A novel approach for functionalising and separating Tröger's Base Analogues

Emil Jakobsson

Master Thesis, 2023
Department of Chemistry
Lund University
Sweden

MSc, 15 hp

A novel approach for functionalising and separating Tröger's Base Analogues

Emil Jakobsson

Master Thesis

Lund University
January 2023- June 2023

Supervisor:
Eric Anguera Aixalà

Examiner:
Ulf Nilsson

Abstract

Tröger's Base (TB) is a bicyclic compound containing a methanodiazocine group between two aromatic rings. The methylene bridge forces the molecule to have a bent formation; thus, the aromatic rings are close to 90 degrees relative to each other, resulting in a rigid concave aromatic cavity. These unique properties make TB a great candidate as a molecular cleft compound and a good structure as a molecular receptor towards unfunctionalised molecules. The Tröger's Base framework has therefore been found to be a useful building block in supramolecular chemistry. The Tröger's Base project aims to complete a total synthesis of a linearly fused heptakis Tröger's Base analogue. As a part of this project, the goals of this master thesis are to acylate the benzylic position of a TB analogue and to separate the resulting diastereomers with dry column vacuum chromatography. In order to achieve these two goals, six synthesis steps have been performed, starting from a commercially available aniline analogue. The aniline analogue was halogenated, followed by a condensation reaction to form the first TB analogue. After four more synthesis steps, including dehalogenation, Pd-catalyzed amination, amine protection, and acylation, where the benzylic position of a TB analogue finally functionalised. Afterwards, one of the diastereomers was successfully separated from the mix of diastereomers with a dry vacuum column using silica. As a result, this thesis work has shown it possible to acylate a TB analogue at the benzylic position and shown that the resulting mix of diastereomers is separable by dry column vacuum chromatography. In addition, the work has given valuable TB analogues, which can be used in further synthesis in the Tröger's Base project.

Popular abstract

Supramolecular chemistry focuses on the forces between molecules and how molecules interact to form complex systems of molecules. Supramolecular systems can be designed for specific purposes, such as transporting specific molecules or speeding up a particular chemical reaction. One molecule that has shown exciting properties within this field is Tröger's Base (TB). This molecule has a V-shaped structure, resulting in a cavity in which hydrophobic molecules can interact. TB also possesses a rigid structure and therefore does not tend to alter its shape, making this molecule an excellent building block for making supramolecular systems.

In this project, called the Tröger's Base project, the goal is to synthesize a large analogue of TB consisting of seven TB bridges, a heptakis Tröger's Base analogue. This molecule is envisioned to function as a host molecule, in other words, to bind to smaller molecules reversibly. This could be useful in medicinal applications, like drug delivery. By synthesizing this molecule, the supramolecular properties and the potential applications of the molecule could be discovered.

As a part of this project, the focus of this work has been to form a TB analogue needed as a building block for the heptakis TB analogue. The procedure for obtaining this TB analogue can be described as doing multiple reactions; starting with a simple molecule on which new pieces are added under specific conditions until the final structure is formed. In addition, much work has been done to separate the diastereomers of this TB analogue which are formed in the final reaction step. Diastereomers of a compound can be described as molecules that differ in molecular configuration; in other words, having different arrangement of atoms but are made of the same set of atoms. In many cases, it is desirable to have the diastereomers separated, this because they have different chemical and physiological properties. Therefore, a method called chromatography has been used to investigate if these diastereomers can be separated. Chromatography is a separation method in which a column is packed with a stationary (solid) phase together with the product and rinsed with a mobile (liquid) phase. Due to diastereomers having differences in the affinity to the stationary and the mobile phase, the diastereomers will elute from the column at different times and can therefore be collected separately.

As a result, six synthesis steps have been completed, and one of the two diastereomers has been separated from the mix of diastereomers. The outcome from these results is that it has been shown possible to make this TB analogue with the implemented method. Also, the result from the chromatography shows that the mix of TB diastereomers is separable by using dry column vacuum chromatography. These findings are valuable for further TB research. In addition, this work has resulted in useful TB analogues that can be used as building blocks for obtaining the heptakis TB analogue in the future.

Acknowledgements

Table of contents

Abbreviations

aq	aquoeus
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
DCM	dichloromethane
EtOAc	ethyl acetate
EtOH	ethanol
nBuLi	n-butyllithium
NMR	nuclear magnetic resonance
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
PE	petroleum ether
ppm	parts per million
Rf	retardation factor
TB	Tröger's Base
t-BuLI	tert-butyllithium
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMSCl	chlorotrimethylsilane
TMS	trimethylsilane

1 Introduction

Chemistry is about much more than just intramolecular interactions, and the science focusing on the chemistry beyond the molecule has developed into a chemical discipline called supramolecular chemistry. Supramolecular chemistry is the study of high-order assemblies of molecules formed by non-covalent intermolecular forces [1]. The concept of the field is that two or more molecules interact to form a supramolecular structure called the supermolecule [2]. This system of molecules can be of various sizes due to the diversity of molecular interactions. The smallest supramolecular structure is the guest-host system, wherein a host molecule selectively coordinates the guest molecule through a molecular recognition process [3]. This principle of binding molecules together to create a supramolecular system shares the fundamental concept of how our body operates in many biological processes, because biological systems also rely on specific and complex intermolecular interactions [3], [4]. For example, many cellular functions are dependent on complicated assemblies of molecules such as nucleic acid transcription, ribosomes, and bilayer membranes to work [5].

Biological supramolecular systems like these have therefore inspired research in supramolecular chemistry, which can be seen in fields such as molecular transport and molecular conversion [3]. Interestingly, it has been shown within molecular transport that supermolecules can be designed to function as drug-delivery systems [6]. Supramolecular chemistry can therefore be said to have an important role in the development of new pharmaceuticals and in the advancement in medicine [7].

In order to develop an efficient supermolecule, a good building block is needed. One molecule that has shown exciting features for this purpose is Tröger's Base (TB) molecule (Figure 1.1.1). TB has a rigid aromatic structure and a concave arrangement. These features have made TB an attractive compound for further research in molecular recognition and supramolecular chemistry, making this compound the foundation of this project [8].
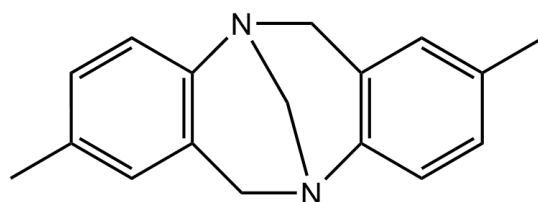

Figure 1.1.1: Tröger's Base.

Tröger's Base exists as a racemic mixture of two possible enantiomeric configurations [9]. If TB-based drugs are to be developed in the future, it is essential to have an efficient method to resolve the racemates. This is because all living systems are enantioenriched, and stereoisomers of a chiral drug might have different physiological effects [10].

Today most of the enantiomers of TB are separated by relying on chiral chromatography techniques such as chiral HPLC [9]. These methods involve chiral stationary phases sensitive to chromatographic conditions, resulting in tedious and difficult method development. Also, using chiral columns is more expensive than using achiral columns [11]. In this thesis, one of the main goals is therefore to separate the diastereomers of a TB analogue by using dry column vacuum chromatography with silica. In parallel to this, another aim of this work is to acylate the benzylic position of the TB scaffold and thus give rise to new cleft compounds that could be used in future applications.

2 Background

This project relies on the chemistry of Tröger's Base molecule. This section of the report will review the history, properties, general condensation, and applications of Tröger's Base.

2.1 History

The first person to work with the TB molecule was Carl Julius Ludwig Tröger, who studied a condensation reaction between amines and dimethoxymethane [12]. Tröger was the first to isolate the compound in 1887, but it took a long time until the actual structure of the molecule was known and determined. It was not until 1935 that Spielman fully elucidated the chemical structure as a racemic 2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (Figure 1.1.1) [13]. At the same time, Wagner also investigated the condensation reaction, which yielded TB, and suggested a mechanism for the reaction [14]. The investigation of the properties of TB continued, and in 1948 the first report about the synthesis of polysubstituted TB analogues was published by Smith and Schubert [15]. Four years before, in 1944, Prelog successfully performed chromatographic separation of the TB enantiomers with an enantiopure stationary phase using lactose hydrate [16]. This result was an accomplishment in stereochemistry as it was the first time a chiral amine was resolved using this methodology [17]. In 1986, one year before Jean-Marie Lehn was awarded the Nobel Prize in chemistry for innovating the field of supramolecular chemistry, Wilcox confirmed the structure of TB predicted by Spielman by using single-crystal X-ray diffraction analysis (XRD) [18], [17]. However, the exact spatial arrangement of TB was not determined until 1991, when XRD analysis proved that (+)-TB has the 5S,11S configuration [19].

In addition to proving TB's correct structure in the 1980s, Wilcox synthesized several new TB analogues. Wilcox proposed that the scaffold of TB could be used for chelation, and it might be used to develop macrocyclic host molecules. Wilcox did also suggest that TB, due to its rigid structure, has the potential to serve as a building block for creating synthetic enzymes and anion receptors [20]. When Wilcox presented the analogues, TB became an intriguing subject for research which led to the development of new analogues that has proved useful in many different

fields of chemistry [9]. However, before the significant work by Wilcox, TB was primarily used for analyzing different separation techniques [15].

2.2 Properties

Tröger's Base (TB) is a bicyclic compound containing a methanodiazocine group between two aromatic rings. The methylene bridge forces the molecule to have a bent formation; thus, the aromatic rings are close to 90 degrees relative to each other, resulting in a rigid concave aromatic cavity [9]. These properties make TB a great candidate as a molecular cleft compound and a good structure as a molecular receptor towards unfunctionalised molecules [21]. Also, if the TB molecule rotates 180 degrees around the symmetry axis, the molecule will be identical; thus, TB possesses a C2-rotational axis [21].

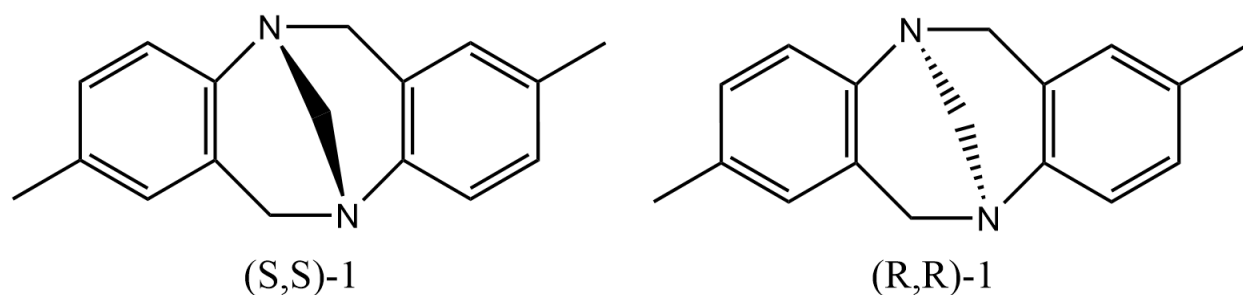(S,S)-1   (R,R)-1

Figure 2.2.1: The two possible configurations of TB.

Tröger's Base (TB) has two stereocenters in the positions of the two nitrogens. As a result of the methylene bridge, TB only exists in the R,R, and S,S configurations, thus making the compound a chiral molecule [21], [9] (Figure 2.2.1). The diastereomeric R,S configuration is too strained due to the geometry of the bridge. The enantiomeric configurations of TB are relatively stable because the methylene bridge hinders pyramidal inversions of the stereocenters [9]. However, racemization still happens in low-acidic environments due to the protonation of one of the nitrogens. The protonation promotes the free electron pair of the unprotonated nitrogen to form a methylene iminium ion **2** (Scheme 2.2.1), leading to racemization [16]. Although, this does not occur in the presence of strong acids because both nitrogen atoms are then protonated, and therefore there are no free electrons to form the intermediate [22], [9].
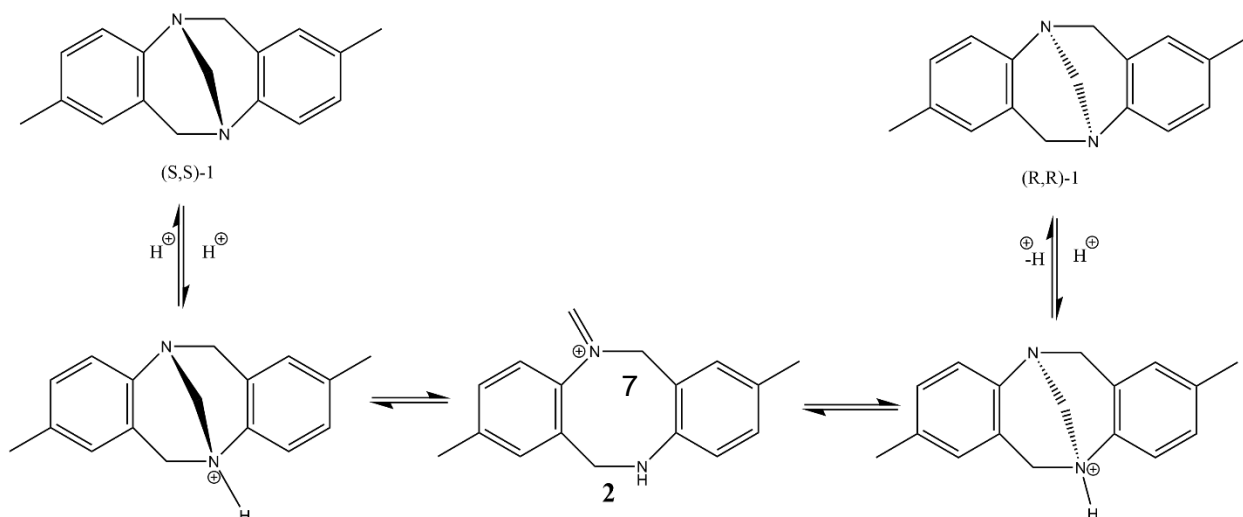
Scheme 2.2.1: The mechanism leading to the formation of a methylene iminium ion (**2**) and to the racemization of TB, in a low acidic environment [9].

