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„Investigations regarding the reaction of Weinreb amides with specific carbenoids“

verfasst von / submitted by

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INDEX

1. INTRODUCTION AND RESEARCH QUESTION

This thesis deals with the synthesis of α-oxyketones via the addition of carbenoids to Weinreb amides in THF. α-Oxyketones are important in organic and pharmaceutical synthesis but also in food and flavour chemistry.[1] Thus their significance and application are summarized at the beginning of this work.

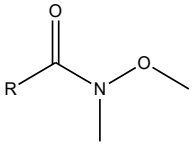


Figure 1 *General structure of Weinreb amides*

1.1 Structure and characteristics of α-oxyketones

α-Oxyketones are distinguished by a keto group and an ether group separated by one carbon atom, also spoken of as the α-carbon atom. A keto group contains a carbon-oxygen double bond, which is also referred to as a carbonyl group. Due to the higher electronegativity of oxygen in comparison to carbon, the carbonyl group is polar, the carbon atom is positively polarized whereas the oxygen is negatively polarized, resulting in the carbon atom being electrophilic and the oxygen being nucleophilic.[2] The ether group as an electron-donating group, stabilizes the ionized form of the ketone, through reduction of the positive charge of the carbon atom of the carbonyl group, hence, the ether group in α-oxyketones decreases the electrophilicity of the carbonyl group.[3]

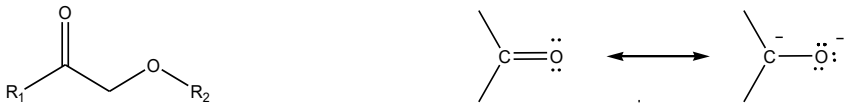


Figure 2 *General structure of α-oxyketones (left) and the polarity of carbonyl groups (right)*[2]

Ketones that contain a minimum of one so called α-hydrogen atom at the α-carbon atom are capable of keto-enol tautomerism, which means that the α-hydrogen, which is 'acidic' due to the influence of the carbonyl group, can leave in the influence of acids or bases, resulting in an enol or a resonance stabilized enolate.

Enols are less stable structural isomers of ketones, which can convert back to carbonyl compounds, this results in the presence of both forms in an equilibrium depending on the reaction conditions.[4]

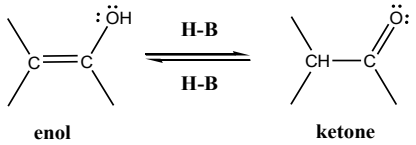


Figure 3 *Structures of keto-enol tautomerism*[4]

The carbonyl C-atom in ketones is characterized by a large chemical shift of approximately 200 ppm. This can be attributed – amongst others – to the positive charge localized at the carbonyl C-atom in the canonical form b. In contrast, ester carbonyl C-atoms exhibit smaller chemical shifts (compared to those of ketones) due to the contribution of a canonical form c, in which no positive charge is localized at the carbonyl C-atom (figure 4a).[5]

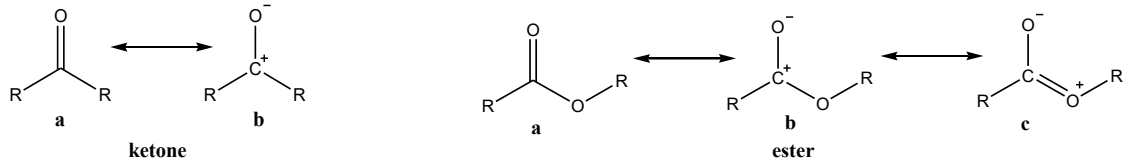


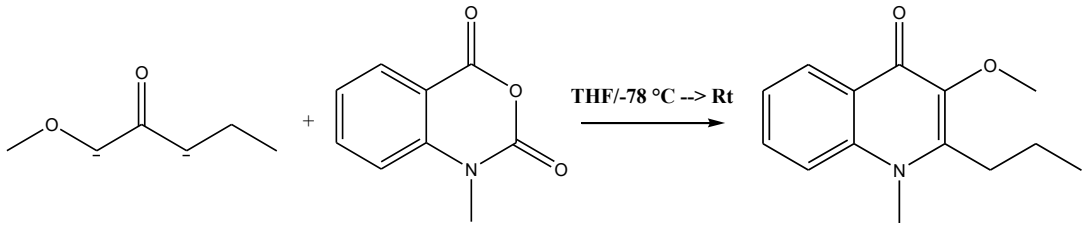
Figure 4 *Resonance structures of ketones (left) and esters (right)*

α-Oxyketones are very reactive and open to attack at different positions in behalf of keto-enol tautomerism and the polarity of the carbonyl group, therefore α-oxyketones are used as versatile reactants in synthetic chemistry.

1.2 Use in synthetic chemistry of natural products

1.2.1 Leiokinine A

α-Oxyketones are widely used in the total synthesis of natural compounds like the 4-quinoline alkaloids Leiokinine A and Leiokinine B,[6] which can also be isolated from the leaves of *Esenbeckia leiocarpa.* These compounds exhibit antifeedant activity against the pink bollworm.



Scheme 1 *Synthesis of Leiokinine A by Nakatsu*[6]

Leiokinine B could not be obtained with this approach due to sterical difficulties with the two ethyl groups.

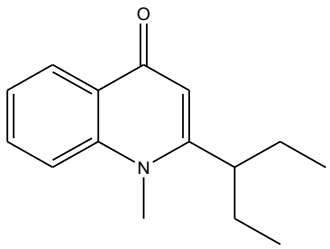
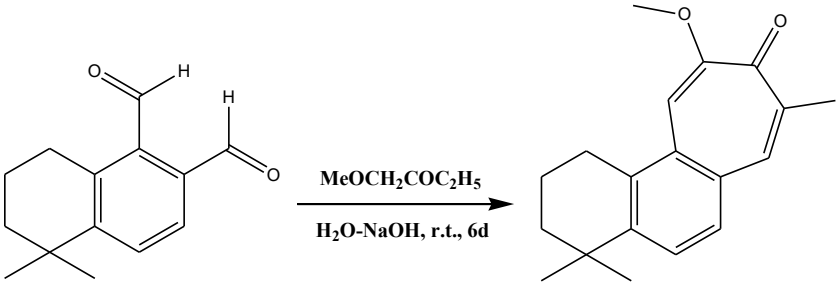


Figure 5 *Leiokinine B*[6]

1.2.2 Salviolone

Mori used α-oxyketones for the synthesis of the cytotoxic Benzotropolonoid Bisnorditerpene Salviolone,[7,8] which is contained in the roots of *Salvia miltiorrhiza*.



Scheme 2 *Step 5 of the synthesis of Salviolone*[7,8]

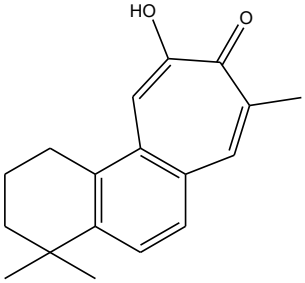


Figure 6 *Salviolone*[7,8]

1.2.3 Lardolure

Kuwahara synthesised the aggregation pheromone 1,3,5,7-tetramethyldecylformate Lardolure in 11 steps, using the reaction of methoxyacetonitrile with 2-methylpentyl magnesium bromide to get methoxymethyl ketone in the second step.[9]

1.3 Use in pharmaceutical synthetic chemistry

α-Oxyketones are not only reactants for the syntheses of natural products but also for those of medicinal drugs such as ring fused pyrazoles, where particularly simple α-oxyketones such as 1-methoxybutan-2-one, 1-methoxypentan-2-one and 1-methoxyhexan-2-one are utilized. These ring fused pyrazoles are for example used as CFR-1 receptor ligands by Loughhead[10] and Gilligan[11], Loughhead[12] also used them in the synthesis of fused pyrazoles as GABA-A α2 subtype selective receptor modulators. They are also applied in the preparation of 5-lipoxygenase inhibitors, with a naphthylmethoxy phenylalkohol or

naphthylmethoxy phenylether structure[13] or phenylpiperazines as melanocortin-4-receptor antagonists.[14] As well as the synthesis of tetrahydroquinolines as analogues of the antiviral compound Virantmycin by Francis.[15]

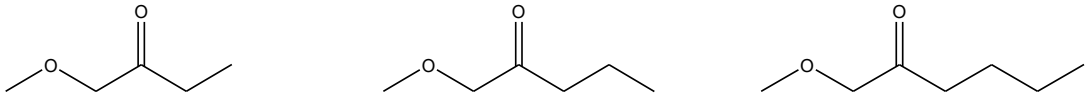


Figure 7 *1-methoxybutan-2-one, 1-methoxypentan-2-one and 1-methoxyhexan-2-one used in pharmaceutical synthesis*

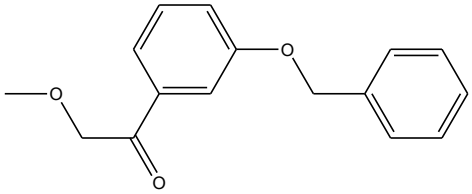


Figure 8 *1-(3-(benzyloxy)phenyl)-2-methoxyethanone used in the synthesis of 5-lipoxygenase inhibitors by Girodeau*[13]

1.4 Use in food and flavour chemistry

Aliphatic α-oxyketones play a huge role in food and flavour chemistry,[16] where they are useful in producing or enhancing various flavours or aromas such as green/spicy, fresh/fruity, grape, nutty, caramel-like and many more. They are, for example identified as flavour compounds of Burgundy Pinot Noir red wines by Schreier.[17] Other foods that have been discovered to contain α-oxyketones as volatile compounds are cognac,[18] pineapple pulp,[19] dry-cured meat[20] and sake.[21]

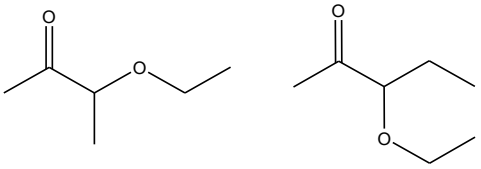


Figure 9 *3-ethoxybutan-2-one and 3-ethoxypentan-2-one volatile α-oxyketone compounds of red wine and pineapple pulp*[17,19]

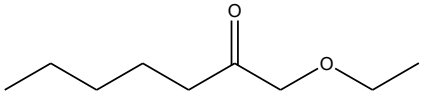


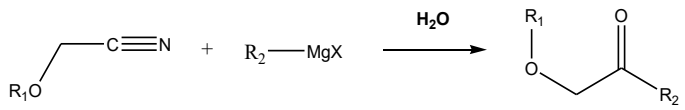
Figure 10 *1-ethoxyheptan-2-one a volatile α-oxyketone compound of dry-cured meat*[20]

1.5 Literature known synthetic routes to obtain α-oxyketones

There are various strategies to obtain α-oxyketones, for example via organometallic compounds such as Grignard reagents or an unusual Wittig reaction involving lithium chloride. Other strategies involve the reversion of polarity through hypervalent iodine starting from silyl-vinyl ethers or general routes to α-oxyketones through the use of α-alkoxy ketimines as precursors or iridium/nickel catalysed photoredox cross-coupling reactions.[22]

1.5.1 Synthesis of α-oxyketones via Grignard reagents

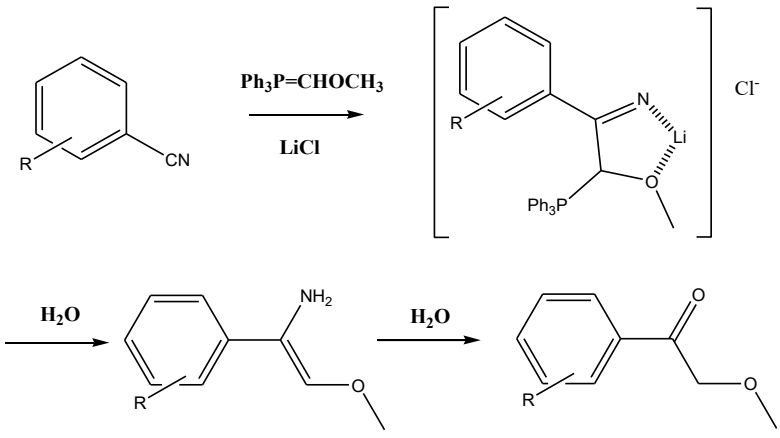
One of the oldest methods for their synthesis involves a multistep procedure, starting from chloropropyl methyl ether, which is converted into an alkoxynitrile that subsequently reacts with Grignard reagents to obtain the desired α-oxyketones.[23,24]



Scheme 3 *Reaction of alkoxynitriles with Grignard reagents to α-oxyketones*[23,24]

1.5.2 Synthesis of α-oxyketones through an unusual Wittig reaction

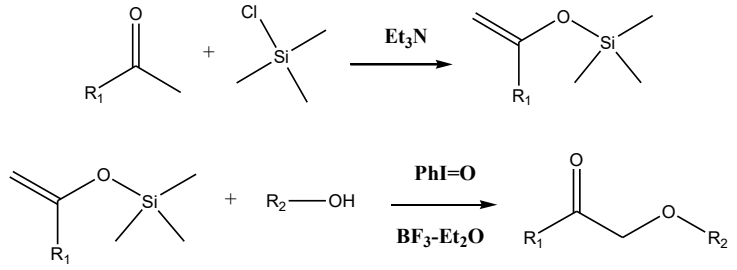
A similar approach by Mayrargue is based on an unusual Wittig reaction between phosphorous ylides and nitriles. In this process lithium chloride is obtained in a way that allows its dissolution in THF and therefore it is able to activate nitriles, which react with nucleophilic ylides to suitable intermediates, which are hydrolysed to α-methoxy acetophenones.[25,26]



Scheme 4 *Synthesis of α-methoxy acetophenones via phosphorous ylides and nitriles*[26]

1.5.3 Synthesis of α-oxyketones via umpolung strategies starting from silyl-vinyl ethers

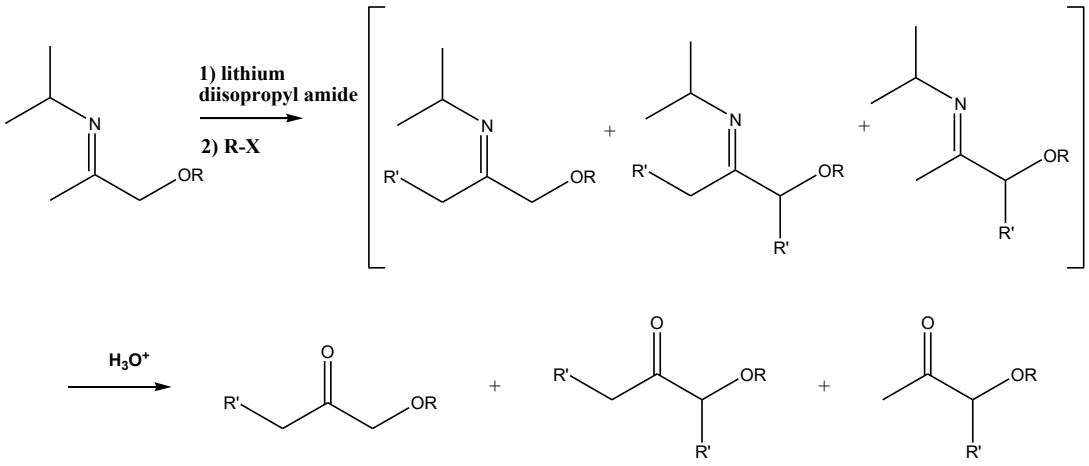
In this method silyl-vinyl ethers are used to generate nitrogen and oxygen substituted ketones after a reversion of polarity through hypervalent iodine as shown by Moriarty[27] and recently by Wirth.[28]



Scheme 5 *Synthesis of α-oxyketones through umpolung strategies by Moriarty*[27]

1.5.4 Synthesis of α-oxyketones from α-alkoxy ketimines

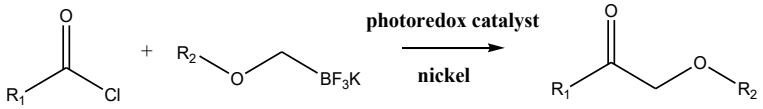
De Kimpe used α-alkoxy ketimines to obtain α-oxyketones, thus beating out the problems with direct displacement of halogens from α-haloketones. This route provides a two-step procedure involving the synthesis of the α'-alkylated and α,α'-dialkylated ketimines through condensation of α-alkoxyacetone with isopropylamine to α-alkoxy ketamines followed by a deprotonation with lithium diisopropyl amide and the reaction with alkylhalides in the first step and the hydrolysis of the imine function resulting in the wanted α-oxyketones in the second step.[1,29]



Scheme 6 *Synthesis of α-oxyketones from α-alkoxy ketimines*[1,29]

1.5.5 Synthesis of α-oxyketones via iridium/nickel catalysed photoredox cross-coupling

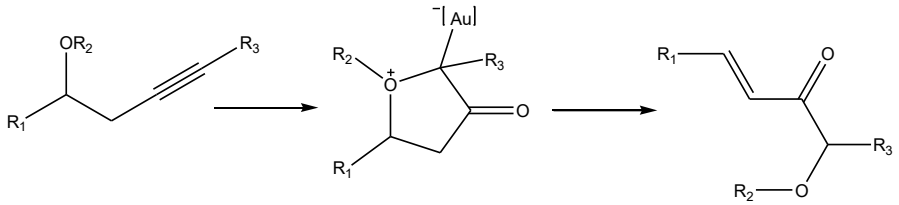
Molander introduced this method using visible photoredox cross-coupling of a wide range of acyl chlorides with potassium alkoxymethyltrifluoroborates to gain the desired α-oxyketones.[30]



Scheme 7 *Synthesis of α-oxyketones via photoredox cross-coupling*[30]

1.5.6 Synthesis of α-oxyketones through gold catalysed rearrangement

α,β-unsaturated alkoxyketones and other α,β-unsaturated carbonyl compounds can be achieved through a gold-catalysed oxidative rearrangement of homopropargylic ether introduced by Li.[31]



Scheme 8 *Mechanism of the gold catalysed rearrangement, including the proposed intermediate*[31]

1.6 Research question

The majority of the synthetic routes mentioned above have disadvantages, such as restricted efficiency and therefore low yields, long reaction times and multiple step procedures, as well as the need of harsh conditions.[22]

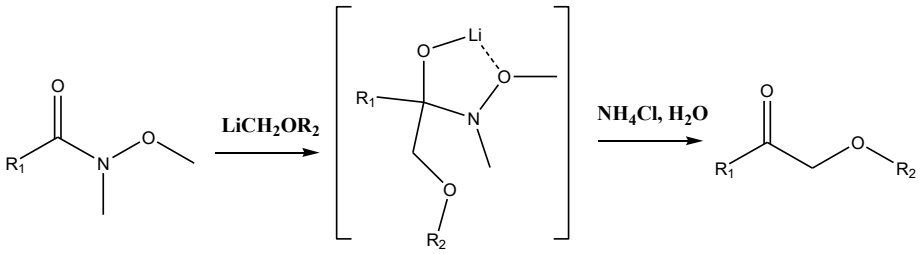
Other researches have shown that lithium carbenoid reagents qualify for the transfer of a functionalized methylene group into an electrophilic partner without the need of further steps[32,33]

Hence, for this thesis the question was posed whether the reaction of lithium carbenoid reagents with Weinreb amides proves to be an efficient and direct method for the production of functionalized α-oxyketones.

To explore the scope and especially the stereoselectivity of this method, a wide range of reactions was accomplished.

2. RESEARCH ON THE SYNTHESIS OF α-OXYKETONES VIA THE REACTION OF LITHIUM CARBENOIDS WITH WEINREB AMIDES

In the course of this work the addition of carbenoids of the type $LiCH_2OR$ to Weinreb amides was investigated in order to establish a generally applicable method for the synthesis of the target α-oxyketones (see scheme 9).



Scheme 9 *Addition of $LiCH_2OR_2$ to Weinreb amides, including the metal chelated intermediate*[34]

For the synthesis of α-oxyketones Weinreb amides and lithium carbenoids were used as reactants. The name carbenoid was established by Closs and Moss for an organometallic compound where one carbon atom has a bond to a metal like lithium, magnesium or zinc and a bond to an electrophilic element such as halogens, OR or NR_2.[33,35]

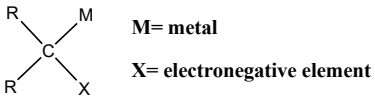


Figure 11 *Structure of carbenoids*

This structure results in nucleophilic as well as electrophilic behaviour considering the experimental conditions, low temperatures bring out their nucleophilic character and higher temperatures result in electrophilicity.[32]

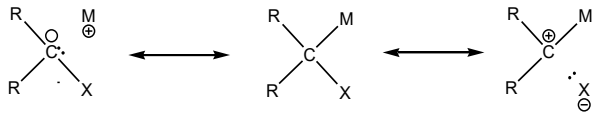


Figure 12 *Nucleophilic (left) and electrophilic (right) structures of carbenoids*[32,35]

Because of their high reactivity and thermolability, reactions with carbenoids have to be carried out at low temperature, in this case at -78°C. The following table (table 1) shows the reactants used in this thesis.

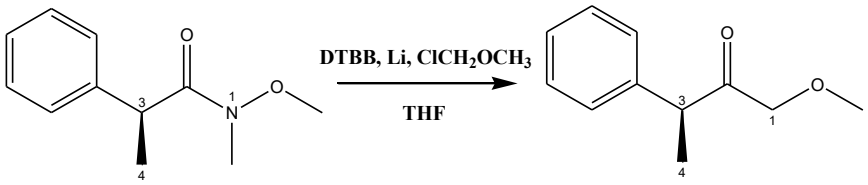
Lithium	**Weinreb amides**
Metallic lithium dispersion in mineral oil	(2*S*)-*N*-methoxy-*N*-methyl-2-phenylpropanamide
Chloroethers	*N*-methoxy-*N*-methyldecanamide
Chloromethyl methyl ether	*N*-methoxy-*N*-methyltetradecanamide
Chloromethyl ethyl ether	1-(adamantan-1-yl)-2-[methoxy(methyl)amino] ethanone
Chloromethyl menthyl ether	*N*-methoxy-*N*-methylcyclohexanecarboxamide
	4-chloro-*N*-methoxy-*N*-methylbenzamide
	3-bromo-*N*-methoxy-*N*-methylbenzamide
	(2*Z*)-2-fluoro-*N*-methoxy-*N*-methyl-3-phenylacryl amide
	N-methoxy-*N*-methyl-3-phenylpropanamide
	N-methoxy-*N*-methyl-4-biphenylcarboxamide
	N-methoxy-*N*-methyl-3-phenyl-2-propynamide
	N-methoxy-*N*-methyl-2-thiophenecarboxamide
	N-methoxy-*N*-methylbenzamide
	N,3-dimethoxy-*N*-methylbenzamide

Table 1 *Used reactants*

Advantages of this route of synthesis are very high yields and robustness regarding electronic and steric factors of the starting material. Also a wide range of starting materials and chloromethyl ether precursors can be used, even preserving the optical purity during the process.[22] Thus, it is a fast and efficient protocol to obtain especially enantiopure substituted α-oxyketones.

