Bistable [2]Catenate-Based Functional Surfaces

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Synthetic molecular systems which can demonstrate molecular motions via application of an external signal are currently of special interest, both as mimics of biological systems and as potential bistable molecular devices. The possible utility of organic molecules as molecular machines, motors and switches has recently increased in popularity. Organic-based bistable [2]catenates are discussed with regard to the preparation of a target system, their mode of operation and their utility, focusing on the molecular design and proposed synthetic strategy.

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Introduction

Synthetic molecular systems which can demonstrate molecular motions via application of an external signal are currently of special interest, both as mimics of biological systems and as potential bistable molecular devices. The usage of these molecular devices in advanced technology has created an arising field at the junction of biology, physics and chemistry. Many of these molecular machines and motors are based upon catenanes and rotaxanes since molecular motions using interlocked or threaded macrocycles can easily be performed.[1, 2] Rotaxanes are composed of a 'dumbbell' component with binding sites along the axis and stoppers at both ends and a macrocycle component which is capable of binding to the sites along the axis dependent upon chemical conditions. Catenanes, on the other hand, are composed of two interlocked macrocycles which can rotate around one another to facilitate different binding motifs, again dependent upon chemical conditions. The most common approaches to achieve switching in these systems are accomplished photochemically, electrochemically, or chemically.

Within a copper-based [2]catenate, in which there are two interlocked macrocycles, this rotary motion coincides with moving one macrocycle around the metal center with respect to the other interlocked ring, switching between two stable configurations. This motion is triggered by the oxidation/reduction of the copper center between Cu(I) and Cu(II) followed by ligand exchange (Figure 1). The oxidation state of the metal center controls the favored coordination number and therefore, the favored geometry of the complex; Cu(I) prefers to be 4-coordinate and Cu(II) to be 5- or sometimes 6-coordinate.

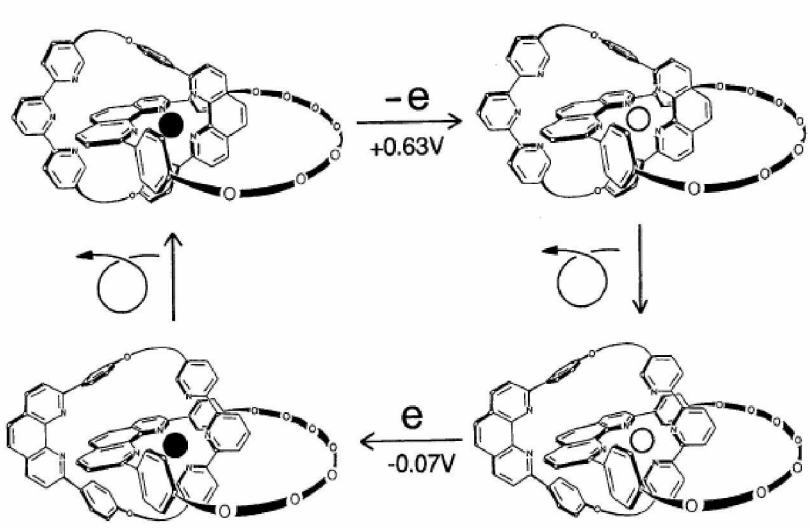


Figure 1. Catenate rotary motion between 4-coordinate Cu(I) to 5-coordinate Cu(II) via oxidation/reduction.[3]

Catenane and rotaxane molecular machines are well established, many research groups have developed working molecular machines based upon a variety of binding schemes. Sauvage has recently done a lot of the pioneering work in this field and has constructed several varieties of catenanes and rotaxanes as well as other classes of interlocked compounds and has been able to show ring-gliding motions of these systems in solution. However, in order for these systems to find utility as molecular machines in real life applications they must be attached to surfaces. Sauvage has shown success with rotaxanes and their attachment to surfaces, however, he has been unsuccessful in utilizing the deposition of catenanes onto gold.[4, 5, 6]

The goal for this project is the synthesis of novel Cu(II/I) [2]catenates with structurally controlled kinetics for self assembly onto gold surfaces. The targeted catenate of interest $\mathbf{C}^{+}$ (**Scheme 5**) employs a *rigid* terpyridine ligand with a *flexible* bipyridine

ligand incorporated into one macrocycle, vice versa to that of Sauvage's systems, and Sauvage's traditional phenanthroline ligand within the second macrocycle.

