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CHIRALITY-ASSISTED SYNTHESIS OF SUPRAMOLECULAR RECEPTORS

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ABBREVIATIONS

Ac – acetyl group
BCN – bicyclo[3.3.1]nonane
Boc – *tert*-butyloxycarbonyl group
bpy – 2,2'-bipyridine
Bn – benzyl group
COSY – correlation spectroscopy
DAN - 2,7-diamido-1,8-naphthyridine
DCM - dichloromethane
Dec – decyl group
DIPEA – N,N-diisopropylethylamine
DMC – dimethyl carbonate
DMF – N,N-dimethylformamide
DMSO - dimethyl sulfoxide
DFT – density functional theory
DNA – deoxyribonucleic acid
DOSY – diffusion ordered spectroscopy
Ee – enantiomeric excess
Et – ethyl group
EMA – European Medicines Agency
eq. - equivalent
FDA – U.S. Food and Drug Administration
FRET – fluorescence resonance energy transfer
Gua – guanidinium ion
HBTU - hexafluorophosphate benzotriazole tetramethyl uronium
HMBC – heteronuclear multiple bond correlation
HPLC – high-performance liquid chromatography
ICyt - isocytosine
IR - infrared
Me – methyl group
MS – mass spectrometry
nBu – *n*-butyl group
NMR – nuclear magnetic resonance
NOESY – nuclear Overhauser effect spectroscopy
Nosyl – para-nitrobenzenesulfonyl group
PCC – pyridinium chlorochromate
PE – petroleum ether
Ph – phenyl group
Pin - pinacol
PUPy – pyrrole-fused 2-ureido-4-pyrimidinone
Py - pyridine
ROESY – rotating frame nuclear Overhauser effect spectroscopy
R_f – retention factor
rt – room temperature
TFA – trifluoroacetic acid

THF - tetrahydrofuran
TEG – tetraethylene glycol
Tf – trifluoromethanesulfonyl group
TLC – thin layer chromatography
Ts – para-toluenesulfonyl group
TMS – trimethylsilyl group
tpada - 4'-(adamantan-1-yl)-2,2':6',2″-terpyridine
tBu – *tert*-butyl group
UPy - 2-ureido-4-pyrimidinone

INTRODUCTION

The concepts of supramolecular interactions and self-assembly, while still under-utilized and under-developed in the field of organic chemistry, are an essential part of biology. The formation of intricate multi-molecular structures through various dynamic non-covalent interactions (e.g. van der Waals forces, solvophobic effects, hydrogen bonding, dipole-dipole and pi-pi interactions) enables many functions that are required for life to exist, such as the storage of information and self-replication in nucleic acids, the folding of proteins, enzyme-based catalysis of chemical transformations and the assembly of cellular scaffolds. However, due to the difficulty of designing, preparing and analyzing synthetic analogues of such supramolecular systems, these concepts were unreachable to the organic chemist, being limited only to studies of naturally occurring compounds such as the cyclodextrins.

The beginning of synthetic supramolecular chemistry can be attributed to the 1967 paper of C. J. Pedersen [1], which described the ability of cyclic polyethers (now referred to as crown ethers) to form complexes with various metal ions. This research was further developed, mainly by the group of D. J. Cram [2], to produce larger cavity-containing molecules that could bind alkylammonium ions. With further iterations, the systems increased in their size and complexity, gaining the ability to bind a large variety of molecular guests with high selectivity. Various types of hosts – such as corands, cavitands and carcerands – had evolved.

However, the ever-increasing complexity was limited by the ever-growing difficulty to prepare such hosts. The solution was once again inspired by the billions of years of chemical evolution in nature – much like the macrostructures in biological systems, the hosts be prepared through self-assembly of smaller molecules containing structurally encoded information for self-complimentary non-covalent binding. This approach, pioneered by the group of J. Rebek [3], allowed for the development of incredibly complex functional supramolecular systems and polymers from relatively simple structural monomers.

A similar self-assembly approach has also been used by the group of E. Orentas to prepare numerous supramolecular host systems, such as cavitands, capsules and tubular polymers, from simple monomers based on the enantiomerically pure bicyclo[3.3.1]nonane (BCN) scaffold. When fused with aromatic systems, the BCN fragment features as a chiral, semi-rigid, 90°-angled spacer between the flat and rigid aromatic walls, allowing for preparation of rectangle-shaped frameworks. The main goal of this master thesis is to develop the next generation of BCN-based supramolecular cavitands, centered around the use of both enantiomers of the chiral BCN backbone, which would allow for increased geometric complexity, enabling preparation of systems with large cavities containing unique surface geometries, potentially offering novel selectivity for host-guest binding.

1. REVIEW OF LITERATURE

1.1 Cavitands

Cavitands are macrocyclic molecules containing an enforced cavity that is large enough to form host-guest complexes with other molecules or ions through various non-covalent interactions. While this group encompasses many types of synthetic and biological compounds, the most commonly encountered sub-type is the cyclic phenol-aldehyde oligomers, e.g. resorcinarenes, calixarenes and pillararenes (figure 1). As seen in figure 2, these cavitands can fold into a conformation containing a hollow bowl-like cavity with a wide upper ridge and a narrow lower ridge. The conformation is often stabilized by intramolecular hydrogen bonding between phenolic hydroxy groups and through steric repulsion of bulky R-groups.

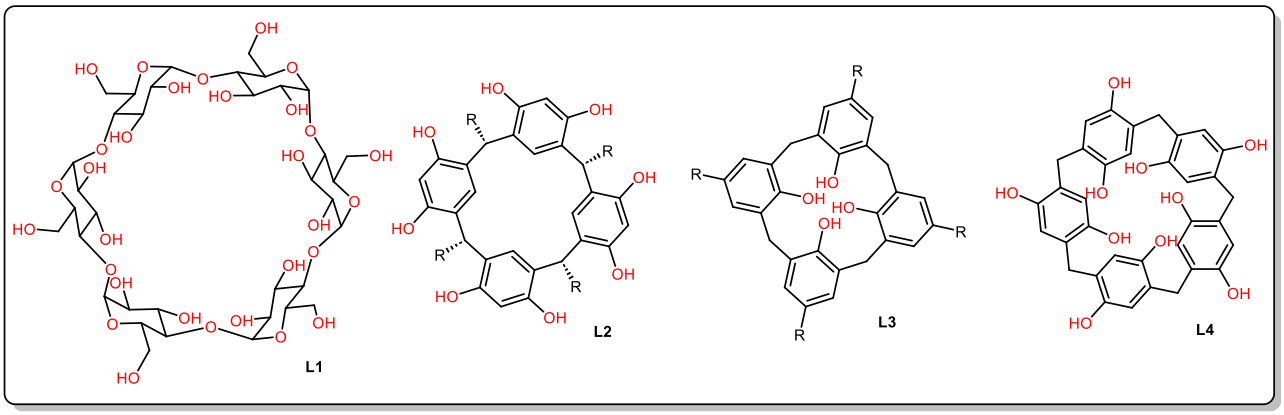


Figure 1. Parent compounds of the most common cavitand subtypes: α-cyclodextrin **L1**, resorcin[4]arene **L2**, calix[4]arene **L3**, pillar[5]arene **L4**.

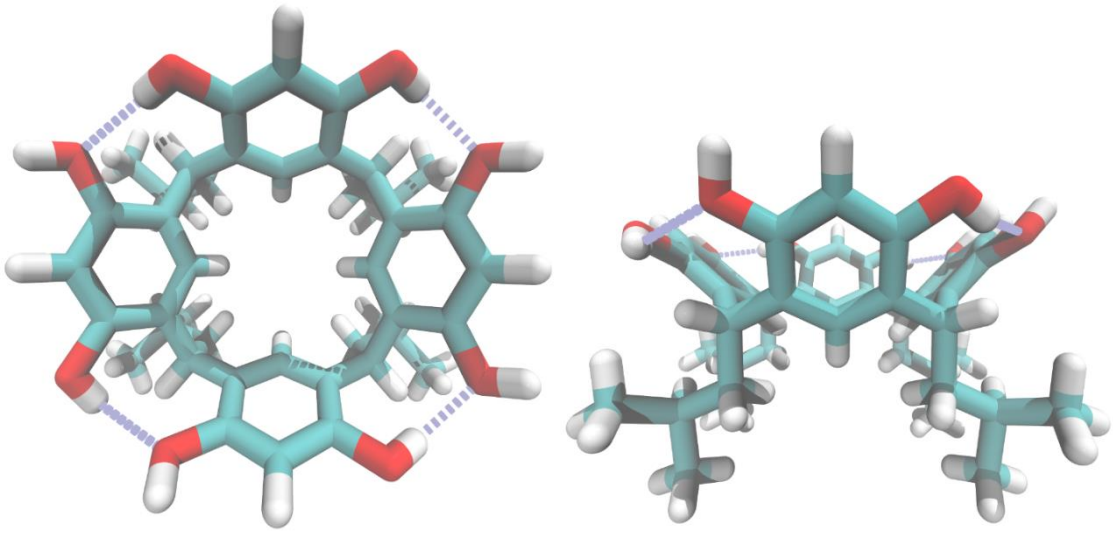


Figure 2. Crystal structure of resorcin[4]arene (R=iPr): top view (left) and side view (right) [4].

While the parent cavitand structures do already contain a relatively large concave surface and polar groups on the ridge which allow for host-guest interactions, most use cases rely on the so called "deep cavity" cavitands, that are usually prepared by extending the rigid aromatic "walls" of the bowl-shaped surface. An example is provided in figure 3. The increased rigidity and surface area allow for increased guest variety, complexation selectivity and complex stability.

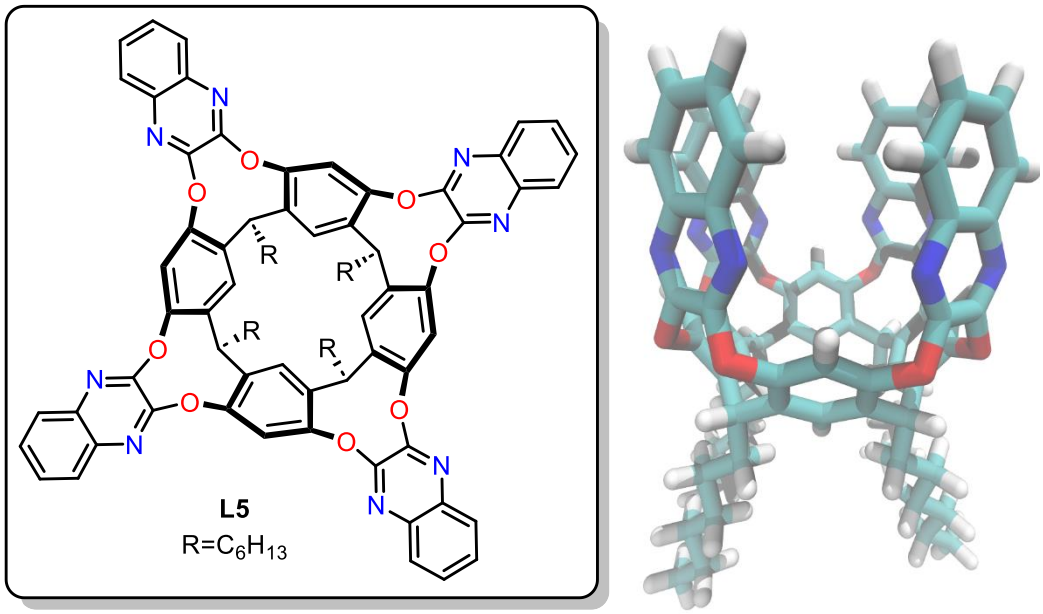


Figure 3. Chemical (left) and crystal (right) structure of deep-cavity quinoxaline cavitand **L5** [5].

Many applications for cavitands have been found in fields such as chemistry, biochemistry, materials science and medicine. For example, cavitands with high selectivity and binding affinity for specific targets can be used for molecular recognition. Chen et al. prepared a molecular recognition system for phosphorylated peptides based on water-soluble deep cavitands [6]. The system consists of a fluorescent cationic styrylpyridinium dye and a modified resorcinarene **L6**. It was shown that peptides can form complexes with both the dye and the cavitand, leading to a different equilibrium of binary and ternary complexes unique for each peptide and each phosphorylated variant of a peptide. As each dye containing element in the equilibrium has a different emission intensity, each phosphorylated peptide will have a different concentration-emission curve, which was shown to be enough to fully distinguish between the different variants.

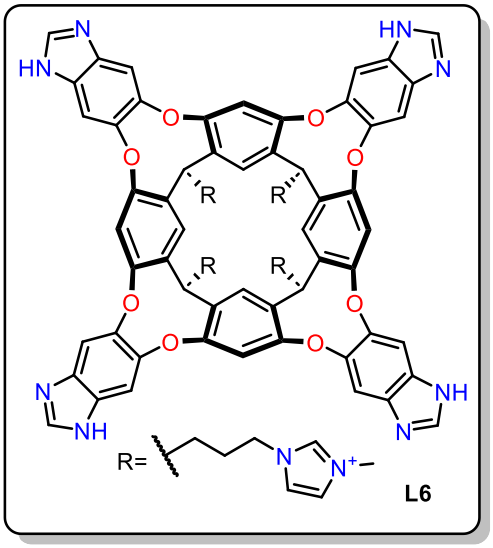


Figure 4. Structure of water-soluble deep cavitand **L6**.

In the field of materials science, Roithmeyer et al. prepared pillar[6]arene functionalized electrodes that serve as a versatile and robust base for various electrocatalytic transformations [7].

The electrodes, prepared simply by immersing mesoporous indium tin oxide electrodes in a pillararene solution, can then be functionalized with various catalytic metal complexes containing hydrophobic groups (e.g. [Ru(tpada)(bpy-NMe_2)(Cl)](PF_6) **L7** containing a ligand with an adamantyl group). Such a strategy allows for hydrophobic catalysts to be used in aqueous media, as well as increasing their overall stability. The immobilized electrocatalysts were successfully used for alcohol and ammonia oxidation reactions in both acidic and alkaline conditions (pH 1-11) without significant desorption of the host. The electrode material can be reused for further reactions by reabsorption of the catalyst after its degradation.

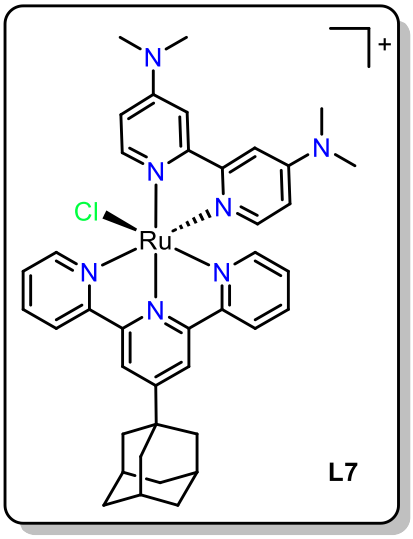
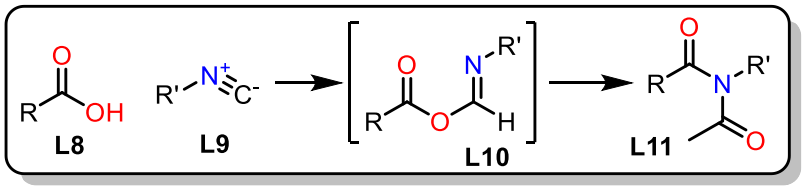


Figure 5. Catalytic complex **L7**, featuring an adamantyl group allowing for cavitand complexation.

Another perspective field of cavitand applications is for supramolecular catalysis. In this field, cavitands function as bio-mimetic versions of enzymes, catalyzing reactions of their guest molecules through many of the same mechanisms: creation of a solvent-free micro-environment, steric blocking, stabilization of intermediates or specific orientation towards functional groups of the host or other molecules. Many catalytic enzyme systems based on these mechanisms have already been tested [8–10]. For example, Hou et al. used a dimeric resorcinarene-based capsule to catalyze a bimolecular reaction between carboxylic acids and isonitriles to provide formylated secondary amides (scheme 1) [11]. Previous reports of this reaction required vigorous conditions – heating up to 150°C using a microwave reactor. In the resorcinarene capsule, however, the reaction proceeded to completion at 40°C in 20 hours. Control experiments without the cavitand did not provide any product. The authors postulate that both the acid and isonitrile are complexed into the capsule, thus effectively amplifying the concentration of the reactants. The polar reactive groups are also oriented towards each other, being guided by the hydrogen bond donors and acceptors of the cavitand rims.



Scheme 1. Reaction between carboxylic acids and isonitriles.

In another research paper, the group used a cavitand to stabilize and allow for the observation of the intermediate **L10** by NMR and IR methods [12]. The group used a cavitand **L12** featuring a carboxylic group directed towards the center of the cavity (figure 6). As the isonitrile reacts with the acid, the formed intermediate is stabilized by steric blockage of the confined cavity and remains detectable for multiple hours. The authors show the possibility of using cavitands and other supramolecular systems as new complimentary methods for elucidating reaction mechanisms and modelling enzymes.

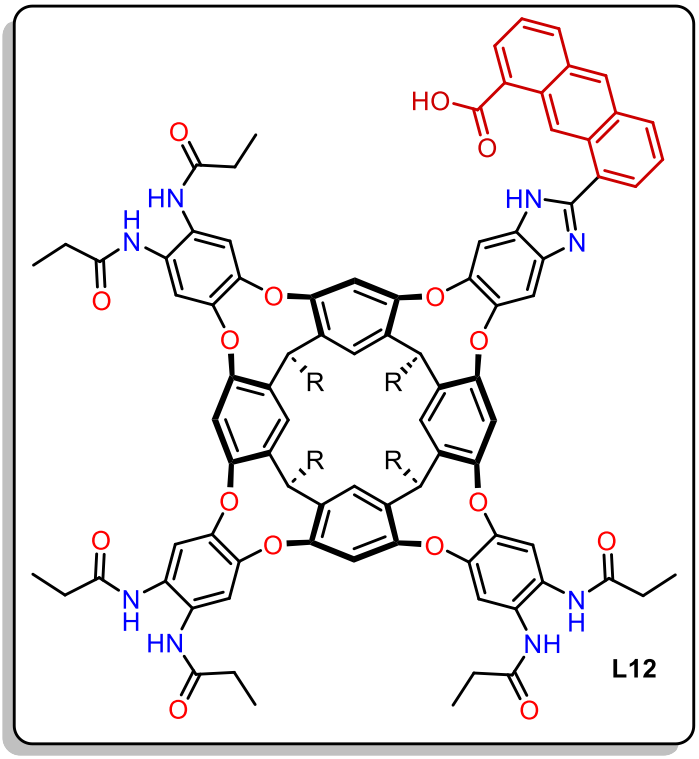


Figure 6. Structure of cavitand featuring cavity-oriented carboxylic group (marked in red).

Similarly, cavitands have been used to showcase new and underutilized concepts in organic chemistry. One of these is the halogen bond, an analogue of the well-known hydrogen bond, which results from charge transfer between Lewis bases and polarized halogen atoms (containing a so-called "σ-hole"). Despite being known in materials science for decades, it remains severely under-represented and under-taught in organic and medicinal chemistry [13]. The possibilities of the halogen bond have been previewed by the group of K. Rissanen. Beyeh et al. constructed the resorcinarene **L13** functionalized with N-alkyl ammonium bromide groups on the seam [14]. The bromide anions are incorporated into the structure through hydrogen bonding, and, upon addition of CCl_3Br to the solution, the bromide ions can form halogen bonds with the strongly polarized bromine atoms of CCl_3Br, thus effectively extending the size of the cavity and allowing for binding of larger guests, which was confirmed by X-ray analysis of the halogen-bonded complexes (figure 7). In another work, Turunen et al. created a dimeric cavitand capsule stabilized by a three-center-four-electron [N···I^+···N] halogen bond [15]. The resorcinarene-based cavitands are functionalized with four pyridine rings, which allowed for dimerization through the formation of a complex with Ag^+. Addition of molecular iodine led to a redox reaction to give the iodonium-bridged capsule, which was confirmed by NMR and MS methods. While these new designs may not yet offer much use, they serve to showcase an underutilized concept in modern organic chemistry.

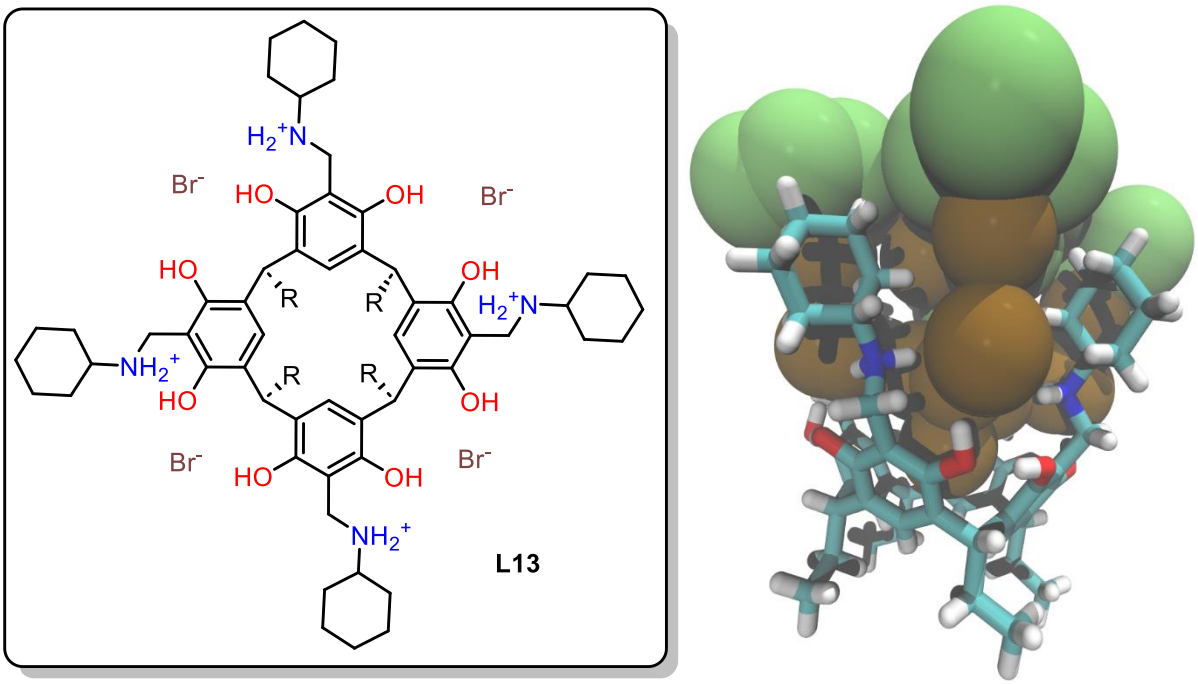


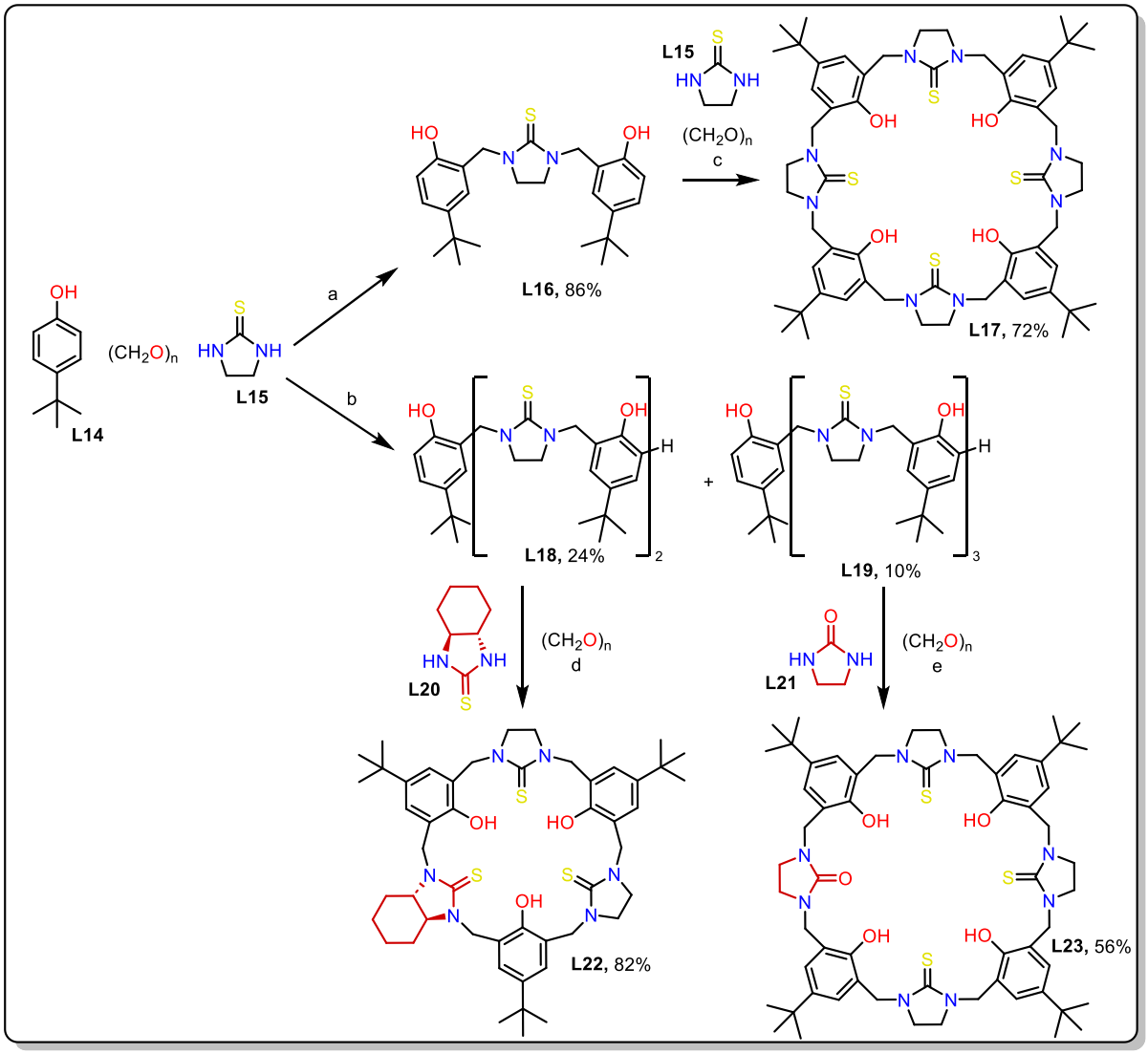
Figure 7. Structure of **L13** (left) and crystal structure of **L13** - CCl_3Br complex (right).

Out of all the cavitands, cyclodextrins have taken the spotlight in the field of medical applications due to their excellent biocompatibility. Numerous cyclodextrin-containing pharmaceutical products have been approved by the FDA and EMA [16], though other cavitand structures have also been used in academic research. In most cases, the cavitands are used as excipients that form complexes with the active ingredient, but some exceptions do exist. For example, Chen et al. used cucurbit[7]uril to reverse the effects of an anesthetic (tricaine mesylate) in zebrafish, presumably by acting as a competitive synthetic receptor and promoting dissociation of the drug from sodium channels. Nevertheless, the dominant use case is in complexes with the active pharmaceutical ingredient. The use of such complexes can have many potential advantages: strongly hydrophilic hosts can increase the solubility, and thus the bioavailability of the drug [17]. Steric shielding of the guest can improve chemical stability and extend both shelf life and half-life by preventing side reactions with biomolecules or small molecules [18]. Complexation can be used to modulate the pK_a of acidic and basic groups of the drug, enhancing bioavailability and therapeutical activity [19]. But while cyclodextrins have been dominating this field, much of the current research is centered around other types of cavitands that provide more versatility, tunability and functionalization capabilities. Pillararenes have attracted much attention in the field of cancer therapy due to their low toxicity, easy synthesis and customizability [20]. Many pillararene derivatives have been developed which directly exhibit cytotoxicity under specific conditions that are generally only present in cancer cells, such as acidic microenvironments [21] or overexpression of certain proteins [22].

