Covalent template-assisted synthesis of mechanically interlocked molecules

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Luuk Steemers

" Because a thing seems difficult for you, do not think it impossible for anyone to accomplish "

- Marcus Aurelius (Roman emperor 161-180 AD)

COVALENT TEMPLATE-ASSISTED SYNTHESIS

OF MECHANICALLY INTERLOCKED MOLECULES

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

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Chapter I: General Introduction

Interlocked structures are present all around us. They can be found in functional materials such as chains, knots and nooses, but also in shoelaces or a ring on a finger, for example. They are also found in decorative patterns such as in jewelry and clothing, but also in religious objects and architecture. Historically, mankind has given strong spiritual and symbolic meaning to these kinds of interlocked structures and are therefore found in cultures all around the world. Some well-known stories include interlocked structures, such as Alexander the Great's cutting of the Gordian knot which is still used as a metaphor for thinking outside-the-box.

Scientific interest in interlocked structures started in the 19th century with the development of mathematical knot theory. Further interest was sparked in the 20th century with the discovery of naturally occurring interlocked structures, starting with the discovery of catenated DNA[1,2]. Later, trefoil knots in single- and double-stranded DNA[3,4] and even higher types of knotted DNA were found.[5] Discovery of these knots was made possible *via* imaging by electron microscopy, owing to the relatively large size of DNA strands. Smaller knots were identified only relatively recently, starting with the discovery of a peptide knot in (*S*)-adenosylmethionine synthetase.[6,7] Advances in X-ray crystallographic analysis have led to the discovery of a multitude of knotted protein and peptide structures.

In addition to the knotted interlocked structures, so-called mechanically interlocked molecules have been synthesized. These consist of two or more separate molecules interlocked in such a way that they behave as a single entity. The best example is the catenane that consists of two interlocked rings. To separate these rings it would need the breaking of a covalent bond in one of the rings. Another well-known class of mechanically interlocked molecules are the rotaxanes that contain a thread that is trapped within a ring. This thread contains large stopper groups to prevent the dissociation of the two components. It can also incorporate certain functionalities, allowing for the creation of 'stations' to which the ring can move to depending on the conditions, for instance stimulus by pH change, heating or irradiation. The 'shuttling' between stations can be translated as 'on' and 'off', leading to potential applications as molecular switches or molecular storage devices.[8] Due to the nanometer scale of these molecular switches, a storage device based on these switches could potentially allow a 100- to 1000-fold increase in storage capacity.

Intriguingly, mechanically interlocked products have also been identified in natural products, most notably in the lasso peptides (see the end of this chapter). Besides their unique topology, some of these peptides display interesting biological activity that probably arises from its interlocked and well-defined structures. Some of the reported biological activities include enzyme inhibition, antimicrobial and receptor antagonist activity. Most interestingly, microcin J25 (the most well-known lasso peptide) displays inhibition of Gram negative RNA polymerase, giving it a potential application as an antibiotic.[9] Siamycin type lasso peptides display activity against HIV fusion and replication.[10] Lastly, sungsanpin displays activity against certain lung cancer cell lines.[11]

The 2016 Nobel Prize for Chemistry was awarded to professors Sauvage (Fr), Stoddart (UK/US) and Feringa (NL) for their work on the development of molecular machines. A major part of these developments in the field of nano-technology was made possible due to the discovery of mechanically interlocked molecules. The Nobel prize is the crowning glory of this work, underscoring the potential of mechanically interlocked molecules and molecular machines in science.

General structural aspects of mechanically interlocked products

Rotaxanes and catenanes are the most important types of mechanically interlocked compounds. A rotaxane is a molecule that consists of a thread with bulky stopper groups that is mechanically interlocked ('trapped') within a ring fragment. The bulky stopper groups prevent dissociation (or 'dethreading') of the ring *via* steric hindrance (see figure 1). Throughout this thesis ring and thread fragments are schematically depicted in blue or red, respectively. A pseudorotaxane is structurally related, but lacks stopper groups that are sufficiently large to prevent dissociation. A closely related class of molecules are the catenanes, consisting of two mechanically interlocked rings. In general, the rotaxanes and catenanes as discussed have the [2] prefix, meaning that the molecule consists of two components (one ring and one thread for the rotaxane, two rings for the catenane). [1]rotaxanes are also known, in which the ring and thread fragments are covalently linked. Interestingly, the naturally occurring lasso peptides show this [1]rotaxane architecture (see end of this chapter). The more elaborate rotaxanes and catenanes, such as a [3]rotaxane, are outside the scope of this thesis.[12]
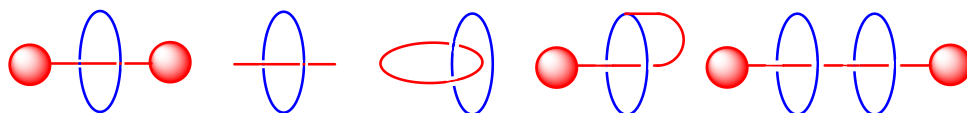

Figure 1: Left to right: a [2]rotaxane, pseudorotaxane, [2]catenane, [1]rotaxane and [3]rotaxane

Rotaxane syntheses strategies

Before going into detail, at first an overview of the synthetic strategies towards rotaxanes is presented. Rotaxane syntheses can be categorized in two main types, i.e. templated or non-templated. For the templated rotaxane three main types of strategies can be discriminated: clipping, capping and by active-metal templating. For rotaxanes that are made *via* the non-templated strategies, slipping and statistical approaches have been reported. In the following paragraphs examples of these methods will be discussed.

<u>Non-templated strategies towards [2]rotaxanes</u>

Historically, a non-templated strategy was among the first synthetic approaches for the synthesis of a [2]rotaxane. From the non-templated approaches, the slipping approach (see scheme 1, A) encompasses the heating of a mixture containing preformed ring and thread fragments, forming the rotaxane *via* slippage of the ring over the stopper groups of the thread. After cooling, the ring gets kinetically trapped, forming the rotaxane skeleton. It is for this method a prerequisite that the stopper groups are not too bulky, otherwise slippage cannot occur. On the other hand, if the stopper groups are too small, an unstable product will be formed that will dethread over time. Whether this method is a true rotaxane synthesis strategy remains to be debated, as the products are basically kinetically trapped pseudorotaxanes.
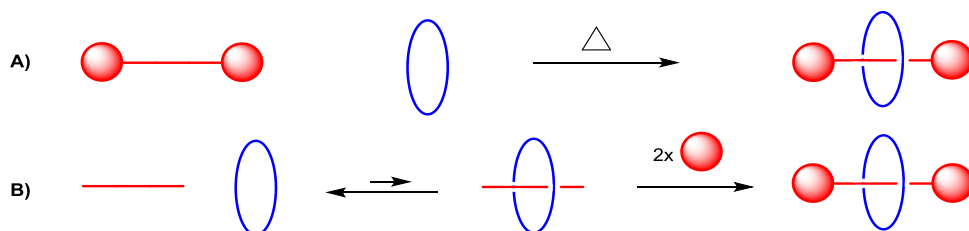

Scheme 1: Slipping approach (A) and statistical approach (B)

The non-templated statistical approach (scheme 1, B) is one of the least used and more a historical method relying on the statistical 'capture' of a thread fragment within a completed ring. Apart from weak Van der Waals forces, there are no interactions between the ring and thread fragments, thereby lacking a preference for the formation of the pseudorotaxane intermediate. Usually, a large excess of thread fragment and capping reagent is added to form some product. Conceptually, the 'capping' method is the same, but non-covalent interactions favor formation of the pseudorotaxane intermediate.

Syntheses of [2]rotaxanes using templated strategies

Among the templated strategies, the clipping approach uses a preformed thread fragment and a linear ring fragment precursor. This linear ring-precursor is coordinated to the thread *via* non-covalent interactions (depicted as dashed lines in scheme 2, A), such as crown ether-ammonium, electrostatic, or H-bonding. Subsequent ring-closure yields the entrapped thread due the pre-organization and completes the rotaxane. Alternatively, a missing fragment may be added (scheme 2, B) that reacts with the termini on the ring precursor, thus completing the rotaxane. Usually the non-covalent interactions used during pre-organization are retained in the final product.
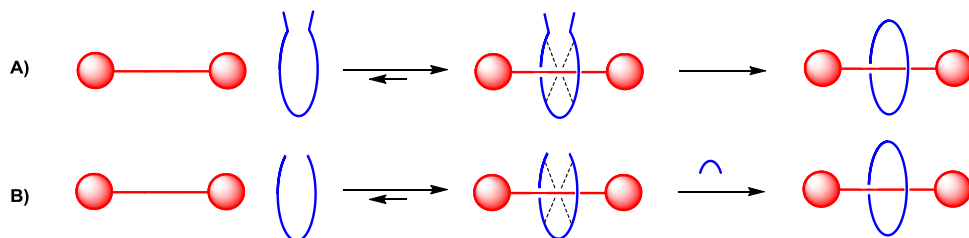
Scheme 2: The clipping approach. A) *via* a ring closing reaction B) *via* addition of a missing fragment

The capping approach starts from a preformed macrocycle that forms a complex with an unstoppered thread fragment (see scheme 3). It is conceptually the same to the statistical approach, but non-covalently interacting functional groups at the ring and thread fragments favor the formation of a pseudorotaxane intermediate. Subsequent reaction of the thread termini with two bulky stopper groups completes the rotaxane. The capping approach is by far the most used method, due to its robustness, ease of synthesis and/or the easy availability of the components.
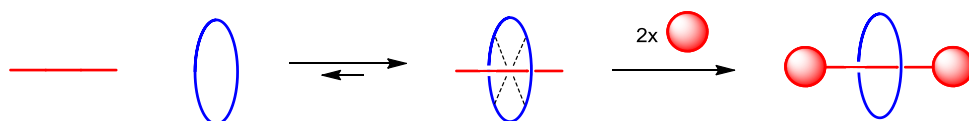
Scheme 3: The capping approach

The active-metal template approach is the latest development and therefore the most advanced. In this strategy (see scheme 4), a catalytically active transition-metal (black dot) is coordinated within a preformed ring fragment. Subsequent coordination of two non-equivalent thread halves (= bulky group with a functionality attached) leads to the formation of a rotaxane-like intermediate (scheme 4, bottom right). Due to steric reasons the thread halves each occupy one side of the ring. In most approaches, reductive elimination from the metal ion results in covalent bond formation between the two halves, thereby completing the rotaxane. Alternatively, the metal-ion may only activate the functional groups, leading to the covalent bond formation, without change in oxidation state. The metal ion can be subsequently decomplexed from the ring, or it may dissociate spontaneously. Also syntheses were described using the metal in a catalytic amount.[13,14,15]
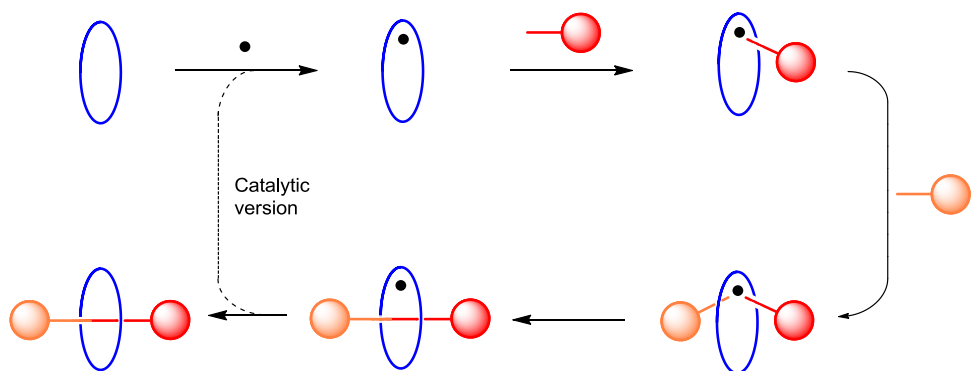
Scheme 4: Active metal template approach

Special strategies towards [2]rotaxanes

In addition to the three main templated methods for synthesizing rotaxanes, some special (i.e. non-classical) strategies have been reported. The swelling approach (see scheme 5, A) involves the formation of a pseudorotaxane *via* non-covalent interactions with a thread that has one or two small stopper groups.[16,17] Upon stimulus (i.e. heating or irradiation) of these small groups, a chemical reaction, such as an electrocyclization, forms a new and larger stopper group. This new stopper group is sufficiently large to prevent slipping of the thread out of the ring.

The shrinking method (scheme 5, B) involves the formation of a pseudorotaxane with a thread fragment bearing stopper groups that are sufficiently small to allow the ring to slip over.[18,19,20] The ring fragment subsequently undergoes a transformation that leads to a ring-contraction. Due to the decreased ring-size, the stopper groups are now sufficiently bulky to prevent dethreading.
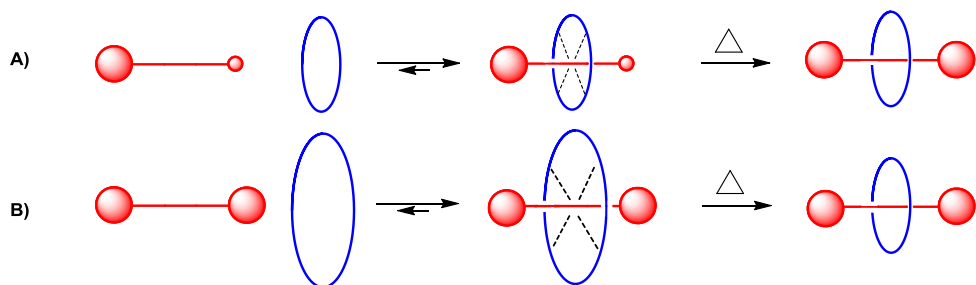
Scheme 5: The swelling (A) and shrinking (B) approaches

Finally, also covalent methods exist that are in most cases analogous to the 'clipping' or 'capping' approaches. The difference, as the name implies, is the use of a temporary covalent bond between the ring and thread. Cleavage in a later stage liberates the free rotaxane or catenane. As will be discussed below, the pioneering work in the 1960's on mechanically interlocked molecules was performed using the covalent approach. Recently, some groups have re-introduced the concept (see later on in this chapter), but the covalent approach remains an underused strategy, although it obviates the need for non-covalent interactions to pre-organize the components.

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Historic overview of the synthesis of mechanically interlocked molecules

The early work toward [2]rotaxane and [2]catenane syntheses was described in a very important book by Schill in 1971, summarizing both the successful and unsuccessful attempts by the various groups that pioneered this field.[21]

One of the first reported rotaxane syntheses relied on a statistical synthesis and was reported by Harrison and Harrison in 1967 (see scheme 6).[22] As the method, 2-hydroxycyclotriacontanone **1** was reacted with succinic anhydride to introduce a tethered carboxyl group in **2**. The sodium carboxylate of this acid was immobilized *via* reaction with chloromethylated Merrifield resin, leading to immobilized macrocycle **3**. Subsequent treatment with 70 (!) cycles of 1,10-decanediol and trityl chloride gave, after cleavage from the resin, 6% yield of [2]rotaxane **4**. This construct was reported stable up to 200 ^{o}C and the molecular structure was confirmed *via* two methods. Firstly, acidolytic cleavage of the trityl moiety gave the separated individual trityl alcohol, 1,10-decanediol and macrocycle **1**. Secondly, oxidative cleavage of the α-hydroxyketone to the diacid with silver dioxide gave, after esterification, 1,28-octacosanoic-diacid dimethylester and the intact thread fragment (1,10-decanediol-bis-trityl ether).
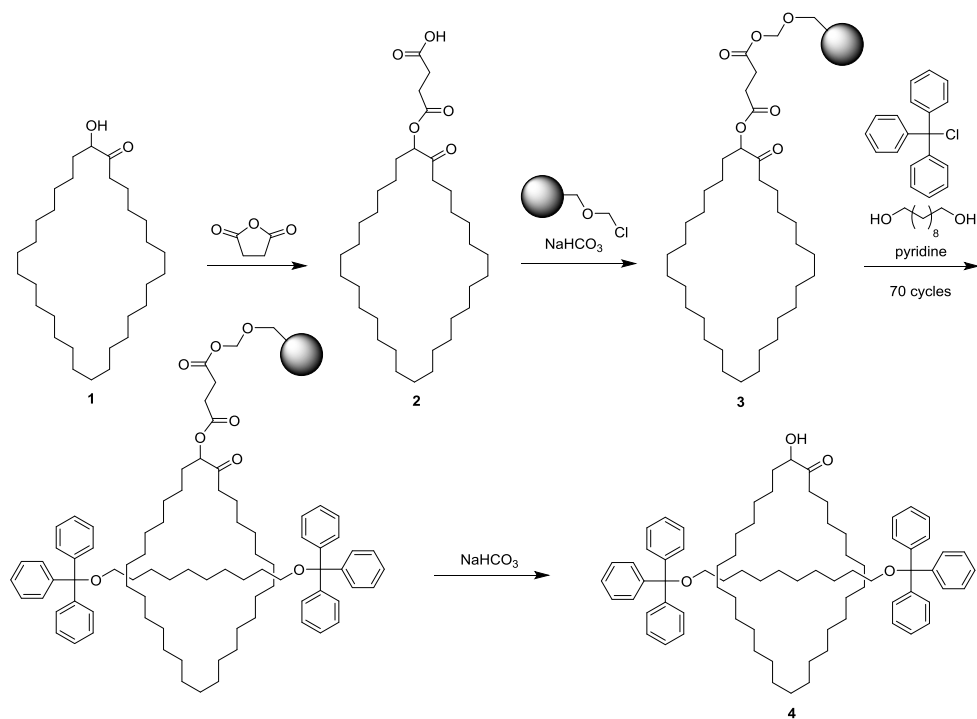
Scheme 6: Statistical synthesis of a [2]rotaxane as described by Harrison and Harrison[22]

Although generally inefficient, a related statistical method was used to construct a [2]catenane, as reported by Zilkha in 1976 (see scheme 7).[23] In this work, crown ether **5** containing a polyethylene glycol chain with on average 20 oxygen atoms, was mixed with an equimolar amount of polyethylene glycol **6** (with on average of 9 oxygen atoms) and stirred at 120 ^{o}C for 30 min to form pseudorotaxane intermediate **7.** Subsequent reaction with a slight excess of trityl bromide **8** and solid K$_2$CO$_3$ yielded [2]rotaxane **9** in a relatively good 18% yield, after just one cycle. The relatively high yield suggests the presence of attracting interactions between the two components and not

only statistical capture of the thread fragment. Also the fact that despite the huge size of the ring (average 60-membered) in combination with relatively small stoppers, no dissociation of the ring was observed suggests this attraction. After subjection of the [2]rotaxane to a Zn/Cu couple, the two benzylic positions in the trityl groups were connected *via* a reductive coupling, giving [2]catenane **10** in 14% yield.
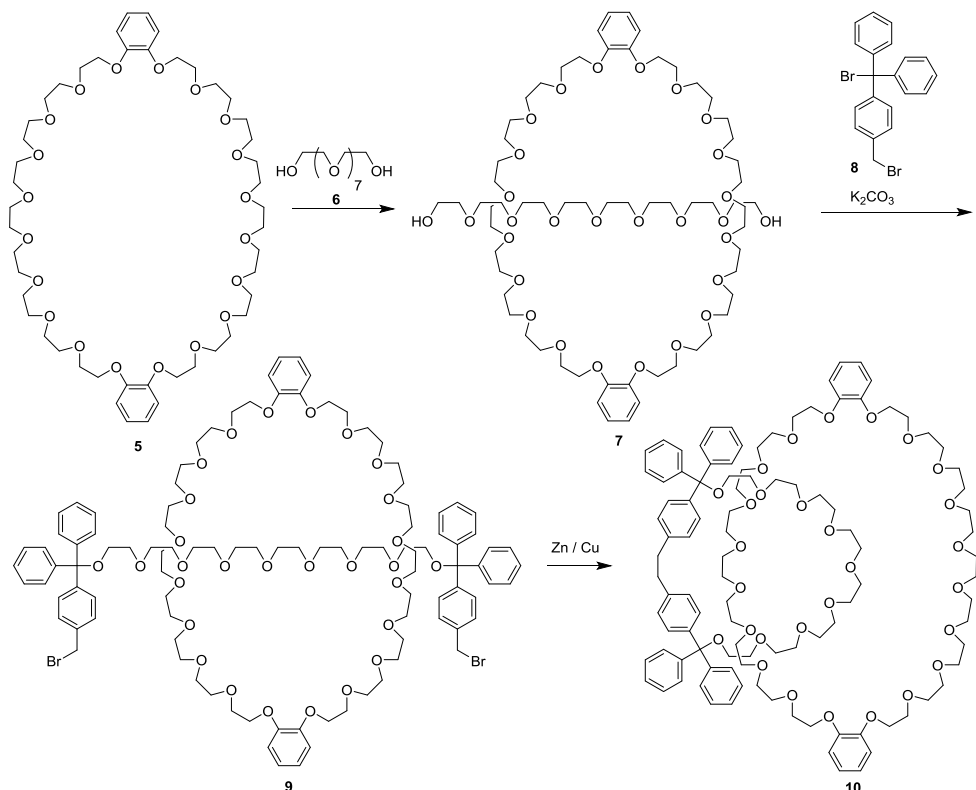
Scheme 7: Statistical synthesis of [2]catenane **10** as reported by Zhilka *et al*[23]

The first covalent template-assisted syntheses of a [2]rotaxane and [2]catenane were reported in the 1960's by Lüttringhaus, Schill and Zollenkopf.[24,25] Although the first [2]catenane synthesis by Schill and Lüttringhaus was reported in 1964, an almost analogous [2]catenane was reported in 1967 by Schill from common intermediate **19**, which was also used for one of the first [2]rotaxane synthesis.

The synthesis started with the methylation of guiacol dialdehyde **11**, followed by a double Wittig reaction to introduce the C_{11}-carbon chains. Saponification gave di-acid **12** as a crystalline solid (see scheme 8). Treatment with HBr in acetic acid led to demethylation and the alkenes were hydrogenated with Pd/C, followed by $LiAlH_4$ reduction to give tetra-ol **13**. Subsequent acid-catalyzed ketal formation with 1,25-dichloropentacosa-13-one **14** gave ketal **15**. Next, the alcohol groups were protected as acetates and the phenyl ring was nitrated using cupric nitrate in acetic anhydride. Saponification of the acetates gave diol **16**, which was subsequently hydrogenated with Pd/C to give aniline **17**. This aniline was alkylated in the subsequent intramolecular macrocyclization step, under high dilution and *in-situ* Finkelstein conditions to give macrocycle **18**. Treatment with PPh_3Br_2 converted the alcohols to bromides, finishing the synthesis of common intermediate **19**.
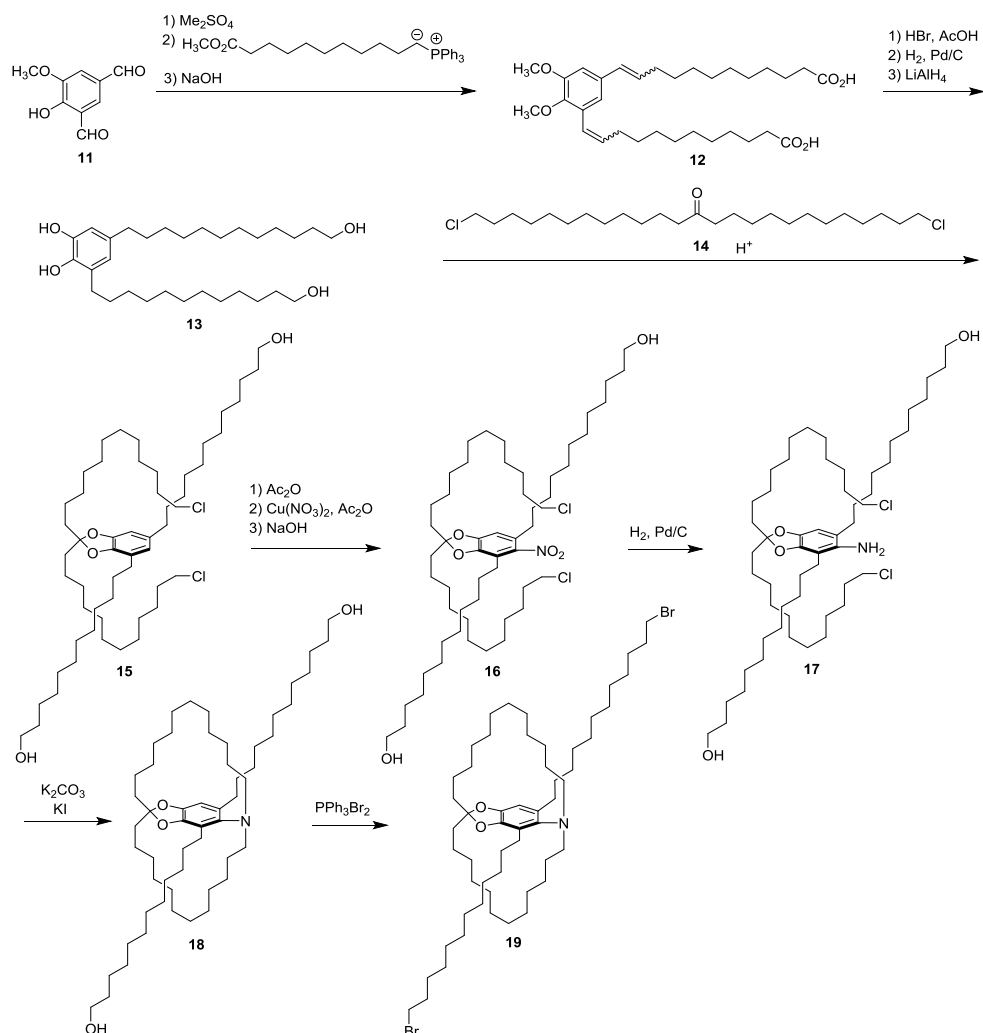
Scheme 8: Schill and Zollenkop's synthesis of precursor **19**

The Schill group reported in 1967 the subsequent transformation of precursor **19** to a [2]catenane (see scheme 9).[26] First, dibromide **19** was treated under diluted conditions with *p*-toluenesulfonamide and base, forming the macrocycle *via* double alkylation. Removal of the tosyl group with sodium and re-protection with acetic anhydride gave acetamide **20**. Hydrolysis of the ketal was accomplished with aqueous HBr, yielding **21**. To liberate the [2]catenane, the catechol derivative was oxidized with ferric sulfate to the *o*-quinone. Subsequent treatment with aqueous acid led to hydrolysis of the C-N bond. The liberated secondary amine and newly formed phenolic OH were acetylated and the *o*-benzoquinone core was subsequently reduced to the hydroquinone with metallic zinc. Further protection with acetic anhydride yielded [2]catenane **22**. The first synthesis of a [3]catenane was also reported by Schill in 1969 *via* a similar strategy.[27]
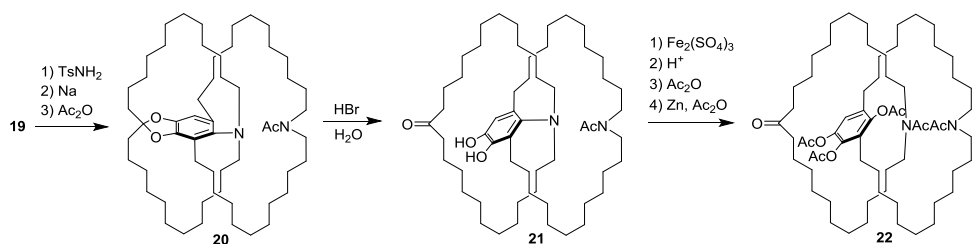
Scheme 9: Schill's synthesis of [2]catenane **22**

Schill and Zollenkopf reported two years later the first directed synthesis of a [2]rotaxane, starting again from common intermediate **19**.[28] To achieve this, the two bromides were substituted by the bulky sodium salt of 2,4,6-tris(p-tolyl)phenylacetamide **23**, giving pre-rotaxane **24** (see scheme 10). Analogous to the previous article by Schill, the ketal was hydrolyzed with aqueous HBr to give **25** and the aromatic C-N bond was oxidatively cleaved, eventually giving [2]rotaxane **26**.
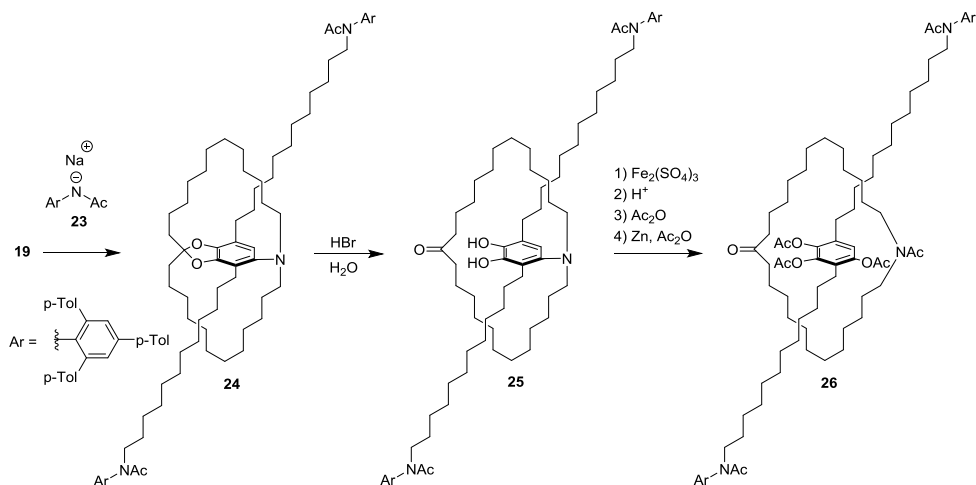
Scheme 10: Schill and Zollenkopf's synthesis of [2]rotaxane **26**

Rise of the non-covalent interactions

The field of rotaxane and catenane synthesis remained relatively quiet during the 1970's, until a breakthrough was reported in 1984 by Sauvage and Dietrich-Büchecker.[29] In this article, the use of a copper(I)-ion was reported for the pre-organization of two fragments containing a phenanthroline motif, giving organometallic complex **27** (see scheme 11). Subsequent alkylation of the phenolic OH's with diiodide **28** gave the bicyclic interlocked structure due to the directed tetrahedral pre-organization. Treatment with cyanide led to chemical removal of the copper(I) ion, yielding free [2]catenane **29**.
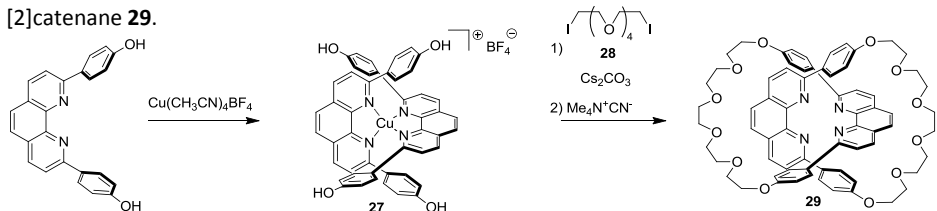
Scheme 11: Sauvage's synthesis of [2]catenane **29**, templated by a metal-ion

The use of non-covalent interactions from then on became very popular. In 1991, Stoddart reported the use of electrostatic interactions between an electron-rich aromatic core with an electron-poor cyclobis(paraqua-*p*-phenylene) ring for the synthesis of [2]rotaxane **32** (see scheme 12).[30] In this strategy, bis-ammonium ion **31** was clipped over the electron rich aromatic core in the thread **30**, followed by S$_N$1-type ring-closure by reaction with 1,4-bis(bromomethyl)benzene and AgPF$_6$, forming [2]rotaxane **32**.
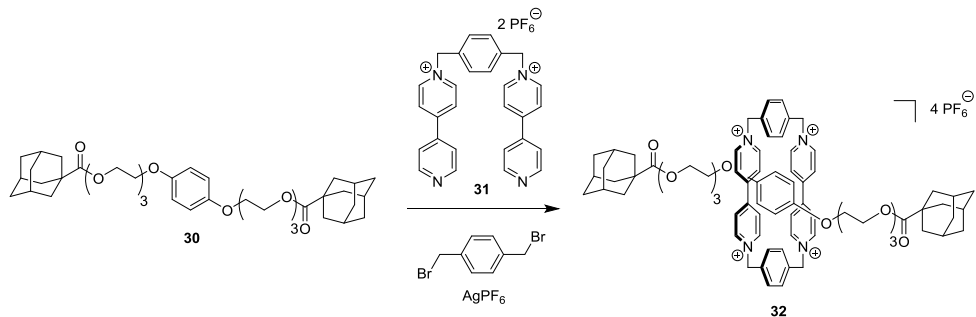
Scheme 12: Stoddart's synthesis of a rotaxane *via* electrostatic interactions

In 1995 the Vögtle group reported H-bonding as a non-covalent template strategy for the synthesis of a [2]rotaxane (see scheme 13).[31] In this approach, tetra-amide macrocycle **33** was complexed with isophthaloyl dichloride, forming intermediate **34**. In this pseudorotaxane intermediate, the amide N-H's form a hydrogen bond with the carbonyl oxygen atoms of the acid chlorides, thereby holding it into place. Subsequent stopper introduction by the addition of bulky aniline **35** provided [2]rotaxane **36**. Follow-up research by Vögtle showed that isophthaloyl dichloride can be substituted with other di-acid chlorides or sulfonyl chlorides, forming structurally similar [2]rotaxanes.[32]
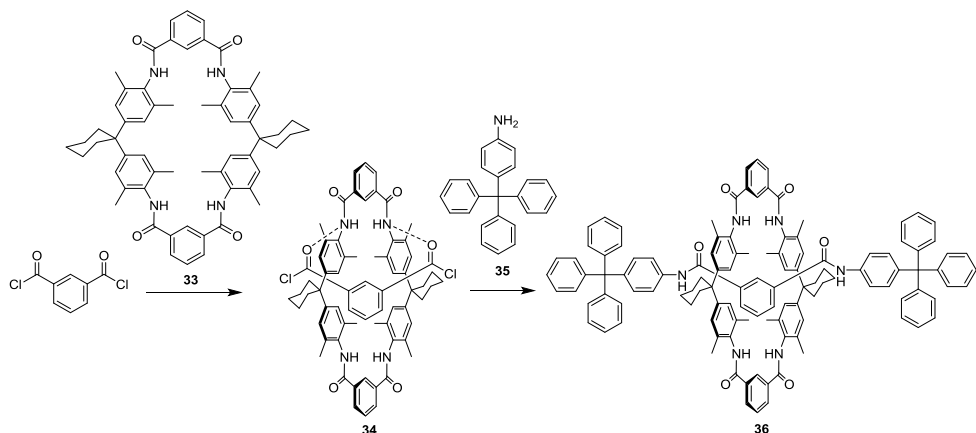
Scheme 13: Vögtle's synthesis of a [2]rotaxane *via* H-bonding

In 1996, Leigh *et al.* reported a related H-bond templated synthesis of a [2]rotaxane (see scheme 14).[33] Unlike Vögtle, the amide bonds in the thread fragment were used as the template, inducing a stepwise clipping-type ring-formation around this motif. Thread **37** was reacted with isophthaloyl chloride and *p*-xylylene diamine in chloroform, where **37** acted as the H-bonding template for the growing polyamide, eventually forming intermediate **38**. This intermediate can undergo a final cyclization, forming the tetra-amide bond containing ring around the thread. The structure was

proven by reacting the [2]rotaxane product **39** with NaOCH$_3$ to give transesterification, thereby cleaving off the stopper groups *via* methanolysis. Without the stopper groups present, the [2]rotaxane readily dissociated into the individual components. Follow-up chemistry by Leigh showed that multiple diamide groups may act as a H-bonding template for the ring-forming reaction, with the glycine-glycine motif being a popular one.[34]
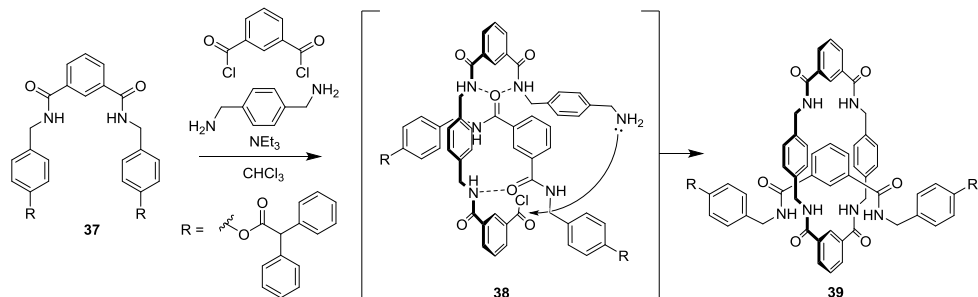
Scheme 14: Leigh's synthesis of a [2]rotaxane via H-bonding

The currently most popular methodology for rotaxane synthesis was first reported in 1996 by the Stoddart group using electrostatic interactions between secondary ammonium salts and crown ethers as the template motif (see scheme 15).[35] Due to the easy accessibility of secondary ammonium ions and the commercial availability of crown ethers (such as dibenzo-[24]-crown-8), using this strategy a wide variety of rotaxanes have been reported over the last 20 years.[36] In the first reported synthesis, secondary ammonium ion **40** and dibenzo-[24]-crown-8 were dissolved in CH$_2$Cl$_2$ to form pseudorotaxane **41** spontaneously in a reversible manner due to electrostatic interactions. Subsequent addition of di-*tert*-butylacetylenedicarboxylate and gentle heating initiated the concerted Huisgen cycloaddition between the azide and the alkyne to form the corresponding triazole. These were bulky enough to prevent dissociation of the ring, providing [2]rotaxane **42**.
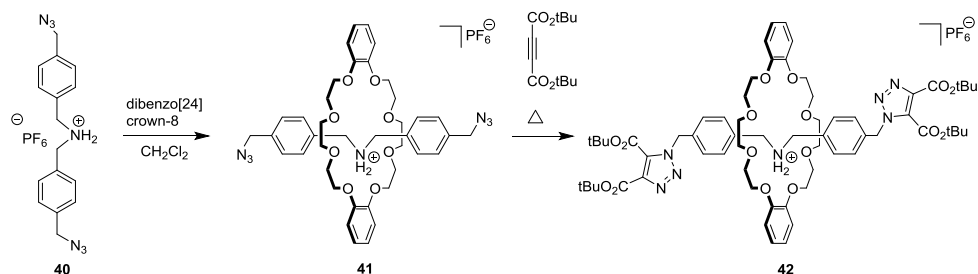
Scheme 15: Stoddart's syntheses of a [2]rotaxane via crownether ammonium interactions

The types of different reactions for covalent connection of a dibenzo-[24]-crown-8 pseudorotaxane (like **41**) and stopper groups is very diverse. Over the years, several functional groups for stopper connection have been reported, of which imine[37], ester[38], amide[39], urea[40], alkyne[41], alkene[42], phosphoamidate[43], silyl ether[44], thioether[45], isoxazole[46] and pyradizine[47] are the most common examples.

Covalent strategies

Despite the rise of non-covalent strategies, also some covalent strategies have been reported to follow up on the early work by Schill and Lüttringhaus. Due to the inherent necessity for certain motifs in non-covalent strategies, some research group reintroduced the covalent strategy, with the

aim to prevent the presence of such motifs in rotaxane and catenane products. In 1999, the group of Godt reported the use of a temporary covalent linker for the synthesis of a [2]catenane (see scheme 16).[48] In this approach, a preformed macrocycle is transformed into its chloroformate ester **43** and reacted with the sodium salt of ring-precursor **44**, giving carbonate ester **45**. Removal of the TMS groups from the acetylenes, followed by Glaser coupling led to the formation of precatenane **46**, together with some non-interlocked product (not shown). Hydrolysis of the endocyclic carbonate ester proved difficult, but eventually it was found that fluoride anions successfully cleaved the carbonate ester to give symmetric [2]catenane **47** in 63% yield, together with 23% yield of the non-interlocked ring. An overview regarding carbonate esters as temporary covalent linkers was reported by Godt in 2004.[49]
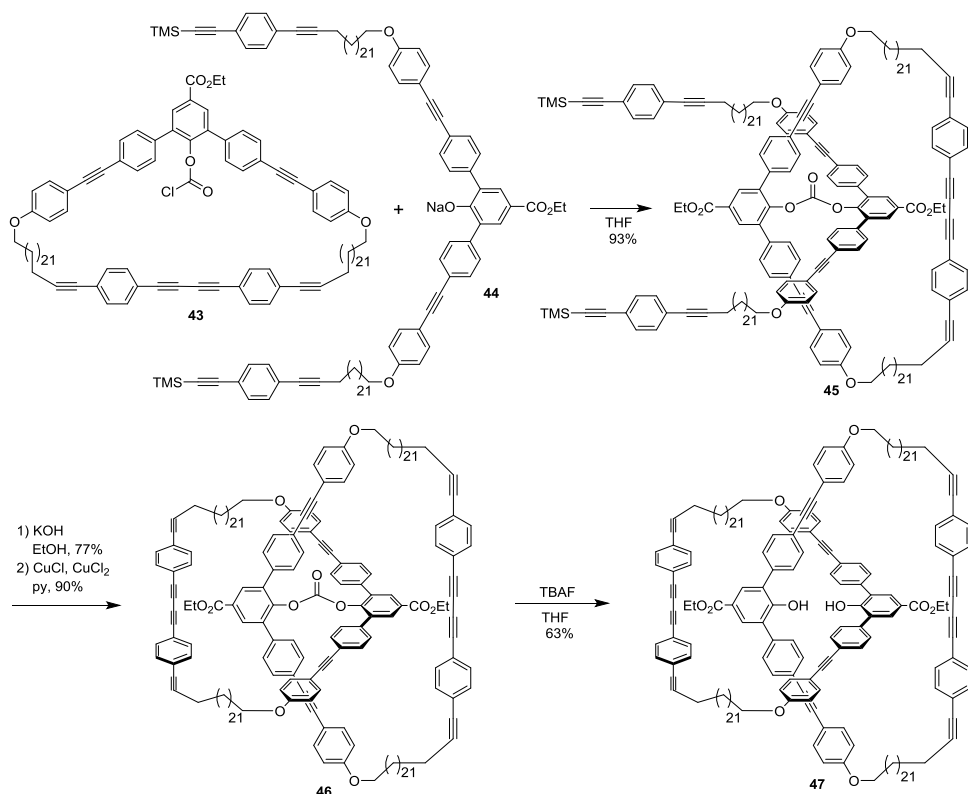
Scheme 16: Godt's [2]catenane synthesis employing a carbonate ester as temporary scaffolding covalent linker

The group of Yashima reported a very similar strategy to make a [2]catenane, although instead of a covalent carbonate ester, a carboxylate/amidinium ion pair was used as a non-covalent template.[50]

Suzuki *et al* reported in 2006 the synthesis of [2]rotaxane *via* a temporary imine bond (see scheme 17).[51] In this approach, macrocycle **48** was reacted with dialdehyde **49**, in which the aldehydes were positioned *trans* with respect to each other, forming almost quantitatively pseudorotaxane **50**. Removal of the TBS groups, followed by Williamson etherification with **51** installed the bulky stopper groups. To complete the [2]rotaxane **52**, the imine groups were hydrolyzed with aqueous TFA. To ensure that the reaction was irreversible, some 1,2-ethanedithiol was added to form acid-stable dithioacetals, thus stopping reversible imine formation.[52]
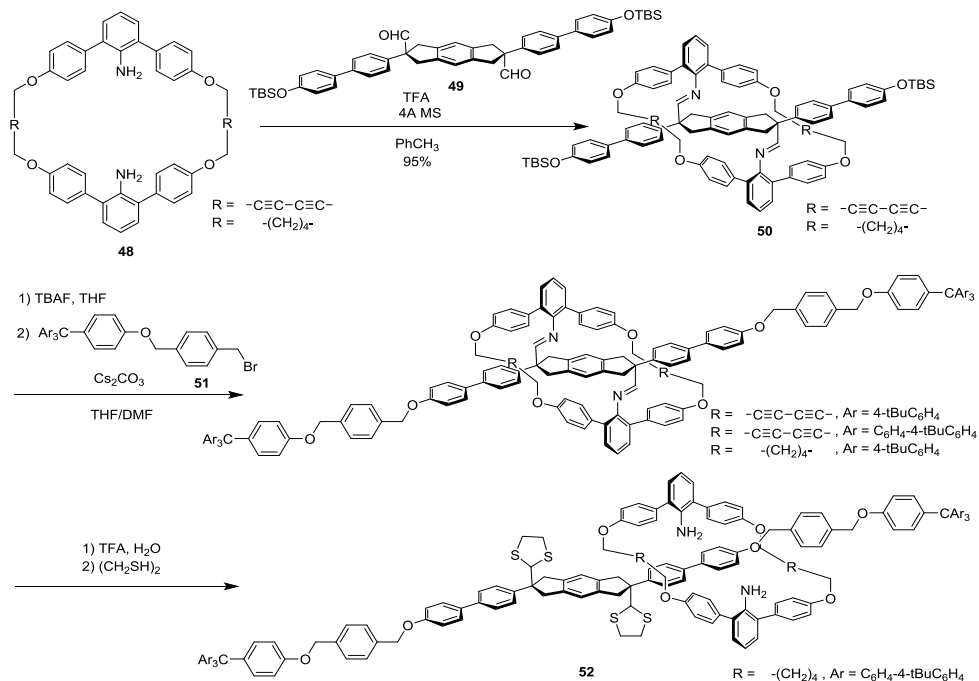
Scheme 17: Approach by Suzuki *et al* employing a temporary imine bond for the synthesis of a [2]rotaxane.

An elegant example of a rotaxane synthesis employing the covalent template approach was reported by the group of Watanabe in 2002 (see scheme 18).[53] In this approach, macrocycle **53** that contains two phenolic OH's was esterified with glutaroyl dichloride, giving bis-lactone **54.** Subsequent addition of a bulky primary amine led to aminolysis of the slightly activated esters. First, mono-ester intermediate **55** is formed that can undergo a second aminolysis reaction. This second aminolysis reaction can occur from either the same side as the ester (top-side of **55** in scheme 18), or from the sterically less hindered backside (bottom side), leading to [2]rotaxane **56**. Depending on the primary amine used, the yields varied from 26-56%. No reaction was observed for the anilines. As side products, the free macrocycle **53** and the non-interlocked bis-amides were formed, resulting from the second aminolysis to happen from the same side in intermediate **55**.

Scheme 18: [2]Rotaxane synthesis *via* ester aminolysis as reported by Watanabe *et al.*

In a related article by Kanesoto in 2004, a similar covalent strategy was used for the synthesis of a [1]rotaxane that is structurally similar to the lasso peptides (see next section).[54] To achieve this, the ring macrocycle **57** was functionalized with a secondary amine, which upon reaction with dodecanoyl dichloride formed an amide and a ester with one of the phenolic OH's, producing bridged bicycle **58** in a rather poor 24% yield (see scheme 19). Upon addition of bulky primary amine **59** in DMF, the ester moiety underwent aminolysis, producing [1]rotaxane **60** in 45% yield, together with non-interlocked product **61** in 20% yield. The [1]rotaxane was reported to be stable up to 160 °C.

Scheme 19: Synthesis of a [1]rotaxane as reported by Kanesto *et al.*

Although **60** is a chiral molecule, this was not identified as such. Nevertheless, the same group reported in 2004 one of the first deliberate syntheses of a chiral [2]rotaxane, although it was synthesized as a racemate.[55] Similarly, the group of Tobe reported in 2007 an aminolysis strategy for the syntheses of [2]rotaxanes containing an unusually small ring of 24 atoms.[56] As a result, the

thread fragments introduced *via* this aminolysis reaction did not require very bulky groups. A 3,5-dimethylphenyl group was already bulky enough to prevent the dissociation of the ring from the thread. To date, the smallest synthesized rings in rotaxanes contain a 21-membered crown ether ring. Smaller rings seem unfavorable due to steric repulsion.[57]

Naturally occurring interlocked compounds

Most interestingly, several interlocked compounds have been found in nature, mostly as knotted architectures in proteins and DNA.[58,59] More recently, also rotaxane or catenane structures were identified. Probably the most well-known class of naturally occurring mechanically interlocked compounds are the lasso peptides.[60] Lasso peptides are small (15-26 amino acids in total) and contain a macrocycle with 7-9 amino acids that emerges from tail-to-side chain cyclization of the *N*-terminus with a glutamic acid or aspartic acid side chain residue. The rest of the peptide forms a loop and a part of this loop is mechanically interlocked within the macrocycle. The stopper groups that hold the peptide macrocycle in place are the side chains of tryptophan, tyrosine, phenylalanine, histidine and (iso)leucine. A 2015 article reported 38 different lasso peptides had been identified.[60] Recently, the group of Sulkowska reported the existence of even more complex mechanically interlocked, naturally occurring peptides/protein (see figure 2).[61] Among these structures are doubly and triply threaded lasso's and double strand lasso's.
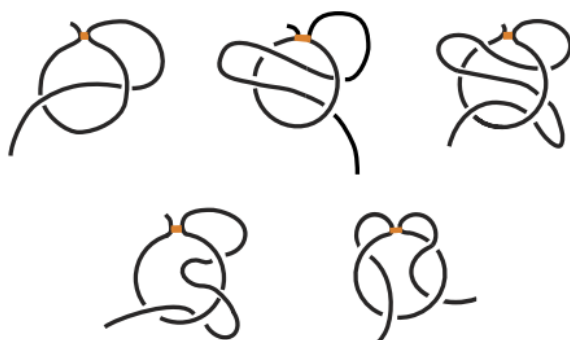

Figure 2: Complex interlocked peptides and proteins. Figure taken from ref 61.

Within the lasso peptide series, one of the first identified and most well studied member is the 21-amino acid microcinJ25 (see figure 3).[62] Previously this was thought to be a peptide macrocycle, but in 2003 it was unequivocally and independently proven by three groups that it possesses a lariat (lasso) structure, more specifically a [1]rotaxane (see beginning of this chapter).[63,64,65] Microcin J25 consists of a 26-membered ring, built up from eight amino acid residues in which the *N*-terminus of Gly_1 has ring-closed to the side chain of Glu_8. Through this cyclic octapeptide the rest of the peptide loops back. The thread is locked by the side chains of Phe_{19} and Tyr_{20}. These relatively large amino acid side chain residues act as stopper groups, to prevent the dethreading of the ring. Moreover, because these two residues are so close together, the ring is locked very tightly. Other lasso peptides usually have more space between the two stopper groups. MccJ25 is highly stable towards dethreading. Thermolysin mediated cleavage of the loop between the Phe_{10}-Val_{11} bond gave a [2]rotaxane that was stable in 8 M urea at 65 °C (strongly denaturing condition) and did not dethread until heated at 165 °C.[66,67]
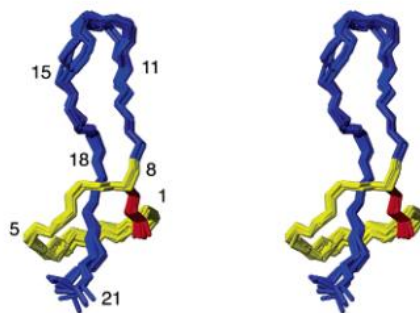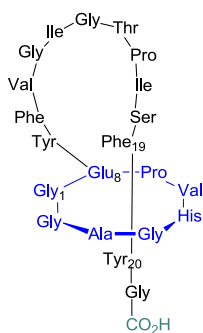
Figure 4. Twenty lowest energy structures selected to represent the solution structure of MccJ25 shown in stereoview. The structures are superimposed over all backbone atoms. Residues 1−8 (shown in yellow) together with the link between the N-terminus and Glu8 side chain (red) form a ring through which the C-terminal is threaded.

Figure 3: structure of microcin J25 and overlays of the calculated 20 lowest energy structures of MccJ25. Figure taken from ref 64.

Meanwhile, the bio-synthesis of microcin J25 has been elucidated and follows a clipping approach. So far, attempts to synthesize the native structure from the linear precursor have been unsuccessful.[68] However, the backbone-to-backbone cyclized and backbone-to-sidechain cyclized products have been synthesized[69,70], but they do not show any of biological activity of the native peptide, indicating that the rigid [1]rotaxane structure is important for activity. Similarly, in 2016 the group of Cobb reported a backbone-to-sidechain cyclized lassomycin and lassomycin-amide, (i.e. a δ-shaped molecule), but due to the missing mechanical bond no biological activity was observed.[71]

Outline of this thesis

As a pioneering study to arrive at a total synthesis of the natural lasso peptides in the future, this thesis will explore covalent strategies towards the synthesis of [2]rotaxanes that do not contain the non-covalent motifs that are usually required during assembly. To accomplish this, a temporary scaffold is covalently attached which pre-organizes the components for cyclization. Similar to the bio-synthesis of lasso peptides, this scaffold induces a perpendicular arrangement of the ring and thread fragments, pre-organizing them for the formation of a mechanically interlocked molecule. The ultimate goal of this new strategy would be the synthesis of a peptide [1]- or [2]rotaxane that cannot be made with the current methodologies as described in this chapter. Therefore, with the application towards peptides in mind, the strategies rely on amide backbone modifications for the formation of temporary covalent bonds with the scaffold. These amide backbone modifications can be installed on all proteogenic amino acids, except proline. Once the rotaxane skeleton is achieved, the amide backbone modifications can be removed to give the native secondary amides, making it (in principle) a traceless method. Chapters II and III will focus on these temporary covalent template assisted rotaxane syntheses. In Chapter IV a very similar strategy is used for the syntheses of two previously unknown classes of compounds, dubbed the quasi[1]catenanes and quasi[1]rotaxanes. Chapter V describes a modified strategy as those used in Chapters II and III, but now incorporating the scaffold in the final product. Chapter VI leaves the amide backbone modifications and focusses on a terephthalic acid as covalent template for a short and convergent synthesis of a 'impossible' [2]rotaxane. Lastly, Chapter VII focusses on the outlook for this thesis.

References

[1] Clayton, D. A.; Vinograd, J. *Nature* **1967**, *216*, 652

[2] Hudson, B.; Vinograd, J. *Nature* **1967**, *216*, 647

[3] Liu, L. F.; Depew, R. E.; Wang, J. C. *J. Mol. Biol*. **1976**, *106*, 439

[4] Liu, L. F.; Liu, C. C.; Alberts, B. M. *Cell* **1980**, *19*, 697

[5] Dean, F. B.; Stasiak, A.; Koller, T.; Cozzarelli, N. R. *J. Biol. Chem*. **1985**, *260*, 4975

[6] Takusagawa, F.; Kamitori, S. *J. Am. Chem. Soc*. **1996**, *118*, 8945

[7] Takusagawa, F.; Kamitori, S.; Misaki, S.; Markham, G. D. *J. Biol. Chem*. **1996**, *271*, 136

[8] Erbas-Cakmak, S.; Leigh, D.A.; McTernan, C.T.; Nussbaumer, A.L. *Chem. Rev.* **2015**, *115*, 10081-10216

[9] Salomon, R. A.; Farias, R. N. *J. Bacteriol*. **1992**, *174*, 7428– 7435

[10] Constantine, K. L.; Friedrichs, M. S.; Detlefsen, D.; Nishio, M.; Tsunakawa, M.; Furumai, T.; Ohkuma, H.; Oki, T.; Hill, S.; Bruccoleri, R. E.; Lin, P.-F.; Mueller, L. *J. Biomol. NMR* **1995**, *5*, 271–286

[11] Um, S.; Kim, Y. J.; Kwon, H.; Wen, H.; Kim, S. H.; Kwon, H. C.; Park, S.; Shin, J.; Oh, D. C. *J. Nat. Prod*. **2013**, *76*, 873–879

[12] Bruns, C.J; Stoddart, J.F. **2016**, The Nature of the Mechanical Bond: from Molecules to Machines, Wiley publishers

[13] Aucagne, V.; Hanni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 2186-2187

[14] Leigh, D. A.; Crowley, J. D.; Hanni, K. D.; Lee, A. L. *J. Am. Chem. Soc.* **2007**, *129*, 12092

[15] Leigh, D. A.; Berna, J.; Crowley, J. D.; Goldup, S. M.; Hanni, K. D.; Lee, A. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5709-5713

[16] Chin, S. H.; Ko, J. L.; Ueng, S. H.; Chiu, C. W.; Lai, C. C.; Liu, Y. H.; Peng, S. M. *Chem. Eur. J.* **2010**, *16*, 6950-6960

[17] Zhou, W.; Xu, J.; Zheng, H.; Liu, H.; Li, Y.; Zhu, D. *J. Org. Chem.* **2008**, 7702-7709

[18] Yoon, I.; Narita, M.; Shimizu, T.; Asakawa, M. *J. Am. Chem. Soc.* **2004**, *126*, 16740-16741

[19] Shueh, Y.-S.; Ko, J.-L.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Angew. Chem. Int. Ed.* **2011**, *50*, 6643-6646

[20] Wang, L.-Y.; Ko, J.-L.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Chem. Eur. J.* **2013**, *19*, 8850-8860

[21] Gottfried Schill, Organic Chemistry Vol. 22. **1971** 'Catenanes, Rotaxanes and Knots'

[22] Harrison, I.T.; Harrison, S. *J. Am. Chem. Soc.* **1967**, *89*, 5723-5724

[23] Agam, G.; Zhilka, A. *J. Am. Chem. Soc.* **1976**, *98*, 5214-5216

[24] Schill, G.; Lüttringhaus, A. *Angew. Chem. Int. Ed.* **1964**, *3*, 546-547

[25] Lüttringhaus, A.; Isele, G. *Angew. Chem. Int. Ed.* **1967**, *6*, 956-957

[26] Schill, G. *Chem. Ber.* **1967**, *100*, 2021

[27] Schill, G.; Zürcher, C. *Angew. Chem. Int. Ed.* **1969**, *8*, 988

[28] Schill, G.; Zollenkopf, H. *Liebigs Ann. Chem.* **1969**, 721, 53-74

[29] Dietrich-Buchecker, C.O.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1984**, *106*, 3043-3045

[30] Ashton, P.R.; Grognuz, M.; Slawin, A.M.Z.; Stoddart, J.F.; Williams, D.J. *Tetrahedron Lett.* **1991**, *32*, 6236-6238

[31] Vögtle, F.; Händel, M.; Meier, S.; Ottens-Hildebrandt, S.; Ott, F.; Schmidt, T. *Liebigs Ann. Chem.* **1995**, 739

[32] Vögtle, F.; Dünnwald, T.; Schmidt, T.; *Acc. Chem. Res.* **1996**, 2*9*, 451-460

[33] Johnston, A.G.; Leigh, D.A.; Murphy, A.; Smart, J.P.; Deegan, M.D. *J. Am. Chem. Soc.* **1996**, *118*, 10662-10663

[34] Leigh, D.A.; Murphy, A.; Smart, J.P.; Slawin, A.M.Z. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 728-732

[35] Ashton, P.R.; Glink, P.T.; Stoddart, J.F.; Tasker, P.A.; White, A.J.P.; Williams, D.J. *Chem. Eur. J.* **1996**, *2*, 729-736

[36] Thibeault, D.; Morin, J.-F. *Molecules*, **2010**, *15*, 3709-3730

[37] Cantrill, S. J.; Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1363-1366

[38] Kawasaki, H.; Kihara, N.; Takata, T. *Chem. Lett.* **1999**, 1015-1016

[39] Zehnder, D. W.; Smithrud, D. B. *Org. Lett.* **2001**, *3*, 2485-2487

[40] Cantrill, S. J.; Fulton, D. A.; Fyfe, M. C. T.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Tetrahedron Lett.* **1999**, *40*, 3669-3672

[41] Giguere, J. B.; Thibeault, D.; Cronier, F.; Marois, J. S.; Auger, M.; Morin, J. F. *Tetrahedron Lett.* **2009**, *50*, 5497-5500

[42] Rowan, S. J.; Stoddart, J. F. *J. Am. Chem. Soc* **2000**, *122*, 164-165

[43] Hung, W. C.; Liao, K. S.; Liu, Y. H.; Peng, S. M.; Chiu, S. H. *Org. Lett.* **2004**, *6*, 4183-4186

[44] Domoto, Y.; Fukushima, A.; Kasuga, Y.; Sase, S.; Goto, K.; Kawashima, T. *Org. Lett.* **2010**, *12*, 2586-2589

[45] Li, Y. L.; Zheng, H. Y.; Zhou, C. J.; Li, Y. J.; Yang, W. L.; Zhou, W. D.; Zuo, Z. C.; Liu, H. B. *Chem.- Eur. J.* **2011**, *17*, 2160-2167

[46] Matsumura, T.; Ishiwari, F.; Koyama, Y.; Takata, T. *Org. Lett.* **2010**, *12*, 3828-3831

[47] Chiu, S. H.; Hsu, C. C.; Lai, C. C. *Tetrahedron* **2009**, *65*, 2824-2829

[48] Ünsal, Ö.; Godt, A. *Chem. Eur. J.* **1999**, *5*, 1728-1733

[49] Godt, A. *Eur. J. Org. Chem.* **2004**, 1639-1654

[50] Nakatani, Y.; Furusho, Y.; Yashima, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 5463-5467

[51] Kawai, H.; Umehara, T.; Fujiwara, K.; Tsuji, T.; Suzuki, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4281-4286

[52] Sugino, H.; Kawai, H.; Umehara, T.; Fujiwara, K.; Suzuki, T. *Chem. Eur. J.* **2012**, *18*, 13722-13732

[53] Hiratani, K.; Suga, J-I.; Nagawa, Y.; Houjou, H.; Tokuhisa, H.; Numata, M.; Watanabe, K. *Tetrahedron Lett.* **2002**, *43*, 5747-5750

[54] Hiratani, K.; Kaneyama, M.; Nagawa, Y.; Koyama, Y.; Kanesoto, M. *J. Am. Chem. Soc.* **2004**, *126*, 13568-13569

[55] Kameta, N.; Hiratani, K.; Nagawa, Y.; *Chem. Comm.* **2004**, 466-467

[56] Hirose, K.; Nishihara, K.; Harade, N.; Nakamura, Y.; Masuda, D.; Araki, M.; Tobe, Y. *Org. Lett.* **2007**, *9*, 2969-2972

[57] Dasgupta, S.; Wu, J. *Chem. Sci.* **2012**, *3*, 425-432

[58] Taylor, W.R. *Nature*, **2000**, *406*, 916-919

[59] Dean, F.B.; Stasiak, A.; Koller, T.; Cozzarelli, N.R. *J. Biol. Chem.* **1985**, *260*, 4975-4983

[60] Hegemann, J.D.; Zimmerman, M.; Xie, X.; Marahiel, M.A. *Acc. Chem. Res.* **2015**, *48*, 1909-1919

[61] Niemyska, W.; Dabrowski-Tumanski, P.; Kadlof, M.; Haglund, E.; Sulkowski, P.; Sukowska, J.I. *Sci. Rep.* **2016**, *6*, 36895-36905

[62] Vincent, P. A.; Morero, R. D *Curr. Med. Chem*. **2009**, *16*, 538–549

[63] Bayro, M. J.; Mukhopadhyay, J.; Swapna, G. V. T.; Huang, J. Y.; Ma, L. C.; Sineva, E.; Dawson, P.E.; Montelione, G. T.; Ebright, R. H. *J. Am. Chem. Soc* **2003**, *125*, 12382-12383

[64] Rosengren, K. J.; Clark, R. J.; Daly, N. L.; Goransson, U.; Jones, A.; Craik, D. J. *J. Am. Chem. Soc* **2003**, *125*, 12464-12474

[65] Wilson, K. A.; Kalkum, M.; Ottesen, J.; Yuzenkova, J.; Chait, B. T.; Landick, R.; Muir, T.; Severinov, K.; Darst, S. A. *J. Am. Chem. Soc* **2003**, *125*, 12475-12483

[66] Blond, A.; Cheminant, M.; Destoumieux-Garzon, D.; Segalas-Milazzo, I.; Peduzzi, J.; Goulard, C.; Rebuffat, S. *Eur. J. Biochem.* **2002**, *269*, 6212-6222

[67] Rosengren, K. J.; Blond, A.; Afonso, C.; Tabet, J. C.; Rebuffat, S.; Craik, D. J. *Biochemistry,* **2004**, *43*, 4696–4702.

[68] Solbiati, J. O.; Ciaccio, M.; Farias, R. N.; Gonzalez-Pastor, J. E.; Moreno, F.; Salomon, R. A. *J. Bacteriol*. **1999**, *181*, 2659–2662

[69] Pavlova, O.; Mukhopadhyay, J.; Sineva, E.; Ebright, R.H.; Severinov, K. *J. Biochem*. **2008**, *283*, 25589-25595

[70] Rebuffat, S.; Blond, A.; Destoumieux-Garzon, D.; Goulard, C.; Peduzzi, J. *Curr. Protein & Peptide Sc.* **2004**, *5*, 383-391

[71] Lear, S.; Hudson, A.S.; Hatton, C.; Clardy, J.; Mosely, J.A.; Bull, T.J.; Sit, C.S.; Cobb, S.L. *Org. Biomol. Chem.* **2016**, *14*, 4534-4541

Chapter II: Development of a covalent template clipping approach towards rotaxanes. Design of the ring and template components.

Introduction

Current syntheses of [2]rotaxanes and related catenanes are limited by the fact that most strategies rely on non-covalent interactions for pre-organization, followed by ring closure ('clipping') or addition of stopper groups ('capping'). As outlined in the Chapter I, the covalent strategy has remained a somewhat underused strategy, despite obviating the presence of functional groups that are required for these non-covalent interactions. In other words, interlocked products synthesized *via* the covalent template method do not have these recognition motifs in the final product. Although also motifs for covalent attachment will remain in the final product, these are usually benign and easily modified. When one wants to prepare complex (natural) interlocked molecules such as the lasso peptides, the common methods will fall short. Peptides are usually highly polar molecules with a plethora of backbone amide or amino acid residues (acidic, basic, polar and apolar) which will prevent or disrupt the common recognition motifs used in rotaxane syntheses. Moreover, these natural products do not have a dominant recognition motif retained in the final structures. The covalent strategy therefore seems the most suitable strategy to address this class of complex interlocked molecules, even though the synthetic route is considerably longer. Inspired by the biosynthesis of microcinJ25, this chapter will present a unprecedented strategy using a temporary covalent scaffold to access complex rotaxanes. Key steps in the assembly include macrocyclizations and backfolding of the components to pre-organize the ring and thread fragment in such a way that ring closure can only produce mechanically interlocked products.

Design of the strategy

The outline of our strategy is depicted in scheme 1 (see next page) and bond angles and orientations are idealized for clarity. The molecules will likely adopt a less well defined structure than the ones shown. Firstly, the ring fragment **I** will be attached to bifunctional scaffold **II** *via* formation of the blue bonds. Next, the thread fragment **IV** will form a temporary yet covalent bond with the ring-scaffold adduct **III**, forming the yellow bond in **V**. This temporary yellow bond is necessary to ensure that the ring and thread fragments are oriented at the same side of the scaffold. To further constrain **V** to force the clipping-type ring-formation, the thread fragment will undergo a second backfolding macrocyclization with the scaffold (red bonds), at reaction sites perpendicular to the ring fragment. This highly constrained intermediate **VI** is pre-organized for the final ring closure (gray bonds) around the thread fragment, forming **VII**. Cleavage of the temporary bonds to the scaffold yields prerotaxane **VIII**. Final cleavage of the temporary bond between the ring and thread fragments (i.e. the yellow bond) liberates the free [2]rotaxane **IX**.
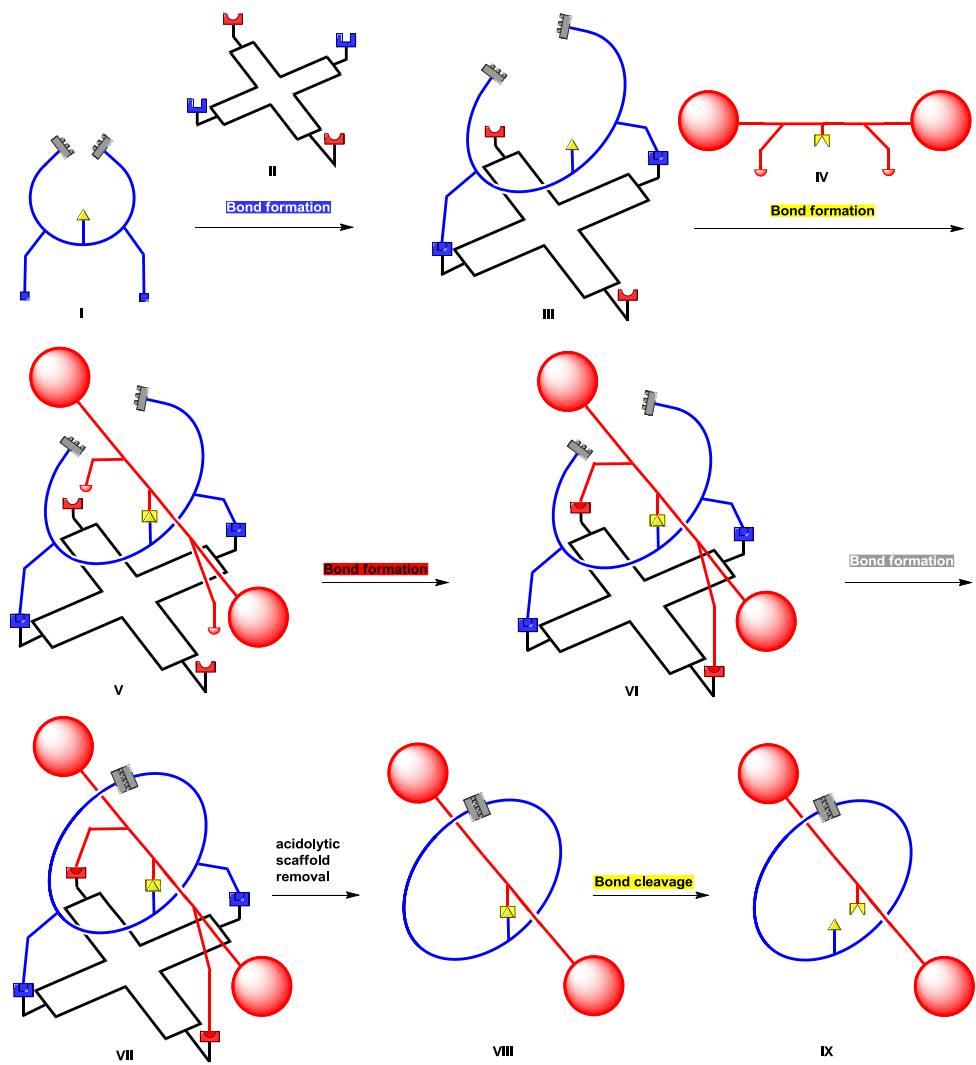
Scheme 1: Generalized strategy using a covalent template to synthesize a [2]rotaxane. Note: bond angles and orientations are idealized for clarity.

Design of the building blocks

Ring fragment

For the scaffold connection, the ring fragment **I** is designed to have two temporary *N*-amide backbone modifications based on the acid labile 2,4-dimethoxybenzyl group. These backbone modifications (schematically represented as blue squares in figure 1) can form covalent bonds *via* modifications on either the 2- or 4-position with the scaffold and are inherently acid labile, allowing for acidolytic cleavage in the final step. For synthetic reasons, the ring fragment itself contains two triethylene glycol chains with terminal alkenes, allowing for facile ring-closing metathesis (RCM). The RCM reaction is robust, high yielding and does not require protective groups due to the relatively inert nature of alkenes. The other bond forming reactions should be compatible with RCM. In the center of the ring fragment a reactive group (yellow triangle) is required for covalent yet temporary bond formation with the thread fragment.
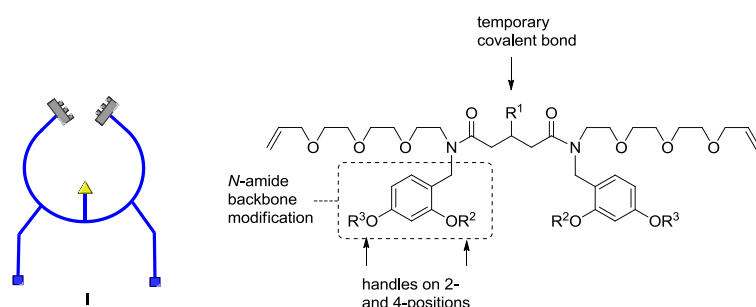

Figure 1: Schematic (left) and general design (right) of the ring fragment

Scaffold

The functional groups of the *N*-amide backbone modifications (see figure 1 in box) on both the thread and ring fragments will form covalent bonds with scaffold **II** on which the complementary, orthogonal functional groups (in red and blue) are present. The scaffold (or template) should ideally be square and planar, therefore assuring a mutually perpendicular arrangement between the ring and thread fragments. Therefore, the same functionalities should be in a trans/para positions with respect to each other. These bond forming reactions should be high yielding and work orthogonally, ideally without the need for protecting groups. As will become apparent, many types of scaffolds were envisioned, so no general design can be given of the scaffold.
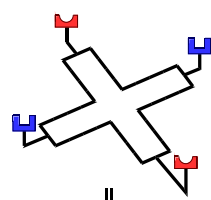

Figure 2: Schematic representation of the scaffold

Thread fragment

The thread fragment **IV** will be attached *via* a temporary covalent bond to the center of the ring fragment. Therefore, a complementary handle (yellow in the schematic representation in figure 3) is installed at the center of the thread. To allow fine-tuning of the length of the thread fragment, a

spacer unit (R_2 in figure 3, right) is placed between the center and the amide bonds. Analogous to the ring fragment, the thread fragment contains two *N*-amide backbone modifications (red half-circles) for covalent bond formation with the scaffold in a perpendicular arrangement with respect to the ring fragment. This reaction needs to be orthogonal to both the RCM step and the bond forming reaction(s) of the ring fragment. The thread fragment should be capped at both sides with a bulky stopper group. For this a tris-4-*tert*-butyltrityl group was chosen, as it possesses considerable bulk. As this chapter will focus on the first macrocyclization to attach the ring fragment to the scaffold only, no thread fragments are presented here. See Chapter III for thread fragments.
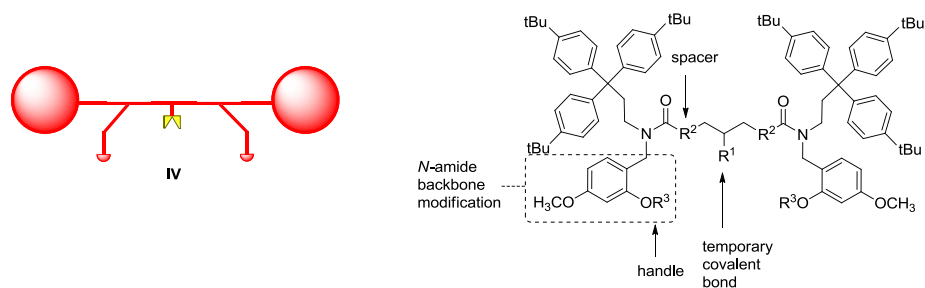

Figure 3: Schematic (left) and general design (right) of the thread fragment

Synthesis of the building blocks for the ring fragment

The synthesis of the ring fragment (see figure 1) required the known amine **4**.[1] Although reported before, the synthesis was optimized as some steps were troublesome when following literature procedures. Triethylene glycol was alkylated with allyl bromide to form compound **1** in 80% yield (see scheme 2).[2] Mesylation of the remaining alcohol yielded mesylate **2** in almost quantitative yield. Substitution with NaN_3 in DMF yielded azide **3** in 89% over the two steps. Staudinger reduction of the azide also proceeded cleanly, although column purification of primary amine **4** (as reported in literature procedures) was troublesome due to contamination with PPh_3O and/or low obtained yields of the amine. Fortunately, the product could be purified by Kugelrohr distillation, obviating the need for column purification. In this way, amine **4** was obtained in 90% yield as a clear colorless oil.
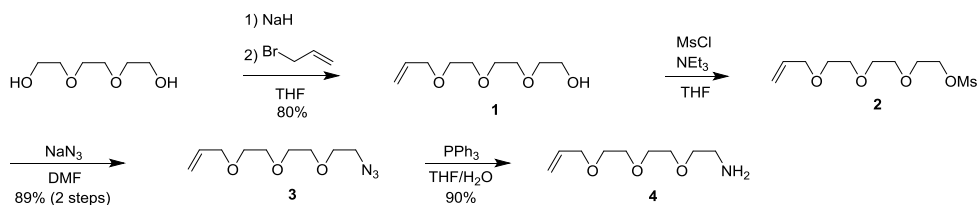
Scheme 2: Synthesis of amine **4**

Although the center part of the ring fragment requires a handle for subsequent formation of a temporary covalent bond with the thread (see strategy), in this chapter only a model center part will be used due to focus on the first macrocyclization step only. As a model center part glutaric acid was used, as 3-functionalized analogues are easily accessible (see Chapter III). For carboxyl group activation, glutaroyl dichloride was converted into its bis *N*-hydroxysuccinimide ester *via* a literature procedure to give **5** in 89% yield (see scheme 3).[3] The reason to use this less reactive ester was related to foreseen reactivity issues when using (di-)acid chlorides. *N*-Hydroxysuccinimide (OSu)

esters are known to react selectively with amines, whereas acid chlorides can give side reactions with other functional groups. Also, *N*-hydroxysuccinimide esters are stable compounds (usually solids) allowing purification to remove any coupling reagent residues or impurities. This activation, although more laborious, allows for a cleaner subsequent amidation reaction as *N*-hydroxysuccinimide is easily extracted and no coupling reagent residues remain in the reaction mixture.
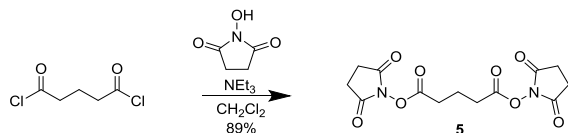
Scheme 3: Synthesis of bis-OSu ester **5**

Oxime macrocyclization strategy

As it was yet unknown which macrocyclization strategy would work for the template connection in the strategy (see Introduction) it was decided to test oxime formation first. The advantage of this reaction over others is the fact that it proceeds selectively, quickly, high-yielding and at low concentrations. Moreover, catalysts have been developed to accelerate the reaction in case of low reactivity. All these criteria made it a suitable candidate for a macrocyclization reaction. To minimalize the number of atoms in the macrocycle it was decided to place the oxyamine moiety directly on the 4-position of the phenyl ring, thereby retaining the electronic properties of the benzylic group necessary during the acidolytic cleavage. Therefore, the *N*-amide backbone modification had to be a 2-methoxy-4-oxyamine benzyl group (see target compound in figure 4). As synthetic routes towards *O*-phenyloxyamines are quite limited, we investigated the synthesis of the desired N-O bond *via* electrophilic amination of a phenol hydroxyl group.
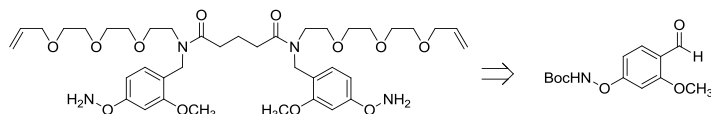

Figure 4: retrosynthesis of bis-oxyamine target compound

In 2000, the group of Knight *et al.* reported the use of oxaziridine **10** as an electrophilic amination agent, reacting under basic conditions with aliphatic alcohols to give a hydroxylamine.[4] Although not reported by Knight, we set out to use **10** for the amination of a phenol to obtain an *N*-Boc-*O*-arylhydroxyamine. Firstly, hydrazine was mono-protected with a Boc-group, giving *tert*-butylcarbazate **6** in 74% yield (see scheme 4). Subsequent diazotation with $NaNO_2$ in aqueous acetic acid gave the unstable Boc-N_3 **7** in solution, which was directly reacted with PPh_3 in anhydrous diethyl ether to produce iminophosphorane **8**.[5] This stabilized ylide was recrystallized from EtOAc to give the pure product in 81% yield over two steps. The aza-Wittig reaction of **8** with chloral gave imine **9** as a white powder in 75% yield after Kugelrohr distillation. Lastly, the imine was oxidized with excess Oxone in a biphasic system and oxaziridine **10** was obtained in 64% yield after column purification.[6] According to the authors the reagent is stable in the freezer for at least two months. With reagent **10** in hand, the amination of 4-hydroxy-2-methoxybenzaldehyde was tested according to Knight's protocol. Unfortunately, only complex mixtures were obtained with no trace of the desired product **11**.
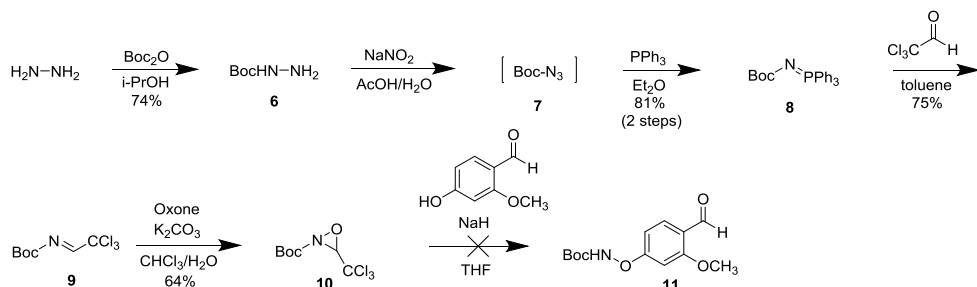
Scheme 4: Synthesis of oxaziridine **10** and attempted reaction with 4-hydroxy-2-methoxybenzaldehyde

After literature screening for the transformation of phenols to hydroxylamines, a 2010 article by Boger was found, describing the use of BocNH-OTs **13** as the electrophilic aminating reagent, reacting with nucleophiles in an S_N2-like substitution.[7] **13** was synthesized according to a literature procedure by protecting hydroxylamine hydrochloride with a Boc-group in 78% yield and subsequent reaction of product **12** with tosyl chloride to give **13** in 65% yield after trituration (see scheme 5).[8] Fortunately, the reaction of the sodium salt of 4-hydroxy-2-methoxybenzaldehyde with reagent **13** yielded oxyamine product **11**, although with incomplete conversion. Three cycles of deprotonation/ addition of **13** were necessary (see Experimental Section) to give full conversion. Nevertheless, desired product **11** was only isolated in a moderate 52% yield as an extremely sticky oil. Subsequent reductive amination of **11** with amine **4** led to an unexpected result. According to the LC-MS trace of the crude reaction mixture several compounds were present, with the main products identified as desired **14**, hydrazine **15** and de-aminated product **16**. Attempted separation of these polar compounds by column chromatography was unsuccessful. The presence of **15** and **16** can be explained *via* a nucleophilic attack of the secondary amine of product **14** on the (still somewhat) electrophilic nitrogen atom of the *O*-arylhydroxylamine, leading to a cleavage of the N-O bond *via* a S_N2–type reaction. The reaction of amines with electrophilic amination reagents to form *N*-Boc hydrazines has been reported before, although none of those procedures use a *N*-Boc-*O*-arylhydroxyamine as the aminating reagent.[9,10,11] Due to the apparent electrophilic nature of *N*-Boc-*O*-arylhydroxyamines it was decided that a spacer had to be installed between the oxyamine functionality and the phenol ring.
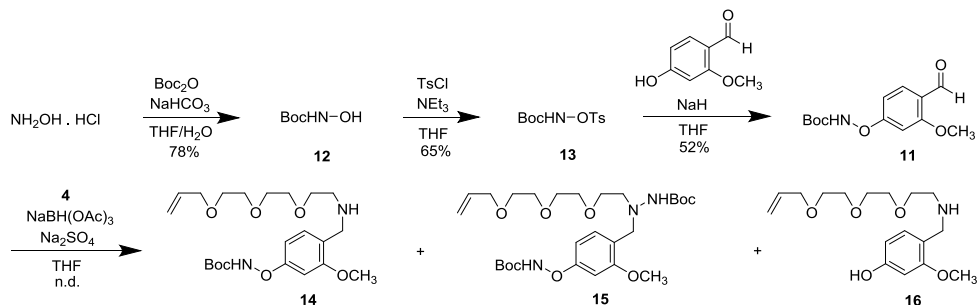
Scheme 5: Synthesis of oxyamine **14** and formation of hydrazine byproduct **15** during reductive amination

The smallest possible spacer would be an ethyl bridge. Therefore, *N*-hydroxyphthalimide was alkylated with 1,2-dibromoethane, giving **17** in 73% yield (see scheme 6).[12] Deprotection of the phthalimide was performed in boiling concentrated HBr and acetic acid to give the corresponding ammonium salt in 96% crude yield after concentration of the filtrate.[13] Subsequent Boc-protection

gave **18** in a moderate 61% yield.[14] Unfortunately, subsequent alkylation of 4-hydroxy-2-methoxybenzaldehyde with **18** failed to give the desired alkylated product (see scheme 7). It was speculated that the N-H moiety of the oxyamine was also be deprotonated under the reaction conditions, leading to side reactions such as aza-oxetane formation. To avoid this, **18** was protected with a second Boc-group, catalyzed by DMAP as acylation catalyst, giving bromide **19** in 95% yield. Alternatively, **19** could also be obtained in a shorter and more efficient route starting from commercially available *O*-benzylhydroxylammonium chloride, which was protected with two Boc groups in one pot to give **20** in 97% yield. Hydrogenolysis of the benzyl group with a poisoned palladium catalyst, to prevent overreduction of the N-O bond, proceeded smoothly, giving Boc₂NOH **21** in 92% yield.[15] Subsequent alkylation of **21** with excess 1,2-dibromoethane and DBU gave **19** in 83% yield.
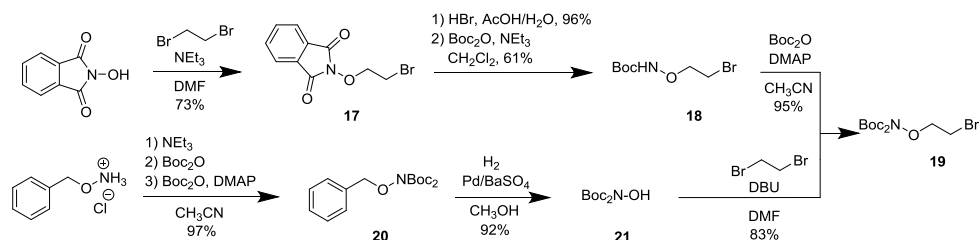

Scheme 6: Synthesis of hydroxylamine **19** *via* two different routes

The alkylation of 4-hydroxy-2-methoxybenzaldehyde with doubly protected bromide **19** now proceeded uneventful, giving benzaldehyde **22** in 80% yield as a thick oil (see scheme 7). Fortunately, subsequent reductive amination of this aldehyde with amine **4** also proceeded well, giving no hydrazine byproducts. However, it was found that upon storage of **23** a byproduct formed, due to Boc-transfer from one of the Boc-groups on the oxyamine to the newly formed, nucleophilic secondary amine. Therefore, the crude reaction mixture was treated with TFA (4 equiv), leading to selective removal of one of the Boc-groups to give mono-Boc product **24** in 70% isolated yield over the two steps.
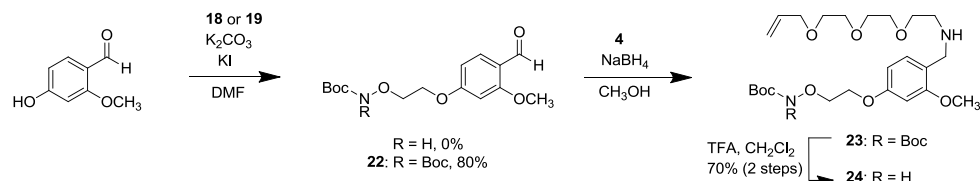
Scheme 7: Synthesis of hydroxylamine functionalized amine **24**

Mixing secondary amine **24** with bis-*N*-hydroxysuccinimide ester **5** led to a clean conversion to the desired bis-amide **25**, although the reaction was quite slow. To speed up the reaction, it was found that the addition of catalytic DMAP as acylation catalyst greatly enhanced the rate and with these optimized conditions bis-amide **25** was isolated in 89% yield (see scheme 8). Next, removal of the Boc-groups was tested. Because the Boc-groups were thought to be more acid labile than the benzyl groups, diluted TFA was used. Unfortunately, LC-MS analysis of the reaction mixture always showed (besides desired **26**) the formation of mono-debenzylated product **27** as a side product, independent of the TFA concentration used. Because separation of the polar products was impossible, it was decided to abandon the oxime macrocyclization strategy in search of a more compatible approach.
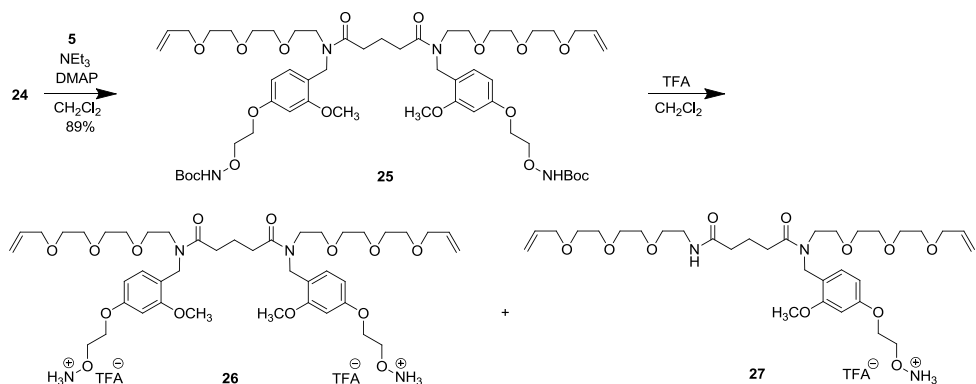
Scheme 8: Synthesis of model compound **25** and attempted selective Boc-deprotection
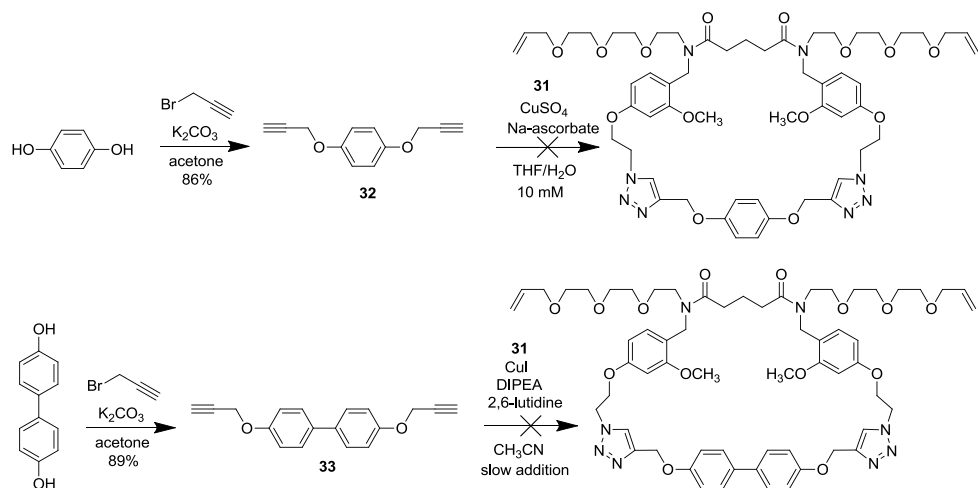
CuAAC reaction macrocyclization strategy

The Cu(I) catalyzed alkyne azide cycloaddition (CuAAC) has proven to be a valuable reaction for macrocyclizations, due to the selectivity of the reaction and high yields. Because the required functional groups are acid stable, it was decided to test this reaction for macrocyclizations. Therefore, 4-hydroxy-2-methoxybenzaldehyde was alkylated with excess 1,2-dibromoethane, giving monobromide **28** in 81% yield (see scheme 9).[16] This was cleanly transformed into azide **29** in 95% yield and subsequent reductive amination with amine **4** proceeded cleanly and almost quantitative to give amine **30**, requiring no purification. Finally, aminolysis of the aforementioned model central part **5** under the optimized conditions gave di-azide **31** in 70% yield.
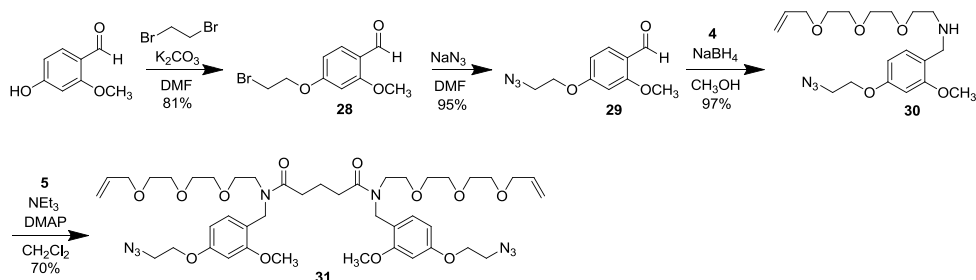
Scheme 9: Synthesis of di-azide functionalized model ring fragment **31**

Next, the desired CuAAC macrocyclization reaction was tested. As model scaffolds, hydroquinone and the longer 4,4'-dihydroxybiphenyl were alkylated with propargyl bromide, giving **32**[17] and **33**[18] in 86% and 89% yield, respectively (see scheme 10). Unfortunately, under standard 'click' conditions (CuSO$_4$, sodium ascorbate) at 10 mM the reaction between di-azide **31** and di-alkyne scaffold **32** quickly gave rise to polymer formation and no desired product was observed in the LC-MS traces. To ensure low concentrations of the reactants, slow addition of **31** and **33** to a CuI solution was tested, however this also led to severe polymer formation. In hindsight, the optimized 'click' conditions as described in Chapter IV should have been tested as well, as these gave acceptable yields with similar CuAAC macrocyclizations, although slightly smaller macrocycles were formed. As these conditions were unknown at the time and this reaction failed to give any desired product, it was decided to abandon the CuAAC reaction macrocyclization strategy.

