8, 2.8 Hz, 1H; OCH_2), 3.47 (m, 1H; OCH_2), 2.79 (dd, *J* = 5.8, 1.4 Hz, 1H; CHCO), 2.17 (m, 1H; CH or CH_2), 2.05 (m, 2H; CH or CH_2), 1.66 (m, 2H; CH or CH_2).

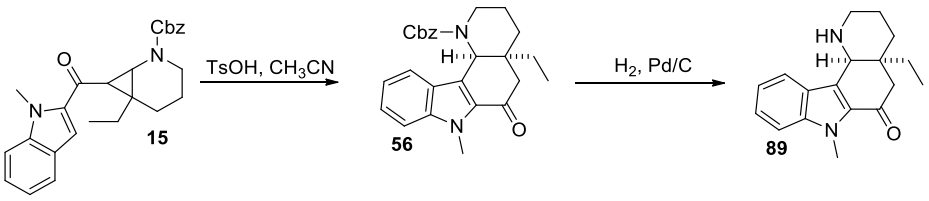
^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.7, 137.1, 135.7, 127.7, 126.1, 123.0, 120.8, 112.1, 109.1, 64.8, 63.6, 32.4, 25.2, 22.0, 19.2.

IR ν (cm-1): 3307 (w), 2952 (w), 2865 (w), 1629 (m), 1523 (m), 1424 (w), 1343 (w), 1276 (w), 1232 (w), 1207 (w), 1177 (w), 1132 (m), 1065 (m), 958 (w), 925 (w), 896 (w), 874 (w), 850 (w), 810 (m), 743 (s), 667 (s).

HRMS(ESI) calcd for $C_{15}H_{16}NO_2^+$ (M+H) 242.1181, found 242.1187.

7 Cyclization of amino- and oxycyclopropanes

Benzyl 4a-ethyl-7-methyl-6-oxo-2,3,4,4a,5,6,7,11c-octahydro-1*H*-pyrido[3,2-c]carbazole-1-carboxylate (56) and 4a-ethyl-7-methyl-3,4,4a,5,7,11c-hexahydro-1*H*-pyrido[3,2-c]carbazol-6(2*H*)-one (89)



The reaction was performed following general procedure **GP4**, starting from cyclopropane **15** (14 mg, 0.034 mmol, 1.0 equiv) and tosic acid (1 mg, 7 μmol, 0.2 equiv). The reaction was quenched after 5 min to give **56** (14 mg, 0.034 mmol, quant) without further purification as yellow oil (R_f 0.65 (PET/AcOEt 7:3, Anisaldehyde)). The indole derivative **56** (14 mg, 34 μmol, 1.0 equiv) was deprotected following general procedure **GP5**, using Pd/C (3 mg 10% w/w) in Et_2O (1.5 mL) and H_2 balloon. The suspension was filtered on celite and washed with DCM to afford **89** as green oil in quantitative yield (9.6 mg, 34 μmol).

R_f 0.75 (DCM/MeOH/Et_3N 3:1:2%, Anisaldehyde).

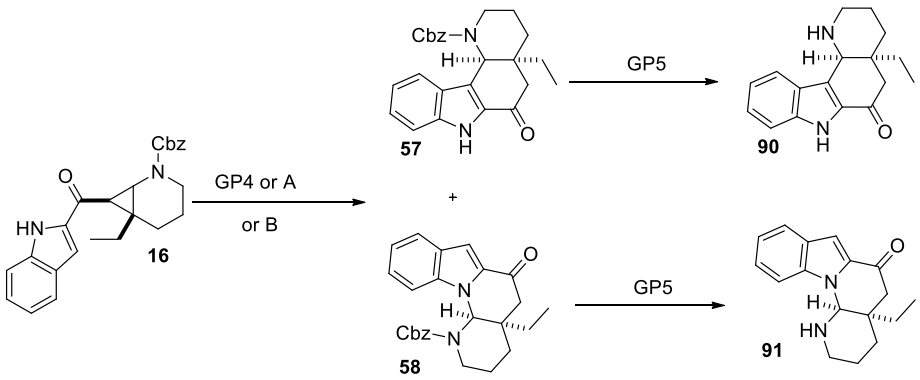
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (d, *J* = 8.2 Hz, 1H; ArH), 7.45-7.32 (m, 2H; ArH), 7.22 (t, *J* = 7.2 Hz, 1H; ArH), 4.16 (s, 1H; CHN), 4.08 (s, 3H; NCH_3), 3.53 (d, *J* = 17.0 Hz, 1H; CH_2CO), 2.52 (m, *J* = 14.6 Hz, 2H; CH_2N), 2.26 (d, *J* = 16.8 Hz, 1H; CH_2CO), 1.87-1.21 (m, 7H; CH_2 and NH), 0.75 (t, *J* = 7.4 Hz, 3H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.6, 139.8, 129.9, 126.6, 124.3, 121.5, 120.8, 110.3, 110.3, 55.6, 45.0, 44.0, 40.2, 32.6, 31.6, 31.2, 29.7, 27.5.

IR ν (cm-1): 3300 (w), 2960 (m), 2935 (m), 2902 (w), 1702 (s), 1662 (s), 1615 (w), 1601 (w), 1542 (w), 1448 (m), 1411 (m), 1314 (m), 1252 (m), 1179 (w), 1117 (w), 1070 (w), 751 (m), 698 (m), 641 (m), 627 (m), 607 (m).

HRMS(ESI) calcd for $C_{18}H_{23}N_2O^+$ (M+H) 283.1810, found 283.1813.

Benzyl 4a-ethyl-6-oxo-2,3,4,4a,5,6,7,11c-octahydro-*1H*-pyrido[3,2-c]carbazole-1-carboxylate (57); 4a-ethyl-7-3,4,4a,5,7,11c-hexahydro-1*H*-pyrido[3,2-c]carbazol-6(2*H*)-one (58); benzyl 4a-ethyl-6-oxo-2,3,4,4a,5,6-hexahydroindolo[1,2-a][1,8]naphthyridine-1(*12aH*)-carboxylate (90); 4a-ethyl-1,2,3,4,4a,5-hexahydroindolo[1,2-a][1,8]naphthyridin-6(*12aH*)-one (91)



The reaction was performed following general procedure **GP4**, starting from cyclopropane **16** (35 mg, 0.087 mmol, 1.0 equiv) and tosic acid (3.0 mg, 16 µmol, 0.20 equiv). The reaction was quenched after 15 min and the crude oil was purified by column chromatography (PET/AcOEt 9:1, Anisaldehyde) to give the product **57** (*Rf* 0.65, 16 mg, 39 µmol, 45 %) and the product **58** (*Rf* 0.75, 10 mg, 25 µmol, 29%). The tetracyclic compound **57** (16 mg, 16 µmol, 1.0 equiv) was deprotected following the general procedure **GP5** to give **90** (10 mg, 38 µmol, 97 %) as a yellow oil without further purification. Product **58** (10 mg, 25 µmol, 1.0 equiv) was deprotected

following the general procedure **GP5** to give **91** (6.7 mg, 25 µmol, 99 %) as a yellow oil without further purification.

A: C-3 carbon cyclization

A solution of Copper(II) triflate (9.0 mg, 25 µmol, 0.10 equiv) in anhydrous CH_3CN (250 µL) was added dropwise to a solution cyclopropane **16** (100 mg, 0.250 mmol, 1.00 equiv) in anhydrous CH_3CN (12.5mL). The reaction was stirred during 15 min then quenched with $NaHCO_3$ (10 mL) and extracted with Et_2O (3x10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude oil was purified by column chromatography (PET/AcOEt 7:3, Anisaldehyde) to give the product **57** (*Rf* 0.65, 80 mg, 0.20 mmol, 80 %) and the product **58** (*Rf* 0.75, 11 mg, 30 µmol, 11%). The tetracyclic compound **57** (70 mg, 0.17 mmol, 1.0 equiv) was deprotected following the general procedure **GP5** to give **90** (45 mg, 0.17 mmol, quant.) as a yellow oil without further purification.

B: N-1 nitrogen cyclization

Toluenesulfonic acid (4.7 mg, 25 µmol, 0.1 equiv) was added to a solution of cyclopropane **16** (0.10 g, 0.25 mmol, 1.0 equiv) in DCM (12.5 mL). The reaction was stirred during 15 min then quenched with $NaHCO_3$ (10 mL) and extracted with Et_2O (3x10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude oil was purified by column chromatography (PET/AcOEt 7:3, Anisaldehyde) to give the product **57** (*Rf* 0.65, 4.0 mg, 10 µmol, 4 %) and the product **58** (*Rf* 0.75, 85 mg, 0.22 mmol, 85 %). The tetracyclic compound **58** (50 mg, 0.12 mmol, 1.0 equiv) was deprotected following the general procedure **GP5** to give **91** (33 mg, 0.12 mmol, quant.) as a yellow oil without further purification.

From **58** to **57**

Copper II triflate (4.0 mg, 11 µmol, 0.20 equiv) was added into a solution of **58** (22 mg, 55 µmol, 1.0 equiv) in CH_3CN (2 mL). The reaction was stirred at rt during 48 h then quenched with a saturated aqueous solution of $NaHCO_3$, extracted with Et_2O (3x), dried on Na_2SO_4 and concentrated on reduced pressure. NMR of crude compound showed exclusively the presence of **57**.

90

R_f 0.0 (AcOEt/PET 6:4, Anisaldehyde).

^{1}H NMR (CD_3OD, 400 MHz) δ 7.91 (d, *J* = 8.2 Hz, 1H; ArH), 7.51 (d, *J* = 8.4 Hz, 1H; ArH), 7.40 (d, *J* = 7.2 Hz, 1H; ArH), 7.23 (t, *J* = 7.5 Hz, 1H; ArH), 4.61 (s, 1H; CHN), 3.40-3.11 (m, 3H; CH_2N and CH_2CO), 2.37 (d, *J* = 17.6 Hz, 1H; CH_2CO), 2.16 (s, 1H; NH), 1.92 (m, 2H; CH_2), 1.80 (m, 2H; CH_2), 1.45 (m, 2H; CH_2), 0.83 (t, *J* = 7.5 Hz, 3H; CH_3).

^{13}C NMR (CD_3OD, 100 MHz) δ 191.2, 140.0, 132.6, 128.2, 126.1, 122.4, 122.0, 121.6, 114.1, 55.6, 45.3, 42.7, 41.5, 33.0, 32.7, 20.4, 7.8.

IR ν (cm-1): 2961 (s), 2943 (s), 2866 (s), 2142 (m), 1660 (w), 1543 (w), 1493 (m), 1464 (m), 1366 (w), 1263 (w), 1167 (m), 1105 (m), 1073 (m), 1021 (m), 884 (m), 804 (m), 751 (m), 673 (s), 635 (s).

HRMS(ESI) calcd for $C_{17}H_{21}N_2O^+$ (M+H) 269.1654, found 269.1655.

For X-ray image see the spectra in section 6.

91

R_f 0.4 (AcOEt/PET 3:7 Anisaldehyde).

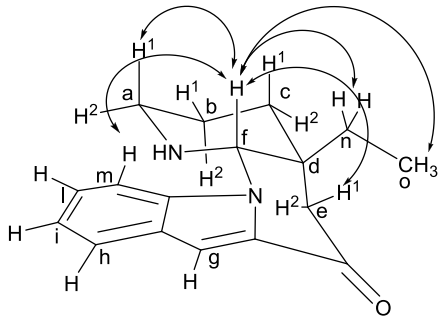
^{1}H NMR (CD_3OD, 400 MHz) δ 7.71 (d, *J* = 8.1 Hz, 1H; H_h), 7.63 (d, *J* = 8.4 Hz, 1H; H_m), 7.43 (t, *J* = 7.9 Hz, 1H; H_i or H_l), 7.28 (s, 1H; H_g), 7.18 (t, *J* = 7.7 Hz, 1H; H_i or H_l), 5.22 (s, 1H; H_f), 3.36 (d, *J* = 17.6 Hz, 1H; H_e^2), 3.12 (m, 1H; H_a^2), 2.97 (m, 1H; H_a^1), 2.32 (d, *J* = 17.6 Hz, 1H; H_e^1), 1.87-1.60 (m, 5H; H_b^1 ; H_b^2 ; H_c^1; H_c^2 and NH), 1.31 (q, *J* = 7.6 Hz, 2H; $2H_n$), 0.80 (t, *J* = 7.5 Hz, 3H; $3H_o$).

^{13}C NMR (CD_3OD, 100 MHz) δ 192.9, 138.5, 133.1, 128.6, 127.5, 124.3, 122.8, 111.7, 107.4, 70.7, 45.9, 41.4, 40.2, 33.6, 31.6, 22.1, 7.4.

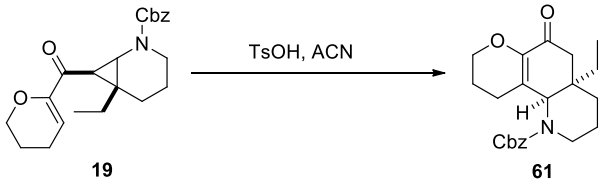
IR ν (cm-1): 2934 (w), 2861 (w), 1676 (s), 1532 (s), 1446 (w), 1407 (w), 1360 (w), 1322 (m), 1247 (w), 1196 (w), 1173 (w), 1146 (w), 1119 (w), 1044 (w), 929 (w), 894 (w), 872 (w), 846 (w), 811 (w), 740 (m), 634 (w).

HRMS(ESI) calcd for $C_{17}H_{21}N_2O^+$ (M+H) 269.1654, found 269.1652.

Important correlations NOESY: H_f-H_a^1; H_f-$2H_n$; H_f-$3H_o$; H_f-H_e^1; H_f-H_m (see the 2D spectra in section 6)



Benzyl 4a-ethyl-6-oxo-2,3,4,4a,5,6,8,9,10,10b-decahydro-1H-pyrano[2,3-h]quinoline-1-carboxylate (61)



19 61

The reaction was performed following **GP4**, starting from cyclopropane **19** (22 mg, 60 μmol, 1.0 equiv) and tosic acid (2.3 mg, 12 μmol, 0.2 equiv). The reaction was quenched after 10 min and purified on flash chromatography (AcOEt/PET 3:7) to yield **61** (17 mg, 46 μmol 78%) as colorless oil.

R_f 0.3 (PET/AcOEt 7:3, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.30 (m, 5H; H_m), 5.17 (m, 2H; H_l), 5.04 (s, 0.5H; H_f rotamer A), 4.86 (s, 0.5H; H_f rotamer B), 4.30-4.17 (m, 1.5H; H_i and H_a rotamer A), 4.11 (m, 0.5H; H_a rotamer B), 3.82 (m, 1H; Hi), 2.56 (m, 1H; H_a), 2.41 (m, 1H; H_e^2), 2.32 (m, 1H; H_e^1), 2.12-1.75 (m, 4H; H_h and H_g), 1.64 (m, 2H; H_b), 1.53 (m, 2H; Hn), 1.41 (m, 2H; H_c), 0.85 (t, J = 7.5 Hz, 1.5H; H_o rotamer A), 0.78 (t, J = 7.6 Hz, 1.5H; H_o rotamer B).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 192.3, 192.1, 156.3, 156.0, 146.5, 136.6, 136.3, 128.5, 128.5, 128.3, 128.1, 127.7, 126.8, 126.4, 67.6, 67.4, 65.8, 65.7, 58.4, 58.1, 47.1, 47.0, 40.2, 39.9, 39.0, 39.0, 28.5, 27.4, 27.2, 22.1, 22.0, 21.4, 20.7, 20.2, 7.6, 7.5.

IR ν (cm-1): 2953 (w), 2938 (w), 2937 (w), 2868 (w), 1688 (s), 1634 (w), 1519 (w), 1462 (w), 1444 (w), 1426 (m), 1386 (w), 1349 (w), 1314 (w), 1298 (w), 1271 (m), 1240 (w), 1209 (w),

1186 (w), 1159 (w), 1141 (m), 1084 (w), 987 (w), 957 (w), 889 (w), 770 (w), 748 (w), 734 (w), 728 (w), 700 (w), 677 (w), 656 (w), 634 (m), 607 (w).

HRMS(ESI) calcd for $C_{22}H_{28}NO_4^+$ (M+H) 370.2018, found 370.2012.

Important correlations NOESY: H_f-$2H_n$; H_f-H_e[1](see the 2D spectra in section 6)

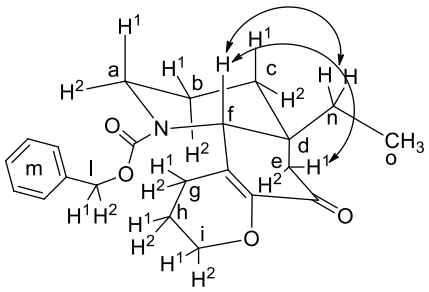
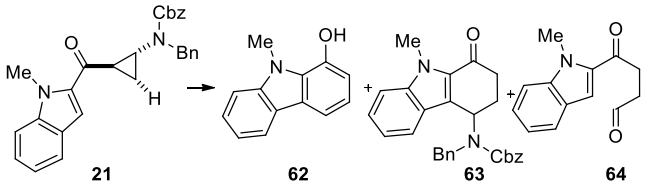


Table 2. Cyclization of acyclic carbamate 21 .



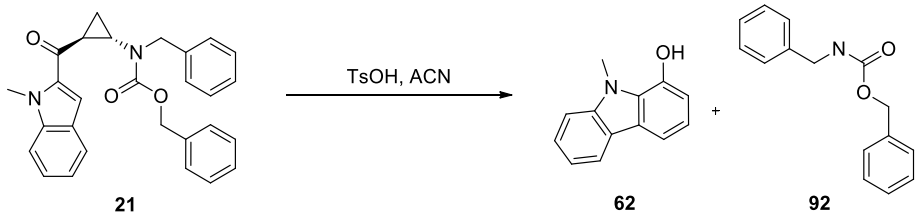
Cyclopropane **21** (10-50 mg, 20-120 μmol) was dissolved on the indicated solvent (0.02 M). The indicated catalyst was added and the solution was stirred at rt during the indicated time. The reaction was quenched with a saturated solution of $NaHCO_3$, extracted with Et_2O (3x), dried over Na_2SO_4 and concentrated on reduced pressure.

Scale of reactions with cyclopropane **21** is the following:

Entry 1, 2, 3, 5, 7, 8: 21 (10 mg, 22 μmol).

Entry 4, 6: 21 (40 mg, 91 μmol).

9-Methyl-9H-carbazol-1-ol (62)



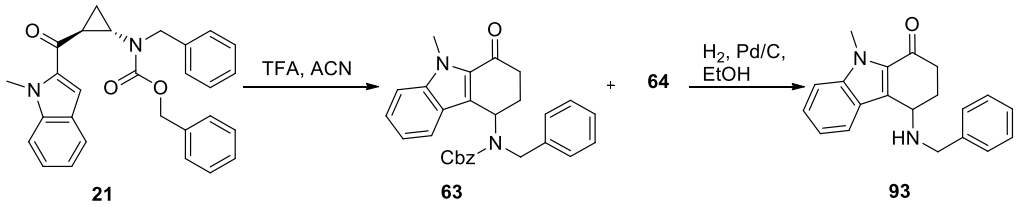
The reaction was performed following **GP4**, starting from cyclopropane **21** (40 mg, 91 μmol, 1.0 equiv) and tosic acid (3.5 mg, 18 μmol, 0.2 equiv). The reaction was quenched after 30 min and purified on flash chromatography (PET/AcOEt 8:2) affording **62** and *N*-benzyl-benzylcarbamate **92** as inseparable mixture (26 mg, **62/92** 1:2.5 molar ratio, 1:3 mass ratio, 36% yield of **62** by NMR estimation).

R_f 0.5 (AcOEt/PET 3:7 Anisaldehyde).

^{1}H NMR (acetone-d_6, 400 MHz) δ 8.73 (s, 1H; OH), 8.09 (m, 1H; C(5)-H), 7.66 (dd, *J* = 7.6, 0.9 Hz, 1H; C(4)-H), 7.53-7.44 (m, 2H; C(7)-H, C(8)-H), 7.20 (m, 1H; C(6)-H), 7.01 (t, *J* = 7.7 Hz, 1H; C(3)-H), 6.94 (dd, *J* = 7.8, 0.9 Hz, 1H; C(2)-H), 4.23 (s, 3H; NCH_3).

The obtained values for ^{1}H NMR fitted perfectly with the reported ones. [34]

4-(Benzylamino)-9-methyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (93)



TFA (1.4 μL, 18 μmol, 0.2 equiv) was added to a solution of indole **21** (40 mg, 91 μmol, 1.0 equiv) in distilled acetonitrile (4 mL). The reaction was stirred at rt during 1.5 h then quenched with a saturated aqueous solution of $NaHCO_3$ (4 mL), extracted with Et_2O (3 x 4 mL) dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was obtained as a mix of product **63** (R_f = 0.6 AcOEt/pentane 8:2) and aldehyde **64** (38 mg, **63/64** 7:1 molar ratio, 14:1 mass ratio, 89% by NMR estimation). Indole **63** was deprotected following the general procedure **GP5** to give **93** as a crude oil. Purification on flash chromatography (PET/AcOEt 6:4 Et_3N 1%) afforded **93** as a yellow oil (10 mg, 33 μmol, 36%).

R_f 0.5 (AcOEt/PET 4:6 Et_3N 1% Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 8.1 Hz, 1H; ArH), 7.45-7.32 (m, 6H; ArH), 7.29 (m, 1H; ArH), 7.14 (m, 1H; ArH), 4.40 (t, *J* = 4.4 Hz, 1H; CHNH), 4.08 (s, 3H; NCH_3), 4.04 (d, *J* =

[34] Oliveira, M. M.; Carvalho, L. M.; Moustrou, C.; Samat, A.; Guglielmetti, R.; Oliveira-Campos, A. M. F., *Helv. Chim. Acta* **2001,** *84*, 1163-1171.

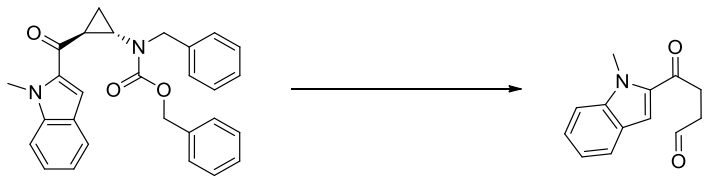
13.2 Hz, 1H; CH_2Ar), 3.93 (d, *J* = 13.2 Hz, 1H; CH_2Ar), 3.05 (ddd, *J* = 16.9, 10.4, 4.6 Hz, 1H; CH_2), 2.53 (m, 1H; CH_2), 2.36 (m, 1H; CH_2), 2.27 (m, 1H; CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.4, 140.5, 129.6, 128.5, 128.1, 127.1, 126.5, 124.3, 121.8, 120.4, 110.3, 51.8, 49.9, 36.1, 31.5, 30.2.[35]

IR ν (cm-1): 3466 (w), 3385 (w), 3384 (w), 3383 (w), 3371 (w), 3361 (w), 2950 (w), 2949 (w), 2937 (w), 1657 (s), 1615 (w), 1530 (w), 1520 (w), 1494 (w), 1474 (w), 1473 (w), 1456 (w), 1430 (w), 1413 (w), 1412 (w), 1355 (w), 1317 (w), 1247 (w), 1165 (w), 1158 (w), 1132 (w), 1125 (w), 1124 (w), 1074 (w), 1009 (w), 911 (m), 744 (s), 702 (w), 692 (w), 652 (w), 642 (m), 631 (s), 615 (m).

HRMS(ESI) calcd for $C_{20}H_{21}N_2O^+$ (M+H) 305.1654, found 305.1667.

4-(1-Methyl-1H-indol-2-yl)-4-oxobutanal (64)



The aldehyde **64** was obtained as major compound in the cyclization reactions carried out in presence of trace of water.

R_f 0.6 (AcOEt/PET 3:7 Anisaldehyde).

^1H NMR ($CDCl_3$, 400 MHz) δ 9.92 (s, 1H; CHO), 7.70 (dt, *J* = 8.0, 0.9 Hz, 1H; ArH), 7.39 (m, 3H; ArH), 7.16 (m, 1H; ArH), 4.06 (s, 3H; NCH_3), 3.38 (t, *J* = 6.3 Hz, 2H; CH_2CO), 2.92 (t, *J* = 6.5 Hz, 2H; CH_2CHO).

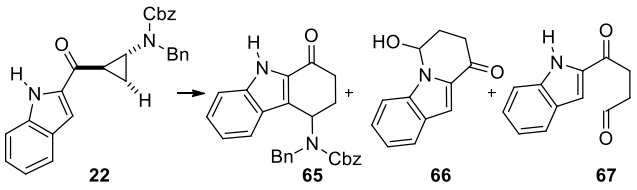
^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.7, 191.6, 128.1, 127.5, 126.0, 125.8, 122.9, 120.8, 111.5, 110.4, 37.8, 32.2, 32.0.

IR ν (cm-1): 2922 (w), 2907 (w), 2819 (w), 2717 (w), 1729 (m), 1661 (s), 1611 (w), 1514 (m), 1466 (m), 1410 (m), 1392 (m), 1355 (w), 1320 (w), 1284 (m), 1168 (m), 1127 (w), 995 (m), 912 (w), 807 (m), 754 (s), 745 (m), 680 (w), 634 (w).

[35] Not all the aromatic signals were resolved

HRMS(ESI) calcd for $C_{13}H_{14}NO_2^+$ (M+H) 216.1024, found 216.1025.

Table 3. Selective cyclization of acyclic carbamate 22.



Cyclopropane **21** (5-30 mg, 12-70 μmol) was dissolved on the indicated solvent (0.02 M). The indicated catalyst was added and the solution was stirred at rt during the indicated time. The reaction was quenched with a saturated solution of $NaHCO_3$, extracted with Et_2O (3x), dried over Na_2SO_4 and concentrated on reduced pressure.

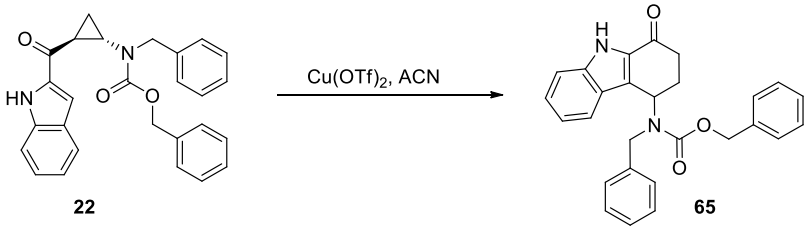
Scale of reactions with cyclopropane **22** is the following:

Entry 1: 22 (5 mg, 12 μmol).

Entry 2: 22 (30 mg, 71 μmol).

Entry 3: 22 (30 mg, 71 μmol).

Benzyl benzyl(1-oxo-2,3,4,9-tetrahydro-1H-carbazol-4-yl)carbamate (65)



$Cu(OTf)_2$ (4.7 mg, 13 μmol, 0.2 equiv) was added to a solution of indole **22** (28 mg, 66 μmol, 1.0 equiv) in distilled acetonitrile (3 mL). The reaction was stirred at rt during 10 min then quenched with a saturated aqueous solution of $NaHCO_3$ (3 mL), extracted with Et_2O (3 x 4 mL) dried over $MgSO_4$ and concentrated under reduced pressure. The crude product (70% by NMR estimation) was purified on flash chromatography (PET/AcOEt 8:2 on deactivated silica) affording **65** as a yellow oil with tendency to aromatize (12 mg, 28 μmol, 43%).

R_f 0.5 (AcOEt/PET 3:7).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (m, 1H; NH), 7.47-7.15 (m, 12H; ArH), 7.08 (m, 2H; ArH), 6.15 (m, 0.6H; CHN rotamer A), 5.83 (m, 0.4H; CHN rotamer B), 5.42-5.16 (m, 2H; OCH_2Ar),

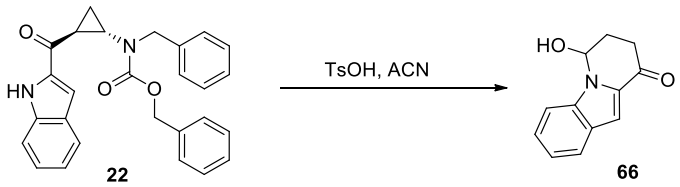
4.86 (m, 0.4H; CH_2Ar rotamer B), 4.77 (m, 0.6H; CH_2Ar rotamer A), 4.11 (m, 0.4H; CH_2Ar rotamer B), 4.00 (m, 0.6H; CH_2Ar rotamer A), 2.59 (m, 2H; $CNCH_2$), 2.25 (m, 2H; $COCH_2$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.9, 156.8, 139.0, 137.6, 136.4, 132.0, 128.5, 128.1, 127.2, 126.9, 126.4, 126.2, 125.0, 121.6, 121.5, 112.6, 67.7, 52.1, 47.4, 36.7, 30.8.[36]

IR ν (cm-1): 3324 (w), 3283 (w), 3274 (w), 3262 (w), 3250 (w), 3064 (w), 3033 (w), 2952 (w), 2937 (w), 1699 (s), 1660 (s), 1537 (m), 1471 (m), 1455 (m), 1454 (m), 1413 (m), 1364 (m), 1346 (m), 1332 (m), 1289 (m), 1252 (m), 1211 (m), 1114 (m), 1079 (w), 1048 (w), 1030 (w), 960 (w), 921 (w), 737 (s), 699 (s), 628 (m).

HRMS(ESI) calcd for $C_{27}H_{25}N_2O_3^+$ (M+H) 425.1865, found 425.1877.

6-Hydroxy-7,8-dihydropyrido[1,2-a]indol-9(6H)-one (66)



The reaction was performed following **GP4**, starting from cyclopropane **22** (28 mg, 66 μmol, 1.0 equiv) and tosic acid (2.5 mg, 13 μmol, 0.2 equiv). The reaction was quenched after 30 min. The crude product was purified on flash chromatography (PET/AcOEt 8:2 on deactivated silica) affording **66** as a yellow oil (10 mg, 50 μmol, 75%).

R_f 0.5 (AcOEt/PET 3:7).

^1H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, J = 8.1 Hz, 1H; ArH), 7.51 (m, 1H; ArH), 7.42 (m, 1H; ArH), 7.31 (s, 1H; ArH), 7.21 (m, 1H; ArH), 6.23 (t, J = 2.8 Hz, 1H; CH-OH), 3.10 (m, 1H; CH_2), 2.68 (m, 1H; CH_2), 2.41-2.59 (m, 2H; CH_2).

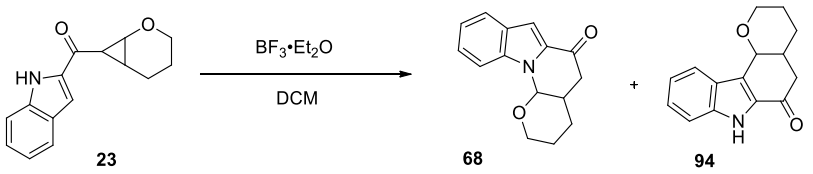
^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.1, 136.5, 132.4, 127.2, 126.4, 123.7, 121.8, 110.2, 107.3, 72.9, 31.6, 30.2.

IR ν (cm-1): 3348 (w), 3068 (w), 2958 (w), 1673 (s), 1530 (s), 1446 (m), 1404 (m), 1354 (m), 1328 (m), 1249 (m), 1207 (m), 1168 (m), 1141 (m), 1066 (m), 1026 (m), 955 (m), 910 (m), 814 (m), 742 (s), 701 (m), 673 (m)

[36] Not all the aromatic signals were resolved

HRMS(ESI) calcd for $C_{12}H_{12}NO_2^+$ (M+H) 202.0868, found 202.0862.

3,4,4a,5-Tetrahydro-2H-pyrano[3',2':5,6]pyrido[1,2-a]indol-6(12aH)-one (68)



23 68 94

BF_3•Et_2O (2.0 µL, 16 µmol, 0.20 equiv) was added to a solution of indole **23** (18 mg, 75 µmol, 1.0 equiv) in distilled DCM (5 mL). The reaction was stirred at rt during 15 min then quenched with a saturated aqueous solution of $NaHCO_3$ (3 mL), extracted with Et_2O (3 x 4 mL) dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified on flash chromatography (PET/AcOEt 7:3) to afford **68** and its regioisomer **95** (as pink oil (14 mg, 58 µmol, 65% **68** and 14% **95**). The pure **68** was obtained resubmitting the mixture of regioisomers to stoichiometric amount of BF_3•Et_2O during 24 hours.

68

R_f 0.3 (AcOEt/PET 3:7).

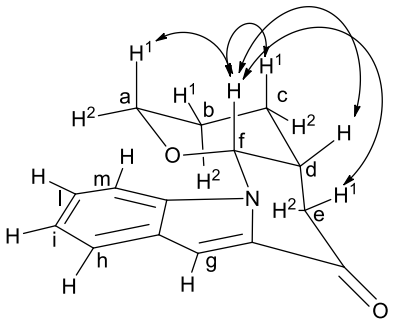
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (dt, *J* = 8.1, 0.9 Hz, 1H; ArH), 7.51 (dd, *J* = 8.4, 0.8 Hz, 1H; ArH), 7.41 (m, 1H; ArH), 7.32 (m, 1H; ArH), 7.20 (m, 1H; ArH), 5.72 (d, *J* = 2.7 Hz, 1H; H_f), 4.04 (m, 1H; H_a^2), 3.82 (m, 1H; H_a^1), 3.16 (dd, *J* = 16.5, 12.4 Hz, 1H; H_e^1), 2.62 (m, 1H, H_d), 2.53 (m, 1 H dd, *J* = 16.5, 4.1 Hz, 1H; H_e^2), 2.08 (m, 1H; H_b^1), 1.89 (m, 2H; H_c^{1-2}), 1.58 (m, 1H; H_b^2).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.1, 137.1, 132.4, 127.3, 126.3, 123.5, 121.8, 110.9, 106.9, 80.3, 66.8, 37.7, 33.9, 27.3, 20.4.

IR ν (cm-1): 3297 (w), 2852 (w), 1678 (s), 1619 (w), 1593 (w), 1532 (s), 1485 (m), 1449 (m), 1383 (m), 1367 (m), 1342 (m), 1325 (s), 1248 (m), 1223 (m), 1211 (m), 1184 (m), 1170 (m), 1146 (m), 1090 (m), 1068 (m), 1047 (s), 994 (w), 938 (m), 919 (m), 905 (m), 904 (m), 821 (m), 808 (m), 754 (s), 636 (s), 627 (m).

HRMS(ESI) calcd for $C_{15}H_{16}NO_2^+$ (M+H) 242.1176, found 242.1182.