This combination of ligands was chosen in an effort to examine the kinetics of the system on account of the fact that the rate of rotary motion is an important factor in the usage of these machines and not here-to-fore either studied much or used. In studying [2]rotaxanes and [2]catenanes, Sauvage has found that upon oxidation from Cu(I) to Cu(II), the reorganization of Cu(II) from 4-coordinate to 5-coordinate is slow while upon reduction from Cu(II) to Cu(I), the reorganization of Cu(I) from 5-coordinate back to 4-coordinate is quick. These two reorganization steps are the rate limiting steps within the system.[7,8] Successful attempts to improve the rates of pirouetting motion within a rotaxane have been made by lowering the steric hinderance for ligand exchange by introducing a bipyridine ligand in place of phenanthroline along the dumbbell component. This substitution did in fact speed up the motion around the rotaxane axis.[8] The mechanism of switching, however, is still not fully understood.

Based upon this functional work, the target molecules have been designed to alter the traditional catenate in efforts to investigate the effect of structure on the kinetics of catenate circumrotation. Sauvage has traditionally worked with rigid and pre-organized phenanthroline and floppy terpyridine ligands.[9] The phenanthroline units include reinforcing π-π stacking as well as offering the copper center protection sterically from solvent displacement. The target molecule has been designed around a macrocycle containing a rigid and pre-organized terpyridine ligand and replacing the phenanthroline with a flexible bipyridine ligand both of which employ reinforcing π-π stacking. In addition, a terminal benzylic alcohol functionality is also being employed to the

interlocking macrocycle to allow for coupling to thioctic acid, an "alligator clip," which will permit self-assembly onto a gold electrode for surface studies.

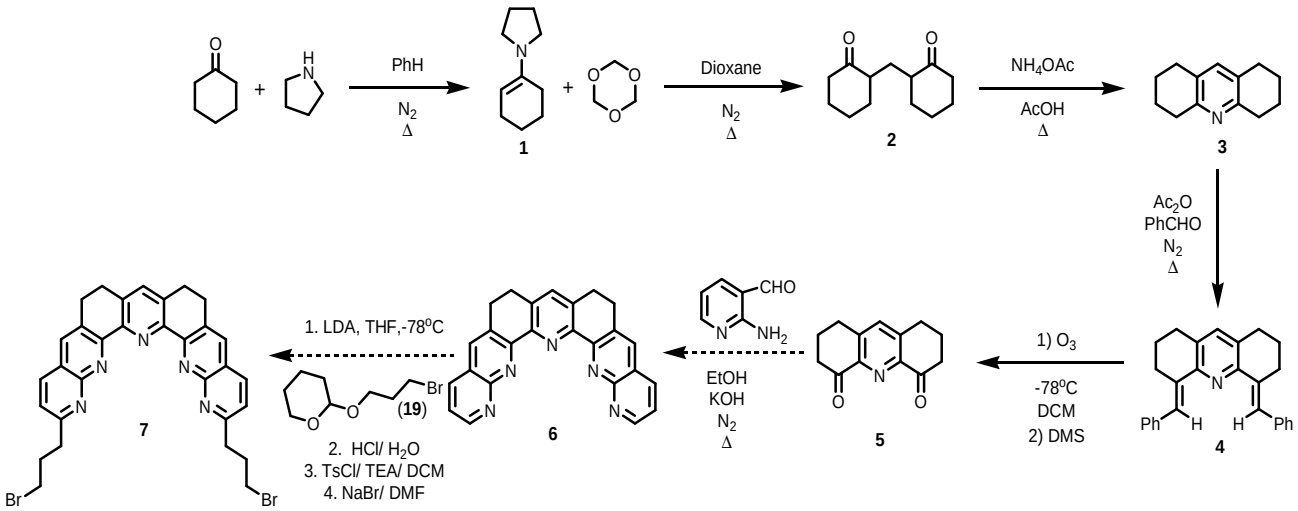
If this system demonstrates circumrotation on gold surfaces its utility in real life applications arises. Molecular machines have potential usefulness in several day-to-day applications. Some of these applications which have been suggested for a range of nanomechanical systems include logic circuits or memory devices, electronic switches and shuttles, and even solar cells. The fact is, until these systems can be applied to surfaces and demonstrate successful switching between states we won't know to what potential they have utility.

