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Studies of Cyclization reactions for the Formation of Carbazole Alkaloids

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Chemistry and Biotechnology

Preface

The work described in this thesis was performed in the Department of Chemistry, at the Faculty of Chemistry, Biotechnology and Food Science, at the Norwegian University of Life Sciences fall of 2022 and spring of 2023.

I wish to express my gratitude towards my main supervisor Professor Yngve H. Stenstrøm, and my co-supervisors, Professor Trond Vidar Hansen and Simen Antonsen, for an exciting project and excellent guidance. I would also like to thank Associate Professor Marius Aursnes for his excellent guidance with the practical work. Thank you to Senior Engineer Anne Gravdahl for ordering chemicals.

I would lastly like to thank the master's students in the Department of Chemistry for all the long lunches and good conversations.

Ås, June 2023

Maria Bentzen

Sammendrag

Karbazol-alkaloider er en gruppe naturstoffer kjent for sine spennende biologiske aktiviteter. Karbazol-alkaloidet Clausenalansine A ble isolert fra frukten til *Clausena lansium* og har vist nevrobeskyttende aktivitet mot Parkinsons sykdom. Clausenalansine A og dens analoger er derfor verdifulle ressurser i søken etter nye behandlinger for nevrodegenerative sykdommer. I denne oppgaven ble mellomprodukter mot Clausenalansine A syntetisert.

Utgangsmaterialet var 3-aminofenol og 4-bromanisol. 3-Aminofenol ble beskyttet med *t*-butyldifenylsilyl. Produktet av denne reaksjonen var 3-((*t*-butyldifenylsilyl)oksy)anilin med et utbytte på 77%.

Produktet reagerte med 4-bromanisol i en Buchwald-Hartwig aminering. Produktet av denne reaksjonen var 3-((*t*-butyldifenylsilyl)oksy)-N-(4-metoksyfenyl)anilin med et utbytte på 30%.

En oksidativ krysskoblingsreaksjon ble forsøkt for å danne karbazol-enheten. Dette resulterte i produktet 2-((*t*-butyldifenylsilyl)oksy)-6-metoksy-9*H*-karbazol. Karbazolet ble avbeskyttet, og 6-metoksy-9*H*-karbazol-2-ol ble syntetisert med et utbytte på 5% over to trinn.

Det var interessant i dette prosjektet å utforske en *orto*-formylering på et karbazol-derivat. Grunnet lavt utbytte ble reaksjonen utført på N(4-metoksifenyl)-3-aminofenol, som ble syntetisert fra 3-((*t*-butyldifenylsilyl)oksy)-N-(4-metoksyfenyl)anilin med et utbytte på 81%. *Orto*-formylering ga ikke ønsket produkt.

En ny syntesevei til Clausenalansine A ble utforsket med 3-brom-4-nitroanisol og 4-hydroksyfenylborsyre som utgangsmaterialer. En Suzuki-kobling ble utført på 4-brom-3-nitroanisol og 4-hydroksyfenylborsyre, og 2-nitro-4-metoksy-4'-hydroksybifenyl ble isolert med kvantitativt utbytte. Det ble forsøkt å danne karbazol-enheten med en reduktiv sykliseringsreaksjon. Dette var ikke vellykket, og det ønskede produktet ble ikke observert.

Abstract

Carbazole alkaloids are a group of natural products known for their exciting biological activities. The carbazole alkaloid Clausenalansine A was isolated from the fruits of *Clausena lansium* and was found to have neuroprotective activity against Parkinson's disease. Clausenalansine A and its analogues are valuable resources in the search for new treatments for neurodegenerative diseases. In this thesis, intermediates towards Clausenalansine A were prepared.

The starting material was 3-aminophenol and 4-bromoanisole. 3-aminophenol was protected with TBDPS. The product of this reaction was 3-((*t*-butyldiphenylsilyl)oxy)aniline in a yield of 77%.

The product reacted with 4-bromoanisole in a Buchwald-Hartwig amination. The product of this reaction was 3-((*t*-butyldiphenylsilyl)oxy)-N-(4-methoxyphenyl)aniline in a yield of 30%.

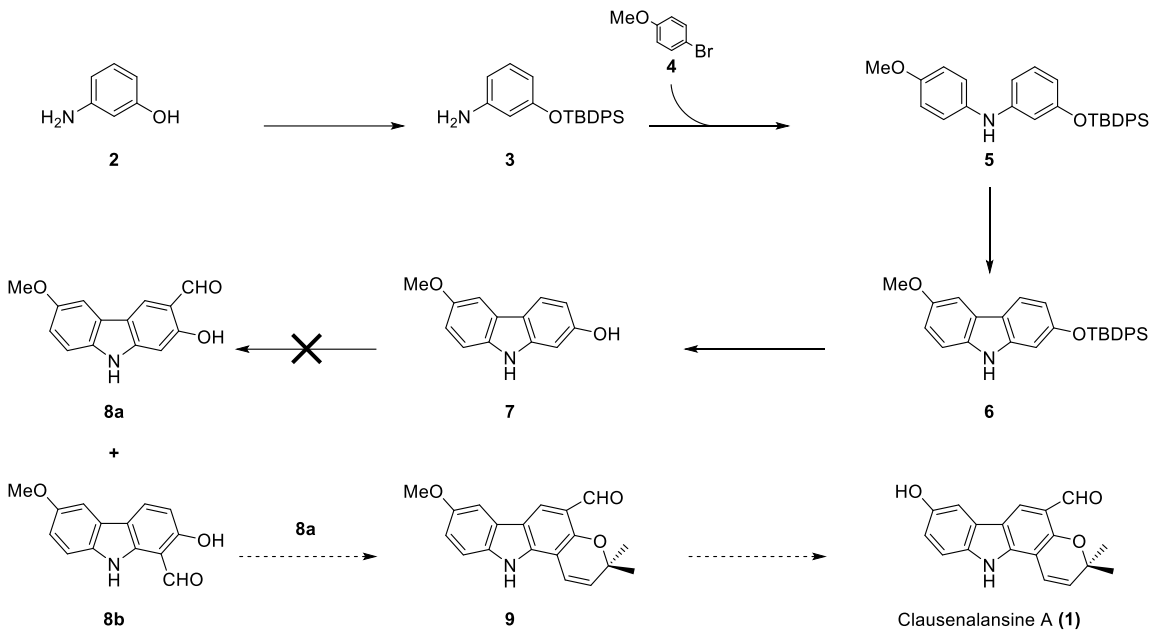
An oxidative cross-coupling reaction was performed to form the carbazole moiety. This led to the product 2-((*t*-butyldiphenylsilyl)oxy)-6-methoxy-9*H*-carbazole. The carbazole product was deprotected, and 6-methoxy-9*H*-carbazole-2-ol was synthesised with a yield of 5% over two steps.

It was interesting in this project to explore the *ortho*-formylation reaction on a carbazole product. Due to low yields, it was instead performed on N(4-methoxyphenyl)-3-aminophenol, which was synthesized from 3-((*t*-butyldiphenylsilyl)oxy)-N-(4-methoxyphenyl)aniline with a yield of 81%. The *ortho*-formylation did not yield the desired product.

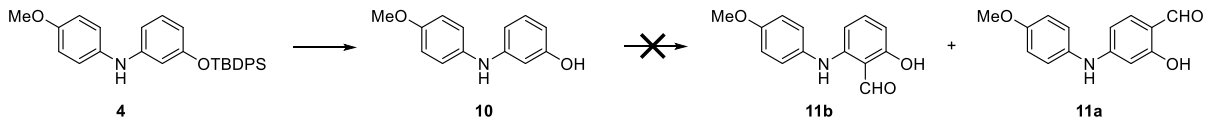
A new synthesis path to Clausenalansine A was explored with 3-bromo-4-nitroanisole and 4-hydroxyphenylboronic acid as starting materials. A Suzuki coupling was performed on 4-bromo-3-nitroanisole and 4-hydroxyphenylboronic, and 2-nitro-4-methoxy-4'-hydroxybiphenyl was isolated with a quantitative yield. A reductive cyclization reaction was performed to form the carbazole moiety. This was not successful, and the desired product was not observed.

Graphical abstract

Strategy one:



Strategy 2



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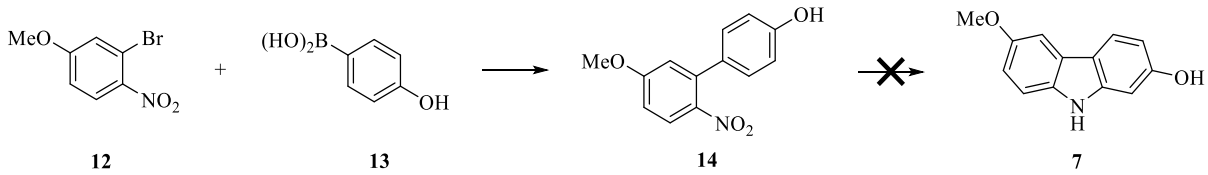

Abbreviations

AcOH	Acetic acid
AIDS	Acquired immunodeficiency syndrome
API	Active pharmaceutical ingredient
Clausenalansine A	Pyrano[3,2-*a]carbazol-5-carboxaldehyde, 3,11-dihydro-8-hydroxy-3,3-dimethyl*
CNS	Central nervous system
CoA	Coenzyme A
COX	Cyclooxygenase
DavePhos	2'-(Dicyclohexylphosphino)-N,N-dimethyl-2-biphenylamine
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DNA	Deoxyribonucleic acid
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMPTA	Hexamethylphosphoric triamide
HPV	Human papillomavirus
HSV	Herpes simplex virus
L-DOPA	Levodopa
MAOS	Microwave assisted heating in organic synthesis
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MW	Microwave
NaO*t*-Bu	Sodium *t*-Butoxide
ND	Neurodegenerative disease
6-OHDA	6-Hydroxydopamine
Otf	Triflate
PD	Parkinson's disease
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)

Phen	1,10-Phenanthroline
PTI	Potential therapeutic index
RNA	Ribonucleic acid
rt	Room temperature
SN	Substantia nigra
TBAF	Tetra-*n*-butylammonium fluoride
TBDPSO	*t*-Butyldiphenylsilyl*oxy*
TBSO	*t*-Butyldimethylsilyloxy
TEA	Triethylamine
THF	Tetrahydrofurane
TLC	Thin layer chromatography
TMSO	Trimethylsilyloxy

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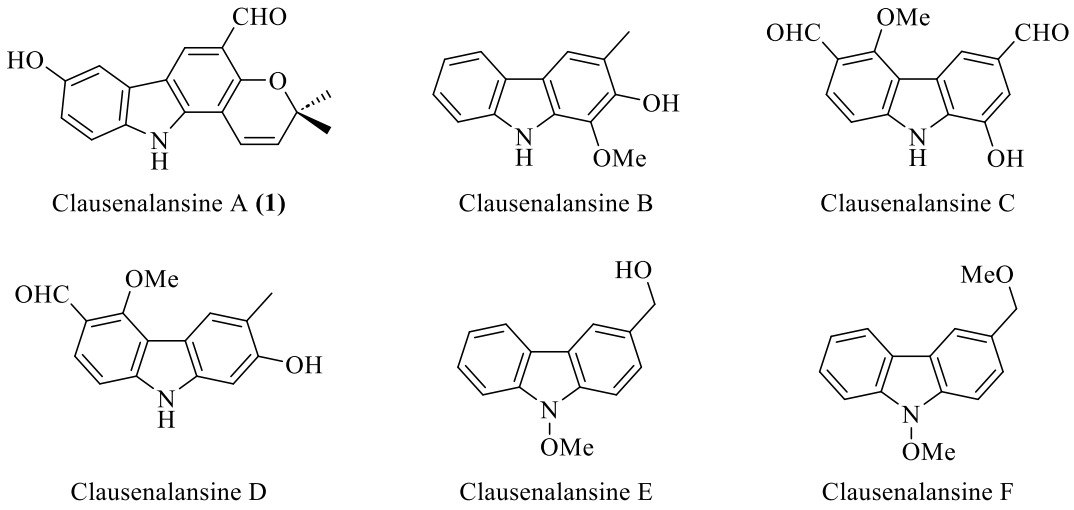
1 Introduction

1.1 Background and aims

Clausena lansium, commonly called wampee, is an ornamental citrus tree that grows in southern China, India, Vietnam, and Thailand. [1] It is widely used in Chinese folk medicine. For example, the leaves traditionally have been used to treat coughs, asthma, and gastrointestinal problems. [2] The fruits are popular for their sweet flavour and are believed to possess several beneficial biological activities. [3] Additionally, other parts of the plants have been used to treat various issues such as snake bites, dandruff and malaria. [3] In 2019, an article was published describing the isolation and identification of ten known and six novel carbazole alkaloids discovered in the wampee fruit. [3] Figure 1.1 shows the structures of the six novel carbazole alkaloids, clausenalansines A-F.



Clausenalansine A **(1)** | Clausenalansine B | Clausenalansine C

Clausenalansine D | Clausenalansine E | Clausenalansine F

Figure 1-1: *Clausenalansines A-F. 6 Novel carbazole alkaloids isolated from C. lansium by Fu and coworkers.*[3]

With promising results, clausenalansines A-F were tested for neuroprotective activity against 6-OHDA on SH-SY5Y cell lines. [3] These carbazole alkaloids may be a promising lead in discovering new treatments for Parkinson's disease.

Following this, Knölker and co-workers reported the first total synthesis of Clausenalansine A. [4] His group synthesised Clausenalansine A via a 6-step process involving a Buchwald-Hartwig amination, oxidative cross-coupling, Lewis acid-mediated annulation, and selective oxidation of a methyl group to a formyl group. Most of the first strategy presented in this text

was based on their work. Figure 1.2 shows the difference between the system that Knölker and co-workers used and the one used in this project after the cyclisation reaction that produced the carbazole moiety.

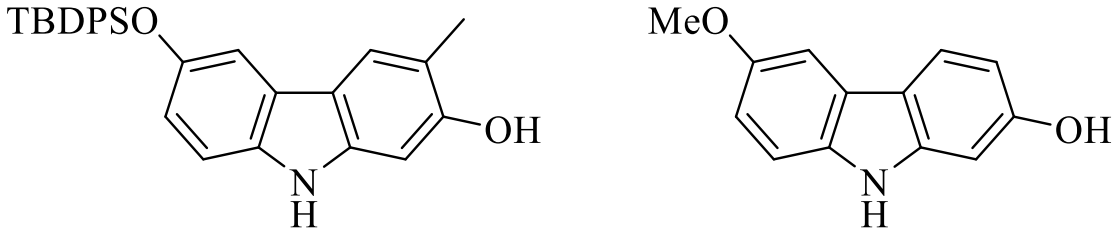


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Figure 1-2: *The initial carbazole intermediate produced in Knölker and co-workers' synthesis (left) and the analogue system used in this project (right).*

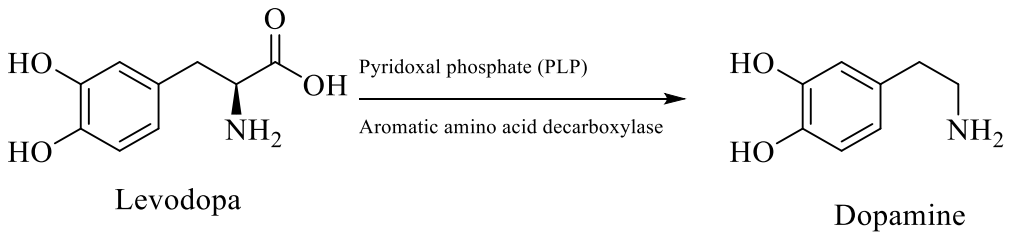
As shown in Figure 1.2, the system used in this project does not have a C-3 methyl group. This makes the system less activated. Another big difference is how the formyl group was introduced. The hydroxyl group has two non-equivalent open *ortho*-positions. The aim of this project is a total synthesis of Clausenalansine A starting with a system that lacks a C-3 methyl group, and to explore the use of *ortho*-formylation reactions on a carbazole system with a primary interest in exploring and optimising the regioselectivity of the reaction. The work described in this thesis is a continuation of work started by three former master's students. [5-7]

1.2 Neuroprotection

Neuroprotection is the protection of the central nervous system (CNS) against cell damage and -death, a process associated with neurodegenerative diseases (NDs). [8] An understanding of the mechanisms behind neuronal cell death may provide leads to exploring targets for neuroprotection and the discovery of effective treatments for neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. [9] Multiple factors are believed to contribute to neuronal cell death, such as oxidative stress, inflammation, and mitochondrial dysfunction. [10, 11] Additionally, abnormal protein aggregations, such as Lewy bodies in Parkinson's disease (PD), appear to contribute to symptoms. [12] As the world population ages, the increasing prevalence of NDs becomes a growing burden for society. [9] NDs, characterised by irreversible degradation of the CNS, have no cure and are only treated symptomatically. A

neuroprotective treatment for neurodegenerative diseases would potentially slow down or stop the progression of this type of disease. [10]

PD is a neurodegenerative disease characterised by the death of dopaminergic neurons in the substantia nigra (SN), a part of the basal ganglia. [13] The basal ganglia play an important role in voluntary movement. Consequently, a degeneration of this area causes motor symptoms such as resting tremors, postural instability and slowed movement. [14] In the case of PD, the most effective treatment available at present is Levodopa (L-DOPA). [15] L-DOPA is a biosynthetic precursor to dopamine that is able to pass through the blood-brain barrier and is converted to dopamine in the brain by the process shown in Scheme 1-1. [16] This alleviates the motor symptoms of PD. However, patients treated with L-dopa experience fluctuating symptoms and often develop drug resistance. [14] Another complication associated with L-DOPA is dyskinesia. [9]



Scheme 1-1: *Biosynthesis of dopamine from levodopa.* [16]

Another common treatment type is dopamine agonists. Dopamine agonists work by acting on dopamine receptors in the striatum instead of dopamine. This treatment avoids the fluctuating symptoms experienced with L-DOPA. [9, 17] Some dopamine agonists are shown in Figure 1-3.

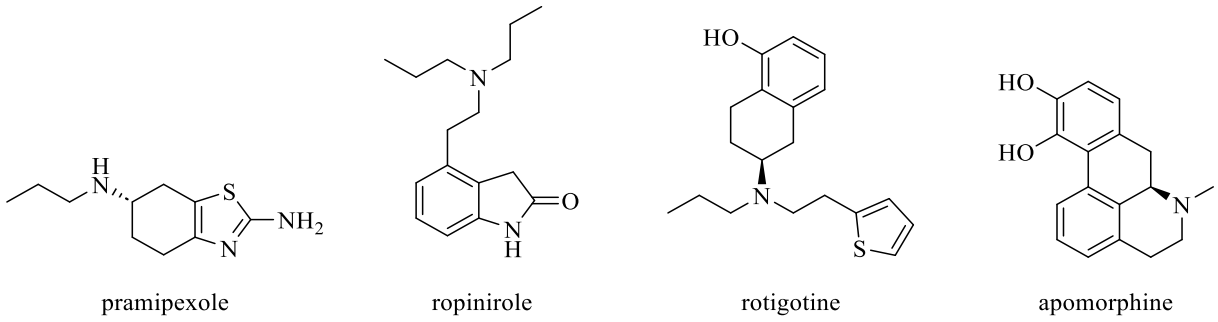
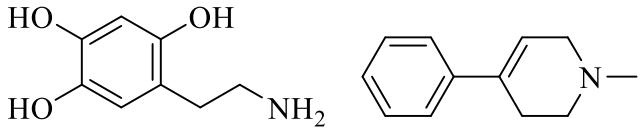


Figure 1-3: *Some dopamine agonists used to treat Parkinson's disease.* [18]

While these treatments improve the quality of life by alleviating the motor symptoms of PD, they do not treat the root cause, nor do they slow down the cell death or improve the non-motor symptoms such as depression, sleep disorders and cognitive impairements. [9, 14] Several carbazole alkaloids isolated from plants of the *Rutaceae* family have been found to have neuroprotective activity. [3, 19] Additionally, some studies have shown caffeine as a possible neuroprotective agent. [10] In their study, Liu *et al*. found that among the carbazole alkaloids isolated from *C lansium*, the most potent neuroprotective agents were the ones with a formyl group at C-3. [3]

To evaluate a potential neuroprotective agent, several models can be used. The models are based on the exposure of animal neurons or cell lines to neurotoxins such as MPTP and 6-OHDA. [20] 6-OHDA is a hydroxylated dopamine derivative that can cause oxidative stress and impair mitochondrial function. [3, 20] MPTP is a neurotoxin known to cause irreversible Parkinson-like symptoms in humans by destroying nigral dopaminergic neurons. [20]



6-OHDA MPTP

Figure 1-4: 6-OHDA and MPTP, two neurotoxins used in disease models for PD research.

