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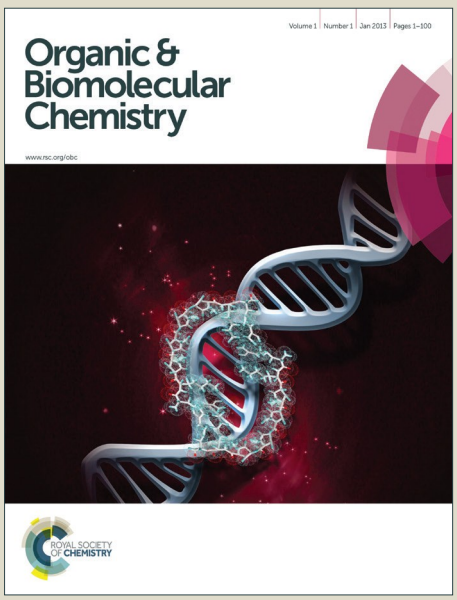




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# Synthesis, characterization of chiral aza-macrocycles and study of their enantiomer recognition ability of organo phosphoric acid and phosphonic acid derivatives by $^{31}$P NMR and fluorescence spectroscopy

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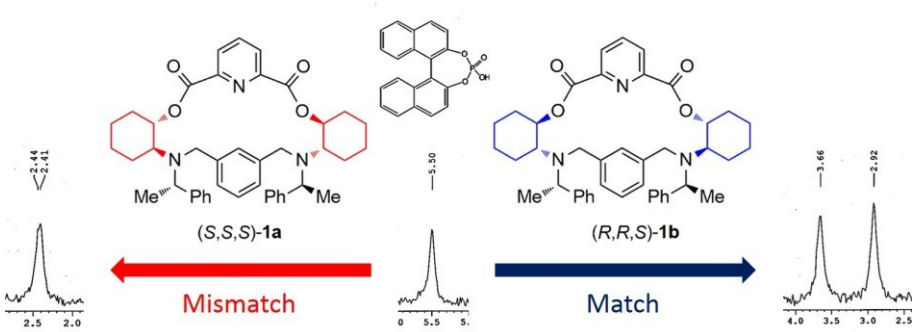


**ABSTRACT:** Two diastereomers of optically active N,O-containing new macrocycles with duel chirality of the ring and pendent group were synthesized and characterized. Difference in accessibility of the cavity was explored to discriminate enantiomers of derivatives of organo phosphoric and phosphonic acids by $^{31}$P NMR and fluorescence spectroscopy.

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**Introduction**:

Crown ethers and other macrocyclic compounds have a unique place in the field of supramolecular chemistry. These host molecules interact with guest entities by predictable and non-covalent manner. This phenomena has been well studied over the last several decades.[1] Importance of optically active molecules in the field of medicine, fragrance and flavours, material science and supramolecular chemistry has already been well established. The supramolecular interactions in biological systems between the chiral receptors and guest substrates are in general more enantiospecific. Many studies have been conducted on large complex biological assemblies and their interactions based on supramolecular principles.[2] Optically active crown ethers and other macrocyclic compounds can be prepared by introducing chirality in the backbone of the ring itself or by attaching chiral pendent groups to the achiral framework of the crown. Chiral macrocyclic hosts can selectively recognize isomers of optically active guest molecules based on supramolecular interactions. Few such macrocyclic compounds with chiral ring[3] or with suitable chiral pendent groups[4] have been reported and their molecular recognition ability with chiral guests has been investigated.

Optical purity of chiral materials is usually confirmed by more than one analytical methods such as chromatography (GC or HPLC with chiral stationary phase), spectroscopy (NMR, CD), capillary electrophoresis etc. For accurate determination of the ratio of enantiomers by NMR spectroscopy, it is necessary to convert the analyte to the diastereomers, quantitatively. This can be achieved by making diastereomeric derivatives of the analyte with appropriate chiral derivatizing agents (CDA), such as Mosher's acid,[5] involving a covalent bond. In other approach, chiral solvating agent (CSA)[6] can be mixed during the NMR analysis where it may bind temporarily with the chiral analyte, creating *in situ* diastereomers. Their ratio can be established by detecting the signals. This has been achieved by chiral crown ethers[7] or macrocyclic[8] CSAs capable of supramolecular interactions with optically active analytes. Also some crown ethers with chiral pendent groups have been used as CSA for determination of optical purity.[9] The molecular recognition of chiral macrocycles with optically active guests has also been measured by analyzing the change in their fluorescence properties.[10] Here we report synthesis of new macrocycles **1** with chiral backbone along with chiral pendent groups. We evaluate their ability to discriminate chiral organic compounds by NMR and fluorescence spectroscopy (Scheme 1). Two chiral elements will allow the study of match, mismatch effect to fine tune the CSA for such applications for different analytes. In this report we have screened derivaties of 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate, α-hydroxy phosphonic acid and α -amino phosphonic acid as analytes employing $^{31}$P NMR analysis. Chiral BINOL deived phosphoric acid derivatives have acquired significant interest in asymmetric catalysis. Chiral phosphoric acids have

