Aalto University
School of Chemical
Technology

School of Chemical Technology
Degree Programme of Chemical Technology

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SYNTHESIS OF CHIRAL OPEN-CHAINED TETRAHYDRO-B-CARBOLINE ANALOGUES FROM NATURAL AMINO ACIDS

Master's thesis for the degree of Master of Science in Technology submitted for inspection, Espoo, 20 September, 2013.

Supervisor Professor Ari Koskinen

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Foreword

Research described in this thesis was carried out in the Aalto University School of Chemical Technology in the Laboratory of Organic Chemistry during 14.1.2013-30.8.2013.

I wish to thank Professor Ari Koskinen for the possibility to do this thesis in his research group. I also owe special acknowledgments to my instructor M Sc., Hipster and Robocop Christopher Lood for providing me not only competent advice but also friendship often making me laugh while learning. I also want to thank all the other members of this laboratory for their help, advice and joyful company.

Thank you also for my amazing husband and friends for their support and understanding.

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Abstract of master's thesis

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Abstract

The aim of this thesis was to study a recently developed synthesis route to tetrahydro-β-carbolines (THβCs) and their open-chained analogues. Furthermore, the aim was also to build a small compound library of these analogues.

Tetrahydro-β-carbolines are a pharmacologically important group of compounds belonging to the indole alkaloids. 2-indolylamines are structurally analogous to tetrahydro-β-carbolines and their pharmacological activities are relatively unstudied. Recently, a novel synthesis route with chiral pool approach to THβCs was developed in the Koskinen laboratory, Aalto University. Using this synthesis route, chiral THβCs can be derived from natural amino acids and their enantiopurity is retained by using 9-phenyl-9-fluorenyl protecting group chemistry. In addition to THβCs, also 2-indolylamines can be synthesized with this approach.

The literature part of this thesis reviews pharmacological importance of tetrahydro-β-carbolines, while the synthetic part concentrates on synthesis of open-chained THβC analogues. Four chiral 2-indolylamines were synthesized using natural amino acids, namely alanine, phenylalanine, serine and proline, as starting materials. Furthermore, a library of 6 derivatives was established by simple manipulations of the amine. In subsequent studies that will be conducted in the Koskinen laboratory, this library will be extended and bioactivities of the compounds will be studied.

This thesis illustrates the potential of this synthetic route in the preparation of THβCs as well as 2-indolylamines with > 99 % ee. The work clearly shows that this synthetic route can be applied to a range of amino acids.

Keywords Tetrahydro-β-carboline, 2-indolylamine, amino acid, natural product synthesis

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Diplomityön tiivistelmä

Tekijä Aino Laine		
Työn nimi Kiraalisten avoketjuisten tetrahydro-β-karboliinianalogien synteesi luonnollisista aminohapoista		
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Tiivistelmä

Diplomityön tavoitteena oli tutkia hiljattain kehitettyä synteesireittiä tetrahydro-β-karboliineihin ja niiden avoketjuisiin analogeihin. Lisäksi tavoitteena oli valmistaa pieni yhdistekirjasto tetrahydro-β-karboliinianalogeja.

Tetrahydro-β-karboliinit kuuluvat indolialkaloideihin ja ovat lääketieteellisesti merkittävä ryhmä sekä luonnollisia että synteettisiä yhdisteitä. 2-indolyyliamiinit ovat rakenteeltaan samankaltaisia kuin tetrahydro-β-karboliinit, mutta niiden lääkekäyttöä on tutkittu melko vähän. Hiljattain Koskisen ryhmässä Aalto-yliopistossa kehitettiin uusi synteesireitti, jonka avulla kiraalisia tetrahydro-β-karboliineja voidaan valmistaa luonnollisista aminohapoista. Tässä synteesireitissä tuotteen stereokemia saadaan lähtöaineen luonnollisesta stereokemiasta ja enantiopuhtaus säilytetään käyttämällä 9-fenyyli-9-fluorenyylisuojaryhmää. Tällä synteesireitillä voidaan valmistaa myös 2-indolyyliamiineja.

Työn kirjallisuusosassa tutkitaan tetrahydro-β-karboliinien käyttöä lääketieteessä, kun taas työn synteettisessä osassa keskitytään avoketjuisten analogien synteesiin. Neljä 2-indolyyliamiinia syntetisoitiin käyttäen lähtöaineina alaniinia, fenyylialaniinia, seriiniä ja proliinia. Amiinin yksinkertaisilla manipulaatioilla indolyyliamiineista luotiin kuuden johdannaisen kirjasto. Jatkotutkimuksissa kirjastoa tullaan laajentamaan ja yhdisteiden biologiset aktiivisuudet määritetään.

Diplomityö osoittaa, että tetrahydro-β-karboliineja ja 2-indolyyliamiineja voidaan syntetisoida käyttämällä tätä synteesireittiä. Synteesillä saavutetaan enantiopuhdas tuote (ee > 99 %) ja tämän työn perusteella lähtöaineiksi soveltuvat useat erilaiset aminohapot.

Avainsanat Tetrahydro-β-karboliini, 2-indolyyliamiini, aminohappo, luonnonainesynteesi

Contents

Symbols used in text

IC_{50}	the concentration that is needed for 50 % inhibition
R_f	TLC retention factor
$[\alpha]_D$	optical rotation
J	coupling constant, Hz
δ	chemical shift, ppm
M	molarity, mol dm^{-3}

Abbreviations used in text

5HT	serotonin receptor
Ala	alanine
Ar	aryl
Arg	arginine
Asp	asparagine
ATH	asymmetric transfer hydrogenation
βC	β-carboline
Bn	benzyl
t-Bu	tert-butyl
Cbz	carboxybenzyl
cGMP	cyclic guanosine monophosphate
CNS	central nervous system
CTAB	cetyltrimethylammonium bromide
DHβC	dihydro-β-carboline
ED	erectile dysfunction
ee	enantiomeric excess
Et	ethyl
FAAH	fatty acid amide hydrolase

GHSR	growth hormone secretagogue receptor
Gly	glycine
GMP	guanosine monophosphate
HPV	Human Papilloma virus
HSV	Herpes Simplex virus
i-Pr	iso-propyl
KSP	kinesin spindle protein
LAH	lithium aluminum hydroxide
MDCK	Madin-Darby canine kidney
Me	methyl
MIC	minimum inhibitory concentration
n-Bu	primary butyl
PDE	phosphodiesterase
Pf	9-phenyl-9-fluorenyl
Pg	protecting group
Ph	phenyl
Phe	phenylalanine
Pht	phthaloyl
Pro	proline
PTP	protein tyrosine phosphatase
R	any group
RGD	arginine-glycine-asparagine
RNA	ribonucleic acid
r.t.	room temperature
s-Bu	secondary butyl
Ser	serine
SSTR	somatostatin receptor

STR	Strictosidine synthase
TBDPS	tert-butyl triphenyl silyl
TBS	tert-butyl silyl
TFA	trifuoroacetic acid
THβC	tetrahydro-β-carboline
THF	tetrahydrofuran
TRP	transient receptor potential
Ts	tosyl
Val	Valine
WHO	World Health Organization

1 Introduction

Alkaloids are a group of some 10 000 compounds that was originally defined by Carl Friedrich Wilhelm Meissner in 1819 as natural compounds similar in behavior to alkalis, basic compounds.[1] Among alkaloids, one of the most notable subgroups is indole alkaloids, a group comprising *ca.* 1500 compounds that contain the indole moiety in their structure.[2] Tetrahydro-β-carbolines (THβCs), a compound class within the indole alkaloids, consist of a variety of both simple and complex natural and synthetic compounds.[2] These compounds possess a vast spectrum of biological activities and their use in novel pharmacological applications is constantly being studied. The THβC structure is present in drugs currently available on the market, drug candidates under development and many other pharmacologically interesting compounds. Thus, there is an obvious need for asymmetric synthetic methods to gain access to this compound class.

Indeed, there are several asymmetric routes to THβCs. However, many of these routes exploit expensive and complicated chiral auxiliaries. In lieu of using chiral auxiliaries, chirality can also be introduced by using the chiral pool approach, i.e. using chiral starting materials to introduce the chirality to the molecule. THβC syntheses using the chiral pool approach exist; however, they generally lack flexibility and/or have a great dependence on factors such as reaction conditions and substitution patterns. Thus, there is still a need for improved methods to synthesize chiral THβCs. The question remains, whether we can establish a general protocol to prepare chiral THβCs without the use of chiral auxiliaries in an uncompromised 100 % ee.

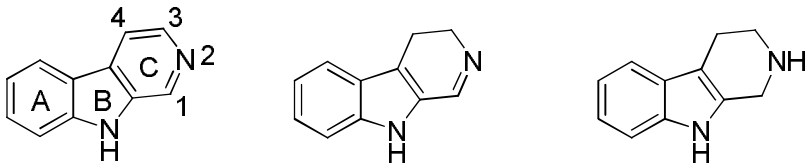
In the Koskinen group, Aalto University, a novel synthesis route to chiral THβCs has been developed, and its synthetic power has already been demonstrated by completing the total syntheses of two naturally occurring THβCs, tetrahydroharmane and harmicine. This method uses natural and inexpensive amino acids as starting materials, thus providing a natural source of chirality. The synthetic route also enables access to chiral open-chained THβC analogues – 2-indolylamines – that have remained relatively unstudied until now. This thesis successfully demonstrates the suitability of the synthesis route to access 2-indolylamines using four different amino acids as starting materials. Furthermore, a small library of 2-indolylamine derivatives was synthesized. In subsequent studies in the Koskinen laboratory, this library will be extended and the pharmacological activities of the 2-indolylamines will be evaluated.

2 Tetrahydro-β-Carbolines

2.1 Structure and nomenclature

β-carboline alkaloids are an important group of natural and synthetic indole alkaloids which all bear the common feature of a tricyclic pyrido[3,4-b]indole ring structure.[3] The first β-carboline alkaloid recognized was harmalin and it was originally isolated in 1841 from *Peganum harmala*[4], also known as Syrian rue. The occurrence of β-carbolines in nature is widespread, presumably due to the simple biogenesis from tryptamine (or tryptophan) and today β-carbolines have been isolated from various plant families, fungi genera, animal tissues and marine sources.[2]

The fully aromatic members of this group are named β-carbolines (βCs), whereas the partially saturated members are known as 3,4-dihydro-β-carbolines (DHβCs) and the completely saturated are the 1,2,3,4-tetrahydro-β-carbolines (THβCs) which contain the general structures **1**, **2** and **3** respectively (Figure 1). The three rings are often referred to as A, B and C-ring, as labeled in structure **1**.

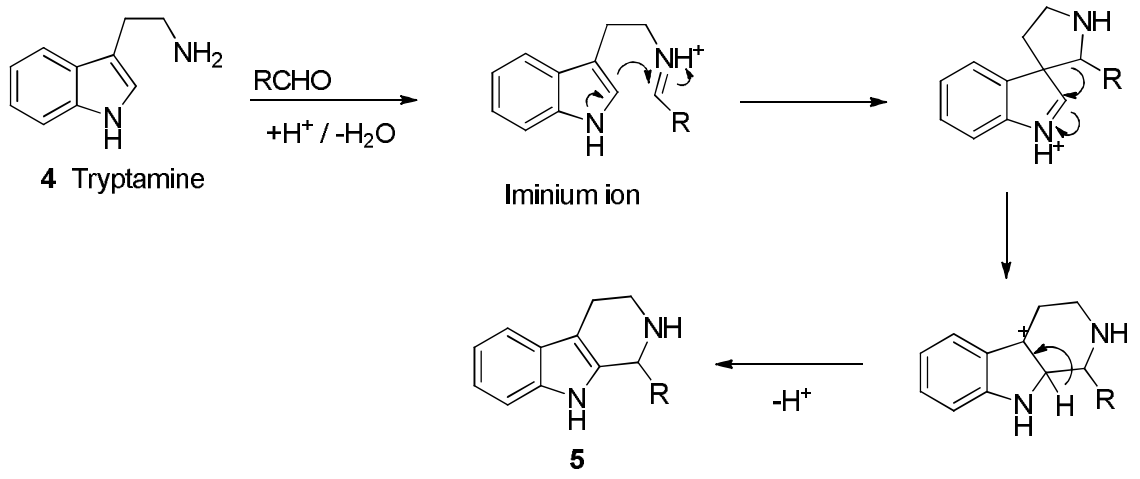


1 **2** **3**

Figure 1. The basic structural units of βC (1), DHβC (2) and THβC (3).

2.2 Biosynthesis

The biosynthesis from tryptamine **4** or tryptophan and a carbonyl compound to THβC **5** is simple and the starting materials and their derivatives are widely available in nature. The reaction from tryptamine to THβC is an enzymatic Pictet-Spengler cyclization and several "Pictet-Spenglerases" have been isolated. The Pictet-Spengler reaction is essentially a two-part reaction (Scheme 1). First, the amine and an aldehyde condense to form an iminium ion. Second, the indole attacks the iminium species from the 3-position, forming a spirocycle that rearranges to a positively charged intermediate which then finally undergoes aromatization via deprotonation to yield THβC **5**.[2, 5]



Scheme 1. Biosynthesis of THβCs.

In nature the carbonyl species is often the iridoid glucoside secologanin. The condensation reaction between secologanin and tryptamine is catalyzed by the enzyme Strictosidine Synthase (STR). The corresponding THβC strictosidine is a common precursor in a number of β-carboline as well as other alkaloids, such as ajmalicine, strychnine, reserpine, quinine, catharanthine and vindoline (Figure 2).[5, 6]

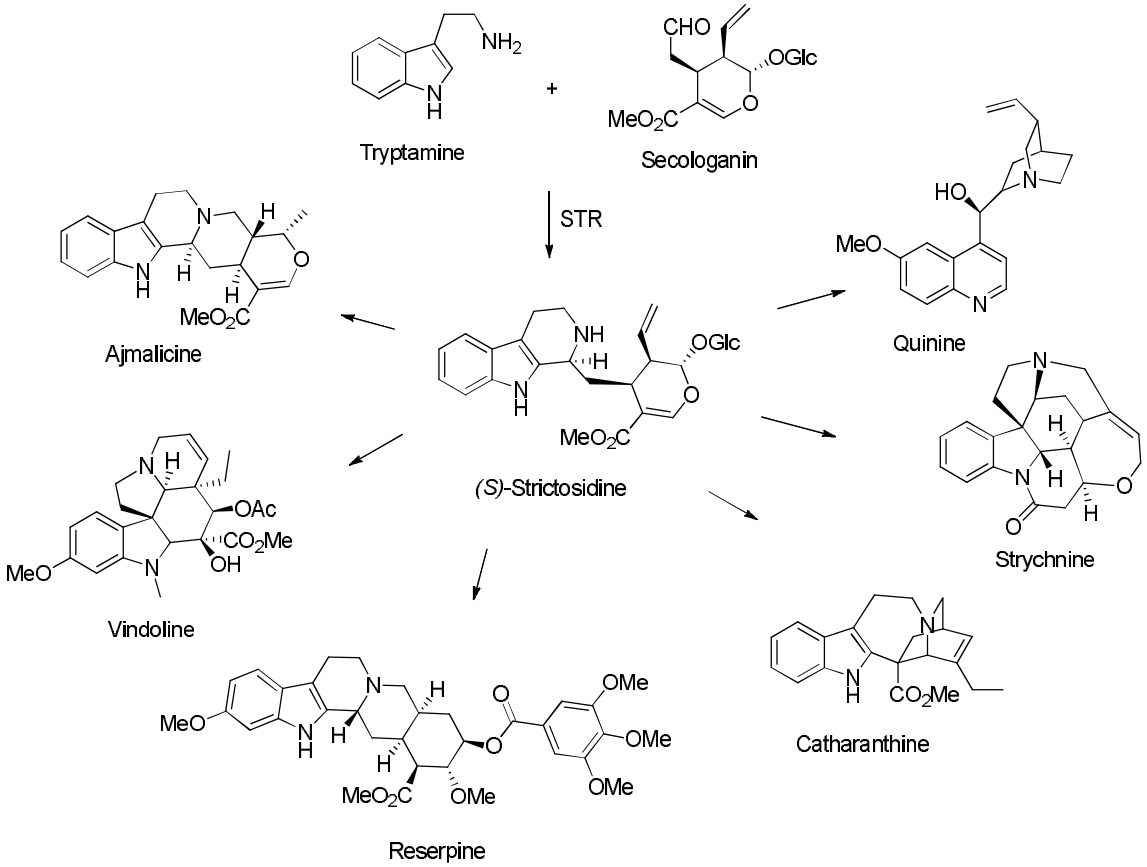
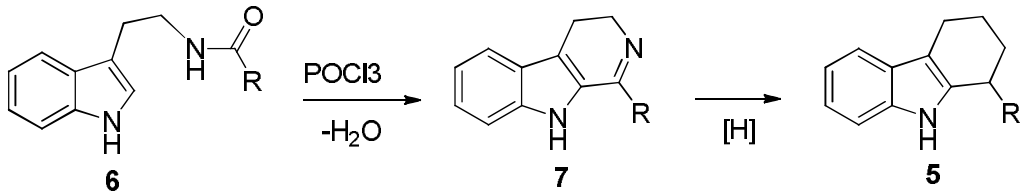


Figure 2. Alkaloids formed from strictosidine.

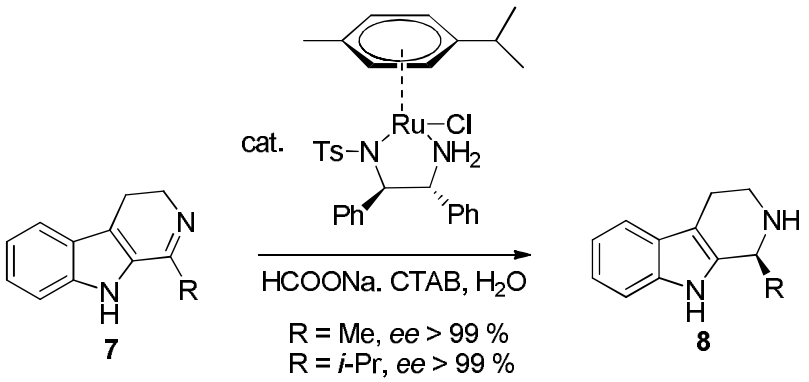
2.3 Common synthetic routes

The THβC skeleton is found in numerous pharmacologically interesting compounds and hence these alkaloids have been in the focus of synthetic efforts for a long time. The most popular synthetic routes utilize the Pictet-Spengler cyclization[7] (extensively reviewed in 1995 by James Cook[8] and more recently by Joachim Stöckigt in 2011[6]) that could be considered as a biomimetic approach. Alternatively, a rather similar Bischler-Napieralski cyclization[9] can be used. In a Bischler-Napieralski reaction, a tryptamide **6** is cyclized. Usually dehydration reagents, such as PCl_5, $POCl_3$, $SOCl_2$ or $ZnCl_2$, are needed to promote the loss of the carbonyl oxygen. The product of the Bischler-Napieralski reaction is a DHβC (**7**) which can then be further reduced to form the corresponding THβC **5** (Scheme 2).



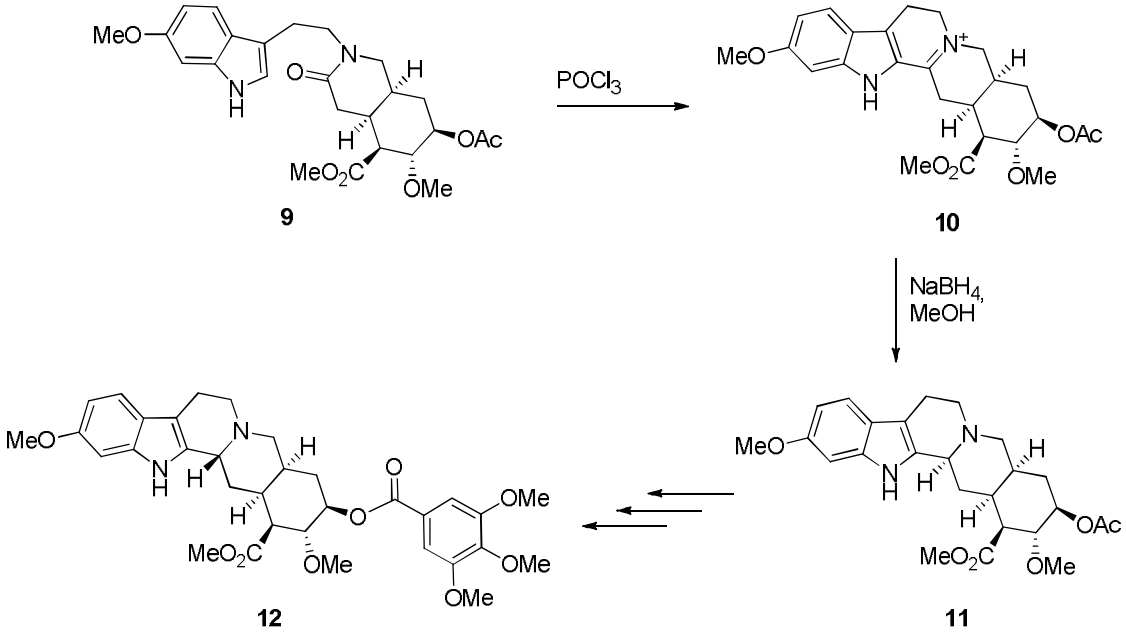
Scheme 2. A general Bischler-Napieralski cyclization and reduction to THβC.

Chirality can be introduced to the DHβC product by using asymmetric reduction protocols. Asymmetric transfer hydrogenation (ATH) using Noyori –type catalysts[10] offers a powerful method of accessing a chiral THβC skeleton. Due to the highly stereoselective nature of the reaction in question, this remains one of the most commonly employed procedures. ATH of dihydro-β-carbolines to THβCs has been developed extensively, and modifications have been suggested to the classical Noyori conditions in which an azeotropic mixture of Et_3N and HCOOH is used as the hydrogen source. One example of such modification was presented by the Pihko group in 2009 when they established new aqueous conditions for the traditional Noyori hydrogenation(Scheme 3).[11] The modified ATH conditions of **7** lead to the enantioselective formation of compound **8**.



Scheme 3. The Noyori ATH in aqueous media by Pihko et. al.[11]

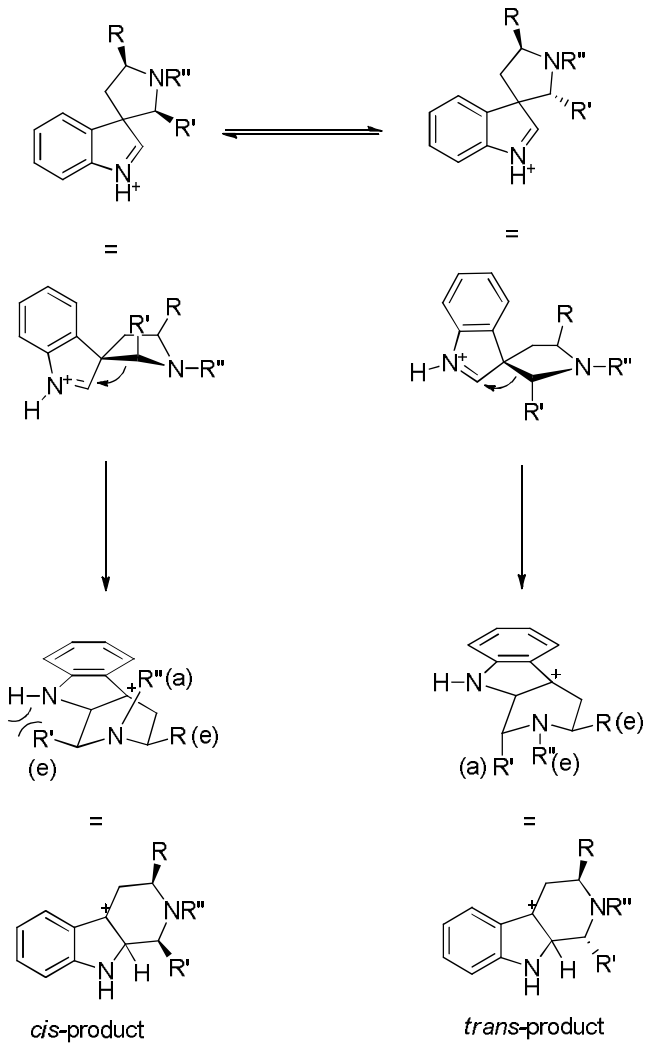
In addition to ATH, stereochemistry of the reduction product can be controlled also by preexisting directing moieties in a diastereoselective fashion. In Woodward's classic total synthesis of reserpine[12], published in 1958 (Scheme 4), a Bischler-Napieralski reaction from amide **9** to DHβC **10** was followed by a $NaBH_4$ reduction selectively forming THβC **11**. Interestingly but not very surprisingly, this reduction selectively yielded the wrong diastereomer. However, in this case the stereo chemical configuration at C1 could be reversed at a later stage of the synthesis.



Scheme 4. Bischler-Napieralski reaction and diastereoselective reduction in the total synthesis of reserpine.[12]

The stereochemistry in the THβCs can also be controlled by using chiral inductors in the Pictet-Spengler reaction. Internal induction as a mean to control the stereochemistry of C1 uses chiral starting materials that are often derived from tryptophan. The existing

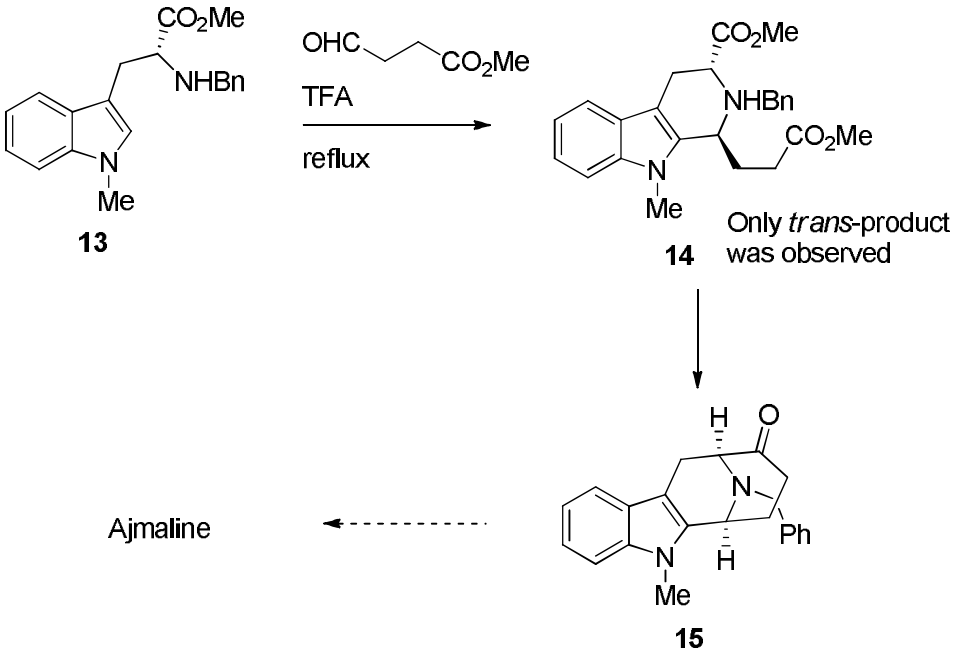
stereochemistry guides the formation of second chiral center in cases when C1 is substituted.[13, 14] The diastereoselectivity of Pictet-Spengler reaction has been studied and discussed in detail in the works of Bailey *et al.* and Cook *et al.*[8, 15] The conformation of the spiroindolenine intermediate determines whether a *trans*- or a *cis*-product is formed (Scheme 5). The *trans*-product is predominantly formed under thermodynamic control and under kinetic control the selectivity is turned towards the *cis*-product. However, the overall control of the *cis/trans*-selectivity is very complicated; in addition to the reaction temperature, the substitution pattern together with the size and electronic properties of the substituents have a considerable impact on the selectivity.



Scheme 5. Formation of *cis*- and *trans*-products from the spiroindolenine intermediate. a = axial, e = equatorial.

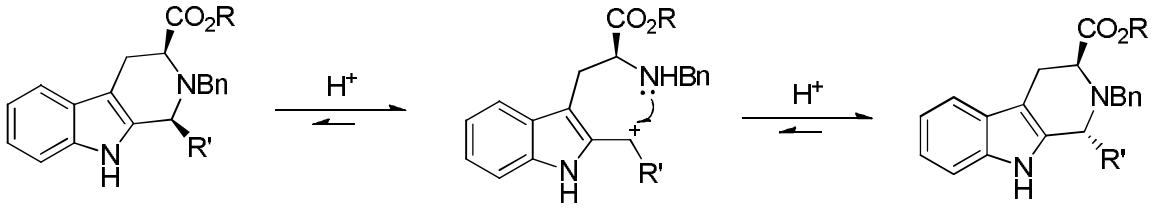
Despite the complicated nature of this type of internal chiral induction, the reaction outcome has the potential of being highly stereoselective. It has been used extensively in indole alkaloid synthesis to control the stereochemistry at C1.[14, 16] An early example of

successful use of internal induction is found in the ajmaline synthesis by Cook *et al.*[17] In this work, Cook *et al.* use benzyl protected tryptophan **13** for a Pictet-Spengler reaction. The yield of *trans*-product **14** was enhanced by acid induced epimerization that was conducted simultaneously with the Pictet-Spengler reaction.



Scheme 6. Synthesis of ajmaline by Cook *et al.*[17]

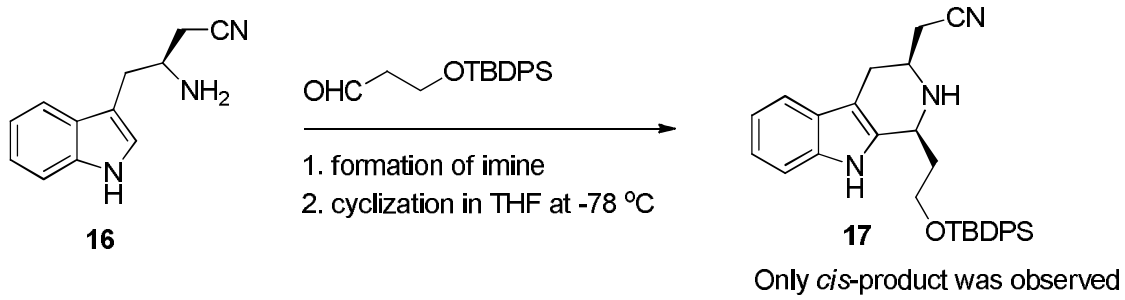
The key in the epimerization is reversible ring opening that favors the thermodynamically more stable *trans*-product (Scheme 7). Hence, a reliable protocol exists to yield *trans*-product in very high selectivity from N2 benzyl substituted tryptophan derivatives. The same strategy to reach intermediate **15** has been successfully used to synthetize other related alkaloids such as 11-methoxymacroline and alstophylline.[18]



Scheme 7. Epimerization of 1,2,3-substituted THβCs favor *trans*-product.

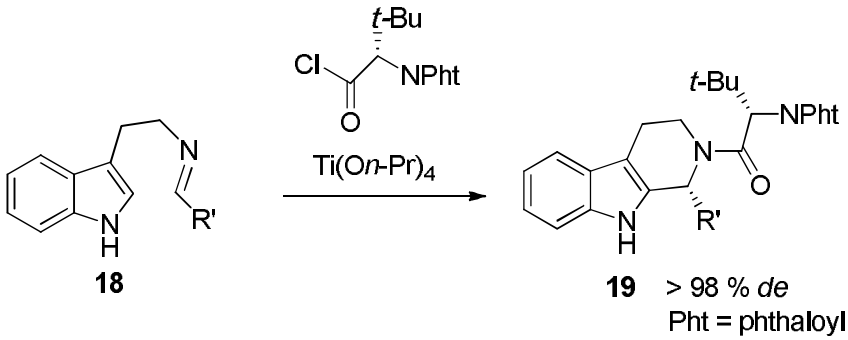
Bailey *et al*. have studied kinetically controlled Pictet-Spengler reactions and found that in addition to *trans*-selectivity, under suitable reaction conditions and substitution pattern, the Pictet-Spengler reaction can become highly *cis*-selective.[15] In a representative

example (Scheme 8), the cyano substituent in the tryptophan derivative **16** is necessary for the reaction outcome to achieve good *cis*-selectivity, to form product **17.** The kinetically controlled reaction has been subsequently used e.g. in (-)-raumacline synthesis[19] and the conditions leading to the *cis*-selectivity have been studied thereafter.[20, 21]



Scheme 8. The Kinetically controlled Pictet-Spengler reaction in (-)-raumacline synthesis[19].

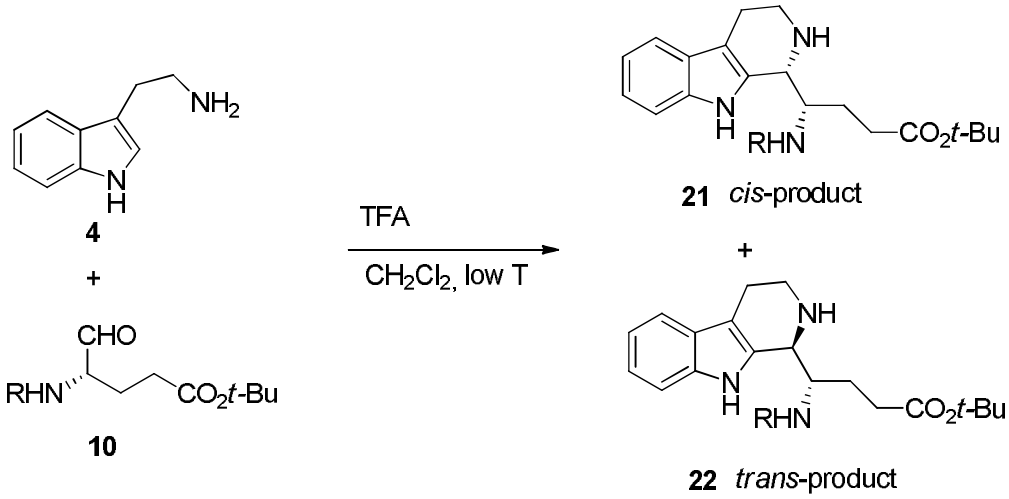
In addition to a directing group in C3, also chiral auxiliaries on N2 have been studied as an alternative. A benefit of an auxiliary on the nitrogen would be the easy attachment and removal of the chiral auxiliary. However, simple benzyl or naphthyl derived chiral groups provide only moderate diastereoselectivity with only 30 – 80 % *de*.[22, 23] Yet, good diastereoselectivities have been obtained using *N,N*-phthaloylamino acids (Scheme 9).[24] In this example the pre-formed imine **18** is protected with a phthaloylamino acid derivative and the *N*-protected THβC **19** is formed diastereoselectively.



Scheme 9. Asymmetric Pictet-Spengler using chiral *N2*-auxiliary[24].

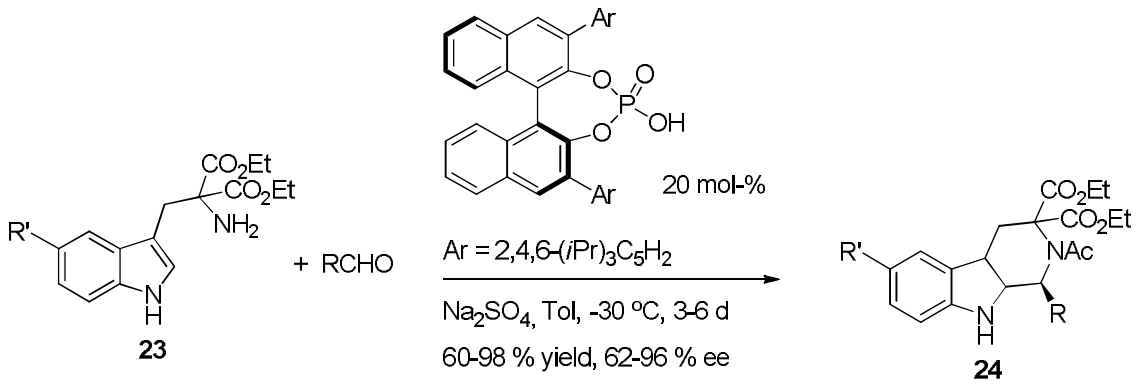
Moreover, the source of stereochemical information in Pictet-Spengler reactions can be from chiral carbonyl compounds. In the work of Ducrot *et al.* tryptamine **4** was condensed with a chiral aldehyde **10** derived from L-glutamic acid (Scheme 10).[25] The preferred *cis*-compound **21** was formed exclusively when a carboxybenzyl (Cbz) protecting

group was used (R = Cbz) and the selectivity was turned towards *trans*-product **22** when the amine was protected with a pyrrole. Ducrot *et al.* speculated that the size of the protecting group is an important factor, but since pyrrole and Cbz –protecting groups are rather similar in size it seems more likely that this selectivity is guided by other factors.



Scheme 10. Pictet-Spengler reaction with chiral carbonyl species.[25]

External asymmetric induction can also be used in the Pictet-Spengler reaction. The first enantioselective Pictet-Spengler reactions using external asymmetric induction were conducted in 1996 by Kawate *et al.* using diisopinocampheylchloroboranes and reaching 90 % ee.[26] Today, various asymmetric reagents have been used for Pictet-Spengler reactions providing moderate to high ee:s. In recent publications, popular catalysts in asymmetric Pictet-Spengler reactions includes thiourea based catalysts[27, 28] and chiral phosphoric acid diesters[29, 30] (Scheme 11).



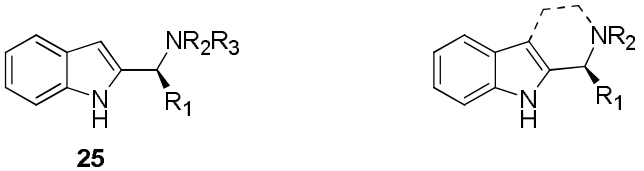
Scheme 11. Pictet-Spengler reaction using external asymmetric induction.[29]

Despite the amount of publications related to asymmetric Pictet-Spengler reaction with external asymmetric induction, these methods have several limitations: the C 1 substitu-

ent usually has to be rather bulky in order to achieve >80 % ee's; reaction times can increase to several days and the catalyst loading is often rather high, >10 %.

2.4 2-Indolylamines - open-chained analogues of THβCs

In the synthetic part of this thesis, major emphasis is put on the synthesis of 2-indolylamines (**25**) that have a structural resemblance to THβCs but lack the C-ring bridge between the N2 and the indole C3 (Figure 3).



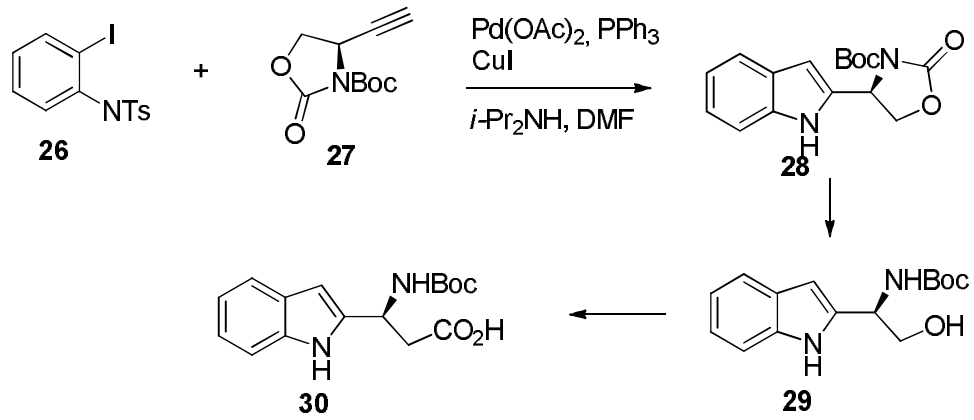
25

R_1 = alkyl, aryl, etc.
R_2, R_3 = H, alkyl, ester, etc.

Figure 3. 2-indolylamine – an open chained analogue of 1-substituted THβC.

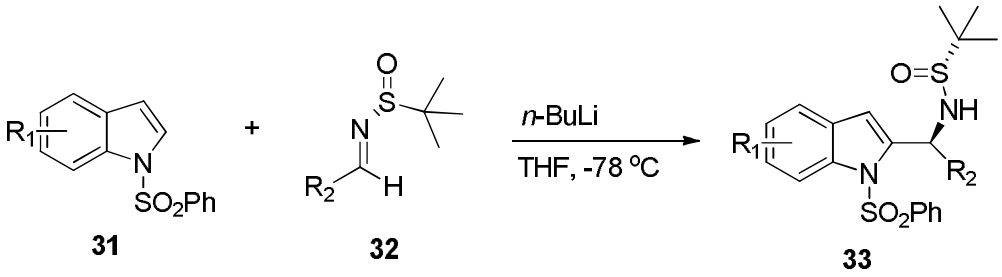
Both 2-indolyl and 3-indolyl moieties are found in natural products. Compounds encompassing a 2-indolylamine structure have been studied as HIV protease inhibitors[31], serotonin receptor antagonists[32] and estrogen receptor ligands[33]. Recently, 3-indolylglycines have received attention due to their presence in marine alkaloids, namely dragmacidins[34] and hamacanthins[35]. This has also brought new synthetic approaches to chiral 2-indolylamines.[36, 37] Surprisingly few approaches have been made to synthetize optically active 2-indolylamines though syntheses to other chiral 2-substituted indoles and racemic 2-indolylamines have been reported.

