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]

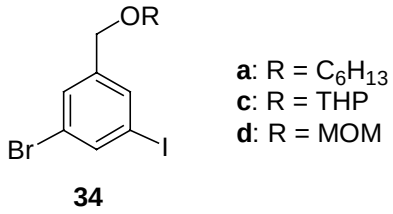
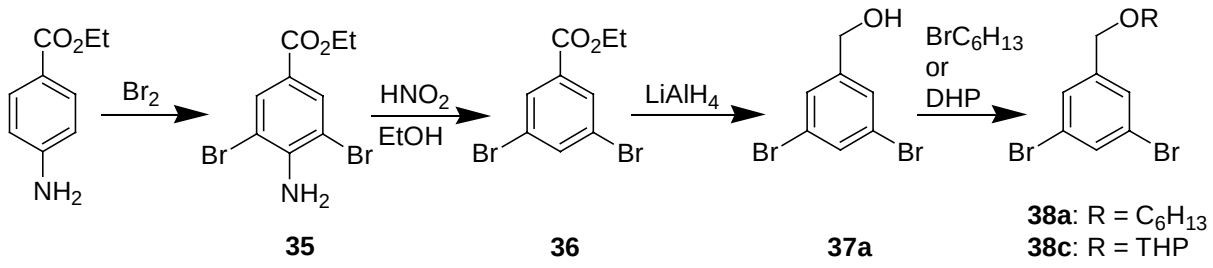


*Fig. 4. Henze's ring corner precursor **34**.*[30]

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

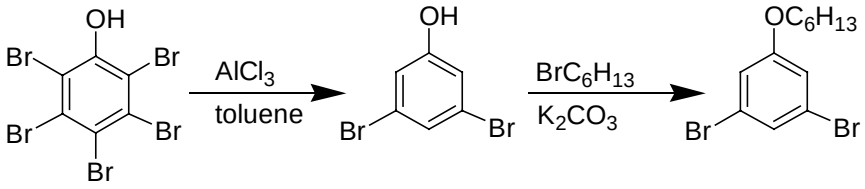


*Scheme 17. Synthesis of corner precursors **38a** and **38c** according to Henze.*[31]

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.[111] The ester **36** was then reduced with lithium aluminium hydride to benzyl alcohol **37a**.

37a was deprotonated by KO*t*-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**.



37b **38b**

*Scheme 18. Synthesis of alternative corner precursor **38b**.*

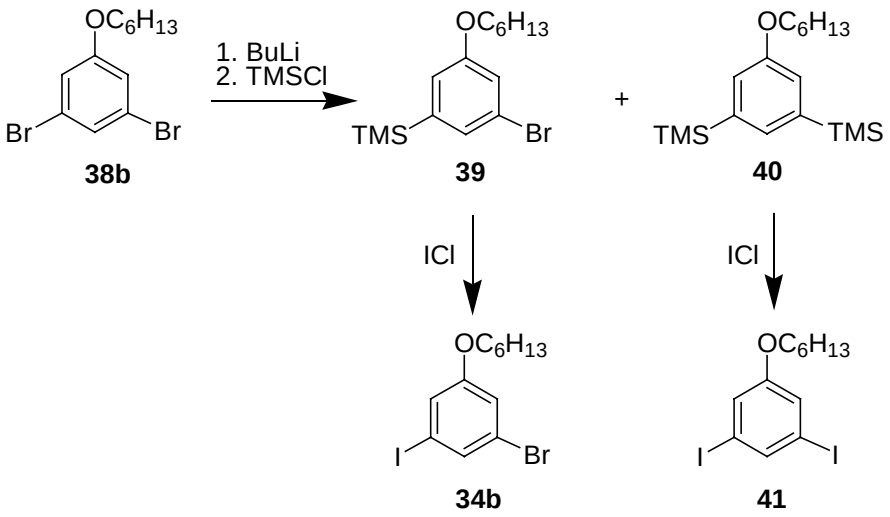
Alternatively, a much shorter reaction sequence to the phenyl ether analogue **38b** of benzyl ether **38a** was developed here (Scheme 18). The hydro-de-halogenation of the three activated bromo substituents in commercially available pentabromophenol to yield *meta* disubstituted phenol **37b** has been described by Kraus.[112,113] A solution of pentabromophenol is refluxed with $AlCl_3$ 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 K_2CO_3 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).