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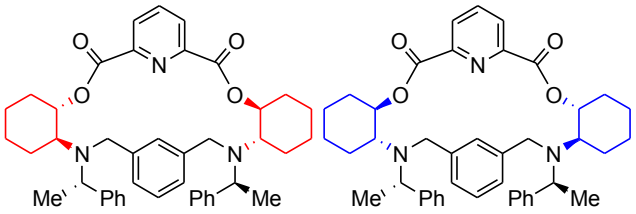
cemented their status as an efficient synthetic tool in Bronsted acid catalysis.[11] α-Hydroxy phosphonic acids and α-amino phosphonic acids have received considerable attention in the field of medicinal chemistry. Aminophosphonic acid derivatives, being structurally analogous to amino acids, have been incorporated in to many drug molecules due to their physiological activity as antiviral, antibacterial, anticancer and neuroactive compounds.[11a]

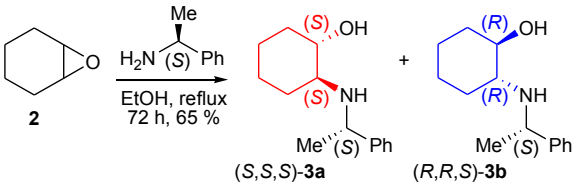
**Scheme 1** New macrocycles with chiral backbone and chiral pendent group




**Result and Discussion:**

The two diastereomers of the aminocyclohexanol, **3a** and **3b**, were obtained by ring opening reaction of cyclohexene oxide **2** with (*S*)-2-phenylethyl amine (Scheme 2).[12]

**Scheme 2** Preparation of amino alcohols from cyclohexeneoxide




The two separated diastereomers were condensed with *m*-xylene dibromide to afford two diastereomers of diol **4a** and **4b** (Scheme 3). The final eighteen member macrocycles were prepared by transesterification with dimethyl 2,6-pyridinedicarboxylate by a slightly modified procedure.

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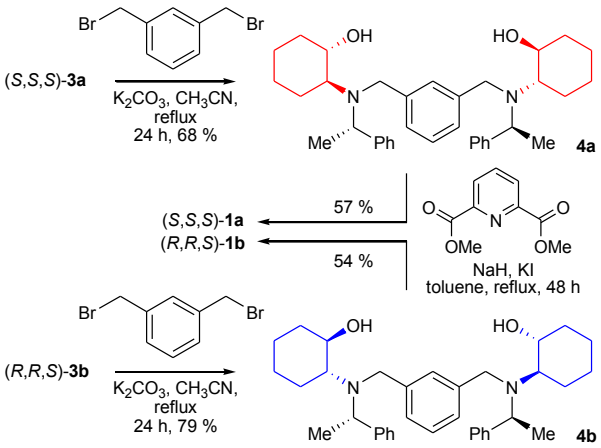
**Scheme 3** Synthesis of the macrocycle




Single crystal X-ray analysis of both the diastereomers of macrocycles revealed interesting features. In case of (*S*,*S*,*S*)-**1a** the phenyl unit of the pendent groups were seen to lie on the top and cover the bottom of the macrocyclic cavity while in case of (*R*,*R*,*S*)-**1b** they appear to be away (Figure 1).

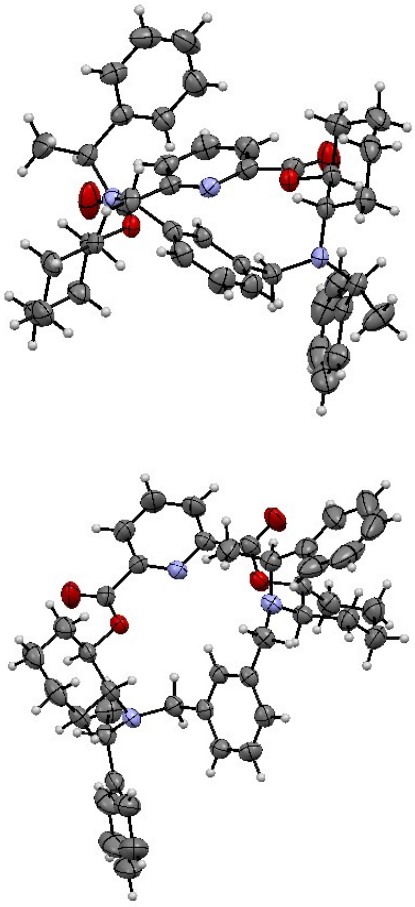


**Figure 1** X-ray structure of (*S*,*S*,*S*)-**1a** [top] (CCDC N0. 1004162) and (*R*,*R*,*S*)-**1b** [bottom] (CCDC N0. 1016922).

