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The One-pot β -Halogenation of Enones and its Application for the Synthesis of *Kopsia* Alkaloids

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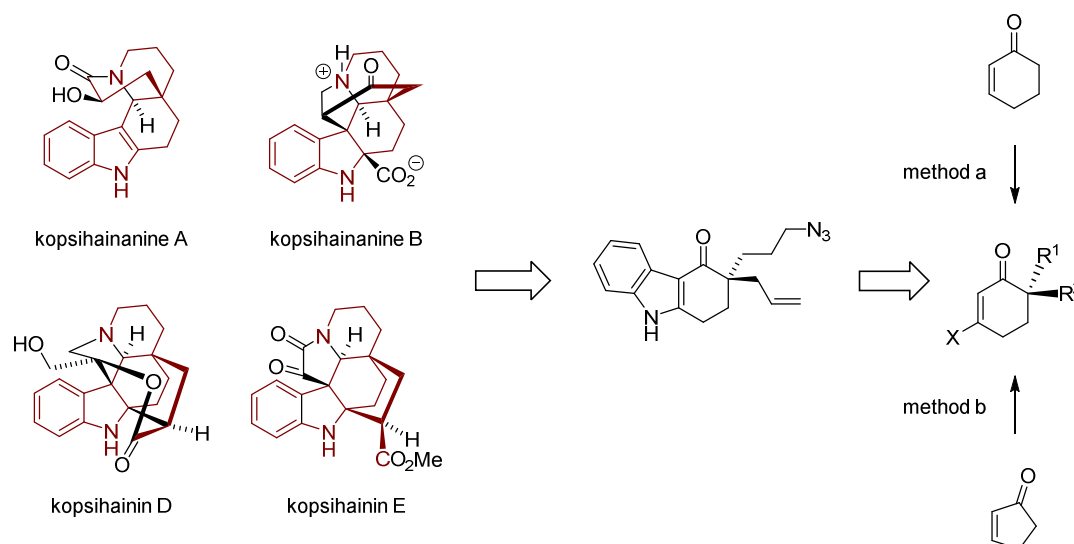
1 Abstracts

1.1 English abstract

Herein, we present the development of a one-pot protocol for the selective β -halogenation of α,β -unsaturated carbonyl compounds. Several different strategies are described, including the bromination of hydrazones, the use of a Pummerer-type rearrangement and the attempted synthesis of a dihalogenated Corey–Chaykovsky reagent.

The envisioned transformation was realised employing a three-step one-pot procedure. This includes the formation of a hydrazone and bromination of the double bond, followed by selective α -bromide elimination and final cleavage of the hydrazone to yield the brominated enone. The developed method was successfully tested on several cyclic and acyclic ketones and aldehydes.

Additionally, our efforts toward the synthesis of *Kopsia* alkaloids are presented. We envision to access these natural products by using our newly developed method for the β -functionalisation of enones. First steps were already taken in these syntheses, with further investigations being under way in our laboratory.

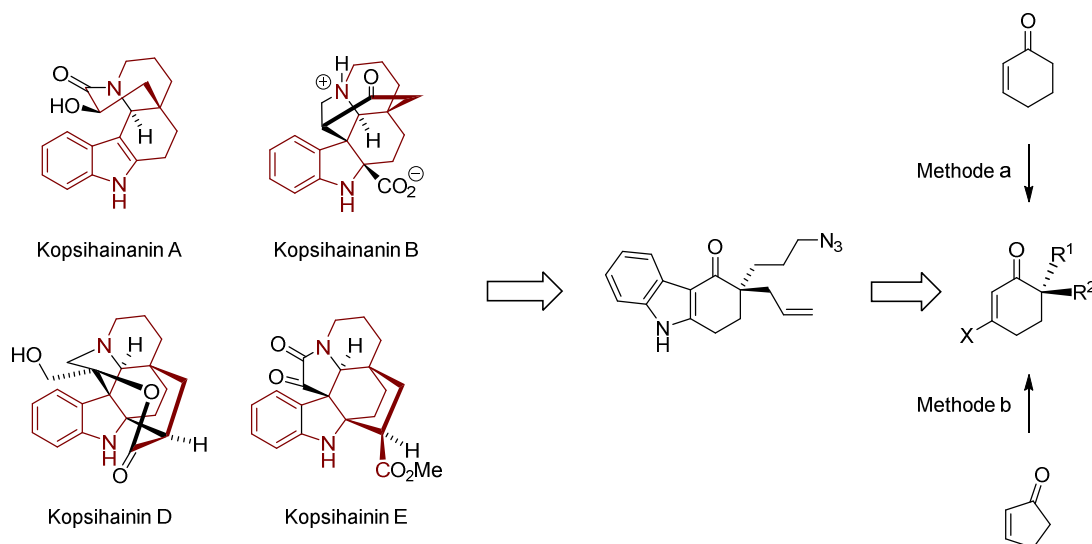


1.2 Deutsche Zusammenfassung

In dieser Arbeit stellen wir die Entwicklung einer Eintopf-Methode für die selektive β -Halogenierung von α,β -ungesättigten Carbonylverbindungen vor. Verschiedene Ansätze wurden im Zuge der Untersuchungen verfolgt, darunter die Bromierung von Hydrazonen, eine Variante der Pummerer-Umlagerung, sowie die Synthese eines dihalogenierten Corey–Chaykovsky-Reagenzes.

Die angestrebte Transformation konnte als eine Drei-Stufen-Eintopf-Vorschrift verwirklicht werden. Hierbei folgen auf eine Hydrazonbildung die Bromierung der Doppelbindung und eine selektive α -Bromid-Eliminierung, bevor im letzten Schritt das Hydrazon gespalten wird. Die entwickelte Methode konnte erfolgreich auf mehrere cyclische, sowie acyclische Ketone und Aldehyde angewandt werden.

Zusätzlich wurde an der Synthese von *Kopsia*-Alkaloiden gearbeitet. Unsere Pläne sehen vor, diese Naturstoffe mithilfe unserer neu entwickelten Methodik zur selektiven Funktionalisierung der β -Position von Enonen zu synthetisieren. Erste Schritte der Synthese konnten bereits verwirklicht werden – weitere Untersuchungen werden derzeit in unserem Labor vorgenommen.



2 Table of Abbreviations

Ac	acetyl
AChE	acetylcholinesterase
AcOH	acetic acid
app	apparent (NMR)
aq	aqueous
ATR	attenuated total reflection
Boc	<i>tert</i> -butyloxycarbonyl
br	broadened (NMR)
brsm	based on recovered starting material
Bu	butyl
c	concentration
<i>c</i>	concentration [g/100 mL]
calcd	calculated
CAM	ceric ammonium molybdate
cat.	catalyst
d	days
d	doublet
δ	chemical shift (NMR)
DCE	1,2-dichloroethane
decomp.	decomposition
DCI	desorption chemical ionisation
DIPA	diisopropylamine
DMF	<i>N,N</i> -dimethylformamide

EI	electron ionisation
ESI	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
equiv	equivalent
FTIR	Fourier transform infrared spectroscopy
<i>gem</i>	geminal
h	hours
HMPA	hexamethylphosphoric triamide
HRMS	high resolution mass spectroscopy
IBX	2-iodoxybenzoic acid
IC ₅₀	half maximal inhibitory concentration
IR	infrared
LDA	lithium diisopropylamide
m	multiplet
M	molar
Me	methyl
MeCN	acetonitrile
MeOH	methanol
μM	micromolar
mmol	millimole
μmol	micromole
MPO	4-methoxypyridine N-oxide
MS	mass spectroscopy

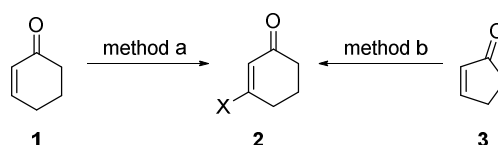
MS	molecular sieves
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
n.d.	not determined
NMR	nuclear magnetic resonance
NXS	<i>N</i> -halosuccinimide
Ph	phenyl
ppm	parts per million
PTC	phase-transfer catalyst
<i>p</i> -TsOH	<i>para</i> -toluenesulfonic acid
quant.	quantitative
quin	quintet
R_f	retention factor
rfx	reflux
s	singlet
SET	single-electron transfer
SM	starting material
solv.	solvent
t	triplet
<i>t</i> -Bu	<i>tert</i> -butyl
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBCHD	2,4,4,6-tetrabromo-2,5-cyclohexadienone
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TBSOTf	<i>tert</i> -butyldimethylsilyl trifluoromethanesulfonate

TCCA	trichloroisocyanuric acid
TEBA	benzyltriethylammonium chloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
UV	ultraviolet
$\tilde{\nu}$	wavenumber [cm^{-1}]
X	halogen

3 Introduction

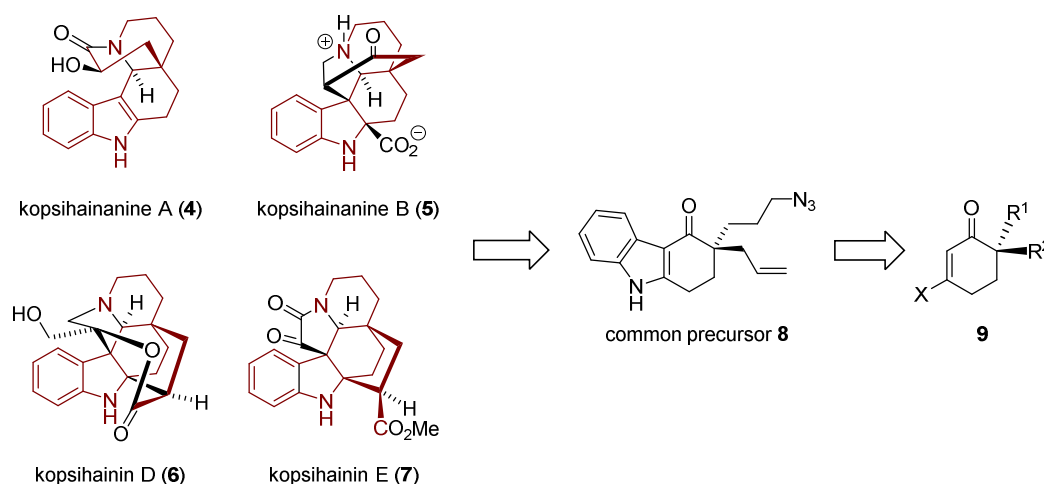
3.1 Overview

The aim of this work was to develop a one-pot protocol for the β -halogenation of α,β -unsaturated carbonyl compounds. This was envisioned either through a direct functionalisation of the β -position, or via *gem*-dihalocyclopropanation of the carbon–carbon double bond, followed by fragmentation and concomitant ring expansion (Scheme 1).



Scheme 1. Envisioned methodologies.

The newly developed protocol was then to be applied to the total syntheses of kopsihainanine A (**4**) and B (**5**), as well as kopsihainin D (**6**) and E (**7**), which were recently isolated from *Kopsia hainanensis* (Scheme 2).

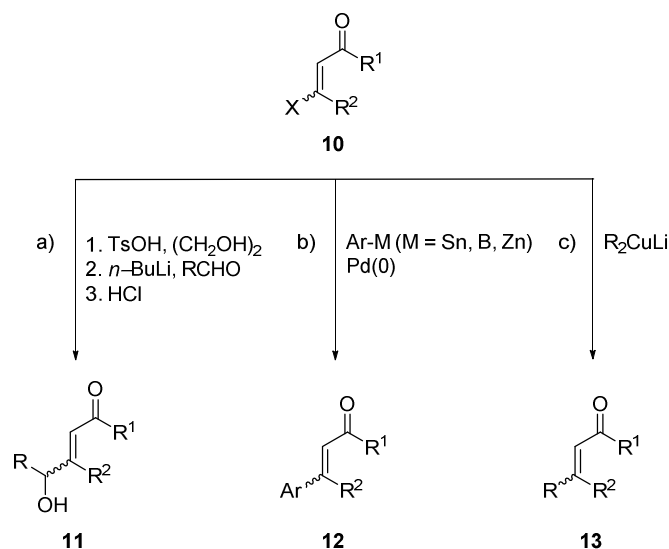


Scheme 2. Selected *Kopsia* alkaloids. The carbon framework of the common precursor **8** is highlighted in red in the natural products.

3.2 The use of β -halogenated enones

While the α -halogenation of enones is a common and routinely executed transformation^[1], there are no established methods for the synthesis of the corresponding β -halogenated analogues in a simple and efficient way. This is surprising, considering that α,β -unsaturated carbonyl compounds bearing a halogen at their β -position are versatile synthetic intermediates (Scheme 3).

Several highly valuable transformations can be carried out using this class of compound as the starting material. One of these reactions is the metalation of the vinyl halide moiety, which enables the addition of an electrophile at the sp^2 -carbon (Scheme 3, path a).^[2] Transition metal catalysed cross-coupling reactions with traditional coupling partners, such as alkenes^[3], organotin^[4], organozinc^[5], and organoboron^[6] species are also possible and lead to products such as **12** (Scheme 3, path b). The 1,4-addition of a nucleophile to halide **10**, followed by a retro-Michael reaction promoted expulsion of the halide—this could also be classified as an E1cB-type elimination—allows for the introduction of various substituents at the β -position (Scheme 3, path c).^[7]



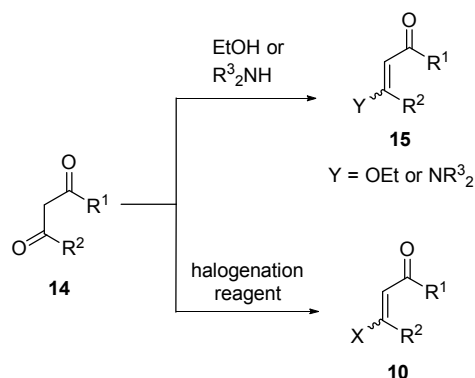
Scheme 3. Synthetic transformations of β -halogenated enones.

3.3 The synthesis of β -functionalised α,β -unsaturated carbonyl compounds

Several methods for the synthesis of β -functionalised α,β -unsaturated carbonyl compounds have been reported in the literature.

The transformation that has found the most applications uses 1,3-diketones as the starting materials. Converting one of the carbonyl functionalities into a heteroatom-substituted alkene can generally be accomplished by two different methods (Scheme 4):

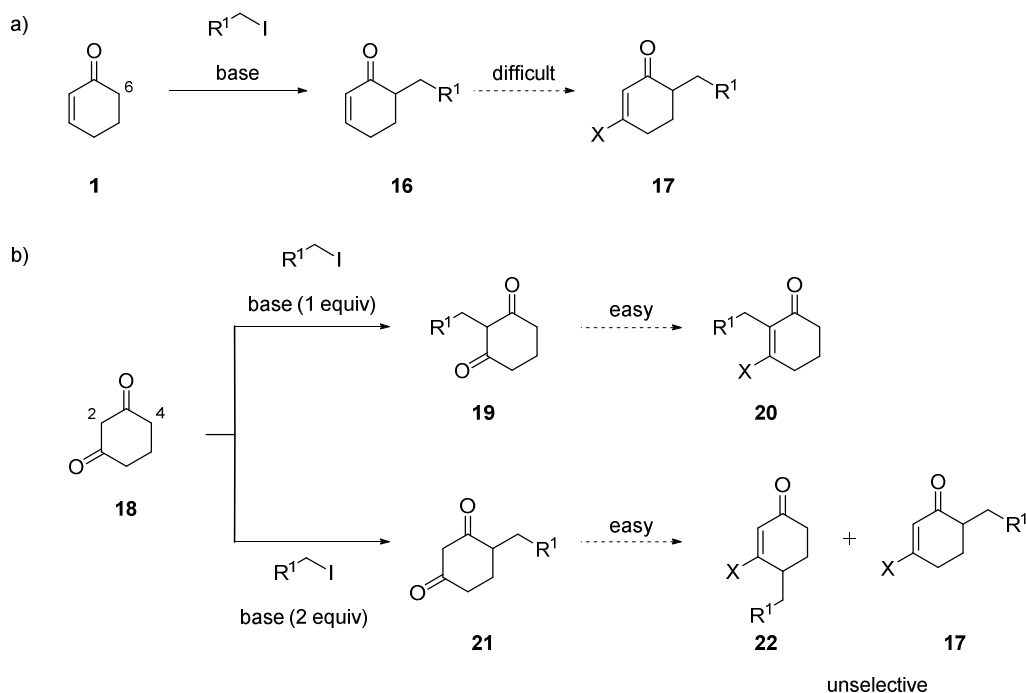
Condensation of the diketone with alcohols, amines or other nucleophiles gives vinylogous esters, amides and related compounds.^[8] Furthermore, the preparation of enones bearing a β -halogen is possible through treatment of the 1,3-dicarbonyl with one of several common halogenation reagents, including phosphorous trichloride (PCl_3), phosphoryl chloride (POCl_3), phosgene (COCl_2), acetyl chloride (CH_3COCl), oxalyl chloride ($(\text{COCl})_2$), triphenylphosphine–carbon tetrachloride ($\text{PPh}_3\text{--CCl}_4$), triphenylphosphine–carbon tetrabromide ($\text{PPh}_3\text{--CBr}_4$), phosphorous tribromide (PBr_3), and triphenylphosphine dihalides (Ph_3PX_2).^[9]



Scheme 4. Synthesis of functionalised enones from 1,3-diketones.

However, the use of β -diketones as the starting materials for the formation of β -substituted α,β -unsaturated carbonyl compounds is often inefficient. This can be exemplified when comparing the reactivities of 2-cyclohexen-1-one (**1**) and 1,3-cyclohexanedione (**18**) (Scheme 5). The addition of an electrophile to **1** typically occurs at C6, due to the increased acidity of the α' -protons (Scheme 5a). For the resulting substrates **16**, however, selective β -functionalisation of the enone is a problematic task, the difficulties being elaborated below. In contrast, the most acidic position of **18** is obviously located at C2, leading to alkylation of that position when one equivalent of a base is used. Treatment of **18** with two equivalents of a base, creating the corresponding dianionic species, and an electrophile, leads to the formation of the C4-alkylated dione **21**. Halogenation using one of the aforementioned methods is unselective, and it is difficult to predict the regiochemistry of the product (Scheme 5b). Therefore the preparation of substrates that would be readily accessible starting from

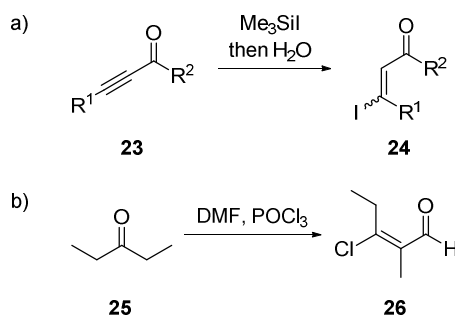
2-cyclohexen-1-one (**1**) is much more tedious with 1,3-cyclohexanedione (**18**) as the starting material.



Scheme 5. Different nucleophilic properties of enones and 1,3-diketones.

The conjugate addition of nucleophiles to alkynones utilises the inherent high electrophilicity of the β -position of this Michael acceptor system (Scheme 6a). The addition of metal halides or trialkylsilyl halides can selectively provide either *E*- or *Z*- β -halo enones, depending on the reaction conditions.^[10] The use of sodium iodide in the presence of trifluoroacetic acid predominantly gives the *E*-alkene. Under kinetic conditions, with sodium iodide and acetic acid, the *Z*-alkene is formed as the major product.^[10] However, the use of alkynones is mainly limited to acyclic systems.

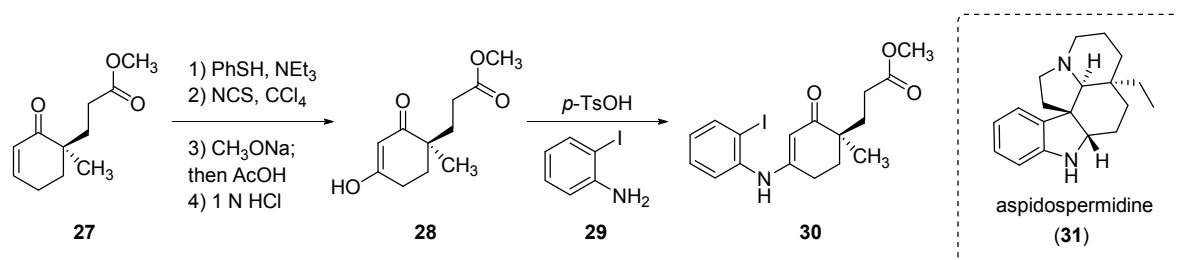
The Vilsmeier–Haack-type transformation of ketones into vinyl halides is another viable strategy. For example, treatment of 3-pentanone (**25**) with *N,N*-dimethylformamide and phosphoryl chloride results in the formation of (*E*)-3-chloro-2-methylpent-2-enal (**26**) (Scheme 6b).^[11]



Scheme 6. Synthesis of β -halogenated enones from (a) ynones and (b) ketones.

The β -selective incorporation of heteroatom-substituents such as nitrogen and sulfur into unfunctionalised enone systems is also possible. These processes, however, often require several steps and suffer from poor selectivity.^[12-13]

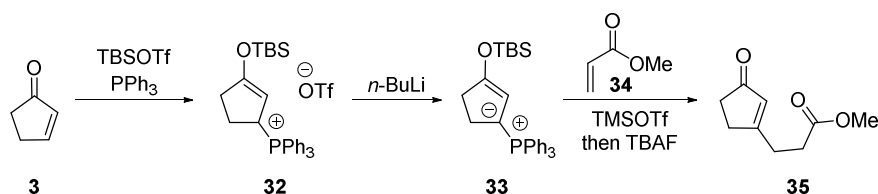
Desmaele's synthetic efforts toward the enantioselective synthesis of the *Aspidosperma* alkaloid aspidospermidine (**31**) clearly demonstrate the inefficiency of the available methods. Five steps are needed to introduce a primary amine into the β -position of enone **27** (Scheme 7).^[14]



Scheme 7. Desmaele's five-step β -amination of **27**.

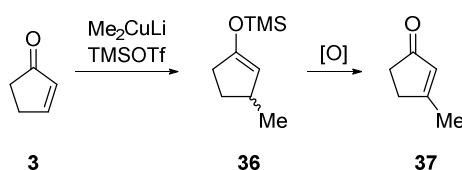
This sequence commences with the Michael-addition of thiophenol to the enone **27**, followed by oxidation to the vinylogous thioester, as developed by Bakuzis (chapter 3.4.1).^[13] Substitution with sodium methanolate yields an enol ether, which is then hydrolysed to form the vinylogous acid **28**. Treatment of this product with 2-iodoaniline (**29**) yields the enamine **30**, which is a key-intermediate en route to aspidospermidine (**31**).

Carbon–carbon bond formation between the β -position of enones and an electrophile is possible in a one-pot process. Phosphoniosilylation of the model substrate 2-cyclopentenone (**3**) gives **32** and deprotonation affords phosphonium ylide **33**. Lewis-acid promoted electrophilic attack on a Michael acceptor such as **34** leads to the formation of the β -alkylated product **35** (Scheme 8).^[15]



Scheme 8. Carbon–carbon bond formation through phosphoniosilylation.

Many other well-known methods for the incorporation of a β -carbon-substituent rely on the regeneration of the α,β -double bond by a separate oxidation step after the introduction of the β -substituent, as illustrated in the formation of 3-methyl-2-cyclopenten-1-one (**37**) in Scheme 9. Noteworthy are the Saegusa–Ito oxidation^[16], implementing palladium(II) salts—either used stoichiometrically or catalytically in the presence of another oxidant—and a procedure developed by Nicolaou, using an IBX–MPO-complex as the oxidant.^[17]

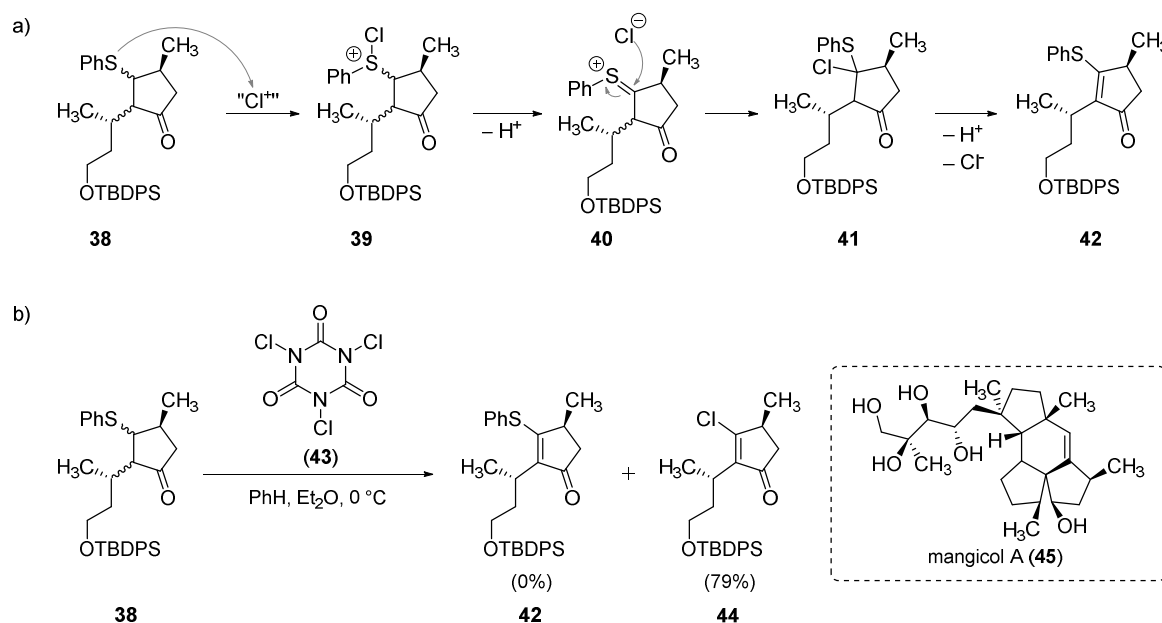


Scheme 9. Oxidation of silyl enol ethers to enones.

3.4 Previous work toward the β -halogenation of carbonyl compounds

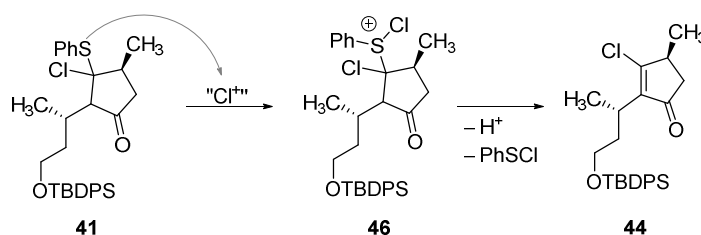
3.4.1 The Pummerer-type reaction approach

In 1981, Bakuzis published a method for the synthesis of vinylogous thioesters starting from simple enones.^[13] In the Uemura synthesis of mangicol A (**45**), a four-step approach was planned to achieve the β -chlorination and olefination of the substituted cyclopentanone **38**.^[18] The desired intermediate **42** was then to be further oxidised to the sulfoxide and then substituted by a chloride anion. The reaction mechanism, as postulated by Bakuzis and envisioned by Uemura, is depicted in Scheme 10a. Addition of *N*-chlorosuccinimide, or similar reagents, provides chlorine for the oxidation of **38** to **39**. The Pummerer-type rearrangement of **39** initially gives **40**, which then converts to the S–Cl acetal **41**. Deprotonation of the α -position and subsequent chloride elimination was supposed to furnish **42**. Unexpectedly, treatment of **38** with trichloroisocyanuric acid (**43**), did not lead to the formation of the vinylogous thioester **42**, but **44** was obtained as the exclusive product (Scheme 10b).



Scheme 10. (a) Bakuzis' mechanistic hypothesis. (b) The serendipitously discovered β -chlorination.

Unfortunately, no information was given about the detailed experimental procedure. A possible mechanism leading to the formation of this compound is outlined in Scheme 11.

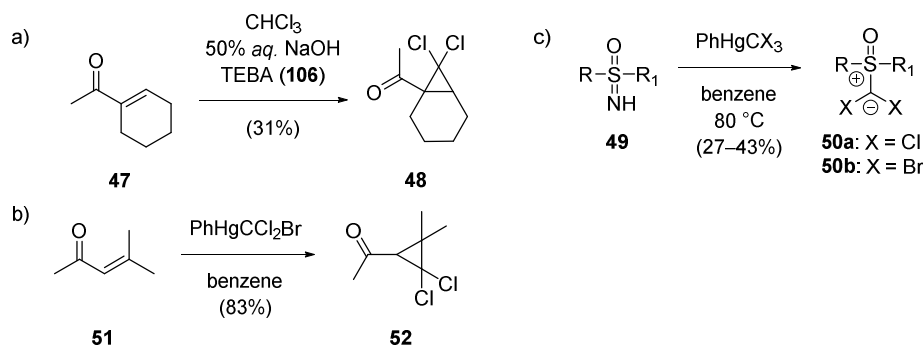


Scheme 11. A putative mechanism for the formation of **44**.

It was proposed that this reaction also proceeds via the Pummerer-type intermediate **41**.^[18] In the presence of an excess of the oxidant, this intermediate is converted to the corresponding sulfonium species **46**. Thereafter, the leaving group ability of the sulfur species should exceed that of the halide. Loss of a proton and elimination of the sulfur moiety affords the β -chlorinated cyclopentenone **44**. Surprisingly, there have been no reports on the elucidation of the reaction mechanism and there are no further examples of this transformation in the literature.

3.4.2 The *gem*-dihalocyclopropanation strategy

Only a few examples for the formation of *gem*-dihalocyclopropanes from α,β -unsaturated carbonyls are known in the literature.^[19] In most cases, treatment of a haloform with a base generates a dihalocarbene, which reacts with the double bond to form a cyclopropane moiety. Another mechanistic possibility involves the 1,4-addition of a trihalomethyl anion to form an enolate, which then bites back to furnish the *gem*-dihalocyclopropane (Scheme 12a). The major drawback of these reactions is that they suffer from moderate to poor yields. In some cases, the yields can be improved using Seyferth's dihalocarbene-precursor, trihalomethyl(phenyl)mercury (Scheme 12b). However this method is not broadly applicable and the use of highly toxic organomercury compounds is not practical. Interestingly, no complementary methods for the synthesis of 2-acyl-1,1-dihalocyclopropanes are known.



Scheme 12. (a) PTC-mediated dihalocyclopropanation of **47**. (b) Dihalocyclopropanation with Seyferth's precursor. (c) Synthesis of α -dihalo sulfoxonium ylides **50**.

The preparation of the α -dihalo sulfoxonium ylides **50a** and **50b** was reported by Rahman in 1979. Seyferth's precursor had to be used as the carbene source for the conversion of dialkyl sulfoximines (**49**) to the desired compounds (Scheme 12c).^[20]

Surprisingly, no synthetic applications of these reagents in a Corey–Chaykovsky-type cyclopropanation have been reported so far (Figure 1). For instance, the reaction of cyclopentenone **3** with **50** could directly yield 2-acyl-1,1-dihalocyclopropane **53**.

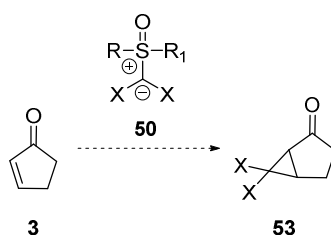
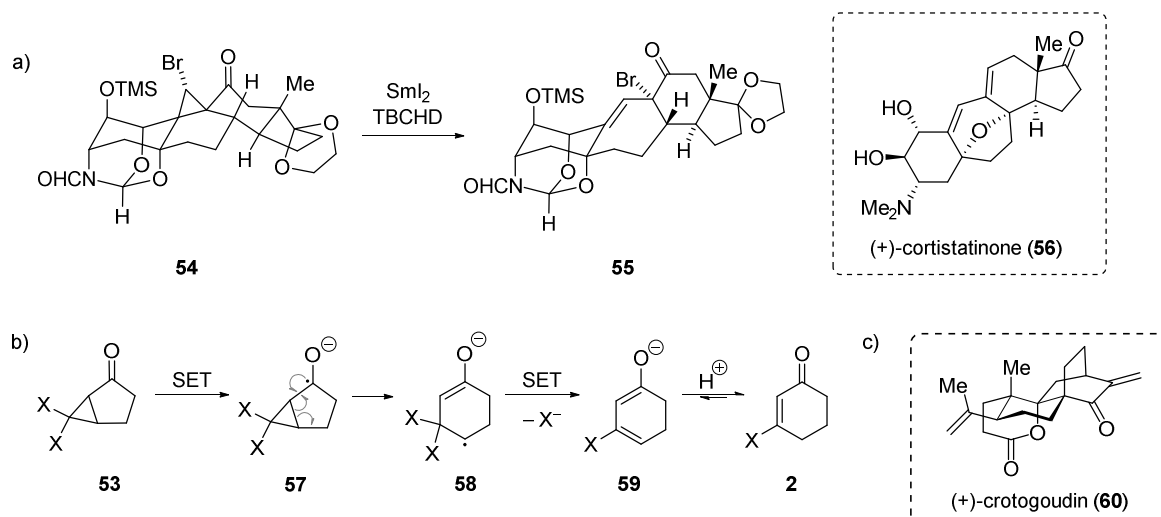


Figure 1. Unknown Corey–Chaykovsky-type *gem*-dihalocyclopropanation.

We believe that using an optimised reagent combination should allow the regioselective ring-opening of such substrates to give the corresponding β -halogenated enone. So far, these types of transformations are unexplored and little is known in the literature. In the synthesis of (+)-cortistatinone (**56**), Baran and colleagues used samarium(II) iodide to promote the ring expansion of a monohalogenated α -cyclopropyl ketone with loss of a bromide. The resulting samarium(III) enolate was trapped with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD) to give **55** (Scheme 13a).^[21] Our hypothesis is further supported by Carreira's synthesis of (+)-crotooudin (**60**) (Scheme 13c), in which samarium(II) iodide is also used to cleave an acceptor-substituted cyclopropyl moiety, albeit without halogen-substitution.^[22] Treatment of *gem*-dihalocyclopropanes with this or similar reducing agents should, similarly, induce the fragmentation of the cyclopropyl moiety to give the ring expanded product (Scheme 13b).