If the structure of TB is thoroughly inspected, it can be observed that the bent arrangement of the molecule pushes the free electrons of the nitrogen atoms out of phase from the conjugated system of the aromatic rings. Consequently, the nitrogen atoms are not in conjugation, which results in higher electron density. A high electron density on the nitrogen atoms should increase the pKa of TB and the pKa of monoprotonated TB should be in a range of 5-10 [9], [23], [24]. However, Wepster reported the pKa of monoprotonated TB to be 3.2, which differs from the expected basicity [23]. By inspecting the molecular orbitals in the region of the diazocine bridge, it is possible to argue for the low pKa. It has been shown by comparing the bond lengths upon protonation of the nitrogen atoms that an anomeric effect is present [9]. An anomeric effect is a stereoelectronic effect that might occur when two heteroatoms are bound to the same atom. This effect causes the molecule to align an electron lone pair with the antibonding orbital of the bond between the other heteroatom and the central atom. This makes the molecule adapt into a conformation that might be more sterically unfavored. An explanation for this phenomenon is that the molecule becomes stabilized by hyperconjugation when the lone pair of the heteroatom overlaps with the antibonding orbital [25]. An anomeric effect could therefore explain the lower pKa of TB. In the case of TB, an anomeric effect should stabilize the lone pair of the nitrogen when it overlaps the antibonding orbital of the bond between the methylene carbon and the other nitrogen. This stabilization should make the free electron pair of the nitrogen more delocalized, thus lowering the pKa [9].

2.3 Trögers's Base condensation

There are several methodologies for obtaining TB analogues. One of the first methods was the one developed by Tröger in 1887, reacting p-toluidine and formaldehyde in hydrochloric acid. However, the general protocol is to perform a condensation reaction between an aromatic amine and a synthon of methylene under acidic conditions (Scheme 2.3.1). Either way, all methodologies must consider that aromatic amines often have more than one reactive center, and polymerization, therefore, can occur. The aromatic amines should therefore be substituted on the para position to avoid polymerization. In fact, all aromatic positions on the amine can be substituted, but one of the two ortho positions must be accessible for the TB condensation to occur [15].

A TB condensation protocol that has given rise to new possibilities is the one developed by the Wärnmark's group in 2001, which allows for making halogenated TB analogues [26]. In this protocol, paraformaldehyde and TFA are used to overcome the limiting need for electron-donating substituents on the aromatic ring of aniline, making it possible to functionalise [27].
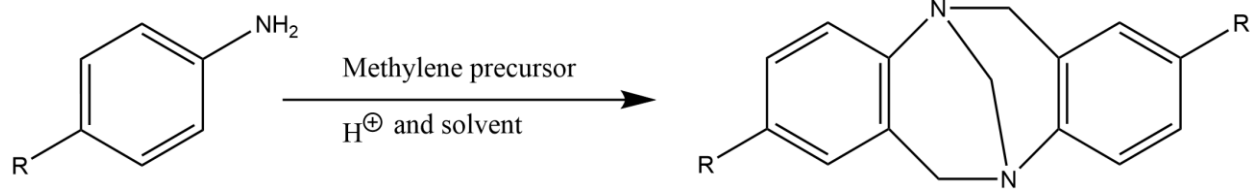
Scheme 2.3.1: The general principle of TB condensation [9].

2.4 Applications

After the dedicated work done by Wilcox and his team, much research has been done into the development of molecular receptors using the TB scaffold [15]. TB analogues has proved to be useful building blocks for applications in fields such as molecular recognition, catalysis and for enzyme inhibition [28]. In addition, some of the applications in which TB has shown potential will be discussed in the following section.

Global warming is an ongoing problem mainly caused by CO_2 releases [29]. As a result, physical adsorption methods for adsorbing CO_2 have been developed. These methods use porous solid materials, such as organic polymers, as adsorbents. For the adsorbent to selectively adsorb CO_2, there must be an efficient dipole-dipole interaction between the CO_2 and the N-functional groups on the porous solid. TB is one way to incorporate the N functionalities into the adsorbent. Using TB has shown to be an excellent method, as it offers a simple synthetic pathway without toxic by-products. The TB-derived TP-MOP is an example of a porous Tröger's Base polymer that has shown promising CO_2 uptake (Figure 2.4.1). This polymer has shown high CO_2 selectivity and CO_2 uptake capacity [29].
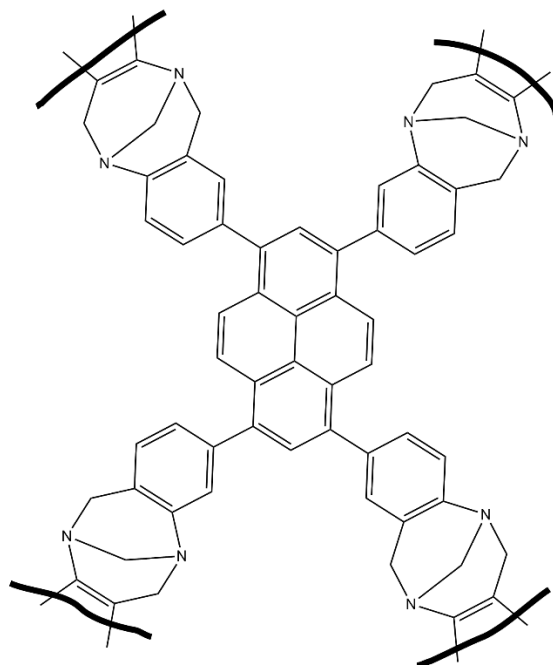
Figure 2.4.1: Showing the porous Tröger's Base polymer TP-MOP [29].

Tröger's Base framework has also been used in the development of molecular torsion balances [30]. Wilcox has, for example, synthesized a TB analogue (seen in figure 2.4.2) which can be used to quantify functional group interactions and weak intermolecular interactions such as CH-π or aromatic edge-to-face forces [31], [30]. TB analogues like this can therefore be used to measure the folding energies in proteins, thus functioning as models for protein folding [30].
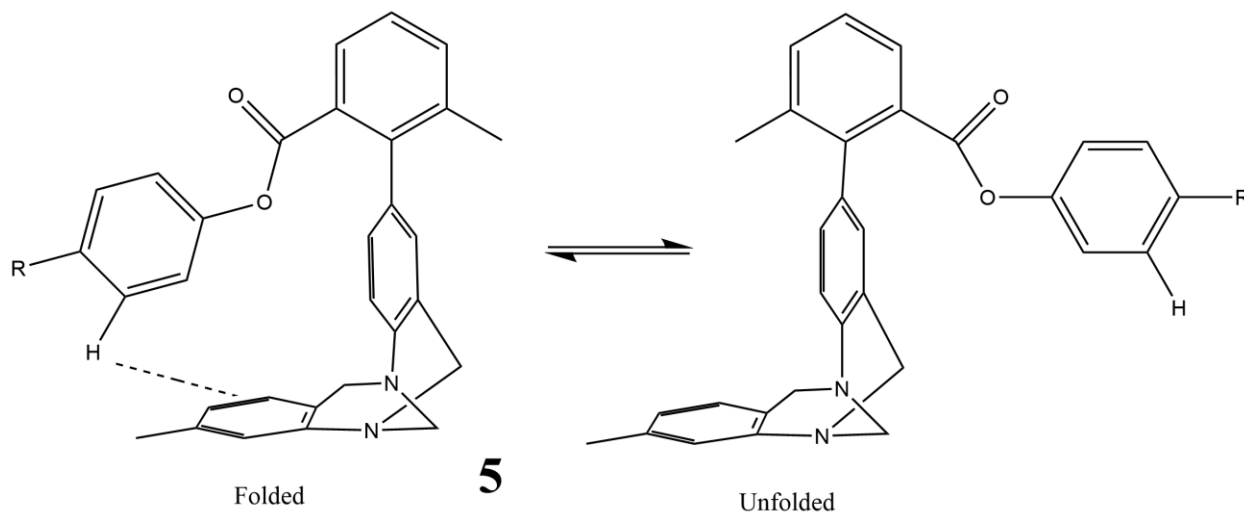

Figure 2.4.2: Showing the principle of how the TB framework of analogue **5** can be used as a molecular torsion balance for the quantification of aromatic edge-to-face forces [31].

TB analogues has also shown promising features as light-emissive materials that could be used to bypass some frequently occurring challenges in optics [32]. A big obstacle in this field is that most light-emissive materials are only weakly luminescent in the aggregate state, a phenomenon called aggregation quenching. Emission quenching becomes a problem when developing optoelectronic devices made of luminescent materials, as these materials are often used as solid thin films, in which aggregation is inevitable [32]. However, it has been presented that fluorene-derived TB analogues exhibit strong fluorescence in both aggregate states and dilute solutions [32]. Therefore, these fluorene-derived TB analogues could find applications as organic light-emitting diodes (OLEDs). For example, analogue **6** (Figure 2.4.3), when used for this purpose, has shown high efficiency, low turn-on voltage, and high brightness [33].
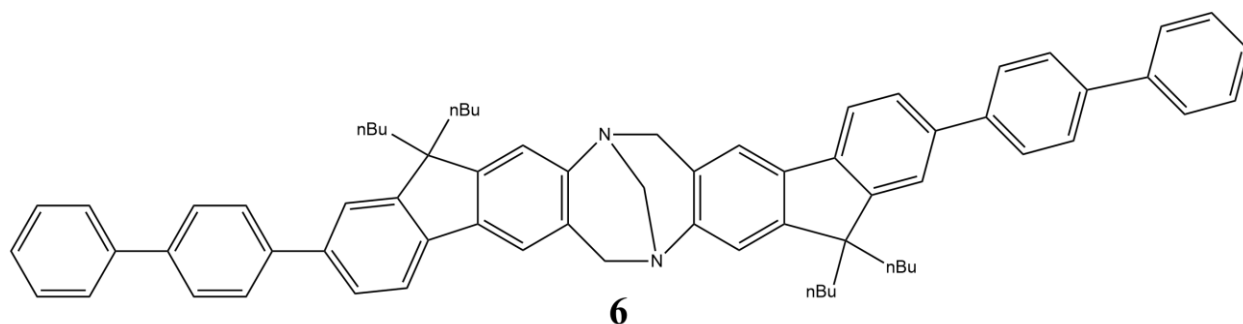
6

Figure 2.4.3: Fluorene-based TB analogue which has shown great features for optical applications [33].

Beyond the optoelectronic capabilities, TB has also demonstrated impressive potential in medicinal chemistry. For example, Veale and Gunlaugsson have shown that fluorescent 1,8-Naphthalimide TB analogues **7** (Figure 2.4.4) could act as promising supramolecular binders for DNA. In addition, the study demonstrated that the presence of the diazocine ring is a factor that enhances all these three TB analogues affinities to the DNA.

The same study also performed a detailed biological investigation showing that different cancer cell lines quickly take up TB analogues **7** and that the cells accumulate the analogues inside the nuclei, leading to cell death [34].
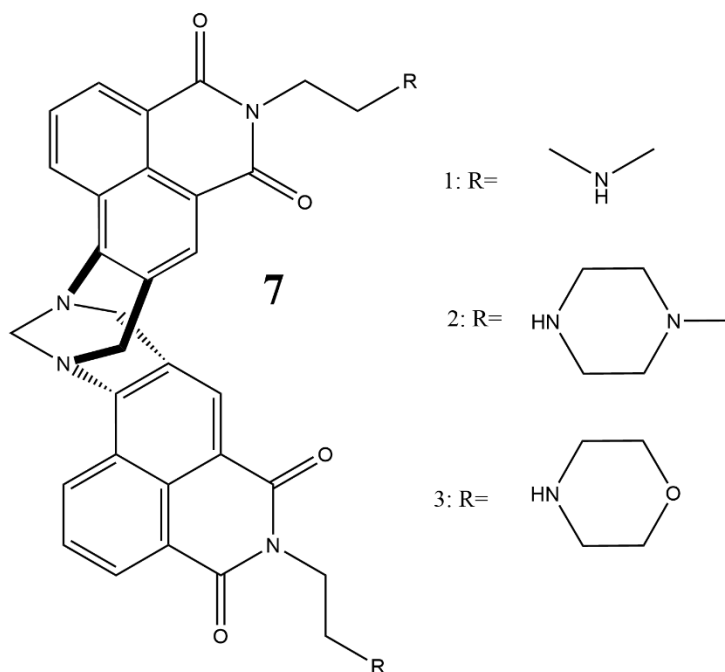

7

1: R=

2: R=

3: R=

Figure 2.4.4: Showing the TB analogues based on a fluorescent structure [34].

3 Project outline

This thesis work is a part of the total synthesis project of the Wärnmark's group at CAS in Lund University. The final goal of this project is to successfully synthesize and isolate a heptakis TB analogue. However, the two goals of this thesis are to acylate the benzylic position of TB analogue **13** to yield a mixture of TB diastereomers **14b** and **14a** (Figure 3.1.1) and to separate these diastereomers by using dry column vacuum chromatography with silica.
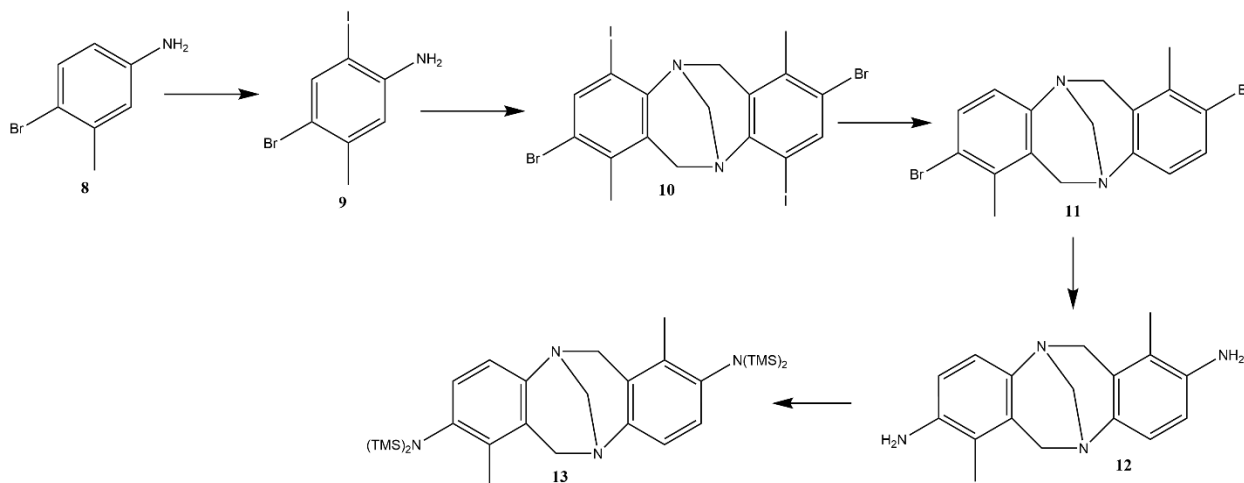
Scheme 3.1.1: The initial route.