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Recently chiral Brønsted acids such as phosphoric acid derivative 1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate **5a** and its analogues have found wide uses as chiral catalysts.[11b,c] There can be three different types of chiral organic phosphorous containing acid derivatives (Chart 1).

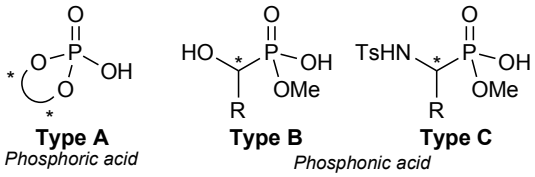
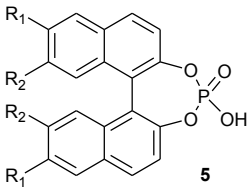



**Chart 1** Types of phosphorous containing analytes

The two derivatives of **1** were screened to study their ability to discriminate the $^{31}$P NMR signals[13] of derivatives of **5** by measuring the chemical shift non-equivalence (ΔΔδ) (Table 1). A clear pattern of better discrimination for (*R*,*R*,*S*)-**1b** was observed in all the examples, while the other derivative (*S*,*S*,*S*)-**1a**, with closed cavity was found ineffective (Figure 2).

**Table 1** Discrimination of Binaphthyl phosphoric acids **5**[a]




| No | Comd. No. | $R_1$ | $R_2$ | ΔΔδ (ppm) | |
|---|---|---|---|---|---|
| | | | | (*S*,*S*,*S*)-**1a** | (*R*,*R*,*S*)-**1b** |
| 1 | **5a** | H | H | 0.03 | 0.74 |
| 2 | **5b** | H | OMe | --[b] | 0.68 |
| 3 | **5c** | H | O-iPr | --[b] | 0.76 |
| 4 | **5d** | $NO_2$ | H | --[b] | 0.81 |
| 5 | **5e** | Br | H | --[b] | 0.40 |

[a]In $CDCl_3$ (20 mM), 162 MHz ($^{31}$P NMR), ratio of 5:1 (2:1);
[b]Not resolved.

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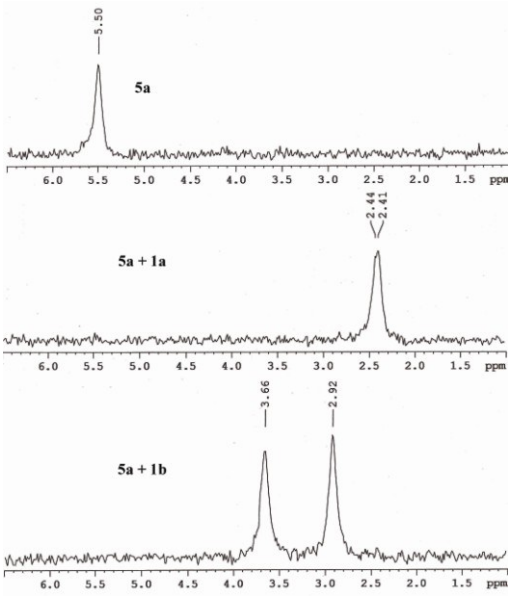


**Figure 2** $^{31}$P NMR signals for (±)-**5a** with **1a** and **1b**.

The separation of signals was further studied to establish linear relationship between experimental and actual values of optical purity for establishing practical utility of CSA (see ESI).

The nature of complex between **5** and the isomers of macrocycle was determined by IR spectroscopy. Complex of **5** with **1a** showed a weak band at 1098 $cm^{-1}$ for phosphoryl bond stretching,[14] but appears much stronger for **1b** (see ESI). This may indicate a better complexation in case of **1b** supporting the observation.

Use of fluorescence spectroscopy for understanding the recognition of chiral molecules has received considerable attention.[15] Many chiral fluorescent host molecules have been known to exhibit enantioselective quenching[15c] or enhancement[15g] on interaction with chiral guests. In this study the fluorescence property of the analyte **5a** was utilized to evaluate the interactions with the two isomers of macrocycle. Such chirality dependent quenching of both enantiomers of **5a** in presence of macrocycles **1a** and **1b** have been investigated. The recognition ability of macrocycles towards the phosphoric acid was evident from the extent of quenching (Figure 3). The static quenching is probably attributed to the deprotonation of phosphoric acid **5a**, which is indicated by appearance of new peak in the UV-Vis spectra[15c] (at the higher wavelength at 327 nm; see ESI).