2.1 Optimization of the reaction

For the optimization of the reaction in this work (3*S*)-1-methoxy-3-phenyl-2-butanone (**1**) was used as model product, therefore it was possible to assess not only the outcome of the reaction but also the optical purity.[22]



Scheme 10 *Synthesis of (3S)-1-methoxy-3-phenyl-2-butanone (**1**)*

Entry	"CH_2OMe" Precursor (equiv.)	Lithiating agent (equiv.)	Catalyst (mol%)	Solvent	Yield (%)/er
1	$ClCH_2OMe$ (2.0)	Li (7.0)	5	THF	95/99:1
2	$ClCH_2OMe$ (2.0)	Li (7.0)	5	THF	73/99:1
3	$ClCH_2OMe$ (2.0)	Li (4.0)	5	THF	71/99:1
4	$BrCH_2OMe$ (2.0)	*t*-BuLi (2.0)	–	ET_2O	18/95:5
5	$BrCH_2OMe$ (2.0)	*t*-BuLi (2.0)	–	ET_2O	10/94:6
6	$ClCH_2OMe$ (2.0)	*t*-BuLi (2.0)	–	THF	–
7	$BrCH_2OMe$ (2.0)	*n*-BuLi (2.0)	–	THF	–
8	$BrCH_2OMe$ (2.0)	*n*-BuLi (2.0)	–	THF	–
9	$BrCH_2OMe$ (2.0)	MeLi-LiBr (2.0)	–	THF	–
10	$ClCH_2OMe$ (2.0)	Li (7.0)	5	CPME	–
11	$ClCH_2OMe$ (2.0)	Li (7.0)	5	2-MeTHF	84/99:1

Table 2 *Results of the reaction optimization*[22]

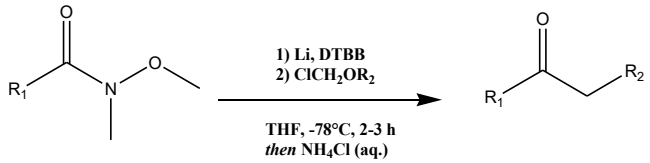
Initially, to optimize the procedure, different ways to form the methoxymethylating agent were evaluated. The Br/Li exchange mediated by *t*-BuLi resulted in poor yields of 10-18% (table 2, entries 4 and 5).[22] Attempted lithiation of $ClCH_2OMe$ with *t*-BuLi, *n*-BuLi or MeLi-LiBr was not successful (table 2, entries 6-9). Metallic lithium turned out to be the most effective agent, whereby the amount of applied lithium significantly correlated with the reaction yields as shown in table 1, entries 1 and 3.[22]

THF turned out to be the most appropriate solvent. The application of 2-MeTHF resulted in a lower conversion, and with CPME (cyclopentyl methyl ether) no product yields were obtained (table 1, entries 10 and 11).[22]

To summarize, the Cl/Li exchange meditated by 7.0 equivalents of metallic lithium in THF as solvent resulted in the highest yield, whereas the use of other solvents or lithiating agents significantly reduced the outcome.

After establishing the optimal reaction conditions, a wide range of reactions was tested to check the potential of this method.

2.1.1 Addition of $LiCH_2OR$ to Weinreb amides (General Procedure 1)



Scheme 11 *Addition of $LiCH_2OR$ to Weinreb amides*

The following procedure proved to be the most effective way for the addition of $LiCH_2OR$ to Weinreb amides.

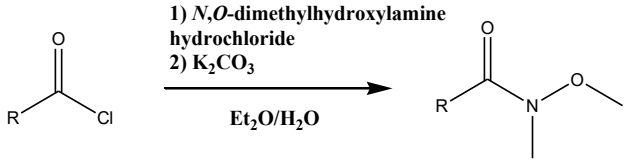
Metallic lithium was washed with dry THF and suspended in the same solvent. DTBB (4,4′-di-tert-butylbiphenyl catalyst) was added and the mixture was stirred until the appearance of a dark green colour could be recognized. This suspension was cooled down to -78°C prior further processing. Subsequently, the appropriate α-chloro ether $ClCH_2OCH_3$, $ClCH_2OCH_2CH_3$, (+)-chloromethyl menthyl ether, (-)-chloromethyl menthyl ether was added dropwise and the mixture was stirred. After adding the Weinreb amide, which was suspended in dry THF, the mixture was stirred at -78°C for 1-4 hours. After quenching the reaction with aqueous NH_4Cl, the reaction mixture was allowed to warm to room temperature. The resulting organic phase was extracted with Et_2O, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude compounds were purified as reported in the experimental part through flash column chromatography.

2.1.2 General Procedure 2 (via cannula)

To prevent interactions between the metallic lithium and halogens or double bonds, the methoxymethylating agent was generated separately and then added to the Weinreb amide, thus lithium did not come in contact with the precursors. Therefore General Procedure 1 was modified. The carbenoid $LiCH_2OCH_3$ or $LiCH_2OCH_2CH_3$ was generated in a separate flask then the solution of the appropriate Weinreb amide. After cooling down both flask to -78°C the suspension containing the carbenoid was added via cannula, thus preventing the metallic lithium from directly interacting with the Weinreb amide.

2.2 Weinreb amides

The Weinreb amides given below were synthesised according to standard synthetic routes.[34,36] Other Weinreb amides used in this work were either synthesised by other people working on this project or obtained from Sigma-Aldrich.



Scheme 12 *Synthesis of Weinreb amides*

N,O-dimethylhydroxylamine hydrochloride was solved in a mixture of Et_2O and water. Potassium carbonate was added and the mixture was cooled down to 0°C. To this mixture the starting material was added and the reaction was stirred for several hours at room temperature, until it was completed. The organic phase was extracted, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure.

The purity of the compound could be evaluated using NMR.

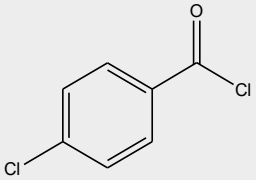
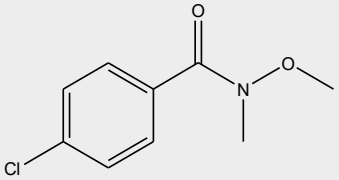
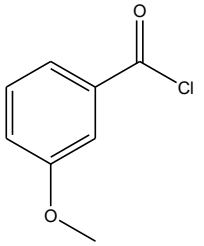
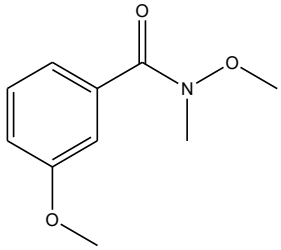
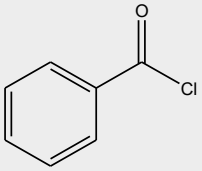
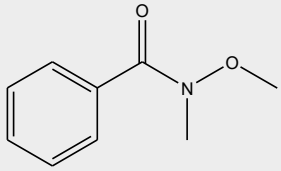
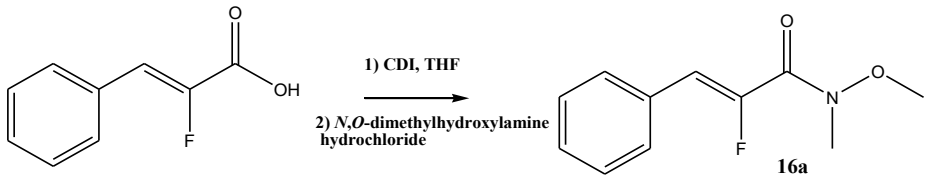
Reaction	**Starting material**	**Weinreb amide**
6a	 4-chlorobenzoyl chloride	 4-chloro-*N*-methoxy-*N*-methylbenzamide (**6a**)
13a	 3-methoxybenzoyl chloride	 *N*,3-dimethoxy-*N*-methylbenzamide (**13a**)
17a	 benzoyl chloride	 *N*-methoxy-*N*-methylbenzamide (**17a**)

Table 3 *Synthesised Weinreb amides*

2.2.1. (2*Z*)-2-fluoro-*N*-methoxy-*N*-methyl-3-phenylacryl amide (**16a**)



Scheme 13 *Synthesis of (2Z)-2-fluoro-N-methoxy-N-methyl-3-phenylacryl amide (**16a**)*

(*Z*)-2-fluoro-3-phenylacrylic acid was solubilized in dry THF the solution was cooled down to 0°C. CDI (1,1'-carbonyldiimidazole) was added to activate the acid, therefore the solution was stirred for 1 hour. Then *N*,*O*-dimethylhydroxylamine hydrochloride was added and the reaction was stirred for several hours at room temperature until it was completed. The reaction was quenched with aqueous NH_4Cl, then the organic phase was extracted, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure.

2.3 Reactions

The following syntheses of compounds **1-18** show that the reaction of Weinreb amides with carbenoids resulted in a wide range of products. Various combinations are possible, such as employment of aliphatic or aromatic Weinreb amides and even sterically hindered Weinreb amides or such with optical activity.

The procedure resulted in a high outcome, furthermore the products could easily be purified by flash column chromatography.

Variation of the ether precursor was also possible (α-ethoxymethyl ketones and chloromethyl menthyl ether as shown in the reactions **8-14** and **17-18**) and did not interfere with the outcome of the reaction.

2.3.1 Reaction of optically active Weinreb amides with $ClCH_2OCH_3$

The synthesis of optically active α-oxyketones resulted in high yields and the preservation of the optical purity throughout the process.

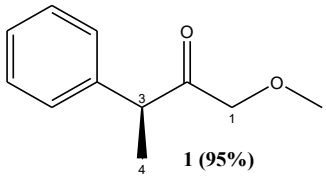
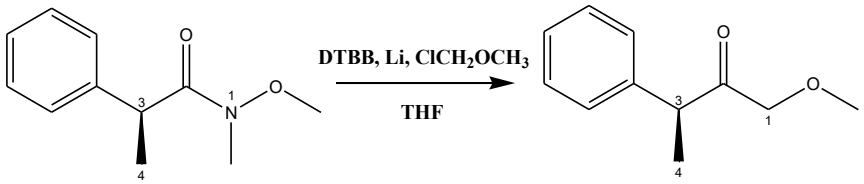


Figure 13 *Compound **1** and yield*

2.3.1.1 Synthesis of compound **1**



Scheme 14 *Synthesis of (3S)-1-methoxy-3-phenyl-2-butanone (**1**)*

Following the reaction of (2*S*)-*N*-methoxy-*N*-methyl-2-phenylpropanamide with lithium metal and chloromethyl methyl ether in THF at a temperature of -78°C the product was extracted and subsequently purified via flash column chromatography. The compound was obtained in high yield, adequate purity and the preservation of the optical purity.

2.3.2 Reaction of aliphatic Weinreb amides with $ClCH_2OCH_3$

The reaction of aliphatic Weinreb amides with chloromethyl methyl ether gave good results. All compounds were obtained with high purity and in good yields.

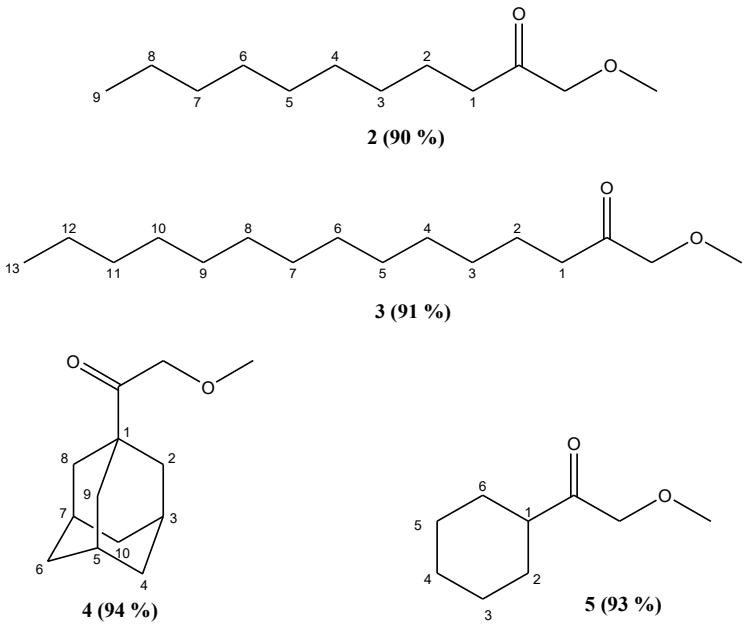
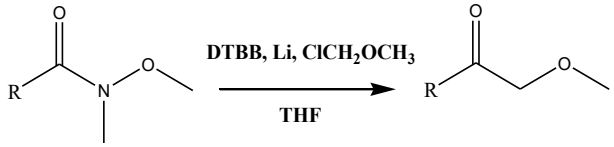


Figure 14 *Compounds* ***2-5*** *and yields*

2.3.2.1 Synthesis of compound **2-5**



Scheme 15 *Synthesis of compounds* ***2-7***

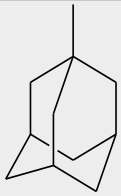
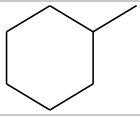
Reaction	**R**	**Name**
2	$(CH_2)_8CH_3$	*N*-methoxy-*N*-methyldecanamide
3	$(CH_2)_{12}CH_3$	*N*-methoxy-*N*-methyltetradecanamide
4		1-(adamantan-1-yl)-2-[methoxy(methyl)amino] ethanone
5		*N*-methoxy-*N*-methylcyclohexane-carboxamide

Table 4 *Starting materials for the reactions* ***2-5***

After the reaction of the starting material with the carbenoid, generated from lithium metal and chloromethyl methyl ether, in THF at a temperature of -78°C the products were extracted and subsequently purified via flash column chromatography.

2.3.3 Reaction of aromatic Weinreb amides with $ClCH_2OCH_3$

The reaction of aromatic Weinreb amides with chloromethyl methyl ether worked well. All α-oxyketones were obtained with high purity and good yield.

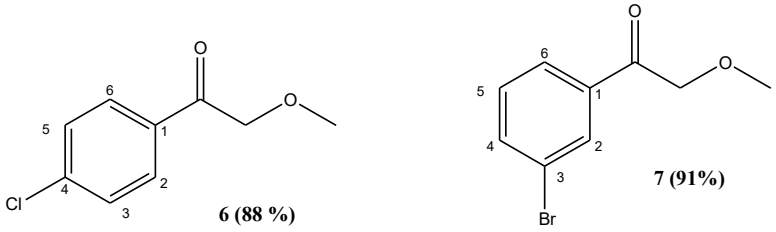


Figure 15 *Compounds* ***6-7*** *and yields*

2.3.3.1 Synthesis of compound **6-7**

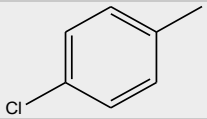
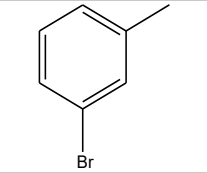
Reaction	**R**	**Name**
6		4-chloro-*N*-methoxy-*N*-methylbenzamide
7		3-bromo-*N*-methoxy-*N*-methylbenzamide

Table 5 *Starting materials for the reactions* ***6-7***

Following the general procedure with chloromethyl methyl ether as reactant the compounds were obtained in high yield and adequate purity.

2.3.4 Reaction of aliphatic Weinreb amides with $ClCH_2OCH_2CH_3$

The reaction of aliphatic Weinreb amides with chloromethyl ethyl ether resulted in compounds with adequate purity and good yield.

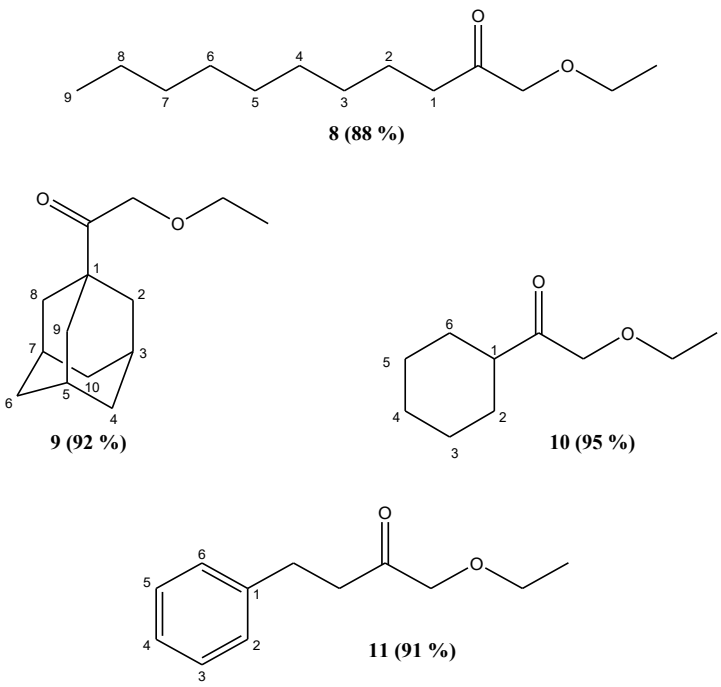
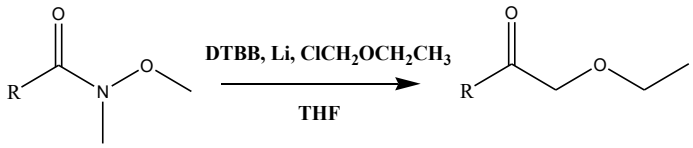


Figure 16 *Compounds* ***8-11*** *and yields*

2.3.4.1 Synthesis of compound **8-11**



Scheme 16 *Synthesis of compounds* ***8-14***

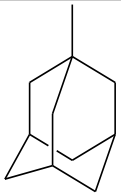
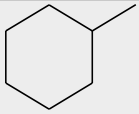
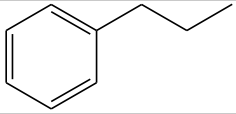
Reaction	**R**	**Name**
8	$(CH_2)_8CH_3$	*N*-methoxy-*N*-methyldecanamide
9		1-(adamantan-1-yl)-2-[methoxy(methyl)amino] ethanone
10		*N*-methoxy-*N*-methylcyclohexane-carboxamide
11		*N*-methoxy-*N*-methyl-3-phenylpropanamide

Table 6 *Starting materials for the reactions* ***8-11***

After the reaction of the starting material with lithium metal and chloromethyl ethyl ether the compounds were acquired in good yield and high purity.

2.3.5 Reaction of aromatic Weinreb amides with $ClCH_2OCH_2CH_3$

The reaction of aromatic Weinreb amides with chloromethyl ethyl ether turned out well. All α-oxyketones were extracted with adequate purity and in high yield.

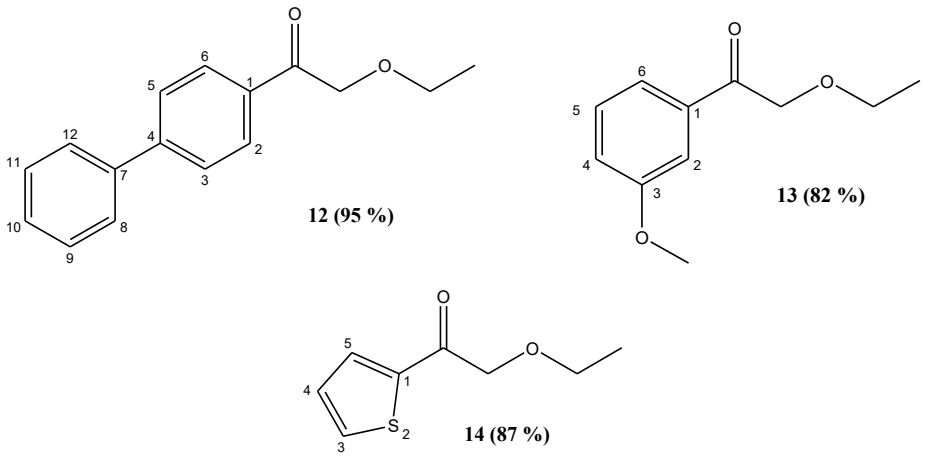


Figure 17 *Coumpounds* ***12-14*** *and yields*

2.3.5.1 Synthesis of compound 1**2-14**

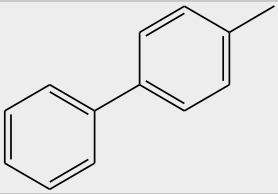
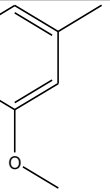
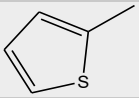
Reaction	**R**	**Name**
12		*N*-methoxy-*N*-methyl-4-biphenylcarboxamide
13		*N*,3-dimethoxy-*N*-methylbenzamide
14		*N*-methoxy-*N*-methyl-2-thiophenecarboxamide

Table 7 *Starting materials for the reactions* ***12-14***

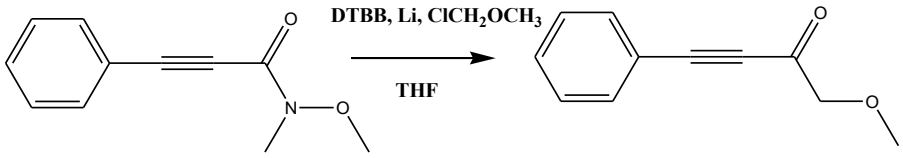
Resulting from the general procedure with chloromethyl ethyl ether as reactant the α-oxyketones were synthesised in high yield and adequate purity.

2.3.6 Reaction of α,β-unsaturated Weinreb amides with $ClCH_2OCH_3$

The reaction of α,β-unsaturated Weinreb amides with chloromethyl methyl ether was effective. Both α-oxyketones were obtained with high purity and in good yields.

Figure 18 *Compounds* ***15-16*** *and yields*

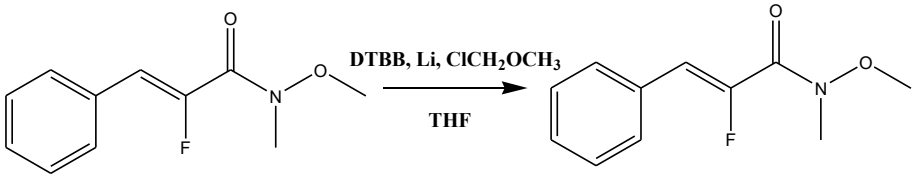
2.3.6.1 Synthesis of compound **15**



Scheme 17 *Synthesis of 1-methoxy-4-phenyl-3-butyn-2-one (**15**)*

Following the reaction of *N*-methoxy-*N*-methyl-3-phenyl-2-propynamide with lithium metal and chloromethyl methyl ether in THF at a temperature of -78°C the product was extracted and subsequently purified via flash column chromatography.

2.3.6.2 Synthesis of compound **16**



Scheme 18 *Synthesis of (3Z)-3-fluoro-1-methoxy-4-phenyl-3-buten-2-one (**16**)*

After the reaction of (2*Z*)-2-fluoro-*N*-methoxy-*N*-methyl-3-phenylacryl amide with lithium and chloromethyl methyl ether in THF at a temperature of -78°C the product was extracted and subsequently purified via flash column chromatography.

2.3.7 Reaction of aromatic Weinreb amides with optically active chloromethyl menthyl ether

The reaction of aromatic Weinreb amides with chloromethyl menthyl ether gave good results. Both α-oxyketones were obtained with sufficient purity and in high yield.

