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# Synthetic routes to large tripodal organic receptors and the structural characterisation of intermediates

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ABSTRACT

This contribution explores synthetic routes adopted and optimized for the preparation of three new hexatopic tripodal organic ligands designed for Ln(III) complexation. In these ligands, three strands bearing two pyridyldicarbonyl binding moieties are anchored with a small aliphatic triamine. The described synthesis is not straightforward and depends on the nature of the spacer between coordinating moieties. In addition to the characterisation of targeted ligands, the structure of ditopic intermediates is assessed by X-ray crystallography and discussed with respect to the spacer nature.



## 1. Introduction

The preparation of sophisticated supramolecular compounds usually requires well designed polytopic ligands, which encode chemical informations for predictable self-assembly processes.[1] The synthesis of targeted organic receptors may become a time-demanding process and several synthetic steps are usually required.[2] The choice of a synthetic strategy is governed by its feasibility and the obtained yield in each synthetic step.

Since several years we are interested in designing new tripodal receptors for complexing Ln(III) cations. These ligands possess three strands attached to a suitable anchoring molecule, i.e., a triamine. Each strand bears a tridentate coordination moiety specially designed for complexing Ln(III). Playing with the nature of coordination moieties and with the size and chemical structure of the anchor allows a fine tuning of the receptor for targeted assemblies. The synthesis of such symmetrical ligands ($C_{3v}$) is carried out by a successive coupling of building blocs to the central core, which reminds the synthesis of dendrimers. Simple symmetrical tripods (i.e., **L1**,[3] **L2**,[4] see Scheme 1) can be thus synthesised by the coupling of selected coordinating moieties in one step. A relatively high symmetry of tripodal ligands is often maintained in related supramolecular systems, as it is shown for the assembly of tetrahedral tetranuclear complexes.[3–5] The preparation of unsymmetrical tripodal ligands is more complex and less efficient, since the attachment of different coordinating strands must be carried out at least in two steps. This is the case of an unsymmetrical tripodal ligand **L3**, which have been designed and used for assembling pentanuclear edifices (see Scheme 1).[6]

In this contribution, we report on synthetic routes adopted for preparing hexatopic tripodal ligands. Three symmetrical organic receptors **L4**–**L6** (see Scheme 2), where each strand bears two coordinating moieties, differ in the nature of the spacer between pyridyldicarbonyl coordination moieties. Our interest is also focused on the characterisation of ditopic linear by-products (**1es**, **2es** and **3es**) by X-ray crystallography. Their analysis provides structural information for better understanding intra- and intermolecular interactions occurring within synthesised polytopic receptors.

## 2. Results and discussion

**Ligand design**. The targeted hexatopic $C_{3v}$ symmetrical receptors consist of three ditopic strands attached to the trifunctional central anchor 1,1,1-tris(aminomethyl)ethane (TAME). Each strand is composed of two identical coordination pyridyldicarbonyl moieties connected to a spacer **X**. The nature of this spacer may play a crucial role in the assembly of the expected supramolecular complex especially with respect to its length and rigidity. We have identified three potentially suitable spacers having different structural properties. All spacers **X** are commercially available as diamino derivatives ($NH_2$-**X**-$NH_2$, **Y**=**1**–**3**), which allows their convenient insertion between coordination moieties by forming

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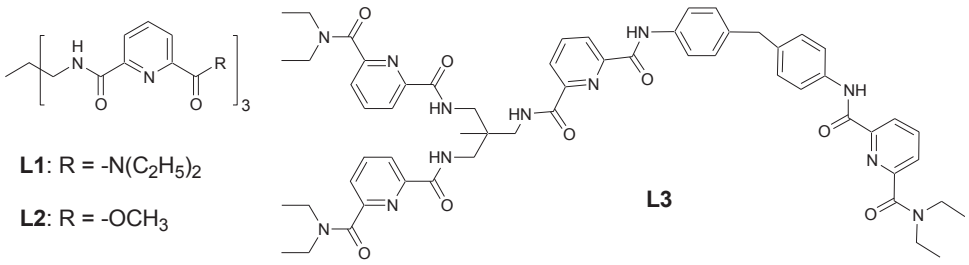
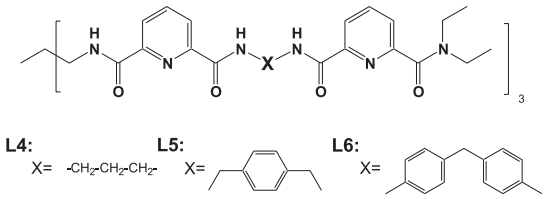