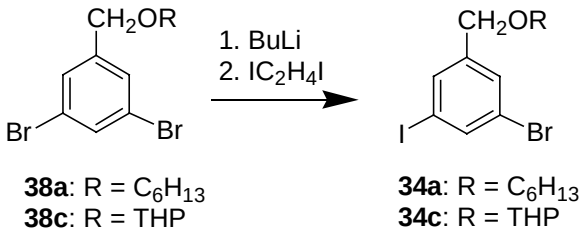
Monolithiation of **38b** with BuLi at -78°C and scavenging of the generated aryl anion with trimethylsilyl chloride led to Br,TMS-difunctionalized **39** (Scheme 19). The TMS group was easily replaced by treatment with ICl to give the bromo,iodo-functionalized compound

34b.[67,114] Thus, the two bromo functions had been differentiated, effectively leading from an A,A- (in **38b**) to an A,B-pattern (in **34b**).



*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).[31,70] 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.[30] The advantage of this scheme is the possibility to purify the stannylated compound very easily from unreacted starting material. A disadvantage is the high toxicity of the organostannyls.

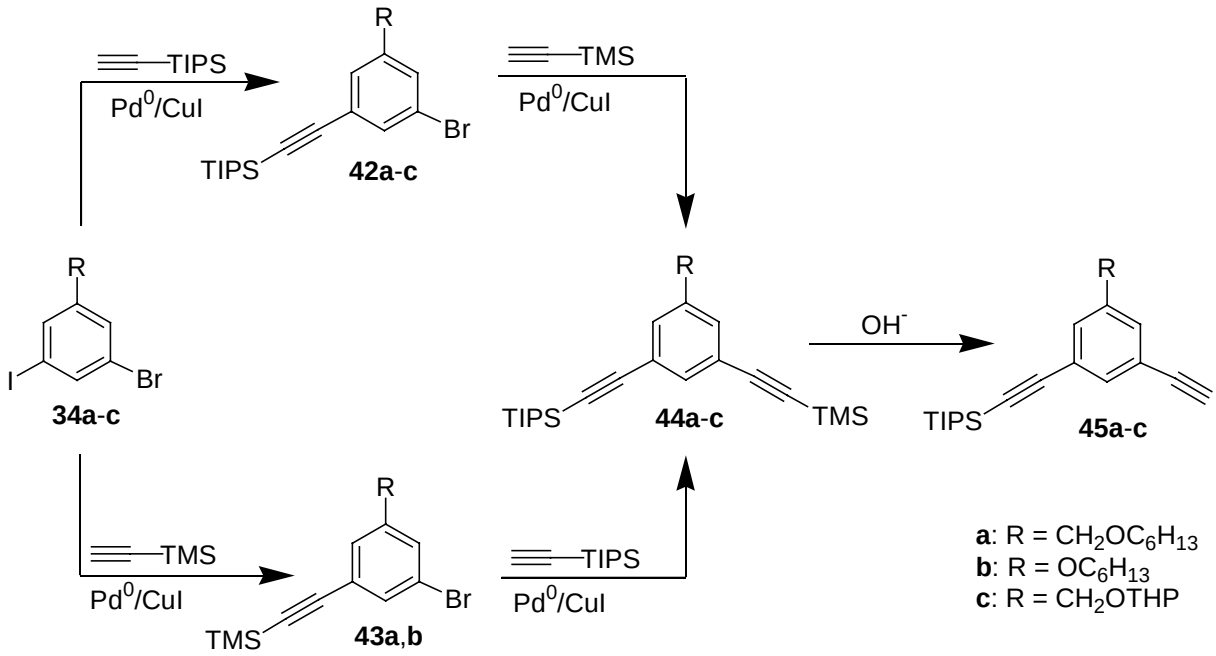


*Scheme 20. Differentiation of the coupling functionalities for compound **34a** according to Henze.*

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 diiodo 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.[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.[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.



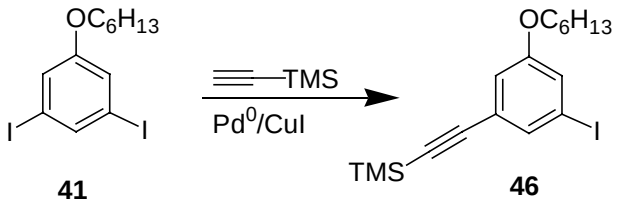
*Scheme 21. Synthesis of phenyacetylenes **45a-c**.*

Henze described the Sonogashira coupling of **34a** with TIPS-acetylene to **43a**, and with TMS-acetylene further to **44a** (Scheme 21).[32] The TMS protecting group was then selectively cleaved off to give **45a**.[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.[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.

