4.4 Synthesis of the 58-membered cycles

The objective to open access to a second, larger set of terpyridine containing macrocycles arises from the interest into examining the influence of size on the accessibility as well as properties of the cycles.

Moore showed that the cyclization of the 30-membered phenylacetylene $5$ (Scheme 3, p. 5) and a structurally closely related 66-membered macrocycle (not shown) proceeds in yields of 75 % and 70 %, respectively. Indeed, there does not seem to be a general trend of the yields depending on ring size in the literature. For example, the largest ring prepared in our group so far, a 90-membered macrocycle consisting of 24 phenylene units, has been prepared in a yield of 68 %. It should be noted, however, that the structures cited do not contain any functionalities or heteroatoms, and were ring-closed from a single precursor. For heteroaromatic cycles, there is a tendency to form in lower yields than hydrocarbon ones. The main reason for that, however, is probably the simple fact that synthetic access to unsymmetrically functionalized precursors which allow an efficient single-step cyclization is much more difficult for heteroaromatics, and ring closure normally has to be done from 2 or even more precursors. The largest shape-persistent macrocycle prepared so far, 144-membered structure $21$ (Scheme 8, p. 10) with 6 porphyrine subunits, was prepared in 8–30 % yield. As the amounts reported were in the 1 mg-range, there is some uncertainty associated with the correct determination of these yields, though.

From the above, one can assume for the accessibility of the envisaged set of macrocycles: (i) For the cyclization step alone, one may expect yields in the line of what has been observed for macrocycles of type $95$; (ii) The handling of the extended terpyridines becomes probably more difficult with increasing size, especially as far as purification is concerned. Manickam made the experience that the chemistry of functional groups (e.g., the stability of boronic acids) is influenced by the size of the compounds, when he tried to extend Lehmann's set of terpyridine ring precursors by larger analogs; (iii) Characterization of the macrocycles, but possibly also cyclization yield, may be affected by size related phenomena like poor solubility or aggregation. Manickam had to encounter severe drawbacks when trying to furnish Lehmann's terpyridine macrocycle by larger analogs. Here, macrocycle $88$ proved to be considerably less soluble than Lehmann's structurally related, but smaller cycle $26$ (Scheme 11, p. 13).
4.4 Synthesis of the 58-membered Cycles

4.4.1 A cycle with one terpyridine unit

The synthetic strategy for macrocycle 106 (Scheme 43) rests upon the one developed before for macrocycles 95 (ref. Scheme 37, p. 43), i.e., ring-closure from a "small" terphenyl and a "large" terpyridine precursor. While the terphenyl precursor is exactly the same as used for 95, a larger, "47-membered" extended terpyridine half ring 105 was coupled. 105 was built up by a strategy similar to what in previous chapters had been described as Route 2, i.e., with the terpyridine unit formed in the last coupling step. The main reason for this approach was, that it would also allow an investigation into the accessibility of larger extended terpyridines. If a compound of a size like 105 was synthesized and purified well, one could suppose - according to what has been said above - that macrocycles with over 90 ring members from precursors which are similar to 105 but have a different geometry would be synthetically accessible.

1-Bromo-4-TMS-ethynylbenzene 98 was prepared according to Henze. The other steps of synthesis are straightforward and comparable to those depicted in Scheme 40 (p. 46). The yield of 41 % for the twofold Stille coupling to terpyridine 104 is in the range of what has been observed for the smaller terpyridines 89. The purity of the deprotected half ring 105 can be seen from its 1H-NMR (Figure 13).

![Figure 13. 1H-NMR spectrum of compound 105 (270 MHz, * = CDCl3).](image)

The cyclization reaction of precursors 105 and 74b was done according to the standard procedure. The GPC trace of the raw product mixture (Fig. 14) is similar to those observed for the smaller cycles with one or two terpyridine units (Fig. 11/12, p. 49/51). By preparative
Scheme 43. Synthesis of 58-membered macrocycle 106 with one terpyridine unit.

GPC, two macrocyclic compounds, the expected macrocycle 106 and the higher mass cyclic oligomer \([106]_2\) were separated. Yields calculated from GPC are comparable to those of the smaller cycles described before, the isolated yields, however, are somewhat lower. The reason
for this is not clear, as both compounds are well soluble in a wide range of solvents like CHCl₃ or toluene. 106: 32 % (GPC), 18 % (isolated); [106]₂: 19 % (GPC), 9 % (isolated).

![Fig. 14. GPC trace of the raw product of the cyclization of 74b and 105 (Scheme 43). The compounds 106 and [106]₂ were separated by preparative GPC and gave monomodal traces (not shown).](image)