Important correlations ROESY: H_f-H_d, H_f-H_c^1, H_f-H_b^1, H_f-H_e^1 (see 2D spectra in section 6)



8 Computational data

Cartesian coordinates for 57-60

57

56

scf done: -1303.604044

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58

56

scf done: -1303.593543

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59

56

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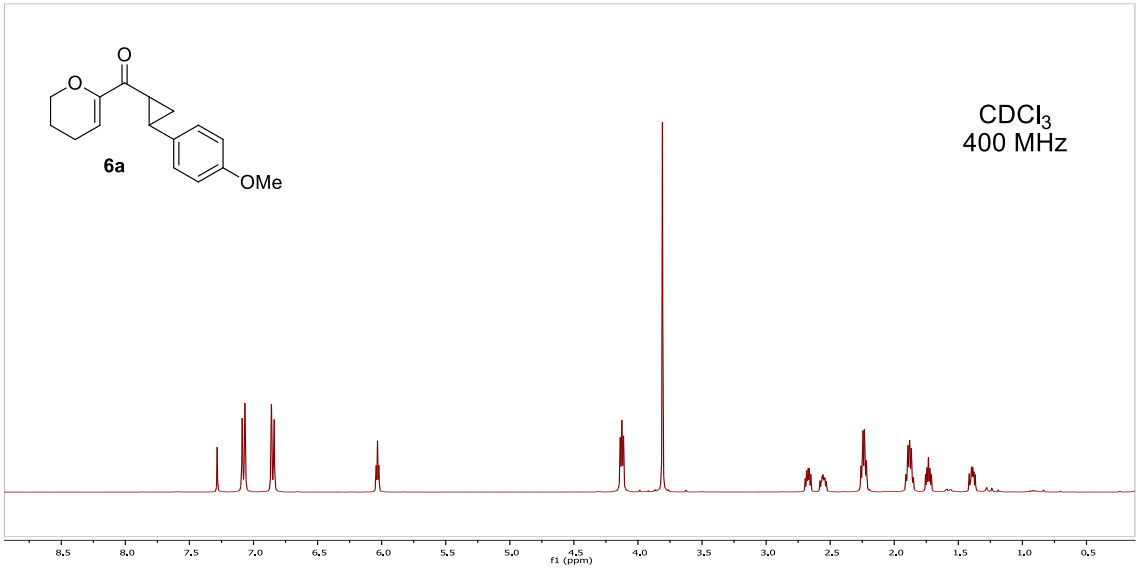
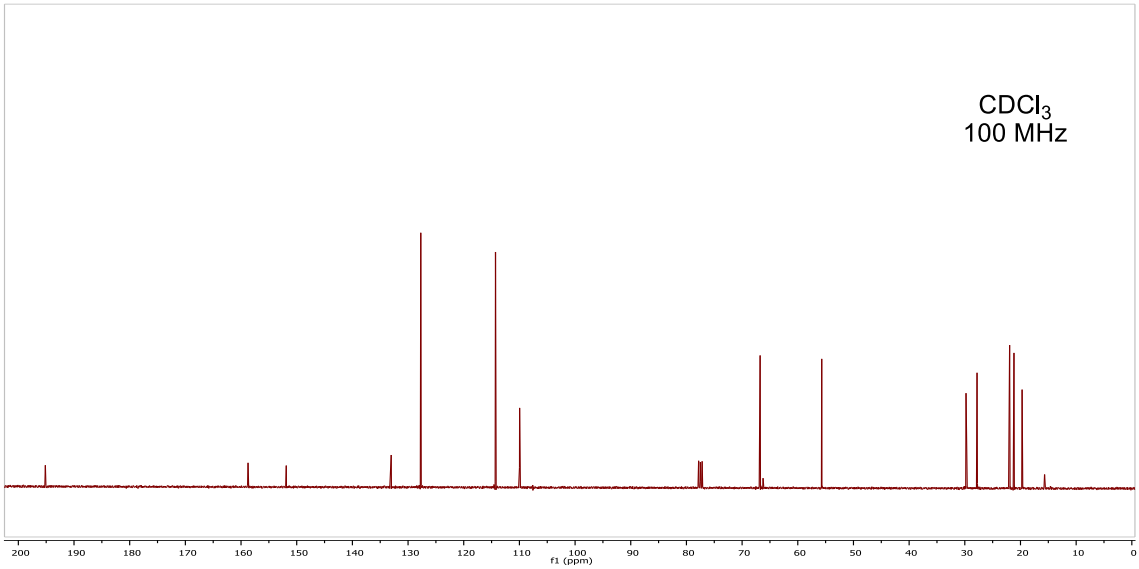
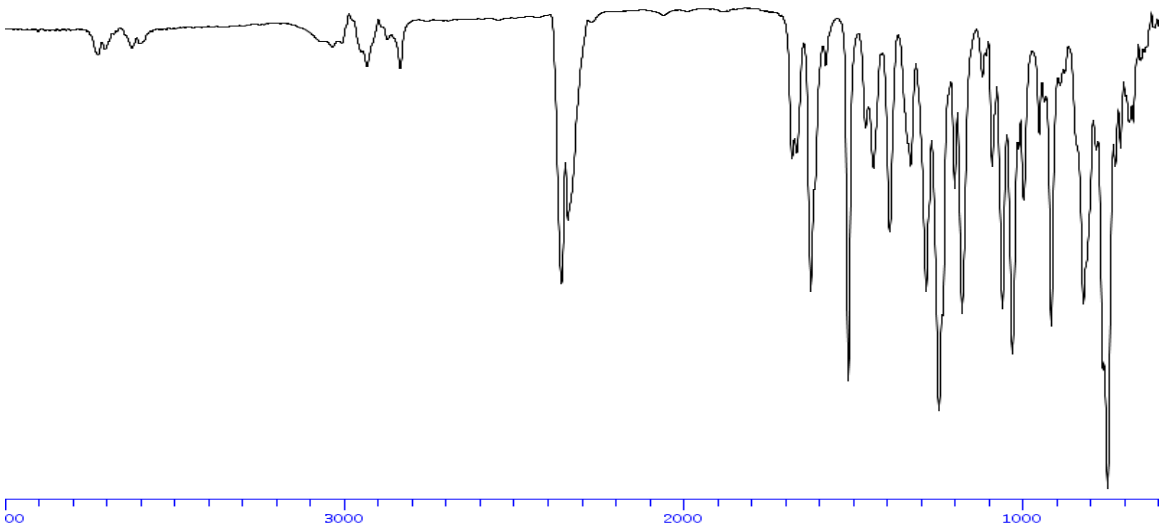
9 Spectra of new compounds







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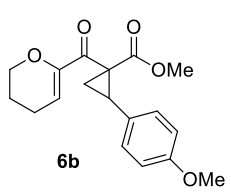

6b

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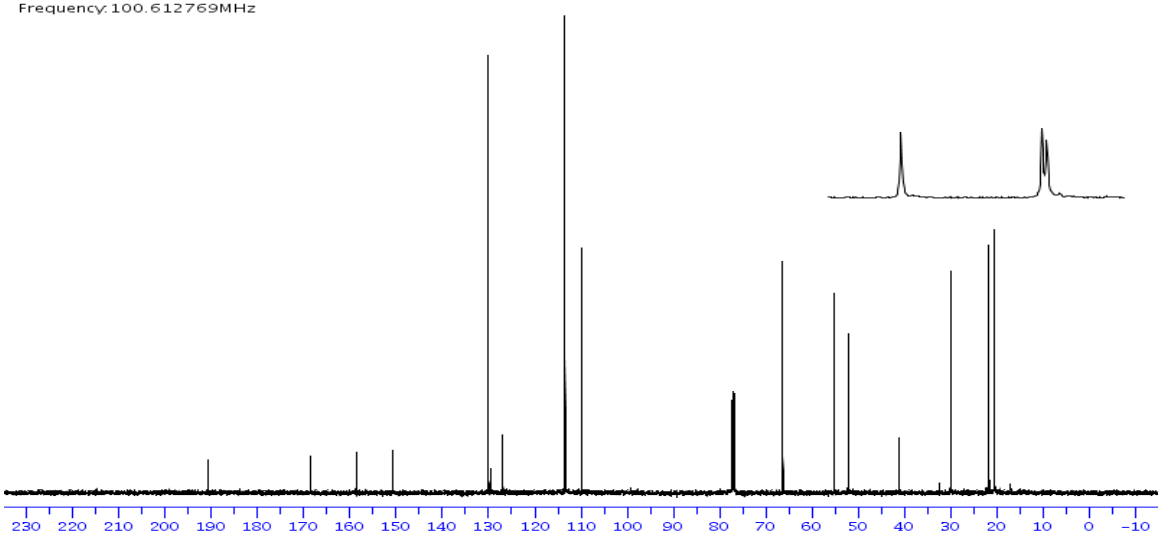

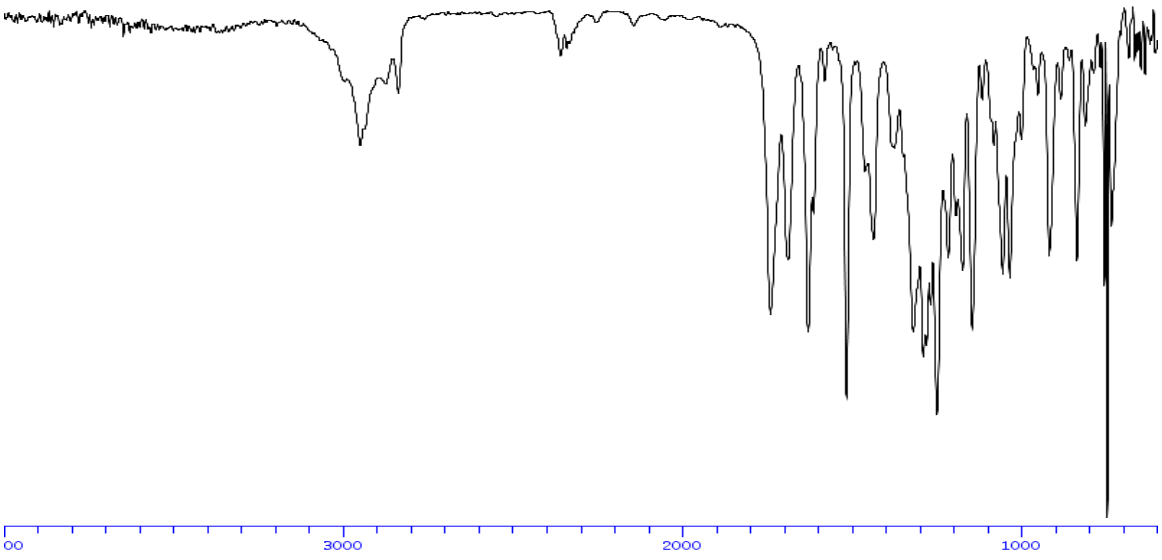

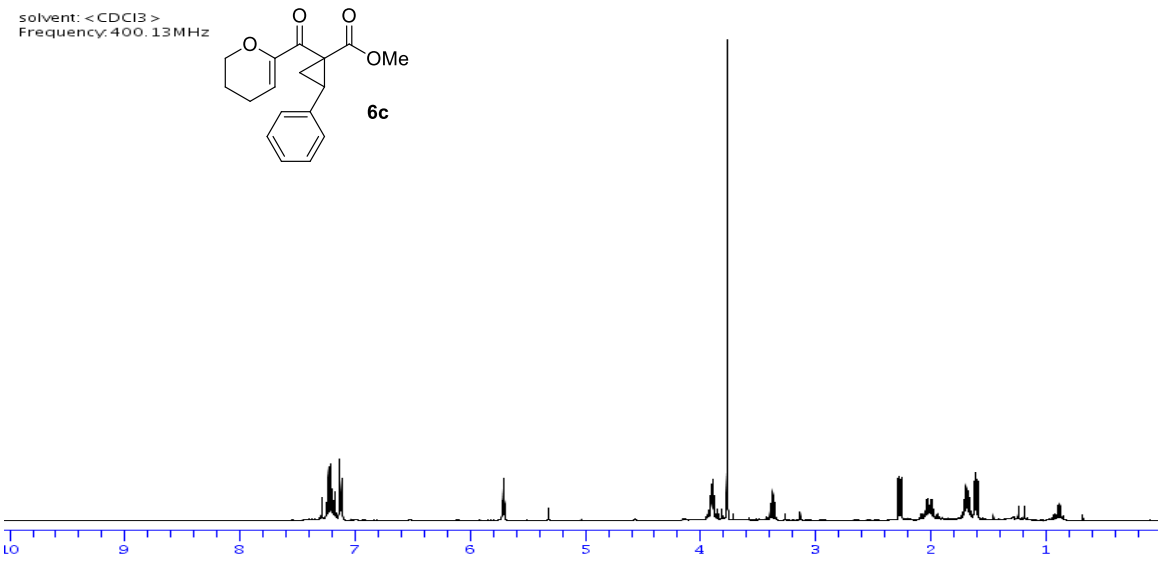
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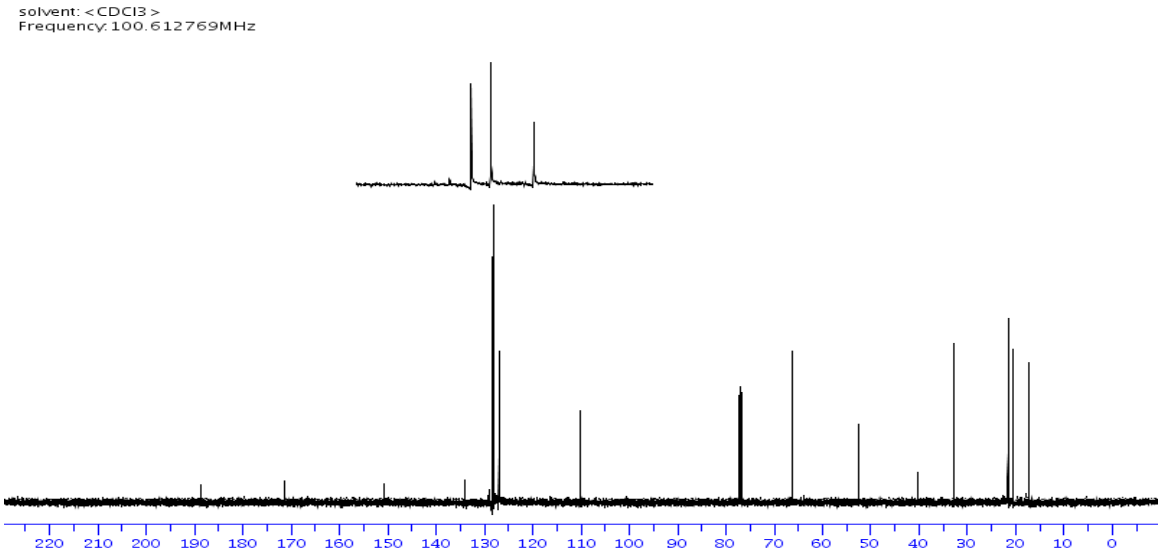
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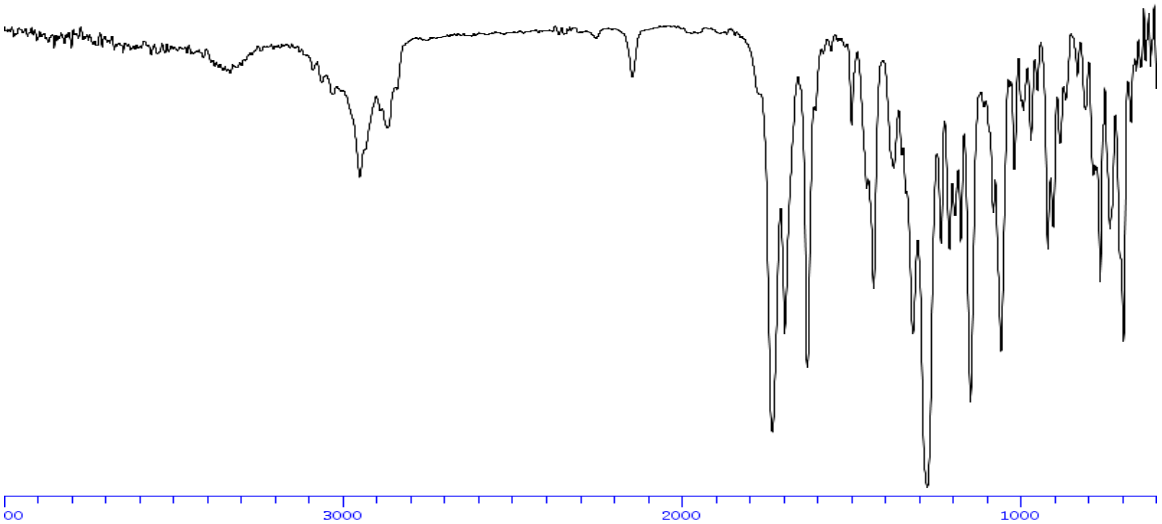
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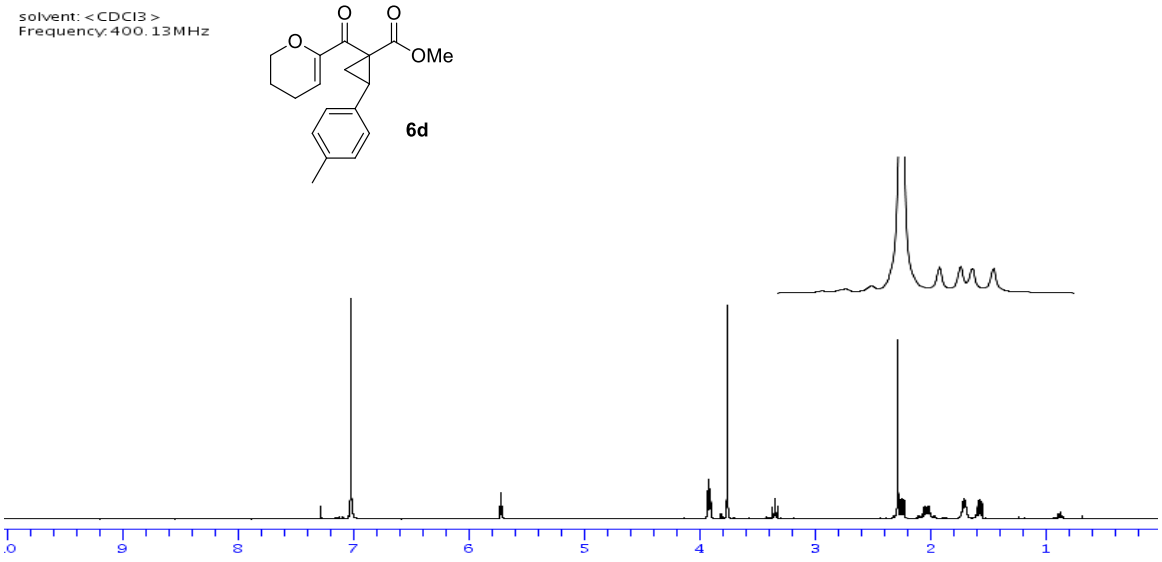
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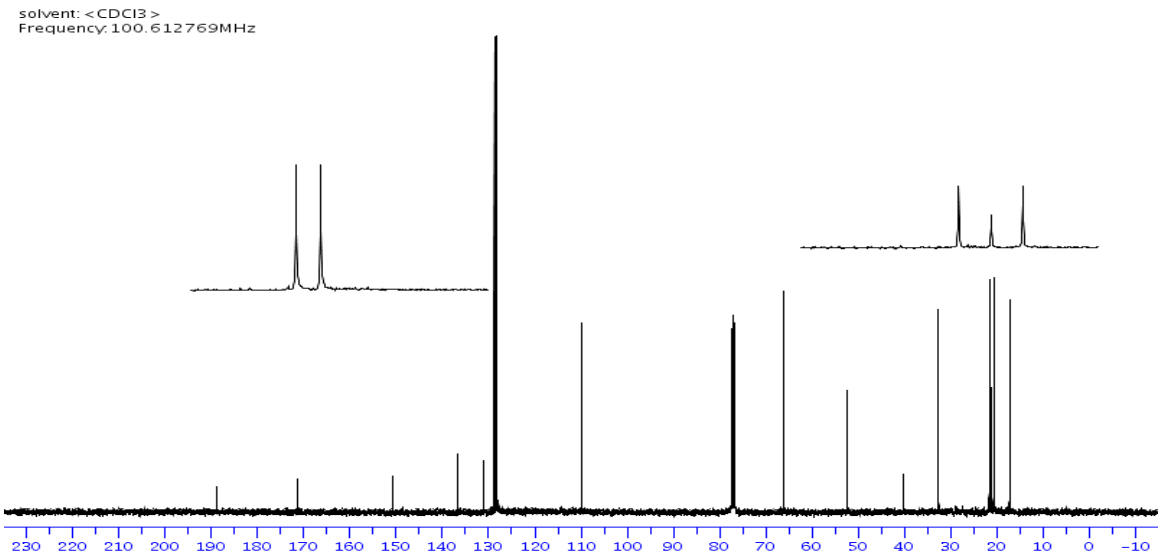
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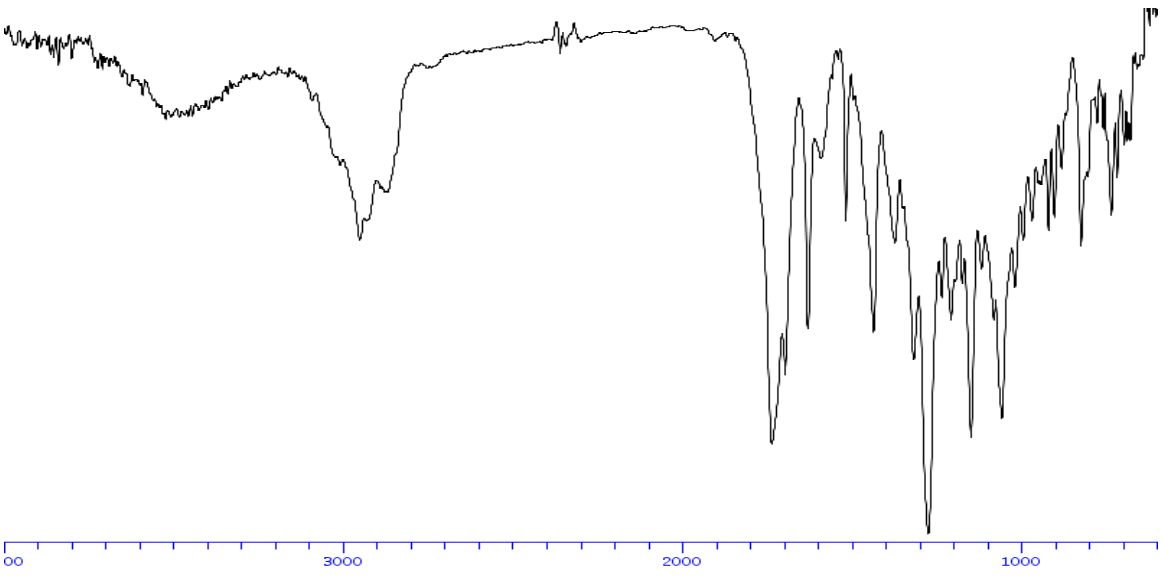
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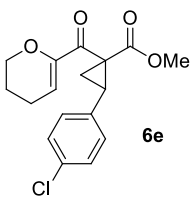
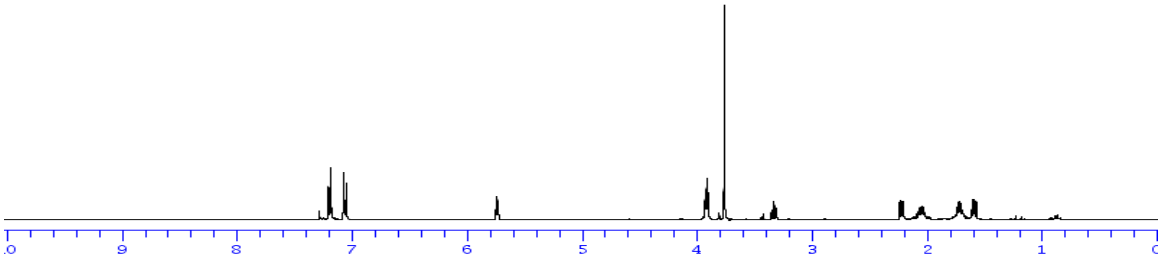
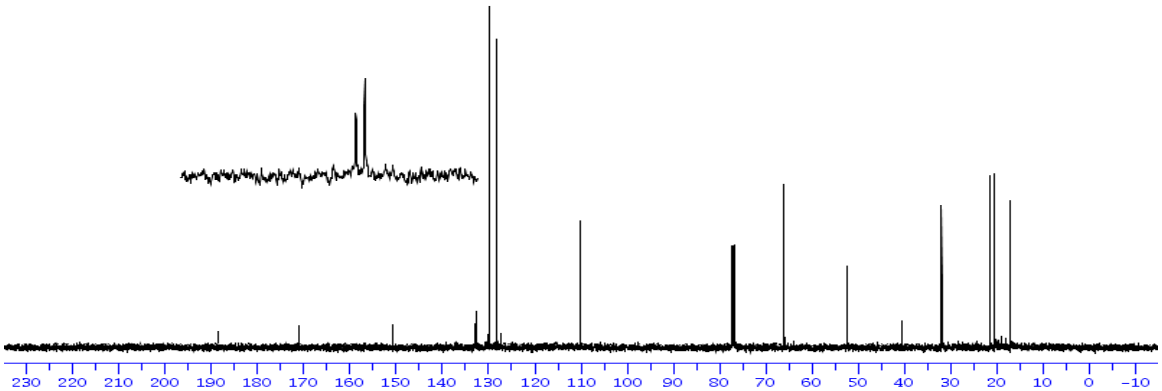
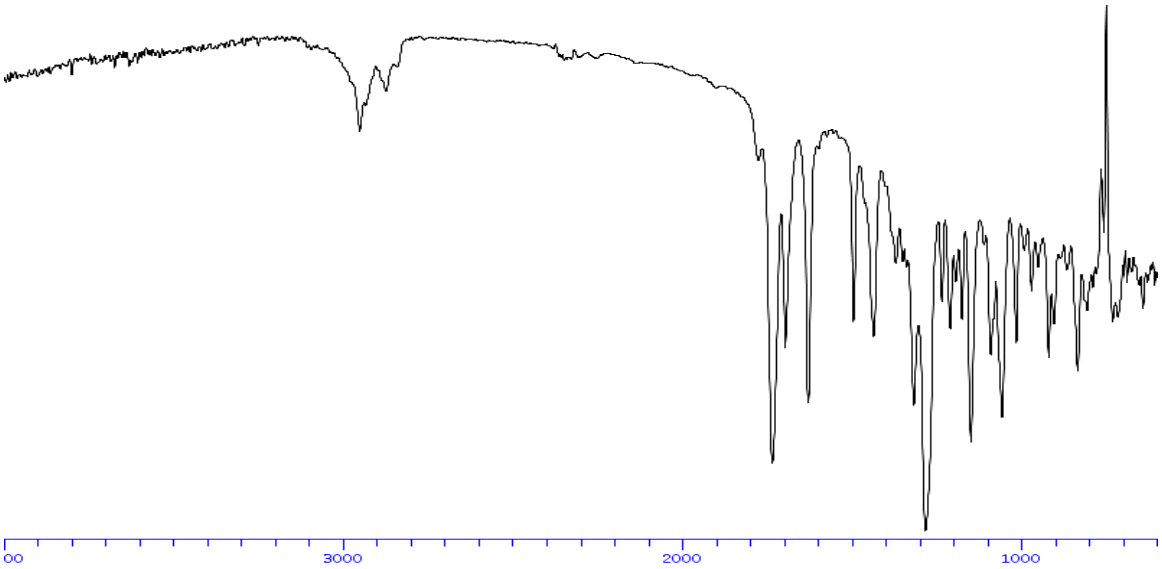


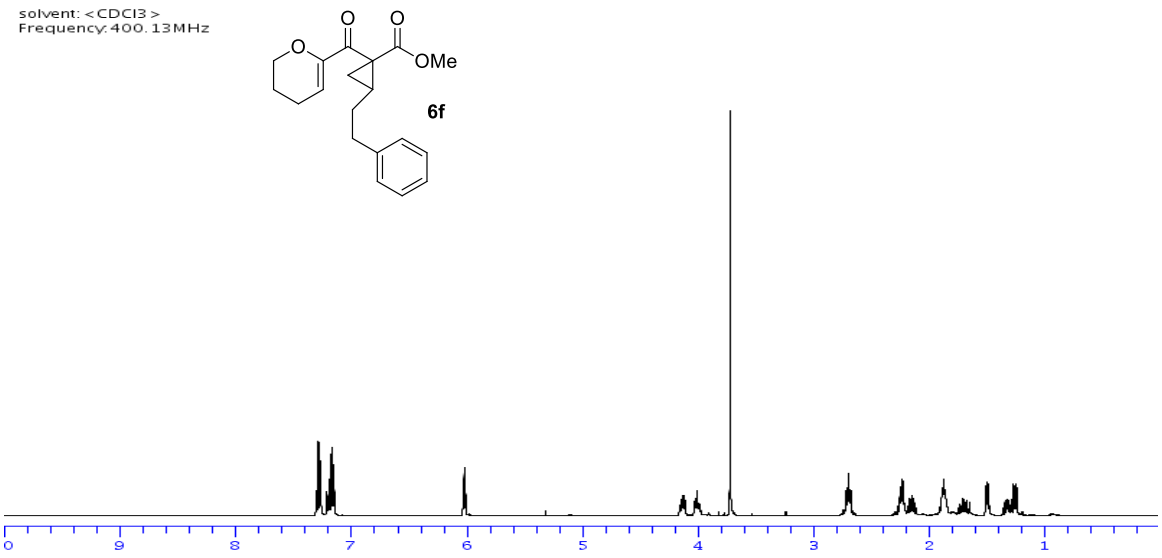
6e

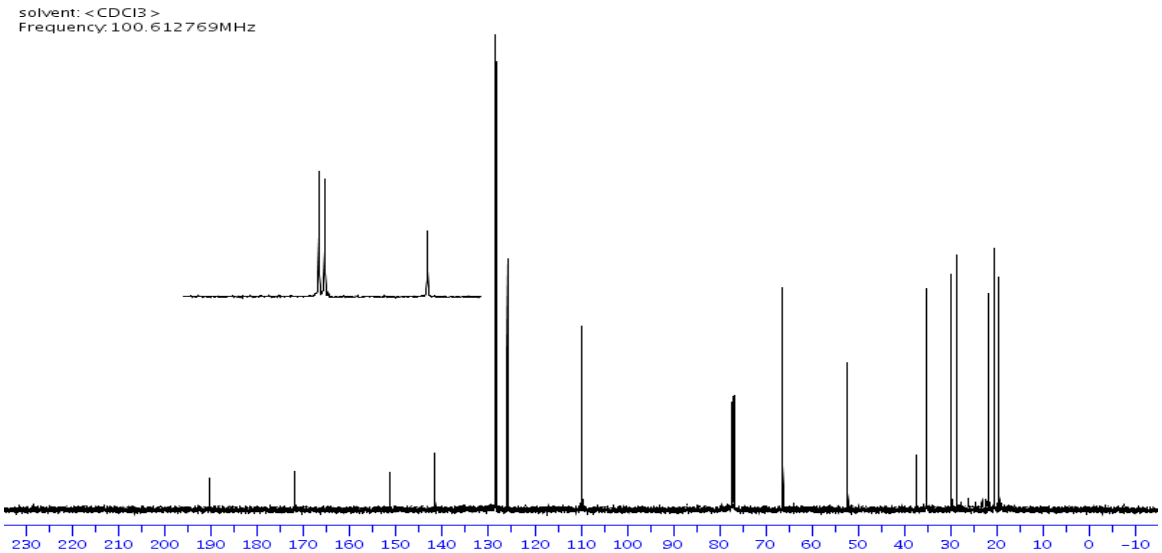


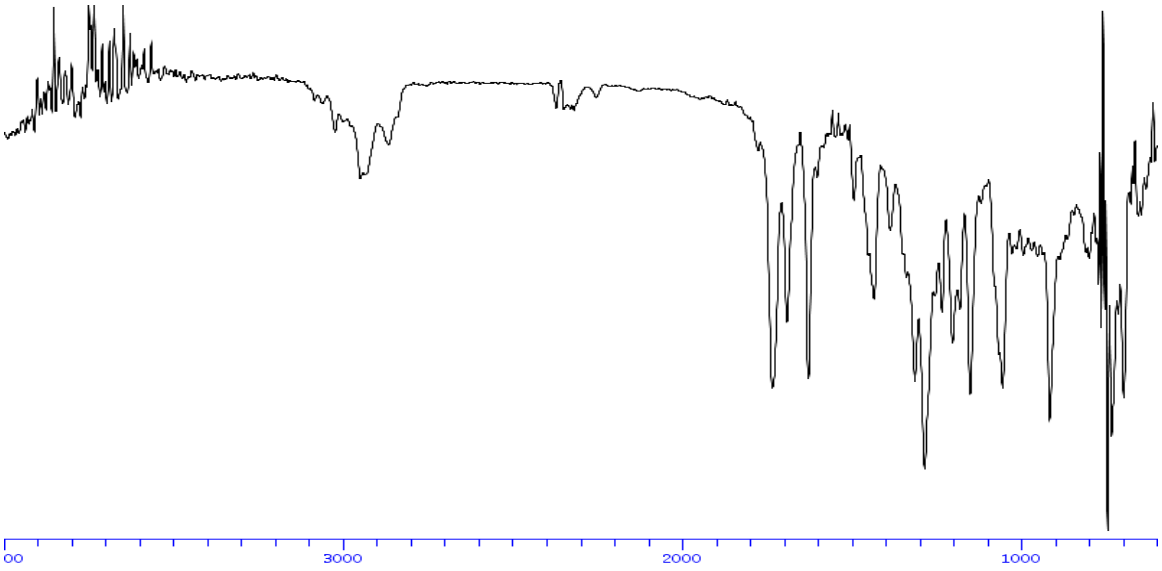
solvent: <CDCl3>
Frequency: 100.612769MHz

