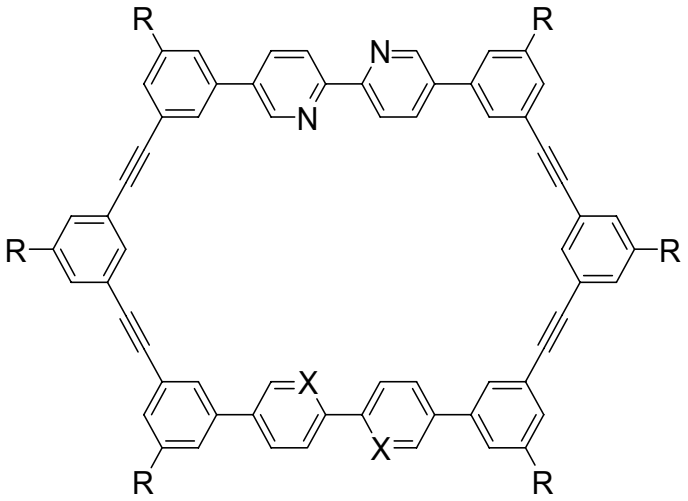
4. General part

4.1. Retrosynthetic analysis of cycle synthesis

The macrocycle **E** (Figure 27) has in its backbone only sp and sp^2 hybridized atoms which provide it with a rigid frame and a defined interior and exterior. It contains one or two bipyridine units which can be used for complexation with transition metals. The macrocycle has in its corners the six substituents R which serve mainly two purposes: mediate sufficient solubility and allow, depending on their chemical nature, for further functionalization of the already existing cycle. This latter point is important because it allows to modify and decorate the cycle in its final state, thus, avoiding to have to carry all different substituents through the entire sequence leading to cycle.



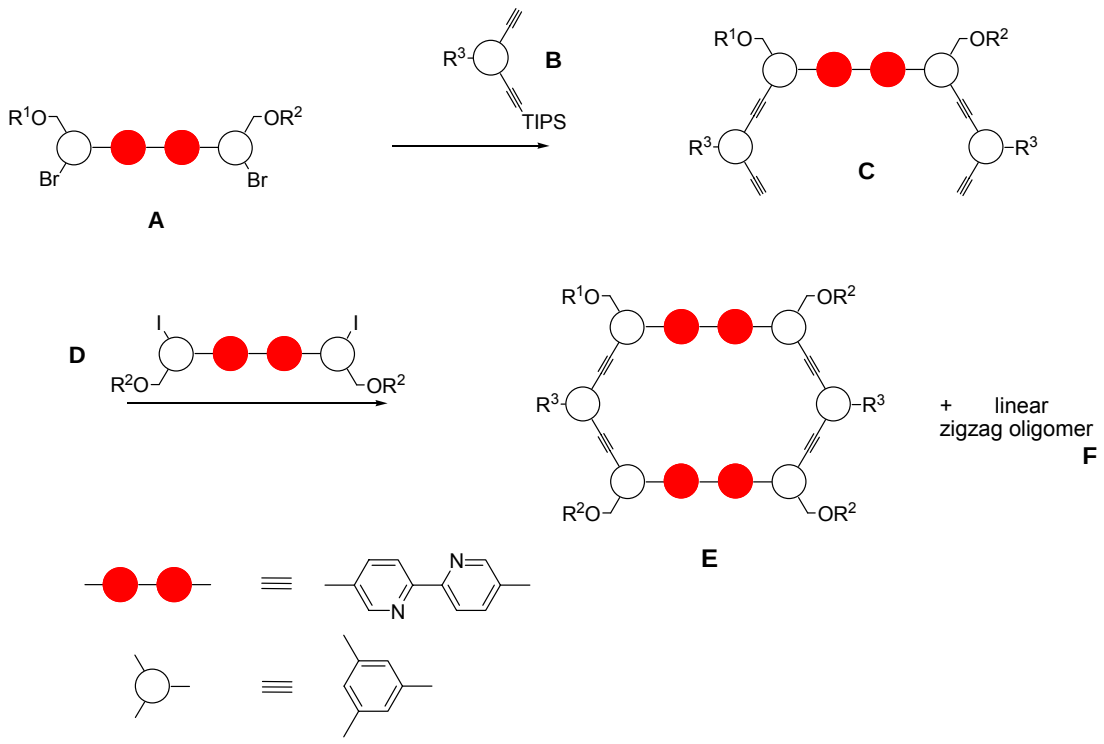
E: X = N or CH_2

Figure 27. The structure of the desired macrocycle **E** with two bipyridine units.

The strategy used for the construction of the bpy-containing shape-persistent cycles of kind **E** required two side stones **A** and **D** and a corner stone **B** (Scheme 21). Side **A** was reacted with the acetylenic cornerstone **B** to the cycle precursor **C** which was then reacted with side **D** according to a Sonogashira protocol and under pseudo high dilution conditions to give a roughly 1:4 mixture of cycle **E** and linear (zigzag) oligomers **F**.

Side **A** carries two bromo functions and side **D** two iodo ones. Attempts to cyclize **C** with **A** gave practically no cycle. This is why side **D** which has a more highly reactive iodo groups is used to close the cycle. Corner stones **B** carry acetylenes

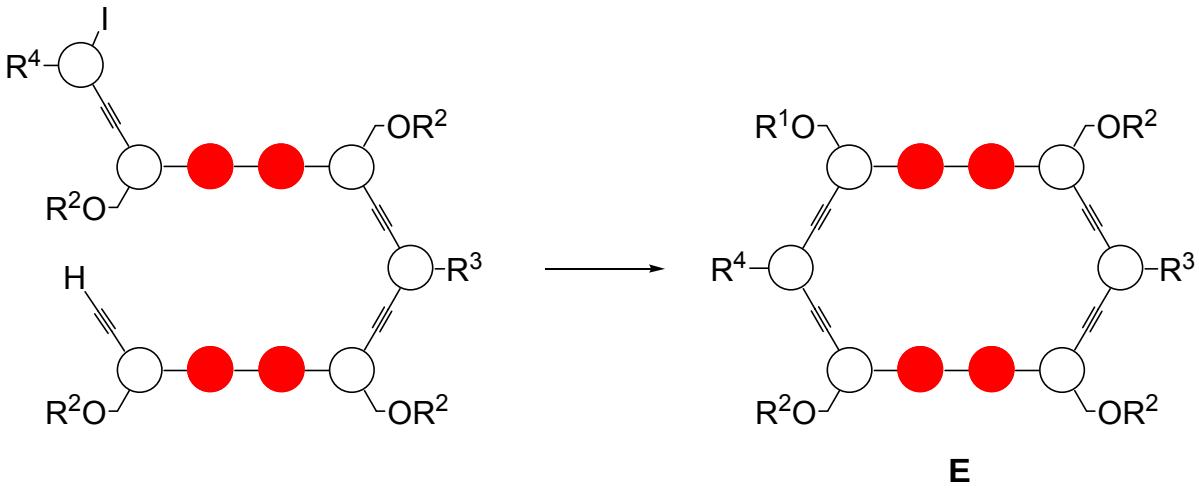
with selectively deprotectable acetylenes [e.g. trimethylsilyl (TMS) and triisoproyplsilyl (TIPS)] in order to allow for its selective coupling to **C**. Sides **A** and **C** can be either symmetrical ($R^1 = R^2$) or non-symmetrical ($R^1 \neq R^2$). By combining different sides **D** and **C** with different substitution pattern, different macrocycles become available which have different applicability.



Scheme 21. The synthetic strategy to macrocycles of kind **E**.

The macrocycle with only one bipyridine unit can be prepared using the same procedure, by replacing the bipyridine unit **D** by a diiodo functionalised quaterphenyl unit.

In an extreme case macrocycle **E** was closed from one precursor (Scheme 22). For such cyclizations yields of up to 75% were reported. The stepwise synthesis of the ring precursor was quite difficult, because the repeating unit is the half macrocycle itself. It requires also a non-symmetrical functionalised bipyridine. However such approach has the advantage that different functional groups R can be introduced at certain positions on macrocycle.



Scheme 22. Ring closure reaction of bipyridine macrocycles from one precursor

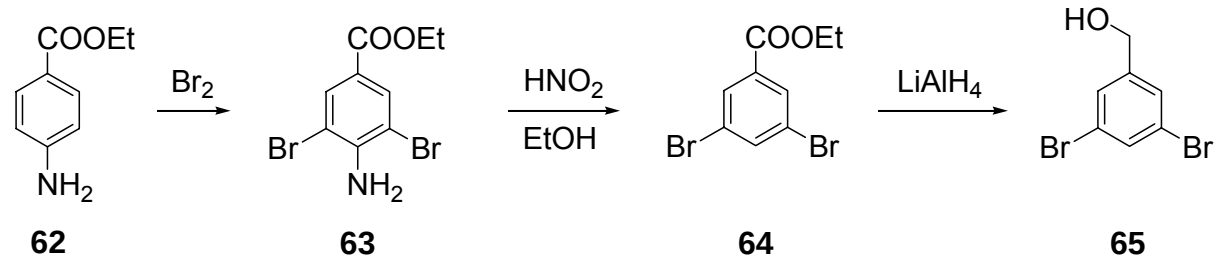
4.2. Improvements and new building blocks

Synthetic ways to the side stone **A** and **D** and corner stone **B** were developed by Henze. The syntheses of **A** and **D** suffer from using a sequence of Stille cross couplind reactions which involves working with hazardous tin compounds, providing the desired compound in relatively low yield. Additionally the isolation of product is quite difficult. It was clear that a better accessibility to these building blocks was required and improvements of their synthesis were unavoidable. The main objectives are to reduce the number of steps, increase their yields, replace Stille cross-coupling wherever possible[53] by the generally more efficient Suzuki cross-coupling, and improve work-up procedures.[3] Compound **B** (Scheme 21) did not need improvement and is available on the 30 g scale.[17]

4.2.1. Synthesis of side stones A

Side **A** has in its structure a bipyridine unit and two phenyl groups which carry not only the bromo functions but also the substituent R. Sides **A** can be obtained symmetrically and non-symmetrically depending on whether the R are like or unlike, respectively. Normally they are prepared such that the bpy unit (and thus the completed side) is generated in the last step by Stille cross-coupling.[53] The route to symmetrical side **A** is shown in Scheme 23-28. The synthesis of the corner compound **67** was achieved using Henze's procedure and carried out with two different substituent R (R = tetrahydropyranyl (THP) or hexyl).[53] It starts with the commercially available 4-aminobenzoic acid ethyl ester **62** which was brominated to

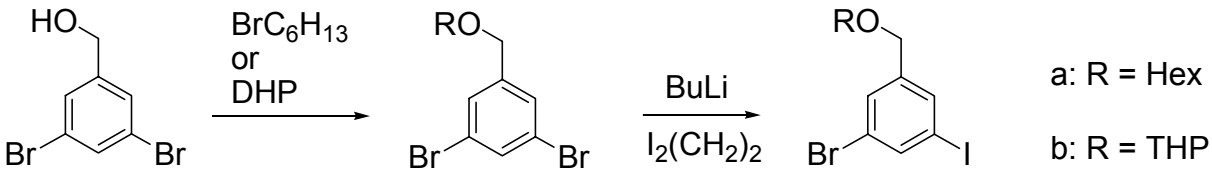
63[54] and than desaminated to **64**,[55] followed by the reduction of the product to its alcohol **65** with lithium aluminium hydride in dry diethyl ether (Scheme 23).