Most of the previously discussed cavitand backbones are prepared by cyclooligomerization of the appropriate monomeric building blocks (e.g. substituted p-alkylphenols and formaldehyde for calixarenes). During such syntheses, competing polymer growth and macrocyclization reactions lead to many side products, and separation of the desired cyclic molecules from various other oligomers is often difficult. Therefore, every new synthesis of cavitands possessing a different structure or cycle size requires tedious optimization and very precise stoichiometry to achieve practical yields [23]. This method of synthesis also imposes high symmetry of the cavitand, as using more than one different monomer would make such reactions practically impossible to control. Besides that, many

monomeric building blocks simply cannot be used due to the resulting product mixtures being too difficult to purify.

Numerous methods have been developed to try and solve these problems, such as using various sized metal ions as templates to preferentially prepare different size macrocycles [24], or by using pre-made small linear oligomers (e.g. dimers, trimers) as the building blocks [25]. The latter strategy can even be used to prepare asymmetric cavitands [26]. Parvari et al. used similar strategies to prepare multifarenes – novel modular cavitands containing alternating 4-t-butylphenol **L14** and 2-imidazolidinethione **L15** building blocks (scheme 2) [27]. By varying the ratios of the monomers used in the condensation, linear co-oligomers were obtained in useful yields (up to 86% for the 3-membered **L16**). These co-oligomers can then be cyclized with 2-imidazolidinethione or with each other to provide various sized cavitands. To display the possible modularity of this method, the group also performed macrocyclizations with a modified chiral 2-imidazolidinethione **L20** or the oxo-analogue **L21** to provide asymmetric cavitands (**L22** and **L23** in scheme 2, respectively). Such methods provide unprecedented structural control compared to the traditional synthetic methods, potentially allowing to design cavitands with specific selectivity towards desired guest molecules or featuring specific functional groups that may interact with the guest and catalyze chemical reactions.



Scheme 2. Synthesis of various multifarene cavitands. a – 4:3:1 reactant ratio, 30 mol% TsOH, PhMe, 65°C, 2d. Other conditions are minor variations thereof [27].

1.2 Self-assembling systems

As synthesizing larger and more complex host molecules rapidly becomes impractically difficult, a different strategy must be used. One concept that has recently emerged is self-assembly. By using multiple monomeric molecules that can bind with one another (e.g., through hydrogen bonds) in solution through self-complimentary binding motifs, one can essentially prepare the supramolecular hosts *in situ*. Just like in biomolecules such as proteins and nucleic acids, the geometry of the hydrogen-bonding motifs encodes the information needed for assembly in solution. Besides that, the dynamic nature of hydrogen bonds allows for the resulting strictures to be stimuli-responsive: by changing various properties of the solution (e.g. the pH or ionic strength) or upon addition of other hydrogen-bonding-capable compounds, the monomers can rearrange into different macro-structures with different cavity sizes and guest selectivities, or simply dissociate, releasing the guest back into solution.

One of the first applications of this strategy was demonstrated in 1993 by the group of Julius Rebek, Jr. [28]. The cucurbituril-like compound **L24** was prepared through a condensation of diphenyl glycoluril and durene tetrabromide. The 7-membered rings that form during the reaction allow the molecule to curve into a C shape. When dissolved in $CHCl_3$, two molecules can assemble into a tennis ball shaped dimer, stabilized by a network of intermolecular hydrogen bonding between the urea groups. The presence of dimeric structures in solution and gas phase was confirmed by vapor pressure osmometry, NMR spectrometry as well as multiple mass spectroscopy methods. It was also found that the capsules could be disassembled by increasing the polarity of the solvent – the monomeric form dominates in DMSO.

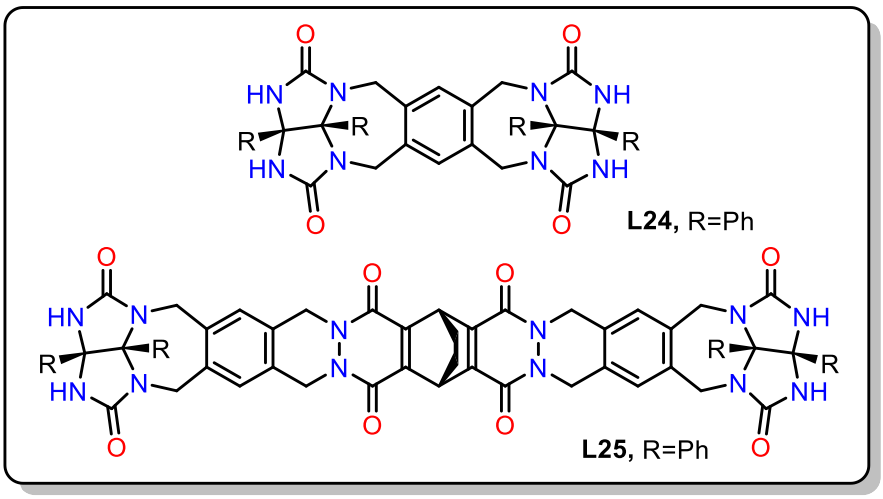


Figure 8. Structures of monomeric **L24** and **L25**.

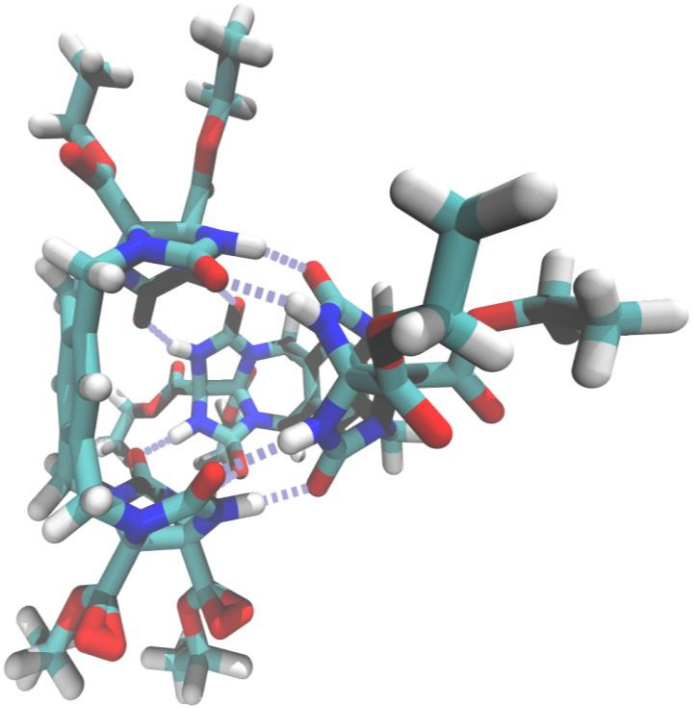


Figure 9. Crystal structure of tennis ball-like dimer of **L24**.

While the original compound worked as a proof-of-concept, the size of the internal cavity was quite small, only being capable of encapsulating molecules such as methane or ethylene [29]. In a later work, the Rebek group presented a modified design **L25** featuring an extended linker between the glycoluril termini [30]. The semi-rigid linking region retains the similar C shape of **L24**, and thus forms a similar spherical dimer in benzene solution. Other solvents, however, required addition of a guest to stabilize the dimeric capsule. Regardless, it was shown that the capsule forms complexes with various derivatives of adamantane and ferrocene, even allowing to draw insoluble compounds into solution.

Following the ideas of their previous work, the Rebek group continued to develop new self-assembling systems [3]. Inspired by earlier work of Cram et al. on van der Waals-bonded dimeric resorcinarene velcraplexes [31], the group began to develop similar self-complimentary hydrogen bonding cavitand dimers [32]. The first iteration featured a design based on the same ideas as their previous work – the deep-cavity resorcinarene **L26** is functionalized with imide groups on the rim of the cavity, which allows two molecules to form a large cylindrical capsule stabilized by 8 intermolecular hydrogen bonds. The capsule was found to have reasonable conformational stability, with no changes in the NMR spectra in the temperature interval of 220-330K. A variety of larger guests were successfully encapsulated, such as terphenyl and dicyclohexyl carbodiimide. When smaller guests were added, multiple molecules could be accommodated inside of the cavity, featuring remarkable selectivity: in a solution with an excess of toluene, benzene and p-xylene, the capsule was filled preferentially (~90%) with a molecule of benzene and p-xylene, as such a combination likely maximizes packing within the cavity. Such results were suggestive of the ability to use such cavitand complexes as microreactors for catalyzing bimolecular processes.

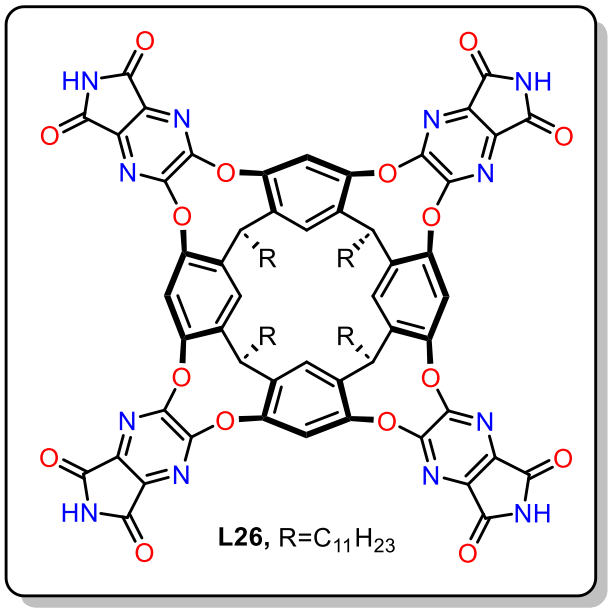


Figure 10. Cavitand **L26**, featuring self-complimentary imide motifs.

Concurrently, the group was also working on other capsules based on urea-functionalized calixarenes (figure 11) [33]. Rather than focusing on expanding the scope and selectivity of the guest binding, the group developed larger and more intricate self-assembling systems. It was found that using combinations of cavitands functionalized with sulfonyl and aryl urea derivatives, exclusively the heterodimers were formed, likely due to the increased acidity of the sulfonyl urea compared to the more basic aryl urea [34]. More complicated structures were prepared based on the ideas of covalently linked hetero-complimentary cavitands, such as dumbbell and propeller shaped assemblies [35]. By connecting two self-complimentary calixarenes through the lower rim with a covalent linker, it was possible to form one of the first dynamic hydrogen-bonded polymers [36]. These polymers retained most of the desired features of cavitand capsules, such as the ability to encapsulate guests and rapid reversible disassociation in polar solvents. Besides that, the polymers also had other interesting features, such as the variable resistance to disassociation based on encapsulated guests, and, upon functionalization with long alkyl chains, the formation of a liquid crystal phase. The group later provided a concept of a different polymer – a polypeptide consisting of amino acids functionalized with either aryl or sulfonyl ureas. Drawing parallels to the base pairing in double-stranded DNA, the polypeptide strands could encode information for heterodimerization and self-replication [33]. Finally, the group presented a potential molecular sensing system based on fluorescence resonance energy transfer (FRET). The heterodimer-forming calixarenes are each functionalized with different molecular dye. When the dyes are close enough in space to one another (i.e. upon formation of a heterodimeric capsule), energy transfer can occur, resulting in emissions of different wavelengths. This can easily be monitored to detect the formation of the dimer. When using a solvent which cannot fit in the cavity, the heterodimerization only occurs when an appropriately sized guest is in the solution, allowing for small molecule detection [37]. All these systems successfully highlight the immense potential of cavitand-based self-organized systems.

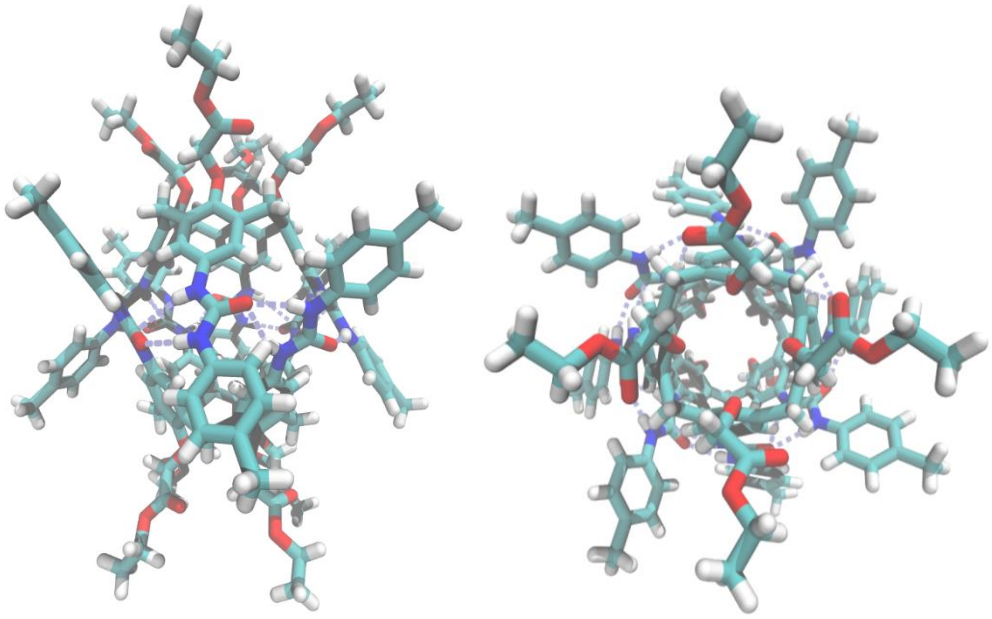
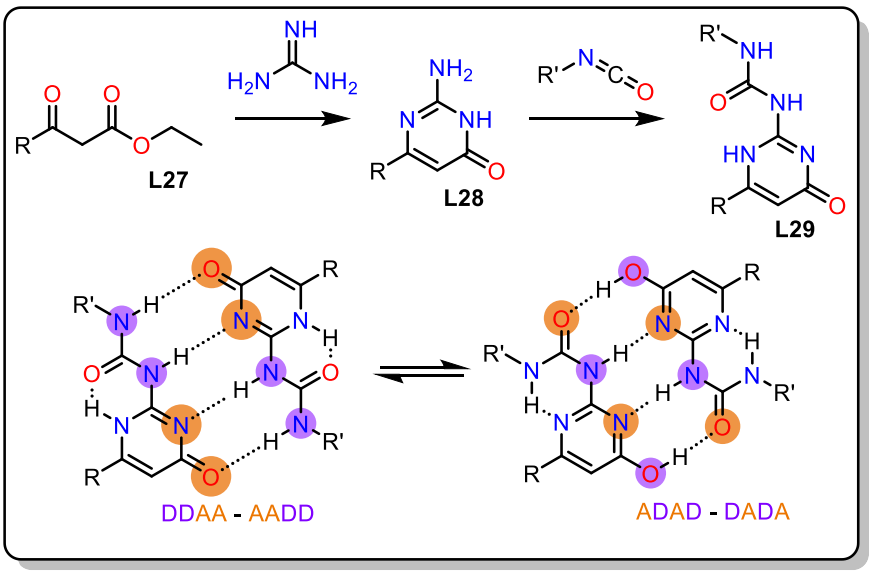


Figure 11. Side (left) and top (right) views of the solid-state structure of aryl-urea-calixarene homodimer.

However, as impressive and promising as these self-assembling systems may have been, their potential was still limited due to their size and, as a result, difficult and expensive synthesis. One possible solution was to 'shrink' the self-assembling system into a hydrogen-bonded array motif that could be easily attached to various molecules of interest to provide self-complementarity. Many double- and triple-hydrogen bonding systems were known, but their difficult syntheses and relatively weak homo- or heterodimerization limited their potential use. In 1997, the group of E.W. Meijer presented a system based on 2-ureido-4-pyrimidinone (UPy) that not only featured an impressively strong ($K_{dim} > 10^6$ M^{-1} in $CHCl_3$) self-complimentary four hydrogen bond (either DDAA – donor/donor/acceptor/acceptor – or ADAD, depending on tautomer) array, but was also relatively easy to prepare [38,39]. The synthesis of the arrays from the corresponding α-keto esters consisted of condensation with guanidine, followed by reaction of the intermediate isocytosine with an isocyanate (scheme 3).



Scheme 3. Synthesis of the UPy motif (top) and visualization of self-complimentary tautomer bonding (bottom).

The UPy motif quickly found use in many fields of supramolecular chemistry. The most popular application has been in supramolecular polymers. The first designs by the Meijer group consisted of two UPy arrays connected by alkyl and siloxane spacers [38]. Due to the high association constant, the resulting polymers had significantly higher degrees of polymerization than any preceding supramolecular polymers. The obtained materials had many of the same macroscopic properties as traditional polymers, but the dynamic nature (dimer life time ranges from 0.1 to 1 second) made them easily adaptable, reformable and recyclable [40], especially at higher temperatures. These UPy-based materials have therefore seen much use not only in academia, but also in the real world: self-healing composite materials [41], adhesives [42], ink-jet printing inks [43], and biocompatible degradable hydrogels [44], the latter having recently been used in multiple clinical trials for bioabsorbable heart valves [45,46].

Besides that, UPy has also been used for preparation of various discrete supramolecular aggregates (vide infra). In one recent example, UPy-capped cyclotriveratrylene cavitands **L30** were used to create self-assembling capsules that can form complexes with fullerenes [47], with selectivity towards the larger allotropes. These compounds provide a potential new method of fullerene purification as an alternative to the laborious and ineffective methods currently in use: by performing a solid-liquid extraction with a solution of **L30**, fullerenes can be pulled into solution out of the crude mixture through host-guest complexation. Upon addition of an acid, the capsule can be disassembled, releasing its contents.

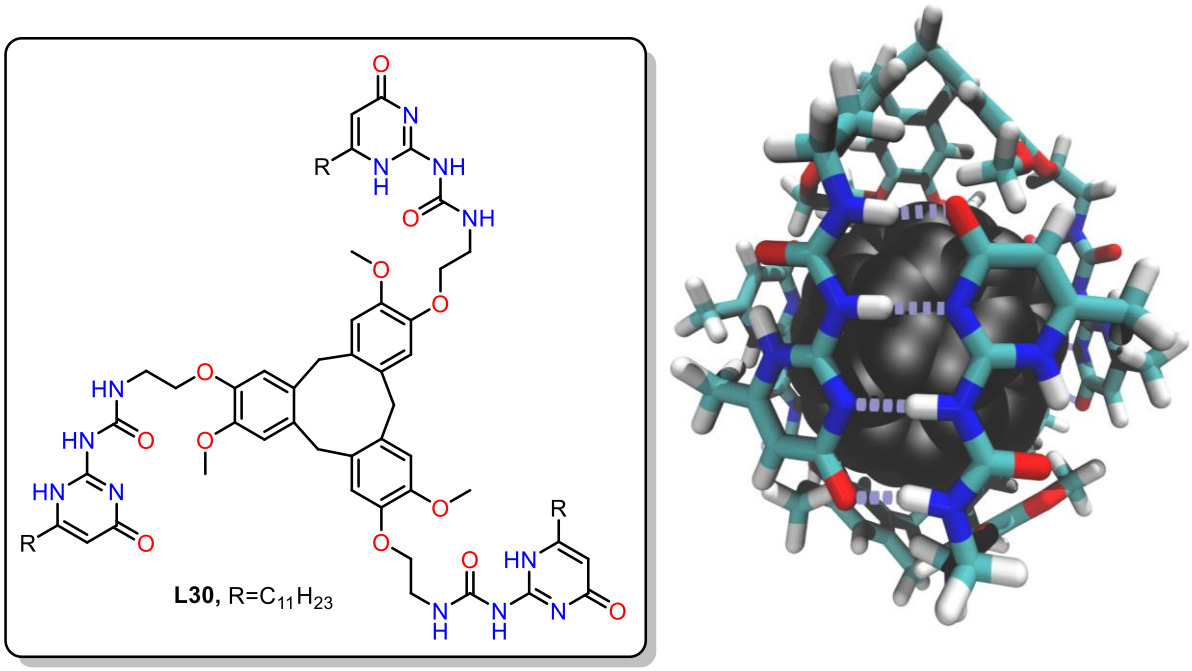
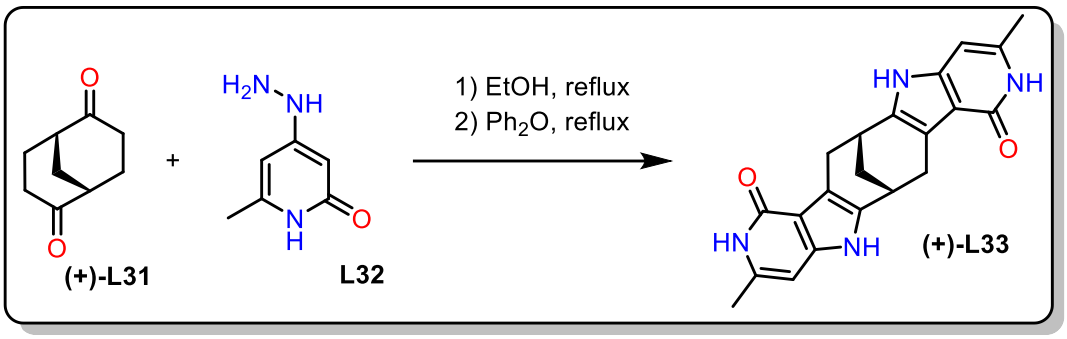


Figure 12. Structure of cavitand monomer **L30** (left) and DFT-minimized spatial structure of dimeric capsule with C_{60} (right).

1.3 Bicyclo[3.3.1]nonane-based supramolecular systems

The bicyclo[3.3.1]nonane (BCN) scaffold and its oxo/aza derivatives are commonly encountered in many fields of organic chemistry, such as natural product synthesis [48,49], asymmetric catalysis [50], and studies of fundamental organic chemistry [51]. More relevant, however, is its use in the field of supramolecular chemistry. The BCN framework consists of two fused cyclohexane rings, which, depending on the pattern of substitution, can adopt boat or chair conformations. When stabilized in the chair-chair conformation, the molecule obtains a V-shaped structure, forming a semi-rigid, almost 90° angle between the three-carbon bridges. By incorporating these bridges into aromatic systems, one can begin to build systems with orthogonally-angled aromatic "walls" – a feature that was previously unseen in the mostly sphere- and pyramid-like structures of supramolecular systems and one that has been heavily researched in groups from Vilnius and Lund universities.

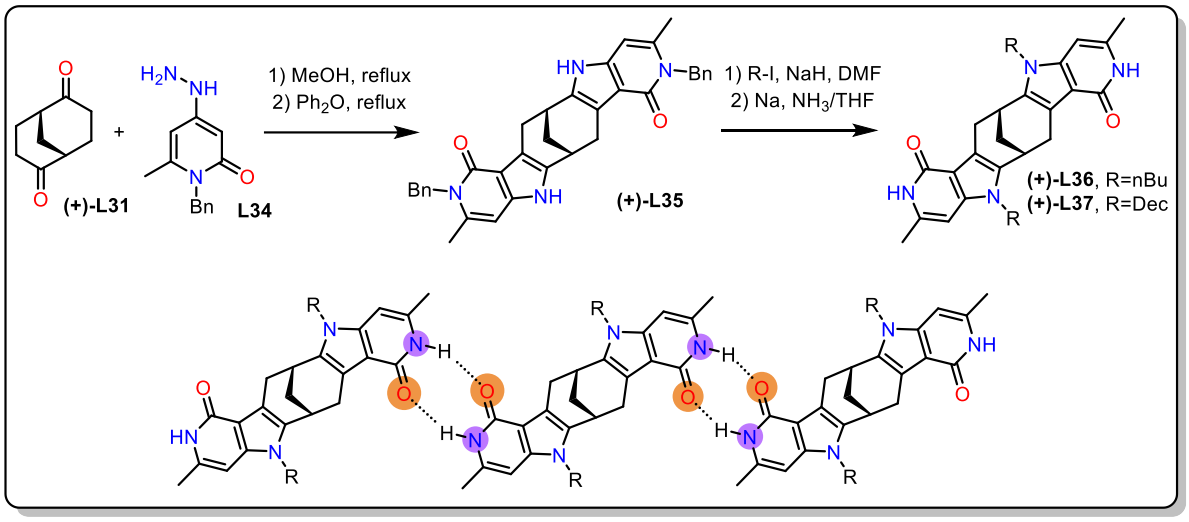
Following the years of synthetic, structural and chiroptical studies of various BCN derivatives in the E. Butkus group [52], and after inspiration from the works of R. Bishop [53], Stončius et al. presented their first entry into the field of supramolecular chemistry – a cleft-shaped molecule featuring the ability to self-assemble into rectangular shaped cavities in the solid state [54]. The molecule **(+)-L33**, formed through a double Fischer indolization of bicyclononane[3.3.1]-2,6-dione **(+)-L31** (easily and inexpensively producible in large scale through kinetic resolution with yeast [55]) and hydrazine **L32**, contains a 2-pyridone motif that is capable of self-complimentary hydrogen bonding. The poor solubility of **(+)-L33** prevented any study of its behavior in solution, but X-ray diffraction analysis showed the formation of planar arrays of dimeric "cages", each containing two molecules of the solvent (DMF).



Scheme 4. Synthesis of **(+)-L33**.

While the initial plan was to develop a molecular tubular helix structure, the poor solubility and competing hydrogen bonding with polar solvent molecules in the solid state prevented the helix formation. Fortunately, the next synthetic iteration led to better results [56]. Through a modified synthesis route, derivatives of **(+)-L33** with N-alkylated pyrroles were obtained. The alkyl groups significantly increased solubility in less polar solvents while also preventing any undesired hydrogen bonding through the pyrrole N-H. X-ray diffraction results of the N-butylated **(+)-L36**, however, showed that a helical structure does not form in the solid state. NMR titration studies of the N-decylated **(+)-L37** in $CDCl_3$ suggested the formation of a self-complimentary aggregate, which, based on the rigid structure of the monomer, were assumed to be helical in nature. Vapor pressure osmometry, electronic spectroscopy and circular dichroism experiments were also in agreement with

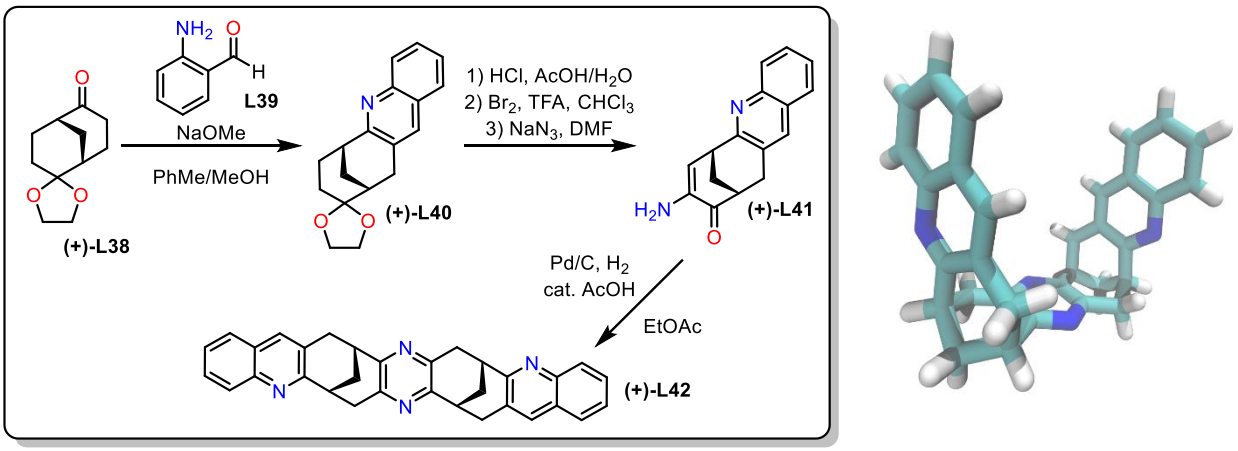
the hypothesis. The degree of polymerization however, was quite low, likely due to the relatively weak association between the 2-pyridone units.



Scheme 5. Synthesis of second-generation helical monomers **(+)-L36** and **(+)-L37** (top) and hydrogen bonding scheme of **(+)-L37** (bottom).