1.3 Natural products

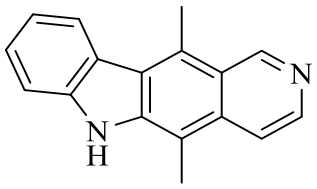
Natural products are chemical compounds produced by living organisms, also known as secondary metabolites. [21] Secondary metabolites are a diverse group of compounds, with products often unique to an organism. They differ from primary metabolites by not being present in the organism's entire life cycle, giving the organism a survival advantage rather than contributing to regular growth and energy production. [22]

Natural products are produced in nature through intricate metabolic pathways controlled with incredible specificity by enzymes. [21] Some examples are the shikimate pathway, where shikimic acid is the common precursor[23], and the acetate pathway, where polyketides and fatty acids are produced by connecting units of malonyl-CoA. [24] End products include polyphenols, fatty acids and natural products such as prostaglandins and leukotrienes.

Natural products are of great interest to synthetic chemists and the medical society. Several natural products have beneficial biological and pharmacological activities. [25] They are varied and complex synthetic targets, hence serving as inspiration for developing new synthetic methods among academics. [26]

Several characteristics can be used to categorise natural products. They can be grouped by natural origin, common biosynthetic precursors or by common structural patterns, to name a few. [21] Alkaloids are secondary metabolites characterised as having a low molecular weight and containing at least one, usually basic, nitrogen atom. [16] They often have activity on the central nervous system, making them excellent defence mechanisms for the producing organism. In controlled doses, they may be used in medicine. An example is morphine, which is used clinically to relieve pain. [16]

Ellipticine is an anti-cancer drug from *Ochrosia elliptica*, inhibiting cancer via DNA intercalation. [16] It is a tetracyclic terpenoid indole alkaloid with a carbazole moiety. Its protonated monocation form intercalates with DNA and inhibits RNA polymerase. [27] Several metabolites of ellipticine also have anti-cancer activity. [27]



Ellipticine

Figure 1-5: *Structure of ellipticine. A carbazole alkaloid with anti-cancer activity.*

1.3.1 Carbazole alkaloids

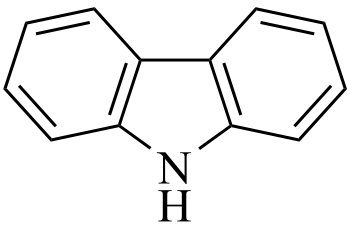
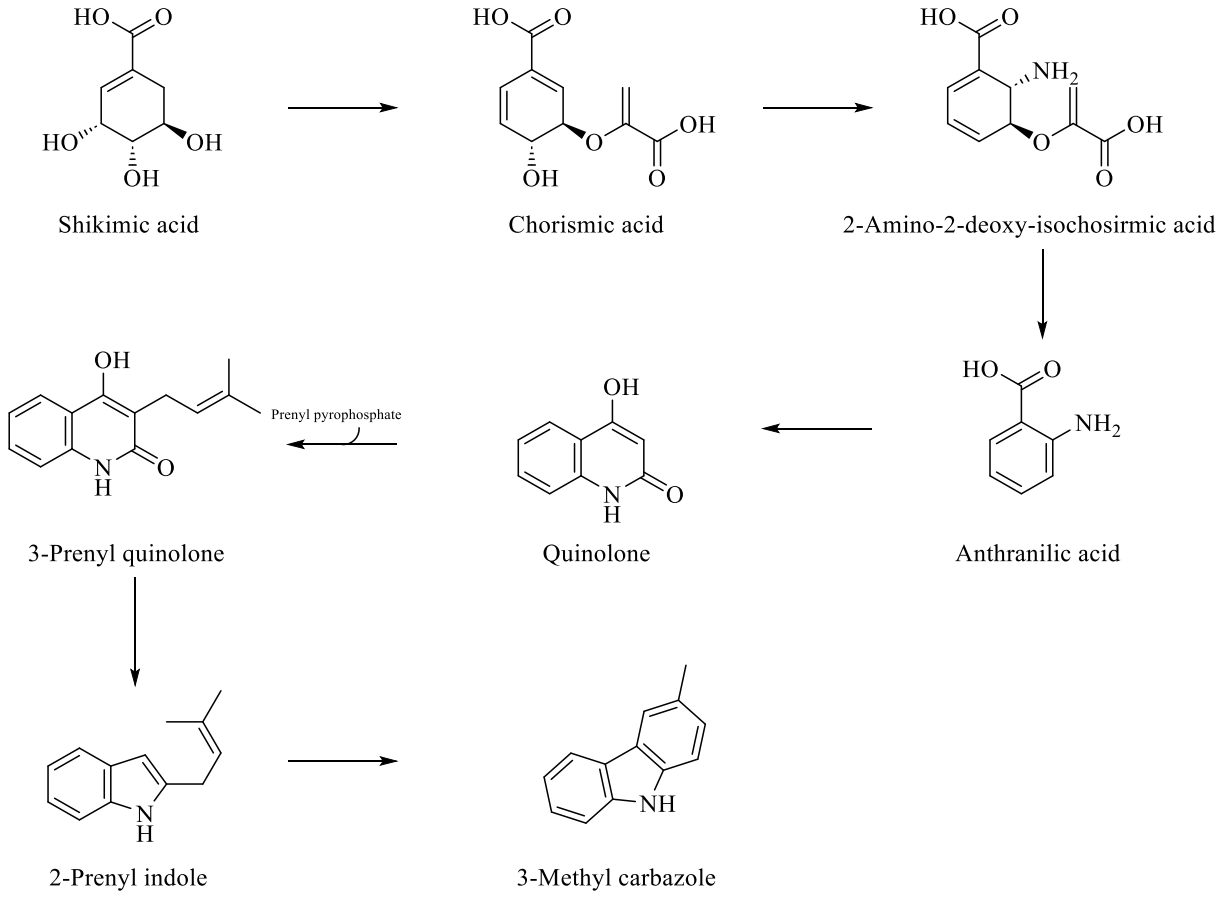


Figure 1-6: *9-H carbazole*

9*H*-Carbazole was first isolated from coal tar by Graebe and Glaser in 1872. [28, 29] Since then, its derivatives, known as carbazole alkaloids, have proven to be an abundant and structurally

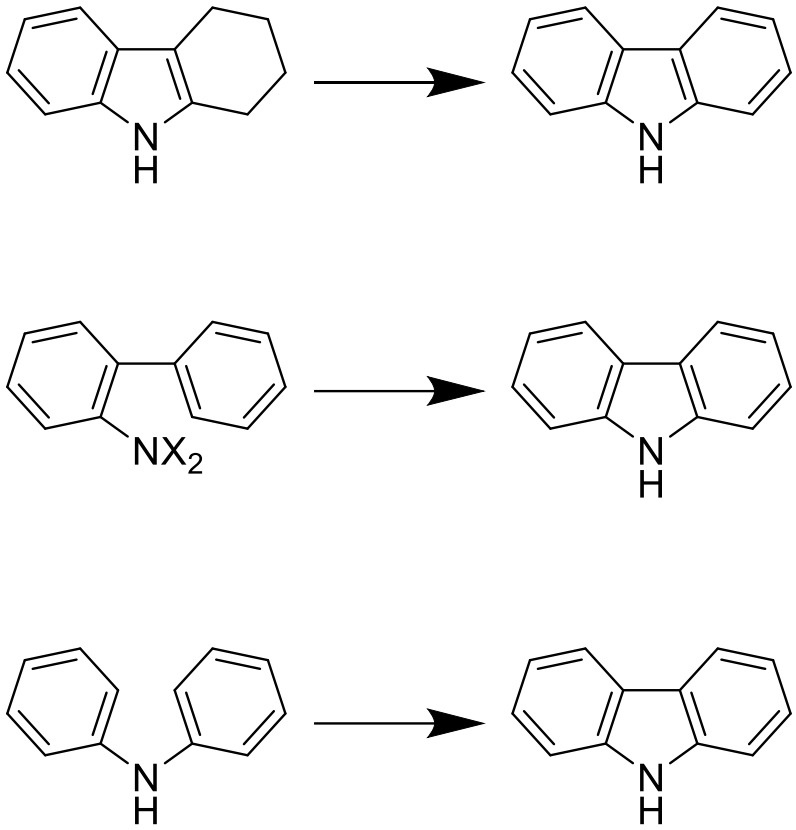
diverse group of natural products with several beneficial biological and pharmacological properties such as neuroprotection, antiviral, antibacterial, anti-inflammatory and anti-cancer activity. [3, 30] Some of these activities will be explored in the following chapters. The carbazole core is a so-called privileged scaffold, meaning it can bind to many different types of receptors and, therefore, possesses great promise as a pharmacological agent. [31-33]

The carbazole structure consists of a pyrrole ring fused with a benzene ring on either side, as shown in Figure 1-6. Phyto-carbazole alkaloids typically have a C_1 substitution on C-3, for example, a methyl group or an oxidation product of a methyl group. [29] Carbazole alkaloids derived from other natural sources typically lack this group. [29] The biosynthesis of phyto-carbazole alkaloids has been hypothesised to proceed from shikimic acid via the anthranilic acid pathway, as shown in Scheme 1-2. [29] Experimental support for the entire pathway is lacking. However, recent transcriptomic and genomic studies support the hypothesised pathway. [1, 34]



Scheme 1-2: *Proposed biosynthetic pathway for phyto-carbazole alkaloids.* [1, 29, 34]

Due to their biological and pharmacological interest and diverse structures, several methods have been developed to synthesise carbazole alkaloids. Knölker and Reddy published a review of some of these in 2002, [35] and an updated review 10 years later. [29] Some common synthetic intermediates are 1,2,3,4-tetrahydrocarbazoles, *o*-nitrogen-substituted biphenyls, and diarylamines. [35]

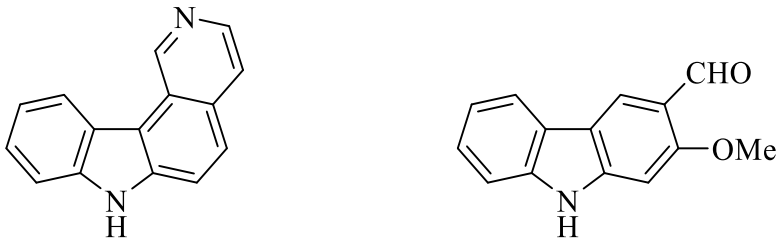


Scheme 1-3: *Some common intermediates in carbazole synthesis.* [29]

1.3.1.1 Carbazole alkaloids as antiviral agents

Viruses cause a variety of infectious diseases worldwide. They are the pathogens responsible for many well-known diseases such as human immunodeficiency virus (HIV), herpes simplex virus (HSV), human papillomaviruses (HPV), the common cold, influenza and hepatitis C virus (HCV). [36] They are of great concern as they spread quickly and readily mutate to gain drug resistance. [31] Carbazole alkaloids present a low-studied but interesting field for potential antiviral drugs. [31] Several carbazole alkaloids with antiviral activity have been discovered. Potential carbazole alkaloid drugs have been found for life-changing human pathological viruses such as HIV, HPV, HCV and HCV. [31]

HIV is a challenging virus that readily adapts; no cure is currently available. HIV causes chronic infection, and, if left untreated, leads to AIDS and eventually death. [31] Anti-retroviral drugs are offered to stop the progression of the disease, and a symptom-free life is now possible. [37] However, lifelong drug use is necessary. [31] New treatments for HIV are therefore of interest. In a study from 1999 by Hirata *et al*., several 7*H*-pyrido[4,3-*c*]carbazoles were found to inhibit the replication of HIV. [38] The most optimal ratio of antiviral activity to cytotoxicity was found for 5-methoxy-7-methyl-7*H*-pyrido[4,3-*c*]carbazole. Phyto carbazole alkaloids from the rhizomes of *Clausena excavata* were also tested for anti-HIV activity with promising results, With *o*-methylmukonal having the highest potential therapeutic index (PTI) value. [39] However, the anti-HIV mechanism is unknown. [31, 39]



7H-pyrido[4,3-c]carbazole O-Methylmukonal

Figure 1-7: *Some carbazole alkaloids with anti-HIV activity*

1.3.1.2 Carbazole alkaloids as antibacterial agents

The oldest clinical antibiotics are the penicillins. These are still used as invaluable treatments for gram-positive bacterial infections. [40] Since their discovery, many different antibiotics have been discovered to fight a broad spectrum of bacterial infections. However, antibiotic-resistant bacteria strains have become an increasing threat, and alternatives are imperative for treating difficult bacterial infections. [41]

Carbazole alkaloids have been found to have activity against a wide range of bacteria and other microorganisms, including gram-positive, gram-negative, and fungi. [30] Many carbazole alkaloids with anti-tuberculosis activity have been uncovered. [30] Among the most potent antibacterial carbazole alkaloids is clausenal. [42] As for the structure-activity relationship, C-1 hydroxylation and C-4 isoprenylation improved antibacterial activity, and C-1 methoxylation reduced activity. [42, 43]

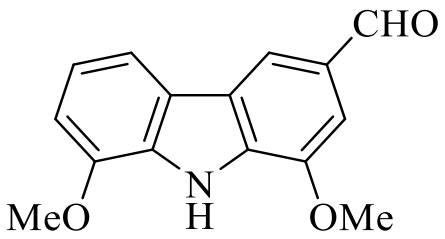


Figure 1-8: *The structure of clausenal.*

1.3.1.3 Carbazole alkaloids as anti-inflammatory agents

Inflammation is an immune system response to harmful stimuli such as pathogens, cell damage and toxic chemicals. [44] Inflammation has been related to autoimmune disorders and the development of cancer[45, 46] and may be linked to NDs. [47-49]

Four monomeric carbazole alkaloids from the rutaceous plant *Murraya kwangsiensis* were found to have anti-inflammatory activity. [50] Several prenylated carbazole alkaloids isolated from *Clausena vestita* have shown remarkable anti-inflammatory activity, with the most potent one being clausevestine. [45] The synthesis of several 3-substituted carbazole alkaloids with anti-inflammatory activity was also reported by Bandgar *et al*. [46]

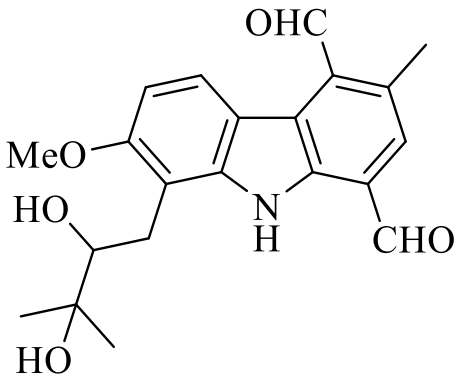
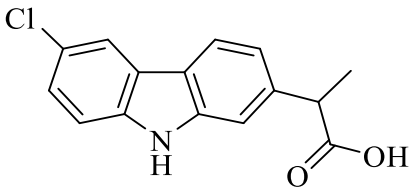


Figure 1-9: *The structure of clausevestine*

Carprofen is an anti-inflammatory API approved for use in cows, dogs and horses. [30] Carprofen inhibits COX-2, an enzyme that promotes inflammation by catalysing the production of prostaglandins. [24]



Carprofen

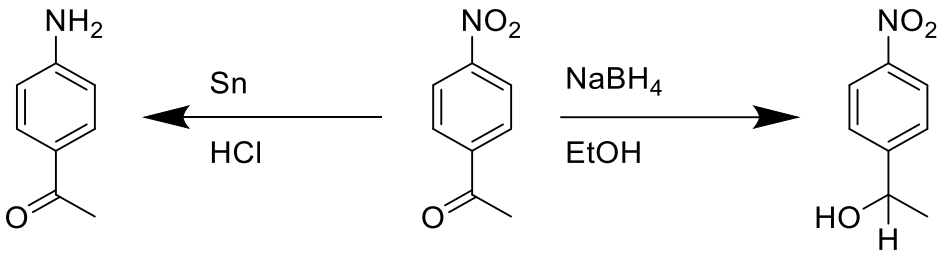
Figure 1-10: *The structure of carprofen*

1.4 Chemical background

1.4.1 Chemoselectivity and protecting groups

In organic chemistry, selectivity may refer to where a compound will react, how it will react and what functional group will react. Chemoselectivity describes a reaction's ability to react with a particular functional group selectively. [51] Understanding this is a vital tool when planning efficient syntheses. [51] A chemist with a good grasp of chemoselectivity can choose the most practical starting reagents and plan the sequence of reactions in order to achieve the desired products.

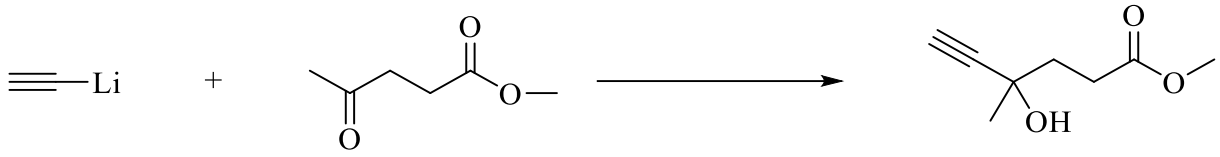
Isac-Garcia *et al*. excellently illustrated this concept with an experiment where 4-nitroacetophenone was selectively reduced to either 4-aminoacetophenone or 1-(4-nitrophenyl)ethanol by choosing a reducing agent selective to each functional group. [52] This reaction is illustrated in Scheme 1-4. $NaBH_4$ selectively reduced the ketone group, leaving the nitro group unchanged. Only the nitro group was reduced when tin was used as a reducing agent.