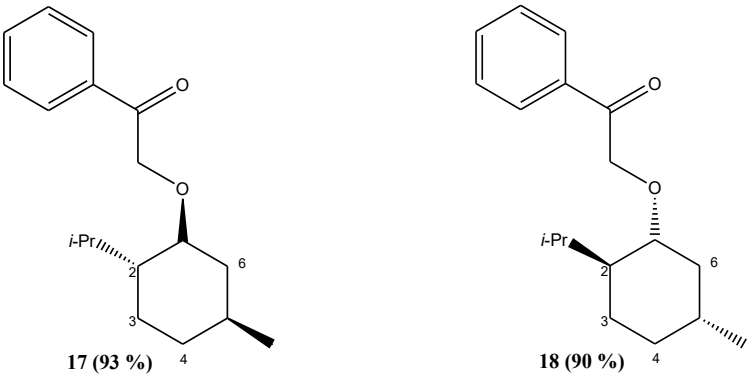
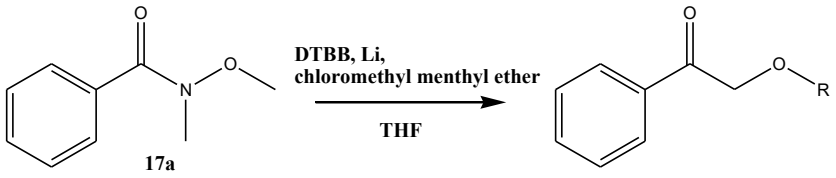


Figure 19 *Compounds* ***17-18*** *and yields*

2.3.7.1 Synthesis of compounds **17-18**



Scheme 19 *Synthesis of compounds* ***17-18***

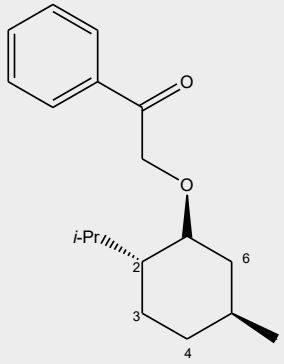
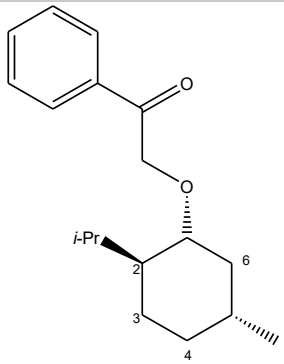
Reaction	Compound	Name
17		2-{[(1*S*, 2*R*, 5*S*)-2-isopropyl-5-methylcyclohexyl]oxy}-1-phenylethanone (**17**)
18		2-{[(1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexy]oxy}-1-phenylethanone (**18**)

Table 8 *Compounds* ***17-18***

Following the reaction of *N*-methoxy-*N*-methylbenzamide (**17a**) with lithium and (-)-chloromethyl menthyl ether or (+)-chloromethyl menthyl ether in THF at a temperature of -78°C the products were extracted and subsequently purified via flash column chromatography.

3. EXPERIMENTAL PART

3.1 Instrumentation and General Analytical Methods

Uncorrected melting Points were measured using a Reichert-Kofler hot-stage microscope.

Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS).

^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance III 400 NMR spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) at 297 K by applying a „directly“ detecting broadband observe (BBFO) probe. The center of the solvent signal was chosen as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H in $CDCl_3$) and δ 77.00 ppm (^{13}C in $CDCl_3$).

In nearly all cases, full and unambiguous assignment of all resonances could be performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, COSY and NOESY experiments.

All reactions were performed in an inert atmosphere of argon. Chemicals were obtained from Sigma-Aldrich, Acros, Alfa Aesar and TCI Europe. THF was distilled over Na / benzophenone. All solvents were evaporated under reduced pressure with a rotary evaporator.

TLC was carried out on aluminium sheets precoated with silica gel 60F254 (Merchery-Nagel, Merk). The spots were visualised under UV light (λ=254 nm) and/or $KMnO_4$ (aq.) was used as revealing system.

3.2 General procedure 1 for the synthesis of α-oxyketones

Metallic lithium (7.0 equiv, 25% dispersion in mineral oil) was placed in a Schlenk tube, flushed by Argon. The lithium was washed with dry THF for three times and suspended in the same solvent (1.4 M concentration). DTBB (4,4′-di-tert-butylbiphenyl catalyst, 5% mol) was added and the mixture was stirred until the appearance of a dark green colour could be recognized. This suspension was cooled down to -78°C prior further processing. Subsequently, the appropriate α-chloro ether $ClCH_2OCH_3$, $ClCH_2OCH_2CH_3$, (+)-chloromethyl menthyl ether, (-)-chloromethyl menthyl ether (2.0 equiv) was added dropwise and the mixture was stirred for 10 min. After adding a 1.0 M solution of the

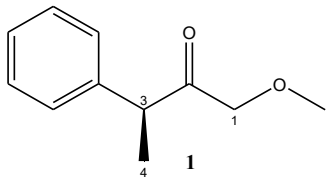
Weinreb amide (1.0 equiv), which was suspended in dry THF, the mixture was stirred at -78°C for 1-4 hours. After quenching the reaction with aqueous NH_4Cl, the reaction mixture was allowed to warm to room temperature. The resulting organic phase was extracted three times with Et_2O, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude compounds were purified as reported below through flash column chromatography.

3.3 General procedure 2 (via cannula) for the synthesis of α-oxyketones

Lithium metal (7.0 equiv, 25% dispersion in mineral oil) was placed under argon in a Schlenk tube, washed with dry THF for three times and suspended in the same solvent (1.4 M concentration). DTBB (4,4′-di-tert-butylbiphenyl catalyst 5% mol) was added and the mixture was stirred until the appearance of a dark green colour. To this suspension, cooled down to -78°C, the appropriate α-chloro ether $ClCH_2OCH_3$, $ClCH_2OCH_2CH_3$ was added dropwise and stirred for 10 minutes to allow the formation of the corresponding carbenoid $LiCH_2OCH_3$ or $LiCH_2OCH_2CH_3$. In a separate flask the appropriate Weinreb amide was dissolved in dry THF (1M concentration) and the solution was cooled to -78°C under argon atmosphere. To this cooled solution, the suspension containing the carbenoid was added via cannula. The resulting reaction mixture was stirred at -78°C for the required time and quenched at the same temperature with aqueous NH_4Cl. Subsequently, the system was allowed to warm to room temperature and the resulting organic phase was extracted three times with Et_2O, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude compounds were purified as reported below through flash column chromatography.

3.4 Reactions

(3*S*)-1-methoxy-3-phenyl-2-butanone (1)



1

By following general procedure 1, starting from (2*S*)-*N*-methoxy-*N*-methyl-2-phenyl-propanamide (0.193 g, 1.0 mmol, 1.0 equiv), DTBB (0.013 g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_3$ (0.161 g, 0.151 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **1** was obtained in 95% yield (0.169 g, 0.95 mmol) as a pale oil after flash column chromatography on silica gel by using n-hexane / ethyl acetate (9:1) as the eluent.

The corresponding racemic sample has been prepared starting from racemic *N*-methoxy-*N*-methyl-2-phenylpropanamide and spectroscopic data match with those ones reported below.

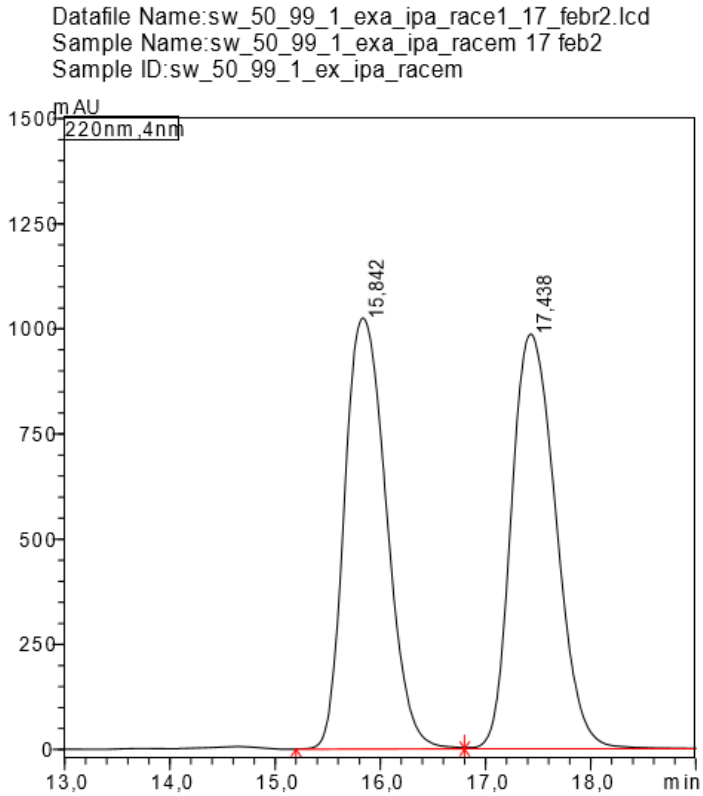
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 2H, Aryl H-3, 5), 7.25 (m, 1H, Aryl H-4), 7.23 (m, 2H, Aryl H2, 6), 3.98 (s, 2H, $C\underline{H}_2OCH_3$), 3.89 (q, ^3J = 7.0 Hz, 1H, H-3), 3.28 (s, 3H, OCH_3), 1.41 (d, ^3J = 7.0 Hz, 3H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ 207.8 (Ketone C), 139.9 (Aryl C-1), 128.9 (Aryl C-3, 5), 127.8 (Aryl C-2, 6), 127.2 (Aryl C-4), 76.1 ($\underline{C}H_2OCH_3$), 59.1 (OCH_3), 48.9 (C-3), 17.2 (C-4).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{14}NaO_2^+$ 201.0886 $[M+Na]^+$; found 201.0890.

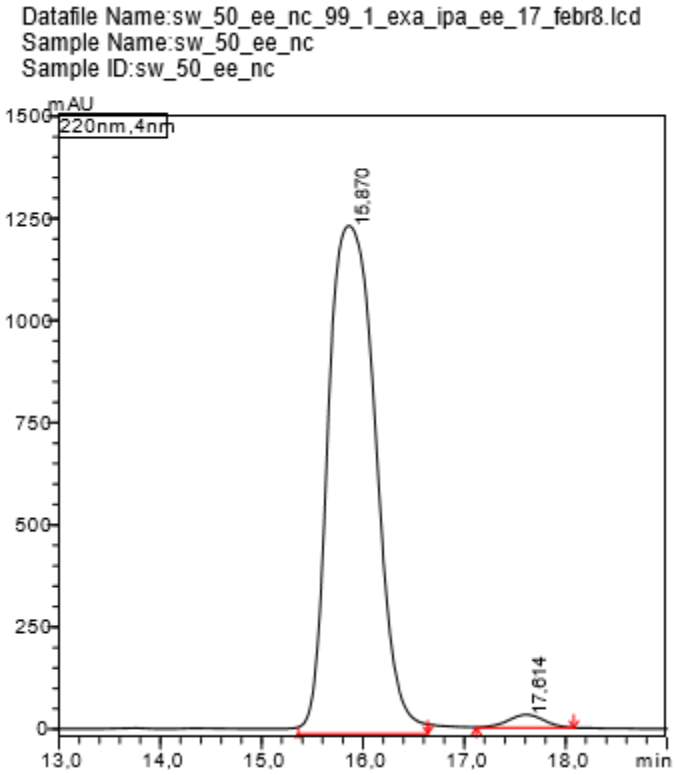
$[\alpha]_D$ = +129 (*c* 0.6, $CHCl_3$).

HPLC analysis: Chiralpak IA Column, λ 220 nm, eluent: n-hexane / *i*-propanol 99/1. Flow: 0.5 mL/min



Peaks	Ret.Time	Area	Area%
1	15.842	28312270	49.387
2	17.438	29015280	50.613
Total		57327550	100.000

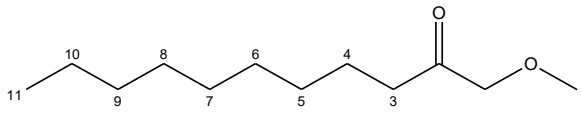
Figure 20 *HPLC analysis of the racemic compound*



Peaks	Ret.Time	Area	Area%
1	15.870	38887741	98.857
2	17.614	449788	1.143
Total		39337530	100.000

Figure 21 *HPLC analysis of the enantioenriched compound*

1-methoxy-2-undecanone (2)



2

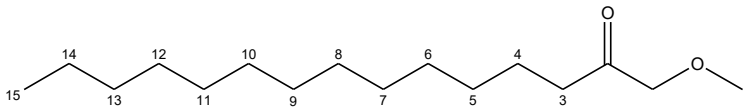
By following general procedure 1, starting from *N*-methoxy-*N*-methyldecanamide (0.215 g, 1.0 mmol, 1.0 equiv), DTBB (0.013g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_3$ (0.161 g, 0.151 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **2** was obtained in 90% yield (0.181 g, 0.90 mmol) as a yellow oil after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (9:1) as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (s, 2H, $C\underline{H}_2OCH_3$), 3.40 (s, 3H, OCH_3), 2.40 (t, ^3J = 7.6 Hz, 2H, H-3), 1.57 (m, 2H, H-4), 1.24 (m, 12H, H-5, 6, 7, 8, 9, 10), 0.86 (t, ^3J =7.0 Hz, 3H, H-11).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7 (Ketone C), 77.5 ($\underline{C}H_2OCH_3$), 59.2 (OCH_3), 38.7 (C-3), 31.8 (C-9), 29.30-29.15 (C-6, 7, 8), 29.12 (C-5), 23.3 (C-4), 22.6 (C-10), 14.0 (C-11).

HRMS (ESI), *m/z*: calcd. for $C_{12}H_{24}O_2^+$ 201.1849 $[M+H]^+$; found 201.1847.

1-methoxy-2-pentadecanone (3)



3

By following general procedure 1, starting from *N*-methoxy-*N*-methyltetradecanamide (0.257 g, 1.0 mmol, 1.0 equiv), DTBB (0.013g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_3$ (0.161 g, 0.151 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **3** was obtained in 91% yield (0.252 g, 0.91 mmol) as a white solid after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (9:1) as the eluent.

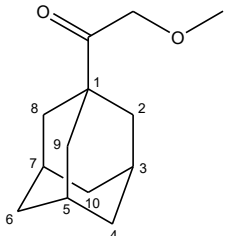
MP: 29-31°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (s, 2H, $C\underline{H}_2OCH_3$), 3.40 (s, 3H, OCH_3), 2.41 (t, ^3J = 7.5 Hz, 2H, H-3), 1.57 (m, 2H, H-4), 1.20-1.30 (m, 20H, H-5, 6, 7, 8, 9, 10, 11, 12, 13, 14), 0.87 (t, ^3J = 7.0 Hz, 3H, H-15).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.8 (Ketone C), 77.6 ($\underline{C}H_2OCH_3$), 59.3 (OCH_3), 38.8 (C-3), 31.9 (C-13), 29.63-29.31 (C-6, 7, 8, 9, 10, 11, 12), 29.2 (C-5), 23.3 (C-4), 22.6 (C-14), 14.1 (C-15).

HRMS (ESI), *m/z*: calcd. for $C_{16}H_{32}O_2^+$ 257.2475 $[M+H]^+$; found 257.2478.

1-(adamantan-1-yl)-2-methoxythanone (4)



4

By following general procedure 1, starting from 1-(adamantan-1-yl)-2-[methoxy(methyl)amino] ethanone (0.233 g, 1.0 mmol, 1.0 equiv), DTBB (0.013g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_3$ (0.161 g, 0.151 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **4** was obtained in 94% yield (0.196 g, 0.94 mmol) as a white solid after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (8:2) as the eluent.

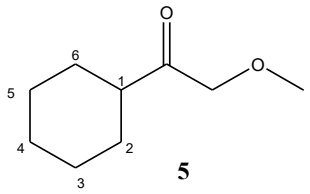
MP: 48-50 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (s, 2H, $COCH_2$), 3.38 (s, 3H, OCH_3), 2.01 (m, 3H, Adamantyl H-3, 5, 7), 1.81 (m, 6H, Adamantyl H-2, 8, 9), 1.70 (m, 6H, Adamantyl H-4, 6, 10).

^{13}C NMR (100 MHz, $CDCl_3$): δ 211.0 (Ketone C), 73.1 ($CO\underline{C}H_2$), 59.1 (OCH_3), 45.0 (Adamantyl C-1), 37.9 (Adamantyl C-2, 8, 9), 36.4 (Adamantyl C-4, 6, 10), 27.7 (Adamantyl C-3, 5, 7).

HRMS (ESI), *m/z*: calcd. for $C_{13}H_{20}NaO_2^+$ 231.1356 $[M+Na]^+$; found 231.1357.

1-cyclohexyl-2-methoxyethanone (5)



5

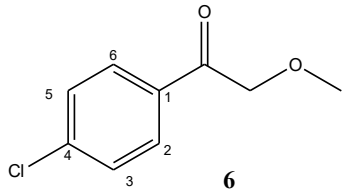
By following general procedure 1, starting from *N*-methoxy-*N*-methylcyclohexane-carboxamide (0.171 g, 1.0 mmol, 1.0 equiv), DTBB (0.013g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_3$ (0.161 g, 0.151 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **5** was obtained in 93% yield (0.146 g, 0.93 mmol) as a colourless oil after column chromatography on silica gel by using *n*-hexane / ethyl acetate (from 9:1 to 8:2) as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.08 (s, 2H, $C\underline{H}_2OCH_3$), 3.40 (s, 3H, OCH_3), 2.46 (m, 1H, Cyclohexane H-1), 1.79 (m, 2H, Cyclohexane H-2, 6), 1.78 (m, 2H, Cyclohexane H-3, 5), 1.66 (m, 1H, Cyclohexane H-4), 1.36 (m, 2H, Cyclohexane H-2', 6'), 1.25 (m, 2H, Cyclohexane H-3', 5', 4').

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.9 (Ketone C), 76.2 ($\underline{C}H_2OCH_3$), 59.2 (OCH_3), 47.0 (Cyclohexane C-1), 28.2 (Cyclohexane C-2, 6), 25.7 (Cyclohexane C-4), 25.5 (Cyclohexane C-3, 5).

HRMS (ESI), *m/z*: calcd. for $C_9H_{16}NaO_2^+$ 179.1043 $[M+Na]^+$; found 179.1045.

1-(4-chlorophenyl)-2-metoxyethanone (6)



6

By following general procedure 2, starting from 4-chloro-*N*-methoxy-*N*-methylbenzamide (**6a**) (0.200 g, 1.0 mmol, 1.0 equiv), DTBB (0.013 g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_3$ (0.161 g, 0.151 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **6** was obtained in 88% yield (0.192 g, 0.88 mmol)

as a yellow solid after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (8:2) as the eluent.

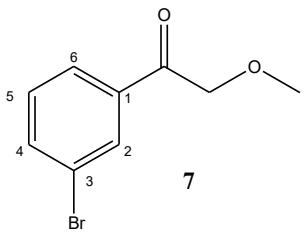
MP: 60-61 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (m, 2H, Aryl H-2, 6), 7.44 (m, 2H, Aryl H-3, 5), 4.65 (s, 2H, $C\underline{H}_2OCH_3$), 3.49 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1 (C=O), 140.0 (Aryl C-4), 133.1 (Aryl C-1), 129.4 (Aryl C-2, 6), 129.0 (Aryl C-3, 5), 75.3 ($\underline{C}H_2OCH_3$), 59.4 (OCH_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_{10}ClO_2^+$ 185.0364 $[M+H]^+$; found 185.0365.

1-(3-bromophenyl)-2-methoxyethanone (7)



7

By following general procedure 2, starting from 3-bromo-*N*-methoxy-*N*-methylbenzamide (0.243 g, 1.0 mmol, 1.0 equiv), DTBB (0.013g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_3$ (0.104 g, 0.099 mL, 1.3 mmol, 1.3 equiv) in dry THF (6 mL), compound **7** was obtained in 91% yield (0.209 g, 0.91 mmol) as a white solid after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (7:3) as the eluent.

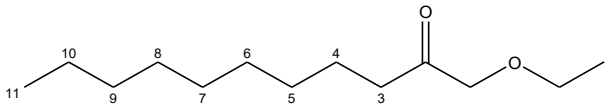
MP: 44-46°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (m, 1H, Aryl H-2), 7.86 (m, 1H, Aryl H-6), 7.71 (m, 1H, Aryl H-4), 7.36 (m, 1H, Aryl H-5), 4.66 (s, 2H, $C\underline{H}_2OCH_3$), 3.50 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.0 (Ketone C), 136.5 (Aryl C-1), 136.4 (Aryl C-4), 131.0 (Aryl C-2), 130.3 (Aryl C-5), 126.4 (Aryl C-6), 123.1 (Aryl C-3), 75.3 ($\underline{C}H_2OCH_3$), 59.5 (OCH_3).

HRMS (ESI), *m/z*: calcd. for $C_9H_9BrNaO_2^+$ 228.9858 $[M+Na]^+$; found 250.9679.

1-ethoxy-2-undecanone (8)



8

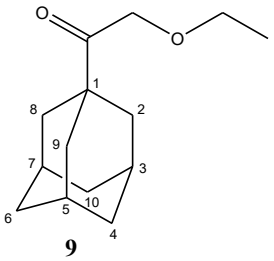
By following general procedure 1, starting from *N*-methoxy-*N*-methyldecanamide (0.215 g, 1.0 mmol, 1.0 equiv), DTBB (0.013g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_2CH_3$ (0.189 g, 0.185 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **8** was obtained in 88% yield (0.189 g, 0.88 mmol) as a pale oil after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (9:1) as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (s, 2H, $C\underline{H}_2OCH_3$), 3.53 (q, ^3J = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 2.43 (t, ^3J = 7.5 Hz, 2H, H-3), 1.57 (m, 2H, H-4), 1.31-1.24 (m, 12H, H-5, 6, 7, 8, 9, 10), 1.24 (t, ^3J = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$) 0.86 (t, ^3J = 7.0 Hz, 3H, H-11).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.3 (Ketone C), 75.8 ($\underline{C}H_2OCH_3$), 67.1 ($O\underline{C}H_2CH_3$), 38.9 (C-3), 31.8 (C-9), 29.4- 29.2 (C-6, 7, 8), 29.2 C-5), 23.4 (C-4), 22.6 (C-10), 15.0 ($OCH_2\underline{C}H_3$), 14.0 (C-11).

HRMS (ESI), *m/z*: calcd. for $C_{13}H_{26}O_2^+$ 215.2005 $[M+H]^+$; found 215.2007.

1-(adamantan-1-yl)-2-ethoxythanone (9)



9

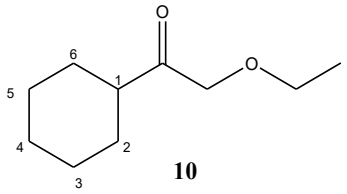
By following general procedure 1, starting from 1-(adamantan-1-yl)-2-[methoxy(methyl)amino]ethanone (0.233 g, 1.0 mmol, 1.0 equiv), DTBB (0.013g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_2CH_3$ (0.189 g, 0.185 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **9** was obtained in 92% yield (0.205 g, 0.92 mmol) as a yellow oil after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (8:2) as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (s, 2H, $COCH_2$), 3.52 (q, ^3J = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 2.02 (m, 3H, Adamantyl H-3, 5, 7), 1.83 (m, 6H, Adamantyl H-2, 8, 9), 1.71 (m, 6H, Adamantyl H-4, 6, 10), 1.24 (t, ^3J = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 211.3 (Ketone C), 71.3 ($CO\underline{C}H_2$), 66.9 ($O\underline{C}H_2CH_3$), 45.1 (Adamantyl C-1), 38.0 (Adamantyl C-2, 8, 9), 36.4 (Adamantyl C-4, 6, 10), 27.8 (Adamantyl C-3, 5, 7), 15.0 ($OCH_2\underline{C}H_3$).

