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„I. [1,5]-Hydride Transfer Approach to Macrocycles II. Protodesulfination of Sulfoxides"

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Abstract English

This MSc thesis is divided into two parts. The first part focusses on the synthesis of macrocyclic compounds *via* intramolecular [1,5]-hydride transfer, starting from a suitable precursor. Since macrocycles are ever-present in Nature and have found applications in a variety of fields, including the perfume industry and drug development, finding efficient methods for their enantioselective synthesis is of high relevance. We therefore envisioned an intramolecular variant of our group's linear-selective aldehyde-alkene coupling protocol to access macrocycles in an efficient enantioselective fashion, starting from readily available compounds. The development of a robust route for the synthesis of several substrates for the key-step, as well as a first screening of conditions for this reaction will be described herein.

The second part of this MSc thesis focused on the investigation of a Brønsted Acid-catalyzed desulfination reaction of aryl sulfoxides. We envisioned that this mild method could be orthogonal to well established C–S bond cleavage reactions *via* organolithium reagents or Raney Nickel reduction. Our studies of this process and its dependence on the electronic properties of the substrate will be detailed in this thesis.

Abstract German

Diese Masterarbeit ist in zwei Teile gegliedert. Der erste Teil befasst sich mit der Synthese makrocyclischer Verbindungen über intramolekularen [1,5]-Hydridtransfer ausgehend von geeigneten Substraten. Da Makrocyclen in der Natur allgegenwärtig sind und in einer Vielzahl von Bereichen, einschließlich der Parfümindustrie und der Arzneistoffentwicklung, Anwendung finden, ist die Suche nach effizienten Methoden für ihre enantioselektive Synthese von großer Bedeutung. Basierend auf der linear-selektiven Aldehyd-Alkenkopplungsreaktion, die zuvor in unserer Arbeitsgruppe entwickelt wurde, wollten wir eine intramolekulare Variante dieser Reaktion entwickeln. Dies würde eine enantioselektive Synthsese von Makrocyclen, ausgehend von leicht verfügbaren Strartmaterialien, ermöglichen. Die Entwicklung eines robusten Synthesewegs für mehrere Substrate für den Schlüsselschritt, sowie ein erstes Screening der Bedingungen für diese Reaktion werden hier beschrieben.

Der zweite Teil dieser Masterarbeit befasst sich mit der Untersuchung einer Brønsted-Säure-katalysierten Desulfinierungsreaktion von Arylsulfoxiden. Hierbei wolten wir eine milde Methode entwickeln, die orthogonal zu den bereits etablierten C–S Bindungsspaltungsreaktionen über Organolithiumreagenzien oder Raney-Nickel Reduktion sein könnte. Unsere Untersuchungen dieses Prozesses und seiner Abhängigkeit von den elektronischen Eigenschaften des Substrats werden in dieser Arbeit im Detail beschrieben.

Abbreviations

^{1}H-NMR	^{1}H-nuclear magnetic resonance
^{13}C-NMR	^{13}C-nuclear magnetic resonance
calcd.	calculated
δ	chemical shift
CC	column chromatography
COSY	correlation spectroscopy
J	coupling constant
DCM	dichlormethane
DOSY	Diffusion ordered spectroscopy
d	dublet
EE	ethyl acetate
FT-IR	Fourier transform infrared spectroscopy
HMBC	Heteronuclear Multiple Bond Coherence
HMQC	Heteronuclear Multiple-Quantum Correlation
HRMS-ESI	high resolution mass spectrometry electrospray ionization
IR	infrared
MS	mass spectrum
mg	milligram
ml	milliliter
mmol	millimole
m	multiplet
Nu	nucleophile
ppm	parts per million
q	quartet
s	singlet
TMS	tetramethylsilane
TLC	thin-layer chromatography
t	triplet
UV	ultra violet
ν	wavenumber

I. [1,5]-Hydride Transfer Approach to Macrocycles

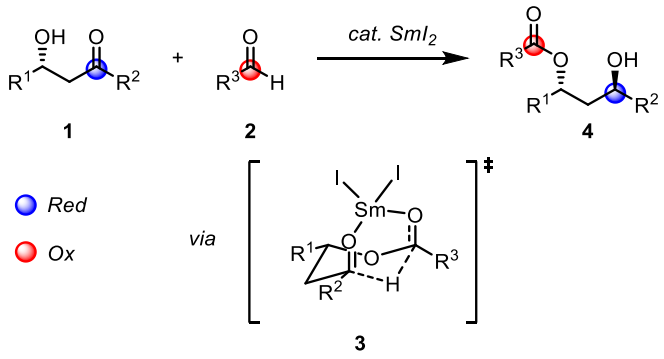
I.1. Introduction

It could be stated that the main focus of synthetic organic chemistry is the assembly of simple building blocks into complex substances through the formation of carbon-carbon (C–C) bonds. This goal can be conventionally achieved by combining building blocks carrying suitable reactive functional groups predestined for bond formation. In this regard, perhaps the most famous underdog is the carbon-hydrogen (C–H) bond, famously described by Goldman and Goldberg as the "un-functional group".[1] The proximal electronegativity of carbon and hydrogen as well as the high pK_a values (50-70) of unactivated C-H bonds (i.e., CH bonds that do not reside adjacent to activating functional groups) play a pivotal role in the inert character of the C–H bond. Paraffin (*parum affinis*), the historical namesake of long-chain alkanes, further affirms this fact. However, in the last two decades the field of so-called "C–H bond activation" became the subject of intense investigation.[1] Thus, reactions using transition metal C-H activation, as highlighted in reviews by Shilov and Fujiwara, have been explored for the direct functionalization of carbon-hydrogen bonds.[2] Following the pioneering work of Lewis and Murai who first discovered that C–H bonds can be activated *via* transition metal-catalysis with the help of a nearby coordinating group, a plethora of studies on such processes have been reported.[3], [4], [5]

This increase in research activity mirrors the recent drive towards atom-economic reactions and emphasis on green chemistry. According to Trost's classical definition, the key factor regarding atom economy is how much of the reactants actually end up in the product.[6], [7] Traditional cross-coupling reactions, which form C–C bonds by combining C–X electrophiles (X = halide) with C–M nucleophiles (M = metal), necessarily generate stoichiometric waste in the form of M–X salts. The environmental friendliness of selective C–H activation therefore becomes apparent.

A second economic aspect is redox-neutrality.[8] According to Hendrickson, the only indispensable step in a synthesis is the formation of the molecular skeleton.[9] Thus, the least redox-manipulating steps a synthesis entails, the higher the potential efficiency of that route towards the desired product. If one sector of the reactant molecule is oxidized while another sector is reduced, we arrive at what is termed a "redox-neutral process". The Evans-Tishchenko reaction of β-

hydroxycarbonyl (aldol) products is an elegant example of such a reaction (Scheme 1).[10] The mechanism involves hemiacetal formation and two-point coordination to SmI_2 in a chair-like arrangement, followed by intramolecular hydride transfer.



Scheme 1: Evans-Tishchenko reaction.

Complementary to metal-catalyzed processes, C–H activation can be achieved utilizing hydride transfer processes. In particular, intramolecular hydride transfer offers a path proceeding *via* entirely different mechanisms and without the necessity of using noble transition metals.[5] This redox-neutral variant requires a hydride acceptor within appropriate distance to the C–H bond. The acceptor group is formally reduced and the donating group oxidized, leading to simultaneous functionalization of both participating moieties (Figure 1).

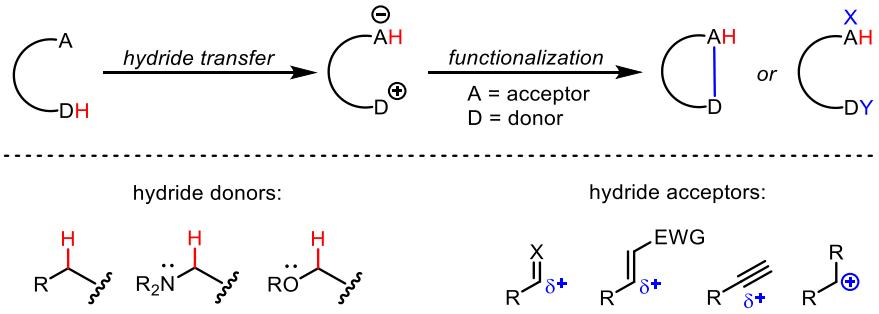
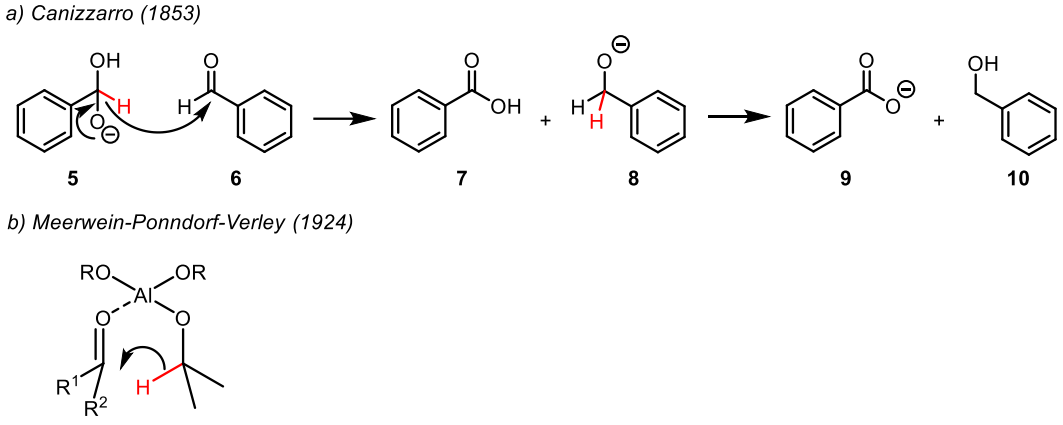


Figure 1: Hydride shift mediated C–H functionalization.[5]

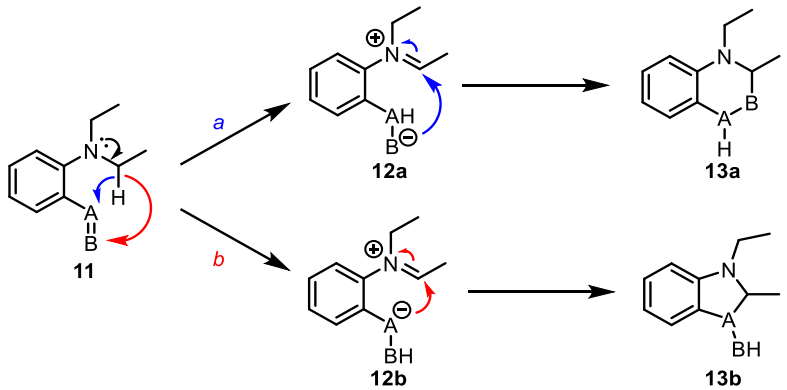
When looking back at the historical background of organic molecules as hydride donors, the Cannizzaro reaction reported in 1853 is one of the first examples in the literature (Scheme 2a).[11] Under base-catalysis, two equivalents of benzaldehyde disproportionate to one equivalent of benzyl alcohol and one equivalent of benzoic acid. This reaction proceeds *via* an intermolecular hydride transfer from the deprotonated hemiacetal onto the second equivalent of

aldehyde.[12] Later in 1924, the Meerwein-Ponndorf-Verley (MPV) reduction, also proceeding through an *intra*molecular [1,5]-hydride transfer process, was described (Scheme 2b).[13], [14], [15]



Scheme 2: Organic molecules as hydride donors.[5]

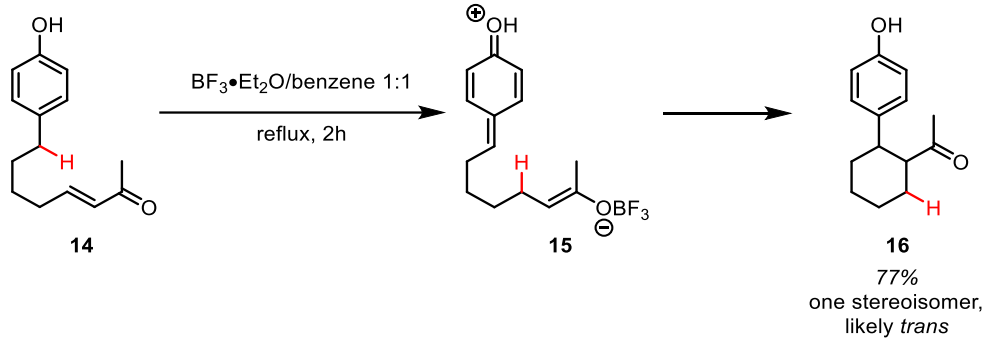
Most interesting were results obtained by Meth-Cohn using *N*,*N*-dialkylanilines with appropriate *ortho*-acceptor substituents. This has been historically known as the "*tert*-amino effect".[16] These compounds can undergo redox-neutral isomerization enabled by the stabilization of developing positive charge α-to the nitrogen atom. The cyclization of ortho-substituted tertiary anilines involves one of the α-methylene groups next to the nitrogen and leads to the formation of five- or six-membered rings (Scheme 3).[17], [18]



Scheme 3: Types of *tert*-amino effect promoted cyclizations.

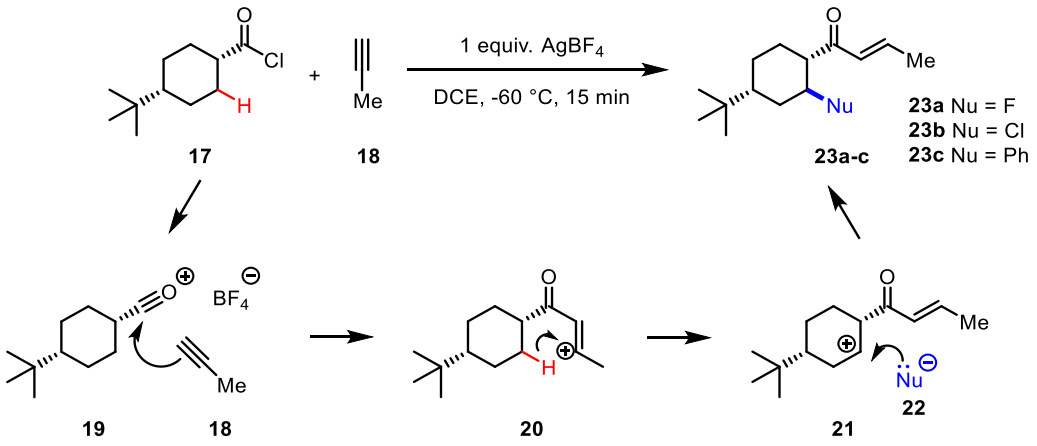
One of the first examples of an intramolecular C–H functionalization without the help of the "*tert*-amino effect" has been reported by Atkinson and co-workers in 1969. Therein, it was shown that treating *p*-hydroxy-phenyl substituted enone **14** with excess BF_3•Et_2O also facilitates

[1,5]-hydride transfer and, upon cyclisation of the resulting enolate **15**, affords a 6-membered product **16** diastereoselectively and in high yields (Scheme 4).[19]



Scheme 4: Lewis Acid catalyzed C-H functionalization.

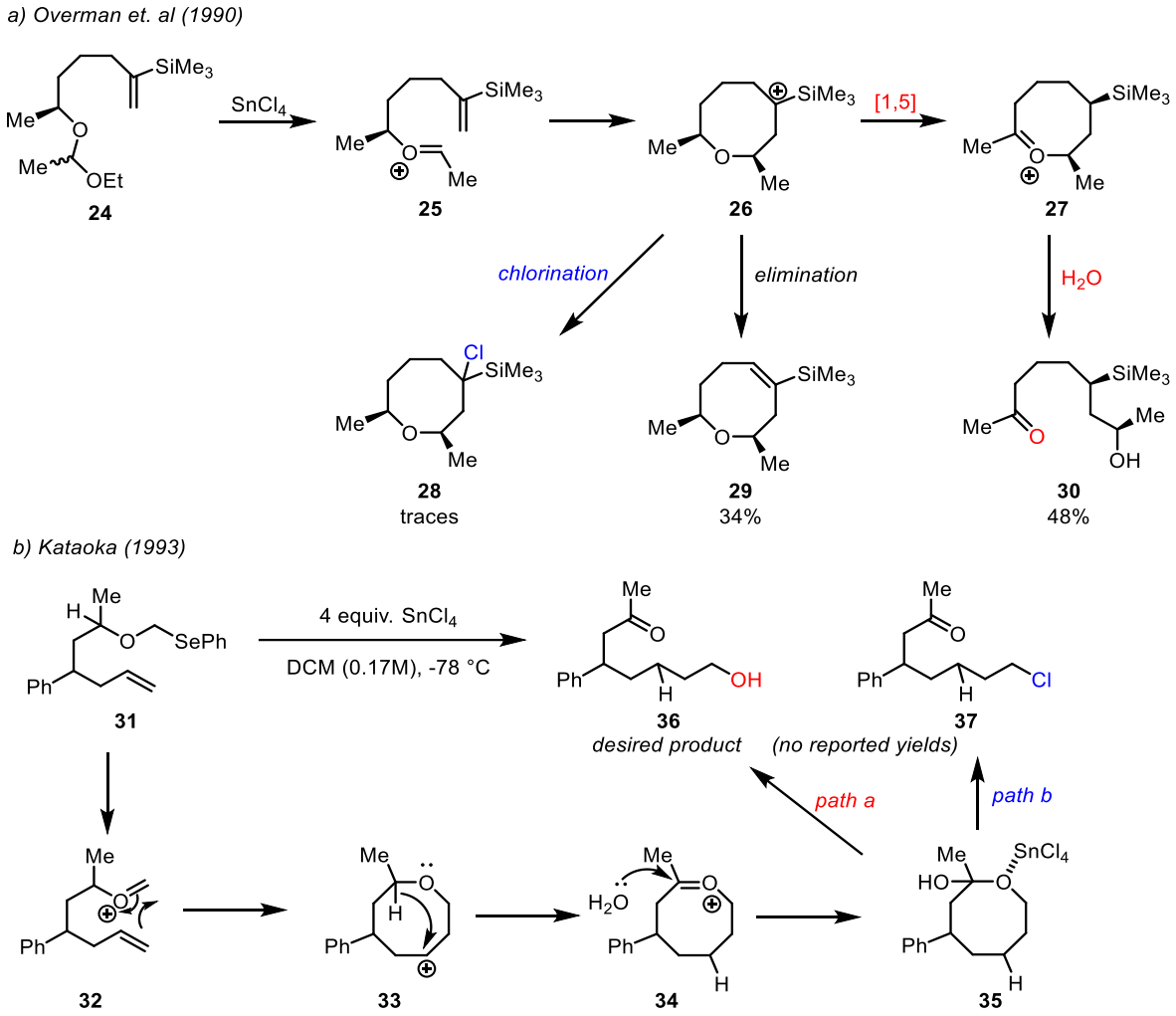
In contrast to the previous example, where the sequence is terminated by a C–C bond forming event, Smit and Caple showed that halogenation of the C–H bond is also feasible.[20] This can be achieved by treating aliphatic acid chlorides with $AgBF_4$ leading to an acylium-cation **19**. This cation can be captured by a terminal alkyne. Upon [1,5]-hydride transfer to the resulting vinyl-cation **20**, the new reactive carbocation **21** is finally intercepted by a nucleophile to generate *β*-substituted ketones (Scheme 5).



Scheme 5: C-H halogenation and arylation.

Back in 1990, Overman and coworkers reported the synthesis of eight-membered cyclic ethers starting from 5-alkenyl acetals *via* Lewis Acid catalysis. A mixture of the eight-membered elimination product **29** and chlorides **28** were observed as the major products. Curiously, the reaction of vinyl-silane substrate **24** under standard conditions led to ketoaldehyde **30** as byproduct, along with the desired, eight-membered ether. The formation of this side product could

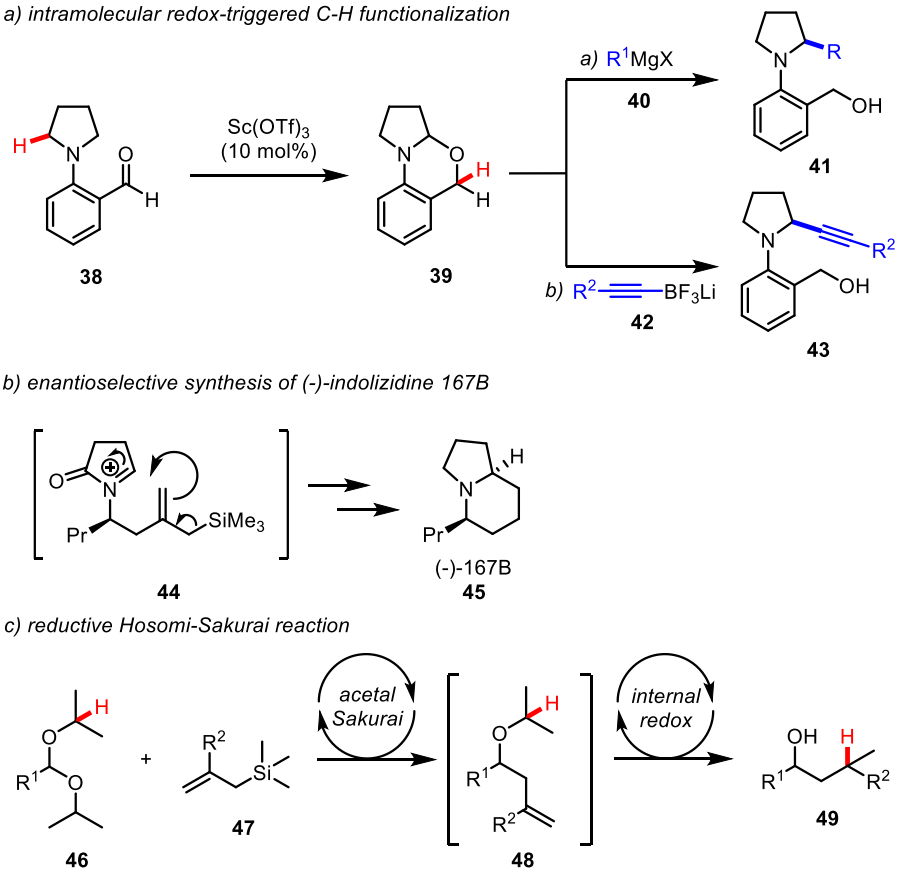
be explained by a [1,5]-hydride transfer event (Scheme 6a).[21] Later, Kataoka reported a hydrofunctionalization of olefins bearing mixed acetals using excess amounts of $SnCl_4$.[22] The proposed mechanism involves the formation of an oxocarbenium ion **32** mediated by Sn^{IV}. This intermediate undergoes a Prins cyclization, followed by [1,5]-hydride transfer and aqueous workup to afford the corresponding hydroxy-ketone **36** from the hemiacetal product **35** (Scheme 6b, path a) Reductive elimination or ligand-coupling of the hemiacetal-complex **35** explains the formation of the keto chloride **37** (Scheme 6b, path b) as major side-product.



Scheme 6: Hydrofunctionalization of olefins bearing acetals.

