Pergamon

Tetrahedron Letters 39 (1998) 2659–2662

TETRAHEDRON
LETTERS

A New Convenient Synthesis of Bifunctional Chelating Agent 1-(4-Aminobenzyl)-1,4,8,11-tetraazacyclotetradecane-N',N",N'"-triacetic acid [1-(H_2NBn-TETA)]

M. Maillet,[a] C.S. Kwok,[b] A.A. Noujaim,[c] and V. Snieckus[a,*]

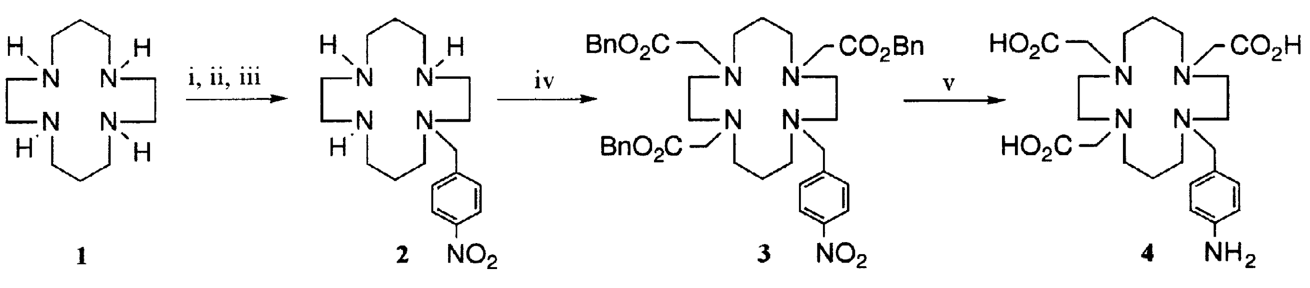
[a]Guelph-Waterloo Center Graduate Work in Chemistry, University of Waterloo, Waterloo, ON, N2L 3G1 Canada
Fax : (519) 746 5884, email : snieckus@buli. uwaterloo.ca
[b]The Ontario Cancer Treatment and Research Foundation, Hamilton Regional Cancer Center
699 Concession St., Hamilton, ON, L8V 5C2 Canada
[c]Biomira Research Inc. 1134 Dentistry Pharmacy Building, University of Alberta, Edmonton, Alberta, T6G 2N8 Canada

Received 26 November 1997; revised 6 February 1998; accepted 11 February 1998

Abstract : A convenient and short synthesis (3 steps , 50% overall yield) of the bifunctional chelating agent 1-(4-aminobenzyl)- 1,4,8,11 - tetraazacyclotetradecane - N'-, N"-, N'"- triacetic acid (**4**) via a boron-protection strategy is reported. © 1998 Elsevier Science Ltd. All rights reserved.

The promise of radiolabelled macrocyclic antibody conjugates for radioimmunotherapy,[1,2] has stimulated the synthesis and evaluation of several series of tetraaza macrocycles bifunctional chelating ligands.[3-11] As part of continuing efforts to design and synthesize tetraaza macrocyclic ligands,[11] we report, with experimental details, a new efficient synthesis of 1-(4-aminobenzyl)-1,4,8,11-tetraazacyclotetradecane-N', N", N'"- triacetic acid (**4**) and provide comment and comparison with the previous described syntheses of this compound.[9,10]

The inventive boron-protection strategy of Bernard *et al.*[3] for chemoselective mono N-alkylation of commercially available tetraazacyclotetradecane (**1**) was considered to circumvent predictable over-alkylation difficulties. However, the described conditions for this one-pot reaction ($B(NMe_2)_3$ / *n*-BuLi / BnBr) were found inappropriate with p-$NO_2C_6H_4CH_2Br$ presumably due to proton exchange and incompatibility of nitroaromatics with lithium amide bases[12] (**Scheme 1**).