In 2012 Goswami *et al*. published a synthesis to 2-indolylglycines using the chiral pool approach. They used Sonogashira[38] conditions to do a Larock[39] inspired indolization to couple the iodoaniline **26** with the chiral alkene **27** (Scheme 12). Alkene **27** was derived from Garner's aldehyde[40] thus providing a natural source of chirality. Lactone **28** was then reduced to 2-indolylamine **29** which was then oxidized to 2-indolylglycine **30**. Chiral alkenes under similar conditions have also been used to prepare other chiral 2-substituted indoles.[37]



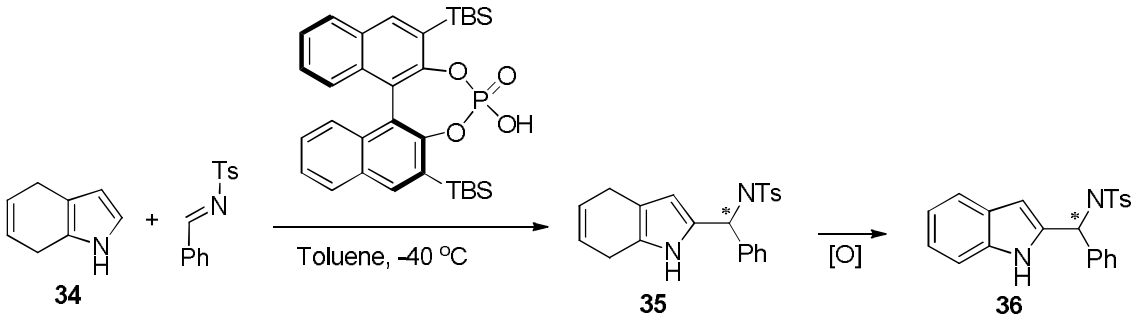
Scheme 12. Chiral pool approach to optically active 2-indolylglycines by Goswami *et al.*

In another approach, an *ortho*-metallation reaction of indole **31** with *n*-BuLi is followed by an addition to chiral aldimine species **32**. Asymmetric addition to *ortho*-lithiated heteroaromatics was studied by Enders *et al.* in 2004 using a range of different heteroromatics including also indole derivatives.[41] In 2007, this approach was efficiently used by Cheng *et al.* to synthetize a series of chiral 2-indolylamines (**33**, Scheme 13).[42]



Scheme 13. *Ortho*-metallation approach to 2-indolylamines by Cheng *et al*[42].

Yet another interesting approach to reach 2-indolylamines is asymmetric Friedel-Crafts reaction using chiral phosphoric acid catalyst. This route, however, has proven difficult especially for C3-unsubstituted indoles due to the reactivity of C3 in Friedel-Crafts reaction. It was reported by Kang *et al.* that 4,7-dihydroindole **34** undergoes Friedel-Crafts reaction at the 2-position (Scheme 14) and this method has been used to reach 2-indolylamines.[43-45] The obvious downside of this method is the additional oxidation step from dihydro species **35** to the fully aromatic compound **36**.



Scheme 14. Asymmetric Friedel-Crafts reaction for 4,7-dihydroindoles by Kang *et al.* [43]

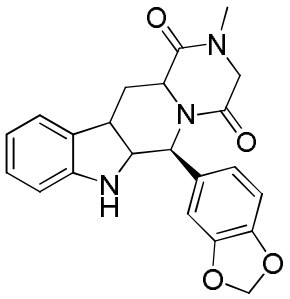
3 Pharmacological importance

This chapter concentrates on the pharmacological importance of 1,2,3,4-THβCs. As the skeleton is a common feature in many natural and synthetic compounds, both the multitude of compounds belonging to this group as well as their corresponding biological activities is vast. This work emphasizes the role of relatively simple THβCs carrying a C1 substituent, as the research work of this thesis is closely related to C1 substituted THβCs and their analogues. Moreover, emphasize is rather put on the recent studies than the more traditional applications of THβCs that are not discussed in great detail. The biochemical and pharmacological functions of β-carbolines (incl. THβCs) has been reviewed in 2007[46] as well as the pharmacological importance of indole alkaloid marine natural products in 2005[47].

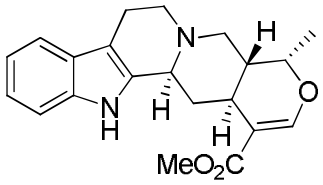
3.1 THβC based drugs currently on the market

Today, there are at least three drugs on the market that encompass the THβC structure. The most well-known is tadalafil (**37**, Figure 4) which is sold under the brand name Cialis by Eli Lilly Co for erectile dysfunction (ED). Tadalafil is a phosphodiesterase 5 (PDE5) inhibitor and was first described in 2003.[48] Cialis was brought to the market as a competitor to sildenafil (Viagra by Pfizer) and vardenafil (Levitra by Bayer Pharmaceuticals) and in 2012 it had reached sales of $1.93 billion[49] almost surpassing the market leader for ED, Viagra ($2.05 billion in 2012)[50]. The feature that distinguishes tadalafil from its competitors is a longer half-life. Tadalafil is also sold for pulmonary arterial hypertension under the market name Adcirca®.

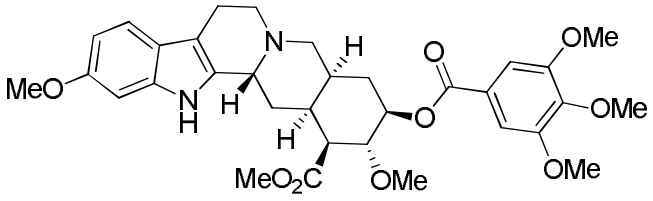
Other THβC encompassing molecules currently on market are natural yohimbine type alkaloids ajmalicine (**38**, numerous brand names) and reserpine (**12**, Serpalan®). They are both prescribed for high blood pressure. Ajmalicine acts as a α_1-adrenergic receptor antagonist.[51] The use of reserpine has been limited due to side effects such as drowsiness, nightmares and depression but the low price of reserpine has still kept it competitive.[52]



37 tadalafil



38 ajmalicine



12 reserpine

Figure 4. THβC-based drug molecules currently on market.

3.2 Antiprotozoal activity

Several THβCs have been reported to exhibit antiprotozoal, most notably antimalarial, activity (Figure 5). This section summarizes the antimalarial properties along with the antileishmanial and the trypanocidal properties of such compounds.

3.2.1 Antimalarial activity

Malaria is one of the most important infectious diseases in the world. According to the World Health Organization (WHO) 200-300 million people are infected and 1.5-2.5 million people die of malaria annually. 90 % of malaria deaths occur in Africa and 85 % of the deceased are younger than 5-years-old.[53, 54] Malaria is caused by red blood cell infecting protozoan parasites belonging to the *Plasmodium* genus, mainly *Plasmodium falciparum.*[54] Traditionally, malaria has been treated with quinine type drugs such as chloroquine. However, the emergence of drug resistant strains has created new challenges for efficient treatments.[55] There have been many recent studies of the use of different THβC type compounds in the treatment of malaria.[56-62]

(+)-7-bromotrypargine (**39**) is a marine natural product that was recently isolated from a sponge, *Ancorina* sp. Davis *et al.* reported the isolation and the structural elucidation of the compound together with tests towards antimalarial activity. The compound was tested against both the chloroquine-resistant (Dd2) and the chloroquine-sensitive (3D7) strains of *P. falsiparum* and (+)-7-Bromotrypargine was shown to display IC_{50} values of

5.4 μM (Dd2) and 3.5 μM (3D7).[56] Similar compounds were also studied by Chan *et al.* and moderate antimalarial activity was reported.[57]

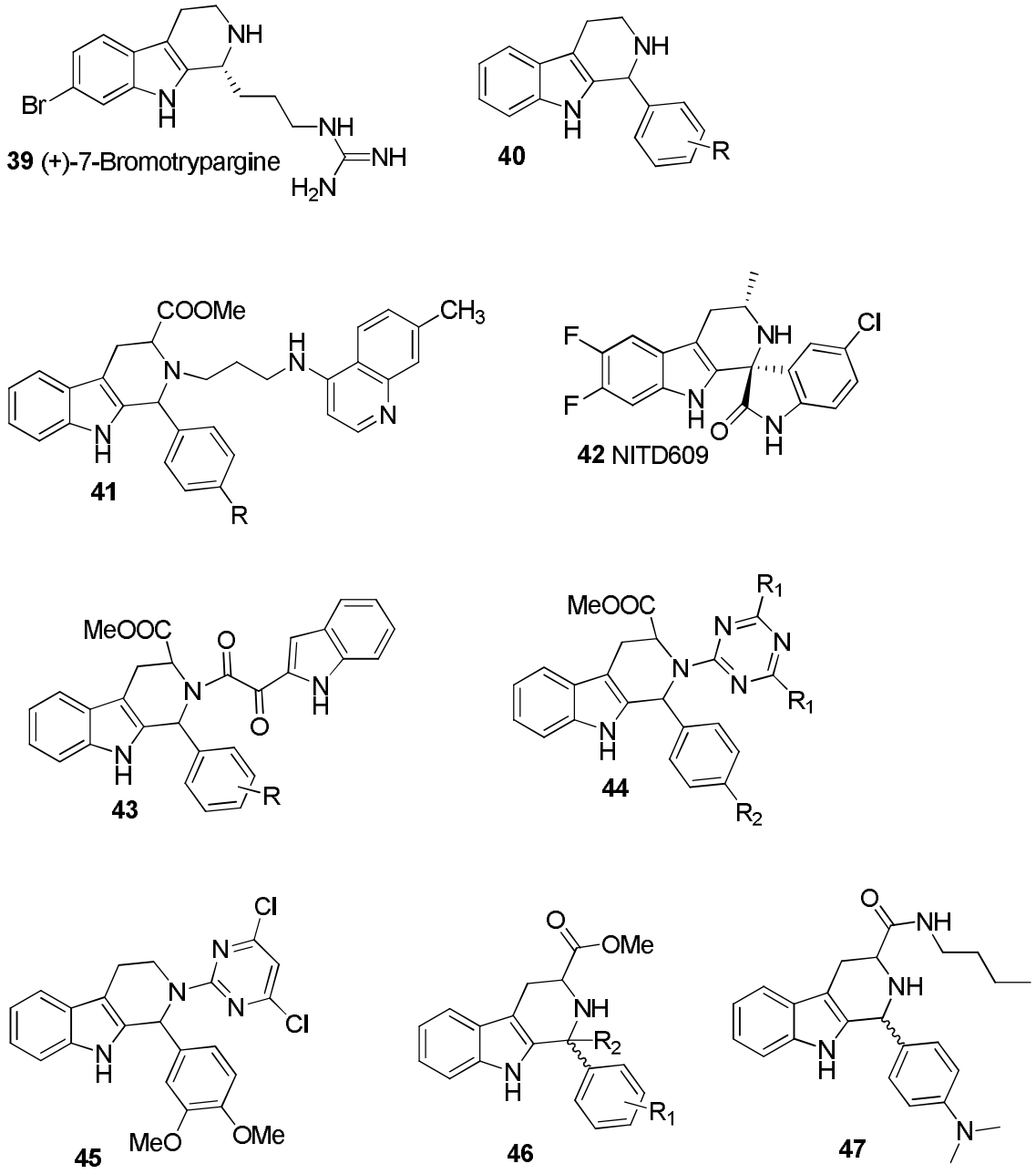


Figure 5. THβCs with antiprotozoan properties.

In 2012, Gellis *et al.* synthesized series of simple 1-substituted THβC derivatives with the general structure **40** with one or more substituents on the phenyl moiety. They tested a series of 20 compounds against *P. falciparum* resistant to chloroquine, pyrimethamine and proguanil and 9 compounds showed antiplasmoidial activity. The most active was a *para*-methoxy substituted compound which had an IC_{50} of 0.7μM.[58]

In 2008, Gupta *et al.* synthesized a series of chloroquine-THβC hybrid molecules with the general structure **41**. 23 compounds were screened against *P. falsiparum* and the most active compounds had R = *i*-Pr, R = Me and R = Et and showed minimum inhibitory concentration (MIC) of 0.05, 0.06, and 0.11 μM respectively, thus showing significantly greater activity than the standard drug chloroquine (MIC = 0.391 μM)[59].

A new class of potent antimalarials that has recently gained attention is spiroindolones with a THβC structure. In 2010, these types of compounds were recognized as antimalarials in high-throughput screenings by Novartis Institute of Tropical diseases.[60, 61] These compounds act against *P. falciparum* with a mechanism distinct from that of the existing antimalarial drugs[60] and the optimized lead compound NITD609 (**42**) has a very high activity of IC_{50}=0.2 nM.[61] In 2012 NITD609 entered phase 2 clinical trials.[62]

3.2.2 Antileishmanial and trypanocidal activity

In addition to antimalarial studies, THβCs have recently also gained attention as potential antileishmanial and trypanocidal compounds. Leishmaniasis is a tropical infectious disease and the amount of people infected with leishmaniasis is ~ 12 million. The annual incidence of leishmaniasis is ~ 2 million cases and the numbers are increasing. Leishmaniasis is caused by protozoan flagellate *Leishmania* spp., most notably *L. donovani*, which is spread by sand flies (*Phlebotomus* and *Lutzomyia* spp.). 90 % of leishmaniasis cases occur on the Indian Peninsula, in Brazil and in Sudan.[54]

Trypanosoma spp. cause trypanosomiasis that can either be manifested as African trypanosomiasis (sleeping sickness) caused by *T. brucei* or as Chaga's disease caused by *T. cruzi*. The incidence of African trypanosomiasis is 50 000 – 70 000 cases annually and it is endemic to the tropical Africa, while Chaga's disease occur in the Middle and Southern America. The approximated amount of people with Chaga's disease is 8-11 million.[54]

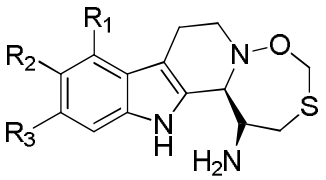
It has been known for a long time that such complicated THβC alkaloids as α-yohimbine, corynanthine and buchtienine exhibit antileishmanial activity.[63, 64] However, during the last 5 years a new interest has ascended towards smaller, synthetic THβC derivatives and several publications have reported antileishmanial activity. In 2010, Chauhan *et al.* synthesized a series of indolylglyoxylamides with the general structure **43** and reported good antileishmanial activities with IC_{50} values of 3.79 μM and 5.17 μM for the *ortho*-bromosubstituted and *para*-ethylated compounds, respectively.[65]

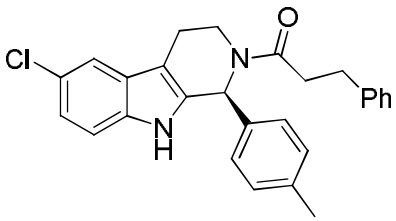
These values were several folds better than the standard drug activities. Furthermore, Kumar *et al.* have reported triazine derivatives **44** as well as other similar derivatives **45** as leishmanicidals.[66, 67] The triazino derivatives have also been tested *in vivo*. Furthermore, Gellis *et al.* have tested their antimalarial compounds with the general structure **40** for antileishmanial activity. A *p*-bromosubstituted compound showed the most promising inhibitory activity towards *L. Donovani,* with IC_{50} value of 6.1 μM.[58]

Some THβC derivatives have also been studied for trypanocidal activity. In 2010 Tonin and Valdez published studies on similar THβC derivatives (**46** and **47**).[68] These compounds showed promising activity and compound **47** has been further studied for synergistic activity with other medication[69] but these publications remain the only publications so far on trypanocidal activity of THβC derivatives.

3.3 Antiviral activity

THβCs have been recognized as antiviral compounds since 1984 when Rinehart *et al.* first studied eudistomins against herpes simplex virus-1 (HSV-1). Eudistomins are marine alkaloids isolated from the colonial tunicate *Eudistoma olivaceum*, and four eudistomins contain the THβC scaffold (**48** – **51**, Figure 6).[70]





48 Eudistomin C R_1=H R_2=OH R_3=Br
49 Eudistomin E R_1=Br R_2=OH R_3=H
50 Eudistomin K R_1=H R_2=H R_3=Br
51 Eudistomin L R_1=H R_2=Br R_3=H
52 (-)-Debromoeudistomin K R_1=H R_2=H R_3=H

53

Figure 6. THβCs with antiviral properties.

In addition to the basic THβC structure, the eudistomins C, E K and L have a condensed oxathiazepine ring system, only reported in these compounds. It has been reported that these four eudistomins have *in vitro* activities against Herpes Simplex virus-1 (HSV-1) ranging from 25-250 ng / 12.5 mm disc.[71] Later it was also reported that eudistomins K showed activity against the polio vaccine type-1 virus.[72] Eudistomins C and E are also known to possess activities against RNA viruses such as Coxsachie A-21 virus and equine rhinovirus.[70] In 1992, (-)-debromoeudistomin K (**52**) and its structural analogues

were tested against a number of viruses and significant antiviral activities were reported against influenza A and B in Madin-Darby canine kidney (MDCK) cells. Activities have been reported also against respiratory cyncytial virus, vesicular stomatitis virus, Coxsachie virus B4 and polio vaccine type-1 virus.[73]

The antiviral activities of these eudistomins have never been further studied or developed but a different series of THβCs have been more recently studied against the human papilloma virus (HPV). In a study done at GlaxoSmithKline Research and Development, a series of 1-substituted THβC derivatives were optimized and resulted in compound **53** possessing nanomolar activity against HPV. The optimized compound had an activity of IC_{50} = 23 nm.[74] GlaxoSmithKline has patented the use of this type of THβCs for the treatment of HPV.[75]

3.4 Anticancer

Since the 1980's, THβC derivatives have been tested against cancer cell lines. During the last decade, the interest has increased tremendously as traditional THβC targets such as the mitotic kinase Eg5 and phosphodiesterase 5 have been recognized as cancer targets.

3.4.1 The cytotoxicity of THβCs

The first reports on the cytotoxicity of compounds with THβC structure came in 1990 when the newly isolated eudistomins where studied for antileukemic properties. Eudistomin B (**54**) showed antitumour activity against leukemic cell lines L1210 and L5178Y.[76] Later also Eudistomin K (**50**, Figure 6) was described as an antitumor lead against the murine leukemia cell line P-388, the human leukemia cell line L-1210 and human adenocarcinoma cell lines A-549 and HCT-8.[73] Eudistomin E (**49**, Figure 6**)** has also known to be active against the human mouth epidermal carcinoma KB cell line.[77] Apart from eudistomins, only few THβC derivatives had been studied for antitumor properties until recent years. However, the group of THβCs that are today recognized as antitumor compounds is growing (Figure 7).

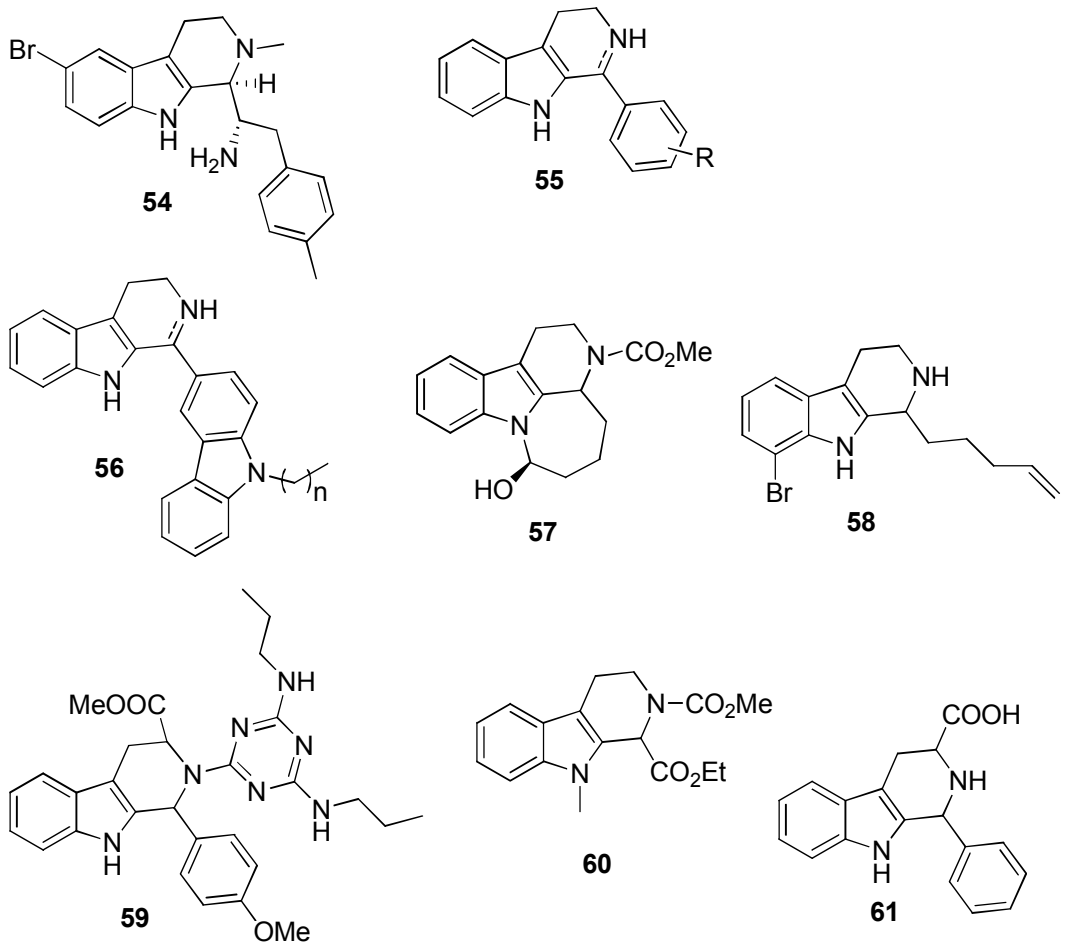


Figure 7. THβCs with cytotoxicity activity.

In 2005, Shen *et al.* synthesized a series of simple THβC and DHβC derivatives with the general structure **55**. The compounds were trialed against murine cell line P-388 and human cell lines KB-16 and A-549, and the human colon adenocarcinoma cell line HT-29. All synthesized compounds exhibited moderate cytotoxicity.[78] In 2011, Shen *et al.* published a new study in which they had increased the size of the substituent in C1 and had a series of THβCs and DHβCs with general structure **56**. The series was evaluated for antitumor activity against human tumor cells including KB, DLD, NCI-H661, Hepa, and HepG2/A2 cell lines. In this study, the DHβC derivatives gave generally better results though also the THβCs showed significant cytotoxicity.[79]

In 2009, Santos *et al.* inspired by arborescidine alkaloids, synthesized tetracyclic compounds resembling arborescidines and tested them for antitumor activity towards human lung fibroblasts (MRC-5), human gastric adenocarcinoma (AGS), human lung cancer (SK-MES-1), human bladder carcinoma (J82) and human leukemia (HL-60) cells. From the arborescidine resembling compounds, compound **57** showed most activity having

IC_{50} values in micromolar range. The research group also tested all the intermediate compounds they had synthesized and found that a non-cyclic compound **58** actually gave better response to almost all tested cell lines IC_{50} values ranging from 8.8 to 18.1 μM for lung fibroblasts, gastric adenocarcinoma, lung cancer and bladder carcinoma.[80] Kumar *et al.* have also tested their leishmanicidals triazine THβC hybrids (**44**, Figure 5) for cytotoxicity and found that they experience nanomolar cytotoxic activity. Their best hit was compound **59** which had an IC_{50} value 122 nM.[81] In 2012, Skouta *et al.* synthesized a series of 1,2-disubstituted THβCs and found that compound **60** showed a unique selectivity towards tumorigenic versus non-tumorigenic cells and induced cell death without the activation of caspases, hence inducing a *non-apoptotic* cell death.[82] Simple 1,3-disubstituted THβCs have also been tested for cytotoxic activity against the insect origin *Spodoptera frugiperda* Sf9 cell line and the most promising compound was 1-phenyl-THβC-3-carboxylic acid (**61**). Furthermore, these compounds experienced substantial insecticidal activity against mosquito larvae of *Culex pipiens quinquefasciatus* species and mustard aphid (*Lipaphis erysimi*).[83]

3.4.2 THβCs targeting mitotic kinesin spindle protein (KSP)

Today, one very interesting feature in THβCs is their recognition as mitotic kinesin spindle protein (KSP, also referred to as Eg5) inhibitors. Mitosis is the part of cell division in which the chromosomes condense and divide into two identical sets. The mitotic kinesins are intimately involved in the formation of mitotic spindle, chromosome segregation, checkpoint control and cytokinesis (Figure 8). The kinesin spindle proteins are highly expressed in breast, ovary, colon, lung, uterine and retinoblastoma tumors.[84]

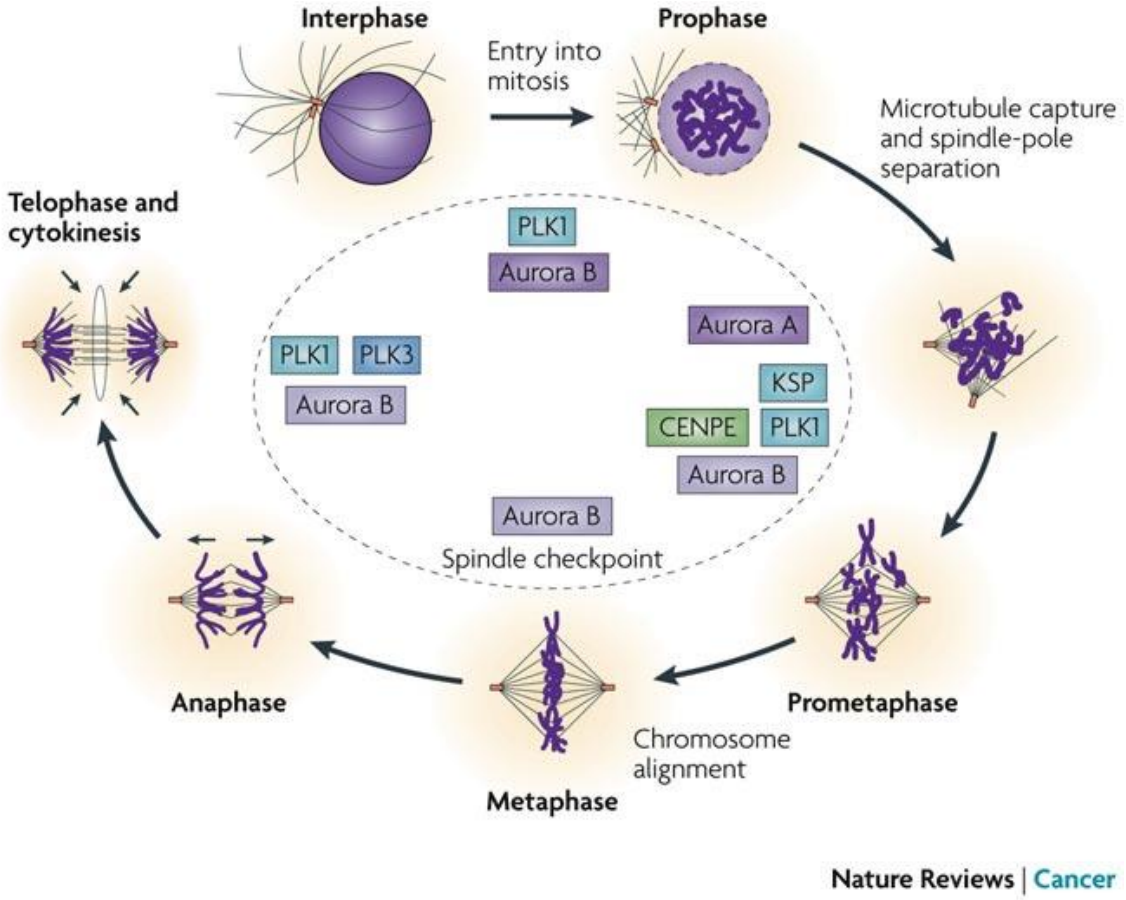


Figure 8. Mitosis and the mitotic kinesins involved in the five steps.[85]

KSPs became an important cancer target when Monastrol, the first KSP inhibitor, was discovered in 1999. During the last decade, the development of KSP inhibitors has been rapid and many pharmaceuticals companies now have KSP inhibitor drugs in clinical trials.[84] During the last ten years, several papers have been published on the KSP inhibitory properties of THβC derivatives (Figure 9).[86-92] The mitotic kinesin spindle proteins as cancer targets have been the subject of several recent reviews such as the extensive reviews by Schmidt and Bastians in 2007[93] and Chan *et al.* in 2012[94].

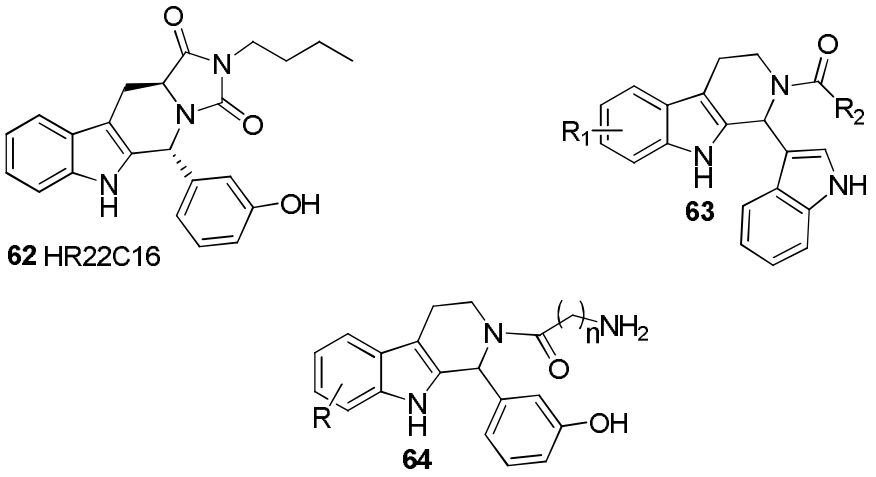


Figure 9. Mitotic kinesin spindle protein (KSP) inhibitors.

In 2003 Hotha *et al.* published the results of an extensive screening that revealed a THβC derivative HR22C16 (**62**) as a potential lead compound for KSP inhibition (Figure 10). They reported that HR22C16 had an IC_{50} value of 800 nM against KSP.[86]

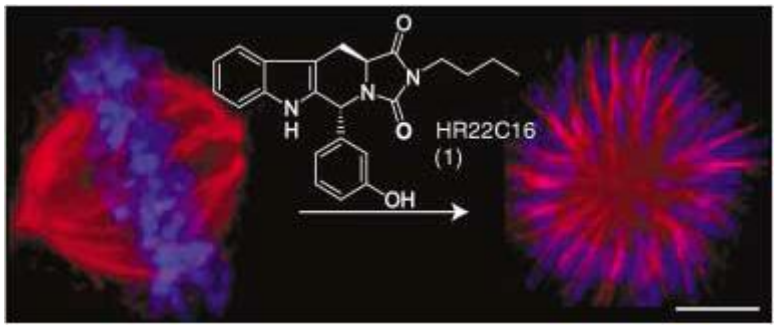


Figure 10. Configuration of microtubules (red: stained with antitubulin antibodies) and DNA (blue: stained with Hoechst 33342) in a control cell (left) and a HR22C16-treated cell (right); scale bar: 5 mm[86].

After the discovery of HR22C16, several related derivatives and their inhibitory actions have been reported. In 2005, Sunder-Plassmann *et al.* published series of HR22C16 derivatives and reported that replacing the N-butyl side chain with N-benzyl side chain increases inhibitory activity to IC_{50} = 650 nM.[87] These type of indolopyridines were patented in 2009 as KSP inhibitors by a German pharmaceutical company, 4SC[88]. The company has now one KSP inhibitor in clinical Phase I trials (SC4-205)[89] and although its structure is not yet revealed, it was speculated in a recent review that it is based on the indolopyridine scaffold.[90]

HR22C16 inspired compounds have also been further studied by Liu *et al.* who reported that the metabolically liable phenol group can be replaced with indolyl without losing inhibitory activity. The research group also replaced the fourth ring in the HR22C16 structure with a simple acyl group on N2 giving compounds of general structure **63**, thus returning to the original THβC three-ring system.[91] Barsanti *et al.* also published a paper in which 1,2-disubstituted THβCs **64** were evaluated as KSP inhibitors. The structures of Barsanti's compounds **64** and Liu's compounds **63** are highly alike. Their most promising lead had an IC_{50} value of 58 nM. The group was also able to co-crystallize the inhibitor with KSP making it possible to observe the major interactions in the binding site of KSP with their ligand (Figure 11)[92].

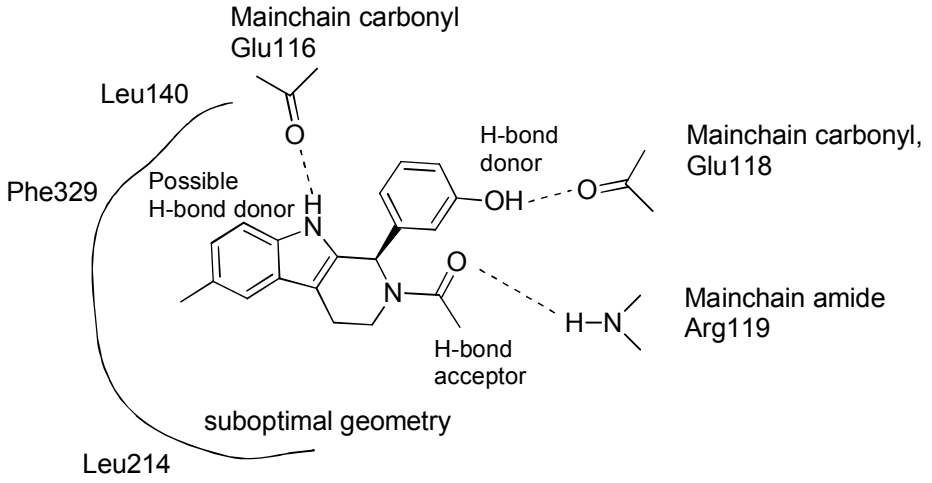


Figure 11. Schematic presentation of interactions between the ATP binding pocket of KSP an inhibitor.[92]

3.4.3 PDE5 as a new cancer target

A novel application for THβCs ascended when phosphodiesterase 5 (PDE5) became a promising cancer treatment target. Phosphodiesterases are enzymes that catalyze the breakdown of cyclic guanosine monophosphate (cGMP) to guanosine monophosphate (GMP). PDE5 inhibition is one of the common targets for compounds with the THβC structure. It has traditionally been a target for treating ED and pulmonary arterial hypertension. Increased concentration of cGMP in vascular smooth muscle cells leads to vasodilation and subsequently erection. In 2006, Serafini *et al.* first recognized PDE5 inhibitors as antitumor agents.[95] The use of PDE5 inhibitors in the treatment of cancer was reviewed in 2009.[96]

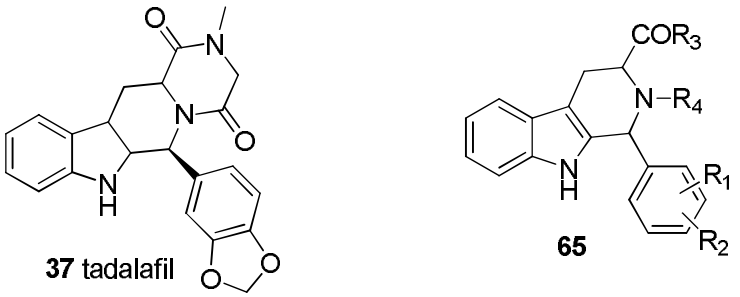


Figure 12. PDE5 inhibitors.

As tadalafil, **37,** (Figure 12) was one of the PDE5 inhibitors Serafini *et al.* used when testing antitumor properties, it is not surprising there are many published papers regarding the cytotoxicity of tadalafil inspired compounds. Tadalafil acts as a PDE5 inhibitor in low nanomolar range and analogues with similar IC_{50} values have been synthesized.[97-100] The generalized Markush structure **65** and its use as a PDE5 inhibitor was patented in 2011.[101]

3.5 Other pharmacological uses

Complex natural alkaloids that encompass the THβC structure such as yohimbine or reserpine have a wide range of pharmacological activities. The extracts from *Rauwolfia* spp. has been a part of traditional medicine in tropical and subtropical areas. Some known mechanisms of action of this type of molecules are serotonin receptor (5HT) antagonism and α-adrenergic receptor antagonism. Hence these molecules have profound effect on the CNS, being hallucinogens, vasodilators and analgesics. However, as the range of activities is broad and these compounds lack inherent selectivity, they haven't been very useful in modern medicine.[52]

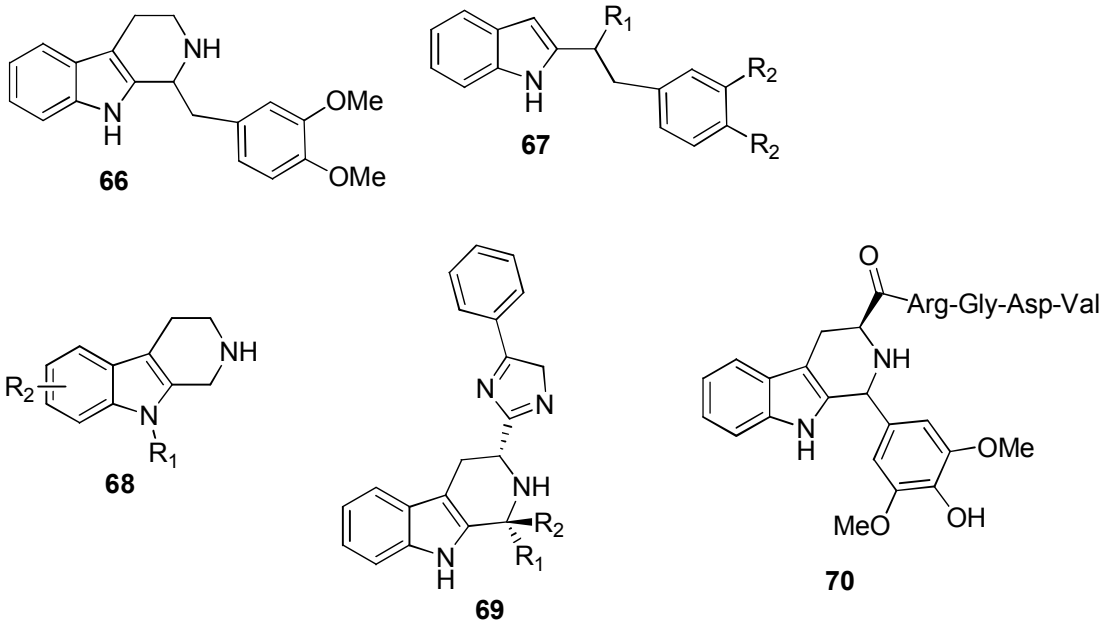


Figure 13. THβC derivatives with miscellaneous pharmacological activities.

Serotonin receptor antagonism has been studied with simple THβCs. An example of one such study was done in the Lilly research laboratories in 1996 by Audia *et al.* who synthetized a series of 1-substituted THβCs in which the substituent consisted of various benzyl or naphthyl groups, as in compound **66**. The compounds showed moderate selective antagonism towards the $5HT_{2B}$–receptor, but this particular antagonistic effect of $5HT_{2B}$ wasn't further explored.[102] Though interest in THβCs as 5HT receptor antagonists has waned, in 2005 Giorgioni *et al.* studied the affinity of their series of open chained THβC analogues **67** towards $5HT_{2B}$. Some compounds acted as antagonists; however, affinity was clearly lower than that of the reference compound, yohimbine.[32] No new studies have been published on THβCs as 5HT antagonists during the recent years.

