Towards Higher Generations of Linear Tröger's Base Analogues

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Towards Higher Generations of Linear Tröger's Base Analogues

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I am also very grateful to my supervisor at Universiät Leipzig, Prof. Dr. Berthold Kersting, for his assistance and encouragement to take this step and go abroad again. Without him this cooperation and this thesis would not have been possible.

At last I want to thank my family and friends for their support, not only during the work for this thesis but throughout the whole course of my studies.

Disclaimer

I, the undersigned, hereby declare that I have produced this scientific work myself and have used no other material or resources than the ones listed. All cited content is marked accordingly.

Leipzig, May 1st, 2012

Michaela Klische

Summary

This project work was done at the Centre for Analysis and Synthesis (CAS) at the Department of Chemistry at Lund University in cooperation with the Universität Leipzig in the period of November 2011 to April 2012. In that time the synthesis of the precursor leading to the so called tris-Tröger's base was accomplished. Starting point of the synthesis was 4-bromo-3-methylaniline, which was functionalized in *para* position to the methyl group with an iodine residue, followed by a condensation reaction to the Tröger's base. Two different reactions were tested for the removal of the iodine moiety. The dehalogenation with zinc powder and HCl in EtOH proved to be the more suitable than the lithiation with *n*-BuLi and exchange with a proton. The bromine substituents were transformed into amine groups *via* a Buchwald-amination and were subsequently protected with TMS-groups. The racemic mixture was lithiated with *t*-BuLi and further reacted with *R*-menthyl chloroformate. The corresponding diastereomers of the Tröger's base were formed and separated with column chromatography. With the single diastereomer at hand the ester was reduced to an alcohol with LAH.

From there the next steps would have been the alkylation of the hydroxyl groups, the deprotection of the amine groups with TBAF and the monoprotection by trifluoroacetic anhydride to achieve a desymmetrization. This would have been necessary for the following condensation with paraformaldehyde in TFA that leads to the tris-Tröger's base. This molecule should have been the subject of further isomerization studies. Optimization of the syntheses and the full characterization of the compounds were also in the focus of this project.

Contents

List of Abbreviations

br	broad signal (NMR)
COFs	covalent organic frameworks
COSY	correlated spectroscopy
d	doublet (NMR)
DCM	dichloromethane
EtOAc	ethylacetate
EtOH	ethanol
h	hours
HCl	hydrochloric acid
HMBC	heteronuclear multiple bond correlation
HRMS-ESI	high resolution mass spectrometry - electro spray ionization
ICl	iodine monochloride
ICPs	infinite co-ordination polymers
LAH	lithium aluminium hydride
m	multiplet (NMR)
HMTA	hexamethylenetetraamine
MeOH	methanol
mp.	melting point
MS	mass spectrometry
MW	molecular weight
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
PE	petroleum ether
r.t.	room temperature
R_f	retardation factor
s	singlet (NMR)
t	triplet (NMR)
TBAF	tetra-*n*-butylammonium fluoride
t-BuLi	*t*-butyllithium
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Tol	Toluene
XRD	X-ray diffraction

1 Introduction

Supramolecular chemistry has been described as 'chemistry beyond the molecule' and the 'supermolecule' is an aggregate of covalent molecules or ions, held together by non-covalent interactions. These building blocks or units usually form reversible intermolecular bonds, which include electrostatic interactions, hydrogen bonding, π-π-interactions, dispersion interactions and hydrophobic or solvophobic effects.

Supramolecular Chemistry combines multiple fields and disciplines. There are the organic and inorganic chemistry, so one can synthesize the supramolecular hosts. Physical chemistry is needed to understand the properties of these systems. A lot of spuramolecular concepts can be found in biological chemistry as well and computational modelling can be of help to understand those concepts and complex supramolecular behaviour.[1]

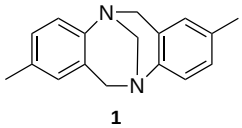

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Figure 1.0.1: 2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine.

A valuable and versatile structural motif for supramolecular applications is the so called Tröger's base, seen above in figure 1.0.1. It is a C_2-symmetric molecule. Two aromatic rings, nearly perpendicular to each other, are connected by a 1,5-diazocine bridge. The chirality of that compound inheres in this bridge, as the two nitrogen atoms are hindered in their inversion by a methylene bridge that generates a bicyclic structure. In this way the molecule provides a chiral, hydrophobic, concave cavity that can be used as building block for compounds that shall be utilized for example as receptors for molecular recognition or ligands in asymmetric synthesis. Due to its chirality and its rigid structure one can anticipate regio- and stereoselective properties of Tröger's base-containing catalysts. In the following, the way from an underestimated and unappreciated discovery to an important and valued building unit in today's supramolecular chemistry shall be shown.[2,3]

2 The Tröger's Base

In this chapter the history behind the Tröger's base shall be outlined and miscellaneous examples for the use of the Tröger's base as important structural motif are to be given. Special attention will be turned to the attempt of synthesizing higher generations of linear Tröger's base analogues with a unique structure, which is the driving force behind this thesis project.

2.1 Julius Tröger and the belatet Fame

JULIUS TRÖGER, the eponym of this base, was born on October 10th 1862 in Leipzig as the son of the manufacturer CARL FRIEDRICH TRÖGER. He studied natural sciences from 1882 until 1888 in Leipzig. He submitted his dissertation for achieving his doctoral degree in 1887. In that thesis "Ueber einige mittels nascirenden Formaldehydes entstehende Basen"[1] he described the synthesis of the compound, that later on was going to carry his name. Without any doubt, he described its molecular formula $C_{17}H_{18}N_2$, the melting point (134°C) and characterized also its derivatives. Back then it was not possible to determine the true structure of the molecule, though. Julius Tröger was rewarded for his dissertation with the rather moderate grade three by Prof. Dr. JOHANNES WISLICENUS and Prof. Dr. GUSTAV WIEDERMANN. They criticized that the determination of the compounds constitution was necessary and undoubtedly within the realms of possibility. TRÖGERs efforts were honoured, but it was thought that his work was only a stepping stone for further investigations in the future and it only was of marginal value for that time being. Nonetheless TRÖGER went to Braunschweig, habilitated in 1891, and from there on, climbed the ranks of university hirarchy, from associate professor up to full professor and head of the department in 1920. He retired eight years later and died on July 29th 1942 in Braunschweig.[4]

Still it took 48 years from the synthesis to the determination of the true structure by SPIELMAN[5] and 31 more years for its verification with the help of X-ray diffraction analysis.[6] The dispute was finally disclosed in 1991 by further XRD analysis of WILEN and WILLIARD.[7] Also remarkable is the fact that the Tröger's base was the first racemic mixture that was resolved. PRELOG and WIELAND[8] used a modified lactose chromatography to separate the enantiomers of the base. Nowadays it is still used as a model compound to evaluate new chiral chromatography stationary phases.

[1] "About some bases generated by nascent formaldehyde"

2.2 Structural Diversity of oligo-Tröger's Bases

When Julius TRÖGER synthesized 2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine for the first time, he let *p*-toluidine react with dimethoxymethane in aqueous hydrochloric acid. Most of the procedures used nowadays are variations of that described methodology.[9] The most commonly used sources of methanal are formalin, paraformaldehyde and hexamethylenetetraamine (HMTA). Also dimethoxymethane and trioxane are possible among others, but rarely used. Together with the aniline the methanal synthon is submitted to acidic conditions. Hydrochloric acid, trifluoroacetic acid (TFA), in few cases acetic acid or methanesulfonic acid are the acids of choice. As solvent serves either a slight excess of the acid or methanol, ethanol, THF, dioxane or chloroform. Reaction conditions can vary from -15°C to 90°C, reaction times lie between hours and days.

Problematic is the aniline because it does not allow too many variations. Electron-withdrawing groups often result in a slow course of reaction with low yields. Regioselectivity is also an issue. An un-substituted *para* position at the aniline is the reason for polymerization and therefore, a decrease in yield. There are two *ortho* positions capable of electrophilic substitution and if they are equivalent, this can lead to a mixture of products. Hence blocking of this position can be beneficial to the regioselectivity and yield.[10]

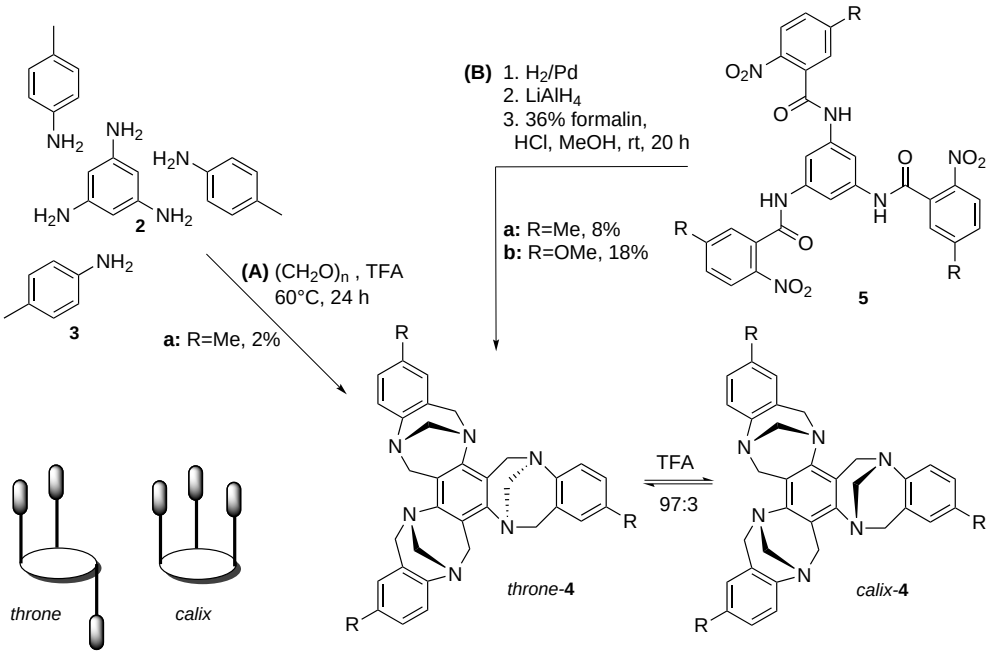


Figure 2.2.1: Different syntheses of tris-Tröger's base **4**.

In general, there are two different routes that lead to oligo-Tröger's bases. One can use an all-at-once strategy, where all Tröger's base units are formed simultaneously. Or, the Tröger's base units are formed step by step and they are

already part of the starting material. An example for the all-at-once strategy is the tris-Tröger's base **4**. (see figure 2.2.1)[10]

The approach that comes to mind as the easyest way is a one-pot reaction, where a mix of aryl-amine **3** and -polyamine **2** is submitted to the Tröger's base reaction conditions described in figure 2.2.1. The *throne*-shaped product **4a** was only gained in 2% yield.[11] Another possibility is route **(B)**, where the sidewall arenes are already contained in the starting material. First **5** is reduced into a hexaamine. The condensation to the Tröger's base is carried out with 36% formalin and HCl in MeOH at r.t. in 20 h and gave the *throne*-product **4a**, with R beeing a methyl group, in 8% yield and **4b** with methoxy groups in slightly better yield of 18%.[12] After getting only the *throne*-diastereomer it was tried to isomerize it, by submitting it to TFA at 110°C in 15-17 h, but only 3% of the corresponding *calix*-diastereomer **4a/b** were formed.[11]

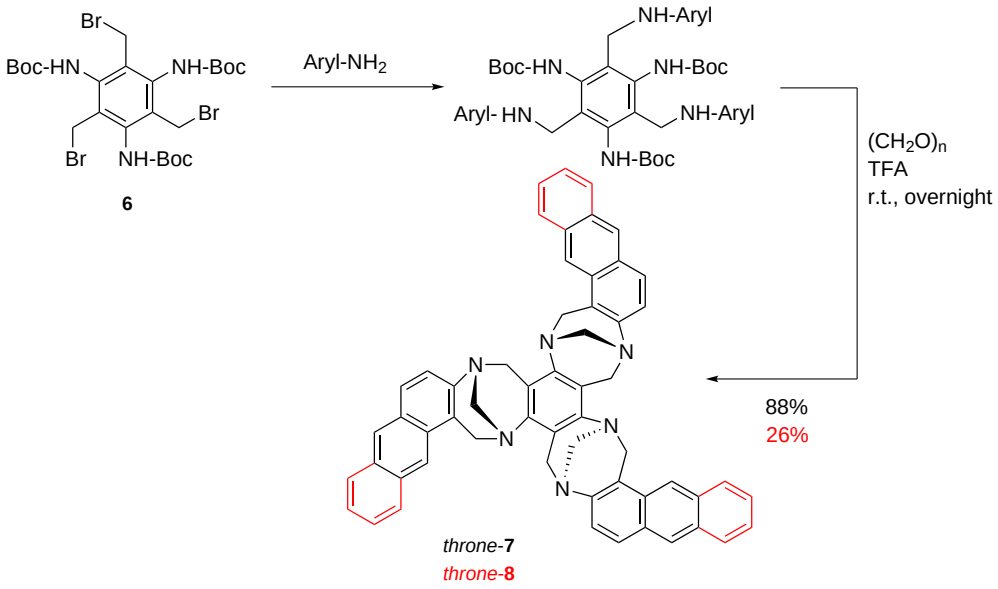


Figure 2.2.2: Tris-Tröger's base *via* central reagent protocol.

The tris-Tröger's bases **7** and **8** (marked red in figure 2.2.2) are prepared in a similar way. First **6** was reacted with naphthalen-2-amine and anthracen-2-amine respectively to give the corresponding hexaamine. This central reagent already contains the sidewall arenes and is submitted to the Tröger's base condensation conditions. It gives the *throne*-diastereomers in good (*throne*-**7**: 88%) to moderate (*throne*-**8**: 26%) yield. But also, for these products the isomerization only gave 2-4% yield of the *calix*-diastereomer.[13] Especially the *calix*-diastereomers would be of particular interest, for example as a molecular compartment or box, maybe suitable as reaction containers. XRD analysis showed that these chiral cavitands possess a cavity volume about 0.092 nm^3 (*calix*-**4b**) and 0.215 nm^3 (*calix*-**8**), not unsimilar to cyclodextrines (α-CD 0.174 nm^3, β-CD 0.262 nm^3).[14]

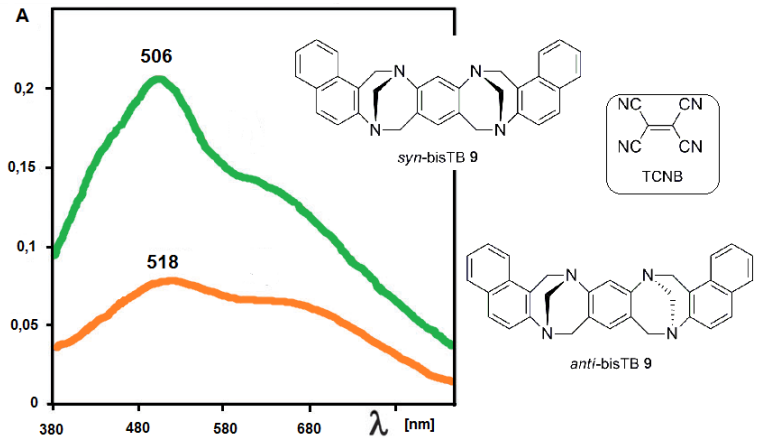


Figure 2.2.3: Colour changes of bis-Tröger's base **9** induced by addition of TCNB.[15]

The Tröger's base, with its rigid structure, displays the perfect scaffold for synthesizing so called molecular 'clefts' or 'tweezers'. One could describe the structure with the looks of a 'pince'. The binding sites are at two side arms that are connected with each other through the rigid spacer. Thus a high degree of preorganisation is achieved, which means that the host already has a conformation that allows the guest to fit in and that it can be bound in the most stable way.[1] The binding abilities of *syn*-bis-Tröger's bases and *syn, syn*-tris-Tröger's bases have been in the focus of studies only recently.[15] Figure 2.2.3 shows schematically the absorption spectrum that was recorded by Král et al.[15] when adding equimolar amounts of TCNB (tetracyanoethylene) to a colourless solution of *syn*-**9** or *anti*-**9**. A charge-transfer complex is formed with the ligand **9** and the solution takes a dark violett colour in case of the *syn*-**9** complex and a light violett colour in case of the *anti*-**9** complex. This can be explained by the fact, that the *anti*-**9** isomer has not the 'tweezer-conformation', therefore it binds the TCNB not that well and the charge-transfer complex does not absorb the visible light as strongly as the *syn*-**9** complex does.

Because *syn-syn*-tris-Tröger's bases have a unique concave structure, the idea stands to reason, that if several bases in *syn-syn* conformation are combined a helical structure will be taken. This task has been of interest to the group around WÄRNMARK.[16]

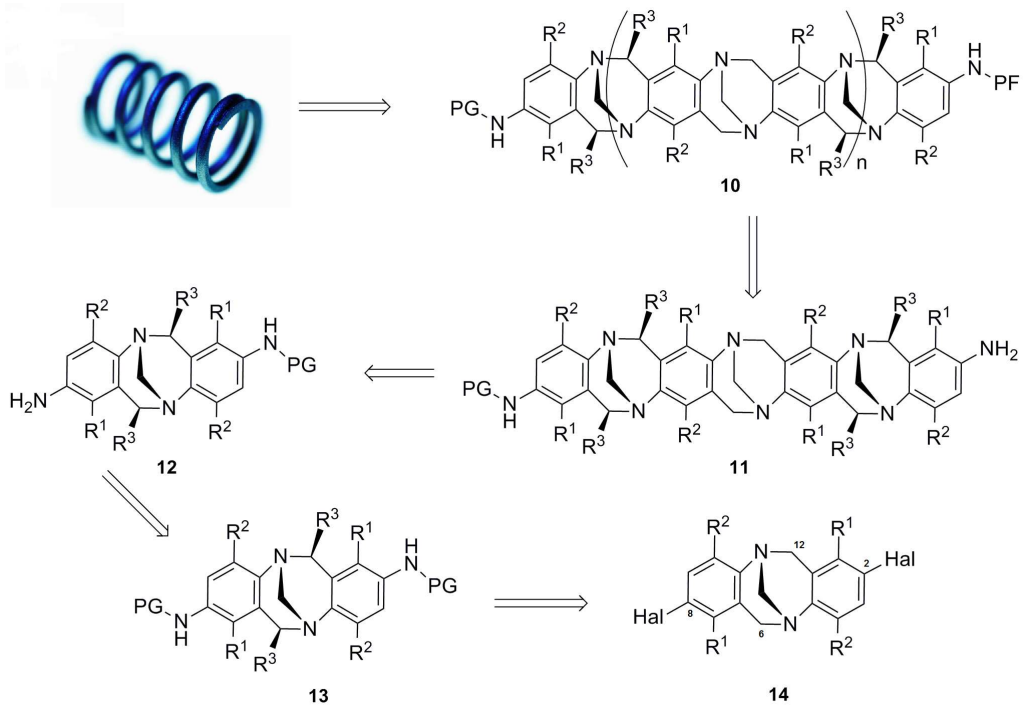


Figure 2.2.4: Retrosynthetic strategy for synthesizing higher generations of linear Tröger's base analogues.

In figure 2.2.4 the retrosynthetic strategy is depicted. When the Tröger's base with the envisaged substitution pattern of a 2,8-dihalo analogue is achieved, and the positions 2 and 8 are transformed into protected amine groups, the positions 6 and 12 at the diazocine ringe should be substituted in *exo,exo*-configuration. Previous investigations in the group lead to the establishment of procedures to diaminate 2,8-dibromo analogues of Tröger's base through Pd-catalysis[17] and to conduct *exo* and *endo* 6,12-substitutions on Tröger's base by metalation.[16] By functionalization of the diazocine ring, it is anticipated to circumvent the solubility problems that occured in prior studies with the tris-Tröger's base.[18]

Here the before mentioned step-by-step approach is used to generate poly-Tröger's bases. The Tröger's base units are already present in the starting material **13** and after desymmetrizing it, through monoprotection or monodeprotection, one can employ it in a following condensation reaction to give the wanted tris-Tröger's base **11**. The idea is, that these steps of desymmetrization and condensation can be carried out again and again (from the tris-analogue to the heptakis, from the heptakis to the decapentakis-analogue and so on), until one has a tubular shaped poly-Tröger's base. Possible applications could be the incorporation into a membrane, where it acts as a channel for the transport of ions or molecules. Or it may be used as an anti-cancer drug. It could intercalate with the DNA of cancer-cells and inhibit their proliferation by that.

2.3 Molecular Recognition

Before, an example of an oligo-Tröger's base which can act as a tweezer with binding abilities has been given. But there are a lot of other compounds that have been functionalized with special substituents to enable molecular recognition.

The first to use a Tröger's base backbone with its curvature shape for the design of receptors was WILCOX.[19, 20] In 1986 he developed a water-soluble macrocyclic receptor that had the ability to recognize neutral molecules. As seen in figure 2.3.1, the cyclophane receptor **15** combines the Tröger's base scaffold with a biphenyl moiety through alkyl chains with secondary ammonium groups and forms association complexes with benzoid substrates. Analysis in acidic aqueous media showed that the receptor **15** prefers aromatic structures with electron-withdrawing groups. With receptor **16** even enantioselective and diastereoselective molecular recognition of alicyclic guests, such as isomeric menthols, is possible.[21]

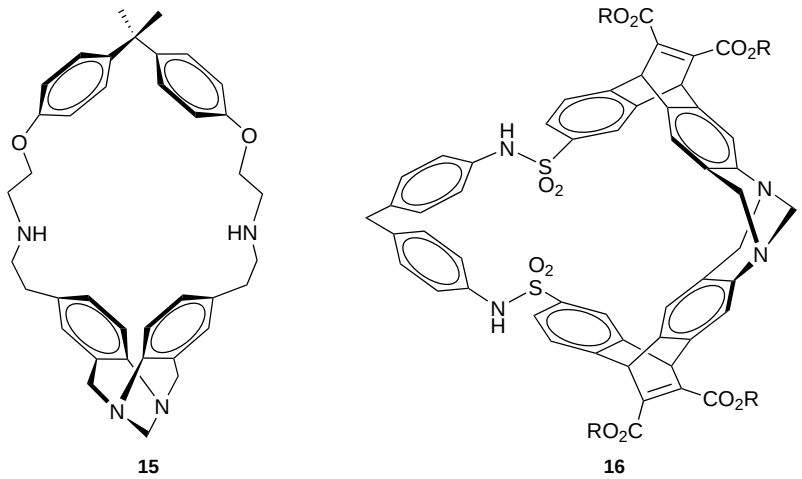


Figure 2.3.1: Cyclophanes with a Tröger's base backbone.

