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Synthesis of novel phosphonated tripodal ligands for actinides chelation therapy

Vincent Chaleix and Marc Lecouvey*

BIOMOCETI (UMR 7033-CNRS), UFR SMBH, Universités Paris XIII-Paris VI, 74, Rue Marcel Cachin, F-93017 Bobigny Cedex, France

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Abstract—Efficient synthetic routes for preparation of a new family of aldehyde–bisphosphonate conjugates were presented. These compounds appeared as promising intermediates for incorporation of bisphosphonate moiety in various substrates under mild conditions. We report here a first application to the synthesis of a series of three phosphonated tripods designed for actinides chelation therapy.

For many years, different groups have undertaken research work focusing their attention on the biological effects of actinides, with the kidney and bone being the main target organs for uranium poisoning.[1–3] It appears that the major long-term effect of this heavy metal is the induction of cancer.[4] Currently, decorporation therapy based on the use of a chelating agent is a more effective method of reducing the radiation dose and chemical toxicity of actinides to people following accidental internal contamination with a transportable radionucleoid.

In contrast with other actinides, such as plutonium or americium where chelating agent treatment is efficient,[5] this therapeutic approach used for uranium contamination is widely ineffective. During the past decade, promising results have been obtained with polydentate ligands bearing hydroxypyridinone or phosphonate units, but the search for new, more efficient chelators still represents a considerable challenge.[6,7] Design of good candidates for decorporation therapy is complex and is based on various physicochemical and biological criterions such as stereocompatibility, denticity, toxicity or biodistribution.[8,9]

Compounds bearing methylene bisphosphonic moieties possess well-known strong chelating properties, due to their ability to form very stable complexes with many metals in a bidental manner. This tendency is in agreement with *hard and soft acid/base* (HSAB) rule, with these ligands having a very high affinity for heavy metal ions such as uranyl. Moreover, it was established that a well-preorganized sequestering agent can achieve many orders of magnitude of additional stability upon metal complex formation.[10,11] On the basis of these criterions, we recently described convenient methods for the synthesis of new tripodal phosphonated preorganized ligands, where the key step was the condensation of the carboxy-bisphosphonate groups onto several tripodal triamine such as triaminotriethylamine.[12] Though the resulting compounds show, as expected, excellent complexation properties toward uranyl in vitro,[13] poor results were obtained for decorporation in vivo. One hypothesis to explain this result was the relative sensitivity of amide bonds toward enzymatic hydrolysis and the presumed resulting destructuration of the sequestering molecule. In order to avoid this, we propose the synthesis of new chelating agents (Fig. 1) derived from

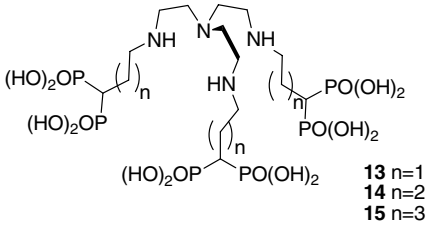

Figure 1. Structures of chelating agents synthesized.

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* Corresponding author. Tel.: +33 148387709; e-mail: marc.lecouvey@smbh.univ-paris13.fr

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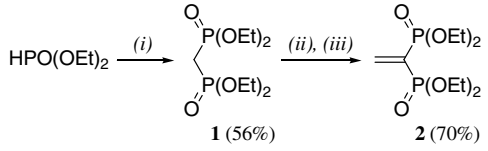
triaminotriethylamine bearing bisphosphonic groups via an amine linkage. The use of reductive-amination strategy was the methodology of choice to accomplish this task.

Application of this methodology to the synthesis of tripods **13**–**15** involved the development and preparation of three tetraethylbisphosphonate precursors **7**–**9** bearing aldehyde functions. For the synthesis of these precursors, compounds **1** and **2** were used as the starting material (Scheme 1).