Scheme 10: Attempted CuAAC reaction macrocyclization

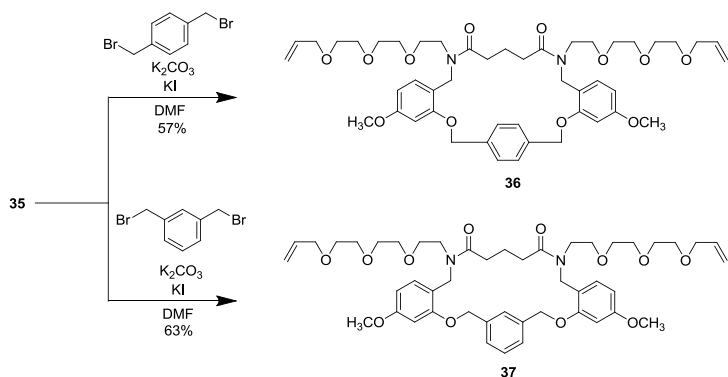**Williamson etherification macrocyclization strategy**

As the CuAAC reaction also failed to give a working macrocyclization, it was decided to test a different reaction to accomplish this. Moreover, it was thought that the macrocycle formed should be as small as possible, because this might help the macrocyclization step and reduce the formation of polymers. The smallest possible functional group which can act as a handle is a hydroxyl group, which can be alkylated with an alkyl halide (i.e. Williamson etherification). Also, to ensure the formation of a smaller ring it was decided to functionalize the 2-position of the benzyl group, as resulting macrocycles would be smaller than those derived *via* functionalized on the 4-position.

Importantly, this new approach also greatly simplified the synthesis, as the required 2-hydroxy-4-methoxybenzaldehyde was commercially available. Reductive amination with amine **4** proceeded smoothly and required no purification, giving secondary amine **34** in 97% yield (see scheme 11). Subsequent reaction with bis-OSu ester **5** smoothly gave bis-amide **35** in 75% yield as a thick oil.
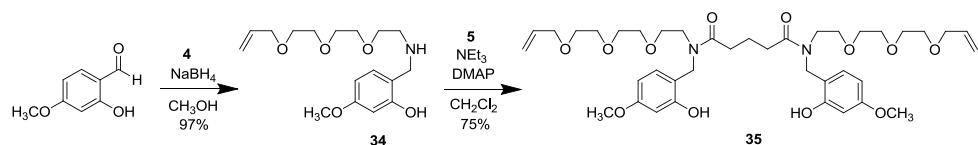

Scheme 11: Synthesis of bis-hydroxyl functionalized model ring fragment **35**

Next, the reaction of model substrate **35** with bis-benzylic bromides was tested as these produce the smallest possible macrocycles incorporating a phenyl ring that is amenable for further functionalization. Gratifyingly, reaction of **35** with 1,4-bis(bromomethyl)benzene, mediated by K_2CO_3 and KI (for *in-situ* Finkelstein reaction to activate the scaffold further) in DMF at high dilution gave a clean conversion to the desired 21-membered macrocycle as determined from the LC-MS trace (see scheme 12). Work-up and purification gave product **36** in 57% isolated yield. Similarly, reaction with the isomeric 1,3-bis(bromomethyl)benzene gave the 20-membered macrocycle **37** in 63% yield. After reaction optimization, it was found that DMF could be substituted for CH_3CN, allowing for easier work-up. Additionally, the reaction proceeded better with Cs_2CO_3 as base by making a more reactive phenoxide. This also obviated the need for the *in-situ* Finkelstein reaction with KI.

Scheme 12: Macrocyclizations *via* Williamson ether synthesis with benzylic bromides

To explore the versatility of the Williamson etherification macrocyclization, other aliphatic alkyl halides were tested under the optimized conditions (CH_3CN as the solvent and Cs_2CO_3 as the base). Reaction with bis-bromoacetate **38** gave macrocycle **39** in a similar yield (see scheme 13).[19] This motif installs an orthogonally cleavable ester moiety in the ring, but simultaneously creates a somewhat larger ring than the previously tested benzylic bromides (24-membered in this case). This motif generates a more flexible macrocycle due to the presence of multiple sp^3-hybridized atoms in the ring. Reaction of **35** with 1,5-diiodopentane **40** gave product **41** in 92% yield, the best yield found overall for the Williamson macrocyclization step in this thesis. If the 1,5-diiodopentane moiety is 3,3-difunctionalized, a bifunctionalized scaffold with perpendicular arrangement of the substituents will be obtained, as described in the introduction. To test whether a smaller alkyl halide would be possible that already had the desired difunctionality in the center, it was decided to react **35** with 2,2-dimethyl-1,3-diiodopropane **42** as a model substrate.[20] Unfortunately, most probably due to the neopentyl effect the reaction was sluggish and not clean, although some of the 18-membered product **43** did form according to the LC-MS traces. Refluxing conditions were required to give any conversion, however these high temperatures are undesirable as the macrocyclization step(s) should be as mild as possible.
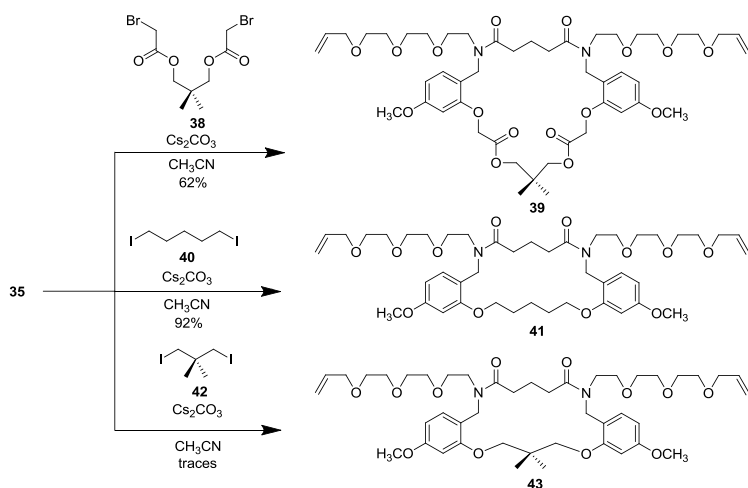
Scheme 13: Macrocyclizations *via* Williamson ether synthesis with various alkyl halides

With the aforementioned macrocycle **37** as model substrate in hand, the RCM step was tested, as this macrocyclization step would later on be crucial and would generate an even larger 29-membered macrocycle. To prevent competing intermolecular reactions, the initial reaction was run at 1 mM. Fortunately, the reaction of **37** with Grubbs 2nd generation catalyst cleanly gave product **44** in 71% isolated yield as an undetermined E/Z mixture (see scheme 14).
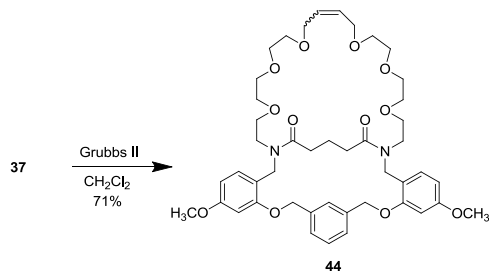
Scheme 14: Ring closing metathesis of compound **37**

Scaffolds

As outlined in the introduction, the strategy requires a square planar bifunctional template with both types of reacting groups oriented in a para/trans fashion. As the research presented in this subchapter was performed over a three year period, the functional groups used for this para/trans positioning vary, depending on what was thought most desirable at that time. Therefore, it might seem odd that the functionalities in one approach are different from the next approach. Nevertheless, many of these functional groups are easily interconvertible (for instance, a carbonyl moiety could be transformed into an azide *via* reduction and substitution). True square planar organic molecules are rare and one of the first attempted syntheses of such a molecule was based on a porphyrin as these can be bifunctionalized in the desired trans positions (so called ABAB functionalization, see figure 5). However, soon into the synthesis it was found that porphyrin syntheses suffer from many practical problems, such as low yields, insolubility in any solvent other than CH$_2$Cl$_2$ or CHCl$_3$ and poor separation on column. Therefore, this route was soon abandoned.
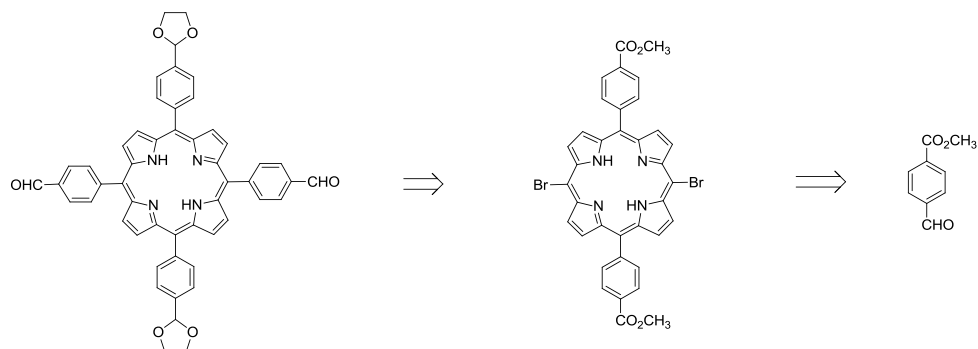

Figure 5: Retrosynthesis of target porphyrin scaffold

Next, it was attempted to synthesize an anthracene based scaffold (see figure 6), based on a report by Marks *et al* describing a maleimide that reacted with an *in-situ* generated *ortho*-quinodimethane in a Diels-Alder reaction.[21] The resulting cyclohexene ring is subsequently aromatized *via* a bromination/elimination sequence.
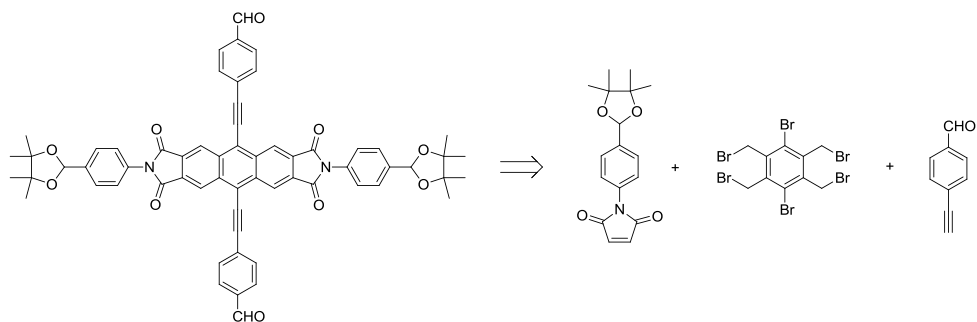
Figure 6: Retrosynthesis of desired anthracene based scaffold

The synthesis of the required maleimide **47** started with 4-nitrobenzaldehyde, which was protected as a pinacol acetal to give **45** in 93% yield (see scheme 15). Other more common acetals were found to slightly hydrolyze upon column purification in subsequent steps. Reduction of the nitro group was accomplished *via* hydrogenolysis with H_2 and Pd/C in 89% yield.[22] It is worth to note that **45** had to be first filtered over a plug of basic alumina to remove impurities which poisoned the catalyst. Subsequent reaction of aniline **46** with maleic anhydride, followed by dehydration with Ac_2O yielded maleimide **47** in 53% yield over the two steps. For the central core of the molecule 1,4-dibromodurene was brominated with NBS under UV-irradiation, giving hexabromide **48** in almost quantitative yield as a rather insoluble white powder.[23] Next, the crucial double Diels-Alder reaction was performed by reacting **47** and **48** with NaI in DMF at 80 °C. During this reaction NaI reacts with the benzylic bromides in an unusual way, forming IBr, NaBr and a reactive *ortho*-quinodimethane. This reactive diene quickly reacts with the maleimides forming the cyclohexene rings on either side. Product **49** was isolated in 83% yield. Unfortunately, subsequent radical bromination gave a complex mixture of products, probably due to radical bromination of the acetal proton, and no square planar anthracene product was observed. In hindsight, DDQ mediated aromatization might have solved this problem.
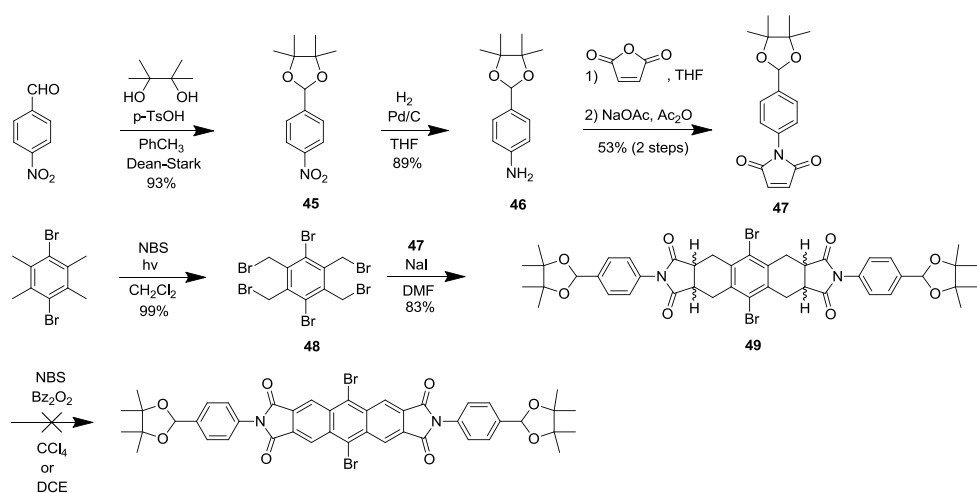
Scheme 15: Attempted synthesis of an anthracene based scaffold

After this setback, the benzobisoxazoles were investigated as these molecules are also square planar and syntheses have been reported in the literature (see figure 7 for retrosynthesis).[24] The group of Jeffries reported the use of 2,5-dibromo-3,6-diaminohydroquinone **53** for the synthesis of benzobisoxazoles.[25] As the bromides can later on be further functionalized *via* palladium chemistry, **53** was chosen as a synthetic target.
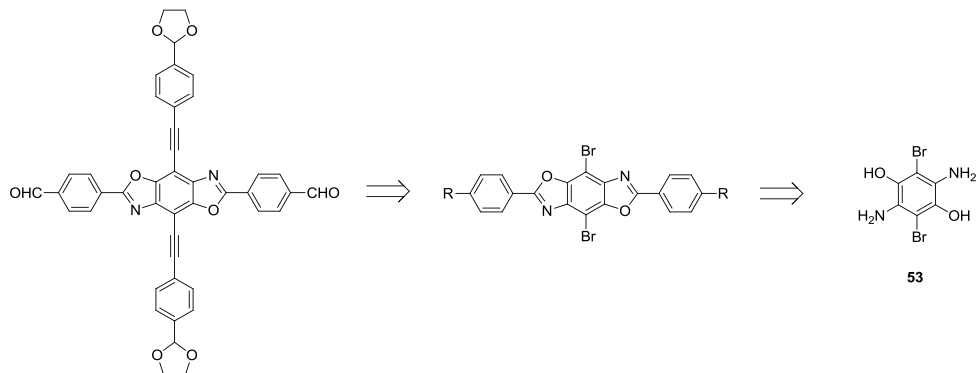

Figure 7: Retrosynthesis of the target benzobisoxazole based scaffold

The synthesis started with the bromination of 1,4-benzoquinone in acetic acid, giving tetrabromide **50** in 85% yield (see scheme 16). Oxidation with chromium trioxide gave tetrabromobenzoquinone **51** in 95% yield as a bright yellow solid. Subsequent reaction with aqueous ammonia in 2-methoxyethyl acetate gave diamino-derivative **52** in 89% yield. Reduction with $Na_2S_2O_4$ gave **53** in 95% yield as a gray air-sensitive powder (slowly oxidizing back to quinone **52**).
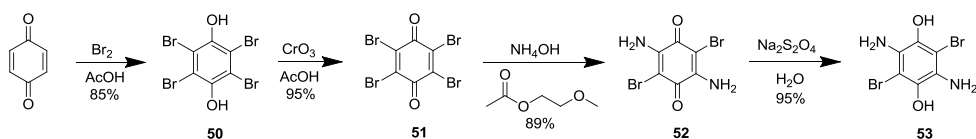
Scheme 16: Synthesis of 2,5-dibromo-3,6-diaminohydroquinone **53**

Next, the reaction and condensation of **53** with benzoyl chlorides was tested as described by Miljanic *et al* to obtain benzobisoxazoles.[26] Reaction of **53** with 4-cyanobenzoyl chloride in 1,4-dioxane at 170 °C in a sealed tube gave the desired benzobisoxazole **54** in 85% yield as a very poorly soluble powder (see scheme 17). Any attempted follow-up reaction (hydrolysis or reduction of the nitriles) gave unidentified mixtures. Reaction of **53** with 4-formyl benzoyl chloride under the same conditions proceeded equally well, giving **55** in 90% yield. Nevertheless, also here the insolubility of the product prevented any follow-up chemistry. Lastly, **53** was reacted with terephthaloyl chloride **56** bearing a long, solubilizing aliphatic chain giving product **57** in 88% yield. Remarkably, despite bearing these glycol ether chains, the product was still a solid (melting point 180-182 °C), although displaying better solubility than the previous two products. Nevertheless, attempted follow-up chemistry *via* a Sonogashira reaction with phenylacetylene gave mixtures consisting of starting material, mono-substituted, di-substituted and bromide-eliminated products, which could not be separated with column chromatography. This fact, together with the low solubility of products lacking the long alkyl chains, led us to abandon the 1,4-dibromobenzobisoxazoles as scaffolds.

Scheme 17: Synthesis of benzobisoxazoles **54**, **55** and **57**

Presumably, the bromides were (partially) responsible for the low solubility. Therefore, it was envisioned to synthesize an analogue which was already functionalized at these positions, hopefully creating more soluble products. At this point in time a scaffold with two benzylic bromides and two azides was required, so our target compound was the compound shown in figure 8.

Figure 8: Retrosynthesis of desired benzobisoxazole based scaffold

An ester moiety seemed the most versatile and solubilizing, thus we chose to synthesize compound **62** (see scheme 18) which was unknown in literature. For this, diethyl succinate was dimerized in a Claisen/Dieckmann condensation sequence, producing compound **58** in 63% yield (see scheme 18).[27] Subsequent reaction with excess bromine produced almost quantitatively hydroquinone **59** in a one-pot aromatization/bromination sequence. Oxidation was accomplished with ceric ammonium nitrate (CAN), giving quinone **60** in quantitative yield as a somewhat water-sensitive molecule. Immediate reaction with aqueous ammonia in THF gave diaminoquinone **61** in 81% yield as a golden colored solid. Subsequent reduction to the hydroquinone with aqueous $Na_2S_2O_4$ gave the desired product **62** in 91% yield as a blood-red, oxidation-sensitive solid. Despite the electron-withdrawing properties of the esters, this compound proved more oxidation-sensitive than the analogous dibromo compound **53**.

Scheme 18: Synthesis of diethyl 2,5-dihydroxy-3,6-diaminoterephthalate **62**

The acid catalyzed reaction of **62** with trimethyl orthoacetate, which is an milder alternative method for synthesizing benzobisoxazoles, gave product **63** in 68% yield (see scheme 19). Unfortunately, any attempted further functionalization of the methyl groups, such as radical bromination[28], SeO$_2$ oxidation[29] or condensation with *N,N*-dimethylformamide dimethylacetal[30] gave no conversion or complex mixtures. Reaction of **62** with chlorine-functionalized orthoacetate gave some conversion to the desired dichloride **64**, but purification was troublesome due to the many side products with similar polarity, as well as the presence of quinone **61** due to unwanted oxidation of the starting material.
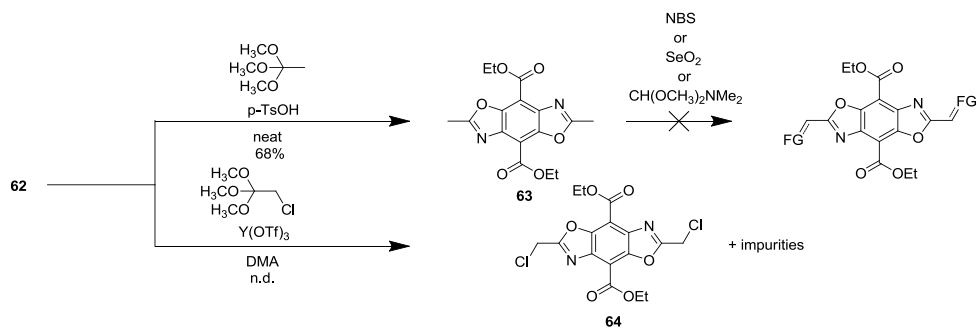
Scheme 19: Synthesis of benzobisoxazole products of **62**

Due to the problems faced with benzobisoxazoles it was decided to look for a less oxidation sensitive analogue that was more soluble and for which less harsh conditions were needed. It was envisioned to synthesize a bis-isoindoline, which, although not a flat aromatic anymore, still possesses the perpendicular arrangement of the functionalities. Due to the increased solubility and versatility of the ester group, this group was envisioned on the 1- and 4-positions of the aromatic ring (see figure 9 for target molecule and retrosynthesis).
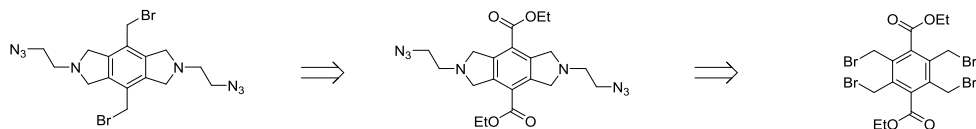

Figure 9: Retrosynthesis of the desired bisisoindoline based scaffold

The synthesis started with the bromination of durene, giving **65** in 97% yield (see scheme 20).[31] This dibromide was subsequently reacted in a Rosenmund-von Braun reaction, giving bis-nitrile **66** in 91% yield.[32] Treatment with concentrated sulfuric acid in AcOH led to hydration of the nitriles, giving bis-amide **67** in 90% yield. Basic hydrolysis of primary amides is difficult, but the reaction with NaNO$_2$ under acidic conditions gave *in-situ* formation of an acyl-diazonium species that quickly expels nitrogen gas, forming an acylium ion. This acylium ion was quickly trapped by water present in the solvent, giving bis-acid **68** in 84% yield. Acidic esterification of **68** failed to give **69,** presumably due to steric hindrance. Therefore it was first transformed into the corresponding bis-acid chloride with oxalyl chloride and subsequently reacted with methanol, giving **69** in 59% yield over the two steps. Final radical bromination with NBS smoothly gave novel tetrabromide **70** in 74% yield as a white solid.
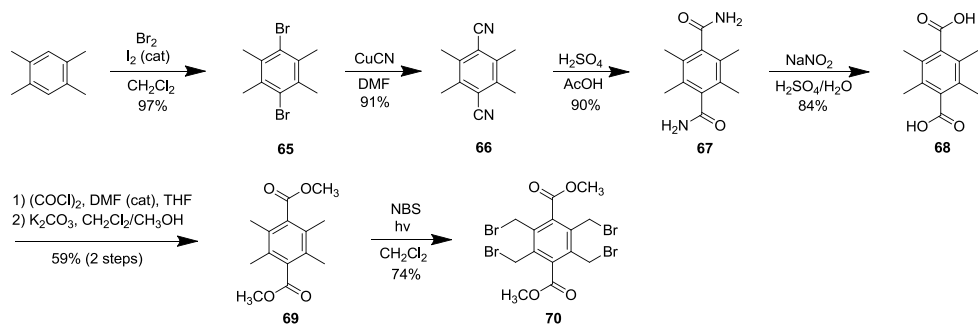
Scheme 20: Synthesis of tetrabromide **70**

Next, tetrabromide **70** was reacted with *n*-butylamine as a model amine to see if the bis-isoindoline formation would work correctly (see scheme 21). To our big surprise LC-MS traces of the crude reaction mixture did not show any formation of the expected product. However, the two main products were identified as bis-lactams **71** and **72**. This means that after the substitution of the first bromide, the newly formed secondary amine in intermediate **73** prefers to lactamize (pathway **a**) instead of substituting the flanking bromide (pathway **b**), despite the 24(!) pKa units difference that reflects the large leaving group ability between bromide and methoxide.
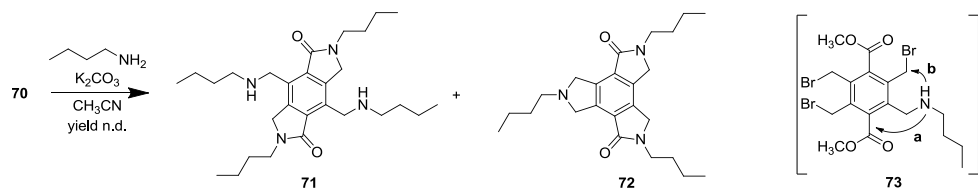

Scheme 21: Reaction of tetrabromide **70** with *n*-butylamine

To overcome this unexpected problem, it was decided to substitute the reactive ester for a different group, that will not interfere in the bis-indoline formation. A protected alcohol was thought to be as equally versatile as the ester, allowing for later modifications. Durene was bromomethylated with paraformaldehyde in 33% HBr in AcOH, giving **75** in 93% yield (see scheme 22).[33] Substitution of the bromides with NaOAc in refluxing CH_3CN smoothly gave di-acetate **76** in 85% yield.[34] Subsequent radical bromination with NBS under irradiating conditions gave tetrabromide **77** in a moderate 54% yield. Interestingly, no side products due to bromination of the acetate or adjacent CH_2 group were observed, likely due to steric hindrance. As coupling partner, 2-azidoethylamine **74** was synthesized according to a literature procedure and was found to be perfectly stable, despite being a low-molecular weight azide.[35] Reaction of amine **74** with tetrabromide **77** gave the desired bis-isoindoline **78** cleanly in 95% crude yield and no side-reactions were observed. Deprotection *via* transesterification of the acetate groups with K_2CO_3 in MeOH gave diol **79** in 83% yield. However, subsequent transformation into benzylic bromides or mesylates led to the formation of insoluble products. Most likely, the slightly nucleophilic tertiary amines reacted with either the reagents or the desired product, forming quaternary ammonium ions.
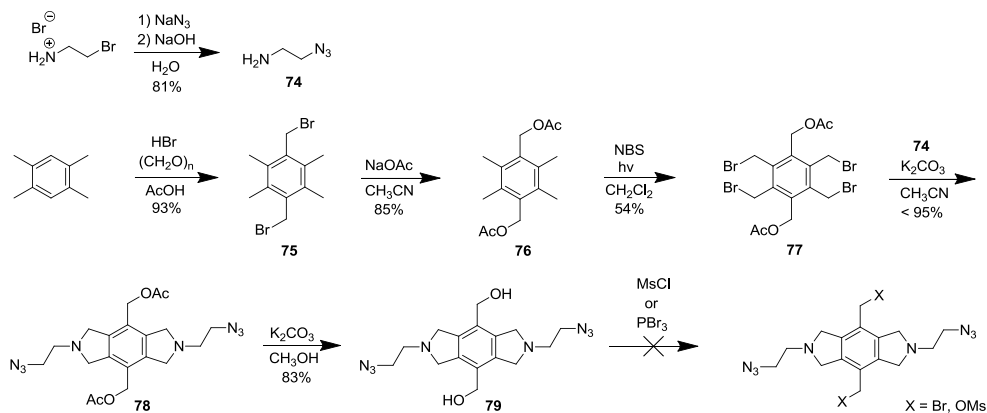
Scheme 22: Synthesis of bis-isoindoline scaffold **79**

To decrease the nucleophilicity of the amines in the bis-isoindolines, it was decided to transform them into amides. Therefore, the *N*-unsubstituted isoindolines had to be obtained. Reaction of tetrabromide **77** with aqueous ammonia failed to give any of the desired product **82**, instead giving quaternary ammonium ion **80** as the main product. This reflects the higher nucleophilicity of secondary amines compared to ammonia. Even the addition of a large excess of ammonia (ca. 1000 equiv) resulted in the same product, together with varying amounts of acetate deprotection due to aminolysis. To obtain the *N*-unsubstituted isoindolines, **77** was reacted with benzylamine, giving **81** in 72% crude yield (see scheme 23). Hydrogenolysis of the benzyl groups was performed in acetic acid, because protonation of the amines allowed for full solvation of the substrate, as well as deactivating the product, preventing over-reduction. In this way, bis-isoindoline **82** was isolated in 73% crude yield and did not require further purification. Subsequent reaction of **82** with the *N*-hydroxysuccinimide (OSu) ester of azidoacetic acid gave the desired bis-amide **83** in 72% yield.[36] This product was deprotected similarly with K_2CO_3 in CH_3OH to give diol **84** in 74% crude yield. Unfortunately, despite the electron withdrawing groups on the nitrogen atom, no further functionalization of the alcohol groups was possible, leading again to the formation of insoluble products and/or complex mixtures.
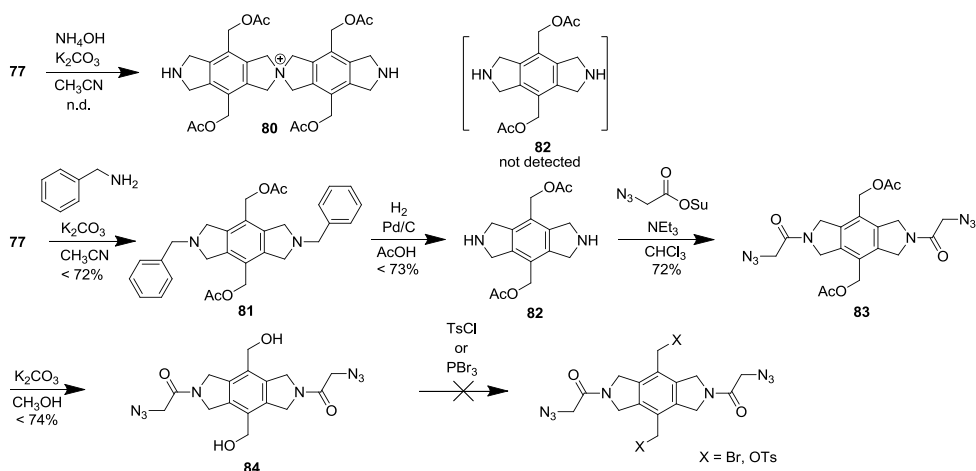
Scheme 23: Synthesis of bis-isoindoline amide scaffold **84**

Conclusions

In this chapter, various macrocyclization strategies were tested to attach the (model) ring fragment to a scaffold. Of these the Williamson etherification gave good and reproducible results. The best results were obtained when the macrocyclization was performed with Cs_2CO_3 and 4Å MS in CH_3CN at 50-60 ^{o}C under high dilution.
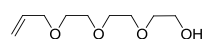
For the scaffolds, multiple types of square planar molecules were synthesized or were attempted to synthesize. However, with none of these (porphyrin, anthracene type, benzobisoxazoles or bis-isoindolines) it was possible to complete the desired bifunctional scaffold. Insolubility and functional group incompatibility of the intermediates were the main problems encountered. Therefore, in the next chapter different types of scaffolds were successfully prepared which were not truly square planar, but X-shaped or based on a tetrahedral sp^3 carbon atom.

**Experimental Section**

General methods and materials

Unless stated otherwise, reactions were performed without special precautions like drying or N_2/Argon atmosphere. Dried CH_2Cl_2 and CH_3CN were obtained by distilling these solvents with CaH_2 as drying agent. Dried THF and Et_2O were obtained by distillation with sodium. All dried solvents were stored under N_2 atmosphere. Dry DMF on 4Å molecular sieves was obtained from Sigma-Aldrich and stored under N_2 atmosphere. Reagents were purchased with the highest purity (usually >98%) from Sigma Aldrich and Fluorochem and used as received. Grubbs 2nd generation catalyst was purchased from AK Scientific. Reactions were monitored with thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254). SilaFlash® P60 (particle size 40-63 μm) was used for silica column chromatography. NMR spectra were recorded on Bruker DRX-500, 400 and 300 MHz instruments and calibrated on residual undeuterated solvent signals as internal standard. The ^{1}H-NMR multiplicities were abbreviated as followed: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet. High resolution mass spectra (HRMS) were recorded on a Mass spectra were collected on an AccuTOF GC v 4g, JMS-T100GCV Mass spectrometer (JEOL, Japan). FD/FI probe equipped with FD Emitter, Carbotec or Linden (Germany), FD 10 μm. Current rate 51.2 mA/min over 1.2 min machine using coldspray or electrospray as ionization method. Depending on the molecule, either the (M)$^+$ or (M+H)$^+$ were observed; sometimes the (M+Na)$^+$ signal was also observed. Melting points were recorded on a Wagner & Munz Polytherm A melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Alpha FTIR machine.

Compound **1**

20 mL triethyleneglycol (ca. 150 mmol) was dissolved in 80 mL dry THF under N_2 atmosphere and cooled to 0 ^{o}C. Next, 3.00 g NaH (60% w/w, 75 mmol) was added portionwise and the mixture was stirred for 20 min, after which 4.32 mL allylbromide (50 mmol) was added. The mixture was stirred at 0 ^{o}C for 1h and overnight at room temperature. The volatiles were removed and the residue was partitioned between 50 mL CH_2Cl, 40 mL brine and 10 mL H_2O. The water layer was extracted with 3 x 50 mL CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated. The yellow oil was purified by column chromatography (PE/EtOAc 1:1 → 0:1) to give **1** (7.56 g, 39.73 mmol, 80%) as a colorless oil. The spectra matched those reported in literature.[2]

Compound 2
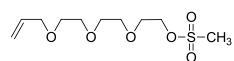
14.18 g **1** (74.55 mmol) was dissolved in 250 mL dry CH_2Cl_2 and cooled to 0 °C. After cooling, 12.40 mL Et_3N (89.46 mmol, 1.2 equiv) was added, followed by the dropwise addition of a solution of 6.94 mL methanesulfonyl chloride (89.46 mmol, 1.2 equiv) in 20 mL dry CH_2Cl_2 over 10 minutes. The mixture was stirred at 0 °C for 2h and was subsequently quenched with 100 mL saturated $NaHCO_3$. The biphasic system was stirred vigorously for 15 min, and then separated. The water layer was extracted with 80 mL CH_2Cl_2 and the combined organic layers were washed with 150 mL 1M HCl, dried $MgSO_4$ and concentrated in *vacuo* to give **2** (19.74 g, 73.57 mmol, 99%) as a yellow oil, which was used without further purification. The spectra matched those reported in literature.[2]

Compound 3
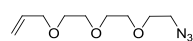
19.74 g **2** (73.57 mmol) and 7.17 g NaN_3 (110.35 mmol, 1.5 equiv) were dissolved in 75 mL DMF and stirred overnight at 50 °C. The mixture was concentrated in *vacuo* and partitioned between 150 mL CH_2Cl_2 and 150 mL H_2O. The water layer was extracted with 2 x 75 mL CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo.* The crude yellow oil was purified by column chromatography (PE/EtOAc 6:1) to give **3** (14.19 g, 65.91 mmol, 89%) as a colorless oil. The spectra matched those reported in literature.[1]

Compound 4
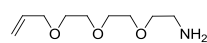
14.19 g **3** (65.90 mmol) and 20.73 g PPh_3 (79.08 mmol, 1.2 equiv) were dissolved in 200 mL THF and 40 mL H_2O and the mixture was stirred overnight at room temperature. The solution was concentrated in *vacuo* and ca. 25 mL dry Et_2O was added. The precipitate was filtered off (rinsed with 2 x 10 mL Et_2O) and the organic layer was concentrated in *vacuo*. The crude product was purified by Kugelrohr distillation (0.04 mbar, 140-150 °C) to give **4** (11.17 g, 59.06 mmol, 90%) as a colorless, odorless oil. The spectra matched those reported in literature.[1]

Compound 5
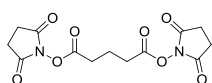
2.53 g *N*-hydroxysuccinimide (22 mmol, 2.2 equiv) and 3.47 mL NEt_3 (25 mmol, 2.5 equiv) were dissolved in 25 mL dry CH_2Cl_2 under N_2 atmosphere and cooled to 0 °C. Next, 1.15 mL glutaroyl chloride (10 mmol) was added dropwise over 10 minutes and the mixture was stirred at 0 °C for 1h and at room temperature for 1h. The reaction was diluted with 15 mL 1M $KHSO_4$ and the water layer was extracted with 10 mL CH_2Cl_2. The combined organic layers were washed with 15 mL saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated in *vacuo* to give an off-white solid. The crude product was crystallized from CH_2Cl_2/PE to give **5** (2.90 g, 8.89 mmol, 89%) as a white solid, which was stored in the fridge. Melting-point: 141-144 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.86 (s, 8H), 2.81 (t, 4H), 2.21 (quint, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 169.07, 167.82, 29.74, 25.71, 19.76; IR (cm^{-1}): 1812, 1780, 1726, 1200, 1068, 1047

Compound **6**

BocHN−NH$_2$

4.36 mL hydrazine hydrate (90 mmol, 3.0 equiv) was dissolved in 12 mL i-PrOH and cooled to 0 °C. Next, 6.54 g Boc$_2$O (30 mmol, 1.0 equiv) was dissolved in 6 mL i-PrOH and added dropwise to the solution. The icebath was removed and the reaction was stirred for 30 minutes at room temperature, after which it was concentrated *in vacuo*. The residue was partitioned between 20 mL EtOAc and 20 mL H$_2$O. The organic layer was washed with 20 mL H$_2$O and the water layers were extracted with 20 mL EtOAc. The combined organic layers were washed with 20 mL brine, dried over MgSO$_4$ and concentrated *in vacuo* to give **6** (2.93 g, 22.13 mmol, 74%) as a colorless oil that solidified upon cooling. The spectra matched those reported in literature.[5]

Compound **8**

Ph$_3$P$\diagdown$N$\diagdown$Boc

2.93 g **6** (22.13 mmol, 1.0 equiv) was dissolved in a mixture of 2.5 mL AcOH and 3.7 mL H$_2$O and cooled to 0 °C. Next, 1.68 g NaNO$_2$ (24.34 mmol, 1.1 equiv) was dissolved in 2.4 mL H$_2$O and added dropwise over 1h to the previously prepared solution. After the addition the reaction was stirred for an additional 30 minutes at 0 °C, after which 3.7 mL H$_2$O was added. The yellow organic layer was separated the water layer was extracted with 4 x 2 mL Et$_2$O. The combined organic layers were washed with 3 x 2 mL H$_2$O and 3 x 2 mL NaHCO$_3$, dried over MgSO$_4$ and used without further purification.

4.56 g PPh$_3$ (17.37 mmol) was dissolved in 14 mL dry Et$_2$O and the aforementioned Boc-N$_3$ solution was added dropwise over 30 minutes. The reaction was stirred for 30 minutes, after which it was cooled to 0 °C. After standing for 1h at 0 °C the crystals were filtered off and the crude product was recrystallized from ca. 20 mL EtOAc. The mother liquor was concentrated and the residue was crystallized from 7 mL EtOAc. The combined crops gave **8** (5.33 g, 14.12 mmol, 81%) as a colorless solid. The spectra matched those reported in literature.[5]

Compound **9**

Cl$_3$C$\diagup\diagup$N$\diagdown$Boc

5.33 g **8** (14.12 mmol) was dissolved in 10 mL dry PhCH$_3$ under N$_2$ atmosphere. Next, 1.40 mL chloral (14.12 mmol, 1.0 equiv) was added and the reaction was refluxed for 1h. The mixture was concentrated *in vacuo* and dry hexanes were added. The precipitate was filtered off and the filtrate was concentrated *in vacuo* to give yellow crystals. The crude product was purified by Kugelrohr distillation (0.4 mbar, 110-115 °C) to give **9** (2.63 g, 10.65 mmol, 75%) as a colorless solid. The spectra matched those reported in literature.[6]
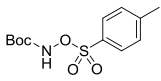
Compound **10**

Cl$_3$C$\diagup$N$\diagdown$Boc (with O above)

First, 2 stock solutions were prepared. Stock solution A: 26 g K$_2$CO$_3$ in 195 mL H$_2$O. Stock solution B: 32.43 g Oxone in 324 mL H$_2$O. Next, 2.63 g **9** (10.65 mmol) was dissolved in 27 mL CHCl$_3$ and cooled to 0 °C. After cooling, 32 mL solution A and 54 mL solution B were added. After stirring for 1h the water layer was discarded and replaced with the same volumes of solutions A and B. In total 6 of such cycles were performed. The organic layer was washed with 3 x 15 mL H$_2$O, dried over MgSO$_4$ and concentrated *in vacuo* (bath temperature 25 °C). The yellow oil was purified by column chromatography (CH$_2$Cl$_2$) to give **10** (1.80 g, 6.86 mmol, 64%) as a colorless oil. The spectra matched those reported in literature.[6]
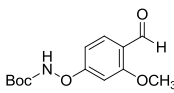
Compound **12**

2.50 g Hydroxylamine hydrochloride (36 mmol) and 7.85 g Boc₂O (36 mmol, 1.0 equiv) were dissolved in 85 mL THF/H$_2$O and cooled to 0 °C. Next, 6.05 g NaHCO$_3$ (72 mmol, 2 equiv) was added and the mixture was stirred at 0 °C for 2h. The mixture was diluted with 40 mL EtOAc and the layers were separated. The organic layer was washed with 40 mL NaHCO$_3$, 40 mL H$_2$O and 40 mL brine, after which it was dried over MgSO$_4$ and concentrated in *vacuo* to give **12** (3.77 g, 28.3 mmol, 78%) as a clear colorless oil. The spectra matched those reported in literature.[8]
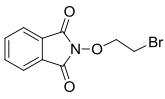
Compound **13**

3.49 g **12** (26.2 mmol) and 4.77 g TsCl (25 mmol, 0.95 equiv) were dissolved in 50 mL dry THF and cooled to 0 °C. After cooling, 3.64 mL Et$_3$N (26.2 mmol, 1.0 equiv) was added dropwise over 5 min and the mixture was stirred at 0 °C for 2h. The mixture was filtered and concentrated in *vacuo*. The residual yellow oil was dissolved in 40 mL EtOAc and washed with 25 mL 1M HCl, 25 mL H$_2$O and 25 mL brine, after which it was dried over MgSO$_4$ and concentrated in *vacuo* to give the crude product as a yellow solid. The crude product was triturated with 3 x 15 mL hexanes to give **13** (4.90 g, 17.07 mmol, 65%) as a white solid. The spectra matched those reported in literature.[8]
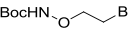
Compound **11**

609 mg 4-hydroxy-2-methoxybenzaldehyde (4.0 mmol) was dissolved in 40 mL dry CH$_3$CN under N$_2$ atmosphere and cooled to 0 °C. After cooling, 160 mg NaH (60% w/w in mineral oil, 4.0 mmol, 1.0 equiv) was added and stirred for 10 minutes, after which 1.15 g **13** (4.0 mmol, 1.0 equiv) was added. The icebath was removed and the mixture was stirred at room temperature for 30 min. The cycle of cooling/deprotonation/addition of **13**/warming was repeated twice with 0.55 eq and 0.30 eq of NaH and **13**. The mixture was concentrated in *vacuo* and partitioned between 70 mL EtOAc and 70 mL H$_2$O. The water layer was extracted with 50 mL EtOAc and the combined organic layers were washed with 50 mL brine, dried over MgSO$_4$ and concentrated in *vacuo* to give a yellow oil. The mixture was loaded on silica and purified by column chromatography (PE/EtOAc 4:1 → 3:1) to give **11** (560 mg, 2.10 mmol, 52%) as a very sticky yellow oil. ^{1}H-NMR (400 MHz): δ 10.41 (s, 1H), 7.87 (d, 1H), 7.33 (bs, 1H), 6.90 (d, 1H), 6.84 (d, 1H), 3.94 (s, 3H), 1.35 (s, 9H) ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 188.69, 162.76, 156.65, 129.75, 122.21, 113.34, 105.04, 82.21, 55.81, 26.09
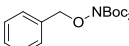
Compound **17**

1.63 g *N*-hydroxyphthalimide (10.0 mmol), 3.42 mL 1,2-dibromoethane (45.0 mmol, 4.5 equiv) and 3.06 mL Et$_3$N (22.0 mmol, 2.2 equiv) were dissolved in 12.5 mL DMF and stirred overnight at room temperature. The mixture was concentrated in *vacuo* and partitioned between 50 mL EtOAc and 50 mL 1M KHSO$_4$. The water layer was extracted with 20 mL EtOAc and the combined organic layers were washed with 40 mL H$_2$O and 40 mL brine, dried over MgSO$_4$ and concentrated to give **17** (1.98 g, 7.33 mmol, 73%) as a slightly yellow solid. The spectra matched those reported in literature.[12]

Compound **18**

BocHN–O–Br 15.82 g **17** (58.57 mmol) was suspended in 80 mL 48% HBr and 50 mL AcOH and heated to 100 $^{\circ}$C for 30 min, after which all the solids were dissolved. The mixture was cooled to room temperature and then cooled to 0 $^{\circ}$C. The precipitate was filtered off (solid rinsed with 10 mL 48% HBr) and the filtrate was concentrated in *vacuo* (bath temperature 70 $^{\circ}$C). The solid was co-evaporated with 2 x 20 mL H_2O and dried thoroughly under vacuum to give a yellow powder. The crude product was triturated with 3 x 50 mL dry Et_2O to remove most of the yellow color. The product was dried under vacuum to give the ammonium salt (12.36 g, 55.94 mmol, 96%) as an off-white powder.

The ammonium salt was suspended in 35 mL dry CH_2Cl_2 and cooled to 0 $^{\circ}$C. Next, 4.24 mL Boc_2O (18.45 mmol, 1.5 equiv) and 3.40 mL NEt_3 (24.60 mmol, 2.0 equiv) were added and the mixture was stirred at 0 $^{\circ}$C for 30 min and overnight at room temperature. The organic layer was washed with 40 mL 1M $KHSO_4$ and 25 mL saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/EtOAc 12:1) to give **18** (1.813 g, 7.55 mmol, 61%) as a colorless oil. The spectra matched those reported in literature.[14]

Compound **20**

O–NBoc$_2$ 4.286 g *O*-benzylhydroxyamine hydrochloride (26.85 mmol) and 4.05 mL NEt_3 (29.54 mmol, 1.1 equiv) were stirred in 35 mL dry CH_3CN for 1h at room temperature. The precipitate was filtered off and rinsed with 10 mL dry CH_3CN. The filtrate was added dropwise to an ice-cooled solution of 6.31 mL Boc_2O (29.52 mmol, 1.1 equiv) in 20 mL dry CH_3CN. The mixture was stirred at 0 $^{\circ}$C for 1h and room temperature for 3h, after which 9.16 mL Boc_2O (42.96 mmol, 1.6 eq) in 13 mL dry CH_3CN was added and 250 mg DMAP. The reaction mixture was stirred overnight at 40 $^{\circ}$C, after which an additional 1.14 mL Boc_2O (5.37 mmol, 0.2 eq) was added. The reaction was monitored with TLC for completion. The volatiles were removed and the residue was partitioned between 45 mL EtOAc and 25 mL 1M phosphate buffer (pH = 7.4). The organic layer was washed with 25 mL brine, dried over $MgSO_4$ and concentrated in *vacuo* to give **20** (8.40 g, 25.98 mmol, 97%) as an off-white solid. Melting-point: 75-78 $^{\circ}$C. The spectra matched those reported in literature.[21]

Compound **21**

Boc$_2$N–OH 8.40 g **20** (25.98 mmol) was dissolved in 105 mL CH_3OH and 1.00 g 5% Pd/BaSO$_4$ was added. The flask was degassed with vacuum / H_2 three times, and the reaction was stirred overnight at room temperature under H_2 atmosphere. After completion of the reaction (checked by TLC), N_2 gas was bubbled through the solution for 10 minutes and the reaction was filtered over Hyflow (rinsed with 2 x 10 mL CH_3OH). The filtrate was concentrated in *vacuo* and the crude product was purified by column chromatography (PE/EtOAc 4:1) to give **21** (5.54 g, 23.76 mmol, 92%) as a white solid. Melting-point: 89-90 $^{\circ}$C. The spectra matched those reported in literature.[21]

Compound **19**

Boc$_2$N$\sim$O$\sim\sim$Br   Method 1:   1.98 g **18** (8.26 mmol), 1.94 mL Boc$_2$O (9.08 mmol, 1.1 equiv) and 99 mg DMAP (0.826 mmol, 0.10 equiv) were dissolved in 20 mL dry CH$_3$CN and stirred at 40 ^{o}C for 1h. The mixture was diluted with 80 mL EtOAc and washed with 40 mL 1M KHSO$_4$, 40 mL saturated NaHCO$_3$ and 40 mL brine, dried over MgSO$_4$ and concentrated in *vacuo* to give **19** (2.67 g, 7.86 mmol, 95%) as a pale yellow oil.

Method 2: **21** (6.0 mmol) and 4.15 mL 1,2-dibromoethane (48 mmol, 8.0 equiv) were dissolved in 20 mL dry DMF and cooled to 0 ^{o}C. After cooling, 4.50 mL DBU (30 mmol, 5.0 equiv) was added dropwise and the ice bath was removed. The mixture was stirred overnight at 50 ^{o}C and concentrated in *vacuo*. The residue was dissolved in 50 mL EtOAc and washed with 30 mL 1M HCl. The water layer was extracted with 20 mL EtOAc and the combined organic layers were washed with 30 mL H$_2$O, 30 mL saturated NaHCO$_3$ and 30 mL brine, dried over MgSO$_4$ and concentrated. The crude product was purified by column chromatography (PE/EtOAc 9:1) to give **19** (1.69 g, 4.97 mmol, 83%) as a colorless oil. ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 4.24 (t, 2H), 3.55 (t, 2H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 150.73, 84.36, 75.57, 28.20, 27.20

Compound **22**

Boc$_2$N$\sim$O$\sim\sim$O—⬡—CHO, OCH$_3$ 2.84 g **19** (8.35 mmol, 1.1 equiv), 1.15 g 4-hydroxy-2-methoxybenzaldehyde (7.59 mmol, 1.0 equiv), 1.73 g K$_2$CO$_3$ (12.53 mmol, 1.5 equiv) and 126 mg KI (0.76 mmol, 0.1 equiv) were dissolved in 25 mL dry DMF and stirred overnight at 50 ^{o}C. The mixture was concentrated in *vacuo* and the residue was partitioned between 50 mL EtOAc and 30 mL 1M HCl. The water layer was extracted with 20 mL EtOAc and the combined organic layers were washed with 30 mL saturated Na$_2$CO$_3$ and 30 mL brine, dried over MgSO$_4$ and concentrated in *vacuo* to give a yellow oil. The crude product was purified by column chromatography (PE/EtOAc 10:3) to give **22** (2.52 g, 6.12 mmol, 80%) as a slightly yellow oil. ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 10.30 (s, 1H), 7.80 (d, 1H), 6.54 (d, 1H), 6.50 (s, 1H), 4.30 (bs, 4H), 3.90 (s, 3H), 1.54 (s, 18H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 188.22, 164.88, 163.83, 149.92, 130.55, 119.06, 105.87, 98.52, 83.96, 73.77, 65.74, 55.44, 27.85

Compound **24**

1.04 g **4** (5.50 mmol, 1.1 equiv) and 2.06 g **22** (5.00 mmol, 1.0 equiv) were dissolved in 16 mL absolute CH$_3$OH. Two drops of acetic acid were added and the mixture was stirred overnight at room temperature. The mixture was cooled to 0 ^{o}C and 378 mg NaBH$_4$ (10 mmol, 2.0 equiv) was added. The reaction was stirred at 0 ^{o}C for 1h and room temperature for 2h, after which it was concentrated in *vacuo*. The residue was partitioned between 30 mL EtOAc and 30 mL saturated NaHCO$_3$. The water layer was extracted with 2 x 20 mL EtOAc and the combined organic layers were washed with 30 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The residue was dissolved in 25 mL CH$_2$Cl$_2$ and 1.92 mL TFA (25 mmol, 5.0 equiv) was added and the mixture was stirred overnight at room temperature. The reaction was quenched with 4.17 mL Et$_3$N (30 mmol) and diluted with 25 mL saturated NaHCO$_3$. The water layer was extracted with 2 x 15 mL CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo.* The crude product was purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 96:4 → 95:5) to give **24** (1.69 g, 3.48 mmol, 70% over 2 steps) as a thick yellow oil. ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 7.66 (bs, 1H), 7.17 (d, 1H), 6.49 (s, 1H), 6.43 (d, 1H), 6.05

(bs, 1H), 5.85 (m, 1H), 5.24 (d, 1H), 5.15 (d, 1H), 4.17 (m, 4H), 4.00 (s, 2H), 3.97 (d, 1H), 3.80 (s, 3H), 3.67 (t, 2H), 3.63-3.55 (m, 8H), 2.98 (t, 2H), 1.46 (s, 9H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 160.63, 158.88, 157.09, 134.73, 132.01, 117.21, 114.48, 105.12, 99.41, 81.91, 74.57, 72.22, 70.58, 70.35, 69.38, 67.21, 65.87, 55.50, 47.15, 46.60, 28.25; IR (cm^{-1}): 2874, 2360, 1679, 1199, 1164, 1113

Compound 25
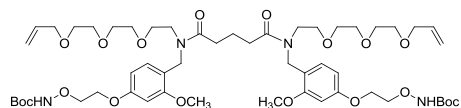
254 mg 24 (0.525 mmol, 2.1 equiv), 82 mg 5 (0.25 mmol, 1.0 equiv), 0.14 mL NEt$_3$ (1.00 mmol, 4.0 equiv eq) and 15 mg DMAP (0.125 mmol, 0.5 equiv) were dissolved in 4 mL dry CH$_2$Cl$_2$ and stirred overnight at room temperature. The mixture was diluted with 30 mL EtOAc and washed with 15 mL 1M KHSO$_4$. The water layer was extracted with 10 mL EtOAc and the combined organic layers were washed with 20 mL saturated NaHCO$_3$, 10 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The yellow oil was purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 195:5 → 192:8) to give 25 (237 mg, 0.222 mmol, 89%) as an thick colorless oil. ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 7.68 (m, 2H), 6.86 + 6.43 (dt, 2H), 6.45 (s, 2H), 6.44-6.33 (m, 2H), 5.84 (m, 2H), 5.22 (d, 2H), 5.11 (d, 2H), 4.51 + 4.45 (dd, 4H), 4.16-4.11 (m, 8H), 4.11 (d, 4H), 3.72 (s, 6H), 3.60-3.41 (m, 24H), 2.48-2.34 (m, 4H), 1.93 (quint, 2H), 1.43 (s, 9H); ^{13}C (CDCl$_3$, 100 MHz) δ 173.28, 173.21, 173.07, 159.26, 158.90, 158.26, 158.08, 156.93, 134.72, 129.94, 127.98, 118.71, 117.84, 116.93, 104.85, 104.44, 99.24, 98.99, 81.65, 74.49, 72.11, 70.62, 70.55, 70.50, 70.25, 69.36, 69.22, 69.17, 68.98, 65.70, 55.26, 55.16, 47.48, 46.88, 45.27, 42.75, 32.44, 32.30, 28.15, 21.03, 20.76 (complexity due to rotamers); IR (cm^{-1}): 3246, 2934, 2871, 1735, 1614, 1450, 1250, 1107

Compound 28
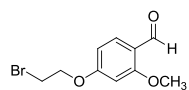
760 mg 4-hydroxy-2-methoxybenzaldehyde (5.00 mmol), 3.45 mL 1,2-dibromoethane (40 mmol, 8.0 equiv) and 3.45 g K$_2$CO$_3$ (25 mmol, 5.0 equiv) were dissolved in 10 mL dry DMF and stirred at room temperature for 3 days. The mixture was diluted with 50 mL H$_2$O and extracted with 3 x 25 mL EtOAc. The combined organic layers were washed with 40 mL H$_2$O and 40 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (CH$_2$Cl$_2$) to give 28 (1.05 g, 4.05 mmol, 81%) as an off-white solid. Melting-point: 70 ^{o}C; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 10.28 (s, 1H), 7.78 (d, 1H), 6.52 (d, 1H), 6.49 (s, 1H), 4.35 (t, 2H), 3.89 (s, 3H), 3.65 (t, 2H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 188.25, 164.59, 163.62, 130.77, 119.59, 106.03, 98.85, 68.05, 55.75, 28.67; IR (cm^{-1}): 2870, 1670, 1593, 1574, 1298, 1267, 1203, 1166, 1115

Compound 29
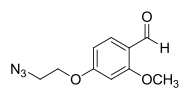
996 mg 28 (3.84 mmol) and 374 mg NaN$_3$ (5.76 mmol, 1.5 equiv) were dissolved in 15 mL DMF and the mixture was stirred overnight at 50 ^{o}C. The mixture was diluted with 50 mL H$_2$O and extracted with 3 x 50 mL EtOAc. The combined organic layers were washed with 75 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The residual yellow oil was purified by column chromatography (PE/EtOAc 1:1) to give 29 (807 mg, 3.65 mmol, 95%) as a pale yellow oil. ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 10.30 (s, 1H), 7.81 (d, 1H), 6.55 (d, 1H), 6.50 (s, 1H), 4.22 (t, 2H), 3.91 (s, 3H), 3.65 (t, 2H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 188.36, 164.77, 163.69, 130.86, 119.68, 106.01, 98.88, 67.31, 55.79, 50.12; IR (cm^{-1}): 2944, 2860, 2107, 1675, 1602, 1262

48

Compound **30**
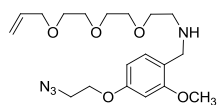
736 mg **4** (3.89 mmol, 1.1 equiv) and 782 mg **29** (3.54 mmol, 1.0 equiv) were dissolved in 10 mL absolute CH_3OH and stirred overnight at room temperature. The mixture was cooled to 0 °C and 535 mg $NaBH_4$ (14.14 mmol, 4.0 equiv) was added portionwise. The mixture was stirred at 0 °C for 1h and room temperature for 1h, after which it was diluted with 20 mL saturated $NaHCO_3$ and extracted with 3 x 25 mL EtOAc. The combined organic layers were washed with 50 mL brine, dried over $MgSO_4$ and concentrated in *vacuo* to give **30** (1.35 g, 3.42 mmol, 97%) as a slight yellow oil. ^1H-NMR ($CDCl_3$, 400 MHz) δ 7.17 (d, 1H), 6.50 (s, 1H), 6.43 (d, 1H), 5.29 (m, 1H), 5.28 (d, 1H), 5.19 (d, 1H), 4.16 (t, 2H), 4.03 (d, 2H), 3.83 (s, 3H), 3.78 (s, 2H), 3.69-3.60 (m, 12H), 2.81 (t, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 158.77, 134.86, 130.48, 121.33, 117.10, 104.47, 99.38, 72.29, 70.71, 70.65, 70.57, 70.38, 69.52, 67.11, 55.42, 50.28, 48.65, 58.44; IR (cm^{-1}): 2866, 2102, 1611, 1588, 1505, 1452, 1287, 1097

Compound **31**
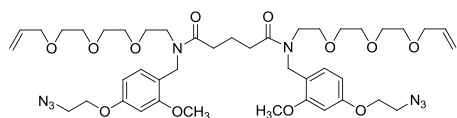
828 mg **30** (2.10 mmol, 2.1 equiv), 326 mg **5** (1.00 mmol, 1.0 equiv), 0.56 mL Et_3N (4.00 mmol, 4.0 equiv) and 61 mg DMAP (0.50 mmol, 0.5 equiv) were dissolved in 10 mL dry CH_2Cl_2 and stirred overnight at room temperature. The solution was diluted with 40 mL EtOAc and washed with 20 mL 1M $KHSO_4$. The water layer was extracted with 20 mL EtOAc and the combined organic layers were washed with 50 mL saturated $NaHCO_3$, 50 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The yellow oil was purified by column chromatography (CH_2Cl_2/CH_3OH 97:3 → 96:4) to give **31** (620 mg, 0.70 mmol, 70%) as a slightly yellow oil. ^1H-NMR ($CDCl_3$, 400 MHz) δ 7.07 + 6.89 (dt, 2H), 6.44-6.33 (m, 4H), 5.22 (m, 2H), 5.21 (d, 2H), 5.11 (d, 2H), 4.52+4.47 (dd, 4H), 4.07 (quint, 4H), 3.96 (d, 4H), 3.74 (ds, 6H), 3.61-3.42 (m, 28H), 2.49-2.35 (m, 4H), 1.94 (quint, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 173.19, 173.12, 173.05, 158.82, 158.46, 158.24, 158.10, 158.07, 134.65, 129.87, 127.91, 118.96, 118.11, 116.89, 104.64, 104.26, 104.23, 99.11, 98.87, 72.04, 70.56, 70.49, 70.43, 70.18, 69.30, 69.16, 69.13, 68.90, 66.93, 55.21, 55.12, 50.02, 47.40, 46.86, 45.16, 42.79, 42.74, 32.40, 32.34, 32.24, 20.96, 20.72 (complexity due to rotamers); IR (cm^{-1}): 2871, 2105, 1614, 1506, 1289, 1260

Compound **32**
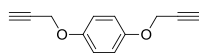
110 mg hydroquinone (1.0 mmol), 0.33 mL propargylbromide (80% w/w in toluene, 3.0 mmol, 3.0 equiv) and 414 mg K_2CO_3 (3.0 mmol, 3.0 equiv) were dissolved in 3 mL acetone and the mixture was stirred overnight at reflux. The reaction was partitioned between 10 mL 1M $KHSO_4$ and 15 mL EtOAc. The organic layer was washed with 15 mL Na_2CO_3. The water layer was extracted with 2 x 5 mL EtOAc and the combined organic layers were washed with 20 mL brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EtOAc 10:1) to give **32** (160 mg, 0.86 mmol, 86%) as a faint yellow oil, which crystallized upon standing. The spectra matched those reported in literature.[17]

Compound 33
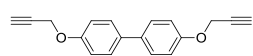
186 mg 4,4'-dihydroxybiphenyl (1.0 mmol), 0.33 mL propargylbromide (80% w/w in toluene, 3.0 mmol, 3.0 equiv) and 414 mg K_2CO_3 (3.0 mmol, 3.0 equiv) were dissolved in 5 mL dry DMF and the mixture was stirred overnight at 70 °C. The reaction was diluted with 50 mL H_2O and the precipitate was filtered and washed with 2 x 10 mL H_2O. The beige residue was dried under vacuum and was subsequently purified by crystallization from PE/EtOAc to give 33 (233 mg, 0.89 mmol, 89%) as bronze plates. The spectra matched those reported in literature.[18]

Compound 34
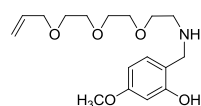
2.84 g 4 (15.0 mmol) and 2.28 g 4-methoxy-2-hydroxybenzaldehyde (15.0 mmol, 1.0 equiv) were dissolved in 45 mL absolute CH_3OH and stirred overnight at room temperature. The mixture was cooled to 0 °C and 907 mg $NaBH_4$ (30.0 mmol, 2.0 equiv) was added and stirred at 0 °C for 1h and room temperature for 1h. The reaction was concentrated and partitioned between 60 mL EtOAc and 60 mL saturated $NaHCO_3$. The water layer was extracted with 3 x 30 mL EtOAc and the combined organic layers were washed with 60 mL brine, dried over $MgSO_4$ and concentrated in *vacuo* to give 34 (4.75 g, 14.58 mmol, 97%) as a yellow oil. ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 6.88 (d, 1H), 6.43 (s, 1H), 6.35 (d, 1H), 5.93 (m, 1H), 5.28 (d, 1H), 5.19 (d, 1H), 4.04 (d, 1H), 3.97 (s, 2H), 3.78 (s, 3H), 3.69-3.60 (m, 10H), 2.83 (t, 2H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 160.40, 159.46, 134.75, 128.91, 117.19, 114.74, 104.82, 101.92, 72.27, 70.67, 70.57, 70.37, 69.58, 69.43, 55.25, 51.69, 47.64; IR (cm^{-1}): 2862, 1621, 1590, 1510, 1452, 1286, 1099

Compound 35
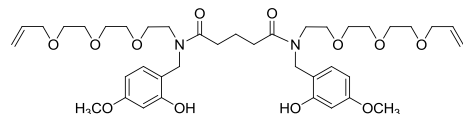
1.50 g 34 (4.60 mmol, 2.3 equiv), 652 mg 5 (2.00 mmol, 1.0 equiv), 1.11 mL NEt$_3$ (8.0 mmol, 4.0 equiv) and 122 mg DMAP (1.0 mmol, 0.5 equiv) were dissolved in 20 mL dry CH_2Cl_2 and stirred overnight at room temperature. To the reaction were added 10 mL CH_2Cl_2 and 15 mL 1M $KHSO_4$. The water layer was extracted with 10 mL CH_2Cl_2 and the combined organic layers were washed with 15 mL saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated in *vacuo* to give a slight yellow oil. The crude product was purified by column chromatography (CH_2Cl_2/CH_3OH 99:1 → 98:2) to give 35 (1.13 g, 1.51 mmol, 75%) as a thick colorless oil. ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 9.71 (s, 2H), 6.97 (d, 2H), 6.39 (s, 2H), 6.30 (d, 2H), 5.83 (m, 2H), 5.21 (d, 2H), 5.12 (d, 2H), 4.41 (s, 4H), 3.95 (d, 4H), 3.70 (s, 6H), 3.65-3.53 (m, 10H), 3.42 (t, 4H), 2.42 (t, 4H), 1.91 (quint, 2H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 175.08, 161.17, 157.29, 134.55, 132.04, 116.92, 114.84, 105.20, 102.28, 71.99, 70.57, 70.48, 70.44, 69.24, 68.97, 55.05, 46.81, 46.27, 31.50, 20.49; IR (cm^{-1}): 2865, 1601, 1506, 1440, 1106

Compound 36
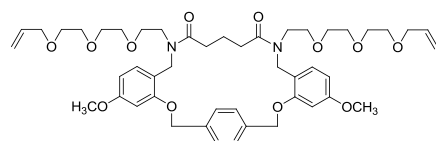
149 mg 35 (0.20 mmol, 1.0 equiv), 53 mg 1,4-bis(bromomethyl)benzene (0.20 mmol, 1.0 equiv), 276 mg K_2CO_3 (2.0 mmol, 10 equiv) and 33 mg KI (0.2 mmol, 1.0 equiv) were dissolved in 4 mL dry DMF and stirred overnight at 70 °C. The reaction was

concentrated *in vacuo* and the residue was partitioned between 15 mL EtOAc and 10 mL H_2O. The water layer was extracted with 2 x 5 mL EtOAc and the combined organic layers were washed with 10 mL brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/CH_3OH 98:2 → 97:3 → 96:4) to give **36** (96 mg, 0.113 mmol, 57%) as a slightly yellow oil. ^{1}H-NMR complex due to rotamers; IR (cm^{-1}): 2867, 1728, 1636, 1610, 1588, 1125; LC-MS: calcd for $C_{47}H_{65}N_2O_{12}$ [$(M+H)^+$]: 849.45, found: 849.4

Compound **37**
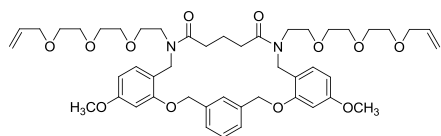
37 mg **35** (0.05 mmol, 1.0 equiv), 13 mg 1,3-bis(bromomethyl)benzene (0.05 mmol, 1.0 equiv), 17 mg K_2CO_3 (0.125 mmol, 2.5 equiv) and 2 mg KI (0.01 mmol, 0.2 equiv) were dissolved in 2.5 mL dry DMF and stirred overnight at 70 °C. The reaction was concentrated *in vacuo* and the residue was partitioned between 25 mL EtOAc and 15 mL H_2O. The water layer was extracted with 2 x 5 mL EtOAc and the combined organic layers were washed with 15 mL brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/CH_3OH 98:2 → 97:3 → 96:4) to give **37** (27 mg, 0.032 mmol, 63%) as a slightly yellow oil. ^{1}H-NMR complex due to rotamers; IR (cm^{-1}): 2869, 1731, 1632, 1608, 1583, 1121; LC-MS: calcd for $C_{47}H_{65}N_2O_{12}$ [$(M+H)^+$]: 849.45, found: 849.4

Compound **38**
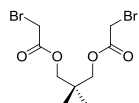
520 mg 2,2-dimethyl-1,3-propanediol (5.0 mmol, 1.0 equiv) and 1.66 g K_2CO_3 (12 mmol, 2.4 equiv) were dissolved in 30 mL dry CH_2Cl_2 under N_2 atmosphere. The mixture was cooled to 0 °C and 0.96 mL bromoacetylbromide (11 mmol, 2.2 equiv) was added dropwise. The icebath was removed and the reaction was stirred overnight at room temperature. The reaction was quenched with 20 mL H_2O and the water layer was extracted with 2 x 8 mL CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EtOAc 9:1) to give **38** (1.66 g, 4.79 mmol, 96%) as a colorless oil. The spectra matched those reported in literature.[19]

Compound **39**
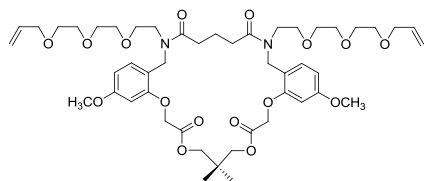
37 mg **35** (0.05 mmol, 1.0 equiv), 26 mg **38** (0.075 mmol, 1.5 equiv) and 162 mg Cs_2CO_3 (0.500 mmol, 10 equiv) were dissolved in 50 mL dry CH_3CN and stirred at 50 °C for 4h. The mixture was concentrated *in vacuo*, loaded on silica and purified by column chromatography (CH_2Cl_2/CH_3OH 97:3 → 96:4 → 95:5) to give **39** (29 mg, 0.031 mmol, 62%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.08 (d, 2H), 6.46 (dd, 2H), 6.30 (s, 2H), 5.90 (m, 2H), 5.26 (d, 2H), 5.17 (d, 2H), 4.62 (m, 8H), 4.01 (d, 4H), 3.88 (s, 4H), 3.78 (s, 6H), 3.67-3.49 (m, 24H), 2.56 (t, 4H), 2.00 (quint, 2H);); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.54, 168.21, 160.37, 156.34, 134.92, 130.73, 130.02, 129.84, 118.12, 117.20, 104.94, 99.39, 72.32, 70.68, 70.36, 69.51, 69.25, 65.45, 65.02, 55.50, 47.59, 44.69, 34.70, 32.78, 21.67, 21.16; IR (cm^{-1}): 2867, 1738, 1638, 1613, 1589, 1507, 1444, 1419, 1118; LC-MS: calcd for $C_{48}H_{71}N_2O_{16}$ [$(M+H)^+$]: 931.48, found: 931.4

Compound **41**
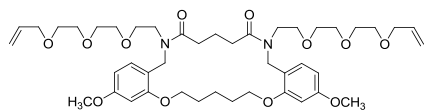
75 mg **35** (0.10 mmol, 1.0 equiv), 49 mg 1,5-diiodopentane (0.15 mmol, 1.5 equiv) and 324 mg Cs_2CO_3 (1.00 mmol, 10 equiv) were dissolved in 100 mL dry $CH_3CN$ and stirred at 60 ^oC for 18h. The mixture was concentrated *in vacuo*, loaded on silica and purified by column chromatography (CH_2Cl_2/CH_3OH 97:3 → 96:4 → 95:5) to give **41** (75 mg, 0.092 mmol, 92%) as a colorless oil. ^{1}H-NMR complex due to rotamers; LC-MS: calcd for $C_{44}H_{67}N_2O_{12}$ [(M+H)$^+$]: 815.47, found: 815.3

Compound **44**
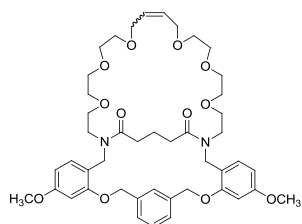
31 mg **37** (0.036 mmol) was dissolved in 36 mL dry CH_2Cl_2 and the solution was degassed with three vacuum/N_2 cycles. After degassing 3 mg Grubbs II (0.004 mmol, 0.1 equiv) was added and the reaction was stirred overnight at 40 ^oC. After cooling to room temperature the mixture was concentrated *in vacuo* and the residue was purified by column chromatography (CH_2Cl_2/CH_3OH 94:6 → 95:5 → 94:6) to give **44** (21 mg, 0.026 mmol, 71%) as a slightly brown oil. Peaks of the major rotamer shown: ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 7.50-7.42 (m, 4H), 7.17 (d, 2H), 6.58 (s, 2H), 6.48 (dd, 2H), 5.78 (m, 2H), 4.93 (s, 4H), 4.51 (s, 4H), 4.01 (d, 4H), 3.82 (s, 6H), 3.66-3.38 (m, 24H), 2.07 (t, 4H), 1.56 (t, 2H); No ^{13}C-NMR was measured; LC-MS: calcd for $C_{45}H_{61}N_2O_{12}$ [(M+H)$^+$]: 821.42, found: 821.4

Compound **45**
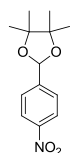
3.02 g 4-nitrobenzaldehyde (20.0 mmol), 3.07 g pinacol (26.0 mmol, 1.33 equiv) and 112 mg p-TsOH (0.59 mmol) were dissolved in 35 mL toluene and the mixture was refluxed for 4h under Dean-Stark conditions. After cooling, 108 mg NaOH in 1.5 mL EtOH was added to quench the reaction. After stirring at room temperature for 30 min, the organic layer was washed with 3 x 50 mL brine, dried over $MgSO_4$ and concentrated *in vacuo* to give **45** (4.68 g, 18.6 mmol, 93%) as an amber colored solid. The spectra matched those reported in literature.[22]

Compound **46**
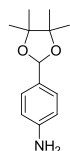
1.00 g **45** (4.00 mmol) was dissolved in 30 mL dry THF and passed through a plug of basic alumina (washed with 10 mL THF). The filtrate was transferred to a 100 mL 3-neck and 100 mg Pd/C (10% w/w) was added. The solution was degassed with five vacuum/H_2 cycles and the reaction was stirred overnight at room temperature under H_2 atmosphere (balloon). The reaction was bubbled through with N_2 gas for 10 min and the solution was filtered through a short plug of Hyflow (washed with 2 x 10 mL THF). The filtrate was concentrated *in vacuo* to give **46** (790 mg, 3.57 mmol, 89%) as a white solid. The spectra matched those reported in literature.[22]

Compound **47**
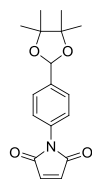
350 mg (3.57 mmol, 1.0 equiv) of maleic anhydride was dissolved in 4 mL dry THF. Next, 790 mg **46** (3.57 mmol, 1.0 equiv) was dissolved in 4 mL dry THF and added dropwise to the maleic anhydride solution. Precipitation was observed and the mixture was stirred at room temperature for 1h. The mixture was concentrated *in vacuo* to give the product as a yellow solid, which was used in the next step without purification. Yield: 1.14 g (3.57 mmol, 100% yield).

0.965 g of this product (3.02 mmol) and 1.24 g (15.1 mmol, 5 equivalents) of NaOAc were dissolved in 12 mL Ac$_2$O and the mixture was heated at reflux under N$_2$ atmosphere for 90 minutes. The mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* and the brown residue was purified by column chromatography (PE/EtOAc 4:1) to give **47** (570 mg, 1.89 mmol, 63% yield) as a slightly yellow solid. Melting point: 116-119 ^{o}C; ^{1}H-NMR (DMSO-*d6*, 400 MHz) δ 7.54 (d, 2H), 7.35 (d, 2H), 7.20 (s, 2H), 5.95 (s, 1H), 1.28 (s, 6H), 1.21 (s, 6H; ^{13}C-NMR (DMSO-*d6*, 100 MHz) δ 170.18, 139.61, 135.00, 131.95, 127.00, 126.78, 98.87, 82.66, 24.39, 22.29; IR (cm^{-1}): 1704, 1371, 1143, 1112

Compound **48**
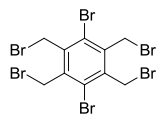
5.84 g (20.0 mmol) of 1,4-dibromodurene was dissolved in 50 mL CCl$_4$ in a 100 mL 3-neck round bottom, equipped with a dropping funnel and a reflux condenser. Next, 6.15 mL Br$_2$ (120 mmol, 6 equivalents) was added and the mixture was irradiated to reflux with a 75 W lamp. The mixture was refluxed overnight and then cooled to room temperature. The excess of bromine was displaced by purging with N$_2$ gas. The precipitate was filtered and washed with 3 x 40 mL CCl$_4$. The crude product was recrystallized from 500 mL toluene to give **48** (9.38 g, 15.44 mmol, 77% yield) as an dense, insoluble white solid. Melting point: 268 ^{o}C; ^{1}H-NMR (DMSO-*d6*, 400 MHz) δ 4.96 (s, 8H); No ^{13}C-NMR could be obtained due to insolubility; IR (cm^{-1}): 3025, 1438, 1217, 1184, 1094, 655

Compound **49**
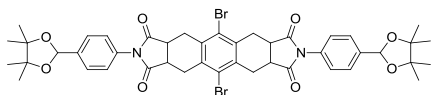
60 mg **47** (0.20 mmol, 2.0 equiv), 61 mg **48** (0.10 mmol) and 148 mg NaI (1.00 mmol, 10 equiv) were dissolved 1.5 mL dry DMF. The mixture was heated to 80 ^{o}C and was stirred overnight under N$_2$ atmosphere. After cooling, the black solution was poured in a separating funnel containing 20 mL H$_2$O. The solution was extracted with 2 x 30 mL CH$_2$Cl$_2$ and the organic layer was washed with 10 mL 1M NaOH. The organic layer was dried over MgSO$_4$ and concentrated *in vacuo* to give crude **49** as a brown solid. Attempted column purification was unsuccessful. Yield: 74 mg (0.083 mmol, 83% yield) ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 7.50 (d, 4H), 7.06 (d, 4H), 5.95 (s, 2H), 3.88 (d, 4H), 3.46 (bs, 4H), 2.97 (d, 4H), 1.31 (s, 12H), 1.22 (s, 12H)

Compound **50**
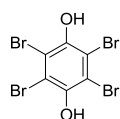
2.09 g freshly sublimed *p*-benzoquinone (19.3 mmol) was dissolved in 22 mL AcOH under N$_2$ atmosphere and brought to reflux. Next, 4.97 mL bromine (96.7 mmol, 5.0 equiv) in 5 mL AcOH was added *via* dropping funnel over 30 minutes. The mixture was

refluxed for an additional 2 hours. After cooling, 15 mL H_2O was added and the mixture was filtered. The solid was washed with cold H_2O and EtOH. The solid was dried under vacuum to give **50** (7.01 g, 16.47 mmol, 85% yield) as a yellow powder, which was used in the next step without further purification. The spectra matched those reported in literature.[25]

Compound **51**
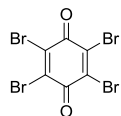
7.01 g **50** (16.47 mmol) was sluried in 30 mL AcOH and 3.38 g (33.76 mmol, 2.05 equivalents) of CrO_3 was added and the mixture was stirred at 50 ^{o}C for 1h. The mixture was cooled to room temperature and ca. 50 g of ice was added. The mixture was filtered and the solid was sluried with 25 mL EtOH, filtered and dried under vacuum. Product **51** (6.60 g, 15.57 mmol, 95% yield) was obtained as a bright yellow powder, which was used in the next step without further purification. The spectra matched those reported in literature.[25]

Compound **52**
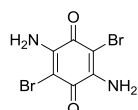
6.60 g **51** (15.57 mmol) was stirred vigorously in 26 mL 2-methoxyethylacetate and the mixture was warmed to 60 ^{o}C. Next, 7.20 mL of 25% NH_4OH (46.71 mmol) was added dropwise over 30 minutes and the mixture was stirred at 80 ^{o}C for 3 h. The mixture was cooled in an icebath for 1h and the precipitate was filtered. The solid was triturated with 100 mL H_2O, and was subsequently sluried in 10 mL acetone and filtered. The resulting solid was dried under vacuum to give **52** (4.08 g, 13.78 mmol, 89% yield) as a dark red solid, which was used in the next step without further purification. The spectra matched those reported in literature.[25]

Compound **53**
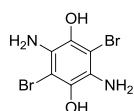
1.18 g **52** (4.00 mmol) and 1.74 g $Na_2S_2O_4$ (10.0 mmol, 2.5 equiv) were heated in 16 mL H_2O to 60°C under N_2 atmosphere for 1h. The mixture was cooled to room temperature, filtered and the solid was triturated with 10 mL H_2O and 10 mL cold EtOH. The residue was dried under vacuum to give **53** (1.09 g, 3.65 mmol, 91% yield) as an insoluble, tan powder. Due to air sensitivity, this compound should be made directly before use. The spectra matched those reported in literature.[25]
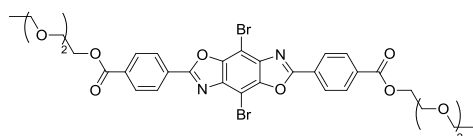
Compound **54**
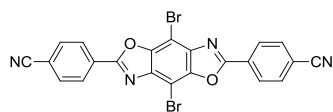
149 mg **53** (0.50 mmol), 207 mg 4-cyanobenzoyl chloride (1.25 mmol, 2.5 equiv) and 10 mg p-TsOH were dissolved in 4 mL dry 1,4-dioxane in a sealed tube. The mixture was stirred overnight at 210 ^{o}C and turned cream brown during the reaction. After cooling to room temperature, 10 mL of saturated K_2CO_3 solution was added to the mixture and the precipitate was filtered. The solid was washed with H_2O and dried under vacuum to give **54** (195 mg, 0.375 mmol, 75% yield) as a light brown powder. Melting point: >300 ^{o}C; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 8.52 (d, 4H), 7.90 (d, 4H); Due to insolubility, no ^{13}C NMR could be obtained; IR (cm^{-1}): 2231, 1582, 1555, 1490, 1412, 1321

Compound **55**
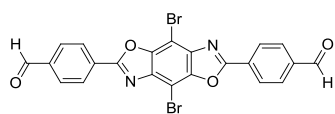
298 mg **53** (1.00 mmol), 421 mg 4-formylbenzoyl chloride (2.50 mmol, 2.5 equiv) and 10 mg p-TsOH were dissolved in 5 mL dry 1,4-dioxane in a sealed tube. The mixture was stirred at 190 °C for 1h. After cooling to room temperature, 30 mL of saturated K$_2$CO$_3$ solution was added to the mixture and the precipitate was filtered. The solid was washed with H$_2$O and dried under vacuum to give **55** (473 mg, 0.899 mmol, 90% yield) as an ochre solid. Melting point: >300 °C; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 10.17 (s, 2H), 8.58 (d, 4H), 8.11 (d, 4H); Due to insolubility, no ^{13}C NMR could be obtained; IR (cm^{-1}): 2840, 2741, 1698, 1583, 1558, 1321, 1203

Compound **57**

343 mg **53** (1.15 mmol), 729 mg 2-(2-ethoxyethoxy)ethyloxycarbonylbenzoyl chloride (2.42 mmol, 2.1 equiv) and 10 mg p-TsOH were dissolved in 8 mL dry 1,4-dioxane in a sealed tube The mixture was stirred at 200 °C for 1h. After cooling to room temperature, 100 mL H$_2$O was added to the mixture and the precipitate was filtered. The solid was washed with 50 mL H$_2$O and dried under vacuum to give **57** (802 mg, 1.02 mmol, 88% yield) as a brown solid. Melting point: 180-182 °C; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 8.39 (d, 4H), 8.21 (d, 4H), 4.54 (t, 4H), 3.89 (t, 4H), 3.74 (t, 4H), 3.65 (t, 4H), 3.56 (q, 4H), 1.24 (t, 6H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 165.69, 163.60, 147.20, 140.03, 133.43, 130.39, 129.79, 128.11, 92.48, 70.91, 70.00, 69.26, 66.88, 64.72, 15.32; IR (cm^{-1}): 2973, 2866, 1721, 1586, 1561, 1268

Compound **58**
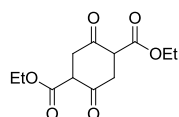
4.60 g sodium (200 mmol) was cut in small chunks and added to 55 mL absolute EtOH. The mixture was stirred at reflux under N$_2$ atmosphere for 3h until no more sodium was present. Next, 16.6 mL diethyl succinate (100 mmol) was added in one portion and the reaction was stirred for 3 days at 100 °C. The volatiles were removed *in vacuo* and 500 mL H$_2$O and 8 mL conc H$_2$SO$_4$ were added. The water layer was extracted with 3 x 100 mL CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo*. The crude product was crystallized from ca. 50 mL EtOAc to give **58** (8.28 g (31.48 mmol, 63%) as a colorless solid. The spectra matched those reported in literature.[27]

Compound **59**
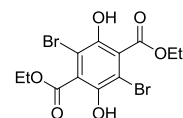
4.09 g **58** (15.95 mmol) was dissolved in 40 mL dry CHCl$_3$ and cooled to 0 °C. Next, 8.22 mL Br$_2$ in 10 mL CHCl$_3$ was added dropwise over 10 minutes to the solution. After the addition the reaction was heated to 60 °C for 4h and was subsequently concentrated *in vacuo*. The residue was dissolved in 100 mL CHCl$_3$ and washed with 50 mL H$_2$O. The water layer was extracted with 25 mL CHCl$_3$ and the combined organic layers were washed with 50 mL 10% NaS$_2$O$_3$. The organic layer was dried over MgSO$_4$ and concentrated *in vacuo* to give **59** (6.44 g, 15.64 mmol, 98%) as a yellow solid. ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 8.99 (s, 2H), 4.52 (q, 4H), 1.48 (t, 6H)

Compound 60
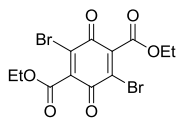
2.06 g **59** (5.00 mmol) was dissolved in 30 mL CH$_3$CN and a solution of 5.75 g ceric ammonium nitrate (10.50 mmol, 2.1 equiv) in 5 mL H$_2$O was added. The reaction was stirred at room temperature for 1h and the volatiles were concentrated *in vacuo*. The solid was filtered and washed with cold H$_2$O and dried *in vacuo* to give **60** (2.04 g, 4.98 mmol, quant) as a yellow powder. Melting point: 222-226 °C. ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 4.47 (q, 4H), 1.42 (t, 6H); IR (cm^{-1}): 1732, 1677, 1285, 1124, 1105

Compound 61
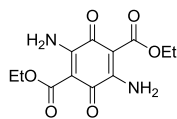
1.84 g **60** (4.48 mmol) was dissolved in 20 mL THF and cooled to 0 °C. Next, 2.88 mL 25% NH$_4$OH (18.35 mmol, 4.1 equiv) was added and the reaction was stirred at room temperature for 2h. The reaction was concentrated *in vacuo* and the remaining solid was triturated with 10 mL cold H$_2$O and dried thoroughly *in vacuo* to give **61** (1.02 g, 3.61 mmol, 81%) as a golden colored solid. ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 9.84 (s, 2H), 7.87 (s, 2H), 4.39 (q, 4H), 1.41 (t, 6H)

Compound 62
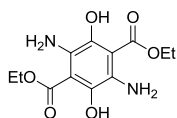
564 mg **61** (2.00 mmol) was dissolved in 30 mL THF/H$_2$O 2:1 and 2.09 g Na$_2$S$_2$O$_4$ (12.0 mmol, 6 equiv) was added. The reaction was stirred at 60 °C for 1h and the volatiles were removed *in vacuo*. The solid was triturated with 20 mL cold H$_2$O and dried thoroughly *in vacuo* to give **62** (516 mg, 1.82 mmol, 91%) as a blood red solid. Note: as this compound is oxidation sensitive, it should be used immediately in subsequent steps. Melting point: 126-128 °C; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 10.82 (s, 2H), 4.93 (s, 4H), 4.53 (q, 4H), 1.50 (t, 6H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 170.91, 140.86, 127.48, 103.22, 62.38, 14.36; IR (cm^{-1}): 3490, 3369, 3059, 1654, 1591, 1446, 1338, 1170

Compound 65
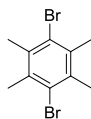
5.00 g 1,2,4,5-durene (37.25 mmol) and 0.20 g I$_2$ (0.80 mmol, 0.02 equiv) were dissolved in 30 mL dry CH$_2$Cl$_2$. Next, 4.80 mL Br$_2$ (93.3 mmol, 2.5 equiv) in 6.7 mL dry CH$_2$Cl$_2$ was added dropwise to the solution. The mixture was refluxed for 1h and was subsequently cooled to room temperature and 20 mL 6M NaOH was added to quench the unreacted bromine. An additional 100 mL CH$_2$Cl$_2$ was added to dissolve the material. The organic layer was concentrated *in vacuo* and the residual solid was triturated with cold H$_2$O. The powder was dried *in vacuo* to give **65** (10.54 g, 36.11 mmol, 97%) as a colorless solid. The spectra matched those reported in literature.[31]

Compound **66**
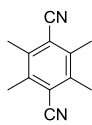
2.92 g **65** (10.0 mmol) and 2.69 g CuCN (30.0 mmol, 3.0 equiv) were dissolved in 30 mL dry DMF and the reaction was stirred overnight at 150 ^{o}C. The mixture was concentrated *in vacuo* and the solid residue was dissolved in 50 mL 25% NH$_4$OH and extracted with 3 x 50 mL Et$_2$O. The combined organic layers were washed with 50 mL 25% NH$_4$OH, 50 mL brine, dried over MgSO$_4$ and concentrated *in vacuo* to give **66** (1.68 g, 9.10 mmol, 91%) as a colorless solid. Melting point: 203-205 ^{o}C ; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 2.51 (s, 12H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 138.60, 118.09, 116.99, 18.65; IR (cm^{-1}): 2928, 2220, 1434, 1385, 1273

Compound **67**
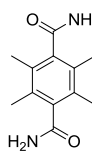
1.68 g **66** (9.11 mmol) was dissolved in 18 mL AcOH/H$_2$SO$_4$ 2:1 and heated to 130 ^{o}C for 3h. The mixture was cooled to room temperature and poured on 140 mL cold H$_2$O. The solid was filtered and washed with 2 x 8 mL H$_2$O, 8 mL cold CH$_3$OH and dried thoroughly *in vacuo* to give **67** (1.81 g, 8.21 mmol, 90%) as an off-white solid. Melting point: >300 ^{o}C; ^{1}H-NMR (DMSO-d6, 300 MHz) δ 7.68 (s, 2H), 7.51 (s, 2H), 2.14 (s, 12H); ^{13}C-NMR (DMSO-d6, 75 MHz) δ 172.04, 139.16, 128.84, 16.44; IR (cm^{-1}): 3373, 3154, 1651, 1434, 1355

Compound **68**
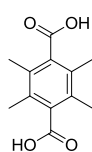
1.80 g **67** (8.17 mmol) was dissolved in 24 mL H$_2$SO$_4$/H$_2$O 2:1 and heated to 90 ^{o}C. To the mixture was added 1.69 g NaNO$_2$ (24.51 mmol, 3.0 equiv) portionwise over 1h. The mixture was stirred at 90 ^{o}C for an additional 3h, after which it was cooled and poured in 160 mL H$_2$O and extracted with 3 x 50 mL EtOAc. The combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo*. The residue was dissolved in 30 mL boiling 0.5 M HCl and slowly cooled to room temperature. The crystals were filtered and washed with 2 x 5 mL cold H$_2$O and 5 mL cold CH$_3$OH. The powder was dried *in vacuo* to give **68** (1.54 g, 6.91 mmol, 84%) as an off-white solid. Melting point: >300 ^{o}C; ^{1}H-NMR (DMSO-d6, 300 MHz) δ 13.25 (s, 2H), 2.14 (s, 12H); ^{13}C-NMR (DMSO-d6, 75 MHz) δ 171.40, 136.94, 129.00, 16.56; IR (cm^{-1}): 2860, 2594, 1686, 1434, 1293, 1205

Compound **69**
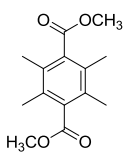
584 mg **68** (2.63 mmol) was dissolved in 25 mL dry THF and 0.50 mL (COCl)$_2$ (5.78 mmol, 2.2 equiv) was added and 1 droplet DMF. The reaction was stirred at room temperature for 2h and was concentrated *in vacuo* and co-evaporated with 5 mL dry THF to give the crude bis-acid chloride (692 mg, 2.67 mmol, quant) as a slightly yellow solid.

