4.3 Synthesis of the 46-membered Cycles

4.3.1 Attempt to close a cycle from a dibromo functionalized precursor

The most straightforward way to the envisaged structure A (Figure 3, p. 15) is by cyclization of two half rings of about the same size (ref. Scheme 15, p. 19). A bisethynyl and a dihalo functionalized precursor can be cyclized under Sonogashira conditions. Different strategies to build up these precursors were examined (i.e., Route 1 and 2, Scheme 16, p. 20).

**Synthesis of the ring precursors**

\[ 
\text{Scheme 31. Synthesis of half ring 80b via route 1.} 
\]

According to Route 1, the half ring is synthesized from an already existing terpyridine (Scheme 31). The bisethynyl functionalized terpyridine 63 was Sonogashira coupled with two equivalents of bromo functionalized 42b to give the silyl protected half ring 79. The isolated yield of the coupling reaction after chromatography over silica gel, however, was only 27-32 %. For different runs, amounts of 28-56 % of starting material 42b could be regained; no traces of unreacted 63 were found by TLC. The side products, which were more polar and remained on the starting line for TLC with hexane/ethyl acetate mixtures, were not analyzed. From other couplings between bromoaryls and acetylene, however, it is known that dimerization products of acetylenes can form.\(^{139a}\) It is not clear if this kind of oxidative side
reaction happens during the synthesis – which was performed under nitrogen – or during work-up.\textsuperscript{139b} When the above reaction is performed with the iodo functionalized precursor 46, the yield rises up to 84 % of pure 79. This was quantitatively deprotected to ethynyl functionalized half ring 80b.

Scheme 32. Synthesis of half ring 82 via route 2.

In another approach according to Route 2 (Scheme 16, p. 20), the pyridines were coupled in the final step to give the dibromo functionalized half ring 82 (Scheme 32). First, difunctional pyridine 60 was reacted with difunctional aromatic 34b; the Sonogashira coupling was selective regarding both the ethynyl and the iodo functionality, leaving the bromo substituents unaffected. The coupling product 81 was purified by column chromatography (74-82 %). Stille coupling of two equivalents of 81 with bistannylated central pyridine 52 yielded dibromo half ring 82 in isolated yields of 50-60 % after purification by column chromatography.

Bipyridine side product 82x, which results from the homocoupling of two molecules of 81, was separated from one batch (7 %, ref. to 81). All terpyridine couplings afforded a bipyridine side product, easily identified by its characteristic spot on the TLC, which is more strongly fluorescent, sharper, and at higher \( R_f \)-values than the largely smeared terpyridine
Fig. 8. $^1$H-NMR spectrum of compounds 82 and 82x (270 MHz, $\approx$ CDCl$_3$ (signal cut)).
spot. In some cases, the bipyridines were separated and characterized; yields of these side-products were generally around 10-20%.

The characteristic features of the $^1$H-NMR spectra of bi- and terpyridins are shortly described on the example of the compounds 82 and 82x; only the pyridine signals are considered here (Fig. 8). Terpyridine 82 shows an A$_2$B spin system (for H-3',4',5') and an ABC spin system (for H-3,4,6,3''',4''',6''). As expected from the resonance structure of pyridine, the doublet of H-6,6'' has the highest chemical shift with $\delta = 8.75$ ppm. The doublet of H-3,3''' is shifted to $\delta = 8.53$ ppm, and the doublet of H-3',5' to $\delta = 8.41$ ppm. These two signals show the strongest downfield change in shift compared to unsubstituted pyridine. This can be explained by a favorite trans,trans-conformation of the terpyridine. The protons H-3,3''' and H-3',5' are then especially influenced by the deshielding effect of the free pairs of electron on the nitrogen atoms. The doublet assigned to H-4,4''' and the triplet of the single H-4' overlay at $\delta = 7.87$ ppm. Bipyridine 82x shows an ABC spin system. Also here, the highest shifted signal with $\delta = 8.78$ ppm can be assigned to H-6,6', which is neighbored to the nitrogen atom. A doublet for H-3,3' appears at $\delta = 8.45$ ppm, and a doublet of doublet for H-4,4' at $\delta = 7.92$ ppm. Also here, the large change of shift for H-3,3' compared to pyridine can be attributed to a favored trans-conformation of the bipyridine.

