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.[44,107] 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 %.[72] 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.[63,64] 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 accessability 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;[34,35] (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).

4.4.1 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.[31] 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 ^{1}H-NMR (Figure 13).

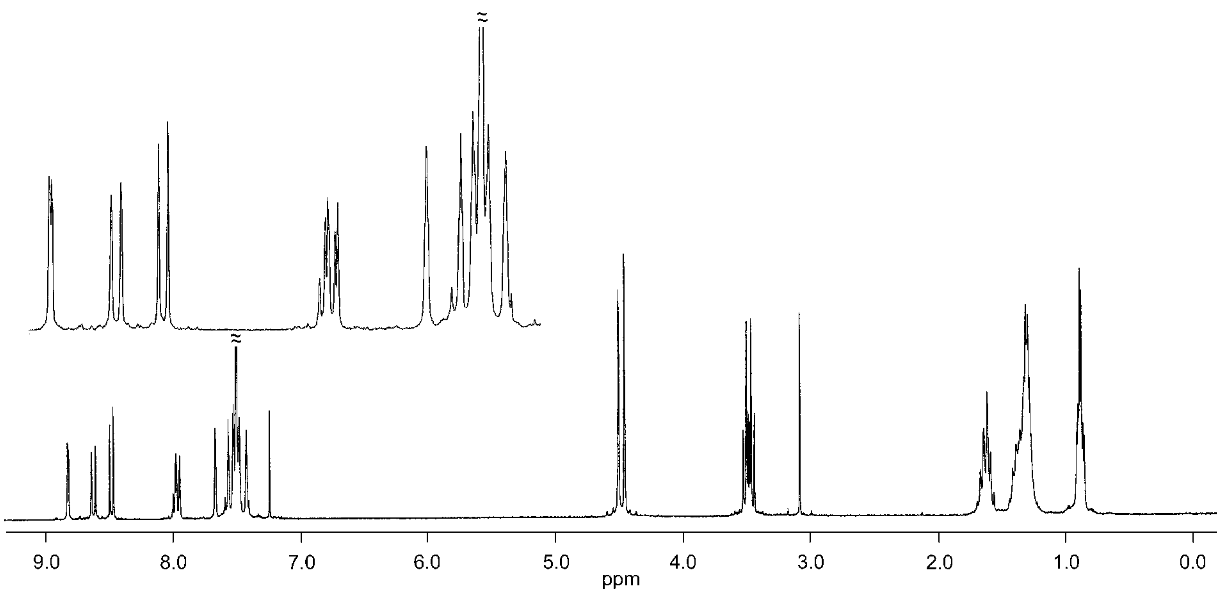
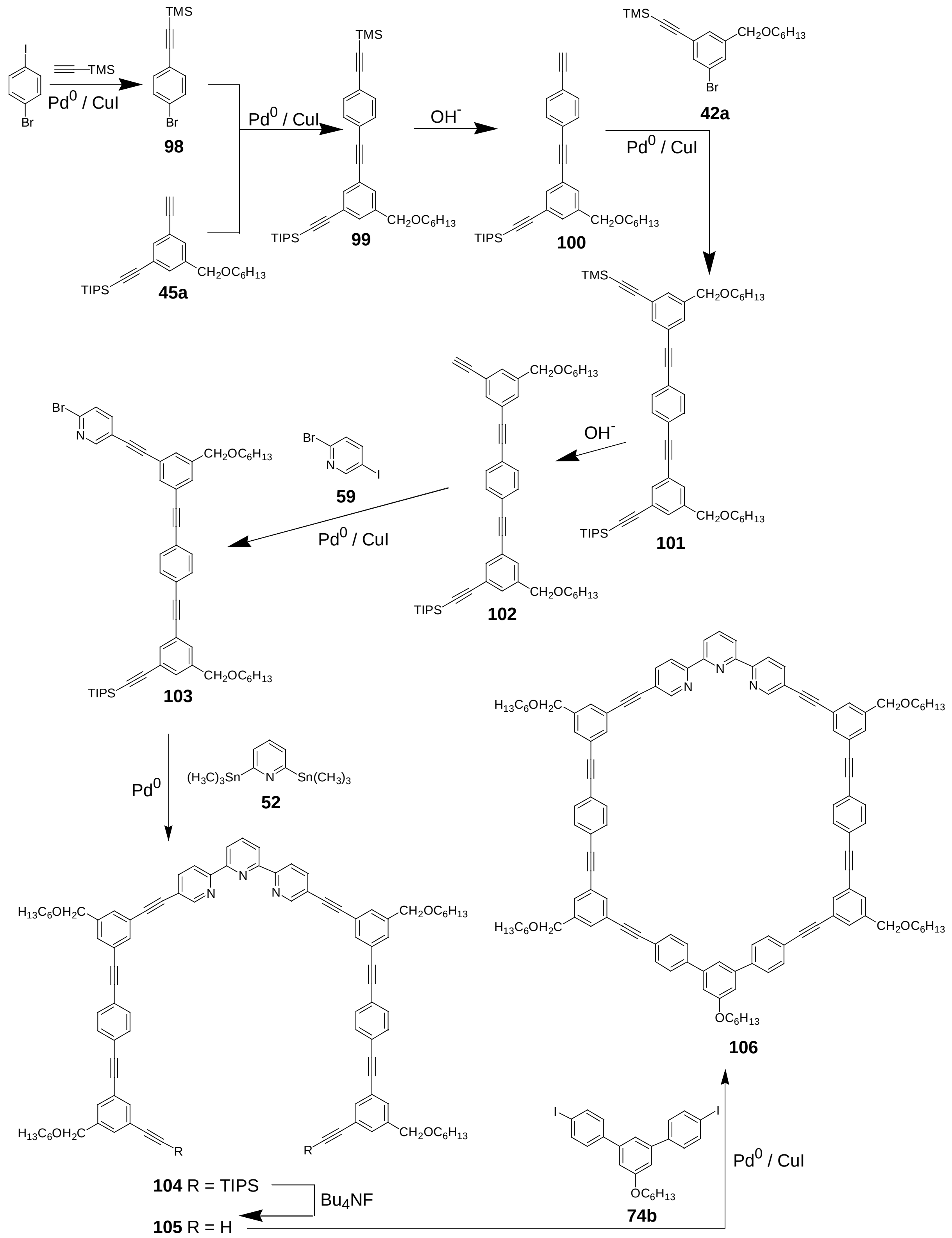