432 mg (< 1.67 mmol) of the crude bis-acid chloride was dissolved in 6 mL CH$_2$Cl$_2$/CH$_3$OH 5:1 and solid K$_2$CO$_3$ was added. After stirring for 15 minutes, the reaction was concentrated *in vacuo* and the residue was partitioned between 10 mL CH$_2$Cl$_2$ and 10 mL H$_2$O. The water layer was extracted with 2 x 5 mL CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (CH$_2$Cl$_2$/PE 1:1 → 2:1 → 3:1) to give **69** (246 mg, 0.98 mmol, 59% over two steps) as a white powder. Melting point: 159-162 ^{o}C; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 3.93 (s, 6H), 2.16 (s, 12H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 171.10, 136.10, 130.50, 52.16, 16.85; IR (cm^{-1}): 2955, 1722, 1434, 1290, 1191, 1161

Compound **70**
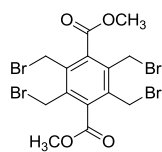
125 mg **69** (0.50 mmol) and 534 mg NBS (3.00 mmol, 6.0 equiv) were dissolved in 5 mL dry CH_2Cl_2 and the mixture was degassed with three vacuum/N_2 cycles. The mixture was irradiated with a 500W construction lamp for 2h and subsequently concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/PE 1:1 → 2:1) to give **70** (210 mg, 0.371 mmol, 74%) as a white solid. Melting point: 193-197 $^{\circ}$C; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 4.60 (s, 8H), 4.07 (s, 6H); IR (cm^{-1}): 2949, 1721, 1439, 1301, 1195

Compound **74**
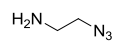
4.09 g 2-bromoethylammonium bromide (20.0 mmol) and 3.25 g NaN$_3$ (50.0 mmol, 2.5 equiv) were dissolved in 25 mL H_2O and stirred overnight at 75°C. The mixture was cooled to room temperature and 880 mg solid NaOH (22.0 mmol, 1.1 equiv) was added. After stirring for 5 minutes, the mixture was extracted with 3 x 50 mL CH_2Cl_2 and the combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo* (bath temperature < 40 $^{\circ}$C) to give **74** (1.39 g, 16.12 mmol, 81%) as a colorless oil. The spectra matched those reported in literature.[35]

Compound **75**
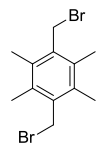
3.36 g 1,2,4,5-durene (25.0 mmol) and 3.00 g paraformaldehyde (100 mmol, 4.0 equiv) were dissolved in a mixture of 40 mL AcOH and 20 mL HBr in AcOH (33% w/w). The reaction was stirred at 120 $^{\circ}$C for 3 days. The mixture was cooled to room temperature and diluted with 200 mL H_2O. The precipitate was filtered and washed with 2 x 20 mL H_2O and 20 mL cold EtOH. The residue was dried *in vacuo* to give **75** (7.42 g, 23.18 mmol, 93%) as a colorless powder. The spectra matched those reported in literature.[33]

Compound **76**
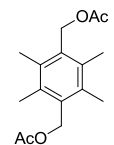
11.61 g **75** (36.29 mmol) and 8.93 g NaOAc (108.9 mmol, 3.0 equiv) were suspended in 70 mL dry CH_3CN and stirred overnight at 70 $^{\circ}$C. The mixture was cooled to room temperature and diluted with 140 mL H_2O and 140 mL CH_2Cl_2. The water layer was extracted with 50 mL CH_2Cl_2 and the combined organic layers were washed with 70 mL H_2O, dried over MgSO$_4$ and concentrated *in vacuo*. The residue was crystallized from 130 mL boiling EtOAc to give **76** (8.56 g, 30.75 mmol, 85%) as white needles. Melting point: 184-187°C; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 5.28 (s, 4H), 2.33 (s, 12H), 2.10 (s, 6H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 171.36, 134.88, 132.78, 62.04, 21.04, 16.37; IR (cm^{-1}): 2983, 2934, 1729, 1236, 1023

Compound 77
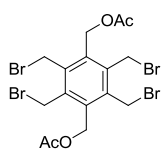
1.39 g **76** (5.00 mmol) and 5.34 g NBS (30.0 mmol, 6.0 equiv) were dissolved in 60 mL dry CH_3CN and the mixture was degassed with three vacuum/N_2 cycles. Next, the mixture was irradiated with a 500W construction lamp for 4h, allowing gentle reflux. The reaction was cooled and concentrated *in vacuo* and the residue was partitioned between 20 mL $CHCl_3$ and 20 mL 1M NaOH. The water layer was extracted with 10 mL $CHCl_3$ and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/PE 2:1 → 3:1) to give **77** (1.60 g, 2.70 mmol, 54%) as a white powder. Melting point: 212-216 ^{o}C ; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.40 (s, 4H), 4.80 (s, 8H), 2.15 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 170.64, 139.09, 136.53, 58.91, 25.68, 21.18; IR (cm^{-1}): 1736, 1231, 1027

Compound 78
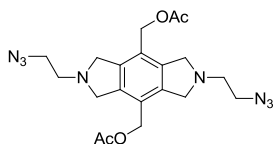
256 mg **77** (0.431 mmol) and 82 mg **74** (0.949 mmol, 2.2 equiv) were dissolved in 10 mL dry CH_3CN and 298 mg solid K_2CO_3 (2.16 mmol, 5.0 equiv) was added. The reaction was stirred at 60 ^{o}C for 2h and was subsequently concentrated *in vacuo*. The residue was partitioned between 20 mL CH_2Cl_2 and 10 mL 1M NaOH. The water layer was extracted with 2 x 10 mL CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give **78** (181 mg, 0.409 mmol, 95%) as a slightly yellow solid. Melting point: 79-81 ^{o}C ; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.00 (s, 4H), 4.08 (s, 8H), 3.51 (t, 4H), 3.01 (t, 4H), 2.07 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 170.73, 139.01, 124.54, 61.69, 57.74, 54.67, 50.15, 20.85; IR (cm^{-1}): 2879, 2792, 2097, 1730, 1361, 1237

Compound 79
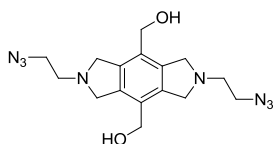
181 mg **78** (0.409 mmol) and 124 mg K_2CO_3 (0.899 mmol, 2.2 equiv) were dissolved in 4 mL CH_3OH and stirred at 50 ^{o}C for 4h. The volatiles were removed *in vacuo* and the obtained solid was transferred to a glass filter and washed with 2 x 5 mL H_2O (most of the yellow color disappeared) and 5 mL EtOH. The powder was dried on air and then on vacuum to give **79** (122 mg, 0.341 mmol, 83%) as an off-white powder. ^{1}H-NMR (DMSO-*d*6, 400 MHz) δ 4.95 (t, 2H), 4.36 (d, 4H), 3.95 (s, 8H), 3.45 (t, 4H), 2.93 (t, 4H); ^{13}C-NMR (DMSO-*d*6, 100 MHz) δ 137.25, 128.64, 59.07, 57.15, 54.44, 49.03

Compound 81
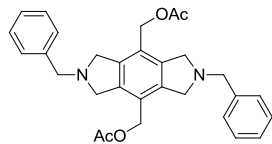
2.80 g **77** (4.71 mmol), 1.13 mL benzylamine (10.37 mmol, 2.2 equiv) and 3.26 g K_2CO_3 (23.57 mmol, 5.0 equiv) were dissolved in 25 mL dry CH_3CN and stirred at 80 ^{o}C for 2 hours. The mixture was cooled to room temperature and concentrated *in vacuo*. The solid residue was transferred to a glass filter and triturated with 2 x 15 mL cold H_2O and 2 x 10 mL cold CH_3OH. The solid was dried on air and vacuum to give **81** (1.65 g, 3.41 mmol, 72%) as an off-white solid. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.43-7.31 (m, 10H), 4.95 (s, 4H), 3.99 (s, 8H), 3.94 (s, 4H), 2.03 (s, 6H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 170.69, 139.30, 138.87, 128.76, 128.51, 127.27, 124.55, 61.92, 60.46, 57.55, 20.77

Compound **83**
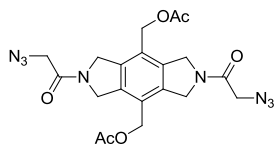
880 mg **81** (1.82 mmol) was dissolved in 8 mL AcOH and 65 mg Pd/C (10% w/w) was added. The mixture was degassed by bubbling H_2 gas for 10 minutes. The reaction was stirred overnight at room temperature under H_2 atmosphere and was subsequently bubbled with N_2 gas for 10 minutes. The mixture was filtered through a plug of Celite, which was washed with CH_3OH. The filtrate was concentrated *in vacuo* and co-evaporated with 2 x 5 mL CH_3OH to give the secondary amine **82** (401 mg, 1.32 mmol, 73%) as an off-white solid.

84 mg of the secondary amine (0.276 mmol), 115 mg azidoacetic acid OSu ester (0.580 mmol, 2.1 equiv) and 0.252 mL NEt_3 (0.690 mmol, 2.5 equiv) were dissolved in 3 mL $CHCl_3$ and stirred for 2h at room temperature. The mixture was diluted with 10 mL CH_2Cl_2 and washed with 10 mL $NaHCO_3$, 10 mL 1M $KHSO_4$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/CH_3OH 192:8 → 191:9) to give **83** (94 mg, 0.200 mmol, 72%) as an off-white foam. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.99 (s, 4H), 4.90 + 4.84 (s (rotamer), 8H), 4.01 (s, 4H), 2.06 + 2.04 + 2.02 (s (rotamers), 6H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 170.46, 170.44, 170.34, 166.12, 166.06, 136.33, 136.26, 136.13, 126.44, 125.93, 125.41, 61.25, 61.05, 60.90, 51.39, 51.23, 50.89, 50.53, 50.50, 20.68, 20.63, 20.59

Compound **84**
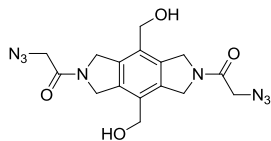
89 mg **83** (0.189 mmol) was dissolved in 2 mL CH_3OH/CH_2Cl_2 1:1 and 52 mg K_2CO_3 (0.378 mmol, 2.0 equiv) was added. The reaction was stirred overnight at room temperature and concentrated *in vacuo*. The dry residue was transferred to a glass filter and triturated with 5 mL cold H_2O, 3 mL cold CH_3OH and 3 mL CH_2Cl_2, dried on air and vacuum to give **84** as an off-white solid. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 5.21 (bs, 2H), 4.80 (s, 4H), 4.74 (s, 4H), 4.45 (t, 4H), 4.19 (s, 4H)

References

[1] Brun, M.A.; Tan, K.T.; Griss, R.; Kielkowska, A.; Reymond, L.; Johnsson, K. *J. Am Chem. Soc.* **2012**, *134*, 7676-7678

[2] Sawant, P.; Maier, M.E. *Eur. J. Org. Chem.* **2012**, *33*, 6576-6585

[3] Van den Berg, T.A.; Feringa, B.L.; Roelfes, G. *Chem. Comm.* **2007**, 180-182

[4] Foot, O.F.; Knight, D.W. *Chem. Comm.* **2000**, 975-976

[5] Carpino, L.A.; Carpino, B.A.; Giza, C.A.; Terry, P.H. *Org. Syn.* **1964**, *44*, 15-17

[6] Vidal. J.; Hannachi, J.-C.; Hourdin, G.; Mulatier, J.-C.; Collet, A. *Tetrahedron Lett.* **1998**, *39*, 8845-8848

[7] Lajiness, J.P.; Robertson, W.M.; Dunwiddie, I.; Broward, M.A.; Vielhauer, G.A.; Weir, S.J.; Boger, D.L. *J. Med. Chem.* **2010**, *53*, 7731-7738

[8] Masruri; Willis, A.C.; McLeod, M.D. *J. Org. Chem.* **2012**, *77*, 8480-8491

[9] Boyles, D.C.; Curran, T.T.; Greene, D.; Macikenas, D.; Parlett, R.V. *Tetrahedron Lett.* **2002**, *43*, 6735-6737

[10] Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A.; Aubry, A. *Chem. Eur. J.* **1997**,*3*,1691-1709

[11] Vidal, J. Guy, L.; Sterin, S.; Collet, A. *J. Org. Chem.* **1993**, *58*, 4791-4793

[12] Tang, F.; Yang, Y.; Tang, Y.; Tang, S.; Yang, L. Sun, B.; Jiang, B.; Dong, J.; Liu, H.; Huang, M.; Geng, M.-Y.; Huang, W. *Org. Biomol. Chem.* **2016**, *14*, 9501-9518

[13] Bauerand, L.; Suresh, K.S. *J. Org. Chem.* **1963**, *28*, 1604-1608

[14] Javorskis, T.; Sriubaite, S.; Bagdziunas, G.; Orentas, E. *Chem. Eur. J.* **2015**, *21*, 9157-9164

[15] Jayasekara, P.S.; Jacobsen, K.A. *Chem. Comm.* **2014**, *44*, 2344-2347

[16] Madsen, P.; Ling, A.; Plewe, M.; Sams, C.K.; Knudsen, L.B.; Sidelmann, U.G.; Ynddal, L.; Brand, C.L.; Andersen, B.; Murphy, D.; Teng, M.; Truesdale, L.; Kiel, D.; May, J.; Kuki, A.; Shi, S.; Johnson, M.D.; Teston, K.A.; Feng, J.; Lakis, J.; Anderes, K.; Gregor, V.; Lau, J. *J. Med. Chem.* **2002**, *45*, 5755-5775

[17] Erbas-Cakmak, S.; Akkaya, E.U. *Angew. Chem. Int. Ed.* **2013**, *52*, 11364-11368

[18] Hemamalini, A.; Das, T.M. *New J. Chem.* **2013**, *37*, 2419-2425

[19] Xu, J.-F.; Chen, Y.-Z.; Wu, D.; Wu, L.-Z.; Tung, C.-H.; Yang, Q.-Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 9738-9742

[20] Barrionuevo, C.A.; Schmidt, L.C.; Arguello, J.E. *New J. Chem.* **2016**, *40*, 4550-4555

[21] Usta, H.; Kim, C.; Wang, Z.; Lu, S.; Huang, H.; Facchetti, A.; Marks, T.J. *J. Mater. Chem.* **2012**, *22*, 4459-4472

[22] Albers, H.M.H.G.; Hendrickx, L.J.D.; van Tol, R.J.P.; Perrakis, A.; Ovaa, H. *J. Med. Chem.* **2011**, *54*, 4619-4626

[23] Guo, X.; Watson, M.D. *Macromolecules* **2011**, *44*, 6711-6716

[24] Tlach, B.C.; Tomlinson, A.L.; Ryno, A.G.; Knoble, D.D.; Drochner, D.L.; Krager, K.J.; Jeffries-EL, M. *J. Org. Chem.* **2013**, *78*, 6570-6581

[25] Tlach, B.C.; Tomlinson, A.L.; Bhuwalka, A.; Jeffries-EL, M. *J. Org. Chem.* **2011**, *76*, 8670-8681

[26] Osowska, K.; Miljanic, O.S. *Chem. Comm.* **2010**, *46*, 4276-4278

[27] Lemouchi, C.; Vogelsberg, C.S.; Zorina, L.; Simonov, S.; Batail, P.; Brown, S.; Garcia-Garibay, M. *J. Am.Chem. Soc.* **2011**, *133*, 6371-6379

[28] Wood, P.M.; Woo, L.W.L.; Labrosse, J.-R.; Thomas, M.P.; Mahon, M.F.; Chander, S.K.; Purohit, A.; Reed. M.J.; Potter, B.V.L. *ChemMedChem* **2010**, *5*, 1577-1593

[29] Mike, J.F.; Makowski, A.J.; Jeffries-EL, M. *Org. Lett.* **2008**, *10*, 4915-4918

[30] Lagadic, E.; Bruyneel, F.; Demeyer, N.; Herent, M.-F.; Garcia, Y.; Marchant-Brynaert, J. *Synlett.* **2013**, *24*, 817-822

[31] Kaur, I.; Jazdzyk, M.; Stein, N.N.; Prusevich, P.; Miller, G.P. *J. Am. Chem. Soc.* **2010**, *132*, 1261-1263

[32] Horcajada, P.; Salles, F.; Wuttke, S.; Devic, T.; Heurtaux, D.; Maurin, G.; Vimont, A.; Daturi, M.; David, O.; Magnier, E.; Stock, N.; Filinchuck, y.; Popov, D.; Riekel, C.; Ferey, G.; Serre, C. *J. Am. Chem. Soc.* **2011**, *133*, 17839-17847

[33] Wang, C.; Tang, S.; Lv, X.; Li, L.; Zhao, X. *Eur. J. Inorg. Chem.* **2014**, 3133-3139

[34] Xu, Y.; Vermeulen, N.A.; Liu, Y.; Hupp, J.T.; Farha, O.K. *Eur. J. Inorg. Chem.* **2016**, 4345-4348

[35] Beld, J.; Cang, H.; Burkart, M.D. *Angew. Chem. Int. Ed.* **2014**, *53*, 14456-14461

[36] Shrimp, J.H.; Hu, J.; Dong, M.; Wang, B.S.; MacDonald, R.; Jiang, H.; Hao, Q.; Yen, A.; Lin, H. *J. Am. Chem. Soc.* **2014**, *136*, 5656-5663

Chapter III: Oxime connection between ring- and thread fragments approach

Introduction

With a working macrocyclization reaction for connecting the ring fragment to the scaffold in hand, as described in Chapter II, we set out to complete the strategy towards a [2]rotaxane. Importantly, for the temporary connection between the ring and thread fragments (see scheme 1 in Chapter II), a reaction is required that is high yielding and robust, yet also potentially reversible. In our laboratory the oxime ligation proved to be a robust and reliable reaction.[1] This ligation technique, which even works *in vivo*, is the condensation of an oxyamine with an aldehyde or ketone to give an oxime (see scheme 1). Oxime formation is inherently reversible, but generally the equilibrium lies completely at the oxime side. Although oxime formation is a condensation, this reaction is still high yielding in aqueous environment. Therefore, this is an attractive ligation technique for biological systems. The reaction is spontaneous, however, reaction rates are usually quite slow. Due to activation of the carbonyl by protonation, the reaction is faster at low pH. However, in many biological systems this is not desirable, therefore multiple aniline-based catalysts have been developed over the last years. These increase reaction rates and allow oxime formation at (near) neutral pH.[2,3,4]
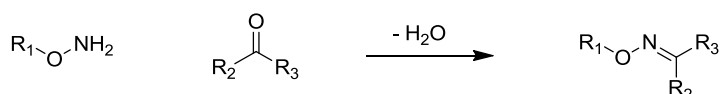

Scheme 1: oxime ligation

For this project, oxime formation appears to be ideal as a temporary linkage of the rotaxane fragments, because this reaction is high yielding, reversible, mild and orthogonal with the other reactions (CuAAC reaction, RCM and Williamson etherification). Moreover, the oxime bond is short, therefore keeping the ring and thread fragments in close proximity.

Strategy

The currently envisioned strategy is almost identical to the original concept strategy as described in Chapter II, with a few changes to ensure full compatibility of all functional groups (see scheme 2)

In the first step, the ring fragment **I** is covalently attached to the thread **II** by the temporary oxime bond formation. Connection of product **III** to the template is envisioned at first *via* a Williamson etherification. The subsequent double intramolecular CuAAC reaction of **IV** backfolds the thread over the ring fragment. As a result the final RCM reaction is forced to 'clip' over the thread resulting in pre-rotaxane skeleton **V**. Subsequent acidolysis cleaves the acid labile tethers connecting the pre-rotaxane and template, giving **VI**. Although oximes are inherently acid-sensitive, it is postulated that due to the congested environment the oxime will not be cleaved at this stage. For this, a stronger acidic environment (HCl instead of TFA) is necessary. The addition of methoxyamine captures the newly liberated ketone forming [2]rotaxane **VII.**

Interestingly, the order of the first two reactions is not really important. Either the ring fragment is first coupled to the thread fragment, followed by Williamson etherification to the scaffold. Or, as originally outlined in Chapter II, the ring fragment is first connected to the scaffold and subsequently coupled to the thread fragment *via* the oxime ligation. As will be seen in this chapter, both approaches proceed well with comparable yields.
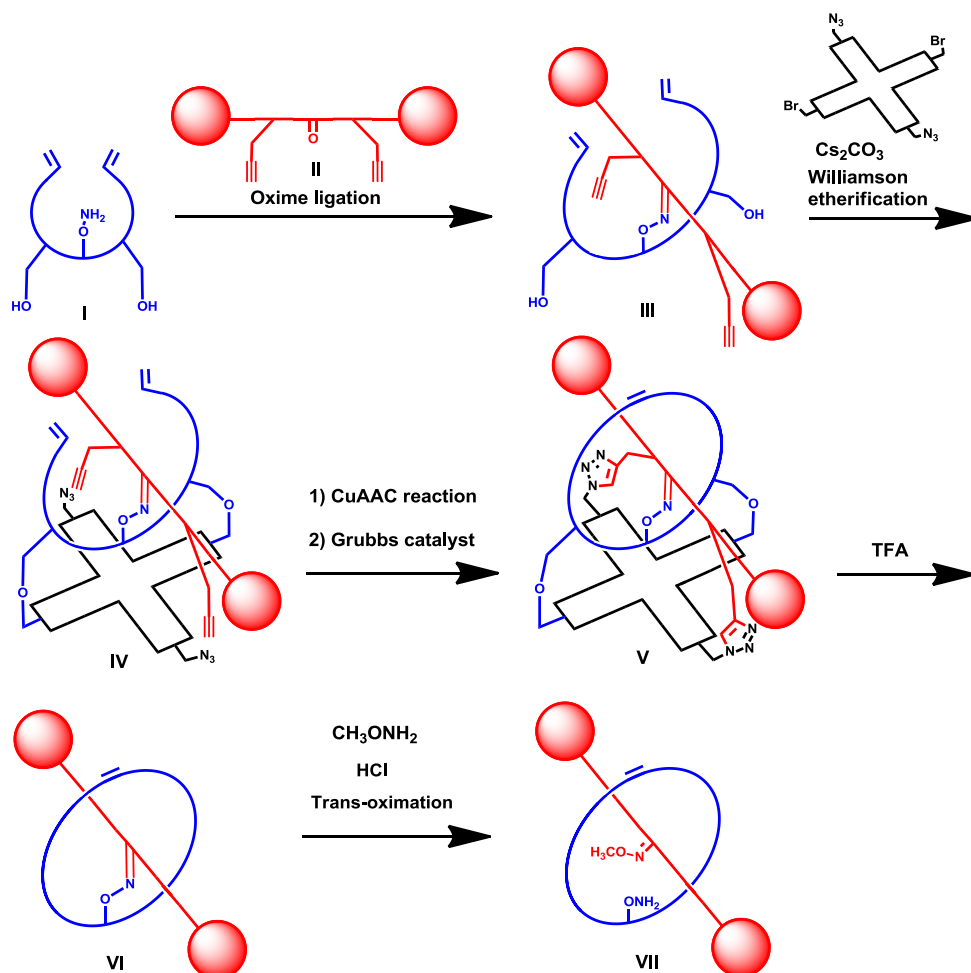
Scheme 2: Synthetic strategy towards a [2]rotaxane using a oxime connection between ring and thread.

Design of the components

To facilitate spectroscopic analysis and the synthesis of the building blocks, all components were designed to be symmetric. Moreover, robust reactions were chosen. Key synthetic steps during the rotaxane assembly include oxime formation, Williamson etherification, CuAAC reaction, RCM reaction and acidolytic cleavage of the benzyl groups. Therefore, all these required functionalities are incorporated in the building blocks.

Ring fragment

The ring fragment was designed to bear acid labile 2-hydroxy-4-methoxybenzyl groups as temporary tethers to the amide backbone.[5] As shown in Chapter II this group allows for further temporary covalent connections *via* the phenolic hydroxyl group and can be removed in the penultimate step by TFA treatment. The allyl capped triethyleneglycol motif remains unaltered, allowing for the RCM during the rotaxane assembly. The central *N*-hydroxyphthalimide group allows (after deprotection) for facile oxime ligation with aldehydes and ketones.

Also in the design of the thread fragment a 4-methoxybenzyl group was included as amide backbone modification. This derivative, now bearing a 2-propargyloxy moiety, would allow for the robust intramolecular CuAAC 'click' reaction with the scaffold (see strategy, scheme 2). Also this amide backbone modification was designed to be cleaved by TFA in the penultimate step towards the [2]rotaxane. The central part of the molecule has a ketone moiety as coupling partner in the oxime ligation, derived from either 4-ketopimelic acid or 6-ketoundecanoic acid.[6] In this chapter the synthesis of several thread fragments are described varying in tether length between the amides (R-groups in figure 1). The molecule is capped at both ends with a bulky trityl group that will mechanically lock the rotaxane framework, thus preventing dissociation of the ring from the thread. As substrates for model reactions also some analogues were synthesized bearing methyl groups instead of the bulky stoppers.

Scaffolds

The scaffold design includes two activated bromides and two azides, allowing for sequential Williamson etherification with the ring fragment and intramolecular CuAAC reaction with the thread fragment, respectively. Ideally, these groups are placed in a square planar orientation (as depicted in scheme 2). However, as seen in the Chapter II, true square planar organic molecules were hard to synthesize or suffered from insolubility. Therefore, in this chapter two new types of scaffolds were synthesized, namely aliphatic scaffolds with a central quaternary sp^3 hybridized atom, showing a perpendicular (though three-dimensional) arrangement of the substituents, and 1,2,4,5-tetrasubstituted benzenes that are planar, but lack the ideal 90° angles. As activated bromides, for the aliphatic scaffolds bromoacetate esters were chosen and for the 1,2,4,5-tetrasubstituted benzenes benzylic bromides. As seen in Chapter II, both types of activated bromides are well tolerated in the Williamson etherification macrocyclization reaction.
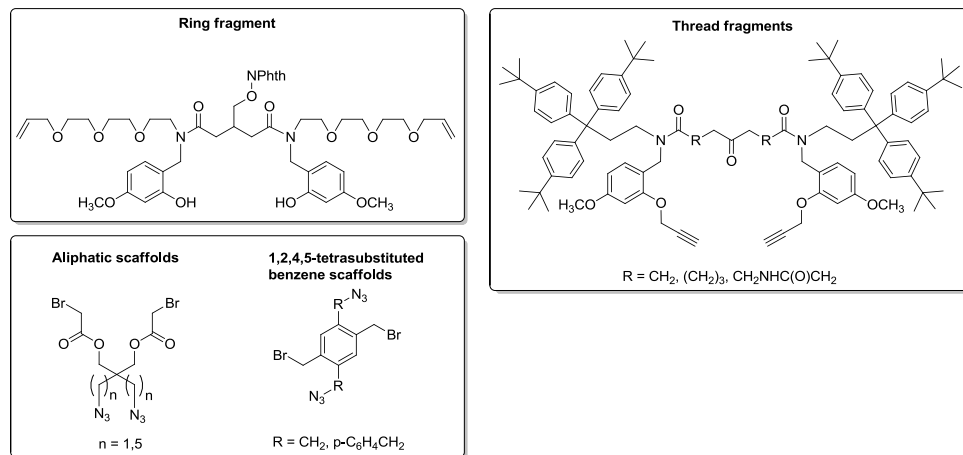

Figure 1: Generalized designs of the required building blocks

Synthesis of the ring fragment

As most of the chemistry for the ring fragment was performed in Chapter II, only the center part containing the oxyamine moiety had to be synthesized. The synthesis of the ring fragment (see scheme 3) started with the double alkylation of dimethyl malonate with *tert*-butyl bromoacetate using NaH as the base to give **1** in quantitative yield. Saponification of the methyl esters with LiOH

and subsequent acidification yielded a mixture of mono- and di-acid. This mixture was refluxed in toluene for 2 hours, ensuring full decarboxylation to the mono-acid **2**. Reduction with borane dimethyl sulfide smoothly gave primary alcohol **3** in 82% yield. Despite the ease of γ-lactone formation, this alcohol was observed to only slowly lactonize over time, owing to the steric bulk of the *tert*-butyl esters. The oxyamine moiety was introduced *via* a Mitsunobu reaction of alcohol **3** with *N*-hydroxyphthalimide, giving product **4** in 88% yield. Lastly, deprotection of the *tert*-butyl esters with TFA smoothly yielded di-acid **5** in quantitative yield as a white powder. The desired ring fragment was completed by coupling of di-acid **5** with secondary amine **2.34** (see Chapter II) using PyBOP as the coupling reagent, giving ring fragment **6** in 78% yield as a thick colorless oil. It is worth to note that in contrast with other tertiary amides, products with a 2-hydroxybenzyl group do not show different rotamers in the ^{1}H-NMR spectra. This could presumably be due to intramolecular H-bonding of the phenolic OH's with the adjacent tertiary amide carbonyl, thereby 'locking' the conformation of the tertiary amide (see scheme 3, bottom right), although there is no experimental proof for such an 8-membered ring.
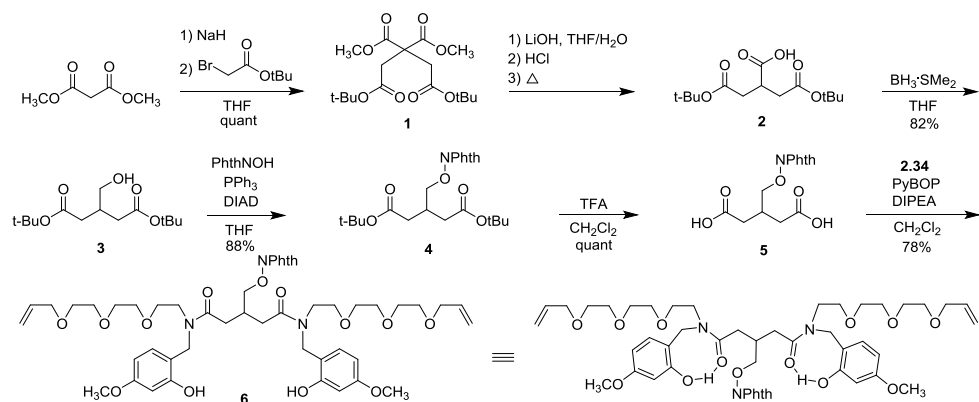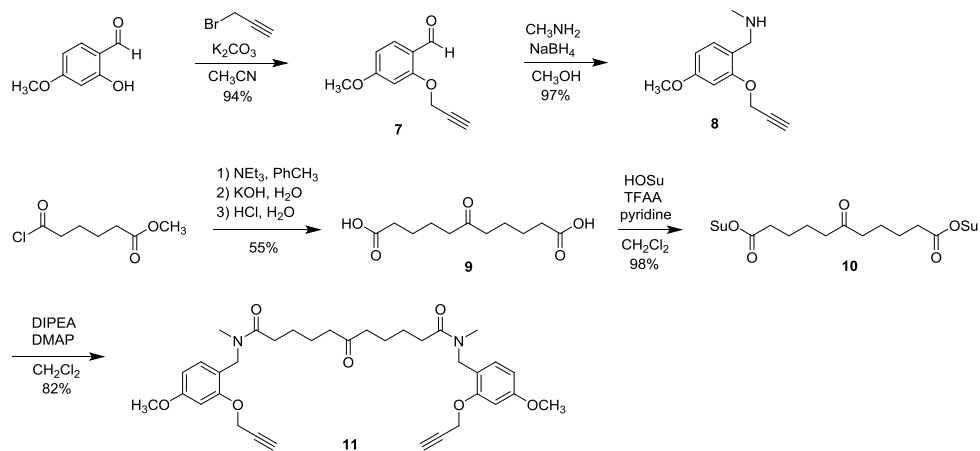

Scheme 3: Synthesis of ring fragment **6**

Synthesis of the thread fragments

Model thread fragment

To test whether the outlined strategy was feasible and to prove the structures of the intermediates, a model thread fragment was synthesized that did not include the bulky stopper groups. Consequently, the final steps of the assembly do not include the acidolytic cleavage (this would lead to dissociation of the ring fragment), but rather hydrolysis of the ester bonds in the aliphatic scaffolds. If successful, subsequent trans-oximation with methoxyamine would yield a [2]catenane product, instead of a [2]rotaxane, but still showing the feasibility of the concept.

To synthesize the model thread fragment, 2-hydroxy-4-methoxybenzaldehyde was alkylated with propargyl bromide to give **7** in 94% yield (see scheme 4). Subsequent reductive amination with methylamine gave secondary amine **8** essentially pure in 97% yield. For the central part of the molecule, 6-ketoundecanoic diacid **9** was synthesized according to literature procedure in 55% yield, starting from monomethyl adipoyl chloride.[6] Transformation of the acids into the *N*-hydroxysuccinimide esters proceeded almost quantitative.[7] Bis OSu-ester **10** was mixed with amine **8** and 10 mol% DMAP as acylation catalyst to give model thread fragment **11** in 82% yield.

Scheme 4: Synthesis of model thread fragment **11**

Synthesis of 'Real' thread fragment

In addition to the model thread fragment, also two 'real' thread fragments were synthesized that vary in tether length. As the bulky stopper group capping the thread fragment at both sides, the (tris-4-*tert*-butyl)trityl group was selected, due to its ease of synthesis and considerable bulk. Many rotaxane syntheses also employ derivatives of this stopper group for the steric bulk it imposes.

The stopper synthesis (see scheme 5) started by treating 4-bromo-*tert*-butylbenzene with *n*-BuLi at -78 °C, leading to bromine lithium exchange. Addition of dimethyl carbonate and acidic workup yielded trityl alcohol **12** in 84% yield. Next, this product was heated with excess malonic acid to form propionic acid **13** in 91% yield.[8] During this reaction, the malonic acid serves a dual role: protonation of the trityl alcohol leading to formation of the trityl cation and subsequent attack of the slightly nucleophilic methylene of malonic acid (in its enol form) on this cation. The product, as well as any excess of malonic acid, subsequently decarboxylates under the high temperature conditions, yielding the mono-acid. To transform acid **13** into a primary amine (necessary for the reductive amination), the fastest way was to perform a Curtius rearrangement. Thus, acid **13** was reacted with diphenylphosphoryl azide (DPPA) under basic conditions in toluene at 80 °C to give the corresponding isocyanate. This was directly hydrolyzed with NaOH in aqueous THF to give amine **14** in 77% yield. Reductive amination of aldehyde **7** with amine **14** gave secondary amine **15** in 81% yield. It was observed that this product did not show the high polarity usually associated with secondary amines. Indeed, any attempt for further functionalization of this amine, like coupling with Fmoc-Gly-OH, only resulted in recovered starting amine **15**. Consequently, the bulky trityl group is too close to the amine part, shielding it for further reactions. The reason that the reductive amination did work is probably because of the less hindered nature of primary amine **14**.
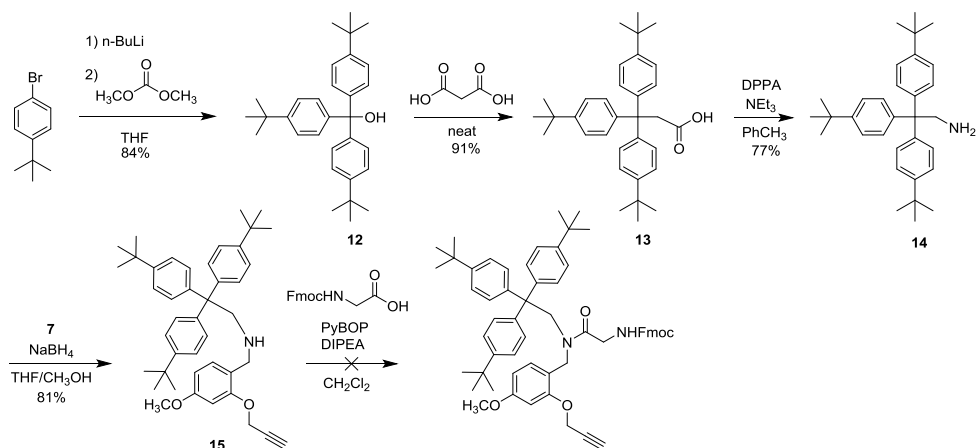
Scheme 5: Synthesis of bulky amine **15** and attempted follow-up chemistry

To overcome the steric problem, it was decided to increase the distance between the bulky trityl group and the amine. For this, acid **13** was reduced with borane dimethyl sulfide complex, giving alcohol **16** in 84% yield (see scheme 6). Next, alcohol **16** was reacted with DPPA under Mitsunobu conditions, providing azide **17** in 79% yield. Hydrogenation of the azide proceeded smoothly, giving amine **18** in 93% yield. However, it was observed that this amine had a purple color that could not be removed *via* column chromatography. As there are no chromophores in this molecule (all precursors are also colorless) the purple color was attributed to residual palladium nanoparticles that had leached out of the Pd/C during hydrogenation. Nevertheless, amine **18** was reacted with aldehyde **7** to give the reductive amination product **19**. However, ^{1}H-NMR analysis showed the formation of both desired product **19** and de-alkylated product **20**. Chromatographic separation of the two polar amines was troublesome. De-alkylation of **19** to give **20** is postulated to be caused by the residual palladium nanoparticles still present. Palladium oxidatively inserts in the oxygen-propargyl bond, and addition of a reducing agent (NaBH₄) liberates the free phenol, propyne and regenerates Pd(0). In 2003, the group of Yeleswarapu reported a similar propargyl ether cleavage, although under harsher conditions.[9]
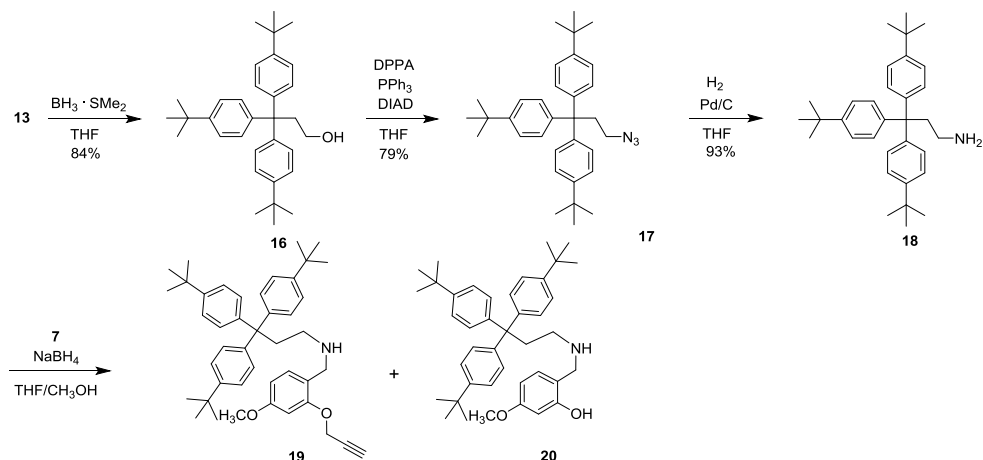
Scheme 6: Synthesis of bulky amine **19** *via* azide reduction and subsequent reductive amination

To overcome this problem, a palladium-free route to amine **18** had to be followed and two routes were considered, namely Staudinger reduction of azide **17** or a Gabriel synthesis of alcohol **16**. As the Staudinger reduction produces stoichiometric amounts of PPh$_3$O that can be hard to remove, especially from polar compound like amines, the Gabriel synthesis route was selected. Alcohol **16** was reacted with phthalimide under Mitsunobu conditions to give product **21** in 92% yield (see scheme 7). Deprotection with hydrazine hydrate in a mixture of CH$_2$Cl$_2$ and EtOH smoothly liberated primary amine **18** in 87% yield. Fortunately, the polar hydrazide byproduct was easily removed by column chromatography. Subsequent reductive amination with aldehyde **7** produced the desired secondary amine **19** in 67% yield, with no trace of de-alkylated product **20**.
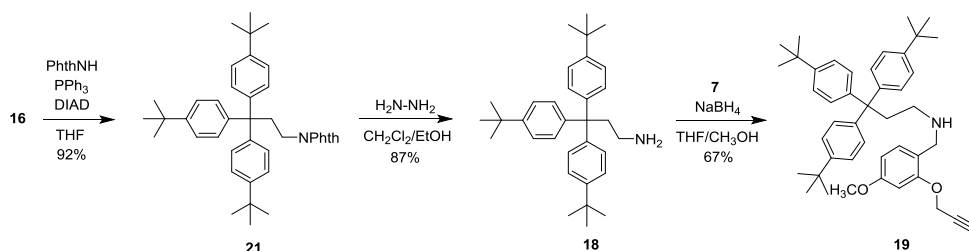

Scheme 7: Synthesis of bulky amine **19** *via* a Gabriel synthesis

The central part of the thread fragment that contains the ketone was derived from the commercially available 4-ketopimelic acid. Diethyl 4-ketopimelate was saponified with aqueous NaOH to give the free diacid **22** in 79% yield (see scheme 8).[10] Transformation into the bis-OSu ester using literature conditions gave **23** in almost quantitative yield.[7]
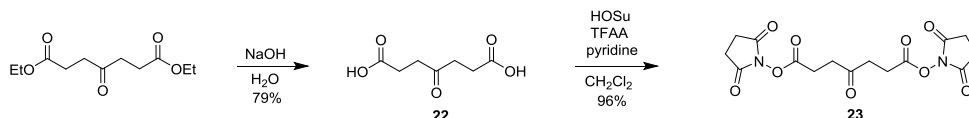
Scheme 8: Synthesis of bis OSu ester **23**

Next, secondary amine **19** was extended with a glycine moiety, as this would increase the length of the thread to be comparable to the previously synthesized model thread fragment **11**. Also, this would ensure that the CuAAC reaction would not yield a strained product. Coupling of **19** with Fmoc-Gly-OH, mediated by PyBOP gave product **24** in 94% yield (see scheme 9). Fmoc-deprotection by diethylamine in CH$_2$Cl$_2$ yielded the primary amine **25** in 68% yield as a foam. Coupling of **25** with bis-OSu ester **23**, catalyzed by DMAP, gave thread fragment **26** in 92% yield as a fine white powder. The ^{1}H-NMR spectrum of the product showed, as expected, a mixture of rotamers.
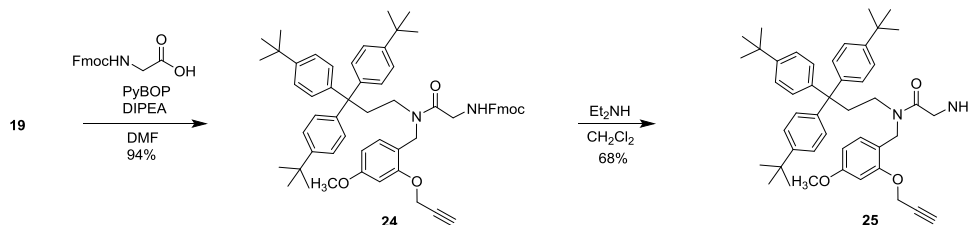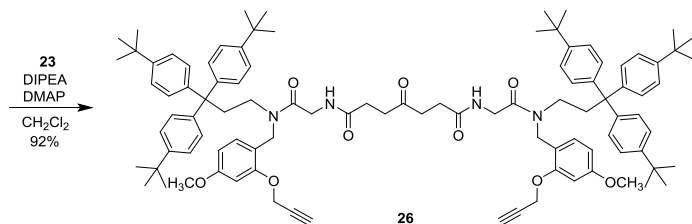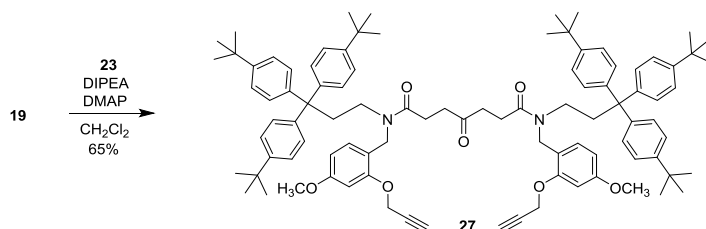
Scheme 9: Synthesis of thread fragment **26**

Shorter thread fragment

In addition to thread **26**, a smaller truncated analogue was synthesized for intramolecular CuAAC reactions with the smaller scaffolds (see next part). To reduce the length of the thread fragment, the glycine motifs were omitted. Therefore, secondary amine **19** was directly reacted with bis-OSu ester **23**, giving truncated thread fragment **27** in 65% yield (see scheme 10).


Scheme 10: Synthesis of truncated thread fragment **27**

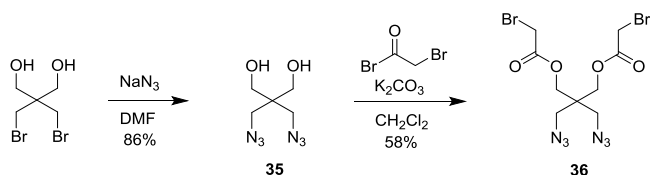## Synthesis of the scaffolds

Aliphatic scaffolds

The synthesis of the sp^3-carbon atom centered aliphatic scaffold started with the double alkylation of dimethyl malonate with 5-hexenyl-1-bromide using NaH as the base to give **28** in 81% yield (see scheme 11). LAH reduction in THF gave diol **29** in 87% yield and subsequent reaction with 2,2-dimethoxypropane gave acetonide **30** in almost quantitative yield. Ozonolysis, followed by reductive workup with NaBH$_4$, yielded diol **31** in 52% yield. This was transformed quantitatively into its bis-mesylate and subsequent substitution using NaN$_3$ in DMF gave di-azide **32** in 77% yield over the two steps. Acidic hydrolysis of the ketal gave diol **33** and was subsequently esterified with bromoacetyl bromide to give scaffold **34** in 94% yield over the two steps. It was crucial to keep the concentration of the base low by using insoluble and inorganic K$_2$CO$_3$ during this last reaction, as the use of NEt$_3$ or DIPEA led to a colored product and lower yields, presumably due to base-induced ketene formation.
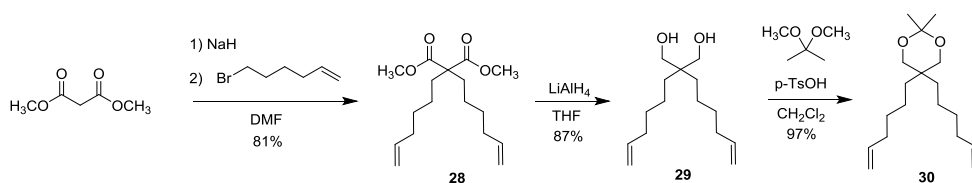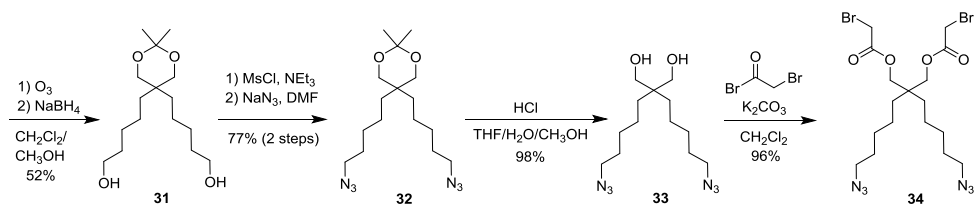
Scheme 11: Synthesis of bis-ester scaffold **34**

As it was yet unknown which length the tethers ideally should have, an analogue was made that only had one methylene between the azides and the central tetrahedral sp^3 atom. Fortunately, this would also greatly simplify the synthesis of this truncated scaffold, as the precursor 2,2-dibromomethyl-1,3-propanediol was commercially available and could be easily converted to the diazide **35** in 86% yield *via* a literature procedure (see scheme 12).[11] No instability of this low weight di-azide was observed. Reaction with bromoacetyl bromide and K$_2$CO$_3$ in CH$_2$Cl$_2$ yielded scaffold **36** in a moderate but acceptable 58% yield.

Scheme 12: Synthesis of truncated bis-ester scaffold **36**

Aromatic scaffolds

Because of the inherent flexibility of aliphatic sp^3 carbon based scaffolds, it was decided to also make two aromatic scaffolds that are much more rigid. Therefore, it was decided to synthesize a triaryl scaffold, with the central benzene core bearing the benzylic bromides in the *para* positions. At the outer side two benzylic azides were designed, thereby allowing some flexibility during the CuAAC reaction. According to molecular models of the intermediates, there should be no strain in the molecule during any cyclization step in the assembly. The synthesis of the triaryl scaffold started with radical bromination of commercially available 2,5-dimethyl-1,4-dibromobenzene (see scheme 13).[12] Although a mixture of tri-, tetra- and pentabromides was obtained, the desired tetrabromide **37** could be obtained in pure form in 51% yield after recrystallization. Substitution with NaOAc in refluxing CH$_3$CN gave bis-benzylic acetate **38** in 84% yield. In this synthesis the benzylic acetates served as protective groups for the eventual re-introduction of benzylic bromides, as the latter are incompatible with the subsequent palladium chemistry.

As coupling partner, 4-bromobenzaldehyde was reacted with B$_2$Pin$_2$ and KOAc, catalyzed by Pd(dppf)Cl$_2$, to give the corresponding pinacolborate ester[13], which was directly reduced with NaBH$_4$ to give **39** in 75% yield over two steps. Reaction of the benzylic alcohol with DPPA under basic conditions yielded benzylic azide **40** in 65% yield. Subsequent Suzuki coupling of dibromide **38** and boronic ester **40** required extensive optimization (solvent, catalyst, temperature, base), but eventually it was found that Pd(dppf)Cl$_2$ and K$_3$PO$_4$ successfully gave coupling product **41**, although in a moderate 44% yield. The reaction worked optimally at 50 ^{o}C. Higher temperatures only led to decomposition and lower temperatures gave incomplete conversion. It is worth to note that there are not many literature precedents regarding Suzuki couplings of benzylic azide containing

compounds. Nevertheless, the group of Davis *et al* reported this desired transformation in several articles.[14,15,16,17]

Saponification of the benzylic acetates with LiOH proceeded cleanly and almost quantitatively, giving **42** that was unexpectedly insoluble in many solvents. As a result, final conversion of the alcohols to benzylic bromides required some optimization. The use of PBr$_3$ in Et$_2$O or CH$_2$Cl$_2$ (common solvents for this reaction) led to complex mixtures with still some remaining insoluble material. However, when diol **42** was dissolved in the more polar solvent THF under dilute conditions, it reacted quickly and cleanly with PBr$_3$ to give scaffold **43** in 86% yield. The excess of PBr$_3$ used reacted with THF to form (after workup) 4-bromobutanol, thus requiring column purification of **43**.
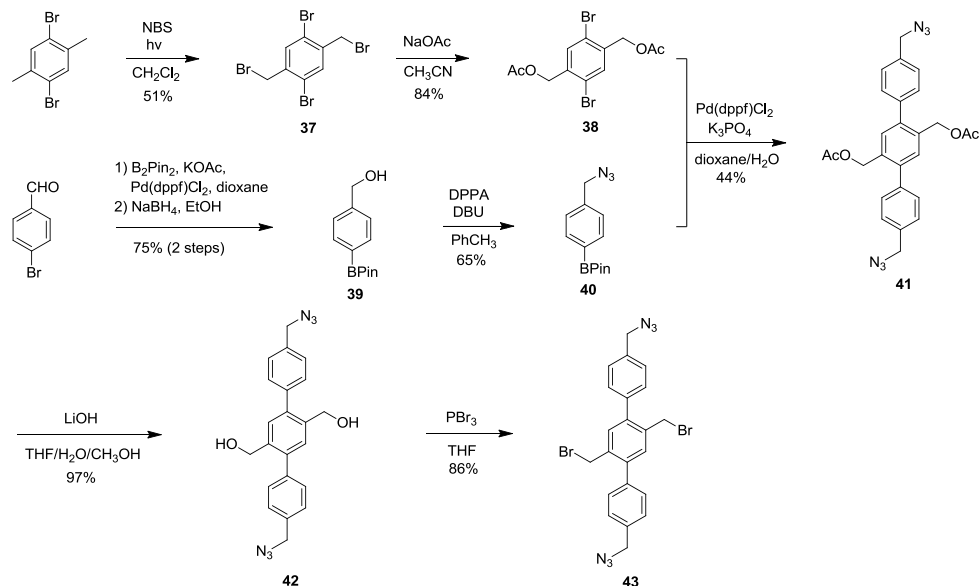
Scheme 13: Synthesis of triaryl scaffold **43**

Analogous to the aliphatic scaffold, it was decided to also make a truncated version of this scaffold by omitting the two outer aryl groups, and synthesize 2,5-di(azidomethyl)-1,4-bis(bromomethyl)benzene as one of the smallest possible aromatic scaffolds for this project. Despite the small size and versatility of this molecule, it was not reported before in literature.

The synthesis of this smaller scaffold started with bromomethylation of p-xylene to give dibromide **44** in a moderate but acceptable 54% yield (see scheme 14).[18] Substitution with NaOAc cleanly gave di-acetate **45** in 71% yield. However, subsequent radical bromination gave a complex mixture. Presumably also the methylene next to the acetate is brominated, leading to side reactions.
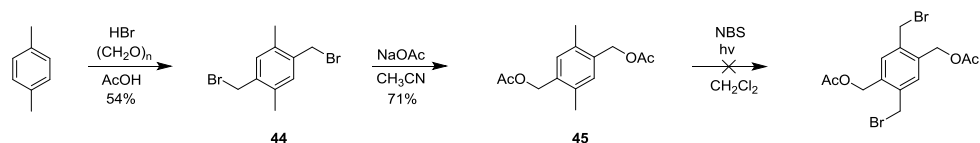
Scheme 14: Synthesis of compound **45** and attempted radical bromination

Different protective groups were also installed to solve this problem. First, the acetate was deprotected with K_2CO_3 in CH_3OH to give the corresponding diol in 93% yield as a fine powder. Protection with pivaloyl chloride or TIPS-chloride yielded the pivalate ester and TIPS ether in yields of 91% and 93%, respectively. Unfortunately, neither of these analogues performed better in the radical bromination, giving only complex mixtures. For a radical bromination to work well, the presence of electron withdrawing groups on the aromatic ring seems beneficial. To arrive at our scaffold, it is important that these electron withdrawing groups may be converted back to a benzylic alcohol or bromide. To fulfill our needs, an ester would be the best one carbon precursor for a benzylic bromide.

As 2,5-dimethylterephthalic acid (or derivative) is not commercially available, it had to be synthesized. Bis-benzylic bromide **44** was oxidized to di-aldehyde **46** with 2-nitropropane (Hass-Bender oxidation) in 75% yield (see scheme 15).[19] Subsequent direct oxidation to the esters with V_2O_5 and hydrogen peroxide in acidic ethanol yielded the terephthalic ester **47** in 69% yield.[20] The yield could have been higher, as also some mono-carboxylic acid was also present due to hydrolysis. Fortunately, the subsequent radical bromination went cleanly, giving dibromide **48** in 66% yield after recrystallization.
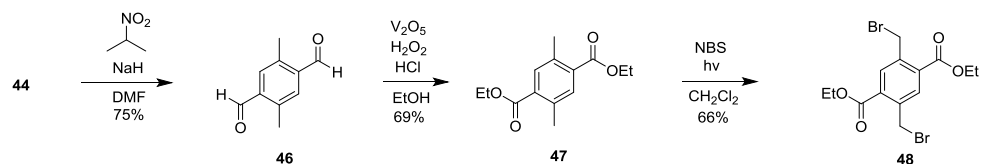

Scheme 15: Synthesis of dibromide **48**

The azides were introduced cleanly and almost quantitatively, giving di-azide **49** as a colorless solid (see scheme 16). Next, the esters had to be reduced back to the benzylic alcohols. However, reaction of **49** with the relatively mild $LiBH_4$ led to full decomposition. Saponification with LiOH gave di-acid **50** in quantitative yield, but reduction of the acids with the aforementioned borane dimethyl sulfide complex also led to a complex mixture. Thus, the acids had to be transformed into activated esters, which could be reduced with 'mild' $NaBH_4$ to give the desired benzylic alcohols. Fortunately, the group of Kaur reported[21] the reduction of N-acylbenzotriazoles to alcohols with $NaBH_4$, so di-acid **50** was first transformed into bis-benzotriazoleester **51** via a protocol by Katrizky et al.[22]
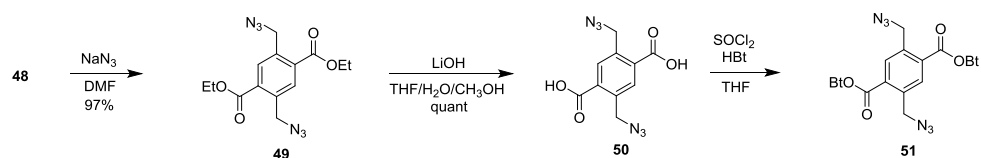
Scheme 16: Synthesis of bis-benzotriazole ester **51**

Reduction of **51** with $NaBH_4$ was quite clean, although $CHCl_3$ had to be added as co-solvent due to the low solubility of the starting material. After column purification, diol **52** was obtained in 63% yield over the two steps (see scheme 17). Lastly, the diol had to be transformed into the bis-benzylic bromide. Reaction with PBr_3 in CH_2Cl_2 gave some product, but yields were generally low. Therefore, diol **52** was first transformed into bis-mesylate **53** in 79% yield. Lastly, the bis-mesylate was reacted with LiBr in THF to give scaffold **54** in 83% yield as a colorless solid via a Finkelstein-type substitution. Remarkably, in the ^{1}H-NMR spectrum all benzylic protons appeared in the same singlet ($CDCl_3$ was used as solvent).
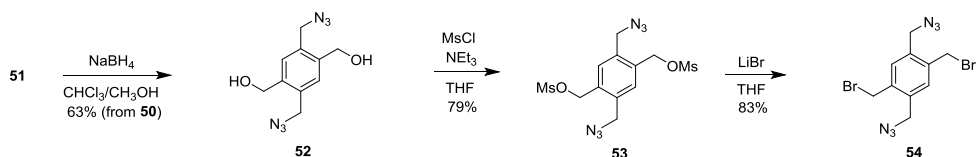
Scheme 17: Synthesis of scaffold **54**


Assembly of the ring, thread and scaffold components

<u>With aliphatic scaffolds</u>

Firstly, the assembly using ring fragment **6**, model thread fragment **11** and aliphatic scaffold **34** was tested. Williamson etherification of the ring fragment with a slight excess of scaffold **34** was the first reaction. As found in Chapter II, the use of Cs_2CO_3 in CH_3CN at 60 °C gave full conversion to the macrocyclic bis-lactone product **55**. The reaction was performed in multiple runs between 1-5 mM concentration to prevent intermolecular side reactions that would give oligo- or polymers. After column chromatography, **55** was obtained in 69% yield. The ^{1}H-NMR spectrum of the product, as well as all following intermediates, was complex due to the presence of multiple tertiary amides, giving mixtures of rotamers. Therefore, the products were analyzed with LC-MS or HR-MS for purity.

Next, the oxime ligation was to be tested and optimized. From previous research in our laboratory, it was known that the *N*-hydroxyphthalimide moiety had to be removed using methylhydrazine to prevent diazene mediated hydrogenation of the double bonds in the ring fragment. Addition of 4 equiv of methylhydrazine in THF at 0 °C cleanly gave the free oxyamine within 30 min. The use of THF was crucial, as other solvents such as CH_2Cl_2 or CH_3OH unexpectedly led to partial formation of formaldehyde oximes, presumably due to traces of formaldehyde in these solvents. Also, it was essential to use dried glassware to prevent the formation of acetone oximes due to traces during cleaning. Subsequent addition of the ketone gave only slow conversion to the oxime product **56**. The reaction could be accelerated with aniline, however, removal of the aniline catalyst, as well as dark-colored side products, was troublesome. As an alternative, the reaction rate could also be increased by addition of 0.2 M acetic acid as the catalyst, using the pH dependency of oxime formation at our advantage. Remarkably, the presence of some water during the oxime ligation was required, as the reaction did not give full conversion in anhydrous solvents. Using these optimized conditions, oxime **56** was obtained in 75% yield over the two steps (deprotection and oxime formation).

Initial experiments showed that also the subsequent intramolecular CuAAC 'click' reaction required optimization. Addition of CuI, DIPEA and 2,6-lutidine (classic catalytic system for the CuAAC reaction) to a diluted solution of **56** only led to rapid polymerization of the starting material, seen as a cloudy precipitation. Apparently the conformation of **56** hampered the azides and alkynes to come in close proximity, therefore favoring intermolecular reactions instead. After some experimentation, the reaction was optimized by slowly adding a solution of **56** to a solution of CuI, DIPEA and 2,6-lutidine at 60 °C. Despite the slow addition, some polymer formation could not be prevented. Nevertheless, **57** was now obtained in a good 77% yield. Subsequent RCM with Grubbs 2nd generation catalyst at 1 mM was uneventful and cleanly gave tricyclic cage-type compound **58** in 59% yield as an undetermined E/Z mixture.
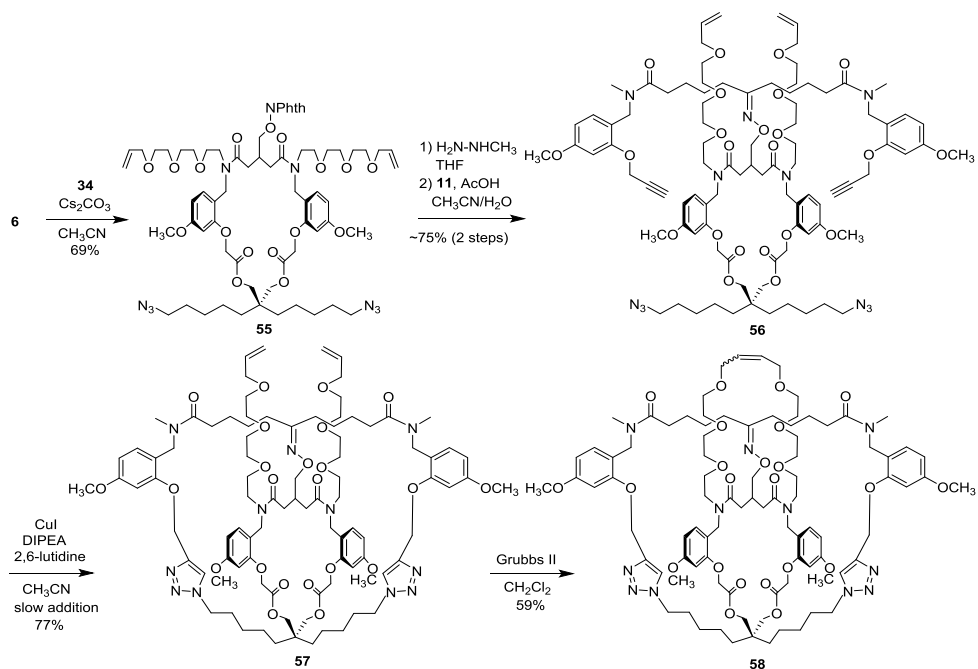
Scheme 18: Assembly starting from ring fragment **6**, model thread fragment **11** and scaffold **34**

To reveal the interlocked nature of the intermediates, the ester bonds to the scaffold had to be broken *via* saponification, followed by cleavage of the oxime *via* transoximation. These steps were executed by reaction of **58** with excess K_2CO_3 in a mixture of CH_2Cl_2, CH_3OH and H_2O to give the hydrolyzed product, which was used without further purification (see scheme 19, A). Subsequent addition of a large excess (ca. 1000 equiv) of methoxyamine under acidic conditions cleanly cleaved the oxime bond between the ring and thread fragments. The newly liberated ketone was trapped by methoxyamine to form a new oxime. Disappointingly, analysis of the LC-MS trace showed the presence of two products. The molecular mass of these products corresponded with the free components **59** and **60** and no trace of the desired mechanically interlocked product was observed. It may be concluded that during the RCM step cyclization had occurred in a non-interlocked fashion to give isomer **III** (scheme 19, B). It was speculated that the large size of the 40-membered macrocycle (red in scheme 19) formed during the CuAAC reaction (i.e. compound **I**) still would allow slipping of the oxime connected ring fragment through this ring, forming sterically more relaxed conformer **II**. As a consequence no interlocked product was formed during the RCM step towards **III**.
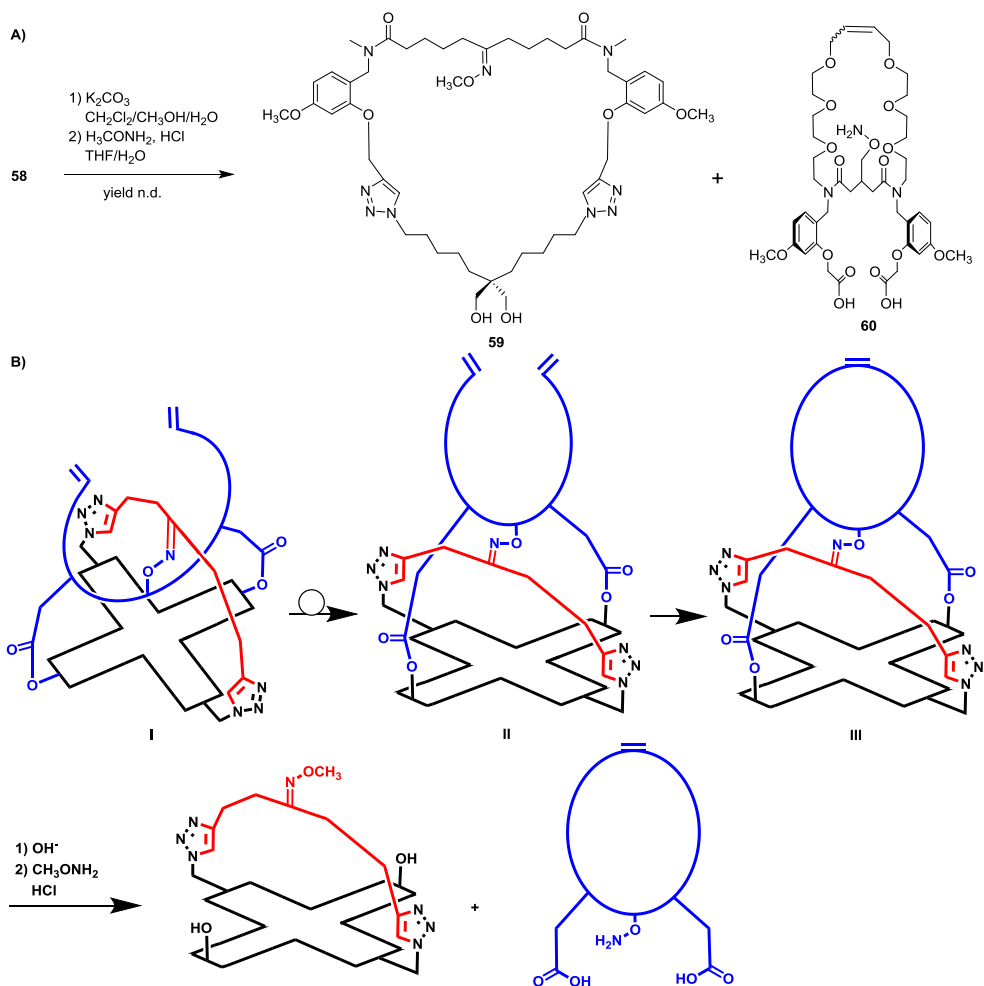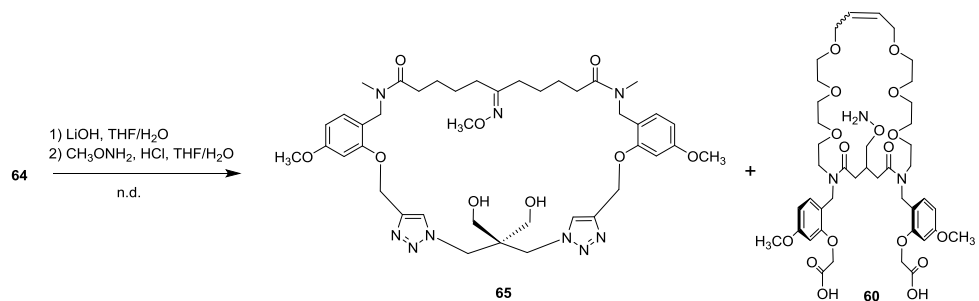
Scheme 19: A) Hydrolysis and trans-oximation of compound **58.** B) proposed formation of non-interlocked products **59** and **60**

Next, the macrocyclization steps were repeated with truncated scaffold **36**. Using the previously optimized conditions, ring fragment **6** was reacted with the smaller scaffold **36** and Cs_2CO_3 to give bis-lactone **61** in 69% yield. Subsequent deprotection with methylhydrazine and oxime ligation with model thread **11** under the optimized conditions gave oxime **62** in 77% yield over the two steps. Subsequent intramolecular CuAAC reaction using the optimized slow addition conditions gave 58% yield of product **63**. According to LC-MS the product consisted of two compounds with identical masses in a ca. 3:1 ratio. Nonetheless, subsequent ring closing metathesis with Grubbs II catalyst gave multicyclic compound **64** in 51% yield, again as a mixture of two products with identical masses.
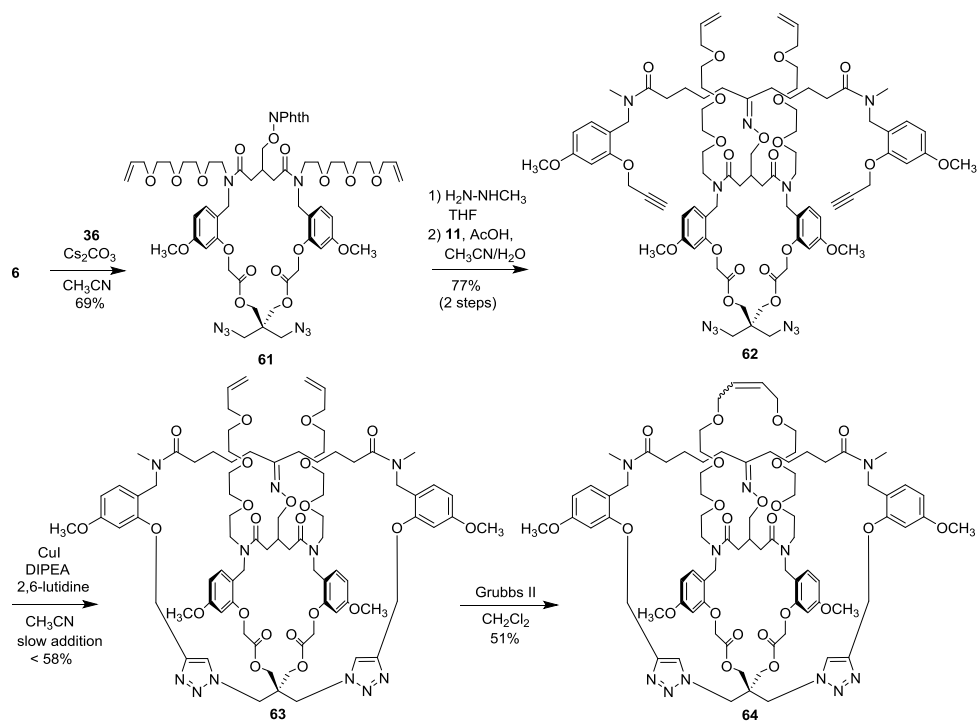
Scheme 20: Macrocyclizations with truncated scaffold **36**

Saponification with LiOH (instead of K$_2$CO$_3$) and transoximation with excess methoxyamine under acidic conditions completed the sequence of reactions to the [2]catenane skeleton. Even more disappointingly, also this time the LC-MS trace only showed the formation of the non-interlocked products **65** and **60** with molecular masses [M+H]$^+$ of 820 Da and 880 Da, respectively (see scheme 21). This meant that RCM had yet again formed the undesired non-interlocked product (analogous to compound **III**, scheme 19), despite the reduction of the ring size to 32 atoms (instead of the 40-membered ring in compound **58**).


Scheme 21: Hydrolysis and trans-oximation of compound **64**

It was postulated that the aliphatic sp^3 carbon based scaffolds allowed too much flexibility in the intermediates, leading to formation of undesired non-interlocked products. Therefore it was thought that the rigid aromatic scaffolds would perform better in these steps. As time was also running out, it was decided to use the 'real' thread fragments from now on (i.e. with stopper groups present).

Coupling of ring fragment **6** with scaffold **43** under the optimized Williamson etherification conditions gave macrocycle **66** in 84% yield (see scheme 22). Phthalimide removal, followed by oxime ligation with thread fragment **26** under the optimized conditions gave oxime product **67** in 47% yield over two steps. Fortunately, the intramolecular CuAAC proceeded smoothly, giving **68** in 60% yield. Also RCM went uneventful, giving product **69** in 72% yield. However, the crucial scaffold removal using a TFA/Et$_3$SiH cocktail failed to give a product with the correct mass and only lighter masses were observed. We speculated that also in this case no interlocked product had formed. This is likely the reason for the formation of light-weight products, because the rest of the molecule is acid stable. Even if the acid-sensitive oxime would have hydrolyzed under these condition, the corresponding product should give a mass comparable with **69**.
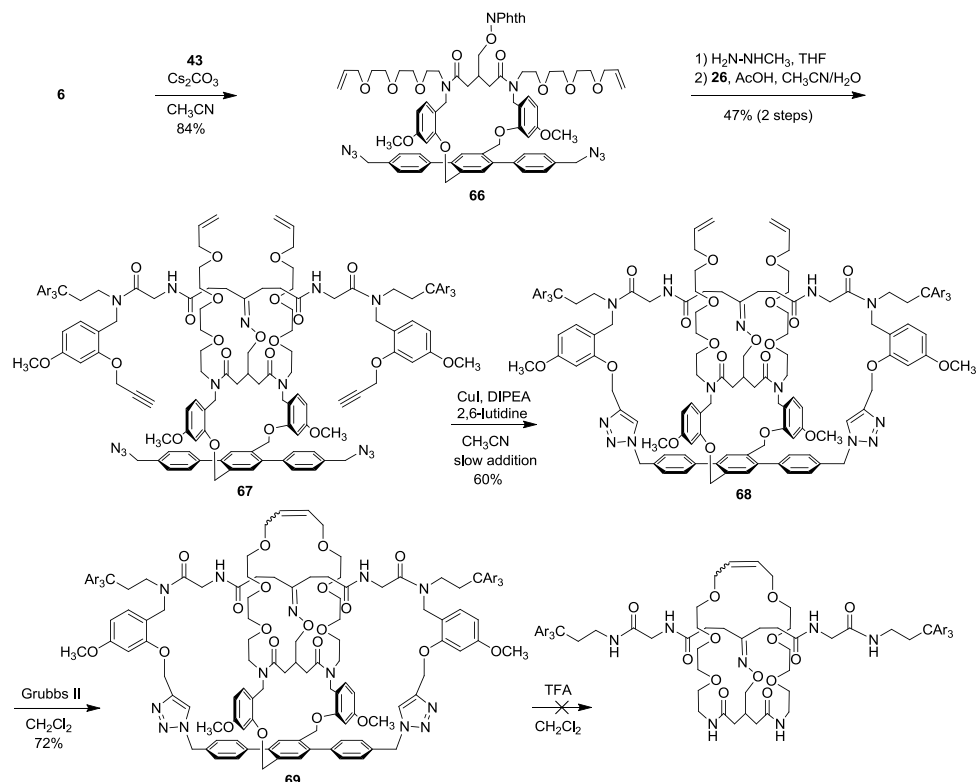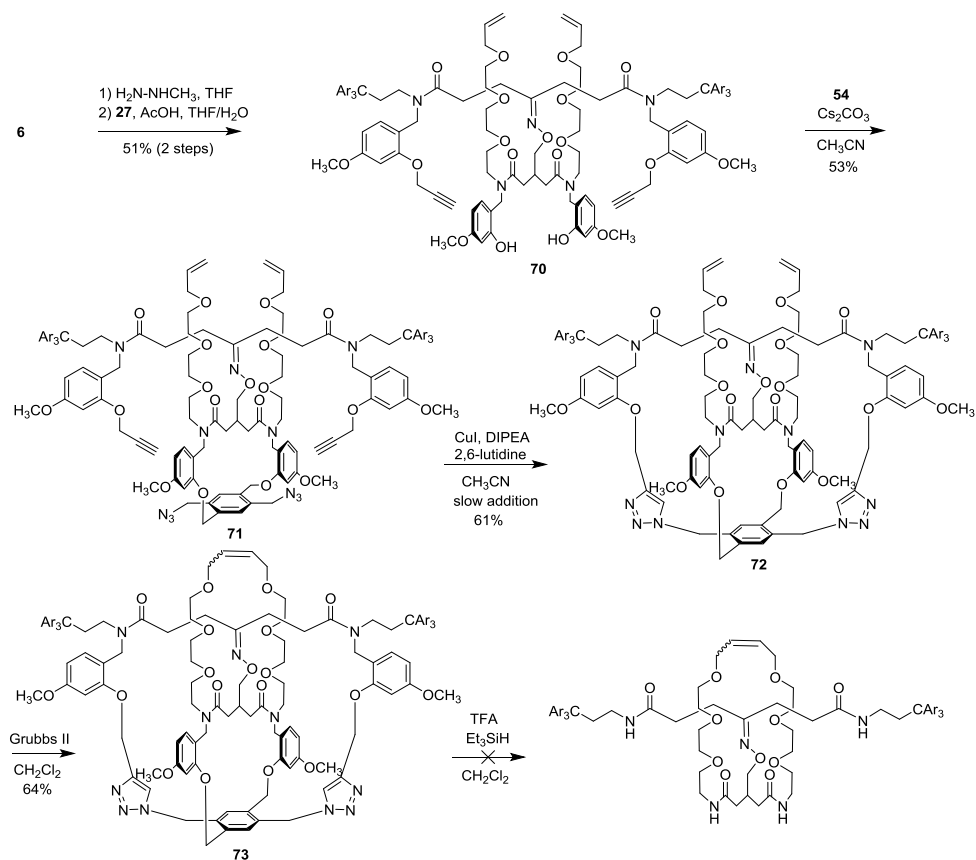

Scheme 22: Macrocyclizations with triaryl scaffold **43**

In a final effort to reduce the ring size of all macrocycles involved during assembly, it was decided to use the smallest possible truncated thread fragment **27** and small scaffold **54**. Ring fragment **6** was first coupled with truncated thread fragment **27** under the optimized oxime ligation conditions, giving oxime **70** in a moderate 51% yield (see scheme 23). Subsequent Williamson etherification with scaffold **54** gave a somewhat lower yield, producing macrocycle **71** in 53% yield. Subsequent

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intramolecular CuAAC reaction *via* slow addition to the CuI solution gave product **72** in 61% yield. The final RCM macrocyclization went uneventful, giving **73** in 72% yield as an undetermined E/Z mixture. Subsequent cleavage of the benzylic amide groups with the TFA/Et$_3$SiH cocktail, did, yet again, fail to give the desired [2]rotaxane product. Analysis of the mass spectrum showed that a range of products formed, with both higher and lower masses than the desired mass of 1522 Da. Despite extensive efforts to identify possible (side-)products, no positive identifications could be made. At this point it was decided that the designed strategy would not work as intended, either due to the formation of non-interlocked products or incompatibilities of functional groups during the penultimate acidolysis step. Therefore, no more efforts were tried and the approach with an oxime as temporary covalent bond had to be abandoned.

Scheme 23: Macrocyclizations with small scaffold **54**
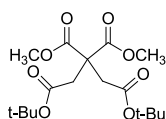
Conclusions

In this chapter a covalent template assisted strategy towards [2]rotaxanes was envisioned, synthesized and tested. Unfortunately, the envisioned route failed to give rotaxane products. Either the formation of non-interlocked products or incompatibility of the acid labile oxime bond prevented a successful approach. Nevertheless, many of the individual macrocyclizations worked well, forming products in moderate to good yields.

Experimental section

<u>General methods and materials</u>

Unless stated otherwise, reactions were performed without special precautions like drying or N_2/Argon atmosphere. Dried CH_2Cl_2 and CH_3CN were obtained by distilling these solvents with CaH_2 as drying agent. Dried THF and Et_2O were obtained by distillation with sodium. All dried solvents were stored under N_2 atmosphere. Dry DMF on 4Å molecular sieves was obtained from Sigma-Aldrich and stored under N_2 atmosphere. Reagents were purchased with the highest purity (usually >98%) from Sigma Aldrich and Fluorochem and used as received. Grubbs 2nd generation catalyst was purchased from AK Scientific. Reactions were monitored with thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254). SilaFlash® P60 (particle size 40-63 μm) was used for silica column chromatography. NMR spectra were recorded on Bruker DRX-500, 400 and 300 MHz instruments and calibrated on residual undeuterated solvent signals as internal standard. The ^{1}H-NMR multiplicities were abbreviated as followed: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet. High resolution mass spectra (HRMS) were recorded on a Mass spectra were collected on an AccuTOF GC v 4g, JMS-T100GCV Mass spectrometer (JEOL, Japan). FD/FI probe equipped with FD Emitter, Carbotec or Linden (Germany), FD 10 μm. Current rate 51.2 mA/min over 1.2 min machine using coldspray or electrospray as ionization method. Depending on the molecule, either the $(M)^+$ or $(M+H)^+$ were observed; sometimes the $(M+Na)^+$ signal was also observed. Melting points were recorded on a Wagner & Munz Polytherm A melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Alpha FTIR machine.

