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Synthesis of a new bifunctional chelating agent for samarium complexation

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Abstract—A novel bifunctional chelating agent for samarium complexation has been synthesised in eight steps. A novel synthetic approach involving the introduction of methanephosphonic functions has been developed. The complexing properties of this compound has also been confirmed by labelling with ^{153}Sm.

The use of ^{153}Sm in cancer radioimmunotherapy protocols will be possible only if stable antibodies radiolabelled with this isotope are formed.[1–5] Stability can be increased by modifying different parameters, such as the number and nature of the coordination sites, the chelation cavity size and the chelating agent skeleton.[6] As the synthesis of bifunctional chelating agents (BCAs) is always very long and with no guarantee of success, a reliable methodology has to be defined to select from several chelating agents and the most promising bifunctional analogue then synthesised. Few new chelating agents have been developed using these criteria and then synthesised in the laboratory.

Our first intention was to design chelating agents with multi-ligating sites that form ^{153}Sm complexes requiring high coordination numbers. The results of preliminary studies[7] enabled us to define the essential parameters (a 10 coordination number, mixed functional groups, a semi-rigid structure), which could influence and thus increase the chelation power of the chelate relative to ^{153}Sm (Fig. 1). This preliminary study enabled us to select a chelating structure prior to starting the synthesis of the BCA analogue.

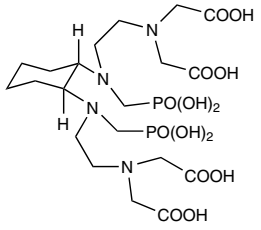

Figure 1.

This paper reports the synthesis of a new BCA for samarium complexation (Scheme 1). 4-Nitrophenyl alanine **1** is used as the starting material and 1-(4-nitrobenzyl)ethylenediamine **2**, which is the most widely used intermediate for the design and synthesis of BCAs was synthesised according to the procedure of Meares and co-workers.[8] The aminophosphonomethylation of compound **2** protected by a methylene bridge between the two nitrogen atoms was carried out as previously described.[10] Compound **3** was obtained through the action of paraformaldehyde and diethyl phosphite in the presence of $NaHPO_4$ in THF. The protecting group was removed under acidic conditions using CH_3OH/HCl (12 M) yielding bisphosphonate **4**.

Dialkylation with the branching group[11] *N*,*N*-bis(ethoxycarbonylmethyl)-2-bromoethylamine **5** was performed in a mixed solvent system in the presence of $NaHPO_4$ at 70 °C for 24 h and afforded compound **6**. Hydrogenation under basic conditions proceeded in

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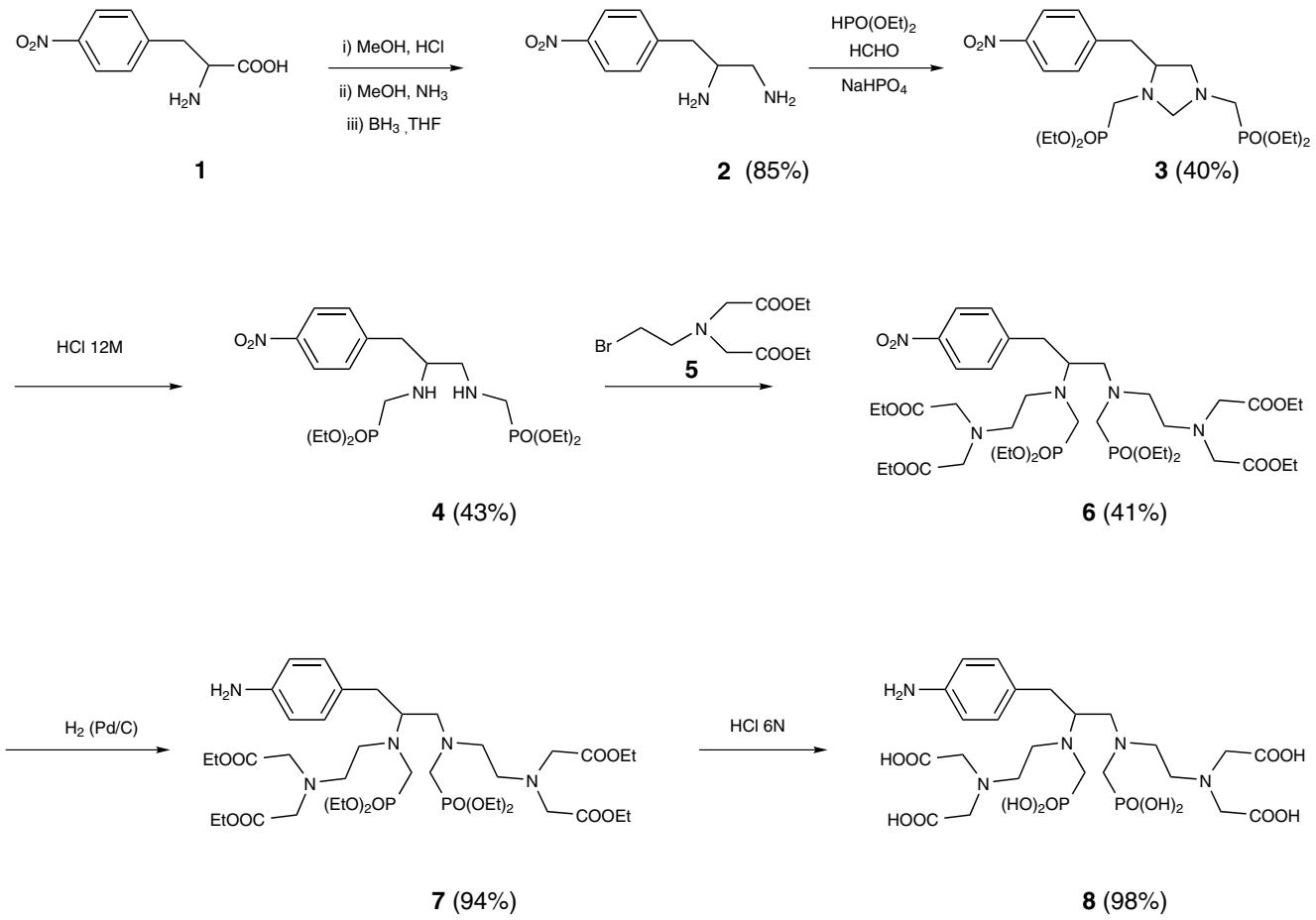

