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Short and straightforward synthesis of 1,7-dimethyl-1,4,7,10-tetraazacyclododecane

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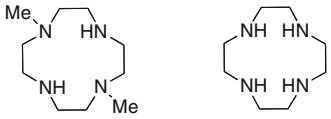
ABSTRACT

A novel, cost-effective, and efficient process for the synthesis of 1,7-dimethyl-1,4,7,10-tetraazacyclododecane **1** has been developed. The two-step process involved the selective conversion of commercially available cyclen to *N*1,*N*7-diethylcarbamate cyclen **3** that afforded the title compound in high yield after the reduction step.

In the past decade, step economy has become a fundamental synthetic strategy for the construction of organic molecules and it is a prominent goal of organic synthesis.[1] A step-economical synthesis has the potential to reduce the number and amount of reagents employed by reducing the number of synthetic steps as well as the length, waste, environmental impact, development and execution time, separation science, effort, and cost. This should also lead to an increase in chemical yield of the desired product, and therefore the capacity to efficaciously deliver a meaningful supply of the desired target, as well as speed, scientific advancement, safety, return on investment, and most importantly human economy. Traditionally, this has meant limiting the use of protecting group manipulations;[2] now, judicious choice and development of reactions or sequences of reactions allow for the step-economical synthesis of a given target structure.

Cyclic tetraamines have attracted increasing attention owing to their versatile coordination properties which allow their use in many fields, especially for medical purposes.[3] In particular, the 1,4,7,10-tetraazacyclododecane (cyclen) **2** and its N-functionalized derivatives have been extensively used and pursued[4] since the generated metal-chelates have wide applications as contrast agents in MRI,[5] radiodiagnostic and radiotherapeutic agents,[6] fluorescent sensors,[7] molecular recognition, and catalysis compounds,[8] and as anti-HIV and anticancer agents (Fig. 1).[9]



1,7-Dimethylcyclen (DMC) (**1**) Cyclen (**2**)

Figure 1. The cyclic tetramines DMC **1** and cyclen **2**.

In this context, 1,7-dimethyl-1,4,7,10-tetraazacyclododecane **1** (Me2[12]aneN4), also called Dimethylcyclen (DMC), has received considerable attention from the chemistry community,[10] culminating recently in the discovery of its antitumor activity against HeLa and A549 cell lines and its ability to hydrolyze double-strand DNA under physiological conditions (Fig. 1).[10c,d]

During our studies on the design, synthesis, and application of novel molecular receptors for the molecular recognition and sensing of cations,[11] anions, and neutral molecules,[12] we have employed DMC **1** as a macrocyclic base upon which we built powerful recognition systems by linking two identical side-arms containing binding sites. More recently, the unsymmetrical difunctionalization of **1** by an Ugi multicomponent reaction has been disclosed by us[13] with the aim of preparing bifunctional chelating agents (BCAs) bearing different pendant arms, with potential novel radiodiagnostic and radiotherapeutic properties.

There is clearly a strong need for an easy, practical, short, and economical synthesis of DMC. The title compound has been prepared for the first time by Micheloni and co-workers,[14a] from acyclic precursors by reacting the disodium salts of *N*′-methyl-

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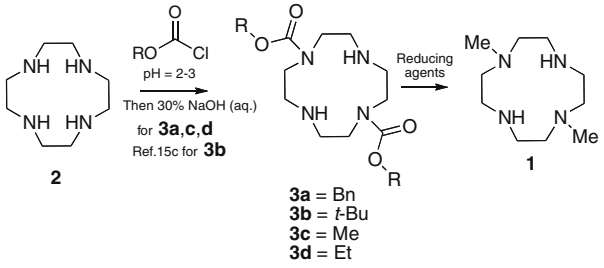
N,*N*″-bis(toluene-p-sulphonyl)diethylenetriamine, prepared in five steps, with bis(2-chloroethyl)methylamine, obtained in three steps, to give a protected form of the macrocyclic base. Removal of the protecting groups gave the title compound in 30% overall yield. Although this approach is currently used in practice, it is too long and impractical to be used on a process scale. In addition, the use of potentially dangerous chemicals renders this approach environmentally unfriendly. More recently, two syntheses of DMC (1) that rely upon a strategy of selective protection followed by methylation and deprotection have been reported.[14b,c] Unfortunately, both methods proved to be inefficient in terms of chemical yield when **1** was prepared in large scale. However, deficiencies associated with the available procedures clearly provide an opportunity for further process refinement.