Compound **1**

2.29 mL dimethyl malonate (20.0 mmol) was dissolved in 80 mL dry THF under N_2 atmosphere and cooled to 0 °C. After cooling, 1.68 NaH (60% w/w, 42 mmol, 2.1 equiv) was added portionwise and the mixture was stirred for 15 min. Next, 6.21 mL *t*-butyl-bromoacetate (42.0 mmol, 2.1 equiv) was added and the mixture was stirred at 0 °C for 1h and room temperature for 4h. The volatiles were removed in *vacuo* and the residue was portioned between 50 mL Et_2O and 50 mL saturated NH_4Cl. The water layer was extracted with 2 x 10 mL Et_2O and the combined organic layers were washed with 50 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/EtOAc 15:1 → 10:1) to give **1** (7.20 g, 19.98 mmol, quant) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 6H), 3.03 (s, 4H), 1.42 (s, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$): 169.92, 169.52, 81.45, 53.56, 53.02, 39.09, 28.03; IR (cm^{-1}): 2979, 1727, 1367, 1146

Compound **2**
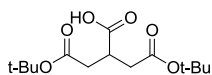
2.61 g **1** (7.23 mmol) and 667 mg LiOH·H_2O (15.90 mmol, 2.2 equiv) were dissolved in 80 mL THF/H_2O/CH_3OH 7:7:2 and the mixture was stirred overnight at 100 °C. The volatiles were removed in *vacuo* and 40 mL Et_2O was added. The water layer was carefully acidified with 20 mL 1M $KHSO_4$ and the pH was checked with pH paper (pH = 1-2). The water layer was extracted with 3 x 40 mL Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. The residue was dissolved in 50 mL $PhCH_3$, refluxed for 2h and concentrated in *vacuo* to give **2** (2.02 g, 6.99 mmol, 97%) as a thick colorless oil, which was sufficiently pure to be used without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.40-9.35 (bs, 1H), 3.20 (quint, 1H), 2.67 (d, 1H), 2.63 (d, 1H), 2.54 (d, 1H), 2.50 (d, 1H), 1.44 (s, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 179.77, 170.65, 81.41, 37.74, 36.43, 28.09; IR (cm^{-1}): 2922, 2869, 1731, 1601, 1467, 1442, 1106

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Compound **3**
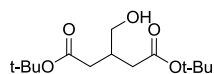
3.44 g **2** (11.91 mmol) was dissolved in 100 mL dry THF under N_2 atmosphere and cooled to 0 ^{o}C. After cooling, 2.24 mL $BH_3 \cdot SMe_2$ (23.82 mmol, 2.0 equiv) was added dropwise and the mixture was stirred for 1 hour at 0 ^{o}C and overnight at room temperature. The mixture was quenched with 10 mL H_2O, stirred for 30 min and concentrated in *vacuo*. The residue was partitioned between 40 mL Et_2O and 40 mL H_2O. The water layer was extracted with 2 x 20 mL Et_2O and the combined organic layers were washed with 40 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/EtOAc 5:1 → 1:1) to give **3** (2.69 g, 9.80 mmol, 82%) as a colorless oil. <u>Note:</u> the product will slowly lactonize upon storage, so it is advisable to use this compound directly in subsequent steps, or store in a freezer. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 3.64 (t, 2H), 2.60 (bs, 1H), 2.42-2.34 (m, 5H), 1.47 (s, 18H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 172.27, 80.89, 65.31, 37.42, 35.00, 28.16; IR (cm^{-1}): 3469, 2978, 2935, 1724, 1367, 1140

Compound **4**
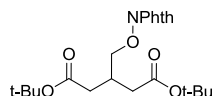
1.95 g **3** (7.09 mmol), 1.73 g *N*-hydroxyphtalimide (10.63 mmol, 1.50 equiv) and 2.05 g PPh$_3$ (7.80 mmol, 1.10 equiv) were dissolved in 50 mL dry THF under N_2 atmosphere and cooled to 0 ^{o}C. Next, 1.52 mL DIAD (7.80 mmol, 1.1 equiv) was slowly added dropwise over 5 minutes and the reaction mixture was stirred at 0 ^{o}C for 30 min and overnight at room temperature. The mixture was concentrated in *vacuo*, dry-loaded on silica and purified by column chromatography (PE/EtOAc 6:1 → 5:1) to give **4** (2.62 g, 6.24 mmol, 88%) as a thick colorless oil. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.84 (m, 2H), 7.75 (m, 2H), 4.26 (d, 2H), 2.69-2.47 (m, 5H), 1.48 (s, 18H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 171.26, 163.39, 134.54, 128.98, 123.56, 80.77, 79.76, 36.18, 31.76, 28.16; IR (cm^{-1}): 2978, 1791, 1727, 1392, 1144

Compound **5**
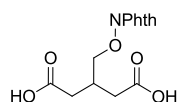
2.62 g **4** (6.24 mmol) was dissolved in 9 mL TFA and 1 mL CH_2Cl_2. The mixture was stirred at room temperature for 2h and concentrated in *vacuo*. The residue was co-evaporated with 3 x 10 mL CH_2Cl_2 to give **5** (1.92 g, 6.24 mmol, quant) as a white powder, which was used without further purification. ^{1}H-NMR (400 MHz, DMSO-*d6*) δ 12.50-11.85 (bs, 2H), 7.86 (s, 4H), 4.15 (d, 2H), 2.60-2.39 (m, 5H); ^{13}C (100 MHz, DMSO-*d6*) δ 173.15, 163.23, 134.85, 128.61, 123.32, 79.27, 34.39, 30.80

Compound **6**
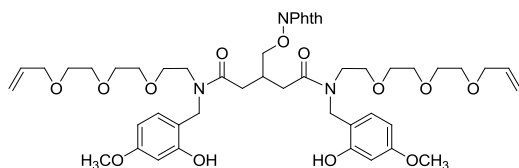
2.04 g **5** (6.63 mmol, 1.0 equiv) and 2.78 mL DIPEA (15.91 mmol, 2.4 equiv) were dissolved in 65 mL dry CH_2Cl_2 under N_2 atmosphere and cooled to 0 ^{o}C. Next, 7.21 g PYBOP (13.92 mmol, 2.1 equiv) was added portionwise and the mixture was stirred for 10 min, after which 4.48 g **2.34** (14.58 mmol, 2.2 equiv) in 10 mL dry CH_2Cl_2 was added. The reaction was stirred at 0 ^{o}C for 1h and overnight at room temperature. The mixture was diluted with 60 mL saturated NH_4Cl and the water layer was extracted with 3 x 20 mL CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/EtOAc 1:4 → 1:5) to give **6** (4.79 g, 5.20 mmol, 78%) as a thick, slightly yellow oil. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 9.62 (s, 2H), 7.75 (m, 4H), 7.02 (d, 2H), 6.39 (s, 2H), 6.34 (d, 2H), 5.88 (m, 2H), 5.25 (d, 2H), 5.15 (d, 2H), 4.45 (dd, 4H), 4.30 (d, 2H), 4.00 (d, 4H), 3.76-3.54 (m, 30H), 2.85-2.69 (m, 5H); ^{13}C-

NMR (100 MHz, CDCl$_3$) δ 174.15, 163.41, 161.35, 157.42, 134.72, 134.53, 132.30, 128.89, 123.58, 117.31, 115.01, 105.52, 102.47, 80.67, 72.29, 70.79, 70.67, 70.64, 69.40, 69.31, 55.28, 47.20, 46.70, 33.33, 32.18; IR (cm^{-1}): 2979, 2934, 1725, 1709, 1367, 1143


Compound 7
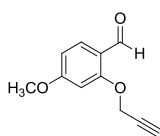
3.80 g 4-methoxy-2-hydroxybenzaldehyde (25 mmol) and 4.15 g K$_2$CO$_3$ (30 mmol, 1.20 equiv) were dissolved in 50 mL dry CH$_3$CN and 3.06 mL propargylbromide (80% w/w in PhCH$_3$, 27.5 mmol, 1.1 eq) was added. The mixture was stirred overnight at 50 °C and was subsequently concentrated in *vacuo* and the residue was partitioned between 75 mL EtOAc and 50 mL H$_2$O. The water layer was extracted with 2 x 20 mL EtOAc and the combined organic layers were washed with 50 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The brown crude product was purified by column chromatography (CH$_2$Cl$_2$) to give 7 (4.45 g, 23.40 mmol, 94%) as an off-white solid. Melting-point: 79-82 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 10.29 (s, 1H), 7.81 (d, 1H), 6.58 (m, 2H), 4.80 (d, 2H), 3.87 (s, 3H), 2.60 (t, 1H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 188.12, 165.96, 161.53, 130.64, 119.49, 106.89, 99.43, 77.63, 76.20, 56.40, 55.76; IR (cm^{-1}): 3228, 2960, 2903, 2835, 2124, 1666, 1600, 1106


Compound 8
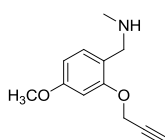
750 mg 7 (3.94 mmol) and 3.94 mL 2M methylamine in CH$_3$OH (7.88 mmol, 2.0 equiv) were dissolved in 10 mL absolute CH$_3$OH and stirred overnight at room temperature. The mixture was cooled to 0 °C and 448 mg NaBH$_4$ (11.82 mmol, 3.0 equiv) was added portionwise. The reaction was stirred at 0 °C for 90 minutes and room temperature for 90 minutes. The mixture was quenched with 20 mL 1M NaOH and extracted with 3 x 25 mL Et$_2$O. The combined organic layers were washed with 20 mL 1M NaOH, dried over MgSO$_4$ and concentrated in *vacuo* to give 8 (774 mg, 3.77 mmol, 96%) as a yellow oil. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.15 (d, 1H), 6.58 (s, 1H), 6.48 (d, 1H), 4.70 (d, 2H), 3.80 (s, 3H), 3.69 (s, 2H), 2.52 (t, 1H), 2.40 (s, 3H), 2.04 (bs, 1H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 159.84, 156.56, 130.83, 121.23, 104.88, 99.99, 78.55, 75.69, 55.96, 55.40, 50.59, 35.67; IR (cm^{-1}): 3285, 2933, 2837, 2792, 1611, 1587, 1503, 1156, 1025


Compound 9
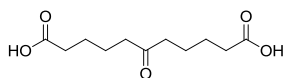
1.55 mL monomethyl-adipoyl chloride (10.0 mmol) was dissolved in 10 mL dry PhCH$_3$ under N$_2$ atmosphere. The solution was cooled to 0 °C and 1.39 mL NEt$_3$ (10.0 mmol, 1.0 equiv) was added dropwise. The thick slurry was stirred for 15 minutes at 0 °C and 15 minutes at 40 °C. The mixture was diluted with 40 mL THF and filtered to remove the salts. The filtrate was concentrated in *vacuo* and the residue was treated with 10 mL 2M KOH and refluxed for 4 hours. The water layer was extracted with 3 x 5 mL Et$_2$O and subsequently acidified with 2 mL concentrated HCl. The mixture was cooled in an ice bath for 30 min, than filtered and washed with 2 x 5 mL cold H$_2$O. The crude product was recrystallized from boiling H$_2$O to give 9 (637 mg, 2.77 mmol, 55%) as an off-white solid. Melting point: 108-109 °C; ^{1}H-NMR (400 MHz, DMSO-*d6*) δ 12.03 (bs, 2H), 2.41 (t, 4H), 2.19 (t, 4H), 1.44 (quint, 8H); ^{13}C-NMR (100 MHz, DMSO-*d6*) δ 210.41, 174.55, 41.59, 33.63, 24.18, 22.87; IR (cm^{-1}): 3210, 2933, 1686, 1423, 1403, 1259, 1208

Compound 10
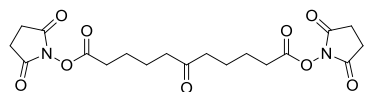
493 mg **9** (2.14 mmol), 1.23 g *N*-hydroxysuccinimide (10.70 mmol, 5.0 equiv) and 1.67 mL pyridine (21.40 mmol, 10.0 equiv) were dissolved in 12 mL dry CH_2Cl_2 under N_2 atmosphere and cooled to 0 °C. After cooling, 1.45 mL TFAA (10.48 mmol, 4.9 equiv) was added dropwise and the mixture was stirred at 0 °C for 1h and overnight at room temperature. The reaction was quenched with 10 mL 1M $KHSO_4$ and the solution was stirred vigorously for 15 min. The water layer was extracted with 10 mL CH_2Cl_2 and the combined organic layers were washed with 10 mL 1M $KHSO_4$, 2 x 10 mL saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated in *vacuo* to give **10** (894 mg, 2.11 mmol, 98%) as a white solid. Melting point: 117 – 119 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.81 (bs, 8H), 2.60 (t, 4H); 2.44 (t, 4H), 1.69 (m, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.91, 169.31, 168.45, 41.88, 30.75, 25.60, 24.04, 22.77; IR (cm^{-1}): 2946, 1814, 1781, 1730, 1367, 1204, 1064

Compound 11
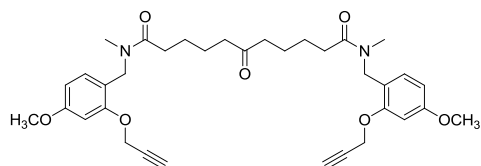
639 mg **10** (1.51 mmol), 680 mg **8** (3.31 mmol, 2.2 equiv), 0.52 mL NEt_3 (3.76 mmol, 2.50 equiv) and 18 mg DMAP (0.151 mmol, 0.10 equiv) were dissolved in 15 mL dry CH_2Cl_2 and stirred overnight at room temperature. The mixture was washed with 10 mL 1M $KHSO_4$ and the water layer was extracted with 10 mL CH_2Cl_2. The combined organic layers were washed with 10 mL $NaHCO_3$, dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (CH_2Cl_2/CH_3OH 97:3 → 96:4) to give **11** (743 mg, 1.23 mmol, 82%) as a slightly yellow oil. ; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.11+6.89 (dd, 2H), 6.53-6.43 (m, 4H), 4.64 (t, 4H), 4.49+4.39 (ds, 4H), 3.75+3.73 (ds, 6H), 2.88+2.84 (ds, 6H), 2.57+2.51 (dt, 2H), 2.41-2.28 (m, 8H), 1.59-1.52 (m, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 210.67, 173.09, 172.55, 160.12, 159.77, 156.33, 155.95, 130.63, 128.10, 118.55, 117.37, 105.36, 104.96, 99.84, 99.58, 78.34, 78.04, 76.05, 75.67, 55.86, 55.33, 55.26, 48.29, 44.89, 42.49, 35.09, 33.45, 33.22, 32.55, 24.77, 24.53, 23.45; IR (cm^{-1}): 2936, 1708, 1613, 1506, 1161

Compound 12
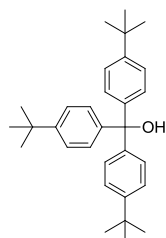
5.20 mL 4-bromo-tertbutylbenzene (30 mmol, 3.0 equiv) was dissolved in 60 mL dry THF under N_2 atmosphere and cooled to -78 °C. After cooling, 18.75 mL n-BuLi (1.6 M in hexane, 30 mmol, 3.0 equiv) was added slowly over 15 minutes and the solution was stirred for 45 minutes, after which 0.84 mL dimethyl carbonate (10 mmol) was added dropwise. The dry-ice bath was removed and the reaction was stirred overnight at room temperature. The mixture was concentrated in *vacuo* and the residue was partitioned between 120 mL Et_2O and 60 mL 1M HCl. The water layer was extracted with 30 mL Et_2O and the combined organic layers were washed with 60 mL saturated $NaHCO_3$, 60 mL H_2O, 60 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was triturated with 2 x 20 mL cold PE to give **12** (3.62 g, 8.44 mmol, 84%) as a white powder. Melting point: 220-221 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 (d, 6H), 7.21 (d, 6H), 2.74 (s, 1H), 1.33 (s, 27H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.92, 144.32, 127.69, 124.82, 81.65, 34.58, 31.51; IR (cm^{-1}): 3570, 2956, 2865, 1508, 1400, 1361, 1267

Compound **13**
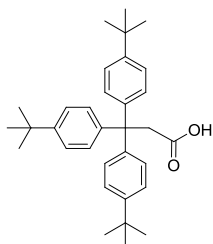
6.24 g **12** (14.57 mmol) and 15.15 g malonic acid (145.60 mmol, 10 equiv) were heated to 180 ^{o}C in a 250 mL flask. Around 120 ^{o}C the mixture became a viscous yellow liquid and around 170 ^{o}C the mixture started to evolve CO_2 gas with bubbling. The mixture was stirred at 180 ^{o}C until it dried up, after which it was cooled to room temperature. The slightly yellow residue was dissolved in 150 mL Et_2O and washed with 2 x 50 mL H_2O, 50 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The slightly yellow powder was triturated with 2 x 15 mL cold CH_3OH, which removed most of the yellow color. The product was dried in *vacuo* to give **13** (6.22 g, 13.20 mmol, 91%) as a faintly yellow fine powder. Melting point: 249 – 252 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.80 (bs, 1H), 7.29 (d, 6H), 7.14 (d, 6H), 3.72 (s, 2H), 1.35 (s, 27H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.10, 148.76, 143.67, 128.76, 124.69, 54.30, 46.20, 34.41, 31.49; IR (cm^{-1}): 2960, 2867, 1698, 1508, 1398

Compound **14**
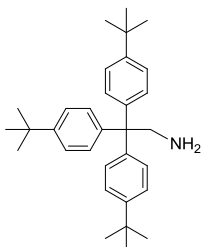
2.49 g **13** (5.82 mmol), 1.28 mL DPPA (5.93 mmol, 1.02 equiv) and 0.808 mL Et_3N (5.82 mmol, 1.00 equiv) were dissolved in 60 mL $PhCH_3$. The mixture was stirred at 120 ^{o}C for 5h, cooled to room temperature and concentrated in *vacuo*. The crude isocyanate was dissolved in a mixture of 50 mL THF and 30 mL 1M NaOH. The reaction was stirred for 1h, and the THF was removed in *vacuo*. The water layer was extracted with 3 x 40 mL Et_2O and the combined organic layers were washed with 40 mL 1M NaOH and 40 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/CH_3OH 100:0 → 97:3) to give **14** (1.79 g, 4.47 mmol, 77%) as an off-white solid. Melting point: 246 – 255 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 (d, 6H), 7.21 (d, 6H), 3.81 (s, 2H), 1.35 (s, 27H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.64, 143.19, 128.98, 124.91, 57.73, 51.00, 34.40, 31.48; IR (cm^{-1}): 2958, 2866, 1506, 1362, 1268

Compound **15**
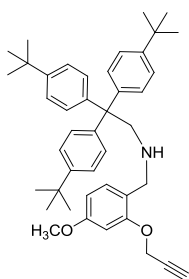
380 mg **7** (2.0 mmol, 1.0 eq), 879 mg **14** (2.2 mmol, 1.1 equiv) and 0.500 g $MgSO_4$ (2.2 mmol, 1.1 eq) and 5 drops of AcOH were dissolved in 20 mL THF/CH_3OH 1:1 and stirred overnight at room temperature. The mixture was cooled to 0 ^{o}C and 303 mg $NaBH_4$ (8.0 mmol, 4.0 equiv) was added portionwise. The ice bath was removed and the reaction was stirred at room temperature for 1h, after which it was concentrated in *vacuo*. The residue was partitioned between 40 mL Et_2O and 40 mL 1M NaOH. The water layer was extracted with 20 mL Et_2O and the combined organic layers were washed with 30 mL 1M NaOH, 30 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/EtOAc 9:1) to give **15** (925 mg, 1.61 mmol, 81%) as a colorless powder. Melting-point: 61 – 68 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (d, 6H), 7.16 (d, 6H), 7.08 (d, 1H), 6.57 (s, 1H), 6.47 (d, 1H), 4.53 (d, 2H), 3.81 (s, 5H), 3.64 (s, 2H), 2.50 (t, 1H), 1.32 (s, 27H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.71, 156.74, 148.48, 144.08, 130.66, 129.14, 124.71, 115.45, 104.86, 99.95, 78.74, 75.78, 58.54, 55.95, 55.81, 55.48, 49.21, 34.42, 31.53; IR (cm^{-1}): 3309, 2959, 2358, 1612, 1505, 1159;

84

Compound **16**
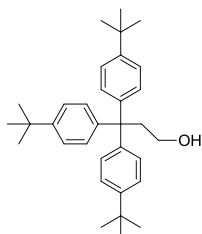
6.20 g **13** (13.17 mmol) was dissolved in 100 mL dry THF under N_2 atmosphere and cooled to 0 ^{o}C. After cooling, 3.12 mL $BH_3 \cdot SMe_2$ (32.93 mmol, 2.5 equiv) was added dropwise and the ice bath was removed. The reaction was stirred overnight at room temperature and was quenched carefully with 10 mL H_2O and stirred for 15 minutes. The mixture was concentrated in *vacuo* and the residue was partitioned between 150 mL Et_2O and 75 mL H_2O. The water layer was extracted with 30 mL Et_2O and the combined organic layers were washed with 75 mL brine and dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (CH_2Cl_2) to give **16** (5.07 g, 11.11 mmol, 84%) as a colorless foam. Melting trajectory: 98 – 110 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 (d, 6H), 7.24 (d, 6H), 3.54 (t, 2H), 2.93 (t, 2H), 1.35 (s, 27H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.55, 144.32, 128.65, 124.80, 60.84, 54.08, 43.13, 34.41, 31.51; IR (cm^{-1}): 3340, 2957, 2901, 2866, 1508, 1362, 1269

Compound **17**
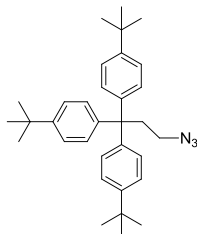
2.32 g **16** (5.08 mmol) was dissolved in 50 mL dry THF under N_2 atmosphere. The solution was cooled to 0 ^{o}C and 1.46 g PPh_3 (5.58 mmol, 1.1 equiv) and 1.10 mL DIAD (5.58 mmol, 1.1 equiv) were added and the mixture was stirred for 5 minutes. Next, 1.20 mL DPPA (5.58 mmol, 1.1 equiv) was added dropwise, the ice bath was removed and the reaction was stirred overnight at room temperature. The mixture was concentrated in *vacuo* and the residue was dry-loaded on silica and purified by column chromatography (PE/CH_2Cl_2 7:1) to give **17** (1.94 g, 4.03 mmol, 79%) as a colorless foam. Melting point: 166-169 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29 (d, 6H), 7.18 (d, 6H), 3.08 (t, 2H), 2.88 (t, 2H), 1.34 (s, 27H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.82, 143.63, 128.57, 124.95, 54.04, 49.06, 39.21, 34.46, 31.50; IR (cm^{-1}): 2960, 2902, 2867, 2092, 1508, 1363, 1268

Compound **21**
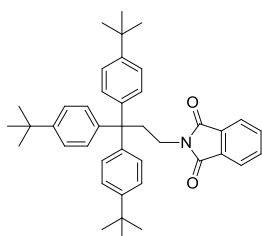
2.73 g **16** (5.98 mmol), 1.32 g phthalimide (8.97 mmol, 1.5 equiv) and 1.80 g PPh_3 (6.88 mmol, 1.15 equiv) were dissolved in 60 mL dry THF under N_2 atmosphere and cooled to 0 ^{o}C. After cooling, 1.30 mL DIAD (6.58 mmol, 1.10 eq) was added dropwise and the mixture was stirred at 0 ^{o}C for 2 h and overnight at room temperature. The mixture was concentrated in *vacuo*, dry-loaded on silica and purified by column chromatography (PE/EtOAc 8:1) to give **21** (3.24 g, 5.53 mmol, 92%) as a white powder. Melting-point: 256 – 264 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.72 (m, 2H), 7.33 (d, 6H), 7.28 (d, 6H), 3.47 (t, 2H), 2.93 (t, 2H), 1.32 (s, 27H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.38, 148.60, 143.85, 133.94, 132.35, 128.78, 124.83, 123.15, 54.18, 38.88, 36.24, 34.40, 31.48; IR (cm^{-1}): 2961, 2902, 2866, 1711, 1397, 1360

Compound **18**
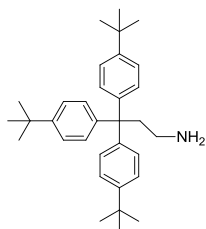
2.32 g **21** (3.97 mmol) was dissolved in a mixture of 20 mL CH_2Cl_2 and 20 mL absolute EtOH. Next, 1.93 mL hydrazine hydrate (39.70 mmol, 10 equiv) was added and the reaction was stirred at 50 °C for 3h. The mixture was cooled to room temperature and filtered (cake washed with 10 mL CH_2Cl_2) and the filtrate was concentrated in *vacuo*. The crude product was dry-loaded on silica and purified by column chromatography (CH_2Cl_2/CH_3OH 94:6 → 90:10) to give **18** (1.58 g, 3.46 mmol, 87%) as a colorless solid. Melting-point: 151 - 158 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.28 (d, 6H), 7.19 (d, 6H), 2.78 (t, 2H), 2.55 (t, 2H), 1.31 (s, 27H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.37, 144.53, 128.72, 124.66, 54.56, 44.48, 39.33, 34.38, 31.49; IR (cm^{-1}): 2958, 2901, 2866, 1507, 1362, 1269

Compound **19**
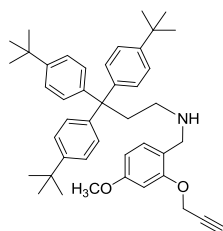
2.29 g **18** (5.02 mmol) and 954 mg **7** (5.02 mmol, 1.0 eq) were dissolved in a mixture of 35 mL dry THF and 15 mL absolute CH_3OH and the mixture was stirred overnight at room temperature. The reaction was cooled to 0 °C and 471 mg $NaBH_4$ (10.36 mmol, 2.0 equiv) was added portionwise and stirred for 30 minutes at 0 °C. The ice bath was removed and the reaction was stirred at room temperature for 1h and was subsequently concentrated in *vacuo*. The residue was partitioned between 50 mL Et_2O and 50 mL 1M NaOH. The water layer was extracted with 20 mL Et_2O and the combined organic layers were washed with 25 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/CH_3OH 98:2 → 97:3) to give **19** (2.12 g, 3.36 mmol, 67%) as a colorless foam. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27 (d, 6H), 7.22 (d, 6H), 7.10 (d, 1H), 6.55 (s, 1H), 6.46 (d, 1H), 4.67 (d, 2H), 3.80 (s, 3H), 3.68 (s, 2H), 2.81 (t, 2H), 2.47 (m, 3H), 1.31 (s, 27H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.86, 156.23, 148.25, 144.54, 130.64, 128.76, 124.59, 121.14, 105.08, 100.02, 78.60, 75.78, 56.08, 55.39, 54.54, 48.36, 46.03, 40.56, 34.34, 31.48; IR (cm^{-1}): 3308, 2962, 2903, 2867, 1613, 1506

Compound **22**
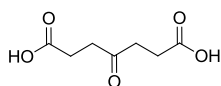
5.36 mL diethyl-4-oxopimelate (25 mmol) and 2.20 g NaOH (55 mmol, 2.2 equiv) were dissolved in 25 mL H_2O and stirred overnight at room temperature. The water layer was extracted with 10 mL PE, cooled in an ice-bath and acidified with 37% HCl to pH = 1-2. The mixture was kept in the ice bath for 1h, after which it was filtered. The solid was washed with 5 mL cold H_2O, dried on air and dried on vacuum to give **22** (3.44 g, 19.73 mmol, 79%) as an off-white powder. Melting-point: 141-142 °C; ^{1}H-NMR (400 MHz, DMSO-*d6*) δ 12.12 (bs, 2H), 2.66 (t, 4H), 2.40 (t, 4H); ^{13}C-NMR (100 MHz, DMSO-*d6*) δ 173.77, 36.64, 27.68; IR (cm^{-1}): 2966, 2910, 1681, 1406, 1306, 1219

Compound **23**
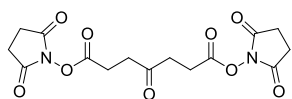
174 mg **22** (1.00 mmol), 587 mg *N*-hydroxysuccinimide (5.1 mmol, 5.1 equiv) and 0.81 mL pyridine (10 mmol, 10.0 equiv) were dissolved in 6 mL dry CH_2Cl_2 and cooled to 0 °C. After cooling, 0.70 mL TFAA (5.0 mmol, 5.0 equiv) was added dropwise and the mixture was stirred at 0 °C for 1h and at room temperature for 3h. The reaction was quenched with 10 mL 1M $KHSO_4$ and the biphasic system was stirred vigorously for 10 min. The water layer was extracted with 10 mL CH_2Cl_2 and the combined organic layers were washed with 2 x 10 mL saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to give **23** (352 mg, 0.96 mmol, 96%) as an off-white solid. Melting-point: 172-175 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.95 (dd, 8H), 2.85 (s, 8H); IR (cm^{-1}): 1811, 1783, 1725, 1360, 1057

Compound **24**
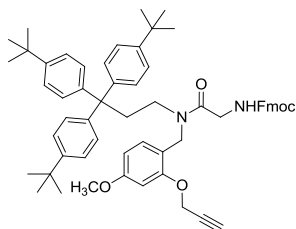
458 mg Fmoc-Gly-OH (1.54 mmol, 1.1 equiv) and 0.61 mL DIPEA (3.38 mmol, 2.2 equiv) were dissolved in 10 mL dry DMF. The solution was cooled to 0 °C and 801 mg PyBOP (1.54 mmol, 1.1 equiv) was added. The mixture was stirred for 10 minutes and then 881 mg **19** (1.40 mmol) in 1 mL dry DMF was added dropwise. The mixture was stirred at 0 °C for 1h and overnight at room temperature. The mixture was diluted with 60 mL Et_2O and washed with 30 mL 1M $KHSO_4$, 30 mL $NaHCO_3$ and 30 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography to give **24** (1.20 g, 1.32 mmol, 94%) as a colorless foam. ^{1}H-NMR complex due to rotamers; IR (cm^{-1}): 3307, 2964, 1718, 1643, 1507

Compound **25**
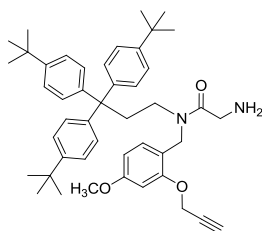
1.24 g (1.37 mmol) **24** was dissolved in 14 mL CH_2Cl_2/Et_2NH 1:1 and stirred overnight at room temperature. The reaction mixture was concentrated in *vacuo* and the residue was purified by column chromatography (EtOAc/CH_3OH 98:2 → 95:5) to give **25** (634 mg, 0.923 mmol, 68%) as a white foam. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.16 (m, 12H), 6.61-6.31 (m, 3H), 4.65 (d, 0.66 H), 4.60 (d, 2H), 4.16 (s, 1.20 H), 3.80+3.76 (ds, 3H), 3.64 (bs, 1H), 3.09+3.06 (dt, 2H), 3.05 (bs, 1H), 2.75 (m, 2H), 2.54+2.47 (dt, 1H), 1.31 (s, 27H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.39, 160.08, 156.51, 156.36, 148.72, 148.21, 144.23, 143.67, 131.31, 129.91, 128.73, 128.51, 124.80, 124.61, 118.58, 116.99, 105.50, 105.01, 99.86, 99.71, 78.48, 78.04, 76.14, 75.95, 56.09, 55.99, 55.40, 55.38, 54.30, 54.17, 45.66, 43.90, 43.41, 43.24, 39.09, 37.37, 34.35, 34.31, 11.43, 31.40; IR (cm^{-1}): 3306, 2960, 1641, 1613, 1507, 1459

Compound **26**
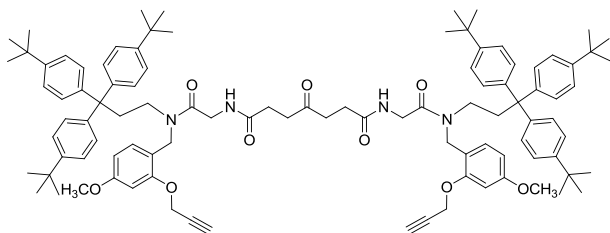
110 mg **23** (0.300 mmol), 433 mg **25** (0.630 mmol, 2.1 equiv), 0.264 mL DIPEA (1.50 mmol, 5 equiv) and 4 mg DMAP (0.030 mmol, 0.1 equiv) were dissolved in 12 mL dry CH_2Cl_2 and stirred overnight at room temperature. The mixture was concentrated in *vacuo* and the residue was partitioned between 30 mL EtOAc and washed with 20 mL 1M HCl, 20 mL NaHCO₃, 20 mL brine, dried over MgSO₄ and concentrated in *vacuo*. The residue was purified by column chromatography (PE/EtOAc 1:6) to give **26** (417 mg, 0.276 mmol, 92%) as a colorless powder. ^{1}H-NMR (400 MHz, CDCl₃) δ 7.29-7.13 (m, 24H), 6.77 (t, 2H), 6.58-6.29 (m, 6H), 4.60 (d, 4.50H), 4.28+4.14 (ds, 6.65H), 3.81+3.76 (ds, 6H), 3.05+3.01 (dt, 4H), 2.88-2.69 (m, 8H), 2.62-2.45 (m, 6H), 1.29, (s, 54H); ^{13}C-NMR (100 MHz, CDCl₃) δ 208.49, 173.26, 171.54, 168.26, 160.66, 160.26, 156.61, 148.80, 148.36, 147.12, 144.43, 144.19, 143.64, 131.31, 130.39, 128.76, 128.55, 124.98, 124.70, 118.05, 116.36, 113.58, 105.49, 105.11, 99.94, 99.78, 77.86, 76.67, 76.06, 56.08, 55.45, 54.33, 54.28, 46.15, 43.60, 41.88, 41.79, 40.98, 37.71, 37.55, 37.23, 34.42, 34.39, 31.50, 31.45, 30.09, 29.75


Compound **27**
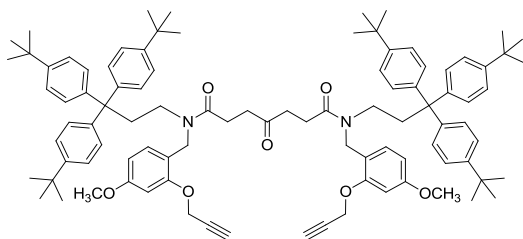
520 mg **23** (1.41 mmol), 1.96 g **19** (3.11 mmol, 2.2 equiv), 0.59 mL DIPEA (3.39 mmol, 2.4 equiv) and 17 mg DMAP (0.141 mmol, 0.1 equiv) were dissolved in 30 mL dry CH_2Cl_2 and stirred overnight at room temperature. The mixture was washed with 15 mL 1M HCl, 15 mL saturated NaHCO₃, dried over MgSO₄ and concentrated in *vacuo*. The crude product was purified by column chromatography (CH₂Cl₂/CH₃OH 99:1) to give **27** (1.29 g, 0.92 mmol, 65%) as a faint yellow foam. ^{1}H-NMR (300 MHz, CDCl₃) δ 7.28-7.18 (m, 26H), 6.64-6.35 (m, 4H), 4.63 + 4.29 (bt + d, 8H), 3.81 + 3.77 (ds, 6H), 3.07-2.48 (m, 16H), 2.22 + 2.14 (dt, 2H), 1.31 (s, 54H); ^{13}C-NMR (75 MHz, CDCl₃) δ 209.14, 208.77, 172.12, 171.77, 160.20, 159.93, 156.40, 148.59, 148.15, 144.35, 143.82, 130.90, 129.63, 128.79, 128.61, 124.79, 124.61, 118.85, 117.52, 105.55, 104.95, 99.87, 99.73, 78.65, 78.22, 76.40, 75.91, 56.13, 56.03, 55.38, 54.37, 54.28, 53.51, 46.59, 43.63, 37.83, 37.43, 37.22, 34.36, 34.33, 31.46, 27.15

Compound **28**
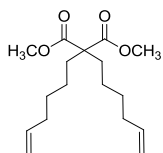
1.26 g NaH (60% w/w, 31.50 mmol, 2.1 equiv) was suspended in 30 mL dry DMF under N₂ atmosphere and cooled to 0 °C. After cooling, 1.71 mL dimethyl malonate (15 mmol) was added dropwise and the mixture was stirred at 0 °C for 10 minutes, after which 4.21 mL 5-hexenyl-1-bromide (31.50 mL, 2.1 equiv) was added dropwise. The ice bath was removed and the mixture was stirred overnight at room temperature. The mixture was concentrated in *vacuo* and the residue was partitioned between 120 mL Et₂O and 60 mL saturated NH₄Cl. The water layer was extracted with 30

mL Et_2O and the combined organic layers were washed with 2 x 50 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude yellow product was purified by column chromatography (PE/EtOAc 100:0 → 30:1) to give **28** (3.59 g, 12.10 mmol, 81%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 2H), 5.01 (d, 2H), 4.95 (d, 2H), 3.72 (s, 6H), 2.06 (q, 4H), 1.89 (m, 4H), 1.41 (quint, 4H), 1.16 (m, 4H)

Compound **29**
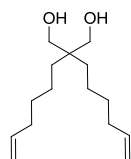
1.00 g $LiAlH_4$ (26.55 mmol, 2.2 equiv) was suspended in 30 mL dry THF under N_2 atmosphere and cooled to 0 °C. Next, 3.58 g **28** (12.07 mmol) was dissolved in 10 mL dry THF and added dropwise to the $LiAlH_4$ suspension. The reaction was stirred at 0 °C for 15 minutes, after which the icebath was removed. The reaction was heated to reflux and stirred for 3h, after which it was cooled to 0 °C and carefully quenched with 1 mL H_2O, followed by addition of 1 mL 15% NaOH and 3 mL H_2O. The suspension was stirred for 5 minutes, and then excess $MgSO_4$ was added and the suspension was filtered over Celite. The filter cake was rinsed with 3 x 10 mL THF and the filtrate was concentrated in *vacuo* to give **29** (2.52 g, 10.49 mmol, 87%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.80 (m, 2H), 5.02 (d, 2H), 4.96 (d, 2H), 3.56 (s, 4H), 2.69 (bs, 2H), 2.08 (q, 4H), 1.41 (quint, 4H), 1.25 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.05, 114.51, 69.37, 41.12, 33.75, 30.62, 29.80, 22.37; IR (cm^{-1}): 3341, 2930, 2859, 1462, 1438, 1031

Compound **30**
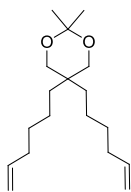
2.52 g **29** (10.49 mmol) and 2.58 mL 2,2-dimethoxypropane (20.98 mmol, 2.0 equiv) were dissolved in 25 mL dry CH_2Cl_2 and 100 mg p-TsOH (0.524 mmol, 0.05 equiv) was added. The reaction was stirred at room temperature for 3h and was subsequently quenched with 20 mL saturated $NaHCO_3$. The water layer was extracted with 2 x 10 mL CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo* to give **30** (2.84 g, 10.13 mmol, 97%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 2H), 5.02 (d, 2H), 4.98 (d, 2H), 3.56 (s, 4H), 2.08 (q, 4H), 1.45-1.20 (m, 18H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.01, 114.52, 98.08, 68.38, 35.04, 33.75, 31.91, 29.77, 23.97, 22.24; IR (cm^{-1}): 2929, 2857, 1454, 1369, 1192

Compound **31**
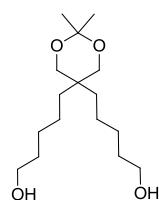
2.84 g **30** (10.13 mmol) was dissolved in a mixture of 30 mL CH_2Cl_2 and 30 mL CH_3OH and the solution was cooled to -78 °C. Ozone was bubbled through the solution until it turned blue, after which O_2 was bubbled through the solution until it was colorless. To the solution was added 1.53 g $NaBH_4$ (40.52 mmol, 4 equiv) and the dry-ice bath was replaced by a normal ice bath. The mixture was stirred at 0 °C for 2h and subsequently concentrated in *vacuo*. The residue was partitioned between 40 mL EtOAc and 40 mL 1M NaOH. The water layer was extracted with 2 x 40 mL EtOAc and the combined organic layers were washed with 20 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/EtOAc 1:2 → 1:3) to give **31** (1.53 g, 5.30 mmol, 52%) as a viscous colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.64 (t, 4H), 3.56 (s, 4H), 1.79 (bs, 2H), 1.58 (quint, 4H), 1.41-1.29 (m, 14H), 1.24 (quint, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 98.14, 68.33, 62.91, 34.99, 32.70, 32.03, 26.66, 23.95, 22.61; IR (cm^{-1}): 3378, 2932, 2860, 1455, 1371, 1204, 1056

Compound **32**
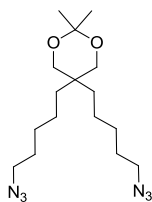
721 mg **31** (2.50 mmol) and 1.39 mL Et$_3$N (10 mmol, 4 equiv) were dissolved in 15 mL dry THF under N$_2$ atmosphere and cooled to 0 °C. After cooling, 0.465 mL MsCl (6.00 mmol, 2.4 equiv) was added dropwise and the reaction was stirred at 0 °C for 15 minutes and at room temperature for 3h. The reaction was quenched with 30 mL H$_2$O and stirred for 15 minutes. The mixture was extracted with 3 x 30 mL CH$_2$Cl$_2$ and the combined organic layers were washed with 30 mL saturated NH$_4$Cl, dried over MgSO$_4$ and concentrated in *vacuo* to give the bis-mesylate (1.11 g, 2.49 mmol, quant) as a slightly yellow oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 4.10 (t, 4H), 3.60 (s, 4H), 2.89 (s, 6H), 1.65 (quint, 4H), 1.34-1.11 (m, 18H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 97.68, 70.02, 67.72, 36.98, 34.50, 31.45, 28.68, 25.93, 23.55, 21.89; IR (cm^{-1}): 2939, 2863, 1349, 1171

1.11 g of the bis-mesylate (2.49 mmol) and 421 mg NaN$_3$ (6.48 mmol, 2.6 equiv) were dissolved in 12½ mL DMF and stirred overnight at 70 °C. The mixture was cooled to room temperature and diluted with 50 mL EtOAc and 50 mL H$_2$O. The water layer was extracted with 2 x 15 mL EtOAc and the combined organic layers were washed with 2 x 15 mL H$_2$O, 15 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The slightly yellow oil was purified by column chromatography (PE/EtOAc 16:1) to give **32** (650 mg, 1.92 mmol, 77%) as a colorless oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 3.53 (s, 4H), 3.25 (t, 4H), 1.59 (quint, 4H), 1.40-1.30 (m, 14H), 1.20 (quint, 4H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 98.02, 68.09, 51.42, 34.85, 31.89, 28.80, 27.55, 23.82, 22.38; IR (cm^{-1}): 2935, 2860, 2088, 1455, 1369, 1256, 1098

Compound **33**
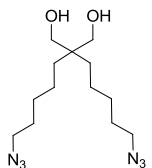
648 mg **32** (1.915 mmol) was dissolved in a mixture of 6 mL THF, 6 mL 1M HCl and 2 mL CH$_3$OH. The solution was stirred at room temperature for 3h, after which 20 mL brine was added. The mixture was extracted with 3 x 20 mL CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo* to give **33** (559 mg, 1.874 mmol, 98%) as a colorless oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 3.51 (s, 4H), 3.27 (t+bs, 6H), 1.60 (quint, 4H), 1.35 (m, 4H), 1.23 (m, 8H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 68.68, 51.44, 40.91, 30.57, 28.78, 27.62, 22.47; IR (cm^{-1}): 3363, 2935, 2862, 2092, 1463, 1258, 1038

Compound **34**
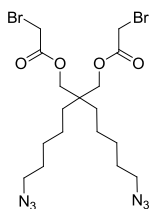
559 mg **33** (1.874 mmol) was dissolved in 20 mL dry CH$_2$Cl$_2$ under N$_2$ atmosphere and cooled to 0 °C. After cooling, 777 mg K$_2$CO$_3$ (5.62 mmol, 3 equiv) was added and to the suspension was added dropwise 0.39 mL bromoacetylbromide (4.50 mmol, 2.4 equiv). The reaction was stirred at 0 °C for 30 minutes and overnight at room temperature. The reaction was quenched with 20 mL H$_2$O and stirred vigorously for 5 minutes. The water layer was extracted with 3 x 10 mL CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/EtOAc 9:1) to give **34** (970 mg, 1.796 mmol, 96%) as a colorless oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 4.02 (s, 4H), 3.83 (s, 4H), 3.26 (t, 4H), 1.60 (quint, 4H), 1.38-1.23 (m, 12H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 167.00, 67.45, 51.30, 39.84, 30.97, 28.68, 27.32, 25.62, 22.21; IR (cm^{-1}): 2939, 2864, 2090, 1734, 1272, 1162, 1108

Compound 35

2.62 g 2,2-dibromomethyl-1,3-propanediol (10 mmol) and 2.62 g NaN$_3$ (40 mmol, 4 equiv) were dissolved in 40 mL DMF and stirred overnight at 120 °C. The mixture was cooled to room temperature and concentrated in *vacuo*. The residue was partitioned between 50 mL EtOAc and 40 mL H$_2$O. The organic layer was washed with 40 mL H$_2$O, 40 mL brine, dried over MgSO$_4$ and concentrated in *vacuo* to give **35** (1.60 g, 8.57 mmol, 86%) as a pale yellow oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 3.62 (s, 4H), 3.42 (s, 4H), 2.66 (bs, 2H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 63.63, 51.75, 44.93; IR (cm^{-1}): 3353, 2936, 2886, 2092, 1357, 1035

Compound 36
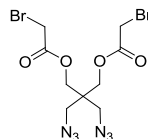
1.43 g **35** (7.66 mmol) and 3.17 g K$_2$CO$_3$ (22.97 mmol, 3 equiv) were dissolved in 75 mL dry CH$_2$Cl$_2$ under N$_2$ atmosphere and cooled to 0 °C. After cooling, 2.00 mL bromoacetylbromide (22.97 mmol, 3 equiv) was added dropwise, after which 47 mg DMAP (0.385 mmol, 0.05 equiv) was added. The ice bath was removed and the mixture was stirred overnight at room temperature. The reaction was quenched with 30 mL H$_2$O and stirred vigorously for 15 min. The water layer was extracted with 2 x 20 mL CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo* to give a brown oil. The crude product was purified by column chromatography (PE/EtOAc 10:1 → 8:1) to give **36** (1.90 g, 4.44 mmol, 58%) as a colorless oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 4.17 (s, 4H), 3.88 (s, 4H), 3.50 (s, 4H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.64, 64.14, 50.98, 43.41, 25.27; IR (cm^{-1}): 2961, 2097, 1736, 1264, 1107

Compound 37
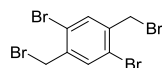
2.64 g 2,5-dimethyl-1,4-dibromobenzene (10 mmol) and 3.64 g NBS (20.50 mmol, 2.05 equiv) were dissolved in 40 mL dry CH$_2$Cl$_2$ under N$_2$ atmosphere. The mixture was degassed with three vacuum/N$_2$ cycles and irradiated with a 500W construction lamp for 2.5h (gentle reflux) and cooled to room temperature. The organic layer was washed with 20 mL H$_2$O and the water layer was extracted with 10 mL CH$_2$Cl$_2$. The combined organic layers were washed with 2 x 20 mL H$_2$O, dried over MgSO$_4$ and concentrated. The crude product was dissolved in ca. 75 mL boiling EtOH, cooled to room temperature and overnight at 0 °C. The precipitate was filtered and the glassware was rinsed with 10 mL cold EtOH. The product **37** (2.16 g, 5.12 mmol, 51%) was obtained as white crystals. Melting-point: 150-153 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.68 (s, 2H); 4.53 (s, 4H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 139.11, 135.48, 123.42, 31.63; IR (cm^{-1}): 1472, 1433, 1358, 1217, 1061

Compound 38
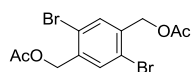
3.18 g **37** (7.53 mmol) and 3.71 g NaOAc (45.20 mmol, 6.0 equiv) were dissolved in 60 mL dry CH$_3$CN and the reaction was stirred overnight at reflux. The mixture was concentrated in *vacuo* and the residue was partitioned between 50 mL CH$_2$Cl$_2$ and 50 mL H$_2$O. The water layer was extracted with 20 mL CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo*. The crude product was crystallized from ca. 200 mL EtOH to give **38** (2.41 g, 6.33 mmol, 84%) as a white powder. Melting-point: 161-162 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.62 (s, 2H), 5.16 (s, 4H), 2.19 (s, 6H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 170.51, 136.97, 133.33, 121.96, 64.87, 20.97; IR (cm^{-1}): 1736, 1365, 1226, 1042

Compound **39**
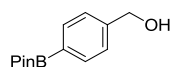
1.85 g 4-bromobenzaldehyde (10 mmol), 3.04 g B_2Pin_2 (12 mmol, 1.2 equiv) and 2.94 g anhydrous KOAc (30 mmol, 3 equiv) were dissolved in 50 mL dry 1,4-dioxane. The mixture was degassed with three argon/vacuum cycles, after which 41 mg Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (0.05 mmol, 0.005 equiv) was added and the reaction was stirred overnight at 85 °C. The mixture was cooled to room temperature and filtered. The filtrate was concentrated in *vacuo* and partitioned between 60 mL Et_2O and 50 mL H_2O. The water layer was extracted with 30 mL Et_2O and the combined organic layers were washed with 60 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*.

The residue was dissolved in 60 mL absolute EtOH and cooled to 0 °C. Then, 454 mg $NaBH_4$ (12 mmol, 1.2 equiv) was added portionwise and the mixture was stirred at 0 °C for 30 minutes and at room temperature for 30 minutes. The reaction was quenched with 30 mL 0.1M HCl, stirred for 15 minutes and then the volatiles were removed in *vacuo*. The residual waterlayer was extracted with 2 x 50 mL Et_2O. The combined organic layers were washed with 50 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/EtOAc 4:1) to give **39** (1.76 g, 7.52 mmol, 75%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.82 (d, 2H), 7.38 (d, 2H), 4.74 (s, 2H), 1.76 (s, 1H), 1.36 (s, 12H)

Compound **40**
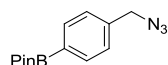
3.10 g **39** (13.25 mmol) and 4.00 mL DPPA (18.55 mmol, 1.4 equiv) were dissolved in 80 mL $PhCH_3$ and cooled to 0 °C. After cooling, 2.77 mL DBU (18.55 mmol, 1.4 equiv) was added dropwise and the reaction was stirred at 0 °C for 15 minutes and overnight at room temperature. The mixture was diluted with 80 mL EtOAc and the combined organic layers were washed with 80 mL 1M HCl and 80 mL NaCl, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was dry-loaded on silica and purified by column chromatography (PE:Et_2O 18:1) to give **40** (2.21 g, 8.55 mmol, 65%) as a colorless oil, which solidified to a waxy solid upon cooling. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (d, 2H), 7.33 (d, 2H), 4.35 (s, 2H), 1.37 (s, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.42, 135.40, 129.06, 127.55, 84.03, 54.88, 24.99; IR (cm^{-1}): 2979, 2932, 2096, 1613, 1358

Compound **41**
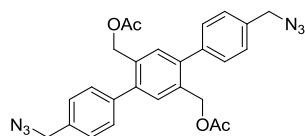
2.14 g **40** (8.27 mmol, 2.8 equiv), 1.12 g **38** (2.95 mmol) and 3.76 g K_3PO_4 (17.72 mmol, 6 equiv) were dissolved in 60 mL 1,4-dioxane/H_2O 2:1. The mixture was degassed with three argon/vacuum cycles, after which 120 mg Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (0.147 mmol, 0.05 equiv) was added. The reaction mixture was stirred overnight at 50 °C, cooled to room temperature and diluted with 120 mL Et_2O and 75 mL H_2O. The water layer was extracted with 2 x 30 mL Et_2O and the combined organic layers were washed with 60 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The brown oil was purified by column chromatography (CH_2Cl_2/CH_3OH 500:0 → 499:1) to give **41** (630 mg, 1.30 mmol, 44%) as a pale yellow waxy solid. Melting-trajectory: 89-99 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 2H), 7.44 (s, 8H), 5.09 (s, 4H), 4.45 (s, 4H), 2.07 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.72, 141.15, 139.78, 135.01, 133.50, 131.44, 129.69, 128.31, 63.99, 54.62, 21.05; IR (cm^{-1}): 3027, 2935, 2093, 1734, 1376, 1217

Compound **42**
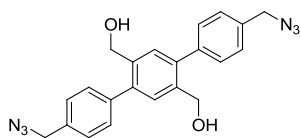
723 mg **41** (1.49 mmol) was dissolved in 20 mL THF/H$_2$O/CH$_3$OH 2:1:1 and 249 mg LiOH · H$_2$O (5.97 mmol. 4.0 equiv) was added and the mixture was stirred overnight at 50 °C. The volatiles were removed in *vacuo* and the precipitate was filtered off. The filtrate was extracted with 20 mL CH$_2$Cl$_2$ and the organic layer was dried over MgSO$_4$ and concentrated and pooled with the precipitated material. The CH$_2$Cl$_2$ was distilled off and the residual powder was dried in *vacuo* to give **42** (581 mg, 1.45 mmol, 97%) as an off-white solid. Melting-point: 143-146 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.50 (s, 8H), 7.44 (s, 2H), 5.21 (bs, 2H), 4.54 (s, 4H), 4.44 (s, 4H); Due to poor solubility no ^{13}C could be obtained. IR (cm^{-1}): 3250, 2917, 2856, 2104, 1032

Compound **43**
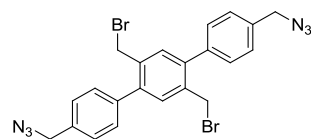
400 mg **42** (1.00 mmol) was suspended in 12 mL dry THF under N$_2$ atmosphere and cooled to 0 °C. After cooling, 0.237 mL PBr$_3$ (2.50 mmol, 2.5 equiv) was added dropwise and the mixture was stirred at 0 °C for 1h and overnight at room temperature. The mixture was carefully quenched with 20 mL saturated NaHCO$_3$, stirred for 15 minutes and then extracted with 3 x 20 mL Et$_2$O. The combined organic layers were washed with 20 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (CH$_2$Cl$_2$) to give **43** (451 mg, 0.857 mmol, 86%) as a colorless solid. Melting-point: 143-147 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.53 (d, 4H), 7.44 (d, 6H), 4.44 (s, 8H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 141.37, 139.38, 135.80, 135.28, 133.14, 129.61, 128.44, 54.69, 21.33; IR (cm^{-1}): 3030, 2925, 2872, 2091, 1489, 1213

Compound **44**
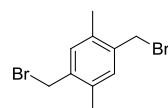
6.17 mL p-xylene (50 mmol) and 3.00 g paraformaldehyde (100 mmol, 2.0 equiv) were dissolved in a mixture of 25 mL AcOH and 35 mL 33% HBr in AcOH. The mixture was stirred overnight at 130 °C and cooled to room temperature. The mixture was poured on 300 mL cold H$_2$O and the precipitate was filtered. The residue was washed with 2 x 30 mL H$_2$O and 20 mL cold CH$_3$OH. The solid was dried on air and vacuum. The crude product was crystallized from ca. 50 mL CCl$_4$ to give **44** (7.86 g, 26.92 mmol, 54%) as a slight pink solid. Note/warning: the product is a lachrymator! Melting point: 155-158 °C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.29 (s, 2H), 4.49 (s, 4H), 2.39 (s, 6H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 136.48, 135.35, 132.53, 31.88, 18.30; IR (cm^{-1}): 1503, 1448, 1397, 1204, 1192

Compound **45**
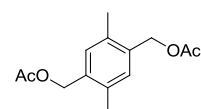
6.41 g **44** (21.96 mmol) and 7.20 g NaOAc (87.84 mmol, 4.0 equiv) were suspended in 20 mL dry DMF stirred overnight at 100 °C. The mixture was concentrated in *vacuo* and the residue was partitioned between 50 mL EtOAc and 50 mL H$_2$O. The water layer was extracted with 10 mL EtOAc and the combined organic layers were washed with 50 mL H$_2$O, 50 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (CH$_2$Cl$_2$) to give **45** (3.91 g, 15.65 mmol, 71%) as a colorless oil, which slowly crystallized. Melting point: 53-55 °C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.18 (s, 2H), 5.10 (s, 4H), 2.34 (s, 6H), 2.12 (s, 6H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 170.97, 134.63, 134.09, 131.49, 64.42, 21.02, 18.41; IR (cm^{-1}): 2975, 2922, 1730, 1380, 1367, 1226

Compound **46**
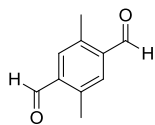
5.06 mL 2-nitropropane (56.43 mmol, 3 eq) was dissolved in 56 mL dry DMF under N_2 atmosphere and cooled to 0 °C. After cooling, 1.65 g NaH (60% w/w, 41.38 mmol, 2.2 eq) was added portionwise and the mixture was stirred for 10 min. Next, 5.49 g **44** (18.81 mmol) was added in one portion and the mixture was stirred at 0 °C for 45 min and room temperature for 90 min. The reaction was quenched with 5 mL H_2O, stirred for 5 min and concentrated in *vacuo*. The residue was partitioned between 100 mL Et_2O and 100 mL H_2O. The water layer was extracted with 50 mL Et_2O and the combined organic layers were washed with 100 mL 1M NaOH, 100 mL H_2O, 100 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by Kugelrohr distillation (0.02 mbar, 140 – 170 °C) and the product was recrystallized from PE/EtOAc to give **46** (2.29 g, 14.15 mmol, 75%) as a colorless solid. Melting point: 90 – 93 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.33 (s, 2H), 7.69 (s, 2H), 2.70 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 102.27, 138.24, 137.01, 134.79, 18.90; IR (cm^{-1}): 2910, 1678, 1383, 1161

Compound **47**
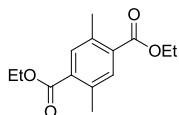
1.41 g **46** (8.67 mmol) was dissolved in 43 mL absolute EtOH and 0.72 mL 37% HCl (8.67 mmol, 1.0 equiv) was added. Next, 157 mg V_2O_5 (0.87 mmol, 0.10 equiv) was added and the mixture was cooled to 0 °C. Next, 7.80 mL 30% H_2O_2 (69.36 mmol, 8.0 equiv) was added dropwise over 1h via a syringe pump. The ice bath was removed and the mixture was stirred overnight at room temperature. The mixture was diluted with 40 mL CH_2Cl_2 and 40 mL H_2O. The water layer was extracted with 2 x 20 mL CH_2Cl_2 and the combined organic layers were washed with 40 mL saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (CH_2Cl_2) to give **47** (1.51 g, 6.04 mmol, 69%) as a colorless solid. Melting point: 79-82 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 2H), 4.39 (q, 4H), 2.59 (s, 6H), 1.43 (t, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.32, 136.98, 133.51, 132.80, 61.17, 21.10, 14.43; IR (cm^{-1}): 2978, 2931, 1713, 1249, 1194, 1096

Compound **48**
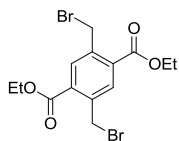
1.51 g **47** (6.04 mmol) and 2.36 g NBS (13.29 mmol, 2.2 equiv) were dissolved in 60 mL dry CH_2Cl_2 and degassed with three vacuum/N_2 cycles. The mixture was irradiated with an 500 W construction lamp for 2.5 hours, after which it was cooled to room temperature. The organic layer was washed with 60 mL H_2O and the water layer was extracted with 30 mL CH_2Cl_2. The combined organic layers were washed with 2 x 30 mL H_2O, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was crystallized from ca. 135 mL absolute EtOH to give **48** (1.62 g, 3.96 mmol, 66%) as colorless crystals. Melting point: 159 – 162 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 2H), 4.95 (s, 4H), 4.56 (q, 4H), 1.47 (t, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.51, 139.37, 134.50, 132.81, 62.11, 30.32, 14.34; IR (cm^{-1}): 2983, 1714, 1263, 1099
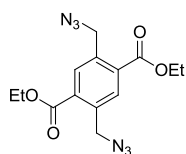
Compound 49

2.31 g **48** (5.67 mmol) and 885 mg NaN$_3$ (13.61 mmol, 2.4 equiv) were dissolved in 11 mL DMF and stirred overnight at room temperature. The mixture was diluted with 50 mL Et$_2$O and 50 mL H$_2$O. The water layer was extracted with 2 x 10 mL Et$_2$O and the combined organic layers were washed with 2 x 25 mL H$_2$O, 25 mL brine, dried over MgSO$_4$ and concentrated in *vacuo* to give **49** (1.84 g, 5.53 mmol, 97%) as a white solid. Melting point: 78 – 81 °C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 8.13 (s, 2H), 4.88 (s, 4H), 4.45 (q, 4H), 1.46 (t, 6H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 165.87, 137.22, 132.25, 132.21, 62.03, 52.56, 14.36; IR (cm^{-1}): 2985, 2941, 2100, 1708, 1298, 1244, 1217, 1099

Compound 50
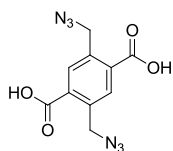
1.84 g **49** (5.53 mmol) was dissolved in 40 mL THF/H$_2$O/CH$_3$OH 2:1:1 and 925 mg LiOH · H$_2$O (22.18 mmol, 4 equiv) was added. The mixture was stirred overnight at room temperature and was subsequently diluted with 20 mL 2M HCl and extracted with 3 x 20 mL EtOAc. The combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo* to give **50** (1.53 g, 5.53 mmol, quant) as a slight yellow solid. Melting point: 230 – 232 °C (dec.); ^{1}H-NMR (300 MHz, CD$_3$OD) δ 8.11 (s, 2H), 4.85 (s, 4H); ^{13}C-NMR (75 MHz, CD$_3$OD) δ 168.77, 138.42, 134.12, 133.49, 53.40; IR (cm^{-1}): 2854, 2103, 1680, 1415, 1253

Compound 52
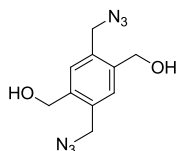
4.76 g 1*H*-benzotriazole (39.96 mmol, 8.4 eq) was dissolved in 70 mL dry THF under N$_2$ atmosphere. To the solution was added 0.726 mL SOCl$_2$ (10.01 mmol, 2.1 equiv) and the mixture was stirred at room temperature for 1h, after which 1.32 g **50** (4.77 mmol) was added and 5 mL dry THF. The reaction was stirred overnight at room temperature and was concentrated in *vacuo*. The solid residue was triturated with 3 x 30 mL H$_2$O, dried on air and vacuum to give the bis-benzotriazole as a slight yellow solid.

The crude bis-benzotriazole ester was suspended in a mixture of 20 mL CHCl$_3$ and 20 mL CH$_3$OH and 439 mg NaBH$_4$ (11.62 mmol, 2.5 equiv) was added portionwise. The mixture was stirred at room temperature until the reaction mixture became clear, after which it was stirred for 30 min. The reaction was concentrated in *vacuo* and partitioned between 40 mL CHCl$_3$ and 40 mL 1M NaOH. The water layer was extracted with 2 x 15 mL CHCl$_3$ and the combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo*. The crude yellow product was purified by column chromatography (CH$_2$Cl$_2$/EtOAc 4:1 → 3:1) to give **52** (730 mg, 2.94 mmol, 63%) as a slightly yellow solid. Melting point: 81 – 84 °C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.44 (s, 2H), 4.77 (d, 2H), 4.51 (s, 4H), 2.12 (bs, 2H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 139.15, 134.24, 130.43, 62.69, 52.19; IR (cm^{-1}): 3325, 2935, 2883, 2084, 1236, 1037

Compound 53
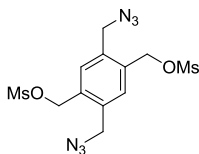
725 mg **52** (2.92 mmol) and 1.01 mL Et₃N (7.30 mmol, 2.5 equiv) were dissolved in 15 mL dry THF and cooled to 0 °C. After cooling, 0.544 mL MsCl (7.01 mmol, 2.4 equiv) was added dropwise over 5 min. The ice bath was removed and the reaction was stirred overnight at room temperature. The reaction was quenched with 2 mL H₂O and stirred for 10 min. The mixture was concentrated in *vacuo* and the residue was partitioned between 20 mL CH₂Cl₂ and 20 mL 1M HCl. The wate rlayer was extracted with 10 mL CH₂Cl₂ and the combined organic layers were washed with 20 mL H₂O, dried over MgSO₄ and concentrated in *vacuo* to give **53** (933 mg, 2.31 mmol, 79%) as a slightly yellow solid. Melting point: 125 – 129 °C (dec.); ¹H-NMR (300 MHz, CDCl₃) δ 7.54 (s, 2H), 5.36 (s, 4H), 4.54 (s, 4H), 3.05 (s, 6H); ¹³C-NMR (75 MHz, CDCl₃) δ 135.62, 133.87, 132.15, 67.45, 51.55, 38.41; IR (cm⁻¹): 3016, 2937, 2100, 1333, 1162, 903

Compound 54
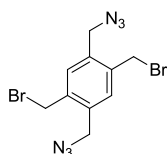
933 mg **53** (2.31 mmol) and 802 mg LiBr (9.24 mmol, 4.0 equiv) were dissolved in 23 mL dry THF and stirred overnight at room temperature. The mixture was concentrated in *vacuo* and the residue was partitioned between 20 mL CH₂Cl₂ and 20 mL H₂O. The water layer was extracted with 2 x 10 mL CH₂Cl₂ and the combined organic layers were dried over MgSO₄ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/CH₂Cl₂ 3:1 → 2:1) to give **54** (721 mg, 1.93 mmol, 83%) as a colorless solid. Melting point: 77 – 79 °C; ¹H-NMR (400 MHz, CDCl₃) δ 7.41 (s, 2H), 4.56 (s, 8H); ¹³C-NMR (100 MHz, CDCl₃) δ 137.07, 135.13, 132.28, 51.40, 29.49; IR (cm⁻¹): 2094, 1446, 1214
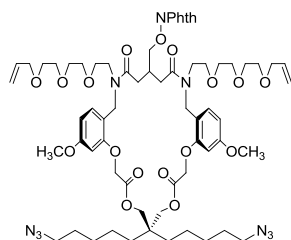
Compound 55

46 mg **6** (0.050 mmol), 32 mg **34** (0.060 mmol, 1.4 equiv), 130 mg Cs₂CO₃ (0.400 mmol, 8 equiv) and 200 mg 4Å MS were dissolved in 20 mL dry CH₃CN under N₂ atmosphere. The mixture was heated to 50 °C for 3h, cooled and filtered. The filtrate was concentrated in *vacuo* and the residue was purified by column chromatography (CH₂Cl₂/CH₃OH 98:2 → 97:3) to give **55** (45 mg, 0.035 mmol, 69%) as a thick colorless oil. ¹H-NMR: complex; LC-MS: calcd for C₆₅H₉₀N₉O₁₉ [(M+H)⁺]: 1300.64; found: 1300.5

Compound 56
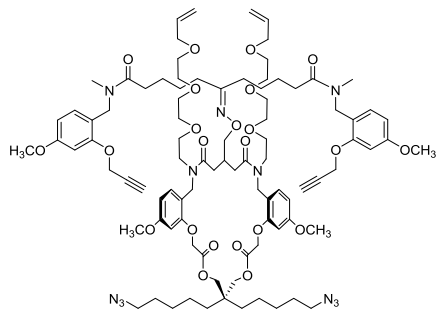
24 mg **55** (0.018 mmol, 1.1 equiv) was dissolved in 2 mL dry THF and cooled to 0 °C. Next, 0.002 mL methylhydrazine (0.036 mmol, 2.0 equiv) was added and the mixture was stirred for 30 minutes at 0 °C. The mixture was concentrated in *vacuo* and 10 mg **11** (0.0166 mmol) and 0.026 mL AcOH (0.45 mmol, 25 equiv) was added. The mixture was stirred overnight at 50 °C, cooled and concentrated in *vacuo*. The residue was purified by column chromatography (CH₂Cl₂/CH₃OH 195:5 → 193:7 → 191:9) to give **56** (22 mg, 0.0125 mmol, 75%) as a colorless film. ¹H-NMR: complex; LC-MS: calcd for C₉₂H₁₃₀N₁₁O₂₃ [(M+H)⁺]: 1756.93; found: 1756.6

Compound **57**
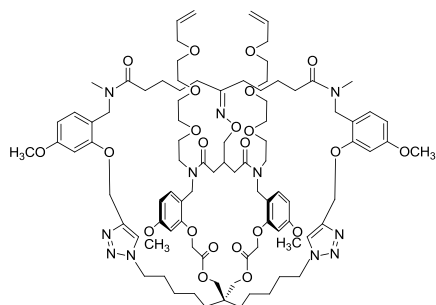
34 mg **56** (0.019 mmol) was dissolved in 2 mL dry CH$_3$CN and added dropwise over 12h to a mixture of 14 mg CuI (0.077 mmol, 4 equiv), 0.033 mL DIPEA (0.193 mmol, 10 equiv) and 0.021 mL 2,6-lutidine (0.193 mmol, 10 equiv) in 20 mL dry CH$_3$CN, 80 ^{o}C under N$_2$ atmosphere. The mixture was stirred for an additional 8 hours and was cooled and concentrated in *vacuo*. The residue was partitioned between 6 mL 1M KHSO$_4$ and 6 mL CH$_2$Cl$_2$. The water layer was extracted with 2 x 6 mL CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 97:3 → 95:5 → 93:7) to give **57** (26 mg, 0.015 mmol, 77%) as a slightly yellow film. ^{1}H-NMR: complex; LC-MS: calcd for C$_{92}$H$_{130}$N$_{11}$O$_{23}$ [(M+H)$^+$]: 1756.93; found: 1756.8; IR (cm^{-1}): 2931, 2862, 1738, 1611, 1588, 1441, 1117

Compound **58**
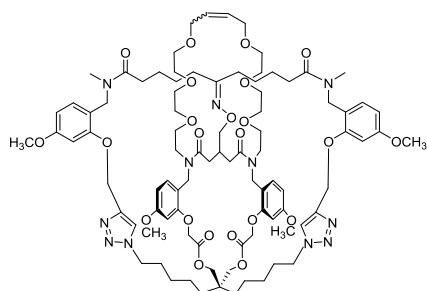
26 mg **57** (0.015 mmol) was dissolved in 15 mL dry CH$_2$Cl$_2$ and the solution was degassed with three vacuum/N$_2$ cycles. After degassing, 1.3 mg Grubbs II (0.0015 mmol, 0.10 equiv) was added and the mixture was stirred overnight at 40 ^{o}C. The mixture was concentrated in *vacuo* and the residue was purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 190:10 → 185:15 → 180:20) to give **58** (15 mg, 0.0087 mmol, 59%) as a brown film. ^{1}H-NMR: complex; LC-MS: calcd for C$_{90}$H$_{126}$N$_{11}$O$_{23}$ [(M+H)$^+$]: 1728.90; found: 1728.8; IR (cm^{-1}): 2932, 2863, 1738, 1612, 1507, 1443, 1119

Compound **61**
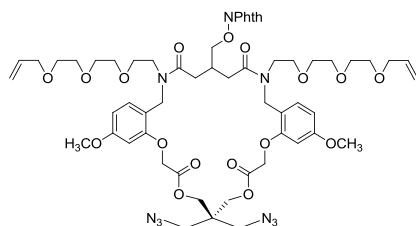
92 mg **6** (0.100 mmol), 60 mg **36** (0.140 mmol, 1.4 equiv), 324 mg Cs$_2$CO$_3$ (1.00 mmol, 10 equiv) and 500 mg 4Å MS were dissolved in 100 mL dry CH$_3$CN and stirred overnight at 60 ^{o}C under N$_2$ atmosphere. The mixture was concentrated in *vacuo*, dissolved in 10 mL CH$_2$Cl$_2$ and filtered through a pad of Celite (flushed with 10 mL CH$_2$Cl$_2$). The filtrate was concentrated in *vacuo* and the residue was purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 195:5 → 194:6) to give **61** (82 mg, 0.069 mmol, 69%) as a slightly yellow oil. ^{1}H-NMR: complex. HRMS (ESI) calcd for C$_{57}$H$_{74}$N$_9$O$_{19}$ [(M+H)$^+$]: 1188.5101, observed: 1188.5045; IR (cm^{-1}): 2868, 2102, 1731, 1636, 1613, 1446, 1120

Compound **62**
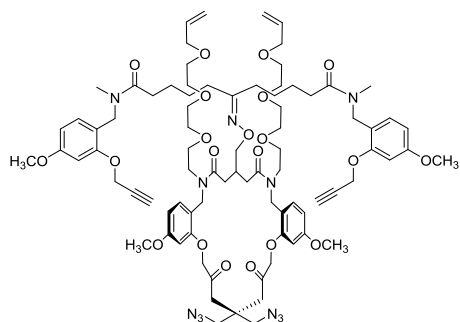
47 mg **61** (0.040 mmol, 1.33 equiv) was dissolved in 2 mL dry THF. The solution was cooled to 0 °C and 0.004 mL methylhydrazine (0.080 mmol, 2.66 equiv) was added. The mixture was stirred at 0 °C for 1h and was subsequently concentrated in *vacuo*. The residue was dissolved in 4 mL CH$_3$CN/H$_2$O 3:1 and 18 mg **11** (0.030 mmol) and 0.048 mL AcOH (0.800 mmol, 26 equiv) were added. The mixture was stirred overnight at 50 °C and was concentrated in *vacuo*. The residue was purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 97:3 → 96:4) to give **62** (38 mg, 0.023 mmol, 77%) as a colorless film. ^{1}H-NMR: complex; HRMS (ESI) calcd for C$_{84}$H$_{113}$N$_{11}$O$_{23}$ [(M)[+]]: 1644.8089, observed: 1644.7993; IR (cm^{-1}); 2934, 2866, 2104, 1745, 1636, 1613, 1589, 1507, 1119

Compound **63**
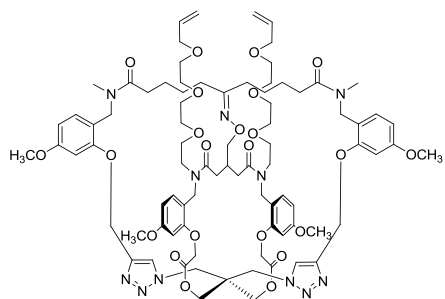
33 mg **62** (0.020 mmol) was dissolved in 2 mL dry CH$_3$CN and added dropwise over 12h to a solution of 15 mg CuI (0.080 mmol, 4 equiv), 0.035 mL DIPEA (0.200 mmol, 10 equiv) and 0.023 mL 2,6-lutidine (0.200 mmol, 10 equiv) in 20 mL dry CH$_3$CN at 80 °C under N$_2$ atmosphere. The solution was concentrated in *vacuo* and the residue was partitioned between 10 mL CH$_2$Cl$_2$ and 10 mL 1M KHSO$_4$. The water layer was extracted with 3 x 5 mL CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 97:3 → 96:4 → 95:5) to give **63** (19 mg, 0.012 mmol, 58%) as a slightly yellow film. ^{1}H-NMR: complex; LCMS calcd for C$_{84}$H$_{114}$N$_{11}$O$_{23}$ [(M+H)[+]]: 1644.81; found: 1644.8; IR (cm^{-1}): 2925, 2857, 1743, 1630, 1612, 1589, 1507, 1443, 1119

Compound **64**
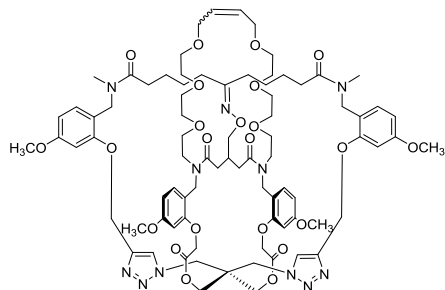
16 mg **63** (0.010 mmol) was dissolved in 10 mL dry CH$_2$Cl$_2$ and the solution was degassed with three vacuum/N$_2$ cycles. After degassing, 1.7 mg Grubbs II (0.002 mmol, 0.20 equiv) was added and the mixture was stirred overnight at 40 °C under N$_2$ atmosphere. The mixture was concentrated in *vacuo* and the residue was purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 96:4 → 95:5 → 94:6) to give **64** (8 mg, 0.005 mmol, 51%) as a brown film. ^{1}H-NMR complex; LCMS calcd for C$_{82}$H$_{110}$N$_{11}$O$_{23}$ [(M+H)[+]]: 1616.78; found: 1616.7

Compound 66
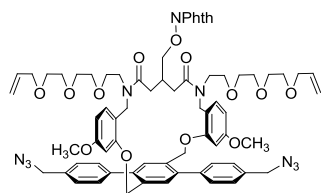
307 mg **6** (0.333 mmol), 263 mg **43** (0.500 mmol, 1.5 equiv), 1.08 g Cs$_2$CO$_3$ (3.33 mmol, 10.0 equiv) and 500 mg 4Å MS were dissolved in 330 mL dry CH$_3$CN under N$_2$ atmosphere. The mixture was stirred overnight at 50 ^{o}C and concentrated in *vacuo.* The residue was dissolved in 10 mL EtOAc and filtered over a plug of Celite (flushed 10 mL EtOAc). The combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 97:3 → 96:4) to give **66** (360 mg, 0.277 mmol, 84%) as a slightly yellow oil. ^{1}H-NMR: complex; LCMS calcd for C$_{70}$H$_{80}$N$_9$O$_{15}$ [(M+H)$^+$]: 1286.58; found: 1286.4

Compound 67
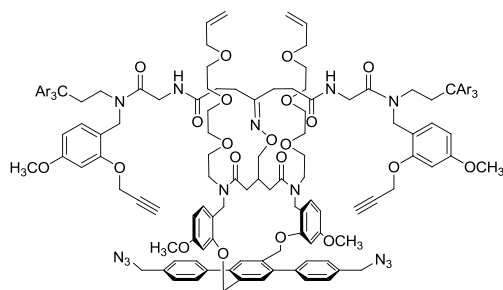
129 mg **66** (0.100 mmol) was dissolved in 5 mL dry THF. The mixture was cooled to 0 ^{o}C and 0.026 mL methylhydrazine (0.500 mmol, 5.0 equiv) was added. The mixture was stirred at 0 ^{o}C for 1 hour and was concentrated in *vacuo*. The residue was dissolved in 50 mL CH$_3$CN/H$_2$O 4:1 and 151 mg **26** (0.100 mmol) and 0.57 mL AcOH (10 mmol, 100 equiv) were added. The mixture was stirred overnight at room temperature and was concentrated in *vacuo*. The residue was purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 194:6 → 193:7 → 192:8) to give **67** (124 mg, 0.047 mmol, 47%) as an off-white foam. ^{1}H-NMR: complex; HRMS [CSI] calcd for C$_{161}$H$_{198}$N$_{13}$O$_{21}$ [(M+H)$^+$]: 2650.4857; found: 2650.4527

Compound 68
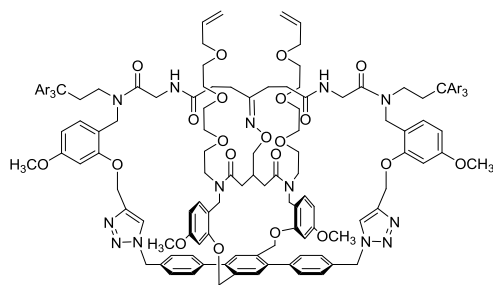
53 mg **67** (0.020 mmol) was dissolved in 2 mL dry CH$_3$CN and added dropwise over 24h to a solution of 19 mg CuI (0.100 mmol, 5 equiv), 0.068 mL DIPEA (0.400 mmol, 20 equiv) and 0.044 mL 2,6-lutidine (0.400 mmol, 20 equiv) in 40 mL dry CH$_3$CN at 80 ^{o}C under N$_2$ atmosphere. The mixture was stirred for another 24h at 80 ^{o}C and was cooled and concentrated in *vacuo*. The residue was partitioned between 20 mL EtOAc and 20 mL 1M KHSO$_4$. The water layer was extracted with 10 mL EtOAc and the combined organic layers were washed with 15 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 96:4 → 95:5) to give **68** (32 mg, 0.012 mmol, 60%) as a yellow solid. ^{1}H-NMR: complex; HRMS [CSI] calcd for C$_{161}$H$_{198}$N$_{13}$O$_{21}$ [(M+H)$^+$]: 2650.4857; found: 2650.4845

Compound 69
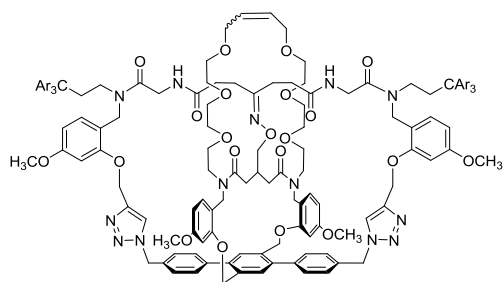
27 mg **68** (0.010 mmol) was dissolved in 15 mL dry CH_2Cl_2 and the mixture was degassed with three vacuum/N_2 cycles. After degassing, 1.7 mg Grubbs II (0.002 mmol, 0.20 equiv) was added and the mixture was stirred overnight at 40 ^{o}C under N_2 atmosphere. The mixture was cooled to room temperature, concentrated in *vacuo* and the residue was purified by column chromatography (CH_2Cl_2/CH_3OH 96:4 → 95:5) to give **69** (19 mg, 0.0072 mmol, 72%) as a brown film. ^{1}H-NMR: complex; HRMS [CS] calcd for $C_{159}H_{194}N_{13}O_{21}$ [(M+H)$^+$]: 2622.4544; found: 2622.4120

Compound 70
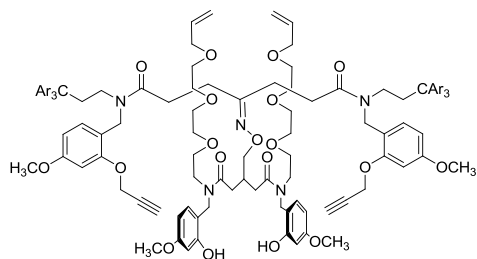
110 mg **6** (0.120 mmol, 1.2 equiv) was dissolved in 5 mL dry THF. The solution was cooled to 0 ^{o}C and 0.029 mL methylhydrazine (0.600 mmol, 6.0 equiv) was added and the reaction was stirred for 30 minutes at 0 ^{o}C. The mixture was concentrated in *vacuo* and the residue was dissolved in 3 mL THF/H_2O 2:1 and 140 mg **27** (0.100 mmol) was added, followed by 0.114 mL AcOH (2.00 mmol, 20.0 equiv). The reaction was stirred overnight at 50 ^{o}C and was concentrated in *vacuo*. The residue was purified by column chromatography (CH_2Cl_2/CH_3OH 198:2 → 197:3 → 196:4) to give **70** (111 mg, 0.051 mmol, 51%) as a colorless foam. ^{1}H-NMR: complex; HRMS (CSI) calcd for $C_{135}H_{176}N_5O_{19}$ [(M+H)$^+$]: 2171.2959, found: 2171.2691; IR (cm^{-1}): 2955, 2866, 1609, 1506, 1441, 1109

Compound 71
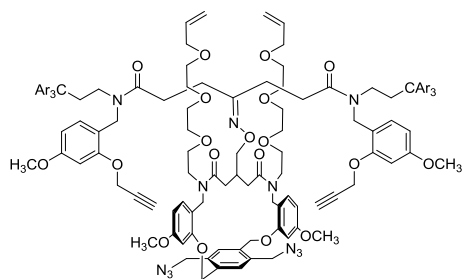
258 mg **70** (0.119 mmol) and 49 mg **54** (0.131 mmol, 1.1 equiv) were dissolved in 120 mL dry CH_3CN and 232 mg Cs_2CO_3 (0.714 mmol, 6.0 equiv) was added. The reaction was stirred overnight at 50 ^{o}C under N_2 atmosphere and was concentrated in *vacuo*. The residue was partitioned between 10 mL CH_2Cl_2 and 10 mL H_2O. The water layer was extracted with 2x 5 mL CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (CH_2Cl_2/CH_3OH 198:2 → 197:3 → 196:4 → 195:5) to give **51** (150 mg, 0.063 mmol, 53%) as a colorless film. ^{1}H-NMR: complex. HRMS (CSI) calcd for $C_{145}H_{184}N_{11}O_{19}$ [(M+H)$^+$]: 2383.3770, found: 2383.3598

Compound **72**
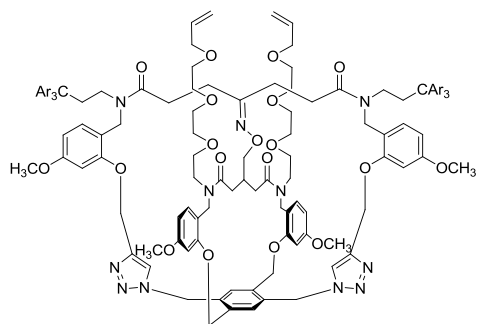
150 mg **71** (0.063 mmol) was dissolved in 2 mL dry CH_3CN and added over 18h to a solution of 24 mg CuI (0.126 mmol, 2.0 equiv), 0.055 mL DIPEA (0.315 mmol, 5.0 equiv) and 0.037 mL 2,6-lutidine (0.315 mmol, 5.0 equiv) in 63 mL dry CH_3CN at 80 ^{o}C under N_2 atmosphere. After the addition was completed, the reaction was stirred an additional 8h at 80 ^{o}C and was cooled and concentrated in *vacuo*. The residue was partitioned between 15 mL CH_2Cl_2 and 15 mL saturated NH_4OH. The waterlayer was extracted with 2 x 5 mL CH_2Cl_2 and the combined organic layers were washed with 10 mL 1M HCl, dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (CH_2Cl_2/CH_3OH 196:4 → 195:5 → 194:6) to give **72** (91 mg, 0.038 mmol, 61%) as a slightly yellow powder. ^{1}H-NMR: complex. HRMS (CSI) calcd for $C_{145}H_{183}N_{11}O_{19}Na$ [(M+Na)$^+$]: 2405.3589 found: 2405.3421

Compound **73**
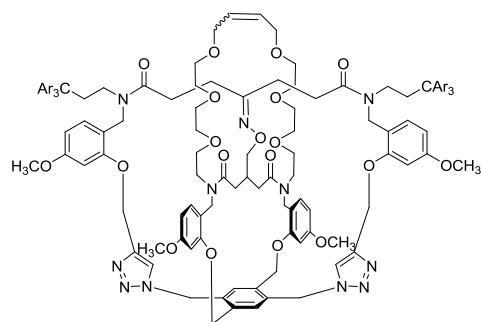

24 mg **72** (0.010 mmol) was dissolved in 20 mL dry CH_2Cl_2 and the solution was degassed with three vacuum/N_2 cycles. After degassing, 2.5 mg Grubbs II (0.003 mmol, 0.30 equiv) was added and the mixture was stirred overnight at 40 ^{o}C under N_2 atmosphere. The reaction mixture was cooled to room temperature and concentrated in *vacuo*. The residue was purified by column chromatography (CH_2Cl_2/CH_3OH 196:4 → 195:5 → 194:6) to give **73** (15 mg, 0.0064 mmol, 64%) as a brownish powder. ^{1}H-NMR: complex; HRMS (CSI) calcd for $C_{143}H_{180}N_{11}O_{19}$ [(M+H)$^+$]: 2355.3457, found: 2355.3245

References

[1] Ulrich, S.; Boturyn ,D.; Marra, A.; Renaudet, O.; Dumy, P. *Chem. Eur. J.* **2014**, *20*, 34-41

[2] Dirksen, A.; Hackeng, T.L.; Dawson, P.E. *Angew. Chem. Int. Ed.* **2006**, *45*, 7581-7584

[3] Wendeler, M.; Grinberg, L.; Wang, X.; Dawson, P.E.; Baca, M. *Bioconjugate Chem.* **2014**, *25*, 93-101

[4] Rashidian, M.; Mahmoodi, M.M.; Shah, R.; Dozier, J.K.; Wagner, C.R.; Distefano, M.D. *Bioconjugate Chem.* **2013**, *24*, 333-342

[5] Packman, L.C. *Tetrahedron Lett.* **1995**, *36*, 7523-7526

[6] Durham, L.J.; McLeod, D.J.; Cason, J. *Org. Synth.* **1958**, *38*, 38

[7] Leonard, N.M.; Brunckova J.; *J. Org. Chem.* **2011**, *76*, 9169-9174

[8] Barlan, A.U.; Basak, A.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 5849-5852

[9] Pal, M.; Parasuraman, K.; Yeleswarapu, K. *Org. Lett.* **2003**, *5*, 349-352

[10] Berger, M.; Jakob, B.; Schneider, M.P. *Bioorg. Med. Chem.* **1994**, *2*, 573-588

[11] Yang, L.; Xiao, H.; Yan, L.; Wang, R.; Huang, Y.; Xie, Z.; Jing, X. **2014**, *J. Mater. Chem. B*, *2*, 2097-2106

[12] Mangalum, A.; Gilliard, R.J.; Hanley, J.M.; Parker, A.M.; Smith, R.C. *Org. Biomol. Chem.* **2010**, *8*, 5620-5627

[13] Hai, J.; Zhu, E.; Bian, L.; Wang, J.; Wang, Z.; Li, Y.; Yin, L.; Zhang, F.; Tang, W. *Eur. Polym. J.* **2013**, *49*, 3610-3618

[14] Sookcharoenpinyo, B.; Klein, E.; Ferrand, Y.; Walker, B.; Brotherhood, P.R.; Ke, C.; Crump, M.P.; Davis, A.P. *Angew. Chem. Int. Ed.* **2012**, *51*, 4586-4590

[15] Joshi, G.; Davis, A.P. *Org. Biomol. Chem.* **2012**, *10*, 5760-5763

[16] Howgego, J.D.; Butts, C.P.; Crump, M.P.; Davis, A.P. *Chem. Commun.* **2013**, *49*, 3110-3112

[17] Challinor, L.; Klein, E.; Davis, A.P. *Synlett* **2008**, *14*, 2137-2141

[18] Zhang, H.L.; Zhu, G.Y.; Wang, G.; Meng, M.; Liu, C.Y.; Lei, H. *Inorg. Chem.* **2015**, *54*, 11314-11322

[19] Hass, H. B.; Bender, M. L. *J. Am. Chem. Soc.* **1949**, *71*, 1767

[20] Gopinath, R.; Patel, B.K. *Org. Lett.* **2000**, *2*, 577-579

[21] Singh, K.N.; Kaur, A. *Synth. Comm.* **2005**, *35*, 2935-2937

[22] Singh, S.K.; Zhang, Y.; Katrizky, A.R. *Synthesis,* **2002**, *18*, 2795-2798

Chapter IV: Synthesis of a quasi[1]catenane and quasi[1]rotaxane *via* a backfolding strategy[1]

Introduction

Mechanically interlocked molecules have inspired chemists for decades. Initially, this interest was primarily a creative synthetic exercise (see Chapter I) and many different types of these interlocked molecules have been synthesized over the last 50 years. It was soon discovered that mechanically interlocked compounds also occur in nature. Examples of these naturally occurring entangled molecules are the lasso peptides, specific proteins and DNA.[2,3,4]

Spiro compounds are well-defined three dimensional structures and are quite abundant in nature, usually in optically pure form. Due to their rigidity, spiro compounds are also widely utilized in drug research, ensuring high selectivity. Besides the regular spiro structure, an inverted spiro connectivity may be envisioned. Noteworthy of this yet unprecedented structure is the increased compactness due to the tightly interlocking rings. The central connecting tetrahedral sp^3-hybridized carbon atom assures mutual perpendicular arrangement of the rings. The inverted spiro connectivity was dubbed a quasi[1]catenane (see figure 1) because it strongly resembles a catenane, but instead of two mechanically interlocked rings it has two covalently interlocked rings. Uniquely, a quasi[1]catenane is diastereomeric to its non-interlocked spiro counterpart, for it requires the breaking of a covalent bond to transform one into the other, despite retaining the C_2 symmetry.
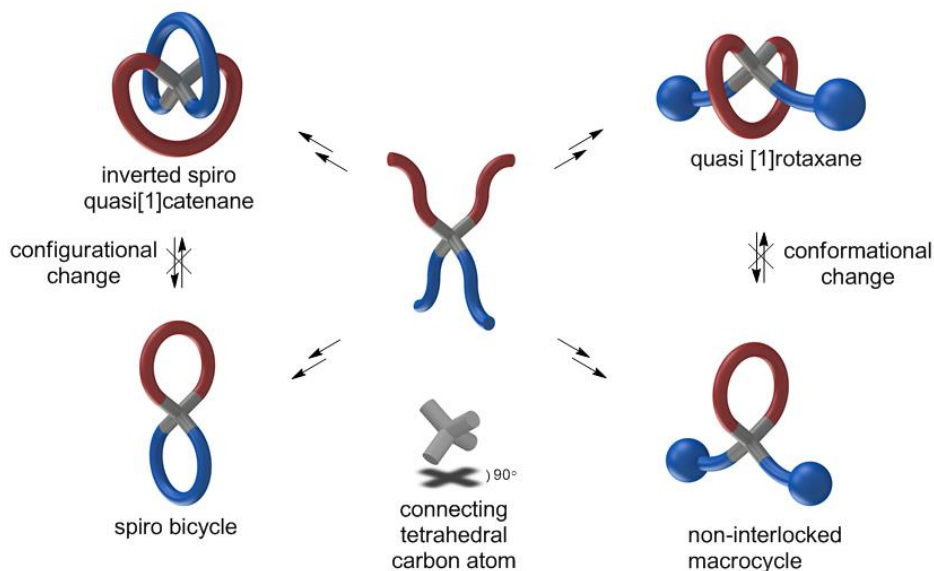
Figure 1: cyclizations of a common precursor towards novel quasi[1]catenane (top left), quasi[1]rotaxane (top right) and their non-interlocking analogues: spiro bicycle (bottom left) and macrocycle (bottom right)

Alternatively, an analogous quasi[1]rotaxane may be envisioned by replacing one of rings by a thread which has two bulky groups to prevent the slipping-out of these groups (figure 1, top right). The quasi[1]rotaxane is conformationally different from its non-interlocked macrocycle, for it requires theoretically no breaking of covalent bonds to transform one into the other.
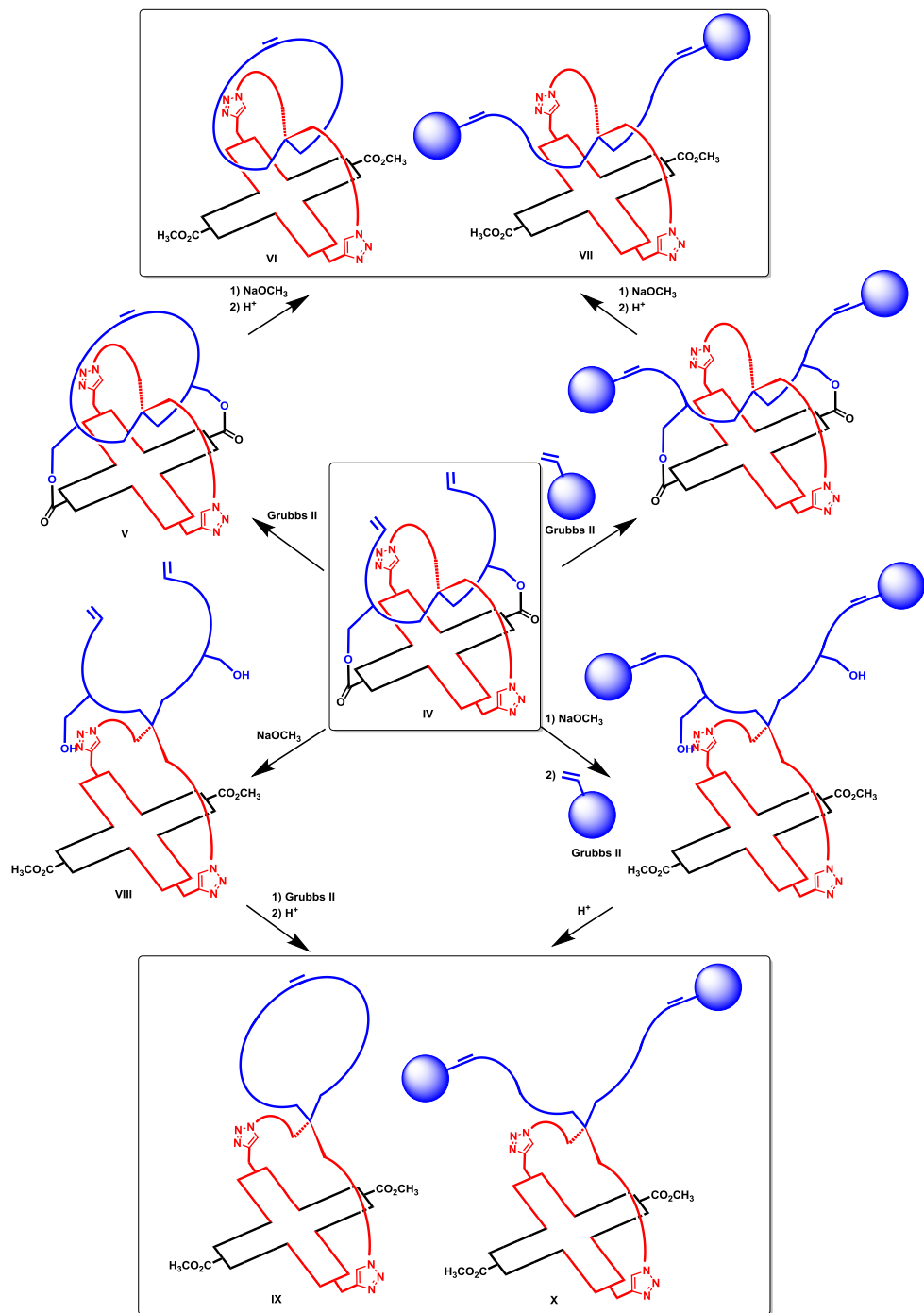
To synthesize the quasi[1]catenanes and -rotaxanes a covalent approach seems most suitable, for it requires the constraining of intermediates into an extent that is not well achievable *via* the common non-covalent syntheses of interlocked molecules, i.e. *via* H-bonds, metal-ion interactions, electrostatic interactions. In this chapter the strategy towards the quasi[1]catenanes and rotaxanes is outlined and followed, resulting in the synthesis of both unprecedented connectivities. Key in the strategy will be template-directed backfolding cyclization steps. Building on our experiences using a covalent template as described in Chapters II and III, we set out a strategy to access the unprecedented quasi[1]catenane and quasi[1]rotaxane structures (see scheme 1). For this strategy to succeed, the scaffold has to be incorporated in the final molecule, so one of the orthogonal reactions on the scaffold should give a permanent connection (CuAAC reaction, forming the red ring), while the other is temporary (ester bond, forming the blue ring).