I.1.1. Contributions of the Maulide Group

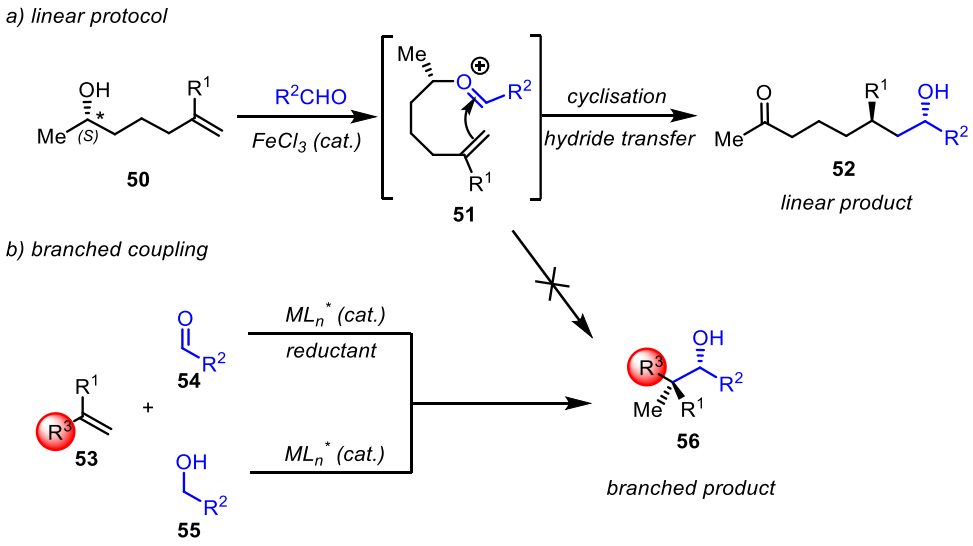
As one of the key research points of the Maulide group is the development of waste-free processes, previous work already focused on the utilization of hydride transfer for redox-neutral C–C bond formation. It has been shown that C–H functionalization can be achieved by treatment of aminoaldehyde **38** with a suitable Lewis Acid. Therein, [1,5]-hydride transfer onto the aldehyde moiety leads to an iminium alkoxide, which collapses to form benzoxazine **39**. Further treatment with a Grignard reagent or lithium alkynylborate resulted in the formation of alcohol **41** and alkyne **43** respectively (Scheme 7a). This method was employed in a concise synthesis of (−)-indolizidine 167B **45** (Scheme 7b).[23] Later, the Maulide group also developed a protocol for the reductive Hosomi-Sakurai reaction (Scheme 7c). In this report, acetal **46** reacts with allyl-silane **47** to form *β*,*γ*-unsaturated ether **48**. In the presence of a strong acid, 48 can be protonated to trigger [1,5]-hydride transfer, directly furnishing the reduced product **49** in a single operation. (Scheme 7).[24–29]



Scheme 7: a) Intramolecular C–H functionalization. b) (-)-indolizidine 167B. c) Reductive Hosomi-Sakurai reaction.

More recently, the Maulide group has reported a redox neutral Lewis-acid catalyzed approach for the coupling of aldehydes and alkenes (Scheme 8a). Whilst previous methods using noble transition metal catalysis to achieve such transformations have resulted in the exclusive formation of branched products (scheme 8b),[30] the recent development is the first example of complete selectivity towards the linear product. This is the result of a fundamentally different approach.

Whilst previous methods relied on oxidative-coupling mechanism using transition metal catalysis, this report utilizes a carbocationic mechanism to ensure selectivity for the linear products. Mechanistically, this reaction proceeds *via* oxocarbenium ion **51**, generated by treatment of chiral alcohol 52 with an aldehyde in the presence of a Lewis Acid. Attack of the olefin-moiety on this highly electrophilic species leads to the more stabilized, tertiary carbocation, ensuring selectivity for the linear coupling products. Hydride transfer and hydrolysis then release the desired products.[31], [32]



Scheme 8: Redox neutral approach for the coupling of aldehydes and alkenes.[31], [32]

I.1.2. Macrocycles in Nature

Macrocyclic structures are ubiquitous in Nature. Their cyclic structure is believed to increase stability towards enzymatic degradation, a reason why macrocycles have found increasing application in drug development within the last years.[33–35] An important naturally occurring macrocycle is muscone, a natural product secreted by the gland of the musk deer's pod and a very popular ingredient in the fragrance industry. Since the last century, muscone is obtained by synthesis without further endangering the musk deer population. Ružička was the first to elucidate its structure in 1926 (Figure 2).[36]

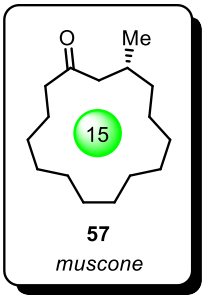


Figure 2: Muscone and exaltone.

Since muscone appears in Nature as the enantiopure (*R*)-3-methylcyclopentadecanone, an enatioselective synthesis has been reported by Hagiwara, starting from commercially available (+)-citronellal. Grignard addition followed by oxidation gives ketone **61**. Ring-closing metathesis is used to forge the 15-membered ring, leading to macrocycle **60**. Subsequent double-bond reduction delivers the target compound.[37], [38] The main disadvantages of Hagiwara approach is the requirement of multiple redox-adjustments for the synthesis of diene x. Since one of the key intermediates contains a terminal isopropylidene group, the RCM leads to dimerization (Figure 3a). In order to bypass this inconvenience, an additional ozonolysis step followed up by a Wittig reaction was performed and substrate **60** was synthesized, which can selectively lead to the desired mixture of cyclic alkenes. The final hydrogenation step leads to enantiopure (*R*)-muscone (Scheme 3b).

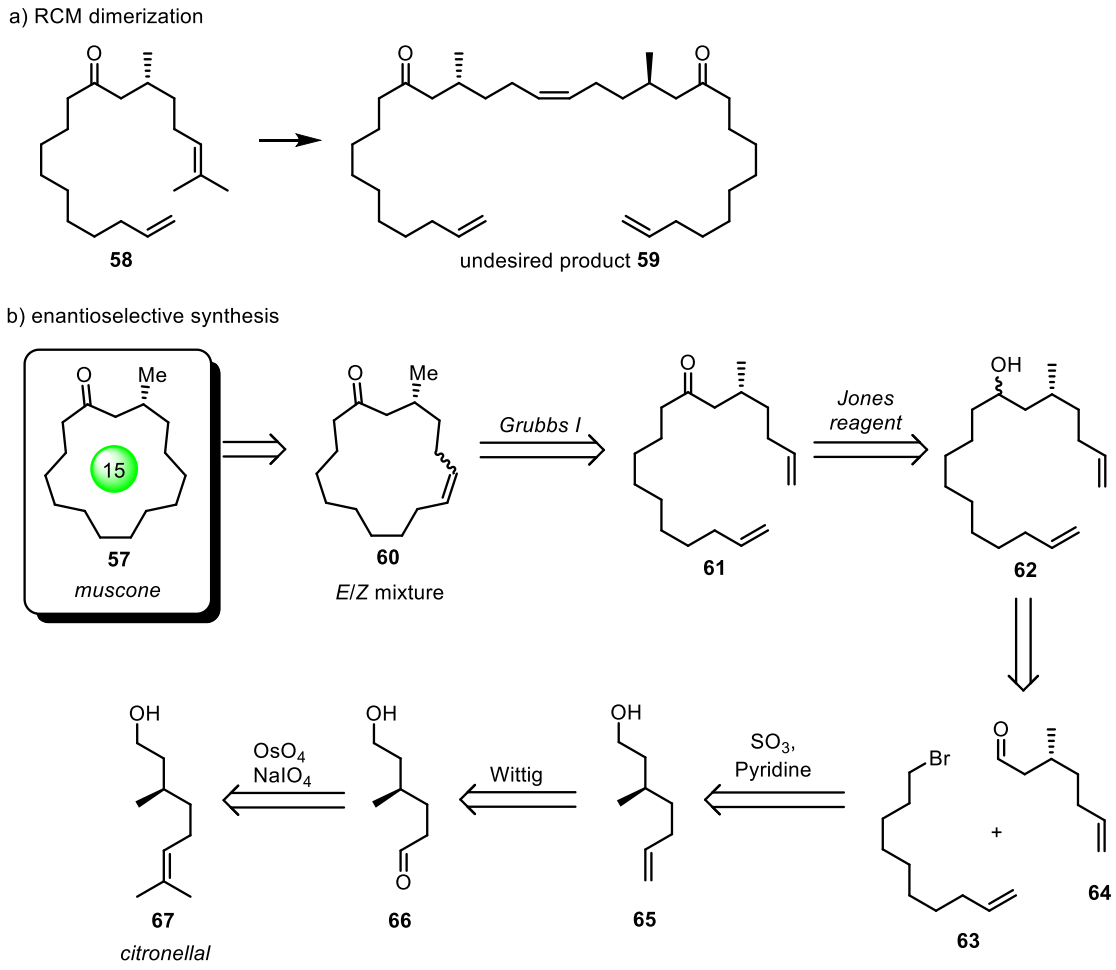


Figure 3: Enantioselective synthesis of (*R*)-(–)-Muscone **57**.

Ružička also synthesized exaltone using Thorium dioxide (Figure 4, left).[39] Similarly to muscone, exaltone and civetone have been used in the perfume industry. Interestingly, their fragrance becomes more perceptive when diluted below 1% in the perfume oil (Figure 4, right).[40], [41]

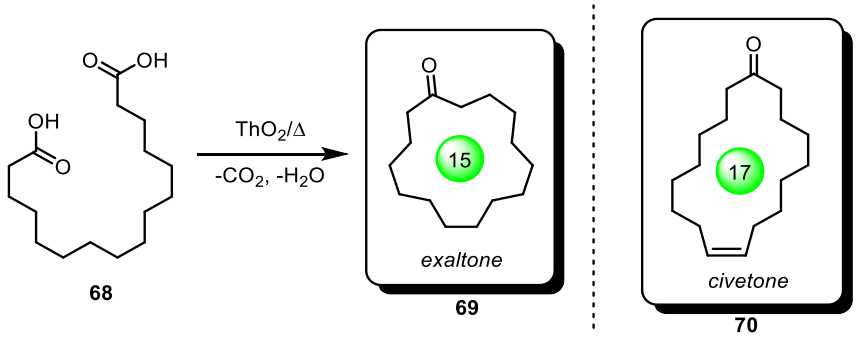
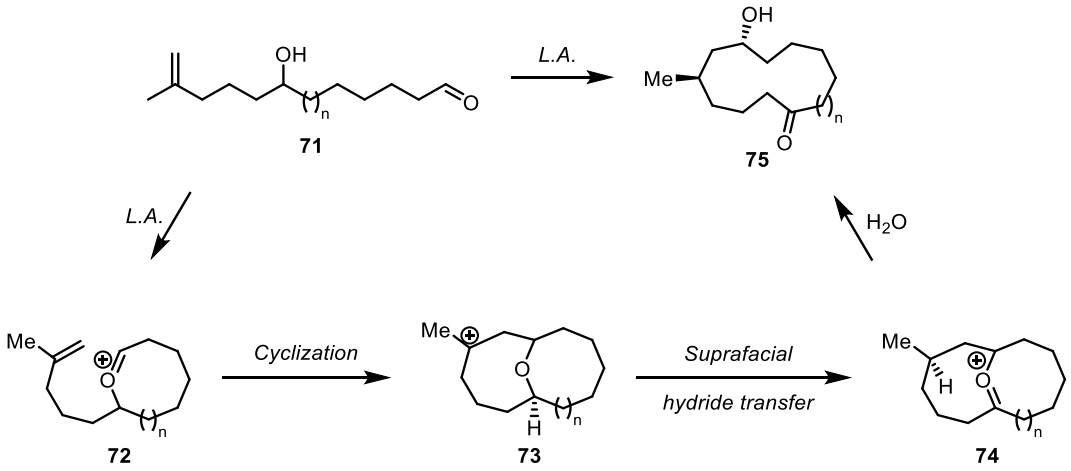


Figure 4: Exaltone and civetone.

I.1.3. Outline of this Work

The aim of this thesis is to develop an efficient enantioselective method for the synthesis of macrocycles. Based on our group's previous report, we envisioned that the linear-selective aldehyde-alkene coupling could also be rendered *intra*molecular. Since the previously developed *inter*molecular reaction proceeds through intramolecular [1,5]-hydride transfer, we hypothesized that macrocyclization could be promoted using the same mechanism starting from a suitable precursor. This precursor should have all required functional groups (aldehyde, alcohol and alkene) present in the same molecule. Its successful transformation could deliver a macrocyclic hydroxyl-ketone **75** carrying two stereocenters with high levels of enantio- and diastereoselectivity (Scheme 7).

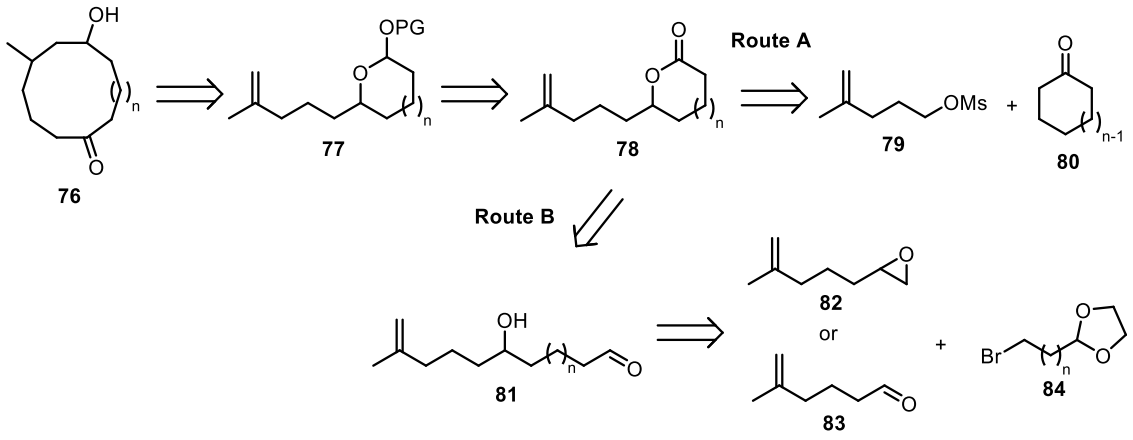


Scheme 9: Proposed approach to macrocyclization.

I.2. Results and Discussion

I.2.1. Proposed Approach Towards Macrocycles

We envisioned two possible pathways to reach lactone **78**. This pivotal intermediate should, upon reduction to its acetal counterpart, serve as substrate for our attempted macrocyclization strategy. One approach to reach lactone **78** would be alkylation of a cyclic ketone followed by Baeyer-Villiger oxidation (Route A). Another option would start from bromo-dioxolanes **84** and epoxide **82** or aldehyde **83** (Route B). After deprotection of the acetal motif, aldehyde **81** could be obtained. Pinnick oxidation followed up Mukaiyama lactonization should also lead to lactone **78**.[42] Finally, reduction and installation of different protecting groups would afford suitable substrates to test our macrocyclization (c.f. acetal **77)**. Alternatively, the macrocyclization could already be attempted directly from aldehyde x. This would significantly shorten the substrate synthesis, but would also necessitate efficient *in-situ* cyclisation of the alcohol onto the aldehyde moiety, which might be more challenging to achieve. Importantly, both route A and route B would readily allow variations on the value of n, an important parameter to study the efficiency of the hydride transfer event. Previous work in the Maulide group already showed that n has to be at least three to achieve hydride-transfer over competing elimination processes. However, no further studies were undertaken to investigate the effect of n on the reaction outcome and shall be studied within this thesis.

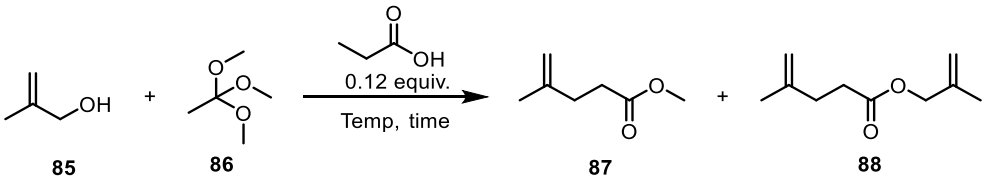


Scheme 10: Retrosynthetic analysis.

I.2.2. Synthesis of Starting Materials

I.2.2.1. Synthesis of Alcohol 91 *via* Johnson-Claisen Rearrangment

For the substrate synthesis *via* Route A, the electrophile (mesylate **79**, Table 1) was prepared from ester x, obtained from a Johnson-Claisen rearrangement. Initial attempts led to the transesterification product **88** as the main product (Table 1). Given that the Johnson-Claisen reaction as well as the transesterification is catalyzed by acid, the ratio of 1:2.5 **85**:**86** seemed to be too low to ensure fast reaction of **85** and thus pushed the equilibrium towards undesired product **88**.

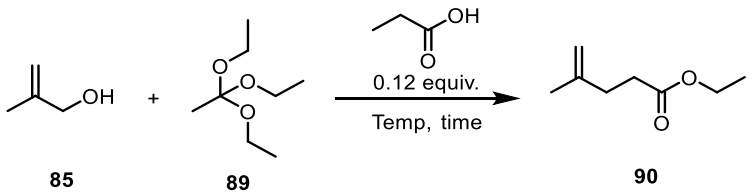


desired product

Entry	Equiv. 85	Equiv. 86	Temp.	time	Yield 87	Yield 88
1	1	2.5	140	1h	-	22%
2	1	2.5	110	1h	-	55%

Table 1: Johnson-Claisen rearrangement of alcohol **85** and orthoester **86**.

Upon further exploration of the literature,[43] we tried using a different orthoester **89** and higher excess of this reagent. As expected, increasing the loading of orthoester led to the desired product in excellent yields, efficiently suppressing transesterification (Table 2).

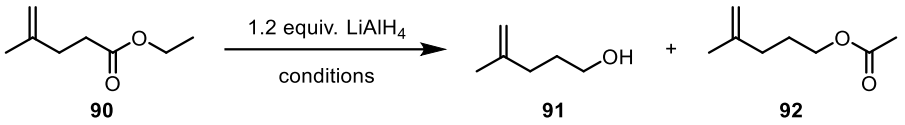


Entry	Equiv. x	Equiv. x	Temp.	time	Conversion
1	1	3	140	12h	17
2	1	5	140	12h	26
3	1	15	140	12h	80

Table 2: Johnson-Claisen rearrangement of alcohol **85** and orthoester **89**.

The next step involved a lithium aluminum hydride reduction (Table 3). In our initial attempt, we obtained a mixture of alcohol **91** and ester **92**. Transesterification product **92** was

obtained during the quench of the reaction with ethyl acetate (Entry 1). Quenching slowly with water avoided the formation of this side product and alcohol **92** could be obtained in 88% yield.

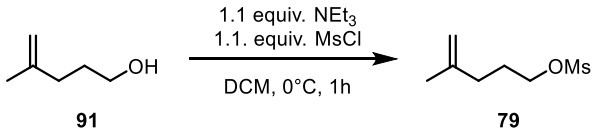


90 **91** **92**

Entry	Temp.	time	Yield x	Yield x	Comment
1	rt	12h	57%	32%	quenched with NaOH 1 M/EtOAc
2	rt	12h	88%	-	quenched with NaOH 1 M/H_2O

Table 3: LAH reduction of ester **x.**

Next, alcohol **91** was treated with triethylamine and methanesulfonyl chloride leading to mesylate **79** in high yield (Scheme 11).



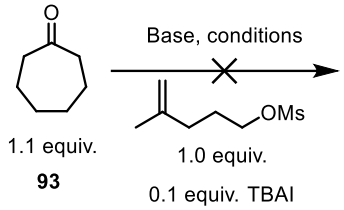
91 **79**

93%

Scheme 11: Synthesis of mesiylate **79**.

I.2.2.2 Alkylations of Cycloheptanone

Having the suitable electrophile in hand, alkylation of cycloheptanone was attempted using mesylate **79** under different conditions (Table 4). This would, after Baeyer-Villiger oxidation (following Route A), lead to the 8-membered lactone, having the smallest possible ring-size to achieve hydride-transfer. LDA and potassium tert-butoxide were used as bases with 0.1 equivalents TBAI for *in situ* Finkelstein exchange. Initial attempts showed no conversion and only recovery of starting material (Entry 1-2). Adding 1 equivalent of HMPA (Entry 3) also did not facilitate the alkylation. These initial setbacks, in combination with the tedious synthesis of mesylate **79**, prompted us to focus our efforts on Route B for the substrate synthesis.

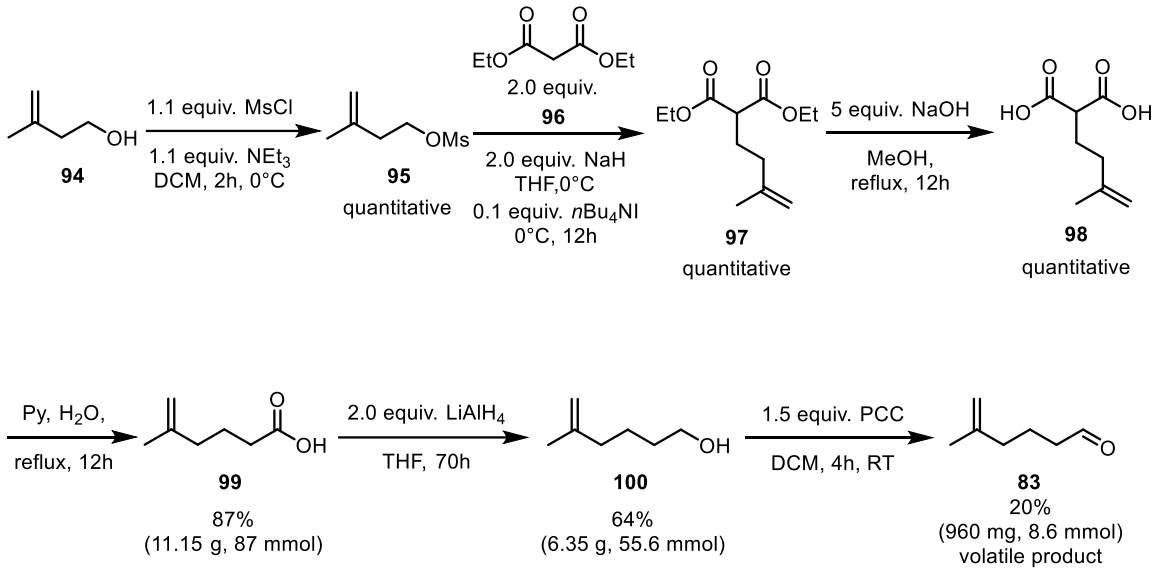


Entry	Base (1.1 equiv.)	Temp.	time	Comments
1	tBuOK	-78 °C-rt	12h	only SM
2	LDA	-78 °C-rt	12h	only SM
3	LDA	-78 °C-rt	12h	1 eq. HMPA, only SM

Table 4: Attempted alkylations of cyclic ketones.