All the synthesis performed has followed the prior procedures developed earlier by the Wärnmark group to save time and resources for future research. All analogues are synthesized from the initial route (Scheme 3.1.1), starting from a substituted aniline **8** that is commercially available. After product **13** of the initial route is reached, the two goals of this thesis are challenged. The furthest TB analogue successfully synthesized was TB analogue **14**.
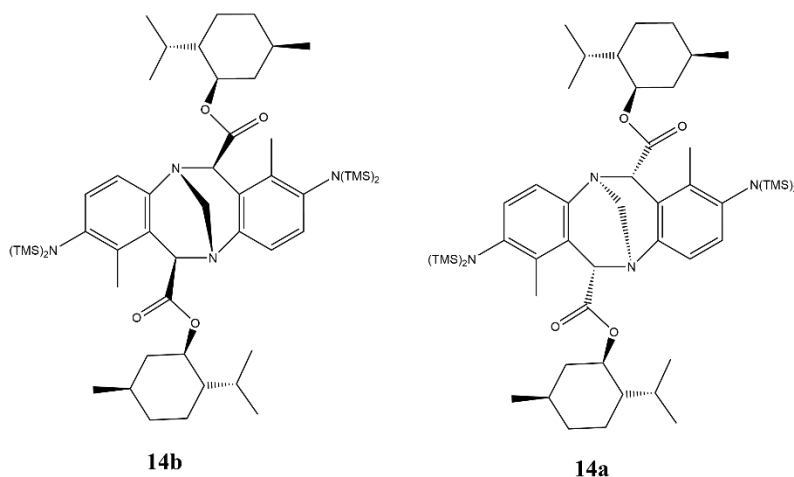

Figure 3.1.1: The two diastereomers of TB analogue **14**.

4 Result and Discussion

4.1 Halogenation (Analogue 8→9)

The initial route begins with an electrophilic aromatic substitution (EAS) between 4-Bromo-3-methylamine and iodine monochloride (Scheme 5.1.1). This reaction yielded analogue **9** in a yield of 56%. The reaction was performed to substitute the ortho-position of carbon six of the 4-Bromo-3-methylamine, thus controlling the following condensation reaction to take place on carbon two of the compound. Because there are three possible positions in which the EAS can happen, iodine could also bind to other positions of the aniline and yielding regioisomers. Because of the strongly activating properties of the amine group, the electrophilic aromatic substitution is directed to the two ortho positions of the amine functional group. However, carbon two of aniline analogue **8** is influenced by the steric effect from the methyl group; thus, this position is not as susceptible to taking part in the EAS as carbon six [35]. Therefore, this reaction yields aniline analogue **9** as the main product.
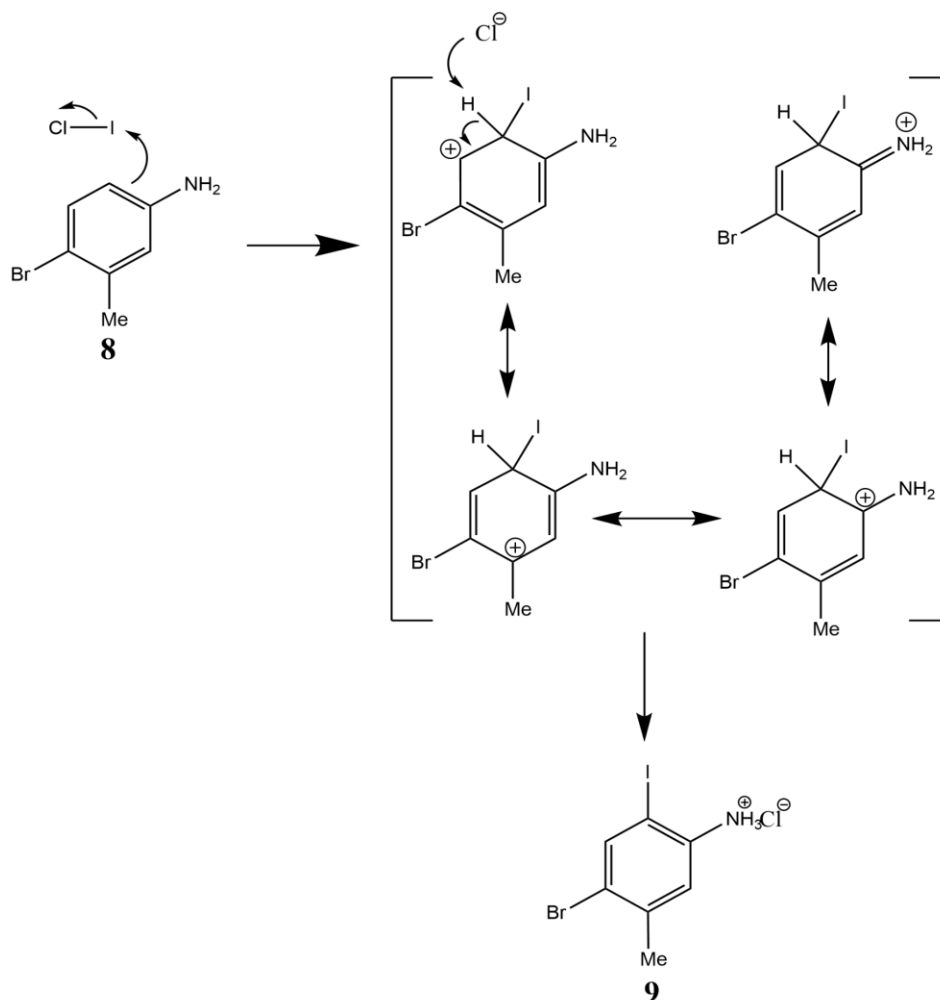

Scheme 5.1.1: Showing the proposed mechanism of the EAS which yields analogue **9**.

13

The proposed mechanism for the EAS starts when a pair of electrons from the aniline ring attacks the iodine monochloride (Scheme 5.1.1). The high reactivity of the aniline analogue is given from the amine group as the lone pair of electrons are in conjugation with the aromatic ring, making the compound more nucleophilic [35]. In the process of donating the electrons to the electrophile, the aromaticity of the compound is lost due to the formation of a sp^3 hybridized carbon. However, the formed cation is stabilized by resonance, and the intermediate conveniently regains the aromaticity as the product is formed by losing a proton from the tetrahedral carbon atom to a Lewis base [35].

4.2 Condensation (Analogue 9→10)

After the aniline analogue had been successfully halogenated into compound **9**, the next step was to perform a condensation reaction to yield the first TB analogue **10** (Scheme 4.2.1). This condensation reaction was performed several times, and the product was formed with the highest yield of 44%. For this reaction, TFA and paraformaldehyde were used. The proposed mechanism for this reaction is based on the paper published by Wagner [36]. The mechanism starts with TFA, which induces the reaction between the aniline and the aldehyde, resulting in the formation of a Schiff base cation (I) (Scheme 4.2.1). This cation operates as an electrophile and takes part in an electrophilic aromatic substitution with the second aniline molecule, resulting in an intermediate (II). This intermediate then reacts with another formaldehyde, resulting in an intramolecular ring closure and the formation of an intermediate (III). As before, intermediate (III) undergoes a nucleophilic attack on an aldehyde, forming an iminium cation (IV). TB analogue **10** is formed as the iminium cation (IV) takes part in an intramolecular electrophilic aromatic substitution with the other aromatic ring, leading to another and final ring closure [36], [37].
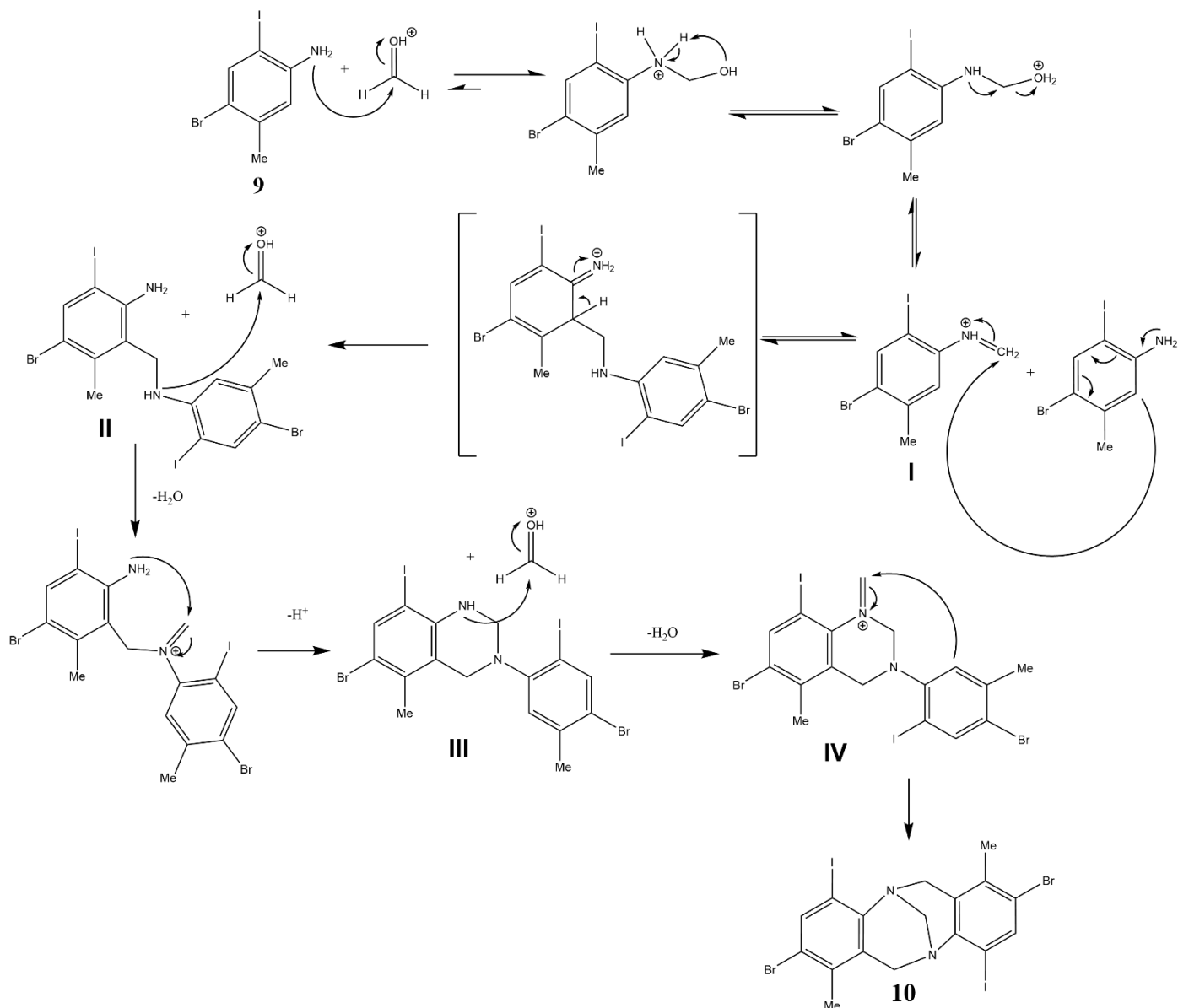
Scheme 4.2.1: The proposed mechanism for the condensation of TB analogue **10**.

4.3 Dehalogenation (Analogue 10→11)

When the first TB analogue had been formed, the next step was to remove the iodine groups introduced in the first reaction by performing a dehalogenation reaction using zink and hydrochloric acid (Scheme 4.3.1). The iodines are removed since they would likely cross-react in the upcoming palladium-catalyzed amination and give rise to side products. The dehalogenation reaction ended up with a yield of 75%.

The proposed mechanism for the dehalogenation reaction starts when C-I is added onto the Zink by oxidative addition. As a result, the oxidation state of Zink changes from Zn(0) to Zn(II), and it is this change in oxidation state that drives the reaction as Zn(II) is more stable [38]. In the

following step, the carbon coordinated to the Zink attacks a proton from the hydrochloric acid, and the product is formed as the Zink is replaced with a proton [38], [39]. The Zn(ΙΙ) then coordinates with free chloride and iodine ions in the solution to equalize the charge to get electroneutrality.
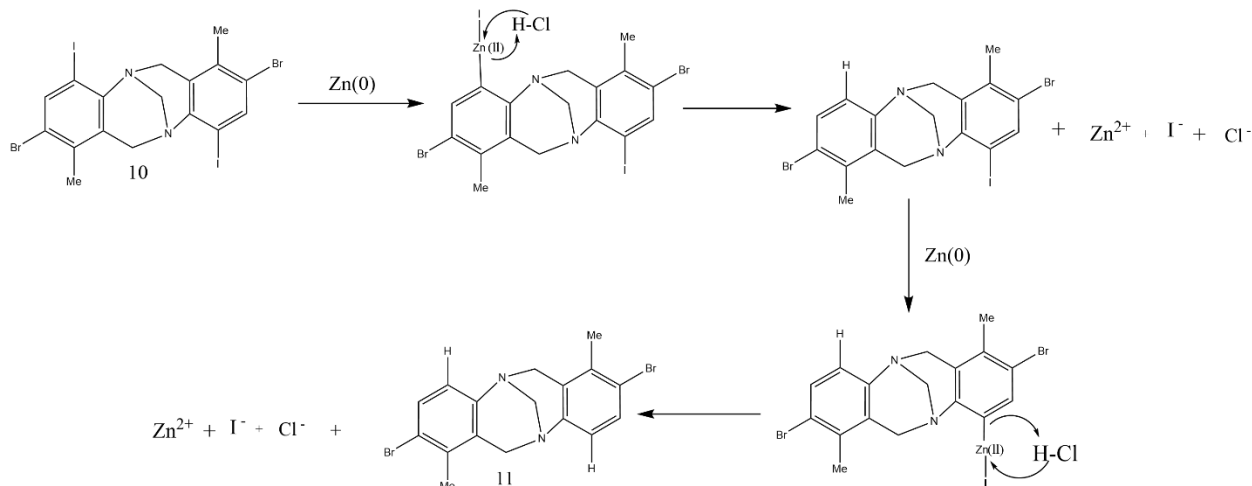

Scheme 4.3.1: The mechanism for the formation of TB analogue 11.

4.4 Amination (Analogue 11→12)

The bromine substituents of TB can be functionalised into amines. By aminating these bromines, the amine groups could potentially be used to perform a condensation reaction between two TB molecules and fuse them to a tris-Tröger's Base analogue [21]. The amination of TB analogue **11** is, therefore, an essential step for the upcoming reactions in the B-route.