Herein, we report a new, straightforward, step-economical, and practical synthesis of **1** from commercial materials without using any protecting groups. We envisioned a two-step process that would allow rapid and selective access to **1**. We assumed that the *N*1 and *N*7 methyl groups might be introduced via conversion of the appropriate carbamate system into methyl groups by hydride reduction. The selective formation of *N*1,*N*7-bis-carbamates **3a–d** was achieved in high yields by a slight modification of the procedure developed by Kovacs and Sherry in order to scale up the reaction.[15] Four different bis-carbamates **3a–d** were prepared in almost quantitative yields. More specifically, treatment of commercially available cyclen **2**[16] with various chloroformates under acidic conditions (pH 2–3) resulted in the formation of **3a**, **3c**, and **3d**; while **3b** was prepared using *N*-(*tert*-butoxycarbonyloxy) succinimide in chloroform at room temperature (Scheme 1).

Although the conversion of a carbamate to a methyl group is well documented in the literature[17] by the use of different reducing reagents, only few examples of a contemporary double reduction have been reported.[18]

Table 1 reports the yields for the reduction of bis-carbamates **3a–d** to **1**, using different reducing agents and conditions. In all cases, the yields were from good to excellent, although significant differences were observed. The first experiments were performed using the *N*1,*N*7-di-Cbz derivative **3a**, adding a commercially available solution (1 M in THF, Aldrich) of $LiAlH_4$ (8 equiv) at 0 °C. After 3 h, most of the starting material was reduced, as judged by HPLC and TLC analysis, and the reaction was stopped. The title compound was isolated by neutral alumina chromatography purification, in only 54% yield (entry 1). When the reaction was performed using a suspension of solid $LiAlH_4$ (8 equiv) in THF under refluxing conditions, the reaction went to completion and the reduced compound was isolated in a gratifying 75% yield (entry 3). Any attempt to avoid the neutral alumina chromatography to remove the traces of benzylic alcohol was unsuccessful. Meanwhile, different reducing reagents were tested, including Red-Al (entry 4), Dibal-H (entry 5), and BH_3 (entry 7), but the yields were from poor to moderate (13–65%), depending on the reducing reagent and conditions; the use of $LiBH_4$ resulted in no reaction (entry 6). After establishing the experimental conditions necessary to



Scheme 1. Reaction sequence for the preparation of **1**.

Table 1
Reagents and conditions for reduction step

Entry	Carbamate	Reducing agent and conditions	Reduction yield (%)	Overall yield[a] (%)
1	**3a**	$LiAlH_4$ (1 M in THF), rt	54	49
2	**3a**	$LiAlH_4$ (solid), THF, rt	35	28
3	**3a**	$LiAlH_4$ (solid), THF reflux	75	68
4	**3a**	Red-Al	65	59
5	**3a**	Dibal-H	15	14
6	**3a**	$LiBH_4$	NR[b]	
7	**3a**	BH_3THF, reflux	60	58
8	**3b**	$LiAlH_4$ (solid), THF reflux	87	81
9	**3c**	$LiAlH_4$ (solid), THF reflux	78	76
10	**3d**	$LiAlH_4$ (solid), THF reflux	**90**	**88**

Bold entries indicates the best result obtained.
[a] From cyclen.
[b] No reaction.