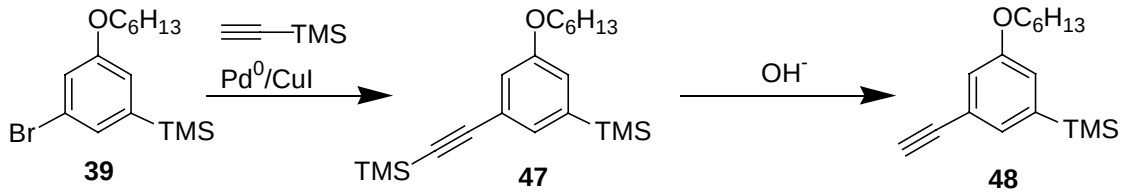
The building blocks gained by this strategy open synthetic access in different directions. Compounds **45** with their terminal acetylene functionality can be Sonogashira coupled with a halo functionalized aryl, while halo functionalized compounds **42** or **43** can be used for either Sonogashira, 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.



*Scheme 22. Synthesis of iodo functionalized phenylethynylene **46**.*

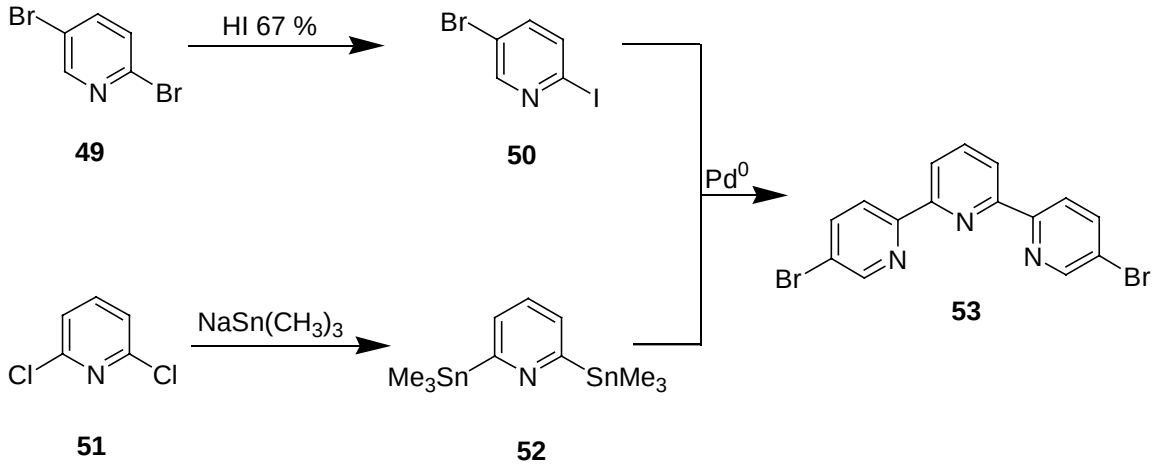
It may be useful to introduce an iodo functionality at a later stage in synthesis; **48** contains a terminal acetylene functionality for Sonogashira coupling and a TMS functionality as a placeholder for iodo, which can easily be iodo-de-silylated with iodine chloride (Scheme 23). The Sonogashira coupling 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.



*Scheme 23. Synthesis of TMS protected phenylethyne **48**.*

4.2.2 Synthesis of the terpyridine unit

2,2':6',2"-Terpyridine derivatives are important ligands in coordination chemistry,[118,119] e.g., as photosensitizers,[120] and a large number of synthetic approaches have been published.[121] While in the most widely used methods, e.g., by Kröhnke,[122] the central pyridine ring is assembled by the condensation of the two appropriately functionalized side pyridines, another strategy is to couple three pyridine rings.