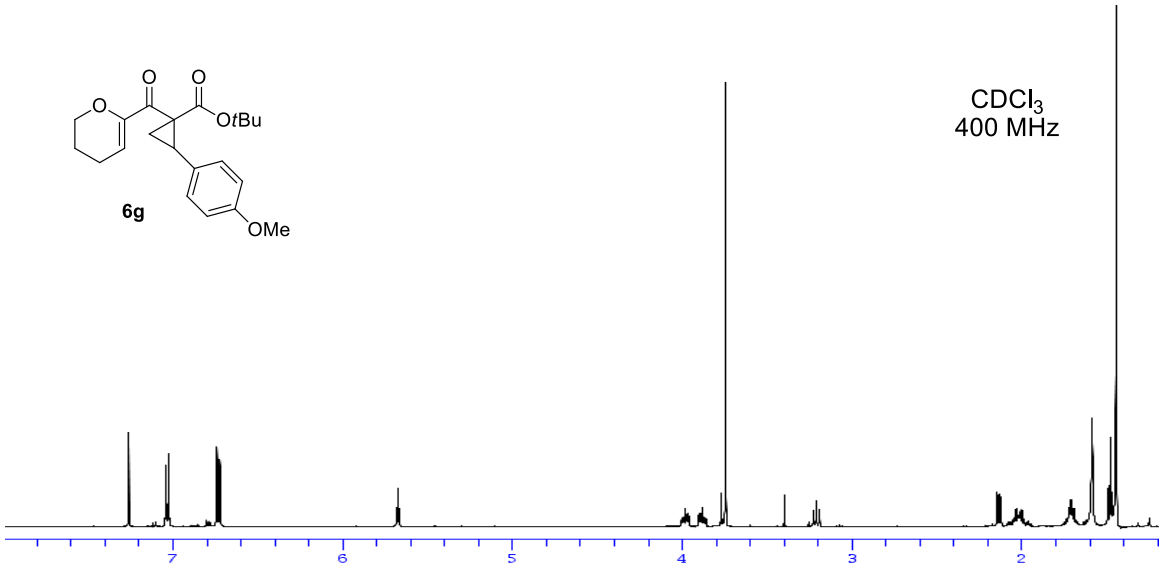


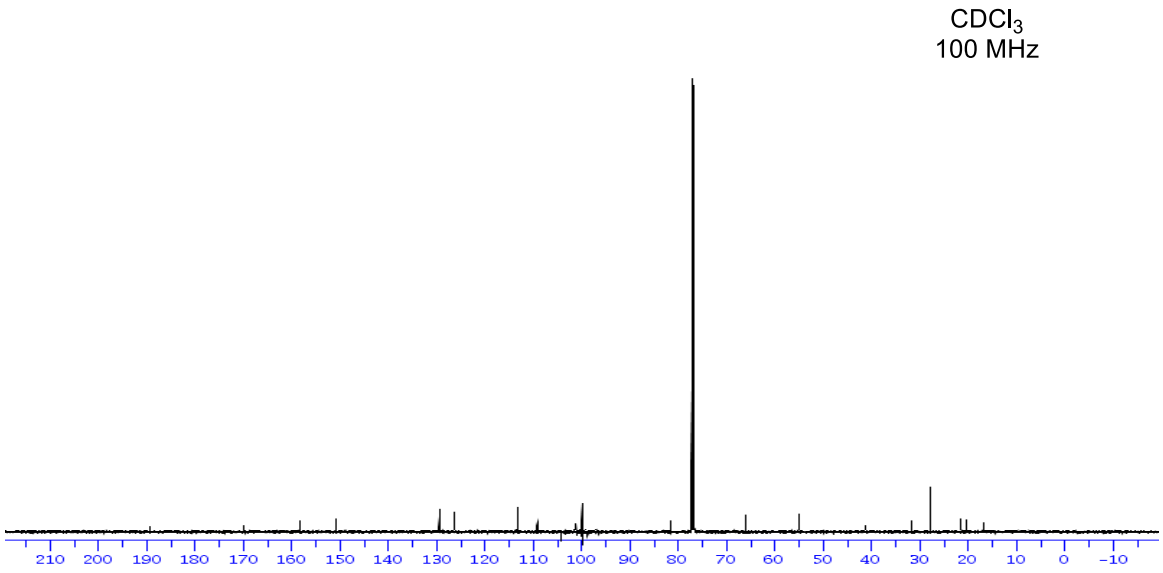


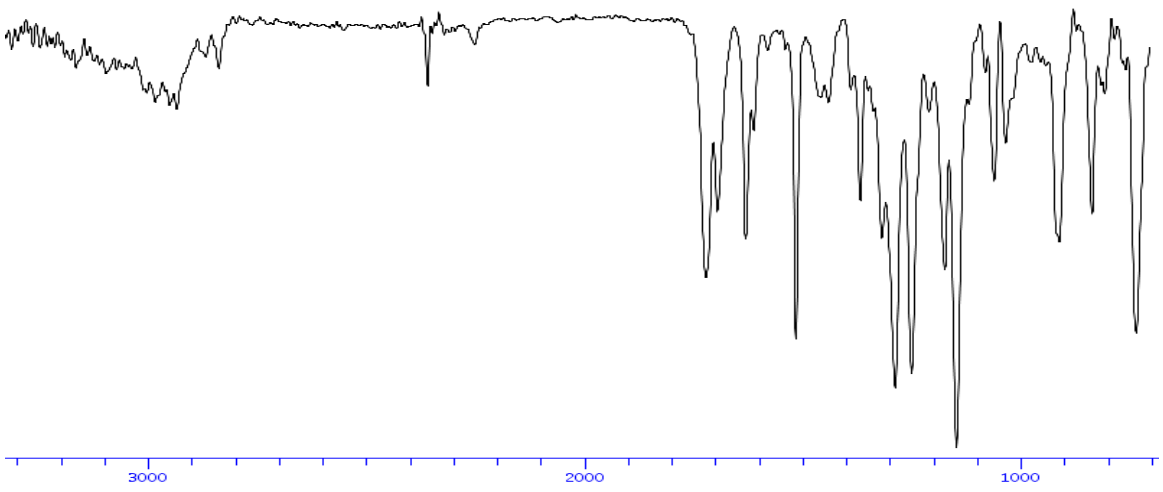

solvent: <CDCl3>
Frequency: 400.13MHz
O
O
O
OMe
6f
0
9
8
7
6
5
4
3
2
1

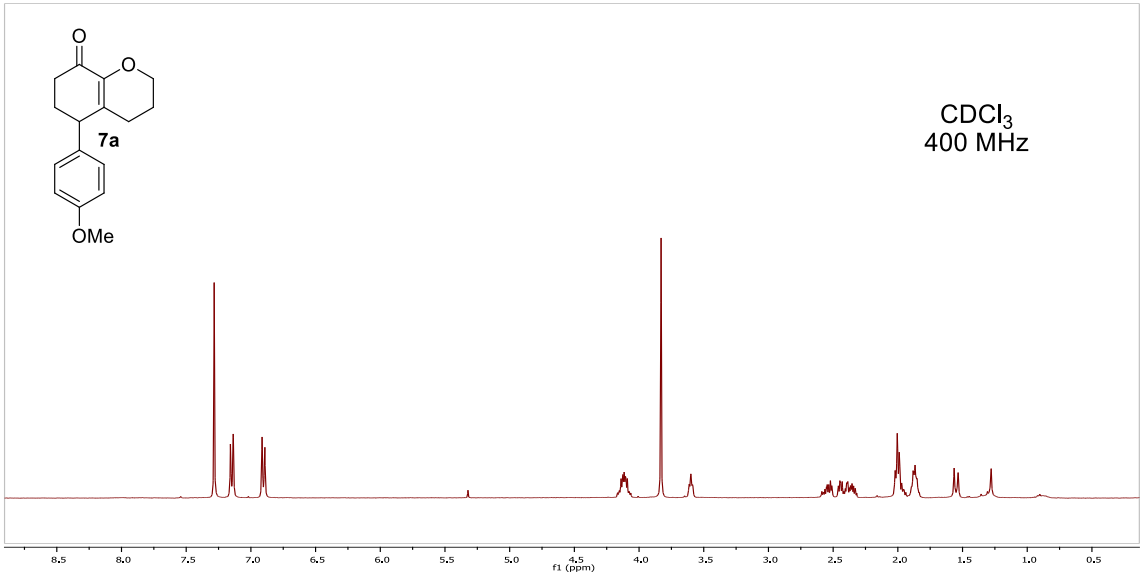

solvent: <CDCl3>
Frequency: 100.612769MHz
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

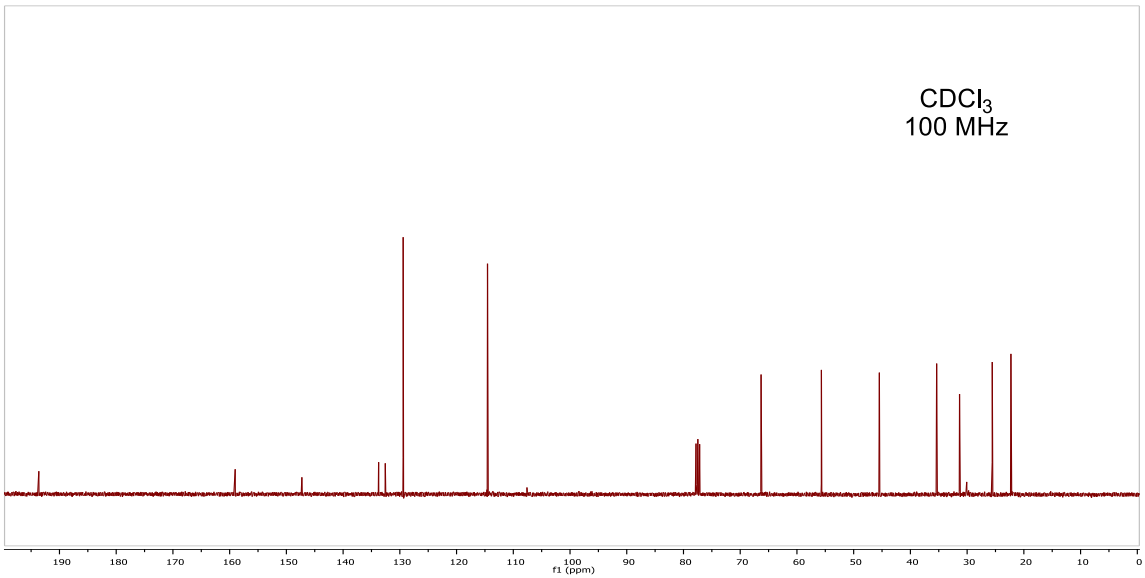

00
3000
2000
1000

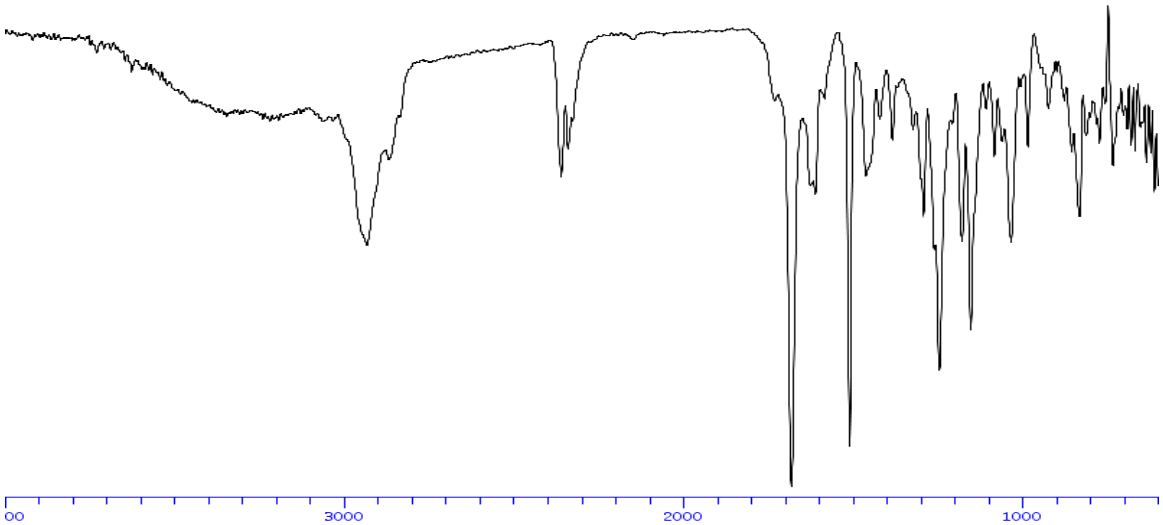

O
O
O
OtBu
6g
OMe
CDCl3
400 MHz
7
6
5
4
3
2


CDCl3
100 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

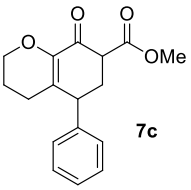

3000
2000
1000


O
O
7a
OMe
CDCl3
400 MHz
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

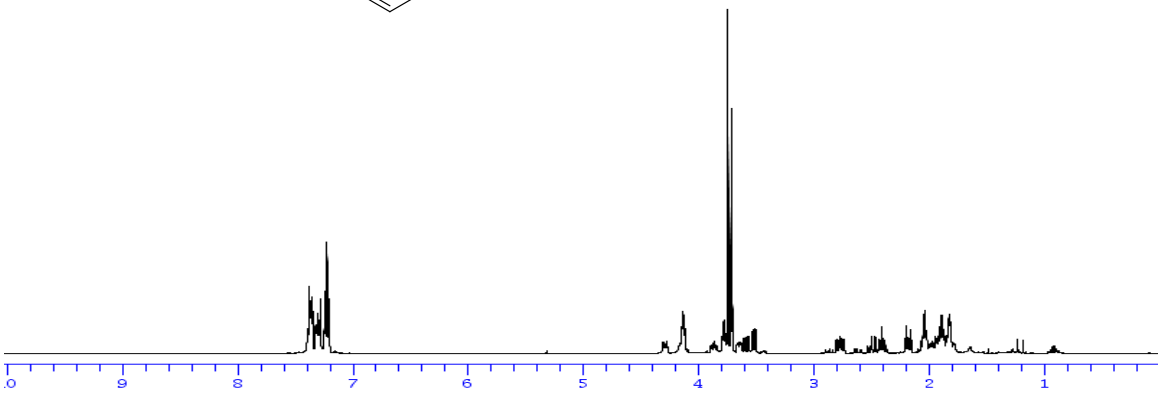

CDCl3
100 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


00
3000
2000
1000

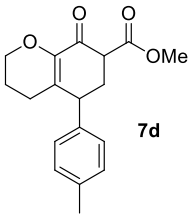
solvent: <CDCl3>
Frequency: 400.13MHz



7c

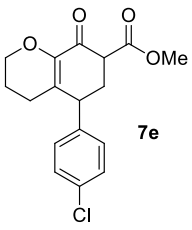


solvent: <CDCl3>
Frequency: 400.13MHz

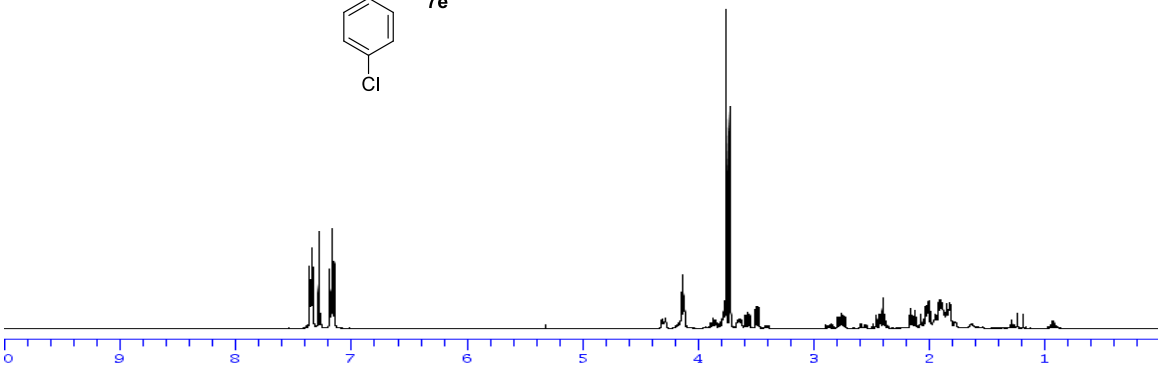


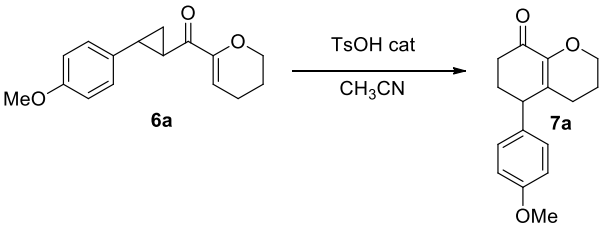
7d

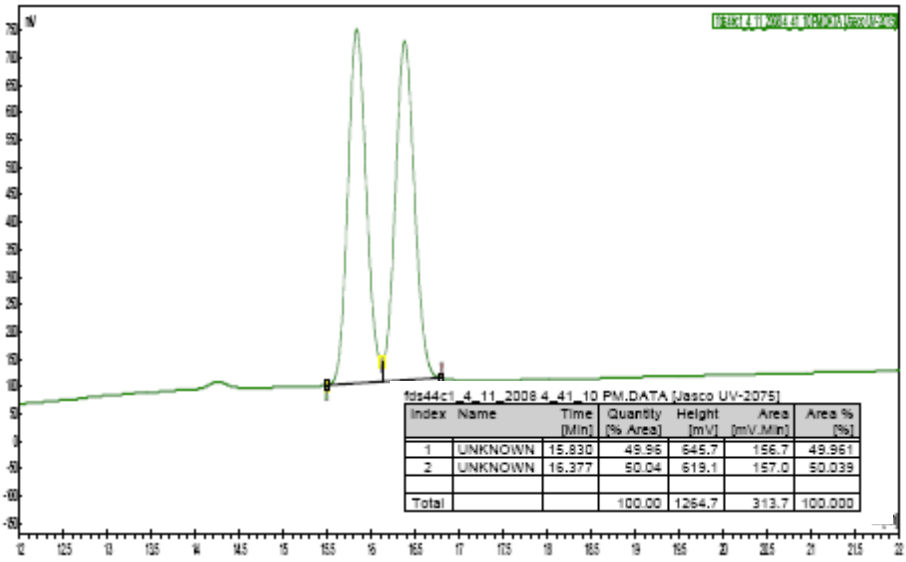
solvent: <CDCl3>
Frequency: 400.13MHz



7e

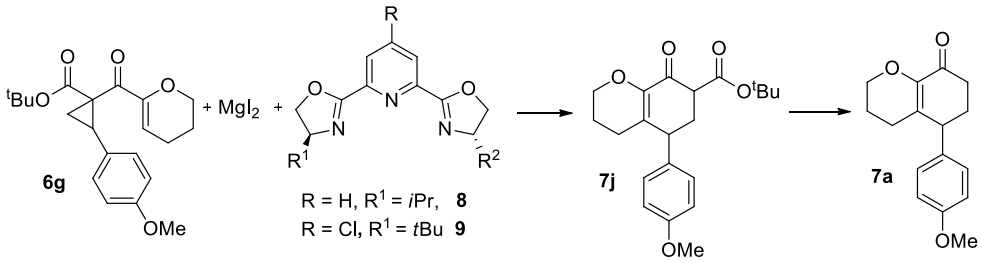


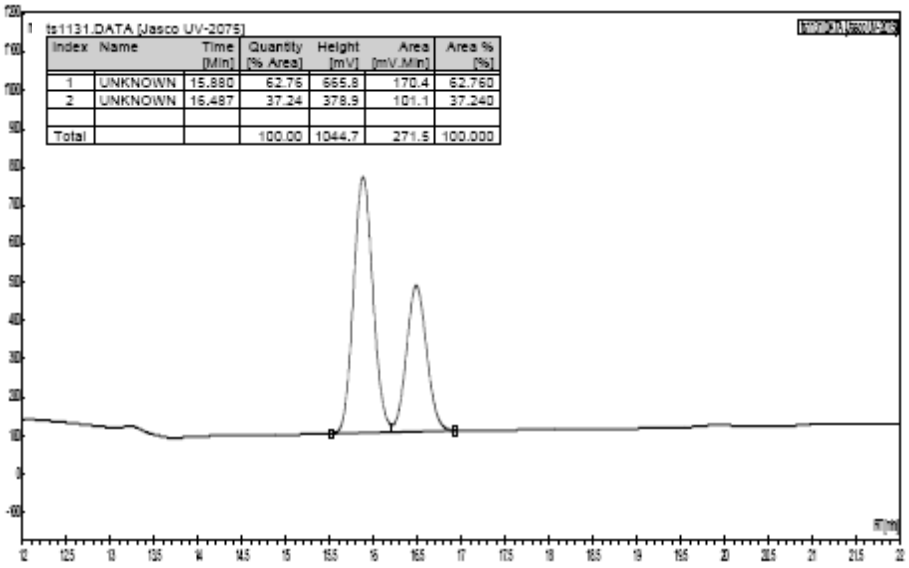




fds44c1_4_11_2008 4_41_10 PM.DATA [Jasco UV-2075]

Index	Name	Time [Min]	Quantity [% Area]	Height [mV]	Area [mV.Min]	Area % [%]
1	UNKNOWN	15.830	49.96	645.7	156.7	49.961
2	UNKNOWN	16.377	50.04	619.1	157.0	50.039
Total			100.00	1264.7	313.7	100.000





ts1131.DATA [Jasco UV-2075]

Index	Name	Time [Min]	Quantity [% Area]	Height [mV]	Area [mV.Min]	Area % [%]
1	UNKNOWN	15.880	62.76	665.8	170.4	62.760
2	UNKNOWN	16.487	37.24	378.9	101.1	37.240
Total			100.00	1044.7	271.5	100.000

