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Synthetic strategy of new powerful tris-bisphosphonic ligands for chelation of uranyl, iron, and cobalt cations

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Abstract—New tripodal uranyl ion chelators containing *gem*-bisphosphonic units have been synthesized. All bisphosphonic units present a side chain with 0, 1, or 2 methylene group terminated by $-NH_2$ or $-CO_2H$ group. These units were respectively coupled with a $-CO_2H$ or $-NH_2$ functions of a suitable tri-functional platform. The shape and size of the new designed ligands were selected and validated through computer molecular modelization.

Numerous tripodal hexadentate ligands have already been reported as therapeutic chelating agents. Some of these compounds are siderophore analogues of enterobactin, desferrioxamine or ferrichrome. These ligands may be used for the treatment of accidental intoxication by actinides or other transition metals like Fe and Co.[1,2] The low toxic *gem*-bisphosphonic species, like HEDP or MAMDP, have proved their efficiency to make very stable UO_2^{2+} complexes.[3,4] To improve the association constant reported for these species, we have recently synthesized a number of hexadentate ligands bearing three bidentate *gem*-bisphosphonic units all able to form 1-1 complexes with uranyl, Fe, and Co cations.[5,6] In a similar way the new compounds **1a**, **2d**, **2e** (Fig. 1), have been synthesized.

These units were designed as an esterified *gem*-bisphosphonic framework bearing an NH_2 group (compounds **a**–**c** Table 1) or a COOH group (compounds **d**–**h** Table 1). An amidic coupling reaction has been used to bind these bidentate units with a suitable tripodal, linear, or cyclic molecular backbones such as triacids or polyamines.[5,6,12]

The *gem*-bisphosphonic units were designed because their structures are in agreement with the following criteria: (a) denticity, (b) hard–soft principle, (c) high ionization at physiological pH, (d) Free P–OH group so as to improve their solubility in aqueous solution or the possibility of hydrogen bonding with the apical uranyl oxo group, (e) the ability of *gem*-bisphosphonic unit to form a six-membered chelate ring from one deprotonated oxygen atom of both phosphonic groups and the metallic atom as proved by X-ray diffraction,[7] and finally, (f) the possibility to form a hexacoordinated monomeric complex bearing three chelate rings, hence the low sensitivity to 'dilution effect' (the weak dissociation of the complex in very dilute solution highlighted by Martell and co-workers).[8]

The size of ligand and the required arm length are the major structure determinants, for example, excessive spacing between the uranyl apical oxo group and the carbon (or nitrogen) anchor in ligands **2d** or **2′** (Fig. 2) would certainly decrease the entropic contribution of the complex, whereas an insufficient spacing would compromise the formation of a stable chelate. In a first

