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# Synthesis of a New Linear-Cyclic Ditopic Polyazaligand with a Xylenyl Linker

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**Abstract:** The synthesis of a new linear-cyclic ditopic polyazaligand with a xylenyl linker **1** is described. The sequence is based on the stoichiometric reaction of a dissymmetrical biselectrophilic reagent, *p*-(chloromethyl)benzyl-*p*-toluenesulfonate, with phosphorylcyclam to give rise to an original intermediate possessing a *p*-chloroxylenyl pendant arm. The subsequent reaction of this compound with glyoxal-protected linear tetraamine, followed by deprotection steps, leads to the desired ditopic ligand with a good overall yield.

**Keywords:** Bisaminal, cyclam, ditopic ligand, linear tetraamine, phosphoryl group

## INTRODUCTION

Ditopic ligands based on polyazamacrocycles are widely described in the literature, especially bismacrocycles, which are able to form stable complexes with two metal ions ranging from transition metals to lanthanides and other heavy metals.[1]

A few ditopic compounds constituted by a cyclic subunit combined with an acyclic polyamine are also described.[2,3] The combination of macrocyclic and open-chain polyamines is interesting because it produces ligands with very different properties, notably in regard to their complexation with metal ions. T. A. Kaden recently showed that the

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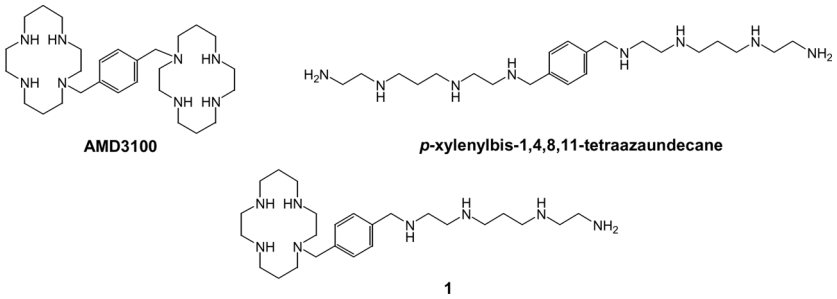
noncyclic moiety, acting as a flexible hook, interacts rapidly with a metal ion to form a first complex that subsequently rearranges itself: the ion is translocated from the linear branch inside the macrocyclic core to give the thermodynamically more stable form. The free acyclic subunit can coordinate a second metal ion added afterward to give rise selectively to heterodinuclear metal complexes.[3,4]

However, the syntheses of these dissymmetrical ditopic ligands require time-consuming protection and deprotection multistep sequences involving Boc or Ts as protecting groups.[2,3]

Herein, we report the synthesis of a new ditopic ligand with a *p*-xylenyl linker **1**. This compound is structurally close to the well-known bismacrocycle AMD3100[5] and the open chain octaamine *p*-xylenylbis-1,4,8,11-tetraazaundecane (Scheme 1).[6]

The molecular recognition of anionic species with polyazaligands is also a very important objective with numerous applications in biological processes or in environmental areas,[1a,6b] and these latter ligands recently have proved to be efficient receptors for inorganic phosphates and especially triphosphate anion in aqueous solution.[8] It was shown that, on one hand, the ability of the bis-linear tetraamine to form easily polyprotonated species constitutes undoubtedly the driving force favoring the formation of ternary species; on the other hand, the rigidity of AMD3100, because of organizing hydrogen bonds, represents a benefit for the selectivity of the binding of anionic species. From this point of view, the linear part of compound **1** should preserve a good ability to form complexes with anionic species while its macrocyclic moiety should introduce more selectivity in the recognition process.

Studies concerning the influence of the architecture of these ditopic polyazaligands on factors governing the recognition of anionic species and π-stacking interactions[9] with nucleotides should be of great interest.




***Scheme 1.*** Ditopic ligands.

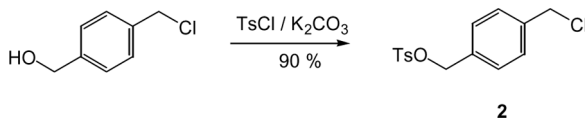
## RESULTS AND DISCUSSION

In a recent article, we described the synthesis of a new polyazaditopic ligand constituted by the linear tetraamine 1,4,8,11-tetraazaundecane and a cyclam moiety linked by a propyl bridge.[10] It consisted, in the first step, of the functionalization of a phosphoryl-triprotected cyclam by a 3-bromopropyl pendant side chain after reaction with an excess of 1,3-dibromopropane. The reaction of this stable functionalized intermediate with a glyoxal-protected linear tetraamine, followed by the subsequent deprotection steps, gave the desired ligand with good overall yield.

