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An Expeditious Synthesis of a Biscyclam with an Aromatic Linker

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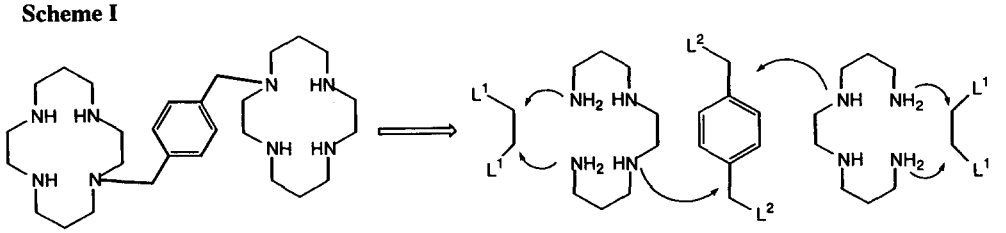
Abstract: An efficient synthesis of **1** starting from N,N'-bis(3-aminopropyl)ethylenediamine **2** is described. Two salient features of the present work are the selective bis or tris-trifluoracetylation of **2** and a novel bis-macrocyclization of the hexatosyl intermediate **5** using ethylene glycol ditosylate. Copyright © 1996 Elsevier Science Ltd

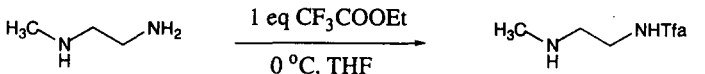
The interest in biscyclams with alkyl or aromatic linkers was triggered by the finding that they inhibit several strains of human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2).[1] Recently Bridger et al. reported the synthesis and structure-activity relationships of several of these derivatives and identified *p*-phenylenebismethylene linked biscyclam **1** (HCl salt referred to as JM 3100) as the compound of choice for further development.[1] The reported synthesis of **1** starting from cyclam is inefficient in that the first step is a problematic and low-yielding selective tritosylation. Additionally, cyclam is quite expensive and not readily available. Other methods such as mono N-alkylation of cyclam resulting in the direct synthesis of **1**, based on the general concept of complexation/bonding of three of the four amino groups to a fragment such as chromium tricarbonyl, boron, and phosphoryl are reported in the literature.[2] However, these methods were found not to be amenable for large-scale preparation. During our brief investigation of **1**, we envisioned that this molecule could be assembled *de novo* from tetraamine **2**, a two-carbon unit and *p*-phenylenebismethylene fragment as shown in Scheme I. We report herein these studies resulting in a new synthesis of **1**.

Scheme I

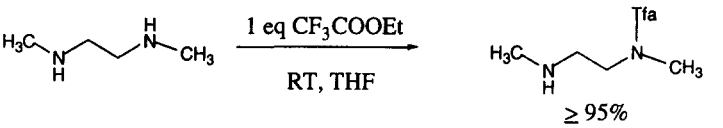


1

Highly efficient differentiation of three of four amino groups of tetraamine **2** was accomplished by a method previously disclosed by us on selective protection of primary amines in the presence of secondary amines (eq. 1) and monofunctionalization of symmetric secondary diamines (eq. 2) using ethyl trifluoroacetate.[3]



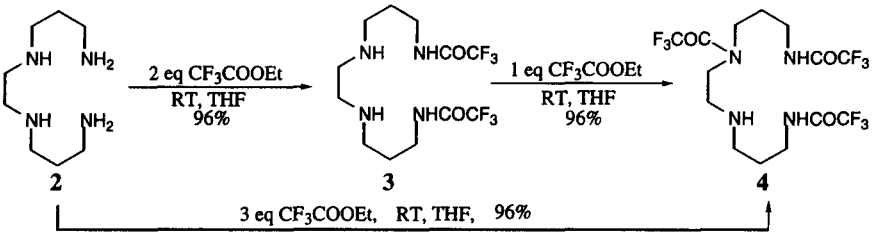
(eq. 1)



(eq. 2)

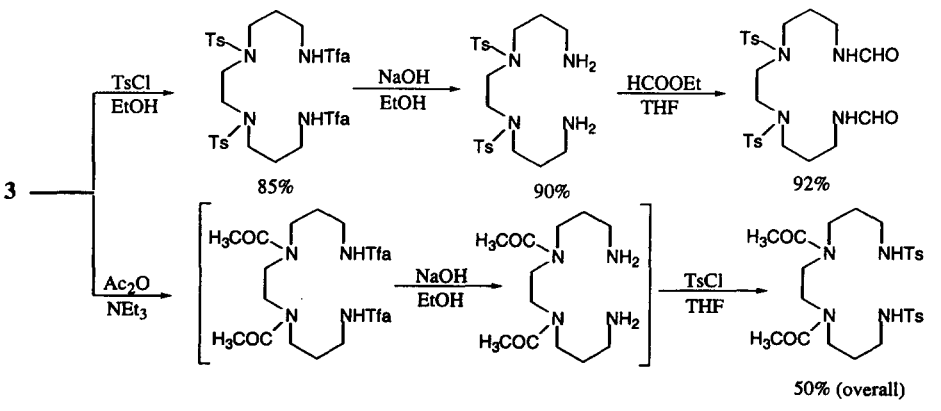
Reaction of **2** with two equivalents of ethyl trifluoroacetate gave exclusively the primary-amine-protected product **3**[4] in excellent yield (Scheme II). When **3** was further treated with another equivalent of