Synthesis

A series of synthetic approaches towards catenates have been developed, and described herein, based upon the template-directed self-assembly of catenates as well as known ligand syntheses. The synthetic strategy towards the synthesis of the *rigid* terpyridine unit **7** is outlined in **Scheme 1**. This ligand is synthesized by the addition of paraformaldehyde to cyclohexenylpyrrolidine **1** which is prepared via Stork enamine synthesis.[10] The resulting diketone **2** can then be treated with an ammonia source to form the acridine derivative **3**. The reaction of **3** with acetic anhydride and benzaldehyde affords **4** followed by conversion to the diketone **5** via ozonolysis. The *rigid* terpyridine **6** can then be formed via Friedlander condensation with 2-amino-3-pyridine carboxyaldehyde.[11,12] **6** can then be further functionalized by first lithiating at the - positions on the terpyridine followed by the addition of bromopropanol-THP ether.[13]

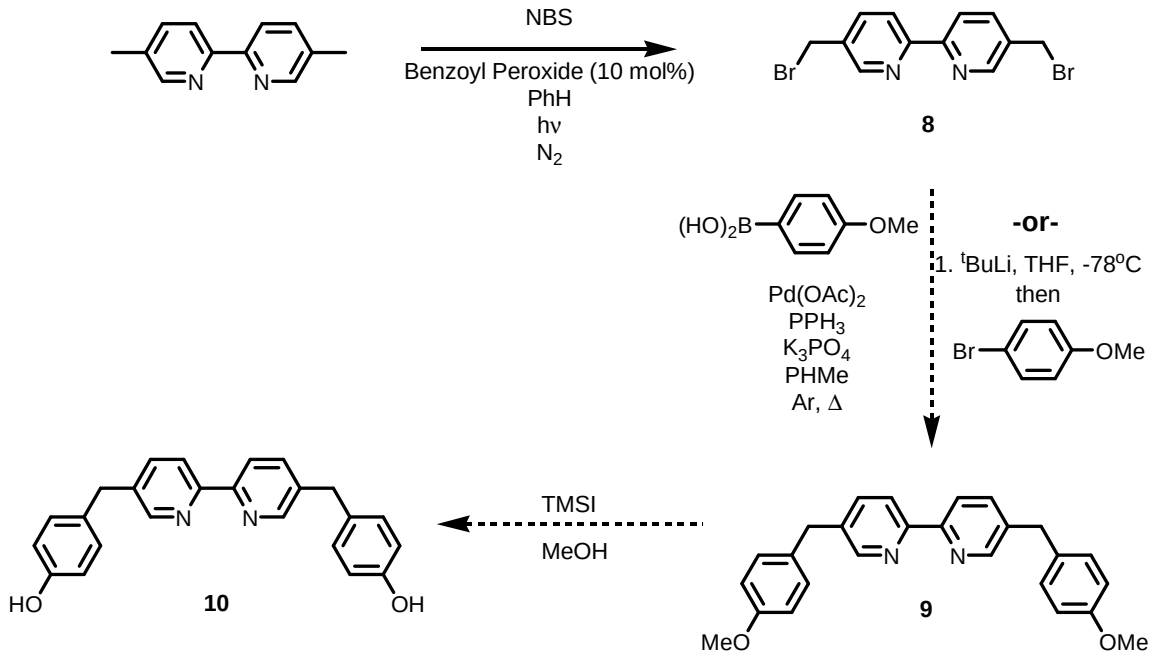
Deprotection affords the primary alcohol which can be tosylated and finally brominated to give **7**.

Scheme 1. Proposed synthesis of the *rigid* terpyridine precursor.



