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A Convenient, Novel Approach for the Synthesis of Polyaza Macrocyclic Bifunctional Chelating Agents

Anil Kumar Mishra*, Karine Draillard, Alain Faivre-Chauvet, Jean François Gestin, Chantal Curtet and Jean-François Chatal

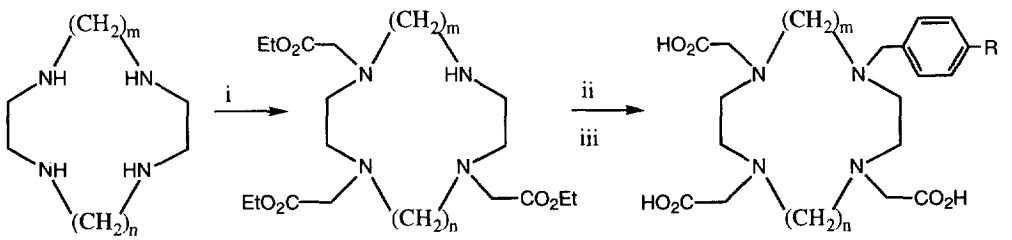
INSERM, Unit U-211

9 Quai Moncousu, 44035 Nantes, France

Abstract: The convenient, synthetically useful bifunctional chelating agents, (10-p-aminobenzyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetate (p-ABz-DO3A) **3** and (11-p-aminobenzyl)-1,4,8,11-tetraazacyclotetradecane-1,4,8-triacetate (p-ABz-TE3A) **6**, were obtained by reaction of an ethyl bromoacetate with 1,4,7,10-tetraazacyclododecane and 1,4,8,11-tetraazacyclotetradecane followed by reaction with nitrobenzyl bromide. This method proved more efficient than any described in the literature since the overall yield in a two-step synthesis sequence starting from tetraazamacrocycles was 68%. Copyright © 1996 Published by Elsevier Science Ltd

The continued interest in new macrocyclic bifunctional chelating agents stems mainly from their use in labeling monoclonal antibodies (mAbs) with radioactive metals for cancer diagnosis and therapy[1-4] and with paramagnetic ions for magnetic resonance imaging[5, 6]. Our ongoing studies are currently concerned with simple, convenient means of ligand preparation. This paper describes a novel approach for the synthesis of polyaza macrocyclic bifuntional chelating agents using inexpensive, readily available materials.

Scheme : Synthesis of Abz-DO3A, **3** and Abz-TE3A, **6**.



m = n = 2	**1**	**2** (R = NO_2)
		3 (R = NH_2)
m = n = 3	**4**	**5** (R = NO_2)
		6 (R = NH_2)

Reagents: i, ethyl bromoacetate, CH_2Cl_2; ii, nitrobenzyl bromide, MeCN, Na_2CO_3; iii, Pd/C, NaOH.

1,4,7-tris(carboethoxymethyl)-1,4,7,10-tetraazacyclododecane **1**[7] was prepared by adding 2.24 equivalent of ethyl bromoacetate to a solution of one equivalent tetraazacyclododecane produced a mixture of the two products. The tetrasubstituted product was then removed by filtration, and the resulting filtrate was

washed with water and purified by flash chromatography (10% MeOH- CH_2Cl_2), yielding 72% of tri-N-substituted tetraazacyclododecane **1**.

The nitrobenzyl derivative **2**[7] with a side arm was obtained by adding an equivalent of p-nitrobenzyl bromide to a solution of **1** using 8 equivalent of Na_2CO_3 in MeCN at 70°C for 12 h. After filtration, the product was purified by flash chromatography (9.6% MeOH-CH_2Cl_2), yielding 93% of **2**.

1,4,7-tris(carboxymethyl)-10-(4-aminobenzyl)-1,4,7,10-tetraazacyclododecane **3**, an amino derivative, was prepared from an aqueous solution of 400 mg (0.70 mmol), pH 11, [NaOH] of **2** hydrogenated (16 h) [3 atm. H_2 0°C] over palladium on charcoal [10%, 500 mg]. After filtration, pH was adjusted to 6 using 3M HCl and water was removed to give a glassy solid which was then lyophilized. Yield 80% in a ^{57}Co metal binding assay. Reverse-phase C_{18} HPLC: solvent A, 0.1M ammonium acetate, pH 6; solvent B, MeOH; 15-65% B, 0-25 min., 65-100% B, 30-35 min.; 100-15% B, 35-40 min.; product peak 5.62 min.

The tri-N-substituted tetraamine **4**[7] was prepared by reacting 2.7 equivalent of ethyl bromoacetate with one equivalent of tetraazacyclotetradecane, yielding 74% tri-N-substituted product. The remaining tetrasubstituted product was removed by filltration at the end of reaction. The resulting filtrate was washed with water and purified by flash chromatography (10% MeOH- CH_2Cl_2).

The nitrobenzyl derivative **5**[7] was prepared from trisubstituted 1,4,8-tris(carboethoxymethyl)-1,4,8,11-tetraazacyclotetradecane **4** in the same way as compound **2**.