\[ \text{Scheme 33. Attempts to transform bromo functionalized terpyridine compound 82 into iodo functionalized 83.} \]

Attempts to transform the bromo functionalities of 82 into iodo failed (Scheme 33). Lithiation of 82 with BuLi led to a dark solution; the supposed anion then was scavenged with diiodoethane. After work-up, only 50% of starting material was regained. Similar problems with extended terpyridine compounds and BuLi have been described by Lehmann. A strategy, which is only second choice due to its laborious chemistry and the highly toxic intermediates, but was successfully applied by Lehmann and Manickam for similar transformations on extended bi- or terpyridines, has also been tried here. The nucleophilic substitution of the halo functionalities in 82 with in situ generated sodium stannane, however, led to an inseparable mixture of products.
By Route 2 (Scheme 16, p. 20), also ethynyl functionalized half rings with different side chains were prepared (Scheme 34). Sonogashira coupling of 59 with ethynyl functionalized aromatics 45a-c gave 72-87 % of pure 84a-c after purification by column chromatography. Stille cross coupling of two equivalents of the substituted pyridine sides 84a-c with stannylated central pyridine 52 yielded the TIPS protected terpyridines 85a-c in yields varying from 45 % for 85c to 61 % for 85b. The terpyridines were purified by column chromatography from side products. In all cases, bipyridine side products could be observed (not shown in Scheme 34). For 85a and 85b, the bipyridines 85x (15 %) and 85y (22 %) were isolated and characterized. Cleavage of the TIPS protecting group to yield ethynyl half ring 80a-c was less efficient compared with TMS deprotection (Scheme 31); yields are around 80 %, and the purification of the half ring from TIPS-F by column chromatography is tedious.

\[ R \text{Br} \rightarrow R \text{TIPS} \]

**Scheme 34. Synthesis of half rings 80b-80c via Route 2.**

Additionally to the extended terpyridines, also a purely hydrocarbon half ring basing on the terphenyl unit was prepared (Scheme 35). Iodo functionalized terphenyl 74b was coupled with an excess of ethynyl functionalized ring corner unit 48 to yield the silyl protected half ring 86. Iodo-de-silylation with an excess of ICl in CHCl₃ at –30°C afforded only 43 % isolated yield of 87 after column chromatography. The remaining material
consisted mainly of unreacted 86 and TMS,I-functionalized intermediate product as revealed by MS. The reaction was obviously not complete; even though, product 87 was slightly contaminated with a small percentage of side products, as seen from the $^1$H-NMR. The MS revealed two side products at [M+Cl]$^+$ and [M+2Cl-2H]$^+$, which probably arise from chlorination of the $\alpha$-methylene groups. The characteristic peak at $\delta \approx 60$ ppm for the CHCl-carbon in the $^{13}$C-NMR spectrum, however, could not be detected, as the amount of side product was too small. This side reaction has been described by Lützow;69 by using the very same reaction conditions as were applied here, however, she had been able to oppress the chlorination. For the similar transformation of 73b into 74b, this side reaction was fortunately not observed (Scheme 30, p. 33).

Scheme 35. Synthesis of hydrocarbon half rings 86 and 87.

Cyclization

With 82 and 80b, a dibromo and a bisethynyl half ring precursor were available. The ring closure reaction to attempt macrocycle 88 was performed under Sonogashira conditions in an oxygen free TEA/toluene mixture with Pd[PPh$_3$]$_4$(=“Pd$^{0\text{th}}$)/Cul as catalytic system (Scheme 36).

For his phenylene ethynylene macrocycles, Moore reacted the precursors under “pseudo high dilution” conditions by inserting them with a syringe pump to a solution of the catalyst system over a long period of time.44 The injection speed is chosen in a way that the concentration of the precursors in the reaction mixture remains low and constant during the
reaction. For his bipyridine containing phenylene ethynylene macrocycles, Henze adopted Moore’s procedure but could not achieve satisfying results. Only when he omitted the syringe pump, i.e., brought the precursors to reaction directly together with the catalyst, he succeeded. In test runs, he compared the yields of cycle for different conditions and came to the following standard protocol: concentration of precursor: 0.0014 mol/l; catalyst concentration: 4 mol% Pd⁰/CuI; solvent: TEA/toluene 1:1; temperature: 60°C; reaction time: 4 days.