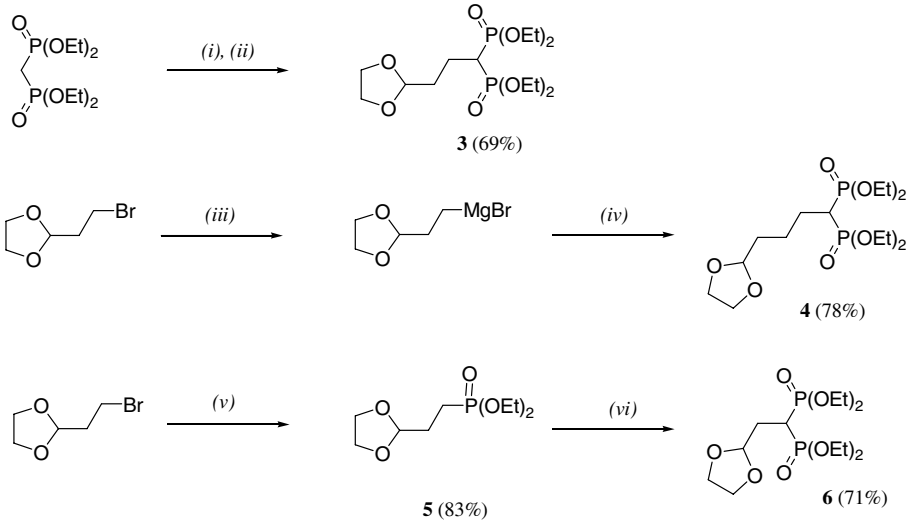
Tetraethyl methylenebisphosphonate **1** was synthesized from sodium ethoxide, diethylphosphite and methylene chloride in a one-pot procedure described by Hormi et al.[14] Ethylidene bisphosphonate **2**, was prepared in multigram quantities from **1** by the method reported by Degenhardt and Burdsall.[15] Briefly, treatment of **1** with paraformaldehyde in the presence of diethylamine in methanol produced tetraethyl β-methoxyethylene-1,1-bisphosphonate, which was dehydrated under Dean–Stark conditions to give **2** in 70% overall yields. Formation of requisite aldehyde precursor with variable carbon chain length was achieved by using stable 1,3-dioxolane as protecting group. Synthetic routes are described in Scheme 2.

Tetraethyl ethenylidenebisphosphonic ester **2**, due to its electrophilic character, can undergo efficient Michael type addition reactions with various nucleophiles such as Grignard reagents.[16] This strategy, applied to the formation of compound **4**, gave excellent results. The reaction was run by the dropwise addition of a THF solution of the suitably functionalized organomagnesium reagent, obtained from commercially available 2-(2-bromoethyl)-1,3-dioxolane, to a stirred solution of **2** in THF under Argon at −15 °C. The expected 1,4-addition was completed after 30 min and compound **4** was isolated in good yield (78%) after flash-chromatography ($CHCl_3$–EtOH, 100:0–98:2). No product derived from 1,2-addition was observed. For the functionalized bisphosphonate **3**, which contains one less methylene group, this synthesis route was not applied because of the impossible formation of the appropriated Grignard reagent from bromomethyl-1,3-dioxolane. Thereby, we turned our attention to the reactive tetraethyl methylenebisphosphonate carbanion. This carbanion, prepared from the treatment of **1** with sodium hydride in THF at 0 °C, was efficiently reacted with 2-(2-bromoethyl)-1,3-dioxolane as the alkylation reagent. Typically, compound **3** was obtained by the slow addition of the carbanion to a stirred solution of bromoethyl-1,3-dioxolane in THF at 0 °C. The reaction was monitored by ^{31}P NMR. The total disappearance of the characteristic carbanion signal at 42 ppm indicated the end of the reaction after 48 h. The desired compound **3** was isolated in 69% yield by flash-chromatography ($CHCl_3$–EtOH, 100:0–98:2). Attempts to synthesize bisphosphonate **6** under the same reaction conditions by treatment of the carbanion with bromomethyl-1,3-dioxolane led to poorer results, in the yield not exceeding 10%. Therefore we chose to proceed with the synthesis of **6** in two steps. In a first step, diethyl (2-(1,3-dioxolane-2-yl)ethylidene)phosphonate **5** was prepared by the classical Michaelis–Arbusov reaction, in which 2-(2-bromoethyl)-1,3-dioxolane was heated with triethyl phosphite to give the corresponding product in good yield (83%) after vacuum distillation. The phosphonate intermediate **5** was then treated by butyl lithium in THF and then subjected to a substitution reaction with diethyl chlorophosphate. The reaction was carried out



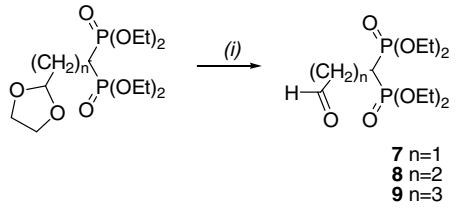
1 (56%) 2 (70%)

Scheme 1. Reagents and conditions: (i) EtONa, 1 h, rt and when excess CH_2Cl_2, rt, 2 weeks; (ii) Et_2NH, $(CH_2O)_n$, MeOH, Δ; (iii) cat. TsOH, toluene, Δ, 24 h.



