Bioorganic & Medicinal Chemistry Letters, Vol.3, No.6, pp. 1071-1072, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

SYNTHESIS OF N-[3-(p-AMINOPHENYL)-1-CARBOXYPROPYL] DERIVATIVES OF 1,4,7-TRIAZACYCLONONANE-N,N'-DIACETIC ACID AND 1,4,7,10-TETRAAZACYCLODODECANE-N,N',N"-TRIACETIC ACID: MACROCYCLIC BIFUNCTIONAL CHELATING AGENTS USEFUL FOR ANTIBODIES LABELLING

Mohammad H Ansari*, Mashood Ahmad[a] and Karel A Dicke[b]+

[a]Department of Chemistry, Aligarh Muslim University, Aligarh-202 002, India
[b]University Of Nebraska Medical Center, Clinical Cancer Center, 600 South 42nd Street, Omaha, NE 68198-1210, USA

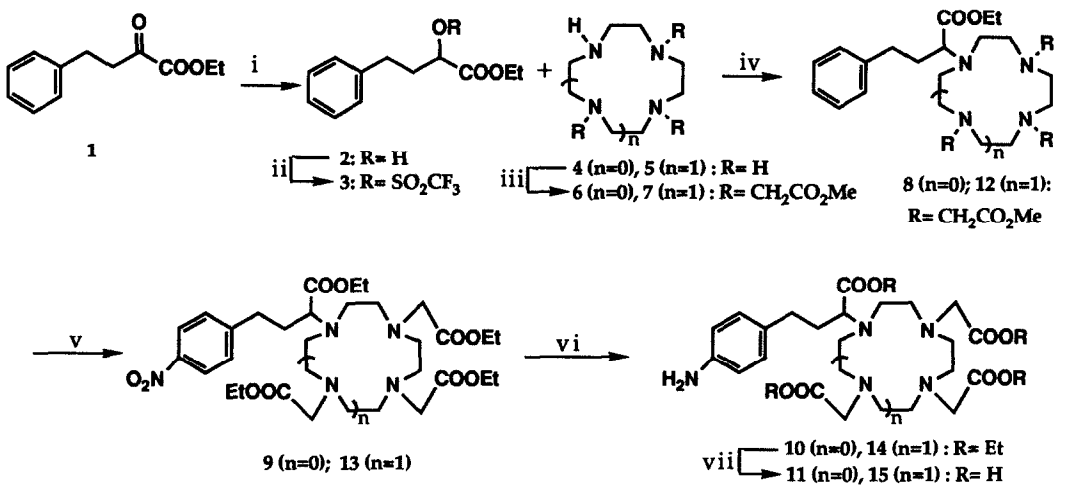
(*Received in USA* 26 *January* 1993)

Abstract: Reactions of dicarboxymethylated triazacyclononane (**6**) and tricarboxymethylated tetraazacyclododecane (**7**) with ethyl 2-(trifluorosulfonyloxy)-4-phenylbutanoate (**3**) afforded corresponding N-functionalised cyclic ester derivatives (**8**) and (**12**) which served as precursors of above titled macrocyclic bifunctional chelating agents.

In the foregoing paper,[1] we reported a convenient synthesis of macrocyclic bifunctional chelating agents based on cyclic tetraaza and triaza polyaminocarboxylates derivatized at methylene carbon atoms of polyamine backbone with p-aminobenzyl side chain. Recently, the preparation of cyclic triaza[2,3] and tetraaza[2-5] polyaminocarboxylates in which protein reactive side chain incorporated into one carboxymethyl arm of the chelator was developed by N-alkylation of the parent cyclic polyamines with requisite α-bromoesters. It was also observed that some such type of ligands conjugated with chimeric B72.3 antibody and labeled with ^{111}In or ^{90}Y showed an *in vivo* stability and better biodistribution results in tumor and non-tumor animals as compared to an analogous experiments with acyclic DTPA derivatives.[3] However, the preparation of such types of ligands by use of above methods[2-4] requires drastic conditions and always accompanied by low yield. Here, we describe an efficient synthesis of analogs of such types of cyclic ligands which is based on a facile displacement of a triflate group of (**3**) by a secondary amino group of carboxymethylated parent cyclic polyamines such as (**6**) and (**7**) to give their corresponding N-alkylated products (**8**) and (**10**) which were utilized in the complete synthesis of ligands (**11**) and (**15**) as shown in Scheme-1.

