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**by**

**Paul C. Hellier, Jerald S. Bradshaw and Reed M. Izatt**

**Prepared for Publication**

**Department of Chemistry  
Brigham Young University  
Provo, UT 84602-4678**

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**Synthesis of Chiral Pyridine-Based Macrobicyclic Clefts**

**Paul C. Hellier, Jerald S. Bradshaw and Reed M. Izatt**

**Department of Chemistry and Biochemistry**

**Brigham Young University,**

**Provo, UT 84602.**

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## Abstract

An achiral (3) and two chiral pyridine-based macrobicyclic clefts (4 and 5) have been prepared by treating 2,6-bis[2',6'-bis(bromomethyl)-4'-methylphenoxy]pyridine (2) with the appropriate achiral and chiral glycols. Starting 2 was prepared by first treating 2,6-bis(hydroxymethyl)-4-methylphenol with 2,6-pyridinedimethyl ditosylate followed by phosphorous tribromide.

## Introduction

The study of chirality at the molecular level has emerged as a central theme in contemporary chemistry. Much of the stimulus for this interest originated from the chiral nature of many biomolecules and their interaction with other molecules. Chiral molecules find use in pharmaceuticals and agrochemicals. While the field of asymmetric synthesis has progressed at a tremendous rate in recent years,<sup>1</sup> there are still many instances where these methods do not provide a practical means for the preparation of pure homochiral compounds. Thus, there is a continuing interest in the chromatographic separation of racemic mixtures using chiral stationary phases.<sup>2</sup> Fundamental to the development of such materials is a thorough understanding of the factors affecting chiral recognition at the molecular level.<sup>3</sup> The knowledge gained through the study of this aspect of supramolecular chemistry is also of importance because of the insight it may give us into the forces driving biological recognition phenomena such as enzyme-substrate and antibody-antigen interactions.

The seminal work of Cram and co-workers<sup>4</sup> on the host-guest chemistry of primary ammonium salts and 1,1-binaphthol derived chiral crown ethers illustrates clearly the validity of this approach. Enantiomeric recognition was optimised using a rational approach to host design. The subsequent covalent attachment of such compounds to an inert support resulted in systems capable of effecting the enantiomeric separation of racemic amino acid and ester salts.<sup>5</sup>

Our work has focused on the enantiomeric recognition of chiral organic ammonium salts by chiral crown ethers based on the pyridine-18-crown-6 structure.<sup>3a</sup> This host-guest pairing is particularly suited to such studies because of the strong intermolecular binding observed, arising

from 3-point hydrogen bonding of the ammonium hydrogen atoms to the pyridine nitrogen atom and two of the oxygen atoms within the ring.<sup>6</sup> A further contribution to the overall stability of the supramolecular complex comes from the charge-dipole electrostatic interactions. The systematic introduction of various substituents around the macrocyclic ring has shed much light on the effect that such structural modifications have upon the differential binding of a pair of enantiomers. These studies have been guided by the characterisation of the host-guest interactions using a variety of physical techniques including <sup>1</sup>H NMR spectroscopy,<sup>7-11</sup> calorimetric titration,<sup>7</sup> X-ray crystallography<sup>7,10</sup> and molecular mechanics calculations.<sup>10,11</sup> Crown ethers of this type, when bound to silica gel, have been shown to successfully effect the separation of the (*R*) and (*S*) forms of  $\alpha$ -(1-naphthyl)ethylammonium perchlorate.<sup>12</sup>

As a result of their complexity, the synthesis of chiral macrobicyclic hosts has been left relatively unexplored.<sup>13</sup> Even less attention has been given to their use in enantiomeric recognition studies, even though they offer a number of potentially advantageous properties in comparison to macromonocyclic structures. Macrobicycles possess a 3-dimensional cavity in which the recognition event may take place, thus, possibly leading to improved discrimination. In addition, recognition can be encouraged by the large degree of preorganisation that is typically found in such molecules. The chiral recognition of amides and carboxylic acids has been demonstrated in macrobicyclic hosts by Still and co-workers<sup>14</sup> and Kilburn and co-workers,<sup>15</sup> respectively. The great potential of polycyclic structures in such studies is well illustrated in a recent publication of Yoon and Still,<sup>16</sup> where a macrotricyclic receptor showed binding of L-amino acid derivatives with enantioselectivities as high as 99% e.e. Chiral cage-type cyclophanes of a similar topology have also been investigated by Murakami and co-workers.<sup>17</sup>

