4.2 Synthesis of the building blocks

4.2.1 Synthesis of the ring corner

An appropriate ring corner molecule should carry two different coupling functionalities in *meta* positions and an anchoring group for different side chains. Henze has established 34\(^{30}\) (Fig. 4) for his bipyridine macrocycles, making use of the well known bromo/iodo selectivity in palladium catalyzed coupling reactions.\(^{67,110}\) Via ether linkage, different side chains were introduced. He chose the rather inert, but strongly solubility enhancing hexyl group and two different OH-protection groups, THP and MOM, which could open access to a later introduction of new side groups on the cycle itself. It was not clear in the beginning whether the more labile THP group would cleave at some unexpected stage in synthesis.\(^{30}\)

![Fig. 4. Henze’s ring corner precursor 34.\(^{30}\)](image)

As the synthesis of 34 can be performed in large batches and high yields, compounds 38\(^a\) and 38\(^c\) were chosen as corner modules here; the THP group was proven by Henze to be unaffected by the coupling chemistry involved. The synthesis is described shortly (Scheme 17).\(^{31}\)

![Scheme 17. Synthesis of corner precursors 38\(^a\) and 38\(^c\) according to Henze.\(^{31}\)](image)

Bromination of 4-aminobenzoic acid ethyl ester in acetic acid gives 35. The regiochemistry is defined by the directing effects of both the amino and the carboxylic ester
functionality. Diazotation of 35 and reduction of the product in ethanol leads under vigorous gas evolution to the deaminated product 36. Modrakowski could show that the addition of copper(I)oxide as reducing agent was not necessary, but that ethanol took this part itself. The ester 36 was then reduced with lithium aluminium hydride to benzyl alcohol 37a.

37a was deprotonated by KOr-Bu and refluxed with hexyl bromide to give the etherification product 38a. The THP protecting group was introduced by reacting the alcohol 37a with DHP in the presence of p-toluenesulfonic acid to form acetal 38c.

\[
\begin{align*}
\text{OH} & \quad \text{BrBr} & \quad \text{OC}_6\text{H}_{13} \\
\text{BrBr} & \quad \text{OH} & \quad \text{BrBr} \\
\text{Br} & \quad \text{BrBr} & \quad \text{BrBr} \\
\end{align*}
\]

37b 38b

Scheme 18. Synthesis of alternative corner precursor 38b.

Alternatively, a much shorter reaction sequence to the phenyl ether analogue 38b of benzyl ether 38a was developed here (Scheme 18). The hydro-de-halogenation of the three activated bromo substituents in commercially available pentabromophenol to yield meta disubstituted phenol 37b has been described by Kraus. A solution of pentabromophenol is refluxed with AlCl₃ in benzene (here, toluene was used). By crystallization from toluene, pure 37b was isolated. Etherification of the acidic OH group was then performed with hexyl bromide in methyl ethyl ketone under reflux with K₂CO₃ as proton scavenger. 38b could be purified by a short column chromatography.

This new reaction sequence needed two steps less than Henze’s; but, unlike in his, the process could not be upscaled. This is due to the high loss in molar mass during the first step combined with the necessity to use a sufficiently high amount of solvent, which also acts as reagent here; attempts to work in higher concentrations led to a decrease in yield.

The different electronic structure of 38b, which is more electron rich than 38a, had no notable influence on the further modifications. The different polarity, however, facilitates purification by column chromatography (see below). Interestingly, the properties of the macrocycles were clearly determined by the small differences between the hexyloxy and the hexyloxymethyl side chains (ref. Chapter 4.6.1).