The preparation of (**11**) and (**15**) was commenced with the known ethyl 2-oxo-4-phenylbutanoate (**1**).[6] $NaBH_4$ reduction of **1** afforded ethyl 2-hydroxy-4-phenylbutanoate (**2**)[7] which on treatment with triflic anhydride afforded desired triflate ester derivatives (**3**).[7] Carboxymethylated polyamines (**6**) and (**7**) were prepared by controlled carboxymethylation of their respective parent cyclic polyamines (**4**) and (**5**)[4] as described in Scheme-1. Reaction of the triflate (**3**) with polyamine (**6**) gave N-alkylated derivative (**8**)[7] in 77% yield. Similarly, reaction of **3** with polyamine (**7**) afforded N-alkylated product (**12**)[7] in 83% yield. The conversion of macrocyclic esters (**8**) and (**12**) into their corresponding chelating agents was accomplished with their nitration[8] followed by esterification to afford cyclic nitrophenyl ester derivatives (**9**) and (**13**),[7] catalytic hydrogenation (10% Pd-C) of **9** and **13** to afford their corresponding amino derivatives (**10**) and (**14**)[7] in 94-95% yields and finally their acidic hydrolysis with HCl to give their corresponding macrocyclic chelating agents (**11**) and (**15**)[7] in 96-97% yields.

Scheme-1



i) $NaBH_4$ (93%); ii) $(CF_3SO_2)_2O$ (1.1 equiv.)(88%); iii) a: **4** (1 equiv.), CH_2BrCO_2Me(2.5 equiv.), Et_3N(2.1 equiv.) MeOH, reflux, overnight (**6**, 48%); b: **5** (1 equiv.), CH_2BrCO_2Me (4 equiv.),Et_3N (3.1 equiv.), MeOH, reflux, overnight (**7**, 51%); iv) **6** or **7** (1 equiv), Et_3N (1.1 equiv.),CH_2Cl_2, r.t., overnight (**8**, 77%, **12**, 83%); v) conc. HNO_3 (1.2 equiv.), 96%H_2SO_4, 0 ^{0}C, 4-5 hrs, pH 5 (7N NaOH), evaporated, then dry EtOH, $SOCl_2$(8-10 equiv.), 20-24 hrs, evaporation, then Et_2O, 0 ^{0}C, Et_3N(4-5 equiv.), then workup(Et_2O) (**9**, 82%; **13**, 76%); vi) H_2, 10% Pd-C, EtOAc, r.t., overnight (**10**, 94%; **14**, 95%); vii) HCl (6M), r.t, 42-48 hrs. (**11**, 97%; **15**, 96%)

In summary, the macrocyclic ligands (**11**) and (**15**) having p-aminophenethyl group incorporated into one of the carboxyl arm of the ligands were prepared in good yields from easily available starting material (**1**). The p-amino group of ligands can easily be converted into isothiocyanato and bromoacetamido groups suitable for the conjugation of antibody. Inclusion of the above method also allows the incorporation of long fatty acid chain to ligands[9] by using the appropriate triflate of long chain fatty 2-hydroxy acid ethyl ester, and the synthesis of optically active ligands by using optically active triflates.[10]

References and Notes

*Current address: Sagami Chemical Research Center, 4-4-1 Nishiohnuma, Sagamihara, Kanagawa 229, Japan. +Currently a physician at Houston City, Texas, USA.

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6. Available from Aldrich Chemical Company, USA.
7. All new compounds displayed satisfactory spectral and analytical data.
8. Attempts to introduce the p-nitrobenzyl functionality in ligands by reaction of triflate of p-nitrophenyllactic acid ethyl ester with polyamines (**6**) and (**7**) and to avoid the nitration step always resulted in the β-elimination of the triflate to give ethyl p-nitrocinnamate only due to high basic nature of polyamines (**6**) and (**7**).
9. Chelates-bearing fatty acid chain were used to study the model cell membranes by observing various spectroscopic signals from chelated metals (Yeh, S.M., and Meares, C.F., *Experentia*, **1979**, *35*, 715).
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