62 **63** **64** **65**

Scheme 23. Synthesis of the corner precursor **65** according to the Henze protocol.

The hexyl and tetrahydropyranyl ether were easily made from alcohol **65** and hexyl bromide in the presence of a base or DHP in presence of p-toluenesulfonic acid, respectively.

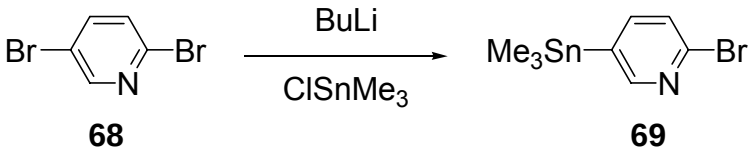


65 **66** **67**

Scheme 24. Synthesis of **67** by Henze.

Lithiation of **66** followed by trapping the anion with 1,2-diiodoethane gave **67** (Scheme 24). The different reactivity of the halogens in this compound towards Pd catalysts allowed for a selective transformation of iodo and bromo in the next step.

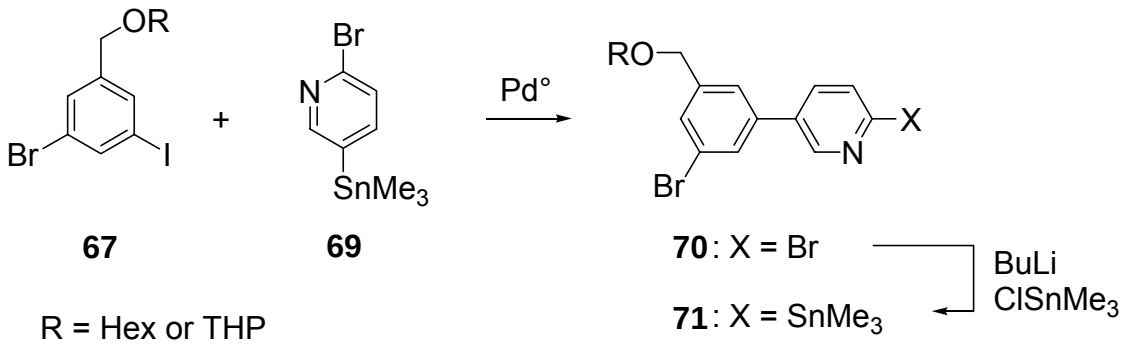
The commercially available 2,5-dibromopyridine **68** was selectively stannylated at position C-5 to give **69** in quantitative yield (Scheme 25).[56] **69** was purified either by column chromatography through silica gel or by distillation, whereby no destannylation was observed.



68 **69**

Scheme 25. Differentiation of the lithiation of 2,5-dibromopyridine.

Compound **67** and **69** were subjected to a Stille cross coupling reaction using the standard conditions (3 mol % of Pd^0 catalyst) to give **70** in 55-66% yield (Scheme 26).[53] The pure compound was achieved by repetitive column chromatography through silica gel.



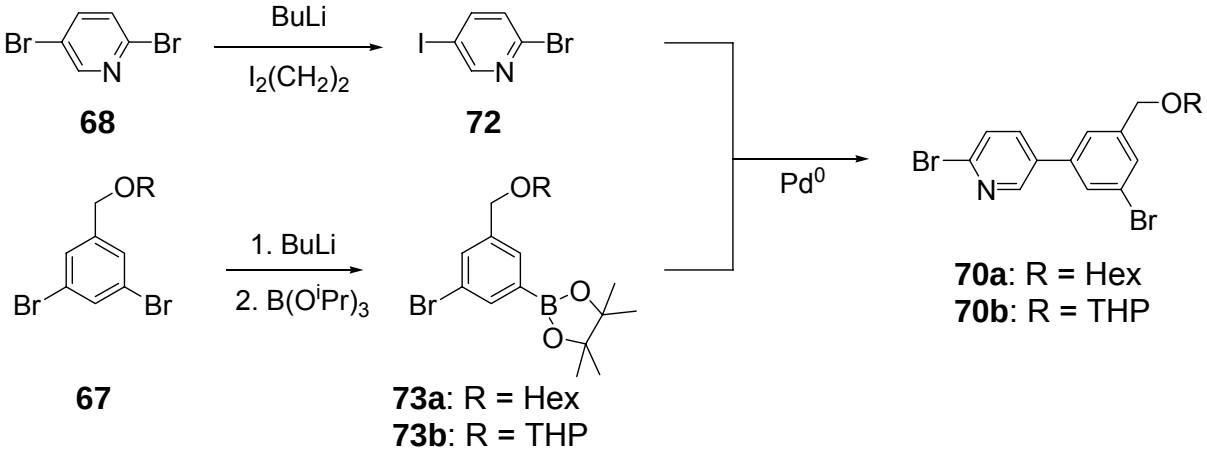
67 **69** **70**: X = Br

71: X = $SnMe_3$

R = Hex or THP

Scheme 26. Synthesis of the pyridine derivative according to Henze.

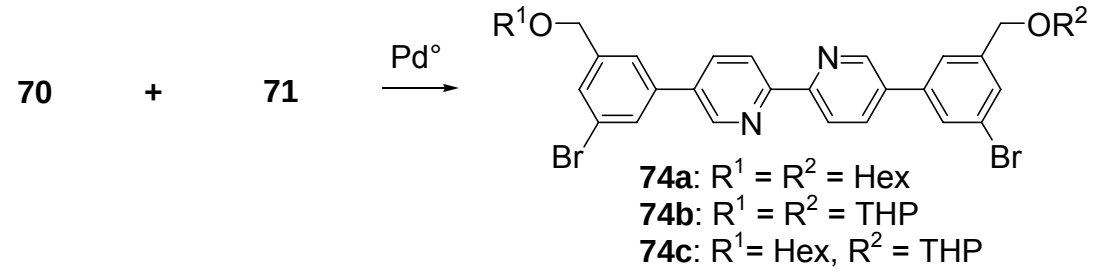
Alternatively, a more efficient way to pyridine derivatives **70** was developed (Scheme 27). This avoided the Stille coupling of **67** with **69** replacing it with the more efficient Suzuki cross coupling of **72** and **73** (Scheme 27). Henze had prepared **72** from the stannylated derivative **69** which was cleaved off quantitatively by simple treatment with iodine (not shown).[57] Alternatively, a direct introduction of iodine in position C-5 was achieved by treating the lithiated compound with diiodoethan (Scheme 27). The regioselectivity of this reaction can be explained by assuming thermodynamic control.[56b] The 2-lithiated compound forms faster, but repulsion of the negative charge next to the free pair of electrons of the nitrogen leads to a rearrangement which gives the product lithiated at C-5.[30]



Scheme 27. A different approach to functionalyzed pyridine **70**.

72's iodo selective coupling with the benzene boronic acid ester **73** gave half sides **70a** and **70b** in yields of 85-90%. In this case the nature of the base was very important. When K_2CO_3 was used the reaction was incomplete after 5 days, whereas Na_2CO_3 alone or with Bu_4NI as additive increased the reaction yield considerably and decreased the reaction time to 3 days. The boronic esters **73** was obtained by treating dibromide **67** first with butyllithium and triisopropylborate, followed by esterification of the resulting boronic acid with pinacol on the 10 g scale. [58]

Side stone **A** was finally generated using a Stille cross coupling reaction, this being the last Stille reaction remaining in the entire sequence (Scheme 28). For this purpose a stannylated pyridine was required. This was easily obtained by reacting pyridine derivative **70** with butyllithium in dry diethylether followed by an electrophilic stannylation with trimethylstannylchloride (Scheme 26).[53] When the solvent used for the lithiation was changed to toluene a slightly improved product yield was observed. Toluene as solvent was appropriate not only for the preparation of the Stille reagent but also for the Stille cross coupling reaction itself. An additional work up step was thus eliminated. This is quite important since the stannylated pyridines in *ortho* to nitrogen are not very stable and tend to proto-de-stannylate when exposed to humidity.[58] Compound **74** (**A**) was made using a Stille cross coupling reaction between the two pyridine derivatives **70** and **71** (Scheme 28).[53] The different combinations of these compounds gave the symmetrical sides **A** ($R^1 = R^2$ = Hexyl or THP) and the new non-symmetrical one **A** ($R^1 \neq R^2$). The pure compound was obtained by repetitive column chromatography. The reaction yields were rather low, basically more than half of the material was lost.



Scheme 28. Synthesis of the symmetrical and non-symmetrical building block **A** (**74**) using a Stille reaction between **70** and **71**.

The new building block **74c** was fully characterised and gave also correct elemental composition. Figure 28 illustrates the ^{1}H NMR spectrum of **74c** and gives the signals assignment.