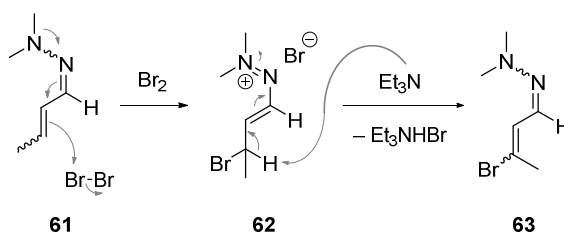


Scheme 13. (a) Cyclopropane opening in Baran's synthesis of (+)-cortistatinone (**56**). (b) Envisioned mechanism of the desired fragmentation. (c) (+)-crotogoudin (**60**).

3.4.3 Functionalisation of hydrazones

In the 1980s and 1990s, Severin showed that α,β -unsaturated hydrazones and derivatives thereof could be selectively β -halogenated.^[23-24] The introduction of the hydrazone moiety allows for the Umpolung of the formerly electrophilic β -position. This can be explained by the electron donating nature of the sp^3 -nitrogen, in a structure that resembles a dienamine.

The condensation product of *N,N*-dimethylhydrazine (**169**) and 2-butenal, hydrazone **61**, was treated with bromine and triethylamine to afford the β -brominated compound **63** in 57% yield.^[23] A possible mechanism is shown in Scheme 14.

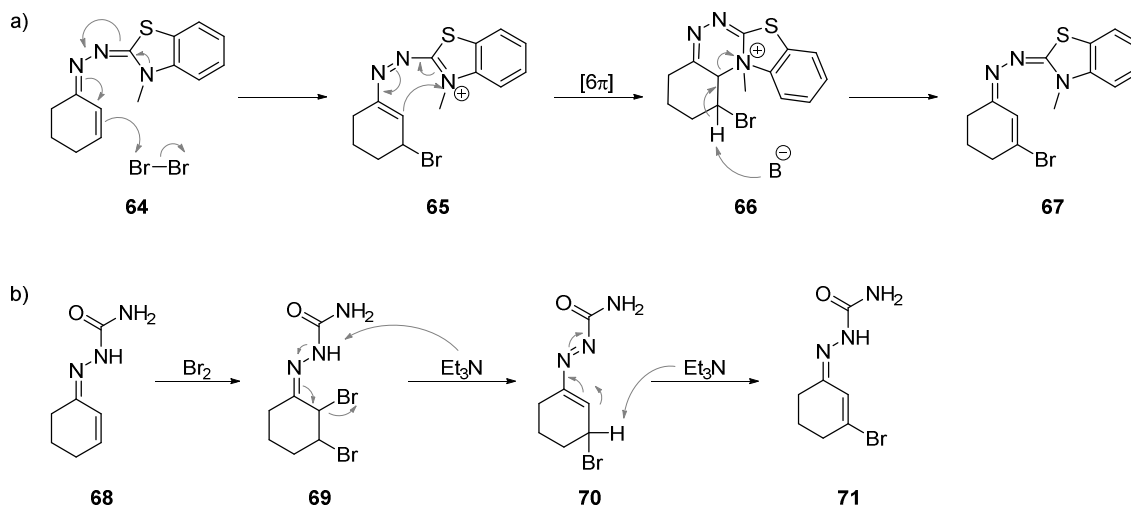


Scheme 14. Bromination of an α,β -unsaturated hydrazone.

Bromination of the double bond, a process that is assisted by the lone-pair of the terminal nitrogen, leads to the formation of the ammonium salt **62**, with the expulsion of a bromide anion. Subsequent deprotonation at the β -position regenerates the carbon–carbon double bond, yielding **63** as a mixture of *E*- and *Z*-isomers.

Similar transformations are also known for oximes. In addition to this, the semicarbazones of α,β -unsaturated carbonyl compounds, as well as certain semicarbazone derivatives such as **64**, can also be β -brominated.^[24]

The latter two transformations presumably proceed via slightly different mechanisms, due to the differences in reactivity of the corresponding heteroatom moieties. The mechanisms, as previously postulated, are illustrated in Scheme 15.^[24] The putative intermediates have not been isolated so far and clear evidence for these mechanisms is still missing.



Scheme 15. (a) Bromination of the condensation product **64** of cyclohexenone (**1**) with 2-methyl-benzothiazolinone hydrazone (**174**). (b) Bromination of the semicarbazone **68**.

Similar to the mechanism presented above, the thiosemicarbazone moiety of **64** assists the bromination of the β-position of the substrate molecule (Scheme 15a). This product presumably undergoes a 6π-electrocyclisation to form the intermediate **66**. Deprotonation leads to the cleavage of the newly formed carbon–nitrogen bond and furnishes the β-brominated product **67**.

Dibromination of cyclohexenone semicarbazone (**68**), to give **69**, can be rationalised by the diminished Lewis-basicity of the N–H moiety and therefore a decreased tendency for electron donation. According to the sequence shown in Scheme 15b, base-assisted deprotonation and elimination of the α-bromide affords **70**. A second equivalent of the base induces the necessary double bond isomerisation to form 3-bromo-cyclohexenone semicarbazone (**71**).

The major disadvantages of the reported sequences are: 1) The introduction of the hydrazones was not practical due to the necessity of elevated temperatures, in combination with long reaction times, 2) both the hydrazone and the halogenated product had to be isolated due to the incompatibility of the solvents used for the individual steps, 3) harsh conditions (hydrobromic acid, aqueous formaldehyde) were used for the cleavage of the hydrazone, and 4) some of the used reagents were expensive (2-methyl-benzothiazolinone hydrazone (**174**)) or inherently incompatible with aprotic organic solvents (semicarbazide).

In light of these drawbacks of the literature procedures, it was our goal to develop a conceptually similar method, which benefits from operational simplicity and better overall yields (for literature yields, see Figure 3).

3.5 *Kopsia* alkaloids

The genus *Kopsia* (Apocynaceae) comprises 24 species of shrubs and trees, mainly found in Southeast Asia.^[25-26] Many monomeric and dimeric monoterpenes—among these several *Aspidosperma* alkaloids—have been isolated from this genus.

Recent studies of the chemical composition of *Kopsia hainanensis* led to the discovery of the novel indole alkaloids kopsihainin A–F (**6**, **7**, **72–75**) as well as kopsihainanine A (**4**) and B (**5**) (Figure 2).^[27-29]

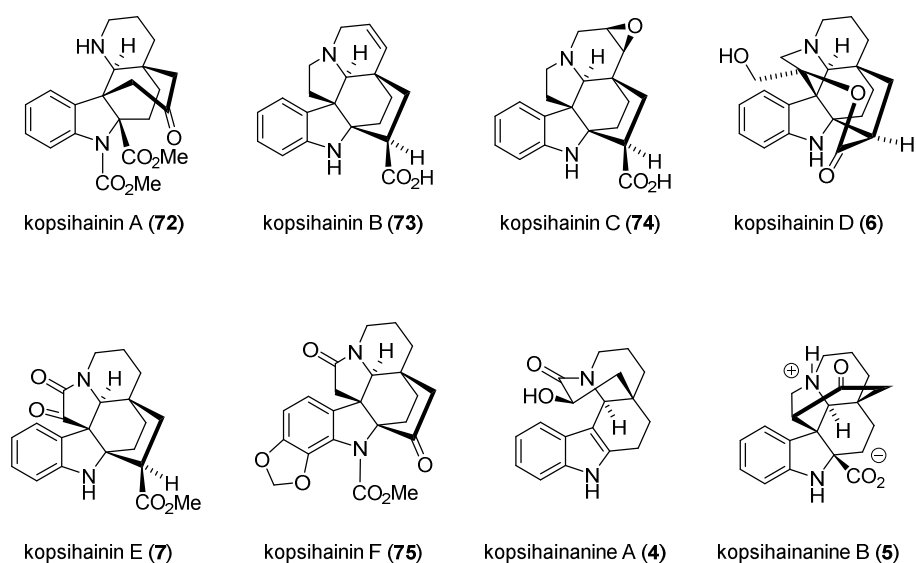
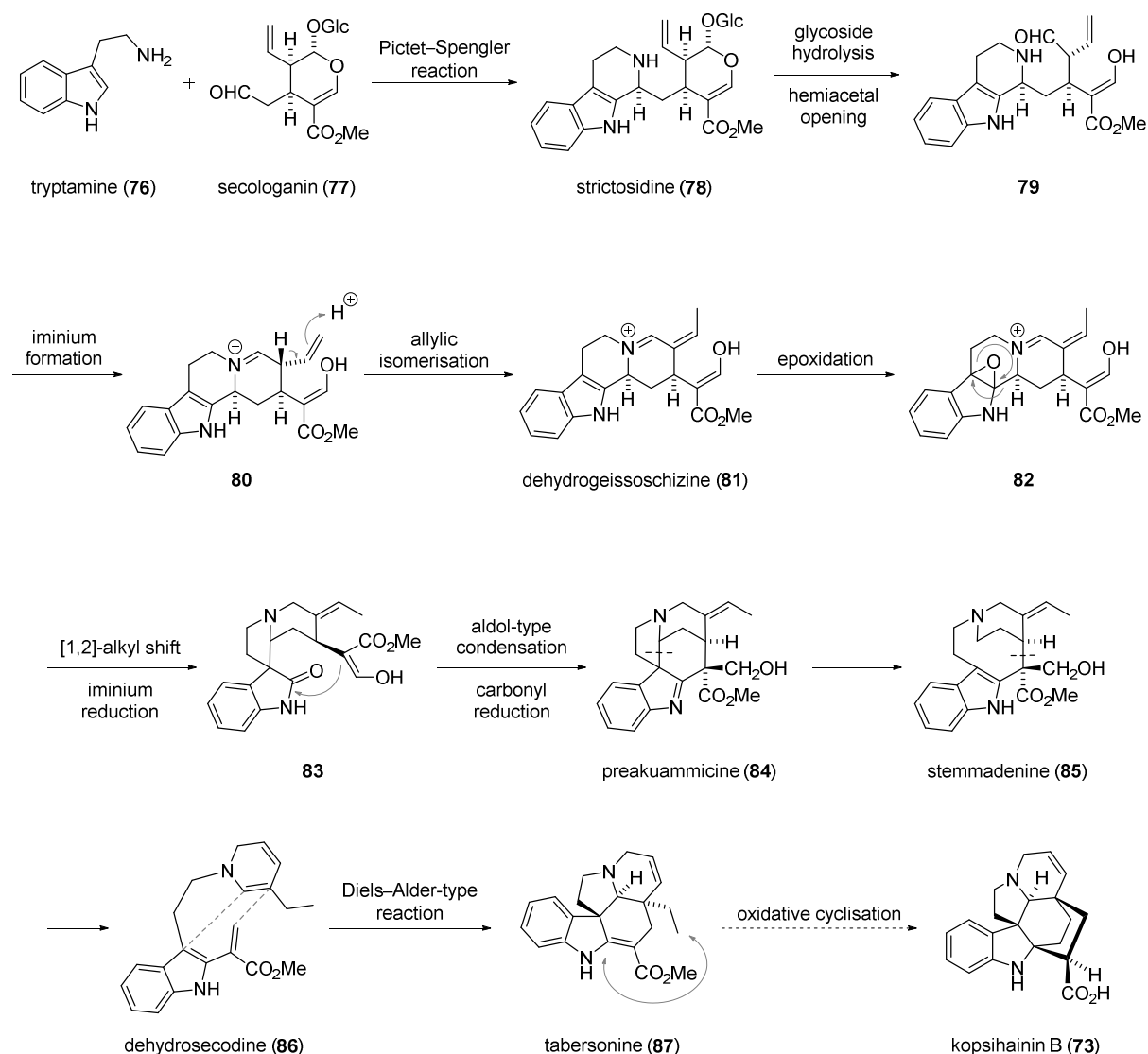


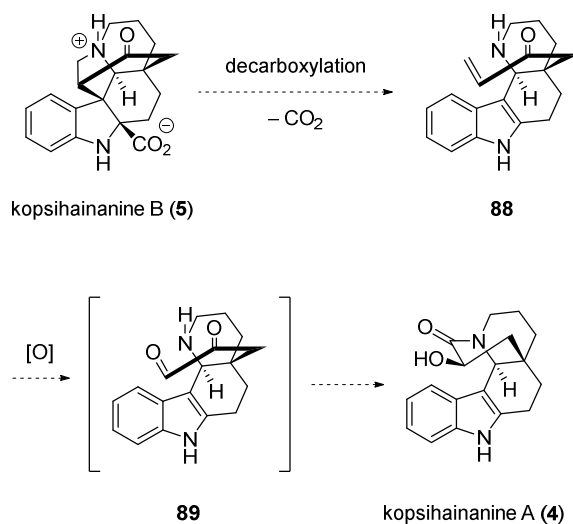
Figure 2. Novel alkaloids from *Kopsia hainanensis*.

The biosynthesis of *Aspidosperma* alkaloids, in general, is believed to start with tryptamine (**76**) and secologanin (**77**).^[30] The biosynthesis of the *Aspidosperma* alkaloid tabersonine (**87**) and its structural relationship to the kopsihainin-family is illustrated in Scheme 16. Details about the specific biosyntheses of the *Kopsia* alkaloids (**4–7** and **72–75**) are unknown, yet it seems plausible that the kopsihainins (**6**, **7** and **72–75**) share tabersonine's (**87**) general biosynthetic pathway.



Scheme 16. Proposed biosynthesis of tabersonine (**87**)^[30] and its relation to kopsihainin B (**73**).

While the biosynthesis of tabersonine (**87**) gives an idea of the putative biosynthesis of the kopsihainins—involving possible late-stage oxidative cyclisation—the biological pathway to kopsihainanine A (**4**) and B (**5**) remains elusive. However, we believe that kopsihainanine B (**5**) is the biogenetic precursor of kopsihainanine A (**4**). A possible linkage between the two can be seen in Scheme 17 and will be further discussed in chapter 4.4.1.1.



Scheme 17. Putative biosynthesis of kopsihainanine A (**4**) from kopsihainanine B (**5**).

The common structural feature of all compounds is the 6,5,6,6-skeleton (Figure 2, Scheme 16). The varying functionalisation and substitution on the *Kopsia* alkaloids (**4–7**, **72–75**), as well as the occurrence of additional ring systems, make these molecules challenging targets for organic synthesis.

So far, only syntheses of kopsihainanine A (**4**) have been reported—a total synthesis by the groups of She and Shao, as well as a formal synthesis by the Lupton group.^[31–33]

Kopsihainanine A (**4**) shows inhibitory activity against acetylcholinesterase (AChE) with an IC₅₀ value of 38.5 μM. However, the biological activity has not yet been fully investigated.^[28] There have been no reports on the biological activities of compounds **5–7** and **72–75**.

4 Results and Discussion

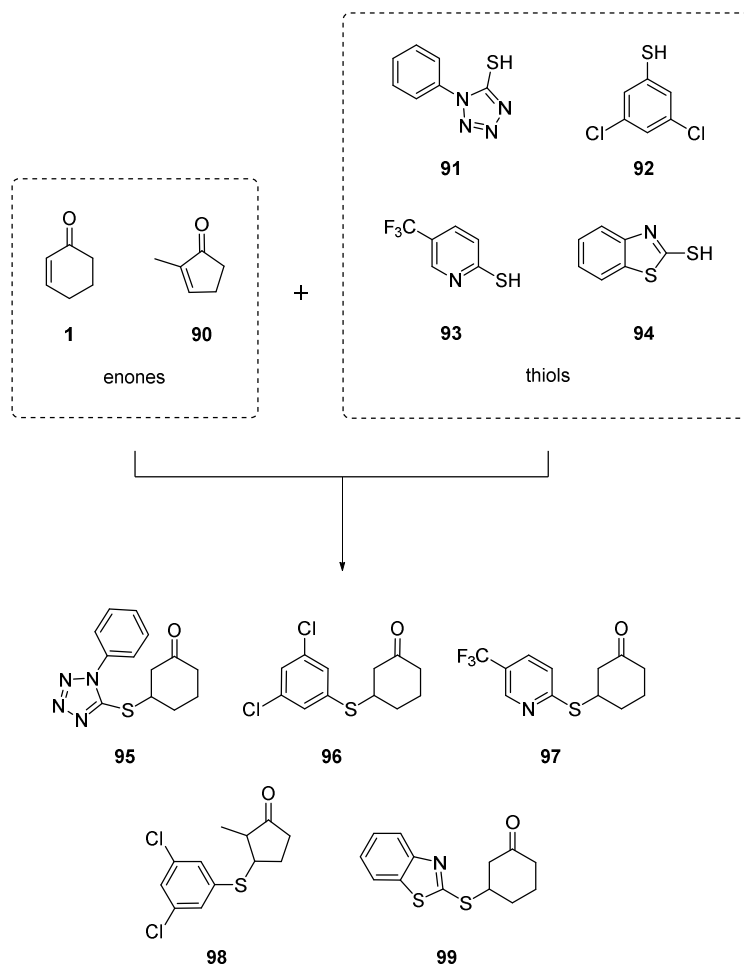
Based on the transformations discussed above, several methods were envisioned to achieve the desired one-pot β -halogenation.

4.1 The Pummerer-type approach

The first attempts to access β -halogenated α,β -unsaturated ketones from the corresponding unfunctionalised enones, were based on the Pummerer-type rearrangement described in chapter 3.4.1.

This part of the project followed Uemura's serendipitous discovery that β -chloro cyclopentenone **44** could be directly obtained from the corresponding saturated thioether **38**.^[18] The aim was to elaborate the substrate scope of this reaction and to make it more practical both by developing a one-pot protocol and by the use of nonodorous thiols.

Initially, the sequence was tested stepwise, beginning with the 1,4-addition of arylthiols to cyclohexenone (**1**) and 2-methylcyclopentenone (**90**). Several thiols were screened for the Michael addition and the following Pummerer-type rearrangement; Scheme 18 shows an overview of the used components. The thiols were chosen as less malodorous or nonodorous alternatives to commonly used thiols, such as thiophenol. The heteroaromatic thiols **91**, **93** and **94** contain additional sites for possible activation and were expected to be more susceptible to the envisioned oxidation.



Scheme 18. Thioether substrates for the Pummerer-type oxidation.

The addition of 1-phenyl-1*H*-tetrazole-5-thiol (**91**), 3,5-dichlorobenzenethiol (**92**), and 5-(trifluoromethyl)pyridine-2-thiol (**93**) to **1** and **90**, in the presence of triethylamine, yielded **95**, **96**, **97**, and **98** in moderate to high yields (Scheme 18; Table 1). Other thiols, such as 2-mercaptobenzothiazole (**94**), were unreactive for the conjugate addition.

Table 1. Screened reaction conditions for the conjugate addition of thiols to enones.

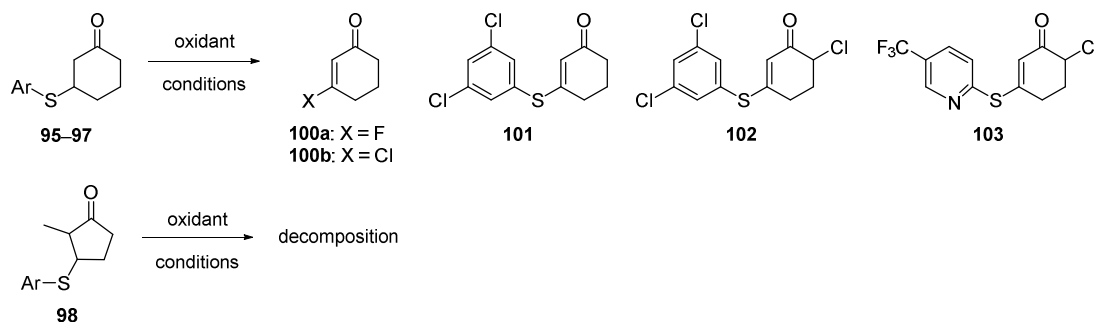
Entry	Enone	Thiol	Cat. (mol%)	Solv.	c [M]	T [°C]	t [h]	Prod.	Yield [%]
1	1	91	Et ₃ N (5.0)	THF	0.77	23	46	95	55
2	1	92	Et ₃ N (3.6)	CDCl ₃	4.60	23	2.5	96	97
3	1	93	Et ₃ N (3.6)	CDCl ₃	1.40	23	1.5	97	83
4	90	92	Et ₃ N (3.6)	CH ₂ Cl ₂	1.45	23	8	98	57
5	1	94	Et ₃ N (3.0)	CHCl ₃	5.00	23	2.5	no reaction	0
6	1	94	Et ₃ N (5.0)	THF	0.52	66	48	no reaction	0
7	1	94	Et ₃ N (56)	acetone/CHCl ₃	1.30	23	60	no reaction	0
8	1	94	Et ₃ N (110)	CHCl ₃	2.50	61	24	no reaction	0
9	1	94	FeCl ₃ (2.0)	EtOAc	1.00	23	4	no reaction	0
10	1	94	FeCl ₃ (4.0)	MeCN	0.16	23	48	no reaction	0
11 ^{a)}	1	94	NaH (2.0)	THF	0.52	45	140	no reaction	0
12 ^{a)}	1	94	NaH (2.0)	EtOH	1.00	45	100	no reaction	0
13	1	94	H ₃ BO ₃ (10)	EtOH	0.55	23	98	no reaction	0

^{a)} The reaction with NaH was envisioned to furnish the N-addition product.

Initial attempts for the Michael addition of the thiols were carried out using a catalytic amount of triethylamine in halogenated solvents (chloroform and dichloromethane). For **92** and **93**, these conditions proved to give good to excellent results (entries 2, 3, and 4), while **91** reacted sluggishly in dichloromethane due to poor solubility. Changing the solvent to tetrahydrofuran—and thereby increasing the solubility of **91**—led to some improvement of the reaction, but the yields were still moderate (entry 1).

The treatment of cyclohexenone (**1**) with **94** did not lead to the formation of any product. The screened reaction conditions included triethylamine in various concentrations and different solvents (entries 5–8), Lewis-acid (entries 9 and 10) and Brønsted-base catalysts (entries 11 and 12), as well as the use of boric acid (entry 13). After failure to produce the desired compound, the use of **94** as an inexpensive and practical reagent had to be abandoned.

With the four different thioethers **95–98** in hand, the oxidative rearrangement and elimination was attempted. The results of these studies are summarised in Table 2. The reactions were conducted with *N*-chlorosuccinimide (NCS), trichloroisocyanuric acid (TCCA) and SelectfluorTM as the oxidants, both in the presence and absence of triethylamine.

Table 2. Screening of the oxidative rearrangement-halogenation sequence.

Entry	SM	Oxidant (equiv)	Base (equiv)	Solvent	c [M]	T [°C]	t [h]	Prod.	Yield [%]
1	95	NCS (1.10)	none	CH ₂ Cl ₂	0.15	23	1.5	no reaction	0
2 ^{a)}	95	NCS (1.10)	Et ₃ N (3.00)	CH ₂ Cl ₂	0.15	23	51	no reaction	0
3 ^{b)}	95	NCS (1.10)	Et ₃ N (3.00)	CH ₂ Cl ₂	0.30	0 to 23	7	no reaction	0
4 ^{c)}	95	NCS (2.20)	Et ₃ N (3.00)	CH ₂ Cl ₂	0.30	0 to 23	25	no reaction	0
5	95	TCCA (1.20)	none	PhH/Et ₂ O	0.13	0 to 23	27	no reaction	0
6 ^{b)}	96	NCS (1.10)	Et ₃ N (3.00)	CH ₂ Cl ₂	0.30	0 to 23	7	101	n.d.
7 ^{b)}	96	NCS (2.25)	Et ₃ N (3.00)	CH ₂ Cl ₂	0.30	0 to 23	21	complex mixture	0
8	96	TCCA (1.20)	-	PhH/Et ₂ O	0.25	0 to 23	24	102	23
9	96	Selectfluor TM (2.20)	-	CH ₂ Cl ₂	0.18	0 to 23	17	101	56
10	97	TCCA (1.20)	-	PhH/Et ₂ O	0.25	0 to 23	23	103	11
11	98	TCCA (1.20)	-	PhH/Et ₂ O	0.24	0 to 23	23	complex mixture	0

^{a)} Immediate addition of the base. ^{b)} Addition of the base after 3 h. ^{c)} Addition of the base after 4 h.

Thioether **95** failed to react in all cases and all reactions only gave the unaltered starting materials. Treatment of **96** with one equivalent of NCS, however, gave **101**, as previously described in Bakuzis' work.^[13] Increasing the amount of the oxidant, in this case, led to a complex mixture of **101** together with several inseparable compounds. The use of an excess of TCCA also led to the formation of a mixture of products, from which **102** could be isolated in low yield. Treatment of **95** with SelectfluorTM furnished **101** in moderate yield. The reaction of **97** with TCCA led to the formation of **103** in poor yield, while the same reaction implementing **98** as the starting material gave complete decomposition. In summary, the attempted oxidation produced some unexpected products (**102** and **103**) and often led to

complex product mixtures. The desired compounds **100a** and **100b**, however, could not be observed in any of the conducted experiments.

The experimental results suggest that the elimination of the chloride anion from the putative S–X-acetal is faster than the oxidation of this intermediate and the expulsion of the arylsulfenyl chloride. In several cases (entries 7 and 11) the use of an excess of oxidant led to the formation of complex product mixtures, the separation of which often proved impossible by column chromatography. One side reaction, which was observed in two cases (entries 8 and 10), arises from the α -halogenation of the α' -methylene group (C6).

As none of the procedures gave even trace amounts of the desired products, we focused on alternative strategies to achieve the envisioned transformation.

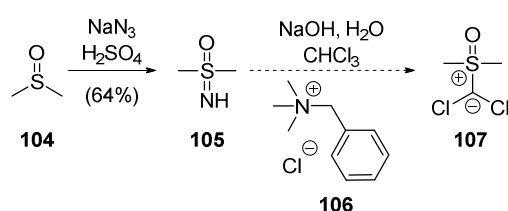
4.2 Extending the Corey–Chaykovsky cyclopropanation

The synthesis of α -dihalo sulfoxonium ylides **50** (Scheme 12b) was first reported in 1979 by Iqbal and Rahman.^[20] However, surprisingly, there have been no studies on synthetic applications of these interesting compounds. This might, in part, be due to the fact that the dihalo sulfoxonium ylides can only be obtained from sulfoximines **49** via the treatment with highly toxic organomercury reagents.

Nevertheless, we were intrigued to study the reactivities of this class of compounds. In order to avoid the use of the mercury species, we envisioned several different approaches.

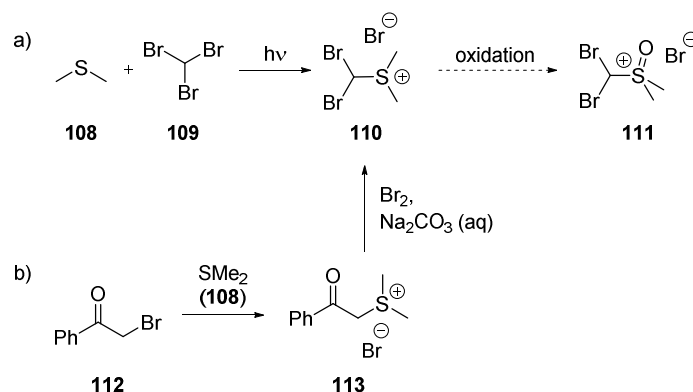
Our initial goal was to find a more practical solution for the conversion of dialkyl sulfoximine (**49**) to the corresponding α -dihalo sulfoxonium ylides **50a** and **50b**, and substitute Seyferth's carbene precursor (Scheme 12b). Using a different carbene source was the logical first step.

We started our investigations with dimethyl sulfoximine (**105**), which was prepared from dimethyl sulfoxide (**104**) through the reaction with sodium azide and sulphuric acid in dichloromethane (Caution! This procedure can lead to the formation of highly explosive diazidomethane^[34]). We hypothesised that a solution of **105** in aqueous sodium hydroxide with chloroform in the presence of the phase-transfer catalyst benzyltriethylammonium chloride (TEBA, **106**) would react to provide **107** (Scheme 19). The reaction of sodium hydroxide with chloroform is well known to form dichloromethyl carbene. Unfortunately, subjecting **105** to these conditions did not result in any transformation and only unreacted starting material was recovered from the reaction mixture.



Scheme 19. Envisioned synthesis of dichloro sulfoxonium ylide **107**.

Further attempts focused on the formation of (dibromomethyl)dimethyl sulfonium bromide (**110**), which we expected to be able to oxidise to the corresponding sulfoxonium species **111** (Scheme 20a).^[35]



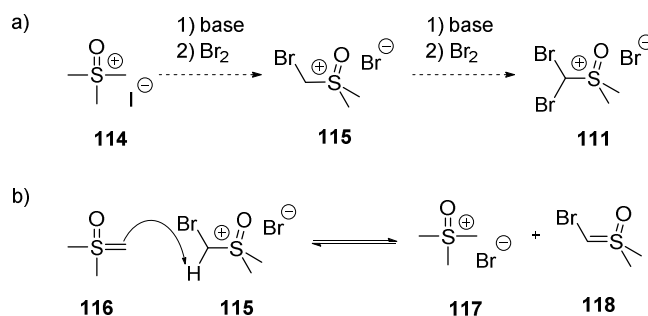
Scheme 20. (a) Photochemical preparation of known **110** and envisioned oxidation to **111**. (b) Haloform-type degradation to form **110** from 2-bromoacetophenone (**112**).

The preparation of the sulfonium species **110** was previously reported in the literature using two different approaches.^[36] The first one involves the unspecific irradiation of a mixture of bromoform (**109**) and dimethyl sulfide (**108**). According to the literature, this should produce **110** in 5% yield (Scheme 20a).

Additionally, the substitution of the bromide of 2-bromoacetophenone (**112**) with dimethyl sulfide (**108**) was reported to produce the β -keto sulfonium compound **113**. Treatment of **113** with bromine and aqueous sodium carbonate first leads to the formation of an α,α -dibromo ketone and then, through haloform-type degradation, to benzoic acid and the target compound **110** (Scheme 20b).

As both pathways were not reproducible in our hands and we failed to obtain the sulfonium compound **110**, a different strategy for the formation of **111** was attempted.

The treatment of trimethylsulfoxonium iodide (**114**) with a base leads to the formation of the corresponding sulfoxonium ylide **116**, which readily adds to electrophiles, such as carbonyls and enones (Corey–Chaykovsky reaction).^[37] We were confident to be able to extend the range of viable electrophiles to halogens, more specifically, bromine. Sequential addition of one equivalent of a base (sodium hydride) and one equivalent of bromine to a solution of **114** in tetrahydrofuran was intended to yield monobrominated compound **115**. Repeating this sequence should then lead to the formation of the desired dibrominated sulfoxonium salt (**111**) (Scheme 21a).



Scheme 21. (a) Proposed synthesis of **111** from trimethylsulfoxonium iodide (**114**). (b) Possible side reaction during the bromination of **114**.

While we expected side reactions triggered by sequential double deprotonation, even in the first step (Scheme 21b), it turned out that treatment of the sulfoxonium ylide **116** with bromine in tetrahydrofuran did not lead to any transformation and only **114** was recovered after workup.

After several further unsuccessful attempts to synthesise the desired reagent, or precursors thereof, we decided to pursue a different strategy. However, the general cyclopropanation-fragmentation concept is being further explored by Adriana Grossmann in her master thesis.

4.3 The hydrazone-type approach

In the 1980s and 1990s, the Severin group published methods for the introduction of a halogen atom into the β -position of α,β -unsaturated hydrazones and hydrazone derivatives (chapter 3.4.3).^[23-24, 38] The compounds that were synthesised by this method included **63**, **67**, **71**, and **119–122** and are shown in Figure 3. The hydrazone could then be cleaved in a separate step in moderate to excellent yields to afford the corresponding carbonyl compounds.

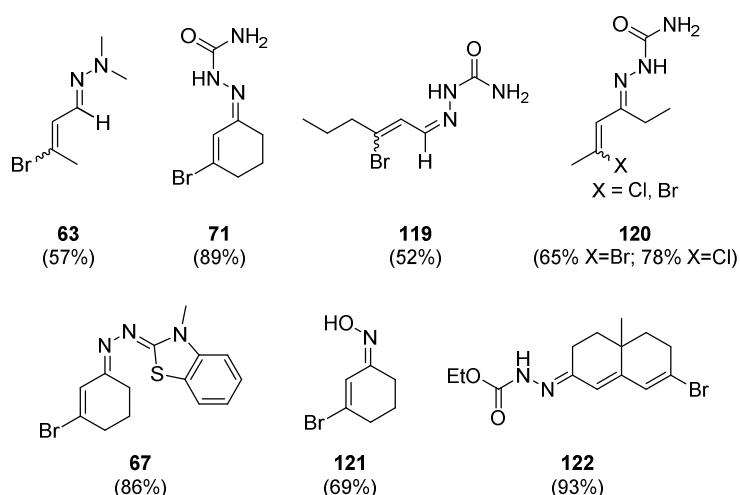


Figure 3. Bromination of α,β -unsaturated hydrazone derivatives.

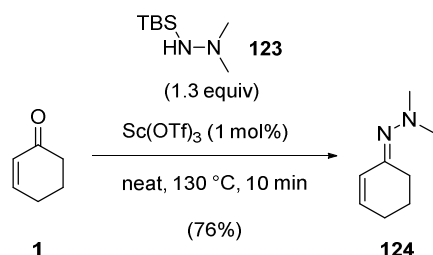
Inspired by this transformation, we envisioned to develop a one-pot procedure which combines the formation of the hydrazone derivative, the selective β -halogenation and the mild cleavage of the hydrazone to release the carbonyl compound.

4.3.1 Dimethylhydrazone

The first variant of this type of reaction that we studied implemented cyclohexenone *N,N*-dimethylhydrazone (**124**). As the bromination of *N,N*-dimethylhydrazones had been previously reported (see Figure 3), our initial experiments focused on the development of a fast and simple protocol for the formation of α,β -unsaturated hydrazones from enones.