I.2.2.3. Synthesis of Aldehyde 83

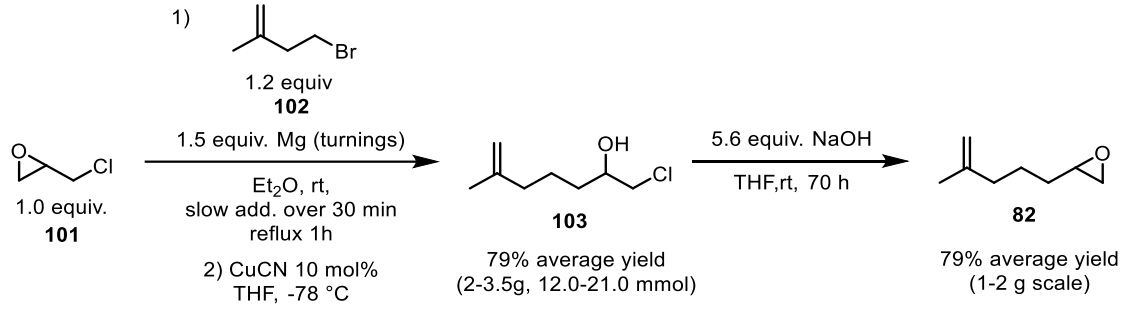
For the synthesis of aldehyde **83**, a 6-step route using robust chemistry was envisaged and is depicted in Scheme 12. In the first step, alcohol **94** was reacted with methanesulfonyl chloride and trimethylamine to form **95** quantitatively. Nucleophilic substitution using diethylmalonate resulted in quantitative formation of alkylated product x. Saponification under basic conditions yielded dicarboxylic acid **98**, which was decarboxylated by heating in pyridine. The resulting acid **99** was reduced to alcohol **100** using $LiAlH_4$. After purification, alcohol **100** was oxidized to aldehyde **83** using PCC at room temperature. The low yield of the final step can be explained by the volatile nature of aldehyde **83**.



Scheme 12: Synthetic route of aldehyde **83**.

I.2.2.4. Synthesis of Epoxide 82

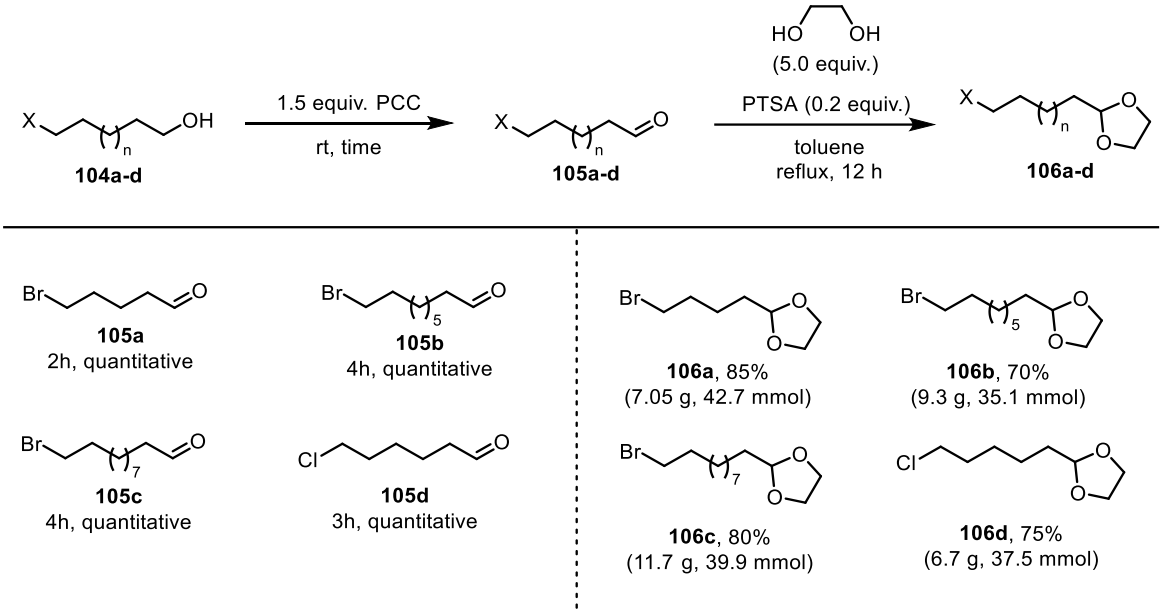
To enable a divergent synthesis of substrates with different chain lengths, epoxide **82** was prepared in two steps from epichlorohydrin (Scheme 13) to complement the aforementioned aldehyde **83**. In the first step, epichlorohydrin **101** was treated with the Grignard reagent derived from bromide **102** in the presence of Cu(I), promoting epoxide-opening and leading to alcohol **103**. The second step involved treating alcohol **103** with excess NaOH at room temperature, affording epoxide **82** in high yield on a gram scale.



Scheme 13: Synthesis of epoxide **82**.

I.2.2.5. Synthesis of Dioxolanes 106a-d

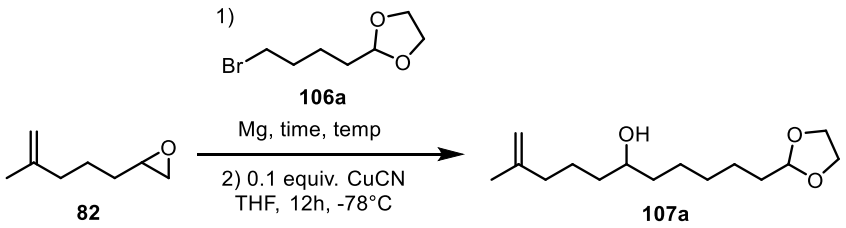
Having previously synthesized epoxide **82** and aldehyde **83**, we then focused our attention to dioxolanes **106a-d** (Scheme 14), the second building blocks necessary for route B. At the outset, aldehydes **105a-d** were obtained *via* PCC oxidation of the corresponding alcohols **104a-d** and used crude for the next step, without further purification. Refluxing with ethylene glycol in the presence of catalytic amounts of PTSA in toluene yielded the corresponding dioxolanes **106a-d** in high yields over two steps.



Scheme 14: Synthesis of dioxolanes **106a-d**.

I.2.2.6. Synthesis of Alcohols 107a-c

Having both necessary building blocks in hand, we proceeded with the Grignard addition of bromide **106a** to epoxide **82** (Table 5). However, Grignard preparation from bromide **106a** proved to be challenging and several different conditions were tested). Commercially available magnesium turnings or powder was used, as well as HClwashed turnings. Different solvents, reaction times, activating agents, temperatures, concentrations and addition methods were investigated. As seen in entry 6, 24% product was obtained along with different side products. Upon further analysis of entry 6, two side products were observed, dimer **108** and alcohol **109** (Scheme 15). Slow addition of the bromide to the reaction mixture could prevent dimer formation. We hypothesized that alcohol **107a** could be formed by reaction of dissolved oxygen with the Grignard reagent in presence of Cu(I)-salts. This could be prevented by degassing of the reaction mixture.

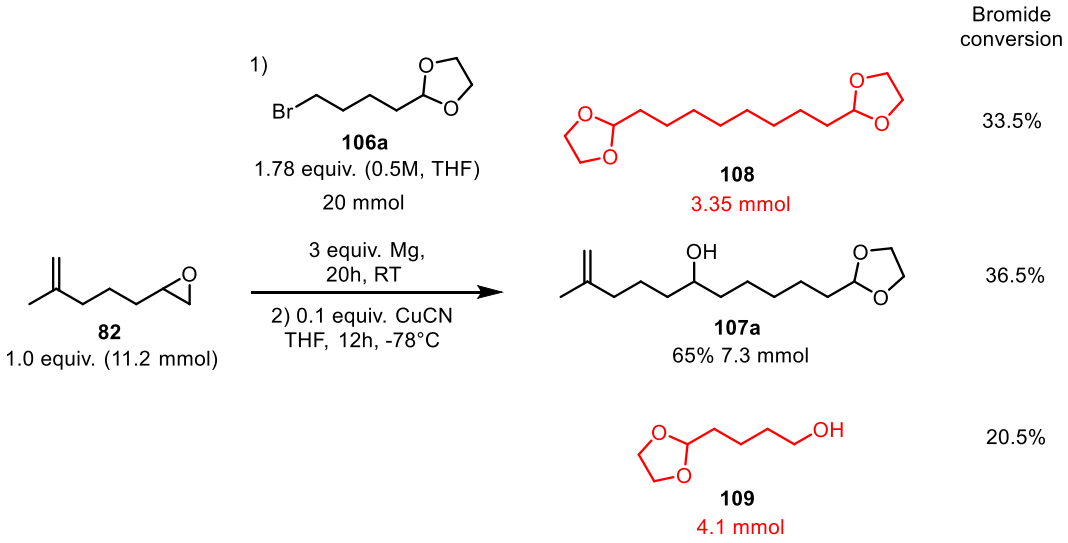


Entry	Bromide conc.	Solvent	Temp.	Time	Magnesium	Activation	Comments
1	1M	Et_2O	rt, reflux	2h, 1h	3.0 equiv. turnings	I_2, DBE	Direct add.
2	1.5M	Et_2O	rt	12h	3 equiv. turnings	I_2, DBE	add. over 20 min
3	1.5M	Et_2O	rt, then reflux	12h, 12h	3.0 equiv powder	I_2, DBE	add. over 20 min
4	1.5M	New Et_2O	rt	12h	3.0 equiv. turnings	I_2, DBE	add. over 20 min
5	1M	Et_2O	rt	12h	1.5 equiv. powder	I_2, DBE	add. over 30 min
6	0.5M	Et_2O	rt	12h	3.0 equiv. powder	I_2	24%, 153 mg, 0.6 mmol
7	0.5M	THF	rt	20h	3.0 equiv. powder	I_2	23%, 660 mg, 2.6 mmol

8	0.5M	THF	rt, then reflux	12h, 2h	3.0 equiv. powder	I_2	SM
9	0.5M	THF	rt	12h	3 equiv. turnings	I_2	Direct addition only SM
10	0.5M	Ether	rt	12h	3 equiv. turnings	I_2	1.0 equiv. LiCl
11	0.5M	THF	rt	12h	3.0 equiv. turnings	I_2	dropwise add.
12	0.5M	THF	rt	12h	3.0 equiv. powder	I_2	neat
13	1M	THF	rt	12h	3.0 equiv. powder	I_2	impurity of bromide (TLC)

Table 5: Screening conditions for the Grignard reaction of bromide **106a**.

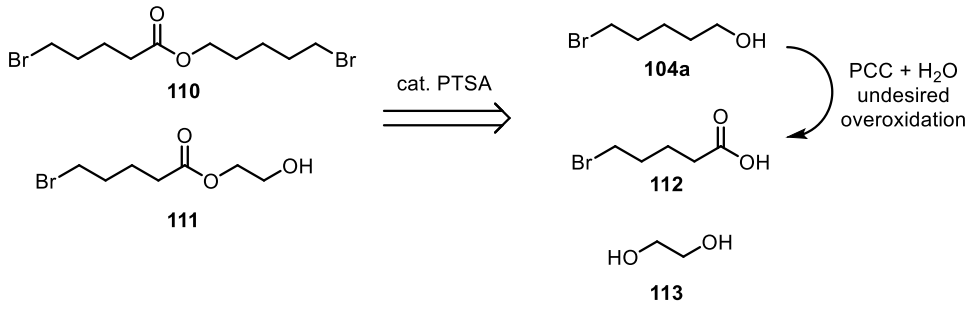
The reproducibility issues of entry 6 prompted us to recheck the purity of Bromide **106a**. In most cases, starting material was recovered after the attempted Grignard-reaction, implying that the reaction did not start. ^{1}H-NMR, ^{13}C-NMR and MS-analysis of the bromide showed less than one per cent impurities, which could be removed after laborious screening of different purification conditions and two consecutive column chromatography steps. Finally, the colorless bromide **106a** obtained from this procedure was a competent Grignard precursor.



Scheme 15: Side product analysis of entry 6.

Upon further analysis, the impurity was identified as being an inseparable mixture of 5-bromopentyl 5-bromopentanoate **110** and 2-hydroxyethyl 5-bromopentanoate **111** (Scheme 16).

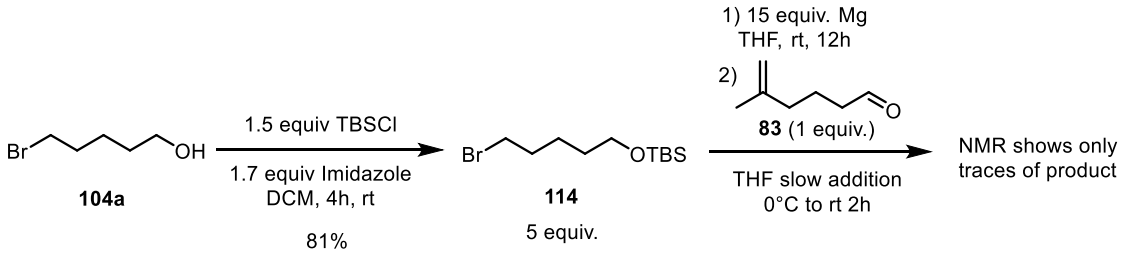
These compounds likely arise from traces of unreacted substrate (alcohol c) and overoxidation (acid x).



Scheme 16: Identified impurities.

Intrigued by these results, we decided to test the ability of these isolated compounds to inhibit Grignard formation. Two Grignard reactions using clean bromide **106a**, which was doped with 4% or 12% of ester mixture **110** and **111**, were carried out. In both reactions, no initiation of the Grignard reaction was observed, thus strongly suggesting that our tribulations to achieve effective Grignard formation were caused by these trace impurities.

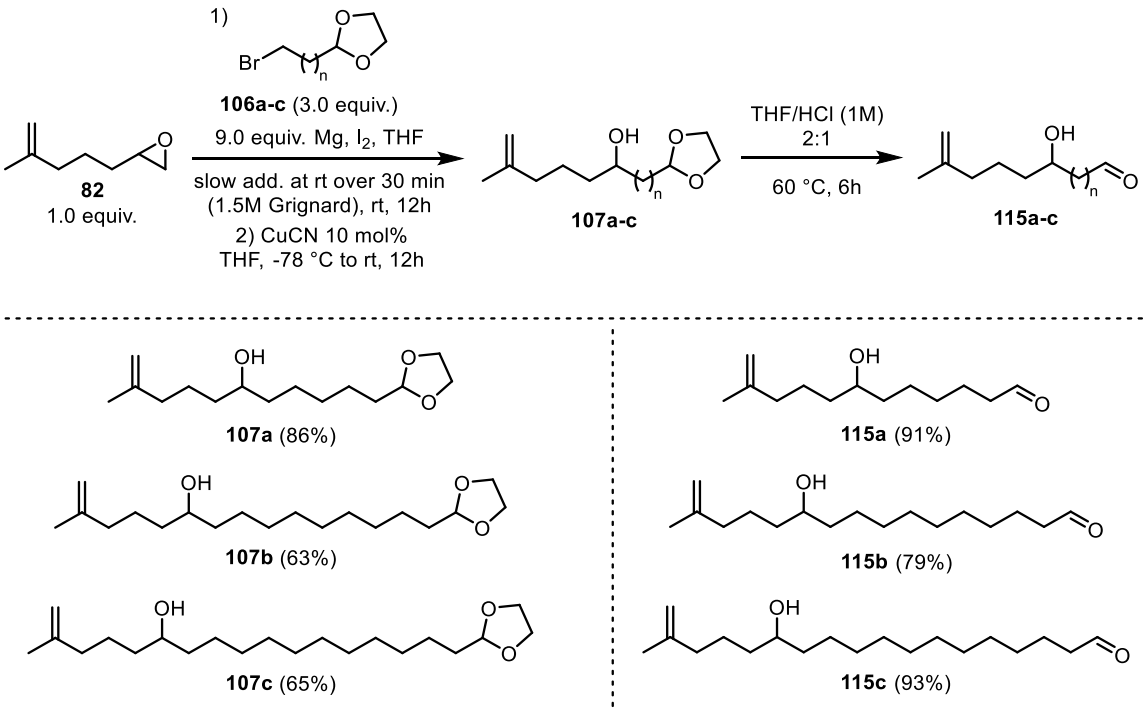
During the course of these investigations, a different approach using a TBS-protected bromide **114** was attempted (Scheme 17). However, Grignard formation on this substrate proved challenging and NMR analysis showed only traces of the desired product.



Scheme 17: A different Grignard-based approach.

I.2.2.7. Synthesis of Aldehydes 115a-c

Having an efficient protocol for Grignard formation in hand, we decided to prepare aldehydes with different lengths of the spacing chain. After purifying the bromides a second time, Grignard formation was successful and alcohols **106a-c** were synthesized in moderate to high yields (Scheme 18). After optimization, deprotection of the cyclic acetals was achieved under acidic conditions using a 2:1 mixture of THF and HCl (1 M) at 60 °C for 6h. Initially, separation of the protected and deprotected aldehyde proved to be challenging. Longer reaction times, however, led to decomposition. A solvent system of DCM/ethyl acetate 95:5 proved to be ideal and aldehydes **115a-c** were successfully isolated from the remaining traces of starting material in high yields.



Scheme 18: Synthesis of aldehydes **115a-c**.

I.2.3. Initial Results on the Macrocyclization-Hydride Transfer Reaction.

The macrocyclization of aldehyde **115c** was attempted using several Lewis Acids at 35° C in DCE under dilute conditions (0.01M). Along the desired product, what appeared to be a dimer was consistently observed from the very first trials. Interestingly, depending on the Lewis Acids (Figure 5, left) used, different monomer/dimer ratios were observed (Table 6). Using $SnCl_4$ mostly resulted in decomposition, while $FeCl_3$ favored formation of an unidentified product. $TiCl_4$ required extended reaction time to reach full conversion and, after 20 hours, a 2.7:1.0 ratio between monomer and dimer was observed. BF_3•Et_2O gave a 1.0:1.1 ratio between monomer and dimer after 1 hour. These ratios were calculated from the crude ^{13}C-NMR spectra after careful separation of the two macrocyclic species and DOSY and HRMS. Signal **a** (Figure 5, right) has been attributed to monomer **116** while **b** has shown to be dimer **117**. These initial results suggest a divergent pathway depending on the nature of the used Lewis Acid. Further optimization could open access to different products starting from one aldehyde.

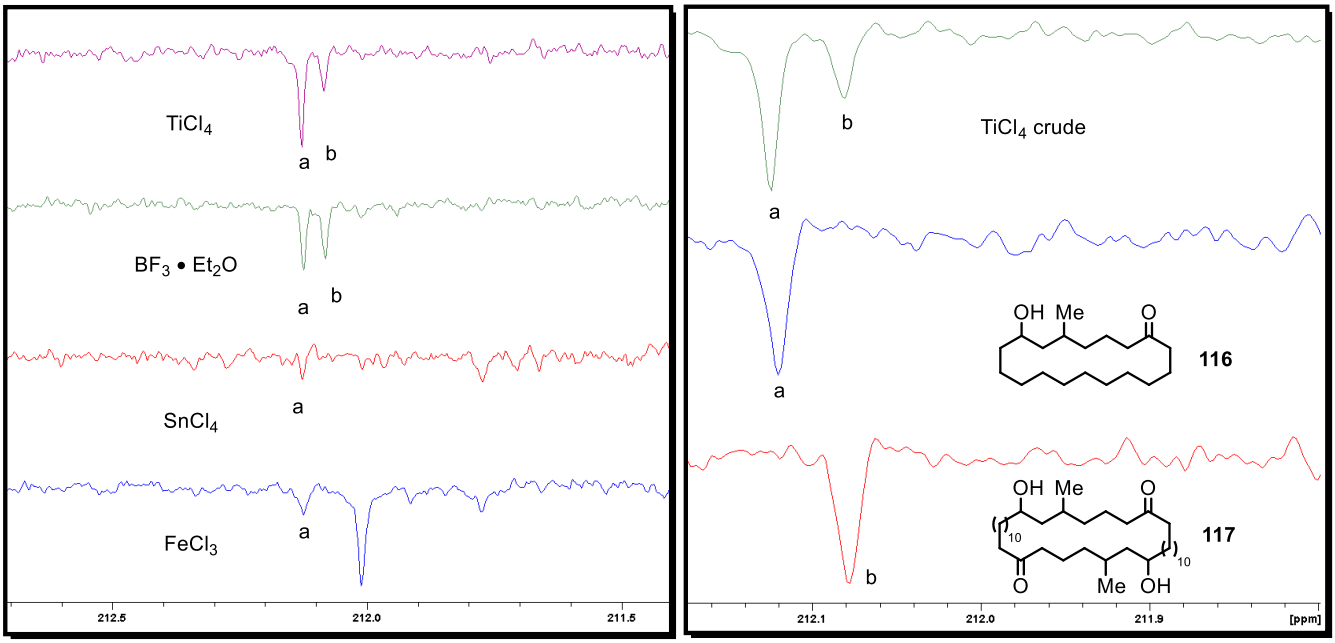


Figure 5: ^{13}C NMR ketone signals (left). Isolated **a** (monomer) and **b** (dimer) signals.

Lewis Acid	Time	Signal ratio a:b
BF_3 Et_2O	1 h	1.0 : 1.1
$TiCl_4$	20 h	2.7 : 1.0

Table 6: Lewis Acid signal ratio.

The relationship between starting material (aldehyde), monomer and dimer is further confirmed by their overlapped DOSY spectra as depicted in Figure 6.

