Syntheses of mono- and diamide cross-bridged cyclens and syntheses of bifunctional chelators based upon cross-bridged tetraamine macrocycles

Yijie Peng

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Syntheses of mono- and diamide cross-bridged cyclens and syntheses of bifunctional chelators based upon cross-bridged tetraamine macrocycles

Abstract
The syntheses of two diamide cross-bridged cyclens (22 and 23) and three monoamide cross-bridged cyclens (24, 25, and 26) are presented. Metal (Li(I), Zn(II), and Cu(II)) coordination studies of 26 are also presented. Evidence suggests that ligand 26 forms intermolecular complexes through the oxygen of an amide with Li(I), Zn(II), and Cu(II), and 26 could form complex with Li(I) through the nitrogen of an amide.*

Appropriate cross-bridged tetraamine macrocycles are promising bifunctional chelators (BFC). Improved synthesis of one BFC (36) is presented, alternative synthesis of one BFC (39) is also presented, the synthesis of a precursor of one BFC (42), the attempted syntheses of four BFCs (40, 41, 43 and 44) and the syntheses of two BFCs (45 and 46) are also presented.*

Keywords
Chemistry, Organic

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SYNTHESES OF MONO- AND DIAMIDE CROSS-BRIDGED CYCLENS

AND

SYNTHESES OF BIFUNCTIONAL CHELATORS BASED UPON CROSS-BRIDGED TETRAAMINE MACROCYCLES

By

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M.S., Sichuan Industrial Institute of Antibiotics, 1996

B.S., Beijing University, 1991

DISSERTATION

Submitted to the University of New Hampshire

in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

in

Chemistry

September 2004
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Dedication

This dissertation is dedicated to my wife Yingchun, whom I love with all my heart.
Acknowledgments

I would first like to thank my advisor Prof. Gary Weisman and co-advisor Prof. Edward Wong for their guidance and support over the years. Both Prof. Chuck Zercher and Prof. Richard Johnson taught organic chemistry with an enthusiasm that was contagious, their interest and guidance really propelled me into seeing the beauty in organic chemistry.

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Abstract

Syntheses of Mono- and Diamide Cross-bridged Cyclens and Syntheses of Bifunctional Chelators Based upon Cross-bridged Tetraamine Macrocycles

By

Yijie Peng

University of New Hampshire, September 2004

The syntheses of two diamide cross-bridged cyclens (22 and 23) and three monoamide cross-bridged cyclens (24, 25, and 26) are presented. Metal (Li(I), Zn(II), and Cu(II)) coordination studies of 26 are also presented. Evidence suggests that ligand 26 forms intermolecular complexes through the oxygen of an amide with Li(I), Zn(II), and Cu(II), and 26 could form complex with Li(I) through the nitrogen of an amide.

\[ \text{22: } R=\text{Me} \quad \text{23: } R=\text{Ph} \]

\[ \text{24: } R=\text{Me} \quad \text{25: } R=\text{Ph} \quad \text{26: } R=\text{H} \]

Appropriate cross-bridged tetraamine macrocycles are promising bifunctional chelators (BFC). Improved synthesis of one BFC (36) is presented, alternative synthesis of one BFC (39) is also presented, the synthesis of a precursor of one BFC (42), the
attempted syntheses of four BFCs (40, 41, 43 and 44) and the syntheses of two BFCs (45 and 46) are also presented.
CHAPTER I

SYNTHESES OF MONO- AND DIAMIDE CROSS-BRIDGED CYCLENS

I. Introduction

Amides are a class of molecules important to several chemical disciplines. Not only do they comprise a major functional group in organic chemistry, but also they provide the linkage between adjacent amino acid residues in proteins and polypeptides. Sigel and Martin provided a summary of the structure and stability of metal carboxamide complexes with a strong emphasis on metal complexes containing proteins and peptides. Experimental stability constant data, kinetic information, spectroscopy (IR and NMR) measurements and some data from x-ray crystal structures were provided regarding the changes in the amide bond lengths upon metal coordination and the effect of metal coordination upon amide bond rotation. It has been presumed that most metals complex with the oxygen atom of an amide. According to Hay, the monodentate binding of amide ligands to metals occurs predominantly through the carbonyl oxygen atom rather than the amide nitrogen atom. Out of the 227 instances examined where monodentate amides were bound to metal ions, in 223 cases the amide was bound to the metal through the carbonyl oxygen atom. There are a few examples in which multidentate ligands bearing amide functionality are bound to the metal through the amide’s nitrogen. Common chelate rings occur in these ligands, and most are primary and secondary amides that
exhibit deprotonation of the amide nitrogen. Only one example presents spectroscopic and crystallographic proof of coordination of the amide nitrogen in tertiary amides.

Amide isomerization plays an important role in protein folding, where it can be the rate-determining step with proline-containing polypeptides and proteins. Peptidyl prolyl isomerases (PPIases), including cyclophilin and FKBP, are "rotamase" enzymes that catalyze protein folding in vitro and in vivo through the isomerization of proline residues. The catalysis of amide bond isomerization by Brønsted acids is a well-documented reaction that proceeds through a putative N-protonated intermediate.

On the other hand, the catalysis of amide bond isomerization by Lewis acid (metal ion) complexation with the nitrogen atom of an amide still remains to be clarified. It has been presumed that coordination with the oxygen of an amide should increase the barrier to rotation around the C-N bond and enhance its double bond character. Coordination with the nitrogen of an amide is expected to reduce the resonance delocalization of the nitrogen lone pair, decrease the barrier to rotation around C-N bond, and weaken its double bond character (Figure 1.1). The N-coordination should catalyze amide bond isomerization.

\[
\begin{align*}
\text{R}_1 \text{N} = \text{O}^- & \quad \leftrightarrow \quad \text{R}_2 \text{N} = \text{O}^- \\
\text{R}_3 \text{N} = \text{O}^- & \quad \leftrightarrow \quad \text{R}_4 \text{N} = \text{O}^-
\end{align*}
\]

**Figure 1.1** Resonance structures of an amide

Polyamine macrocycles are able to tightly binding and stabilize a variety of main group and transition metal cations. Metal complexes of these ligands exhibit extra thermodynamic stability that is not found for acyclic ligands, which is attributed to the
macrocyclic effect. This effect has been attributed to the macrocycles having both a larger enthalpy and a smaller entropy of complexation than their nearest open-chained analogues. Depending upon the detailed structure of the ligand, macrocycles also have some flexibility in their coordination geometries. This flexibility allows the ligands to adopt isomeric geometries about the same metal. As a result of this mixed stereochemistry, modifications have been made to “pre-organize” these ligands to favor specific coordination geometries.

Wainwright made a structural modification to the parent polyamine macrocycles "cyclen" and "cyclam" ligands (1 and 2, Figure 1.2) whereby two adjacent nitrogens (i.e., those without intervening nitrogens) were bridged with an ethylene (\(-\text{CH}_2\text{CH}_2\)-) unit (3 and 4, Figure 1.3), reinforcing the tendency towards trans-coordination (square planar or octahedral tetraequatorial) of transition metal ions. Hancock later carried out further investigations of the coordination chemistry of ligands of this type.

A new class of "cross-bridged" tetraamine ligands, which have nonadjacent nitrogens bridged with an ethylene unit, was first reported in 1990 by Weisman and Wong. The first cross-bridged tetraamine ligand ‘dimethyl cross-bridged cyclam’ was shown to be strongly basic and a good Li\(^+\) complexer. Cross-bridged tetraaza
macrocycles adopt a cis-folded coordination geometry when coordinated with small metal cations. The bridge creates a bicyclic system of two fused triaza macrocycles that conjointly bind a metal cation. A cavity or cleft is created by this bridging in an arrangement that can be equated to a clam shell. The free ligands are flexible, but when complexed to metal cations “they can adopt low energy conformations having all four nitrogen lone pairs convergent upon the cleft of the ligand”. Figure 1.4 illustrates the cleft created by the cross-bridged arrangement and the low energy conformation of these ligands upon metal complexation. 

![Figure 1.4 A clam shell arrangement and the cis-folded coordination geometry of the cross-bridged tetraaza macrocycles](image)

Therefore, if we convert one or two secondary amines (R=H) to amides (R=COR'), the geometry of the cross-bridged tetramines might allow the amide derivatives to coordinate with metals through the nitrogen of the amide (Scheme 1.1).

![Scheme 1.1 Hypothetical structure of amide cross-bridged derivative’s metal complex](image)
II. Background

Tabushi and coworkers\textsuperscript{14} have synthesized the 13- to 15-membered macrocyclic dioxotetraamines, 1,4,7,10-tetraazacyclotridecane-11,13-dione (5, Figure 1.5), 1,4,8,11-tetraazacyclotetradecane-12,14-dione (6, Figure 1.5), and 1,4,8,12-tetraazacyclopentadecane-9,11-dione (7, Figure 1.5), and Kimura and coworkers\textsuperscript{15,16} have studied their Cu(II) complexes. All three ligands form the neutral amide-ionized Cu(L-2H) species.

![Figure 1.5](image)

Figure 1.5 13, 14, and 15-Membered macrocyclic dioxo tetraamines

Lectka and coworkers used specially designed ligands (8\textsubscript{a}, 8\textsubscript{b} and 8\textsubscript{c}) to study their Cu(II) complexes. They found that the amide rotation barrier was lowered up to 6 kcal/mol by N-coordination (nitrogen of tertiary amide) (Scheme 1.2).\textsuperscript{3}

![Scheme 1.2](image)

Scheme 1.2 Cu(II)-catalyzed amide isomerization

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However, Konig and coworkers studied the binding properties of urea or amide derivatives of 1,4,7,10-tetraazaacyclododecane, and found that Zn(II) and Cu(II) didn’t coordinate the nitrogen of the tertiary amide at all (Figure 1.6).\textsuperscript{17,18}

![Figure 1.6 Metal complexes of amide- and urea-functionalized cyclens](image)

Weisman and Wong recently studied new class of cross-bridged tetraamine ligands. They have developed a series of refined methods to synthesize different derivatives of cross-bridged tetraamine ligands and have studied their metal complexes.\textsuperscript{11,12,13}
Our approach to synthesize diamide derivatives of cross-bridged cyclens is based upon previous synthetic work in the group. The synthesis of di-N-H-cross-bridged cyclen (1,4,7,10-tetraazabicyclo[5.5.2]tetradecane, 17) was first reported by Weisman, Wong and coworkers in 1996 (Scheme 1.3). The synthetic route involves the condensation of cyclen with glyoxal to give a bisaminal 14 followed by highly regioselective dialkylation with benzyl bromide to give the bisquaternary salt 15. By allowing the bis-quaternary salt to react with sodium borohydride, a reductive ring expansion leads to N-benzyl protected cross-bridged cyclen 16. Debenzylation of the cross-bridged cyclen then leads to the key intermediate 17 having two secondary amines which are available for acylation.

Scheme 1.3 The synthesis of key intermediate 17 toward the diamide cross-bridged cyclens

The synthesis of N-H, N-methyl cross-bridged cyclen (4-methyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane, 21) which is the key intermediate for mono-amide cross-bridged cyclen was carried out by Daniel C. Hill, a former student of Weisman and Wong (Scheme 1.4). In the first step of the synthetic sequence, cyclen was condensed
with glyoxal to form the cis-fused tetracyclic bisaminal 14. Selective monoalkylation with benzyl bromide followed by another monoalkylation with methyl iodide forms a bis-quaternized ammonium salt 19. Reaction of the bis-quaternary salt with reducing agent sodium borohydride leads to N-benzyl, N-methyl cross-bridged cyclen 20. Debenzylation of the cross-bridged cyclen then leads to the key intermediate 21 having one secondary amine which is available for acylation. Hill had difficulties obtaining pure compound 21. Therefore, we needed to address that problem in order to prepare monoacyl derivatives.

**Scheme 1.4** The synthesis of key intermediate 21 toward the monoamide cross-bridged cyclens

The details of the synthesis of mono- and diamide cross-bridged cyclens will be described in the Results and Discussion section of this chapter. Furthermore, attempted complexations with Li(I), Cu(II) and Zn(II) will also be discussed.
II. Results and Discussion

A. Diamide Derivatives of Cross-bridged Cyclen

The strategy outlined in Scheme 1.3 was used to synthesize two diamide cross-bridged cyclens (Scheme 1.5). We started from commercially available cyclen, and followed the synthetic route that was developed by Weisman, Wong and coworkers to make key intermediate 17, di-N-H cross-bridged cyclen.\textsuperscript{12} NMR spectra of intermediates were consistent with those of authentic compounds.

![Scheme 1.5 The synthesis of diamide cross-bridged cyclens](image)

1. The Synthesis and Characterization of 4,10-Diacetyl-tetraazabicyclo[5,5,2]tetradecane (22)

Treatment of the key intermediate 17 with excess acetic anhydride gave the solid product 22 in good yield (85\%) after basic extraction (Scheme 1.6). The compound was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS).
**Scheme 1.6** The synthesis of compound 22

It should be noted that there are two conformational diastereomers, one has time-averaged $C_s$ symmetry on the NMR time scale; the other has time-averaged $C_2$ symmetry (Scheme 1.7).

![Scheme 1.6](attachment:image.png)

**Scheme 1.7** Schematic representation of two conformational diastereomers of compounds 22 and 23

Two sets of peaks appear in the $^1H$ NMR spectrum, and 14 peaks in the $^{13}C$ NMR spectrum, which is one less than we predicted. The isomer which has $C_s$ symmetry should have 8 carbon peaks, and the isomer which has $C_2$ symmetry should have 7 carbon peaks. Thus, two peaks overlap by coincidence.

2. The Synthesis and Characterization of 4,10-Dibenzoyl-tetraazabicyclo[5.5.2]-tetradecane (23)
Treatment of the key intermediate 17 with excess PhCOCl in CH₂Cl₂ gave crude 23 which was recrystallized from acetone to give the desired product as white crystals in moderate yield (50%) (Scheme 1.8). The compound was characterized by NMR, IR and CHN analysis.

Like diamide 22, 23 also has two conformational diastereomers. One has Cs symmetry; the other has C₂ symmetry (Scheme 1.7). There are 20 peaks in its ¹³C NMR spectrum, which is a smaller number than predicted. The isomer which has Cs symmetry should have 11 carbon peaks, and the isomer which has C₂ symmetry should have 10 carbon peaks. The total should thus be 21 peaks, so two aromatic carbon peaks are accidentally coincident.

B. Monoamide Derivatives of Cross-bridged Cyclen

The synthetic strategy outlined in Scheme 4 was used to synthesize the monoamide cross-bridged cyclen via the key intermediate 21 (Scheme 1.9). Starting from commercially available cyclen and following the synthetic route that was developed by Weisman, Wong and Hill led to compound 20, precursor to the key intermediate 21.
Scheme 1.9 The synthesis of monoamide cross-bridged cyclen

However, the debenzylation failed to give pure 21 by using the conditions that Dan Hill used (Scheme 1.10). As previously mentioned, Hill was never able to obtain pure 21 using his conditions.19

Scheme 1.10 The attempted debenzylation

We analyzed the NMR spectrum of 21 that we obtained in the reaction, and we found the same impurity of unknown identity as reported by Hill. Thus, modifications had to be made in order to get pure 21. After we tried a number of different methods (Table 1.1), we finally found reliable debenzylation conditions (Table 1.1, entry 5). The hydrogenolysis (atmospheric pressure) of N-benzyl, N-methyl cross-bridged cyclen 20
was carried out using 10% Pd/C in a 1% (v/v) solution of conc. HCl in methanol at room temperature. After the workup with base followed by benzene extraction, the crude product was converted to an HCl salt which was recrystallized from hot absolute EtOH. After basic extraction, pure N-methyl, N-H cross-bridged cyclen 21 was obtained in 30% yield (Scheme 1.11).

Scheme 1.11 The Synthesis of the key intermediate 21
Table 1.1 Investigation of debenzylation conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>Starting material</th>
<th>Reaction condition</th>
<th>Results</th>
<th>%yield after purification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>4.4%HCO₂H in CH₃OH 10% Pd/C rt 12 h</td>
<td><img src="image2.png" alt="Image" /> 26</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td>HCOONH₄ 10% Pd/C MeOH/EtOH rt 12 h</td>
<td><img src="image4.png" alt="Image" /> <img src="image5.png" alt="Image" /></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image6.png" alt="Image" /></td>
<td>H₂ 10% Pd/C MeOH rt</td>
<td>NO REACTION</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Image" /></td>
<td>Cyclohexene 10% Pd/C MeOH rt</td>
<td>NO REACTION</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image8.png" alt="Image" /></td>
<td>H₂ 10% Pd/C acidic MeOH rt 12 h</td>
<td><img src="image9.png" alt="Image" /> 21</td>
<td>30</td>
</tr>
</tbody>
</table>

1. The Synthesis and Characterization of 4-Formyl-10-methyl-tetraazabicyclo[5.5.2]-tetradecane (26)

During the investigation of the debenzylation of 20, we were very surprised to find that we obtained cross-bridged cyclen monoformamide 26 when we used HCO₂H as the hydrogen donor according to a literature procedure²⁰,²¹ (Table 1.1, entry 1). After we optimized the reaction conditions, we were able to synthesize the compound in good...
yield (85%) (Scheme 1.12). The compound was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS).

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{Ph} \\
\text{N} & \quad \text{N}
\end{align*}
\]

\[
\begin{align*}
\text{20} & \quad \xrightarrow{10\% \text{Pd/C}} \\
4.4 \% \text{HCO}_2\text{H} & \quad \text{MeOH} \\
\text{rt} & \quad 85\%
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{26}
\end{align*}
\]

Scheme 1.12 The synthesis of compound 26

One possibility for formation of 26 is that initially formed monomethyl cross-bridged cyclen reacts with HCO₂CH₃, which is formed \textit{in situ} via the reaction of HCO₂H and CH₃OH. Alternatively, the mechanism could involve Pd/C catalyst. Control experiments were needed to discern between these possibilities. We did two control experiments: one was treatment of N-methyl, N-H cross-bridged cyclen 21 with 5% HCO₂H in MeOH; the other was treatment of 21 with 10% Pd/C, and 5% HCO₂H in MeOH. Both control reactions gave the monomethyl cross-bridged cyclen 26 (Scheme 13). Although the results don’t rule out the second possible mechanism, they strongly suggest the first mechanism.
Scheme 1.13 Investigation of possible mechanism

2. The Synthesis and Characterization of 4-Acetyl-10-methyl-tetraazabicyclo[5.5.2]-
tetradecane (24)

Treatment of the monomethyl cross-bridged cyclen 21 with excess acetic
anhydride formed the desired product 24 in good yield (80%) after basic extraction
(Scheme 1.14). The compound was characterized by NMR, IR and high resolution FAB
mass spectrometry (HRFABMS).

Scheme 1.14 The synthesis of compound 24
3. The Synthesis and Characterization of 4-Benzoyl-10-methyl-tetraazabicyclo[5.5.2]-
tetradecane (25)

Treatment of the monomethyl cross-bridged cyclen 21 with PhCOCl in CH$_2$Cl$_2$
yielded the desired product 25 in excellent yield (99%) after basic extraction (Scheme
1.15). The compound was characterized by NMR, IR and high resolution FAB mass
spectrometry (HRFABMS).

![Scheme 1.15 The synthesis of monoamide 25](image)

C. Metal Coordination Studies of 4-Formyl-10-methyl-tetraazabicyclo[5.5.2]
tetradecane 26

As mentioned in the Introduction and Background sections of this chapter, the
amide derivatives of cross-bridged cyclen were postulated to have a good chance of
binding metal ions through the nitrogen of the amide. There are several methods which
can determine whether the ligand binds the metal through the nitrogen of amide.$^3$ Amide
rotational barriers of free ligand and metal complex can be measured by dynamic NMR
spectroscopy. Of course the most compelling evidence for N-coordination is the X-ray
structure of the complex. A convenient method is IR.$^{2,3}$ If the N-coordinated complex is
formed, there will be a strengthened C=O bond, and the amide carbonyl stretch will shift
to higher frequency than that of free ligand. Although NMR is a powerful tool for investigation of complexation, typically it can’t definitively confirm whether the ligand binds the metal through the nitrogen or through the oxygen. The following metal complexes were mainly studied by IR and NMR (where possible), since we had no luck obtaining X-ray-quality crystals of these complexes.

1. **Lithium complexation of 4-Formyl-10-methyl-tetraazabicyclo[5.5.2] tetradecane (26LiClO₄)**

Equimolar amounts of ligand 26 (0.167 M) and LiClO₄ were dissolved in CD₃CN in an NMR tube. NMR analysis of this mixture indicated that complexation had occurred, but the results were more complicated than we had expected. For example, ¹³C NMR showed at least two groups of peaks. One set is sharp, and the other is dynamically broadened. After three more equivalents of LiClO₄ were added, the sharp set of peaks increased, and the broadened set of peaks decreased (Figure 1.7A and Figure 1.7B).
Figure 1.7A Comparison of full $^{13}\mathrm{C}\left({}^1\mathrm{H}\right)$ NMR spectra of 26 with and without added LiClO$_4$
Figure 1.7B Comparison of $^{13}$C{\textsuperscript{1}H} NMR upfield spectra of 26 with and without added LiClO$_4$
We are sure that there was no free ligand left after the addition of 1 equivalent of LiClO₄, since the chemical shifts are different from those of free ligand. There are 12 sharp peaks including one C=O peak and at least 9 dynamically broadened peaks including one C=O peak apparent in the ¹³C NMR spectrum. Although we don’t know what kinds of complexes we have based upon the NMR data, we can rule out some possibilities. Simple intramolecular O-coordination can be ruled out, because this kind of coordination would be expected to exhibit Cs time-averaged symmetry on the NMR time scale, which will lead to 7 peaks at most. The η²-CO amide binding mode can be eliminated, because in this kind of η²-coordination the C=O resonance in ¹³C NMR should dramatically move to higher field. Solvent was removed under reduced pressure to give solid product, and the IR of the solid product was compared with the IR of free ligand. The amide carbonyl stretch actually shifts to lower frequency by 26.7 cm⁻¹ (Table 1.2) upon addition of excess LiClO₄. This strongly suggests that the dominant (sharp peaks in ¹³C NMR at higher concentration of LiClO₄) complexes cannot be amide N-coordinated, but O-coordinated. However, the dominant (broadened peaks in ¹³C NMR at lower concentration of LiClO₄) complex could be amide N-coordinated. As we discussed in the Introduction section of this chapter, coordination with the nitrogen of an amide is expected to decrease the barrier to rotation around C-N bond, which could cause the peaks to broaden on the NMR time scale. After addition of three more equivalent of LiClO₄, the magnitude of broad set of peaks decreased, and the sharp set of peaks increased, which could mean that the amide N-coordination was weak. So we decided to screen less oxophilic late transition metals cations, including Zn(II) and Cu(II).
Table 1.2 Carbonyl stretching frequencies ($\nu_{\text{C}=\text{O}}$, cm$^{-1}$) in ligand 26 and its complexes with Li(I), Zn(II) and Cu(II)

<table>
<thead>
<tr>
<th></th>
<th>26</th>
<th>26 + 4LiClO$_4$</th>
<th>26 + Zn(ClO$_4$)$_2$ $\cdot$6H$_2$O</th>
<th>26 + ZnCl$_2$</th>
<th>26 + CuCl$_2$</th>
<th>26 + Cu(ClO$_4$)$_2$ $\cdot$6H$_2$O</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\nu_{\text{C}=\text{O}}$</td>
<td>1680.7</td>
<td>1654.0</td>
<td>1669.3</td>
<td>1671.7</td>
<td>1665.1</td>
<td>none</td>
</tr>
<tr>
<td>$\Delta \nu_{\text{C}=\text{O}}$</td>
<td>---</td>
<td>-26.7</td>
<td>-11.4</td>
<td>-9</td>
<td>-15.6</td>
<td>---</td>
</tr>
</tbody>
</table>

$\Delta \nu_{\text{C}=\text{O}} = \nu_{\text{C}=\text{O}}$ of its metal complexes - $\nu_{\text{C}=\text{O}}$ of ligand 26

2. Zn(II) complexation of 4-Formyl-10-methyl-tetraazabicyclo[5.5.2]tetradecane

(26$\cdot$Zn(ClO$_4$)$_2$)

Equimolar amounts of ligand 26 (0.191 M) and Zn(ClO$_4$)$_2$ $\cdot$6H$_2$O were heated to reflux in methanol solution for 40 h, the solvent was removed to give solid product. NMR analysis indicated that Zn(II) complexes were formed. The $^{13}$C NMR spectrum showed one major set of peaks, although a minor set of peaks was still visible. Comparison of the $^{13}$C NMR resonance signals with those of free ligand showed significant changes upon metal ion binding, but no significant changes if compared to the Li(I) complexes (Figure 1.8A and Figure 1.8B). The amide carbonyl stretch shifted to lower frequency by 11.4 cm$^{-1}$ (Table 1.2). We have to draw the same conclusion as for Li(I) complexes. The Zn(II) complexes formed are intermolecular amide O-coordination complexes.
Figure 1.8A Comparison of full $^{13}$C{\textsuperscript{1}H} NMR spectra of 26 + 4eq LiClO\textsubscript{4}, 26 + 1eq Zn(ClO\textsubscript{4})\textsubscript{2} and 26. 

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Figure 1.8B Comparison of $^{13}$C($^1$H) NMR upfield spectra of 26 + 4eq LiClO$_4$, 26 + 1eq Zn(ClO$_4$)$_2$ and 26

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3. Cu(II) complexation of 4-Formyl-10-methyl-tetraazabicyclo[5.5.2] tetradecane (26•Cu(ClO₄)₂)

The ligand 26 was refluxed with an equimolar amount of Cu(ClO₄)₂•6H₂O in methanol. To investigate a possible participation of the amide moiety in metal ion coordination, IR spectra were carefully compared. We were surprised to find that the amide carbonyl stretch had disappeared. After recrystallization (ether diffusion), the blue crystalline product was subjected to CH&N analysis, consistent with Cu(ClO₄)₂•(26-CO)•H₂O and confirming that the formyl group was gone. We decided to do two more complexation experiments with the ligand to rule out some possible factors.