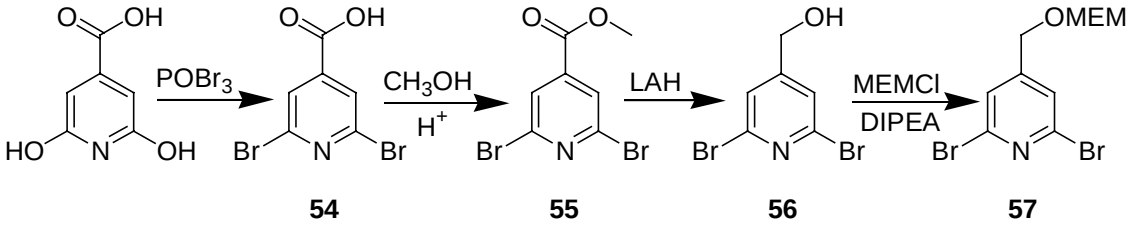


*Scheme 24. Synthesis of dibromo terpyridine **53** according to Lehmann.*

Basing on the pioneering work by Yamamoto[123] and Sauvage[124] 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.[27,29] **53** was prepared according to this protocol using the Stille cross coupling to connect the bisstannylated central pyridine **52** and the 5-bromo-2-iodo functionalized pyridine sides **50** (Scheme 24).[29] 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.[125-127] Pyridine compounds which carry a TMSn functionality *ortho* to the nitrogen atom generally tend to proto-de-stannylate on the chromatography column or when exposed to humidity.[28] 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**.[128] 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^0 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.[27] Very recently, Sauvage reported an improved method by coupling two 5-bromo-2-TMSn-pyridine sides to a central 2,6-diiodopyridine.[129]

Stille reactions are generally worked up by extraction with potassium fluoride solution and filtration of the precipitate to bind the highly toxic trimethylstannyl halogenides.[130] **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.

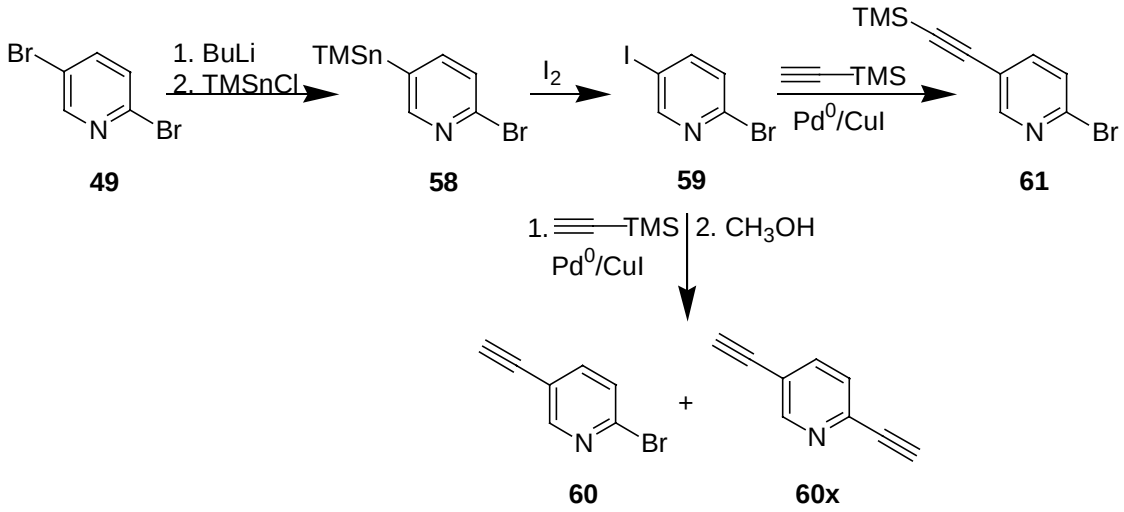


*Scheme 25. Synthesis of 4-functionalized pyridine **57** according to Lehmann.[27]*

A 4-functionalized central unit **57** was prepared according to Lehmann (Scheme 25).[27] 2,6-Dihydroxypyridine-4-carboxylic acid is brominated with in situ generated phosphorous oxy chloride to give **54**[131] 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.[27] 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[132] and Bolm.[133] This regioselectivity is explained by a thermodynamic regime of the reaction.[134] The 2-lithiated compound forms faster, but repulsion of the negative charge next to the free pair of electrons of the nitrogen