Scheme 1-4: *Selective reduction of 4-nitroacetophenone.* [52]

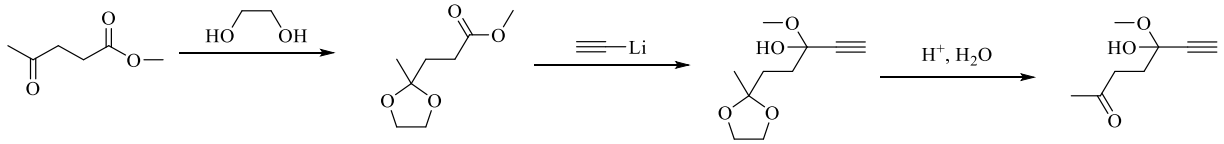
In general, with carbonyl groups, carbonyl groups bound to a more electronegative substituent are less susceptible to a nucleophilic attack than one bound to a less electronegative

substituent. [51] In a molecule containing two or more of these groups, one could, therefore, predict which one will react in a nucleophilic attack. Pfizer used this to synthesise the drug oblivion, where they reacted lithium acetylide with methyl 4-oxopentanoate. Since the ketone is more electrophilic than the ester group, the nucleophile reacts selectively with the ketone, as shown in Scheme 1-5. [51]



Scheme 1-5: *Chemoselective synthesis of oblivon*

In many cases, it is not quite as simple as this. For example, a compound may contain several instances of the same functional group, or one may want the less reactive group to react. [51] In such cases, protecting groups may be employed to achieve total selectivity. Protecting groups are unreactive groups selectively bound to a functional group to keep it from reacting or interfering with a reaction. [51] In the above example, if one wanted the nucleophile to react with the ester group instead, one may employ a protecting group on the ketone as shown in Scheme 1-6. [51]



Scheme 1-6: *Chemoselective synthesis employing protecting groups.*

Employing protecting groups comes with the disadvantage of adding two extra steps to a synthesis, protection and deprotection, [52] consequently affecting the efficiency, total yield and the atom economy of the synthesis. To minimise the effect of these disadvantages, the protecting group needs to be sufficiently stable in its given reaction conditions while also being selectively removable without damaging the rest of the molecule or losing too much yield. [53]

Several different protecting groups are available and can be selected based on the functional group that needs protecting and reaction conditions. [51, 53] For hydroxyl groups, for instance,

silyl ethers or simple ethers may be employed. Amines may be protected with a boc group, and carboxylic acids may be protected with a *t*-butyl ester. [51]

In the case of silyl ethers, stability increases with the bulkiness of the silyl group. [51] And except for *t*-butyl ethers, which are easily cleaved, simple ethers are generally highly stable and mainly used to protect phenols. [51] Silyl ethers are produced in basic conditions and removed with acid or fluoride ions, typically in the form of TBAF. [51]

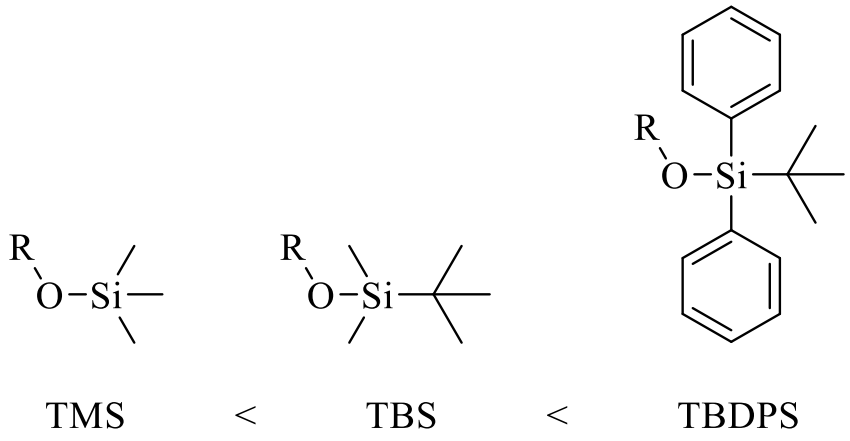


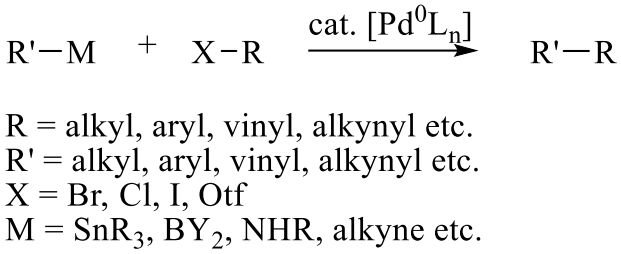
Figure 1-11: *Three silyl ethers arranged in order of stability.*

1.4.2 Organometallic catalysis in organic synthesis

Grignard reactions and Ullmann couplings are some of the earliest examples of organometallic compounds in organic synthesis. [54] Since then, organometallic catalysts in organic synthesis have been developed to enable scientists to produce complex targets using mild conditions in so-called cross-coupling reactions. [55] Traditionally, the term cross-coupling reactions refers to transition metal-catalysed reactions where a bond is formed between an sp^2 hybridised aryl halide and an organometallic nucleophile. [56]

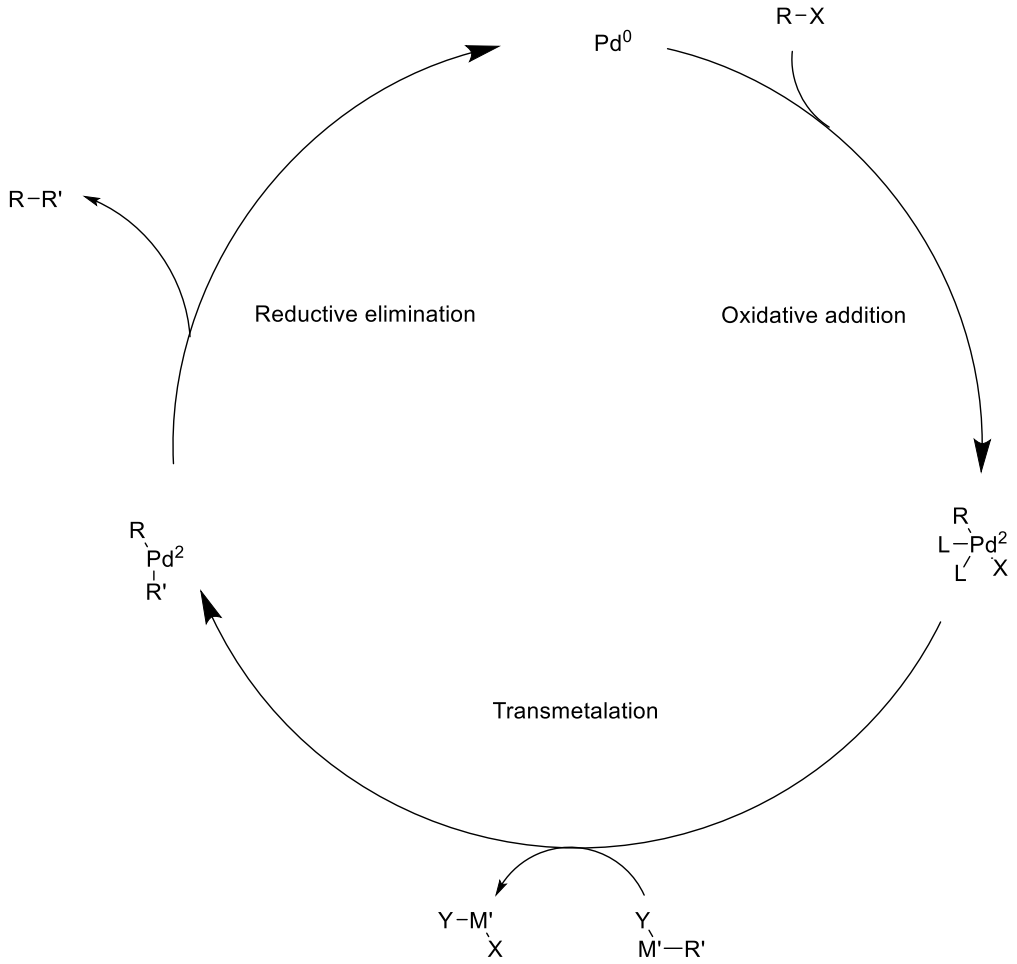
Organometallic compounds contain at least one covalent bond between a metal and a carbon atom in an organic ligand. Transition metals form complexes with ligands to fulfil the 18-electron rule. [57] Several transition metals can form organometallic complexes. However, platinum group metals, especially palladium, are particularly useful. [57] Palladium is widely employed as it can exist in three easily interconvertible oxidation states and forms stable 16e complexes and 18e complexes, allowing it to take part in the steps in a catalytic cycle as needed. [57, 58] Nickel and other first-row transition metal catalysts have recently been employed more in modern cross-coupling reactions. [56]

Cross-coupling reactions have received a lot of attention from the chemical society and are now a well-developed technology with several applications. Indeed, the 2010 Nobel Prize in chemistry was awarded to Heck, Negishi, and Suzuki for their work on palladium-catalysed reactions. [59] Cross-coupling reactions are named after their inventors and are typically told apart by the nature of the nucleophile. [56] The Buchwald-Hartwig amination employs an amine nucleophile, a cross-coupling reaction involving an organoborane is a Suzuki coupling, and a copper-mediated cross-coupling involving a terminal alkyne is a Sonogashira coupling. [55, 60]



Scheme 1-7: *General palladium catalysed cross-coupling reaction.* [55, 60]

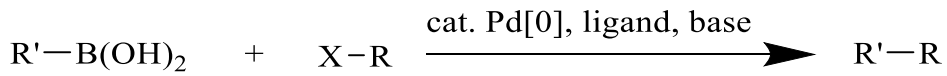
The term cross-coupling can also be defined mechanistically, as the reaction mechanisms for palladium-catalysed cross-coupling reactions tend to follow the same three steps, oxidative addition, transmetalation, and reductive elimination, as shown in Scheme 1-8. [61] Indeed, some cross-coupling reactions diverge from this cycle, examples of this are the Buchwald-Hartwig amination and Heck reaction. [60, 61] In the oxidative addition step, the transition metal is inserted into the electrophile's C-X bond. The halogen and the R group are then added as ligands to the transition metal, and a Pd(II) complex is formed. [57] The R' group from the nucleophile is introduced into the complex in the transmetalation step. Transmetalation is a slow reaction that involves transferring the R' to the palladium complex. The halogen or triflate thus moves to the main group metal from the nucleophile. [57] The last step is reductive elimination, the inverse of the oxidative addition step. The coupling product is released, and the catalyst is regenerated to a Pd(0) complex. [57]



Scheme 1-8: *General catalytic cycle for a palladium catalysed cross-coupling reaction.* [61]

More recently, the development of ligands has improved the efficiency and substrate scope of organometallic catalysis. [56] Several sterically hindered phosphine ligands, such as DavePhos, have been developed by the Buchwald group. [62]

1.4.2.1 C-C coupling

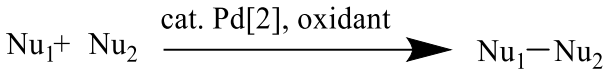


Scheme 1-9: *General Suzuki-Miyaura cross-coupling.*

The Suzuki-Miyaura cross-coupling couples an organohalide or -triflate to an organoborane in the presence of a base and a catalyst. Suzuki and Miyaura developed the reaction in the 1990s, and it has since become one of the most used C-C-generating reactions in medicinal

chemistry. [56, 63] The reaction tolerates a broad substrate scope and has mild reaction conditions.

Oxidative cross-coupling reactions are an alternative to classic cross-coupling reactions. The coupling reactions described above couple a nucleophile and an electrophile. An oxidative cross-coupling reaction involves two nucleophiles. [64] Unlike the classic cross-coupling methods, these reactions are not electronically neutral. An oxidant must, therefore, be present in stoichiometric amounts. [65] The oxidant can be internal or external and metallic or non-metallic. In oxidative couplings, an ideal non-metallic oxidant is dioxygen, as this system produces water as the only stoichiometric by-product. [64]



Scheme 1-10: *General palladium catalysed oxidative cross-coupling reaction.*

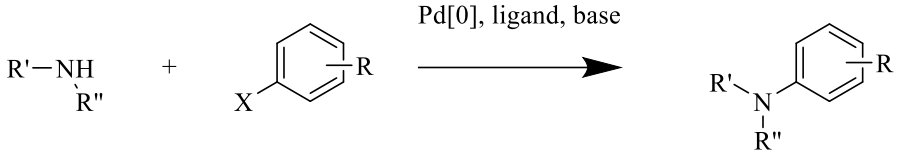
These reactions are highly attractive alternatives to classic cross-coupling reactions because they don't require prefunctionalization of the substrates, improving the efficacy of synthesis by eliminating steps, improving atom economy and simplifying by-product removal. [65] Additionally, nucleophiles are more common in nature than electrophiles. [66]

1.4.2.2 C-N coupling

Aromatic amines and heterocycles appear in various synthetic and naturally bioactive compounds. This makes efficient and selective methods for C-N, especially C(sp^2)-N bond formation, particularly interesting. [60] Before cross-coupling reactions were discovered, arylamines were synthesised via electrophilic nitration of aromats and subsequent reduction of the nitro-group. [62] Copper-mediated condensation to produce C(sp^2)-N bonds were introduced by the groups of Ullmann and Goldberg in the early 20th century. [62, 67] Both methods require harsh conditions and are limited in substrate scope. Ullmann and Goldberg's amination reactions require high temperatures and large amounts of copper. [60]

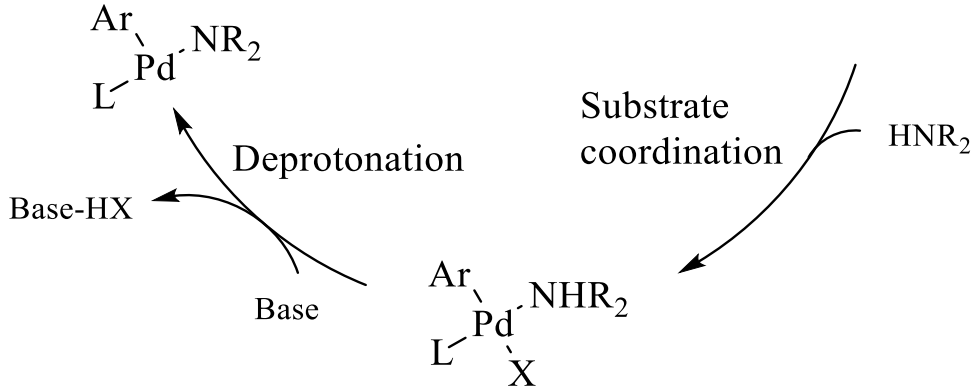
The work of Migita and coworkers in the 1980s, followed by the independent works of Buchwald's and Hartwig's groups in the 1990s, pioneered what is now known as the Buchwald-Hartwig amination. [68-72] The Buchwald-Hartwig amination is a transition metal catalysed reaction between a primary or secondary amine and an aryl halide in the presence of

a base, as shown in Scheme 1-11. [60] The Buchwald-Hartwig amination tolerates a wide range of substrates, uses only small amounts of palladium and provides mild conditions and easy handling. By choosing a suitable ligand, good yields and high selectivity can be achieved with this method. [62, 73]



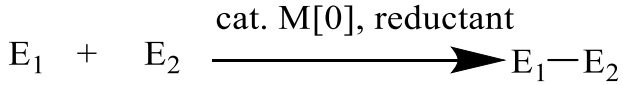
Scheme 1-11: *General reaction for a Buchwald-Hartwig amination.*

The catalytic cycle of the Buchwald-Hartwig amination resembles the general cycle for cross-coupling reactions, as the first and last steps are conserved. [60] The transmetalation step has been replaced with substrate coordination and deprotonation. [60]



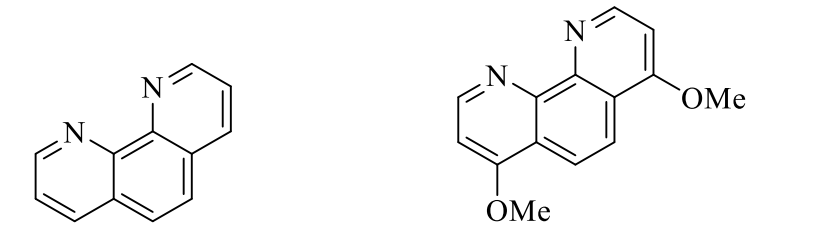
Scheme 1-12: *Substrate coordination and Deprotonation in the catalytic cycle of the Buchwald-Hartwig amination.* [60, 62]

As with C-C bond-producing cross-coupling reactions, the Buchwald-Hartwig amination reaction produces stoichiometric by-products that can be challenging to remove and negatively affect the atom economy of the reaction. Reductive coupling methods are an efficient way to create several N heterocycles, such as carbazole-[74] and indole alkaloids. [75]



Scheme 1-13: *General reductive coupling reaction.*

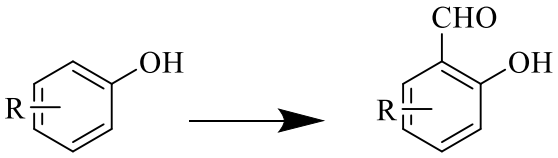
CO is an ideal reductant in reductive couplings, as it produces only carbon dioxide as a stoichiometric by-product. However, CO is challenging to handle, making in-situ CO-surrogates such as phenyl-formate attractive options. [74] This type of reaction can be achieved with a Pd or Pd/Ru-based catalyst system in the presence of a reductant. Typically, a Pd/1,10-phenanthroline (Phen) complex, as Phen and its derivatives produce robust catalytic complexes for this type of reaction. [76]



1,10-phenanthroline 4,7-dimethoxy-1,10-phenanthroline

Figure 1-12: *Two ligands used in reductive cyclisation reactions by Ramadan et al.* [74]

1.4.3 *Ortho*-formylation



Scheme 1-14: *General Ortho-formylation reaction.*

A formylation is a reaction where a formyl group is introduced directly into a molecule. In an ortho-formylation, the formyl group is introduced in the *ortho*-position to a phenol group to produce salicylaldehydes, as shown in Scheme 1-14. Some well-known formylation methods are the Vilsmeier-Haack, [77] Reimer-Tiemann, [78] Duff[79, 80] and Gattermann[81, 82] reactions. These methods tend to suffer from low or moderate yields and a lack of stereospecificity, or they are not specific to monoformylation.

In 1999, Hofsløkken and Skattebøl developed a simple method for *ortho*-formylation of phenols using paraformaldehyde as a formylating agent. [83] Their method improved upon studies performed by Casiraghi *et al*., who developed a stereoselective *ortho*-formylation method. [84, 85] Casiraghi's synthesis involved toxic reagents such as HMPTA, which

Hofsløkken and Skattebøl avoided. Hofsløkken and Skattebøl also simplified the method by replacing the Grignard reagent used by Casiraghi with a $MgCl_2$-TEA base system. [83]

1.5 Microwave-Assisted heating in Organic Synthesis

Microwave-assisted organic synthesis (MAOS) has emerged as an alternative heating method in organic synthesis. The unique properties of microwaves, as opposed to conductive heating methods, allow for exciting new synthesis methods. [86] Microwave heating allows for shorter reaction times, fewer side reactions, improved yields and improved reproducibility. [86]

Microwaves are electromagnetic waves with frequencies between 0.3 and 300 GHz, with domestic and laboratory microwave ovens using frequencies of 2.45 GHz. [86] Electromagnetic radiation consists of perpendicular, oscillating electric and magnetic fields. The electric field is mostly responsible for the heating effect. [87] The electric field exerts a force on the poles of a dipole, causing them to orient themselves with the field. When the field turns, the dipole will reorient itself in the new direction of the field. [86] As the field oscillates approximately $2.45 * 10^9$ a second, some energy is lost in the form of heat via dielectric loss and molecular friction. [86, 87] The ability to heat a substance using microwaves depends on the substance's ability to convert electromagnetic energy to heat. The loss factor, $\tan\delta$, expresses this ability. A higher value means more efficient heating. [86] Thus, microwaves transfer heat directly into a reaction solution to achieve volumetric heating. However, they depend on dipoles to release heat.

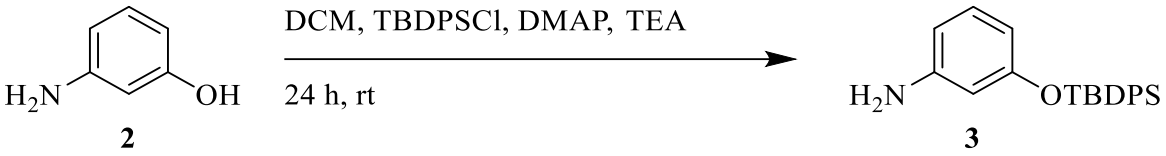
The unique heating properties of microwaves cause accelerations to chemical reactions that cannot be replicated with conductive heating. These are called specific microwave effects. The scientific community generally accepts thermal microwave effects, but non-thermal effects remain controversial. [86, 88] Thermal effects are MW effects that can be explained by thermal conditions. This includes superheating, rapid heating, selective heating, volumetric heating and eliminating wall effects. [86, 88] MAOS also provides more reproducible results by giving precise and continuous monitoring of the internal temperature of the reaction medium. One possible explanation of non-thermal microwave effects is that the highly polarising electric field stabilises polar transition states, thus favouring mechanisms involving polarised transition states. [88]

Limitations to MAOS include batch sizes and choice of solvent and reagent. Microwaves have a limited penetration depth; the reaction vessel, therefore, has a limited diameter range.