Keywords: *gem*-Bisphosphonates; Tripodal ligands; Polyamines; Amino acids; Uranyl ion; Iron; Cobalt; Chelates.
Abbreviations: HEDP, 1-hydroxyethane1,1′-diphosphonic acid; MAMDP, *N*,*N*′-dimethylaminomethylene diphosphonic acid; TREN, Tris(3-aminoethyl)amine; TRPN, Tris(3-aminopropyl)amine; Hopo, Hydroxypyridinone; TMSBr, Trimethyl bromo silane; DFO, Desferrioxamine.
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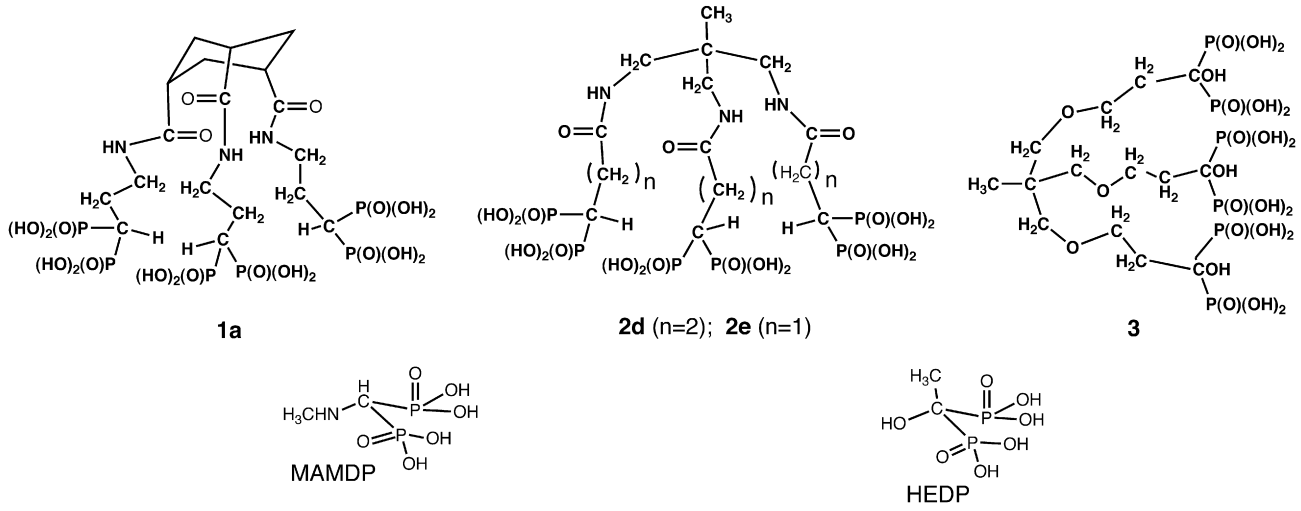
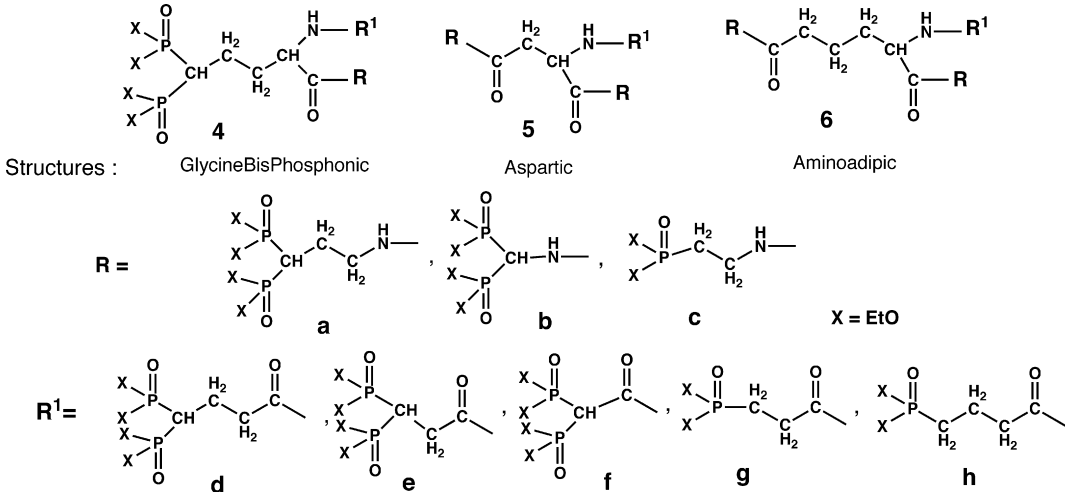


Figure 1.

