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Synthesis of new semi-rigid chelating agents for samarium-153

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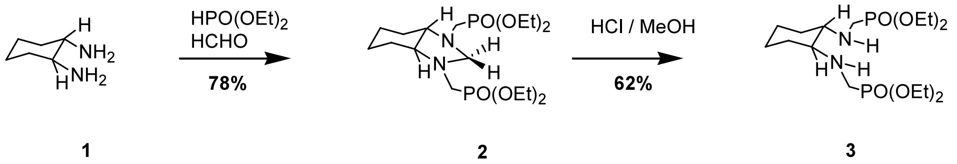
Abstract—This study describes a simple, efficient synthesis pathway from *trans*-1,2-diaminocyclohexane that provides access to a new class of semi-rigid polyamine, polycarboxylic, and polyphosphonic ligands. The key steps in synthesis were the functionalisation (with an appropriate branching group) of a bisphosphonate diaminocyclohexane derivative and the introduction of methanephosphonic functions by a rarely used method. © 2003 Published by Elsevier Science Ltd.

Techniques used in nuclear medicine, such as imaging and radiotherapy, have required the synthesis and evaluation of new chelating agents to provide kinetically stable metal complexes in biological systems.[1] For instance, EDTMP is known to provide extremely stable ^{153}Sm complexes.[2,3] Clinical radiotherapy trials currently in progress with this promising complex have led to the synthesis and evaluation of novel ligands. In this context, our group is investigating the synthesis of a class of novel ^{153}Sm chelators likely to form stable complexes in vivo and perform at least as efficiently as EDTMP.

An important ligand property affecting the stability of the resulting complex is the preorganisation[4,5] brought about by the semi-rigid *trans*-cyclohexylenediamine skeleton through preorientation of chelating functions in a skew position. Special consideration has also been given to chelating agents bearing phosphonic acid moieties because of their enhanced ligating abilities for ^{153}Sm. For instance, our intention was to design chelating agents with multi-ligating sites that form ^{153}Sm complexes requiring high coordination numbers.[6] Accordingly, four novel chelating agents (two with eight and two with ten coordination numbers), all bearing aminophosphonate and mixed chelate groups, were specially synthesised for use as a model in complexation studies with ^{153}Sm.

The access route starting with *trans*-1,2-diaminocyclohexane allowed the synthesis of two polyaminophosphonic acids and two mixed semi-rigid complexing agents. Certain diamines such as *trans*-1,2-diaminocyclohexane **1** (Scheme 1), allowed aminophosphonomethylation of amines protected by a methylene bridge between the two nitrogen atoms of **1**. This protecting group subsequently provides for a different functionalisation on the amine. The Kabachnick–Field reaction reported by Baily and Burgada[7] gave compound **2**, which was prepared from paraformaldehyde and diethylphosphite in THF. The protecting group was removed in soft acidic conditions using CH_3OH/HCl 3 M, yielding bisphosphonate **3**.[8]



Scheme 1.