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{22}NaO_2^+$ 245.1512 $[M+H]^+$; found 245.1513.

1-cyclohexyl-2-ethoxyethanone (10)



10

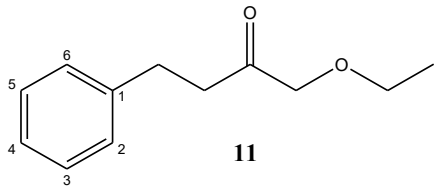
By following general procedure 1, starting from *N*-methoxy-*N*-methylcyclohexane-carboxamide (0.171 g, 1.0 mmol, 1.0 equiv), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv), DTBB (0.013g, 5% mol catalyst) and $ClCH_2OCH_2CH_3$ (0.189 g, 0.185 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **10** was obtained in 95% yield (0.162 g, 0.95 mmol) as a yellow liquid after column chromatography on silica gel by using *n*-hexane / ethyl acetate (from 9:1 to 8:2) as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (s, 2H, $C\underline{H}_2OCH_2CH_3$), 3.53 (q, ^3J = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 2.48 (m, 1H, Cyclohexane H-1), 1.79 (m, 2H, Cyclohexane H-2, 6), 1.77 (m, 2H, Cyclohexane H-3, 5), 1.66 (m, 1H, Cyclohexane H-4), 1.35 (m, 2H, Cyclohexane H-2', 6'), 1.26 (m, 2H, Cyclohexane H-3', 5'), 1.24 (t, ^3J = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.23 (m, 1H, Cyclohexane H-4').

^{13}C NMR (100 MHz, $CDCl_3$): δ 211.3 (Ketone C), 74.3 ($\underline{C}H_2OCH_2CH_3$), 67.1 ($O\underline{C}H_2CH_3$), 47.0 (Cyclohexane C-1), 28.2 (Cyclohexane C-2, 6), 25.7 (Cyclohexane C-4), 25.6 (Cyclohexane C-3, 5), 15.0 ($OCH_2\underline{C}H_3$).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{18}NaO_2^+$ 193.1199 $[M+Na]^+$; found 193.1202.

1-ethoxy-4-phenyl-2-butanone (11)



11

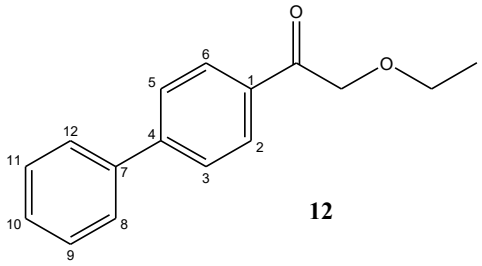
By following general procedure 1, starting from *N*-methoxy-*N*-methyl-3-phenylpropanamide (0.193 g, 1.0 mmol, 1.0 equiv), DTBB (0.013g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_2CH_3$ (0.122 g, 0.120 mL, 1.3 mmol, 1.3 equiv) in dry THF (6 mL), compound **11** was obtained in 91% yield (0.175 g, 0.91 mmol) as a colourless oil after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (from 9:1 to 8:2) as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 2H, Aryl H-3, 5), 7.20 (m, 3H, Aryl H-2, 4, 6), 4.00 (s, 2H, $C\underline{H}_2OCH_2CH_3$), 3.51 (q, ^3J = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 2.92 (m, 2H, H-4), 2.79 (m, 2H, H-3), 1.23 (t, ^3J = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4 (Ketone C), 140.9 (Aryl C-1), 128.5 (Aryl C-3, 5), 128.3 (Aryl C-2, 6), 126.1 (Aryl C-4), 76.0 ($\underline{C}H_2OCH_2CH_3$), 67.1 ($O\underline{C}H_2CH_3$), 40.5 (C-3), 29.3 (C-4), 15.0 ($OCH_2\underline{C}H_3$).

HRMS (ESI), *m/z*: calcd. for $C_{12}H_{16}O_2^+$ 193.1223 $[M+H]^+$; found 193.1225.

1-(4-biphenylyl)-2-ethoxyethanone (12)



12

By following general procedure 1, starting from *N*-methoxy-*N*-methyl-4-biphenylcarboxamide (0.241 g, 1.0 mmol, 1.0 equiv), DTBB (0.013g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_2CH_3$ (0.189 g, 0.185 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **12** was obtained in 95%

yield (0.228 g, 0.95 mmol) as a yellow solid after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (8:2) as the eluent.

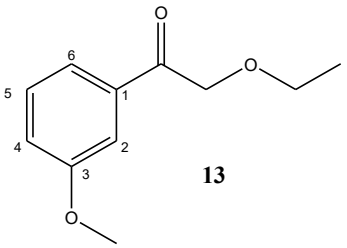
MP: 73-75°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (m, 2H, Aryl H-2, 6), 7.68 (m, 2H, Aryl H-3, 5), 7.62 (m, 2H, Aryl H-2', 6'), 7.47 (m, 2H, Aryl H-3', 5'), 7.40 (m, 1H, Aryl H-4'), 4.76 (s, 2H, $C\underline{H}_2OCH_2CH_3$), 3.67 (q, ^{3}J = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 1.31 (t, ^{3}J = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1 (Ketone C), 146.1 (Aryl C-4), 139.8 (Aryl C-1'), 133.7 (Aryl C-1), 128.9 (Aryl C-3', 5'), 128.5 (Aryl C-2, 6), 128.2 (Aryl C-4'), 127.23 (Aryl C-3, 5), 127.20 (Aryl C-2', 6'), 73.6 ($\underline{C}H_2OCH_2CH_3$), 67.2 ($O\underline{C}H_2CH_3$), 15.1 ($OCH_2\underline{C}H_3$).

HRMS (ESI), *m/z*: calcd. for $C_{16}H_{16}NaO_2^+$ 263.1043 $[M+H]^+$; found 263.1043.

2-ethoxy-1-(3-methoxyphenyl)ethanone (13)



13

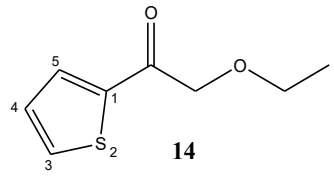
By following general procedure 1, starting from *N*,3-dimethoxy-*N*-methylbenzamide (**13a**) (0.195 g, 1.0 mmol, 1.0 equiv), DTBB (0.013g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_2CH_3$ (0.189 g, 0.185 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **13** was obtained in 82% yield (0.197 g, 0.82 mmol) as a pale yellow oil after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (7:3) as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (m, 1H, Aryl H-6), 7.48 (m, 1H, Aryl H-2), 7.36 (m, 1H, Aryl H-5), 7.12 (ddd, ^{3}J = 8.2 Hz, ^{4}J = 2.7 Hz, ^{5}J = 1.0 Hz, 1H, Aryl H-4), 4.73 (s, 2H, $C\underline{H}_2O\ CH_2CH_3$), 3.85 (s, 3H, Aryl -$OCH_3$), 3.64 (q, ^{3}J = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 1.29 (t, ^{3}J = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3 (Ketone C), 159.8 (Aryl C-3), 136.2 (Aryl C-1), 129.6 (Aryl C-5), 120.2 (Aryl C-6), 119.9 (Aryl C-4), 112.2 (Aryl C2), 73.6 ($\underline{C}H_2O\ CH_2CH_3$), 67.2 ($O\underline{C}H_2CH_3$), 55.4 (Aryl-$OCH_3$), 15.1 ($OCH_2\underline{C}H_3$).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{14}NaO_2^+$ 195.1015 $[M+Na]^+$; found 217.0836.

2-ethoxy-1-(2-thienyl)ethanone (14)



14

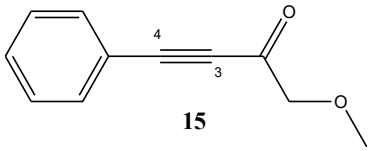
By following general procedure 1, starting from *N*-methoxy-*N*-methyl-2-thiophenecarboxamide (0.171 g, 1.0 mmol, 1.0 equiv), DTBB (0.013g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_2CH_3$ (0.189 g, 0.185 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **14** was obtained in 87% yield (0.148 g, 0.87 mmol) as an orange oil after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (8:2) as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, ^3J = 3.8 Hz, ^4J = 1.1 Hz, 1H, Th H-5), 7.67 (dd, ^3J = 4.9 Hz, ^4J =1.1 Hz, 1H, Th H-3), 7.14 (dd, ^3J = 4.9 Hz, ^3J = 3.8 Hz, 1H, Th H-4), 4.56 (s, 2H, C$\underline{H}_2$O CH_2CH_3), 3.65 (q, ^3J = 7.0 Hz, 2H, OC$\underline{H}_2$$CH_3$), 1.29 (t, ^3J = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3 (Ketone C), 141.0 (Th C-1), 134.0 (Th C-3), 132.6 (Th C-5), 128.0 (Th C-4), 74.2 ($\underline{C}H_2O$ CH_2CH_3), 67.4 (O$\underline{C}H_2CH_3$), 15.1 ($OCH_2\underline{C}H_3$).

HRMS (ESI), *m/z*: calcd. for $C_8H_{10}O_2NaS^+$ 193.0294 $[M+H]^+$; found 193.0295.

1-methoxy-4-phenyl-3-butyn-2-one (15)



15

By following general procedure 1, starting from *N*-methoxy-*N*-methyl-3-phenyl-2-propynamide (0.189 g, 1.0 mmol, 1.0 equiv), DTBB (0.013 g, 5% mol catalyst), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv) and $ClCH_2OCH_3$ (0.161 g, 0.151 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **15** was obtained in 83% yield (0.145 g, 0.83 mmol)

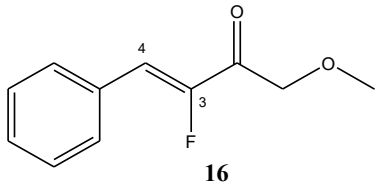
as a yellow oil after flash column chromatography on silica gel by using n-hexane / ethyl acetate (9:1) as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (m, 2H, Aryl H-2, 6), 7.48 (m, 1H, Aryl H-4), 7.40 (m, 2H, Aryl H3, 5), 4.28 (s, 2H, $C\underline{H}_2OCH_3$), 3.52 (m, 3H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 185.0 (Ketone C), 133.2 (Aryl C-2, 6), 131.0 (Aryl C-4), 128.7 (Aryl C-3, 5), 119.5 (Aryl C-1), 93.6 (C-4), 85.6 (C-3), 78.5 ($\underline{C}H_2OCH_3$), 59.6 (OCH_3).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{10}NaO_2^+$ 197.0573 $[M+Na]^+$; found 197.0575.

(3*Z*)-3-fluoro-1-methoxy-4-phenyl-3-buten-2-one (16)



16

By following general procedure 1, starting from (2*Z*)-2-fluoro-*N*-methoxy-*N*-methyl-3-phenylacryl amide (**16a**) (0.209 g, 1.0 mmol, 1.0 equiv), lithium 25% in mineral oil (0.193 g, 7.0 mmol, 7.0 equiv), DTBB (0.013 g, 5% mol catalyst) and $ClCH_2OCH_3$ (0.161 g, 0.151 mL, 2.0 mmol, 2.0 equiv) in dry THF (6 mL), compound **16** was obtained in 90% yield (0.175 g, 0.90 mmol) as a yellow oil after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (from 9:1 to 8:2) as the eluent.

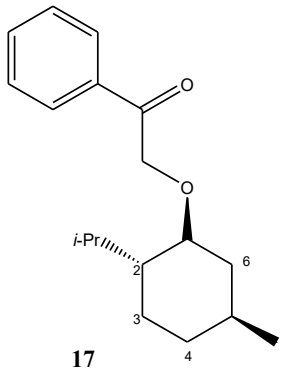
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (m, 2H, Aryl H-2, 6), 7.40 (m, 3H, Aryl H-3, 4, 5), 6.91 (d, $^{3}J_{H,F}$ = 37.9 Hz, 1H, H-4), 4.51 (d, $^{4}J_{H,F}$ = 2.0 Hz, 2H, $C\underline{H}_2OCH_3$), 3.50 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8 (d, $^{2}J_{C,F}$ = 32.3 Hz, Ketone C), 152.9 (d, $^{1}J_{C,F}$ = 271.0 Hz, C-3), 130.8 (d, $^{4}J_{C,F}$ = 8.2 Hz, Aryl C-2, 6), 130.7 ($^{3}J_{C,F}$ = 3.8 Hz, Aryl C-1), 130.2 (Aryl C-4), 128.9 (Aryl C3, 5), 115.9 (d, $^{2}J_{C,F}$ = 3.7 Hz, C-4), 74.7 ($\underline{C}H_2OCH_3$), 59.5 (OCH_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ: −129.9 (d, $^{3}J_{F,H}$ = 37.9 Hz).

HRMS (ESI), *m/z*: calcd. for $C_{11}H_{11}FO_2Na^+$ 217.0635 $[M+Na]^+$; found 217.0639.

2-{[(1*S*, 2*R*, 5*S*)-2-isopropyl-5-methylcyclohexyl]oxy}-1-phenylethanone (17)



17

By following general procedure 1, starting from *N*-methoxy-*N*-methylbenzamide (**17a**) (0.165 g, 1.0 mmol, 1.0 equiv), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv), DTBB (0.013 g, 5% mol catalyst) and (+)-chloromethyl menthyl ether (0.412 mL, 2 mmol) in dry THF (6 mL), compound **17** was obtained in 93% yield (0.255 g, 0.93 mmol) as a yellow liquid after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (from 9:1 to 8:2) as the eluent.

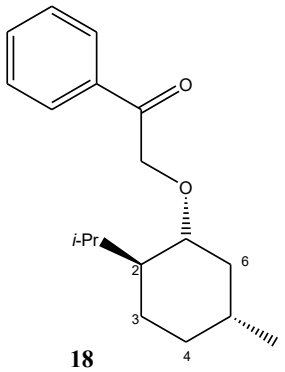
^{1}H NMR (400 MHz, $CDCl_3$): 7.95 (m, 2H, Aryl H-2, 6), 7.57 (m, 1H, Aryl H-4), 7.46 (m, 2H, Aryl H-3, 5), 4.82 (d, $^{2}J_{AB}$ = 16.0 Hz, 1H 1H *diast* AB-system, O=CC$\underline{H}_2$O), 4.67 (d, $^{2}J_{AB}$ = 16.0 Hz, 1H *diast* ABsystem, O=CC$\underline{H}_2$O), 3.22 (dt, ^{3}J = 4.2 Hz, ^{3}J = 10.5 Hz, 1H, Cyclohexane H_{1ax}), 2.27 (dsept, ^{3}J = 2.7 Hz, ^{3}J = 7.0 Hz, 1H, $(CH_3)_2C\underline{H}$), 2.13 (m, 1H, Cyclohexane H-6_{eq}), 1.65 (m, 1H, Cyclohexane H-4_{eq}), 1.63 (m, 1H, Cyclohexane H-3_{eq}), 1.35 (m, 1H, Cyclohexane H-5_{ax}), 1.34 (m, 1H, Cyclohexane H-2_{ax}), 0.97 (m, 1H, Cyclohexane H-3_{ax}), 0.95 (m, 1H, Cyclohexane H-6_{ax}), 0.85 (m, 1H, Cyclohexane H-4_{ax}), 0.92 (d, ^{3}J = 6.6 Hz, 3H, C$\underline{H}_3$-C-5), 0.88 (d, ^{3}J = 7.0 Hz, 3H, $(C\underline{H}_3)_2$CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9 (Ketone C), 135.2 (Aryl C-1), 133.3 (Aryl C-4), 128.6 (Aryl C-3, 5), 128.1 (Aryl C-2, 6'), 80.1 (Cyclohexane C-1), 71.5 (O=C$\underline{C}H_2$O), 48.2 (Cyclohexane C-2), 40.0 (Cyclohexane C-6), 34.4 (Cyclohexane C-4), 31.6 (Cyclohexane C-5), 25.4 $(CH_3)_2\underline{C}$H), 23.2 (Cyclohexane C-3), 22.3 ($\underline{C}H_3$-C-5), 21.0 $(\underline{C}H_3)_2$CH), 16.1 $(\underline{C}H_3)_2$CH).

$[\alpha]_D$ = +59 (*c* 0.6, $CHCl_3$)

HRMS (ESI), *m/z*: calcd. for $C_{18}H_{27}O_2^+$ 275.2011 $[M+H]^+$; found 275.2010.

2-{[(1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexy]oxy}-1-phenylethanone (18)



18

By following general procedure 1, starting from *N*-methoxy-*N*-methylbenzamide (**17a**) (0.165 g, 1.0 mmol, 1.0 equiv), lithium 25% in mineral oil (0.196 g, 7.0 mmol, 7.0 equiv), DTBB (0.013 g, 5% mol catalyst) and (-)-chloromethyl menthyl ether (0.412 mL, 2 mmol) in dry THF (6 mL), compound **18** was obtained in 90% yield (0.247 g, 0.90 mmol) as a yellow liquid after flash column chromatography on silica gel by using *n*-hexane / ethyl acetate (from 9:1 to 8:2) as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$): 7.95 (m, 2H, Aryl H-2, 6), 7.57 (m, 1H, Aryl H-4), 7.46 (m, 2H, Aryl H-3, 5), 4.82 (d, $^{2}J_{AB}$ = 16.0 Hz, 1H 1H *diast* AB-system, O=CC$\underline{H}_2$O), 4.67 (d, $^{2}J_{AB}$ = 16.0 Hz, 1H diast ABsystem, O=CC$\underline{H}_2$O), 3.22 (dt, ^{3}J = 4.2 Hz, ^{3}J = 10.5 Hz, 1H, Cyclohexane H_{1ax}), 2.27 (dsept, ^{3}J = 2.7 Hz, ^{3}J = 7.0 Hz, 1H, $(CH_3)_2C\underline{H}$), 2.13 (m, 1H, Cyclohexane H-6_{eq}), 1.65 (m, 1H, Cyclohexane H-4_{eq}), 1.63 (m, 1H, Cyclohexane H-3_{eq}), 1.35 (m, 1H, Cyclohexane H-5_{ax}), 1.34 (m, 1H, Cyclohexane H-2_{ax}), 0.97 (m, 1H, Cyclohexane H-3_{ax}), 0.95 (m, 1H, Cyclohexane H-6_{ax}), 0.85 (m, 1H, Cyclohexane H-4_{ax}), 0.92 (d, ^{3}J = 6.6 Hz, 3H, C$\underline{H}_3$-C-5), 0.88 (d, ^{3}J = 7.0 Hz, 3H, $(C\underline{H}_3)_2$CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9 (Ketone C), 135.2 (Aryl C-1), 133.3 (Aryl C-4), 128.6 (Aryl C-3, 5), 128.1 (Aryl C-2, 6′), 80.1 (Cyclohexane C-1), 71.5 (O=C$\underline{C}H_2$O), 48.2 (Cyclohexane C-2), 40.0 (Cyclohexane C-6), 34.4 (Cyclohexane C-4), 31.6 (Cyclohexane C-5), 25.4 $(CH_3)_2\underline{C}$H), 23.2 (Cyclohexane C-3), 22.3 ($\underline{C}H_3$-C-5), 21.0 $(\underline{C}H_3)_2$CH), 16.1 $(\underline{C}H_3)_2$CH).

$[\alpha]_D$ = -59 (*c* 0.6, $CHCl_3$)

HRMS (ESI), *m/z*: calcd. for $C_{18}H_{27}O_2^+$ 275.2011 $[M+H]^+$; found 275.2010

4. SYNOPSIS

Im Zuge der vorliegenden Diplomarbeit wurde ein Verfahren zur Herstellung von α-Alkoxyketonen durch Reaktion von Weinreb Amiden mit Lithium Carbenoiden entwickelt. Dabei wurden verschiedene aliphatische und aromatische Weinreb Amide mit Lithium Carbenoiden, hergestellt aus (Chlormethyl)methylether, (Chlormethyl)ethylether oder (Chlormethyl)menthylether umgesetzt.

Unter den optimierten Reaktionsbedingungen (7.0 Äquivalente metallisches Lithium, Tetrahydrofuran (THF) als Lösungsmittel, Reaktionstemperatur von -78°C) wurde ein breites Spektrum an Zielverbindungen in sehr guten Ausbeuten, zufriedenstellender Reinheit und unter Beibehaltung der Stereochemie synthetisiert.

Alle synthetisierten Verbindungen wurden mittels NMR-spektroskopischer Methoden (^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR) unter Verwendung von Standardmesstechniken (HSQC, HMBC, COSY, NOESY) eingehend charakterisiert und ihre Struktur bestätigt. Weiters wurden alle Verbindungen mittels HRMS charakterisiert.

In the course of this thesis a protocol for the synthesis of α-oxyketones through the reaction between Weinreb amides with lithium carbenoids was developed. In this process different aliphatic and aromatic Weinreb amides were converted with lithium carbenoids, obtained from chloromethyl methyl ether, chloromethy ethyl ether or chloromethyl menthyl ether.

Following the optimized reaction conditions (7.0 equiv. metallic lithium, tetrahydrofuran (THF) as solvent, temperature of -78°C) a wide scope of target compounds was synthesised in high yield, satisfying purity and with preservation of the stereochemical information.

All synthesised compounds were characterised and confirmed using combined application of standard NMR techniques (^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, HSQC, HMBC, COSY, NOESY). Furthermore, all compounds were characterised via HRMS.