3 (69%) 4 (78%) 5 (83%) 6 (71%)

Scheme 2. Reagents and conditions: (i) NaH, dried THF, 1 h, 0 °C; (ii) 2-(2-bromoethyl)-1,3-dioxolane, dried THF, 0 °C–rt, 48 h; (iii) Mg, THF, −15 °C, 2 h; (iv) compound **2**, THF, −15 °C, 30 min; (v) $P(OEt)_3$, reflux, 6 h; (vi) *n*-BuLi, dried THF, −78 °C, 1 h then $ClPO(OEt)_2$, −78 °C to rt, 24 h.



Scheme 3. Reagents and conditions: (i) CH_3COOH, H_2O 80/20, 60 °C, 4 h.

under an inert argon atmosphere with mechanical stirring at −78 °C. As for the other bisphosphonate previously described, the reaction was followed by ^{31}P NMR spectroscopy. Finally, the expected compound **6** was obtained after flash-chromatography in satisfactory yield (58% overall yield). The unprotected aldehydes **7**, **8** and **9** were then recovered by classical hydrolysis of acetal groups (Scheme 3).

Treatment of **3**, **4** and **6** with acetic acid in water (8/2) at 60 °C during 3 h followed by usual workup and flash-chromatography ($CHCl_3$–EtOH, 98:2–90:10) gave the expected aldehyde–bisphosphonate conjugates in good yields (72–75%).

The next step of our strategy was the formation of tripod via the coupling of the reactive phosphorylated precursors **7**–**9** with tris(2-aminoethyl)amine (TREN) by reductive amination. To avoid the formation of a more complex macro-structure due to further polyalkylation of each amino group, we opted for an indirect reductive amination as shown in Scheme 4.

The imines were synthesized by refluxing TREN (1 equiv) and aldehyde **7**, **8** or **9** (3 equiv) in toluene. Removal of water was achieved by using Dean–Stark apparatus. The reaction was monitored by ^{31}P NMR and after 1 h, the reaction mixture was complete and evaporated to dryness. In a second step, crude tripodal imines were reduced to the corresponding amines **10**, **11** and **12** by reaction with $NaBH_3CN$ in MeOH. $NaBH_3CN$ is one of the most frequently used reducing agent for reductive amination and it appeared in this case, perfectly compatible with tetraethyl bisphosphonate. Indeed, no side reaction like phosphonate reduction was observed and after a reaction time of 48 h, the expected tripods **10**–**12** were obtained after usual workup and flash-chromatography in good yield (68%, 80% and 75% respectively). Dealkylation of bisphosphonic ester functions was carried out by using trimethylsilyl bromide in CH_2Cl_2 followed by methanolysis.[17] In this way, the free tripodal bisphosphonic acids **13**, **14** and **15** were obtained in satisfactory yields after purification by RP-C18 column chromatography (73%, 79% and 76% respectively). All new compounds reported here gave analytical and spectral data consistent with the assigned structures.[18]

In summary, we report in this paper for the first time convenient synthetic route for the preparation of a new family of aldehyde–bisphosphonate conjugates. These compounds appear as promising intermediates for incorporation of a bisphosphonate moiety in various substrates with the use of mild conditions. Application to the synthesis of a series of three phosphonated tripods, produced compounds which exhibit excellent results in uranyl complexation studies. Further investigation to evaluate uranyl decorporation properties in vivo are actually in progress. Data on the chelating and decorporation potency of this new sequestering agents will be published elsewhere.