The present work is concerned with the synthesis of one achiral and two chiral macrobicyclic hosts containing pyridine rings (3-5) (Schemes 1 and 2). This topology was chosen as previous studies on similar achiral compounds had shown that the 1,2,3-substitution pattern on the aromatic bridgeheads would result in the formation of a cleft-like structure.<sup>18</sup> This would allow ready access into the cavity for a guest organic ammonium salt. The incorporation of the rigid pyridine unit would impart a good deal of preorganization to the molecule resulting in a fixed conformation with the basic pyridine nitrogen atom directed towards the base of the cleft. The opening of the cleft is defined by the two polyether chains. Our synthesis of the achiral pyridine-containing cleft (Scheme 1) was flexible thus allowing us to readily control the nature of the cavity through the use of the appropriate (*e.g.* chiral) diol in the final macrobicyclization step. An analogous pyridine-based macrobicycle was recently described by Luning and co-workers,<sup>19</sup> although the potential to render their macrobicycle chiral has yet to be realized.

## Results and Discussion

The key precursor in the planned syntheses of the chiral macrobicycles was the pyridine-bridged tetrabromide **2**. This material was prepared according to the route depicted in Scheme 1. 2,6-Pyridinedimethyl ditosylate was treated with two equivalents of 4-methyl-2,6-*bis*(hydroxymethyl)phenol in acetone using potassium carbonate as a base. Regioselective alkylation of the more acidic phenolic oxygen atoms occurred to give tetraalcohol **1** in an 83% yield. This gave access to **2** *via* bromination with phosphorous tribromide.

We decided to begin our studies by preparing the achiral pyridine-containing macrobicyclic host **3**. This would allow us to demonstrate the feasibility of the cyclisation strategy and verify that successful complexation of organic ammonium salts would occur, before embarking on more lengthy syntheses of chiral hosts. Thus, **2** was treated with two equivalents of diethylene glycol (Scheme 1) in THF using NaH as a base. The desired compound (**3**) was isolated as a white crystalline solid in a 13% yield. This represents a reasonable yield for such a reaction, probably the result of a convergent nature of the bromomethyl groups and the rigidity of precursor **2**. The  $^1\text{H}$  NMR spectrum of this compound gave clear evidence that the expected cleft-like structure was maintained in solution. The bulk and rigidity of the pyridine group prevents the macrobicyclic host from inverting on itself. Thus, the two hydrogens of the benzylic methylene groups on the aromatic bridgeheads are magnetically inequivalent, giving rise to two doublets of an AB system in contrast to the singlet observed for the corresponding protons of acyclic precursor **2**.

Chiral analogues of achiral macrobicyclic host **3** were prepared. For this purpose the homochiral methyl substituted diethylene glycol, (1*S*,5*S*)-3-oxapentane-1,5-diol, was prepared in four steps from ethyl (*S*)-lactate according to the reported procedure.<sup>20,21</sup> Chiral tetramethyl-substituted macrobicyclic host **4** was synthesised in a 14% yield by treating the previously mentioned tetrabromide **2** with two equivalents of the dianion derived from the chiral diol (Scheme 2). In a similar fashion a related chiral macrocycle (**5**), with a smaller cavity, was prepared from (2*R*,4*R*)-pentanediol which is commercially available. The analogous reaction using (2*R*,3*R*)-butanediol was unsuccessful, possibly reflecting the increased strain in the still smaller cavity size.

The  $^1\text{H}$  NMR spectrum of highly organized chiral host **4** is beautifully resolved (Figure 1), and clearly reflects the  $C_2$  symmetry of the molecule that results from the introduction of chirality,