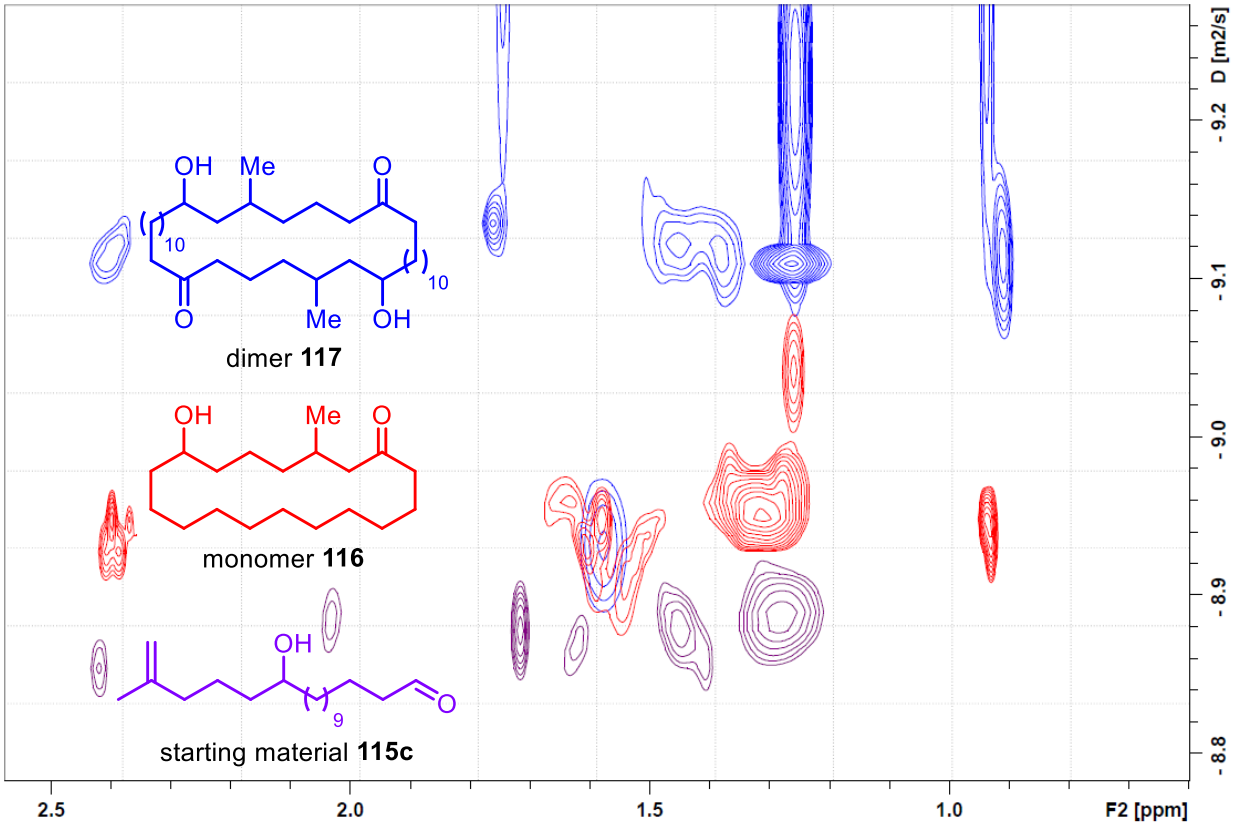
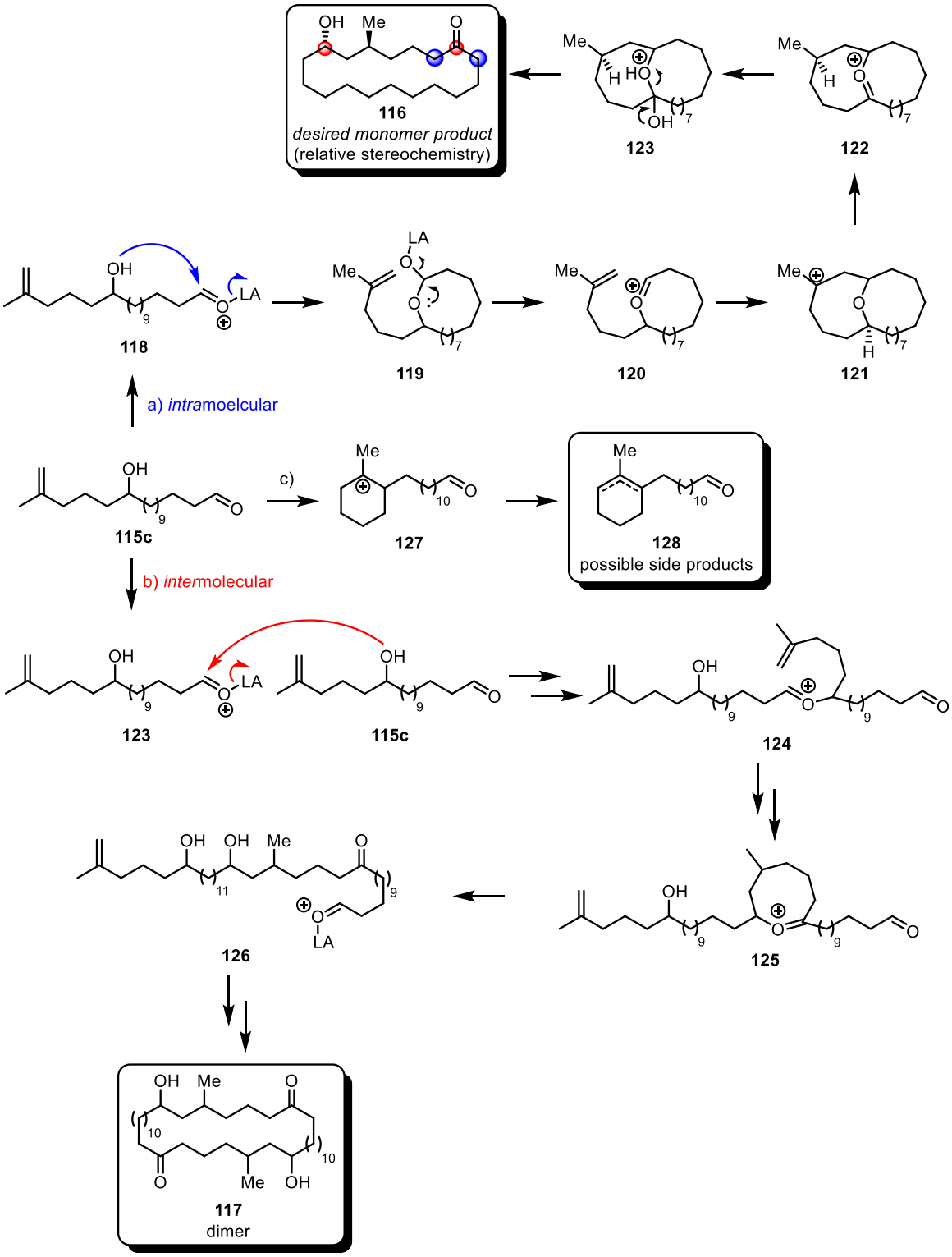


Figure 6: Overlapped DOSY spectra of starting material, monomer and dimer.

As for the mechanistic rationale, we presume that the corresponding Lewis Acid will activate the carbonyl **118**, making it more electrophilic and more susceptible to an *intra*molecular nucleophilic attack by the alcohol (Scheme 19a), arriving at intermediate **119**. This can form carbocation **121**, which then undergoes a [1,5] hydride transfer and, after nucleophilic attack of water, yields the desired product **116**. If instead, an *inter*molecular nucleophilic attack of the alcohol occurs, dimeric structure **117** is formed after two consecutive hydride-transfer events. (Scheme 19b). An additional side product mixture **128** was observed in the crude NMR, which could arise from loss of water followed by cyclization and elimination (Scheme 19c).

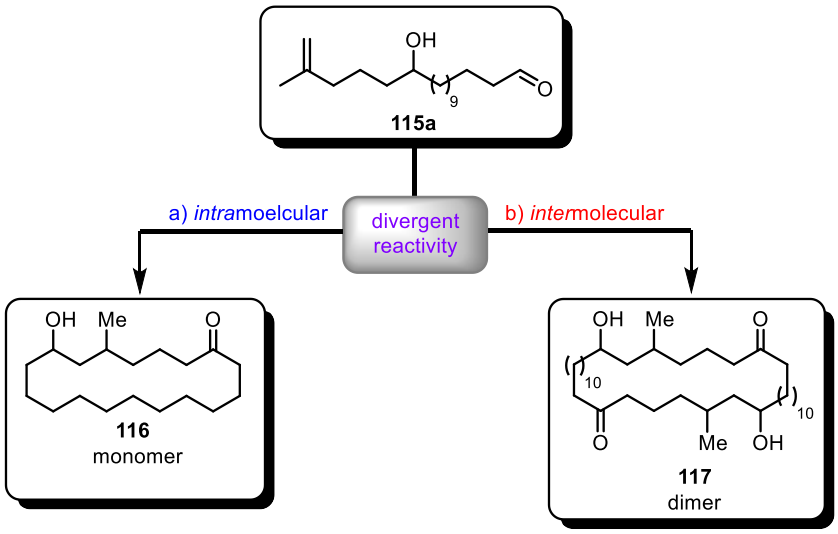


Scheme 19: a) intramolecular pathway, b) intermolecular pathway, c) elimination pathway.

I.3. Summary and Outlook

In conclusion, a range of aldehydes that could serve as substrates for the macrocyclization were successfully synthesized, embodying all required functional groups (aldehyde, alcohol and alkene) in the same precursor. During the synthesis of these substrates, we ascertained the remarkable inhibiting nature of two bromo-ester impurities on the Grignard initiation, even when present in trace amounts.

The macrocyclization of a representative precursor was attempted using different Lewis acids. Surprisingly, a propensity for dimer formation (even under dilute conditions) was observed. Depending on the nature of the Lewis Acid employed, different monomer/dimer ratios were observed. To this end, $TiCl_4$ showed the highest potential towards monomer synthesis with a monomer/dimer ratio of 2.7:1. By lowering the concentration further or slow addition *via* syringe pump we hope to further increase selectivity towards the *inter*molecular product. Additionally, installation of Thorpe-Ingold elements to favor the intramolecular oxocarbenium-ion formation event could also be beneficial. Ideally further optimization could allow us selectively access either monomeric of dimeric macrocyclic structures of these type depending on the conditions used.



Scheme 20: Divergent macrocyclization.

II. Protodesulfination of Sulfoxides

II.1. Introduction

Although the central aim of organic chemistry is the forging of new bonds, breaking bonds selectively is of similar importance. It might seem counterintuitive to deconstruct molecules, but controlled ways to cleave specific bonds can also create complexity in new ways. Additionally, several aspects highlight the necessity to develop bond breaking reactions as synthetic tools in the future. Firstly, the development of new drugs is essential to maintaining and improving the lifestyle of humankind. Drug development *via* bond cleavage of an elaborate core structure has emerged as a new way to explore new bioactive derivatives.[44] When more sustainable access to basic chemicals through routes not relying on petrol is considered, one potential solution relies on the conversion of highly functionalized, renewable feedstocks abundant in Nature. This process generally requires selective *defunctionalisation* methodologies to be developed – again relying on the development of bond-breaking reactions. Unsurprisingly, bond-breaking reactions have become more and more popular in recent years and several new elegant approaches have emerged.[45–47]

II.1.1. Sulfoxides as Versatile Reagents

Sulfoxides are interesting reagents in organic synthesis.[48] While sulfur favors coordination to transition metals, oxygen has an affinity for alkali metals. This versatility lies at the heart of the widespread application of sulfoxides in organic synthesis (Figure 7).[44]

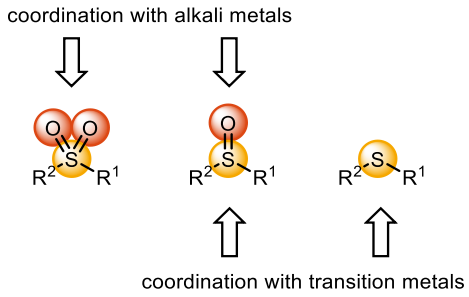
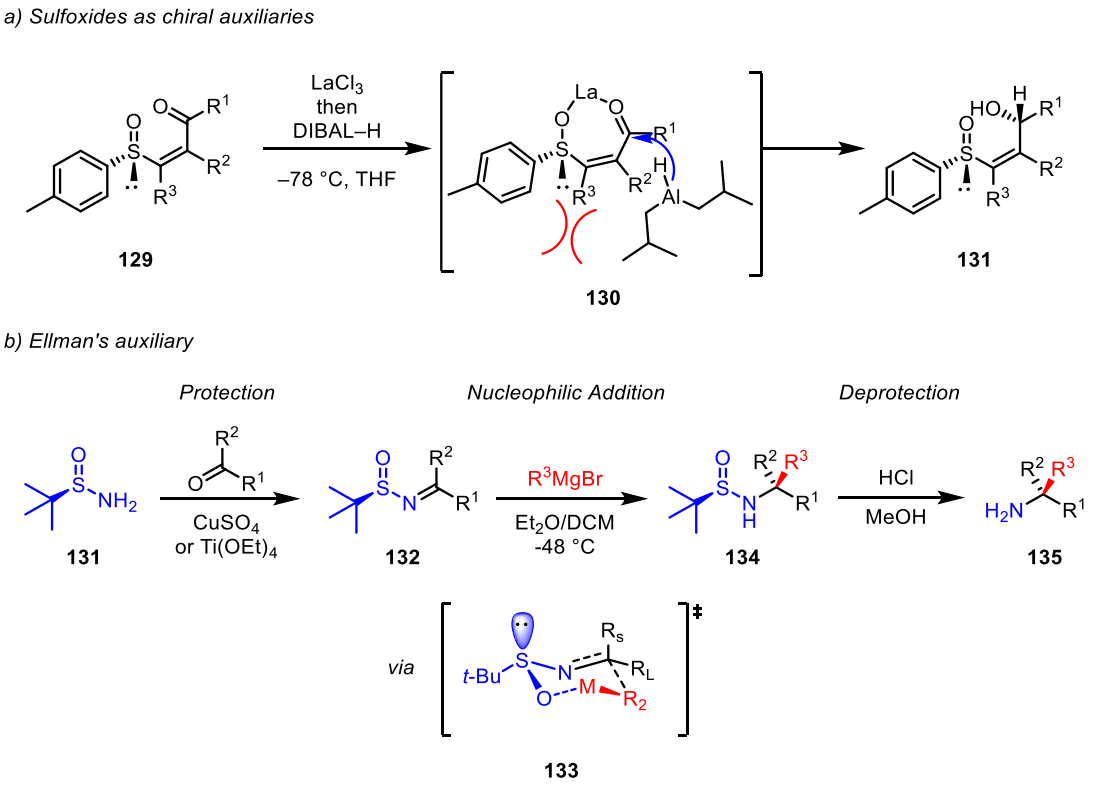


Figure 7: Coordination ability of sulfoxides.

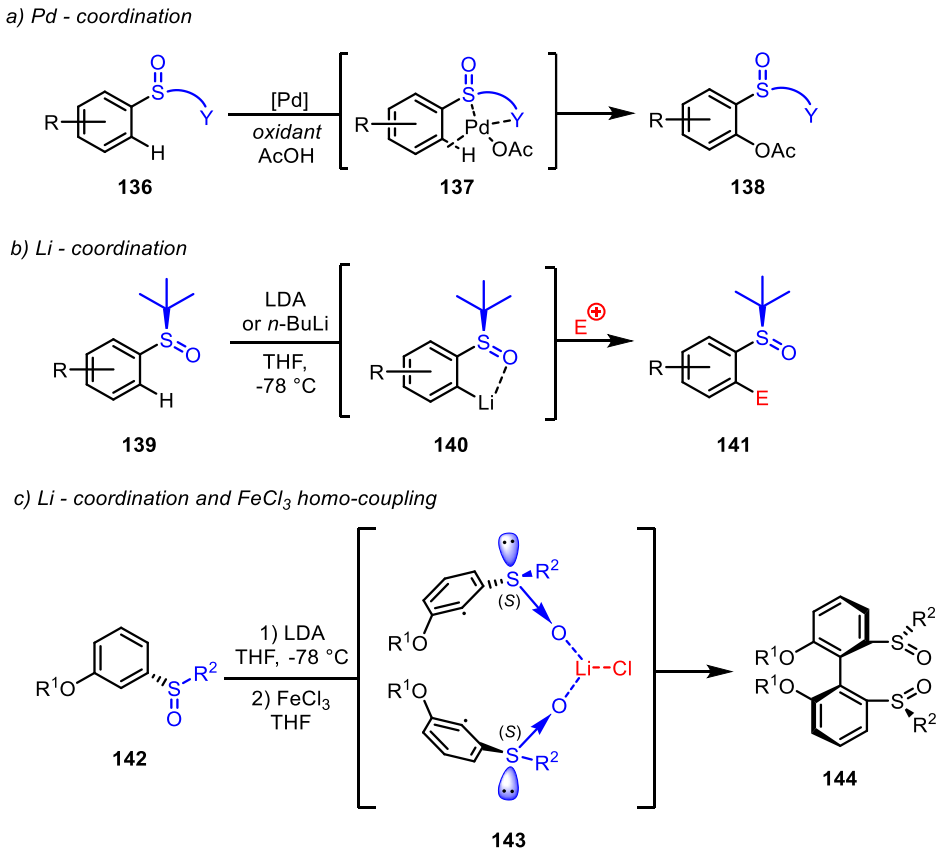
Sulfoxides are widely employed as chiral auxiliaries, given that their additional stereogenic center on sulfur as well as their highly polarized S–O bond often lead to excellent chiral induction. Therefore, sulfoxides are valuable chiral auxiliaries in Diels-Alder processes,[49] synthesis of axially chiral C–N scaffolds or asymmetric reductions in combination with La(III)-salts (Scheme 21).[50]

A *t*-butylsulfinamide has been introduced by Ellman as a chiral auxiliary for the asymmetric synthesis of amines by addition of a Grignard reagent followed up by simple HCl/MeOH hydrolysis (Scheme 21b).[50], [51] Ellman's sulfonamide, allegedly the most widely employed chiral reagent in the patent literature,[52] has been applied to the synthesis of numerous versatile building blocks including *syn*- and *anti*- 1,2- or 1,3-amino alcohols,[53], [54] α-branched and α,α-dibranched amines,[55] , chiral heterocycles,[56] and α- or β-amino acids and esters.[57], [58]



Scheme 21: Chirality induced *via* sulfoxides.

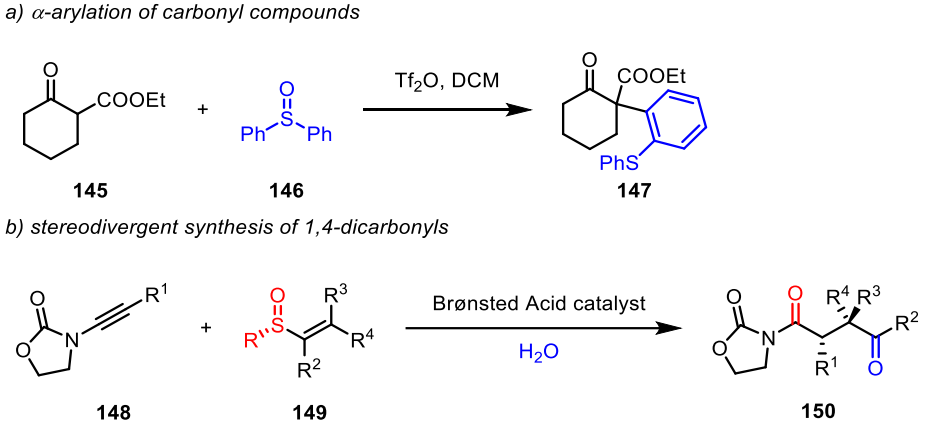
Additionally, sulfoxides have gained considerable attention for their ability to direct further functionalisations in the parent molecule. Mancheño's group has reported a transition-metal catalyzed C-H activation using *ortho*-sulfoxide tethers as directing groups (Scheme 22a).[44], [59], [60] Sulfoxides can also be used for directed *ortho*-lithiation (Scheme 22b).[61,62] The resulting organolithium species can easily react with a broad range of electrophiles. Another interesting example is the use of sulfoxide tethers for directed oxidative aryl homo-coupling (Scheme 22c).[63]



Scheme 22: *o*-Sulfur tethers as directing groups.

There have also been a plethora of reports where activated sulfoxides undergo [3,3]- and [2,3]-sigmatropic rearrangements.[64] In particular, the Maulide group has pioneered this field, one early representative example being the metal-free α-arylation of carbonyls (Scheme 23a).[48,64–69] Under mild conditions, a sulfonium species is generated which rearranges to the *ortho*-functionalised product containing an all carbon quaternary center. Other contributions to sulfoxide chemistry include the hydrative arylation of ynamides, the Umpolung of alkali halide salts and the development of sulfoxide-driven oxidative cyclizations.[65] Recently, the Maulide group has reported a stereodivergent synthesis of 1,4-dicarbonyls *via* coupling of vinylsulfoxides and ynamides (Scheme 23b).[48,64–69] In this case, the chirality at sulfur, within the vinylsulfoxide partner, is transferred to the coupling product. Most interestingly, by changing the double bond geometry of the same reactant, access to all four possible stereoisomers of the substituted 1,4-dicarbonyl products was ultimately possible.

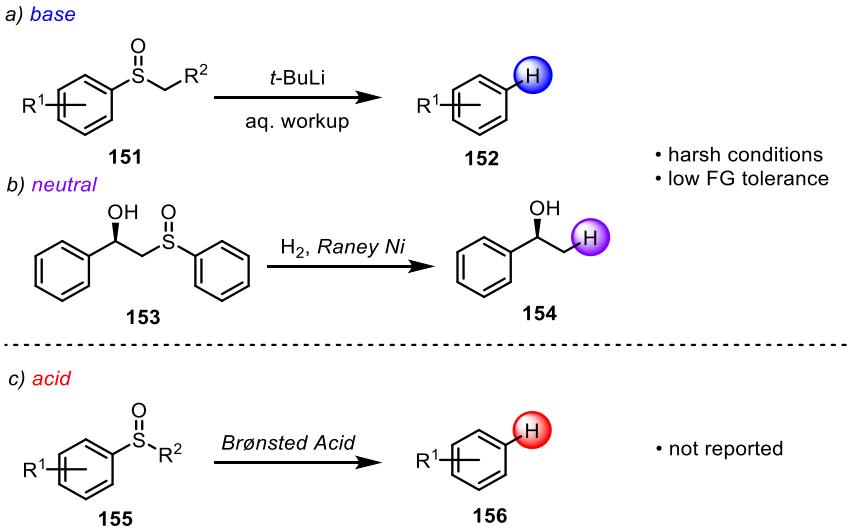
During ongoing studies of sulfoxide-mediated C–C bond forming reactions (Scheme 23),[65] we have recently discovered that in certain cases C–S bond cleavage occurs under acidic conditions. This selective defunctionalisation has gained our interest since the ability to cleave such C-S-sulfinyl bonds, opposed to the facile cleavage of N-S-sulfinamides, is not an obvious transformation especially under mild conditions.



Scheme 23: Selected examples of sulfoxide applications from the Maulide group.[60], [70]

II.1.2. Cleaving the C–S Bond in Sulfoxides

When it comes to defunctionalization of sulfoxides, most examples in the literature resort to harsh reagents such as *n*-BuLi or *t*-BuLi. Such reactions proceed *via* sulfoxide-lithium exchange mechanisms, followed by protonation of the resulting organolithium species (Scheme 24a).[71], [72], [73] Alternatively, Raney Nickel can be used to cleave the C–S bond of sulfides, sulfoxides and sulfones by hydrogenation (Scheme 24b).[74], [75] Both of these methods, the use of organolithium reagents as well as reductive conditions using Raney Nickel, have substantial limits in the functional group diversity that can be present in the substrate. Due to the widespread applications of sulfoxides in contemporary organic chemistry, conditions that allow the removal a sulfinyl group orthogonally to other functional groups have the potential to open up new approaches in synthesis. Furthermore, a deeper understanding of this reaction will lead to a more complete picture of the reactivity that can be anticipated for reactions with sulfoxides in acidic media (Scheme 24c).



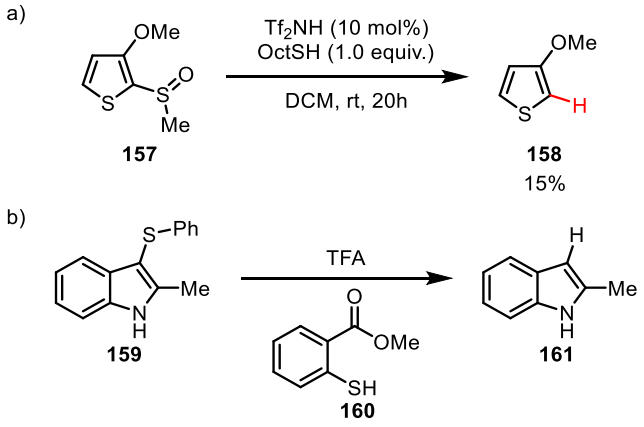
Scheme 24: Deprotection of sulfoxides.

For the second part of my MSc thesis, the scope and limitations of this Brønsted Acid-catalyzed desulfination reaction of sulfoxides were investigated, especially in respect to understanding the electronic requirements of the sulfoxide substituents.

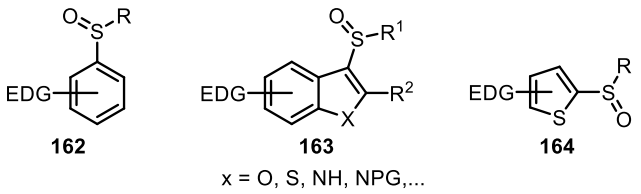
II.2. Results and Discussion

The results detailed in this section have been obtained in collaboration with M.Sc. Immo Klose.