Acknowledgements

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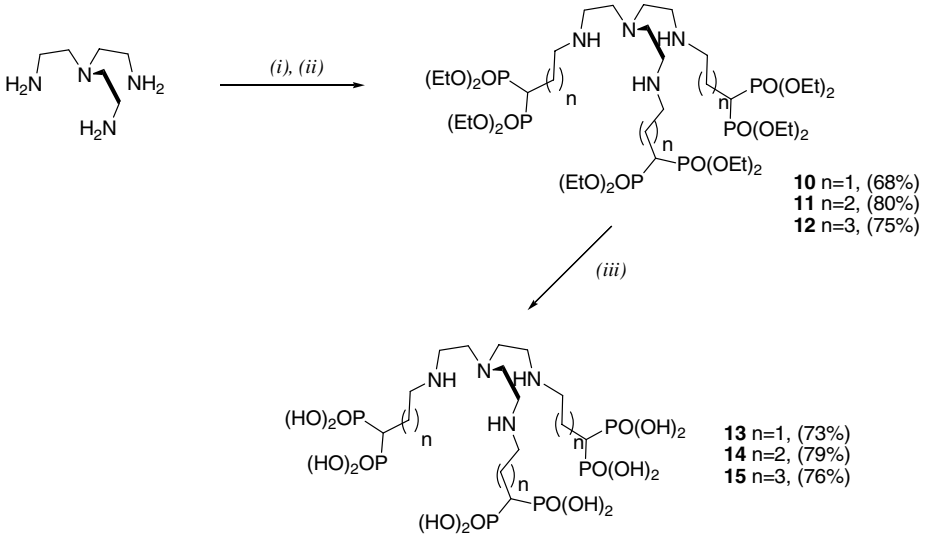

Scheme 4. Reagents and conditions: (i) compound **7**, **8** or **9**, toluene, $T = 110$ °C, Dean–Stark, 2 h; (ii) MeOH, $NaBH_3CN$, 25 °C, 48 h; (iii) dried CH_2Cl_2, Me_3SiBr, 25 °C, 72 h and then MeOH, 25 °C, 2 h.

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18. All new compounds reported here gave analytical and spectral data consistent with the assigned structures. NMR spectra were recorded on a VARIAN Gemini 200 spectrometer. Chemical shifts are reported in ppm. ^{31}P NMR spectra were recorded with phosphoric acid as external references Selected experimental data: compound **3**: yield = 69% $R_f = 0.42$ ($CHCl_3$/EtOH: 98/2); ^1H NMR (200 MHz, $CDCl_3$): 1.26 (t, 12H, O–CH_2–CH_3, $J = 7.0$ Hz); 1.7–2.2 (m, 5H, CH_2–CH_2–CH), 3.73–3.92 (m, 4H, O–CH_2–CH_2–O), 4.11 (quint., 8H, O–CH_2–CH_3, $J = 7.0$ Hz); 4.79 (t, 1H, O–CH–O, $J = 6.8$ Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): 15.79, 19.32, 31.94, 35.71 (t, $J_{CP} = 131.28$), 62.00, 64.30, 103.59. ^{31}P NMR {^1H} (80 MHz, $CDCl_3$): 24.34. Compound **8**: yield = 73% $R_f = 0.38$ ($CHCl_3$/EtOH: 95/5); ^1H NMR (200 MHz, $CDCl_3$): 1.34 (t, 12H, O–CH_2–CH_3, $J = 7.0$ Hz); 2.12–2.31 (m, 2H, –CH–CH_2–CH_2), 2.42 (tt, –CH–CH_2–, $J_{HH} = 6.6$ Hz, $J_{PH} = 23.8$ Hz), 2.87 (t, 2H, –CH_2–CHO, $J = 7.0$ Hz), 4.17 (dquint., 8H, O–CH_2–CH_3, $J_{HH} = 7.4$ Hz, $J_{PH} = 3.2$ Hz), 9.77 (s, 1H, CH_2–CHO). ^{13}C NMR (50.3 MHz, $CDCl_3$): 16.38, 20.81, 32.28, 35.20 (t, $J_{CP} = 133.89$ Hz), 62.95, 175.45. ^{31}P NMR {^1H} (80 MHz, $CDCl_3$): 23.58. Compound **14**: ^1H NMR (200 MHz, D_2O): 1.82–2.35 (m, 15H, –CH_2–CH_2–CH–), 2.35–2.45 (m, 6H, –NH–CH_2–), 2.52–2.63 (m, 12H, N(–CH_2–CH_2–NH–)$_3$; ^{13}C NMR (50.3 MHz, D_2O): 20.6, 27.6, 32.2, 47.6, 51.2, 56.3; ^{31}P NMR {^1H} (80 MHz D_2O): 20.06.