Flow chemistry solutions may circumvent this. [89] The dependence on dielectric heating also limits the choice of solvent and may impact the solubility of organic reagents. [90] The price of dedicated microwave reactors is also a limitation. [86]

2 Results and discussion

2.1 Synthesis of 3-((*t*-butyldiphenylsilyl)oxy)aniline (**3**)



2 **3**

Scheme 2.1: *synthesis of 3-((t-butyldiphenylsilyl)oxy)aniline (**3**)*

This synthesis was performed as described by Schiaffino-Ortega *et al*. using 1.4 equivalents of TBDPSCl for improved ease in the purification process. [91] TBDPS was chosen as the protection group because it is known to be sufficiently non-reactive in the subsequent reactions. A solution of 3-aminophenol, TEA, TBDPSCl and DMAP in DCM was stirred at room temperature for 24 hours. This provided aniline in a 77% yield.

After washing the reaction mixture with water and subsequent extraction with DCM, a TLC analysis showed some impurities with similar R_f values to the product. Purification with flash column chromatography was performed, and aniline **3** was obtained. Some yield was lost due to overlapping bonds on the column.

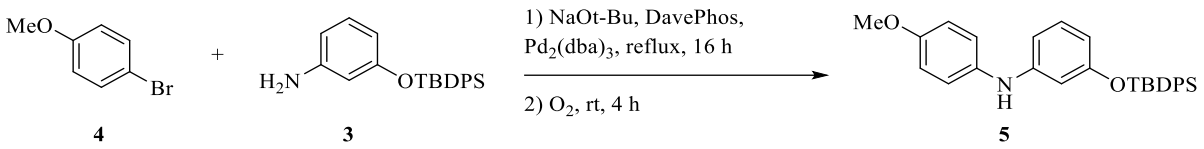
^{1}H and ^{13}C NMR data revealed that the reaction was successful. The characteristic singlet at δ 1.08 ppm shows that the *t*-butyl group is present. The multiplet at δ 6.15-6.18 (2H), multiplet 6.20-6.23 (1H), and the multiplet 6.83-6.87 (1H) ppm are from the aniline. The broad singlet at δ 3.47 (2H) ppm confirms the amine group. The aromatic proton integrals are somewhat low, suggesting that there might be impurities in the aliphatic area, which was used to calibrate the integrals. The integrals of the multiplets at δ 7.34-7.44 (6H) and 7.71-7.74 (4H) ppm correspond to the aromatic rings of the silyl group. They are somewhat high, suggesting impurities in this area. These signals group together due to the symmetry of the silyl group.

The small peaks approximately at δ 4, 2 and 1 ppm suggest some leftover ethyl acetate in the product; the yield may therefore be somewhat overestimated.

Aniline **3** consists of 12 chemically unique carbon nuclei. This corresponds well with the ^{13}C NMR spectrum. The peaks at 19.80 and 26.86 correspond to the *t*-butyl group. Carbon one and three are bound to nitrogen and oxygen atoms, respectively, this gives them a higher chemical shift, and they are confirmed by the peaks at δ 135.85 and 147.78 ppm.

An excess of TBDPSCl was used in the reaction. Consequently, some silanol product remained after completed reaction. Given its similar polarity and results reported by a former master's student on the project, this may have coeluted with aniline **3**. Obtaining product was simple; however, the yield was low compared to the quantitative yield reported in the literature. The yield may be improved by further decreasing the amount of TBDPSCl to 1.1 equivalents. The impurities confirmed in the ^{1}H NMR spectrum overlapping with the protecting group shifts suggest that some leftover silanol was left in the product after flash column chromatography and that the yield is somewhat overstated.

2.2 Synthesis of 3-((*t*-butyldiphenylsilyl)oxy)-N-(4-methoxyphenyl)aniline (**5**)



Scheme 2.2: *Synthesis of 3-((t-butyldiphenylsilyl)oxy)-N-(4-methoxyphenyl)aniline (**5**)*

This synthesis was executed following the procedure of Lösle *et al.* [4] The reaction was attempted once as described, and once with halide **4** in excess to make the purification easier. The latter did not improve the simplicity of the workup. Halide **4**, aniline **3**, the base NaO*t*-Bu, the ligand DavePhos and the catalyst $Pd_2(dba)_3$ were heated to reflux in toluene for 16 h and then stirred in air at room temperature for four hours. This yielded diarylamine **5** in a 30 % yield.

Spectral data from ^1H and ^{13}C NMR revealed that the reaction was successful. The characteristic singlets at δ 1.08 (9H) and 3.78 (3H) ppm confirm the *t*-butyl and methoxy groups, respectively. These groups stem from the two different coupling partners. The ratio between the integrals strongly supports a successful coupling. The singlet at δ 5.95 (1H) ppm confirms the amine group.

The multiplets at δ 7.33-7.44 (6H) and 7.69-7.71 (4H) ppm correspond to the phenyl groups in the silyl group. The integrals are somewhat high, suggesting impurities in this area, possibly from unreacted reagent.

By comparing the ^1H NMR spectrum of diarylamine **5** with aniline **3**, one can find that the doublet of doublets at δ 6.26-6.28 (1H), the triplet at δ 6.34-6.35 (1H) and the doublet of doublets at δ 6.39-6.41 ppm correspond to the peaks in the spectrum for aniline 3, and therefore confirm the phenyl group on the right. The proton on C-2 in the ring on the right may have long-distance coupling with the protons on C-4 and C-6, possibly explaining the triplet at δ 6.34-6.35 ppm (1H), and the appearance of two doublets of doublets at δ 6.26-6.28 ppm (1H) and δ 6.39-6.41 ppm (1H) with similar coupling constants *J* 2.21, 2.16, and 2.03 Hz respectively. The proton on C-5 was confirmed by the triplet observed at δ 6.90-6.94 ppm (1H) with a coupling constant *J* 8.05 Hz, which matches the coupling constants of the J_{AB} coupling in the doublets of doublets.

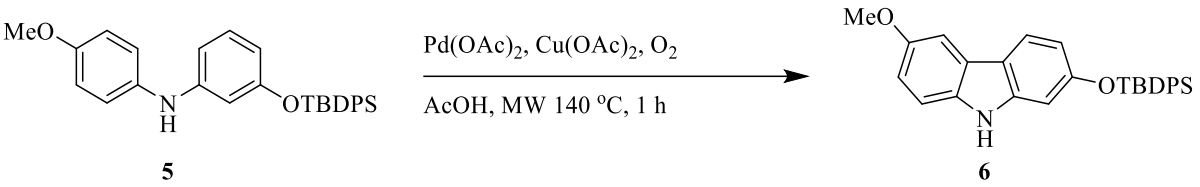
The phenyl group on the left side of the structure is symmetrical. Therefore, the protons are confirmed by two peaks with integrals corresponding to 2H each. These are found as two triplets of doublets at δ 6.72-6.75 (2H) and 6.82-6.86 (2H) ppm. The roof effect shows clear coupling between these peaks. These signals' coupling constants *J* of 9.9 and 9.8 Hz suggest AB coupling. This confirms the phenyl group on the left.

The peaks around the *t*-butyl group peak could suggest some leftover solvent.

Diarylamine **5** contains 17 chemically unique carbon atoms. This corresponds well with the 17 peaks in the ^{13}C spectrum. The peaks at δ 19.78 and 26.88 ppm overlap with the spectrum of aniline **3** and correspond to the *t*-butyl group. The peak at δ 55.89 ppm corresponds to the methoxy group. There are 14 unique carbon atoms in the aromatic area. Four are bonded to oxygen or nitrogen, giving the shifts observed at δ 135.88, 146.35, 155.36, and 156.95 ppm.

After filtration over celite to remove palladium, extraction with EtOAc and washing with brine, a TLC analysis revealed an impurity with an R_f value close to the R_f value of diarylamine **5.** This by-product also overlapped on the column, and only a small amount of pure product was obtained. Several different eluent systems were tested, and 15% ether and 5% DCM in n-hexane was promising when analysed with TLC but did not provide any pure product with flash column chromatography.

2.3 Synthesis of 2-((*t*-butyldiphenylsilyl)oxy)-6-methoxy-9*H*-carbazole (**6**)



5 **6**

Scheme 2.3: *Synthesis of 2-((t-butyldiphenylsilyl)oxy)-6-methoxy-9H-carbazole (**6**)*

This synthesis was executed following method A of Lösle *et al.* [4] using optimised microwave conditions determined by two former students on this project. This provided a mixture of carbazole **6** and carbazole **7.**

Diarylamine **5**, the catalyst $Pd(OAc)_2$, and the oxidant $Cu(OAc)_2$ in acetic acid were heated to 140 °C for one hour by microwave irradiation. After cooling to room temperature, the reaction mixture was worked up with workup A or B. A crude ^{13}C NMR spectrum was recorded after the work-up and revealed peaks corresponding to two different carbazole products. Analysis with TLC also revealed the desired product and a highly polar by-product. After purification, carbazoles **6** and **7** were confirmed with ^{1}H NMR.

Workup A:

Filtration over celite to remove leftover metal was simple. However, it did not remove all palladium from the solution, as this was observed as a black solid between the phases during the washing and extraction.

During washing with K_2CO_3, a salt precipitated from the solution and had to be filtered off. Several rounds of washing were required to remove all leftover copper. An emulsion formed during the extraction with EtOAc and black palladium particles gathered between the phases, making it difficult to get a good separation of the aquatic and organic phases. After working up the reaction, TLC analysis revealed that several by-products were present in the reaction mixture, some of which had R_f values similar to carbazole **6.** It also revealed the presence of a highly polar by-product. Some leftover reagent was also observed by TLC analysis.

No pure product was obtained with flash column chromatography. However, carbazole **6** crystalised in some of the fractions. Some of these crystals were gathered, and the structure

was confirmed with ^{1}H NMR. Carbazole **7** was isolated with flash column chromatography and confirmed with ^{1}H NMR.

The product was challenging to purify, with all pure product gained through crystallisation. In addition, the reaction seemed to react further, cleaving the silyl ether to produce the following product in the synthesis. The latter of these was possible to purify through flash column chromatography.

The ^{13}C spectrum of the crude oil contained parallel peaks corresponding to two carbons in the pyrrole ring in the carbazole skeleton. This seems to suggest that two different carbazole products were produced in this synthesis. This combined with the TLC analysis results suggests that some of the product reacts further by cleaving the silyl group. This was not problematic in this case, as the following step in the synthesis was to cleave the silyl group.

Due to low yield and challenging work-up and purification, a new work-up method was planned and tested. The following reaction in this synthesis was to cleave the silyl ether. The deprotection reaction is simple to perform and not very sensitive. Therefore, a workup that removes leftover metals from the cyclisation should be sufficient.

Workup B:

Evaporation of the solvent followed by suspension of the residue in toluene and filtration over celite followed by filtration through silica easily removed copper and palladium from the reaction mixture. Evaporation with toluene facilitated the removal of leftover acetic acid by providing a positive azeotrope. This workup was greatly simplified and provided a sufficiently pure crude oil to react in the subsequent reaction. Analysis with TLC and NMR showed that both carbazoles **6** and **7** were still present in the solution.

Due to low yields, only ^{1}H NMR was recorded for the carbazole **6** crystals. The spectrum corresponds well with the carbazole product, confirming that the reaction was successful. The structure contains two 1,2,4-substituted phenyl groups; ABX coupling is therefore expected. The characteristic singlets at δ 1.12 (9H) and 3.88 (3H) ppm correspond to the *t*-butyl and the methoxy group, respectively.

The coupling constants of the doublet at δ 6.72-6.76 ppm suggest short-range coupling with a possible doublet observed in the multiplet at δ 7.72-7.74 with J_{AB} = 8.4, and the roof effect

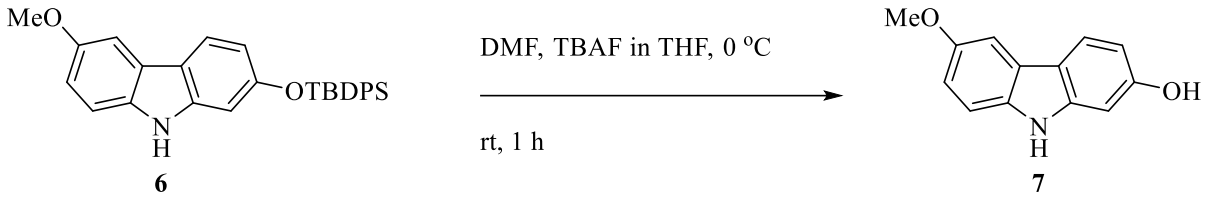
suggests long-range coupling with the doublet at δ 6.70 ppm, with J_{AX} = 2.0. This confirms the three protons in one of the phenyl groups.

The doublet of doublets at δ 6.92-6.94 ppm has a coupling constant *J* 8.7 corresponding with short-range coupling with the doublet observed at δ 7.18-7.20 ppm. The roof effect also supports this coupling. The last proton in this ring system is probably found in one of the multiplets with integrals of 8 and 5, respectively, and would be confirmed by a doublet with a coupling constant *J* of approximately 2.5.

δ 7.34-7.44 (8H) and δ 7.75-7.78 (5H) ppm confirm the silyl group and the missing protons from the carbazole skeleton. The integrals in this area are a little high, suggesting impurities in the area, probably from unreacted reagent.

The broad singlet at δ 7.59 (1H) ppm confirms proton bound to the nitrogen. The high shift is due to the nitrogen being part of a pyrrole ring conjugated with two other aromatic rings.

2.4 Synthesis of 6-methoxy-9*H*-carbazole-2-ol (**7**)



Scheme 2.4: *Synthesis of 6-methoxy-9H-carbazole-2-ol (7)*

The reaction was performed as described by Schuster *et al*.[92] Crude carbazole **6** was dissolved in DMF mixed with TBAF in THF at 0 °C, and then stirred at room temperature. After one hour, a TLC analysis revealed the full conversion of carbazole **6**.

After washing with water and extraction with EtOAc, an analysis with TLC showed that the reaction mixture was not pure, and flash column chromatography was performed. Further purification with trituration provided carbazole **7** in a 5 % yield calculated over two steps.

The reaction was simple to perform, and DMF was removed efficiently with water. However, carbazole **7** is relatively polar. Some product may therefore have been lost in the aqueous phase. This was not explored further. This could be improved by replacing DMF with THF as a reaction solvent. Extraction with EtOAc was unproblematic except for a human error where some of the organic phase was lost, and flash column chromatography yielded almost pure carbazole **7**. When attempting to record an NMR spectrum of carbazole **7**, it was observed that the impurities that coeluted with the product were soluble in chloroform, but carbazole **7** was poorly soluble.

It was therefore determined that trituration in chloroform should be attempted. This yielded pure carbazole **7**, in yield too low to be useful. Some of the product may also have been lost in the cyclisation reaction. The reaction mixture was not pure, and some leftover reagent was observed. The impurities could be unwanted by-products.

The spectral data from ^{1}H and ^{13}C NMR revealed that the reaction was successful. Like carbazole **6**, carbazole **7** contains two 1,2,4-substituted phenyl groups, ABX coupling is therefore expected.

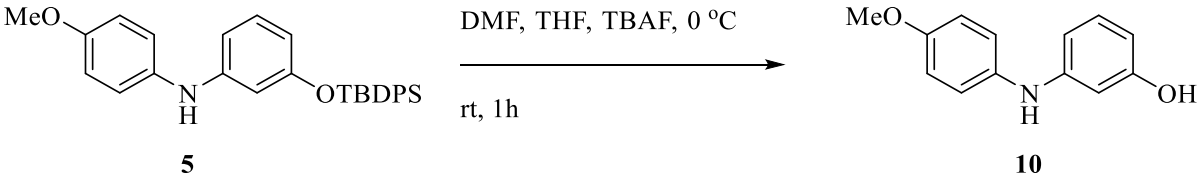
The characteristic singlets at δ 1.12 (9H) and 3.88 (3H) ppm correspond to the *t*-butyl and methoxy groups, respectively. The singlet at δ 3.88 (3H) ppm is characteristic of the methoxy group. The broad singlet observed at δ 8.95 (1H) ppm confirms the amine group.

The doublet of doublets at δ 6.69-6.72 (1H) has coupling constants *J* 8.44 and 2.08 Hz. This, along with the roof effect, suggests short-distance coupling with the doublet at δ 7.85-7.87 ppm (1H) and long-distance coupling with the doublet at δ 6.87 ppm (1H). This is consistent with the expected ABX spin system of a 1,2,4-substituted phenyl group and confirms the three protons on one phenyl ring in the carbazole structure.

The doublet of doublets observed at δ 6.94-6.97 ppm (1H) has coupling constants *J* 8.74 and 2.46 Hz. This and the roof effect show short-distance coupling with the doublet observed at δ 7.32-7.35 ppm (1H) and long-distance coupling with the doublet observed at δ 7.53 ppm (1H). This confirms the three protons on the second phenyl group.

Carbazole **7** contains 13 chemically unique carbon atoms. The ^{13}C spectrum shows 13 peaks. The peak at δ 56.39 ppm corresponds to the carbon in the methoxy group. Four carbon atoms in the aromatic system are bonded to oxygen and nitrogen and are found at higher shifts. Due to long relaxation times, the signals corresponding to these carbon nuclei are weak; they are found at δ 135.56, 143.14, 154.78 and 157.02 ppm, with the two highest shifts being characteristic of carbon 8a and 9a in the carbazole skeleton. Carbon 4a and 4b were confirmed by the weak signals at δ 117.39 ppm and 124.77 ppm due to long relaxation periods.

2.5 Synthesis of N(4-methoxyphenyl)-3-aminophenol (**10)**



5 **10**

Scheme 2.5: *Synthesis of N(4-methoxyphenyl)-3-aminophenol (10)*

The reaction was performed as described by Schuster *et al*.[92] Diarylamine **5** was suspended in DMF mixed with TBAF in THF at 0 °C, and then stirred at room temperature. After one hour, a TLC analysis revealed the full conversion of diarylamine **5**. The *ortho*-formylation is a highly interesting reaction to explore in this project. Due to low yields in the oxidative cross-coupling reaction, only a small amount of carbazole **7** was obtained. It was determined that diarylamine **5** should be deprotected to attempt an *ortho*-formylation on diarylamine **10** instead.

After washing with water and extraction with EtOAc, an analysis with TLC showed that the reaction mixture was not pure, and flash column chromatography was performed. This provided diarylamine **10** in an 81% yield.

NMR spectra were recorded, and the structure was confirmed by spectrum interpretation and comparison to literature data.[91] The signal at δ 1.08 ppm in the reagent is not present in the spectrum, confirming the successful cleaving of the silyl ether. The singlet at δ 3.71 (3H) ppm confirms the methoxy group.

The ring on the left side is symmetrical, meaning the protons were expected to appear in the spectrum as two signals with integrals 2H each. This was confirmed by the doublets of triplets observed at δ 6.75-6.77 (2H) and 6.94-6.98 (3H) ppm. The extra proton may be caused by an overlap with one proton from the phenyl ring on the right side. These two peaks show the same AB coupling pattern as in diarylamine **5** with *J* 8.80 and 8.90 Hz.