During ongoing work on sulfoxide-mediated C–C bond forming reactions, an interesting observation was made in our research group. Substantial amounts of the protodesulfinated product **158** were observed in a process mediated by triflimide, where the corresponding sulfoxide **157** had been employed (Scheme 25). The idea of a sulfoxide-cleavage process (effectively a *desulfination*) under conditions requiring only a Brønsted Acid catalyst and a thiol attracted our attention. A literature survey revealed a related study by Girard reporting the desulfenylation of indolyl-sulfides by reaction with a thiol in trifluoroacetic acid.[75] To the best of our knowledge, sulfoxides have not been used in this or related transformations. We decided to investigate this process by synthesizing and testing different sulfoxides. Surmising that the mechanism might involve protonation of the aromatic ring, we speculated that electron-rich aryl sulfoxides would be the ideal substrates and designed our substrate panel with the aim to understand the stereoelectronic requirements for this transformation. Our plan involved synthesis of the electron-rich sulfoxides **162-164** (Scheme 26) which, after optimization of the reaction parameters, would be tested in this transformation.



Scheme 25: a) Initial observation. b) Desulfenylation reaction as reported by Girard.



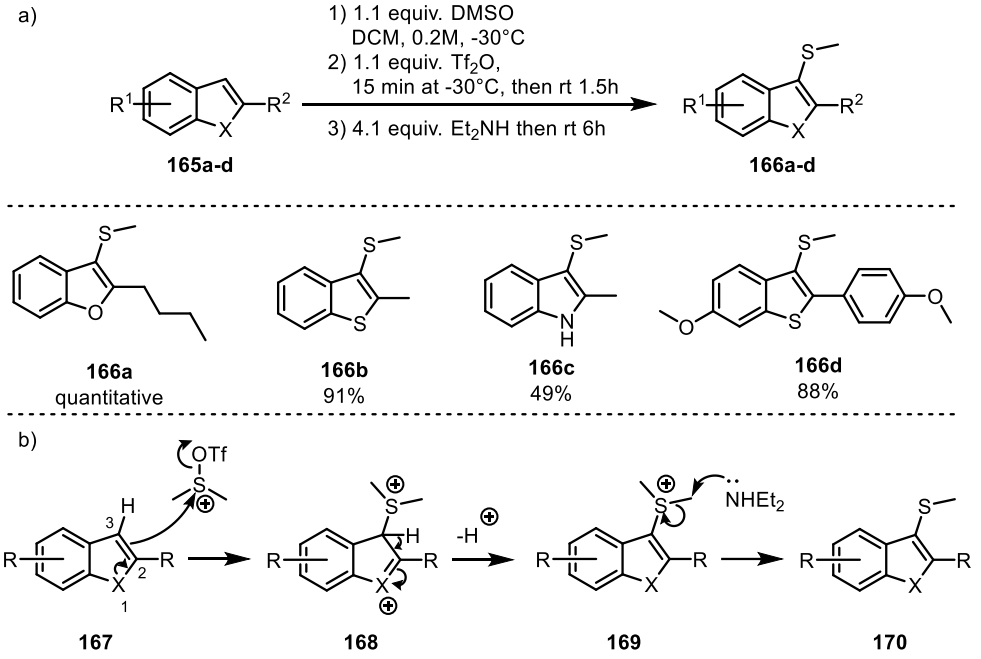
Scheme 26: Planned substrate scope.

II.2.1. Synthesis of Starting Material

Most sulfoxides are most conveniently prepared *via* oxidation of the corresponding sulfide. The aryl sulfides that were prepared in this work were obtained by direct C–H thioarylation either from an electrophilic aromatic substitution or *via* lithiation followed by sulfenylation.

II.2.1.1. Synthesis of Sulfides 166a-d *via* Triflic Anhydride Activated DMSO

Following a protocol by Procter *et al.*,[76] aryl sulfides **166a-d** (Scheme 27a) were synthesized from the respective arenes using triflic anhydride to activate DMSO towards electrophilic aromatic substitution. The initially formed dimethyl sulfonium species **168** (Scheme 27b) is demethylated by subsequent treatment with a nucleophile such as diethylamine, to obtain the methyl sulfides in a very efficient manner. All desired sulfides were formed very efficiently, the lower yield in the case of indole sulfide **166c** is due to purification difficulties.

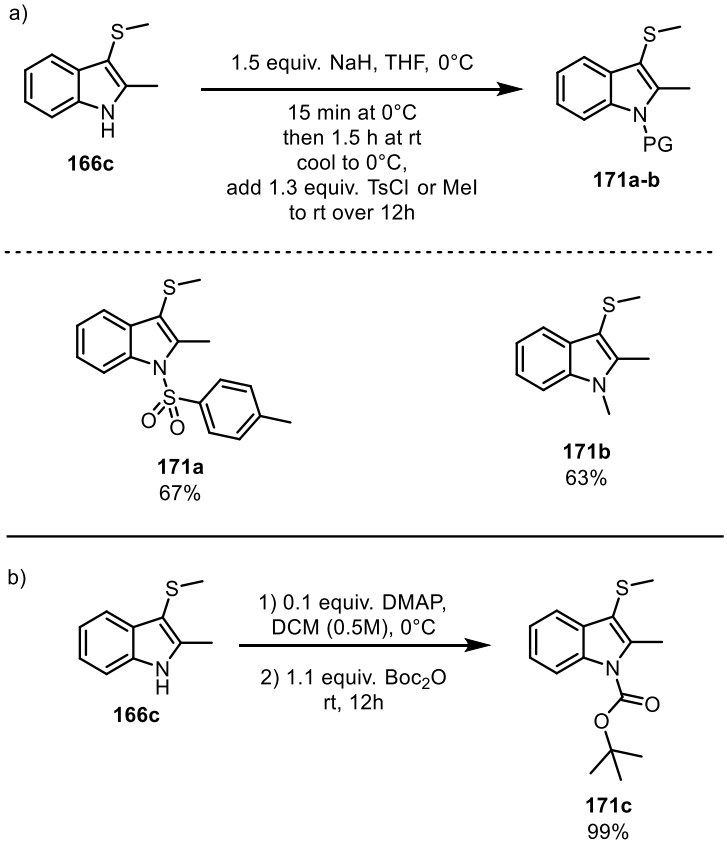


Scheme 27: a) General procedure **I** for sulfide synthesis b) Mechanism of sulfide formation

II.2.1.2. Synthesis of Protected Sulfides 171a-c[77]

For a better understanding of the protodesulfination reaction, we decided to prepare and compare differently N-protected indolyl(methyl)sulfoxides. At the outset, N–H and N–methyl substitution constitute electron-rich aryl systems. On the other hand, protection of the nitrogen either as a sulfonamide or a carbamate lowers the electron density of the aromatic system – such substrates could be considered moderately electron-rich (in a relative sense).

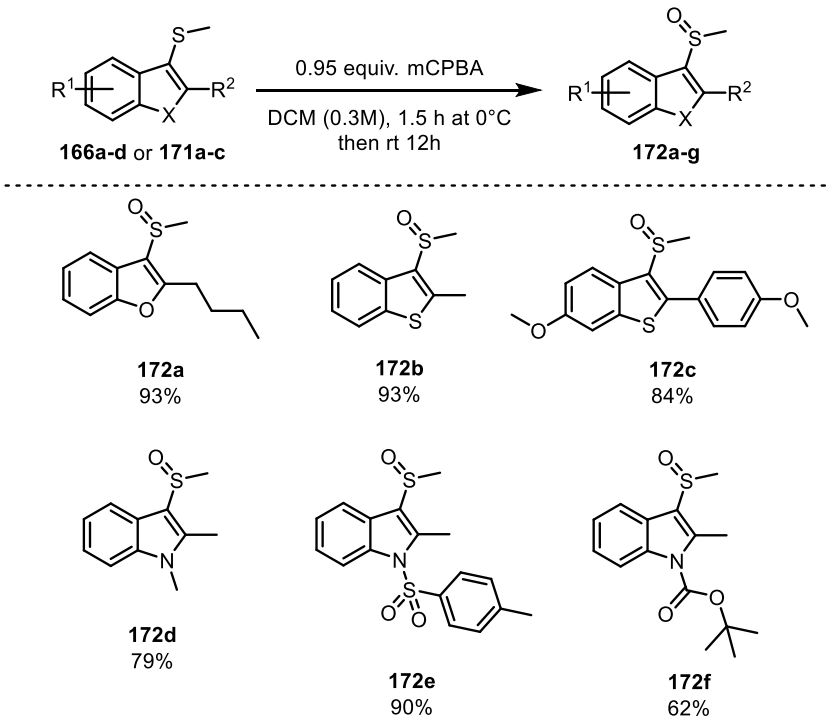
All derivatives were readily prepared. Sulfides **171a-b** were synthesized in moderate yields *via* deprotonation with NaH and treatment with iodomethane and tosyl chloride respectively (Scheme 28a). As carbamate group we selected the acid-labile Boc protecting group, as it would enable us to study the competing deprotection under the proposed reaction conditions of desulfination. Sulfides **172** was easily Boc-protected using DMAP/Boc_2O in high yield (Scheme 28b).



Scheme 28: General procedure **I** for protected sulfide synthesis.

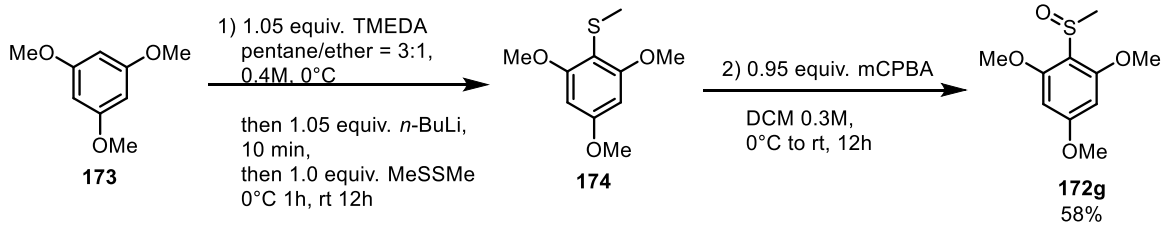
II.2.1.3. Synthesis of Sulfoxides 172a-g[76]

With the desired sulfides in hand, we turned to the subsequent oxidation step. Sulfoxides **172a-g** were obtained by oxidation using *m*-CPBA in good to high yields as shown in Scheme 29.



Scheme 29: General procedure **I** for sulfoxide synthesis.

For the synthesis of sulfoxide **172g** (Scheme 30), we decided to use a lithiation reaction. *O*-lithiation of 1,3,5-trimethoxy benzene using *n*-BuLi and TMEDA followed by the addition of dimethyldisulfide afforded crude sulfide **174**. The crude sulfide was filtered through a pad of silica and used for the next step without further purification. Treatment of sulfide **174** with *m*-CPBA in DCM afforded the desired sulfoxide **172g** in 58% over 2 steps.

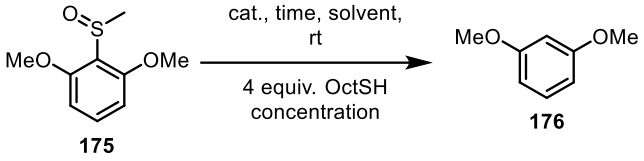


Scheme 30: General procedure **II** for sulfoxide synthesis.

II.2.2. Optimization Study

To understand and optimize the desulfination reaction we set out to investigate several reaction parameters. For this purpose, the moderately electron rich 1,3-dimethoxy-2-(methylsulfinyl)benzene **175** was chosen as default substrate. As initial reaction conditions, we decided to run reactions at room temperature with an excess of thiol to ensure full conversion. Octhanethiol was selected as standard thiol as it is conveniently a less toxic and low cost alternative to thiophenol. Room temperature was chosen, given that previous reactions using sulfoxides have led to decomposition when higher temperatures were used.

We first investigated different solvents (Table 7). After 16 hours at room temperature, no product could be detected in acetone, diethyl ether or methanol. HFIP showed traces of product while DCM showed full conversion. Thus, we continued our investigation using DCM as a solvent.



Entry	Catalyst	Solvent	Time	Conc.	Comment
1	TfOH 80 mol%	DCM	16h	0.2 M	full conversion
2	TfOH 80 mol%	MeOH	16h	0.2 M	no conversion
3	TfOH 80 mol%	acetone	16h	0.2 M	no conversion
4	TfOH 80 mol%	Et_2O	16h	0.2 M	no conversion
5	TfOH 80 mol%	HFIP	16h	0.2 M	traces of product

Table 7: Screening conditions of sulfoxide **175**.

Next, we looked at the different concentrations (Table 8, Entry 1 and 2) but no clear difference was observed between 0.2 M and 0.5 M. We decided to continue with a concentration of 0.2 M sulfoxide for further investigations given the small scale of our standard reaction. The influence of water and air was analyzed and showed that we had full conversion with a mixture of 5:1 DCM/water (Table 8, Entry 3) or open flask (Table 8, Entry 4).

Entry	Catalyst	Solvent	Time	Conc.	Comment
1	TfOH 50 mol%	DCM	16h	0.5 M	traces of product
2	TfOH 50 mol%	DCM	16h	0.2 M	traces of product
3	TfOH 80 mol%	dry DCM	20 h	0.2 M	added 0.1 ml H_2O, full conversion
4	TfOH 80 mol%	dry DCM	20 h	0.2 M	open flask, full conversion

Table 8: Screening conditions of sulfoxide **175**.

When bistriflimide (Table 9, Entry 1) was used instead of triflic acid, full conversion was also observed after 20 hours. Given that triflic acid is a liquid at room temperature, it was easier to handle and thus we continued using it. Changing the 1-octanethiol with thiophenol (Table 9, Entry 2) had no significant influence and we continued to use the less toxic 1-octanethiol. To rule out any potential influences of light and oxygen. Irradiation with blue light (Table 9, Entry 4) gave similar results to the reaction performed in the dark (Table 9, Entry 3). Similarly, O_2 atmosphere showed no beneficial effect on our reaction (Table 9, Entry 5).

Entry	Catalyst	Solvent	Time	Conc.	Comment
1	Tf_2NH 80 mol%	dry DCM	20 h	0.2 M	full conversion
2	TfOH 50 mol%	dry DCM	28h	0.2 M	thiophenol instead of OctSH product:SM = 1:1 ratio
3	TfOH 50 mol%	dry DCM	4h, dark	0.2 M	sulfoxide/sulfide/product = 75%/4%/9%[a)]
4	TfOH 50 mol%	dry DCM	4h, blue light	0.2 M	sulfoxide/sulfide/product = 80%/20%/0%[a)]
5	TfOH 50 mol%	dry DCM	4h, O_2 atmosphere	0.2 M	sulfoxide/sulfide/product = 87%/9%/2%[a)]

Table 9: Screening conditions of sulfoxide **175**.

We have, in later experiments, noted reproducibility issues with certain substrates. While we believe this might be due to a potential radical nature of this reaction and some of its intermediates, investigations are currently underway to elucidate this aspect.

In conclusion, we found that polar, aprotic solvents such as dichloromethane gave the best results. Furthermore, a high dependence the acid concentration was observed, with no significant conversion being detected below a 50 mol% loading of the respective Brønsted Acid.

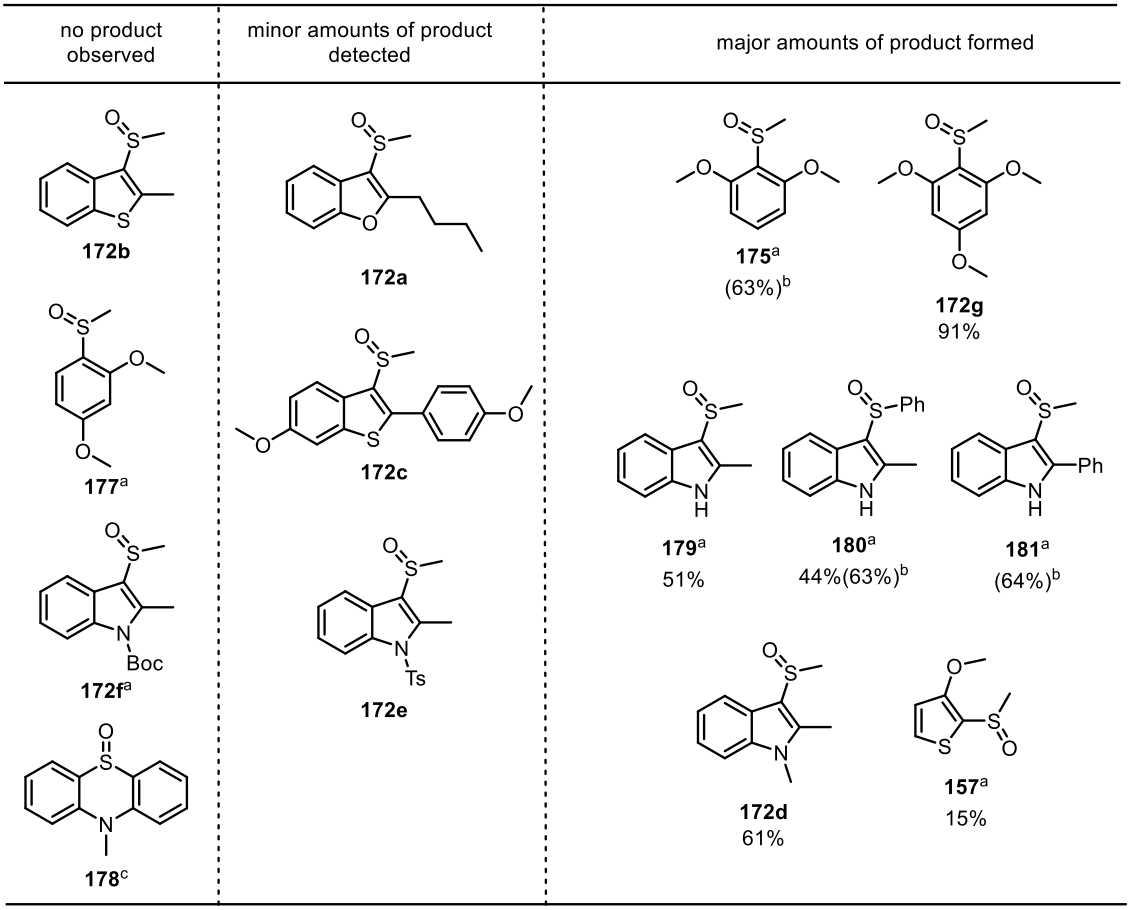
II.2.3. Substrate Scope

Simultaneously with the latter stages of optimization, we treated the different sulfoxides prepared previously with 50 mol% triflic acid and four equivalents of 1-octanethiol at room temperature for 2 to 20 h (Figure 8). With these reaction conditions, the substrates tested could be divided into three different categories depending on the efficiency of the reaction.

For the first category no conversion was observed under the reaction conditions. This category includes mostly sulfoxides with the least electron rich aryl moieties amongst sulfoxides tested. In case of sulfoxide **178**, full conversion to the respective sulfide was observed, likely due to its cyclic structure disfavoring endocyclic C–S bond cleavage.

With increased electron density of the arene part, small amounts of product were detected by ^{1}H-NMR. These sulfoxides **172a**, **172c,** and **172e** thus show the desired reactivity yet likely require further adjustment of the reaction condition to undergo the reaction efficiently.

The third category contains substrates that led to high conversion and the product was observed as a major component. This was the case for the most electron rich substrates such as indoles and arenes bearing several methoxy substituents. The successful reaction of the model substrate **175** suggests also sterical factors to influence the reaction. In comparison to sulfoxide **177** which differs only by the substitution pattern, the reaction was more successful, a sign for additional driving force in case of **175** to evade the crowded substitution pattern. However, it should be mentioned that in some cases also low conversion was observed for **175**. Sulfoxide **172g** bearing an additional methoxy substituent afforded the product smoothly in 91% isolated yield. Unfortunately, especially the electron rich heterocycles that are formed can undergo undesired side reactions under the reaction conditions and lead to decreased isolated yields. These side reactions include substitution on electrophilic sulfur intermediates as well as oxidative dimerization. In the extreme case of thiophene sulfoxide **157** the product could only be isolated in 15% yield due to extensive degradation. Additionally we were able to see for substrate **179** full conversion with 5 mol% triflic acid after 4 h, suggesting overreaction or decomposition could be hindered by employing milder conditions.



a) Compounds prepared by MSc. Immo Klose. b) NMR Yield using mesithylene as an internal standard.

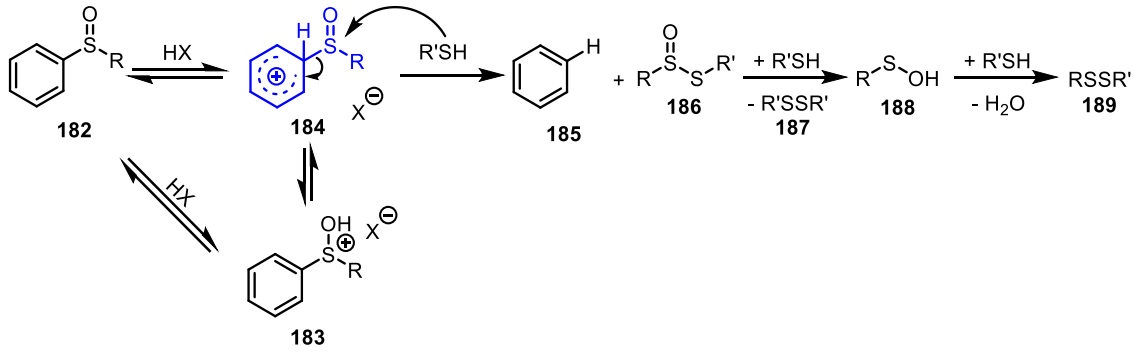
c) Full conversion to the respective sulfide was observed.

Figure 8: Overview sulfoxides substrates.

II.2.4. Proposed Mechanism

One possible mechanism for the desulfination reaction is shown in Scheme 31. Due to its highly negatively charged oxygen atom, sulfoxides can be protonated to sulfonium species **183**, a process that is even more favorable in case of electron rich substituents that stabilize the positive charge on sulfur. However, the substrate could also be protonated on the aromatic ring leading to intermediate **184**. This intermediate has two possibilities to rearomatize: either through deprotonation or by desulfinylation. The latter would proceed through nucleophilic attack of a thiol leading to the product and the thiosulfinate **186**. This process would closely resemble the well-known acid-catalyzed desulfonylation of arenes from aryl sulfonic acids. Thiosulfinates are not very stable and tend to undergo further reactions. In the presence of a thiol, the sulfenic acid **188** is formed which itself will lead to the formation of disulfide **189** and water.

Alternatively, a radical pathway could be operative in which the newly formed C–H bond would be formed by hydrogen atom transfer. At this point, the mechanism is still under investigation. To this end, intramolecular trapping experimenst could help identifying a potential radical process.



Scheme 31: Mechanistic Proposals.

II.3. Summary and Outlook.

In the second part of this MSc thesis, a new possibility of cleaving aryl sulfoxides under acidic conditions was investigated. For this study, several aryl sulfoxides were prepared with heteroaryl and aryl moieties ranging from moderately to very electron rich. Optimization study revealed the need for highly acidic Brønsted Acids as well as a high dependence of the acid loading. Several conclusions could be drawn from investigating the stereoelectronic requirements for this transformation:

1) Sulfoxides with moderately electron rich aryl moieties do not react or only react very slowly at room temperature with 50 mol% TfOH. However, the product could be detected in several cases suggesting that longer reaction times, higher temperature or a higher concentration of Brønsted Acid likely lead to an efficient reaction.
2) Electron-rich sulfoxides readily undergo the desulfination reaction under the reaction conditions. Especially with heteroarenes such as indoles and thiophenes degradation of the products is observed leading to only moderate yields of the products. In these cases, lower reaction temperatures and a lower acid loading could be necessary to prevent undesired side reactions.
3) Steric hindrance around the sulfoxides also influences the reaction with more hindered sulfoxides undergoing the reaction more easily.