In a first experiment, anhydrous CuCl₂ was used instead of Cu(ClO₄)₂•6H₂O, all other conditions remaining the same. This time, the IR of the complex formed showed the amide carbonyl stretch at 1665.1 cm⁻¹, which is 15.6 cm⁻¹ lower than the free ligand stretch, and almost the same as that of the Zn(ClO₄)₂ complex. In a second experiment, anhydrous ZnCl₂ was used instead of Zn(ClO₄)₂•6H₂O to complex the ligand. The IR and NMR spectra of 26•Zn(ClO₄)₂ and 26•ZnCl₂ were carefully compared. No significant changes upon the change of counterion could be detected. It can be assumed that Zn(II) and anhydrous Cu(II) salts form the same type of complex with free ligand 26. Therefore, it is believed that 26•CuCl₂ formed an intermolecular amide O-coordinated complex. In our initial experiments, 26•Cu(ClO₄)₂•6H₂O formed the same complex. Then Cu(II) can act as a Lewis acid to catalyze amide hydrolysis, and then the nitrogen subsequently coordinated the Cu(II) to form a more stable complex (Scheme 1.16).
D. Conclusions

Two diamide cross-bridged cyclens (22 and 23) and three monoamide cross-bridged cyclens (24, 25, and 26) were synthesized. A method was developed to synthesize compound 21 which is the key intermediate in the synthesis of monoamide cross-bridged cyclens.

Metal (Li(I), Zn(II), and Cu(II)) coordination of compound 26 was investigated. We anticipated that this ligand can form metal complexes through the nitrogen and not the oxygen of the amide. In the Li(I) coordination study, the ligand 26 could form complex with Li(I) through the amide nitrogen, but the binding was weak. After more addition of Li(I) salt, they converted to the more stable intermolecular amide O-coordinated complex. Under our conditions, the evidence suggested that our ligand forms intermolecular coordination complexes with Zn(II) and Cu(II) through the oxygen of an amide.

Scheme 1.16 Lewis acid-catalyzed amide hydrolysis

\[
\begin{align*}
\text{N} & \quad \text{Cu(II)} \\
\text{O} & \quad \text{H} \\
\text{H} & \quad \text{HOH}
\end{align*}
\]

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CHAPTER II
SYNTHESES OF BIFUNCTIONAL CHELATORS BASED UPON CROSS-BRIDGED TETRAAMINE MACROCYCLES

I. Introduction

Radiopharmaceuticals are drugs containing a radionuclide, and are designed for diagnostic or therapeutic purposes, such as to deliver small doses of ionizing radiation to the disease sites in the body. Radiopharmaceuticals are mostly small organic or inorganic compounds with definite composition. They can also be macromolecules, such as monoclonal antibodies and antibody fragments. Biodistribution of radiopharmaceuticals can be determined either by their chemical and physical properties or by receptor binding or other biological interactions. Radiopharmaceuticals which act through receptor binding, are called receptor-based target-specific radiopharmaceuticals.\textsuperscript{23,24,25}

The use of radiometal-labeled small complexes and biomolecules as diagnostic agents is a relatively new area of medical research. In the late 1940s and early 1950s, the use of nuclear technology for medical purposes began with nuclear reactors, accelerators, and cyclotrons being applied to medical isotope production. Within the last 15 years, there has been a considerable amount of research in the area of radiometal-labeled receptor targeting agents. Receptor ligands can be larger biomolecules such as peptides or smaller organic molecules such as dopamine or folic acid. The radiometal is connected to these biomolecules via a bifunctional chelator (BFC),\textsuperscript{25,26} which consists of a chelate to complex the radiometal and a functional group for attachment to the biomolecule.
(targeting molecule) by forming amide, thiourea, urea, Schiff base, or thioether linkages with amine or thiol groups on proteins and peptides (Figure 2.1).

![Diagram](targeting molecule) by forming amide, thiourea, urea, Schiff base, or thioether linkages with amine or thiol groups on proteins and peptides (Figure 2.1).

**Figure 2.1** Diagrammatic representation of a bifunctional chelator (BFC)

The first BFCs described were analogs of EDTA and DTPA (27 and 28, Figure 2.2), such as 29 (Figure 2.3). Octreotide, an 8-amino acid somatostatin (SS) analog has been labeled with $^{111}\text{In}$ using DTPA as a BFC, and is approved for human use in the USA and Europe as a diagnostic imaging agent for neuroendocrine tumors. This development has spurred the search for new target-specific radiopharmaceuticals. Currently, the field of radiometal-labeled radiopharmaceuticals for imaging and therapy of disease is rapidly growing. New therapeutic targeting molecules are being developed at a rapid pace.

![Chemical Structures](27 (EDTA) and 28 (DTPA))

**Figure 2.2** Structures of EDTA and DTPA

The functionalized polyaminopolycarboxylic acids have served as good bifunctional chelators for radiolabeling biomolecules, especially with $^{111}\text{In}$, but they are less applicable for chelation of many other radionuclides such as Cu and Y that are
superior for diagnostic and therapeutic applications. Studies have shown that Cu complexes of these analogs of EDTA and DTPA are insufficiently stable in vivo. It's well known that Cu(II) binds readily and strongly to proteins, particularly albumin. EDTA and DTPA derivatives don't bind Cu(II) well enough to prevent competitive binding of Cu(II) by albumin. Therefore, it seems that stable complexes cannot be formed by using either EDTA or DTPA as bifunctional chelating agents to label antibodies with Cu(II). It has also been shown that $^{90}$Y-DTPA is not very stable in vivo, and free $^{90}$Y accumulates in the bone.

![Figure 2.3 Structure of $^{[111}$In]DTPA-octreotide (OctreoScan)](image)

New bifunctional chelating agents composed of polyazamacrocycles began to draw attention in the 1980s. Generally, macrocyclic complexes are less sensitive to acid dissociation and are more kinetically inert at lower pH. In 1985 Moi and coworkers synthesized a new BFC composed of a 14-membered macrocyclic ring with four carboxymethyl-substituted nitrogens (32, Figure 2.4), which is a derivative of 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid (TETA) (30, Figure 2.4). Even though

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Cu(II)-32 is less thermodynamically stable than Cu(II)-EDTA or Cu(II)-DTPA, it decomposes in human serum at a rate of about 1% per day which is much lower than that of Cu(II)-EDTA or Cu(II)-DTPA.\textsuperscript{33,37} In 1989 Craig and coworkers\textsuperscript{32} also reported that 1,4,7,10 tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) (31, Figure 2.4) forms a more kinetically inert complex with \textsuperscript{90}Y than DTPA. Therefore TETA- and DOTA-based BFCs have been investigated and have been used to radiolabel a number of different cancer-associated antibodies. \textsuperscript{90}Y-DOTA-peptide conjugates for radioimaging and radiotherapy are in clinical trials,\textsuperscript{38} and \textsuperscript{64}Cu-TETA-peptide conjugates are also being evaluated as radioimaging agents for neuroendocrine tumors.\textsuperscript{39}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2_4.png}
\caption{TETA, DOTA and a TETA Derivative 32}
\end{figure}

II. Background

There are several strategies for the design of receptor-based target-specific metalloradiopharmaceuticals. These include the integrated approach, the bifunctional
approach and the peptide-hybrid approach. The integrated approach involves the replacement of part of a known high affinity receptor ligand with the requisite ‘unnatural’ metal chelate in such a way that there are minimal changes in size, conformation, and receptor binding affinity. The bifunctional approach uses a high affinity receptor ligand as the targeting biomolecule, a bifunctional chelator (BFC) for conjugation of the biomolecule and chelation of the radionuclide. In the peptide-hybrid approach, the radionuclide is chelated by a tripeptide sequence containing an N₄, N₃S, or N₂S₂ donor set. However, the bifunctional approach is the most popular approach for the development of receptor-based target-specific radiopharmaceuticals. There are several requirements for an ideal BFC. The BFC has to be able to withstand radiolysis because a large dose of β-radiation can produce very reactive free radicals and result in a significant amount of decomposition of the metal chelate during process and transportation. The BFC must form a metal chelate with high thermodynamic stability and kinetic inertness at biological pH in order to keep the metal chelate intact under physiological conditions. Decomposition of the metal chelate produces free radiometal ion, which may damage healthy cells. The conjugation group of the BFC should be easily attached to the biomolecule.

The most common way to increase the thermodynamic stability and kinetic inertness of a metal complex is to use a polydentate chelator. Compared to open-chained analogues, polydentate macrocyclic ligand metal complexes exhibit extra thermodynamic stability, which is attributed to the macrocyclic effect: a larger enthalpy and smaller entropy of formation. Three common tetraaza macrocycles that we are interested in are cyclen, 13-ane-N₄, (sometimes called homocyclen) and cyclam (Figure 2.5). These...
macrocycles also have flexibility in their coordination geometries. The flexibility allows macrocycles to coordinate many different metals, but it also allows the ligands to adopt isomeric geometries about the same metal. As a result of this mixed stereochemistry, modifications have been made to “preorganize” these ligands to favor specific coordination geometries. The higher the degree of preorganization of an uncoordinated ligand, the more stable the metal complex.\textsuperscript{23,39,40} Preorganization of the ligand framework also tends to improve the kinetic inertness,\textsuperscript{41} which is the determining factor for the release of radionuclide from the metalloradiopharmaceutical.

![Figure 2.5 Cyclen, 13-ane-N\textsubscript{4}, and cyclam](image)

As discussed in Chapter one, Weisman and Wong made a structural modification to the parent polyamine macrocycles cyclen, 13-ane-N\textsubscript{4}, and cyclam ligands whereby two nonadjacent nitrogens were bridged with an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) unit (17, 34 and 35, Figure 2.6)\textsuperscript{11,12,13,19}. These cross-bridged tetraaza macrocycles adopt a cis-folded coordination geometry when coordinated with small metal cations. Figure 2.7 illustrates the cleft created by the cross-bridged arrangement and the low energy conformation of these ligands upon metal complexation. For example, the copper (II) complex of the
dimethyl cross-bridged cyclam was found to be over eight orders of magnitude more stable to acid decomplexation than its closest unbridged analog\(^\text{42}\).

\[
\begin{align*}
\text{N} & \text{H} & \text{N} \\
\text{N} & \text{H} & \text{N} \\
\text{N} & \text{H} & \text{N}
\end{align*}
\]

17 \hspace{1cm} 34 \hspace{1cm} 35

**Figure 2.6** Cross-bridged cyclen 17, cross-bridged 13-ane-N\(_4\) 34, and cross-bridged cyclam 35

\[
\begin{align*}
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\text{N} & \text{N}
\end{align*}
\]

**Figure 2.7** A clam shell arrangement and the cis-folded coordination geometry of the cross-bridged tetraaza macrocycles

A further enhancement of the already high kinetic stability of these cross-bridged ligand copper(II) complexes can be realized through the attachment of ionizable pendant arms at the two secondary nitrogens. As shown by a number of X-ray studies, these pendent arms can serve to fully envelop a six coordinate cation as well as neutralize a dicationic charge. The latter property is desirable for optimal \(^{54}\text{Cu(II)}\) complex biodistribution and clearance characteristics.\(^{12, 43, 44}\)
Analogs of TETA are currently the most common chelators used for copper radionuclides. However, nearly all radio-Cu(II) complexes (e.g. radio-Cu(II)-TETA) exhibit in vivo instability due to transchelation of the Cu(II) to proteins. A current challenge in the development of copper radiopharmaceuticals is to design appropriate macrocyclic chelators that can form complexes with copper radionuclides that exhibit a high kinetic stability in vivo. Results on the complex of Cu(II) with the ligand, 4,11-bis-(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (CB-TE2A) (36, Figure 2.8) indicate the ligand can be radiolabeled in high radiochemical purity and that the labeled complex was found to be highly stable in rat serum for 24 hours. As a neutral complex it cleared rapidly from all tissues and had more optimal clearance properties than $^{64}$Cu-TETA. $^{64}$Cu-36 behaves ideally in vivo, suggesting that 36 itself or other bifunctional chelators based on 36 will have significant potential as a labeled copper radionuclide for diagnostic imaging and targeted radiotherapy.

![Structure of 36](image)

**Figure 2.8 Structure of 36**

36 as a BFC was conjugated with a special biomolecule (e.g. Y3-TATE, which is a well-characterized SSTr2 ligand and a good model for evaluating novel BFC-peptide conjugates). The bioconjugate, 36-Y3-TATE (37, Figure 2.9), was then labeled with

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It was determined that $^{64}\text{Cu}$-37 has better microPET data for imaging cancer than $^{64}\text{Cu}$-TETA-Y3-TATE (38, Figure 2.10), which is superior in tumor uptake and biological clearance in a tumor-bearing rat model. Therefore, 36 is a superior chelator for $^{64}\text{Cu}$ due to improved liver and blood clearance, resulting in higher tumor/tissue ratios compared to the $^{64}\text{Cu}$-labeled TETA conjugate. Modifications to 36 to reduce the net positive charge of the Cu(II) complex may further improve the biodistribution.\(^{49}\)

**Figure 2.9 A BFC application of 36**

**Figure 2.10 Structure of TETA-Y3-TATE**

Thus, appropriate cross-bridged tetraamine macrocycles are promising BFCs, and 36 shows excellent results for diagnostic imaging. In Figure 2.11 are listed known BFCs based upon cross-bridged ligands whose syntheses needed to be improved as well as new designed BFCs based upon the cross-bridged tetraamine macrocycles (Figure 2.11). Our general strategy for synthesis of BFCs based on the pendant-arm cross-bridged tetraamine motif requires BFC precursor targets having a remote unprotected carboxyl
group for bioconjugation (peptide or protein coupling) and carboxyls for coordination protected as t-butyl esters. After conjugation, the esters are to be deprotected to carboxyl groups for radiolabelling with metal. Synthetic designs also must minimize stereochemical complications. Dr. Carolyn Anderson’s group and collaborators at the Washington University School of Medicine then carry out bioconjugation and evaluate the efficacy of the bioconjugates as carriers of cancer diagnostic and therapeutic copper, gallium, and indium radionuclides.

![Chemical Structures](image)

**Figure 2.11** The structures of targeting molecules

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The synthesis of the HCl salt of ligand 36 (36•4HCl) was originally developed by Hill (Scheme 2.1).\textsuperscript{12,13,19}

Scheme 2.1 The synthesis of 36•4HCl

An alternative synthesis was needed. We proposed the following retrosynthetic pathway for 36 (Scheme 2.2).

Scheme 2.2 Retro-synthetic routes for 36

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The ligand 39 was originally developed by Condon\textsuperscript{50} in our research group (Scheme 2.3).

\begin{center}
\begin{tikzpicture}

\node[draw, shape=circle, fill=white, minimum size=1cm] (a) at (0,0) {14};
\node[draw, shape=circle, fill=white, minimum size=1cm] (b) at (2,0) {52};
\node[draw, shape=circle, fill=white, minimum size=1cm] (c) at (4,0) {39};

\draw[->] (a) -- node[above] {t-butyl bromoacetate (xs)} (b);
\draw[->] (b) -- node[above] {\text{CH}_3\text{CN}} node[below] {74\%} (c);
\draw[->] (b) -- node[above] {\text{NaBH}_4} node[below] {95\% \text{ EtOH}} (c);
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.3} Condon's synthesis of 39$\cdot$1TFA

An alternative synthesis could be realized as indicated in Scheme 2.4.

\begin{center}
\begin{tikzpicture}

\node[draw, shape=circle, fill=white, minimum size=1cm] (a) at (0,0) {39};
\node[draw, shape=circle, fill=white, minimum size=1cm] (b) at (2,0) {53};
\node[draw, shape=circle, fill=white, minimum size=1cm] (c) at (4,0) {17};

\draw[->] (a) -- node[above] {TFA} node[below] {67\%} (b);
\draw[->] (b) -- node[above] {1:1 (v:v) TFA:CH_2Cl_2} (c);
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.4} Retro-synthetic routes for 39

Condon's initial work on a benzo-annelated cross-bridged cyclam had focused on utilizing the synthetic approach developed by Weisman, Wong and coworkers toward cross-bridged tetraazamacrocycles with dibenzocyclam, which has been reported in the literature.\textsuperscript{51,52,53,54} Needing this ligand for his study, Condon had worked out the protocol for the synthesis of dibenzocyclam 56 shown in Scheme 2.5.\textsuperscript{50}

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Scheme 2.5 The Synthesis of dibenzocyclam 56

Having the dibenzocyclam ligand 56 in hand, Condon performed a glyoxal condensation to obtain the cis-fused glyoxal adduct 57, and also carried out the synthesis of one example of a cross-bridged dibenzocyclam (Scheme 2.6).

Scheme 2.6 The synthesis of cross-bridged dibenzocyclam 59

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With the synthesis of dibenzo biaminal 57 in hand, we proposed the following retrosynthetic pathway for 44 (Scheme 2.7).

Scheme 2.7 Retro-synthetic routes for 44

Bist's initial work on the C-substituted cross-bridged tetraazamacrocycles in our group had focused on utilizing the synthetic approach of Weisman, Wong and coworkers toward cross-bridged tetraazamacrocycles. She performed a pyruvaldehyde condensation with cyclen to obtain the cis-fused pyruvaldehyde adduct 66 which was finally converted to C-substituted cross-bridged cyclen 68 (Scheme 2.8).
Scheme 2.8 The synthesis of C-substituted cross-bridged cyclen 68

We are encouraged by the example of C-substituted cross-bridged cyclen 68. It is envisioned that we can use same synthetic strategy to approach our BFC 40. The retrosynthetic pathway for 40 is shown in Scheme 2.9.

Scheme 2.9 Retro-synthetic route for 40

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Condon\textsuperscript{50} also had worked on the N-carbo-tert-butoxymethyl cross-bridged cyclen 73, which is a very useful compound due to its secondary amine. The precursor 72 was synthesized, but clear debenzylation was not achieved after several trials (Scheme 2.10).\textsuperscript{50}

![Chemical diagram]

**Scheme 2.10** Toward the synthesis of mono-tert-butyl cross-bridged cyclen 73

We are encouraged by the debenzylation method that we developed earlier for synthesizing N-methyl cross-bridged cyclen 21 (Chapter one). Therefore, our retro-synthetic pathway toward BFC 41 is proposed based upon compound 72 (Scheme 2.11).

![Chemical diagram]

**Scheme 2.11** Retro-synthetic routes for BFC 41

It is also envisioned that we could use same strategy to approach BFC 43, 45 and 46. Scheme 2.12 shows the retro-synthetic pathway for BFC 43, 45 and 46.
Scheme 2.12 Retro-synthetic route for BFC 43, 45 and 46

Hill’s synthesis of 34, the cross-bridged analog of 14-ane-N₄ 33 is shown in Scheme 2.13.loyd19

Scheme 2.13 The synthesis of cross-bridged 14-ane-N₄ 34

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With the synthesis of 34 in hand, we proposed the following retrosynthetic pathway for 42 (Scheme 2.14).

![Scheme 1.14 Retro-synthetic route for 42](image)

The successes and failures of our synthetic approaches to the BFCs of Figure 2.11 will be discussed in the Results and Discussion section.

III. Results and Discussion

A. The Synthesis and Characterization of the Bis-(trifluoroacetic acid) Salt of 4,11-Bis-(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (36•2TFA)

The synthetic strategy which was outlined in Scheme 2.2 was used to synthesize 4,11-bis-(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (36•2TFA) (Scheme 2.15).

![Scheme 2.15 The synthesis of 36•2TFA](image)
Di-N-H cross-bridged cyclam 35 which was originally synthesized by Weisman, Wong and Hill was allowed to react with a slightly excess of tert-butyl bromoacetate in CH$_3$CN to give the desired product 51 as a white solid in excellent yield (93%). 51 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS). 51 was then stirred in 1:1 (v:v) solution of TFA: CH$_2$Cl$_2$ for 48 h. Solvent removal gave oil, which crystallized after removal of residual solvent under vacuum. This solid passed elemental analysis as a di-TFA salt. Compound 36’s proton and carbon NMR spectra were consistent with this formulation.

This method was preferred over the former method which was developed by Hill.$^{12,13,19}$ The deprotection of t-butyl ester is much easier than the deprotection of ethyl ester.

B. The Synthesis of 4-(tert-Butyl)carboxymethvl-10-(2-hvdroxv-benzvl)-1,4,7,10-tetraazabicvclo[5,5,21tetradecane (83) and The Attempted Synthesis of 3-(10-tert-Butoxycarbonylmethyl-1,4,7,10-tetraazabicvclo[5,5,21tetradec-4-vlmethvl)-4-hvdroxy-benzoic acid (41)

Compound 41 (Figure 2.12) was a good candidate for BFC. The synthetic strategy which was outlined in Scheme 2.11 was used to synthesize the target.

![Figure 2.12 The Structure of BFC 41](image-url)
Before we tried to synthesize desired BFC 41, we first tried a model compound. This approach has at least two advantages, one is that we can check the method that we try to use to make the desired compound; the other is that we can use the model compound to perform the coordination chemistry to check if the desired BFC has good kinetic and thermodynamic properties in coordination chemistry. The model compound 83 was synthesized as indicated in Scheme 2.16.

The precursor of N-carbo-tert-butoxymethyl cross-bridged cyclen 72 was synthesized by following the method that was developed by Condon50 (Scheme 2.10), and its selective debenzylolation was performed by using the acidic condition hydrogenolysis that we developed earlier for synthesizing N-methyl cross-bridged cyclen 21 (Chapter One) as indicated in Scheme 2.16. The compound 73 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS). And then the mono-tert-butyl cross-bridged cyclen 73 and salicylaldehyde were mixed in ClCH₂CH₂Cl, and sodium
triacetoxyborohydride was then added. After base extraction, solvent removal gave the desired product in moderate yield (40%). The compound 83 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS).

Having synthesized the model compound 83, it was envisioned that the BFC 41 could be made in a similar fashion (Scheme 2.17).

Before its reductive alkylation was attempted, we needed to synthesize the 3-formyl-4-hydroxy benzoic acid 85 first. We used a Duff reaction to synthesize the compound from commercially available starting material 4-hydroxy benzoic acid 84 (Scheme 2.18).
4-Hydroxy benzoic acid 84 and hexamethylene tetramine were dissolved in HOAc. The mixture was refluxing for 5 hours, and 33% aq H$_2$SO$_4$ solution was added into the mixture, the resulting mixture was refluxed for an additional 1 hour. After CHCl$_3$ extraction, solvent removal gave white solid product 85 in 39% yield.

The reductive alkylation was then attempted. We used the same procedure as we developed for synthesis of the model compound 83. The mono-tert-butyl cross-bridged cyclen 73 and 3-formyl-4-hydroxy benzoic acid 85 were mixed in CH$_2$CICH$_2$Cl, and sodium triacetoxyborohydride was then added (Scheme 2.17). The workup was difficult, because the product should be an amino acid if we made the compound. The solution’s pH was adjusted to try to precipitate, or to extract with organic solvent such as C$_6$H$_6$ and CHCl$_3$, but that approach failed. Finally, all solvents were removed under reduced pressure to generate the crude product. NMR shows that we made the compound 41, and also shows some unknown impurities. We tried to isolate the product by chromatography, but it failed. Because the desired BFC is too polar, in the future we might isolate the product by reverse phase chromatography.

C. The Synthesis and Characterization of Hydrochloride Salt of 4-Carboxymethyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (87·4HCl).

During the investigation of BFC 41 we found that we could easily synthesize the monoionizable cross-bridged cyclen 87, which is a very interesting ligand for metal complexation study.

87 was synthesized by acidic hydrolysis as indicated in Scheme 2.19.
Scheme 2.19 The synthesis of 87

The cross-bridged cyclen 72 was dissolved in a solution of 4.4% HCOOH in MeOH, and 10% Pd/C as catalyst was also added into the mixture. After workup, the solvent was removed under reduced pressure to give pure product in excellent yield (99%). 86 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS). 86 was then dissolved in 6 M HCl and allowed to reflux for 3 days. Solvent removal gave the product as a white solid HCl salt, the mass calculation indicated that there are four HCl molecules. The compound 87 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS).

D. Attempted Synthesis of C-functionalized BFC 40

40 (Figure 13) was a good candidate for BFC. The synthetic strategy which was outlined in Scheme 2.9 was used to approach the target.
According to the strategy, first step is that cyclen reacts with 4,5-dioxopentanoic acid (91). Compound 91 isn't commercially available, but 91 is a known compound, and can be prepared in two steps using a published method which starts from commercially available laevulinic acid and benzaldehyde (Scheme 2.20). Laevulinic acid and benzaldehyde were dissolved in dry benzene, and acetic acid and dry piperidine were also added to the mixture. The resulting solution was then refluxed for 72 hours. After workup, solvent removal gave white crystalline product 90 in 81% yield. The melting point and \(^1\)H NMR were consistent with the reported spectra, and \(^1\)3C NMR was also consistent with the formulation. After we made the benzylidene laevulinic acid 90, we followed the literature ozonolysis to give the 4,5-dioxopentanoic acid 91 in 90% yield (calculated based upon monohydrate compound).

![Scheme 2.20](image)

**Scheme 2.20** The synthesis of 4, 5-dioxopentanoic acid 91

However, the compound wasn't fully characterized in the literature, even in the original published paper. The authors only showed one complex \(^1\)H NMR, and mentioned that the compound passed CHN analysis as a monohydrate compound. We
believe that the product is a mixture of at least three molecules as indicated in Scheme 2.21. NMR showed that the hydrate form 92 is likely the dominant molecule. The monohydrate was used in our next step without further purification.

Scheme 2.21 Possible three molecules

Compound 70 was synthesized by the condensation reaction as indicated in Scheme 2.22.

Scheme 2.22 The synthesis of 70

Cyclen (13) and excess 4,5-dioxopentanoic acid monohydrate 91 were dissolved in CH₃CN or MeOH, and the solution was heated to 50-60 °C for 4 hours. Solvent removal gave crude product which was subjected to chromatography to give pure product in, at best, 13% yield. The compound 70 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS).

Alkylation of tetracyclic bisaminal 70 with excess tert-butyl bromoacetate was attempted (Scheme 2.23).
Scheme 2.23 Attempted synthesis of 69

Generally, CH$_3$CN is our first choice as the solvent of this kind of alkylation reaction in our group, but 70 has very poor solubility in CH$_3$CN and is more soluble in CH$_2$Cl$_2$. Therefore, 70 and excess t-butyl bromoacetate was dissolved in CH$_2$Cl$_2$ and then the mixture was stirred for 3 days. Unfortunately, no precipitate was formed. Diethyl ether was added to form precipitate which was isolated and subjected to NMR analysis. The NMR spectra were complex, indicating a mixture. t-Butyl signals were present in both $^1$H NMR and $^{13}$C NMR spectra. The free carboxylic acid group likely caused this failure, so we decided to protect the carboxylic acid. In addition, the best yield of condensation reaction between cyclen and excess 91 was only 13%, and we hoped to increase the percent yield after protection of free carboxylic acid.