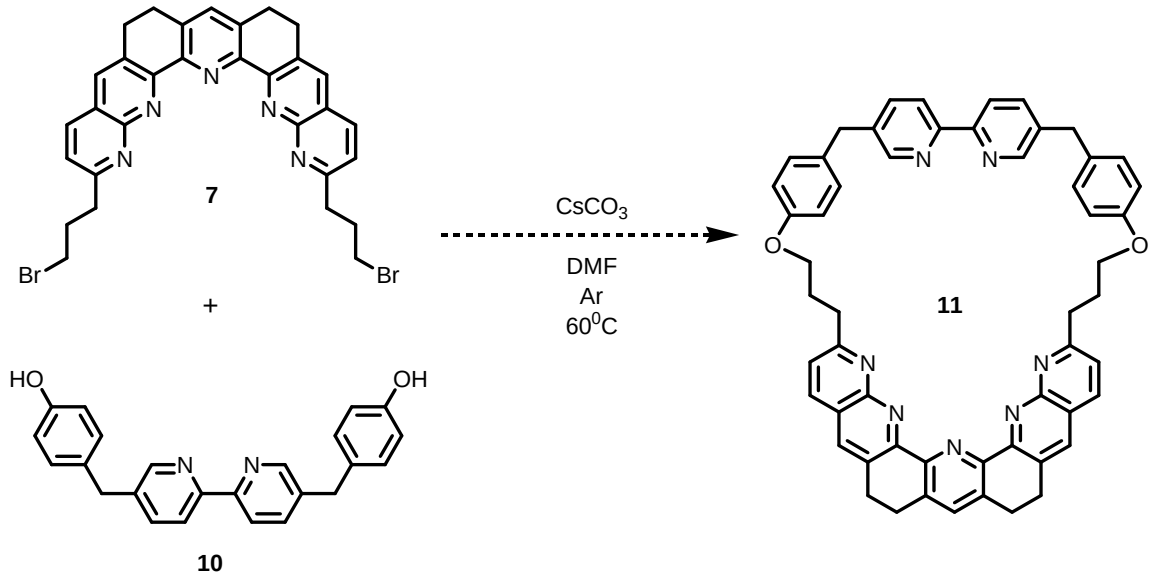
The synthetic route towards the synthesis of the second half of the macrocycle to which **7** will be add to complete macrocyclization (**Scheme 3**) is depicted in **Scheme 2.** The bipyridine unit will be synthesized by carrying out a benzylic bromination of 5,5'-dimethyl-2,2'-bipyridine to afford the dibrominated derivative **8**.[14] There are two possible routes for preparing **9** from **8**. The first method of approach is a Suzuki coupling with 4-methoxyboronic acid with **8**.[15,16,17] And the alternative approach is to carry out a lithium halogen exchange using tert-butyl lithium following with the addition of 4-bromoanisole. Deprotection of the methyl ether with trimethylsilyl iodide in methanol results in the dialcohol **10**.[18]

Scheme 2. Proposed synthesis of bipyridine ligand.



