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ORIGINAL ARTICLE

Microwave assisted synthesis of 72-membered chiral hexanuclear [6+6] macrocyclic Schiff base

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Abstract Two new 72-membered chiral macrocyclic Schiff bases (**1** and **2**) possessing six salen pockets have been synthesized by employing a [6+6] cyclocondensation. The procedure involves short reaction time under microwave irradiation and aqueous reaction conditions. Moreover, the macrocycle synthesis uses salts of chiral diamines in contrast to free diamines normally employed. Spectral studies of these macrocyclic systems indicate the formation of diastereomeric structures.

Keywords [6+6] Cyclocondensation · Diastereomers · Large central cavity · Macrocyclic ligands · Schiff bases

Introduction

The synthesis of large-ring macrocyclic receptors is of current interest and importance in host-guest chemistry, molecular recognition and supramolecular chemistry [1]. The successful application of these macrocyclic receptors require the availability of macrocycles with different cavity sizes, easy synthesis and functionalities to allow binding of guest molecules. Among different classes of macrocyclic systems, macrocycles containing a Schiff base and hydroxyl moieties are particularly attractive as they form multimetal complexes which exhibit catalytic and fluorescent properties [2]. The reversible imine-bond formation together with conformational bias afforded by the precursors provides a facile method for the construction of achiral [3] and chiral macrocyclic Schiff bases by [2+2] and [3+3] cyclocondensation [4, 5]. Since these macrocyclic structures are formed under thermodynamic control and depending on the type of dialdehydes employed, the strategy can be extended for the synthesis of macrocycles with larger central cavities. However, chiral macrocyclic Schiff bases with large central cavity formed by [3+3] cyclocondensation of long chain dialdehydes displayed poor solubility in organic solvents [6]. The other strategy for the construction of large ring macrocycles involves a higher order [n+n] macrocyclisation. Though a few examples of chiral [4+4] macrocycles are known [7], there are no available reports on large ring chiral macrocyclic Schiff bases higher than [4+4] macrocycles. However, an appropriate choice of dialdehyde can provide a facile conformational bias for the construction of large ring macrocyclic Schiff bases. Recently, MacLachlan and coworkers reported the synthesis of achiral [6+6] macrocyclic Schiff bases using a series of dialdehydes of related structures [8]. These macrocycles however displayed limited solubility in common organic solvents. It was earlier observed by us that 5,5′-*bis*-salicylaldehyde unusually formed [6+6] macrocycle along with the corresponding [2+2] macrocycle during condensation with chiral diamines [9]. In the present communication we report the first example of soluble chiral macrocyclic [6+6] macrocycles (**1** and **2**) formed in a short reaction time.

Experimental

General information

^{1}H NMR spectra were recorded on 400 MHz Bruker AVANCE 400 spectrometer and ^{13}C NMR spectra were recorded on 100 MHz Bruker AVANCE 400 spectrometer,

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respectively using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT/IR 100 spectrometer. Mass spectra were recorded on MALDI TOF mass spectrometer. Optical rotations were measured by a Rudolph Autopol V polarimeter. All the reactions were monitored by thin layer chromatography (TLC). TLC was performed on F_{254}, 0.25 mm silica gel plates (Merck). Plates were eluted with appropriate solvent systems, and then stained with either alkali $KMnO_4$ or Ceric ammonium molybdate solutions prepared in the laboratory. The developed plates were first analysed under UV 254nm then stained with appropriate reagent. Column chromatography was performed using silica gel with particle size 100–200 mesh.

4,4′-Bis(Methoxymethoxy)biphenyl **5**

To a stirred suspension of 60% NaH (62 mg, 2.58 mmol) in dry DMF (5 mL) was added 4,4′-biphenol **4** (200 mg, 1.08 mmol) in dry DMF (1.5 mL) and the resulting mixture was stirred for 30 min at room temperature. The reaction mixture was cooled to 0 °C and methoxymethyl chloride (MOM-Cl) (226 mg, 2.808 mmol) was added dropwise over 5 min. The reaction was allowed to warm to room temperature and stirred further for 2 h. Upon completion, water (10 mL) was added to the mixture and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product which was purified by column chromatography using 15% EtOAc in hexane to yield the title compound **5** as a white solid (251 mg, 85% yield). ^{1}H NMR [400 MHz, $CDCl_3$, 28 °C] δ 3.53 (s, 6H), 5.23 (s, 4H), 7.11–7.13 (d, J = 8.6 Hz, 4H), 7.48–7.51 (d, J = 8.6 Hz, 4H); ^{13}C NMR [100 MHz, $CDCl_3$, 28 °C] δ 56.0, 94.5, 116.5, 127.8, 134.6, 156.4; MS (ESI) *m/z* 275 ($[M+H]^+$).