Table 1.



approach, to optimize the size and the geometry, the computer models of the putative uranyl complex structure have been built, bond lengths and angles based on the RX results available from a dozen of already solved hexadentate complexes including uranyl tricarbonate[9] and then refined by energy minimization (Picture 1). It has been shown that a small change in the structure of the ligand may strongly influence the stability of the complex. For example, starting from TREN the synthesis of tris{2-[(*N*-acetyl-*N*-hydroxy)]glycylaminoethyl} amine (TAGE) has been reported.[10a] The Fe(III)-TAGE complex shows a high stability ($\log\beta = 28.7$), close to the Fe(III)–desferrioxamine complex ($\log\beta = 30.6$) Using TRPN, whose side chains are one methylene group longer than TREN. The same authors synthesized tris[3-(*N*-acetyl-*N*-hydroxy glycylamino)] propyl amine (TAGP). The TAGP-FeIII complex presents a better stability ($\log\beta = 30.6$) identical to DFO.[10b] We have observed a similar effect with TRPN-1,2 Hopo ligand.[11] Hexadentate structure (Fig. 2) resulting from the 1-1 complex is not yet confirmed by single crystal X-ray diffraction, nor the possible equilibrium, in aqueous solution, between the five- and six-coordinated isomers which should be shifted with the pH following a ring-closure/ring-opening process. In spite of this lack of data, some evidence may be obtained from the measurement of the conditional constant (pH 7.4, 5.5 and 9) $\log K_{cond}$.[12] For example,[4] the K_{cond} of the bidentate 1-1 complex HEDP-UO_2^{2+} is about 10,[11] whereas the conditional constant of the presumed hexadentate complex **3**-UO_2^{2+}, (Fig. 1), is about $10^{17.5}$.[12] Compound **3** can be considered as a prototype of tripodal tris HEDP stereochemically compatible with the model presented in Figure 2. All the hexadentate ligands presented here are powerful chelating species[12] for UO_2^{2+} with K_{cond} in the range 10^{17}–10^{19} at pH 7.4. It has been observed that the stability constant and the denticity increase together in the same way: bidentate < tetradentate < hexadentate. The homogeneity of the carriers used (only three $-NH_2$ or three $-CO_2H$ groups) requires a single coupling reaction with three identical bisphosphonic units so as to give symmetrical ligands like **1–3** (Fig. 1).[5,6,12]

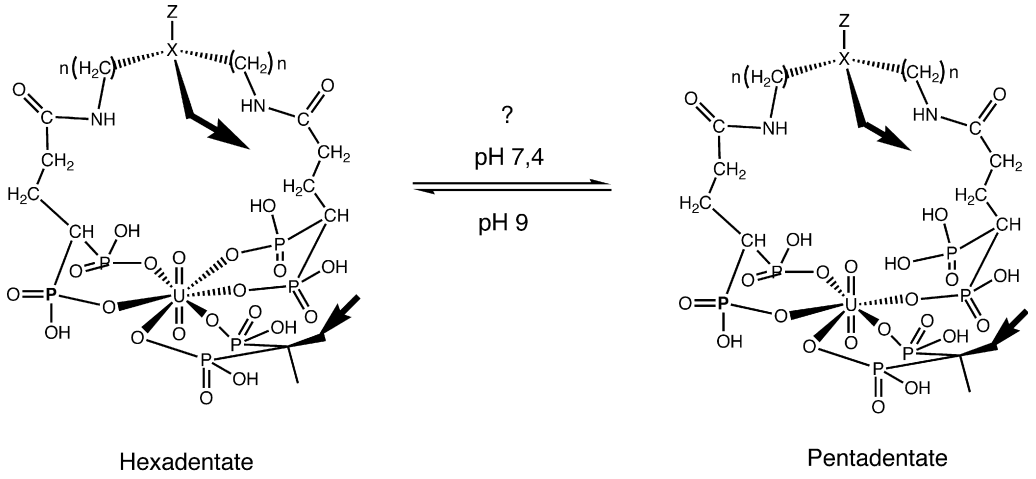
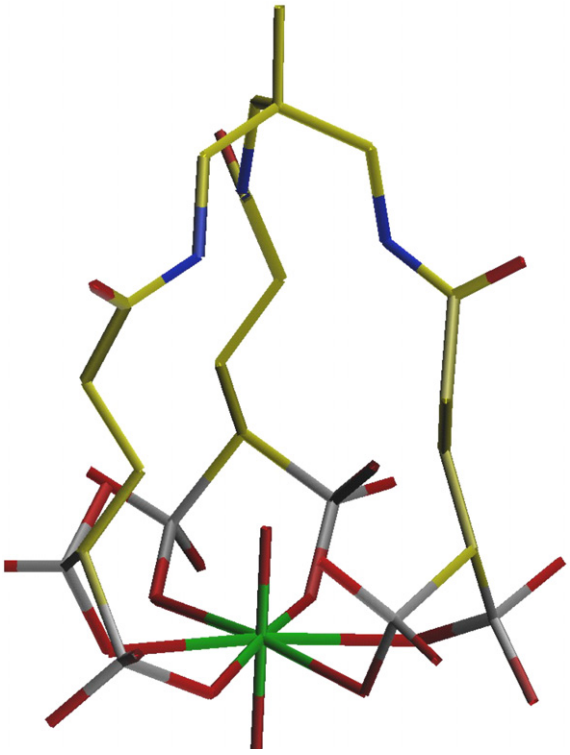