Scheme 1.

high yield to give compound **7**, which was purified by HPLC. Cleavage of the ester groups with hydrochloric acid then yielded the final compound **8**.[12]

Preliminary complexation studies between compound **8** and ^{153}Sm have been carried out. They showed that the kinetics of complexation to **8** is adaptable to radioimmunotherapy protocols.[13]

In conclusion, we describe a new synthesis starting with 1-(4-nitrobenzyl)ethylenediamine **2** that provides access to a new class of bifunctional polyamine, polycarboxylic and polyphosphonic ligands. The key steps in the synthesis were the functionalisation of a bisphosphonate 1-(4-nitrobenzyl)ethylenediamine derivative and the introduction of methanephosphonic functions by a rarely used method. The complexing properties of this mixed BCA have been confirmed by labelling with ^{153}Sm. The next step will be the functionalisation of the semi-rigid chelating agent (Fig. 1) to compare the stability of both BCAs with ^{153}Sm and to show the influence of the semi-rigid structure.

Acknowledgements

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10. Preparation of **4**: **3** was synthesised in our laboratory according to the procedure of Baily and Burgada,[9] with minor modifications. Compound **2** (1.5 g, 7.69 mmol) and diethyl phosphite (2.28 mL, 17.6 mmol) were dissolved in

THF (20 mL). The mixture was stirred at reflux, and paraformaldehyde (0.72 g, 23.6 mmol) was added over a 60-min period. $NaHPO_4$ (1.31 g, 11.5 mmol) was then added and the reaction mixture was stirred at reflux for 18 h. After filtration, the solvent was evaporated to afford a residue that was taken up in $CHCl_3$. The organic layer was washed with brine (200 mL), dried and evaporated to leave a crude oil. Purification by column chromatography (silica gel, EtOAc–EtOH 80:20, CH_2Cl_2–EtOH 95:5) gave **3** (1.57 g, 30.90 mmol, 40%), which was then dissolved in MeOH (15 mL) before addition of 35% HCl (2.7 mL). After overnight stirring at 50 °C, MeOH was removed from the mixture. The pH of the aqueous layer was then adjusted to 10.5 with NaOH 1 M before the bisphosphonate was extracted with $CHCl_3$. The organic layers were collected, dried and evaporated. Purification by column chromatography (silica gel, $CHCl_3$–EtOH 95:5) gave 0.69 g of bisphosphonate **4** (13.9 mmol, 43%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.33 (m, 12H), 2.49 (dd, 1H, $J_2 = 11.9$ Hz, $J_3 = 7.1$ Hz), 2.71 (dd, 1H, $J_2 = 12.0$ Hz, $J_3 = 3.8$ Hz), 2.98 (dd, 2H, $J_2 = 11.9$ Hz), 3.05 (m, 1H), 3.15 (s, 2H), 4.15 (m, 8H), 7.42 (d, 2H, $J_3 = 8.9$ Hz), 8.14 (d, 2H, $J_3 = 8.9$ Hz); ^{13}C NMR (75 MHz $CDCl_3$): δ 16.3, 16.3, 16.4, 16.4, 38.3, 42.5 ($J_{P-C} = 152.8$ Hz), 45.1 ($J_{P-C} = 151.3$ Hz), 52.8, 59.2, 61.8, 61.9, 61.9, 62.1, 123.4, 130.1, 166.5, 146.6; ($M+H^+$): 496.4.

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12. All compounds gave satisfactory spectroscopic and analytical data. Representative data for compound **8** are ^{1}H NMR (250 MHz, D_2O): δ 2.5–3.2 (m, 17H), 4.1 (s, 8H), 7.35 (d, 2H, $J_3 = 7.8$ Hz), 7.44 (d, 2H, $J_3 = 8.3$ Hz); ^{13}C NMR (75 MHz, D_2O): δ 35.1, 51.1, 52.5, 53.5, 53.8, 57.5, 58.3, 58.5, 58.9, 59.5, 64.4, 126.7, 131.0, 134.2, 141.2, 171.7; ($M-H^+$): 670.4.
13. Complexation studies with ^{153}Sm. To form the ^{153}Sm chelating agent complex, 1 equiv of ^{153}Sm (5.3 nmol) was added to 1 equiv of compound **8** (5.3 nmol). The solution was made up to 0.5 mL in 0.02 M citrate buffer (the final pH of the solution was 5) and incubated at 37 °C for 1 h. The complexation was measured on a phosphoimager 445SI after elution with methanol–NH_4OH (50:1) using instant thin-layer chromatography/silica-gel (ITLC/SG) plates.