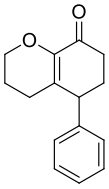
Acquisition time: 30 min

Flow: 0.8 mL/min

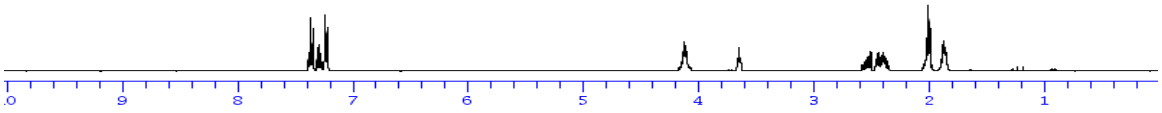
Wavelength: 254 nm

Time (min)	AcOEt (%)	Hexane (%)
0	30	70
8	50	50
20	60	40
30	100	0

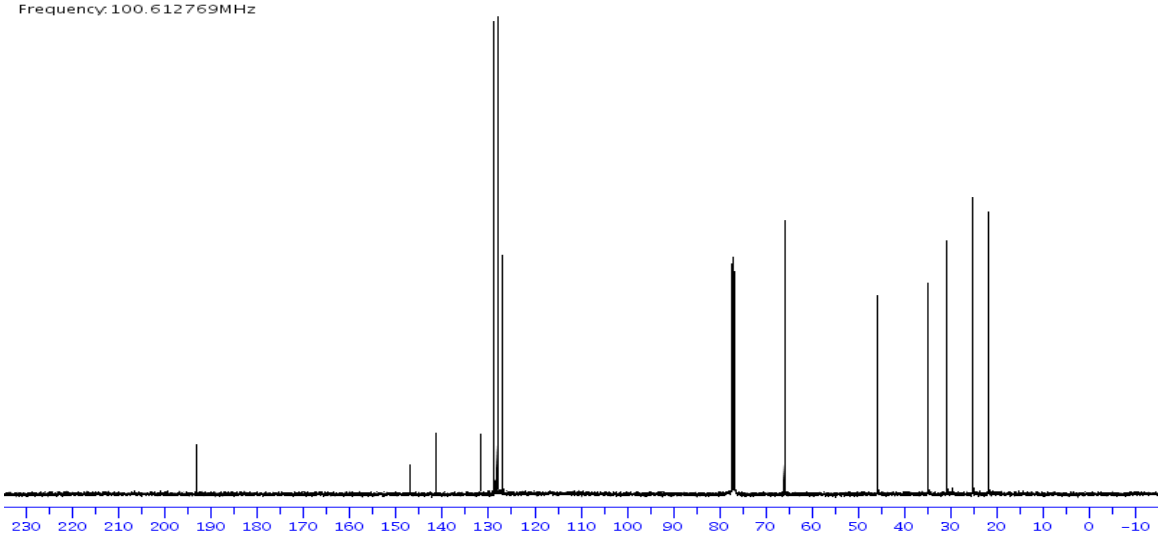
solvent: <CDCl3>
Frequency: 400.13MHz

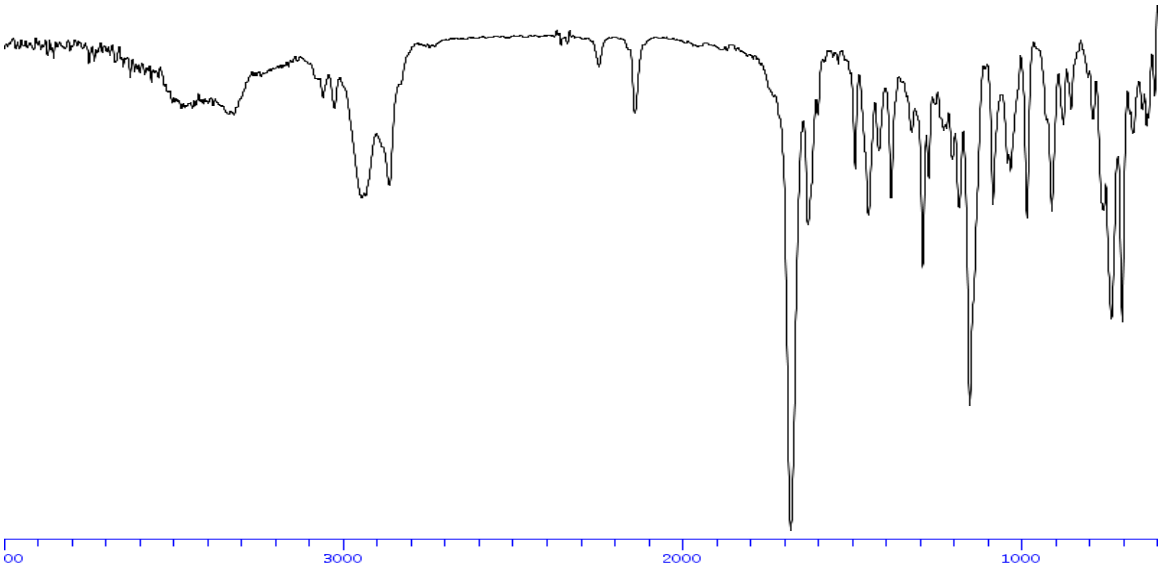


7f

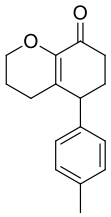


solvent: <CDCl3>
Frequency: 100.612769MHz

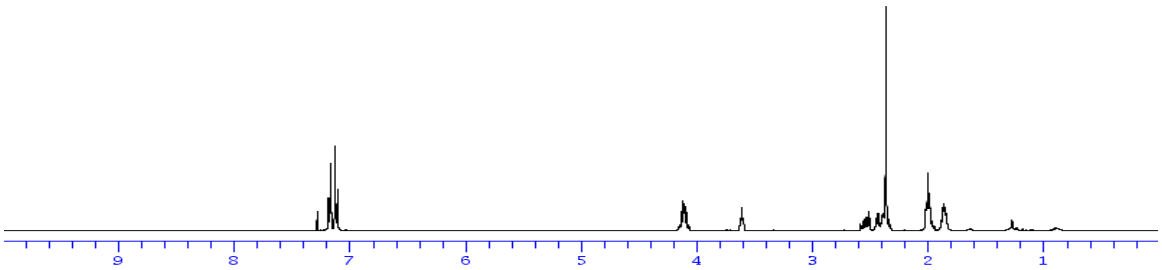




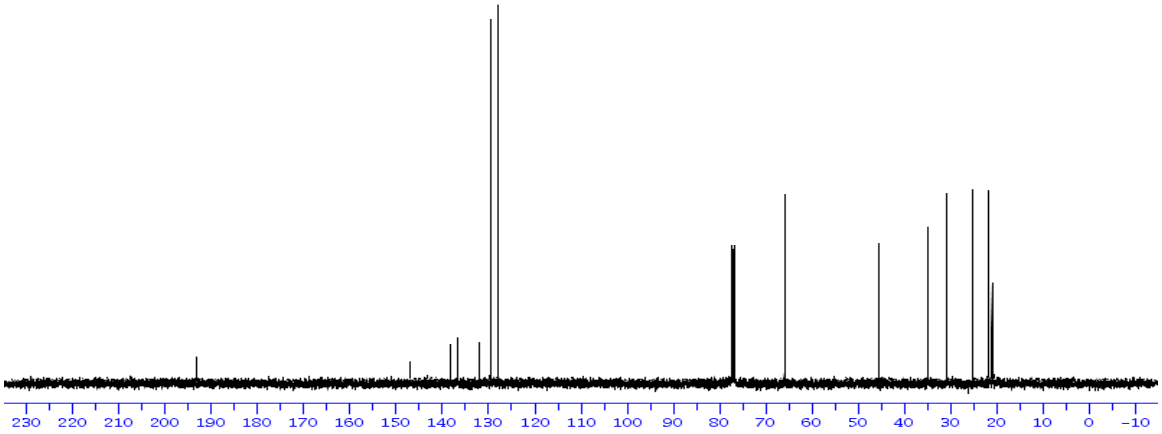
solvent: <CDCl3>
Frequency: 400.13MHz

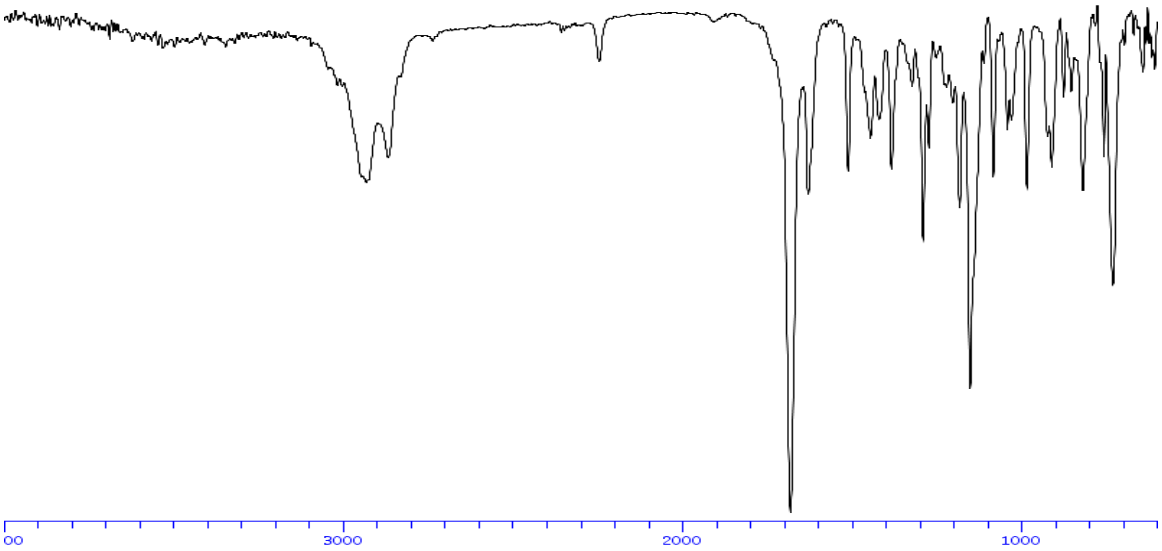


7g

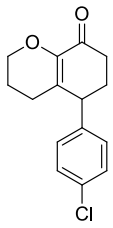


solvent: <CDCl3>
Frequency: 100.612769MHz

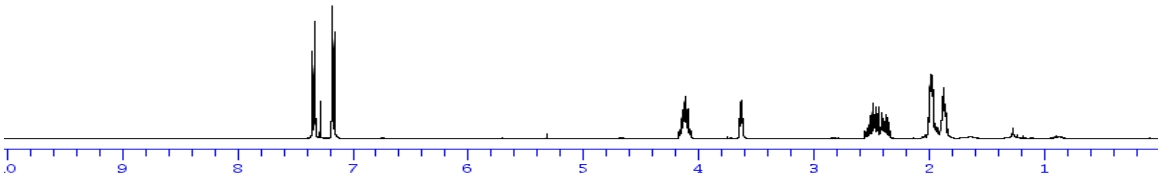




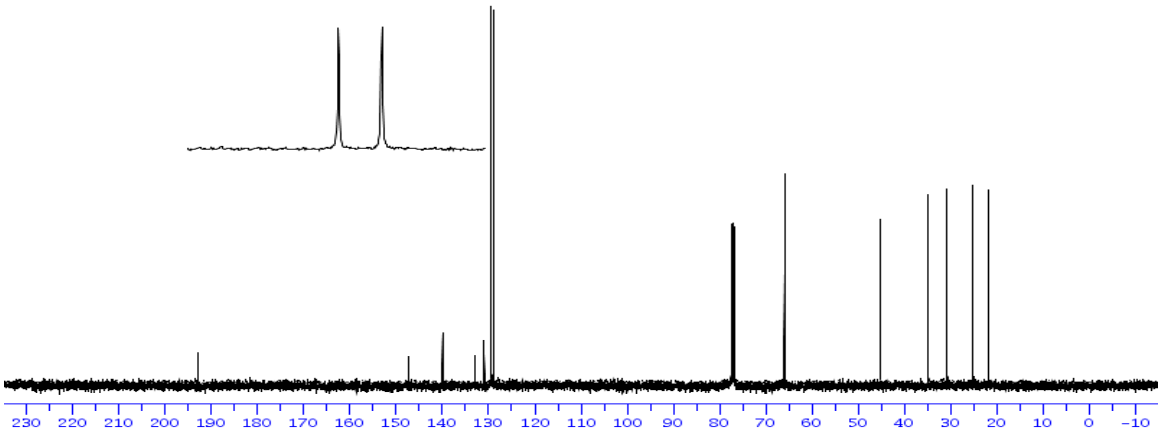
solvent: <CDCl3>
Frequency: 400.13MHz

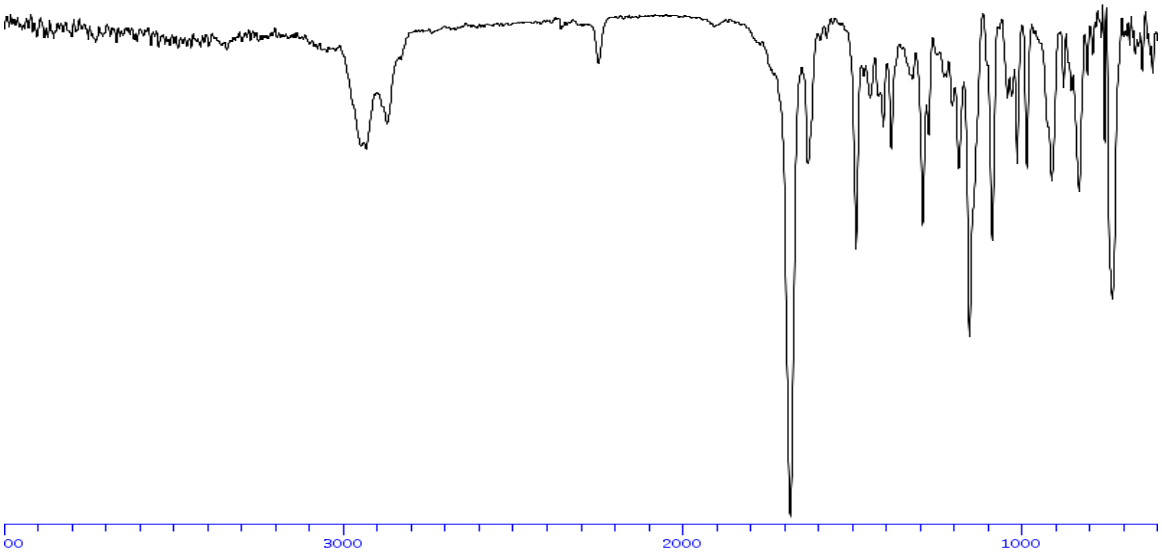


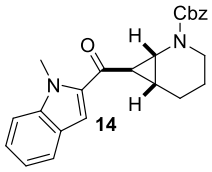
7h



solvent: <CDCl3>
Frequency: 100.612769MHz



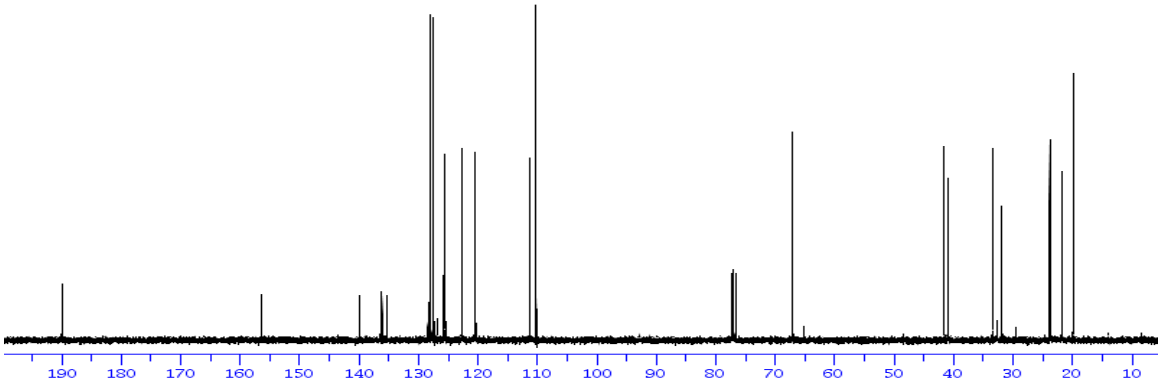


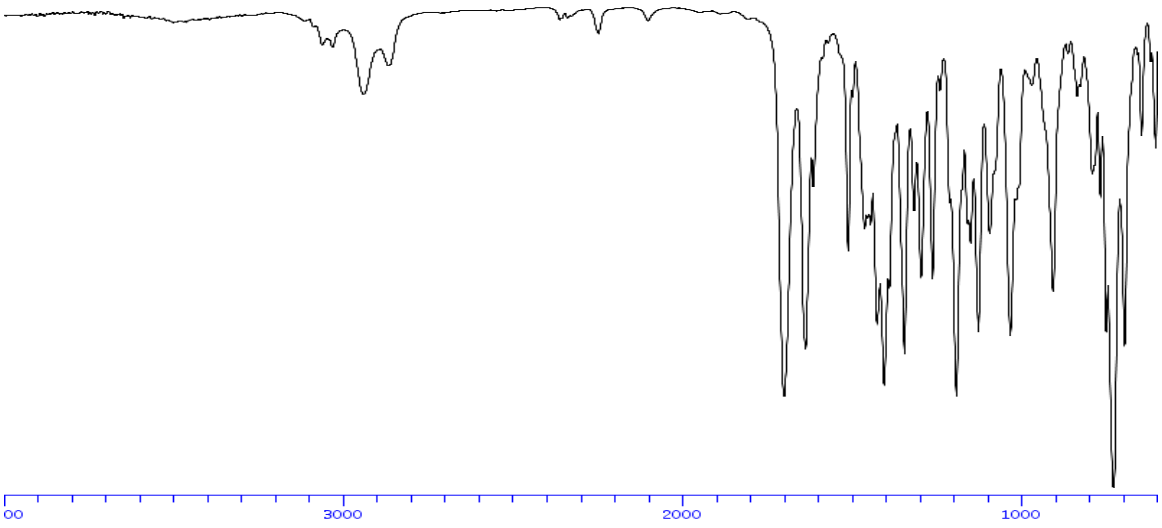


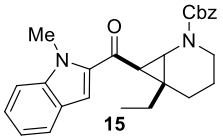
14

$CDCl_3$
400 MHz

$CDCl_3$
100 MHz

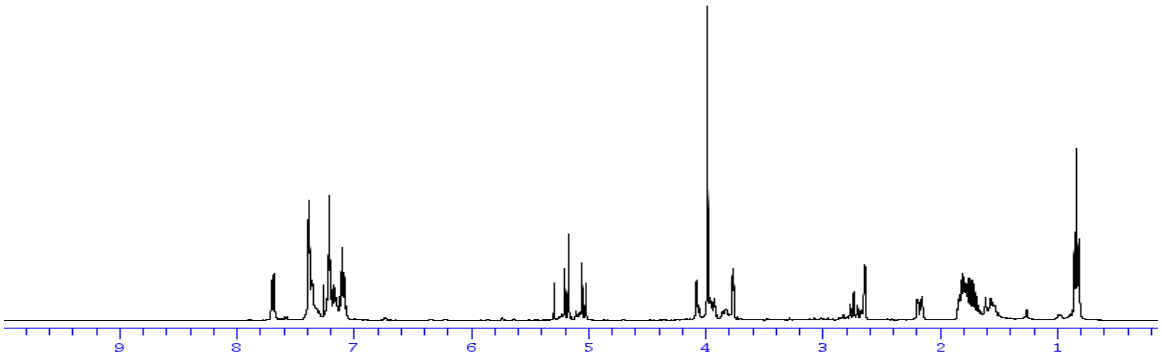




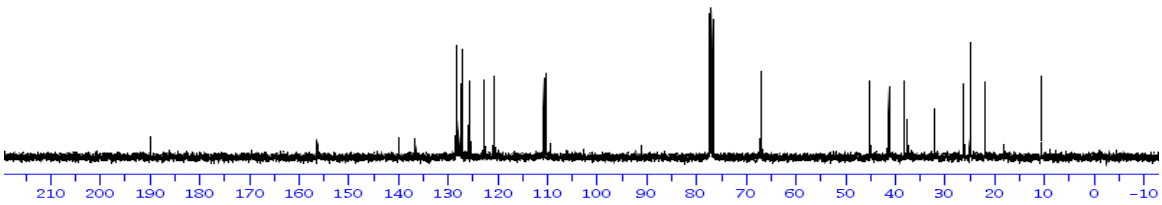


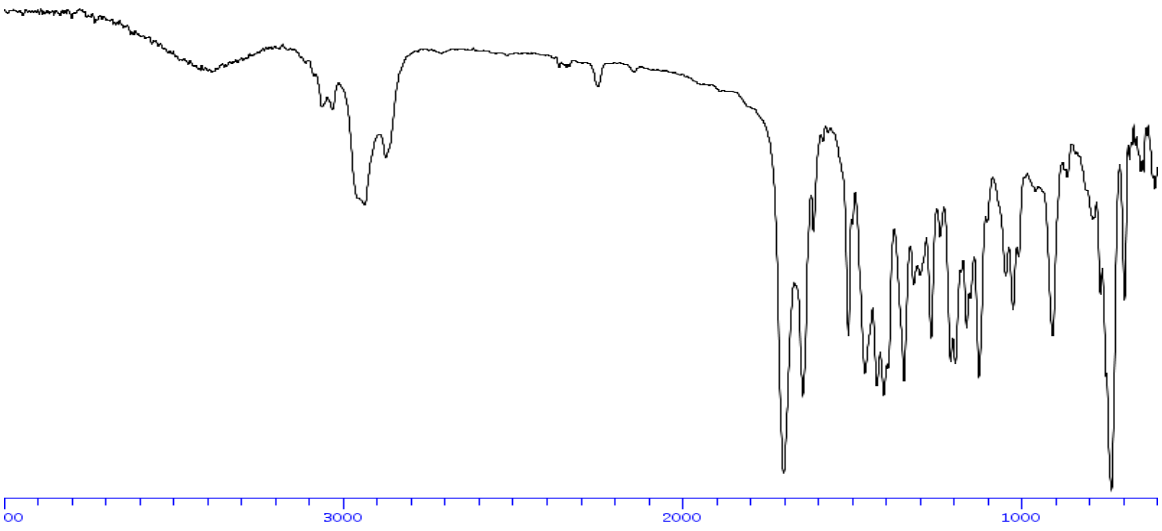
15

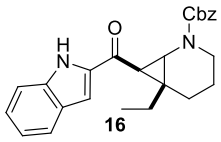
$CDCl_3$
400 MHz



$CDCl_3$
100 MHz

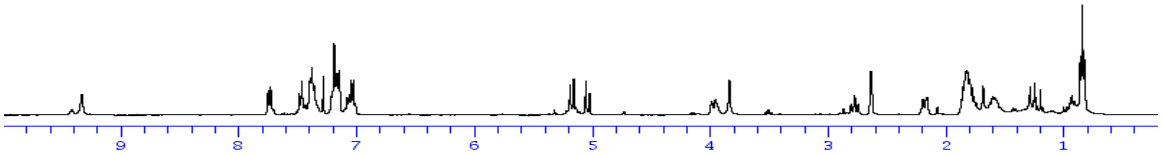




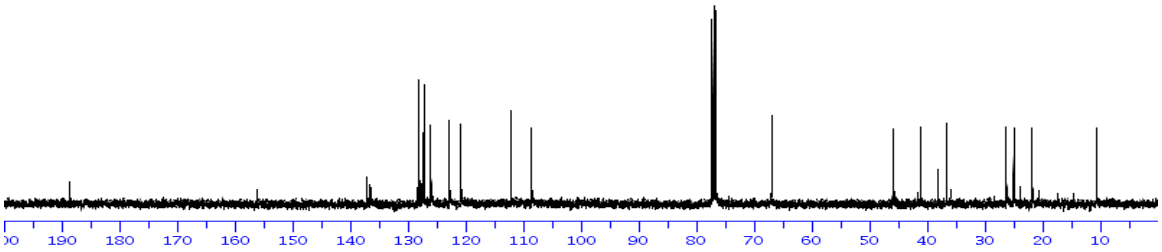


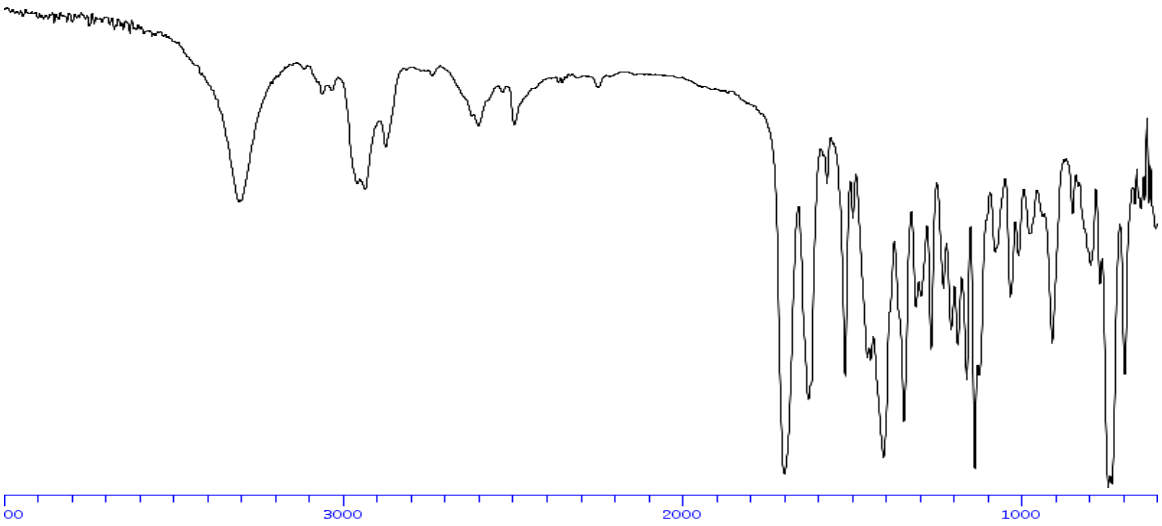
16

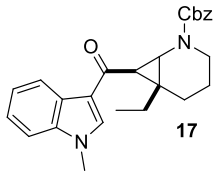
$CDCl_3$
400 MHz



$CDCl_3$
100 MHz



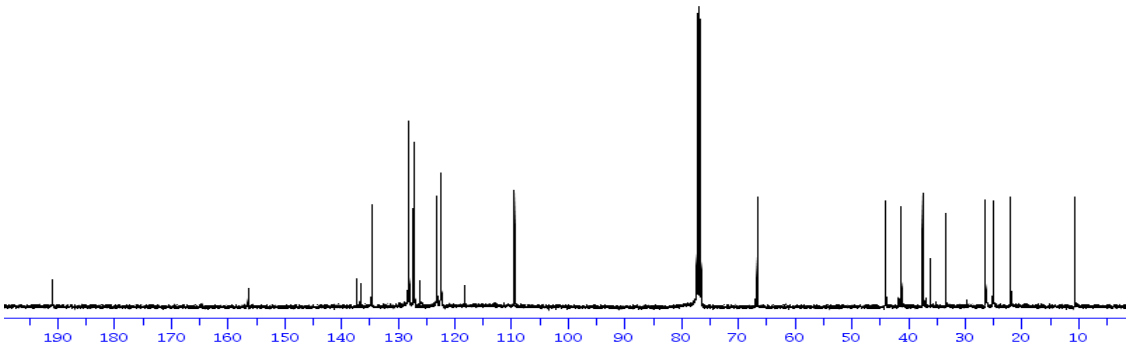


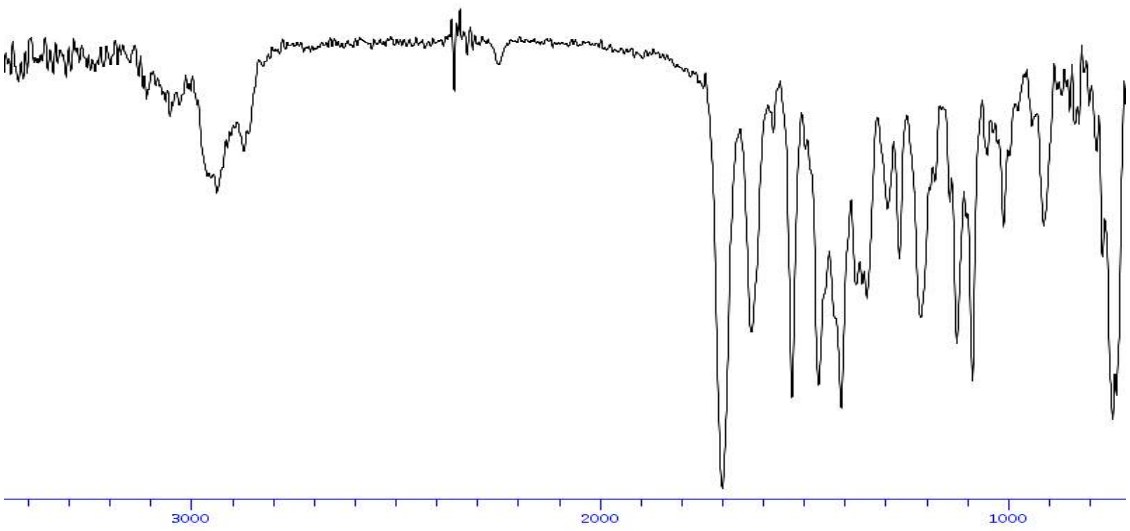


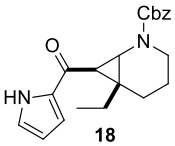
17

$CDCl_3$
400 MHz

$CDCl_3$
100 MHz

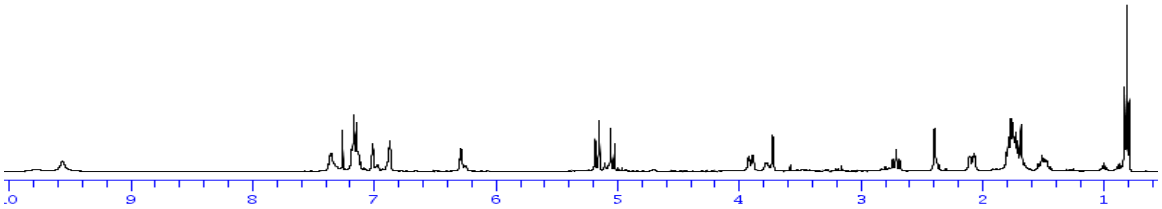




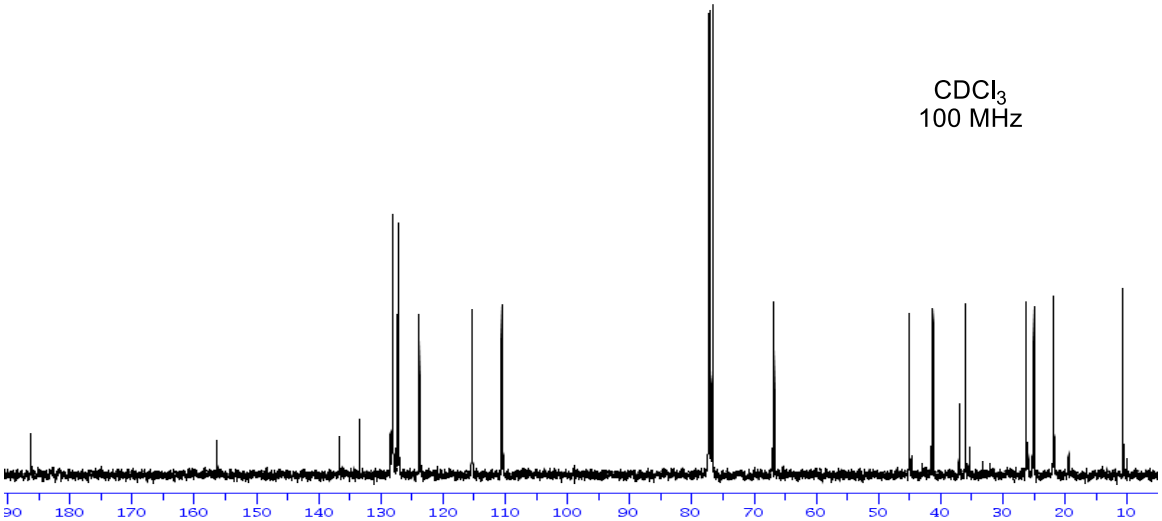


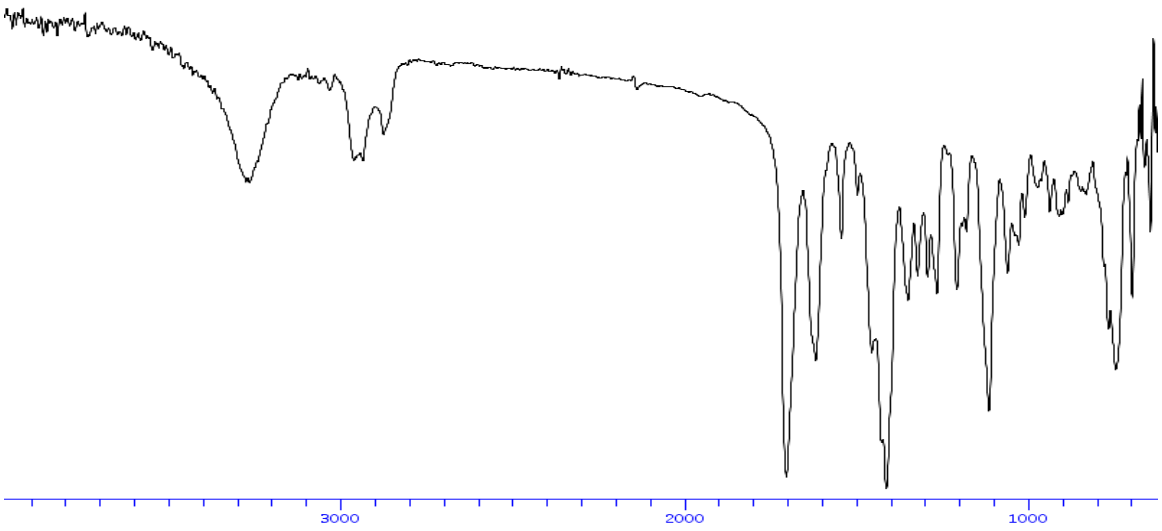
18

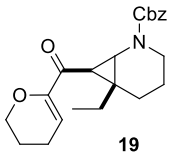
$CDCl_3$
400 MHz



$CDCl_3$
100 MHz

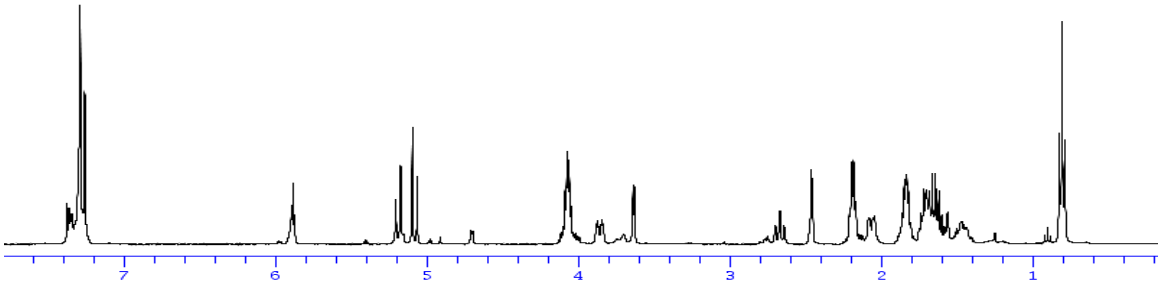






19

$CDCl_3$
400 MHz



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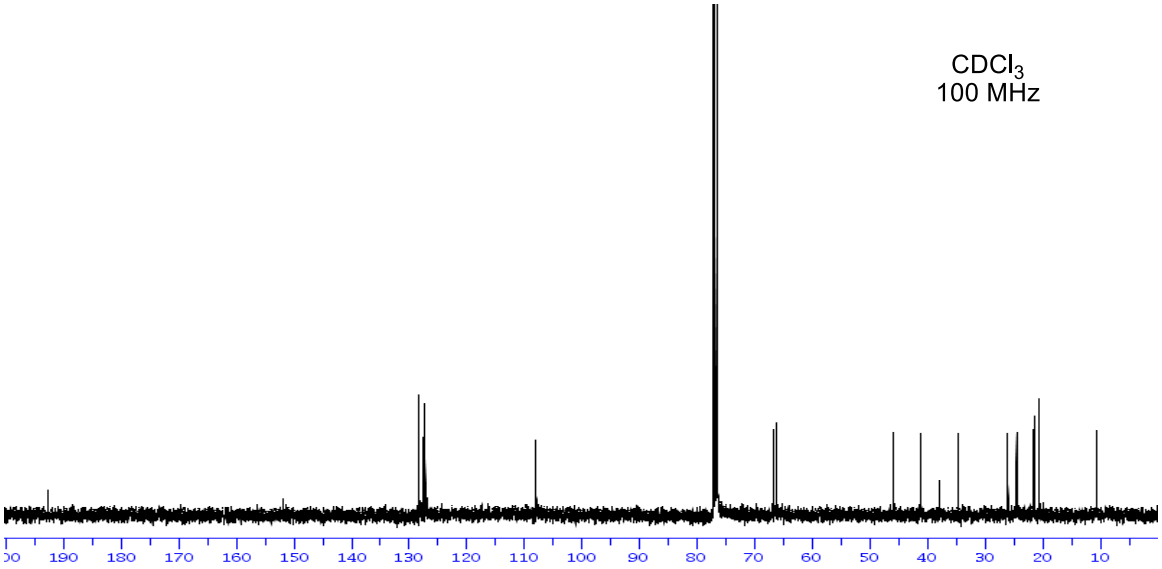

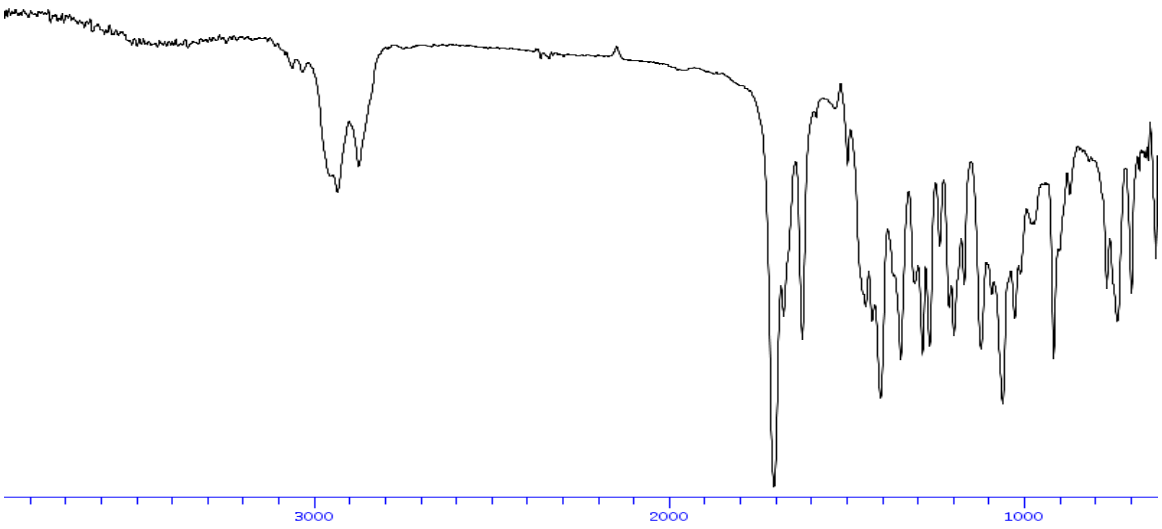

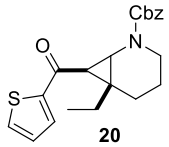

20

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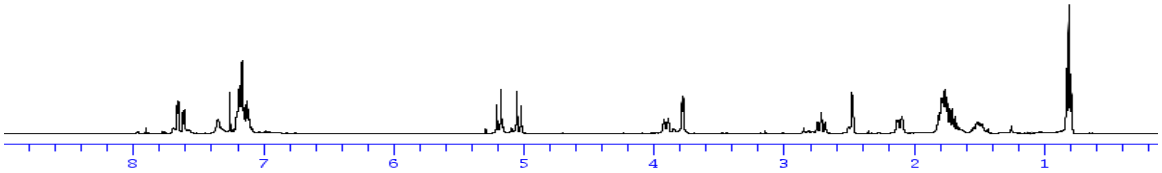

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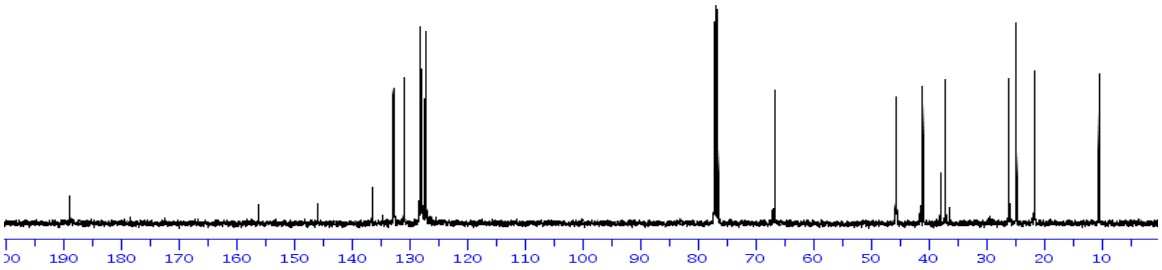

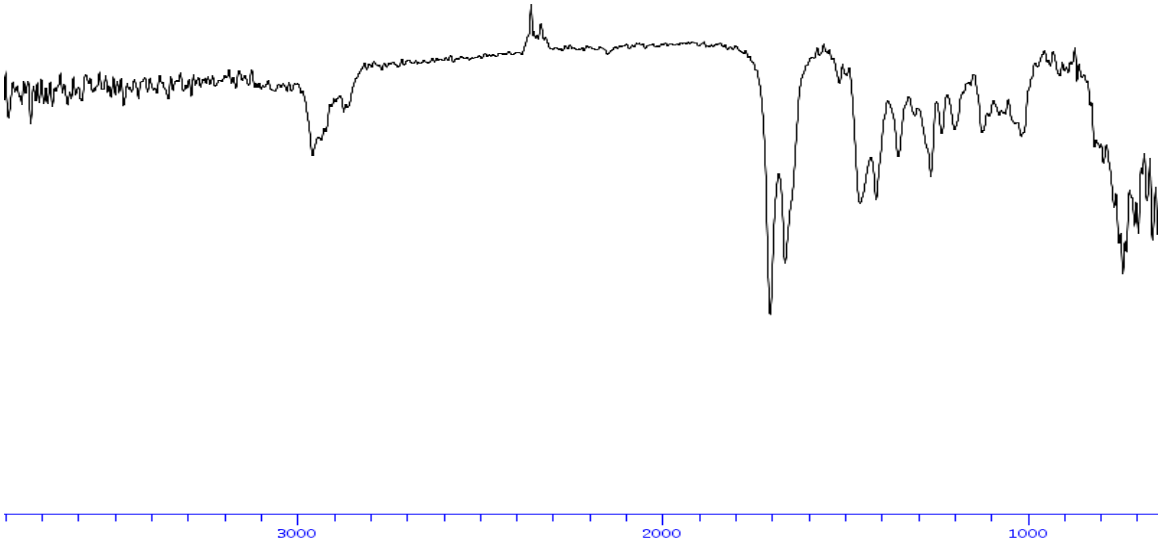

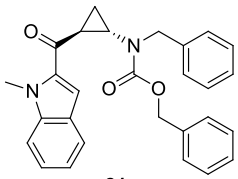
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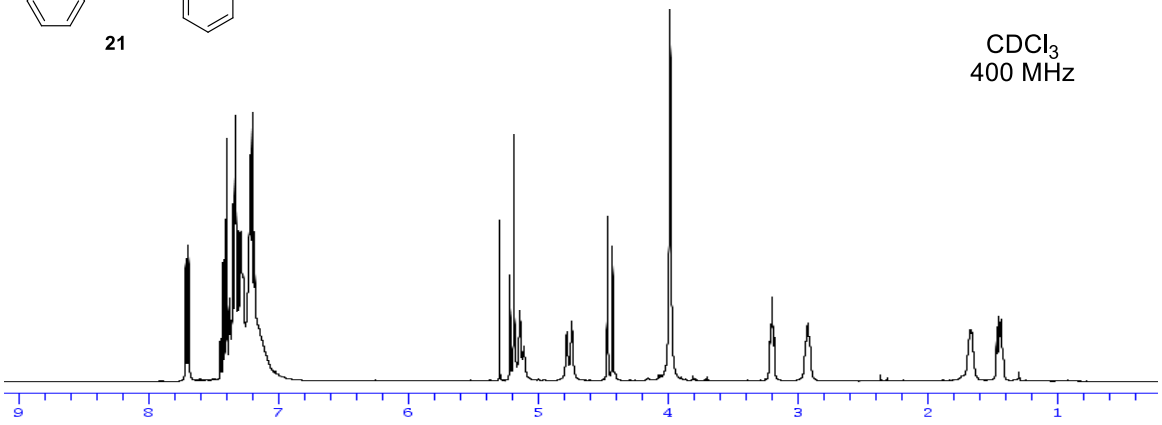
21


CDCl3
400 MHz
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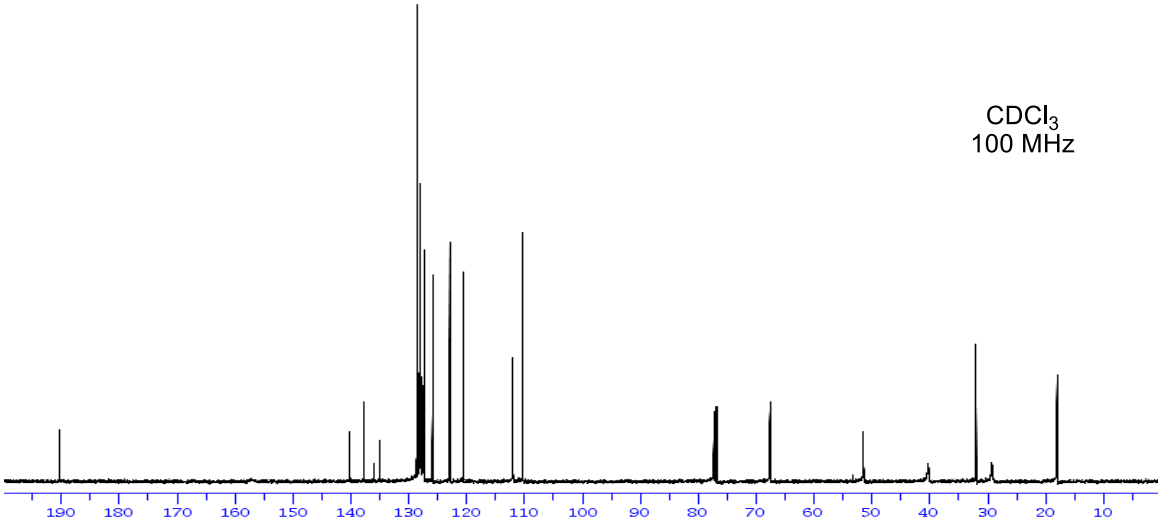
CDCl3
100 MHz
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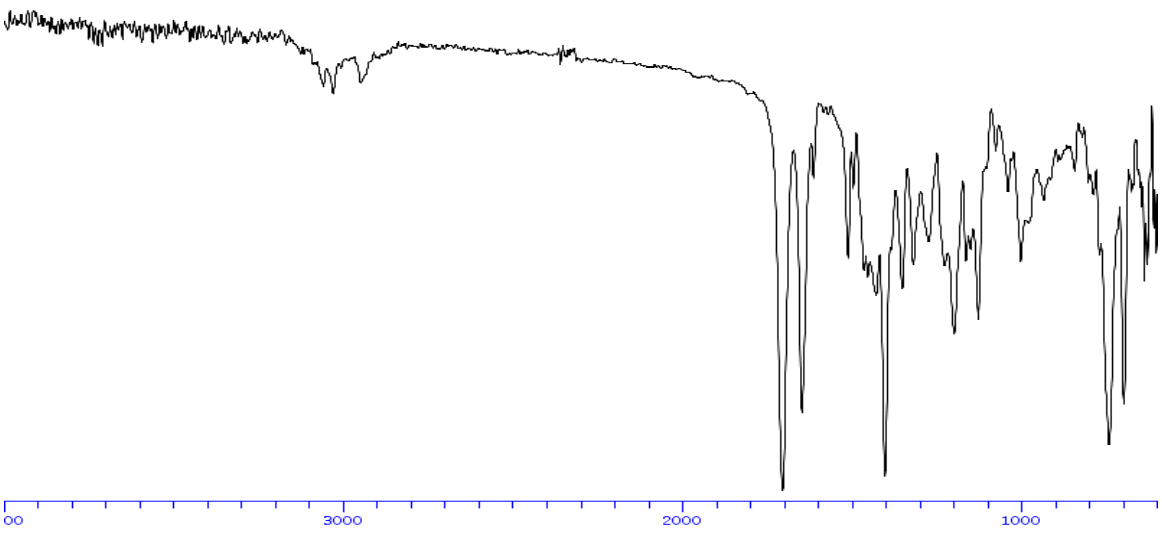
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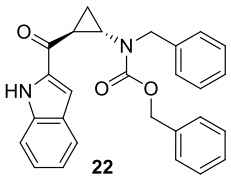