During the last decade, several novel receptor interactions and possible application of THβC derived compounds have been suggested. Glennon *et al.* has reported the binding of simple C1-unsubstituted THβCs **68** to bind to imidazole receptors I_2 and I_3.[103] In 2001, Poitout *et al.* first described 1,3-substituted THβC derivatives **69** as selective somatostatin receptor type 3 (SSTR3) antagonists.[104, 105] Somatostatin receptors are G-protein coupled receptors inhibiting adenylyl cyclase, thus exerting various other effects on intracellular messenger systems. SSTRs are known to mediate cognitive effects, growth hormone inhibition and insulin secretion inhibition.[106] Merck and Co have been

granted a patent in the use of THβC based compounds similar to **69** as SSTR3 antagonists in the treatment of type 2 diabetes mellitus.[107]

THβC derivatives have also been patented for several other uses: protein tyrosine phosphatase (PTP) inhibition[108], growth hormone secretagogue receptor (GHSR) antagonism[109] and histamine receptor modulation[110]. In 2013, THβC derivatives were reported to target fatty acid amide hydrolase (FAAH) and transient receptor potential (TRP) channels.[111] Furthermore, two publications have suggested that THβC RGD peptidomimetic conjugate **70** acts as antithrombotic agents and have free radical scavenging properties.[112, 113]

4 Pf group as an epimerization preventing protecting group

The 9-phenyl-9-fluorenyl (Pf) group is increasingly being used as a protecting group for the amine functionality in amino acids. The bulky group protects the amine by suppressing reactivity, but unlike other commonly used protecting groups such as carbamates or benzyl groups, it also protects the labile stereocenter of α-amino acids and its corresponding carbonyl derivatives such as α-amino aldehydes, ketones, esters and amides against epimerization. The Pf group was first introduced in 1985 when Christie and Rapoport decided to use the Pf group as an alternative to the highly acid labile trityl group[114]. The ability of the group to prevent epimerization of the α-chiral center of amino acids was further investigated later in the 1980's.[115] To date, the Pf group has been used for amino acid protection in over 250 papers and a comprehensive review on its use in asymmetric synthesis was published in 2010.[116]

Structurally, the Pf group resembles the trityl protecting group (Scheme 14) and both groups can help retain the enantiopurity of amino compounds.[117] However, the use of trityl is limited due to its acid lability even in protic solvents, whereas the more robust Pf group is known to be solvolytically >6,000 times more stable than trityl.[118]

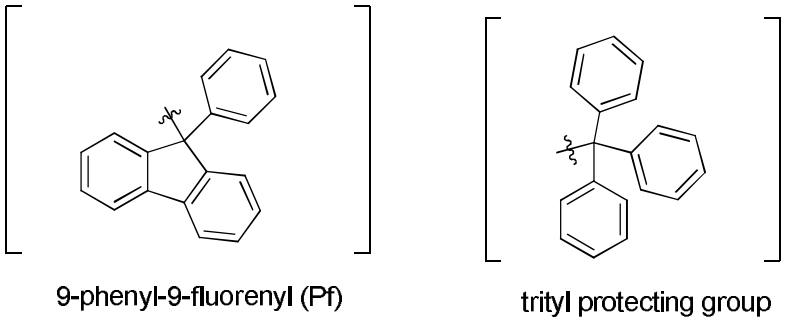


Figure 14. The Pf and trityl protecting groups have structural similarity.

α-amino acid derivatives undergo epimerization in basic conditions due to the acidity of the α-proton. The most favorable conformation for deprotonation is when the α-hydrogen-carbon bond lies in a plane orthogonal to the plane of the carbonyl π-system. The configuration allows maximum orbital overlap as the α-carbon hybridizes from sp^3 to sp^2.[116] It has been speculated that the bulkiness of the Pf group forces the α-proton to adopt a conformation in which this orbital overlap can't take place, effectively suppressing the potential epimerization of the stereocenter in question. In 1993, calculations using molecular mechanics indicated that the Pf-protected amino acids adopt a confor-

mation in which the dihedral angle between the α-proton and the carbonyl oxygen is ~ 0 ° or ~ 180 °, meaning as far away from the optimal 90 ° as possible (Figure 15). These calculations are unpublished and only briefly commented in a related paper[119]. The calculations were repeated as part of this thesis and the results are reported in chapter 5.4. In cyclic compounds, the Pf group forces the α-proton to occupy an equatorial position[120].

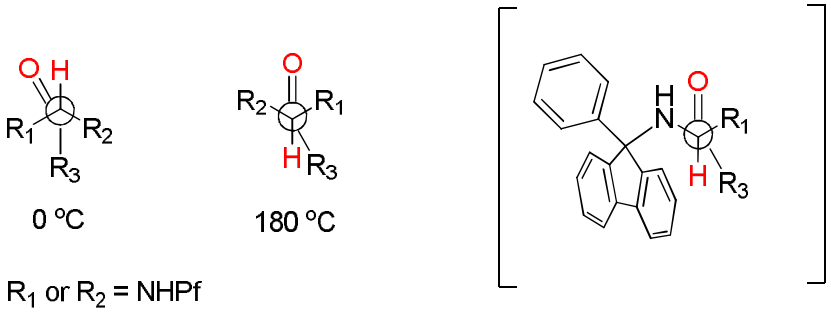
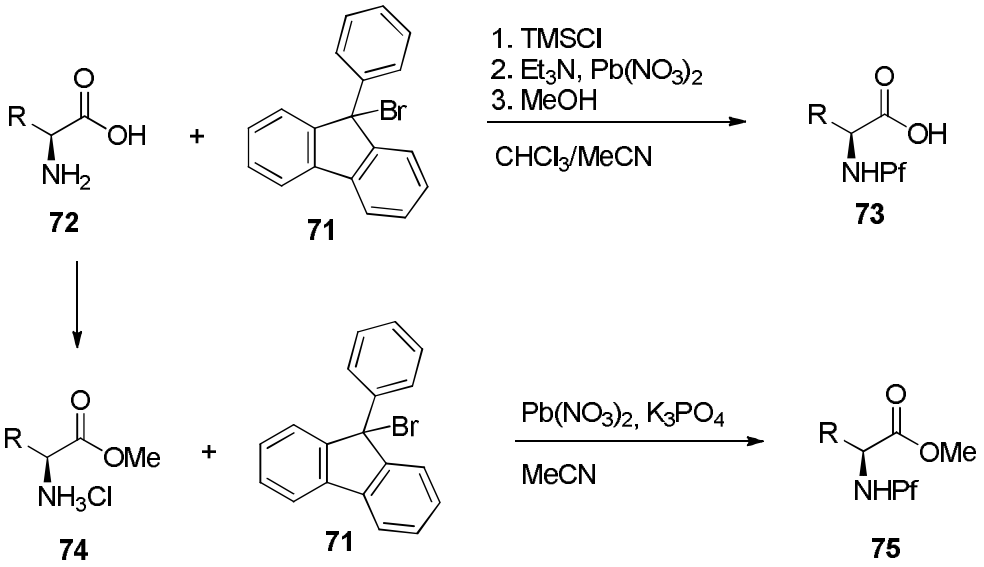


Figure 15. Dihedral angle between carbonyl oxygen and α-proton.

Pf protection is usually a high yielding reaction, performed using 9-bromo-9-phenylfluorene (PfBr, **71**, Scheme 15). The protection can be done to the amino acid **72** to form the Pf-protected amino acid **73**. However, in this case the carboxylic acid has to be temporarily protected as a TMS ether. If a methyl ester hydrochloride **74** is used, the protection to the Pf-protected amino acid methyl ester **75** is more straightforward. The leaving group ability of bromide in the reaction is enhanced by using halogenophilic lead nitrate to scavenge out the bromide ions from the solution, but nevertheless the reaction is slow and takes several days.[121]



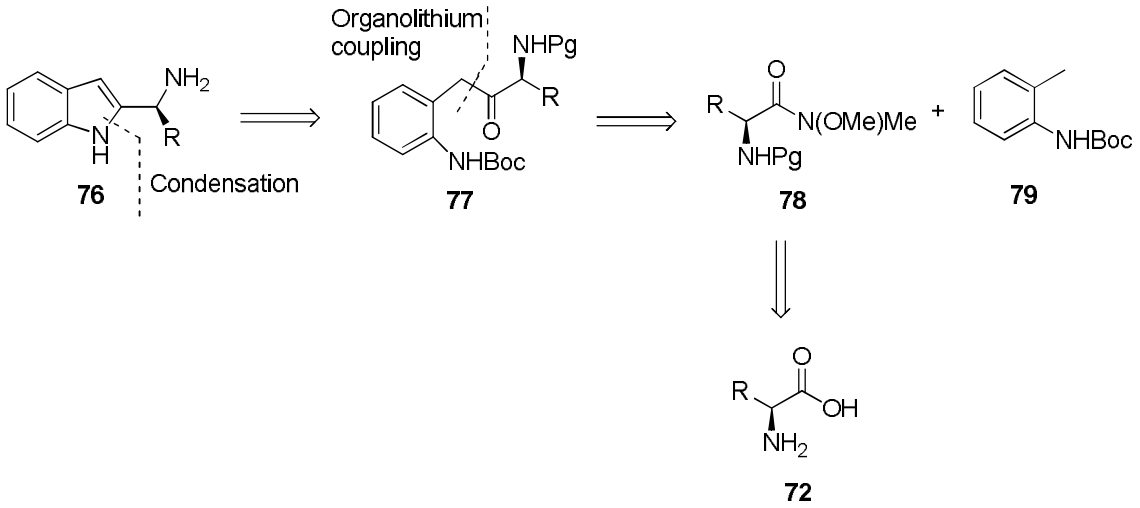
Scheme 15. Phenylfluorenylation[121].

The Pf group is usually removed by hydrogenolysis[122] or solvolysis[115] under strongly acidic conditions.

5 Research work and results

5.1 The synthesis route to open chained analogues

A novel synthetic route towards tetrahydroharmane and harmicine was recently developed in our research group.[123] This synthesis uses amino acids as starting material and also as the source of chirality in the compounds. With a slight variation to this protocol we could obtain 2-indolylamines, which would in principle constitute open-chained analogues of THβCs. A short retrosynthetic analysis shows 2-indolylamine **76** being formed by a stepwise version of the Madelung-Houlihan indolization (Scheme 16).[124] Ketone **77** could be formed by an organolithium coupling of a Weinreb amide from a corresponding amino acid **78** and a Boc-protected *o*-toluidine **79**. The Weinreb amidewas considered to be a good starting material for the organolithium coupling due to its ability to prevent over addition of the organometallic reagent to the carbonyl group with subsequent formation of the tertiary alcohols.[125] The organolithium coupling is followed by a ring closing condensation to afford the 2-indolylamines.[126]



Scheme 16. Retrosynthesis

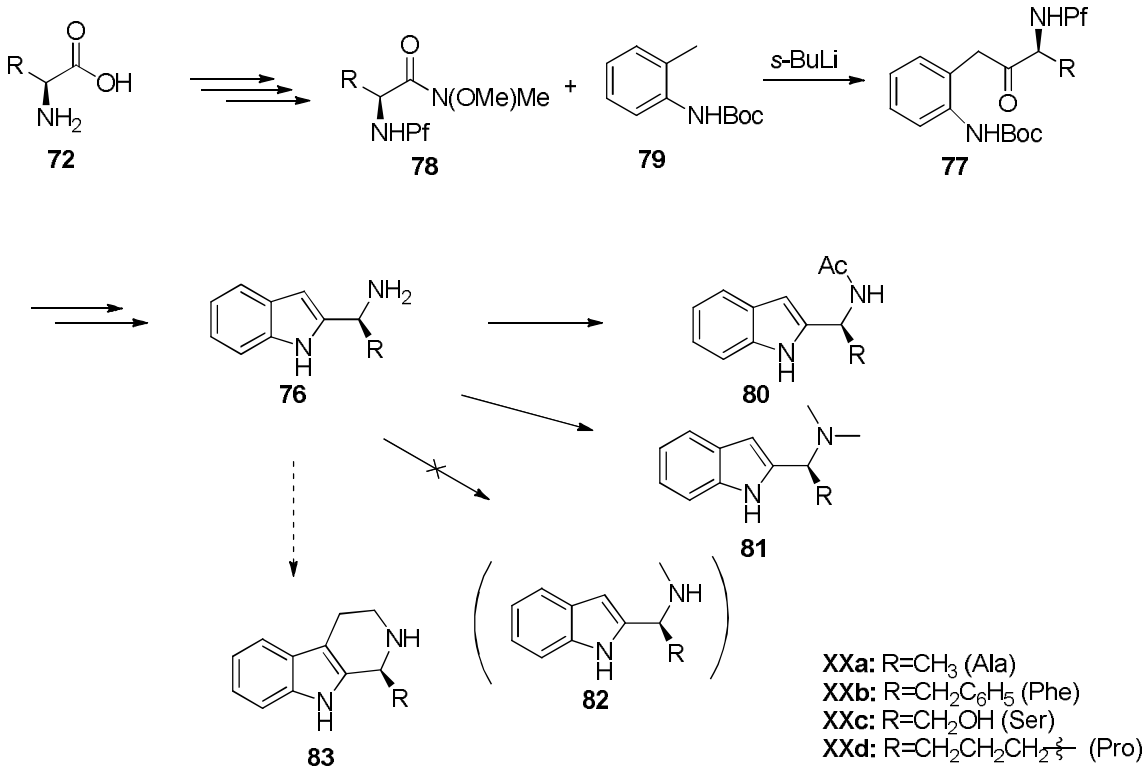
The aim of this thesis was to demonstrate the suitability of the synthetic route for different amino acids and to furthermore build a small library of open chained THβC analogues using different amino acids as starting materials (Scheme 17). This library would then be screened for biological activity. The starting material amino acids were chosen to be alanine (Ala), serine (Ser), phenylalanine (Phe) and proline (Pro). These amino acids were selected in order to achieve a good level of structural and chemical diversity in the side chain of the resulting 2-indolyl amines: Alanine being a simple amino acid

with an aliphatic side chain; serine having a hydroxyl functionality; phenylalanine containing an aromatic ring and proline being cyclic in itself brings and additional heterocycle to the product. Serine would also introduce an additional functional group, opening up the possibility for further synthetic manipulations in a later stage.

Due to the harsh basic conditions during the transformation from the amino acid to the corresponding indolylamine, the labile α- center had to be protected against epimerization. In this work, the Pf group was therefore used.

To achieve even more diversity in the library, the indolylamines were further modified by acetylating and dimethylating the reactive free amine to yield amides **80** and tertiary amines **81**, respectively. Initial aim was also to do a monomethylation reaction to yield the secondary amines **82**. However, due to the difficulties associated with a good 1-step method for monomethylation these compounds where omitted from the library.

Furthermore, this thesis and related research work in the Koskinen laboratory aims to establish a method for ring closure from the indolylamine **76** to the corresponding THβC **83**. However, due to time limitations this was not explored.



Scheme 17. Summary of the research work.

5.2 Indolylamine synthesis

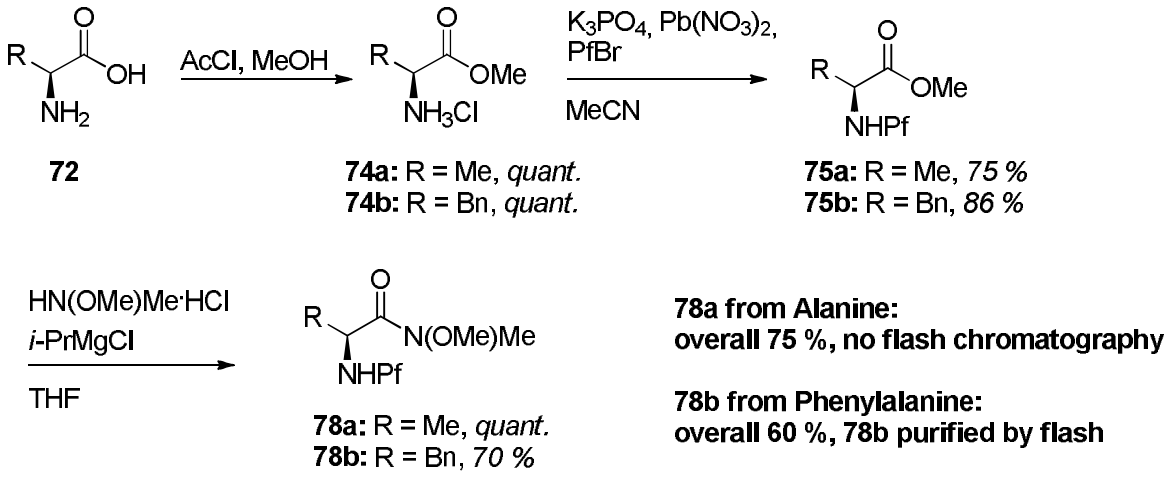
The first aim of this thesis was to test and refine the previously established synthetic route to 2-indolylamines and to show that it can be applied ta amino acids with different properties. This section summarizes the synthesis of the indolylamines.

5.2.1 Weinreb amide formation

The Weinreb amides can be formed from the corresponding amino acid in three steps (Scheme 18). This procedure can be used as such for alanine and phenylalanine and the corresponding Weinreb amides are formed with good overall yields of 75 % and 60 % respectively.

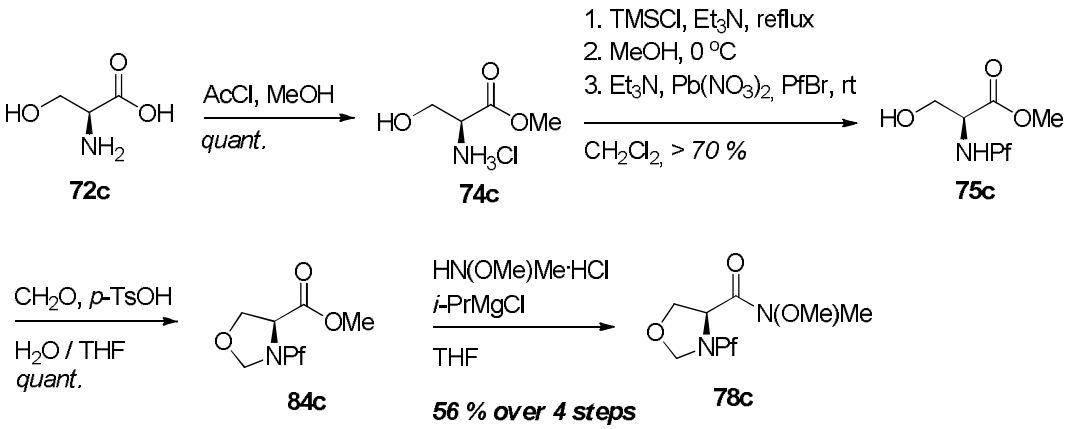
First methyl ester hydrochloric salts **74** were formed from amino acids **72** by Fischer esterification,[127] generally giving quantitative yields. The standard procedure of Pf-protection[115] uses 9-phenyl-9-fluorenyl bromide as the Pf source, K_3PO_4 as the base and $Pb(NO_3)_2$ to scavenge out the bromide ions in order to increase the rate of the reaction. The reaction took several days, but the yields were generally good, ~80 %.

The Weinreb amides **78** were formed by using a Grignard reagent as a base. Compound **78a** was formed in a quantitative yield. However, possibly due to the more bulky nature of the phenyl group in comparison to the methyl group, the reaction for the Pf-protected phenylalanine methyl ester **75b** to form the corresponding Weinreb amide **78b** was slow, required an increased amount of reagents to reach good conversion and gave only moderate yields. The Weinreb amide **78a** was prepared from alanine without the use of flash chromatography and the only purification step needed was the recrystallization of **75a,** after the Pf protection step. For the phenylalanine series a single flash purification was performed due to failures in attempting to separate the unreacted starting material **75b** from the Weinreb amide **78b** by recrystallization.



Scheme 18. The Weinreb amide formation.

For serine, the route had to be modified because of the side chain hydroxyl group (Scheme 19). In the Pf-protection, the hydroxyl group of serine methyl ester **74c** was temporarily TMS-protected *in situ* after which the 9-phenyl-9-fluorenylation could take place, to yield compound **75c.**[128] Despite the variation in the Pf-protection protocol, the Pf-protected amino acid methyl ester **75c** was obtained in a good, > 70 % yield. The free hydroxyl group was then protected as a hemiaminal. The difficulty of hemiaminal removal has limited its use in protecting group chemistry, but recently a new and simple protocol that uses hydroxylamine to trap the cleaved formaldehyde equivalent was published.[129] The hemiaminal formation to give **84c** was quantitative. The Weinreb amide **78c** was then formed using the previously reported procedure. It was possible to conduct all four steps consecutively with only one recrystallization, at the Weinreb amide, **78c,** stage. This protocol was used on a 50 mmol scale and the overall yield over 4 steps was good 56 %.



Scheme 19. Weinreb amide formation for serine.

Initially, the Weinreb amide **78d** from proline was prepared using the general synthesis (Scheme 18). However, proline being more sensitive towards epimerization, it was recognized in a related work that this protocol led to a slight diminishing of the ee in the corresponding proline methyl ester and thus modifications for the synthetic route were made. This work was not part of this thesis and is therefore not discussed in detail.

5.2.2 Step wise version of the Madelung-Houlihan indolization

The synthesis from the Weinreb amides **78** to the corresponding Pf-protected indolylamines **85** is a two-step procedure consisting of organolithium coupling[124] and indolization in acidic conditions[126]. These reaction steps were applicable for alanine, phenylalanine and proline (Scheme 20).

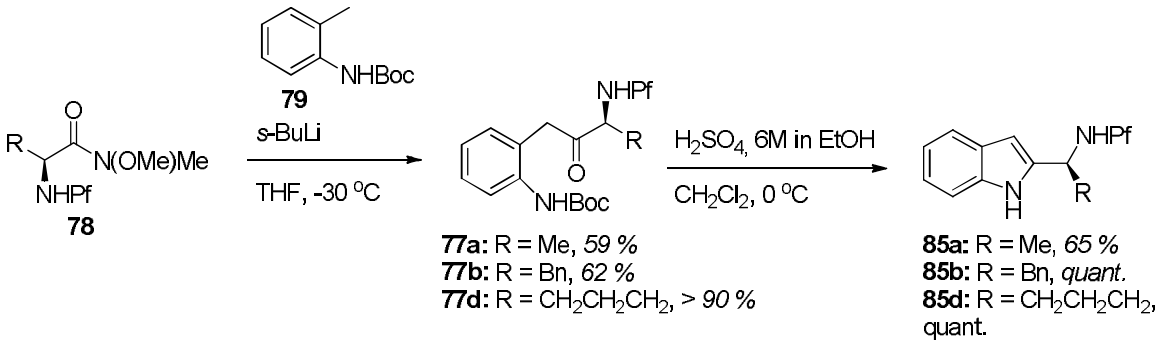
The organolithium coupling reaction brought some unexpected challenges and the yields varied for different substrates. While the reaction gave the proline ketone **77d** in consistently excellent >90 % yields, the yields of alanine and phenylalanine ketones **77a** and **77b** were moderate and inconsistent. In the alanine series the conversion of the Weinreb amide **78a** to the desired ketone **77a** was only ~60 %. ~20 % of the starting material remained unreacted and ~20 % was consumed in a side reaction. In the phenylalanine series, the conversion from the Weinreb amide **78b** to the ketone **77b** was also incomplete, 85 - 95 % and the reaction profile was not clean although no significant side products were detected.

The reaction for alanine and phenylalanine series also suffered from reproducibility issues and the yields of **77a** typically varied from 40 to 60 % and the yields of **77b** from 50 to 80 %. It is possible that the amine proton NH present in the alanine and phenylal-

anine Weinreb amides, **78a** and **78b,** but not in the proline Weinreb amide **78d** is somehow related to these outcomes. However, the role of this proton is not fully understood.

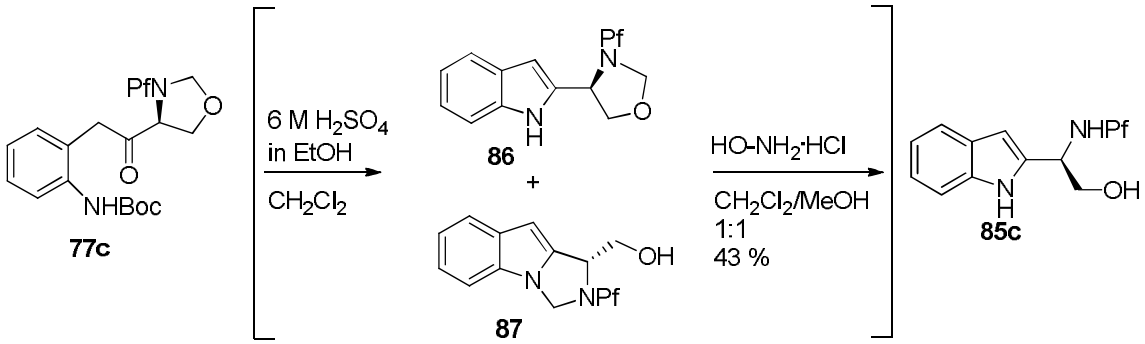
Another downside in the organolithium coupling reaction of alanine and phenylalanine series was the need for column chromatography in the purification of ketones **77a** and **77b** as their recrystallization was not successful. In contrast ketone **77d** was purified with an efficient trituration from diethyl ether.

In the indolization step, strongly acidic conditions were applied to initiate the indolization with simultaneous Boc-cleavage. The standard conditions used for the indolization step were 10 eq of 6M H_2SO_4 in EtOH. These conditions were best for the phenylalanine and proline ketones **77b** and **77d** for which the indolization step was clean, fast and gave the indolylamines **85b** and **85d** in quantitative yields. For the alanine series, the same conditions gave the Pf-protected indolylamine **85a** in moderate yields of ~ 60 %.



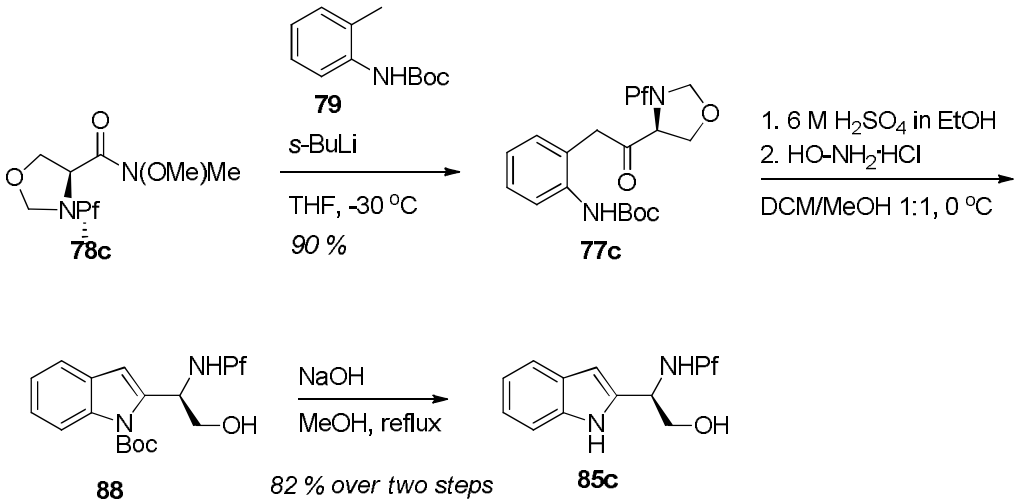
Scheme 20. The organolithium coupling and the Madelung-Houlihan indolization.

The organolithium coupling for the serine derived Weinreb amide **78c** bore much resemblance to the corresponding proline reaction, giving rise to ketone **77c** formed in excellent yields. For the ketone **77c**, the indolization conditions had to be modified due to the acid lability of the hemiaminal. When standard conditions were applied, the hemiaminal group partially cleaved from the hydroxyl group and reattached as an aminal (Scheme 21). The hemiaminal **86** and the aminal **87** were both isolated and the rearrangement was verified by 2D–NMR experiments. The aminal and the hemiaminal could both be cleaved with hydroxylamine to yield the Pf-protected indolylamine **85c**, and the whole sequence could be done in one pot, however due to the greater stability of the aminal over the hemiaminal, the cleavage reaction was slow and the yields were poor.



Scheme 21. Standard indolization and deprotection conditions for serine derived ketone 77c.

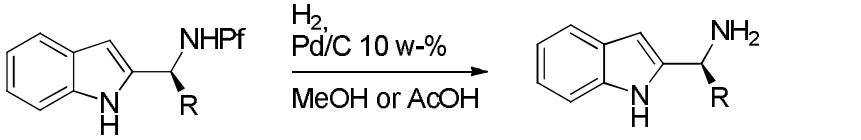
Another route was developed for the indolization of ketone **77c** (Scheme 22). It was recognized that when a 1:1 mixture of CH_2Cl_2/MeOH was used as solvent instead of CH_2Cl_2, the Boc-protecting group did not cleave and hence the rearrangement of the hemiaminal to the aminal was prevented. After the indolization, the hemiaminal cleavage was performed in the same pot to yield the Boc-protected indole **88**. Without any purification of **88**, the Boc protecting group could then be cleaved either under acidic or basic conditions. Basic conditions were proven to be superior, giving a cleaner reaction profile. The overall yield from ketone **77c** to Pf-protected indolylamine **85c** using these conditions was 82 %, which is considerably higher than the 43 % obtained using the previously designed conditions.



Scheme 22. Improved route for serine analogue.

5.2.3 Pf deprotection

The Pf cleavage from indolylamines **85** to yield the free indolylamines **76** was done by straight forward hydrogenolysis using Pd/C. The alanine derived indolylamine **85a** was deprotected in MeOH while phenylalanine and serine derived indolylamines **85b** and **85c** were deprotected in AcOH due to the lower reactivity of **85c** and the poor solubility of **85b** in MeOH. The indolylamines **76a-c** were purified by active extraction. The work up of compound **76c** was demanding due to the water solubility of the amino alcohol, requiring large amounts of extraction solvent.



85

76a: R = Me, *quant.*
76b: R = Bn, *87 %*
76c: R = CH_2OH, *95 %*
76d: R = $CH_2CH_2CH_2$, *n. d.*

Scheme 23. Pf deprotection.

Pf deprotection of the indolylamine **85d** was not possible with the same protocol. The Pf group was readily cleaved from the indolylamine. However, a mixture of two products possessing very similar NMR spectra was obtained. The products proved inseparable by flash chromatography. Trials were furthermore made by varying the work up and purification conditions and also an attempt to further acetylate the crude material was made, yielding a complicated mixture of products.

The Pf-cleavage of **85d** was the attempted under transfer hydrogenation conditions. Preliminary results from the transfer hydrogenation trials suggest that a single product was obtained. Furthermore, the transfer hydrogenation reaction could be telescoped, with an acetylation, without performing a full work up and there is also a clear indication that the acetylated indolylamine **80d** was obtained under these conditions. These compounds, however, have not been fully characterized and conclusions have been drawn based on NMR spectral data only (Appendix 23).

The enantiomeric excesses of the 2-indolylamines were not determined as a part of this thesis. This was a carefully chosen judgment due to several reasons.

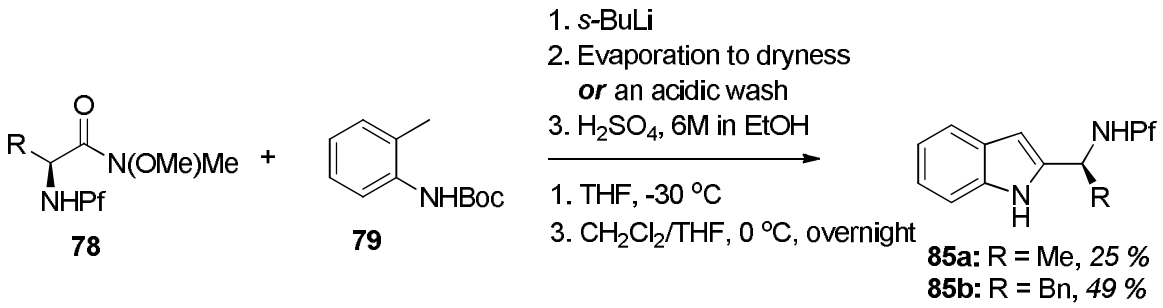
1. The synthesis of the ketone **77a** derived from alanine has been conducted in the Koskinen laboratory formerly using the exact same methods. Within that work, the corresponding THβC tetrahydroharmane was synthesized and the ee at this stage was determined by HPLC to be > 99 % Because the stereocenter is labile especially in basic conditions and only at the carbonyl stage, the organolithium coupling step would be the most likely cause of epimerization. Further manipulations used in this thesis are not likely to epimerize the stereocenter of the alanine derivative.
2. The proline ketone **77d** has also been previously been synthesized in the Koskinen laboratory. The corresponding THβC harmicine was consequently synthesized and its ee was determined to be > 99 % by HPLC. Further manipulations used in this thesis are not likely to epimerize the stereocenter of the proline derivative.
3. The phenylalanine series resembles the alanine series. Because phenylalanine has a bulkier side chain than alanine, it is less likely to epimerize.
4. The Pf-protection of serine series from **74c** to **75c** is a literature reaction. It has been reported that compounds prepared using this exact method have an ee > 99%.[128] Furthermore, after the hemiaminal protection the serine series holds high resemblance to the proline series. Thus it can be assumed that if the proline ketone **77d** is formed without epimerization, also the serine series withstands the organolithium coupling without epimerization.

5.2.4 One-pot procedure for the step wise version of the Madelung-Houlihan indolization

Aiming to improve the synthesis route, it was also studied whether the organolithium coupling and the indolization could be conducted as a one-pot reaction. As THF was the solvent used in the organolithium coupling, the indolization step was examined in THF. The indolization took place, but the reaction was considerably slower than the corresponding reaction in CH_2Cl_2. Diethyl ether was also investigated as a solvent, but the low solubility of the Weinreb amides **78a** and **78b** in ether prevented its use. A major problem upon the addition of acid, in order to facilitate the Boc-removal/ring closure, was severe gelling of the reaction mixture making stirring somewhat of a challenge. It was assumed that the gelling took place due to the presence of the N,O-

dimethoxyhydroxylamine generated in the organolithium coupling. Hence an acidic wash or evaporation to remove the distracting species was needed before addition of the acid. Both methods were tried and the results were similar (Scheme 24).

The reaction could be conducted in a one-pot procedure but the yields were poor and the reaction time of the indolization step increased considerably. For the alanine series, full conversion of ketone **77a** to indolylamine **85a** was necessary as these two compounds couldn't be separated by flash chromatography. For this reason the reaction had to be monitored by HPLC in addition to TLC. Furthermore, the one-pot reaction was not considered to be a better option for either the serine or the proline derivatives due to the easiness of purification at the ketone stage, **77c** and **77d**. Hence the organolithium coupling and the indolization were conducted as two separate steps.



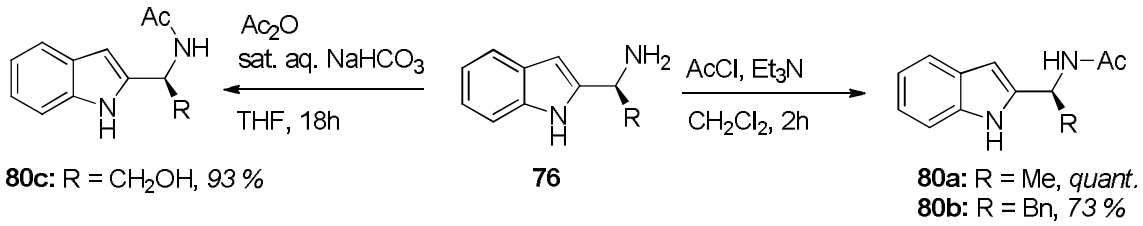
Scheme 24. Conditions for the one-pot reaction.

5.3 The library

The second aim of this thesis was to apply this newly established synthesis route to 2-indolylamines in order to build a small library of derivatives. The initial plan was to acetylate, monomethylate and dimethylate the free amine thus providing a library of a total of 11 derivatives from 4 different indolylamines (ALA, PHE, SER and PRO). However, as the synthesis of the proline derived indolylamine remained unfinished only 3 indolylamines were used to construct the following library.

The acetylation reaction (Scheme 25) for amines **76a** and **76b** was straightforward and gave good yields of the corresponding amides **80a** and **80b**. The standard acetylation of the indolylamine **76c** led to acetylation of both the amine and the hydroxyl group. How-

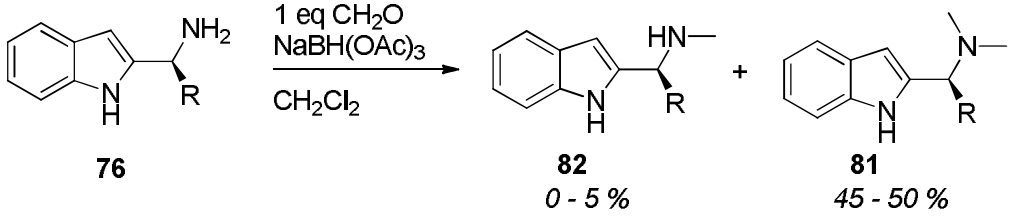
ever, when the indolylamine **76c** was reacted in a two phase system with a mildly basic aqueous phase, the ester was not formed and the amide was the sole product.



80c: R = CH_2OH, *93 %* **76** **80a:** R = Me, *quant.* **80b:** R = Bn, *73 %*

Scheme 25. Acetylation of 2-indolylamines.

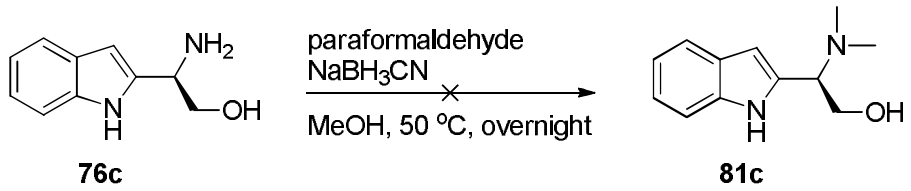
A monomethylation was attempted using a reductive amination procedure described by Abdel-Magid *et al.*[130] The procedure led selectively to the dimethylated product (Scheme 26) as could be expected, and as was also acknowledged by Abdel-Magid in a later review[131]. It would be possible to reach the monomethylated product by first forming a carbamates and then reducing it to the methyl group using LAH. However, the synthesis of the monomethylated product was not deemed necessary for this work. As a two-step procedure is heavy for the introduction of a simple methyl group, it was decided to exclude the monomethylated amines from the library.



76 **82** *0 - 5 %* **81** *45 - 50 %*

Scheme 26. Unsuccesful monomethylation procedure.

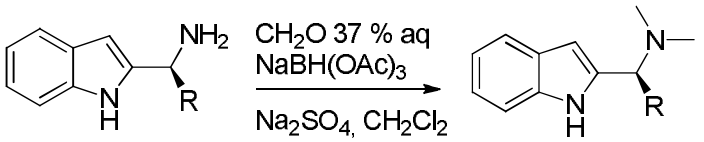
The same procedure using excess formaldehyde was tried for dimethylation. However, since formaldehyde is sold as a 37 % aqueous solution, the amount of water interfered with the reduction when more than 1 eq of formaldehyde was used. An attempt was made by using paraformaldehyde as the formaldehyde source, but the reaction did not take place (Scheme 27).



76c 81c

Scheme 27. Dimethylation with paraformaldehyde as the formaldehyde source.

Fortunately, adding a desiccant, Na_2SO_4, solved the problem of using aqueous formaldehyde solution and the reaction finally gave excellent yields providing three dimethylated products.



76

81a: R = Me, *91 %*
81b: R = Bn, *quant*
81c: R = CH_2OH, *90 %*

Scheme 28. Dimethylation of 2-indolylamines.