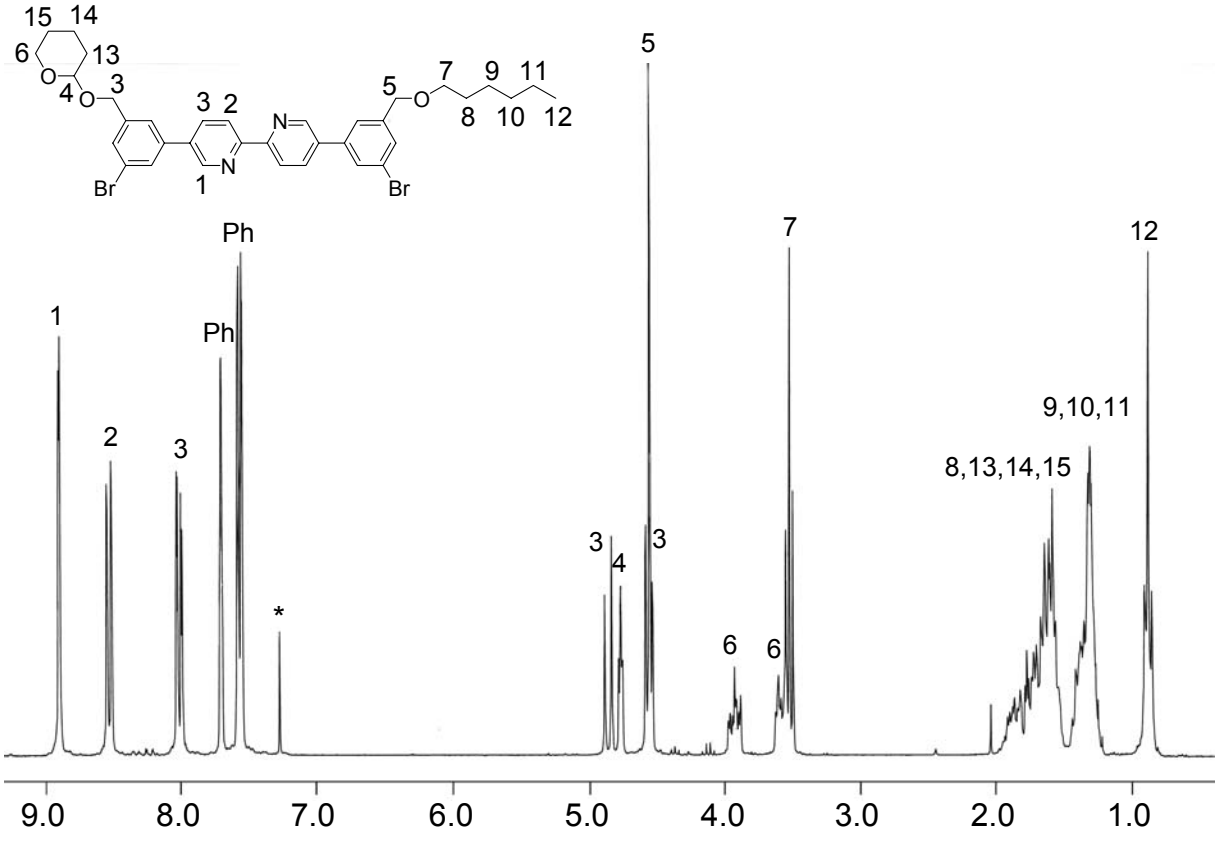
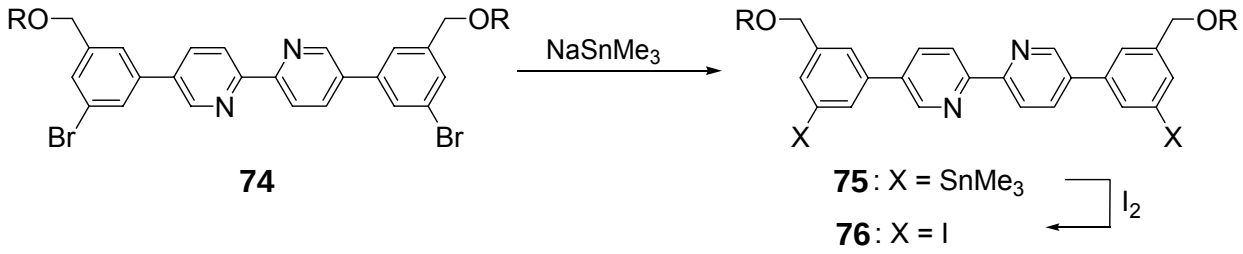


Figure 28. ^{1}H NMR spectrum of compound **74c** with signals assignment (*: $CDCl_3$, 250 MHz, 20 °C).

4.2.2. Synthesis of side stone D

It is well known that Pd-catalyzed cross-coupling reactions of arylbromides are inferior to the analogous aryliodides. This was also confirmed by the cyclization of bipyridine macrocycles involving Sonogashira chemistry when the coupling of arylbromides did not give any cycle, whereas that with aryliodides went satisfactory. It was clear therefore that the two bromides in **74** should be exchanged by iodides. Henze developed a synthetic strategy to convert the dibromobipyridine derivative **74** into diiodopyridine derivative **76** by a nuecleophilic stannylation/iodo destannylation sequence (Scheme 29). [17a]



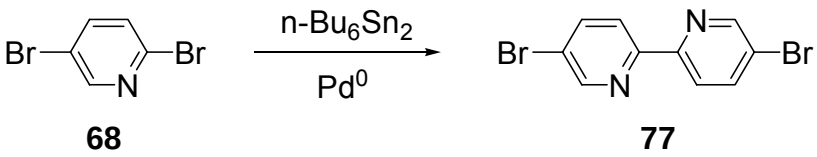
Scheme 29. Henze approuch to the building block **D** (**76**).

The dibromide **74** was reacted with in situ generated sodium trimethylstannane to give **75** in 70% yields. However it turned out that this reaction was hard to reproduce. Since it also involved working with toxic compounds and a complex isolation of the desired product from the starting material or partially stannylated product. The trimethylstannyl group on **75** was then easily replaced with iodo using iodine. Henze tried also to obtain **76** by using a lithiation/silylation/iododesilylation sequence, but this was unsuccessful.

During this work it became clear that improvements were necessary in order to be able to prepare gram amounts of this important building block. Henze generated the bipyridine unit at a late stage of the synthetic sequence, which involved a critical Stille cross coupling reaction.[53] The approach followed in the present work was to construct the bipyridine unit at the beginning of the sequence rather than at its end. This was the most critical step could be dealt with easily on and loss of valuable material was prevented.

Bipyridines are one of the most important ligands in supramolecular chemistry and many synthesis have been reported.[59] One synthetic access to 5,5'-disubstituted bipyridines uses 5,5'-dibromobipyridines **77** as starting material.[60] In 1938 Brustall first obtained **77** by direct bromination of 2,2' bipyridine hydrobromide salts in a stream of bromine gas. Because of the harsh conditions applied the reaction yield were low and the isolation of the compound from reaction mixture was difficult.[61] An Ullmann coupling is also known, but this also gives pretty low yields.[62]

An efficient synthesis of **77** has been developed in the group of Michl (Scheme 30).[63] They found that when 50 mol % hexa-(n-butyl)distannane was added to 2,5-dibromopyridine **68** in the presence of catalytic amounts of Pd^0, the desired **77** formed almost quantitatively. However the purification of **77** from the starting material was quite difficult.

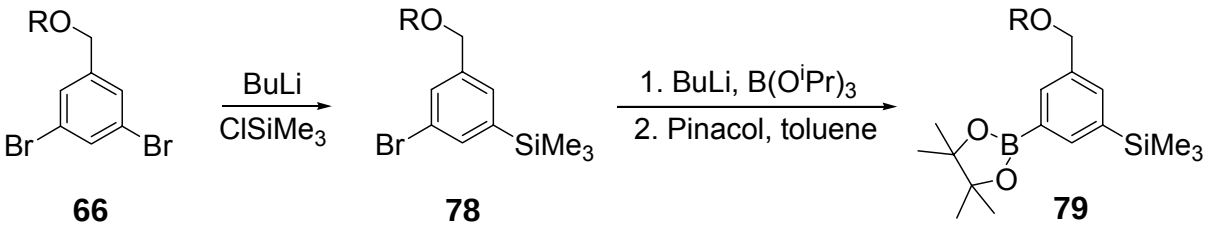


68 **77**

Scheme 30. Michl's synthesis of 5,5'-dibromo-2,2'-bipyridine **77**.

The purification problem was overcome by Sauvage.[64] He published a similar synthesis but described that the purification of the compound can be easily done by column chromatography through silica gel using as eluent chloroform and 0.1% methanol. According to Sauvage's and Michl's new procedures, bipyridine **77** is now available on the 10 g scale. Based on this, the symmetrical side stone **D** was prepared from **77** and the silylated benzene derivative **79** using a Suzuki cross coupling reaction (Scheme 32). The synthesis of compound **79** was achieved in two steps starting from **66** and was prepared on 30 g scale. The dibromoderivative **66** was selectively lithiated at one brominated carbon, followed by the addition of trimethylsilylchloride to give **78**.[65] This compound was easily purified by column chromatography through silica gel or by distillation. For the conversion of **78** to **79**, it was shown that the solvent plays an important role. The yield of the reaction was much improved by going from ether or THF to a mixture of ether/THF (1:1). In the former case only traces of product were obtained, whereas in the latter yields of 55-60% could be reached. A small but important change was done in this synthesis.[65]

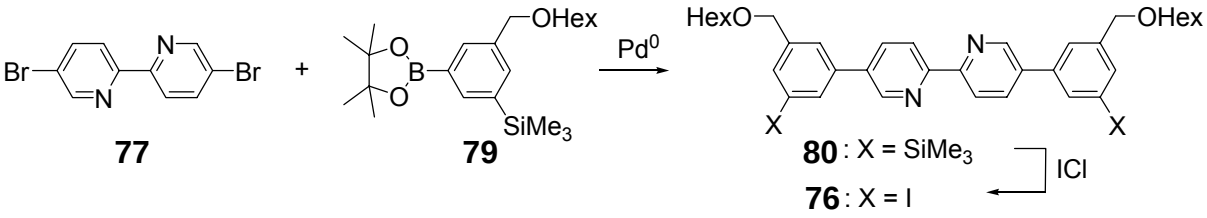
The esterification (pinacolization) of the free boronic acid precursor of **79** (not shown) was done in toluene instead of dioxan, with concomitant removal of water. This change led to an increase in yield for **79** from approximately 50% to 80%. Having the compounds **77** and **79** available at such large scale the obtainment of side **D** also on 10 g scale was no problem.



66 **78** **79**

Scheme 31. Manickam synthesis to boronic ester **79**.

Using Suzuki cross-coupling reaction between **77** and the silylated benzene derivative **79** the symmetrical building block **80** is formed in almost quantitative yield (Scheme 32). The purification of the compound is easily done by column chromatography. The ^{1}H NMR spectrum (Figure 29a) and the correct data for elemental analysis proved the purity of **80**.



77 **79**

Scheme 32. A new synthesis to side stone **D** (**76**).