The proton on C-2 in the ring on the right may have long-distance coupling with the protons on C-4 and C-6, explaining the triplet at δ 6.28-6.29 ppm (1H), and the appearance of two doublets of doublets at δ 6.19-6.21 ppm (1H) and δ 6.35-6.37 ppm (1H) with similar coupling constants *J* 2.20, 2.10, 1.92 Hz. The proton on C-5 would be confirmed by a triplet with a

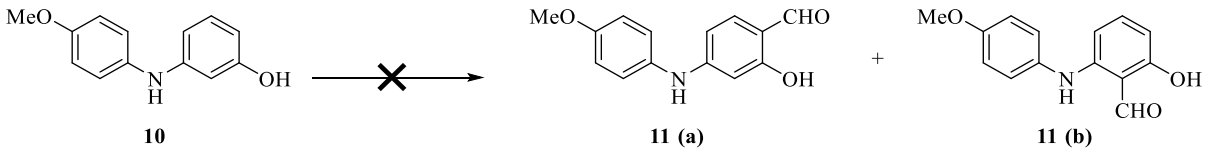
coupling constant of approximately J 8 Hz and may be the proton signal overlapping with the signal from the left ring.

The signals between δ 0 and 2 ppm could stem from leftover solvent, suggesting that the yield may have been overestimated.

The ^{13}C NMR spectrum shows 11 peaks corresponding to the 11 chemically unique carbon atoms in the diarylamine **10**. The phenyl group on the left only has 4 chemically unique carbon atoms due to symmetry.

Four carbon atoms in the product are bound to carbon or nitrogen. These are found at a higher shift and are probably the signals found at δ 135.14, 147.91, 155.49, and 156.71 ppm.

2.6 Synthesis of N(4-methoxy)-4-amino-2-hydroxy-benzaldehyde (**11**)



Scheme 2.6: *Synthesis of N(4-methoxy)-4-amino-2-hydroxy-benzaldehyde (11)*

This reaction was performed as described by Hofsløkken and Skattebøl. [83] diarylamine **10,** paraformaldehyde, $MgCl_2$ and TEA were dissolved in acetonitrile and stirred under reflux. After four hours, a TLC analysis showed that all starting material had reacted.

After cooling to room temperature and quenching the reaction with HCl, extraction with ether, drying, filtering and concentration in vacuo, a crude NMR spectrum was recorded that revealed the reaction was unsuccessful. The reaction mixture was complex, and the formyl group was not observed.

A test reaction was run on 4-bromophenol to check that the reagents were in order. This test was successful, and ^{1}H NMR data confirmed the formylation. An excerpt showing the aromatic part of the crude spectrum is shown in Figure 2.1. The formyl group was confirmed by the singlet at δ 9.77 (1H) ppm. The hydroxyl group is confirmed by the broad singlet at δ 10.85 (1H) ppm. The hydroxyl group forms an intramolecular hydrogen bond with the formyl group, causing exceptionally high shifts. Some impurities are present in the aromatic area. However, three peaks are present with integral ratios of 1:1:1. A doublet at δ 6.83-6.85 ppm, a doublet of doublets at δ 7.51-7.54 ppm and a doublet at δ 7.60-7.61. The coupling patterns correspond well with the 1,2,4-substituted benzene ring, and the structure could be more strongly confirmed with a COSY spectrum. It can be concluded that the reagents work and that something else is inhibiting the reaction.

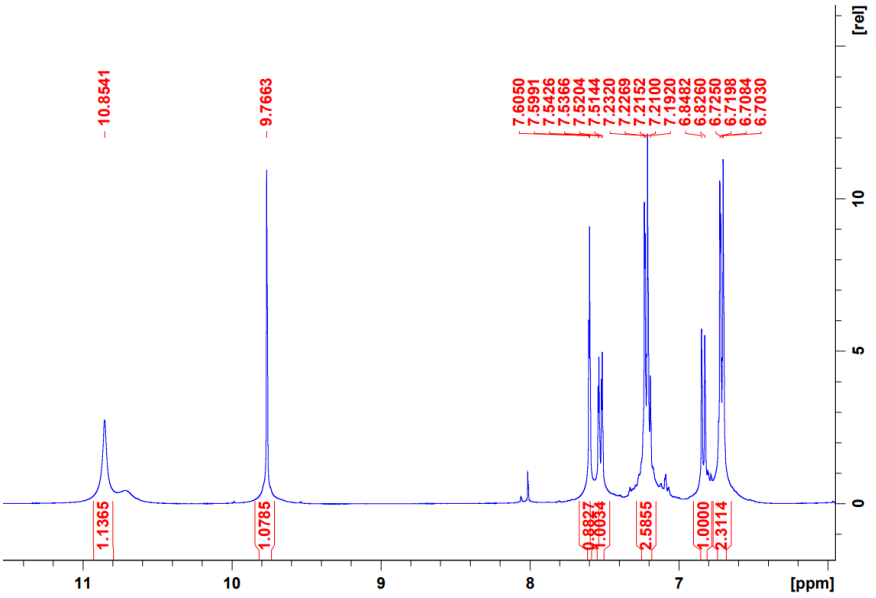
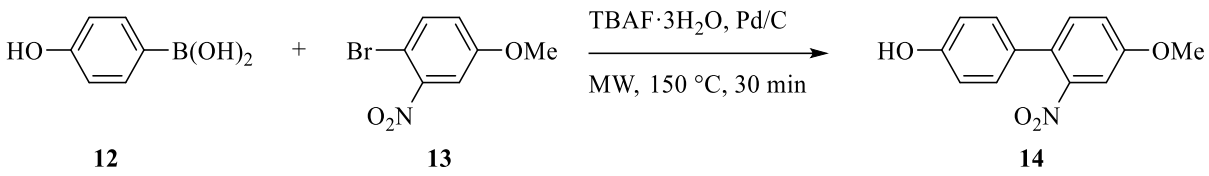


Figure 2.1: *Excerpt of the aromatic area of the 1H NMR spectrum of 4-bromo salicylaldehyde*

This reaction has been attempted on a carbazole product with a TBDPSO protecting group by former students on the project. The reaction was unsuccessful, and it seemed that the silyl ether was cleaved, and the product was not observed. It was suggested that the silyl ether was not sufficiently stable in the reaction conditions. A new strategy was planned for the more stable methoxy group to replace the silyl ether. Due to low yields, it was determined to test the reaction on a diarylamine instead of the corresponding carbazole, carbazole **7**. The aldehyde proton was not observed in the crude NMR spectrum, suggesting that the reaction was unsuccessful. Hofsløkken and Skattebøl's article only described the formylation of one nitrogen-containing phenol. They also reported a relatively low yield of 24%. It is, therefore, possible that the amine group hinders the reaction somehow. Protecting the amine or following a different procedure could be a relevant approach in the future.

2.7 Synthesis of 2-nitro-4-methoxy-4'-hydroxybiphenyl (**14**)



12 **13** **14**

Scheme 2.7: *Synthesis of 2-nitro-5-methoxy-4'-hydroxybiphenyl (**14**)*

This reaction was performed as described by Schmidt and Riemer.[93] Bromoanisole **13**, boronic acid **12**, TBAF·3H$_2$O, Pd/C were suspended in water and heated to 150 °C for 30 minutes. Biphenyl **14** was produced in a quantitative yield.

After cooling to room temperature, the solution was acidified with HCl, followed by extraction, drying, filtering, and concentrating in vacuo. After this, a TLC analysis revealed that two compounds were present in the solution with very different R_f values, making them simple to separate by flash column chromatography.

The reaction was simple in practice, and the workup was unproblematic. Flash column chromatography was an excellent and quick purification method for this reaction. The product was clearly visible on the column as a bright yellow band, with the by-product eluting before the product with no co-elution observed. The product was challenging to transfer to the column without using too much solvent; it was therefore purified in two batches.

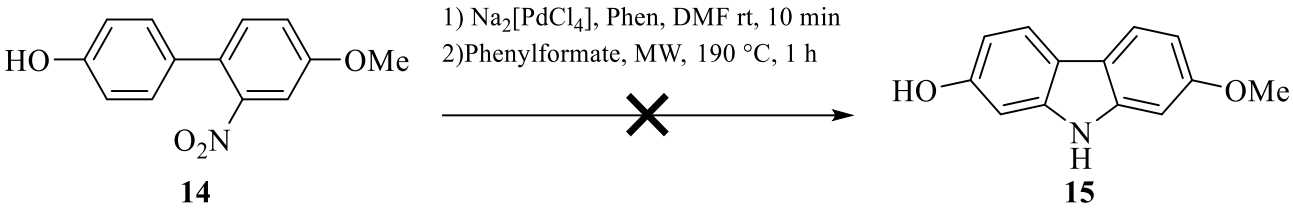
Spectral data revealed that the reaction was successful. The singlet at δ 3.89 (3H) ppm confirms the methoxy group, and the singlet at δ 4.81 (1H) ppm confirms the hydroxyl group. The multiplet at δ 6.84-6.88 (2H) ppm confirms the phenyl group on the left side. This ring is symmetrical and is only visible on NMR as two signals. The multiplet at δ 7.11-7.18 ppm appears to be a doublet of doublets (1H) overlapping with a doublet of triplets (2H), the latter confirming the remaining pair of chemically equivalent protons on the left ring. The roof effect on the two doublets of triplets shows clear coupling between the signals. The doublet of doublets and the multiplet at δ 7.30-7.33 (2H) ppm corresponds to the three protons on the right ring. The remaining peaks could stem from leftover solvent, meaning the yield may be overestimated.

The ^{13}C NMR spectrum contains 11 peaks, confirming the product's 11 chemically unique carbon nuclei. The peak at δ 56.24 ppm corresponds to the methoxy group. The rest of the

peaks are in the aromatic area and correspond to the carbon atoms in the aromatic rings. Three carbon atoms in the product are bound to oxygen and nitrogen, giving them a higher shift. Therefore, these probably correspond to the peaks found at δ 150.03, 155.70 and 159.20 ppm. The weak signals at 128.48 and 130.07 could stem from the carbons binding the two rings together.

The two tall peaks at δ115.94 and 129.78 ppm could stem from the carbon atoms on the left phenyl group. These are stronger because they correspond to two carbon atoms each in the structure. The three peaks at δ 109.24, 118.98 and 133.09 ppm correspond to the three remaining carbon atoms on the ring on the right.

2.8 Synthesis of 6-Methoxy-9*H*-carbazole-2-ol (**15**)



14 **15**

Scheme 2.8: *Synthesis of 6-Methoxy-9H-carbazole-2-ol (**15**)*

This reaction was performed as described by Ramadan *et al.* [74] with reaction conditions modified to work with microwave heating.

A TLC analysis was performed after the reaction had cooled to room temperature and CO development ceased. This showed that some reagent remained. However, it was clear that a reaction had taken place. A crude NMR spectrum was recorded after filtration over celite, extraction, and evaporation. A high boiling liquid remained in the crude oil, and the ^{1}H NMR spectrum showed clear DMF signals. DMF was removed by making an azeotrope with toluene and evaporating in vacuo at 60 °C. After this, a TLC analysis revealed that all compounds in the reaction mixture except the reagent and an unknown highly non-polar by-product had evaporated. The crude NMR spectrum and the amount of reagent left in the crude revealed that the reaction was unsuccessful.

In the referenced literature, two workup methods were described. These were performed on 9*H*-carbazole and Clausine V.[39] Clausine V has a similar structure as carbazole **15**, except that Clausine V has two methoxy groups. In contrast, carbazole **15** contains one hydroxyl group and only one methoxy group. Because of the difference in functional groups, these workup methods did not seem to fit this synthesis. Schuster *et al.* described a work-up of a similar carbazole product, only differing in the placements of the substituents and the presence of a methyl group on carbon 3.[90] Schuster *et al*. also used DMF as a solvent, making this workup seem like a good alternative for this product.

Due to the relative simplicity of the procedure, and tolerance for different functional groups, moisture and air, this procedure is an exciting procedure to follow in the production of different carbazoles. In the synthesis of Clausenalansine A, this reaction should be performed on 2-nitro-5-methoxy-4’-hydroxybiphenyl to produce carbazole **7**. This was not done due to time constraints.

To improve this reaction, the MW conditions should be optimised. The optimal reaction temperature found by Ramadan *et al.* was 170 °C; the reaction should be attempted in MW at this temperature.[39] The reaction time could be increased to be closer to the conditions defined in the literature. The reaction could also be attempted with conventional heating, as this is what was described in the literature; this would reveal the time needed for full conversion of the reagent in the synthesis of carbazole **7**. The organic phase was washed once with water. This was insufficient to remove DMF from the reaction mixture, and in future attempts, more rounds of washing could be introduced. However, carbazole **7** does not appear to be volatile, possibly making evaporation of a DMF/toluene azeotrope a practical purification step.

3 Conclusion and future prospect

Protection of 2-aminophenol with TBDPS was a simple reaction and gave acceptable yields. Aniline **3** may have co-eluted with the silanol by-product of the reaction, causing a possible overestimation of the yield.

Amination of 4-bromophenol with a Buchwald-Hartwig amination to produce diarylamine **5** was performed. The reaction was successful; however, it produced a by-product that was challenging to separate from **5**, causing low yields.

Production of the carbazole moiety with an oxidative cross-coupling was performed with different microwave parameters. No further optimization was obtained, and due to a complex reaction mixture, no pure product was isolated with flash column chromatography. Some pure product was collected by crystallisation. It was determined that the synthesis could proceed without the purification of carbazole **6**. Thus, a simplified work-up procedure was developed. This quickly removed the metals from the reaction mixture, and the crude oil was successfully used to produce carbazole **7**.

Carbazole **7** was synthesized by cleaving the silyl ether with TBAF. This was a simple reaction to perform, and purification with flash column chromatography removed most impurities. Carbazole **7** was observed to be poorly soluble in chloroform, making trituration an appealing purification method. Pure carbazole **7** was isolated in low yields.

Diarylamine **10** was synthesised with the same method as carbazole **7**. This reaction was successful, and the product was easily purified with flash column chromatography.

Ortho-formylation of diarylamine **10** was not successful. The reaction was stopped after 4 hours, at which point analysis with TLC showed full conversion. It is possible that the nitrogen atom interferes with the reaction somehow. In the future, it could be interesting to protect the amine group before performing this reaction. Introducing the formyl group earlier in the process could also be interesting. Other methods for ortho-formylation or using a different solvent, such as DCM or THF, should be considered.

Suzuki coupling to produce biphenyl **14** worked excellently. The workup was simple. Purification with flash column chromatography was efficient due to the bright yellow colour of the product and relatively pure crude oil. Exploring this reaction on a larger scale could be interesting to improve efficiency.

Reductive cyclization to form the carbazole moiety was not successful. The procedure described diverged from the literature procedure in several ways. First, it was adapted for microwave heating. Second, the reaction time was decreased, and the reaction temperature was increased from the literature. Lastly, the workup followed a procedure from a different article that worked well with similar former products in this project. In the future, this reaction should be performed as described in the literature with conventional heating and parallel analysis on TLC. This will reveal the required reaction time to get a full conversion.

After the synthesis of carbazole **7**, three steps remained in the synthesis of the target molecule clausenalansine A. At this point, the synthesis described in this project diverges from the synthesis described by Knölker and co-workers.[4] Formylation, annulation of the pyran ring, and deprotection of the remaining phenol are the remaining reactions.

4 Experimental

All reactions were performed in oven-dried glassware and anhydrous, septum-sealed solvents under a dry nitrogen atmosphere unless otherwise stated. All reaction vessels were evacuated three times and filled with N_2 to remove air unless otherwise stated.

For TLC, Merck TLC silica gel 60 F_{254} was used. UV light was used to detect chromophores, and $KMnO_4$ was used to detect oxidisable compounds.

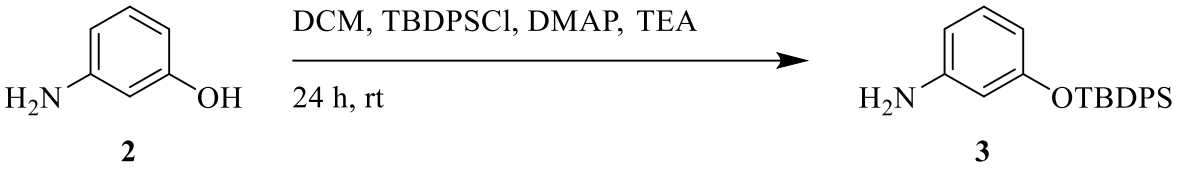
Silica gel 60 (40-63 µm) from Merck was used as the stationary phase for purification with flash column chromatography.

All microwave reactions were performed in a Biotage Initiator+ reactor.

NMR spectra were recorded on a Bruker Ascend 400-instrument at 25 °C at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. $CDCl_3$ was used as a solvent and internal standard unless otherwise stated. The reference peaks were calibrated to 7.26 ppm (^{1}H NMR) and 77.00 ppm (^{13}C NMR). When acetonitrile-d_3 was used, the reference peaks were calibrated to δ1 .94 ppm (^{1}H NMR) and δ 1.39 and 188.7 ppm (^{13}C NMR). Chemical shifts were reported in ppm, with standard abbreviations used to denote multiplicities of signals. Coupling constants were reported in Hz.

All synthesised material was kept cold (0-4 °C) and under an N_2 atmosphere.

4.1 Synthesis of 3-((*t*-butyldimethylsilyl)oxy)aniline **(3)**



Scheme 4.1: *synthesis of 3-((t-butyldimethylsilyl)oxy)aniline (**3**)*

This synthesis was performed following the procedure described by Schiaffino-Ortega *et al.* [91] with reaction conditions modified by a former student on this project.

To a solution of 3-aminophenol (2.0 g, 18.3 mmol) in DCM (60 mL), TEA (5.57 g, 7.67 mL, 55 mmol), TBDPSCl (7.05 g, 7.17 mL, 25.65 mmol), and DMAP (225 mg, 1.8 mmol) were added. The reaction was stirred at room temperature for 24 hours. The reaction mixture was washed repeatedly with water, and the combined aqueous layers were extracted with DCM. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo.

The crude oil was purified with flash column chromatography (silica gel, 10% EtOAc and 10% ether in n-hexane), and aniline **3** was isolated as a pale yellow solid.