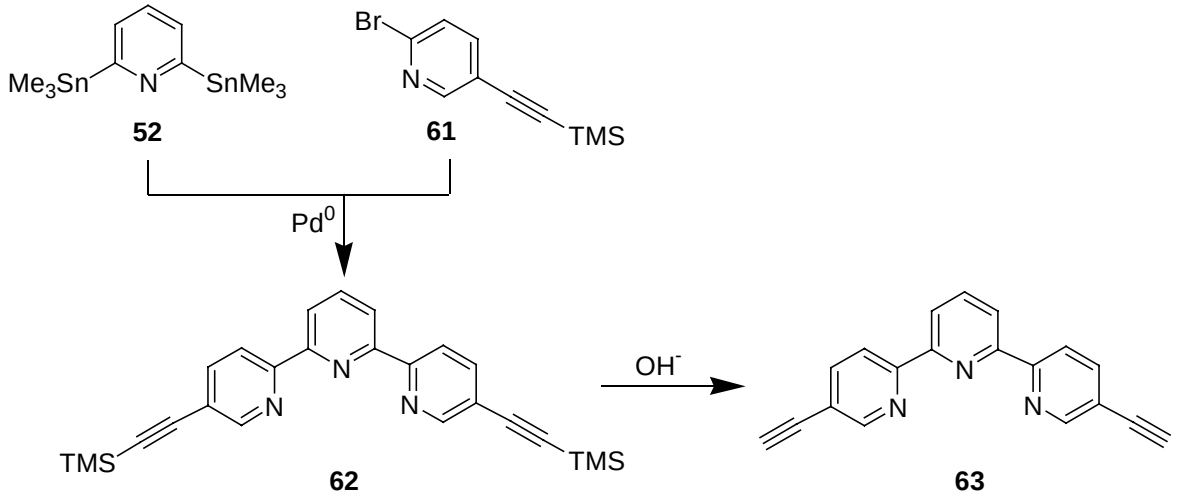
leads to rearrangement to the 5-lithiated species. Henze used this to prepare 2-bromo-5-iodopyridine **59** (Scheme 26).[31] **49** was lithiated and stannylated to give **58**, which can be purified by column chromatography without any problems; here, recrystallization proved to be ineffective as it 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**.[135]