Monolithiation of 38b with BuLi at -78°C and scavenging of the generated aryl anion with trimethylsilyl chloride led to Br,TMS-difunctionalized 39 (Scheme 19). The TMS group was easily replaced by treatment with ICl to give the bromo,iodo-functionalized compound
Thus, the two bromo functions had been differentiated, effectively leading from an A,A- (in 38b) to an A,B-pattern (in 34b).

\[
\begin{align*}
\text{38b} & \quad \text{39} & \quad \text{40} \\
\text{OC}_6\text{H}_{13} & \quad \text{TMS} & \quad \text{TMS} \\
\text{Br} & \quad \text{Br} & + \\
\text{OC}_6\text{H}_{13} & \quad \text{Br} & \quad \text{OC}_6\text{H}_{13} \\
& \quad \text{TMS} & \quad \text{TMS} \\
& \quad \text{Br} & \\
\text{34b} & \quad \text{41} \\
\text{OC}_6\text{H}_{13} & \quad \text{I} & \quad \text{I}
\end{align*}
\]

Scheme 19. Differentiation of the coupling functionalities of compound 38b

A direct introduction of iodine was done by Henze; the anion generated by reacting 38a/c with BuLi was then scavenged with 1,2-diiodoethane to yield 34a/c (Scheme 20). He also published a route via a tri-t-butylstannylated compound; this functionality is introduced by treatment of the anionic intermediate with tri-t-butylstannyl chloride and cleaved off later quantitatively by simple treatment with iodine. The advantage of this scheme is the possibility to purify the stannyalted compound very easily from unreacted starting material. A disadvantage is the high toxicity of the organostannyls.

\[
\begin{align*}
\text{38a} & \quad \text{34a} \\
\text{CH}_2\text{OR} & \quad \text{OC}_6\text{H}_{13} \\
\text{Br} & \quad \text{Br} & \quad \text{Br} & \quad \text{Br} \\
\text{38a: } R = \text{C}_6\text{H}_{13} & \quad \text{34a: } R = \text{C}_6\text{H}_{13} \\
\text{38c: } R = \text{THP} & \quad \text{34c: } R = \text{THP}
\end{align*}
\]

Scheme 20. Differentiation of the coupling functionalities for compound 34a according to Henze.

In fact, the monolithiation was generally selective enough to yield pure material according to $^1$H-NMR. Furthermore, the purification of the compounds with hexyloxy side chain (34b-45b) from starting material or biscoupled side products by column chromatography proved to be much easier than the purification of the more polar benzyl ether
species. From one batch, which gave a rather unsuccessful result, bissilylated side product 40 was separated from monosilylated product 42b (Scheme 19). Treatment with iodine chloride led to diodo compound 41, which could easily be purified by a short filtration column. Recently, an alternative route towards a THP protected analogue of 41 was opened up by Höger.\textsuperscript{115} He synthesized 3,5-diiodophenol in 4 steps from 1-nitroaniline and protected the OH functionality with DHP.

Lehmann easily prepared 34a in two steps from commercially available 3-bromo-5-iodobenzoic acid via reduction and etherification.\textsuperscript{29} The synthesis itself is quite attractive, but the starting material is by far too expensive to supply with the amounts of corner compound needed here.

\begin{center}
\textbf{Scheme 21. Synthesis of phenyacetylenes 45a-c.}
\end{center}

Henze described the Sonogashira coupling of 34a with TIPS-acetylene to 43a, and with TMS-acetylene further to 44a (Scheme 21).\textsuperscript{32} The TMS protecting group was then selectively cleaved off to give 45a.\textsuperscript{116} This procedure was extended here to the series with the hexyloxy (34b-45b) and the THP-oxymethyl side chain (34c-45c). While the coupling of the second ethynyl substituent could be driven to completion by an excess of reagent, and the deprotection of the TMS group was quantitative, the stoichiometric ratio of coupling partners in the first step was important to avoid either incomplete reaction or undesired coupling of the bromo functionality; the purification of the resulting mixture was tedious.\textsuperscript{117} An easier
separation of the TIPS protected monocoupled compound compared to the TMS protected one was given by Henze as reason for the former route. Here, the latter route via 42b was preferred, because the low boiling point of TMS-acetylene makes its coupling at the iodo functionality more suitable, as this coupling can be performed at lower temperature than the bromo coupling. A biscoupled side product 43x (not shown) from the synthesis of 43b was isolated and characterized.