The response of quenching the emission of enantiomers of **5a** with **1a** follows the Stern-Völmer equation. The florescence quenching efficiency can be expressed as a ratio of $K_{sv}^{R\text{-}5a}/K_{sv}^{S\text{-}5a}$ which was observed to be 1.05 (Figure 3, A-2). On the other hand quenching of enantiomers of **5a** with the other macrocycle **1b** indicated the ratio $K_{sv}^{R\text{-}5a}/K_{sv}^{S\text{-}5a}$ to be 1.40 (Figure 3, B-2), indicating

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its higher quenching ability.[16] This data confirms the recognition observed in $^{31}$P NMR analysis. These observations substantiate the assumption that the relatively open cavity of **1b** facilitates efficient complexation between protonated macrocycle and phosphate ion as well as π-π interaction of naphthyl ring of **5** (see ESI for geometrical model).

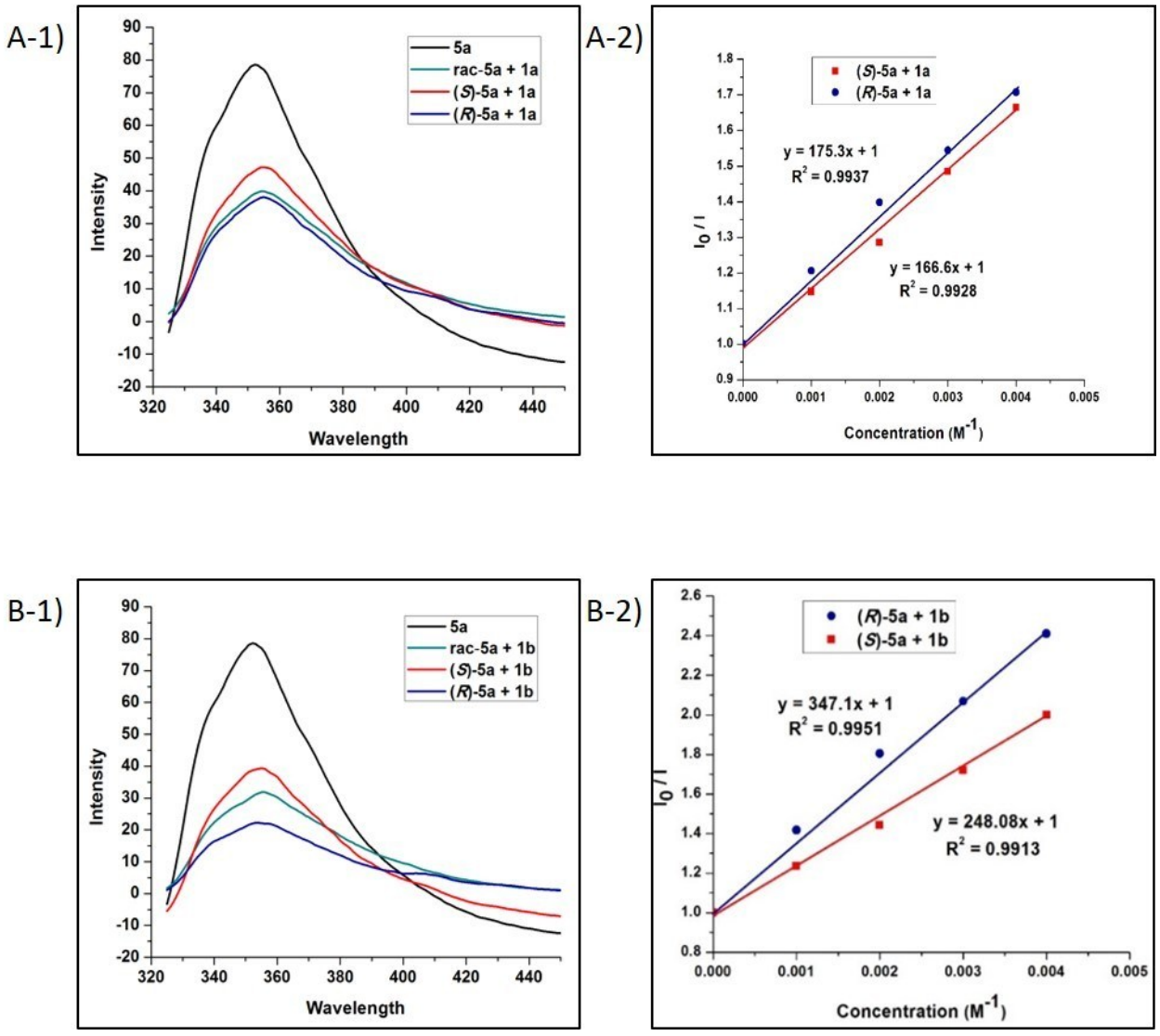


**Figure 3** Quenching study: A-1) Fluorescence spectra of **5a** ($10^{-5}$ M, $CHCl_3$); (±)-**5a**, (*S*)-**5a** and (*R*)-**5a** in presence of **1a** ($\lambda_{ex}$ = 305 nm); A-2) Stern-Völmer plots of (*S*)-**5a** and (*R*)-**5a** with **1a**; B-1) Fluorescence spectra of **5a** ($10^{-5}$ M, $CHCl_3$); (±)-**5a**, (*S*)-**5a** and (*R*)-**5a** in presence of **1b** ($\lambda_{ex}$ = 305 nm); B-2) Stern-Völmer plots of (*S*)-**5a** and (*R*)-**5a** with **1b**.

Preliminary investigation was made to determine effective stoichiometric ratio of host-guest association in the present system (Table 2). Although each macrocycle contains three basic sites, out

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of which the two tertiary nitrogens undergo protonation to generate ion pairs, as evident from entry 2 of Table 2. While the third site of pyridine is expected to show π-π interaction with the naphthyl ring of guest molecule.

**Table 2** Determination of stoichiometry of host (**1b**) and guest (**5a**) association.

| No | Ratio[a] **1b** : **5a** | ΔΔδ (ppm) |
|---|---|---|
| 1 | 1 : 3 | 0.58 |
| 2 | 1 : 2 | 0.74 |
| 3 | 1 : 1 | 0.66 |
| 4 | 1 : 0.5 | 0.63 |

[a]In $CDCl_3$ (20 mM), 162 MHz ($^{31}P$ NMR).

Chiral phosphonic acid derivatives which resemble closely have also been found useful in medicinal chemistry and in asymmetric transformations.[17] It was noteworthy to see a reverse trend for a second group of analytes of α-substituted phosphonic acids (**6** to **10**) with the same set of macrocyclic CSAs (Table 3). These analytes, being smaller in size are better accommodated in the partially closed cavity of macrocycle **1a**. Presence of hydrogen bond donor group at the α position of phosphonic acid is essential to effect the discrimination. In case of α-chloro derivative **8** both the macrocycles are found to be ineffective in the discrimination.