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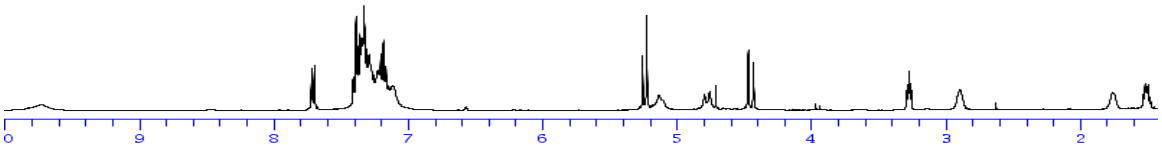

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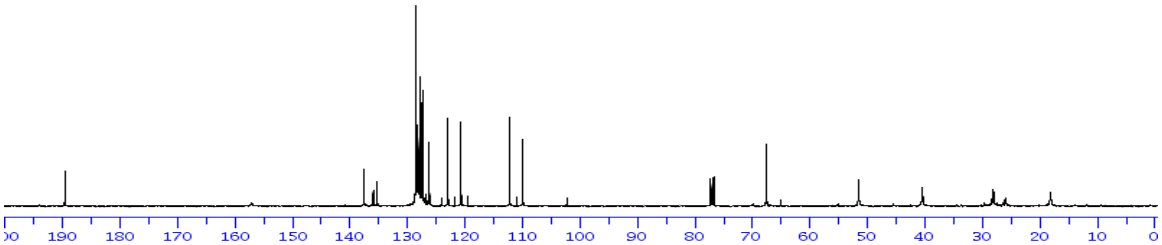
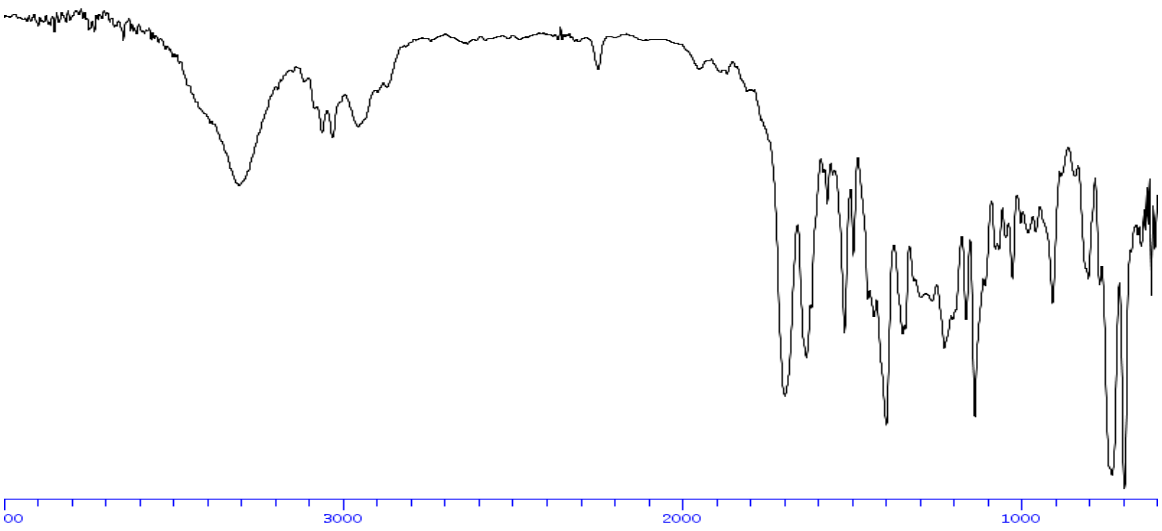
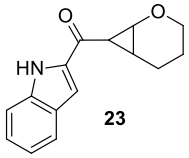
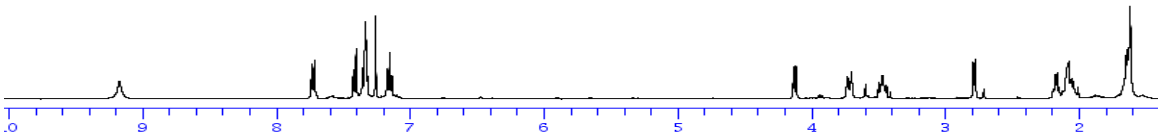






23

$CDCl_3$
400 MHz



$CDCl_3$
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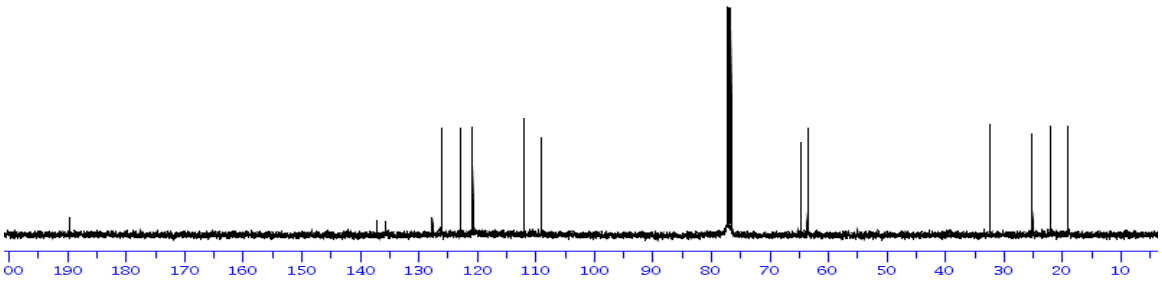
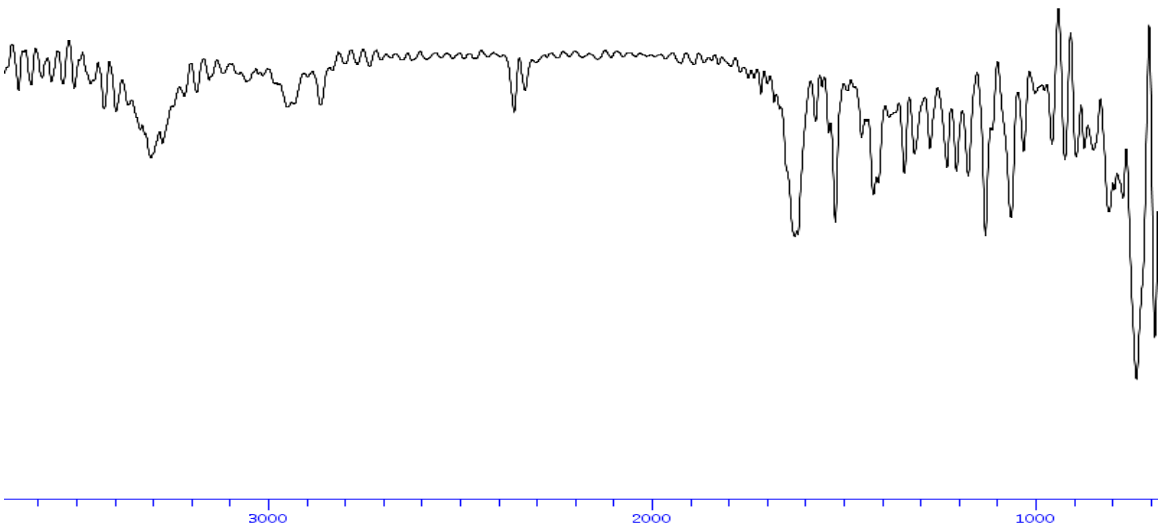
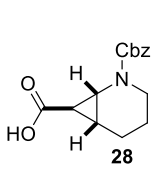


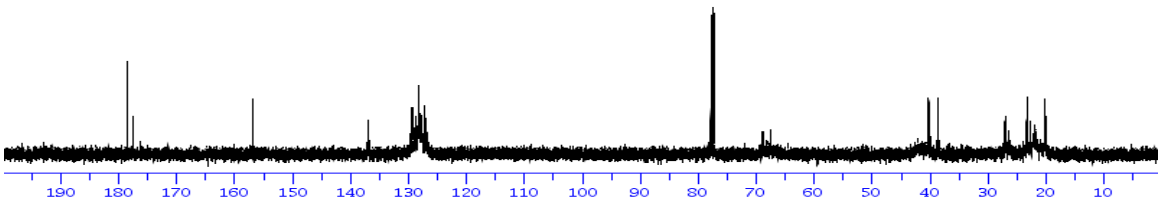


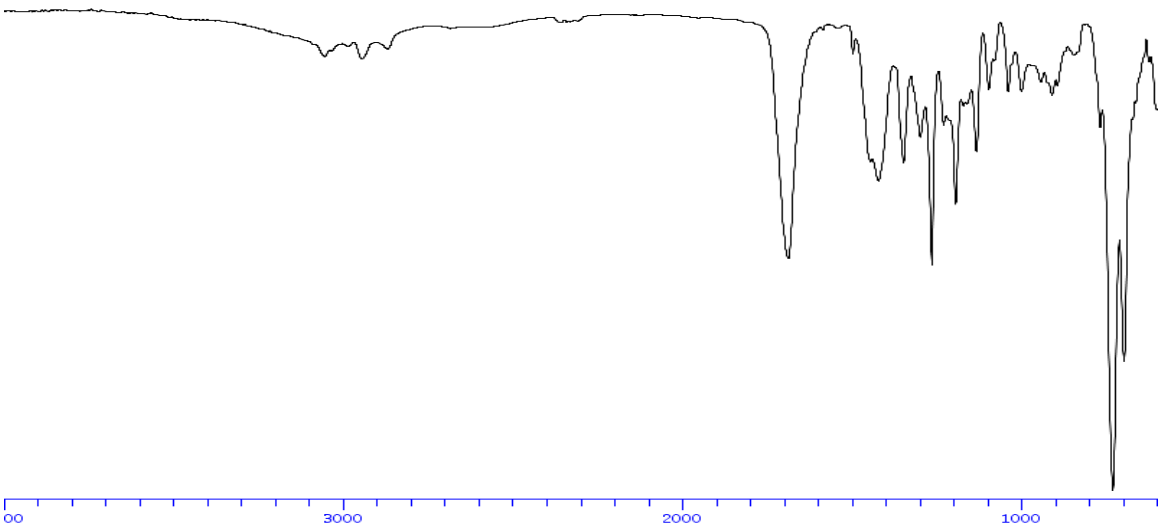


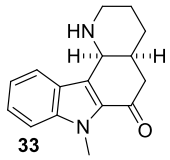
28

$CDCl_3$
400 MHz

$CDCl_3$
100 MHz

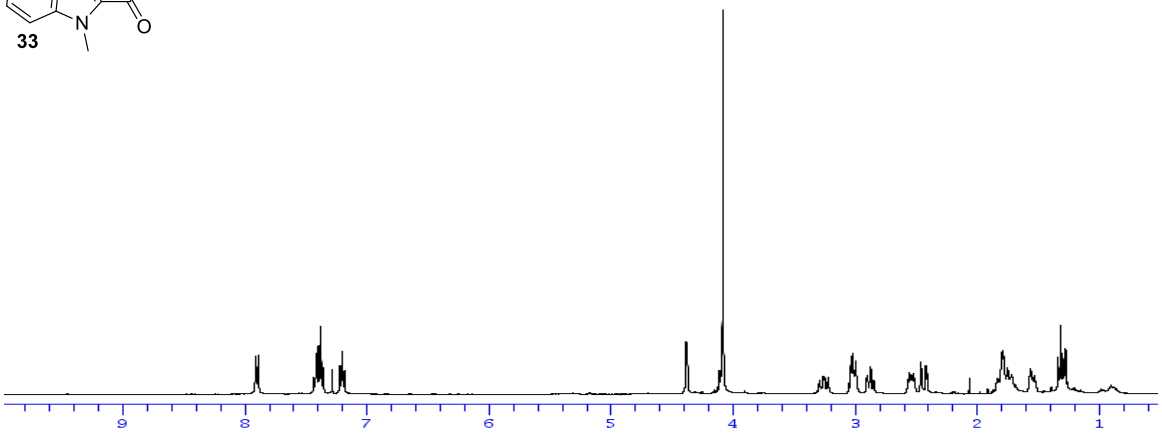




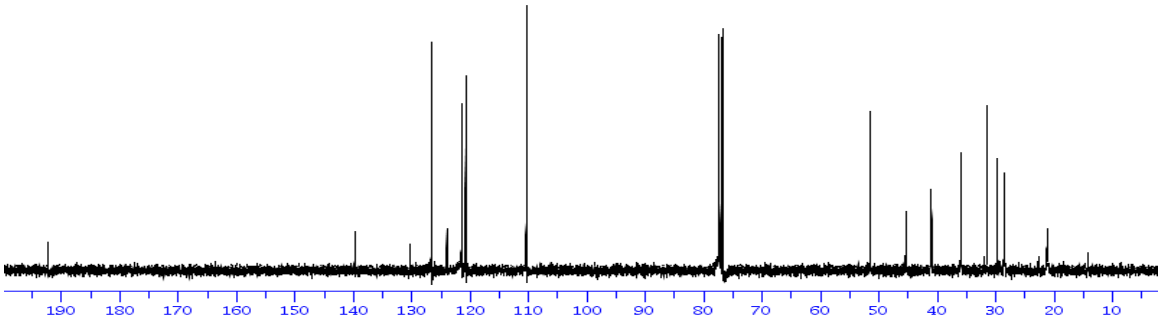


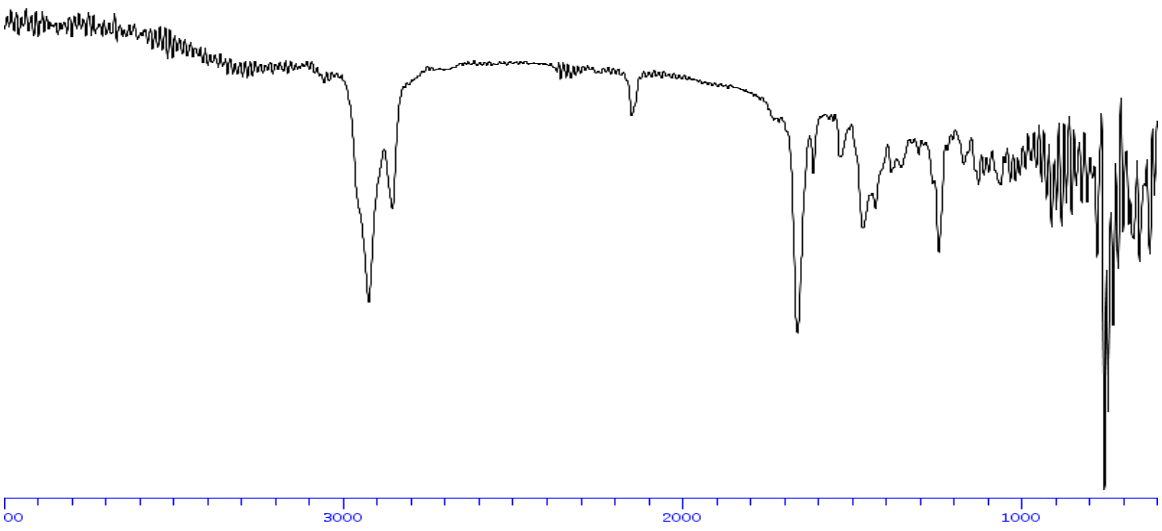
33

$CDCl_3$
400 MHz

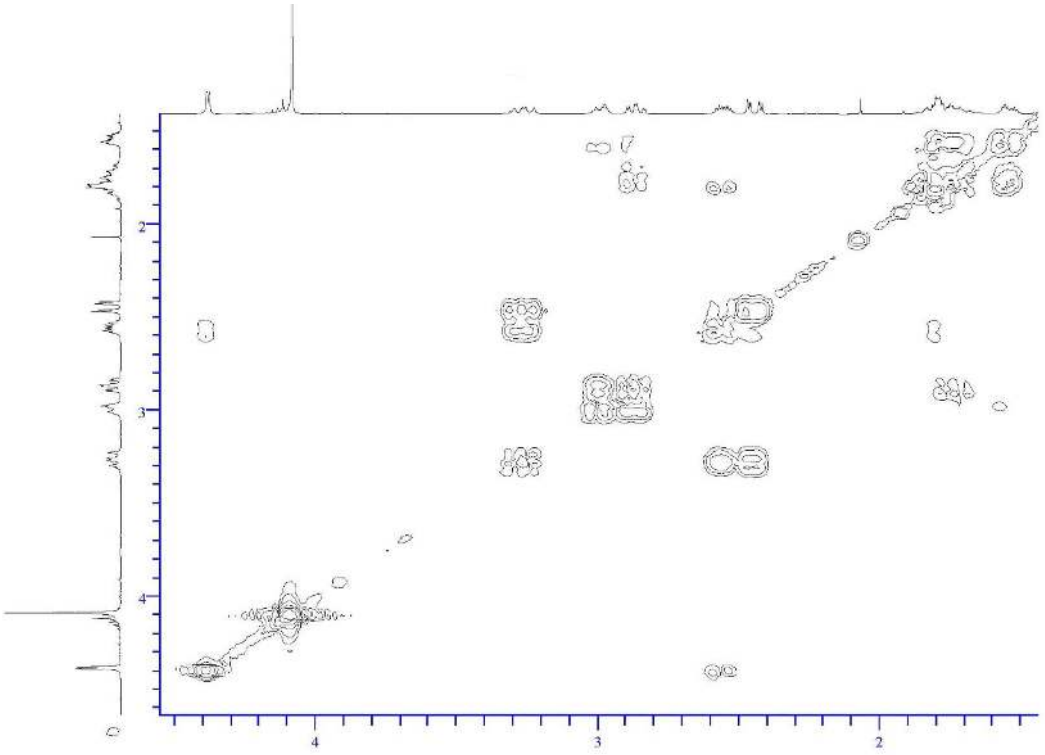


$CDCl_3$
100 MHz

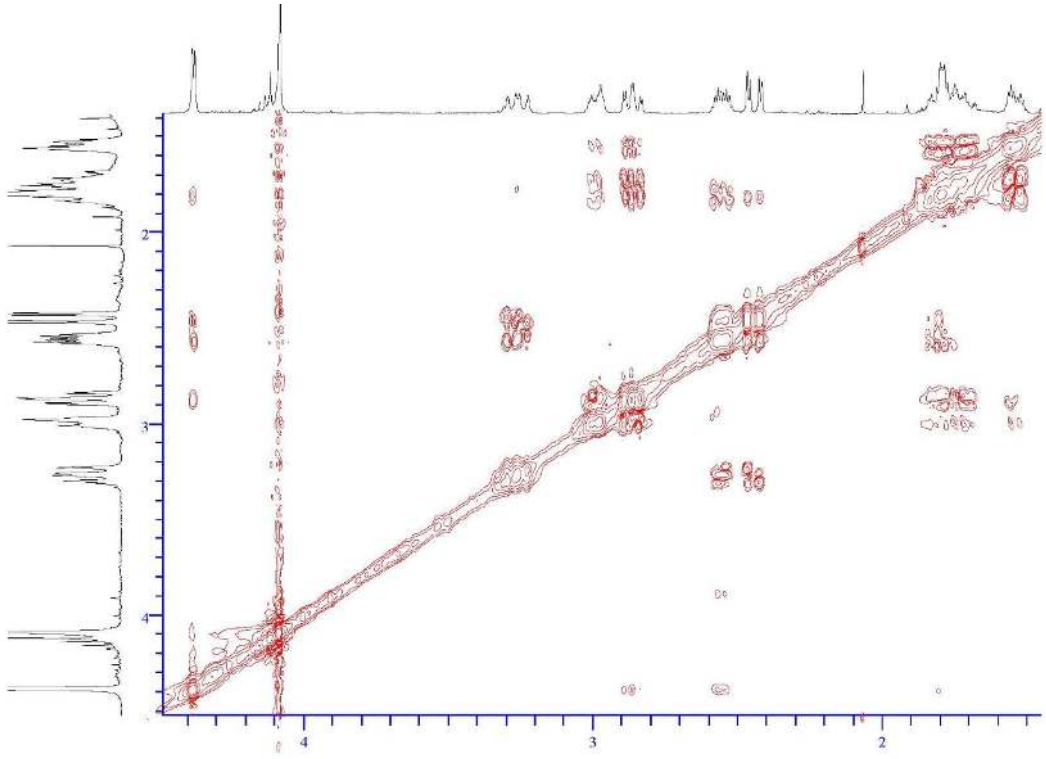


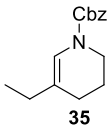


COSY



ROESY





35

$CDCl_3$
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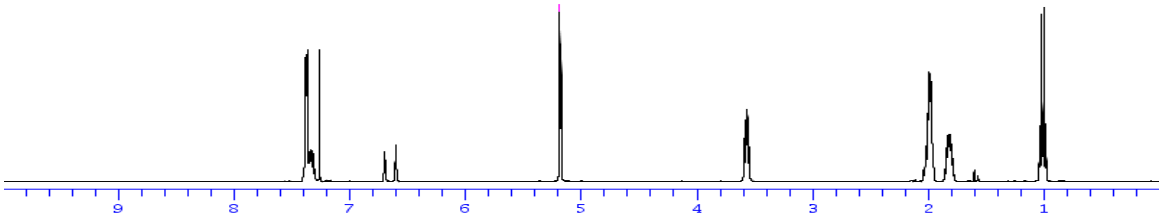

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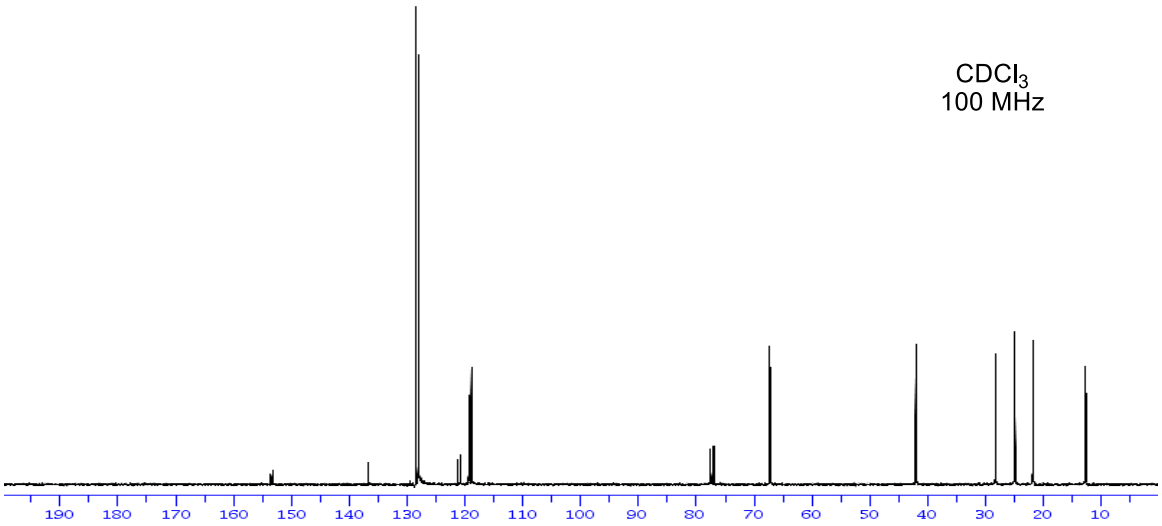

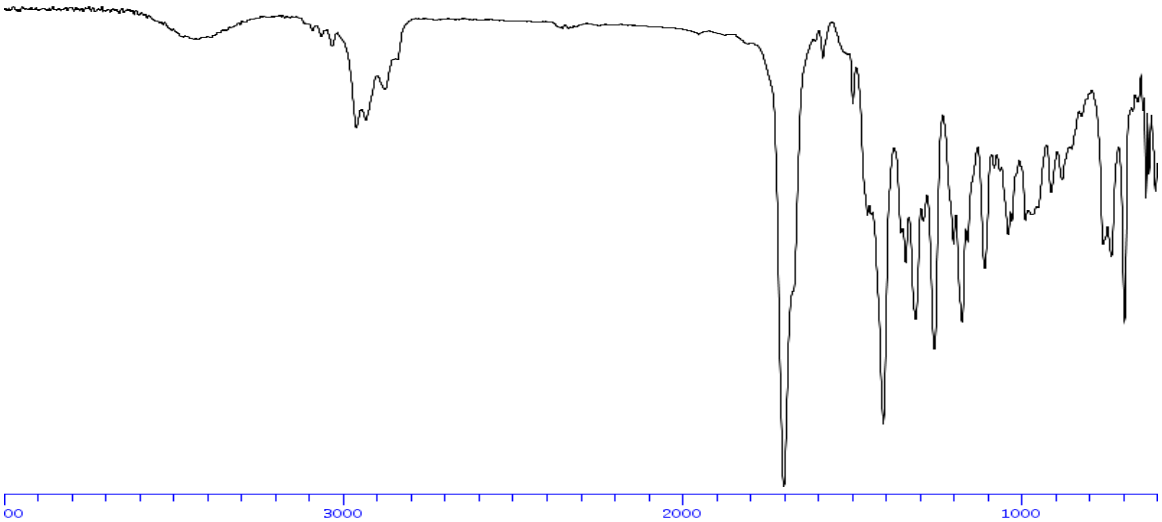

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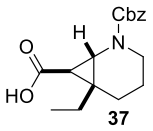
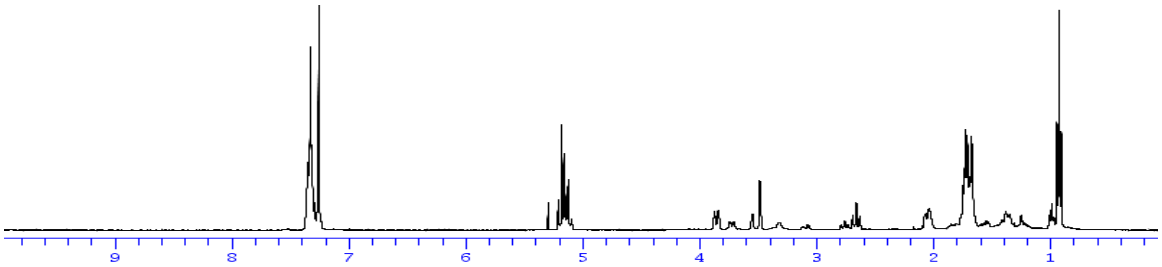


37



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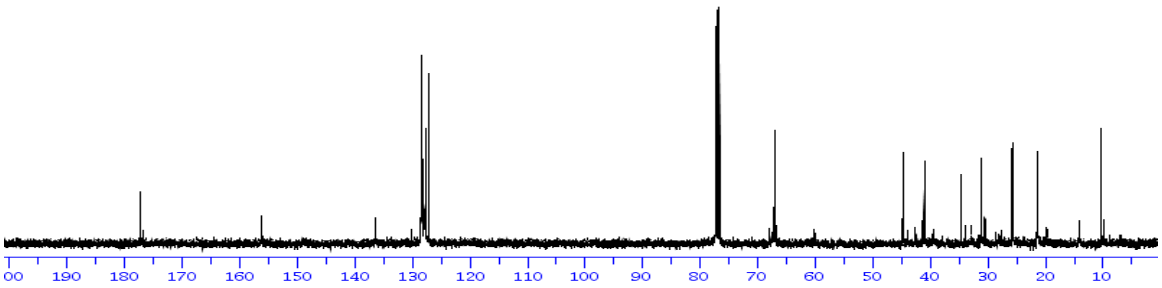

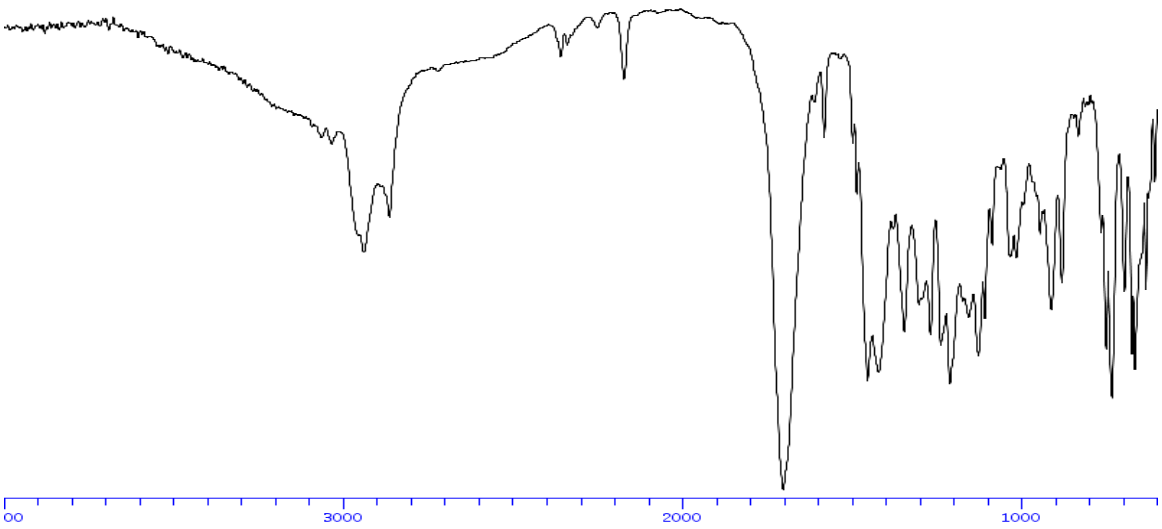

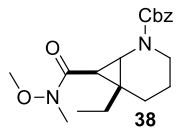

38

$CDCl_3$
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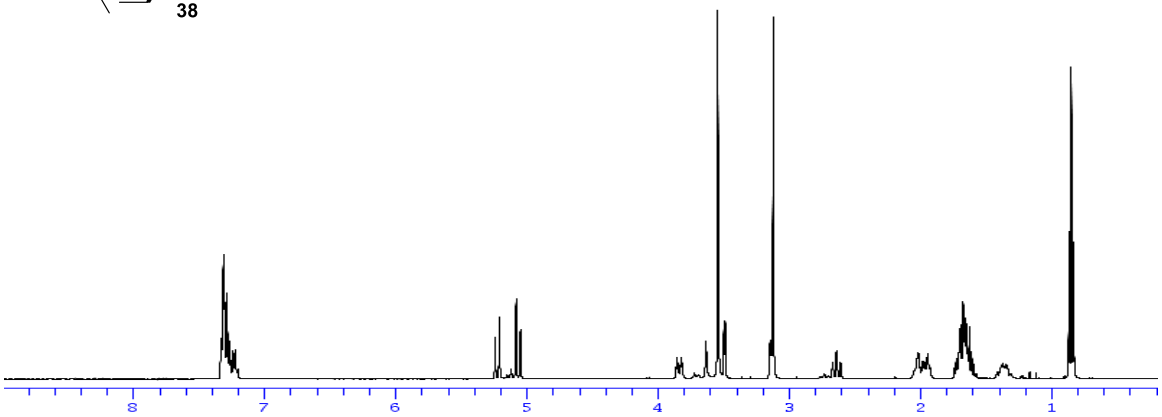

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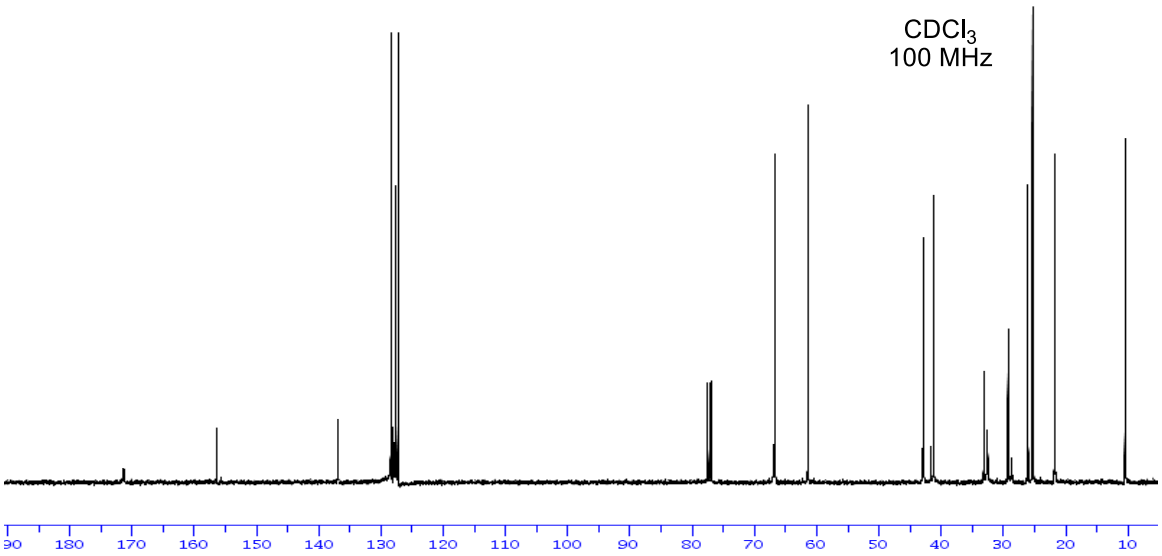