Thus the optimal reaction conditions for certain sulfoxides have been found to be highly dependent on the inherent electron density of the aryl substituent. The higher the electron density, the milder the optimal reaction conditions.

Concerning the mechanism, an ionic pathway seems the most plausible. Protonation of the aromatic ring followed by nucleophilic attack of the sacrificial thiol could lead to formation of the desired product. Alternatively, a radical mechanism cannot be excluded at the current stage.

In summary, we have investigated a C–S cleavage of aryl sulfoxides which could become an orthogonal transformation.

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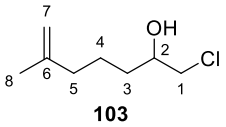
Experimental Part

General information

All glassware was dried before use. All solvents were used in p.a. quality. All reagents were used as received from commercial suppliers unless otherwise stated. Reaction progress was monitored using TLC on aluminum sheets coated with silica gel 60 with 0.2 mm thickness (Pre-coated TLC-sheets ALUGRAM® Xtra SIL G/UV254). Visualization was achieved by UV light (254 nm and 363 nm) and/or by treatment with potassium manganite (VII) and heat. CC was performed using silica gel 60 (230-400 Mesh, MERCK AND CO.). All ^{1}H-NMR, ^{13}C-NMR, COSY, HMQC, HMBC spectra were recorded on BRUKER AVIII400 in $CDCl_3$. Chemical shifts (δ) were given in "parts per million" (ppm), referenced to the peak of TMS (δ = 0.00 ppm), using the solvent as internal standard (^{1}H: $\delta(CDCl_3)$ = 7.26 ppm; ^{13}C: $\delta(CDCl_3)$ = 77.16 ppm).[78] Coupling constants (*J*) were given in Hz. Spectroscopy splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) or combinations of that. MS were obtained using a BRUKER maXis spectrometer with ESI and the main signals were given in *m/z* units. IR were recorded on a BRUKER VERTEX FT-IR spectrometer. The following computer programs were used: MestReNova from Mestrelab Research and ChemDraw from PerkinElmer.

1-chloro-6-methylhept-6-en-2-ol (**103**)[79]



103

To a flame-dried Schlenk flask containing a suspension of Mg powder (37.5 mmol, 1.5 equiv.) in dry Et_2O (25 ml) were added 5 drops 1, 2-dibromoethane and 5 drops of alkyl bromide at ambient temperature and the mixture was stirred for 10 minutes. Then alkyl bromide (30.0 mmol, 1.2 equiv.) was slowly added and the reaction was kept stirring at room temperature for 1 hour. The Grignard reagent was added to a suspension of epichlorohydrin (25.0 mmol, 1.0 equiv.) and CuCN (2.5 mmol, 0.1 equiv.) in THF (50 ml) at -78° C. The reaction mixture was allowed to warm to room temperature over 12 h. Then sat. NH_4Cl solution was slowly added, extracted with ether and the combined organic phases were dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (pentane/ether = 95:5, R_f = 0.29) and isolated as a yellow oil (3.52 g, 21.0 mmol, 84%).

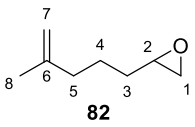
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.70 (ddd, J = 2.9, 1.7, 0.8 Hz, 2H, H_7), 3.98 – 3.74 (m, 1H, H_2), 3.62 (dt, J = 18.8, 9.4 Hz, 1H, H_1), 3.48 (dd, J = 11.1, 7.1 Hz, 1H, H_1), 2.16 (d, J = 4.9 Hz, 1H), 2.05 (t, J = 6.8 Hz, 2H, H_5), 1.71 (s, 3H, H_8), 1.67 – 1.57 (m, 1H, H_3+H_4), 1.57 – 1.44 (m, 3H, H_3+H_4);

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4 (C_6), 110.4 (C_7), 71.5 (C_2), 50.7 (C_1), 37.6 (C_5), 33.9 (C_3), 23.6 (C_4), 22.4 (C_8);

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_8H_{16}ClO$) requires *m/z* 163.1480, found *m/z* 163.1475;

IR (neat) vmax: 3391, 3074, 2937, 2866, 1649, 1444, 1433, 1374, 1352, 1298, 1275, 1258, 1213 cm^{-1}

2-(4-methylpent-4-en-1-yl)oxirane (**82**)[80]



82

Powdered NaOH (100.8 mmol, 5.6 equiv.) was added to a solution of 1-chloro-6-methylhept-6-en-2-ol (18.0 mmol, 1 equiv.) in THF (30 ml). The mixture was stirred vigorously for 70 h and then water (30 ml) was added to the solution. After separation of the layers, the aqueous layer was extracted with Et_2O (3 x 30 ml) and the combined

organic layers were dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure afforded the desired volatile product as yellow oil (2.02 g, 16.0 mmol, 89%).

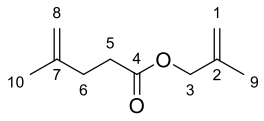
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.70 (d, J = 22.2 Hz, 2H, H_7), 2.92 (ddd, J = 6.6, 5.5, 3.9 Hz, 1H, H_2), 2.75 (dd, J = 5.0, 3.9 Hz, 1H, H_1)2.47 (dd, J = 5.0, 2.7 Hz, 1H, H_1), 2.07 (t, J = 7.4 Hz, 2H, H_5), 1.72 (s, 3H, H_8), 1.67 – 1.47 (m, 4H, H_3+H_4);

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.6 (C_6), 110.3 (C_7), 52.4 (C_2), 47.2 (C_1), 37.6 (C_5), 32.2 (C_3), 24.1 (C_4), 22.4 (C_8);

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_8H_{15}O$) requires *m/z* 126.1045, found *m/z* 126.1039;

IR (neat) ν_{max}: = 3074, 3046, 2970, 2936, 2863, 1720, 1650, 1482, 1451, 1411, 1374, 1325, 1259, 1213 cm^{-1}.

2-methylallyl 4-methylpent-4-enoate (**88**)[81]



88

To a solution of 2-methylprop-2-en-1-ol (26.2 mmol, 2.5 equiv.) and trimethyl orthoacetate (10.5 mmol, 1.0 equiv.) was added propionic acid (1.3 mmol, 0.12 equiv.) at room temperature. The reaction was heated to 140 °C for 1 hour. After 1 hour, the reaction flask was cooled to 110 °C and fitted with a short path distillation head and the volatile side products were collected for 1 hour. The mixture was then heated to 160 °C for 4 hours and the waste was collected. The mixture was cooled to room temperature, then extracted with Et_2O (3 x 15 ml), and washed with water (2 x 10 ml) and brine (10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the desired product **88** as a colorless oil (1.31 g, 7.8 mmol, 55%).

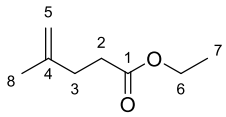
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 (dt, J = 19.8, 1.2 Hz, 2H, H_1), 4.82 – 4.62 (m, 2H, H_8), 4.51 (s, 2H, H_3), 2.58 – 2.45 (m, 2H, H_5), 2.36 (dd, J = 9.0, 6.4 Hz, 2H, H_5), 1.75 (dd, J = 4.2, 1.3 Hz, 6H, H_9+H_{10});

^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.1 (C_4), 144.2 (C_7), 140.2 (C_2), 113.1 (C_1), 110.5 (C_8), 67.8 (C_3), 32.8 (C_6), 32.7 (C_5), 22.7 (C_{10}), 19.7 (C_9);

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{10}H_{17}O_2$) requires *m/z* 169.1223, found *m/z* 169.1224;

IR (neat) ν_{max}: = 2957, 2922, 2852, 2360, 1737, 1727, 1658, 1642, 1632, 1464, 1411, 1378, 1358, 1261, 1234 cm^{-1}.

ethyl-4-methylpent-4-enoate (**90**)[75]

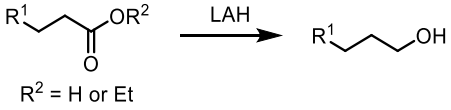


90

The solution of methallyl alcohol (100.0 mmol, 1.0 equiv.), propionic acid (12.0 mmol, 0.12 equiv.) in triethyl orthoacetate (1.5 mol, 15 equiv.) was refluxed for 8 hours. The reaction mixture was diluted with ether (200 ml) extracted with 10% HCl solution (200 ml), saturated $NaHCO_3$ and brine. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the desired ester **90** as a yellow oil (13.7 g, 80.0 mmol, 80%). The product was used for the next step without further purification. Spectral data was in agreement with the literature.[75]

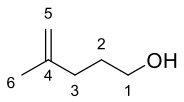
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.82 – 4.64 (m, 2H, H_5), 4.13 (q, J = 7.1 Hz, 2H, H_6), 2.49 – 2.42 (m, 2H, H_2), 2.36 – 2.29 (m, 2H, H_3), 1.74 (d, J = 0.7 Hz, 3H, H_8), 1.25 (t, J = 7.1 Hz, 3H, H_7).

General Procedure 1 (GP1): Synthesis of unsaturated alcohol substrates[75], [82], [83]



$LiAlH_4$ pellets (96.0 mmol, 1.2 equiv.) were added to an open round-bottom flask containing a solution of ester or acid (80.0 mmol, 1.0 equiv.) in THF (160 ml) at 0 °C. The reaction mixture was stirred for 12 hours and slowly quenched with H_2O. The reaction mixture was diluted with ether (50 ml) extracted with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afforded the desired alcohol in quantitative yield.

4-methylpent-4-en-1-ol (**91**)

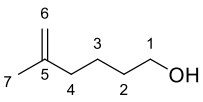


91

According to the general procedure **GP1, 91** was isolated as a yellow oil (7.8 g, 70.0 mmol, 88%). The product was used for the next step without further purification. Spectral data was in agreement with the literature.[82]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.90 – 4.53 (m, 2H, H_5), 4.06 (t, J = 6.7 Hz, 2H, H_1), 2.11 – 2.05 (m, 2H, H_3), 1.82 – 1.73 (m, 2H, H_2), 1.73 (t, J = 1.1 Hz, 3H, H_6).

5-methylhex-5-en-1-ol (**100**)

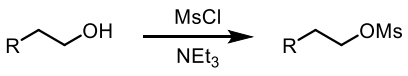


100

According to the general procedure **GP1, 100** was isolated after purification by column chromatography (hexane/ethyl acetate = 3:1, Rf = 0.36) as as a yellow oil (6.4 g, 55.6 mmol, 64%). Spectral data was in agreement with the literature.[83]

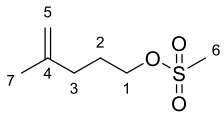
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 – 4.48 (m, 2H, H_6), 3.76 – 3.60 (m, 2H, H_1), 2.19 – 1.95 (m, 2H, H_4), 1.72 (s, 3H, H_7), 1.67 – 1.45 (m, 4H, H_3 + H_4), 1.26 (d, J = 4.7 Hz, 1H, OH_1).

General Procedure 2 (GP2): Synthesis of mesylate substrates[82], [84]



To the solution of alcohol (80.0 mmol, 1.0 equiv.) in dry DCM (160 ml), was added triethylamine (88.0 mmol, 1.1 equiv.) at 0 °C. Methanesulfonyl chloride (88.0 mmol, 1.1 equiv.) was then added dropwise over 5 min then stirred for 1 h at 0 °C. The reaction mixture was diluted with DCM (40 ml), washed with 1 M HCl (200 ml), saturated aq. $NaHCO_3$ (250 ml) and brine (200 ml). The combined organic layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give the desired product.

4-methylpent-4-en-1-yl methanesulfonate (**79**)



79

According to the general procedure **GP2**, **79** was isolated as a yellow oil (11.6 g, 65.0 mmol, 93%).

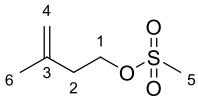
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.88 – 4.62 (m, 2H, H_5), 4.25 (t, J = 6.5 Hz, 2H, H_1), 3.02 (s, 3H, H_6), 2.15 (dd, J = 8.3, 6.7 Hz, 2H, H_3), 2.00 – 1.85 (m, 2H, H_5), 1.75 (s, 3H, H_7).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 (C_4), 111.3 (C_5), 69.7 (C_1), 37.49 (C_6), 33.5 (C_3), 27.08 (C_2), 22.4 (C_7);

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_8H_{15}O$) requires *m/z* 126.1045, found *m/z* 126.1039;

IR (neat) ν_{max}: = 2958, 2933, 2872, 1726, 1463, 1350, 1207, 1172 cm^{-1}.

3-methylbut-3-en-1-yl methanesulfonate (**95**)



95

According to the general procedure **GP2, 95** was isolated as a yellow oil (quantitative) and used for the next step without further purification.

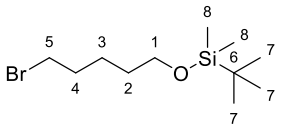
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.83 (d, J = 49.5 Hz, 2H, H_4), 4.33 (t, J = 6.8 Hz, 2H, H_1), 3.00 (s, 3H, H_5), 2.46 (t, J = 6.8 Hz, 2H, H_2), 1.77 (s, 3H, H_6);

^{13}C NMR (150 MHz, $CDCl_3$): δ 140.3 (C3), 113.5 (C4), 68.0 (C1), 37.7 (C5), 37.2 (C2), 22.5 (C6);

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_6H_{12}O_3SNa$) requires *m/z* 187.0399, found *m/z* 126.0398;

IR (neat) ν_{max}: = 3080, 3028, 2972, 2941, 2917, 1651, 1446, 1415, 1348, 1333, 1207 cm^{-1}.

((5-bromopentyl)oxy)(tert-butyl)dimethylsilane (**114**)



114

According to the general procedure **GP2, 114** was isolated after filtration through a short silica column (pentane/ether = 20:1, R_f = 0.9 in 5:1 hexane/ethyl acetate) as a colorless oil (1.14 g, 4.065 mmol, 81%).

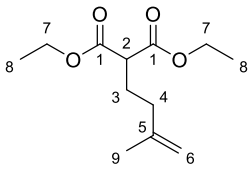
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.62 (t, J = 6.2 Hz, 2H, H_1), 3.41 (t, J = 6.8 Hz, 2H, H_5), 1.92 – 1.84 (m, 2H, H_2-H_4), 1.61 – 1.40 (m, 4H, H_2-H_4), 0.89 (s, 9H, H_8), 0.05 (s, 6H, H_8);

^{13}C NMR (150 MHz, $CDCl_3$): δ 63.0 (C_1), 34.0 (C_5), 32.8 (C_2), 32.1 (C_4), 26.1 (C_7), 24.7 (C_3), 18.5 (C_6), -5.2 (C_8);

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{11}H_{26}BrOSi$) requires *m/z* 281.0931, found *m/z* 281.0931;

IR (neat) ν_{max}: = 2953, 2929, 2892, 2857, 1471, 1462, 1439, 1388, 1361, 1277, 1253, 1201 cm^{-1}.

diethyl 2-(3-methylbut-3-en-1-yl)malonate (**97**)[82]

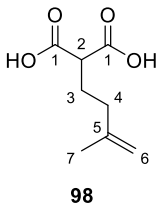


97

In a 1 L two-neck round-bottomed flask equipped with a stir bar was added sodium hydride (200.0 mmol, 2.0 equiv.). After washing 3 times with pentane, and short drying under reduced pressure, THF (350 ml) and Tetrabutylammonium iodide (10 mmol, 0.1 equiv.) were added at 0 °C. To this solution diethyl malonate (200 mmol, 2.0 equiv.) was added dropwise. After 5 min, 3-methyl-3-buten-1-yl methanesulfonate (100 mmol, 1.0 equiv.) was added dropwise over 10 min. After 12 h, the reaction mixture was quenched by the addition of saturated aq. NH_4Cl (600 mL). The mixture was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. **97** was isolated as a yellow oil (quantitative) and used for the next step without further purification. Spectral data was in agreement with the literature[8].

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.04 – 4.60 (m, 2H, H_6), 4.35 – 4.10 (m, 4H, H_7), 3.38 (s, 1H, H_2), 2.07 (d, J = 3.7 Hz, 4H, H_3+H_4), 1.74 (s, 3H, H_9), 1.34 – 1.25 (m, 6H, H_8). With Diethyl malonate 1:1

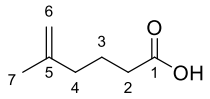
2-(3-methylbut-3-en-1-yl)malonic acid (**98**)[82]



98

In a 500 mL round-bottomed flask equipped with a stir bar was added diethyl 2-(3-methyl-3- buten-1-yl)malonate (100.0 mmol, 1.0 equiv.), NaOH (1.0 mol, 10.0 equiv.), Methanol (200 ml) and H_2O (5 ml). The reaction mixture was refluxed for 12 h, then cooled to rt. Methanol was removed under reduced pressure and the crude mixture was dissolved in water (100 ml). After extraction with ethyl acetate, the aquatic phase was acidified to pH = 1 and extracted with ethyl acetate. The organic solvent was removed under reduced pressure and the crude mixture was used for the next step without further purification.

5-methylhex-5-enoic acid (**99**)[82]

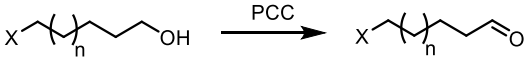


99

In a 250 ml round-bottomed flask equipped with a stir bar was added 2-(3-methylbut-3-en-1-yl)malonic acid (100.0 mmol, 1.0 equiv.), pyridine (100 ml) and water (5 ml). The reaction mixture was refluxed for 12 h then cooled to rt, diluted with ethyl acetate and acidified with a solution of 1 M HCl to pH = 1, extracted with ethyl acetate, dried over $MgSO_4$ and solvent was removed under reduced pressure. **99** was isolated as a yellow oil (11.1 g, 86.7 mmol, 87%) and used for the next step without further purification. Spectral data was in agreement with the literature.[82]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.79 (s, 1H, OH_1), 5.06 – 4.43 (m, 2H, H_6), 2.28 (t, J = 7.5 Hz, 2H, H_2), 2.02 – 1.97 (m, 2H, H_4), 1.73 (qd, J = 7.2, 1.2 Hz, 2H, H_3), 1.65 (s, 3H, H_7).

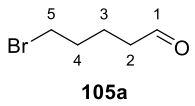
General Procedure 3 (GP3): Synthesis of haloaldehyde substrates[83], [83]



The corresponding alcohol (50.0 mmol, 1.0 equiv.) was dissolved in DCM (160.0 ml) and 10 g of silica was added. Then PCC (75.0 mmol, 1.5 equiv.) was added and the reaction mixture was stirred for 2-6 hours until TLC analysis showed full conversion of alcohol. Then, the reaction mixture was diluted with DCM (40 ml), filtered through a short pad of silica, washed with ether

and concentrated under reduced pressure. The crude mixture was used for the next step without further purification.

5-bromopentanal (**105a**)



105a

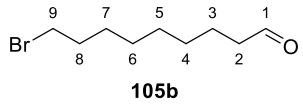
According to the general procedure **GP3**, **105a** was isolated as a volatile yellow oil (quantitative) and used for the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (d, J = 1.6 Hz, 1H), 3.52 – 3.44 (m, 2H), 3.41 (t, J = 6.5 Hz, 2H), 1.98 – 1.85 (m, 2H), 1.80 (p, J = 7.1 Hz, 2H).);

HRMS (ESI+): exact mass calculated for $[M-H]^+$ ($C_5H_8O_2Br$) requires *m/z* 162.9753, found *m/z* 162.9753;

IR (neat) ν_{max}: = 3420, 3406, 3390, 3063, 2939, 2866, 2787, 1730, 1634, 1610, 1486, 1455, 1434, 1391, 1356, 1253 cm^{-1}.

9-bromononanal (**105b**)

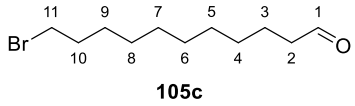


105b

According to the general procedure **GP3**, **105b** was isolated as a yellow oil (quantitative) and used for the next step without further purification. Spectral data was in agreement with the literature.[85]

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (t, J = 1.8 Hz, 1H, H_1), 3.40 (t, J = 6.8 Hz, 2H, H_9), 2.42 (td, J = 7.3, 1.9 Hz, 2H, H_2), 1.85 (dq, J = 8.4, 6.9 Hz, 2H, H_8), 1.63 (p, J = 7.3 Hz, 2H, H_3), 1.43 (dq, J = 12.5, 6.9, 6.4 Hz, 2H, H_7), 1.37 – 1.28 (m, 6H, H_4+H_5+H_6).

11-bromoundecanal (**105c**)

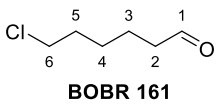


105c

According to the general procedure **GP3**, **105c** was isolated as a yellow oil (quantitative) and used for the next step without further purification. Spectral data was in agreement with the literature.[86]

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (t, J = 1.9 Hz, 1H, H_1), 3.43 (t, J = 6.9 Hz, 2H, H_{11}), 2.44 (td, J = 7.3, 1.9 Hz, 2H, H_2), 1.94 – 1.80 (m, 2H, H_{10}), 1.64 (q, J = 7.1 Hz, 2H, H_3), 1.45 (t, J = 7.4 Hz, 2H, H_4+H_5+H_6+H_7+H_8), 1.32 (q, J = 4.3, 3.2 Hz, 10H, H_4+H_5+H_6+H_7+H_8).

6-chlorohexanal (**105d**)

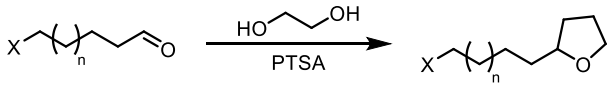


BOBR 161

According to the general procedure **GP3**, **105d** was isolated as a volatile colorless oil (quantitative) and used for the next step without further purification. Spectral data was in agreement with the literature.

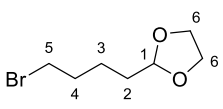
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H, H_1), 3.54 (t, J = 6.6 Hz, 2H, H_6), 2.46 (td, J = 7.2, 1.6 Hz, 2H, H_2), 1.80 (dq, J = 8.1, 6.7 Hz, 2H, H_3+H_5), 1.74 – 1.61 (m, 2H, H_3+H_5), 1.56 – 1.41 (m, 2H, H_4).

General Procedure 4 (GP4): Synthesis of dioxolanes[84], [83]



In a 500 mL round-bottomed flask equipped with a stir bar, Dean-Stark apparatus, was added the corresponding aldehyde (50.0 mmol, 1.0 equiv.), ethylene glycol (250.0 mmol, 5.0 equiv.), toluene (160 ml) and p-toluenesulfonic acid monohydrate (10.0 mmol, 0.2 equiv.). The resulting solution was heated to reflux over 14 h and then water (30 ml) was added, The organic layer was separated, washed with a solution of saturated aqueous $NaHCO_3$ (30 ml) and brine (30 ml), dried over $MgSO_4$ and solvent was removed under reduced pressure. The crude residue was purified by column chromatography to yield the desired product.

2-(4-bromobutyl)-1,3-dioxolane (**106a**)



106a

According to the general procedure **GP4**, **106a** was isolated after purification by column chromatography (heptane/ethyl acetate = 5:1, Rf = 0.36) as a colorless oil (7.05 g, 42.7 mmol, 85%).