Also designed by WILCOX[22] is the following receptor **17** in figure 2.3.2, which is capable of establishing four hydrogen bonds. It has two acceptor sites and two hydrogen donor sites through the functionalization with carboxylic groups. It can form complexes with aromatic amines and cyclic amides, such as the depictet adenine derivative. Association constants could be determined by NMR spectroscopy.

Other kinds of substrates could also be recognized by changing the substituents at the Tröger's base scaffold. The pyridine functionalized receptor **18**, synthesized by GOSWAMI and GHOSH,[23] binds, through hydrogen-bond formation as well, dicarboxylic acids of varying chain length. And NMR titration experiments revealed that this host is selectively binding octanedioic acid ($C_6H_{12}(COOH)_2$).

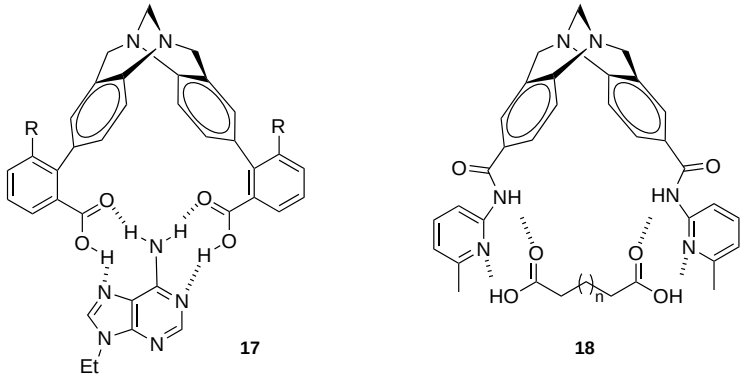


Figure 2.3.2: Receptors for molecular recognition by hydrogen-bond formation.

A receptor that combines a crown ether with the Tröger's base was designed by WÄRNMARK et al.[24] in 1998. It was observed that this bis-crown ether analogue **19** can recognise achiral and chiral bis-ammonium salts. (see figure 2.3.3)

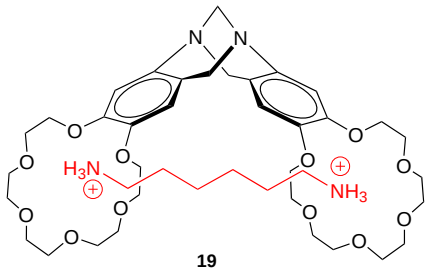


Figure 2.3.3: Tröger's base-bis-crown ether receptor for bis-ammonium salts.

Amino acids and aliphatic diamines are suitable guests for a bis-porphyrin based host **20**, synthesized by the group of CROSSLEY.[25] The Zn-complexing porphyrins are fused together by the Tröger's base scaffold and the metal ions are coordinated by the amine groups of the guest molecules.

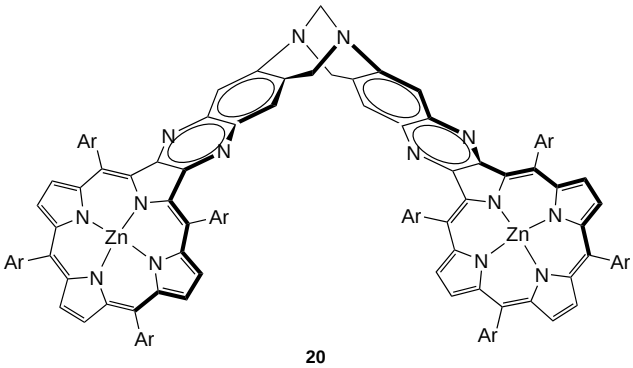


Figure 2.3.4: Bis-Porphyrin receptor **20**.

2.4 Other Applications

With its chiral cavity the Tröger's base could also be utilized as ligand for a catalyst that displays stereo- or regioselectivity. In 1995 GOLDBERG and ALPER[3] synthesized probably the first Tröger's base-based catalyst. When a solution of (±)-Tröger's base in ethanol is submitted to a solution of $RhCl_3$ hydrate at r.t. the corresponding complex TB·2 $RhCl_3$ is readily formed. The Rh(III)-complex **21** catalyses the hydrosilylation of terminal alkynes. This catalyst system can generate the usual *syn*-additon product (*β-trans*-alkenylsilane), the less stable *anti*-addition product (*β-cis*-alkenylsilane) and the *α*-isomer. (see figure 2.4.1)

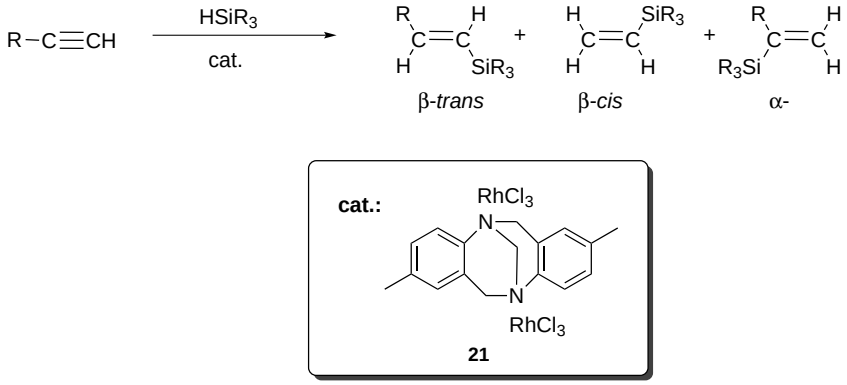


Figure 2.4.1: Hydrosilylation of terminal alkynes catalyzed by a Tröger's base-Rh(III)-complex.

The Tröger's base is not only applicable to catalyse hydrosilylations of alkynes, but also to other reactions, such as the addition of diethylzinc to aromatic aldehydes. WANG et al.[26] generated a nanoporous polymer that incorporates the catalytically active Tröger's base-funtionality. A covalent organic framework (COFs) was prepared by reacting the catalytic moiety **22** with 1,3,5-triethylbenzene **23** as linker in a Sonogashira-Hagihara cross-coupling, as seen in figure 2.4.2. The amorphous polymer showed a comparable catalytic activity and performance as the homogeneously catalyzed reaction. The polymer is unsoluble in a wide range of organic solvents and has the main advantage of heterogeneous catalysis: the catalyst and reactands have different state of aggregation and the solid catalyst can be separated from the reactands more easily.

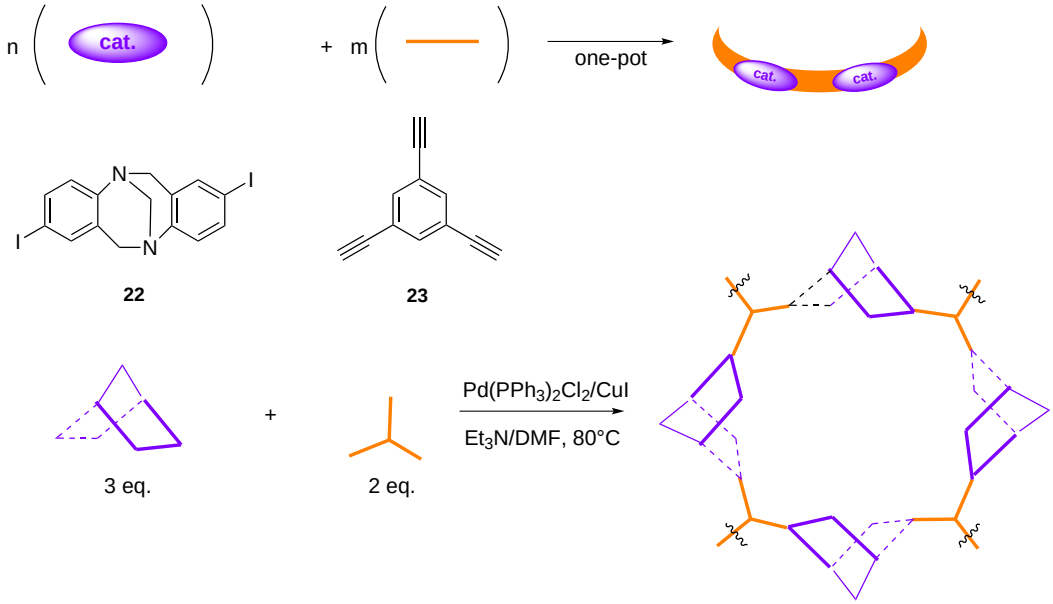


Figure 2.4.2: Preparation of a Tröger's base-functionalized nanoporous polymer.

MIRKIN et al.[27] generated particles that are made of so called infinite coordination polymers (ICPs). They chose the Tröger's base derivative **24** as a ligand, because they thought that with its V-shape a zigzag-type of structure would be created with Zn^{2+} as ion nodes (see figure 2.4.3). It was hypothesized that small channels or pores will be formed and by that the possibility of differentiation between gases with a different kinetic diameter occurs. Indeed it has been shown that this material can discriminate between H_2 and N_2 and has a high selectivity for H_2. With these abilities this polymer is a promising material for hydrogen storage.

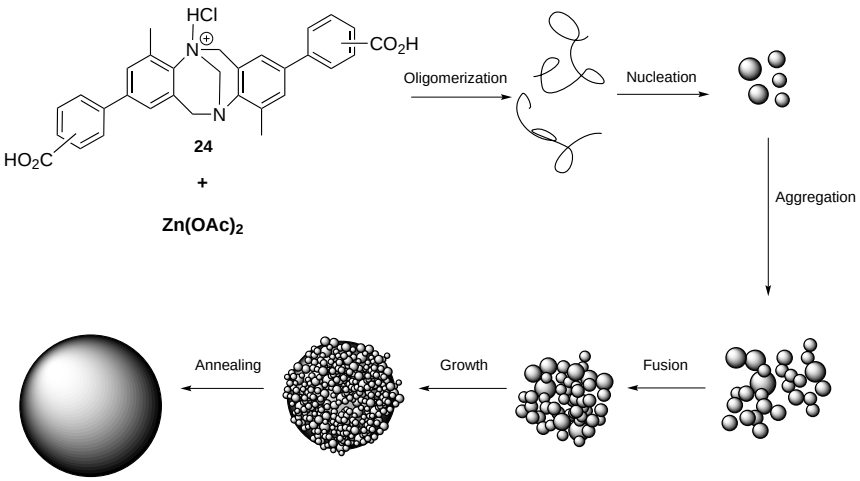


Figure 2.4.3: Synthesis of the ICP.

With the discovery of YASHIMA et al.[28] in 1991, that a phenantroline-Tröger's base-analogue interacts highly with DNA and even shows higher affinity than the 1,10-phenanthroline from which it was derived, an interesting field of chiral probes of nucleic acid structures adapted from the Tröger's base developed. Compound **25** could not only bind to DNA, but also cleave it in the presence of Cu^{2+} ions. Later the group around DEMEUNYNCK and LHOMME[29] developed another ligand, based on proflavine **26** (see figure 2.4.4) and it showed that this kind of Tröger's base only binds selectively to DNA sequences that contain A·T and G·C base pairs, such as the motifs 5'-GTT·AAC and 5'-ATGA·TCAT. This recognition-ability is enantiospecific, meaning that only the (-)-**26** enantiomer is capable this sequence-selective binding.

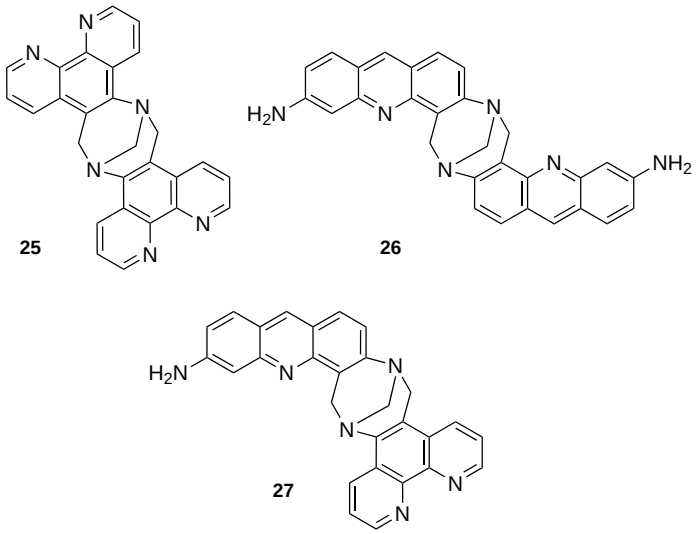


Figure 2.4.4: Analogues of the Tröger's base incorporating the proflavine and phenanthroline structures.

As the elucidation of the binding-mechanism of both compounds **25** and **26** to DNA was complicated by their symmetric structures, the asymmetric derivative **27** was synthesized.[30] These studies provided further insight into the binding mode and it showed that the proflavine unit intercalates between the DNA base pairs and the phenanthroline ring occupies the DNA groove.

3 Project Strategy

The aim of this project was the synthesis of the tris-Tröger's base, as seen in figure 3.0.1. The tris-Tröger's base is an important building unit in the formation of higher generations of linear Tröger's base analogues, that are thought to ultimately lead to a helix shaped Tröger's base-polymer, as it was described in section 2.2.

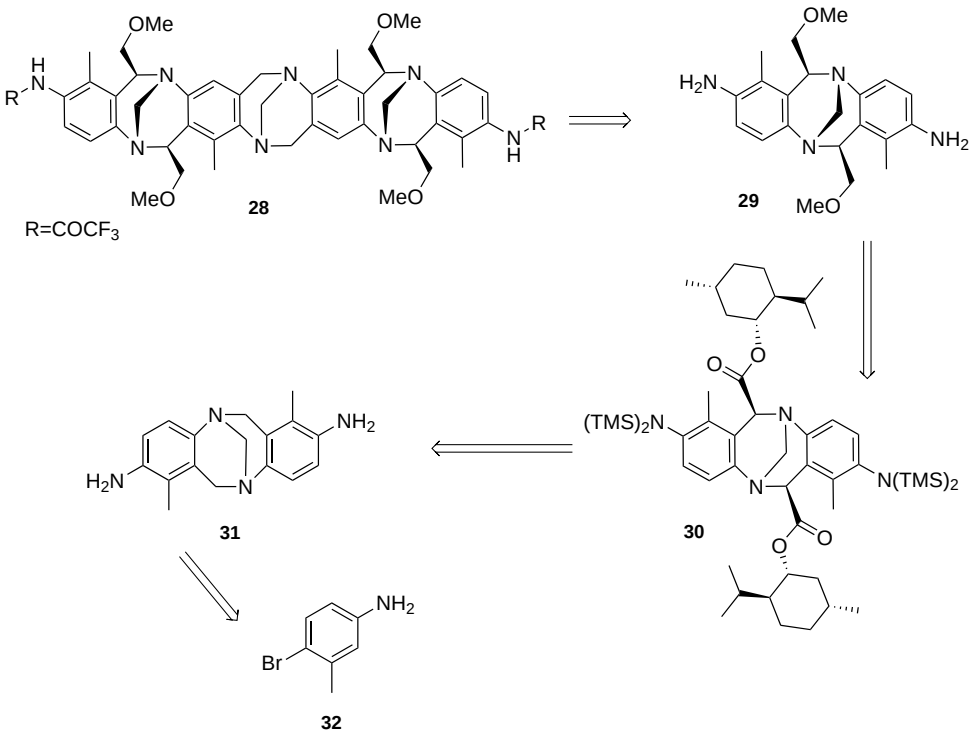


Figure 3.0.1: Outline of the Synthesis route of tris-Tröger's base **28**.

Starting from the aniline **32** the diaminated Tröger's base **31** should be synthesized in four steps. After two following reactions the diastereomers **30a** and **30b** were ment to be obtained, from which two synthetic routes were possible. In the first route the *R*-menthyl esters shall be preserved during the synthesis of the higher Tröger's base generations. In the second, which should be chosen for this study project, the menthyl-esters should be reductively removed and an alkyl-ether sidechain was ought to be established. After desymmetrization and subsequent condensation the tris-Tröger's base would be obtained. If possible, the synthesis of these compounds should be optimized and the compounds should be fully characterized.

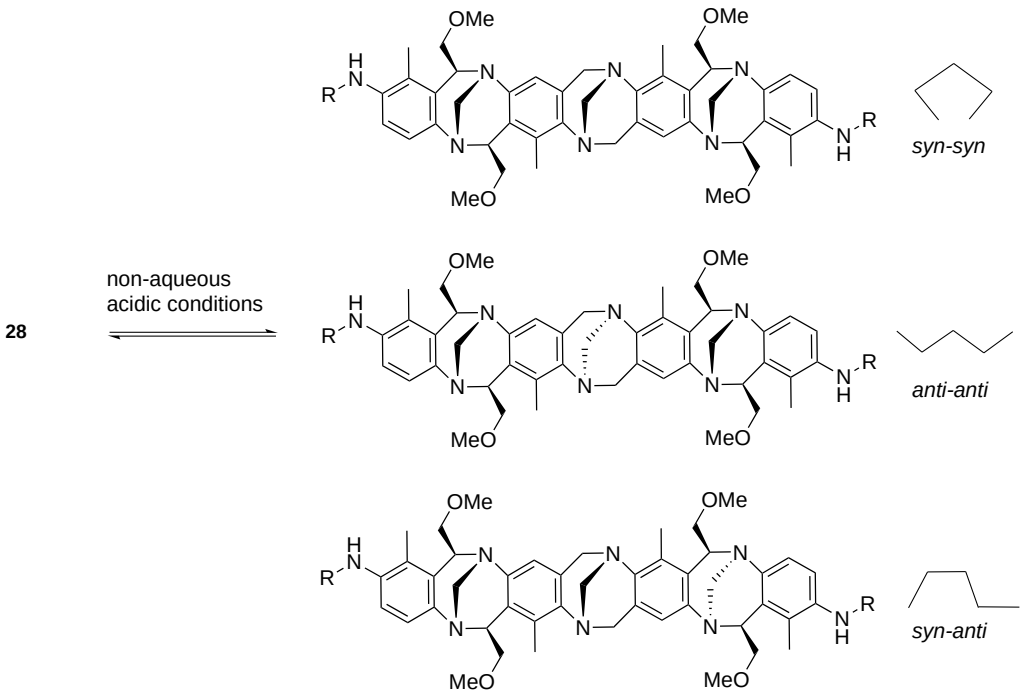


Figure 3.0.2: Isomerization of tris-Tröger's base **28** and possible isomers.

When the target molecule **28** is synthesized, not only its structure is of interest, which should be determined by X-ray diffraction analysis, but also its behaviour in non-aqueous acidic conditions. Under these conditions isomerization should occur and three different diastereoisomers are possible, which are displayed in figure 3.0.2. It is of great importance to determine which one is preferably formed, if and how one can influence this equilibrium, so one has a tool at hand to interconvert these diastereomers.

4 Results and Discussion

4.1 Synthesis of the Tröger's Base

Choosing the starting material is of great importance, given the fact that the outcome of the following reactions is highly affected by the substituation pattern of the aniline. The first important group is the bromine substituent in *para* position to the amine group, which will be discussed in more detail in section 4.3. Secondly, to assure the formation of linear Tröger's base analogues, the methyl group in *meta* position with respect to the amine group is of significance. With both *ortho* positions unfunctionalized, a condensation reaction to the Tröger's base would give a mixture of regioisomers, as depicted in figure 4.1.1. To prevent the formation of the unwanted regioisomer the position *para* to the methyl group was iodinated.

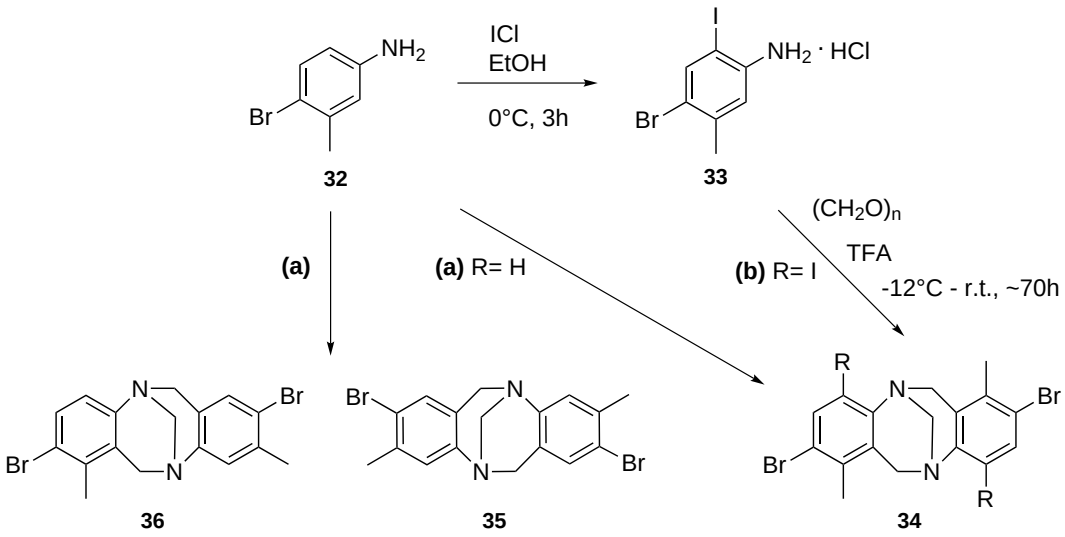


Figure 4.1.1: Synthesis of the Tröger's Base and possible regioisomers.