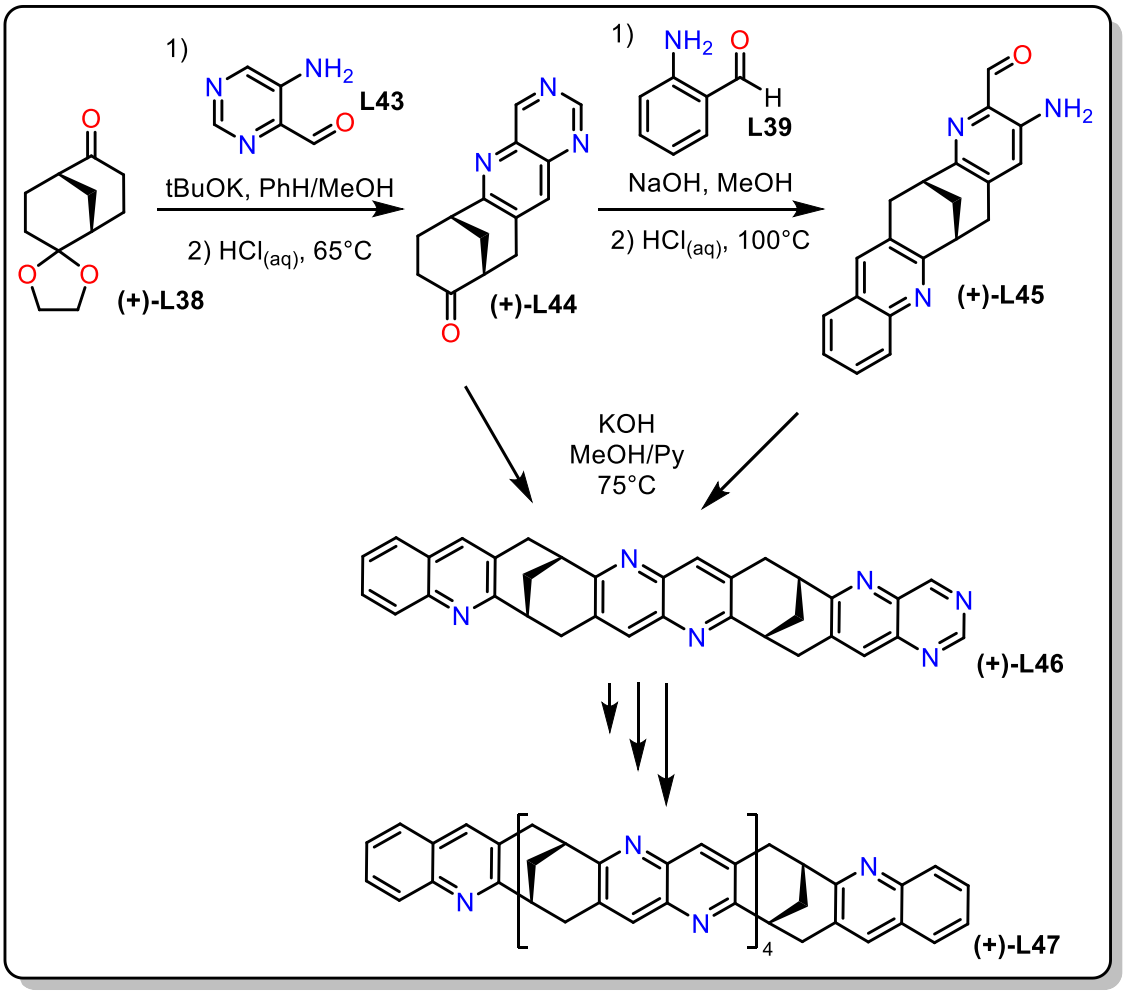
From this point, the further development of BCN based supramolecular systems can be split into two paths – fully covalent molecular hosts (developed mainly by the Wärnmark group) and self-assembling systems with stronger self-complimentary bonding motifs (mainly by the Butkus/Orentas groups), both of which will be discussed below.

The first fully covalent host was presented in 2010 by Wallentin et al. The group developed a staggered molecular tweezer-like structure containing two BCN units [57]. The synthesis consisted of a Friedländer condensation between a mono-ketal of bicyclo[3.3.1]nonane-2,6-dione **(+)-L38** and amino-aldehyde **L39** to form the aromatic "wall" fragment. Upon ketal hydrolysis and introduction of an enamine group, dimerization through a pyrazine condensation was performed to yield the molecular tweezer. Syntheses and further studies were performed with both the racemic and enantiomerically pure BCN derivatives. In the solid state, the racemic tweezers formed homochiral intercalated dimers, where the wall of one molecule enters the cavity between the two walls of the other tweezer. NMR studies in $CDCl_3$ also suggested dimerization in solution, but without any homochiral fidelity.



Scheme 6. Synthesis of **(+)-L42** (left) and solid-state structure of **(+)-L42** (right).

A similar strategy was then used by Wixe et al. in 2013 to prepare a "orthogonal topological analogue of helicene" – a short monomolecular tubular helix [58]. The synthesis relies on much of the same strategies, but the low-yielding pyrazine condensation is replaced with a double Friedländer condensation of 5-amino-4-pyrimidinecarboxaldehyde **L43** – a synthon that functions as a protected version of the C_2-symmetric 2,3-diaminosuccinaldehyde. The synthesis essentially extended the dimeric molecular tweezer – a helix half turn – into a pentameric full turn. The authors suggested a potential use as shape-selective hosts; however, no host-guest complexation studies were performed.

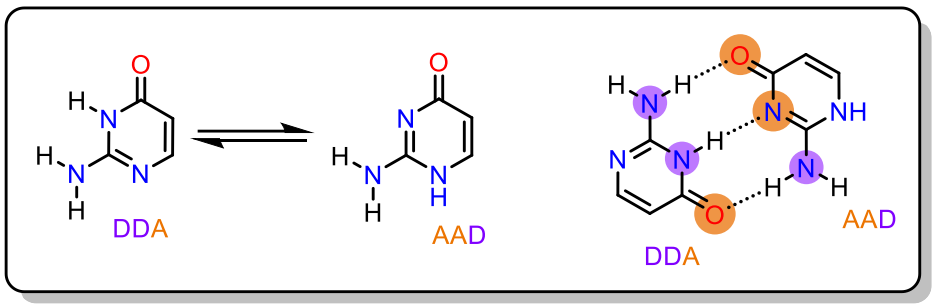


Scheme 7. Abridged synthesis of tubular helix **(+)-L47**.

A year later, the group presented a heptameric organic nanotube [59]. The synthetic strategy remained practically identical, using the same double Friedländer synthon to dimerize fragments of increased length. Just like in the case of the helix, a crystal structure of the final product could not be obtained, but other pieces of evidence, such as trends in specific rotation and circular dichroism spectra were used as proof of the tubular structure. Host-guest complexation studies with acetylcholine and guanidine were performed, but the results indicated only very weak binding. Due to the relatively narrow diameter of the tube, which limits the range of possible guests, and the helical structure, which leads to poor hydrophobic and pi-interactions, the potential of these systems as molecular hosts was clearly quite limited, and further developments were not seen.

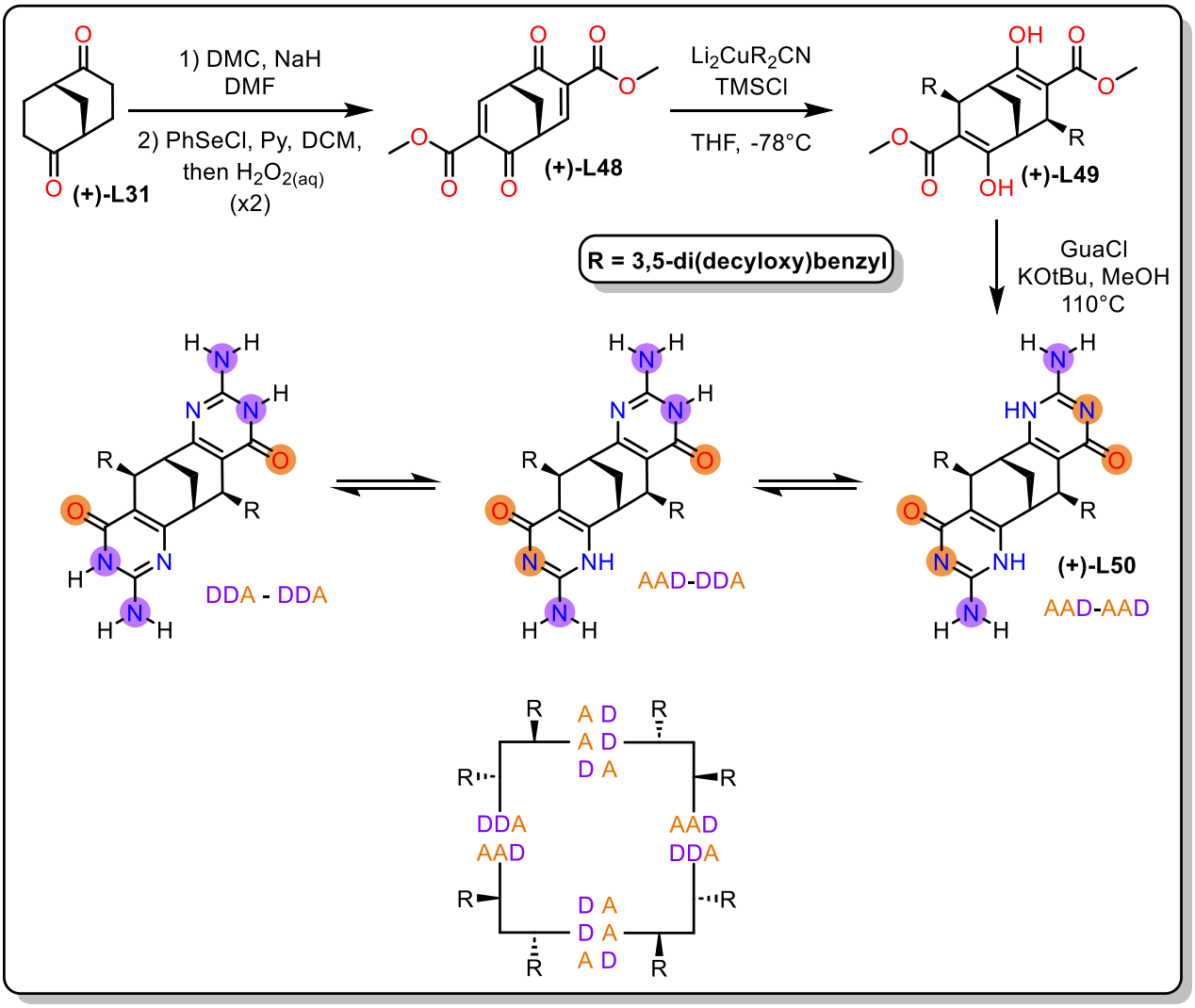
During this time, Orentas et al. also presented the next generation of self-assembling BCN based supramolecular hosts – a tetrameric chiral rectangular cavity ("supramolecular belt") [60]. This system replaces the previously used 2-pyridone hydrogen bonding motif with an isocytosine (2-

amino-3H-pyrimidin-4-one) group, which, as discovered in previous research [61], can function as a self-complimentary triple hydrogen bonding motif through tautomerization between an ADD and DAA array (scheme 8). This leads to stronger intermolecular aggregation compared to the double hydrogen bonding of the 2-pyridone motif and, compared to other available triple bonding systems, requires only one type of motif, which greatly simplifies the synthesis by retaining the symmetry of the molecule. Also, unlike the 2-pyridone group, in which the hydrogen bonds were oriented at an angle to the overall orientation of the molecular cleft, which led to helix formation, the isocytosine hydrogen bonds are oriented parallel to the direction of the aromatic "wall", which favors formation of closed cyclic aggregates.



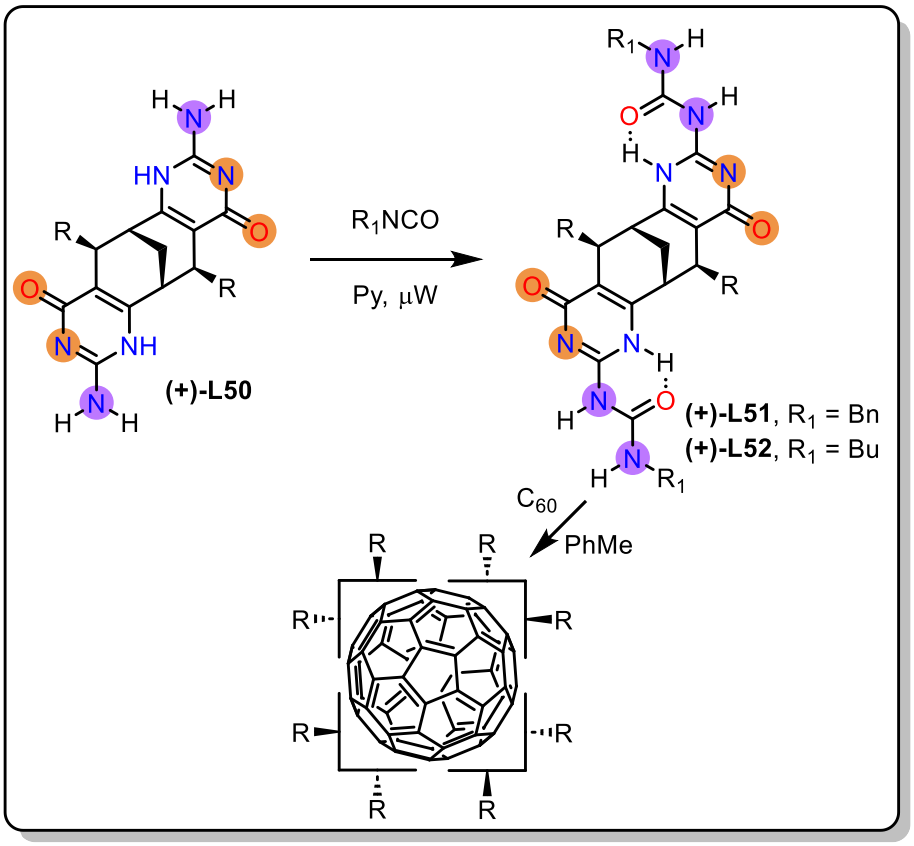
Scheme 8. Tautomerization of isocytosine (left) and triple hydrogen bonding of self-complimentary tautomers (right).

For the system of **(+)-L50** (scheme 9), computations were in agreement with this theory, showing tetramers and pentamers as possible stable species. **(+)-L50** was prepared through functionalization of the diketone **(+)-L31** to form the bis-(α-keto ester), which was converted to the α,β-unsaturated derivative **(+)-L48** through a selenoxide elimination strategy. (3,5-Di(decyloxy)benzyl) solubilizing groups were added through a conjugate addition of the corresponding dialkylcuprate salt, and condensation with guanidine afforded **(+)-L50**. The behavior of **(+)-L50** in $CDCl_3$ solution was studied through NMR methods. The ^{1}H NMR spectrum showed that **(+)-L50** is present in an asymmetric tautomer – likely containing ADD and DAA arrays at opposing ends, which suggested formation of aggregates. ^{13}C, NOESY and DOSY spectra supported the hypothesis. Multiple other analysis methods, including gel permeation chromatography and vapor osmometry, also gave results that supported the tetrameric aggregation theory.



Scheme 9. Synthesis (top), tautomerization (middle), and self-assembly (bottom) of **(+)-L50**.

Following unsuccessful attempts at forming host-guest complexes with **(+)-L50** and fullerene, the next generation system was presented in 2013 [62]. Through a reaction of **(+)-L50** with isocyanates, derivatives containing the previously discussed quadruple hydrogen bonding UPy motif were obtained. NMR studies of **(+)-L51** and **(+)-L52** in $CDCl_3$ once again showed the formation of well-defined tetramers, though in this case monomer C_2 symmetry was retained, as both UPy fragments in the molecule remain as the same (4[1H]-pyrimidinone) tautomer. Interestingly, in aromatic solvents, the formation of pentameric aggregates was also observed, with both oligomers being in equilibrium. This shows that the UPy-based system is capable of solvent-responsive self - assembly.



Scheme 10. Synthesis of next-generation UPy monomers **(+)-L51** and **(+)-L52** and self-assembly of C_{60}-tetramer complex.

Molecular modelling of the tetrameric aggregates showed that the internal cavity was almost the perfect size to host a molecule of C_{60}. Upon addition of the fullerene into the toluene solution of **(+)-L52**, the tetramer-inclusion complex was immediately formed. If fullerene was added in excess, the pentameric aggregate was also fully consumed, indicating the capability of dynamic guest-responsive self-assembly. The complex was also quite stable, with a titration-determined binding constant of ~10^5 M^{-1}. Finally, self-sorting of **(+)-L51** and **(+)-L52** was also tested. Upon addition of equimolar quantities of **(+)-L51** and **(+)-L52** into toluene, self-sorting into homo-tetramers was observed, however, over the course of hours, monomer exchange and formation of pentamers leads to a complex mixture of hetero-aggregates. When C_{60} was added, the formation of inclusion complexes effectively "froze" the monomer exchange process in the current state, allowing homo-tetramer complexes to be preserved even at 353K. In $CDCl_3$, the monomer self-sorting is even stronger, with no detectable formation of any hetero-aggregates. These results show that solvent interactions play a very important role in self-assembly processes.

Following these results, a return to the previous generation monomer **(+)-L50** was made in order to study its aggregation in other non-polar solvents. A hypothesis was made that the inherent tautomeric distribution of the isocytosine would allow for formation of a wide variety of aggregates stabilized through single, double and triple hydrogen bonds in various arrangements of different tautomeric forms, including tubular supramolecular polymers stabilized by inter-tetrameric hydrogen bonding (figure 13, left). In 2015, Račkauskaitė et al. presented the characterization of a complex decameric capsule that forms in solutions of **(+)-L50** in CS_2 [63]. In-depth analysis of the COSY, ROESY and DOSY spectra as well as molecular mechanics calculations allowed for the structure to be elucidated. It consists of two stacked tetrameric belts that are capped with additional monomers

on both ends to form a closed capsule-like structure. A structural variant of **(+)-L50** featuring N-arylation on one of the isocytosine groups was prepared. It was hypothesized that the phenyl rings would introduce steric hindrance which would prevent the monomers at the top and bottom of the capsule from binding, leading to formation of an octameric tubular aggregate. However, only the formation of cyclic tetramers and pentamers was observed.

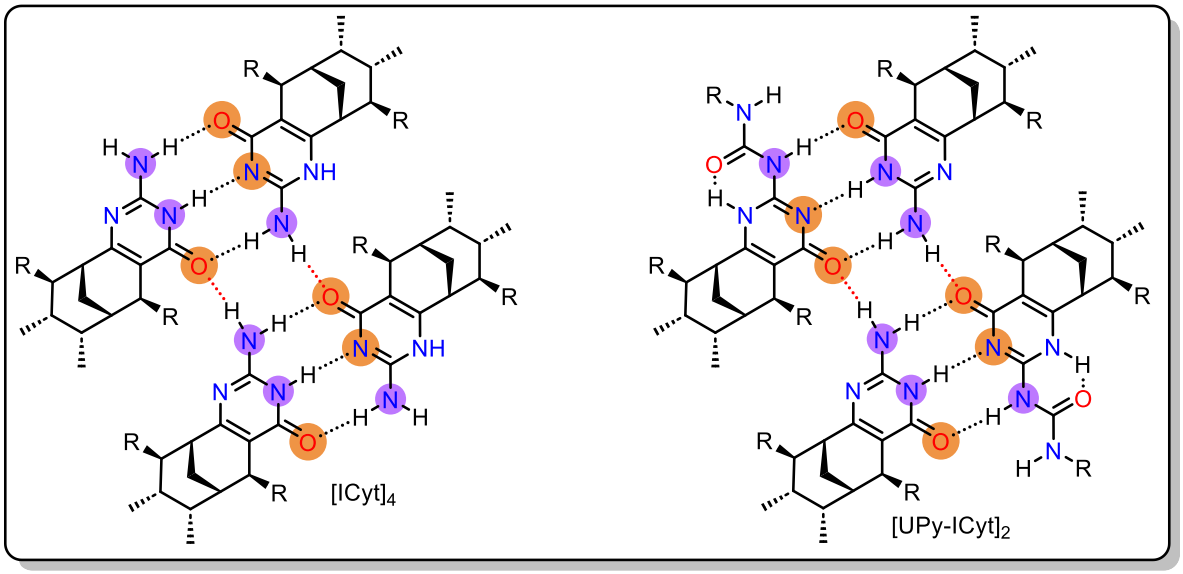


Figure 13. Secondary hydrogen bonding interactions (marked in red) that allow for stacking of cyclic tetramers.

Nevertheless, a successful strategy for the preparation of an octameric tube was later found [64]. By using the mixed UPy-ICyt monomer **(+)-L53** with decyl solubilizing groups, the maximum hydrogen bonding order per monomer could be achieved only in a tetramolecular bonding network (figure 13, right), which would correspond to an octameric aggregate. The hypothesis was confirmed through NMR analysis. Upon addition of fullerene to the (toluene or $CDCl_3$) solution of **(+)-L53**, disassembly into the more thermodynamically stable tetrameric inclusion complex was observed (figure 14, bottom). Interestingly, in a mixture of **(+)-L53**, the bis-UPy **(+)-L52** and C_{60} in $CDCl_3$, almost only free tetrameric **(+)-L52** and the C_{60}-tetrameric **(+)-L53** were observed, once again indicating the impressive self-sorting capabilities of these systems.

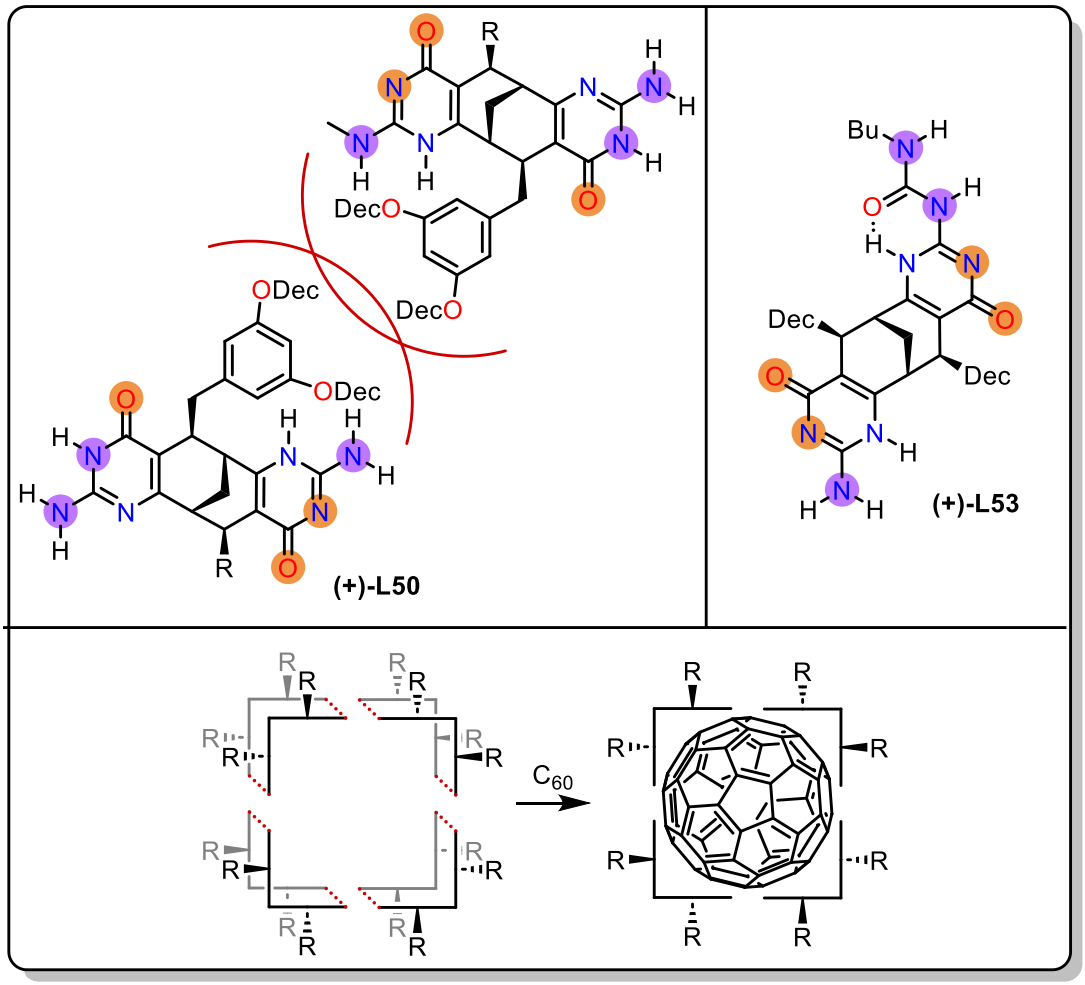
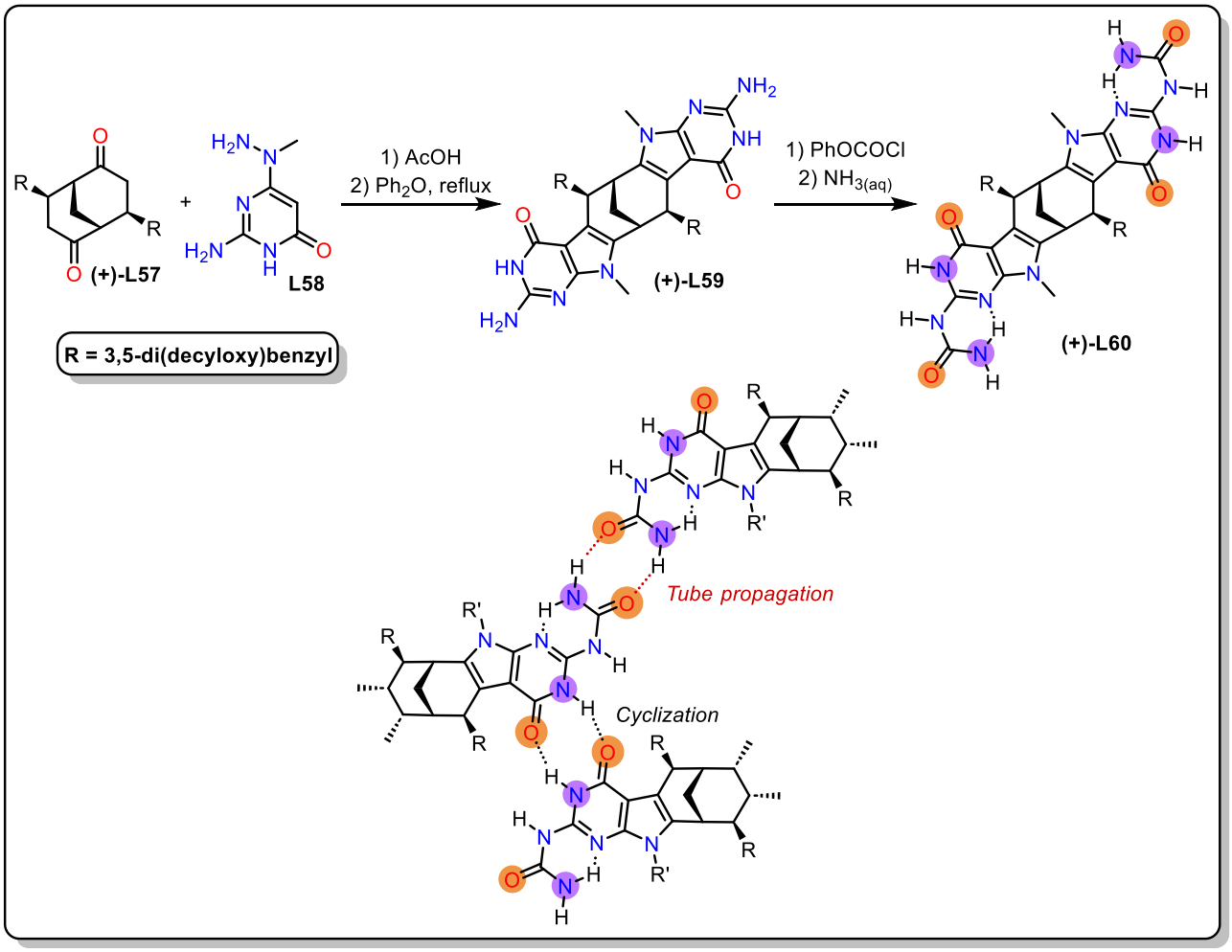


Figure 14. Steric clashing of solubilizing groups preventing tubular stacking (top left); mixed UPy-ICyt monomer featuring decyl side groups **(+)-L53** (top right) and guest-responsive disassembly of octameric **(+)-L53** (bottom).