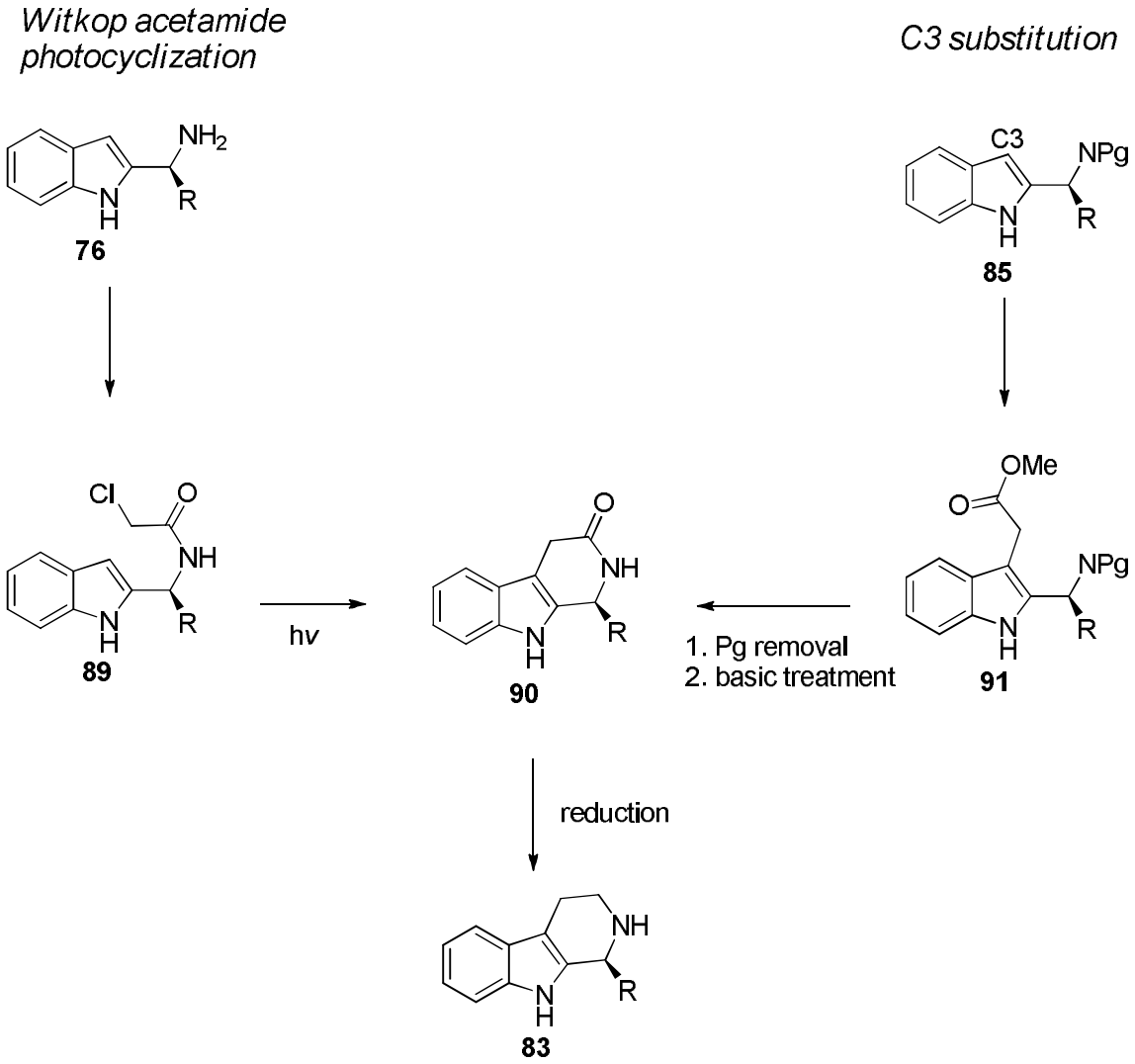
5.4 Ring-closure to THβC

Initial aim was to do a ring closure of the 2-indolylamines **76** to form the THβCs **83** as a part of this thesis. However, due to time limitations this ring closure could not be attempted.

Two approaches were considered for the ring closure (Scheme 29). The first approach is based on a Witkop chloroacetamide photocyclization.[132] Chloroacetamide **89** is formed and subjected to photolysis to yield the lactam **90** which can be further reduced to the corresponding THβC **83**. Photolytic strategies have been successfully used for similar cyclizations e. g. in the (±)-quebrachamine synthesis by Bajtos *et al.*[133], in the work of Sundberg *et al.* with catharanthine derivatives[134], in the synthesis of (-)-tubifoline, (-)-tubifolidine, and (-)-19,20-dihydroakuammicine by Amat *et al.*[135] and in the work of Bremner *et al* towards paullones[136].

The second approach is based on C3 substitution of the indole. There is evidence that a selective 3-substitution of 2-substituted indoles takes place when metalated indoles, using e.g. lithium or Grignard bases, are subjected to a suitable electrophile in the pres-

ence of $ZnCl_2$.[137, 138] In this approach the amine would be deprotected only after the C3 substitution. Deprotection of indole **91** and subsequent treatment with base induce cyclization to the lactam **90.**



Scheme 29. Ring closure from 2-indolylamines to THβCs 83.

5.5 Molecular modeling of Pf-protected amino acids

The Pf group was selected to protect the amine of the amino acids in order to prevent epimerization of the labile α-center of the substrates under basic conditions. It is well known that Pf group prevents this kind of epimerization[114-116, 139] and it has been modeled in 1993 by Paz and Sardina[119] that the Pf group forces the dihedral angle between the α-proton and the carbonyl oxygen to be ~0 ° or ~180 °, effectively lowering the acidity of the α-proton in question. As the results are still to date unpublished and no

other modeling studies have been reported, these calculations were tried and repeated and also refined using quantum mechanical (QM) methods.

The initial conformation search was attempted using different force fields. In the original calculations, Paz and Sardina most likely used either the MM2 force field[140] or the MM3 force field[141] which were designed for small molecules and were available at the time of the publication. When the conformational search for Pf-protected alanine methyl ester was repeated with either MM2 or MM3, the results resembled that what had been commented previously. However, when the quality of the results was assessed in terms of the quality of the force field parameters, these force fields did not perform well. The conformational searches where repeated with two later developed force fields, the Merck Molecular Force Field (MMFF)[142] and the OPLS2005 force field[143]. For each search, the quality of stretch parameters, bend parameters and torsional parameters is determined and the accuracy of the search is indicated especially by the quality of the torsional parameters. OPLS 2005 performed best with no low quality torsional parameters for neither of the searched molecules. It is presumed that the reason for the low performance of MM2 and MM3 force fields is that they have been designed especially for hydrocarbons with no or scarcely spaced functional groups. As the modeled compounds have an amino group and an ester group in close proximity, it seems to greatly affect the performance, ultimately rendering them unsuitable for these specific calculations.

The conformational search was refined using QM-methods to give the lowest energy conformation which was then further investigated by modeling the rotational energies of the α-C – carbonyl C bond. For the QM calculations Jaguar 8.0 was used.[144] In the conformational search the scf type used was DFT=M06-2X[145] and the basis set was 6-31G**++. In the coordinate scan the scf type used was DFT=B3LYP[146-148] and the basis set was 6-31G**. C1 point group was used. The calculations where performed in gas phase, without the use of any solvent models. The change of the energy of the studied compounds as the function of the dihedral angle between the α-proton and the carbonyl oxygen was plotted (Figure 16).

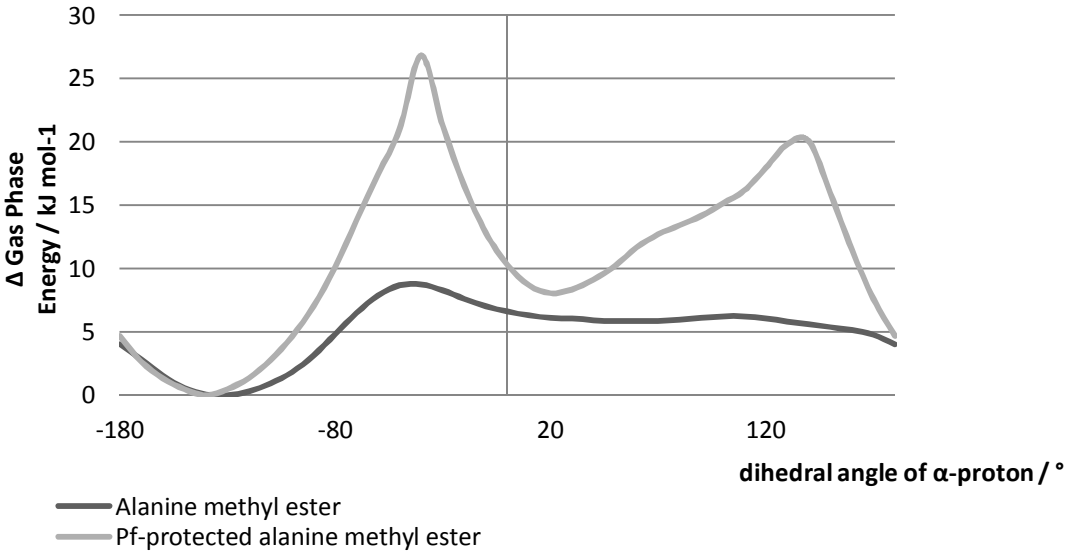


Figure 16. The change in the gas phase energy of the compound against the rotation of the α-C – carbonyl C bond.

The Pf protection highly restricts the rotation of the bond. However, these results do not meet the previously reported results with the minimum energy conformations having dihedral angles of ~ 0 ° or ~ 180 °. According to the QM-refined conformational search executed with the OPLS 2005 force field, the global minimum conformation has a dihedral angle of ~ -140 ° (Figure 17) and the local minimum conformation has a dihedral angel of ~ 20 °. Even though these results are not the same as previously reported, they still support the same reasoning for the epimerization preventing action of the Pf group. The energy barrier to reach the -90 ° dihedral angle from the global minimum is 3.1 kJ/mol for an unprotected alanine methyl ester (**74a**) and 7.0 kJ/mol for the Pf-protected alanine methyl ester **75a**). Thus the rotational barrier is over twice as high when Pf protection is used. Furthermore, the Pf group also prevents spontaneous rotation from a global minimum conformation to a local minimum as the highest energy conformations are very unfavorable and the rotational barrier is 20,0 or 26,9 kJ/mol.

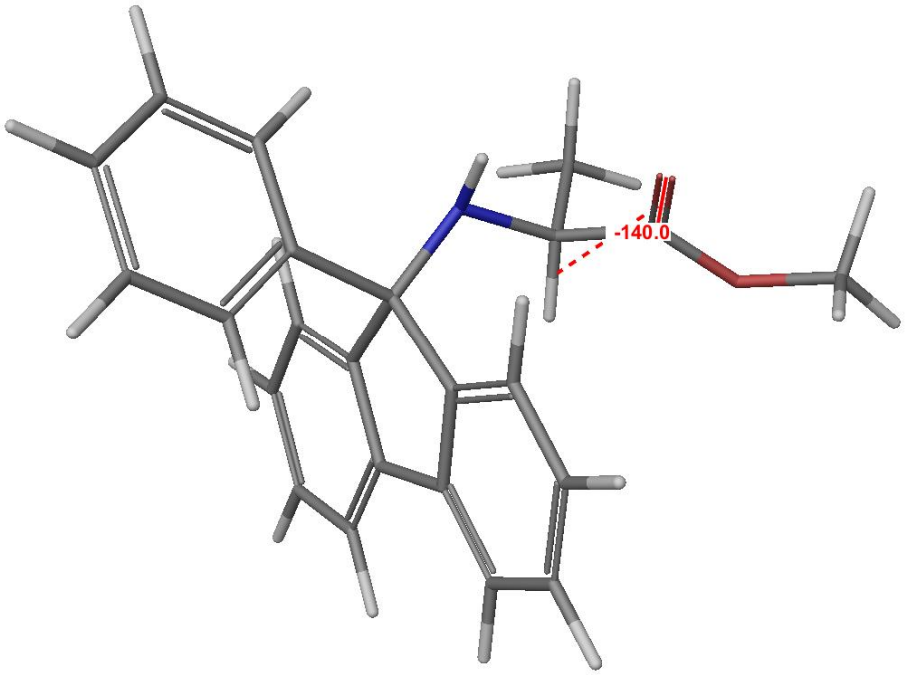


Figure 17. Modeled conformation of (S)-methyl-2-((9-phenyl-9H-fluoren-9-yl)amino)propanoate 75a in the conformation with lowest energy dihedral angle (-140 °).

In our laboratory, we have also managed to obtained crystal structures of Pf-protected amino acids.[149] Surprisingly, the dihedral angle between α-proton and carbonyl oxygen (O2 and H(1)) estimated from the crystal structure is 119.6 ° (Figure 18). This is very close to the modeled -140 ° and does not correlate to the calculations by Paz and Sardina. The crystal structure, however, does not necessarily resemble the conformation of the molecule in solvent phase or gas phase.

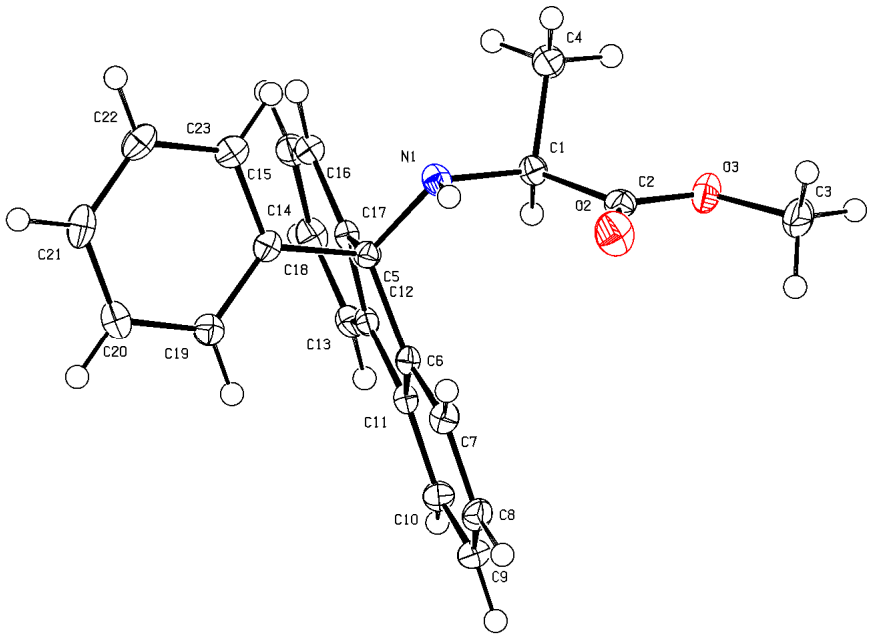
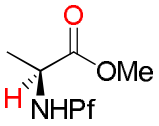
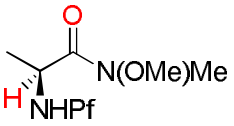


Figure 18. Crystal structure of (S)-methyl-2-((9-phenyl-9H-fluoren-9-yl)amino)propanoate 75a has the dihedral angle – 119.6 °.

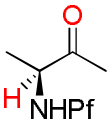
Furthermore, crystal structures obtained for similar molecules, namely the alanine derived Weinreb amide **78a** and a related methyl ketone **92**, also have dihedral angles of -120 ° – -140 °[149]. Thus it seems evident that the calculations conducted within this work challenge the previously reported calculations by Paz and Sardina and moreover are strongly supported by the crystal structures obtained in our laboratory.



75a



78a



92

Figure 19. According to the crystal structure analysis, the dihedral angles between the α-hydrogen and the carbonyl oxygen for compounds 75a, 78a and 92 are -119.6 °, -146.5 ° and -147.5 °, respectively.

6 Conclusions

Syntheses of three 2-indolylamines that are analogous to THβCs were completed. The overall yield for the 2-indolylamines synthesized from alanine, phenylalanine and serine were 26 %, 37 % and 39 %, respectively. Furthermore, a library of 6 derivatives was established.

The synthesis of the proline derived 2-indolylamine was not completed as Pf cleavage was not possible using the protocol used with other indolylamines. The Pf-protected 2-indolylamine from proline was synthesized with 51 % overall yield. Preliminary results from transfer hydrogenation trials indicated that the deprotection was accomplished. Moreover, the reaction may be telescoped straight to the acetylated product. These experiments will be completed in due course at the Koskinen laboratory.

This thesis clearly demonstrated that the synthetic route is applicable to a range of amino acids. In addition to alanine, phenylalanine, serine and proline, this synthesis can most likely be expanded to include any aliphatic amino acid, such as valine or leucine, without further modifications. In cases where the amino acid contains a side chain functionality, the synthesis route most likely have to be modified to include additional protection and deprotection steps, as demonstrated with serine. These steps can be easily included in the synthesis without additional loss of material. On the contrary, carrying out this synthetic work also demonstrated flaws in the synthetic route. We still lack full understanding of the organolithium coupling reaction. It is not understood how the choice of the starting material affects the reaction and why the outcomes are inconsistent. A better understanding of this reaction would increase the reliability of the developed route. Furthermore, the Weinreb amide formation and the condensation step also posed some inconsistent results. Nevertheless, these steps were in general reasonably reliable.

A library of 2-indolylamines was decided to establish due to the lack of biological evaluation of 2-indolylamines. Within the work of this thesis, a library of 6 compounds was accomplished by acetylating and dimethylating the synthesized 2-indolylamines. In the subsequent work that will be conducted in the Koskinen laboratory, the library will be extended and subjected to biological evaluation. Furthermore, attempts will be made to complete the ring closure of the third ring to obtain the THβC structure. Evidence exist

that such ring closure should be possible either by chloroacetamide photocyclization or by substitution of suitable electrophile to indole C3.

The results of this study support the previous results obtained in this laboratory providing a novel chiral pool approach to chiral THβCs. In addition, these results demonstrate that this synthetic route readily provides access to chiral 2-indolylamines. The results also add to the growing body of knowledge regarding the use of Pf chemistry in the asymmetric synthesis.

7 Experimental

7.1 General

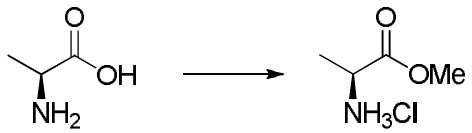
All moisture sensitive reactions were conducted under dry conditions. Dry CH_2Cl_2, MeCN and THF were obtained from a solvent drying system (MB SPS-800). Other solvents used in reactions or chromatography were p.a. quality. MeCN for HPLC were HPLC grade solvent.

Reagents were obtained from TCI, Sigma Aldrich or Acros and used as such unless otherwise specified. s-BuLi was titrated internally in the lithiation reaction, which was possible due to the color change of the solution, from the colorless mono anion to bright yellow dianion, when the amount of *s*-Buli was equal to the amount of *N*-Boctoluidine. Reactions were monitored by TLC analysis (Merck silica gel 60 F_{254}, 230 – 400 mesh, aluminum) and the plates were visualized by UV light (λ = 254 nm) and standard vanillin and ninhydrin solutions. In addition, reactions were followed by HPLC equipped with a reversed phase C18 Kinetex column from supplied by Phenomenex, a Waters 501 pump and a Waters 2478 dual absorbance detector when so specified. The NMR spectra were recorded with a Bruker Advance DPX-400 Spectrometer (^{1}H 399.98 MHz, ^{13}C 100.59 MHz). The chemical shifts are reported in ppm relative to TMS internal standard (δ = 0 ppm) or to residual solvent signal (^{1}H: CD_3CN 1.94, ^{13}C NMR: $CDCl_3$ 77.0, MeOD-d_4 49.0). In flash column chromatography, Merck Silica Gel 60–silica gel was used. HRMS were recorded using a Waters Micromass LCT Premier (ESI) mass spectrometer or with Waters SYNAPT-g2 (ESI) mass spectrometer. Optical rotations were measured with a Perkin-Elmer 343 polarimeter equipped with a Na-lamp (λ = 589 nm) and a 1 dm cuvette. FTIR spectra were recorded with a Bruker Alpha FTIR Eco-ATR spectrometer.

7.2 Synthesis of the indolylamine 76a derived from alanine

Compounds **74a**, **75a**, **77a** and **78a** have previously been prepared and fully characterized in this laboratory using exactly same methods and thus their identification within this work was based on ^{1}H-NMR data only.

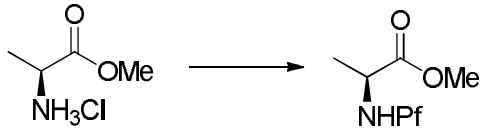
(S)-Alanine methyl ester hydrochloride (74a)



MeOH (240 mL) was cooled down to 0 °C after which freshly distilled AcCl (47.9 mL, 673 mmol, 200 mol-%) was added drop wise. The reaction mixture was stirred at 0 °C for 15 minutes and let warm to r. t. Alanine (30 g, 337 mmol, 100 mol-%) was added and the reaction was stirred at r. t. for 18 h. Solvents were evaporated to yield a white solid. The crude product was triturated from MTBE to give 47.0 g (quant.) of a white solid.

^{1}H-NMR ($CDCl_3$) δ = 8.76 (br. s, 3 H) 4.25 - 4.30 (q, *J* = 7.3 Hz, 1 H), 3.82 (s, 3 H) 1.74 (d, *J* = 7.3 Hz, 3 H)

(S)-methyl-2-((9-phenyl-9H-fluoren-9-yl)amino)propanoate (75a)

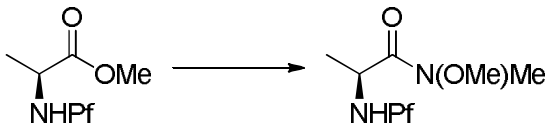


74a (14.6 g, 105 mmol, 100 mol-%) was dissolved in MeCN (400 mL) in a Morton flask. K_3PO_4 (46.1 g, 220 mmol, 210 mol-%), $Pb(NO_3)_2$ (29.4 g, 89 mmol, 85 mol-%) and PfBr (42.4 g, 131 mmol, 125 mol-%) were added. The suspension was stirred vigorously at r. t. for 40 h. MeOH (40 mL) was added and the reaction mixture was stirred for 30 min. The suspension was filtered through a pad of celite which was eluated with $CHCl_3$ until no chromophore could be observed. Solvents were evaporated and the residue was dissolved in Et_2O (400 mL). The solution was washed with H_2O (300 mL) and the aqueous phase was extracted with Et_2O (2 x 200 mL). Combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvents were evaporated to give a brown syrup. Recrystallized from MeOH yielded 22,4 g (62 %) of beige powder.

R_f: 0.45 (25 % EtOAc/Hex, UV, ninhydrin)

^{1}H-NMR ($CDCl_3$) δ = 7.20 - 7.70 (m, 13 H), 3.30 (s, 3 H), 2.96 (br. s, 1H), 2.78 (q, *J* = 7.0 Hz, 1 H), 1.12 (d, *J* = 7.1 Hz, 3 H)

(S)-N-methoxy-N-methyl-2-((9-phenyl-9H-fluoren-9-yl)amino)propanamide (78a)

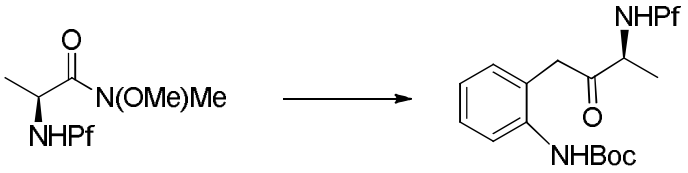


75a (22.1 g, 64 mmol, 100 mol-%) and HN(OMe)Me·HCl (7.5 g, 77 mmol, 120 mol-%) were suspensed in THF (80 mL). The suspension was cooled down to 0 °C and *i*-PrMgCl (77 mL, 154 mmol, 2M in Et_2O, 240 mol-%) was added drop wise via a dropping funnel. The reaction was stirred at 0 °C for 3 h. before being quenched with citric acid (200 mL, 5 w-%). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 150 mL). Combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvents were evaporated to give 23.9 g (quant.) of a pale yellow solid.

R_f: 0.18 (25 % EtOAc/Hex, UV)

^{1}H-NMR ($CDCl_3$) δ = 7.65 (d, *J* = 7.3 Hz, 2 H), 7.40 – 7.46 (m, 3H), 7.15 - 7.33 (m, 8 H), 3.57 (br. s, 1 H), 2.86 - 2.93 (br. m, 7 H), 1.06 (d, *J* = 7.0 Hz, 3 H)

(S)-tert-butyl(2-(2-oxo-3-((9-phenyl-9H-fluoren-9-yl)amino)butyl)phenyl)carbamate (77a)



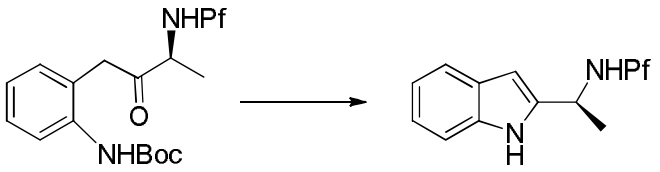
N-Boc-*o*-toluidine (4.17 g, 20.1 mmol, 250 mol-%) was dissolved in THF (50 mL) and cooled down to -30 °C. s-BuLi (30.0 mL, 40.2 mmol, 1.34 M in Et_2O, 500 mol-%) was added drop wise. The reaction was stirred at – 30 °C for 45 min. **78a** (3.0 g, 8.5 mmol, 100 mol-%) in THF (10 mL) was added and the reaction was stirred 30 min. The reaction was quenched at – 30 °C with sat. NH_4Cl (10 mL), let warm to r. t. and H_2O (10

mL) was added to dissolve the precipitated LiCl. The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvents were evaporated to yield a yellow syrup. The crude product was purified by silica gel column chromatography (10 % EtOAc/Hex) to yield 2.6 g (59 %) of white foam.

R_f: 0.47 (25 % EtOAc/Hex, UV, vanillin)

^{1}H-NMR ($CDCl_3$) δ = 7.63 - 7.70 (m, 3 H), 7.13 - 7.41 (m, 11 H), 7.08 (m, 1 H), 6.90 (dt, *J* = 7.5 Hz, 1.3 Hz, 1 H), 6.67 (dd, *J* = 7.6 Hz, 1.4 Hz, 1 H), 3.30 (d, *J* = 15.4 Hz, 1 H), 2.96 (d, *J* = 15.4 Hz, 1 H), 2.86 (q, *J* = 7.1 Hz, 1 H), 1.53 (s, 9 H), 1.03 (d, *J* = 7.1 Hz, 3 H)

(S)-N-(1-(1H-indol-2-yl)ethyl)-9-phenyl-9H-fluoren-9-amine (85a)



77a (3.27 g, 6.3 mmol, 100 mol-%) was dissolved in CH_2Cl_2 (70 mL) and cooled to 0 °C. H_2SO_4 (10,5 mL, 63 mmol, 6 M in EtOH, 1000 mol-%) was added and the reaction mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with sat. $NaHCO_3$ (300 mL) causing vigorous gas evolution and the aqueous layer was extracted with CH_2Cl_2 (2 x 150 mL). Combined organic layers were dried over Na_2SO_4 and filtered. The solvents were evaporated to give a reddish foam. The crude product was purified by flash column chromatography (10 % EtOAc/Hex) to yield 1.65 g (65 %) of white foam.

R_f: 0.47 (17 % EtOAc/Hex, UV, ninhydrin)

$[\alpha]_D$ = -195.5 (*c* = 1.1, CH_2Cl_2)

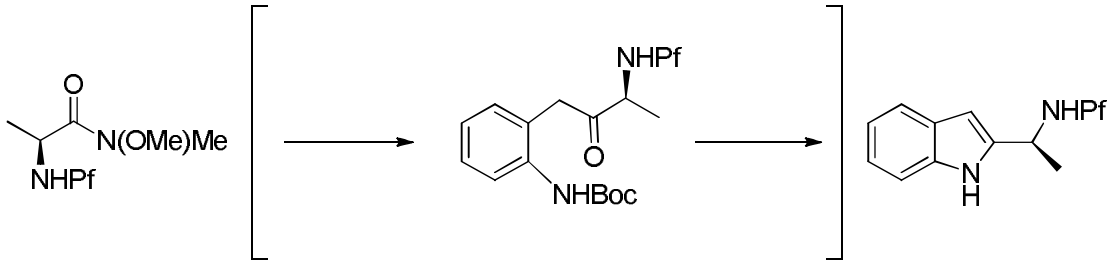
^{1}H-NMR ($CDCl_3$) δ = 8.05 (br. s, 1 H), 7.74 (m, 1 H), 7.64 (m, 1 H), 7.16 - 7.46 (m, 11 H), 7.04 - 7.10 (m, 2 H), 6.99 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1 H), 6.88 (dt, *J* = 7.5, 1.1 Hz, 1 H), 5.82 - 5.93 (m, 1 H), 3.47 (q, *J* = 6.8 Hz, 1 H), 1.17 (d, *J* = 6.8 Hz, 3 H)

^{13}C-NMR ($CDCl_3$) δ = 150.2, 149.0, 144.9, 144.1, 141.0, 139.9, 135.1, 128.7, 128.4, 128.3, 128.1, 127.9, 127.5, 127.2, 126.0, 125.1, 124.8, 120.9, 120.0, 119.9, 119.9, 119.3, 110.5, 97.7, 73.1, 46.8, 24.0

HRMS (ESI): found 401.2014 ($M + H^+$) **calculated** 401.2018 ($C_{29}H_{24}N_2 + H$)

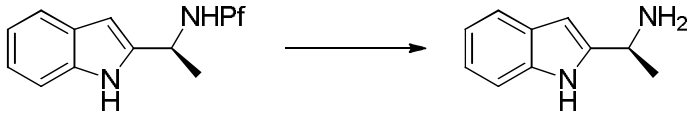
IR υ = 3429, 3057, 2966, 2867, 1616, 1599, 1449, 1295, 1156, 907, 732 cm^{-1} (film)

One-pot procedure for the step wise version of the Madelung-Houlihan indolization



N-Boc-*o*-toluidine (410 mg, 2 mmol, 200 mol-%) was dissolved in THF (5 mL) and cooled down to -30 °C. s-BuLi (3.0 mL, 4 mmol, 1.4 M in Et_2O, 400 mol-%) was added drop wise. Internal titration point at which solution turns from colorless to yellow was at 1.5 mL. The reaction was stirred at – 30 °C for 45 min. Compound **78a** (370 mg, 1 mmol, 100 mol-%) in THF (2 mL) was added and the reaction was stirred for 30 min. The reaction was quenched at – 30 °C with 2-propanol (0.4 mL) and the solvents were evaporated. The residue was dissolved in CH_2Cl_2 (10 mL) and cooled down to 0 °C. H_2SO_4 (1.7 mL, 10 mmol, 6 M in EtOH, 1000 mol-%) was added and the reaction mixture was stirred at 0 °C for 18 h. The reaction was monitored by HPLC (77 % $MeCN/H_2O$) due to the difficulty of distinguishing compounds **77a** and **85a** on TLC. The reaction was quenched with sat. $NaHCO_3$ (30 mL) and aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL) Combined organic layers were dried over Na_2SO_4 and filtered. The solvents were evaporated giving a brown syrup. The crude product was purified by silica gel column chromatography (10 % EtOAc/Hex) to yield 100 mg (25 %) of white foam.

(S)-1-(1H-indol-2-yl)ethanamine (76a)



85a (400 mg, 1 mmol, 100 mol-%) was dissolved in MeOH (8 mL) and the solution was degassed with argon. Pd/C (45 mg, 0.05 mmol, 10 w-%, 5 mol-%) was added and hydrogen atmosphere (1 atm) was introduced and the reaction was stirred for 18 h. at r. t. The reaction mixture was filtered through a pad of celite and the solvents were evaporated. The residue was partitioned between HCl (50 mL, aq. 1M) and Et_2O (100 mL). The organic layer was extracted with HCl (50 mL, aq. 1M). The combined aqueous phases were basified with NaOH (aq. 1M) until pH > 8. The aqueous phase was extracted with Et_2O (3 x 100 mL). Combined organic layers were dried over Na_2SO_4 and filtered. The solvents were evaporated to give 160 mg (quant.) of yellowish solid. No further purification was necessary.

$[\alpha]_D$ = 4.3 (*c* = 1.3, CH_2Cl_2)

^{1}H-NMR (CD_3OD) δ = 8.52 (br. s, 1 H), 7.55 (m, 1 H), 7.34 (app. dq, *J* = 8.1, 0.7 Hz, 1 H), 7.14 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1 H), 7.07 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1 H), 6.30 (m, 1 H), 4.33 (q, *J* = 6.6 Hz, 1 H), 1.52 (d, *J* = 6.6 Hz, 3H)

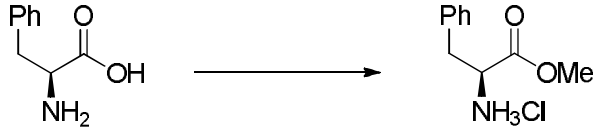
^{13}C-NMR ($CDCl_3$) δ = 144.1, 135.6, 128.5, 121.4, 120.1, 119.6, 110.7, 97.7, 45.3, 24.9

HRMS (ESI): found 161.1078 ($M + H^+$) **calculated** 161.1079 (**$C_{10}H_{12}N_2$** + H)

IR υ = 3600, 3398, 3150-3350 (br.), 3050, 2969, 2869, 1587, 1457, 1341, 1302, 943, 789, 751 cm^{-1} (film)

7.3 Synthesis of the indolylamine 76b derived from phenylalanine

(*S*)-Phenylalanine methyl ester hydrochloride (74b)



Compound **74b** was prepared using the same procedure as compound **74a**. The crude product was triturated from Et_2O to yield 34.1 g (quant.) of light green solid.

$[\alpha]_D$ = 32.4 (*c* = 1.0, MeOH)

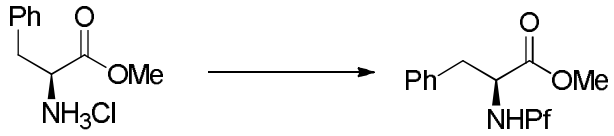
^{1}H-NMR (CD_3OD) δ = 7.26 - 7.39 (m, 5 H), 4.33 (dd, *J* = 7.2, 6.3 Hz, 1 H), 3.80 (s, 3 H), 3.27 (dd, *J* = 14.3, 6.2 Hz, 1 H), 3.19 (dd, *J* = 14.3, 7.1 Hz, 1 H)

^{13}C-NMR (CD_3OD) δ = 170.4, 135.3, 130.4, 130.2, 128.9, 55.2, 53.6, 37.4

HRMS (ESI): found 202.0841 ($M + Na^+ - Cl^-$) **calculated** 202.0844 (**$C_{10}H_{13}NO_2$** + Na)

IR υ = 3383 (br.), 3030, 2956, 2893, 1735, 1604, 1497, 1226, 670 cm^{-1} (film)

(S)-Methyl-3-phenyl-2-((9-phenyl-9H-fluoren-9-yl)amino)propanoate (75b)



Compound **75b** was prepared using the same procedure as compound **75a**. The crude product was recrystallized from EtOH to yield 36.2 g (86 %) of white crystals.

R_f: 0.53 (25 % EtOAc/Hex, UV, ninhydrin)

$[\alpha]_D$ = -206.7 (*c* = 1.2, CH_2Cl_2)

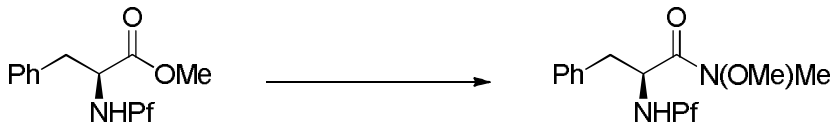
^{1}H-NMR ($CDCl_3$) δ = 7.66 (m, 1 H), 7.61 (m, 1 H), 7.31 - 7.36 (m, 3 H), 7.14 - 7.28 (m, 9 H), 7.02 - 7.07 (m, 2 H), 6.96 (dt, *J* = 7.5, 1.1 Hz, 1 H), 6.63 (m, 1 H), 3.20 (s, 3 H), 2.64 - 2.92 (m, 4 H)

^{13}C-NMR ($CDCl_3$) δ = 176.2, 148.6, 148.5, 144.6, 141.0, 140.0, 137.6, 129.7, 128.2, 128.2, 128.1, 128.0, 127.8, 127.2, 127.1, 126.4, 126.2, 126.1, 125.0, 119.8, 119.6, 72.9, 57.5, 51.4, 41.4

HRMS (ESI): found 442.1780 ($M + Na^+$) **calculated** 442.1783 (**$C_{29}H_{25}NO_2$** + Na)

IR υ = 3312, 3061, 3028, 2948, 1733, 1449, 1169, 733, 698 cm^{-1} (film)

(S)-N-methoxy-N-methyl-3-phenyl-2-((9-phenyl-9H-fluoren-9-yl)amino)propanamide (78b)



75b (804 mg, 2 mmol, 100 mol-%) and HN(OMe)Me·HCl (234 mg, 2.4 mmol, 120 mol-%) were suspensed in THF (2.4 mL). The suspension was cooled down to 0 °C and *i*-PrMgCl (2.4 mL, 4.8 mmol, 2M in Et_2O, 240 mol-%) was added drop wise via a dropping funnel. The reaction was stirred at 0 °C for 1 h and at r. t. for 3 h. The reaction mixture was cooled down to 0 °C and HN(OMe)Me·HCl (234 mg, 2.4 mmol, 120 mol-%) and i-PrMgCl (2.4 mL, 4.8 mmol, 2M in Et_2O, 240 mol-%) were added. The reaction mixture stirred at r. t. for 3 h. The reaction was quenched with citric acid (10 mL, 5 w-%) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 10 mL). Combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvents were evaporated to give a yellow foam. The crude product was purified by silica gel column chromatography (17 % EtOAc/Hex) to yield 700 mg (70%) of white foam.

R_f: 0.27 (17 % EtOAc/Hex, UV)

$[\alpha]_D$ = -224.4 (*c* = 1.1, CH_2Cl_2)

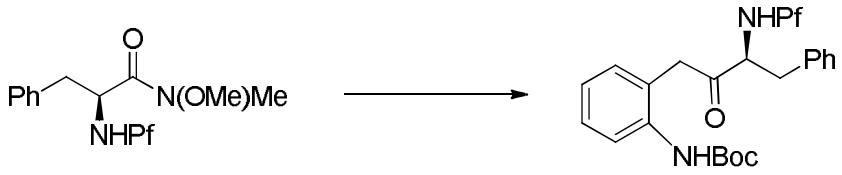
^{1}H-NMR ($CDCl_3$) δ = 7.69 (d, *J* = 7.3 Hz, 1 H), 7.51 (d, *J* = 7.5 Hz, 1 H), 7.34 - 7.04 (m, 14 H), 6.77 (t, *J* = 7.4 Hz, 1 H), 6.40 (d, *J* = 7.3 Hz, 1 H), 3.38 (br. s, 1 H), 3.01 (br. m, 1 H), 2.81 (s, 3 H), 2.85 (s, 3 H), 2.47 - 2.71 (m, 2 H)

^{13}C-NMR ($CDCl_3$) δ = 176.0, 149.2, 148.8, 145.2, 141.3, 139.2, 138.8, 130.1, 128.0, 128.0, 127.9, 127.8, 127.5, 127.1, 126.9, 126.0, 126.0, 125.3, 119.3, 118.9, 73.0, 60.2, 54.4, 41.4, 31.8

HRMS (ESI): found 471.2048 ($M + Na^+$) **calculated** 471.2048 (**$C_{30}H_{28}N_2O_2$** + Na)

IR υ = 3296, 3061, 3027, 2936, 1655, 1449, 1178, 909, 732, 698 cm^{-1} (film)

(S)-tert-butyl(2-(2-oxo-4-phenyl-3-((9-phenyl-9H-fluoren-9-yl)amino)butyl)phenyl)carbamates (77b)



Compound **77b** was prepared using the same procedure as compound **77a**. The crude product was purified by silica gel column chromatography (6 % EtOAc/Hex) to yield 1.25 g (62 %) of white foam.

R_f: 0.57 (17 % EtOAc/Hex, UV, vanillin)

$[\alpha]_D$ = -146.7 (*c* = 1.2, CH_2Cl_2)

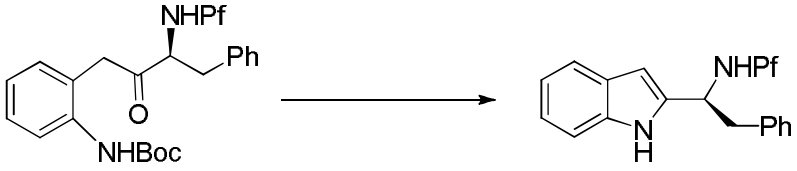
^{1}H-NMR ($CDCl_3$) δ = 7.64 - 7.67 (m, 3 H), 7.17 - 7.37 (m, 12 H), 7.02 - 7.09 (m, 2 H), 6.96 (dt, *J* = 7.5, 1.1 Hz, 1 H), 6.84 - 6.92 (m, 3 H), 6.64 (m, 1 H), 6.48 (dd, *J* = 7.6, 1.4 Hz, 1 H), 3.20 (br. s, 1 H), 2.99 (d, *J* = 15.9 Hz, 1 H), 2.93 (dd, *J* = 7.6, 5.8 Hz, 1 H), 2.73 (d, *J* = 15.9 Hz, 1 H), 2.56 (dd, J = 13.6, 5.9 Hz, 1H), 2.51 (dd, J = 13.6, 8.3, 1H), 1.53 (s, 9 H)

^{13}C-NMR ($CDCl_3$) δ = 213.3, 153.4, 149.1, 148.8, 144.2, 141.1, 139.7, 137.2, 137.1, 130.6, 129.6, 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.2, 126.6, 126.5, 126.1, 125.1, 123.9, 123.4, 119.8, 119.6, 119.5, 80.2, 72.9, 62.8, 45.2, 40.5, 28.4

HRMS (ESI): found 595.2967 ($M + H^+$) **calculated** 595.2961 (**$C_{40}H_{38}N_2O_3$** + H)

IR υ = 3311, 6062, 3027, 2978, 2930, 1716, 1450, 1155, 908, 732, 699 cm^{-1} (film)

(S)-N-(1-(1H-indol-2-yl)-2-phenylethyl)-9-phenyl-9H-fluoren-9-amine (85b)



Compound **85b** was prepared using the same procedure as compound **85a.** The crude yield was 710 mg (quant) of yellow solid, which was used in the next step without further purification.