Yield: 77% (4,90 g)

R_f value: 0,23 (10% EtOAc and 10% ether in n-hexane)

Data:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 9H), 3.47 (brs, 2H), 6.15-6.18 (m, 2H), 6.20-6.23 (m, 1H), 6.83-6.87 (m (td), 1H), 7.34-7.44 (m, 6H), 7.71-7.74 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.80, 26.86, 107,08, 108,60, 110,60, 128.04, 130.07, 130.13, 133.51, 135.85, 147.78, 156.95

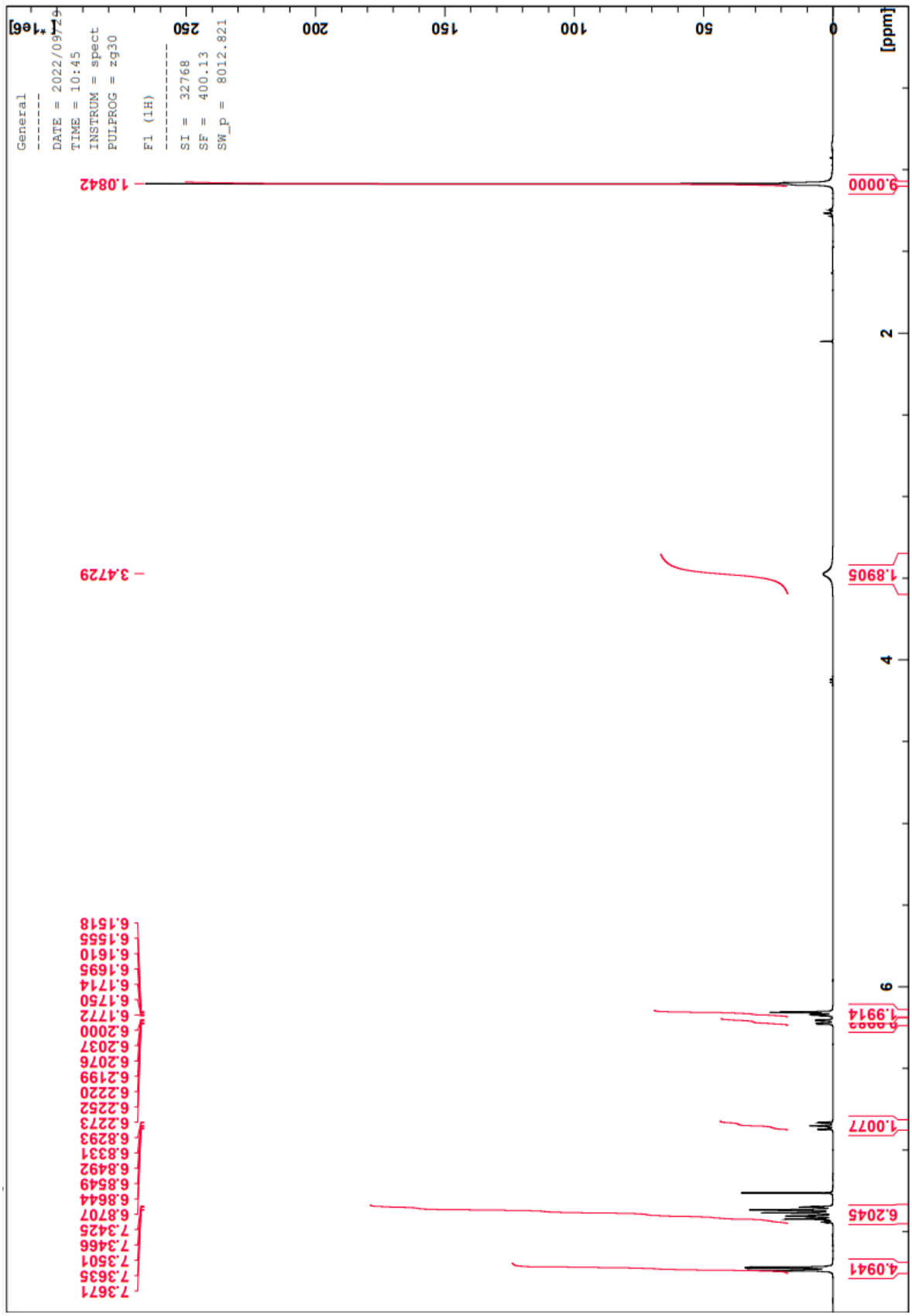


Figure 4.1: *^{1}H NMR spectrum of 3-((t-butyldimethylsilyl)oxy)aniline* ***(3)***

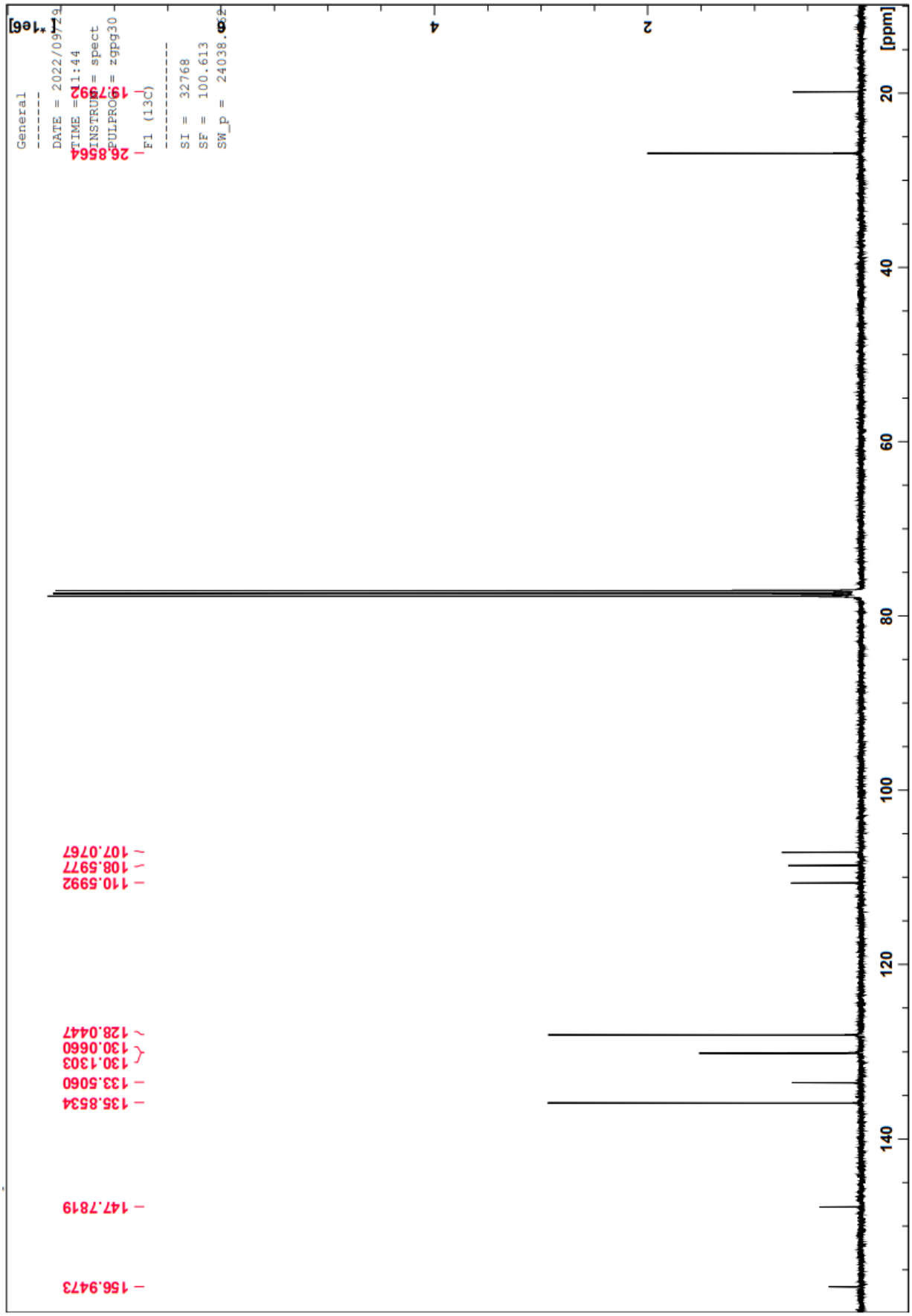
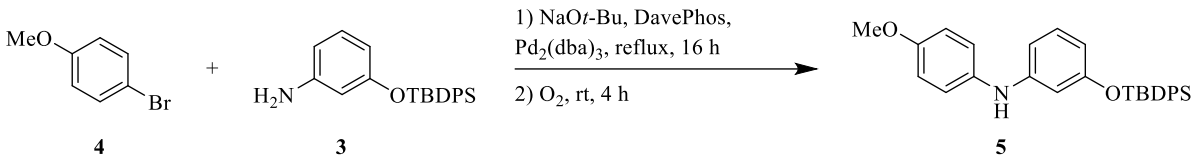


Figure 4.2: ^{13}*C NMR spectrum of 3-((t-butyldimethylsilyl)oxy)aniline* ***(3)***

4.2 Synthesis of 3-((*t*-butyldiphenylsilyl)oxy)-N-(4-methoxyphenyl)aniline (**5**)



Scheme 4.2: *Synthesis of 3-((t-butyldiphenylsilyl)oxy)-N-(4-methoxyphenyl)aniline* ***(5)***

This synthesis was performed following the procedure described by Knölker and co-workers.[4]

A solution of 4-bromoanisole (849 mg, 0.74 mL, 4.54 mmol) in toluene (26 mL) was carefully added to a vigorously stirred solution of aniline **3** (2.06 g, 5.94 mmol), $Pd_2(dba)_3$ (241 mg, 264 µmol), DavePhos (230 mg, 585 µmol) and NaO*t*-Bu (651 mg, 6.76 mmol) in toluene (61 mL) at reflux temperature. Stirring was continued at reflux for 16 hours, then in air at room temperature for 4 hours.

The reaction mixture was filtered over celite and extracted with EtOAc. The organic phase was washed repeatedly with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was purified with flash column chromatography (silica gel, 3% EtOAc in n-hexane), and the product diarylamine **5** was isolated as a brown oil.

Yield: 30 % (0,805 g)

R_f = 0.162 (5% EtOAc in n-Hexane)

Data:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 9H), 3.78 (s, 3H), 5.95 (brs, 1H), 6.26-6.28 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.34-6.35 (t, *J* = 2.2 Hz, 1H), 6.39-6.41 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.72-6.75 (d, *J* = 9.9 Hz, 2H), 6.82-6.86 (d, *J* = 9.8 Hz, 2H), 6.90-6.94 (t, *J* = 8.1 Hz, 1H), 7.33-7.44 (m, 6H), 7.69-7.71 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.78, 26.88, 55.89, 107.29, 109.14, 111.54, 114.87, 122.19, 128.05, 130.06, 130.12, 133.36, 135.82, 135.88, 146.35, 155.36, 156.95

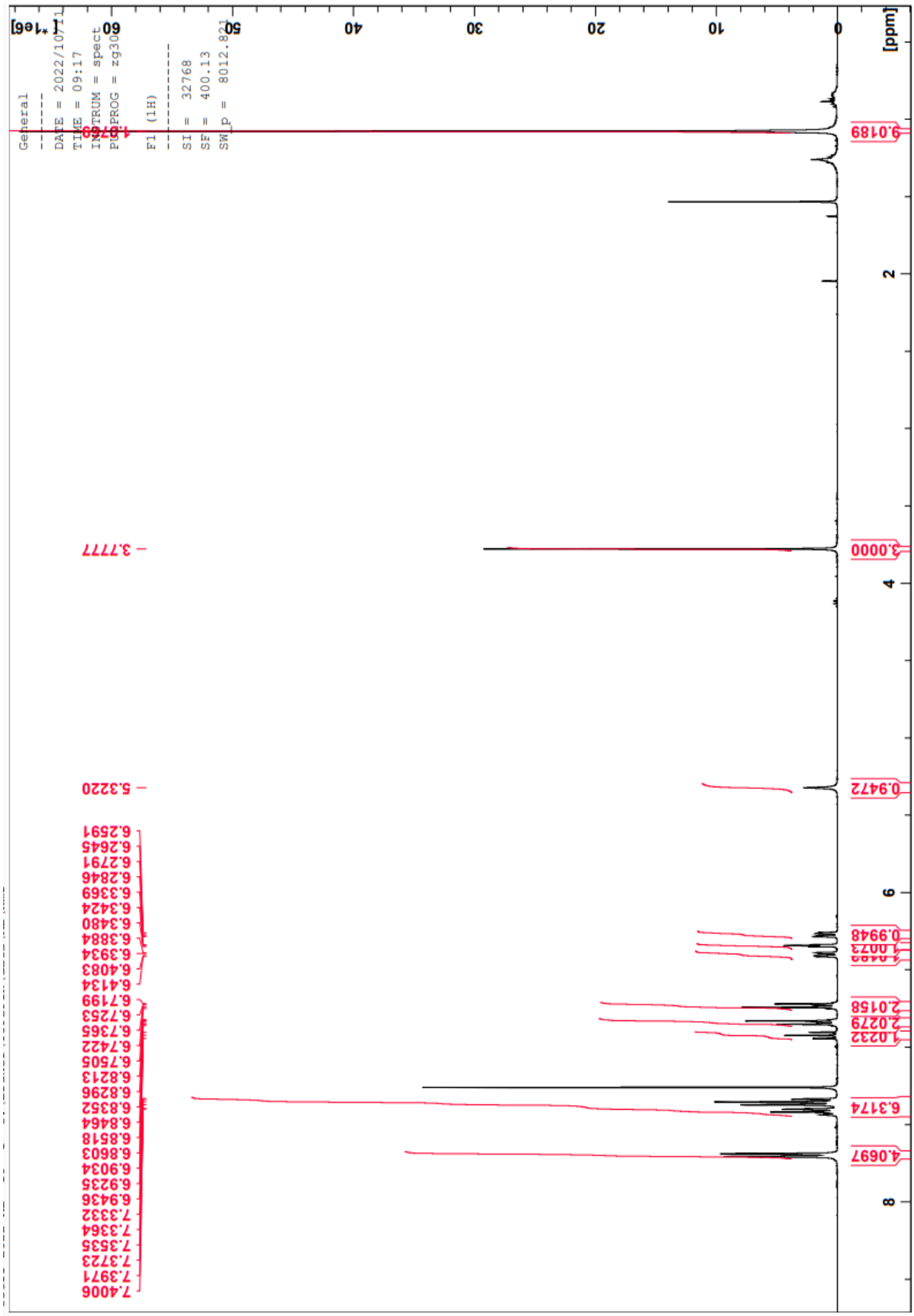


Figure 4.3: *^{1}H NMR spectrum of 3-((t-butyldiphenylsilyl)oxy)-N-(4-methoxyphenyl)aniline (**5**)*

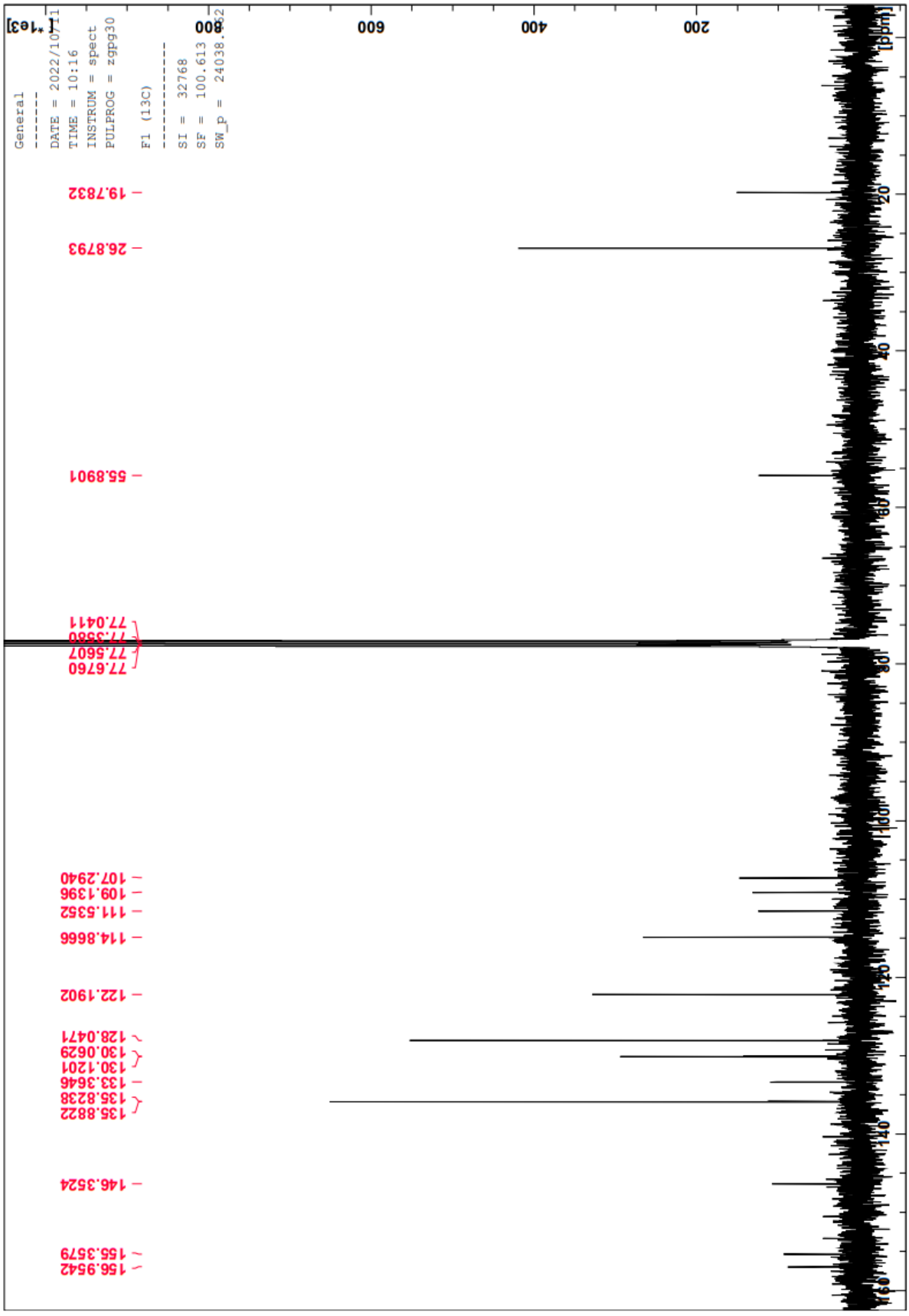
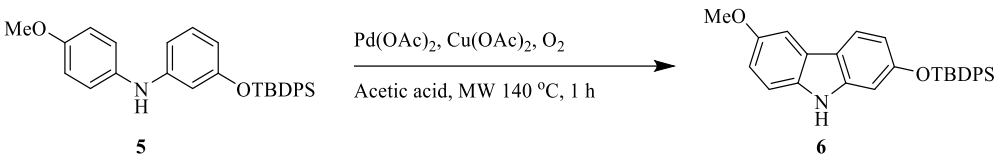


Figure 4.4: *13C NMR spectrum of 3-((t-butyldiphenylsilyl)oxy)-N-(4-methoxyphenyl)aniline (**5**)*

4.3 Synthesis of 2-((*t*-butyldiphenylsilyl)oxy)-6-methoxy-9*H*-carbazole (**6**)



5 **6**

Scheme 4.3: *synthesis of 2-((t-butyldiphenylsilyl)oxy)-6-methoxy-9H-carbazole (**6**)*

The synthesis was executed following method A of Lösle *et al.* [4] using optimised MW conditions defined by former students on this project.

Diarylamine **5** (55.3 mg, 112 µmol) was added to a 5 mL microwave vial and dissolved in Acetic acid (2-2.5 mL). $Pd(OAc)_2$ (5.8 mg, 26 µmol) and $Cu(OAc)_2$ (57,6 mg, 317 µmol) were added to the solution in air, and the reaction mixture was heated to 140 °C by microwave irradiation for 1 hour. After cooling to room temperature, the reaction mixture was worked up following workup A or B as described below.

4.3.1 Workup A:

The reaction mixture was filtered over celite and washed repeatedly with saturated aqueous K_2CO_3 until no blue colour was observed in the aqueous phase. The aqueous phase was extracted repeatedly with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was purified using flash column chromatography (EtOAc in n-Hex, 5%-20%). This yielded impure carbazole **6** as a viscous brown fluid, as well as carbazole **7** product as a white porous solid.

Precipitation of crystals was observed in some of the fractions containing carbazole **6**. Some of the crystals were gathered and analysed with 1H NMR. The crystals were then dissolved in small amounts of DCM and MeOH and stored at 0-4 °C. After three days, the solvents had evaporated, and some crystals had formed.

Yield: n.d.

4.3.2 Workup B:

This workup was performed on 8 reaction parallels gathered in one container.

The solvent was removed in vacuo. The residue was dissolved in toluene and filtered over celite to remove copper. The solvent was removed in vacuo, and the residue was dissolved in 30% EtOAc in n-heptane and filtered through a short silica gel column to remove leftover palladium. The solvent was removed in vacuo. No further purification was performed, and the crude oil was used as a reagent in the next step in the synthesis.