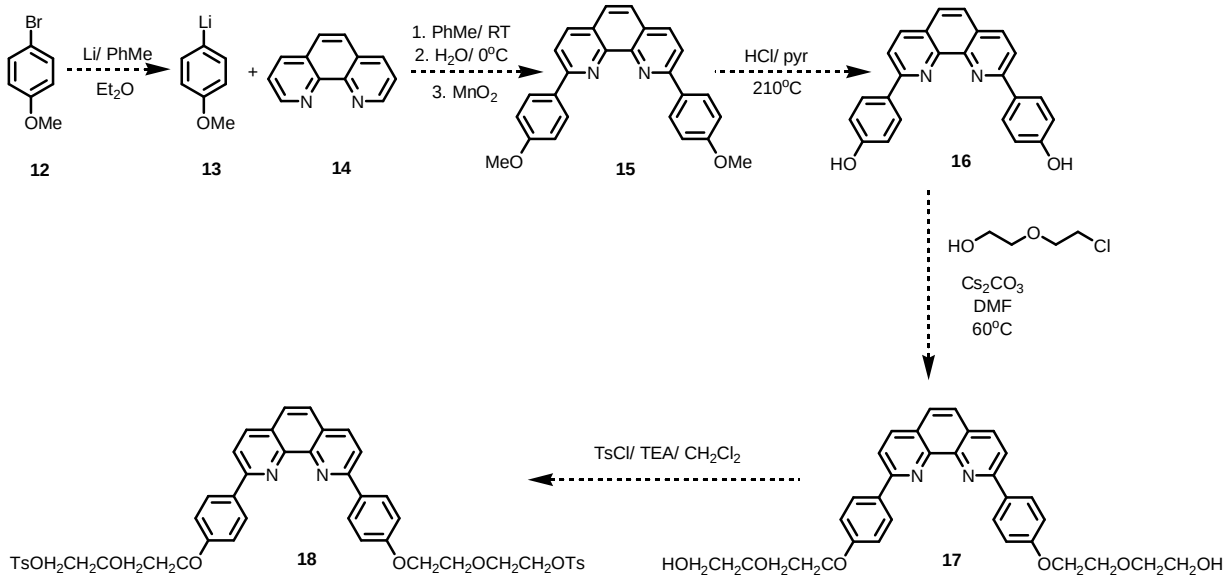
Macrocyclization of **10** and **7** in the presence of $CsCO_3$ should give rise to macrocycle **11** (**Scheme 3**). Likely side products include oligomers, and so, the macrocycle-forming reaction will be carried out under high dilution conditions.

Scheme 3. Macrocyclization of bipyridine and terpyridine ligands.



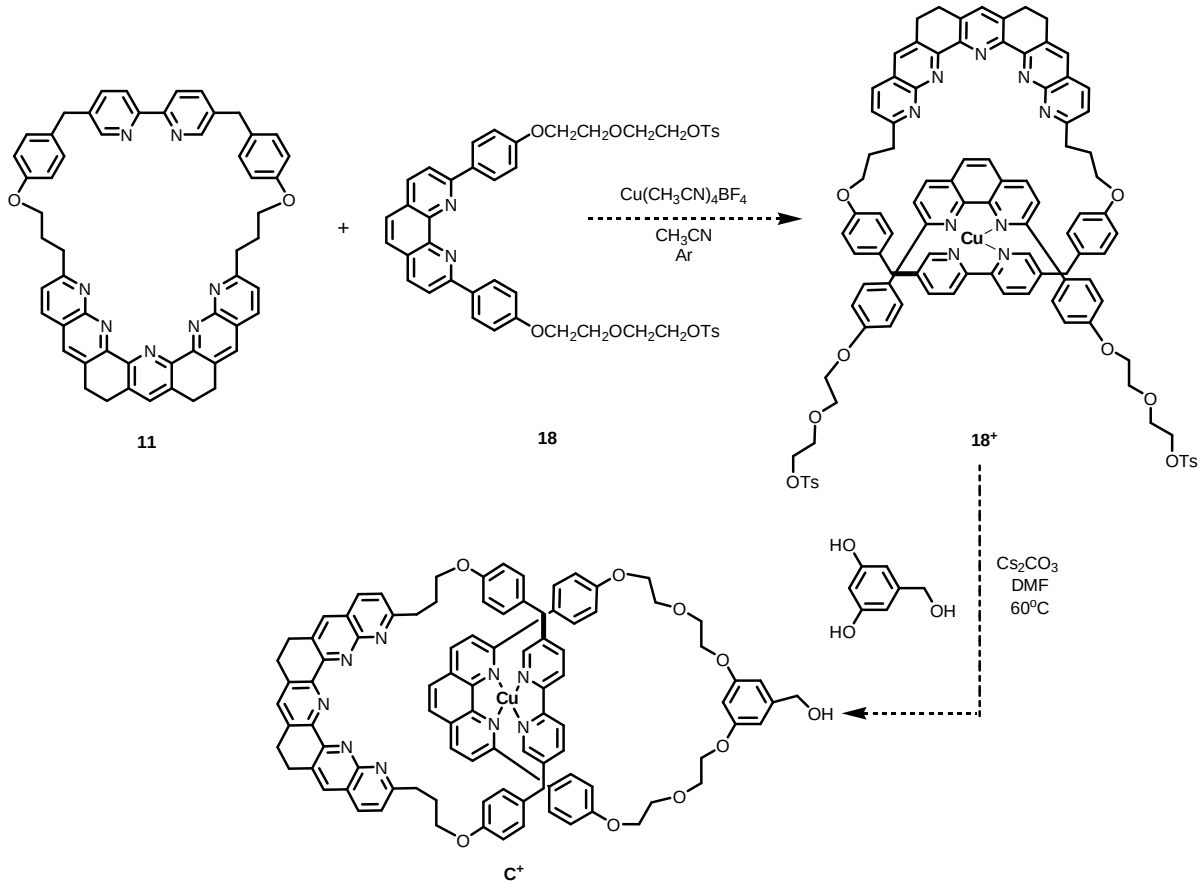
The phenanthroline unit, which will comprise the second macrocycle, will be synthesized following the procedure outlined in the current literature (**Scheme 4**).[9,19] The final catenate is constructed, utilizing copper(I) as the templating metal center, by threading the phenanthroline-based dialcohol **18** through macrocycle **11** to form the precatenate $\mathbf{18}^{+}$ (**Scheme 5**). Macrocyclization is effected with 5-(hydroxylmethyl)benzene-1,3-diol to complete the catenate $\mathbf{C}^{+}$ (**Scheme 5**).