The cross-coupling reaction performed was very similar to a Buchwald-Hartwig amination (Scheme 4.4.1), using $Pd_2(dba)_3$ as Pd(0) source, benzophenone imine as the source for the amine, t-BuONa as the alkoxide base and BINAP as the coordinating ligand. The catalytic cycle begins when the solution of $Pd_2(dba)_3$ and BINAP forms a complex of (BINAP)Pd(dba), which stands in equilibrium with a (BINAP)Pd(0) complex by releasing the dba ligand [40]. Both complexes (BINAP)Pd(dba) and (BINAP)Pd have been shown to react with the aryl bromide by oxidative addition [41]. The formed complex of (BINAP)Pd(R)(Br) then interacts with t-BuONa, and a ligand exchange occurs; thus, the coordination site occupied by bromide is replaced with the alkoxide base. The cycle continues when the benzophenone imine substitutes tert-butoxide, thus forming the amido complex. The amido complex then undergoes a reductive elimination followed by acid-catalyzed hydrolysis to yield the aminated TB analogue **12**, in a yield of 94%. As the amido complex undergoes reductive elimination, the Pd(0) catalyst is reformed, and the cycle repeats one more time [40].

16
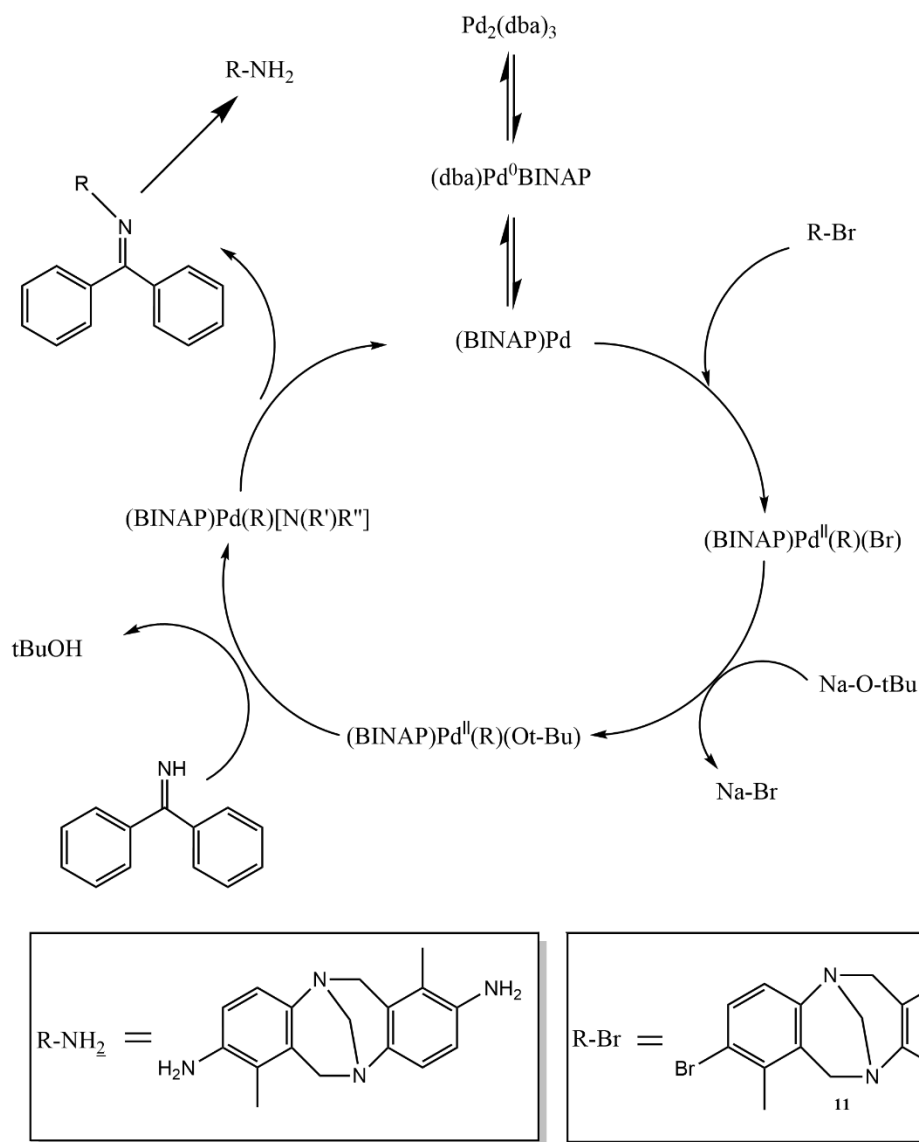
Scheme 4.4.1: The palladium catalyzed cycle for the amination of TB analogue **11.**

The purpose of having BINAP as a bidentate ligand coordinated to the metal center is to enforce the TB ligand in cis coordination relative to the imine ligand. This is essential because it is required that the eliminating ligands are in cis coordination for the reductive elimination to take place [42].

4.5 Protection (Analogue 12 → 13):

Once the palladium-catalyzed amination was finished, the last step in the initial route was reached. This reaction aimed to add trimethylsilyl (TMS) protecting groups on both amine functional groups. The protection of the amines is important because if these are not protected, the amines would be the most reactive part of the molecule. That would be a problem in the following reaction when t-BuLi is used because the amines would become nucleophilic and attack the electrophilic menthyl chloroformate.

TMS was the right protecting group for this purpose because this group is resistant to strong bases like t-BuLi and does not require an aqueous acid for deprotection. The reason for avoiding the use of aqueous acids is that the product formed after the upcoming acylation contains ester functional groups. These are sensitive to acid-catalyzed hydrolysis; thus, aqueous acids cannot be used. Instead, it is possible to use fluoride salts to remove the TMS-protecting groups [43].
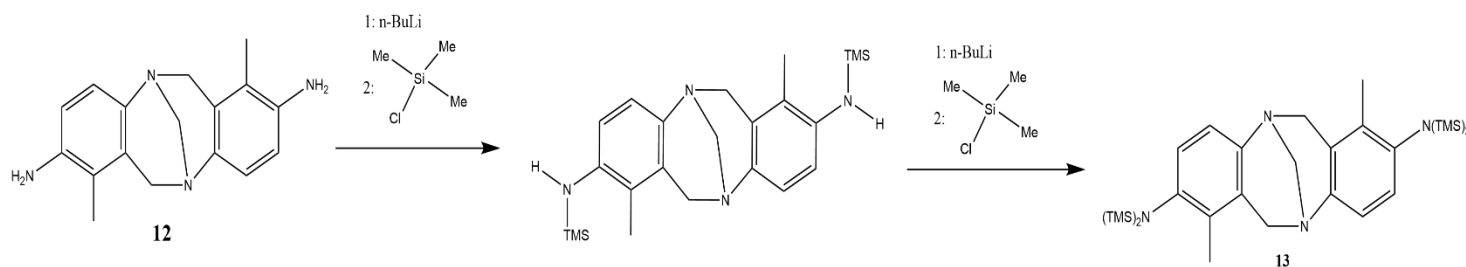
Scheme 4.5.1: The reaction of TB12 to TB13.

The proposed mechanism for the protection of TB analogue **12** happens in two steps (Scheme 4.5.1). First, n-BuLi is added, which is a strong base that deprotonates the amines. The two nucleophilic amines then attack one electrophilic trimethylsilyl chloride each, and the chloride atom is removed as a leaving group. This results in a partly protected TB analogue because only one proton on each amine is replaced with a TMS group. Therefore, this reaction is repeated once more until four trimethylsilyl amine groups have been formed, resulting in TB analogue **13** [43]. This reaction was successfully performed, and TB analogue **13** was synthesized with a yield of 99%.

4.6 Acetylation and separation (Analogue 13 → 14):

The acylation of TB analogue **13** was performed by using (1R)-(–)-Menthyl chloroformate as the acylating agent, together with tert-Butyllithium (Scheme 4.6.1). The synthesis was successful and resulted in a mix of TB **14** diastereomers in a yield of 41%.

The proposed reaction mechanism begins with the base deprotonating the most acidic proton in the benzylic position, thus generating a Sp^2-hybridized nucleophile to attack the electrophilic menthyl chloroformate on the less sterically hindered side. The protons in the benzylic position are the most acidic hydrogens of the compound because this position has more resonance structures to delocalize the negative charge. When the benzylic carbon attacks the menthyl chloroformate, the chloride atom will leave as a leaving group. Because the reaction is

18

diastereospecific, only the exo diastereomer will form and thus gives rise to the two diastereomers of TB **14** [44].
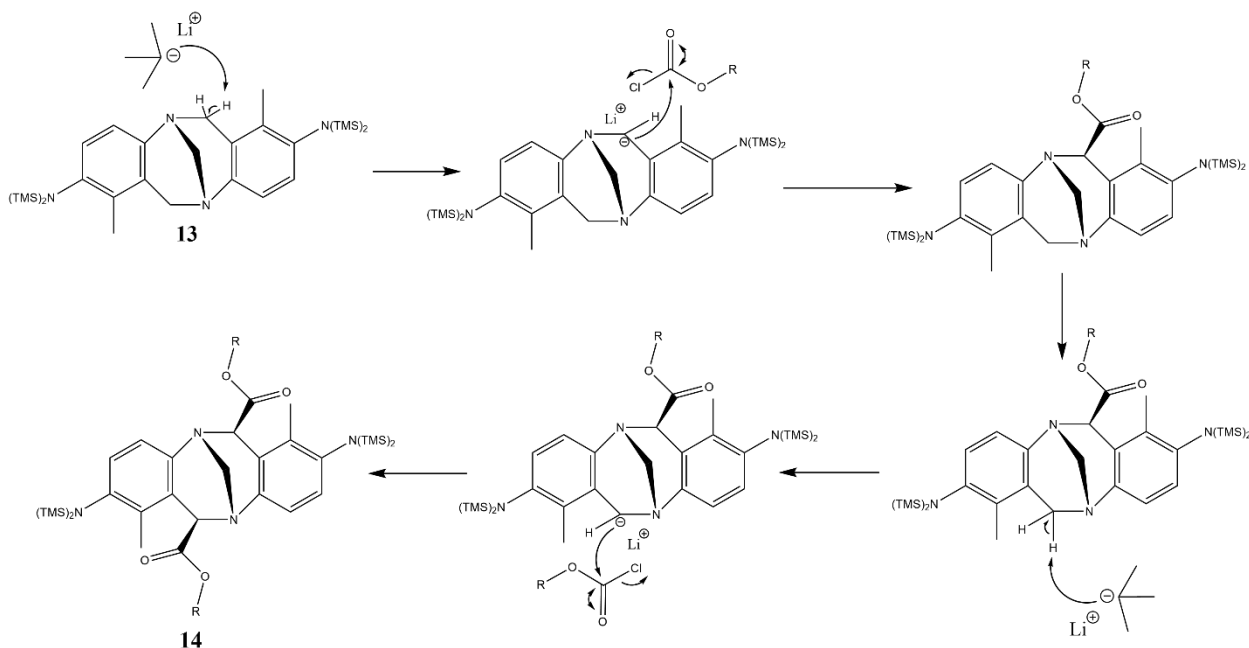
Scheme 4.6.1: The mechanism for the formation of TB analogue **14**.

The two diastereomers **14a** and **14b** were separated by chromatography using a silica column. The silica gel has a large surface area in which the silica surface contains silanol groups, giving hydrophilic adsorption properties [45]. Because diastereomers physical and chemical properties are different, interactions with the mobile phase and the adsorption to the silica will differ slightly [46]. Therefore, the retention time in the column for the diastereomers will not be the same, making it possible to collect the diastereomers in different fractions. Unfortunately, there is a minor problem with using silica as a stationary phase when loading TB analogue **14** to the column. The problem is that the acid-sensitive TMS protecting groups are deprotected, caused by the slightly acidic silanol groups. Therefore, triethylamine is used to deactivate the silica to prevent this from occurring.

At the beginning of the work, flash chromatography was used once to separate the TB **14** diastereomers. However, since the dry column vacuum chromatography showed promising results and consumed less solvent, the rest of the separation attempts were made with a dry column. With that methodology, the goal of separating the diastereomers was almost achieved. TB **14b** was separated from the mixture with a yield of 7%. However, the result from the ^{1}H-NMR (Figure 8.7) indicates that the rest of the product eluted as a mixture of both diastereomers. Since the column resulted in a partial separation of **14b**, the mix of diastereomers would most likely be separated if the column was performed more times with the same product. This is

because there should be less **14b** in the mixture after each column, eventually leading to a separation of the diastereomers.

It is also likely that diastereomer **14a** could have become partly separated at the first column if more attempts had been made. According to the TLCs performed, the product eluted too fast, probably caused by a high polarity in the mobile phase. The use of a wrong concentration gradient might have caused the high polarity, or the product was not completely dried when loaded into the column. Therefore, more attempts are needed to investigate if it is possible to partly separate diastereomer **14a** on the first column.

5 Conclusion

In this work, TB analogue **14** has been synthesized. It has been shown that an analogue of TB can be acylated at the benzylic position when menthyl chloroformate and tert-Butyllithium are used as reagents. In addition, TB **14b** was separated from a diastereomeric mixture of TB **14** by using dry column vacuum chromatography. Therefore, this work has demonstrated a new reliable separation method that requires less solvent, which can simplify future separations of Tröger's Base analogues. This method can therefore be helpful for other persons working with the Tröger's Base project.

6 Future work

As a result of several attempts to achieve the goals in this master thesis, many intermediate TB analogues have been made. These analogues can be used in future work regarding the Tröger's Base project, and hopefully, the products synthesized in this work will contribute to obtaining the heptakis TB analogue. Besides the fact that more lab work is required to finish the B-route, effort could also be put into improving the yields for each reaction step. Likewise, the dry vacuum column could be improved and optimized to make the separation of the diastereomers more effective, making it possible to separate the diastereomer **14a** on the first column.

7 Experimental

All the synthesis and procedures performed has followed the prior procedures developed earlier by the Wärnmark group to save time and resources for future research. The following method and protocol have been developed by the Wärnmark group.