An electrophilic aromatic substitution was carried out, where the ICl served as source of the electrophile I^+. This substitution reaction consist of several steps. In the first one the electrophile forms a π-complex with the aromatic ring. In the following the electrophile is attacked by the electron-rich aromatic ring and forms the so called σ-complex, which inheres an unstable carbocation. The formation of this carbocation, which is stabilized to some extent by resonance, is characterized by the short-time loss of aromaticity. The chloride

ion acts as a Lewis base. It deprotonates the carbocation and the aromaticity is beeing re-established (see figure 4.1.2).[31]

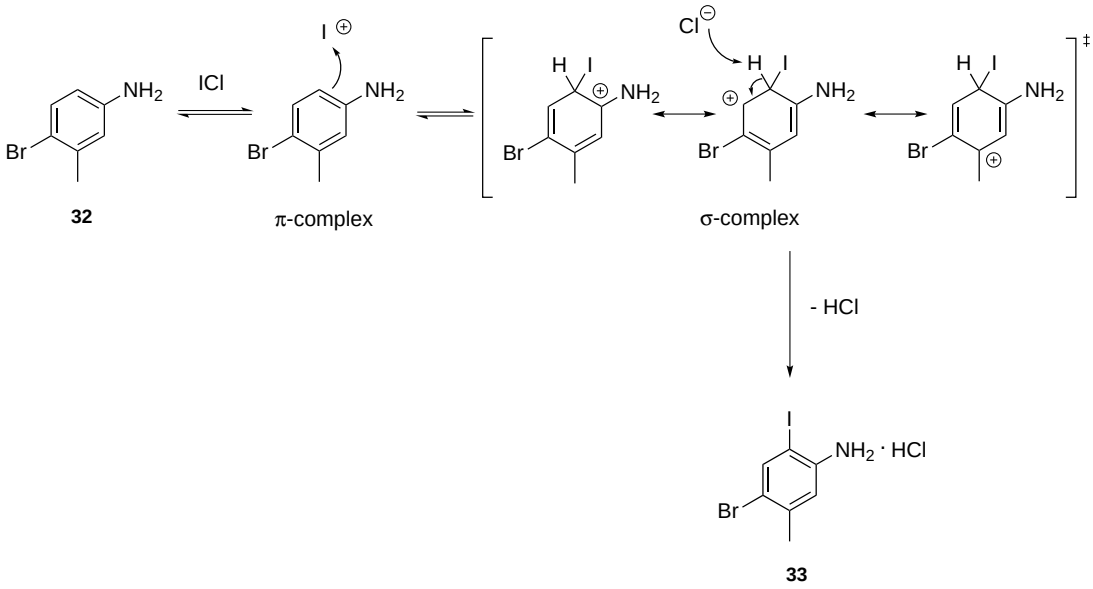


Figure 4.1.2: Reaction mechanism of the electrophilic aromatic substitution.

Ethanol was cooled to 0°C using a water/ice bath, before ICl was added. The cooling was necessary, because of the otherwise occuring vivid decomposition reaction of ICl with the solvent. To the dark brown solution 4-bromo-3-methylaniline was added in small portions. After 3 h the formation of large amounts of precipitate could be observed, which was collected by filtration and was washed with PE and chloroform to give the product **33** as beige-pinkish coloured powder in 87% yield.

The Tröger's base **34** was formed in a following condensation reaction of the aniline **33** and paraformaldehyde in TFA (see figure 4.1.1 **(b)**). The conversion was faster, if the reaction mixture was heated to 50°C and took 19 h. When the reaction was carried out at r.t., the completion of the conversion took up to 70 h and resulted in similar yields. Previous work in the group has shown, that an amount of five gram of the aniline **33** is ideal for the reaction. The set-up at r.t. was more practical to handle, if several batches should be run in parallel. In this manner it was possible to carry out nine reactions in parallel, with 6 g of starting material **33** in each flask. The batches were combined for the following workup and after column chromatography the Tröger's base **34** was gained as cream-white solid in 56% yield. An elongation of the reaction time by 24 h did not result in a beneficial effect on behalf of the yield.

Several studies have dealt with the elucidation of the involved reaction mechanism that leads to formation of the Tröger's base. One of the first proposed mechanisms was by WAGNER[32] in 1935. In this article he discussed the condensation of aromatic amines with formaldehyde in acidic media. This

work was re-assesed later not only by himself,[33,34] but also bei FARRAR.[35] From these studies the following five steps could be derived to be part of the assumed mechanism that leads to the Tröger's base. (see figure 4.1.3)

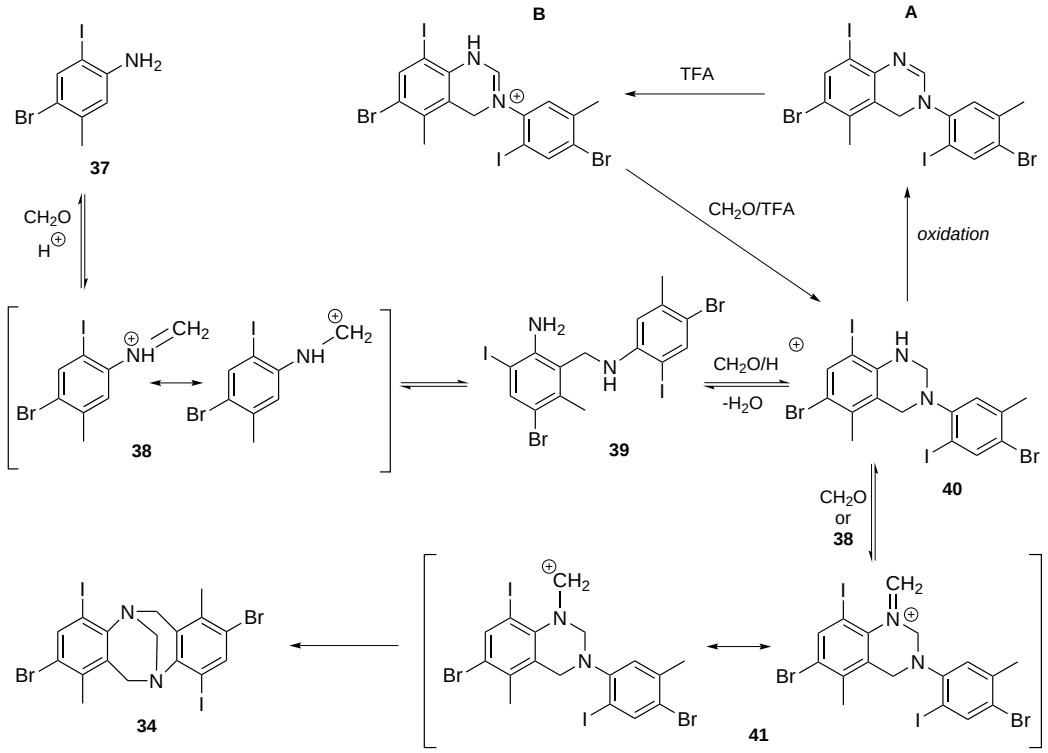


Figure 4.1.3: Proposed mechanism for the formation of Tröger's base **34** and possible side reactions.

It is composed of several electrophilic aromatic substitutions and everything starts with the formation of the iminium ion **38** by an acid-catalyzed reaction of *p*-toluidine with paraformaldehyde. This iminium ion **38** reacts with another molecule *p*-toluidine to the *p*-aminobenzylarylamine **39**. The latter converts to the tetrahydroqzinazoline **40** by reaction with yet another equivalent paraformaldehyde. Now the reason why the reaction is carried out in TFA instead of hydrochloric acid in ethanol, for instance, will become apparent. For anilines with electron-withdrawing substituents, such as **37**, it is assumed that the nucleophility of tetrahydroquinazoline **40** is not strong enough to react on to **41**, but instead the dehydrogenation to the dihydroquinazoline **A** is favoured.[36] Previous studies in the WÄRNMARK group[37] have led to the proposition, that the reaction system paraformaldehyde in TFA is preferable over conditions as formalin/HCl in ethanol, because there is an increased concentration of electrophilic formaldehyde in comparison to the HCl/EtOH system. This has a beneficial influence on the conversion rate from **40** to **41**, which is increased. Besides that, it is thought that the possible side product **A** can again be reduced to **41** by protonation through the TFA to **B**, followed

by a hydride transfer from paraformaldehyde to the electron-deficient methine carbon (**B**). These positively charged species **41** and **B** should also be stabilized in the highly ionizable TFA as solvent, that benefits the Tröger's base formation.[38]

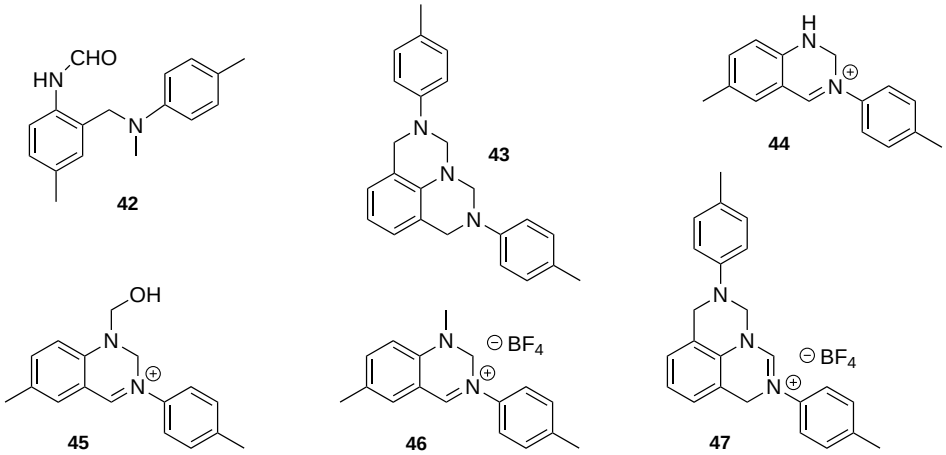


Figure 4.1.4: Other intermediates and byproducts of the formation of the Tröger's base.

The results of FARRAR[35] stand in contrast to the above described mechanism. He doubtet the participation of an intermediate like **41**, but proposed a mechanism containing intermediate **42** (see figure 4.1.4). Besides that, he also found the byproduct **43**. Though he isolated it, it was not possible to derive the Tröger's base from that compound.[39] WAGNER's proposed mechanism is supported by the findings of EBERLIN and COELHO.[40] They monitored the condensation of *p*-toluidine with formaldehyde or hexamethylenetetramine in TFA by ESI-MS/MS (electrospray ionization mass and tandem mass spectrometry), which made it possible to detect and characterize the cationic intermediates **44** and **45** (see figure 4.1.4) as well the iminium ion **38** (figure 4.1.3). Further validation was given by the results of the group of WU.[41] They carried out the Tröger's base synthesis in an ionic liquid (1-butylpyridinium tetrafluoroborate) utilizing a 1-methyl-3-(2-(sulfoxy)ethyl)-1*H*-imidazol-3-ium chloride catalyst and isolatet the species **46** and **47**, seen in figure 4.1.4. These compounds could be transformed into the corresponding Tröger's base, when subjected to the reaction conditions at 150°C and are therefore to be considered as intermediates of the mechanism.

4.2 Dehalogenation

As the Iodine moiety was no longer needed and might have caused formation of unwanted side products in the following Buchwald-amination, it needed to be removed. This was attempted by two different reactions. The first efforts with reaction **A** (see figure 4.2.1) gave only low yields around 20%. Often it did not show the desired purity after 4 h reaction time, when the TLC indicated full conversion of the starting material to the product. But reaction **B**, where **34** was dehalogenated with *n*-Buthyllithium, gave several side products. Therefore reaction **A** is preferred over **B**, because of its clean reaction process and simple purification by recrystallization from EtOAc.

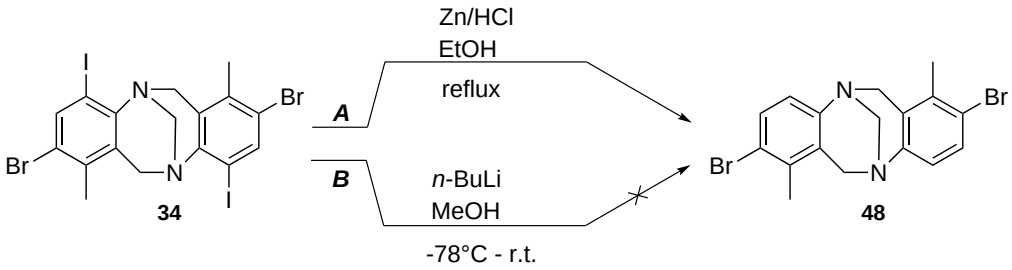


Figure 4.2.1: Dehalogenation of the Tröger's Base **34**.

It proved to be important that the reaction mixture is vigorously stirred and heated, above the boiling point, to 130°C. Also, the conversion time was shortened by increasing the amount of hydrochloric acid. The reaction mixture was filtered hot through a glass filter with Celite and washed with hot ethanol and DCM. After further workup and recrystallization from EtOAc the product **48** was gained as colourless crystals in 77% yield.

4.3 Amination and Protection of the Diamine

As depicted in figure 4.3.1, the next steps consisted of an amination of the Tröger's base **48** and the protection of the two newly generated amine groups with TMSCl.

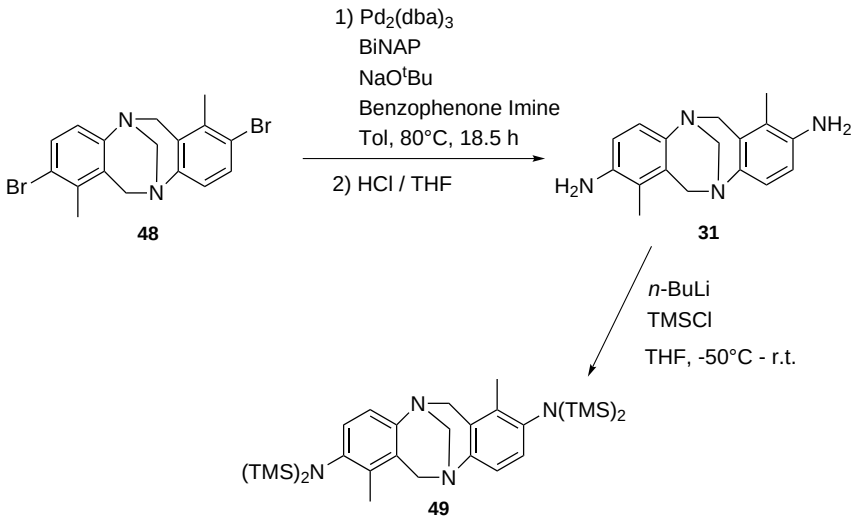


Figure 4.3.1: Synthesis of the diaminated Tröger's base and its protection.

Previous work in the group has shown, that an amination using the methodology designed by BUCHWALD and HARTWIG[42–46] is prefered to other methods, such as a bromine-lithium exchange, addition of an azide and following reduction by $NaBH_4$.[17] DIDIER and SERGEYEV[47] used a benzophenone imine/BINAP/NaO*t*Bu/$Pd_2(dba)_3$ catalytic system for generating the diamino Tröger's base as well, but they applied the system to a 2,8-diiodo Tröger's base instead of a 2,8-dibromo Tröger's base. Similar yields were achieved in comparison to the work of the WÄRNMARK group, but a much higher amount of pre-catalyst was necessary. This discrepancy was investigated by WÄRNMARK et al.[17] and it showed, that the diiodo Tröger's base had a lower reactivity and a mixture of mono- and diaminated products were formed. It was observed that the yields of the diamino Tröger's base increased with increasing amount of pre-catalyst (0.25-5 mol%) and therefore the nominal ratio of I^-:Pd was decreased. When submitting 2,8-dibromo Tröger's base to the reaction conditions and also adding a source of iodide (tertbutylammonium iodide), a severe drop in the yield of the diamino Tröger's base could be observed and additionally the monoaminated Tröger's base was formed with 43% yield. These findings lead to the assumption, that somehow the iodide poisons the active catalyst species.

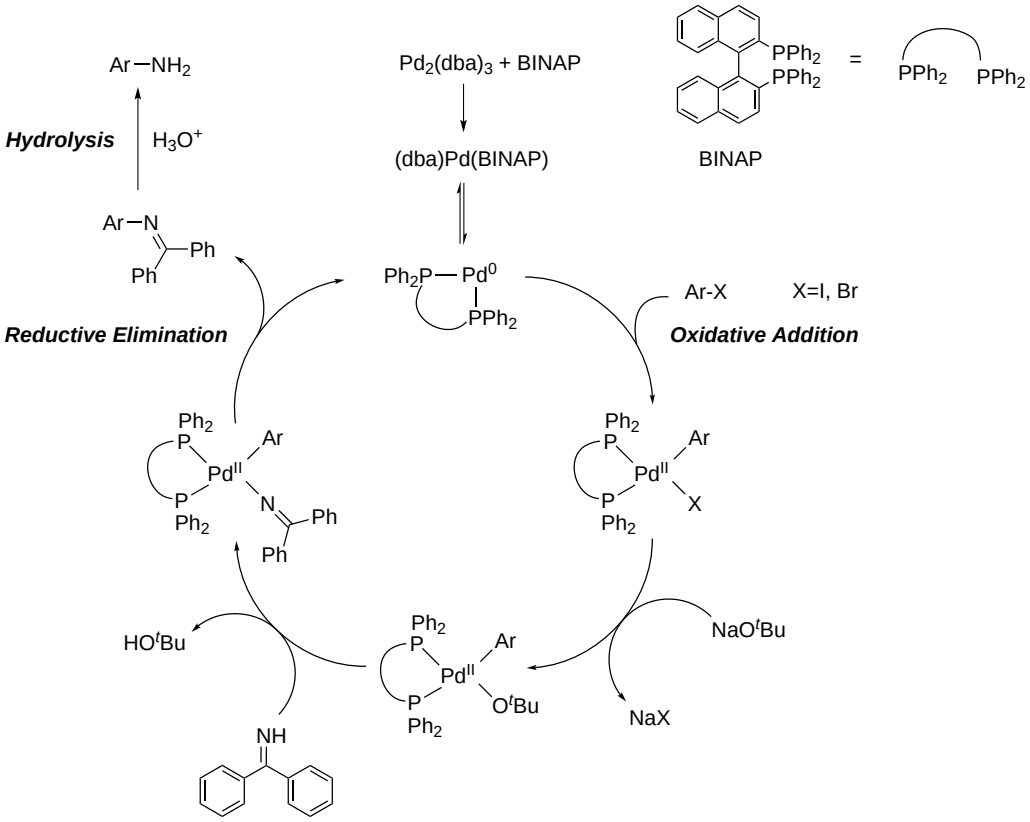


Figure 4.3.2: The catalytic cycle of the Pd-catalyzed C-N-bond formation of aryl halides and generation of the amine through subsequent hydrolysis.[48, 49]

The catalytic cycle of the Pd-catalyzed amination of halogenarenes consist of several steps:

- ▷ the formation of the active catalytic species from the ligand and the pre-catalyst[50]
- ▷ the oxidative addition of the aryl halide
- ▷ a ligand substitution by the ammonia equivalent
- ▷ the reductive elimination, where the product is released and the active catalytic species is reformed (see figure 4.3.2)

It is harder for the NaO*t*Bu to attack the L-Pd-(Ar)(X)-species when it is an Pd^{II}-I-complex, because these complexes are more stable than the corresponding Br-complex.[51] The lower reactivity of the diiodo Tröger's base in this amination reaction can therefore be attributed to the stronger Pd^{II}-I bond.

In general the use of chelating ligands, such as BINAP, has one major advantage. It blocks the β-hydrogen elimination. This unwanted side reaction occurs

from a three-coordinate species. With a bidentate ligand four-coordinate intermediates are formed, from which the reductive elimination still occurs, while the β-hydrogen elimination can not.[49] A chelating ligand also facilitates the coupling of benzophenone imine, which is a valuable partner for this kind of reaction.[52, 53] It is sterically relatively unhindered, its nitrogen is sp^2-hybridized and it cannot undergo a β-hydrogen elimination in the first place.[54] To generate the amine group, a hydrolysis was carried out afterwards in THF and hydrochloric acid (4 M). Scaling up to 4 mmol starting material **48** resulted in a decrease of the yield, so instead, two reactions with 2.5 mmol starting material **48** were carried out in parallel and were worked up together to increase the efficiency. After purification by column chromatography a pale brown solid **31** was gained in 90% yield.

Previous experiences of the group have led to the decision of utilising TMS groups for the protection of the diamine. They have proven to be robust enough to withstand alkyllithium reagents,[55] that will be employed in the next reaction step. The TMS groups can be cleaved off by nucleophilic displacement with fluoride. As source of fluoride TBAF (tetra-*n*-butylammonium fluoride) can be used, where one can avoid an aqueous acidic removal of the protecting groups, which most likely would lead to an unwanted racemization of the Tröger's base (see figure 4.3.3).

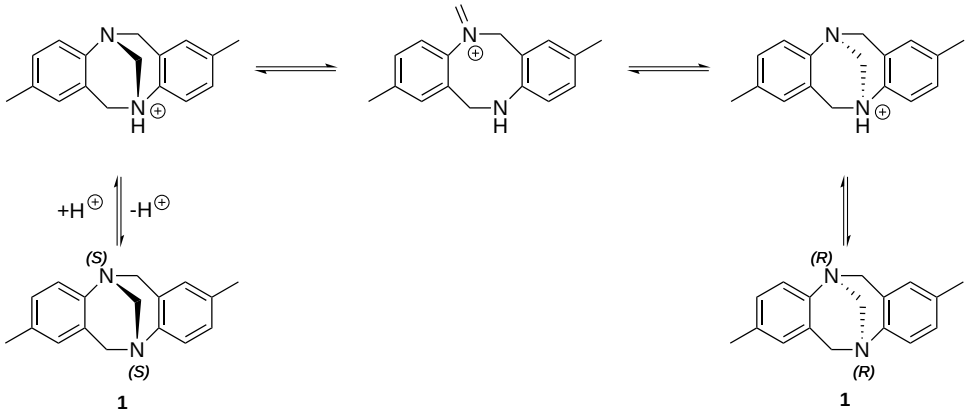


Figure 4.3.3: Racemization of Tröger's base in acidic media.

As indicated in figure 4.3.1, the amine groups were deprotonated with *n*-butyllithium, the nitrogen performed a nucleophilic attack at the silicon of the trimethylsilyl chloride and the chloride served as leaving group. No further purification was carried out, except filtration through a pad of activated neutral alumina. The protected Tröger's base **49** was obtained as an ochre solid in 73% yield.