Figure 2.



Picture 1. Molecular model of the expected uranyl complex with ligand **2e**. Colors are for uranium: green, oxygen: red, nitrogen: blue, phosphorus: grey and carbon: yellow. The three six-membered chelate rings are in a boat conformation, in the amidic groups, C(*O*) and N*H* are *anti*. Selected distances: U–O (axial) 1.9 Å, U–O (equatorial) 2.4 Å. Energy minimization was performed with *CHARMM* using standard force-field for light atoms. The uranium coordination, topology parameters were selected from X-ray structures.[9]

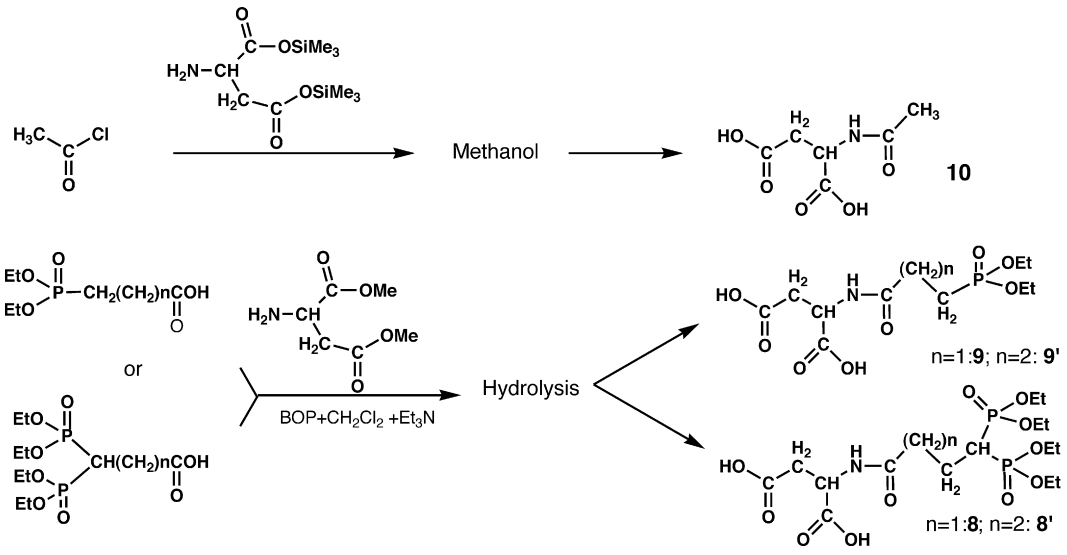
The use of tri-functional amino acids as carrier molecules opens a new way for easy sequential synthesis of unsymmetrical ligands bearing different arm lengths and denticities. In addition, chirality can be introduced in these compounds. Conversely to the symmetric ligands used above, the synthesis requires two steps represented in Schemes 1 and 2.