7.1 General procedures

All commercial reagents in this work have been used as they were delivered. Dry toluene and DCM were taken from a solvent dispenser (MBRAUN SPS-800) and stored over 4 Å MS. THF was taken and used directly from the distillation using benzophenone ketyl and sodium. Dropwise additions were accomplished by using an NE-4000 programmable 2 channel syringe pump. All thin-layer chromatography (TLC) was performed by using TLC Silica gel 60 F254 and the results from these were obtained by using a UV-lamp (254 nm). The reactions performed in room temperature are in the range of 20-23 °C. For the reactions achieved at higher temperatures, metal heating mantels were used. Flash column chromatography was performed on silica gel column ((∅,h), 60 Å, 230-400 mesh, obtained from Sigma Aldrich). Dry vacuum column chromatography was done with silica gel column (Dry-column silica) (Silica gel 60, 0.015-0.040 mm) for column chromotography (CAS No. 7631-86-9, EC Number 231-545-4, from Merck), by using reagent-grade solvents. The ^{1}H NMR was recorded at room temperature on a Bruker Avance II at 400.1 MHz. The spectra were recorded in MeOH-d4 or CDCl3 and the residual solvent signals (3.31/7.26) ppm were used as reference. Chemical shifts (δ) are written in parts per million (ppm) and the coupling constants (J) are shown in Hertz (Hz). This is the abbreviations used for the different multiplicities: s, singlet; d, doublet; dq, doublets of quartets; m, multiplet; t, triplet; dd, doublet of doublets; td, triplet of doublets; br, broad singlet; q, quartet.

7.2 The synthetic routes

The synthesis of 4-Bromo-2-iodo-5-methylaniline hydrochloride (9)

550 ml of 99.5% EtOH was collected into a 1 L round bottom flask which was cooled to 0 ºC. The flask of EtOH was placed under stirring and Iodide monochloride (ICl) (15,8 mL, 0.315 mol) was added to the flask. 4-Bromo-3-methylaniline (8) (50.0g, 0.269 mol) was then added to the same flask and the slurry was left to cool for about 5 minutes. The cooling bath was then removed, and the slurry was stirred at room temperature for 3 hours. This solution was then filtrated by using vacuum and the solid from the retentate was washed with 0 ºC acetone until a light grey/pink powder was collected as aniline analogue (9) (47g, 0.151 mol) in a yield of 56%. This product was finally analyzed with H NMR (400.1 MHz, MeOH-d4): δ = 8.06 (s, 1H, H-3), 7.25 (s, 1H, H-6), 2.37 (s, 3H, CH3) ppm.

The synthesis of 2,8-dibromo-4,10-diiodo-1,7-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (10)

Aniline analogue (**9**) (5.00g, 14.4 mmol) and paraformaldehyde (1.04g, 34.6 mmol) was added to the same flask under cooling (-15ºC). The mixture in the flask was dissolved in TFA (40 mL) and the solution was placed under stirring for 40 minutes. The cooling bath was then removed, and the mixture was heated up to 60 ºC. 24 hours later, TFA was removed using vacuo and afterwards water (25 mL) was added to the flask. This slurry was made alkaline (pH 8-10) by adding NH_3 (32% aq) carefully. The formed solid was then dissolved by adding some drops DCM and the solution was once again made alkaline (pH 8-10). This two-phase mixture was then extracted by using DCM (50 mL) four times and the organic phases were combined and washed with brine (50 mL). The organic phase was afterwards dried over anhydrous $MgSO_4$ and the solution was filtrated before DCM was removed in vacuo, yielding the crude as an orange/yellow solid.

The crude was later combined with two other batches (prepared as above) and dissolved in DCM. Silica for Dry-column (9 g) was added to the solution and the DCM was evaporated in vacuo until the mixture was completely dry. The resulting powder was then added to a dry vacuum column (4 x 5 cm) using $PE:CHCl_3$ gradient from 30% $CHCl_3$ to 70% by an increment of 5% every 100 ml, to yield TB analogue (**10**) (6,3g, 9.53 mmol) as a light-yellow solid in 44% yield. Rf = 0.35 (PE:CHCl3, 1:1), 1H NMR (400.1 MHz, CDCl3): δ = 7.95 (s, 2H, H-3 and H-9), 4.40 (d, J = 17.4 Hz, 2H, H-6x and H-12x), 4.24 (s, 2H, H-13), 4.18 (d, J = 17.4 Hz, 2H H-6n and H-12n), 2.18 (s, 6H, Ar-CH3) ppm.

The synthesis of 2,8-Dibromo-1,7-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (11)

Ethanol (95%, 650 mL) was added to a vessel containing TB analogue (**10**) (9.0 g, 13.7 mmol) and zink dust (17.9 g, 0.27 mol). HCl (aq, 10%, 13 mL) was added to the vessel and the mixture was heated to 165 ºC and left under stirring for 24 hours**.** After 24 hours, the mixture was filtrated hot through celite and the retentate was washed with refluxing ethanol (66 mL) and refluxing DCM (66 mL). The filtrate was then evaporated in vacuo and the resulting crude was dissolved in DCM (132 mL) and the solution was washed with water (53 mL x 2). The aqueous phases were combined and made alkaline (pH 8-10) by carefully addition of NaOH (aq, 1.0 M). This aqueous phase was then extracted with DCM (105 mL) and the organic phases from both extractions were combined and washed with water (132 mL), followed by Brine (132 mL). The solution was afterwards dried over $MgSO_4$, filtrated and dried by evaporation in vacuo. The solid was then recrystallized in refluxing EtOAc (66 mL) to form white crystals of TB analogue (**11**) (4.16 g, 10.3 mmol) in 75% yield. Rf = 0.17 (PE:EtOAc 85:15); 1H NMR (400.1 MHz, CDCl3): δ = 7.37 (d, J = 8.6 Hz, 2H, H-3 and H-9), 6.91 (d, J = 8,6 Hz, 2H, H-4 and H-10), 4.54 (d, J = 16.8 Hz, 2H, H-6x and H-12x), 4.20 (s, 2H, H-13), 4.14 (d, J = 16.8 Hz, 2H, H-6n and H-12n), 2.17 (s, 6H, Ar-CH3) ppm.

The synthesis of 1,7-Dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine-2,8-diamine (12)

To a 100-mL flask containing TB analogue (**11**) (1.00 g, 2.46 mmol), Pd$_2$(dba)$_3$ (15.7 mg, 0.0172 mmol), BINAP (23.4 mg, 0.036 mmol) and t-BuONa (0.71 g, 7.4 mmol) were added. The flask was flushed five times with vacuum/nitrogen before dry toluene (10 mL) and benzophenone imine (0.9 mL, 5.4 mmol) was added. After all additions, the flask was placed in nitrogen atmosphere, heated to 85 ⁰C and left under stirring until the next day. The next day, the reaction mixture was concentrated in vacuo and afterwards THF (50 mL) was added followed by HCl (2 M, 10 mL) and left to stir at room temperature for 4 hours. After 4 hours, more HCl (2M, 5 mL) was used and PE:EtOAc (2:1, 30 mL) was added to partition the phases. Once again HCl (2M, 10 mL) was added, and the organic phase was extracted. The aqueous phases were then combined and washed with PE:EtOAc (2:1, 40 mL), DCM (40 mL) and PE:EtOAc (2:1, 20 mL x 2). The aqueous phase was made alkaline (pH 10-12) by carefully addition of NaOH (aq, 10M), then extracted with CHCl$_3$ (40 mL x 3). The organic phases were then combined and washed with Brine (60 mL), dried over MgSO$_4$, filtrated and dried in vacuo to give TB analogue (**12**) (0.65g, 2.31 mmol) in a yield of 94%. Rf = 0.21 (MeOH:CHCl3, 5:95); 1H NMR (400.1 MHz, CDCl3): δ = 6.89 (d, J = 8.5 Hz, 2H, H-4 and H-10), 6.58 (d, J = 8.5 Hz, 2H, H-3 and H-9), 4.50 (d, J = 16.6 Hz, 2H, H-6x and H-12x), 4.22 (s, 2H, H-13), 4.12 (d, J = 16.7 Hz, 2H, H-6n and H-12n), 3.38 (br, 4H, -NH2), 1.88 (s, 6H, Ar-CH3) ppm.

The synthesis of 1,7-Dimethyl-N2,N2,N8,N8-tetrakis(trimethylsilyl)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine-2,8-diamine (13)

To a 100-ml flask containing TB analogue (**12**) (1.00 g, 3.57 mmol) in N$_2$ atmosphere, anhydrous THF (39 mL) was added with a syringe. The flask was placed in a cooling bath (-78 ⁰C) and n-BuLi (3.10 mL, 7.74 mmol, 2.5 M in hexane) was added dropwise for 20 minutes during stirring. The cooling bath was then removed, and the solution was heated up to 25 ⁰C under stirring for 1 hour. Afterwards, the solution was cooled to -78 ⁰C and TMSCl (1.00 mL, 7.88 mmol) was added dropwise for 20 minutes under stirring. The cooling was then removed, and the reaction mixture was heated up to 25 ⁰C and stirred for 1 hour. After 1 hour, the reaction mixture was cooled to -78 ⁰C and n-BuLi (3.10 mL, 7.74 mmol, 2.5 M in Hexane) was added dropwise under 20 minutes. The mixture was then removed from cooling and heated up to 25 ⁰C and stirred for 1 hour. The solution was afterwards cooled to -78 ⁰C and TMSCl (1.00 mL, 7.88 mmol) was transferred dropwise over 20 minutes under stirring. The cooling bath was removed and the solution heated up to 25 ⁰C under stirring for 2 hours. The reaction was finally quenched using NaHCO$_3$ (10 mL, 10 wt%) and DCM (50mL) followed by water (50 mL) were added to the resulting solution and the phases were separated. DCM (20 mLx 2) was used to extract the aqueous phase and the organic phases were combined and washed with Brine (20 mL). The solution was then dried over anhydrous MgSO$_4$, filtrated and dried in vacuo to result in TB analogue (**13**) (2.01 g, 3.53 mmol) in a yield of 99%. Rf = 0.35 (PE:EtOAc, 85:15); 1H NMR (400.1 MHz, CDCl3): δ = 6.83 (d, J = 8.4 Hz, 2H, H-4 and H-10), 6.68 (d, J = 8.4 Hz, 2H, H-3 and H-9), 4.44 (d, J = 16,6 Hz, 2H, H-6x and H-12n), 4.27 (s, J = 1.1 Hz, 2H, H-13), 4.06 (d, J =

16.6 Hz, 2H, H-6n and H-12n), 1.94 (s, 6H, Ar-CH3), 0.03 (s, 18H, -Si(CH3)3), -0.16 (s, 18H, -Si(CH3)3 ppm.

**The synthesis of (–)-Bis((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) (5R,6S,11R,12S)- 1,7-dimethyl-N^2,N^2,N^8,N^8-tetrakis(trimethylsilyl)-6H,12H5,11-methanodibenzo[b,f][1,5]diazocine-6,12-dicarboxylate ((–)-14a)
and (+)-bis((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) (5S,6R,11S,12R)-1,7-dimethyl-N^2,N^2,N^8,N^8-tetrakis(trimethylsilyl)- 6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine-6,12-dicarboxylate ((+)-14b)**

To a 50 mL flask containing TB analogue (**13**) in N_2 atmosphere (1.00 g, 1.76 mmol), anhydrous THF (17 mL) was added. This flask was cooled to -78 ⁰C and t-BuLi (3.33 mL, 5.3 mmol) was added dropwise over 40 minutes under stirring. After the addition of t-BuLi, the mixture was left to stir for 2 hours. (1R)-(–)-Menthyl chloroformate (1.65 mL, 7.80 mmol) was then added dropwise to the cooled solution over 30 minutes and the reaction mixture was left to stir and reach room temperature in the cooling bath over 16 hours. The next day, THF was evaporated in vacuo and EtOAc (50 mL) was added to the resulting crude. This solution was then washed with water (20 mL x 2), Brine (20 mL), dried over $MgSO_4$, filtrated and dried in vacuo.
Purification method 1: The crude was purified by silica gel chromatography. First the silica was poisoned with triethylamine (1%) in heptane (500 ml) under stirring for 1 hour. The silica was then transferred to the column and washed with 500 ml heptane before the crude was added to the column (5 x 10 cm, 0.5-2% EtOAc in n-heptane. The first liter with 0.5% then a liter of 1% until TB 14b starts elute from column, then increase to a liter of 2% until the product stops coming out from the column).
Purification method 2: The resulting crude was dissolved in DCM and celite (10 g) was added. The mixture was evaporated to dryness in vacuo, yielding a fine and dry powder. This powder was then loaded on a dry vacuum column (4 x 7.5 cm, 50 mL fractions with constant 0.2% triethylamine in n-hept:DCM with a gradient of DCM % of: 0, 10, 15, 16-35 (increment 1%), every 50 mL fraction). Prior loading the product, the silica gel was deactivated by adding 1% triethylamine in heptane under stirring for 1 hour, packed and washed with heptane (50 mL). The column was finally washed again with 0.2% triethylamine in heptane (50 mL) before the loading. From the dry vacuum column, TB analogue (**14b**) (0.115 g, 0.123 mmol) was collected in a yield of 7%. The mixture of both diastereomers (0.67 g, 0.722 mmol) resulted in a yield of 41%.
(+)-14b: Rf = 0.09 (PE:tert-Butyl methyl ether 97:3); 1H NMR (400.1 MHz, CDCl3): δ = 7.04 (d, J = 8.4 Hz, 2H, H-4 and H-10), 6.81 (d, J = 8.4 Hz, 2H, H-3 and H-9), 4.83 (td, J = 10.9, 4.4 Hz, 2H, -CO2CH-R2), 4.62 (s, 2H, H-6 and H-12), 4.44 (s, 2H, H-13), 2.05-1.98 (m, 4H, menthyl),1.91 (s, 6H, Ar-CH3), 1.71-1.70 (m, 4H, menthyl), 1.54-1.41 (m, 4H, menthyl), 1.11-0-97 (m,4H, menthyl), 0.94-0.89 (m, 14H, menthyl), 0.80 (d, J = 6.9 Hz, 6H, menthyl), 0.00 (s, 18H, -Si(CH3)3), -0.13 (s, 18H, -Si(CH3)3) ppm.

8 Appendix

The following section will present and discuss all ^{1}H-NMR results obtained.