Our attempts to synthesize the analogous ligand bearing a *p*-xylenyl linker **1** according to this method failed, certainly because of the high reactivity of the functionalized phosphorylcyclam that led to polymeric products and also because of the difficulties removing the excess $\alpha,\alpha'$-dibromo-*p*-xylene. So, we decided to use a dissymmetrical biselectrophilic reagent able to react selectively toward the free secondary amino group of phosphorylcyclam **3** in a stoichiometric reaction. We chose the *p*-(chloromethyl)benzyl-*p*-toluenesulfonate **2** because the tosylate anion is known to be a better leaving group than the chloride one. This original product **2** was synthesized in good yield according to an atypical solvent-free tosylation at solid state, in a mortar,[11] from commercially available *p*-(chloromethyl)phenylmethanol (Scheme 2).

As expected, in the usual alkylation conditions, the free secondary amino function of phosphorylcyclam **3** reacted univocally on the methylene group bearing the sulfonate function to give the functionalized intermediate *p*-chloroxylenephosphorylcyclam **4**.[10,12] The $^{13}C$ NMR spectrum confirmed this selectivity because no signal was observed in the characteristic area (around 71 ppm) of a methylene group close to a sulfonate function. One can note that this intermediate **4** bearing a pendant arm possessing a chloride function is stable enough to be isolated and stocked for later use.

The subsequent selective monoalkylation of one of the secondary nitrogen atoms of glyoxal-protected linear tetraamine **5** with compound **4** was easily obtained according to our previously described procedure.[6] The reaction gave the fully protected ligand **6** as a mixture




**2**

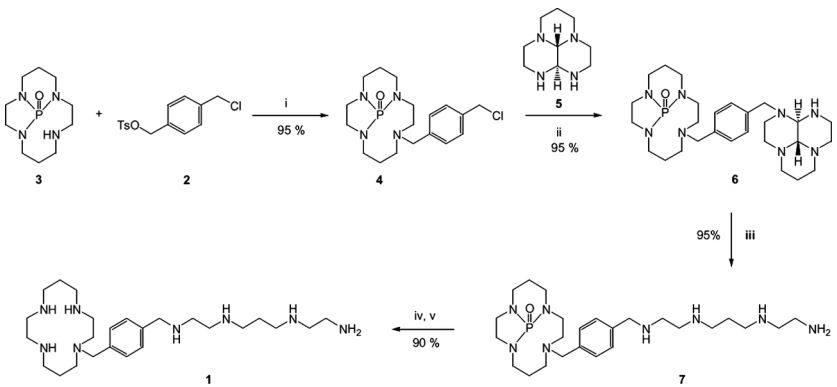
***Scheme 2.*** Synthesis of biselectrophilic reagent **2**.

of diastereoisomers, a consequence of the chirality of the two protected subunits.[10] NMR spectra of **6** are complex and difficult to interpret.

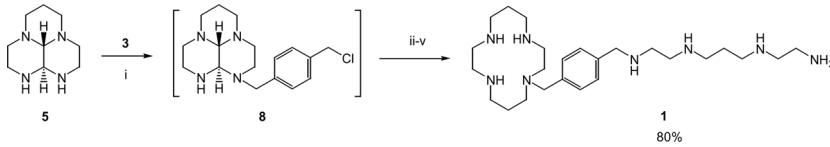
The deprotection of compound **6** was reached in two steps. In the first one, the removal of the bisaminal bridge of glyoxal-protected linear tetraamine moiety in hydrazine hydrate led to the partially deprotected compound **7**. In the second step, the hydrolysis of the triprotecting phosphoryl group of the macrocycle under mild acidic conditions gave the fully deprotected octaamine **1** as hydrochloride salt.[10] Further treatment with potassium carbonate in acetonitrile led to the free octaamine **1** with an overall yield from phosphorylcyclam **3** of 80% (Scheme 3).

With the aim of studying the potentialities of the functionalized intermediate **8** obtained in the reverse sequence, the reaction was undertaken starting from glyoxal-protected linear tetraamine **5**. The general course of this sequence led to the desired compound with the same overall yield. Nevertheless, intermediate **8** showed weaker stability than its analog **4** because of the presence of reactive secondary and ternary amino functions; consequently, further alkylation involving phosphorylcyclam **2** was realized in a one-pot procedure (Scheme 4).