![Scheme 36. Attempted ring closure between 82 and 80b.](image)

Under adapted conditions, 82 and 80b were brought to reaction [for a test run, a high concentration of precursor (0.025 mol/l) was chosen to enforce reaction]. Work-up followed a standard protocol by Henze. The reaction mixture was extracted with an aqueous NaCN solution to bind the copper, which might complex the terpyridines. The phases were separated and the aqueous one extracted with dichloromethane. The combined organic phases were dried over MgSO₄, the solvent evaporated and the residue freeze-dried from benzene.

The raw GPC elution curve showed that practically all dibromo precursor 82 had remained unreacted, while the bisethynyl precursor 80b has reacted to oligo- or polymeric material (Fig. 9). These homocoupling reactions may be catalyzed by traces of Pd²⁺ which forms during work-up. The only peak, which could be assigned to the expected macrocycle 88, appeared at a retention time of 14.4 min, Mₚ = 2249. It is obviously not monodisperse, as can be seen from the dominant shoulder in the GPC curve (ref. Chapter 4.3.2 for a discussion of GPC, and Chapter 4.3.4 for a GPC of the successful approach towards 88). For a different catalyst/solvent system – Pd⁰ without cocatalyst in a 1:1 pyrrolidine/toluene mixture – this peak was likewise small.
4. General Part

Fig. 9: GPC trace of the soluble part of the raw product of the reaction of 82 and 80b (Scheme 35).

The macrocyclization by Suzuki-coupling was shown by Hensel to proceed with dramatically higher yields when reacting an iodo instead of a bromo functionalized halide precursor. Even with an improved catalytic system, he was not able to improve the yields for the bromo-macrocyclization. Among the large number of shape-persistent macrocycles which can be found in the literature over the past four years, to my knowledge only one example is cyclized from a bromoaryl precursor under Sonogashira conditions. Parallel to the work presented here, Henze failed in synthesizing his bipyridine macrocycles (Scheme 12, p. 14) from a bromo precursor under Sonogashira couplings, while he succeeded with analog iodo precursors. For all this, it seemed not promising to further try to close the cycles from bromo functionalized precursors. Even if a range of new and more potential Pd$^0$ catalysts awaits to be tested for the macrocyclization of the above precursors, alternative strategies via an iodo functionalized half ring seemed more promising. First attempts aiming at those structures have been shown in this chapter; two successful alternative strategies towards a final cyclization step from an iodo and an ethynyl precursor will be described in the next chapter.

4.3.2 Cycles containing one terpyridine unit

The synthetic principle here bases upon ring closure from one “large” and one “small” precursor (Scheme 37). The “small” one can be an easily accessible diiodo terphenyl. The other, “large” one, is an extended terpyridine. Also here, two retrosynthetic routes can be distinguished, where the half ring is either built up on the existing terpyridine (Route 1), or, the terpyridine unit is generated last in the synthesis (Route 2; ref. Scheme 16, p. 20).
**Synthesis of the ring precursors**

Coupling of dibromoterpyridine 82 with an excess of ethynyl functionalized corner 45b according to Route 1 yielded product mixtures of one- and twofold coupling product 89b and 89m besides homocoupling butadiyne product 89n and unreacted starting material 82 (Scheme 38). The separation of these products by repeated column chromatography proved to be extremely tedious.

**Table 1. Yields of product 89b and side product 89m for different reaction conditions (to Scheme 38).**

<table>
<thead>
<tr>
<th>solvent</th>
<th>catalyst</th>
<th>89b</th>
<th>89m</th>
<th>82</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEt3/toluene</td>
<td>[Pd] / CuI</td>
<td>49–55 %</td>
<td>42–46 %</td>
<td>3–5 %</td>
</tr>
<tr>
<td>DIPA/toluene</td>
<td>[Pd]</td>
<td>45 %</td>
<td>49 %</td>
<td>6 %</td>
</tr>
<tr>
<td>propylamine</td>
<td>[Pd]</td>
<td>63 %</td>
<td>8 %</td>
<td>29 %</td>
</tr>
</tbody>
</table>