Precursor **I** is characterized by a central sp^3-hybridized C-atom at which two orthogonal reactivities are present in the two pairs of linear ring precursor chains. The red chains bear azides at the termini and the blue chains bear alkenes. Moreover, at the blue chains cleavable tethers are installed employing a phenolic hydroxyl group, schematically depicted as OH-groups. In this strategy, the phenolic OH groups are acylated at scaffold **II**, containing two activated phenol esters, leading to bis-lactone intermediate **III**. The alkynes on the scaffold and the azides are now well oriented to perform two intramolecular CuAAC reactions, leading to common cage-type tricyclic intermediate **IV** (see scheme 1).
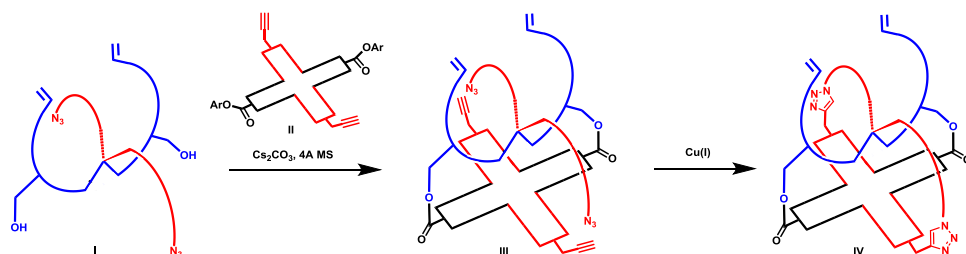
Scheme 1: Synthesis of the common cage-type intermediate **IV**

Depending on the sequence of steps, from this common cage-type intermediate the quasi[1]catenane **VI**, quasi[1]rotaxane **VII**, spiro bicycle **IX** and macrocycle **X** may all be synthesized (see scheme 2). Ring-closing metathesis (RCM) of common intermediate **IV** leads to multicyclic intermediate **V**. Subsequent methanolysis of the esters, followed by acidolytic cleavage of the 2-hydroxy-4-methoxybenzyl groups leads to quasi[1]catenane **VI**.[5] Quasi[1]rotaxane **VII** is synthesized *via* the same sequence of steps, except for replacing the RCM step by cross-metathesis with a bulky electron deficient alkene to prevent slipping through the red ring.[6] When common intermediate **IV** is subjected to methanolysis first, the sterically less hindered macrocycle **VIII** will be obtained. It is postulated that the red macrocycle is large enough to allow the blue ring to slip out. RCM followed by acidic cleavage leads to spiro bicycle **IX**. Analogously, the non-interlocked macrocycle **X** can be accessed by the same sequence of steps, except by replacing the RCM step by cross-metathesis with a bulky electron deficient alkene.

Scheme 2: Synthesis of quasi[1]catenane **VI** & quasi[1]rotaxane **VII** (top box) and their non-interlocked equivalents **IX** and **X** (bottom box) from common cage-type intermediate **IV** (center box)

Design of the building blocks

For the central sp³-hybridized carbon atom that forms the crossroads between the red and blue rings, the methylene-bridge carbon atom of fluorene was chosen (see figure 2). There are multiple benefits for use of the fluorene moiety.[7] Firstly, the fluorene core is rigid. Secondly, the central sp³-hybridized carbon atom is easily alkylated owing to the stabilization of the methylide anion. Thirdly, the fluorene core may be easily modified by halogenation on the 2- and 7-positions, allowing for further functionalization using palladium(0) chemistry. Lastly, the fluorene motif gives sharp and distinctive signals in the ¹H-NMR spectra, allowing facile identification.

The synthesis started with the double alkylation of the methylene carbon atom with bromoacetate esters. These may be transformed into the tertiary amides as shown in figure 2, with the acid-labile 2-hydroxy-4-methoxybenzyl group as amide backbone modification and an 10-undecene chain, obtained from commercially available 10-undecen-1-ol for RCM ring-closure. As the ring precursor, it was decided to use an all carbon chain instead of the oligoglycol derivative used in Chapters II and III, because of the faster (two-step) synthesis of the amine and its compatibility with the concept of an 'impossible' interlocked molecule. The 2- and 7- positions of the fluorene moiety are functionalized with an 3-azidopropyl group, obtained in multiple steps *via* the Sonogashira reaction of a 2,7-diiodofluorene with propargyl alcohol.

Figure 2: Design of the central building block

The scaffold contains a terephthalic acid core, functionalized at the 2- and 5-positions with two alkyne chains for the CuAAC reaction (see figure 3). Because it was yet unknown which size the alkyne tethers should have for optimal cyclizations, scaffolds with a propargyl and 4-pentyne chain were synthesized. The acid groups were activated either as a *p*-nitrophenol ester[8] or pentafluorophenol[9] ester, both moderately activating groups (pKa *p*-nitrophenol = 7.2, pKa pentafluorophenol = 5.5) known for forming amide bonds with amines. It should be noted that in our hands it was found that these activating groups are also suitable for transesterification with phenols under mild basic conditions.

Figure 3: Design of the scaffold

For the bulky electron deficient alkenes used for cross metathesis, the acrylamide derivative of 3,3,3-tris(4-*tert*-butylphenyl)-1-aminopropane was chosen (see figure 4), as the required amine had already been synthesized in Chapter III. Acrylamides are well known substrates for cross metathesis, forming exclusively cross-metathesized product with a very high, usually >25:1, E/Z ratio.[10]


Figure 4: Design of the bulky, electron deficient alkene

Synthesis of the building blocks

### Synthesis of the fluorene based molecule

Fluorene was diiodinated on the 2- and 7-positions following a literature procedure, although in our hands a lower yield (52%) was obtained for compound **1** (see scheme 3, A).[11] The methylene carbon atom was di-alkylated with *tert*-butyl bromoacetate using NaH as the base and DMF as the solvent to give **2** in 84% yield. The use of K_2CO_3, KOtBu or DBU as bases was unsuccessful. The resulting 9,9'-disubstituted fluorene **2** was reacted with excess propargylalcohol, Pd(PPh$_3$)Cl$_2$ and CuI under classic Sonogashira conditions, giving 2,7-bis-alkyne functionalized **3** in a good 85% yield. Full reduction of the alkyne to the alkane was troublesome. Under standard hydrogenation conditions with Pd/C in THF a mixture of products was obtained, of which the main product was identified as mono-deoxygenated compound **5**. This can be rationalized by insertion of Pd(0) in the intermediate (Z)-allylic alcohol, followed by reductive elimination from a palladium-hydride species. This forms an allyl group that is subsequently hydrogenated further to a propyl group (see scheme 3, B). The problem was easily overcome by using Raney nickel instead of Pd/C to give a clean and almost quantitative conversion to desired diol **4**.
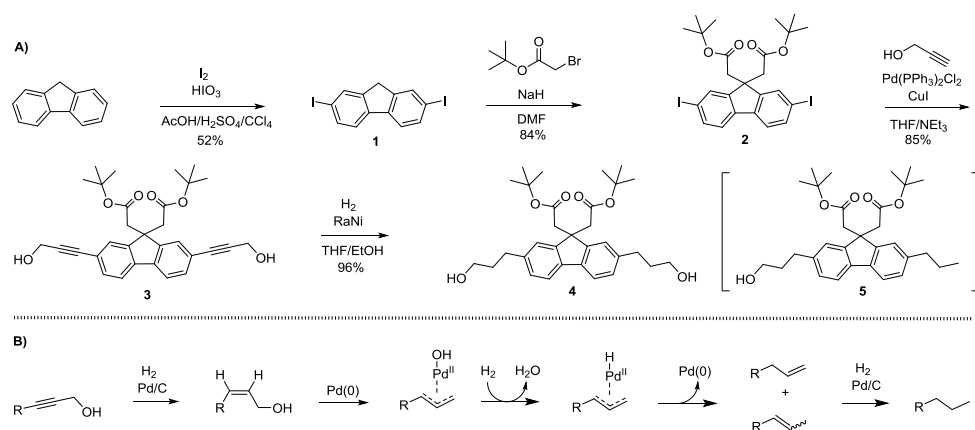
Scheme 3: A) Synthesis of diol **4**   B) Postulated mechanism for propyl formation during hydrogenation

Diol **4** was bis-mesylated to give **5** in 84% yield (see scheme 4). Initially, this compound was transformed into the bis-azide in good yields using NaN_3 in DMF. However, subsequent removal of the *tert*-butylesters with TFA or HCO_2H was unsuccessful, leading to decomposition of the resulting di-acid. Reversal of the reaction sequence solved this problem. The *tert*-butylgroups of bis-mesylate **5** were first cleaved by HCO_2H treatment to give di-acid **6**, followed by S_N2 substitution of the mesylates with NaN_3 in DMF to give **7** in 90% yield over the two steps. It is worth to note that the deprotection step with HCO_2H should be stopped after 18 hours. After a 3-day experiment at room temperature some E1 elimination to the mono-allyl compound **7-allyl** was observed (scheme 4, bottom right). The diacid **7** was transformed into the bis-*N*-hydroxysuccinimide ester using conditions reported by Brunckova *et al*, giving **8** in 90% yield.[12]
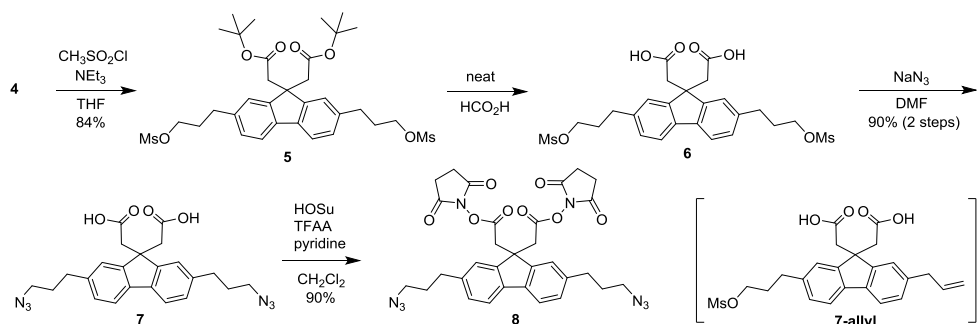
Scheme 4: Synthesis of bis *N*-hydroxysuccinimide ester **8** and E1-elimination side product **9**

The alkene part of the central fluorene core was synthesized from commercially available 10-undecen-1-ol, which was transformed in one step to phthalimide **9** using Mitsunobu conditions in 82% yield (see scheme 5). The phthalimide was deprotected using methylhydrazine in THF giving amine **10** in 88% yield after Kugelrohr distillation. As mentioned in Chapter III, methylhydrazine was used instead of hydrazine to prevent unwanted diazene-mediated hydrogenation of the terminal alkene.[13] Reductive amination of 2-hydroxy-4-methoxybenzaldehyde with amine **10** in CH_3OH cleanly gave secondary amine **11** in almost quantitative yield. This secondary amine was reacted with bis *N*-hydroxysuccinimide ester **8** and NEt_3, giving bis-amide **12** in 73% yield. No DMAP was added as an acylation catalyst to prevent unwanted intramolecular lactonization of the phenolic OH with the activated ester.
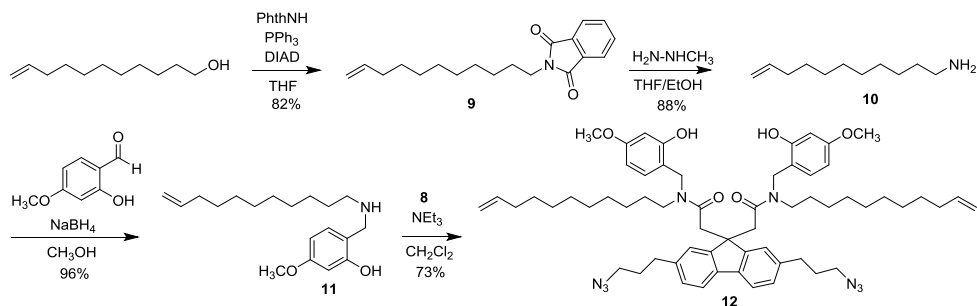
Scheme 5: Synthesis of central core molecule **12**

Synthesis of terephthalic acid-type scaffolds

As described in Chapter II, it is very hard to obtain a rigid square planar tetrasubstituted scaffold. In contrast, as described in Chapter III, an X-shaped scaffold was much easier accessible, such as terephthalic acid derivatives that are well described in literature. Due to the easy functionalization of the 2- and 5-positions *via* simple alkylation it was decided to use the 2,5-hydroxyterephthalic acid core. As explained before, two types of scaffold were synthesized bearing a propargyl chain and a pentyn chain. Dimethyl-2,5-hydroxyterephthalate **13** was obtained *via* a literature procedure by oxidizing commercially available dimethyl-2,5-dioxocyclohexane-1,4-dicarboxylate with *N*-chlorosuccinimide in AcOH in 96% yield (see scheme 6).[14] Next, **13** was alkylated with propargylbromide to give **14** in 86% yield. Subsequent saponification and HBTU mediated coupling with either *p*-nitrophenol or pentafluorophenol gave the activated propargyl scaffolds **15** and **16** in 93 and 55% yields, respectively. Bis *p*-nitrophenol ester **15** showed really poor solubility in common solvents. The pentyne scaffolds were synthesized analogously, starting with the mesylation of 4-pentyn-1-ol, giving **17** in 98% yield. Subsequent alkylation of terephthalic acid derivative **13** with mesylate **17** gave product **18** in 78% yield. NMR analysis revealed the presence of ~10% of mono-pentynol ester as a side product, however this was of no consequence since the esters were saponified in the next step. HBTU mediated coupling with *p*-nitrophenol or pentafluorophenol gave the activated pentyne scaffolds **19** and **20** in 69 and 79% yields, respectively. It is noteworth that all molecules containing the 2,5-dialkoxy-terephthalate core exhibit strong blue fluorescence under 350 and 254 nm. This property has been really helpful, because this fluorescence is also exhibited at extremely low concentrations, allowing for facile UV-identification of derived products that elute really diluted from silica columns.
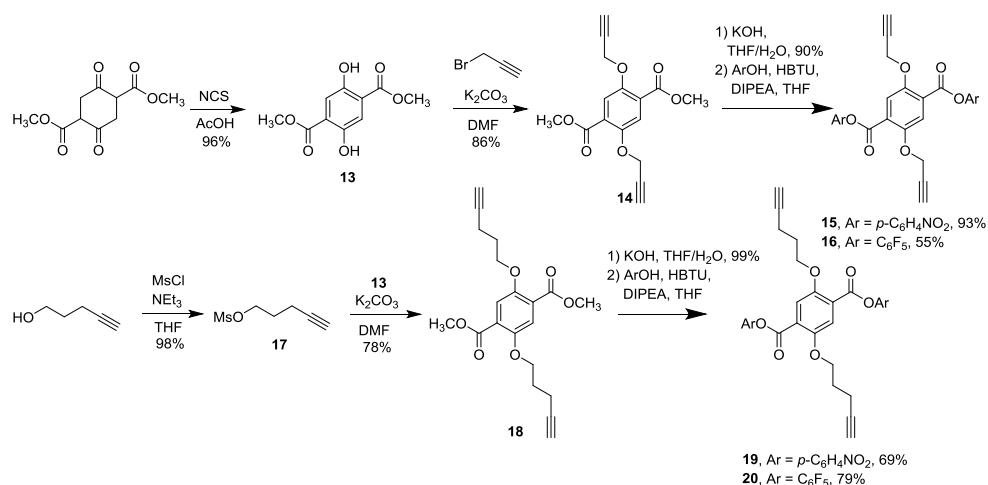

Scheme 6: synthesis of bis-propargyl scaffolds **15** & **16** and bis-pentyn scaffolds **19** & **20**

# Towards the quasi[1]catenanes and quasi[1]rotaxanes

Synthesis of the common cage-type intermediate

With all building blocks in hand, at first macrocyclization by double esterification of the 2-hydroxy-4-methoxybenzyl groups of the central tetrahedral compound **12** to the activated scaffolds was optimized. It was decided to apply the same reaction conditions as for the Williamson etherification in Chapters II and III as the mechanism includes the same nucleophilic phenoxide. Thus, core molecule **12** was reacted with the poorly soluble bis-4-nitrophenol ester **15**, Cs_2CO_3 and 4Å MS in CH_3CN at 1 mM concentration at 60 ^{o}C (see scheme 7). LC-MS traces showed rapid conversion to product **21**, but upon workup only 48% isolated yield was obtained. Moreover, separation from 4-nitrophenol was troublesome. Accounting for the low yield, presumably polymers had formed that were removed by filtration during workup together with the molecular sieves. Nevertheless, the product could be used for the next step being the double intramolecular CuAAC reaction. The same slow addition conditions as in Chapter III were tested, i.e. addition of the substrate to a solution of CuI (1 equiv) and DIPEA (10 equiv) in CH_3CN at 50 ^{o}C by a syringe pump. Unfortunately, extensive polymerization was observed and no product could be isolated. It was postulated that the propargyl chains were too short for this cyclization, therefore favoring intermolecular reactions and giving rise to polymers.
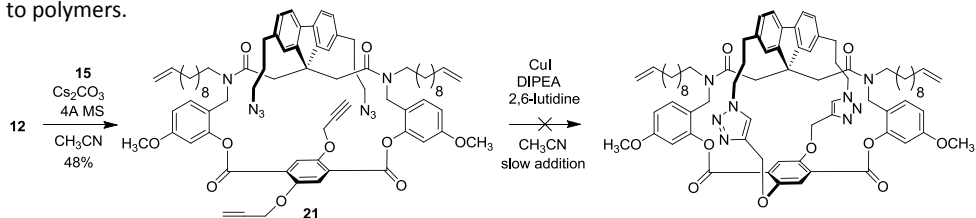
Scheme 7: macrocyclizations of **12** with bis-propargyl scaffold **15**

Next, the bis-pentyne functionalized scaffold was used of which the longer alkyne chains should allow for the formation of an unstrained macrocycle during the CuAAC reaction due to increased flexibility. During optimization of the trans-esterification to give the pentyn scaffold adduct, it was found that the bis-pentafluorophenol esters were far more efficient for this step. Using the aforementioned conditions and at a bit higher concentration, bis-ester product **22** was isolated in a reproducible 69% yield (see scheme 8). During workup, pentafluorophenol could be easily separated from the product by extraction followed by chromatography. The following intramolecular CuAAC reaction, on the other hand, still required optimization. Despite the use of slow addition to give the tricyclic cage-type intermediate **23**, yields were low (10-30%) and annoyingly irreproducible. Polymerization remained the main pathway in all cases. The use of CuI / DIPEA in refluxing toluene (instead of CH_3CN) initially seemed to improve the yields somewhat, but the results were still irreproducible. After considerable optimization, the use of organic solvent compatible $Cu(CH_3CN)_4BF_4$ as the Cu(I) source with TBTA as the ligand in refluxing CH_2Cl_2 solved the problem.[15] Surprisingly, no more polymerization was observed, even at a fairly high concentration of 5 mM to give a dramatically improved yield of 79% of **23**. Moreover, catalytic amounts (20-25 mol%) of copper and ligand could be used, without affecting conversion and yield. The reason(s) for this major improvement could be solvent effects, but also the fact that no external base is necessary due the innate basicity of the TBTA ligand, thereby accelerating reaction rates. In hindsight, it would still be interesting to apply these new 'click' conditions to the aforementioned bis-propargyl compound **21** (see scheme 7).
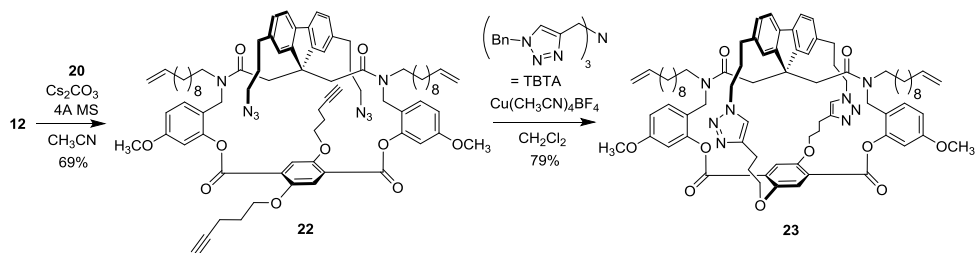
Scheme 8: Synthesis of common intermediate **23**

Synthesis of the quasi[1]catenane

With a reliable synthesis of the common precursor for all four desired target molecules in hand, we set out for the synthesis of the quasi[1]catenane. Compound **23** was subjected to RCM conditions using 20 mol% Grubbs 2nd generation catalyst at 1 mM in refluxing CH_2Cl_2. The reaction worked smoothly on the first run, giving product **24** as an undetermined E/Z mixture in 71% yield (see scheme 9). However, LC-MS analysis of the purified product showed the minor presence (ca. 10%) of a side product with a m/z of 14 lower than the desired mass. This was attributed to a known side reaction of Grubbs catalysts. During the reaction, ruthenium hydride species are formed that isomerize terminal alkenes to internal alkenes.[16,17] After subsequent RCM propene is expelled instead of ethylene, giving truncated products with one methylene less in the chain. Although this side product could be separated by analytical reversed phase LC-MS, TLC gave one spot only. Known inhibitors of this side reaction, such as AcOH addition and lower catalyst loading, led to no change and incomplete reactions, respectively. However, lowering the reaction temperature from 40 °C to 30 °C did greatly suppress the side reaction, but at the risk of incomplete conversion due to a lowered reaction rate. Subsequent methanolysis of the ester bonds in **24** with excess $NaOCH_3$ in THF/CH_3OH gave complete conversion within 2h at room temperature. It was necessary to add 4Å MS or $MgSO_4$ to the reaction to ensure anhydrous conditions. Without these additives, a small amount of ester hydrolysis was observed due to residual water in glassware and/or solvents. To complete the synthesis of the quasi[1]catenane, the 2-hydroxy-4-methoxybenzyl groups in **25** were removed with TFA/CH_2Cl_2 9:1 and Et_3SiH as cation scavenger. After column chromatography, product **26** was obtained in 93% yield as a solid compound. To unequivocally proof the quasi[1]catenane structure, it was attempted to grow crystals. Although crystals did form in this stage by slow diffusion of pentane into a solution of **26** in ethyl acetate, they were unsuitable for X-ray analysis. It was postulated that alkene which was still present as E/Z mixture was the reason for the disorder in the crystal. Therefore, **26** was hydrogenated to give the fully aliphatic analogue **27** in 77% isolated yield after a final purification by column chromatography.
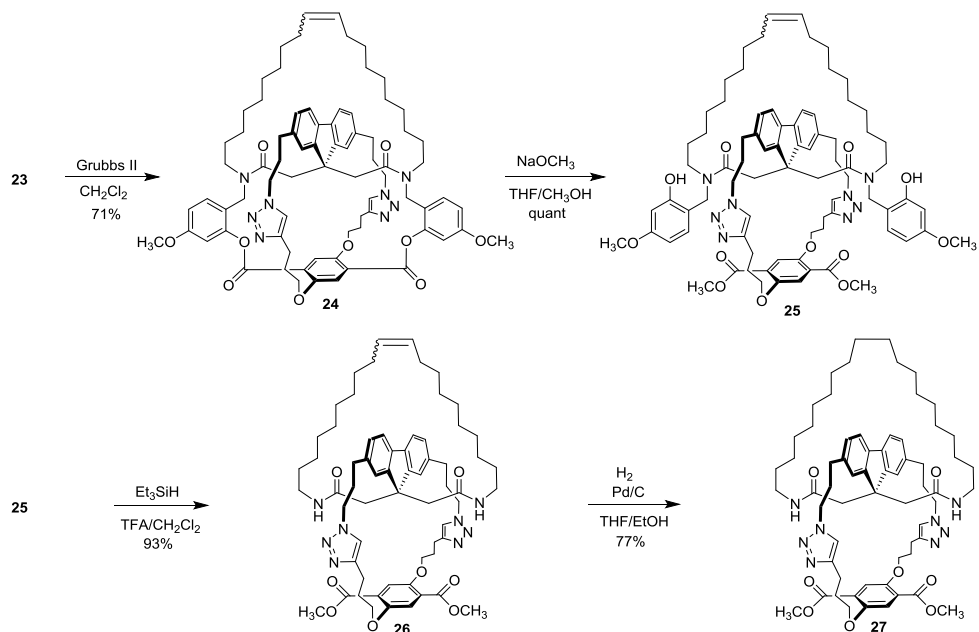
Scheme 9: completion of the synthesis of quasi[1]catenane **27**

Fortunately, this time suitable crystals were grown from EtOAc/pentane system and the molecular structure could be elucidated. The crystal structure shows disorder in the aliphatic chain likely arising from the high flexibility in this part of the molecule. Nevertheless, the X-ray crystallographic analysis reveals the interlocked nature of the two rings. Also noteworthy is the orientation of the amides, in which the oxygen atoms are pointing towards the triazole CH's. This is indicative of a intramolecular H-bond between the carbonyl oxygen and triazole CH.
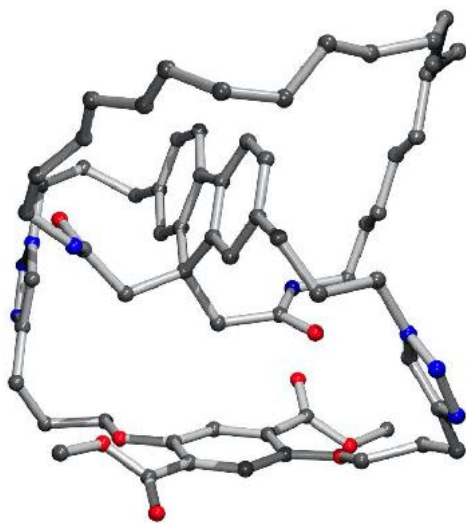

Figure 5: X-ray structure of hydrogenated quasi[1]catenane **27**
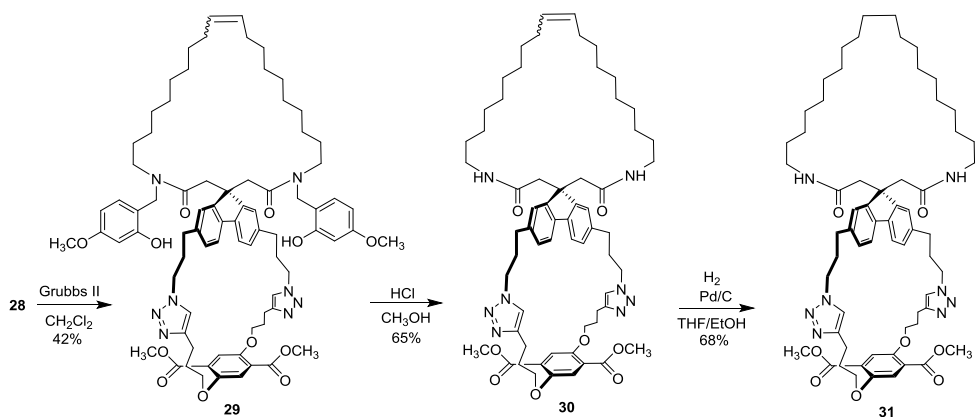
Synthesis of the spiro bicycle

Next, for comparison reasons we prepared the non-interlocked spiro bicycle to show the differences in physical and spectroscopic properties between the two isomers. Common intermediate **23** was treated with NaOCH$_3$ in THF/CH$_3$OH under anhydrous conditions to give macrocycle **28** in quantitative yield (see scheme 10, A). Due to strain relief, the aliphatic chain in intermediate **28-TS** will twist out of the constrained position. The macrocycle is sufficiently wide to allow the aliphatic chain and 2-hydroxy-4-methoxybenzyl groups to slip out. Macrocycle **28** may be obtained in a much shorter synthetic route by performing directly a CuAAC reaction between central core molecule **12** and dimethylester scaffold **18** (see scheme 10, B). When employing the initial CuAAC conditions, i.e. slow addition of the components to a CuI solution in CH$_3$CN, low yields (14-17%) were obtained due to extensive polymerization. However, by using Cu(CH$_3$CN)$_4$BF$_4$ and TBTA in refluxing CH$_2$Cl$_2$ at a 1 mM concentration, product **28** was obtained reproducibly in 35-42% yield. Although the yield is somewhat poor, it obviates several steps and chromatographic column purifications. The LC-MS traces and NMR spectra obtained *via* the two separate routes were identical, indicating that the aliphatic part indeed flipped out of the ring, because it is unlikely the CuAAC reaction would yield the sterically unfavored intermediate **28-TS**. It was also important in route B to use a slight excess of bis-azide **12** (1.1 equiv), to prevent formation of the inseparable linear acyclic bis-scaffold adduct.
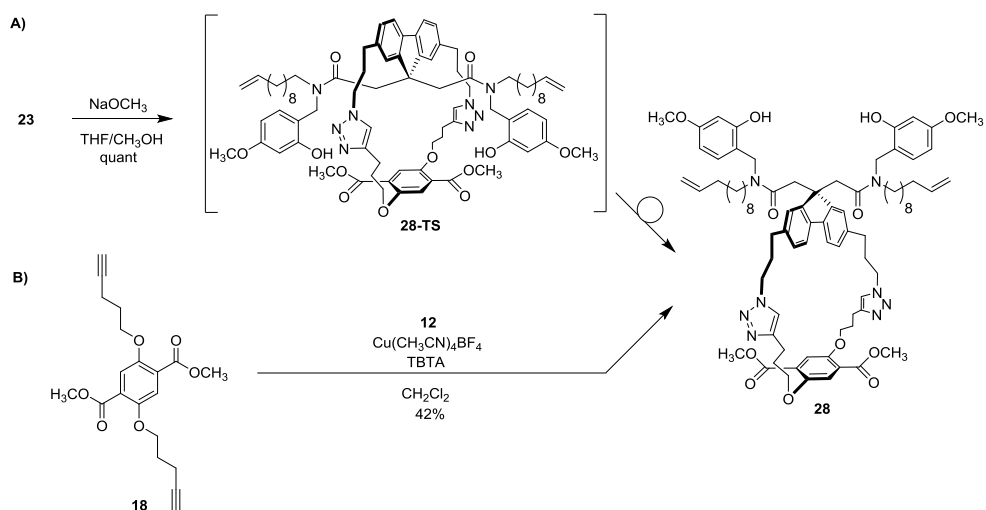
Scheme 10: Synthesis of macrocycle **28** *via* A) methanolysis of **23** or B) *via* a direct CuAAC reaction of **18** with **12**

Unexpectedly, RCM of compound **28** at 1 mM at 30-35 ^{o}C went sluggishly, giving only 40-42% yield in multiple experiments (see scheme 11). Despite testing various conditions (temperature, catalyst loading) no improvements were achieved. Analysis of the apolar sideproduct isolated during chromatography showed besides starting material also formation of nor- (one or more CH$_2$ lost due to isomerization) and homo-compounds (additional CH$_2$ due to metathesis with propene). All of these compounds gave a single spot on TLC. We assume that the RCM reaction of this particular substrate is slow due to an unfavorable conformation of the starting material for macrocyclization

giving rise to long-lived Ru-carbenes, leading to unwanted side reactions. As lowering the temperature did not suppress these side reactions as found for the quasi[1]catenane, it is postulated that the rate of the RCM reaction is important. A slower RCM allows for more time for the formation of reactive Ru-H species that initiate the formation of side products. Removal of the 2-hydroxy-4-methoxybenzyl turned also out to be a troublesome step because with the aforementioned conditions (TFA/CH_2Cl_2) LC-MS analysis showed the exclusive formation of an adduct of product **30** with one or two molecules of TFA. Despite treatment of this crude product with either organic (NEt$_3$) or inorganic base (NaHCO$_3$) followed by column chromatography, the only product observed by LC-MS analysis remained the TFA adduct. It is speculated that the macrocycle with the two slightly basic triazole moieties acts as a ligand for TFA, forming a stable adduct. Also, the cavity of the macrocycle is apolar and might stabilize the trifluoromethyl group of TFA *via* apolar interactions. After evaluating some conditions, it was found that anhydrous 3M HCl in methanol (made *in situ* via addition of acetyl chloride to cold absolute methanol) was an efficient system to cleave the acid labile protective groups, although the reaction required stirring overnight at 50 ^{o}C. Washing with saturated NaHCO$_3$ neutralized the triazoles and chromatographic purification yielded the pure spiro bicycle **30** in 65% yield as a thick oil. Attempted crystallization from the aforementioned EtOAc/pentane system was unsuccessful. The E/Z mixture of the olefin was removed by hydrogenolysis at 50 ^{o}C to give the fully aliphatic spiro bicycle **31** in 68% yield.

Scheme 11: Synthesis of spiro bicycle **31**
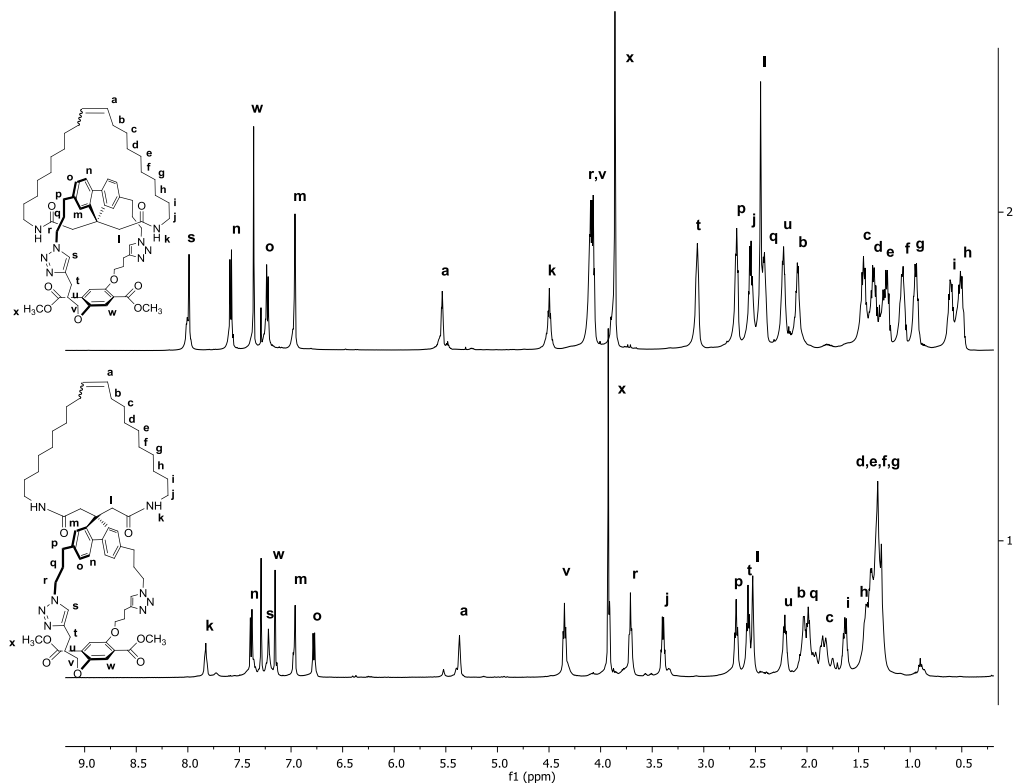
^{1}H-NMR analysis

Figure 6: ^{1}H-NMR spectra and assignments of quasi[1]catenane **26** (upper) and spiro bicycle **30** (lower). Note: these are the non-hydrogenated products

Comparison of the ^{1}H-NMR spectra between quasi[1]catenane **26** and spiro bicycle **30** revealed some interesting signal shifts (see figure 6). As compared to spiro bicycle **30**, the methylene protons **h**, **i** and **j** of the quasi[1]catenane **26** are shifted almost 1 ppm upfield. This shielding effect can be explained by the shifts observed in the fluorene core, as the aromatic protons **n** and (especially) **o** in the quasi[1]catenane are downfield compared to the spiro bicycle. These observations suggest, as is apparent from the structure, interactions between the fluorene core and the aliphatic ring closely encircling it. Also, nOe contacts were observed between **n**, **o** and the aliphatic methylene protons **c,d,e,f,g,h** and **i** (see figure 7). Surprisingly, allylic position **b** did not give any nOe contacts with **n** or **o**, but olefinic proton **a** did give, albeit weak, NOe contact with aromatic proton **o.**
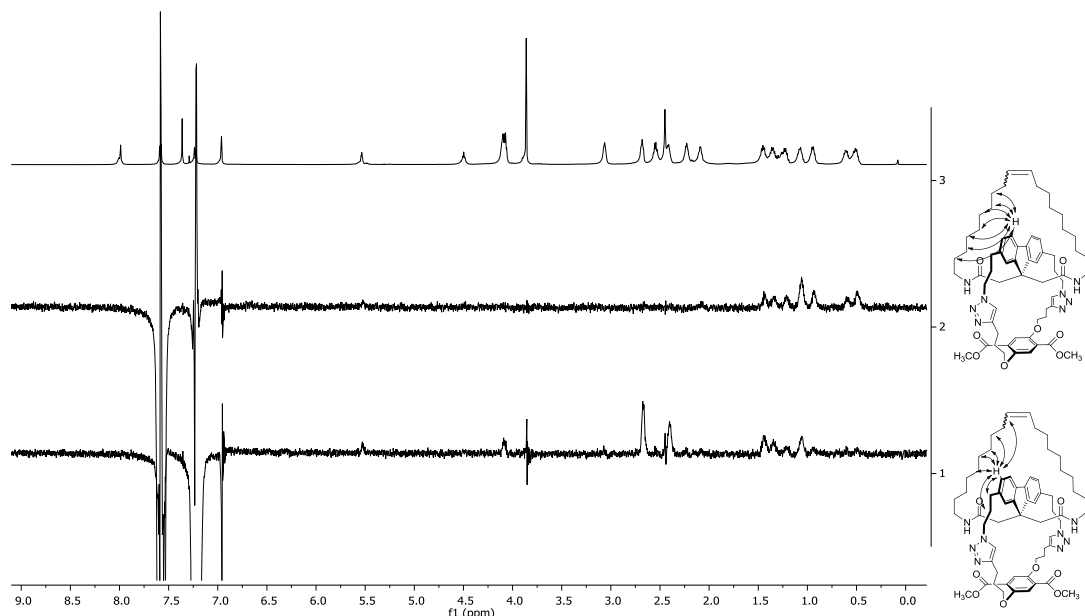
Figure 7: NOe signals from quasi[1]catenane **26** between fluorene protons **n** and **o** and the aliphatic chain

Most spectacularly, the N-H protons **k** have shifted almost 3.5 ppm downfield in spiro bicycle **30**. Another noteworthy shift comes from the triazole moiety. Aromatic proton **s** has shifted over 0.7 ppm upfield in the spiro bicycle. Similarly, adjacent methylenes **t** and **r** have shifted around 0.5 ppm upfield. The reason for these shifts become apparent when closely examining the crystal structure, showing that both amide oxygen atoms are pointing towards the triazole C-H's, indicating an intramolecular hydrogen bond (see figure 8). The electron withdrawing properties of the carbonyl explain the downfield shifting of the triazole C-H, whereas the amide N-H (and the adjacent methylene **j**) becomes more electron rich due to these electrostatic interactions and is thus shifted upfield. H-bonding with the triazole C-H bond has been reported before in literature.[18] In 2011 the groups of Goldup and Schalley reported hydrogen bonds in their [2]rotaxanes between the triazole C-H and a phenanthroline or amide C=O, respectively.[19,20]
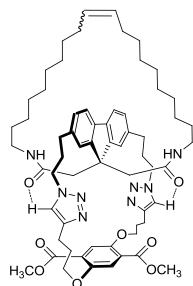

Figure 8: Intramolecular H-bond in **26**

Synthesis of the quasi[1]rotaxane

Next to the quasi[1]catenanes, the analogous and equally unique quasi[1]rotaxanes were targeted in which one of the rings is replaced by two stoppered threads to prevent slipping out of the confined ring. To achieve this, also the common intermediate **23** was used as the precursor, by replacing RCM by a cross metathesis reaction. Bulky amine **3.18** (see Chapter III) could easily be converted to electron deficient acrylamide **32** by reaction with acryolyl chloride in 79% yield. Cross metathesis between terminal alkenes and these acrylamides is known to proceed smoothly and with high selectivity.[6]
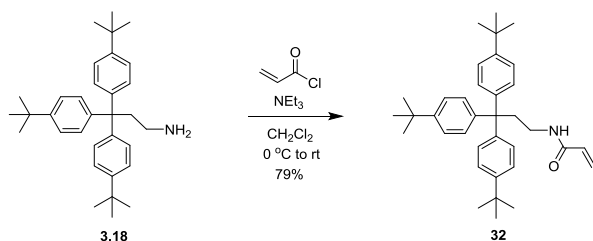
Scheme 12: Synthesis of bulky stoppered acrylamide **32**

Common tricyclic compound **23** was reacted with acrylamide **32** at 5 mM concentration to give cross-metathesis product **33** in 61% yield. As expected, NMR analysis showed exclusive formation of the *E*-isomer. Lactone opening by treatment of **33** with NaOCH$_3$ in THF/CH$_3$OH yielded dimethylester **34** in almost quantitative yield without problems. Final cleavage of the 2-hydroxy-4-methoxybenzyl groups was performed using 3M HCl in CH$_3$OH at 50 $^{\circ}$C, identically as applied for the spiro bicycle. TLC analysis of the crude product revealed two spots close together that, as a result, could not easily be separated by column chromatography. Fortunately, some pure fractions could be collected, after depletion of the more apolar side product. In this way, 27% yield of the pure product was obtained, together with 58% of impure fractions. This impure material was send to Mercachem in Nijmegen and successfully purified by supercritical CO$_2$ straight phase preparative HPLC. The slightly more apolar side product was also isolated and identified as the debenzylated, mono cross-metathesized product. This means that cross metathesis did not gave full conversion. ^{1}H-NMR analysis (see next part) of quasi[1]rotaxane **35** showed signals that matched remarkably well with those of quasi[1]catenane **26**, thereby indirectly confirming the structure.
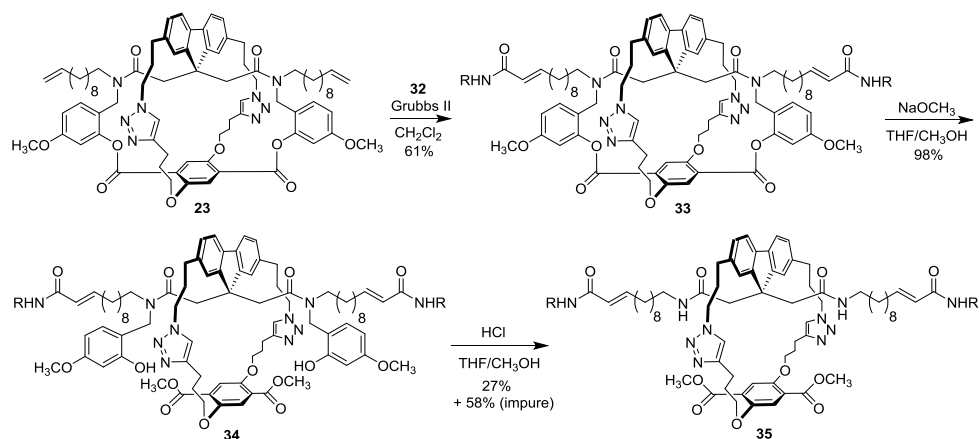
Scheme 13: Synthesis of quasi[1]rotaxane **35.** Note: R = CH$_2$-CH$_2$-C(C$_6$H$_4$tBu)$_3$

Synthesis of non-interlocked macrocycle

To access the non-interlocked analogue, the same strategy was chosen as for bicyclic compound **31**, replacing the RCM reaction for cross metathesis with acrylamide **32**. Macrocycle **28** (obtained *via* methanolysis of common intermediate **23**) was reacted with acrylamide **32** at a 10 mM concentration to give cross metathesis product **36** in 42% yield. As was the case with the RCM reaction of this compound, the yield was lower than in the quasi[1]rotaxane case. Presumably the phenolic OH's hamper the reaction leading to undesired side products. Cleavage of the 2-hydroxy-4-methoxybenzyl groups was accomplished after stirring in a 3M solution of HCl in CH$_3$OH overnight at 50 ^{o}C to give macrocycle **37** in 66% yield. Also in this case, ^{1}H-NMR analysis showed remarkable resemblances with spiro bicycle **30**, together with significant proton shift with respect to the isomeric interlocked quasi[1]rotaxane **35.**
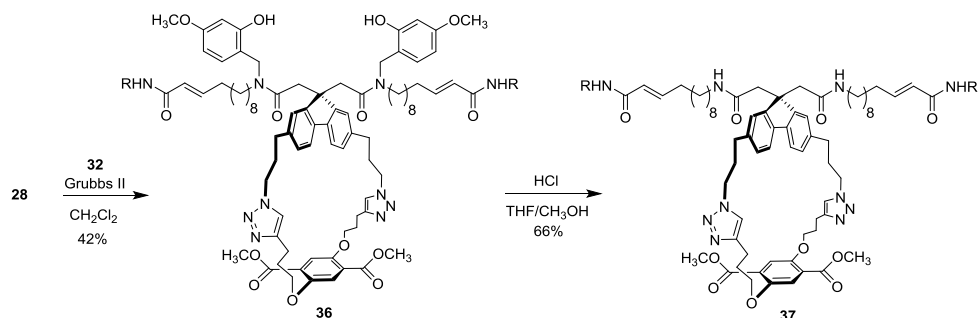
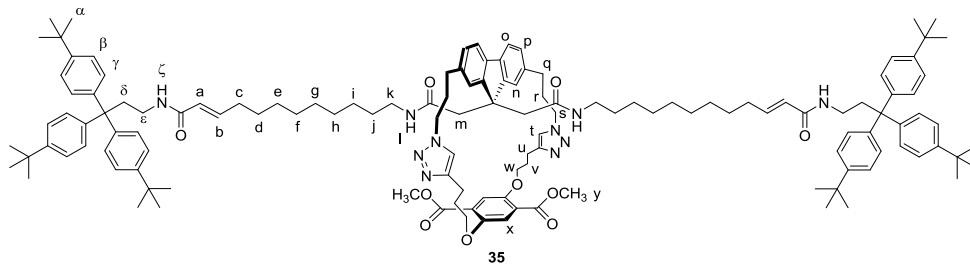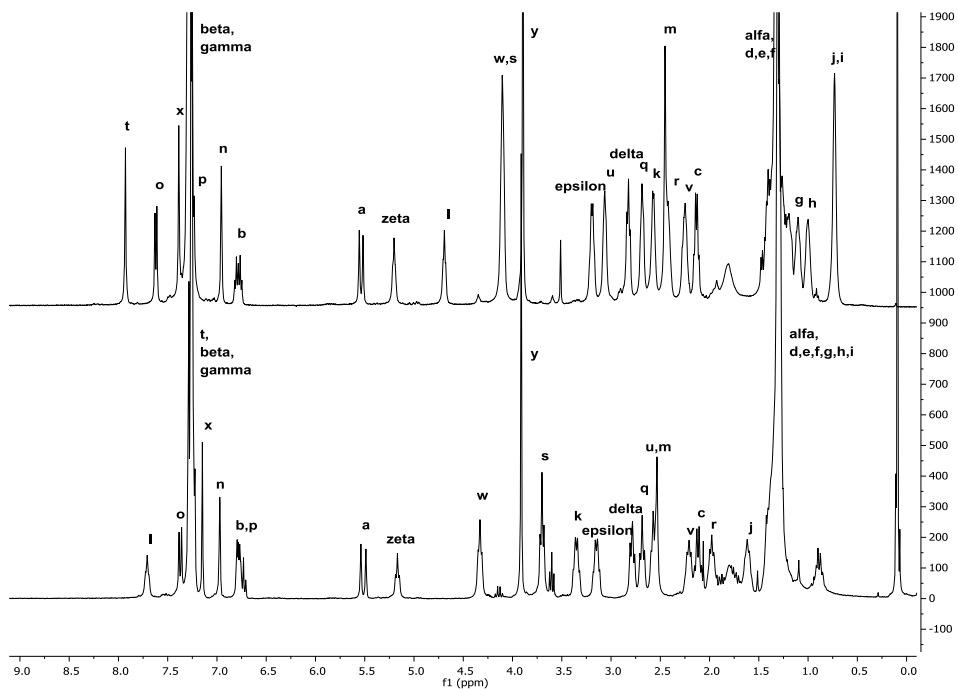Scheme 14: Synthesis of macrocycle **37.** Note: R = CH$_2$-CH$_2$-C(C$_6$H$_4$tBu)$_3$

Figure 9: ^{1}H-NMR spectra of quasi[1]rotaxane **35** (upper) and macrocycle **37** (lower)

Comparison of the ^{1}H-NMR spectra of the quasi[1]rotaxane **35** purified by preparative HPLC and macrocycle **37** again reveal some interesting shifts (see figure 9). Analogous to quasi[1]catenane **26**, quasi[1]rotaxane **35** appears to have a intramolecular H-bond between the carbonyl *O*-atom and the triazole C-H, as both these signals have shifted significantly, and have almost identical shifts compared with the quasi[1]catenane. The nice separation of all the individual methylene protons is striking again, pointing to a relatively rigid and well-defined structure. What is less understood in this case, is also the presence of downfield shifts in the 0.9-0.7 ppm region for the protons of the three methylenes **h,i** and **j** in the aliphatic chain (see figure 9, bottom). These signals, together with the observation that the fluorene core is shifted upfield, suggests that analogous to quasi[1]catenane **26**, the presence of interactions between the fluorene core and the aliphatic chain, despite they cannot form a tightly wrapped ring. Moreover, steric repulsion between the bulky trityl groups would prevent such a ring-like structure.

Miscellaneous reactions

After finding the optimal conditions for the CuAAC reaction, we were interested how the debenzylated analogue **38** would perform in this reaction. It was postulated that this analogue would react in the subsequent RCM reaction to give exclusively the sterically favored spiro bicycle **39**, thereby significantly reducing the amount of steps. Amine **10** was reacted with bis-OSu ester **8** to give bis-amide **38** in 89% yield. Subsequent CuAAC reaction with dimethylester scaffold **18** gave click product **39** in a rather poor 33% yield (but comparable to the CuAAC reaction of the benzylated analogue in scheme 10, B). Also here 1.1 equivalent of the bis-azide had to be used to prevent formation of the bis-scaffold adduct. When click product **39** was subjected to RCM conditions, two products with a m/z of 1081 were observed in the LC-MS traces. As the retention times were already known from previous experiments, both products were identified as spiro bicycle **30** and, most unexpectedly, quasi[1]catenane **26**. Based on the LC-MS traces, **30** and **26** were formed in a ca. 2:1 ratio, respectively. This ratio was confirmed after column purification of the RCM reaction mixture, as **30** was obtained in 38% and **26** in 20% yield. The reason that both products are formed indicates that the energy difference between the two structures is really small. This suggests that CuAAC product **39** already partially adopts the quasi[1]catenane structure **39b** (more specifically a pseudo quasi[1]rotaxane structure). This structure is likely stabilized *via* the aforementioned intramolecular H-bonds and therefore close in energy to the sterically relaxed conformer **39a**.
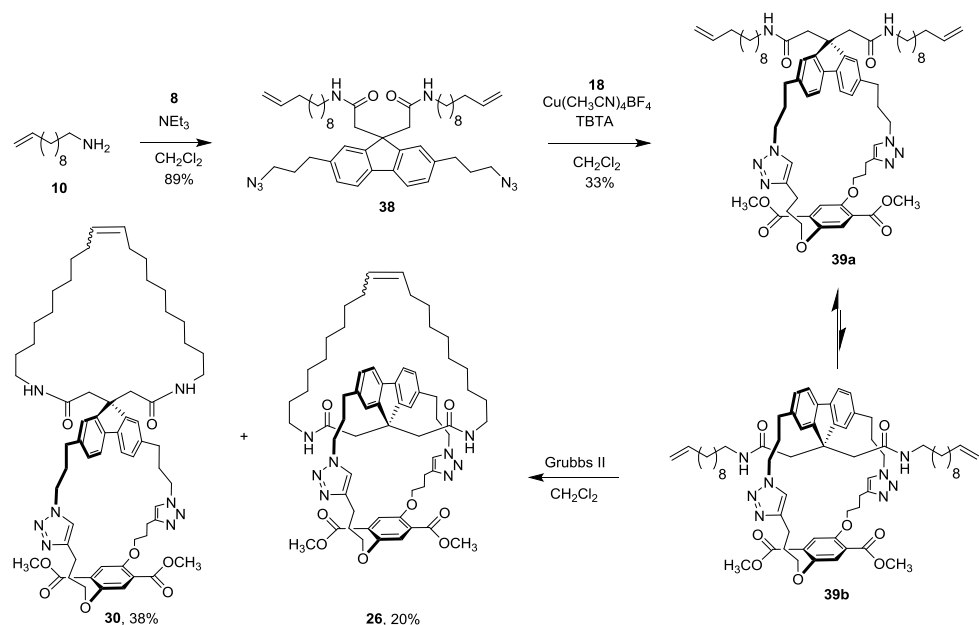
Scheme 15: Macrocyclizations of analogue **39**, yielding both quasi[1]catenane **26** and spiro bicycle **30**

Conclusions

With the covalent template approach (outlined in schemes 1 and 2) it was possible to construct a novel class of interlocked compounds, which were dubbed quasi[1]catenanes and quasi[1]rotaxanes by us. The synthesis of these compounds was achieved *via* a series of macrocyclizations and disconnections. Depending on the sequence of reaction steps, both the interlocked quasi[1] products and non-interlocked analogues could be obtained from a single common intermediate (compound **23**). Fortunately, it was possible to grow crystals of quasi[1]catenane product **27**, thereby unequivocally confirming its interlocked structure *via* X-ray crystallographic analysis. The compounds were analyzed with various NMR techniques to fully assign the structures. It became quickly evident that quasi[1]catenane **27** and non-interlocked spiro bicycle **31** gave very different NMR shifts, showing the unique properties of this new class of diastereomeric compounds. Most noteworthy, quasi[1]catenane **27** possess an intramolecular H-bond between the amide *O*-atom and the triazole C-H proton. Moreover, electrostatic interactions between the fluorene core and the aliphatic chain were observed, which were confirmed by nOe contacts between these protons. Quasi[1]rotaxane **35** exhibits the same behavior, thereby indirectly confirming its interlocked structure. Based on ^{1}H-NMR analysis, the non-interlocked spiro bicycle **31** and macrocycle **37** do not contain the intramolecular H-bonds or the electrostatic interactions.

Experimental section

Unless stated otherwise, reactions were performed without special precautions like drying or N_2/Argon atmosphere. Dried CH_2Cl_2 and CH_3CN were obtained by distilling these solvents with CaH_2 as drying agent. Dried THF and Et_2O were obtained by distillation with sodium. All dried solvents were stored under N_2 atmosphere. Dry DMF on 4Å molecular sieves was obtained from Sigma-Aldrich and stored under N_2 atmosphere. Reagents were purchased with the highest purity (usually >98%) from Sigma Aldrich and Fluorochem and used as received. Grubbs 2nd generation catalyst was purchased from AK Scientific and TBTA was purchased from TCI Europe. Reactions were monitored with thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254). SilaFlash® P60 (particle size 40-63 µm) was used for silica column chromatography. NMR spectra were recorded on Bruker DRX-500, 400 and 300 MHz instruments and calibrated on residual undeuterated solvent signals as internal standard. The ^{1}H-NMR multiplicities were abbreviated as followed: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet. High resolution mass spectra (HRMS) were recorded on a Mass spectra were collected on an AccuTOF GC v 4g, JMS-T100GCV Mass spectrometer (JEOL, Japan). FD/FI probe equipped with FD Emitter, Carbotec or Linden (Germany), FD 10 µm. Current rate 51.2 mA/min over 1.2 min machine using field desorption (FD) as ionization method. Depending on the molecule, either the (M)[+] or (M+H)[+] were observed; often the (M+Na)[+] signal was also observed. Melting points were recorded on a Wagner & Munz Polytherm A melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Alpha FTIR machine. For the purification of quasi-rotaxane **35** a Waters Prep 100 SFC UV directed system was used; Column: Waters Viridis Prep Silica 2-EP, OBD (100x19 mm, 5 µm), Flow: 70 mL/min, Column temp: 35°C; ABPR: 120 bar; Eluent A: CO_2, Eluent B: 20 mM Ammonia in EtOH,Isocratic: 18 % B for 10 min, Injection: Sandwich 100 µL methanol, Collection: Based on PDA TIC.

Synthetic procedures

Compound **2**
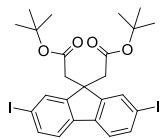
4.18 g 2,7-diiodofluorene **1** (10 mmol) was dissolved in 60 mL dry DMF, under N_2 atmosphere and cooled to 0 °C. After cooling, 880 mg NaH (60% w/w in mineral oil, 22 mmol, 2.2 equiv) was added; the suspension was stirred for 5 minutes and then 3.25 mL tert-butyl bromoacetate (22 mmol, 2.2 equiv) was added dropwise. The reaction was stirred for 1h at 0 °C and overnight at room temperature, and then concentrated *in vacuo*. The residue was partitioned between 100 mL EtOAc and 50 mL 1M HCl. The water layer was extracted with 2 x 50 mL EtOAc and the combined organic layers were washed with 2 x 50 mL H_2O, 50 mL brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was dry-loaded on silica and purified by column chromatography (PE:EtOAc 30:1 → 25:1 → 20:1) to give compound **2** (5.44 g, 8.42 mmol, 84%) as a yellow solid. Melting point: 110-115 °C; ^{1}H-NMR (300 MHz, $CDCl_3$,): δ 7.88 (s, 2H), 7.70 (d, 2H), 7.42 (d, 2H), 2.93 (s, 4H), 1.13 (s, 18H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.80, 150.16, 139.26, 136.98, 133.38, 121.61, 92.90, 80.77, 50.69, 44.09, 27.68; IR (cm^{-1}): 2977, 1717, 1367, 1142

Compound **3**
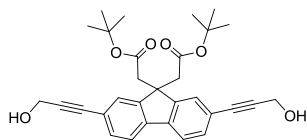
4.35 g **2** (6.73 mmol) and 1.55 mL propargylalcohol (26.93 mmol, 4 equiv) were dissolved in 60 mL dry THF/NEt_3 1:1 and the mixture was degassed with 3 vacuum/N_2 cycles. After degassing, 189 mg $Pd(PPh_3)_2Cl_2$ (0.269 mmol, 0.04 equiv) and 102 mg CuI (0.538 mmol, 0.08 equiv) were added. The reaction was stirred overnight at room temperature and concentrated *in vacuo*. The residue was partitioned between 50 mL EtOAc and 50 mL 1M HCl. The water layer was extracted with 2 x 25 mL EtOAc and the combined organic layers were washed with 25 mL brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EtOAc 5:2 → 2:1 → 1:1) to give **3** (2.88 g, 5.73 mmol, 85%) as a beige solid. Melting point: 175-178 °C (dec.); ^{1}H-NMR (300 MHz, $CDCl_3$,) δ 7.64-7.61 (m, 4H), 7.46 (d, 2H), 4.53 (s, 4H), 2.94 (s, 4H), 2.04 (bs, 2H), 1.03 (s, 18H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.91, 148.79, 140.36, 131.62, 127.47, 121.69, 120.02, 87.88, 86.21, 80.66, 51.77, 50.50, 44.63, 27.55; IR (cm^{-1}): 3504, 2978, 1697, 1468, 1347, 1151

Compound **4**
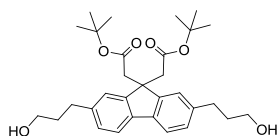
2.98 g **3** (5.92 mmol) was dissolved in 50 mL THF/EtOH 1:1 and 15 mL of a slurry of Raney nickel in H_2O was added. The mixture was degassed by 5 cycles of vacuum/H_2 and the mixture was stirred overnight at 60 °C under H_2 atmosphere. After completion, the mixture was purged with N_2 gas for 15 minutes, and then filtered over Celite. The filter cake was washed with 2 x 10 mL EtOAc and the combined organic layers were concentrated *in vacuo*. The remaining water layer was partitioned with 20 mL EtOAc and separated. The water layer was extracted with 2 x 10 mL EtOAc and the combined organic layers were washed with 20 mL brine, dried over $MgSO_4$ and concentrated *in vacuo* to give **4** (2.91 g, 5.69 mmol, 96%) as a viscous yellow oil and was used without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.55 (d, 2H), 7.35 (s, 2H), 7.16 (d, 2H), 3.66 (t, 4H), 2.93 (s, 4H), 2.78 (t, 4H), 2.16 (bs, 2H), 1.94 (quint, 4H), 1.01 (s, 18H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.62, 148.52, 140.68, 138.57, 127.89, 124.27, 119.37, 80.21, 61.84, 50.34, 44.97, 34.43, 32.35, 27.51; IR (cm^{-1}): 3394, 2977, 2932, 1718, 1471, 1367, 1155

Compound **5**
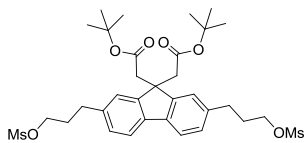
2.77 g **4** (5.43 mmol) and 2.50 mL Et$_3$N (17.92 mmol, 3.3 equiv) were dissolved in 25 mL dry THF under N$_2$ atmopshere, cooled to 0 ^{o}C and 1.27 mL methanesulfonylchloride (16.29 mmol, 3 equiv) was added dropwise. The icebath was removed and the reaction was stirred overnight at room temperature, and was subsequently quenched with 5 mL H$_2$O and stirred for 15 min. The mixture was diluted with 50 mL Et$_2$O and 50 mL H$_2$O. The water layer was extracted with 25 mL Et$_2$O and the combined organic layers were washed with 25 mL 1M HCl, 25 mL brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc 4:2 → 3:2 → 2:2) to give **5** (3.04 g, 4.56 mmol, 84%) as a yellow solid. Melting point: 96-100 ^{o}C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.57 (d, 2H), 7.34 (s, 2H), 7.16 (d, 2H), 4.25 (t, 4H), 3.03 (s, 6H), 2.93 (s, 4H), 2.82 (t, 4H), 2.10 (quint , 4H), 0.99 (s, 18H); ^{13}C-NMR (75 MHz, CDCl$_3$,) δ 169.18, 148.77, 139.16, 138.83, 127.95, 124.14, 119.60, 80.01, 69.22, 50.38, 44.86, 37.26, 31.72, 30.98, 27.43; IR (cm^{-1}): 2974, 2932, 1714, 1353, 1171

Compound **6**
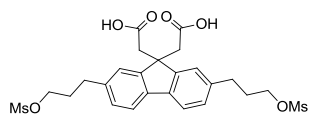
3.21 g **5** (4.81 mmol) was dissolved in 30 mL HCO$_2$H and stirred overnight at room temperature. The mixture was concentrated *in vacuo* and dried thoroughly on a high vacuum pump to give **6** (2.66 g 4.80 mmol, quant) as a thick yellow oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.62 (d, 2H), 7.37 (s, 2H), 7.20 (d, 2H), 4.21 (t, 4H), 3.08 (s, 4H), 3.00 (s, 6H), 2.81 (t, 4H), 2.09 (quint, 4H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 175.94, 148.63, 139.64, 138.01, 128.60, 124.03, 120.24, 69.08, 49.03, 41.46, 37.36, 31.61, 30.67; IR (cm^{-1}): 3028, 2940, 1708, 1346, 1170

Compound **7**
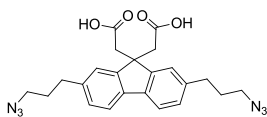
2.66 g **6** (4.79 mmol) and 1.24 g NaN$_3$ (19.18 mmol, 4 equiv) were dissolved in 20 mL DMF and stirred overnight at 70 ^{o}C. The mixture was cooled to room temperature and diluted with 40 mL Et$_2$O and 40 mL 1M HCl. The water layer was extracted with 20 mL Et$_2$O and the combined organic layers were washed with 30 mL brine, dried over MgSO$_4$ and concentrated *in vacuo.* The product was dried further on a high vacuum pump to give **7** (1.94 g, 4.32 mmol, 90%) as a yellow solid. Melting point: 101-104 ^{o}C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.62 (d, 2H), 7.39 (s, 2H), 7.20 (d, 2H), 3.27 (t, 4H), 3.10 (s, 4H), 2.77 (t, 4H), 1.92 (quint, 4H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 176.79, 148.82, 140.31, 137.88, 128.56, 124.08, 120.11, 50.57, 48.89, 41.23, 33.02, 30.62; IR (cm^{-1}): 2933, 2858, 2095, 1695, 1261, 1196

Compound **8**
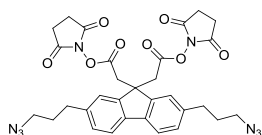
1.93 g **7** (4.30 mmol) was dissolved in 40 mL dry CH$_2$Cl$_2$ under N$_2$ atmosphere and cooled to 0 ^{o}C, after which 3.47 mL pyridine (43 mmol, 10 equiv) and 2.03 g *N*-hydroxysuccinimide (17.63 mmol, 4.1 equiv) were added, followed by dropwise addition of 2.39 mL TFAA (17.20 mmol, 4 equiv). The mixture was stirred overnight at room temperature and quenched by addition of 20 mL 1M HCl and stirred for 15 min. The water layer was extracted with 2 x 10 mL CH$_2$Cl$_2$ and the combined organic layers were washed with 20 mL 1M HCl and 2 x 20 mL NaHCO$_3$, dried over MgSO$_4$ and concentrated in *vacuo.* The crude product was purified by column chromatography (PE/EtOAc 3:2 → 2:3 → 2:4). The product was dried on a high vacuum

pump to give **8** (2.47 g, 3.85 mmol, 90%) as a colorless foam. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.65 (d, 2H), 7.50 (s, 2H), 7.25 (d, 2H), 3.37 (s, 4H), 3.33 (t, 4H), 2.82-2.78 (m, 12H), 1.97 (quint, 4H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 169.00, 165.92, 147.13, 140.84, 137.72, 129.09, 124.17, 120.11, 50.56, 48.59, 38.30, 32.87, 30.39, 25.60; IR (cm^{-1}): 2944, 2865, 2094, 1814, 1784, 1734, 1162, 1061

Compound **9**
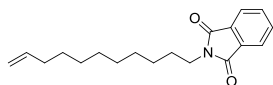
6.01 mL 10-undecylalcohol (30 mmol), 7.87 g PPh$_3$ (30 mmol, 1 equiv) and 4.41 g phthalimide (30 mmol, 1 equiv) were dissolved in 150 mL dry THF under N$_2$ atmosphere and cooled to 0 ^{o}C, followed by dropwise addition of 5.91 mL DIAD (30 mmol, 1 equiv). The reaction was stirred overnight at room temperature and the mixture was concentrated *in vacuo* and loaded on silica. The dry-loaded product was purified by column chromatography (PE/EtOAc 30:1 → 25:1) to give a slightly yellow oil, which slowly crystallized to give **9** (7.38 g, 24.64 mmol, 82%) as a waxy solid. Melting point: 39-40 ^{o}C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.82 (m, 2H), 7.71 (m, 2H), 5.81 (m, 1H), 4.95 (dd, 2H), 3.67 (t, 2H), 2.02 (q, 2H), 1.67 (quint, 2H), 1.33-1.27 (m, 12H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 168.52, 139.27, 133.89. 132.26, 123.21, 114.19, 38.14, 33.87, 29.49, 29.45, 29.15, 28.97, 28.67, 26.93; IR (cm^{-1}): 2916, 2848, 1693, 1398, 1052

Compound **10**

7.31 g **9** (24.42 mmol) was dissolved in 100 mL THF/EtOH 1:1 and 2.57 mL methylhydrazine (48.85 mmol, 2 equiv) was added. The mixture was stirred overnight at 70 ^{o}C and the mixture was concentrated *in vacuo* and to the residue was added 100 mL Et$_2$O. The precipitate was filtered off and washed with Et$_2$O. The combined organic layers were concentrated *in vacuo* and the crude product was purified by Kugelrohr distillation (0.02 mbar, 90-110 ^{o}C) to give **10** (3.66 g, 21.61 mmol, 88%) as a clear colorless oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 5.78 (m, 1H), 4.93 (dd, 2H), 2.65 (t, 2H), 2.02 (q, 2H), 1.40-1.26 (m, 16H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 139.23, 114.14, 42.31, 33.92, 33.85, 29.62, 29.54, 29.49, 29.17, 28.97, 26.93; IR (cm^{-1}): 3333, 2920, 2852, 1568, 1487

Compound **11**
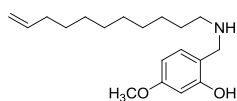
1.02 g **10** (6.00 mmol) and 913 mg 2-hydroxy-4-methoxybenzaldehyde (6.00 mmol, 1 equiv) were dissolved in 30 mL absolute CH$_3$OH and stirred overnight at room temperature. The mixture was cooled to 0 ^{o}C and 454 mg NaBH$_4$ (12 mmol, 2 equiv) was added in one portion. The reaction was stirred for 1h at 0 ^{o}C, 1h at room temperature and then concentrated *in vacuo*. The residue was partitioned between 40 mL EtOAc and 20 mL NaHCO$_3$. The water layer was extracted with 2 x 10 mL EtOAc and the combined organic layers were washed with 20 mL brine, dried over MgSO$_4$ and concentrated *in vacuo* to give **11** (1.77 g, 5.78 mmol, 96%) as a faint yellow oil, which was used without further purification. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 6.88 (d, 1H), 6.44 (s, 1H), 6.35 (s, 1H), 5.82 (m, 1H), 4.97 (dd, 2H), 3.95 (s, 2H), 3.78 (s, 3H), 2.68 (t, 2H), 2.06 (q, 2H), 1.54 (quint, 2H), 1.39-1.30 (m, 12H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 160.46, 159.62, 139.34, 128.78, 115.05, 114.25, 104.89, 102.02, 55.34, 52.28, 48.73, 33.92, 29.68, 29.60, 29.53, 29.21, 29.03, 27.25; IR (cm^{-1}): 2923, 2852, 1622, 1590, 1510, 1456, 1157

Compound 12
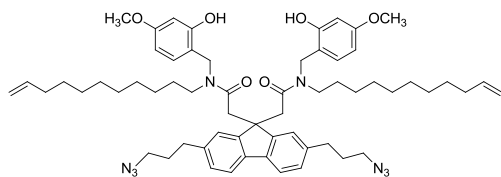
1.80 g **8** (2.80 mmol), 1.76 g **11** (5.75 mmol, 2.05 equiv) and 0.93 mL Et₃N (6.71 mmol, 2.4 equiv) were dissolved in 17 mL dry CH_2Cl_2 and the mixture was stirred for 3 days at room temperature. The reaction mixture was washed with 10 mL 1M HCl and the water layer was extracted with 10 mL CH_2Cl_2. The combined organic layers were washed with 10 mL NaHCO₃, dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc 6:1 → 5:1) to give a colorless oil, which slowly crystallized to give **12** (2.10 g, 2.05 mmol, 73%) as a colorless waxy solid. Melting point: 81-82 °C; ¹H-NMR (300 MHz, CDCl₃) δ 10.15 (s, 2H), 7.60 (d, 2H), 7.28 (s, 2H), 7.13 (d, 2H), 6.96 (d, 2H), 6.54 (s, 2H), 6.38 (d, 2H), 5.83 (m, 2H), 4.99 (dd, 4H), 4.39 (bs, 4H), 3.82 (s, 6H), 3.18 (m, 8H), 2.90 (t, 4H), 2.43 (t, 4H), 2.08 (q, 4H), 1.73 (quint, 4H), 1.46-1.12 (m, 30H); ¹³C-NMR (75 MHz, CDCl₃) δ 173.56, 161.50, 157.82, 150.09, 140.53, 139.22, 137.30, 132.29, 128.11, 124.23, 119.87, 114.95, 114.24, 105.19, 102.66, 55.31, 50.88, 50.67, 47.51, 46.23, 37.80, 33.85, 32.82, 30.53, 29.43, 29.12, 28.95, 27.77, 26.69; IR (cm⁻¹): 2925, 2854, 2094, 1595, 1466, 1158

Compound 13
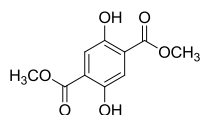
5.70 g dimethyl-2,5-dioxocyclohexane-1,4-dicarboxylate (25 mmol) was suspended in 25 mL AcOH and heated to 80 °C and 3.41 g *N*-chlorosuccinimide (25.5 mmol, 1.02 equiv) was added portionwise over 30 minutes. The reaction was stirred at 80 °C for 90 minutes and was then cooled to room temperature and diluted with 25 mL H_2O. The solid was filtered and washed with 2 x 25 mL H_2O, 2 x 5 mL CH₃OH and dried on air and vacuum to give **13** (5.43 g, 24.02 mmol, 96%) as a yellow powder. Melting point: 173-175 °C; ¹H-NMR (300 MHz, CDCl₃) δ 10.05 (s, 2H), 7.45 (s, 2H), 3.97 (s, 6H); ¹³C-NMR (75 MHz, CDCl₃) δ 169.57, 152.99, 118.40, 117.84, 52.88; IR (cm⁻¹): 3234, 2957, 1672, 1440, 1328, 1193, 1172

Compound 14
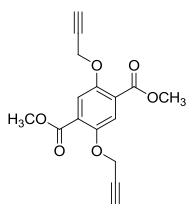
1.13 g **13** (5.00 mmol), 1.30 mL propargylbromide (80% w/w in toluene, 12 mmol, 2.4 equiv) and 1.66 g K₂CO₃ (12 mmol, 2.4 equiv) were suspended in 20 mL dry CH₃CN and the mixture was heated overnight at 80 °C. The organic layer was concentrated *in vacuo* and the residue was partitioned between 50 mL CH_2Cl_2 and 50 mL H_2O. The water layer was extracted with 2 x 20 mL CH_2Cl_2 and the combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product was crystallized from ca. 35 mL EtOH to give **14** (1.30 g, 4. 31 mmol, 86%) as a beige solid. Melting point: 130-132 °C; ¹H-NMR (300 MHz, CDCl₃) δ 7.58 (s, 2H), 4.78 (d, 4H), 3.93 (s, 6H), 2.57 (t, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 165.57, 151.17, 125.37, 118.65, 77.99, 76.51, 58.04, 52.66; IR (cm⁻¹): 3272, 2955, 2120, 1695, 1408, 1200, 1185

Compound 14 acid
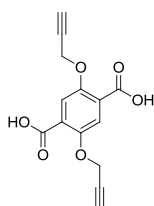
604 mg **14** (2.00 mmol) was dissolved in 45 mL THF/H₂O/CH₃OH 4:4:1 and 449 mg KOH (8.00 mmol, 4 equiv) was added. The reaction was stirred overnight at room temperature and cooled to 0 °C. The reaction was acidified with 4 mL 37% HCl and stirred for 20 minutes, after which the solid was filtered. The solid was washed

with H_2O and a small amount of cold CH_3OH and dried on air and subsequently on high vacuum to give **14 acid** (489 mg, 1.78 mmol, 89%) as a slightly yellow powder. Melting point: 238-242 ^oC (dec); ^{1}H-NMR (300 MHz, CD_3OD) δ 7.66 (s, 2H), 4.85 (d, 4H), 3.03 (t, 2H); ^{13}C-NMR (75 MHz, CD_3OD) δ 166.49, 149.59, 125.77, 116.68, 79.06, 78.79, 56.98 ; IR (cm^{-1}): 3262, 2128, 1682, 1574, 1511, 1456, 1208

Compound **15**

482 mg **14 acid** (1.76 mmol), 733 mg 4-nitrophenol (5.28 mmol, 3 equiv), 1.83 mL DIPEA (10.56 mmol, 6 equiv) and 2.00 g HBTU (5.28 mmol, 3 equiv) were dissolved in 35 mL dry THF and stirred overnight at room temperature. The precipitate that had formed was filtered, and washed on the filter with 10 mL THF, 10 mL $NaHCO_3$, 10 mL H_2O and 5 mL cold CH_3OH. The powder was air-dried and subsequently dried on high vacuum to give **15** (845 mg, 1.63 mmol, 93%) as a white powder. Due to the insolubility of the product, no spectroscopic data were acquired.

Compound **17**

1.86 mL 4-pentynol (20.0 mmol) and 3.33 mL Et_3N (24.0 mmol, 1.2 equiv) were dissolved in 40 mL dry THF and cooled to 0 ^oC and 1.70 mL methanesulfonyl chloride (22.0 mmol, 1.1 equiv) was added dropwise. The icebath was removed and the reaction was stirred overnight at room temperature and was then quenched with 20 mL H_2O and stirred for 15 min. The mixture was diluted with 40 mL Et_2O and 20 mL 1M HCl and the water layer was extracted with 2 x 20 mL Et_2O. The combined organic layers were washed with 40 mL brine, dried over $MgSO_4$ and concentrated *in vacuo* to give **17** (3.11 g, 19.18 mmol, 96%) as a slightly yellow oil, which was used without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.37 (t, 2H), 3.05 (s, 3H), 2.38 (dt, 2H), 2.03 (t, 1H), 1.98 (quint, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 82.21, 69.92, 68.38, 37.37, 27.87, 14.79; IR (cm^{-1}): 3287, 3029, 2940, 1346, 1331, 1168

Compound **18**

2.93 g **17** (18.04 mmol, 2.4 equiv), 1.70 g **13** (7.52 mmol, 1.0 equiv), 2.49 g K_2CO_3 (18.04 mmol, 2.4 equiv) and 124 mg KI (0.75 mmol, 0.1 equiv) were dissolved in 50 mL dry DMF and stirred overnight at 80 ^oC. The mixture concentrated *in vacuo* and the residue was taken in EtOAc and filtered. The filter cake was washed with EtOAc and the combined organic layers were washed with 2 x 20 mL H_2O and 20 mL brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc 4:1) to give **18** (2.11 g, 5.89 mmol, 78%) as a slightly yellow solid. Melting point: 89-93 ^oC; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 2H), 4.14 (t, 4H), 3.92 (s, 6H), 2.47 (dt, 4H), 2.06 (quint, 4H), 1.98 (t, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.15, 151.92, 124.59, 117.04, 83.57, 69.04, 68.16, 52.46, 28.33, 15.18; IR (cm^{-1}): 3299, 2884, 2116, 1725, 1504, 1408, 1201

Compound **18 acid**

1.44 g **18** (4.02 mmol) was dissolved in 30 mL THF/CH$_3$OH/H$_2$O 2:1:1 and 901 mg KOH (15.08 mmol, 4 equiv) was added. The mixture was stirred overnight at room temperature and was acidified with 3 mL 37% HCl and stirred for 15 minutes. The mixture was diluted with 20 mL H$_2$O and 20 mL EtOAc. The water layer was extracted with 3 x 20 mL EtOAc and the combined organic layers were washed with 20 mL brine, dried over MgSO$_4$ and concentrated *in vacuo* to give **18 acid** (1.30 g, 3.94 mmol, 98%) as a faint yellow solid. Melting point: 175-178 °C; Yield: ^{1}H-NMR (300 MHz, CD$_3$OD) δ 7.48 (s, 2H), 4.17 (t, 4H), 2.45 (dt, 4H), 2.25 (t, 2H), 2.02 (quint, 4H); ^{13}C-NMR (75 MHz, CD$_3$OD) δ 168.75, 152.91, 126.30, 117.60, 84.14, 70.04, 69.34, 29.42, 15.72; IR (cm^{-1}): 3267, 2938, 2875, 1673, 1505, 1217

Compound **20**
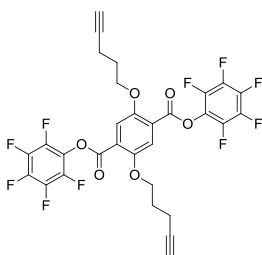
1.30 g **18 acid** (3.94 mmol), 2.17 g pentafluorophenol (11.82 mmol, 3 equiv), 4.11 mL DIPEA (23.64 mmol, 6 equiv) and 4.48 g HBTU (11.82 mmol, 3 equiv) were dissolved in 80 mL dry THF and stirred overnight at room temperature. The mixture was concentrated *in vacuo* and dry-loaded on silica and purified by column chromatography (PE/EtOAc 10:1 → 8:1 → 6:1) to give **20** (2.07 g, 3.13 mmol, 79%) as an off-white solid. Melting point: 113-115 °C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.67 (s, 2H), 4.26 (t, 4H), 2.46 (dt, 4H), 2.08 (quint, 4H), 1.98 (t, 2H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 160.92, 152.90, 143.20, 139.84, 138.34, 136.50, 122.35, 117.31, 83.21, 69.24, 68.17, 28.13, 15.08; IR (cm^{-1}): 3316, 2943, 1755, 1519, 1416, 1390, 1230, 1201

Compound **21**
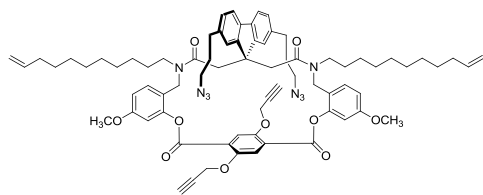
26 mg **12** (0.025 mmol), 15 mg **15** (0.030 mmol, 1.2 equiv), 81 mg Cs$_2$CO$_3$ (0.25 mmol, 10 equiv) and 50 mg 4A MS were dissolved in 12.5 mL dry CH$_3$CN and the reaction was stirred at 60 °C under N$_2$ atmosphere for 3h hours. The reaction mixture was concentrated *in vacuo*, dry-loaded on silica and purified by column chromatography (PE/EtOAc 4:1 → 3:1 → 1:1) to give **21** (15 mg, 0.012 mmol, 48%) as a colorless film. ^{1}H-NMR spectrum: complex. LC-MS analysis: calcd for C$_{75}$H$_{89}$N$_8$O$_{10}$ [(M+H)$^+$]: 1261.67, found 1261.6

Compound **22**
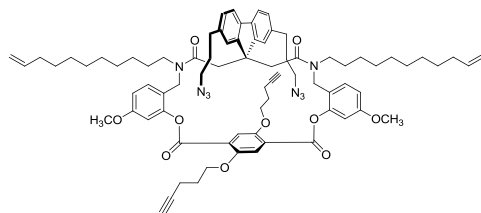
1.94 g **5** (1.89 mmol), 1.38 g **6a** (2.08 mmol, 1.1 equiv), 2.45 g Cs$_2$CO$_3$ (7.58 mmol, 4 equiv) and 1.00 g 4Å MS were stirred in 750 mL dry CH$_3$CN overnight at 60 °C under N$_2$ atmosphere. The reaction mixture was filtered through a plug of Celite, concentrated, dry-loaded on silica and purified by column chromatography (PE:EtOAc 4:1 → 3:1) to give **22** (1.72 g, 1.31 mmol, 69%) as a thick colorless oil. ^{1}H-NMR spectrum: complex; IR (cm^{-1}): 2924, 2853, 2093, 1740, 1637, 1618, 1504, 1410, 1183, 1108; HRMS (FD) calcd for C$_{79}$H$_{96}$N$_8$O$_{10}$ [M$^+$]: 1316.7249, found: 1316.7239

Compound 23
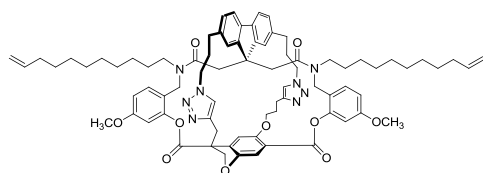
420 mg **22** (0.319 mmol) and 42 mg TBTA (0.080 mmol, 0.25 equiv) were dissolved in 65 mL dry CH_2Cl_2 and degassed with 5 vacuum/N_2 cycles, after which 25 mg Cu(CH_3CN)_4BF_4 (0.080 mmol, 0.25 equiv) was added and the mixture was stirred overnight at reflux under N_2 atmosphere.