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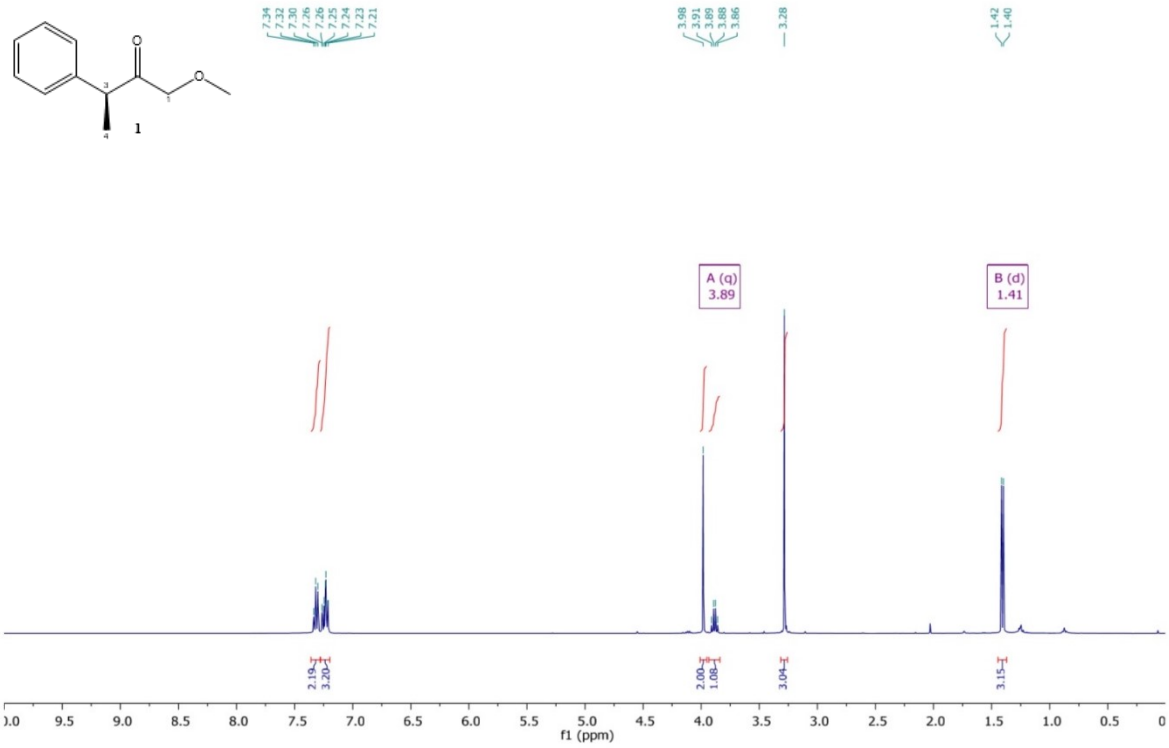
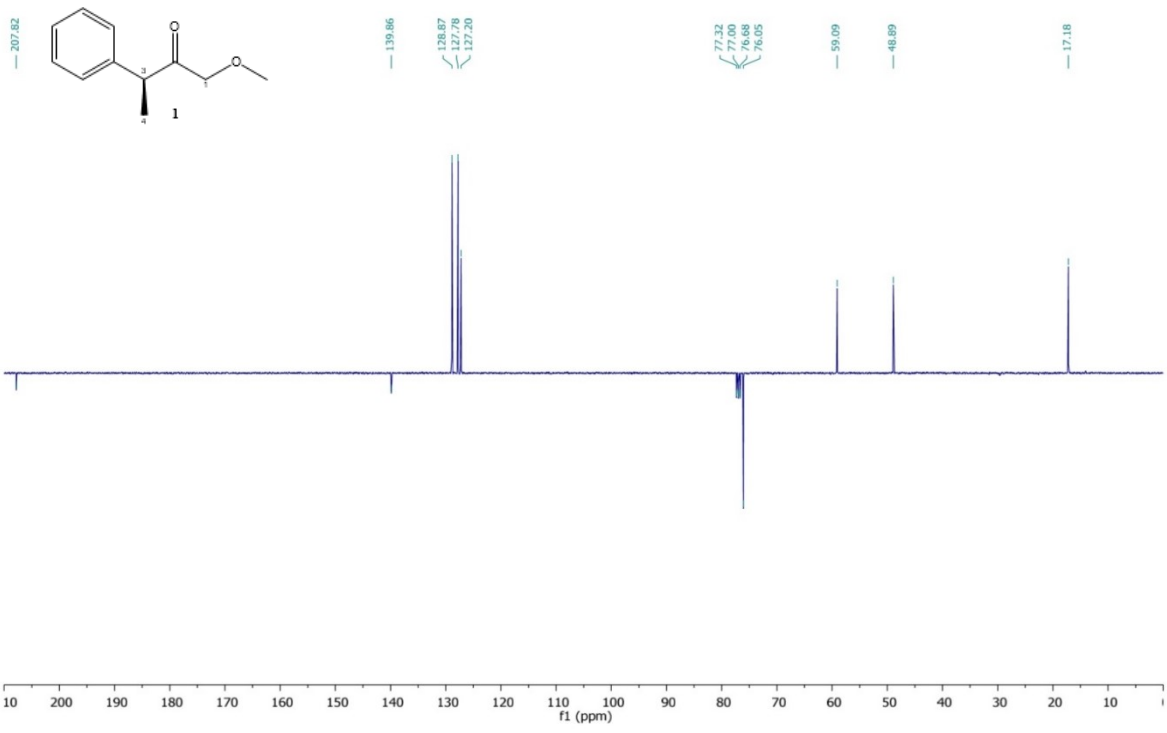
6. APPENDIX

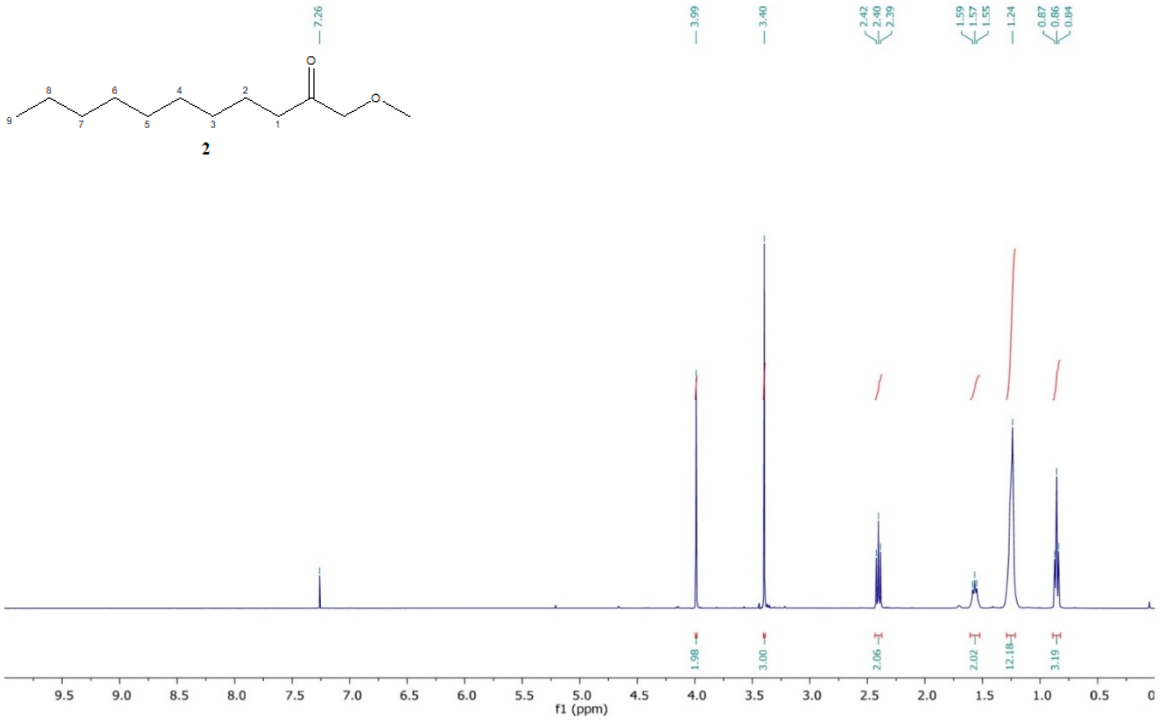
(3*S*)-1-methoxy-3-phenyl-2-butanone (**1**) ^{1}H NMR (400 MHz, $CDCl_3$)



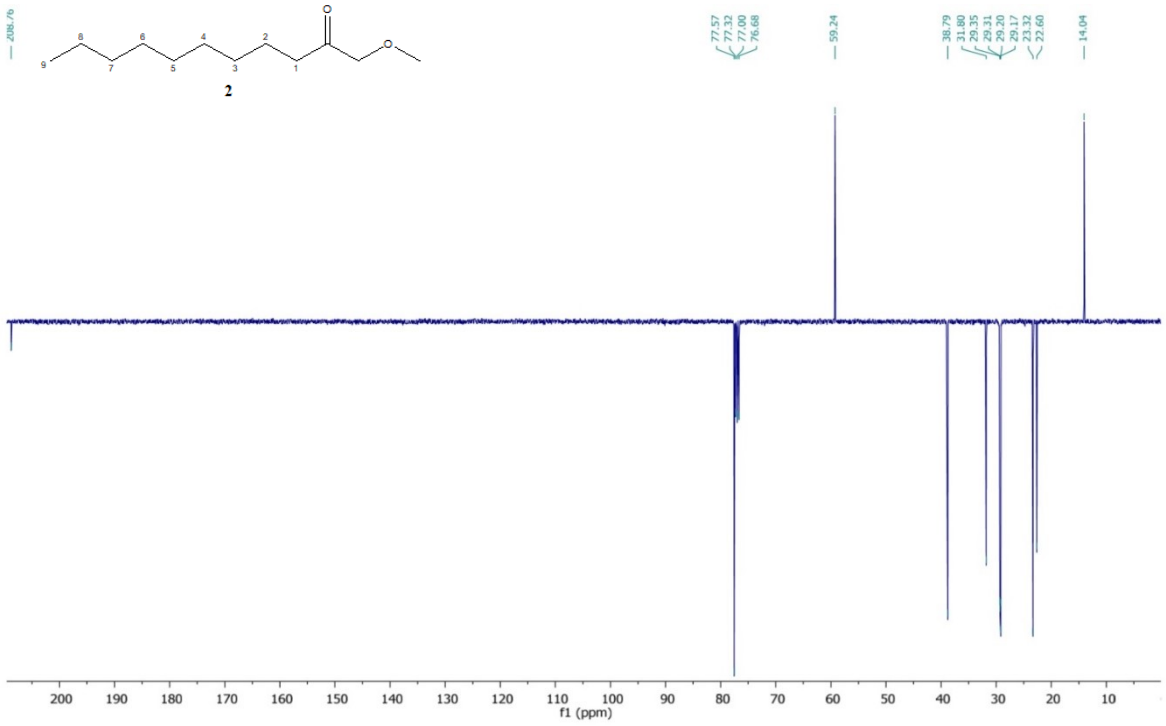
(3*S*)-1-methoxy-3-phenyl-2-butanone (**1**) ^{13}C NMR (100 MHz, $CDCl_3$)



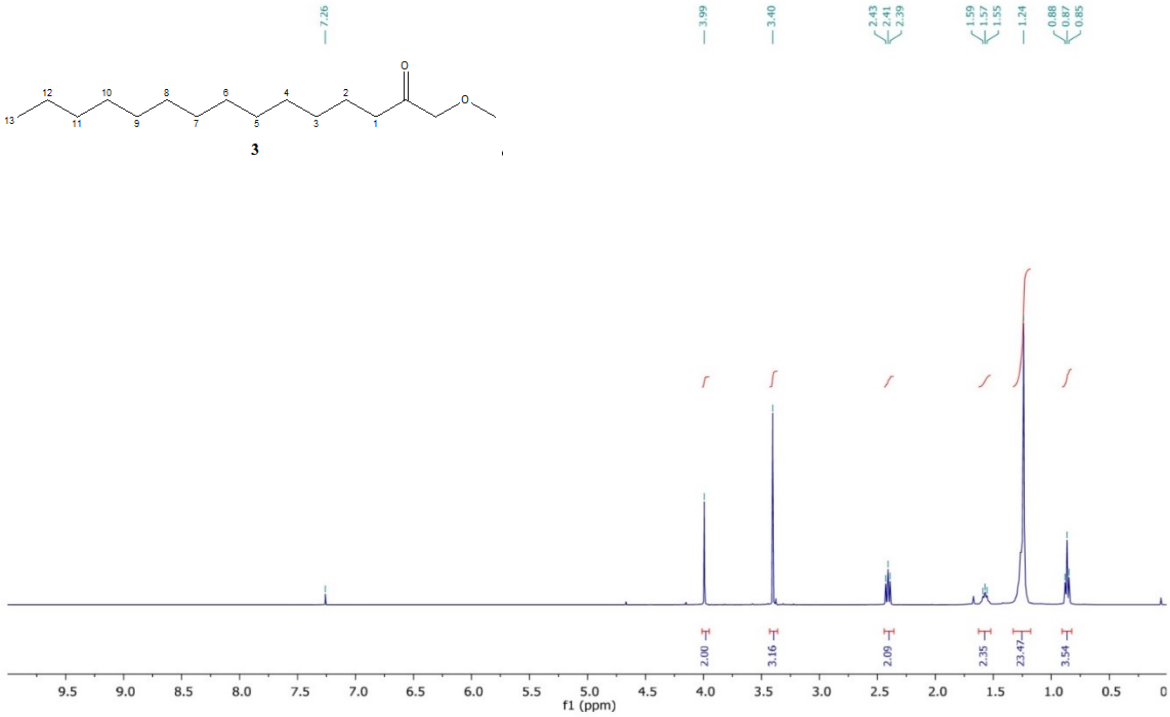
1-methoxy-2-undecanone (**2**) ^{1}H NMR (400 MHz, $CDCl_3$)



1-methoxy-2-undecanone (**2**) ^{1}H NMR (400 MHz, $CDCl_3$)

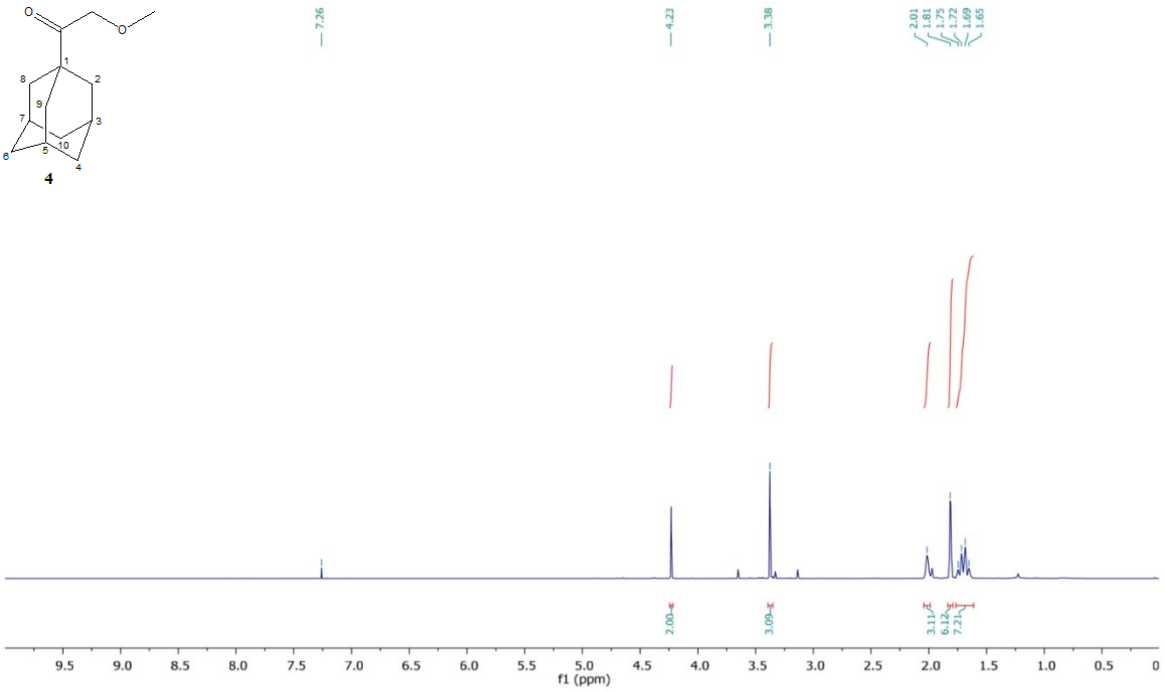


1-methoxy-2-pentadecanone (**3**) ^{1}H NMR (400 MHz, $CDCl_3$)

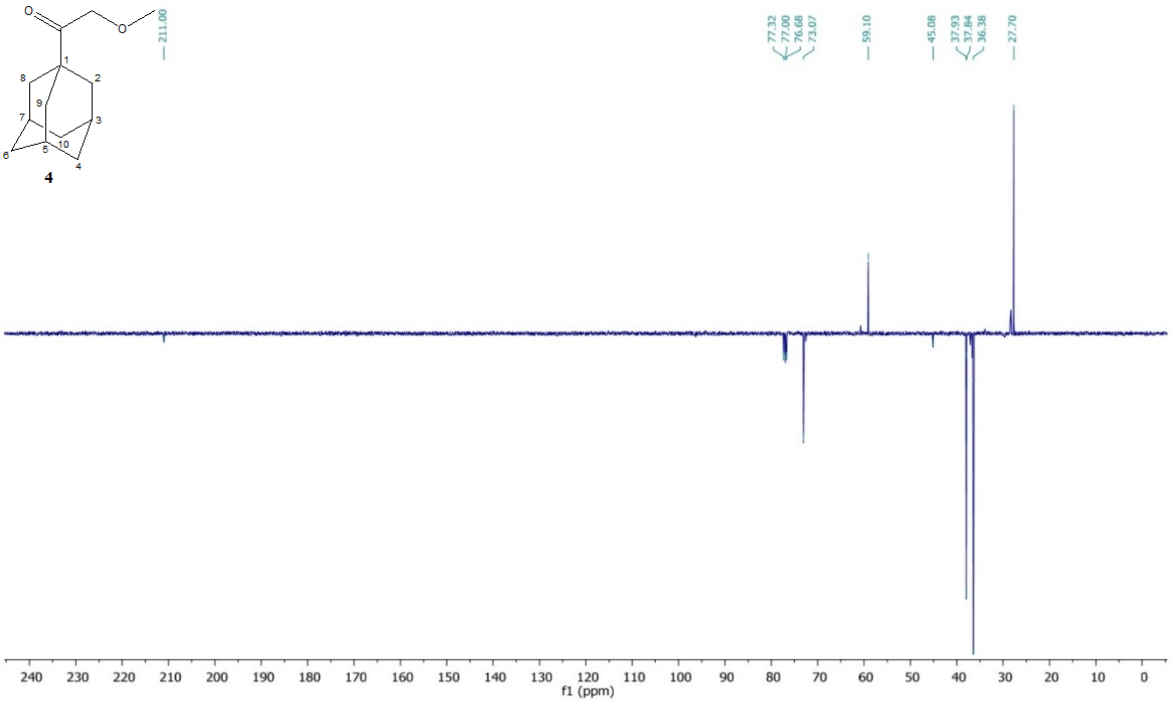


1-methoxy-2-pentadecanone (**3**) ^{13}C NMR (100 MHz, $CDCl_3$)

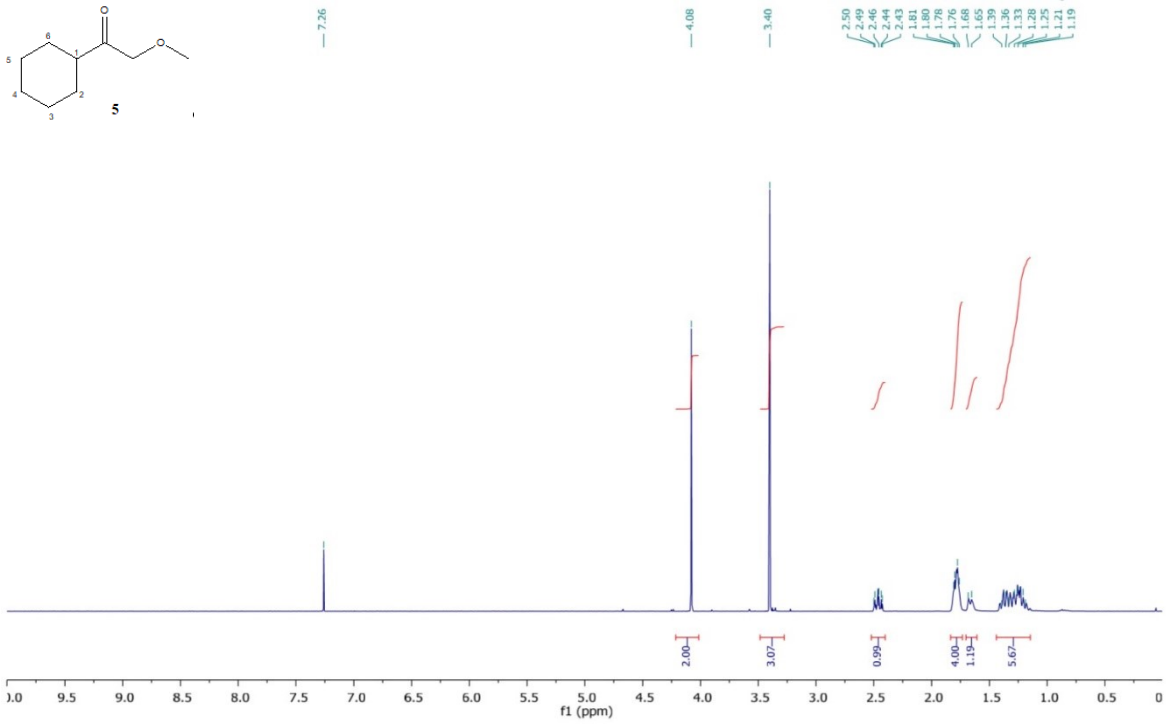
1-(adamantan-1-yl)-2-methoxythanone (**4**) ^{1}H NMR (400 MHz, $CDCl_3$)



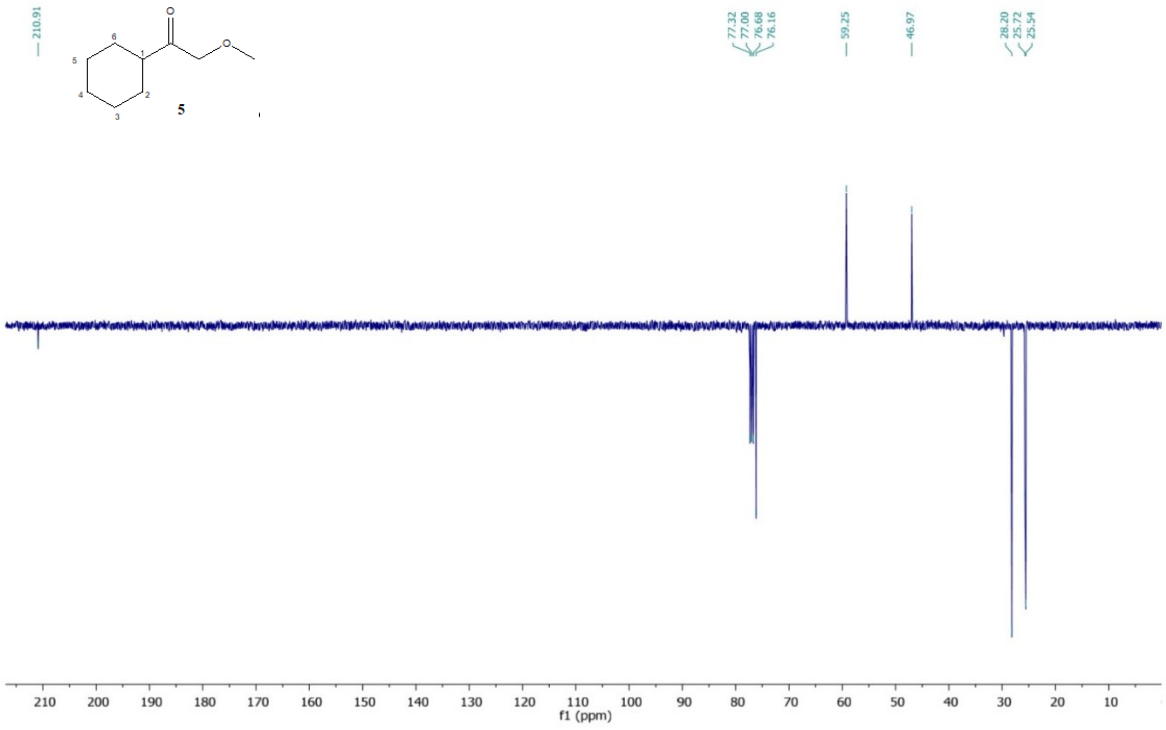
1-(adamantan-1-yl)-2-methoxythanone (**4**) ^{13}C NMR (100 MHz, $CDCl_3$)