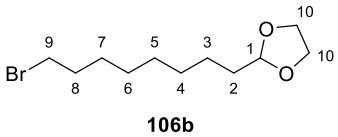
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.86 (t, J = 4.6 Hz, 1H, H_1), 4.03 – 3.91 (m, 2H, H_6), 3.91 – 3.79 (m, 2H, H_6), 3.41 (t, J = 6.8 Hz, 2H, H_5), 1.91 (dt, J = 14.6, 6.9 Hz, 2H, H_2+H_4), 1.74 – 1.62 (m, 2H, H_2+H_4), 1.64 – 1.53 (m, 2H, H_3);

^{13}C NMR (100 MHz, $CDCl_3$): δ 104.4 (C1), 65.0 (C6), 33.6 (C2+C4+C5), 33.0 (C2+C4+C5), 32.7 (C2+C4+C5), 22.8 (C4);

HRMS (EI+): exact mass calculated for $[M-H]^+$ ($C_7H_{12}O_2Br$) requires *m/z* 208.9995, found *m/z* 209.0002;

IR (neat) ν_{max}: = 2948, 2878, 1475, 1455, 1433, 1409, 1360, 1285, 1256, 1240 cm^{-1}.

2-(8-bromooctyl)-1,3-dioxolane (**106b**)



106b

According to the general procedure **GP4**, **106b** was isolated after purification by column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.39) as a colorless oil (9.3 g, 35.1 mmol, 70%).

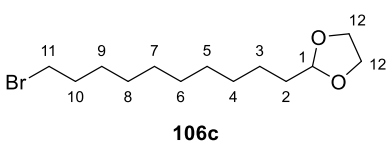
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.84 (t, J = 4.8 Hz, 1H, H_1), 4.02 – 3.90 (m, 2H, H_{10}), 3.91 – 3.80 (m, 2H, H_{10}), 3.40 (t, J = 6.9 Hz, 2H, H_9), 1.84 (dq, J = 8.6, 6.9 Hz, 2H, H_8), 1.70 – 1.60 (m, 2H, H_2-H_7), 1.48 – 1.37 (m, 4H, H_2-H_7), 1.37 – 1.27 (m, 6H, H_2-H_7);

^{13}C NMR (100 MHz, $CDCl_3$): δ 104.8 (C_1), 65.0 (C_{10}), 34.1 (C_9), 34.0 (C_2-C_8), 33.0 (C_2-C_8), 29.6 (C_2-C_8), 29.5(C_2-C_8), 28.8 (C_2-C_8), 28.3 (C_2-C_8), 24.2 (C_2-C_8);

HRMS (EI+): exact mass calculated for $[M-H]^+$ ($C_{11}H_{20}O_2Br$) requires *m/z* 265.0621, found *m/z* 265.0613;

IR (neat) ν_{max}: = 2927, 2855, 1736, 1463, 1437, 1409, 1360, 1251, 1221 cm^{-1}.

2-(10-bromodecyl)-1,3-dioxolane (**106c**)



106c

According to the general procedure **GP4**, **106c** was isolated after purification by column chromatography (heptane/ethyl acetate = 20:1, Rf = 0.33) as a colorless oil (11.7 g, 40.0 mmol, 80%).

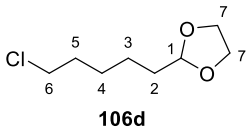
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.84 (t, J = 4.8 Hz, 1H, H_1), 4.02 – 3.90 (m, 2H, H_{12}), 3.90 – 3.78 (m, 2H, H_{12}), 3.40 (t, J = 6.9 Hz, 2H, H_{11}), 1.85 (dt, J = 14.5, 7.0 Hz, 2H, H_{10}), 1.70 – 1.60 (m, 2H, H_2-H_9), 1.48 – 1.36 (m, 4H, H_2-H_9), 1.36 – 1.26 (m, 10H, H_2-H_9);

^{13}C NMR (100 MHz, $CDCl_3$): δ 104.9 (C_1), 65.0 (C_{12}), 34.2 (C_{11}), 34.1 (C_2-C_{10}), 33.0 (C_2-C_{10}), 29.7 (C_2-C_{10}), 29.6 (C_2-C_{10}), 29.5 (C_2-C_{10}), 29.5 (C_2-C_{10}), 28.9 (C_2-C_{10}), 28.3 (C_2-C_{10}), 24.2 (C_2-C_{10});

HRMS (EI+): exact mass calculated for $[M\text{-}H]^+$ ($C_{13}H_{24}O_2Br$) requires *m/z* 291.0954, found *m/z* 291.0951;

IR (neat) ν_{max}: = 2924, 2853, 1464, 1437, 1408, 1360, 1255, 1240, 1229.90, 1212 cm^{-1}.

2-(5-chloropentyl)-1,3-dioxolane (**106d**)



106d

According to the general procedure **GP4**, **106d** was isolated after purification by column chromatography (heptane/ethyl acetate = 5:1, Rf = 0.35) as a colorless oil (6.7 g, 37.5 mmol, 75%).

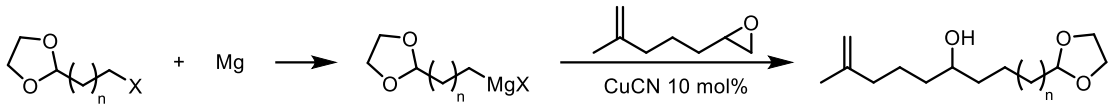
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.84 (t, J = 4.7 Hz, 1H, H_1), 4.10 – 3.89 (m, 2H, H_7), 3.90 – 3.76 (m, 2H, H_7), 3.53 (t, J = 6.7 Hz, 2H, H_6), 1.78 (dq, J = 8.1, 6.7 Hz, 2H, H_5), 1.72 – 1.61 (m, 2H, H_2), 1.56 – 1.36 (m, 4H, H_3+H_4);

^{13}C NMR (100 MHz, $CDCl_3$): δ 104.6 (C_1), 65.0 (C_7), 45.1 (C_6), 33.8 (C_2), 32.7 (C_5), 26.9 (C_4), 23.4 (C_3);

HRMS (EI+): exact mass calculated for $[M\text{-}H]^+$ ($C_8H_{14}O_2Cl$) requires *m/z* 177.0677, found *m/z* 177.0686;

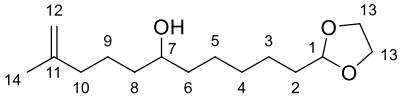
IR (neat) ν_{max}: 2944, 2865, 1736, 1462, 1446, 1434, 1409, 1361, 1309, 1259, 1238, 1212 cm^{-1}.

General Procedure 5 (GP5): Synthesis of alcohols 107a-c



To a flame-dried Schlenk flask containing a suspension of Mg powder (90.0 mmol, 9 equiv.) in dry THF (40.0 ml) was added an iodine crystal ambient temperature and the mixture was stirred for 10 minutes. Then the coresponding bromide (30.0 mmol, 3.0 equiv.) was added *via* syringe pump over 1 h and the reaction was kept stirring at room temperature for 12 h. The Grignard reagent was added to a suspension of epoxide **82** (10.0 mmol, 1.0 equiv.) and CuCN (1.0 mmol, 0.1 equiv.) in THF (5 ml) at -78 °C. The reaction mixture was allowed to warm to room temperature over 12 h. Then sat. NH_4Cl solution was slowly added, extracted with ether and the combined organic phases were dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified by column chromatography.

11-(1,3-dioxolan-2-yl)-2-methylundec-1-en-6-ol (**107a**)



107a

According to the general procedure **GP5**, **107a** was isolated after purification by column chromatography (heptane/ethyl acetate = 5:1 to 2:1, R_f = 0.32 in 2:1) as a colorless oil (332 mg, 1.29 mmol, 86%).

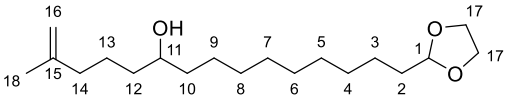
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.84 (t, J = 4.8 Hz, 1H, H_1), 4.74 – 4.64 (m, 2H, H_{12}), 4.00 – 3.94 (m, 2H, H_{13}), 3.91 – 3.78 (m, 2H, H_{13}), 3.60 (s, 1H, H_7), 2.03 (dd, J = 8.7, 6.0 Hz, 2H, H_{10}), 1.72 (t, J = 1.2 Hz, 3H, H_{14}), 1.69 – 1.56 (m, 3H, H_2-H_6+H_8-H_9+OH_7), 1.52 – 1.24 (m, 12H, H_2-H_6+H_8-H_9+OH_7);

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9 (C_{11}), 110.1 (C_{12}), 104.8 (C_1), 71.9 (C_7), 65.0 (C_{13}), 37.9 (C_{10}), 37.5 (C_6), 37.2 (C_8), 33.9 (C_2-C_5 + C_9), 29.7 (C_2-C_5 + C_9), 25.7 (C_2-C_5 + C_9), 24.1 (C_2-C_5 + C_9), 23.7 (C_2-C_5 + C_9), 22.5 (C_{14});

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{15}H_{29}O_3$) requires *m/z* 257.2111, found *m/z* 257.2109;

IR (neat) ν_{max}: = 3453, 3441, 3376, 2931, 2859, 1740, 1649, 1454, 1408, 1373, 1325, 1300, 1240, 1214 cm^{-1}.

15-(1,3-dioxolan-2-yl)-2-methylpentadec-1-en-6-ol (**107b**)



107b

According to the general procedure **GP5**, **107b** was isolated after purification by column chromatography (heptane/ethyl acetate = 5:1 to 2:1, R_f = 0.28 in 5:1) as a colorless oil/solid (586 mg, 1.88 mmol, 63%).

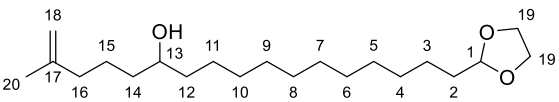
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.84 (t, J = 4.8 Hz, 1H, H_1), 4.69 (d, J = 11.4 Hz, 2H), 4.07 – 3.91 (m, 2H, H_{17}), 3.91 – 3.77 (m, 2H, H_{17}), 3.60 (td, J = 7.8, 3.8 Hz, 1H, H_{11}), 2.03 (t, J = 7.4 Hz, 2H, H_{14}), 1.72 (s, 3H, H_{18}), 1.67 – 1.62 (m, 2H, H_2-H_9 + H_{13} + OH_{11}), 1.60 – 1.55 (m, 1H, H_2-H_9 + H_{13} + OH_{11}), 1.51 – 1.36 (m, 8H, H_2-H_9 + H_{13} + OH_{11}), 1.28 (s, 12H, H_2-H_9 + H_{13} + OH_{11});

^{13}C NMR (150 MHz, $CDCl_3$): δ 146.0 (C_{15}), 110.1 (C_{16}), 104.9 (C_1), 72.0 (C_{11}), 65.0 (C_{17}), 37.9 (C_{14}), 37.7 (C_{10}), 37.2 (C_{12}), 34.1 (C_2-C_9 + C_{13}), 29.8 (C_2-C_9 + C_{13}), 29.7 (C_2-C_9 + C_{13}), 29.7 (C_2-C_9 + C_{13}), 29.7 (C_2-C_9 + C_{13}), 29.6 (C_2-C_9 + C_{13}), 25.8 (C_2-C_9 + C_{13}), 24.2 (C_2-C_9 + C_{13}), 23.7 (C_2-C_9 + C_{13}), 22.5 (C_{18});

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{19}H_{36}O_3Na$) requires *m/z* 335.2557, found *m/z* 335.2559;

IR (neat) ν_{max}: = 3444, 3074, 2926, 2855, 1734, 1653, 1647, 1457, 1410, 1373, 1217 cm^{-1}.

17-(1,3-dioxolan-2-yl)-2-methylheptadec-1-en-6-ol (**107c**)



107c

According to the general procedure **GP5**, **107c** was isolated after purification by column chromatography (heptane/ethyl acetate = 9:1 to 3:1, R_f = 0.27 in 5:1) as a white solid (1100 mg, 3.23 mmol, 65%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.84 (t, J = 4.8 Hz, 1H, H_1), 4.70 (dd, J = 10.9, 8.8 Hz, 2H, H_{18}), 4.14 – 3.90 (m, 2H, H_{19}), 3.90 – 3.78 (m, 2H, H_{19}), 3.60 (tq, J = 8.5, 4.5 Hz, 1H, H_{13}), 2.11 – 1.93

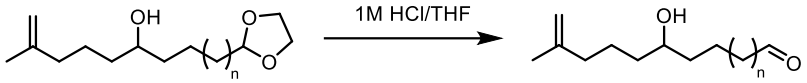
(m, 2H, H_{16}), 1.72 (s, 3H, H_{20}), 1.67 – 1.62 (m, 2H, H_2-H_{12} + H_{14}-H_{15}), 1.61 – 1.56 (m, 1H, H_2-H_{12} + H_{14}-H_{15} + OH_{13}) 1.52 – 1.36 (m, 8H, H_2-H_{12} + H_{14}-H_{15} + OH_{13}), 1.35 – 1.23 (m, 16H, , H_2-H_{12} + H_{14}-H_{15} + OH_{13});

^{13}C NMR (150 MHz, $CDCl_3$): δ 146.0 (C_{17}), 110.1 (C_{18}), 104.9 (C_{17}), 72.1 (C_{13}), 65.0 (C_{19}), 37.9 (C_{16}), 37.7 (C_{12}), 37.2 (C_{14}), 34.1 (C_2-C_{11} + C_{15}), 29.8 (C_2-C_{11} + C_{15}), 29.8 (C_2-C_{11} + C_{15}), 29.8 (C_2-C_{11} + C_{15}), 29.7 (C_2-C_{11} + C_{15}), 29.7 (C_2-C_{11} + C_{15}), 29.7 (C_2-C_{11} + C_{15}), 29.7 (C_2-C_{11} + C_{15}), 25.8 (C_2-C_{11} + C_{15}), 24.2 (C_2-C_{11} + C_{15}), 23.7 (C_2-C_{11} + C_{15}), 22.5 (C_2-C_{11} + C_{15});

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{21}H_{40}O_3Na$) requires *m/z* 363.2870, found *m/z* 363.2871;

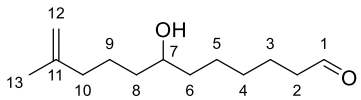
IR (neat) ν_{max}: = 3466, 2926, 2854, 2349, 1739, 1455, 1372, 1217, 1142, 1032 cm^{-1}.

General Procedure 6 (GP6): Synthesis of aldehydes 115a-c



The corresponding alcohol (3.0 mmol) was dissolved in a mixture of 1 M HCl (9 ml) and THF (18 ml). The reaction mixture was stirred for 6 h 60 °C. The reaction was quenched with saturated aq. $NaHCO_3$, extracted with ether, dried over $MgSO_4$ and solvent was removed under reduced pressure. The crude product was purified by column chromatography.

7-hydroxy-11-methyldodec-11-enal (**115a**)



115a

According to the general procedure **GP6**, **115a** was isolated after purification by column chromatography (DCM/ethyl acetate = 96:4, R_f = 0.27) as a colorless oil (443 mg, 2.09 mmol, 91%).

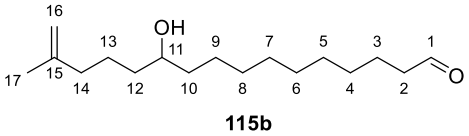
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.77 (s, 1H, H_1), 4.69 (d, J = 19.7 Hz, 2H, H_{12}), 3.60 (s, 1H, H_7), 2.43 (td, J = 7.3, 1.8 Hz, 2H, H_2), 2.07 – 1.96 (m, 2H, H_{10}), 1.73 – 1.69 (m, 3H, H_{13}), 1.65 (dt, J = 14.5, 7.2 Hz, 2H, H_3), 1.61 – 1.54 (m, 1H, H_4-H_6 + H_8-H_9 + OH_7), 1.53 – 1.41 (m, 5H), 1.41 – 1.38 (m, 2H), 1.38 – 1.31 (m, 2H), 1.29 (s, 1H);

^{13}C NMR (150 MHz, $CDCl_3$): δ 202.9 (C_1), 145.9 (C_{11}), 110.1 (C_{12}), 71.9 (C_7), 44.0 (C_2), 37.9 ($C_6 + C_8 + C_{10}$), 37.4 ($C_6 + C_8 + C_{10}$), 37.2 ($C_6 + C_8 + C_{10}$), 29.3 ($C_{3\text{-}5} + C_9$), 25.6 ($C_{3\text{-}5} + C_9$), 23.7 ($C_{3\text{-}5} + C_9$), 22.5 (C_{13}), 22.2 ($C_{3\text{-}5} + C_9$);

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{24}O_2Na$) requires *m/z* 235.1669, found *m/z* 235.1669;

IR (neat) ν_{max}: = 2953, 2923, 2854, 2349, 1739, 1460, 1375, 1230, 1158 cm^{-1}.

11-hydroxy-15-methylhexadec-15-enal (**115b**)



115b

According to the general procedure **GP6**, **115b** was isolated after purification by column chromatography (DCM/ethyl acetate = 19:1, R_f = 0.24) as a colorless oil (212 mg, 0.79 mmol, 79%).

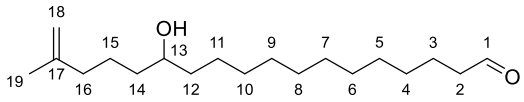
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.76 (s, 1H, H_1), 4.69 (d, J = 17.5 Hz, 2H, H_{16}), 3.60 (d, J = 3.1 Hz, 1H, H_{11}), 2.41 (td, J = 7.4, 1.8 Hz, 2H, H_2), 2.06 – 1.97 (m, 2H, H_{14}), 1.71 (s, 3H, H_{17}), 1.66 – 1.54 (m, 3H, $H_{3\text{-}9} + H_{13} + OH_{11}$), 1.52 – 1.36 (m, 6H, $H_{3\text{-}9} + H_{13} + OH_{11}$), 1.29 (d, J = 10.1 Hz, 12H, $H_{3\text{-}9} + H_{13} + OH_{11}$);

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.1 (C_1), 146.0 (C_{15}), 110.1 (C_{16}), 72.0 (C_{11}), 44.1 (C_2), 37.9 ($C_{10} + C_{12} + C_{14}$), 37.7 ($C_{10} + C_{12} + C_{14}$), 37.2 ($C_{10} + C_{12} + C_{14}$), 29.8 ($C_{3\text{-}9} + C_{13}$), 29.7 ($C_{3\text{-}9} + C_{13}$), 29.5 ($C_{3\text{-}9} + C_{13}$), 29.5 ($C_{3\text{-}9} + C_{13}$), 29.3 ($C_{3\text{-}9} + C_{13}$), 25.8 ($C_{3\text{-}9} + C_{13}$), 23.7 ($C_{3\text{-}9} + C_{13}$), 22.5 (C_{17}), 22.21 ($C_{3\text{-}9} + C_{13}$). ;

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{32}O_2Na$) requires *m/z* 291.2295, found *m/z* 291.2295;

IR (neat) ν_{max}: = 3403, 3073, 2925, 2854, 2717, 1724, 1648, 1457, 1410, 1373, 1093, 1013, 885 cm^{-1}.

13-hydroxy-17-methyloctadec-17-enal (**115c**)



115c

According to the general procedure **GP6**, **115c** was isolated after purification by column chromatography (DCM/ethyl acetate = 98:2, R_f = 0.38) as a white solid (802 mg, 2.71 mmol, 93%).

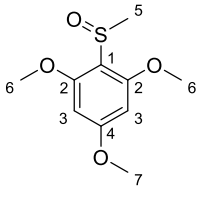
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.76 (t, J = 1.6 Hz, 1H, H_1), 4.69 (d, J = 17.6 Hz, 2H, H_{18}), 3.73 – 3.51 (m, 1H, H_{13}), 2.42 (td, J = 7.4, 1.7 Hz, 2H, H_2), 2.06 – 1.97 (m, 2H, H_{16}), 1.72 (s, 3H, H_{19}), 1.66 – 1.51 (m, 4H, $H_{3\text{-}12}$ + $H_{14\text{-}15}$ + OH_{13}), 1.48 – 1.37 (m, 6H, $H_{3\text{-}12}$ + $H_{14\text{-}15}$+ OH_{13}), 1.28 (d, J = 19.8 Hz, 15H, $H_{3\text{-}12}$ + $H_{14\text{-}15}$ + OH_{13}).

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.1 (C_1), 146.0 (C_{17}), 110. (C_{18}), 72.1 (C_{13}), 44.1 (C_2), 37.9 (C_{12} + C_{14} + C_{16}), 37.7 (C_{12} + C_{14} + C_{16}), 37.2 (C_{12} + C_{14} + C_{16}), 29.8 ($C_{3\text{-}11}$ + C_{15}), 29.7 ($C_{3\text{-}11}$ + C_{15}), 29.7 ($C_{3\text{-}11}$ + C_{15}), 29.7 ($C_{3\text{-}11}$ + C_{15}), 29.6 ($C_{3\text{-}11}$ + C_{15}), 29.5 ($C_{3\text{-}11}$ + C_{15}), 29.3 ($C_{3\text{-}11}$ + C_{15}), 25.8 ($C_{3\text{-}11}$ + C_{15}), 23.7 ($C_{3\text{-}11}$ + C_{15}), 22.5 (C_{19}), 22.2 ($C_{3\text{-}11}$ + C_{15});

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{19}H_{36}O_2Na$) requires *m/z* 319.2608, found *m/z* 319.2613;

IR (neat) ν_{max}: = 3434, 2925, 2854, 2716, 1725, 1652, 1647, 1458, 1419, 1410, 1373, 1229, 1217, 1094, 1011, 885. cm^{-1}.

1,3,5-trimethoxy-2-(methylsulfinyl)benzene (**172g**)



172g

Following a reported procedure,[76] methoxyarene (25.0 mmol, 1.0 equiv.), TMEDA (26.0 mmol, 1.05 equiv) were dissolved in pentane:ether (50:25 mL) at 0 °C. *n*-BuLi (10.5 ml, 2.5M solution in hexane, 26.2 mmol, 1.05 equiv.) was added dropwise at 0 °C. After 30 minutes, dimethyl disulfide (25 mmol, 1.0 equiv.) was added dropwise and the reaction was stirred at 0°C for 1 h and at rt for 6 h. The reaction was quenched by addition of 1 M sulfuric acid and extracted with ether, dried over $MgSO_4$ and concentrated. The crude residue was filtered through a short pad of silica and used for the next step without further purification. The crude sulfide was dissolved in DCM (100 ml) at 0 °C and *m*-CPBA (23.8 mmol, 0.95 equiv.) was added. The reaction mixture was stirred to rt over 12h and quenched by addition of sat. $NaHCO_3$ solution, extracted with DCM,

dried over $MgSO_4$ and concentrated under reduced pressure to give a crude sulfoxide which was isolated after recrystallization (DCM/heptane 1:1) as a white solid **172g** (3.3 g, 14.4 mmol, 58%).