R_f: 0.38 (10 % EtOAc/Hex, UV, ninhydrin)

$[\alpha]_D$ = -127.9 (*c* = 1.1, CH_2Cl_2)

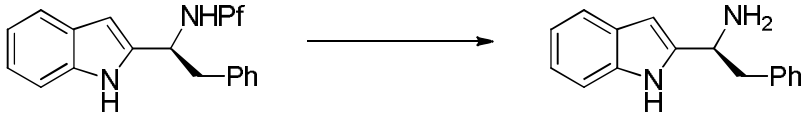
^{1}H-NMR ($CDCl_3$) δ = 7.86 (br. s, 1 H), 7.70 (d, *J* = 7.5 Hz, 1 H), 7.55 (d, *J* = 7.7 Hz, 1 H), 7.31 - 7.38 (m, 4 H), 7.15 - 7.21 (m, 7 H), 7.96 - 6.09 (m, 4 H), 6.85 - 6.92 (m, 2 H), 6.74 (d, *J* = 7.7 Hz, 1 H), 6.57 (d, *J* = 7.6 Hz, 1 H), 6.47 - 6.53 (m, 1 H), 5.73 (m, 1 H), 3.40 (dd, *J* = 6.1, 8.0 Hz, 1 H), 2.88 (dd, J = 13.5, 6.1, 1H), 2.84 (dd, J = 13.5, 8.0, 1H), 2.62 (br. s, 1 H)

^{13}C-NMR ($CDCl_3$) δ = 148.9, 148.4, 144.8, 142.6, 141.1, 139.5, 138.1, 135.0, 129.4, 128.7, 128.5, 128.3, 128.1, 127.8, 127.7, 127.1, 127.0, 126.5, 126.0, 125.3, 124.7, 120.8, 119.9, 119.4, 119.4, 119.1, 110.5, 98.6, 73.0, 53.1, 44.8

HRMS (ESI): found 477.2325 ($M + H^+$) **calculated** 477.2331 (**$C_{35}H_{28}N_2$** + H)

IR υ = 3433, 3312, 3058, 3026, 2922, 2857, 1454, 1287, 907, 729, 698 cm^{-1} (film)

(S)-1-(1H-indol-2-yl)-2-phenylethanamine (76b)



85a (420 mg, 0.9 mmol, 100 mol-%) was dissolved in AcOH (16 mL) and degassed with argon. Pd/C (46 mg, 0.05 mmol, 10 w-%, 5 mol-%) was added and hydrogen atmosphere (1 atm) was introduced. The reaction mixture was stirred at r. t. for 18 h. The reaction mixture was filtered through a pad of celite and solvents were evaporated. The residue was partitioned between HCl (50 mL, aq. 1M) and Et_2O (100 mL). The organic layer was extracted with HCl (50 mL, aq. 1M). The combined aqueous phase was basified with NaOH (aq. 1M) until pH > 8. The aqueous phase was extracted with Et_2O (3 x 100 mL). Combined organic layers were dried over Na_2SO_4 and filtered. The solvents

were evaporated to give the crude product 180 mg (87 %) of orange solid. No further purification.

$[\alpha]_D$ = 20.1 (*c* = 0.9, CH_2Cl_2)

^{1}H-NMR ($CDCl_3$) δ = 8.91 (br. s, 1 H), 7.55 (d, *J* = 7.7 Hz, 1 H), 7.05 - 7.33 (m, 8 H), 6.34 (m, 1 H), 4.35 (dd, *J* = 9.1, 4.6 Hz, 1 H), 3.23 (dd, *J* = 13.4, 4.6 Hz, 1 H), 2.85 (dd, *J* = 13.4, 9.2 Hz, 1 H), 1.96 (br. s, 2 H)

^{13}C-NMR ($CDCl_3$) δ = 142.1, 138.2, 135.6, 129.3, 128.6, 128.4, 126.7, 121.4, 120.2, 119.6, 110.8, 98.5, 51.3, 44.9

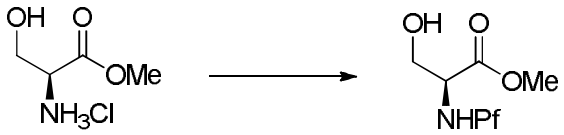
HRMS (ESI): found 237.1391 ($M + H^+$) **calculated** 237.1392 ($C_{16}H_{16}N_2 + H$)

IR υ = 3403, 3345, 3180-3280 (br.), 3058, 2919, 2854, 1584, 1455, 1289, 750, 699 cm^{-1} (film)

7.4 Synthesis of the indolylamine 76c derived from serine

Serine methyl ester hydrochloride **74c** was prepared by literature methods and obtained from a related project.

***N*-(9-phenylfluoren-9-yl)-L-serine methyl ester**[128] **(75c)**



74c (1.55 g, 10 mmol, 100 mol-%) was dissolved in CH_2Cl_2 (30 mL) in a Morton flask. TMSCl (3.2 mL, 25 mmol, 250 mol-%) was added and the solution was cooled down to 0 °C. Et_3N (4.9 mL, 35 mmol, 350 mol-%) was added drop wise. The reaction mixture was refluxed for 1 h and cooled down to 0 °C. MeOH (0.75 mL in 3 mL of CH_2Cl_2) was added and the reaction mixture was allowed to warm to r. t. and stirred for 1 h. Et_3N (1.4 mL, 10 mmol, 100 mol-%), $Pb(NO_3)_2$ (3.00 g, 9 mmol, 90 mol-%) and PfBr (4.01 g, 12.5 mmol, 125 mol-%) were added. The suspension was stirred vigorously for 72 h. The suspension was filtered through a pad of celite which was washed with $CHCl_3$ until no chromophore was detected. Solvents were evaporated. Citric acid (40 mL, 10 w-% in MeOH) was added and the solution was stirred for 1 h after which the solvents were

evaporated. The residue was dissolved in Et_2O (80 mL). The solution was washed with H_2O (40 mL) and the aqueous phase was extracted with Et_2O (2 x 60 mL). Combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvents were evaporated to yield a brown syrup. The crude can be purified by flash chromatography (50 % EtOAc/Hex) to yield 2.71 g (76 %) of white solid or used in the next step without further purification.

R_f: 0.17 (25 % EtOAc/Hex, UV)

$[\alpha]_D$ = -321.9 (*c* = 1.0, CH_2Cl_2), literature reference[128]: -324 °

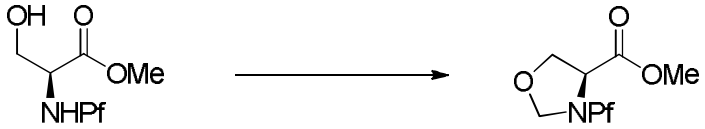
^{1}H-NMR ($CDCl_3$) δ = 7.66 - 7.72 (m, 2 H), 7.31 - 7.42 (m, 5 H), 7.21 - 7.28 (m, 6 H), 3.44 (m, 1 H), 3.42 (s, 3 H), 3.31 (br. s, 1 H), 3.27 (m, 1 H), 2.77 (dd, *J* = 5.7, 4.8 Hz, 1 H), 2.67 (t, *J* = 6.3 Hz, 1 H)

^{13}C-NMR ($CDCl_3$) δ = 174.2, 148.7, 148.4, 144.0, 141.2, 139.9, 128.7, 128.6, 128.4, 128.3, 127.7, 127.4, 125.9, 125.7, 125.0, 120.2, 120.0, 72.6, 63.8, 57.1, 52.1

HRMS (ESI): found 382.1414 ($M + Na^+$) **calculated** 381.1419 **(**$C_{23}H_{21}NO_3$ + Na)

IR υ = 3462 (b), 3310, 3060, 2951, 1730, 1600, 1447, 1334, 1175, 1052 cm^{-1} (film)

(S)-methyl 3-(9-phenyl-9H-fluoren-9-yl)oxazolidine-4-carboxylate (84c)



75c (2.58 g, 7.2 mmol, 100 mol-%) was dissolved in THF (72 mL). *p*-TsOH·H_2O (83 mg, 0.43 mmol, 6 mol-%) and CH_2O (8.1 mL, 108 mmol, aq 37 %, 1500 mol-%) were added and the solution was stirred at r. t. for 20 h. The reaction mixture was washed with sat. aq. $NaHCO_3$ (2 x 50 mL) and brine. The organic phase was dried over Na_2SO_4, filtered and the solvents were evaporated to yield 2.69 g (quant.) of white foam.

R_f: 0.54 (25 % EtOAc/Hex, UV)

$[\alpha]_D$ = 169.6 (*c* = 1.0, CH_2Cl_2)

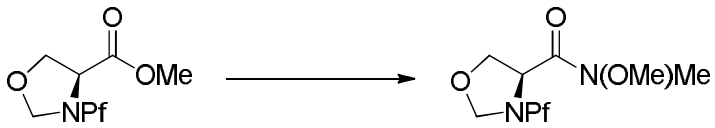
^{1}H-NMR ($CDCl_3$) δ = 7.70 (m, 1 H), 7.63 (m, 1 H), 7.55 (m, 1 H), 7.41 - 7.51 (m, 4 H), 7.16 - 7.34 (m, 6 H), 4.93 (d, *J* = 6.4 Hz, 1 H), 4.74 (d, *J* = 6.4 Hz, 1 H), 3.62 (d, J = 7.5 Hz, 1H), 3.62 (d, J = 6.3 Hz, 1H), 3.56 (s, 3 H), 3.30 (dd, *J* = 7.5, 6.2 Hz, 1 H)

^{13}C-NMR ($CDCl_3$) δ = 173.5, 148.7, 146.7, 143.9, 141.5, 139.1, 128.9, 128.5, 128.0, 127.8, 127.5, 127.1, 126.5, 125.8, 119.8, 119.7, 85.0, 77.1, 69.0, 60.8, 51.9

HRMS (ESI): found 372.1614 ($M + H^+$) **calculated** 372.1600 (**$C_{24}H_{21}NO_3$** + H)

IR υ = 3063, 2952, 2870, (2252), 1746, 1450, 1173, 904, 723, 646 cm^{-1} (film)

(S)-N-methoxy-N-methyl-3-(9-phenyl-9H-fluoren-9-yl)oxazolidine-4-carboxamide (78c)



84c (2.13 g, 5.7 mmol, 100 mol-%) and HN(OMe)Me·HCl (670 mg, 6.9 mmol, 120 mol-%) were suspensed in THF (7 mL). The suspension was cooled down to 0 °C and *i*-PrMgCl (6.9 mL, 13.8 mmol, 2M in Et_2O, 240 mol-%) was added drop wise via a dropping funnel. The solution was stirred at 0 °C for 1 h. The reaction was quenched with citric acid (20 mL, 5 w-%) and the layers were separated. The aqueous layer was extracted with Et_2O. Combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvents were evaporated to give a pale yellow solid. The crude product was recrystallized from EtOAc/Hex to yield a white powder 1.35 g (59 % over two steps).

In a scale up, serine methyl ester was Pf-protected, hemiaminal protected and converted to the Weinreb amide with only one recrystallization step of **78c** to yield 22.8 g (56 % over three steps) of **78c**.

R_f: 0.11 (25 % EtOAc/Hex, UV)

$[\alpha]_D$ = 176.0 (*c* = 1.0, CH_2Cl_2)

^{1}H-NMR ($CDCl_3$) δ = 7.71 (d, *J* = 7.3 Hz, 1 H), 7.61 (d, *J* = 7.7 Hz, 2 H), 7.49 - 7.54 (m, 3 H), 7.44 dt, *J* = 7.5, 0.9 Hz, 1 H), 7.34 (dt, *J* = 7.7, 1.1 Hz, 1 H), 7.16 - 7.27 (m, 5

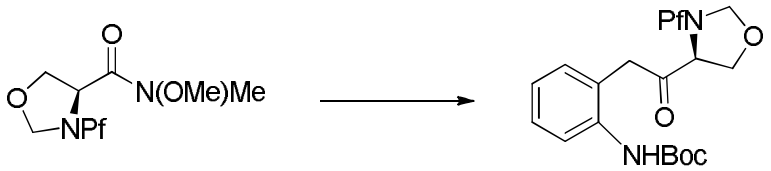
H), 4.98 (d, *J* = 6.6 Hz, 1 H), 4.82 (d, *J* = 6.6 Hz, 1 H), 3.63 - 3.71 (m, 2 H), 3.40 (m, 1 H), 3.00 (br. s, 3 H), 2.88 (br. s, 3 H)

^{13}C-NMR ($CDCl_3$) δ = 149.5, 147.3, 144.3, 141.3, 139.2, 128.7, 128.4, 128.3, 128.1, 128.1, 127.4, 127.2, 126.8, 125.9, 119.5, 119.4, 85.9, 77.4, 69.2, 60.3, 58.6

HRMS (ESI): found 401.1869 ($M + H^+$) **calculated** 401.1865 ($C_{25}H_{24}N_2O_3 + H$)

IR υ = 3057, 2966, 2938, 2972, 1660, 1449, 1176, 1021, 889, 735, 701 cm^{-1} (film)

(S)-tert-butyl(2-(2-oxo-2-(3-(9-phenyl-9H-fluoren-9-yl)oxazolidin-4-yl)ethyl)phenyl)carbamates (77c)



N-Boc-*o*-toluidine (15.54 g, 67.5 mmol, 250 mol-%) was dissolved in THF (140 mL) and cooled down to -30 °C. s-BuLi (102 mL, 125 mmol, 1.23 M in Et_2O, 500 mol-%) was added drop wise. The reaction was stirred at – 30 °C for 45 min. **77c** (10.03 g, 25 mmol, 100 mol-%) in THF (65 mL) was added and the reaction was stirred for an additional 15 min. The reaction was quenched at – 30 °C with sat. NH_4Cl (60 mL), taken to r. t.. H_2O (50 mL) was added to dissolve the white precipitate. The aqueous layer was extracted with EtOAc (2 x 150 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvents were evaporated to give a white solid. The crude product was triturated with Et_2O to yield 12.3 g (90 %) of white powder.

R_f: 0.43 (25 % EtOAc/Hex, vanillin)

$[\alpha]_D$ = 139.6 (*c* = 1.0, CH_2Cl_2)

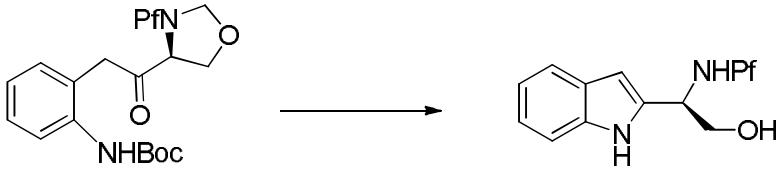
^{1}H-NMR ($CDCl_3$) δ = 7.66 - 7.74(m, 3 H), 7.56 (d, *J* = 7.5 Hz, 1 H), 7.45 - 7.51 (m, 4 H), 7.18 - 7.36 (m, 8 H), 7.12 (br. s, 1 H), 6.99 (dt, *J* = 7.5, 1.1 Hz, 1 H), 6.83 (dd, *J* = 7.7, 1.3 Hz, 1 H), 5.06 (d, *J* = 6.4 Hz, 1 H), 4.73 (d, *J* = 6.6 Hz, 1 H), 3.83 (d, *J* = 15.6 Hz, 1 H), 3.65 (d, *J* = 15.6 Hz, 1 H), 3.62 (m, 1 H), 3.26 - 3.33 (m, 2 H), 1.52 (s, 9 H)

^{13}C-NMR ($CDCl_3$) δ = 209.3, 153.6, 148.7, 146.0, 143.1, 141.5, 139.4, 137.3, 130.5, 129.2, 128.9, 128.7, 128.2, 128.1, 128.0, 127.7, 127.0, 126.9, 125.8, 125.7, 124.3, 123.9, 120.1, 119.8, 85.0, 80.3, 77.2, 67.5, 66.2, 43.3, 28.4

HRMS (ESI): found 547.2597 ($M + H^+$) **calculated** 547.2597 ($C_{35}H_{34}N_2O_4 + H$)

IR υ = 3341, 3062, 2978, 2870, 1718, 1515, 1450, 1236, 1156, 909, 734 cm^{-1} (film)

(R)-2-(1H-indol-2-yl)-2-((9-phenyl-9H-fluoren-9-yl)amino)ethanol (85c)



77c (1.09 g, 2 mmol, 100 mol-%) was dissolved in 1:1 MeOH/ CH_2Cl_2 (20 mL) and the resulting solution was cooled to 0 °C. H_2SO_4 (3.4 mL, 20 mmol, 6 M in EtOH, 1000 mol-%) was added and the reaction mixture was stirred at 0 °C for 1 h at r. t. for 1 h. HO-NH_2·HCl (1.40 g, 20 mmol, 1000 mol-%) was added and the reaction was stirred at r. t. for 1.5 h. The reaction mixture was poured very carefully to sat. $NaHCO_3$ (60 mL) under vigorous gas evolution, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). Combined organic layers were dried over Na_2SO_4 and filtered and the solvent were evaporated. The residual was dissolved in MeOH (20 mL) and NaOH (5.0 mL, 10 mmol, aq. 5M, 500 mol-%) was added. The reaction mixture was refluxed for 0.5 h. H_2O (20 mL) and CH_2Cl_2 (40 mL) were added and layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL) Combined organic layers were dried over Na_2SO_4, filtered and the solvents were evaporated. The crude product was purified by trituration from MeOH to yield 630 mg (75 %) of white powder over two steps.

R_f: 0.22 (25 % EtOAc/Hex, ninhydrin)

$[\alpha]_D$ = -229.6 (*c* = 1.0, CH_2Cl_2)

^{1}H-NMR ($CDCl_3$) δ =8.25 (br. s., 1 H), 7.74 (*J* = m, 1 H), 7.73 (*J* = m, 1 H), 7.38 - 7.44 (m, 5 H), 7.28 - 7.34 (m, 2 H), 7.19 - 7.25 (m, 4 H), 7.11 (ddd, *J* = 8.2, 7.0, 1.1 Hz,

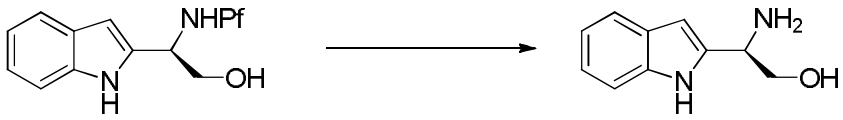
1 H), 6.99 - 7.04 (m, 3 H), 5.93 (m, 1 H), 3.50 (dd, *J* = 11.0, 4.5 Hz, 1 H), 3.37 (t, *J* = 4.5 Hz, 1 H), 3.24 (dd, *J* = 11.0, 4.6 Hz, 1 H), 2.69 (br. s., 1 H), 2.55 (br. s., 1 H)

^{13}C-NMR ($CDCl_3$) δ = 142.2, 141.7, 141.6, 139.6, 138.0, 136.4, 130.7, 129.8, 129.5, 128.9, 128.8, 127.8, 127.2, 126.4, 126.3, 125.7, 122.3, 120.6, 120.1, 119.9, 119.6, 111.7, 104.1, 74.8, 63.2, 58.0

HRMS (ESI): found 439.1788 ($M + Na^+$) **calculated** 439.1786 **(**$C_{29}H_{24}N_2O + Na$)

IR υ = 3548, 3425, 3330 (br.), 3057, 2948, 2875, 1449, 733, 699 cm^{-1} (film)

(R)-2-amino-2-(1H-indol-2-yl)ethanol (76c)



85c (1.67 g, 4 mmol, 1000 mol-%) was dissolved in AcOH (32 mL) and degassed with argon. Pd/C (180 mg, 0.2 mmol, 10 w-%, 5 mol-%) was added and hydrogen atmosphere (1 atm) was introduced. The reaction mixture was stirred at r. t. for 18 h. The reaction mixture was filtered through a pad of celite and solvents were evaporated. The residue was partitioned between HCl (50 mL, aq. 1M) and Et_2O (100 mL). The organic layer was extracted with HCl (25 mL, aq. 1M). The combined aqueous phases were basified with NaOH (aq. 1M) until pH > 8. The aqueous phase was extracted with 20 % 2-propanol in $CHCl_3$ (5 x 200 mL). Combined organic layers were dried over Na_2SO_4 and filtered. The solvents were evaporated to give 670 mg (95 %) of grey solid. No further purification.

$[\alpha]_D$ = -21.7 (*c* = 1.1, MeOH)

^{1}H-NMR (CD_3OD) δ = 7.45 (dt, *J* = 7.8, 1.1 Hz, 1 H), 7.30 (dq, *J* = 8.1, 0.9 Hz, 1 H), 7.04 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1 H), 6.95 (ddd, *J* = 8.2, 7.0, 0.9 Hz, 1 H), 6.32 - 6.38 (m, 1 H), 4.13 (dd, *J* = 7.2, 4.7 Hz, 1 H), 3.85 (dd, *J* = 10.8, 4.8 Hz, 1 H), 3.70 (dd, *J* = 10.8, 7.3 Hz, 1 H)

^{13}C-NMR (CD_3OD) δ = 141.2, 137.8, 129.7, 122.0, 120.9, 120.1, 111.8, 99.5, 67.7, 53.0

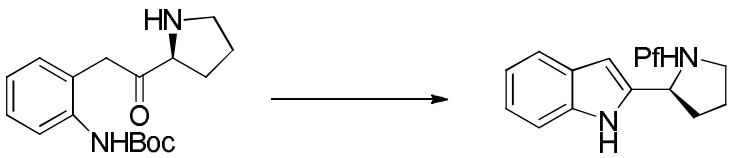
HRMS (ESI): found 177.1027 ($M + H^+$) **calculated** 177.1028 (**$C_{10}H_{12}N_2O$** + H)

IR υ = 3392, 3347, 3284, 3050-3300 (br.), 3082, 3055, 2918, 2869, 1587, 1456, 1342, 1289, 1035, 792, 743 cm^{-1} (film)

7.5 Synthesis of the indolylamine 76d derived from proline

Compound **77d** was obtained from a related project and thus procedures of its preparation are not reported here.

(S)-2-(1-(9-phenyl-9H-fluoren-9-yl)pyrrolidin-2-yl)-1H-indole (85d)



85d was prepared with the same procedure as compound **85a**. The crude product (462 mg, quant., white foam) was used in the next step without further purification.

R_f: 0.83 (17 % EtOAc/Hex, ninhydrin)

$[\alpha]_D$ = -49.4 (*c* = 1.2, CH_2Cl_2)

^{1}H-NMR ($CDCl_3$) δ = 8.12 (br. s, 1 H), 7.75 (d, *J* = 7.5, Hz, 1 H), 7.58 (d, *J* = 7.5 Hz, 1 H), 7.50 – 7.54 (m, 3 H), 7.46 (dt, *J* = 7.5, 1.1 Hz, 1 H), 7.30 - 7.36 (m, 3 H), 7.18 - 7.24 (m, 3 H), 7.08 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1 H), 6.96 - 7.02 (m, 3 H), 6.53 (dt, *J* = 7.5, 1.1 Hz, 1 H), 5.70 (m, 1 H), 3.73 (m, 1 H), 3.41 (m, 1 H3.15 (m, 1 H), 1.69 - 1.90 (m, 4 H)

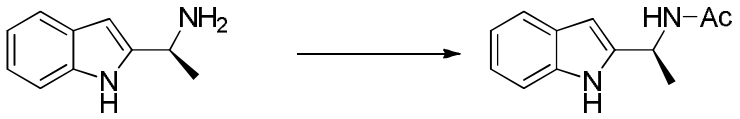
^{13}C-NMR ($CDCl_3$) δ = 149.0, 147.0, 144.8, 143.7, 142.2, 138.6, 135.0, 129.2, 128.5, 128.2, 127.7, 127.4, 127.2, 127.1, 127.0, 126.5, 125.8, 120.5, 119.8, 119.8, 119.2, 119.1, 110.4, 97.6, 77.2, 56.6, 50.8, 35.2, 25.2

HRMS (ESI): found 427.2174 ($M + H^+$) **calculated** 427.2174 (**$C_{31}H_{26}N_2$** + H)

IR υ = 3448, 3056, 2965, 2868, 1449, 1285, 736, 702 cm^{-1} (film)

7.6 Synthesis of the library

(S)-N-(1-(1H-indol-2-yl)ethyl)acetamide (80a)



76a (160 mg, 1 mmol, 100 mol-%) was dissolved in CH_2Cl_2 (2.5 mL). Et_3N (0.17 mL, 1.2 mmol, 120 mol-%) was added. The solution was cooled down to 0 °C and AcCl (0.09 mL, 1.2 mmol, 120 mol-%) was added drop wise. The solution was stirred at 0 °C for 15 min and at r. t. for 2 h. The reaction mixture was washed with citric acid (10 mL, 5 w-%) and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) Combined organic layers were dried over Na_2SO_4 and filtered. The solvents were evaporated to give 215 mg (quant.) of yellow solid. No further purification.

R_f: 0.27 (10 % MeOH/ CH_2Cl_2, UV, ninhydrin)

$[\alpha]_D$ = -216.5 (*c* = 1.0, CH_2Cl_2)

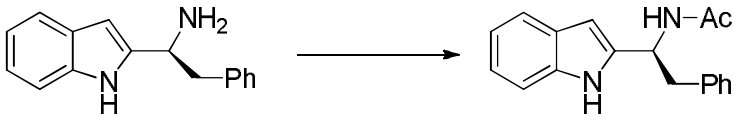
^{1}H-NMR ($CDCl_3$) δ = 9.17 (br. s., 1 H), 7.53 (m, 1 H), 7.29 (*J* = m, 1 H), 7.14 (ddd, *J* = 8.0, 7.2, 1.3 Hz, 1 H), 7.05 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1 H), 6.30 (m, 1 H), 6.06 (br. d, *J* = 7.3 Hz, 1 H), 5.22 (dq, *J* = 7.3, 7.1 Hz, 1 H), 1.95 (s, 3 H), 1.59 (d, *J* = 7.0 Hz, 3 H)

^{13}C-NMR (CD_3OD) δ = 170.9, 141.1, 135.9, 127.4, 121.9, 120.2, 119.6, 111.0, 98.0, 42.9, 23.1, 18.1

HRMS (ESI): found 203.1181 ($M + H^+$) **calculated** 203.1184 **(**$C_{12}H_{14}N_2O + H$)

IR υ = 3386, 3272, 3081, 3057, 2978, 2932, 1643, 1541, 1457, 1301, 1165, 790, 738 cm^{-1} (film)

(S)-N-(1-(1H-indol-2-yl)-2-phenylethyl)acetamide (80b)



80b was prepared with same procedure as compound **80a** to yield 200 mg of yellow solid. The crude product was purified using flash column chromatography (50 % EtOAc/Hex) to give 134 mg (73 % over two steps) of a pale yellow solid.

R_f: 0.49 (10 % MeOH/ CH_2Cl_2, UV, ninhydrin)

$[\alpha]_D$ = -120.5 (*c* = 1.1, MeOH)

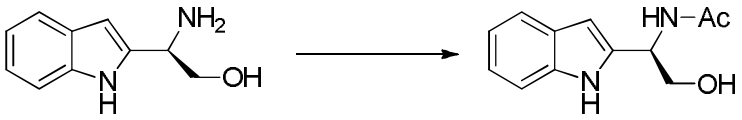
^{1}H NMR (CD_3CN) δ = 9.32 (br. s., 1 H), 7.48 (m, 1 H), 7.35 (*J* = m, 1 H), 7.18 - 7.30 (m, 5 H), 7.09 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 7.01 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1 H), 6.80 (m, 1H), 6.32 (s, 1 H), 5.31 - 5.36 (m, 1 H), 3.30 (dd, *J* = 13.9, 6.2 Hz, 1 H), 3.12 (dd, *J* = 13.9, 8.8 Hz, 1 H), 1.82 (m, 3 H)

^{13}C-NMR (CD_3OD) δ = 172.6, 140.6, 139.4, 137.9, 130.3, 129.6, 129.2, 127.5, 122.2, 120.9, 120.1, 111.9, 99.7, 50.5, 41.8, 22.5

HRMS (ESI): found 301.1315 ($M + Na^+$) **calculated** 301.1317 **(**$C_{18}H_{18}N_2O + Na$)

IR υ = 3389, 3273, 3088, 3058, 2926, 1632, 1455, 1288, 789, 750, 699 cm^{-1} (film)

(R)-N-(2-hydroxy-1-(1H-indol-2-yl)ethyl)acetamide (80c)



76c (88 mg, 0.5 mmol, 100 mol-%) was dissolved in THF (1 mL) and aqueous sat. $NaHCO_3$ (3 mL) was added. Acetic anhydride (0.14 mL, 1.5 mmol, 300 mol-%) was added drop wise and the reaction mixture was stirred for 18 h. The reaction mixture was diluted with EtOAc (5 mL) and the organic phase was washed with H_2O (5 mL). The combined aqueous phase was extracted with EtOAc (2 x 10 mL). Combined organic layers were dried over Na_2SO_4 and filtered. The solvents were evaporated to give a white solid. The crude product was purified by silica gel column chromatography (7 % MeOH/CH_2Cl_2) to yield 101 mg (93 %) of white solid.

R_f: 0.41 (10 % MeOH/ CH_2Cl_2, UV, ninhydrin)

$[\alpha]_D$ = -130.6 (*c* = 1.0, CH_2Cl_2)

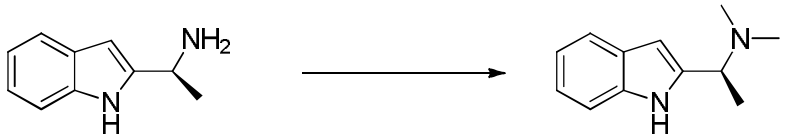
^{1}H-NMR (CD_3OD) δ = 7.45 (m, 1 H), 7.31 (dq, *J* = 8.1, 0.9 Hz, 1 H), 7.04 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1 H), 6.95 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1 H), 6.34 (m, 1 H), 5.22 (app. t, *J* = 5.9 Hz, 1 H), 3.93 (dd, *J* = 11.2, 5.3 Hz, 1 H), 3.84 (dd, *J* = 11.2, 6.6 Hz, 1 H), 2.03 ppm (s, 3 H)

^{13}C-NMR (CD_3OD) δ = 173.2, 138.4, 137.9, 129.6, 122.2, 120.9, 120.1, 111.9, 100.0, 64.9, 51.2, 22.7

HRMS (ESI): found 219.1136 ($M + H^+$) **calculated** 219.1134 (**$C_{12}H_{14}N_2O_2$** + H)

IR υ = 3379, 3279 (br.) 3083, 3058, 2928, 2879, 1639, 1541, 1456, 1291, 1041, 794, 787 cm^{-1} (film)

(S)-1-(1H-indol-2-yl)-N,N-dimethylethanamine (81a)



76a (80 mg, 0.5 mmol, 100 mol-%) was dissolved in CH_2Cl_2 (12 mL) and CH_2O (0.18 mL, 2 mmol, aq. 37 %, 400 mol-%), Na_2SO_4 (400 mg) and $NaBH(OAc)_3$ (1.00 g, 5 mmol, 1000 mol -%) were added. The reaction was stirred at r. t. for 18 h and quenched with aq. sat. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The solvents were evaporated to give a pale yellow solid. The crude product was purified by flash column chromatography (10 % of MeOH/CH_2Cl_2) to yield 99 mg (90 %) of pale yellow solid.

R_f: 0.26 (10 % MeOH/ CH_2Cl_2, UV, ninhydrin)

$[\alpha]_D$ = -1.7 (*c* = 1.2, CH_2Cl_2)

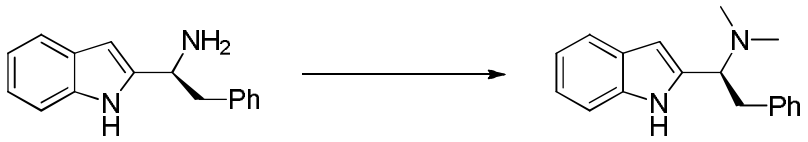
^{1}H-NMR ($CDCl_3$) δ = 8.73 (br. s., 1 H), 7.55 (m, 1 H), 7.32 (*J* = m, 1 H), 7.13 (ddd, *J* = 8.0, 7.0, 1.3 Hz, 1 H), 7.06 (ddd, *J* = 7.8, 7.2, 1.1 Hz, 1 H), 6.31 (m, 1 H), 3.82 (q, *J* = 6.8 Hz, 1 H), 2.26 (s, 6 H), 1.41 (d, *J* = 6.8 Hz, 3 H)

^{13}C-NMR ($CDCl_3$) δ = 141.0, 135.9, 128.2, 121.4, 120.1, 119.4, 110.8, 99.8, 58.1, 41.3, 13.0

HRMS (ESI): found 189.1388 ($M + H^+$) **calculated** 189.1392 ($C_{12}H_{16}N_2 + H$)

IR υ = 3402, 3236 (br.), 3081, 3056, 2975, 1455, 1301, 1081, 908, 790, 730 cm^{-1} (film)

(S)-1-(1H-indol-2-yl)-N,N-dimethyl-2-phenylethanamine (81b)



81b was prepared with the same method as compound **81a**. The crude product was purified by flash column chromatography (EtOAc) to yield 130 mg (quant.) of a brown oil.

R_f: 0.32 (EtOAc, UV, ninhydrin)

$[\alpha]_D$ = -123.7 (*c* = 0.8, CH_2Cl_2)

^{1}H-NMR ($CDCl_3$) δ = 8.55 (br. s., 1 H), 7.49 - 7.51 (m, 1 H), 7.30 (m, 1 H), 7.10 - 7.22 (m, 6 H), 7.04 (ddd, *J* = 7.8, 7.2, 1.0 Hz, 1 H), 6.22 (m, 1 H), 3.87 (dd, *J* = 9.3, 4.4 Hz, 1 H), 3.27 (dd, *J* = 13.7, 4.4 Hz, 1 H), 3.06 (dd, *J* = 13.7, 9.3 Hz, 1 H), 2.33 ppm (s, 6 H)

^{13}C-NMR ($CDCl_3$) δ = 139.3, 138.4, 135.8, 129.0, 128.3, 128.2, 126.1, 121.4, 120.2, 119.4, 110.7, 101.7, 65.6, 42.2, 36.2

IR υ = 3410, 3239 (br.), 3083, 3059, 2933, 2861, 2824, 2781, 1495, 1032, 1019, 787, 749, 699 cm^{-1} (film)

(R)-2-(dimethylamino)-2-(1H-indol-2-yl)ethanol (81c)

81c was prepared with the same method as compound **81a**. The crude product was purified by flash column chromatography (25 % MeOH/CH_2Cl_2) to yield 95 mg (93 %) of white solid.

R_f: 0.43 (25 % MeOH/ CH_2Cl_2, UV, ninhydrin)

$[\alpha]_D$ = -100.1 (*c* = 0.8, CH_2Cl_2)

^{1}H-NMR ($CDCl_3$) δ = 8.77 (br. s, 1 H), 7.57 (d, *J* = 7.9 Hz, 1 H), 7.33 (d, *J* = 8.1 Hz, 1 H), 7.16 (ddd, *J* = 8.4, 6.7, 1.3 Hz, 1 H), 7.09 (ddd, *J* = 7.7, 7.0, 0.9 Hz, 1 H), 6.35 (m, 1 H), 3.94 (dd, *J* = 11.0, 5.1 Hz, 1 H), 3.87 (dd, *J* = 11.2, 6.0 Hz, 1 H), 3.66 (b, 1H), 3.63 (app. t, *J* = 5.45, 1H), 2.29 (s, 6 H)

^{13}C-NMR ($CDCl_3$) δ = 134.0, 135.2, 127.8, 121.9, 120.3, 119.8, 111.0, 102.1, 64.5, 61.6, 42.5

HRMS (ESI): found 205.1334 ($M + H^+$) **calculated** 205.1341 **(**$C_{12}H_{16}N_2O + H$)

IR υ = 3398, 3276 (br.), 3082, 3055, 2946, 2871, 2830, 2785, 1456, 1290, 1032, 791, 746 cm^{-1} (film)

8 References

(1) Meissner, W. *J. Chem. Phys* **1819**, *25*, 377-381.

(2) Hesse, M. In *Alkaloids: Nature's Curse or Blessing;* Wiley-VCH: Weinheim, Chichester: Zürich, 2002; pp 14-27.

(3) Allen, J. R. F.; Holmstedt, B. R. *Phytochemistry* **1980**, *19*, 1573-1582.

(4) Goebel, F. *Justus Liebigs Ann. Chem.* **1841**, *38*, 363.

(5) Maresh, J. J.; Giddings, L.; Friedrich, A.; Loris, E. A.; Panjikar, S.; Trout, B. L.; Stöckigt, J.; Peters, B.; O'Connor, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 710-723.

(6) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angewandte Chemie International Edition* **2011**, *50*, 8538-8564.

(7) Pictet, A.; Spengler, T. *Berichte der deutschen chemischen Gesellschaft* **1911**, *44*, 2030-2036.

(8) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797-1842.

(9) Bischler, A.; Napieralski, B. *Berichte der deutschen chemischen Gesellschaft* **1893**, *26*, 1903-1908.

(10) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916-4917.

(11) Evanno, L.; Ormala, J.; Pihko, P. *Chemistry: A European Journal* **2009**, *15*, 12963-12967.

(12) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1-57.

(13) Bailey, P. D.; Cochrane, P. J.; Lorenz, K.; Collier, I. D.; Pearson, D. P. J.; Rosair, G. M. *Tetrahedron Lett.* **2001**, *42*, 113-115.

(14) Koskinen, A. M. P. In *Asymmetric synthesis of natural products;* Wiley. com: 2012; pp 259-261.

(15) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc. , Perkin Trans. 1* **1993**, 431-439.

(16) Ardeo, A.; García, E.; Arrasate, S.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2003**, *44*, 8445-8448.

(17) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998-7010.

(18) Liu, X.; Deschamp, J. R.; Cook, J. M. *Org. Lett.* **2002***, 4*, 3339-3342.

(19) Bailey, P. D.; Clingan, P. D.; Mills, T. J.; Price, R. A.; Pritchard, R. G. *Chem. Commun.* **2003**, 2800-2801.

(20) Alberch, L.; Bailey, P. D.; Clingan, P. D.; Mills, T. J.; Price, R. A.; Pritchard, R. G. *European Journal of Organic Chemistry* **2004***, 2004*, 1887-1890.

(21) Bailey, P. D.; Beard, M. A.; Phillips, T. R. *Tetrahedron Lett.* **2009***, 50*, 3645-3647.

(22) Yamada, H.; Kawate, T.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **1999***, 64*, 8821-8828.

(23) Soe, T.; Kawate, T.; Fukui, N.; Nakagawa, M. *Tetrahedron Lett.* **1995***, 36*, 1857-1860.

(24) Waldmann, H.; Schmidt, G.; Henke, H.; Burkard, M. *Angewandte Chemie International Edition in English* **1995***, 34*, 2402-2403.

(25) Ducrot, P.; Rabhi, C.; Thal, C. *Tetrahedron* **2000***, 56*, 2683-2692.

(26) Kawate, T.; Yamada, H.; Soe, T.; Nakagawa, M. *Tetrahedron: Asymmetry* **1996***, 7*, 1249-1252.

(27) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007***, 129*, 13404-13405.

(28) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009***, 11*, 887-890.

(29) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006***, 128*, 1086-1087.

(30) Wanner, M.,J.; van der Haas,Richard,N.,S.; de Cuba, K.,R.; van Maarseveen, J.,H.; Hiemstra, H. *Angewandte Chemie* **2007***, 119*, 7629-7631.

(31) Varney, M. D.; Appelt, K.; Kalish, V.; Reddy, M. R.; Tatlock, J.; Palmer, C. L.; Romines, W. H.; Wu, B.; Musick, L. *J. Med. Chem.* **1994***, 37*, 2274-2284.

(32) Giorgioni, G.; Accorroni, B.; Stefano, A.; Marucci, G.; Siniscalchi, A.; Claudi, F. *Medicinal Chemistry Research* **2005***, 14*, 57-73.

(33) Dykstra, K. D.; Guo, L.; Birzin, E. T.; Chan, W.; Yang, Y. T.; Hayes, E. C.; DaSilva, C. A.; Pai, L.; Mosley, R. T.; Kraker, B.; Fitzgerald, P. M. D.; DiNinno, F.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2007***, 17*, 2322-2328.

(34) Kawasaki, T.; Enoki, H.; Matsumura, K.; Ohyama, M.; Inagawa, M.; Sakamoto, M. *Org. Lett.* **2000***, 2*, 3027-3029.

(35) Kouko, T.; Matsumura, K.; Kawasaki, T. *Tetrahedron* **2005***, 61*, 2309-2318.

(36) Goswami, K.; Duttagupta, I.; Sinha, S. *J. Org. Chem.* **2012**, *77*, 7081-7085.

(37) Wang, C.; Sperry, J. *Tetrahedron* **2013**, *69*, 4563-4577.

(38) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467-4470.