Scheme II



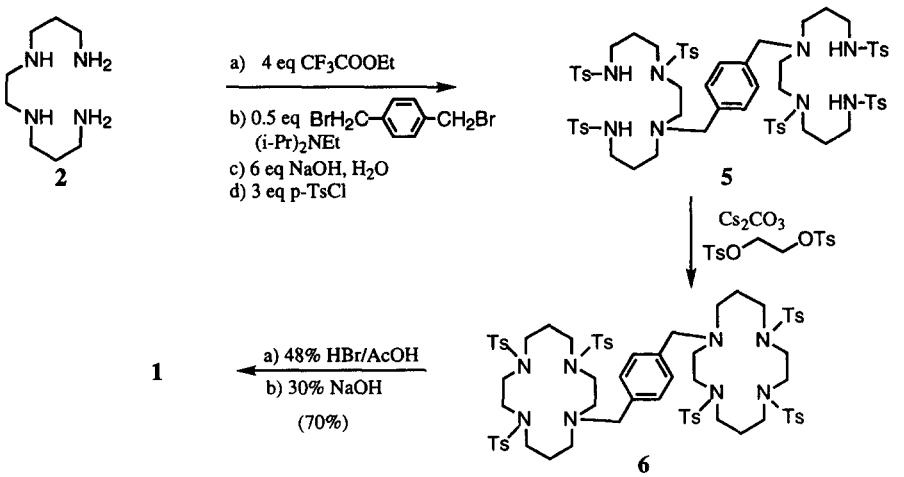
ethyl trifluoracetate, the tristrifluoroacetylated product **4** was obtained in very high yield. Compounds **3** and **4** are novel synthons easily transformable into many interesting selectively functionalized tetraamine derivatives. Some of the examples that were made in this context are shown in Scheme III.

Scheme III



Although there are many literature examples of alkylations of trifluoroacetamides,[5] attempts to achieve alkylative cyclization of either **3** or **4** using ethylene glycol bistosylate as the two-carbon unit to generate a protected cyclam were unsuccessful. This prompted consideration of alternative strategies. The generally applied Richman-Atkins' cyclization method[6] which employs tosyl as the protecting group for amines for preparing polyazamacrocycles led us to believe it was necessary to switch the protecting group from trifluoroacetyl to tosyl. This is the genesis for our bismacrocyclization approach as we decided to bring in the *p*-xylene unit earlier in the synthesis to achieve higher efficiency. Alkylation of primary-amine-protected **3** with α,α'-dibromo-*p*-xylene followed by hydrolysis of trifluoroacetyl groups with NaOH and reprotection with tosyl chloride *in situ* gave the hexatosyl intermediate **5** in a moderate yield of 20% after chromatography. Unfortunately the alkylation of **3** with α,α'-dibromo-*p*-xylene was not as selective as we had hoped, and the observed low yield is attributed to this. However, we were gratified when the above procedure was repeated with **4** to achieve a yield of 80% of **5**. A big advantage of our present methodology[7] is that we could obtain **5** from **2** in a one-pot operation simply via a sequential addition of reagents followed by work up as shown in Scheme IV. Treatment of **5** with ethylene glycol bistosylate in the presence of Cs_2CO_3 in DMF then afforded the hexatosyl bismacrocycle **6** in 35% yield.

Scheme IV



The detosylation of **6** was carried out using literature conditions[1] in refluxing concentrated HBr in acetic acid. The precipitated HBr salt of **1** on treatment with 30% of NaOH gave the free base in 70% yield. Since no chromatographic separation is involved and all the materials used are readily available, the synthesis depicted in Scheme III is adaptable to large-scale production.

In summary, we have demonstrated a new and practical synthesis of **1** utilizing the selective trifluoroacetylation and bismacrocyclization as two key features. Studies are currently underway to utilize this selective trifluoroacylation approach to the synthesis of other biologically interesting polyamines.

References and Notes

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7. Although initially we used three equivalents of ethyl trifluoroacetate for selective tristrifluoroacetylation of **2**, we found that using four equivalents gave a more reproducible yield while not harming the selectivity. Typical experimental procedure thus developed is as follows:
   Compound **5**: To a solution of N,N'-bis(3-aminopropyl)ethylenediamine **2** (17.43 g, 0.1 mol) in 100 mL of THF was added ethyl trifluoroacetate (56.83 g, 0.4 mol) at 0 °C. The mixture was stirred at rt for 4 h, followed by the addition of N,N-diisopropylethylamine (19.39 g , 0.15 mol) and α,α'-dibromo-*p*-xylene (13.46 g, 0.051 mol). After stirring the mixture for 10 h, a solution of 28 g (0.7 mol) of NaOH in 50 mL of water was added, and the mixture was heated for 2 h at 60 °C. The mixture was cooled to 0 °C, a solution of *p*-toluenesulfonyl chloride (59.1 g, 0.31 mol) was added and stirred for 1 h at rt. The mixture was diluted with 400 mL of EtOAc and 50 mL of water and the organic layer was washed with a $NaHCO_3$ solution. The organic layer was concentrated to dryness and chromatographed on SiO_2 using hexane/EtOAc/NEt_3 (1:1:0.05) to give 110 g of **5** in 80% yield.
   Compound **6**: To a stirred solution of **5** (38.12 g, 27.7 mol) and cesium carbonate (72.1 g, 221.5 mmol) in 1 L of DMF at 110 °C was added a solution of ethylene glycol ditosylate (41 g, 110.7 mmol) in 400 mL of DMF over a period of 4 h. After heating for one more hour, the mixture was poured into 1.5 L of chilled (5 °C) water, the precipitate was filtered and dissolved in 500 mL of EtOAc. The organic solution was washed with 500 mL of a NaOH solution and the organic extract was evaporated to dryness. Recrystallization of the residue from 100 mL of CH_3CN gave 13.83 g of **6** (35% yield).

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