Following a procedure by Myers^[39], we planned to access **124** by the reaction of **1** with TBS-protected *N,N*-dimethylhydrazine (**123**). Reacting an excess (3.5 equivalents) of neat *N,N*-dimethylhydrazine (**169**) with *tert*-butyldimethylsilyl chloride at 75 °C for 3 hours cleanly afforded **123**. The latter was obtained in pure form after separation of the precipitate from the liquid layer and removal of excess **169** by evaporation under reduced pressure (see

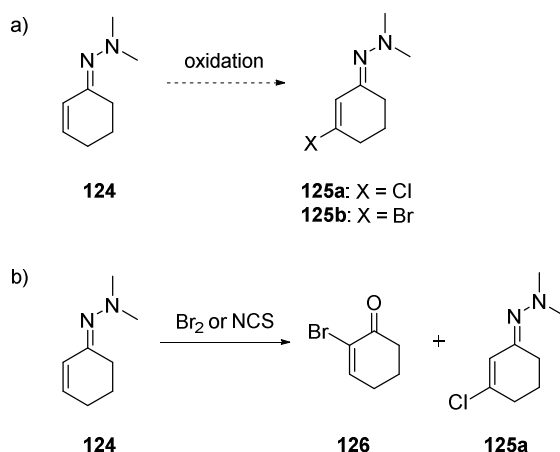
experimental details). A screening of the reaction conditions identified a procedure that yields cyclohexenone *N,N*-dimethylhydrazone (**124**) from **1** and **123** within 10 min (Scheme 22, see experimental details).



Scheme 22. Solvent-free synthesis of cyclohexenone *N,N*-dimethylhydrazone (**124**).

The improved procedure for the formation of **124** had two advantages: 1) the reaction time could be shortened from several hours^[40] to 10 min and 2) the condensation does not yield an equivalent of water. Avoiding the formation of water was believed to be essential for the following bromination step, since water could lead to the formation of the corresponding bromohydrin. The by-product *tert*-butyl dimethylsilanol could be easily removed under reduced pressure.

With **124** in hand, the β -halogenation was attempted according to the conditions reported in the literature and the results are summarised in Table 3 (Scheme 23).^[23-24]



Scheme 23. (a) Envisioned halogenation of **124**. (b) Products of the oxidation of **124**.

Table 3. Attempted β -halogenation of cyclohexenone *N,N*-dimethylhydrazone (**124**).

Entry	Oxidant (equiv)	Additive (equiv)	Solv.	c (M)	T [°C]	t [h]	NMR conversion	Yield [%]
1	Br ₂ (1.00)	Et ₃ N (1.00)	CH ₂ Cl ₂	0.28	−15 to 0	1	decomp.	0
2	Br ₂ (1.00)	Et ₃ N (1.20)	CH ₂ Cl ₂	0.28	−25	0.3	decomp.	0
3	Br ₂ (1.00)	H ₂ O (111)	CH ₂ Cl ₂	0.20	0 to 23	8	126	5
4	NCS (1.50)	Et ₃ N (1.00)	CH ₂ Cl ₂	0.25	23	0.25	125a (traces)	-
5 ^{a)}	NCS (1.40)	Et ₃ N (1.00)	CH ₂ Cl ₂	0.25	0 to 23	21	0	0
6	NCS (1.05)	Et ₃ N (1.05)	CH ₂ Cl ₂	0.25	−78	4.5	0	0
7 ^{b)}	NCS (1.05)	Et ₃ N (1.05)	CH ₂ Cl ₂	0.25	0 to −78	6.5	0	0

^{a)} Addition of triethylamine at 0 °C. ^{b)} Addition of triethylamine at −78 °C. - not isolated.

All attempts to reproduce the literature—a 48% yield is reported for the chlorination of the *N,N*-dimethylhydrazone of 2-butenal (**63**), no yield is given for the *N,N*-dimethylhydrazone of cyclohexenone (**124**)^[23]—failed and only trace amounts of the product **125a** could be detected by mass spectroscopy, in one case. We therefore decided to substitute the dimethylhydrazone **124** and focused on alternative, more efficient hydrazone derivatives. For us, several criteria were important: 1) The hydrazone source had to be inexpensive and/or readily accessible from commercially available starting materials, 2) good solubility of the hydrazone compound in chlorinated solvents in order to assure compatibility with the halogenation step was essential, 3) the halogenation itself should be high-yielding and practical, and 4) the use of mild conditions for the cleavage of the hydrazone was desirable.

4.3.2 The hydrazide method

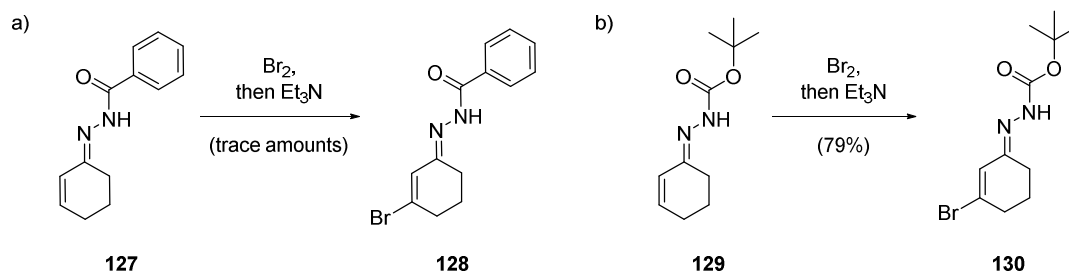
A slightly different approach included the use of an electron-deficient hydrazone derivative. According to Severin, the mechanism for the bromination of these compounds differs from that of electron-rich hydrazones. Dibromination was believed to occur prior to deprotonation of the nitrogen and subsequent elimination of the α -bromine (see Scheme 15b). Only few such derivatives were previously reported in the literature, foremost brominated semicarbazone **71**.^[24] The corresponding procedure proved highly reproducible and gave good to excellent yields (73–98%).

However, commercially available semicarbazide suffers from poor solubility in most organic solvents. The envisioned one-pot procedure, consisting of the condensation, the

halogenation and the cleavage of the semicarbazone, would therefore not be able to take place in a common solvent. Additionally, the condensation step, which was only possible with water as the solvent, was low yielding for the reaction of semicarbazide with cyclohexenone (**1**) (39%). These facts make the sequence impractical and inefficient.

We envisioned that readily available and inexpensive benzhydrazide (**170**) or *tert*-butyl carbazate (**132**) would have similar electronic properties, and show improved solubility, thereby providing suitable alternatives. Initial experiments investigated the feasibility of the β -bromination of several semicarbazone derivatives. The two model substrates, **127** and **129**, were synthesised following slightly modified literature procedures (reflux in EtOH for **127**; reflux in MeOH with 10 mol% AcOH for **129**—see experimental details).^[41-42]

These compounds were then subjected to the conditions previously employed for the β -bromination of semicarbazone **68** (CH_2Cl_2 ; $-10\text{ }^\circ\text{C}$; Br_2 (1.00 equiv), Et_3N (2.00 equiv); see experimental details). In the case of **127**, only trace amounts of the desired compound **128** could be detected by mass spectroscopy. However, treatment of **129** with bromine and triethylamine gave **130** in 79% yield (Scheme 24, Table 5).



Scheme 24. Brominations of the hydrazone derivatives **127** and **129**.

Motivated by this result, we tried to find a way to make the formation of the hydrazone compatible with the following bromination.

Adapting the approach described in chapter 4.3.1, we attempted to synthesise 2-(*tert*-butyldimethylsilyl)-*tert*-butyl carbazate (**131**) (Figure 4a). We then planned to condense this compound with cyclohexenone (**1**) analogously to the method described in chapter 4.3.1. However, all attempts to obtain TBS-*t*-Bu-carbazate (**131**) failed.

This prompted us to investigate different methods for the hydrazone formation. We envisioned that adding a drying agent, in order to remove the accumulating water, might accelerate the reaction (Figure 4b). The screened conditions for the condensation of **1** and **132** can be seen in Table 4. It soon became evident that the use of magnesium sulfate, together with halogenated solvents, was a very suitable way of keeping the reaction mixture free of water and increasing the rate of the condensation reaction.

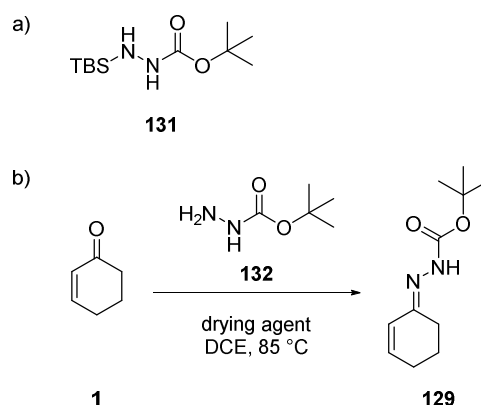


Figure 4. (a) TBS-*t*-Bu-carbazate (**131**). (b) Condensation to yield hydrazone **129**.

Whereas reactions of cyclohexenone (**1**) with *t*-Bu-carbazate (**132**) in dichloromethane, both at 25 °C (entries 4 and 5) and 40 °C (not listed) proceeded sluggishly, the use of 1.5 equivalents of **132** and 3 equivalents of magnesium sulfate in 1,2-dichloroethane, at elevated temperatures (85 °C, entries 7 and 9), gave full conversion to **129**.

Table 4. Screened reaction conditions for the condensation of cyclohexenone (**1**) with *t*-Bu-carbazate (**132**).

Entry	<i>t</i> -Bu-carbazate (132) (equiv)	Additives (equiv)	Solv.	c (M)	T [°C]	t [h]	NMR conversion	Yield [%]
1	1.00	AcOH (0.100)	MeOH	1.17	rt	11	> 90%	48
2	1.00	MS 4Å	CH ₂ Cl ₂	1.98	25	16	~ 45%	-
3	1.00	SiO ₂ (1.30)	CH ₂ Cl ₂	1.98	25	16	~ 55%	-
4	1.00	MgSO ₄ (3.00)	CH ₂ Cl ₂	1.98	25	16	~ 63%	-
5	1.00	MgSO ₄ (1.00)	CH ₂ Cl ₂	0.99	25	43	~ 58%	-
6 ^{a), b)}	1.30 + 0.20	MgSO ₄ (3.00)	(CHCl ₂) ₂	1.48	85	6.5	> 95%	-
7 ^{c)}	1.05	MgSO ₄ (3.00)	(CHCl ₂) ₂	1.48	87	23	~ 74%	-
8	1.50	MgSO ₄ (3.00)	(CHCl ₂) ₂	1.48	80	6	> 99%	quant.

^{a)} The Reaction mixture was used directly in the next step. ^{b)} The 2nd portion of *t*-Bu-carbazate (**132**) was added after 5 h. ^{c)} *t*-Bu-carbazate (**132**) was added in four portions over the course of 2.5 h. - not isolated.

The initial screening of the condensation reaction (entries 4–8) revealed that an excess of *t*-Bu-carbazate (**132**) in the presence of magnesium sulfate gave the product in high yield. Encouraged by these experiments, we decided to attempt the one-pot condensation-halogenation sequence. The results are summarised in Table 5.

Interestingly, the bromination of the pure hydrazone **129** in dichloromethane gave excellent conversion and good yields of **130** (entries 1 and 2), whereas directly using the crude reaction mixture (with residual 1,2-dichloroethane) only led to approximately 75% conversion (entry 3). Subsequent experiments showed that increasing the amount of bromine does not lead to an improvement of the conversion (entries 4–7). Using 2.20 equivalents of bromine resulted in the formation of a complex product mixture (entry 8) and the use of 1,2-dichloroethane as the solvent, instead of dichloromethane, also gave dissatisfactory results (entry 9).

Table 5. Initial screening of the bromination of **129**.

Entry ^{a)}	SM	MgSO ₄ (equiv)	Br ₂ (equiv)	Et ₃ N (equiv)	c (M)	T [°C]	t ^{b)} [h]	NMR conversion	Yield [%]
1	Pure 129	-	1.00	2.00	0.34	–15 to 25	13	> 96%	79
2 ^{c)}	Pure 129	-	1.00	2.00	0.34	–15 to 25	24	> 94%	46 ^{f)}
3 ^{c), d)}	One-pot	2.00	1.00	2.00	0.28	–20 to 25	15	~ 75%	-
4 ^{c), d)}	One-pot	2.00	1.15	2.00	0.28	–20 to 25	1.5	~ 48%	43 ^{f)}
5 ^{c), d)}	One-pot	3.00	1.15	4.00	0.28	–20 to 25	1.25	n.d.	48 ^{f)}
6 ^{c), d)}	One-pot	3.00	1.32	4.00	0.28	–11 to 25	2.5	~ 49% ^{f)}	-
7 ^{d)}	One-pot	3.00	1.30	4.00	0.28	–12 to 25	5.5	~ 44%	32
8 ^{d)}	One-pot	3.00	2.20	4.00	0.28	–8 to 25	2.5	complex mixture	-
9 ^{e)}	One-pot	2.00	1.15	2.00	0.29	–20 to 25	18	~ 30% + mixture	-

^{a)} All reactions were performed in CH₂Cl₂, unless stated otherwise. ^{b)} After the addition of Br₂, the reaction mixture was stirred for 10 min. t represents the time after the addition of Et₃N. ^{c)} The resulting reaction mixture was used directly in the next step. ^{d)} The starting material was 1.48 M in (CHCl₂)₂. ^{e)} The reaction was performed in (CH₂Cl)₂. ^{f)} Yield after hydrazone-cleavage (see Table 7). - not isolated.

At this point we struggled to find an explanation for the low conversion ($\leq 50\%$) of **129** to **130** using our one-pot conditions. We therefore decided to investigate the first two steps, the hydrazone formation and the bromination, in more detail. Using less than 1.5 equivalents of *t*-Bu-carbazate (**132**) under the established conditions only led to partial conversion of cyclohexenone (**1**) ($\sim 80\%$) and therefore also left some **132** unreacted. On the other hand, it seemed that an excess of **132** prevented the bromination from going to completion. It turned out that isolation of the pure hydrazone **129** and running a series of experiments was the key to confirm our assumption. Six individual reactions were set up in parallel. In each case, a solution of the hydrazone **129** in a 5:1 mixture of dichloromethane and 1,2-dichloroethane was cooled to $-15\text{ }^{\circ}\text{C}$. For each experiment, one or two selected additives that are present in the one-pot sequence (water, sodium sulfate and *t*-Bu-carbazate (**132**)) were added. A solution of bromine in dichloromethane (1.05 equivalents) was then transferred to the mixtures and after stirring the resulting solution for 10 min, triethylamine (4.00 equivalents) was added in one portion. The results of this screening are summarised in Table 6.

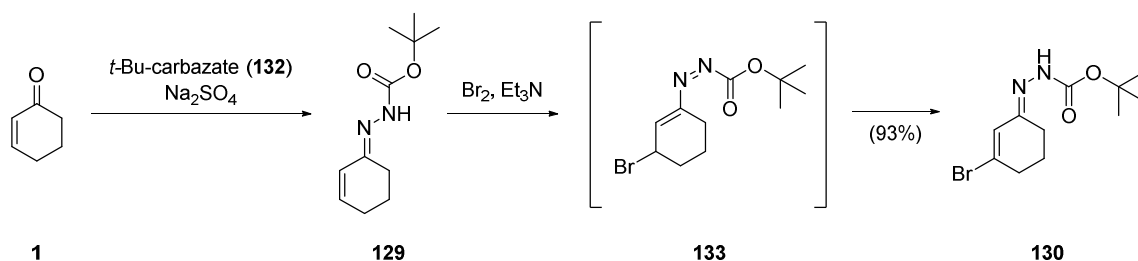
Table 6. Screening of additives for the bromination of **129**.

Entry	SM	Additive 1 (equiv)	Additive 2 (equiv)	NMR conversion ^{a)}
1	Pure 129	none	none	> 99%
2	Pure 129	Na ₂ SO ₄ (3.00)	none	> 99%
3	Pure 129	Na ₂ SO ₄ (3.00)	H ₂ O (1.00)	> 99%
4	Pure 129	none	H ₂ O (1.00)	> 99%
5	Pure 129	<i>t</i> -Bu-carbazate (132) (0.50)	none	$\sim 10\%$
6	Crude 129 ^{b)}	none	none	$\sim 75\%$

^{a)} NMR conversion refers to the relative intensities of the product **130** to the starting material **129**. Minor impurities were disregarded. ^{b)} The condensation product was partitioned between water and dichloromethane, the layers were separated and the organic layer was washed with brine. The washed organic phase was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated.

It turned out that an excess of *t*-Bu-carbazate (**132**) was detrimental to the efficiency of the bromination step. Therefore we tried to find conditions which would allow us to achieve full conversion for the condensation step, without having to use an excess of **132**. Finally, we discovered that, in contrast to the reaction with magnesium sulfate, only 1.05 equivalents of *t*-Bu-carbazate (**132**) had to be used in combination with sodium sulfate as the drying agent. The ¹H NMR of the crude reaction mixtures showed greater than 95% conversion of **1** to the hydrazone **129**.

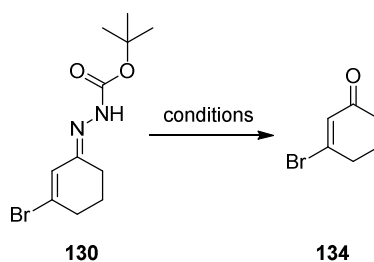
Following this protocol, the one-pot condensation and bromination was attempted. Employing 1.05 equivalents of *t*-Bu-carbazate (**132**) and 3.00 equivalents of sodium sulfate in 1,2-dichloroethane, followed by dilution with dichloromethane and treatment with bromine and triethylamine, gave the β -brominated hydrazone **130** in an excellent yield of 93% (Scheme 25).



Scheme 25. One-pot formation of the β -brominated hydrazone **130** from cyclohexenone (**1**).

In the course of these investigations, we were able to obtain one of the proposed intermediates of the bromination reaction. Treatment of **129** with bromine formed a dibromide, which, when treated with triethylamine, led to the formation of the allylic bromide **133**. This crucial intermediate was stable to column chromatography on silica gel and could be fully characterised. Further addition of triethylamine to **133** then furnished vinyl bromide **130**.

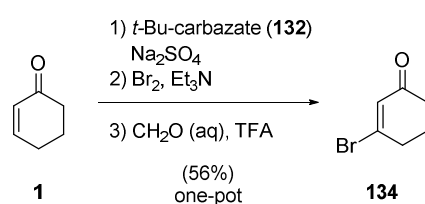
Various conditions for the one-pot hydrolysis of the hydrazone were investigated next. The experiments are summarised in Table 7. Cleavage of the hydrazone and regeneration of the carbonyl moiety was attempted with hydrobromic acid, copper(II) bromide/water, trifluoroacetic acid/acetone, and trifluoroacetic acid/aqueous formaldehyde. Previous investigations had shown that hydrobromic acid/aqueous formaldehyde was a viable system for the cleavage of brominated cyclohexenone benzothiazolinone hydrazone **67** and copper(II) chloride dihydrate effected the cleavage of brominated semicarbazone **71**, albeit also leading to an exchange of the β -bromide for a chloride.

Table 7. Screening of one-pot hydrazone-cleavage conditions.

Entry	Additive 1 (equiv)	Additive 2 (equiv)	Observation	Yield [%]
1 ^{a)}	HBr (14.60)	none	full conversion	26
2 ^{b)}	CuBr ₂ (1.50)	H ₂ O (3.00)	no conversion	-
3	TFA (3.10)	acetone (20.00)	partial conversion	-
4	TFA (3.10)	formaldehyde (aq) ^{c)} (10.00)	full conversion	56

^{a)} Tetrahydrofuran was added to promote phase-miscibility. ^{b)} Acetonitrile was added to the reaction mixture prior to the addition of CuBr₂. ^{c)} 37% aqueous solution of formaldehyde. - not isolated.

The use of trifluoroacetic acid in combination with aqueous formaldehyde proved to be our method of choice for the one-pot sequence. While showing full conversion and no obvious side products in the crude NMR, the hydrolysis of the hydrazone employing trifluoroacetic acid and aqueous formaldehyde gave dissatisfactory isolated yields (48–56%) of the slightly volatile product **134**. Due to time limitations, the search for an improved system had to be suspended in favour of investigating the substrate scope of the method. However, the search for improved conditions for hydrazone cleavage is under way in our laboratory.

**Scheme 26.** The one-pot β -bromination of cyclohexenone (**1**).

After having established a one-pot three-step protocol giving acceptable and reproducible yields and sufficiently high conversions for the first two steps (Scheme 26), we started to screen further possible substrates (Figure 5).

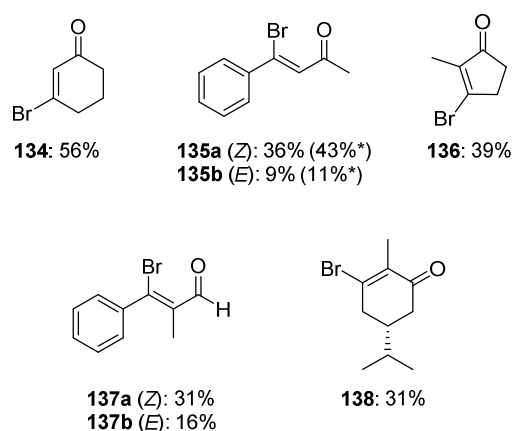
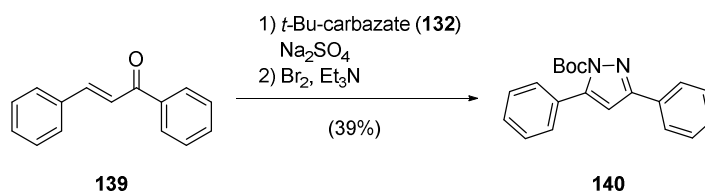


Figure 5. β -Bromination of various substrates. * brsm.

The products derived from cyclohexenone (**1**), **134**, benzylideneacetone (**171**), **135a** and **135b**, 2-methylcyclopentenone (**90**), **136**, α -methyl-*trans*-cinnamaldehyde (**172**), **137a** and **137b**, and the chiral substrate, (–)-carvotanacetone (**173**), **138**, were easily obtained in comparable yields via the established one-pot three-step procedure. Interestingly, however, the conversion of cyclopentenone (**3**) to its β -brominated derivative proved to be problematic. Both the initial condensation and the bromination of the isolated hydrazone did not go to full conversion and no isolated yield can be reported.

When trying to achieve β -bromination of *trans*-chalcone (**139**), pyrazole **140** was isolated as the sole product, arising from the 1,4-addition of the nitrogen and subsequent retro-Michael reaction to eliminate the bromide (Scheme 27). This side reaction was originally considered as a possibility for all acyclic systems. Surprisingly, however, cyclisation was only observed in this case and not for the reactions that lead to the formation of **135** and **137**, as shown in Figure 5.



Scheme 27. Pyrazole synthesis from *trans*-chalcone (**139**).

4.4 *Kopsia* alkaloids

Aiming to demonstrate one of the possible applications of our newly developed protocol, we set out to implement the one-pot β -halogenation of enones in the synthesis of alkaloids from *Kopsia hainanensis*. Our retrosynthetic analysis of kopsihainanine A (**4**) and B (**5**), as well as kopsihainin D (**6**) and E (**7**) revealed the common tetrahydrocarbazolone precursor **8**, which can be easily accessed from β -halogenated cyclohexenone (**134**).

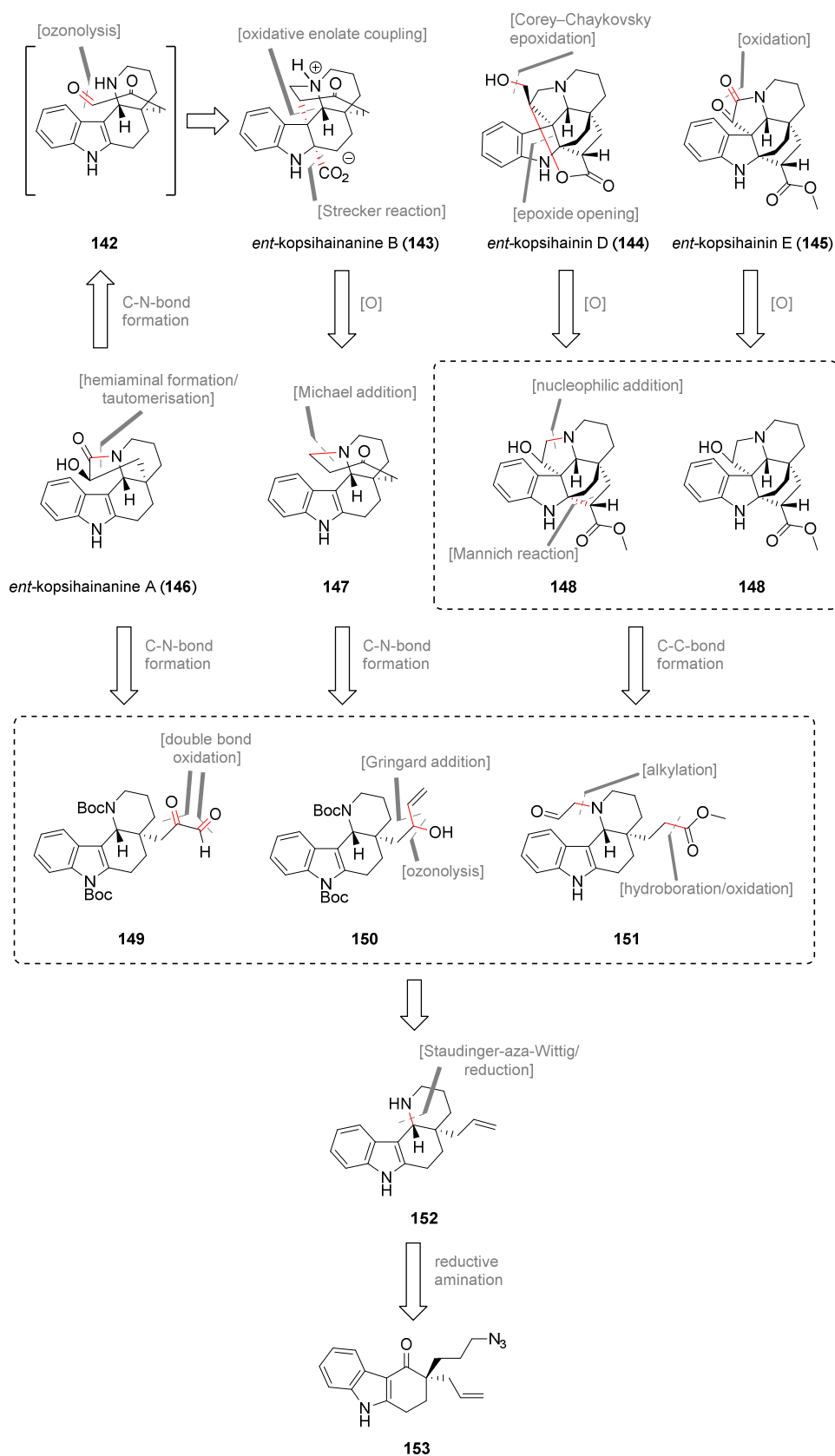
4.4.1 Retrosynthetic analysis

4.4.1.1 Kopsihainanine A (**4**) and B (**5**) and kopsihainin D (**6**) and E (**7**)

Our retrosynthetic planning focused on the functionalisation of 2-cyclohexen-1-one (**1**), which should form the core of the tetrahydrocarbazolone skeleton of compounds **4–7**. Furthermore, it was our goal to design a synthesis which would support our hypothesis for the biogenesis of kopsihainanine A (**4**) from kopsihainanine B (**5**).

For practical reasons, we decided to aim for the preparation of the enantiomeric natural products. The (*S*)-*t*-Bu-PHOX ligand (**141**) can be prepared from inexpensive (*S*)-*t*-leucinol^[43] and is also commercially available, whereas the corresponding (*R*)-configured ligand is not commercially available and the starting material for its preparation is considerably more expensive.

The designed retrosyntheses for *ent*-kopsihainanine A (**146**) and B (**143**), as well as *ent*-kopsihainin D (**144**) and E (**145**) are illustrated in Scheme 28.

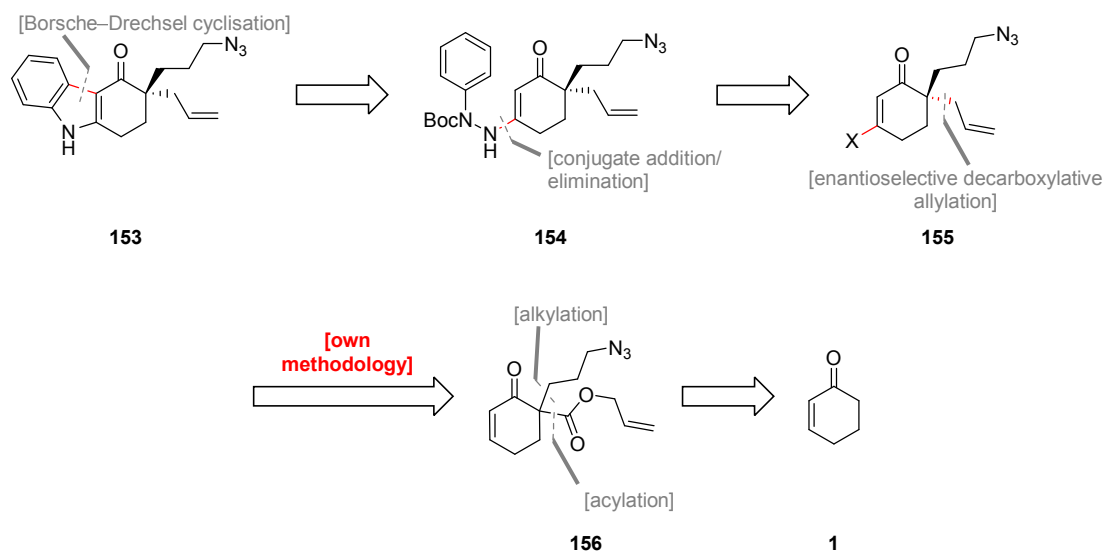


Scheme 28. Retrosynthetic analyses of the *Kopsia* alkaloids **143–146**.

Ent-kopsihainanine A (**146**) could be accessed from intermediate **149** via C–N-bond formation. **149** is formed through oxidation of the allyl moiety of precursor **152**,^[44] which itself is derived from **153** via azide reduction and reductive amination.^[45] The formation of the core of *ent*-kopsihainanine B (**143**) could be achieved by performing an oxidative enolate coupling^[46] on intermediate **147**. Synthesis of **147** from **150** is achieved through chain elongation and subsequent C–N-bond formation. Aiming to prove the putative biogenesis of kopsihainanine A (**146**), we envision to investigate the decarboxylative C–N-bond cleavage of kopsihainanine B (**143**), followed by oxidation and subsequent C–N-bond formation to furnish **146**. The final steps of the proposed synthesis of heptacyclic *ent*-kopsihainin D (**144**) involve oxidation and epoxidation of **148**, followed by ring formation.^[47-49] Precursor **148** can be accessed from **151** by double C–C-bond formation, building up two cyclic structures.^[50-53] N-alkylation and subsequent double bond oxidation lead to **151** from **152**. Oxidation of *ent*-kopsihainin D-precursor **148** can also lead to the formation of *ent*-kopsihainin E (**145**).^[54-55]

4.4.1.2 Retrosynthesis of the common precursor

The common precursor **153** for all four possible syntheses of *Kopsia* alkaloids **143–146** can be easily accessed from cyclohexenone (**1**).



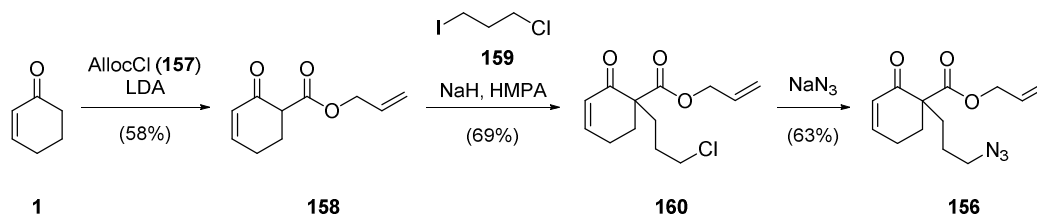
Scheme 29. Retrosynthetic analysis of the common precursor **153**.

The key fragment **153** is formed through a Borsche–Drechsel-type cyclisation of intermediate **154**, which can also be seen as an intermediate of the Fischer-indole synthesis. Compound **154** is expected to be derived from **156** after introduction of a halogen at the β -position through our newly developed methodology (chapter 4.3.2). The stereochemistry at C6 can be

introduced by an enantioselective decarboxylative allylation reaction, which was developed by Stoltz and used by Lupton.^[33, 43] The necessary allyl ester is installed by simple acylation of cyclohexenone (**1**) followed by alkylation of the β -keto ester.

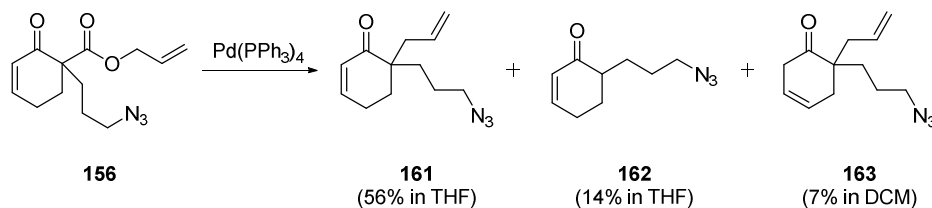
4.4.2 Synthetic efforts toward the common precursor

The route toward **153** commenced with cyclohexenone (**1**), which was acylated with allyl chloroformate (**157**) and lithium diisopropylamide in toluene, to form the γ,δ -unsaturated β -ketoester **158**. Treatment of this compound with sodium hydride and 1-chloro-3-iodopropane (**159**) in tetrahydrofuran furnished the racemic chloride **160**. Substitution of the chloride with sodium azide in *N,N*-dimethylformamide led to the formation of the azide **156** (Scheme 30).



Scheme 30. Synthetic route from cyclohexenone (**1**) to intermediate **156**.

Treatment of **156** with Pd(PPh₃)₄ in either dichloromethane or tetrahydrofuran yielded **161** in moderate yields (Scheme 31). The major side products isolated from this step were compounds **162** and **163**. It is interesting to note that a competing Staudinger reduction of the azide by the phosphine ligands was not observed. Exchange of triphenylphosphine for the *t*-Bu-PHOX ligand (**141**) would allow us to prepare this intermediate in an enantioselective fashion.



Scheme 31. Decarboxylative allylation of **156**.

The stage is now set to test the methodology developed in chapter 4.3.2. We are aware that bromination of the enone could compete with the reaction of the terminal double bond. However, we are confident that we can develop a strategy of either avoiding this side reaction or of incorporating the formation of the vicinal dibromide into our synthetic plans. These experiments are currently under way in our laboratory.