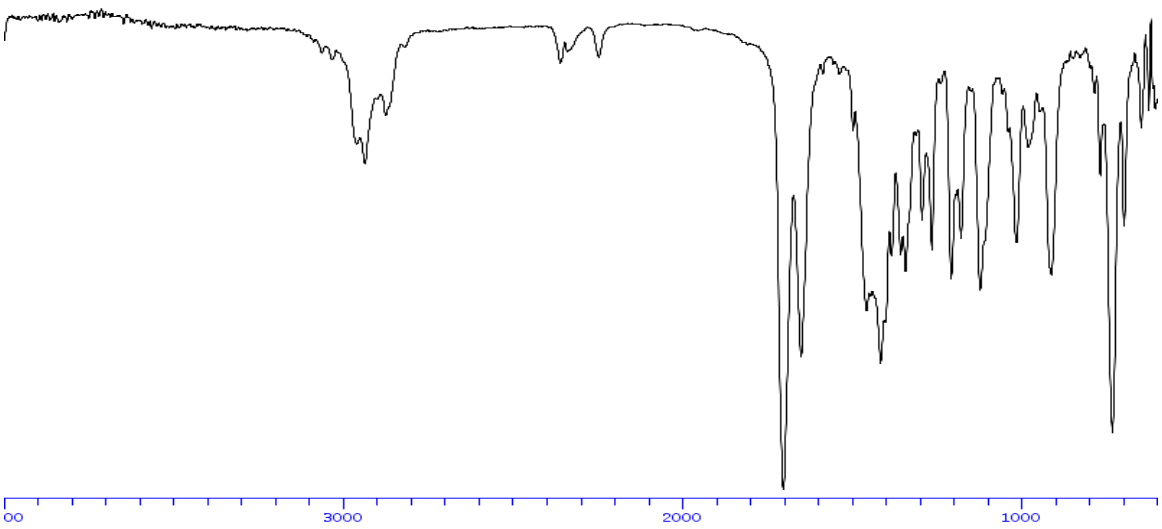

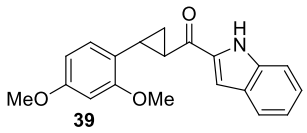

39

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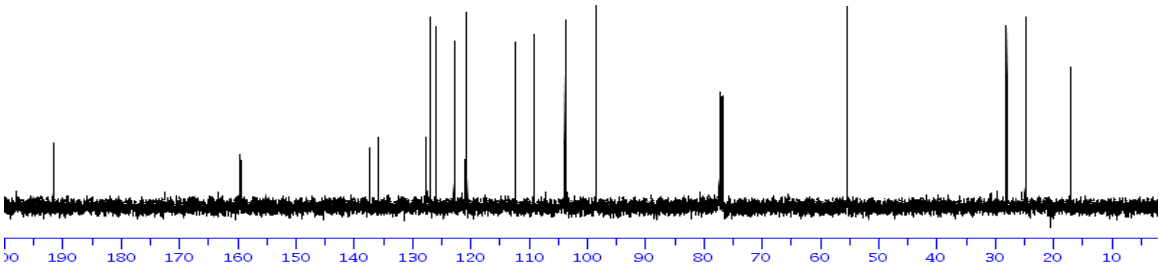

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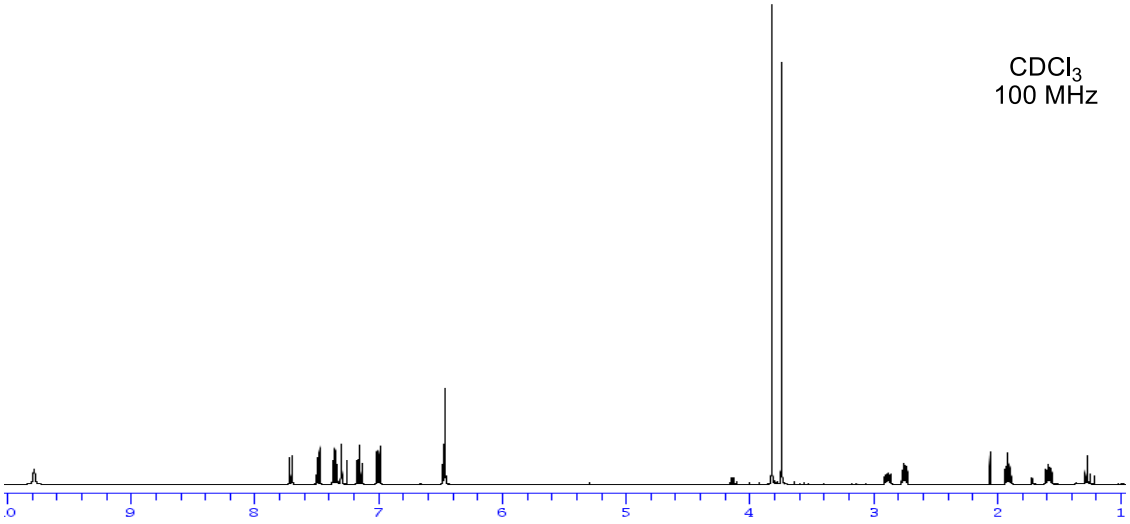

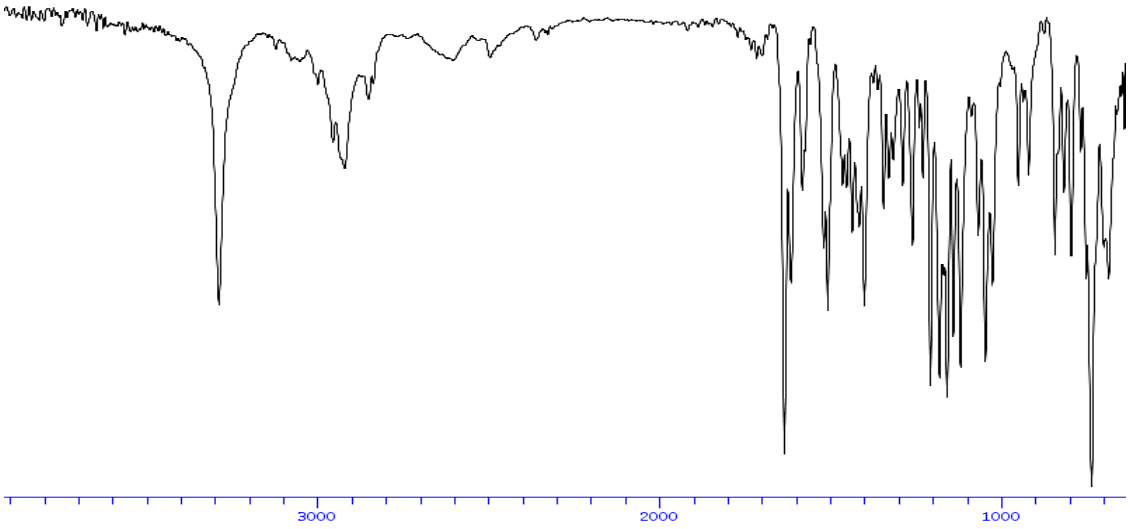

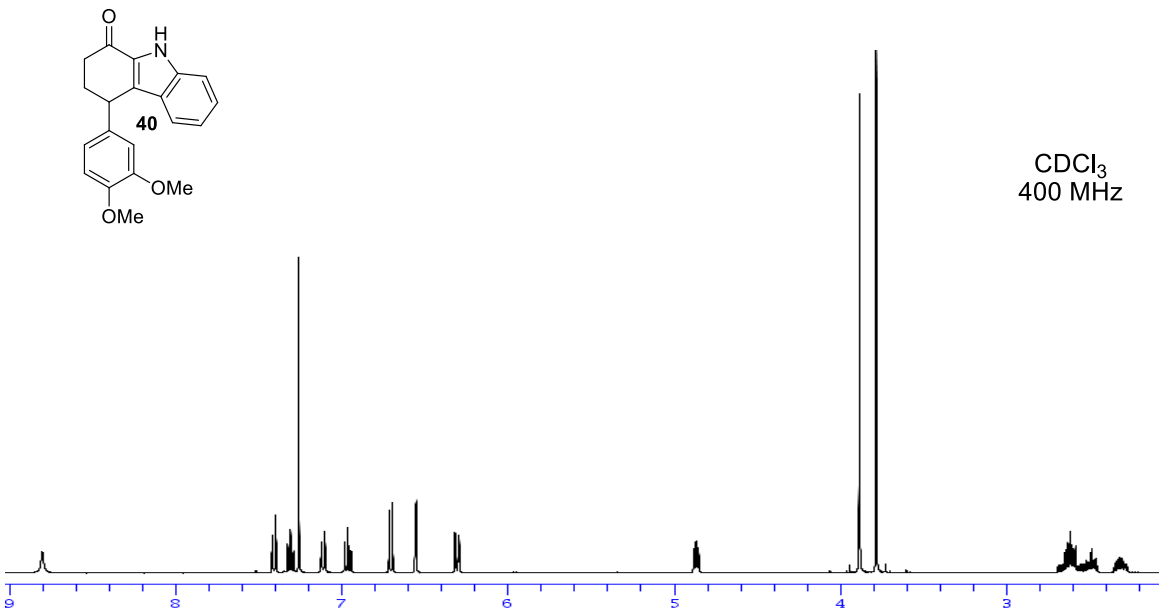
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400 MHz
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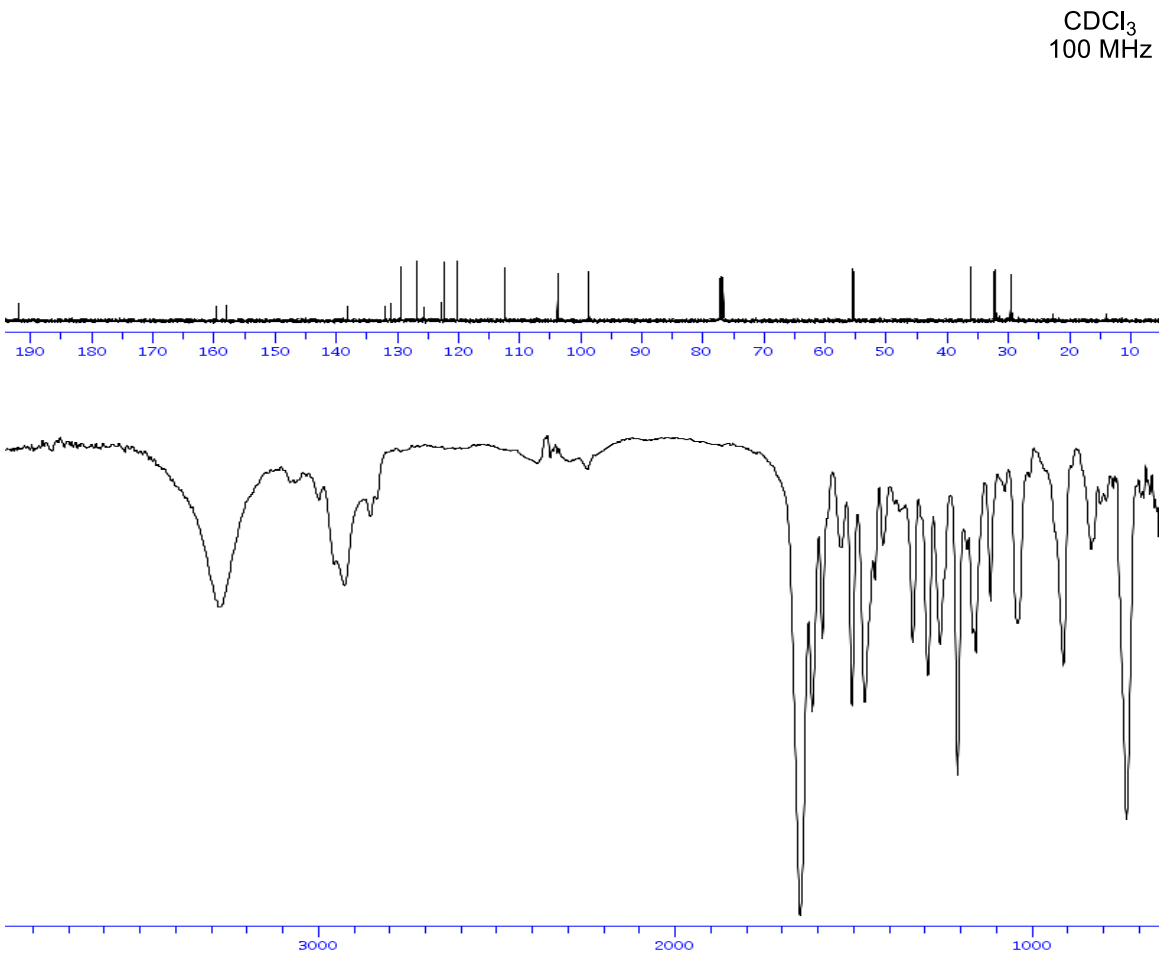
CDCl3
100 MHz
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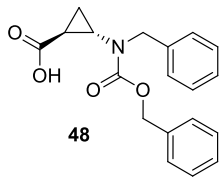
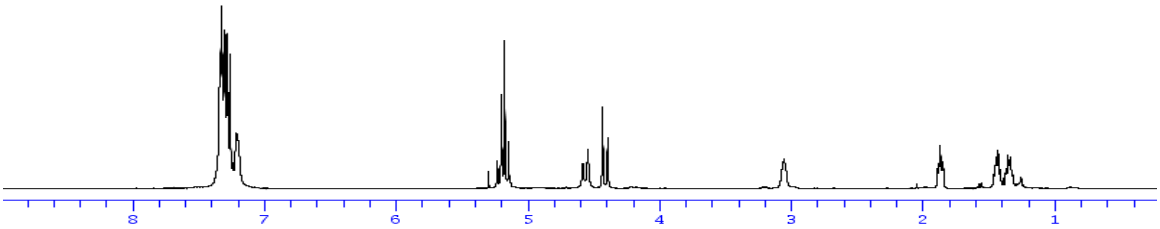
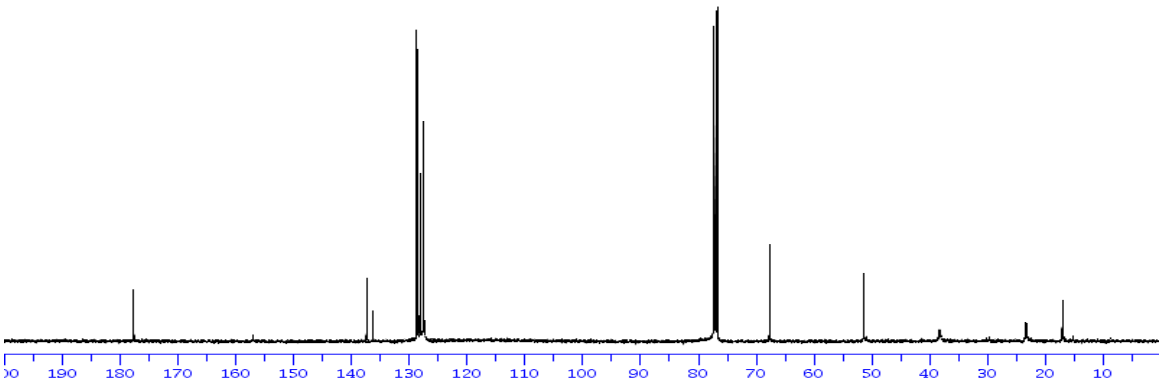


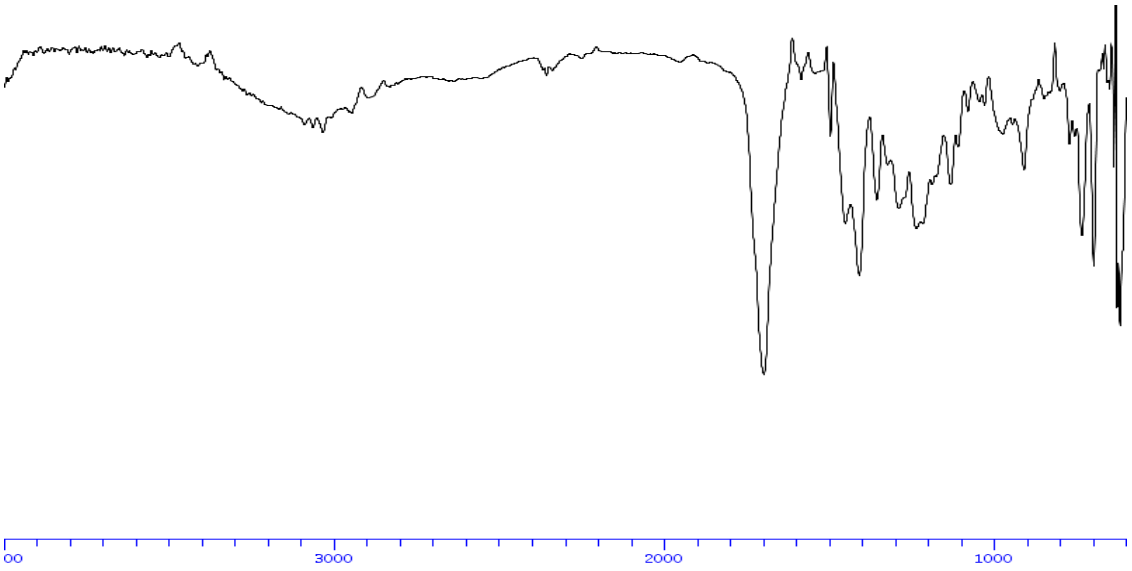
48

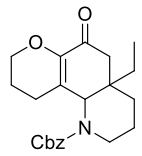
$CDCl_3$
400 MHz



$CDCl_3$
100 MHz

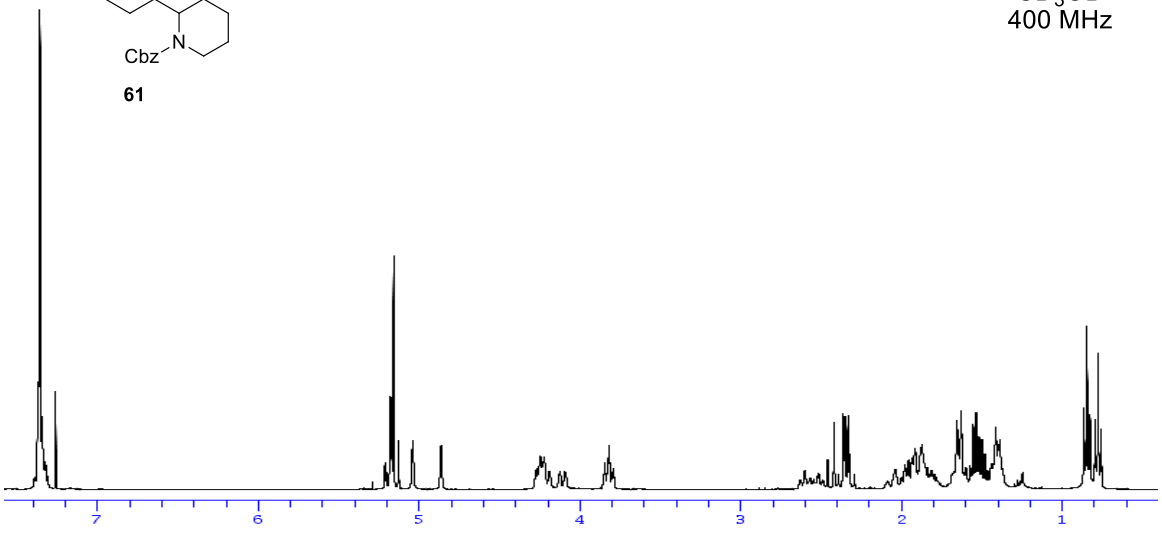




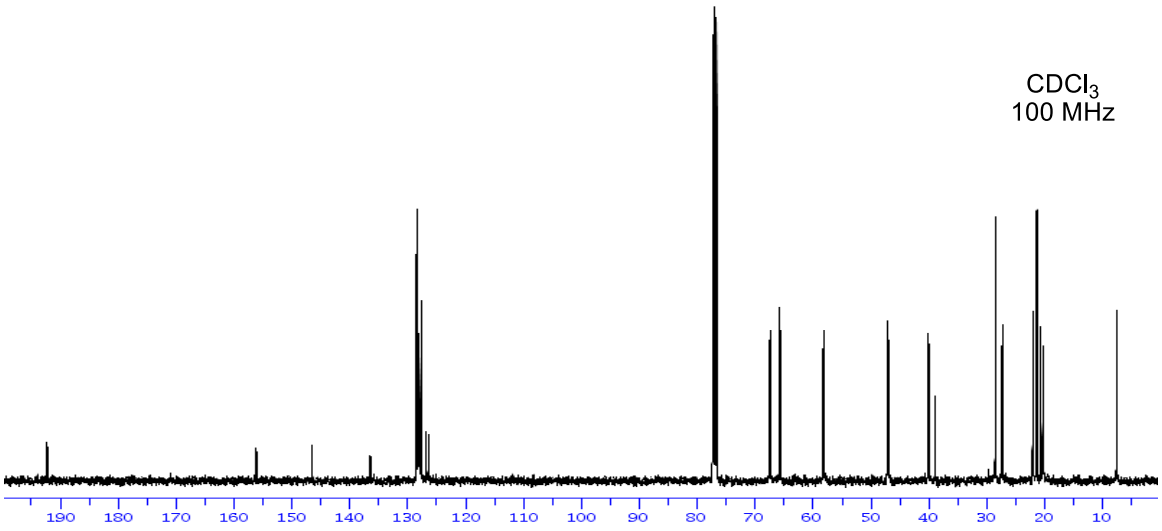


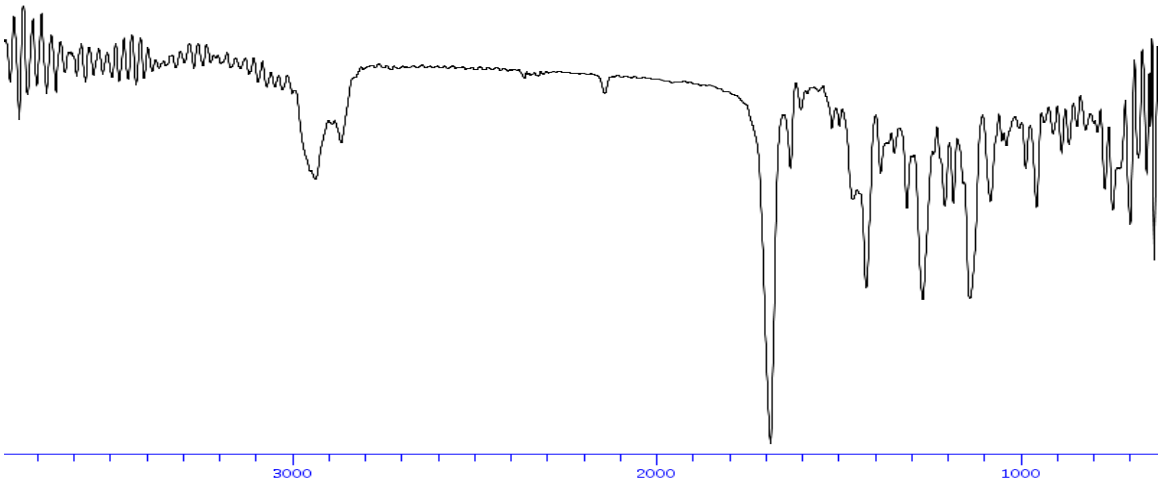
61

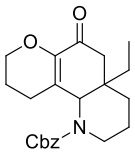
CD_3OD
400 MHz



$CDCl_3$
100 MHz






O
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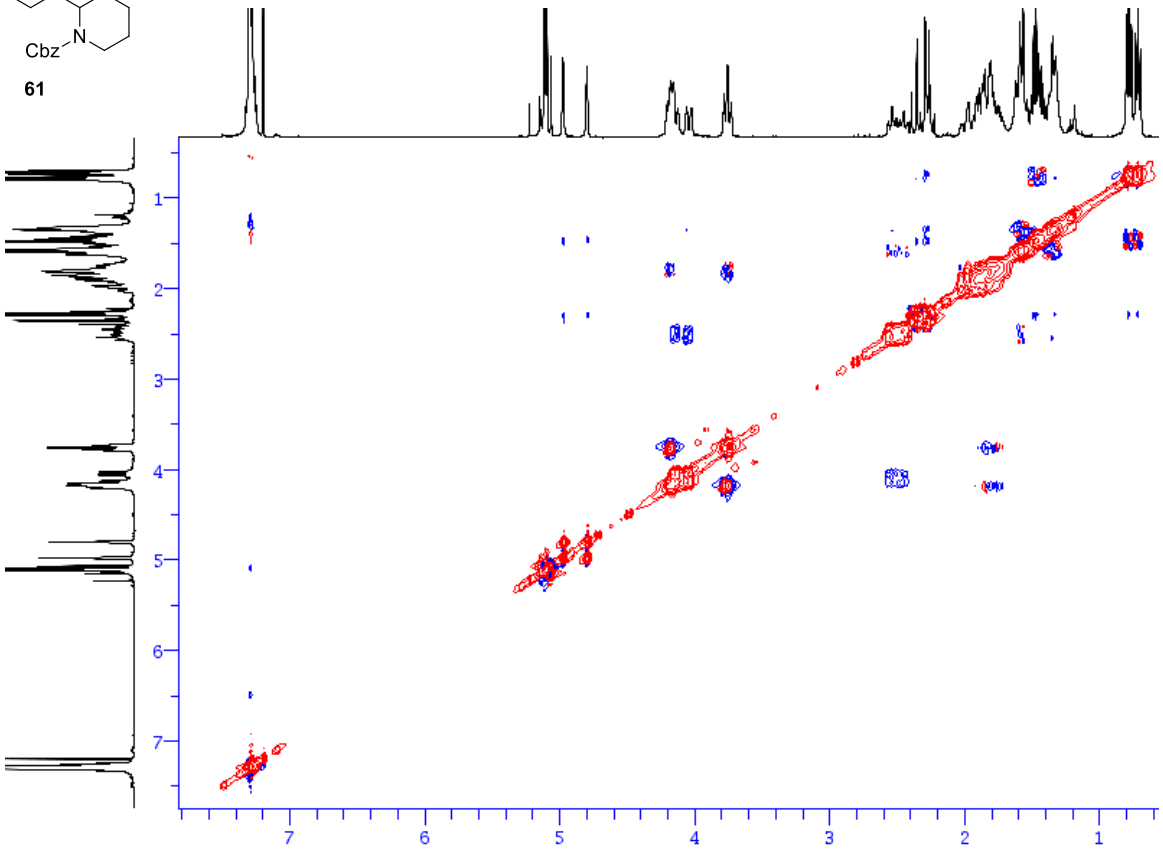
61

ROESY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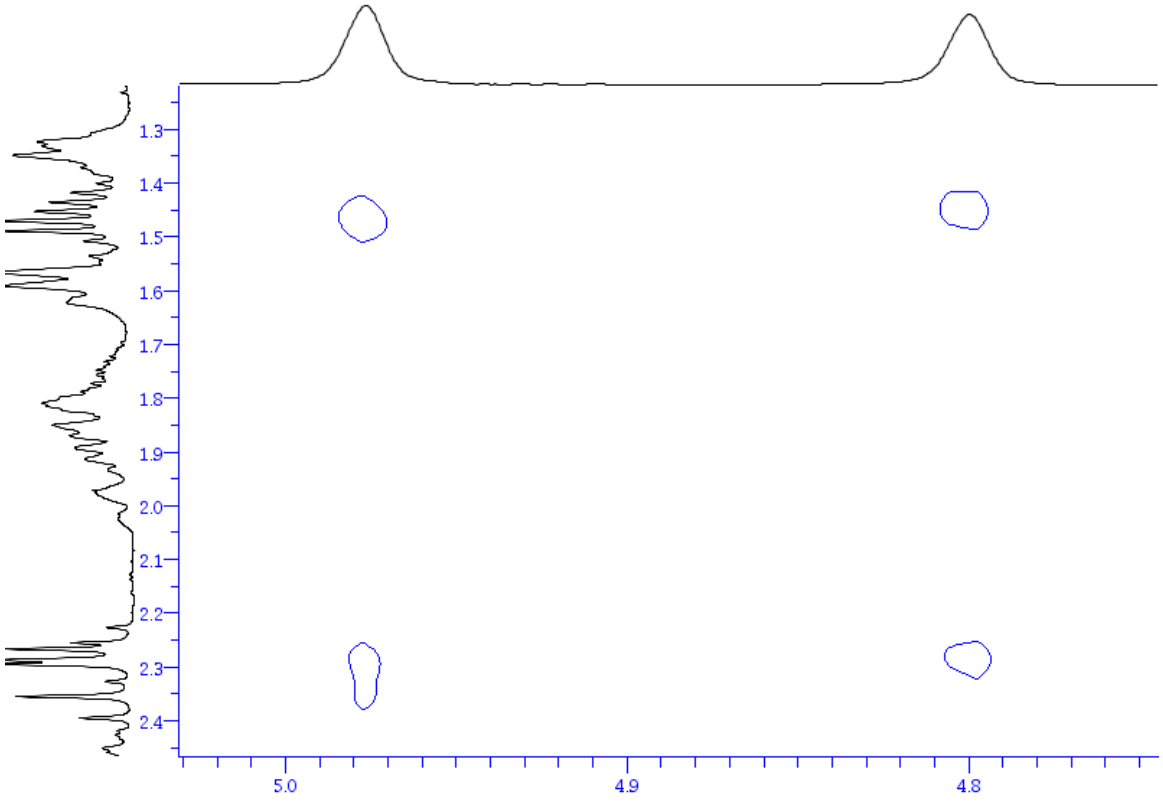
1.3
1.4
1.5
1.6
1.7
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1.9
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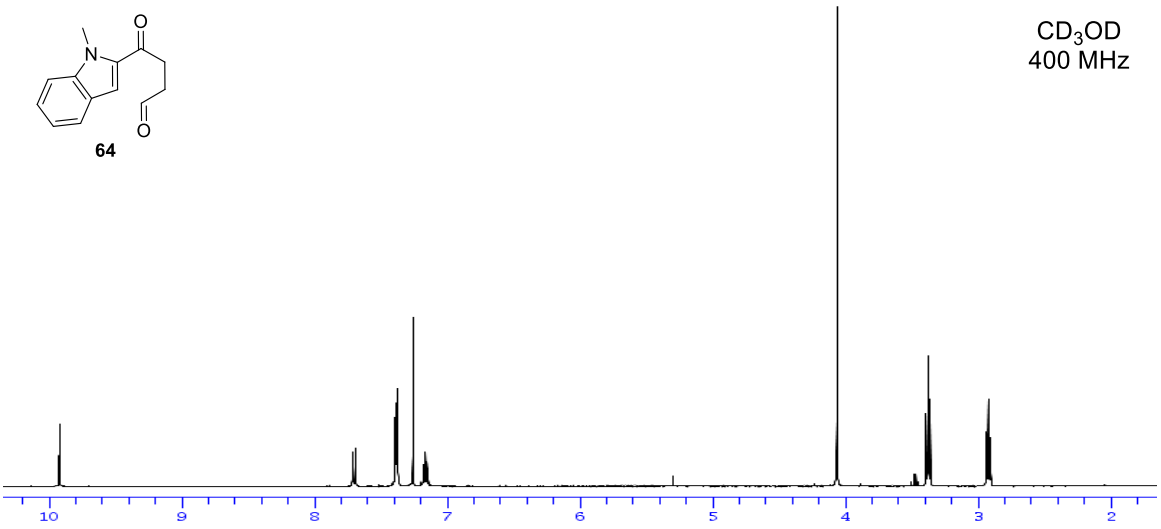
4.8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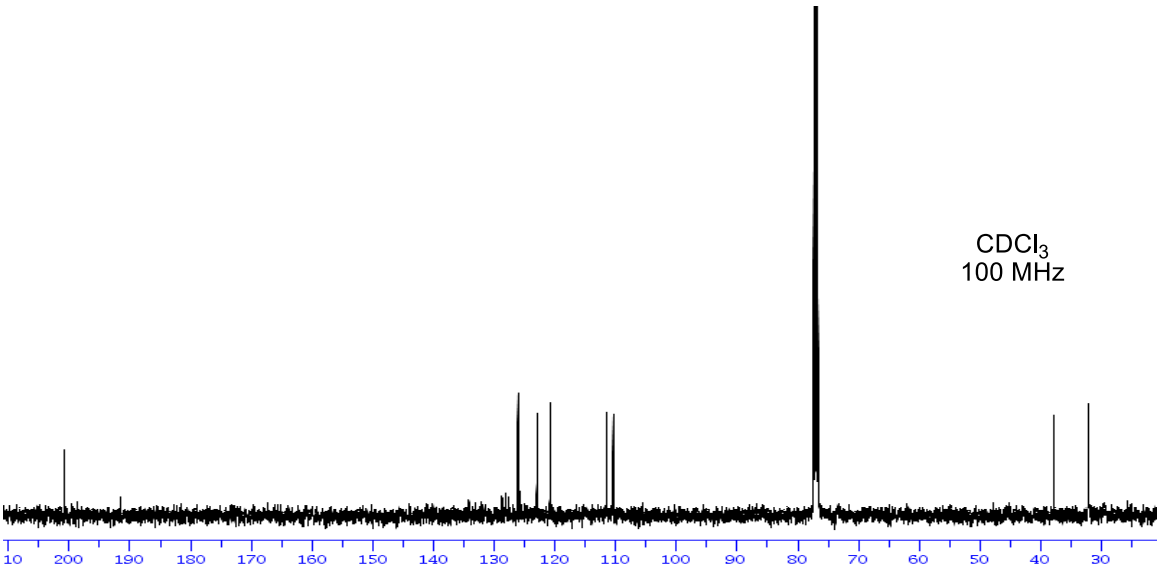
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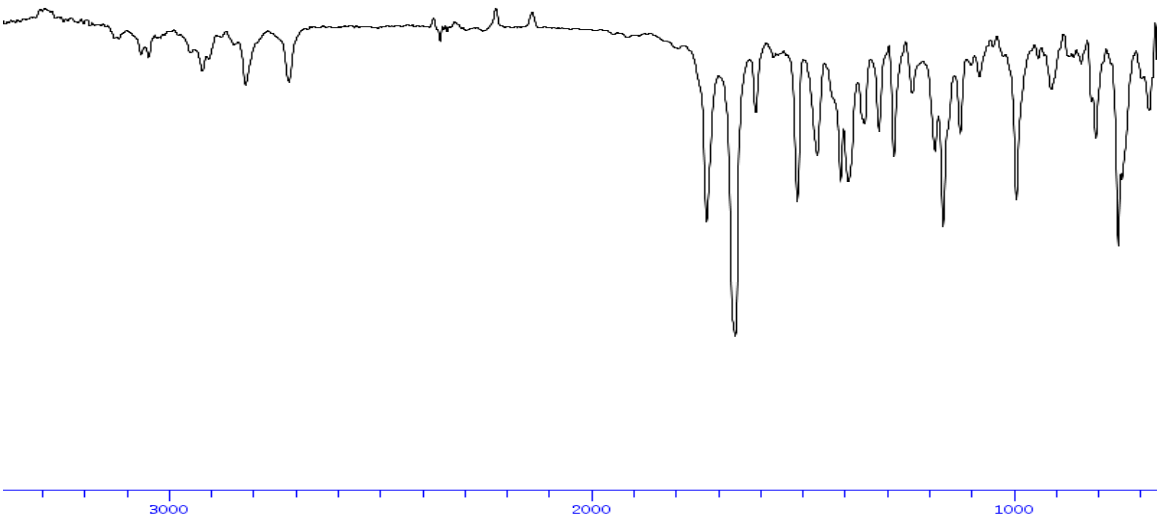
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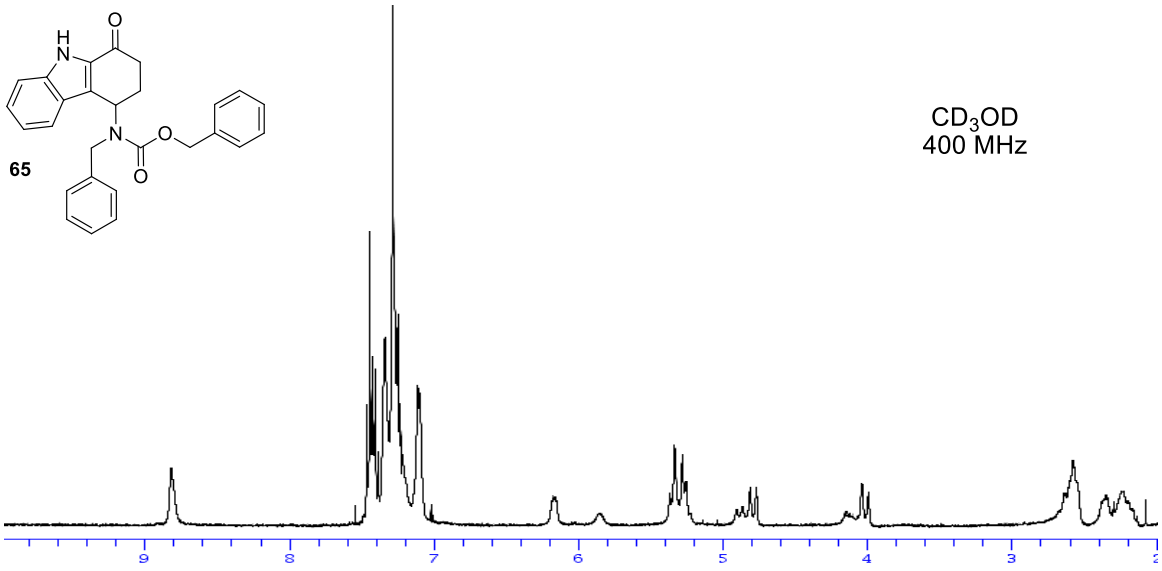
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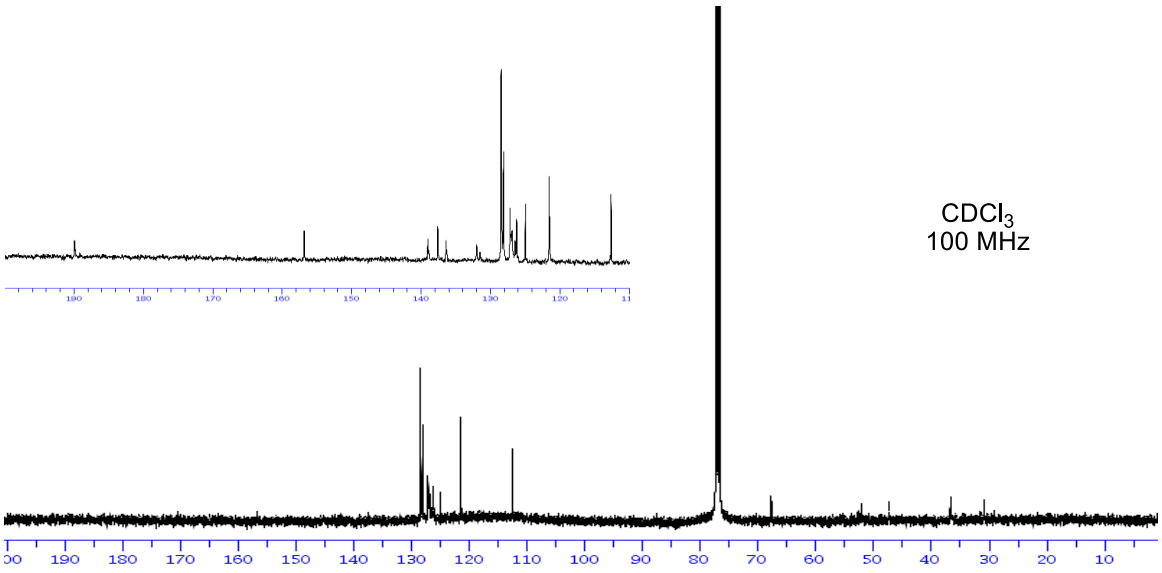
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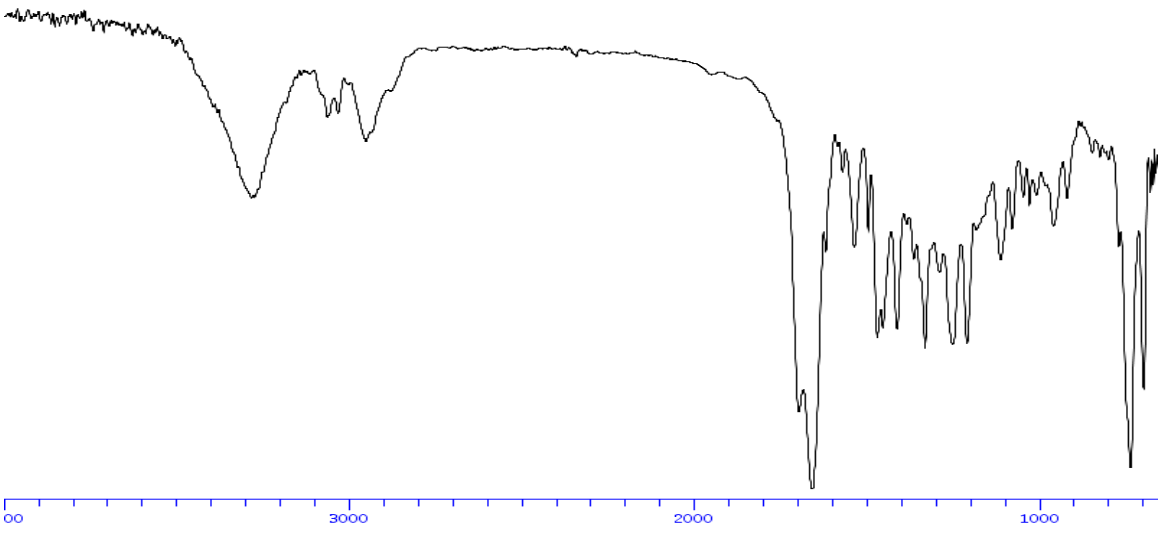