in contrast to the  $C_{2v}$  symmetry of its achiral analogue (3). Thus the benzylic methylene groups of the aromatic bridgeheads now give rise to two separate AB systems, resulting in a pair of doublets at  $\delta$  5.02 and 4.44; and  $\delta$  4.25 and 3.98. Similarly the protons of the methylene group adjacent to the pyridine ring are characterised by another AB system with signals at  $\delta$  5.33 and 4.97 instead of the usual singlet. The two distinct environments of the polyether ring methyl groups are identified by two doublets at  $\delta$  1.22 and 1.04. The  $^1\text{H}$  NMR spectrum when recorded at 500 MHz shows, in the region  $\delta$  3.19 to 3.81, clear resolution of the remaining six inequivalent protons on a single dimethyl substituted polyether section. Together with the two previously mentioned methyl groups these constitute two independent spin systems, the coupling interconnectivities of which have been clearly established by a 2D-COSY  $^1\text{H}$  NMR experiment. An NOE  $^1\text{H}$  NMR experiment aimed at unambiguously assigning the relative spatial positions of the ring methyl groups with respect to the pyridine ring was not successful. A similar logic to that detailed above allowed the interpretation of the  $^1\text{H}$  NMR spectrum of the smaller macrobicyclic cleft (5).

### Experimental Section

$^1\text{H}$  NMR spectra were recorded at 200 and 500 MHz. Solvents and starting materials were purchased from commercial sources where available.

#### **2,6-Bis[2',6'-(bishydroxymethyl)-4'-methylphenoxy]methyl]pyridine (1) (Scheme 1).**

A solution of 4-methyl-2,6-bis(hydroxymethyl)phenol (50.9 g, 0.30 mol) and  $\text{K}_2\text{CO}_3$  (45.4 g, 0.33 mol) in 1.5 L of acetone was refluxed for 30 mins. 2,6-Pyridinedimethyl ditosylate (67.82 g) was added to the reaction mixture and rinsed in with 0.5 L of acetone. The reaction mixture was

heated at reflux for 16 h. H<sub>2</sub>O (680 mL) was added and the reaction mixture was filtered hot. The volume of the filtrate was reduced to 1 L on a rotary evaporator. The analytically pure product precipitated as white crystals on standing at 4 °C to give 53.7 g (83%) of 1; mp 180 °C; IR (KBr) 3407, 2917, 1599, 1481, 1203, 1155, 1039, 1017, 995 cm<sup>-1</sup>; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO) δ: 2.30 (s, 6H), 4.55 (d, 8H, J = 4.5 Hz), 4.95 (s, 4H), 5.13 (t, 4H, J = 4.5 Hz), 7.17 (s, 4H), 7.65 (d, 2H, J = 8.2 Hz), 8.00 (t, 1H, J = 8.2 Hz); <sup>13</sup>C NMR (d<sup>6</sup>-DMSO) δ 20.7, 58.1, 76.1, 120.6, 127.9, 132.7, 134.7, 138.1, 151.2, 156.7; MS (CI) *m/z* 440 (M<sup>+</sup>+1). Anal. Calcd. for C<sub>22</sub>H<sub>22</sub>NO<sub>2</sub>: C, 68.32; H, 7.47; N, 3.19. Found: C, 68.13; H, 7.34; N, 3.12.

**2,6-Bis[2',6'-(bisbromomethyl)-4'-methylphenoxy]pyridine (2)** (Scheme 1). A 1.0 M solution of PBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (90 mL) was added to a solution of 1 (9 g, 0.02 mol) in THF (700 mL) under a nitrogen atmosphere at 0 °C over a period of 30 min. Stirring was continued at 0 °C for 3h. The reaction mixture was evaporated under vacuum. The residue was added to a mixture of ice water (300 mL) and CH<sub>2</sub>Cl<sub>2</sub> (250 mL). The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 250 mL). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub>, dried (Mg<sub>2</sub>SO<sub>4</sub>), filtered and evaporated under vacuum. The crude product was recrystallised from ClCH<sub>2</sub>CH<sub>2</sub>Cl/MeOH (2 : 3.5) to give 7.06 g (54%) of 2 as a white solid; mp 155-156 °C; IR (KBr) 2920, 1595, 1480, 1365, 1236, 1210, 1160, 972, 792 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.31 (s, 6H), 4.60 (s, 8H), 5.29 (s, 4H), 7.21 (s, 4H), 7.69 (d, 2H, J = 8.1 Hz), 7.91 (t, 1H, J = 8.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 21.2, 28.4, 77.0, 121.4, 132.3, 133.4, 135.6, 139.6, 153.5, 156.9; MS (CI) *m/z* 691 (M<sup>+</sup>). Anal. Calcd. for C<sub>25</sub>H<sub>25</sub>Br<sub>4</sub>NO<sub>2</sub>: C, 43.44; H, 3.64; N, 2.03. Found: C, 43.66; H, 3.81; N, 1.88.