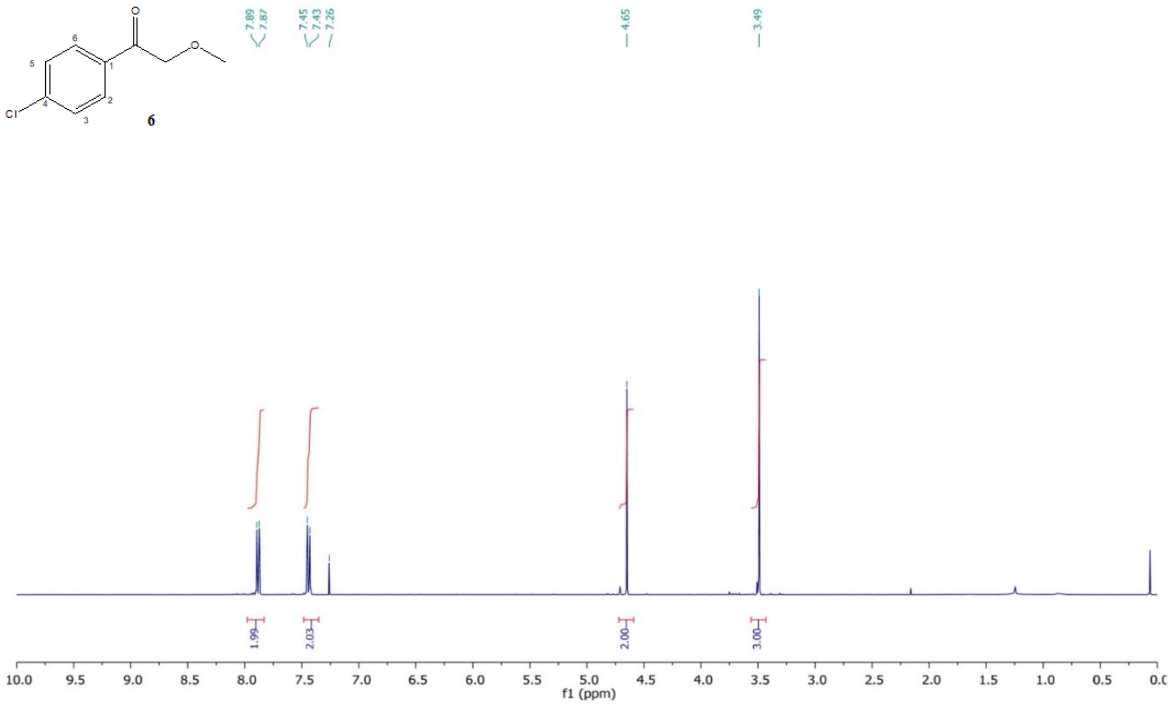
1-cyclohexyl-2-methoxyethanone (**5**) ^{1}H NMR (400 MHz, $CDCl_3$)



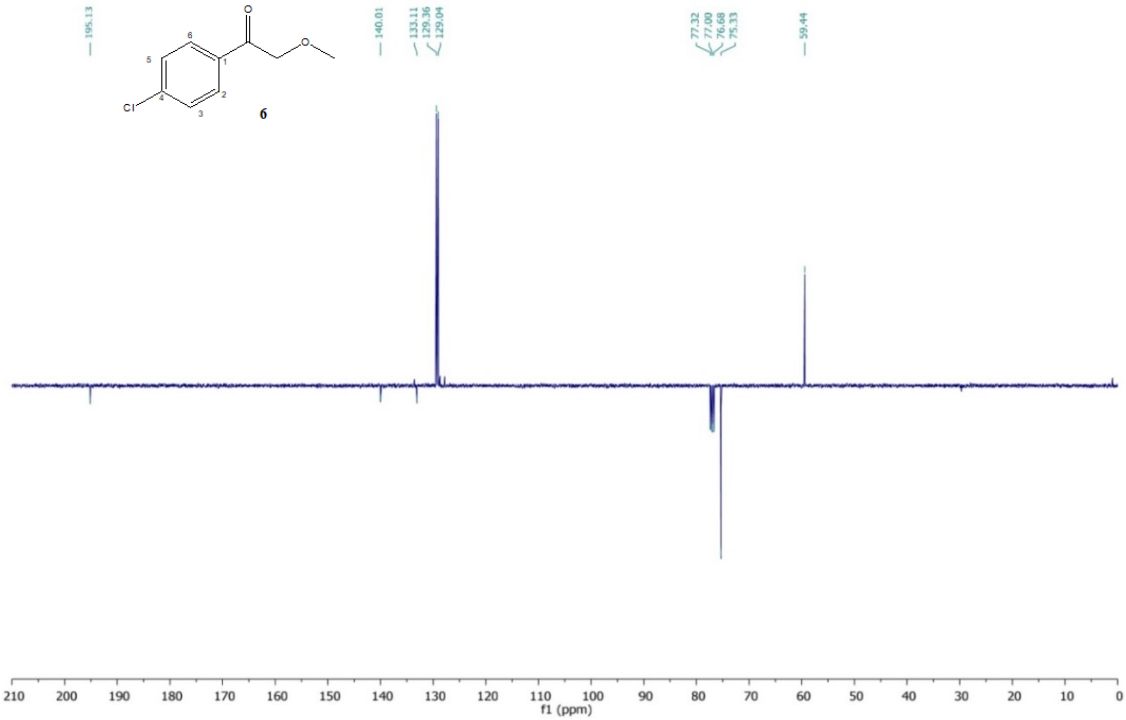
1-cyclohexyl-2-methoxyethanone (**5**) ^{13}C NMR (100 MHz, $CDCl_3$)



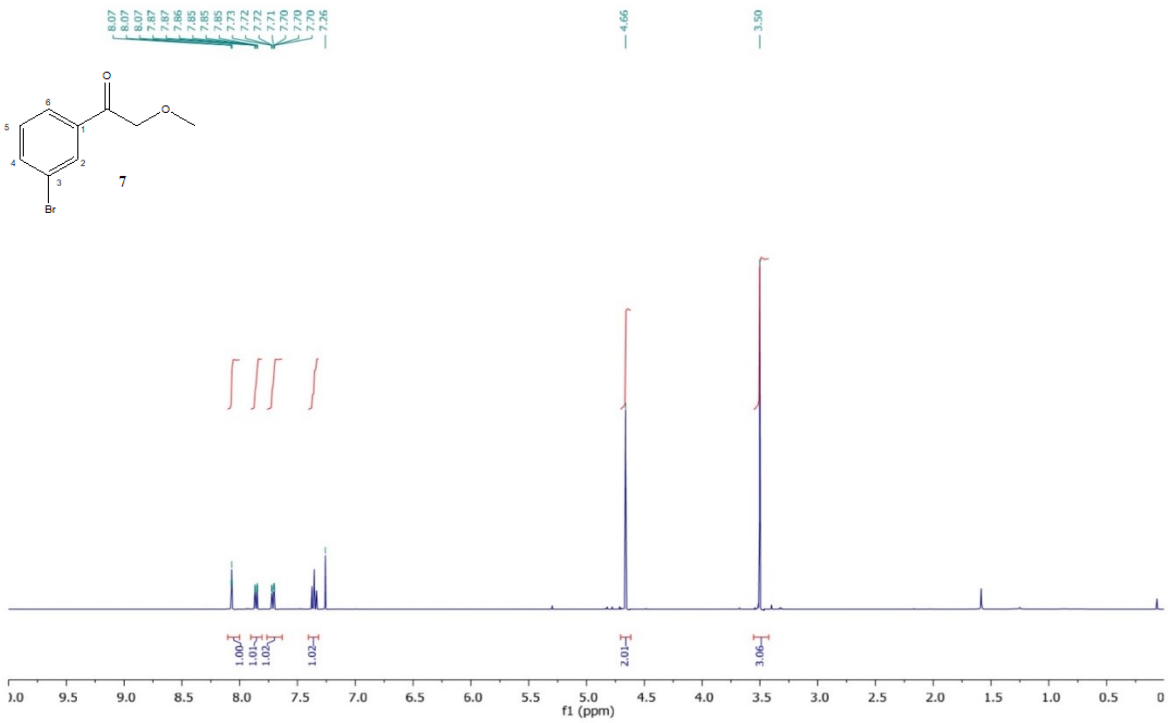
1-(4-chlorophenyl)-2-metoxyethanone (**6**) ^{1}H NMR (400 MHz, $CDCl_3$)



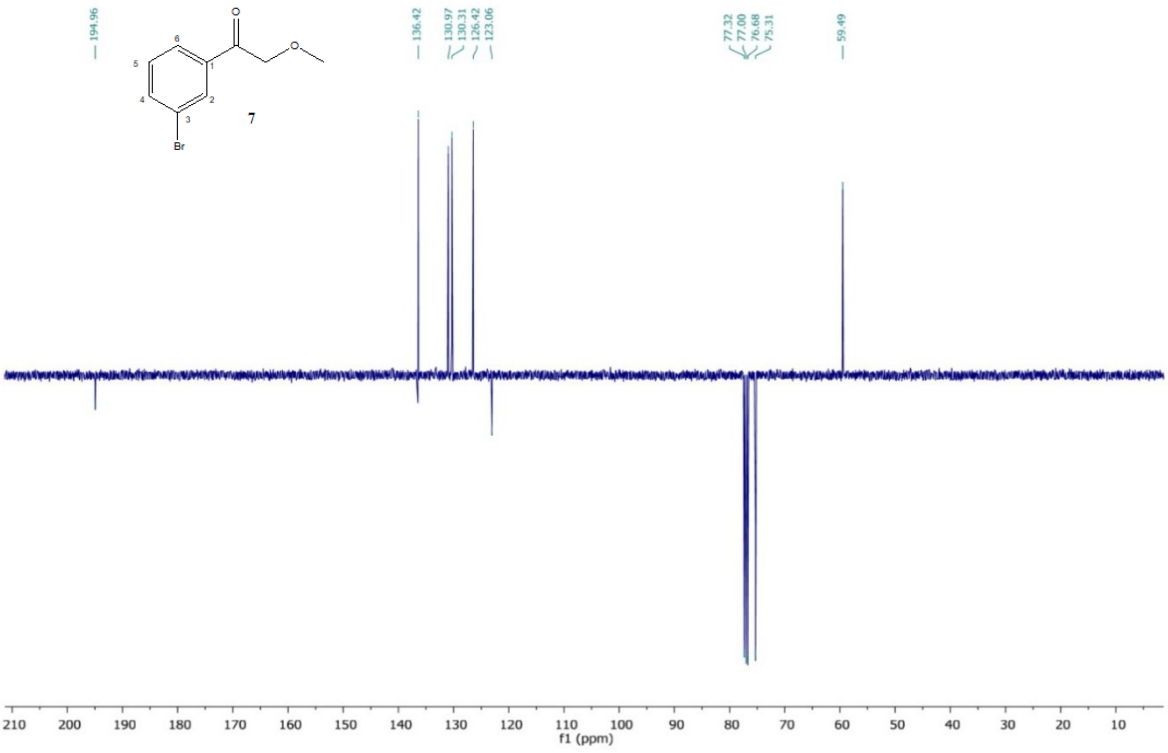
1-(4-chlorophenyl)-2-metoxyethanone (**6**) ^{13}C NMR (100 MHz, $CDCl_3$)



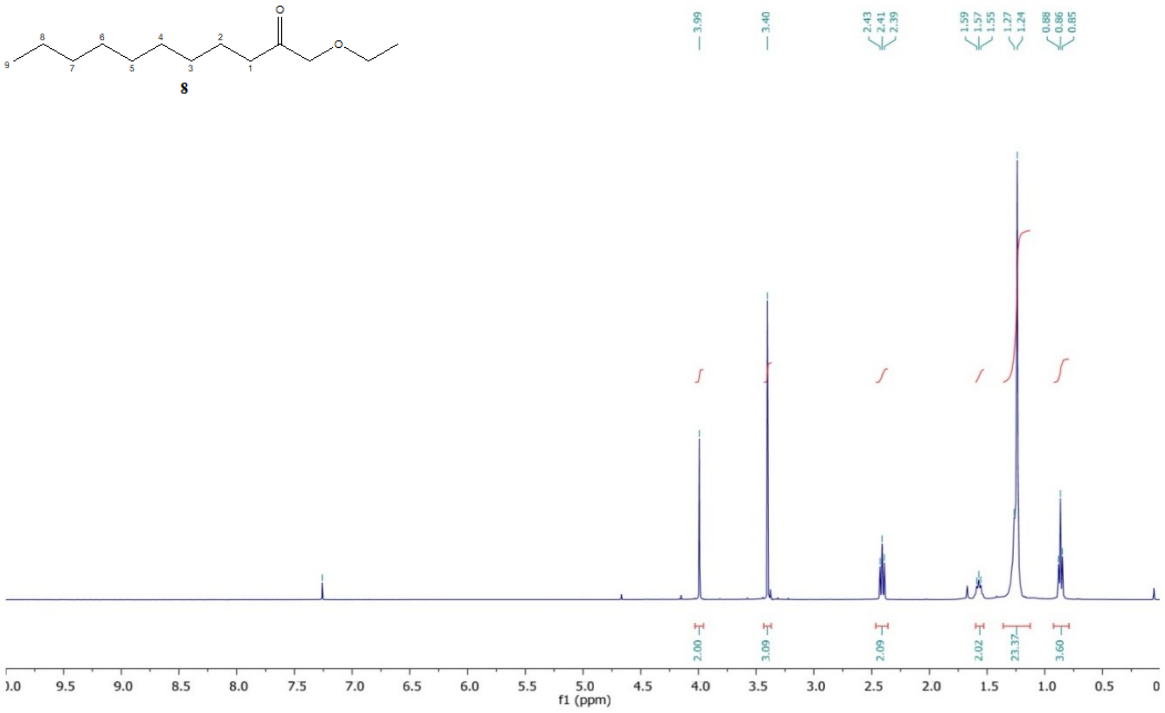
1-(3-bromophenyl)-2-methoxyethanone (**7**) ^{1}H NMR (400 MHz, $CDCl_3$)



1-(3-bromophenyl)-2-methoxyethanone (**7**) ^{13}C NMR (100 MHz, $CDCl_3$)

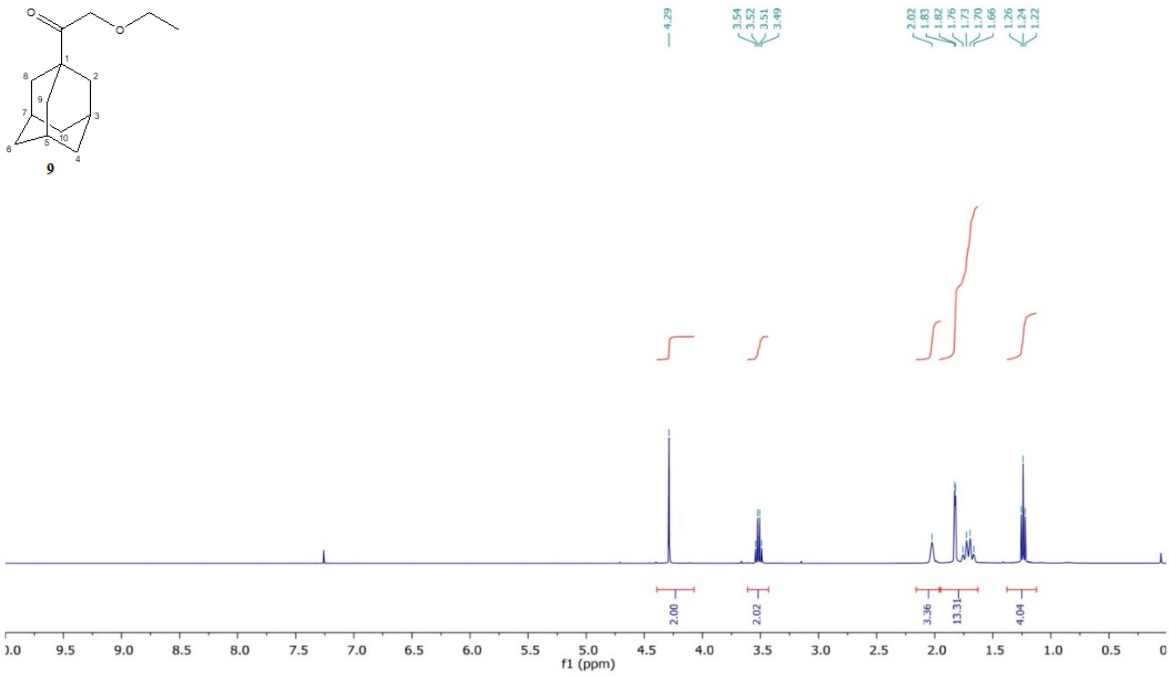


1-ethoxy-2-undecanone (**8**) ^{1}H NMR (400 MHz, $CDCl_3$)

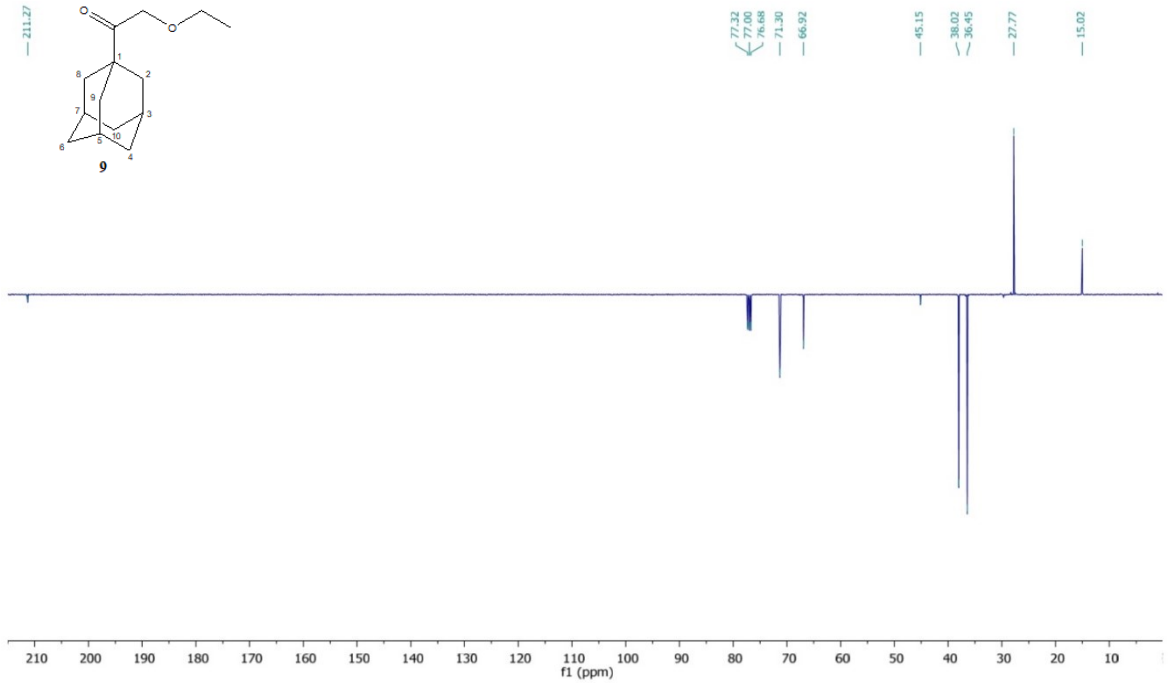


1-ethoxy-2-undecanone (**8**) ^{13}C NMR (100 MHz, $CDCl_3$)

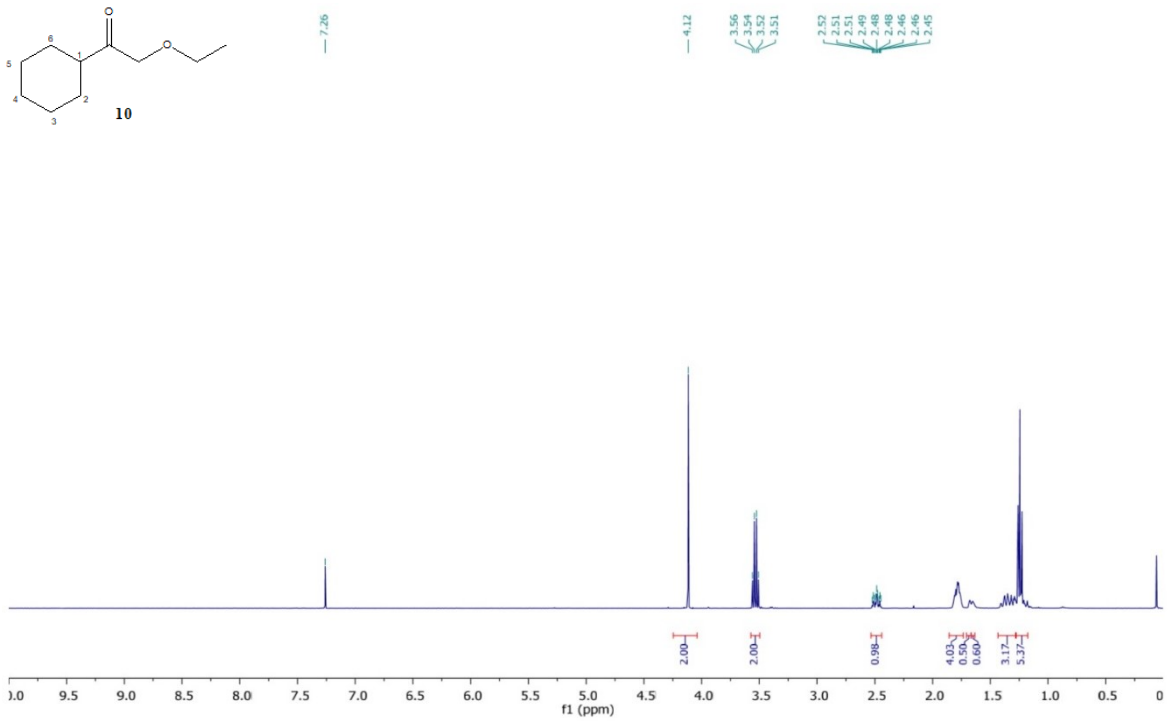
1-(adamantan-1-yl)-2-ethoxythanone (**9**) ^{1}H NMR (400 MHz, $CDCl_3$)



