Pergamon

Tetrahedron Letters 39 (1998) 9107–9108

TETRAHEDRON LETTERS

An Efficient Synthesis of a Novel Bifunctional Chelating Agent

Belma Erdogan and Engin U. Akkaya*

Department of Chemistry, Middle East Technical University, TR-06531, Ankara, Turkey

Received 10 August 1998; revised 15 September 1998; accepted 21 September 1998

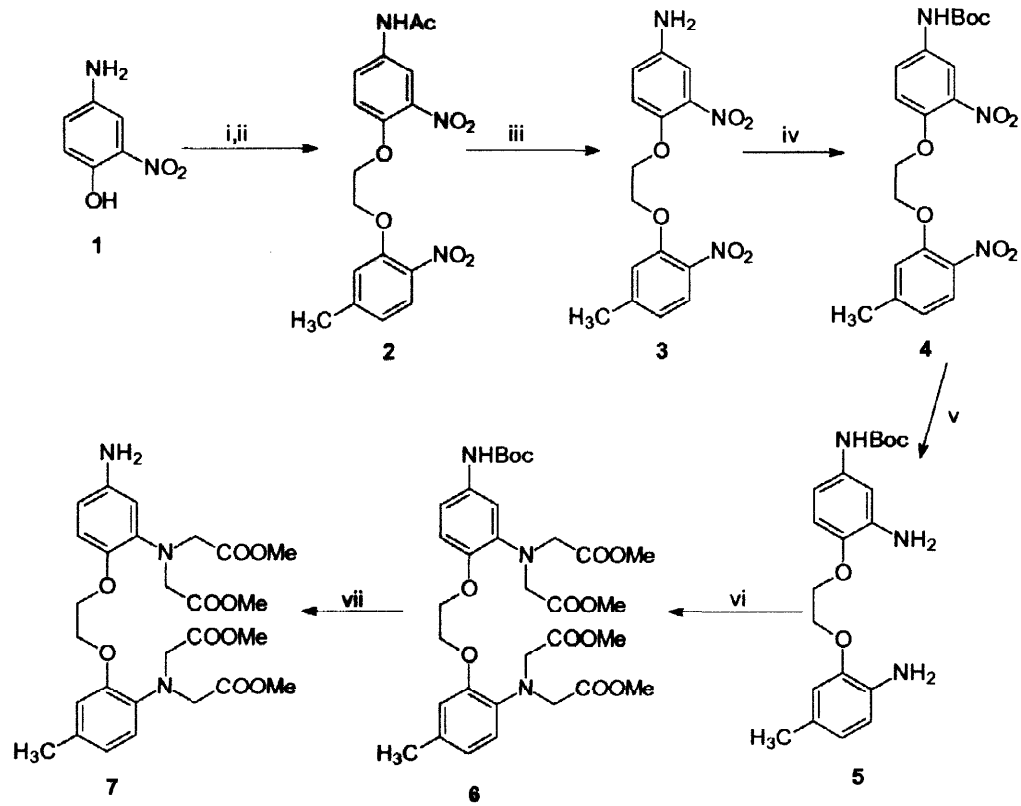
A novel bifunctional chelating agent, a derivative of the well-known calcium chelator, BAPTA has been synthesized in 6 steps. The added amino-functionality is likely to expand the use of this chelator.

The defining characteristic structural elements of a bifunctional chelating agent (BFC) are a strong metal-chelating group and a chemically reactive functional group. Bioconjugates of such compounds are especially important in the context of radiotherapy.[1-6] Although current work in this field is mostly focused on the applications of multidentate cyclen and cyclam derivatives, additional novel ligands are proposed. BAPTA (1,2-bis-(o-aminophenoxy)-ethane-N,N,N',N'-tetraacetic acid) has been designed and synthesized by Tsien[7] as a calcium-selective chelator with higher on-off rates compared to EGTA. The parent BAPTA structure was further modified to yield fluorescent probes of intracellular calcium.[8] This chelator is known to form strong complexes not only with calcium ions, but also with a number of transition metals. An amino-derivative of BAPTA, is likely to find applications in the design and synthesis of novel fluorescent chemosensors of calcium, especially based on photoinduced electron transfer (PET) approaches, in addition to being useful as a novel BFC.