The methyl ester derivative 95$^{61a}$ was synthesized as indicated in Scheme 2.24. Benzyldiene laevulinic acid 90 was dissolved in MeOH, a few drops of conc. H$_2$SO$_4$ were added, and the mixture was refluxed for 0.75 hours. Solvent was removed under reduced pressure to give crude product which was recrystallized from a hot mixture of ethyl acetate and hexane (1: 4, v:v) to yield crystalline product 94$^{61b}$ in 75% yield. Compound 94 was converted to methyl 4, 5-dioxopentanoate 95 by ozonolysis.
Another alternative synthetic approach of compound 95 is indicated in Scheme 2.25. Compound 99 was prepared in three steps by published methods, and then converted to methyl 4, 5-dioxopentanoate 95 by TPAP (tetra-n-propylammonium perruthenate) oxidation.

Scheme 2.24 The synthesis of 95

Scheme 2.25 The alternative synthesis of 95

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Treatment of laevulinic acid 96 with Br\(_2\) in refluxing methanol gave a mixture of methyl 5-bromolaevulinate (97), 3-bromolaevulinate (100), and 3,5-dibromolaevulinate (101).\(^{62a}\) After column chromatography, we isolated the methyl 5-bromolaevulinate 97 in 24% yield. S\(_{N}\)2 displacement by formate under basic conditions in benzene yielded the formyloxy compound 98 which was easily hydrolyzed to the 5-hydroxy methyl ester 99 by passing it through a column of neutral alumina.\(^{62b}\) The methyl 4,5-dioxopentanoate 95 was prepared by TPAP oxidation.\(^{63}\)

Interestingly, during one early attempt to synthesize 95 by ozonolysis, using H\(_2\) and 10% Pd/C in the reductive workup instead of dimethyl sulfide, an unknown product was obtained. Comparison of the spectra of this product with those of methyl 5-hydroxylaevulinate 99, showed them to be the same (Scheme 2.26).

![Scheme 2.26 The synthesis of 99](image)

Although the methyl 4,5-dioxopentanoate 95 was a known compound,\(^{61}\) no NMR data were available in the literature. By searching the literature we found that there was a complex proton NMR spectrum of the ethyl 4,5-dioxopentanoate\(^{64}\) which was made by ozonolysis, and the authors mentioned that the compound was unstable, and used immediately without further purification.
Condensation of the compound 95 with cyclen (13) was attempted as indicated in Scheme 2.27.

![Scheme 2.27 The attempted synthesis of 102](image)

Cyclen (13) and excess methyl 4,5-dioxopentanoate 93 were dissolved in CH₃CN or MeOH, and the solution was heated to 50-60 °C for 4 hours. Solvent removal gave crude product which was subjected to chromatography to give compound 102 in less than 7%. But some extra peaks in both ¹H NMR and ¹³C NMR were observed, the extra peaks were located in aromatic region.

As all of the attempts failed, an alternative strategy toward the BFC 40 is needed. Time constraints prevented the investigation of such an approach. We hope that some other member of the Weisman and Wong groups can finish the job in the future.

E. An Alternative Synthesis of 53

The precursor of BFC 39, di-t-butyl ester 53, had been synthesized and converted to compound 39 by Condon⁵⁰ as indicated in Scheme 2.3.

We investigated the possibility of direct monoalkylation of cross-bridged cyclen 17 with t-butyl bromoacetate, the pure mono-tert-butyl ester cross-bridged cyclen 73.
wasn’t obtained by direct alkylation of cross-bridged cyclen 17. Instead the pure di-tert-butyl ester cross-bridged cyclen 53 was obtained as indicated in Scheme 2.28.

\[
\text{Scheme 2.28 The formal synthesis of 39}
\]

Cross-bridged cyclen 17 was dissolved in toluene, and anhydrous sodium carbonate and 1 equivalent of t-butylbromoacetate were added. The mixture was stirred for 24 h at room temperature. After solid KOH was used to adjust pH to 14, the organic layer was separated, dried (\(\text{Na}_2\text{SO}_4\)), and evaporated to dryness under reduced pressure to yield pure 53 as slightly yellow oil in 49% yield. At that time we didn’t recover the equivalent of starting material from aqueous phase. NMR spectra of 53 were consistent with spectra of authentic material.

F. The Synthesis and Characterization of 4,11-Bis-(carbo-tert-butoxymethyl)-1,4,8,11-tetraazabicyclo[6.5.2]pentadecane (82).

As discussed in the Background of this chapter, the precursor Di-NH, cross-bridged 14-ane-N₄ 34 was synthesized according to the procedure outlined by Hill (Scheme 2.9).¹⁹

The compound 82 was synthesized as indicated in Scheme 2.29.
Treatment of di-NH, cross-bridged 14-ane-N₄ 34 with excess tert-butyl bromoacetate under basic conditions in MeCN gave crude product. After chromatography the pure compound 82 was obtained in moderate yield (55%).

Although time and sample quantity constraints prevented our conversion of 82 to the trifluoroacetic acid salt of 4,11-bis-(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.5.2]-pentadecane (42•nTFA), this will be carried out in the future as indicated in Scheme 2.27. The small sample of 82 that we prepared was provided to Professor Carolyn Anderson’s group at Washington University for conversion to 42 and subsequent labeling with ⁶⁴Cu(II). The Weisman and Wong groups will scale this up and carry out cold Cu(II) coordination chemistry in the future.

G. Progress Toward Dibenzo BFC 44

The synthetic strategy which was outlined in Scheme 2.7 was used to approach the interesting BFC 44 (Figure 2.14).
Figure 2.14 The Structure of BFC 44

The compound 64 was synthesized as indicated in Scheme 2.30.55,66

Scheme 2.30 The synthesis of 64

Starting material 57 was synthesized by following the method that was developed by Condon (Scheme 2.6)50. Treatment of 57 with 1 equivalent of tetrabutylammonium tribromide (TBABr3) in CHCl3 didn’t give exclusively the mono-para-brominated (para to aniline nitrogen) compound, but a mixture of monobrominated compound 64, dibrominated compound 103 and starting material 57. When we used more than 1 equivalent TBABr3 up to slight excess of 2 equivalents TBABr3, dibrominated 103 became major product.
From NMR spectra, approximately 40% of the product was mono-substituted product 64, which can be purified by chromatography. Unfortunately, the mono- and dibromination derivatives have very similar solubility, and both have very poor solubility in almost all solvents, which makes isolation very difficult. Small amounts of sample had to be dissolved in large amounts of solvent. By flash chromatography product of approximately 70% purity was obtained and this was subsequently used without further purification. A small amount of pure compound was acquired by repeated flash chromatography (4 times). The compound 64 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS).

The compound 63 was synthesized from 64 by a Heck coupling reaction as indicated in Scheme 2.31.

![Scheme 2.31 The synthesis of 63](image)

Treatment of monobrominated derivative 64 with NaOAc, tri(o-tolyl)phosphine, Palladium(II)acacetate, and benzyl acrylate in DMF at 150 °C for 20 h gave crude product after workup and removal solvent. After chromatography, pure 63 was obtained in 21%
yield. 63 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS).

Hydrogenation of the olefin of 63 without debenzylation was attempted (Scheme 2.32). A variety of conditions for hydrogenation of alkenes containing the hydrogenolysis-susceptible O-benzyl (Bn) group are reported in the literature.\(^{68,69,70,71}\)

![Scheme 2.32 The attempted synthesis of 62](image)

Maki and coworkers\(^{71}\) had reported the use of Pd black as a catalyst to perform hydrogenolysis-free hydrogenation of olefins. One example is showed in Scheme 2.33.

![Scheme 2.33 An example of hydrogenolysis-free hydrogenation of olefin](image)

Therefore, the chemoselective hydrogenation was attempted using the literature condition. Unfortunately, a mixture containing mostly starting material was obtained. As
the attempted hydrogenation failed to afford compound 62, other metal catalysts or other methods are needed to overcome the problem. Time constraints prevented the investigation of such an attempt.

In his investigation of C2 dibenzoannelated dimethyl cross-bridged cyclam 59, Condon has found that dibenzo bisaminal 57 had a solubility limit toward alkylation: The formation of the bis-quaternized bisaminal was hampered by poor solubility of 57 in our typical reaction solvents (MeCN, MeOH, EtOH) for Sn2 alkylation. A possible solution to this problem involves appending flexible alkyl or alkaryl groups to this molecule. When we investigated the conditions for monobromination of 64, we found that dibrominated derivatives are easily prepared. That’s a good starting point for modification of this molecule.

The dibromo bisaminal 103 was synthesized by TBABr3 bromination as indicated in Scheme 2.34.

![Scheme 2.34 The synthesis of 103](image)

Treatment of dibenzoannelated bisaminal 57 with a slight excess of 2 equivalents of TBABr3 in refluxing CHCl3 gave crude product. Recrystallization from hot chloroform gave x-ray quality crystals in moderate yield (50%). The x-ray crystal structure of 103.
(Figure 2.15), solved by Roger Sommers and Arnold Rheingold (Crystallography Laboratory, Department of Chemistry and Biochemistry, University of Delaware), was similar to the structure of its parent compound 57. The crystal structure shows its $C_2$ symmetry and the flanking of the benzene rings about the cleft of this compound. Selected bond lengths and angles from the crystal structure of compound 103 are shown in Table 2.1.

**Figure 2.15** The crystal structure of the dibromo bisaminal 103
Table 2.1 Selected bond lengths and angles from the crystal structure of compound 103

<table>
<thead>
<tr>
<th>Bond Lengths (Å)</th>
<th>Bond Angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(l)-C(l)</td>
<td>N(1)-C(3)</td>
</tr>
<tr>
<td>1.447</td>
<td>1.464</td>
</tr>
</tbody>
</table>

The compound 106 was synthesized by a Heck coupling reaction as indicated in Scheme 2.35.

Treatment of dibrominated derivative 103 with NaOAc, tri(o-tolyl)phosphate, palladium(II)acetate, and benzyl acrylate in DMF at 130 °C for 3 days gave crude product after workup and removal solvent. After chromatography, we got a white solid consisting of a mixture of two products: 106 and 107. The major product was the desired product 106 and the minor product was 2-bromo-9-styril-5,6,12,13,13b,13c-hexahydro-7H,14H-

Scheme 2.35 The synthesis of 106

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4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene (107). The ratio of major to minor was 4.7:1. The mixture was used for next step without further purification.

The compound 108 was synthesized by hydrogenation as indicated in scheme 2.36.

82% purity of 106 was converted to product 108 by the standard conditions for hydrogenation using 10% Pd/C and atmospheric H\textsubscript{2} in ethyl acetate. 108 was obtained in moderate yield (60%) after chromatography. 108 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS).

Two alkylating agents were used for the attempted alkylation of compound 108 as indicated in Scheme 2.37.
Scheme 2.37 Two attempted alkylation of 108

The solubility of 108 in CH$_3$CN, CH$_3$OH and EtOH is almost as poor as that of its parents, but the solubility in CHCl$_3$ and CH$_2$Cl$_2$ is better than that of its parents. Therefore, CHCl$_3$ was used for the alkylation. In the first reaction, the compound 108 was treated with excess tert-butyl bromoacetate in CHCl$_3$, after 3 days at room temperature no precipitate was formed. Diethyl ether was added to the solution to precipitate out the contents, which proved to be starting materials determined by NMR.
In the second reaction, 108 was allowed to react with an excess of benzyl bromide in CHCl₃. After 3 days at room temperature no precipitate was formed. Diethyl ether was added to the solution to precipitate out the contents, which had complex NMR spectra indicative of a mixture. Further investigation of this reaction seems warranted more conclusions here.

H. Attempted Synthesis of BFC 36 and Synthesis of Diamide 115 By a Short Synthetic Route

Since Condon⁵⁰ has already synthesized BFC 39 by using a short synthetic route (Scheme 2.3), we hoped to use same strategy to approach the BFC 36. The retrosynthetic pathway for 36 is indicated in Scheme 2.38.

Scheme 2.38 Short retro-synthetic route for BFC 36

The bisaminal compound 47 was reacted with excess t-butyl bromoacetate in a variety different solvents (CH₃CN, CH₂Cl₂, CHCl₃ and MeOH) (Scheme 2.39). No precipitate formed in any of these reactions. After diethyl ether was added to each
reaction, a white precipitate formed. The precipitate was isolated, and analyzed by NMR. NMR spectra showed that it wasn’t the pure desired product, but a mixture.

Scheme 2.39 The attempted synthesis of 111

However, when cyclam glyoxal adduct 47 was allowed to react with excess ethyl bromoacetate in CH$_3$CN (Scheme 2.40), a small amount of white precipitate formed. This precipitate was isolated and shown to be pure product 112, but the % yield was very poor (7%). When diethyl ether was added to the mother liquid, a white precipitate formed. The precipitate was isolated, and analyzed by NMR, which showed it to be a mixture.

Scheme 2.40 The synthesis of 112

When cyclam glyoxal adduct 47 was allowed to react with an excess (8 equivalents) of 2-bromoacetamide in CH$_3$CN for less than 5 days, the white precipitate that formed was isolated and shown to be the unexpected monoalkylated product 113 (52% yield) (Scheme 2.41). 113 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS).
When the heterogeneous cyclam glyoxal adduct 47 and an excess (8 equivalents) of 2-bromoacetamide reaction mixture was stirred for 15 days, the dialkylated product 114 was obtained in 67% yield. 114 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS). 114 was then reductively ring-expanded to cross-bridged compound 116 (Scheme 2.42), which had already been synthesized by Hill using a longer synthetic route\textsuperscript{12,19}. NMR spectra of 115 were consistent with spectra reported by Hill\textsuperscript{12,19}.

The success (113 and 114) and the failure (111 and 112) of alkylation of 47 show that the driving force for this kind of alkylation reaction is the precipitation/crystallization of product. If the right solvent or solvent mixture is chosen, it should be possible, in theory, to synthesize 111 and 112.

Since we had already synthesized the mono, t-butyl ester cross-bridged cyclen 73 (Scheme 2.16), naturally we thought that we could use same strategy to approach the mono, t-butyl ester cross-bridged cyclam 74 (Scheme 2.43).

Scheme 2.43 a retro-synthetic route for 74

Synthesis of compound 77 was attempted by the alkylation reaction shown in Scheme 2.44.

Scheme 2.44 The attempted mono-alkylation of 47

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Treatment of cyclam glyoxal adduct 47 with t-butyl bromoacetate in nonpolar solvents (Et$_2$O, toluene, hexane) gave a precipitate product. Unfortunately the product that we isolated showed strange properties in different NMR solvents. In D$_2$O it appeared to be one pure compound 77 whose data fit the formulation. However, in other NMR solvents such as CDCl$_3$, CD$_3$CN and CH$_2$Cl$_2$ the product exhibited two sets of peaks. Our first thought was that the compound 77 could be partially protonated, but we couldn’t answer where the proton came from. Another possible explanation is that the product was a mixture of mono- and dialkylated. When dissolved in D$_2$O, the product repeatedly dealkylated and realkylated; this made the NMR spectra appear to be one pure compound by coincidence. Of course more investigation is needed before we know exactly what’s going on.

According to our strategy we can either put on the t-butyl ester pendant-arm first, and then the benzyl group or put on the benzyl group first, and then t-butyl ester pendant-arm. Since we failed in the first route, we had to try the second. We started from compound 78, which was synthesized originally by Hill.$^{12,19}$ Treatment of the compound 78 with t-butyl bromoacetate in different solvents (CH$_3$CN, CHCl$_3$, MeOH, DMF) (Scheme 2.41) gave no precipitate. After diethyl ether addition, precipitate formed. The precipitate was isolated by suction filtration to give white solid product. Unfortunately, the NMR spectra confirmed that it wasn’t the desired product, but a mixture (Scheme 2.45).
Scheme 2.45 The attempted synthesis of 76

As a result of the above investigation, it looked like it could be very difficult to use the same strategy as we used to synthesize the mono-t-butyl ester cross-bridged cyclen 73. In order to approach the mono, t-butyl ester cross-bridged cyclam 74. An alternative strategy was needed to synthesize critical synthetic intermediate 74.

As shown in Scheme 2.15, treatment of cross-bridged cyclam 35 with a slight excess (2.2 equivalents) of t-butyl bromoacetate gave pure product 51 after simple workup. We predicted that treatment of cross-bridged cyclam 35 with 1 equivalent of alkylation agent would give a mixture of monoalkylated, dialkylated, and starting material, and the mono-alkylated should be major product.

As predicted, treatment of 35 with 1 equivalent of t-butyl bromoacetate gave a mixture of monoalkylated 74 (45%-50% from NMR), dialkylated 51, and starting material 35 as indicated in Scheme 2.46.

Scheme 2.46 The synthesis of 74

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Cross-bridged cyclam 35 was dissolved in dry MeCN, sodium carbonate was added in one portion, and 1 equivalent t-butyl bromoacetate was added in one portion by syringe. The solution was stirred for 14 hours at room temperature, and then solvent was removed under reduced pressure. Lucky, the mono-t-butyl cross-bridged cyclam can be isolated by flash chromatography (SiO$_2$, MeOH : CH$_2$Cl$_2$=1.5:1) to give product 74 as an oil in 39% yield. The compound 74 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS).


With compound 74 in hand, we decided to convert the t-butyl ester 74 to the acid 116, which is a very interesting monoionizable ligand for metal complexation studies (Scheme 2.47).

![Scheme 2.47 The synthesis of 116•2TFA](image)

Compound 74 was stirred in CF$_3$CO$_2$H (TFA) for 15 hours. TFA removal gave product 116 as a TFA salt (2 equiv. TFA calculated on the basis of mass and $^1$H NMR). NMR, IR, and HRFABMS data were consistent with this formulation.
K. The Attempted Synthesis of Benzyl-3-(11-carbo-tert-butoxymethyl-1,4,8,11-
tetraazabicyclo[6.6.2]hexadec-4-ylmethyl)-4-hydroxybenzoate (43)

BFC 43 was attempted by reductive alkylation as indicated in Scheme 2.48. When we treated mono, t-butyl ester cross-bridged cyclam 74 with 3-formyl-4-hydroxy-benzoic acid 85 and NaBH₃CN in MeOH, it seemed that we synthesized the reductive alkylation product 43 on the basis of the NMR spectra, but we had difficulty isolating the amino acid 43. We attempted to solve the problem by protection of carboxylic acid prior to reaction.

![Scheme 2.48 The attempted synthesis of 43]

Lee and coworkers had introduced a new method for efficient and chemoselective esterification of carboxylic acids using a CsF-Celite/alkyl halide/CH₃CN reaction system. One example is shown in Scheme 2.49.

![Scheme 2.49 CsF-Celite mediated chemoselective esterification of phenolic carboxylic acid]
The benzoic acid benzyl ester compound 119 was synthesized using the CsF-Celite/BnBr/CH₃CN reaction system as indicated in Scheme 2.50.

When benzoic acid derivative 85 was allowed to react with BnBr and CsF-Celite in CH₃CN, pure product 119 was obtained in 32% yield after solvent removal and flash chromatography. NMR spectra were consistent with the structure.

With the benzoic acid benzyl ester derivative 119 and mono, t-butyl ester cross-bridged cyclam 74 in hand, the reductive alkylation was attempted (Scheme 2.51).

74 was allowed to react with 119 and NaBH₃CN or NaB(OAc)₃H in MeOH. After solvent removal, basic extraction, and then solvent removal gave a solid, whose NMR spectra indicated that it could be the desired product, but there definitely was some
dynamic process going on. The NMR spectra were so complex that more investigation is needed before we can draw a conclusion.

L. The Synthesis of three model compounds - 122, 124 and 126, and Synthesis of 4-(2-(11-tert-Butoxycarbonylmethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-4-yl)-acetylamino)benzoic acid (45)

Before we tried to synthesize the desired BFC 45 (Figure 2.16), we first synthesized three model compounds for BFC 45.

The first model compound 122 was synthesized as indicated in Scheme 2.52.
Treatment of mono-tert-butyl ester cross-bridged cyclam 74 with an excess of 2-bromoacetamide in CH$_3$CN at room temperature yielded N-tert-butyl ester, N-acetamido cross-bridged cyclam 121 in 43% yield. 121 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS). 121 was subsequently stirred in a 1:1 (v:v) solution of TFA:CH$_2$Cl$_2$ for 12 hours. Solvent removal gave product 122 as a TFA salt (2 equiv. TFA calculated on the basis of mass). NMR, IR, and HRFABMS were consistent with this formulation.

The second model compound 124 was synthesized as indicated in Scheme 2.53.
Treatment of compound 74 with 2-chloro-N-methylacetamide in CH$_3$CN at room temperature generated the product 123 in 98% yield. 123 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS). Compound 123 was then stirred in a 1:1 (v:v) solution of TFA:CH$_2$Cl$_2$ for 12 h. Solvent removal gave product 124 as a TFA salt (2 equiv. TFA calculated on the basis of mass), NMR, IR, and HRFABMS were consistent with this formulation.

The third model compound 126 was synthesized as indicated in Scheme 2.54.
Treatment of compound 74 with 2-chloro-N-phenylacetamide in CH$_3$CN at room temperature gave compound 125 in 73% yield. 125 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS). Compound 125 was then stirred in a 1:1 (v:v) solution of TFA:CH$_2$Cl$_2$ for 12 h. Solvent removal gave product 126 as a TFA salt. NMR, IR, and HRFABMS were consistent with this formulation, and there are four TFAs according to the $^1$H NMR.

With the synthesis of the three model compounds for BFC 45, it was envisioned that BFC 45 could be made in a similar fashion. The direct alkylation was first attempted as indicated in Scheme 2.55.
When compound 74 was allowed to react with a slight excess of commercially available 4-(2-chloroacetamido) benzoic acid (127)\(^6\) in \(\text{CH}_3\text{CN}\), solvent removal gave crude product. Purification by flash chromatography failed. We realized that the problem could be caused by unprotected carboxylic acid, so we decided to protect it as methyl ester. The Fischer esterification of compound 127 was carried out in a refluxing mixture of MeOH and cat. conc. \(\text{H}_2\text{SO}_4\). The esterification went very well, but the amide functional group didn’t withstand these conditions, and was hydrolyzed as indicated in Scheme 2.56.

\[ \text{HO}_2\text{C-} -\text{NH} -\text{Cl} \xrightarrow{\text{MeOH}, \text{ Conc. H}_2\text{SO}_4 (\text{cat.}) \text{ reflux}} \text{MeO}_2\text{C-} -\text{NH}_2 \]

Scheme 2.56 The Fischer esterification of 127
Since the direct esterification of compound 127 failed to give the desired product 129, an alternative preparation of compound 129 was needed. The approach taken is shown in Scheme 2.57.

![Scheme 2.57 The synthesis of 129](image)

When 128, which is commercially available was allowed to react with chloroacetyl chloride in acetic acid, the desired product 129 was synthesized in good yield (98%).

With methyl 4-(2-chloroacetylamino)benzoate 129 in hand, the alkylation of mono, t-butyl ester cross-bridged cyclam 74 was performed as indicated in Scheme 2.58.

![Scheme 2.58 The synthesis of 130](image)

Treatment of mono, t-butyl ester cross-bridged cyclam 74 in CH3CN with the methyl benzoate derivative 129 gave product as a light yellow oil in 91% yield after workup. 130 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS).
Selective deprotection of the methyl ester in the present of the t-butyl ester wasn’t expected to be a problem, there are a few sets of conditions\textsuperscript{79} that can be used to deprotect the methyl ester, but not touch the t-butyl ester. The attempted conversion is indicated in Scheme 2.59.

![Scheme 2.59 The attempted synthesis of 45](image)

In the first attempt the compound 130 was allowed to react with 1N NaOH in a mixture of dioxane and H\textsubscript{2}O\textsuperscript{79a}. After the mixture was stirred for 3 h, workup and solvent removal gave a product whose NMR indicated that both the methyl ester and the t-butyl ester were saponified. In the second attempt, the compound 130 was allowed to react with K\textsubscript{2}CO\textsubscript{3} in mixture of MeOH and H\textsubscript{2}O\textsuperscript{79c}. After the mixture was stirred for 16 h at room temperature, solvent removal gave a product whose NMR indicated that there was a mixture of desired product and product having both esters deprotected. Since our desired product is an amino acid, we decided to avoid the use of acid and base in the deprotection step. We decided to switch to a benzyl ester protecting group.

Although we failed to convert compound 130 to BFC 45 in our attempted synthesis (Scheme 2.60), 130 was converted to model compound 131 of BFC 45. The reaction is indicated in Scheme 2.60.
Compound 130 was stirred in 1:1 (v:v) solution of TFA and CH$_2$Cl$_2$ for 16 h. Solvent removal gave product as a TFA salt. NMR and HRFABMS were consistent with this formulation, and there are 3.76 equivalents of TFA according to the calculation based upon mass of the product. Compound 131 may be used as a model compound of BFC 45 to test coordination chemistry.

With the synthesis of 130, it was envisioned that benzyl ester derivative 128 could be made in a similar fashion. But first we needed to synthesize benzyl 4-(2-chloroacetylamino)benzoate (134). Compound 134 was made as indicated in Scheme 2.61.
4-Aminobenzoic acid 132 was allowed to react with benzyl bromide in basic DMSO to regioselectively give desired product 133 in 51% yield. Compound 133 was then allowed to react with chloroacetyl chloride in acetic acid to give the desired product 134 in 91% yield. The alkylating agent 134 was characterized by NMR, IR, and high resolution FAB mass spectrometry (HRFABMS).

With the alkylating agent 134 in hand, cross-bridged BFC precursor 135 was synthesized by alkylation as indicated in Scheme 2.62.

Treatment of the mono-t-butyl ester cross-bridged cyclam 74 with the alkylation agent 134, Na$_2$CO$_3$, and KI in CH$_3$CN gave the desired product 135 in 99% yield. 135 was characterized by NMR, IR, and HRFABMS.

With the BFC precursor 135 in hand, the debenzylation was carried out in our glass hydrogenation apparatus designed for exclusion of O$_2$ and for measurement of H$_2$ uptake with maintenance of constant pressure. It was experimentally determined that the precursor was soluble in ethyl acetate. Thus the standard conditions for hydrogenolysis using 10% Pd/C and atmospheric H$_2$ in ethyl acetate was carried out. After workup, the

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desired BFC 45 was isolated in 81% yield (Scheme 2.63). 45 was characterized by NMR, IR, and HRFABMS.

Scheme 2.63 The synthesis of 45

M. The Synthesis and Characterization of 3-(4-(2-(11-tert-Butoxycarbonylmethyl-Octa-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-4-yl)-ethylsulfamoyl)phenyl)propionic Acid (46)

There are many possible strategies to synthesize BFC 46, Scheme 2.64 shows the approach that we used to synthesize the compound. When we disconnect the long arm, it will generate two fragments whose synthetic equivalents are mono-t-butyl ester cross-bridged cyclam 74, which was previously synthesized and an aziridine derivative (e.g. 136 or 137)
The aziridine derivative is not commercially available, however, there are a couple of strategies that we designed to approach the target. One of them which started from 4-bromobenzenesulfonyl chloride 141 is shown in Scheme 2.65.