Yield: 79% (334 mg) crude product

R_f = 0.46 (20% EtOAc in n-Hexane)

Mp: 138-139 °C

Data:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 9H), 3.88 (s, 3H), 6.70-6.70 (d, *J* = 2.0 Hz, 1H), 6.72-6.76 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.92-6.94 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.18-7.20 (d, *J* = 8.7Hz, 1H), 7.34-7.44 (m, 8 H), 7.59 (brs, 1H), 7.72-7.74 (d, *J* = 8.5 Hz, 1H), 7.75-7.78 (m, 4H)

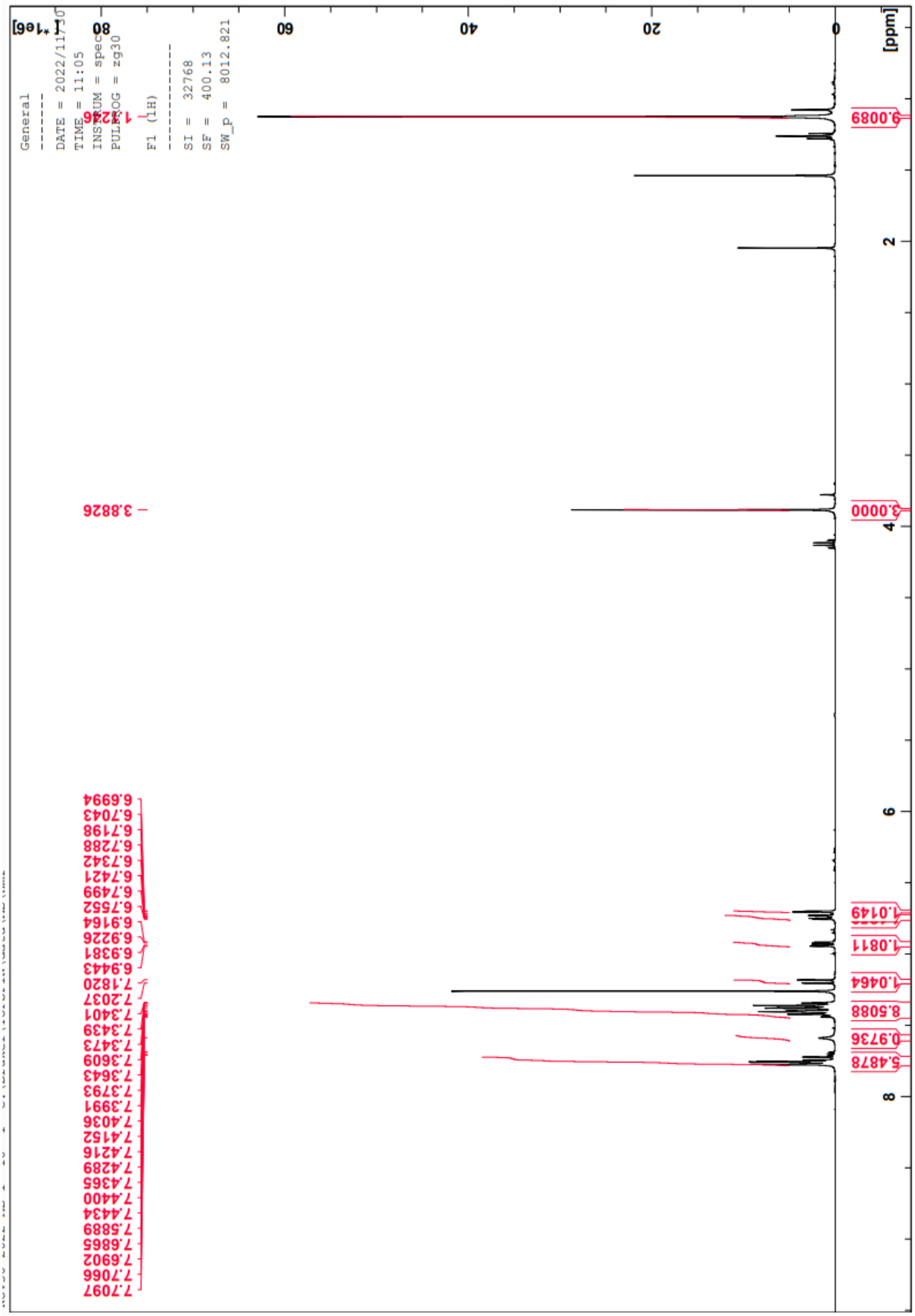
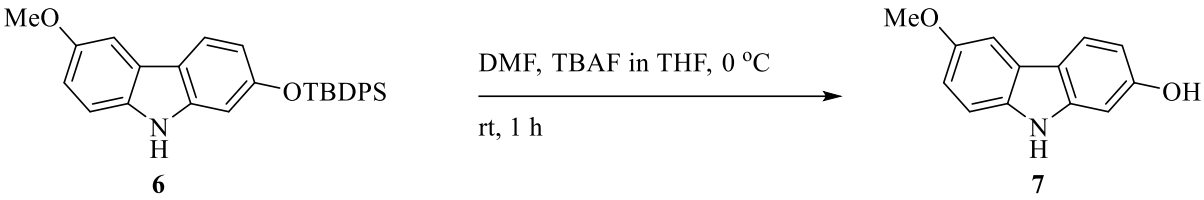


Figure 4.5: [1]*HNMR spectrum of 2-((t-butyldiphenylsilyl)oxy)-6-methoxy-9H-carbazole (***6***).*

4.4 Synthesis of 6-methoxy-9*H*-carbazole-2-ol (**7**)



Scheme 4.4: *Synthesis of 6-methoxy-9H-carbazole-2-ol (7)*

This reaction was performed following the procedure of Schuster *et al.* [92]

Carbazole **6** (334 mg, 740 µmol) was dissolved in DMF (23 mL) at 0 °C. 1M TBAF in THF (1.2 mL, 1.2 mmol) was added carefully with stirring. The reaction was heated to room temperature and was stirred for 1h.

Water (15 mL) was added to the solution, and the aqueous phase was extracted with ether (3x 40 mL). The combined organic layers were washed with brine and dried with $MgSO_4$, filtered, and the solvent was removed in vacuo.

Development of the crude oil using flash column chromatography (silica gel: 30% EtOAc in n-heptane) yielded a purer product as a brown viscous fluid with white precipitation. The product was further purified with trituration. The impure product was suspended in a small amount of chloroform at room temperature until the impurities were dissolved. The solution was cooled to 0 °C to promote precipitation and filtered by pipette through a Büchner funnel. The white solid was gathered.

Yield: 5 % (9.7 mg) calculated over two steps.

Rf = 0.146 (30% EtOAc in n-heptane)

Data:

^{1}H NMR (400 MHz, acetonitrile D_3): δ = 3.88 (s, 3H), 6.69-6.72 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.87-6.87 (d, *J* = 2.0 Hz, 1H), 6.94-6.97 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.32-7.35 (d, *J* = 8.7 Hz, 1H), 7.53-7.53 (d, *J* = 2.3 Hz, 1H), 7.85-7.87 (d, *J* = 8.4 Hz, 1H), 8.95 (brs, 1H)

^{13}C NMR (400 MHz, acetonitrile D_3): δ = 56.39, 97.41, 103.39, 109.39, 109.06, 112.05, 113.83, 117.39, 121.85, 124.77, 135.56, 143.14, 145.78, 157.02

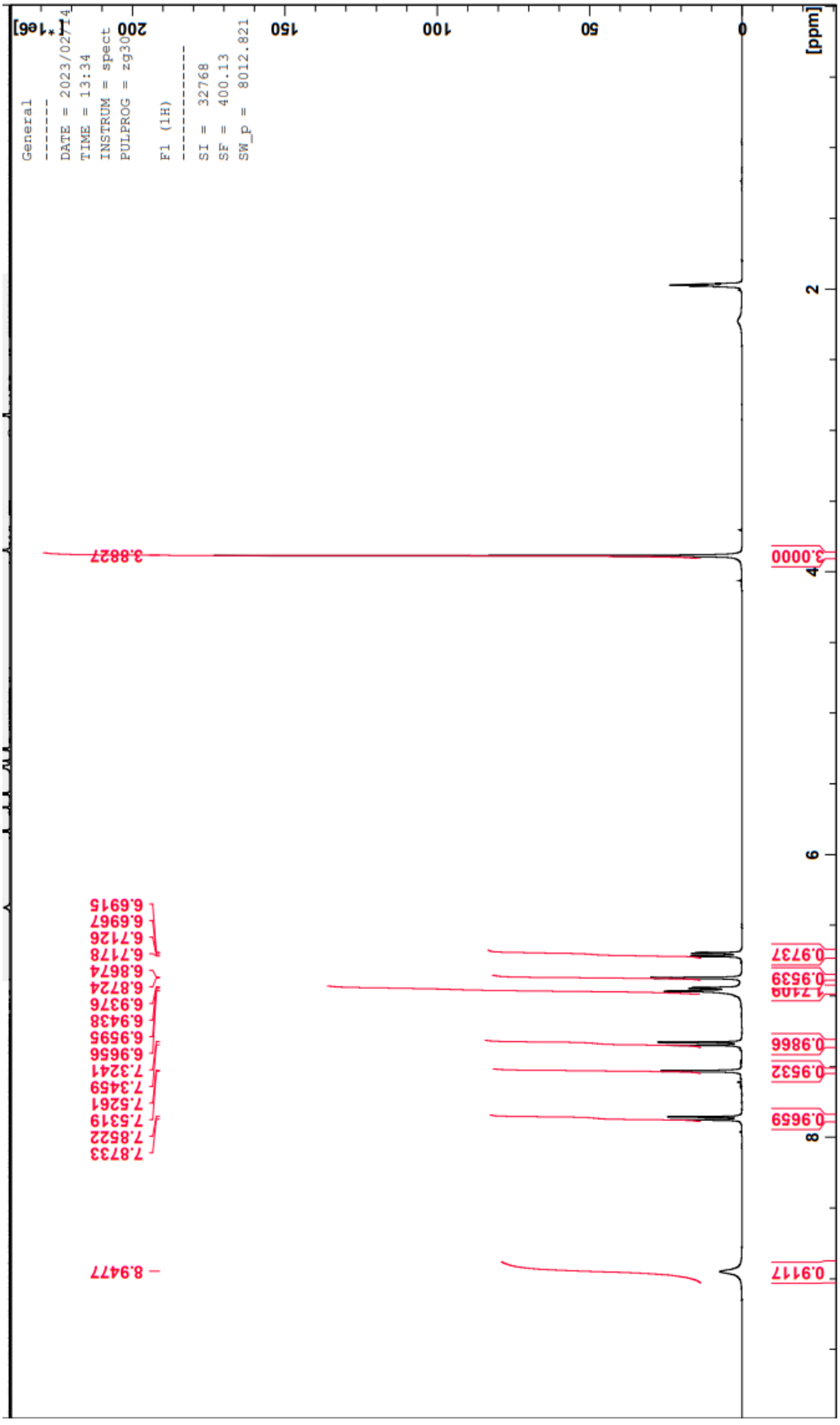


Figure 4.6: *^{1}H NMR spectrum of 6-methoxy-9H-carbazole-2-ol (**7**)*

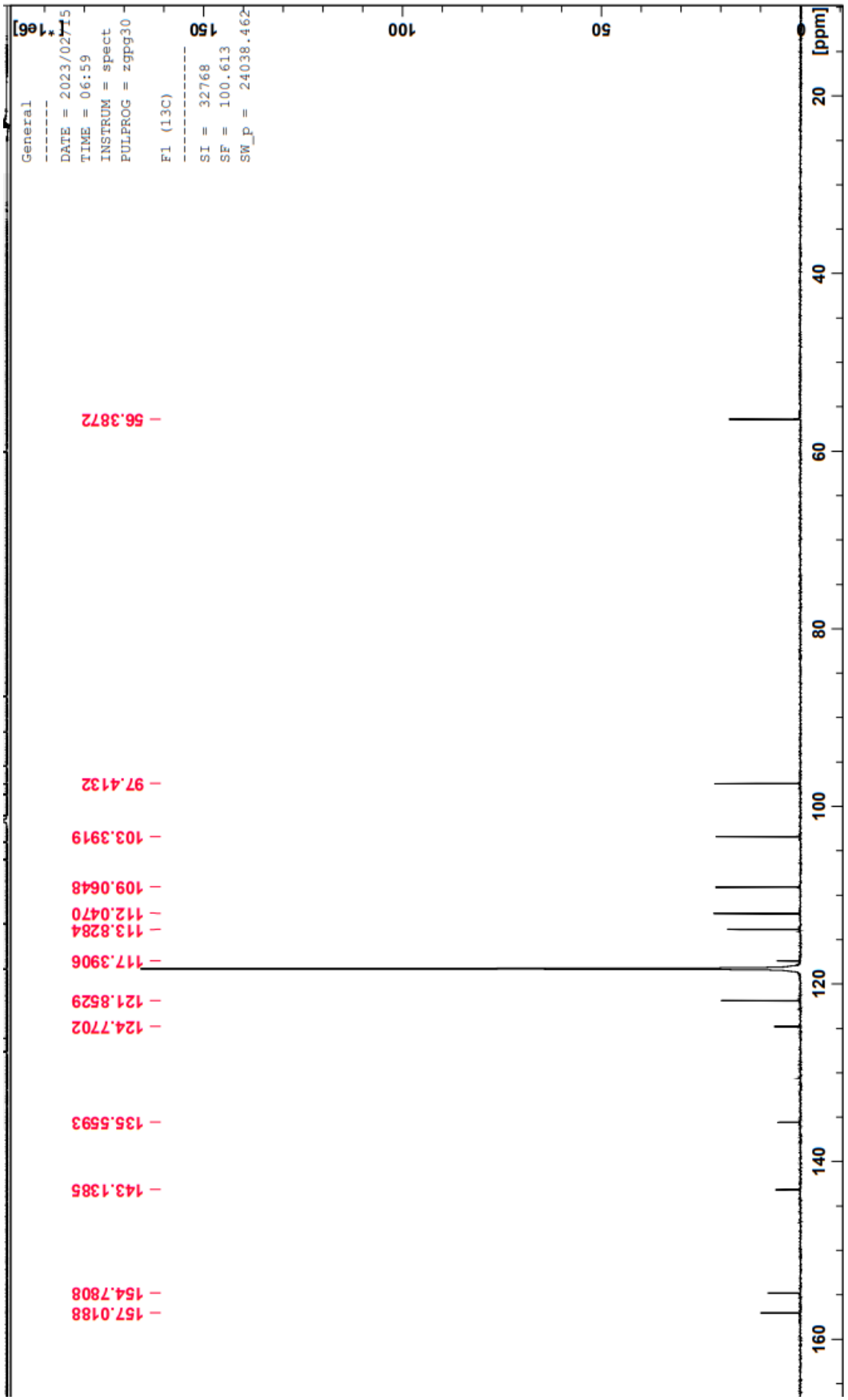
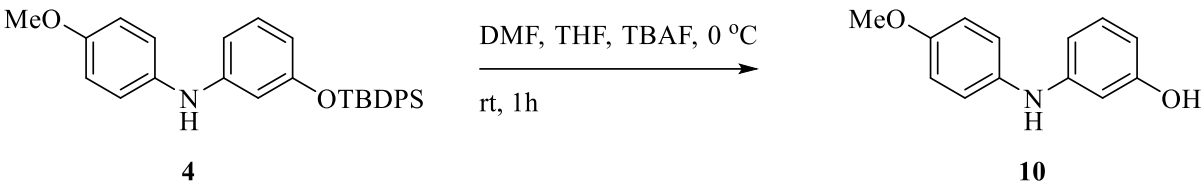


Figure 4.7: *^{13}C NMR spectrum of 6-methoxy-9H-carbazole-2-ol (7)*

4.5 Synthesis of Synthesis of N(4-methoxyphenyl)-3-aminophenol (**10)**



4 **10**

Scheme 4.5: *Synthesis of N(4-methoxyphenyl)-3-aminophenol (**10**)*

This reaction was performed as described by Schuster *et al.* [92]

Diarylamine **4** (116 mg, 0.26 mmol) was dissolved in DMF (7,9 mL) at 0 °C. 1M TBAF in THF (0.41 mL, 0.41 mmol) was added, and the solution was heated to room temperature. The reaction was stirred at room temperature for 1 hour.

Water (5 mL) was added to the solution, and the reaction mixture was extracted with ether (3 x 13 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo. Development of the crude oil with flash column chromatography (10% EtOAc in n-heptane) yielded diarylamine **10** as a brown oil.

Yield: 81 % (44,6 mg)

Rf = 0.027 (10% EtOAc in n-heptane)

Data:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.71 (s, 3 H), 6.19-6.21 (dd, *J* = 8.0, 2.2 Hz, 1 H), 6.28-6.29 (t, *J* = 2.1 Hz, 1 H), 6.35-6.37 (dd, *J* = 8.0, 1.9 Hz, 1 H), 6.75-6.78 (d, *J* = 8.8 Hz, 2 H), 6.94-6.98 (m, *J* = 8.9 Hz 3 H)

^{13}C NMR (400 MHz, $CDCl_3$): δ = 55.64, 102.13, 106.44, 108.20, 114.73, 123.00, 130.34. 135.14, 147.91, 155.49, 156.71