The reaction mixture was concentrated in *vacuo* and dry-loaded on silica and purified by column chromatograph (PE:EtOAc 1:1 → 1:2 → 0:1) to give **22** (333 mg, 0.253 mmol, 79%) as a colorless foam. Melting point: 113-119 °C; [^1]H-NMR spectrum: complex; IR (cm[^-1]): 2925, 2853, 1746, 1640, 1617, 1504, 1411, 1187, 1100; HRMS (FD) calcd for $C_{79}H_{96}N_8O_{10}$ [M[+]]: 1316.7249, found: 1316.7243

Compound 24
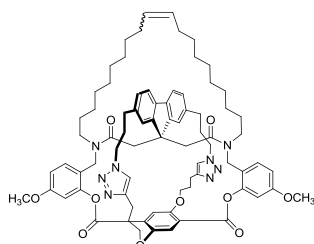
79 mg **23** (0.060 mmol) was dissolved in 60 mL dry CH_2Cl_2 and degassed with 5 vacuum / N_2 cycles. To the solution was added 10 mg Grubbs II catalyst (0.012 mmol, 0.2 equiv) and the mixture was stirred overnight at 40 °C. The mixture was concentrated in *vacuo*, dry-loaded on silica and purified by column chromatography (PE:EtOAc 1:2 → 1:3 → 1:4) to give **24** (55 mg, 0.0427 mmol, 71%) as a beige solid. [^1]H-NMR spectrum: complex; IR (cm[^-1]): 2924, 2853, 1749, 1618, 1505, 1411, 1187, 1111; HRMS (FD) calcd for $C_{77}H_{92}N_8O_{10}$ [M[+]]: 1288.6936, found: 1288.6911

Compound 25
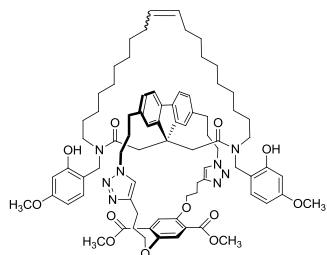
55 mg **24** (0.0427 mmol) was dissolved in 2 mL dry THF/CH_3OH 1:1 and 12 mg anhydrous NaOCH_3 (0.214 mmol, 5 equiv) was added and the mixture was stirred at room temperature for 1h. The reaction was quenched by addition of 0.5 mL AcOH and the reaction was diluted with 15 mL EtOAc and 10 mL saturated NaHCO_3. The water layer was extracted with 2 x 5 mL EtOAc and the combined organic layers were dried over MgSO_4 and concentrated in *vacuo* to give **25** (58 mg , 0.0427 mmol, quant) as a slight yellow film. [^1]H-NMR spectrum: complex; IR (cm[^-1]): 2923, 2853, 1726, 1619, 1599, 1436, 1203; HRMS (FD) calcd for $C_{79}H_{101}N_8O_{12}$ [(M+H)[+]]: 1353.7539, found: 1353.7597

Compound 26
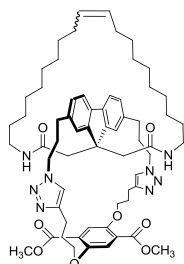
58 mg **25** (0.0427 mmol) was dissolved in 5 mL TFA/CH_2Cl_2 9:1 and 0.136 mL Et_3SiH (0.854 mmol, 20 equiv) was added. The mixture was stirred overnight at room temperature and concentrated in *vacuo*. The residue was dissolved in 10 mL CH_2Cl_2 and 0.5 mL NEt_3 was added and stirred for 5 minutes. The organic layers was washed with 10 mL 1M HCl, 10 mL NaHCO_3, dried over MgSO_4 and concentrated in *vacuo*. The crude product was dry-loaded on silica and purified by column chromatography (CH_2Cl_2/ CH_3OH 96:4 → 94:6) to give **26** (43 mg, 0.0397 mmol, 93%) as a colorless foam. [^1]H-NMR (300 MHz, CDCl_3) δ 7.98 (s, 2H), 7.57 (d, 2H), 7.35 (s, 2H), 7.21 (d, 2H), 6.95 (s, 2H), 5.52 (m, 2H), 4.49 (t, 2H), 4.07 (m, 8H), 3.85 (s, 6H), 3.05 (t, 4H), 2.67 (t, 4H), 2.52 (q, 4H), 2.44 (s, 4H), 2.41 (m, 4H), 2.21

(quint, 4H), 1.43 (quint, 4H), 1.35 (quint, 4H), 1.22 (sext, 4H), 1.05 (quint, 4H), 0.92 (sext, 4H), 0.66-0.42 (m, 8H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 167.66, 166.18, 151.40, 146.77, 146.07, 139.61, 139.17, 130.52, 128.52, 124.59, 124.38, 123.55, 120.51, 115.81, 66.89, 52.34, 50.87, 47.12, 38.70, 32.58, 31.57, 30.41, 29.65, 29.55, 29.36, 29.23, 29.10, 28.97, 28.52, 26.28, 20.96; IR (cm^{-1}): 3325, 2925, 2853, 1726, 1659, 1436, 1205; HRMS (FD) calcd for C$_{63}$H$_{84}$N$_8$O$_8$ [M$^+$]: 1080.6412, found: 1080.6432

Compound **27**
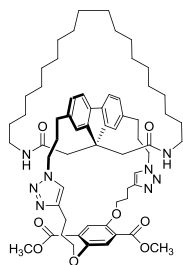
40 mg **26** (0.037 mmol) was dissolved in 3 mL THF/EtOH 1:1 and 20 mg Pd/C (10 % w/w) was added. Through the solution was bubbled H$_2$ gas (balloon) for 5 minutes and the reaction was stirred overnight under H$_2$ atmosphere at 50 ^{o}C. The mixture was filtered through a plug of Celite and concentrated in *vacuo*. The crude product was dry-loaded on silica and purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 96:4 → 94:6) to give **27** (31 mg, 0.029 mmol, 77%) as a colorless solid.

A crystal was grown in the following way: The purified product was dissolved in ca. 0.5 mL EtOAc and transferred to a test tube, which was put in a closed container filled with pentane, allowing for diffusion of the solvents. After standing overnight, small crystals had formed on the walls of the test tube, which were suitable for the X-ray analysis.

Melting point: 164-166 ^{o}C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.98 (s, 2H), 7.59 (d, 2H), 7.36 (s, 2H), 7.23 (d, 2H), 6.96 (s, 2H), 4.50 (t, 2H), 4.09 (m, 8H), 3.86 (s, 6H), 3.06 (t, 4H), 2.68 (t, 4H), 2.53 (q, 4H), 2.44-2.38 (m, 8H), 2.22 (quint, 4H), 1.44-1.34 (m, 16H), 1.22 (quint, 4H), 1.08 (quint, 4H), 0.95 (quint, 4H), 0.67-0.48 (m, 8H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 167.69, 166.32, 151.50, 146.91, 146.20, 139.77, 139.30, 128.60, 124.71, 124.48, 123.67, 120.56, 115.90, 67.00, 52.47, 51.03, 47.26, 47.14, 38.78, 31.69, 30.53, 29.46, 29.44, 29.31, 29.16, 29.04, 28.93, 28.81, 28.60, 26.31, 21.06; IR (cm^{-1}): 3413, 2925, 2853, 1727, 1660, 1436, 1207; HRMS (FD) calcd for C$_{63}$H$_{86}$N$_8$O$_8$ [M$^+$]: 1082.6569, found: 1082.6533

Compound **28**
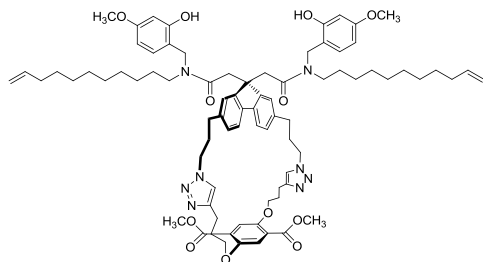
Method 1: 129 mg **23** (0.098 mmol) was dissolved in 4 mL dry THF/CH$_3$OH 1:1 and 105 mg NaOCH$_3$ (1.96 mmol, 20 equiv) was added. The reaction was stirred for at room temperature for 2h and was quenched with 0.2 mL AcOH. The mixture was diluted with 15 mL EtOAc and 10 mL H$_2$O. The water layer was extracted with 2 x 5 mL EtOAc and the combined organic layers were washed with 10 mL saturated NaCl, dried over MgSO$_4$ and concentrated in *vacuo* to give **28** (138 mg, 0.098 mmol, quant) as a colorless film.

Method 2: 112 mg **12** (0.110 mmol, 1.1 equiv), 36 mg **18** (0.100 mmol) and 11 mg TBTA (0.020 mmol, 0.2 equiv) were dissolved in 100 mL dry CH$_2$Cl$_2$ and the mixture was degassed with 5 vacuum/N$_2$ cycles. After degassing, 6 mg Cu(CH$_3$CN)$_4$BF$_4$ (0.02 mmol, 0.2 equiv) was added and the mixture was stirred overnight at reflux under N$_2$ atmosphere. The reaction was concentrated *in vacuo* and dry-loaded on silica and purified by column chromatography (PE:EtOAc 1:2 → 1:3) to give **28** (58 mg, 0.042 mmol, 42%) as a colorless film. ^{1}H-NMR spectrum: complex; IR (cm^{-1}): 2926, 2854, 1726, 1600, 1505, 1437, 1202; HRMS (FD) calcd for C$_{81}$H$_{104}$N$_8$O$_{12}$ [(M+H)$^+$]: 1381.8, found: 1381.5

Compound 29
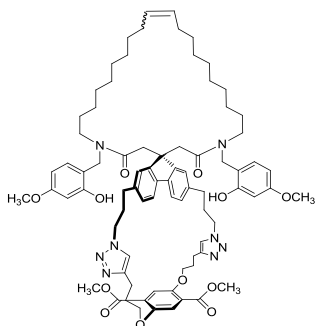
151 mg **28** (0.109 mmol) was dissolved in 110 mL dry CH_2Cl_2 and was degassed with 5 vacuum/N_2 cycles. After degassing, 18 mg Grubbs II catalyst (0.021 mmol, 0.2 equiv) was added and the mixture was stirred overnight at 35 °C. The mixture concentrated *in vacuo* and the crude product was dry-loaded on silica and purified by column chromatography (PE/EtOAc 1:3 → 1:5 → 1:7 → 0:1) to give **29** (62 mg, 0.0458 mmol, 42%) as a slight brown film. ^{1}H-NMR spectrum: complex; IR (cm^{-1}): 2923, 2852, 1728, 1599, 1435, 1201; HRMS (FD) calcd for $C_{79}H_{101}N_8O_{12}$ [(M+H)$^+$]: 1353.7539; found: 1353.7556

Compound 30
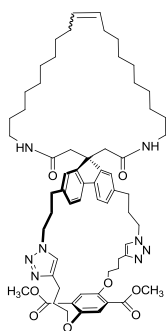
62 mg **29** (0.0458 mmol) was dissolved in 1 mL dry CH_3OH and added dropwise to a 5 mL 3M HCl in CH_3OH solution (made *via* addition of acetyl chloride to CH_3OH at 0 °C). The reaction was stirred overnight at 50 °C and was concentrated in *vacuo*. The residue was partitioned between 20 mL CH_2Cl_2 and 15 mL $NaHCO_3$. The water layer was extracted with 2 x 5 mL CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was dry-loaded on silica and purified by column chromatography (EtOAc/CH_3OH 97:3 → 96:4) to give **30** (32 mg, 0.0296 mmol, 65%) as a colorless film. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.84 (t, 2H), 7.39 (d, 2H), 7.22 (s, 2H), 7, 15 (s, 2H), 6.96 (s, 2H), 6.78 (d, 2H), 5.37 (s, 2H), 4.35 (t, 4H), 3.93 (s, 6H), 3.71 (t, 4H), 3.40 (q, 4H), 2.69 (t, 4H), 2.57 (t, 4H), 2.53 (s, 4H), 2.20 (quint, 4H), 2.07-1.94 (m, 8H), 1.91-1.81 (m, 8H), 1.63 (quint, 4H), 1.48-1.25 (m, 32H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 171.26, 166.07, 151.62, 149.46, 139.17, 136.91, 130.75, 127.91, 124.40, 124.13, 119.54, 116.26, 68.19, 52.45, 50.25, 50.10, 42.84, 39.77, 33.84, 32.29, 31.19, 29.65, 29.53, 29.43, 29.04, 28.35, 27.94, 27.27, 27.09, 26.93, 26.41, 26.24, 21.50; IR (cm^{-1}): 3256, 2925, 2853, 1727, 1637, 1436, 1206; HRMS (FD) calcd for $C_{63}H_{84}N_8O_8$ [M$^+$]: 1080.6412; found: 1080.6391

Compound 31
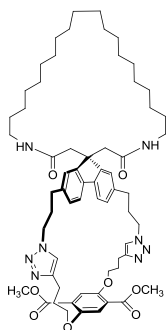
19 mg **30** (0.0176 mmol) was dissolved in 2 mL THF/EtOH 1:1 and 8 mg Pd/C (10% w/w) was added. H_2 gas (balloon) was bubbled through the solution for 5 minutes, and the reaction was stirred overnight at 50 °C under H_2 atmosphere. The solution was filtered through a plug of Celite (washed with EtOH) and the combined organic layers were concentrated in *vacuo*. The crude product was dry-loaded on silica and purified by column chromatography (EtOAc/CH_3OH 96:4) to give **31** (13 mg, 0.012 mmol, 68%) as a colorless film. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.79 (t, 2H), 7.39 (d, 2H), 7.22 (s, 2H), 7.15 (s, 2H), 6.96 (s, 2H), 6.77 (d, 2H), 4.35 (t, 4H), 3.93 (s, 6H), 3.70 (t, 4H), 3.39 (q, 4H), 2.68 (t, 4H), 2.57 (t, 4H), 2.53 (s, 4H), 2.26 (quint, 4H), 2.03-1.60 (m, 16H), 1.45-1.27 (m, 52H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 171.27, 166.09, 151.64, 149.46, 146.25, 139.21, 136.94, 127.95, 124.41, 124.15, 122.46, 119.57, 116.28, 68.21, 52.49, 50.32, 50.11, 42.94, 39.91, 35.64, 35.16, 33.87, 32.07, 31.23, 29.84, 29.59, 29.21, 29.12, 29.08, 28.83, 28.58, 28.53, 28.29, 27.99, 27.10, 27.00, 26.45, 26.42, 26.26, 22.83, 21.52; IR (cm^{-1}): 3262, 2924, 2853, 1728, 1637, 1410, 1206; HRMS (FD) calcd for $C_{63}H_{86}N_8O_8$ [M$^+$]: 1082.6569; found: 1082.6559

Compound 32
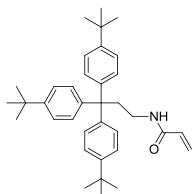
455 mg **3.18** (1.00 mmol) and 0.166 mL NEt$_3$ (1.20 mmol, 1.2 equiv) were dissolved in 10 mL dry CH$_2$Cl$_2$ and cooled to 0 ^{o}C. After cooling, 0.097 mL acryloyl chloride (1.10 mmol, 1.1 equiv) was added dropwise and the mixture was stirred for 1h at 0 ^{o}C and overnight at room temperature. The organic layer was washed with 10 mL 1M HCl and the water layer was extracted with 5 mL CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (CH$_2$Cl$_2$) to give **32** (400 mg, 0.79 mmol, 79%) as a colorless powder. Melting point: 254-256 ^{o}C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.29 (d, 6H), 7.25 (d, 6H), 6.17 (d, 1H), 5.85 (dd, 1H), 5.53 (d, 1H), 5.22 (t, 1H), 3.20 (q, 2H), 2.82 (t, 2H), 1.32 (s, 27H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 165.47, 148.64, 144.06, 130.98, 128.77, 125.98, 124.89, 54.65, 40.00, 37.31, 34.42, 31.49; IR (cm^{-1}): 3279, 2953, 2902, 2866, 1656, 1555

Compound 33
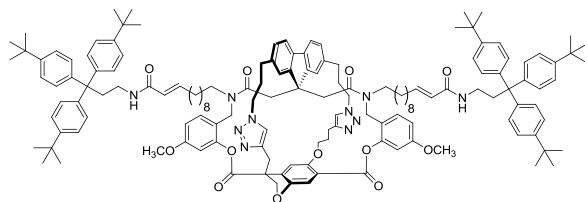
66 mg **23** (0.050 mmol) and 102 mg **32** (0.200 mmol, 4 equiv) were dissolved in 10 mL dry CH$_2$Cl$_2$ and the mixture was degassed with 5 vacuum/N$_2$ cycles. After degassing, 9 mg Grubbs II catalyst (0.010 mmol, 0.2 equiv) was added and the mixture was stirred overnight at 40 ^{o}C. The solution was concentrated in *vacuo* and dry-loaded on silica and purified by column chromatography (PE/EtOAc 1:1 → 1:2) to give **33** (65 mg, 0.0285 mmol, 57%) as a faint yellow solid film. Melting point: 153-160 ^{o}C; ^{1}H-NMR spectrum: complex; IR (cm^{-1}): 3293, 2961, 2928, 2858, 1746, 1668, 1618, 1506, 1201; HRMS (FD) calcd for C$_{147}$H$_{183}$N$_{10}$O$_{12}$ [(M+H)$^+$]: 2280.4017, found 2280.4065

Compound 34
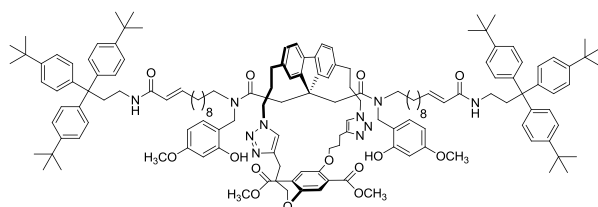
65 mg **33** (0.0285 mmol) was dissolved in 2 mL THF/CH$_3$OH 3:1 and 16 mg NaOCH$_3$ (0.285 mmol, 10 equiv) was added and the reaction was stirred at room temperature for 2h and was subsequently quenched with 0.1 mL AcOH. The reaction was diluted with 20 mL CH$_2$Cl$_2$ and 10 mL NaHCO$_3$. The water layer was extracted with 2 x 5 mL CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo* to give **34** (66 mg, 0.0281 mmol, 98%) as a faint yellow glassy solid. Melting point: 133-140 ^{o}C; ^{1}H-NMR spectrum: complex; IR (cm^{-1}): 2960, 2928, 2857, 1726, 1669, 1622, 1601, 1507, 1203; HRMS (FD) calcd for C$_{149}$H$_{191}$N$_{10}$O$_{14}$ [(M+H)$^+$]: 2344.4541, found: 2344.4529

Compound **35**
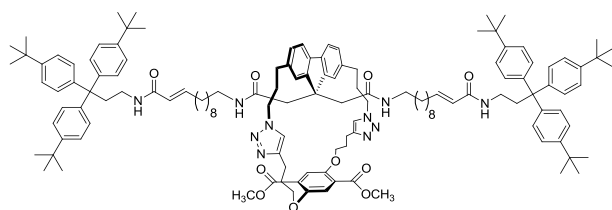
66 mg **34** (0.0281 mmol) was dissolved in 1 mL THF and added dropwise to 4 mL 3M HCl in CH$_3$OH (made *via* addition of acetyl chloride to CH$_3$OH at 0 ^{o}C). The reaction was stirred overnight at 50 ^{o}C and was subsequently concentrated in *vacuo*. The residue was partitioned between 20 mL CH$_2$Cl$_2$ and 15 mL NaHCO$_3$ and the water layer was extracted with 2 x 5 mL CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo.* The crude product was dry-loaded on silica and purified by column chromatography (EtOAc/CH$_3$OH 99:1 → 98:2 → 97:3) to give **35** (16 mg, 0.0077 mmol, 27%, together with 34 mg mixed fractions (< 0.0164 mmol, < 58%)) as a faint yellow solid.

Note: two products are formed, which do separate on TLC, but badly on column resulting in only a limited amount of pure fractions of the desired product. To obtain analytically pure material, the mixed fractions of above were subjected to supercritical preparative HPLC using liquid CO$_2$ as an eluent (see general methods for details) to give a white powder. Melting point: 106-111°C (stays thick and oily); ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.92 (s, 2H), 7.61 (d, 2H), 7.37 (s, 2H), 7.30-7.21 (m, 26H), 6.94 (s, 2H), 6.78 (dt, 2H), 5.53 (d, 2H), 5.18 (t, 2H), 4.68 (t, 2H), 4.08 (m, 8H), 3.89 (s, 6H), 3.18 (q, 4H), 3.05 (t, 4H), 2.81 (t, 4H), 2.56 (q, 4H), 2.44 (m, 8H), 2.24 (quint, 4H), 2.12 (q, 4H), 1.46-1.18 (m, 68H), 1.09 (quint, 4H), 0.98 (quint, 4H), 0.70 (bs, 8H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 168.04, 166.42, 166.06, 151.44, 148.58, 147.38, 146.16, 144.38, 144.12, 139.47, 139.19, 128.80, 128.41, 124.86, 124.58, 124.51, 123.72, 123.68, 120.64, 115.84, 67.04, 54.64, 52.55, 50.86, 47.35, 46.56, 40.11, 38.89, 37.28, 34.44, 32.05, 31.66, 31.51, 30.51, 29.50, 29.43, 29.31, 29.24, 28.60, 28.41, 26.56, 21.13; IR (cm^{-1}): 3294, 2957, 2926, 2856, 1726, 1665, 1630, 1507, 1206; HRMS (FD) calcd for C$_{133}$H$_{175}$N$_{10}$O$_{10}$ [(M+H)$^{+}$]: 2072.3493, found 2072.3424

Compound **36**
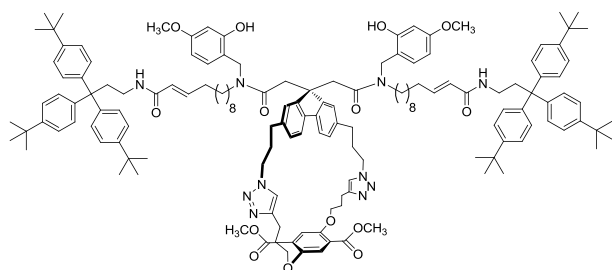
58 mg **28** (0.042 mmol) and 51 mg **32** (0.101 mmol, 2.4 equiv) were dissolved in 4 mL dry CH$_2$Cl$_2$ and the mixture was degassed with 5 vacuum/N$_2$ cycles. After degassing, 7 mg Grubbs II catalyst (0.0084 mmol, 0.2 equiv) was added and the mixture was stirred overnight at 35 ^{o}C. The solution was concentrated in *vacuo* and dry-loaded on silica and purified by column chromatography (PE/EtOAc 1:2 → 1:3) to give **36** (41 mg, 0.0175 mmol, 42%) as a faint yellow solid film. Melting trajectory: 140-156 ^{o}C (stays thick and oily); ^{1}H-NMR spectrum: complex; IR (cm^{-1}): 2959, 2928, 2856, 1729, 1670, 1622, 1601, 1506; HRMS (FD) calcd for C$_{149}$H$_{191}$N$_{10}$O$_{14}$ [(M+H)$^{+}$]: 2344.4541, found: 2344.4423

Compound **37**
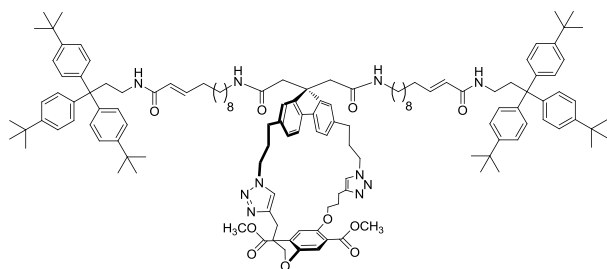
41 mg **36** (0.0175 mmol) was dissolved in 1 mL THF and added dropwise to 3 mL 3M HCl in CH$_3$OH (made *via* addition of acetyl chloride to CH$_3$OH at 0 ^{o}C). The reaction was stirred overnight at 50 ^{o}C and was subsequently concentrated in *vacuo*. The residue was partitioned between 20 mL CH$_2$Cl$_2$ and 15 mL NaHCO$_3$ and the water layer was extracted with 2 x 5 mL CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and concentrated in *vacuo.* The crude product was dry-loaded on silica and purified by column chromatography (PE/EtOAc/CH$_3$OH 1:2:0 → 1:4:0 → 1:6:0 →0:1:0 → 0:97:3) to give **37** (24 mg, 0.0116 mmol, 66%) as a faint yellow solid film. Melting trajectory: 130-138 ^{o}C (stays thick and oily); ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.71 (t, 2H), 7.37 (d, 2H), 7.29-7.22 (m, 26H), 7.15 (s, 2H), 6.97 (s, 2H), 6.80-6.73 (m, 4H), 5.51 (d, 2H), 5.17 (t, 2H), 4.33 (t, 4H), 3.91 (s, 6H), 3.70+3.60 (dt, 6H), 3.69 (q, 4H), 3.36 (q, 4H), 2.78 (t, 4H), 2.68 (t, 4H), 2.60-2.53 (m, 8H), 2.19 (quint, 4H), 2.12 (q, 4H), 1.95 (quint, 4H), 1.80-1.59 (m, 10H), 1.43-1.21 (m, 90H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 171.20, 166.08, 151.60, 149.39, 148.55, 146.26, 144.42, 144.11, 139.18, 136.95, 128.78, 127.95, 124.84, 124.39, 124.12, 123.63, 122.46, 119.63, 116.23, 68.12, 54.62, 52.47, 50.33, 50.03, 43.02, 40.07, 39.92, 37.24, 34.42, 33.77, 32.03, 31.49, 31.15, 29.83, 29.72, 29.54, 29.43, 29.19, 28.37, 28.00, 27.22, 21.49; IR (cm^{-1}): 3291, 2961, 2928, 2856, 1726, 1667, 1632, 1507, 1206; HRMS (FD) calcd C$_{133}$H$_{175}$N$_{10}$O$_{10}$ [(M+H)$^+$]: 2072.3493, found: 2072.3566

Compound **38**
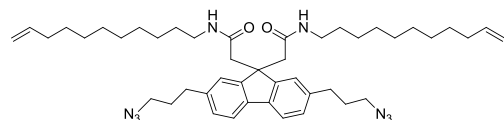
643 mg **8** (1.00 mmol), 356 mg **10** (2.10 mmol, 2.1 equiv) and 0.31 mL NEt$_3$ (2.20 mmol, 2.2 equiv) were dissolved in 6 mL dry CH$_2$Cl$_2$ and the mixture was stirred overnight at room temperature. The organic layer was washed with 10 mL 1M HCl and 10 mL NaHCO$_3$, dried over MgSO$_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (PE/EtOAc 5:2 → 3:2 → 1:1) to give **38** (671 mg, 0.893 mmol, 89%) as a thick oil, which slowly crystallized to an off-white solid. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.61 (d, 2H), 7.22 (s, 2H), 7.19 (d, 2H), 6.51 (t, 2H), 5.84 (m, 2H), 5.01 (d, 2H), 4.95 (d, 2H), 3.33 (t, 4H), 3.22 (q, 4H), 2.76 (t, 4H), 2.67 (s, 4H), 2.06 (q, 4H), 1.94 (quint, 4H), 1.44 (m, 8H), 1.29 (s, 20H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 170.75, 149.33, 140.14, 139.29, 137.45, 128.39, 124.52, 119.97, 114.27, 50.76, 50.44, 43.72, 39.74, 33.92, 33.15, 30.80, 29.67, 29.62, 29.55, 29.43, 29.23, 29.04, 27.11; IR (cm^{-1}): 3269, 3075, 2924, 2853, 2093, 1632, 1555, 1469, 1253

Compound **39**
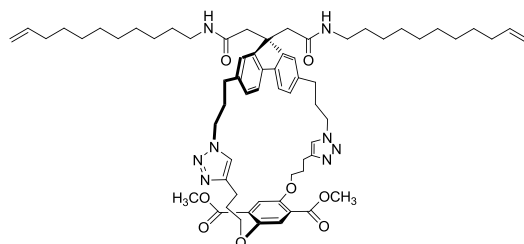
152 mg **38** (0.202 mmol, 1.1 eq), 66 mg **18** (0.184 mmol) and 24 mg TBTA (0.046 mmol, 0.25 equiv) were dissolved in 50 mL dry CH_2Cl_2 and degassed with 5 vacuum / N_2 cycles. After degassing, 15 mg $Cu(CH_3CN)_4BF_4$ (0.046 mmol, 0.25 equiv) was added and the mixture was stirred overnight at reflux. The mixture was concentrated in *vacuo* and dry-loaded on silica and purified by column chromatography (CH_2Cl_2 / CH_3OH 193:7 → 192:8) to give **39** (67 mg, 0.060 mmol, 33%) as a colorless film. ^{1}H-NMR: complex; LC-MS: calcd for $C_{65}H_{89}N_8O_8$ $[(M+H)^+]$: 1109.7; observed: 1109.7

Compounds **26** and **30**
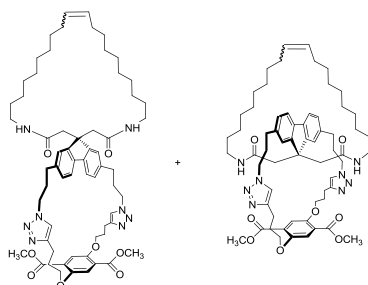
51 mg **39** (0.046 mmol) was dissolved in 46 mL dry CH_2Cl_2 and degassed with 5 vacuum/N_2 cycles. After degassing, 7.5 mg Grubbs II (0.009 mmol, 0.20 equiv) was added and the mixture was stirred overnight at 35 °C under N_2 atmosphere. The mixture was concentrated in *vacuo*, dry-loaded on silica and purified by column chromatography (EtOAc / CH_3OH 97:3 → 96:4 → 94:6 → 90:10) to give **30** (19 mg, 0.018 mmol, 38%) and **26** (10 mg, 0.010 mmol, 20%).

References

[1] Part of this chapter has been published:
Steemers, L.; Wanner, M.W.; Lutz, M.; Hiemstra, H.; van Maarseveen, J.H. *Nat. Comm.* **2017**, *8*, 15392
doi: 10.1038/ncomms15392
[2] Taylor, W.R. *Nature*, **2000**, *406*, 916-919
[3] Dean, F.B.; Stasiak, A.; Koller, T.; Cozzarelli, N.R. *J. Biol. Chem.* **1985**, *260*, 4975-4983
[4] Hegemann, J.D.; Zimmerman, M.; Xie, X.; Marahiel, M.A. *Acc. Chem. Res.* **2015**, *48*, 1909-1919
[5] Packman, L.C. *Tetrahedron Lett.* **1995**, *36*, 7523-7526
[6] Gibson, H.W.; Lee, S.H.; Engen, P.T.; Lecavalier, P.; Sze, J., Shen, Y.X.; Bheda, M. *J. Org. Chem.* **1993**, *58*, 3748-3756
[7] Abbel R.; Schenning, A.P.H.J.; Meijer, E.W.; *J. Polym. Sci. A. Polym. Chem.* **2009**, *47*, 4215-4233
[8] Gagnon, P.; Huang, X.; Therrien, E.; Keillor, J.W.; *Tetrahedron Lett.* **2002**, *43*, 7717-7719
[9] Green, M.; Bermann, J.; *Tetrahedron Lett.* **1990**, *31*, 5851-5852
[10] Choi, T.L.; Chatterjee, A.K.; Grubbs, R.H. *Angew. Chem. Intl. Ed.* **2001**, *113*, 1317-1319
[11] Harris, J.D.; Lui, J.; Carter, K.R; *Macromolecules*, **2015**, *48*, 6970-6977
[12] Leonard, N.M.; Brunckova J.; J. Org. Chem. **2011**, *76*, 9169-9174
[13] Corey, J.; Pasto, J.; Mock, L. J. Am. Chem. Soc. **1961**, 83, 2957
[14] Masuo, R.; Ohmori, K.; Hintermann, L.; Yoshida, S.; Suzuki, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 3462-3465
[15] Chan, T.R.; Hilgraf, R.; Sharpless, K.B.; Fokin, V.V. *Org. Lett.* **2004**, *6*, 2853-2855
[16] Lehman, S.E.; Schwendeman, J.E.; O'Donnell, P.M.; Wagener, K.B. *Inorganica Chimica Acta*, **2003**, 3*45*, 190-198
[17] Hong, S.H.; Sanders, D.P.; Lee, C.W.; Grubbs, R.H. *J. Am. Chem. Soc.* **2005**, *127*, 17160-17161
[18] Schulze, B.; Schubert, U.S; *Chem. Soc. Rev.* **2014**, *43*, 2522-2571
[19] Lahlali, H.; Jobe, K.; Watkinson, M.; Goldup, S. M. *Angew. Chem. Int. Ed*. **2011**, *50*, 4151–4155
[20] Dzyuba, E.V.; Kaufmann, L.; Low, N.L.; Meyer, A.K.; Winkler, H.D.F.; Rissanen, K.; Schalley, C.A. *Org. Lett.* **2011**, *13*, 4838-4841

Chapter V: Approach towards a [2]catenane *via* preorganization with a cyclic ketal[1]

As discussed in Chapter I, the Schill group reported in 1967 one of the first [2]catenane syntheses, using the covalent approach.[2] Crucial in their approach was the use of a cyclic ketal as motif for some preorganization of the ring fragment, ensuring a perpendicular arrangement of the two components (see scheme 1). The ketal motif was cleaved in a late stage using aqueous HBr, liberating the ketone and a catechol moiety. To the best of our knowledge, this (and the related 1969 paper, see Chapter I) is the only successful synthesis of a mechanically interlocked product employing a cyclic ketal as motif for pre-organization, despite the relative simplicity and accessibility of such a moiety.
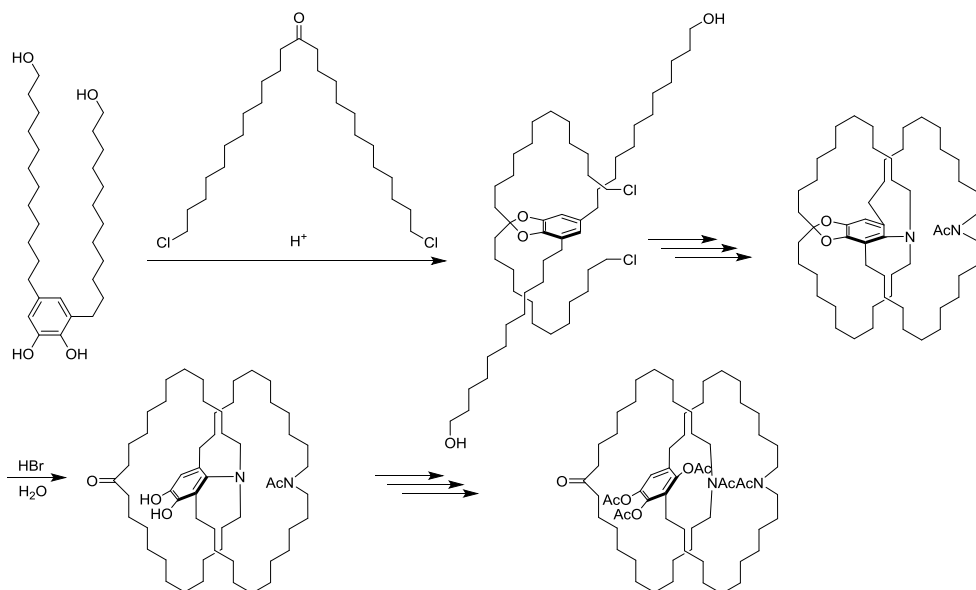
Scheme 1: Schill's approach towards a [2]catenane *via* ketal preorganization (see Chapter I)

Based on the synthetic methodologies described in Chapter III and IV and inspired by the landmark paper by Schill, we set out to combine the best of both of these 'worlds' to arrive at [2]catenanes *via* a quasi[1]catenane by introducing cleavable bonds at the connecting tetrahedral sp^3-atom. The general strategy is the same as described in Chapters III and IV, but some reactions have been altered to allow more facile bond formation/cleavage. Figure 1 illustrates a comparison in design between the two advanced intermediates **A** (Chapter III) and **B** (this chapter) towards a catenane system and the retrosynthesis of **B**. Most crucially, the flexible oxime bond has been replaced by a rigid cyclic ketal linkage based on tartaric acid. This cyclic ketal ensures the desired perpendicular arrangement of the ring and thread fragments and is acid labile, allowing hydrolysis during the final acidolytic cleavage step. Tartaric acid was chosen as building block, as it possesses two carboxylic acid moieties and two hydroxyl functionalities, allowing the ketal formation. Moreover, tartaric acid chemistry is well developed and starting materials are readily available. The Williamson etherification of the ring-precursor to the scaffold has been replaced by transesterification with a bis-pentafluorophenol ester

scaffold. Analogous to Chapter IV, this allows introduction of an ester moiety as an additional scissile site during the final cleavage steps. Because the macrocycle formed during the CuAAC reaction (red macrocycle) should be acid-stabile, the cleavable 2-propargyloxy-4-methoxybenzyl group has been replaced with a simple amide based on 5-amino-1-pentyne. Lastly, the PEG-based ring fragment has been replaced with the aesthetically more appealing 11-undecenyl chain from Chapter IV.
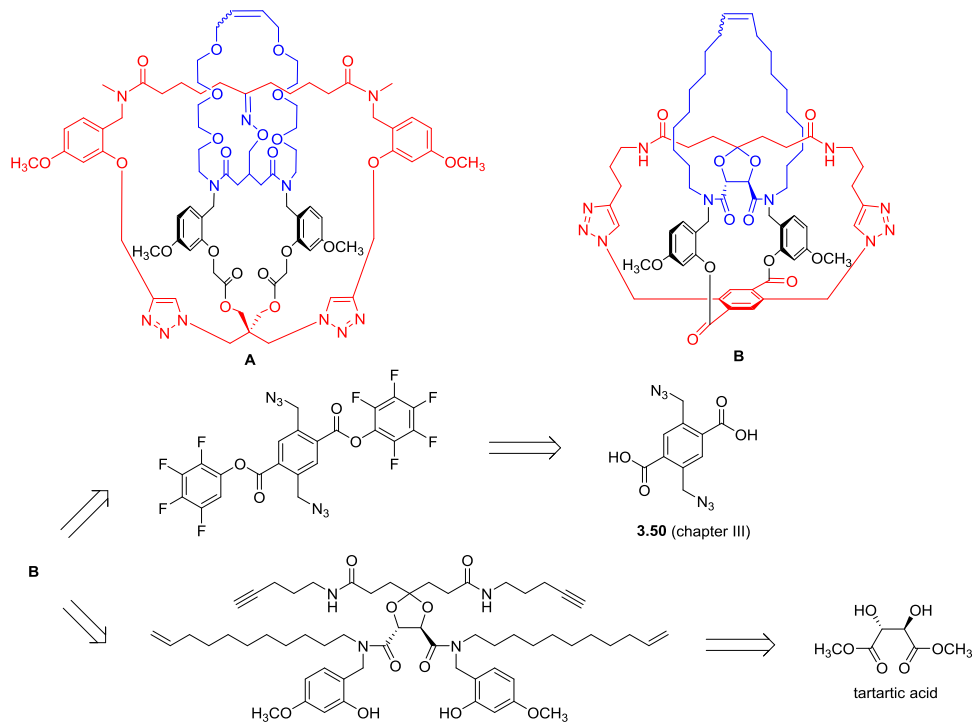

Figure 1) Top: Comparison between advanced intermediates **A** (Chapter III) and ketal **B** (this chapter). Bottom: retrosynthesis of compound **B**

As this new method requires a cyclic ketal as a crucial moiety, it was decided to install this moiety as early on as possible in the synthesis. The most logical reaction to form the desired skeleton was *via* the ketalization of dimethyl tartrate with a diester of 4-oxopimelic acid as this would directly form the desired core with the correct oxidation states. Although orthogonally protected esters would be most desirable, it was decided to first test the ketal formation with dimethyl tartrate and diethyl 4-oxopimelate (both commercially available). To activate the ketone moiety, it was first reacted with excess trimethyl orthoformate in methanol, forming acetal **1** (see scheme 2).[3] Note that under these conditions the ethyl esters were transformed to methyl esters. Subsequent acid catalyzed trans-acetalization with dimethyl tartrate was conducted next. However, under the various reaction conditions tested only hydrolysis of the acetal was observed (forming the starting ketone again) with no traces of the desired tartaric acid ketal. It is thought that the close proximity of the methyl ester moieties to the acetal prevents the desired reaction to take place due to the steric and electronic reasons. Therefore, the ester moieties on the 4-oxopimelic acid side had to be masked during ketalization. It was decided to use an alkene as an carboxylate synthon, eventually transforming it through sequential oxidation *via* the bis-aldehyde to the bis-carboxylic acid.
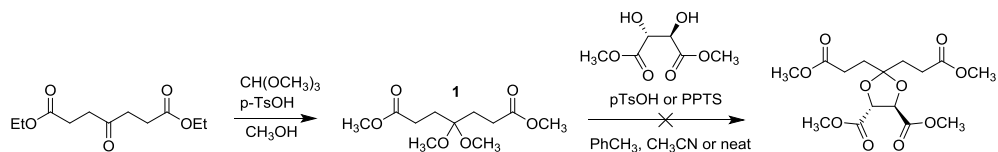
Scheme 2: Attempted synthesis a tartaric acid ketal

The synthesis started with a Grignard reaction of 4-bromo-1-butene with ethyl formate to give secondary alcohol **2** in quantitative yield (see scheme 3).[4] Subsequent oxidation with pyridinium chlorochromate (PCC) gave ketone **3** in 91% yield over the two steps, after column chromatography.[5] Next, the acid catalysed ketal formation of ketone **3** with dimethyl tartrate was tested. Refluxing with p-TsOH in toluene with a Dean-Stark trap gave no conversion and refluxing with $BF_3 \cdot Et_2O$ in dry CH_2Cl_2 also failed to give conversion. Clearly, this reaction needed a different mode of activation. Literature research suggested to transform the ketone moiety into an acetal first, followed by acidic trans-acetalization with dimethyl tartrate.[6,7,8] As a result, the ketone was first transformed into dimethyl acetal **4** with trimethyl orthoformate in dry CH_3OH. Subsequent p-TsOH catalyzed trans-acetalization with two equivalents of dimethyl tartrate in refluxing CH_2Cl_2 gave a clean conversion to cyclic ketal **5**, which was isolated in 71% yield over the two steps**.**

Subsequent oxidation of the terminal alkenes towards the aldehydes was optimized next. Initially, the Lemieux-Johnson reaction[9] (oxidation with OsO_4 and excess $NaIO_4$) was used, but yields of dialdehyde **6** were not satisfactory. Fortunately, ozonolysis of the terminal alkenes, followed by reduction with PPh_3 gave a clean conversion to dialdehyde **6**. Reduction of the ozonide intermediate with dimethyl sulfide, thiourea or NMMO gave lower yields and/or more byproducts. Because isolated yields of the sensitive dialdehyde after column chromatography were mediocre at best, it was decided to use the crude dialdehyde (contaminated with PPh_3 and PPh_3O) directly in the subsequent Pinnick oxidation step.[10,11] Treatment with NaH_2PO_4 and $NaClO_2$ and 2-methyl-2-butene (as HOCl scavenger) yielded diacid **7** in 95% yield over the two steps. Purification of the diacid was achieved by extracting it into the water layer with $NaHCO_3$ and washing the water layer with EtOAc to remove the PPh_3, PPh_3O and other apolar organic residues. Subsequent careful acidification of the water layer allowed extraction of the product into the organic phase, giving fairly pure diacid **7**.
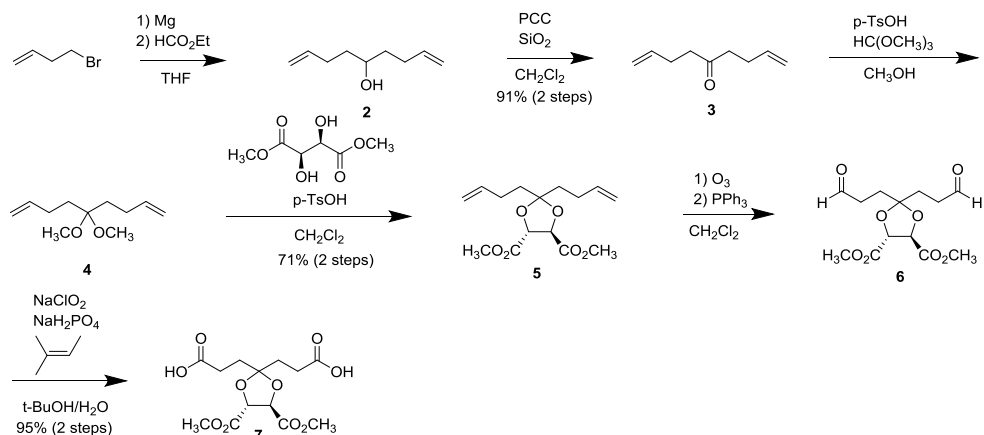

Scheme 3: Synthesis of diacid **7**

Next, coupling of diacid **7** with 5-amino-1-pentyne[12] was optimised. Standard coupling conditions between the amine and diacid **7** with DCC and HOBt gave low yields. However, treatment with 2.5 equivalents of PyBOP gave full conversion, giving diamide **8** in 94% yield, which was pure enough for the next step. The two methyl esters were smoothly saponified with aqueous NaOH, giving diacid **9** in 69% yield. Impurities were removed by washing the basic water layer with EtOAc. The product was extracted after careful acidification of the water layer. Next, diacid **9** was coupled to amine **4.11** (see Chapter IV for synthesis) with DCC and HOBt as coupling reagents, giving ring precursor tetra-amide **10** in 61% yield.
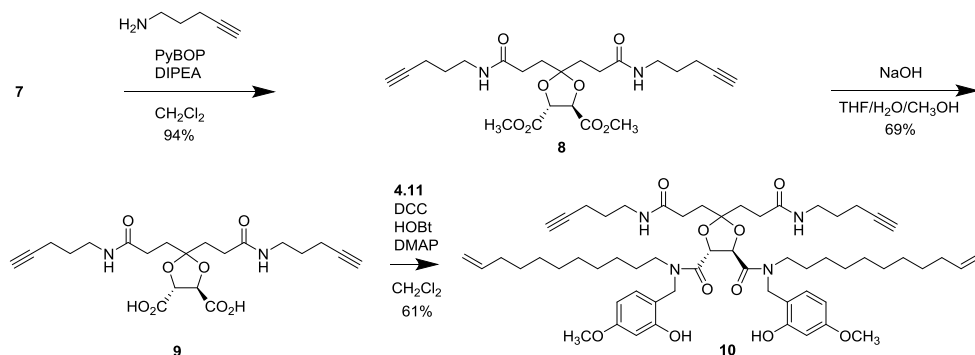
Scheme 4: Synthesis of tetra-amide **10**

With ring precursor **10** in hand, the di-azide template had to be synthesized. As di-acid **3.50** had already been synthesized (see Chapter III), it only had to be converted into its bis-pentafluorophenol ester. Treatment of di-acid **3.50** with pentafluorophenol, DIPEA and HBTU as coupling reagent gave template **11** as a colorless solid in 52% yield.

Next, the macrocyclization of tetra-amide **10** with template **11** was performed with the optimized transesterification conditions of Chapter IV. Thus, the two components were stirred with 10 equiv of Cs_2CO_3 and 4 Å molecular sieves in CH_3CN at high dilution (2 mM), giving macrocycle bis-ester **12** in 67% yield. Subsequent CuAAC reaction with catalytic $Cu(CH_3CN)_4BF_4$ and TBTA as ligand in CH_2Cl_2 gave bis-triazole cage molecule **13** uneventfully in 80% yield.[13] However, subsequent ring closure *via* olefin metathesis with Grubbs 2nd generation catalyst was unexpectedly difficult. Despite various experiments, multicyclic compound **14** was obtained in 25% yield only. Moreover, as previously observed, trace amounts of the CH_2-truncated product were also observed. Cleavage of the ester bonds was achieved by treatment with excess K_2CO_3 in CH_3OH, giving bis-ester **15** in 82% yield. These conditions suppress unwanted saponification due to trace amounts of water in the reaction mixture. This side reaction was occasionally observed as described in Chapter III when employing $NaOCH_3$ in 'anhydrous' CH_3OH.
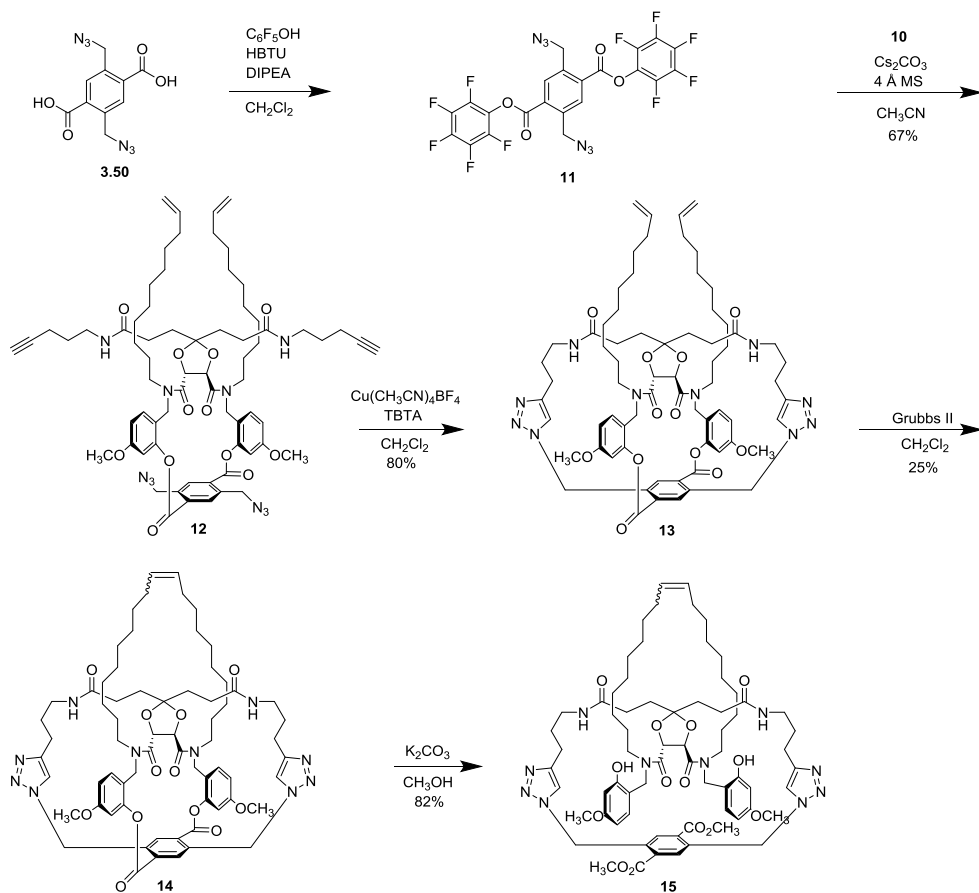
Scheme 5: Synthesis of macrocycle **15**

The final steps of the synthesis included hydrogenation of the olefinic E/Z mixture resulting from the metathesis reaction, acidolytic cleavage of the benzyl groups and acidic hydrolysis of the ketal moiety. Hydrogenation of the alkene gave unclear results, as the (complex) ^{1}H-NMR spectrum did not change much. Treatment with excess triethylsilane in TFA gave product **17** (a quasi[1]catenane) in ca. 85% yield. HRMS of the product showed the presence of the desired mass (m/z 1039, M+Na^{+}), however also trace amounts of m/z 1037 were observed, corresponding to the M+Na^{+} signal of the non-hydrogenated analogue of **17**, meaning that the hydrogenation step had not reached completion yet. Interestingly, but disappointingly, no hydrolysis of the ketal was observed. Moreover, various attempts to hydrolyze the ketal in **17** failed to give any desired [2]catenane, usually resulting in acid catalyzed hydrolysis of the methyl esters of the terephthalate moiety only. However, the esters of the tartaric acid moiety also withdraw electron density from the dioxolane motif, which also thwarts hydrolysis as this hampers protonation of the dioxolane oxygen. The resistance towards hydrolysis might also indicate severe steric hindrance about the endocyclic ketal (similar to the endocyclic esters in the next chapter) and can be seen as an indirect proof of structure of compound **17**. These two combined factors (electronics and steric hindrance) are most likely the cause for the stability of the cyclic ketal motif in **17**.
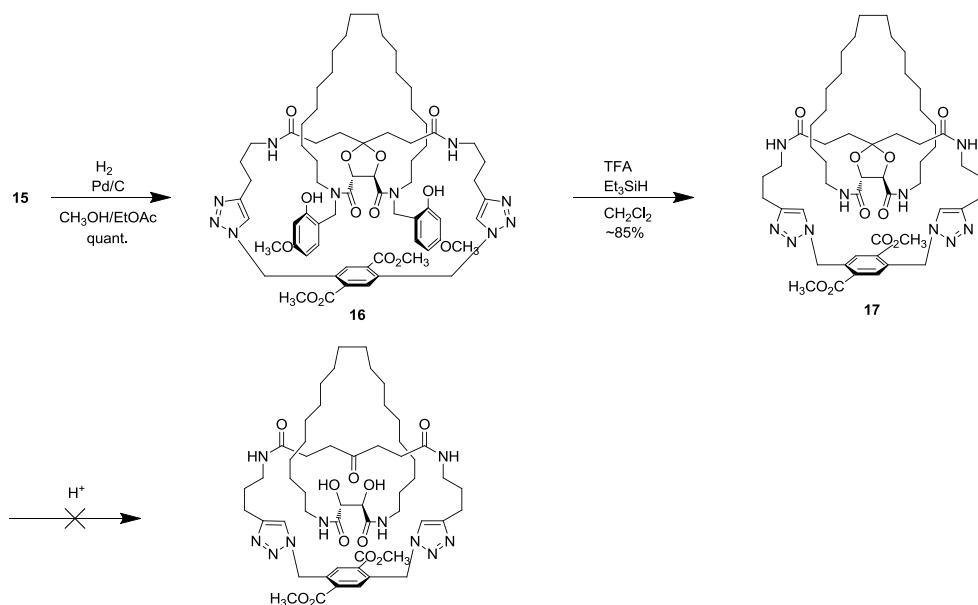
Scheme 6: synthesis of product **17** and attempted hydrolysis towards the desired [2]catenane

As time of this PhD work was running out, no more attempts to construct a cleavable moiety (such as a dioxolane) between the ring and thread fragments were attempted. See Chapter VII (outlook) for future plans regarding this work.

Acknowledgments

**Experimental section**

Dried CH_2Cl_2 and CH_3CN were obtained by distilling these solvents with CaH_2 as drying agent. Dried THF and Et_2O were obtained by distillation with sodium. All dried solvents were stored under N_2 atmosphere. Dry DMF on 4Å molecular sieves was obtained from Sigma-Aldrich and stored under N_2 atmosphere. Reagents were purchased with the highest purity (usually >98%) from Sigma Aldrich and Fluorochem and used as received. Grubbs 2nd generation catalyst was purchased from AK Scientific and TBTA was purchased from TCI Europe. Reactions were monitored with thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254). SilaFlash® P60 (particle size 40-63 µm) was used for silica column chromatography. NMR spectra were recorded on Bruker DRX-500, 400 and 300 MHz instruments and calibrated on residual undeuterated solvent signals as internal standard. The ^{1}H-NMR multiplicities were abbreviated as followed: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet. High resolution mass spectra (HRMS) were recorded on a Mass spectra were collected on an AccuTOF GC v 4g, JMS-T100GCV Mass spectrometer (JEOL, Japan). FD/FI probe equipped with FD Emitter, Carbotec or Linden (Germany), FD 10 µm. Current rate 51.2 mA/min over 1.2 min machine using field desorption (FD) as ionization method.

Compound **2**
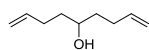
4.60 mL 4-bromo-1-butene (50.0 mmol, 2.5 equiv) was dissolved in 40 mL dry THF and added dropwise to a suspension of 1.24 g magnesium turnings (50.0 mmol, 2.5 equiv) in 10 mL dry THF under N_2 atmosphere, to which one crystal of iodine was added. After initiation of the reaction the rate of addition was controlled to allow gentle reflux. After addition the reaction was stirred at room temperature for 1h. Next, the reaction was cooled to 0 °C and 1.60 mL ethyl formate (20.0 mmol, 1.0 equiv) in 20 mL dry THF was added dropwise. After addition, the reaction was stirred at room temperature for 1h and reflux for 1h. The mixture was quenched with 60 mL saturated NH_4Cl solution and extracted with 3 x 40 mL Et_2O. The combined organic layers were washed with 40 mL brine, dried over $MgSO_4$ and concentrated *in vacuo* to give **2** (2.77 g, 50 mmol, quant) as a slightly yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.85 (m, 2H), 5.05 (dd, 4H), 3.67 (quint, 1H), 2.18 (m, 4H), 1.57 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.68, 114.94, 71.15, 36.59, 30.19; IR (cm^{-1}): 3340, 3078, 1448

Compound **3**
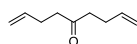
11.2 g **2** (80 mmol) was dissolved in 300 mL dry CH_2Cl_2 under N_2 atmosphere and 24 g silica was added. A water bath was added and 24 g PCC (111 mmol, 1.4 equiv) was added portionwise (the reaction is somewhat exothermic). The reaction was stirred overnight at room temperature and subsequently filtered over a plug of Celite. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (PE/EtOAc 20:1 → 10:1) to give **3** (10.0 g, 72.5 mmol, 91% over two steps) as a colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.82 (m, 2H), 5.02 (dd, 4H), 2.52 (t, 4H), 2.33 (q, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.49, 137.22, 115.36, 42.00, 27.85; IR (cm^{-1}): 3079, 1713

Compound **5**
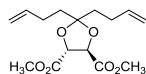
550 mg **3** (3.98 mmol, 1.0 equiv) and 73 mg p-TsOH (0.38 mmol, 0.1 equiv) were dissolved in 5 mL dry CH_3OH and 1.35 trimethyl orthoformate (12.34 mmol, 3.0 equiv) was added. The reaction was stirred overnight at room temperature and subsequently concentrated *in vacuo*. The residue was dissolved in 25 mL dry CH_2Cl_2 and 1.46 g dimethyl tartrate (8.21 mmol, 2.0 equiv) and 73 mg p-TsOH (0.38 mmol) were added. The reaction was heated at reflux overnight under N_2 atmosphere. The reaction was concentrated *in vacuo* and 30 mL saturated $NaHCO_3$ was added. The water layer was extracted with 3 x 20 mL EtOAc and the combined organic layers were washed with 20 mL brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc 100:0 → 6:1) to give **5** (849 mg, 2.83 mmol, 71%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.82 (m, 2H), 4.99 (dd, 4H), 4.75 (s, 2H), 3.83 (s, 6H), 2.18 (q, 4H), 1.81 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.77, 138.00, 116.54, 114.73, 77.23, 52.94, 36.37, 27.90; IR (cm^{-1}): 1745, 1437

Compound **7**
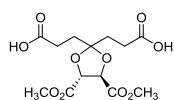
1.50 g **5** (5.00 mmol) was dissolved in 100 mL dry CH$_2$Cl$_2$ and cooled to -78 ^{o}C. Ozone gas was bubbled through the mixture until the mixture turned blue. After completion of the reaction, oxygen was bubbled through the mixture for 5 minutes to give a colourless solution. Next, 2.88 g PPh$_3$ (11.0 mmol) was added and the dry-ice bath was removed. The reaction was stirred overnight at room temperature and was subsequently concentrated *in vacuo*. The residue was dissolved in 100 mL tBuOH and 35 mL H$_2$O and 6.90 g NaH$_2$PO$_4$ (50.0 mmol) and 10.6 mL 2-methyl-2-butene were added and the mixture was cooled to 0 ^{o}C. Next, 3.62 g NaClO$_2$ (40.0 mmol) was dissolved in 5 mL H$_2$O and added dropwise to the solution. The reaction was stirred for 4h and was subsequently diluted with aqueous 5% K$_2$CO$_3$ solution. The water layer was washed with 2 x 40 mL EtOAc and the organic layers were extracted with aqueous 5% K$_2$CO$_3$ solution. The combined water layers were acidified to pH 2.5 with 2M HCl solution and the water layer was extracted with 3 x 40 mL EtOAc. The combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo* and co-evaporated with THF to give **7** (1.59 g, 4.76 mmol, 95%) as a yellow oil. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 4.77 (s, 2H), 3.84 (s, 6H), 2.54 (t, 4H), 2.14 (t, 4H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 178.67, 169.55, 115.12, 77.43, 53.13, 31.83, 28.49; IR (cm^{-1}): 1739, 1711, 1438

Compound **8**
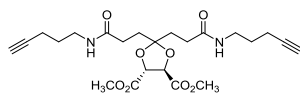
1.34 g **7** (4.00 mmol, 1.0 equiv) and 4.1 mL DIPEA (32.0 mmol, 8.0 equiv) were dissolved in 30 mL dry CH$_2$Cl$_2$ under N$_2$ atmosphere and cooled to 0 ^{o}C. Next, 5.20 g PyBOP (10.0 mmol, 2.5 equiv) was added and the mixture was stirred for 5 minutes, after which 0.70 g 5-amino-1-pentyne (8.8 mmol, 2.2 equiv) in 5 mL dry CH$_2$Cl$_2$ was added dropwise. The mixture was stirred overnight at room temperature and was washed with 40 mL 1M HCl. The organic layer was dried over MgSO$_4$ and concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/CH$_3$OH 100:0 → 97:3 → 95:5) to give **8** (1.75 g, 3.77 mmol, 94%) as a yellow oil. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 6.16 (t, 2H), 4.73 (s, 2H), 3.84 (s, 6H), 3.35 (q, 4H), 2.40-2.24 (m, 8H), 2.08 (m, 4H), 2.02 (t, 2H), 1.74 (quint, 4H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 172.89, 169.98, 115.83, 83.46, 68.97, 52.95, 38.52, 32.15, 30.58, 27.93, 15.90

Compound **9**
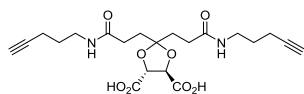
2.23 g **8** (5.11 mmol) was dissolved in a mixture of 25 mL THF, 20 mL H$_2$O and 10 mL CH$_3$OH. Next, 44 mL 1M NaOH (21.0 mmol, 10 equiv) was added and the mixture was stirred overnight at room temperature. The volatiles were removed *in vacuo* and the water layer was washed with 20 mL EtOAc. The organic layer was extracted with 10 mL 1M NaOH and the combined water layers were acidified with HCl to pH 2.5 and extracted with 3 x 20 mL EtOAc. The combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo* and the residue was co-evaporated with EtOAc to give **9** (1.53 g, 3.51 mmol, 69%) as a thick oil which slowly crystallized. ^{1}H-NMR (400 MHz, CDCl$_3$ + CD$_3$OD) δ 4.71 (s, 2H), 3.21 (t, 4H), 2.28 (q, 4H), 2.18 (dt, 4H), 1.99-1.94 (m, 6H), 1.66 (quint, 4H); ^{13}C-NMR (100 MHz, CDCl$_3$ + CD$_3$OD) δ 173.95, 171.36, 115.00, 83.13, 68.82, 38.30, 32.16, 30.20, 27.58, 15.61

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Compound **10**
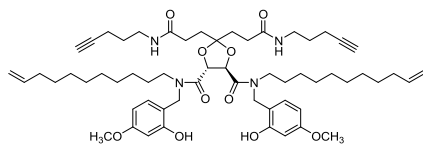
654 mg **9** (1.50 mmol, 1.0 equiv), 0.52 g HOBt (3.4 mmol, 2.25 equiv) and 25 mg DMAP were dissolved in 35 mL dry CH_2Cl_2 and 2.06 g DCC (10.0 mmol, 6.6 equiv) was added. After stirring for 1h, 1.04 g **4.11** (3.4 mmol, 2.25 equiv) in 5 mL dry CH_2Cl_2 was added. The mixture was stirred overnight at room temperature and was filtered. The filtrate was washed with 20 mL $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by column chromatography (PE/EtOAc 1:1 → 1:2 → 0:1) to give **10** (925 mg, 0.92 mmol, 61%) as a thick yellow oil. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 9.34 (bs, 2H), 7.03 (d, 2H), 6.48 (s, 2H), 6.40 (d, 2H), 6.34 (t, 2H), 5.85 (m, 2H), 5.30 (s, 2H), 5.01 (dd, 4H), 4.61 (d, 2H), 4.26 (d, 2H), 3.78 (s, 6H), 3.49 (quint, 2H), 3.34 (m, 8H), 2.25 (m, 6H), 2.18 (t, 4H), 2.11 (quint, 8H), 2.02 (t, 2H), 1.76 (quint, 8H), 1.50-1.22 (m, 24H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 172.74, 169.75, 161.39, 156.81, 139.00, 132.13, 115.41, 114.05, 113.90, 105.57, 102.30, 83.37, 75.69, 68.98, 55.13, 46.86, 45.94, 38.51, 33.64, 32.83, 30.61, 29.34, 29.27, 29.14, 28.96, 28.76, 28.20, 27.97, 26.64, 15.92

Compound **11**
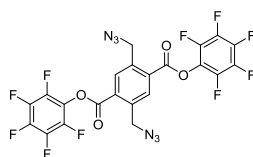
276 mg **3.50** (1.00 mmol), 1.14 g HBTU (3.00 mmol, 3.0 equiv), 460 mg pentafluorophenol (2.50 mmol, 2.5 equiv) and 0.68 mL DIPEA (4.00 mmol, 4.0 equiv) were dissolved in 6 mL dry CH_2Cl_2 and stirred overnight at room temperature. The mixture was concentrated *in vacuo*, loaded on silica and purified by column chromatography (PE/EtOAc 98:2 → 97:3). The product was triturated with PE to give **11** (314 mg, 0.52 mmol, 52%) as a colourless solid. Melting point: 119-122 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.53 (s, 2H), 5.01 (s, 4H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 161.88, 139.44, 132.63, 129.92, 52.12; IR (cm^{-1}): 2162, 1752, 1517

Compound **12**
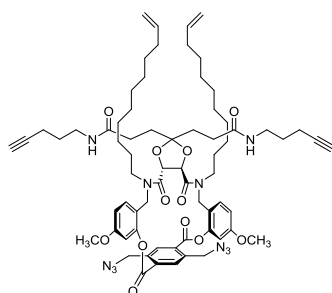
925 mg **10** (0.92 mmol, 1.0 equiv), 560 mg **11** (0.92 mmol, 1.0 equiv) and 3.0 g Cs$_2$CO$_3$ (9.20 mmol, 10 equiv) and 10 g 4Å MS were dissolved in 400 mL dry CH$_3$CN and the mixture was stirred overnight at room temperature under N$_2$ atmosphere. The mixture was filtered over a plug of Celite, which was washed with EtOAc. The filtrate was concentrated *in vacuo*, dry-loaded on silica and purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 197:3 → 196:4 → 195:5) to give **12** (773 mg, 0.618 mmol, 67%) as a colourless oil. ^{1}H-NMR: complex; LC-MS: calcd for C$_{69}$H$_{91}$N$_{10}$O$_{12}$ (M+H$^+$): 1251.68, found: 1251.5

Compound 13
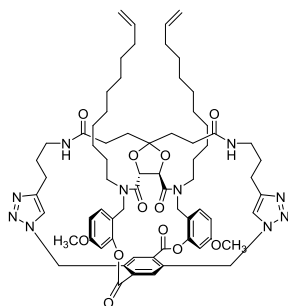
773 mg **12** (0.618 mmol, 1.0 equiv) and 106 mg TBTA (0.20 mmol, 0.3 equiv) were dissolved in 300 mL dry CH_2Cl_2 and the mixture was degassed with 5 vacuum/N_2 cycles. After degassing 63 mg $Cu(CH_3CN)_4BF_4$ (0.20 mmol, 0.3 equiv) was added and the reaction was stirred overnight at reflux under N_2 atmosphere. The reaction was washed with 100 mL 1M $KHSO_4$ and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give **13** (620 mg, 0.496 mmol, 80%) as a colourless film. ^{1}H-NMR: complex; LC-MS: calcd for $C_{69}H_{91}N_{10}O_{12}$ (M+H^{+}): 1251.68, found: 1251.6

Compound 14
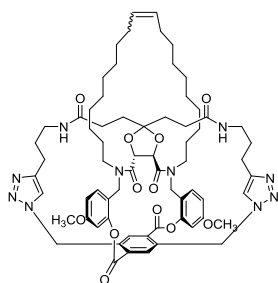
600 mg **13** (0.479 mmol) was dissolved in 250 mL dry CH_2Cl_2 and the solution was degassed by three vacuum/N_2 cycles. After degassing, 40 mg Grubbs II (0.047 mmol, 0.10 equiv) was added and the mixture was stirred overnight at 40 ^{o}C. The mixture was concentrated *in vacuo* and dry-loaded on silica and purified by column chromatography (CH_2Cl_2/CH_3OH 196:4 → 195:5 → 194:6) to give **14** (145 mg, 0.119 mmol, 25%) as a brownish oil. Note: LC-MS analysis also showed the formation of the CH_2-truncated product (ca. 10%). ^{1}H-NMR: complex; LC-MS: calcd for $C_{67}H_{87}N_{10}O_{12}$ (M+H^{+}): 1223.65, found: 1223.6

Compound 15
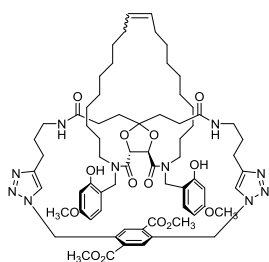
145 mg **14** (0.119 mmol) was dissolved in 10 mL CH_3OH and 4 g K_2CO_3 was added. The mixture was stirred at room temperature for 5h and was neutralized with acetic acid. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/CH_3OH 98:2 → 97:3 → 96:4) to give **15** (125 mg, 0.0971 mmol, 82%) as a faint yellow oil. Note: LC-MS analysis also showed the presence of the CH_2-truncated product (ca. 10%). ^{1}H-NMR: complex; LC-MS: calcd for $C_{69}H_{95}N_{10}O_{14}$ (M+H^{+}): 1287.70, found: 1287.3

Compound 16
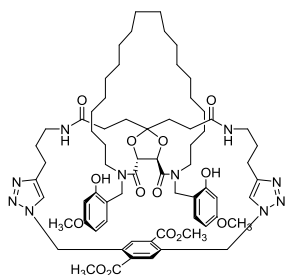
125 mg **15** (0.0971 mmol) was disolved in 5 mL EtOAc/CH_3OH 1:1 and 10 mg Pd/C (10% w/w) was added. Through the solution was bubbled H_2 gas for 10 minutes. Next, the solution was stirred overnight at 45 ^{o}C under H_2 atmosphere (balloon). The solution was bubbled with N_2 gas for 5 minutes and the solution was filtered through a plug of Celite (flush with EtOAc) and concentrated *in vacuo* to give **16** (125 mg, 0.097 mmol, quant) as a colourless film. ^{1}H-NMR: complex

Compound **17**
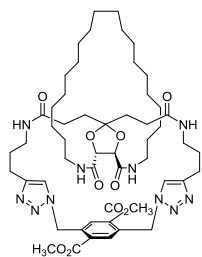
125 mg **16** (0.097 mmol) was dissolved in 3 mL TFA and 0.15 mL Et$_3$SiH was added. The reaction was stirred overnight at room temperature and subsequently diluted with 10 mL PhCH$_3$. The mixture was concentrated *in vacuo* and purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH 95:5 → 90:10 → 85:15). The most polar fraction was isolated and concentrated *in vacuo* to give **17** (84 mg, 0.083 mmol, 85%) as a colourless film. Accurate mass spectra shows also the presence of non-hydrogenated product from the previous step. ^{1}H-NMR: complex; HRMS: calcd for C$_{53}$H$_{80}$N$_{10}$O$_{10}$Na (M+Na$^+$): 1039.5957, found: 1039.5929

References

[1] Manuscript in preperation

[2] Schill, G. *Chem. Ber.* **1967**, *100*, 2021

[3] Sander, M.; Dehmlow, E.V. *Eur. J. Org. Chem.* **2001**, *2*, 399-404

[4] Lemiere, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993-3006

[5] Legeay, J.-C.; Lewis, W.; Stockman, R.A. *Chem. Comm.* **2009**, *16*, 2207-2209

[6] Weng, J.; Li, Y.-B.; Wang, R.-B.; Li, F.-Q.; Liu, C.; Chan, A.S.C.; Lu, G. *J. Org. Chem.* **2010**, *75*, 3125-3128

[7] Crich, D.; Hao, X. *J. Org. Chem.* **1999**, *64*, 4016-4024

[8] Lajkiewicz, N.J.; Roche, S.P.; Gerard, B.; Porco Jr, J.A. *J. Am. Chem. Soc.* **2012**, *134*, 13108-13113

[9] Pappo, R.; Allen, D.S.; Lemieux, R.U.; Johnson, W.S. *J. Org. Chem.* **1956**, *21*, 478-479

[10] Lindgren, B.O.; Nilsson, T.; Husebye, S. Mikalsen, O.; Leander, K.; Swahn, C.-G. *Acta Chemica Scandinavica*, **1973**, *27*, 888

[11] Bal, B.S.; Childers, W.E.; Pinnick, H.W. *Tetrahedron,* **1981**, *37*, 2091-2096

[12] Yu, T.B.; Bai, J.Z.; Guan, Z. *Angew. Chem. Int. Ed.* **2009**, *48*, 1097-1101

[13] Chan, T.R.; Hilgraf, R.; Sharpless, K.B.; Fokin, V.V. *Org. Lett.* **2004**, *6*, 2853-2855

# Chapter VI: Rotaxane assembly with a terephthalic acid template[1]

Almost all common rotaxane syntheses *via* the 'clipping' approach (see Chapter I) rely on non-covalent interactions for the mutually perpendicular arrangement of the ring and thread fragments, so that subsequent ring closure occurs around the thread. Commonly used motifs are crown ether-ammonium[2], π-π[3] , H-bonding[4] and metal-pyridine/bipy/phenanthroline interactions.[5,6] While all these strategies work well and give rotaxanes and catenanes in high yield, they all suffer from a fundamental drawback. The structural motif needed for pre-organization is retained in the final product. For the common rotaxanes/catenanes this is usually no problem, as this creates 'stations' on the thread for the ring to coordinate to. Nevertheless, it somewhat limits the number of structures one can build. Especially when addressing complex and/or natural mechanically interlocked compounds, such as the lasso peptides (see Chapter I), these traditional methods fall short. Therefore, it is synthetically more challenging to synthesize a rotaxane/catenane lacking such a permanent motif. Nevertheless, some of these so-called 'impossible' rotaxanes have been reported.

In 2004, the group of Leigh published the first 'impossible' rotaxane synthesis, i.e. a rotaxane that lacks a permanent recognition motif between the ring and thread.[7] To accomplish this, a temporary bis-amide motif was first attached *via* an ester bond to an aliphatic chain, stoppered with a bulky group on the terminus (see scheme 1). Addition of isophthaloyl chloride and p-xylyne diamine yielded the [2]rotaxane in 25% yield. The bis-amide serves as H-bonding template for the ring synthesis (see also Chapter I). The ring is locked in place by the diphenylmethane stopper on the left side and the CH2OTBS group on the right. However, upon removal of the TBS group *via* TBAF treatment, the whole thread becomes accessible for the ring. It was found that in DMSO as the solvent the ring prefers to be on the aliphatic chain. DMSO disrupts the H-bonds that normally hold it in place on the left side of the rotaxane. Re-installment of the TBS group in DMSO gave the [2]rotaxane with the ring now locked in the aliphatic part. Subsequent trans-esterification with the bulky 3,5-bis(*tert*-butyl)benzyl alcohol yielded [2]rotaxane in good yield. Because the thread contains only aliphatic methylenes and a very weakly coordinating ester, there are almost no more interactions between the ring and thread, making it a 'impossible' rotaxane.
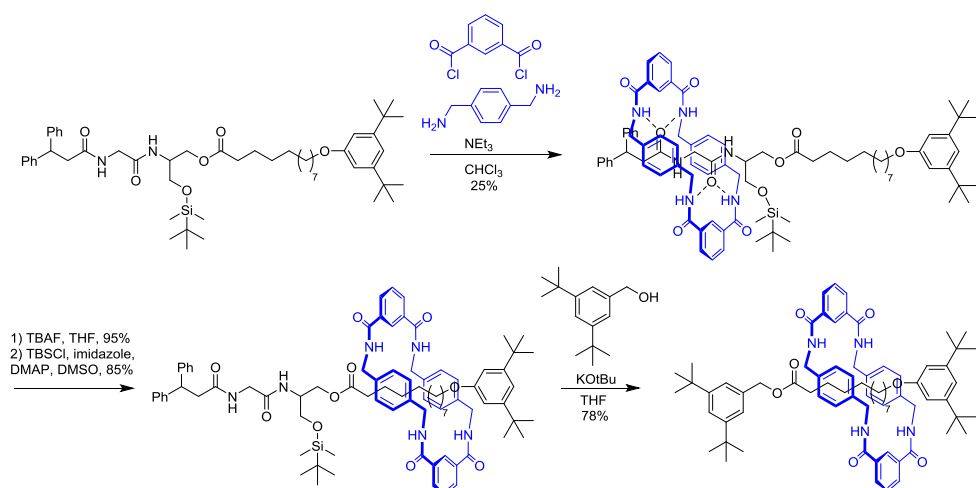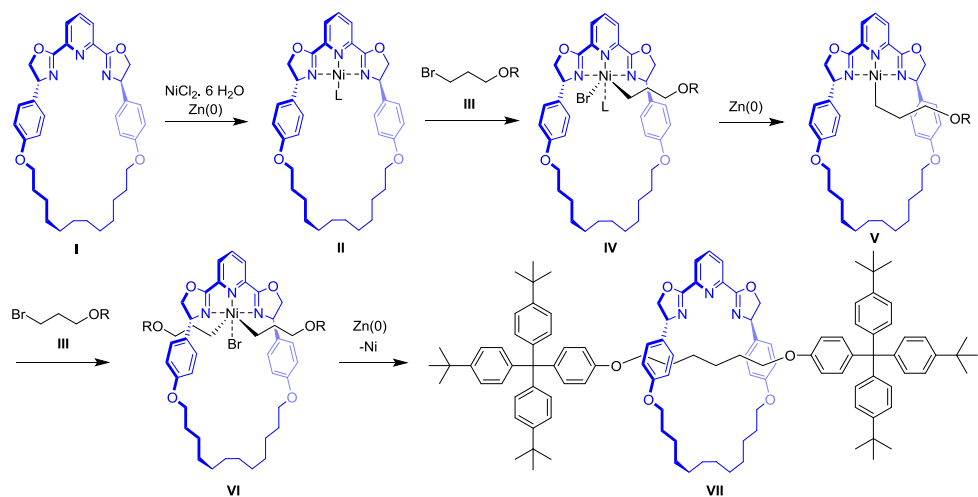

Scheme 1: Leigh's approach to an 'impossible' rotaxane

In 2014, the group of Coutrot reported a conceptually similar synthesis of an 'impossible' rotaxane (see scheme 2).[8] First, a 'classic' crown ether-ammonium rotaxane was synthesized containing a *N*-hydroxysuccinimide derived ester within the thread. The ammonium ion was subsequently neutralized by a strong base and reacted with Boc$_2$O, cancelling its ability to coordinate to the crown ether. On the other side of the thread a triazolium ion was incorporated that could also bind (albeit weakly) to the crown ether, giving the rotaxane with the ring on the triazolium ion. Next, a bulky amine was added that lead to aminolysis of the activated ester, forming an amide bond. The resulting rotaxane does not contain any strongly coordinating groups between the thread and ring anymore, making it a 'impossible' rotaxane. Admittedly, there are still some electrostatic interactions between the crown ether and the triazolium ion.
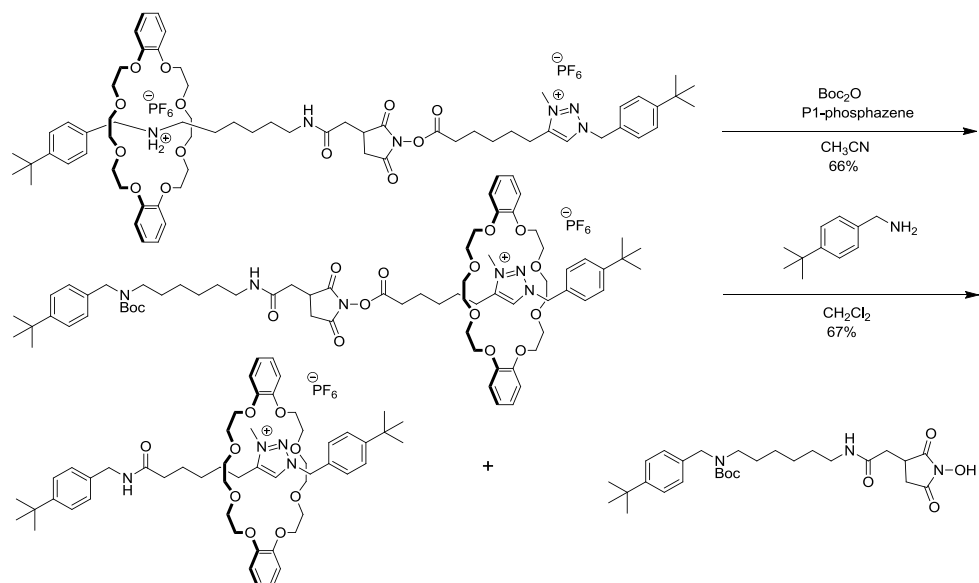
Scheme 2: Synthesis of an 'impossible' rotaxane as described by Coutrot *et al*

Another example of an 'impossible' rotaxane in which the thread fragment has no interactions with the ring was reported by Leigh in 2010 (see scheme 3).[9] This article employs the 'active metal template' method for rotaxane synthesis, in which the metal ion has a dual role: pre-organization of the components and activation of the functional groups that lead to a covalent bond. Macrocycle **I** (a PyBOX type ligand) was reacted with NiCl$_2$, Zn and an alkyl bromide **III**, which had been stoppered with a bulky *tert*-butyltrityl group. The postulated reaction sequence started with the *in situ* reduction of Ni(II) to Ni(0). This electron rich species coordinates within the PyBOX–type macrocycle (**II**). Subsequent oxidative insertion in the C-Br bond leads to Ni(II) species **IV**, which is reduced to Ni(I) species **V** *via* a single electron reduction by metallic zinc. A subsequent second oxidative addition, which can only occur on the sterically accessible backside gives Ni(III) species **VI**. This unstable species was again reduced by zinc, inducing reductive elimination of the two alkyl fragments, liberating [2]rotaxane **VII** and generating Ni(0).

Scheme 3: Leighs approach to give a 'impossible' rotaxane *via* the active metal template strategy

With similar 'active metal template' strategies, employing alkyne homocoupling[10,11,12], alkyne heterocoupling[13], Diels-Alder reaction[14], Michael addition[15], CuAAC reaction[16] and Suzuki coupling[17], more [2]rotaxanes have been synthesized lacking a permanent recognition motif between the thread and ring fragments. Nevertheless, in all these cases the ring fragment contains a large bi- or tridentate ligand, which is retained in the final product and cannot be removed or altered. Ideally, a true 'impossible' rotaxane/catenane should contain no functional groups at all, like the very first rotaxane synthesized by Harrison and Harrison in 1967, see Chapter I. Otherwise, benign/small functional groups that are easily transformed or removed are desirable.

While the non-covalent templated strategies to make macrocycles are plentiful[18], the use of covalent scaffolds that temporarily pre-organize certain functional groups in the correct position have also been reported for the synthesis of macrocycles.[19] However, this approach has been rarely applied for the syntheses of mechanically interlocked products like rotaxanes or catenanes. In 2016, the group of Höger reported the first successful use of a substituted terephthalic acid derivative as a covalent scaffold for the synthesis of a [2]rotaxane (see scheme 4).[18] In this approach, (the chemistry is similar to a previously published article from 2007 [20]), a terephthalic acid derivative was esterified with two phenols, which each had two terminal alkynes present in the sidechains to produce the terephthalic di-ester. Next, these alkynes were homo-coupled *via* an Eglington coupling to make a macrocycle. Subsequent installation of stopper groups *via* a Sonogashira reaction on the iodides and cleavage of the ester groups by aminolysis eventually yielded a [2]rotaxane with a molecular mass of 8340 Da. Remarkably, the rotaxane was unstable at elevated temperatures, yielding the free ring and thread fragments, despite the significant bulk of the stopper groups. In earlier work, the group of Höger reported the use of a temporary covalent template for the synthesis of macrocycles.[21,22,23,24,25,26,27]
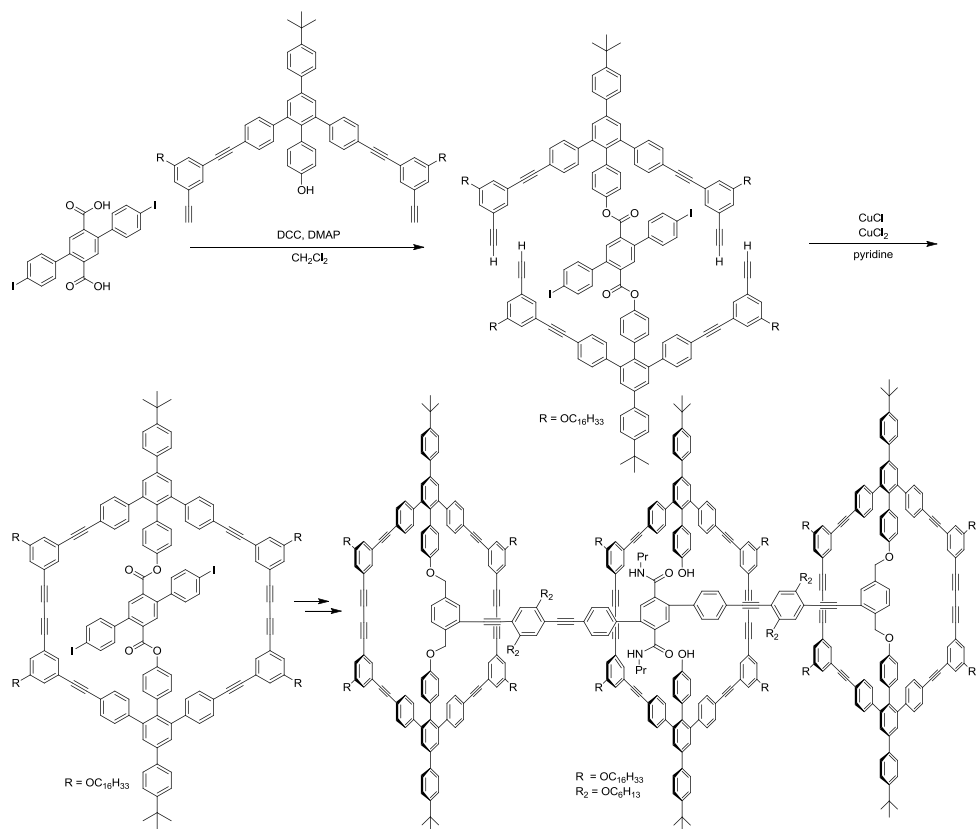
Scheme 4: Synthesis of a [2]rotaxane *via* a covalent template synthesis by Höger *et al.*

However, the first attempted use of a terephthalic acid scaffold to synthesize a [2]rotaxane was performed by the group of Morin in 2012 (see scheme 5).[28] In that article, they followed a very similar route as Höger *et al*, although in their case an aliphatic tether was present between the phenols and the terephthalic acid core. Likewise, the macrocycle was synthesized with an Eglington coupling of two terminal alkynes and the stopper groups were also introduced by Sonogashira couplings. However, in the final step of their synthesis (ester cleavage *via* saponification), only the free ring and thread fragments were obtained. This means that during the assembly the molecule had never been interlocked, but had rather formed a non-interlocked intermediate product like in scheme 6 (bottom). The reason for the formation of this undesired product is probably the use of the flexible aliphatic tether between the ring and the terephthalic acid core. This allowed the formation of the sterically less hindered and energetically more favorable non-interlocked product.
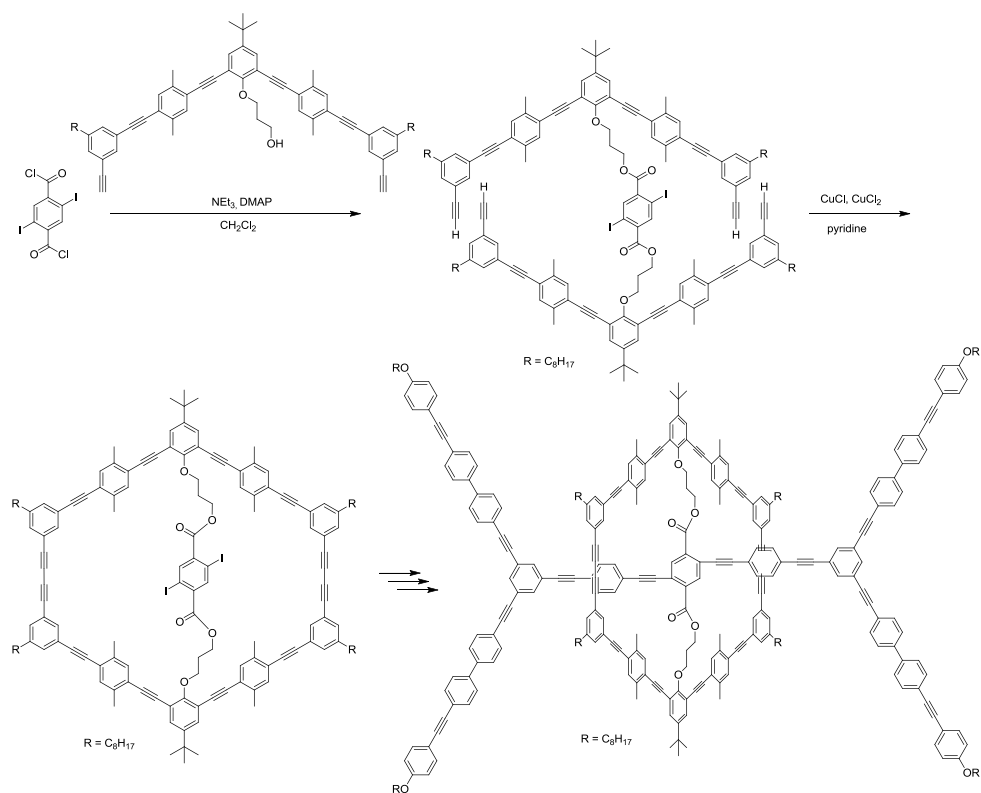
Scheme 5: Attempted synthesis of a terephthalic acid based [2]rotaxane by Morin *et al*

Goal of this chapter

Inspired by the articles by Höger and Morin, we envisioned to synthesize a similar but smaller [2]rotaxane using a terephthalic acid as the temporary covalent template. Likewise, the terephthalic acid core has to be functionalized with bulky stopper groups to prevent dissociation of the ring in the final rotaxane product. Like Höger, the acid groups of the template are envisioned as phenol esters as these are more rigid than aliphatic esters. Moreover, phenol esters are easily functionalized on the 2- and 6-positions, resulting in terephthalic phenol di-esters, in which the functional groups of the phenols are directed toward each other (see scheme 6). However, it is also possible that the mutually reactive functional groups at the same phenol ring will reach each other (especially with a sterically demanding substituent in between) forming a product with two isolated macrocycles (scheme 6, top). Also possible is the formation of non-interlocked product, due to too flexible/large rings (scheme 6, bottom). This side reaction was observed in the work of Morin.