During development of the octameric tube it was realized that the solubilizing 3,5-di(decyloxy)benzyl groups used in most of the previous synthetic iterations prevented the non-staggered tubular stacking of cyclic tetramers (figure 14, top left). The replacement with less sterically demanding decyl groups was essential for the formation of octamers from UPy-ICyt monomers. Later, the same strategy was applied for the ICyt-ICyt monomer, which finally allowed for a tubular supramolecular polymer to be obtained [65]. In addition, two other synthetic strategies for functionalized tubular polymers were presented, including universal ethanethiol linkers and N-functionalized 9-azabicyclo[3.3.1]nonanes. Chloroform solutions of these monomers displayed high viscosity, and, in higher concentrations, a gel was formed. The ability to form fullerene-inclusion complexes (without depolymerization) also remained. Solid-state magic angle spinning NMR spectroscopy and atomic force microscopy were used to characterize the polymers.

At this time, an alternative strategy for obtaining tubular polymerization was also applied [66]. By fusing the UPy fragment with an electron-rich pyrrole ring (forming the PUPy motif), the relative stability of pyrimidinone tautomers is switched, and the 6[1H]-pyrimidinone form (having an ADDA hydrogen bonding array) becomes the most stable [67]. Similarly to the case of UPy-ICyt **(+)-L53** octamers, self-complimentary tetrameric bonds can no longer be formed, and the highest hydrogen bonding order can only be reached through tubular aggregation. Instead of changing the solubilizing groups, the strategy in this case relied on translocating the polymer-forming hydrogen bonding sites

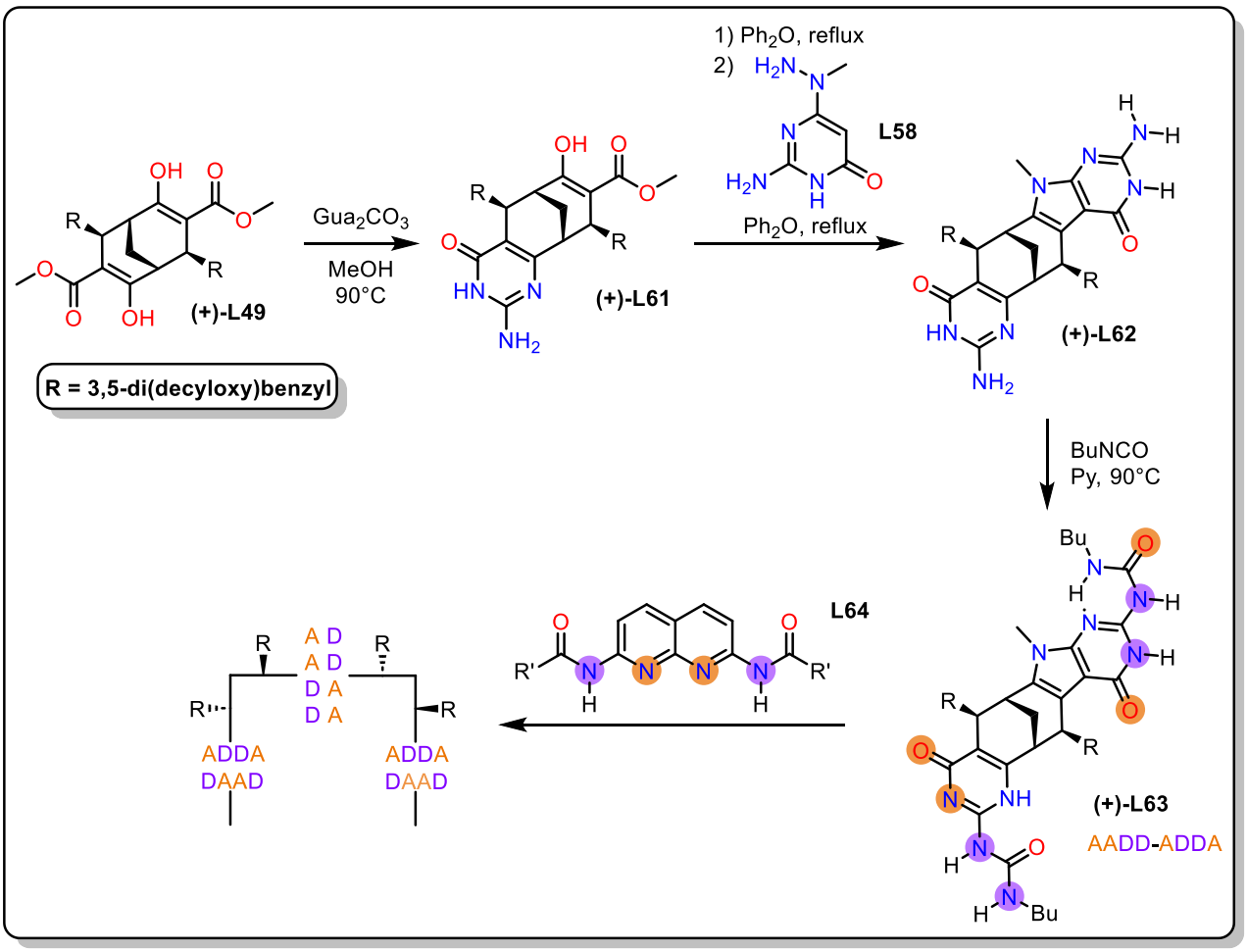
so they are less affected by steric crowding. **(+)-L60** was prepared through a Fischer indole synthesis similar to the one used in the original cleft syntheses by Stončius et al. [54]. The behavior of **(+)-L60** was tested in multiple solvents of varying polarity. In $CDCl_3$, only cyclic tetramers were formed. However, the addition of C_{70} could trigger tubular polymerization, as confirmed by atomic force microscopy and gel permeation chromatography. In less polar solvents, such as toluene or benzene, polymerization was observed even without guest stabilization. Addition of C_{60}, however, led to the formation of a completely different system – a tetrameric capsule-C_{60} complex, where, unlike in all other BCN based systems, the monomers were arranged side-to-side, not end-to-end.



Scheme 11. Synthesis of PUPy derivative **(+)-L60** (top) and hydrogen bonding in tubular aggregates of **(+)-L60** (bottom).

Finally, the PUPy motif was also used for the design of a self-assembling supramolecular tweezer [68]. The system consists of an asymmetric PUPy-UPy-functionalized monomer **(+)-L63**. While the UPy motif can form self-complimentary hydrogen-bonding arrays (AADD or ADAD), the PUPy motif is most stable in the ADDA-containing tautomer, which could selectively bind to another molecule containing a complimentary DAAD array. Surprisingly, **(+)-L63** was still able to form tetrameric aggregates (through unprecedented tautomerization of PUPy to an ADAD array, likely due to geometrical constraints). However, the addition of an equimolar amount of 2,7-diamido-1,8-naphthyridine (DAN, **L64**), containing a DAAD hydrogen bonding array, led to quantitative formation of the tetramolecular tweezer complex. In cyclohexane, the tweezer complex also formed a helical zipper-like supramolecular polymer, through intercalation interactions similar to the ones in

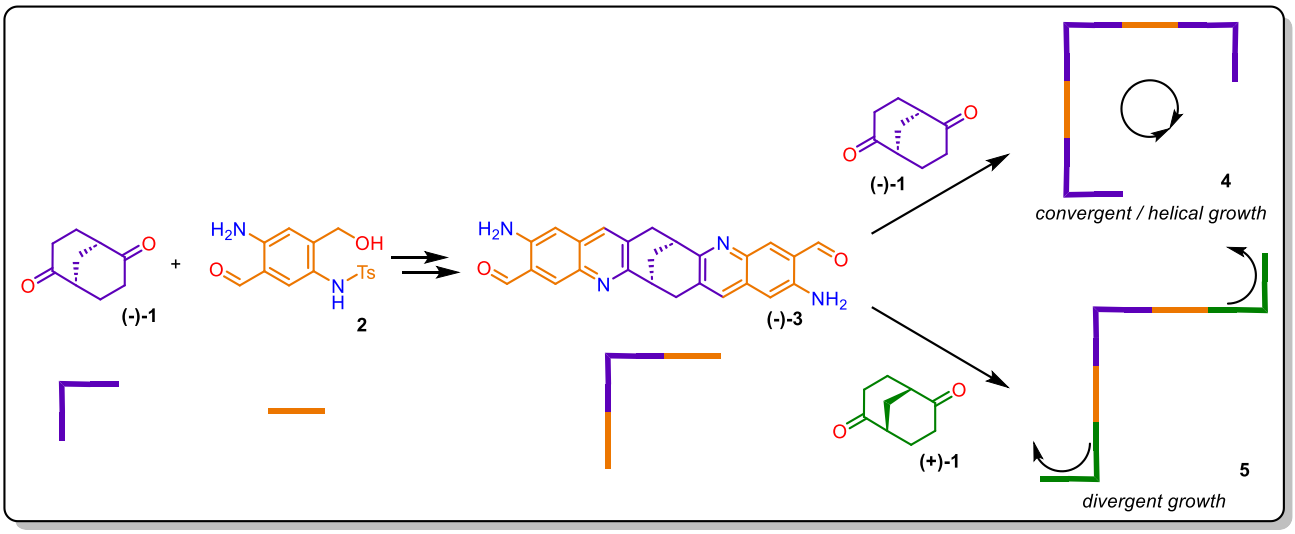
the previously-discussed covalent tweezer [57]. The stimuli-responsiveness of this system was tested using a redox-active DAN derivative (red-DAN). Upon oxidation, the oxidized ox-DAN array was no longer complimentary to PUPy, and the cyclic **(+)-L63** tetramer was recovered. In another experiment, a photoacid was added into solution, and, upon irradiation, protonation of the UPy led to fragmentation of the tweezer into DAN:PUPy-UpyH+ dimers. This transformation was found to be fully reversible in darkness, serving as another example of dynamic stimuli-responsiveness of BCN based supramolecular systems.



Scheme 12. Synthesis of **(+)-L63** and formation of molecular tweezer complex with **L64**.

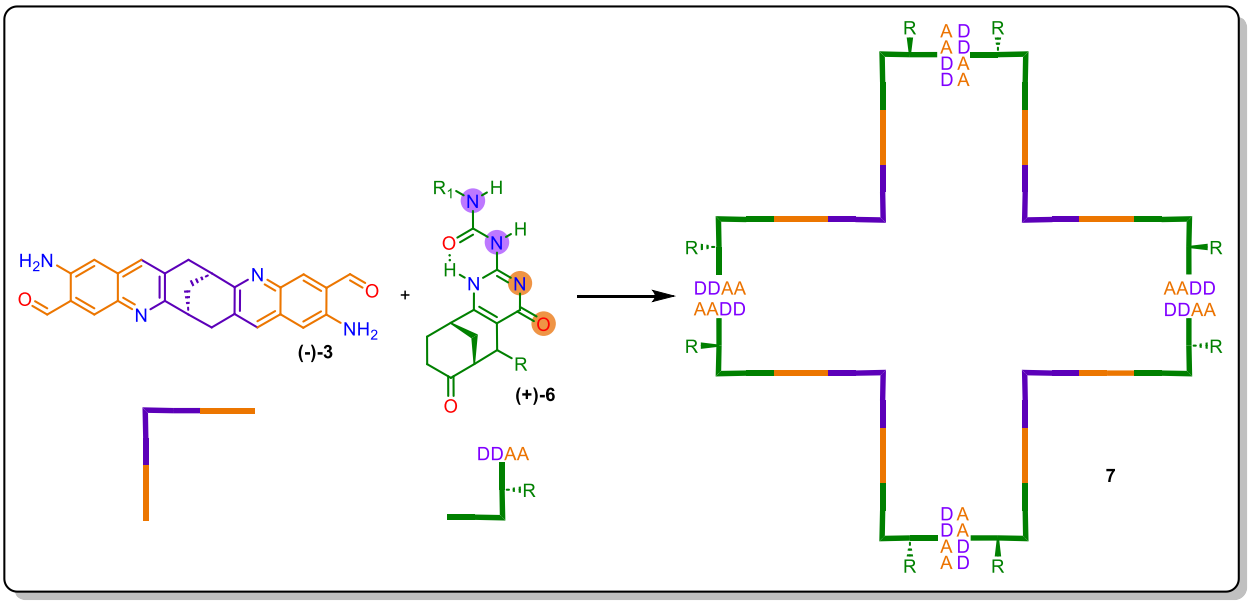
2. RESULTS AND DISCUSSION

The results of this master thesis are a direct continuation of the work described in the previous bachelor thesis [69]. The objective is to develop a next-generation system of BCN-based supramolecular cavitands that is based on both enantiomers of the chiral bicyclo[3.3.1]nonane-2,6-dione **1**. As depicted in scheme 13, derivatives of homochiral **1** tend to form convergent structures, such as the covalent helices prepared in the Wärnmark group [59] or the hydrogen-bonded rectangular tubular structures of the Orentas group [60].The rigidty of homochiral **1** ensures that the curvature and direction of growth remains the same. However, if both enantiomers of **1** are incorporated into the structure, both positive and negative curvature can be achieved, which allows for higher control of the direction of growth, thus enabling far greater structural variety in the resulting carcasses.



Scheme 13. Directions of growth for homochiral (top) and heterochiral (bottom) derivatives of **1**.

To display the capabilities of such systems, a design for a supramolecular tetrameric cavitand featuring both positive and negative surface curvature was developed. As depicted in scheme 14, condensation of both enantiomers of BCN with a rigid aromatic linker (such as the previously developed C_2-symmetric Friedländer synthon **2** [69]) would allow for the formation of a "bird"-shaped monomer (see **5**). If the termini of the monomer are functionalized with self-complimentary UPy motifs, such a system should be structurally predisposed to self-assemble into a tetrameric "Swiss cross" shaped cavitand **7**. The unique geometry and large volume of the resulting cavity could allow for host-guest complexation of either larger guests or multiple molecules, while the internal curvature could increase the selectivity (e.g. between E/Z enantiomers).

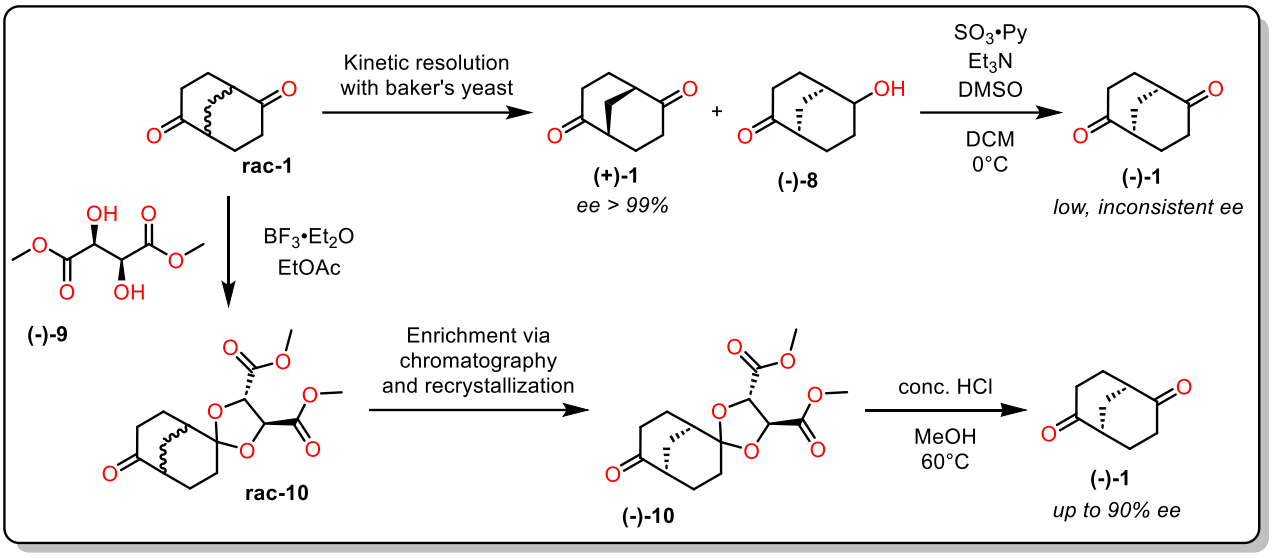


Scheme 14. Synthesis plan of 'Swiss cross' shaped cavitand **7**.

The first obstacle that had to be overcome was the preparation of enantiomerically pure **(-)-1** (Note: to maximize clarity, all derivatives of **1** in this thesis are labelled as **rac-**, **(+)-** or **(-)-** based on which enantiomer of **1** they are related to). While **(+)-1** can easily be obtained in large scale through kinetic resolution with baker's yeast [55], no practical route for the other enantiomer had been developed. The yeast reduction does provide the keto-alcohol **(-)-8**, but the enantiomeric excess is typically quite poor, and, more importantly, not very consistent. The envisioned route to obtain **(-)-1** was through formation of diastereomeric derivatives of the dione, that could then be separated either through column chromatography or recrystallization. Such a method would be easy to execute in practice, and the diastereomeric excess could be easily analyzed through NMR spectroscopic analysis of the chemically distinct diastereomer mixture, rather than having to rely on chiral HPLC or polarimetry to evaluate enantiomeric excess, as these methods tend to be more problematic. Past research in the group has shown that the BCN skeleton is quite resistant to racemization under vigorous conditions, so it was assumed that the diastereomeric derivatives could be converted back to the dione after separation while retaining the corresponding enantiomeric excess.

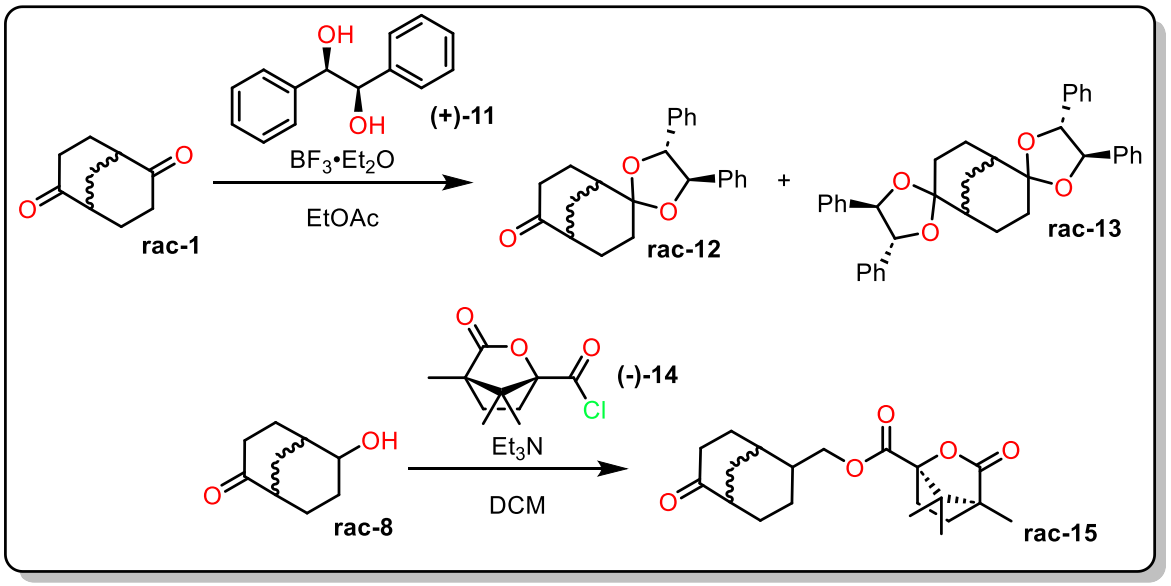
The first attempted method was based on a strategy applied by Paquette et al. for the separation of enantiomers of the structurally similar 5,7-dioxobicyclo[2.2.2]oct-2-ene [70]. The authors formed a pair of diastereomeric acetals with diethyl (+)-tartrate, which could then be separated through multiple passes of column chromatography and later hydrolyzed to provide the enantiomerically pure diones. The same strategy was applied to dione **rac-1** with dimethyl (+)-tartrate **(+)-9** (scheme 15). By using BF_3 etherate as a Lewis acid catalyst and dehydrating agent, the bis-acetal could be obtained in high yields (~80%) under mild conditions. The mono-acetal **rac-10** could also be obtained with a decent yield (~60%) by using a 2:1 ratio of **rac-1** to tartrate. The bis-tartrate diastereomer mixture could not be separated or even significantly enriched through either chromatography or recrystallization. However, the mono-tartrate could be enriched through column chromatography: the first eluted fractions contained mostly the less polar diastereomer (up to 20:1 ratio, analyzed through NMR), and the excess could be 'amplified' through recrystallization from EtOAc/PE to provide nearly pure single diastereomer. The obtained acetal was hydrolyzed to provide **(+)-1**. As this was not the desired enantiomer, the method was simply modified to use commercially available dimethyl (-)-tartrate **(-)-9**. This method, while very labor- and resource-intensive, allowed to obtain sufficient

quantities of **(-)-1** for further studies while the search for better resolution methods was performed in parallel.



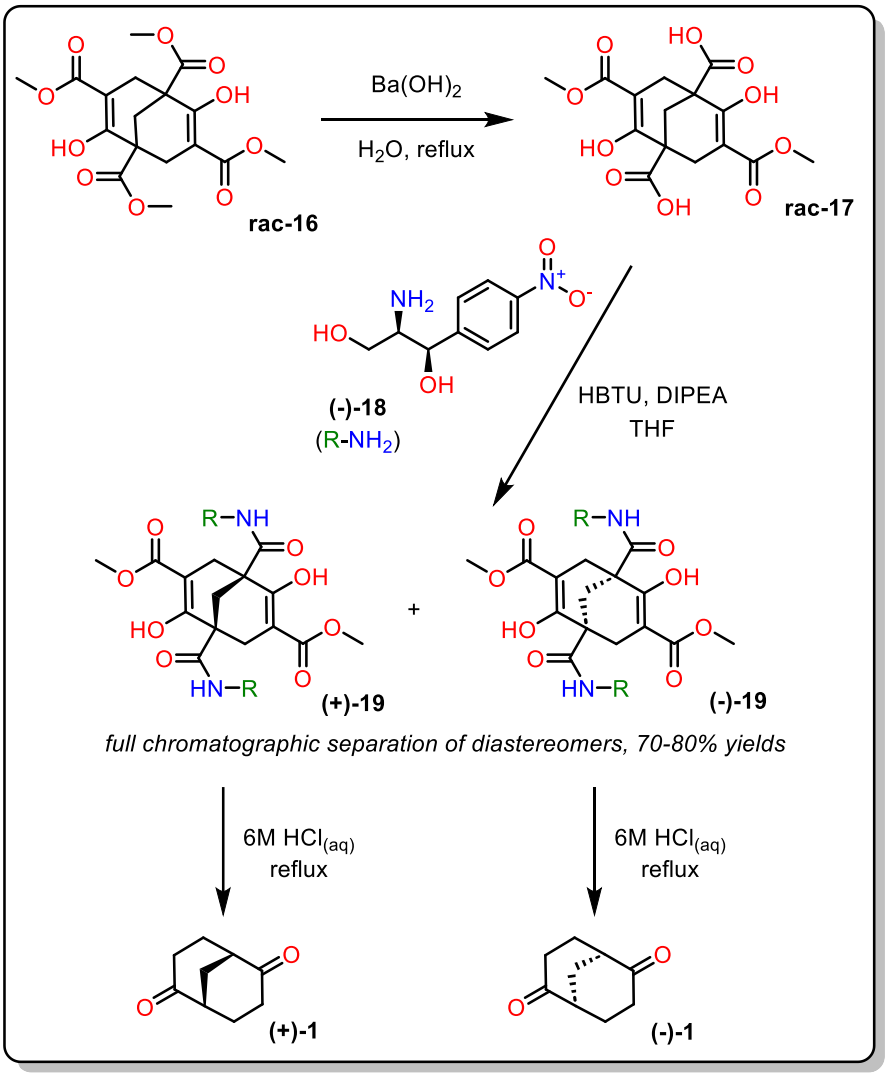
Scheme 15. Methods for resolution of **1**.

Following this, multiple other strategies for formation of diastereomeric derivatives were attempted (scheme 16). (+)-Hydrobenzoin **(+)-11** was postulated as a potential resolving agent, as the steric effects of the large, closely oriented phenyl rings could cause a larger divergence in the physical properties of the diastereomers, while also increasing the crystallinity of the otherwise greasy BCN derivatives. The acetals were prepared through the same method as with dimethyl tartrate, however, no enantiomeric enrichment through chromatography or recrystallization could be obtained. Another strategy relied on the formation of camphanic acid esters, which have previously been used for resolution of alcohols [71]. This method would also allow for the use of residual enantioenriched keto-alcohol **rac-8** as a feedstock, allowing for complementarity with the baker's yeast resolution. The reaction between **rac-8** and (-) camphanic acid chloride **(-)-14** gave the mixture of diastereomeric esters, but separation was once again unsuccessful.



Scheme 16. Unsuccessful resolution strategies.

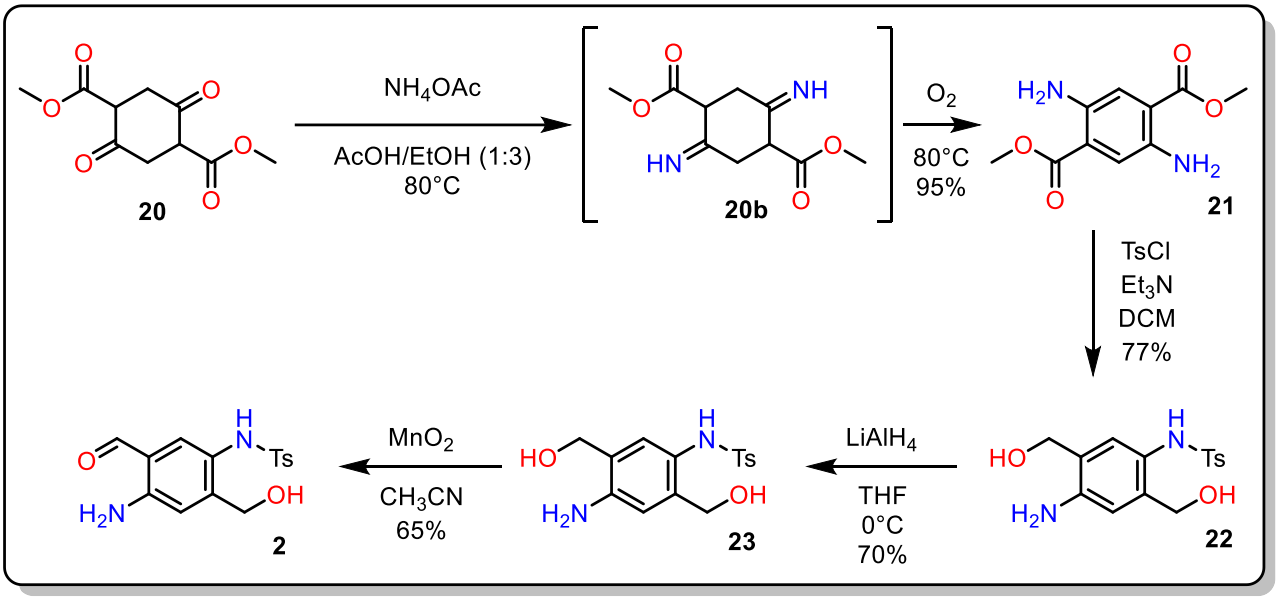
The next resolution strategy relied on the use of Meerwein's ester **rac-16**, an intermediate in the synthesis of the dione **1**. Following a procedure by Meerwein et al [72], selective hydrolysis of the bridgehead ester groups with $Ba(OH)_2$ could be achieved in high yields (~80%) at a large scale. This allows for the use of the wide variety of available chiral alcohols and amines as potential resolving agents, either as ammonium carboxylate salts, or esters/amides. The first chosen agent was levobase **(-)-18**, which was used by Slegel et al. to achieve TLC resolution of various chiral carboxylic acids [73]. **18** is also commercially available as both pure enantiomers at a low cost (<1 EUR/g), allowing the potential use of this method at larger scales. As depicted in scheme 17, The bis-amide mixture of **(+)-19** and **(-)-19** was obtained through standard amide coupling conditions using HBTU as a coupling reagent. After a screening of various chromatographic eluent systems, a set of conditions were found that allowed for complete separation of the diastereomers both in TLC and large-scale column chromatography in 70-80% yields. Subsequent hydrolysis and decarboxylation of the diastereomers with aqueous HCl provided both enantiomerically pure **(+)-1** and **(-)-1** in 60-80% yield. The method has so far been successfully scaled up to provide up to 500 mg of **(-)-1** in one batch. Besides that, this method allows for enantiomerically pure derivatives of Meerwein's ester to be obtained, which could function as (or be converted to, e.g. through selective Krapcho decarboxylation of only the ester groups in **19**) pre-functionalized derivatives of **1**.