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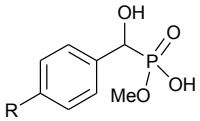
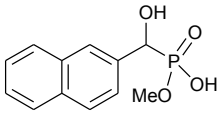
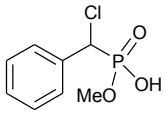
**Table 3** Discrimination of monomethyl esters of substituted phosphonic acids **6** to **10**[a]




**6**

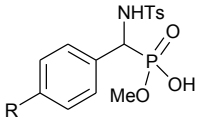



**7**

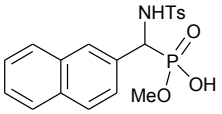



**8**

| No | Comd. No. | R | ΔΔδ (ppm) | |
|---|---|---|---|---|
| | | | (*S*,*S*,*S*)-**1a** | (*R*,*R*,*S*)-**1b** |
| 1 | **6a** | H | 0.17 | 0.04 |
| 2 | **6b** | Me | 0.19 | --[b] |
| 3 | **6c** | Cl | 0.16 | --[b] |
| 4 | **7** | -- | 0.17 | --[b] |
| 5 | **8** | -- | --[b] | --[b] |




**9**




**10**

| | | | | |
|---|---|---|---|---|
| 6 | **9a** | H | 0.40 | --[b] |
| 7 | **9b** | Me | 0.42 | --[b] |
| 8 | **9c** | Cl | 0.45 | 0.10 |
| 9 | **9d** | OMe | 0.43 | --[b] |
| 10 | **9e** | $NO_2$ | 0.40 | 0.12 |
| 11 | **10** | -- | 0.37 | --[b] |

[a]In $CD_3OD$ (5%) in $CDCl_3$ (20 mM), 162 MHz ($^{31}P$ NMR), ratio of **6** to **10**:**4** (2:1); [b]Not resolved.

In both the cases protonation of nitrogen of macrocycles result in electrostatic interactions holding the diastereomers together effecting the chiral discrimination. In the second set of analytes there could be additional H-bonding interaction working in tandem. The formation of H-bond be-

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tween phosphonic acid analyte and H-bond acceptor sites of macrocyclic CSA are probably favored by partially close cavity of **1a**. This could also explain better discrimination for the α-amino derivatives (**9** and **10**) where the H-bonding will be stronger.

In summary, two diastereomers of eighteen member N,O-macrocycles are synthesized and evaluated as CSA for effective discrimination of $^{31}P$ NMR signals and fluorescence quenching of several organo phorphoric and phosphonic acid derivatives. Combination of chirality on the backbone of macrocycle and of the pendant group was explored for molecular recognition of optically active hosts for quantifiable discrimination. Further studies on the binding between isomers of macrocycles and two sets of guest molecules are in progress.