5 Conclusions and Outlook

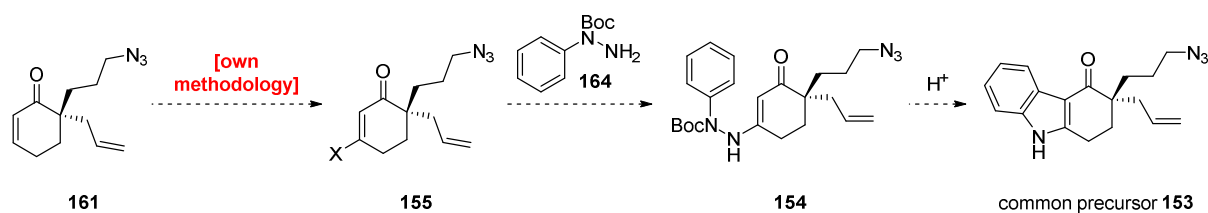
In summary, we were able to develop a one-pot procedure for the β -bromination of α,β -unsaturated ketones and aldehydes. The protocol benefits from simple and mild reaction conditions, inexpensive reagents and operational simplicity. Each step can be easily monitored either by TLC or by ^1H NMR analysis.

As of now, the method is limited solely by the final step, the hydrazone cleavage, with the first two steps giving an overall isolated yield of 93% for the model substrate cyclohexenone (**1**). Future work will focus on improving and further investigating the final step. Many different options for hydrazone cleavage were reported in the literature and it seems to be merely a matter of optimisation.

Furthermore, the substrate scope of the developed protocol has to be extended, to prove its compatibility with a variety of functional groups, such as protected alcohols, esters, nitriles, heteroaromatic substituents, acetals, epoxides, other halogens and—with a view to our planned *Kopsia* alkaloid syntheses—azides, to name a few.

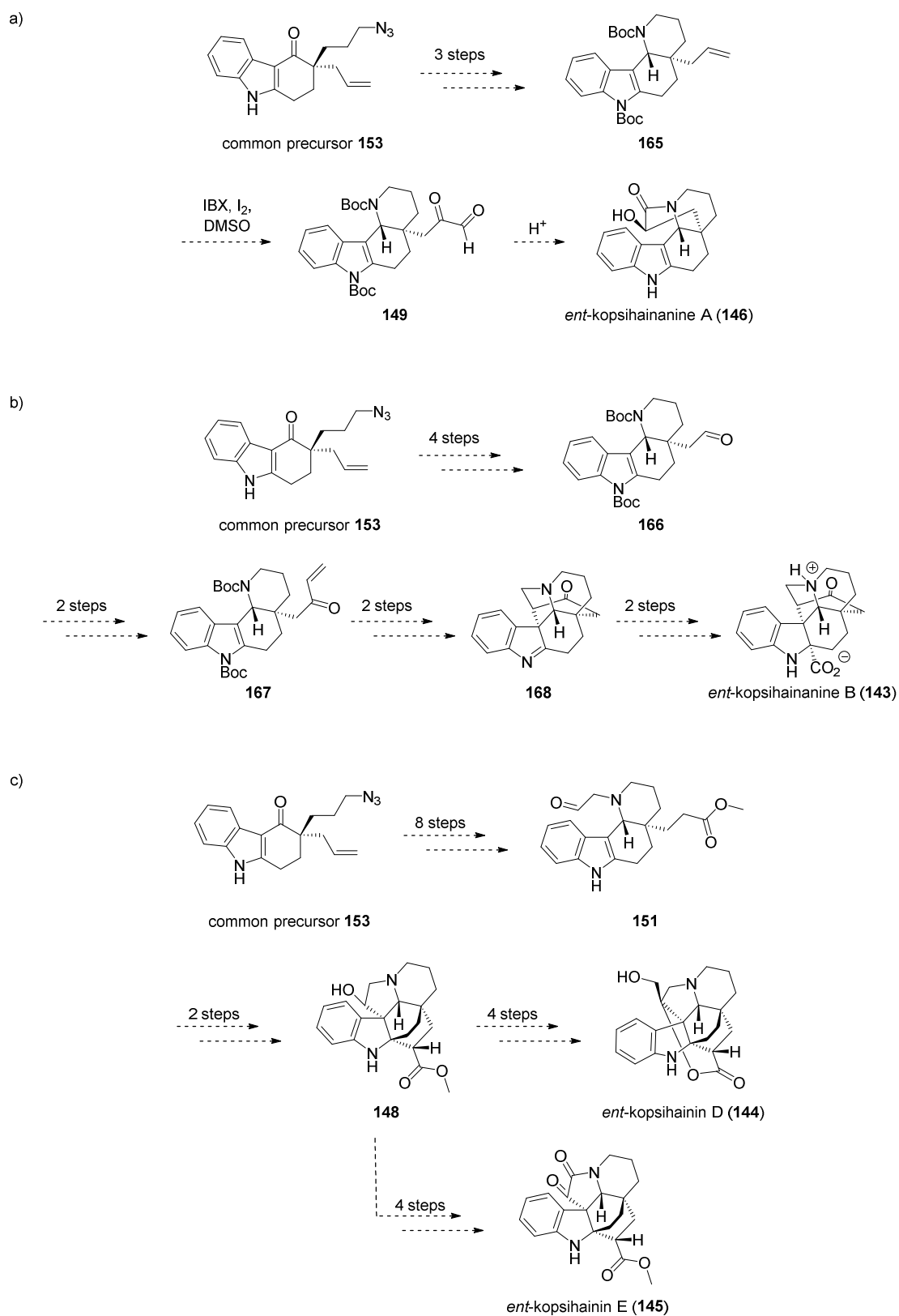
Also, the possible incorporation of other halides at the β -position of enones will be important and interesting to investigate. Due to the mechanism of the reaction, methods to effect dihalogenation of the double bond without the use of hazardous fluorine or chlorine gas will have to be found. Possible ways include the use of tetraalkylphosphonium trihalides^[56], interhalogen fluorides generated from xenon difluoride and halonium compounds^[57], ionic liquids, such as 3-ethyl-1-methylimidazolium oligo hydrogen fluoride (EMIMF(HF)_{2.3}), in combination with NXS^[58], or a system of TCCA (**43**)^[59] or oxone[®]^[60] with sodium chloride.

For the syntheses of the *Kopsia* alkaloids, formation of the common precursor **153** will be the next important task. Applying the β -halogenation protocol to intermediate **161** will furnish **155**. Coupling of this compound with Boc-protected phenylhydrazine (**164**)—either via an addition-elimination sequence or through transition-metal catalysis—and subsequent acid-catalysed cyclisation will yield **153** from which the *Kopsia* alkaloids can be accessed (Scheme 32).



Scheme 32. Planned synthesis of the common precursor **153**.

The following transformations that lead to compounds **143–146** are outlined in Scheme 33.



Scheme 33. Planned synthetic route toward the *Kopsia* alkaloids **143–146**.

6 Experimental Part

6.1 General experimental details

Unless stated otherwise, all reactions were performed in oven-dried or flame-dried glassware under a positive pressure of argon. Commercial reagents and solvents were used as received with the following exceptions: Tetrahydrofuran (THF) was distilled from benzophenone and sodium immediately prior to use. Triethylamine (Et_3N) and diisopropylamine (DIPA) were distilled over calcium hydride immediately prior to use. Reactions were magnetically stirred and monitored by crude NMR spectroscopy or analytical thin-layer chromatography (TLC) using E. Merck 0.25 mm silica gel 60 F_{254} precoated aluminium plates. TLC plates were visualised by exposure to ultraviolet light (254 nm) and/or exposure to an aqueous solution of ceric ammonium molybdate (CAM), an aqueous solution of potassium permanganate (KMnO_4) or an ethanolic solution of 4-anisaldehyde, followed by heating with a heat gun. Flash column chromatography was performed as described by Still et al. employing silica gel (60 Å, 40-63 μm , Merck) using 1.3–1.5 bar pressure (nitrogen or air).^[61] Yields refer to chromatographically and spectroscopically (^1H NMR and ^{13}C NMR) pure material.

6.2 Instrumentation

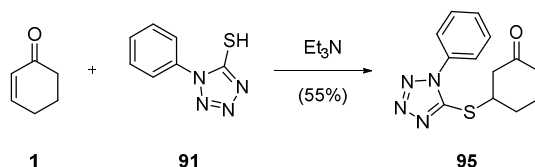
Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Varian Mercury 200, VNMRS 300, VNMRS 400, INOVA 400, VNMRS 600 or Bruker Avance III HD 400 spectrometers. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are calibrated using residual undeuterated solvent as an internal reference (CHCl_3 : δ 7.26). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broadened, app = apparent, or combinations thereof. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400, VNMRS 600 or Bruker Avance III HD 400 spectrometers. Carbon chemical shifts are expressed in parts per million (δ scale) and are referenced to the carbon resonances of the solvent (CDCl_3 : δ 77.0).

Infrared (FTIR) spectra were recorded on a Perkin Elmer Spectrum BX II (FTIR System), using a *SMITHS DETECTION DuraSamplIR II Diamond ATR* sensor for detection. FTIR data are reported in frequency of absorption (cm^{-1}) and the relative intensities are abbreviated as follows: very strong (vs), strong (s), medium (m), weak (w).

Mass spectroscopy (MS) experiments were performed on a Thermo Finnigan MAT 95 (EI), on a Thermo Finnigan LTQ FT (ESI) or on a JEOL MS700 MAT 95 (DCI) instrument.

6.3 Experimental procedures

6.3.1 The Pummerer-type approach



Thioether 95

A solution of 2-cyclohexen-1-one (**1**) (200 μL , 2.07 mmol, 1 equiv) in tetrahydrofuran (2.7 mL) was cooled to $-78\text{ }^\circ\text{C}$. 1-Phenyl-1-*H*-tetrazole-5-thiol (**91**) (479 mg, 2.69 mmol, 1.30 equiv) was added to the stirred solution in small portions, followed by the addition of triethylamine (15 μL , 0.11 mmol, 0.052 equiv). The solution was allowed to warm to $-10\text{ }^\circ\text{C}$ and kept at that temperature for 15 min. The mixture was then allowed to warm to $23\text{ }^\circ\text{C}$ and stirring was continued for 46 h. The reaction mixture was concentrated and the crude residue was purified by flash column chromatography on silica gel (9% ethyl acetate–toluene) to give the title compound **95** (310 mg, 55%) as a white solid.

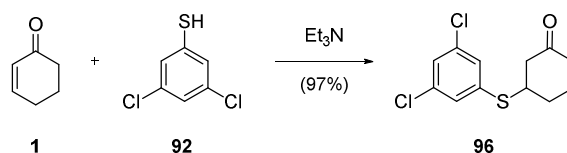
TLC (10% ethyl acetate–toluene): $R_f = 0.40$ (CAM, UV)

^1H NMR (300 MHz, CDCl_3): δ 7.96–7.90 (m, 2H), 7.56–7.43 (m, 3H), 5.18 (tdd, $J = 9.9, 5.5, 4.3\text{ Hz}$, 1H), 3.02–2.84 (m, 2H), 2.55–2.40 (m, 2H), 2.38–2.20 (m, 2H), 2.19–2.05 (m, 1H), 1.89–1.73 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3): δ 205.8, 162.3, 134.4, 129.5, 129.1, 123.6, 56.1, 45.0, 40.2, 28.8, 21.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$, cm^{-1} : 2953 (w), 1715 (vs), 1595 (w), 1497 (m), 1414 (m), 1358(s), 1302 (s).

HRMS (EI): Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_1^{32}\text{S}_1$: 274.0888. Found: 274.0880.



Thioether 96

A stirred solution of 3,5-dichlorobenzenethiol (**92**) (300 mg, 1.68 mmol, 1.01 equiv) in dichloromethane (0.36 mL) was treated with 2-cyclohexen-1-one (**1**) (161 μL , 1.67 mmol, 1 equiv) and the reaction mixture was cooled to 0 °C. Triethylamine (8.4 μL , 0.060 mmol, 0.036 equiv) was added and the solution was allowed to warm to 23 °C. After 3 h, the reaction mixture was diluted with chloroform (2 mL) and the solution was concentrated. The residue was purified by flash column chromatography on silica gel (9% ethyl acetate–toluene) to give the title compound **96** (446 mg, 97%) as a colourless oil, which solidified upon refrigeration within several days.

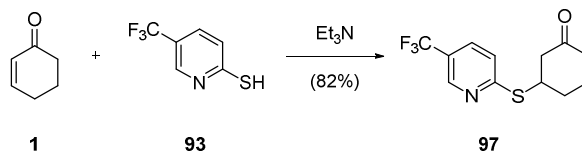
TLC (10% ethyl acetate–toluene): R_f = 0.71 (CAM, UV)

^1H NMR (600 MHz, CDCl_3): δ 7.25–7.27 (m, 3H), 3.51 (tdd, J = 10.0, 4.5, 3.3 Hz, 1H), 2.71 (ddt, J = 14.5, 4.6, 1.7 Hz, 1H), 2.37–2.43 (m, 2H), 2.36–2.30 (m, 1H), 2.21–2.12 (m, 2H), 1.81–1.61 (m, 2H).

^{13}C NMR (150 MHz, CDCl_3): δ 207.3, 137.4, 135.1, 129.7, 127.3, 47.3, 45.8, 40.7, 30.9, 23.8.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$, cm^{-1} : 2944 (w), 1713 (s), 1565 (m), 1555 (vs), 1423 (w), 1403 (m), 797 (m).

HRMS (EI): Calcd for $\text{C}_{12}\text{H}_{12}^{35}\text{Cl}_2\text{O}_1^{32}\text{S}_1$: 273.9986. Found: 273.9982.



Thioether 97

2-Cyclohexen-1-one (**1**) (27 μL , 0.28 mmol, 1 equiv) was added to a suspension of 5-(trifluoromethyl)pyridine-2-thiol (**93**) (50.0 mg, 0.279 mmol, 1.01 equiv) in deuterated chloroform (0.20 mL). The reaction mixture was cooled to 0 °C, followed by the addition of triethylamine (1.4 μL , 0.010 mmol, 0.036 equiv). The suspension was stirred for 5 min and was then allowed to warm to 23 °C. Dissolution of all compounds occurred within 15 min.

After 1 h, the reaction mixture was diluted with deuterated chloroform (0.5 mL) and the solution was concentrated. The residue was purified by flash column chromatography on silica gel (9% ethyl acetate–toluene) to give the title compound **97** (63 mg, 82%) as a yellow oil.

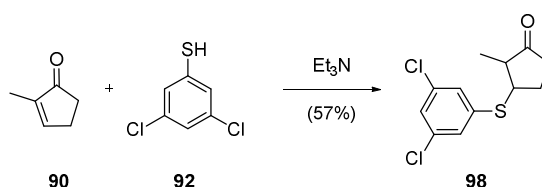
TLC (9% ethyl acetate–toluene): R_f = 0.43 (CAM, UV)

^1H NMR (300 MHz, CDCl_3): δ 8.64 (app ddd, J = 2.4, 1.8, 0.9 Hz, 1H), 7.66 (app ddd, J = 8.5, 2.4, 0.7 Hz, 1H), 7.21 (app td, J = 8.5, 0.8 Hz, 1H), 4.31 (tdd, J = 10.0, 4.8, 3.8 Hz, 1H), 2.88 (ddt, J = 14.4, 4.8, 1.5 Hz, 1H), 2.53 (app ddd, J = 14.4, 10.0, 1.2 Hz, 1H), 2.25–2.46 (m, 3H), 2.06–2.19 (m, 1H), 1.80–1.97 (m, 2H).

^{13}C NMR (75 MHz, CDCl_3): δ 208.3, 162.7 (q, J = 1.5 Hz), 146.3 (q, J = 4.3 Hz), 132.6 (q, J = 3.4 Hz), 123.7 (q, J = 271.7 Hz), 122.5 (q, J = 33.2 Hz), 122.0, 47.4, 42.0, 40.9, 30.9, 24.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$, cm^{-1} : 2945 (w), 1711 (m), 1597 (m), 1325 (vs), 1167 (m), 1116 (vs), 1075 (m).

HRMS (EI): Calcd for $\text{C}_{12}\text{H}_{12}\text{F}_3\text{N}_1\text{O}_1^{32}\text{S}_1$: 275.0592. Found: 275.0590.



Thioether **98**

A solution of 2-methylcyclopentenone (**90**) (100 μL , 1.02 mmol, 1 equiv) in dichloromethane (0.70 mL) was treated with 2,3-dichlorobenzenethiol (**92**) (184 mg, 1.03 mmol, 1.01 equiv) at 23 °C. The mixture was immediately cooled to 0 °C and triethylamine (5.1 μL , 37 μmol , 0.036 equiv) was added. The resulting solution was allowed to warm to 23 °C. After 7.5 h, the reaction mixture was diluted with chloroform (3 mL) and the solution was concentrated. The crude residue was purified by flash column chromatography on silica gel (6% ethyl acetate–toluene) to give the title compound **98** (161 mg, 57%) as a colourless oil.

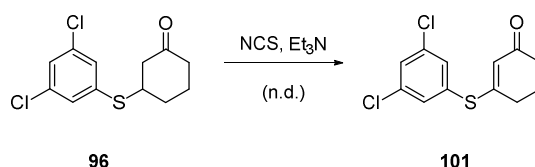
TLC (9% ethyl acetate–toluene): $R_f = 0.58$ (CAM, UV)

^1H NMR (300 MHz, CDCl_3): δ 7.29 (d, $J = 1.8$ Hz, 2H), 7.27 (s, 1H), 3.30 (td, $J = 9.8, 6.0$ Hz, 1H), 2.55–2.39 (m, 2H), 2.24 (dd, $J = 18.9, 9.4$ Hz, 1H), 2.15–2.04 (m, 1H), 1.88 (app dd, $J = 13.6, 9.7$ Hz, 1H), 1.20 (d, $J = 7.1$ Hz, 3H).¹

^{13}C NMR (75 MHz, CDCl_3): δ 216.5, 137.8, 135.3, 129.3, 127.4, 50.8, 49.8, 36.6, 28.9, 13.0.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$ cm^{-1} : 3467 (w), 2968 (w), 1741 (vs), 1565 (s), 1554 (vs), 1403 (m), 798 (s).

HRMS (EI): Calcd for $\text{C}_{12}\text{H}_{12}^{35}\text{Cl}_2\text{O}_1^{32}\text{S}_1$: 273.9986. Found: 273.9972.



Vinylogous thioester **101**

A solution of thioether **96** (50.0 mg, 0.182 mmol, 1 equiv) in dichloromethane (0.3 mL) was cooled to 0 °C. *N*-Chlorosuccinimide (26.7 mg, 0.200 mmol, 1.10 equiv) was added in one portion under vigorous stirring. The colourless solution so obtained turned yellow within 1 min. The mixture was allowed to warm to 23 °C over 3 h. The solution decolourised and a white precipitate was formed. The reaction mixture was cooled to 0 °C and a solution of triethylamine (76 μL , 0.55 mmol, 3.00 equiv) in dichloromethane (0.3 mL) was added in one portion. The stirred mixture was allowed to warm to 23 °C over 4 h. The reaction mixture was diluted with diethyl ether (5 mL) and was washed successively with 1 N hydrochloric acid (5 mL), water (5 mL) and saturated aqueous sodium chloride solution (5 mL). The combined organic phases were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (toluene initially, grading to 6% ethyl acetate–toluene) to give **101** as a colourless oil.²

TLC (9% ethyl acetate–hexanes): $R_f = 0.31$ (CAM, UV)

^1H NMR (300 MHz, CDCl_3): δ 7.45 (t, $J = 1.7$ Hz, 1H), 7.39 (d, $J = 1.8$ Hz, 2H), 5.51 (br s, 1H), 2.56 (t, $J = 5.7$ Hz, 2H), 2.44 (m, 2H), 2.11 (m, 2H).

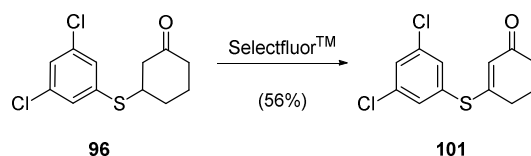
^{13}C NMR (75 MHz, CDCl_3): δ 164.8, 136.1, 133.5, 131.0, 130.5, 123.0, 38.1, 30.1, 22.9.

¹ Traces of the other diastereomer: 4.13 (m, 0.2 H), 1.89 (app dd, $J = 29.1, 13.6$ Hz, 0.2 H).

² The yield could not be determined due to a broken flask.

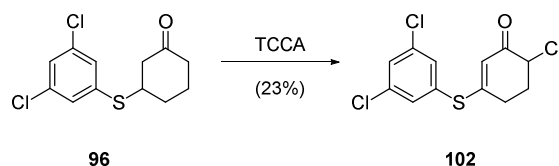
IR (Diamond-ATR, neat) $\tilde{\nu}_{\max}$, cm^{-1} : 2923 (w), 1656 (s), 1582 (s), 1558 (s), 1406 (m), 1340 (m), 1290 (m), 798 (m).

HRMS (EI): Calcd for $\text{C}_{12}\text{H}_9^{35}\text{Cl}_2\text{O}_1^{32}\text{S}_1$ $[\text{M}-\text{H}]^-$: 270.9746. Found: 270.9752.



Vinylogous thioester **101**

SelectfluorTM (142 mg, 0.401 mmol, 2.20 equiv) was added in one portion to a solution of thioether **96** (50.0 mg, 0.182 mmol, 1 equiv) in dichloromethane (1 mL) at 0 °C. Acetonitrile (1 mL) was added to the resulting suspension, which was then allowed to warm to 23 °C. After 16 h, excess SelectfluorTM was quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL). The aqueous phase was extracted with chloroform (2 × 5 mL) and the combined organic extracts were washed with water (10 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (6% ethyl acetate–hexanes) to give the title compound **101** (28 mg, 56%) as a colourless oil. The obtained characterization data were in full agreement with the values reported above.



Vinylogous thioester **102**

A solution of thioether **96** (51.3 mg, 0.186 mmol, 1 equiv) in benzene (0.5 mL) and diethyl ether (0.25 mL) was cooled to 0 °C. Trichloroisocyanuric acid (52.0 mg, 0.224 mmol, 1.20 equiv) was added under vigorous stirring at 0 °C. After 24 h, the reaction mixture was diluted with diethyl ether (2 mL) and the organic phases were washed with saturated aqueous ammonium chloride solution (4 mL), water (4 mL) and saturated aqueous sodium chloride solution (4 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash

column chromatography on silica gel (5% ethyl acetate–hexanes) to give the title compound **102** (13 mg, 23%) as a colourless oil.

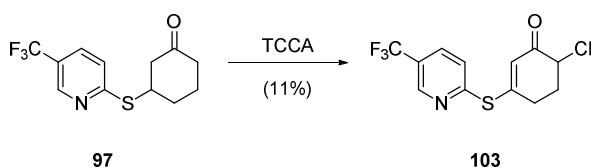
TLC (14% ethyl acetate–hexanes): R_f = 0.52 (CAM, UV)

^1H NMR (300 MHz, CDCl_3): δ 7.34 (d, J = 1.8 Hz, 2H), 7.26 (s, 1H), 6.25 (s, 1H), 3.86 (dd, J = 6.4, 4.5 Hz, 1H), 2.92 (m, 1H), 2.69 (dt, J = 10.9, 5.2 Hz, 1H), 2.46 (m, 1H), 2.26 (ddd, J = 14.3, 11.8, 5.5 Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3): δ 191.4, 157.5, 136.3, 135.2, 130.0, 128.0, 126.8, 50.8, 31.8, 28.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$ cm^{-1} : 2925 (w), 1678 (s), 1610 (m), 1566 (s), 1556 (vs), 1422 (m), 1403 (m), 798 (s).

HRMS (EI): Calcd for $\text{C}_{12}\text{H}_9^{35}\text{Cl}_3\text{O}_1^{32}\text{S}_1$: 305.9440. Found: 305.9441.



Vinylogous thioester **103**

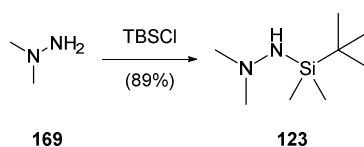
A solution of thioether **97** (63.0 mg, 0.229 mmol, 1 equiv) in benzene (0.6 mL) and diethyl ether (0.3 mL) was cooled to 0 °C. Trichloroisocyanuric acid (63.8 mg, 0.275 mmol, 1.20 equiv) was added to the yellow solution in one portion. The solution turned colourless, the cooling bath was removed and stirring was continued for 23 h at 23 °C. Excess trichloroisocyanuric acid was quenched by the addition of saturated aqueous sodium bicarbonate solution (2 mL). The aqueous layer was extracted with diethyl ether (5 mL) and chloroform (2 × 5 mL). The combined organic phases were washed with water (15 mL), the washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (6% ethyl acetate–hexanes), to give **103** (8 mg, 11%) as a light yellow oil.

^1H NMR (200 MHz, CDCl_3): δ 8.60–8.68 (m, 1H), 7.66–7.73 (m, 1H), 7.33 (td, J = 8.4, 0.8 Hz, 1H), 6.35 (dd, J = 1.9, 1.0 Hz, 1H), 4.81 (dd, J = 10.7, 4.9 Hz, 1H), 2.81–3.04 (m, 2H), 2.30–2.65 (m, 2H).

HRMS (EI): Calcd for $C_{12}H_9^{35}ClF_3N_1O_1^{32}S_1$: 305.9962. Found: 305.9957.

Extensive analysis could not be performed due to the decomposition of the title compound **103** at $-30\text{ }^{\circ}\text{C}$ within 3 months.

6.3.2 The hydrazone approach



TBS-dimethylhydrazine **123**

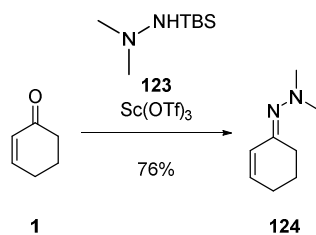
tert-Butyldimethylsilyl chloride (15.0 g, 99.5 mmol, 1 equiv) was placed in a pressure vessel under a stream of argon. *N,N*-dimethylhydrazine (**169**) (26.5 mL, 348 mmol, 3.50 equiv) was added dropwise. After the addition was complete, the reaction mixture was heated to $70\text{ }^{\circ}\text{C}$. After 3 h, the colourless solution was allowed to cool to $23\text{ }^{\circ}\text{C}$, upon which a colourless liquid phase separated from a white precipitate. The liquid phase was pipetted off and residual **169** was removed by careful distillation on a rotary evaporator (150 mbar, $40\text{ }^{\circ}\text{C}$) to yield pure **123** (15.54 g, 89%) as a colourless liquid. The compound could be stored at $6\text{ }^{\circ}\text{C}$, under an argon atmosphere, for a minimum of two months without any decomposition.

^1H NMR (300 MHz, CDCl_3): δ 2.37 (s, 6H), 0.89 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (75 MHz, CDCl_3): δ 52.8, 26.5, 17.6, -5.3 .

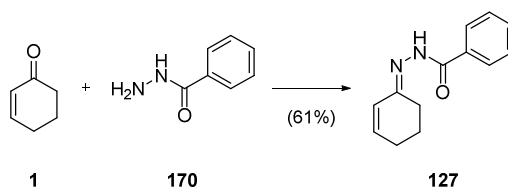
IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}\text{ cm}^{-1}$: 2950 (m), 2855 (m), 1462 (m), 1246 (m), 885 (vs), 829 (s), 776 (s).

HRMS (ESI): Calcd for $\text{C}_8\text{H}_{23}\text{N}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 175.1631. Found: 175.1627.



Dimethylhydrazone **124**

A solution of scandium trifluoromethanesulfonate (0.01 M in acetonitrile, 0.207 mL, 2.07 μmol , 0.100 mol%) was transferred to a flask and stirred at 25 °C. The flask was evacuated to remove the solvent. To the solid scandium trifluoromethanesulfonate was added TBS-dimethylhydrazine **123** (468 mg, 2.69 mmol, 1.30 equiv) and cyclohexenone (**1**) (0.200 mL, 2.07 mmol, 1 equiv). The flask was immersed in an oil bath and heated at 130 °C. After 10 min, the reaction mixture was cooled to 23 °C with a water bath. The crude mixture was purified by flash column chromatography on silica gel (20% diethyl ether–dichloromethane), to give **124** (218 mg, 76%) as a slightly volatile, light yellow oil. The obtained characterisation data were in full agreement with those reported in the literature.^[40]



Hydrazone **127**

Benzhydrazide (**170**) (639 mg, 4.70 mmol, 0.910 equiv) was added to a solution of cyclohexenone (**1**) (0.500 mL, 5.16 mmol, 1 equiv) in ethanol (7 mL) and the resulting solution was heated to 80 °C. Two further portions of benzhydrazide (**170**) (total: 410 mg, 3.01 mmol, 0.580 equiv) were added to the solution after 1.5 and 3.5 h. After 22 h, the reaction mixture was concentrated and the crude residue was purified by flash column chromatography on silica gel (2% methanol–dichloromethane), to give an approximate 5/1 mixture of *E/Z*-isomers **127** (675 mg, 61%) as an off-white solid.

TLC (2% methanol–dichloromethane): R_f = 0.34 & 0.27 (*E/Z*-isomers) (anisaldehyde, UV)

^1H NMR (400 MHz, CDCl_3), **127a**: δ 8.95 (br s, NH), 7.72–7.89 (m, 2H), 7.46–7.53 (m, 1H), 7.38–7.46 (m, 2H), 6.30–6.44 (m, 1H), 2.42–2.52 (t, J = 6.5 Hz, 2H), 2.23 (ddt, J = 6.3, 4.4, 2.7 Hz, 2H), 1.86 (app quin, J = 6.3 Hz, 2H).

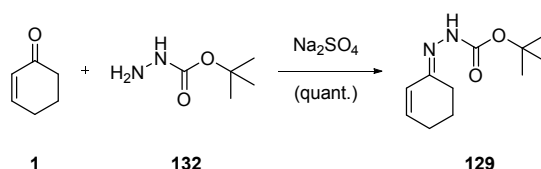
127b: δ 9.12 (br s, NH), 7.72–7.89 (m, 2H), 7.46–7.53 (m, 1H), 7.38–7.46 (m, 2H), 6.46–6.52 (br s, 1H), 2.55–2.64 (br s, 2H), 2.30 (app td, J = 6.1, 1.8 Hz, 2H), 1.86 (app quin, J = 6.3 Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3), **127a**: δ 163.9, 154.1, 137.9, 133.6, 131.8, 128.7, 127.8, 127.1, 24.7, 23.7, 20.9.

127b: δ 163.9, 154.1, 143.3, 133.6, 131.8, 128.7, 127.1, 116.2, 31.5, 26.5, 22.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$ cm^{-1} : 3216 (w), 2928 (w), 1645 (vs), 1519 (s), 1271 (s), 1131 (s), 910 (m).

HRMS (EI): Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_1$: 214.1106. Found: 214.1101.



Hydrazone 129

A suspension of sodium sulfate (660 mg, 4.65 mmol, 3.00 equiv) and *t*-Bu-carbazate (**132**) (225 mg, 1.70 mmol, 1.05 equiv) in 1,2-dichloroethane (1 mL) was treated with cyclohexenone (**1**) (150 μL , 1.55 mmol, 1 equiv) and the resulting mixture was heated to 85 $^\circ\text{C}$. After 3.5 h, NMR-analysis showed full conversion of **1** to **129a** and **129b** (dr = 4:1). The crude reaction mixture was used directly in the next step.

TLC (dichloromethane): R_f = 0.20 (anisaldehyde, UV)

^1H NMR (400 MHz, CDCl_3), **129a**: δ 7.55–8.01 (br s, NH), 6.12–6.25 (m, 2H), 2.28 (t, J = 6.6 Hz, 2H), 2.12 (tdd, J = 5.8, 3.9, 1.5 Hz, 2H), 1.71–1.81 (m, 2H), 1.41–1.48 (s, 9H).

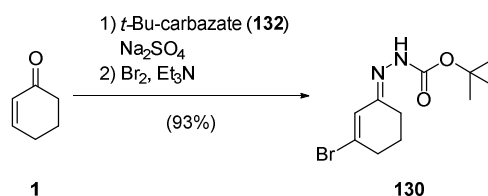
129b: δ 7.55–8.01 (br s, 1H), 6.29–6.36 (br s, NH), 2.39–2.46 (m, 2H), 2.19 (app td, J = 6.0, 1.6 Hz, 2H), 1.71–1.81 (m, 2H), 1.41–1.48 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3), **129a**: δ 152.8, 149.7, 135.5, 127.9, 81.0, 28.2, 24.5, 23.4, 21.0.

129b: δ 152.8, 148.6, 141.4, 116.3, 81.0, 31.5, 28.2, 26.4, 22.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\max}$ cm^{-1} : 3237 (w), 2931 (w), 1713 (m), 1691 (m), 1238 (s), 1159 (vs), 1138 (s).

HRMS (EI): Calcd for $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_2$: 210.1368. Found: 210.1359.



Bromide 130

A suspension of sodium sulfate (440 mg, 3.10 mmol, 3.00 equiv) and *t*-Bu-carbazate (**132**) (143 mg, 1.08 mmol, 1.05 equiv) in 1,2-dichloroethane (0.7 mL) was treated with cyclohexenone (**1**) (100 μL , 1.03 mmol, 1 equiv) and the resulting mixture was heated to 85 °C. After 3 h, the reaction mixture was allowed to cool to 23 °C, dichloromethane (3 mL) was added and the light yellow solution was cooled to –14 °C. Bromine (2 M in dichloromethane, 0.542 mL, 1.08 mmol, 1.05 equiv) was added dropwise to give a red solution. After 10 min, triethylamine (0.574 mL, 4.13 mmol, 4.00 equiv) was added in one portion and the resulting dark brown slurry was allowed to warm to 23 °C. After stirring at this temperature for 1.5 h, the reaction mixture was diluted with dichloromethane (10 mL). The solution was washed with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was extracted with dichloromethane (2 $\times$ 10 mL), the combined organic phases were dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (75% ethyl acetate–hexanes), to give **130** (278 mg, 93%) as an orange sticky oil.