Silyl groups on aromatics are known to be place holders for various functional groups including iodo.[39d] Compound **80** could, thus, be easily and quantitatively converted into side **D** (**76**) by exchanging its silyl groups to iodo with iodochloride. This was demonstrated by the total disappearance of the signal of the 18 protons of the silyl groups of the starting material **80** at δ = 0.35 ppm in ^{1}H NMR spectrum of **76** (Figure 29).

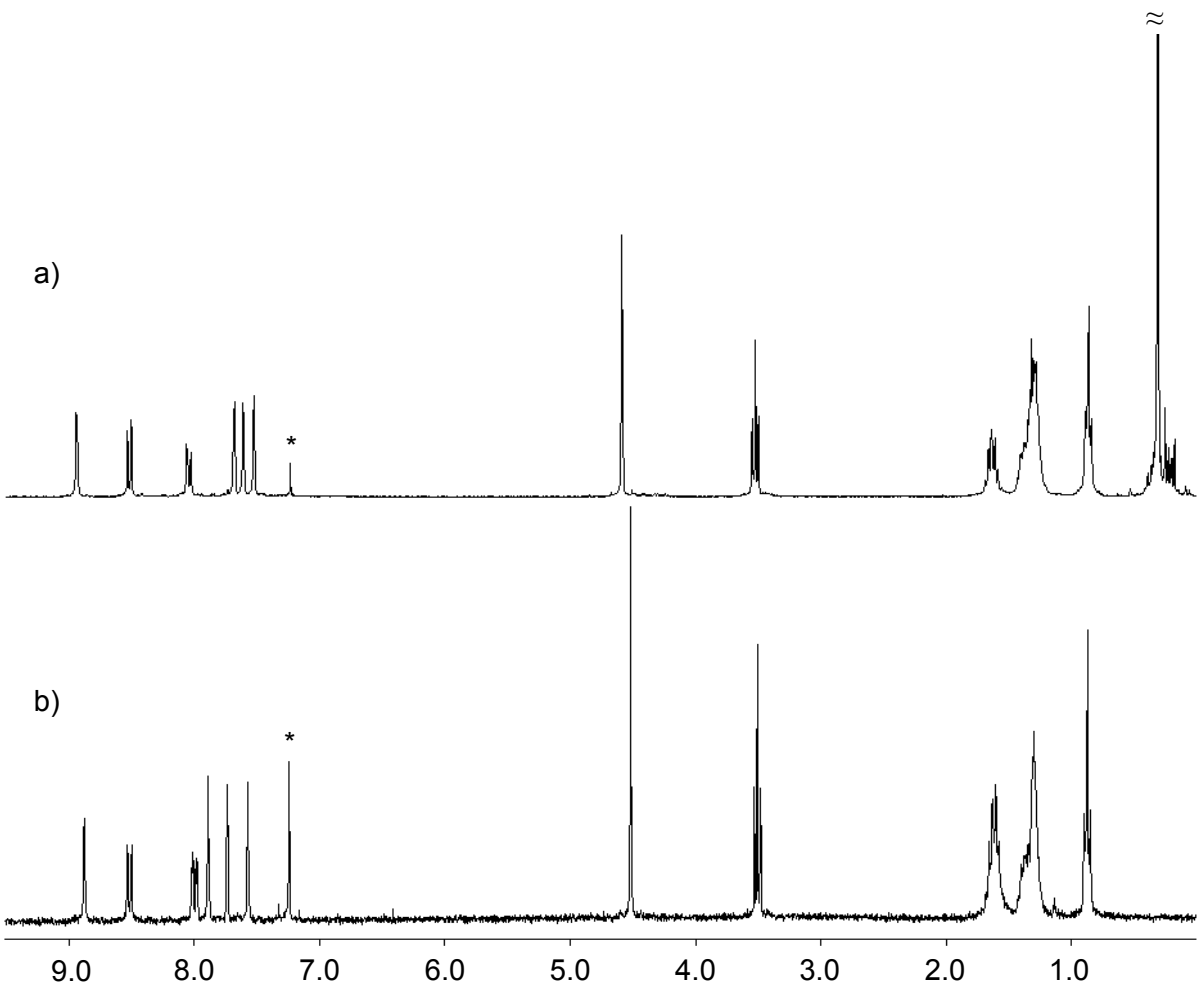
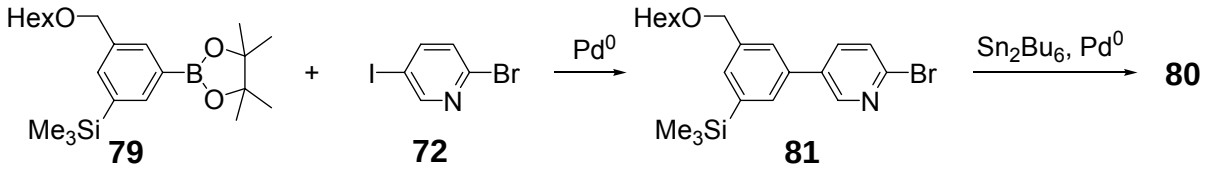


Figure 29. ^{1}H NMR spectra of compound **80** (a) and compound **76** (b) (*: $CDCl_3$, 270 MHz, 20 °C). The signal of $Si(CH_3)_3$ was reduced in size, as indicated by (≈).

An alternative reaction pathway to compound **80** was also investigated (Scheme 33) though it turned out to be less attractive from the moment on when the above-mentioned improved accessibility of compound **77** was published. In this synthesis the bipyridine unit is constructed at the end of the sequence, by a Stille cross-coupling reaction of pyridine derivative **81**. This derivative was obtained from compounds **72** and **79** which were coupled under Suzuki reaction conditions (Scheme 33). The isolation of the product from the small excess of pyridine **72** which is required in order to prevent the coupling of the boronic ester to bromine was no problem. Figure 30 shows the ^{1}H NMR spectrum of **81** with a signal assignment.



Scheme 33. The synthesis of compound **81** from **72** and **79** using a Suzuki cross coupling reaction followed by a homocoupling via Stille cross coupling of **81** to **80**.

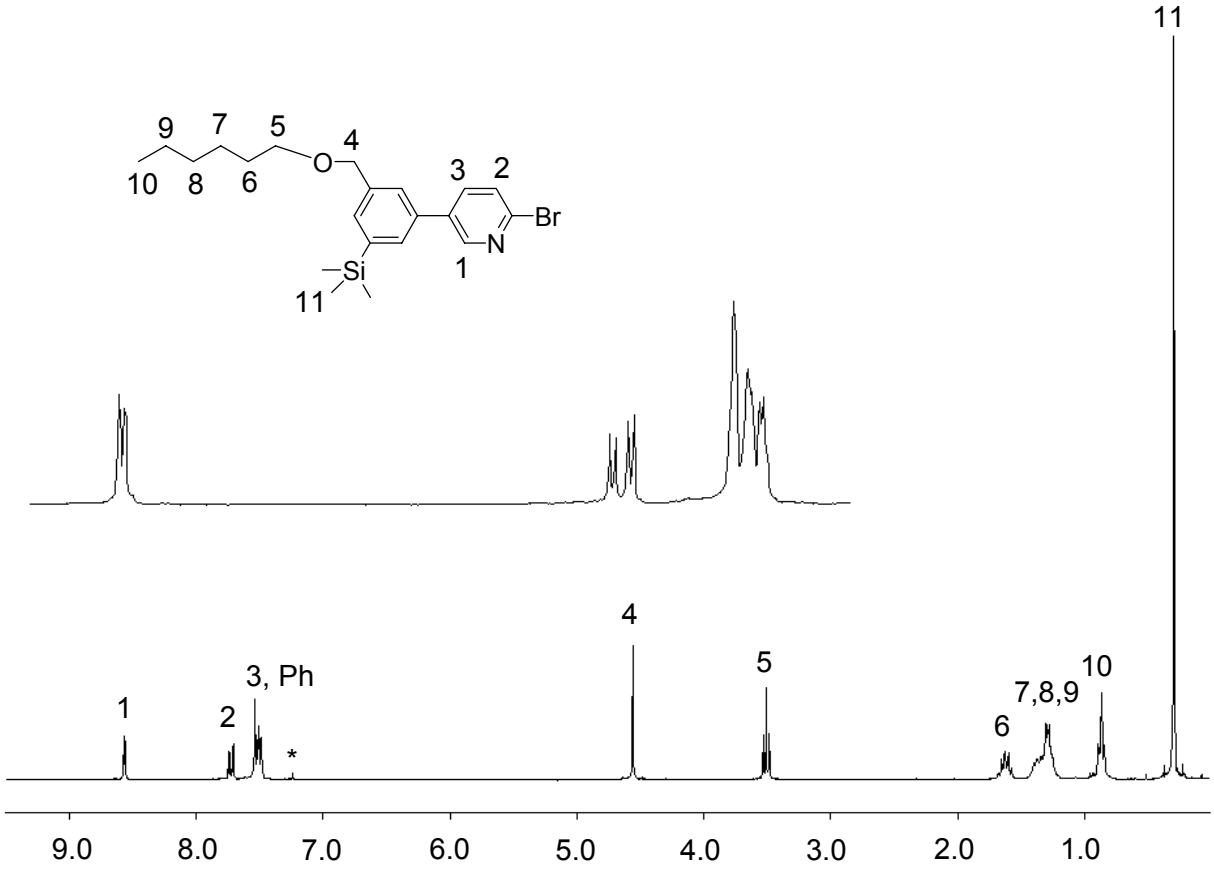


Figure 30. The ^{1}H NMR spectrum of compound **81** (*: $CDCl_3$, 270 MHz, 20 °C), with the aromatic part enlarged.

81 was than homocoupled in presence of Sn_2Bu_6 and Pd^0 catalyst. The reaction went completely and the compound **80** was easily purified by column chromatography through silica gel.

The main advantages of the new routes are:

(a) Reduction of number of steps from 12 to 9.

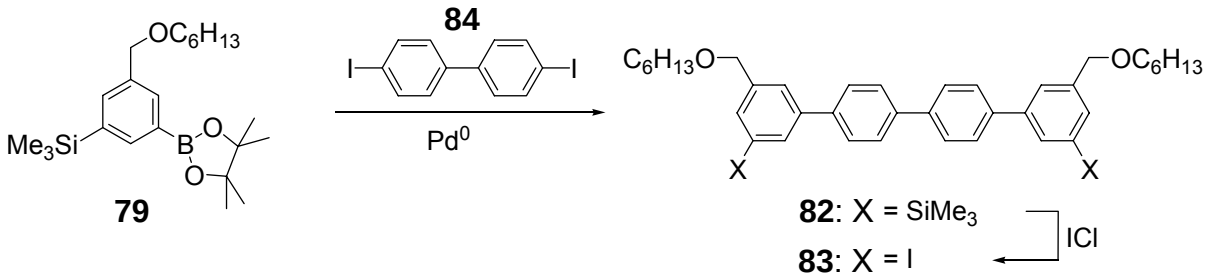
(b) Increase of total yield from starting material (2,5-dibromopyridine) from 14% to 83%.