The building blocks gained by this strategy open synthetic access in different directions. Compounds 45 with their terminal acetylene functionality can be Sonogashira coupled with a halo functionalized aryl, while halo functionalized compounds 42 or 43 can be used for either Sonogashira, Stille or Suzuki coupling reactions. After cleavage of the TMS or TIPS protecting groups, the molecules in a second step can be further connected at the other side.

46 is the iodo functionalized analogue of 43b (Scheme 22); therefore, it should be much more reactive in palladium catalyzed coupling reactions. 46 was statistically prepared by coupling of diiodo compound 41 with one equivalent of TMS-acetylene and isolated in a respectable yield of 56 %. Its straightforward separation of unreacted starting material and twofold coupling product by column chromatography with hexane was again a striking example of the easier purification of the phenyl ether compounds compared to the benzyl ether series.

\[
\begin{align*}
\text{OC}_6\text{H}_{13} & \quad \text{OC}_6\text{H}_{13} \\
\text{I} & \quad \text{I} \\
\text{TMS} & \quad \text{TMS} \\
Pd^0/\text{CuI} & \\
\text{OC}_6\text{H}_{13} & \quad \text{OC}_6\text{H}_{13} \\
\text{I} & \quad \text{I} \\
\text{TMS} & \quad \text{TMS}
\end{align*}
\]

\text{Scheme 22. Synthesis of iodo functionalized phenylethynylene 46.}

It may be useful to introduce an iodo functionality at a later stage in synthesis; 48 contains a terminal acetylene functionality for Sonogashira coupling and a TMS functionality as a placeholder for iodo, which can easily be iodo-de-silylated with iodine chloride (Scheme 23). The Sonogashira coupling of 39 with TMS-acetylene nearly quantitatively yielded 47, as an excess of the free acetylene could be applied due to the inertness of the TMS functionality to coupling conditions. The acetylenic TMS group was then quantitatively cleaved off to yield 48, with the aryl TMS functionality remaining unaffected.
4. General Part

4.2.2 Synthesis of the terpyridine unit

2,2':6',2"-Terpyridine derivatives are important ligands in coordination chemistry, e.g., as photosensitizers, and a large number of synthetic approaches have been published. While in the most widely used methods, e.g., by Kröhnke, the central pyridine ring is assembled by the condensation of the two appropriately functionalized side pyridines, another strategy is to couple three pyridine rings.

\[
\text{Br} \quad \text{Br} \quad \text{HI 67 \%} \quad \text{Br} \quad \text{I} \quad \text{Pd}^0
\]

Scheme 24. Synthesis of dibromo terpyridine 53 according to Lehmann.

Basing on the pioneering work by Yamamoto and Sauvage on Stille coupling of pyridines, Lehmann developed a synthetic strategy to 5,5"-difunctionalized 2,2';6',2"-terpyridines, which had not been accessible by other routes. 53 was prepared according to this protocol using the Stille cross coupling to connect the bisstannylated central pyridine and the 5-bromo-2-iodo functionalized pyridine sides (Scheme 24). These two coupling partners were generated from 49 and 51. 2,6-Dichloropyridine 51 is reacted in a nucleophilic substitution reaction with in situ generated sodium trimethylstannane to yield 52, which can be purified by distillation. Pyridine compounds which carry a TMS functionality ortho to the nitrogen atom generally tend to proto-de-stannylate on the chromatography column or when exposed to humidity. Reaction of 2,5-dibromopyridine 49 with 67% HI at elevated
temperature led to selective substitution of the ortho bromine by iodine to give 50. The Stille cross coupling of 50 with 52 regioselectively afforded terpyridine 53 with the desired 2,2',6',2'' connectivity. This is not only because of the iodo/bromo selectivity of the Pd catalyzed reaction, but also due to the fact that the 2-position in pyridines is more electron deficient than the 5-position. Therefore, also 49 instead of 50 can be used in this reaction, in which case, however, the yield is lower. Very recently, Sauvage reported an improved method by coupling two 5-bromo-2-TMSn-pyridine sides to a central 2,6-diiodopyridine. Stille reactions are generally worked up by extraction with potassium fluoride solution and filtration of the precipitate to bind the highly toxic trimethylstannyl halogenides. 53 can then be extracted with 15 % HCl; further purification by column chromatography is possible. It was found here, however, that direct filtration of the precipitate formed during the reaction prior to work up with KF also yielded a fraction of product; the solubility of 53 is quite limited.