**13,27-Dimethyl-3,6,9,17,20,23,30,38-octaoxa-40-azahexacyclo[23.3.1.9<sup>29,39</sup>.3<sup>11,15</sup>.1<sup>11,15</sup>.1<sup>32,36</sup>]tetraconta-1(29),11,13,15(39),25,27,32,34,36(40)-nonaene (3)** (Scheme 1). A solution of diethylene glycol (0.95 mL, 10 mmol) in THF (90 mL) was added to a suspension of 95 % NaH (0.76 g, 30 mmol) in THF (90 mL) under N<sub>2</sub> over 10 mins. The reaction mixture was heated at reflux for 1 h. After cooling to rt, a solution of **2** (3.45 g, 5 mmol) in THF (190 mL) was added with vigorous stirring over a period of 3 h. The reaction mixture was stirred at rt for a further 16 h. After cooling to 0 °C, H<sub>2</sub>O (20 mL) was added. The reaction mixture was evaporated under vacuum. The residue was dissolved in a mixture of H<sub>2</sub>O (100 mL) and CH<sub>2</sub>Cl<sub>2</sub> (200 mL). The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL). The combined organic layers were dried (Mg<sub>2</sub>SO<sub>4</sub>), filtered and evaporated under vacuum. The residue was chromatographed on silica gel eluting with first MePh/MeCO<sub>2</sub>Et (20:1) and then MePh/MeOH (100:1). The crude product was isolated by evaporation of the second elutant under vacuum. The isolated product was further purified by chromatography on silica gel eluting with MeOH/30% aqueous NH<sub>3</sub> (1:20) to give 0.37 g (13%) of **3** as a white crystalline solid; mp 57 °C; IR(KBr) 2919, 1596, 1452,1242, 1097, 697 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.27 (s, 6H), 3.23-3.60 (m, 16H), 4.19 (d, 4H, J = 11.5 Hz), 4.61 (d, 4H, J = 11.0 Hz), 5.25 (s, 4H), 7.07 (s, 4H), 7.54 (d, 2H, J = 8.0 Hz), 7.80 (t, 1H, J = 8.0 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 20.6, 68.6, 68.7, 69.9, 78.5, 121.4, 130.6, 131.1, 132.7, 136.8, 154.1, 156.9; MS (CI) *m/z* 578 (M<sup>+</sup> + 1). Anal. Calcd. for C<sub>33</sub>H<sub>41</sub>NO<sub>8</sub>: C, 68.37; H, 7.13; N, 2.42. Found: C, 68.05; H, 7.22; N, 2.27.

**4S,8S,18S,22S-4,8,13,18,22,27-Hexamethyl-3,6,9,17,20,23,30,38-octaoxa-40-azahexacyclo[23.3.1.9<sup>29,39</sup>.3<sup>11,15</sup>.1<sup>11,15</sup>.1<sup>32,36</sup>]tetraconta-1(29),11,13,15(39),25,27,32,34,36(40)-**

**nonaene (4)** (Scheme 2). (2*S*, 6*S*)-4-Oxaheptane-2,6-diol<sup>20,21</sup> (1.34 g, 10 mmol) was treated with **2** (3.45 g, 5 mmol) according to the procedure described above for the synthesis of **3**. The crude product was purified by chromatography on silica gel eluting with MePh/MeCO<sub>2</sub>Et (20:1) to give 0.454 g (14.2%) of **4** as a white crystalline solid; mp 131-2 °C;  $[\alpha]_D^{25} = +11.2$  (*c* = 1.70, CH<sub>2</sub>Cl<sub>2</sub>); IR(KBr) 2922, 1592, 1453, 1372, 1207, 1108 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.04 (d, 6H, *J* = 5.9 Hz), 1.22 (d, 6H, *J* = 6.2 Hz), 2.27 (s, 6H), 3.18-3.23 (m, 2H), 3.25-3.36 (m, 4H), 3.37-3.42 (m, 2H), 3.47-3.52 (m, 2H), 3.75-3.82 (m, 2H), 3.98 (d, 2H, *J* = 11.6 Hz), 4.25 (d, 2H, *J* = 11.6 Hz), 4.44 (d, 2H, *J* = 12.5 Hz), 4.97 (d, 2H, *J* = 12.5 Hz), 5.02 (d, 2H, *J* = 12.5 Hz), 5.37 (d, 2H, *J* = 12.5 Hz), 7.04 (s, 2H), 7.10 (s, 2H), 7.49 (d, 2H, *J* = 7.6 Hz), 7.79 (t, 1H, *J* = 7.6 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 16.5, 17.2, 20.9, 65.5, 66.1, 70.0, 74.3, 74.6, 75.8, 77.2, 120.9, 129.8, 129.9, 131.3, 132.5, 132.9, 137.1, 153.3, 156.9; MS (CI) *m/z* 636 (M<sup>+</sup>). Anal. Calcd. for C<sub>37</sub>H<sub>49</sub>NO<sub>8</sub>: C, 69.89; H, 7.77; N, 2.20. Found: C, 70.02; H, 7.94; N, 2.35.

