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Synthesis of a novel bifunctional chelating agent for actinium complexation

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Abstract

A novel bifunctional chelating agent for actinium was synthesized in eight steps. Bimolecular cyclization between an iminodiester and a polyamine was achieved through the action of a molar equivalent of sodium methoxide.

Immunotherapy with radiolabeled antibodies should allow fairly specific targeting of some cancers.[1,2] One promising candidate for such applications[3] is ^{225}Ac, an α-emitter. The very short range (< 100 μm) of α particles and their high energy transfer should be conducive to efficient destruction of tumor cells, whereas normal cells should be relatively spared. The development of new bifunctional chelating agents (BCAs) is essential for this purpose, but no suitable BCA has been reported for ^{225}Ac.[4–6]

Our investigations, in agreement with other studies,[5] indicated that HEHA (1,4,7,10,13,16-hexaazacarboxylmethyl-1,4,7,10,13,16-hexaazacyclooctadecane) was the best candidate for ^{225}Ac complexation (Scheme 1), which led us to synthesize the C-functionalized analogue.

We prepared 2-(4-isothiocyanatobenzyl)-1,4,7,10,13,16-hexakis (2-carboxymethyl)hexaazacyclooctadecane, which is functionalized at C-2 on the ring by an isothiocyanate termination for covalent attachment to biomolecules (Scheme 2).

A commercial product, 4-nitrophenylalanine **1**, was used as starting material. Treatment of **1** with HCl gas in methanol yielded 4-nitrophenylalanine methyl ester hydrochloride. *N*-((methoxycarbonyl)methyl)-4-nitrophenylalanine methyl ester was prepared by reacting 3 equivalents of

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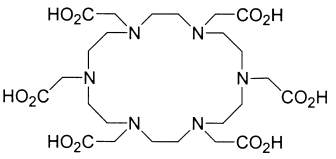
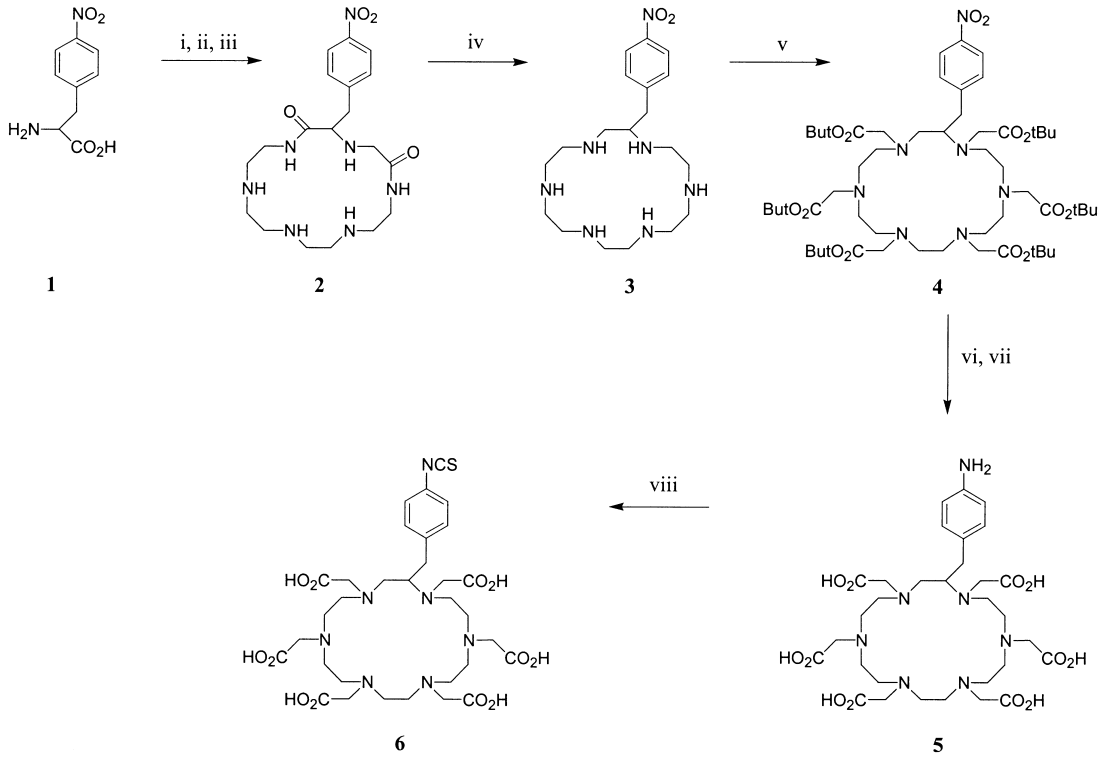


Scheme 1. HEHA



Scheme 2. Reagents: (i) MeOH/HClg; (ii) $NEt_3/BrCH_2CO_2Me/THF$; (iii) NaOMe/tetraethylenepentamine/MeOH/reflux; (iv) BH_3/THF; (v) $Na_2CO_3/BrCH_2CO_2tBu/DMF$; (vi) $SnCl_2/MeOH$; (vii) TFA; (viii) $CSCl_2$

methylbromoacetate and triethylamine with 1 equivalent of 4-nitrophenylalanine methyl ester. Treatment with tetraethylenepentamine in the presence of sodium oxide in refluxing methanol induced macrocyclization, producing the cyclic diamide **2** in a 50% yield.[7] Reduction with BH_3 afforded after treatment with HCl gas and purification by anion-exchange chromatography 2-(4-nitrobenzyl)-1,4,7,10,13,16-hexaazacyclooctadecane **3** in a 55% yield. The hexa-*t*-butyl ester **4** was prepared by reacting 6 equivalents of *tert*-butyl bromoacetate and 11 equivalents of sodium carbonate with 1 equivalent of hexaazacyclooctadecane. The nitrobenzyl function was selectively reduced by using tin chloride in ethanol to obtain the aminobenzyl compound. Cleavage of the ester groups with trifluoroacetic acid, followed by purification on an ion-exchange chromatography column, gave *p*-aminobenzyl-HEHA **5**,[8] and treatment with thiophosgene yielded the final compound, *p*-isothiocyanatobenzyl-HEHA **6**.