Table 1 shows the basic models **4**–**6** bearing R and R^1 (R = **a**, **b**, **c**; R^1 = **d**, **e**, **f**, **g**, **h**). The tris (trimethylsilyl) protected[13] aspartic acid or the commercially available dimethoxy aspartic acid can be used (Scheme 1) for the synthesis of intermediates **8**, **8′**, **9**, **9′**, and **10**.

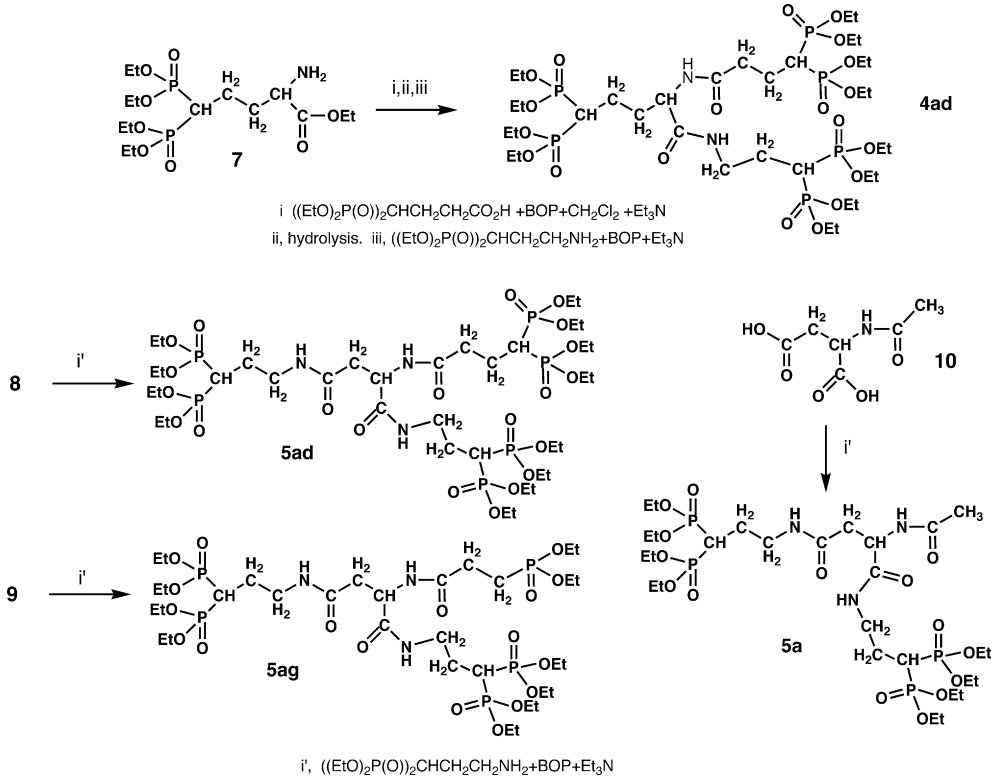
Starting from these intermediates (Scheme 2), ligands **5ad** (hexadentate), **5ag** (pentadentate) and **5a** (tetradentate) were successfully synthesized. To summarize, nine hexadentate, four pentadentate and two tridentate ligands can be obtained, without any tedious protection–deprotection steps, from the aspartic model **5** and units **a** to **h.** The same protocol is used for the synthesis of **6ad** (adipic**)** or **4ad** (glycine bisphosphonic). Compound **7** (Scheme 2) has already been described.[14]

All reactions were carried out in CH_2Cl_2 at 20 °C with BOP (Castro's reagent) as amidic coupling agent following the well-known procedure. Chromatography on silica gel was used for purification. Ligands **4ad**, **5ad**, **5ag**, **5a**, and **6ad** were isolated as bisphosphonic esters. The free phosphonic acid form, necessary to complex metals, was subsequently obtained by treatment with a large excess of TMSBr in CH_2Cl_2 for a few days at 20 °C. The final purification was conducted by acid-base procedure, with Dowex resin AGX8 and if necessary, on Sefadex as sodium salt.[15]

In conclusion, the application of several known principles and the design of a target molecular model has allowed us to synthesize some powerful ligands of the uranyl ion. However the structures of these complexes have not yet been proved by X-ray diffraction nor the equilibrium able to occur by pH variation of their aqueous solutions. All our efforts will point in this direction.