*Scheme 26. Synthesis of ethynylated pyridine **61**.*

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** (δ = 0.28 ppm) has totally disappeared. The characteristic peak at δ = 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**.*

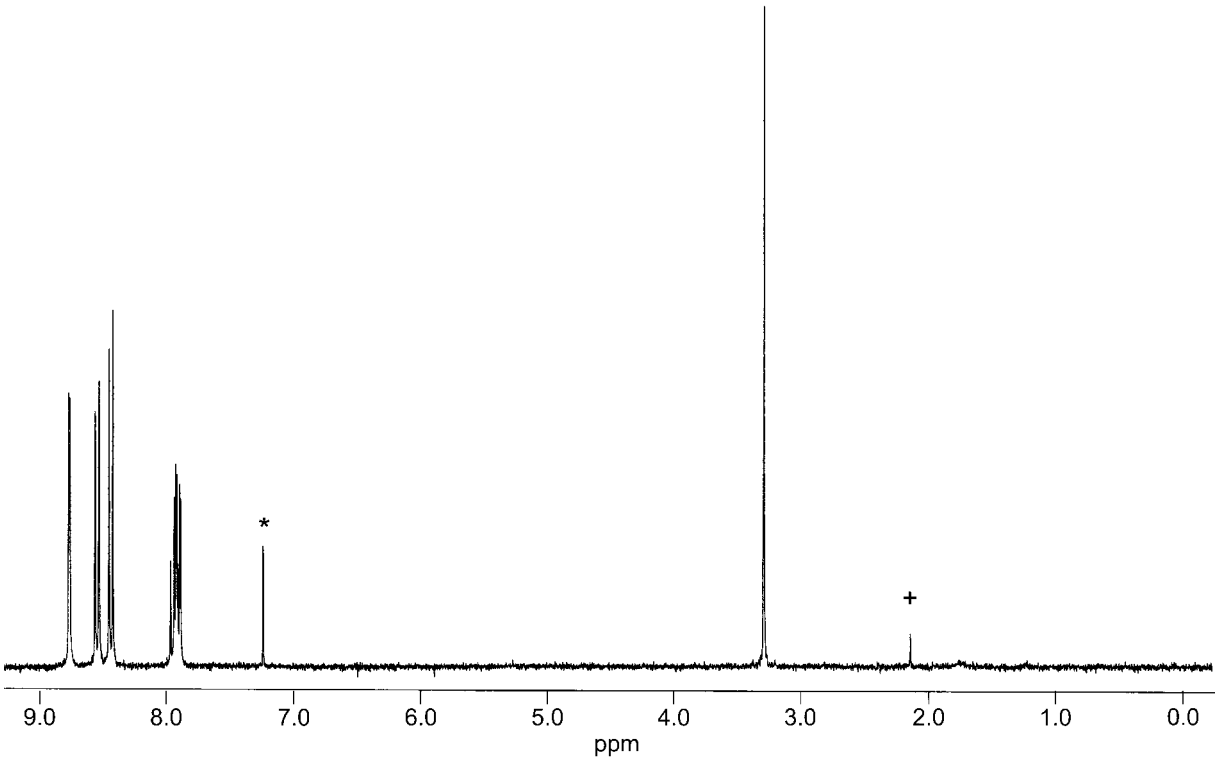
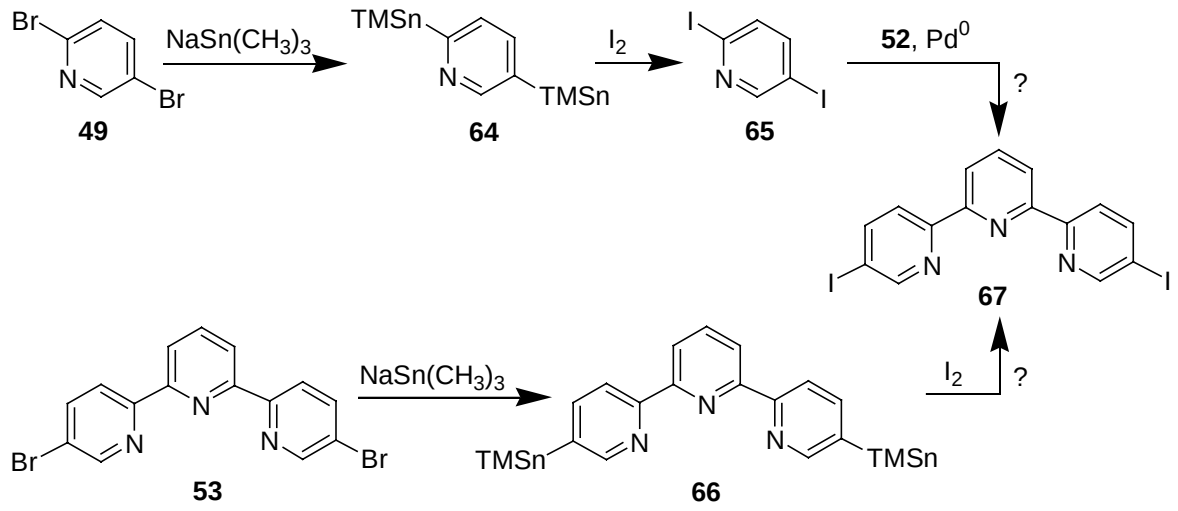