TLC (75% ethyl acetate–hexanes): R_f = 0.32 (KMnO_4 , UV)

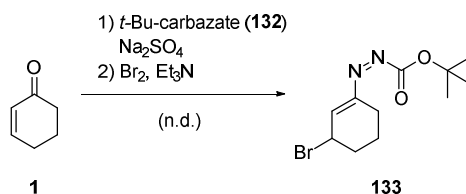
^1H NMR (400 MHz, CDCl_3), **130a**: δ 7.56 (s, NH), 6.70 (s, 1H), 2.63 (t, J = 6.2 Hz, 2H), 2.29 (t, J = 6.6 Hz, 2H), 1.93 (app quin, J = 6.4 Hz, 2H), 1.51 (s, 9H).

130b: δ 7.69 (s, NH), 6.72 (s, 1H), 2.70 (t, J = 6.2 Hz, 2H), 2.50 (t, J = 6.4 Hz, 2H), 1.93 (app quin, J = 6.4 Hz, 2H), 1.60 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): δ 152.6, 148.4, 130.9, 130.2, 81.6, 34.9, 28.2, 22.1, 21.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\max}$ cm^{-1} : 3228 (w), 2978 (w), 1711 (m), 1695 (m), 1512 (m), 1235 (s), 1151 (vs).

HRMS (EI): Calcd for $\text{C}_{11}\text{H}_{17}\text{N}_2\text{O}_2^{79}\text{Br}_1$: 288.0473. Found: 288.0450.



Bromide 133

Cyclohexenone (**1**) (0.200 mL, 2.07 mmol, 1 equiv) was added to a mixture of *t*-Bu-carbazate (**132**) (410 mg, 3.10 mmol, 1.50 equiv) and sodium sulfate (746 mg, 6.20 mmol, 3.00 equiv) in 1,2-dichloroethane (1.4 mL) and the resulting mixture was heated to 85 °C. After 6 h, the light orange suspension was allowed to cool to 25 °C, dichloromethane (5 mL) was added and the solution was cooled to –20 °C. Bromine (2.12 M in dichloromethane, 1.12 mL, 2.38 mmol, 1.15 equiv) was added dropwise. The resulting red solution was stirred at –20 °C for 15 min and triethylamine (0.574 mL, 4.13 mmol, 2.00 equiv) was added. The resulting black slurry was stirred vigorously at 23 °C. After 20 h, the reaction mixture was diluted with water (10 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 15 mL), the combined organic phases were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude residue was purified by filtration through a short plug of silica gel (dichloromethane), to give the title compound **133** (yield not determined) as a dark orange sticky oil.

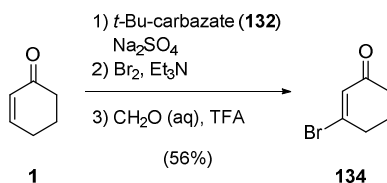
TLC (dichloromethane): R_f = 0.80 (KMnO_4 , UV)

^1H NMR (600 MHz, CDCl_3): δ 7.23 (ddt, J = 4.9, 1.9, 1.0 Hz, 1H), 5.13 (app q, J = 3.8 Hz, 1H), 2.49–2.55 (m, 1H), 2.20–2.28 (m, 2H), 2.09–2.15 (dddd, J = 14.4, 11.6, 4.5, 2.9 Hz, 1H), 1.98–2.06 (m, 1H), 1.82–1.88 (m, 1H), 1.61 (s, 9H).

^{13}C NMR (150 MHz, CDCl_3): δ 161.6, 155.0, 144.2, 84.9, 46.0, 32.1, 27.8, 21.3, 17.8.

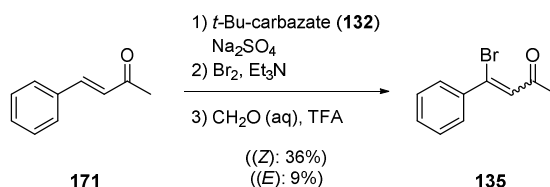
IR (Diamond-ATR, neat) $\tilde{\nu}_{\max}$ cm^{-1} : 2981 (w), 1747 (s), 1477 (w), 1370 (m), 1270 (m), 1251 (s), 1133 (vs).

HRMS (ESI): Calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2^{79}\text{Br}_1$ $[\text{M}-\text{H}]^-$: 287.0390. Found: 287.0397.



3-Bromo-2-cyclohexen-1-one (**134**)

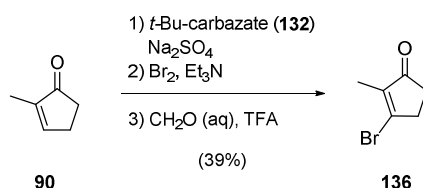
Cyclohexenone (**1**) (0.100 mL, 1.03 mmol, 1 equiv) was added to a mixture of sodium sulfate (440 mg, 3.10 mmol, 3.00 equiv), *t*-Bu-carbazate (**132**) (143 mg, 1.08 mmol, 1.05 equiv) and 1,2-dichloroethane (0.7 mL) and the resulting suspension was heated to 85 °C. After 5 h, the yellow mixture was allowed to cool to 23 °C, dichloromethane (3 mL) was added and the solution was cooled to –25 °C. Bromine (2 M in dichloromethane, 0.542 mL, 1.08 mmol, 1.05 equiv) was added dropwise at –25 °C, forming a red supernatant. After 10 min, triethylamine (0.574 mL, 4.13 mmol, 4.00 equiv) was added and the resulting brown slurry was allowed to warm to 23 °C. After 1.5 h, tetrahydrofuran (2 mL), formaldehyde (37% aq. solution, 0.774 mL, 10.3 mmol, 10.0 equiv) and trifluoroacetic acid (0.238 mL, 3.20 mmol, 3.10 equiv) were added and the resulting brown solution was stirred at 23 °C. After 13 h, the reaction mixture was treated with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL), the combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated (35 °C, 300 mbar) and the crude residue was purified by flash column chromatography on silica gel (20% diethyl ether–pentane), to give the title compound **134** (101 mg, 56%) as a light yellow liquid. The obtained characterisation data were in full agreement with those reported in the literature.^[9]



4-Bromo-4-phenyl-3-buten-2-one (**135**)

Benzylideneacetone (**171**) (151 mg, 1.03 mmol, 1 equiv) was added to a mixture of sodium sulfate (440 mg, 3.10 mmol, 3.00 equiv), *t*-Bu-carbazate (**132**) (143 mg, 1.08 mmol, 1.05 equiv) and 1,2-dichloroethane (0.7 mL) and the resulting suspension was heated to 85 °C. After 4 h, the colourless mixture was allowed to cool to 23 °C, dichloromethane (3 mL) was added and the solution was cooled to –35 °C. Bromine (2 M in dichloromethane,

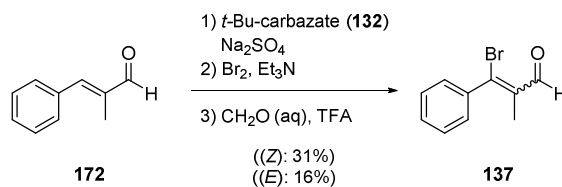
0.542 mL, 1.08 mmol, 1.05 equiv) was added dropwise at $-35\text{ }^{\circ}\text{C}$, forming a red supernatant. After 10 min, triethylamine (0.574 mL, 4.13 mmol, 4.00 equiv) was added and the resulting red slurry was allowed to warm to $23\text{ }^{\circ}\text{C}$. After 2 h, tetrahydrofuran (2 mL), formaldehyde (37% aq. solution, 0.774 mL, 10.3 mmol, 10.0 equiv) and trifluoroacetic acid (0.238 mL, 3.20 mmol, 3.10 equiv) were added and the resulting yellow solution was stirred at $23\text{ }^{\circ}\text{C}$. After 14 h, the reaction mixture was treated with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was extracted with dichloromethane ($3 \times 10\text{ mL}$), the combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (33% toluene–dichloromethane), to give the title compound **135** (105 mg, 45%, $Z/E = 4/1$) as a light yellow liquid together with the starting material **171** (25 mg, 17%). The obtained characterisation data for **135** were in full agreement with those reported in the literature.^[62]



3-Bromo-2-methyl-2-cyclopenten-1-one (136)

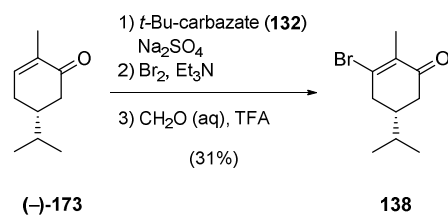
2-Methylcyclopentenone (**90**) (0.100 mL, 1.02 mmol, 1 equiv) was added to a mixture of sodium sulfate (434 mg, 3.06 mmol, 3.00 equiv), *t*-Bu-carbazate (**132**) (141 mg, 1.07 mmol, 1.05 equiv) and 1,2-dichloroethane (0.69 mL) and the resulting suspension was heated to $85\text{ }^{\circ}\text{C}$. After 3 h, the mixture was allowed to cool to $23\text{ }^{\circ}\text{C}$, dichloromethane (2.96 mL) was added and the solution was cooled to $-35\text{ }^{\circ}\text{C}$. Bromine (2 M in dichloromethane, 0.535 mL, 1.07 mmol, 1.05 equiv) was added dropwise at $-35\text{ }^{\circ}\text{C}$, forming a red supernatant. After 10 min, triethylamine (0.566 mL, 4.07 mmol, 4.00 equiv) was added and the resulting dark red slurry was allowed to warm to $23\text{ }^{\circ}\text{C}$. After 2 h, tetrahydrofuran (2 mL), formaldehyde (37% aq. solution, 0.763 mL, 10.2 mmol, 10.0 equiv) and trifluoroacetic acid (0.235 mL, 3.16 mmol, 3.10 equiv) were added and the resulting dark brown solution was stirred at $23\text{ }^{\circ}\text{C}$. After 14 h, the reaction mixture was treated with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was extracted with dichloromethane ($3 \times 10\text{ mL}$), the combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated ($25\text{ }^{\circ}\text{C}$, 80 mbar) and the crude residue was purified by flash column chromatography on silica gel (20% diethyl ether–pentane), to give the title compound

136 (69 mg, 39%) as a light yellow liquid. The obtained characterisation data were in full agreement with those reported in the literature.^[9]



3-Bromo-2-methyl-3-phenylacrylaldehyde (**137**)

α -Methyl-*trans*-cinnamaldehyde (**172**) (0.144 mL, 1.03 mmol, 1 equiv) was added to a mixture of sodium sulfate (440 mg, 3.10 mmol, 3.00 equiv), *t*-Bu-carbazate (**132**) (144 mg, 1.08 mmol, 1.05 equiv) and 1,2-dichloroethane (0.7 mL) and the resulting suspension was heated to 85 °C. After 5 h, the colourless mixture was allowed to cool to 23 °C, dichloromethane (3 mL) was added and the solution was cooled to –20 °C. Bromine (2 M in dichloromethane, 0.541 mL, 1.08 mmol, 1.05 equiv) was added dropwise at –20 °C, forming a light orange supernatant. After 10 min, triethylamine (0.573 mL, 4.13 mmol, 4.00 equiv) was added and the resulting orange slurry was allowed to warm to 23 °C. After 2 h, tetrahydrofuran (2 mL), formaldehyde (37% aq. solution, 0.772 mL, 10.3 mmol, 10.0 equiv) and trifluoroacetic acid (0.237 mL, 3.20 mmol, 3.10 equiv) were added and the resulting yellow solution was stirred at 23 °C. After 12 h, the reaction mixture was treated with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was extracted with dichloromethane (3 $\times$ 10 mL), the combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (3% diethyl ether–pentane), to give the title compound **137** (109 mg, 47%, *Z/E* ~ 2/1) as a yellow liquid. The obtained characterisation data were in full agreement with those reported in the literature.^[63]



(-)-Bromide 138

(-)-Carvotanacetone (**173**) (100 mg, 0.657 mmol, 1 equiv) was added to a mixture of sodium sulfate (280 mg, 1.97 mmol, 3.00 equiv), *t*-Bu-carbazate (**132**) (91.2 mg, 0.690 mmol, 1.05 equiv) and 1,2-dichloroethane (0.45 mL) and the resulting suspension was heated to 85 °C. After 5.5 h, the light pink mixture was allowed to cool to 23 °C, dichloromethane (1.9 mL) was added and the solution was cooled to -20 °C. Bromine (2 M in dichloromethane, 0.345 mL, 0.690 mmol, 1.05 equiv) was added dropwise at -20 °C, forming a red supernatant. After 10 min, triethylamine (0.365 mL, 2.63 mmol, 4.00 equiv) was added and the resulting orange slurry was allowed to warm to 23 °C. After 2.5 h, tetrahydrofuran (1.28 mL), formaldehyde (37% aq. solution, 0.492 mL, 6.57 mmol, 10.0 equiv) and trifluoroacetic acid (0.151 mL, 2.04 mmol, 3.10 equiv) were added and the resulting yellow solution was stirred at 23 °C. After 18 h, the reaction mixture was treated with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL), the combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated (35 °C, 200 mbar) and the crude residue was purified by flash column chromatography on silica gel (2% diethyl ether–pentane), to give the title compound **138** (47 mg, 31%) as a colourless liquid.

TLC (dichloromethane): R_f = 0.73 (KMnO₄, UV)

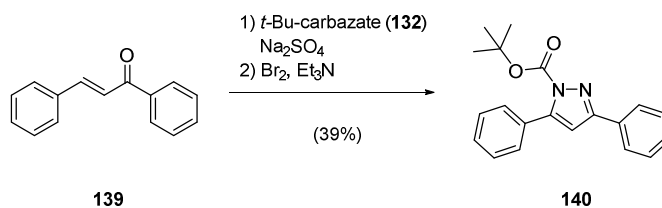
¹H NMR (400 MHz, CDCl₃): δ 2.89 (app ddt, J = 18.1, 4.7, 1.5 Hz, 1H), 2.62–2.73 (m, 1H), 2.57 (ddd, J = 15.9, 3.7, 1.6 Hz, 1H), 2.15 (dd, J = 15.9, 13.5 Hz, 1H), 1.88–1.99 (m, 1H), 1.93 (dd, J = 2.5, 1.4 Hz, 3H), 1.58 (app dq, J = 13.5, 6.8 Hz, 1H), 0.92 (dd, J = 6.8, 3.5 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 196.1, 147.0, 136.0, 41.6, 41.4, 41.2, 31.8, 19.4, 19.4, 15.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$ cm⁻¹: 2961 (m), 2874 (w), 1677 (vs), 1627 (m), 1328 (w), 1288 (s), 970 (w).

Optical rotation $[\alpha]_{\text{D}}^{23} = -87.8$ (c = 0.51, CH₂Cl₂)

HRMS (EI): Calcd for C₁₀H₁₅O₁⁸¹Br₁: 232.0286. Found: 232.0295.



Pyrazole 140

trans-Chalcone (**139**) (215 mg, 1.03 mmol, 1 equiv) was added to a mixture of sodium sulfate (440 mg, 3.10 mmol, 3.00 equiv), *t*-Bu-carbazate (**132**) (143 mg, 1.08 mmol, 1.05 equiv) and 1,2-dichloroethane (0.7 mL) and the resulting suspension was heated to 85 °C. After 7 h, the resulting mixture was allowed to cool to 23 °C, dichloromethane (3 mL) was added and the solution was cooled to –23 °C. Bromine (2 M in dichloromethane, 0.542 mL, 1.08 mmol, 1.05 equiv) was added dropwise at –23 °C, forming a dark orange supernatant. After 10 min, triethylamine (0.574 mL, 4.13 mmol, 4.00 equiv) was added and the resulting orange slurry was allowed to warm to 23 °C. After 2 h, the reaction mixture was treated with saturated aqueous ammonium chloride solution (10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL), the combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (15% diethyl ether–pentane), to give the title compound **140** (128 mg, 39%) as a colourless oil.

TLC (15% diethyl ether–pentane): R_f = 0.54 (KMnO₄, UV)

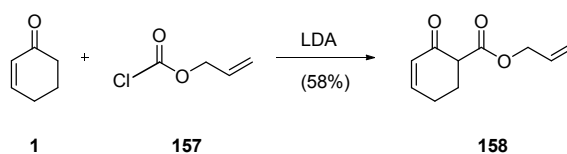
¹H NMR (400 MHz, CDCl₃): δ 7.92–7.96 (m, 2H), 7.35–7.46 (m, 8H), 6.68 (s, 1H), 1.36 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 153.5, 148.1, 47.3, 132.0, 131.8, 128.9, 128.9, 128.6, 128.5, 127.9, 126.3, 108.6, 84.9, 27.4.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\max}$ cm^{–1}: 2981 (w), 1754 (s), 1460 (m), 1298 (s), 1141 (vs), 768 (s), 693 (s).

HRMS (EI): Calcd for C₂₀H₂₀N₂O₂: 320.1525. Found: 320.1518.

6.3.3 Toward the *Kopsia* alkaloids



Ketoester 158

A solution of diisopropylamine (8.75 mL, 62.0 mmol, 2.00 equiv) in toluene (72 mL) was cooled to $-78\text{ }^{\circ}\text{C}$. *n*-Butyllithium (1.9 M in hexanes, 32.6 mL, 61.9 mmol, 2.00 equiv) was added to the cooled solution. The mixture was warmed to $0\text{ }^{\circ}\text{C}$ for 10 min, and subsequently cooled to $-78\text{ }^{\circ}\text{C}$. A solution of cyclohexenone (**1**) (3.00 mL, 31.0 mmol, 1 equiv) in toluene (18 mL) was added to the cooled solution of lithium diisopropylamide. After 30 min, allyl chloroformate (**157**) (3.30 mL, 31.0 mmol, 1.00 equiv) was added dropwise. The reaction mixture was allowed to warm to $23\text{ }^{\circ}\text{C}$. After 1 h, excess lithium diisopropylamide was quenched with aqueous potassium bisulfate solution (1 N, 50 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate ($2 \times 100\text{ mL}$). The combined organic phases were washed with saturated aqueous sodium chloride solution (100 mL), the washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (9% ethyl acetate–toluene), to give the title compound **158** (3.23 g, 58%) as a colourless oil. Alternatively, the crude residue can be purified by vacuum distillation ($95\text{--}100\text{ }^{\circ}\text{C}/7.5\text{ mbar}$), to yield a mixture of the keto-enol tautomers ($\sim 1:1$), which equilibrates to the keto-form over time.

TLC (12.5% ethyl acetate–hexanes): $R_f = 0.28$ (KMnO_4 , UV)

^1H NMR (400 MHz, CDCl_3): δ 11.96³ (s, 0.25H), 7.00⁴ (dt, $J = 8.6, 3.7\text{ Hz}$, 0.75H), 6.36* (dt, $J = 9.3, 4.5\text{ Hz}$, 0.25H), 6.07' (dt, $J = 10.3, 2.0\text{ Hz}$, 0.75H), 5.96–6.02* (m, 0.25H), 5.86–5.96 (m, 1H), 5.21–5.37 (m, 2H), 4.66 (ddt, $J = 5.7, 4.3, 1.5\text{ Hz}$, 2H), 3.44' (dd, $J = 9.4, 5.2\text{ Hz}$, 0.75H), 2.18–2.56 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.7', 172.0*, 169.7', 166.2*, 150.6', 139.4*, 132.1*, 131.8', 129.1', 123.9*, 118.5', 117.9*, 94.0*, 65.8', 64.8*, 53.4', 25.7', 24.3', 23.5*, 19.4*.

³ * denotes the enol-tautomer.

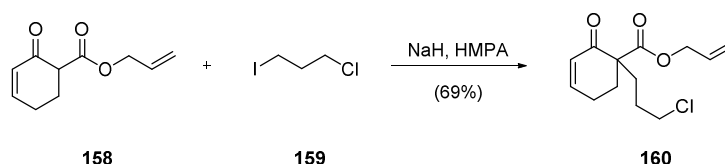
⁴ ' denotes the keto-tautomer.

^1H NMR (400 MHz, $\text{CDCl}_3 + \text{D}_2\text{O}$): δ 7.00 (dt, $J = 10.3, 3.8$ Hz, 1H), 6.07 (dt, $J = 10.3, 2.0$ Hz, 1H), 5.91 (ddt, $J = 17.4, 10.7, 5.6$ Hz, 1H), 5.21–5.37 (m, 2H), 4.66 (ddt, $J = 5.7, 4.3, 1.5$ Hz, 2H), 3.44 (dd, $J = 9.9, 4.9$ Hz, 1H), 2.18–2.56 (m, 4H).

^{13}C NMR (100 MHz, $\text{CDCl}_3 + \text{D}_2\text{O}$): δ 193.7, 169.6, 150.6, 131.7, 129.1, 118.5, 65.7, 53.4, 25.6, 24.3.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$ cm^{-1} : 2940 (w), 1739 (s), 1680 (vs), 1656 (m), 1308 (m), 1232 (vs), 1165 (m).

HRMS (EI): Calcd for $\text{C}_{10}\text{H}_{12}\text{O}_3$: 180.0786. Found: 180.0793.



Chloride **160**

Sodium hydride (60% suspension, 24.4 mg, 0.610 mmol, 1.10 equiv) was suspended in tetrahydrofuran (9.2 mL) at 23 °C and hexamethylphosphoric triamide (0.116 mL, 0.666 mmol, 1.20 equiv) was added to the resulting suspension. The mixture was cooled to 0 °C and a solution of the ketoester **158** (100 mg, 0.555 mmol, 1 equiv) in tetrahydrofuran (1.2 mL), was added dropwise. After the addition was complete, the mixture was allowed to warm to 23 °C. After 3 h, 1-chloro-3-iodopropane (**159**) (0.238 mL, 2.22 mmol, 4.00 equiv) was added in one portion and stirring was continued for 21 h. The reaction mixture was diluted with ethyl acetate (30 mL) and excess sodium hydride was quenched by the addition of water (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with water (10 mL) and saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate–hexanes), to give the title compound **160** (99 mg, 69%) as a colourless liquid.

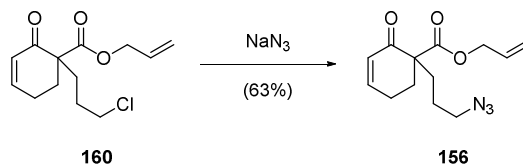
TLC (17% ethyl acetate–hexanes): $R_f = 0.47$ (KMnO_4 , UV)

^1H NMR (600 MHz, CDCl_3): δ 6.91 (app dddd, $J = 10.1, 4.8, 3.2, 1.0$ Hz, 1H), 6.04 (ddd, $J = 10.1, 2.5, 1.7$ Hz, 1H), 5.86 (ddt, $J = 17.2, 10.5, 5.6$ Hz, 1H), 5.21–5.31 (m, 2H), 4.57–4.64 (m, 2H), 3.50–3.57 (m, 2H), 2.46–2.55 (m, 2H), 2.33–2.40 (m, 1H), 2.00–2.06 (m, 1H), 1.88–1.99 (m, 2H), 1.73–1.87 (m, 2H).

^{13}C NMR (150 MHz, CDCl_3): δ 195.7, 171.0, 149.3, 131.5, 129.1, 118.6, 65.8, 56.5, 45.0, 31.2, 30.2, 27.9, 23.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$ cm^{-1} : 2955 (w), 1727 (vs), 1677 (vs), 1386 (m), 1245 (s), 1188 (s), 1173 (s).

HRMS (EI): Calcd for $\text{C}_{13}\text{H}_{17}^{35}\text{Cl}_1\text{O}_3$: 256.0866. Found: 256.0869.



Azide **156**

Sodium azide (124 mg, 1.91 mmol, 5.00 equiv) was added to a solution of chloride **160** (98.0 mg, 0.382 mmol, 1 equiv) in *N,N*-dimethylformamide (2 mL) and the resulting suspension was heated to 80 °C. After 3 h, the reaction mixture was diluted with ethyl acetate (15 mL) and washed with water (4 × 10 mL). The aqueous layer was extracted with diethyl ether (2 × 25 mL). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (12.5% ethyl acetate–hexanes), to give the title compound **156** (64 mg, 63%) as a yellow oil.

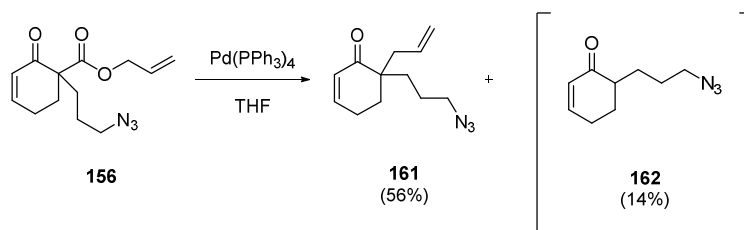
TLC (12.5% ethyl acetate–hexanes): R_f = 0.31 (KMnO_4 , UV)

^1H NMR (600 MHz, CDCl_3): δ 6.91 (app dddd, J = 10.1, 4.7, 3.1, 1.0 Hz, 1H), 6.05 (ddd, J = 10.1, 2.5, 1.6 Hz, 1H), 5.86 (ddt, J = 17.2, 10.4, 5.7 Hz, 1H), 5.20–5.32 (m, 2H), 4.60 (m, 2H), 3.29 (t, J = 6.8 Hz, 2H), 2.44–2.56 (m, 2H), 2.30–2.40 (m, 1H), 1.92–2.01 (m, 1H), 1.78–1.87 (m, 2H), 1.49–1.72 (m, 2H).

^{13}C NMR (150 MHz, CDCl_3): δ 195.7, 171.0, 149.4, 131.5, 129.1, 118.7, 65.8, 56.6, 51.5, 30.9, 30.3, 24.2, 23.6.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$ cm^{-1} : 2931 (w), 2094 (vs), 1729 (s), 1680 (s), 1245 (m), 1184 (s), 989 (w).

HRMS (ESI): Calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 286.1168. Found: 286.1165.



Enone 161

A solution of azide **156** (500 mg, 1.90 mmol, 1 equiv) in degassed tetrahydrofuran (23 mL) was added to $\text{Pd(PPh}_3)_4$ (219 mg, 0.190 mmol, 0.100 equiv) in a Schlenk tube and the resulting solution was heated to 40 °C. After 50 min, the solution was allowed to cool to 23 °C. The suspension was filtered through a pad of silica gel, the filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (20% diethyl ether–hexanes), to give **161** (233 mg, 56%) as a yellow oil. Additionally, the deallylated product **162** (47 mg, 14 %) was isolated as a colourless liquid.

TLC (20% diethyl ether–hexanes): R_f = 0.40 (KMnO_4 , UV)

^1H NMR (600 MHz, CDCl_3): δ 6.87 (dt, J = 10.1, 4.0 Hz, 1H), 5.92 (dt, J = 10.0, 2.1 Hz, 1H), 5.70 (ddt, J = 16.9, 10.2, 7.4 Hz, 1H), 5.04–5.10 (m, 2H), 3.24 (t, J = 6.4 Hz, 2H), 2.39 (dt, J = 6.0, 4.0, 2.1 Hz, 2H), 2.34 (ddt, J = 14.0, 7.2, 1.2 Hz, 1H), 2.23 (ddt, J = 14.0, 7.6, 1.2 Hz, 1H), 1.90 (t, J = 6.1 Hz, 2H), 1.61–1.67 (m, 1H), 1.46–1.61 (m, 3 H).

^{13}C NMR (150 MHz, CDCl_3): δ 202.5, 148.6, 133.6, 128.7, 118.3, 51.9, 47.2, 38.9, 31.3, 30.7, 23.4, 22.9.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$ cm^{-1} : 2930 (w), 2093 (vs), 1600 (s), 1386 (w), 1260 (w), 1220 (w), 915 (w).

HRMS (DCI): Calcd for $\text{C}_{12}\text{H}_{18}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 220.1450. Found: 220.2.

Azide 162

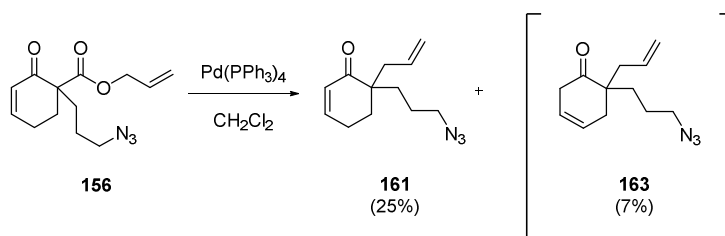
TLC (10% diethyl ether–toluene): R_f = 0.49 (KMnO_4 , UV)

^1H NMR (600 MHz, CDCl_3): δ 6.89–6.97 (m, 1H), 5.98 (dt, J = 10.1, 2.0 Hz, 1H), 3.30 (app dt, J = 6.8, 1.4 Hz, 2H), 2.35–2.47 (m, 2H), 2.25–2.35 (m, 1H), 2.06–2.16 (m, 1H), 1.72–1.95 (m, 2H), 1.66 (app dq, J = 8.9, 6.8 Hz, 2H), 1.40–1.53 (m, 1H).

^{13}C NMR (150 MHz, CDCl_3): δ 201.2, 149.5, 129.5, 51.5, 46.1, 28.1, 26.6, 26.4, 25.2.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\max}$ cm^{-1} : 2929 (w), 2863 (w), 2093 (vs), 1674 (s), 1387 (w), 1255 (w), 1221 (w).

MS (DCI): Calcd for $\text{C}_9\text{H}_{14}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 180.1137. Found: 180.2.



Enone **161**

A solution of azide **156** (70.0 mg, 0.266 mmol, 1 equiv) in dichloromethane (1.7 mL) was added to a solution of $\text{Pd}(\text{PPh}_3)_4$ (30.7 mg, 26.6 μmol , 0.100 equiv) in dichloromethane (1 mL). The resulting solution was stirred at 23 °C for 3.5 h, after which the reaction mixture was filtered through a pad of silica gel/Celite (dichloromethane rinse). The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (20% diethyl ether–hexanes), to give **161** (15 mg, 25%), the olefin **163** (4 mg, 7%) as a light yellow oil, and recovered starting material **156** (24 mg, 34%).

Olefin **163**

TLC (10% ethyl acetate–hexanes): R_f = 0.33 (KMnO_4)

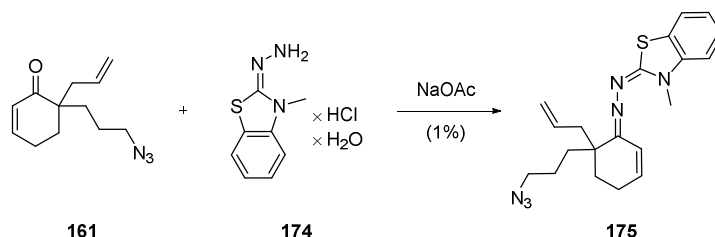
^1H NMR (600 MHz, CDCl_3): δ 5.71–5.79 (m, 2H), 5.63–5.70 (m, 1H), 5.05–5.11 (m, 2H), 3.22–3.31 (m, 2H), 2.90 (dt, J = 3.3, 2.0 Hz, 2H), 2.27–2.43 (m, 4H), 1.69–1.76 (m, 1H), 1.56–1.62 (m, 2H), 1.37–1.45 (m, 1H).

^{13}C NMR (150 MHz, CDCl_3): δ 211.8, 133.3, 125.2, 123.7, 118.5, 51.8, 50.0, 39.1, 38.5, 36.4, 31.4, 23.5.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\max}$ cm^{-1} : 2930 (w), 2096 (vs), 1709 (s), 1259 (w), 919 (w), 671(w).

MS (DCI): Calcd for $\text{C}_{12}\text{H}_{18}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 220.1450. Found: 220.

6.3.4 Miscellaneous compounds



Hydrazone **175**

A solution of 3-methyl-2-benzothiazolinone hydrazone hydrochloride hydrate (**174**) (157 mg, 0.730 mmol, 2.00 equiv) and sodium acetate (59.9 mg, 0.730 mmol, 2.00 equiv) in ethanol (1 mL) was heated to reflux. After 40 min, a solution of **161** (80.0 mg, 0.365 mmol, 1 equiv) in ethanol (1 mL) was added to the suspension and heating was continued. The resulting solution turned dark red within 3 min. After 1 h, the reaction mixture was diluted with dichloromethane (5 mL) and the resulting solution was concentrated. The residue was dissolved in dichloromethane (5 mL) and washed with saturated aqueous sodium bicarbonate solution (5 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (1% diethyl ether–toluene), to give the compound **175** (1.3 mg, 1%) as a brown solid.

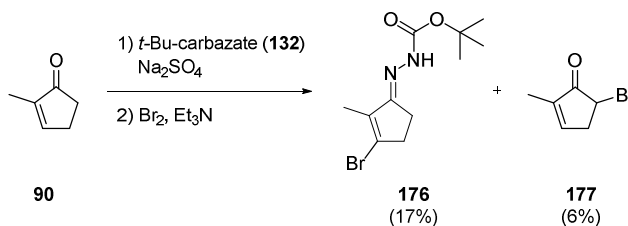
TLC (2.5% diethyl ether–toluene): $R_f = 0.56$ (KMnO_4 , UV)

^1H NMR (600 MHz, CDCl_3): δ 7.37–7.41 (m, 1H), 7.24 (dd, $J = 7.8, 0.9$ Hz, 1H), 7.08 (dt, $J = 10.6, 2.1$ Hz, 1H), 7.03 (td, $J = 7.6, 0.9$ Hz, 1H), 6.97 (d, $J = 8.0$ Hz, 1H), 6.26 (dt, $J = 10.2, 3.9$ Hz, 1H), 5.91 (ddt, $J = 17.4, 10.2, 7.3$ Hz, 1H), 5.05–5.11 (m, 2H), 3.59 (s, 3H), 3.27 (td, $J = 6.9, 1.4$ Hz, 2H), 2.48 (ddt, $J = 14.0, 7.2, 1.2$ Hz, 1H), 2.36 (ddt, $J = 14.1, 7.4, 1.2$ Hz, 1H), 2.26–2.31 (m, 2H), 1.70–1.79 (m, 4H), 1.61–1.70 (m, 2H).

^{13}C NMR (150 MHz, CDCl_3): δ 166.3, 159.5, 141.3, 137.1, 135.2, 125.8, 125.0, 122.1, 121.4, 119.6, 117.3, 108.9, 52.4, 41.2, 41.0, 32.8, 31.2, 31.0, 23.5, 23.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$ cm^{-1} : 2927 (w), 2092 (m), 1620 (m), 1601 (s), 1582 (vs), 1546 (s), 1477 (s).

MS (EI): Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_6^{32}\text{S}_1$: 380.1783. Found: 380.1784.