The first ^{1}H-NMR spectrum received is from the first compound (**9**) synthesized in the initial route (Figure 8.1). For this NMR, deuterated methanol was used as a solvent which can be seen as the peak at 3.31 ppm. There is another peak at 4.87 ppm that does not belong to the product, which comes from the presence of water. All other singlets in the spectrum are, however, from the product. The singlet at 2.37 ppm is from the methyl group, the singlet at 8.06 is from the proton on carbon 3 and the last aromatic proton at carbon 6 is seen as a peak at 7.25 ppm.
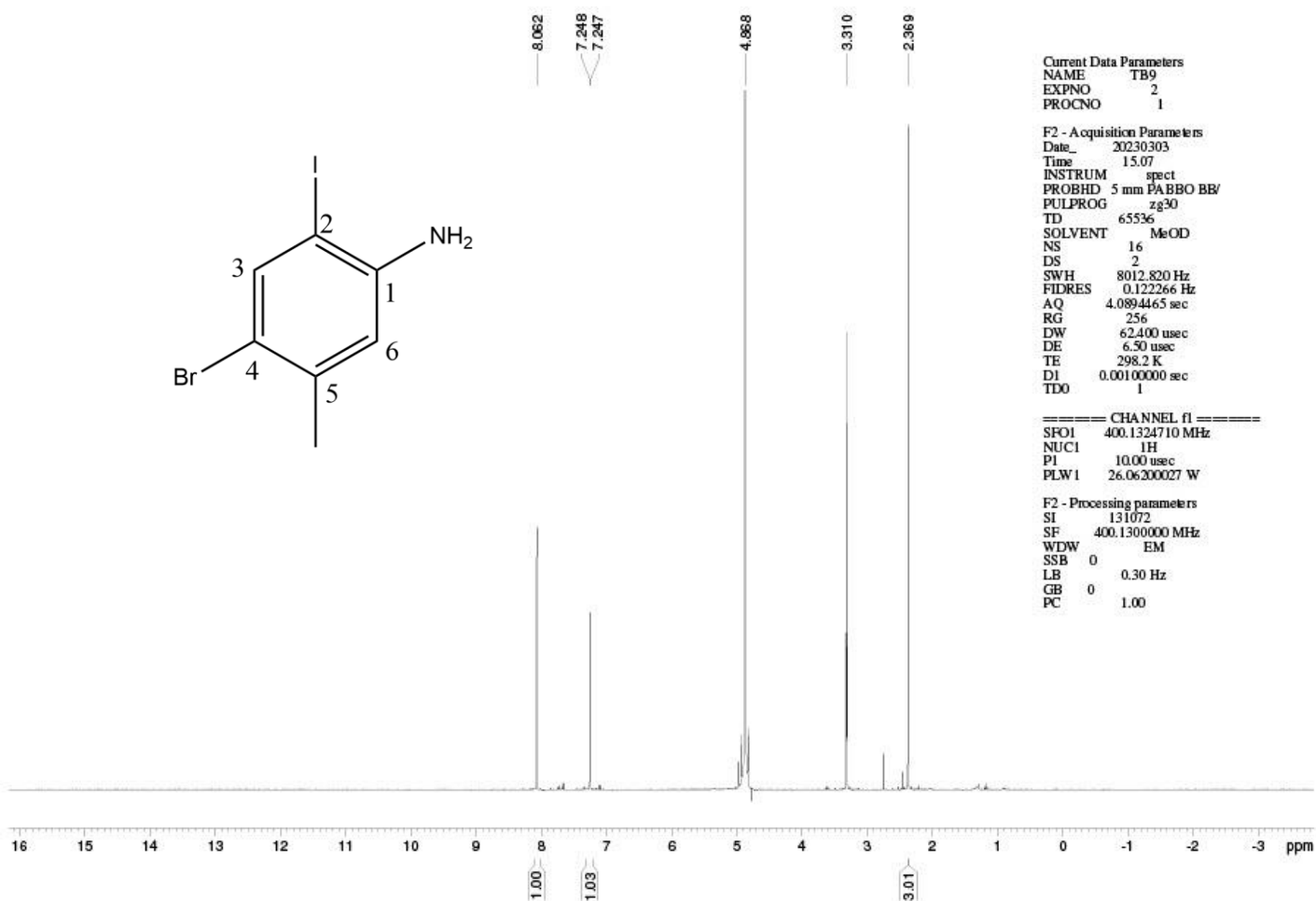

Figure 8.1: Showing the spectrum of the ^{1}H-NMR of analogue (**9**).

The ^{1}H-NMR spectrum for the first TB analogue synthesized is shown in Figure 8.2. For this ^{1}H-NMR and all other TB ^{1}H-NMRs, deuterated chloroform was used. The solvent residual signal is seen as a singlet at 7.26 ppm. Because the TB molecule is symmetric, many protons will be seen as the same signals, thus giving stronger signals. For example, the protons of the two methyl groups will be seen as one singlet at 2.18 ppm. The same principle is applied to the two aromatic protons on carbon 3 and 9, which can be seen as one singlet at 7.9 ppm. The two protons at the methylene bridge are seen as a singlet at 4.24 ppm. The other peaks in this region come from the four protons on carbon 6 and 12, which gives a quartet.
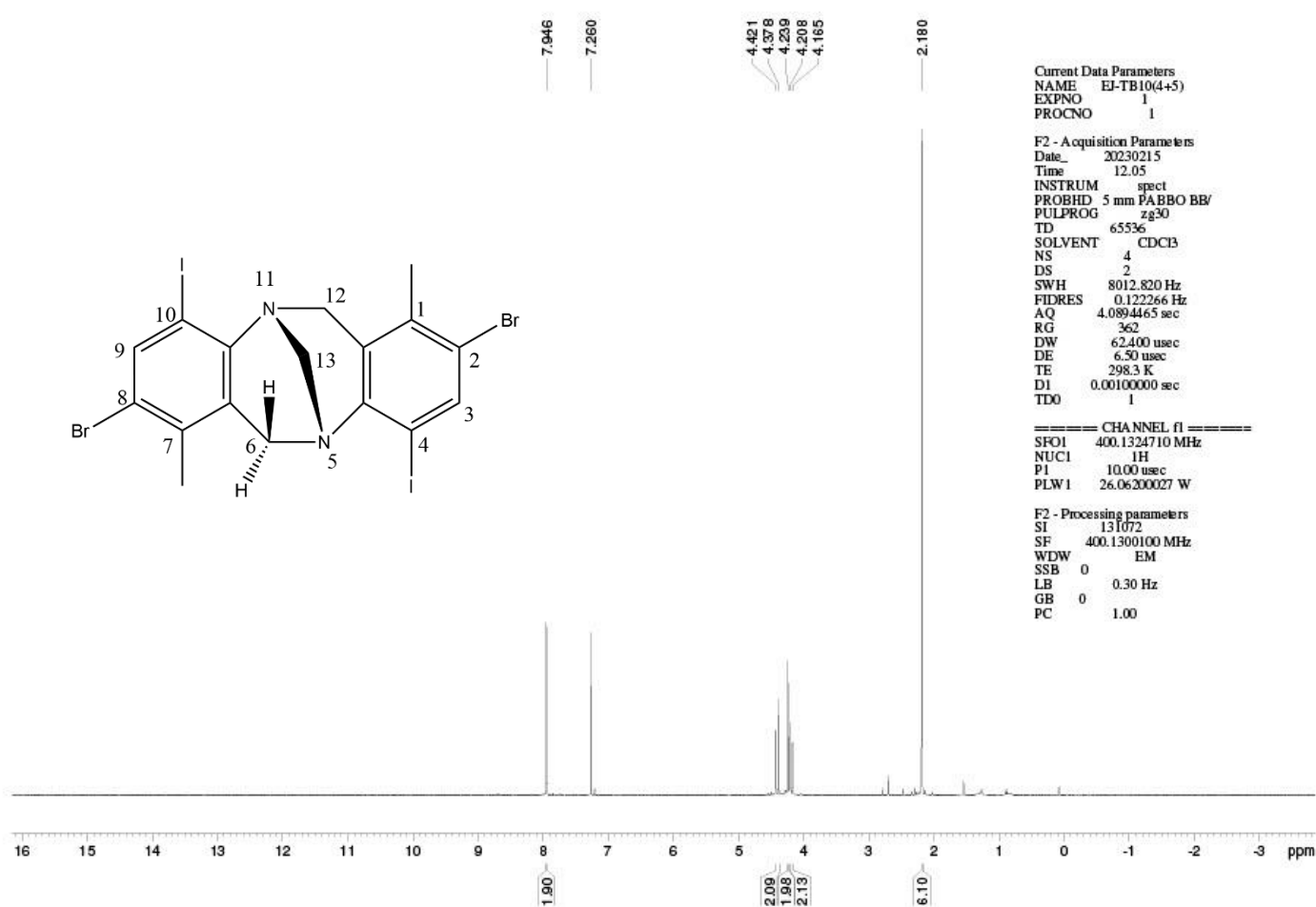

Figure 8.2: Showing the spectrum of the ^{1}H-NMR of TB analogue (**10**).

The ^{1}H-NMR spectrum of the product from the dehalogenation reaction is seen in Figure 8.3. The only difference from this NMR compared to the spectrum of TB analogue (**10**) (Figure 8.2) is the change in the aromatic region. There is an additional signal at 7.38 ppm, and the signals from the aromatic protons have become doublets. This change results from the iodine atoms have been replaced by hydrogens, thus giving rise to another environment of protons.
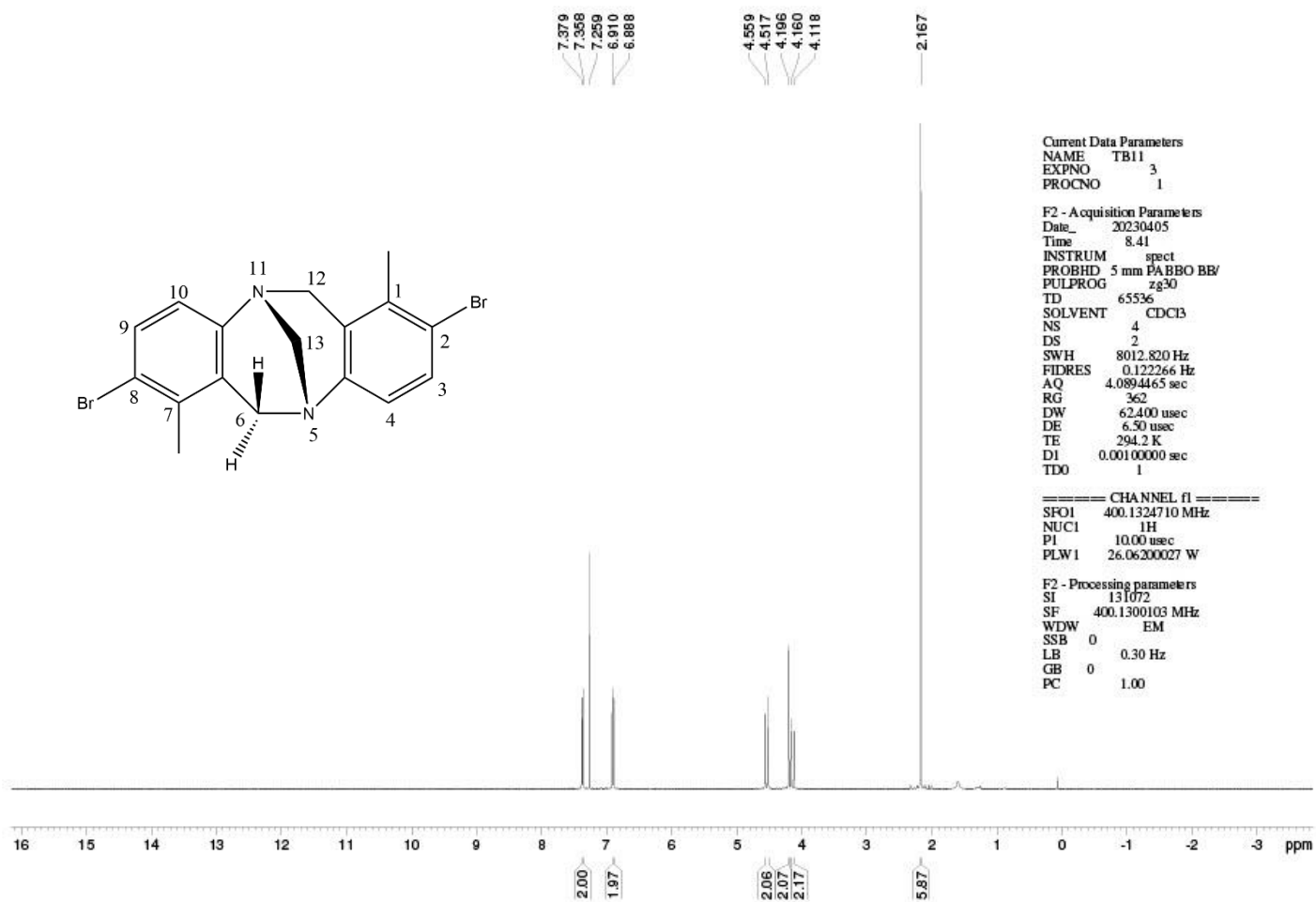

Figure 8.3: Showing the spectrum of the ^{1}H-NMR of TB analogue (**11**).