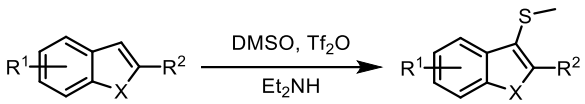
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.12 (s, 2H, H_3), 3.88 (s, 6H, H_6), 3.84 (s, 3H, H_7), 3.04 (s, 3H, H_5);

^{13}C NMR (150 MHz, $CDCl_3$): δ 164.7 (C_4), 161.3 (C_2), 91.3 (C_1), 56.3 (C_6), 55.7 (C_7), 38.0 (C_5);

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{14}O_4SNa$) requires *m/z* 253.0505, found *m/z* 253.0512;

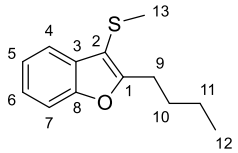
IR (neat) ν_{max}: = 2943, 1582, 1465, 1458, 1436, 1412, 1340, 1230, 1208, 1187, 1162, 1125, 1086, 1026 cm^{-1}.

General Procedure 7 (GP7): Synthesis of sulfides[76]



Trifluoromethanesulfonic anhydride (11 mmol, 1.1 equiv.) was added to a solution of DMSO (11 mmol, 1.1 equiv.) and the corresponding arene (1.0 equiv.) in DCM (50 ml) in a dry round-bottom flask under inert atmosphere at −30 ºC. After 15 min at −30 ºC, the reaction was stirred at room temperature for 1.5 h. Et_2NH (41.0 mmol, 4.1 equiv.) was then added, and the reaction mixture was stirred at room temperature for 6 h. The solution was quenched with H_2O (30 ml) and the aqueous layer was extracted with DCM (3 × 30 ml). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced presure. The crude product was purified by column chromatography.

2-butyl-3-(methylthio)benzofuran (**166a**)



166a

According to the general procedure **GP7**, **166a** was filtered through a short pad of silica and washed with heptane (heptane 100%, R_f = 0.66) as a yellow solid (2.2 g, 10.0 mmol, quantitative).

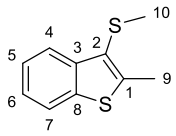
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 – 7.56 (m, 1H; H_4), 7.48 – 7.37 (m, 1H, H_7), 7.28 (d, J = 4.3 Hz, 1H, H_6), 7.25 (t, J = 3.7 Hz, 1H, H_5), 2.94 (t, J = 7.5 Hz, 2H, H_9), 2.31 (s, 3H, H_{13}), 1.73 (dt, J = 13.1, 7.5 Hz, 2H, H_{10}), 1.40 (dq, J = 14.7, 7.4 Hz, 2H, H_{11}), 0.96 (t, J = 7.4 Hz, 3H, H_{12});

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1 (C_1), 154.2 (C_8), 130.0 (C_3), 124.0 (C_6), 122.9 (C_5), 119.4 (C_4), 111.2 (C_7), 108.6 (C_2), 30.4 (C_9), 26.4 (C_{10}), 22.4 (C_{11}), 19.0 (C_{13}), 13.9 (C_{12});

HRMS (ESI+): exact mass calculated for $[M]^+$ ($C_{13}H_{16}OS$) requires *m/z* 220.0916, found *m/z* 220.0906;

IR (neat) ν_{max}: = 2956, 2924, 2871, 2861, 1580, 1465, 1452, 1427, 1378, 1269, 1251, 1206, 1172, 1143, 1109, 1031, 1007, 970, 853, 745 cm^{-1}.

2-methyl-3-(methylthio)benzo[b]thiophene (**166b**)



166b

According to the general procedure **GP7**, **166b** was filtered through a short pad of silica and washed with heptane (heptane 100%, R_f = 0.57) as a yellow solid (879 mg, 4.52 mmol, 91%).

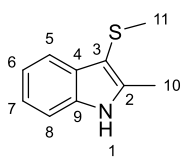
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (d, J = 8.0 Hz, 1H; H_4), 7.76 (d, J = 7.9 Hz, 1H, H_7), 7.41 (t, J = 7.5 Hz, 1H, H_5), 7.32 (t, J = 7.5 Hz, 1H, H_6), 2.71 (s, 3H, H_9), 2.29 (s, 3H, H_{10});

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.7 (C_1), 140.8 (C_3), 137.9 (C_8), 124.6 (C_6), 124.4 (C_5), 124.2 (C_2), 122.7 (C_4), 122.4 (C_7), 18.8 (C_{10}), 15.1 (C_9);

HRMS (ESI+): exact mass calculated for $[M]^+$ ($C_{10}H_{10}S_2$) requires *m/z* 194.0224, found *m/z* 194.0210;

IR (neat) ν_{max}: = 3057, 3024, 2984, 2917, 2848, 1518, 1453, 1430, 1373, 1314, 1296, 1252, 1168, 1150, 1131, 1066, 1028, 1012, 969, 935, 854, 753, 729, 714, 699 cm^{-1}.

2-methyl-3-(methylthio)-1*H*-indole (**166c)**



166c

According to the general procedure **GP7**, **166c** was isolated after purification by column chromatography (heptane/ethyl acetate = 15:1 to 10:1, R_f = 0.21 in 15:1) as a pale yellow solid (3.46 g, 19.5 mmol, 49%).

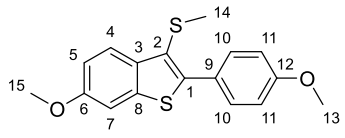
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H, H_1), 7.73 – 7.66 (m, 1H, H_5), 7.32 – 7.27 (m, 1H, H_8), 7.21 – 7.13 (m, 2H, $H_{6\text{-}7}$), 2.54 (s, 3H, H_{11}), 2.27 (s, 3H, H_{10}).

^{13}C NMR (150 MHz, $CDCl_3$): δ 139.01(C_2), 135.34(C_9), 130.20(C_3), 122.0 (C_6), 120.4 (C_7), 118.8 (C_5), 110.7 (C_8), 104.56 (C_3), 19.9 (C_{11}), 12.2 (C_{10});

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{10}H_{13}NS$) requires *m/z* 178.0685, found *m/z* 178.0667;

IR (neat) ν_{max}: = 3388, 3055, 2982, 2916, 2853, 1617, 1579, 1543, 1453, 1403, 1382, 1343, 1317, 1288, 1222, 1192, 1148, 1114, 1076, 1034, 1008, 964, 851, 807, 741, 670, 646, 582 cm^{-1}.

6-methoxy-2-(4-methoxyphenyl)-3-(methylthio)benzo[b]thiophene (**166d)**



166d

According to the general procedure **GP7**, **166d** was isolated after purification by column chromatography (heptane 100%, R_f = 0.11) as pale yellow solid (1.39 g, 4.38 mmol, 88%).

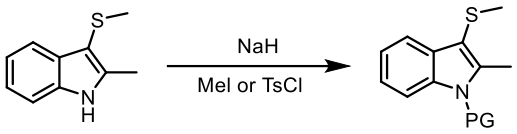
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (d, J = 8.8 Hz, 1H, H_4), 7.72 – 7.67 (m, 2H, H_{11}), 7.30 (d, J = 2.3 Hz, 1H, H_7), 7.08 (dd, J = 8.8, 2.4 Hz, 1H, H_5), 7.02 – 6.98 (m, 2H, H_{10}), 3.89 (s, 3H, H_{15}), 3.87 (s, 3H, H_{13}), 2.24 (s, 3H, H_{14});

^{13}C NMR (150 MHz, $CDCl_3$): δ 159.9 (C_{12}), 157.9 (C_6), 143.5 (C_9), 139.5 (C_8), 135.5 (C_3), 131.1 (C_{11}), 126.6 (C_1), 124.1 (C_4), 122.3 (C_2), 114.7 (C_5), 114.0 (C_{10}), 105.1 (C_7), 55.9 (C_{15}), 55.5 (C_{13}), 19.1 (C_{14}).

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{17}H_{17}O_2S_2$) requires *m/z* 317.0664, found *m/z* 317.0659;

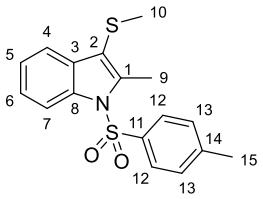
IR (neat) ν_{max}: = 2996, 2955, 2933, 2834, 1604, 1524, 1470, 1437, 1248, 1177, 1064, 1031, 830, 805, 766 cm^{-1}.

General Procedure 8 (GP8): Synthesis of protected sulfides[77]



To a two-neck round-bottomed flask equipped with a stir bar was added sodium hydride (7.5 mmol, 1.5 equiv.). After washing 3 times with pentane, and short drying under reduced pressure, THF (17 ml) and the corresponding indole (5.0 mmol, 1.0 equiv.) was added at 0 °C. The reaction mixture was kept at 0 °C for 15 minutes then at rt for 1.5 h. After cooling back to 0 °C, iodomethane or p-toluenesulfonyl chloride (6.5 mmol, 1.3 equiv.) was added and the reaction mixture was let to worm up to rt over 12 h. The reaction mixture was quenched at 0 °C with water and extracted with ether. The combined organic layers were dried over $MgSO_4$, and the solvent removed under reduced pressure. The resulting crude product was purified *via* flash column chromatography to give the desired *N*-protected indole.

2-methyl-3-(methylthio)-1-tosyl-1*H*-indole (**171a)**



171a

According to the general procedure **GP8**, **171a** was isolated after purification by column chromatography (heptane/ethyl acetate = 19:1 to 9:1, R_f = 0.33 in 19:1) as a pale yellow solid (1141 mg, 3.44 mmol, 67%).

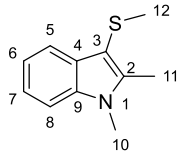
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20 (dd, *J* = 7.2, 1.4 Hz, 1H, H_4), 7.67 (d, *J* = 8.4 Hz, 2H, H_{12}), 7.62 (dd, *J* = 6.9, 1.9 Hz, 1H, H_7), 7.30 (pd, *J* = 7.2, 1.3 Hz, 2H, $H_{5\text{-}6}$), 7.21 (d, *J* = 8.2 Hz, 2H, H_{13}), 2.75 (s, 1H, H_9), 2.35 (s, 1H, H_{15}), 2.22 (s, 1H, H_{10});

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.1 (C_{14}), 140.4 (C_1), 136.3 (C_{11} or C_8), 136.3 (C_{11} or C_8), 130.9 (C_3), 130.1 (C_{13}), 126.6 (C_{12}), 124.7 (C_5 or C_6), 123.9 (C_5 or C_6), 119.3 (C_7), 114.7 (C_4), 114.5 (C_2), 21.7 (C_{15}), 18.9 (C_{10}), 13.7 (C_9).

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{17}H_{18}NO_2S_2$) requires *m/z* 332.0773, found *m/z* 332.0777;

IR (neat) ν_{max}: = 3050, 2986, 2922, 2854, 1597, 1552, 1493, 1450, 1435, 1369, 1236, 1217, 1187, 1174, 1152, 1117, 1102, 1011 cm^{-1}.

1,2-dimethyl-3-(methylthio)-1*H*-indole (**171b)**



171b

According to the general procedure **GP8**, **171b** was isolated after purification by column chromatography (heptane/ethyl acetate = 19:1 to 9:1, R_f = 0.29 in 19:1) as a pale yellow solid (606 mg, 3.17 mmol, 63%).

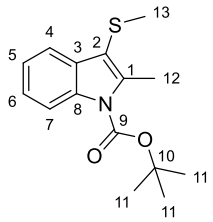
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (d, J = 7.7 Hz, 1H, H_5), 7.29 (d, J = 8.0 Hz, 1H, H_8), 7.21 (dd, J = 11.0, 4.0 Hz, 1H, H_7), 7.17 (t, J = 7.3 Hz, 1H, H_6), 3.70 (s, 3H, H_{10}), 2.55 (s, 3H, H_{11}), 2.25 (s, 3H, H, H_{12});

^{13}C NMR (150 MHz, $CDCl_3$): δ 141.0 (C_2), 136.9 (C_9), 129.5 (C_4), 121.5 (C_7), 120.1 (C_6), 118.7 (C_5), 109.1 (C_8), 103.4 (C_3), 30.3 (C_{10}), 20.3 (C_{11}), 10.9 (C_{12});

HRMS (ESI+): exact mass calculated for $[M]^+$ ($C_{11}H_{13}NS$) requires *m/z* 191.0763, found *m/z* 191.0769;

IR (neat) ν_{max}: = 2953, 2923, 2869, 2852, 1726, 1654, 1559, 1507, 1458, 1377, 1266, 972, 731 cm^{-1}.

tert-butyl 2-methyl-3-(methylthio)-1*H*-indole-1-carboxylate (**171c)**

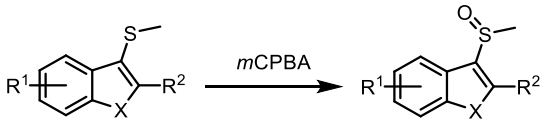


171c

To a solution of indole sulfide **166c** (5.0 mmol, 1.0 equiv.) was added DMAP (0.5 mmol, 0.1 equiv.) in DCM (10 ml) at 0 °C. Then Boc_2O (5.5 mmol, 1.1 equiv.) was added and the reaction mixture was stirred to rt over 12 h. The reaction mixture was quenched with brine, extracted with DCM, dried over $MgSO_4$ and solvent was removed under reduced pressure. The crude mixture was filtered through a short pad of silica and used for the next step without further purification (1371 mg, 4.9 mmol, 99%).

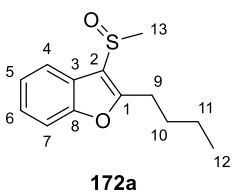
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 – 8.01 (m, 1H, H_4), 7.70 – 7.64 (m, 1H, H_7), 7.31 – 7.24 (m, 2H, H_5 + H_6), 2.76 (s, 3H, H_{12}), 2.26 (s, 3H, H_{13}), 1.69 (s, 9H, H_{11}).

General Procedure 9 (GP9): Synthesis of sulfoxides



The corresponding sulfide (10.0 mmol) was dissolved in DCM (30 ml) at 0 °C and *m*-CPBA (9.5 mmol, 0.95 equiv.) was added. The reaction mixture was stirred to rt over 12h and quenched by addition of sat. $NaHCO_3$ solution, extracted with DCM, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude sulfoxide which was isolated *via* column chromatography. Yields were calculated based on starting material. Given that the sulfoxide/sulfide mixtures are easier to separate than sulfoxide/sulfone ones, only 0.95 equiv. of *m*-CPBA were used to prevent sulfone formation

2-butyl-3-(methylsulfinyl)benzofuran (**172a**)



172a

According to the general procedure **GP9**, **172a** was isolated after purification by column chromatography (ethyl acetate 100%, R_f = 0.51) as a white solid (2.19 g, 9.3 mmol, 93%).

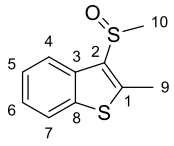
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 – 7.92 (m, 1H, H_4), 7.53 – 7.45 (m, 1H, H_7), 7.37 – 7.26 (m, 2H, $H_{5\text{-}6}$), 3.04 (s, 3H, H_{13}), 2.99 – 2.88 (m, 2H, H_9), 1.81 – 1.66 (m, 2H, H_{10}), 1.47 – 1.30 (m, 2H, H_{11}), 0.95 (t, J = 7.4 Hz, 3H, H_{12});

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8 (C_1), 154.5 (C_8), 125.1 (C_6), 124.0 (C_3), 123.9 (C_7), 120.36 (C_4), 118.1 (C_2), 111.8 (C_7), 40.5 (C_{13}), 30.5 (C_9), 27.0 (C_{10}), 22.4 (C_{12}), 13.8 (C_{13});

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{16}O_2Na$) requires *m/z* 259.0763, found *m/z* 259.0765;

IR (neat) ν_{max}: = 2957, 2930, 2871, 1583, 1470, 1453, 1420, 1379, 1316, 1273, 1252, 1205, 1175, 1110, 1060, 1031cm^{-1}.

2-methyl-3-(methylsulfinyl)benzo[b]thiophene (**172b**)



172b

According to the general procedure **GP9**, **172b** was isolated after purification by column chromatography (DCM/methanol = 98:2, R_f = 0.4) as a pale yellow solid (824 mg, 3.92 mmol, 93%).

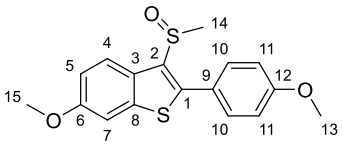
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (dd, J = 7.3, 1.0 Hz, 1H, H_4), 7.80 (dd, J = 7.3, 1.0 Hz, 1H, H_7), 7.44 – 7.39 (m, 1H, H_5), 7.39 – 7.34 (m, 1H, H_6), 3.02 (s, 3H, H_{10}), 2.74 (s, 3H, H_9);

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.7 (C_1), 138.4 (C_3 or C_8), 136.1 (C_3 or C_8), 130.8 (C_2), 125.2 (C_5 C_6), 125.0 (C_5 or C_6), 122.6 (C_4 or C_7), 122.5 (C_4 or C_7), 40.1 (C_{10}), 14.6 (C_9);

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{10}OS_2Na$) requires *m/z* 233.0065, found *m/z* 233.0060;

IR (neat) ν_{max}: = 2919, 2347, 1741, 1684, 1653, 1634, 1559, 1540, 1507, 1489, 1473, 1457, 1435, 1419, 1374, 1296, 1217, 1151, 1055, 959 cm^{-1}.

6-methoxy-2-(4-methoxyphenyl)-3-(methylsulfinyl)benzo[b]thiophene (**172c)**



172c

According to the general procedure **GP9**, **172c** was isolated after purification by column chromatography (heptane/ethyl acetate = 1:1, R_f = 0.19) as a white solid (1.17 g, 3.53 mmol, 84%).

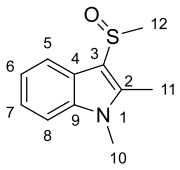
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, J = 9.0 Hz, 1H, H_4), 7.45 – 7.40 (m, 2H, H_{11}), 7.32 (d, J = 2.4 Hz, 1H. H_7), 7.08 (dd, J = 9.0, 2.4 Hz, 1H, H_5), 7.02 – 6.92 (m, 2H, H_{10}), 3.90 (s, 3H, H_{13}), 3.87 (s, 3H, H_{15}), 3.04 (s, 3H, H_{14});

^{13}C NMR (150 MHz, $CDCl_3$): δ 160.7 (C_{12}), 158.0 (C_6), 145.0 (C_9), 140.9 (C_8), 131.4 (C_{11}), 130.4 (C_3), 130.4 (C_2), 124.4 (C_4), 124.3 (C_1), 115.1 (C_5), 114.3 (C_{10}), 105.3 (C_7), 55.8 (C_{15}), 55.6 (C_{13}), 40.1(C_{14});

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{17}H_{16}O_3S_2Na$) requires *m/z* 355.0433, found *m/z* 355.0424;

IR (neat) ν_{max}: 3001, 2959, 2937, 2836, 1605, 1571, 1552, 1530, 1490, 1473, 1438, 1406, 1324, 1301, 1253, 1238, 1216, 1179, 1065, 1051, 1031 cm^{-1}.

1,2-dimethyl-3-(methylsulfinyl)-1*H*-indole (**172d)**



172d

According to the general procedure **GP9**, **172d** was isolated after purification by column chromatography (DCM/methanol = 98:1, R_f = 0.30) as a yellow solid (493 mg, 2.38 mmol, 79%).

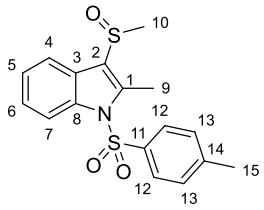
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 7.8 Hz, 1H, H_5), 7.34 (d, J = 8.0 Hz, 1H, H_8), 7.30 – 7.25 (m, 1H, H_7), 7.24 – 7.19 (m, 1H, H_6), 3.69 (s, 3H, H_{10}), 3.06 (s, 3H, H_{12}), 2.58 (s, 3H, H_{11}).

^{13}C NMR (150 MHz, $CDCl_3$): δ 139.62 (C_2), 137.56 (C_9), 123.96 (C_4), 122.68 (C_7), 121.42 (C_6), 119.65 (C_5), 112.41 (C_3), 109.85 (C_8), 40.50 (C_{12}), 29.72 (C_{10}), 11.13 (C_{11}).

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{11}H_{14}NOS$) requires *m/z* 208.0791, found *m/z* 208.0793;

IR (neat) ν_{max}: = 3047, 2996, 2915, 1529, 1470, 1442, 1417, 1398, 1377, 1353, 1336, 1311, 1295, 1240, 1176, 1151, 1131, 1115, 1036, 1022 cm^{-1}.

2-methyl-3-(methylsulfinyl)-1-tosyl-1*H*-indole (**172e)**



172e

According to the general procedure **GP9**, **172e** was isolated after purification by column chromatography (DCM/methanol = 99:1, R_f = 0.46) as a pale yellow solid (703 mg, 2.02 mmol, 90%).

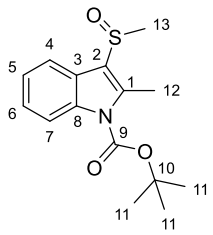
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.25 (d, J = 8.5 Hz, 1H, H_4), 8.07 (d, J = 7.8 Hz, 1H, H_7), 7.75 – 7.67 (m, 2H, H_{12}), 7.38 (ddd, J = 8.5, 7.4, 1.3 Hz, 1H, H_5), 7.35 – 7.29 (m, 1H, H_6), 7.28 – 7.23 (m, 2H, H_{13}), 3.00 (s, 3H, H_{10}), 2.74 (s, 3H, H_9), 2.39 (s, 3H, H_{15});

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.9 (C_{11}), 138.4 (C_1), 136.7 (C_8), 135.8 (C_{14}), 130.4 (C_{13}), 126.7 (C_{12}), 125.4 (C_5), 125.0 (C_2), 124.4 (C_6), 121.0 (C_3), 119.9 (C_7), 115.0 (C_4), 40.4 (C_{10}), 21.8 (C_{15}), 13.7 (C_9);

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{17}H_{18}O_3S_2$) requires *m/z* 348.0723, found *m/z* 348.0729;

IR (neat) ν_{max}: 3017, 2920, 2347, 2329, 2016, 1739, 1596, 1556, 1451, 1373, 1312, 1238, 1217, 1189, 1177, 1122, 1105, 1087, 1049 cm^{-1}.

tert-butyl 2-methyl-3-(methylsulfinyl)-1*H*-indole-1-carboxylate (**172f)**



172f

According to the general procedure **GP9**, **172f** was isolated after purification by column chromatography (DCM/methanol = 99:1, R_f = 0.18) as a white solid (361 mg, 1.23 mmol, 62%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14 (d, J = 8.2 Hz, 1H, H_4), 8.12 (d, J = 7.2 Hz, 1H, H_7), 7.36 – 7.32 (m, 1H, H_6), 7.30 (td, J = 7.5, 1.1 Hz, 1H, H_5), 3.02 (s, 3H, H_{13}), 2.74 (s, 3H, H_{x2}), 1.70 (s, 9H, H_{11});

^{13}C NMR (150 MHz, $CDCl_3$): δ 150.1 (C_9), 139.3 (C_1), 136.4 (C_8), 124.9 (C_6), 124.8 (C_3), 123.7 (C_5), 120.0 (C_2), 119.6 (C_7), 116.1 (C_4), 85.4 (C_{10}), 40.4 (C_{13}), 28.3 (C_{11}), 15.0 (C_{12});

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}NO_3S$) requires *m/z* 294.1158, found *m/z* 294.1157;

IR (neat) ν_{max}: = 2978, 1730, 1554, 1472, 1452, 1435, 1393, 1380, 1368, 1351, 1334, 1314, 1255, 1213, 1154, 1109, 1038, 1024, 967, 924, 851, 841, 768, 744, 705, 689, 675 cm^{-1}.

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