**Experimental Section:**

Reagents were purchased from Sigma-Aldrich Chemicals Limited, SD Fine, Sisco, Qualigens, Avara Chemicals Limited etc. All the glassware were flame dried before experiment. All solvents that were used were stored on oven dried molecular sieves (4Å). All commercial products were used without further purification. Toluene was distilled and dried by passing Sodium wire. Thin Layer Chromatography was performed on Merck 60 F254 Aluminium coated plates. The spots were visualized under UV light or with iodine vapour. All the compounds were purified by column chromatography using SRL silica gel (60-120 mesh). All reactions were carried out under an inert atmosphere (nitrogen) unless other conditions are specified. $^{1}H$, $^{13}C$ and $^{31}P$ NMR spectra are recorded on a 400 MHz Bruker Avance 400 Spectrometer (100 MHz for $^{13}C$ and 162 MHz for $^{31}P$ respectively) spectrometer with $CDCl_3$ as solvent and TMS as internal standard. Signal multiplicity is denoted as singlet (s), doublet (d), doublet of doublet of doublets (ddd), triplet (t), doublet of triplet (dt), quartet (q) and multiplet (m). Mass spectra were recorded on Thermo-Fischer DSQ II GCMS instrument. IR spectra were recorded on a Perkin-Elmer FTIR RXI spectrometer as KBr pallets or neat in case of liquids. UV-vis spectra were recorded on Perkin-Elmer Lambda−35. Fluorescence spectra were recorded on Jasco FP-6300 Spectrofluorometer. The 1,1'-Binaphthyl-2,2'-diylhydrogen phosphate derivatives **5a-5e** were synthesized by reported procedure.[18a] Monomethyl esters of α-hydroxy and α-amino phosphonic acids **6-10** were synthesized by following literature procedure.[18b] All $^{31}P$ CSA NMRs were recorded by mixing 1equiv (10 mmol) of **1a** or **1b** and 2 equiv (20mmol) of hosts (**5-10**) in 0.6ml $CDCl_3$ or indicated otherwise.

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**Synthesis of (1*S*,2*S*)-*trans*-2-(*N*-Benzoyl-*N*-methyl)amino-1-cyclohexanol (3a)**

A mixture of (*S*)-phenylethyl amine (1.0g, 8.3mmol) and cyclohexenoxide (0.97g, 9.9mmol), in 15mL dry ethanol, was refluxed under nitrogen atmosphere for 72 h. The solvent was then evaporated under vacuum and the reaction mixture was subjected to column chromatography (ethyl acetate/petroleum ether, 3:7) yielding compound **3a** as colourless oil. (0.63g, 35 %);

$[\alpha]_D^{25}$= +11.5 (*c* = 1.0 in MeOH) (Lit[12] +20.9 *c* = 1.64, MeOH)

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 0.80-0.91 (1H, m), 1.15-1.35 (3H, m), 1.34-1.36 (3H, d, *J* = 6.4 Hz), 1.66-1.73 (2H, m), 1.94-1.98 (1H, m), 2.09-2.06 (1H, m), 2.32-2.38 (1H, ddd, *J* = 13.2, 9.2, 4.0 Hz), 3.08-3.14 (1H, dt, *J* = 9.2, 4.4), 3.91-3.96 (1H, q, *J* = 6.4 Hz), 7.24-7.28, (1H, m), 7.32-7.36 (4H, m).

**$^{13}$C NMR** (100 MHz, $CDCl_3$):$\delta$ 23.5, 24.2, 25.4, 31.3, 33.0, 55.2, 61.5, 74.0, 126.4, 127.1, 128.5, 146.7.

**IR** (neat): $\upsilon$ 3412, 2980, 1449, 1370, 1062, 762, 700.

**Mass** (ESI): *m/z* 242 (30), 221 (50), 220 (94), 158 (30), 116 (99), 106 (24), 105 (100).

**Synthesis of (1*R*,2*R*)-*trans*-2-[(*S*)-(α-Methylbenzyl)amino]-1-cyclohexanol (3b)**

As described above, the compound **3b** was obtained from the later fractions from column chromatography (ethyl acetate/petroleum ether, 2:3) as white solid. (0.54g, 30%);

**Mp:** 53-54 $^oC$

$[\alpha]_D^{25}$= -99.6 (*c* = 1.0 in MeOH) (Lit[12.] -100.2 *c* = 1.20, MeOH)

**$^1$H NMR** (400 MHz, $CDCl_3$): 0.88-1.01 (1H, m), 1.07-1.13 (2H, m), 1.19-1.30 (1H, m), 1.36-1.38 (3H, d, *J* = 6.4 Hz) 1.64-1.69 (2H, m), 1.99-2.05 (2H, m), 2.14-2.20 (1H, m), 3.14-3.20 (1H, m) 3.99-4.04 (1H, q, *J* = 6.4 Hz), 7.25-7.27 (1H, m), 7.31-7.35 (4H, m)

**$^{13}$C NMR** (100 MHz, $CDCl_3$):$\delta$ 24.2, 25.0, 25.6, 30.3, 32.9, 54.1, 60.0, 74.0, 126.7, 127.1, 128.6, 145.0.