(c) Facilitated work-up procedures (fewer Stille couplings with hazardous tin compounds and much easier column separations).

(d) Gram amounts of cycle are within reach.

4.2.3. Synthesis of the quaterphenyl unit 83

The new functionalized quaterphenyl unit **82** was prepared using a Suzuki cross coupling reaction between diiodobiphenyl **84** which is commercially available and a small excess of boronic esters **79** which was prepared as described before (Scheme 34). The quaterphenyl was purified by column chromatography and obtained on 1.7 g scale in a yield of 57%. Subsequent iododesilylation with iodochloride at 0 °C in dichloromethane gave **83** in 97% yields. The ^{1}H NMR spectra of **82** and **83** illustrate the achieved purity (Figure 31).



Scheme 34. Synthesis of compound **82** from a Suzuki cross coupling between **79** and **84** followed by the replacement of $SiMe_3$ group with ICl to **83**.

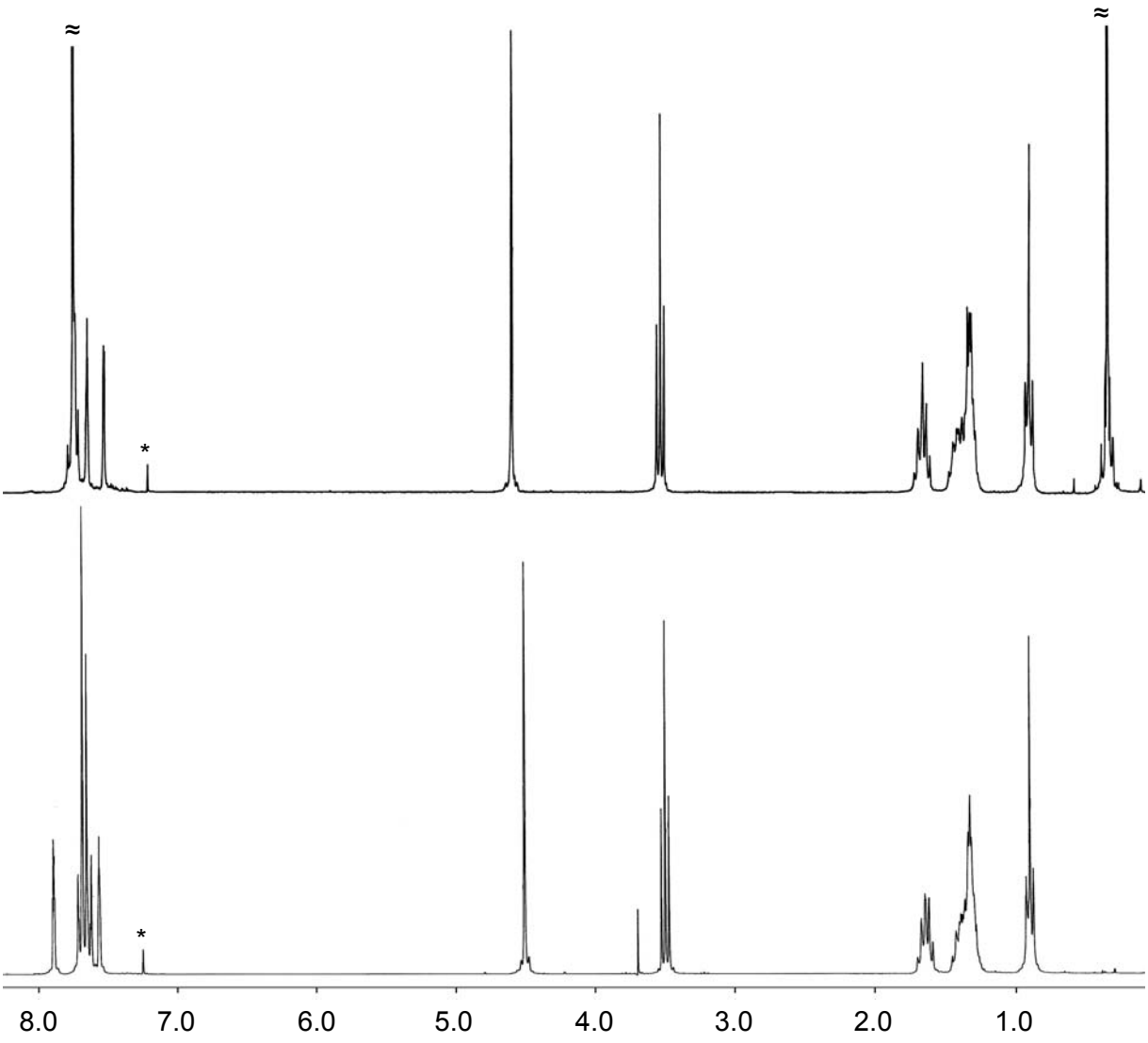
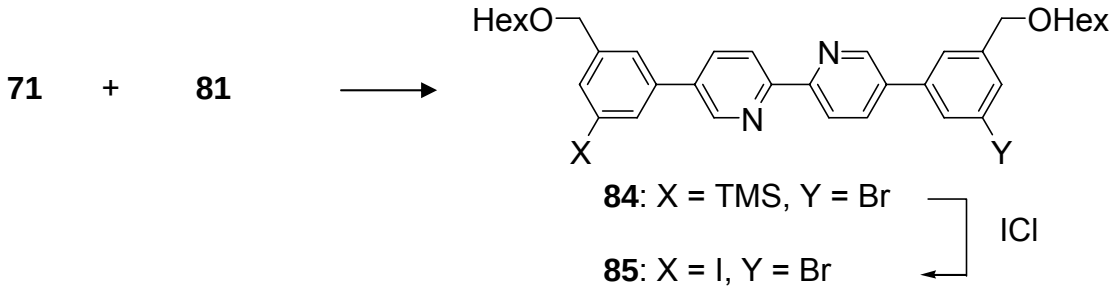


Figure 31. The ^{1}H NMR spectra of compounds **82** and **83** (*: $CDCl_3$, 250 MHz, 20 °C). The characteristic signal for the $SiMe_3$ group at δ = 0.33 is not present in compound **83**.

4.2.4. Synthesis of a non-symmetrical bisfunctionalised building block 85

A bisfunctionalised building block was sought which would allow for the synthesis of bipyridine containing macrocycles from solely one precursor compound. This was expected to lead to extremely high cyclization yields. Also it would open the way for a better and more flexible control over the functional group placement. Side **85** with one bromo and one iodo function was considered an ideal candidate

(Scheme 35). Its synthesis was achieved by first coupling the stannyl compound **71** with bromide **81** using a Stille reaction to give **84**.



Scheme 35. The synthesis of non-symmetrical building block **85**.

As oftenly encountered in Stille coupling reactions, not only the desired cross-coupling product but also the two homocoupling products were formed (ratio **84** : **80** : **74** = 4 : 1 : 1). Because of the polarity difference between the desired compound and the side homocoupling products, the purification was easily done by column chromatography through silica gel. As expected, the first fraction contained the disilyl compound **80**, followed by the non-symmetrical building block **84** in the second fraction. The third fraction represented the homocoupling product **74**. The ^{1}H NMR spectrum of **84** displays two different sets of signals for the bipyridine unit and two distinct singlets for the benzyl protons with their integrals having a 1:1 ratio (Figure 32). The most convincing structural proof for **84** is its ^{13}C NMR spectrum which shows exactly the 22 expected aromatic signals. Additionally the mass spectrum shows the molecular peak at *m/z* = 688.

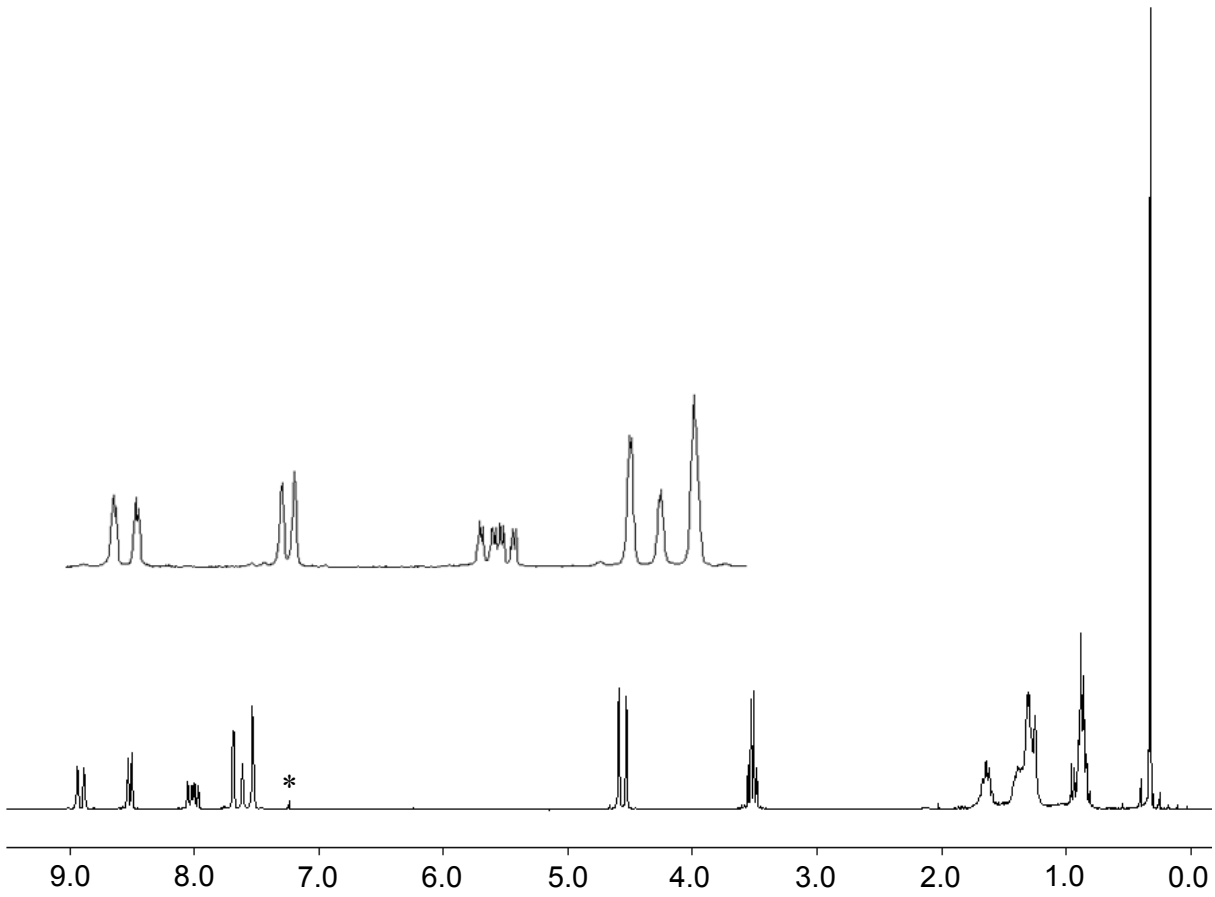


Figure 32. ^{1}H NMR spectrum of compound **84** with the aromatic part enlarged (*: $CDCl_3$, 270 MHz, 20 °C).