4.4 Synthesis of the Menthyl Ester

One way to separate enantiomers is performing column chromatography with a chiral stationary phase. This is often a high-priced procedure.[31] Also other methods exist for resolving a racemix mixture, for example reacting it with an enantiomerically pure compound (compare to figure 4.4.1). The resulting diastereomers have different physical properties. Therefore, they should be separable by chromatography.[31]

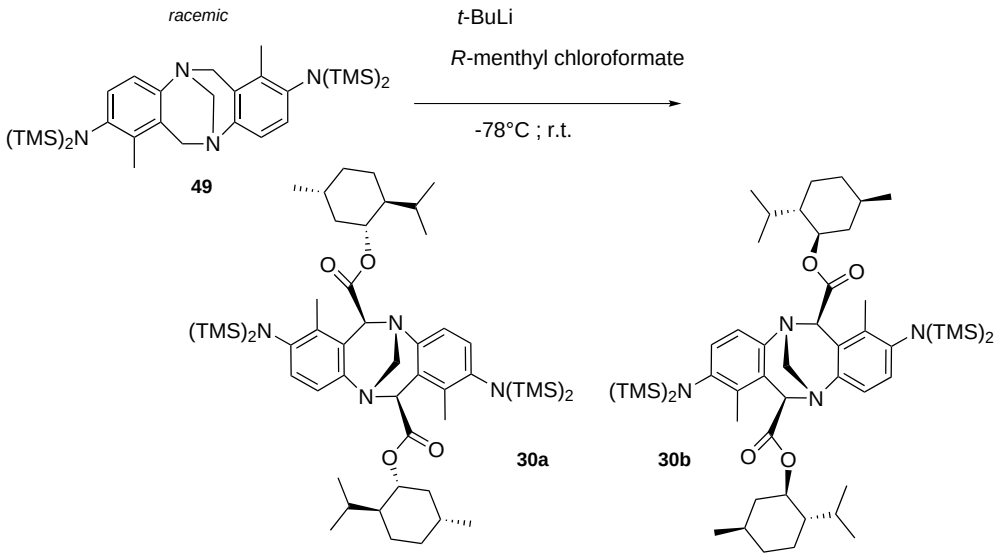


Figure 4.4.1: Synthesis of the Tröger's base menthyl ester **30**.

The Tröger's base **49** was submitted to *t*-BuLi and an α-proton next to the nitrogen atoms was abstracted. Due to the electron withdrawing effect of the nitrogen the protons at this position are more acidic and more easily removed than the other benzylic protons for instance. The deprotonated Tröger's base attacked as a nucleophile the carbonyl group of the *R*-menthyl chloroforamte and the C-Cl bond was broken. These two steps, lithiation and addition of the electrophile, were consecutively carried out two times and the two diastereomers **30a** and **30b** were formed, where the two *R*-menthyl esters are in *exo* position. After the general workup the purification was done by chromatography. Two column chromatographies were necessary and the diastereomers **30a** and **30b** were gained in 11% yield each. The yields were quite low as a result of the fact that the TMS groups are not stable on the silica stationary phase. Once they are cleaved off it is not possible to regain the unprotected Tröger's base from the column, due to polymerization.

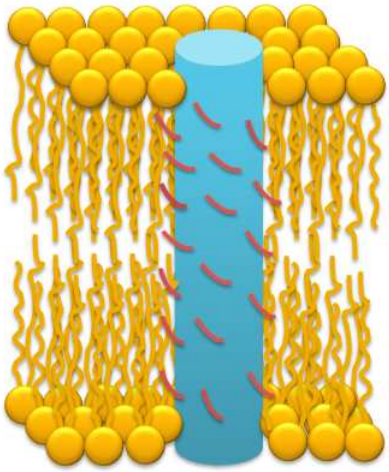


Figure 4.4.2: Schematic Illustration of a Tröger's base Helix in a membrane.

This enantiomerically pure Tröger's base becomes convenient in the condensation reaction to the tris-Tröger's base, since only two (*syn-syn*, *anti-anti*) of three (the latter and *syn-anti*) possible diastereomers can be generated. Also previously encountered problems with the solubility of the tris-Tröger's base are solved by introduction of an alkyl chain at the methylenes of the base.
Besides these two advantageous points it is also beneficial to have these groups in *exo* position. When a complete helix is synthesized and one would like to integrate it into a membrane, these ester moieties (depicted in red in figure 4.4.2) can interact with the lipophilic part of the lipid bilayer. In this way the helix can be better integrated and stabilized in the membrane.

4.5 Reduction to the Diol

Diastereomer **30a** was chosen to continue with on the synthetic route, where the *R*-menthyl ester will be replaced with an alkyl-ether. The Tröger's base **30a** was reduced with LAH to the diol **50** in 85% yield as a colourless solid after purification by column chromatography. LAH is an efficient reducing agent. Without difficulty it attacks the carbonyl group of the ester. A tetrahedral intermediate is formed, which collapses and forms an aldehyde. The aldehyde is more reactive than an ester, it reacts again with the LAH and is reduced to the corresponding alcohol.[31] (see figure 4.5.1)

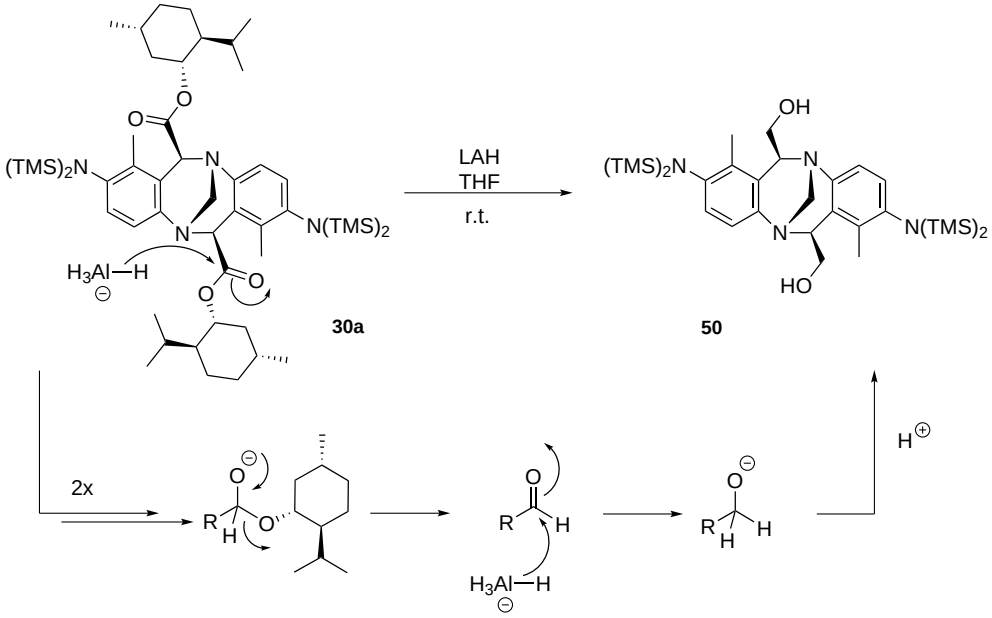


Figure 4.5.1: Mechanism of the reduction of Tröger's base **30a** to the diol **50**.

5 Discussion of the Spectra

For characterizing the synthesized compounds ^{1}H- and ^{13}C-NMR spectroscopy was applied. In the following the NMR-spectra will be discussed and compared.

In figure 5.0.1, shown below, is the ^{1}H-NMR spectrum of the aniline **33** that was iodated with iodo monochloride. The product is not soluble in chloroform, but moderately in methanol and therefore the analysis was carried out in deuterated methanol, which explaines the solvent residue peak at 3.28 ppm. Also the singlet at 4.87 ppm was due to water residues in the solvent. Only two signals in the aromatic region were to be expected. The singlet at 8.09 ppm belongs to proton H-1, that is located between an iodine and a bromine moiety. These electronegative substituents cause a downfield shift of that proton. The second proton is not as strongly deshielded as the first one and can be found at 7.30 ppm. At a closer look, one can see that the signal is actually a doublet. It has a very small coupling constant of 0.6 Hz and indicates a coupling over four or more bonds. In that case it is most likely the proton H-1 that makes a *para*-coupling over five bonds. Usually the signal of the methyl group in *p*-toluidine is to be found at 2.23 ppm, but as a result of the neighbouring electronegative bromine group the methyl group is slyghtly deshielded and showes at 2.36 ppm.

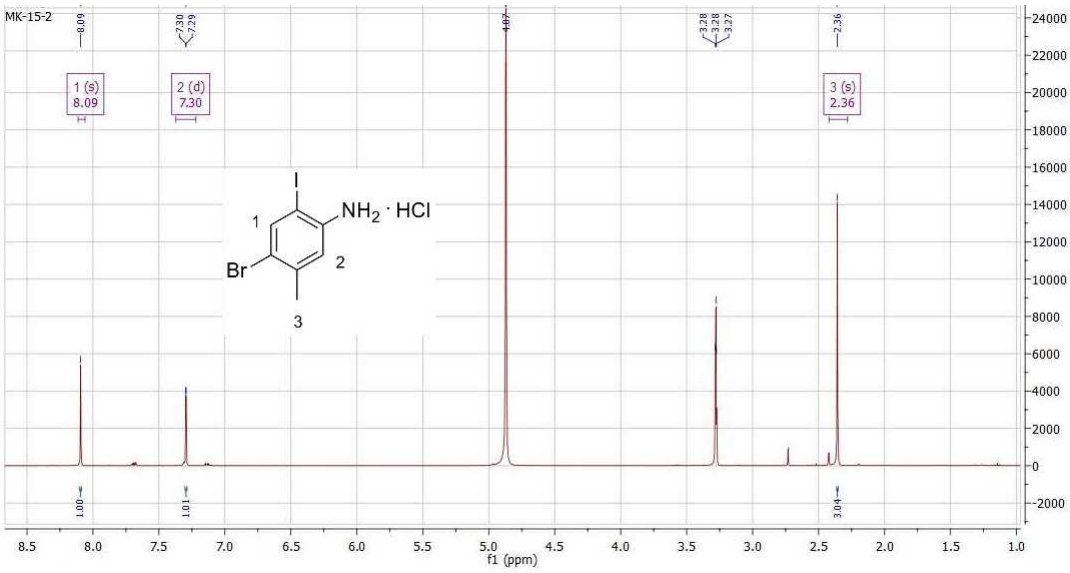


Figure 5.0.1: ^{1}H-NMR assignment of the iodinated aniline **33**.

After the condensation to the Tröger's base one (proton H-2, figure 5.0.1) of the two former signals in the aromatic region disappeared, as it was to be expected. Also three new signals for the protons of the newly formed methylene bridges showed in the region between 4.42 and 4.16 ppm, as it can be seen in figure 5.0.2. Each proton of the CH_2-groups H-14 and H-6 seems to have a slightly different chemical environment and therefore generate two doublets at 4.40 and 4.18 ppm. Also the coupling constant of 17.4 Hz points to a geminal coupling. Each doublet integrates for two protons though, because the CH_2-groups H-14 and H-6 are equivalent. The singlet in their middle can be attributed to the two protons H-13 of the middle methylene bridge and the singlet at 2.18 ppm is integrated for 6 protons and belongs undoubtedly to the two methyl groups.

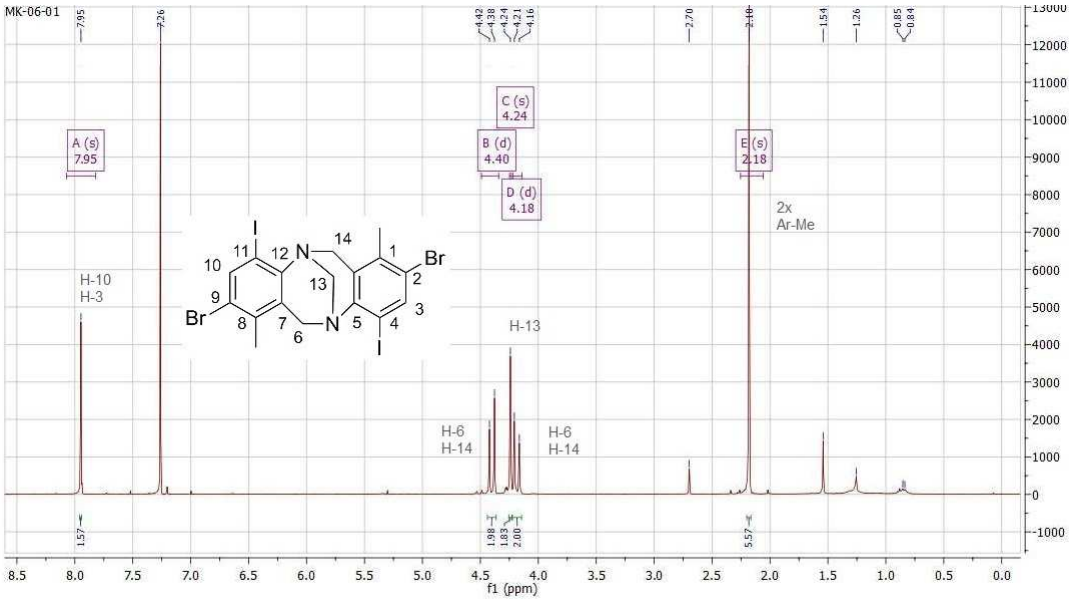


Figure 5.0.2: ^{1}H-NMR assignment of the Tröger's base **34**.

In the next step the iodine was removed and a new doublet appeared at 6.90 ppm (see figure 5.0.3) in the aromatic region. As proton H-4/11 is further away from the electronegative bromine group than proton H-3/10, the latter can be assigned to the signal at 7.37 ppm. The remaining signals located upfield can be attributed to the protons of the methylene bridges and the methyl groups as in the previous example.

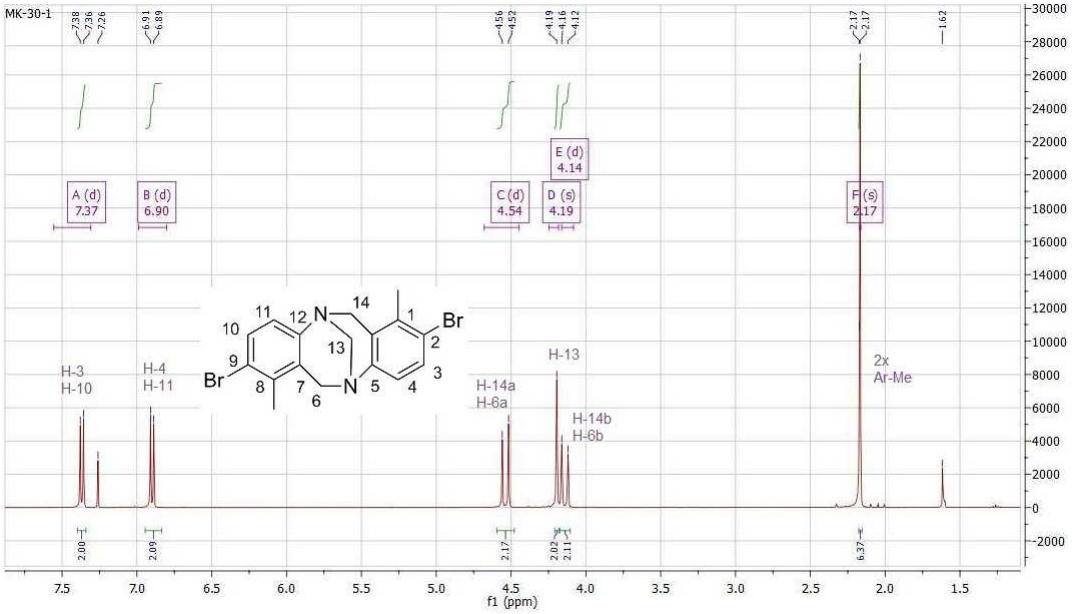


Figure 5.0.3: ^{1}H-NMR assignment of the deiodinated Tröger's base **48**.

When the bromine groups were transfered into amine groups the protons H-10 and H-3 were not shifted so much to higher frequencies like before and now can be found at 6.57 ppm. (see figure 5.0.4) The doublet for the protons H-11 and H-4 is still at 6.88 ppm. The methylene bridge protons are only slightly influenced by the new substituend. The methyl groups shifted from 2.17 to 1.88 ppm. The protons of the amine groups show a broad singlet at 3.40 ppm.

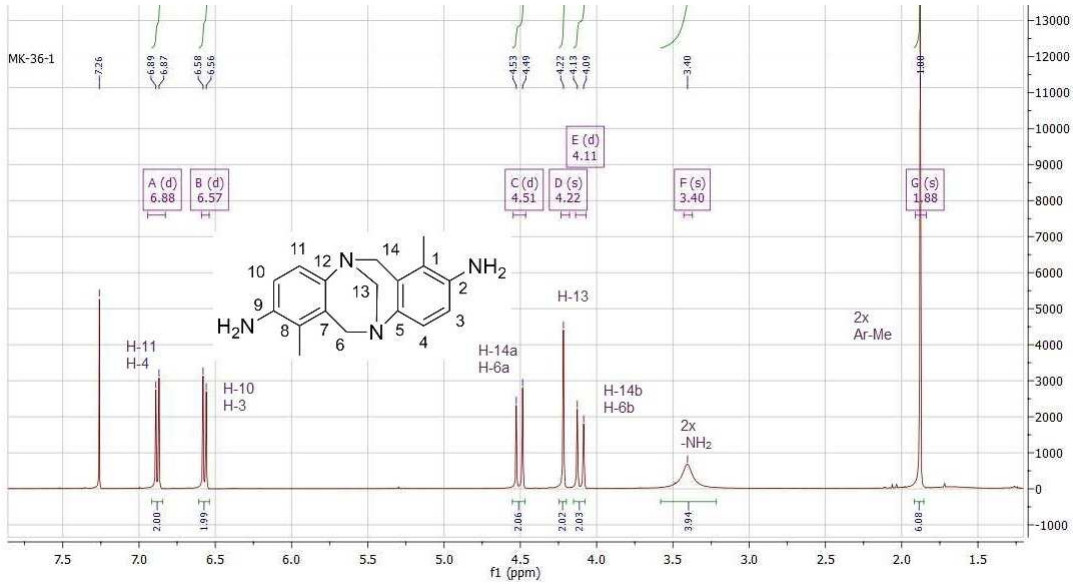


Figure 5.0.4: ^{1}H-NMR assignment of the diaminated Tröger's base **31**.

Figure 5.0.5 showes the spectrum of the protected diaminated Tröger's base. The protons of the amine groups were replaced by four TMS groups, which result in two singlets at 0.02 and -0.16 ppm, which integrate for 18 protons each.

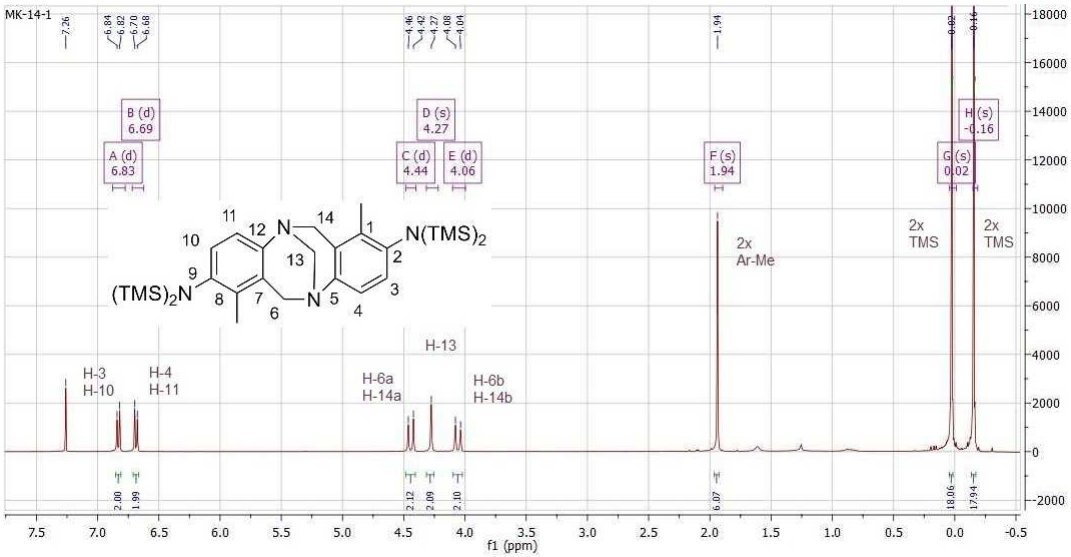


Figure 5.0.5: ^{1}H-NMR assignment of the protected Tröger's base **49**.

For convenience, figure 5.0.6 shows the full ^{1}H-NMR spectrum of both diastereomers **30a** and **30b**, generated by formation ot the corresponding *R*-menthyl ester. They share the same chemical shifts of the *R*-menthyl ester-side chains, severals multiplets in the region between 2.07 and 0.80 ppm, as it can be seen in figure 5.0.9 more closely. The singlet at 1.91 ppm for the two methyl groups at the aromatic ring they have in common though. In the aromatic region several doublets appear. The doublets at 7.04 and 6.99 ppm belong to the protons H-10 and H-3, whereas the signal of diastereomer **30b** is the more deshielded one. The set of doublets assigned to the protons 11 and 4 at 6.81 and 6.79 ppm overlap partially. (see figure 5.0.7) Here also the signal of **30b** is moved downfield in comparison to **30a**. The triplet of triplets depicted in figure 5.0.8 belongs also to the *R*-menthyl ester group (-COO-C*H*-R-). There is only one proton left at positions H-14 and H-6. They are equivalent and result in a singlet signal. Diastereomer **30a** is shifted to a lower frequency than the signal of **30b** at 4.63 ppm. For the next set of singlets at 4.46 and 4.44 ppm it is reversed. Here the protons at position H-13 of diastereomer **30a** are less shielded than the protons of diastereomer **30b**. There are four singlets that can be assigned to two TMS groups each. (see figure 5.0.6) The both innermost signals at 0.00 and -0.13 ppm belong to the protecting groups of diastereomer **30b**, therefore the outermost at 0.02 and -0.16 ppm to **30a**.