Scheme 1.



Scheme 2.

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15. ^{31}P; ^{1}H; ^{13}C NMR: (Varian Inova 500: ^{1}H 500.6; ^{31}P 200.7; ^{13}C 125.9 MHz and Varian Gemini 200: ^{1}H 200; ^{31}P 80.9; ^{13}C 50.3 MHz).
Ligands obtained from triacid or polyamine carriers: Compound **1a** (ester): ^{31}P NMR: 23.6 ($CDCl_3$). ^{1}H NMR: 1.27 t, *J* 6.95 (36H); 1.57 m (3H); 2.04 m (9H); 2.2 m (3H); 2.97 tt, J_{HP} 24, J_{HH} 5.85 (3H); 3.3 m (6H); 4.09 m (24H) ($CDCl_3$). ^{13}C NMR: 16.4; 25.2; 31.9*; 34.6 t, 133.6; 38.7; 44**; 62.9; 174.5 ($CDCl_3$)* CH cycloh.; **CH_2 Cycloh. Compound **1a** (acid): ^{31}P NMR 21.7 (D_2O) ^{13}C NMR: 38.2 t, *J* 128 (P–CH–P) (D_2O). Compound **2d** (ester): ^{31}P NMR: 23.7 ($CDCl_3$). ^{1}H NMR: 0.8 s (3H); 1.34 t, J_{HH} 7 (36H); 2.13–2.45 m (9H); 2.57 t, J_{HH} 7.03 (6H); 2.92 d, J_{HH} 6.25 (6H); 4.18 p, J_{HH} 7.03 (24H) ($CDCl_3$). ^{13}C NMR: 16.3; 19; 21.7; 34.7; 35.7 t, J_{CP} 133; 42.5; 50.3; 62.9; 172.9. ($CDCl_3$). Compound **2d** (acid): ^{31}P NMR: 22.4 (D_2O, pH 1). ^{31}P NMR: 20.1 (D_2O, pH 14) ^{1}H NMR: 0.68 s (3H); 2.02–2.29 m (9H); 2.45 s broad (6H); 2.91 s (6H) (D_2O, pH 1) ^{1}H NMR: 0.54 s (3H); 1.28 tt, J_{HCP} 22.27 J_{HH} 5.24 (3H); 1.6–1.8 m (6H); 2.1–2.29 m (6H); 2.79 s (6H) (D_2O, pH 14). ^{13}C NMR: 20.7; 24; 37.4; 39.3 t, J_{CP} 127.7; 42.8; 45.6; 178. (D_2O, pH 1). Compound **2e** (ester): ^{31}P NMR: 23.8 ($CDCl_3$). ^{1}H NMR: 0.8 s (3H); 1.3 dt, J_1 7.06 J_2 3.07 (36H); 2.74 dt, J_{HP} 16.24 J_{HH} 6.14 (6H); 3.1 d, *J* 6.4 (6H); 3.25 tt, J_{HH} 6.14 J_{HP} 23.77 (3H); 4–4.19 m (24H); 7.5 t, *J* 6.14 (3H) ($CDCl_3$). ^{13}C NMR: 16.5; 20.3; 32; 32.3 t, J_{CP} 135; 37; 41; 44.2; 62.9 dd, J_1 39 J_2 5.8; 170.8. ($CDCl_3$). Compound **2e** (acid): ^{31}P NMR: 21 (D_2O) pH 1; ^{31}P NMR: 19.56 (D_2O) pH 14. ^{1}H NMR: 0.87 s (3H); 2.7–2.9 m (9H); 3.13 s (6H) (D_2O) pH 1. ^{1}H NMR: 0.89 s (3H); 2.11 tt, J_{HH} 5.7 J_{HP} 21.6 (3H); 2.70–2.77 m (6H); 3.12 s (6H) (D_2O) pH 14.