Bromo-hydrazone 176

2-Methylcyclopentenone (**90**) (0.100 mL, 1.02 mmol, 1 equiv) was added to a mixture of sodium sulfate (434 mg, 3.06 mmol, 3.00 equiv), *t*-Bu-carbazate (**132**) (141 mg, 1.07 mmol, 1.05 equiv) and 1,2-dichloroethane (0.69 mL) and the resulting suspension was heated to 85 °C. After 6 h, the mixture was allowed to cool to 23 °C, dichloromethane (2.96 mL) was added and the solution was cooled to –16 °C. Bromine (2 M in dichloromethane, 0.535 mL, 1.07 mmol, 1.05 equiv) was added dropwise at –16 °C, forming a red supernatant. After 10 min, triethylamine (0.566 mL, 4.07 mmol, 4.00 equiv) was added and the resulting orange slurry was allowed to warm to 23 °C. After 1.5 h, the reaction mixture was diluted with dichloromethane (5 mL) and the organic layer was washed with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was extracted with dichloromethane (2 × 10 mL), the combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (dichloromethane initially, grading to 1% methanol–dichloromethane), to give **176** (49 mg, 17%) as an off-white solid and **177** (11 mg, 6%) as a volatile brown oil.

Bromo-hydrazone 176

TLC (dichloromethane): R_f = 0.25 (KMnO₄, UV)

¹H NMR (600 MHz, CDCl₃): δ 7.26–7.28 (br s, NH), 2.85 (dq, J = 7.4, 2.3 Hz, 2H), 2.53–2.56 (m, 1H), 1.90 (t, J = 2.2 Hz, 3H), 1.51 (s, 1H).

¹³C NMR (150 MHz, CDCl₃): δ 158.3, 152.7, 138.4, 134.3, 81.2, 36.5, 28.3, 25.5, 11.1.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\text{max}}$ cm^{–1}: 3201 (w), 2979 (w), 1700 (s), 1530 (m), 1245 (vs), 1162 (vs), 1141 (vs).

MS (EI): Calcd for C₁₁H₁₇N₂O₂⁷⁹Br₁: 288.0473. Found: 288.0462.

Bromide 177

TLC (dichloromethane): $R_f = 0.55$ (KMnO₄, UV)

¹H NMR (600 MHz, CDCl₃): δ 7.28 (tq, $J = 2.8, 1.4$ Hz, 1H), 4.35 (dd, $J = 6.6, 2.1$ Hz, 1H), 3.25 (app dddt, $J = 19.5, 6.6, 5.0, 2.3$ Hz, 1H), 2.86 (ddq, $J = 19.5, 4.8, 2.3$ Hz, 1H), 1.85 (td, $J = 2.3, 1.5$ Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 202.9, 155.1, 139.9, 41.1, 38.2, 10.7.

IR (Diamond-ATR, neat) $\tilde{\nu}_{\max}$ cm⁻¹: 2923 (w), 1711 (vs), 1637 (w), 1432 (w), 1335 (w), 1056 (w), 826 (w).

MS (EI): Calcd for C₆H₇O₁⁷⁹Br₁: 173.9680. Found: 173.9671.

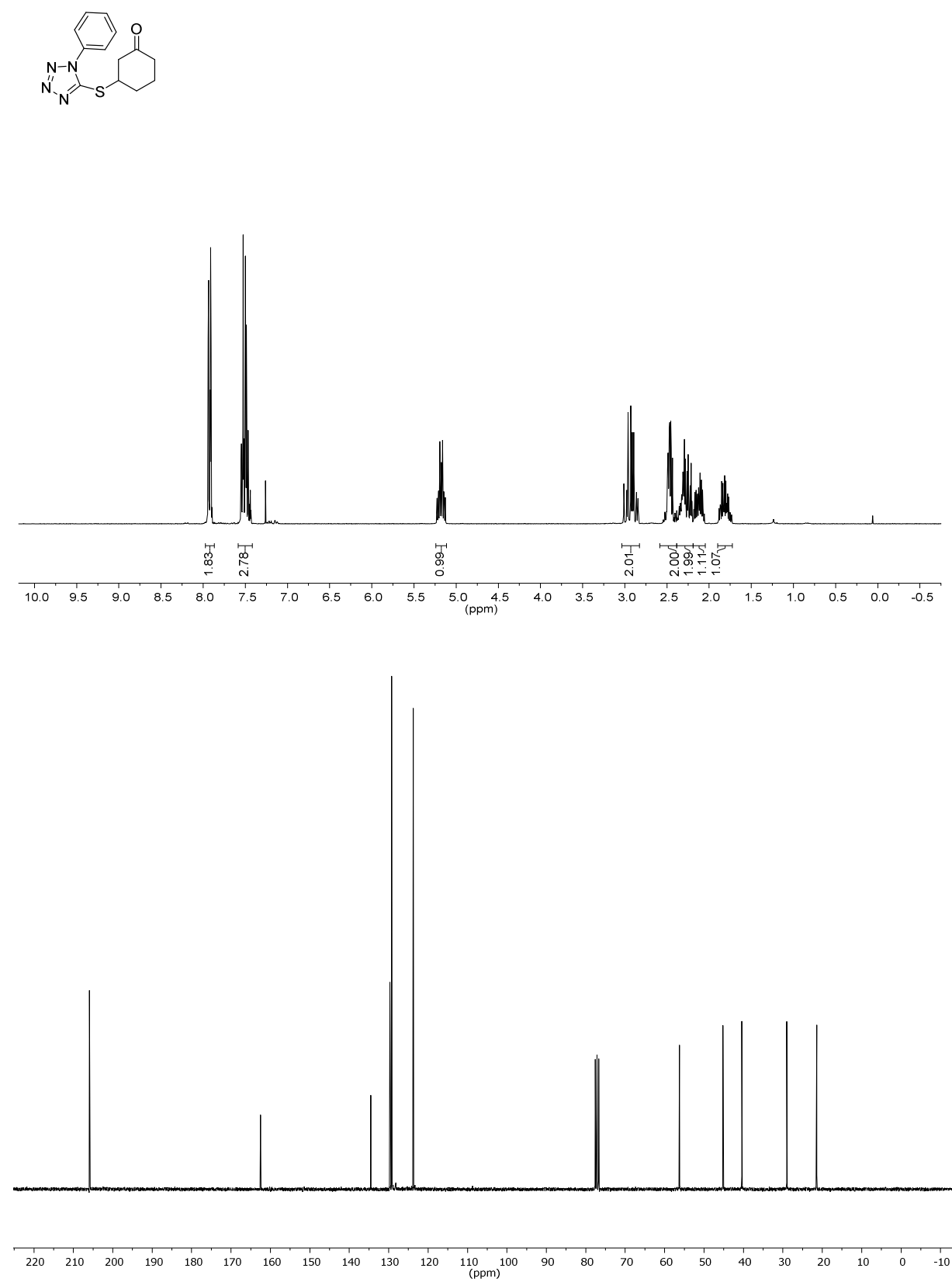
7 Bibliography

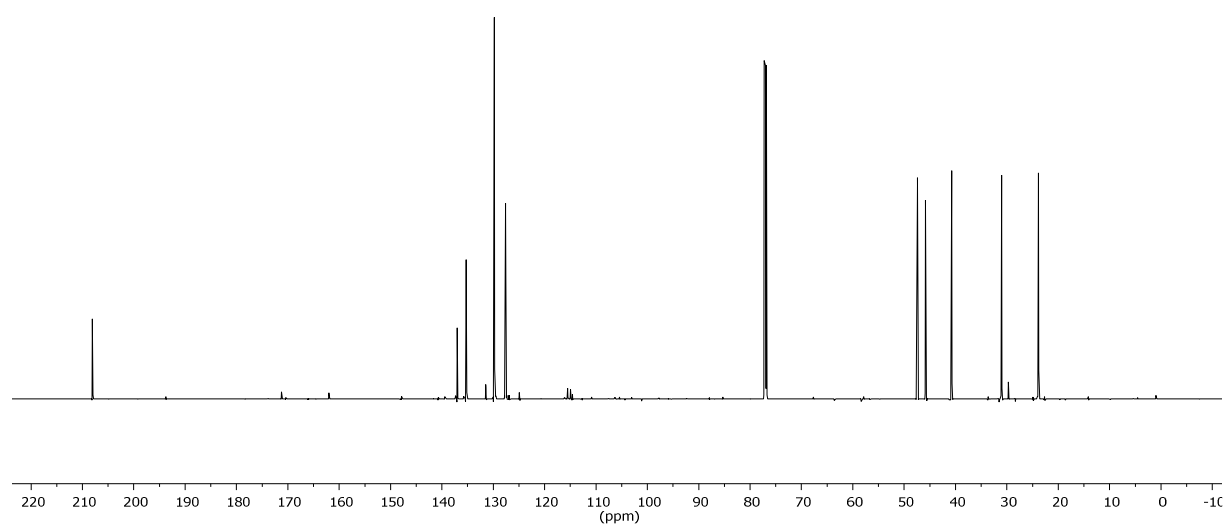
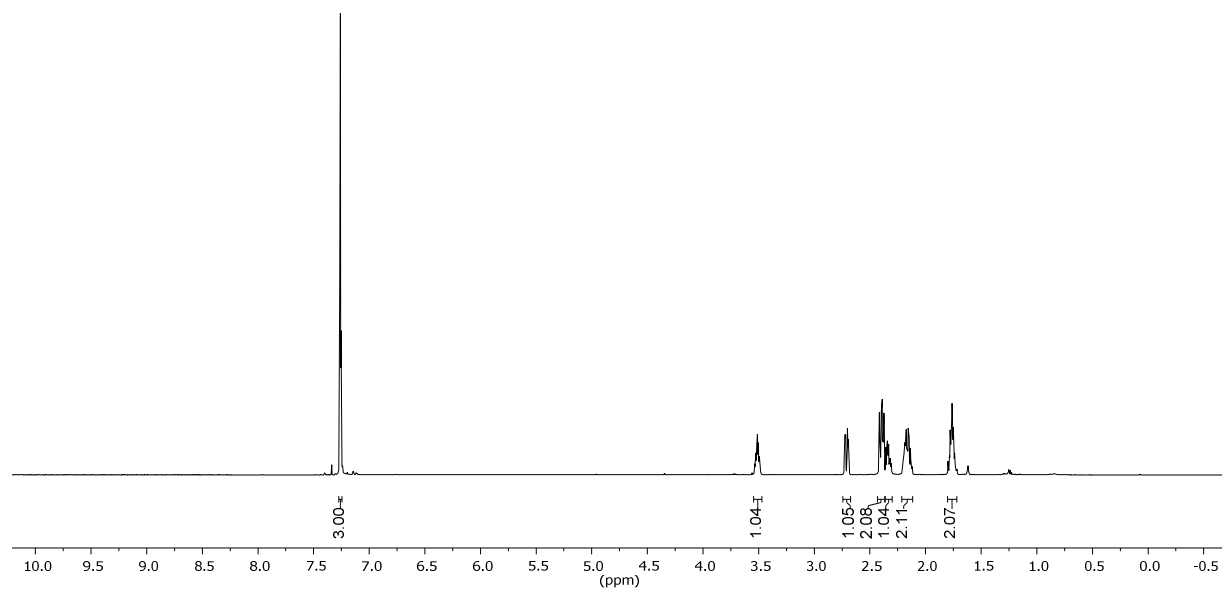
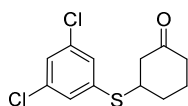
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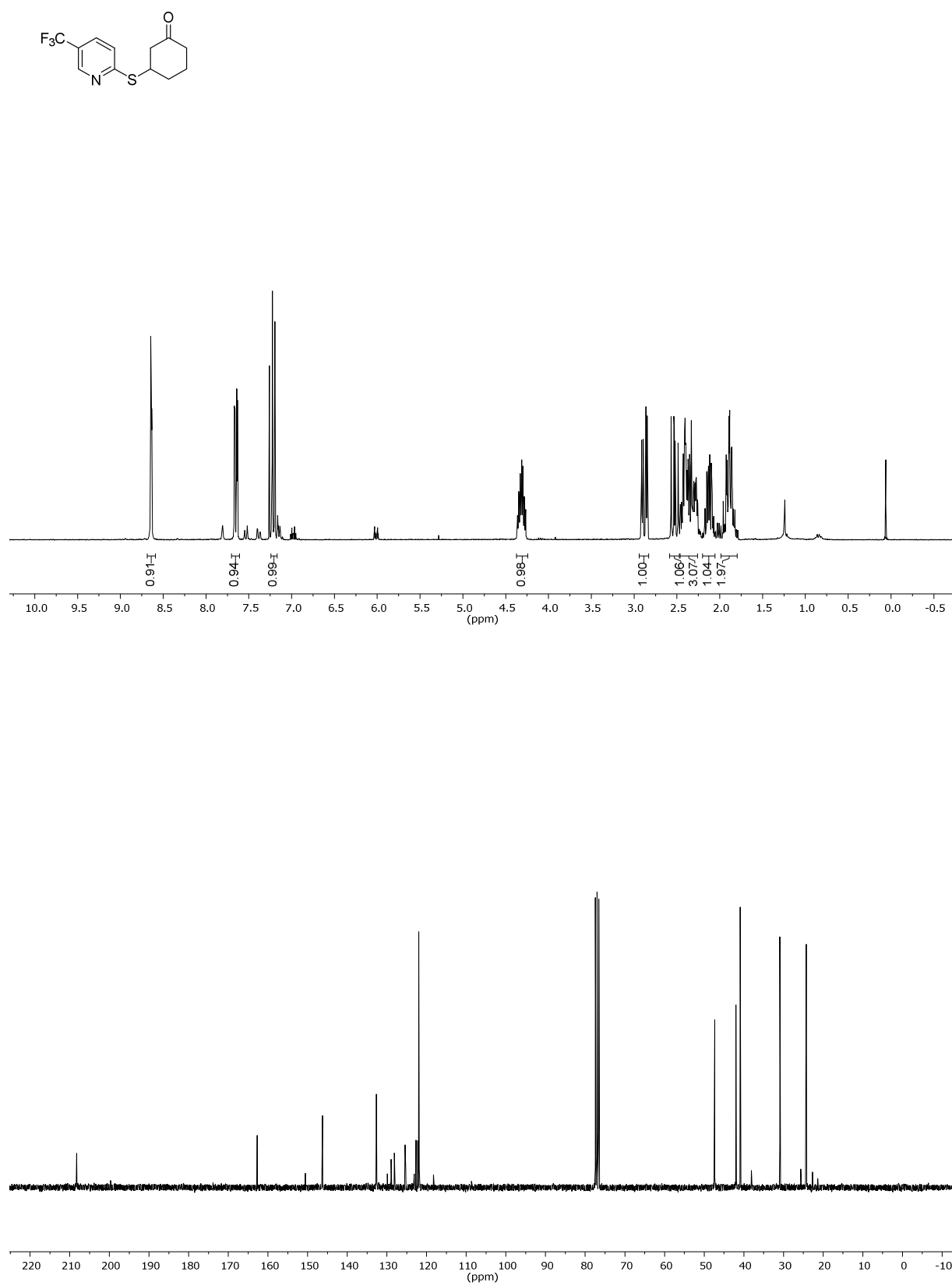
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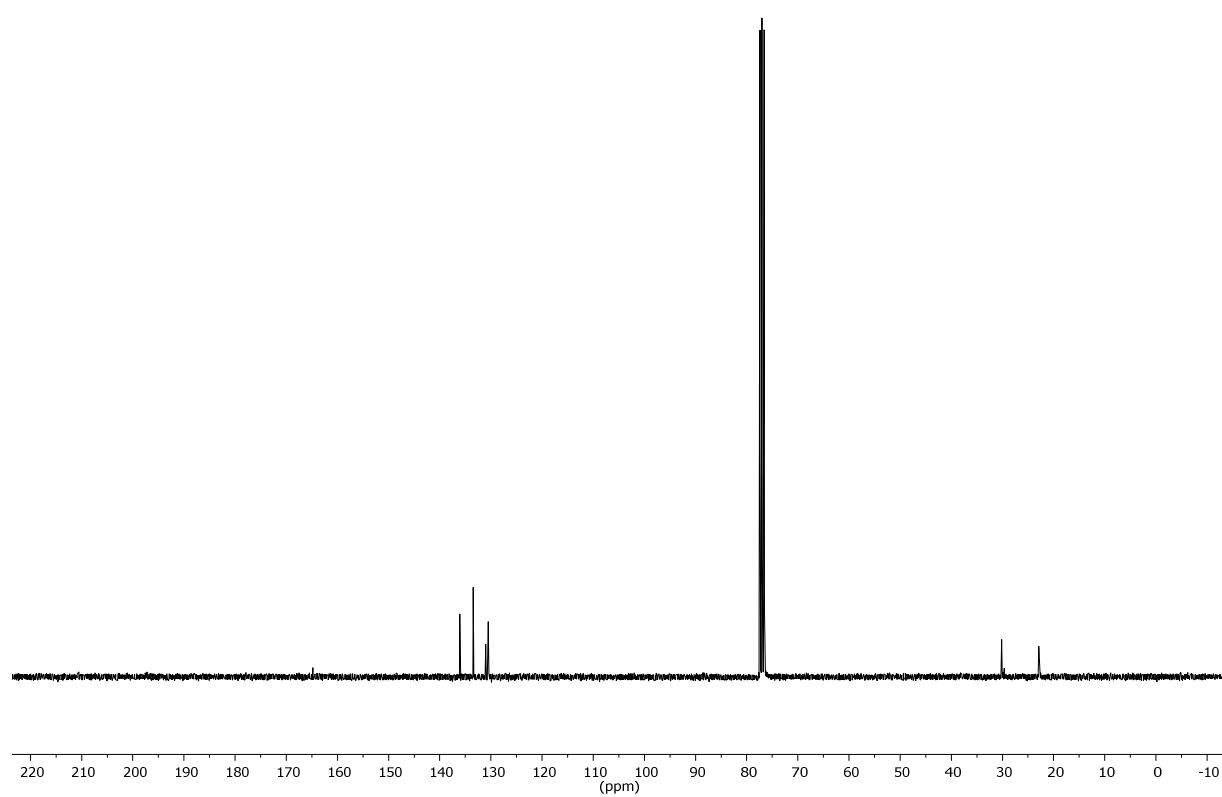
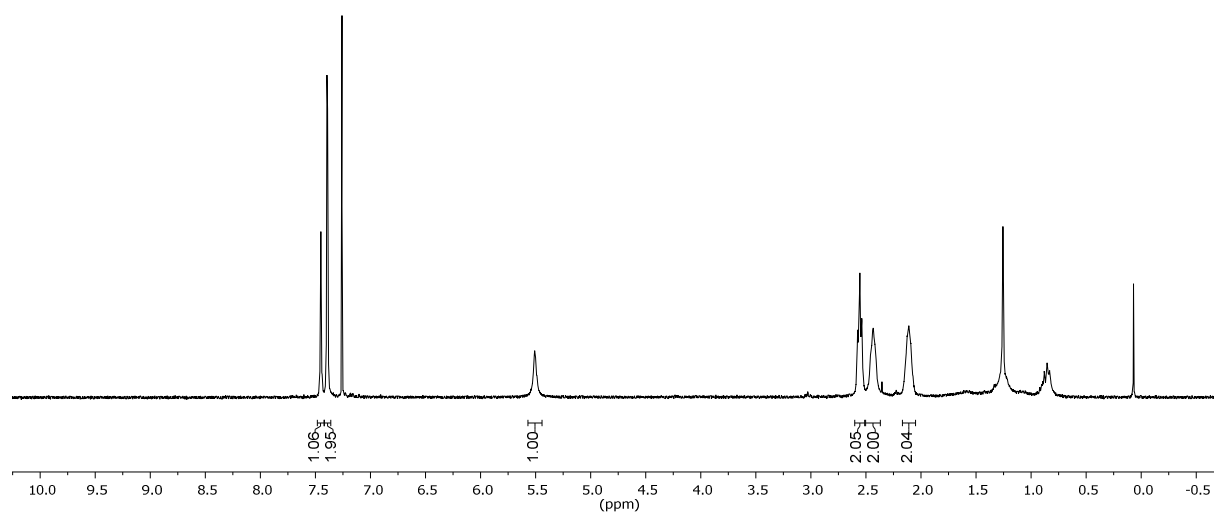
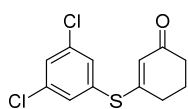
8 Appendix

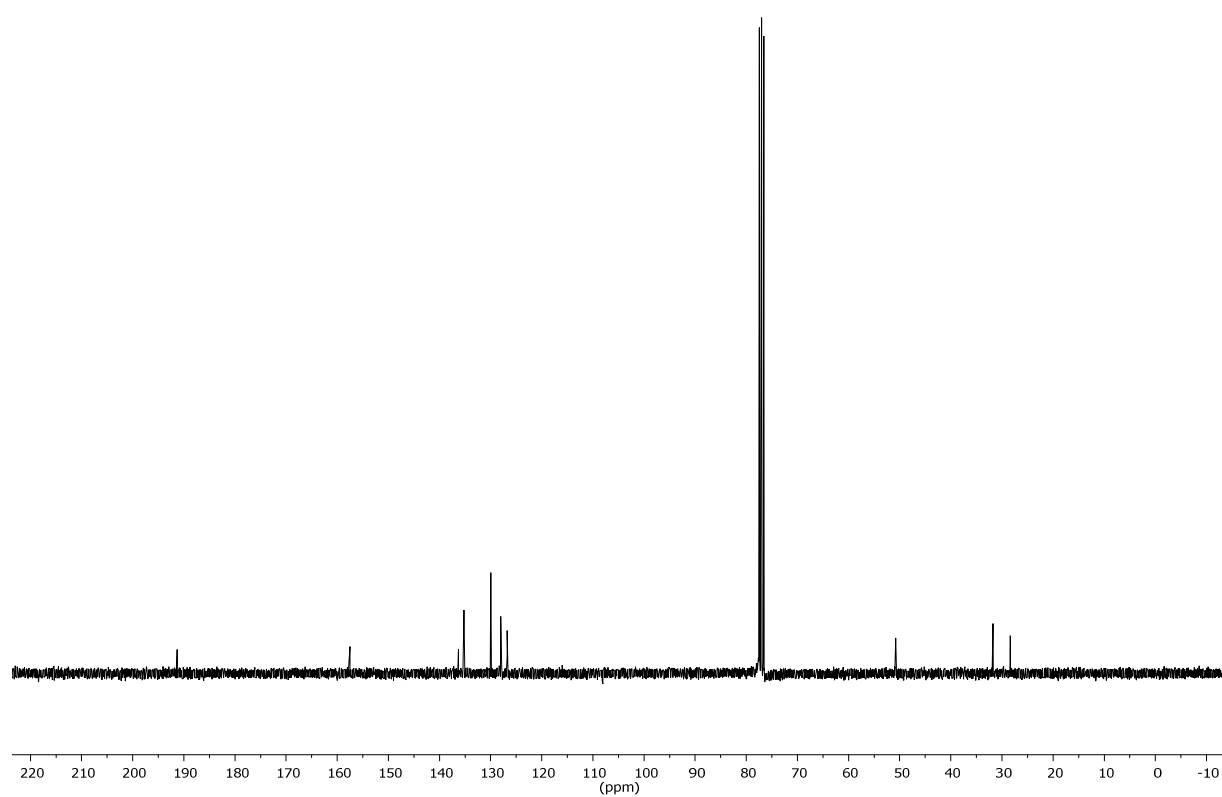
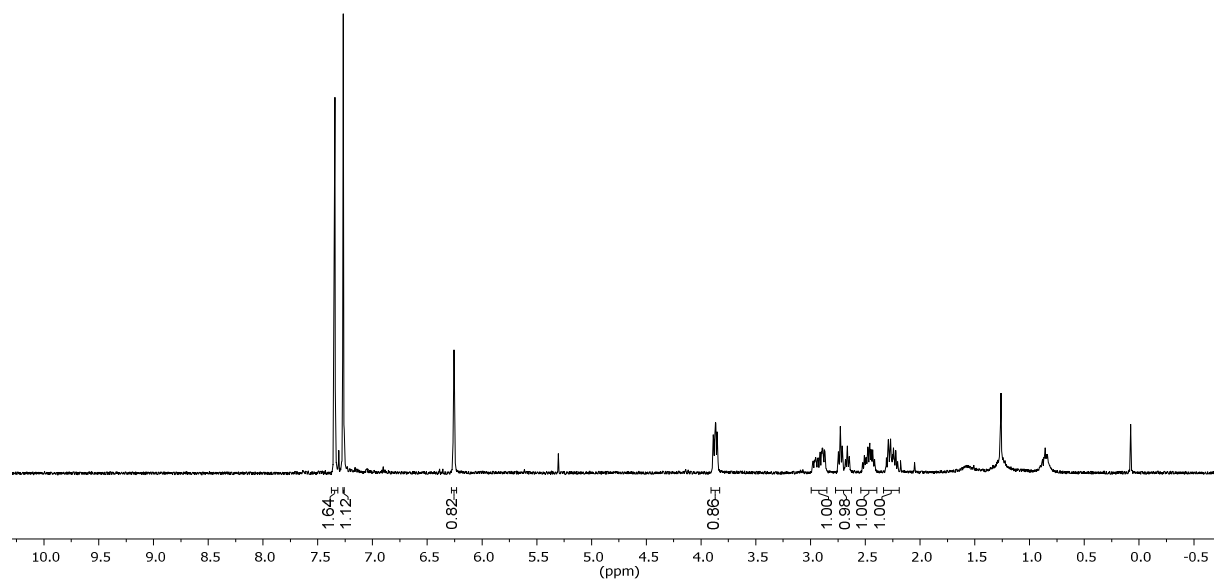
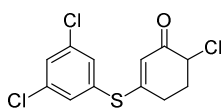
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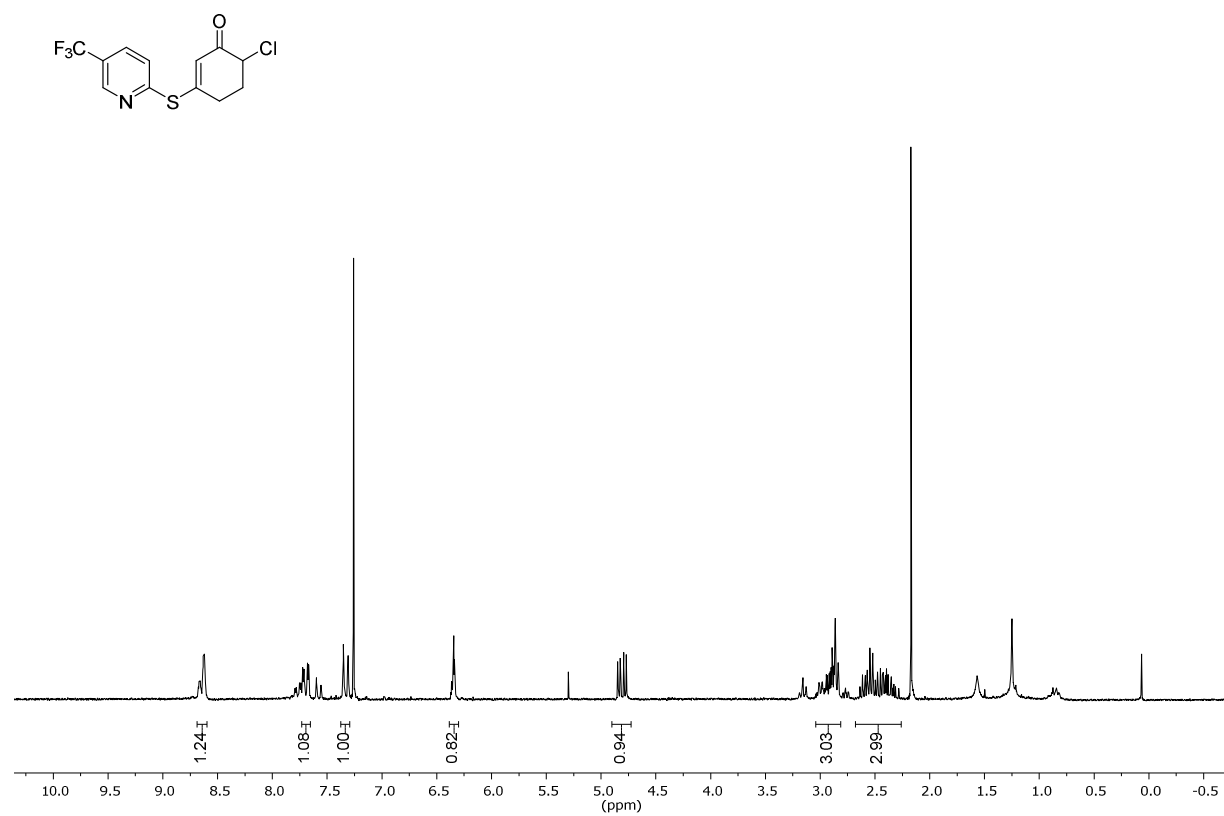


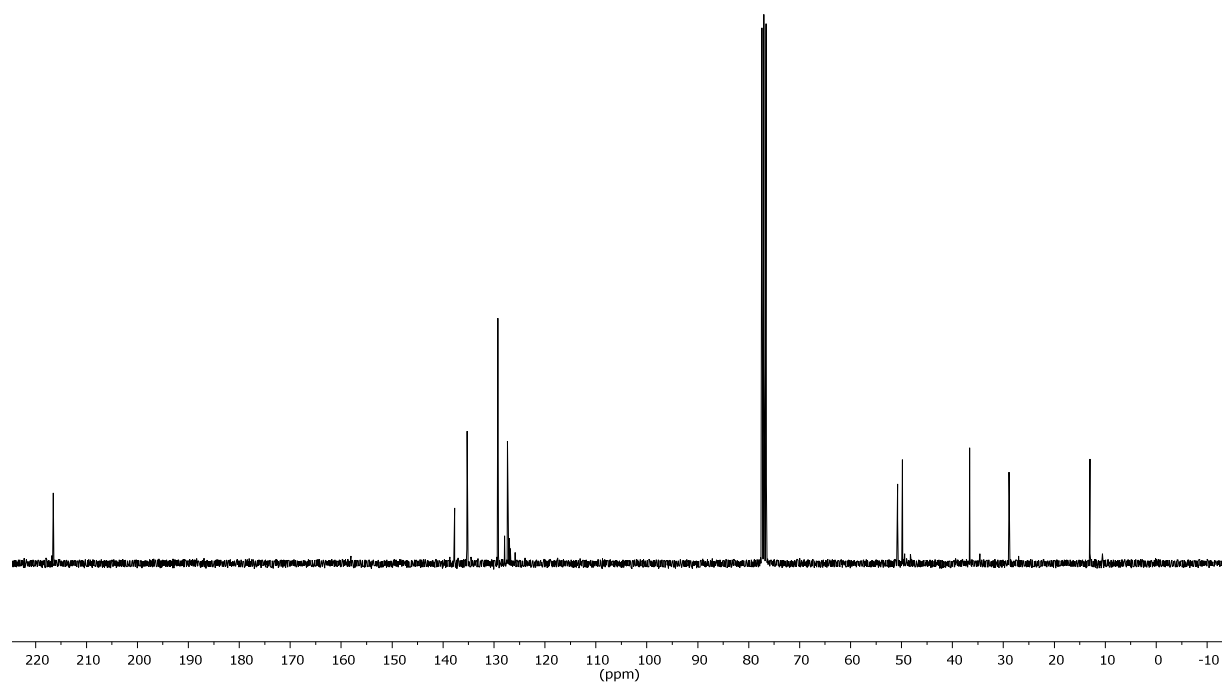
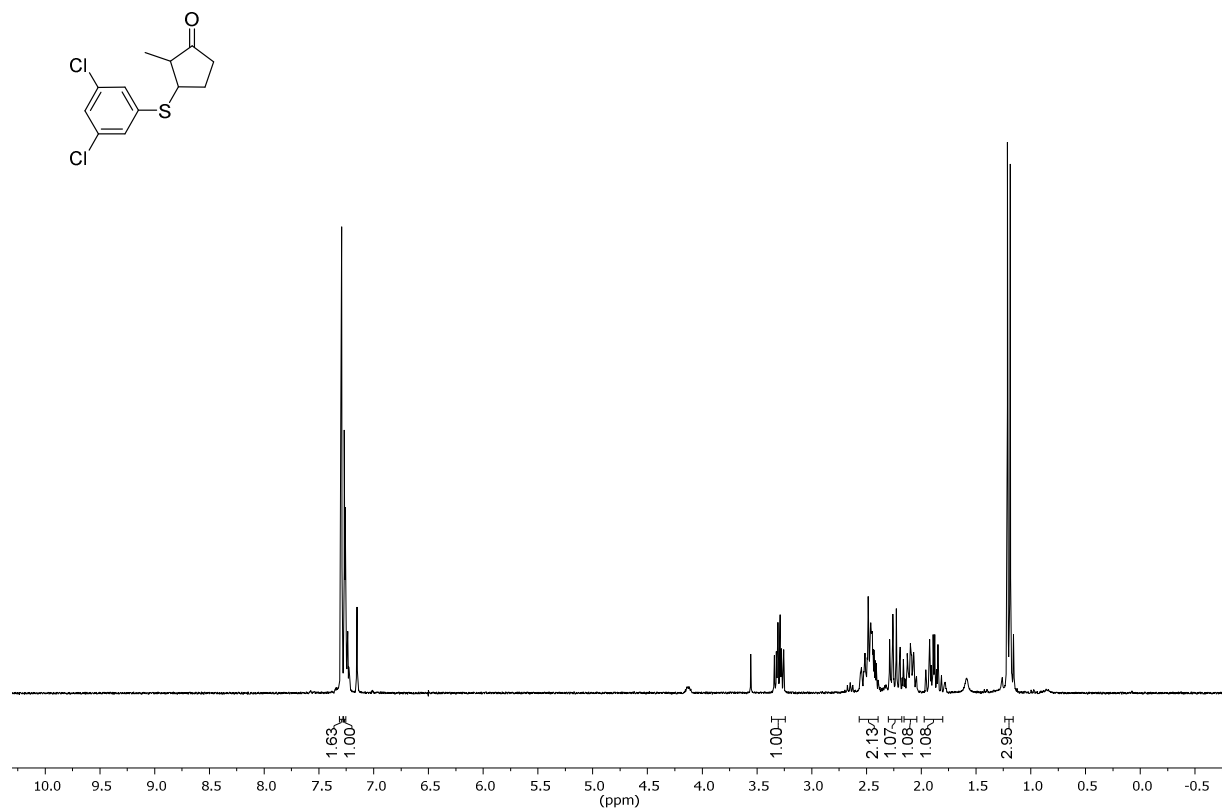