Scheme 4. Proposed synthesis of phenanthroline ligand.



Upon synthesis of the target catenate $\mathbf{C}^{+}$ solution-phase electrochemical switching will be conducted and the circumrotation studied. After this is established the catenane will be derivitized via thiocitic acid in order to permit self-assembly onto gold. This will allow us to conduct surface studies and determine the catenates capability for circumrotation on gold via electrochemical switching.

Scheme 5. Formation of complete catenate.



Completed Work

Synthetic work began with the synthesis of the *rigid* terpyridine unit **7** following the work of Thummel and Anslyn.[11,12] This began with a Stork enamine synthesis by treating cyclohexanone with pyrrolidine in benzene and refluxed under a water separator until the collection of water ceased. Addition of the enamine to paraformaldehyde in refluxing dioxane gave diketone **2** which is known to exist as a mixture of the meso and threo isomers, which is verified by NMR.[20] **2** was converted to the acridine derivative **3** via heating with ammonium acetate in acetic acid. The compounds synthesized thus far were used crude and **3** was purified via column

chromatography to give 62%. This compound was reacted with benzaldehyde in acetic anhydride to provide the dibenzylidine derivative **4** which was straightforwardly purified by washing the crystalline solid with cold 95% EtOH to remove excess benzaldehyde and acetic anhydride. Ozonolysis was carried out in CH_2Cl_2 at –78ºC and the ozonide reduced with dimethyl sulfide *in situ* to yield diketone **5**. The Friedlander condensation between **5** and 2-amino-3-pyridine carboxyaldehyde to yield the rigid terpyridine ligand was attempted once and starting materials were recovered. The reaction conditions favored hydrolysis of imine formation preventing the reaction from product formation. In anticipation of terpyridine **6**, 3-bromopropanol was protected as the THP ether as described by Miyashita.[12] Pyridinium *p*-toluenesulfonate (PPTS) was synthesized for use as a catalyst in the THP ether synthesis by stirring *p*-toluenesulfonic acid monohydrate in excess pyridine at room temperature.

Concurrently, with the preparation of **7**, efforts were also initiated towards the preparation of the bipyridine unit **10**. This began by treating 5,5'-dimethyl-2,2'-bipyridine with N-bromosuccinimide (NBS) in benzene in the presence of an initiator and light (200 W) to generate the dibrominated product **8**. This reaction was carried out twice using two different initiators, the first trial utilized AIBN as the initiator and the second trial was carried out using benzoyl peroxide. The AIBN experiment resulted in approximately 32% of the dibrominated species along with some of the poly-brominated compound. The second experiment, utilizing benzoyl peroxide, gave rise to 34% of the dibrominated compound. In both cases, the reaction was filtered hot to remove succinimide and the filtrate cooled to cause the product to precipitate out. In the second experiment, the filtrate was placed in the freezer overnight which caused the entire contents to freeze but

upon thawing; the product was collected and washed with water followed by sodium thiosulfate solution to remove residual succinimide and bromine. This gave rise to the desired dibrominated compound in good purity as a white solid. Both the lithiation and the Suzuki coupling routes were attempted on the dibromo substrate, however, they were both unsuccessful in their first attempts.