Compound 139 was synthesized as indicated in Scheme 2.66.
Compound 141 was allowed to react with 0.5 equiv ethanolamine in pyridine. After workup and recrystallization from hot CHCl₃, the desired crystalline product 140 was obtained in good yield (66%). The reaction condition was modeled on the method for the synthesis of N-(2-((p-tolylsulfonyl)oxy)ethyl)-p-tolylsulfonamide. Compound 140 was characterized by NMR, IR, and HRFABMS. 140 was then treated with 20% KOH in benzene to give the desired aziridine derivative 139 in 86% yield (the procedure was modeled on the method for the synthesis of N-(p-tolylsulfonyl)aziridine). The compound was characterized by NMR, IR, and HRFABMS.

The next step of this synthetic strategy was attempted by Heck coupling reaction. However, when the aziridine 139 was allowed to react with benzyl acrylate under common Heck coupling condition, a surprising result was obtained. We didn’t get the desired product 138, but the 1,4-distyrylbenzene 142 (Scheme 2.67). We didn’t predict that the aziridinesulfonyl group also was a leaving group for the Heck reaction. Literature
didn’t show any example that sulfonamide group acted as leaving group in Heck reaction according to our search.

\[
\text{Br} \quad \text{benzyl acrylate} \quad \text{Palladium(II)acetate} \quad \text{Tri(o-tolyl)phosphine} \quad \text{NaOAc, DMF} \quad 150 \, ^\circ \text{C} \quad 49\%
\]

139

Scheme 2.67 The attempted synthesis of 138

Since we failed to convert compound 140 to compound 138, another strategy to approach aziridine derivate 136 and 137 is shown as indicated in Scheme 2.68.

\[
\text{COOCH}_3 \quad \text{SO}_2\text{Cl} \quad \text{COOR} \quad \text{R}=\text{Me}, \; 145 \quad \text{R}=\text{Bn}, \; 146
\]

\[
\text{COOR} \quad \text{R}=\text{Me}, \; 143 \quad \text{R}=\text{Bn}, \; 144
\]

Scheme 2.68 Retro-synthetic route for 136 and 137

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136 was synthesized as indicated in Scheme 2.69. When compound 145 was allowed to react with ethanolamine in pyridine, the desired product 143 was isolated in 40% yield after workup and flash chromatography. The reaction condition was modeled on the method for the synthesis of N-(2-((p-tolylsulfonyl)oxy)ethyl)-p-tolylsulfonamide. 143 was characterized by NMR, IR, and HRFABMS. Treatment of compound 143 with 20% KOH in benzene gave desired aziridine derivative 136 in 89% yield. The procedure was modeled on the method for the synthesis of N-(p-tolylsulfonyl)aziridine. 136 was characterized by NMR, IR, and HRFABMS. With the compound 136 in hand, it had been our intention to try the ring opening reaction with mono, t-butyl ester cross-bridged cyclam 74. However, our failure to synthesize the BFC 45 by deprotection of a methyl ester in the final step (Scheme 2.59) convinced us to switch to a benzyl ester protecting group at this stage. The same strategy was used to synthesize the benzyl ester aziridine derivative 137.
Scheme 2.69 The synthesis of 136

Compound 137 was synthesized as indicated in Scheme 2.70. When hydrocinnamic acid 147 was allowed to react with the chlorosulfonic acid, after workup and recrystallization from hot benzene, the desired product 148 was obtained in 65% yield. 148 was converted to the corresponding benzyl ester derivative 146 by Fischer esterification. But at that time we were worried about the aqueous workup which may hydrolyze the sulfonyl chloride group to corresponding acid. The product of Fischer esterification was treated with thionyl chloride. Later on we learned that the step of treatment with thionyl chloride was not necessary by low resolution mass spectrometry (LRMS) and NMR spectra. Compound 146 was then allowed to react with 0.5 equiv ethanolamine in pyridine to give compound 144. The reaction condition (from 146 to 144) was modeled on the method for the synthesis of N-(2-((p-tolylsulfonyl)oxy)ethyl)-p-tolylsulfonylamide. 137 was characterized by NMR, IR, and HRFABMS. 144 was then

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treated with 20% KOH in benzene to yield the benzyl ester aziridine derivative 137 in 90% yield. The reaction condition (from 144 to 139) was modeled on the method for the synthesis of N-(p-tolylsulfonyl)aziridine.\(^3\) 137 was characterized by NMR, IR, and HRFABMS.

\[ \text{Scheme 2.70 The synthesis of 137} \]

Compound 149 was synthesized by the ring opening reaction as indicated in Scheme 2.71.
Treatment of the mono-t-butyl ester cross-bridged cyclam 74 with the aziridine derivative 137 in CH$_3$CN gave the desired product 149 in good yield (77%). 149 was characterized by NMR, IR, and HRFABMS.

With the precursor 149 in hand, the debenzylation was performed as indicated in Scheme 2.72.

Scheme 2.72 The synthesis of BFC 46

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The debenzylation was carried out using standard conditions for hydrogenolysis: 10% Pd/C and atmospheric H₂ in ethyl acetate. After workup, the desired BFC 46 was obtained in good yield (58%). The BFC 46 was characterized by NMR, IR, and HRFABMS. The proton of sulfonamide (SO₂NH) is quite acidic (pKa~7), if the ligand forms a complex with Cu(II), these pendent arms will serve to fully envelop a six coordinate cation as well as neutralize a dicationic charge. The latter property is desirable for optimal ⁶⁴Cu(II) complex biodistribution and clearance characteristics.¹²,43,44

N. The Synthesis and Characterization of Trifluoroacetic Acid Salt of (11-(2-(Toluene-4-sulfonylamino)ethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-4-yl)acetic acid (152•2TFA)

After we synthesized BFC 46, we needed to synthesize a model compound of BFC 46 for metal complexation study. Model compound 152 was synthesized as indicated in Scheme 2.73.
To a solution of mono-tert-butyl ester cross-bridged cyclam 74 in CH$_3$CN, 1-(((4-methylphenyl)sulfonyl) aziridine 150 was added. The mixture was refluxed for 18 hours. The solvent was removed under reduced pressure to give product 151 in good yield (~quant, >90% purity). 151 was then dissolved in a mixture of CF$_3$CO$_2$H (TFA) and CH$_2$Cl$_2$ (1:1, v:v) and solution was stirred for 16 hours at room temperature. Solvent was then removed under reduced pressure to give product 152 as TFA salt. On the basis of the mass and assuming a quantitative yield, the product is a di-TFA salt. 152 will act as a model compound of BFC 46 to study coordination chemistry.
O. Conclusions

Di-carboxylic acid cross-bridged cyclam 36, a BFC whose HCl salt originally had been synthesized by Hill\textsuperscript{12,19}, has been synthesized as its di-TFA salt. Di-carboxyl acid cross-bridged cyclen 39, a BFC which originally had been synthesized by Condon\textsuperscript{50}, has been formally synthesized by a different synthetic approach. The precursor 82 of di-carboxylic acid cross-bridged 13-ane-N\textsubscript{4} 42 has been synthesized and characterized successfully for the first time. Syntheses of BFC 41 and BFC 43 have been attempted, their NMR spectra showed that both BFC had been synthesized, but their isolation and purification still remains unsolved. The synthesis of C-substituted cross-bridged cyclen BFC 40 has failed to date. However, switching to a benzyl ester protecting group of 91 may lead to future success. BFC 45 and BFC 46 have been synthesized and characterized successfully. Related model compounds have also been synthesized and fully characterized. Further research such as coordination chemistry studies and antibody labeling is in progress or will be done in the future. The synthesis of di-benzo BFC 44 was attempted. Some progress was made toward this kind of BFC. The biggest challenge toward this kind of BFC is the solubility problem. Our studies shows that after we appended the phenethyl group, its solubility is better than its parent compound (at least in CHCl\textsubscript{3} and CH\textsubscript{2}Cl\textsubscript{2}). One possible future direction toward this kind of dibenzo BFC (e.g. BFC 156) is shown in Scheme 2.74.
Scheme 2.74 One possible future direction toward this kind of dibenzo BFC 156
CHAPTER III
EXPERIMENTAL DETAILS

I. General Methods

Melting points (mp) were obtained on a Thomas Hoover capillary melting point apparatus and were uncorrected.

Infrared Spectra (IR) were run on a Nicolet MX-1 FT-IR spectrometer and absorptions are reported in wavenumber (cm\(^{-1}\)).

\(^1\)H NMR Spectra (\(^1\)H NMR) were acquired on a Bruker AM360 FT-NMR spectrometer operating at 360.134 MHz, or a Varian Mercury-400BB NMR spectrometer, or a Varian INOVA-500 NMR spectrometer. Chemical shifts are reported in parts per million (ppm) relative to internal Me\(_4\)Si (TMS) unless otherwise noted and coupling constants (J values) are in Hertz (Hz).

\(^13\)C NMR spectra (\(^13\)C NMR) were acquired on a Bruker AM360 FT-NMR spectrometer operating at 90.556 MHz, a Varian Mercury-400BB NMR spectrometer, or a Varian INOVA-500 NMR spectrometer. Chemical shifts are reported in parts per million (ppm) relative to internal Me\(_4\)Si (TMS) unless noted.

Low-Resolution Mass Spectra (MS) were obtained on a Hewlett Packard 5988A GC/MS at the University Instrumentation Center of UNH.

High-Resolution Mass Spectra (HRMS) were obtained from Mass spectrometry Facility at the University of Notre Dame using a JEOL AX505HA high resolution mass spectrometer.

CHN Analysis (CH&N) were obtained on a perkin-Elmer Series II CHNS/O elemental analyzer model 240B at the University Instrumentation Center of UNH.
X-Ray Crystallography (X-ray) was performed by Roger Sommers at the laboratory of Arnold Rheingold, Crystallography Laboratory, Department of Chemistry and Biochemistry, University of Delaware, Newark, DE.

II. Solvents

Absolute ethanol (EtOH) was obtained from AAPER Alcohol and Chemical Co. and was used without further purification.

Acetone was obtained from Pharmco products. It was used without further purification.

Acetonitrile (CH₃CN) was obtained from EM Science. It was distilled from CaH₂ and stored over 3Å molecular sieves.

Benzene (C₆H₆) was obtained from J.T. Baker and was used without purification.

Chloroform (CHCl₃) was obtained from EM Science and was used without purification.

Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories.

Diethyl ether (Et₂O) was obtained from Fisher Chemical Co.

Dichloromethane (CH₂Cl₂) was obtained from Pharmco Products. It was used without further purification.

Dimethylformamide (DMF) was obtained from J.T. Baker and used without purification.

Ethanol (95% EtOH) was obtained from AAPER Alcohol and Chemical Co. and was used without further purification.

Methanol (MeOH) was obtained from Fisher Chemical Co. and was used without further purification.
Methylene Chloride (CH₂Cl₂) was obtained from J. T. Baker. It was distilled from CaH₂ and stored over 3Å molecular sieves.

Tetrahydrofuran (THF) was obtained from Fisher Chemical Co. and was distilled form Sodium prior to use.

Toluene (PhCH₃) was obtained from EM Science. It was distilled from sodium prior to use.

III. Reagents

Acetic anhydride (Ac₂O) was obtained from Fisher Chemical Co. and was used without further purification.

Aluminium trichloride was obtained from Aldrich Chemical Co.

2-Aminobenzylamine was obtained from Aldrich Chemical Co.

Benzyl bromide (PhCH₂Br) was obtained from Aldrich Chemical Co.

Benzyl acrylate was obtained from Lancaster Synthesis, Inc.

Benzaldehyde was obtained from Aldrich Chemical Co.

Benzyl alcohol was obtained from Fisher Scientific Company

N,N'-Bis(2-Hydroxyethyl)-ethylenediamine was obtained from Aldrich Chemical Co.

Bromine was obtained from Aldrich Chemical Co.

t-Butylmalonate was obtained from Aldrich Chemical Co.

t-Butylbromoacetate was obtained from Aldrich Chemical Co.

2-Bromoacetamide was obtained from Aldrich Chemical Co.

4-Bromobenzenesulfonyl chloride was obtained from Aldrich Chemical Co.

Chloroacetyl chloride was obtained from Aldrich Chemical Co.

4-(2-Chloroacetamido)benzoic acid was obtained from Aldrich Chemical Co.
2-Chloro-N-phenylacetamide was obtained from Aldrich Chemical Co.

2-Chloro-N-methylacetamide was obtained from Aldrich Chemical Co.

Cesium carbonate was obtained from Cabot Chemical Co.

Calcium hydride was obtained from Alfa Products Inc.

Diatomaceous earth (Celite) was obtained from Fischer Chemical Co.

Diethyl bromomalonate was obtained from Aldrich Chemical Co.

1,8-Diazabicyclo[5.4.0]undec-7-ene was obtained from Aldrich Chemical Co.

Ethylene diamine was obtained from Lancaster Synthesis, Inc.

Ethanolamine was obtained from Aldrich Chemical Co.

Formic acid was obtained from Aldrich Chemical Co.

Glyoxal (40 wt. % solution in H₂O) was obtained from Aldrich Chemical Co.

Hexamethylenetetramine was obtained from Alfa Products Inc.

Hydrocinnamic acid was obtained from Eastman Organic Chemicals.

4-Hydroxybenzoic acid was obtained from Aldrich Chemical Co.

Levulinic acid was obtained from Aldrich Chemical Co.

Lithium perchlorate was obtained from J.T. Baker Chemical Co.

Magnesium sulfate was obtained from Aldrich Chemical Co.

Methyl 3-(4-chlorosulphonyl)phenyl propionate was obtained from Lancaster Synthesis, Inc.

Methyl iodide was obtained from Aldrich Chemical Co.

Palladium(II) acetate was obtained from Lancaster Synthesis, Inc.

Palladium Black was obtained from Alfa Products.

10% Palladium on carbon (10% Pd/C) was obtained from Aldrich Chemical Co.
Piperidine was obtained from Aldrich Chemical Co.

3-Phenylpropionic acid was obtained from Lancaster Synthesis, Inc.

1,10-Phenanthroline was obtained from Aldrich Chemical Co.

Potassium carbonate was obtained from Flinn Scientific Inc.

Potassium iodide was obtained from J. T. Baker Chemical Co.

Sodium borohydride (NaBH₄) was obtained from Lancaster Synthesis, Inc.

Sodium hydroxide (NaOH) was obtained from Fisher Scientific Company

Sodium acetate anhydrous was obtained from Aldrich Chemical Co.

Sodium carbonate was obtained from Fisher Scientific Company.

Sulfuric acid was obtained from J.T. Baker Chemical Co.

Styrene was obtained from Aldrich Chemical Co.

1,4,7,10-Tetraazacyclododecane (cyclen) was obtained from Strem Chemicals.

1,4,7,11-Tetraazacyclotetradecane (cyclam) was obtained from Strem Chemicals.

Tetrabutylammonium tribromide was obtained from Fluka Chemie GmbH.

Thionyl chloride was obtained from Aldrich Chemical Co.

Triphenylphosphine was obtained from Lancaster Synthesis, Inc.

Tri(0-tolyl)phosphine was obtained from Lancaster synthesis, Inc.

p-Toluenesulfonyl chloride was obtained from Aldrich Chemical Co.

IV. Column Chromatography Solid Supports

Alumina: Aluminum oxide powder (activated, basic, Brockmann 1,150 mesh)

"suitable for chromatography" was obtained from Aldrich Chemical Co.

Silica gel (60-200 mesh) "suitable for column chromatography" was obtained from J.T. Baker Chemical Co.
V. Experimental Procedures

Note: All routine solvent evaporations were carried out on a standard rotary evaporator using aspirator pressure unless otherwise noted.

4-Methyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (21): Hydrogenolysis of 4-benzyl-10-methyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (20) was carried out in a glass apparatus designed for the exclusion of O₂ and for measurement of H₂ uptake with maintenance of constant pressure. Catalyst (250 mg, 10% Pd/C) and a 1% solution of conc. HCl in methanol (10 mL) were added to a 50 mL hydrogenation flask, which was connected to the apparatus. The system was evacuated by means of a water aspirator and flushed with N₂ four times. After another evacuation the system was filled with hydrogen. The catalyst was equilibrated under H₂ for 30 minutes. 4-Benzyl-10-methyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (210 mg, 0.693 mmol) in methanol (2 mL) was then added and the mixture was stirred for 26 h under H₂ at atmospheric pressure. The hydrogenolysis was stopped, the apparatus was evacuated and flushed with N₂, the hydrogenation flask was removed, the contents were filtered through Celite, and the catalyst and Celite were washed with methanol (3×2 mL). The filtrate and washings were concentrated under reduced pressure to give a light yellow oil which was dissolved in H₂O (2 mL), adjusted to pH 14 with solid KOH, and extracted with benzene (3×10 mL). The combined extracts were dried (Na₂SO₄), solvent was removed under reduced pressure, and the crude product was dissolved in a mixture of absolute EtOH (3 mL) and concentrated HCl (3 mL). Mixing resulted in precipitation of a hydrochloride salt (stoichiometry unknown), which was filtered, washed with absolute EtOH (2×1 mL), and air-dried. The hydrochloride salt was recrystallized from hot absolute EtOH.
recrystallized material was dissolved in H₂O (10 mL), the pH was adjusted to 14 with solid KOH, and the aq solution was extracted with benzene (2×10 mL). The combined extracts were dried (Na₂SO₄), and solvent was removed under reduced pressure to give waxy solid product (43.8 mg, 0.207 mmol, 30%). 

\[ ^1H \text{NMR (360 MHz, C₆D₆)} δ 2.21-2.42 (m, 4H), 2.27 (s, 3H), 2.42-2.50 (m, 2H), 2.50-2.68 (m, 10H), 2.69-2.84 (m, 4H); \]

\[ ^13C\{^1H\} \text{NMR (90.6 MHz, C₆D₆)} δ 44.45, 48.04, 51.86, 52.32, 52.41, 56.69; \]

IR(KBr) 3445, 2958, 2936, 2847, 1663, 1575, 1559, 1457, 1413, 1372, 1164 cm⁻¹; MS, m/z 212(M⁺); 

HRFABMS, m/z (M+H)⁺ exact mass calcd for C₆₁H₂₃N₄: 213.2079; Found: 213.2082 (error +0.2 mmu/+1.1 ppm).

**4,10-Diacetyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (22):** 1,4,7,10-Tetraazabicyclo[5.5.2]tetradecane (100 mg, 0.515 mmol) was dissolved in acetic anhydride (5 mL), the mixture was stirred under N₂ for 3 days, and then poured into water (2 mL), adjusted to pH 14 with solid KOH, and extracted with benzene (3×20 mL). The combined extracts were dried (Na₂SO₄) and solvent was removed under reduced pressure to give a solid (122 mg, 0.438 mmol, 85%). 

\[ ^1H \text{NMR (500 MHz, C₆D₆)} δ 1.73 (s, 6H, COCH₃, major), 1.75 (s, 6H, COCH₃, minor), 2.20-2.56 (m, 13H, major and minor), 2.66 (dt, 1H, J=15.1, 2.4 Hz, major and minor), 2.92 (dt, 2H, J=14.9, 2.4 Hz, major), 2.92-2.99 (m, 2H, minor), 3.33 (ddd, 2H, J=15.1, 10.3, 1.7 Hz, minor), 3.35-3.44 (m, 2H, major), 3.92-3.98 (m, 2H, major), 4.01 (ddd, 2H, J=13.4, 3.7, 1.7 Hz, minor), the ratio of major and minor is 64/36; \]

\[ ^13C\{^1H\} \text{NMR (100.5 MHz, C₆D₆)} δ 22.42 (major and minor), 54.92 (minor), 54.97 (major), 55.08 (major), 55.58 (minor), 56.06 (major), 56.36 (minor), 56.48 (minor), 56.93 (major), 57.55 (minor), 57.65 (minor), 57.70 (major), 169.87 \]
(minor), 170.16 (major). (There are 5 major peaks and 6 minor peaks in the mid-field region which indicates that the major conformation has time-averaged C\textsubscript{2} symmetry and the minor conformation has time-averaged C\textsubscript{s} symmetry); IR (KBr) 2924, 2834, 2802, 1638.5, 1470, 1443, 1402, 1353, 1240, 1150, 1028 cm\textsuperscript{-1}; HRFABMS m/z (M+H)+ exact mass calcd for C\textsubscript{14}H\textsubscript{27}N\textsubscript{4}O\textsubscript{2}: 283.2134; Found: 283.2138 (error +0.4 mmu/+1.3 ppm).

4,10-Dibenzoyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane(23): 1,4,7,10-Tetraazabicyclo[5.5.2]tetradecane (50 mg, 0.26 mmol) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (1 mL), and PhCOCl (89 mg, 0.53 mmol) was added in one portion. The mixture was stirred for 12 h at room temperature and then poured into water (2 mL), adjusted to pH 14 with solid KOH, and extracted with benzene (3 x 20 mL). The combined extracts were dried (Na\textsubscript{2}SO\textsubscript{4}) and solvent was removed under reduced pressure to give a solid. The crude product was recrystallized from acetone to give white crystals (24 mg, 0.13 mmol, 50%): \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 2.56-2.80 (m, 5H), 2.81-2.96 (m, 4H), 3.08-3.30 (m, 5H), 3.42-3.54 (m, 2H), 3.57-3.68 (m, 2H), 4.14 (dd, J=13.2, 2.7 Hz, major) & 4.20 (dd, J=13.4, 2.9 Hz, minor) (total integration 2H), 7.33-7.46 (m, 10H), the ratio of major and minor conformations is 55/45; \textsuperscript{13}C \{\textsuperscript{1}H \} NMR (100.5 MHz, CDCl\textsubscript{3}) \( \delta \) 54.20, 54.47, 54.70, 55.03, 55.26, 55.60, 55.70, 56.42, 57.12, 57.25, 57.50, 126.17, 128.53, 128.55, 129.07, 129.11, 137.63, 137.71, 172.29, 172.46; IR (KBr) 2945, 2933, 2833, 1608, 1575, 1469, 1445, 1409, 1375, 1351, 1303, 1123, 743, 709 cm\textsuperscript{-1}; Anal Calcd for C\textsubscript{24}H\textsubscript{30}N\textsubscript{4}O\textsubscript{2}: C, 70.91; H, 7.44; N, 13.78. Found: C, 70.54; H, 7.58; N, 13.81.
4-Acetyl-10-methyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (24): 4-Methyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane 21 (70.0 mg, 0.336 mmol) was dissolved in acetic anhydride (1 mL) and the mixture was stirred under N₂ for 14 h. The reaction mixture was then poured into water (2 mL), adjusted to pH 14 with solid KOH, and extracted with benzene (3×20 mL). The combined extracts were dried (Na₂SO₄) and solvent was removed under reduced pressure to give product as a light yellow oil (67.2 mg, 0.269 mmol, 80%): °H NMR (360 MHz, C₆D₆) δ 1.79 (s, 3H, COCH), 2.20 (s, 3H, NCH₃), 2.24-2.33 (m, 2H), 2.39-2.81 (m, 13H), 2.84-3.06 (m, 3H), 3.51-3.62 (m, 1H), 4.06-4.17 (dm, 1H, J=13.0 Hz); °C{°H} NMR (90.6 MHz, C₆D₆) δ 22.39, 45.60, 54.89 (br), 54.95, 56.06, 56.32 (br), 56.97 (br), 57.03 (br), 57.22 (br), 57.53 (br), 59.71, 60.16, 170.32 (CO); IR(neat) 3020, 2975, 2929, 2875, 2834, 2803, 1627, 1417, 1372, 1215 cm⁻¹; HRFABMS, m/z (M+H)+ exact mass calcd for C₁₃H₂₇N₄O: 255.2185; Found: 255.2199 (error +1.5 mmu/+5.7 ppm).

4-Benzoyl-10-methyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (25): 4-Methyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane 21 (31.0 mg, 0.149 mmol) was dissolved in CH₂Cl₂ (1 mL) and PhCOCl (178 mg, 1.26 mmol) was added in one portion. The mixture was stirred for 12 h at room temperature, and then poured into water (2 mL), adjusted to pH 14 with solid KOH, and extracted with benzene (3×20 mL). The combined extracts were dried (Na₂SO₄) and solvent was removed under reduced pressure to give product as a light yellow oil (46.0 mg, 0.148 mmol, 99%): °H NMR (360 MHz, C₆D₆) δ 2.18 (s, 3H, NCH₃), 2.22-3.20 (m, 20H), 3.26-3.40 (dm, 1H, J=14.6 Hz), 3.72 (br dd, 1H, J=14.6, 10.4 Hz), 4.20-4.30 (dm, 1H, J=12.2 Hz), 7.00-7.15 (m, 3H), 7.25-7.48 (m,
2H); $^{13}$C ($^1$H) NMR (90.6 MHz, C$_6$D$_6$) δ 45.07 (NCH$_3$), 54.55 (br), 54.88 (br), 56.11 (2C, one br), 56.46 (br), 56.77, 56.78 (br), 57.90 (br), 59.34 (br), 60.15 (br), 127.13, 128.80, 129.01, 139.70, 172.09 (NCO); IR (neat) 3020, 2966, 2930, 1619, 1602, 1216, 758, 668 cm$^{-1}$; MS, m/z 316 (M$^+$); HRFABMS, m/z (M+H)$^+$ exact mass calcd for C$_{18}$H$_{29}$N$_4$O: 317.2341; Found: 317.2352 (error +1.1 mmu/+3.3 ppm).

4-Formyl-10-methyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (26). 4-
Benzyl-10 methyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane 21 (130 mg, 0.432 mmol)
was dissolved in methanol solution containing 4.4% HCOOH (10 mL), and 10% Pd/C
catalyst (200 mg) was added in one portion. The mixture was stirred under N$_2$
for 14 h, the contents were filtered through Celite, and the solvent was removed under reduced
pressure. The residual solid was dissolved in H$_2$O (10 mL), pH was adjusted to 14 with
solid KOH, and the aqueous solution was extracted with benzene (3×20 mL). The
combined extracts were dried (Na$_2$SO$_4$) and solvent was removed under reduced pressure
to give product as a white solid (85.2 mg, 0.363 mmol, 84%, >95% purity): $^1$H NMR
(360 MHz, C$_6$D$_6$) δ 2.15 (s, 3H, NCH$_3$), 2.20-2.84 (m, 20H), 2.90 (dt, 1H, J=14.4, 2.4
Hz), 3.33 (app. ddd, 1H, J=15.5, 11.1, 2.2 Hz), 3.74-3.3.84 (dm, 1H, J=13.1 Hz), 8.01 (s,
1H, NCHO); $^{13}$C ($^1$H) NMR (90.6 MHz, C$_6$D$_6$) δ 45.00 (NCH$_3$), 51.28, 52.87 (br), 55.59,
56.12 (2C), 56.39, 56.55, 58.90, 59.71, 59.93, 164.03 (NCHO); IR (KBr) 3450 (H$_2$O),
3055, 2922, 2900, 2875, 2834, 2800, 2773, 1673, 1451, 1426, 1383, 1177, 1151 cm$^{-1}$;
HRFABMS m/z (M+H)$^+$ exact mass calcd for C$_{12}$H$_{25}$N$_4$O: 241.2028; Found: 241.2011
(error -1.7 mmu/-7.2 ppm).
**General Procedure for complex formation:** Equimolar amounts of ligand 26 and metal salt were heated to reflux in methanol solution, the solvent was removed, and the coordination compound was recrystallized from methanol and diethyl ether diffusion.