**Scheme 1.** Structure of ligands **L1**–**L3**.




**Scheme 2.** Structure of targeted ligands **L4**–**L6**.

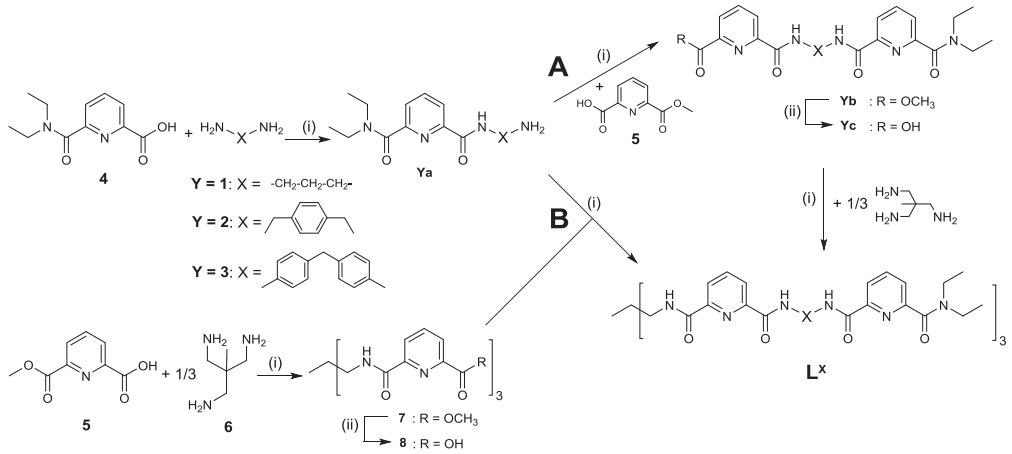
amide bonds. In the serie (propyl, dimethylphenyl, diphenylmethan), the rigidity and length of the spacer are increasing. The terminal carboxamide moieties are identical for all ligands and ensure a reasonable solubility in view of further complexation reactions.

**General synthetic procedures**. The retrosynthetic analysis of the ligand structure (**L4**–**L6**) suggests two possible synthetic routes, where the coupling of amine precursors with carboxylates alternates with the hydrolysis of protected intermediates. The strategy **A** (Scheme 3) consists of the initial preparation of ditopic moieties **Yb** by condensation of carboxylate precursors (**4**, **5**) and diamino derivatives **1**–**3**. A subsequent coupling of the ditopic intermediates **Yc** with the triamine anchor TAME (**6**) provides the desired ligands **L4**–**L6**. The second route **B** (Scheme 3) consists of the initial coupling of three binding moieties **5** with **6**. The obtained tripodal intermediate **8** is then coupled with unsymmetrical amines **Ya**, where one binding moiety is already attached to the spacer. These monoamine precursors are prefered over diamines **Y** for avoiding the formation of undesired polymeric products. It is worth noting that both routes have the same number of reaction steps starting with the same compounds. The preparation of monosubstituted diamines **Ya** is common for both routes. The synthetic routes adapted for each hexatopic ligand **L4**–**L6** are detailed below. All synthesised tripodal ligands are characterized by NMR spectroscopy confirming their expected average $C_{3v}$ symmetry.

**Synthesis of L4**. The ligand **L4** is designed with a flexible propyl spacer. Initially, the synthetic strategy **A** was adopted. The key intermediate **1b** can be synthesized by coupling of **1a** with **5**. The monoamine precursor **1a** is obtained in a very good yield of 69% from the coupling reaction between **4** and **1** (Scheme 3). Alternatively, the precursor **1b** is also prepared by coupling of **4** and **1e**, which is previously prepared by coupling **5** and **1** (Scheme 4). Advantageously, the latter path consumes less of **4**, whose synthesis is more time-consuming. Another way for preparing **1b** is a one pot reaction according to Scheme 5. Owing to similar structural and reactivity properties of **4** and **5**, this reaction theoretically results in a statistical mixture, which consists of 50% of heterosubstituted diamine **1b** and 25% of each homosubstituted diamine by-product **1es** and **1am**, respectively.

The hydrolysis of the ester **1b** provides the monoacid **1c**. However, the final coupling of **1c** with TAME (**6**) using CDI/THF does not give the desired tripodal ligand **L4** despite the use of different coupling agents (DMAP, DCC). Apparently, a possible folding of the ditopic intermediate **1c** decreases its availability for the nucleophilic attack of the triamine and the desired product couldn't be identified in the mixture.[2] Consequently, we have switched to the strategy **B**, where the coupling with the triacid **8** also works with a sufficient yield.[4] The compound **8** is then coupled with the precursor **1a** providing the ligand **L4**, which is then purified (yield: 46%) and characterised by its NMR spectrum showing 18 proton signals (Fig. S1).

**Synthesis of L5.** The strategy **A** based on the preparation of the monoamine precursor **2a** was initially attempted. However, the diamine **2** is badly soluble in aprotic organic solvents (i.e., $CH_2Cl_2$,




**Scheme 3.** General scheme of the ligand synthesis with two main routes **A** and **B**. Conditions: (i) $SOCl_2$/DMF/$CH_2Cl_2$, $Et_3N$/$CH_2Cl_2$; or CDI/THF. (ii) a) KOH/MeOH/$CH_2Cl_2$; b) HCl.