4,4′-Bis(Methoxymethoxy)biphenyl-3,3′-dicarbaldehyde **6**

Bis-MOM ether **5** (1 g, 3.65 mmol) was weighed in a flame dried 3-necked flask under nitrogen. Dry Et_2O (50 mL) was added to the content of the flask and stirred, to form a clear solution. The flask was cooled to 0 °C and 10 mL of *n*-BuLi (2.5 M, 5.84 mL, 14.60 mmol) was added dropwise in 1–2 min at the same temperature. The resulting yellow slurry was stirred for 12 h under nitrogen atmosphere at room temperature. The slurry was cooled to 0 °C and dry DMF (844 μL, 10.95 mmol) was added and the mixture was stirred at room temperature for another 2 h. Saturated NH_4Cl solution was added carefully to quench excess of *n*-BuLi followed by addition of water (25 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product which was purified by column chromatography using 20% EtOAc in hexane to yield the title compound **6** as a white solid (540 mg, 45% yield). ^{1}H NMR [400 MHz, $CDCl_3$, 28 °C] δ 3.56 (s, 6H), 5.36 (s, 4H), 7.31–7.33 (d, J = 8.7 Hz, 2H), 7.76–7.78 (dd, J = 2.5 Hz & 8.7 Hz, 2H), 8.05–8.06 (d, J = 2.5 Hz, 2H), 10.55 (s, 2H); ^{13}C NMR [100 MHz, $CDCl_3$, 28 °C] δ 56.6, 94.7, 115.6, 125.5, 126.2, 133.2, 133.9, 159.1, 189.6; MS (ESI) *m/z* 331 ($[M+H]^+$).

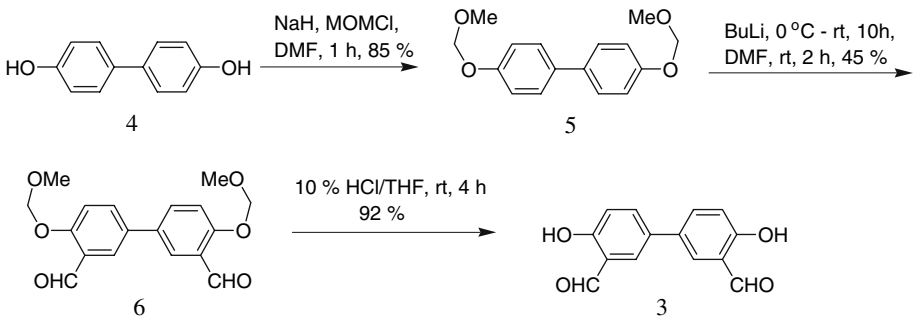
5,5′-Bis-salicylaldehyde **3**

Mixture of 10% HCl/THF (10 mL) was added to the dialdehyde **6** (375 mg, 1.136 mmol) to form a clear solution. It was refluxed for 4 h and then cooled to room temperature. After the removal of THF, water (10 mL) was added and extracted with EtOAc (2 × 10 mL). The combined EtOAc extracts were dried over anhydrous Na_2SO_4 and concentrated to yield the crude product which was recrystallised to yield the title compound **3** [9] as a white solid (254 mg, 92% yield). ^{1}H NMR [400 MHz, $CDCl_3$, 28 °C] δ 7.11–7.13 (d, J = 8.7 Hz, 2H), 7.71–7.73 (dd, J = 2.5 Hz & 8.7 Hz, 2H), 8.00–8.02 (d, J = 2.5 Hz, 2H), 9.24 (s, 2H), 10.20 (s, 2H); ^{13}C NMR [100 MHz, $CDCl_3$, 28 °C] δ 117.6, 125.3, 125.7, 133.2, 133.6, 161.1, 190.2; MS (ESI) *m/z* 243 ($[M+H]^+$).