1,4,8,11-Tetraazabicyclo[6.5.2]pentadecane (34): The compound was prepared according to the procedure of Hill. The hydrogenolysis was carried out in a glass apparatus designed for the exclusion of O₂ and for measurement of H₂ uptake with maintenance of constant pressure. Catalyst (100 mg, 10% Pd/C) and acetic acid (4 mL) were added to a 50 mL hydrogenation flask, which was connected to the apparatus. The system was evacuated by means of a water aspirator and flushed with N₂ four times. After another evacuation the system was filled with hydrogen. The mixture of 10% Pd/C and acetic acid was equilibrated under H₂ for 1.5 h. 4,11-Dibenzyl-1,4,8,11-tetraazabicyclo[6.5.2]-pentadecane 81 (70.0 mg, 0.178 mmol) in acetic acid (1 mL) was then added and the mixture was stirred for 16 h under H₂. The hydrogenolysis was stopped, the apparatus was evacuated, flushed, and the hydrogenation flask was removed from the apparatus. The contents were filtered through Celite, and the catalyst and Celite were washed with acetic acid (2×5 mL). The filtrate and washings were concentrated under reduced pressure to give a light yellow oil which was dissolved in H₂O (3 mL), adjusted to pH 14 with solid KOH, and extracted with benzene (3 × 25 mL). The combined extracts were dried (Na₂SO₄), and solvent was removed under reduced pressure to give product as oil (35.0 mg, 0.165 mmol, 92%), which contained minor impurities and was directly used for the next step. NMR spectra were consistent with spectra of authentic material.
Bis-trifluoroacetate salt of 4,11-bis-(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (36-2TFA·H₂O). 4,11-Bis-(carbo-tert.-butoxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (51) (1.183 g, 2.602 mmol) was dissolved in a 1:1 (vol:vol) mixture of CF₃COOH (TFA) and CH₂Cl₂ (5 mL). The mixture was stirred under N₂ at room temperature for 48 h. Solvent was removed under reduced pressure to give an oil, which crystallized after removal of residual solvent under vacuum to yield 1.510 g (2.566 mmol, 99%) of product as the di-TFA salt monohydrate: mp 165-169 °C; ¹H NMR (400 MHz, CD₃CN, CD₂CN central peak set to 1.94 ppm) δ 1.64-1.74 (dm, 2H, J=16.8 Hz, CH₂CHeqHaxCH₂), 2.18-2.34 (~qm, 2H, J~13 Hz, CH₂CHeqHaxCH₂), 2.57-2.67 (dm, 2H, J=13.6 Hz), 2.89-3.14 (m, 12H), 3.31 (td, 2H, J=13.0, 3.3 Hz), 3.43-3.48 (AA'BB', 4H, NCH₂CH₂N cross-bridge), 3.46 (d, 2H, J=17.0 Hz, NCHA HxC O₂), 4.14 (d, 2H, J=17.0 Hz, NCHA HxC O₂), (Note: N-H/CO₂H fast-exchange signal broadened into baseline. In other spectra, broad signals integrating for up to 4H were observed in the range 8.9-12 ppm); ¹³C NMR (100.5 MHz, CD₃CN, CD₂CN central peak set to 1.39 ppm) δ 20.63, 49.20, 48.48, 48.48, 54.35, 56.28, 59.09, 60.81, 172.69 (OC=O); IR (KBr) 3408, 2960, 2886, 2529, 1723, 1708, 1628, 1433, 1281, 1242, 1198, 1132, 722 cm⁻¹; Anal Calcd for C₁₆H₃₀N₄O₄·2TFA·H₂O: C, 40.82; H, 5.82; N, 9.52. Found: C, 41.14; H, 5.91; N, 9.62.

4-(2-(11-tert-Butoxycarbonylmethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-4-yl)-acetylamino)benzoic acid (45). Hydrogenolysis of benzyl 4-(2-(11-tert-butoxycarbonylmethyl)-1,4,8,11-tetraaza-bicyclo[6.6.2]hexadec-4-yl)-
acetylamino)benzoate 135 was carried out in a glass apparatus designed for the exclusion
of O₂ and for measurement of H₂ uptake with maintenance of constant pressure. Catalyst
(40.0 mg, 10% Pd/C) and ethyl acetate (20 mL) were added to a 50 mL hydrogenation
flask, which was connected to the apparatus. The system was evacuated by means of a
water aspirator and flushed with N₂ four times. After another evacuation the system was
filled with hydrogen. The mixture of 10% Pd/C and ethyl acetate solution was
equilibrated under H₂ for 30 minutes. 135 (65.2 mg, 0.107 mmol) in ethyl acetate (5 mL)
was then added and the mixture was stirred for 16 h under H₂. The hydrogenolysis was
stopped, the apparatus was evacuated and flushed with N₂ at atmospheric pressure. The
contents of the hydrogenation flask were filtered through Celite, and the product, the
catalyst and Celite were washed with ethyl acetate (2×50 mL). The ethyl acetate filtrate
and washings were discarded. The product was then washed out with CH₃CN (6×50 mL),
the washings were combined, and dried (Na₂SO₄). The solvent was removed under
reduced pressure to yield product (45.0 mg, 0.0869 mmol, 81%): ¹H NMR (500 MHz,
CD₃CN, CHD₂CN central peak set to 1.94) δ 1.42 (s, 9H), 1.60-1.80 (m, 4H), 2.43 (br s,
H₂O), 2.70-3.20 (m, 16H), 3.34-3.45 (m, 2H), 3.50-3.62 (m, 2H), 3.33 & 3.34 (AB, 2H,
J=17.1 Hz), 3.53 & 3.60 (AB, 2H, J=16.3 Hz), 7.79-7.84 (XX’ of AA’XX’, 2H), 7.91-
7.96 (AA’ of AA’XX’, 2H), 10.17 (br s, 1H), 10.22 (br s, 1H); ¹H NMR (500 MHz,
CD₃OD, CHD₂OD peak set to 4.87) δ 1.44 (s, 9H), 1.62-1.80 (m, 3H), 1.83-1.95 (m, 1H),
2.66-2.80 (m, 4H), 2.80-3.02 (m, 7H), 3.03-3.13 (m, 4H), 3.16-3.26 (m, 3H), 3.27 & 3.36
(AB, 2H, J=17.3 Hz), 3.33 & 3.54 (AX, 2H, J=16.1 Hz), 3.52-3.63 (m, 1H), 3.69-3.80 (m,
1H), 7.56-7.61 (XX’ of AA’XX’, 2H), 7.90-7.96 (AA’ of AA’XX’, 2H); ¹³C (¹H ) NMR
(125.7 MHz, CD₃CN, CD₃CN central peak set to 1.39) δ 24.67, 25.47, 28.46, 51.43,
51.92, 53.26 (br), 53.61 (br), 54.89 (br), 56.22, 56.35, 56.75, 57.41, 57.66 (br), 58.98 (br), 119.75, 127.67 (br), 131.54, 143.90, 168.26, 171.09, 171.67; $^{13}$C{${}^1$H} NMR (125.7 MHz, CD$_3$OD, CD$_3$OD central peak set to 49.15) δ 24.98, 25.91, 28.59, 51.84, 51.85 (br), 52.57, 53.86 (br), 54.10 (br), 55.58 (br), 56.78, 57.00, 57.03, 58.32 (br), 58.43, 59.67, 82.67 (br), 119.97, 131.36, 134.93, 141.69, 171.234, 172.45, 174.92; IR(CH$_3$CN) 3649, 3629, 3164, 3002, 2944, 1717, 1683, 1455, 1419, 1375, 1039, 918 cm$^{-1}$; HRFABMS, m/z (M+H)$^+$

exact mass for C$_{27}$H$_{44}$N$_5$O$_5$: 6518.3342; Found: 518.3330 (error $-1.2$ mmu/$-2.4$ ppm)

3-(4-(2-(11-tert-Butoxycarbonylmethyl)-1,4,8,11-tetraazabicyclo[6.6.2]-hexadec-4-yl)-ethylsulfamoyl)phenyl)propionic acid (46). Hydrogenolysis of benzyl-3-(4-(2-(11-carbomethoxyethyl)-1,4,8,11-tetraaza-bicyclo[6.6.2]hexadec-4-yl)-ethylsulfamoyl)-phenyl) propionate 149 was carried out in a glass apparatus designed for the exclusion of O$_2$ and for measurement of H$_2$ uptake with maintenance of constant pressure. Catalyst (150 mg, 10% Pd/C) and ethyl acetate (50 mL) were added to a 200 mL hydrogenation flask, which was connected to the apparatus. The system was evacuated by means of a water aspirator and flushed with N$_2$ four times. After another evacuation the system was filled with hydrogen. The mixture of 10% Pd/C and ethyl acetate solution was equilibrated under H$_2$ for 30 minutes. 149 (40.0 mg, 0.0583 mmol) in ethyl acetate (2 mL) was then added and the mixture was stirred for 16 h under H$_2$. The hydrogenolysis was stopped, the apparatus was evacuated and flushed with N$_2$ at atmospheric pressure. The contents of the hydrogenation flask were filtered through Celite, and the product, the catalyst and Celite were washed with ethyl acetate (2×25 mL). The ethyl acetate filtrate and washings were discarded. The product was then

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washed from the Celite with CH$_3$CN (3×30 mL), the washings were combined, and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure to yield product (20.0 mg, 0.0336 mmol, 58%, >90% purity): $^1$H NMR (500 MHz, CD$_3$CN, CHD$_2$CN central peak set to 1.94) δ 1.48 (s, 9H), 1.52-1.63 (m, 2H), 1.64-1.76 (m, 2H), 2.39 (br s, H$_2$O), 2.36-2.70 (m, 6H), 2.72-3.00 (m, 16H), 3.00-3.06 (m, 2H), 3.10-3.17 (m, 2H), 3.19-3.29 (m, 2H), 3.20 & 3.33 (AB, 2H, J=17.6 Hz), 3.75-3.84 (m, 1H), 7.40-7.45 (XX' of AA’XX’, 2H), 7.74-7.78 (AA’ of AA’XX’, 2H), 10.15 (br s, 1H); $^{13}$C{$^1$H} NMR (125.7 MHz, CD$_3$CN, CD$_3$CN central peak set to 1.39) δ 22.61 (impurity), 24.55, 25.69, 28.48, 33.08, 39.38, 40.81, 50.82 (br), 51.86 (br), 52.26, 52.34 (br), 53.80, 54.74 (br), 54.99, 55.74 (br), 55.93, 56.40 (br), 56.68, 59.38 (br), 82.28, 127.75, 130.15, 139.19, 149.41, 171.65, 176.99; IR(CH$_3$CN) 33370, 3281, 3093, 2924, 2853, 1653, 1636, 1559, 1038, 832 cm$^{-1}$; HRFABMS, m/z (M+H)$^+$ exact mass for C$_{29}$H$_{50}$N$_5$O$_6$: 596.3482; Found: 596.3478 (error –0.3 mmu/-0.6 ppm).

4,11-Bis-(carbo-tert-butoxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (51). Anhydrous sodium carbonate (1.18 g, 11.1 mmol) and t-butyl bromoacetate 35 (2.17 g, 11.1 mmol) was added to a solution of 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (1.12 g, 4.95 mmol) in acetonitrile (30 mL). The mixture was stirred under N$_2$ and heated to 50°C for 48 h. Solvent was then removed under reduced pressure and residual material was dissolved in 20% aq NaOH (20 mL) at ice bath temperature (0-5 °C). The aqueous layer was extracted with cold (0-5 °C) toluene (3 × 20 mL), combined extracts were dried (Na$_2$SO$_4$), and solvent was removed under reduced pressure to give a oil which solidified upon standing (2.08 g, 4.58 mmol, 93%): mp 39-40 °C; $^1$H NMR (400 MHz, C$_6$D$_6$)
δ 1.21–1.46 (m, 4H), 1.40 (s, 18H, (CH₃)i), 2.23 (ddd, 2H, J=13.5, 3.9, 1.9 Hz), 2.29 (ddd, 2H, J=13.1, 4.9, 2.5 Hz), 2.42–2.56 (XX' of AA'XX', 2H, NC₃H₁₁H₁₃H₁₃N cross-bridge), 2.60–2.94 (m, 10H), 3.01 and 3.17 (AB, 4H, J=16.4 Hz, N-C₆H₄-C), 3.24–3.40 (AA' of AA'XX', 2H, NC₃H₁₁H₁₃H₁₃N cross-bridge), 3.69 (td, 2H, J=11.9, 4.2 Hz); ¹³C NMR (100.5 MHz, C₆D₆) δ 28.10, 28.20, 50.87, 53.32, 55.96, 56.31, 57.24, 60.13, 79.67, 171.08; IR (KBr) 2976, 2917, 2819, 2784, 1739, 1728, 1477, 1392, 1367, 1323, 1165, 1122 cm⁻¹; HRFABMS, m/z (M+H)⁺ exact mass for C₂₄H₄₇O₄N₄: 455.3597; Found: 455.3600 (error +0.2 mmu/+0.5 ppm).

4,10-Bis(carbo-tert-butoxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (53). 1,4,7,10-Tetraazabicyclo[5.5.2]tetradecane (17) (51.0 mg, 0.263 mmol) was dissolved in toluene (4 mL), anhydrous sodium carbonate (28.0 mg, 0.264 mmol) was added in one portion, and a solution of t-butylbromoacetate (51.0 mg, 0.263 mmol) in toluene (1 mL) was added over 1 minute. The mixture was stirred for 24 h at room temperature, and then poured into ice-water (2 mL). Solid KOH was used to adjust pH to 14. The organic layer was separated, dried (Na₂SO₄), and evaporated to dryness under reduced pressure to yield product as slightly yellow oil (54.0 mg, 0.128 mmol, 49%): NMR spectra were consistent with spectra of authentic material.⁵⁰

2,3,9,10-Dibenzo-1,5,8,12-tetraazaclotetradeca-4,11-diene (55): The compound was prepared according to procedure of Betakis, Piesch, and Ried⁵¹. Dry toluene (450 mL), ethylene diamine (182 mL, 2.72 mol), Cu powder (28.4 g, 0.50 mol), and formic acid (9 mL) were combined in a dry 1L round-bottom flask under N₂ to give a
blue mixture, which was refluxed for 35 min. The mixture was allowed to cool (rt) and a solution of 2-chlorobenzaldehyde (50 mL, 0.44 mol) in toluene (50 mL) was added dropwise with stirring over 1 h. The mixture was refluxed for 4 h to give a green mixture that was hot filtered to remove solids. The filtrate separated into two phases. The upper green organic phase was isolated, and the blue aqueous phase was extracted with toluene (2 × 100 mL). The combined organic phase and toluene extracts were dried (Na$_2$SO$_4$) and the solvent was removed under reduced pressure to give crude product. This was recrystallized from hot 95% EtOH to yield pure product as a yellow solid (24.2 g, 82.8 mmol, 37%). NMR spectra were consistent with spectra of authentic material.

2, 3, 9, 10-Dibenzo-1, 5, 8, 12-tetraazacyclotetradecane (56): The compound was prepared according to procedure of Condon.$^{50}$ 2, 3, 9, 10-Dibenzo-1, 5, 8, 12-tetraazacyclotetradeca-4,11-diene 55 (6.51 g, 22.3 mmol) was dissolved in dry THF (440 mL). The solution was stirred under N$_2$ and cooled (ice/water). NaBH$_4$ powder (33.5 g, 0.886 mol) was added batchwise over 10 min and the resultant mixture was refluxed for 43.5 h. The mixture was cooled (ice/water) and the pH was adjusted to 1 by slow addition of 3 M aq HCl (208 mL) with stirring. Rotary evaporation gave an aqueous mixture. The pH was adjusted to 14 by solid KOH addition, and the solution was extracted with chloroform (4 × 200 mL). The combined extracts were dried (Na$_2$SO$_4$) and the solvent was removed under reduced pressure to give crude product which was washed with boiling MeOH (100 mL) to give product as a white solid (4.70 g, 15.8 mmol, 71%). NMR spectra were consistent with spectra of authentic material.
(13ba, 13ca)-5,6,7,12,13,13b,13c,14-Octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene (57). The compound was prepared according to procedure of Condon. 2, 3, 9, 10-Dibenzo-1, 5, 8, 12-tetraazacyclotetradecane 56 (2.51 g, 8.46 mmol) was dissolved in MeOH (180 mL) in a round-bottom flask under N₂. 40% Aq glyoxal (1.2 mL, 11 mmol) was added dropwise with stirring, and then the mixture was stirred for 14 h at room temperature. The precipitate formed was isolated by suction filtration and washed with MeOH (3 x 20 mL). Removal of solvent gave product as a white solid (2.25 g, 7.08 mmol, 84%). NMR spectra were consistent with spectra of authentic material.

Benzyl-(E)-(13ba, 13ca)-3-(5,6,7,12,13,13b,13c,14-Octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def]chryseneyl)acrylate (63): NaOAc (44.0 mg, 0.537 mmol), tri(o-tolyl)phosphate (26.0 mg, 0.0854 mmol), palladium(II) acetate (13.6 mg, 0.0606 mmol), and benzyl acrylate (86.6 mg, 0.534 mmol) were added to a solution of (13ba, 13ca)-2-bromo-5,6,7,12,13,13b,13c,14-octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene 64 (214 mg, 0.535 mmol) in DMF (20 mL). The mixture was maintained at 150 °C for 20 h, then poured into a flask with ice (200 g) to generate white precipitate which was collected by suction filtration. This was dissolved in CHCl₃ (100 mL), the solution was washed with water (2 x 200 mL), brine (200 mL), and dried (Na₂SO₄). Solvent was removed under reduced pressure to give crude product, which was subjected to flash chromatography (SiO₂, hexane: ethyl acetate = 1: 1) to give product as white solid (50.0 mg, 0.111 mmol, 21%): ¹H NMR (400 MHz, CDCl₃) δ 2.64-2.74 (m, 2H), 2.95-3.13 (m, 2H), 3.14-3.35 (m, 2H), 3.66 (2 overlapping d, 2H, J=16.8 Hz), 3.83-3.94 (m, 2H), 4.22
(d, 1H, unresolved J, (N)2CHCH(N)2), 4.31 (d, 1H, J=2.3 Hz, (N)2CHCH(N)2), 4.51 (d, 1H, J=17.0 Hz), 4.55 (d, 1H, J=17.0 Hz), 5.24 (s, 2H), 6.30 (d, 1H, J=16.0 Hz), 6.72-6.79 (m, 1H), 6.81 (d, 1H, J=8.6 Hz), 6.85 (br d, 1H, J=8.8 Hz), 6.95 (br d, 1H, J=7.0 Hz), 7.10-7.18 (m, 2H), 7.29-7.45 (m, 6H), 7.63 (d, 1H, J=16.0 Hz); 13C{1H} NMR (100.5 MHz, CDCl3) δ 44.87, 45.21, 45.92, 46.22, 54.92, 55.14, 66.27, 70.33, 70.40, 112.53, 112.93, 113.73, 118.81, 120.44, 120.57, 124.39, 127.34, 127.86, 128.33, 128.40, 128.54, 128.77, 136.57, 144.54, 145.32, 146.88, 167.66; IR (KBr) 3066, 2963, 2940, 2859, 1708, 1603, 1493, 1308, 1155, 1144, 1120, 1105, 1084, 802, 747 cm⁻¹.

(13ba, 13ca)-2-Bromo-5,6,7,12,13,13b,13c,14-octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def|chrysene (64). Tetrabutylammonium tribromide (TBABr3) (159.0 mg, 0.3300 mmol) was added to a stirred solution of (13ba, 13ca)-5,6,7,12,13,13b,13c,14-octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def|chrysene 57 (100.0 mg, 0.3140 mmol) in CHCl3 (20 mL), and the mixture was stirred for 36 h at room temperature. The mixture was diluted with additional CHCl3 (200 mL), and the organic solution was washed with aq. sodium thiosulfate (2 × 100 mL), water (2 × 100 mL), aq saturated NaCl (2 × 40 mL), dried (Na2SO4), and evaporated to dryness. Crude product was purified by flash chromatography (SiO2, MeOH: CH2Cl2=1:15) to yield white solid product (52.2 mg, about 70% pure by NMR), which was subsequently used without further purification. A small amount of pure compound was acquired by repeated (4 times) flash chromatography (2 mg from 16 mg of 70% pure product): 1H NMR (500 MHz, CDCl3) δ 2.60-2.71 (m, 2H), 2.96-3.03 (m, 2H), 3.24 (td, 1H, J=11.5, 3.4 Hz), 3.29 (td, 1H, J=11.7, 3.7 Hz), 3.61 (d, 1H, J=16.9 Hz), 3.65 (d, 1H, J=16.9 Hz), 3.80-3.84 (dm, 1H,

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J=11.7 Hz), 3.86-3.92 (dm, 1H, J=11.7 Hz), 4.18 & 4.21 (AB, 2H, J=2.4 Hz), 4.50 (d, 1H, J=16.9 Hz), 4.55 (d, 1H, J=16.6 Hz), 6.71 (d, 1H, J=9.0 Hz), 6.76 (td, 1H, J=7.3, 1.0 Hz), 6.85 (br d, 1H, J=8.3 Hz), 6.94 (d, 1H, J=7.3 Hz), 7.04-7.06 (m, 1H), 7.12-7.17 (~tm, 1H, J=8.3 Hz), 7.21 (ddd, 1H, J=9.0, 2.9, 0.5 Hz); \(^1\)H NMR (125.7 MHz, CDCl\(_3\), CDCl\(_3\) central peak set at 77.23) \(\delta\) 45.25 (2C), 46.11, 46.31, 54.70, 55.09, 70.40, 70.46, 110.51, 112.87, 114.58, 118.74, 120.17, 122.75, 127.32, 127.83, 129.80, 130.44, 143.87, 144.61; IR(KBr) 3080, 2964, 2859, 2859, 2835, 2805, 1602, 1488, 1377, 1330, 1303, 1261, 1229, 1127, 1047, 1029, 907, 817, 799, 747 cm\(^{-1}\); HRFABMS, m/z (M+H)\(^+\) exact mass for C\(_{20}\)H\(_{22}\)N\(_4\)Br: 397.1028; Found: 397.1026 (error −0.2 mmu/−0.4 ppm)

cis-Decahydro-8b-carboxylethyl-2a,4a,6a,8a-tetraazacyclopent[fg]-acenaphthylene (70). A solution of 4,5-dioxopentanoic acid 91 (190.0 mg, 1.283 mmol) and 1,4,7,10-tetraazacyclododecane (13) (200.0 mg, 1.161 mmol) in 20 mL of MeCN were stirred for 1 h at room temperature, and then for 4 h at 50-60 °C. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. Purification by flash chromatography (SiO\(_2\), MeOH) yielded solid product (41.0 mg, 0.154 mmol, 13%). \(^1\)H NMR (CD\(_3\)CN, 400 MHz, CD\(_2\)HCN central peak set at 1.94 ppm) \(\delta\) 1.92-1.96 (m, 2H), 2.33 (ddd, 2H, J=10.9, 5.1, 2.3 Hz), 2.46-2.52 (m, 2H), 2.54-2.62 (m, 2H), 2.88-3.05 (m, 7H), 3.05-3.12 (m, 2H), 3.18 (td, 2H, J=10.5, 6.2 Hz), 3.36-3.45 (m, 2H); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 1.95-2.02 (m, 2H), 2.38-2.44 (m, 2H), 2.60-2.71 (m, 4H), 2.92-3.04 (m, 4H), 3.04-3.10 (m, 2H), 3.06 (s, 1H), 3.14-3.24 (m, 4H), 3.33-3.41 (m, 2H); \(^13\)C\({^1}\)H NMR (CD\(_3\)CN, 90.56 MHz, CD\(_3\)CN central peak set at 1.37) \(\delta\) 27.98, 31.38, 43.14, 43.67, 48.71, 52.00, 77.27, 79.67, 176.74; IR(KBr)
3405(COOH), 2954, 2938, 1560 (C=O), 1447, 1438, 1414, 1200 cm\(^{-1}\); LREIMS, m/z 266(M\(^{+}\)); HRFABMS, m/z (M+H\(^{+}\)) exact mass for C\(_{13}\)H\(_{23}\)N\(_{4}\)O\(_{2}\): 267.1821; Found: 267.1809 (error –1.2 mmu/–4.4 ppm).

Notes: Assignment of the 1.92-1.96 (m, 2H) in the \(^1\)H NMR spectrum (CD\(_3\)CN), as well as some other assignments, were based upon a gHMQC spectrum. No COOH signal was observed in either of the \(^1\)H NMR spectra (CD\(_3\)CN & CDCl\(_3\)). A HRFABMS peak corresponding to sodium salt molecular ion was observed in addition to that of the title compound.

4-(Carbo-tert-butoxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (73).

Hydrogenolysis of 4-(tert-butylcarboxymethyl)-10-(phenylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane 72 was carried out in a glass apparatus designed for the exclusion of O\(_2\) and for measurement of H\(_2\) uptake with maintenance of constant pressure. 10% Pd/C (110mg), conc. HCl (0.2 mL), and EtOH (20mL) were added to a 125 mL hydrogenation flask which was connected to the hydrogenator. The system was evacuated (by means of a water aspirator) and flushed with nitrogen four times. After another evacuation and flushing with hydrogen, the system was filled with hydrogen. The catalyst was equilibrated with stirring under hydrogen for 0.5 h. To the reaction flask was added a solution of 4-(tert-butylcarboxymethyl)-10-(phenylmethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane 72 (110 mg, 0.273 mmol) in EtOH (5 mL). The mixture was stirred for 3 hours under H\(_2\) (1 atm). The theoretical H\(_2\) uptake for this reaction was 6.1 mL; the measured uptake was 4.8 mL, which is 78% of the theoretical value. The hydrogenation apparatus was evacuated and flushed with N\(_2\) four times. The reaction
flask was removed from the apparatus, the contents were filtered through celite, and the catalyst and celite were washed with EtOH (2 × 5 mL). The filtrate and washings were combined and concentrated under reduced pressure to give a white solid, which was dissolved in H₂O (4 mL), adjusted to pH 14 with solid KOH (with cooling), and extracted with benzene (2 × 25 mL). The combined extracts were dried (Na₂SO₄) and solvent was removed under reduced pressure to give product as a light yellow oil (74.4 mg, 0.238 mmol, 87%): ¹H NMR (C₆D₆, 360.15 MHz) 1.38(s, 9H, C(CH₃)₃), 2.39-3.78 (m, 21H), 3.29 (s, 2H, NCH₂C(O)); ¹³C NMR (C₆D₆, 90.56 Hz) 28.25(C(CH₃)₃), 48.04, 52.22, 52.66, 53.06, 55.29, 56.95, 79.96 (C(CH₃)₃), 171.43 (C=O); IR(neat) 1154, 1216, 1368, 1735(C=O), 2804, 2909, 2974, 3193, 3222 (NH) cm⁻¹; HREIMS m/z (M⁺) exact mass calcd for C₁₆H₃₂N₄O₂: 312.2525; Found: 312.2523 (error 0.2 mmu).