achieve reduction, we turned our attention to the reduction of other bis-carbamate derivatives **3b–d** with the aim of facilitating product isolation and avoiding final purification by chromatography. Thus, reaction of carbamate **3d** with $LiAlH_4$ in THF under refluxing conditions resulted in complete reduction of the carbamate moieties to give **1**, after careful work-up of the reaction mixture, in excellent yields (90%) as a pure compound judged by NMR analysis. Under the same reaction conditions, compound **3c** gave comparable yields (87%), whereas the *N*1,*N*7-di Boc cyclen **3b** gave **1** in only 78% yield. A scale-up of the reduction step to 50 mmole of **3d** gave **1** without any deleterious effect on the yield and selectivity.[19] In conclusion, we have designed and executed a new, simple, step-economical, two-step process for the preparation of the interesting cyclic tetraamine 1,7-dimethyl-1,4,7,10-tetraazacyclododecane **1** in 88% overall yield from commercially available cyclen. We were able to make **1** with increasingly selective, efficient, practical, and environmentally friendly procedures. This original synthetic procedure allows the easy and economical synthesis of DCM **1** in sufficient quantities for the needs of various areas of research.

Acknowledgments

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19. *1,7-Dimethyl-1,4,7,10-tetraazacyclododecane* (**1**): An oven-dried, 1 L, three-necked, round-bottomed flask was equipped with a rubber septum, a 250 mL pressure-equalizing addition funnel fitted with a rubber septum, a reflux condenser fitted with an argon inlet adapter, and a Teflon-coated magnetic stirring bar. The flask was charged with 15.2 g (0.4 mol) of lithium aluminum hydride and dry THF (400 mL). (CAUTION: lithium aluminum hydride is very reactive and must be handled carefully to avoid contact with water). The resulting suspension was cooled to −5 °C (bath temperature, ice-salt) in an ice-water bath, and a solution of **3d** (15.2 g, 49.1 mmol) in dry THF (100 mL) was added dropwise over 10 min from the dropping funnel (vigorous bubbling upon addition). The resulting suspension was heated at reflux in a mineral oil bath for 3 h. The reaction mixture was cooled to 0 °C (bath temperature) in an ice-water bath and was diluted with ethyl ether (350 mL). Water (13.4 mL) was added dropwise slowly (water reacts violently with lithium aluminum hydride (LAH) necessitating slow addition of the water and cooling with a 0 °C ice-water bath), followed after 10 min by 3 M aq sodium hydroxide solution (13.4 mL) and, after 5 min, more water (40 mL). The resulting mixture was allowed to warm to ambient temperature and was stirred at this temperature for 2 h. The white precipitate was removed by filtration through a ceramic Büchner funnel lined with filter paper. The white residue was transferred to a 250 mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar. After breaking the precipitate into small pieces with a metal spatula, THF (200 mL) was added and then the suspension was heated at reflux with vigorous stirring for 60 min (This procedure extracts any product trapped in the white precipitate. The majority of the product (~80%) was in the filtrate.). The precipitate was removed by filtration through a medium-porosity, ceramic Büchner funnel lined with filter paper into a 100 mL filter flask and was washed with diethyl ether (3 × 100 mL). The combined filtrates were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure (25 °C, 10 mmHg) to afford the crude product as a brown yellow oil. Water (35 mL) and chloroform (150 mL) were added. The layers were separated and the aqueous solution was extracted with chloroform (3 × 150 mL). The combined organic phase was washed with brine (100 mL), the chloroform solution was dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The yellow oily residue was kept under vacuum at 40 °C overnight to give 8.8 g (88% yield over two steps) of clean 1,7-dimethyl-1,4,7,10-tetraazacyclododecane **1** (Me2[12]aneN4) as judged by ^{1}H, ^{13}C NMR. An analytical sample was obtained by sublimation to give a low melting point brown solid. Mp = 40–41 °C (lit. 41–42 °C Ref. 14a) ^{1}H NMR (200 MHz, CDCl3, 20 °C) δ = 1.99 (s, 6H), 2.18 (bs, 8H), 2.31 (bs,8H) ^{13}C NMR (50 MHz, $CDCl_3$, 20 °C) δ = 43.9, 44.7, 54.3 FT-IR (neat) cm^{-1}: 3369, 3281, 2926, 2863, 1601, 1465, 1380 LRMS (ESI): $C_{10}H_{24}N_4$: [M+H]: 201.1.