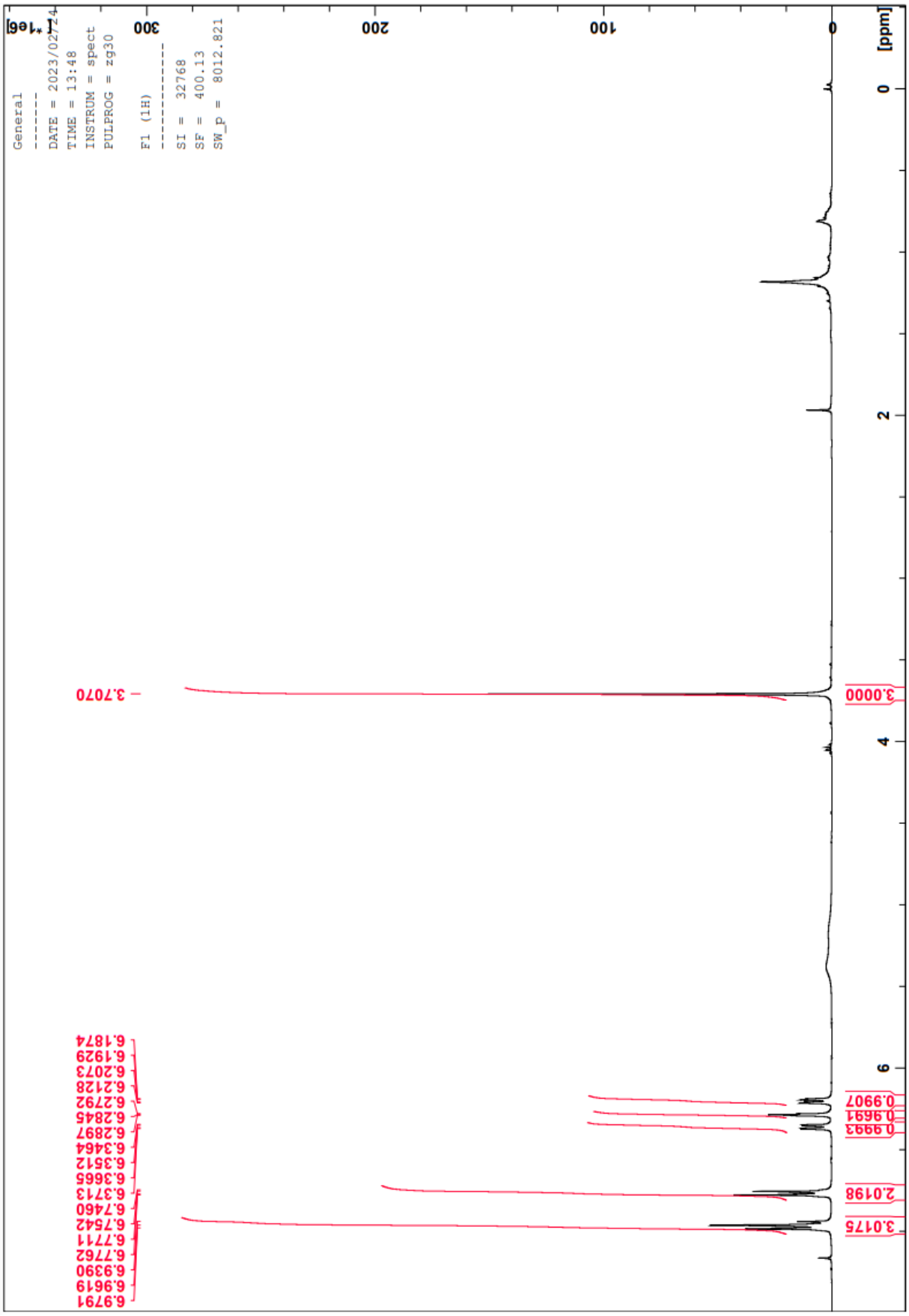


Figure 4.8: *^{1}H NMR spectrum of N(4-methoxyphenyl)-3-aminophenol (**10**)*

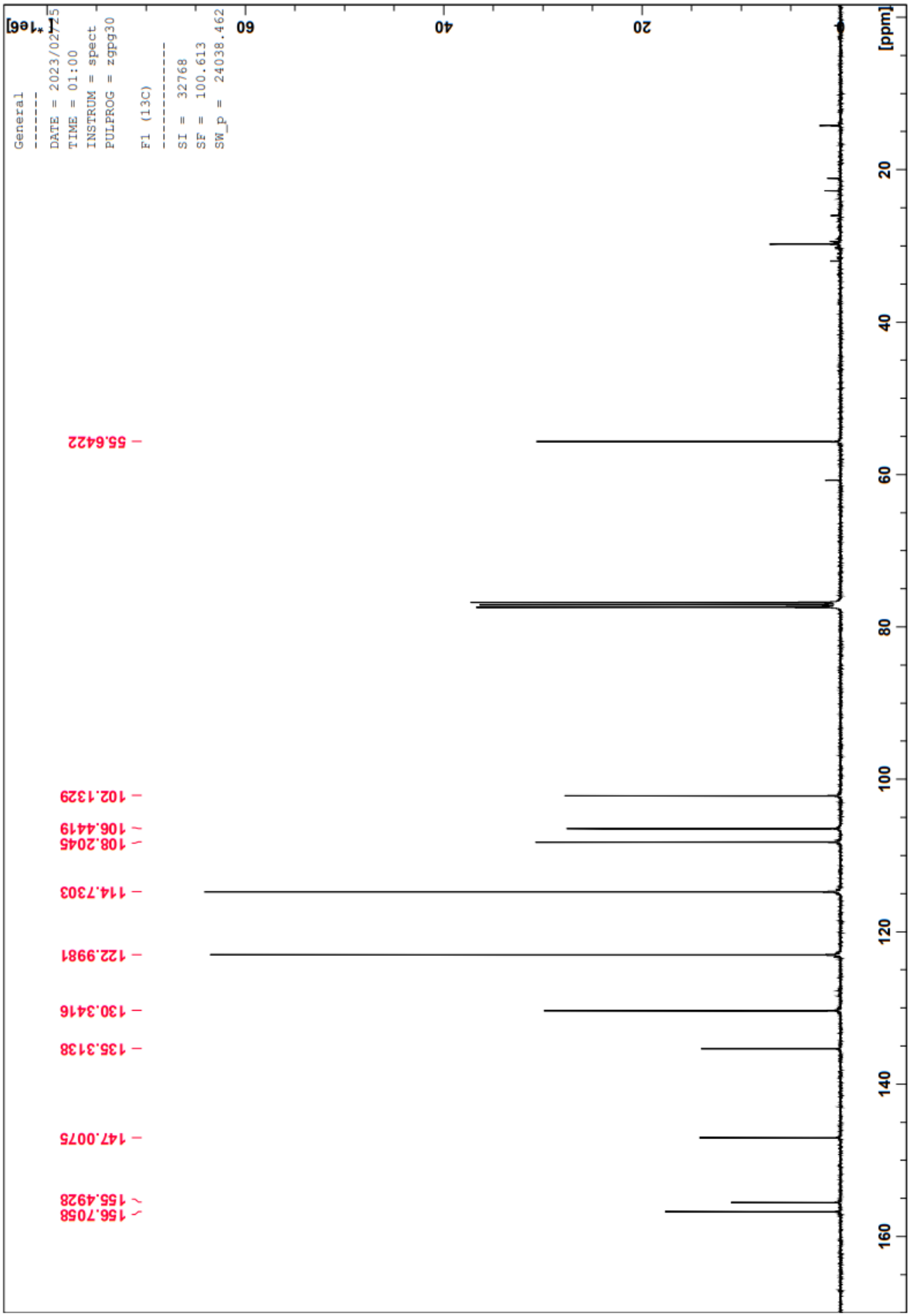
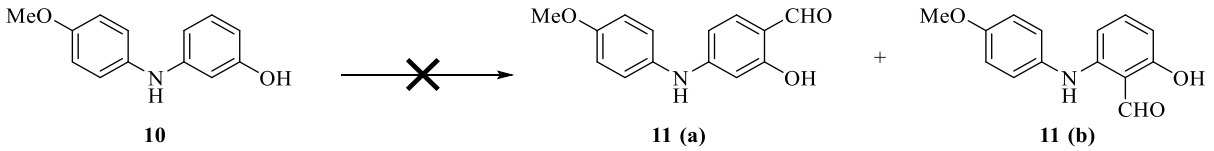


Figure 4.9: ^{13}C *NMR spectrum of N(4-methoxyphenyl)-3-aminophenol (**10**)*

4.6 Synthesis of 2-hydroxy-4-((4-methoxyphenyl)amino)benzaldehyde



Scheme 4.6: *Synthesis of 2-hydroxy-4-((4-methoxyphenyl)amino)benzaldehyde*

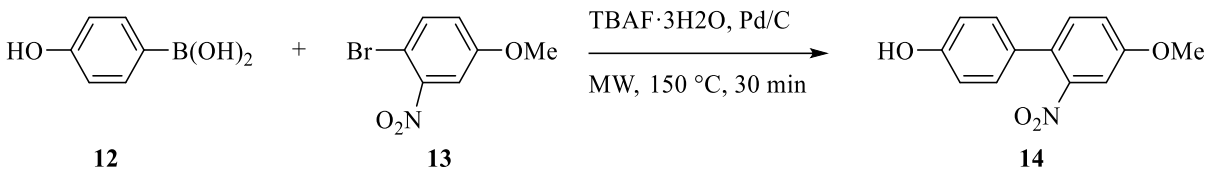
The synthesis was performed following the procedure described by Hofsløkken and Skattebøl.[83]

Paraformaldehyde (126 mg, 1.4 mmol) (dried over molecular sieves) was added to a stirred solution of diarylamine **7** (44.6 mg, 0.207 mmol), $MgCl_2$ (29.6 mg, 319.8 mmol) (dried over molecular sieves) and TEA (0.10 mL, 79 mg, 777 mmol), in acetonitrile (1 mL). The solution was heated to reflux temperature and was stirred under reflux for four hours.

After cooling to room temperature, 5% aq HCl was added, and the mixture was extracted three times with ether. The combined organic phases were dried with $MgSO_4$, and the solution was filtered and concentrated in vacuo.

The ^1H NMR spectrum of the crude showed a complex mixture, and no formyl group was observed.

4.7 Synthesis of 2-nitro-5-methoxy-4'-hydroxybiphenyl (**14**)



12 **13** **14**

Scheme 4.7: *Synthesis of 2-nitro-5-methoxy-4'-hydroxybiphenyl* ***(14)***

This reaction was performed as described by Schmidt and Riemer. [93]

Bromoanisole **13** (116 mg, 0.5 mmol) and boronic acid **12** (90 mg, 0.65 mmol) were weighed and transferred to an evacuated 2-5 mL MW vial and suspended in degassed milli-Q water. TBAF·$3H_2O$ (631 mg, 2 mmol) and Pd/C (10% w, 10 mg, 0.01 mmol) were added to the solution.

The reaction mixture was heated with MW irradiation at 150 °C for 30 minutes. After cooling to room temperature, the solution was acidified by careful addition of 1 M HCl until the pH was approximately 2. The aqueous phase was extracted with ether (3*50 mL), and the combined aqueous layers were dried with $MgSO_4$, filtered, and concentrated in vacuo.

Purification on flash column chromatography with 20 % EtOAc in n-heptane yielded the product as a yellow liquid.

Yield = quantitative

Rf (20 % EtOAc in n-hept) = 0.103

Data:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3H), 4.81 (s, 1H), 6.84-6.88 (dt, *J* = 9.4, 2.5 Hz, 2H), 7.11-7.14 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.15-7.18 (dt, *J* = 9.6, 2.6 Hz, 2H), 7.30-7.33 (d, *J* = 8.4 Hz, 1H), 7.33-7.33 (d, *J* = 2.4 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.04, 56.24, 109.24, 115.94, 118.98, 128.48, 129.78, 130.07, 133.09, 150.03, 155.70, 159.20

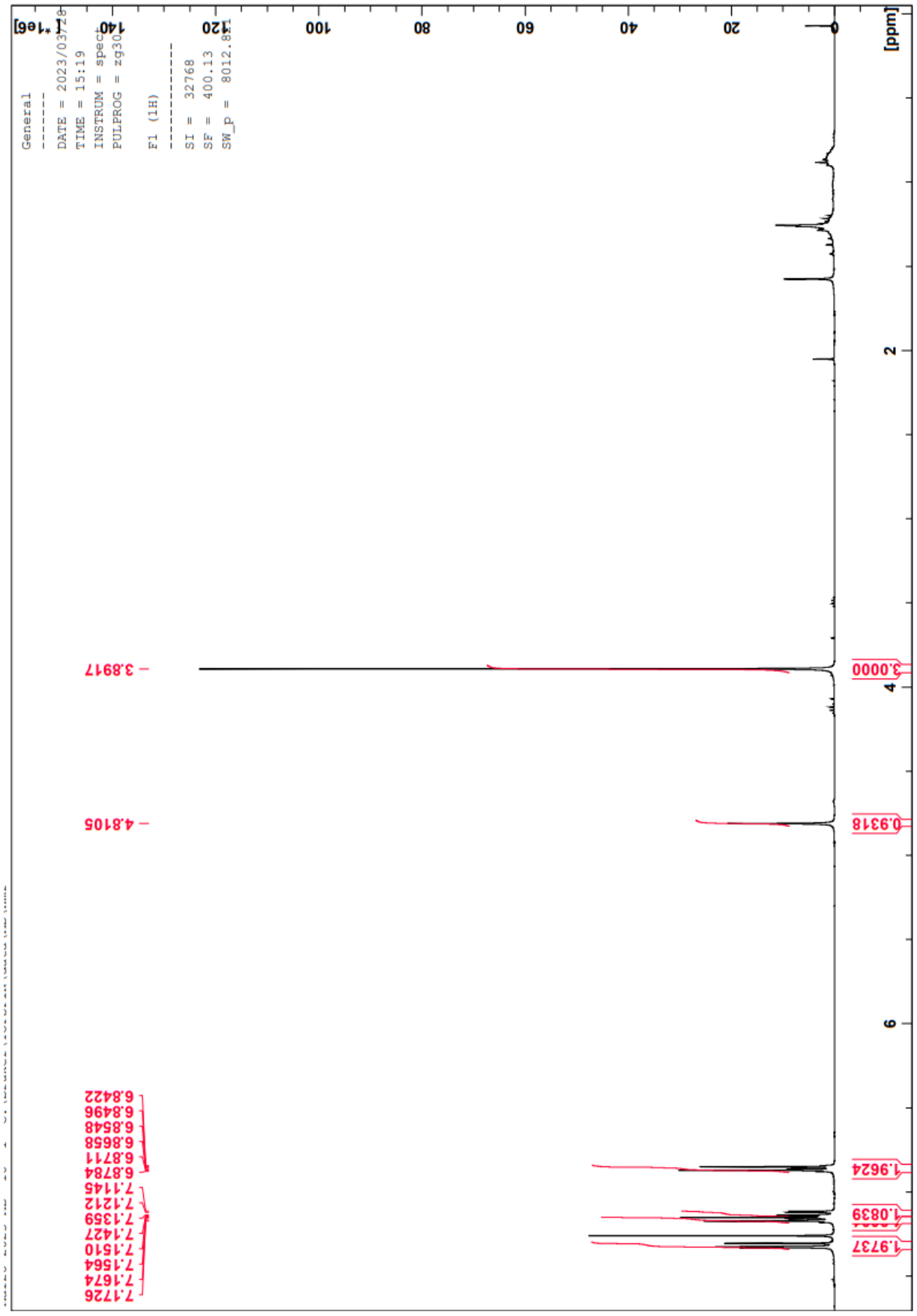


Figure 4.10: *^{1}H NMR spectrum of 2-nitro-5-methoxy-4'-hydroxybiphenyl (**14**)*

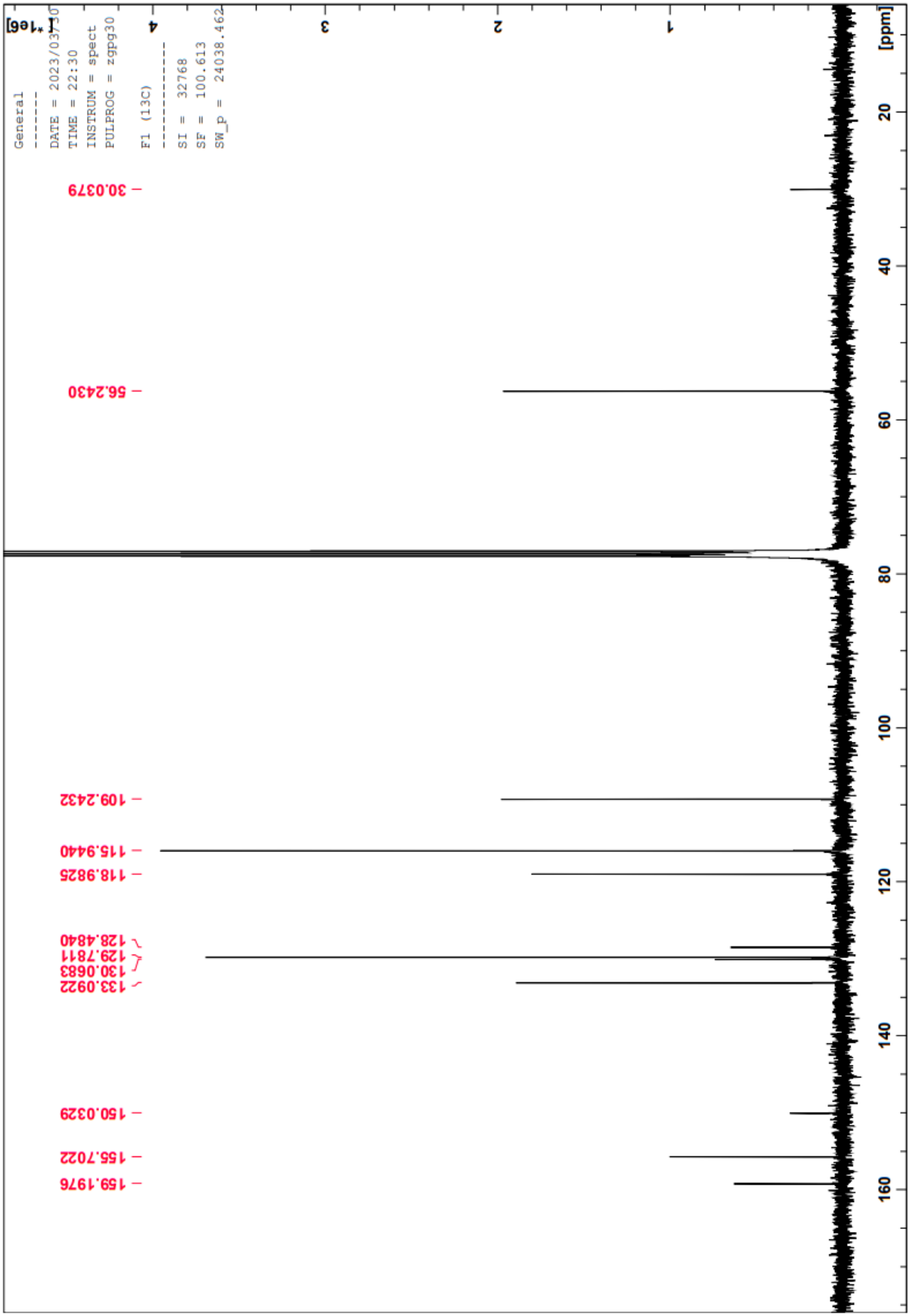
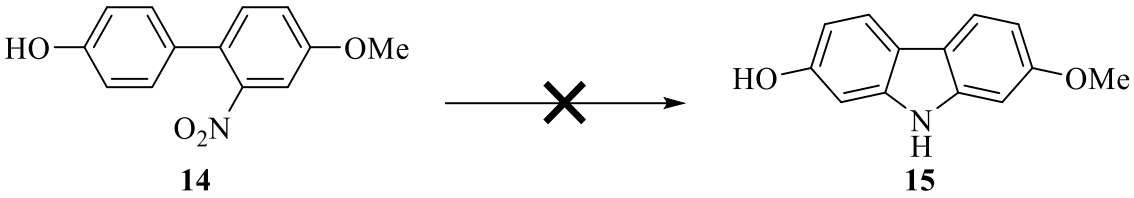


Figure 4.11: *^{13}C NMR spectrum of 2-nitro-5-methoxy-4'-hydroxybiphenyl (**14**)*

4.8 Synthesis of 7-Methoxy-*9H*-carbazole-2-ol (**15**)



Scheme 4.8: *Synthesis of 7-Methoxy-9H-carbazole-2-ol (**15**)*

This reaction was adapted for MAOS from the synthesis described by Ramadan *et al.* [74] The workup was performed as described by Schuster *et al.* [92]

4.8.1 Synthesis of $Na_2[PdCl_4]$

NaCl (0.33 g, 5.6 mmol) and $PdCl_2$ (0.50 g, 2.8 mmol) were suspended in degassed Milli-Q water. The reaction mixture was placed in a preheated oil bath at 70 °C and heated for one hour until complete dissolution of the $PdCl_2$. After cooling to room temperature, the brown-red solution was filtered over filter paper and the filtrate was concentrated in vacuo. The solid residue was crushed to a powder and dried under vacuum at 80 °C for five hours.

Yield: n.d.

4.8.2 Cyclisation reaction

Stock solutions were prepared with Phen (9 mg/mL, 4 mL) and $Na_2[PdCl_4]$ (12 mg/mL, 2 mL) in DMF to avoid weighing errors.

o-Nitrobiphenyl **14** (53.8 mg, 0.22 mmol) was dissolved in DMF and transferred to a 5 mL MW vial. Phen (0.1 mL, 0.9 mg, 5 µmol) and $Na_2[PdCl_4]$ (0.1 mL, 1.2 mg, 4 µmol) were added, and the solution was stirred at room temperature for 10 minutes.

Na_3PO_4 (4.5 mg, 30 µmol) and phenylformate (0.1 mL, 121 mg, 0.99 mmol) were added to the solution. DMF was added to achieve a total volume of 2 mL, and the reaction was heated with MW radiation at 190 °C for 1 hour.

After cooling to room temperature, the MW cap was removed under a fume hood, and the reaction mixture was stirred at room temperature until the development of CO ceased.

Water was added, and the aqueous phase was extracted with ether 3 times. The combined organic layers were washed with brine and dried over $MgSO_4$. The solution was filtered, and the solvent was removed in vacuo.

Toluene was added, and the solvent was removed in vacuo 3 times. At this point, a TLC analysis revealed that only the reagent and a highly non-polar product remained in the crude.

5 References

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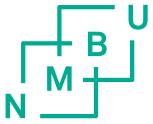

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