4-Carbo-tert-butoxymethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (74).

1,4,8,11-Tetraazabicyclo[6.6.2]hexadecane 35 (100 mg, 0.441 mmol) was dissolved in dry MeCN (4 mL), sodium carbonate (47.0 mg, 0.441 mmol) was added in one portion, and t-butyl bromoacetate (0.065 mL, 0.44 mmol) was added in one portion by syringe. The solution was stirred for 14 h at room temperature, and then solvent was removed under reduced pressure. Purification by flash chromatography (SiO₂, MeOH : CH₂Cl₂=1.5:10) yielded an oil which was dissolved in water (4 mL), adjusted to pH 14 (solid KOH), and extracted with benzene (3 × 50 mL). The combined extracts were dried (Na₂SO₄) and solvent was removed under reduced pressure to yield product as a light yellow oil (60.0 mg, 0.172 mmol, 39%): ¹H NMR (C₆D₆, 500 MHz) δ 1.20-1.32 (m, 2H), 1.38 (s, 9H, C(CH₃)₃), 1.41-1.52 (m, 2H), 1.94-2.01 (dm, 1H, J=15.6 Hz), 2.08-2.14 (dm,
cis-Decahydro-5H-2a,4a,7a,9a-tetraazacyclopenta[cd]phenalene (79): The compound was prepared according to the procedure of Hill. Aq glyoxal (0.30 mL, 0.38 g, 2.6 mmol) was added dropwise over 1 h to a stirred solution of 1,4,7,10-tetraazacyclotridecane (33) (310 mg, 1.67 mmol) in MeCN (10 mL). The mixture was heated to 60 °C for 6 h. Solvent was removed to give a yellow oil, which was dissolved in chloroform (20 mL) and dried (Na₂SO₄), and then solvent was removed under reduced pressure to give crude product. This was purified by flash chromatography on basic alumina (10% EtOH/Et₂O) to give a clear oil which crystallized upon standing at room temperature (178 mg, 0.864 mmol, 52%). NMR spectra were consistent with spectra of authentic material.

(9bα, 9cα)-Decahydro-2a,7a-bis(phenylmethyl)-5H-4a,9a-diaza-2a,7a-dia Zionacyclopenta[cd]phenalene dibromide (80). The compound was prepared...
according to the procedure of Hill\textsuperscript{13,19}. To a stirred solution of cis-decahydro-5H-2a,4a,7a,9a-tetraazacyclopenta[cd]phenalene 79 (178 mg, 0.864 mmol) in MeCN (5 mL) at room temperature, was added benzyl bromide (1.10 mL, 1.58 g, 9.24 mmol). The mixture was stirred at room temperature for 20 days. Precipitate was collected by suction filtration, washed with MeCN (2 × 30 mL), and then CH\textsubscript{2}Cl\textsubscript{2} (3 × 15 mL). Residual solvent was removed under vacuum to give product as white powder (300 mg, 0.545 mmol, 63%). NMR spectra were consistent with spectra of authentic material.

4,11-Bis(phenylmethyl)-1,4,8,11-tetraazabicyclo[6.5.2]pentadecane (81): The compound was prepared according to the procedure of Hill\textsuperscript{13,19}. NaBH\textsubscript{4} (1.31 g, 0.0340 mol) was added in small portions over 20 min to a stirred solution of (9βα, 9αα)-Decahydro-2a,7a-bis(phenylmethyl)-5H-4a,9a-diaza-2a,7a-diazoniacyclopenta[cd]-phenalene dibromide 80 (300 mg, 0.545 mmol) in 95% EtOH (7.5 mL). The mixture was stirred for 10 days at room temperature. Excess NaBH\textsubscript{4} was then decomposed by slow addition 15 mL of 3 M HCl. Evaporation of solvent gave a white solid which was dissolved in water (3 mL), adjusted to pH 14 with solid KOH, and extracted with benzene (3 × 45 mL). The combined extracts were dried (Na\textsubscript{2}SO\textsubscript{4}), and solvent was removed under reduced pressure to yield product as a viscous oil (70.0 mg, 0.178 mmol, 33%). NMR spectra were consistent with spectra of authentic material.

4,11-Bis-(carbo-tert-butoxymethyl)-1,4,8,11-tetraazabicyclo[6.5.2]-pentadecane (82). To a stirred solution of 1,4,8,11-tetraazabicyclo[6.5.2]pentadecane 34 (35.0 mg, 0.165 mmol) in MeCN (8 mL), sodium carbonate (50.0 mg, 0.472 mmol) was
added in one portion, followed by tert-butyl bromoacetate (0.050 mL, 0.34 mmol) via syringe. The mixture was stirred for 3 days at room temperature. Solvent was removed under reduced pressure to yield crude product, which was subjected to flash chromatography (SiO₂, CH₂Cl₂: MeOH=10:1) to yield product as light yellow oil (40.0 mg, 0.0909 mmol, 55%): ³¹H NMR (500 MHz, C₆D₆) δ 1.30-1.46 (m, 2H), 1.40 (s, 18H), 2.25 (dt, 1H, J=13.9, 2.9 Hz), 2.50-2.62 (m, 5H), 2.72-2.88 (m, 10H), 2.88-2.95 (m, 1H), 2.96-3.03 (m, 1H), 3.09 & 3.17 (AB, 2H, J=16.4 Hz), 3.20 (br s, 2H), 3.24-3.31 (m, 1H), 3.59 (ddd, 1H, J= 12.5, 9.8, 4.9 Hz); ¹³C{¹H} NMR (125.7 MHz, C₆D₆) δ 28.36, 28.60, 28.61, 51.24, 53.34, 55.08, 55.82, 56.86, 57.39, 57.52 (2C), 57.66, 57.74, 59.84, 60.22, 80.17, 80.22, 171.52, 172.08; IR(neat) 2976, 2924, 2852, 2800, 1734, 1719, 1457, 1367, 1152, 1124; HRFABMS, m/z (M+H)+ exact mass for C₂₃H₄₅N₄O₄: 441.3441; Found: 441.3456 (error +1.5 mmu/+0.3 ppm)

4-(tert-Butylcarboxymethyl)-10-(2-hydroxybenzyl)-1,4,7,10-tetraazabicyclo[5.5.2]-tetradecane (83): 4-(tert-Butylcarboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]-tetradecane 73 (60.0 mg, 0.192 mmol), salicylaldehyde (71.0 mg, 0.582 mmol), acetic acid (69.0 mg, 1.15 mmol) were dissolved in 1,2-dichloroethane (10 mL). Sodium triacetoxyborohydride (82.0 mg, 0.387 mmol) was added to the above solution and the reaction mixture was stirred at room temperature under N₂ for 16 hours. The reaction mixture was then treated with additional sodium triacetoxyborohydride (41.0 mg, 0.194 mmol). After stirring for an addition 8 hours, the reaction was made basic with 1 N NaOH, and product was extracted with EtOAc (2 × 50 mL). The combined EtOAc extracts were dried (Na₂SO₄) and solvent was removed under reduced pressure to give an
oil, which was dissolved in water (2 mL), adjusted to pH 3 by addition of 3 M HCl, and extracted with Et₂O (2 × 25 mL). The aqueous solution was then adjusted to pH 13 (solid KOH), extracted with benzene (2 × 25 mL), the combined extracts were dried (Na₂SO₄), and solvent was removed under reduced pressure to yield product as an oil (32.0 mg, 0.0766 mmol, 40%): ^1H NMR (C₆D₆, 360 MHz) 1.38 (s, 9H, C(CH₃)₃), 2.34-2.40 (m, 4H), 2.55-2.90 (m, 18H), 3.08 (s, 2H), 3.45 (s, 2H), 6.74-6.80 (m, 1H), 6.85-6.89 (m, 1H), 7.05-7.22 (m, 2H); ^13C{^1H} NMR (C₆D₆, 90.56 Hz) 28.24 (C(CH₃)₃), 56.70, 56.73, 56.76, 57.29, 58.32, 58.91, 62.54, 80.05 (C(CH₃)₃), 116.60, 119.09, 123.42, 128.83, 129.26, 159.20, 171.49 (C=O); IR(KBr) 3485, 3400-2400 (br), 3060, 2975, 2930, 2854, 1733, 1669, 1457, 1393, 1368, 1253, 1223, 1153, 755 cm⁻¹; HREIMS, m/z (M+H)⁺ exact mass calcd for C₂₃H₃₈N₄O₃: 418.2944; Found: 418.2930 (error +1.4 mmu).

4-Formyl-10-(tert-butylcarboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]-tetradecane (86). 4-Benzyl-10-(tert-butylcarboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane 72 (100 mg, 0.248 mmol) was dissolved in a solution of 4.4 % HCOOH (v:v) in MeOH (10 mL) and 10% Pd/C (100 mg) was added in one portion at room temperature. The mixture was then stirred for 18 h under N₂ at room temperature. The contents were filtered through Celite, catalyst and Celite were washed with MeOH (2 × 5 mL), and the filtrate and washings were combined and concentrated under reduced pressure to give a white solid. This solid was dissolved in water (2 mL), the solution pH was adjusted to 14 (solid KOH with cooling) and the aq solution was extracted with benzene (2 × 25 mL). The combined extracts were dried (Na₂SO₄) and solvent was removed under reduced pressure to give product as a light yellow oil (84.0
mg, 0.246 mmol, 99%, >93% purity by $^{13}$C NMR): $^1$H NMR (C$_6$D$_6$, 360.15 MHz) 1.39 (s, 9H, C(CH$_3$)$_3$), 2.23-2.89 (m, 18H), 3.10 (s, 2H, CH$_2$CO), 3.26-3.38 (m, 1H), 3.73-3.84 (dm, 1H, J=13.1 Hz), 7.97 (s, CHO); $^{13}$C {$^1$H} NMR (C$_6$D$_6$, 90.56 Hz) 28.57 (C(CH$_3$)$_3$), 51.53, 53.09, 55.73, 56.48, 56.77, 56.81, 57.29, 58.25, 58.81, 58.84, 59.17, 80.45 (C(CH$_3$)$_3$), 163.98 (CHO), 171.76 (COO); IR (neat) 2974, 2916, 2818, 1734, 1674, 1456, 1392, 1369, 1217, 1150, 1122, 1032 cm$^{-1}$; HRFABMS, m/z (M+H)$^+$ exact mass calcd for C$_{17}$H$_{32}$N$_4$O$_3$: 341.2553; Found: 341.2527 (error -2.5 mmu/-7.4 ppm)

4-Carboxymethyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane • nHCl (87• 3HCl). 4-(tert-Butylcarboxymethyl)-10-formyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (86) (50.0 mg, 0.147 mmol) was dissolved in 6 M aq HCl (10 mL), the solution was refluxed for 3 days, and then the solvent was removed under reduced pressure to give white solid product as hydrochloride salt (3 equiv. HCl calculated on the basis of mass; 56.8 mg): $^1$H NMR (D$_2$O, 360 MHz, DOH peak set to 4.80) 2.96-3.14 (m, 8H), 3.16-3.30 (m, 4H), 3.33-3.44 (m, 6H), 3.68 (s, 2H), 3.68-3.80 (m, 2H); $^{13}$C {$^1$H} NMR (D$_2$O, 90.6 MHz) 47.52, 49.62, 55.48, 55.97, 58.47, 59.18, 179.96 (C=O); IR(KBr) 3389, 2989, 2828, 2634, 2615, 2506, 2413, 1763, 1736, 1488, 1433, 1421, 1407, 1309, 1236, 1194, 1144, 1091, 1027, 981 cm$^{-1}$; HRFABMS, m/z (M+H)$^+$ exact mass calcd for C$_{12}$H$_{25}$N$_4$O$_2$: 257.1978; Found: 257.1974 (error -0.4 mmu/-1.4 ppm).

δ-Benzylidene laevulinic acid (90): The compound was prepared by the published method$^{58}$. Laevulinic acid (29.0 g, 0.250 mol) and benzaldehyde (26.5 g, 0.250 mol) were dissolved in dry benzene (200 mL). Acetic acid (30 mL) and dry piperidine
(10 mL) were also added to the mixture. This solution was then refluxed for 72 h over a Dean-Stark trap. After the solution was cooled, water (100 mL) was added, and the aqueous phase was extracted with ether (3 × 200 mL). The combined extracts were then washed with water (2 × 200 mL) and dried (Na₂SO₄). Removal of solvent under reduced pressure afforded white crystalline product (41.3 g, 0.203 mol, 81%): ¹H NMR (400 MHz, CDCl₃) δ 2.75 (t, 2H, J=6.6 Hz), 3.02 (t, 2H, J=6.6 Hz), 6.76 (d, 1H, J=16.2 Hz), 7.35-7.45 (m, 3H), 7.50-7.60 (m, 2H), 7.60 (d, 1H, J=16.4 Hz); ¹³C {¹H} NMR (100.5 MHz, CDCl₃) δ 28.17, 35.16, 125.87, 128.55, 129.16, 130.81, 134.51, 143.38, 178.90, 198.05.

4, 5-dioxopentanoic acid (91): The compound was prepared by the published method. δ-Benzyldiene laevelinic acid 90 (10 g, 0.049 mol) was dissolved in dry methanol (150 mL) and cooled to -70 °C in acetone/dry ice bath. Ozone was passed through the solution until the excess ozone caused the solution to acquire a slight bluish color. The solution was allowed to warm to -10 °C, when the temperature reached -10 °C, dimethyl sulfide (DMS) (4.2 g, 68 mmol) was added in one portion, the temperature was maintained for 1 h and warmed to room temperature, the solvent was removed under reduced pressure, the residue was dissolved in water (50 ml) and extracted with ether (4 × 50 ml) to remove benzaldehyde, the aqueous layer was removed to produce monohydrate product as green oil (6.5 g, 44 mmol, 90%): ¹³C {¹H} NMR (125.7 MHz, DMSO) δ 27.40, 31.07, 90.72, 173.96, 207.43. The material was used directly in the next reaction.

Methyl δ-Benzyldene laevelinic acid (94): δ-Benzyldiene laevelinic acid 90 (2.0 g, 9.8 mmol) was dissolved in MeOH (150 mL), and conc. H₂SO₄ (0.5 mL) was
added. The mixture was refluxed for 0.75 h. The solvent was removed under reduced pressure, the residue was dissolved in CHCl$_3$ (50 mL), and the solution was washed with aq saturated NaHCO$_3$ (2 × 25 mL) and water (2 × 30 mL), and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure to give crude product which was recrystallized from a hot mixture of ethyl acetate (0.4 mL) and hexane (1.6 mL) to yield crystalline product (1.6 g, 7.4 mmol, 75%). NMR spectra were consistent with reported spectra.$^{61b}$

**Attempted preparation of Methyl 4, 5-dioxo-pentanoate (95).** Actual synthesis of methyl 5-hydroxylaevulinate (99): A stream of Ozone was passed through a stirred solution of methyl benzyl-laevulinate 94 (500 mg, 2.29 mmol) in dry methanol (30 ml) at -10 °C. On completion of reaction (TLC analysis) the resulting light green solution was purged with N$_2$ for 0.5 h, the solution was hydrogenated at room temperature and atmospheric pressure over 10% Pd/C (500 mg) for 4 h, the Pd/C was filtered off and the solvent was evaporated to dryness. The residue was dissolved in water (2 ml) and washed with hexane (2 × 25 ml) to remove the benzaldehyde. The aqueous layer was evaporated to yield product as light green oil (167 mg, 1.14 mmol, 50%): NMR spectra are consistent with reported data for methyl 5-hydroxylaevulinate 99$^{62b}$

**Methyl 4, 5-dioxo-pentanoate (95):** This procedure was modeled on the method for the preparation of 4, 5-dioxopentanoic acid of Cook and coworkers$^{58}$. A steam of Ozone was passed through a stirred solution of methyl benzyl-laevulinate 94 (620 mg, 2.84 mmol) in dry methanol (30 ml) at -40 °C. On completion of reaction (TLC analysis)
the resulting solution was purged with N\textsubscript{2} for 1 h, warmed to -10 °C, DMS (0.25 ml, 2.8 mmol) was added in one portion, the temperature was kept for 1h and warmed to room temperature, the solvent was removed under reduced pressure, the residue was dissolved in water (5 ml) and extracted with hexane (2 x 20 ml) to remove benzaldehyde, the aqueous layer was removed to produce product as an unstable light green oil (240 mg, 1.67 mmol, 59\%): \textsuperscript{13}C{\{^1H\}} NMR (100.5 MHz, CDCl\textsubscript{3}) δ 28.81, 28.87, 51.81, 172.906, 175.46, 187.89. The material was used directly in the next reaction. Alternative method: The procedure was modeled the procedure of the published paper by Griffith and Ley\textsuperscript{63}. Tetra-n-propylammonium perruthenate (TPAP)(5 mol\%, 12 mg) was added in one portion to a stirred mixture of 5-hydroxy-4-oxopentanoic acid methyl ester 99 (100 mg, 0.680 mmol), 4-methyl morpholine N-oxide (NMO)(190 mg, 1.02 mmol), 4A molecular sieves (500 mg) in CH\textsubscript{2}Cl\textsubscript{2} (1.5 ml). The reaction was following by TLC, when completion, the mixture was filtered through a pad of silica, eluting with CH\textsubscript{2}Cl\textsubscript{2}, the filtrate was evaporated to yield product as green oil (97 mg, 0.673 mmol, 99\%).

**Methyl 5-bromolaevulinate (97):** The compound was prepared by a literature method\textsuperscript{62a}. A solution of laevulinic acid (96) (2.00 g, 0.0172 mol) in MeOH (20 mL) was stirred at room temperature while bromine (2.76 g, 0.0173 mol) was added in one portion. After 3.5 h, the KI-Starch test was negative and the solution was refluxed for 1.5 h. After removal of methanol, the residue was stirred with ether (20 mL) and water (10 mL) while sodium bicarbonate (10 g) was added. The ether layer was washed with aqueous saturated sodium bicarbonate (20 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), and then solvent was removed under reduced pressure to give crude product which was subjected to flash chromatography.
(SiO$_2$, hexane: ethyl acetate=4:1) to yield product as a colorless oil (850 mg, 4.07 mmol, 24%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.53 (t, 2H, J=6.4 Hz), 2.85 (t, 2H, J=6.4 Hz), 3.56 (s, 3H), 3.90 (s, 2H); $^{13}$C NMR (100.5 MHz, CDCl$_3$) $\delta$ 27.93, 34.31, 34.35, 51.78, 172.64, 200.44.

**Methyl 5-formyloxylaevulinate (98):** The compound was prepared by a published method$^{62b}$. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (512.7 mg, 3.369 mmol) was added slowly at 0 °C to a mixture of methyl 5-bromolaevulinate (97) (500.0 mg, 2.392 mmol) and formic acid (149.7 mg, 3.249 mmol) in benzene (10 mL). After 2 h at room temperature, water (20 mL) was added and the mixture was extracted with CH$_2$Cl$_2$ (3 $\times$ 20 mL). The organic phase was washed with 0.1 M HCl (2 $\times$ 25 mL) and water (2 $\times$ 25 mL). Drying (Na$_2$SO$_4$), filtration, and evaporation of the solvent under reduced pressure afforded crude formyloxy compound which was subjected to flash chromatography (SiO$_2$, ethyl acetate: hexane=1:2) to give pure formyloxy compound (308 mg, 1.77 mmol, 74%). NMR spectra were consistent with reported spectra.$^{62b}$

**Methyl 5-hydroxylaevulinate (99):** The compound was prepared by the published method$^{62b}$. Methyl 5-formyloxylaevulinate 98 (1.40 g, 8.05 mmol) was deformylated by being subjected to flash chromatography (neutral Al$_2$O$_3$, CH$_2$Cl$_2$:MeOH=1:1) to yield pure product (1.11 g, 7.60 mmol, 94%). NMR spectra were consistent with reported spectra.$^{62b}$

(13ba, 13ca)-2,9-Dibromo-5,6,7,12,13,13b,13c,14-octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene (103). Tetrabutylammonium tribromide (TBABr$_3$) (370.0

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mg, 0.7670 mmol) was added to a stirred solution of (13ba, 13ca)-
5,6,7,12,13,13b,13c,14-octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene
(110.0 mg, 0.3460 mmol) in CHCl₃ (20 mL). The mixture was refluxed for 3 days,
diluted with additional CHCl₃ (300 mL), and the organic solution was washed with water
(2 × 100 mL), aq saturated NaCl (2 × 40 mL), dried (Na₂SO₄), and evaporated to dryness.
Recrystallization from hot CHCl₃ gave x-ray quality crystals (84.0 mg, 0.175 mmol,
50%): mp 132-134 °C (dec); ¹H NMR (400 MHz, CDCl₃) δ 2.67 (ddd, 2H, J=11.0, 3.7,
1.7 Hz), 2.98 (td, 2H, J=11.7, 3.9 Hz), 3.27 (td, 2H, J=11.7, 3.7 Hz), 3.60 (d, 2H, J=17.0
Hz), 3.81 (ddd, 2H, J=11.7, 3.4, 2.0 Hz), 4.17 (s, 2H), 4.49 (d, 2H, J=17.0 Hz), 6.71 (d,
2H, J=8.8 Hz), 7.03-7.06 (m, 2H), 7.21 (ddd, 2H, J=9.0, 2.7, 0.7 Hz); ¹³C{¹H} NMR
(100.5 MHz, CDCl₃, CDCl₃ central peak set at 77.23) δ 45.20, 46.09, 54.68, 70.26,
110.68, 114.66, 122.73, 129.83, 130.49, 143.74; IR(KBr) 2948, 2906, 2862, 2827, 1588,
1487, 1449, 1407, 1380, 1322, 1300, 1241, 1130, 907, 801 cm⁻¹; HRFABMS, m/z
(M+H)⁺ exact mass calcd for C₂₀H₂₁N₄Br₂: 475.0133; Found: 475.0113 (error –2.0
mmu/-4.3 ppm)

(13ba, 13ca)-2,9-Dibromo-5,6,7,12,13,13b,13c,14-octahydro-4b,6a,11b,13a-
tetraazadibenzo[b,def]chrysene (103). Tetrabutylammonium tribromide (TBABr₃)
(370.0 mg, 0.7670 mmol) was added to a stirred solution of (13ba, 13ca)-
5,6,7,12,13,13b,13c,14-octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene
(110.0 mg, 0.3460 mmol) in CHCl₃ (20 mL). The mixture was refluxed for 3 days,
diluted with additional CHCl₃ (300 mL), and the organic solution was washed with water
(2 × 100 mL), aq saturated NaCl (2 × 40 mL), dried (Na₂SO₄), and evaporated to dryness.
Recrystallization from hot CHCl₃ gave x-ray quality crystals (84.0 mg, 0.175 mmol, 50%): mp 132-134 °C (dec); ¹H NMR (400 MHz, CDCl₃) δ 2.67 (ddd, 2H, J=11.0, 3.7, 1.7 Hz), 2.98 (td, 2H, J=11.7, 3.9 Hz), 3.27 (td, 2H, J=11.7, 3.7 Hz), 3.60 (d, 2H, J=17.0 Hz), 3.81 (ddd, 2H, J=11.7, 3.4, 2.0 Hz), 4.17 (s, 2H), 4.49 (d, 2H, J=17.0 Hz), 6.71 (d, 2H, J=8.8 Hz), 7.03-7.06 (m, 2H), 7.21 (ddd, 2H, J=9.0, 2.7, 0.7 Hz); ¹³C{¹H} NMR (100.5 MHz, CDCl₃, CDCl₃ central peak set at 77.23) δ 45.20, 46.09, 54.68, 70.26, 110.68, 114.66, 122.73, 129.83, 130.49, 143.74; IR(KBr) 2948, 2906, 2862, 2827, 1588, 1487, 1449, 1407, 1380, 1322, 1300, 1241, 1130, 907, 801 cm⁻¹; HRFABMS, m/z (M+H)+ exact mass calcd for C₂₀H₂₁N₄Br₂: 475.0133; Found: 475.0113 (error -2.0 mmu/-4.3 ppm)

(13ba, 13ca)-2,9-Bis(4-styryl)-5,6,7,12,13b,13c,14-octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene (106): To a solution of (13ba, 13ca)-2,9-dibromo-5,6,7,12,13b,13c,14-octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene 103 (67.0 mg, 0.140 mmol) in DMF (10 mL) was added NaOAc (23.0 mg, 0.280 mmol), tri(o-tolyl)phosphine (27.2 mg, 0.0894 mmol), palladium(II) acetate (5.0 mg, 0.022 mmol), and styrene (60.0 mg, 0.576 mmol). The mixture was maintained at 130 °C for 3 days. The mixture was then poured into a flask containing ice (300 g) to generate white precipitate which was collected by suction filtration and then dissolved in CHCl₃ (200 mL). The solution was washed with H₂O (2 × 200 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure to give crude product which was subjected to flash chromatography (SiO₂, CH₂Cl₂: MeOH = 30:1) to give 27.2 mg of white solid consisting of a mixture of two products. The major
product was (13ba, 13ca)-2,9-bis((E)-styryl)-5,6,7,12,13,13b,13c,14-octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene 106 (0.0516 mmol, 37% by NMR integration) and the minor product was 2-bromo-9-styryl-5,6,12,13,13b,13c-hexahydro-7H,14H-4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene (107) (0.0109 mmol, 8% by NMR integration). The ratio of major to minor was 4.7:1. Major product: $^1$H NMR (500 MHz, CDCl₃) δ 2.66-2.76 (dm, 2H, J=10.0 Hz), 3.06 (td, 2H, J=11.7, 3.7 Hz), 3.31 (td, 2H, J=11.7, 3.7 Hz), 3.70 (d, 2H, J=16.8 Hz), 3.88-3.96 (dm, 2H, J=10.7 Hz), 4.27 (s, 2H, NC/NCN), 4.58 (d, 2H, J=16.6 Hz), 6.85 (d, 2H, J=8.5 Hz), 6.94 & 7.02 (AB, 4H, J=16.4 Hz), 7.14 (s, 2H), 7.20-7.25 (tm, 2H, J=7.1 Hz), 7.28-7.32 (dm, 2H, J=7.1 Hz), 7.28-7.32 (dm, 2H, J=9.0 Hz), 7.35 (t, 4H, J=7.6 Hz), 7.48 (d, 4H, J=7.8 Hz); $^{13}$C ($^1$H) NMR (125.7 MHz, CDCl₃) δ 45.26, 46.20, 55.15, 70.55, 112.99, 120.68, 125.30, 125.77, 126.34, 126.45, 127.21, 127.92, 128.50, 128.85, 138.09, 144.42.