(39) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652-7662.

(40) Garner, P.; Park, J. M. *Organic syntheses* **1992**, *70*, 18-28.

(41) Enders, D.; Del Signore, G. *Tetrahedron: Asymmetry* **2004**, *15*, 747-751.

(42) Cheng, L.; Liu, L.; Sui, Y.; Wang, D.; Chen, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 1833-1843.

(43) Kang, Q.; Zheng, X.; You, S. *Chemistry: A European Journal* **2008**, *14*, 3539-3542.

(44) Sheng, Y.; Li, G.; Kang, Q.; Zhang, A.; You, S. *Chemistry: A European Journal* **2009**, *15*, 3351-3354.

(45) Blay, G.; Fernández, I.; Pedro, J. R.; Vila, C. *Tetrahedron Lett.* **2007**, *48*, 6731-6734.

(46) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479-500.

(47) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442-453.

(48) Daugan, A.; Grondin, P.; Ruault, C.; Le Monnier, d. G.; Coste, H.; Kirilovsky, J.; Hyafil, F.; Labaudiniere, R. *J. Med. Chem.* **2003**, *46*, 4525-4532.

(49) Eli Lilly and Company: Annual report 2012. *http://investor.lilly.com/annuals.cfm* (accessed 07/24, 2013).

(50) Pfizer: 2012 Financial report. *http://www.pfizer.com/investors/financial_reports/financial_reports* (accessed 07/24, 2013).

(51) Roberts, M. F.; Wink, M. In *Alkaloids: biochemistry, ecology, and medicinal applications;* Plenum Press: New York, 1998; pp 450-451.

(52) Saxton, J. E. In *Monoterpenoid indole alkaloids: supplement to part 4;* Wiley: Chichester, 1994; pp 162-176, 719-725.

(53) World Malaria Report 2012. *http://www.who.int/malaria/publications/world_malaria_report_2012/report/en/index.html* (accessed 07/23, 2013).

(54) Hedman, K.; Heikkinen, T.; Huovinen, P.; Järvinen, A.; Meri, S.; Vaara, M. In *Mikrobiologia, immunologia ja infektiosairaudet (In Finnish);* Duodecim: 2010; pp 355-373.

(55) Sidhu, A. B. S.; Verdier-Pinard, D.; Fidock, D. A. *Science* **2002**, *298*, 210-213.

(56) Davis, R. A.; Duffy, S.; Avery, V. M.; Camp, D.; Hooper, J. N. A.; Quinn, R. J. *Tetrahedron Lett.* **2010**, *51*, 583-585.

(57) Chan, S. T. S.; Pearce, A. N.; Page, M. J.; Kaiser, M.; Copp, B. R. *J. Nat. Prod.* **2011**, *74*, 1972-1979.

(58) Gellis, A.; Dumètre, A.; Lanzada, G.; Hutter, S.; Ollivier, E.; Vanelle, P.; Azas, N. *Biomedicine & Pharmacotherapy* **2012**, *66*, 339-347.

(59) Gupta, L.; Srivastava, K.; Singh, S.; Puri, S. K.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3306-3309.

(60) Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; González-Páez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175-1180.

(61) Yeung, B. K. S.; Zou, B.; Rottmann, M.; Lakshminarayana, S. B.; Ang, S. H.; Leong, S. Y.; Tan, J.; Wong, J.; Keller-Maerki, S.; Fischli, C.; Goh, A.; Schmitt, E. K.; Krastel, P.; Francotte, E.; Kuhen, K.; Plouffe, D.; Henson, K.; Wagner, T.; Winzeler, E. A.; Petersen, F.; Brun, R.; Dartois, V.; Diagana, T. T.; Keller, T. H. *J. Med. Chem.* **2010**, *53*, 5155-5164.

(62) IFPMA Developing World Health Partnerships: Novartis R&D for Malaria. http://partnerships.ifpma.org/partnership/novartis-r-d-for-malaria (accessed 07/23, 2013).

(63) Staerk, D.; Lemmich, E.; Christensen, J.; Kharazmi, A.; Olsen, C. E.; Jaroszewski, J. W. *Planta Med.* **2000**, *66*, 531-536.

(64) Kam, T.; Sim, K.; Koyano, T.; Komiyama, K. *Phytochemistry* **1999**, *50*, 75-79.

(65) Chauhan, S. S.; Gupta, L.; Mittal, M.; Vishwakarma, P.; Gupta, S.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6191-6194.

(66) Kumar, A.; Katiyar, S. B.; Gupta, S.; Chauhan, P. M. S. *Eur. J. Med. Chem.* **2006**, *41*, 106-113.

(67) Kumar, R.; Khan, S.; Verma, A.; Srivastava, S.; Viswakarma, P.; Gupta, S.; Meena, S.; Singh, N.; Sarkar, J.; Chauhan, P. M. S. *Eur. J. Med. Chem.* **2010**, *45*, 3274-3280.

(68) Düsman Tonin, L. T.; Barbosa, V. A.; Bocca, C. C.; Ramos, É R. F.; Nakamura, C. V.; Ferreira da Costa, W.; Basso, E. A.; Nakamura, T. U.; Sarragiotto, M. H. *Eur. J. Med. Chem.* **2009***, 44*, 1745-1750.

(69) Valdez, R. H.; Tonin, L. T. D.; Ueda-Nakamura, T.; Silva, S. O.; Dias Filho, B. P.; Kaneshima, E. N.; Yamada-Ogatta, S. F.; Yamauchi, L. M.; Sarragiotto, M. H.; Nakamura, C. V. *Antimicrobial Agents and Chemotherapy* **2012***, 56*, 507-512.

(70) Rinehart, K. L.; Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Mascal, M.; Holt, T. G.; Shield, L. S.; Lafargue, F. *J. Am. Chem. Soc.* **1987***, 109*, 3378-3387.

(71) Rinehart, K. L.; Kobayashi, J.; Harbour, G. C.; Hughes, R. G.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1984***, 106*, 1524-1526.

(72) Lake, R. J.; Blunt, J. W.; Munro, M. *Aust. J. Chem.* **1989***, 42*, 1201-1206.

(73) Van Maarseveen, J. H.; Hermkens, P. H. H.; De Clercq, E.; Balzarini, J.; Scheeren, H. W.; Kruse, C. G. *J. Med. Chem.* **1992***, 35*, 3223-3230.

(74) Miller, J. F.; Turner, E. M.; Sherrill, R. G.; Gudmundsson, K.; Spaltenstein, A.; Sethna, P.; Brown, K. W.; Harvey, R.; Romines, K. R.; Golden, P. *Bioorg. Med. Chem. Lett.* **2010***, 20*, 256-259.

(75) Gudmundsson, K.; Miller, J. F.; Sherrill, R. G.; Turner, E. M. WO2006015035A1, 2006.

(76) Kobayashi, J.; Cheng, J. F.; Ohta, T.; Nozoe, S.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990***, 55*, 3666-3670.

(77) Adesanya, S. A.; Chbani, M.; Païs, M.; Debitus, C. *J. Nat. Prod.* **1992***, 55*, 525-527.

(78) Shen, Y.; Chen, Y.; Hsieh, P.; Duh, C.; Lin, Y.; Ko, C. - *Chemical and Pharmaceutical Bulletin* **2005***, 53*, 32-36.

(79) Shen, Y.; Chang, Y.; Lin, C.; Liaw, C.; Kuo, Y. H.; Tu, L.; Yeh, S. F.; Chern, J. *Mar. Drugs* **2011***, 9*, 256-277.

(80) Santos, L. S.; Theoduloz, C.; Pilli, R. A.; Rodriguez, J. *Eur. J. Med. Chem.* **2009***, 44*, 3810-3815.

(81) Kumar, R.; Gupta, L.; Pal, P.; Khan, S.; Singh, N.; Katiyar, S. B.; Meena, S.; Sarkar, J.; Sinha, S.; Kanaujiya, J. K.; Lochab, S.; Trivedi, A. K.; Chauhan, P. M. S. *Eur. J. Med. Chem.* **2010***, 45*, 2265-2276.

(82) Skouta, R.; Hayano, M.; Shimada, K.; Stockwell, B. R. *Bioorg. Med. Chem. Lett.* **2012***, 22*, 5707-5713.

(83) Zeng, Y.; Zhang, Y.; Weng, Q.; Hu, M.; Zhong, G. *Molecules* **2010***, 15*, 7775-7791.

(84) Chabner, B. A.; Longo, D. L. In *Cancer chemotherapy and biotherapy: principles and practice;* Chabner, B. A., Longo, D. L., Eds.; Wolters Kluwer Health: 2011; pp 563-570.

(85) Jackson, J. R.; Patrick, D. R.; Dar, M. M.; Huang, P. S. *Nat Rev Cancer* **2007**, *7*, 107-117.

(86) Hotha, S.; Yarrow, J. C.; Yang, J. G.; Garrett, S.; Renduchintala, K. V.; Mayer, T. U.; Kapoor, T. M. *Angewandte Chemie* **2003**, *115*, 2481-2484.

(87) Sunder-Plassmann, N.; Sarli, V.; Gartner, M.; Utz, M.; Seiler, J.; Huemmer, S.; Mayer, T. U.; Surrey, T.; Giannis, A. *Bioorg. Med. Chem.* **2005**, *13*, 6094-6111.

(88) Vennemann, M.; Braunger, J.; Gimmnich, P.; Baer, T. WO2009024190A1, 2009.

(89) 4SC: Product pipeline / SC4-205. http://www.4sc.de/product-pipeline/clinical/4SC-205 (accessed 07/24, 2013).

(90) Rath, O.; Kozielski, F. *Nat Rev Cancer* **2012**, *12*, 527-539.

(91) Liu, F.; Yu, L.; Jiang, C.; Yang, L.; Wu, W.; You, Q. *Bioorg. Med. Chem.* **2010**, *18*, 4167-4177.

(92) Barsanti, P. A.; Wang, W.; Ni, Z.; Duhl, D.; Brammeier, N.; Martin, E.; Bussiere, D.; Walter, A. O. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 157-160.

(93) Schmidt, M.; Bastians, H. *Drug resistance updates* **2007**, *10*, 162-181.

(94) Chan, K.; Koh, C.; Li, H. *Cell Death Dis* **2012**, *3*, e411.

(95) Serafini, P.; Meckel, K.; Kelso, M.; Noonan, K.; Califano, J.; Koch, W.; Dolcetti, L.; Bronte, V.; Borrello, I. *J. Exp. Med.* **2006**, *203*, 2691-2702.

(96) Sandeep, G.; Bhasker, S.; Ranganath, Y. S. *The Internet Journal of Pharmacology* **2009**, *7*.

(97) El-Gamil, D. S.; Ahmed, N. S.; Gary, B. D.; Piazza, G. A.; Engel, M.; Hartmann, R. W.; Abadi, A. H. *Arch. Pharm. (Weinheim)* **2013**, *346*, 23-33.

(98) Abadi, A. H.; Lehmann, J.; Piazza, G. A.; Abdel-Halim, M.; Ali, M. S. M. *Int. J. Med. Chem.* **2011**, 562421, 9 pp.

(99) Mohamed, H. A.; Girgis, N. M. R.; Wilcken, R.; Bauer, M. R.; Tinsley, H. N.; Gary, B. D.; Piazza, G. A.; Boeckler, F. M.; Abadi, A. H. *J. Med. Chem.* **2011**, *54*, 495-509.

(100) Ahmed, N. S.; Gary, B. D.; Tinsley, H. N.; Piazza, G. A.; Laufer, S.; Abadi, A. H. *Arch. Pharm. (Weinheim)* **2011**, *344*, 149-157.

(101) Piazza, G.; Abadi, A. H. WO2011063223A1, 2011.

(102) Audia, J. E.; Evrard, D. A.; Murdoch, G. R.; Droste, J. J.; Nissen, J. S.; Schenck, K. W.; Fludzinski, P.; Lucaites, V. L.; Nelson, D. L.; Cohen, M. L. *J. Med. Chem.* **1996**, *39*, 2773-2780.

(103) Glennon, R. A.; Grella, B.; Tyacke, R. J.; Lau, A.; Westaway, J.; Hudson, A. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 999-1002.

(104) Poitout, L.; Roubert, P.; Contour-Galcera, M.; Moinet, C.; Lannoy, J.; Pommier, J.; Plas, P.; Bigg, D.; Thurieau, C. *J. Med. Chem.* **2001**, *44*, 2990-3000.

(105) Pasternak, A.; Feng, Z.; de Jesus, R.; Ye, Z.; He, S.; Dobbelaar, P.; Bradley, S. A.; Chicchi, G. G.; Tsao, K.; Trusca, D.; Eiermann, G. J.; Li, C.; Feng, Y.; Wu, M.; Shao, Q.; Zhang, B. B.; Nargund, R.; Mills, S. G.; Howard, A. D.; Yang, L.; Zhou, Y. *ACS Med. Chem. Lett.* **2012**, *3*, 289-293.

(106) Ganong, W., Ed.; In *Review of medical physiology;* Lange Medical Books / McGraw-Hill: 2005; , pp 113-114.

(107) Zhou, Y.; Li, J.; Wu, W.; Shang, J.; Thompson, J. R.; Thornberry, N. A. US20090131451A1, 2009.

(108) Mjalli, A. M. M.; Andrews, R. C.; Xie, R.; Yarragunta, R. R.; Ren, T. WO2003033496A1, 2003.

(109) Brandt, P.; Bremberg, U.; Crossley, R.; Graffner, N., Malin; Jenmalm, J., Annika; Ringberg, E.; Ward, T. WO2005048916A2, 2005.

(110) Hung, D.; Protter, A.; Chakravarty, S.; Jain, R.; Dugar, S. WO2009120717, 2009.

(111) Ortar, G.; Petrocellis, L. D.; Moriello, A. S.; Allarà, M.; Morera, E.; Nalli, M.; Marzo, V. D. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 138-142.

(112) Bi, W.; Bi, L.; Cai, J.; Liu, S.; Peng, S.; Fischer, N. O.; Tok, J. B. -.; Wang, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4523-4527.

(113) Bi, W.; Cai, J.; Liu, S.; Baudy-Floc'h, M.; Bi, L. *Bioorg. Med. Chem.* **2007**, *15*, 6909-6919.

(114) Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239-1246.

(115) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236-239.

(116) Karppanen, E. J.; Koskinen, A. M. *Molecules* **2010**, *15*, 6512-6547.

(117) Dellaria Jr., J. F.; Maki, R. G. *Tetrahedron Lett.* **1986**, *27*, 2337-2340.

(118) Bolton, R.; Chapman, N. B.; Shorter, J. *J. Chem. Soc.* **1964**, *0*, 1895-1906.

(119) Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1993**, *58*, 6990-6995.

(120) Sauerland, S. J.; Castillo-Meléndez, J. A.; Nättinen, K.; Rissanen, K.; Koskinen, A. M. *Synthesis* **2010***, 2010*, 757-762.

(121) Jamison, T. F.; Lubell, W. D.; Dener, J. M.; Krisché, M. J.; Rapoport, H. *Organic syntheses* **1993***, 71*, 220.

(122) Campbell, J. A.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1995***, 60*, 4602-4616.

(123) Lood, C.; Koskinen, A. M. P. *Unpublished work from the Koskinen laboratory, Aalto University*.

(124) Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981***, 46*, 4511-4515.

(125) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981***, 22*, 3815-3818.

(126) Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991***, 10*, 871-878.

(127) Fischer, E.; Speier, A. *Berichte der deutschen chemischen Gesellschaft* **1895***, 28*, 3252-3258.

(128) Lubell, W.; Rapoport, H. *J. Org. Chem.* **1989***, 54*, 3824-3831.

(129) Banphavichit, V.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron* **2007***, 63*, 8727-8734.

(130) Abdel-Magid, A.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996***, 61*, 3849.

(131) Abdel-Magid, A.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996***, 61*, 3849-3862.

(132) Yonemitsu, O.; Cerutti, P.; Witkop, B. *J. Am. Chem. Soc.* **1966***, 88*, 3941-3945.

(133) Bajtos, B.; Pagenkopf, B. L. *European Journal of Organic Chemistry* **2009***, 2009*, 1072-1077.

(134) Sundberg, R. J.; Hong, J.; Smith, S. Q.; Sabat, M.; Tabakovic, I. *Tetrahedron* **1998***, 54*, 6259-6292.

(135) Amat, M.; Coll, M. -.; Bosch, J.; Espinosa, E.; Molins, E. *Tetrahedron: Asymmetry* **1997***, 8*, 935-948.

(136) Bremner, J. B.; Sengpracha, W. *Tetrahedron* **2005***, 61*, 5489-5498.

(137) Ito, Y.; Sato, H.; Murakami, M. *J. Org. Chem.* **1991***, 56*, 4864-4867.

(138) Dillard, R. D.; Bach, N. J.; Draheim, S. E.; Berry, D. R.; Carlson, D. G.; Chirgadze, N. Y.; Clawson, D. K.; Hartley, L. W.; Johnson, L. M.; Jones, N. D.; McKinney, E. R.; Mihelich, E. D.; Olkowski, J. L.; Schevitz, R. W.; Smith, A. C.; Snyder, D. W.; Sommers, C. D.; Wery, J. *J. Med. Chem.* **1996**, *39*, 5119-5136.

(139) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859-1866.

(140) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127-8134.

(141) Allinger, N. L.; Yuh, Y. H.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551-8566.

(142) Halgren, T. A. *Journal of Computational Chemistry* **1996**, *17*, 490-519.

(143) Banks, J. L.; Beard, H. S.; Cao, Y.; Cho, A. E.; Damm, W.; Farid, R.; Felts, A. K.; Halgren, T. A.; Mainz, D. T.; Maple, J. R.; Murphy, R.; Philipp, D. M.; Repasky, M. P.; Zhang, L. Y.; Berne, B. J.; Friesner, R. A.; Gallicchio, E.; Levy, R. M. *Journal of Computational Chemistry* **2005**, *26*, 1752-1780.

(144) Bochevarov, A. D.; Harder, E.; Hughes, T. F.; Greenwood, J. R.; Braden, D. A.; Philipp, D. M.; Rinaldo, D.; Halls, M. D.; Zhang, J.; Friesner, R. A. *International Journal of Quantum Chemistry* **2013**, *113*, 2110-2142.

(145) Zhao, Y.; Truhlar, D. *Theoretical Chemistry Accounts* **2008**, *120*, 215-241.

(146) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652.

(147) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785-789.

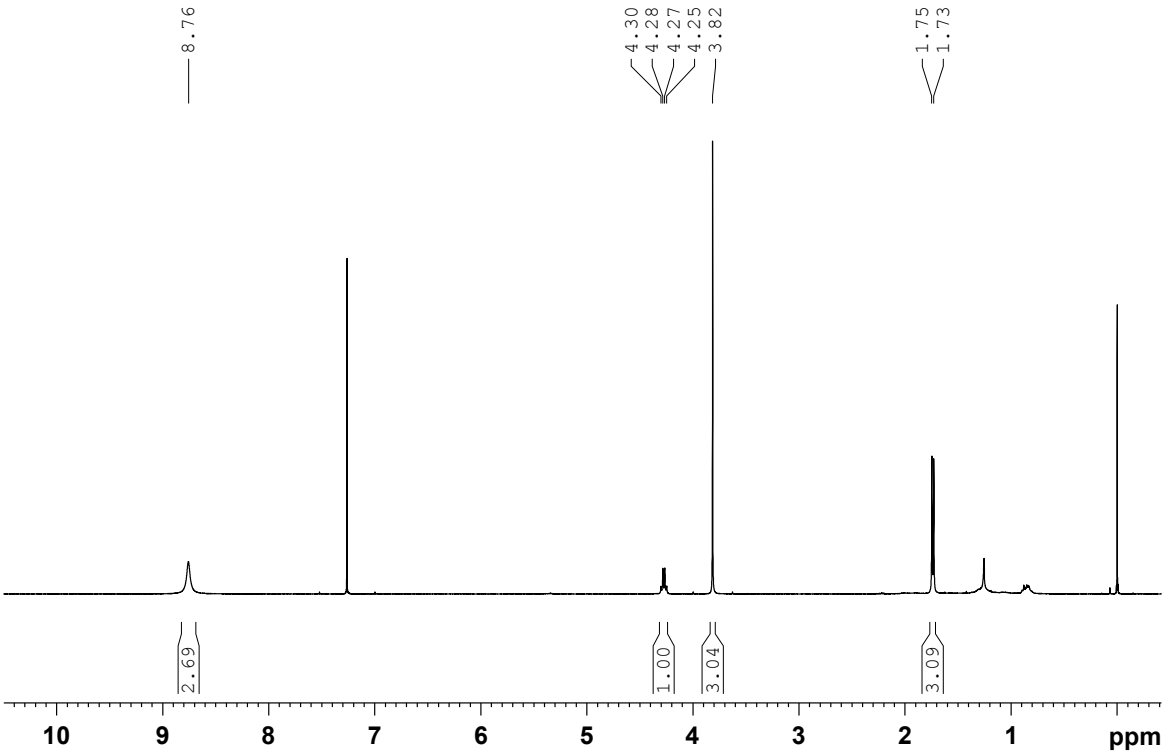
(148) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623-11627.

(149) Lood, C.; Koskinen, A. M. P. *Unpublished data from the Koskinen laboratory, Aalto University*.

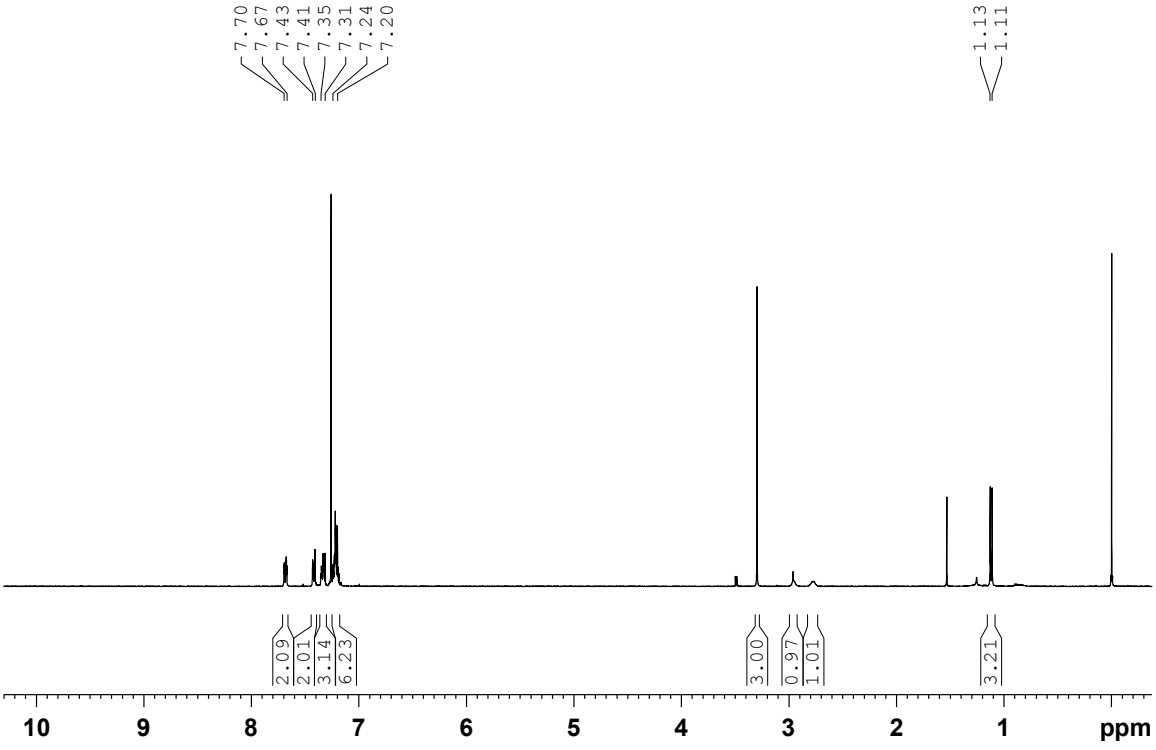
Appendices

Appendix 1: ^{1}H NMR spectra of 74a, 75a, 78a and 77a

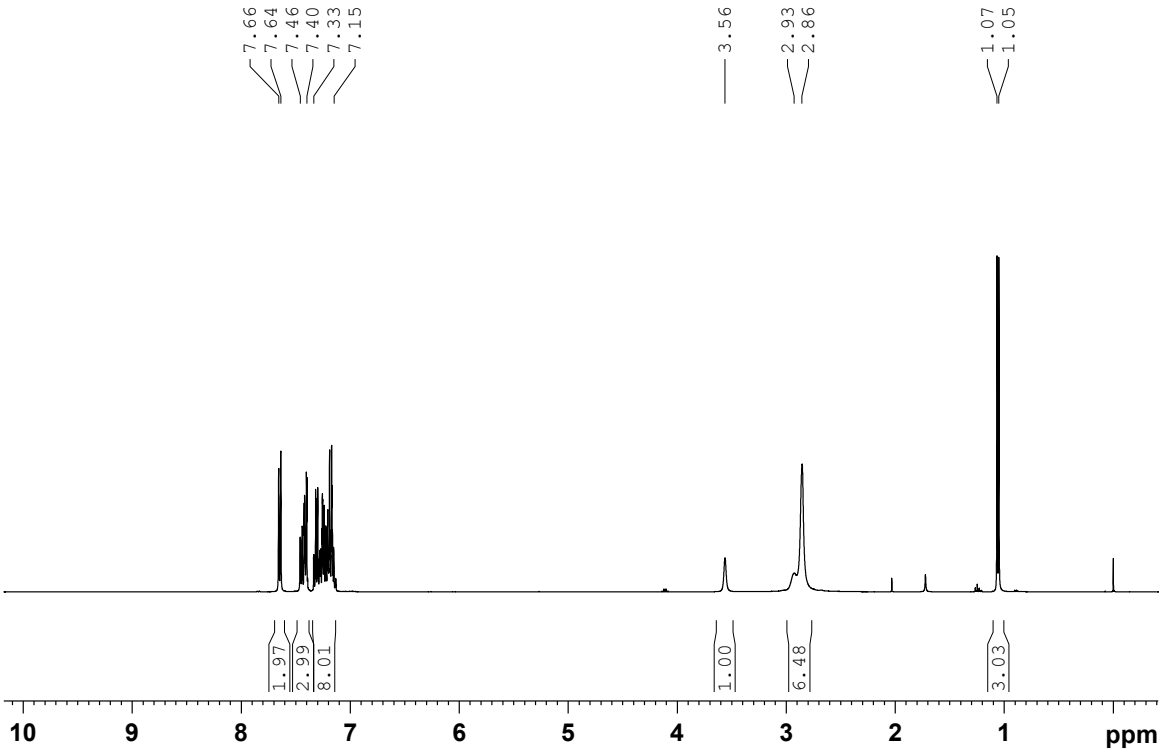
74a



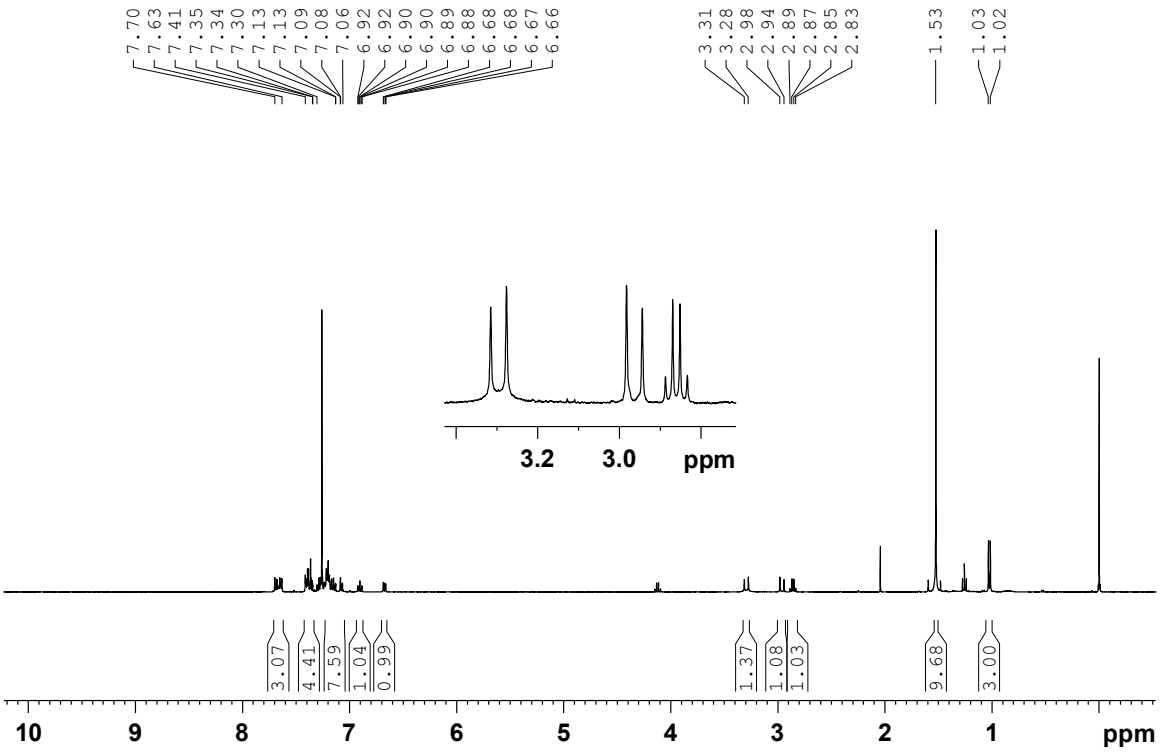
75a



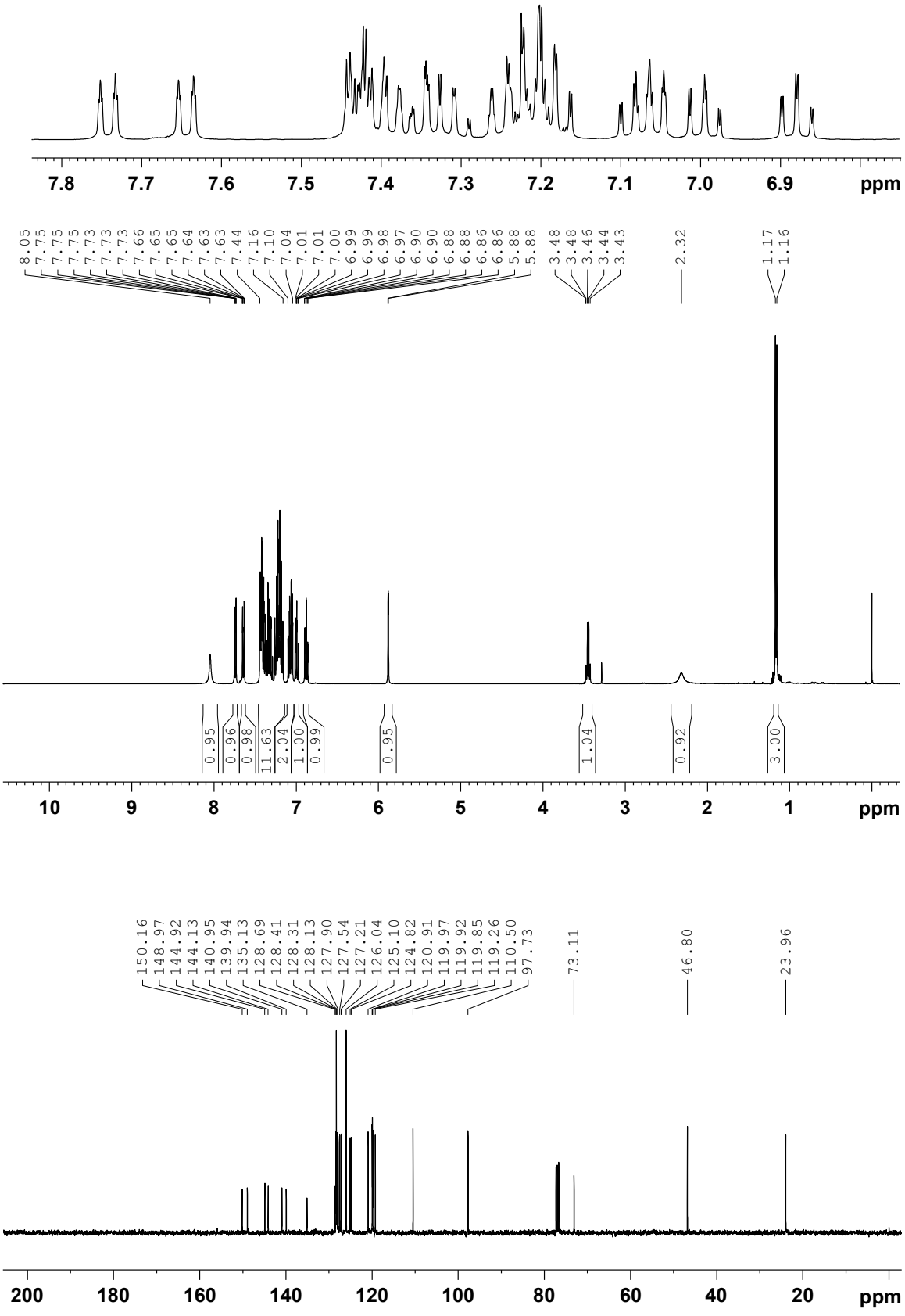
78a


7.66
7.64
7.46
7.40
7.33
7.15
3.56
2.93
2.86
1.07
1.05
1.97
2.99
8.01
1.00
6.48
3.03
10
9
8
7
6
5
4
3
2
1
ppm

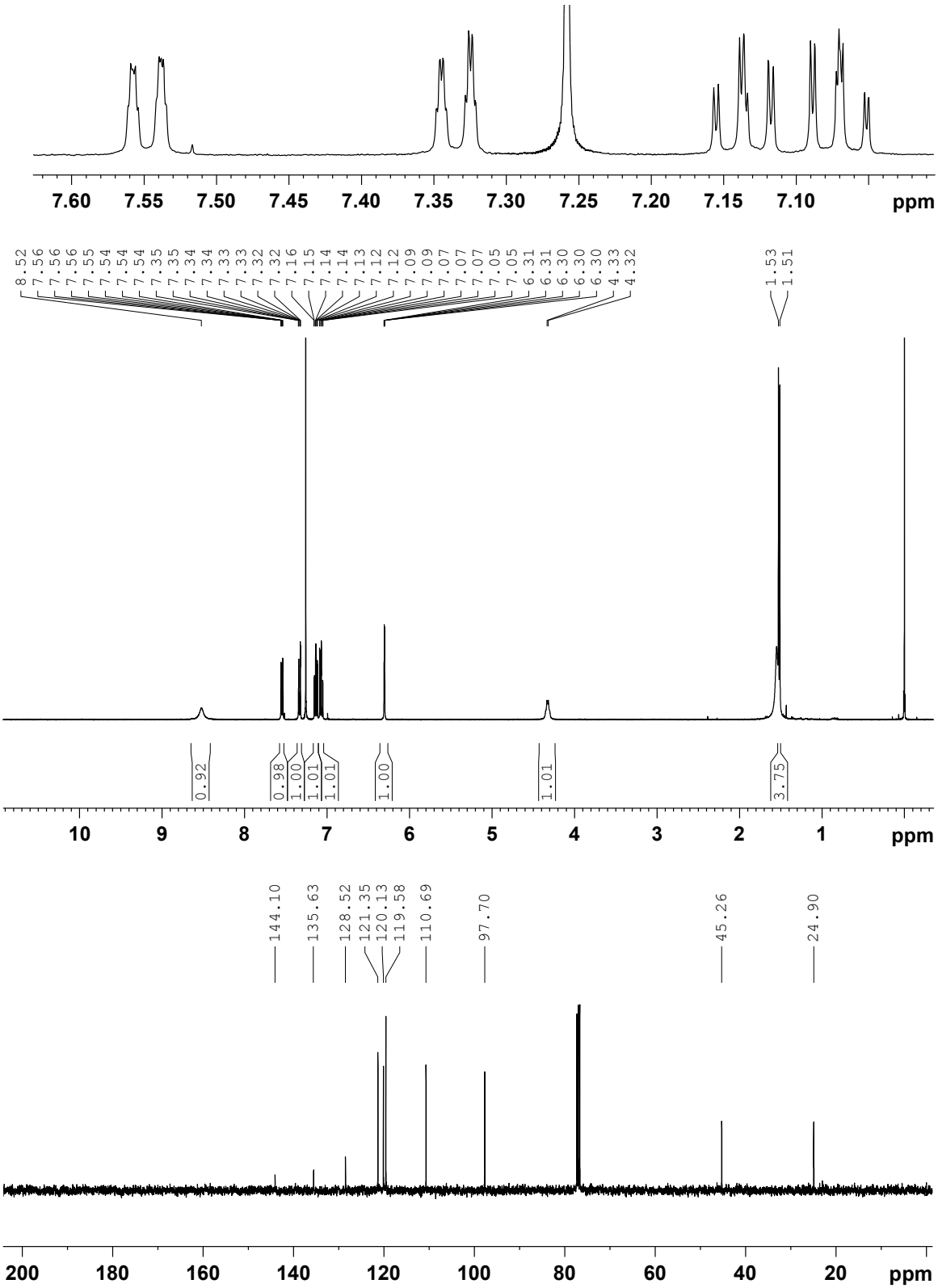
77a


7.70
7.63
7.41
7.35
7.34
7.30
7.13
7.13
7.09
7.08
7.06
6.92
6.92
6.90
6.90
6.89
6.88
6.68
6.68
6.67
6.66
3.31
3.28
2.98
2.94
2.89
2.87
2.85
2.83
1.53
1.03
1.02
3.2
3.0
ppm
3.07
4.41
7.59
1.04
0.99
1.37
1.08
1.03
9.68
3.00
10
9
8
7
6
5
4
3
2
1
ppm

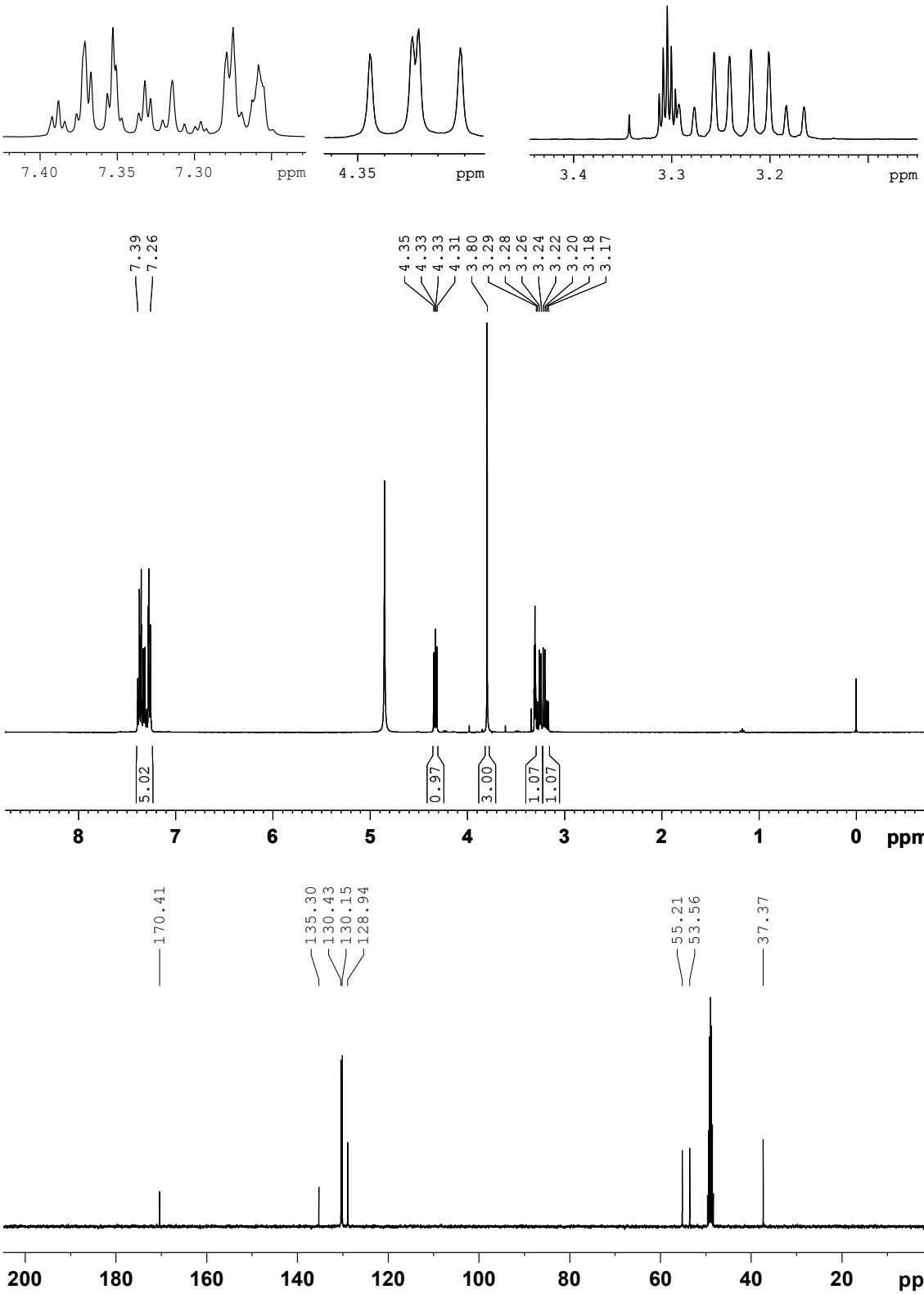
Appendix 2: ^{1}H NMR and ^{13}C NMR data of 85a