General experimental procedure for the preparation of [n+n] macrocycles (**1** and **2**)

To a solution of (1*R*,2*R*)-diammoniumcyclohexane mono-(+)-tartrate (104 mg, 0.392 mmol) or (3*R*, 4*R*)-diamino-1-benzylpyrrolidine hydrochloride (104 mg, 0.392 mmol) and K_2CO_3 (108 mg, 0.784 mmol) in 3 mL of water was added a solution of 5,5′-bis-salicylaldehyde **3** (100 mg, 0.328 mmol) in 5 mL of ethanol. This homogeneous mixture was irradiated in an unmodified domestic microwave oven at low power lable setting for 5 min. The reaction mixture was cooled to room temperature and the solid material formed was filtered off. The residue was dissolved in ethyl acetate and the undissolved material was removed by filtration. The filtrate was dried over sodium sulfate, concentrated under reduced pressure and the crude product was purified by column chromatography using 20% EtOAc–hexane to afford pure [6+6] macrocyclic dodecaimine as a yellow solid. *Spectral data for [6+6] macrocycle* **1:** Yield 14%; $[\alpha]_D^{28}$ = +35 (*c* 0.24, $CHCl_3$); IR (KBr) *v* 3462, 2985, 2256, 1740, 1447, 1374, 1243, 1047 cm^{-1}; ^{1}H NMR [400 MHz, $CDCl_3$] δ 0.81–0.87 (m,

Scheme 1 Synthetic route to 5, 5′-bis-salicylaldehyde **3**



12H), 1.49–1.59 (m, 12H), 1.78–1.88 (m, 24H), 3.16–3.22 (m, 6H), 3.37–3.43 (m, 6H), 4.52–4.55 (dd, J = 2.2 Hz & 8.6 Hz, 6H), 4.88–4.89 (d, J = 2.2 Hz, 6H), 5.91–5.92 (d, J = 2.08 Hz, 6H), 6.27–6.29 (d, J = 8.48 Hz, 6H), 6.37–6.39 (d, J = 8.56 Hz, 6H), 6.53–6.56 (dd, J = 2.08 Hz & 8.6 Hz, 6H), 7.59 (s, 6H), 7.86 (s, 6H), 13.74 (s, 6H); MALDI-TOF (MS) *m/z* 1920 $[M]^+$, 1943 $[M+Na]^+$. *Spectral data for [6+6] macrocycle* **2:** Yield 36 %; $[\alpha]_D^{28}$ = +50 (*c* 0.83, CH_2Cl_2); IR (KBr) *v* 3540, 2985, 2324, 1739, 1629, 1475, 1375, 1243, 1047 cm^{-1}; ^1H NMR [400 MHz, $CDCl_3$] δ 3.20–3.29 (m, 18H), 3.41–3.43 (m, 6H), 3.89–3.96 (m, 12H), 3.99–4.09 (m, 12H), 4.68–4.70 (dd, J = 1.2 Hz & 8.4 Hz, 6H), 5.02–5.03 (d, J = 0.8 Hz, 6H), 5.97–5.98 (d, J = 0.8 Hz, 6H), 6.37–6.39 (d, J = 8.4 Hz, 6H), 6.43–6.45 (d, J = 8.8 Hz, 6H), 6.59–6.62 (dd, J = 1.2 Hz & 8.6 Hz, 6H), 7.34–7.50 (m, 30H), 7.52 (s, 6H), 7.96 (s, 6H), 12.88 (s, 6H); MALDI-TOF (MS) *m/z* 2383 $[M]^+$, 2406 $[M+Na]^+$.