In conclusion, the usefulness of the dissymmetrical biselectrophilic reagent *p*-(chloromethyl)benzyl-*p*-toluenesulfonate **2** for the synthesis of the ditopic ligand possessing a *p*-xylenyl linker **7** was established. In each step, the reaction is stoichiometric and univocal and avoids tedious purifications. Functionalized phosphorylcyclam **4** and to a lesser extent glyoxal-protected tetraamine derivative **8** represent interesting precursors in the synthesis of a wide variety of new ditopic polyazaligands. Further studies to evidence the benefit of such ditopic linear-cyclic structures




***Scheme 3.*** Synthesis of the ditopic ligand **1**. Reagents and conditions: (i) $K_2CO_3$, $CH_3CN$, rt, 2 h; (ii) $K_2CO_3$, $CH_3CN$, rt, 15 h; (iii) $N_2H_4{\cdot}H_2O$, $\Delta$, 15 h; (iv) HCl, 15 h; and (v) $K_2CO_3$, $CH_3CN$, $\Delta$, 15 h.




***Scheme 4.*** Alternative synthetic pathway of ligand **1**. Reagents and conditions: (i) $K_2CO_3$, $CH_3CN$, rt, 2 h; (ii) phosphorylcyclam **3**, $K_2CO_3$, $CH_3CN$, rt, 15 h; (iii) $N_2H_4{\cdot}H_2O$, Δ, 15 h; (iv) HCl, 15 h; and (v) $K_2CO_3$, $CH_3CN$, Δ, 15 h.

toward both metal ions and anions complexation are currently being investigated.

## EXPERIMENTAL

### General

Phosphorylcyclam **3**[10,12] and bisaminal of linear tetraamine **5**[6,10] were synthesized according to previously described procedures. All reagents were of commercial quality, and solvents were dried according to standard procedures. NMR spectra were acquired on Bruker AC 300 or DX Avance Bruker spectrometers. The chemical shifts are in δ values relative to the internal standard tetramethylsilane (TMS). Elemental analyses were performed at the Service de Microanalyse of the CNRS, Gif sur Yvette, France.

### Synthesis and Data of *p*-(Chloromethyl)benzyl-*p*-toluenesulfonate 2[11]

A mortar was charged with *p*-(chloromethyl)phenylmethanol (1.57 g, 10 mmol), dry potassium carbonate (6.91 g, 50 mmol), and *p*-toluenesulfonyl chloride (2.86 g, 15 mmol), and the ingredients were ground vigorously for 5 min. After the completion of tosylation, the remaining *p*-toluenesulfonyl chloride (TsCl) was removed by addition of powered potassium hydroxide (2.81 g, 50 mmol) and vigorously ground for 2 min. Addition of a small quantity of *t*-butanol (20 mg) accelerates the disappearance of TsCl. The product was extracted with $3 \times 20$ mL of $CH_2Cl_2$ and filtered, and the organic solvent was evaporated. The product **2** was recrystallized in *n*-hexane to give a white solid with 90% yield.

F = 58°C. $^1$H NMR (300.13 MHz, $CDCl_3$): δ = 2.44 (s, 3H), 4.55 (s, 2H), 5.05 (s, 2H), 7.20 (m, 6H), 7.77 (d, 2H, $J$ = 9 Hz). $^{13}$C NMR (75.47 MHz, $CDCl_3$): δ = 21.7, 45.6, 71.3, 128.0, 128.9 (2C), 129.9, 133.2,

133.6, 138.4, 144.9. Anal. calcd. for $C_{15}H_{15}O_3SCl$, $0.5H_2O$: C, 56.34; H, 5.04; S, 10.03; Cl, 11.09. Found: C, 56.49; H, 4.99; S, 9.61; Cl, 10.81.

### Synthesis and Data of *p*-Chloroxylenephosphorylcyclam 4

Phosphorylcyclam **3** (2.20 g, 9 mmol) and dry potassium carbonate (6.22 g, 45 mmol) were mixed in acetonitrile (25 mL), and then a solution of *p*-(chloromethyl)benzyl-*p*-toluenesulfonate **2** (2.79 g, 9 mmol) in acetonitrile (25 mL) was added. The mixture was stirred at room temperature for 2 h. The solids were filtered off, and acetonitrile was evaporated. The obtained oil was taken up in ether (30 mL). After filtration and solvent evaporation, compound **4** was obtained as a thick oil with 95% yield.

$^1$H NMR (300.13 MHz, $CDCl_3$): $\delta = 1.64$ (m, 4H), 2.26–3.43 (m, 16H), 3.79 (m, 2H), 4.46 (s, 2H), 7.24 (d, 2H, $J_{C\text{-}H} = 7$ Hz), 7.44 (d, 2H, $J_{C\text{-}H} = 7$ Hz). $^{13}$C NMR (75.47 MHz, $CDCl_3$): $\delta = 21.8$, 26.2, 40.7, 41.7, 42.0, 44.3 (d, $J_{P\text{-}C} = 11$ Hz), 45.5 (d, $J_{P\text{-}C} = 15$ Hz), 46.0, 51.6 (2C), 52.4, 57.9, 128.4, 129.0, 135.7, 139.9. $^{31}$P NMR (121.49 MHz, $CDCl_3$): $\delta = 25.6$.