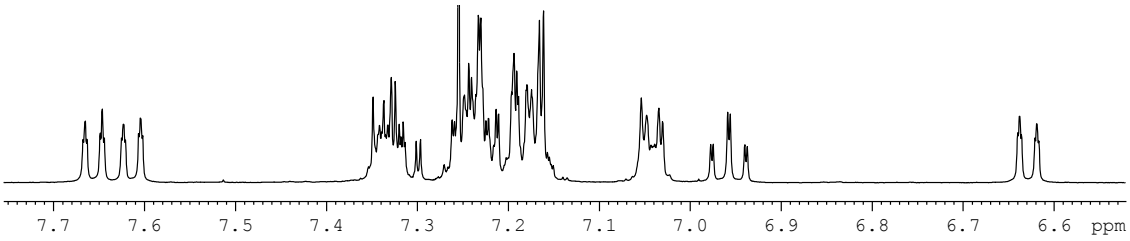
Appendix 3: ^{1}H NMR and ^{13}C NMR data of 76a

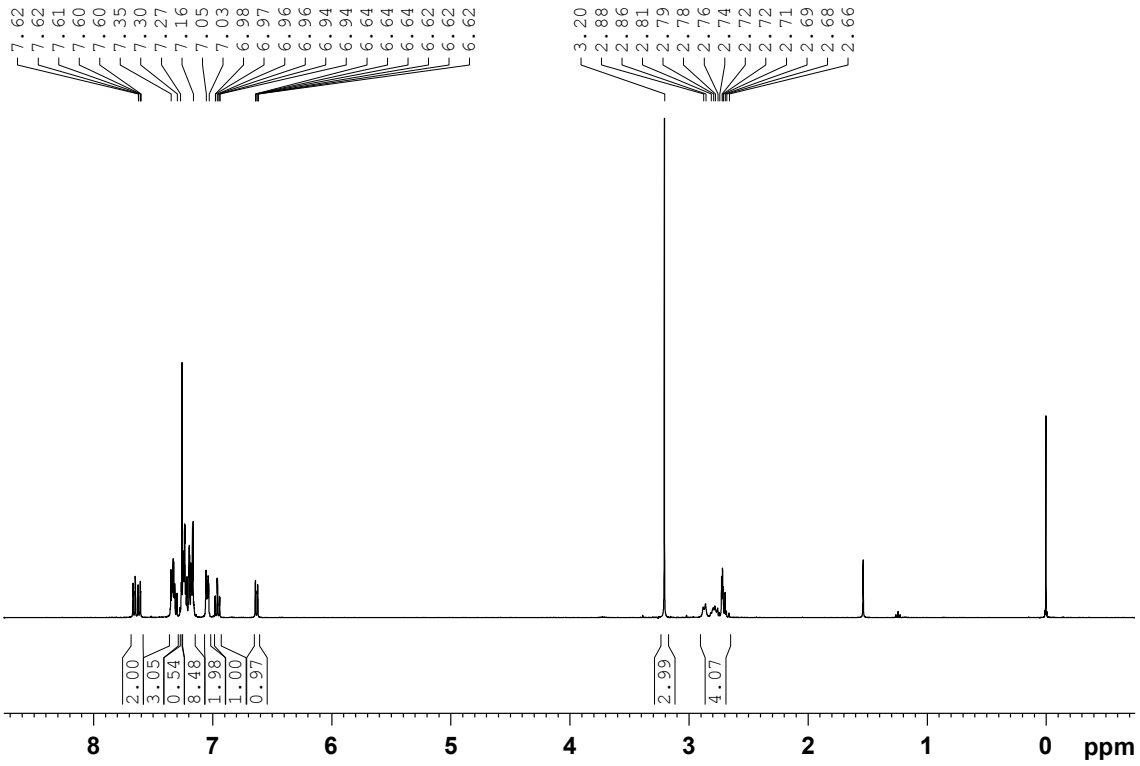


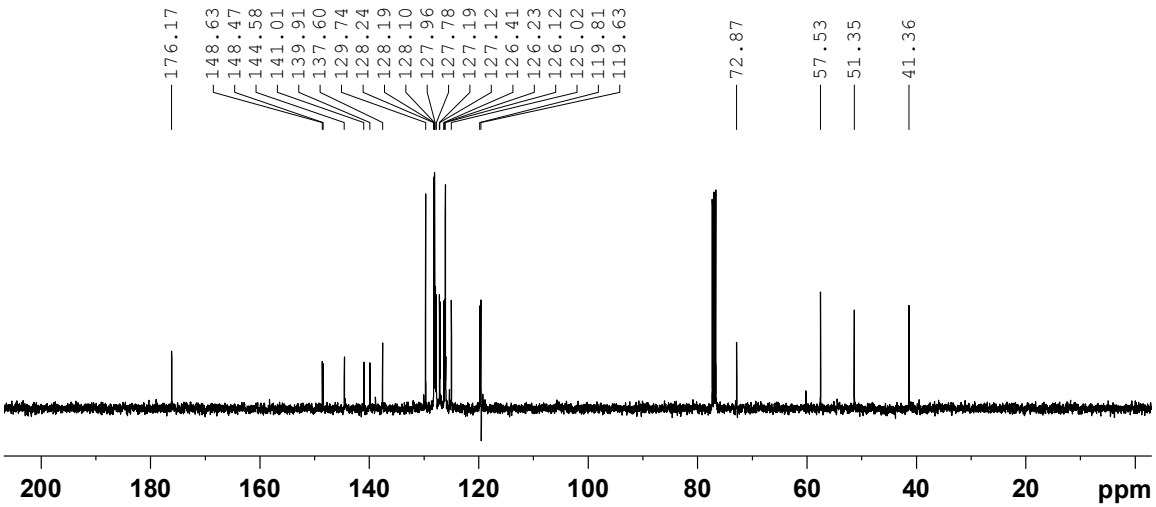
Appendix 4: ^{1}H NMR and ^{13}C NMR data of 74b



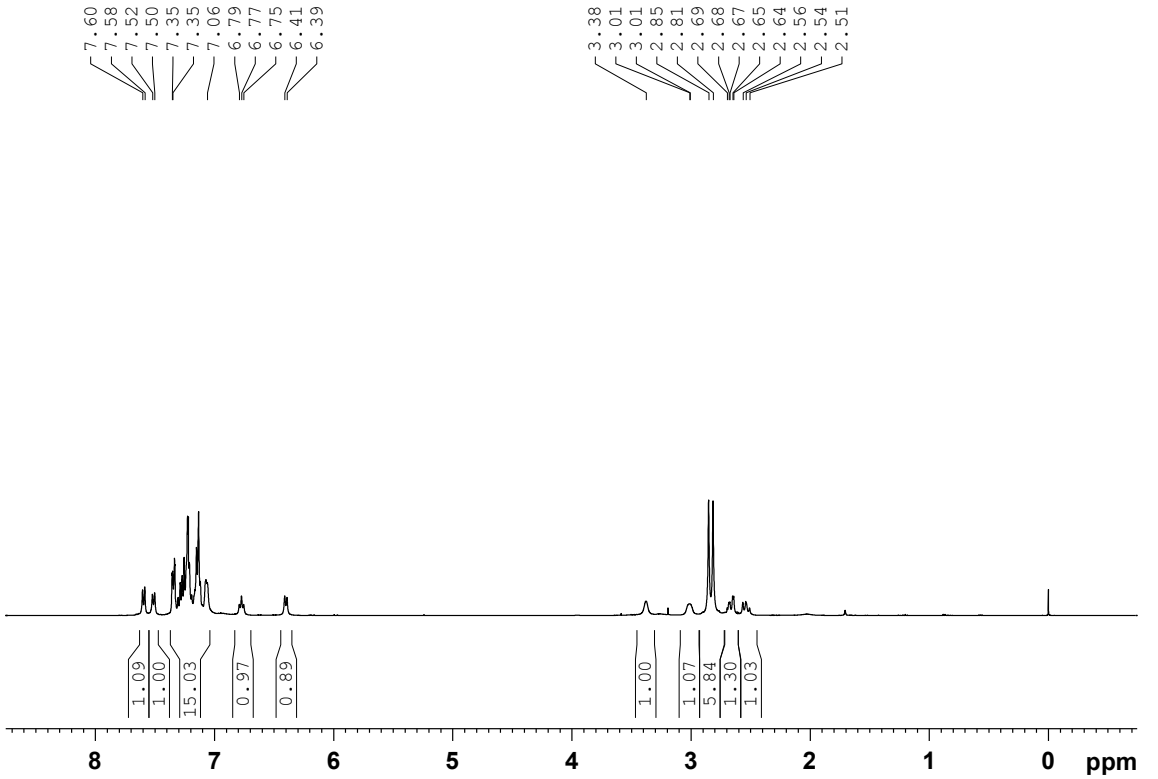
Appendix 5: ^{1}H NMR and ^{13}C NMR data of 75b

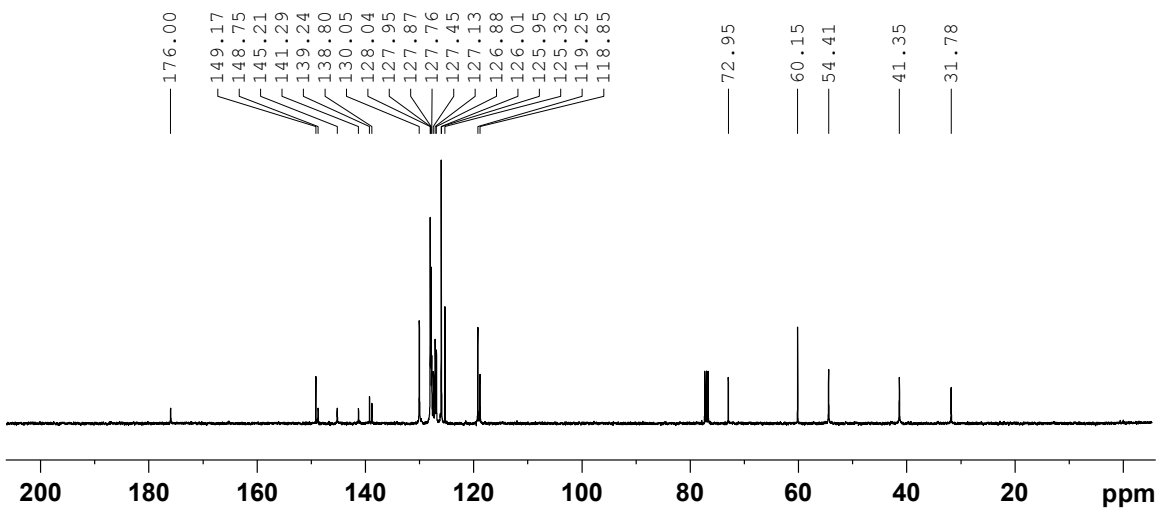




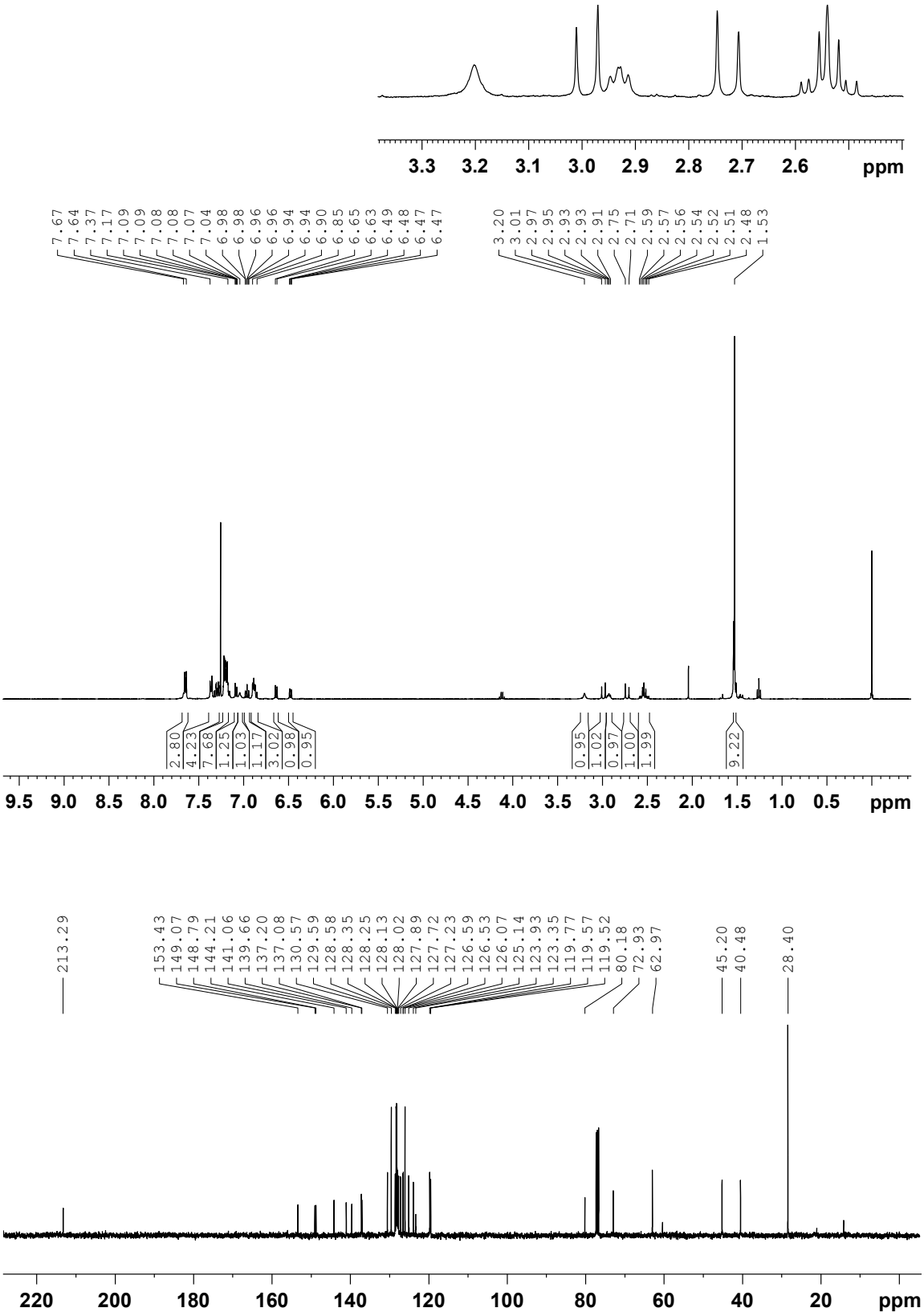


Appendix 6: ^{1}H NMR and ^{13}C NMR data of 78b

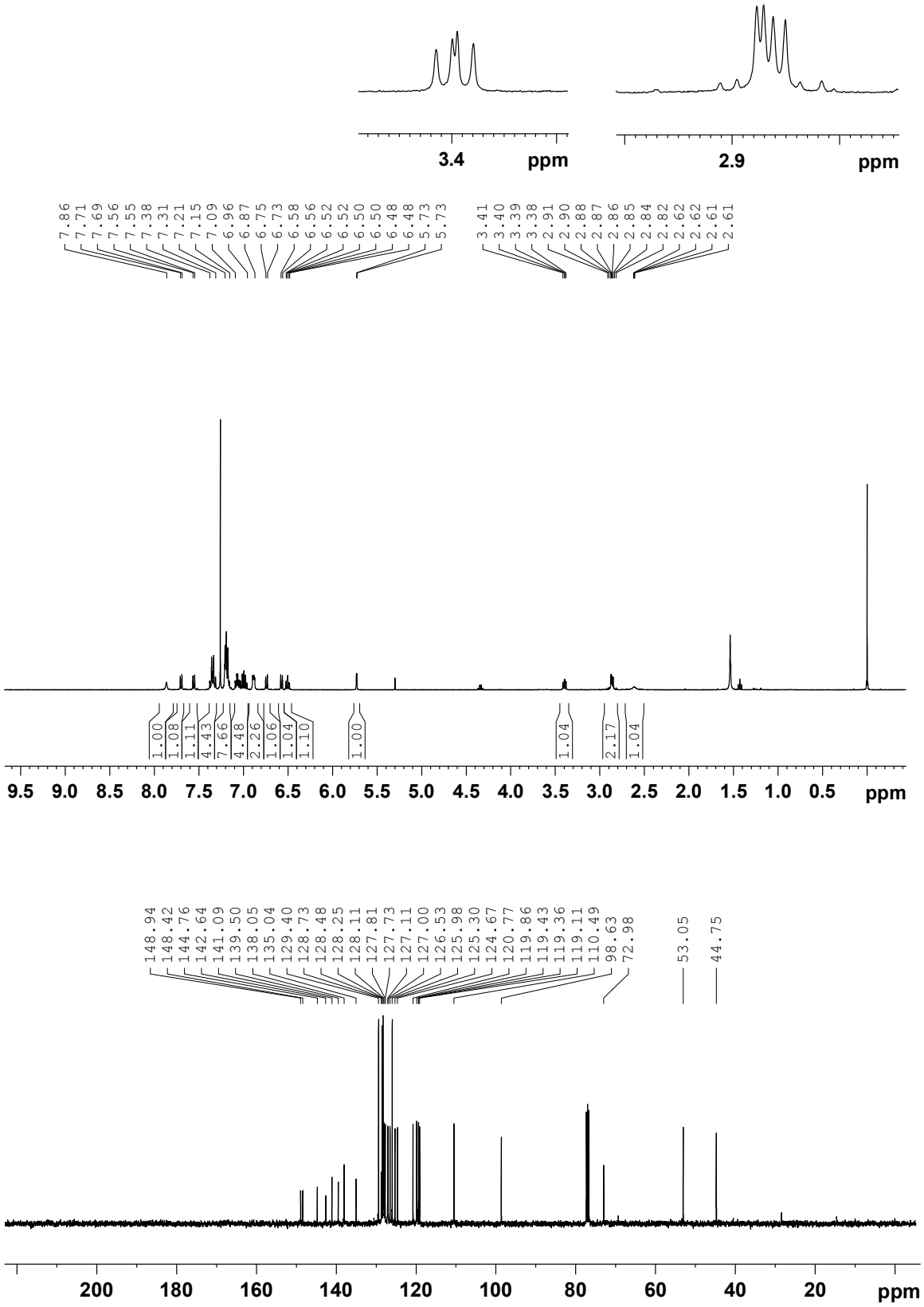




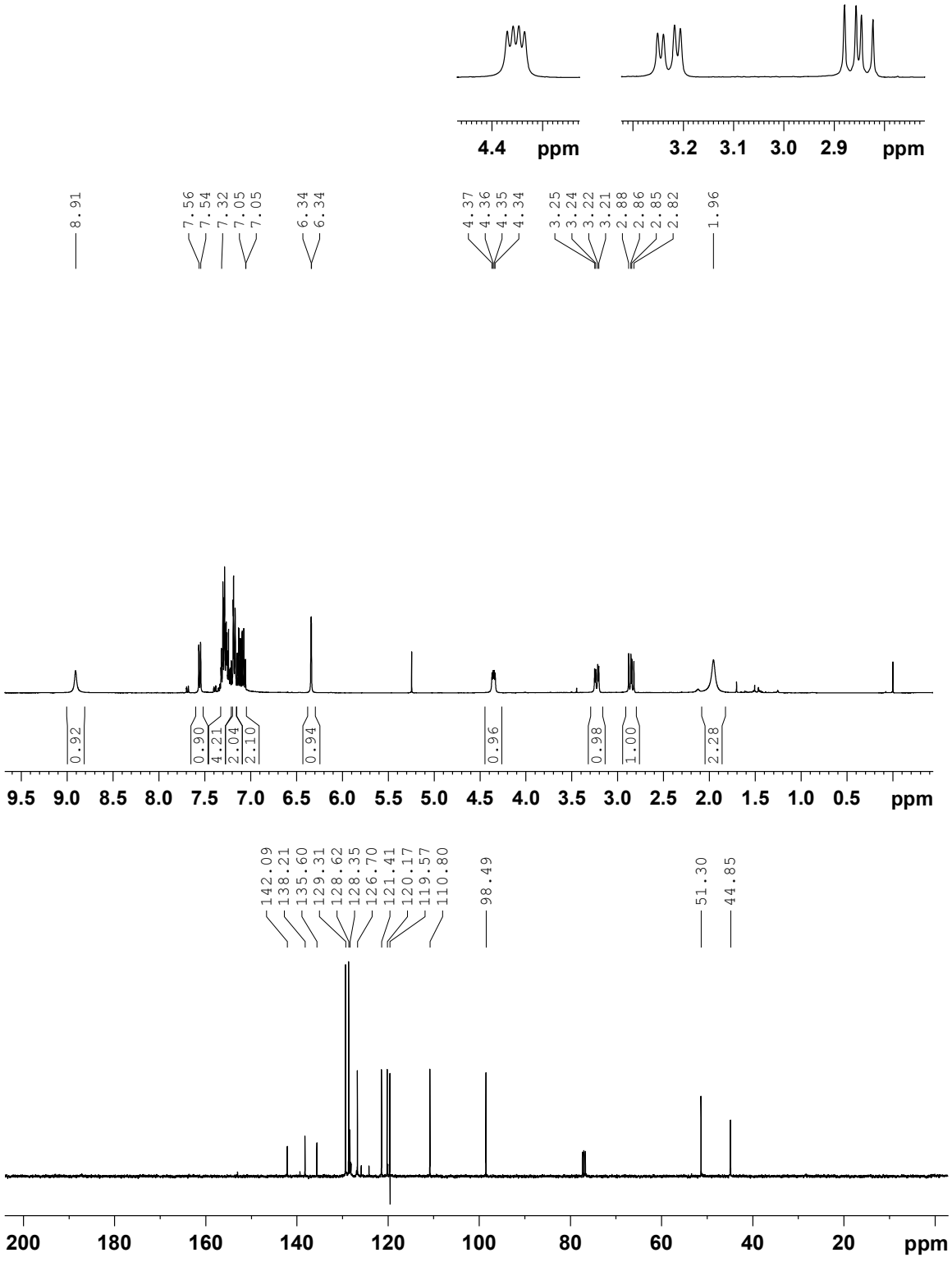
Appendix 7: ^{1}H NMR and ^{13}C NMR data of 77b



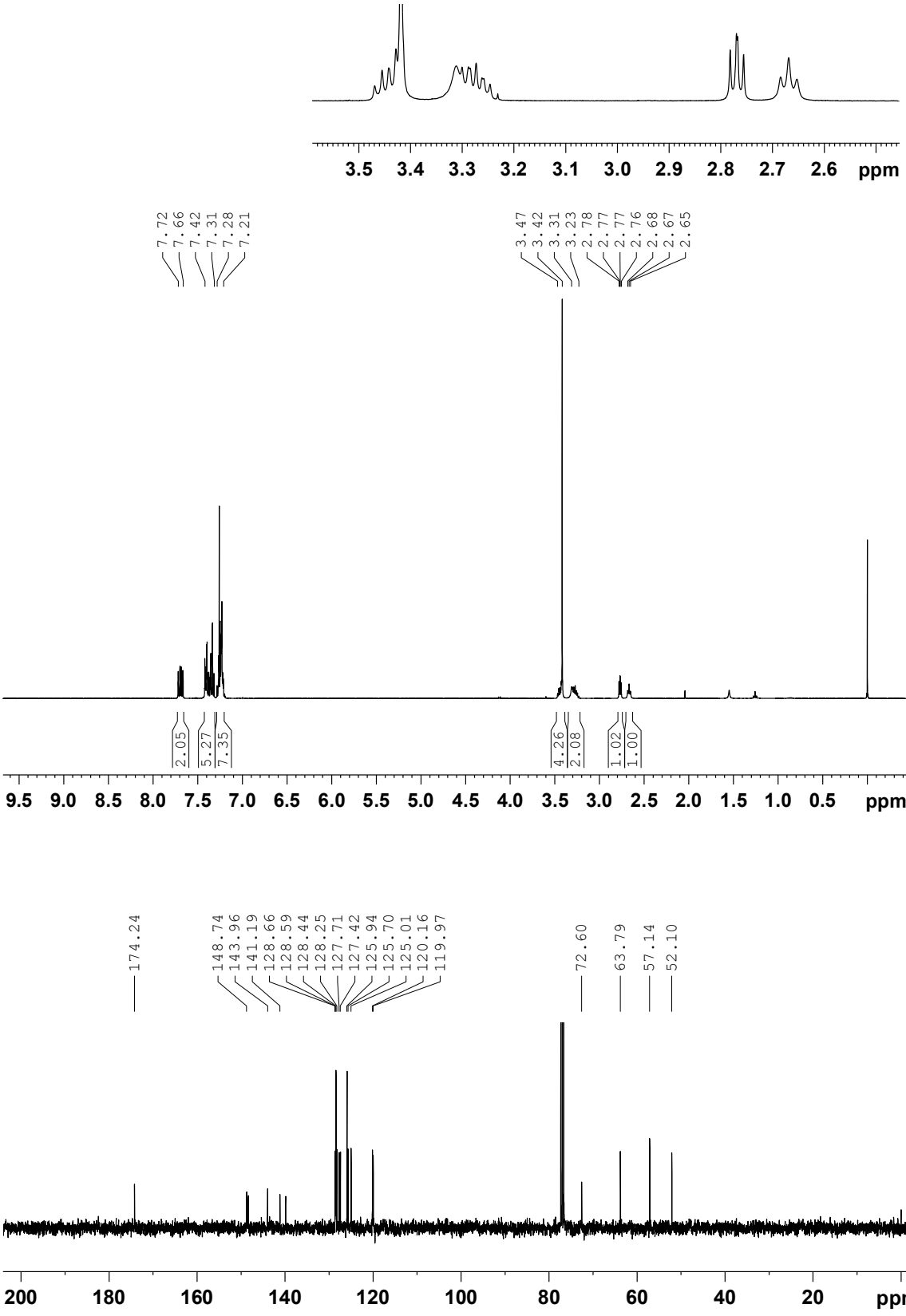
Appendix 8: ^{1}H NMR and ^{13}C NMR data of 85b



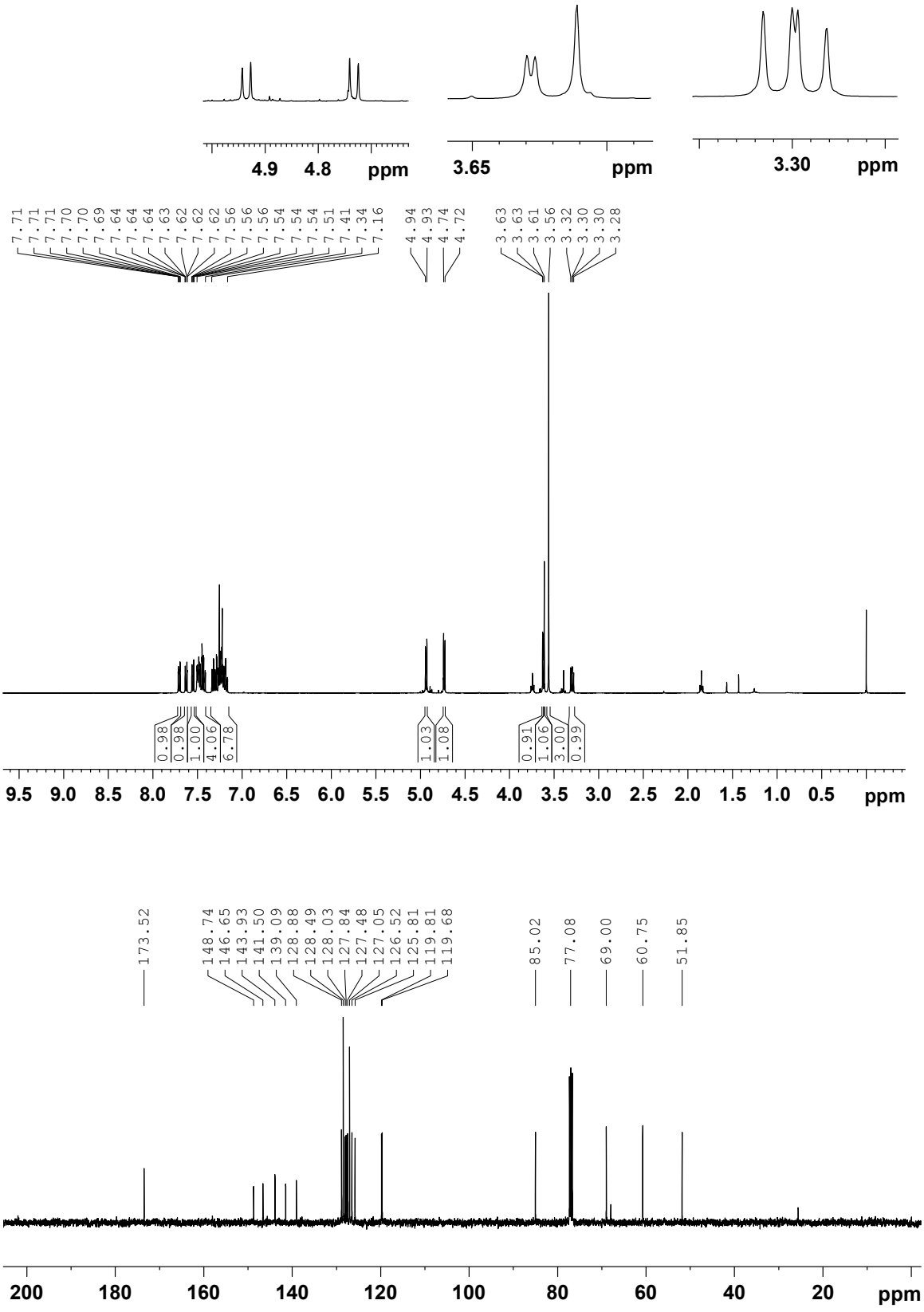
Appendix 9: ^{1}H NMR and ^{13}C NMR data of 76b



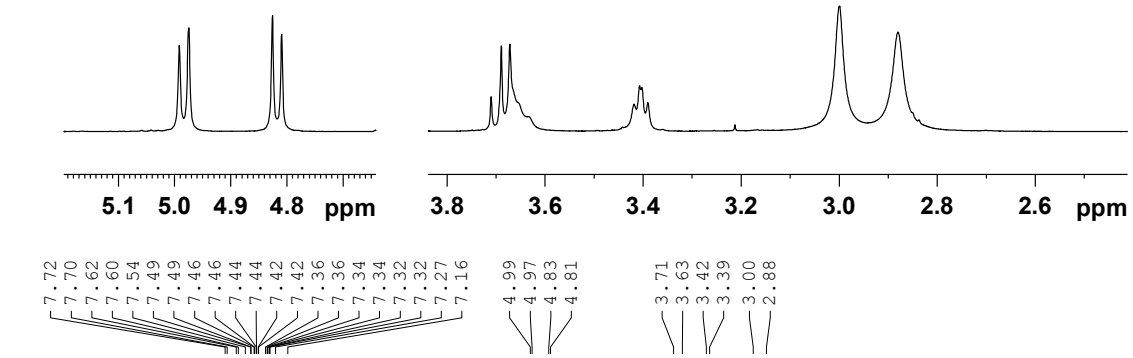
Appendix 10: ^{1}H NMR and ^{13}C NMR data of 75c

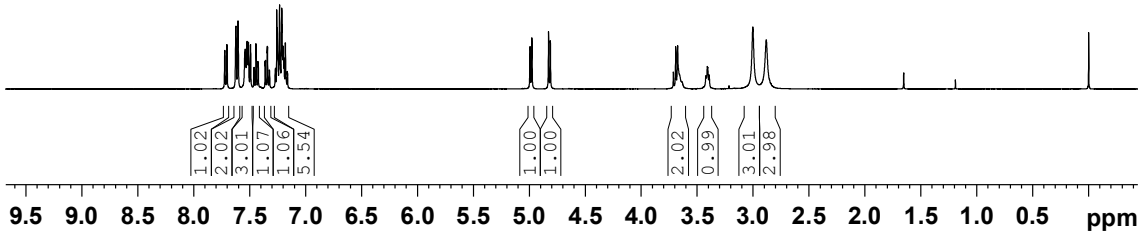


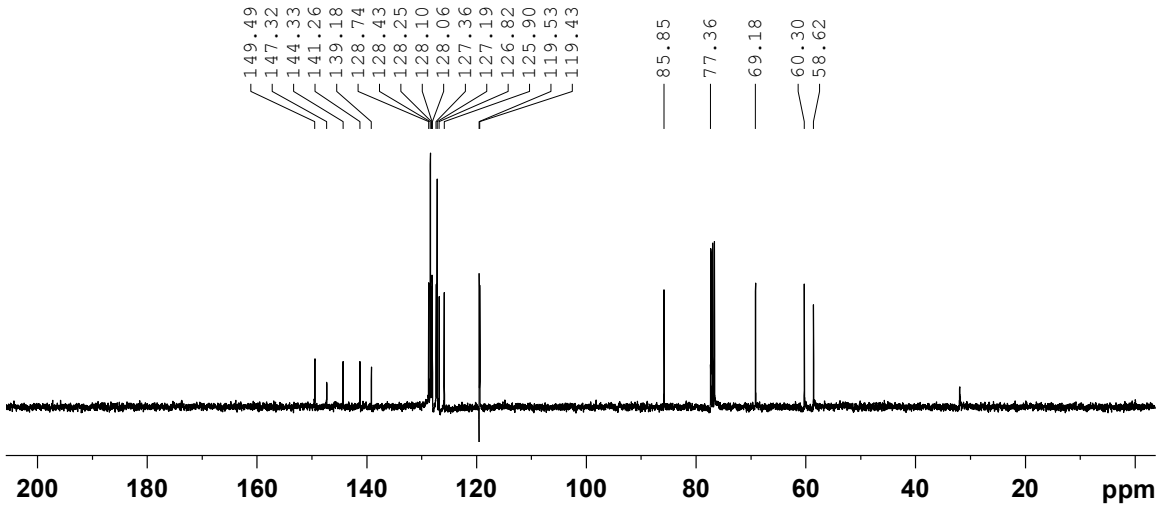
Appendix 11: ^{1}H NMR and ^{13}C NMR data of 84c



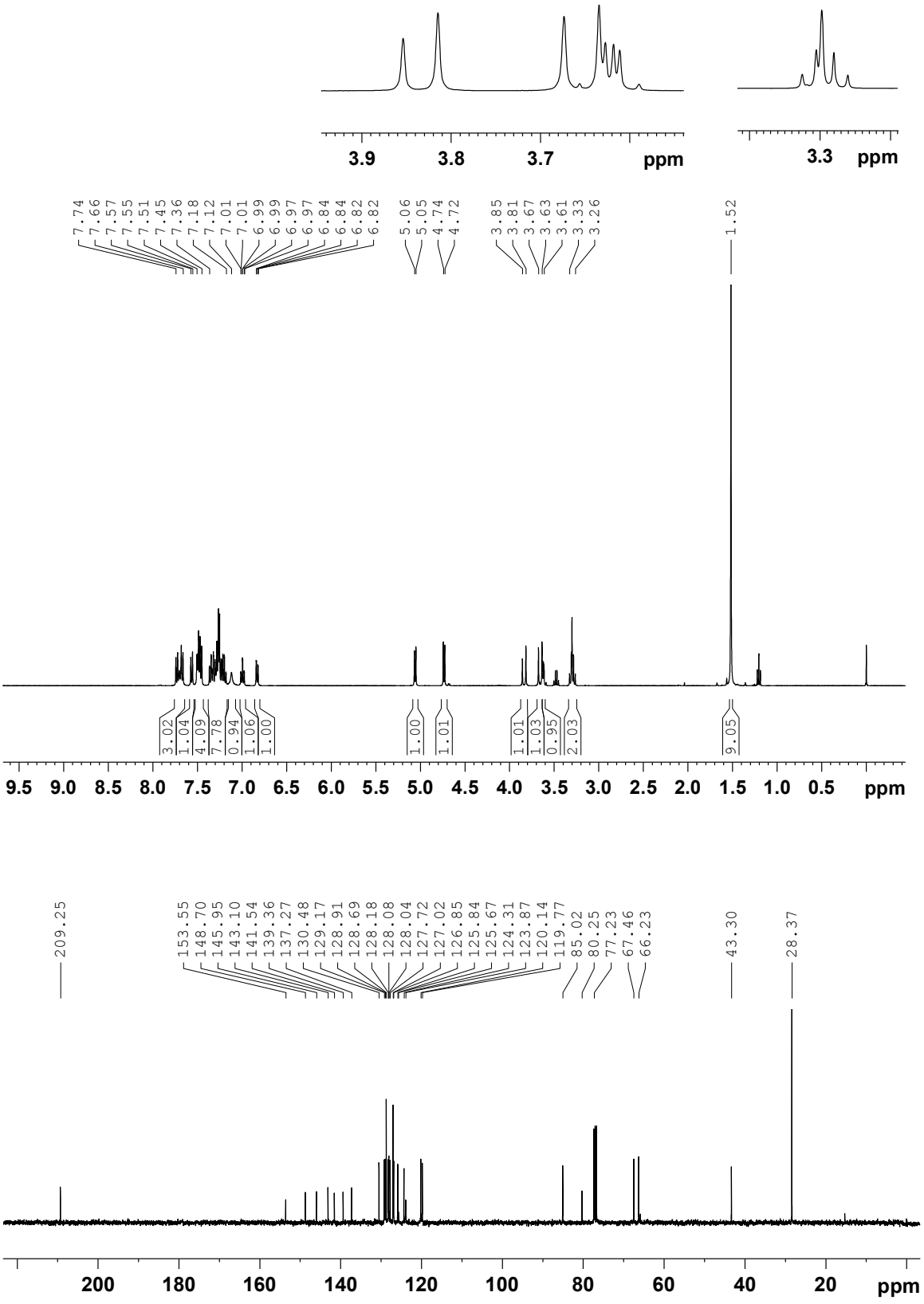
Appendix 12: ^{1}H NMR and ^{13}C NMR data of 78c