Progress towards the preparation of the target catenate has progressed as planned following the design and proposed syntheses herein.

Future Work

Near term goals are to repeat the Friedlander condensation to prepare the rigid terpyridine unit **7**. The Suzuki coupling and lithiation reactions will also be repeated in attempts to prepare 5,5'-bis(4-methoxybenzyl)-2,2'-bipyridine **9**. Future work will continue along the described synthetic plan to prepare the *rigid* terpyridine and biprydine units. Upon successful synthesis of these units, the macrocyclization will be carried out to prepare the first macrocycle. Upon completion of this macrocycle, control studies will be designed and conducted to investigate the efficiency of the ligand combination at circumrotation. Future work also includes synthesis of the counter macrocycle in order to prepare the target catenate.

Experimental

General

Nuclear magnetic resonance spectra were all obtained on Varian GEM-300, Varian I-400 or Varian VXR-400 spectrometers. Samples were dissolved in $CDCl_3$ with residual $CHCl_3$ (= 7.26) as an internal standard. Precoated aluminum backed silica gel plates were used for thin layer chromatography. All starting materials were used as provided from chemical companies without further purification. Solvents were purified using a Pure Solv 400-6-MD solvent purification system and their purity verified by NMR. Compounds **1**-**5**[11,12], **8**[14] and **19**[13] have previously been reported, consequently the ^{1}H NMR data have been included for the purposes of compound identification.

1-Cyclohexenylpyrrolidine (1)

A solution of cyclohexanone (6.83 mL, 0.066 mol) and pyrrolidine (11 mL, 0.13 mol) in benzene (20 mL) was equipped with a Dean and Stark trap and brought to reflux under nitrogen. The reaction mixture was allowed to reflux until the collection of water ceased. The reaction was allowed to cool and the solvent and excess amine removed under reduced pressure. The product, **1**, (yellow oil) was recovered in near quantitative yields (90%) and used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$), = 4.20 (br. s, 1H), 2.10 (t, 4H J = 5.9 Hz), 2.01 (m, 2H), 1.74 (p, 4H, J = 3.3 Hz), 1.61-1.59 (m, 2H), 1.49-1.45 (m, 2H).

2,2′-Methylenebiscyclohexanone (2)

A solution of **1** (3.41 g, 23 mmol), 0.34 g paraformaldehyde (0.34g, 11.3 mmol) and dioxane (0.5 mL) were refluxed for 12 hours under nitrogen. The reaction mixture was allowed to cool and acidified with 5 N HCl. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with water (1 x 20 mL) and dried over $MgSO_4$. Evaporation of the solvent resulted in an orange oil. The crude oil was collected in good yield (70%) and used without further purification. IR (thin film) 2930, 2857, 1708, 1448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 1.0-2.5 (m).

1,2,3,4,5,6,7,8-Octahydroacridine (3)

A mixture of **2** (1.21 g, 5.8 mmol) and NH_4OAc (0.9g, 11.6 mmol) in HOAc (2.5 mL) was refluxed for 3 h. The solution was allowed to cool and made basic with 50% NaOH solution. The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers were washed with water (2 x 25 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure resulting in a brown oil that was purified by column chromatography (SiO_2, hexanes-EtOAc, 20:0-19:1). Evaporation of the solvent produced **3** as a pale yellow solid (62%). ^1H NMR (400 MHz, $CDCl_3$) = 7.02 (s, 1H), 2.85 (t, 4H, J = 6.3 Hz), 2.68 (t, 4H, J = 6.1 Hz), 1.87-1.81 (m, 4H), 1.77-1.71 (m, 4H).