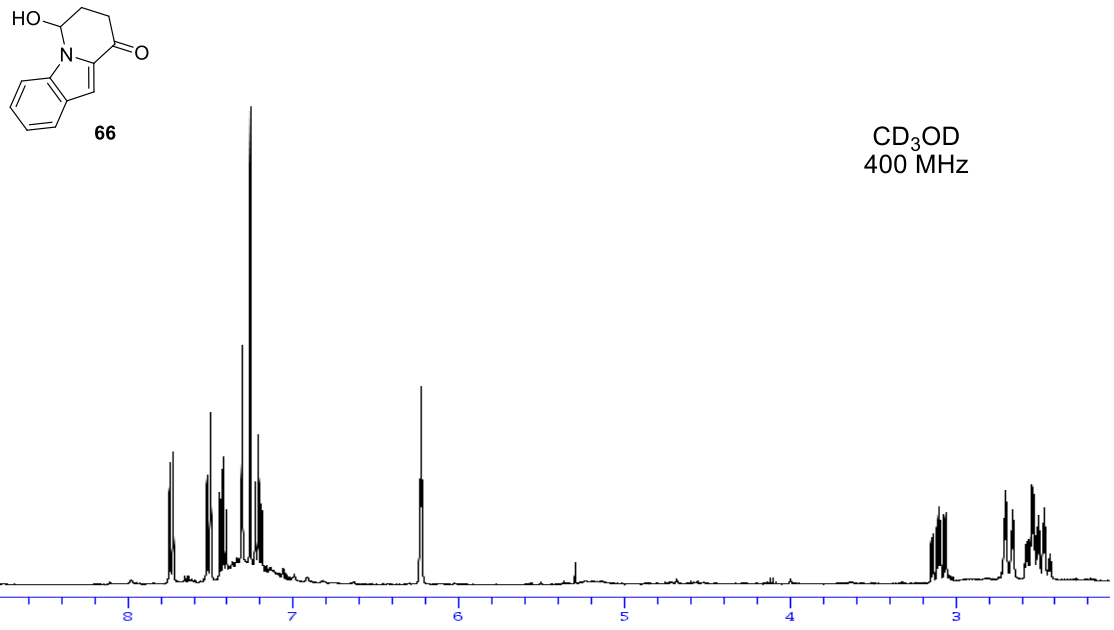
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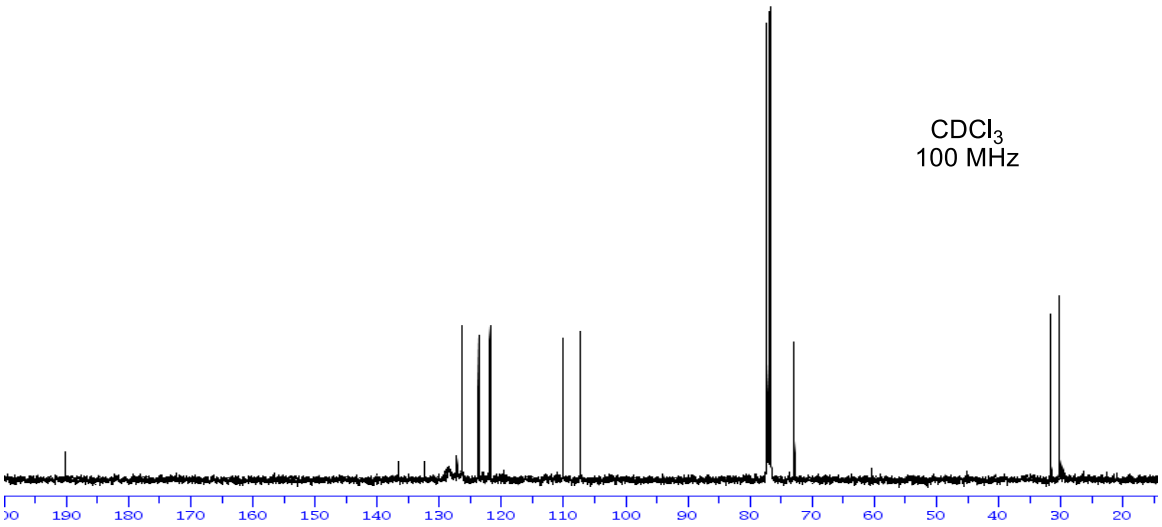
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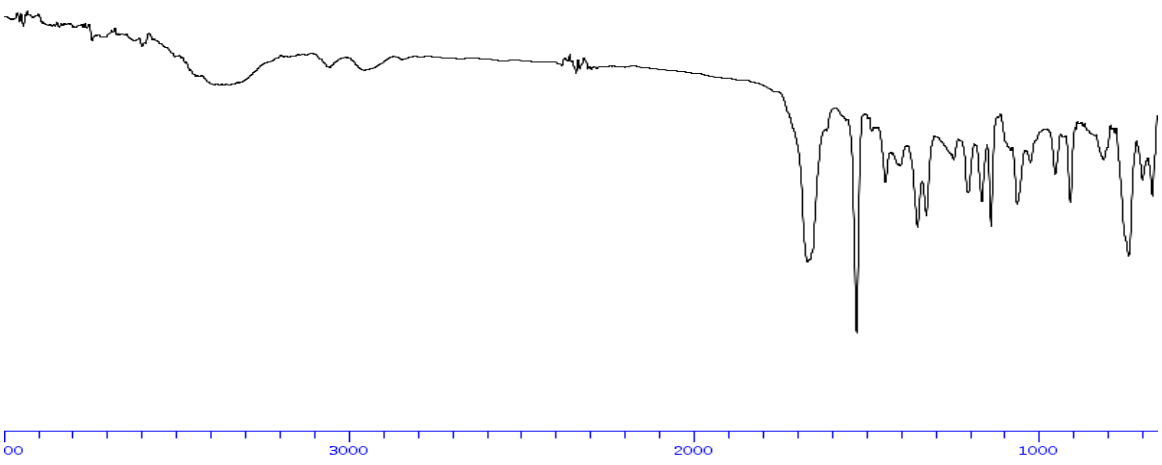
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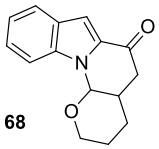

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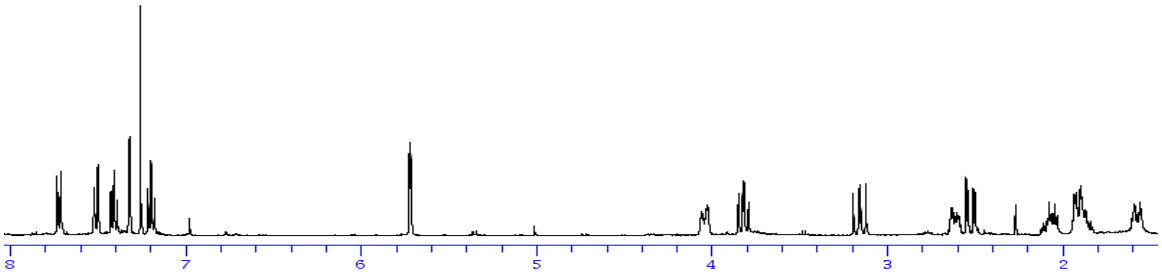

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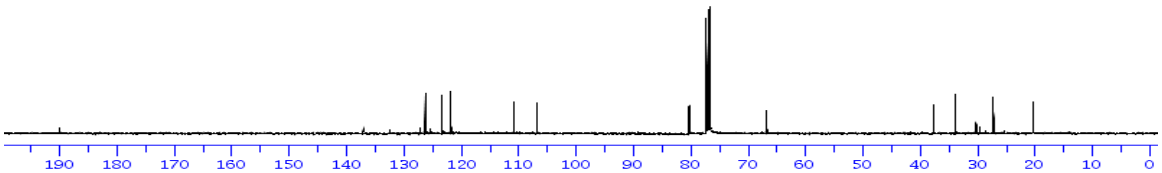
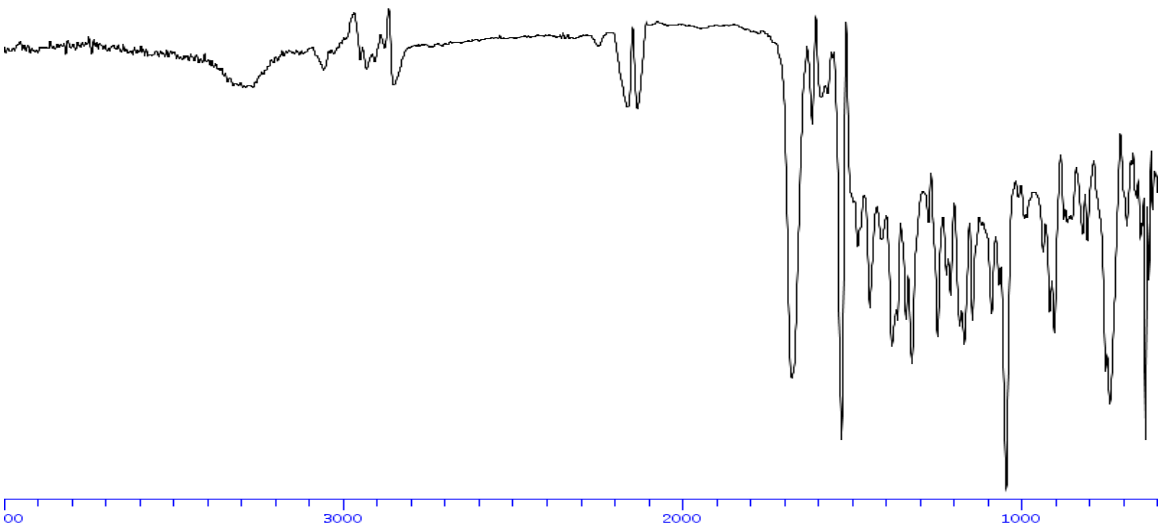
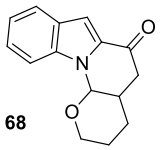
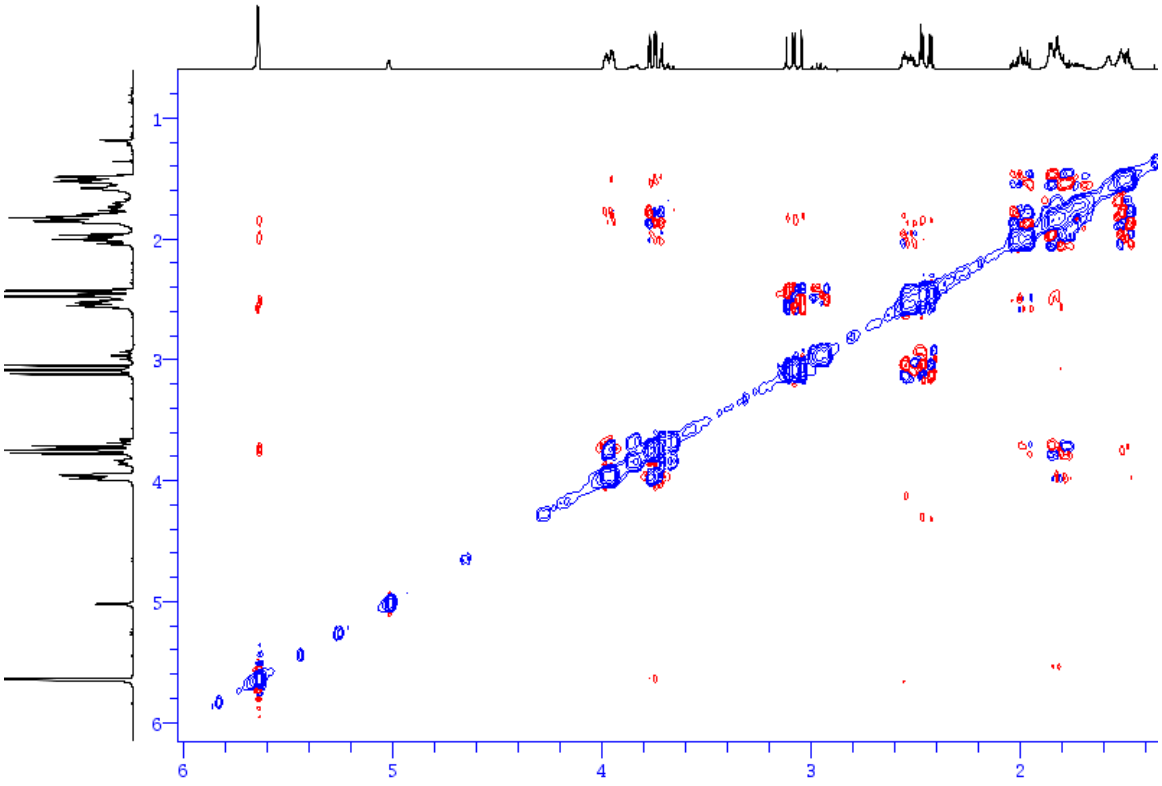


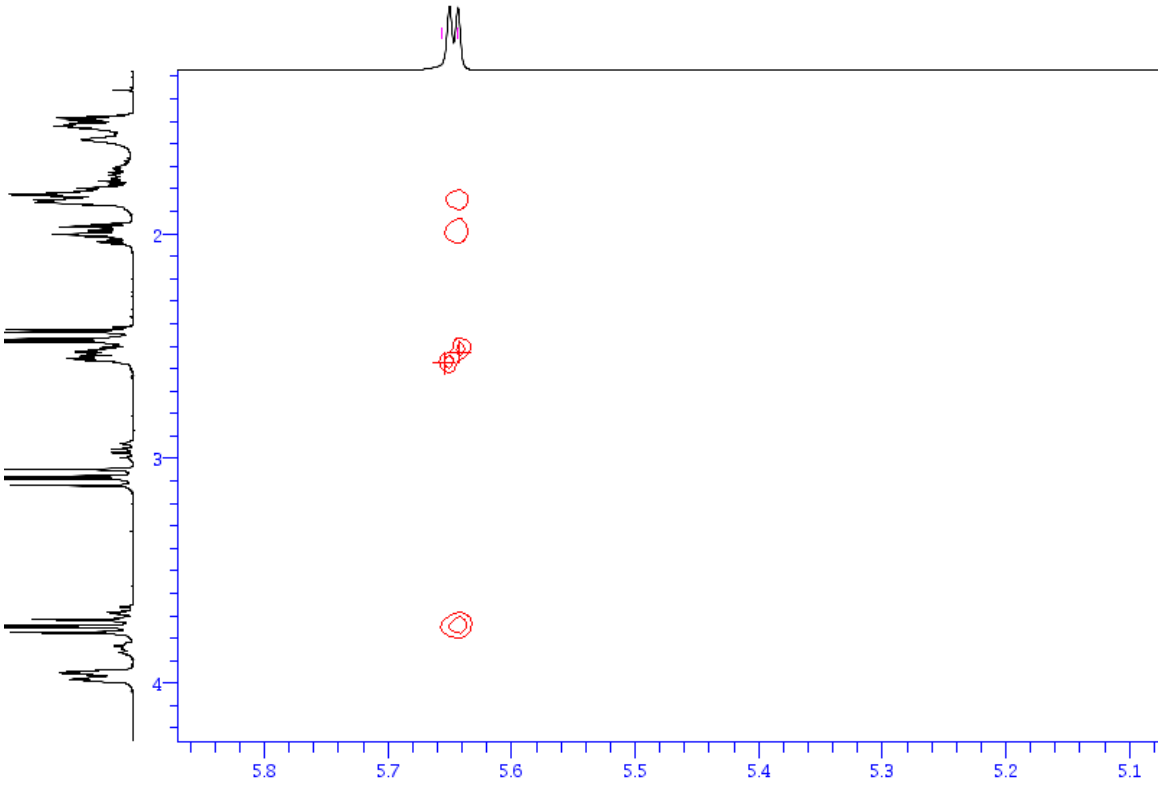


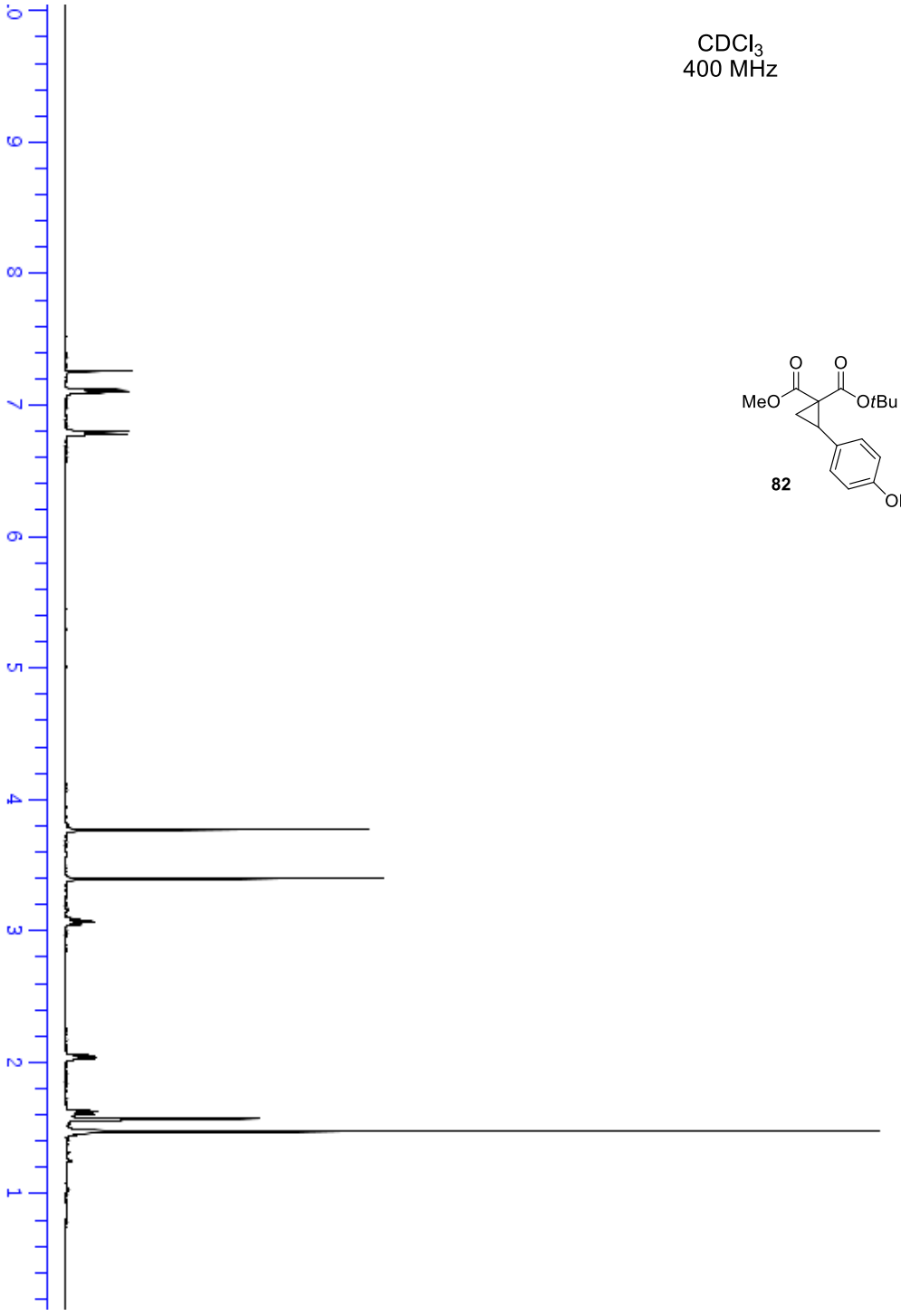


68

ROESY



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OtBu
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OMe
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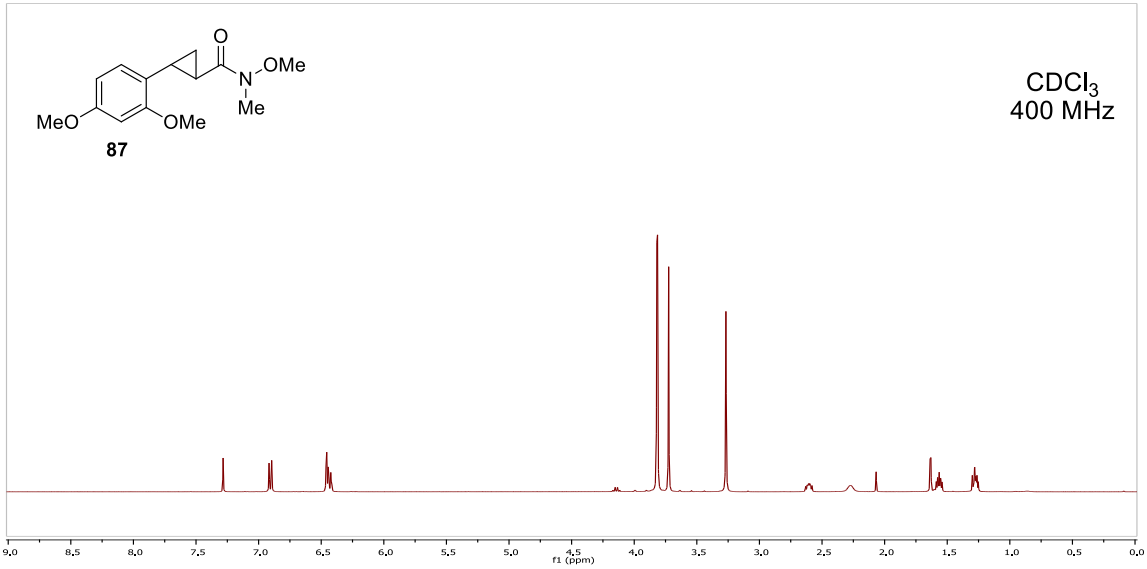
9
8
7
6
5
4
3
2
1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OMe
Me
MeO
OMe
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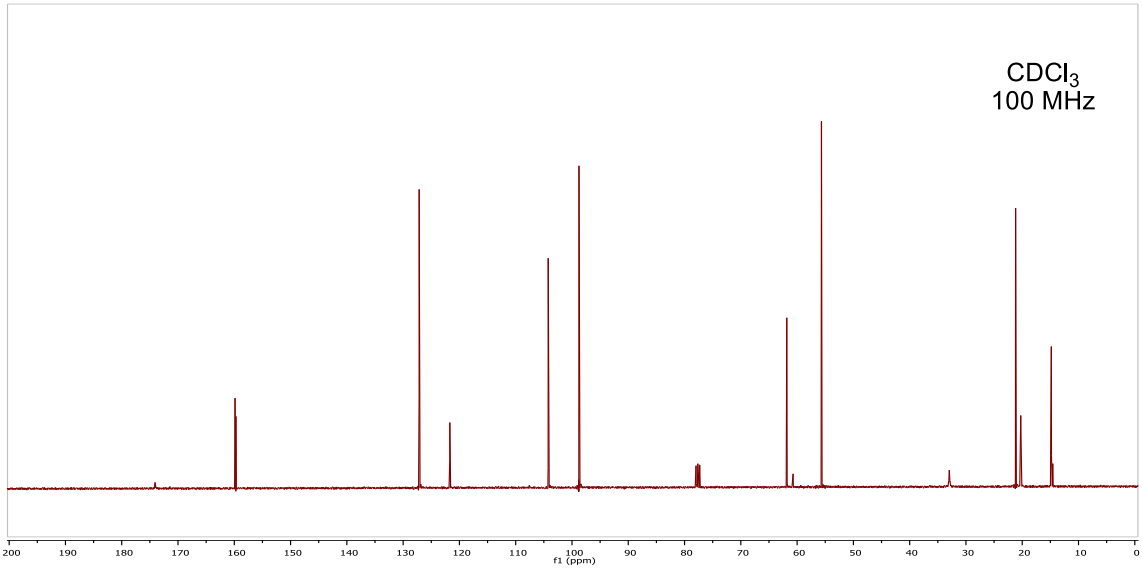
400 MHz
f1 (ppm)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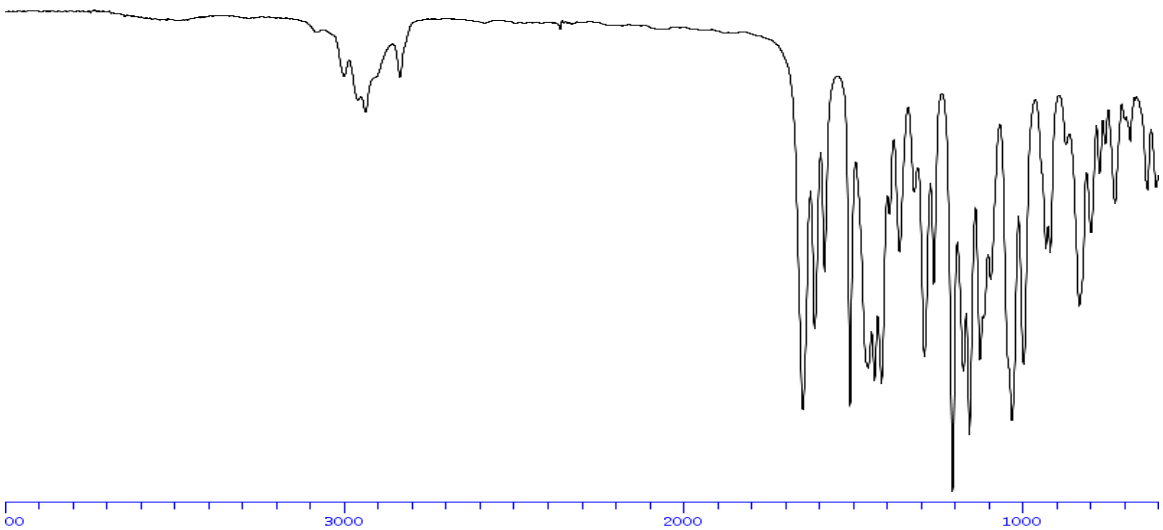
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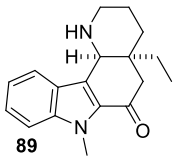

89

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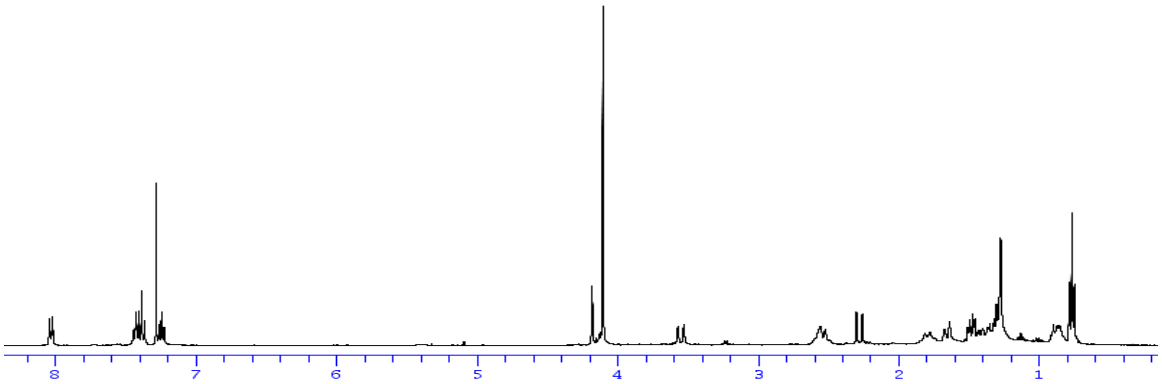
400 MHz



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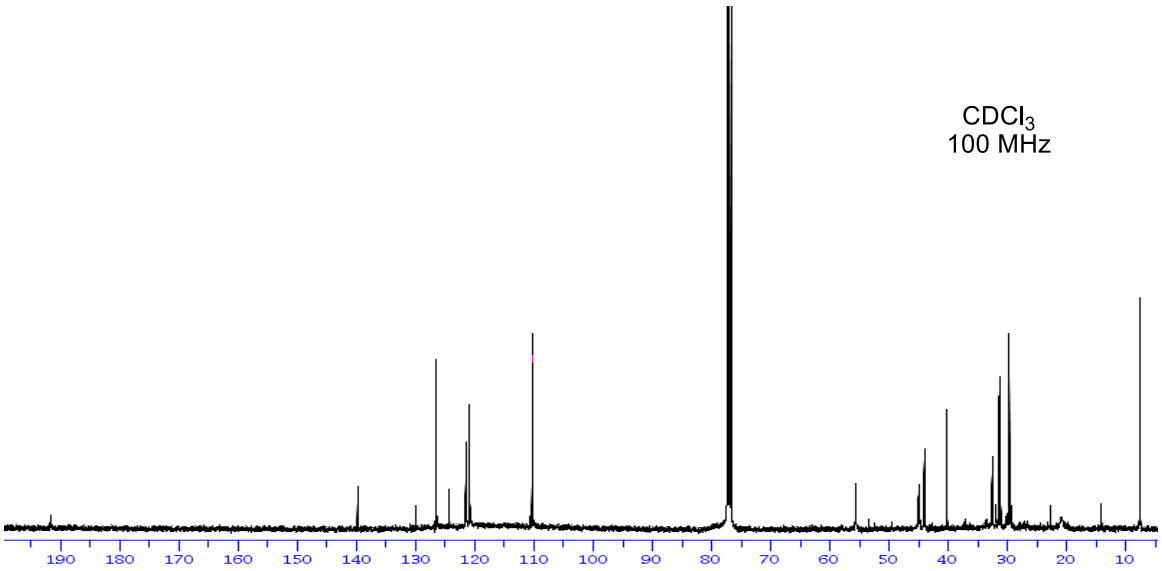