Ligands obtained from amino acid derivatives as supports: Compound **4ad** (ester): ^{31}P NMR: 23.74; 23.79; 23.97 ($CDCl_3$) ^{1}H NMR: 1.33 t, *J* 7.3 (36H); 2–2.52 m (9H); 2.7–2.9 m (2H); 3.2–3.4 m (2H); 4.1 m (24H); 4.6 m (1H) ($CDCl_3$). Compound **5ad** (ester): ^{31}P NMR: 23.7; 24. ($CDCl_3$). ^{1}H NMR: 1.3 t, *J* 7 (36H); 2–2.1 and 2.1–2.37 m (6H); 2.42 tt, J_{HH} 5.5; J_{HP} 24.7 (3H); 2.55 q, *J* 7.3 (4H); 2.6 d, *J* 9.16 (HMPT); 2.7 m (2H); 3.38 m (4H); 4.13 m (24H) ($CDCl_3$). ^{13}C NMR: 16.3; 21; 25; 33.9; 34.9; 35.4; 36.7 (HMPT); 37.7; 38.5; 48.9; 50; 62.9; 171; 172; 172.5. ($CDCl_3$) dept: 34.8 t, *J* 133.6; 35 t, *J* 133.6; 35.2 t, 133.6; 35.9 t, *J* 131.14; 36 t, *J* 131.5. Compound **5ad** (acid) ^{31}P NMR: 24.4 (D_2O, pH 1). Compound **5a** (ester): ^{31}P NMR: 23.9 ($CDCl_3$). ^{1}H NMR: 1.34 t, *J* 7.03 (24H); 2.08 s (3H); 2.16–2.22 m (4H); 2.39–2.88 m (2+2H); 3.46 m (4H); 4.2 p *J* 6.64 (16H); ($CDCl_3$). ^{13}C NMR: 16.3; 24.9; 31.5 t *J* 116; 33.8; 37.4; 38.5; 50.2; 62.8; 170.4; 171.2; ($CDCl_3$). Compound **5a** (acid): ^{31}P NMR: 22 (D_2O, pH 1). ^{1}H NMR: 1.87 s (3H); 1.9–2 m (4H); 2.15 tt, J_{HP} 23.44, J_{HH} 7 (2H); 2.42–2.64 m (3H); 3.26 m (4H); 4.47 m (1H) (D_2O, pH 1). ^{1}H NMR: (D_2O, pH 14): 1.64 tt, J_{HP} 21.5 J_{HH} 7.4 (2H); 1.7–1.83 m (4H); 1.9 s (3H); 2.41–2.76 m (3H); 3.2 m (4H); 4.5 m (1H). ^{13}C NMR: 25.5; 27.8; 39.7 t, *J* 113; 40; 42.5; 53.6; 190.9; 208.7; (D_2O, pH 14). Compound **8**: ^{31}P NMR: 23.4 (D_2O). ^{1}H NMR: 1.31 t, *J* 7 (12H); 2.25 m (3H); 2.52 m (3H); 2.94 m (2H); 4.15 m (8H); 4.6 m (1H) (D_2O). Compound **9**: ^{31}P NMR: 34.6 (D_2O). ^{1}H NMR: 1.3 t, *J* 7.03 (6H); 2.09–2.25 m (2H); 2.49–2.68 m (2H); 2.88 m (2H); 4.1 p, *J* 7.4 (4H); 4.6 m (1H) (D_2O). Compound **9′**: ^{31}P NMR: 32.7 ($CDCl_3$). ^{1}H NMR: 1.3 t, *J* 7.3 (6H); 1.78–1.99 m (4H); 2.6 m (2H); 2.9–3 m (2H); 4 p, *J* 7.3 (4H); 4.8 m (1H) ($CDCl_3$).