There is no literature report of a synthesis of an amino derivative of BAPTA. Our synthesis starts with the protection of 4-amino-2-nitrophenol: treatment of this compound in a 30:70 (v/v) mixture of acetic anhydride-water mixture at 50 °C for 2 hours leads to the N-acetylated product. The reaction of this N-protected compound with 3-(2-bromoethoxy)-4-nitrotoluene[8a] in DMF results in the compound **2**. The acetamide protection was later removed by refluxing this material in 3 M HCl using EtOH as cosolvent to improve solubility. The bright yellow amine **3** was reacted with $(Boc)_2O$ in CH_2Cl_2 to protect the amine function giving **4**. As a mild reduction procedure to convert the nitro groups to amino groups 10% Pd-C catalyzed transhydrogenation using cyclohexene as the hydrogen donor in EtOH was used. This resulted in compound **5**, isolated as shiny white flakes. Alkylation of this material using methyl bromoacetate in MeCN in the presence of 1,8-bis(dimethylamino)naphthalene gave a clean conversion to tetraalkylated product (**6**). The t-Boc protection was removed with TFA/CH_2Cl_2 at RT yielding the tetramethyl ester of the amino-BAPTA (**7**).[9] Alkaline hydrolysis of the tetraester was carried out in 1 M NaOH and the acid form was precipitated from the solution on acidification by the addition of concentrated HCl. Thus, we report here a straight-forward synthesis of a conjugatable form of BAPTA with an overall yield of 40%. This compound is likely to prove valuable in the development of novel conjugates for radiotherapy and new fluorescent chemosensors selective for calcium ion.

We gratefully acknowledge support from TWAS (RGA No. 96-140 RG/CHE/AS).

0040-4039/98/$ - see front matter
PII: S0040-4039(98)02008-5



Scheme 1. i) Ac_2O/H_2O, 50 °C, 2 hrs; ii) 3-(2-bromoethoxy)-4-nitrotoluene, K_2CO_3, DMF, 120 °C, 4 hrs; iii) 3 M HCl/EtOH; iv) $(boc)_2O$, Et_3N, CH_2Cl_2; v) 10% Pd-C, cyclohexene, EtOH, reflux; vi) $BrCH_2COOMe$, MeCN, proton sponge, reflux; vii) TFA/CH_2Cl_2.

References and Notes:

* Author to whom correspondence should be addressed. E-mail: akkayaeu@rorqual.cc.metu.edu.tr

1. Bernard, H.; Yaouanc, J..J.; Clement, J. C.; des Abbayes, H.; Handel, H. *Tetrahedron Lett.* **1991**, *32*, 629.
2. Filali, A.; Yaouanc, J. J.; Handel, H. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 560.
3. McMurry, T. J.; Brechbiel, M.; Kumar, K.; Gansow, O. A. *Bioconjugate Chem.* **1992**, *3*, 108.
4. Ruser, G.; Ritter, W. Maccke, H. R. *Bioconjugate Chem.* **1990**, *1*, 345.
5. Helps, I. M.; Parker, D.; Morphy, J. R.; Chapman, J. *Tetrahedron Lett.* **1989**, *45*, 219.
6. Mishra, A.K.; Draillard, K.; Faivre-Chauvet, A.; Gestin, J.-F.; Curtet, C.; Chatal, J.-F. *Tetrahedron Lett.* **1996**, *37*, 7515.
7. Tsien, R. Y. *Biochemistry*, **1980**, *19*, 2396.
8. (a) Grynkiewicz, G.; Poenie, M.; Tsien, R. Y. *J. Biol. Chem.* **1985**, 260, 3440. (b) Minta, A.; Kao, J. P. Y.; Tsien, R. Y. *J. Biol. Chem.* **1989**, 264, 8171. (c) Akkaya, E. U.; Lakowicz, J. R. *Anal. Biochem.* **1993**, *213*, 285. (d) Akkaya, E. U.; Turkyilmaz, S. *Tetrahedron Lett.* **1997**, *38*, 4513.
9. Characterization of compound **7**: ^{1}H-NMR ($CDCl_3$, 400.1 MHz) δ 2.26 (s, 3H, $ArCH_3$), 3.60 (s, 12H, ($COOCH_3$x4), 4.12 (s, 4H, (NCH_2COx2), 4.15 (s, 4H, (NCH_2COx2), 4.23 (s, 4H, $ArOCH_2CH_2OAr$), 5.20 (s, 2H, $ArNH_2$), 6.31 (m, 3H, ArH), 6.46 (s, 1H, ArH), 6.51 (d, 1H, ArH), 6.65 (s, 1H, ArH). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 21.0, 51.5, 51.6, 53.4, 53.5, 114.1, 119.3, 122.0, 126.4, 128.2, 129.1, 132.1, 132.5, 136.0, 139.9, 147.2, 150.8, 171,8, 172.0. EI Mass Spectrum *m/e* 562 (M^+). Anal. Calcd for $C_{27}H_{35}N_3O_{10}$: C, 57.75; H, 6.28; N, 7.48. Found: C, 57.71; H, 6.62; N, 7.38.