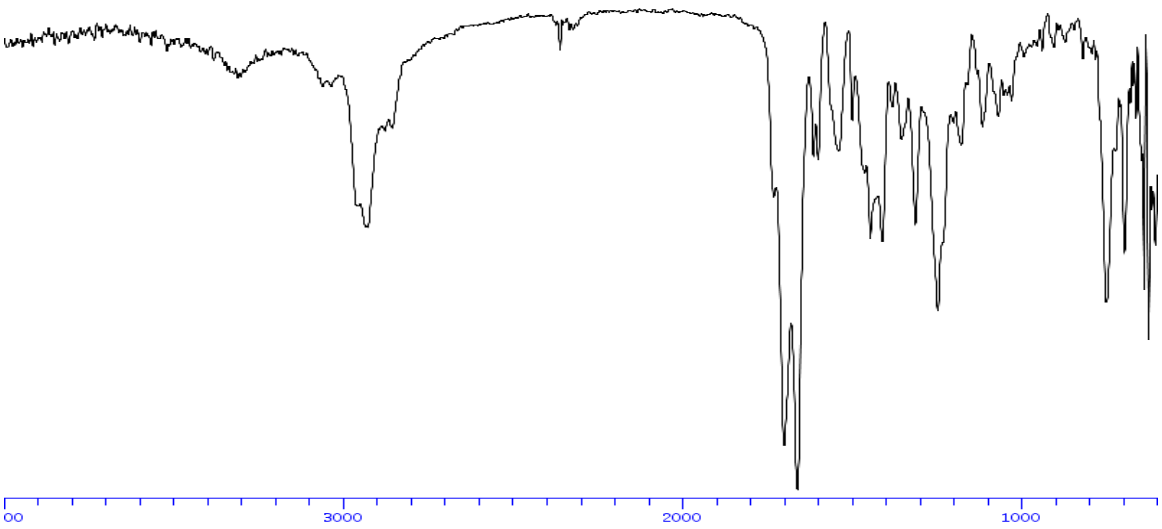

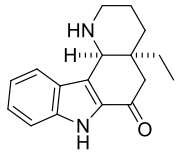

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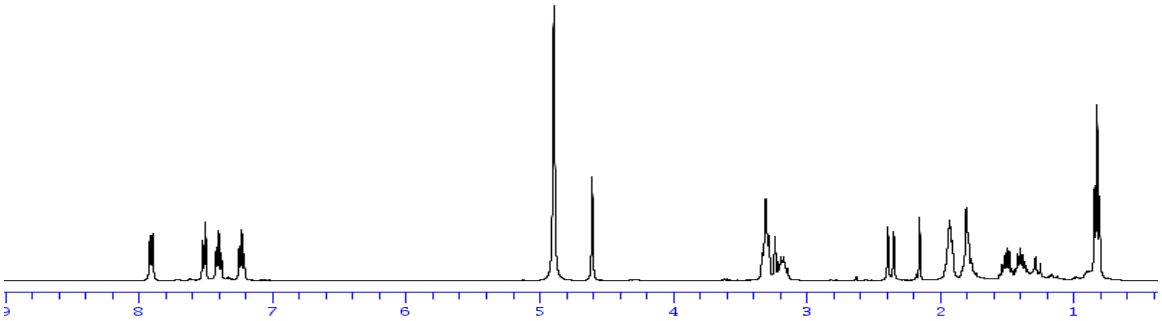

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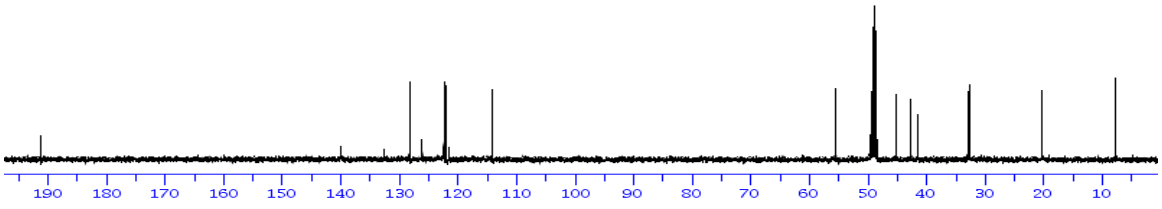
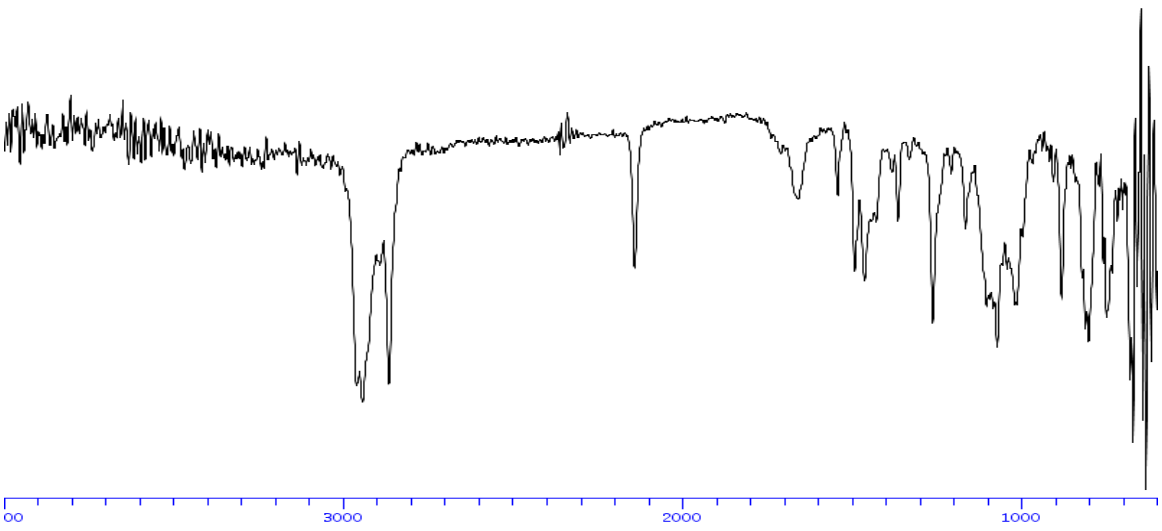




Crystallographic data (CCDC data depository number: 777832).

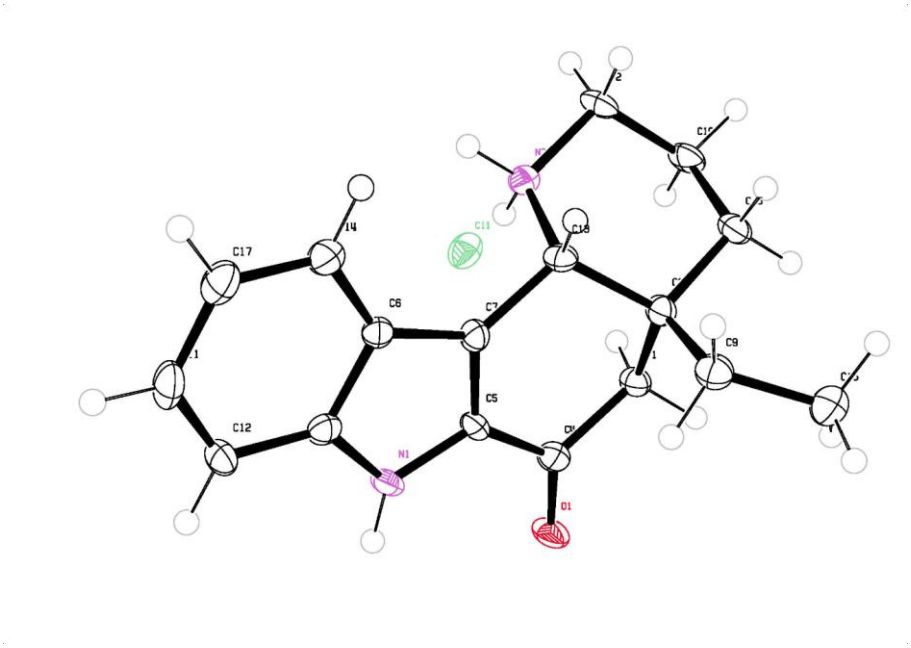


Table 1. Crystal data and structure refinement for fds330.

Identification code	fds330	
Empirical formula	C17 H21 Cl N2 O	
Formula weight	304.81	
Temperature	140(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 9.1506(10) Å	α= 90°.
	b = 15.3882(14) Å	β= 103.618(12)°.
	c = 10.9477(12) Å	γ = 90°.
Volume	1498.2(3) Å^3	
Z	4	
Density (calculated)	1.351 Mg/m^3	
Absorption coefficient	0.256 mm^{-1}	
F(000)	648	
Crystal size	0.15 x 0.11 x 0.09 mm^3	
Theta range for data collection	2.93 to 26.37°.	
Index ranges	-11<=h<=11, -19<=k<=19, -13<=l<=13	
Reflections collected	13092	
Independent reflections	3040 [R(int) = 0.0708]	
Completeness to theta = 26.37°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.92803	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3040 / 0 / 274
Goodness-of-fit on F^2	0.967
Final R indices [I>2sigma(I)]	R1 = 0.0546, wR2 = 0.0992
R indices (all data)	R1 = 0.1022, wR2 = 0.1112
Largest diff. peak and hole	0.380 and -0.237 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for fds330. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	2806(1)	4005(1)	4618(1)	27(1)
O(1)	-709(2)	5221(1)	1532(2)	28(1)
N(1)	3748(3)	5933(2)	4836(2)	19(1)
N(2)	2019(3)	5647(2)	754(2)	20(1)
C(1)	2842(3)	6581(2)	3930(2)	17(1)
C(2)	3758(3)	6081(2)	6187(3)	23(1)
C(3)	2167(3)	6082(2)	6324(3)	24(1)
C(4)	1247(3)	6764(2)	5501(3)	21(1)
C(5)	1213(3)	6668(2)	4094(2)	18(1)
C(6)	273(3)	5867(2)	3555(2)	18(1)
C(7)	317(3)	5612(2)	2231(2)	20(1)
C(8)	1700(3)	5838(2)	1889(2)	17(1)
C(9)	2867(3)	6294(2)	2628(2)	17(1)
C(10)	3988(3)	6389(2)	1933(2)	17(1)
C(11)	3410(3)	5976(2)	759(2)	18(1)
C(12)	4208(3)	5956(2)	-184(3)	23(1)
C(13)	5577(3)	6356(2)	69(3)	27(1)
C(14)	6179(3)	6768(2)	1222(3)	26(1)
C(15)	5402(3)	6784(2)	2151(3)	22(1)
C(16)	521(3)	7495(2)	3402(3)	23(1)
C(17)	-898(3)	7839(2)	3712(3)	28(1)

Table 3. Bond lengths [Å] and angles [°] for fds330.

O(1)-C(7)	1.221(3)

N(1)-C(2)	1.495(3)
N(1)-C(1)	1.510(3)
N(1)-H(1A)	0.91(3)
N(1)-H(1B)	0.95(3)
N(2)-C(11)	1.369(3)
N(2)-C(8)	1.373(3)
N(2)-H(2)	0.88(3)
C(1)-C(9)	1.497(4)
C(1)-C(5)	1.548(3)
C(1)-H(1)	1.00(2)
C(2)-C(3)	1.498(4)
C(2)-H(2A)	0.94(3)
C(2)-H(2B)	0.93(3)
C(3)-C(4)	1.504(4)
C(3)-H(3A)	0.88(3)
C(3)-H(3B)	1.00(2)
C(4)-C(5)	1.541(4)
C(4)-H(4A)	0.98(2)
C(4)-H(4B)	0.96(3)
C(5)-C(16)	1.539(4)
C(5)-C(6)	1.540(4)
C(6)-C(7)	1.511(4)
C(6)-H(6A)	0.97(3)
C(6)-H(6B)	0.97(3)
C(7)-C(8)	1.444(4)
C(8)-C(9)	1.371(3)
C(9)-C(10)	1.422(4)
C(10)-C(15)	1.398(4)
C(10)-C(11)	1.420(4)
C(11)-C(12)	1.398(4)
C(12)-C(13)	1.364(4)
C(12)-H(12)	0.94(2)
C(13)-C(14)	1.404(4)
C(13)-H(13)	0.84(3)
C(14)-C(15)	1.371(4)
C(14)-H(14)	0.93(3)
C(15)-H(15)	0.99(3)
C(16)-C(17)	1.513(4)

C(16)-H(16A)	0.96(3)
C(16)-H(16B)	0.95(3)
C(17)-H(17A)	0.92(3)
C(17)-H(17B)	0.95(3)
C(17)-H(17C)	0.96(3)
C(2)-N(1)-C(1)	115.0(2)
C(2)-N(1)-H(1A)	104.3(15)
C(1)-N(1)-H(1A)	112.1(16)
C(2)-N(1)-H(1B)	106.6(19)
C(1)-N(1)-H(1B)	108.9(19)
H(1A)-N(1)-H(1B)	110(2)
C(11)-N(2)-C(8)	108.3(2)
C(11)-N(2)-H(2)	123(2)
C(8)-N(2)-H(2)	129(2)
C(9)-C(1)-N(1)	107.5(2)
C(9)-C(1)-C(5)	111.5(2)
N(1)-C(1)-C(5)	112.1(2)
C(9)-C(1)-H(1)	108.7(12)
N(1)-C(1)-H(1)	104.7(12)
C(5)-C(1)-H(1)	111.9(12)
N(1)-C(2)-C(3)	108.6(2)
N(1)-C(2)-H(2A)	105.5(15)
C(3)-C(2)-H(2A)	111.8(15)
N(1)-C(2)-H(2B)	103.2(15)
C(3)-C(2)-H(2B)	111.5(16)
H(2A)-C(2)-H(2B)	115(2)
C(2)-C(3)-C(4)	111.1(2)
C(2)-C(3)-H(3A)	105(2)
C(4)-C(3)-H(3A)	109.8(19)
C(2)-C(3)-H(3B)	107.9(14)
C(4)-C(3)-H(3B)	110.2(14)
H(3A)-C(3)-H(3B)	113(2)
C(3)-C(4)-C(5)	114.1(2)
C(3)-C(4)-H(4A)	109.8(13)
C(5)-C(4)-H(4A)	106.3(13)
C(3)-C(4)-H(4B)	107.8(16)
C(5)-C(4)-H(4B)	110.4(16)
H(4A)-C(4)-H(4B)	108(2)

C(16)-C(5)-C(6)	110.2(2)
C(16)-C(5)-C(4)	108.8(2)
C(6)-C(5)-C(4)	109.7(2)
C(16)-C(5)-C(1)	108.1(2)
C(6)-C(5)-C(1)	110.6(2)
C(4)-C(5)-C(1)	109.4(2)
C(7)-C(6)-C(5)	115.9(2)
C(7)-C(6)-H(6A)	103.7(14)
C(5)-C(6)-H(6A)	109.9(14)
C(7)-C(6)-H(6B)	109.7(14)
C(5)-C(6)-H(6B)	105.7(14)
H(6A)-C(6)-H(6B)	112(2)
O(1)-C(7)-C(8)	123.2(2)
O(1)-C(7)-C(6)	122.6(2)
C(8)-C(7)-C(6)	114.2(2)
C(9)-C(8)-N(2)	110.0(2)
C(9)-C(8)-C(7)	125.3(2)
N(2)-C(8)-C(7)	124.7(2)
C(8)-C(9)-C(10)	107.2(2)
C(8)-C(9)-C(1)	121.9(2)
C(10)-C(9)-C(1)	130.8(2)
C(15)-C(10)-C(11)	118.8(2)
C(15)-C(10)-C(9)	135.2(3)
C(11)-C(10)-C(9)	106.1(2)
N(2)-C(11)-C(12)	129.5(3)
N(2)-C(11)-C(10)	108.4(2)
C(12)-C(11)-C(10)	122.0(2)
C(13)-C(12)-C(11)	117.0(3)
C(13)-C(12)-H(12)	123.9(15)
C(11)-C(12)-H(12)	119.0(15)
C(12)-C(13)-C(14)	122.2(3)
C(12)-C(13)-H(13)	120.3(18)
C(14)-C(13)-H(13)	117.4(18)
C(15)-C(14)-C(13)	120.8(3)
C(15)-C(14)-H(14)	117.9(17)
C(13)-C(14)-H(14)	121.3(17)
C(14)-C(15)-C(10)	119.1(3)
C(14)-C(15)-H(15)	121.5(15)

C(10)-C(15)-H(15)	119.3(15)
C(17)-C(16)-C(5)	117.0(3)
C(17)-C(16)-H(16A)	106.6(16)
C(5)-C(16)-H(16A)	110.0(16)
C(17)-C(16)-H(16B)	109.6(17)
C(5)-C(16)-H(16B)	109.2(16)
H(16A)-C(16)-H(16B)	104(2)
C(16)-C(17)-H(17A)	109.4(17)
C(16)-C(17)-H(17B)	111.3(17)
H(17A)-C(17)-H(17B)	110(2)
C(16)-C(17)-H(17C)	110.1(17)
H(17A)-C(17)-H(17C)	108(2)
H(17B)-C(17)-H(17C)	108(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for fds330. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	20(1)	26(1)	35(1)	-2(1)	7(1)	-2(1)
O(1)	19(1)	45(1)	18(1)	-11(1)	3(1)	-12(1)
N(1)	17(1)	22(1)	17(1)	-1(1)	2(1)	-1(1)
N(2)	18(1)	31(1)	12(1)	-5(1)	3(1)	-4(1)
C(1)	15(1)	18(1)	16(2)	-2(1)	2(1)	-5(1)
C(2)	29(2)	26(2)	12(2)	-2(1)	1(1)	-2(1)
C(3)	26(2)	34(2)	11(2)	-2(1)	4(1)	-4(1)
C(4)	20(2)	26(2)	17(2)	-6(1)	6(1)	-6(1)
C(5)	16(1)	23(1)	17(2)	-3(1)	5(1)	-2(1)
C(6)	16(2)	22(2)	17(2)	-1(1)	5(1)	-2(1)
C(7)	21(2)	24(1)	15(2)	1(1)	4(1)	1(1)
C(8)	19(1)	23(1)	10(1)	-1(1)	4(1)	-1(1)
C(9)	17(1)	21(1)	14(1)	1(1)	6(1)	1(1)
C(10)	17(1)	20(1)	15(1)	4(1)	3(1)	4(1)
C(11)	17(1)	20(1)	17(1)	3(1)	1(1)	4(1)
C(12)	25(2)	30(2)	15(2)	1(1)	7(1)	5(1)
C(13)	24(2)	34(2)	28(2)	6(1)	18(2)	7(1)

C(14)	19(2)	31(2)	29(2)	4(1)	9(1)	-1(1)
C(15)	17(2)	26(2)	21(2)	0(1)	4(1)	-1(1)
C(16)	24(2)	23(2)	22(2)	-1(1)	5(1)	-3(1)
C(17)	23(2)	31(2)	29(2)	-1(2)	7(2)	1(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for fds330.

	x	y	z	U(eq)
H(1A)	3400(30)	5384(17)	4680(20)	10(6)
H(1B)	4760(40)	5960(20)	4780(30)	50(10)
H(2)	1480(30)	5340(20)	120(30)	40(10)
H(1)	3410(20)	7140(14)	4114(19)	0(5)
H(2A)	4220(30)	6627(17)	6390(20)	17(7)
H(2B)	4290(30)	5608(17)	6590(20)	15(7)
H(3A)	2230(30)	6205(18)	7120(30)	33(9)
H(3B)	1730(30)	5493(17)	6090(20)	12(6)
H(4A)	1660(30)	7341(16)	5750(20)	9(6)
H(4B)	250(30)	6741(17)	5630(20)	23(7)
H(6A)	660(30)	5355(17)	4050(20)	14(7)
H(6B)	-750(30)	6003(16)	3590(20)	16(7)
H(12)	3810(30)	5644(16)	-930(20)	13(7)
H(13)	6110(30)	6345(16)	-460(20)	15(7)
H(14)	7100(30)	7047(18)	1370(30)	28(8)
H(15)	5840(30)	7044(16)	2990(20)	20(7)
H(16A)	1240(30)	7961(18)	3560(20)	28(8)
H(16B)	350(30)	7405(16)	2520(30)	24(8)
H(17A)	-1560(30)	7390(17)	3700(20)	21(8)
H(17B)	-1360(30)	8270(19)	3130(30)	28(8)
H(17C)	-670(30)	8095(18)	4530(30)	26(8)

Table 6. Torsion angles [°] for fds330.

C(2)-N(1)-C(1)-C(9)	-175.9(2)

C(2)-N(1)-C(1)-C(5)	-52.9(3)
C(1)-N(1)-C(2)-C(3)	57.1(3)
N(1)-C(2)-C(3)-C(4)	-57.6(3)
C(2)-C(3)-C(4)-C(5)	57.6(3)
C(3)-C(4)-C(5)-C(16)	-168.6(2)
C(3)-C(4)-C(5)-C(6)	70.7(3)
C(3)-C(4)-C(5)-C(1)	-50.8(3)
C(9)-C(1)-C(5)-C(16)	-74.1(3)
N(1)-C(1)-C(5)-C(16)	165.3(2)
C(9)-C(1)-C(5)-C(6)	46.6(3)
N(1)-C(1)-C(5)-C(6)	-74.0(3)
C(9)-C(1)-C(5)-C(4)	167.5(2)
N(1)-C(1)-C(5)-C(4)	46.9(3)
C(16)-C(5)-C(6)-C(7)	68.6(3)
C(4)-C(5)-C(6)-C(7)	-171.6(2)
C(1)-C(5)-C(6)-C(7)	-50.9(3)
C(5)-C(6)-C(7)-O(1)	-153.3(3)
C(5)-C(6)-C(7)-C(8)	29.2(3)
C(11)-N(2)-C(8)-C(9)	0.5(3)
C(11)-N(2)-C(8)-C(7)	178.7(2)
O(1)-C(7)-C(8)-C(9)	178.3(3)
C(6)-C(7)-C(8)-C(9)	-4.2(4)
O(1)-C(7)-C(8)-N(2)	0.3(4)
C(6)-C(7)-C(8)-N(2)	177.8(2)
N(2)-C(8)-C(9)-C(10)	-0.6(3)
C(7)-C(8)-C(9)-C(10)	-178.9(2)
N(2)-C(8)-C(9)-C(1)	-179.2(2)
C(7)-C(8)-C(9)-C(1)	2.6(4)
N(1)-C(1)-C(9)-C(8)	98.6(3)
C(5)-C(1)-C(9)-C(8)	-24.6(3)
N(1)-C(1)-C(9)-C(10)	-79.6(3)
C(5)-C(1)-C(9)-C(10)	157.2(3)
C(8)-C(9)-C(10)-C(15)	179.4(3)
C(1)-C(9)-C(10)-C(15)	-2.2(5)
C(8)-C(9)-C(10)-C(11)	0.5(3)
C(1)-C(9)-C(10)-C(11)	178.9(2)
C(8)-N(2)-C(11)-C(12)	-179.1(3)
C(8)-N(2)-C(11)-C(10)	-0.1(3)

C(15)-C(10)-C(11)-N(2)	-179.4(2)
C(9)-C(10)-C(11)-N(2)	-0.3(3)
C(15)-C(10)-C(11)-C(12)	-0.3(4)
C(9)-C(10)-C(11)-C(12)	178.8(2)
N(2)-C(11)-C(12)-C(13)	178.7(3)
C(10)-C(11)-C(12)-C(13)	-0.2(4)
C(11)-C(12)-C(13)-C(14)	0.4(4)
C(12)-C(13)-C(14)-C(15)	0.0(4)
C(13)-C(14)-C(15)-C(10)	-0.5(4)
C(11)-C(10)-C(15)-C(14)	0.7(4)
C(9)-C(10)-C(15)-C(14)	-178.2(3)
C(6)-C(5)-C(16)-C(17)	74.6(3)
C(4)-C(5)-C(16)-C(17)	-45.7(3)
C(1)-C(5)-C(16)-C(17)	-164.4(3)

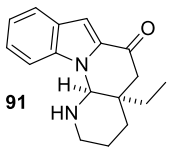
Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for fds330 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1A)...Cl(1)	0.91(3)	2.19(3)	3.082(3)	170(2)
N(1)-H(1B)...Cl(1)#1	0.95(3)	2.17(3)	3.069(2)	159(3)
N(2)-H(2)...O(1)#2	0.88(3)	1.98(3)	2.841(3)	164(3)

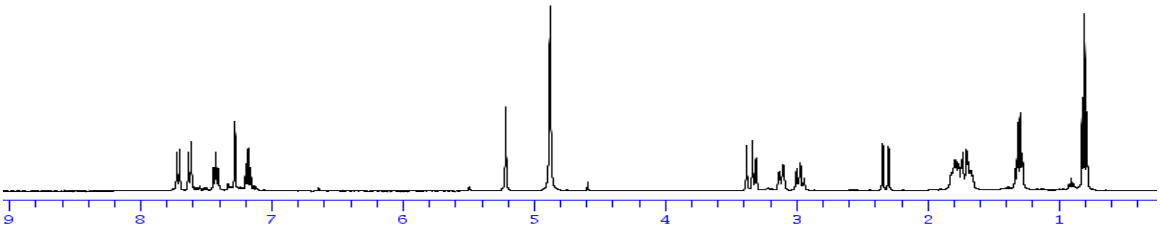
Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z+1 #2 -x,-y+1,-z



91

CD_3OD
400 MHz



CD_3OD
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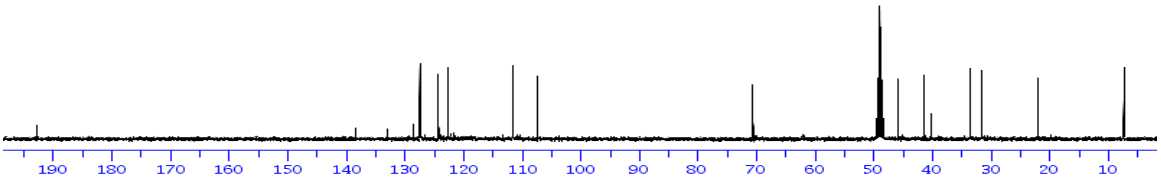

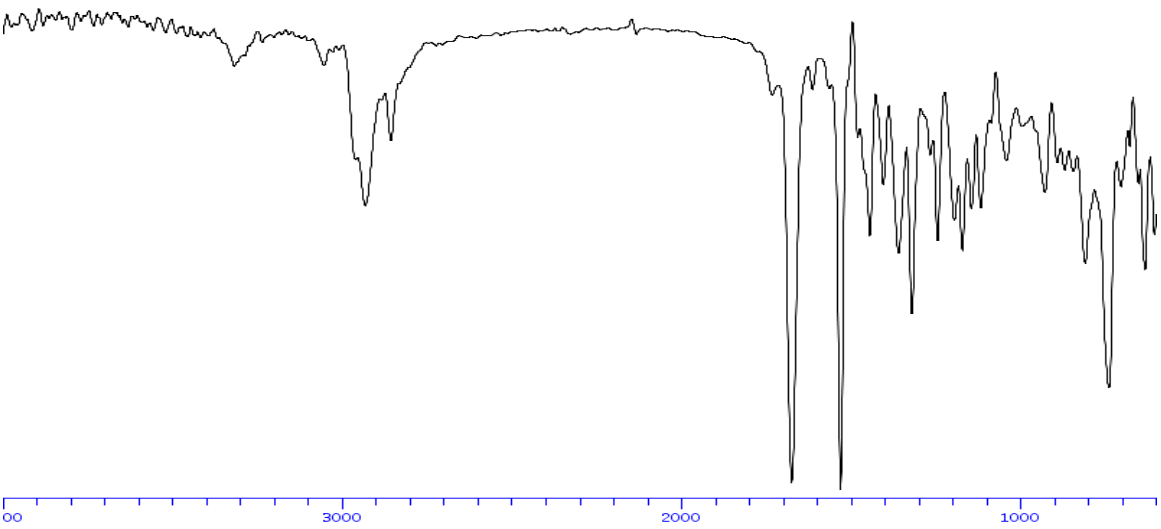

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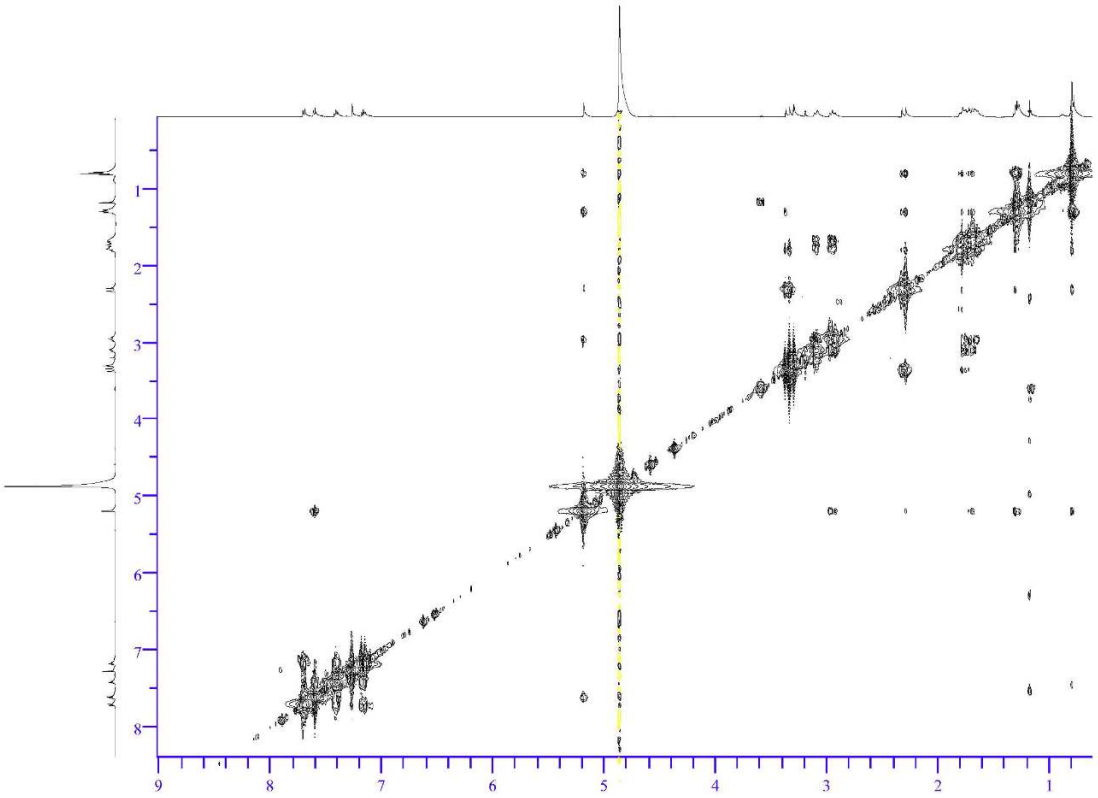

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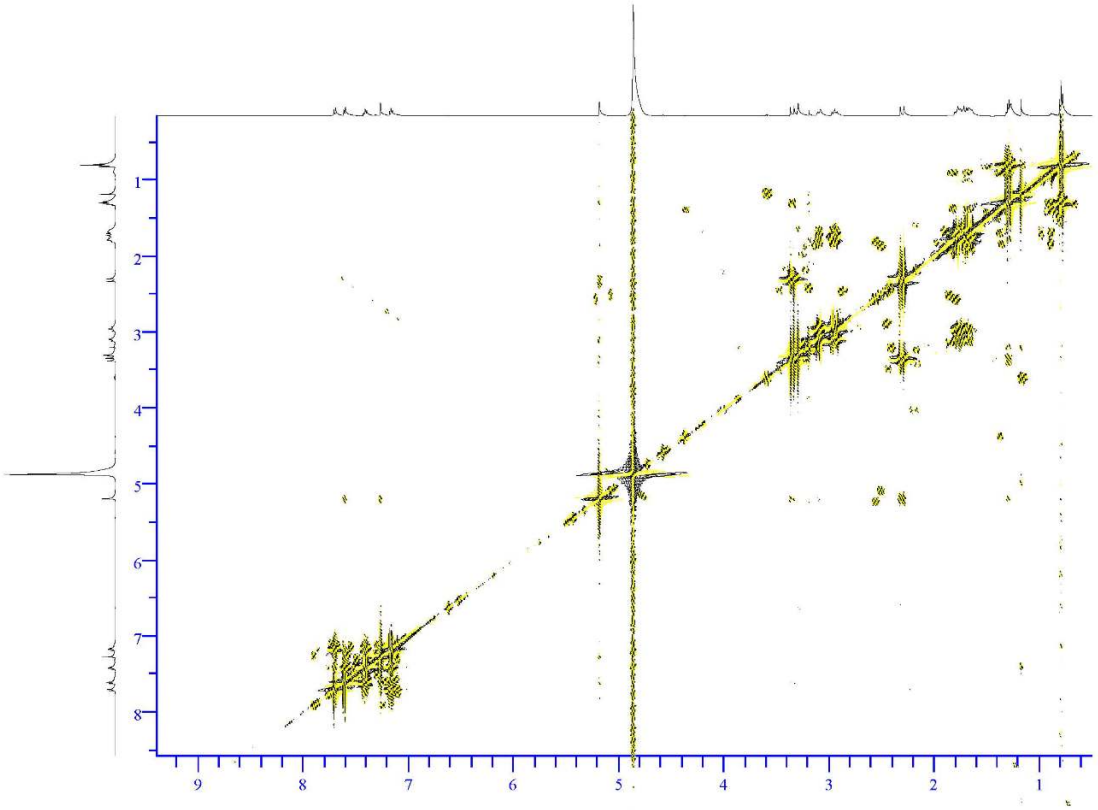

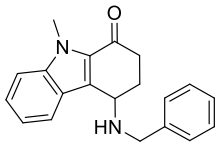

93

CD_3OD
400 MHz

$CDCl_3$
100 MHz