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A New Synthetic Route to 2-(p-Nitrobenzyl)-1,4,7,10-Tetraazacyclododecane

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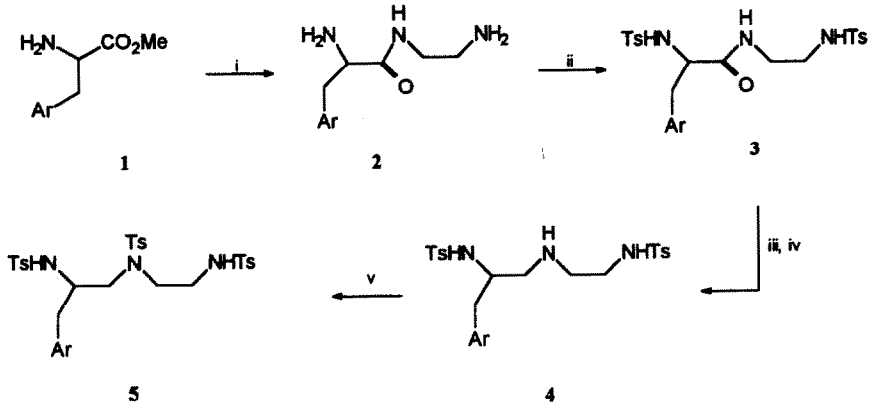
Abstract: A new, general synthetic method for the title compound has been developed, based on the nitration of 2-benzyl-1,4,7,10-tetraazacyclododecane (64 % yield), which provides higher yields and easier purification for scale-up than previously reported methods.

The linkage of metal ions to biologically important molecules has been accomplished with synthetic, bifunctional chelating agents which can form a covalent bond to the material or site of interest. Meares and coworkers prepared a bifunctional derivative of ethylenediaminetetraacetic acid to attach metal ions to proteins.[1] Medical applications such as magnetic resonance imaging, imaging with radioisotopes, and radiotherapy require metal complexes with extreme kinetic and thermodynamic stability to metal ion release, and work in recent years has focused on derivatives of macrocyclic amine-carboxylic acid ligands.[2,3,4,5,6] Complexes of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) have the required stability[2,7], and the synthesis of the 2-(p-nitrobenzyl) derivative of DOTA (NO_2-Bz-DOTA) has been reported.[2,5,6] The nitro- group can be reduced to an amine to provide a point of attachment to biological materials.

In this communication we report a new synthetic route for the macrocyclic backbone of NO_2-Bz-DOTA. The synthetic route reported here is based on the Richman-Atkins[8] method for preparation of tetraazamacrocycles which can be used for large scale synthesis of this macrocycle. In contrast to published methods[2,5] for the preparation of NO_2-Bz-DOTA, high dilution techniques are not required for this procedure. The cyclization procedure developed in this work was demonstrated for the preparation of macrocycles having either benzyl or naphthylmethyl substituents on the tetraazacyclododecane ring.

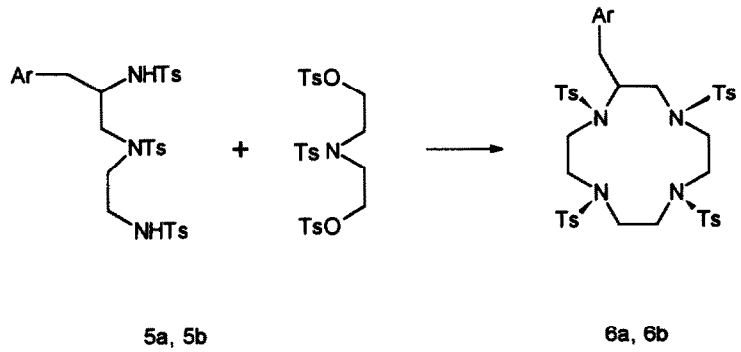
Arylmethyl tosamides **5a-5c** (**a**, Ar = benzyl; **b**, Ar = 2-naphthylmethyl; **c**, Ar = p-nitrobenzyl) were readily prepared from the corresponding amino acids as outlined in Scheme I. Reaction of the hydrochloride salt of the amino acid with a large excess of ethylenediamine in methanol afforded pure substituted N-(2-aminoethyl)alanine amides **2**, which were tosylated, reduced, and further tosylated. Although this material may be obtained more directly by the reduction of **2** followed by tosylation, our method is more amenable to scale-up because the intermediates are readily purified by crystallization.

Direct nitration of the benzyl derivative of tetraazacyclododecane as a means of preparing 2-(p-nitrobenzyl)tetraazacyclododecane (**8**) circumvents problems associated with cyclization of the nitrobenzyl



Scheme I. Reagents and Conditions: *i*, ethylenediamine, MeOH, 20 °C, 90%; *ii*, TosCl/Et_3N, 76 %; *iii*, BH_3-SMe_2, THF; *iv*, HCl/MeOH, 97%; *v*, TosCl/Et_3N, THF, 90%.