Iododesilylation of **84** was done with ICl at reflux for two days in dry DCM affording **85** on the 2 g scale (Scheme 35). The disappearance of the trimethylsilyl group at δ = 0.32 ppm is a clear proof for complete reaction (Figure 33). A series of Sonogashira-type coupling reactions with various silylprotected acetylenes (TMSA and TIPS) followed (Scheme 36). These steps involved a selective deprotection to **86c** which was then reacted with an excess of **87** to give **86d**. The synthesis of **87** was achieved in two steps starting from **67b** (Chapter 4.2.5).

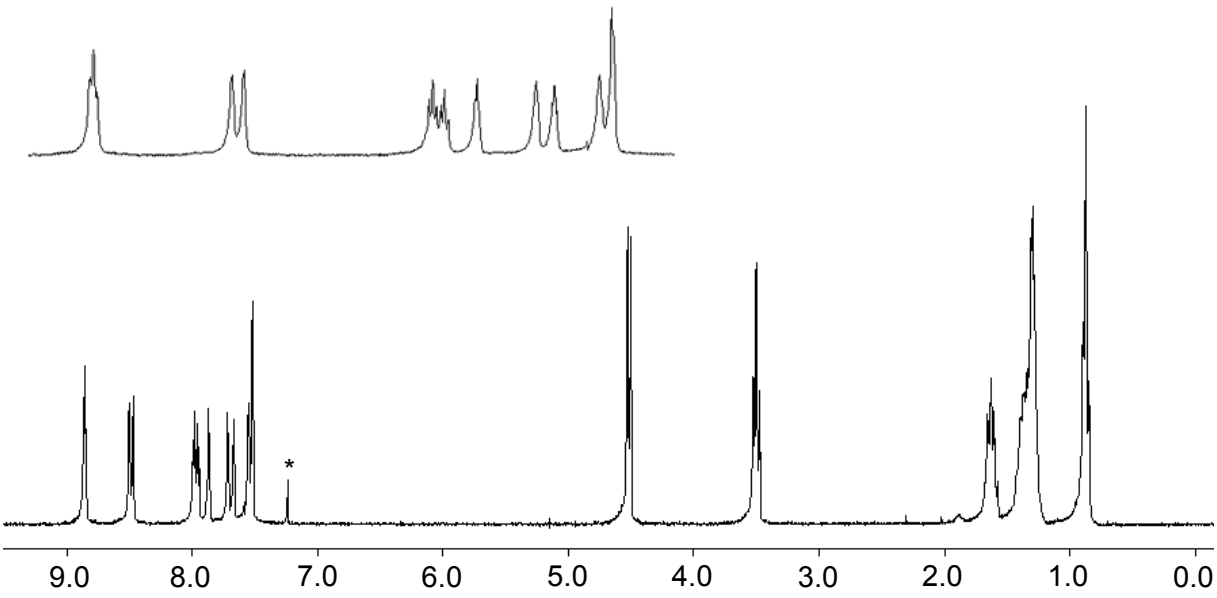
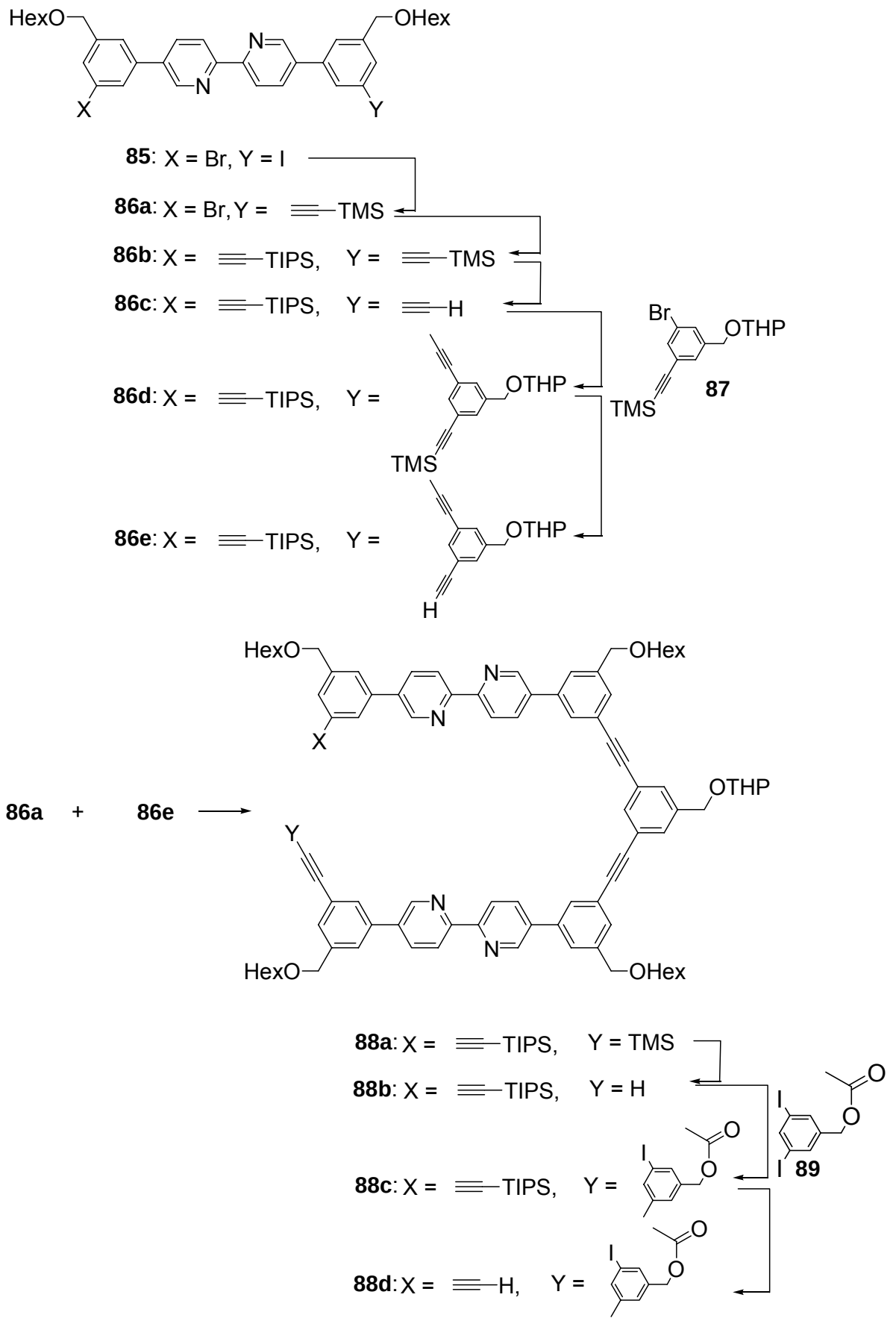


Figure 33. ^{1}H NMR spectrum of **85** with the aromatic part enlarged (*: $CDCl_3$, 270 MHz, 20 °C).

All these procedures went absolutely smoothly and were high-yielding so that **86e** could be isolated on the not yet optimized 500 mg scale. Its coupling with **86a** gave **88a** which was only few steps away from the final cycle precursor **88d** (Scheme 36). These steps involved a selective deprotection to **88b** which was then reacted with an excess of 3,5-diiodobenzylacetate (**89**) to give **88c**. Compound **89** was prepared in one step from methyl 3,5-diiodobenzoate by reduction with DIBALH. The deprotection of the TIPS group of **88c** afforded the cycle precursor **88d** on the 250 mg scale. The purity of compound **88d** was assessed by visual inspection of its ^{1}H NMR spectrum (Figure 34).



Scheme 36. Synthesis of the sole ring precursor **88d** using repetitive protection-deprotection reactions.