**4*R*,6*R*,16*R*,18*R*-4,6,11,16,18,23-Hexamethyl-3,7,15,19,26,34-hexaoxa-36-azahexacyclo[19.3.1.9<sup>25,35</sup>.3<sup>9,13</sup>.1<sup>9,13</sup>.1<sup>28,32</sup>]hexatricula-1(25),9,11,13(35),28,30,32(36)-nonaene (5)** (Scheme 2). (2*R*, 4*R*)-Pentanediol (0.99g, 9.5 mmol) was reacted with **2** (3.28 g, 4.75 mmol) according to the procedure described above for the synthesis of **3**. The crude product was purified by chromatography on silica gel eluting with MePh/MeCO<sub>2</sub>Et (40:1) to give 0.191 g (7.0%) of **5** as a white crystalline solid; mp 62-65 °C;  $[\alpha]_D^{25} = -307.8$  (*c* = 3.84, CH<sub>2</sub>Cl<sub>2</sub>); IR(KBr) 2928, 1591, 1458, 1372, 1287, 1204, 1153, 1093, 1029 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.92 (d, 6H, *J* = 6.2 Hz), 1.32 (d, 6H, *J* = 5.9 Hz), 2.25 (s, 6H), 3.56 (2H, m), 3.95 (d, 2H, *J* = 13.8 Hz), 4.18 (2H, m), 4.27 (d, 2H, *J* = 13.8 Hz), 4.44 (d, 2H, *J* = 12.8 Hz), 4.92 (d, 2H, *J* = 12.8 Hz), 5.25 (d, 2H, *J* = 12.4 Hz), 5.67 (d, 2H, *J* = 12.4 Hz), 6.78 (s, 2H), 6.84 (s, 2H), 7.24 (d, 2H, *J* = 7.7 Hz), 7.71

(t, 1H, J = 7.7 Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 18.6, 20.3, 21.2, 46.3, 63.6, 64.9, 67.0, 73.2, 77.5, 121.3, 126.2, 126.9, 131.2, 133.3, 137.2, 154.3, 158.1; MS (CI)  $m/z$  576 ( $\text{M}^+$ ). Anal. Calcd. for  $\text{C}_{35}\text{H}_{46}\text{NO}_6$ : C, 73.01; H, 7.88; N, 2.43. Found: C, 73.17; H, 8.00; N, 2.27.