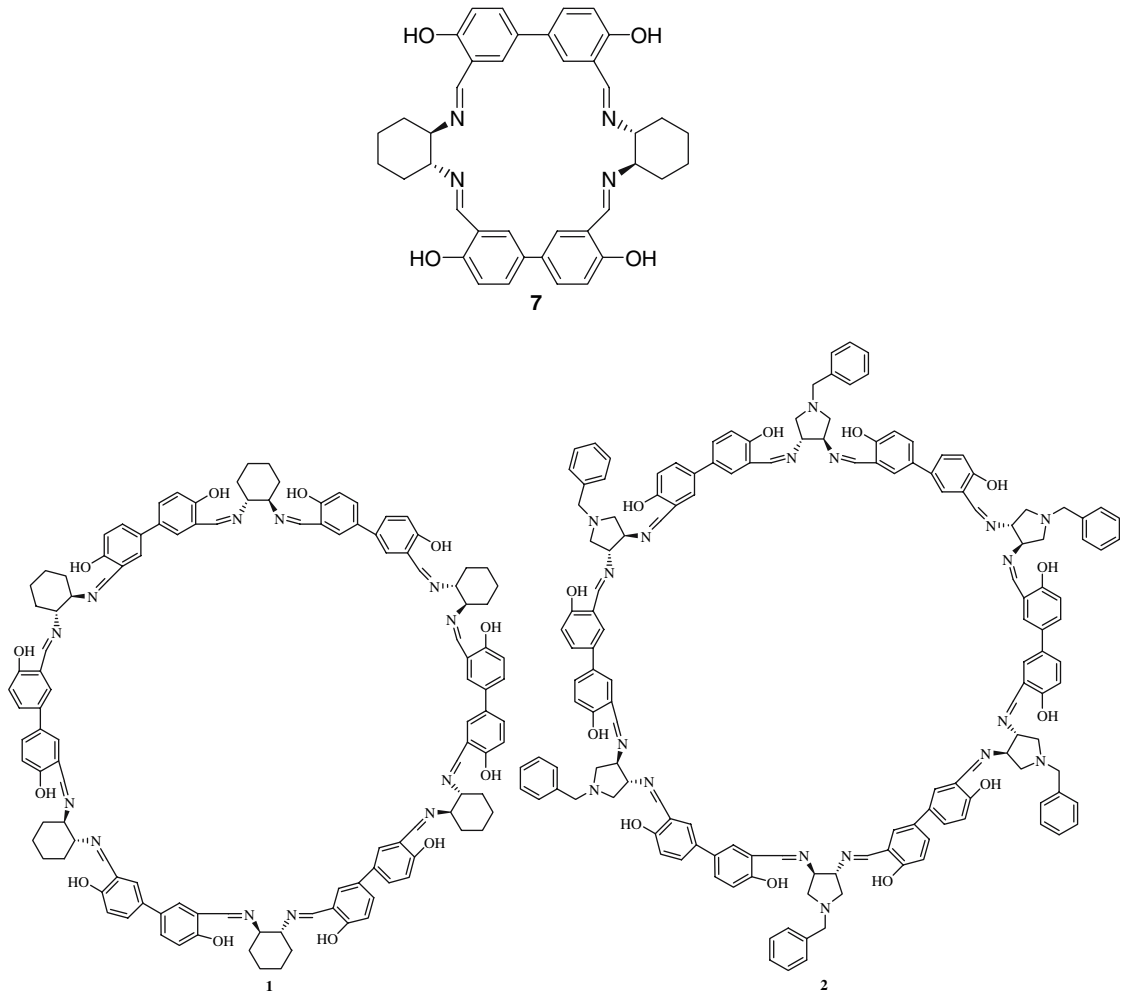


Fig. 1 Structures of macrocycle **7** and 72-membered chiral [6+6] macrocycles (**1** and **2**)

Results and discussion

Among the various dialdehydes screened for macrocycle synthesis with chiral diamines, it has been found that the conformational bias provided by 5,5′-*bis*-salicylaldehyde **3** [9] unusually produced 72-membered [6+6] macrocycles as the thermodynamic product. The dialdehyde **3** was synthesized from the corresponding 4,4′-biphenol **4**. Treatment of **4** with NaH and then with methoxymethyl chloride (MOM-Cl) gave 4,4′-bis(methoxymethoxy)biphenyl **5**. Directed ortho lithiation using *n*-BuLi followed by the addition of DMF generated 3,3′-diformyl-4,4′-bis(methoxymethoxy)biphenyl **6**. Deprotection of the MOM protecting group with 10% HCl/THF at room temperature gave **3** in 32% overall yield (Scheme 1).

Microwave irradiation (5 min) of a mixture of **3** and (1*R*,2*R*)-diammoniumcyclohexane mono-(+)-tartrate in the presence of potassium carbonate afforded two main products (**1** & **7**) in 14% and 36% isolated yield, respectively. The MALDI-TOF mass spectrum of these products corresponds to 24-membered [2+2] macrocycle **7** [9b] and 72-membered [6+6] macrocycle **1**. The corresponding thermal reaction produced the [2+2] macrocycle **7** as the major product with traces of [6+6] macrocycle **1** (Fig. 1).