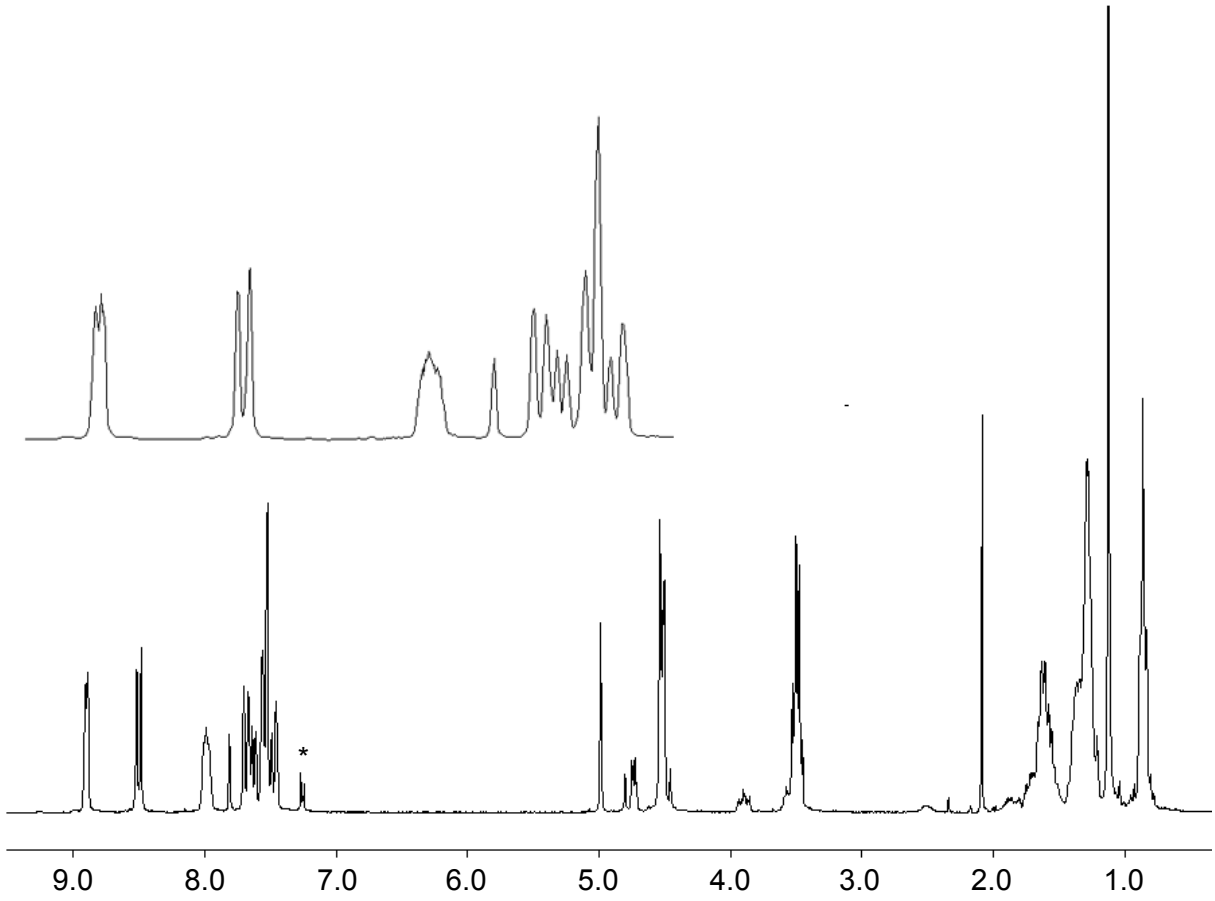
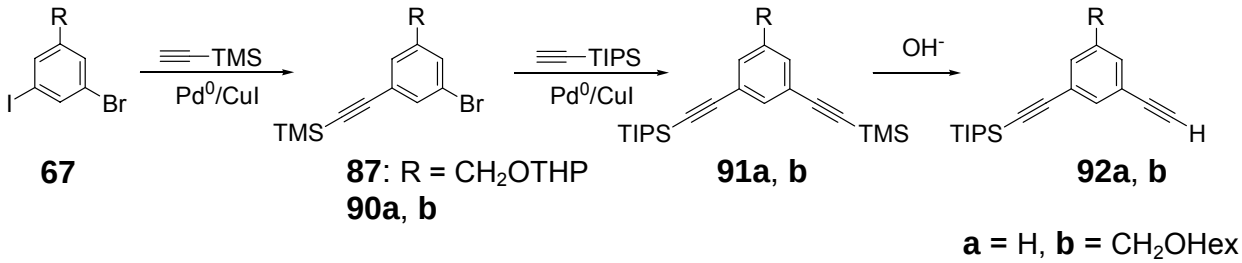


Figure 34. ^{1}H NMR spectrum of compound **88d** with the aromatic part enlarged (*: $CDCl_3$, 270 MHz, 20 °C).

4.2.5. Synthesis of corner stones B

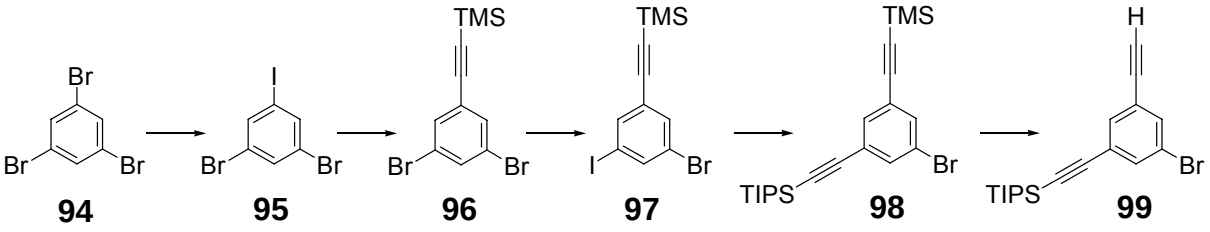
Corner stones **B** carry selectively deprotectable, silylated acetylenes [e.g. trimethylsilyl (TMS) and triisoproyplsilyl (TIPS)] in order to allow for their selective coupling to **C** (Chapter 4.1., Scheme 21, p. 43). Compounds **B** (Scheme 37) were prepared as described earlier and did not need any improvement.



Scheme 37. Synthesis of corner stone **B** (**92**).

Compound **67** was selectively reacted at the iodo function with trimethylsilylacetylene in presence of CuI and Pd^0 catalysts to give **87** or **90**. For this reaction it is very important to have a 1:1 proportion of TMSA and **67**. An excess of acetylene gave the bis-coupling product, and too less acetylene gave incomplete reaction. Because the purification of mixtures of these compounds was complicated, the ratio had to be closely observed. In next step an excess of TIPS-acetylene could of course be used and **91** was obtained straightforwardly. The TMS group of **91** could then be selectively cleaved off with catalytic amounts of NaOH to give **92**.

A new corner stone **B** was also prepared (Scheme 38). It contains a free acetylene, a protected TIPS acetylene, and a bromo function which led to further functionalization. A sequence of Sonogashira cross-coupling reactions was used. The required differently protected acetylenes were introduced by exploiting the reactivity difference of aryliodides and arylbromides. The synthetic sequence starts with commercially available **94** which was converted to iodo derivative **95** by reacting it with one equivalent of BuLi followed by quenching the lithiated intermediate with 1,2-diiodoethane to give **95** in 90% yield.



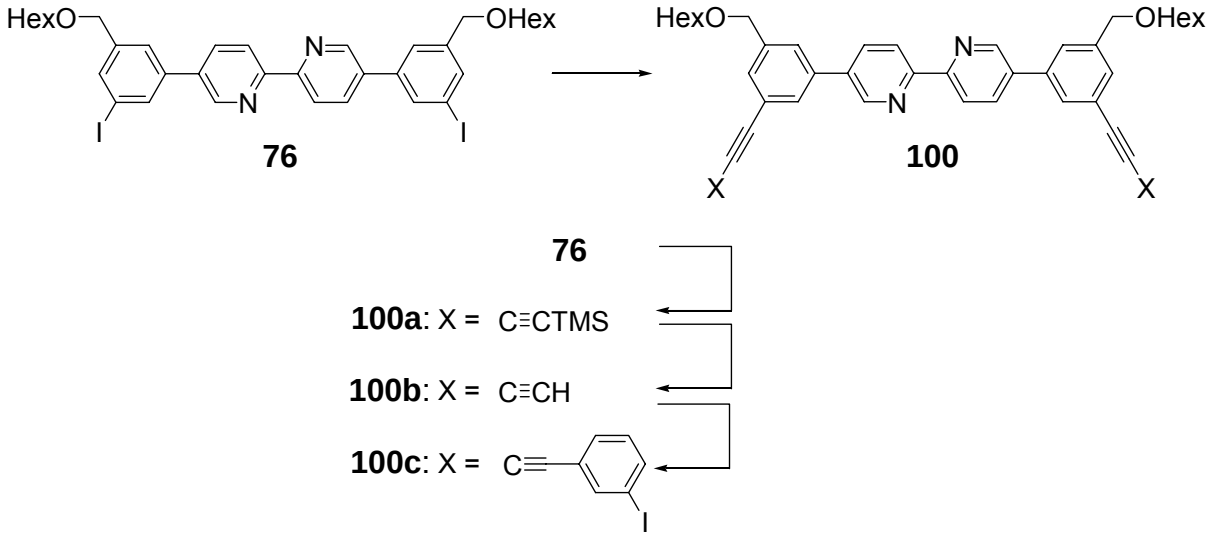
Scheme 38. The synthesis of a new corner stone **99** (**B**) from **94** using a sequence of Sonogashira reactions.

The selective coupling of **95** with one equivalent of TMSA in triethylamine, CuI, and catalytic amounts of Pd^0 gave **96** in 85% yield. The synthesis of compound **96** was also described in literature. A 1:1 stoichiometric reaction between TMSA and **94** gave a mixture of unreacted and desired compound as well as di- and tri-ethynylated products which were difficult to separate by column chromatography. Compound **96** was reacted with one equivalent BuLi in diethyl ether, followed by addition of 1,2-diiodoethan to the lithiated intermediate and gave **97** in 60% yield. Compound **97** was then subjected to a Sonogashira coupling with TIPSA to give **98** which was then

selectively deprotected at its TMS group with a catalytic amount of NaOH. Compound **99** was prepared on the 3.2 g scale.

4.2.6. Synthesis of cycle precursors 100b and 100c

In the case that only four substituents are needed or acceptable on a cycle, a specifically easy route was devised which is based on the commercially available TMSA and 1,3-diiodobenzene. It led to a further reduction of the total number of steps from 17 to 13 (Scheme 39).



Scheme 39. The synthetic sequence to the new macrocycle precursors **100b** and **100c**.

The synthetic sequence starts from **76** (side **D**) which was reacted with an excess of TMSA to give **100a** in an almost quantitative yield. A mixture of toluene/triethylamine was used because of the poor solubility of **76** in triethylamine which is the common solvent for Sonogashira reactions. **100a** was then deprotected from its TMS group to **100b** by base catalysis. Thereafter **100b** was reacted with a large excess of 1,3-diiodobenzene to give the new cycle precursor **100c** in 60% yield and on the 2 g scale. Both precursors were fully characterized. The purity of **100c** was assessed from the ^{1}H NMR spectrum (Figure 35).