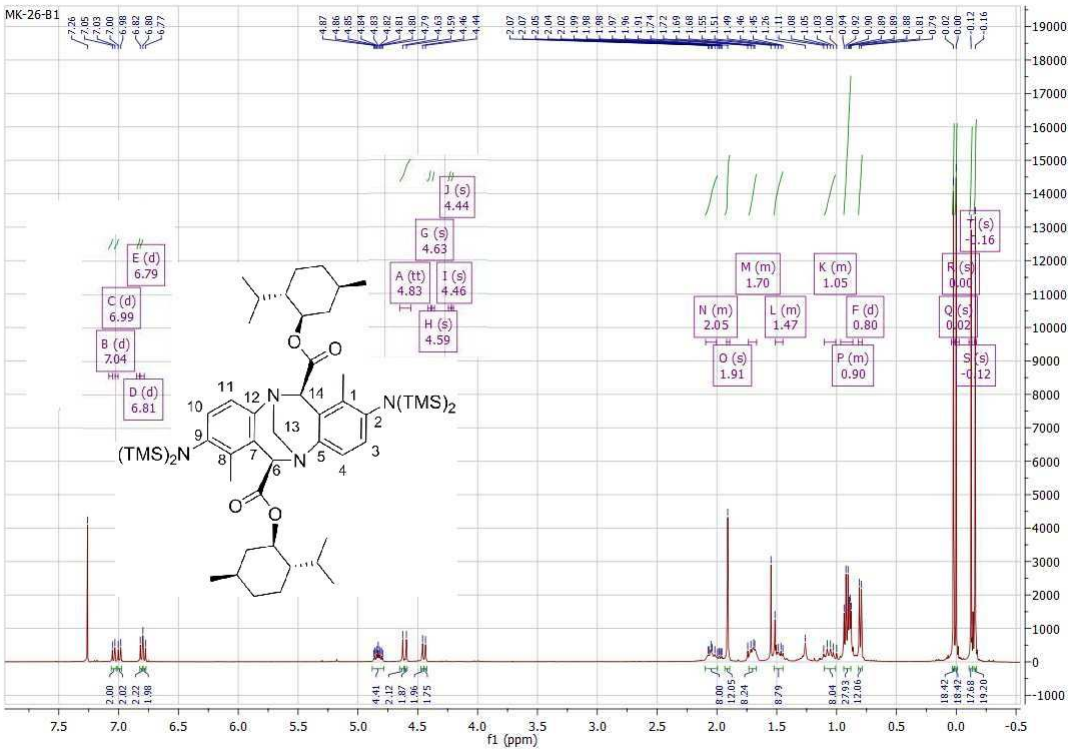


Figure 5.0.6: Full ^{1}H-NMR spectrum of the Tröger's base diastereomers **30a** and **30b**.

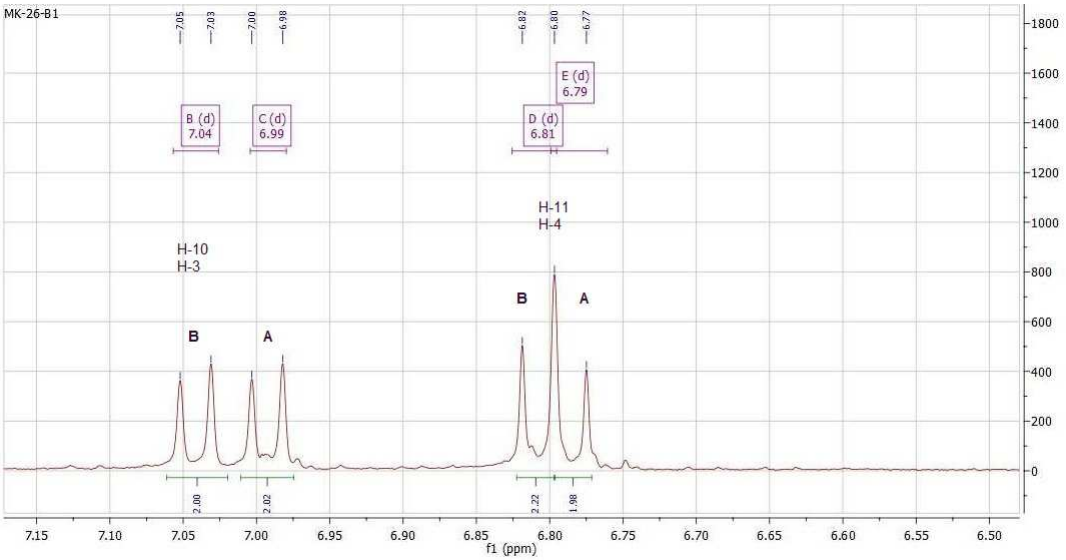


Figure 5.0.7: ^{1}H-NMR assignment of the Tröger's base diastereomers **30a** and **30b** - detail spectrum of the aromatic region.

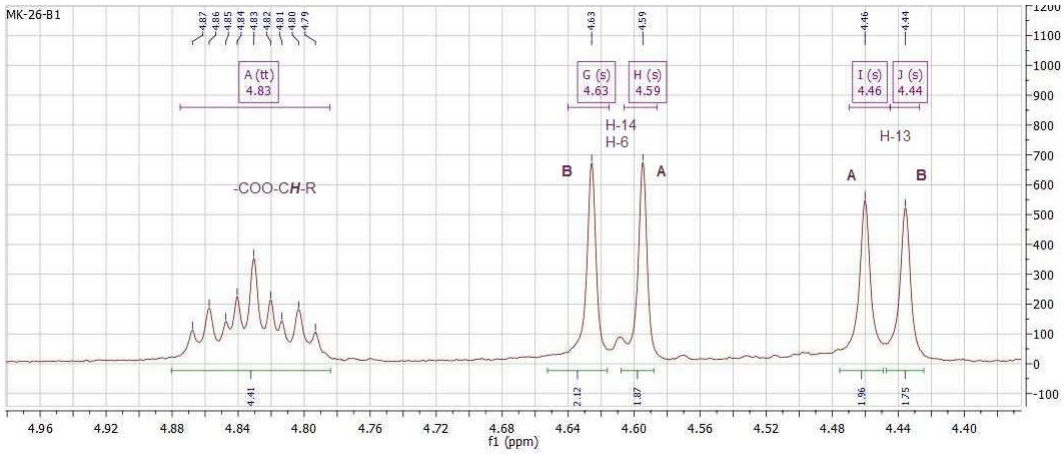


Figure 5.0.8: ^{1}H-NMR assignment of the Tröger's base diastereomers **30a** and **30b** - detail spectrum of the methylene-bridges.

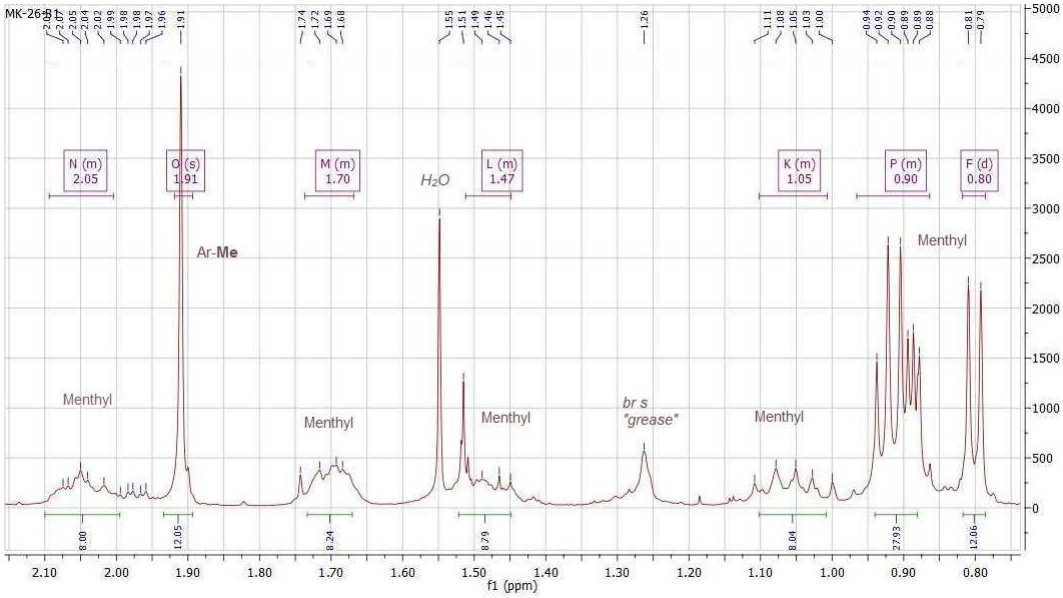


Figure 5.0.9: ^{1}H-NMR assignment of the Tröger's base diastereomers **30a** and **30b** - detail spectrum of *R*-menthyl-moiety.

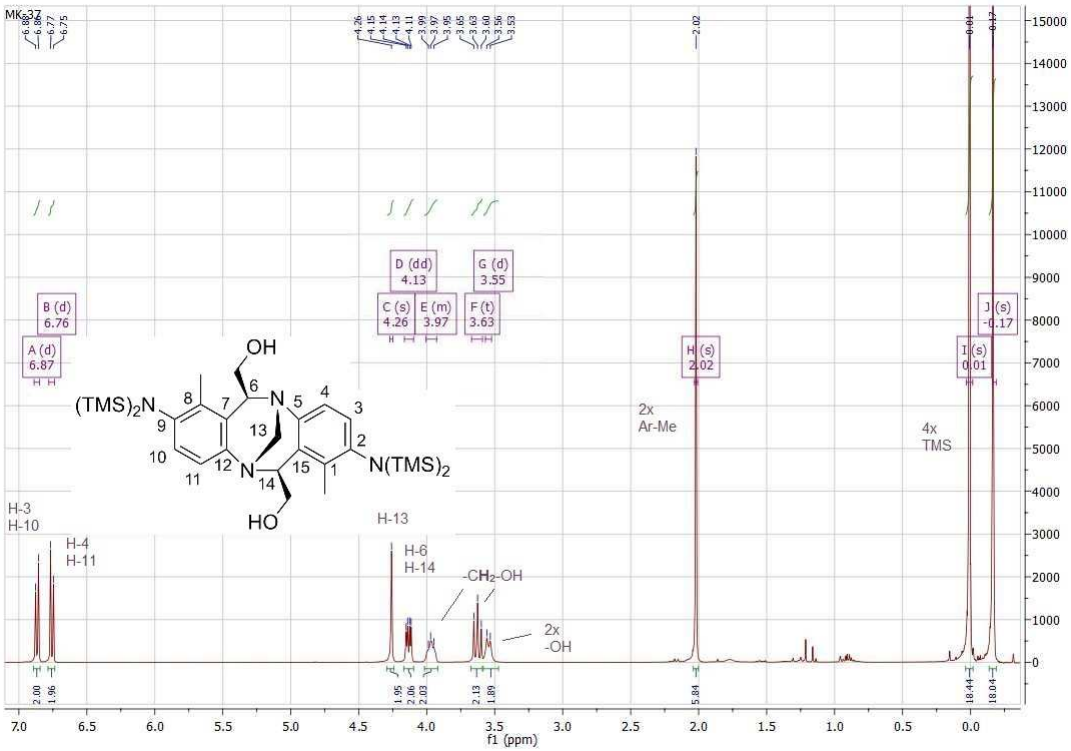


Figure 5.0.10: ^{1}H-NMR assignment of the diol **50**.

After the reduction of the diastereomer **30a** with LAH to the corresponding diol a broad signal appeared at 3.55 ppm for the two hydroxyl groups. The protons of the methylene bridge 13 can be assigned to the singlet at 4.26 ppm. The doublet of doublets at 4.13 ppm next to the previous signal an be attributed to the protons H-14 and H-6. The -CH_2-OH side chains resulted in a multiplet at 3.97 ppm and a signal at 3.63 ppm. This is probably not a genuine triplet but two overlapping doublets. (see figure 5.0.11) In figure 5.0.10 the full spectrum is shown. The remaining protons can be assigned as done before. At 6.87 ppm are the aromatic protons H-10 and H-3 and a little upfield from that are the protons H-11 and H-4. The singlet at 2.02 ppm integrates for the six protons of the two methyl groups. The signals of the TMS groups appear at 0.01 and -0.17 ppm.

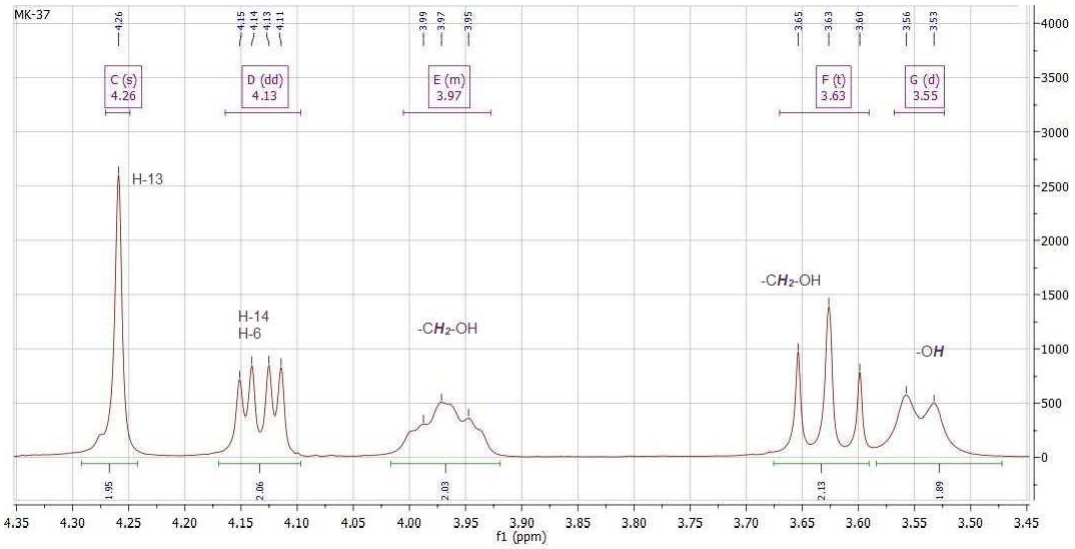


Figure 5.0.11: ^{1}H-NMR assignment of the diol **50** - detail spectrum.

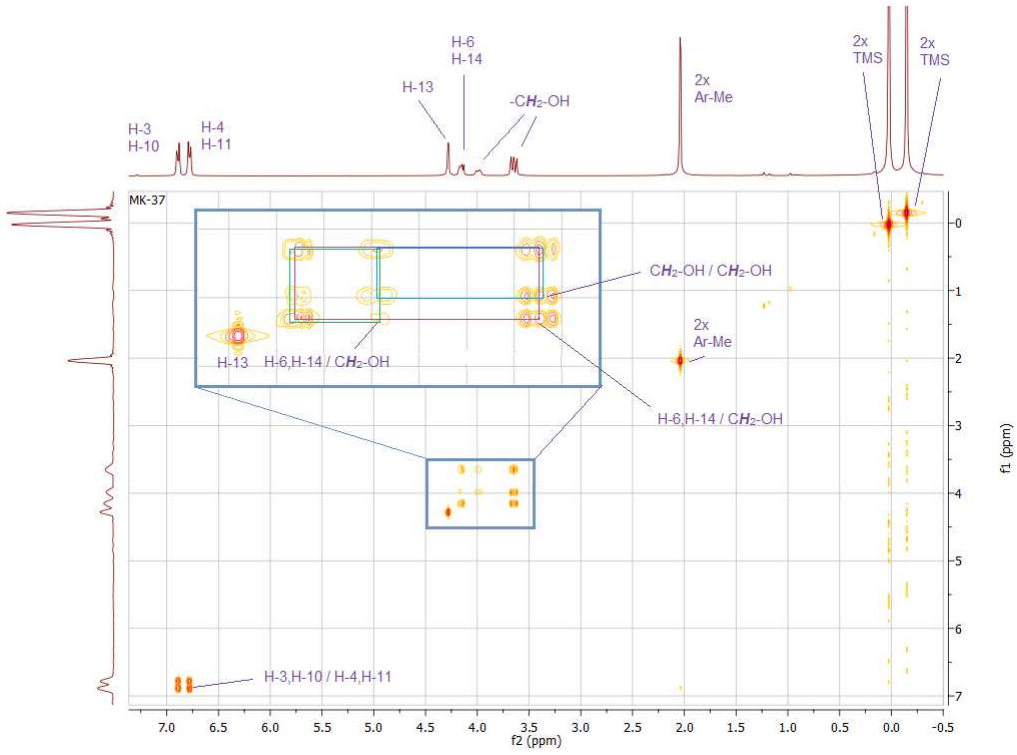


Figure 5.0.12: COSY-NMR assignment of the diol **50**.

To confirm the assignment also a COSY-NMR analysis was carried out and is shown in the following figure 5.0.12. Correlated spectroscopy is a two-dimensional technique, that shows the correlation between adjacent protons. A crosspeak appeared in the aromatic region for the two neighbouring protons

H-10 and H-11 and H-3 and H-4 respectively. For the protons of the methyl groups and of the TMS protecting groups diagonal peaks appear, as they are only coupling with each other. Also the two protons at 4.26 ppm for the methylene bridge H-13 only couple with each other and result in a diagonal peak. There is a crosspeak between the signal at 4.13 ppm of the protons H-14/6 and a proton (3.97 ppm) of the -CH_2-OH side chains. The other cross peak between the signals at 3.97 and 3.63 ppm shows the coupling of the CH_2 groups protons of the side chain among themselves. The cross peak between 4.13 ppm and 3.63 ppm shows the coupling of the protons H-14/6 and the other proton of the -CH_2-OH side chains.

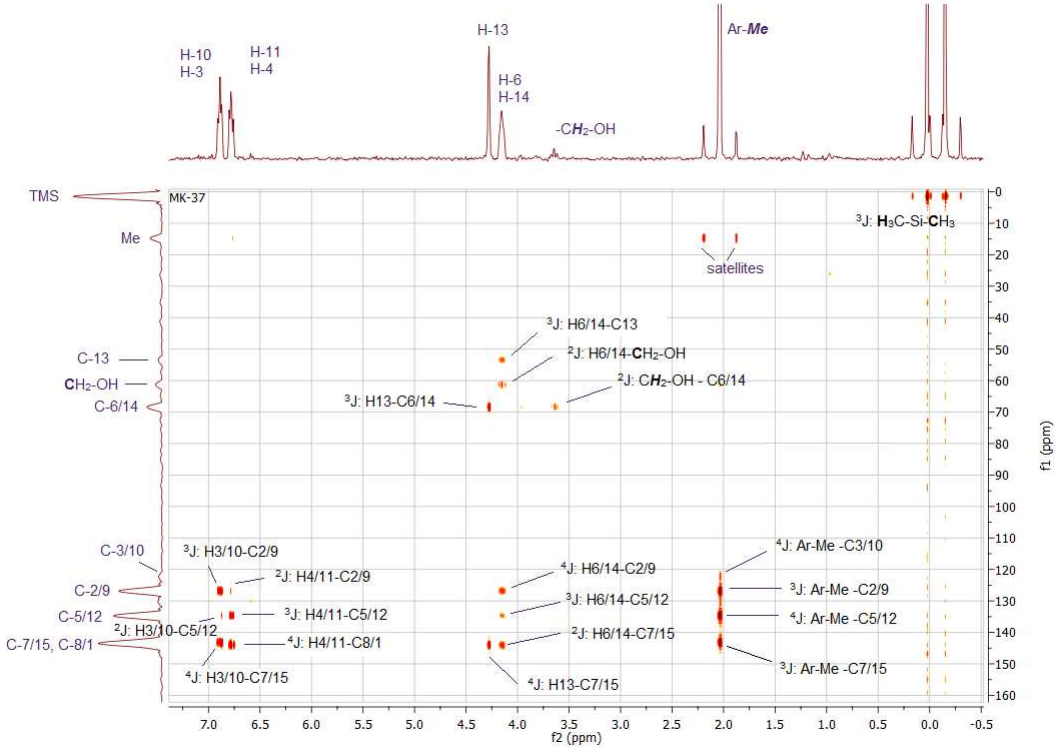


Figure 5.0.13: HMBC-NMR assignment of the diol **50**.

As seen above, figure 5.0.13 shows the HMBC-NMR spectrum of the diol **50**. Heteronuclear multiple-bond correlation spectroscopy was used to verify the previous assignments. With this technique one can see ^{3}J and ^{4}J correlations, in some cases also ^{2}J, between carbon and hydrogen. The protons H-3/10 show a correlation to the carbons C-2/9 and C-5/12 over a ^{3}J and ^{2}J coupling. The ^{2}J coupling is of lower intensity than the ^{3}J coupling. The protons H-4/11 however, correlate with a ^{2}J coupling to C-2/9 and a ^{3}J coupling to C-5/12. The carbon signals at 144.2 and 143.4 ppm are not that good resolved in this spectrum and appear as one peak in the one-dimensional spectrum. The two correlation peaks in that region though show that one signal appears at 144.02 ppm, which is a correlation over four bonds from C-7/15 to the protons H-3/10

and the other signal appears at 143.2 ppm. The latter is a correlation from C-1/8 to the aromatic protons H-4/11, also over four bonds. The methylene bridge protons H-13 have correlations over three and four bonds to C-6/14 and C-7/15 respectively. The protons H-6/14 correlate to the carbon of the middle methylene bridge C-13 over a ^{3}J coupling. These protons also correlate to the carbon of the -CH2-OH side chains over a ^{2}J coupling just as the proton signal of the -CH_2-OH at 3.63 ppm does to the carbon signal of C-6/14. The previous mentioned proton signal H-6/14 has also correlations to the aromatic carbons C-2/9, C-5/12 and C-7/15 over ^{4}J, ^{3}J and accordingly ^{2}J couplings. The methyl groups at the aromatic rings have satellite signals in the proton spectrum. The protons of these methyl groups correlate with the carbon they are directly attached to and show signals in the 2D-spectrum, even though ^{1}J couplings are rare to be seen in HMBC-spectra. There are also small satellite signals for the TMS protecting groups, but there can also a ^{3}J coupling from a proton of one TMS-methyl group to a carbon of an adjacent TMS-methyl group be observed ($\mathbf{H}_3$C-Si(CH_3)-$\mathbf{C}H_3$). At last the ^{4}J couplings of the aromatic methyl group protons to carbon C-3/10 and C-5/12 and the ^{3}J coupling to the carbons C-2/9 and C-7/15 should be mentioned.