*Fig. 13. ^{1}H-NMR spectrum of compound **105** (270 MHz, * = $CDCl_3$).*

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 $CHCl_3$ or toluene. **106**: 32 % (GPC), 18 % (isolated); **[106]$_2$**: 19 % (GPC), 9 % (isolated).

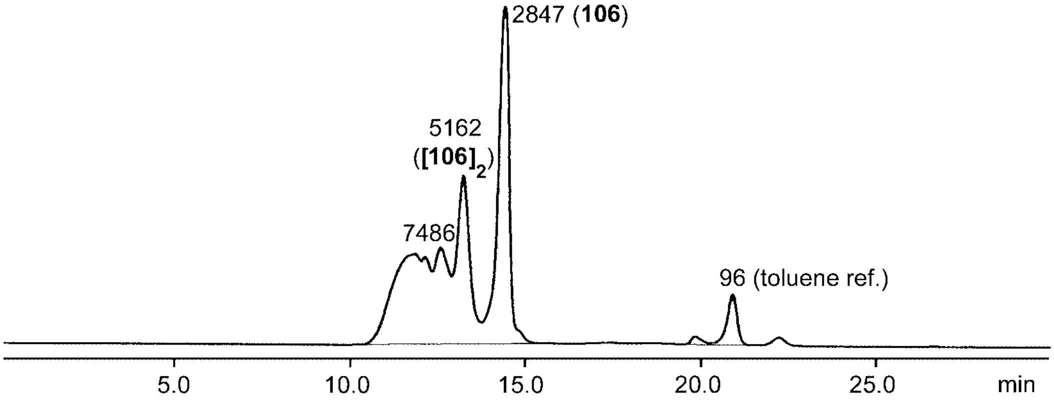
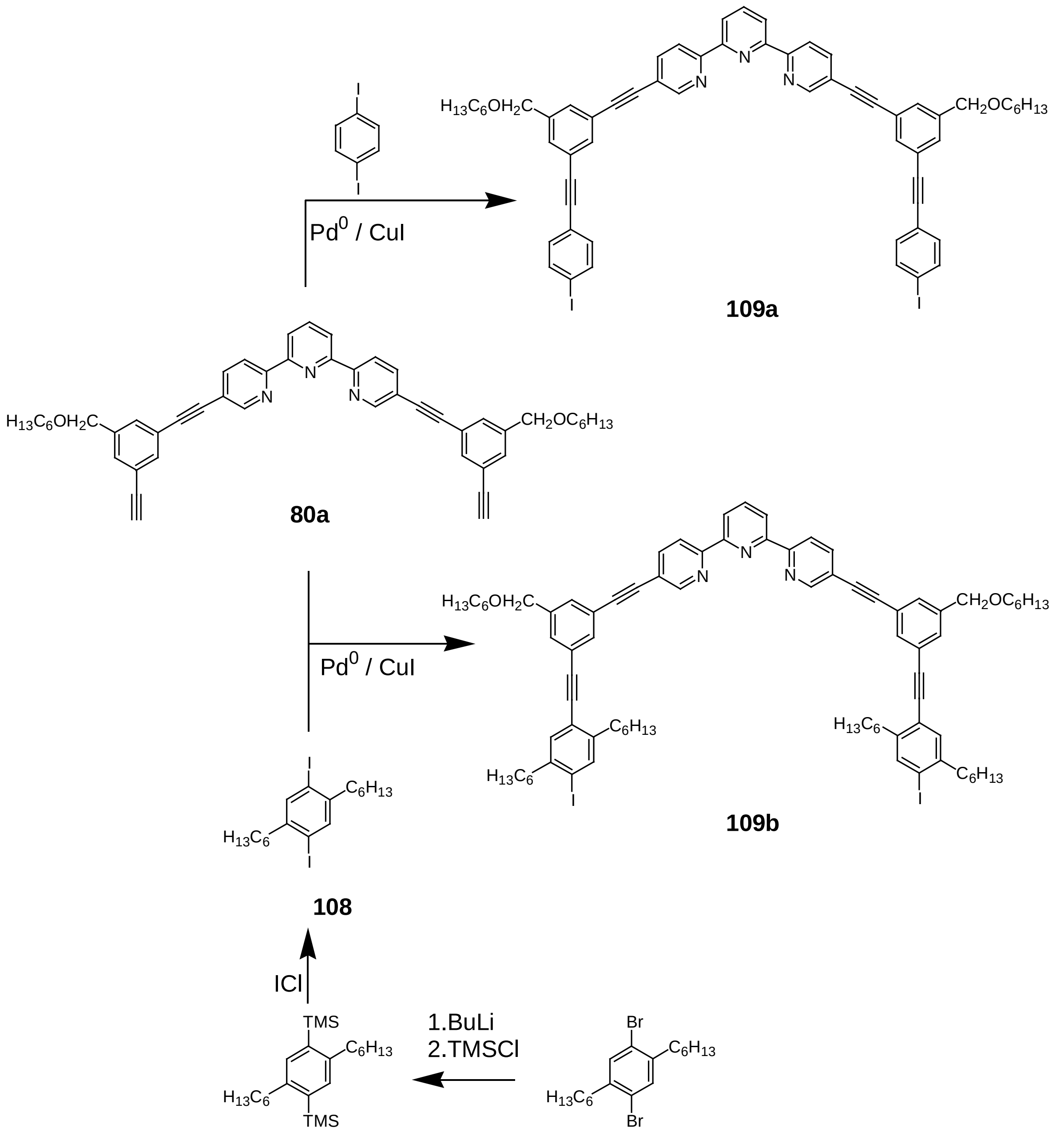