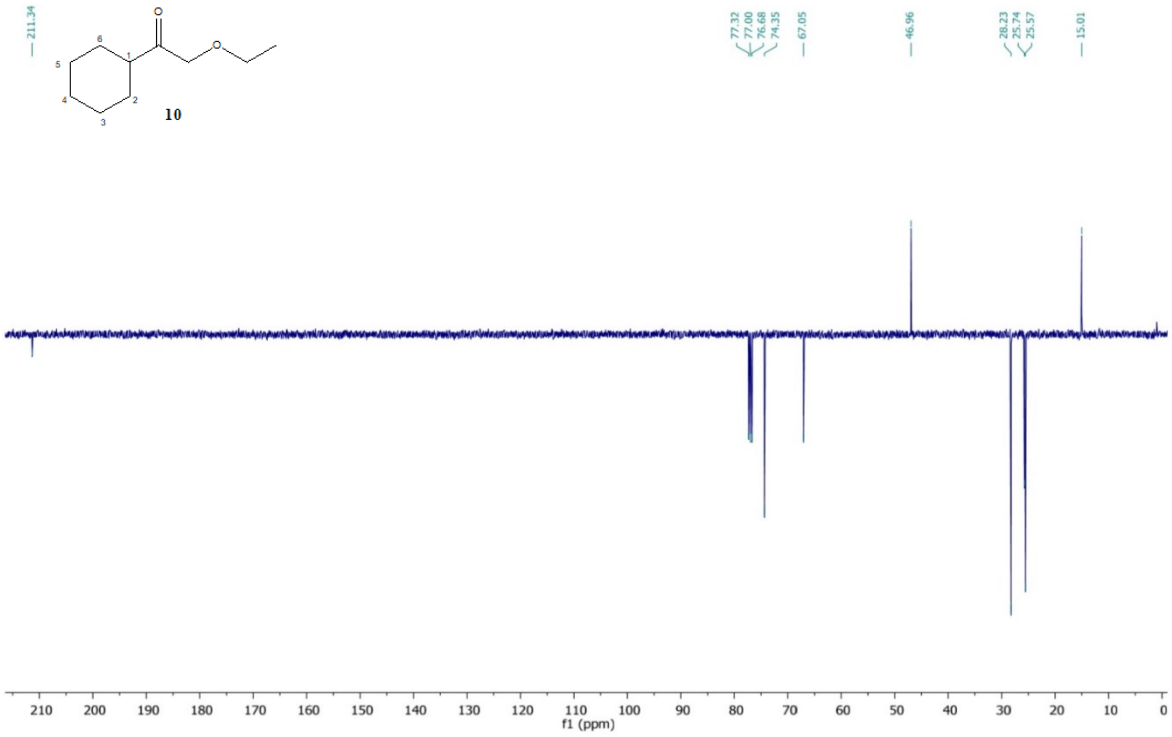
1-(adamantan-1-yl)-2-ethoxythanone (**9**) ^{13}C NMR (100 MHz, $CDCl_3$)



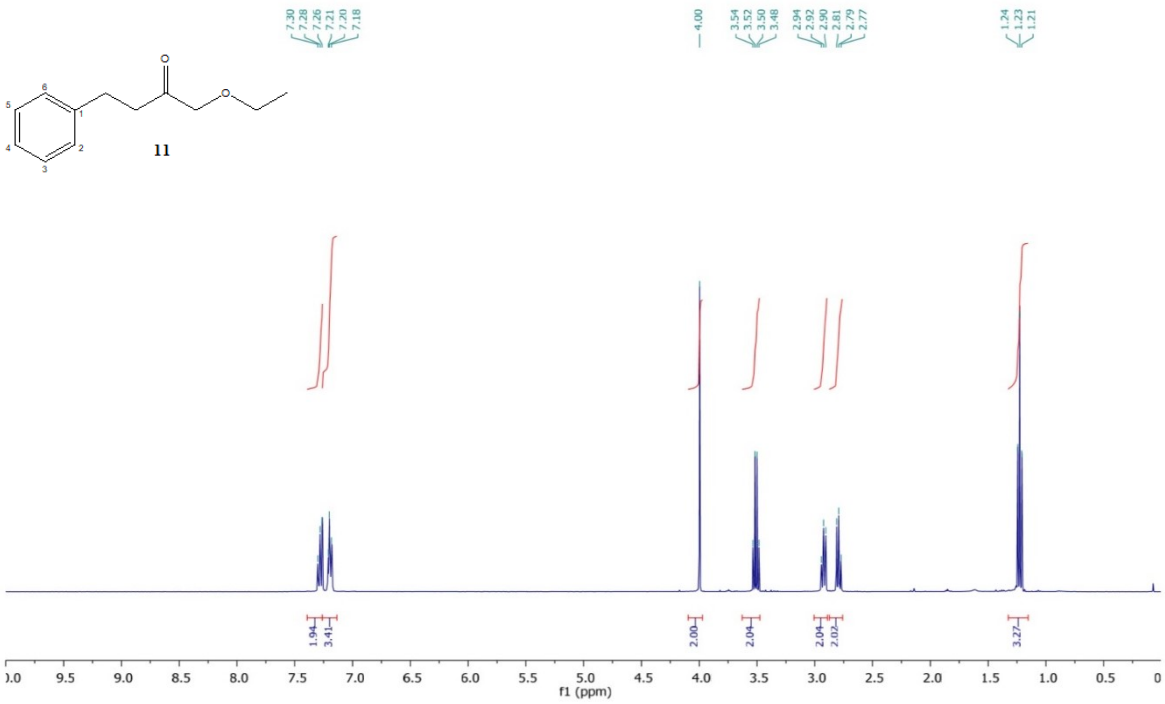
1-cyclohexyl-2-ethoxyethanone (**10**) ^{1}H NMR (400 MHz, $CDCl_3$)



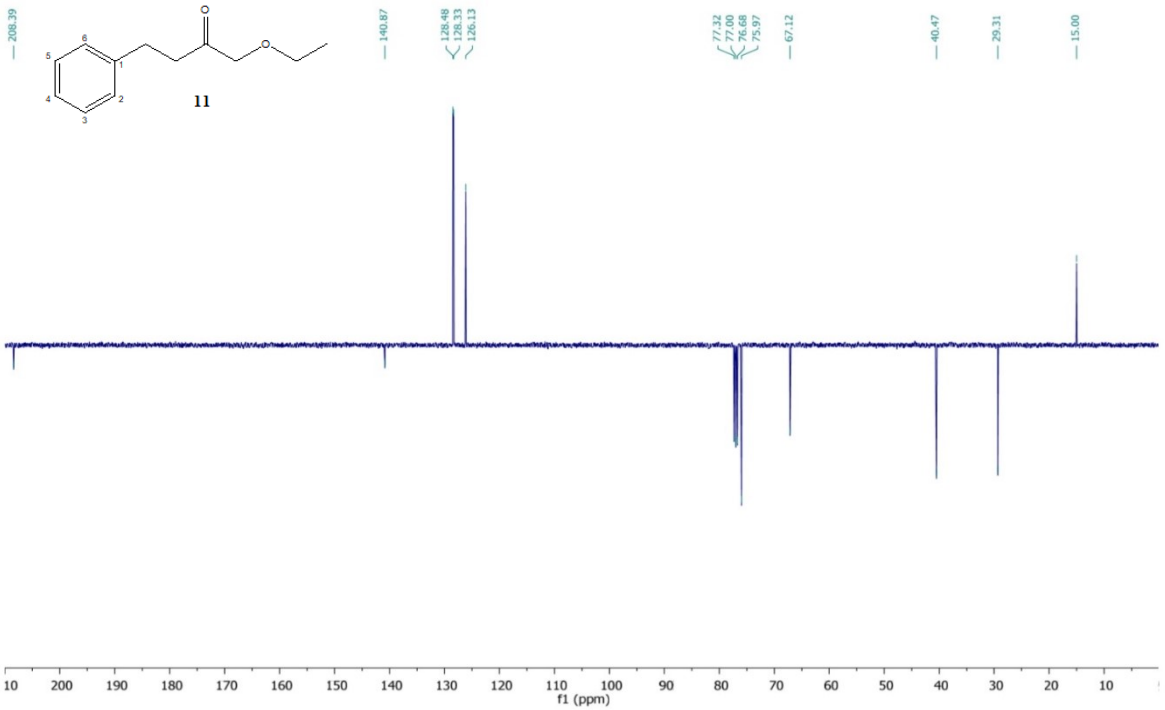
1-cyclohexyl-2-ethoxyethanone (**10**) ^{13}C NMR (100 MHz, $CDCl_3$)



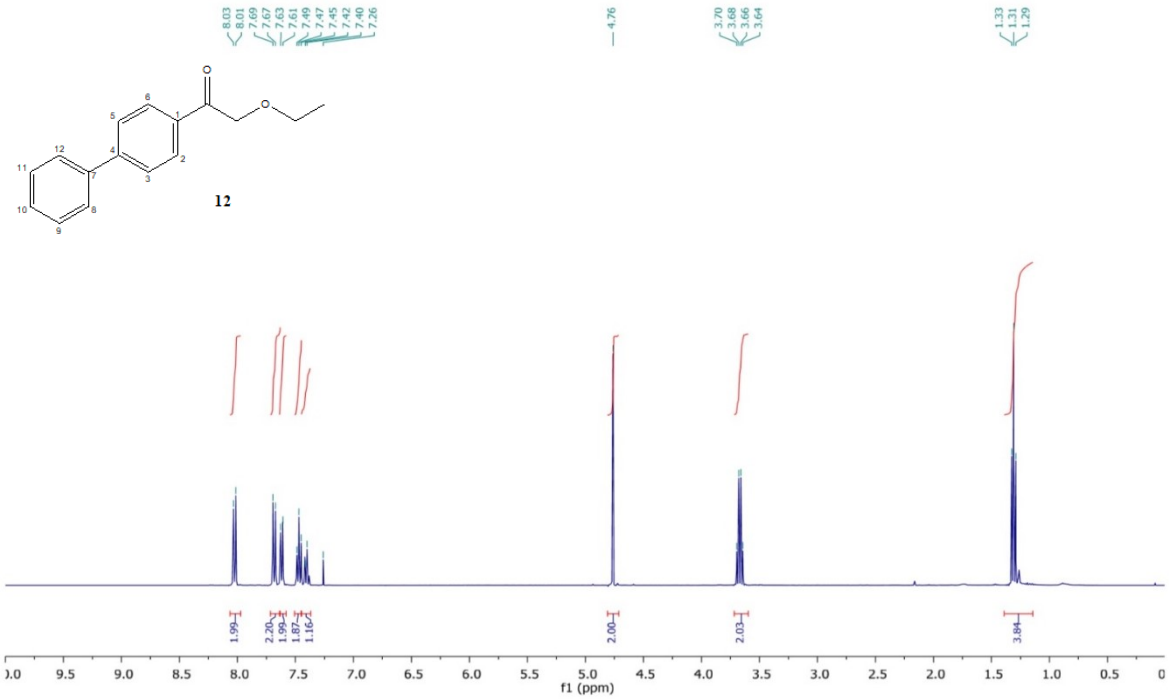
1-ethoxy-4-phenyl-2-butanone (**11**) ^{1}H NMR (400 MHz, $CDCl_3$)



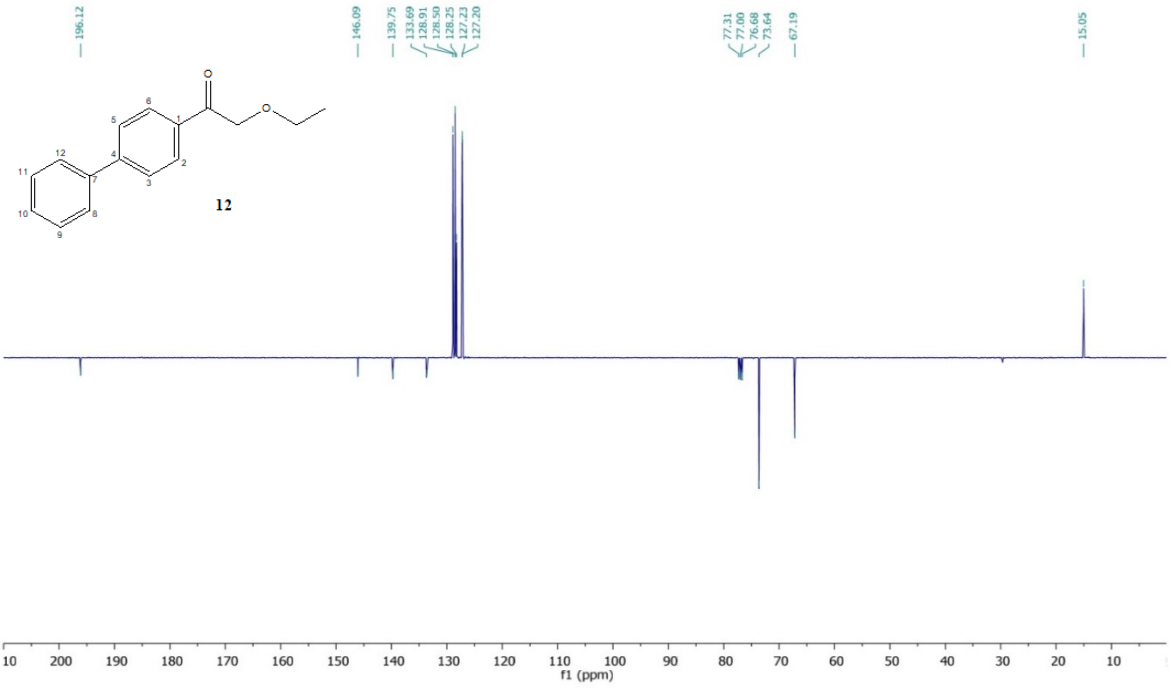
1-ethoxy-4-phenyl-2-butanone (**11**) ^{13}C NMR (100 MHz, $CDCl_3$)



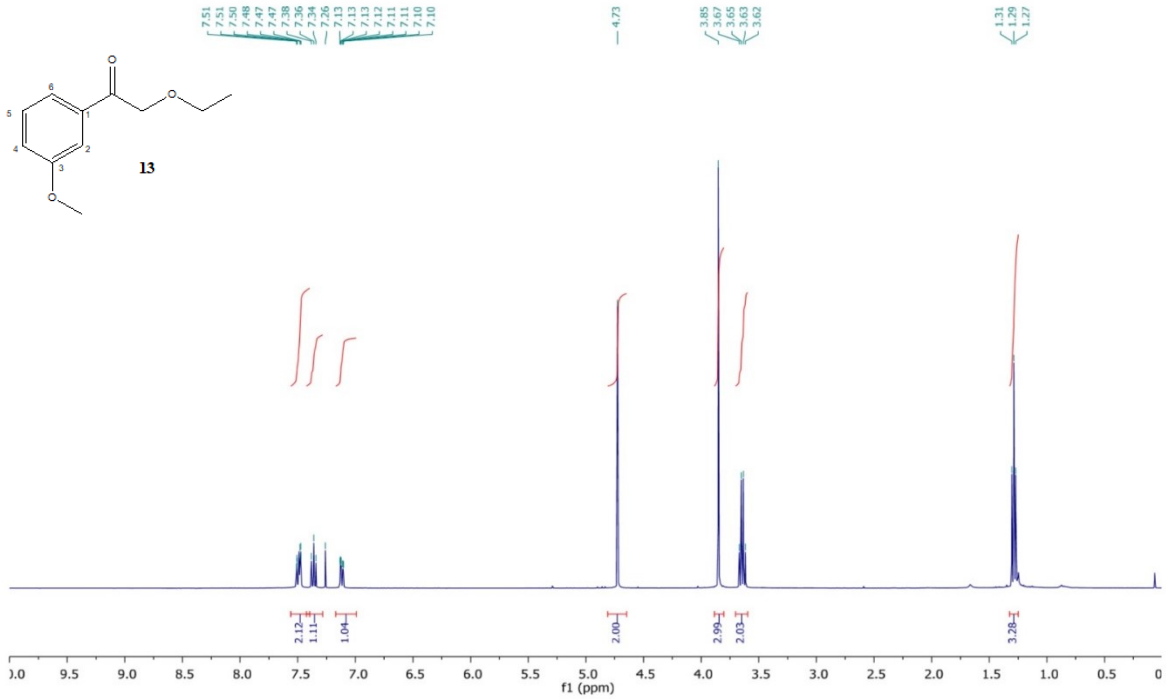
1-(4-biphenylyl)-2-ethoxyethanone (**12**) ^{1}H NMR (400 MHz, $CDCl_3$)



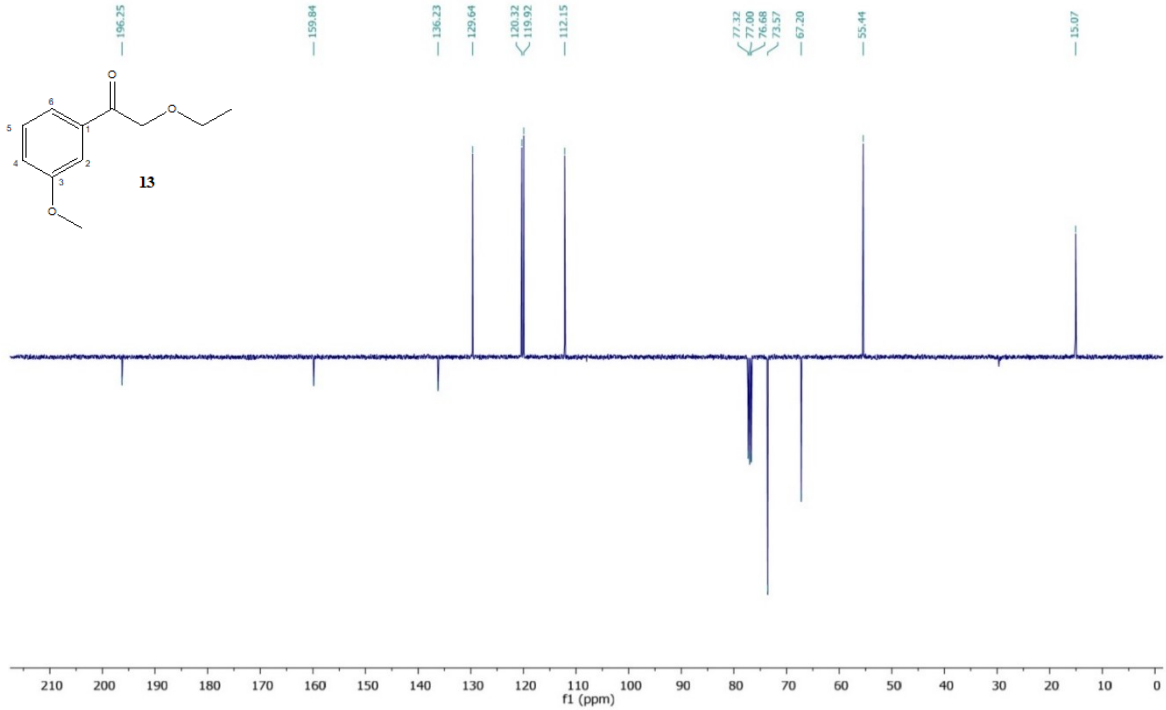
1-(4-biphenylyl)-2-ethoxyethanone (**12**) ^{13}C NMR (100 MHz, $CDCl_3$)



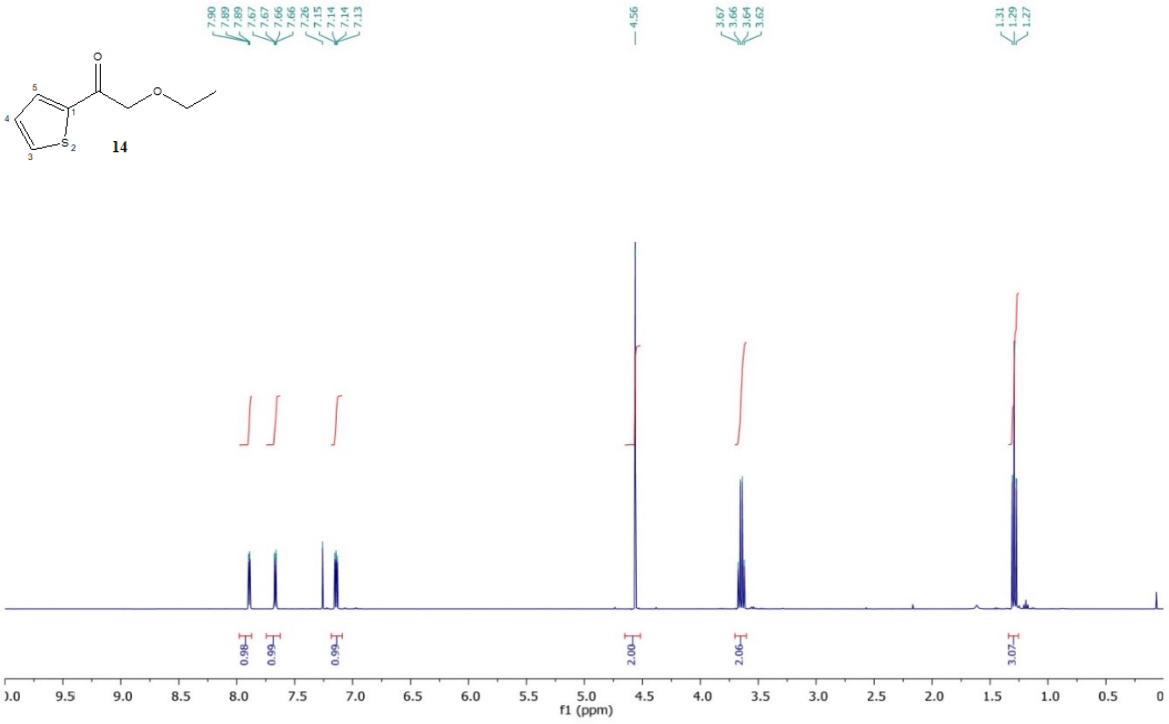
2-ethoxy-1-(3-methoxyphenyl)ethanone (**13**) ^{1}H NMR (400 MHz, $CDCl_3$)



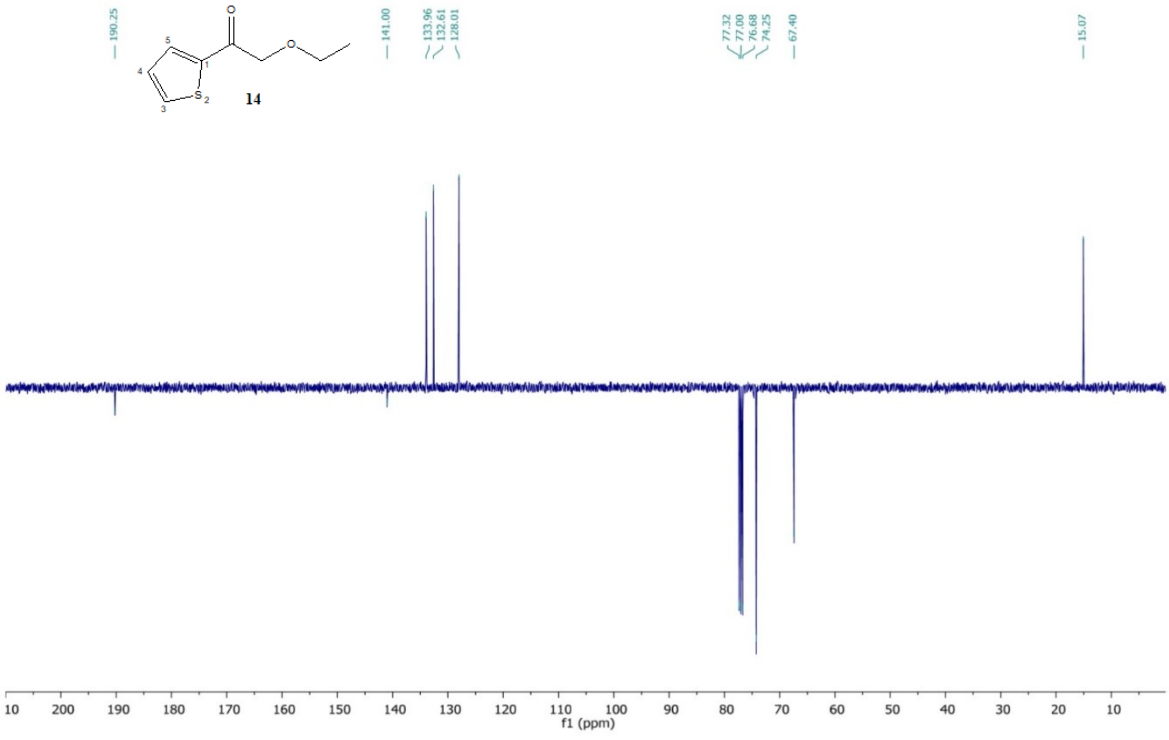
2-ethoxy-1-(3-methoxyphenyl)ethanone (**13**) ^{13}C NMR (100 MHz, $CDCl_3$)