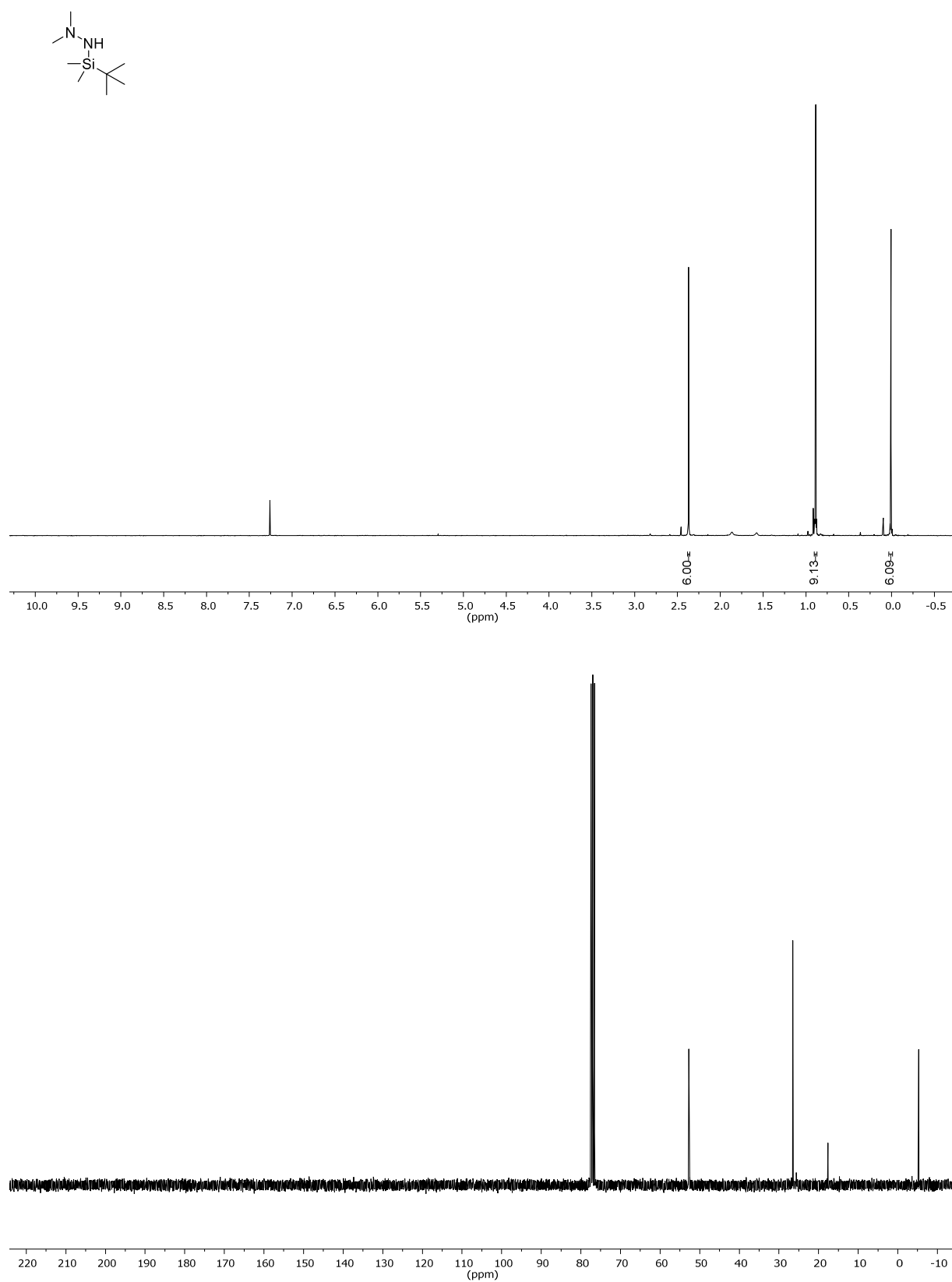


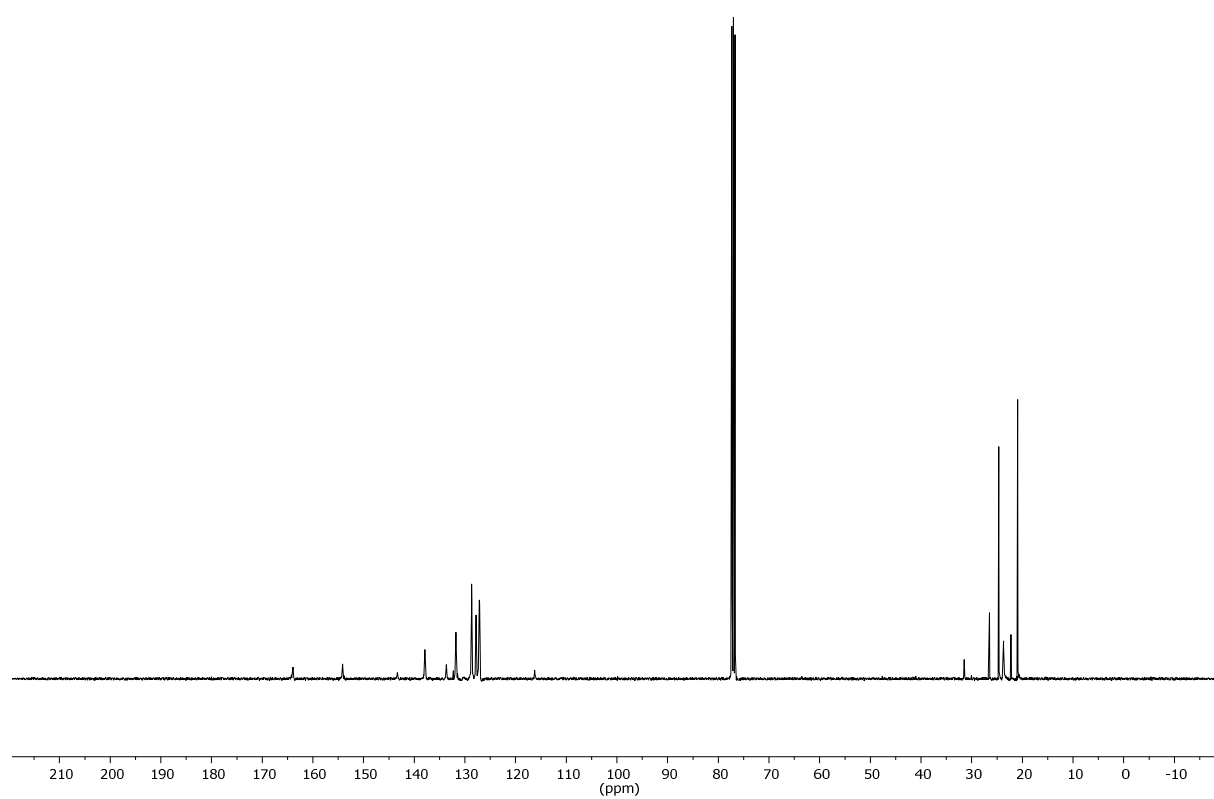
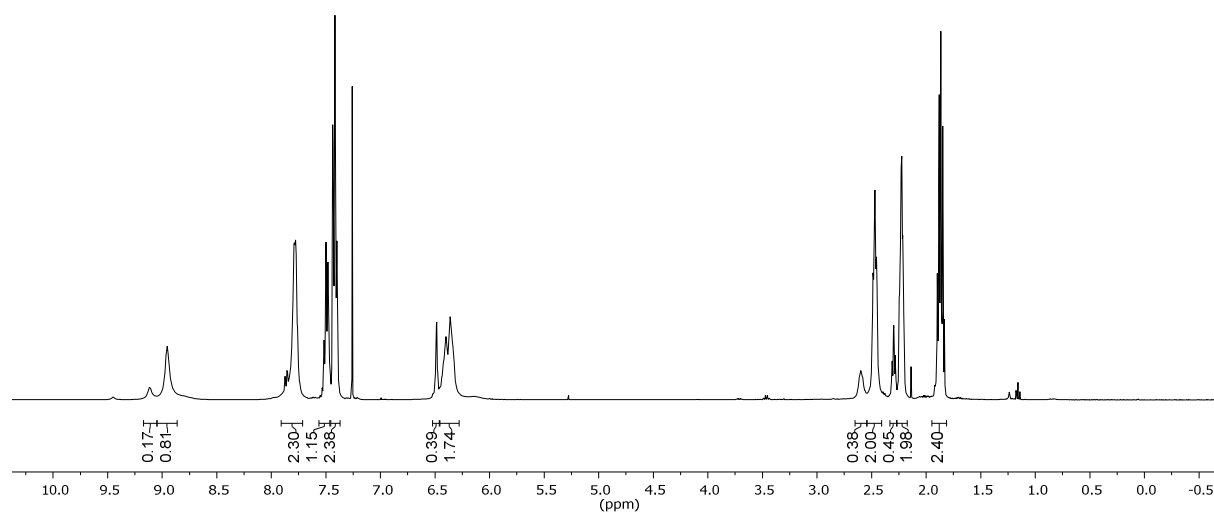
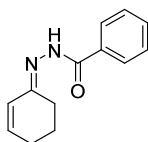


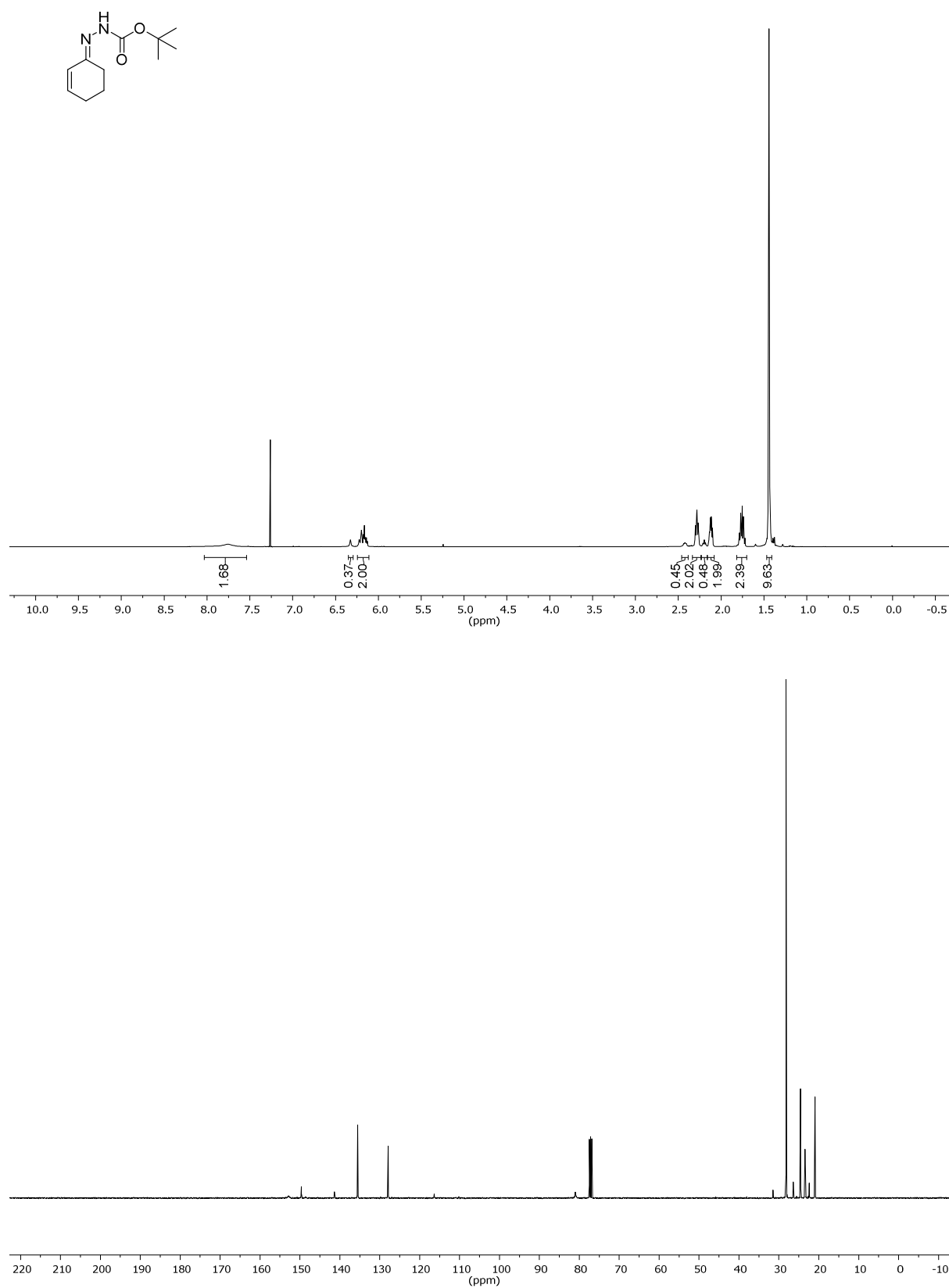


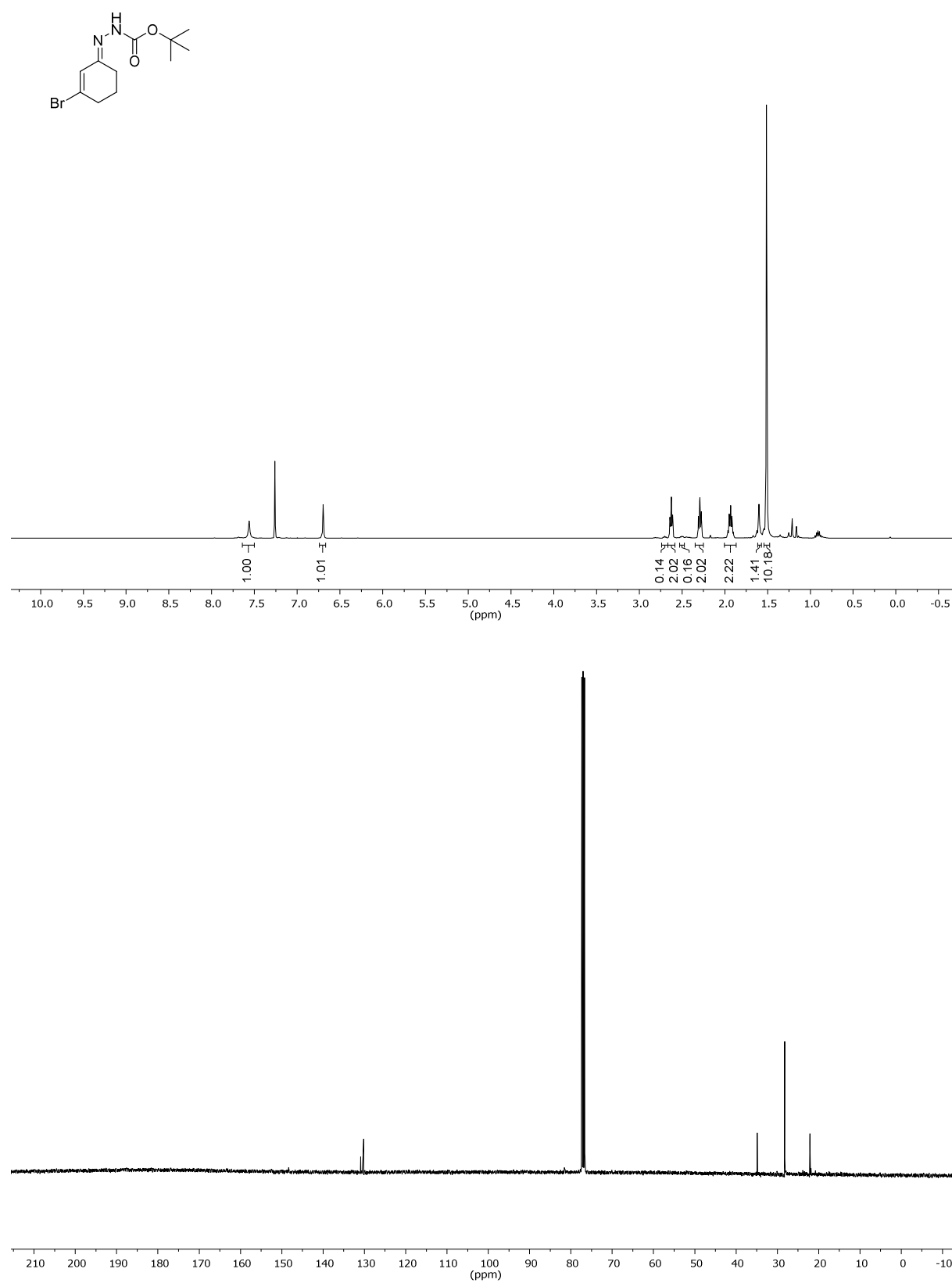


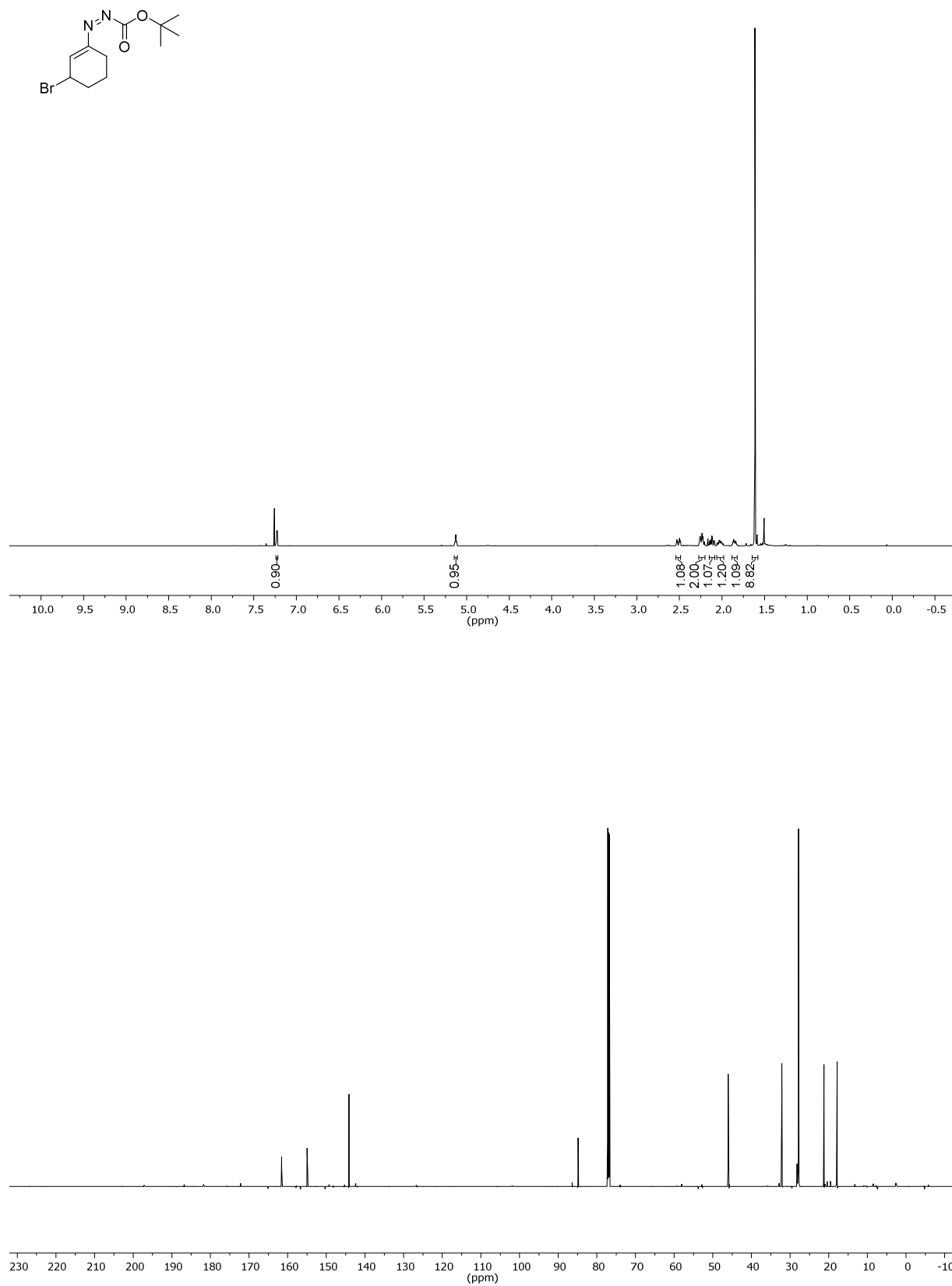


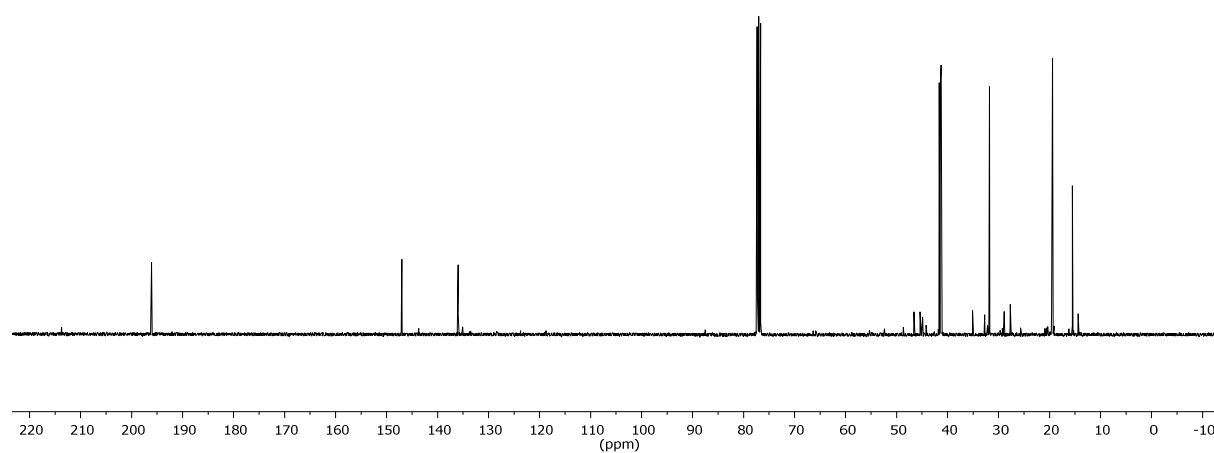
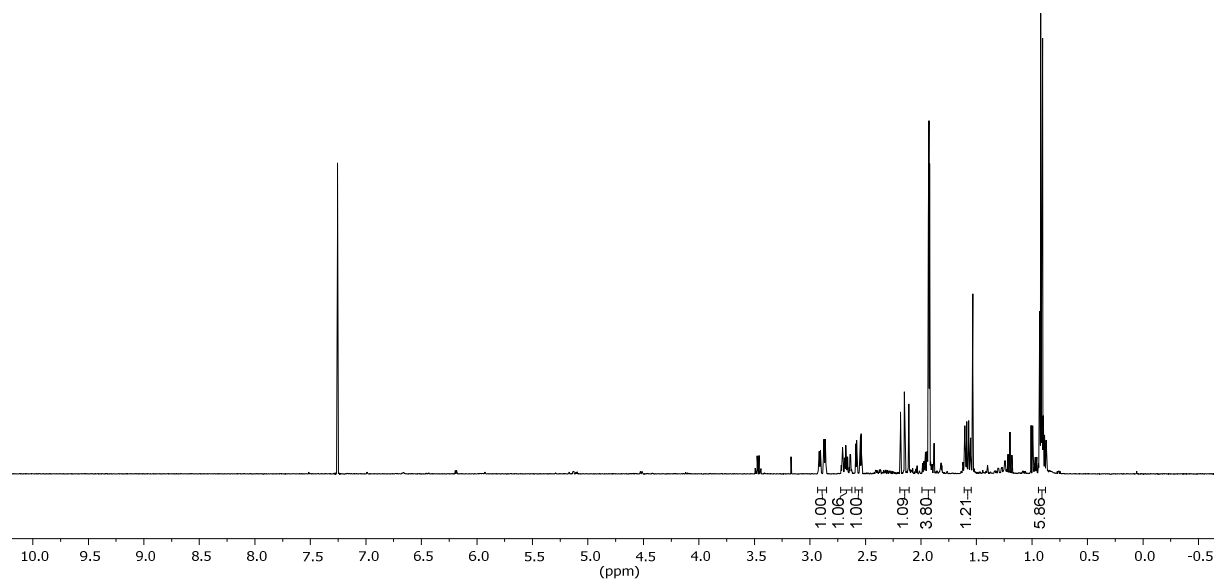
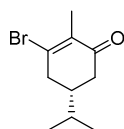


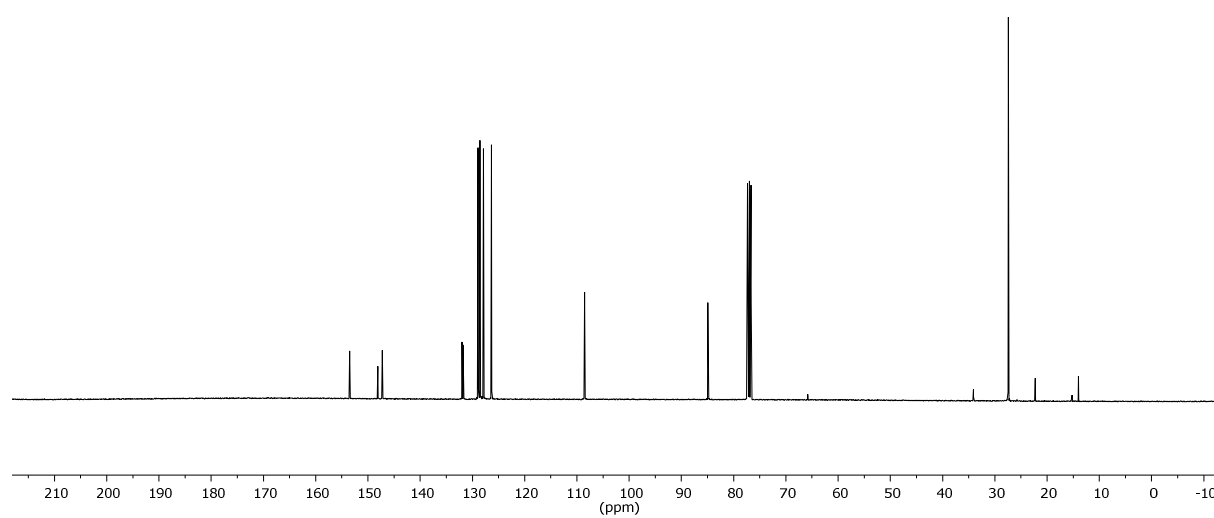
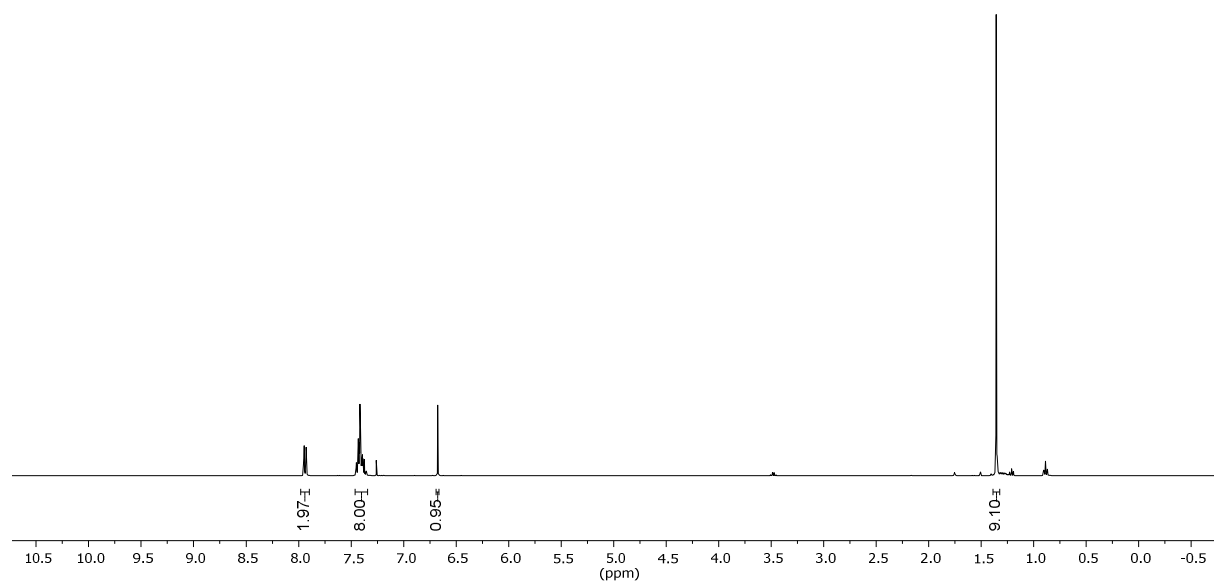
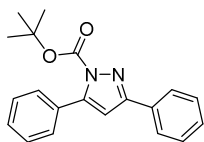


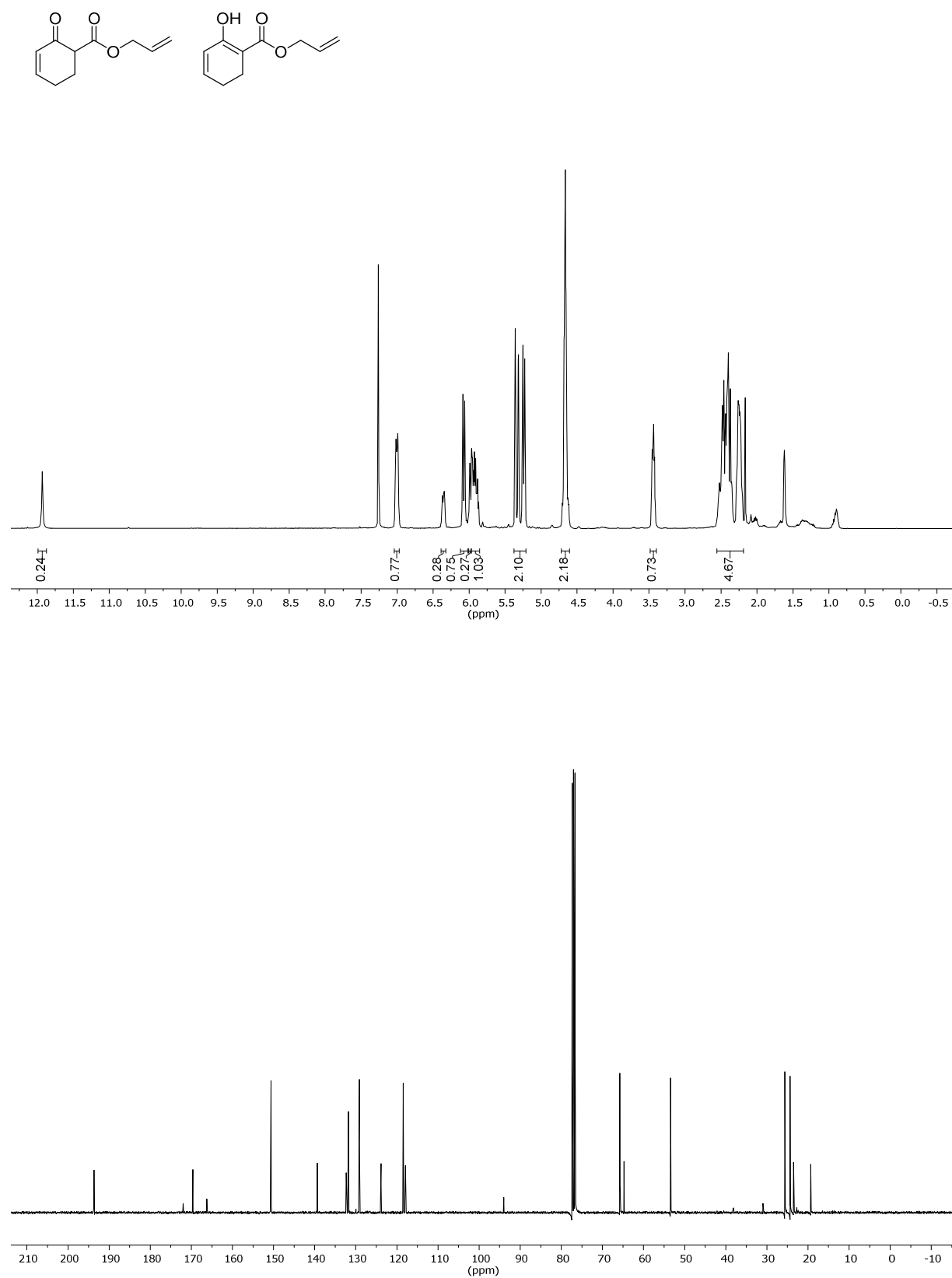


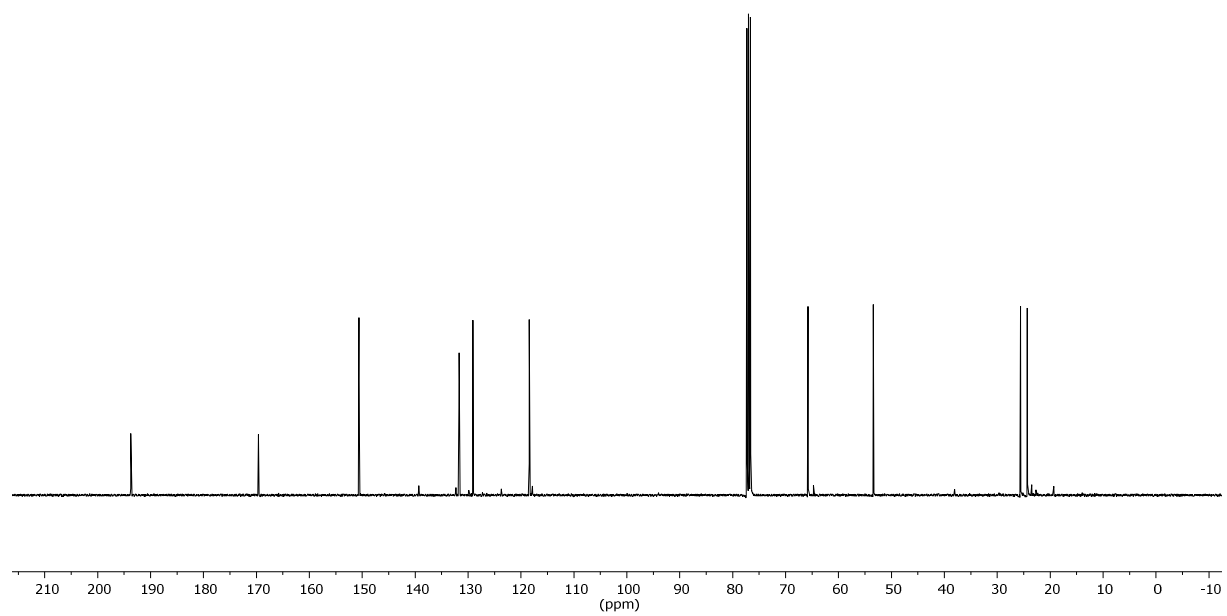
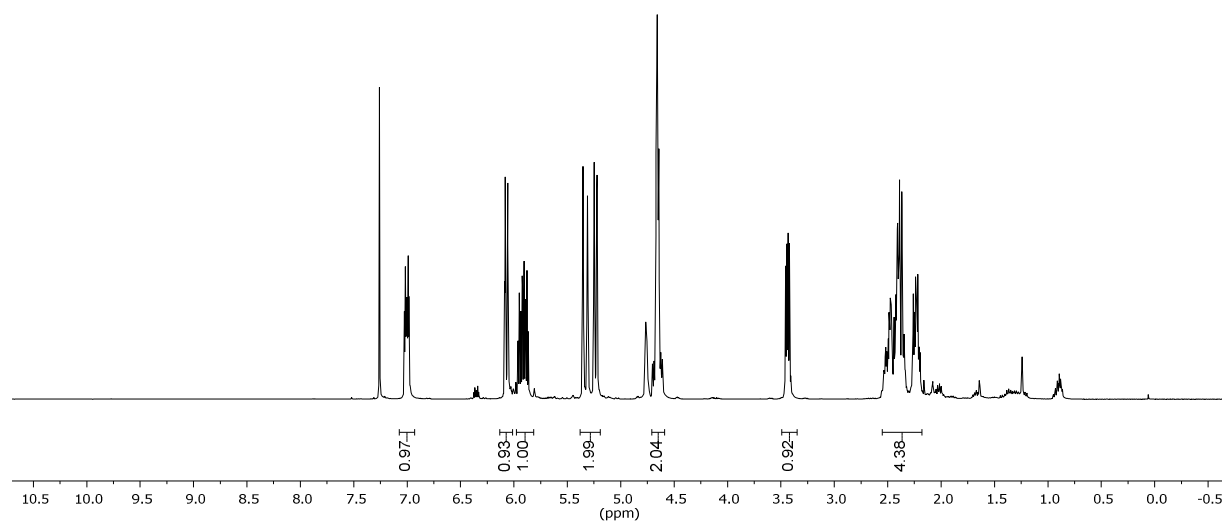
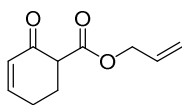