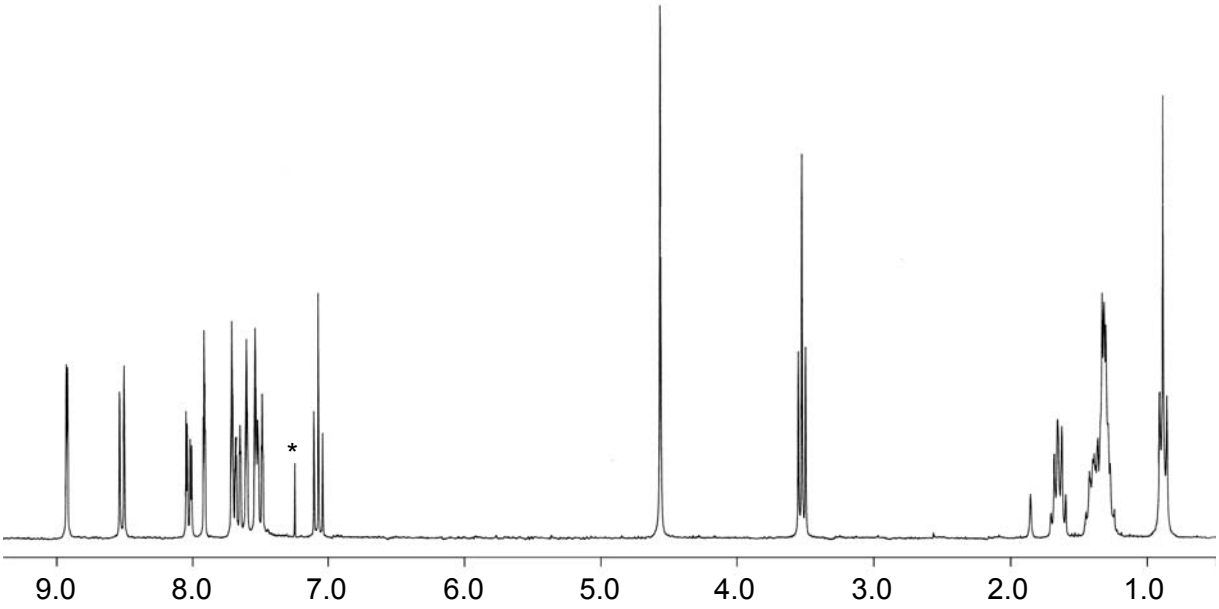
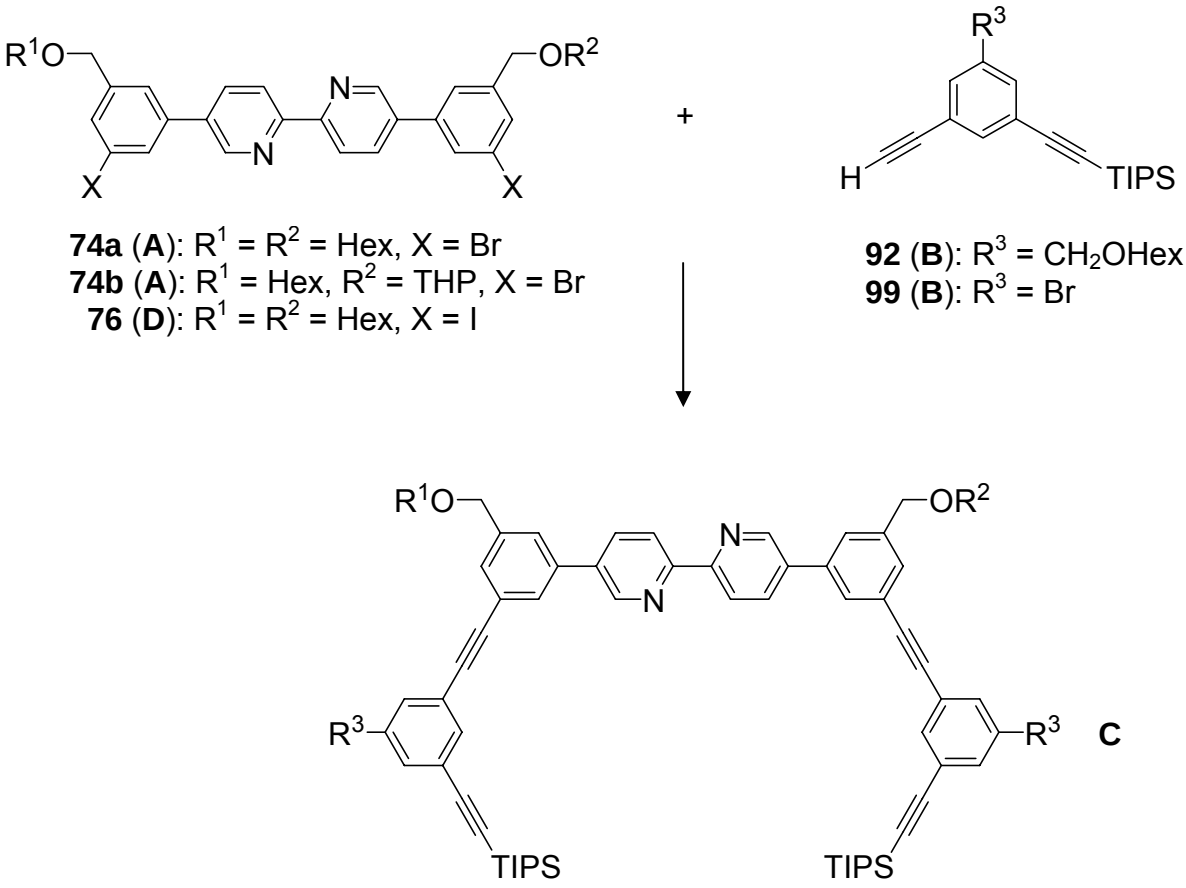


Figure 35. ^{1}H NMR spectrum of compound **100c** (*: $CDCl_3$, 250 MHz, 20 °C).

4.2.7. Synthesis of cycle precursors C

The synthesis of cycle precursor **C**[17] was performed by a Sonogashira reaction of bisfunctionalized building block **A** or **D** with silyl protected acetylene corner stone **B** followed by silyl deprotecting steps of monoprotected bisacetylenes. Scheme 40 illustrates the syntheses of half rings **C** by combining different building blocks **A** or **D** with different corner stones **B**.

Compounds **74a**, **74c**, and **76** were reacted with corner stones **92a**, **92b**, and **99**, respectively under Sonogashira reaction conditions to give **101a**-**c** in 65-85% yield after purification by column chromatography (Scheme 40). For the coupling of **74a**, **74c**, and **76** an excess of **92a** and **92b** was used in order to avoid partial coupling. However, for the reaction of **76** with **99** it was very important not to use any excess but rather try to meet the necessary 1:2 proportion of the two compounds. If a small excess of **99** was applied, the bromo group of the desired compound **101c** got involved. The purification of **101c** from the side product by column chromatography was not possible. It was finally purified by preparative HPLC. However, when a 1:2 proportion of **76** : **99** was used, the product was easily purified by column chromatography through silica gel.



74a (**A**): $R^1 = R^2$ = Hex, X = Br
74b (**A**): R^1 = Hex, R^2 = THP, X = Br
76 (**D**): $R^1 = R^2$ = Hex, X = I

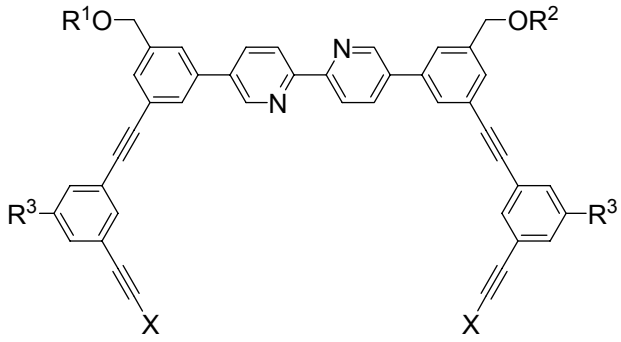
92 (**B**): $R^3 = CH_2OHex$
99 (**B**): R^3 = Br

101a: $R^1 = R^2$ = Hex, $R^3 = CH_2OHex$
101b: R^1 = Hex, R^2 = THP, $R^3 = CH_2OHex$
101c: $R^1 = R^2$ = Hex, R^3 = Br

74a + **92** → **101a**
76 + **92** → **101a**
74c + **92** → **101b**
76 + **99** → **101c**

Scheme 40. Syntheses of silyl protected half ring **101a**-**c**.

In the next step, the TIPS groups of **101a**-**c** were removed cleanly using TBAF in THF (Scheme 41). A clear prove for the complete reaction is the disappearance of the signal of the two TIPS groups at δ = 1.12 ppm in the ^{1}H NMR spectrum of ring precursor **102a**-**c** and the appearance of a new singlet signal at δ = 3.1 ppm for the two acetylene protons (Figure 36).



101: X = TIPS
Bu_4NF
102: X = H

102a: $R^1 = R^2$ = Hex, $R^3 = CH_2OHex$
102b: R^1 = Hex, R^2 = THP, $R^3 = CH_2OHex$
102c: $R^1 = R^2$ = Hex, R^3 = Br

Scheme 41. Deprotection of **101a**-**c** at its TIPS group using Bu_4NF to **102a**-**c**.

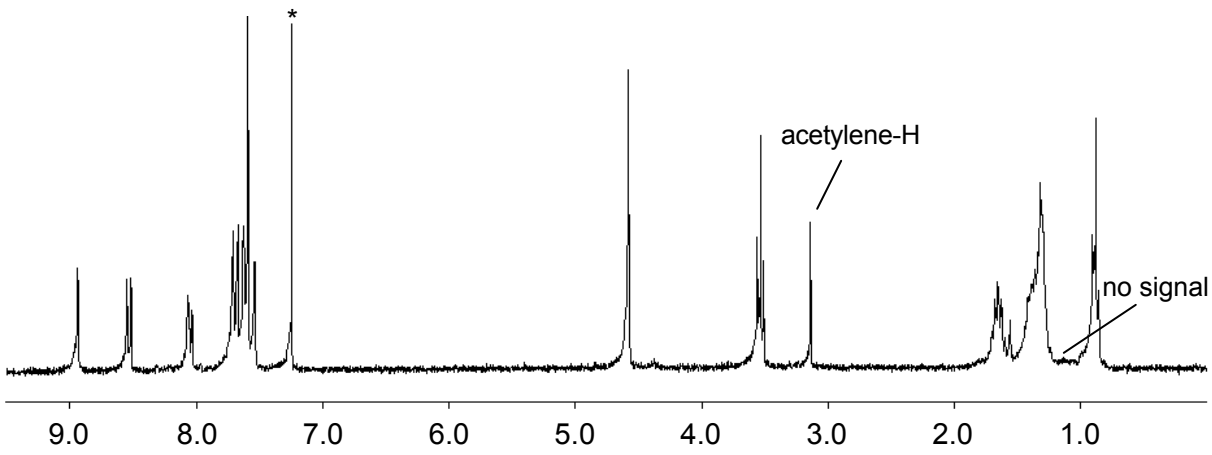


Figure 36. ^1H NMR spectrum of ring precursor **102c** (*: $CDCl_3$, 270 MHz, 20 °C).