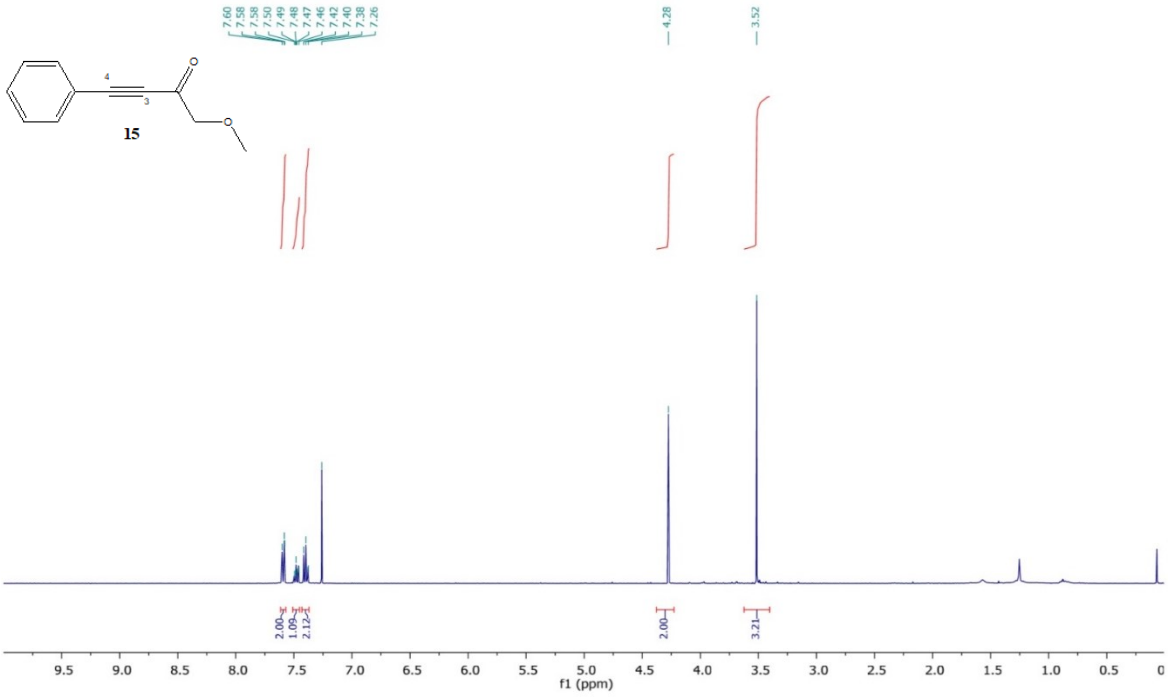
2-ethoxy-1-(2-thienyl)ethanone (**14**) ^{1}H NMR (400 MHz, $CDCl_3$)



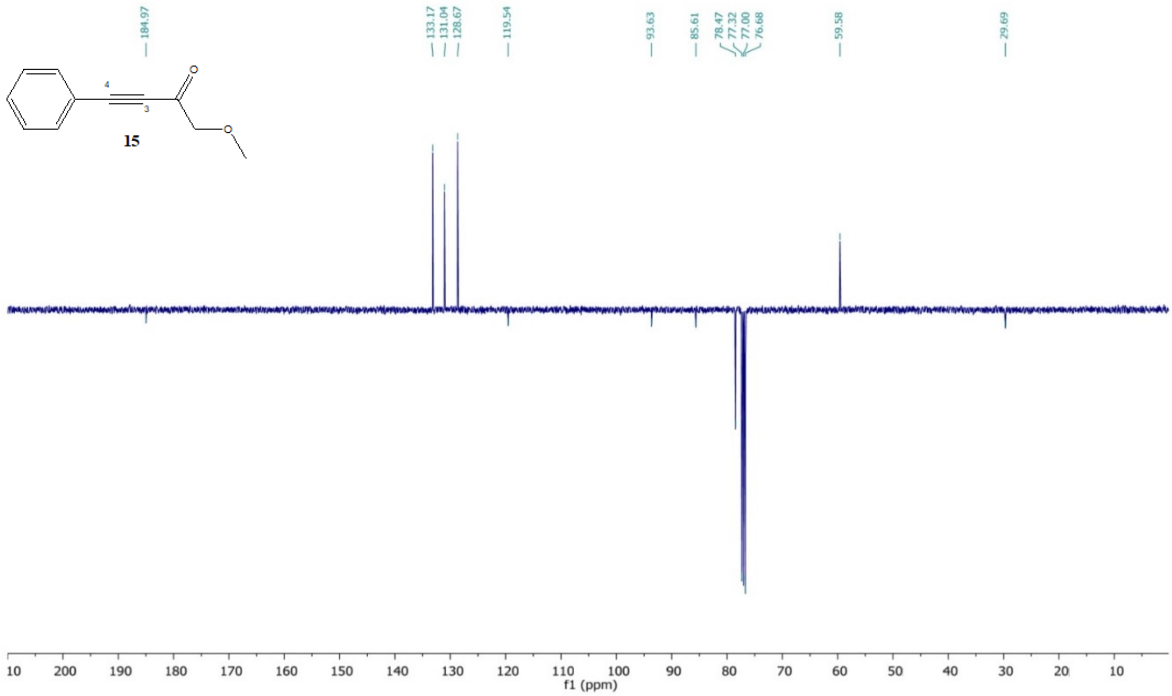
2-ethoxy-1-(2-thienyl)ethanone (**14**) ^{13}C NMR (100 MHz, $CDCl_3$)



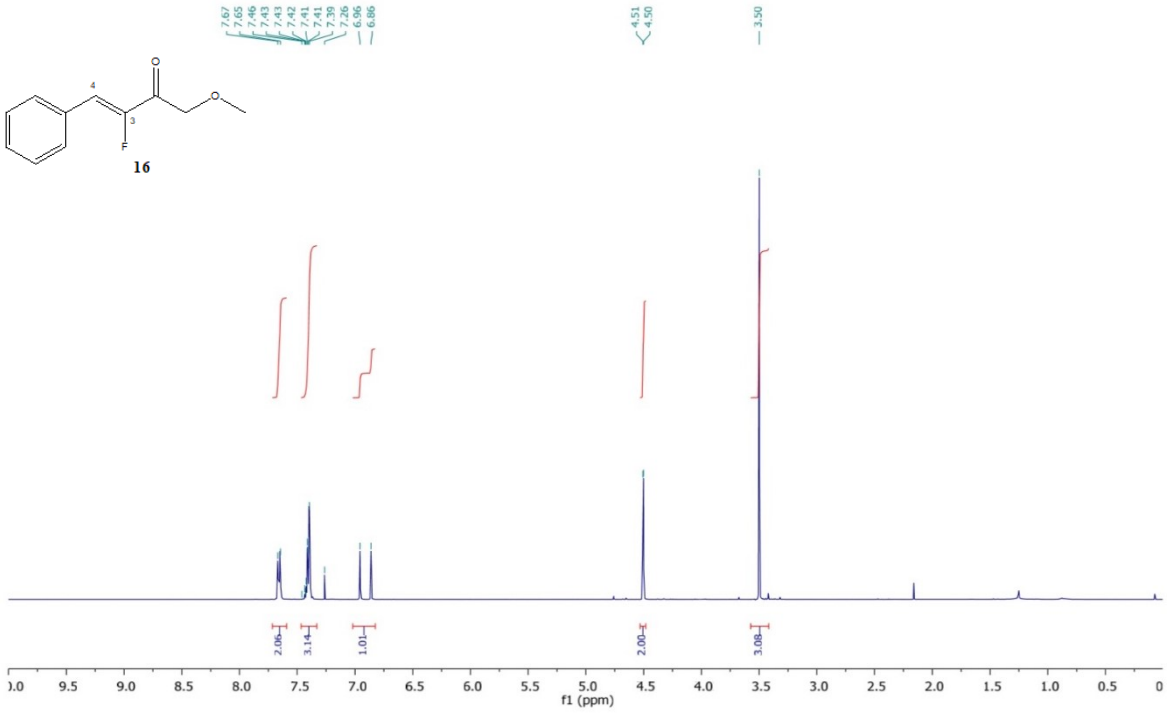
1-methoxy-4-phenyl-3-butyn-2-one (**15**) ^{1}H NMR (400 MHz, $CDCl_3$)



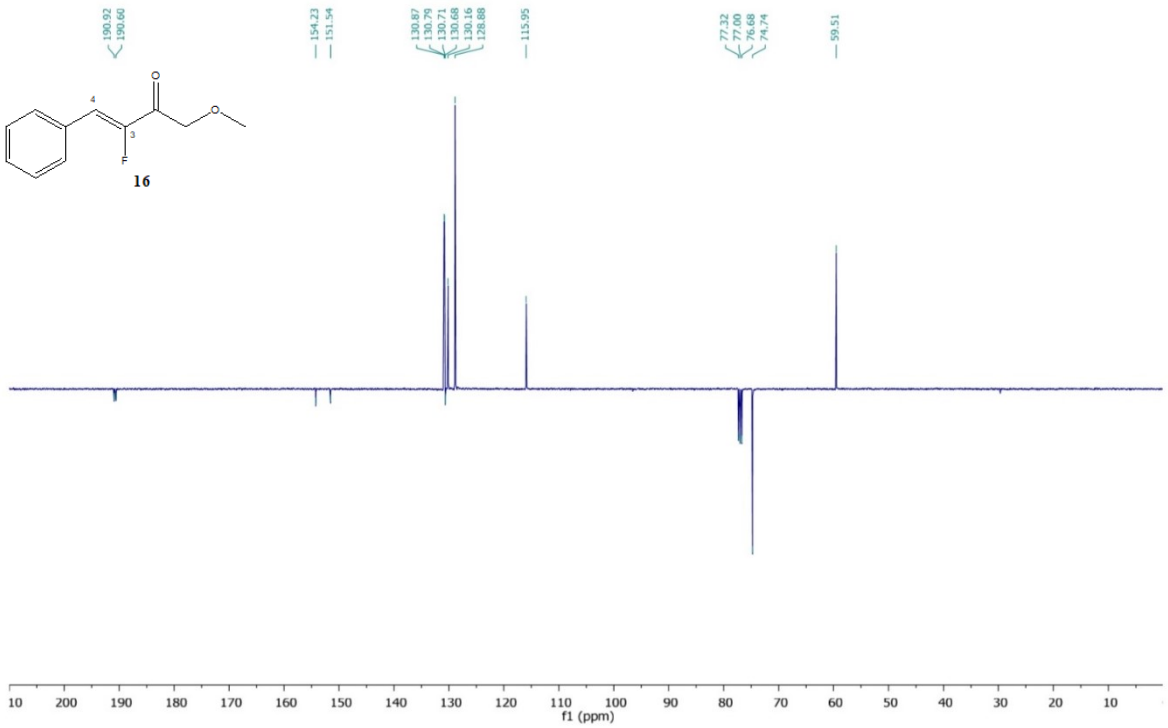
1-methoxy-4-phenyl-3-butyn-2-one (**15**) ^{13}C NMR (100 MHz, $CDCl_3$)



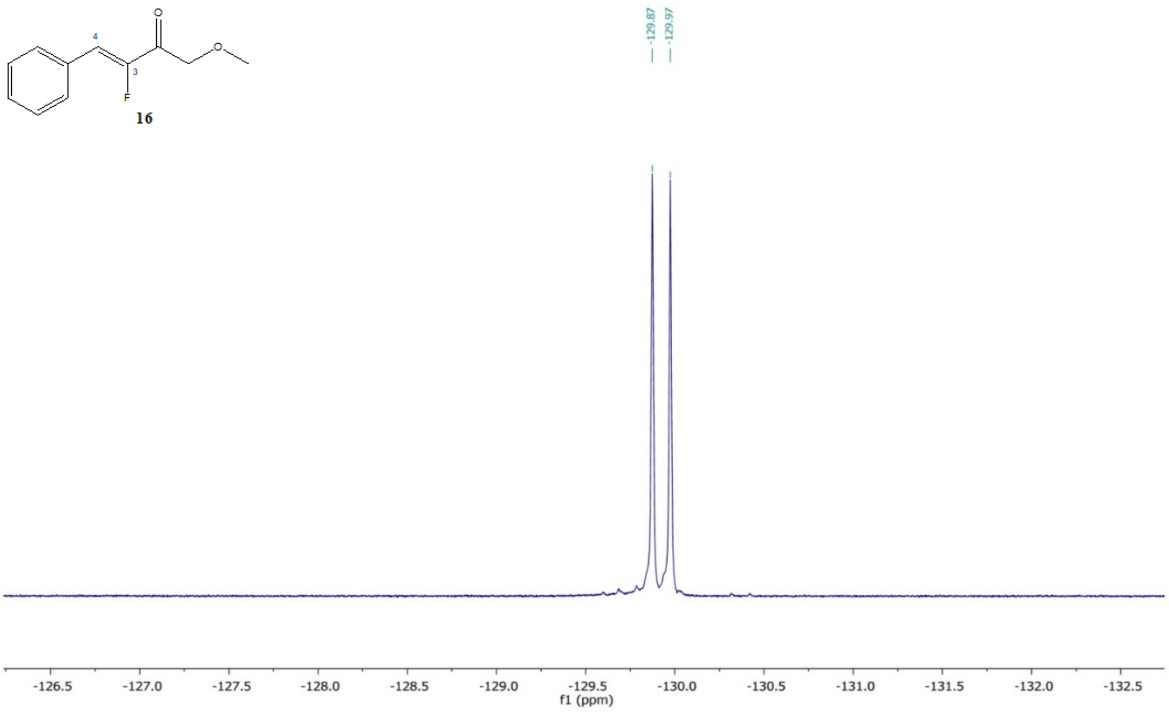
(3Z)-3-fluoro-1-methoxy-4-phenyl-3-buten-2-one (**16**) ^{1}H NMR (400 MHz, $CDCl_3$)



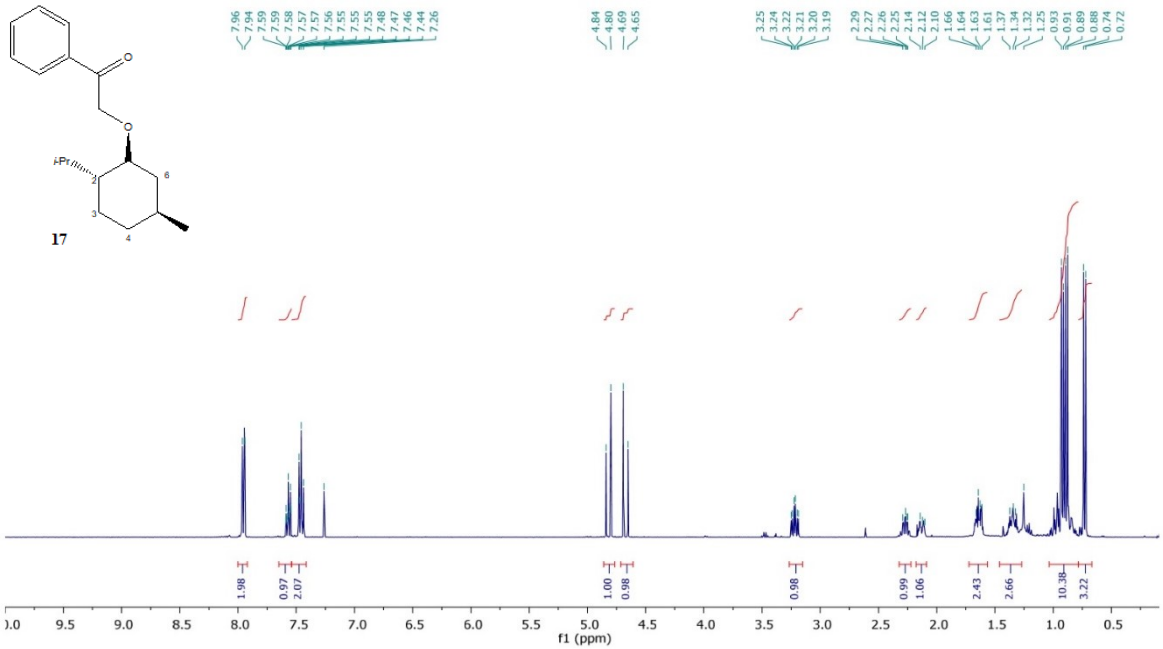
(3Z)-3-fluoro-1-methoxy-4-phenyl-3-buten-2-one (**16**) ^{13}C NMR (100 MHz, $CDCl_3$)



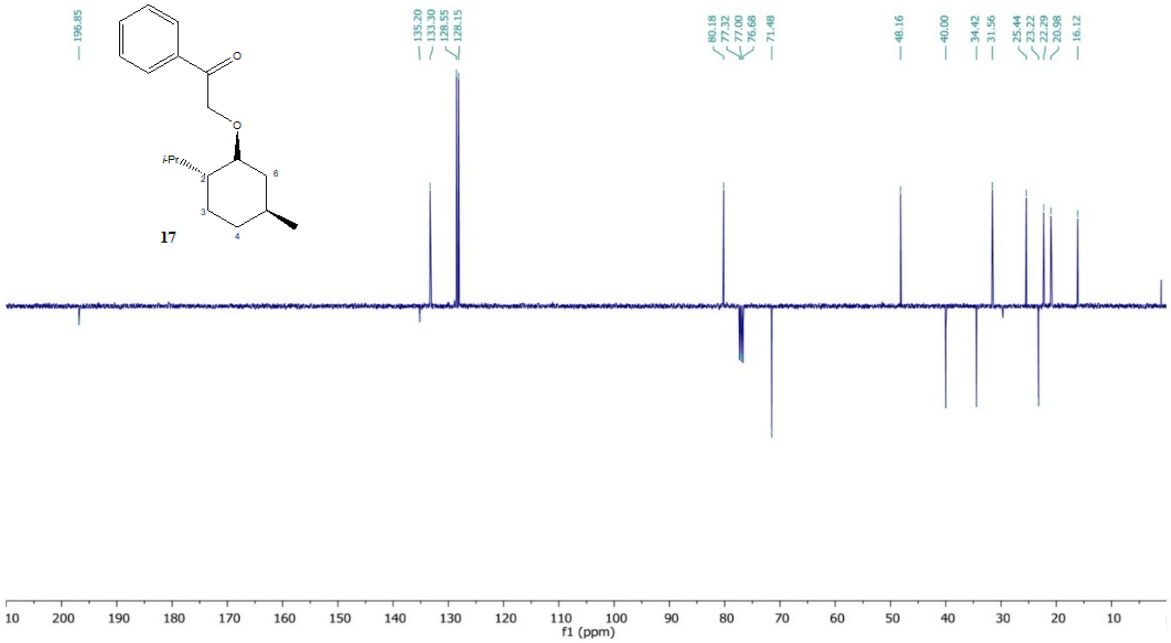
(3Z)-3-fluoro-1-methoxy-4-phenyl-3-buten-2-one (**16**) ^{19}F NMR (376 MHz, $CDCl_3$)



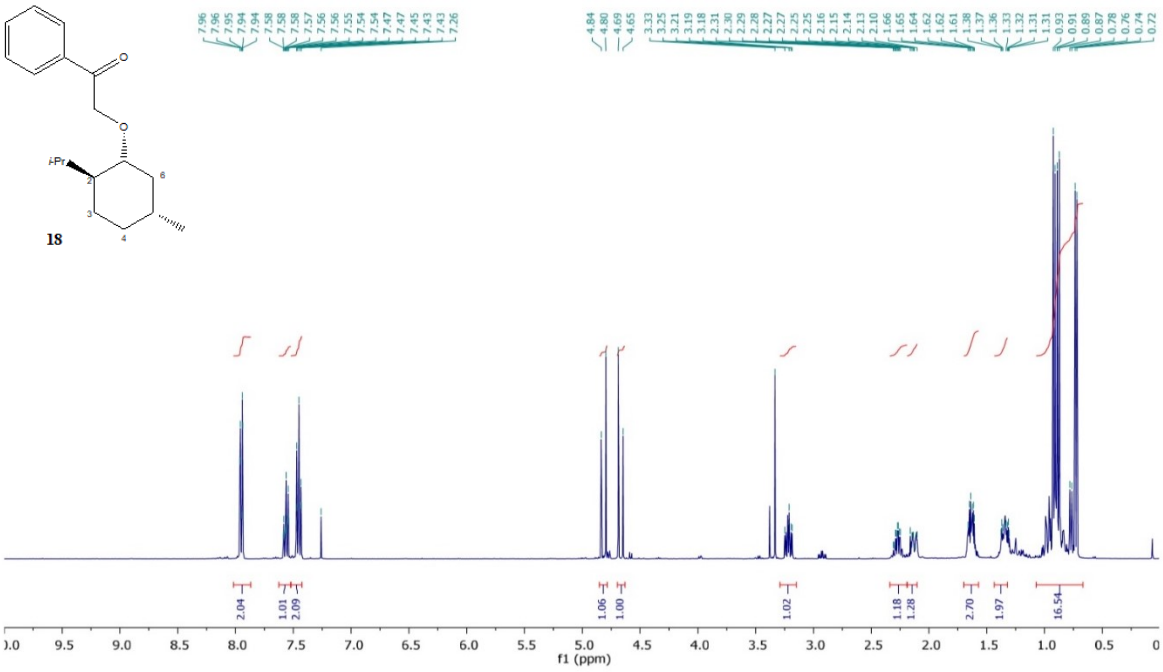
2-{[(1*S*, 2*R*, 5*S*)-2-isopropyl-5-methylcyclohexyl]oxy}-1-phenylethanone (**17**) ^{1}H NMR (400 MHz, $CDCl_3$)



2-{[(1*S*, 2*R*, 5*S*)-2-isopropyl-5-methylcyclohexyl]oxy}-1-phenylethanone (**17**) ^{13}C NMR (100 MHz, $CDCl_3$)



2-{[(1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexy]oxy}-1-phenylethanone (**18**) ^{1}H NMR (400 MHz, $CDCl_3$)



2-{[(1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexy]oxy}-1-phenylethanone (**18**) ^{13}C NMR (100 MHz, $CDCl_3$)