The generality of the dialdehyde **3** for the construction of [6+6] macrocycles was examined by cyclocondensation with (3*R*, 4*R*)-diamino-1-benzylpyrrolidine hydrochloride. Under identical reaction conditions, the condensation produced [6+6] macrocycle **2** in 36% isolated yield with a trace amount of corresponding [2+2] macrocycle. Both the [6+6] macrocycles displayed high solubility in common organic solvents ($CHCl_3$, DMSO, Acetone, EtOAc, etc.) facilitating the spectral characterization. In general, the self-assembled condensation of aromatic dialdehydes with diamines produces a mixture of macrocycles and acyclic products. The MALDI-TOF mass spectrum of such crude reaction products display a set of peaks whose intensities decreases from lower to higher molecular weight. In contrast to such general behavior, the MALDI-TOF spectrum of crude products obtained from cyclocondensation of 5,5′-*bis*-salicylaldehyde **3** with (1*R*,2*R*)-*trans*-diaminocyclohexane is interesting and unusual (Fig. 2a, b). The spectrum shows two prominent peaks corresponding to [2+2] macrocycle **7** and [6+6] macrocycle **1**, and unusually the intermediate macrocycles, namely [3+3], [4+4] and [5+5] macrocycles were formed in traces which indicating unusual stability of the [6+6] macrocycle **1** over the other macrocycles. Similarly, the MALDI-TOF mass spectrum of the crude macrocycle **2** indicated the absence of other intermediate macrocycles ([3+3] to [5+5]) (Fig. 2c). Unlike the macrocycle **1**, the formation of [6+6] macrocycle **2** was free from the corresponding [2+2] macrocycle which was identified as a minor peak from the corresponding MALDI-TOF MS indicating that the [6+6] macrocycle was the preferred product over the corresponding [2+2] macrocycle.

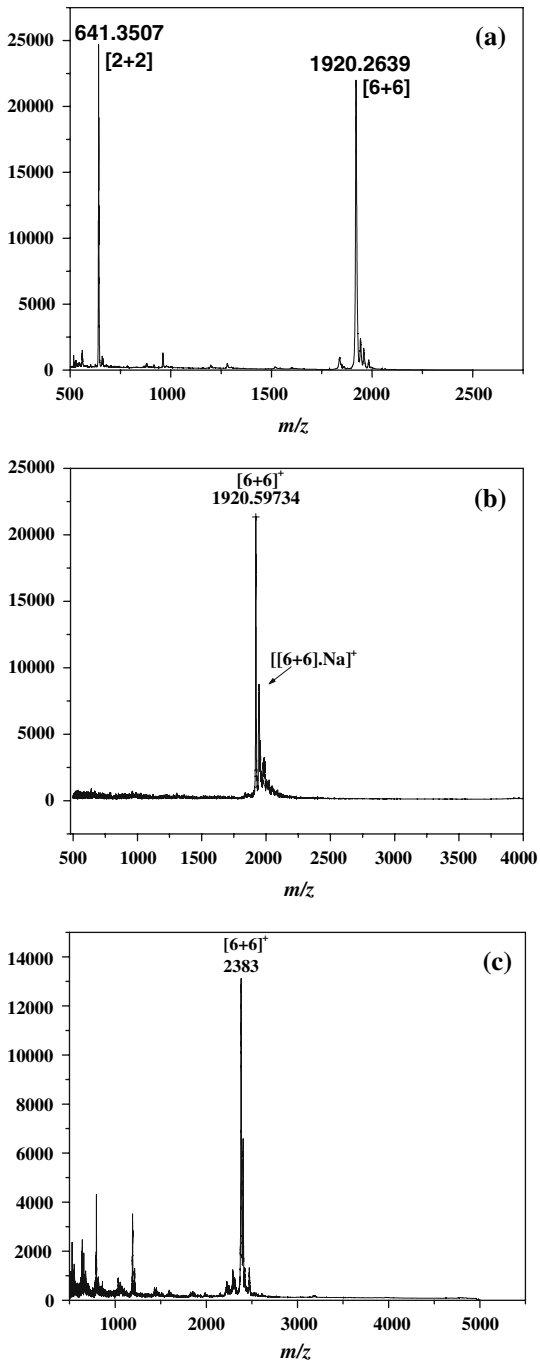


Fig. 2 MALDI-TOF MS spectra of (**a**) condensation products from **3** and (1R,2R)-diammoniumcyclohexane mono-(+)-tartrate; (**b**) pure [6+6] macrocycle **1**, and (c) [6+6] macrocycle **2**

Though, the ^{1}H-NMR spectrum of the [2+2] macrocycle **7** confirmed a highly symmetrical structure displaying a single set of proton signals, the [6+6] macrocycle **1** exhibited two sets of NMR signals in 1:1 ratio indicating a