Construction of the polyazamacrocycle ring is crucial for the successful synthesis of a macrocycle BCA. However, previously reported cyclization methodologies[9–14] proved unsatisfactory in our

hands. The reaction between *N*-methoxycarbonylmethyl-*p*-nitrophenylalanine methyl ester and tetraethylenepentamine, upon refluxing in methanol for several days in the absence of sodium methoxide, failed to yield the desired product. Therefore, an improved procedure was developed for the bimolecular cyclization between an iminodiester and a polyamine through the action of a molar equivalent of sodium methoxide. A 50% yield was obtained, which enabled us to prepare the bifunctional dioxoaza macrocycle without any need for high dilution. This method is simple and easy to perform, allowing the preparation of functionalized macrocyclic polyamines of varying ring sizes.

References

1. Couturier, O.; Faivre-Chauvet, A.; Filippovich, I. V.; Thedrez, P.; Saï-Maurel, C.; Bardiès, M.; Mishra, A. K.; Gauvrit, M.; Blain, G.; Apostolidis, C.; Molinet, R.; Abbé, J. C.; Bataille, R.; Wijdenes, J.; Chatal, J. F.; Chérel, M. *Clin. Cancer. Res.* **1999**, *5*, 3165–3170.
2. Macklis, R. M.; Kinsey, B. M.; Kassis, A. I.; Ferrara, J. L.; Atcher, R. W.; Hines, J. J.; Coleman, C. N.; Adelstein, S. J.; Burakoff, S. J. *Science* **1988**, *240*, 1024–1026.
3. Kaspersen, F. M.; Bos, E.; Doornmalen, A. V.; Geerlings, M. W.; Apostolidis, C.; Molinet, R. *Nucl. Med. Commun.* **1995**, *16*, 468–476.
4. Davis, I. A.; Glowienka, K. A.; Boll, R. A.; Deal, K. A.; Brechbiel, M. W.; Stabin, M.; Bochsler, P. N.; Mirzadeh, S.; Kennel, J. S. *Nucl. Med. Biol.* **1999**, *26*, 581–589.
5. Deal, K. A.; Davis, I. A.; Mirzadeh, S.; Kennel, J. S.; Brechbiel, M. W. *J. Med. Chem.* **1999**, *42*, 2988–2992.
6. Grote Gansey, M. H. B.; de Haan, A. S.; Bos, E. S.; Verboom, W.; Reinhoudt, D. N. *Bioconj. Chem.* **1999**, *10*, 610–623.
7. Preparation of **2**: Sodium (20 mmol) was dissolved in dry methanol (100 ml) at room temperature under a nitrogen atmosphere, and tetraethylenepentamine (18 mmol) and *N*-((methoxycarbonyl)methyl)-4-nitrophenylalanine methyl ester (18 mmol) were then added to this solution. After the solution was refluxed for 72 h, the solvent was removed and the residue was purified on silica gel chromatography with chloroform:methanol:NH_3 (aq) (75:20:5), affording a brown powder with a yield of 50%.
8. All compounds gave satisfactory spectroscopic and analytical data. Representative data for selected compounds are: compound **2**: MS (M+1): 422, IR (Kr, cm^{-1}): 3287 (NH), 3287–2842 (Ar–C–H), 1656 (C=O), 1517 and 1345 (NO_2), ^1H NMR (250 MHz, $CDCL_3$): δ 8.17 (d, 2H), 7.57 (s, NH amide), 7.40 (d, 2H), 7.27 (s, NH amide), 3.14–3.48 (m, 9H), 2.6–2.9 (m, 11H), ^{13}C NMR ($CDCl_3$): CO: 175, 145, 130, 123, 55, 52, 40; compound **3**: MS (M+1): 394, IR (Kr, cm^{-1}): 3428 (NH), 2961–2759 (Ar–C–H), 1518 and 1349 (NO_2), ^1H NMR (250 MHz, $CDCL_3$): δ 8.06 (d, 2H), 7.27 (d, 2H), 2.3–2.9 (m, 25H); compound **5**: MS (M+1): 712, ^1H NMR (250 MHz, D_2O): δ 7.08 (d, 2H), 6.80 (d, 2H), 2.5–4.0 (m, 37H).
9. Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268–2270.
10. Vellacio Jr., F.; Penzar, R. V.; Kemp, D. S. *Tetrahedron Lett.* **1977**, *6*, 547–550.
11. Tabushi, I. *Tetrahedron Lett.* **1977**, *12*, 1049–1052.
12. Moi, M. K.; Meares, C. F. *J. Am. Chem. Soc.* **1988**, *110*, 6266–6267.
13. Krakowiack, K. E.; Bradshaw, J. S.; Izatt, R. M. *J. Heterocycl. Chem.* **1990**, *27*, 1585–1589.
14. McMurry, T. J.; Brechbiel, M.; Kumar, K.; Gansow, O. A. *Bioconj. Chem.* **1992**, *3*, 108–117.