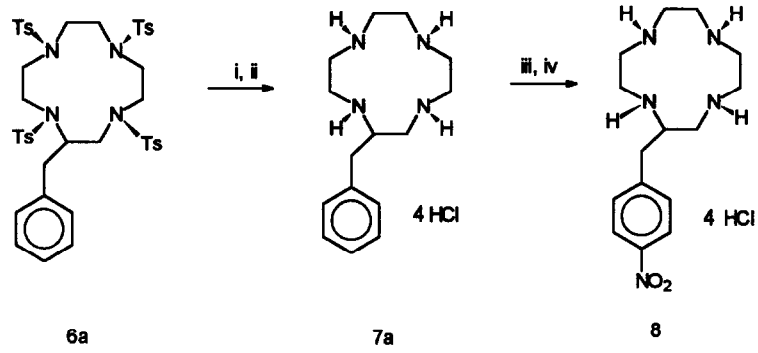
tritosamide **5c**. Cyclization of the tritosamide **5c** with tosyl-protected diethanolamine failed because of side reactions resulting from the presence of the nitro group (Scheme II). This failure to observe the desired cyclic product has also been reported by McMurray, et. al.[5] in a related reaction.



Scheme II. Reagents and conditions: Cs_2CO_3, DMF, 80 °C, 80-90 %.

With the aryl methyl tosamides which did not contain the nitro group, cyclization occurred smoothly and the product was isolated in greater than 85% yield. By carefully monitoring the reaction of tosamides **5a** and **5b** by TLC, a crystalline material free of starting material or other cyclic by-products was isolated by precipitation from the reaction mixture by the addition of water. The benzyl derivative of the cyclic tosamide, **6a**, can be nitrated directly. However, it is more convenient to incorporate the nitro group after deprotection

to an amine as shown in Scheme III. This approach allows removal of the tosyl groups by reduction with



6a 7a 8

Scheme III. Reagents and Conditions: *i*, $LiAlH_4$, 66 °C, 85-95%; *ii*, HCl, EtOH, 75%; *iii*, HNO_3/H_2SO_4, 64%, *iv*, HCl, EtOH, 75%.

lithium aluminum hydride,[9] a reaction for which we found a higher yield and fewer byproducts than the usual method of hydrolysis with concentrated sulfuric acid. The free amine was purified by precipitation as the hydrochloride salt. The naphthylmethyl derivative (**6b**) was also deprotected with $LiAlH_4$, followed by crystallization of the free amine as the hydrochloride salt (**7b**) (85% yield), suggesting these preparations of cyclen derivatives could be developed to a general procedure.[10] The hydrochloride salt of the benzyl-substituted cyclic amine, **7a**, was nitrated by dissolving in concentrated sulfuric acid and adding 10% fuming nitric acid in sulfuric acid. The product was collected, extracted into chloroform, and crystallized as the hydrochloride salt. The ratio of nitration products was > 3:1 para- to ortho- by ^1H NMR, but the para-isomer was preferentially crystallized as the hydrochloride salt. ^1H and ^{13}C NMR indicated that pure p-NO_2-Bz-cyclen (**8**) was isolated (64 % yield).[11] **8** was converted to the tetraacetate by the reaction with t-butylbromoacetate followed by acid hydrolysis. Following the route outlined in this article, the synthesis of p-NO_2-Bz-DOTA was completed in an overall yield that is almost a factor of four higher than the previously best.[6] The synthetic route outlined here has significant advantages over those previously reported: all of the reactions proceed in good yield, chromatographic separation or purification of intermediates was not required, none of the reactions require conditions of high dilution, and the reactions are amenable to scale-up.

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10. Compound **7a** has been previously reported although no spectroscopic data was provided.[5] A satisfactory analysis was obtained for both compound **7a** and **7b**. Selected spectroscopic data: **7a** (Bz-cyclen, free base) ^{1}H NMR ($CDCl_3$, ref TMS) δ 1.85 (broad, s, N-H) 2.5-2.7 (m, 17 H), 7.2-7.3 (m, 5 H, Ar-H); ^{13}C NMR ($CDCl_3$, ref TMS) δ 40.0, 41.9, 43.0, 44.5, 46.5, 46.6, 49.8, 49.9, 50.9, 53.0, 53.1, 56.5, 56.6, 59.5, 127.5, 128.0, 129.5, 139.5; **7b** (Nap-cyclen, free base) ^{1}H NMR ($CDCl_3$) δ 2.15 (broad, s, 4H), 2.35 (m, 2H), 2.5-3.3 (m, 15H), 7.2-7.5 (m, 4H), 7.7-8.1 (m, 3H); ^{13}C NMR ($CDCl_3$, ref TMS) δ 40.4, 43.0, 44.3, 45.0, 47.0, 49.5, 51.3, 122.5, 123.8, 125.2, 127, 129. At room temperature these compounds exist in more than one conformation, and ^{13}C NMR shows additional peaks in the aliphatic region.
11. Spectroscopic data are in agreement with literature values.[5,6] **8a** (p-NO_2-Bz-cyclen, free base): ^{1}H NMR ($CDCl_3$, ref TMS) δ 2.0 (broad, s, 4 H, -NH), 2.6-3.1 (m, 17 H), 7.5(d, J = 8 Hz, 2 H, Ar-H), 8.1 (d, J = 8 Hz, 2 H, Ar-H), ^{13}C NMR ($CDCl_3$, ref TMS) δ 39.6, 39.9, 41.8, 42.5, 44.0, 46.4, 46.7, 46.8, 49.4, 50.7, 52.5, 56.6, 123.5, 129.1, 144.9, 146.6; hydrochloride salt: ^{1}H NMR (D_2O) δ 2.5-3.5 (m, 17 H), 7.7 (m, 2 H), 8.3 (m, 2 H).

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