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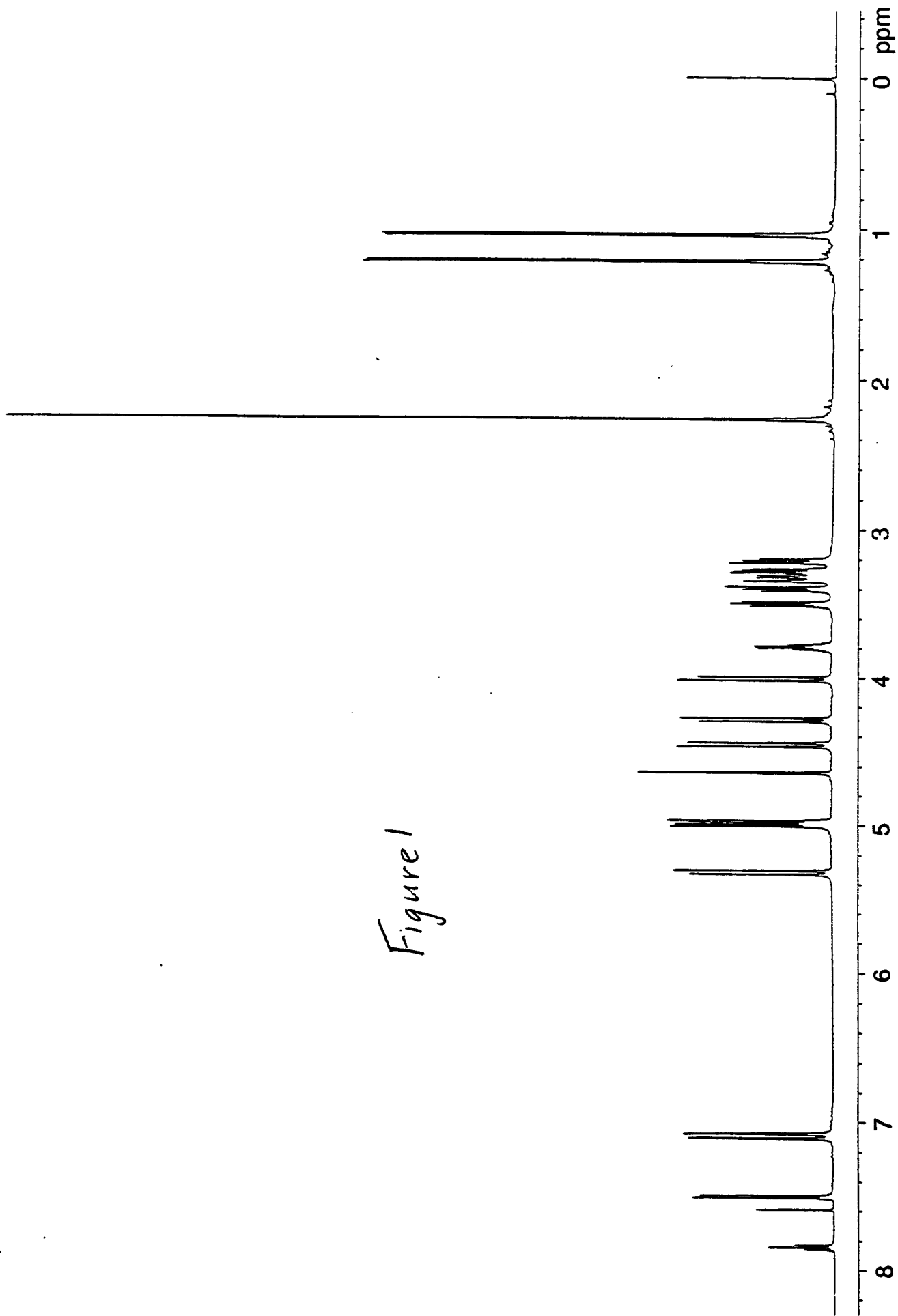
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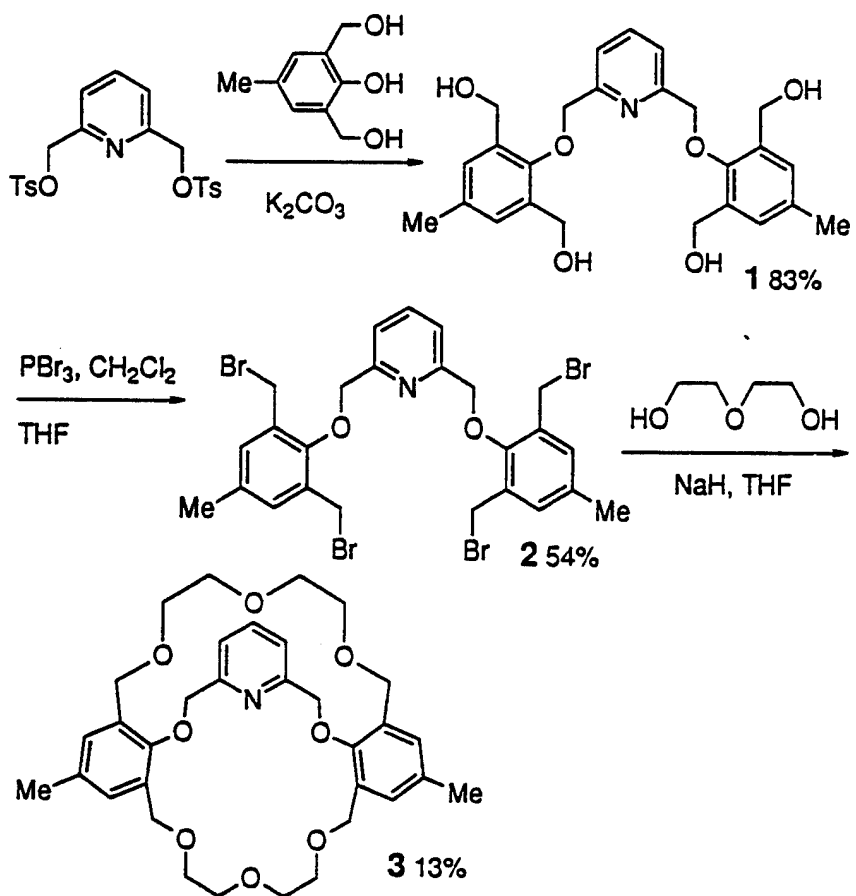