6 Conclusion and Outlook

The main goal of this project study was to synthesize the tris-Tröger's base **28**. Not only its isomerization behaviour in non-aqueous acidic media was the focus of interest, but also the optimization of the synthesis and full characterization of the compounds.

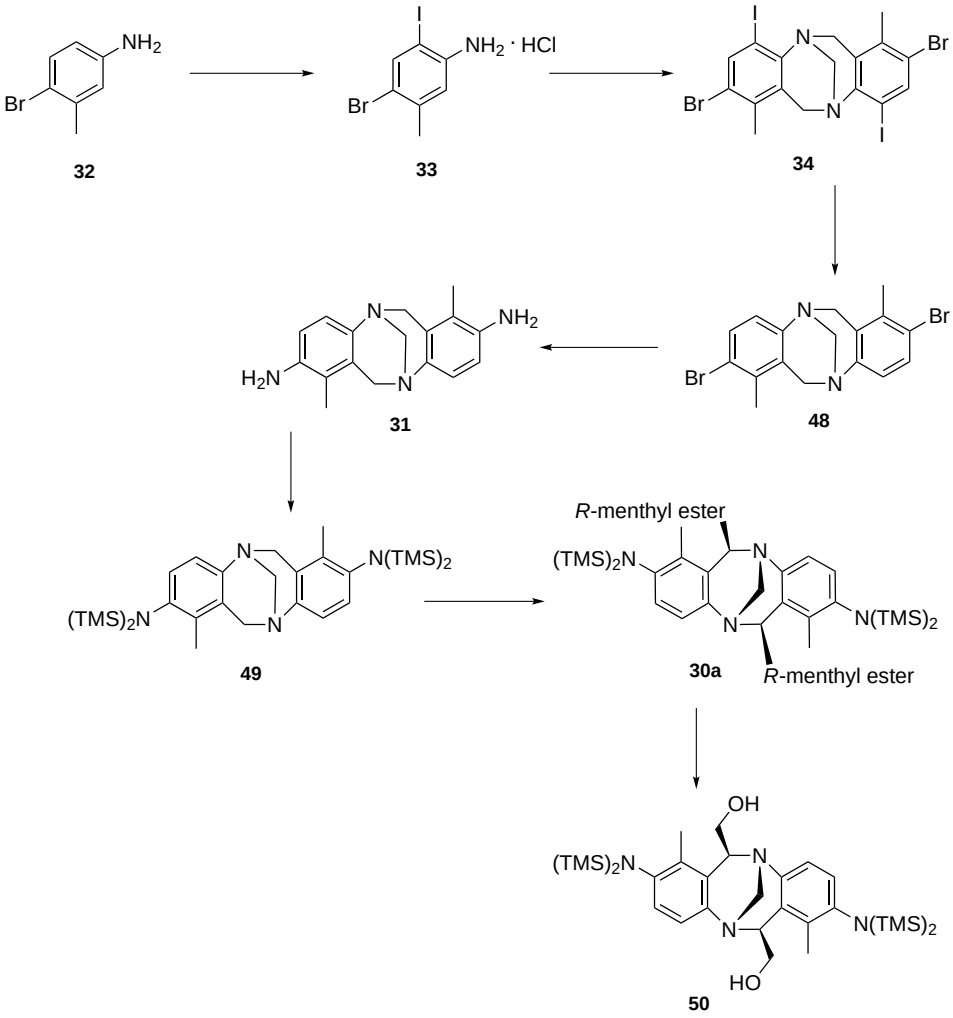


Figure 6.0.1: Overview of the synthesis route.

The first reaction, the iodination of the aniline 32, was scaled up from 202 mmol to 354 mmol starting material and the product **33** was gained in 87% yield. To improve the efficiency of the condensation reaction, nine batches with

17 mmol starting material, which was found to be the optimal quantity for this reaction, were run in parallel. They were worked up and purified together. The condensation yielded in 56% Tröger's base **34**. To remove the iodide groups, that were only needed to ensure the formation of the linear condensation product, lithiation with *n*-BuLi and subsequent quenching with methanol turned out to be unsuitable. Several side products were formed, whereas the dehalogenation with zinc powder and hydrochloric acid in ethanol only resulted in one product **48**. The yield was very good (77%) and the product was highly pure after recrystallization from EtOAc. The studies showed, that vigorous stirring under constant reflux at 130°C is mandatory. By the increase of hydrochloric acid the reaction time could also be shortened. The amination war carried out using the Pd-catalysed methodology developed by HARTWIG and BUCHWALD, with $Pd_2(dba)_3$, BINAP, NaO*t*Bu and benzophenone imine. The diamine was synthesized in excellent 90% yield. This reaction step is still the eye of a needle, because the scale could not be increased over 4 mmol starting material **31**, without decreasing the yield. Doing two reactions in parallel and combined workup was done to improve the efficiency. Subsequently a protection of the amino groups with trimethylsilyl chloride was conducted and gave the product **49** in 73% yield. Another challenging step followed. The menthyl ester **30** of **49** was generated by reacting the racemic mixture with *t*-BuLi and *R*-menthyl chloroformate. The purpose was not only to facilitate a better solubility of higher generations of the Tröger's base in organic solvents later on or establish side chains that could interact with the lipophilic part of a membrane, but resolving the enantiomers of the Tröger's base by transforming them into diastereomers. Like anticipated the TMS-protecting groups remained unaffected by the harsh reaction conditions.

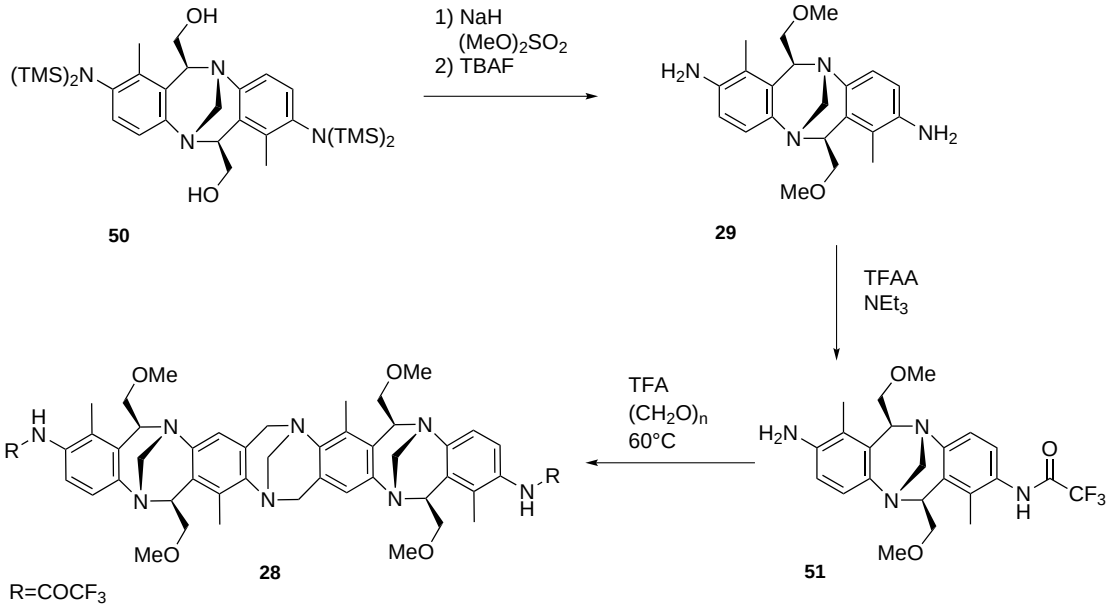


Figure 6.0.2: The last reaction steps to the tris-Tröger's base **28**.

After synthesizing the diol **50**, the next step would have been generating the methyl-ether, as it is depicted in figure 6.0.2. The hydroxy groups of the diol **50** would have been alkylated with dimethyl sulfate. With TBAF the protecting groups would have been removed. The Tröger's base **29** would have been monoprotected by trifluoroacetic anhydride to achieve a desymmetrization. The protecting group should be stable under the highly acidic conditions of the subsequent condensation reaction to tris-Tröger's base **28**, which is carried out in TFA again with paraformaldehyde. Therefore the target molecule was almost obtained. Its structure determination via X-ray diffraction analysis is still pending, as well as the studies concerning its isomerization behaviour.

7 Experimental Section

7.1 General Methods

All chemicals used were commercially available and used without further purification. Standard laboratory glassware and syringe-septum caps were used. When reactions needed an inert atmosphere the glassware was dried in the oven or further with the heating gun prior to use. The flask was heated under vacuum and was purged with nitrogen several times. Dry solvents were collected from a MBRAUN SPS-800 system and stored under nitrogen only for a short time.

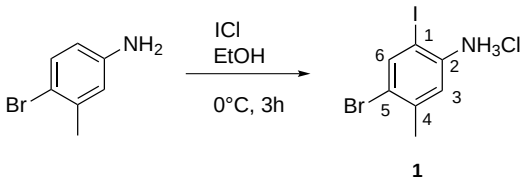
Thin-layer chromatography analysis was performed using silica plates on aluminum (Merck, Silica 60-F_{254} sheets, 2 mm layer thickness). For detection UV light was used. Column chromatography was carried out on silica gel (Merck, 0.063-0.200 mm).

The products were analyzed with ^{1}H- and ^{13}C-NMR spectroscopy. The spectra were recorded with a 400 MHz NMR apparatus from BRUKER (400 MHz ^{1}H-NMR, 100 MHz ^{13}C-NMR). Chemical shifts are given in ppm relative to TMS. The residual solvent peak was used as internal standard ($CHCl_3$ 7.26 ppm / MeOH 3.31 ppm relative to TMS). Proton couplings are described as s (singlet), d (doublet), t (triplet), q (quartet), br (broad) and m (multiplet). Coupling constants are reportet in Hertz.

Melting points were determined in capillary tubes.

7.2 Chemical Synthesis

7.2.1 4-bromo-2-iodo-5-methylaniline hydrochloride (1)



1

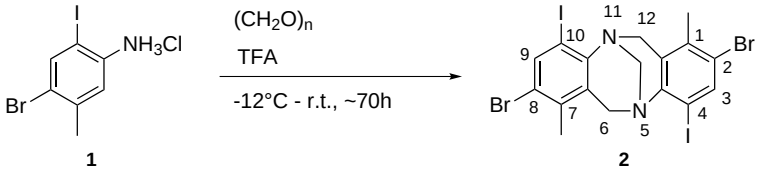
To 650 ml ethanol, which at first was cooled to 0°C, 65.00 g (400.34 mmol, 1.1 eq.) of iodine monochloride were added and allowed to stir for a few minutes. In the following 65.88 g (354.1 mmol, 1 eq.) of 4-bromo-3-methylaniline were added portion wise. The resulting brown slurry was stirred for 3 h. During this time large amounts of precipitate formed, which was collected by filtration and was washed with PE and chloroform and a beige-pinkish powder was gained. The filtrate was evaporated and gave a brown residue, which was taken up in PE and was filtered and washed with PE and chloroform until the filtrate remained clear. The product was dried *in vacuo*.

MW: 348.41

Yield: 108.05 g (310.13 mmol, 87%)

^{1}H-NMR (400 MHz, MeOH-d_4, ppm): δ= 8.09 (s, 1 H, H-6), 7.30 (d, J=0.6 Hz, 1 H, H-3), 2.36 (s, 3 H, Ar-Me).

7.2.2 2,8-dibromo-4,10-diiodo-1,7-dimehtyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (2)



1 **2**

In nine round bottomed flasks 45 ml TFA were cooled to -15°C. To each flask a finely grinded mixture of compound **1** (6 g, 17.35 mmol, 1 eq.) and paraformaldehyde (1.23 g, 40.87 mmol, 2.4 eq.) was added portionwise. The reaction mixture was allowed to stir for 40 min at -12°C, before it was allowed to slowly warm to room temperature and react for 70 h. After that the TFA was

removed *in vacuo*. To the resulting red-brown oil 25 ml water were added and the mixture was made basic with aq. NH_3 solution (28%). The nine batches were combined for the following work-up. The mixture was extracted with DCM three times. The combined organic phases were washed with sodium thiosulfate solution (2M) two times and with brine. The solution was dried over $MgSO_4$, filtrated and evaporated to dryness under reduced pressure.

R_f: 0.35 (PE-$CHCl_3$ 1:1)

MW: 659.92

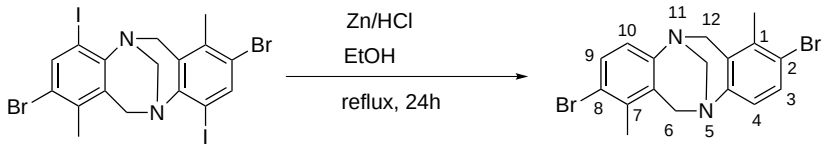
Yield: 28.8 g (43.6 mmol, 56%)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ= 7.95 (s, 2 H, H-9, H-3), 4.40 (d, J=17.4 Hz, 2 H, H-12a, H-6a), 4.24 (s, 2 H, H-13), 4.18 (d, J=17.3 Hz, 2 H, H-12b, H-6b), 2.18 (s, 6 H, 2xAr-Me).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ= 146.9, 140.4, 135.7, 130.4, 121.8, 94.9, 66.2 (1 C), 56.3, 17.8.

HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{17}H_{15}Br_2I_2N_2$: 658.7691; found: 658.7711.

7.2.3 2,8-dibromo-1,7-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (3)



2 **3**

To a supension of compound **2** (9.8 g, 14.9 mmol, 1 eq.) and 19.9 g zinc dust (304.7 mmol, 21 eq.) in 400 ml EtOH (99.5%) were added 12 ml of a aq. HCl solution (10%). The resulting reaction mixture was refluxed (130°C) for 21 h. When TLC showed full conversion the reaction solution was filtered hot through a sintered funnel with celite. The filtrate was brought to dryness by reduced pressure. The residue was taken up in DCM and was washed two times with water. The aqueous phase was made basic and was further extracted with DCM. The combined organic phases were washed with water and brine and were dried over $MgSO_4$. The DCM was removed *in vacuo* and the resulting residue was recrystallized from EtOAc to give colourless crystals.

R_f: 0.17 (PE-EtOAc 85:15)

MW: 408.13

Yield: 4.72 g (11.56 mmol, %)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ= 7.37 (d, J=8.6 Hz, 2 H, H-9, H-3), 6.90 (d, J=8.6 Hz, 2 H, H-10, H-4), 4.54 (d, J=16.8 Hz, 2 H, H-12a, H-6a), 4.19 (s, 2 H, H-13), 4.14 (d, J=16.7 Hz, 2 H, H-12b, H-6b), 2.17 (s, 6 H, 2xAr-Me).

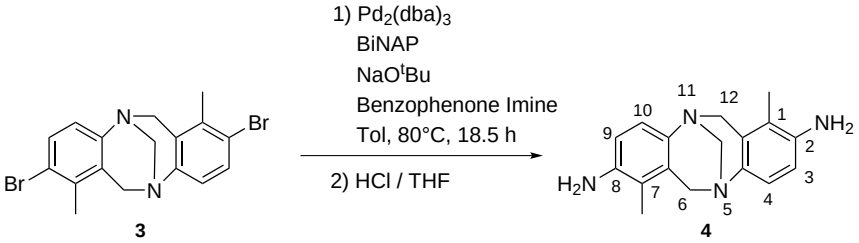
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ= 147.5, 135.1, 131.4, 128.0, 124.3, 120.1, 65.5 (1 C), 58.3, 18.0.

mp.: 234.2 - 236.3°C

HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}Br_2N_2$: 406.9758; found: 406.9722.

Elemental Analysis: calcd for $C_{17}H_{16}Br_2N_2$: C 50.03, H 3.95, N 6.8; found: C 50.06, H 4.02, N 6.85.

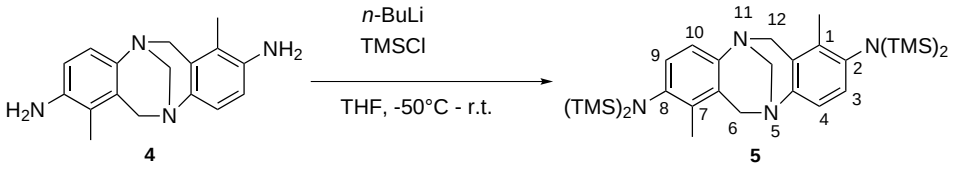
7.2.4 2,8-diamino-1,7-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (4)



The compound **3** (1.02 g, 2.51 mmol, 1 eq.) was placed in an oven-dried flask with a srew cap, as well as 23.0 mg (36.9 µmol, 1.5 mol%) of BiNAP, 0.72 g (7.53 mmol, 3 eq.) Sodium *tert*-butoxide and 15.78 mg (17.2 µmol, 0.7 mol%) $Pd_2(dba)_3$ under N_2. The flask was purged under vacuum and filled with N_2 for at least five times. After suspending the reagents in 10 ml anhydrous Tol 1.1 ml (5.62 mmol, 2.2 eq.) of benzophenone imine were added and the rubber stopper was exchanged quickly with the srew cap. The dark-red suspension was lowered into a preheated oil bath (80°C) and stirred for 18.5 h. A second flask was prepared in that way. The reactions were carried out in parallel and worked up together. When the yellow reaction mixture had reached r.t., it was transfered to an round-bottomed flask and the Tol was removed under reduced pressure. The residue was taken up in THF (80 ml) and was hydrolyzed by addition of ml 4 M HCl solution (20 ml). The mixture was stirred for 4 h. It was partitioned by adding 20 ml of a 2 M HCl solution and 50 ml of a EtOAc/PE (1:2) mixture. After separating the phases, the aqueous phase was extracted further with the EtOAc/PE-mix, DCM and again with the EtOAc/PE-mix. The aqueous phase was made basic with 10 M NaOH solution, resulting in a yellow precipitate. This mixture was further extracted with DCM for three times. The combined organic phases were washed with water and brine, were dried over $MgSO_4$, filtrated and the solvent was removed *in vacuo* at last. The obtained solid was purified by column chromatography (5x12 cm, MeOH-$CHCl_3$, 5:95), which gave the diamine **4** as a pale brown solid.

R_f: 0.21 (MeOH-$CHCl_3$ 5:95)
MW: 280.37
Yield: 1.28 g (4.57 mmol, 90%)
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ= 6.88 (d, J=8.4 Hz, 2 H, H-10, H-4), 6.57 (d, J=8.4 Hz, 2 H, H-9, H-3), 4.51 (d, J=16.6 Hz, 2 H, H-12a, H-6a), 4.19 (s, 2 H, H-13), 4.14 (d, J=16.6 Hz, 2 H, H-12b, H-6b), 3.40 (bs, 4 H, NH_2), 1.88 (s, 6 H, 2xAr-Me).
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ= 140.7, 139.0, 126.1, 122.9, 119.4, 115.3, 65.4 (1 C), 57.5, 11.2.
mp.: 284.2 - 286.0°C
HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{17}H_{21}N_4$: 281.1766; found: 281.1732.
Elemental Analysis: calcd for $C_{17}H_{21}N_4 \cdot 0.091\ CHCl_3$: C 70.49, H 6.95, N 19.24; found: C 70.48, H 6.88, N 19.25.

7.2.5 1,7-dimethyl-*N*,*N*,*N'*,*N'*-tetrakis-trimethylsilanyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-2,8-diamine (5)

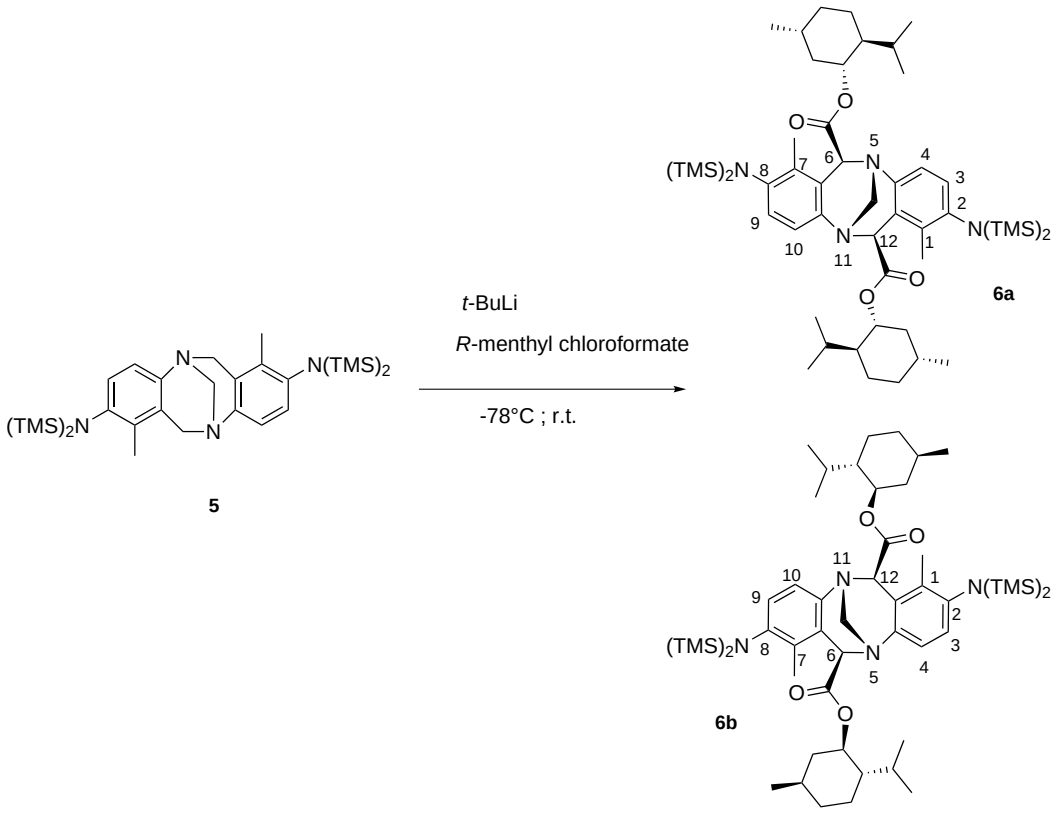


The diamine **4** (0.782 g, 2.79 mmol, 1 eq.) was suspended in ml anhydrous THF and cooled to -50°C under inert N_2-atmosphere. Over 30 min 2.5 ml *n*-BuLi (6.25 mmol, 2.2 eq.) were added dropwise. The resulting mixture was removed from the cooling bath and allowed to reach r.t., at which it was stirred for 1 h. The reaction mixture was cooled to -50°C again, before TMSCl (0.85 ml, 1.26 mmol, 2.4 eq.) was slowly added over 20 min. A clear orange solution resulted, which was stirred at r.t. for 1 h. These steps were repeated a second time with equal amounts of *n*-BuLi (6.25 mmol, 2.2 eq.) and TMSCl (0.85 ml, 1.26 mmol, 2.4 eq.). The clear orange-brown solution was stirred at r.t. for 2 h, before it was evaporated to drynes under vacuum. The resulting oil was take up in DCM and vacuum filtered through active neutral alumina (3 cm). This filter cake was washed with DCM several times. The filtrate was concentrated *in vacuo* and gave the silylated Tröger's Base **5** as a yellow-brown solid.
R_f: 0.35 (PE-EtOAc 85:15)
MW: 569.09
Yield: 1.16 g (2.05 mmol, 73%)
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ= 6.83 (d, J=8.4 Hz, 2 H, H-10, H-4), 6.69 (d, J=8.4 Hz, 2 H, H-9, H-3), 4.44 (d, J=16.6 Hz, 2 H, H-12a, H-6a), 4.27 (s, 2 H, H-13), 4.06 (d, J=16.7 Hz, 2 H, H-12b, H-6b), 1.94 (s, 6 H, 2xAr-Me), 0.02 (s, 18 H, 2xTMS), -0.16 (s, 18 H, 2xTMS).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ= 144.1, 141.8, 133.9, 129.5, 126.7, 121.9, 66.2 (1 C), 58.6, 14.1, 1.95 (6 C), 1.80 (6 C).

HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{29}H_{53}N_4Si_4$: 569.3347; found: 569.3391.

7.2.6 2,8-bis-(1,1,1,3,3,3-hexamethyl-disilazan-2-yl)-1,7-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-dicarboxylic acid *R*-menthyl ester (6)



To a solution of compound **5** (1.164 g,2.05 mmol, 1 eq.) in 18 ml anhydrous THF, which was cooled to -78°C previously, were added 3.6 ml of *t*-BuLi (6.14 mmol, 3 eq.) over 40 min under inert N_2-atmosphere. The reaction mixture was stirred for 2 h at -78°C, before the addition of 1.9 ml (8.99 mmol, 4.4 eq.) *R*-menthyl chloroformate over 30 min. In the following the cooling bath was removed and the reaction mixture was allowed to reach r.t., at which it was stirred for another 16 h. Then the THF was removed in vacuo and the residue was taken up with EtOAc and extracted two times with water, washed with brine, dried over $MgSO_4$ and filtrated. The solvent was removed under reduced pressure to give a yellow oil, which was further purified by a first column chromatography (6x6 cm, 1% EtOAc in PE). The resulting oil was of

a pale yellow colour, still. A second column chromatography (6x6 cm), 0.5% EtOAc in PE) gave the two diastereomers **6a** and **6b**.

MW: 933.61

6a Yield: 237.1 g (0.25 mmol, 12%)

R_f: 0.14 (PE-EtOAC 98:2)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ= 6.99 (d, J=8.4 Hz, 2 H, H-10, H-4), 6.79 (d, J=8.7 Hz, 2 H, H-9, H-3), 4.83 (tt, J=10.8, 8.4 Hz, 2 H, -CO_2C*H*-R), 4.59 (s, 2 H, H-12, H-6), 4.46 (s, 2 H, H-13), 2.09-2.01 (m, 4 H, menthyl), 1.91 (s, 6 H, 2xAr-Me), 1.75-1.68 (m, 4 H, menthyl), 1.57-1.45 (m, 4 H, menthyl), 1.13-1.02 (m, 4 H, menthyl), 0.94-0.89 (m, 14 H, menthyl), 0.80 (d, J=6.9 Hz, 6 H, menthyl), 0.02 (s, 18 H, 2xTMS), -0.16 (s, 18 H, 2xTMS).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ= 170.8, 144.9, 142.5, 135.2, 130.8, 124.9, 122.5, 75.3, 69.4, 58.4 (1 C), 47.3, 40.9, 34.4, 31.6, 26.1, 23.5, 22.2, 21.0, 16.3, 14.8, 2.0 (6 C), 1.7 (6 C).

HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{51}H_{89}N_4O_4Si_4$: 933.5961; found: 933.5953.

6b Yield: 236.9 g (0.25 mmol, 12%)

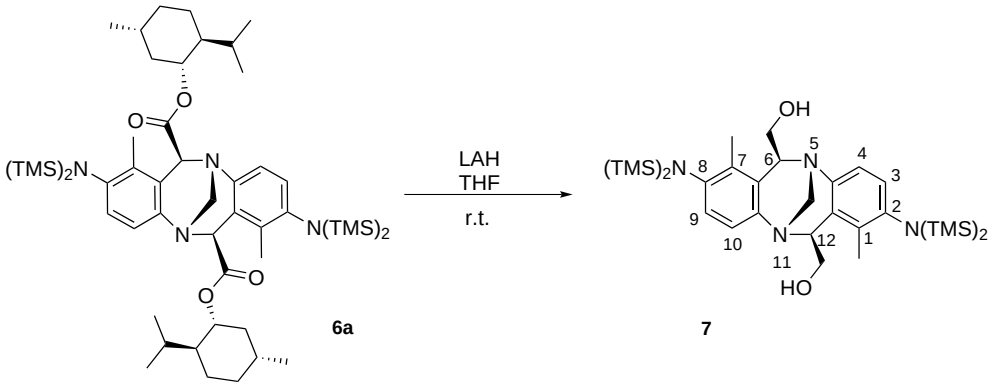
R_f: 0.09 (PE-EtOAc 98:2)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ= 7.04 (d, J=8.4 Hz, 2 H, H-10, H-4), 6.81 (d, J=8.8 Hz, 2 H, H-9, H-3), 4.83 (tt, J=10.8, 8.4 Hz, 2 H, -CO_2C*H*-R), 4.63 (s, 2 H, H-12, H-6), 4.43 (s, 2 H, H-13), 2.05-1.96 (m, 4 H, menthyl), 1.91 (s, 6 H, 2xAr-Me), 1.71-1.66 (m, 4 H, menthyl), 1.54-1.41 (m, 4 H, menthyl), 1.11-0.97 (m, 4 H, menthyl), 0.94-0.89 (m, 14 H, menthyl), 0.80 (d, J=6.9 Hz, 6 H, menthyl), 0.00 (s, 18 H, 2xTMS), -0.13 (s, 18 H, 2xTMS).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ= 170.5, 144.4, 142.6, 135.3, 130.7, 124.8, 122.6, 75.4, 69.5, 58.8 (1 C), 47.0, 40.7, 34.4, 31.5, 26.3, 23.2, 22.1, 21.0, 16.1, 14.7, 1.93 (6 C), 1.75 (6 C).

HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{51}H_{88}N_4Na\ O_4Si_4$: 955.5780; found: 955.5771.

7.2.7 2,8-bis-(1,1,1,3,3,3-hexamethyl-disilazan-2-yl)-1,7-dimehtyl-6*H*,12*H*-5,11-mehtanodibenzo[*b,f*][1,5]diazocine-*exo,exo*-6,12-bis-methanol (7)



To a suspension of LAH (36.43 mg, 0.93 mmol, 6.2 eq.) in 4 ml anhydrous THF was added a solution of **6a** (139.89 mg, 0.15 mmol, 1 eq.) in 2 ml anhydrous THF under inert N_2-atmosphere. The reaction mixture was stirred for 4 h at r.t., before it was quenched by adding an excess of Na_2SO_4 ·10 H_2O portionwise until no developement of gas could be observed. The resulting slurry was stirred for 45 min and vacuum filtered. The residue was washed further with with refluxing THF and refluxing EtOAc. The filtrate was brought to dryness by evaporating the solvent and gave a yellow oil. Purification was carried out by column chromatography (2.5x8 cm, 10% →25% →50% EtOAc in PE) and gave the diol **7** as colourless oil.

R_f: 0.30 (PE-EtOAc 7:3)

MW: 629.14

Yield: 81.9 g (0.13 mmol, 85%)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ=6.87 (d, J=8.4 Hz, 2 H, H-10, H-4), 6.76 (d, J=8.4 Hz, 2 H, H-9, H-3), 4.26 (s, 2 H, H-13), 4.13 (dd, J=10.4, 4.4 Hz, 2 H, H-12, H-6), 3.97 (m, 2 H, -CH_2OH), 3.63 (t, J=11.0 Hz, 2 H, -CH_2OH), 3.55 (d, J=9.9 Hz, 2 H, -OH), 2.02 (s, 6 H, 2xAr-Me), 0.01 (s, 18 H, 2xTMS), -0.16 (s, 18 H, 2xTMS).

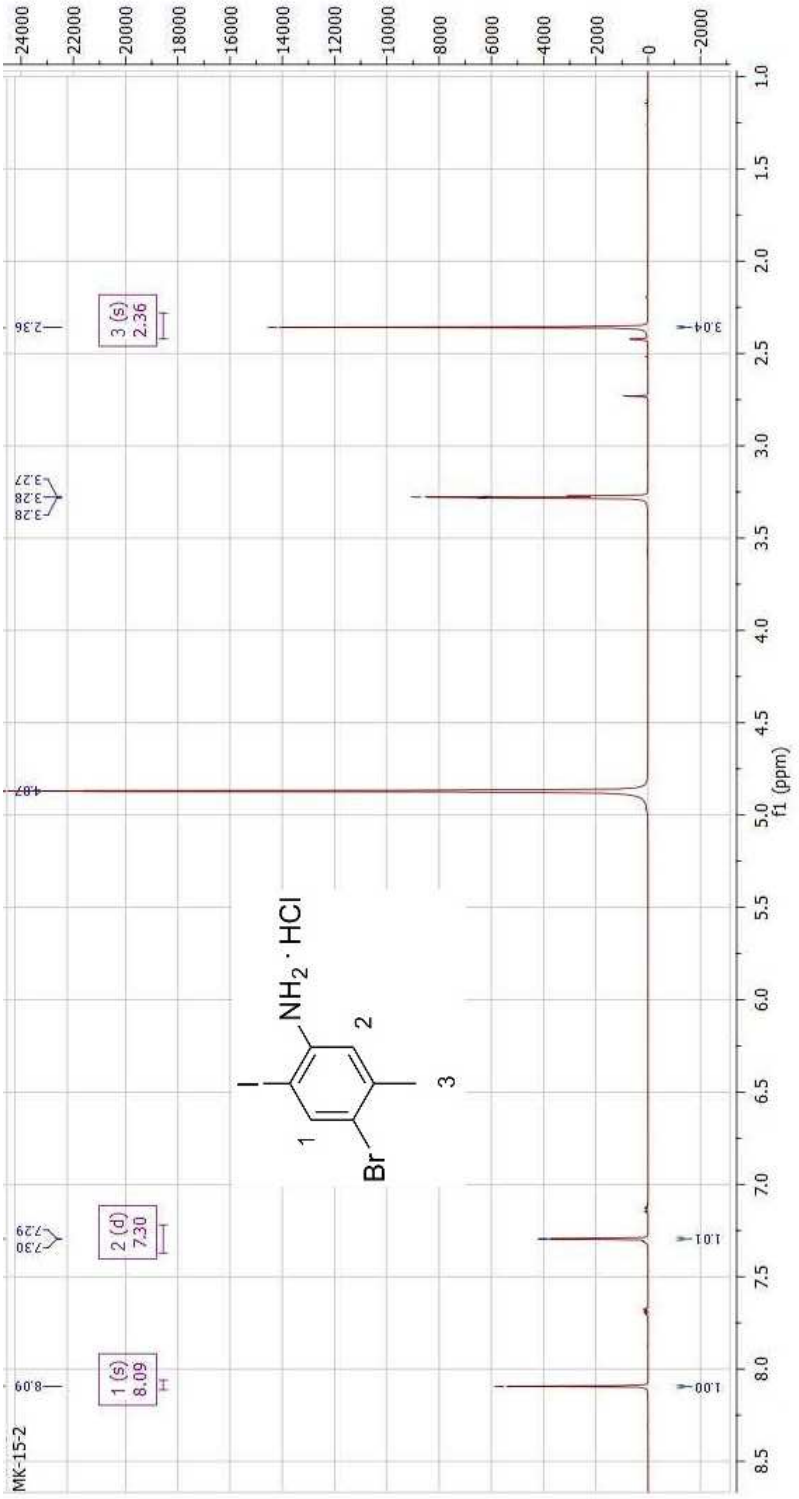
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ= 144.2, 143.4, 134.9, 130.5, 127.1, 122.5, 68.7, 61.6, 53.8 (1 C), 15.2, 1.90 (6 C), 1.76 (6 C).

mp.: 192.9-194.9°C

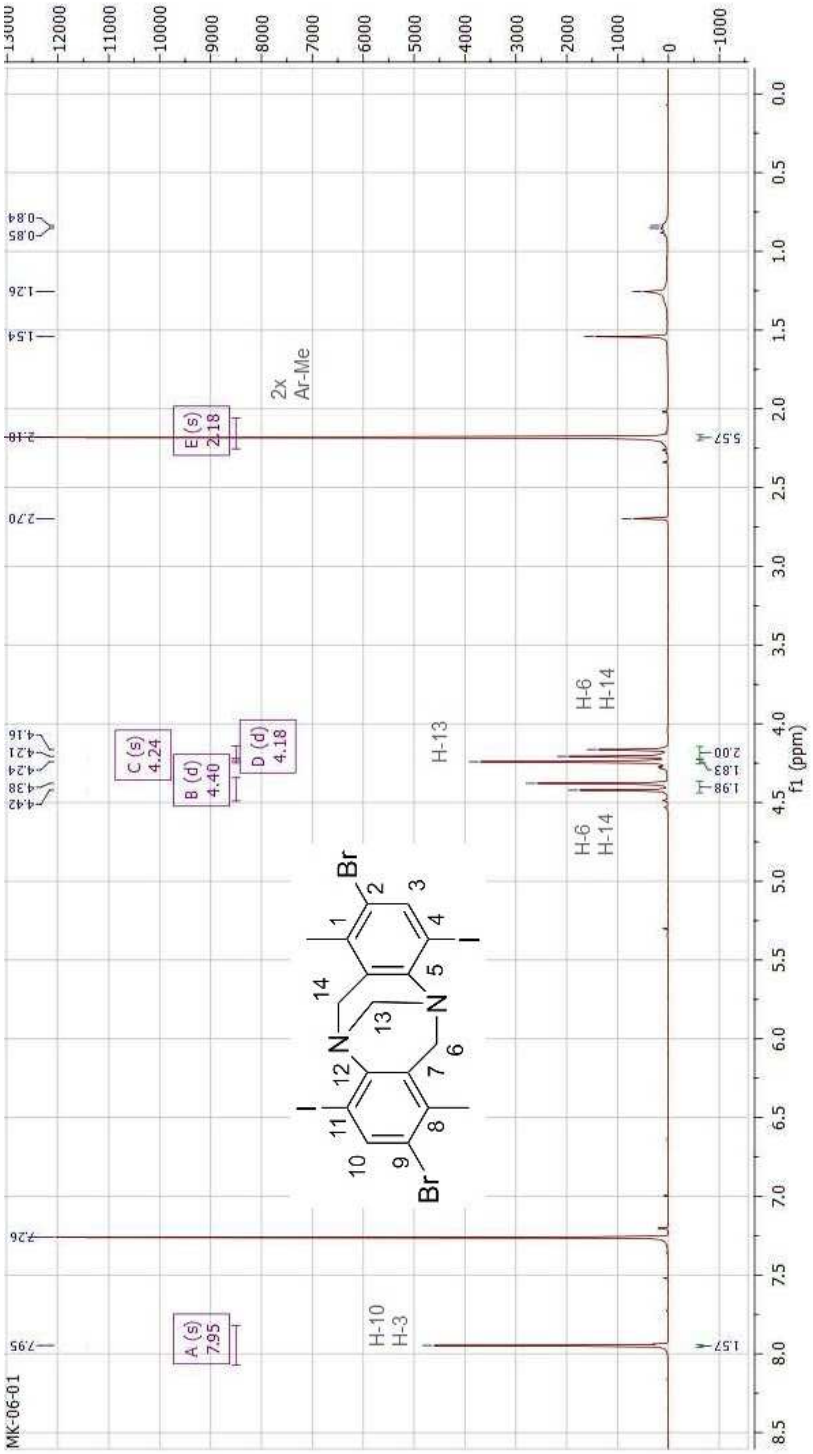
HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{31}H_{57}N_4O_2Si_4$: 629.3559; found: 629.3539.

Appendix

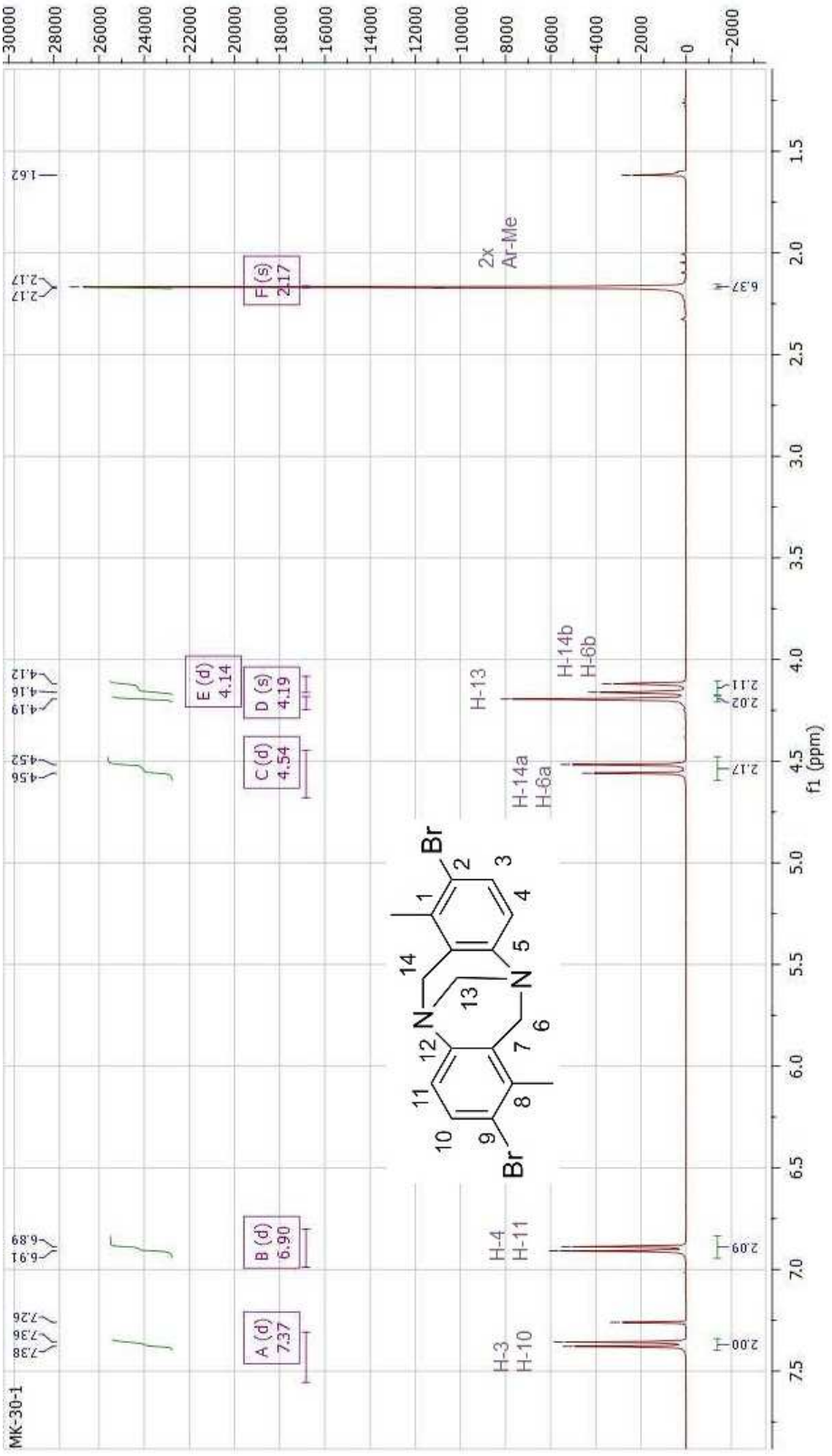
4-bromo-2-iodo-5-methylaniline hydrochloride (1): ^{1}H-NMR Spectrum in MeOH-d_4