*Fig. 14. GPC trace of the raw product of the cyclization of **74b** and **105** (Scheme 43). The compounds **106** and **[106]$_2$** were separated by preparative GPC and gave monomodal traces (not shown).*

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).



Scheme 44. Synthesis of half rings ***109a*** *and* ***109b*** *via Route 1.*

Hensel described the synthesis of diiodo compound **108** in two steps from **76** via lithiation, silylation and iodo-de-silylation (Scheme 44).[70] 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 ^{1}H-NMR (Fig. 15).

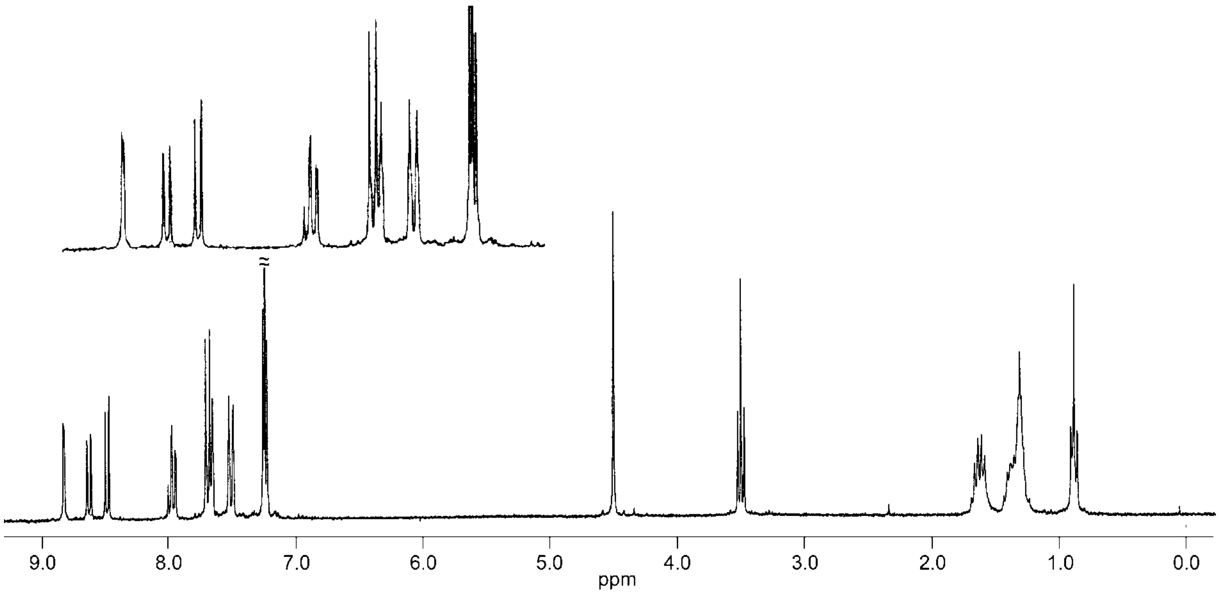
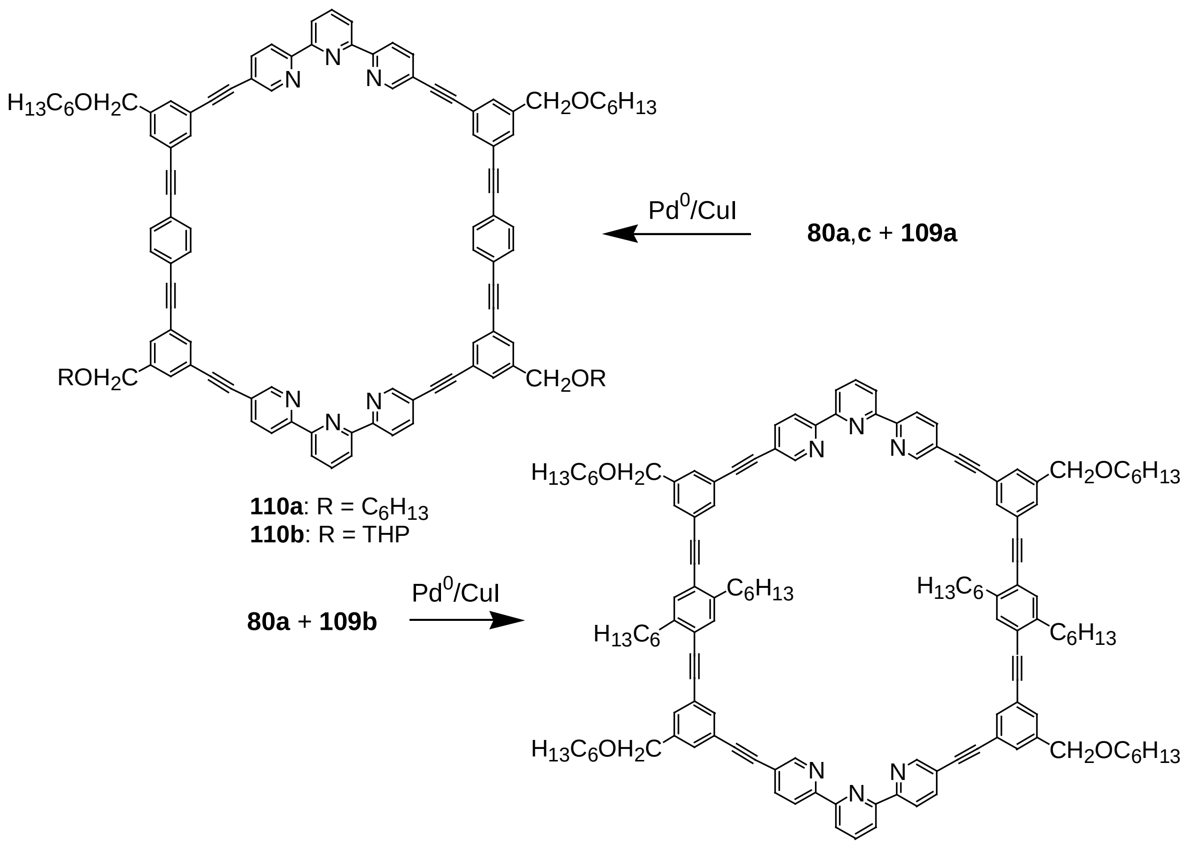


*Fig. 15. [1]H-NMR spectrum of iodo half ring **109a** (270 MHz, * = $CDCl_3$)*

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

cycle	GPC yield	Isolated yield
110a	19-22 %	Ca. 11 %
110b	25 %	19 %
110c	12 %	11 %

dimer	GPC yield	Isolated yield
[110a]$_2$	13-16 %	Ca. 6 %
[110b]$_2$	17 %	13 %
[110c]$_2$	13 %	6 %

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.