Therefore, the composition of the raw product for different reaction conditions was examined by analytic GPC (Table 1). In each case, the solvent of the reaction mixture was removed, the residue dissolved in dichloromethane, washed with water, and dried. Obviously, the samples still contained varying amounts of solvents; the GPC values could therefore not be correlated to the raw yields in mass. Instead, the numbers quoted in Tab. 1 were calculated under the assumption, that all starting material 82, which has been consumed during the
reaction, has been reacted to 89b or 89m, i.e., no other (terpyridine-) side products were formed. While for the standard conditions using triethylamine/toluene mixtures, nearly equal amounts of mono- and biscoupled product were formed, these values were only slightly less favorable for a solvent mixture of DIPA/toluene. For propylamine as solvent, biscoupled product 89b prevailed over 89m, while 29 % of the starting material 82 remained totally unreacted. This astonishing result, for which I have no explanation, suggests that the two bromo functionalities of 82 in this case do not react independently from each other, i.e., statistically like for the other conditions. It is not clear, whether detailed investigation into this reaction could bring up conditions, under which the yield of 89b can be driven to completion. The synthetic approach via Route 2 (Scheme 40), but also via an alternative Route 1 (Scheme 39), proved to be more effective here.

In this alternative Route 1, the functionalities were switched, i.e., a bisethynylterpyridine and a halobenzene unit were coupled. Sonogashira reaction of bisethynylterpyridine 80b with iodo functionalized corner 46 gave TMS protected half ring 90 in 60 % yield (Scheme 39). Deprotection under basic conditions led to ethynyl functionalized terpyridine telechel 91b.
In the strategy according to Route 2, first one halo- and one ethynyl functionalized corner, 42/46 and 45, are Sonogashira coupled to give compound 92, which can be deprotected by selective cleavage of TMS under basic conditions to 93 (Scheme 40). While this deprotection is quantitative – 93 usually was simply purified by extraction with ether – yields for the coupling range from 63 % (for 92c, which was, however, only prepared once) to 88 % (for 92b). Purification was by column chromatography, with hexane for phenyl ether derivative 92b, and hexane/toluene mixtures for benzyl ether derivatives 92a and c. A further Sonogashira coupling of 93 with difunctionalized pyridine 59 was selective at iodo and yielded 94 in yields from 80 % (for 94a) to 93 % (for 94c). Stille coupling of 2 equivalents of 94 with bistannylated pyridine 52 gave the TIPS protected half ring 89. The yields varied between different batches; generally, numbers of around 40 % were achieved. In all cases, bipyridine side products were observed. From the purification of 89a and 89b, bipyridines 89x and 89y were isolated and characterized. Cleavage of the TIPS groups from 89 gave half rings 91. The efficiency of the deprotection is demonstrated by the complete disappearance of the signal for the 42 (!) protons of the silyl protection groups of precursor 89a at $\delta = 1.12$ ppm. (Fig. 10).
Scheme 40. Synthesis of half ring 91b via Route 2.
4.3 Synthesis of the 46-membered Cycles

**Cyclization**

The ring precursors were brought to reaction according to the protocol described in Chapter 4.3.1 (Scheme 41). After work up – in all cases, the residue was completely soluble in dichloromethane -, the crude product was examined by analytic GPC. The result for the very first cyclization of this series, which was done with the precursors \(74a\) and \(91b\) (Fig. 11), shows two distinct signals at retention times of ca. 13.5 and 14.5 minutes, and higher molecular species between 10-13 min. The peak at ca. 20.5 min. belongs to the toluene standard. The fractions represented by the two sharp signals were isolated by preparative GPC. By NMR and mass spectrometry, they were interpreted as the desired cycle \(95b\) and a cyclic side product \([95b]_2\) with double mass. Their real molar masses, 1409 and 2818 Dalton, are significantly lower than those assigned to the according peaks in the GPC, 2620 and 4434 Dalton, resp. This discrepancy can be explained by the rigidity of the cycles. Different from polystyrene, which is used as calibration standard for the GPC, the phenylene ethynlenes cannot adopt randomly coiled conformations; their hydrodynamic volume is larger and therefore pretends a higher molar mass.\(^7^0\)