Scheme 25. Synthesis of 4-functionalized pyridine 57 according to Lehmann.

A 4-functionalized central unit 57 was prepared according to Lehmann (Scheme 25). 2,6-Dihydroxypyridine-4-carboxylic acid is brominated with in situ generated phosphorous oxy chloride to give 54 and esterified to 55 prior to the reduction to pyridylmethanol 56. Lehmann coupled a variety of side chains to the alcohol function; here, by reaction of methoxyethoxymethyl (MEM) chloride in the presence of DIPEA, the MEM group was introduced, which served both as solubility enhancing side chain as well as protecting group for a hydroxy functionality and can be cleaved off later.

Besides dibromo functionalized terpyridine 53, Lehmann described the analogous synthesis of the dichloro, bis-TMS and bisboronic ester species. The yields in the coupling step varied considerably from 27 % for the dibromo to 61 % for the bisboronic ester species. To introduce substituents inert to Stille coupling conditions in 5 position, he made use of the selective lithiation of 49 described by Parham and Bolm. This regioselectivity is explained by a thermodynamic regime of the reaction. The 2-lithiated compound forms faster, but repulsion of the negative charge next to the free pair of electrons of the nitrogen
leads to rearrangement to the 5-lithiated species. Henze used this to prepare 2-bromo-5-iodopyridine 59 (Scheme 26).\textsuperscript{31} 49 was lithiated and stannylated to give 58, which can be purified by column chromatography without any problems; here, recrystallization proved to be ineffective as it does not remove the side product (probably bisstannylated compound). Iodo-de-stannylation with iodine led to 59. Henze could show that 59 under Sonogashira conditions selectively couples in 5 position. From an alternative route, which based on the introduction of a trimethylsilyl functionality and its subsequent iodo-de-silylation with ICl, he could not isolate the desired product 59.\textsuperscript{135}

![Scheme 26. Synthesis of ethynylated pyridine 61.](image)

Based on these results, the synthesis of bisethynyl terpyridine 63 was planned (Scheme 27). The influence of the ethynyl substituent in 61 on the yield of the terpyridine coupling was to be examined. Contrary to 53, the resulting terpyridine 63 can be used as the acetylenic partner in a Sonogashira coupling reaction. 61 was generated by Sonogashira coupling of 59 with TMS-acetylene and purified by column chromatography (Scheme 26). An attempt to purify this compound by recrystallization from methanol led to quantitative deprotection of the TMS group; besides 60, the biscoupled side product 60x could be isolated. Both compounds were separated by column chromatography, and 60 was further used. The Stille coupling of 52 with 61 gave terpyridine 62 in 70 % yield after chromatographic purification, which was a very encouraging result (ref. Lehmann's yields for different terpyridines, p. 27). Deprotection of the ethynyl groups gave 63 in excellent yield and purity, as can be seen from the $^1$H-NMR (Fig. 5). The characteristic singlet of the 18 protons of the silyl protecting groups in compound 62 ($\delta = 0.28$ ppm) has totally disappeared. The characteristic peak at $\delta = 3.3$ ppm can be assigned to the protons at the terminal acetylene
positions. This peak for acetylenic protons is very sharp and well separated throughout (ref. Figures 10, p. 47, and 13, p. 53) and allows an easy detection of terminal acetylenes. For a discussion of the $^1$H-NMR spectra of terpyridines, see Chapter 4.3.1.