**IR** (KBr): $\upsilon$ 3480, 2924, 1452, 1368, 1350, 1127, 1064, 762, 698.

**Mass** (ESI): *m/z* 242 (7), 221 (48), 220 (96), 116 (96), 106 (24), 105 (100).

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**(1*S*,1'*S*,2*S*,2'*S*)-2,2'-((*S*)-(1,3-phenylenebis(methylene))bis(((*S*)-1-phenylethyl)azanediyl))-dicyclohexanol (4a)**

A solution of amino alcohol **3a** (0.5g, 2.2mmol) in 10mL acetonitrile was added $K_2CO_3$ (0.69g, 5.0mmol) and $\alpha,\alpha'$-dibromo-*m*-xylene (0.33g, 1.3mmol). The mixture was then refluxed under nitrogen for 24 h. The solvent was then evaporated under vacuum and the mixture was poured in cold water and extracted from ethyl acetate (3 x 50 mL) and the combined extracts were washed with water (2 x 25mL). The organic layer was dried over anh. $Na_2SO_4$, evaporated under vacuum and then subjected to column chromatography on silica gel (ethyl acetate/ petroleum ether, 1:4) to afford compound **4a** as white solid.(0.42g, 68%);

**Mp:** 58-60 $^oC$.

 = +83.9 (*c* = 1.0 in $CHCl_3$).

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 1.21–1.28 (3H, m), 1.27-1.39 (1H, m), 1.47-1.49 (3H, d, *J* = 6.4 Hz), 1.64-1.66 (1H, m), 1.76-1.78 (1H, m), 1.92-1.93 (1H, m), 1.96- 2.03 (1H, m), 2.34-2.39 (1H, m) 3.33-3.68 (1H, m), 3.64-3.67 (1H, d, *J* = 13.6 Hz), 3.86-3.89 (1H, d, *J* = 13.6 Hz), 4.02-4.07 (1H, q, *J* = 6.8 Hz) 7.13-7.25 (6H, m), 7.29-7.38 (1H, m)

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ 13.9, 24.2, 25.9, 27.7, 33.3, 49.9, 55.9, 62.3, 69.4, 127.1, 127.6, 128.0, 128.4, 128.8, 130.2, 140.7, 143.8.

**IR** (KBr): $\upsilon$ 3465, 2934, 1603, 1450, 1374, 1218, 1076, 759, 701.

**Mass** (ESI): *m/z* 542 (40), 541 (100), 349 (10), 348 (46), 234 (13).

**HRMS**: Calculated for $C_{36}H_{49}N_2O_2$ (M+1) = 541.3788. Found 541.3789.

**(1*R*,1'*R*,2*R*,2'*R*)-2,2'-((*S*)-(1,3-phenylenebis(methylene))bis(((*S*)-1-phenylethyl)azanediyl))-dicyclohexanol (4b)**

The title compound was obtained by following the same procedure as for compound **4a** from the corresponding amino alcohol **3b.** The organic extract was column chromatographed (ethyl acetate/ petroleum ether, 1:4) to yield compound **4b** as white solid. (0.49g, 79%);

**Mp:** 111-112 $^oC$.

 = -161.4 (*c* = 1.0 in $CHCl_3$).

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**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 1.22–1.38 (4H, m), 1.45-1.47 (3H, d, $J$ = 6.8 Hz), 1.70-1.71 (1H, m) 1.77-1.99 (1H, m), 1.95-1.98 (1H, m), 2.09-2.11 (1H, m), 2.59-2.65 (1H, m), 3.41-3.47 (1H, m), 3.67-3.69 (1H, d, $J$ = 13.2 Hz), 3.96-4.02, (2H, m), 5.34 (1H, s), 6.67-6.69 (1H, d, $J$ = 8.0), 7.09-7.17 (3H, m), 7.19-7.22 (2H, m), 7.25-7.29 (1H, m).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ 20.1, 24.2, 25.6, 25.8, 33.4, 50.2, 57.4, 62.8, 69.2, 127.1, 127.3, 127.8, 128.3, 128.7, 128.9, 140.9, 142.0.