When cyclization proceeds correctly, the free rotaxane can be obtained *via* simple hydrolysis (scheme 6, center) or cleavage by methanolysis, aminolysis or reduction of the esters. The rotaxane obtained lacks a permanent recognition motif like in traditional rotaxane syntheses (i.e. crown ether-ammonium interactions, metal ligand interactions, hydrogen bonding or π-π interactions), thereby expanding the scope of methods and structural diversity. In this approach the only residues left in the final product are sterically hindered phenols in the ring and carboxylic acids (or derivatives) in the thread fragment. Moreover, these moieties can easily be transformed into different functional groups.
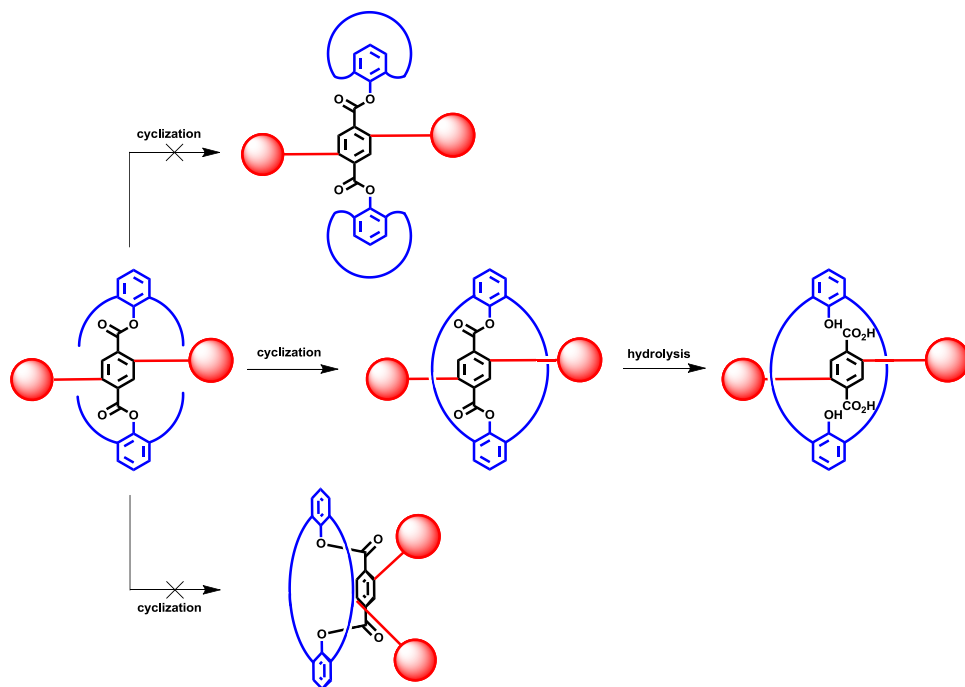
Scheme 6: Schematic strategy towards terephthalic acid derived rotaxanes

If successful, this strategy will quickly yield a truly 'impossible' rotaxane, because the thread and ring fragment do not have interactions and the functional groups required during assembly are small and easily diversified.

Ring-forming strategies

To test whether the strategy of scheme 6 would be feasible, it was necessary to use a reliable ring-forming reaction that would not form the two unwanted isomers during cyclization. To aid synthesis and analysis of the products, the side chains on 2- and 6-positions of both phenols (i.e the blue 'arms' in scheme 6) should have identical mutually reactive end groups. Ideally, these functional groups should react under mild conditions. However, only a few functional groups meet these criteria: alkenes (olefin metathesis), alkynes (alkyne metathesis and Glaser coupling), thiols (disulfide formation) and alkyl halides (Wurtz-type couplings). From these reactions, Glaser coupling is unsuitable for synthesizing small rings, as it constructs four consecutive sp-hybridized atoms on each side of the ring, which would become strained in small systems. Disulfide formation is inherently reversible (i.e. makes a weak bond) and therefore synthetically less attractive because it can lead to statistical as well as thermodynamic mixtures. The homo-coupling of alkyl halides (Wurtz coupling) requires relatively harsh conditions and yields are generally poor. Alkyne and alkene metathesis therefore seem most promising, with preference for the more established alkene metathesis. In contrast to alkyne metathesis, a drawback of alkene metathesis is the inherent formation of E/Z mixtures in unstrained systems that need to be removed with hydrogenation.

Another strategy to complete a ring fragment is *via* addition of a missing fragment (see scheme 7). In this strategy, the functionalities on the blue 'arms' are not mutually reactive, but react with a molecule (green in scheme 7) that has two complementary functional groups. With this

strategy, there is a larger number of functional groups that meets the criteria (mild conditions, easy synthesis, high yields, etc.). In this chapter the following functional groups (in the blue arms) will be explored: azide (CuAAC reaction with a dialkyne), alkyne (CuAAC reaction with a diazide), phenol (alkylation with a dihalide) and *N*-nosylamine (alkylation with a dihalide). The reason these functional groups were chosen is the experience with those reactions as described in previous chapters.
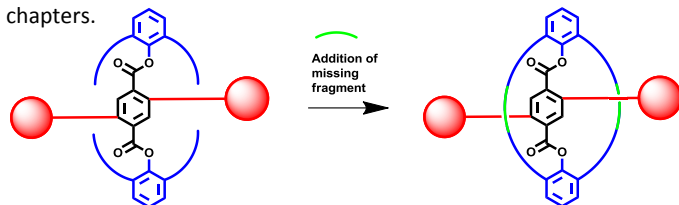

Scheme 7: Ring synthesis *via* addition of missing fragment

Results and discussion

Addition of the missing fragment: Alkylation of *N*-Nosylamines

N-Nosylamines are easily, mildly and selectively alkylated via a S$_N$2 reaction or a Mitsunobu reaction.[29] The strongly electron withdrawing properties of the nosyl group makes the N-H bond acidic, allowing facile deprotonation/alkylation. It was decided to use propargylamine as sidechain at the phenyl 2- and 6-positions, due to the rigidity of the alkyne moiety and ease of functionalization *via* a Sonogashira reaction at the alkyne. For synthetic reasons, 4-*tert*-butylphenol was chosen as phenol core for functionalization on the 2 and 6-positions. The *tert*-butyl group blocks the para position during iodination, increases solubility of intermediates and simplifies the core in ^{1}H-NMR spectra to only singlets (after 2,6-functionalization). Thus, propargyl amine was reacted with nosyl chloride to give nosylamine **1** in 87% yield.[30] Meanwhile, 4-*tert*-butylphenol was iodinated according to a modified literature procedure to give 2,6-diiodo-4-*tert*-butylphenol **3** reproducibly in 70-82% yield.[31] The phenolic OH was protected with an acid-labile MOM group to prevent side reactions in subsequent steps, giving **4** in 98% yield. However, the Sonogashira reaction of diiodide **4** and nosylamine **1** led to the formation of a complex mixture. The somewhat acidic NH was therefore protected with a Boc group to give **2** in 89% yield. Nevertheless, the Sonogashira reaction still failed to give conversion to the desired product. It is speculated that in this case the *N*-Boc-*N*-nosyl group can act as a leaving group, allowing for insertion of palladium to form a palladium-propargyl species.
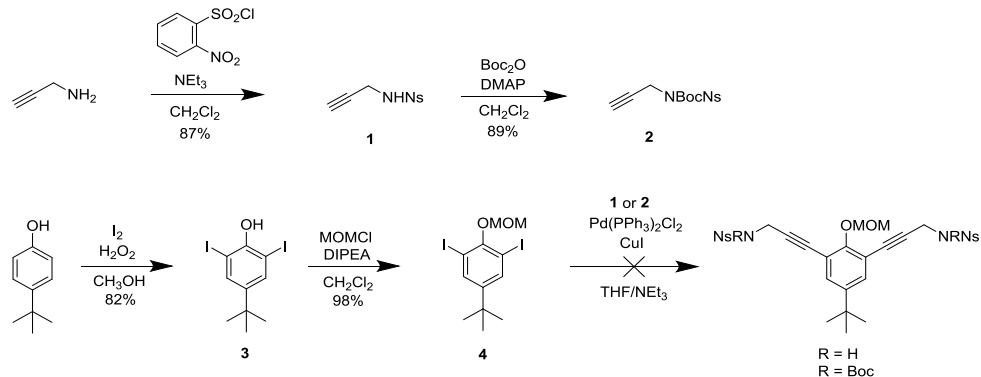
Scheme 8: Synthesis of diiodide **4** and attempted coupling with alkynes **1** and **2**

An alternative route was envisioned, demonstrating the ability of nosylamines to perform the Mitsunobu reaction. Therefore, 2-nitrobenzenesulfonamide was protected (and further activated) with a Boc-group to give *N*-nosyl-*N*-Bocamine **5** in 88% yield.[32] To obtain the coupling partner for the Mitsunobu reaction, diiodide **4** was reacted with propargylalcohol under Sonogashira conditions to give bis-propargylalcohol **6** in 91% yield. Fortunately, the Mitsunobu reaction between **5** and **6** proceeded smoothly, giving product **7** in 80% yield. Acidic deprotection of **7** gave a complex mixture, presumably because protonation of the nitrogen atom leads to formation of a propargylic cation. The problem was overcome by stepwise deprotection, by first removing the Boc-group with pyrrolidine and subsequent treatment of the crude mixture with 6M HCl in THF to give product **8** cleanly in quantitative yield.
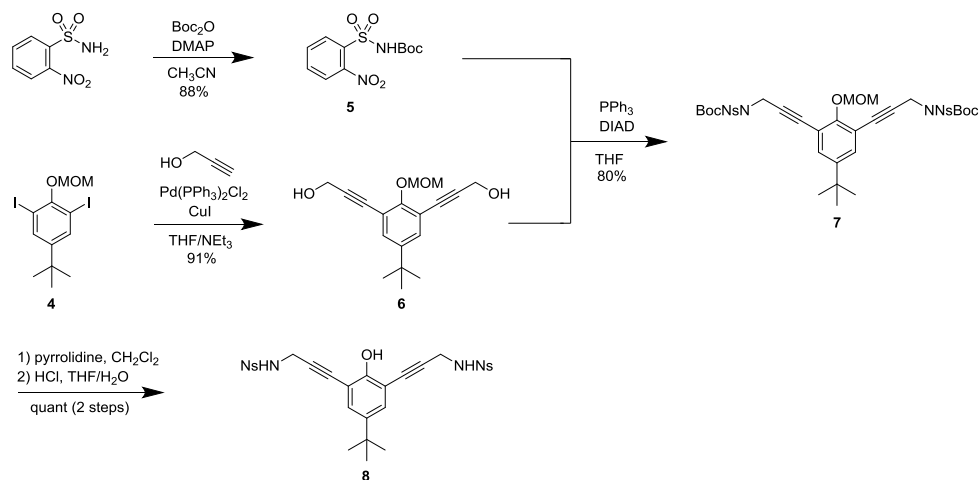
Scheme 9: Synthesis of nosylamine **8**

With the free phenol in hand, the next step was the esterification with a terephthalic acid derivative. The terephthalic acid core should be easily functionalized on the 2 and 5-positions, thereby assuring a linear arrangment of the bulky groups. At this stage in the project, we had not yet 'discovered' the easily functionalized and fluorescing 2,5-dihydroxyterephthalic acid derivatives used in Chapter IV. Therefore, it was envisioned to use 2,5-dibromoterephthalic acid, which could be functionalized later on *via* a Sonogashira reaction on the electron poor bromides.

Commercially available 2,5-dibromoxylene was brominated under radical conditions to give hexabromide **9** in 81% yield. Hydrolysis of the benzylic bromides mediated by aqueous $AgNO_3$ yielded 2,5-dibromoterephthaldehyde **10** in 82% yield.[33] Oxidation of the aldehydes with Oxone® in DMF (as described by the group of Borhan *et al.*[34]) gave the corresponding terephthalic acid **11** in 99% yield and was converted to the bis-acid chloride **12** by treatment with oxalyl chloride in 99% yield. Unfortunately, the reaction of bis-acid chloride **12** and free phenol **8** gave a complex mixture. It is speculated that the acidic NH's also reacted with the acid chlorides, leading to polymers. Nevertheless, also milder Steglich esterification of di-acid **11** and phenol **8** with EDC·HCl/DMAP did not give any desired product. Also here, the acidic NH's are speculated to lead to side reactions. At this point it was decided to abandon this route in favor of a less troublesome strategy.
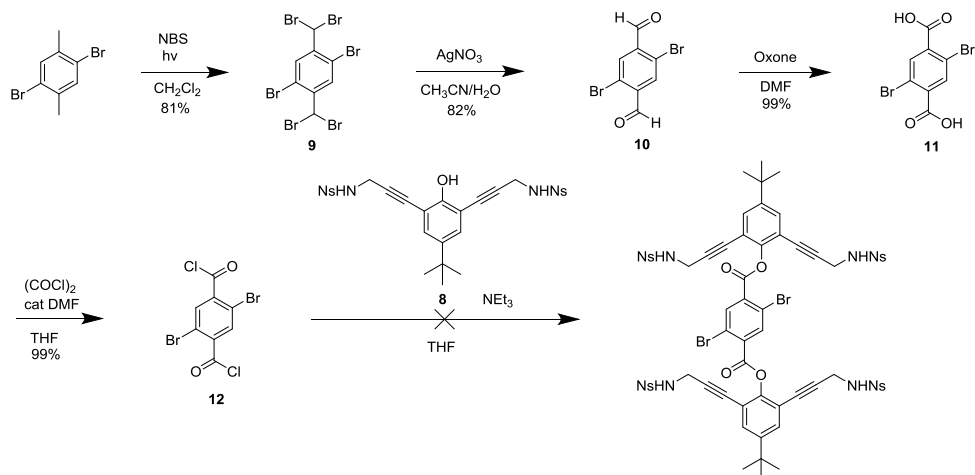
Scheme 10: Synthesis of terephthaloyl dichloride **12** and attempted coupling with **8**

Phenol alkylation

As the *N*-nosylamine alkylation strategy was found to be troublesome, we envisioned the alkylation of a phenol as a good alternative, as phenols are also easily alkylated under relatively mild conditions. Moreover, they are also well tolerated in the Mitsunobu reaction, in case that classical S_N2-type alkylation might not work. Therefore, it was decided to functionalize the 2 and 6-positions of **3** with 4-hydroxyphenyl groups. As judged from molecular ball-and-stick models, these *para*-positions would be in close proximity in the final product. Firstly, 4-bromophenol was protected with a MOM-group, giving **13** in 87% yield (see scheme 11). Lithium bromine exchange, followed by quenching with B(O-iPr)$_3$ and careful acidic hydrolysis gave boronic acid **14** in 64% yield.[35] Subsequent Suzuki coupling of the boronic acid with unprotected diiodide **3** gave triaryl **15** in 88% yield. Esterification with di-acid chloride **12** yielded diester **16** in 51% yield. The moderate yield could be explained due to the considerable steric bulk around the phenolic OH.

Removal of the four MOM-groups was troublesome, however. Overnight stirring of the compound with 6M HCl in THF did not give any conversion and only starting material was recovered. The reason that no reaction had taken place is probably the poor solubility of **16** in aqueous THF. It was therefore dissolved in TFA/CH$_2$Cl$_2$ 9:1 (with a few drops of water) and stirred overnight at room temperature. The following morning, a white precipitation had formed quantitatively, which could not dissolve in any common solvent. Concentration of the filtrate did not yield any material, meaning that the precipitate was indeed the free tetra-ol **17**. However, due to its total insolubility, no follow-up chemistry could be tested.
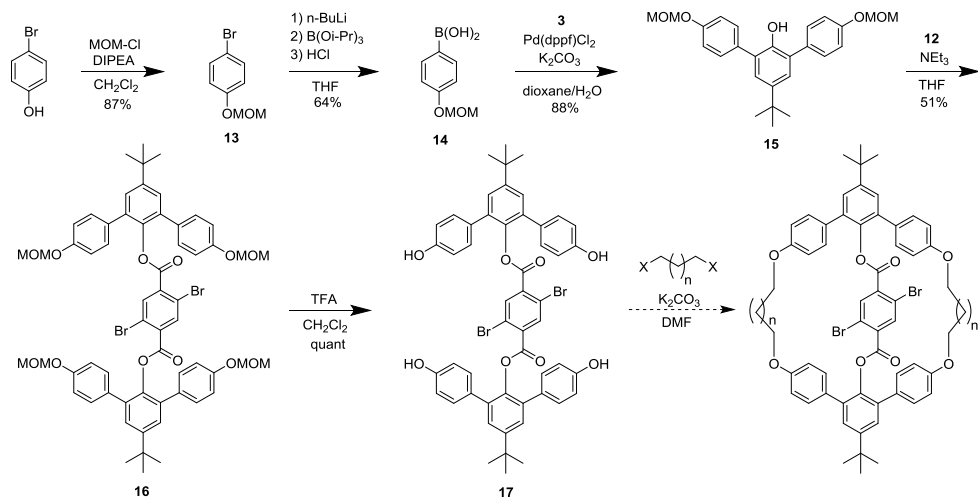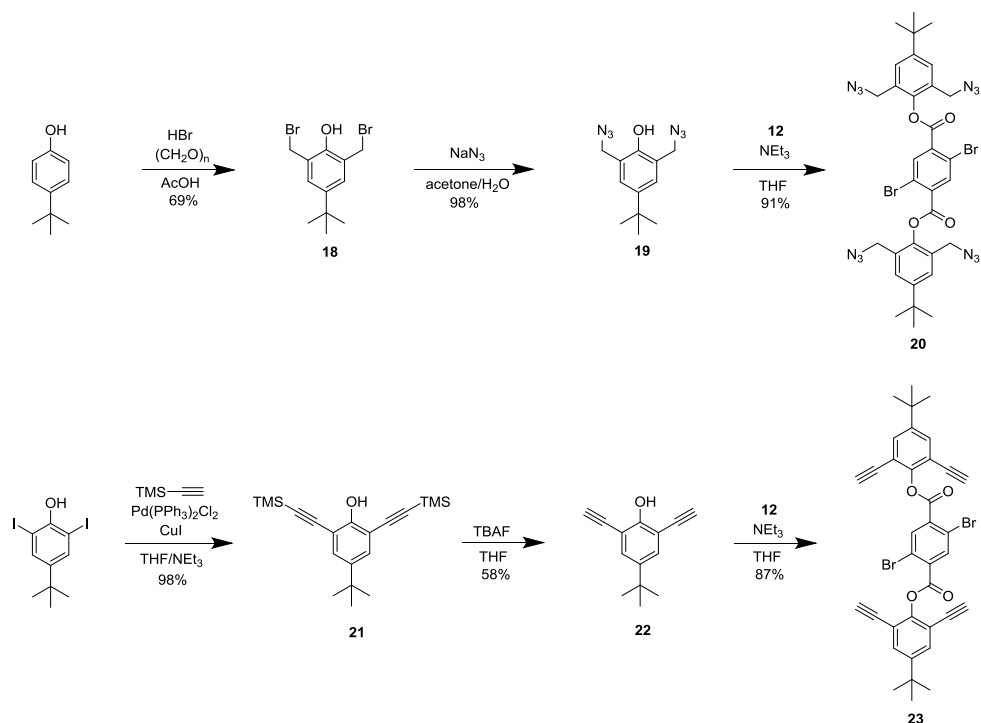
Scheme 11: Synthesis of tetra-ol **17**

CuAAC reaction

Next, the use of the CuAAC reaction was investigated as means for completing the macrocycle. As seen in Chapters III, IV and V, the CuAAC reaction can be successfully employed in difficult macrocyclizations. As we saw no specific preference for the placement of the azide and alkyne, it was decided to synthesize both molecules, i.e. tetra-azide **20** (which would have to react with a dialkyne) and tetra-alkyne **23** (which would have to react with a diazide).

4-tert-Butylphenol was doubly bromomethylated, giving **18** in 69% yield (see scheme 12).[36] Reaction of the dibromide with NaN$_3$ in aqueous acetone yielded diazide **19** in quantitative yield as a yellow oil. No instability of the product was observed, despite being a low weight di-azide. Reaction with di-acid chloride **12** gave di-ester **20** in 91% yield as a white solid.

Next, tetra-alkyne **23** was synthesized: diiodide **3** was reacted with TMS-acetylene under Sonogashira conditions to give bis-alkyne **21** in 98% yield. No side reactions were observed despite the presence of the free phenolic OH on the *ortho* group with respect to the alkynes. However, removal of the TMS groups under standard conditions (K$_2$CO$_3$ in CH$_3$OH) led to decomposition. The use of TBAF at 0 ^{o}C led to a cleaner conversion, although only 58% yield of **22** was obtained. Esterification with di-acid chloride **12** gave tetra-alkyne **23** in 87% yield as a slightly yellow solid.

Scheme 12: Synthesis of tetra-azide **20** and tetra-alkyne **23**

Next, the CuAAC macrocyclization reactions were tested with both compounds (see scheme 13). The optimized CuAAC conditions of Chapter III were used, i.e. slow addition of a solution containing both components to a diluted solution of CuI, DIPEA and 2,6-lutidine. However, reaction of tetra-azide **20** with 1,7-octadiyne led to severe polymerization and only traces of correct mass were observed in the LC-MS traces. Also the reaction of tetra-alkyne **23** with 1,3-bis(azidomethyl)benzene under the same conditions only led to a complex mixture, consisting of oligo- and polymers. At this point it was decided not to further investigate this route. However, in hindsight the 'new' click conditions with Cu(CH$_3$CN)BF$_4$ and TBTA in refluxing CH$_2$Cl$_2$ should have been tested. As described in Chapter IV, these conditions can give a dramatically different outcome in the CuAAC reaction.
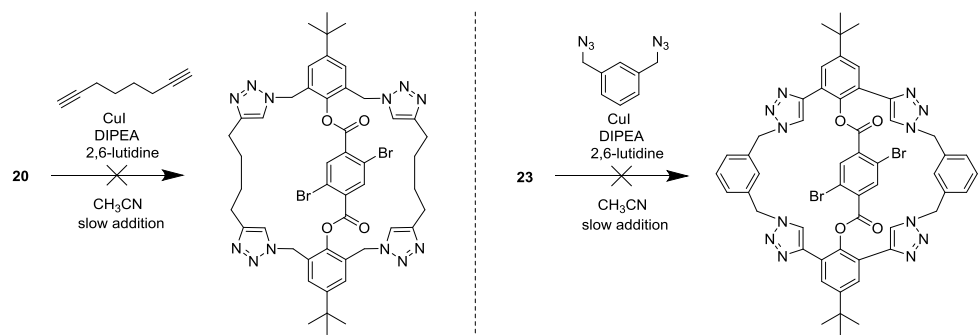

Scheme 13: Attempted CuAAC macrocyclizations

Ring closing metathesis approach from 4-Allyloxyphenyl moieties

At this point the 'addition of the missing fragment' strategy was abandoned, because all routes had shown significant problems. The focus was therefore shifted to an intramolecular cyclization approach. As explained in the introduction, the alkene RCM reaction was preferred for various reasons, but mainly due to its widespread use in macrocyclizations.[37]

Motivated by the efficiency of the Suzuki reaction of diiodide **3** with arylboronic acids, it was decided to install at this product two 4-allyloxyphenyl groups, which would allow for the RCM reaction. The allyl group had to be installed after the Suzuki reaction, because allyloxyphenyl groups are known to give π-allyl complexes with Pd(0). Therefore, 4-hydroxyphenylboronic acid pinacol ester **24** was synthesized from 4-bromophenol and B_2Pin_2 with a palladium catalyst in 78% yield (see scheme 14).[38] Subsequent Suzuki coupling with MOM-protected diiodide **4** gave triaryl **25** in an excellent 90% yield. Alkylation of the phenolic OH's with allyl bromide proceeded smoothly, giving **26** in 94% yield. MOM-deprotection was somewhat difficult, due to the steric inaccessibility of the MOM group. Stirring overnight with 9M HCl was sufficient for complete MOM-removal, giving phenol **27** in 71% yield. Subsequent esterification with bis-acid chloride **12** gave diester **28** in 65% yield as an off-white solid. However, the crucial metathesis reaction of **28** failed to give the desired RCM product and instead polymers were formed in the reaction flask. This suggests that the allyl groups cannot come in close proximity within molecule **28**, therefore preventing macrocyclization by RCM.
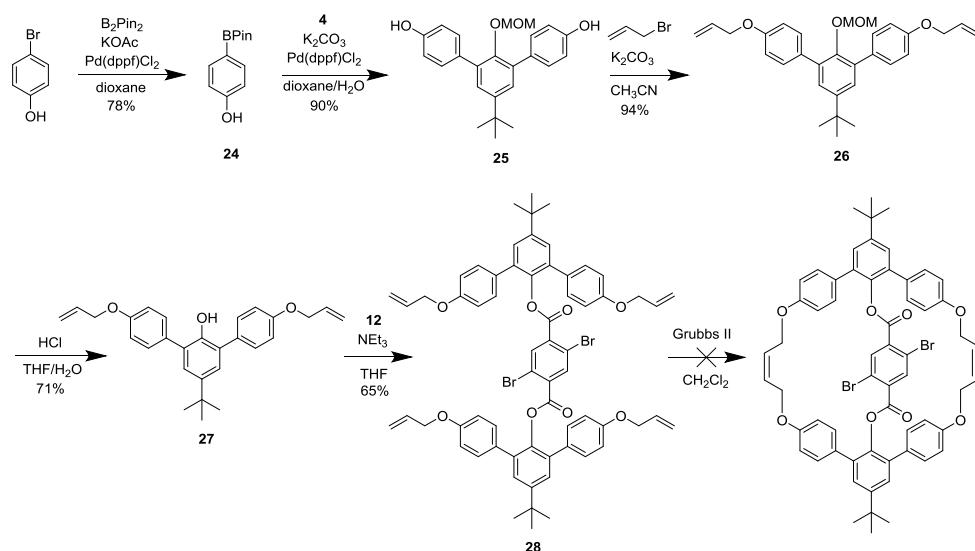
Scheme 14: Synthesis of diester **28** and attempted ring closing metathesis

Allyl propargyl ether RCM

Continuing the quest for a working ring-closing metathesis reaction, it was envisioned to use allyl propargyl ether as coupling partner in the Sonogashira reaction with diiode **4**. The alkyne moiety delivers great structural rigidity and ensures that the allyl groups are pointing toward each other during RCM. Allyl propargyl ether **29** was synthesized according to a literature procedure[39] in 59% yield and coupled with diiodide **4** under Sonogashira conditions to give product **30** in 89% yield (see scheme 15). MOM-deprotection again required some optimization. 3M HCl in THF was found to be

sufficient to complete the deprotection, giving **31** in 68% yield. Esterification with terephtaloyl dichloride gave di-ester **32** in 67% yield. However, when **32** was subjected to the RCM conditions, independent of concentration, solvent, temperature or catalyst loading, no conversion was observed. At first this was surprising, because allyl ethers are well tolerated substrates for Grubbs-type catalysts. It was soon postulated that after initiation of the reaction, the Ru-carbene attached to the allyl ether could come in close proximity to the internal alkyne, probably leading to interactions with the π-orbital of the alkyne and thus catalyst poisoning/deactivation (see scheme 15, bottom right). Although RCM in the presence of internal alkynes has been (scarcely) reported, this strategy was also a dead end, unfortunately.[40]
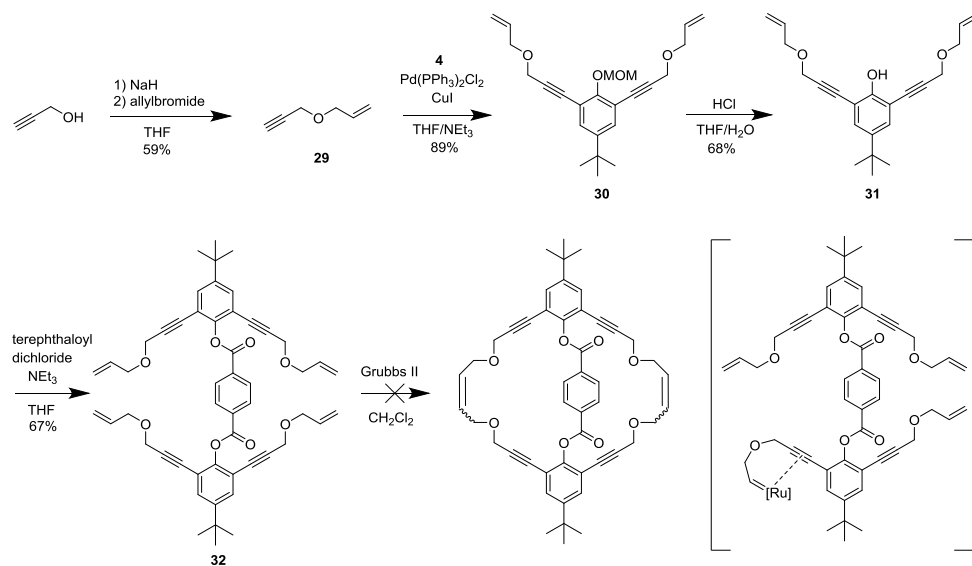

Scheme 15: Synthesis of diester **32** and attempted macrocyclization

RCM with 6-hepten-1-yl arms

With the experience we obtained from the RCM with the allyl propargyl ether, we set out to synthesize a molecule which did not contain any alkyne, or heteroatom, present in the side chains, which could interfere with the metathesis reaction. From making molecular ball-and-stick models, it was observed that 12 C-atoms in the linear chain of each halve of the ring would be optimal for an macrocycle. Consequently, the final product will contain a 30-membered macrocycle. Synthetically, each 'arm' would have to be a 6-heptene-1-yl chain before the RCM step.

The synthesis started with the Sonogashira reaction of **4** with 6-hexyn-1-ol, to give diol **33** in quantitative yield (see scheme 16). The alkyne was hydrogenated with Pd/C at 60 °C (to ensure full conversion) to give aliphatic diol **34** in 92% yield. Parikh-Doering oxidation of the diol yielded dialdehyde **35** in 63% yield, which was transformed in the terminal alkene *via* a Wittig reaction to give dialkene **36** in 87% yield. MOM-deprotection was again difficult, this time requiring 12M (concentrated) HCl in THF to ensure conversion to the free phenol **37**, which was nevertheless obtained in quantitative yield. Esterification with bis-acid chloride **12** yielded diester **38** in 61% yield.
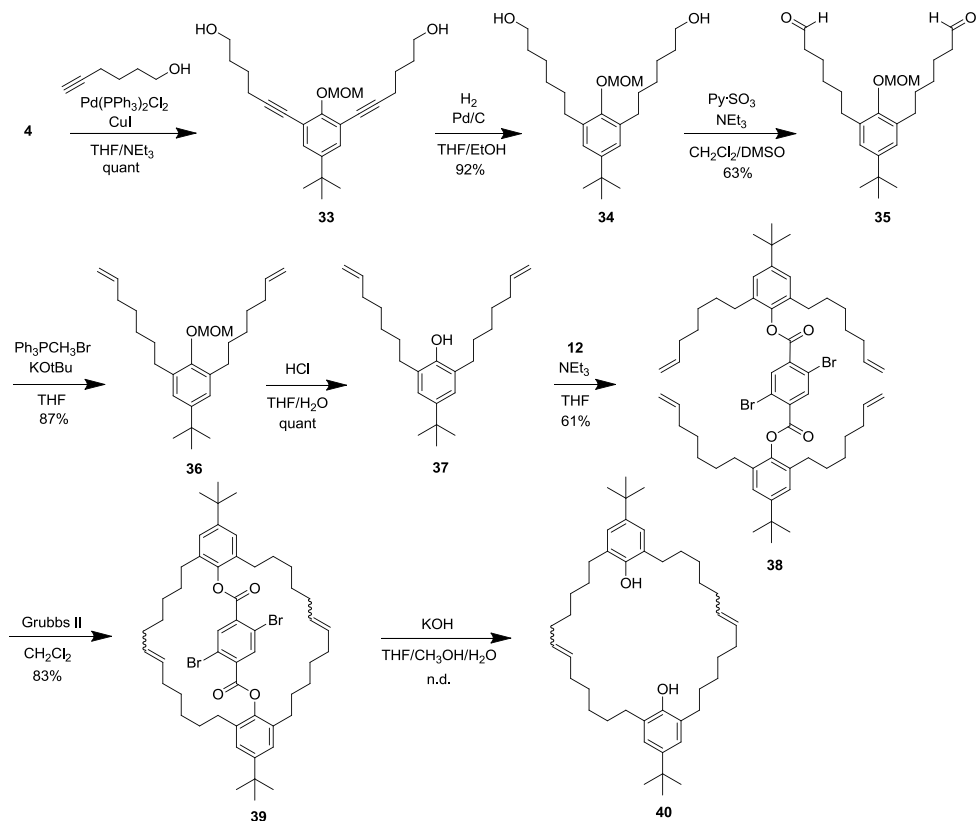
Scheme 16: Synthesis of diester **38** and subsequent ring closing metathesis to successfully give **39**

Fortunately, the crucial intramolecular RCM worked this time uneventfully, giving product **39** with the correct m/z of 914 (from 2x isotope [79]Br) in 83% yield. The ^{1}H-NMR spectrum showed an E/Z mixture, which was somewhat expected for a large unconstrained aliphatic chain. To confirm that the RCM reaction had produced a single macrocycle (and not two isolated macrocycles, like in scheme 6), the esters connecting the macrocycle(s) to the central terephthalic acid core were hydrolyzed with KOH. The exact mass spectrum of the product confirmed the presence of only one species with m/z 628, corresponding to the desired macrocycle **40**. Further functionalization of the bromides in compound **39** *via* palladium chemistry was troublesome, presumably due to steric hindrance around the bromides. It was therefore thought necessary to perform the Sonogashira reaction before the metathesis reaction. Bulky acid **3.13** (see Chapter III)[41] was converted to the corresponding propargylamide **41** in 75% yield, and subsequently coupled to diester **38** in 39% yield (see scheme 17). However, subsequent ring closing metathesis gave a complex mixture this time. Most probably the presence of the alkynes is suspected to cause again side reactions, as was observed in earlier in this chapter.
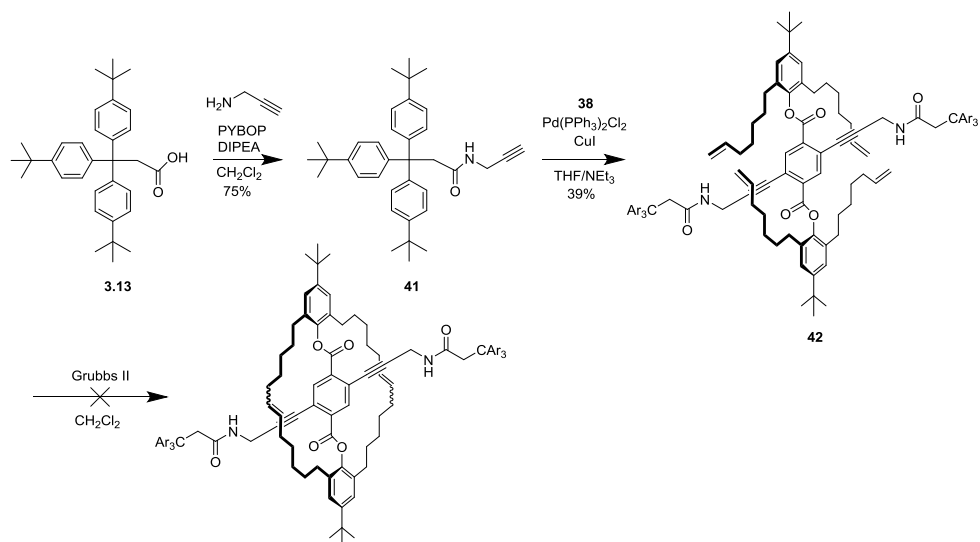
Scheme 17: Synthesis of diester **42** and attempted ring closing metathesis

It was apparent that the bulky stopper groups should to be installed before the RCM step but also *via* a covalent bond that would be compatible with olefin-metathesis. Fortunately, at this point bis-pentafluorophenol ester derivative **4.20** (see Chapter IV) had been synthesized. It was apparent that this versatile scaffold could solve the current problem we faced, by adding a terminal alkyne moiety to the 2- and 5-positions of the terephthalic acid core. These terminal alkynes would allow for mild, high yielding and (most importantly) a metathesis-compatible installment of a triazole moiety in the thread.

Phenol **37** was reacted with scaffold **4.20** under the previously optimized reaction conditions (Cs$_2$CO$_3$ and 4Å in CH$_3$CN at 60 ^{o}C) to give diester **43** in 91% yield (see scheme 18). Subsequent CuAAC reaction with azide **3.17** (see Chapter III) gave bis-adduct **44** in 87% yield as a colorless foam. Subsequent RCM proceeded smoothly to give macrocycle **45** in 80% yield as an undetermined E/Z mixture in a 3:1 ratio. To clean up the ^{1}H-NMR spectrum, the alkenes were hydrogenated with Pd/C in a mixture of THF/EtOH at 60 ^{o}C to give the fully aliphatic product **46**. Despite the removal of the E/Z mixture, analysis of the ^{1}H-NMR spectrum showed a non-symmetrical arrangement of the ring fragment.

The final ester cleavage was troublesome and required extensive testing. Attempted aminolysis with methylamine (similar to Höger's approach) failed to give any conversion. Reaction with sodium methoxide also gave hardly any conversion. However, some hydrolyzed product was obtained due to reaction of methoxide with traces of water. Unexpectedly, attempted hydrolysis with NaOH only gave incomplete conversion, even at 70 ^{o}C. Nevertheless, the reaction was eventually forced to completion by heating **46** in a sealed tube at 130 ^{o}C with KOH in dioxane for 2 hours. To make the polar di-acid product more convenient to handle, it was converted directly to the dimethyl ester by reaction with TMS-diazomethane, giving rotaxane **47** in 89% yield over the two steps.

The reason for the troublesome ester cleavage is likely the sterically hindered nature of the endocyclic esters. In addition, the highly apolar environment of the esters prevent attack of the polar hydroxide anion, as well as amines and methoxide in the earlier described experiments. ^{1}H-NMR analysis revealed sharp signals for both components in the expected 1:1 molar ratio and no more asymmetry was observed, indicating a freely movable ring fragment.[1] Moreover, HRMS gave a mass of 1953.3888 Da (1.3 ppm deviation from theotical mass) as the sole product.
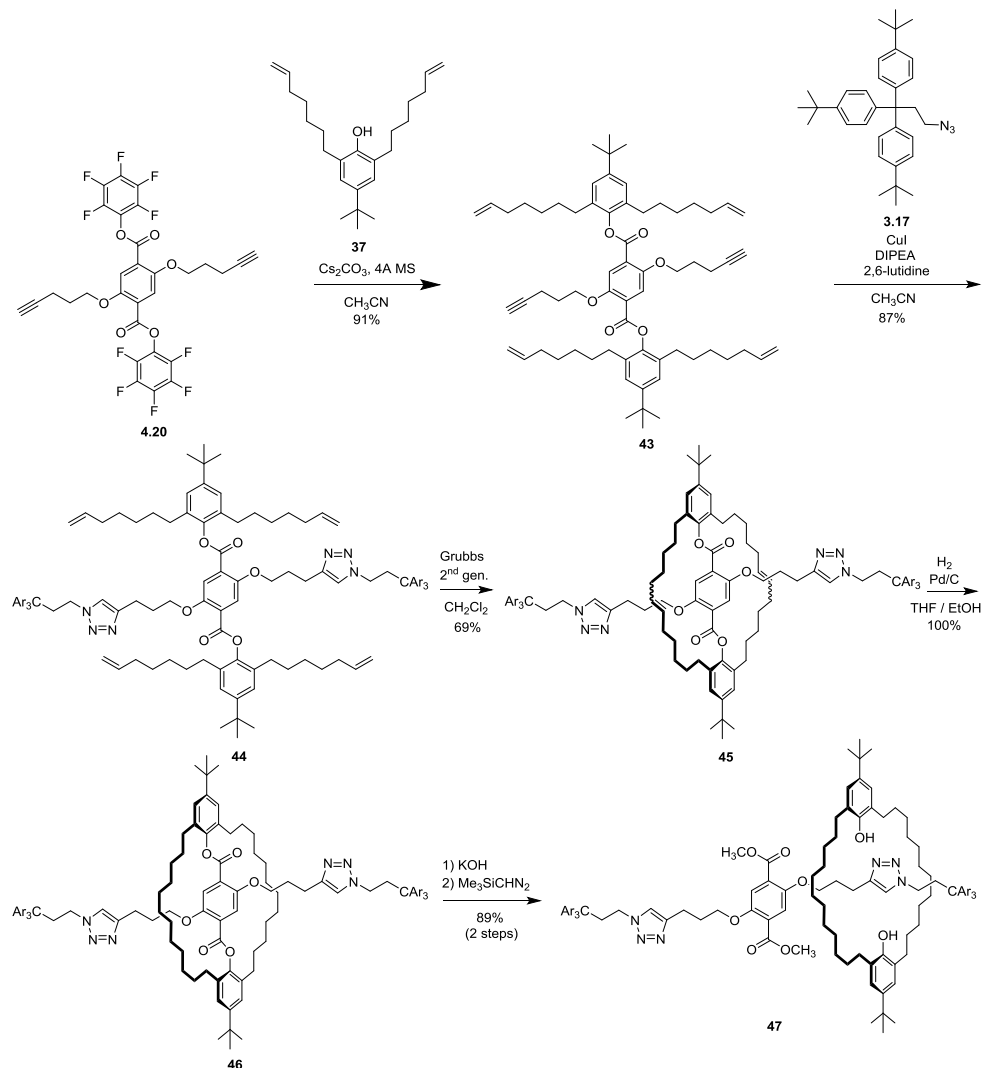
Scheme 18: Synthesis of terephthalic acid based [2]rotaxane **47**

Conclusions

In this chapter a short and robust methodology has been developed for the synthesis of a [2]rotaxane, using a terephthalic acid core as a temporary covalent scaffold. After screening for a suitable macrocyclization reaction, the alkene RCM reaction was found to selectively give the desired ring in high yield.

Experimental section

<u>General remarks</u>

Unless stated otherwise, reactions were performed without special precautions like drying or N_2/Argon atmosphere. Dried CH_2Cl_2 and CH_3CN were obtained by distilling these solvents with CaH_2 as drying agent. Dried THF and Et_2O were obtained by distillation with sodium. All dried solvents were stored under N_2 atmosphere. Dry DMF on 4Å molecular sieves was obtained from Sigma-Aldrich and stored under N_2 atmosphere. Reagents were purchased with the highest purity (usually >98%) from Sigma Aldrich and Fluorochem and used as received. Grubbs 2nd generation catalyst was purchased from AK Scientific. Reactions were monitored with thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254). SilaFlash® P60 (particle size 40-63 µm) was used for silica column chromatography. NMR spectra were recorded on Bruker DRX-500, 400 and 300 MHz instruments and calibrated on residual undeuterated solvent signals as internal standard. The ^{1}H-NMR multiplicities were abbreviated as followed: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet. High resolution mass spectra (HRMS) were recorded on a Mass spectra were collected on an AccuTOF GC v 4g, JMS-T100GCV Mass spectrometer (JEOL, Japan). FD/FI probe equipped with FD Emitter, Carbotec or Linden (Germany), FD 10 µm. Current rate 51.2 mA/min over 1.2 min machine using field desorption (FD) as ionization method. Depending on the molecule, either the $(M)^+$ or $(M+H)^+$ were observed; often the $(M+Na)^+$ signal was also observed. Melting points were recorded on a Wagner & Munz Polytherm A melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Alpha FTIR machine.

Synthetic procedures

Compound **1**
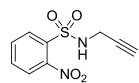
1.21 mL propargylamine (22 mmol, 1.1 equiv) and 3.06 mL NEt_3 (22 mmol, 1.1 equiv) were dissolved in 60 mL dry CH_2Cl_2 and cooled to 0 °C under N_2 atmosphere. After cooling, 4.43 g 2-nitrobenzenesulfonyl chloride (20 mmol) was added portionwise over 10 minutes. The icebath was removed and the reaction was stirred overnight at room temperature. The organic layer was washed with 30 mL 1M HCl and the water layer was extracted with 10 mL CH_2Cl_2. The combined organic layers were washed with 30 mL 1M HCl, 30 mL saturated $NaHCO_3$, dried over $MgSO_4$ and filtered over a short plug of silica (ca. 5 cm ø, 2 cm thick), which was flushed with 30 mL CH_2Cl_2. The organic layer was concentrated in *vacuo* to give **1** (4.18 g, 17.41 mmol, 87%) as an off-white solid. Melting point: 90-94 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.19 (m, 1H), 7.92 (m, 1H), 7.78 (m, 2H), 5.75 (t, 1H), 4.02 (dd, 2H), 2.00 (t, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 147.94, 134.05, 133.85, 133.09, 131.61, 125.60, 77.43, 73.41, 33.47; IR (cm^{-1}): 3319, 3296, 2125, 1591, 1330

Compound **2**
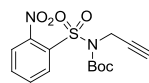
3.56 g **1** (14.81 mmol), 4.76 mL Boc_2O (20.73 mmol, 1.4 equiv) and 181 mg DMAP (1.48 mmol, 0.1 equiv) were dissolved in 30 mL dry CH_2Cl_2 and stirred at room temperature for 2h. The reaction was washed with 15 mL 1M HCl and the water layer was extracted with 10 mL CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (PE/CH_2Cl_2 5:2 → 3:2) to give **2** (4.49 g, 13.18 mmol, 89%) as a white solid. Melting point: 116-119 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.33 (m, 1H), 7.80 (m, 3H), 4.55 (d, 2H), 2.37 (t, 1H), 1.40 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 149.72, 147.83, 134.64, 133.27, 133.09, 132.12, 124.72, 86.01, 78.69, 72.32, 36.69, 27.91; IR (cm^{-1}): 3265, 3100, 2983, 2129, 1731, 1591

Compound **3**
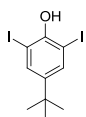
4.50 g 4-*tert*-butylphenol (30 mmol) was dissolved in 150 mL absolute CH_3OH and 7.61 g I_2 (30 mmol, 1.0 equiv) and 6.13 mL 30% H_2O_2 (60 mmol, 2.0 equiv) were added. The reaction was stirred at room temperature for 3 days and was concentrated in *vacuo*. The residue was partitioned between 50 mL CH_2Cl_2 and 50 mL H_2O. The water layer was extracted with 10 mL CH_2Cl_2 and the combined organic layers were washed with 40 mL saturated $Na_2S_2O_3$, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/EtOAc 50:1) to give **3** (10.94 g, 27.22 mmol, 91%) as a red crystalline solid. Melting point: 79-80 ^{o}C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 2H), 5.61 (s, 1H), 1.28 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 151.30, 147.52, 136.50, 82.29, 34.09, 31.40; IR (cm^{-1}): 3462, 2956, 2866, 1737, 1453, 1241

Compound **4**
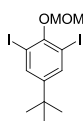
9.93 g **3** (24.70 mmol) and 4.12 mL Et$_3$N (29.64 mmol, 1.2 eq) were dissolved in 50 mL dry CH_2Cl_2 and cooled to 0 ^{o}C. After cooling, 2.25 mL MOMCl (29.64 mmol, 1.2 eq) was added dropwise and the reaction was stirred at 0 ^{o}C for 1h and overnight at room temperature. The reaction was quenched by addition of 10 mL H_2O and stirred for 10 minutes. The organic layer was washed with 30 mL 1M HCl and the water layer was extracted with 10 mL CH_2Cl_2. The combined organic layers were washed with 30 mL 1M NaOH and dried over $MgSO_4$ and concentrated in *vacuo* to give **4** (10.52 g, 23.58 mmol, 95%) as a faint yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 2H), 5.13 (s, 2H), 3.78 (s, 3H), 1.29 (s, 9H)

Compound **5**
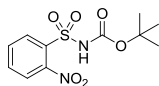
3.68 g 2-nitrophenylsulfonamide (18.22 mmol) was suspended in 40 mL dry CH_2Cl_2 and 3.8 mL Et$_3$N (27.33 mmol, 1.5 equiv), 5.02 mL Boc$_2$O (21.86 mmol, 1.2 equiv) and 111 mg DMAP (0.911 mmol, 0.05 equiv) were added. The reaction was stirred for 1 hour at room temperature and the organic layer was washed with 40 mL 1M HCl and the water layer was extracted with 2 x 10 mL CH_2Cl_2. The combined organic layers were washed with 20 mL 1M HCl, dried over $MgSO_4$ and concentrated in *vacuo*. The residue was triturated with 2 x 10 mL PE/Et$_2$O to give **5** (4.83 g, 15.97 mmol, 88%) as a colorless powder. Melting point: 152-155 ^{o}C (dec.); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.33 (m, 1H), 7.91-7.78 (m, 3H), 7.73 (bs, 1H), 1.45 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.73, 143.80, 134.89, 133.36, 132.64, 132.03, 125.23, 85.02, 27.99; IR (cm^{-1}): 3248, 2980, 1746, 1535, 1356, 1143

Compound **6**
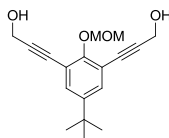
2.23 g **4** (5.00 mmol) and 1.15 mL propargylalcohol (20.0 mmol, 4 equiv) were dissolved in 20 mL dry THF/Et$_3$N 1:1 and degassed with five N_2/vacuum cycles. After degassing, 70 mg Pd(PPh$_3$)$_2$Cl$_2$ (0.10 mmol, 0.02 equiv) and 38 mg CuI (0.20 mmol, 0.04 equiv) were added. The reaction was stirred overnight at room temperature under N_2 atmosphere and concentrated in *vacuo*. The residue was partitioned between 50 mL EtOAc and 30 mL 1M HCl. The water layer was extracted with 2 x 15 mL EtOAc and the combined organic layers were washed with 30 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/EtOAc 1:1) to give a thick yellow oil, which slowly crystallized to give **6** (1.38 g, 4.56 mmol, 91%) as a waxy solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 2H), 5.35 (s, 2H), 4.53 (s, 4H), 3.68 (s, 3H), 2.07 (bs, 2H), 1.29 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.68, 146.96, 131.44, 116.56, 99.31, 91.53, 82.16, 57.94, 51.70, 34.41, 31.23; IR (cm^{-1}): 3354, 2961, 2232, 1456, 1280, 1155
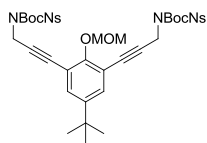
164

## Compound 7

1.08 g **6** (3.58 mmol), 2.27 g **5** (7.52 mmol, 2.1 equiv) and 1.97 mmol PPh_3 (7.52 mmol, 2.1 equiv) were dissolved in 36 mL dry THF and cooled to 0 °C under N_2 atmosphere. After cooling, 1.48 mL DIAD (7.52 mmol, 2.1 equiv) was slowly added dropwise and the reaction was stirred at 0 °C for 1h and overnight at room temperature. The mixture was concentrated in *vacuo* and the crude product was dry-loaded on silica and purified by column chromatography (PE/EtOAc 2:1 → 1:1) to give **7** (2.51 g, 2.88 mmol, 80%) as a slightly yellow foam. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.42 (m, 2H), 7.80 (m, 6H), 7.44 (s, 2H), 5.35 (s, 2H), 4.84 (s, 4H), 3.65 (s, 3H), 1.41 (s, 18H), 1.30 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.35, 149.74, 147.87, 146.48, 134.54, 133.09, 132.83, 132.49, 132.23, 131.64, 125.06, 124.58, 116.32, 99.25, 88.03, 85.86, 80.71, 57.89, 37.52, 34.27, 31.14, 27.82; IR (cm^{-1}): 2969, 2256, 1734, 1591, 1395, 1149

Compound 8
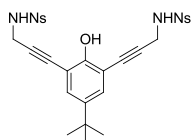
2.33 g **7** (2.68 mmol) was dissolved in 20 mL CH_2Cl_2 and 1 mL pyrrolidine was added. The reaction was stirred overnight at room temperature and the organic layer was washed with 20 mL 1M HCl. The waterlayer was extracted with 10 mL CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. The residue was dissolved in a mixture of 8 mL THF, 8 mL 6M HCl and 2 mL CH_3OH and stirred overnight at room temperature. The mixture was diluted with 30 mL EtOAc and 30 mL H_2O. The water layer was extracted with 2 x 10 mL EtOAc and the combined organic layers were washed with 20 mL brine, dried over $MgSO_4$ and concentrated in *vacuo* to give **8** (1.71 g, 2.68 mmol, quant) as a yellow foam. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.21 (d, 2H), 7.84 (d, 2H), 7.65 (quint, 4H), 6.96 (s, 2H), 5.95 (t + bs, 3H), 4.26 (d, 4H), 1.21 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 155.53, 147.85, 142.91, 133.86, 133.78, 133.09, 131.57, 130.28, 125.61, 108.19, 88.89, 80.07, 34.46, 34.05, 31.27; IR (cm^{-1}): 3461, 3341, 2965, 1536, 1344, 1163

Compound 9
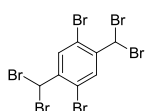
2.64 g 1,4-dibromo-2,5-dimethylbenzene (10.0 mmol) and 8.90 g NBS (50.0 mmol, 5 equiv) were dissolved in 100 mL dry CH_2Cl_2 under N_2 atmosphere and the mixture was irradiated with a 500W construction lamp for 18h, allowing slight reflux. The mixture was cooled to room temperature and was washed with 3 x 50 mL H_2O, dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was crystallized from ca. 100 mL EtOAc to give pure **9** (4.77 g, 8.23 mmol, 82%) as white needles. Melting point: 162-167 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 2H), 6.96 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.07, 135.02, 119.53, 37.27; IR (cm^{-1}): 3010, 1462, 1356, 1215, 1151

Compound 10
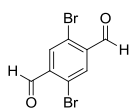
4.74 g **9** (8.18 mmol) was dissolved in 160 mL CH_3CN and a solution of 9.73 g $AgNO_3$ (57.3 mmol, 7 equiv) in 25 mL H_2O was added and the mixture was stirred overnight at reflux, after which it was filtered while hot. The filtered solid residue was washed with an additional 25 mL hot CH_3CN. The combined organic layers were cooled to room temperature and then to 0 °C. The crystals were filtered and washed with cold CH_3CN to give **10** (1.97 g, 6.73 mmol, 82%) as an off-white solid. Melting point: 187-191 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.37 (s, 2H), 8.18 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 189.99, 137.45, 135.12, 125.65; IR (cm^{-1}): 3074, 2972, 2892, 1678, 1340, 1056

Compound 11
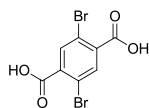
1.97 g **10** (6.73 mmol) was dissolved in 33 mL DMF and 8.69 g oxone (14.1 mmol, 2.1 equiv) was added and the reaction was stirred overnight at room temperature. The organic layer was concentrated in *vacuo* and the residue was partitioned between 60 mL EtOAc and 60 mL 1M HCl. The water layer was extracted with 30 mL EtOAc and the combined organic layers were washed with 30 mL 1M HCl, 30 mL brine, dried over $MgSO_4$ and concentrated in *vacuo* to give **11** (2.15 g, 6.65 mmol, 99%) as a white powder. Melting point: >300 ^{o}C; ^{1}H-NMR (300 MHz, DMSO-*d6*) δ 13.96 (bs, 2H), 8.02 (s, 2H); ^{13}C-NMR (75 MHz, DMSO-*d6*) δ 165.65, 137.08, 134.96, 118.83; IR (cm^{-1}): 2849, 2636, 2501, 1693, 1469, 1244

Compound 12
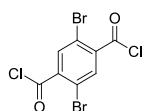
324 mg **11** (1.00 mmol) was dissolved in 6 mL dry THF under N_2 atmosphere and 0.343 mL $(COCl)_2$ (4.00 mmol, 4 equiv) and 1 droplet DMF were added. The mixture was stirred overnight at room temperature and concentrated in *vacuo*. The residue was co-evaporated with dry THF to give **12** (357 mg, 0.989 mmol, 99%) as a beige solid. Due to the sensitivity of acid chlorides, no spectral data were acquired.

Compound 13
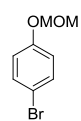
3.46 g 4-bromophenol (20.0 mmol) and 4.89 mL DIPEA (28.0 mmol, 1.4 equiv) were dissolved in 40 mL dry CH_2Cl_2 and cooled to 0 ^{o}C. After cooling, 2.12 mL MOM-Cl (28 mmol, 1.4 equiv) was added dropwise and the reaction was stirred at 0 ^{o}C for 1h and overnight at room temperature. The reaction was quenched with 20 mL H_2O and stirred vigorously for 10 minutes. The water layer was extracted with 20 mL CH_2Cl_2 and the combined organic layers were washed with 20 mL 1M HCl, 20 mL 1M NaOH, dried over $MgSO_4$ and filtered through a plug of silica (7 cm ø, 2 cm high). The silica plug was flushed with 100 mL CH_2Cl_2. The organic layer was concentrated *in vacuo* to give **13** (3.78 g, 17.43 mmol, 87%) as a colorless oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.40 (d, 2H), 6.95 (d, 2H), 5.17 (s, 2H), 3.50 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 156.44, 132.43, 118.18, 114.30, 94.59, 56.15; IR (cm^{-1}): 2954, 2902, 1485, 1231, 1150

Compound 14
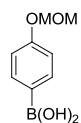
3.78 g **13** (17.4 mmol) was dissolved in 100 mL dry THF under N_2 atmosphere and cooled to -78 ^{o}C. After cooling, 7.67 mL 2.5M n-BuLi (19.2 mmol, 1.1 equiv) was added dropwise to the solution and the reaction was stirred for 30 minutes at -78 ^{o}C. Next, 4.83 mL B(O-iPr)$_3$ (20.9 mmol, 1.2 equiv) was added dropwise and the reaction was stirred at -78 ^{o}C for 15 minutes and 2h at room temperature. The mixture was cooled to 0 ^{o}C and 20 mL 1M HCl was added and stirred for 30 min. The aqueous layer was separated and extracted with 2 x 10 mL EtOAc. The combined organic layers were washed with 40 mL 1M HCl. The water layer was extracted with 2 x 10 mL EtOAc and the combined organic layers were washed with 40 mL brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EtOAc 4:1 → 1:1) to give **14** (2.05 g, 11.25 mmol, 64%) as a faint yellow solid. Melting point: 130-133 ^{o}C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 8.18 (d, 2H), 7.17 (d, 2H), 5.29 (s, 2H), 3.55 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 160.69, 137.60, 115.66, 94.16, 56.32; IR (cm^{-1}): 2901, 1601, 1346, 1150
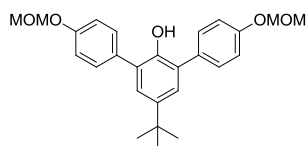
Compound 15

1.69 g **3** (4.21 mmol), 1.99 g **14** (10.96 mmol, 2.6 equiv) and 1.75 g K$_2$CO$_3$ (12.63 mmol, 3.0 equiv) were dissolved in 40 mL 1,4-dioxane/H$_2$O 3:1 and the mixture was degassed with five vacuum/N$_2$ cycles. To the mixture was added 171 mg Pd(dppf)Cl$_2$ · CH$_2$Cl$_2$ complex (0.21 mmol, 0.05 equiv) and the reaction was stirred overnight at 50 °C under N$_2$ atmosphere. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between 40 mL EtOAc and 40 mL NH$_4$Cl solution. The water layer was extracted with 10 mL EtOAc and the combined organic layers were washed with 10 mL H$_2$O, 10 mL brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc 9:1 → 7:1) to give **15** (1.57 g, 3.70 mmol, 88%) as a slight yellow solid. Melting point: 111 – 115 °C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.53 (d, 4H), 7.28 (s, 2H), 7.18 (d, 4H), 5.29 (s, 1H), 5.27 (s, 4H), 3.55 (s, 6H), 1.39 (s, 9H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 156.81, 147.23, 143.31, 131.73, 130.68, 127.72, 126.86, 116.65, 94.52, 56.19, 34.34, 31.70; IR (cm^{-1}): 3401, 2953, 1607, 1508, 1228, 1013

Compound 16
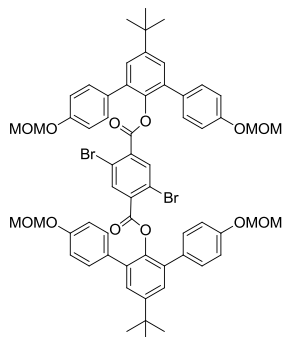
1.05 g **15** (2.49 mmol, 2.1 equiv) and 0.36 mL Et$_3$N (2.60 mmol, 2.2 equiv) were dissolved in 12 mL dry THF under N$_2$ atmosphere and cooled to 0 °C. After cooling, 427 mg **12** (1.18 mmol) was added portionwise and the reaction was stirred 1h at 0 °C and overnight at room temperature. The reaction was diluted with 30 mL EtOAc and washed with 20 mL 1M HCl. The water layer was extracted with 10 mL EtOAc and the combined organic layers were washed with 20 mL saturated NaHCO$_3$, 20 mL NaCl, dried over MgSO$_4$ and concentrated *in vacuo*. The crude product was boiled with 100 mL EtOH, cooled to 0 °C and filtered. The flask was rinsed with cold EtOH and added to the filtered material. The product was dried on air and on vacuum to give **16** (683 mg, 0.603 mmol, 51%) as an off-white solid. Melting point: 243 – 246 °C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.40 (s, 4H), 7.39 (d, 8H), 7.20 (s, 2H), 7.08 (d, 8H), 5.22 (s, 8H), 3.51 (s, 12H), 1.39 (s, 18H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 162.47, 157.01, 149.80, 142.55, 135.57, 135.38, 134.87, 131.64, 130.47, 127.30, 119.42, 116.24, 94.55, 56.17, 34.86, 31.58 ; IR (cm^{-1}): 2954, 1749, 1509, 1228, 1150

Compound 18
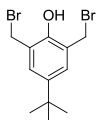
6.00 g 4-*tert*-butylphenol (40.0 mmol) was dissolved in 30 mL 33% HBr/HOAc, cooled to 0 °C and 3.00 g paraformaldehyde (100 mmol, 2.5 equiv) was added portionwise over 30 minutes. The reaction was stirred 1h at 0 °C and overnight at room temperature. The mixture was poured on 150 mL ice-water and extracted with 3 x 40 mL CH$_2$Cl$_2$. The combined organic layers were washed with 3 x 50 mL H$_2$O, dried over MgSO$_4$ and concentrated in *vacuo*. The residue was dissolved in ca. 200 mL boiling PE, and slowly cooled to room temperature. Next, it was stored at -20 °C for 1h and the solid was filtered and washed with cold PE. The powder was dried in *vacuo* to give **18** (9.22 g, 27.4 mmol, 69%) as a colorless powder. Melting point: 85-87 °C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.30 (s, 2H), 5.54 (bs, 1H), 4.60 (s, 4H), 1.32 (s, 9H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 151.18, 144.24, 128.51, 124.61, 34.30, 31.48, 30.21; IR (cm^{-1}): 3496, 2957, 1491, 1207

Compound **19**
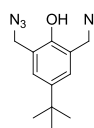
1.68 g **18** (5.00 mmol) was dissolved in 15 mL acetone/H_2O 2:1 and 812 mg NaN_3 (12.25 mmol, 2.5 equiv) was added. The reaction was stirred overnight at room temperature, after which it was diluted with 20 mL Et_2O and 20 mL H_2O. The water layer was extracted with 10 mL Et_2O and the combined organic layers were washed with 15 mL brine, dried over $MgSO_4$ and concentrated in *vacuo* to give **19** (1.27 g, 4.88 mmol, 98%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19 (s, 2H), 6.25 (s, 1H), 4.49 (s, 4H), 1.33 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 151.12, 143.20, 127.15, 122.14, 51.25, 33.97, 31.31; IR (cm^{-1}): 3423, 2961, 2091, 1468, 1199

Compound **20**
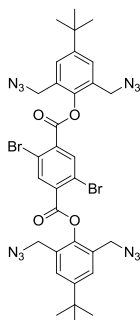
497 mg **19** (1.91 mmol, 2.1 equiv) and 0.278 mL NEt_3 (2.00 mmol, 2.2 eq) were dissolved in 10 mL dry THF under N_2 atmosphere and cooled to 0 °C, after which 328 mg **12** (0.909 mmol, 1.0 eq) was added portionwise. The reaction was stirred at 0 °C for 1h and overnight at room temperature. The mixture was diluted with 30 mL EtOAc and washed with 20 mL 1M HCl. The water layer was extracted with 10 mL EtOAc and the combined organic layers were was with 20 mL 1M NaOH, 20 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (PE/CH_2Cl_2 3:1 → 2:1 → 1:1) to give **20** (666 mg, 0.824 mmol, 91%) as a white solid. Melting point: 142-148 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 2H), 7.48 (s, 4H), 4.41 (s, 8H), 1.41 (s, 18H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.34, 150.89, 144.81, 137.62, 134.96, 128.19, 127.83, 121.26, 50.69, 34.87, 31.41; IR (cm^{-1}): 2962, 2093, 1741, 1276, 1230, 1108, 1040

Compound **21**
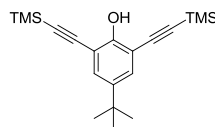
1.01 g **3** (2.50 mmol) and 1.42 mL trimethylsilylacetylene (10.00 mmol, 4.0 equiv) were dissolved in 10 mL dry THF/NEt_3 1:1 and degassed with five vacuum/N_2 cycles. After degassing, 35 mg Pd(PPh$_3$)$_2$Cl$_2$ (0.05 mmol, 0.02 equiv) and 19 mg CuI (0.10 mmol, 0.04 equiv) were added and the reaction was stirred overnight at room temperature. The mixture was diluted with 30 mL EtOAc and 30 mL 1M HCl. The water layer was extracted with 2 x 10 mL EtOAc and the combined organic layers were washed with 25 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (PE/EtOAc 50:1) to give **21** (844 mg, 2.46 mmol, 98%) as a waxy yellow solid. Melting point: 116-128 °C (slow melting trajectory); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 2H), 6.15 (s, 1H), 1.29 (s, 9H), 0.30 (s, 18H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.01, 143.03, 130.37, 109.30, 100.64, 99.67, 34.24, 31.36, 0.11; IR (cm^{-1}): 3477, 2960, 2153, 1462, 1247, 1197

Compound **22**
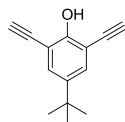
840 mg **21** (2.45 mmol) was dissolved in 10 mL dry THF, cooled to 0 °C and 1.83 g TBAF · $3H_2O$ (5.15 mmol, 2.1 equiv) was added. The mixture was stirred for 1h and concentrated in *vacuo*. The residue was partitioned between 20 mL EtOAc and 20 mL H_2O. The water layer was extracted with 2 x 10 mL EtOAc and the combined organic layers were washed with 20 mL brine, dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (PE/EtOAc 30:1 → 25:1) to give **22** (283 mg, 1.43 mmol, 58%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 2H), 6.08 (s, 1H), 3.43 (s, 2H), 1.29 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.39, 132.32, 131.07, 108.40, 83.10, 78.72, 34.18, 21.29; IR (cm^{-1}): 3498, 3282, 2957, 2100, 1465, 1212, 1198

Compound 23
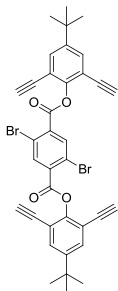
283 mg **22** (1.43 mmol, 2.1 eq) and 0.21 mL NEt$_3$ (1.50 mmol, 2.2 eq) were dissolved in 5 mL dry THF under N$_2$ atmosphere and cooled to 0 ^{o}C, after which 245 mg **12** (0.680 mmol) was added portionwise. The reaction was stirred at 0 ^{o}C for 1h and overnight at room temperature. The reaction was diluted with 20 mL EtOAc and 20 mL 1M HCl and the water layer was extracted with 2 x 10 mL EtOAc. The combined organic layers were washed with 20 mL brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/CH$_2$Cl$_2$ 2:1) to give **23** (405 mg, 0.592 mmol, 87%) as a slight yellow solid. Melting point: 221-224 ^{o}C (dec.); ^{1}H-NMR (300 MHz, CDCl$_3$) δ 8.54 (s, 2H), 7.63 (s, 4H), 3.30 (s, 4H), 1.36 (s, 18H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 161.40, 150.54, 149.86, 137.56, 134.94, 131.57, 121.22, 116.56, 82.72, 78.29, 34.76, 31.21; IR (cm^{-1}): 3281, 2963, 1755, 1441, 1191, 1033

Compound 25
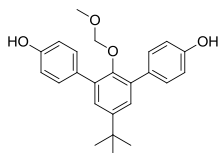
1.02 g **4** (2.29 mmol), 1.53 g 4-hydroxyphenylboronic acid pinacol ester **24** (5.72 mmol, 2.5 equiv) and 946 mg K$_2$CO$_3$ (6.86 mmol, 3 equiv) were dissolved in 25 mL 1,4-dioxane/H$_2$O 3:2 and the mixture was degassed with five vacuum/N$_2$ cycles. After this, 83 mg Pd(dppf)Cl$_2$ (0.114 mmol, 0.05 equiv) was added and the reaction was stirred overnight at 50 ^{o}C under N$_2$ atmosphere. The mixture was diluted with 30 mL EtOAc and 30 mL H$_2$O and the waterlayer was extracted with 2x10 mL EtOAc. The combined organic layers were washed with 20 mL brine, dried over MgSO$_4$, concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc 3:1) to give **25** (776 mg, 2.05 mmol, 90%) as a slightly yellow foam. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.51 (d, 4H), 7.31 (s, 2H), 6.90 (d, 4H), 5.49 (bs, 2H), 4.40 (s, 2H), 2.78 (s, 3H), 1.38 (s, 9H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 154.96, 147.40, 135.19, 132.07, 131.13, 127.10, 115.23, 98.62, 56.90, 34.60, 31.61; IR (cm^{-1}): 3355, 2962, 1612, 1511, 1225

Compound 26
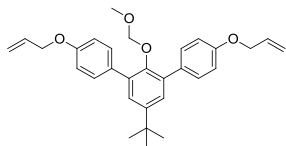
770 mg **25** (2.03 mmol), 840 mg K$_2$CO$_3$ (6.09 mmol, 3.0 equiv) and 0.52 mL allylbromide (6.09 mmol, 3.0 equiv) were dissolved in 10 mL CH$_3$CN and stirred overnight at 50 ^{o}C. The mixture was concentrated *in vacuo* and partitioned between 20 mL CH$_2$Cl$_2$ and 20 mL H$_2$O. The water layer was extracted with 2 x 10 mL CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo* to give **26** (876 mg, 1.91 mmol, 94%) as a brown oil, which was used without further purification. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.60 (d, 4H), 7.36 (s, 2H), 7.05 (d, 4H), 6.12 (m, 2H), 5.49 (d, 2H), 5.36 (d, 2H), 4.64 (d, 4H), 4.41 (s, 2H), 2.75 (s, 3H), 1.42 (s, 9H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ = 157.78, 149.27, 147.15, 135.14, 133.37, 132.29, 130.88, 127.03, 117.79, 114.49, 98.78, 68.90, 56.77, 34.55, 31.59; IR (cm^{-1}): 2961, 1608, 1507, 1238, 1224

Compound 27
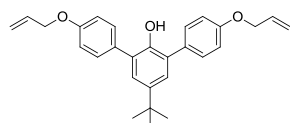
1.01 g **26** (2.20 mmol) was dissolved in 20 mL THF/9M HCl 1:1 and stirred overnight at room temperature. The reaction was diluted with 20 mL EtOAc and 20 mL H$_2$O. The water layer was extracted with 2 x 10 mL EtOAc and the combined organic layers were washed with 20 mL brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc 25:1 → 20:1) to give **27** (645 mg, 1.56 mmol, 71%) as a thick

colorless oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.54 (d, 4H), 7.29 (s, 2H), 7.08 (d, 4H), 6.15 (m, 2H), 5.49 (d, 2H), 5.36 (d, 2H), 5.30 (s, 1H), 4.64 (d, 4H), 1.40 (s, 9H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 158.21, 147.25, 143.27, 133.35, 130.67, 130.63, 127.75, 126.73, 117.90, 115.16, 69.00, 34.34, 31.71; IR (cm^{-1}): 3538, 2959, 1608, 1508, 1460, 1224

Compound 28
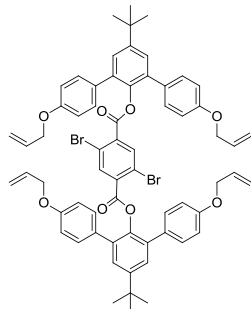
645 mg **27** (1.56 mmol, 2.1 equiv) and 0.23 mL Et$_3$N (1.63 mmol, 2.2 equiv) were dissolved in 7½ mL dry THF under N$_2$ atmosphere and cooled to 0 ^{o}C. After cooling, 267 mg **12** (0.74 mmol) was added portionwise, followed by ca. 10 mg DMAP (catalytic). The reaction was stirred 1h at 0 ^{o}C and overnight at room temperature. The reaction was diluted with 30 mL CH$_2$Cl$_2$ and washed with 15 mL 1M HCl. The wate rlayer was extracted with 2 x 5 mL CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/CH$_2$Cl$_2$ 4:2 → 3:2 → 2:2) to give **28** (534 mg, 0.480 mmol, 65%) as a colorless solid.

Melting point: 206-210 ^{o}C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.41 (s, 4H), 7.39 (d, 4H), 7.19 (s, 2H), 6.97 (d, 8H), 6.10 (m, 4H), 5.45 (d, 4H), 5.32 (d, 4H), 4.58 (d, 8H), 1.42 (s, 18H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 162.53, 158.38, 149.75, 142.65, 135.63, 135.37, 134.92, 133.34, 130.62, 130.43, 127.22, 119.45, 117.90, 114.77, 68.99, 34.85, 31.60; IR (cm^{-1}): 2965, 2870, 1747, 1607, 1508, 1226

Compound 30
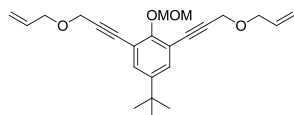
446 mg **24** (1.00 mmol) and 269 mg allyl propargylether **29** (2.80 mmol, 2.8 equiv) were dissolved in 5 mL dry THF/NEt$_3$ 1:1 and degassed with five vacuum/N$_2$ cycles. After degassing, 35 mg Pd(PPh$_3$)$_2$Cl$_2$ (0.05 mmol, 0.05 equiv) and 9 mg CuI (0.05 mmol, 0.05 equiv) were added and the reaction was stirred overnight at 40 ^{o}C. The mixture was concentrated in *vacuo* and the residue was partitioned between 30 mL EtOAc and 20 mL 1M HCl. The water layer was extracted with 10 mL EtOAc and the combined organic layers were washed with 20 mL H$_2$O, 20 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (PE:EtOAc 9:1 → 8:1) to give **30** (300 mg, 0.886 mmol, 89%) as a faint yellow oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.43 (s, 2H), 5.95 (m, 1H), 5.36 (d, 2H), 5.35 (s, 2H), 5.25 (d, 2H), 4.43 (s, 4H), 4.16 (d, 4H), 3.68 (s, 3H), 1.29 (s, 9H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 156.88, 146.76, 143.67, 134.09, 131.56, 118.03, 116.64, 99.23, 89.13, 82.91, 70.81, 58.08, 57.80, 34.38, 31.23; IR (cm^{-1}): 2962, 1456, 1351, 1157, 1074

Compound 31
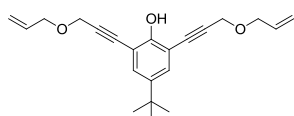
331 mg **30** (0.98 mmol) was dissolved in 9 mL THF/3M HCl 2:1 and stirred overnight at room temperature. The mixture was diluted with 20 mL EtOAc and 20 mL H$_2$O. The water layer was extracted with 10 mL EtOAc and the combined organic layers were washed with 20 mL brine, dried over MgSO$_4$ and concentrated in *vacuo* to give **31** (288 mg, 0.98 mmol, quant) as a yellow oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.39 (s, 2H), 6.08 (bs, 1H), 5.96 (m, 2H), 5.37 (d, 2H), 5.26 (d, 2H), 4.46 (s, 4H), 4.17 (d, 4H), 1.28 (s, 9H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 155.59, 143.18, 134.08, 130.61, 118.24, 108.91, 90.90, 81.29, 70.96, 58.08, 34.21, 31.34; IR (cm^{-1}): 3478, 2961, 2863, 2225, 1466, 1351, 1228, 1063

Compound **32**
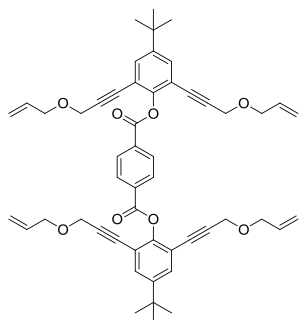
288 mg **31** (0.98 mmol, 2.2 equiv) and 0.149 mL NEt$_3$ (1.07 mmol, 2.4 equiv) were dissolved in 5 mL dry THF under N$_2$ atmosphere and cooled to 0 °C. After cooling, 90 mg terephthaloyl chloride (0.445 mmol, 1.0 equiv) and ~1 mg DMAP (catalytic) was added. The icebath was removed and the reaction was stirred overnight at room temperature. The mixture was diluted with 20 mL EtOAc and washed with 10 mL 1M HCl. The water layer was extracted with 5 mL EtOAc and the combined organic layers were washed with 20 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (PE/EtOAc 9:1 → 8:1) to give **32**

(216 mg, 0.300 mmol, 67%) as a colorless oil, which solidified upon standing. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 8.39 (s, 2H), 7.56 (s, 4H), 5.78 (m, 4H), 5.22 (d, 4H), 5.15 (d, 4H), 4.26 (s, 8H), 3.96 (d, 8H), 1.35 (s, 18H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 163.34, 150.23, 149.28, 133.80, 133.65, 130.77, 130.51, 117.86, 116.97, 90.07, 81.11, 70.48, 57.68, 34.65, 31.19; IR (cm^{-1}): 2965, 2251, 1743, 1259, 1198, 1061

Compound **33**

4.92 g **4** (11.0 mmol) and 2.92 mL 5-hexyn-1-ol (26.5 mmol, 2.4 equiv) were dissolved in 55 mL THF/NEt$_3$ 1:1 and the mixture was degassed with five vacuum/N$_2$ cycles. After degassing, 310 mg Pd(PPh$_3$)$_2$Cl$_2$ (0.441 mmol, 0.04 equiv) and 168 mg CuI (0.882 mmol, 0.08 equiv) were added and the reaction was stirred overnight at 40 °C. The mixture was concentrated in *vacuo* and the residue was partitioned between 50 mL EtOAc and 50 mL

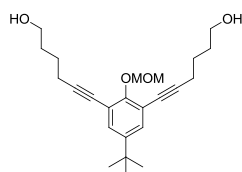1M HCl. The water layer was extracted with 3 x 25 mL EtOAc and the combined organic layers were washed with 50 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/EtOAc 1:1 → 1:2 → 1:3) to give **33** (4.07 g, 10.54 mmol, 95%) as a thick yellow oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.32 (s, 2H), 5.31 (s, 2H), 3.70 (t, 4H), 3.67 (s, 3H), 2.49 (t, 4H), 1.92 (bs, 2H), 1.74 (m, 8H), 1.28 (s, 9H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 156.19, 146.61, 130.41, 117.58, 98.81, 93.90, 77.62, 62.39, 57.71, 34.38, 32.00, 31.26, 24.99, 19.54; IR (cm^{-1}): 3346, 2938, 2232, 1454, 1231, 1201

Compound **34**
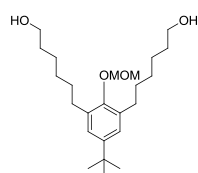
4.07 g **33** (10.50 mmol) was dissolved in 30 mL THF/EtOH 1:1 and 400 mg Pd/C (10% w/w) was added. The mixture was bubbled with H$_2$ gas for 5 minutes and then the reaction was stirred overnight at 60 °C under H$_2$ atmosphere. After completion of the reaction, N$_2$ gas was bubbled through the reaction for 10 minutes and the mixture was filtered through a plug of Celite, which was flushed with EtOAc. The filtrate was concentrated in *vacuo* to give **34** (3.83 g,

9.70 mmol, 92%) as a faint yellow oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.03 (s, 2H), 4.94 (s, 2H), 3.65 (t, 4H), 3.63 (s, 3H), 2.64 (t, 4H), 1.82 (bs, 2H), 1.61 (m, 8H), 1.42 (m, 8H), 1.31 (s, 9H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 151.76, 146.91, 134.95, 124.79, 99.90, 63.03, 57.37, 34.35, 32.82, 31.62, 30.93, 30.78, 29.54, 25.67; IR (cm^{-1}): 3353, 2930, 2858, 1709, 1479, 1158

Compound 35
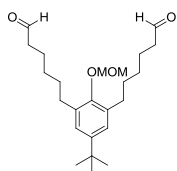
1.34 g **34** (3.39 mmol) and 4.71 mL NEt₃ (33.90 mmol, 10.0 equiv) were dissolved in 25 mL CH₂Cl₂/DMSO 4:1 and cooled to 0 °C. After cooling, 2.16 g pyridine · SO₃ (13.56 mmol, 4.0 equiv) was added and the reaction was stirred at 0 °C for 3 hours, after which the reaction was completed (TLC). The reaction was quenched by addition of 10 mL H₂O and stirred for 10 minutes. The reaction was diluted with 25 mL CH₂Cl₂ and was washed with 50 mL 1M HCl. The waterlayer was extracted with 2 x 10 mL CH₂Cl₂. The combined organic layers were washed with 25 mL 1M HCl and 2 x 15 mL H₂O, dried over MgSO₄ and concentrated in *vacuo*. The crude product was purified by column chromatography (PE/EtOAc 9:1 → 8:1 → 7:1) to give **35** (838 mg, 2.15 mmol, 63%) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ 9.79 (t, 2H), 7.03 (s, 2H), 4.93 (s, 2H), 3.62 (s, 3H), 2.64 (t, 4H), 2.46 (dt, 4H), 1.66 (m, 8H), 1.46 (sext, 4H), 1.32 (s, 9H); ¹³C-NMR (75 MHz, CDCl₃) δ 202.95, 151.91, 146.99, 134.73, 124.84, 99.96, 57.34, 43.97, 34.36, 31.61, 30.74, 30.68, 29.39, 22.09; IR (cm⁻¹): 2929, 2859, 1723, 1479, 1182

Compound 36

1.80 g methyltriphenylphosphonium bromide (5.03 mmol, 2.50 equiv) was put in a flame-dried flask and dried under vacuum at 70 °C for 1 hour. The flask was cooled and backfilled with N₂ gas. Next, 15 mL dry THF was added and the mixture was cooled to 0 °C. After cooling, 564 mg KOtBu (5.03 mmol, 2.50 equiv) was added and the mixture was stirred for 15 minutes at 0 °C. Next, 785 mg **35** (2.01 mmol) was dissolved in 5 mL dry THF and added dropwise to the aforementioned solution. The reaction was stirred for 1h at 0 °C and 1h at room temperature, and was subsequently 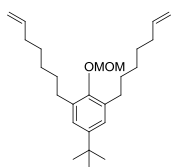quenched with 1 mL acetone. The mixture was concentrated in *vacuo*, dry-loaded on silica and purified by column chromatography (PE/EtOAc 100:0 → 99:1 → 98:2) to give **36** (676 mg, 1.87 mmol, 87%) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ 7.04 (s, 2H), 5.82 (m, 2H), 5.02 (d, 2H), 4.98 (d, 2H), 4.94 (s, 2H), 3.63 (s, 3H), 2.63 (t, 4H), 2.08 (q, 4H), 1.67 (m, 4H), 1.44 (m, 8H), 1.32 (s, 9H); ¹³C-NMR (75 MHz, CDCl₃) δ 151.80, 146.82, 139.26, 135.05, 124.76, 114.34, 99.91, 57.33, 34.37, 33.92, 31.64, 30.94, 30.91, 29.50, 28.97; IR (cm⁻¹): 2926, 2857, 1640, 1479, 1182

Compound 37
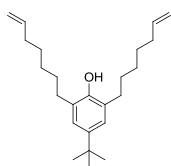
950 mg **36** (2.46 mmol) was dissolved in 13 mL THF/12M HCl/CH₃OH 8:4:1 and was stirred overnight at room temperature. The mixture was diluted with 20 mL H₂O and 20 mL EtOAc. The water layer was extracted with 2 x 20 mL EtOAc and the combine organic layers were washed with 20 mL brine, dried over MgSO₄ and concentrated in *vacuo*. The residue was purified by column chromatography (PE/EtOAc 99:1 → 98:2) to give **37** (844 mg, 2.46 mmol, quant) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ 7.01 (s, 2H), 5.85 (m, 2H), 5.03 (d, 2H), 4.97 (d, 2H), 4.53 (s, 1H), 2.62 (t, 4H), 2.10 (q, 4H), 1.65 (quint, 4H), 1.46 (m, 8H), 1.32 (s, 9H); ¹³C-NMR (75 MHz, CDCl₃) δ 149.16, 142.92, 139.20, 127.36, 124.72, 114.42, 34.13, 33.89, 31.75, 30.70, 29.94, 29.30, 28.92; IR (cm⁻¹): 3618, 2926, 2856, 1640, 1482, 1188; HRMS (FD) calcd for $C_{24}H_{38}O$ [M⁺]: 342.2923, found: 342.2915

Compound **38**
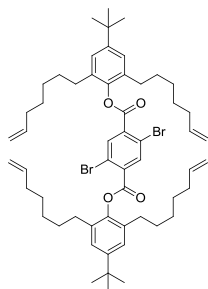
553 mg **37** (1.61 mmol, 2.1 equiv) and 0.235 mL NEt$_3$ (1.69 mmol, 2.2 equiv) were dissolved in 7 mL dry THF under N$_2$ atmosphere. The mixture was cooled to 0 ^{o}C and 277 mg **12** was added portionwise. The reaction was stirred at 0 ^{o}C for 1 hour and room temperature for 1 hour. Next, the reaction was diluted with 20 mL EtOAc and 20 mL 1M HCl. The water layer was extracted with 2x10 mL EtOAc and the combined organic layers were washed with 20 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (PE:EtOAc 99:1 → 98:2) to give **38** (459 mg, 0.47 mmol, 61%) as a colorless solid. Melting point: 77-79 ^{o}C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 8.36 (s, 2H), 7.17 (s, 4H), 5.80 (m, 4H), 4.99 (d, 4H), 4.94 (d, 4H), 2.57 (t, 8H), 2.09 (q, 8H), 1.66 (quint, 8H), 1.43 (m, 16H), 1.32 (s, 18H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 162.76, 149.38, 144.79, 139.05, 137.21, 135.60, 133.79, 125.20, 120.97, 114.45, 34.61, 33.84, 31.61, 31.11, 30.37, 29.30, 28.88; IR (cm^{-1}): 2963, 2926, 2856, 1745, 1641, 1465, 1280, 1232
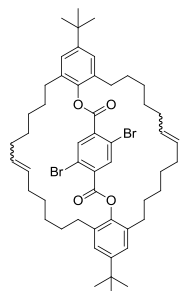
Compound **39**

97 mg **38** (0.100 mmol) was dissolved in 33 mL dry CH$_2$Cl$_2$ and the mixture was degassed with five vacuum/N$_2$ cycles. After degassing, 12 mg Grubbs II (0.020 mmol, 0.20 equiv) was added and the reaction was stirred overnight at 40 ^{o}C. The mixture was concentrated in *vacuo,* dry-loaded on silica and purified by column chromatography (PE/EtOAc 100:0 → 99:1 → 98:2) to give **39** (76 mg, 0.83 mmol, 83%) as a slightly yellow solid. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 8.57 (s, 2H), 7.17 (s, 4H), 5.24 (bs, 4H), 2.53 (m, 8H), 1.89 (quint, 8H), 1.58 (m, 16H), 1.32 (bs, 26H); No ^{13}C-NMR or IR data measured. HRMS (FD), calcd for C$_{52}$H$_{68}$O$_4$Br$_2$ [M$^+$]: 914.3484; found: 914.3467

A small amount of product (ca. 10 mg) was dissolved in 2 mL THF/H$_2$O 4:1 and 20 mg KOH was added. The reaction was stirred for 2h at room temperature and diluted with 10 mL 1M HCl. The mixture was extracted with 3 x 8 mL EtOAc and the combined organic layers were washed with 10 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. From this product was made a sample for mass analysis. HRMS (FD), calcd for C$_{44}$H$_{68}$O$_2$ [M$^+$]: 628.5219; found: 628.5163

Compound **41**
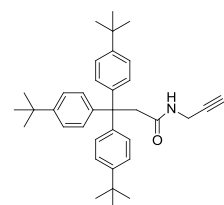
471 mg **3.13** (1.00 mmol) and 0.384 mL DIPEA (2.20 mmol, 2.2 equiv) were dissolved in 10 mL dry CH$_2$Cl$_2$ and cooled to 0 ^{o}C under N$_2$ atmosphere. After cooling, 546 mg PyBOP (1.05 mmol, 1.05 equiv) was added and the mixture was stirred for 10 minutes at 0 ^{o}C. Next, 0.071 mL propargylamine (1.10 mmol, 1.1 equiv) was added and the reaction was stirred at 0 ^{o}C for 30 minutes and room temperature for 1 hour. The mixture was washed with 10 mL 1M HCl and 10 mL NaHCO$_3$ and dried in *vacuo*. The residue was purified by column chromatography (PE/EtOAc 12:1 → 10:1) to give **41** (381 mg, 0.75 mmol, 75%) as a white solid. Melting point: 210-212 ^{o}C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.32 (d, 6H), 7.22 (d, 6H), 4.80 (t, 1H), 3.70 (m, 2H), 3.56 (s, 2H), 2.04 (t, 1H), 1.33 (s, 27H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 170.93, 149.20, 143.38, 128.85, 125.05, 79.16, 71.38, 55.16, 48.86, 34.46, 31.45, 29.43; IR (cm^{-1}): 3311, 2961, 2245, 1652, 1508