Scheme 17. Diastereomeric resolution of Meerwein's ester derivatives.

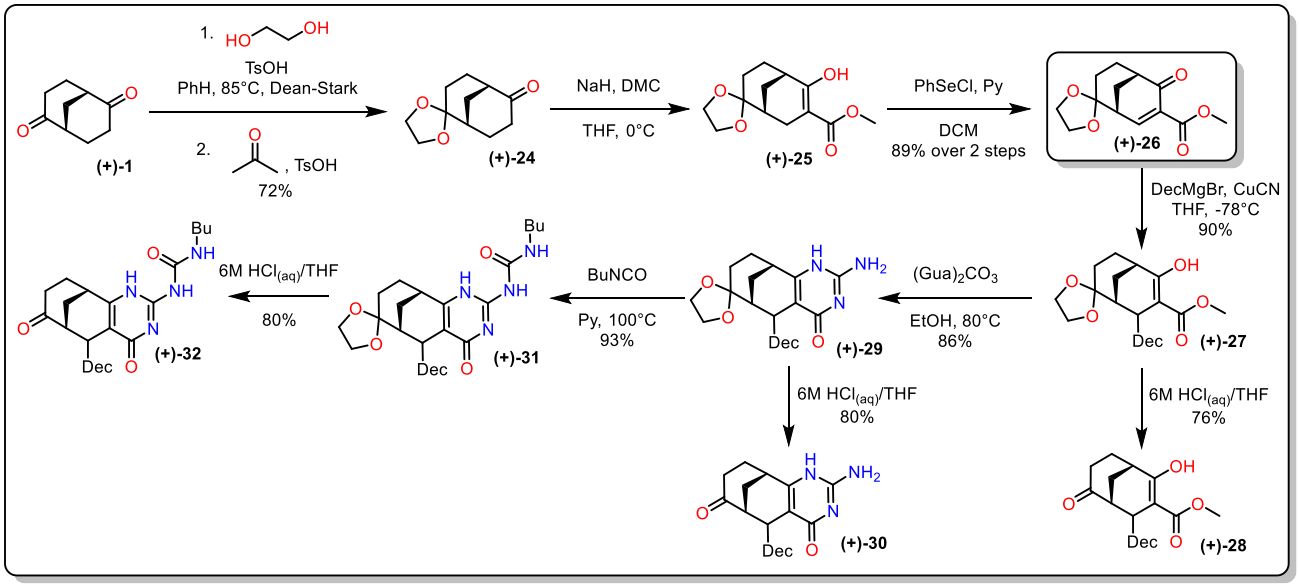
With both enantiomers of **1** at hand, the next step was to obtain the aromatic linker **2**. While the synthesis of **2** was previously described in the bachelor's thesis [69], it had to be optimized to allow for large scale (>10g) preparations. The result is depicted in scheme 18. The previously used method for obtaining **21** from commercially available **20** relied on a condensation-elimination cascade with phenylhydrazine [74], however, this was incredibly time- and resource- intensive, requiring tedious multi-step purification, including filtering, extraction, chromatographic separation and then recrystallization to provide pure **21** in mediocre yield (~30-50%). While this has been the preparation method of choice in most recent literature, a 1914 paper by Liebermann [75] described an alternative synthesis – formation of the bis-imine from **20b** by heating in alcoholic ammonia solution under pressure. The bis-imine, upon isolation and heating under air, would oxidize to **21**. Reports with similar compounds performed the oxidation with catalytic acetic acid under an air atmosphere [76]. These ideas were applied to **20**, and, after some iterations, a high-yielding procedure was achieved: heating **20** and an excess of ammonium acetate in a mixture of ethanol and acetic acid under argon provided the bis-imine **20b**. Then, after full conversion was achieved, oxygen gas was bubbled through the mixture, providing full oxidation in a few hours. Removal of solvents followed by a simple water-DCM extraction provided pure **21** in nearly quantitative yield.

The tosyl mono protection step to provide **22** was also modified. Previously, pyridine was used as the solvent, catalyst and acid scavenger, which led to very rapid reactions that provided poor mono-selectivity. Instead, a small excess of triethylamine was used as a non-catalytic base. This led to far longer reaction times (typically several days), however, the selectivity was far better, with almost exclusively mono-tosylated **22** being formed. Washing the organic layer with aqueous HCl and $NaHCO_3$ provided sufficiently pure **22** in high yield. The reduction and oxidation steps remained mostly unchanged, though it was found that trituration of the crude product mixture after $LiAlH_4$ reduction with $CHCl_3$ could be used to provide pure **23**, avoiding another step of column chromatography (albeit with minor product loss). Overall, these methods allowed for the operationally simple preparation of Friedländer synthon **2** in multi-gram scale with only one chromatographic step for the final product.

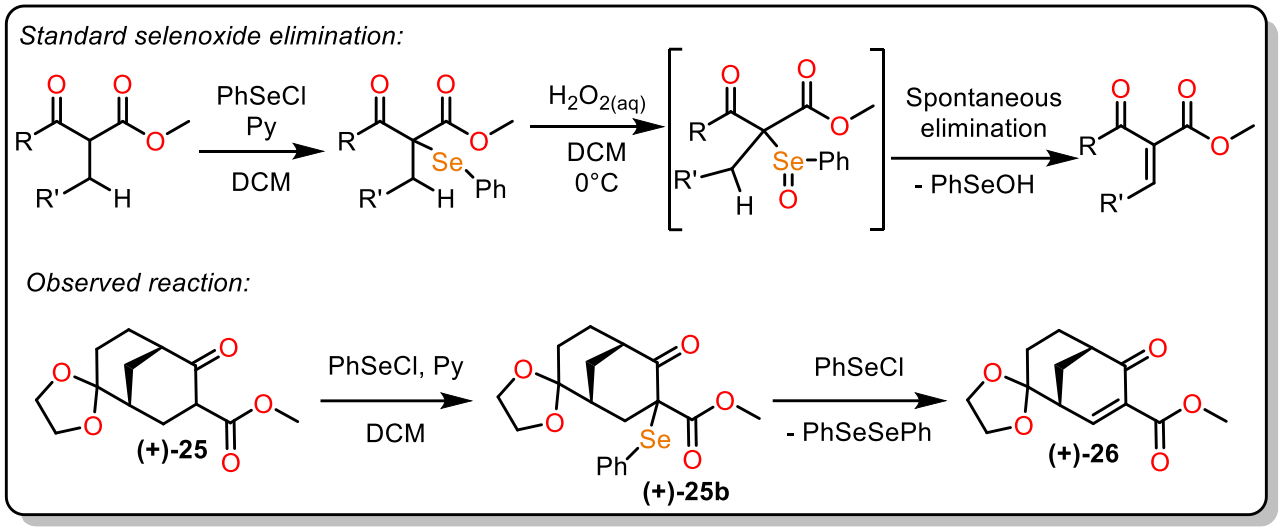


Scheme 18. Preparation of Friedländer synthon **2**.

The final building block needed for the preparation of the target cavitand was the asymmetrically functionalized **(+)-32** (scheme 19). While most of the methods for functionalization of **(+)-1** previously developed in the group were used to prepare symmetrical derivatives (i.e. on both sides of the bicyclic core), mono-ketal protection allowed them to be used for asymmetrical (i.e. on one side of the bicycle) functionalization with minimal modifications. The mono acetal **(+)-24** was prepared following a literature procedure [57]. Condensation with dimethyl carbonate provided the α-keto ester **(+)-25** in nearly quantitative yield. Next, α,β-unsaturation of the keto ester would be performed in order to be able to install solubilizing groups via conjugate addition into the β-position of the ketone. Here, some interesting results were discovered (scheme 20). Typically, this reaction was performed via selenoxide elimination – introduction of the phenylselenyl group via nucleophilic substitution of phenylselenyl chloride, followed by oxidation to the selenoxide with hydrogen peroxide, which spontaneously eliminates through an intramolecular pathway [77]. However, when performing this reaction with an equimolar amount of **(+)-25** and PhSeCl, TLC analysis showed only partial conversion. The newly formed product also remained unchanged after the oxidation procedure. NMR analysis showed a ~50:50 mixture of starting material **(+)-25** and target product **(+)-26**. It was proposed that the phenylselenyl intermediate undergoes spontaneous elimination while reacting with another molecule of PhSeCl through an unknown mechanism. This was tested by using an excess (>2eq) of PhSeCl, which delightfully provided the target product **(+)-26** in nearly quantitative yield. This also provides an explanation for why the reactions with the bis-keto ester in past research efforts of the group required two runs of selenoxide elimination to be successful (scheme 9): unlike previously thought, it is not due to steric crowding preventing the addition of a second phenylselenyl group, but the spontaneous elimination consuming a second equivalent of PhSeCl. Further studies on this reaction are being carried out but are outside the scope of this thesis.



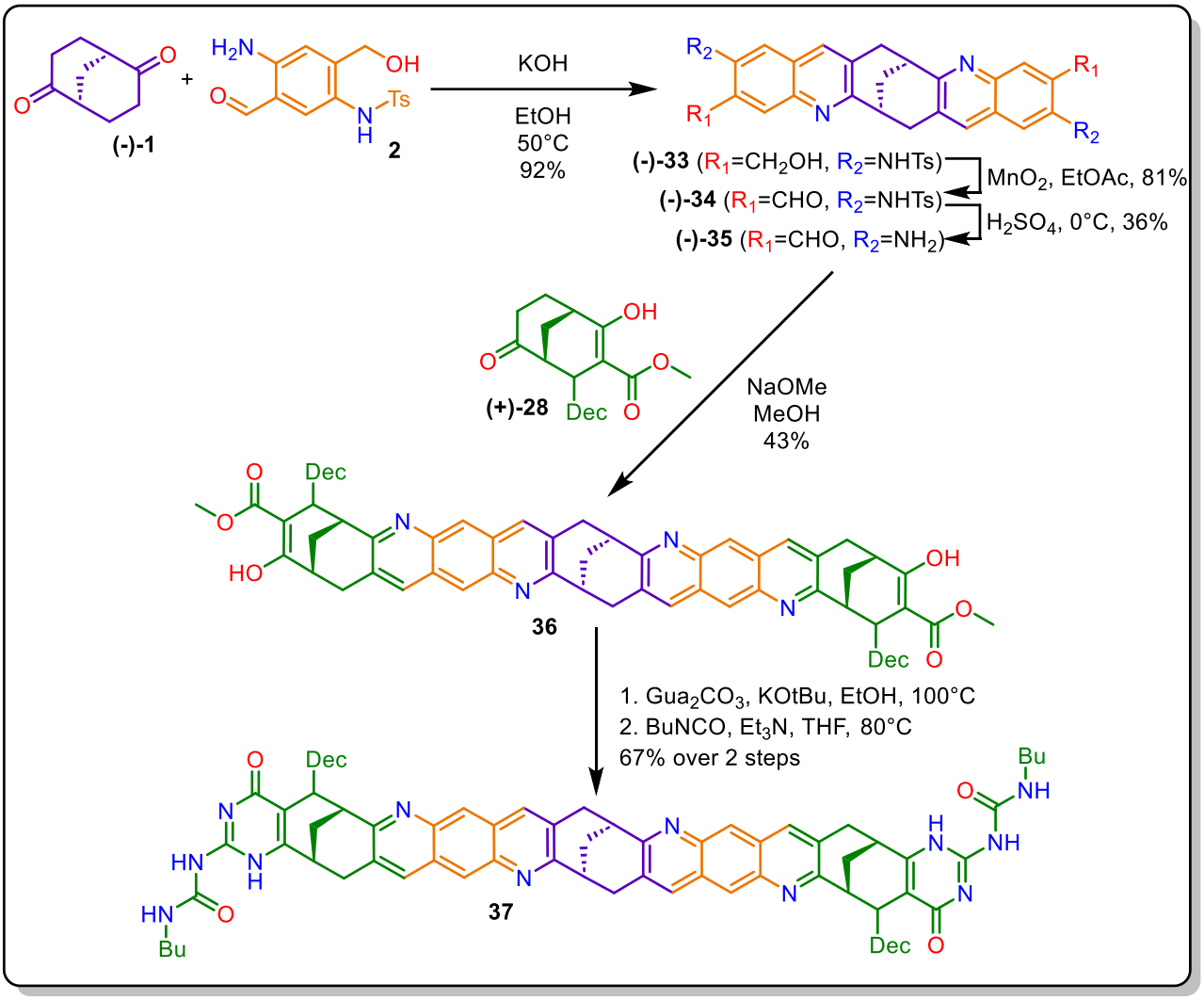
Scheme 19. Synthesis of asymmetrically functionalized BCN derivatives.



Scheme 20. Unusual mechanism of elimination with **(+)-25**.

The unsaturated α-keto ester **(+)-26** can be further functionalized through various conjugate addition reactions. A simple long-chain alkyl solubilizing group was chosen as the first option. As previous research has suggested that n-butyl groups (installed via nBuLi/CuCN) are insufficient [69], n-decyl was chosen instead. Formation of the Grignard reagent from 1-bromodecane and conversion to the Gilman organocuprate with CuCN, followed by addition to **(+)-26** provided **(+)-27**. From this compound, deprotected α-keto ester **(+)-28**, isocytosine **(+)-30** and UPy derivative **(+)-32** were prepared through standard methods. Acetal deprotection through acidic hydrolysis rather than trans-acetalization with acetone was used as the latter often did not provide full conversions. The compounds were prepared to screen for their viability as potential Friedländer condensation partners during the construction of the cavitand.

With all of the building blocks prepared, synthesis of the cavitand could be attempted (scheme 21). The first Friedländer condensation between **(-)-1** and **2**, as well as the subsequent benzylic oxidation to **(-)-34** and tosylamide hydrolysis to **(-)-35** were already performed previously with **(+)-1** [69], though some modifications were made. The first Friedländer condensation works without any problems, giving **(-)-33** in near-quantitative yield after precipitation and washing to remove impurities. For the oxidation, chromium-based PCC was previously used, but was poorly reproducible and required a problematic chromatographic separation. Switching to MnO_2 as the oxidant gave more reproducible results. However, the main problem was the sulfonamide deprotection step, as well as the poor stability and solubility of the product **(-)-35**. This reaction often provided low, inconsistent yields (20-50%), serving as the main bottleneck of the entire route. Many strategies were attempted, such as reversing oxidation/hydrolysis order (only provided insoluble products), alternative deprotection methods (e.g. with stoichiometric amounts of trifluoromethanesulfonic acid), in situ hydrolysis/Friedländer condensation, and re-doing the entire synthesis route with alternative amino protecting groups (with Nosyl group – could not perform ester reduction, with Boc group – could not perform second benzylic oxidation after Friedländer condensation), however, none of them were successful.



Scheme 21. Synthesis of cavitand monomer **37**.

Regardless, sufficient amounts of **(-)-35** could still be obtained, and the second Friedländer condensation was attempted. In the ideal case, condensation between **(-)-35** and the final UPy-functionalized **(+)-32** would be performed, as this would lead to the shortest linear sequence in the overall cavitand synthesis, allowing easy modular construction with different building blocks. This idea was unsuccessful, as attempted Friedländer condensations with both the UPy- and ICyt-functionalized ketones **(+)-32** and **(+)-30** did not provide the desired products. The next option – condensation with the keto-ester **(+)-28**, had a different problem – the ester group was incompatible with the standard Friedländer conditions (KOH in EtOH), as ester hydrolysis and subsequent decarboxylation could occur. While acid-catalyzed Friedländer conditions are also widely used, they often require much more vigorous conditions (typically reflux in toluene with catalytic pTsOH or AcOH/H_2SO_4), and attempts to replicate these conditions did not provide the desired product. Fortunately, a simple modification to the standard conditions gave satisfactory results: by using anhydrous NaOMe (prepared from sodium metal and freshly dried MeOH), product **36** was obtained in decent yields. Formation of the ICyt and UPy moieties proceeded through the standard conditions (condensation with guanidine and urea formation with isocytosine) without major complications. The purification of the UPy product **37**, like with most of the UPy derivatives prepared in the past by the group, could not be performed only through column chromatography, due to co-elution with

presumably the di-butyl urea side product. Fortunately, precipitation from $CHCl_3$ with MeOH, removed the impurity.

NMR analysis of the $CDCl_3$ solution of **37** showed promising results – in the ^1H spectrum, three single peaks (corresponding to the N-H protons in the UPy motif) were visible in the downfield region (9.5-13), suggesting the presence of a single species in solution. In the DOSY spectrum, all of the proton resonances corresponded to a single diffusion coefficient ($D = 2.10 \cdot 10^{-10}$ m^2s^{-1}). By using the Stokes-Einstein relation ($D = (k_bT)/(6\pi\eta R_H)$, T = 293 K, $\eta(CDCl_3)$ = 0.57 mPa·s), a hydrodynamic radius of 17.9 Å was obtained, which is within the range of values expected for a molecule of such size ($M_{(tetra\text{-}37)}$ = 5126.6 g/mol. For reference, a pentameric species previously obtained by the group with M = 4924.5 g/mol had a hydrodynamic radius of 17.5 Å [78]).

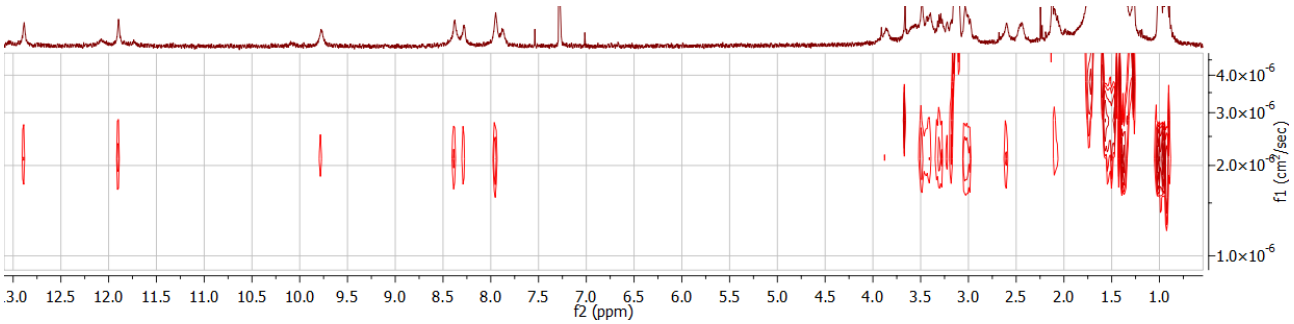
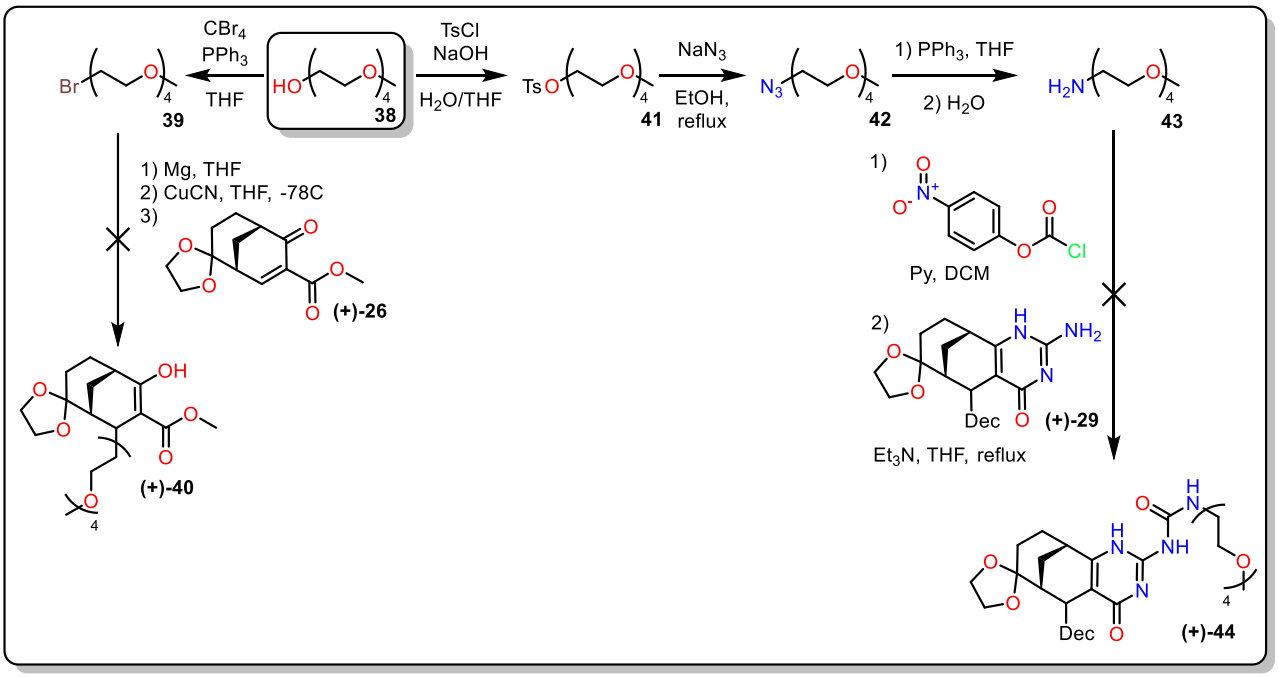


Figure 15. DOSY spectrum of **37** in $CDCl_3$, showing presence of a species with $D = 2.10 \cdot 10^{-10}$ m^2s^{-1}.

Attempts to form complexes with fullerene (C_{60} and C_{70}) were unsuccessful. This was unsurprising, as the larger cavity is no longer optimally sized to fit a fullerene molecule, unlike in the previously developed cavitands. Furthermore, complexation in non-polar solvents, especially chloroform, is often more difficult, as they compete with the guest for complexation. Solvents such as toluene or acetonitrile often provide better results. However, it was found that **37** was insoluble in practically every solvent besides $CHCl_3$ (and $CHCl_3$/MeOH as the monomeric form). Even in the structurally similar DCM the solubility was significantly worse. Therefore, for further research, cavitands featuring larger or more polar solubilizing groups (such as oligomeric ethylene glycol chains) would need to be developed.

The first and most obvious ideas to install the desired polar solubilizing groups were to directly add them through the available functionalization routes – conjugate addition to the enone **(+)-26** or incorporation into the UPy motif (scheme 22). The starting material in both cases was the commercially available tetraethyleneglycol monomethyl ether **38** (TEG-OH). The corresponding bromide **39** was prepared through the Appel reaction [79]. Attempts to prepare a Grignard reagent and perform Gilman-type conjugate addition (as with the decyl bromide previously) were unsuccessful. While the reason for failure was unknown (possibly due to some sort of metal chelation effect with the oxygens of the TEG chain), during the literature search no preparations of similar poly-ethylene glycol organometallic nucleophiles or their additions to electrophiles were found, suggesting that this route is most likely not viable. The next route, direct functionalization through the UPy motif, started with a synthesis of the TEG-amine **43** through literature procedures [80]. An attempt to couple the ICyt derivative **(+)-29** with the TEG-amine **43** were done with 4-nitrophenyl chloroformate, conditions that were previously successfully used in the group [78]. However, only an inseparable mixture of starting materials and unidentified products was obtained. Therefore, more sophisticated functionalization methodologies would need to be developed.



Scheme 22. Attempted TEG-functionalization of BCN derivatives.

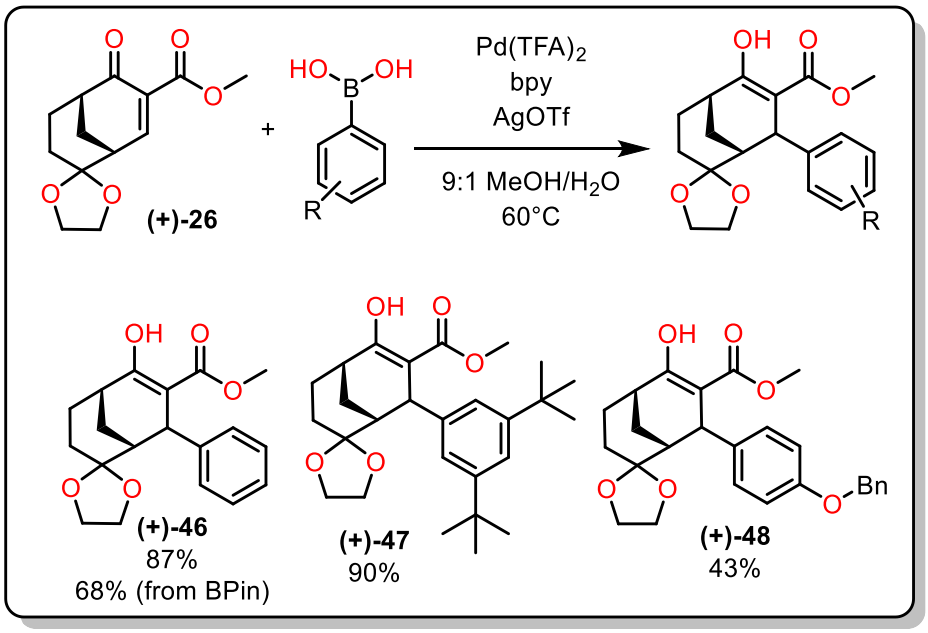
The design of new functionalization methodologies mainly relied on alternative nucleophiles for conjugate addition to the enone **(+)-26**, ideally allowing for further selective functionalization after the final steps of the cavitand synthesis, thus functioning as a universal linker. Inspiration was drawn from unsuccessful past attempts within the group [81], as well as analysis of various 1,4-addition methods available in the literature.

One idea relied on the recently emerged strategy of Rh- and Pd-catalyzed 1,4 addition of arylboronic acids to α,β-unsaturated carbonyl compounds [82–86]. While most of the methodologies in these papers are limited to chemically simple unhindered enones, the possibility of applying such a strategy to BCN derivatives was very desirable due to the large variety of arylboronic acids that are commercially and synthetically available as a result of the popularity of the Suzuki coupling reaction.

Conditions from various methodological papers were screened with **(+)-26** and phenylboronic acid, with the results displayed in table 1. The Rh-catalyzed reaction [82] was tested first, but no conversion was detected, likely due to the sensitivity of the catalytic system to steric interference. Next, a Pd-catalyzed addition using $Pd(OAc)_2/CHCl_3/PPh_3$ [83] was attempted, and some product formation was observed (confirmed by NMR), however the conversion was very poor, likely due to poor stability of the catalytic system, as evidenced by large amounts of Pd(0) precipitate. Following the procedure of Gao et al. [84], with 2,2'-bipyridyl (bpy) as the ligand, significantly better conversion was observed, however the reaction never went to completion. Changing the Pd source to $Pd(TFA)_2$ allowed for full conversion to be achieved in 40h at 80°C. Encouraged by the results, a series of reactions with modified conditions based on the thorough research by the Stoltz group [85] were tested. The optimal system was found to be $Pd(TFA)_2$/bpy/AgOTf in 9:1 MeOH/H_2O. Despite the catalyst being quite unstable in methanol (as seen from the formation of large amounts of Pd(0) precipitate, and also noted in other research [85,86]), it remained the best solvent out of the ones tested, achieving full conversion (and 80% isolated yield) at 60°C overnight. On top of that, full conversion was also achieved when using the pinacol ester of phenylboronic acid, as well as the more sterically challenging 3,5-di-*tert*-butylphenylboronic acid **45**.