(13ba, 13ca)-2,9-Diphenethyl-5,6,7,12,13,13b,13c,14-octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene (108). Hydrogenolysis of (13ba, 13ca)-2,9-distyryl-5,6,7,12,13,13b,13c,14-octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene (106) was carried out in a glass apparatus designed for the exclusion of O₂ and for measurement of H₂ uptake with maintenance of constant pressure. Catalyst (60 mg, 10% Pd/C) and ethyl acetate (50 mL) were added to a 100 mL hydrogenation flask, which was connected to the apparatus. The system was evacuated by means of a water aspirator and flushed with N₂ four times. After another evacuation the system was filled with hydrogen. The mixture of 10% Pd/C and ethyl acetate solution was equilibrated under H₂ for 30 minutes. 106 (20.0 mg, 0.0659 mmol) in ethyl acetate (2
0.0228 mmol, 60%): $^1$H NMR (500 MHz, CDCl$_3$) δ 2.64-2.73 (dm, 2H, J=9.1 Hz), 2.75-2.92 (AA'BB', 4H), 2.99 (td, 2H, J=11.7, 3.2 Hz), 3.31 (br t, 2H, J=11.5 Hz), 3.62 (d, 2H, J=16.6 Hz), 3.81-3.93 (dm, 2H, J=10.7 Hz), 4.18 (s, 2H), 4.54 (d, 2H, J=16.6 Hz), 6.72-6.82 (m, 4H), 6.97 (br d, 2H, J=8.8 Hz), 7.15-7.40 (m, 10H); $^{13}$C($^1$H) NMR (125.7 MHz, CDCl$_3$, CDCl$_3$ central peak set at 77.23) δ 37.27, 38.35, 45.55, 46.42, 55.1, 70.77, 112.94, 120.59, 126.06, 127.21, 127.63, 128.53, 128.67, 131.91, 142.28, 142.86; IR(KBr) 3054, 2987, 1422, 1265, 1280, 739, 705 cm$^{-1}$; HRFABMS, m/z (M+H)$^+$ exact mass for C$_{36}$H$_{39}$N$_4$: 527.3175; Found: 527.3171 (error -0.3 mmu/-0.6 ppm).

(10bo,10ca)-Decahydro-3a-acetamido-1H,6H-3a,5a,8a,10a-tetraazapyrenium bromide (113). cis-Decahydro-1H,6H-3a,5a,8a,10a-tetraazapyrene 47 (200 mg, 0.900 mmol) was dissolved in dry MeCN (15 mL), 2-bromoacetamide (1.02 g, 7.40 mmol) was added in one portion to the solution, and the solution was stirred for 6 days at room temperature under nitrogen. The white precipitate which had formed was collected by suction filtration under a blanket of nitrogen and the filtercake was washed with MeCN (2 × 5 mL) to yield product as a white solid (170 mg, 0.472 mmol, 52%): $^1$H NMR (D$_2$O, 400 MHz, ref CH$_3$CN set at 2.06) δ 1.36-1.44 (dm, 1H, J=14.2 Hz), 1.82-1.91 (dm, 1H, J=16.4 Hz), 2.09-2.30 (m, 1H), 2.26-2.57 (m, 5H), 2.90-3.09 (m, 7H), 3.40-3.51 (m, 1H),

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3.64-3.72 (dm, 1H, J=12.7 Hz), 3.80 (td, 1H, J=13.3, 4.1 Hz), 3.90-3.97 (m, 1H), 4.00 (br s, 1H), 4.05 (d, 1H, J=2.3 Hz), 4.28-4.39 (m, 1H), 4.33 & 4.58 (AB, 2H, J=15.1 Hz); \(^{13}\)C NMR (D\(_2\)O, 100.5 MHz, ref CH\(_3\)CN set at 1.47) \(\delta\) 18.19, 18.82, 42.12, 46.44, 50.62, 51.46, 52.18, 53.47, 53.93, 58.12, 61.53, 69.57, 82.96, 166.04(C=O); IR(KBr) 3457, 3380, 3316, 3150, 3031, 2953, 2869, 2838, 2796, 1694, 1457, 1352, 1145, 1118 cm\(^{-1}\); HRFABMS, m/z (M-Br\(^{+}\)) exact mass for C\(_{14}\)H\(_{26}\)N\(_5\)O: 280.2137; Found: 280.2119 (error – 1.9 mmu/-6.6 ppm).

(10\(\text{ba},10\text{ca}\))-Decahydro-3a,8a-bis-(acetamido)-1H,6H-3a,5a,8a,10a-tetraazapyrenium dibromide (114). cis-Decahydro-1H,6H-3a,5a,8a,10a-tetraazapyrene 47 (30.0 mg, 0.225 mmol) was dissolved in dry MeCN (3.7 mL), 2-bromoacetamide (256 mg, 1.86 mmol) was added in one portion to the stirred solution, and the solution was stirred for 15 days at room temperature. The white precipitate which had formed was isolated by suction filtration under a blanket of nitrogen. The filter cake was washed with MeCN (2 x 5 mL) to yield product as a white solid (75.0 mg, 0.151 mmol, 67%): \(^1\)H NMR (D\(_2\)O, 400 MHz, ref CH\(_3\)CN set at 2.06) \(\delta\) 1.89-1.98 (dm, 2H, J=15.4 Hz), 2.36-2.51 (m, 2H), 2.78 (td, 2H, J=12.7, 3.3 Hz), 3.13-3.30 (m, 4H), 3.32-3.39 (m, 2H), 3.45 (br s, 2H, impurity hypothesized to be 1 eq. strongly complexed H\(_2\)O), 3.63 (dd, 2H, J=13.1, 2.0 Hz), 3.86-4.02 (m, 4H), 4.44 & 4.60 (AB, 4H, J=16.2 Hz, NCH\(_2\)H\(_2\)CO), 4.64 (td, 2H, J=12.9, 4.3 Hz), 5.34 (s, 2H); \(^{13}\)C NMR (D\(_2\)O, 100.5 MHz, ref CH\(_3\)CN set at 1.47) \(\delta\) 18.78 (CH\(_2\)CH\(_2\)CH\(_2\)), 46.77, 49.98, 51.45, 58.17, 62.33, 76.28, 165.80(C=O); IR (KBr) 3468, 3316, 3150, 3058, 2964, 2857, 1697, 1310, 1137 cm\(^{-1}\); HRFABMS, m/z (M-
Br)⁺ exact mass for C₁₆H₉₀N₆O₂Br: 417.1614; Found: 417.1632 (error +1.8 mmu/+4.4 ppm).

1,8-Bisacetamido-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (115).

(10ββ,10αα)-Decahydro-3a,8a-bis-(acetamido)-1H,6H-3a,5a,8a,10a-tetraazapyrenium dibromide 114 (100 mg, 0.201 mmol) was dissolved into a mixture of 95% EtOH (20 mL) and H₂O (1 mL). NaBH₄ (100 mg, 2.70 mmol) was added in small portions over 5 minutes. The mixture was stirred for 14 days at room temperature. Excess NaBH₄ was then decomposed by slow addition of 10 mL of 3M aq HCl. Evaporation of solvent under reduced pressure gave white solid, which was dissolved in H₂O (5 mL). The solution was adjusted to pH 14 by addition of solid KOH, extracted with CHCl₃ (3 × 50 mL), the combined extracts were dried (Na₂SO₄), and solvent was removed under reduced pressure to give white solid product (43.0 mg, 0.128 mmol, 64%). NMR spectra were consistent with those of authentic compound.¹²

4-Carboxy methyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane 2TFA (116•2TFA). 4-Carbo-tert-butoxymethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane 74 (44 mg, 0.13 mmol) was dissolved in CF₃CO₂H (TFA) (5 mL), and the solution was stirred for 15 h at room temperature. Solvent was then removed under reduced pressure to give product as TFA salt (2 equiv. TFA calculated on the basis of mass and ¹H NMR; 66 mg). ¹H NMR (400 MHz, CD₃CN, CHD₂CN central peak set at 1.94) δ 1.60-1.72 (m, 2H), 2.16-2.37 (m, 2H), 2.45-2.57 (m, 2H), 2.64-2.76 (m, 2H), 2.80-2.92 (m, 2H), 2.93-3.05 (m, 3H), 3.06-3.40 (m, 10H), 3.41-3.64 (m, 4H), 4.08 (A of AX, J=16.8 Hz), 8.78
(br s, 1H), 11.14 (br s, 2H); $^{13}$C $^1$H NMR (D$_2$O, 100.5 MHz, ref CH$_3$CN set at 1.47)

$\delta$ 18.70, 19.47, 41.68, 47.95, 48.88, 49.06, 49.15, 54.86, 55.24, 55.79, 57.98, 58.55, 58.92,

116.91 (q, J$_{C,F}=323.2$ Hz), 163.46 (t, J$_{C,F}=39.8$ Hz), 172.28; IR (CH$_3$CN) 3164, 3003, 2944, 1650, 1376, 1199, 1039 cm$^{-1}$; HRFABMS, m/z (M+H)$^+$ exact mass calcd for C$_{14}$H$_{29}$N$_4$O$_2$: 285.2291; Found: 285.2289 (error -0.1 mmu/-0.5 ppm).

4-Acetamido-11-carbo-tert-butoxymethyl-1,4,8,11-tetraazabicyclo[6.6.2]-hexadecane (121). 4-Carbo-tert-butoxymethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane 74 (30 mg, 0.086 mmol) was dissolved in dry MeCN (4 mL), sodium carbonate (9.2 mg, 0.086 mmol) was added in one portion, and 2-bromoacetamide (12 mg, 0.086 mmol) was added in one portion. The mixture was stirred for 14 h at room temperature and then solvent was removed under reduced pressure. The residue was dissolved in water (2 mL), adjusted to pH 14 (solid KOH) with cooling, and the aq solution was extracted with benzene (2 x 20 mL). The combined extracts were dried (Na$_2$SO$_4$) and solvent was removed under reduced pressure to give product as an oil (15.0 mg, 0.0372 mmol, 43%):

$^1$H NMR (C$_6$D$_6$, 400 MHz) $\delta$ 1.01-1.40 (m, 4H), 1.39 (s, 9H, C(CH$_3$)$_3$), 2.00 (dt, 1H, J=12.3, 4.1 Hz), 2.05-2.68 (m, 13H), 2.68-2.86 (m, 3H), 2.79 & 3.04 (AX, 2H, J=16.4 Hz), 3.02 & 3.14 (AB, 2H, J=16.4 Hz), 3.20 (td, 1H, J=8.0, 4.1 Hz), 3.36 (td, 1H, J=12.1, 4.5 Hz), 4.08 (ddd, 1H, J=13.3, 8.2, 3.9 Hz), 6.37 (br s, 1H), 6.42 (br s, 1H); $^{13}$C $^1$H NMR (C$_6$D$_6$, 100.5 MHz) $\delta$ 28.04, 28.22, 28.40. 51.67, 52.27, 53.46, 53.86, 55.89, 56.76, 57.24, 57.52, 57.55, 58.65, 59.94, 61.06, 79.96, 171.18, 174.44; IR (CCl$_4$) 3448, 2978, 2922, 2809, 1739, 1689, 1368, 1155, 1125 cm$^{-1}$; HSFABMS (M+H)$^+$ exact mass calcd for C$_{20}$H$_{40}$O$_3$N$_5$: 398.3131; Found: 398.3106 (error -2.5 mmu/-6.3 ppm).
4-Acetamido-11-carboxymethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane

-2TFA (122•2TFA). 4-Carbo-tert-butoxymethyl-11-acetamido-1,4,8,11-tetraazabicyclo[6.6.2]-hexadecane 121 (15 mg, 0.0372 mmol) was dissolved in a mixture of TFA and CH₂Cl₂ (TFA : CH₂Cl₂ = 1:1, 6 mL) and the solution was stirred for 14 h at room temperature. Solvent was then removed under reduced pressure to give product as TFA salt (2 equiv TFA calculated on the basis of mass; 20 mg): ¹H NMR (D₂O, 400 MHz, DOH peak set to 4.80) δ 1.72-1.80 (dm, 2H, J=17.4 Hz), 2.30-2.45 (m, 2H), 2.70-2.84 (m, 2H), 3.00-3.36 (m, 16H), 3.42-3.72 (m, 4H), 3.56 & 4.08 (AX, 2H, J=17.4 Hz), 3.63 & 4.08 (AX, 2H, J=16.1 Hz); ¹³C NMR (D₂O, 100.5 MHz) δ 19.46, 19.47, 47.56, 47.82, 48.20, 48.30, 52.91, 53.23, 54.98, 55.11, 58.11, 58.13, 58.70, 58.93, 116.4 (q, J=291.4 Hz, CF₃COOH), 163.1 (q, J=35.2 Hz, CF₃COOH), 170.05, 171.77; IR (CH₃CN) 3681, 3540, 3164, 3003, 2944, 1694, 1444, 1422, 1376, 1202, 1039, 918 cm⁻¹; HRFABMS, m/z (M+H)⁺ exact mass for C₁₆H₃₅N₅O₃: 342.2505; Found: 342.2500 (error -0.5 mmu/-1.4 ppm).

4-Carbo-tert-butoxymethyl-11-(N-methylacetamido)-1,4,8,11-tetraazabicyclo[6.6.2]-hexadecane (123). 4-Carbo-tert-butoxymethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane 74 (18 mg, 0.052 mmol) was dissolved in dry MeCN (4 mL), sodium carbonate (13 mg, 0.1226 mmol), potassium iodide (23 mg, 0.1385 mmol), and 2-chloro-N-methyl acetamide (13 mg, 0.1209 mmol) were added in portions, and then the solution was stirred for 14 h at room temperature. Solvent was removed under reduced pressure to yield solid product, which was dissolved in water (2 mL) and...
adjusted to pH 3 by addition of 3 M aq HCl (with cooling). The aq phase was extracted with benzene (2 × 25 mL), the organic layer was discarded, and the aqueous layer was adjusted to pH 14 with solid KOH (with cooling). The basic aq phase was extracted with benzene (2 × 25 mL), combined extracts were dried (Na₂SO₄), and solvent was removed under reduced pressure to yield product an oil (21 mg, 0.051 mmol, 98%, >92% purity by

**1³C NMR**: \(^1^H\) NMR (C₆D₆, 400 MHz) \(\delta\) 1.05-1.40 (m, 4H), 1.40 (s, 9H, C(CH₃)₃), 2.02-2.16 (m, 2H), 2.17-2.36 (m, 2H), 2.36-2.66 (m, 8H), 2.64 (d, 3H, \(J=5.1\) Hz), 2.68-2.94 (m, 5H), 2.86 & 3.07 (AB, 2H, \(J=16.2\) Hz), 3.02 & 3.15 (AB, 2H, \(J=16.4\) Hz), 3.24 (td, 1H, \(J=12.1, 4.3\) Hz), 3.40 (td, 1H, \(J=11.9, 4.3\) Hz), 4.11 (ddd, 1H, \(J=16.6, 10.0, 4.3\) Hz), 6.59 (br s, 1H, NH); **1³C \{¹H\} NMR (C₆D₆, 100.5 MHz) \(\delta\) 25.77, 28.32, 28.53, 28.58, 51.96, 52.70, 53.83, 54.02, 56.29, 57.18, 57.76, 57.95, 58.81, 60.23, 61.58, 80.34, 171.53, 171.69; IR(CCl₄) 3407, 2918, 2809, 1739, 1684, 1559, 1457, 1368, 1155, 1125 cm⁻¹; HSFABMS (M+H)+ exact mass calcd for C₂₁H₄₂N₅O₃: 412.3288; Found: 412.3274 (error -1.4 mmu/-3.3 ppm).

(11-Methylcarbamoylmethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-4-yl)-
acetic acid •2TFA (124•2TFA). 4-(Carbo-tert-butoxymethyl)-11-(N-methylacetamido)-
1,4,8,11-tetraazabicyclo[6.6.2]hexadecane 123 (14 mg, 0.034 mmol) was dissolved in a
mixture of CF₃CO₂H (TFA) and CH₂Cl₂ (TFA: CH₂Cl₂ =1:1, 8 mL), and the solution was stirred for 16 h. Solvent was then removed under reduced pressure to yield product (20 mg): \(^1^H\) NMR (400 MHz, D₂O, DOH peak set at 4.80) \(\delta\) 1.70-1.80 (dm, 2H, \(J=17.0\) Hz), 2.30-2.46 (m, 2H), 2.70-2.85 (m, 2H), 2.74 (s, 3H, NCH₃), 3.00-3.38 (m, 14H), 3.44-3.76 (m, 4H), 3.57 & 4.11 (AX, 2H, \(J=17.4\) Hz), 3.58 & 4.06 (AX, 2H, \(J=16.1\)Hz); **1³C \{¹H\}
NMR (100.5 MHz, D$_2$O) δ 19.41 (2C), 25.95, 47.51, 47.87, 48.26, 48.32, 52.82, 53.29, 55.13 (2C), 58.07 (2C), 58.61, 58.93, 116.43 (q, J$_{CF}$ = 292.2 Hz, CF$_3$COOH), 163.05 (q, J$_{CF}$ = 35.2 Hz, CF$_3$COOH), 167.65, 171.74; IR (CH$_3$CN) 3638-3538 (br), 3164, 3002, 2944, 1682, 1444, 1418, 1376, 1201, 1132, 1039 cm$^{-1}$; HRFABMS, m/z (M+H)$^+$ exact mass for C$_{17}$H$_{34}$N$_5$O$_3$: 356.2662; Found: 356.2664 (error +0.2 mmu/+0.5 ppm). On the basis of the mass and assuming a quantitative yield (no evidence of impurities), the product is a di-TFA salt.

4-(Carbo-tert-butoxymethyl)-11-(N-phenylacetamido)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (125). 4-(Carbo-tert-butoxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane 74 (20 mg, 0.058 mmol) was dissolved in dry MeCN (4 mL), sodium carbonate (74 mg, 0.698 mmol), potassium iodide (13.4 mg, 0.0807 mmol), and 2-chloro-N-phenylacetamide (37 mg, 0.218 mmol) were added in single portions. The solution was stirred for 14 h at room temperature and solvent was removed under reduced pressure to yield a solid. This was dissolved in water (2 mL), the solution was adjusted to pH 3 by addition of 3 M aq HCl (with cooling), and the acidic solution was extracted with benzene (2 × 25 mL). The organic phase was discarded. The aqueous phase was adjusted to pH 14 (solid KOH with cooling), extracted with benzene (2 × 25 mL), combined extracts were dried (Na$_2$SO$_4$), and solvent was removed under reduced pressure to yield product as an oil (20 mg, 0.042 mmol, 73%): $^1$H NMR (C$_6$D$_6$, 500 MHz) δ 1.03-1.40 (m, 4H), 1.40 (s, 9H, C(CH$_3$)$_3$), 2.00-2.03 (m, 2H), 2.08 (dt, 1H, J=13.0, 3.9 Hz), 2.12-2.23 (m, 2H), 2.24-2.35 (m 2H), 2.48-2.55 (m, 2H), 2.55-2.66 (m, 4H), 2.71(td, 1H, J=8.8, 3.6 Hz), 2.76-2.86 (m, 2H), 2.85 & 3.09 (AX, 2H, J=16.4 Hz), 2.97 (td, 1H,
J=11.7, 4.2 Hz), 3.01 & 3.13 (AB, 2H, J=16.4 Hz), 3.25 (td, 1H, J=13.2, 4.6 Hz), 3.33 (td, 1H, J=12.0, 4.4 Hz), 4.17-4.24 (m, 1H), 6.92 (tt, 1H, J=8.6, 1.0 Hz), 7.14-7.22 (m, 2H), 7.91 (dd, 2H, J=8.6, 1.0 Hz), 9.12 (br s, 1H, NH); $^{13}$C{$^{1}$H} NMR (CD$_3$D$_6$, 100.5 MHz) δ 28.30, 28.57(C(CH$_3$)$_3$), 28.69, 51.87, 52.49, 53.84, 54.10, 56.13, 57.22, 57.46, 58.03, 58.36, 59.43, 60.40, 62.44, 80.39, 119.31, 124.24, 129.84, 139.48, 169.63, 171.49; IR (neat) 703, 739, 1126, 1156, 1265, 1368, 1443, 1521, 1601, 1684, 1732, 2818, 2925, 2979, 3053, 3308 cm$^{-1}$; HSFABMS (M+H) exact mass calcd for C$_{26}$H$_{44}$N$_5$O$_3$: 474.3444; Found: 474.3440 (error -0.4 mmu/-0.8 ppm).

(11-Phenylcarbamoylmethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-4-yl)-acetic acid •4TFA (126•4TFA). 4-(Carbo-tert-butoxymethyl)-11-(N-phenyl acetamido)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane 125 (140 mg, 0.296 mmol) was dissolved in a mixture of CF$_3$CO$_2$H (TFA) and CH$_2$Cl$_2$ (TFA: CH$_2$Cl$_2$ =1:1, 20 mL), and the solution was stirred for 16 h. Solvent was then removed under reduced pressure to yield product (255 mg, quant; no impurities by NMR): $^{1}$H NMR (CD$_3$CN, 500 MHz, CHD$_2$CN central peak set to 1.94) δ 1.63-1.72 (m, 2H), 2.20-2.34 (m, 2H), 2.68-2.76 (dm, 2H, J=12.5 Hz), 2.94-3.02 (dm, 2H, J=14.7 Hz), 3.03-3.22 (m, 12H), 3.27 (td, 1H, J=12.9, 3.2 Hz), 3.40-3.61 (m, 4H), 3.62-3.72 (m, 2H), 4.05 (A of AX, 1H, J=16.6 Hz), 4.23 (A of AX, 1H, J=16.6 Hz), 7.12-7.17 (m, 1H), 7.31-7.36 (m, 2H), 7.57-7.61 (m, 2H), 10.02 (s, 1H, NH), 10.90 (br s, 2H), 11.06 (br s, 3H); $^{13}$C{$^{1}$H} NMR (CD$_3$CN, 125.7 MHz, CD$_3$CN central peak set to 1.39) δ 20.73, 20.81, 48.77, 48.98, 49.39, 49.43, 53.73, 53.91, 56.66, 57.70, 59.42, 60.40, 117.25 (q, J$_{CF}$=290.5 Hz, CF$_3$CO$_2$), 121.24, 125.88, 129.94, 138.79, 160.95 (q, J$_{CF}$=36.4 Hz, CF$_3$CO$_2$), 166.73, 171.91; IR (CH$_3$CN) 3648, 3607, 3550, 3002, 2944,
1680, 1632, 1446, 1428, 1375, 1201, 1039, 918, 749 cm⁻¹; HSFABMS (M+H)+ exact mass calcd for C₂₂H₃₆N₃O₃: 418.2818; Found: 418.2811 (error -0.7 mmu/ -1.7 ppm).

**Methyl-4-(2-(11-(carbo-tert-butoxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]-hexadec-4-yl)-acetylamino]-benzoate (130).** To a solution of 4-(carbo-tert-butoxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane 74 (14.0 mg, 0.0412 mmol) in CH₃CN (4 mL), KI (14.0 mg, 0.0843 mmol), Na₂CO₃ (9.0 mg, 0.085 mmol) were added first, and then methyl-4-(2-chloroacetylamino)benzoate 129 (20.0 mg, 0.0879 mmol) was added. The mixture was stirred for 12 h at room temperature. After removal of the solvent, the residue was dissolved in water (2 mL), adjusted pH 3 by careful addition of 3 M HCl and washed with benzene (2 × 25 mL), and then adjusted to pH 14 by addition of solid KOH and extracted with benzene (3 × 35 mL). The combined extracts were dried (Na₂SO₄) and the solvent was removed under reduced pressure to give product as light yellow oil (20.0 mg, 0.0377 mmol, 91%): ¹H NMR (400 MHz, C₆D₆) δ 1.00-1.42 (m, 4H), 1.40 (s, 9H), 1.92-2.02 (m, 2H), 2.02-2.27 (m, 4H), 2.31 (dt, 1H, J=13.4, 4.9 Hz), 2.44-2.64 (m, 6H), 2.71 (td, 1H, J=15.4, 3.9 Hz), 2.66-2.94 (m, 3H), 2.80 & 3.02 (AB, 2H, J=16.4 Hz), 3.02 & 3.15 (AB, 2H, J=16.4 Hz), 3.20-3.38 (m, 2H), 3.50 (s, 3H), 4.16-4.26 (m, 1H), 7.84-7.90 (XX’ of AA’XX’, 2H), 8.15-8.21 (AA’ of AA’XX’, 2H), 9.22 (br s, 1H, NH); ¹³C{¹H} NMR (100.5 MHz, C₆D₆) δ 28.25, 28.51, 28.57, 51.81, 51.89, 52.59, 53.83, 53.89, 56.15, 57.19, 57.62, 57.90, 58.16, 59.06, 60.29, 62.32, 80.41, 118.63, 126.31, 131.85, 143.12, 166.56, 169.96, 171.47.