For the ^{1}H-NMR spectrum of the aminated TB analogue (**12**) (Figure 8.4), the only significant difference compared to the previous spectrum in Figure 8.3 is the peak arising from the hydrogens of the two amine groups. This peak can be seen at 3.38 ppm. The small singlet seen at 0.07 ppm is an impurity of silicone grease and does not belong to the product.
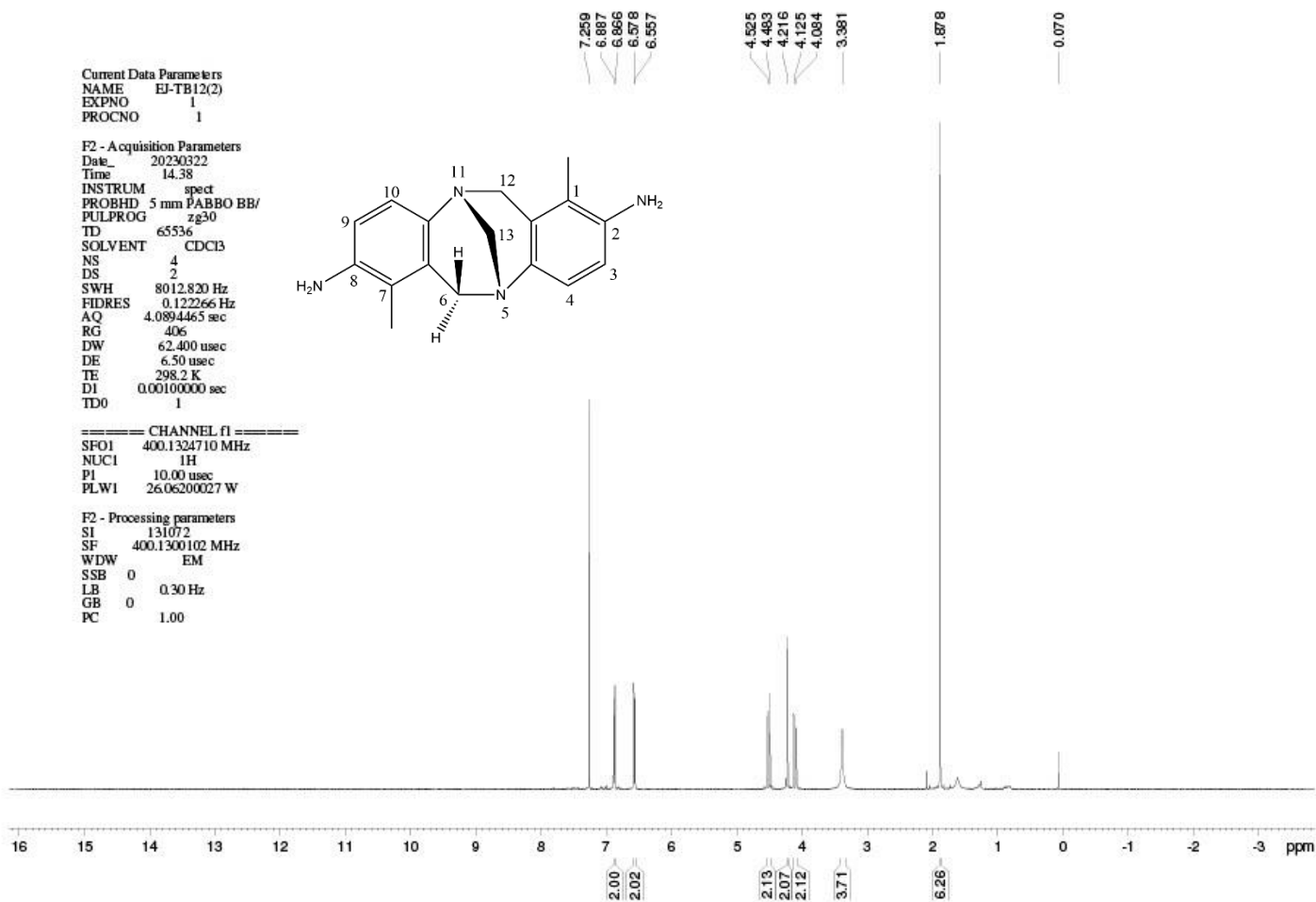

Figure 8.4: Showing the spectrum of the ^{1}H-NMR of TB analogue (**12**).

When TB analogue (**12**) is protected, the hydrogens on the amines are removed, and thus the corresponding signal has disappeared in the ^{1}H-NMR spectrum of TB analogue (**13**) (Figure 8.5). Instead, two new signals will appear for all 36 hydrogens in the TMS groups. These two signals can be seen as two singlets at 0.02 and -0.16 ppm.
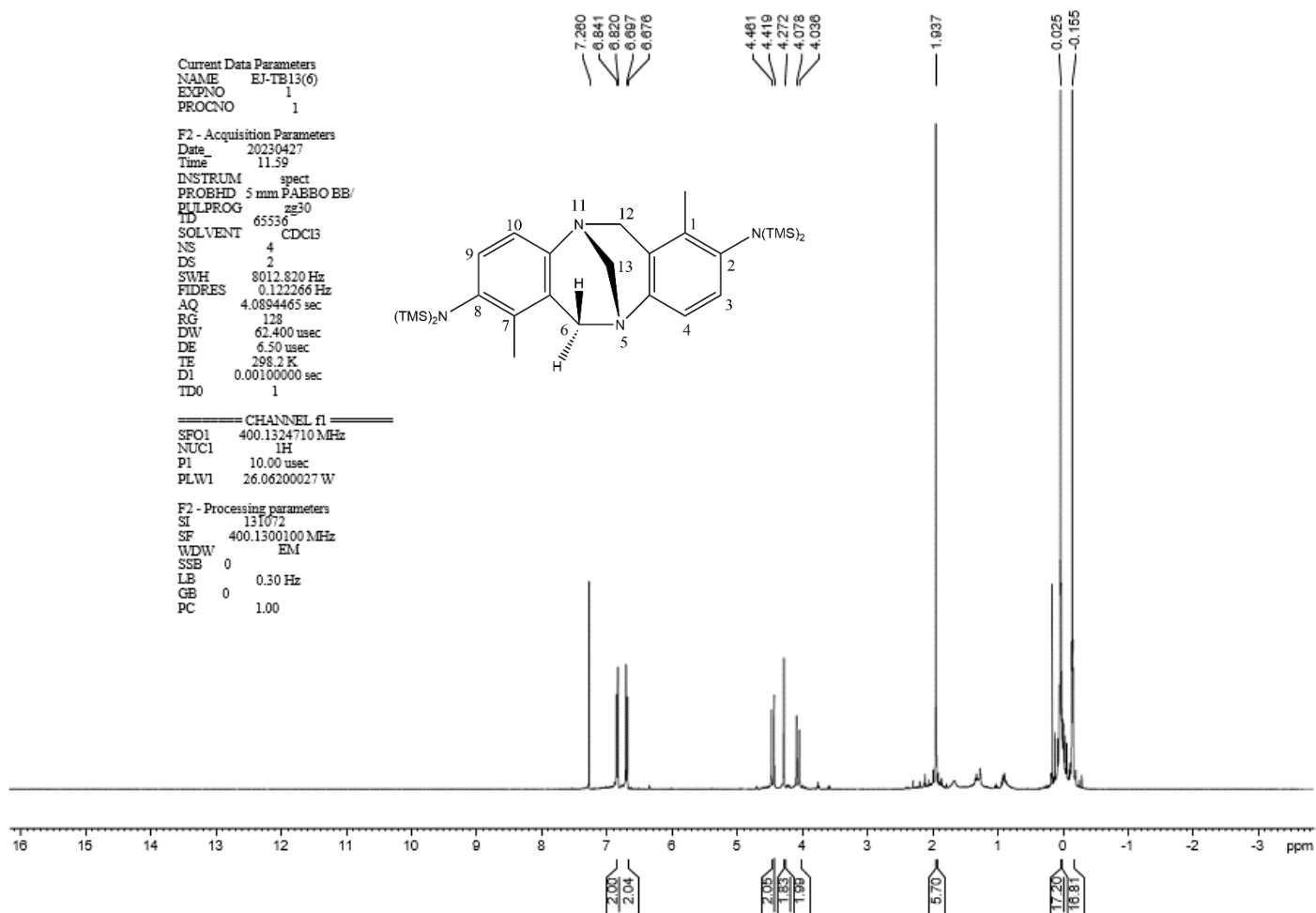

Figure 8.5: Showing the spectrum of the ^{1}H-NMR of TB analogue (**13**).

Once the menthyl ester groups are added to the product, diastereomers (**14a**) and (**14b**) become much richer on hydrogen atoms. These menthyl protons will give rise to several new signals in the ^{1}H-NMR spectrum between 0.8 and 2.05 ppm, including a triplet of doublets at 4.8 ppm (Figure 8.6). When the menthyl group is added to the benzylic position, the group replaces one of the protons, thus changing the quartet into a singlet at 4.6 ppm. The other singlet at 4.4 ppm is still from the methylene protons.

It is possible to compare the differences in the chemical shifts to differentiate the two diastereomers from each other. The signals in the spectra are shifted differently in the regions for the TMS protons, the methylene protons, and the aromatic protons, while the signals for the menthyl group protons are the same for both diastereomers.
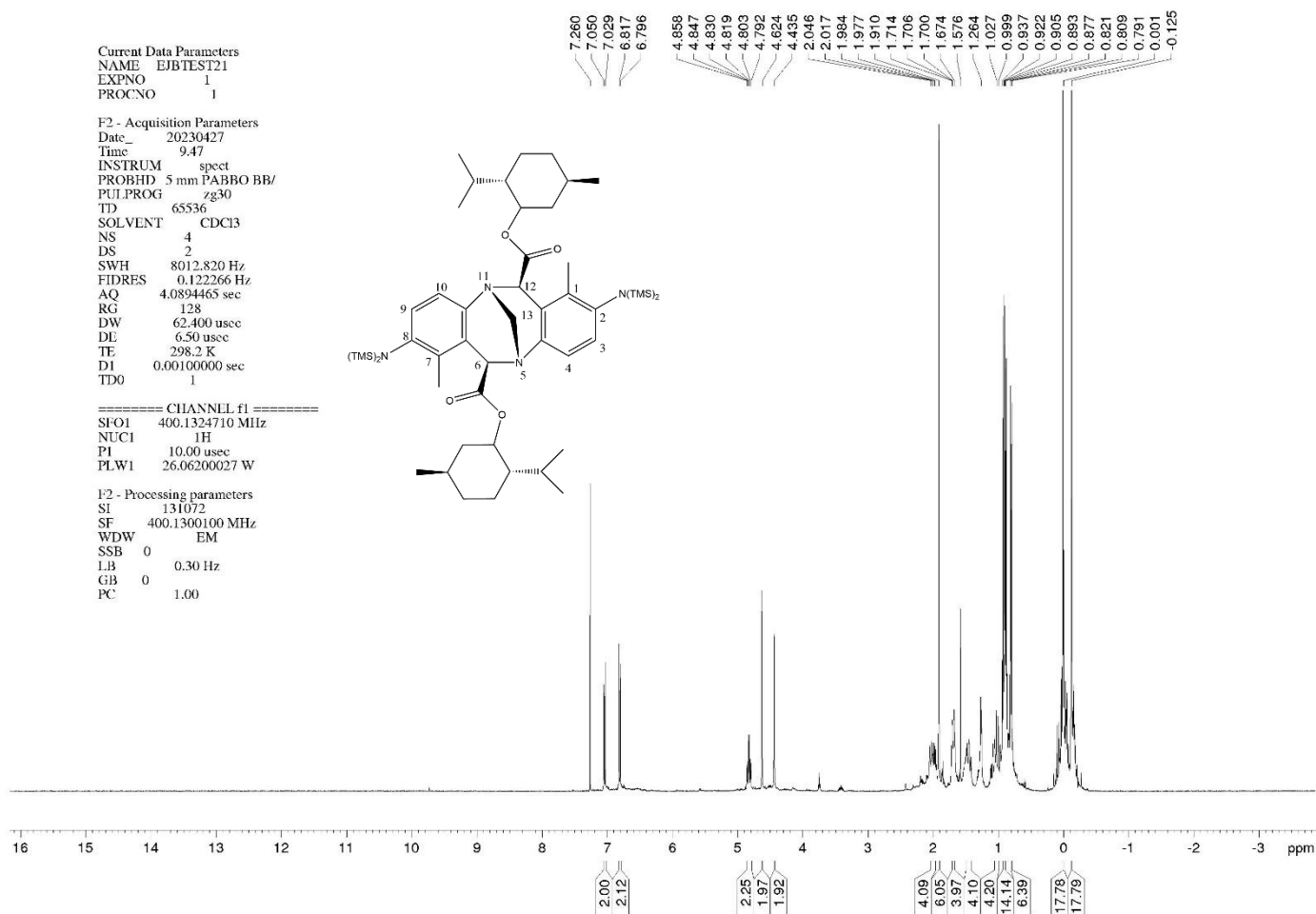

Figure 8.6: Showing the spectrum of the ^{1}H-NMR of analogue (**14b**).

Because TB diastereomer (**14a**) never was separated from the diastereomeric mixture is it difficult to prove that this diastereomer has been formed. However, if the ^{1}H-NMR spectrum for the mix is inspected (Figure 8.7), it possible to see that all regions in the spectrum except the menthyl region has the double number of signals. This is most likely because the chemical shift is slightly different for both diastereomers in these regions. If the spectrum is integrated, the number of protons should be the double amount compered to figure 8.6. In this ^{1}H-NMR spectrum it is possible to see that this is the case in the shifted regions and that the menthyl region contains stronger signals. With these facts, it is at least possible to assume that TB (**14a**) has been formed.
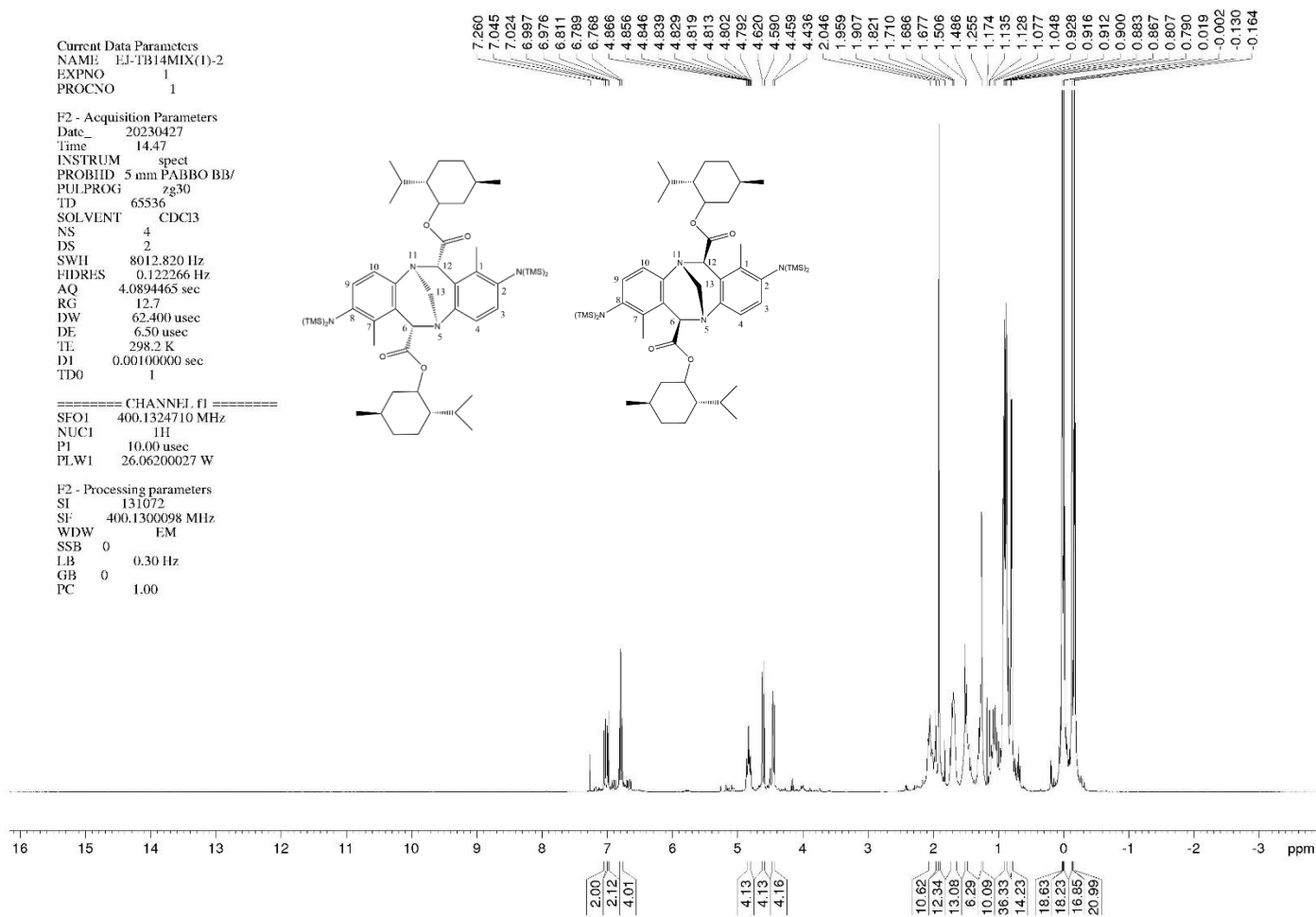

Figure 8.7: Showing the spectrum of the ^{1}H-NMR of the mixture of TB14.

