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BINOL diesters as useful building blocks towards chiral macrocyclic compounds

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ABSTRACT

Double-amidation reaction of (*R*)- or (*S*)-2,2'-([1,1'-binaphthalene]-2,2'-diylbis(oxy))diacetic dimethyl ester with five differing in length α,ω -diaminoethers were used for the synthesis of chiral macrocyclic compounds of different size of the cavity, potential receptors of various chiral guests.

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1. Introduction

Among various areas of modern supramolecular chemistry, molecular recognition has been, since three decades, a subject of intensive exploration, including design, synthesis, structural studies, and application of neutral receptors which could recognize neutral molecules as well as ions.¹ Chiral artificial neutral receptors became attractive targets of studies because of their analogy to natural systems.² These studies have been focused on development of receptors having an increased selectivity and/or binding affinity,³ and also succeeded in practical application, namely in catalysis,⁴ transport processes⁵ and chromatography.⁶ However, a focus on the efficiency and applications of chiral neutral receptors has one serious drawback—a lack of fundamental papers. Without such basis it is hard to generalize and consolidate information discussed by various authors. For instance, the diversity of titration techniques and solvents used for studies of successive generation of hosts, makes it difficult to analyse structural influence on affinity towards guest molecules.⁷ On the other hand, the recently observed growing interest in application of combinatorial approaches to the synthesis of neutral receptors is also a very important aspect of the discussed topic.⁸ In the course of fundamental studies our group, using simple models, has investigated macrocyclic effects,⁹ size complementarity,¹⁰ and introduced new building blocks.¹¹ As

concerns chiral building blocks, we have focused our attention on substrates, which are readily available from natural precursors, such ascarbohydrates¹² and α -amino acids.¹³

In our previous works, we found that α,ω -diamino aliphatic ethers react under ambient conditions with dimethyl α,ω -dicarboxylates in methanol as a solvent, to give macrocyclic diamides in moderate yields.¹⁴ Addition of sodium methoxide improved the kinetics, and to some extent the yield of the macrocyclization reaction.¹⁵ This finding constitutes a simple and versatile procedure for the synthesis of various macrocyclic diamides.

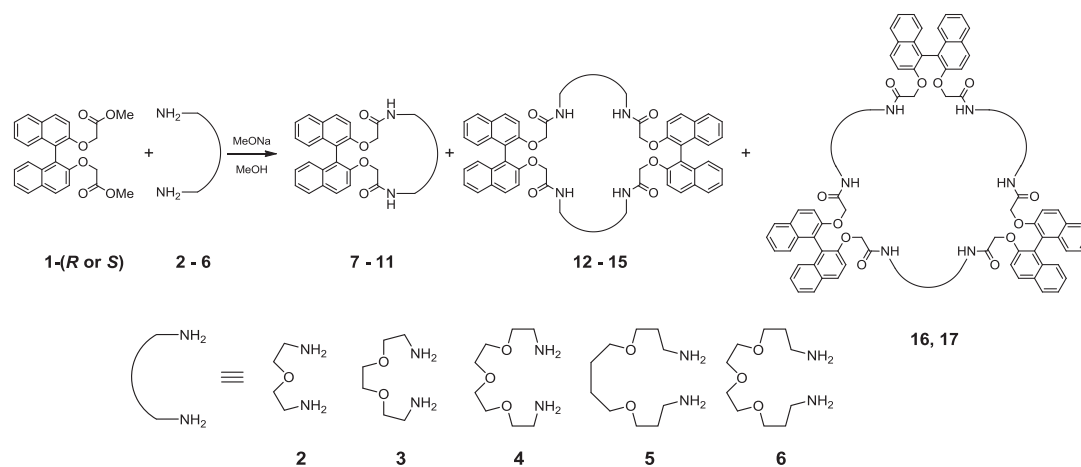
Recently, optically active 1,1'-bi-2-naphthol (BINOL) has been widely used as a source of chirality in the preparation of receptors for recognition of chiral anions¹⁶ or neutral molecules.¹⁷ This unit is also very well known as an efficient chiral auxiliary¹⁸ in asymmetric reactions, such as oxidation,¹⁹ hydrogenation,²⁰ nucleophilic addition to the carbonyl group,²¹ enantioselective aldol²² and Diels–Alder²³ reactions. In supramolecular chemistry, Cram et al.,²⁴ for the first time, used 1,1'-bi-2-naphthyl unit for functionalization of crown ethers.

2. Results

Owing to the valuable properties of the BINOL unit, we decided to apply it to the synthesis of macrocyclic oligoamide type receptors, with the use of the double-amidation method as shown in Scheme 1.

In order to prepare macrocycles containing BINOL units, we reacted diester(*R*)-**1**, and then (*S*)-**1** with five α,ω -diaminoethers

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Scheme 1. Synthesis of macrocyclic compounds using double-amidation method.