The aminobenzyl derivative **6** was obtained from an aqueous solution of **5** subjected to hydrogenation in the same way as compound **3**. Reverse-phase C_{18} HPLC: solvent A, 0.1M ammonium acetate, pH 6; solvent B, MeOH; 15-65% B, 0-25 min., 65-100% B, 30-35 min.; 100-15% B, 35-40 min.; product peak 6.12 min.

This study demonstrates that N-alkylation reactions to form macrocyclic bifunctional chelates do not require complicated starting materials or unusual techniques. The starting macrocycles (1,4,7,10-tetraazacyclododecane and 1,4,8,11- tetraazacyclotetradecane) can be easily prepared by a well-known procedure[8] or obtained commercially. 1,4,7-tris (carboethoxymethyl)-1,4,7,10-tetraazacyclododecane and 1,4,8-tris (carboethoxymethyl)-1,4,8,11-tetraazacyclotetradecane are also very easy to prepare at high yields (in this case, the macrocycles were reacted with ethyl bromoacetate in dichloromethane).

Alkylation reactions performed at room temperature in dichloromethane did not require high-dilution conditions to provide 70-80% yields of the trisubstituted products. Yields were sometimes 5-10% higher when syringe pumps were used to add the two reactants in high-dilution conditions.

Macrocycles 10-nitrobenzyl-1,4,7-tris (carboethoxymethyl)-1,4,7,10-tetraazacyclododecane **2** and 11-nitrobenzyl-1,4,8-tris (carboethoxymethyl)-1,4,8,11-tetraazacyclotetradecane **5** were obtained from the reaction of trisubstituted tetraazamacrocycles and p-nitrobenzyl bromide in MeCN using anhydrous Na_2CO_3 as base. The nitro groups of macrocycles **2** and **5** were selectively reduced without concomitant hydrogenolysis [9] by performing reduction in basic media (pH> 11) to obtain p-amino benzyl substituted triacids **3** and **6**.

Construction of a polyazamacrocyclic ring is crucial for successful synthesis of a macrocyclic bifunctional chelating agent. Previously reported protection methodologies[9-12] for preparing 12- and 14-membered polyazamacrocycles included reactions of benzyl chloroformate and p-toluene sulfonyl chlorides with polyazamacrocycles 1,4,7,10-teraazacyclododecane and 1,4,8,11-tetraazacyclotetradecane to allow for mono-N-alkylation with the required side chain. The use of these methodologies for synthesis of bifunctional chelating agents or the preparation of ligands with sterically hindered side arms requires protection and deprotection steps which make the total procedure longer. Two-step alkylation reactions between a polyaza macrocycle (cyclen and cyclam), ethyl bromoacetate and p-nitrobenzyl bromide require no protection or activation steps in the synthetic approach described here. This alkylation scheme is simpler and more convenient than any previously reported method[9] and is applicable to the preparation of other pendant functions or coordinating groups with an appropriate polyazamacrocycle and a reactive group.

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7. All compounds gave satisfactory spectroscopic and analytical data. Representative data for selected compounds; **compound 1:** FAB-MS m/e 431 ($M+H^+$).^{1}H NMR (250 MHz, $CDCl_3$): 1.25 (2t, 9H), 2.91 (m, 12H), 3.12 (m, 4H), 3.45 (2s, 6H), 4.16 (q, 6H); 10.01 (br, 1H); **Compound 2:** FAB-MS m/e 566 ($M+H^+$). ^{1}H NMR (400 MHz $CDCl_3$): 1.15 (2t, 9H), 2.15-3.50 (m, 24H), 4.20 (2q, 6H), 7.55 (d, 2H, J=

8.5 Hz), 8.15 (d, 2H, J= 9.0 Hz). Anal. Calcd. for $C_{21}H_{31}N_5O_8$: C, 52.38; H, 6.49; N, 14.54; O, 26.58; Found: C, 52.41; H ,6.58; N, 14.6; O, 26.63; **Compound 4:** FAB-MS m/e 459 ($M+H^+$). ^1H NMR (400 MHz $CDCl_3$): 1.26 (2t, 9H),1,69 (quintet, 2H), 2.06 (quintet, 2H), 2.63 to 3.54 (m, 22H), 4.15 (2 q, 6H), 10.01 (br, 1H); **Compound 5:** FAB-MS m/e 594 ($M+H^+$).^1H NMR (250 MHz $CDCl_3$): 1.25 (2t, 9H),1.65 (quintet, 2H), 2.06 (quintet, 2H), 2.39 to 2.95 (m, 16H), 3.20 (s, 2H, CO_2-CH_2-N), 3.35 (s, 2H, CO_2-CH_2-N), 3.40 (s, 2H, CO_2-CH_2-N), 3.60 (s, 2H, Ar-CH_2-N), 4.15 (2 q, 6H) 7.50 (d, 2H, J= 9.0 Hz), 8.20 (d, 2H, J= 9.0Hz). Anal. Calcd. for $C_{29}H_{47}N_5O_8$: C, 58.67; H, 7.98; N, 11.80; O, 21.56; . Found: C, 58.63; H, 7.93; N, 11.76; O, 21.53.

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