References

[1] F. Huang and E. V. Anslyn, "Introduction: Supramolecular chemistry," *Chem. Rev.,* vol. 115, no. 15, pp. 6999-7000, 2015.

[2] J.-M. Lehn, "Supramolecular chemistry-scope and perspectives molecules, supermolecules, and molecular devices(Nobel lecture)," *Angew, Chem. Int. Ed. Engl.,* vol. 27, no. 1, pp. 89-112, 1988.

[3] K. Ariga, ""Supermolecules", in Biomaterials Nanoarchitectonics," *Elsevier,* pp. 25-40, 2016.

[4] C. Bissantz, B. Kuhn and M. Stahl, "A medicinal chemist's guide to molecular interactions," *Med. Chem,* vol. 53, no. 14, p. 5061–5084, 2010.

[5] E. Mattia and S. Otto, "Supramolecular systems chemistry," *Nat. Nanotechnol,* vol. 10, no. 2, p. 111–119, 2015.

[6] C.-Y. Lai and et al, "A mesoporous silica nanosphere-based carrier system with chemically removable CdS nanoparticle caps for stimuli-responsive controlled release of neurotransmitters and drug molecules," *J. Am. Chem. Soc,* vol. 125, no. 15, p. 4451–4459, 2003.

[7] S. Faulkner and A. M. Kenwright, "Supramolecular Chemistry in Medicine," Supramolecular Chemistry," *John Wiley & Sons, Ltd, Chichester,* 2012.

[8] K. Wärnmark and J. Artacho, "On the synthesis of asymmetric and dissymetric amino analogues of - Tröger's base," *Synthesis (Mass.),* vol. 2009, no. 18, pp. 3120-3126, 2009.

[9] Ö. V. Runarsson, J. Artacho and K. Wärnmark, "The 125th Anniversary of the tröger's base molecule: Synthesis and applications of tröger's base analogues," *European J. Org. Chem.,* vol. 2012, no. 36, pp. 7015-7041, 2012.

[10] C. J. Welch, ""9.06 the use of preparative chiral chromatography for accessing enantiopurity in pharmaceutical discovery and development", in Comprehensive Organic Synthesis II," *Elsevier,* pp. 143-159, 2014.

[11] I. Ilisz, R. Berkecz and A. Peter, "Application of chiral derivatizing agents in the high performance liquid chromatographic separation of amino acid enantiomers: a review," *J. Pharm. Biomed. Anal,* vol. 47, no. 1, pp. 1-15, 2008.

[12] J. Tröger, "Ueber einige mittelst nascirenden Formaldehydes entstehende Basen," *J.Prakt, Chem,* vol. 36, no. 1, pp. 225-245, 1887.

[13] M. A. Spielman, "The structure of troeger's base," *J. Am. Chem. Soc,* vol. 57, no. 3, pp. 583-585, 1935.

[14] E. C. Wagner, "Condensation of aromatic amines with formaldehyde in media containing acid. III. The formation of tröger's base," *J. Am. Chem. Soc.,* vol. 57, no. 7, pp. 1296-1298, 1935.

[15] B. Dolensky, J. Elguero, V. Kral, C. Pardo and M. Valik, ""Current Tröger's Base Chemistry" in Advances in Heterocyclic Chemistry," *Elsevier,* vol. 93, pp. 1-56, 2007.

[16] V. Prelog and P. Wieland, "Uber die Spaltung der Tröger'schen Base in optische Antipoden ein Beitrag zur Stereochemie des dreiwartigen Stickstoffs," *Helv. Chim, Acta,* vol. 27, no. 1, pp. 1127-1134, 1944.

[17] S. B. Larson and C. S. Wilcox, "Structure of 5,11-methano-2,8-dimethyl-5,6,11,12-tetrahydrodibenzo[b,f][1,5]diazocine (Tröger's base) at 163 K," *Acta Crystallogr. C,* vol. 42, no. 2, pp. 224-227, 1986.

[18] "Nobelprize.org," [Online]. Available: https://www.nobelprize.org/prizes/chemistry/1987/summary/. [Accessed 09 02 2023].

[19] S. H. Wilen, J. Z. Qi and P. G. Williard, "Resolution, asymmetric transformation, and configuration of Troeger's base. Application of Troeger's base as a chiral solvating agent,," *J. Org. Chem.,* vol. 56, no. 2, pp. 485-487, 1991.

[20] C. S. Wilcox, "Tröger's base analogs. New structural units for the preparation of chiral hosts and metal ligands.," *Tetrahedron Letters,* vol. 26, no. 47, pp. 5749-5752, 1985.

[21] J. Artacho, P. Nilsson, K.-E. Bergquist, O. F. Wendt and K. Wärnmark, "The synthesis and characterization of all diastereomers of a linear symmetrically fused Tris-tröger's base analogue: New chiral cleft compounds," *Chemistry,* vol. 12, no. 10, p. 2692–2701, 2006.

[22] A. Greenberg, N. Molinaro and M. Lang, "Structure and dynamics of Troeger's base and simple derivatives in acidic media," *J. Org. Chem.,* vol. 49, no. 6, p. 1127–1130, 1984.

[23] B. M. Webster, "Steric effects on mesomerism: XI, The ultra-violet absorption spectrum of Tröger's base and the stereochemistry of aromatic amines," *Recl. Trav. Chim. Pays Bas,* vol. 72, no. 8, p. 661–672, 2010.

[24] B. M. Webster, "Steric effects on mesomerism VIII : Benzoquinuclidine, an aromatic amine without mesomeric interaction between the benzene ring and the amino group.," *Recueil Des Travaux Chimiques Des Pays-Bas,* vol. 71, no. 12, pp. 1159-1170, 1920.

[25] I. Alabugin, L. Kuhn, N. Krivoshchapov, P. Mehaffy and M. Medvedev, "Anomeric effect, hyperconjugation and electrostatics: lessons from complexity in a classic stereoelectronic phenomenon," *Chem. Soc. Rev,* vol. 50, no. 18, p. 10212–10252, 2021.

[26] J. Jensen and K. Wärnmark, "Synthesis of halogen substituted analogues of tröger's base,," *Synthesis (Mass.),* vol. 2001, no. 12, pp. 1873-1877, 2001.

[27] A. Hansson, J. Jensen, O. F. Wendt and K. Wärnmark, "Synthesis of dihalo-substituted analogues of tröger's base from ortho- and meta-substituted anilines," *European J. Org. Chem.,* vol. 2003, no. 16, p. 3179–3188, 2003.

[28] T. Urnikaite, T. Braukyla, A. Magomedov, E. Kamarauskas, T. Malinauskas and V. Getautis, "A structural study of Troger's base scaffold-based dyes for DSSC applications," *Dyes Pigm,* vol. 143, p. 48–61, 2017.

[29] H. Hong, Z. Guo, D. Yan and H. Zhan, "A Tröger's base-derived microporous organic polymers containing pyrene units for selective adsorption of CO_2 over N_2 and CH_4," *Microporous Mesoporous Mater,* vol. 294, no. 109870, p. 109870, 2020.

[30] E.-I. Kim, S. Paliwal and C. S. Wilcox, "Measurements of molecular electrostatic field effects in edge-to-face aromatic interactions and CH-π interactions with implications for

protein folding and molecular recognition," *J. Am. Chem. Soc,* vol. 120, no. 43, p. 11192–11193, 1998.

[31] S. Paliwal, S. Geib and C. S. Wilcox, "Molecular torsion balance for weak molecular recognition forces. Effects of 'tilted-T' edge-to-face aromatic interactions on conformational selection and solid-state structure," *J. Am. Chem. Soc,* vol. 116, no. 10, p. 4497–4498, 1994.

[32] C. Yuan, Q. Xin, H. Liu, L. Wang, M. Jiang and X. Tao, "Λ-shaped optoelectronic materials based on Tröger's base," *Sci. China Chem,* vol. 54, no. 4, p. 587–595, 2011.

[33] Q. Xin et al, "Fluorene-based Tröger's base analogues: Potential electroluminescent materials," *Org. Electron.,* vol. 9, no. 6, p. 1076–1086, 2008.

[34] E. B. Veale and T. Gunnlaugsson, "Synthesis, photophysical, and DNA binding studies of fluorescent tröger's base derived 4-amino-1,8-naphthalimide supramolecular clefts," *J. Org. Chem,* vol. 75, no. 16, p. 5513–5525, 2010.

[35] J. Clayden, N. Greeves and S. Warren, Organic Chemistry, 2 ed., Oxford: Oxford University Press, 2012, pp. 471-497.

[36] E. C. Wagner, "A rationalization of acid-induced reactions of methylene-bis-amines, methylene-amines, and of formaldehyde and amines.," *The Journal of Organic Chemistry,* vol. 19, no. 12, pp. 1862-1881, 1954.

[37] T. R. Miller and E. C. Wagner, "Some analogs of troeger's base and related compounds," *J. Am. Chem. Soc,* vol. 63, no. 3, p. 832–836, 1941.

[38] J. Clayden, N. Greeves and S. Warren, Organic Chemistry, 2 ed., Oxford: Oxford University Press, 2012, pp. 185-186, 1073-1075.

[39] J. Maresh, A. Ralko, T. Speltz, J. Burke, C. Murphy, Z. Gaskell, J. Girel, E. Terranova, C. Richtscheidt and M. Krzeszowiec, "Chemoselective zinc/HCl reduction of halogenated β-nitrostyrenes: Synthesis of halogenated dopamine analogues.," *Synlett: Accounts and Rapid Communications in Synthetic Organic Chemistry,* vol. 25, no. 20, p. 2891–2894.

[40] J. Wolfe and S. Buchwald, "Scope and limitations of the Pd/BINAP-catalyzed amination of aryl bromides.," *The Journal of Organic Chemistry,* vol. 65, no. 4, pp. 1144-1157, 2000.

[41] C. Amatore, G. Broeker, A. Jutand and F. Khalil, " Identification of the effective palladium(0) catalytic species generated in situ from mixtures of pd(dba)2 and bidentate phosphine ligands. Determination of their rates and mechanism in oxidative addition," *Journal of the American Chemical Society,* vol. 119, no. 22, p. 5176–5185, 1997.

[42] S. D. Timpa, "CARBON-HETEROATOM REDUCTIVE ELIMINATION AND CATALYSIS , UTILIZING (POCOP)RH AND (POCOP)CO COMPLEXES," Samuel David Timpa, Texas, 2014.

[43] J. Clayden, N. Greeves and S. Warren, Organic Chemistry, 2 ed., Vols. 209, 549-550, Oxford: Oxford University Press, 2012.

[44] J. Clayden, N. Greeves and S. Warren, Organic Chemistry, 2 ed., Oxford: Oxford University Press, 2012, pp. 172-173. 640-654.

[45] J. Nawrocki, "The silanol group and its role in liquid chromatography," *J. Chromatogr. A,* vol. 779, no. 1-2, pp. 29-71, 1997.

[46] I. Alkorta, J. Elguero, C. Roussel, N. Vanthuyne and P. Piras, "Atropisomerism and Axial Chirality in Heteroaromatic Compounds in Advances in Heterocyclic Chemistry," *Elsevier,* vol. 105, pp. 1-188, 2012.

[47] M. D. H. Bhuiyan, K.-X. Zhu, P. Jensen and A. C. Try, "Synthesis of symmetric diester-functionalised tröger's base analogues," *European J. Org. Chem,* vol. 2010, no. 24, p. 4662–4670, 2010.

[48] C. S. Wilcox, "Tröger's base analogs. New structural units for the preparation of chiral hosts and metal ligands," *Tetrahedron Lett,* vol. 26, no. 47, p. 5749–5752, 1985.

[49] T. R. Miller and E. C. Wagner, "Some analogs of troeger's base and related Compounds1," *J. Am. Chem. Soc.,* vol. 63, no. 3, p. 832–836, 1941.

[50] M. Miyake and C. S. Wilcox, "Design and synthesis of a novel cyclophane as host for aryl phosphate," *Heterocycles,* vol. 57, no. 3, p. 515, 2002.

[51] M. Häring, "Die Darstellung von 5,11-Endomethylen-tetrahydrophenhomazinen und 5-Alkyl-tetrahydrophenhomazinen," *Helv. Chim. Acta,* vol. 46, no. 7, p. 2970–2982, 1963.

[52] B. G. Bag and U. Maitra, "A convenient method for the synthesis of tröger's base analogues," *Synth. Commun,* vol. 25, no. 12, p. 1849–1856, 1995.

[53] J. C. Adrian and C. S. Wilcox, "Chemistry of synthetic receptors and functional group arrays. 19. General effects of binding site water exclusion on hydrogen bond based molecular recognition systems: a closed binding site is less affected by environmental changes than an open site," *Chem. Soc,* vol. 114, no. 4, p. 1398–1403, 1992.

[54] H. Salez, A. Wardani, M. Demeunynck, A. Tatibouet and J. Lhomme, "Synthesis of tröger's base analogs derived from 3-aminoacridine and 10-aminobenzo[b][1,7]phenanthroline," *Tetrahedron Lett,* vol. 36, no. 8, p. 1271–1274, 1995.

[55] J. Y. F. Wong and G. Barker, "Recent advances in benzylic and heterobenzylic lithiation," *Tetrahedron,* vol. 76, no. 131704, p. 131704, 2020.