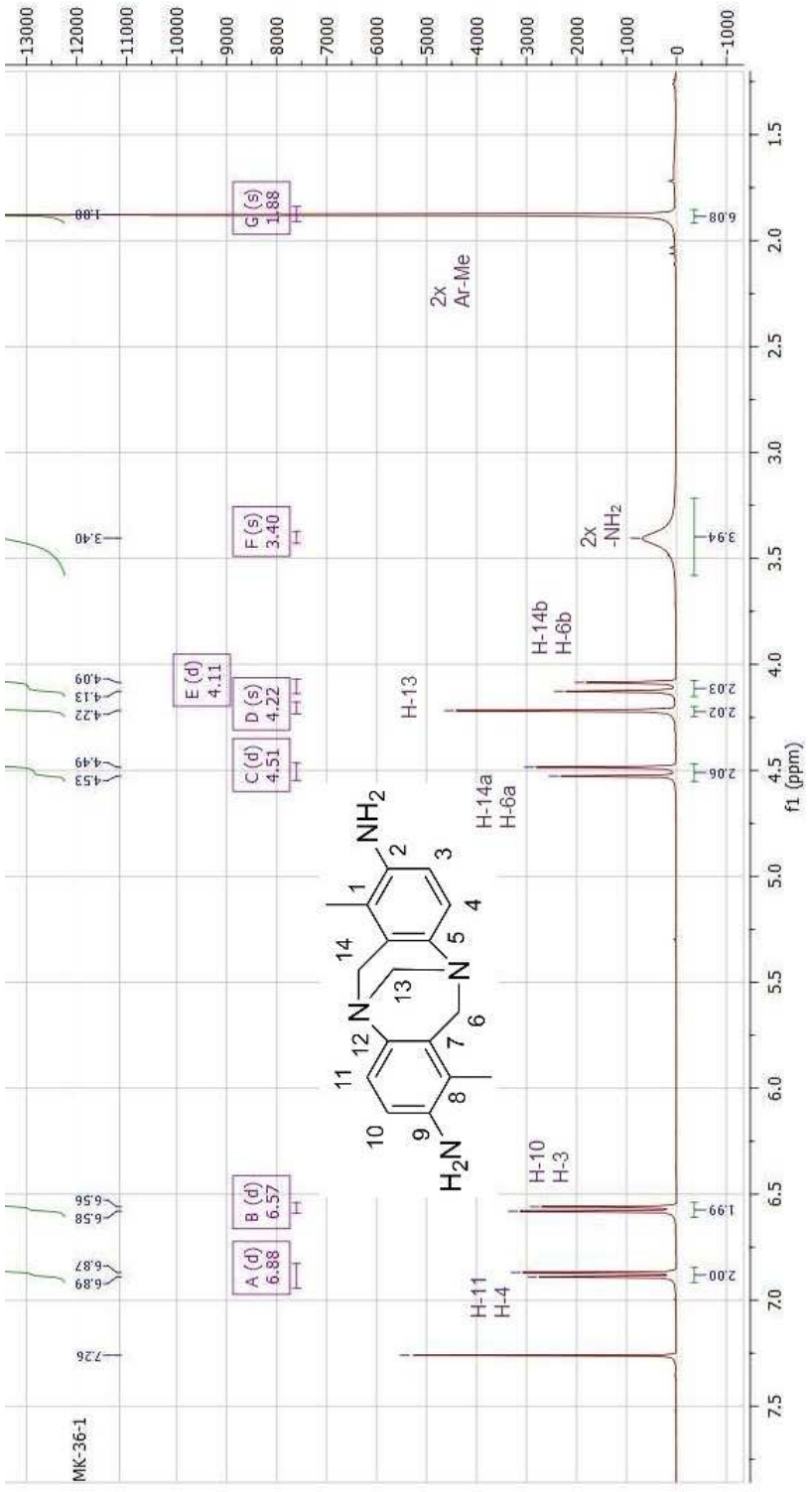
2,8-dibromo-4,10-diiodo-1,7-dimehtyl-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine (2): ^{1}H-NMR Spectrum in $CDCl_3$



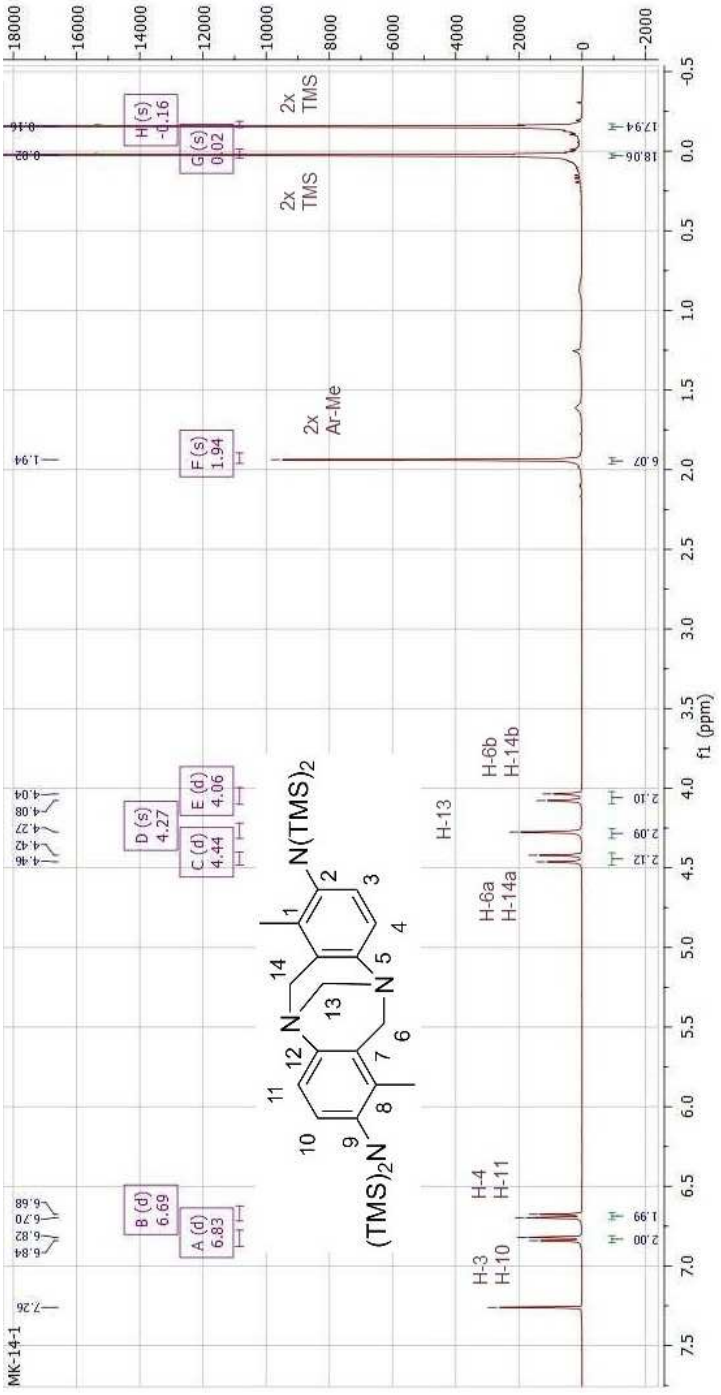
2,8-dibromo-1,7-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine (3): ^{1}H-NMR Spectrum in $CDCl_3$



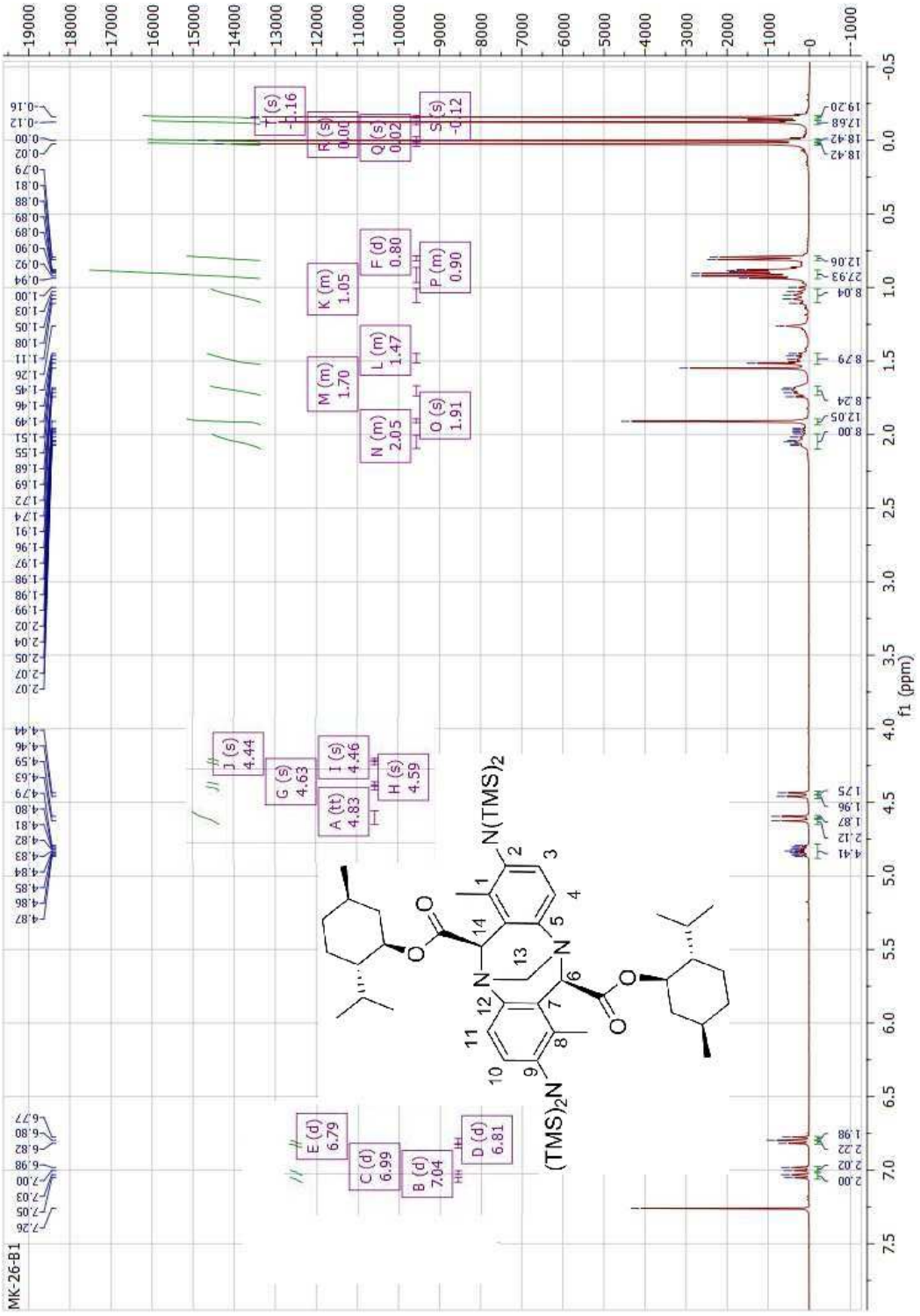
2,8-diamino-1,7-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine (4): ^{1}H-NMR Spectrum in $CDCl_3$



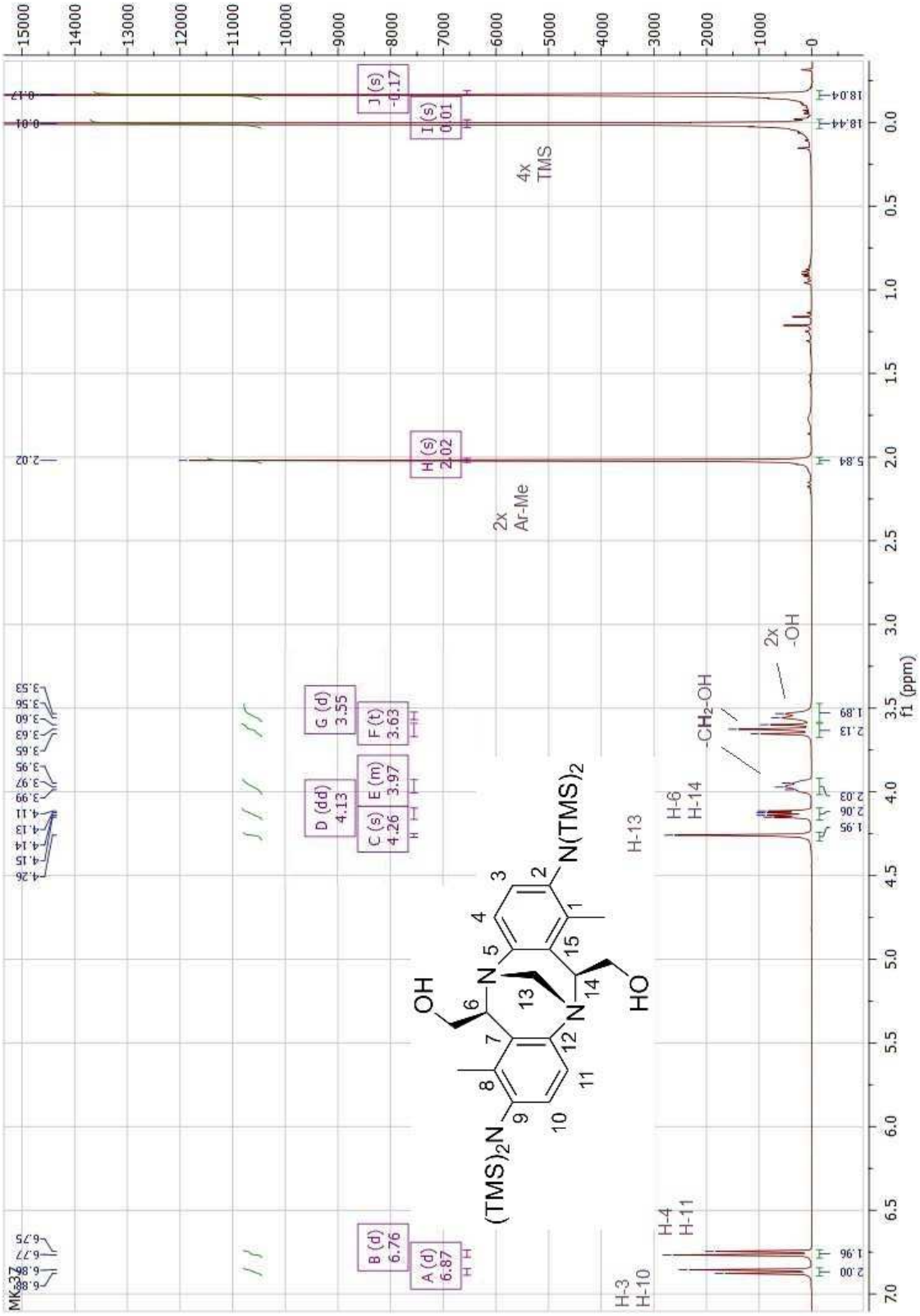
1,7-dimethyl-*N*,*N*,*N'*,*N'*-tetrakis-trimethylsilanyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-2,8-diamine (5): ^{1}H-NMR Spectrum in $CDCl_3$



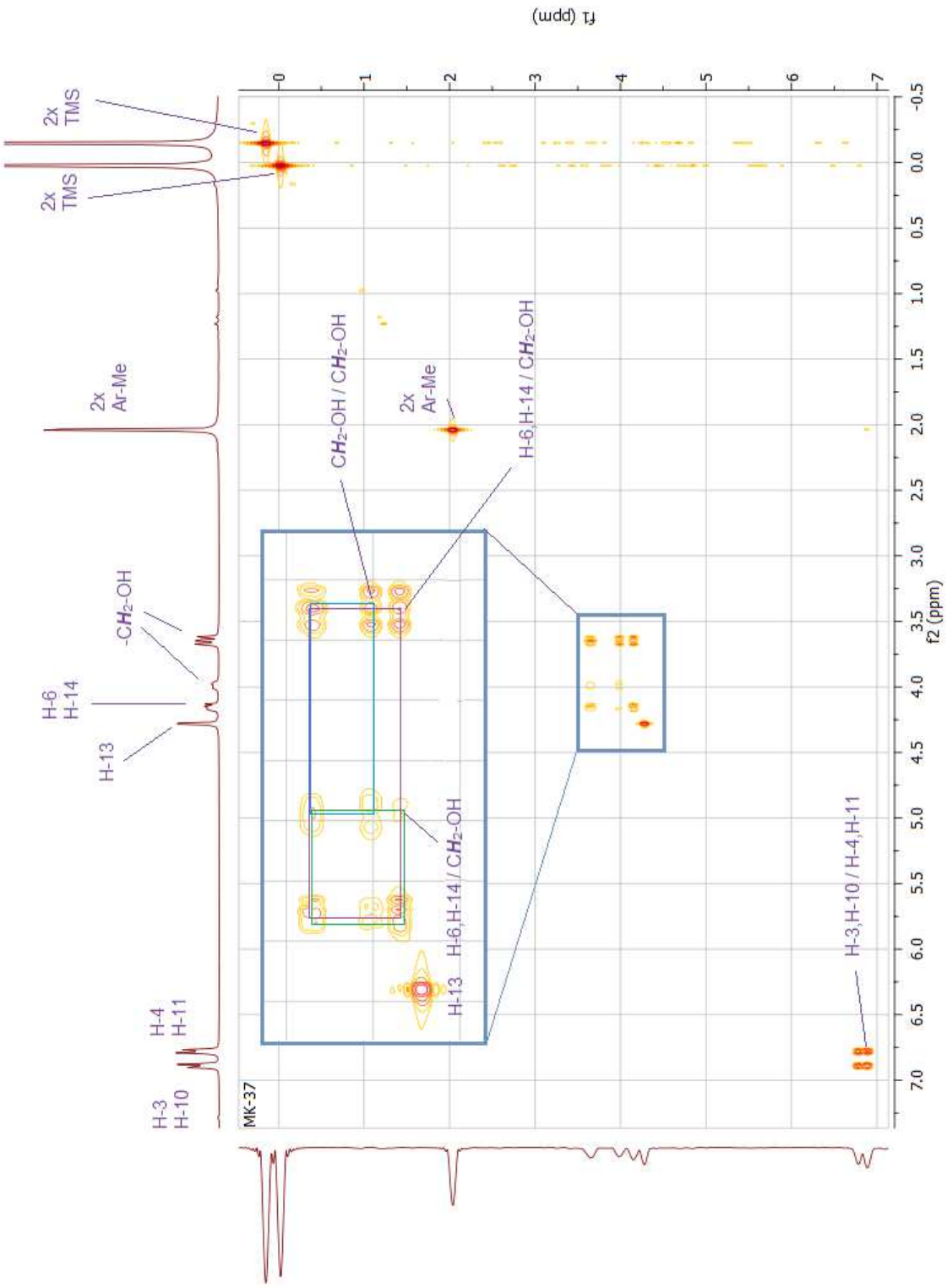
2,8-bis-(1,1,1,3,3,3-hexamethyl-disilazan-2-yl)-1,7-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-dicarboxylic acid *R*-menthyl ester (6): ^{1}H-NMR Spectrum in $CDCl_3$



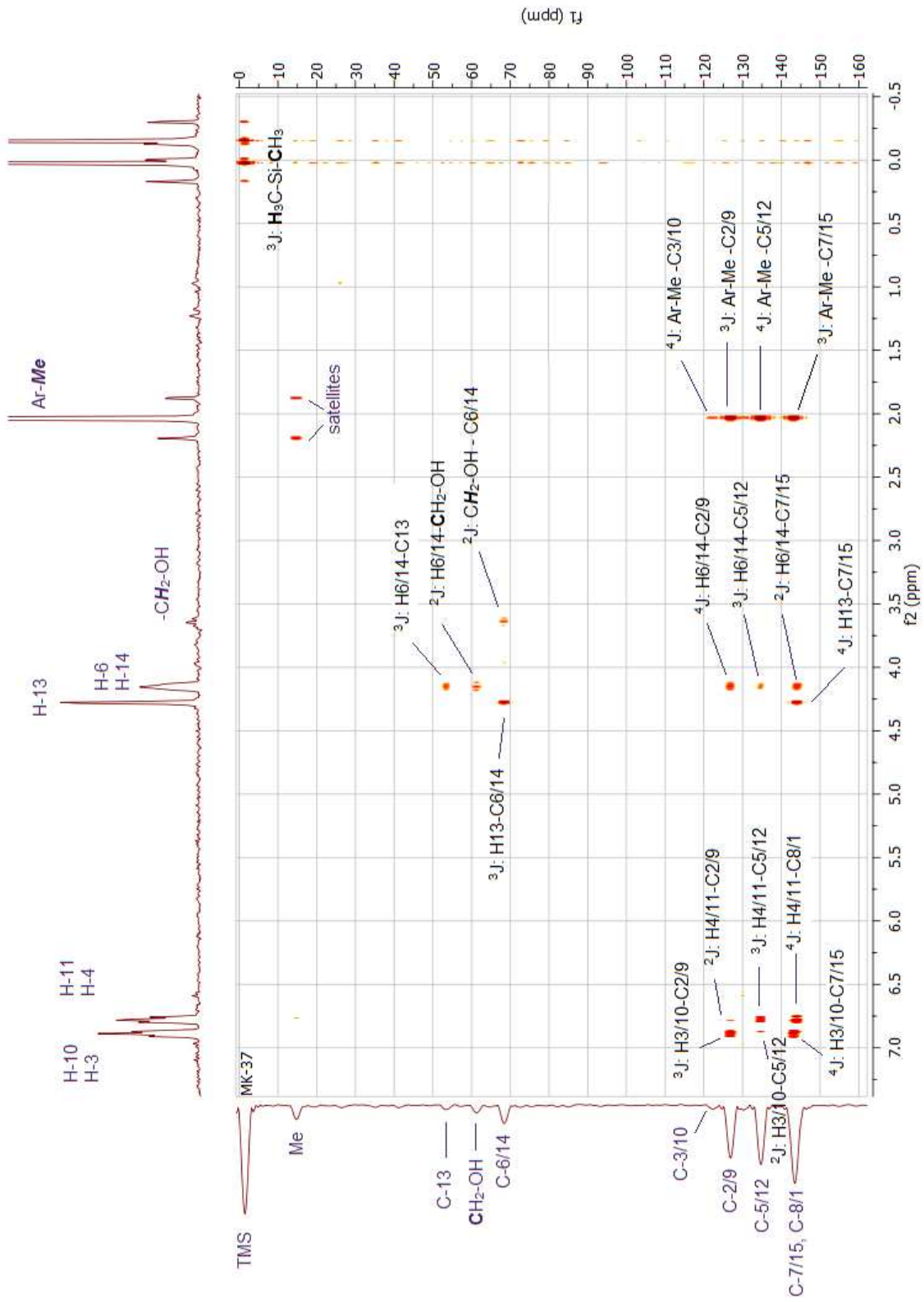
2,8-bis-(1,1,1,3,3,3-hexamethyl-disilazan-2-yl)-1,7-dimehtyl-6*H*,12*H*-5,11-mehtanodibenzo[*b*,*f*][1,5]diazocine-*exo*,*exo*-6,12-bis-methanol (7): ^{1}H-NMR Spectrum in $CDCl_3$



2,8-bis-(1,1,1,3,3,3-hexamethyl-disilazan-2-yl)-1,7-dimehtyl-6*H*,12*H*-5,11-mehtanodibenzo[*b*,*f*][1,5]diazocine-*exo*,*exo*-6,12-bis-methanol (7): COSY-NMR Spectrum in $CDCl_3$



2,8-bis-(1,1,1,3,3,3-hexamethyl-disilazan-2-yl)-1,7-dimehtyl-6*H*,12*H*-5,11-mehtanodibenzo[*b*,*f*][1,5]diazocine-*exo*,*exo*-6,12-bis-methanol (7): HMBC-NMR Spectrum in $CDCl_3$



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