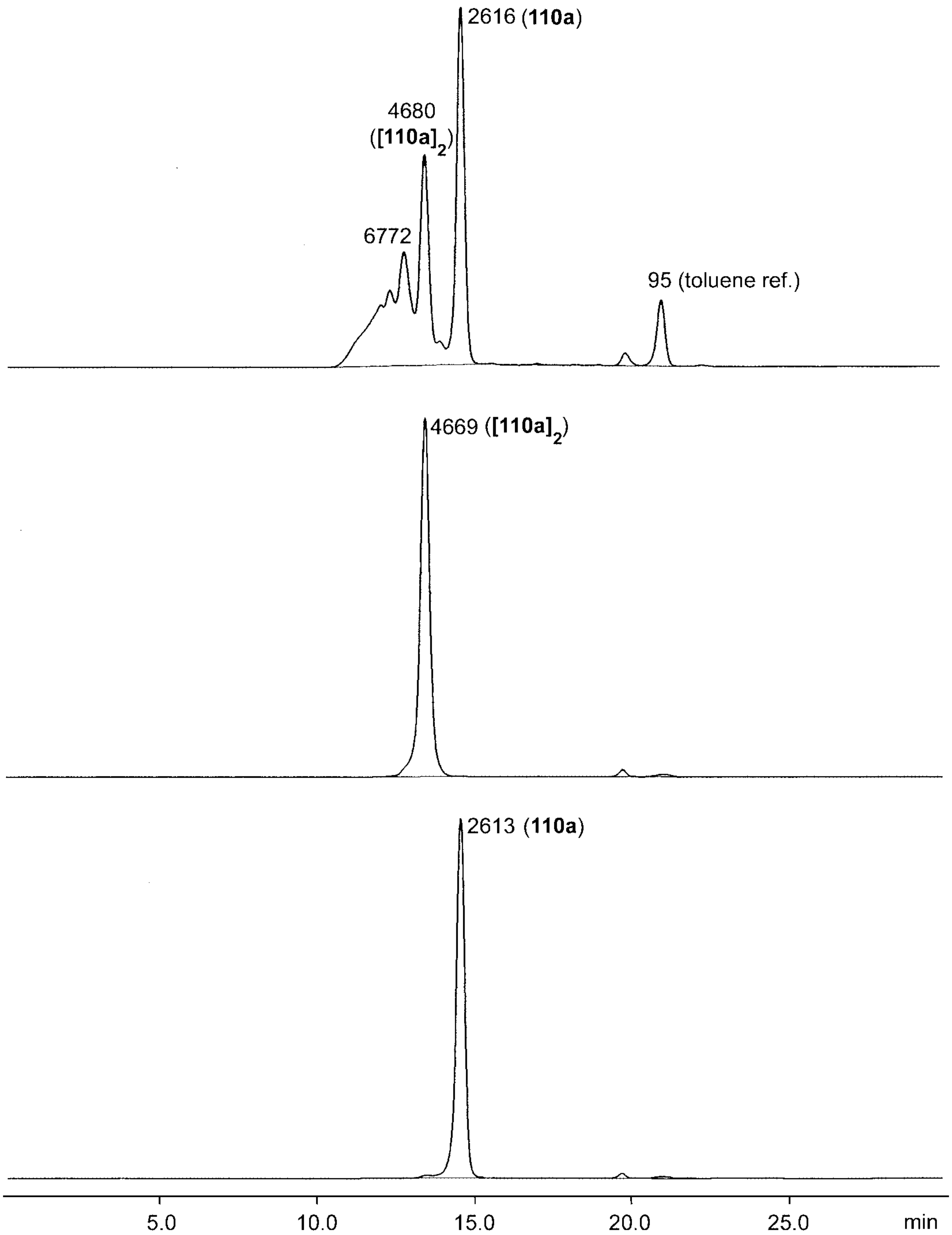


*Fig. 16. GPC traces of the raw product of the cyclization to **110a** (top), of isolated **[110a]$_2$** (middle) and **110a** (bottom). Ref. Scheme 45.*