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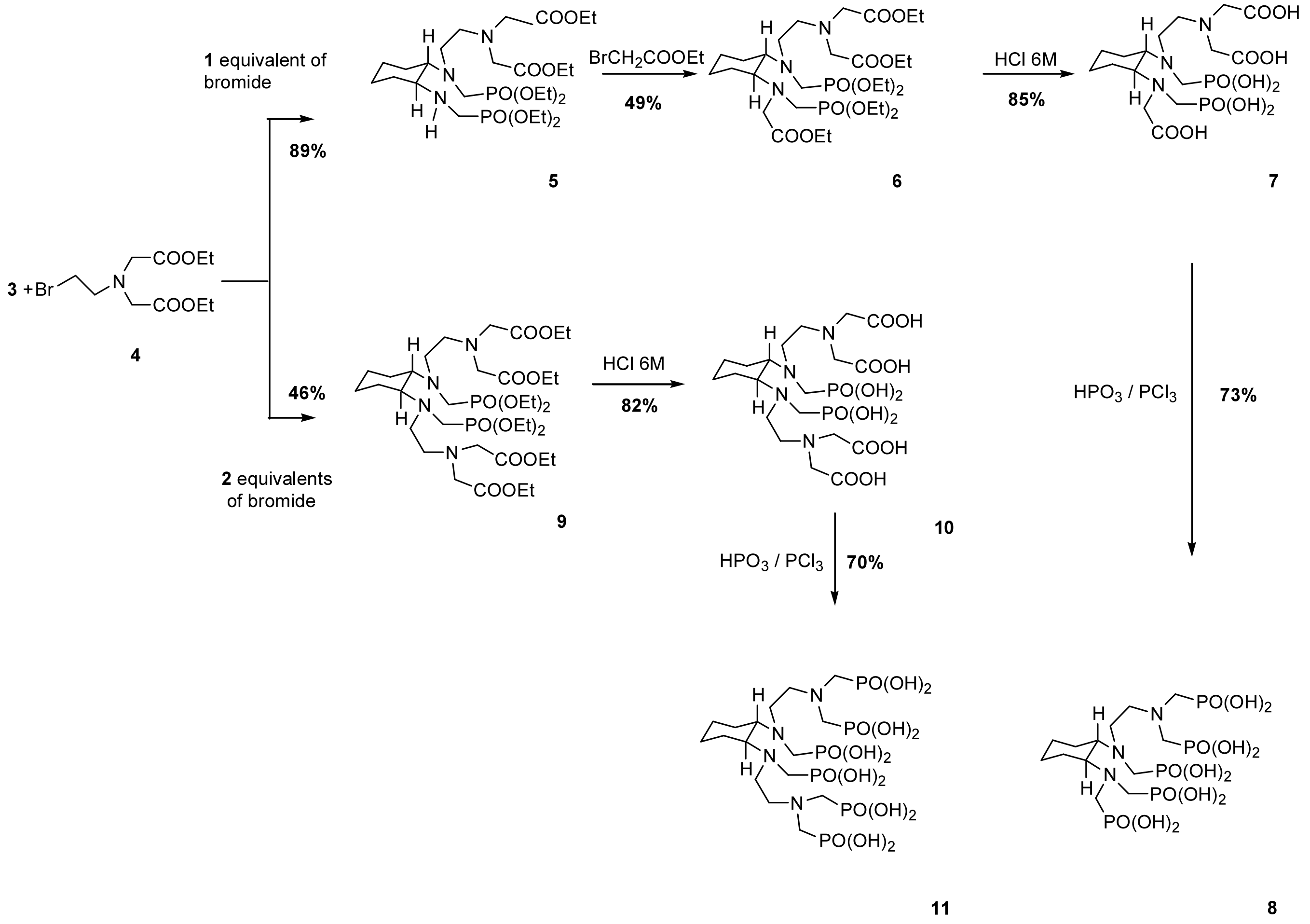

Scheme 2.

This strategy required preparation of protected bis-carboxymethylated amino ethyl bromide. To facilitate deprotecting ethyl ester functions by acid-catalysed hydrolysis, *N*,*N*-bis(ethylacetate)-2-bromoethyl-amine **4** was prepared.[9] Monoalkylation or dialkylation (Scheme 2), depending on the stoichiometry of the reaction with the branching group, was performed in a mixed solvent system (CH_3CN/H_2O, 1:1) in the presence of Na_2HPO_4 at 70°C for 24 h and gave respectively compounds **5** and **9** with a good yield. The synthesis of chelating agents **7** and **8** required an additional step, i.e. alkylation of **5** by ethyl bromoacetate in acetonitrile at 60°C, which gave the mixed ester **6**. Mixed acids **7** and **10** were obtained after acid-catalysed hydrolysis of **6** and **9** in 6 M hydrochloric acid.[10] Finally, in order to generate pentaphosphonic acid **8** and hexaphosphonic acid **11**,[11] carboxylic functions were converted into phosphonic functions according to the method of Krüger and Bauer,[7,12] using H_3PO_3/PCl_3 in toluene.

In conclusion, we described a simple, efficient synthesis pathway from *trans*-1,2-diaminocyclohexane that provides access to a new class of semi-rigid polyamine, polycarboxylic, and polyphosphonic ligands. The key steps in synthesis were the functionalisation of a bisphosphonate diaminocyclohexane derivative and the introduction of methanephosphonic functions. Complexation studies concerning samarium-153 showed that one of the four chelating agents developed, mixed acid **10**, has excellent stability in human serum and deserves further investigation as a potential therapeutic bone agent.