Compound **42**
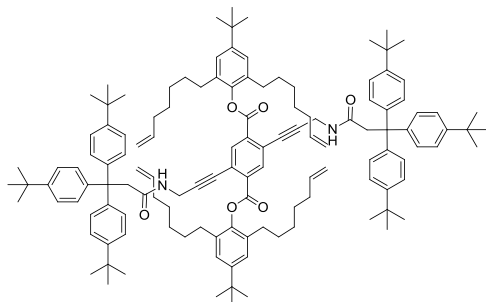
49 mg **38** (0.050 mmol) and 61 mg **41** (0.120 mmol, 2.4 equiv) were dissolved in 2 mL THF/NEt$_3$ 1:1 and the mixture was degassed with five vacuum/N$_2$ cycles. After degassing, 3.5 mg Pd(PPh$_3$)$_2$Cl$_2$ (0.005 mmol, 0.10 equiv) and 1.9 mg CuI (0.010 mmol, 0.20 equiv) were added and the mixture was stirred overnight at 50 ^{o}C under N$_2$ atmosphere. The mixture was diluted with 20 mL EtOAc and 10 mL 1M HCl. The water layer was extracted with 10 mL EtOAc and the combined organic layers were washed with 10 mL brine, dried over MgSO$_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (PE/EtOAc 14:1 → 13:1 → 12:1) to give **42** (36 mg, 0.020 mmol, 39%) as a colorless foam. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 8.29 (s, 2H), 7.26 (d, 12H), 7.18 (d, 12H), 7.14 (s, 4H), 5.74 (m, 4H), 4.94 (d, 4H), 4.88 (d, 4H), 4.82 (t, 2H), 4.14 (d, 4H), 3.89 (s, 4H), 2.50 (t, 8H), 2.04 (q, 8H), 1.59 (quint, 8H), 1.36 (bs, 34H), 1.31 (s, 54H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 170.65, 162.88, 149.03, 144.90, 143.49, 138.97, 136.69, 134.02, 133.67, 128.81, 124.93, 123.60, 114.59, 93.75, 80.71, 55.36, 48.57, 34.56, 34.40, 33.79, 31.61, 31.41, 30.76, 30.42, 30.01, 29.17, 28.79; IR (cm^{-1}): 3409, 2960, 2248, 1747, 1665, 1508, 1218, 1166

Compound **43**
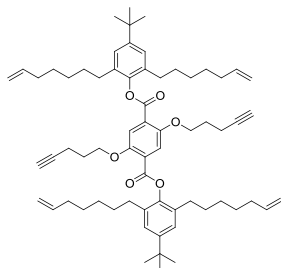
651 mg **37** (1.90 mmol, 2.0 equiv), 629 mg **4.20** (0.95 mmol), 1.23 g Cs$_2$CO$_3$ (3.80 mmol, 4.0 equiv) and 300 mg 4Å MS were dissolved in 20 mL dry CH$_3$CN and the reaction was stirred overnight at 50 ^{o}C under N$_2$ atmosphere. The mixture was concentrated in *vacuo*, dry-loaded on silica and purified by column chromatography (PE/EtOAc 25:1 → 20:1) to give **43** (851 mg, 0.867 mmol, 91%) as a thick colorless oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.72 (s, 2H), 7.18 (s, 4H), 5.80 (m, 4H), 4.98 (d, 2H), 4.94 (d, 4H), 4.26 (t,4H), 2.60 (t, 8H), 2.47 (dt, 4H), 2.09 (m, 12H), 1.96 (t, 2H), 1.67 (quint, 8H), 1.49-1.36 (m, 34H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 163.78, 152.48, 148.73, 145.12, 139.01, 133.85, 124.97, 124.19, 116.97, 114.38, 83.33, 69.16, 67.97, 34.53, 33.80, 31.61, 30.87, 30.14, 29.24, 28.83, 28.28, 15.23 IR (cm^{-1}): 3310, 2927, 2858, 1747, 1718, 1411, 1163; HRMS (FD) calcd for C$_{66}$H$_{90}$O$_6$ [M$^+$]: 978.6758, found: 978.6737

Compound **44**
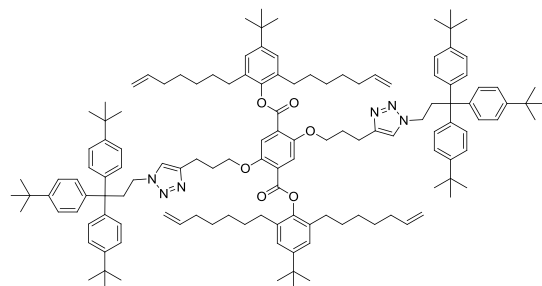
158 mg **43** (0.162 mmol) and 156 mg **3.17** (0.324 mmol, 2.0 equiv), 0.014 mL DIPEA (0.081 mmol, 0.5 equiv) and 0.009 mL 2,6-lutidine (0.081 mmol, 0.5 equiv) were dissolved in 5 mL dry CH$_3$CN/THF 4:1 and was degassed with five vacuum/N$_2$ cycles. After degassing, 6 mg CuI (0.032 mmol, 0.20 equiv) was added and the mixture

was stirred overnight at room temperature. The mixture was concentrated in *vacuo* and the residue was partitioned between 10 mL CH_2Cl_2 and 8 mL 1M HCl. The water layer was extracted with 5 mL CH_2Cl_2 and the combined organic layers were concentrated in *vacuo* and the residue was purified by column chromatography (PE/EtOAc 10:1 → 8:1) to give **44** (274 mg, 0.141 mmol, 87%) as a colorless foam. Melting point: 98-102 ^{o}C; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.71 (s, 2H), 7.34 (d, 12H), 7.26 (d, 12H), 7.18 (s, 4H), 7.14 (s, 2H), 5.77 (m, 4H), 4.98-4.88 (m, 8H), 4.22 (t, 4H), 4.07 (t, 4H), 3.18 (t, 4H), 2.97 (t, 4H), 2.61 (t, 8H), 2.28 (quint, 4H), 2.04 (q, 8H), 1.67 (quint, 8H), 1.46-1.27 (m, 88H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 163.70, 152.41, 148.88, 148.69, 146.91, 145.10, 143.28, 138.80, 133.83, 128.52, 125.35, 125.03, 124.95, 124.16, 120.97, 116.74, 114.32, 77.36, 68.82, 54.21, 47.92, 40.85, 34.49, 34.40, 33.72, 31.60, 31.43, 30.85, 30.08, 29.15, 28.74, 22.15 IR (cm^{-1}): 2957, 2930, 2863, 1745, 1505, 1462, 1164; HRMS (FD) calcd for $C_{132}H_{176}N_6O_6$ [M$^+$]: 1940.3573, found: 1940.3459

Compound **45**
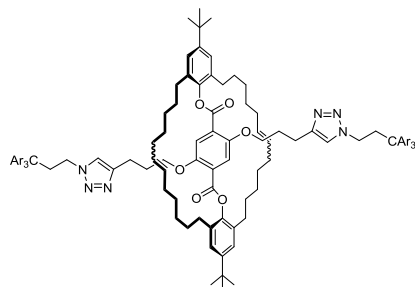
270 mg **44** (0.139 mmol) was dissolved in 140 mL dry CH_2Cl_2 and the solution was degassed with five vacuum/N$_2$ cycles. After degassing, 23 mg Grubbs II (0.028 mmol, 0.20 equiv) was added and the reaction was stirred overnight at 40 ^{o}C under N$_2$ atmosphere. The reaction was concentrated in *vacuo*, dry-loaded on silica and purified by column chromatography (PE/EtOAc 10:1 → 8:1 → 6:1) to give **45** (212 mg, 0.112 mmol, 80%) as an off-white film. ^{1}H-NMR: complex; IR (cm^{-1}): 2957, 2929, 2865, 1743, 1717, 1506, 1461, 1164; HRMS (FD) calcd for $C_{128}H_{168}N_6O_6$ [M$^+$]: 1885.3025, found: 1885.3045

Compound **46**
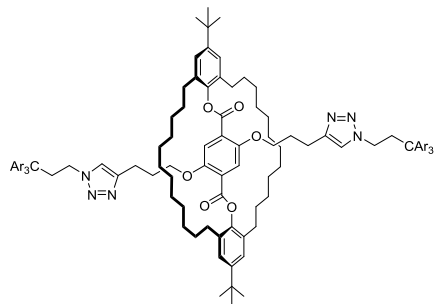
210 mg **45** (0.111 mmol) was dissolved in 5 mL THF/EtOH 1:1 and 60 mg Pd/C (10% w/w) was added. Through the mixture was bubbled H$_2$ gas for 5 minutes and the reaction was stirred overnight at 60 ^{o}C under H$_2$ atmosphere (balloon). The mixture was filtered over a plug of Celite, which was flushed with EtOAc. The filtrate was concentrated in *vacuo* to give **46** (199 mg, 0.105 mmol, 95%) as a colorless film. ^{1}H-NMR: complex; HRMS (FD) calcd for $C_{128}H_{172}N_6O_6$ [M$^+$]: 1889.3338, found: 1889.3275

Compound **47 acid**
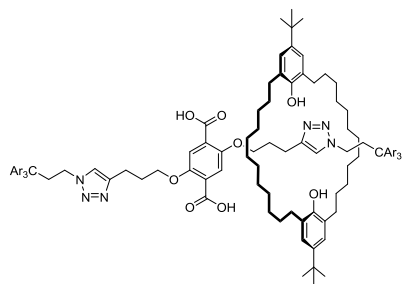
18 mg **46** (0.0095 mmol) was dissolved in 2 mL dioxane in a pressure tube and 0.5 mL 20% KOH was added. The reaction was stirred at 130 °C for 2h and was cooled to room temperature. The mixture was diluted with H_2O and was acidified with HCl to pH 1. To the water layer was added 10 mL EtOAc and the mixture was stirred vigorously for 15 min. The water layer was extracted with an additional 10 mL EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in *vacuo* to give **47 acid** (17 mg, 0.0089 mmol, 94%) as a colorless film. Melting trajectory: 130-140 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 2H), 7.31 (d, 12H), 7.22 (d, 12H), 7.14 (s, 2H), 6.98 (s, 4H), 4.18 (t, 4H), 4.08 (t, 4H), 3.15 (t, 4H), 2.87 (t, 4H), 2.61 (t, 8H), 2.23 (quint, 4H), 1.55 (quint, 8H), 1.32-1.05 (m, 104H); IR (cm^{-1}): 2954, 2924, 2853, 1731, 1462, 1362, 1129; HRMS (FD) calcd for $C_{128}H_{176}N_6O_8$ [M$^+$]: 1925.3550, found: 1925.3619

Compound **47**
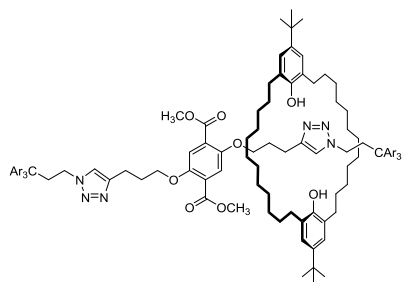
17 mg **47 acid** (0.0083 mmol) was dissolved in 2 mL dry CH_2Cl_2/CH_3OH 1:1, cooled to 0 °C and 0.1 mL TMS-diazomethane (1M in hexane, 0.100 mmol, 12 equiv) was added. The ice bath was removed and the reaction was stirred at room temperature for 2h. The reaction was quenched with 1 droplet of AcOH and the organic layer was concentrated in *vacuo*. The residue was purified by column chromatography (PE/EtOAc 9:1 → 3:2) to give **47** (16.5 mg, 0.0084 mmol, 95%) as a colorless film. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 2H), 7.30 (d, 12H), 7.24 (s, 2H), 7.21 (d, 12H), 7.14 (s, 2H), 6.97 (s, 4H), 4.05 (m, 8H), 3.75 (s, 6H), 3.13 (m, 4H), 2.94 (t, 4H), 2.63 (t, 8H), 2.21 (quint, 4H), 1.57 (quint, 8H), 1.32 (s, 48H), 1.28 (s, 18H), 1.19-1.10 (m, 32H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.73, 151.88, 149.98, 148.76, 146.98, 143.14, 142.31, 129.16, 128.42, 124.94, 124.40, 124.04, 121.16, 116.62, 68.80, 54.03, 52.22, 47.95, 40.76, 34.31, 33.91, 31.68, 31.32, 31.27, 30.61, 29.46, 29.18, 29.13, 29.05, 21.95; IR (cm^{-1}): 2959, 2926, 2854, 1731, 1464, 1205; HRMS (FD) calcd for $C_{130}H_{180}N_6O_8$ [M$^+$]: 1953.3863, found: 1953.3888

References

[1] Part of this chapter has been published:
Steemers, L.; Wanner, M.; Ehlers, A.W.; Hiemstra, H.; van Maarseveen, J.H. *Org. Lett.* **2017**, *19*, 2342-2345

[2] Thibeault, D.; Morin, J.F. *Molecules*, **2010**, *15*, 3709-3730

[3] Barin, G.; Coskun A.; Fouda, M.M.G.; Stoddart, J.F. *Angew. Chem. Int. Ed.* **2012**, *77*, 159-185

[4] Schalley, C.A.; Weilandt, T.; Brüggemann, J.; Vögtle, F. *Topics in current chemistry, 248,* 141-200

[5] Dietrich-Buchecker, C.O.; Sauvage, J.P.; Kintzinger, J.P. *Tetrahedron*, **1983**, *24*, 5095 5098

[6] Beves, J.E.; Blight, B.A.; Campbell, C.J.; Leigh, D.A.; McBurney, R.T. *Angew. Chem. Int. Ed.* **2011**, *50*, 9260-9327

[7] Hannam, J. S.; Lacy, S. M.; Leigh, D. A.; Saiz, C. G.; Slawin A. M. Z.; Stitchell, S. G. *Angew. Chem. Int. Ed.*, **2004**, *43*, 3260–3264

[8] Chao, S; Romuald, C.; Fournel-Marotte, K.; Clavel, C.; Coutrot, F. *Angew. Chem. Int. Ed.* **2014**, *53*, 6914-6919

[9] Goldup, S. M.; Leigh, D. A.; McBurney, R. T.; McGonigal, P. R.; Plant, A. *Chemical Science* **2010**, *1*, 383-386

[10] Saito, S.; Takahashi, E.; Nakazono, K. *Org. Lett.* **2006**, *8*, 5133-5136

[11] Leigh, D. A.; Berna, J.; Crowley, J. D.; Goldup, S. M.; Hanni, K. D.; Lee, A. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5709-5713

[12] Leigh, D. A.; Crowley, J. D.; Goldup, S. M.; Gowans, N. D.; Ronaldson, V. E.; Slawin, A. M. Z. *J. Am. Chem. Soc* **2010**, *132*, 6243-6248

[13] Berna, J.; Goldup, S. M.; Lee, A. L.; Leigh, D. A.; Symes, M. D.; Teobaldi, G.; Zerbetto, F. *Angew. Chem Int. Ed* **2008**, *47*, 4392-4396

[14] Leigh, D. A.; Crowley, J. D.; Hanni, K. D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2010**, *132*, 5309-5314

[15] Leigh, D. A.; Goldup, S. M.; Lusby, P. J.; McBurney, R. T.; Slawin, A. M. Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 3381-3384

[16] Aucagne, V.; Hanni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker, D. B. *J. Am. Chem. Soc* **2006**, *128*, 2186-2187

[17] Leigh, D. A.; Crowley, J. D.; Hanni, K. D.; Lee, A. L. *J.Am.Chem.Soc* **2007**, *129*, 12092-12095

[18] Marti-Centelles, V.; Pandey, M.D.; Burguete, M.I.; Luis, S.V. *Chem. Rev.* **2015**, *115*, 8736-8834

[19] Schweez, C.; Shuskov, P.; Grimme, S.; Höger, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 3328-3333

[20] Becker, K.; Lagoudakis, P.G.; Gaefke, G.; Höger, S.; Lupton, J.M. *Angew. Chem. Int. Ed.* **2007**, *46*, 3450-3455

[21] Höger, S. *J. Polym. Sci. Part A: Polym. Chem.* **1999**, *37*, 2685-2698

[22] Höger, S.; Meckenstock, A-D.; Pellen ,H. *J. Org. Chem.* **1997**, *62*, 4556-4557

[23] Höger, S. *J. Polym. Sci. Part A Polym. Chem.* **1999**, *37*, 2685-2698

[24] Höger, S.; Meckenstock, A-D. *Chem. Eur. J.* **1999**, *5*, 1686-1691

[25] Fischer, M.; Högler, S. *Eur. J. Org. Chem.* **2003**, 441-446

[26] Höger, S. *Chem. Eur. J.* **2004**, *10*, 1320-1329

[27] Ziegler, A.; Mamdouh, W.; Heyen, A.V.; Surin, M.; Uji-i, H.; Abdel-Mottaleb, M.M.S.; De Schryver, F.C.; De Feyter, S.; Lazzaroni, R.; Högler, S. *Chem. Mater.* **2005**, *17*, 5670-5683

[28] Cantin, K.; Lafleur-Lambert, A.; Dufour, P.; Morin, J.-F. *Eur. J. Org. Chem.* **2012**, *27*, 5335-5349

[29] Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831-5834

[30] Kambe T.; Correia, B.E.; Niphakis, M.J.; Cravatt, B.F. *J. Am. Chem. Soc.* **2014**, *136*, 10777-10782

[31] Boughton, B.A.; Hor, L.; Gerrard, J.A.; Hutton, C.A. *Bio-org. Med. Chem.* **2012**, *20*, 2419-2426

[32] Ovaa, H.; Stapper, C.; van der Marel, G.A.; Overkleeft, H.S.; van Boom, J.H.; Blechert, S. *Tetrahedron*, **2002**, *58*, 7503-7518

[33] Yang, X.; Lui, D.; Miao, Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 6786-6790

[34] Travis, B.R.; Sivakumar, M.; Hollist, G.O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031-1035

[35] Hart, M.E.; Suchland, K.L.; Miyakawa, M.; Bunzow, J.R.; Grandy, D.K.; Scanlan, T.S. *J. Med. Chem.* **2006**, *49*, 1101-1112

[36] Baker, M.V.; Bosnich, M.J.; Brown, D.H.; Byrne, L.T.; Hesler, V.J.; Skelton, B.W.; White, A.H.; Williams, C.C. *J. Org. Chem.*, **2004**, 69, 7640–7652

[37] Gradillas, A.; Perez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086-6101

[38] Liu, Y.; Chen, K.; Xing, K.; Wang, Y.; Jiang, H.; Deng, X.; Zhu, M.; Zhu, W. *Tetrahedron*, **2013**, *69*, 4679-4686

[39] Akbey, Ü.; Granados-Focil, S.; Coughlin, E.B.; Graf, R.; Spiess, H.W. *J. Phys. Chem. B.* **2009**, *113*, 9251-9160

[40] Evans, P.A.; Cui, J.; Gharpure S. J.; Polosukhin A.; Zhang H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702 – 14703

[41] Barlan, A.U.; Basak, A.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 5849-5852

Chapter VII: Outlook

In this chapter ideas are presented that might tackle problems encountered. Also, some future directions are given to eventually arrive at the lasso peptide series.

To follow up the research described in Chapter IV it would be interesting to replace the rigid fluorene core with an aliphatic chain and test whether the quasi[1]catenane is still the exclusive product of the CuAAC reaction. Due to the increased flexibility in the system during the CuAAC reaction a mixture of pre-quasi[1]catenane **1** and non-interlocked isomer **2** may be obtained. With eventually the fully aliphatic quasi[1]catenane **3** in hand, the possibility of thermal isomerization towards the normal spiro bicycle **5** may be studied.
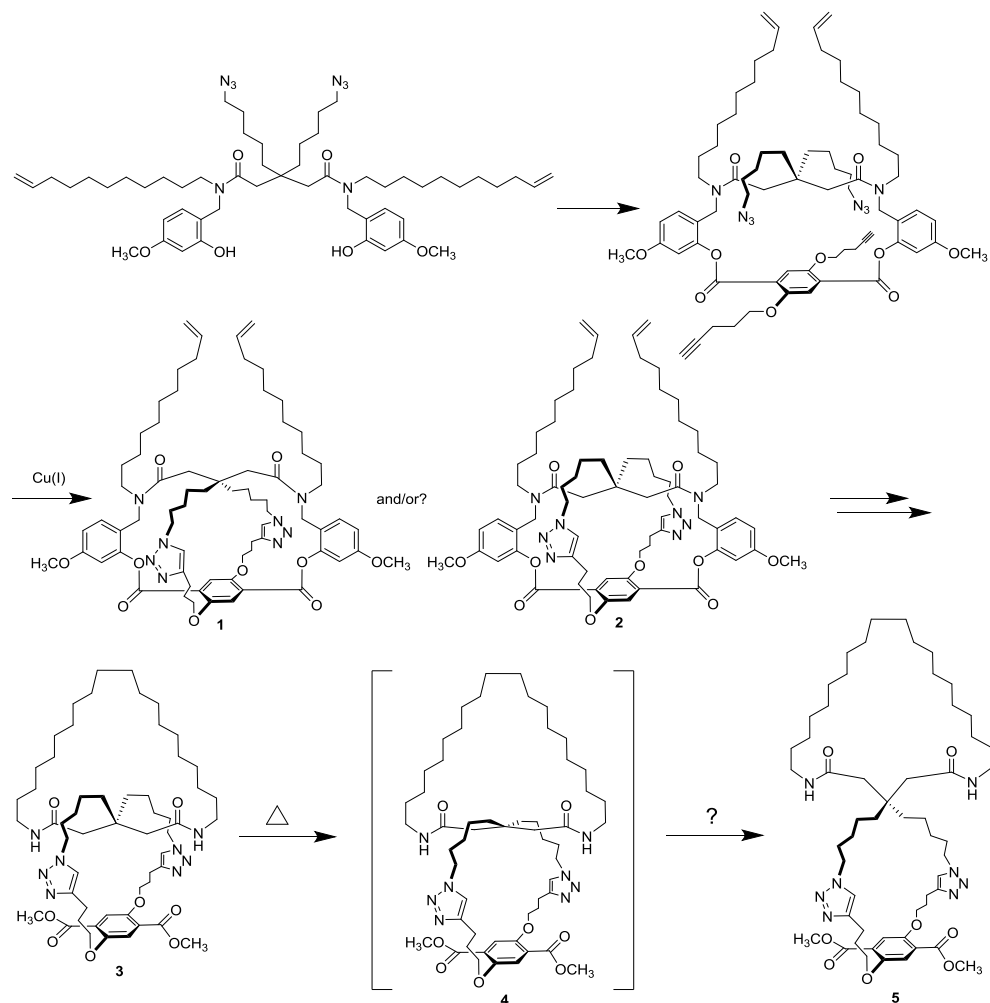
Scheme 1: Synthesis of aliphatic quasi[1]catenane **3** and attempted thermal isomerization towards spiro bicycle **5** *via* square planar carbon

This isomerization proceeds *via* inversion of the central C-atom through a square planar transition state **4** (see scheme 1) to give the sterically more relaxed spiro bicycle. As of yet, no such intermediate square planar carbon atom has been confirmed in literature. Because compounds **3** and **5** are diastereomers the identification of the product (and thereby proof of the mechanism) would be really facile compared to previously attempted syntheses of square planar carbon.[1,2]

To expand the scope of the synthesis (and partially for aesthetic reasons) it would be desirable to replace the triazole moieties with a fully aliphatic carbon chain. Consequently, as a substitute for the CuAAC reaction, the second backfolding reaction may be replaced by a Mitsunobu reaction (see scheme 2). To ensure compatability during the transesterification/macrolactonization step, the phenolic hydroxyl groups should be protected with a mild (Lewis) acid-labile protective group. Simultaneous protective group removal yields tetraol **6**, which is pre-organized for an intramolecular Mitsunobu reaction, forming **7**. Completion of the synthesis provides 'bare' quasi[1]catenane **8**.
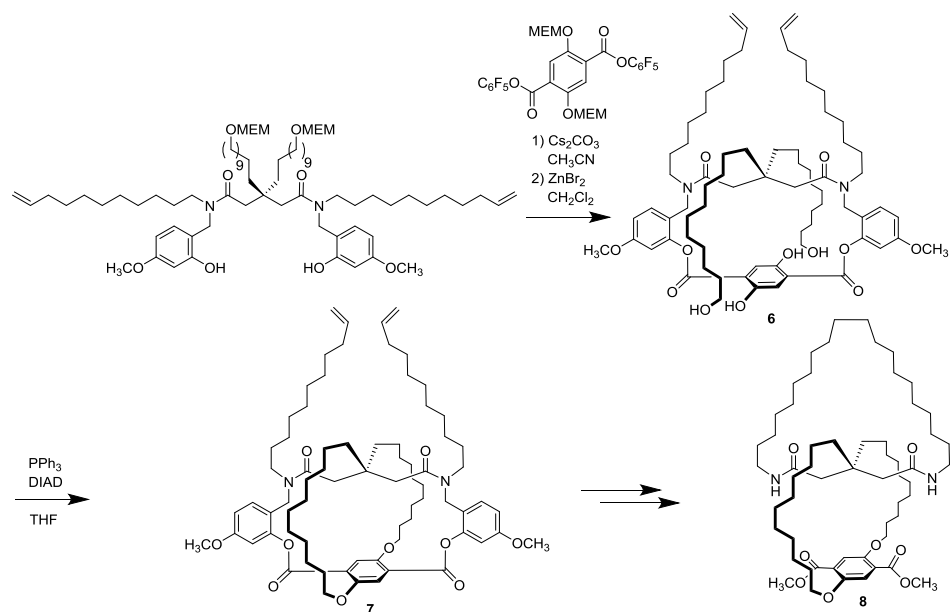
Scheme 2: Synthesis of fully aliphatic quasi[1]catenane **8**

As described in Chapter V, a yet unsolved problem is the stability of the cyclic ketal preventing release of the desired [2]catenane. It is thought that a combination of steric and electronic effects prevent efficient hydrolysis of the cyclic ketal. Due to the close proximity of the carbonyl moieties, protonation of the dioxolane oxygen atom is hindered, thereby hampering the reaction. To circumnavigate this problem the carbonyl moieties might be placed further away from the dioxolane. This may be achieved by reduction of the tartaric ester moieties followed by substitution of the resulting primary alcohols by a secondary amine containing the 2-hydroxy-4-methoxybenzyl group. Eventually, the ring fragments can be installed by coupling the amines with two equivalents of *N*-hydroxysuccinimide ester of 11-dodecenoic acid, giving tetra-amide **9** (see scheme 3). With the carbonyl moieties located further away from the dioxolane, acidolysis is expected to be much more facile to give [2]catenane **10**
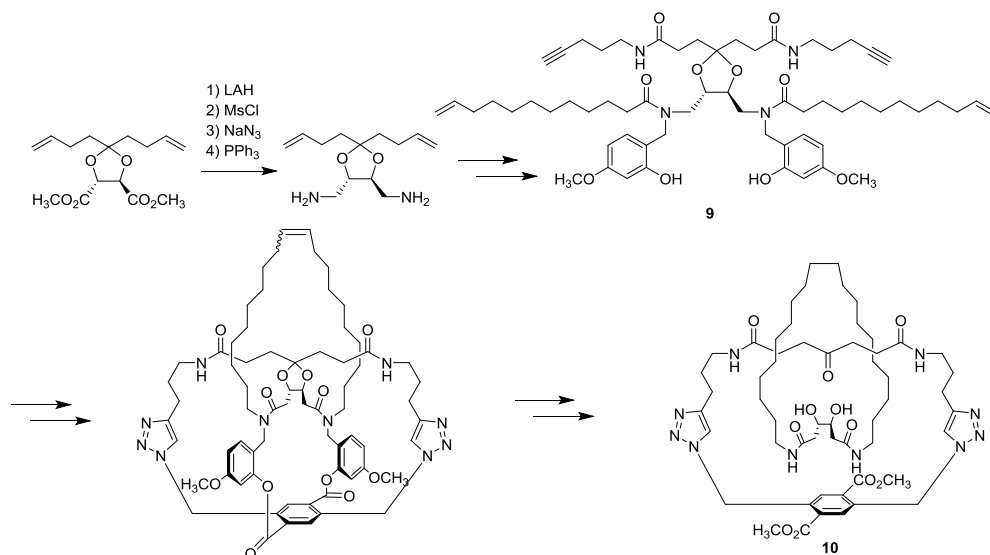
Scheme 3: Synthesis of a more acid labile dioxolane

It is also possible to install a ketal moiety based on a catechol (1,2-dihydroxybenzene) derivative. 2,3-Dihydroxyterephthalic acid would be a perfect scaffold, as this also allows the formation of the two amides containing the ring fragment. Because the terephthalic moiety is flat, the corresponding cyclic ketal induces a perfect perpendicular mutual arrangement of the ring and thread fragments (compound **11**, scheme 4). An additional advantage of a catechol-centered ketal is, besides usual hydrolysis, cleavage *via* oxidation (with ceric ammonium nitrate) to liberate the [2]catenane **12**.
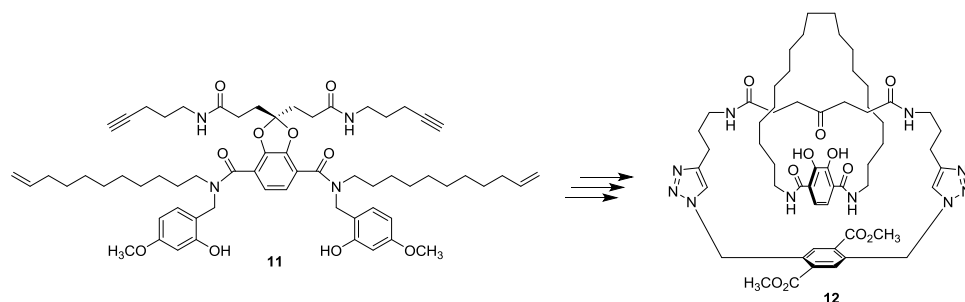
Scheme 4: Use of a catechol-type dioxolane as an acid labile connecting group

In the early development of the backfolding strategies as described in Chapters II-IV, Williamson etherification or acylation of the scaffold to the 2-hydroxy-4-methoxybenzyl group has proven a reliable and robust method for the first macrocyclization step. Nevertheless, more simple and shorter *N*-amide backbone modifications can be envisioned. The group of Plata reported a reliable method for the transformation of amide and carbamate N-H's into their chloromethylated derivatives.[3] These activated intermediates easily form *N*-acyliminium ions, which could react with a variety of nucleophiles, such as thiols[4], alcohols[5] and carboxylates[6], forming mixed acetals that are inherently acid labile (see scheme 5). Moreover, the resulting products contain even smaller macrocycles (16-membered) than those obtained from the 2-hydroxy-4-methoxybenzyl group.
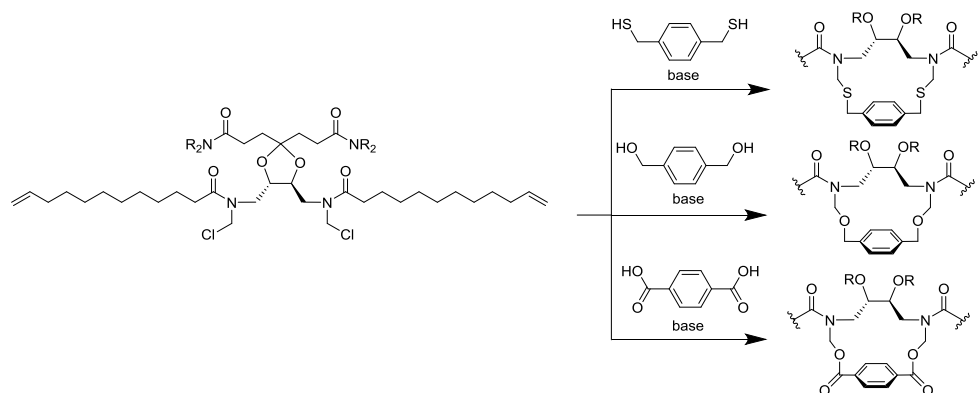
Scheme 5: Macrocyclizations of a bis-chloromethylated precursor with dithiols, dialcohols and dicarboxylates

The main far-future goal of the methodology described in this thesis is to disclose the natural lasso peptide series. The link to peptides can easily be envisioned by means of installing an aminal moiety (imidazolidone) instead of a ketal.
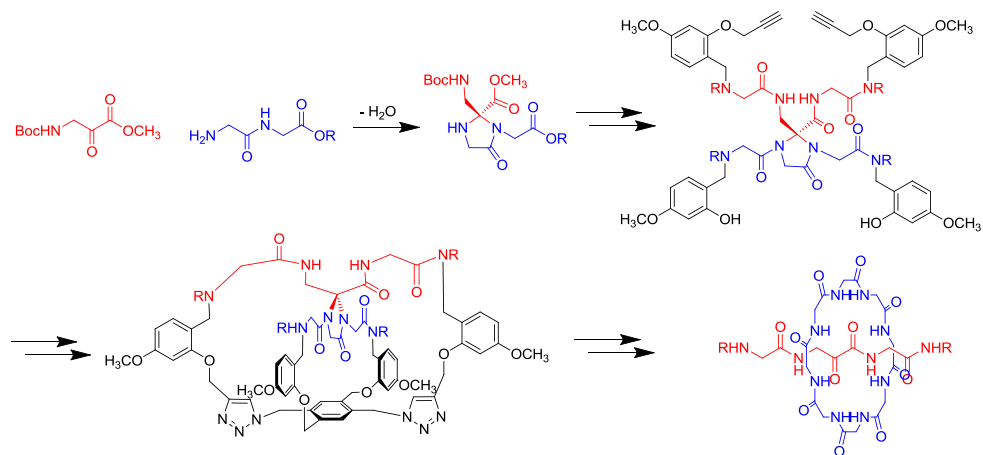
Scheme 6: Imidazolidone as temporary covalent linker (amino acid residues omitted for clarity)

Similar to the ketal, this motif is acid labile and simultaneously incorporates the desired 90° angle between the ring and thread fragments (blue and red in scheme 6, respectively). Unfortunately, the synthesis of imidazolidones in literature is limited to simple substrates and no complex molecules such as in scheme 6 have been synthesized.[7,8] Apart from the considerable synthetic challenge, the only drawback of this strategy is the need for a unnatural α-keto-β-amino acid in the thread fragment. This prerequisite excludes the formation of native (lasso) peptides. Nevertheless, this strategy could be used to access close analogues of these naturally occurring peptides.

The methodology development as described in Chapter VI towards [2]rotaxanes may also provide access to the analogous [2]catenanes. To accomplish this, the 2- and 5- positions of the terephthalic acid core should be functionalized with aliphatic chains that allow for a second ring closing reaction. Thus, RCM of **13**, followed by catalytic hydrogenation to remove the E/Z mixture of the olefins and simultaneously remove the benzyl protective groups, yields **14**. Oxidation of the alcohols and a Wittig reaction with Ph$_3$P=CH$_2$ would yield dialkene **15**. Next, the molecule can undergo the second ring-closing metathesis followed by hydrogenation to give precatenane **16**. Final saponification and re-esterification with TMS-diazomethane will give the desired [2]catenane **17** consisting of two interlocked 30-membered rings.
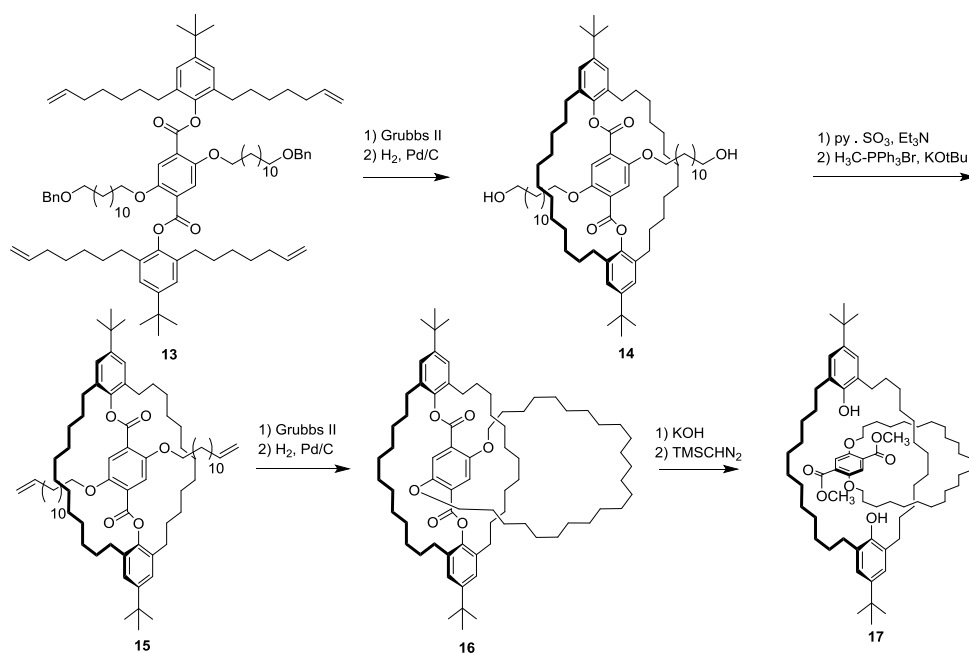
Scheme 7: Proposed synthesis of [2]catenane **17**

As described in Chapter VI, saponification of the esters in the last step required harsh conditions. The reason for this is most likely steric hindrance encountered by the endocyclic esters preventing attack of the polar hydroxide anion in combination with the highly apolar environment. To solve this problem an internal *O-N* acyl transfer reaction could be envisioned. This strategy relies on the facile formation of a 5-membered lactam, as observed in Chapter II. Therefore the terephthalic acid template should be modified to incorporate two protected benzylic amines (compound **18**, see scheme 8). A nosyl protective group on the stopper fragment seems the most suitable protective group as it allows both facile alkylation with bis-benzyl bromide **3.48** (an intermediate from Chapter III) and is compatible with all the subsequent steps. After pre-rotaxane **19** is obtained the nosyl groups are removed with thiophenolate, inducing two consecutive intramolecular *N-O* acyl shifts (intermediate **20**) liberating [2]rotaxane **21** containing a bis-isoindolinone moiety.
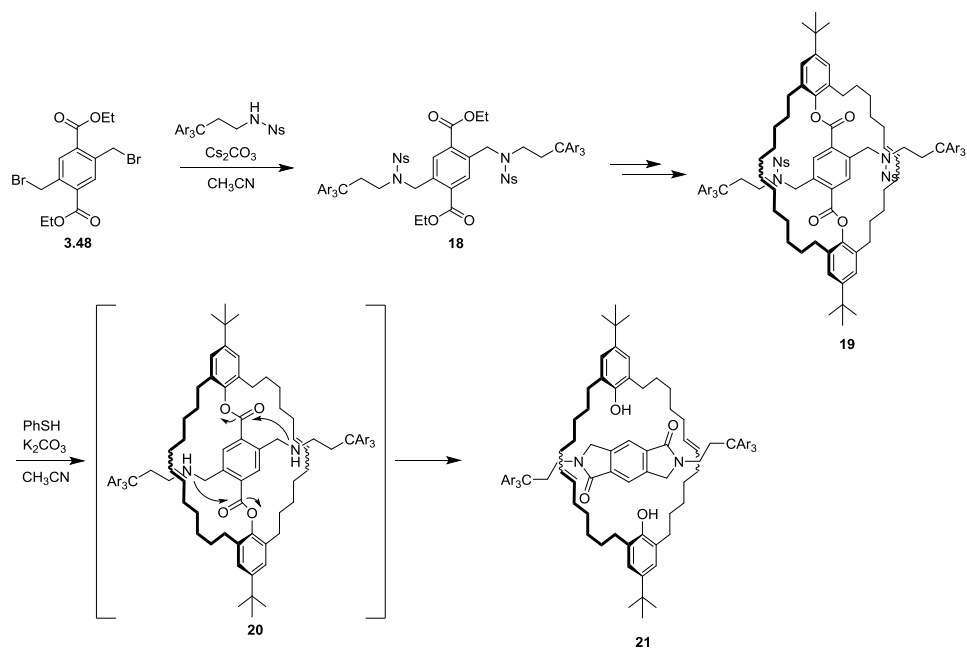
Scheme 8: Synthesis of a [2]rotaxane *via* intramolecular *N-O* acyl transfer. Ar = 4-*tert*-butylphenyl

References

[1] Cooper, O.J.; Wooles, A.J.; McMaster, J.; Lewis, W.; Blake, A.J.; Liddle, S.T. *Angew. Chem. Int. Ed.* **2010**, *49*, 5570-5573

[2] Gordon, M.S.; Schmidt, M.W. *J. Am. Chem. Soc.* **1993**, *115*, 7486-7492

[3] Barnes, D.M.; Barkalow, J.; Plata, D.J. *Org. Lett.* **2009**, *11*, 273-275

[4] Hartung, R.; Golz, G.; Schlaf, S.; Silvennoien, G.; Polborn, K.; Mayer, P.; Pfaendler, H.R. *Synthesis* **2009**, *3*, 495-501

[5] Fernandes-Llamazares, A.I.; Spengler, J.; Albericio, F. *Tetrahedron Lett.* **2014**, *55*, 184-188

[6] Moreira, R.; Mendes, E.; Calheiros, T.; Bacelo, M.J.; Iley, J. *Tetrahedron Lett.* **1994**, *35*, 7107-7110

[7] DeMong, D.E.; Ng, I.; Miller, M.W.; Stamford, A.W. *Org. Lett.* **2013**, *15*, 2830-2833

[8] Hubert, C.; Gariggues, B. *Can. J. Chem.* **1998**, *76*, 234-237

Summary 'Covalent template-assisted synthesis of mechanically interlocked molecules'

With the natural lasso peptides at the far horizon, this thesis investigates multiple strategies towards mechanically interlocked compounds using covalent bonds for pre-organization of components. A small organic template (or scaffold) with orthogonal reactivities is used in all approaches for assembly. These templates were designed to covalently bind to the ring- and thread-fragments and position these in a correct way for cyclizations. Depending on the approach, the scaffold was designed to be either removed completely (Chapters II and III) or incorporated in the final entangled architecture (Chapters IV, V and VI). Chapter I gives an historic overview of mechanically interlocked molecules and the common methods for their synthesis. Starting with the landmark paper by Lütringhaus and Schill in 1964, describing a catenane synthesis using a covalent approach, the three main methods for rotaxanes synthesis are discussed: 'clipping', 'capping' and 'active metal template' methods. The use of non-covalent interactions is near universal in these synthetic methodologies. Nevertheless, the covalent approach has made a comeback over the years, allowing syntheses of rotaxanes and catenanes which would be impossible to synthesize *via* non-covalent interactions. The main advantage of the covalent approach is that the final mechanically interlocked molecules usually lack the physically dominant (usually polar) motifs that are required for a supramolecular approach. In addition, using a covalent approach functionalities may be introduced that are incompatible with the traditional methods. Drawbacks of covalent approaches include the considerably longer synthetic routes and less general applicability. A covalent strategy towards a [2]rotaxane using a temporary scaffold for pre-organization is described in Chapter II (see figure below).
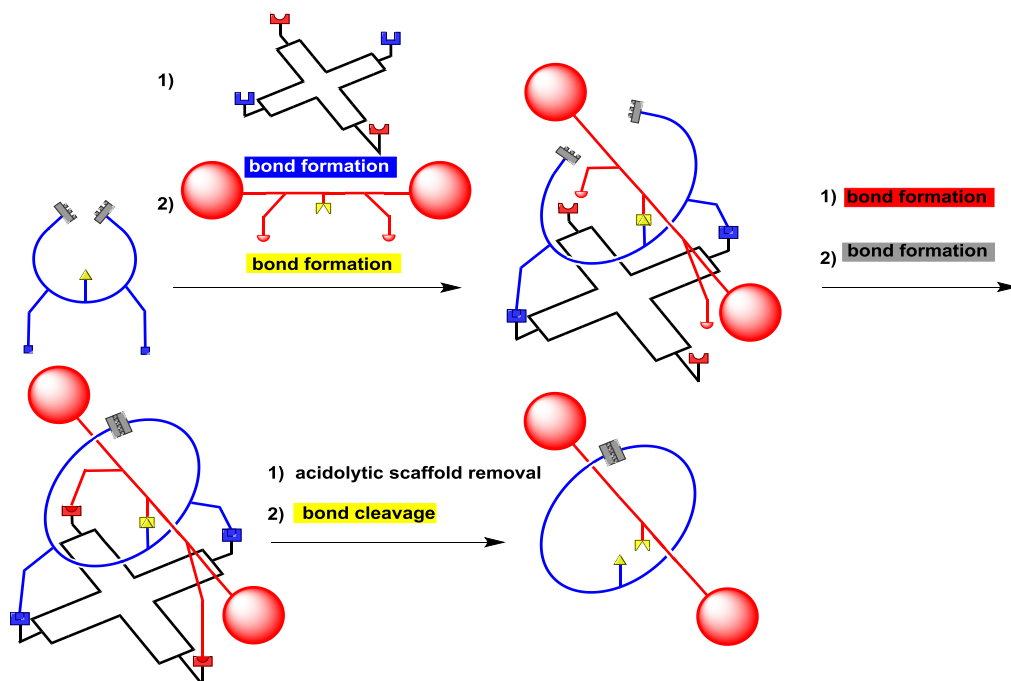
The first step is attachment of the ring-fragment precursor (blue) to the square planar template *via* a macrocyclization reaction. Suitable reactions are studied in Chapter II to achieve this. Key is the use of a amide *N*-backbone modification, as it can later on be removed *via* acidolysis. This modification is based on the well-known 2,4-dimethoxybenzyl group for peptide amide bond protection. The second step is attachment of the thread fragment (red) to the construct *via* a temporary covalent bond (yellow). This bond is necessary to ensure that the subsequent backfolding ring closing macrocyclization proceeds on the same side of the molecule as the ring fragment. The product obtained is a highly constrained multicyclic cage-type molecule, forcing the final cyclization (gray) to occur around the thread fragment. Removal of the temporary scaffold is achieved *via* acidolytic cleavage of the benzylic amide groups. In the last step the temporary connection between the ring and thread fragments is cleaved (yellow bond), liberating the desired [2]rotaxane.

After some fruitless approaches towards the first step in the strategy, i.e. connection of the ring fragment precursor to the template, we realized that the 4-methoxy-2-hydroxybenzyl group was a perfect choice as a tether unit. The free phenolic OH group was functionalizable group in its own right, allowing mild alkylation. Indeed, model compound **I** reacted cleanly with several dihalide compounds as template surrogates, forming a bis-ether macrocycle **II** in good yields. The use of a polar aprotic solvent, such as DMF or CH_3CN was optimal and low concentrations (1-5 mM) were necessary to prevent competing polymerization.
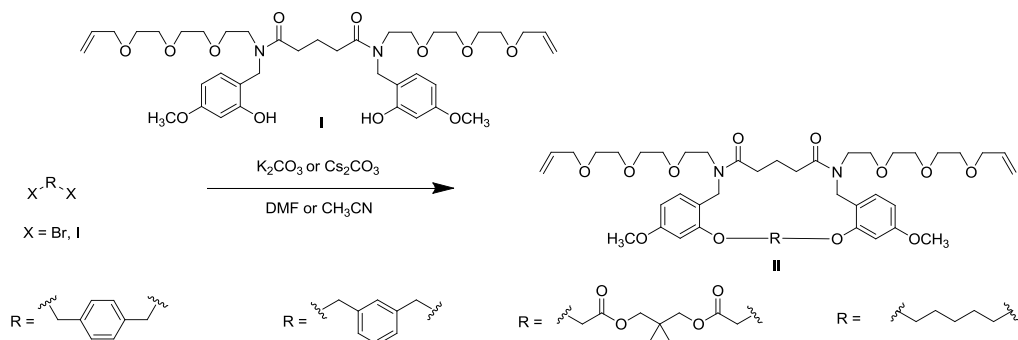
Also square planar scaffolds (templates) were addressed functionalized in a so-called ABAB pattern, i.e. the functional groups are positioned trans with respect to each other. Unfortunately, no compound classes were found that led to a successful synthesis of a complete scaffold. Common problems encountered included functional group incompatibility, insolubility of the product or sensitivity towards oxidation. Therefore, the concept of a true square planar template had to be abandoned.

Chapter III studies the scissile covalent connection between the ring precursor and thread fragments as the next step in the strategy towards a [2]rotaxane. This connection is necessary to ensure that both components are oriented at the same side of the scaffold. For this, oxime ligation was chosen for its robustness and the fact that even at low concentrations high yields may be obtained. In addition, due to its reversibility, an oxime bond can be cleaved under mild conditions. Ring fragment **III** was synthesized containing the centrally-placed required (phthalimide protected) oxyamine

moiety. Next, multiple thread fragments were synthesized containing the complementary reactive ketone moiety in the center and two *N*-amide backbone modifications containing a propargyl group, allowing orthogonal CuAAC reactions with the template. Some of the thread fragments contain the bulky tris-4-*tert*-butyltrityl group as the rotaxane-stopper group. Lastly, several scaffolds were synthesized which contain two activated bromides for the first macrocyclization with the ring fragment and two azides for the CuAAC reaction with the thread fragment. These scaffolds are not true square planar molecules, but based on either a tetrahedral sp^3-atom or a 1,2,4,5-tetrasubstituted benzene.
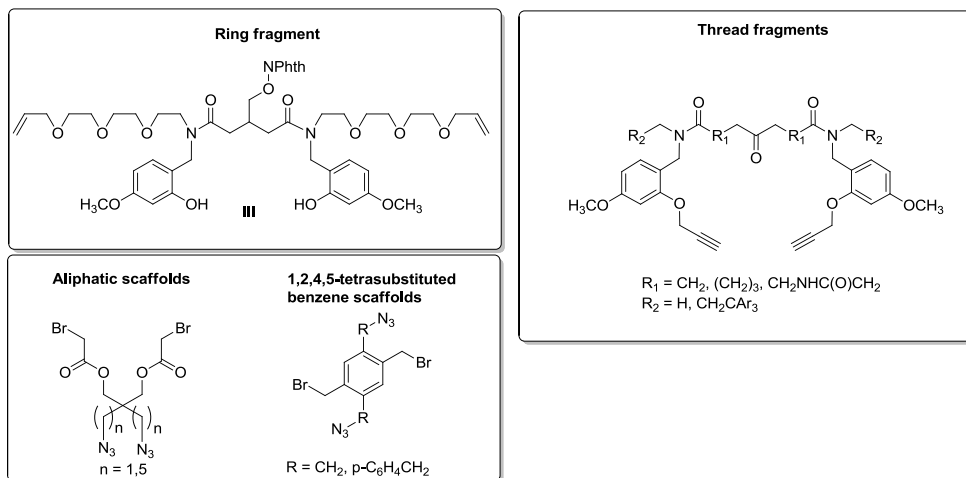
In all cases, the first macrocyclization gives the bis-ether macrocycle between the ring precursor fragment and scaffold in good yields. Also the subsequent oxime ligation proceeds well, giving the best results in a THF/H$_2$O system with acetic acid as a catalyst. The next step in the assembly was the intramolecular CuAAC reaction between the scaffold azides and the thread fragment alkynes. Despite the pre-organization, this step proved troublesome as constructs with the aliphatic sp^3-atom based scaffolds formed non-interlocked products instead. The 1,2,4,5-tetrasubstituted benzene templates performed better in this reaction, as their rigidity prevents the formation of these non-interlocked products. Subsequent ring closing metathesis (RCM) under dilute conditions also proceeded well. The last steps of assembly included acidic removal of the template followed by final cleavage of the oxime bond to separate the ring and thread fragments. Unfortunately, treatment with TFA and Et$_3$SiH resulted in a complex mixture in both constructs tested.
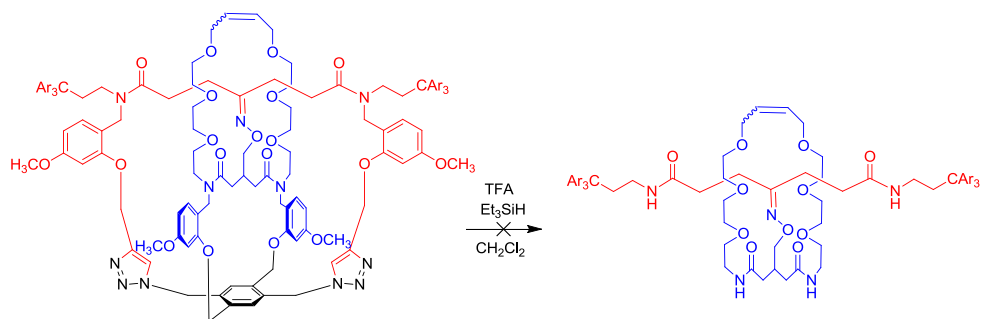
In Chapter IV the strategy is adapted by replacing the oxime temporary bond between the two components with a rigid fluorene core. The central fluorene sp^3-carbon atom ensures a 90° angle between the two components excluding the possibility for misfolding. However, because these bonds cannot be broken, a product with the spiro architecture will be obtained eventually. After creating 3D models of the intermediates we soon realized that actually two products could be formed with our strategy, namely a normal spiro bicycle but also one showing an inverted spiro geometry. By choosing the right order of events during assembly, both products could be obtained. The fluorene-based compound was synthesized incorporating three separate (orthogonal) reactivities, namely phenolic OH's for temporary esterification to the template, azides for CuAAC-type macrocyclization and alkenes for the final RCM-type macrocyclization. Fortunately, the reaction with a bis-pentafluorophenol ester resulted in clean and high yielding formation of the desired bis lactone macrocycle. Subsequent double intramolecular CuAAC reaction was optimized by using Cu(CH$_3$CN)$_4$BF$_4$ and TBTA as the catalyst system, giving reproducible high yields of CuAAC product **IV**. From this cage-type intermediate both spiro geometries could be obtained. RCM, followed by cleavage of the ester bonds with NaOCH$_3$ and TFA removal of the benzyl groups resulted in the unprecedented quasi[1]catenane **V**. By swapping the first two steps, so first NaOCH$_3$ cleavage and then RCM, the sterically more relaxed spiro product **VI** was obtained. Note that the two products are diastereomers, despite the absence of a chiral carbon atom. Indeed, extensive 1D and 2D NMR experiments revealed very different properties of the two isomers.

quasi[1]catenane V

spiro bicycle VI
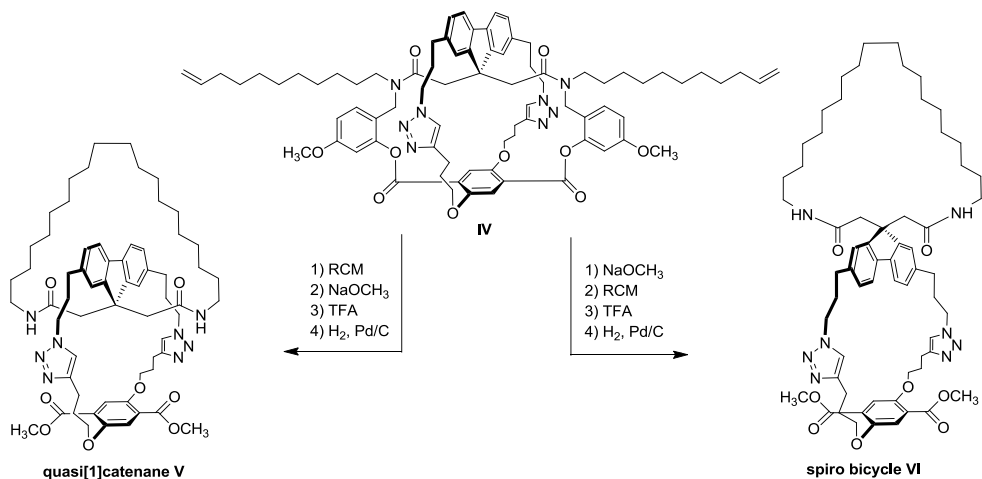
To expand the scope of this new class of compounds, a related quasi[1]rotaxane was synthesized by employing the same strategy, except by replacing the RCM step by cross metathesis with an electron deficient alkene. Also the non-interlocked isomer was synthesized for comparison. NMR analysis of the products revealed similar behavior to the aforementioned quasi[1]catenane and non-interlocked product.

Chapter V describes the final effort to use a templated backfolding concept to construct a [2]catenane. The strategy is similar to that described in Chapters III and IV, however, the connection between the two components is now based on a scissile cyclic ketal derived from tartaric acid. Like the fluorene, a cyclic ketal induces a perpendicular mutual arrangement of the components and allows cleavage by acidolytic hydrolysis in the final step. Cyclic ketal **VII** was synthesized uneventfully and was reacted with bis-azide template **VIII** using the aforementioned optimized conditions to give the bis-lactone macrocycle **IX**. Subsequent CuAAC reactions with the optimized Cu(CH$_3$CN)$_4$BF$_4$ / TBTA system gave the desired product in high yield. The RCM reaction was unexpectedly low yielding, despite testing various conditions. The cleavage steps to remove the benzylic tethers worked well, giving **X**, however, with the tested conditions it was not possible to hydrolyze the cyclic ketal to liberate [2]catenane **XI**. A combination of steric and electronic reasons seems to be the reason for this failure.
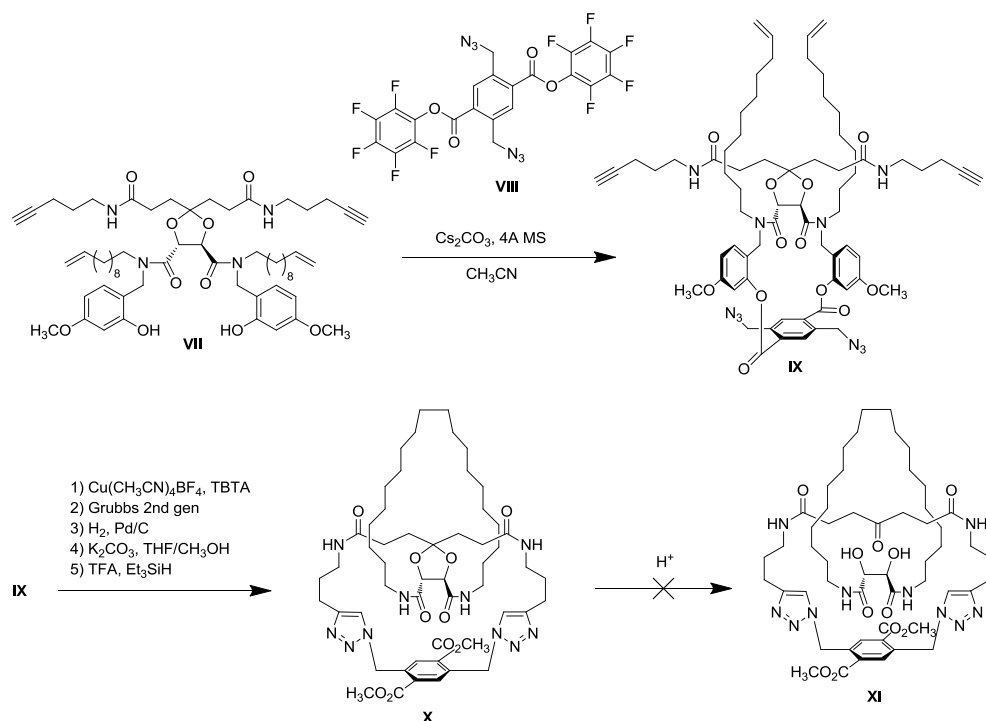
In Chapter VI an entirely different (covalent) approach towards [2]rotaxanes is presented. In this new strategy a terephthalic acid based template is used for pre-organization of two ring precursor halves. These ring precursors contain terminal alkenes allowing RCM as the ring-closing reaction. These ring halves contain a 2,6-difuncionalized phenol, which is esterified *via* the phenolic OH to the

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terephthalic acid template. Due to steric effects, these 2,6-difunctionalized phenols will form a more or less perpendicular angle with respect to the template. The scaffold is functionalized on the 2- and 5-positions, allowing installment of bulky stopper groups, thereby becoming the thread fragment of the [2]rotaxane. Note that by doing so, the template becomes incorporated in the thread of the final product. Next, the ring halves are reacted with each other via RCM forming a ring around the terephthalic acid core. Cleavage of the esters liberates the free [2]rotaxane and the resulting carboxylic acid groups might be functionalized further. Three model substrates were synthesized bearing a terminal alkene moiety on the 2- and 6-positions of the phenol. Subsequent RCM was only successful in one case bearing 6-heptenyl chains. Saponification of the terephthalic acid core produced the desired 30-membered macrocycle as the sole product, as confirmed by HRMS. With a working macrocyclization reaction in hand, a [2]rotaxane could now be assembled. By using 2,5-difunctionalized template it was possible to install two bulky tris-4-*tert*-butyltrityl groups *via* a CuAAC reaction. Subsequent RCM reaction, hydrogenation of the olefinic E/Z mixture and saponification of the ester bonds liberated [2]rotaxane **XII** in good overall yield. Saponification required harsh conditions (130 $^{\circ}$C) to complete the reaction, indicating a strong sterically hindered environment around the esters. HRMS analysis proved that the correct [2]rotaxane product had formed.
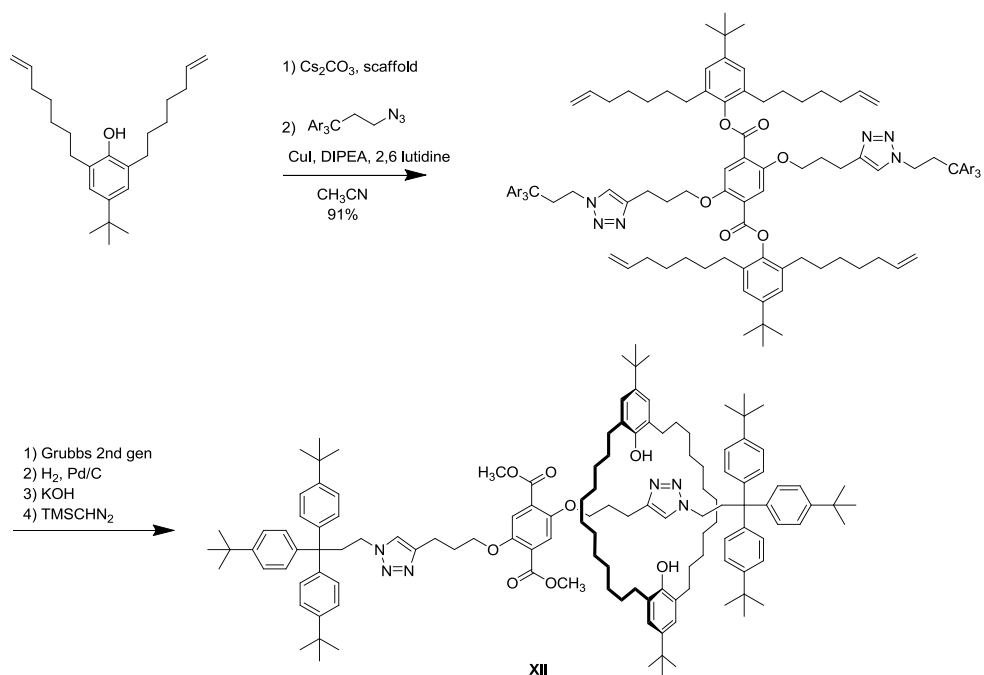
In Chapter VII an outlook is presented suggesting some ideas to tackle standing problems encountered in the previous chapters, as well as ideas to shorten syntheses and some new ideas for follow-up projects regarding this work.

Samenvatting 'Synthese van mechanisch vergrendelde moleculen geassisteerd door een covalent gebonden moleculaire sjabloon'

Dit proefschrift beschrijft onderzoek naar meerdere strategieën om mechanisch vergrendelde verbindingen te verkrijgen met behulp van covalente bindingen voor de pre-organisatie van de componenten, met als ultieme doel om in de toekomst lassopeptiden te kunnen synthetiseren. Een klein 'steiger' of 'sjabloon' molecuul met orthogonale reactiviteiten wordt in alle strategieën gebruikt voor de stapsgewijze assemblage van verknoopte moleculen. Deze sjablonen zijn zo ontworpen dat ze covalent aan de ring- en draadfragmenten binden en deze in een correcte manier positioneren om te kunnen cycliseren. Afhankelijk van de strategie was het sjabloonmolecuul ontworpen om uiteindelijk helemaal verwijderd te kunnen worden (hoofdstukken II en III) of om ingebouwd te worden in het eindmolecuul (hoofdstukken IV, V en VI). Hoofdstuk I geeft een historisch overzicht van mechanisch vergrendelde moleculen en veelgebruikte methoden voor de synthese van deze moleculen. Beginnend met een baanbrekende publicatie van Lüttringhaus en Schill uit 1964, worden in dit hoofdstuk de drie belangrijkste methoden om rotaxanen te synthetiseren uitgelegd: 'clipping', 'capping' en 'active metal template'. In deze strategieën worden vrijwel uitsluitend niet-covalente interacties gebruikt voor de preorganisatie van de componenten. Desalniettemin heeft de covalente strategie de laatste jaren een comeback gemaakt, omdat er moleculen mee gemaakt kunnen worden die met de drie genoemde methodes onbereikbaar zijn. Het grootste voordeel van de covalente strategie is dat de eindproducten niet de grote polaire groepen bevatten die voor niet-covalente preorganisatie nodig zouden zijn. Bovendien kunnen via de covalente strategie functionele groepen worden geïntroduceerd die niet compatibel zijn met de drie bovengenoemde methodes. Nadelen van een covalente strategie zijn onder andere de langere syntheseroutes en minder algemene toepasbaarheid. Een covalente strategie om een [2]rotaxaan te maken via een tijdelijke sjabloon voor de preorganistie wordt beschreven in hoofdstuk II (zie figuur hieronder).

De eerste stap is het binden van het ringfragment (blauw) aan een vlak vierkante sjabloon door middel van een macrocyclisatie. In hoofdstuk II wordt onderzoek naar bruikbare reacties voor deze stap beschreven. Belangrijk is het gebruik van een tijdelijke amide *N*-modificatie, zodat deze later weer verwijderd kan worden via zure behandeling. Deze amide *N*-modificatie is gebaseerd op de 2,4-dimethoxybenzyl groep, bekend om amidebindingen in peptides te beschermen. De tweede stap is het binden van het draadfragment (rood) door middel van een tijdelijke covalente binding (geel). Deze binding is nodig om ervoor te zorgen dat de volgende stap (binden van het draadfragment aan de sjabloon) aan dezelfde kant als het ringfragment plaatsvindt. Het verkregen multicyclische kooi-achtige molecuul ondergaat een laatste cyclisatie (grijs) waarbij de ring om het draadfragment gevouwen wordt. De sjabloon wordt vervolgens losgekoppeld via zure splitsing van de benzylische amide groepen. In de laatste stap wordt de tijdelijke binding tussen het ring- en draadfragment (geel) gesplitst waardoor het beoogde [2]rotaxaan vrijkomt.

Na een paar mislukte pogingen om de eerste stap (ringfragment aan sjabloon koppelen) onder de knie te krijgen realiseerden wij ons dat een 2-hydroxy-4-methoxybenzyl groep een perfecte keuze als amide *N*-modificatie zou zijn. De fenolische OH groep is een kleine, maar functionaliseerbare groep door middel van een milde Williamson-type alkylering. Modelverbinding **I** voldeed aan de verwachtingen en reageerde selectief en in hoge opbrengst met verscheidene dihalides als modelsjablonen om macrocyclische verbindingen **II** te verkrijgen. Het was belangrijk om polaire aprotische oplosmiddelen (zoals CH₃CN en DMF) te gebruiken en lage concentraties van de reactanten (1-5 mM) om polymerisatie als nevenreactie te onderdrukken.

Ook werden vlak vierkante sjablonen onderzocht met een zogenaamd ABAB patroon, oftewel met twee verschillende functionele groepen trans gepositioneerd. Helaas werd er geen klasse verbinding gevonden die een succesvolle synthese van een complete steiger mogelijk maakte. Veelvoorkomende problemen waren incompatibiliteit van de functionele groepen, onoplosbaarheid van de producten en oxidatiegevoeligheid. Mede hierdoor moest het concept van zuiver vlak vierkante sjablonen worden opgegeven.

Hoofdstuk III beschrijft onderzoek naar de tijdelijke covalente verbinding tussen de ring- en draadfragmenten. Deze verbinding is nodig om te verzekeren dat beide componenten aan dezelfde kant van de sjabloon zijn gesitueerd. Om dit te bewerkstelligen werd een oxim binding gekozen vanwege de robuustheid en hoge vormingssnelheid bij lage concentraties. Bovendien is de vorming van een oxim reversibel en kan deze onder milde condities weer gesplitst worden. Ringfragment **III** werd gesynthetiseerd met een beschermd oxyamine in het midden van het molecuul. Vervolgens werden meerdere draadfragmenten gesynthetiseerd met een keton in het midden (voor oxim ligatie) en twee *N*-amide modificaties met een propargyl groep voor de orthogonale CuAAC reactie met de sjabloon. Sommige draadfragmenten bevatten de grote tris-4-*tert*-butyltrityl groep als rotaxaan 'stopper' groep. Als laatste werden enkele sjablonen gemaakt met twee geactiveerde bromides (voor de 1^e stap) en twee azides voor de CuAAC reactie tussen het draadfragment en de sjabloon. Deze sjablonen zijn niet vlak vierkant, maar gebaseerd op een tetrahedraal sp^3–gehybridiseerd koolstofatoom of een 1,2,4,5-tetragesubstitueerd benzeen.

In alle gevallen gaf de eerste macrocyclisatie tussen het ringfragment en de sjabloon het product in goede opbrengsten. Ook de oximligatie stap ging goed in alle gevallen, met TFH/H$_2$O en azijnzuur als optimaal reactiemedium. De volgende stap was de intramoleculaire CuAAC reactie tussen de azides van de sjabloon en de alkynen op het draadfragment. Ondanks de preorganisatie bleek deze stap lastig omdat moleculen met de sjabloon gebaseerd op een tetrahedraal koolstofatoom geen vergrendelde producten opleverde. De 1,2,4,5-tetragesubstitueerde benzeenderivaten presteerden beter omdat hun rigiditeit de vorming van deze niet-vergrendelde moleculen voorkomt. De volgende stap was een ringsluitingsmetathesereactie en verliep zonder problemen onder hoge verdunning. De laatste stap van de assemblage was de zure splitsing van de sjabloon en splitsing van het oxim tussen het ring- en draadfragment. Echter, behandeling van de producten met TFA en triethylsilaan gaven een complex mengsel in beide geteste systemen.
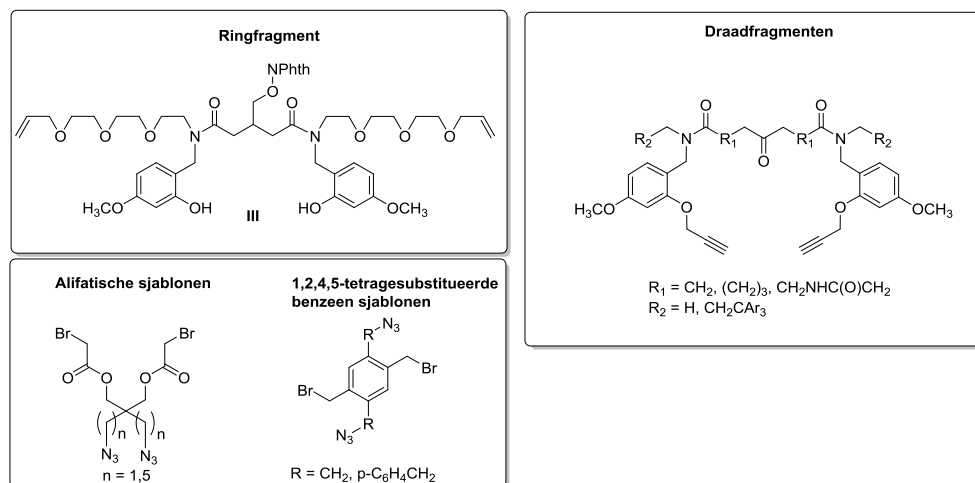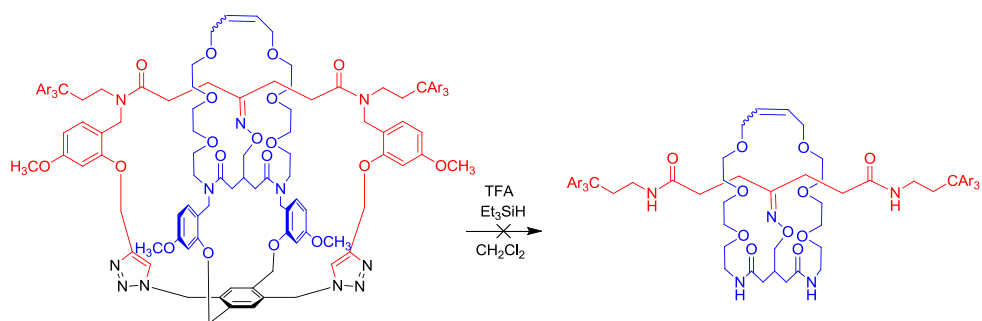
In hoofdstuk IV wordt de strategie aangepast door de tijdelijke oximbinding tussen de ring en de draad te vervangen door een rigide fluoreengroep. Het centrale sp^3-gehybridiseerde koolstofatoom van fluoreen verzekert een ideale hoek van 90° tussen de componenten waardoor het molecuul maar op één manier kan vouwen. Echter, omdat deze bindingen niet gebroken kunnen worden zal er uiteindelijk een spiroverbinding ontstaan. Na 3D modellen te hebben gemaakt van het intermediair realiseerden wij ons dat er twee mogelijke producten gevormd zouden kunnen worden, namelijk het normale spiro bicyclische systeem en een omgekeerde spiroverknoping. Door de juiste volgorde van synthesestappen te kiezen zou het mogelijk moeten zijn om selectief beide verbindingen te kunnen maken. De op fluoreen gebaseerde verbindingen werden gemaakt met drie onafhankelijke (orthogonale) reactiviteiten, namelijk fenolische hydroxylgroepen voor verestering, azides voor CuAAC reacties en alkenen voor een laatste ringsluitingsmetathesereactie. De reactie met een bis-pentafluorfenol ester gaf een schone omzetting naar het gewenste bis-lacton in hoge opbrengst. Vervolgens werd de intramoleculaire CuAAC reactie geoptimaliseerd door Cu(CH$_3$CN)$_4$BF$_4$ en TBTA als katalysator te gebruiken, waardoor product **IV** reproduceerbaar in hoge opbrengst verkregen kon worden. Vanuit dit kooi-achtige intermediair konden beide spiroverbindingen verkregen worden. Ringsluitingsmetathese, gevolgd door estersplitsing en TFA behandeling resulteerde in de niet eerder beschreven geometrie **V**, door ons tot een quasi[1]catenaan gedoopt. Door de eerste twee synthesestappen om te draaien (dus eerst estersplitsing en dan ringsluitingsmetathese) werd het sterisch ontspannen spiroproduct **VI** verkregen. Men moet zich realiseren dat de twee verbindingen diastereomeren zijn, ondanks het ontbreken van een een chiraal koolstofatoom. Gedetailleerde 1D- en 2D-NMR studies lieten inderdaad zeer verschillende eigenschappen zien van de twee isomeren.

quasi[1]catenaan V

IV

1) RCM
2) NaOCH$_3$
3) TFA
4) H$_2$, Pd/C

1) NaOCH$_3$
2) RCM
3) TFA
4) H$_2$, Pd/C

spiro product VI
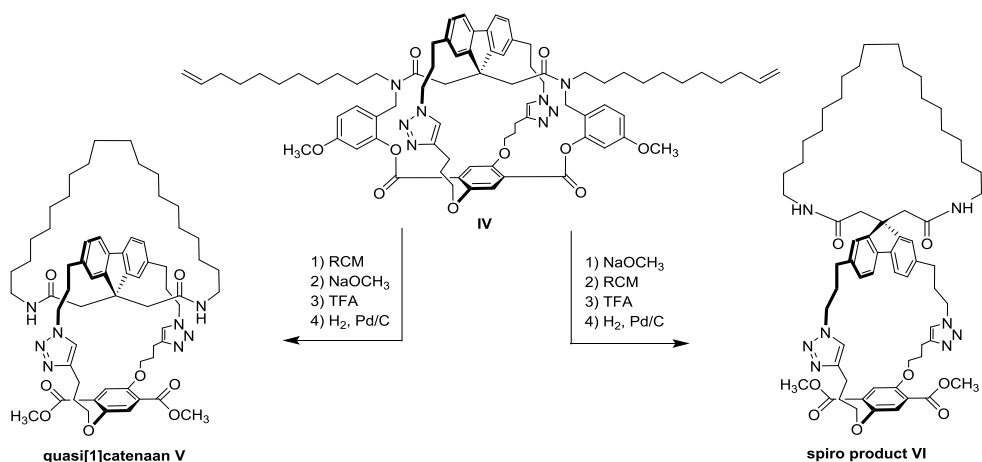
Om meer inzicht te verkrijgen in deze nieuwe klasse van verbindingen werd ook een gerelateerd quasi[1]rotaxaan gesynthetiseerd door dezelfde synthesestrategie te volgen, maar door de ringsluitingsmetathesestap te vervangen door een intermoleculaire metathesereactie met een groot electronarm alkeen dat als stopper fungeerde. Ook werd ter vergelijking de niet-omwonden isomeer gemaakt. NMR analyse van deze twee verbindingen liet vergelijkbare eigenschappen zien met respectievelijk het quasi[1]catenaan en de normale spiro verbinding.

Het onderzoek beschreven in hoofstuk V behelst de laatste inspanningen om een [2]catenaan te synthetiseren met behulp van een een covalent gebonden sjabloonmolecuul. De strategie is gerelateerd aan het in de hoofstukken III en IV beschreven werk, echter is de verbinding tussen de twee componenten nu gebaseerd op een cyclisch ketaal afkomstig van wijnsteenzuur. Net als de fluoreengroep beschreven in hoofdstuk IV induceert een cyclisch ketaal een hoek van 90° tussen de componenten, maar is tegelijkertijd weer te splitsen door zure behandeling. Cyclisch ketaal **VII** werd zonder problemen gemaakt en werd in reactie gebracht met bis-azide steiger **VIII** met de eerder genoemde geoptimaliseerde condities om bis-lacton **IX** te verkrijgen. Vervolgens werd de intramoleculaire CuAAC reactie met het Cu(CH$_3$CN)$_4$BF$_4$ / TBTA systeem uitgevoerd in hoge opbrengst. De ringsluitingsmetathese reactie verliep onverwacht moeizaam en gaf matige opbrengsten, ondanks pogingen tot optimalisatie. Behandeling met zuur om de benzylgroepen te verwijderen gaf verbinding **X** in hoge opbrengst, maar het was helaas niet mogelijk om het cyclische ketaal te hydrolyseren naar het vrije [2]catenaan **XI**. Een combinatie van sterische en elektronische eigenschappen lijkt het probleem te zijn in de hydrolysestap.
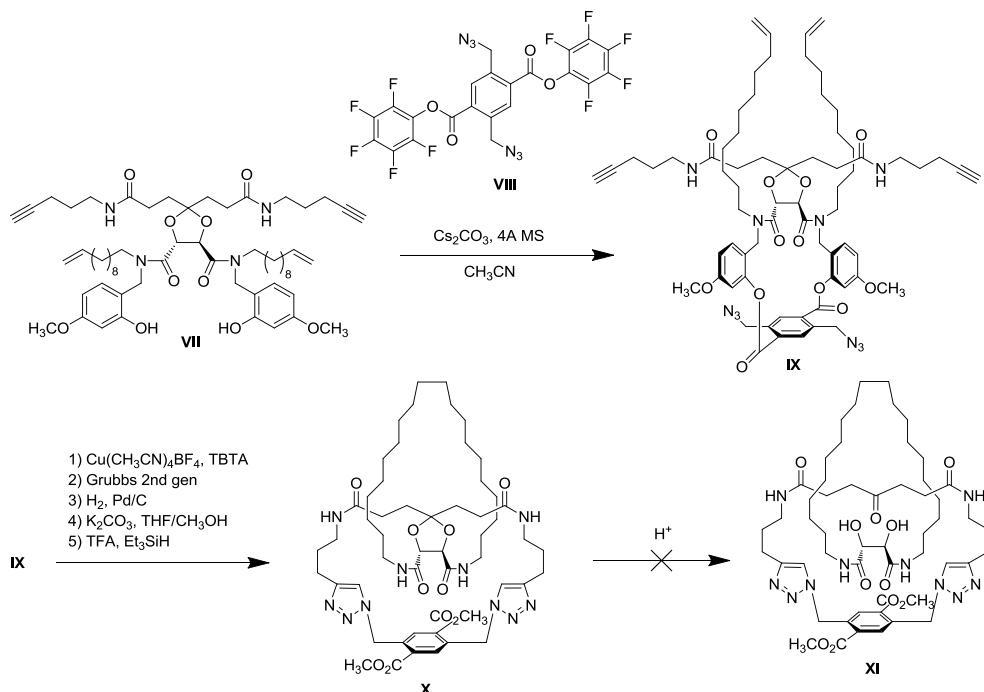
In het onderzoek zoals beschreven in hoofdstuk VI werd een volledig andere (covalente) benadering bestudeerd om een [2]rotaxaan te verkrijgen. In deze nieuwe strategie werd een sjabloon gebasseerd op tereftaalzuur gebruikt voor de preorganisatie van twee ringhelften. Deze ringhelften

bevatten twee terminale alkenen, waardoor de robuuste ringsluitingsmetathesereactie gebruikt kan worden. De ringhelften bevatten een 2,6-digefunctionaliseerd fenol en worden aan de steiger gebonden via een esterbinding tussen de fenolische hydroxylgroepen en de zuurgroepen van tereftaalzuur. Vanwege sterische effecten zullen deze 2,6-digefunctionaliseerde fenolen een vrijwel loodrechte hoek vormen met het sjabloon. Het sjabloon zelf is gefunctionaliseerd op de 2- en 5-posities waardoor grote sterische groepen geïntroduceerd kunnen worden en daarmee het draadfragment van het rotaxaan wordt. Hierdoor wordt het sjabloon dus ook ingebouwd in het uiteindelijke molecuul. Vervolgens worden de ringhelften met elkaar verbonden via ringsluitingsmetathese, waardoor een ring wordt gevormd om de tereftaalzuur kern. Verzeping van de esters bevrijdt de [2]rotaxaan en de resulterende carbonzuren kunnen weer verder gefunctionaliseerd worden. Drie modelsystemen werden gesynthetiseerd met een terminaal alkeen op de 2- en 6-posities van het fenol. Ringsluitingsmetathese was echter alleen succesvol in één van deze systemen, namelijk die met 6-heptenyl staarten. Verzeping van de centrale tereftaalzure esters gaf de gewenste 30-ring als het enige product, bevestigd door HRMS. Met een werkende macrocyclizatie kon nu een [2]rotaxaan gemaakt worden. Door een 2,5-digefunctionaliseerd tereftaalzuur te gebruiken was het mogelijk om twee tris-4-*tert*-butyltritylgroepen te introduceren via een CuAAC reactie. Vervolgens werden de ringhelften gesloten met ringsluitingsmetathese en het resulterende E/Z mengsel werd gehydrogeneerd en vevolgens verzept om [2]rotaxaan **XII** in hoge opbrengst te verkrijgen. De verzepingsstap had zeer drastische condities (130 °C) nodig om af te lopen, wat duidt op (verwachte) sterische hindering rondom de esters. HRMS analyse bewees dat het gewenste [2]rotaxaan inderdaad gevormd was.

XII
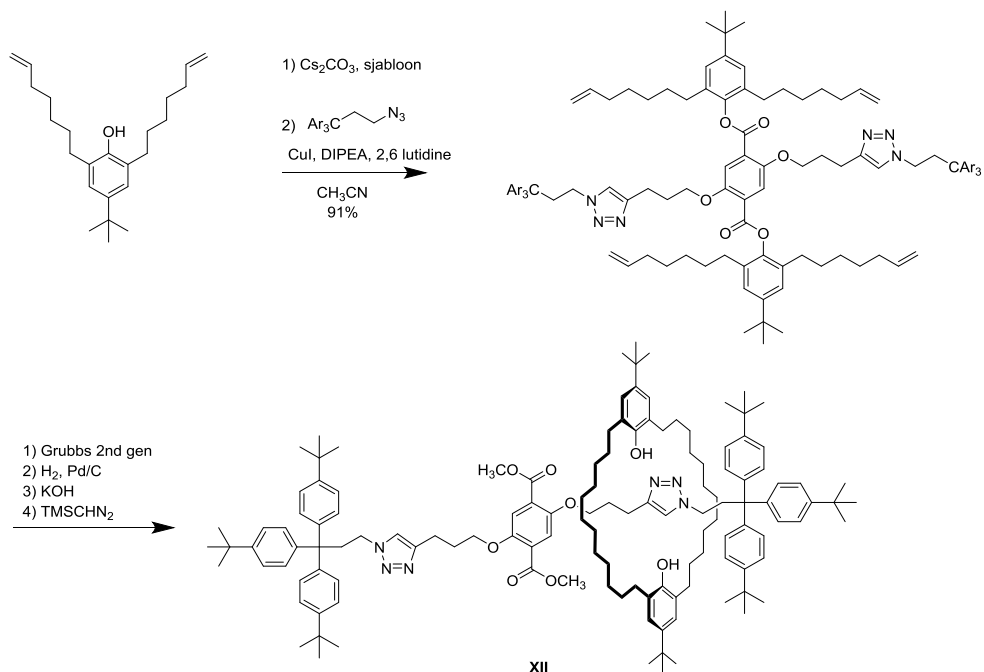
In hoofdstuk VII worden enkele suggesties gepresenteerd om lastige stappen die in dit proefschrift voortgang tegenhielden te verbeteren. Ook worden ideeën aangedragen om sommige syntheses te verkorten en suggesties geopperd voor verder onderzoek.

Dankwoord

Goed, het zit er nu toch echt op, het einde van mijn proefschrift. Graag wil ik een aantal mensen bedanken die mij hebben geholpen en/of ondersteund gedurende deze jaren. Beginnend bij m'n begeleider **Jan**, jij bent met recht een bijzonder persoon. Als docent ben je ongeëvenaard en heb je - met recht- de Docent van het Jaar prijs gewonnen. Jij hebt de unieke gave om hele horden studenten enthousiast te krijgen voor chemie (niet alleen organische chemie). Je toewijding is ook vaak fysiek terug te zien, als je broek, overhemd en gezicht onder het schoolkrijt zitten! Je grote passie is zweefvliegen en je raakt daar nooit over uitgesproken. Als ik je op een mooie dag niet kon vinden in je kantoor was de kans groot dat je op Soesterberg zat. Tijdens groepsuitjes is de BBQ vaak bij jou thuis gehouden, altijd gezellig! (zeker met de luchtbuks erbij). Onze trip naar Florida is me ook bijgebleven als een van de hoogtepunten van mijn PhD-tijd. Op het kantoor ben je altijd druk met van alles en nog wat en hierdoor vergeet je soms afspraken of heb je dubbele boekingen. De chaos zijn we van je gewend ondertussen! Jouw promotie tot professor was ook een moment om niet te vergeten. Als jouw Luuk-met-de-gouden-handjes hebben we samen de Nature Communications als absoluut hoogtepunt weten te krijgen. Dat gezegd te hebben, heeft jouw schrijfstijl zeker de doorslag gegeven om het zover te krijgen. We hebben nu meer ideeën voor de toekomst dan ooit te voren, en ik hoop dat er in de toekomst nog veel AiO's gaan volgen die gaan voortborduren op het onderzoek uit dit proefschrift. **Henk**, ik weet nog goed het moment dat ik jouw kantoor op Roeterseiland binnenliep om te vragen of ik mijn bachelorproject in de SOC groep kon doen. Ik was enigszins zenuwachtig, maar gelukkig bleek je al snel niet de norse Fries te zijn die ik had verwacht, maar een aardige en behulpzame professor. Tijdens de MDSC-master heb ik genoten van de colleges van organische chemie samen met Jan. Dat professor Hiemstra een strak geoliede machine is staat vast, van jouw organisatievermogen kan ik (en vele anderen) nog wat leren. Tijdens group meetings heb je cruciale suggesties gedaan en heb je geholpen reacties mechanistisch te begrijpen (soms tot vervelens aan toe!). Ook jouw kennis in organische chemie en naamreacties is ongekend zoals is gebleken tijdens de quiz op de problemevenings, je bent een wandelende encyclopedie. Volgend jaar ga je met pensioen, en ik hoop dat je ervan gaat genieten. Maar een echte chemicus gaat achter de geraniol zitten en niet achter de geraniums! **Steen**, jou ken ik al sinds het begin van de bacheloropleiding. Je woonde toen nog in Koog aan de Zaan en zag je soms langskomen in de Albert Heijn onder het viaduct waar ik toen nog werkte. Bedankt voor de suggesties tijdens werkbesprekingen en hulp met de LC-MS en interpretaties van massa-spectra, waarin jij koning bent. Je hebt me veel geleerd tijdens de opleiding en je accent is altijd een mooie bonus geweest (drijvende grachten!) Ook veel succes met je nieuwe rol als opa. **Tati**, thanks for the suggestions and discussion during the groupmeetings. You have started a nice research group in the SOC group and your experiences are a bonus to us all. You should still see my band someday, you're gonna like it! Best wishes for the future! **Chris**, jij bent de nieuwste aanwinst van de SOC-groep. Toen ik als verse AiO het 2^e-jaars organisch practicum ging begeleiden op de VU was jij daar de practicumcoördinator en je was (en bent nog steeds) heel relaxt en prettig in omgang. Een paar jaar geleden zag ik jouw praatje op de HRSMC over frustrated Lewis-pairs en je hebt toen mijn interesse gewekt in deze voor mij onbekende tak van chemie. Hoewel de moleculen erg gevoelig zijn hebben ze unieke reactiviteit en zijn ze het onderzoeken meer dan waard! Nu op de UvA ben je helemaal thuis en heb je een fijn team. Veel geluk! Graag wil ik ook reeds gepromoveerde collega's bedanken voor de fijne tijd in de eerste jaren van mijn promotie. Mede-Zaankanter **Arjen**, veel geluk samen met **Andrea** en de kleine! **Linde**, veel geluk in Zwitserland en succes met het aanstaande moederschap. Ook veel succes en geluk aan **Jochem** en zijn gezin. **Stanimir**, you must be the most committed PhD student I've known,

thanks for our discussions and good times and best wished for the future with **Daniela** and the little Popovic! And I hope you've removed the disturbing Sinterklaas striptease from your phone by now…
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