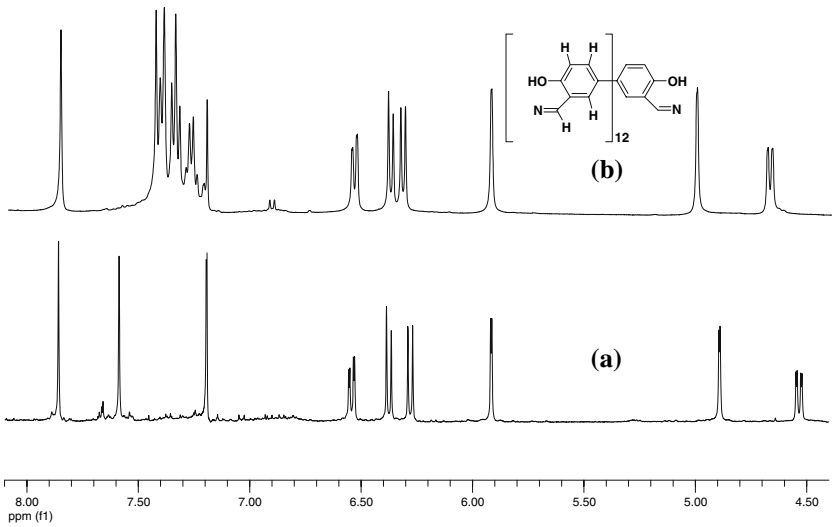


Fig. 3 Expanded downfield regions of the ^{1}H-NMR spectrum of (**a**) [6+6] macrocycle **1** and (**b**) [6+6] macrocycle **2**

highly unsymmetrical structure for the macrocycle (Fig. 3 a). One set of NMR signals was found to be highly shielded in comparison to the other set of signals. The aromatic protons of the highly shielded set unusually resonated around 4.5–5.0 ppm whereas the aromatic proton of the deshielded set resonated around 6.0–6.5 ppm. The order of resonance of aromatic signals in both the set was not identical as identified from the ^{1}H-^{1}H COSY of the macrocycle **1**. The [6+6] macrocycle **2** display identical spectral feature as that of **1** with two sets of signals in 1:1 ratio and high shielding of one set of signals (Fig. 3b). The appearance of two different sets of NMR signals indicated either an unsymmetrical macrocyclic structure or the presence of two different conformers. Variable temperature NMR studies were carried out to confirm the presence of different conformers of the macrocycle. It was observed that the temperature variations in the range of −50 °C to 110 °C did not produce any appreciable changes in NMR signals and no new signals were formed or disappeared. The NMR spectrum was remained unchanged in the temperature range studied indicating the absence of different conformers of the macrocycle that exchange at a rate that fall within the NMR time scale.

It is already known that rotation around N=C–C_{Ar} bonds and *anti-syn* isomerisation of the two R–N=C–C_{Ar} moieties were fast on the NMR time scale. Also the formation of (*Z*)–C=N bond isomers were never observed. Taking into account of the stereogenic nature of the biaryl axis, the two conformers were assigned as diastereomeric structures namely *all*-(S_a)-**1** (**2**) and *all*-(R_a)-**1** (**2**). One diastereomer was characterized by an *all*-(*R*) biaryl axis (six axes with R configuration), whereas the second diastereomer was characterized by an *all*-(*S*) biaryl axis (Fig. 4) [10]. These two highly symmetrical conformations were responsible for two sets of NMR signals which might exhibit a slow interconversion on the NMR time scale.

In summary, this is the first report on a higher order [n+n] macrocyclisation for the synthesis of chiral macrocycle Schiff base with large central cavity. The generality of the conformational bias provided by 5,5′-*bis*-salicylaldehyde for the construction of [6+6] macrocycles has been examined by cyclocondensation with two different chiral diamines. The yields of the [6+6] macrocycles were moderate and they exceptionally exhibit high solubility in a variety of organic solvents extending to the possible applications in the area of supramolecular chemistry.

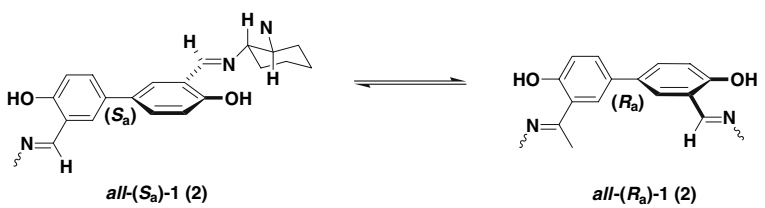


Fig. 4 Possible diastereomeric structures of [6+6] macrocycle **1** and **2**

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