4.4.2 Cycles with two terpyridine units

**Synthesis of the ring precursors**

By the successful synthesis of macrocycle 106 it was shown that the envisaged 58-membered macrocycles are principally accessible, at least as far as the handling of the extended precursors and the cyclization reaction itself are concerned. The impact of the cycles' size on their properties is a further aspect which has to be considered. 46-membered macrocycle 88 with 2 terpyridine units is considerably less soluble than macrocycles 95 with only one terpyridine (for a discussion, see Chapter 4.6.1). It was the question, whether the envisaged macrocycle 110a with 2 terpyridine units (Scheme 45) would be even less soluble due to its more extended shape-persistent backbone compared to macrocycle 88, while having the same number of side chains, or if 110a would be better soluble due to the inherent flexibility of the backbone increasing with size. For this, macrocycle 110c with a larger number of flexible side chains was parallely projected. However, the influence on cyclization yield of the proximity of the hexyl side chain to the iodine functionality in precursor 109b (Scheme 44) had to be taken into consideration; a similar effect was observed before for macrocycle 95d (Scheme 41, p. 48).
Hensel described the synthesis of diiodo compound 108 in two steps from 76 via lithiation, silylation and iodo-de-silylation (Scheme 44). By a strategy similar to that described for macrocycle 88 (Scheme 42, p. 50), the diiodo half rings 109a and 109b were prepared. Yields are around 60 %, and their purification by column chromatography over aluminium oxide was unproblematic. Besides the products, the iodo functionalized reactants, which were applied in a large excess, could be mostly regained (diiodobenzene: 94 %, 108: 89 %). Both half rings 109a and 109b were fully characterized; their purity can be seen from the 1H-NMR (Fig. 15).
4.4 Synthesis of the 58-membered Cycles

Fig. 15. $^1$H-NMR spectrum of iodo half ring 109a (270 MHz, * = CDCl$_3$)

Cyclization

Scheme 45. Cyclization of 58-membered macrocycles 110a-c with two terpyridine units.
The ring precursors were reacted under the standard reaction conditions described before for cyclizations to give the three macrocycles 110a-c (Scheme 45). Their backbones are equal, while the cycles differ, however, in their side chain pattern. 110a carries 4 ether bound hexyl groups, 2 of which are replaced by THP protecting groups in 110b. Thus, the symmetry of 110b is lowered with respect to 110a, while further chemical modifications on the existing macrocycle are possible by cleavage of the THP groups. 110c carries 8 alkyl side chains altogether.

<table>
<thead>
<tr>
<th>cycle</th>
<th>GPC yield</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>110a</td>
<td>19-22 %</td>
<td>Ca. 11 %</td>
</tr>
<tr>
<td>110b</td>
<td>25 %</td>
<td>19 %</td>
</tr>
<tr>
<td>110c</td>
<td>12 %</td>
<td>11 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>dimer</th>
<th>GPC yield</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>[110a]₂</td>
<td>13-16 %</td>
<td>Ca. 6 %</td>
</tr>
<tr>
<td>[110b]₂</td>
<td>17 %</td>
<td>13 %</td>
</tr>
<tr>
<td>[110c]₂</td>
<td>13 %</td>
<td>6 %</td>
</tr>
</tbody>
</table>

Table 3. Yields of cyclization according to GPC and isolated yields (to Scheme 40).

For all three reactions, the desired cyclic products and one higher cyclic oligomer were separated by GPC (Fig. 16). 110c is soluble in common solvents – this was expected due to its high number of flexible side chains - and no problems in separation were observed. This was different for 110a and 110b. The inherently lower solubility of these structures is expressed by the low yield of raw product (i.e., prior to GPC) of ca. 60 %; a considerable amount of material is accordingly lost during work-up, which includes filtration. It has to be noted that the yield of raw product is generally taken into account when calculating the GPC yield of macrocycle from the chromatogram. These yields according to GPC (Table 3) are in the order of what had been observed for the 46-membered analogue 88, but slightly lower than those for the cycles with one terpyridine unit. As also 88 is poorly soluble, one could conclude that in all cases where cycles with 2 terpyridine units were prepared, material was lost due to the low solubility of these materials. The equally low GPC yield for better soluble 110c is not in contradiction to this, as the cyclization reaction may be sterically hindered here (see above). This is backed by the observation that of a total of 3 ring closure batches only one gave 110c in a sufficient yield. Of course, it is highly speculative to reason about different influences of cyclization efficiency and solubility on yield, as both effects may play together, e.g., when the linear dimer of the half rings is too insoluble to cyclize in solution. The observations during preparative GPC, however, clearly show that the low yields in isolated product especially for 110a can be attributed at least partially to the low solubility of the material. During the course of 2-3 hrs, material A precipitated from the solution of the raw product (Fig. 17, top). This
was collected, and could be brought into solution again. Its GPC (Fig. 17, middle) revealed that it was enriched with cyclic material. Also from the solution of A, which was likewise separated by preparative GPC, material precipitated (B), was collected and could be dissolved again. Its GPC (Fig. 17, bottom) showed a further enrichment of 110a with respect to A. However, the precipitate still contained a mixture of products in all cases. The pure compound 110a (according to GPC) could only brought into solution in very low concentrations.

Fig. 16. GPC traces of the raw product of the cyclization to 110a (top), of isolated [110a]$_2$ (middle) and 110a (bottom). Ref. Scheme 45.
Fig. 17. GPC traces of the raw product of the cyclization to 110a (top; here, the result for a different batch is shown than in Fig. 16), of the collected precipitate A from preparative GPC of the raw product (middle), and of the collected precipitate B from preparative GPC of A (bottom). Please note that the peaks for 110a were too intensive for the detector and therefore cut (middle and bottom). Ref. Scheme 45.