Table 1. Optimization of nucleophilic addition of arylboronic acids.

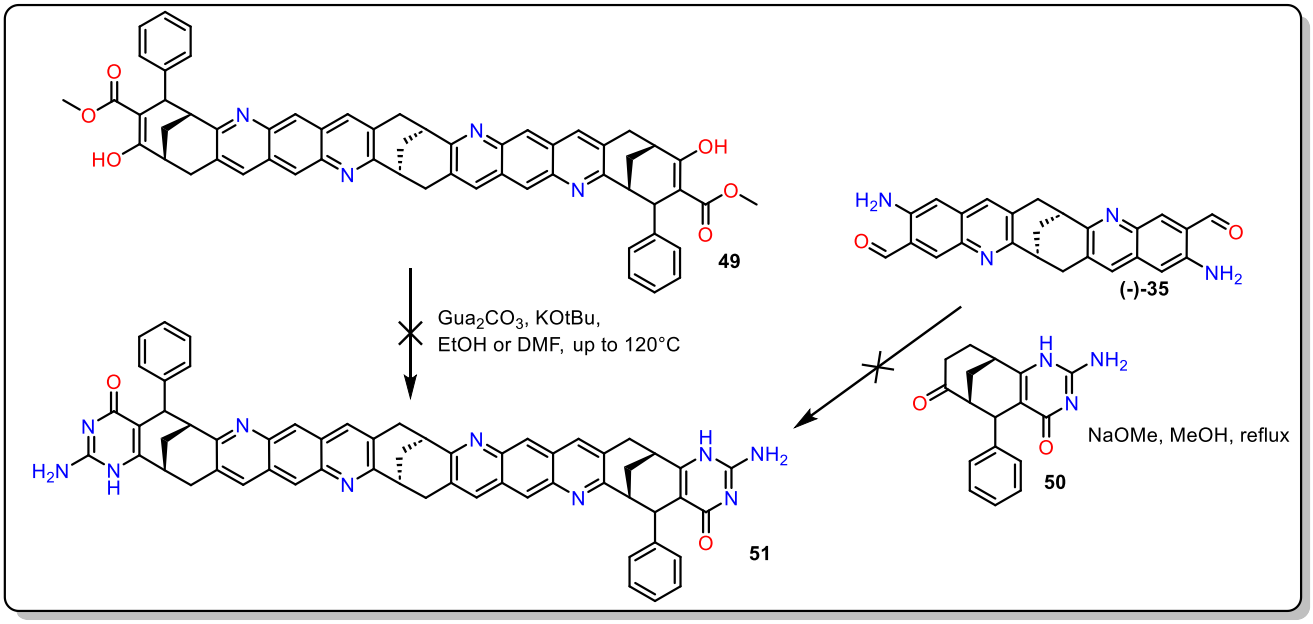
Nucleophile	Reaction conditions	Results
Phenylboronic acid	$[RhCl(cod)]_2$, $NaHCO_3$, dioxane-H_2O 6:1, 80°C	No product observed
	$Pd(OAc)_2$, PPh_3, $CHCl_3$, Cs_2CO_3, toluene, 80°C	Traces of product observed, Pd(0) precipitation
	$Pd(OAc)_2$, bpy, DMF, 80°C	Partial conversion after 40h
	$Pd(TFA)_2$, bpy, DMF, 80°C	Full conversion after 40h
	$Pd(TFA)_2$, bpy, MeOH-H_2O 9:1, 80°C	Full conversion after 40h, Pd(0) precipitation
	$Pd(TFA)_2$, bpy, AgOTf, MeOH-H_2O 9:1, 60°C	Full conversion after 16h, Pd(0) precipitation, 87% isolated
	$Pd(TFA)_2$, bpy, AgOTf, DCE-H_2O, 60°C	Full conversion after 40h
	$Pd(TFA)_2$, bpy, AgOTf, dioxane-H_2O, 60-80°C	Partial conversion after 40h at 60°C, full conversion after additional 16h at 80°C
Phenylboronic acid pinacol ester	$Pd(TFA)_2$, bpy, AgOTf, MeOH-H_2O 9:1, 60°C	Full conversion after 16h, Pd(0) precipitation, 68% isolated
3,5-di-*tert*-butylphenylboronic acid	$Pd(TFA)_2$, bpy, AgOTf, MeOH-H_2O 9:1, 60°C	Full conversion after 16h, Pd(0) precipitation, 90% isolated



Scheme 23. Pd catalyzed arylation of **(+)-26**.

The mildness, effectiveness and robustness of the reaction set a very optimistic outlook, and a potential candidate for a universal linker, the benzylated phenol **(+)-48**, was developed. However, hope was quickly lost. Upon attempting to construct cavitands with the arylated derivatives, it was found that, even though the Friedländer condensation to provide **49** was successful, the ICyt motif could not be constructed (scheme 24). No reaction occurred upon heating to reflux, and changing the solvent to the higher-boiling DMF and heating to 120°C only led to decomposition of starting materials. Interestingly, the free ketone ICyt derivative **50** could be prepared, but, like previously, this route could not be used to construct the cavitand. Such results are not entirely unexpected, as, the

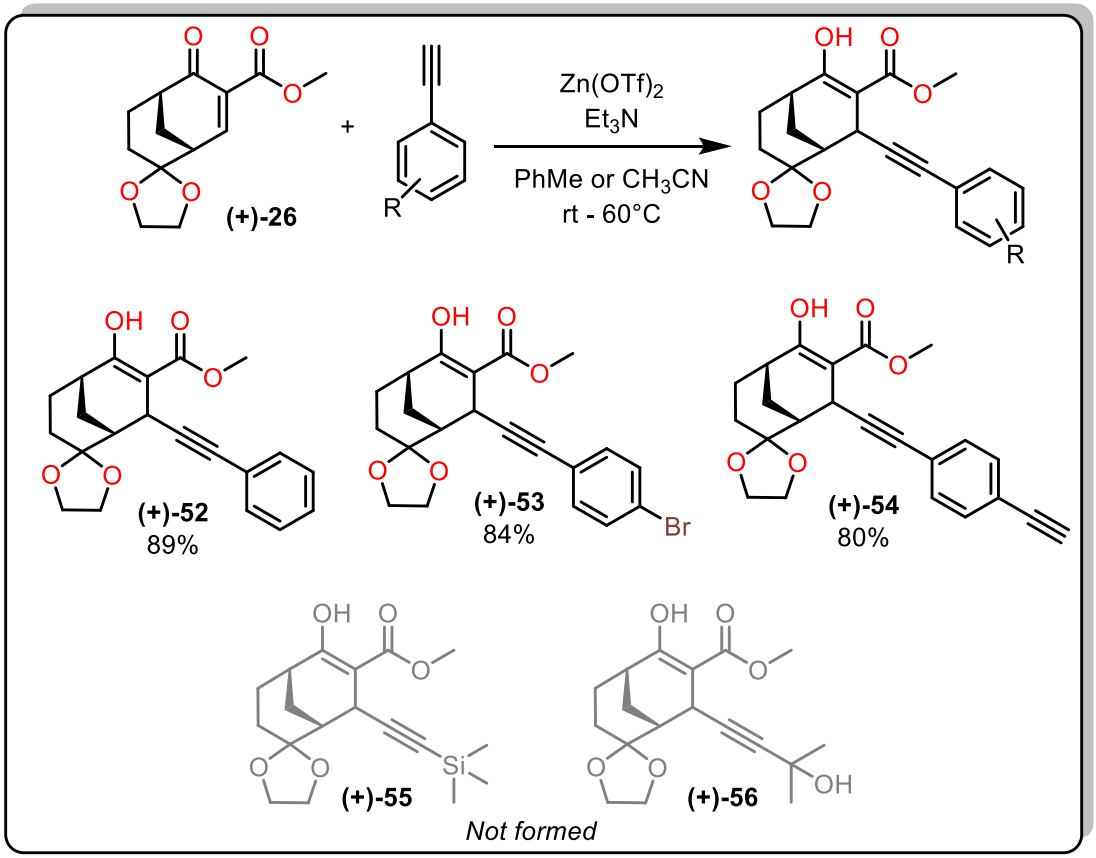
reactivity of various BCN derivatives can be quite sensitive to steric effects (as noted in previous research [69,81]), where even seemingly minor and inconsequential structural differences can completely halt previously successful reactions.



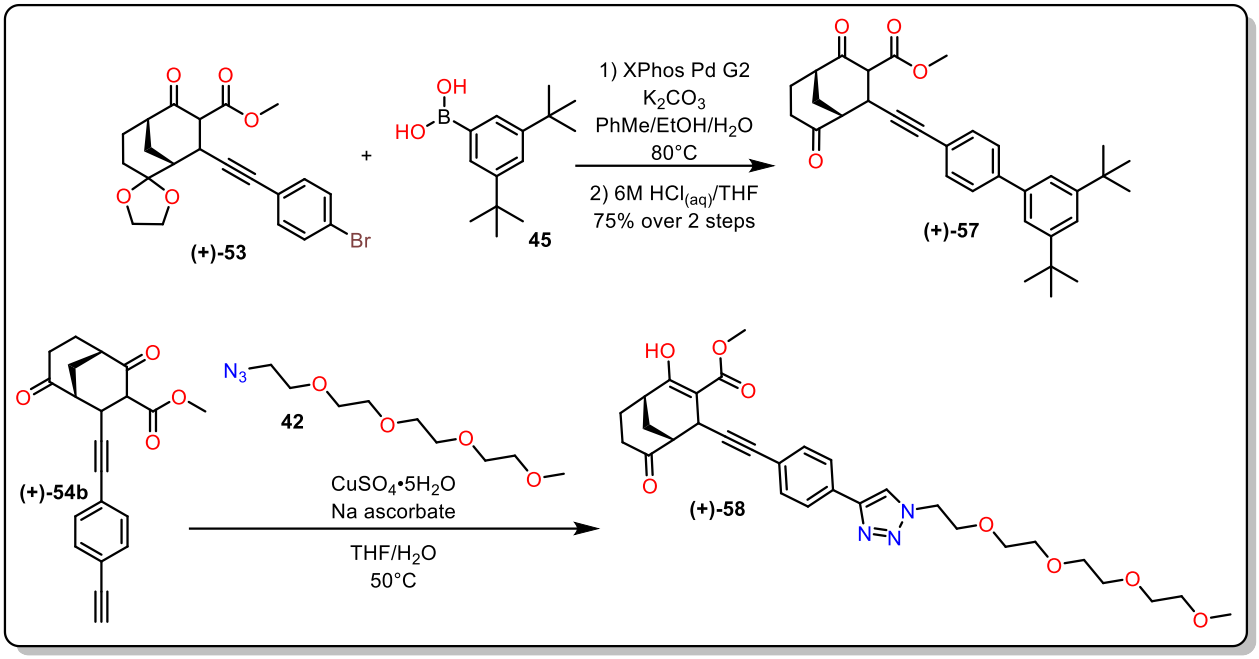
Scheme 24. Attempts to prepare arylated cavitand **51**.

Based on these results, it was clear that further functionalization method designs should minimize steric strain. Alkynes appeared to be the ideal choice, as the linear, hydrogen-free linker would provide minimal steric hindrance. Conjugate addition reactions of copper acetylides, as well as zinc and aluminum derivatives, have previously been tried without success, due to the generally poor nucleophilicity of these species [87]. A literature search for more recent developments in this field was performed, and a paper from the group of E. Carreira, featuring zinc catalyzed terminal alkyne conjugate addition to α,β-unsaturated dicarbonyl compounds [88], caught our interest. The method appeared to be operationally simple (zinc alkynylides are produced *in situ* from alkyne, zinc salt and amine base), high-yielding, and compatible with various alkynes, so analogous conditions were tested with **(+)-26** and phenylacetylene as a model substrate. To our delight, formation of the desired product was observed, and, after minor modifications (increased loading of zinc, alkyne, and base) full conversion (and 89% yield) was achieved. Following these results, other alkynes were tested under analogous conditions. Protected ethylene equivalents (trimethylsilylacetylene and 2-methylbut-3-yn-2-ol) were tried first, as the resulting terminal alkyne could then be used as a handle for functionalization via alkyne-azide cycloaddition click chemistry methods. Despite TMS-acetylene being successfully used as the nucleophile in the original paper, the reaction did not work with our substrate, possibly due to competing alkyne dimerization reactions. 2-Methylbut-3-yn-2-ol, another common ethylene equivalent, was also tested but no product formation was observed. The focus was shifted back to substituted phenylethylenes. Out of the derivatives available at hand, 1-bromo-4-ethynylbenzene was tested first, and **(+)-53** was obtained in 84 yield. The aryl bromide could be functionalized with various substituents through cross-coupling methods (e.g. Suzuki, Sonogashira, Buchwald-Hartwig, Negishi reactions). Some of these were tested with **(+)-53**. Suzuki coupling with the previously used 3,5-di-*tert*-butylphenylboronic acid, followed by acidic hydrolysis, provided the biaryl **(+)-57** in 75% yield (scheme 26). A Sonogashira coupling between **(+)-5** and TMS-acetylene was not successful (likely due to the difficulties in performing the reaction at small scale, as excess

copper (I) salts tend to favour side reactions), but it inspired an idea for a simpler preparation – by using 1,4-diethynylbenzene (prepared from dibromobenzene and TMS-acetylene [89]), the terminal alkyne-containing derivative **(+)-54** was prepared in 80% yield. The diethynyl linker appears to be a good fit from a design perspective – the phenylethylene spacer should have minimal steric hindrance, permitting the condensation reactions required for cavitand assembly. The rigid spacer also distances the terminal alkyne from the cavitand core, thus also reducing any crowding that could interfere with the alkyne-azide click functionalization, as well as distancing the to-be-formed triazole from the UPy motif, preventing any possible interference of hydrogen bonding. The mildness and selectivity of the alkyne-azide cycloaddition should also enable it to be performed at the last stages of the synthesis, thus minimizing the number of synthetic steps needed to prepare a library of variously substituted cavitands. A test click reaction between **(+)-54b** and previously prepared TEG-azide **42** was successfully performed to give the triazole derivative **(+)-58** under standard Cu(I)-catalysed conditions (scheme 26). Friedländer condensation reactions between the prepared derivatives **(+)-54b** and **(+)-57** with amino-aldehyde **(-)-35** were performed to evaluate compatibility with previously used methods, and the functionalized cavitand carcasses were successfully obtained (see experimental part), however, full cavitand monomers were not prepared during this thesis.



Scheme 25. Conjugate addition of alkynes to **(+)-26**.

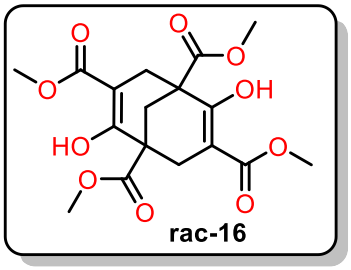


Scheme 26. Suzuki functionalization of **(+)-53** and click functionalization of **(+)-54b**.

3. EXPERIMENTAL PART

All reactions were performed in oven-dried glassware, under an atmosphere of argon, unless noted otherwise. Solvents were dried by distilling from Na (THF), Mg/I_2 (MeOH) or CaH_2 (DIPEA, Et_3N, DCM, CH_3CN) and storing under activated 3Å sieves for at least 48 hours before use. Certain solvents were dried only by storing under activated 3Å sieves (EtOAc, DMC). Other chemicals were used as received from commercial suppliers. Column chromatography was performed using Merck 60 (43,0 – 66,3 µm) silica gel. TLC analysis was performed using aluminium-backed Merck Kieselgel 60 F_{254} plates. Visualization of plates was performed with UV light or chemical stains (I_2, $KMnO_4$, $FeCl_3$). NMR analysis was performed with a Bruker Avance spectrometer equipped with a Bruker Ascend 400 MHz magnet, an Accustar z-axis gradient amplifier and an ATMA BBO probe with a z-axis gradient coil at ambient temperature. Residual undeuterated solvent peaks were used as an internal reference: $CDCl_3$ – 7.26 ppm (^1H) and 77.16 ppm (^{13}C); DMSO-*d6* – 3.31 ppm (^1H) and 49.00 ppm (^{13}C). The following abbreviations were used to explain NMR peak multiplets: s – singlet, br s – broad singlet, d – doublet, t – triplet, q – quartet, p – pentet, m – multiplet. HRMS analysis was performed with a Dual-ESI Q-TOF 6520 spectrometer. Optical rotation was measured with a Krüss P3001RS polarimeter.

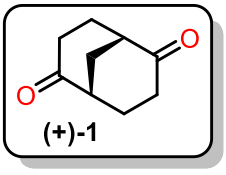
tetramethyl 2,6-dihydroxybicyclo[3.3.1]nona-2,6-diene-1,3,5,7-tetracarboxylate rac-16



Compound **rac-16** was prepared via modified literature procedure [90]. To a 2 L round-bottom flask were subsequently added dimethyl malonate (400 mL, 462.4 g, 3.50 mol), paraformaldehyde (87.6 g, 2.92 mol), piperidine (8.75 mL, 0.087 mol) and benzene (700 mL). The flask was equipped with a Dean-Stark apparatus and a reflux condenser and heated under reflux until water ceased to accumulate in the water trap (approximately 20 hours). Volatile components of the mixture were removed using a rotary evaporator at 60 °C. The oil was transferred to a 2 L round-bottom flask containing freshly prepared sodium methoxide solution (57.24 g, 2.49 mol of Na in 900 mL of MeOH). The flask was equipped with a large magnetic stir bar, a reflux condenser and a $CaCl_2$ drying tube and the mixture was heated under reflux with vigorous stirring overnight. The mixture was cooled to room temperature, then Et_2O (300 mL) was added, and the mixture was cooled in an ice bath for 30 minutes before being filtered. The filter cake was additionally washed with a 1:1 mixture of Et_2O and MeOH (250 mL). The collected solid was dissolved in 1L of H_2O and acidified using 6M HCl (to pH 4-5). The formed precipitate was collected by filtration and dried under vacuum for 4 days, yielding 237.2 g (70%) of **rac-16** as a pinkish white crystalline solid.

^1H NMR (400 MHz, $CDCl_3$) δ 12.18 (s, 2H), 3.79 (s, 6H), 3.77 (s, 6H), 2.88 (s, 4H), 2.33 (s, 2H). ^1H NMR is in accordance with literature [90].

(+)-(1S,5S)-bicyclo[3.3.1]nonane-2,6-dione (+)-1

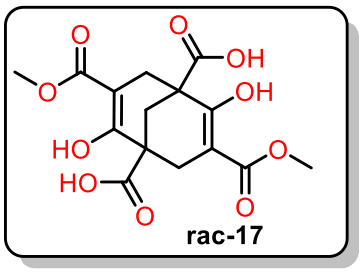


Compound **(+)-1** was prepared via modified literature procedure [90]. In a 2 L round-bottom flask, **rac-16** (237 g, 0.62 mol) was dissolved in 650 mL of glacial AcOH. The flask was equipped with a reflux condenser and dropping funnel, and the mixture was heated under reflux while adding an aqueous solution of HCl (6M, 430 mL) dropwise over 8 hours. The reaction mixture was then further heated under reflux overnight. The solvents were then removed with a rotary evaporator using a water

suction pump. The residue was dissolved in DCM (450 mL) and was washed with saturated aqueous solutions of $NaHCO_3$ (2x100 mL) and NaCl (100 mL). The organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was washed with cold Et_2O (200 mL) and dried to give **rac-1** (40.9 g, 43%) which was immediately subjected to the kinetic resolution procedure. Obtained **rac-1** was dissolved in 800 mL of hot tap water in a 3 L round-bottom flask with a magnetic stir bar. The solution was cooled to room temperature, and baker's yeast (69.5 g) and sugar (136 g) were added. The flask was equipped with a fermentation airlock and was left to slowly stir in a warm location until no more gas bubbling can be observed (about 10 days). Additional portions of sugar (136 g each) were added on the second and third day. The mixture was then saturated with NaCl and filtered through a pad of celite. The filter cake was washed with $CHCl_3$ (200 mL). The layers were separated, and the aqueous phase was further extracted with $CHCl_3$ (3x200 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and the bulk solvent was removed under removed pressure. In order to remove residual $CHCl_3$ (toxic to yeast), the residual oil was diluted with EtOAc (150 mL), and the solvents were removed under reduced pressure to provide a yellow semi-solid. The solid was dried under vacuum for 2 days and was then subjected to the kinetic resolution procedure for a second time. Afterwards, the mixture was purified by column chromatography (3:1 PE:EtOAc) to give white crystals of enantiomerically pure **(+)-1** (8,18 g, 39%, ee>99%)

$[\alpha]_D^{20}$ = 219,0 (c 0,59, $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (br m, 2H), 2.60 (m, 2H), 2.45–2.35 (m, 2H), 2.21 (m, 2H), 2.15–2.01 (m, 4H). ^{1}H NMR is in accordance with literature [90].

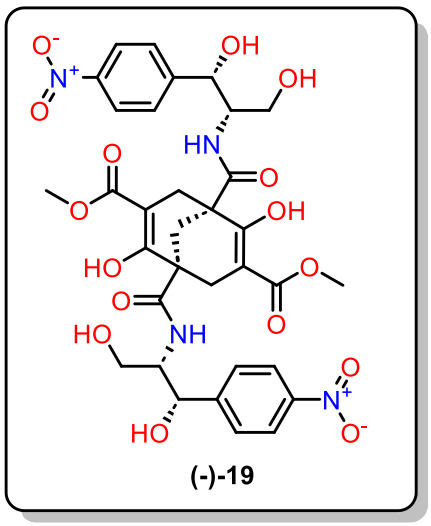
2,6-dihydroxy-3,7-bis(methoxycarbonyl)bicyclo[3.3.1]nona-2,6-diene-1,5-dicarboxylic acid rac-17



Compound **rac-17** was prepared via modified literature procedure [91]. Compound **rac-16** (2 g, 5.2 mmol) and $Ba(OH)_2 \cdot 8H_2O$ (4 g, 12.8 mmol) were dissolved in 20 mL of H_2O in a round-bottom flask equipped with a reflux condenser and a magnetic stir bar. The mixture was heated under reflux for 1 hour. The mixture was then cooled to room temperature, filtered and washed with H_2O (10 mL). The collected solids were dissolved in 30 mL of 2.4 M HCl and stirred for 1h. The suspension was filtered again, washed with H_2O (10 mL) and the product was collected by washing the filter cake with EtOAc. The solvent was removed under reduced pressure to give **rac-17** (1.3 g, 70%) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 13.06 (s, 2H), 12.00 (s, 2H), 3.73 (s, 6H), 2.75 (d, J = 16.6 Hz, 2H), 2.61 (d, J = 16.6 Hz, 2H), 2.23 (s, 2H). ^{1}H NMR is in accordance with literature [91].

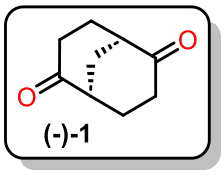
(-)-dimethyl (1R,5R)-1,5-bis(((1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl)carbamoyl)-2,6-dihydroxybicyclo[3.3.1]nona-2,6-diene-3,7-dicarboxylate (-)-19



In a 250 mL round-bottom flask equipped with a magnetic stir bar, **rac-17** (750 mg, 2.1 mmol) was dissolved in 50 mL of dry THF. Dry DIPEA (1.83 mL, 10.5 mmol) was added dropwise to the vigorously mixed solution to prevent clumping of the precipitating salt and keep it in suspension. HBTU (4760 mg, 4.6 mmol) was added in one portion, and the suspension was stirred vigorously for 30 minutes. (1R,2R)-2-amino-1-(4-nitrophenyl)propane-1,3-diol (980 mg, 4.6 mmol) was added in one portion and the suspension was left to stir overnight. The mixture was diluted with EtOAc (100 mL) and brine (100 mL). The layers were separated, and the aqueous phase was extracted with an additional portion of EtOAc (50 mL). The combined organic phases were washed with 1.2M HCl (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (40:1 EtOAc:MeOH, Rf(**(-)-19**)=0.2, Rf(**(+)-19**)=0.1) to provide **(-)-19** (670 mg, 85%) as a white semi-solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 2H), 7.99 (d, J = 8.3 Hz, 4H), 7.40 (d, J = 8.3 Hz, 4H), 7.25 (d, J = 8.9 Hz, 2H), 5.62 (d, J = 5.3 Hz, 2H), 4.86 (dd, J = 5.5, 2.7 Hz, 2H), 4.64 (dd, J = 6.3, 4.7 Hz, 2H), 3.89 (dt, J = 11.0, 7.7 Hz, 2H), 3.50 (s, 4H), 3.45 – 3.34 (m, 2H), 3.13-3.07 (m, 2H), 2.36 (d, J = 16.3 Hz, 2H), 2.21 (d, J = 16.4 Hz, 2H), 1.87 (s, 2H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 172.16, 169.90, 169.13, 152.13, 146.34, 127.34, 122.93, 97.19, 69.46, 60.11, 56.47, 52.01, 47.29, 35.28, 30.22.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 745.2199; found 745.2195.

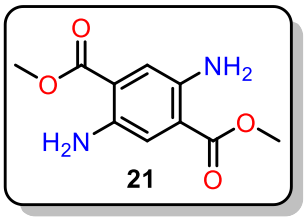
(-)-(1R,5R)-bicyclo[3.3.1]nonane-2,6-dione (-)-1



Compound **(-)-19** (550 mg, 0.7 mmol) and 6 M HCl (25 mL) were added to a 50 mL round-bottom flask equipped with a stir bar and a reflux condenser. The mixture was heated under reflux overnight. The solvent was removed under reduced pressure using a rotary evaporator with a water suction pump. The residue was suspended in DCM (100 mL), sonicated and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (3:1 PE:EtOAc) to give white crystals of enantiomerically pure **(-)-1** (73 mg, 65%, ee>99%).

$[\alpha]_D^{20}$ = -219,0 (c 0.59, $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (br m, 2H), 2.60 (m, 2H), 2.45–2.35 (m, 2H), 2.21 (m, 2H), 2.15–2.01 (m, 4H). ^{1}H NMR matches that of the (+)-enantiomer.

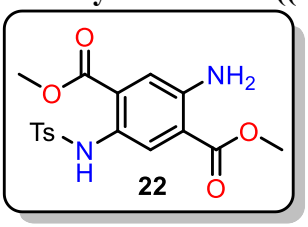
dimethyl 2,5-diaminoterephthalate 21



To a 500 mL round-bottom flask equipped with a large stir bar was added dimethyl 2,5-dioxocyclohexane-1,4-dicarboxylate (9.12 g, 40 mmol), NH_4OAc (30 g, 400 mmol), ethanol (200 mL) and AcOH (15 mL). The mixture was heated to 90°C under vigorous stirring. Within 1-2 hours, the reaction mixture clumped up into a large semi-solid mass and needed to be crushed up to continue stirring. Afterwards, when the suspension had returned to a free-flowing form (~1h), heating was reduced to 80°C and stirring was continued at this temperature overnight. Then, the formed bis-imine was oxidized by bubbling oxygen from a balloon through a large needle while continuing to heat at 80°C. Bubbling was continued until the mixture turned into a deep red homogenous solution and NMR analysis showed full conversion (disappearance of peak at 3.73 ppm), typically 2-6 hours. Afterwards, volatiles were removed under reduced pressure and the crude mixture was dissolved in DCM (250 mL) and washed with saturated aqueous solutions of $NaHCO_3$ (2x100 mL) and NaCl (100 mL). The organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give **21** (8.5g, 95%) as an orange crystalline solid.

1H NMR (400 MHz, $CDCl_3$): δ 7.29 (s, 2H), 5.30 (br s, 4H), 3.85 (s, 6H). 1H NMR is in accordance with literature [92].