*Fig. 5. ^{1}H-NMR spectrum of compound **63** (270 MHz, * = $CDCl_3$, + = acetone).*

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.[28] 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. [27]

First, the route via iodinated pyridine **65** was tried. As described by Yamamoto,[125] 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

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.

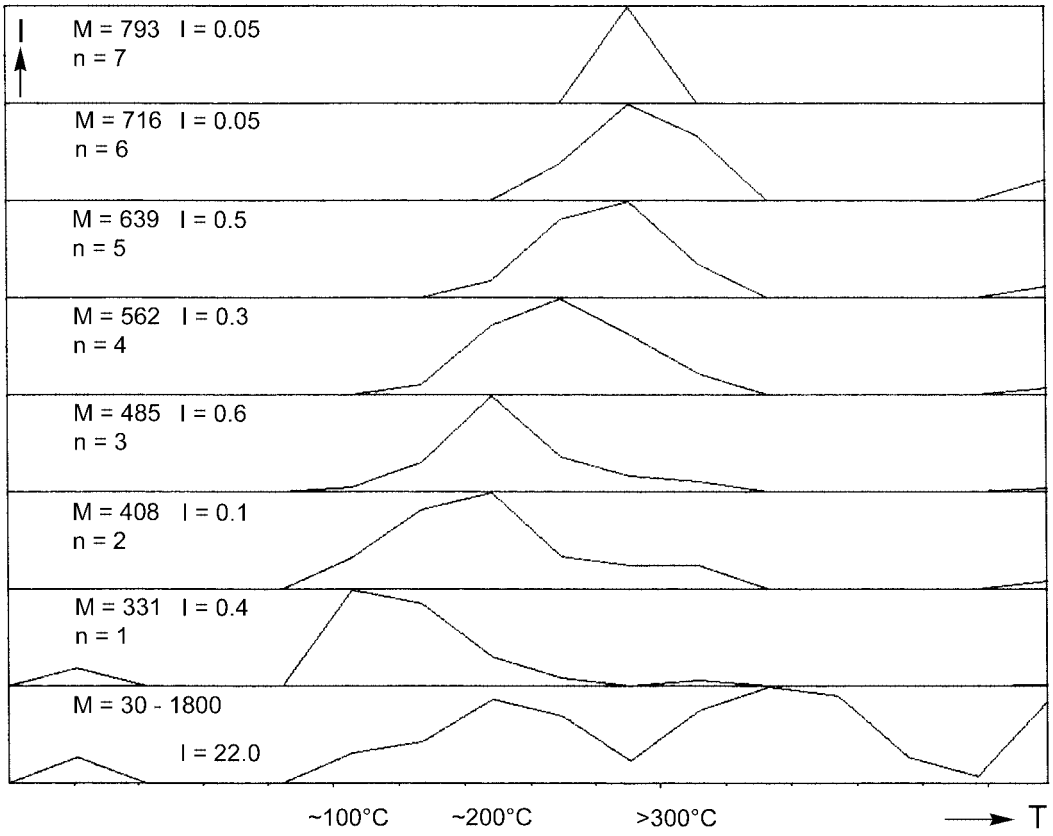
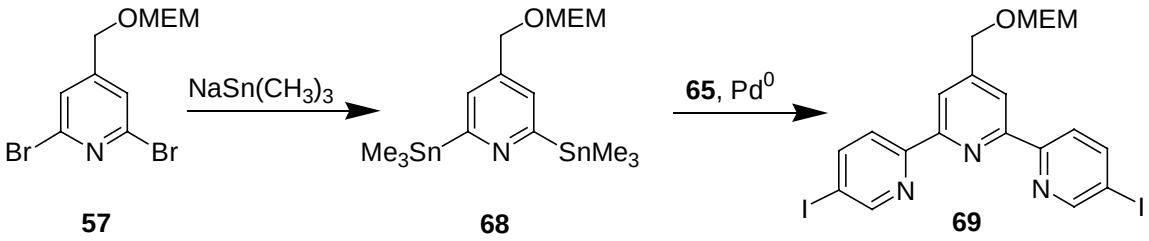