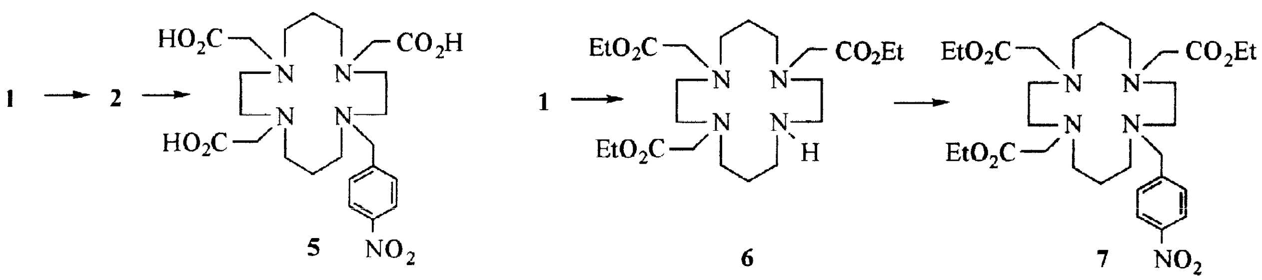


Scheme 1. Reagents: i) $B(NMe_2)_3$/PhMe/reflux; ii) NaH/THF/0°C/30 min; iii) p-nitrobenzyl bromide/0°C to rt; iv) $BrCH_2CO_2Bn/Cs_2CO_3/Bu_4NBr$/THF-$H_2O$/reflux (62% over 2 steps); v) H_2/Pd-C, PhMe/NaOH, pH > 11 (80%) .

0040-4039/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)00372-4

To overcome this problem, a series of bases (t-BuONa, NEt_3, $N(i\text{-}Pr)_2Et$, DBU, NaH) were examined from which only NaH was effective, leading to complete and selective reaction to give pure mono N-subtitued tetraazacyclotetradecane **2** in quantitative yield.[13] Treatment of **2** with excess benzyl bromoacetate under phase transfer catalysis conditions,[11] afforded the triacetic ester **3** in 62% yield.[14] Hydrogenation under basic conditions (pH > 11)[9] proceeded in high yield to give 1-(H_2NBn-TETA) (**4**) which was purified by HPLC.[15]

The present synthesis of **4** (3 steps, 50% overall yield after HPLC purification) appears advantageous over currently available routes.[9,10] In one of these,[9] a 10-fold excess of expensive tetraazacyclotetradecane (**1**) with respect to the electrophile is required for the first step, leading to the precursor 1-(4-nitrobenzyl)-1,4,8,11-tetraazacyclotetradecane-N'-, N"-, N'"- triacetic acid (**5**) in 37% overall yield (**Scheme 2**). In the more recent synthesis,[10] a 3-step route to **4** proceeding from **1** to **7** in overall yield of 69% was reported. In our hands, repeated attempts to reproduce the first step of the synthesis, **1** → **6** resulted in very low yields (< 20%). Effectively, we note that the descibed procedure invokes 2.7 equiv of the alkylating reagent, ethyl bromoacetate, to furnish the tri-N-substitued tetraazacyclotetradecane **6** in 74% yield, a result which appears to be unrealistic.



Scheme 2

Acknowledgments

We are grateful to NSERC Canada for support under the Strategic Program, grant STR0118070. M. Maillet thanks the "Ministère des Affaires Etrangères" for a postdoctoral fellowship (Lavoisier Program).

REFERENCES AND NOTES

1. DeNardo S.J.; DeNardo, G.L.; Peng, J.-S.; Colcher, D. *Monoclonal Antibody Radiopharmaceuticals of Cancer . Radioimmunotherapy. Radioimaging and Radioimmunotherapy*; DeNardo S.J.; DeNardo, G.L.; Peng, J.-S.; Colcher, D.; Ed.; Elsevier : New York, 1983, p 409.

2. Parker, D.; Jankowski, K. J. In *Advances in Metals in Medicine*; Murrer, B. A., Abrams, M. J., Eds.; Jai Press: New York, 1993; Vol. 1, p 29.

3. Bernard, H.; Yaouanc, J.J.; Clement, J.C.; des Abbayes, H.; Handel, H. *Tetrahedron Lett.* **1991**, 32, 629.

4. Filali, A.; Yaouanc, J.-J.; Handel, H. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 560.

5. Patinec, V.; Yaouanc, J.-J.; Clément, J.C.; Handel, H.; des Abbayes, H. *Tetrahedron Lett.* **1995**, 36, 79.

6. McMurry, T. J.; Brechbiel, M.; Kumar, K.; Gansow, O. A. *Bioconjugate Chem.* **1992**, *3*, 108.

7. Ruser, G.; Ritter, W.; Maecke, H. R. *Bioconjugate Chem.* **1990**, *1*, 345.

8. Moran, J. K.; Greiner, D. P.; Meares, C. F. *Bioconjugate Chem.* **1995**, *6*, 296.

9. Helps, I.M.; Parker, D.; Morphy, J.R.; Chapman, J. *Tetrahedron Lett.* **1989**, 45, 219.

10. Mishra, A.K.; Draillard, K.; Faivre-Chauvet, A.; Gestin, J.-F.; Curtet, C.; Chatal, J.-F. *Tetrahedron Lett.* **1996**, 37, 7515.