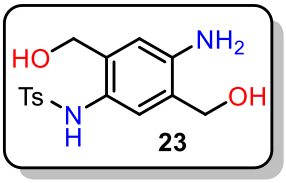
dimethyl 2-amino-5-((4-methylphenyl)sulfonamido)terephthalate 22



In a 250 mL round-bottom flask with a magnetic stir bar, **21** (3.88 g, 17.3 mmol) was dissolved in DCM (300 mL). Et_3N (5.3 mL, 38.1 mmol) and TsCl (3.63 g, 19 mmol) were added sequentially in single portions. The mixture was stirred at room temperature until TLC analysis (DCM as eluent) showed full conversion of TsCl (typically around 72 hours). The reaction mixture was diluted with 1.2M HCl (100 mL) and, after stirring for an additional 10 minutes, the layers were separated, the organic phase was washed with saturated aqueous $NaHCO_3$ (100 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (DCM + 1% Et_3N) gave **22** (5 g, 77%) as bright yellow crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.20 (s, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 7.11 (s, 1H), 3.95 (s, 3H), 3.71 (s, 3H), 2.35 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.58, 166.97, 146.83, 143.69, 136.02, 129.45, 127.58, 127.37, 126.65, 124.80, 118.78, 115.05, 52.64, 52.33, 21.63.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 379.0958, found 379.0956.

N-(4-amino-2,5-bis(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide 23

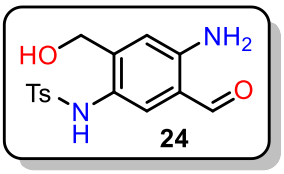


In a 250 mL round-bottom flask with a magnetic stir bar, $LiAlH_4$ (1 g, 26.4 mmol) was suspended in dry THF (50 mL) and cooled to 0°C in an ice bath. **22** (5 g, 13.2 mmol) was dissolved in THF (150 mL) and added dropwise over 1 hour. The reaction mixture was stirred at 0°C until TLC analysis (30:1 DCM:MeOH) showed full conversion (approx. 1 hour). Saturated aqueous NH_4Cl (50 mL), was slowly added, followed by dilution with H_2O (250 mL) and EtOAc (250 mL). The reaction mixture was filtered through a pad of celite, and the pad was washed with an additional 100 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with an additional portion of EtOAc (50 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and

concentrated under reduced pressure. The remaining dark oil was diluted with $CHCl_3$ (20 mL), sonicated and filtered. The filter cake was washed with an additional portion of $CHCl_3$ (20 mL) to give **23** (3 g, 70%) as a lightly gray solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (br s, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 6.63 (s, 1H), 6.60 (s, 1H), 4.97–4.87 (m, 4H), 4.21 (d, J = 5.3 Hz, 2H), 4.14 (s, 2H), 2.37 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 145.71, 144.95, 142.56, 138.79, 137.98, 129.39, 126.73, 126.63, 123.61, 112.99, 60.37, 59.13, 20.99.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 323.1060, found 323.1028.

N-(4-amino-5-formyl-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide 24

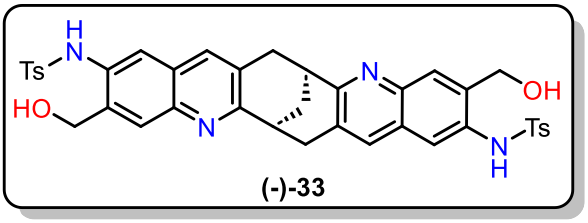


24

In a 250 mL round-bottom flask with a magnetic stir bar, **23** (3 g, 9.3 mmol) and activated MnO_2 (6.5g, 74.4 mmol) were suspended in dry DCM (200 mL) and were sonicated for 10 minutes. The mixture was stirred at room temperature until TLC analysis (1:1 PE:EtOAc + 1% Et_3N) showed full conversion of the starting material (typically overnight, depends on quality of MnO_2). The mixture was filtered through a thick pad of celite, and the pad was washed with EtOAc until TLC analysis showed no more product coming through. The filtrate was concentrated under reduced pressure and purified by column chromatography (gradient 1:1 PE:EtOAc + 1% Et_3N to EtOAc + 1% Et_3N) to give **24** (1.9 g, 65%) as a lightly yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (s, 1H), 9.13 (br s, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.18 (s, 2H), 6.86 (s, 1H), 6.84 (s, 1H), 5.19 (bs, 1H), 4.25 (s, 2H), 2.37 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 192.54, 149.71, 148.73, 142.99, 137.42, 133.86, 129.58, 126.74, 120.41, 115.81, 113.51, 59.09, 21.02.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 321.0904, found 321.0901.

N,N'-((6S,14S)-3,11-bis(hydroxymethyl)-6,7,14,15-tetrahydro-6,14-methanocycloocta[1,2-b:5,6-b']diquinoline-2,10-diyl)bis(4-methylbenzenesulfonamide) (-)-33

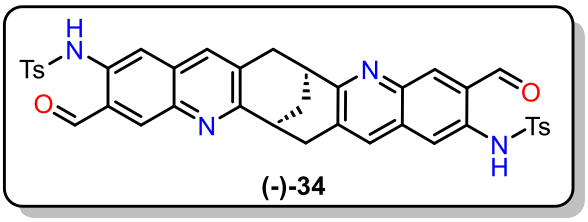


(-)-33

In a 100 mL round-bottom flask with a magnetic stir bar, **(-)-1** (120 mg, 0.8 mmol) and **24** (560 mg, 1.8 mmol) were dissolved in EtOH (10 mL). KOH (112 mg, 2 mmol) was added, and the mixture was vigorously stirred at 50°C overnight. The resulting suspension was diluted with saturated aqueous NH_4Cl (15 mL), H_2O (35 mL) and filtered. The filter cake was washed with H_2O (20 mL), then DCM (20 mL) to remove residual **24**, then the solids were collected and dried under vacuum to give **(-)-33** (520 mg, 92%) as a light gray solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (br s, 2H), 7.84 (s, 2H), 7.75 (s, 2H), 7.54 (d, J = 8.0 Hz, 4H), 7.35 (s, 2H), 7.28 (d, J = 8.0 Hz, 4H), 5.53 (br s, 2H), 4.53–4.40 (m, 4H), 3.59 (br s, 2H), 3.52–3.39 (m, 2H), 3.10 (d, J = 16.7 Hz, 2H), 2.41 (s, 2H), 2.29 (s, 6H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 161.17, 144.57, 143.26, 138.92, 137.10, 134.88, 132.09, 129.70, 128.42, 126.64, 125.89, 125.75, 120.96, 59.79, 40.20, 37.55, 35.63, 20.96.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 721.2149, found 721.2154.

N,N'-((6S,14S)-3,11-diformyl-6,7,14,15-tetrahydro-6,14-methanocycloocta[1,2-b:5,6-b']diquinoline-2,10-diyl)bis(4-methylbenzenesulfonamide) (-)-34

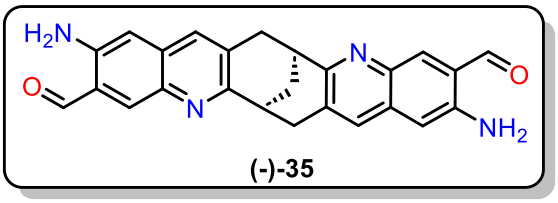


(-)-34

In a 100 mL round-bottom flask with a magnetic stir bar, **(-)-33** (500 mg, 0.7 mmol) and activated MnO_2 (1.8 g, 21 mmol) were suspended in dry EtOAc and were sonicated for 10 minutes. The mixture was stirred at room temperature until TLC analysis (30:1 DCM:MeOH + 1% NH_4OH) showed full conversion of the starting material (typically overnight, depends on quality of MnO_2). The mixture was filtered through a thick pad of celite, and the pad was washed with EtOAc/MeOH until TLC analysis showed no more product coming through. The filtrate was concentrated under reduced pressure and purified by column chromatography (30:1 DCM:MeOH + 1% NH_4OH) to give **(-)-34** (405 mg, 81%) as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 2H), 9.97 (s, 2H), 8.27 (s, 2H), 7.76 (s, 2H), 7.69 (d, J = 8.0 Hz, 4H), 7.65 (s, 2H), 7.13 (d, J = 8.0 Hz, 4H), 3.76 (br s, 2H), 3.57–3.48 (m, 2H), 3.32 (d, J = 17.2 Hz, 2H), 2.53 (s, 2H), 2.28 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.98, 161.90, 144.10, 142.74, 139.88, 136.21, 135.33, 134.71, 132.62, 131.27, 129.70, 127.19, 124.88, 114.52, 38.30, 36.03, 29.71, 21.49.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 717.1836, found 717.1839.

(6S,14S)-2,10-diamino-6,7,14,15-tetrahydro-6,14-methanocycloocta[1,2-b:5,6-b']diquinoline-3,11-dicarbaldehyde (-)-35

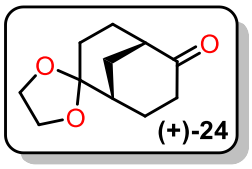


(-)-35

In a 10 mL round-bottom flask with a magnetic stir bar cooled in an ice bath, **(-)-34** (300 mg, 0.4 mmol) was dissolved in concentrated H_2SO_4 (3 mL). The mixture was stirred at 0°C until TLC analysis (30:1 DCM:MeOH + 1% NH_4OH) showed full conversion of the starting material (typically 2h). The reaction mixture was poured onto ice and neutralized with 25% aqueous NH_4OH until pH 8-9 (visually indicated by color change from bright red to yellow). The resulting suspension was extracted with 3:1 $CHCl_3$:iPrOH (5x25 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (30:1 DCM:MeOH + 1% NH_4OH) provided **(-)-35** (62 mg, 36%) as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 2H), 8.25 (s, 2H), 7.43 (s, 2H), 6.65 (s, 2H), 5.77 (br s, 4H), 3.71 (br s, 2H), 3.47 (dd, J = 17.3, 5.4 Hz, 2H), 3.29 (d, J = 17.3 Hz, 2H), 2.51 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.81, 159.06, 145.30, 140.31, 139.26, 133.42, 132.68, 132.09, 124.13, 108.07, 38.59, 36.15, 29.85.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 409.1659, found 409.1657.

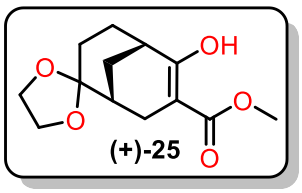
(1S,5S)-spiro[bicyclo[3.3.1]nonane-2,2'-[1,3]dioxolan]-6-one (+)-24



Compound **(+)-24** was prepared via modified literature procedure [57]. To a 50 mL round-bottom flask equipped with a magnetic stir bar was added **(+)-1** (2011 mg, 10.2 mmol), ethylene glycol (2.9 mL, 41 mmol), p-toluenesulfonic acid monohydrate (75 mg, 0.3 mmol) and benzene (35 mL). The flask was equipped with a Dean-Stark apparatus, a reflux condenser and a $CaCl_2$ drying tube, and the mixture was heated under reflux until TLC analysis (3:1 PE:EtOAc as eluent, $KMnO_4$ stain) showed full conversion of starting material (~3.5 hours). The benzene was removed under reduced pressure, and the crude mixture was dissolved in acetone (20 mL). The mixture was stirred at room temperature until TLC analysis showed that most of the di-acetal was converted to the mono-acetal (~2 hours). The mixture was quenched with 1 mL of Et_3N, concentrated under reduced pressure and purified by column chromatography (gradient elution, 5:1 to 3:1 PE:EtOAc) to afford **(+)-24** (1856 mg, 72%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 – 3.90 (m, 4H), 2.51-2.32 (m, 3H), 2.14 (d, J = 13.4 Hz, 1H), 2.07-1.92 (m, 4H), 1.88-1.80 (m, 2H), 1.75-1.63 (m, 2H). ^{1}H NMR is in accordance with literature [93].

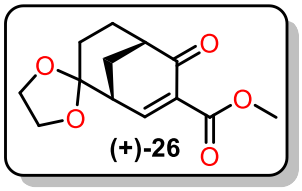
methyl (1R,5S)-6-hydroxyspiro[bicyclo[3.3.1]nonane-2,2'-[1,3]dioxolan]-6-ene-7-carboxylate (+)-25



In a 50 mL round-bottom flask, NaH (60% suspension in mineral oil, 732 mg, 18.4 mmol) was suspended in dry THF (15 mL). The suspension was cooled to 0°C in an ice bath, and to it was added dropwise a solution of **(+)-24** (900 mg, 4.6 mmol) in dry dimethyl carbonate (5 mL). The flask was sealed with a septum and an argon-filled balloon and left to stir at room temperature overnight. The suspension was then slowly quenched with saturated aqueous NH_4Cl (20 mL) and diluted with H_2O (20 mL) and EtOAc (40 mL). The layers were separated, and the aqueous phase was additionally extracted with EtOAc (2x30 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated to provide a mixture of **(+)-25** and residual mineral oil, which can be used in the next step directly (yielding better overall yield of **(+)-26**) or can be purified by column chromatography (5:1 PE:EtOAc) to provide **(+)-24** (1050 mg, 90%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.00 (s, 1H), 4.00 – 3.89 (m, 4H), 3.75 (s, 3H), 2.47 – 2.40 (m, 1H), 2.38-2.28 (m, 1H), 2.05 – 1.95 (m, 2H), 1.91 – 1.51 (m, 6H). ^{1}H NMR is in accordance with literature [93].

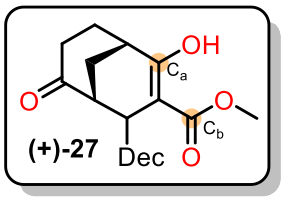
methyl (1R,5S)-6-oxospiro[bicyclo[3.3.1]nonane-2,2'-[1,3]dioxolan]-7-ene-7-carboxylate (+)-26



In a 50 mL round-bottom flask, **(+)-25** (1050 mg, 4.1mmol) was dissolved in dry DCM (25 mL). Pyridine (1 mL, 12.3 mmol) was added, and the solution was cooled to 0°C in an ice bath. PhSeCl (2355 mg, 12.3 mmol) was added in portions over 30 minutes, and the mixture was then sealed and stirred overnight. Afterwards, 1.2M HCl (25 mL) was added, and the mixture was vigorously stirred for 10 minutes. The layers were separated, and the organic layer was dried with anhydrous Na_2SO_4, concentrated under reduced pressure, and purified using column chromatography (gradient, DCM to 1:1 PE:EtOAc, should be performed quickly due to poor stability of product on silica) to provide **(+)-26** (830 mg, 80%) as a yellow waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 6.9, 1.7 Hz, 1H), 4.09 – 3.91 (m, 4H), 3.81 (s, 3H), 2.76 – 2.70 (m, 1H), 2.62 (s, 1H), 2.30 – 2.22 (m, 1H), 2.26 – 2.13 (m, 1H), 1.93 – 1.78 (m, 3H), 1.65 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 196.98, 164.71, 157.53, 135.41, 107.87, 64.91, 64.64, 52.26, 42.31, 40.87, 31.26, 28.72, 25.97.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 253.1071, found 253.1069.

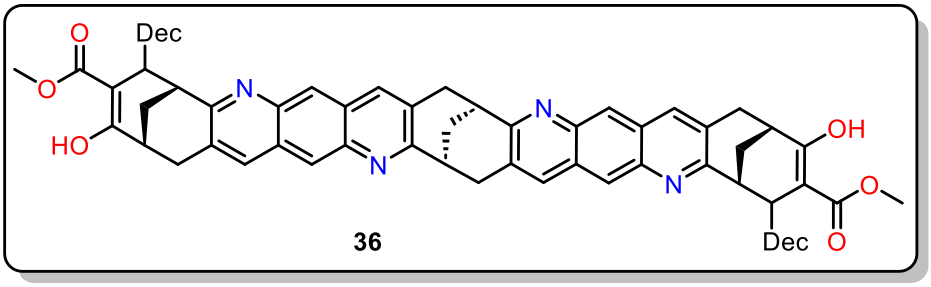
methyl (1S,5R)-4-decyl-2-hydroxy-6-oxobicyclo[3.3.1]non-2-ene-3-carboxylate (+)-27



Preparation of DecMgBr: Mg (61 mg, 2.5 mmol) and a catalytic amount of I_2 were added to a screw-cap vial and were heated carefully with a heat gun under Ar. Afterwards, dry THF (3 mL) was added, and the vial was sealed and heated under reflux until the orange colour of iodine disappeared. The mixture was then cooled to room temperature, and decyl bromide (526 mg, 2.4 mmol) in THF (3 mL) was added dropwise. The mixture was then stirred until all of the Mg was consumed (typically no external heating was required).
Conjugate addition: In a Schlenk tube equipped with a magnetic stir bar, CuCN (224 mg, 2.5 mmol) was suspended in dry THF (5 mL). The reaction mixture was cooled to -30°C, and the previously prepared DecMgBr solution was added dropwise. The reaction mixture was then cooled to -78°C, and a solution of **(+)-26** (150 mg, 0.6 mmol) in dry THF (5 mL) was added dropwise over 30 minutes. The mixture was stirred for 30 more minutes at -78°C and then allowed to warm up to room temperature overnight. The mixture was then diluted with 1.2M HCl (40 mL) and EtOAc (40 mL) and stirred for 10 minutes. The layers were separated, and the aqueous phase was further extracted with EtOAc (2x30 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure.
Acetal hydrolysis: in a 100 mL round-bottom flask, the crude oil was dissolved in THF (30 mL) and 6M HCl (30 mL) was added dropwise. The mixture was stirred overnight. The mixture was neutralized with $NaHCO_3$, the solvent was removed under reduced pressure, and the crude mixture was diluted with H_2O (30 mL) and DCM (30 mL). The layers were separated, and the aqueous phase was further extracted with DCM (2x20 mL). The combined organic phases were dried with anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (20:1 PE:EtOAc) to afford **(+)-27** (141 mg, 68%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.36 (s, 1H), 3.77 (s, 3H), 2.63 (br s, 1H), 2.58 (br s, 1H), 2.35 (m, 3H), 2.19 (m, 2H), 1.94 (m, 1H), 1.85 – 1.75 (m, 1H), 1.56 (m, 1H), 1.42 - 1.19 (m, 17H), 0.88 (t, J = 6.6 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 213.50, 172.75, 101.82, 51.79, 47.36, 36.47, 36.44, 34.57, 33.79, 32.09, 29.84, 29.80, 29.69, 29.54, 29.50, 28.98, 28.24, 25.79, 22.88, 14.32.
Note: both C_a and C_b are attributed to the same ^{13}C peak at 172.75. The presence of both carbons was confirmed by HMBC experiments, where interactions with both enolic OH and ester methyl protons are visible.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 351.2530, found 351.2525.

Compound 36

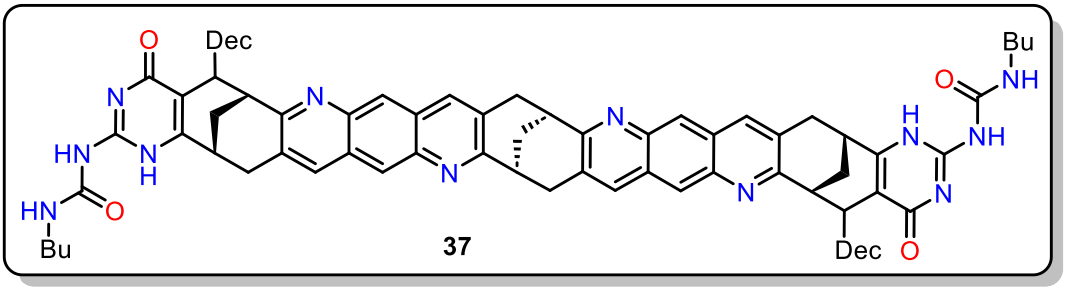


36

In a screw-cap vial, **(+)-27** (71 mg, 0.2 mmol) and **(-)-35** (20.4 mg, 0.05 mmol) were dissolved in 2 mL of dry MeOH. To this solution was added dropwise a freshly made solution of NaOMe (50 mg of Na in 2 mL of dry MeOH). The mixture was sealed and stirred overnight. The resulting suspension was diluted with saturated aqueous NH_4Cl (20 mL) and extracted with DCM (3x15 mL). The combined organic phases were dried with anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography ($CHCl_3$ to 100:1 $CHCl_3$:MeOH) to afford **36** (23 mg, 43%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 2H), 8.43 (s, 2H), 8.35 (s, 2H), 7.98 (s, 2H), 7.91 (s, 2H), 3.88 (s, 2H), 3.60 (s, 6H), 3.52 (s, 2H), 3.33 (d, J = 14.3 Hz, 4H), 3.28 (d, J = 6.1 Hz, 2H), 2.86 (s, 2H), 2.70-2.62 (m, 4H), 2.36 (m, 2H), 1.97 (s, 2H), 1.73-1.20 (m, 38H), 0.87 (t, J = 6.5 Hz, 6H).
13C NMR (101 MHz, CDCl3) δ 172.94, 172.78, 164.41, 163.33, 143.58, 143.55, 136.01, 135.59, 128.62, 128.43, 128.11, 127.86, 125.62, 125.20, 101.17, 51.36, 41.65, 39.42, 38.55, 36.94, 34.74, 34.58, 33.35, 31.97, 29.74, 29.72, 29.62, 29.43, 29.05, 28.87, 28.18, 23.57, 22.73, 14.17.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 1037.6151, found 1037.6145.

Compound 37



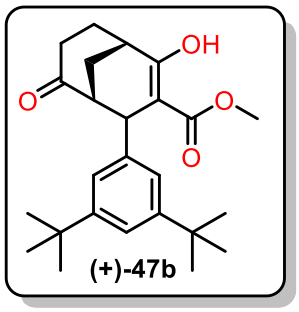
37

In a screw-cap vial, **36** (23 mg, 0.02 mmol), guanidinium chloride (14 mg, 0.15 mmol) and KOtBu (14 mg, 0.12 mmol) were dissolved in EtOH and the mixture was heated at 100°C until TLC analysis (10:1 DCM:MeOH + 1% NH_4OH, TLC plate pre-deactivated by eluting before spotting) showed full

conversion (36 h). The reaction mixture was diluted with H_2O (20 mL) and placed in the refrigerator for 2 hours to allow for agglomeration of the precipitate. The cold mixture was then filtered and washed with H_2O. The product was collected by dissolving it in 1:1 DCM:MeOH (20 mL), concentrated under reduced pressure and dried under vacuum overnight. The obtained isocytosine was immediately subjected to the next reaction – it was suspended in dry THF (3 mL) in a screw-cap vial. BuNCO (17 ul, 0.15 mmol) and Et3N (41 ul, 0.3 mmol) were added, and the suspension was heated to 80°C overnight. The solution was then diluted with MeOH (10 mL), stirred for 30 minutes and concentrated. The residue was dissolved in a minimal amount of $CHCl_3$, precipitated out with MeOH, filtered, washed with MeOH, dried and collected with $CHCl_3$. Concentration under reduced pressure provided **37** (18.5 mg, 67%) as a lightly brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.86 (s, 1H), 11.88 (s, 1H), 9.75 (s, 1H), 8.37 (s, 1H), 8.25 (s, 1H), 7.91 (s, 1H), 7.85 (s, 1H). Analysis of the aliphatic 1H region, as well as the 13C spectra, could not be performed due to low solubility and aggregation.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 1253.7750, found 1253.7744.

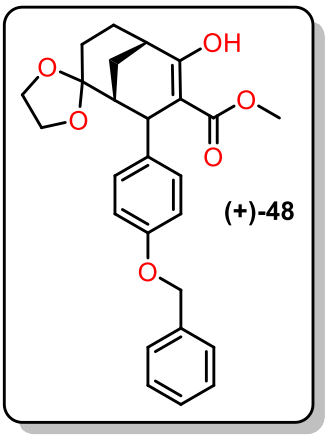
methyl (1S,5R)-4-(3,5-di-tert-butylphenyl)-2-hydroxy-6-oxobicyclo[3.3.1]non-2-ene-3-carboxylate (+)-47b



To a 25 mL round-bottom flask equipped with a stir bar were sequentially added palladium (II) trifluoroacetate (8 mg, 0.024 mmol), 2,2'-bipyridine (4.5 mg, 0.029 mmol), silver (I) trifluoromethanesulfonate (15 mg, 0.058 mmol), methanol (9 mL) and H_2O (0.9 mL). The mixture was stirred for 10 minutes before adding **(+)-26** (60 mg, 0.24 mmol) and 3,5-di-*tert*-butylphenyl)boronic acid (112 mg, 0.48 mmol). The mixture was stirred for 30 minutes at room temperature and then heated at 60°C overnight. The resulting suspension was diluted with DCM (25 mL) and H_2O (25 mL). The suspension was filtered to remove palladium precipitate, the layers were separated, and the aqueous phase was additionally extracted with DCM (2x25 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification with column chromatography (DCM as eluent) afforded the mixture of **(+)-47** and deprotected **(+)-47b** (95 mg, 90%), which was immediately subjected to hydrolysis – it was dissolved in THF (15 mL), and 6M HCl (15 mL) was added dropwise. The solution was stirred overnight. Afterwards, it was neutralized with aqueous $NaHCO_3$ and extracted with EtOAc (3x15 mL). The combined organic phases were dried with anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (DCM) to afford **(+)-47b** (80 mg, 85% total yield) as an oily semi-solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.63 (s, 1H), 7.24 (t, J = 1.8 Hz, 1H), 6.97 (d, J = 1.8 Hz, 2H), 3.84 (s, 1H), 3.52 (s, 3H), 2.79 (br s, 1H), 2.62 (br s, 1H), 2.51 – 2.43 (m, 2H), 2.29 (s, 1H), 2.11 (d, J = 13.5 Hz, 1H), 2.07 – 1.93 (m, 1H), 1.70-1.65 (m, 1H), 1.30 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 212.88, 173.88, 172.45, 150.52, 142.60, 121.81, 120.22, 98.97, 52.84, 51.67, 42.46, 36.29, 34.85, 33.59, 31.55, 28.67, 24.88.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 399.2530, found 399.2541.

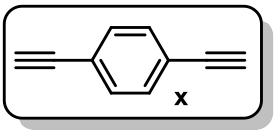
methyl (1R,5S)-8-(4-(benzyloxy)phenyl)-6-hydroxyspiro[bicyclo[3.3.1]nonane-2,2'-[1,3]dioxolan]-6-ene-7-carboxylate (+)-48



To a 25 mL round-bottom flask equipped with a stir bar were sequentially added palladium (II) trifluoroacetate (8 mg, 0.024 mmol), 2,2'-bipyridine (4.5 mg, 0.029 mmol), silver (I) trifluoromethanesulfonate (15 mg, 0.058 mmol) and N,N-dimethylacetamide (10 mL) (Note: unlike with other tested substrates, MeOH/H_2O led to poor yields due to poor solubility of the boronic acid). The mixture was stirred for 10 minutes before adding **(+)-26** (60 mg, 0.24 mmol) and (4-phenoxyphenyl)boronic acid (103 mg, 0.48 mmol). The mixture was stirred for 30 minutes at room temperature and then heated at 60°C overnight. The resulting suspension was diluted with H_2O (30 mL) and filtered. The filter cake was rinsed with H_2O and then collected with DCM. The solvent was evaporated under reduced pressure. Purification with column chromatography (DCM as eluent) afforded **(+)-48** (45 mg, 43%) as a slightly yellow crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.47 (s, 1H), 7.52 – 7.30 (m, 5H), 7.08 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 5.02 (s, 2H), 4.15 – 3.87 (m, 5H), 3.51 (s, 3H), 2.56 – 2.50 (m, 1H), 1.97 – 1.59 (m, 7H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.70, 172.74, 156.95, 139.04, 137.17, 128.58, 128.23, 127.96, 127.60, 114.42, 110.10, 99.39, 70.04, 64.41, 64.39, 51.45, 45.53, 39.08, 33.79, 29.02, 27.53, 23.30.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 437.1959, found 437.1935.