2–6. Diesters(*R*)-**1** and(*S*)-**1** were synthesized according to the known procedure.^{14b} Diamines **3**, **5** and **6** were commercially available. Diamines **2** and **4** were synthesized according to the literature protocol.²⁵ The reactions were carried out in methanol as a solvent, in the presence of sodium methoxide, at room temperature, within 72 h, and the results are presented in Table 1.

When diester(*R*)-**1** was reacted with the shortest diaminoether **2**, only [1:1] macrocycle (*R*)-**7** was formed in 60% yield (Table 1, entry 1). In the case of reaction of (*R*)-**1** with diaminoether **3** apart from [1:1] product (*R*)-**8** (67% yield), [2:2] macrocycle(*R,R*)-**12** was obtained in 7% yield (entry 2). Ratio of 9.5:1 between these two products indicates, that although the longer diaminoether is more flexible, it still prefers formation of the smaller conjugate. Application of the next diaminoether **4** to the macrocyclization reaction also provided [1:1] product (*R*)-**9** (52% yield) and [2:2] macrocycle(*R,R*)-**13** (9% yield), showing that further elongation of diaminoether did not result in enhancement of larger macrocycle formation (entry 3). In the case of longer diaminoether **5**, we obtained three macrocyclic oligoamides: [1:1](*R*)-**10** (42% yield), [2:2](*R,R*)-**14** (8% yield) and [3:3](*R,R,R*)-**16** (2% yield) (entry 4). Similar results were observed for the longest diaminoether **6**. The products [1:1](*R*)-**11** (49% yield), [2:2](*R,R*)-**15** (10% yield) and [3:3](*R,R,R*)-**17** (2% yield) were formed (entry 5). Ratios of products in two latter entries 4 and 5 were 21:4:1 and 24:5:1, respectively. Moreover, we repeated all of the above-presented experiments for diester(*S*)-**1**, obtaining analogous libraries of 11 macrocyclic compounds with (*S*) configuration and with similar yields and distributions of products.

3. Conclusions

The results presented above give another proof of the good applicability of the double-amidation method, earlier developed by us.^{14,15} It provides products even when quite constrained substrates are used, while other approaches fail to give macrocyclic species. The overall yields of these exemplary reactions are better than 50%. It should be emphasized that, especially for the formation of larger macrocycles, these processes occur with no special template present. Distribution of size-varying compounds, in each set of products obtained from diaminoethers **2–6**, is of course statistical. However, from the results of reactions of diaminoethers **4** and **5** with diester **1**, it can be inferred that nonplanar conformation of macrocyclic compounds formed is crucial for the reaction outcome. This approach towards synthesis of chiral receptors may be of high utility, if applied with the use of templates in static combinatorial

chemistry. It is confirmed by presented results, that larger macrocycles are readily obtained, when sodium methoxide is used in formation of both more and less constrained products.

4. Experimental

4.1. General information

Melting points were measured with a Koffler type (BoetiusM) hot-stage apparatus. Specific rotations were determined using a Jasco P-2000 polarimeter. All reagents were obtained from commercial sources and used as received. The column chromatography experiments were carried out using silica Kieselgel 60 (230–400 mesh). The thin-layer chromatography analysis were carried out using Merck DC Kieselgel 60 F₂₅₄ plates. ¹H NMR spectra were recorded on a Varian Mercury 400 spectrometer (400 MHz) in CDCl₃. ¹³C NMR spectra were recorded on a Varian Mercury 400 spectrometer (100 MHz). All chemical shifts are quoted in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00 ppm) and coupling constants (*J*) are measured in Hertz. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; ABq, AB type quartet; m, multiplet. High-resolution mass spectrometry (HRMS) experiments were performed on a Micromass LCT (ESI TOF) instrument.

4.2. General procedure for the synthesis of macrocyclic compounds 7–17

Diester**1** (1 mmol) and the appropriate diamine**2–6** (1 mmol) were dissolved in dry methanol (50 mL) and sodium methoxide (2 mmol) was added. A mixture was stirring for 72 h at room temperature. After completion of the reaction (controlled by TLC), the solvent was evaporated under reduced pressure and the oily residue was purified by column chromatography (1–5% MeOH in CH₂Cl₂). All the macrocyclic products obtained in this way are colourless solids, stable to air.

4.2.1. Macrocycle (*R*)-7.^{14b} Yield: 60% (282 mg); [α]_D²⁵ +86.4 (*c*=0.1, CH₂Cl₂); Mp. 245–246 °C; ¹H NMR (400 MHz, CDCl₃): δ =8.02 (d, *J*=9.0 Hz, 2H), 7.90 (d, *J*=8.2 Hz, 2H), 7.45–7.21 (m, 6H), 7.07 (d, *J*=8.5 Hz, 2H), 6.41 (br s, 2H), 4.60 (d, *J*=15.6 Hz, 2H), 4.36 (d, *J*=15.6 Hz, 2H), 3.71–3.56 (m, 2H), 3.51–3.39 (m, 2H), 3.38–3.27 (m, 2H), 2.97–2.86 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ =168.5, 152.7, 133.6, 130.2, 129.8, 128.1, 127.2, 125.0, 124.6, 119.6, 114.1, 68.9,

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