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8. Preparation of **3**: Tetraethylcyclohexane-*trans*-1,2-bis(aminomethylphosphonate) **3** was synthesised in our laboratory according to the procedure of Baily and Burgada,[7] with minor modifications. Freshly distilled *trans*-1,2-diaminocyclohexane **1** (3.6 mL, 30 mmol) and diethyl phosphite (7.24 mL, 60 mmol) were dissolved in THF (40 mL). The mixture was stirred at reflux, and paraformaldehyde (2.8 g, 93 mmol) was added over a 30 min period. The reaction mixture was then stirred at reflux for 4 h. 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, CH_2Cl_2–EtOH, 96:4) gave **2** (9.2 g, 21.60 mmol, 72%), which was then dissolved in MeOH (40 mL) before addition of 35% HCl (15 mL). After overnight stirring at 50°C, MeOH was removed from the mixture. The aqueous layer was then adjusted to 50 mL with H_2O and neutralised by $NaHCO_3$ before bisphosphonate was extracted by $CHCl_3$. Organic layers were collected, dried, and evaporated to give 5.6 g of bisphosphonate (13.52 mmol, 62%, 45% overall). ^{1}H NMR ($CDCl_3$): δ 1.10 (m, 2H), 1.27 (t, 12H), 1.48 (m, 2H), 1.76 (m, 2H), 2.13 (m, 2H), 2.98 (m, 2H), 3.10 (t, 2H), 3.35 (t, 2H), 4.12 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 16.36, 16.39, 16.45, 16.38, 24,01, 28.23, 39.67 ($J_{P–C}=156$ Hz), 60.74, 60.89, 63.16, 63.23, 63.26, 63.33; ($M+H^+$): 415. Anal. ($C_{16}H_{36}N_2O_6P_2$) C, H, N.
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10. Preparation of **7**: Compound **6** (0.5 g; 0.7 mmol) was dissolved in 6 M aqueous hydrochloric acid (10 mL) and heated to reflux overnight. The refrigerant was removed, and the reaction mixture was kept at 70°C until dryness. The solution was precipitated from HCl/acetone. The precipitate was collected by filtration, washed with acetone, and dried under vacuum to obtain acid **7** as a white powder (0.37 g, 85%): ^{1}H NMR (D_2O): δ 1.25–1.55 (m, 4H), 1.82 (m, 2H), 2.18 (m, 2H), 2.75 (m, 2H), 3.10–3.13 (m, 4H), 3.25 (m, 2H), 3.73 (m, 4H), 4.19 (s, 4H); ^{13}C NMR (D_2O): δ 25.56, 25.73, 26.61, 26.81, 50.23, 53.17, 54.74, 55.61, 57.93, 58.49, 60.12, 61.25, 64.59 (CH), 66.09 (CH), 171.33, 171.48, ($M–H^+$): 518. Preparation of **10**: Compound **9** (0.5 g; 0.59 mmol) was treated in an identical manner to that described above for preparation of mixed acid **7** yielding a white powder (0.31 g, 82%); ^{1}H NMR (D_2O): δ 1.26 (m, 2H), 1.45 (m, 2H), 1.75–2.00 (m, 4H), 2.80 (m, 2H), 3.00–3.70 (m, 12H), 4.10 (br s, 8H); ^{13}C NMR (D_2O): δ 23.66, 24.09, 45.69 (d, $J_{C–P}=145$ Hz), 49.35, 52.35, 55.43, 63.51, 169.18; ^{31}P NMR (D_2O): δ 15.8; ($M–H^+$): 619.
11. Preparation of **8**: A mixture of **7** (0.1 g; 0.193 mmol) and phosphorous acid (63 mg; 0.77 mmol) in 10 mL of dry toluene was heated to 80°C and stirred for 30 min. PCl_3 (110 mg; 0.77 mmol) was then added dropwise, and the reaction mixture was kept at this temperature for 20 h before being cooled to room temperature. The solvent was discarded, and the residual product dissolved in a small volume of water to give a cloudy solution. After filtration, the filtrate was evaporated to give a residue, which was purified by precipitation in warm acetone and collected by filtration. The purification step was repeated twice and the precipitate was dried under vacuum to obtain acid **8** as a white powder. (89 mg, 73%): ^{1}H NMR (D_2O): δ 1.19–1.52 (m, 4H), 1.76 (m, 2H), 2.02 (m, 2H), 2.68 (m, 2H), 3.01–3.85 (m, 6H), 3.73 (m, 4H), 4.19 (s, 4H); ^{13}C NMR (D_2O): δ 24.32, 24.63, 26.65, 26.57, 50.65, 51.88, 56.12, 56.24, 58.45, 58.71, 58.87, 64.73 (CH), 65.47 (CH). ($M–H^+$): 626. Preparation of **11**: Compound **10** (0.10g, 0.16 mmol) was treated in an identical manner to that described above for preparation of mixed acid **8** yielding a white powder (86 mg, 70%): ^{1}H NMR (D_2O): δ 1.26 (m, 4H), 1.81 (m, 2H), 2.18 (m, 2H), 2.62 (m, 2H), 2.95–3.70 (m, 12H), 4.18 (s, 8H); ^{13}C NMR (D_2O):[J.1] δ 23.29, 23.75, 24.23, 24.43, 52.48, 53.14, 53.56, 55.75, 55.94, 56.46, 63.56 (CH); ^{31}P NMR: 13.9, 14.7; ($M–H^+$): 763.
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