Likewise, cycle \(95a\) from \(74a\) and \(91a\), \(95c\) from \(74a\) and \(91c\), and \(95d\) from \(74b\) and \(91a\) were prepared. Yields, which were calculated from GPC under consideration of the amount of raw product, are compared with isolated yields (Table 2). In the cases here, the
GPC values are generally considerably higher than the yields of the isolated products. This, however, does not inevitably hint at losses during separation by preparative GPC. It has to be noted that the GPC yields are calculated from the peak integrals, which are detected by UV light with a wavelength of 280 nm. Different extinction coefficients of compounds therefore make it impossible to compare these values otherwise than relatively.

\[ R^1 = R^2 = \text{OC}_6\text{H}_{13} \]
\[ R^1 = R^2 = \text{CH}_2\text{OC}_6\text{H}_{13} \]
\[ R^1 = \text{CH}_2\text{OTHP}, R^2 = \text{CH}_2\text{OC}_6\text{H}_{13} \]

Scheme 41. Synthesis of 46-membered cycles 95a-d with one terpyridine unit.
4.3 Synthesis of the 46-membered Cycles

Fig. 11. GPC traces of the raw product of the cyclization to 95b (top), of isolated [95b]2 (middle) and 95b (bottom; ref. Scheme 41).

Table 2. GPC and isolated yields of cyclization (to Scheme 41).

<table>
<thead>
<tr>
<th>cycle</th>
<th>GPC yield</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>95a</td>
<td>42 %</td>
<td>21 %</td>
</tr>
<tr>
<td>95b</td>
<td>35 %</td>
<td>21 %</td>
</tr>
<tr>
<td>95c</td>
<td>29 %</td>
<td>18 %</td>
</tr>
<tr>
<td>95d</td>
<td>25 %</td>
<td>14 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>cycle</th>
<th>GPC yield</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>[95a]2</td>
<td>17 %</td>
<td>9 %</td>
</tr>
<tr>
<td>[95b]2</td>
<td>22 %</td>
<td>12 %</td>
</tr>
<tr>
<td>[95c]2</td>
<td>18 %</td>
<td>5 %</td>
</tr>
</tbody>
</table>
The yields are lowest for 95d. Diiodo precursor 74b carries voluminous hexyl side chains neighbored to its coupling functionalities. The lower cyclization yields for 95d may be due to this steric hinderance, in that the geometry of the functionalities in the last of the two coupling steps, which is yet restricted by the connectivity of the two functionalities, becomes even more hindered, and intermolecular couplings to oligomers gain importance.

### 4.3.3 A cycle with two terpyridine units

Scheme 42. Synthesis of 46-membered cycle 88 with two terpyridine units.

Schmittels strategy to prepare his diiodo functionalized half ring 10 based upon the statistic coupling reaction between the diethynyl precursor 11 and a large excess of diiodo functionalized aromatic (Scheme 5, p. 8).\(^5^8\) By this, he could circumvent the standard methods to transform a placeholder group into an iodo functionality, which have proved problematic in the case of extended bi- or terpyridine ring precursors (see, e.g., Scheme 33, p. 38, and
4.3 Synthesis of the 46-membered Cycles

The synthetic pathway towards macrocycle 88 rests on a similar strategy to gain diiodo half ring 97 from the coupling reaction of ethynyl functionalized 63 and an excess of diiodo functionalized ring corner module 96 (Scheme 42). Compound 96 was prepared according to Lehmann by twofold lithiation of 34a in ether/THF, scavenging of the anion with trimethylsilyl chloride, and subsequent treatment with iodine chloride. From the coupling with 63, the raw product was easily purified by column chromatography over aluminium oxide to afford 60 % of product 97; 78 % of unreacted 96 could be regained.

Fig. 12. GPC trace of the raw product of the cyclization to 88 (Scheme 42). The compounds 88 and [88]2 could be separated by preparative GPC and gave clean traces (not shown).

Cyclization of 97 and 80a under standard conditions afforded a raw product which showed a GPC trace (Fig. 12) similar to those observed for the cycles with one terpyridine unit (Fig. 11). By preparative GPC, two macrocyclic compounds, the expected macrocycle 88 and the higher mass cyclic oligomer [88]2 were separated [88: 25 % (GPC), 27 % (isolated); [88]2: 16 % (GPC), 6 % (isolated)]. While 88 precipitated microcrystallinic after separation and was difficult to characterize, [88]2 was well soluble.