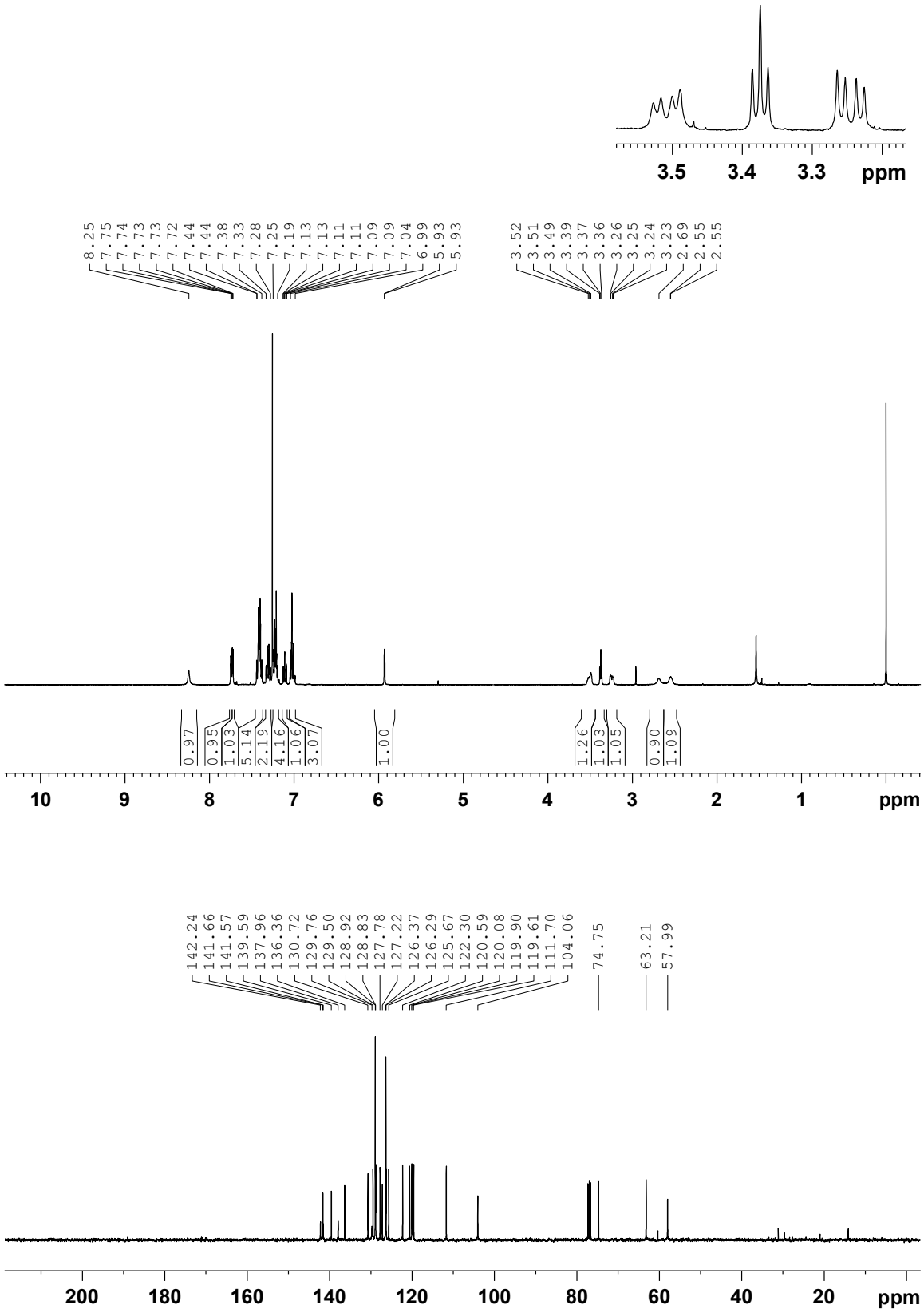




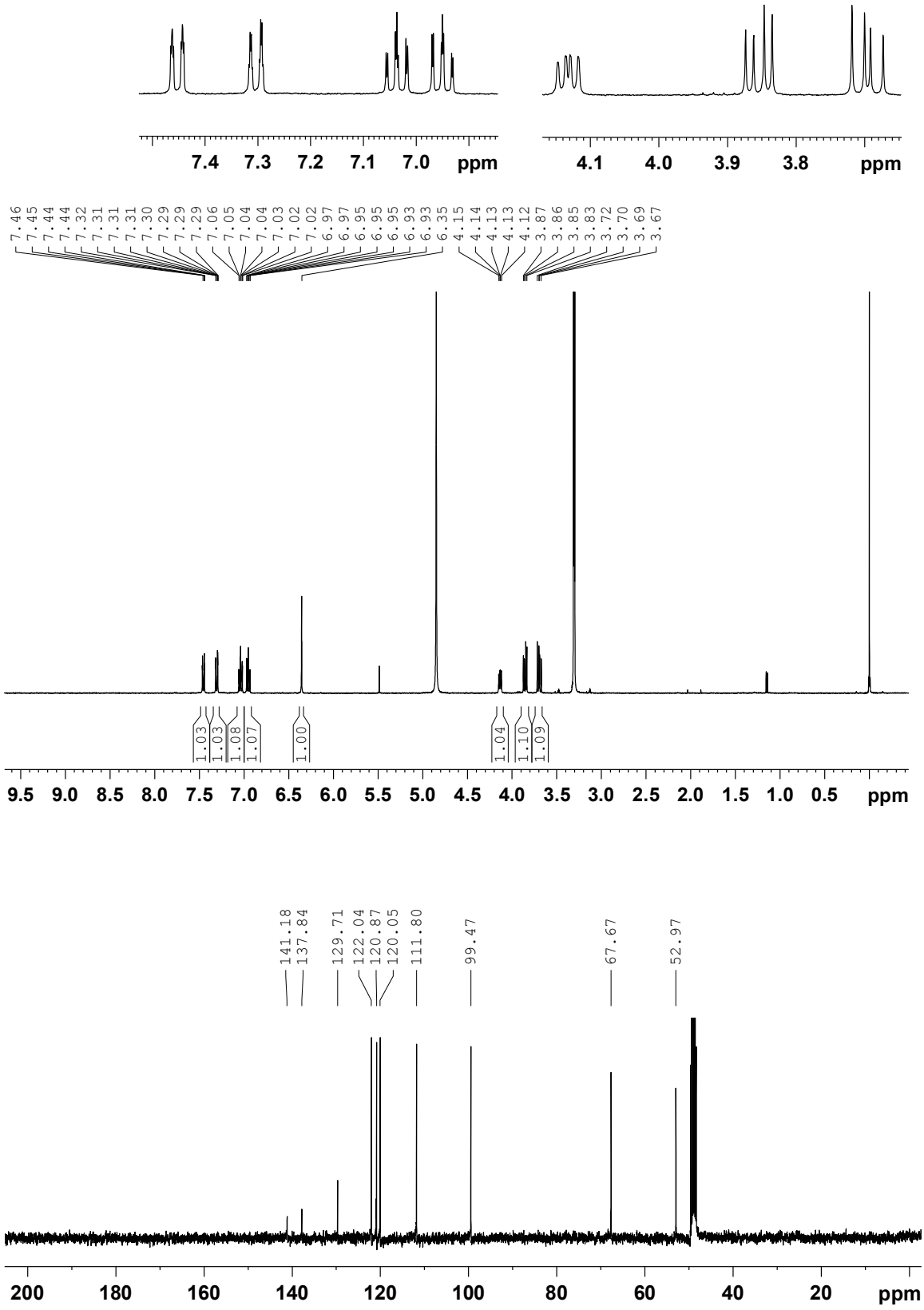
Appendix 13: ^{1}H NMR and ^{13}C NMR data of 77c



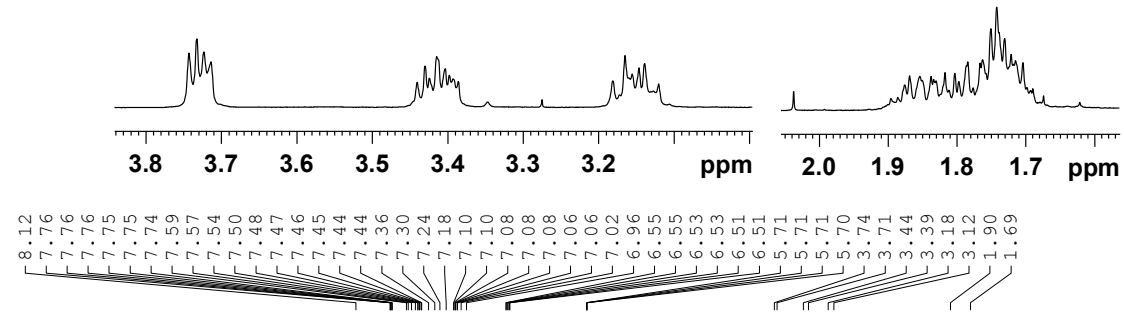
Appendix 14: ^{1}H NMR and ^{13}C NMR data of 85c

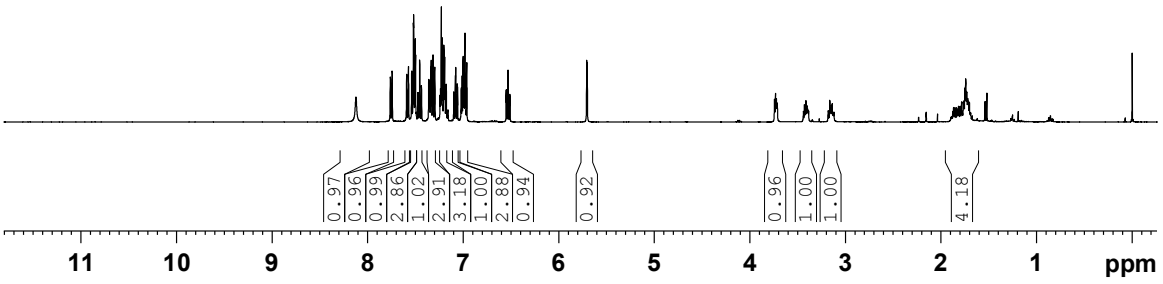


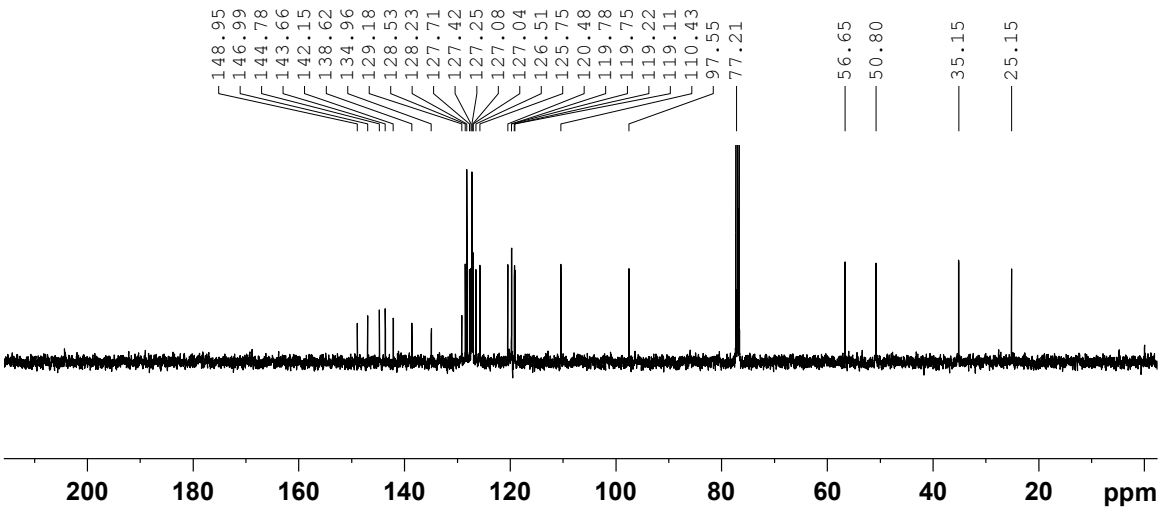
Appendix 15: ^{1}H NMR and ^{13}C NMR data of 76c



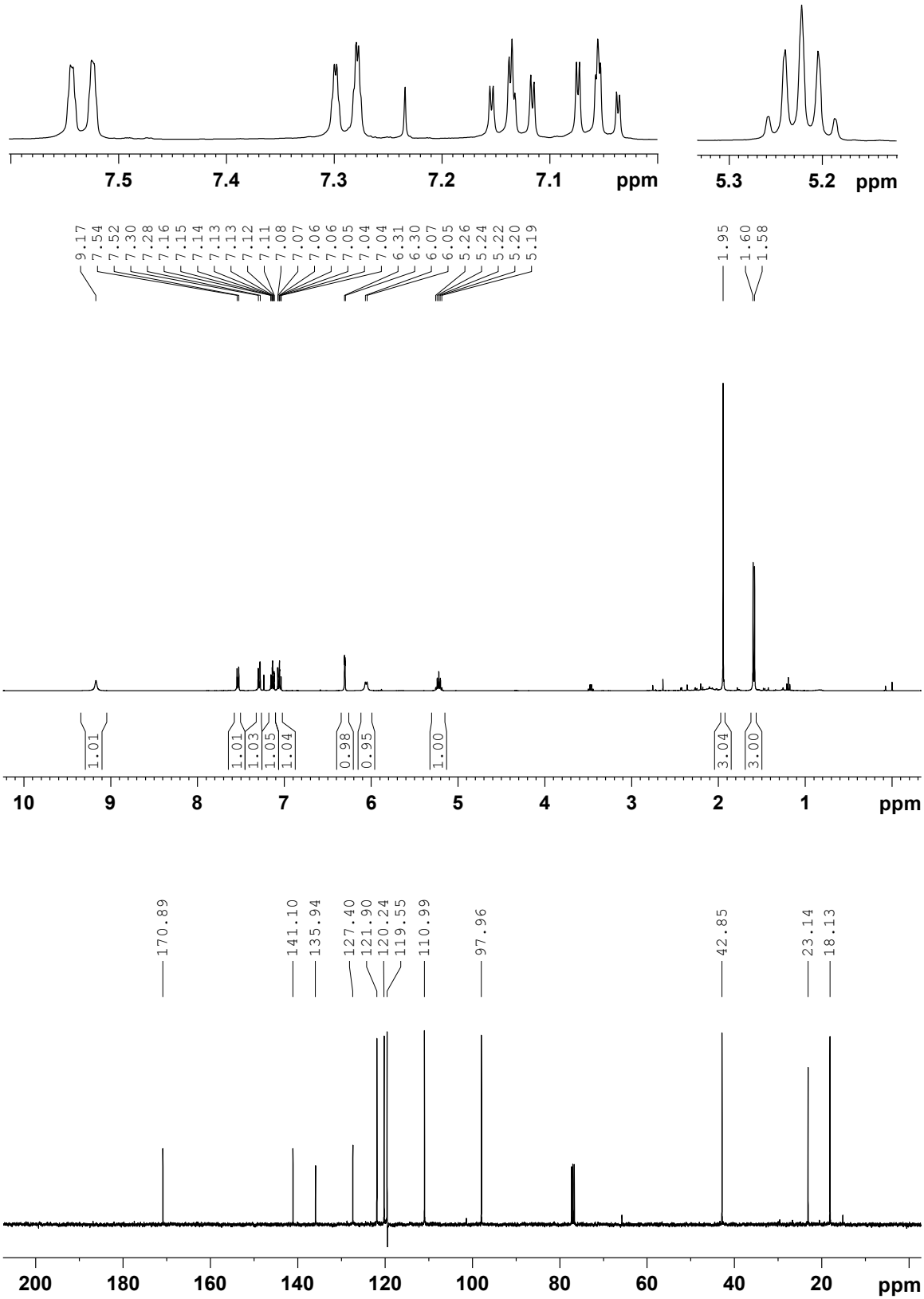
Appendix 16: ^{1}H NMR and ^{13}C NMR data of 85d



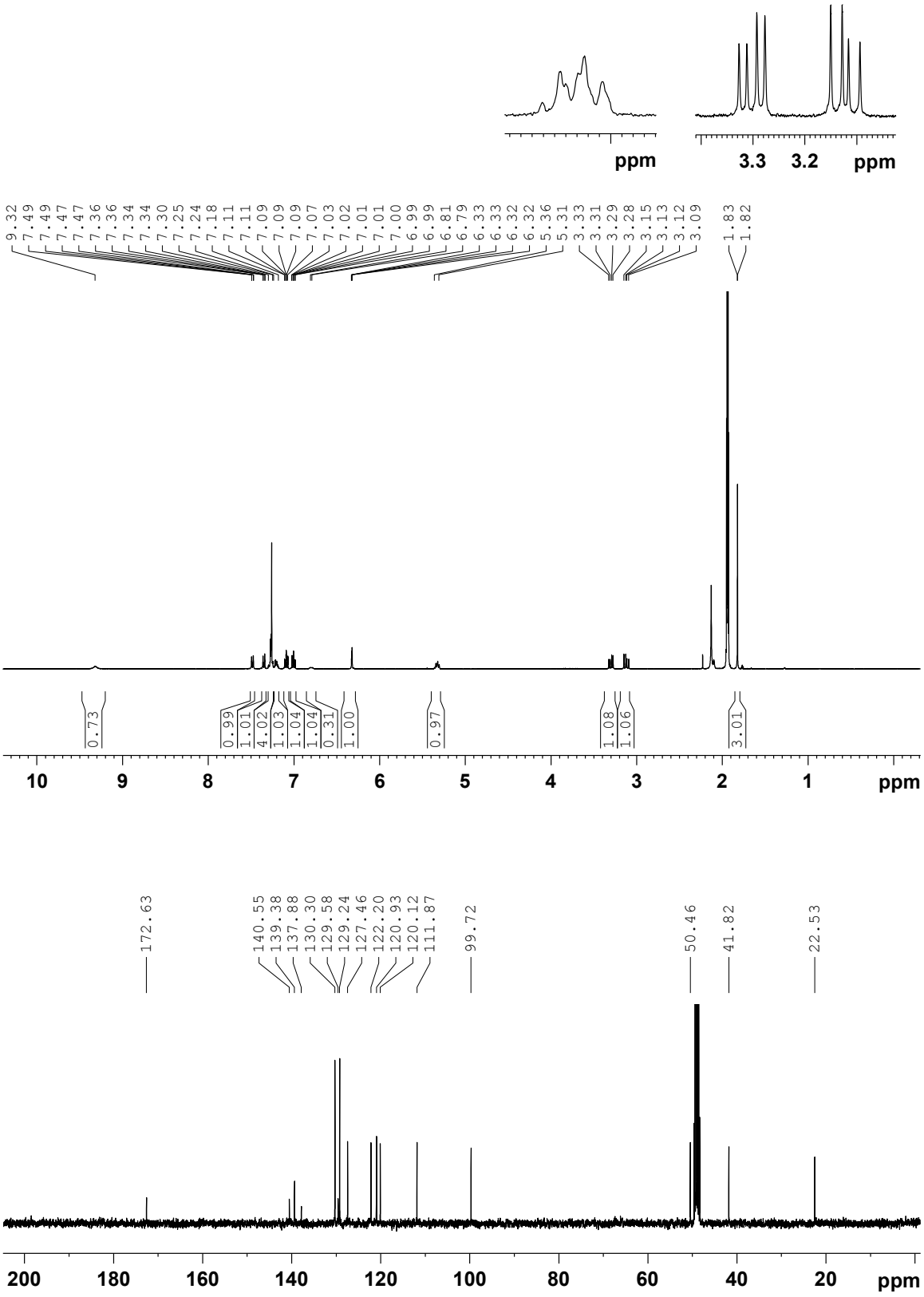




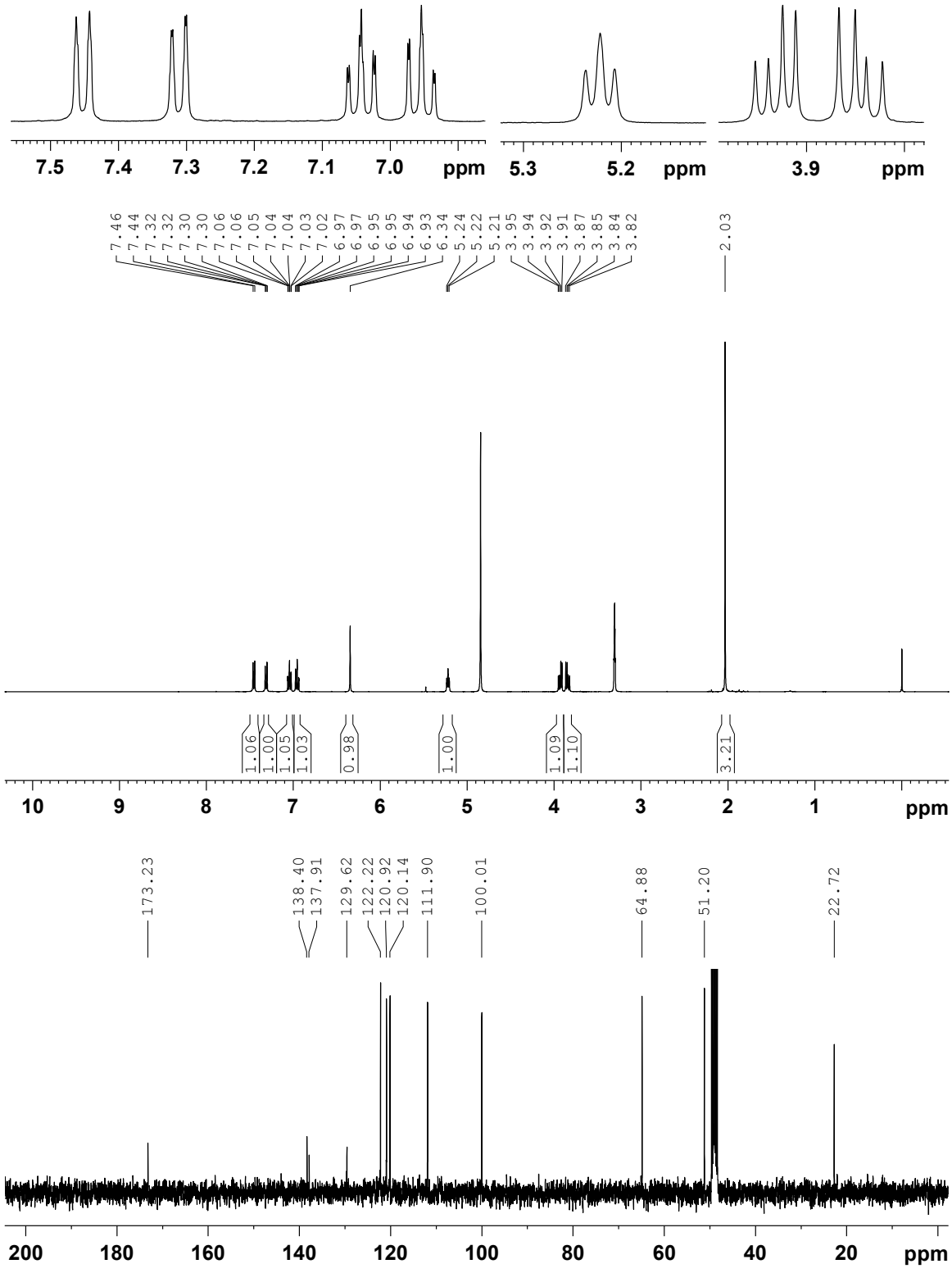
Appendix 17: ^{1}H NMR and ^{13}C NMR data of 80a



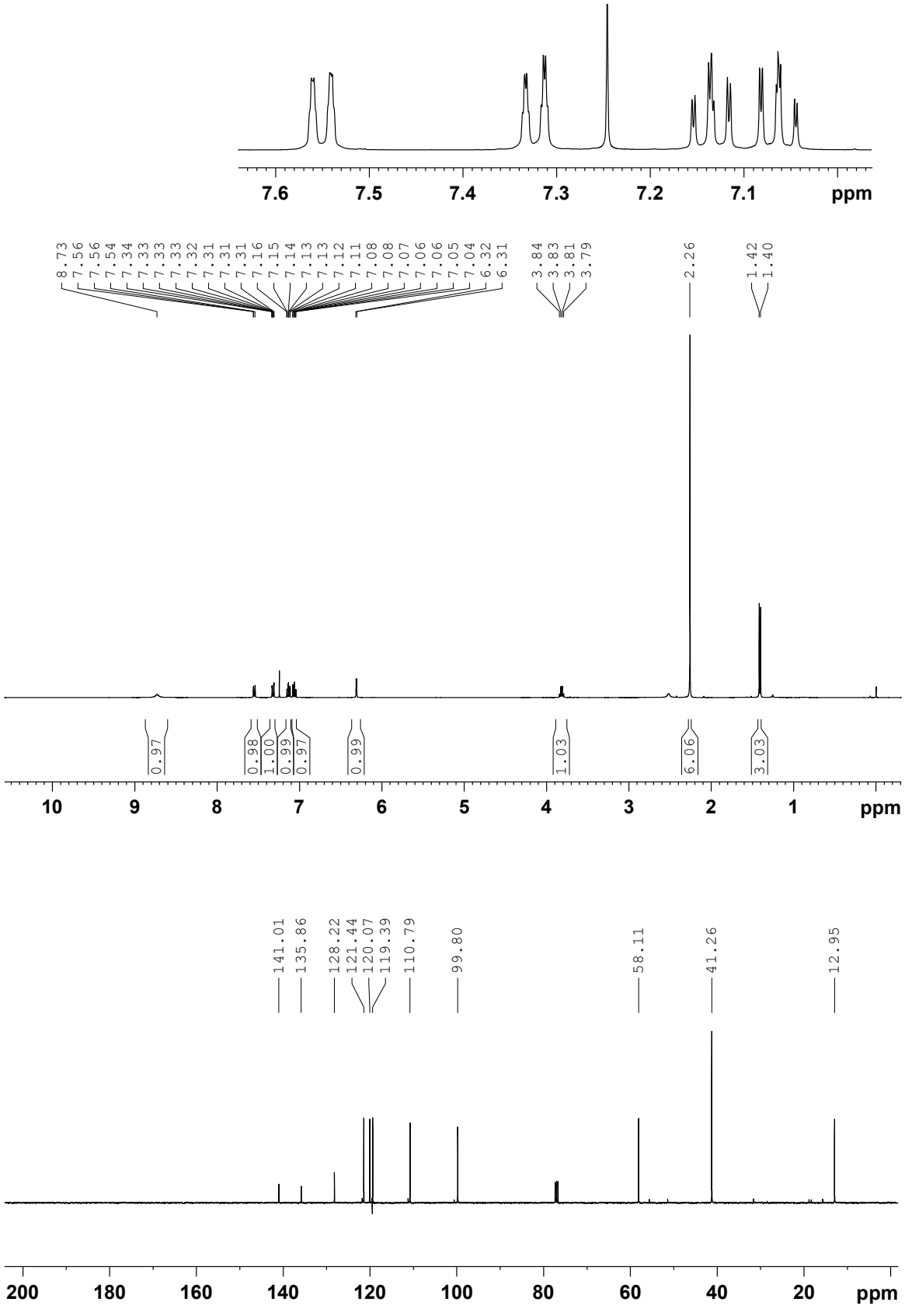
Appendix 18: ^{1}H NMR (CD_3CN) and ^{13}C NMR (CD_3OD) data of 80b



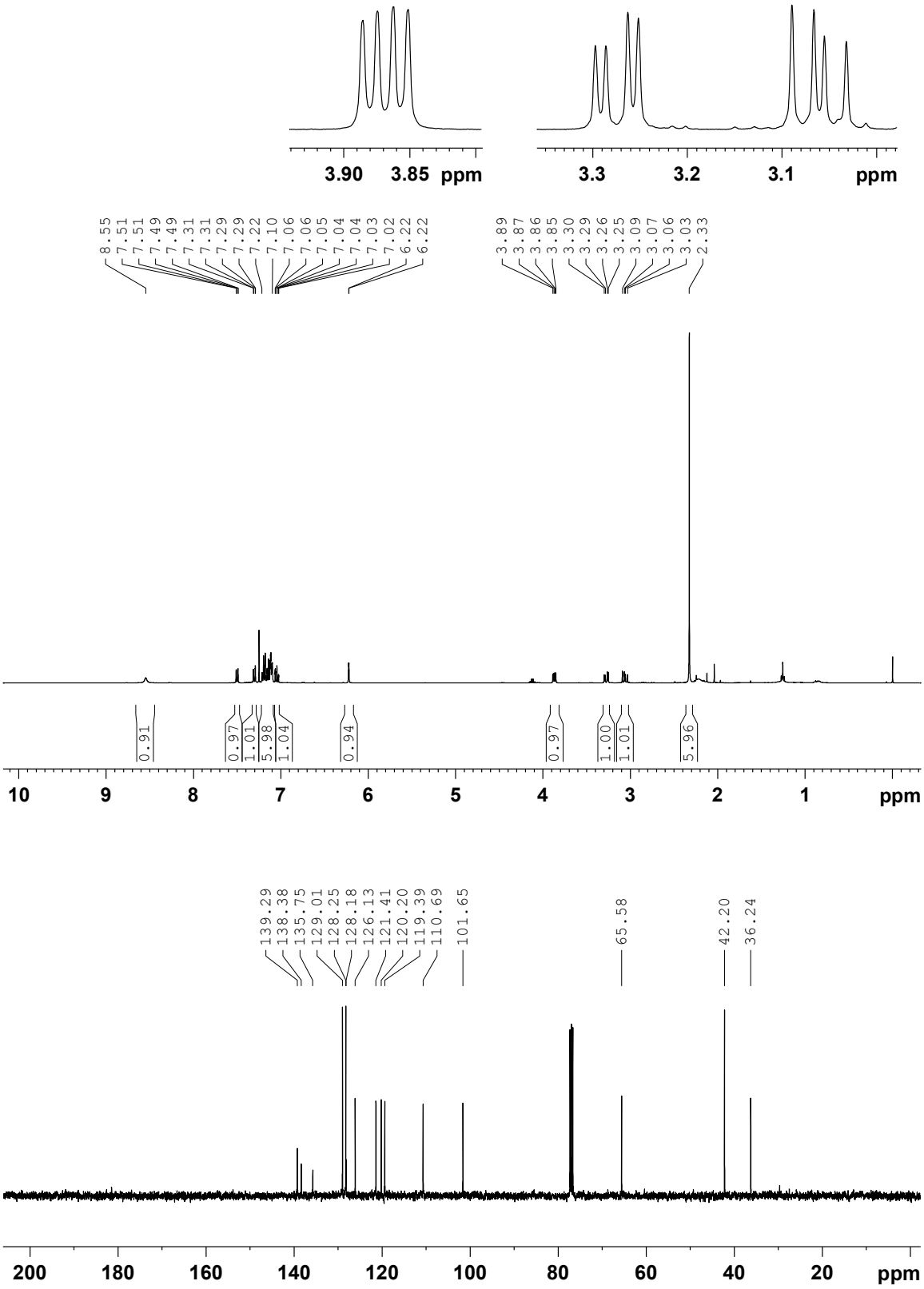
Appendix 19: ^{1}H NMR and ^{13}C NMR data of 80c



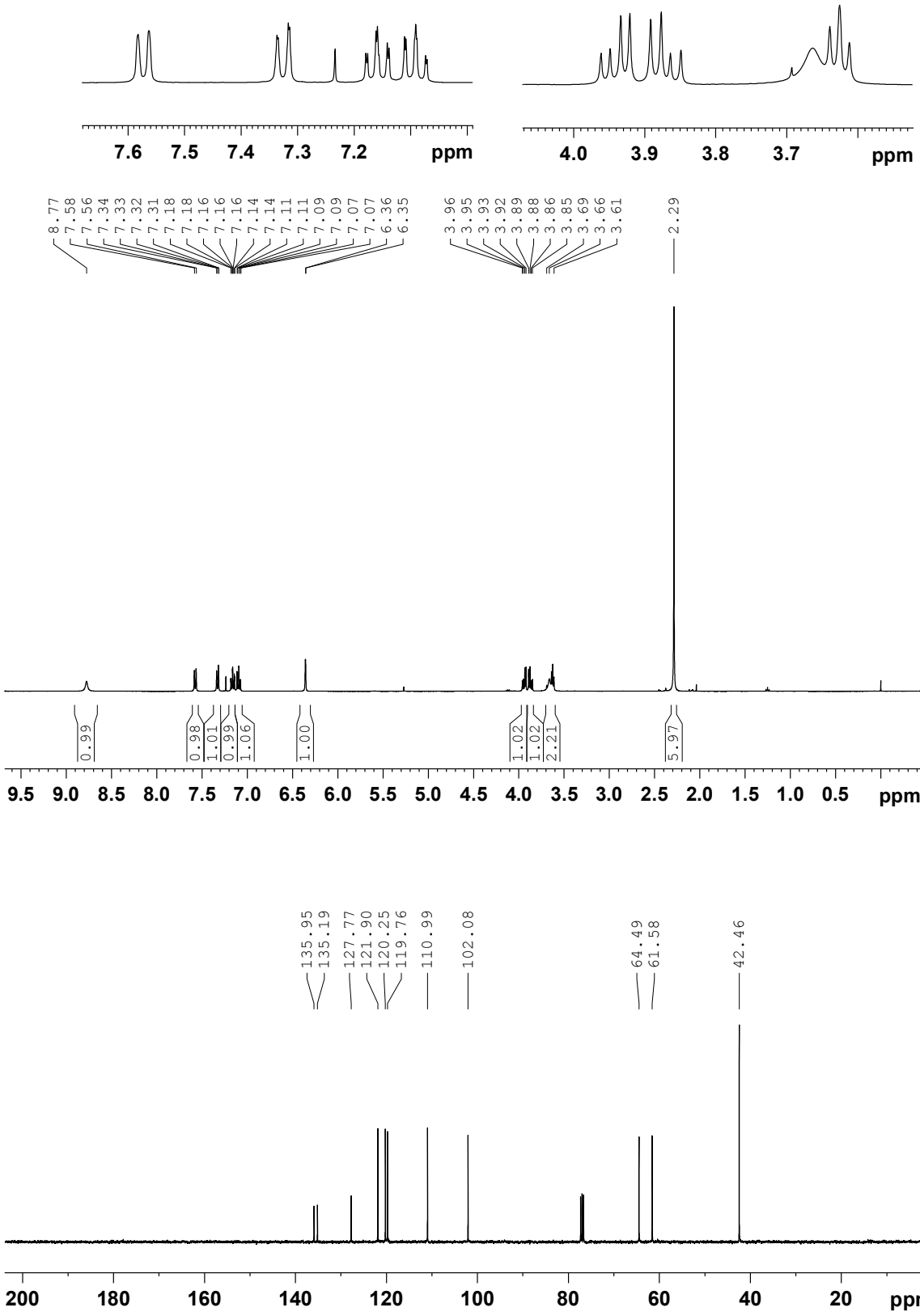
Appendix 20: ^{1}H NMR and ^{13}C NMR data of 81a



Appendix 21: ^{1}H NMR and ^{13}C NMR data of 81b

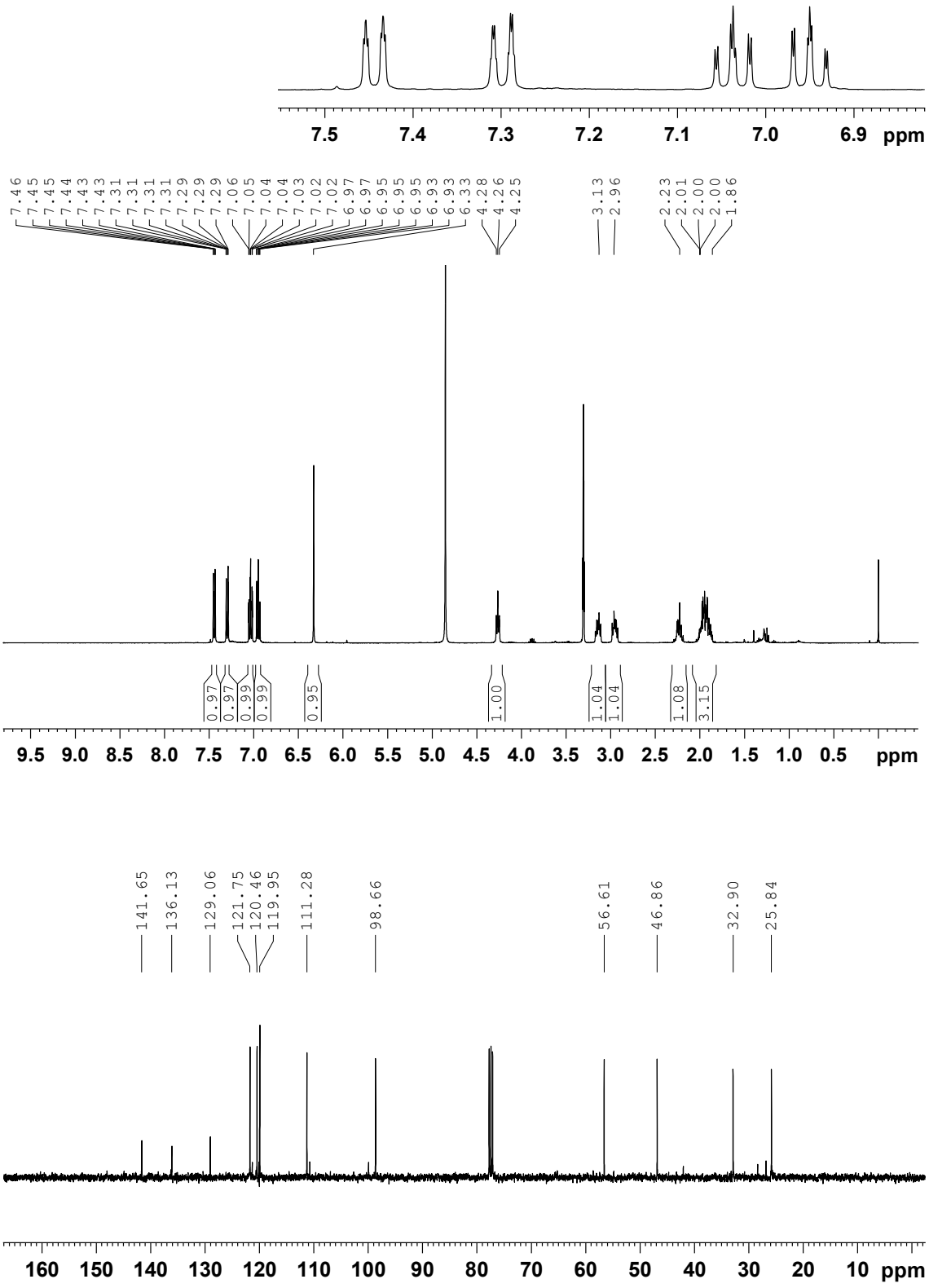


Appendix 22: ^{1}H NMR and ^{13}C NMR data of 81c

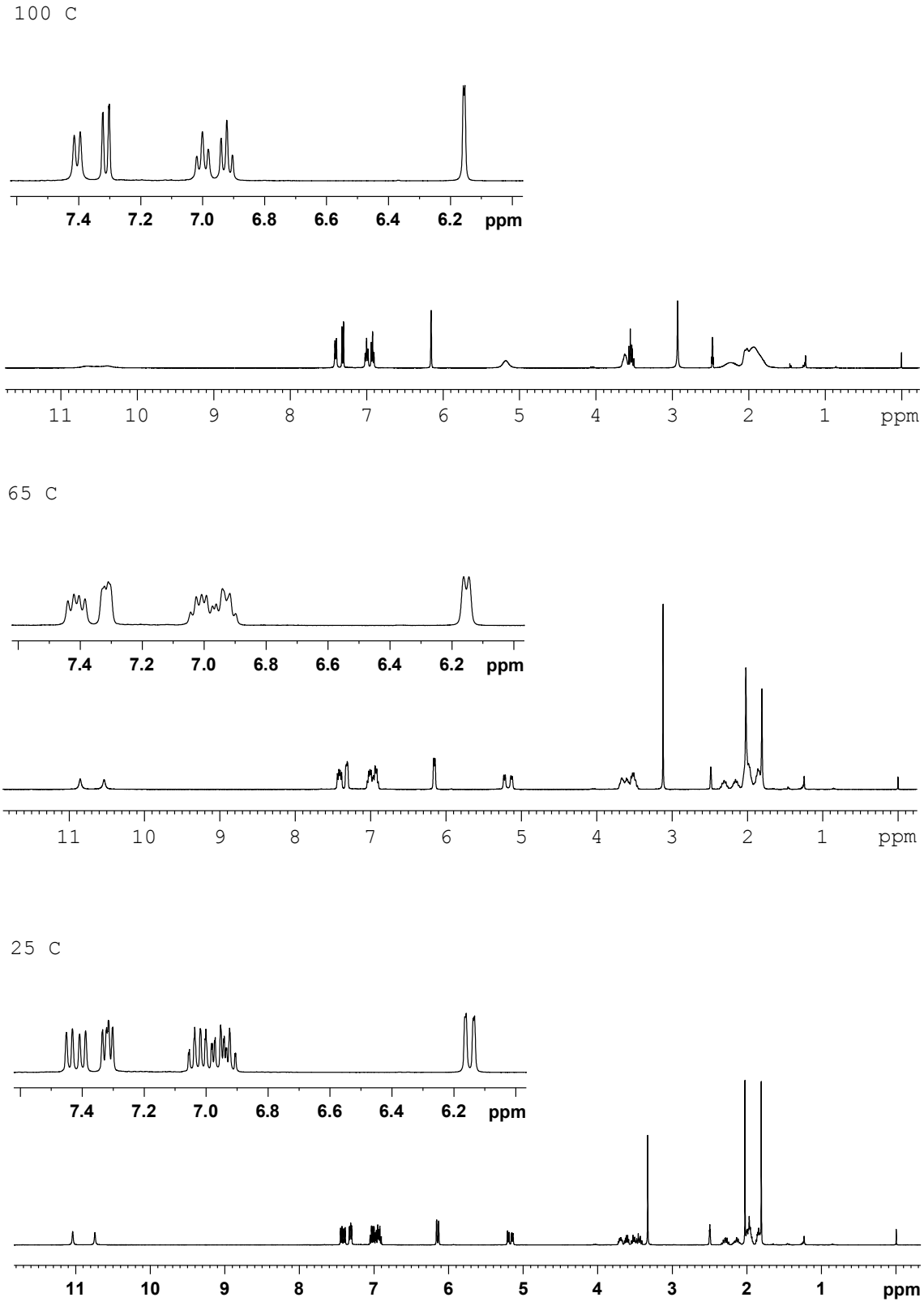


Appendix 23: ^{1}H NMR and ^{13}C NMR data of 76d and 80d

^{1}H NMR (CD_3OD) and ^{13}C NMR ($CDCl_3$) data of 76d



Variable temperature ^{1}H NMR of 80d (DMSO). Compound 80d experienced rotamerism at r. t.



^{13}C NMR data of 80d ($CDCl_3$)