Scheme 27. Synthesis of ethynylated terpyridine 63.

Fig. 5. $^1$H-NMR spectrum of compound 63 (270 MHz, $^*$ = CDCl$_3$, + = acetone).
Diiodo substituted terpyridine 67 (Scheme 28), which had not been described before, was expected to be a much more efficient coupling partner than bromo functionalized 53, e.g., for cyclization with precursor 91 (Scheme 40, p. 48). An unsuccessful attempt to generate 67 by iodo-de-silylation of bissilylated terpyridine with an excess of iodine chloride was described by Lehmann. He observed only partial reaction even after prolonged reaction times.

Scheme 28. Attempts to synthesize diiodo terpyridine 67.

Here, attempts were undertaken to generate 67 by two different routes, (i) the direct Stille coupling from an iodinated precursor 65, and (ii) the conversion of the bromo functionalities at terpyridine 53 into iodo. The question was for (i), whether 65 would react as selectively at its electron deficient 2-position with 52 as it was observed for bromo functionalized 49, or if the strongly activating iodo functionalities at both coupling positions would hamper this regioselectivity. For (ii), both the separation of 67 from starting material 53 and side products due to incomplete conversion and partial proto-de-stannylation of intermediate 66 could be a severe drawback. 66 was shown by Lehmann to partially decompose on the chromatography column and therefore had to be used as raw product.

First, the route via iodinated pyridine 65 was tried. As described by Yamamoto, from nucleophilic stannylation of 49, 64 was isolated as a sandy colored solid which could not be further purified, but was ca. 90 % pure according to NMR. Iodo-de-stannylation with iodine yielded 65, which could be purified by recrystallization from ethanol. An attempt to couple 52 and 65 according to the standard protocol yielded 36 % of a raw product. According to NMR, a considerable amount of unreacted 65 was still present, while the other signals are clearly not attributable to a major product, but show a mixture of different
4.2 Synthesis of the Building Blocks

products. In approach (ii), $53$ was stannylated nucleophilically to yield $66$, $^{27}$ which was further used as raw product. After reaction with iodine and work-up – which included filtration of the organostannanes precipitated with KF – only $8\%$ of raw product was isolated. Also here, the NMR signals revealed a mixture of compounds.

In both cases, the low amount of raw product isolated can only be explained by the low solubility of the major part of the reaction products in toluene. Work-up includes a filtration to isolate the highly toxic organostannyl halides, which are precipitated with KF, and the insoluble material is lost at this stage. Stimulated by the parallel findings for the synthesis of $53$ (see page 27), in another batch of route (i), the product mixture was filtered prior to application of KF. $69\%$ of a red-brownish material was isolated, which was partially soluble only in boiling pyridine or DMSO, but could be analyzed by mass spectrometry.

![Figure 6. EI mass chromatogramms (ion intensity versus temperature) for $67_n$ with $n = 1$ to 7. The integrated intensity values $I$ are given.](image)

In EI and FAB(+) measurements, signals were detected which could be assigned to a variety of diiodo oligopyridines $67_n$, $^1$I-$[C_5H_3N]_n$-$^1$I, with $n = 1$ ($= 65$) to $n = 9$, and fragmentation ions thereof. From diiodo terpyridine $67_3$ to diiodo heptapyridine $67_7$, the
elemental compositions were proven by high resolution MS. For a quantitative analysis of the
different oligomers, a sample was examined by a series of EI spectra at increasing
temperature. The resulting 3D set of data – the ion intensity as a function of both temperature
(of the measurement) and mass (of the detected ion) can be visualized by cutting into 2-D
plots for constant masses (Fig. 6). These mass chromatograms show ion intensities as a
function of temperature and can be interpreted as „chromatographic distillation“ protocol of
the specific oligomers. Integration (of intensity over temperature) gives approximate values
for their relative occurrence in the mixture. Besides starting material 65, diiodo(oligopyridine)s up to n = 5 prevailed. Of course, the connectivity of the pyridines in
the oligopyridines 67n remains unclear. Even if the result does not necessarily prove that
unselective coupling at both positions of 65 has taken place - all „undesired“ oligomers can be
explained by iodo-iodo or stannyl-stannyl homocoupling reactions - the high amount of side
products and the low solubility of the iodinated pyridines make this approach not feasible.