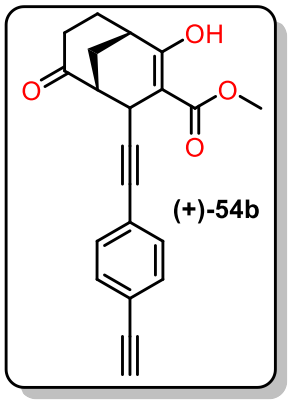
1,4-diethynylbenzene pre-54



Compound **pre-54** was prepared via modified literature procedure [89]. In a 50 mL round-bottom flask equipped with a large stir bar, 1,4-dibromobenzene (1.2 g, 5 mmol) and trimethylsilylacetylene (1.2g, 12.2 mmol) were dissolved in dry Et_3N (20 mL). The solution was degassed by sparging with Ar for 30 minutes. Afterwards, $Pd(dppf)_2Cl_2$ (92 mg, 0.125 mmol) and CuI (14 mg, 0.075 mmol) were added. The suspension was vigorously stirred at 60°C overnight. Afterwards, the solvent was removed under reduced pressure, the solids were loaded onto a plug of silica gel and eluted with petroleum ether to provide the 1,4-bis((trimethylsilyl)ethynyl)benzene (1350 mg, 98%) which was immediately subjected to deprotection – it was dissolved in MeOH (100 mL) and K_2CO_3 (700 mg, 5.05 mmol) was added. The suspension was stirred overnight, and was then diluted with H_2O (200 mL), filtered, and collected from the filter cake with DCM. Concentration under reduced pressure provided **pre-54** (480 mg, 75%) as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 4H), 3.17 (s, 2H). ^{1}H NMR is in accordance with literature [94].

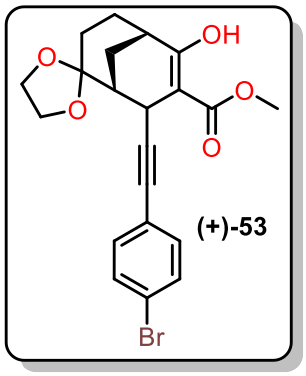
methyl (1S,5R)-4-((4-ethynylphenyl)ethynyl)-2-hydroxy-6-oxobicyclo[3.3.1]non-2-ene-3-carboxylate (+)-54b



In a screw-cap vial equipped with a stir bar, **pre-54** (200 mg, 1.58 mmol), zinc trifluoromethanesulfonate (259 mg, 0.71 mmol) and Et_3N (160 mg, 1.58 mmol) were suspended in dry CH_3CN. The suspension was stirred for 30 minutes, then **(+)-26** (100 mg, 0.40 mmol) was added. The vial was sealed and stirred at room temperature overnight. The resulting suspension was diluted with saturated aqueous NH_4Cl (15 mL) and DCM (15 mL). The layers were separated, and the aqueous phase was further extracted with DCM (2x15 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (5:1 PE:EtOAc) provided **(+)-54** (120 mg, 80%), which was immediately subjected to deprotection: it was dissolved in THF (10 mL) and 6M HCl (10 mL) was added dropwise. The solution was stirred overnight. Afterwards, it was neutralized with aqueous $NaHCO_3$ and extracted with DCM (3x15 mL). The combined organic phases were dried with anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (5:1 PE:EtOAc) to afford **(+)-54b** (97 mg, 73% total yield) as a yellow glassy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.39 (s, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 3.84 (s, 3H), 3.70 (s, 1H), 3.14 (s, 1H), 2.92 (s, 1H), 2.75 (s, 1H), 2.62 – 2.44 (m, 2H), 2.38 – 2.18 (m, 2H), 2.07 – 1.95 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 211.15, 173.40, 171.76, 131.95, 131.55, 123.80, 121.61, 98.07, 92.27, 83.22, 80.72, 78.75, 52.04, 49.63, 36.36, 33.39, 30.05, 28.01, 26.81.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 335.1278, found 335.1227.

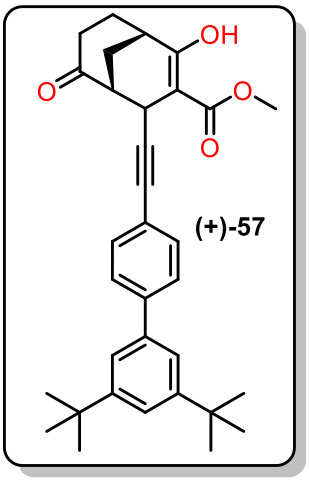
methyl (1R,5S)-8-((4-bromophenyl)ethynyl)-6-hydroxyspiro[bicyclo[3.3.1]nonane-2,2'-[1,3]dioxolan]-6-ene-7-carboxylate (+)-53



In a screw-cap vial equipped with a stir bar, 1-bromo-4-ethynylbenzene (54 mg, 0.3 mmol), zinc trifluoromethanesulfonate (73 mg, 0.21 mmol) and Et_3N (36 mg, 0.36 mmol) were suspended in dry toluene. The suspension was stirred at 60°C for 30 minutes and cooled to room temperature. **(+)-26** (30 mg, 0.21 mmol) was added. The vial was sealed and heated at 60°C overnight. The resulting suspension was diluted with saturated aqueous NH_4Cl (15 mL) and DCM (15 mL). The layers were separated, and the aqueous phase was further extracted with DCM (2x15 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (5:1 PE:EtOAc) provided **(+)-54** (43 mg, 84%) as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (s, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 4.01 – 3.95 (m, 4H), 3.82 (s, 3H), 3.79 (d, J = 1.0 Hz, 1H), 2.50 (p, J = 3.1 Hz, 1H), 2.24 – 2.15 (m, 2H), 1.95 (dt, J = 13.5, 3.4 Hz, 1H), 1.90 – 1.74 (m, 2H), 1.70 – 1.54 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.05, 172.10, 133.06, 131.38, 122.84, 121.71, 109.33, 98.16, 94.00, 78.85, 64.64, 64.57, 51.69, 43.09, 33.65, 29.19, 27.72, 27.17, 25.76.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 433.0645, found 433.0650.

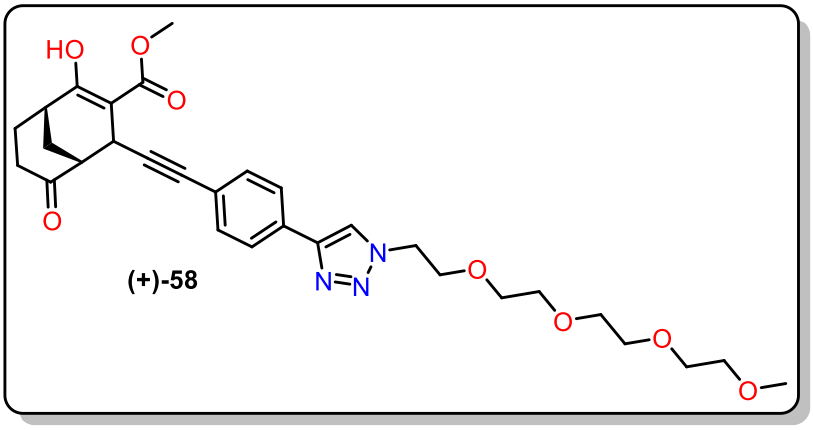
methyl (1S,5R)-4-((3',5'-di-tert-butyl-[1,1'-biphenyl]-4-yl)ethynyl)-2-hydroxy-6-oxobicyclo[3.3.1]non-2-ene-3-carboxylate (+)-57



In a screw-cap vial equipped with a stir bar, **(+)-53** (38.3 mg, 0.09 mmol), 3,5-di-*tert*-butylphenyl)boronic acid (31 mg, 0.14 mmol) and K_2CO_3 (36.6 mg, 0.27 mmol) were dissolved in a mixture of EtOH, H_2O and toluene (1:2:3, 6 mL). The solution was degassed by sparging with argon through a needle for 30 min. Then, XPhos Pd G2 (3.5 mg, 4.5 µmol) was added, the vial was sealed, and the mixture was heated at 80°C overnight. The mixture was diluted with H_2O (15 mL) and DCM (15 mL). The layers were separated, and the aqueous phase was further extracted with DCM (2x15 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was subjected to deprotection: it was dissolved in THF (10 mL) and 6M HCl (10 mL) was added dropwise. The solution was stirred overnight. Afterwards, it was neutralized with aqueous $NaHCO_3$ and extracted with DCM (3x15 mL). The combined organic phases were dried with anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (5:1 PE:EtOAc) to afford **(+)-57** (33 mg, 75% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.40 (s, 1H), 7.55 – 7.38 (m, 7H), 3.85 (s, 3H), 3.73 (s, 1H), 2.96 (s, 1H), 2.77 (s, 1H), 2.65 – 2.58 (m, 1H), 2.53-2.43 (m, 1H), 2.39 – 2.30 (m, 1H), 2.28 – 2.21 (m, 1H), 2.07 – 1.97 (m, 2H), 1.38 (s, 18H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 211.27, 173.26, 171.87, 151.28, 142.02, 139.83, 131.94, 127.20, 121.89, 121.81, 121.49, 98.36, 90.63, 81.19, 51.98, 36.38, 34.99, 33.45, 31.52, 30.11, 28.06, 26.84, 24.92.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 499.2843, found 499.2868.

Methyl (1S,5R)-4-((4-(1-(2,5,8,11-tetraoxatridecan-13-yl)-1H-1,2,3-triazol-4-yl)phenyl)ethynyl)-2-hydroxy-6-oxobicyclo[3.3.1]non-2-ene-3-carboxylate (+)-58

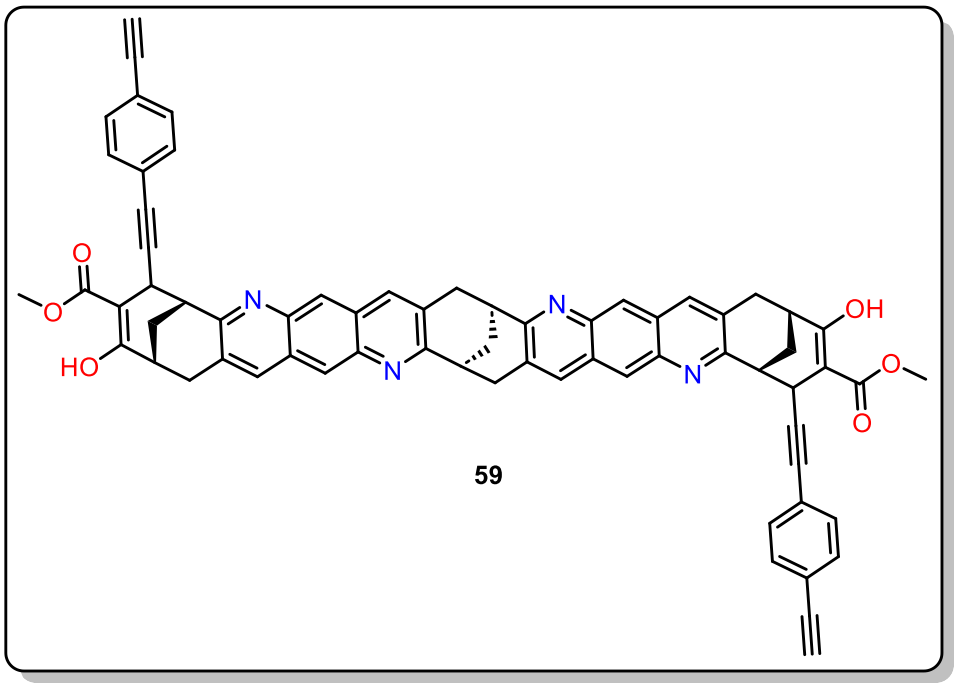


In a screw-cap vial, **(+)-54b** (33.4 mg, 0.1 mmol) and **42** (46.6 mg, 0.2 mmol) were dissolved in 3 mL of dry THF. In a separate vial, $CuSO_4 \cdot 5H_2O$ (2.5 mg, 0.01 mmol) and Na ascorbate (4.0 mg, 0.02 mmol) were dissolved in 1 mL of water. After stirring the aqueous suspension for 10 minutes, the now orange suspension was transferred to the primary vial. The resulting mixture was sealed and stirred at 50°C overnight. The resulting solution was diluted with aqueous NH_4OH (5 mL) and water (10 mL), and then extracted with 3:1 $CHCl_3$:iPrOH (3x15 mL). The organic phases were dried with

anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (30:1 $CHCl_3$:MeOH + 1% Et3N) to afford **(+)-58** (36 mg, 63%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.39 (s, 1H), 8.01 (s, 1H), 7.76 (d, J = 7.9 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 4.58 (t, J = 4.9 Hz, 2H), 3.89 (t, J = 4.9 Hz, 2H), 3.83 (s, 3H), 3.71 – 3.56 (m, 8H), 3.51 – 3.47 (m, 2H), 3.37 (d, J = 4.3 Hz, 2H), 3.32 (s, 3H), 2.92 (s, 1H), 2.74 (s, 1H), 2.62 – 2.55 (m, 1H), 2.51 – 2.43 (m, 1H), 2.36 – 2.17 (m, 2H), 2.08 – 1.94 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 211.26, 173.30, 171.81, 147.01, 132.11, 130.40, 125.41, 122.77, 121.32, 98.23, 90.87, 81.08, 71.88, 70.69, 70.63, 70.54, 70.47, 70.04, 69.48, 59.01, 52.02, 50.41, 49.73, 36.36, 33.40, 30.05, 28.01, 26.80.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 568.2653, found 568.2659.

Compound 59

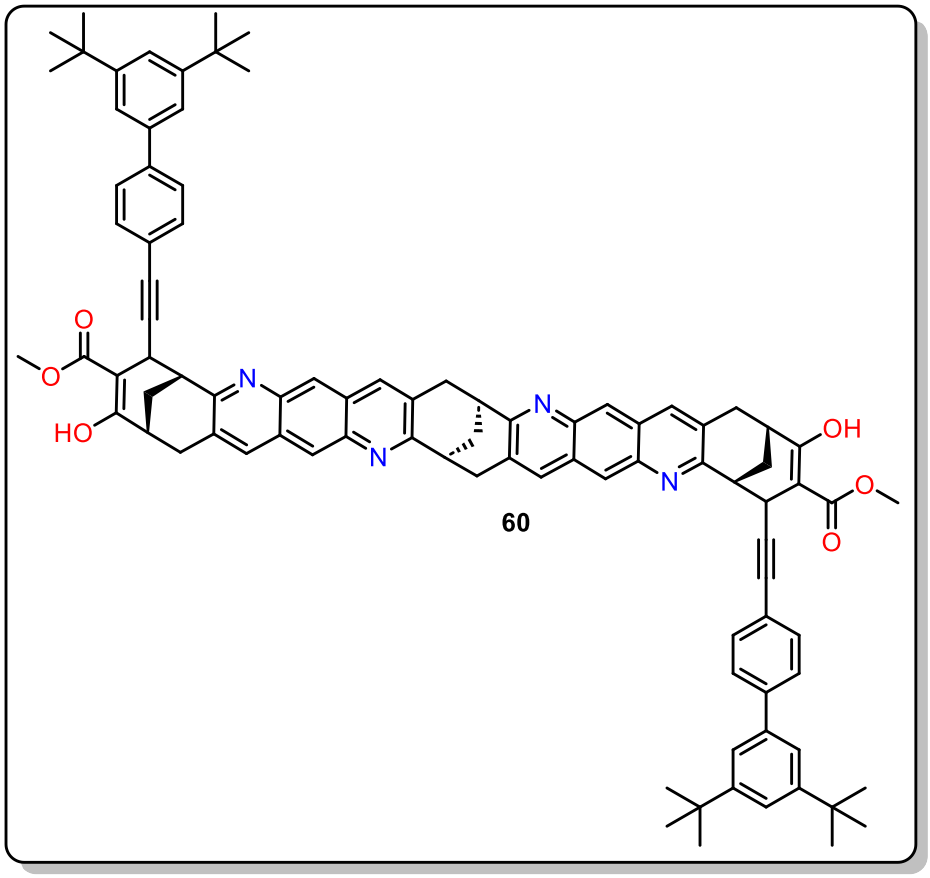


59

In a screw-cap vial, **(+)-54b** (67 mg, 0.2 mmol) and **(-)-35** (20.4 mg, 0.05 mmol) were dissolved in 2 mL of dry MeOH. To this solution was added dropwise a freshly made solution of NaOMe (50 mg of Na in 2 mL of dry MeOH). The mixture was sealed and stirred overnight. The resulting suspension was diluted with saturated aqueous NH_4Cl (20 mL) and extracted with DCM (3x15 mL). The combined organic phases were dried with anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography ($CHCl_3$ to 100:1 $CHCl_3$:MeOH) to afford **59** (32 mg, 65%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.32 (s, 2H), 8.47 (s, 2H), 8.36 (s, 2H), 8.04 (s, 2H), 7.94 (s, 2H), 7.41 (d, J = 8.1 Hz, 4H), 7.36 (d, J = 8.3 Hz, 4H), 3.95 (d, J = 2.2 Hz, 2H), 3.90 (d, J = 4.5 Hz, 2H), 3.72-3.60 (m, 10H), 3.50 (d, J = 16.8 Hz, 2H), 3.42 – 3.25 (m, 4H), 3.14 (s, 2H), 2.97 (s, 2H), 2.77 (d, J = 13.0 Hz, 2H), 2.65 (s, 2H), 2.14 (d, J = 12.8 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.66, 172.08, 163.65, 161.37, 143.72, 143.43, 136.13, 136.05, 131.94, 131.59, 128.68, 128.44, 128.15, 128.07, 125.71, 125.42, 124.28, 121.37, 97.58, 93.85, 83.34, 80.78, 78.60, 51.83, 42.71, 38.63, 36.93, 34.98, 34.14, 33.20, 29.39, 25.23.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 1005.3647, found 1005.3669.

Compound 60



60

In a screw-cap vial, **(+)-57** (94 mg, 0.2 mmol) and **(-)-35** (20.4 mg, 0.05 mmol) were dissolved in 2 mL of dry toluene. To this solution was added dropwise a freshly made solution of NaOMe (50 mg of Na in 2 mL of dry MeOH). The mixture was sealed and stirred at 40°C overnight. The resulting suspension was diluted with saturated aqueous NH_4Cl (20 mL) and extracted with DCM (3x15 mL). The combined organic phases were dried with anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography ($CHCl_3$) to afford **60** (35 mg, 53%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.34 (s, 2H), 8.48 (s, 2H), 8.38 (s, 2H), 8.05 (s, 2H), 7.95 (s, 2H), 7.56 – 7.36 (m, 14H), 3.97 (d, J = 2.2 Hz, 2H), 3.91 (s, 2H), 3.76 – 3.58 (m, 10H), 3.52 (d, J = 16.5 Hz, 2H), 3.42 – 3.26 (m, 4H), 2.99 (s, 2H), 2.82 (d, J = 13.1 Hz, 2H), 2.67 (s, 2H), 2.16 (d, J = 12.9 Hz, 2H), 1.37 (s, 36H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.54, 172.21, 163.62, 161.56, 151.25, 143.47, 141.78, 139.93, 136.02, 131.99, 128.65, 128.52, 128.18, 128.06, 127.20, 125.74, 122.36, 121.76, 121.52, 97.85, 92.17, 81.17, 51.82, 42.86, 38.58, 36.92, 35.03, 35.00, 34.19, 33.24, 31.53, 29.73, 25.24.
HRMS-ESI$^+$: m/z $[M+H]^+$ calcd. for 1333.6777, found 1333.6762.

CONCLUSIONS

1. A practical method for the preparation and separation of diastereomeric Meerwein's ester derivatives, as well as the previously inaccessible enantiomerically pure (-)-(1R,5R)-bicyclo[3.3.1]nonane-2,6-dione **(-)-1** in decigram scale (up to 0.5g) was developed.

2. The synthesis of C_2-symmetric protected Friedländer synthon, N-(4-amino-5-formyl-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide **2**, was optimized to allow for preparation in the decagram scale with improved overall yields and minimal need for chromatographic purification.

3. A methodology for preparation of various asymmetrically functionalized derivatives of bicyclo[3.3.1]nonane-2,6-dione was developed.

4. A proof-of-concept for large dynamic hydrogen-bonded cavitands featuring both positive and negative surface curvature, based on rigid carcasses formed through condensation of both enantiomers of bicyclo[3.3.1]nonane-2,6-dione with aromatic linkers, was designed, synthesized and analyzed through NMR methods. The poor solubility characteristics of first-generation cavitand **37** prompted the need for further iterations.

5. Novel methods for functionalization of methyl (1R,5S)-6-oxospiro[bicyclo[3.3.1]nonane-2,2'-[1,3]dioxolan]-7-ene-7-carboxylate **(+)-26** through 1,4-addition of arylboronic acids and terminal alkynes were developed. Multiple 'universal linker' candidates, featuring relatively inert or protected secondary functional groups that allow for diverse late-stage functionalization, were designed, prepared, and their reactivities were tested.

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SUMMARY

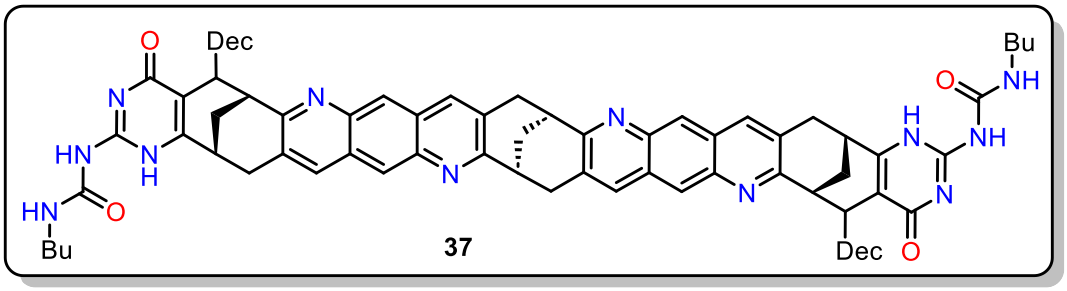
VILNIUS UNIVERSITY
FACULTY OF CHEMISTRY AND GEOSCIENCES

NOJUS RADZEVIČIUS

Chirality-assisted synthesis of supramolecular receptors

The emerging field of supramolecular chemistry is centered around the design and creation of complex dynamic multi-molecular structures, drawing inspiration from various biochemical systems and processes. One group of supramolecular systems are the cavitands – molecules or multi-molecular scaffolds featuring a discrete internal cavity that is capable of forming host-guest complexes with smaller molecular guests. Many potential and practically applied applications for such systems have been found in chemistry, biochemistry, materials science and medicine. However, currently synthetically available cavitands have many problems, including difficult preparation, limited selection of cavity size and geometry, small functionalization capability and high symmetry.

This thesis describes a novel system for preparation of geometrically diverse cavitands from a variety of monomeric building blocks, and presents a proof-of-concept synthesis of a supramolecular tetrameric "Swiss cross" shaped cavitand. The system is based on the use of the bicyclo[3.3.1]nonane structure, which, when fused with aromatic linkers, allows for semi-rigid, 90°-angled chiral carcasses to be obtained. When both enantiomers of the chiral bicyclononane[3.3.1]-2,6-dione are used, positive and negative curvature can be incorporated, allowing for control of the spatial structure of the resulting carcasses. Appending 2-ureido-4-pyrimidinone motifs to the termini of the carcasses allows for self-complimentary hydrogen bonding, resulting in the formation of cyclic oligomeric structures in non-polar solvents.



37

In this thesis, a novel method for the preparation of both pure enantiomers of bicyclononane[3.3.1]-2,6-dione in decigram scale is presented. The synthesis of C_2-symmetric Friedländer synthon N-(4-amino-5-formyl-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide has been optimized to allow for operationally simple and high-yielding decagram-scale synthesis. These building blocks were used to prepare the "Swiss cross" shaped cavitand monomer **37**. Aggregation into tetrameric structures in $CDCl_3$ was confirmed by NMR methods, however, the poor solubility of the resulting structure prevented more in-depth studies and highlighted the need for modified iterations featuring increased solubility in organic solvents of various polarities. The final part of the thesis described the design and development of bicyclononane[3.3.1]-2,6-dione derivatives featuring various functional groups that may serve as universal linkers, allowing for easy late-stage modification with various structures that would allow for fine-tuning of solubility characteristics.

SANTRAUKA

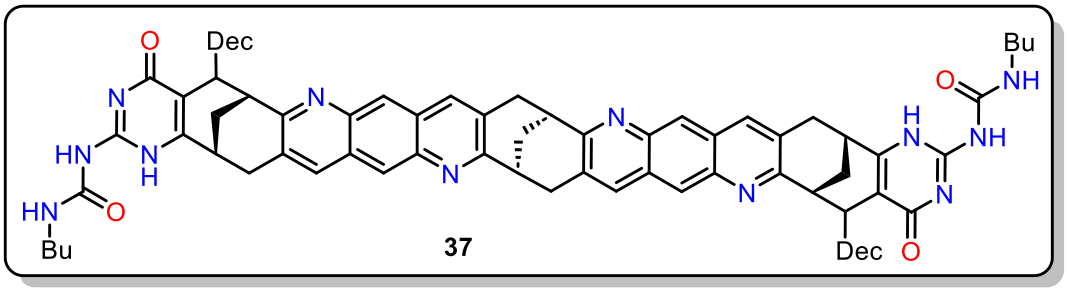
VILNIAUS UNIVERSITETAS
CHEMIJOS IR GEOMOKSLŲ FAKULTETAS

NOJUS RADZEVIČIUS

Chirališkumu programuojama supramolekulinių receptorių sintezė

Sparčiai augančioje supramolekulinės chemijos srityje siekiama kurti sudėtingas, dinamiškas daugiakomponentines struktūras, įkvėptas įvairių biocheminių sistemų ir procesų. Viena iš supramolekulinių sistemų grupių yra kavitandai – molekulės arba daugiakomponentiniai karkasai, turintys apibrėžtų matmenų vidinę ertmę, galinčią formuoti šeimininko-svečio kompleksus su mažesnėmis molekulėmis. Tokios sistemos turi daug potencialių bei praktinių taikymų chemijoje, biochemijoje, medžiagų moksle ir medicinoje. Vis dėlto šiuo metu sintetiškai prieinami kavitandai turi daugeliu problemų, tokių kaip sudėtinga sintezė, ribota ertmės dydžių ir geometrinių formų įvairovė, nedidelės funkcionalizavimo galimybės ir didelė simetrija.

Šiame darbe pristatoma nauja sistema, leidžianti sukurti didelės geometrinės įvairovės kavitandus iš įvairių monomerinių statybinių blokų, ir pateikiama konceptualaus supramolekulinio tetramerinio „Šveicariško kryžiaus“ formos kavitando sintezė. Sistema pagrįsta bicyklo[3.3.1]nonano struktūra, kuri, sujungus su aromatiniais jungtukais, leidžia gauti standžius, 90° kampu susilenkusius chiralius karkasus. Naudojant abu chiralinio bicyklononano[3.3.1]-2,6-diono enantiomerus, galima įterpti tiek teigiamą, tiek neigiamą paviršiaus kreivumą, taip kontroliuojant galutinės struktūros erdvinę struktūrą. Prijungus 2-ureido-4-pirimidinono (UPy) motyvus prie karkasų galų, susidaro savikomplementarios vandenilinės jungtys, kurių deka nepoliniuose tirpikliuose gali susiformuoti ciklinės oligomerinės struktūros.



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Šiame darbe aprašomas naujas metodas abiejų bicyklononano[3.3.1]-2,6-diono enantiomerų paruošimui decigramų kiekiu. Taip pat optimizuota C_2 simetrijos turinčio Friedländer'io sintono N-(4-amino-5-formil-2-(hidroksimetil)fenil)-4-metilbenzensulfonamido sintezė, leidžianti jį gauti dešimčių gramų kiekiu su minimaliu gryninimo procedūrų kiekiu. Šie statybiniai blokai buvo panaudoti „Šveicariško kryžiaus“ formos kavitando monomero **37** sintezei. Tetramerinių struktūrų formavimasis $CDCl_3$ tirpale buvo patvirtintas NMR metodais, tačiau dėl prasto galutinės struktūros tirpumo nebuvo galima atlikti išsamesnių tyrimų, todėl išryškėjo poreikis sukurti modifikuotas versijas, turinčias geresnį tirpumą įvairaus poliškumo organiniuose tirpikliuose. Paskutinėje darbo dalyje aprašomas kūrimas įvairiomis funkcinėmis grupėmis modifikuotų bicyklononano[3.3.1]-2,6-diono darinių, galinčių būti naudojami kaip universalūs jungikliai, leidžiantys lengvai keisti struktūrą vėlyvose sintezės stadijose ir taip modifikuoti tirpumo savybes.