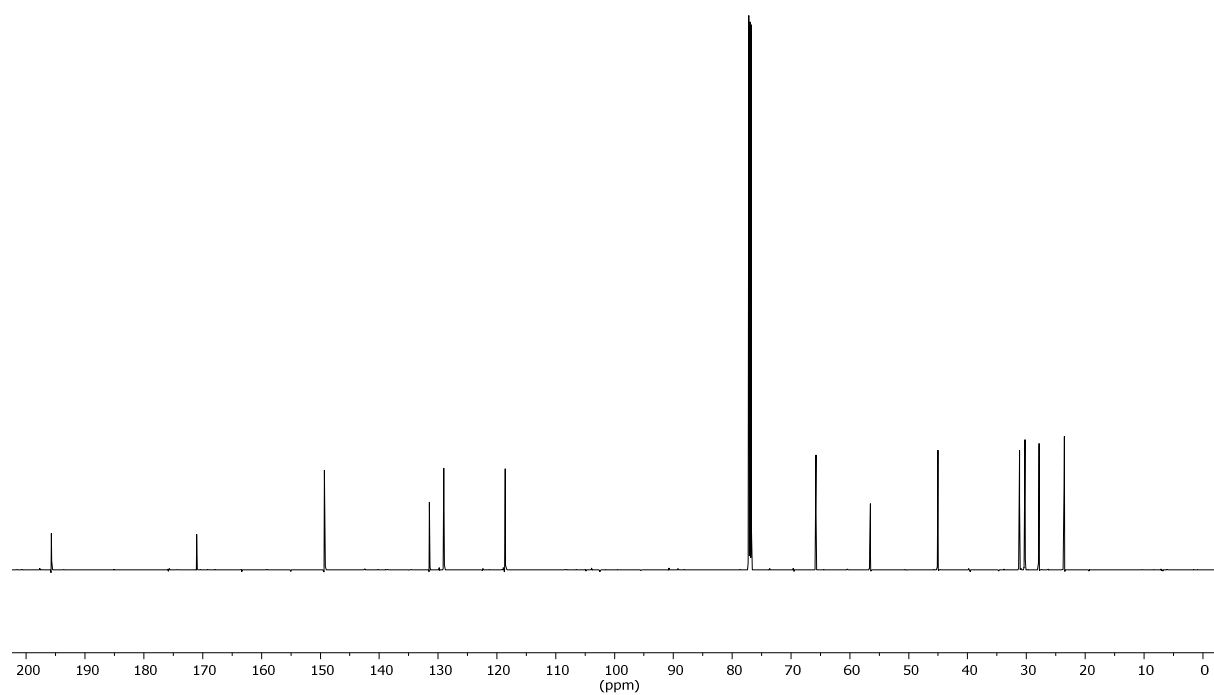
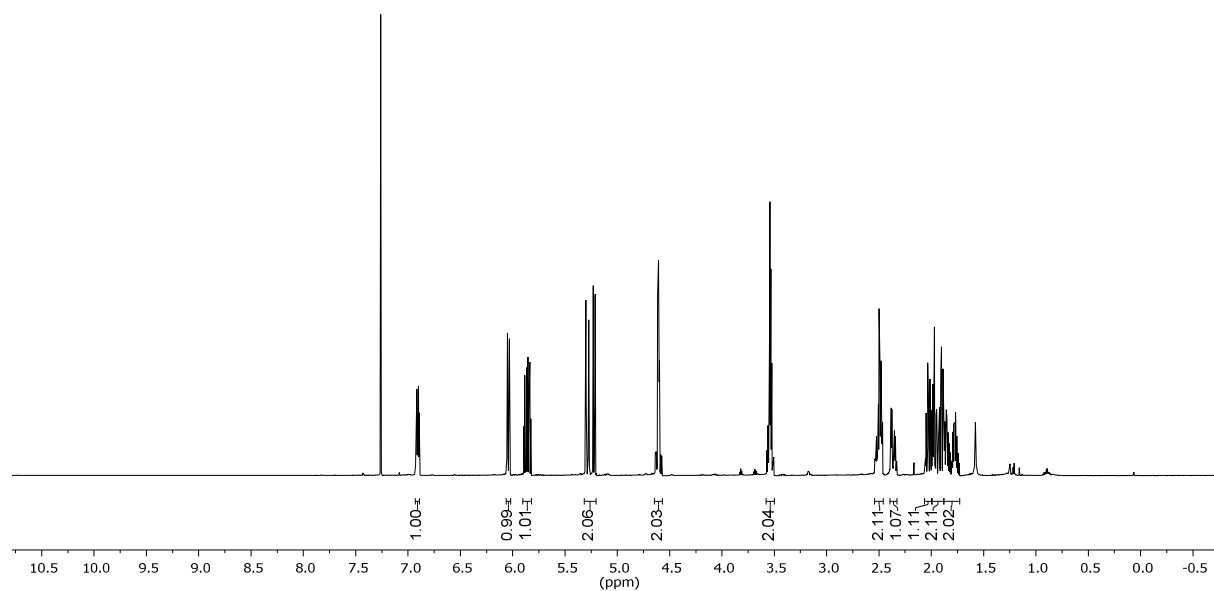
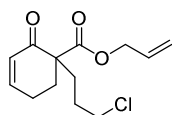


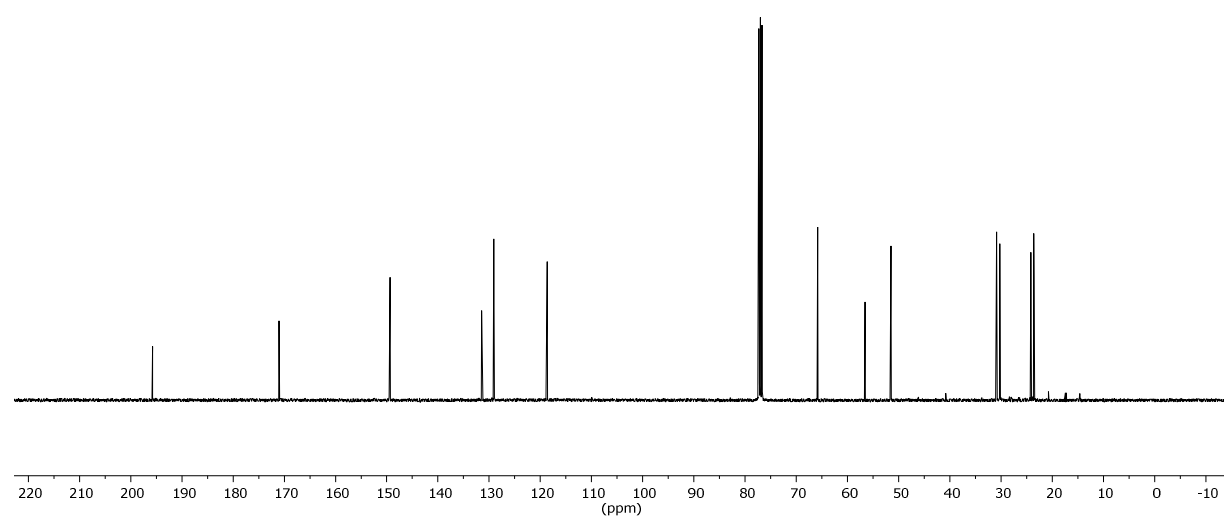
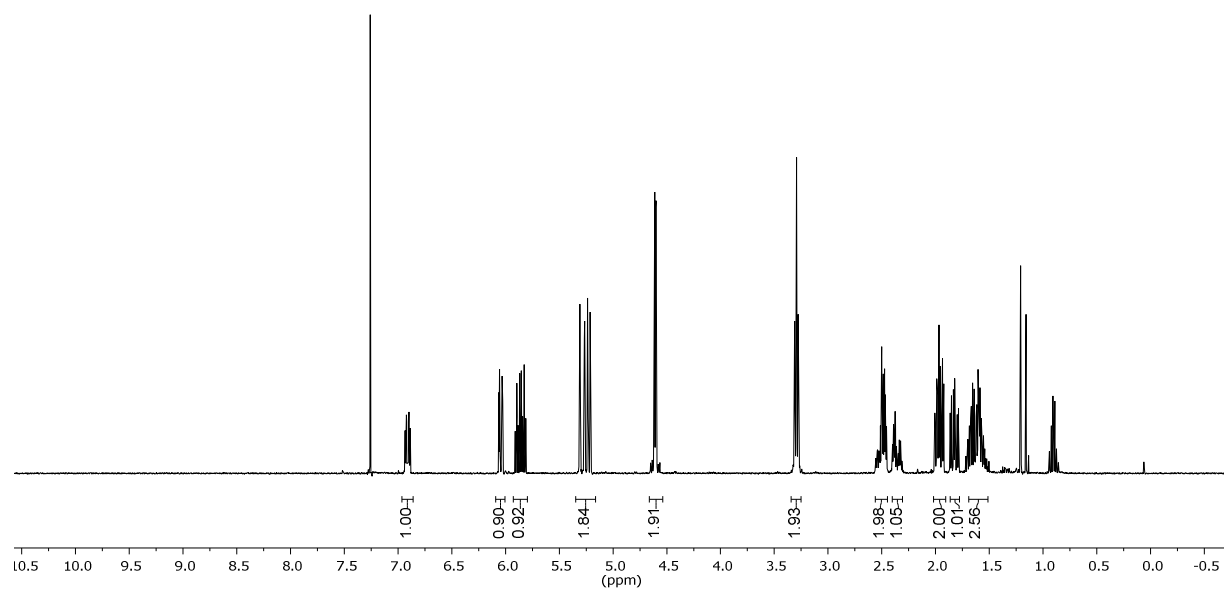
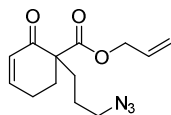


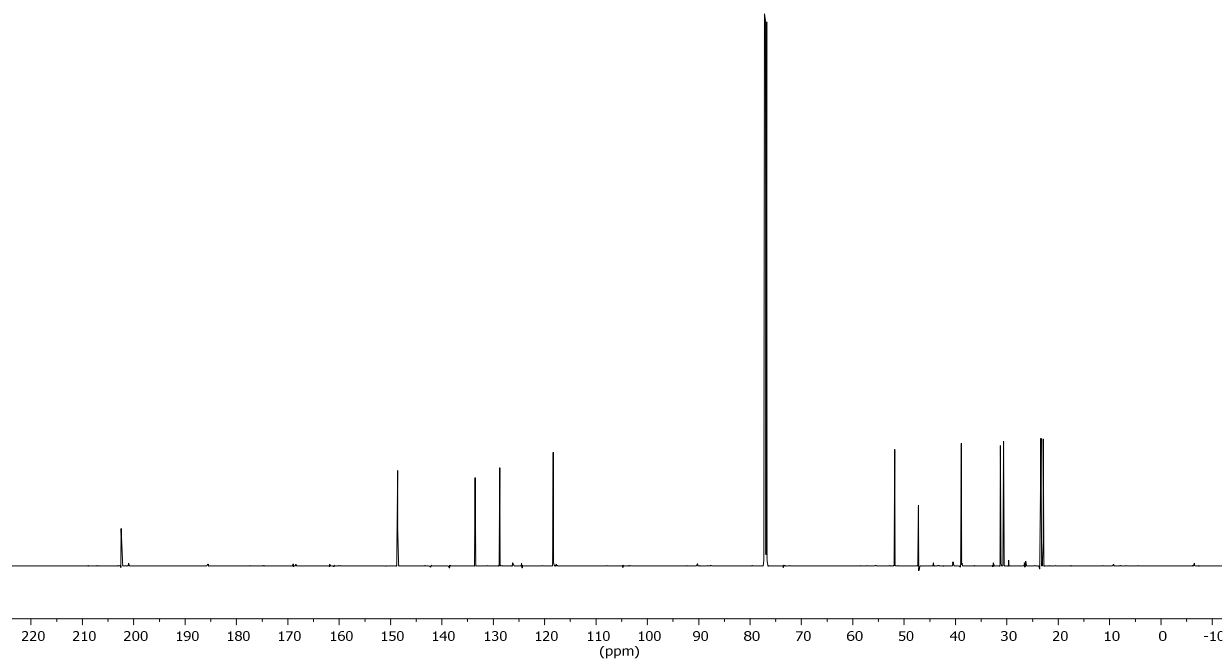
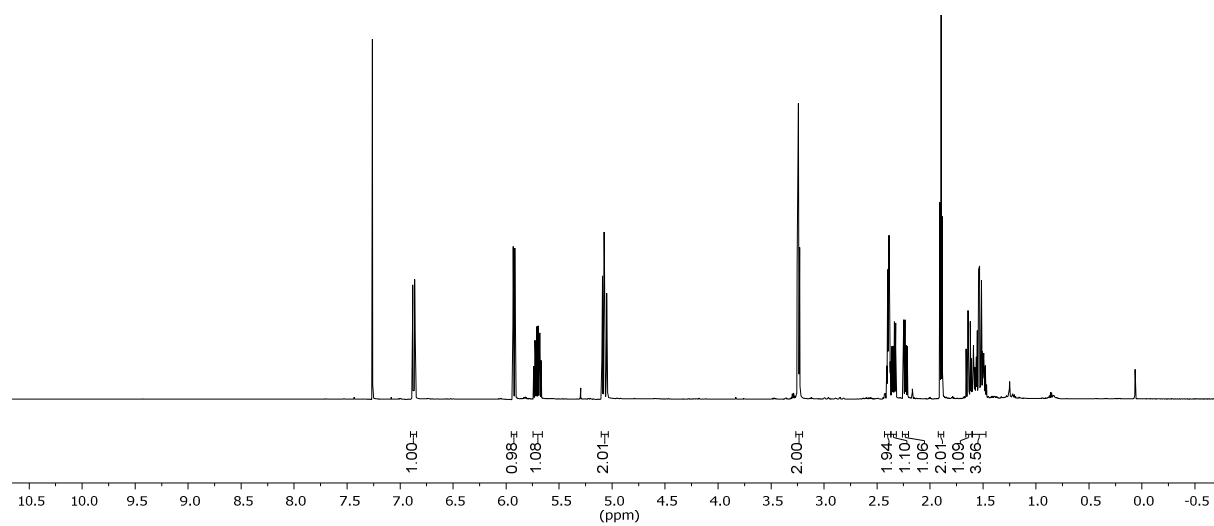
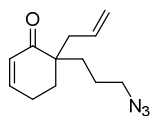


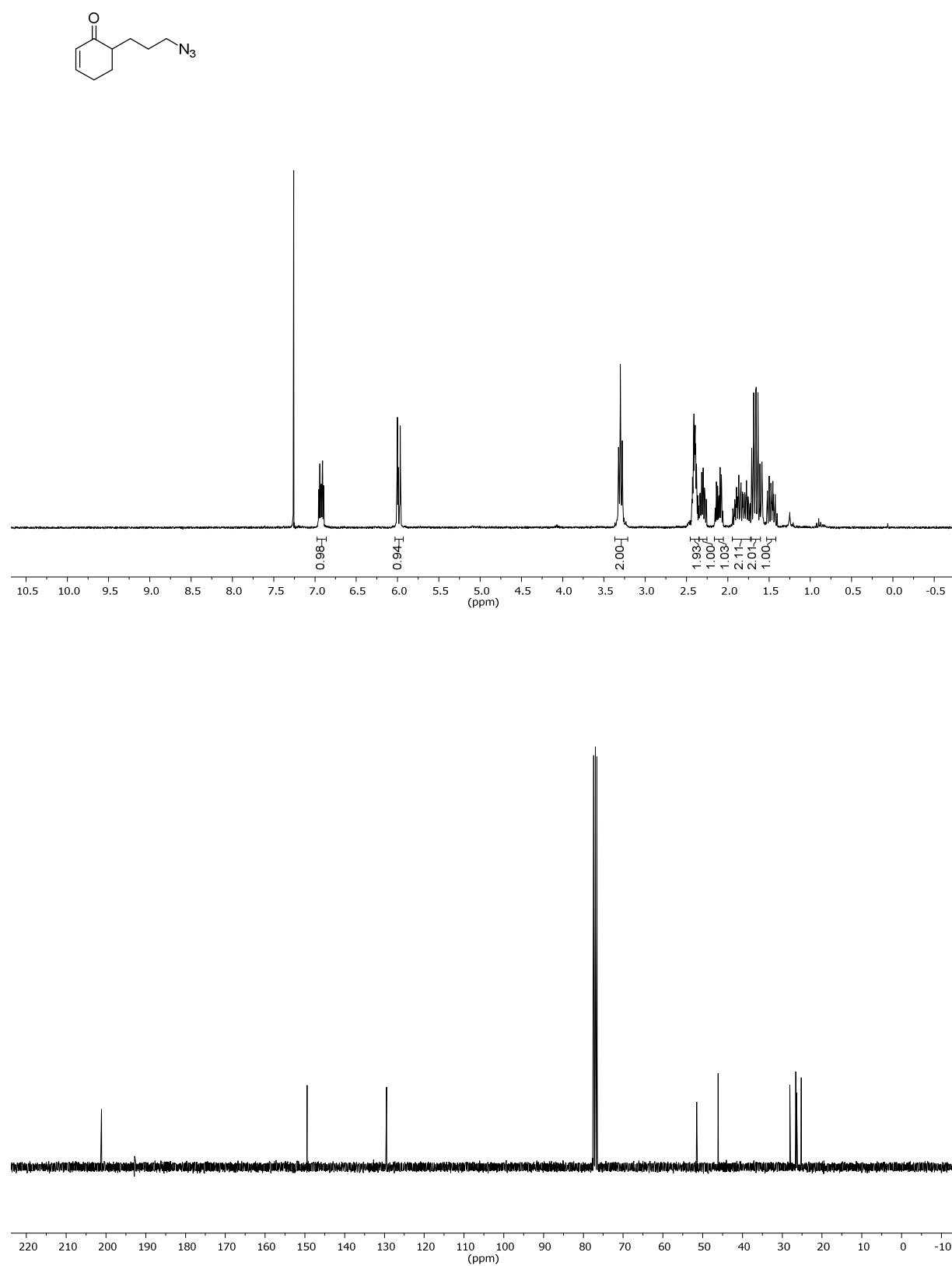


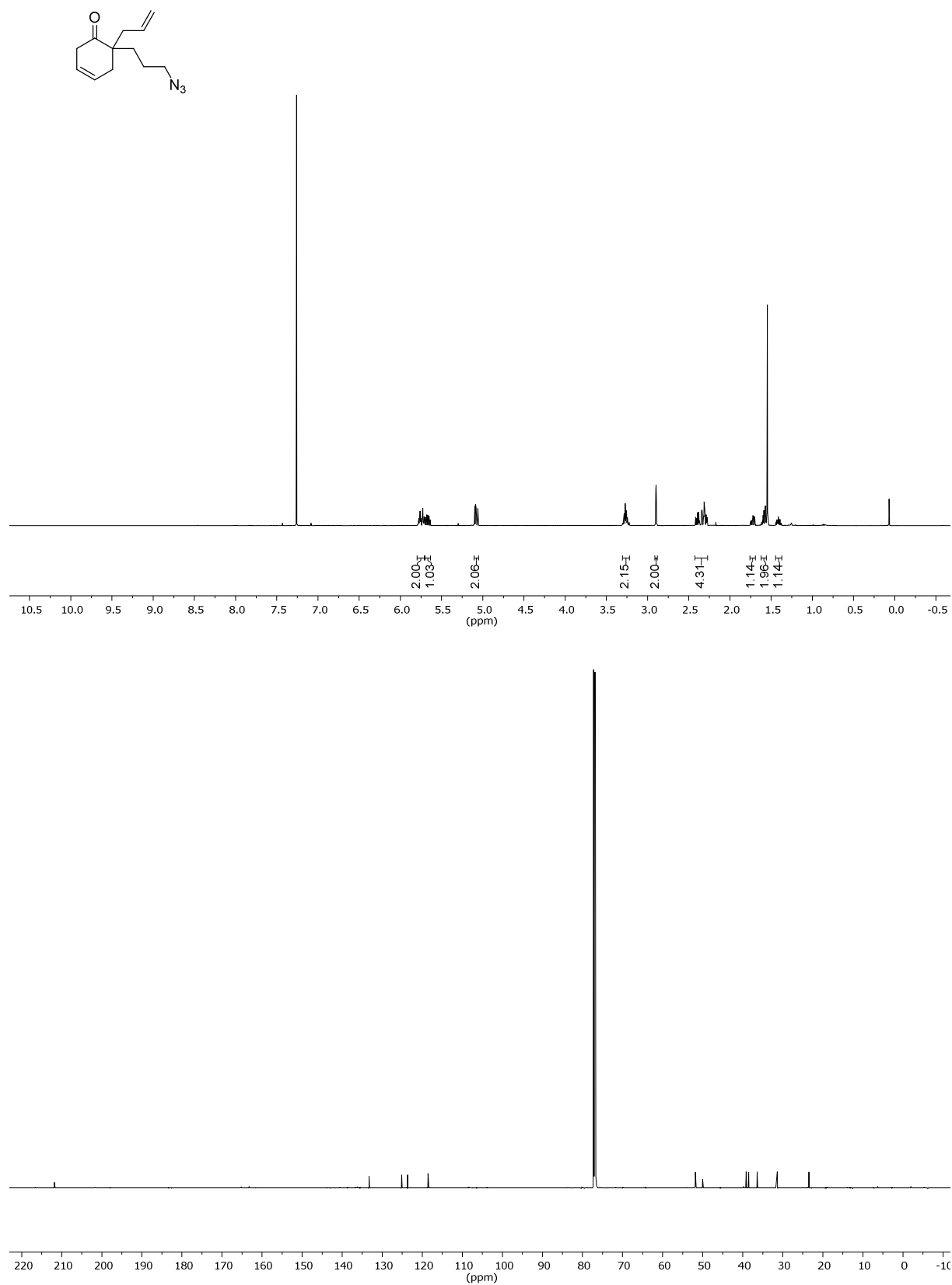


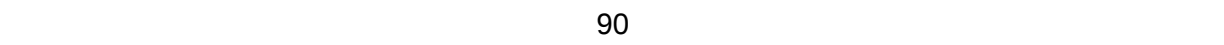


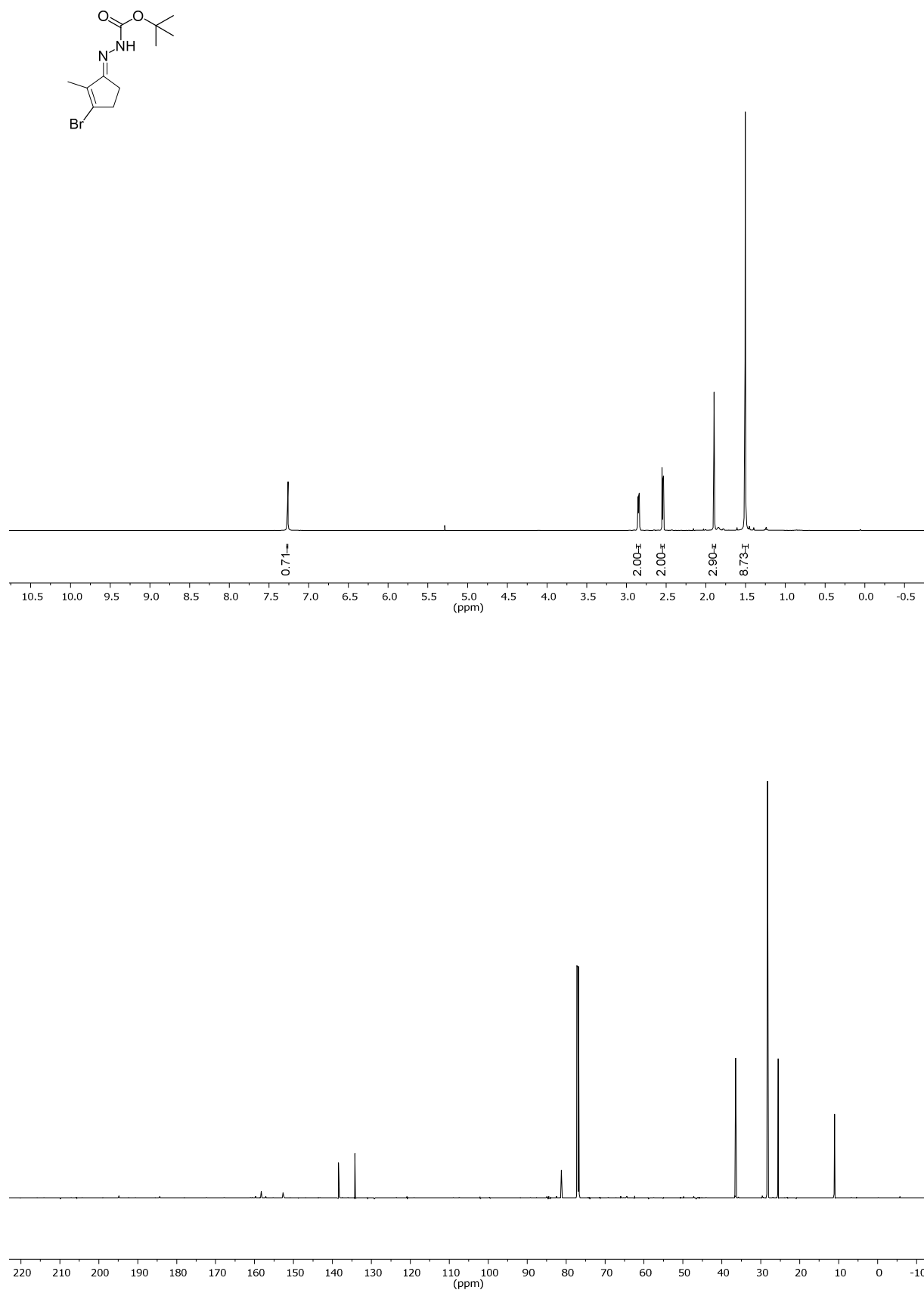


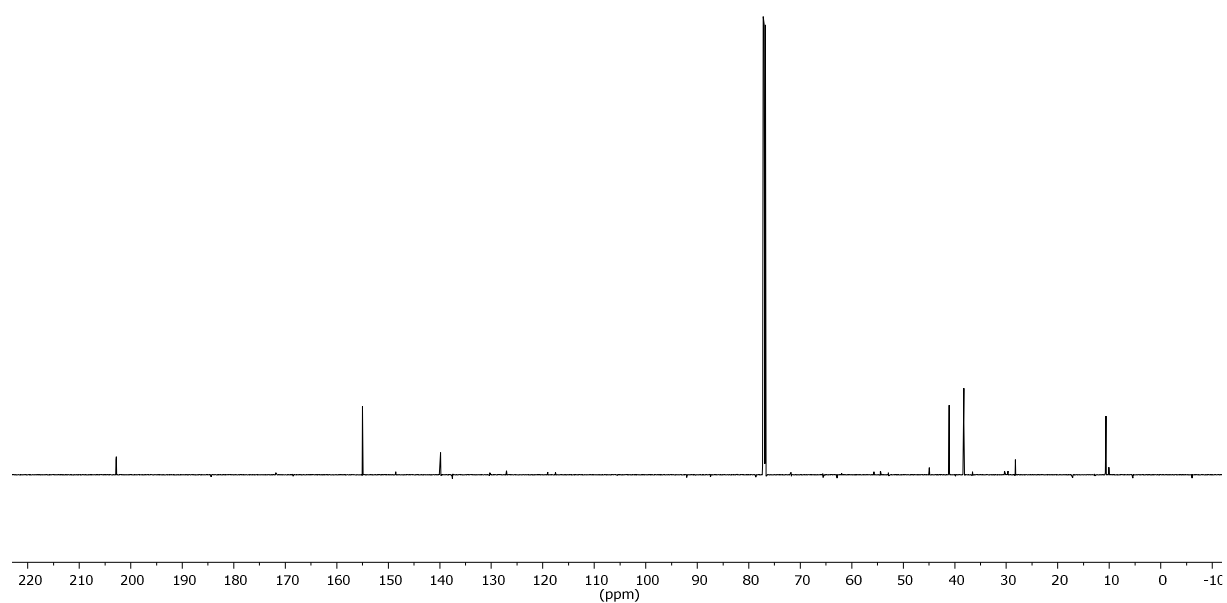
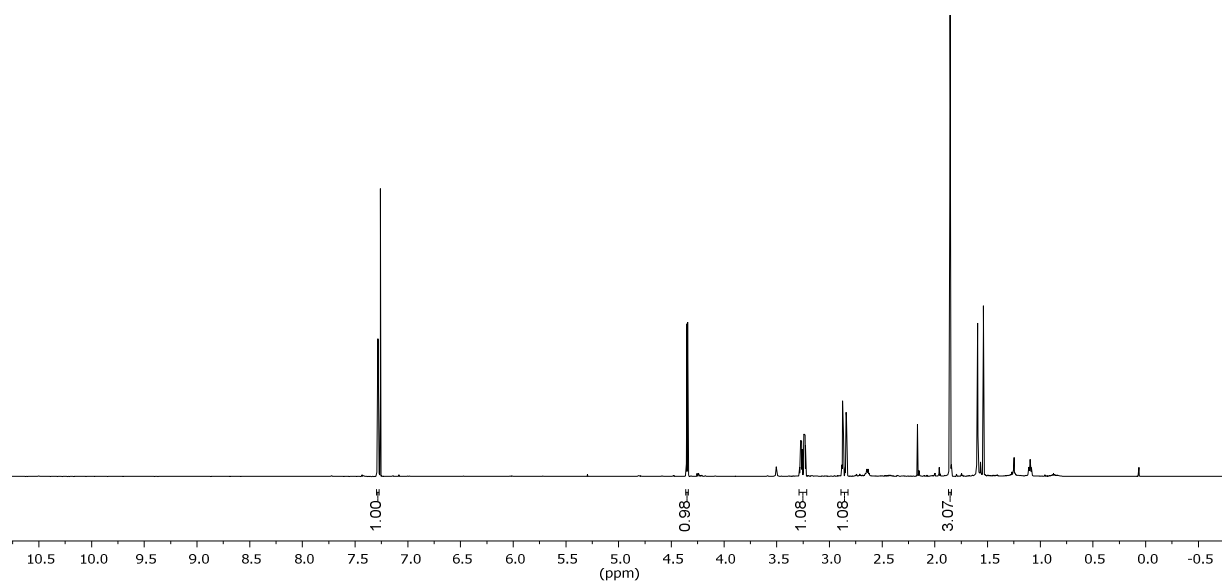
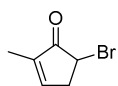












8.2 Curriculum vitae

**Full name:**

Daniel Anton Kaiser

Education:

- 03/2013–09/2013: Master thesis, LMU Munich (Prof. Dr. D. Trauner, Dr. T. Magauer)
10/2011–10/2013: MSc-programme, Chemistry, University of Vienna
10/2008–07/2011: BSc-programme, Chemistry, University of Vienna
(graduated with distinction)
09/1999–07/2007: Secondary school: BRG XIX Krottenbachstraße, Vienna
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Work Experience:

- 2011–2012: Tutor in the "Organisch-chemisches Praktikum" at the University of Vienna
2007–2008: Paramedic with the "Johanniter Unfall-Hilfe" (community service)

Scientific Interests:

- Stereoselective synthesis of natural products
- Development of synthetic methodology in organic chemistry
- NMR-spectroscopy and structural elucidation

Skills:

- Languages: German & English – fluent, spoken and written; French (four years)