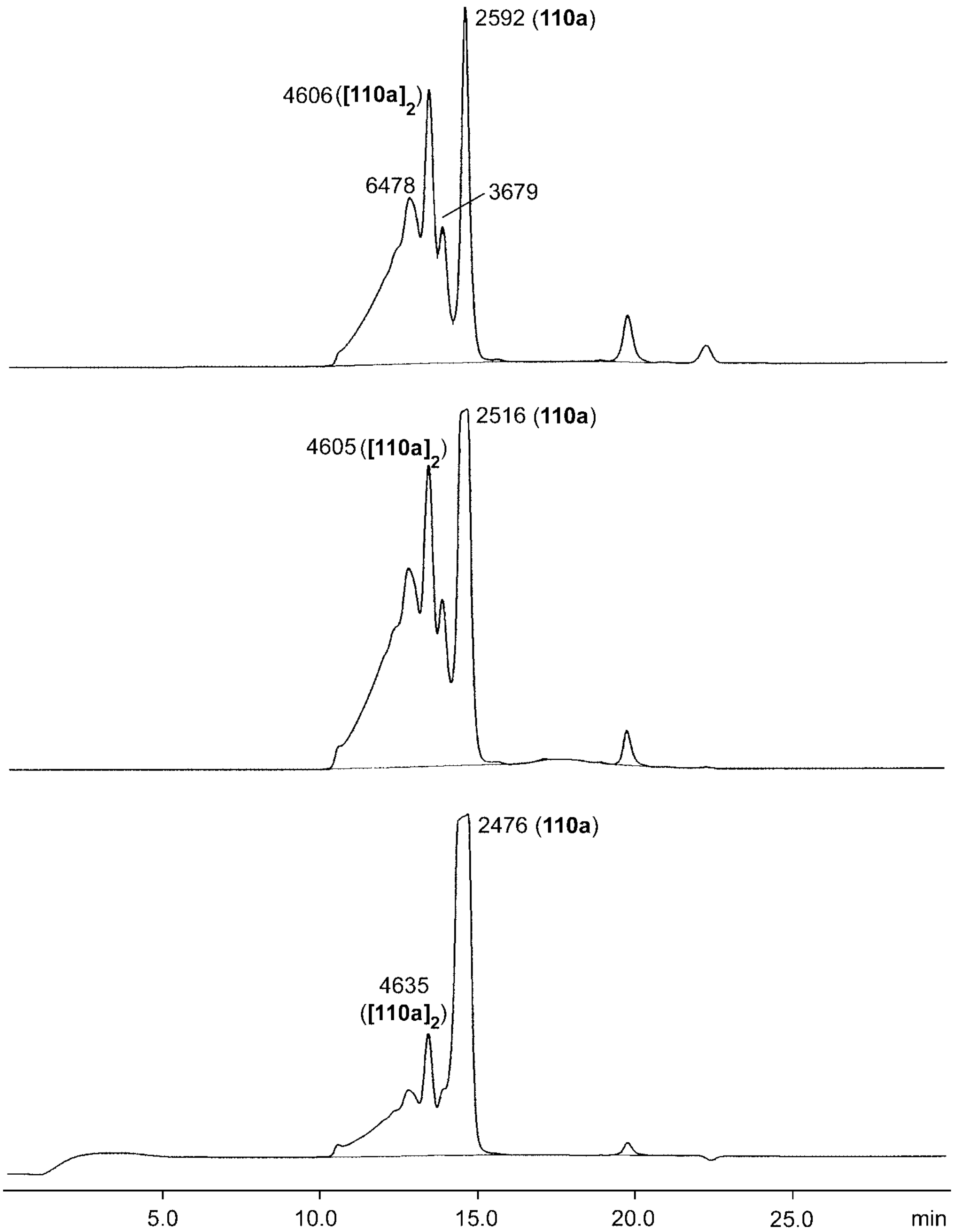


*Fig. 17. GPC traces of the raw product of the cyclization to **110a** (top; here, the result for a different batch is shown than in Fig. 16), of the collected precipitate **A** from preparative GPC of the raw product (middle), and of the collected precipitate **B** from preparative GPC of **A** (bottom).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