**IR** (KBr): $\upsilon$ 3440, 2928, 1603, 1449, 1373, 1349, 1198, 1084, 761, 699.

**Mass** (ESI): *m/z* 542 (37), 541 (100), 523 (5).

**HRMS**: Calculated for $C_{36}H_{49}N_2O_2$ (M+1) = 541.3788. Found 541.3789.

**Synthesis of Aza-macrocycle (1a)**

In a three neck round bottom flask fitted with septa, a mixture of diamino diol **4a** (0.4g, 0.74mmol), NaH (0.15g, 3.7mmol) and KI (0.13g, 0.74mmol) was heated to reflux under nitrogen in 30mL dry toluene for 0.5 h. To this mixture a solution of dimethyl 2,6-pyridinedicarboxylate (0.17g, 0.89mmol) in 10mL dry toluene was added dropwise with a syringe over a period of 0.5 h. The mixture was then refluxed for 48 h. After completion of reaction the solvent was removed under vacuum and the reaction mixture was subjected to column chromatography (ethyl acetate/petroleum ether, 1:9) resulting in white solid. (0.28g, 57%);

**Mp:** >200 $^oC$.


= -162.7 ($c$ = 1.0 in $CHCl_3$).

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 0.9-1-1.10 (2H, m), 1.26-1.42 (4H, m), 1.53-1.54 (1H, m), 1.57-1.59 (6H, d, $J$ = 6.4 Hz), 1.59-1.69 (5H, m), 1.69-1.99 (2H, m), 2.29-2.31 (2H, m), 3.04-3.10 (2H, dt, $J$ = 10.8, 3.2 Hz), 4.01-4.04 (2H, d, $J$ = 13.6 Hz), 4.07-4.10 (2H, d, $J$ = 13.6 Hz), 4.28- 4.30 (2H, q, $J$ = 6.4 Hz), 5.12-5.16 (2H, dt, $J$ = 10.8, 3.6 Hz), 6.98-7.01 (6H, m), 7.17-7.26 (3H, m), 7.64 (4H, s), 7.87-7.91 (1H, t, $J$ = 4.0 Hz), 8.22-8.24 (2H, d, $J$ = 7.6 Hz), 8.51 (1H, s).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ 20.4, 24.6, 25.5, 29.4, 32.0, 50.5, 53.6, 58.7, 77.4, 125.9, 126.5, 127.6, 127.8, 128.5, 130.7, 136.9, 140.6, 145.8, 148.8, 165.3.

**IR** (KBr): $\upsilon$ 2940, 1704, 1602, 1585, 1448, 1368, 1330, 1243, 1144, 957, 701.

**Mass** (ESI): *m/z* 672 (100), 568 (60), 464 (70) 462(20), 105(20).

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**HRMS**: Calculated for $C_{43}H_{50}N_3O_4$ (M+1) = 672.3790. Found 672.3796.

### Synthesis of Aza-macrocycle (1b)

The title compound was obtained by following the same procedure as for compound **1a** from the corresponding diamino diol **4b.** The organic extract was column chromatographed (ethyl acetate/ petroleum ether, 1:9) to yield compound **1b** as white solid. (0.27g, 54%);

**Mp:** >200 $^{o}$C.

 = +36.8 (*c* = 1.0 in $CHCl_3$).

The $^{1}$H and $^{13}$C NMR spectra of compound **1b** exhibit broad signals. This type of observation for macrocyclic system has been reported earlier by Periasamy et al.[3i]

**$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta$ 1.26-1.28 (4H, m), 1.30-1.43 (7H, m), 1.59-1.69 (9H, m), 2.23 (2H, s), 2.97-3.32 (2H, m), 3.61-3.64 (2H, d, *J* = 13.6 Hz) 4.26 (4H, m), 5.31 (2H, s), 7.07 (2H , br s), 7.19-7.20 (4H, m), 7.28-7.30 (4H, m), 7.54 (3H, s), 8.04-8.08 (1H, t, *J* = 8 Hz), 8.47 (3H, m).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta$ 18.3, 24.4, 25.4, 30.0, 31.9, 50.7, 52.2, 53.4, 57.8, 79.2, 126.2, 126.8, 127.6, 127.9, 129.2, 133.6, 137.8, 140.1, 146.5, 149.4, 165.9.

**IR** (KBr): $\upsilon$ 2941, 1705, 1559, 1449, 1369, 1333, 1245, 1082, 700.

**Mass** (ESI): *m/z* 695 (45), 694 (80), 672 (M+1, 100), 568 (10).

**HRMS**: Calculated for $C_{43}H_{50}N_3O_4$ (M+1) = 672.3790. Found 672.3797.

### Supporting Information

The supporting Information is available free of charge on the RSC Publication website at DOI:

This includes copies of the spectral data, details of crystal structure including cif files, spectra of CSA study (as PDF).

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