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Methyl-4-(2-(11-carboxymethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-4-yl)-acetylamino)benzoate •nTFA (131•nTFA): Methyl-4-(2-(11-carbo-tert-butoxymethyl-1,4,8,11-tetraaza-bicyclo[6.6.2]hexadec-4-yl)-acetylamino)benzoate 130 (10.0 mg, 0.0188 mmol) was dissolved in a mixture of CF₃CO₂H (TFA) (3 mL) and CH₂Cl₂ (3 mL). The solution was stirred for 16 h at room temperature, and the solvent was removed under reduced pressure to give product as a TFA salt (17.0 mg, quant (no impurities by NMR)): ¹H NMR (400 MHz, D₂O) δ 1.72-1.82 (dm, 2H, J=16.8 Hz), 2.30-2.48 (m, 2H), 2.85-2.98 (m, 2H), 3.00-3.42 (m, 14H), 3.45 & 4.12 (AX, 2H, J=17.3 Hz), 3.54-3.68 (m, 3H), 3.66 & 4.13 (AX, 2H, J=16.4 Hz), 3.84 (td, 1H, J=13.4, 3.9 Hz), 3.91 (s, 3H), 7.62-7.68 (XX’ of AA’XX’, 2H), 8.00-8.05 (AA’ of AA’XX’, 2H); ¹³C{¹H} NMR (100.5 MHz, D₂O) δ 19.65, 19.72, 47.57, 47.73, 48.01, 48.08, 52.71, 53.10, 53.18, 55.81, 56.66, 57.73, 58.08, 59.45, 59.48, 116.44 (q, J_CF=291.4 Hz), 120.00, 125.87, 130.78, 141.51, 163.09 (q, J_CF=35.2 Hz), 167.59, 168.95, 172.09; HRFABMS, m/z (M+H)⁺ exact mass calcd for C₂₄H₃₈N₅O₅: 476.2873; Found: 476.2856 (error -1.7 mmu/-3.6 ppm). There are 3.76 equivalents of TFA (by calculation based upon mass of product).

4-Benzylxycarbonylaniline (133). The mixture of powdered KOH (1.0 g, 18 mmol) in DMSO (20 mL) was vigorously stirred for 30 minutes at room temperature. To this slurry was added a solution of 4-aminobenzoic acid 132 (1.64 g, 12.0 mmol) in DMSO (20 mL) and the resulting mixture was stirred for 15 minutes. After the addition of benzylbromide (2.00 mL, 16.8 mmol), the mixture was stirred for a further 2.7 hours at room temperature, and then added a mixture of ice-water, the resulting solution was extracted with ethyl acetate (150 mL), the extract was washed with aq. saturated Na₂CO₃.
(100 mL), aq. saturated NaCl (100 mL), dried (Na₂SO₄), the solvent was removed under reduced pressure to give crude product, which was purified by flash chromatography (SiO₂, hexane: ethyl acetate=3:1) to give pure product as white solid (1.38 g, 6.08 mmol, 51%). NMR spectra were consistent with reported spectra.

Phenylmethyl 4-(2-chloroacetylamino)benzoate (134). Phenylmethyl 4-aminobenzoate 133 (140 mg, 0.617 mmol) was dissolved in acetic acid (16 mL), chloroacetyl chloride (0.083 mL, 0.12 g, 1.0 mmol) was added by syringe, and the solution was stirred for 24 hours at room temperature. Solvent was then removed under reduced pressure, the residue was treated with saturated NaHCO₃ solution (50 mL), extracted with Et₂O (120 mL), and the organic layer was washed with saturated aq NaHCO₃ (30 mL), water (50 mL), and saturated aq NaCl (100 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure to yield white solid product (180 mg, 0.593 mmol, 96%). ¹H NMR (500 MHz, CDCl₃, CHCl₃ peak set at 7.27) δ 4.19 (s, 2H), 5.37 (s, 2H), 7.34-7.48 (m, 5H), 7.66 (d, 2H, J=8.8 Hz), 8.08 (d, 2H, J=8.8 Hz), 8.46 (br s, 1H, NH); ¹³C{¹H} NMR (125.7 MHz, CDCl₃, CDCl₃ central peak set to 77.23) δ 43.04, 66.90, 119.37, 128.33, 126.68, 128.45, 128.78, 131.17, 136.14, 141.11, 164.25, 165.93; IR(KBr) 3293, 3209, 3132, 3082, 3035, 1783, 1733, 1674, 1603, 1513, 1411, 1382, 1334, 1299, 1253, 1174, 1130, 1120, 1015, 857, 772, 766 cm⁻¹; HRFABMS, m/z (M+H)⁺ exact mass for C₁₆H₁₅NO₃Cl: 304.0740; Found: 304.0750 (error +1.0 mmu/+3.3 ppm).

Benzyl-4-(2-(11-tert-butoxycarbonylmethyl-1,4,8,11-tetraazabicyclo[6.6.2]-hexadec-4-yl)acetylamino)benzoate (135). 4-Carbo-tert-butoxymethyl-1,4,8,11-
tetraazabicyclo[6.6.2]hexadecane 74 (34 mg, 0.10 mmol) was dissolved in CH$_3$CN (4 mL), KI (25 mg, 0.15 mmol) and Na$_2$CO$_3$ (26 mg, 0.25 mmol) were added, and benzyl 4-(2-chloroacetylamino)benzoate 134 (45 mg, 0.15 mmol) was added in one portion. The solution was stirred for 16 h at room temperature, solvent was removed, and the residue was dissolved in water (2 mL). The pH was adjusted to 3 with aq 3 M HCl and the acidic solution was extracted with benzene (2 x 25 mL). The aq phase was adjusted to pH 14 (solid KOH), extracted with benzene (3 x 35 mL), combined extracts were dried (Na$_2$SO$_4$), and solvent was removed under reduced pressure to yield product as a light yellow oil (60 mg, 0.99 mmol, 99%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.40-1.60 (m, 4H), 1.48 (s, 9H), 2.31 (dt, 1H, $J$=13.1, 4.3 Hz), 2.35-2.48 (m, 2H), 2.52-2.88 (m, 13H), 2.96-3.06 (m, 1H), 3.04 & 3.30 (AB, 2H, $J$=17.0 Hz), 3.08 & 3.22 (AB, 2H, $J$=16.5 Hz), 3.45 (td, 1H, $J$=12.3, .4.7 Hz), 4.45-4.55 (m, 1H), 5.36 (s, 2H), 7.31-7.48 (m, 5H), 7.64-7.68 (XX' of AA’XX’, 2H), 8.05-8.10 (AA’ of AA’XX’, 2H), 9.51 (br s, 1H); $^{13}$C{$^1$H} NMR (100.5 MHz, CDCl$_3$, CDCl$_3$ central peak set at 77.23) $\delta$ 27.53, 28.15, 28.43, 51.87, 52.35, 53.08, 53.65, 55.97, 56.56, 57.23, 57.69, 57.94, 58.76, 59.06, 61.96, 66.75, 80.81, 118.40, 118.48, 125.58, 128.30, 128.39, 128.77, 131.34, 136.34, 142.10, 166.10, 170.72, 171.83; IR(CH$_3$CN) 3164, 3002, 2944, 1717, 1700, 1602, 1458, 1436, 1375, 1272, 1039 cm$^{-1}$; HRFABMS, m/z (M+H)$^+$ exact mass for C$_{34}$H$_{50}$N$_5$O$_5$: 608.3812; Found: 608.3809 (error $-0.3$ mmu/$-0.6$ ppm).

**Methyl-3-(4-(aziridine-1-sulfonyl)phenyl)propionate (136).** A solution of 20% aq KOH solution (3 mL) was added to methyl-3-(4-(2-(4-(2-benzyloxycarbonyl ethyl)-benzensulfonyloxy)ethylsulfamoyl)phenyl)propionate 143 (40.0 mg, 0.0753 mmol) in
benzene (15 mL), the two phases mixture was stirred for 0.5 h at room temperature. The mixture was shaken with water (2 × 40 mL), aq saturated NaCl (2 × 30 mL), and the organic phase was dried (Na$_2$SO$_4$) and solvent was removed under reduced pressure to yield product as light yellow oil (18.0 mg, 0.0669 mmol, 89%): $^1$H NMR (500 MHz, CDCl$_3$) δ 2.39 (br s, 4H), 2.68 (app. t, 2H, J=7.6 Hz), 3.05 (app. t, 2H, J=7.6 Hz), 3.69 (s, 3H), 7.37-7.43 (XX' of AA’XX’, 2H), 7.86-7.92 (AA’ of AA’XX’, 2H); $^{13}$C NMR (125.7 MHz, CDCl$_3$, CDCl$_3$ central peak set at 77.23) δ 27.71, 30.94, 35.14, 52.02, 128.46, 129.32, 136.11, 147.21, 172.89; IR(CH$_2$Cl$_2$) 3055, 2987, 1735, 1438, 1326, 1265, 1165, 739, 704 cm$^{-1}$; HRFABMS, m/z (M+H)$^+$ exact mass for C$_{12}$H$_{16}$NO$_4$S: 270.0800; Found: 270.0810 (error +1.0 mmu/+3.7 ppm).

**Benzyl-3-(4-(aziridine-1-sulfonyl)phenyl)propionate (137).** A solution of 20% aq. KOH solution (5 mL) was added to Benzyl-3-(4-(2-(4-(2-benzyloxycarbonylethyl)benzensulfonyloxy)ethylsulfamoyl) phenyl)propionate 144 (120 mg, 0.180 mmol) in benzene (25 mL) and the two phases mixture was stirred for 1 h. The mixture was shaken with water (2 × 40 mL) and aq saturated NaCl solution (2 × 30 mL), and then the organic phase was dried (Na$_2$SO$_4$) and evaporated to dryness to yield product as yellow oil (60.0 mg, 0.174 mmol, 97%): $^1$H NMR (400 MHz, CDCl$_3$) δ 2.38 (br s, 4H), 2.73 (app. t, 2H, J=7.5 Hz), 3.06 (app. t, 2H, J=7.6 Hz), 5.12 (s, 2H), 7.28-7.40 (m, 7H), 7.82-7.88 (m, 2H); $^{13}$C NMR (100.5 MHz, CDCl$_3$, CDCl$_3$ central peak set at 77.23) δ 27.67, 30.90, 35.30, 66.71, 128.39, 128.49, 128.56, 128.77, 129.30, 135.81, 136.00, 147.06, 172.21; IR(CHCl$_3$) 3428, 3035, 2959, 2928, 1733, 1325, 1240, 1158, 908, 732 cm$^{-1}$; HRFABMS,
m/z (M+H)$^+$ exact mass for C$_{18}$H$_{20}$NO$_4$S: 446.1113; Found: 346.1133 (error +2.0 mmu/+5.8 ppm).

1-((4-Bromophenyl)sulfonyl)aziridine (139). The procedure was modeled on the method for the synthesis of N-(p-tolylsulfonyl)aziridine$^8$. A solution of 20% aq KOH solution (3 mL) was added to ethyl (2-(4-bromophenylsulfonylamino))-4-bromophenylsulphonate 140 (154.5 mg, 0.3096 mmol) in benzene (40 mL), and the two phases mixture was stirred for 1 h at room temperature. The organic phase was then washed with H$_2$O (3 x 100 mL), aq saturated NaCl (2 x 100 mL), and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure to give product as white solid (70.0 mg, 0.267 mmol, 86%): $^1$H NMR (400 MHz, CDCl$_3$) δ 2.41 (br s, 4H), 7.67-7.73 (XX' of AA'XX', 2H), 7.79-7.85 (AA' of AA'XX', 2H); $^{13}$C NMR (100.5 MHz, CDCl$_3$, CDCl$_3$ central peak set at 77.23) δ 27.89, 129.07, 129.64, 132.63, 137.17; IR(KBr) 3093, 3010, 1573, 1468, 1388, 1323, 1276, 1241, 1180, 1156, 1096, 1082, 1065, 1010, 916, 816, 750, 705, 661, 608 cm$^{-1}$; HRFABMS, m/z (M+H)$^+$ exact mass calcd for C$_{8}$H$_{9}$NBrSO$_2$: 261.9537; Found: 261.9556 (error +1.8 mmu/+7.0 ppm).

(2-(4-Bromophenylsulfonylamino)ethyl)-4-bromophenylsulfonate (140). The procedure was modeled on the method for the synthesis of N-(2-((p-tolylsulfonyl)oxy)ethyl)-p-tolylsulfonamide$^7$. To a stirred suspension of 4-bromobenzylsulfonylchloride 141 (5.365g, 21.00 mmol) in pyridine (25 mL) cooled to –40 °C was added dropwise a solution of 2-aminoethanol (0.600 mL, 9.97 mmol) in pyridine (10 mL). After the addition was complete, the temperature was raised to −10 °C.
for 1 hour, and then to 0 °C for 12 hours. After crushed ice was added, the precipitate formed was filtered off, washed with water (2 x 50 mL), dissolved in CHCl₃ (150 mL), washed with water (2 x 200 mL), dried (Na₂SO₄). Solvent was removed under reduced pressure to yield crude product, which was purified by recrystallization from hot CHCl₃ to yield white crystalline product (3.300 g, 6.613 mmol, 66%): ¹H NMR (400 MHz, CDCl₃) δ 3.29 (q, 2H, J=5.3 Hz), 4.11 (t, 2H, J=5.1 Hz), 5.01 (br t, 1H, J=6.4 Hz, NH), 7.64-7.78 (m, 8H); ¹³C{¹H} NMR (100.5 MHz, CDCl₃, CDCl₃ central peak set at 77.23) δ 42.37, 69.19, 128.29, 128.73, 129.59, 129.89, 132.81, 133.06, 134.40, 138.89; IR (KBr) 3268, 3097, 1575, 1472, 1436, 1392, 1371, 1327, 1278, 1186, 1155, 1081, 1066, 1009, 973, 814, 761, 732, 667, 650 cm⁻¹; HRFABMS, m/z (M+H)+ exact mass for C₁₄H₁₄Br₂NO₅S₂: 497.8680; Found: 497.8682 (error +0.2 mmu/+0.4 ppm).

(E,E)-Dibenzyl 1, 4-phenylenediacylate (142): To a solution of l-(4-(bromophenyl) sulfonyl) aziridine 139 (140 mg, 0.534 mmol) in DMF (10 mL), were added anhyd. NaOAc (44.0 mg, 0.536 mmol), tri(o-tolyl)phosphine (13.0 mg, 0.0428 mmol), palladium(II) acetate (2.4 mg, 0.011 mmol), and benzyl acrylate (86.6 mg, 0.534 mmol). The mixture was maintained at 150 °C for 5 h. The solvent was removed under reduced pressure to give crude produce which was subjected to flash chromatography (SiO₂, hexane: ethyl acetate = 6: 1) to give product as yellow solid (49.0 mg, 0.131 mmol, 49%): ¹H NMR (500 MHz, CDCl₃) δ 5.27 (s, 4H), 6.53 (d, 2H, J=16.1 Hz), 7.33-7.45 (m, 10 H), 7.54 (s, 4H), 7.71 (d, 2H, J= 16.1 Hz); ¹³C{¹H} NMR (125.7 MHz, CDCl₃) δ 66.73, 119.26, 128.54, 128.80, 128.85, 136.16, 136.39, 144.19, 166.75. The product has been reported in the literature, but NMR data has not been reported.
Methyl-3-(4-(4-(2-methyloxycarbonylethyl)benzensulfonylamino)-ethoxysulfonyl) phenylpropionate (143). To a stirred suspension of methyl 3-(4-chlorosulfonyl) phenylpropionate 145 (1.10 g, 4.19 mmol) in pyridine (12 mL) cooled to −40 °C, was added dropwise a solution of 2-aminoethanol (128 mg, 2.09 mmol) in pyridine (5 mL). After the addition was completed, the temperature was raised to −10 °C for 1 h, and then maintained at 0 °C for 12 h. After pyridine was removed under reduced pressure, CHCl₃ (200 mL) was added, and the solution was washed with 0.1 M HCl (100 mL), water (2 × 200 mL), aq saturated NaCl solution (2 × 200 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure to give crude product which was purified by flash chromatography (SiO₂, hexane: ethyl acetate =1:1) to give white solid product (430 mg, 0.838 mmol, 40%). ¹H NMR (500 MHz, CDCl₃) δ 2.67 (t, 2H, J=7.8 Hz), 2.69 (t, 2H, J=7.8 Hz), 3.03 (t, 2H, J=7.6 Hz), 3.06 (t, 2H, J=7.6 Hz), 3.25 (q, 2H, J=5.4 Hz), 4.08 (t, 2H, J=5.1 Hz), 4.89 (t, 1H, J=6.4 Hz, NH), 7.34-7.38 (XX' of AA'XX’, 2H), 7.40-7.43 (XX’ of AAXX’, 2H), 7.73-7.76 (AA’ of AA’XX’, 2H), 7.78-7.82 (AA’ of AA’XX’, 2H); ¹³C {¹H} NMR (125.7 MHz, CDCl₃, CDCl₃ central peak set at 77.23) δ 30.82, 30.89, 34.98, 35.12, 42.34, 52.00, 52.04, 69.03, 127.47, 128.41, 129.44, 129.64, 133.38, 137.75, 146.42, 147.92, 172.84, 172.94.

Benzyl-3-(4-(2-(2-benzyloxycarbonylethyl)benzensulfonyloxy)-ethylsulfamoyl) phenylpropionate (144). To a stirred suspension of benzyl 3-(4-chlorosulfonyl)- phenylpropionate 146 (1.43 g, 4.22 mmol) in pyridine (10 mL) cooled to −40 °C was added dropwise a solution of 2-aminoethanol (0.126 mL, 1.40 g, 2.10 mmol)
in pyridine (5 mL). After the addition was complete, the temperature was raised to -10 °C for 0.5 h, and then maintained at 0 °C for 12 h. After pyridine was removed under reduced pressure, CHCl₃ (200 mL) was added, and the solution was washed with water (2 x 200 mL), aq saturated NaCl solution (2 x 200 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure to give crude product which was purified by flash chromatography (SiO₂, hexane: ethyl acetate =1:1) to yield white solid product (1.28 g, 1.92 mmol, 46%): mp 67-68 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.70 (t, 2H, J=7.6 Hz), 2.72 (t, 2H, J=7.4 Hz), 3.03 (t, 2H, J=7.6 Hz), 3.05 (t, 2H, J=7.8 Hz), 3.22 (app. q, 2H, J=5.6 Hz), 4.05 (t, 2H, J=5.2 Hz), 4.88 (t, 1H, J=6.3 Hz, NH), 7.27-7.39 (m, 12H), 7.69-7.78(m, 2H); ¹³C NMR (100.5 MHz, CDCl₃, CDCl₃ central peak set at 77.23) δ 30.78, 30.85, 35.15, 35.29, 42.25, 66.66, 66.71, 68.99, 127.40, 128.33, 128.44, 128.46, 128.52, 128.54, 128.74 (degenerate), 129.40, 129.60, 133.30, 135.77, 135.81, 137.70, 146.22, 147.72, 172.17, 172.28; IR(KBr) 3288, 3033, 2953, 2927, 1731, 1362, 1326, 1188, 1168, 1095, 1008, 915, 756, 700 cm⁻¹; HRFABMS, m/z (M+H)⁺ exact mass for C₃₄H₃₆NO₉S₂: 666.1832; Found: 666.1817 (error -1.4 mmu/-2.2 ppm).

**Benzyl 3-(4-chlorosulfonylphenyl)propionate (146):** A solution of 3-(4-chlorosulfonylphenyl)-propionic acid 148 (1.70 g, 6.84 mmol), benzyl alcohol (960 mg, 8.85 mmol), and p-toluenesulfonic acid monohydrate (23.0 mg, 0.121 mmol) in benzene (150 mL) was refluxed for 18 h under a Dean-Stark trap. The solution was then washed with 0.1 M HCl (250 mL), water (200 mL), and brine (200 mL), and subsequently dried (Na₂SO₄). The solvent was removed under reduced pressure to give product (2.08 g, 6.14 mmol, 90%, >95% purity): ¹H NMR (500 MHz, CDCl₃) δ 2.71 (t, 2H, J=7.3 Hz), 3.05 (t,
2H, J=7.3 Hz), 5.09 (s, 2H), 7.22-7.34 (m, 5H), 7.35-7.40 (XX’ of AA’XX’, 2H), 7.85-
7.89 (AA’ of AA’XX’, 2H); $^{13}$C{^1}H NMR (125.7 MHz, CDCl$_3$) δ 30.65, 34.68, 66.38,
127.08, 128.20, 128.28, 128.50, 129.67, 135.62, 142.09, 149.06, 171.69; MS, m/z, 338
(M$^+$). The compound was used without further purification.

**3-(4-chlorosulfonylphenyl)-propionic acid (148):** Gradual addition of
hydrocinnamic acid 147 (2.7 g, 18 mmol) to chlorosulfonic acid (7.00 mL, 12.3 g, 106
mmol) at 0 °C gave a solution which was maintained at 65 °C for 1.5 h, and then poured
on ice (200 g). The precipitate was collected by suction filtration to give crude product
which was recrystallized from hot benzene to give crystalline product (1.9 g, 7.7 mmol,
43%): $^1$H NMR (400 MHz, CDCl$_3$) δ 2.77 (t, 2H, J=7.4 Hz), 3.09 (t, 2H, J=7.4 Hz), 7.48
(d, 2H, J=8.4 Hz), 7.98 (d, 2H, J=8.6 Hz); $^{13}$C NMR (100.5 MHz, CDCl$_3$) δ 30.58, 34.70,
127.58, 129.86, 142.79, 148.76, 177.79.$^{86}$

**Benzyl-3-(4-(2-(11-carbo-tert-butoxymethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-4-yi)-ethylsulfamoyl)phenyl)propionate (149).** 4-(Carbo-tert-
butoxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane 74 (30 mg, 0.091 mmol) was
dissolved in dry CH$_3$CN (5 mL), Na$_2$CO$_3$ (9.6 mg, 0.091 mmol) and N-(4-(benzyl 3-
propionate) phenylsulfonfyl) aziridine 137 (31.4 mg, 0.0909 mmol) were added, and the
mixture was stirred for 16 h at 80 °C under N$_2$. After cooling to room temperature, the
contents were filtered through Celite, and the filtrate was evaporated to dryness to yield
product (48 mg, 0.070 mmol, 77%): $^1$H NMR (400 MHz, CD$_3$CN, CD$_2$HCN central peak
set at 1.94) δ 1.22–1.50 (m, 4H), 1.43 (s, 9H), 2.20-2.73 (m, 20H), 2.70 (t, 2H, J=7.4 Hz),

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2.73-2.95 (m, 2H), 3.00 & 3.19 (AB, 2H, J=17.0 Hz), 3.00 (t, 2H, J=7.1 Hz), 3.14-3.24 (m, 1H), 3.34-3.58 (m, 1H), 3.58 (br s, 1H), 5.07 (s, 2H), 7.27-7.38 (m, 5H), 7.36-7.42 (XX’ of AA’XX’, 2H), 7.70-7.76 (AA’ of AA’XX’, 2H); \(^1\)H NMR (100.5 MHz, CD\(_3\)CN, CD\(_3\)CN central peak set at 1.37) \(\delta\) 24.52 (br), 25.65 (br), 28.44 ((CH\(_3\))

\[3\]C, 31.31, 35.81, 40.88 (br), 50.66 (br), 51.78, 52.24 (br), 53.80 (br), 54.80 (br), 55.00, 56.01, 56.24 (br), 56.67, 59.63 (br), 66.95, 82.34, 128.10, 129.06, 129.15, 129.58, 130.20, 137.52, 139.36, 146.99, 171.66, 173.22; IR(CH\(_3\)CN) 3400 (br), 3164, 3033, 2981, 2941, 2853, 1734, 1437, 1374, 1159 cm\(^{-1}\); HRFABMS, m/z (M+H)+ exact mass for C\(_{36}\)H\(_{56}\)N\(_{5}\)O\(_{6}\)S: 686.3951; Found: 686.3958 (error +0.6 mmu/+0.9 ppm).

4-(Carbo-tert-butoxymethyl)-11-(2-(tosylamino)ethyl)-1,4,8,11-tetraazabicyclo-[6.6.2]hexadecane (151): To a solution of 4-(carbo-tert-butoxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane 74 (45.0 mg, 0.132 mmol) in CH\(_3\)CN (10 mL), 1-((4-methylphenyl)sulfony) aziridine 150 (26.1 mg, 0.132 mmol) was added. The mixture was refluxed for 18 h. The solvent was removed under reduced pressure to give product (71.1 mg, 0.132 mmol, ~quant, >90% purity): \(^1\)H NMR (500 MHz, CD\(_3\)CN, CD\(_2\)HCN central peak set at 1.94) \(\delta\) 1.20-1.44 (m, 4H), 1.43 (s, 9H), 2.26-2.78 (m, 16H), 2.41 (s, 3H), 2.80-2.92 (m, 2H), 2.92-3.24 (m, 5H), 2.98 & 3.18 (AB, 2H, J=16.6 Hz), 3.44 (td, 1H, J=11.7, 4.2 Hz), 3.66-3.76 (m, 1H), 7.35-7.39 (XX’ of AA’XX’, 2H), 7.69-7.73 (AA’ of AA’XX’, 2H); \(^13\)C\(^{1}\)H NMR (125.7 MHz, CD\(_3\)CN, CD\(_3\)CN central peak set at 1.37) \(\delta\) 21.55, 28.28, 28.47, 42.68, 52.54 (br), 52.55, 54.23, 55.08, 55.10, 56.65, 56.88 (br), 57.03 (br), 57.78, 58.11, 58.82 (br), 59.72 (br), 81.08, 127.94, 130.71, 138.64, 144.36.

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(11-(2-(Toluene-4-sulfonylamino)ethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-4-yl)-acetic acid •2TFA (152•2TFA): tert-Butyl-(11-(2-(toluene-4-sulfonylamino)ethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-4-yl)acetate 151 (71.1 mg, 0.132 mmol) was dissolved in a mixture of CF₃CO₂H (TFA) (10 mL) and CH₂Cl₂ (10 mL). The solution was stirred for 16 h at room temperature. Solvent was then removed under reduced pressure to give product (94.0 mg, quant): ¹H NMR (400 MHz, CD₃CN, CD₂HCN central peak set at 1.94) δ 1.62-1.71 (dm, 1H, J=17.0 Hz), 1.71-1.82 (dm, 1H, J=16.8 Hz), 2.18-2.38 (m, 2H), 2.42 (s, 3H), 2.38-2.49 (m, 1H), 2.51-2.82 (m, 4H), 2.84-3.70 (m, 19H), 3.59 & 4.08 (AB, 2H, J=17.3 Hz), 6.90 (br s, 1H), 7.00-7.70 (br s, 3H), 7.36-7.43 (XX' of AA'XX', 2H), 7.72-7.77 (AA' of AA'XX', 2H); ¹³C(¹H) NMR (100.5 MHz, CD₃CN, CD₂CN central peak set at 1.37) δ 20.31, 20.80 (br, 21.60, 38.32, 49.10, 49.15, 49.48 (br), 49.68, 54.28, 54.54, 55.32 (br), 56.34 (br), 56.75, 58.05 (br), 58.83, 58.98, 117.38 (q, J_CF=290.7 Hz, CF₃CO₂), 128.06, 130.95, 137.29, 145.22, 161.01 (q, J_CF=35.1 Hz, CF₃CO₂), 172.14. There are 2 TFA based upon mass calculation.
Appendix
Spectral Index
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113

D$_2$O

CH$_3$CN set to 1.47
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## Compound Index

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