11. Moreau, P.; Tinkl, M.; Tsukazaki, M.; Bury, P.S.; Griffen, E.J.; Snieckus, V.; Maharajh, R.B.; Kwok, C.S.; Somayaji, V.V.; Peng Z.; Sykes, T.R.; Noujaim, A.A. *Synthesis*, **1997**, 1010.

12. SET reactions may be operating, see Houge-Frydrych, C.S.V.; Motherwell, W.B.; O'Shea, D.M. *J.C.S. Chem. Commun.* **1987**, 1819 and refs cited therein.

13. Preparation of **2**: A solution of tetraazacyclotetradecane (**1**) (5 mmol) and $B(NMe_2)_3$ (5 mmol) in dry toluene (100 mL) under argon was refluxed (3 h), cooled and concentrated under reduced pressure. The residue was dissolved in dry THF (75 mL) and the resulting solution was cooled to 0°C and transferred to a solution of NaH (5.25 mmol) in THF (25 mL) at 0°C. After stirring at 0°C (30 min), a solution of p-nitrobenzyl bromide (5.25 mmol in THF (25 mL)) was added dropwise and the reaction mixture was

allowed to warm to rt over 12 h. 3N NaOH solution was added (pH 14), the whole was concentrated in vacuo, and the residue was extracted with CH_2Cl_2, the extract was dried (Na_2SO_4) and evaporated to dryness. Traces of starting material (< 5%) were removed by ether precipitation to afford pure **2** (quant yield), mp 30-32°C, lit[9] mp 31-33°C which was used directly in the next step.

14. Preparation of **3**: A solution of **2** (5 mmol), Cs_2CO_3 (50 mmol), Bu_4NBr (1.25 mmol) and benzyl bromoacetate (20 mmol) in THF:H_2O (100 mL:10 mL) was refluxed for 12 h. The reaction mixure was concentrated in vacuo, the residue was extracted (CH_2Cl_2), and the extract was dried (Na_2SO_4) and evaporated to dryness. Flash chromatography (silica gel, 2 - 3% MeOH in CH_2Cl_2) gave **2** in 62% as a yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 1.59 (q, J = 6.5 Hz, 4H), 2.49 (m, 4H), 2.55-2.83 (m, 12H), 3.28 (s, 2H), 3.39 (s, 2H), 3.43 (s, 2H), 3.55 (s, 2H), 5.07 (s, 2H), 5.09 (s, 2H), 5.12 (s, 2H), 7.2-7.4 (m, 15H), 7.45 (d, J = 8.6 Hz, 2H), 8.11 (d, J = 8.6 Hz, 2H); ^{13}C (50 MHz, $CDCl_3$) δ 24.97, 25.29, 51.09, 51.28, 51.44, 55.29, 58.47, 65.94, 123.28, 128.24, 128.49, 129.28, 135.70, 135.82,146.89, 148.25, 171.21, 171.33.
FABMS m/z 780.7 (M + H) 100%.

15. HPLC purification of **4**: The purification and storage was performed as previously described[11] using a linear gradient 15-35% MeOH for 35 min, then 35-100% for the next 20 min, flow rate = 2 mL/min, eluent = 0.1 M NH_4OAc pH = 6. An aliquot of 0.25 g of crude **4** was purified to give pure material (0.079 g, 80% based on **3**): ^{13}C (125 MHz, $CDCl_3$) δ 22.55, 22.90, 50.25, 50.57, 53.03, 53.60, 54.64, 56.43, 57.24, 57.80, 117.18, 120.62, 132.94, 146.23, 171.89, 178.55, 179.79.
HRMS calcd for $C_{23}H_{35}N_5O_6$: 477.25873 , found 477.25478.