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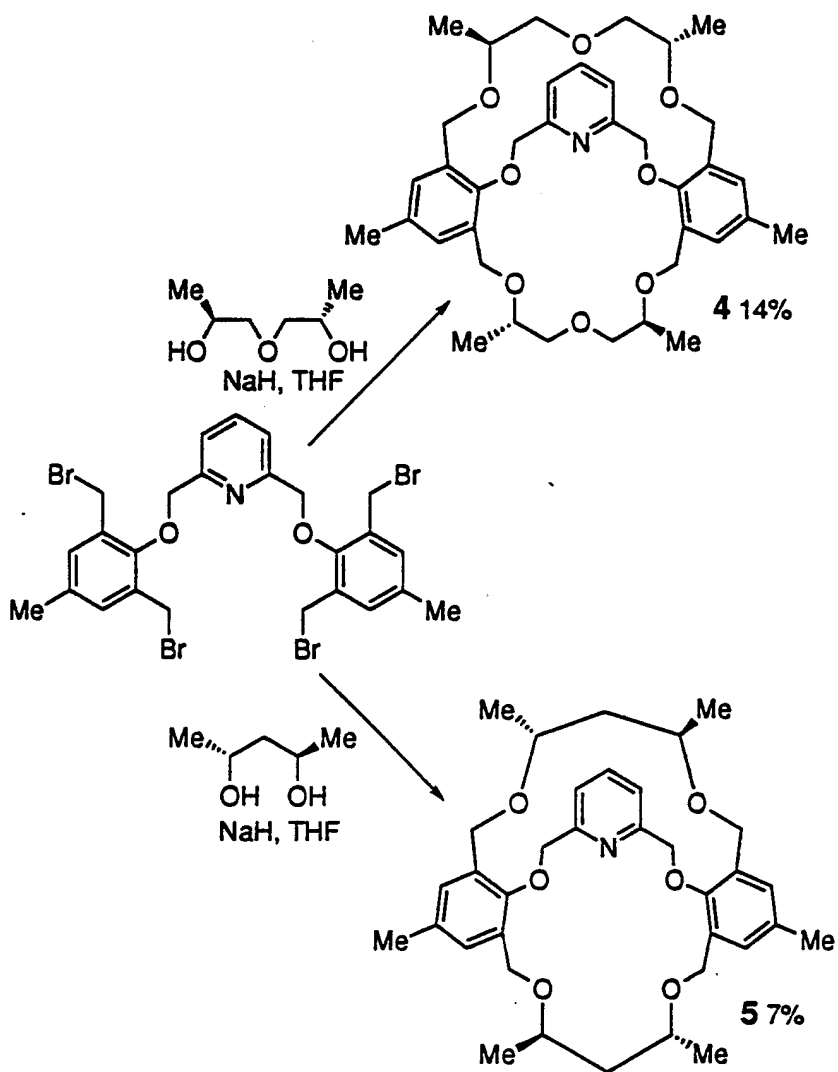
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Figure 1





Scheme 1.



Scheme 2.