1,8-Dibenzylidene-1,2,3,4,5,6,7,8-octahydroacridine (4)

A mixture of **3** (0.7 g, 3.74 mmol), benzaldehyde (3.8 mL, 37 mmol), acetic anhydride 3.6 mL, 38 mmol) were refluxed under nitrogen for 20 h. The mixture was cooled in the refrigerator overnight and washed with cold 95% EtOH and the precipitate collected via

vacuum filtration. The precipitate was washed with cold 95% EtOH and dried to yield **4** (0.82 g, 60%) as a yellow solid. No further purification was necessary. ^{1}H NMR (400 MHz, $CDCl_3$) = 8.11 (s, 2H), 7.44 (d, 4H, *J* = 7.5 Hz), 7.37 (t, 4H, *J* = 7.5 Hz), 7.26-7.25 (m, 2H), 7.15 (s, 1H), 2.9 (t, 4H, *J* = 4.8 Hz), 2.83 (t, 4H, *J* = 5.7 Hz), 1.85 (t, 4H, *J* = 5.6 Hz).

1,8-Dioxo-1,2,3,4,5,6,7,8-octahydroacridine (5)

A solution of **4** (0.66 g, 1.8 mmol) in CH_2Cl_2 (25 mL) was cooled to -78°C and purged with oxygen for approximately 10 min. Ozone was then bubbled through until permanent blue coloration. The dissolved ozone was purged with oxygen (blue coloration disappears) for 30 min and flushed with nitrogen. Dimethylsulfide (0.6 mL, 8 mmol) was added and the reaction mixture was allowed to come to room temperature overnight. The solution was concentrated by heating over a water bath. The resulting residue was washed with hot hexanes (2 x 10 mL) and the remaining solid extracted into CH_2Cl_2 and washed with H_2O (2 x 10 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The resulting orange oil was purified by column chromatography (SiO_2) eluting with CH_2Cl_2 followed by CH_2Cl_2-EtOAc (4:1). Early fractions of the mixed eluent resulted in **5** as an orange residue (50%). ^{1}H NMR (400 MHz, $CDCl_3$) = 7.62 (s, 1H), 3.05 (t, 4H, *J* = 6.0 Hz), 2.80 (t, 4H, *J* = 6.5 Hz), 2.19 (p, 4H, *J* = 6.4 Hz).

5,5′-bis(bromomethyl)-2,2′-bipyridine (8)

A mixture of 5,5′-dimethyl-2,2′-bipyridine (1.99 g, 10.8 mmol), NBS (4.35 g, 24.4 mmol), and benzoyl peroxide (0.267 g, 1.10 mmol) in benzene (60 mL) were irradiated using a 200 W bulb (d = ~ 6 in.) under nitrogen for 50 min. The reaction setup was wrapped in a shrowd of aluminum foil. The reaction was filtered hot to remove succinimide and the filtrate placed in the fridge to cool overnight. The precipitate was collected via vacuum filtration and washed with H_2O followed by 0.5 M $Na_2S_2O_3$ solution to yield 34% of an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) = 8.68 (s, 2H), 8.40 (d, 2H, *J* = 8.2 Hz), 7.86 (dd, 2H, *J* = 8.1, 2.3 Hz), 4.54 (s, 4H).

Bromopropanol THP ether (19)

A solution of 3-bromopropanol (0.2 mL, 2.2 mmol), 3,4-dihydropyran (0.3 mL, 3.3 mmol) and PPTS (0.05 g, 0.2 mmol) in CH_2Cl_2 (14 mL) was stirred at room temperature for 5 hours. The solution was diluted with ether and washed with half-saturated brine solution. Evaporation of the solvent gave rise to a colorless oil which was purified by column chromatography (SiO_2, ether-hexanes 1.5:8.5) to give a colorless oil in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) = 4.60 (br. S, 1H), 3.90-3.84 (m, 2H), 3.55-3.49 (m, 4 H), 2.13 (p, 2H, *J* = 6.1 Hz), 1.59-1.52 (m, 6H).

Pyridinium *p*-toluenesulfonate

p-Toluenesulfonic acid monohydrate (5.70 g, 30 mmol) was added to pyridine (12.1 mL) and stirred at room temperature for 30 min. The excess pyridine was removed under reduced pressure to afford a quantitative yield of slightly hygroscopic crystals. The solid was recrystallized from acetone to give the pure salt, white crystalline solid, in good yield (89%).

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