The incorporation of a flexible side chain could open access to diiodoterpyridine 69
with enhanced solubility (Scheme 29). 57 was therefore stannylated to 68 according to
Lehmann,27 which could not be further purified, but was rather used for the following steps as
an approx. 90 % pure material (NMR). 68 was coupled with two equivalents of 65. After
work-up and column chromatography of the raw product, unreacted starting material 57 and
36 % of unreacted 65 were isolated. Only 8 % of a mixture of products could be gained from
the chromatographic separation. As in the meantime the macrocycles with two terpyridine
units had been successfully prepared via a different route (ref. Chapter 4.3.3), investigations
into the generation of diiodo substituted terpyridines were not continued further.

\[
\begin{align*}
\text{Br} & \quad \text{OMEM} \\
\text{N} & \quad \downarrow \text{NaSn(CH}_3\text{)}_3 \\
\text{N} & \quad \text{Me}_3\text{Sn} \\
\text{Br} & \quad \text{OMEM} \\
& \quad \text{68} \\
\text{65, Pd}^0 & \quad \text{OMEM} \\
& \quad \text{69}
\end{align*}
\]

Scheme 29. Attempts to synthesize diiodoterpyridine 69 with a solubility enhancing side
chain.

4.2.3 Synthesis of the \textit{m}-terphenyl unit

Two new 4,4"-functionalized \textit{m}-terphenyls 74a and 74b were prepared (Scheme 30). In both cases, the central \textit{meta}-difunctionalized aromatic was coupled with two boronic acid
4.2 Synthesis of the Building Blocks

functionalized phenyl sides carrying a masked functionality in *para*-position, which was later transformed into a coupling functionality.

Scheme 30. Synthesis of terphenyls 74a and 74b.

Synthesis of the side ring starts from *p*-dibromobenzene 70 or 1,4-dibromo-2,5-di-*n*-hexylbenzene 76. The latter can be synthesized according to Rehahn via Kumada coupling\textsuperscript{136} of *p*-dichlorobenzene with hexyl bromide\textsuperscript{137,138} and selective dibromination in 2,5-position of
the resulting 75 to give 76. By monolithiation and silylation one of the bromo functionalities of 70 or 76 was transformed into TMS to give 71 or 77, resp., according to Lützow and Hensel.67,69 In a second lithiation step, the remaining bromo functionality was substituted by a boronic ester functionality to give 72 or 78, resp.67,69 These were coupled with the central rings 38b or m-dibromobenzene in a Suzuki cross coupling reaction. The resulting terpyridines 73a or 73b were obtained in good yield after purification by column chromatography. Iodo-de-silylation to 74a or 74b was quantitative; no traces of starting material was found in TLC. The 1H-NMR (Fig. 7) documents the symmetry of pure compound 74b, with the two intensive peaks at $\delta = 7.7$ ppm and $\delta = 7.0$ ppm being assigned to the four protons of the aromatic sides. The purity of 74b is demonstrated by the total disappearance of the signal for the 18 protons of the silyl protection groups of starting material 73b at $\delta = 0.36$ ppm.

![Fig. 7. 1H-NMR spectrum of compound 74b (270 MHz, * = CDCl3, + = H2O).](image)

The terphenyls can be expected to induce different properties into the envisaged macrocycles; 74a contains one hexyloxy side chain, whereas 74b with its four hexyl side chains should much more effectively promote solubility, but may on the other side also prevent the cycles from aggregation. The question was, whether the sterically demanding hexyl substituents in 74b ortho to the coupling functionalities would reduce yields in macrocyclization. The coupling reactions to terphenyls 73a and 73b, however, proceeded with comparable yields of 86 % and 81 %, resp.