Figure 6. EI mass chromatogramms (ion intensity versus temperature) for ***67*** $_{n}$ *with n = 1 to 7. The integrated intensity values I are given.*

In EI and FAB(+) measurements, signals were detected which could be assigned to a variety of diiodo oligopyridines **67**$_{n}$, I-[C_5H_3N]$_n$-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 3 D 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 $\mathbf{67_n}$ 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.



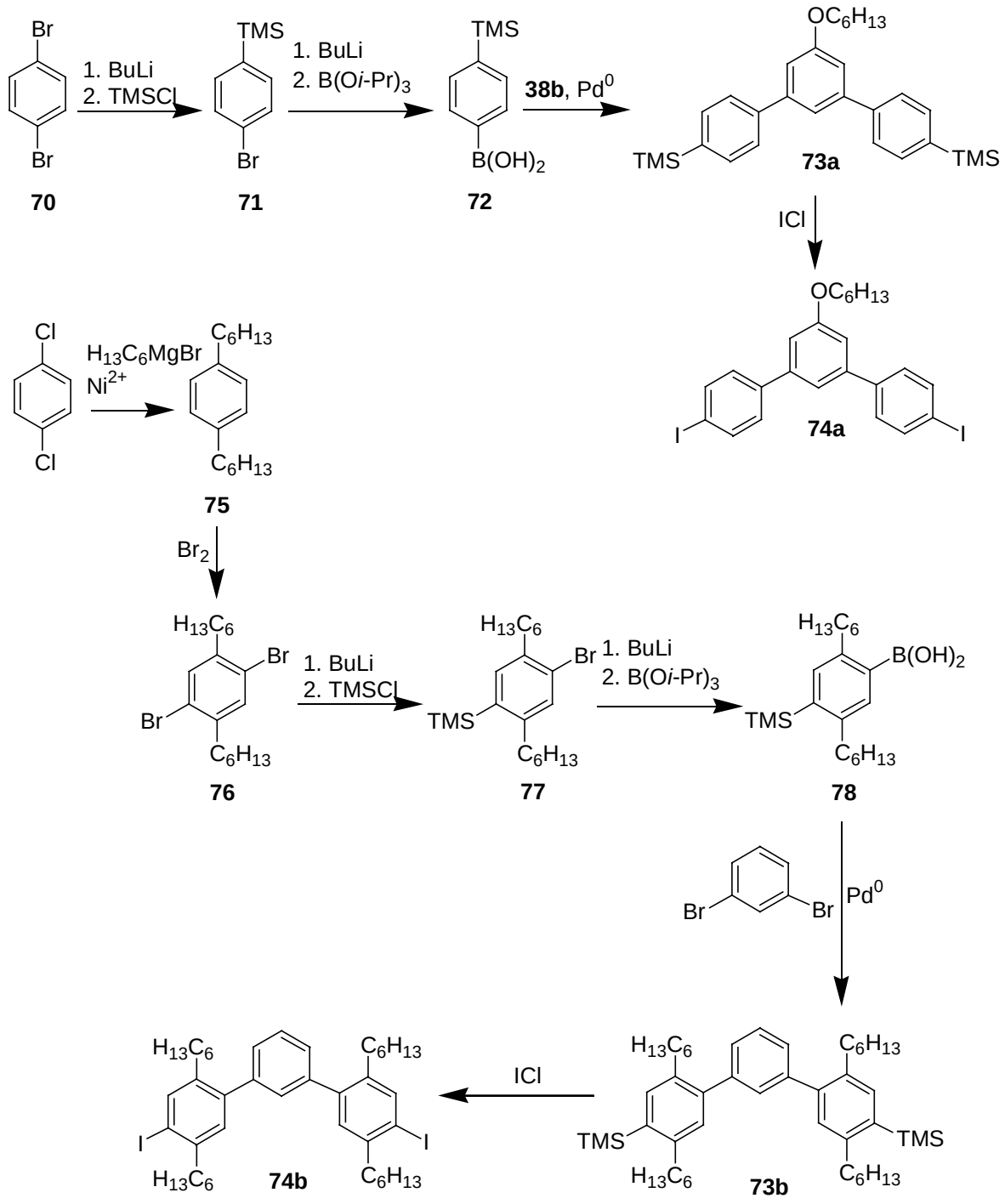
57 **68** **69**

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

4.2.3 Synthesis of the *m*-terphenyl unit

Two new 4,4"-functionalized *m*-terphenyls **74a** and **74b** were prepared (Scheme 30). In both cases, the central *meta*-difunctionalized aromatic was coupled with two boronic acid

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[136] of *p*-dichlorobenzene with hexyl bromide[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 ^{1}H-NMR (Fig. 7) documents the symmetry of pure compound **74b**, with the two intensive peaks at δ = 7.7 ppm and δ = 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 δ = 0.36 ppm.

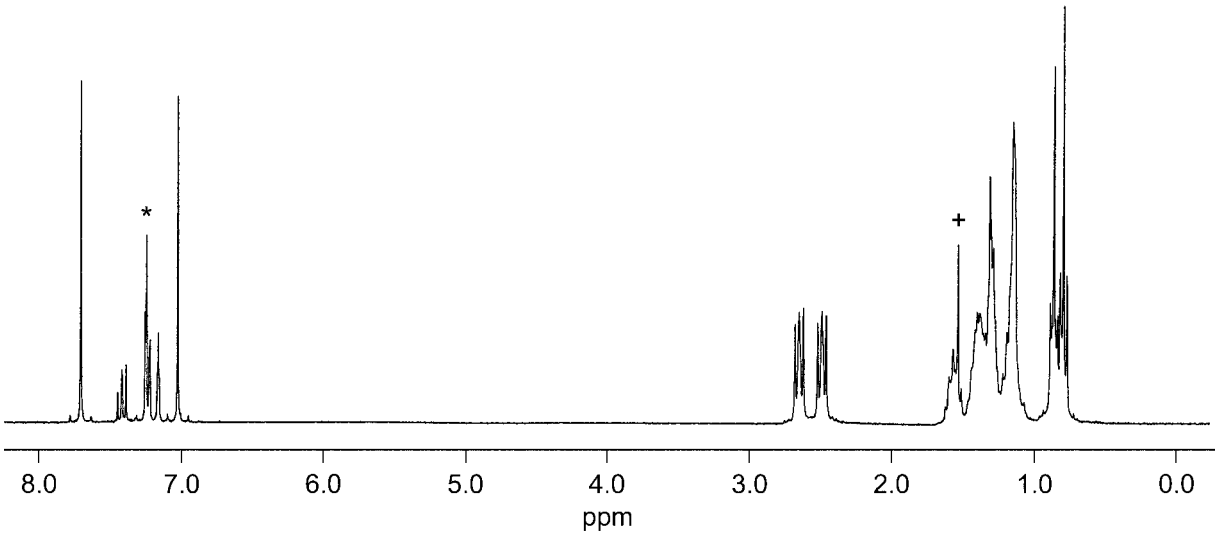


*Fig. 7. ^{1}H-NMR spectrum of compound **74b** (270 MHz, * = $CDCl_3$, + = H_2O).*

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.