### Synthesis and Data of Fully Protected Intermediate 6

A solution of bisaminal **5** (728 mg, 4 mmol) in acetonitrile (20 mL) was added to a solution of *p*-chloroxylenephosphorylcyclam **4** (1.53 g, 4 mmol) and potassium carbonate (2.76 g, 20 mmol) in acetonitrile (20 mL). The mixture was stirred vigorously at room temperature for 15 h. Solids were filtered off, and acetonitrile was evaporated. The oily residue was composed of a mixture of diastereoisomers of compound **6** with 95% yield.

$^{13}$C NMR (75.47 MHz, $CDCl_3$): $\delta = 21.4$, 23.7, 25.7, 40.2–57.4 (complex zone), 71.3, 74.5, 74.9, 87.0, 125.4, 128.3–128.6 (complex zone), 135.3–142.7 (complex zone). $^{31}$P NMR (121.49 MHz, $CDCl_3$): $\delta = 25.5$, 25.6.

### Synthesis and Data of Phosphoryl-Protected Intermediate 7

The mixture of diastereoisomers of compound **6** was dissolved in hydrazine hydrate (30 mL) and refluxed for 15 h. The solution was extracted with chloroform ($3 \times 20$ mL). The organic layer was dried with $MgSO_4$, and solvent was removed under reduced pressure to give a pale oil composed of the phosphoryl-protected intermediate **7** in 90% yield.

$^1$H NMR (300.13 MHz, $CDCl_3$): $\delta = 1.56$ (m, 6H), 2.24–3.48 (m, 28H), 3.61 (s, 2H), 3.77 (m, 2H), 7.13 (d, 2H, $J_{C\text{-}H} = 7$ Hz), 7.32 (d,

2H, $J_{C\text{-}H} = 7$ Hz). $^{13}C$ NMR (75.47 MHz, $CDCl_3$): $\delta = 21.6$, 25.9, 30.0, 40.4, 41.3 (2C), 41.6, 43.9, 43.9 (d, $J_{P\text{-}C} = 11$ Hz), 45.1 (d, $J_{P\text{-}C} = 14$ Hz), 45.1, 47.8 (2C), 48.3, 49.0, 51.3, 52.0, 52.2, 53.2, 57.5, 127.5 (2C), 128.4 (2C), 137.6, 138.5. $^{31}P$ NMR (121.49 MHz, $CDCl_3$): $\delta = 25.5$.

## Octaamine 1

### Synthesis

Compound **7** was dissolved in 3M hydrochloric solution (30 mL) and stirred at room temperature for 15 h. The solvent was removed under reduced pressure. The resulting hydrochloride salt was washed with warm ethanol ($3 \times 20$ mL). The solid was filtered off and dried to give the ligand **7** as hydrochloride salt.

To obtain the free form of compound **1**, the powder was mixed in acetonitrile (20 mL) with potassium carbonate (10 mmol) and refluxed for 15 h. Then solids were filtered off, and the solvent was removed to give a pale oil of octaamine **1** in 90% yield. Overall yield from phosphorylcyclam **3**: 80%.

### Data of Octaamine **1** as Hydrochloride Salt

$^1H$ NMR (300.13 MHz, $D_2O$): $\delta = 2.20$ (m, 6H), 3.20–3.78 (m, 28H), 4.38 (s, 2H), 4.57 (s, 2H), 7.61 (m, 4H). $^{13}C$ NMR (75.47 MHz, $D_2O$): $\delta = 20.7$, 21.3, 25.5, 38.2, 39.6, 40.4 (2C), 43.7 (2C), 44.3, 45.6, 46.1, 47.1 (2C), 47.7 (2C), 50.4, 53.9, 61.7, 132.5, 133.8, 134.8, 135.4. Anal. calcd. for $C_{24}H_{50}N_8$, 7.3HCl, $4H_2O$: C, 37.49; H, 8.22; N, 13.99; Cl, 32.31. Found: C, 37.42; H, 8.09; N, 13.96; Cl, 32.34.

### Data of Free Octaamine **1**

$^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta = 1.520$ (m, 4H), 1.68 (m, 2H), 2.28–2.82 (m, 28H), 3.38 (s, 2H), 3.59 (m, 2H), 7.12 (m, 4H). $^{13}C$ NMR (75.47 MHz, $CDCl_3$): $\delta = 25.8$, 28.2, 30.1, 41.4, 47.0, 47.6, 47.9 (2C), 48.5, 48.6, 48.9, 49.0 (2C), 50.5, 52.3, 53.0, 53.3, 54.1, 57.1, 127.5, 128.9, 137.0, 138.7.

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