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Novel C_2-Symmetric Macrocycles Bearing Diamide−Diester Groups: Synthesis and Enantiomeric Recognition for Primary Alkyl Ammonium Salts

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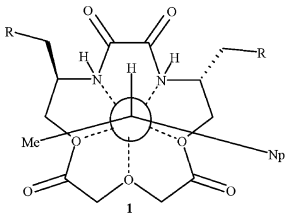

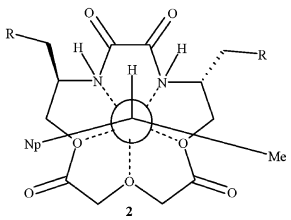

We synthesized a series of novel macrocycles with diamide−diester groups (*S*,*S*)-**1**, (*S*,*S*)-**2**, (*S*,*S*)-**3**, and (*R*,*R*)-**1**, derived from dimethyloxalate and amino alcohols by high dilution technique, and evaluated enantiomeric recognition properties of these macrocycles toward primary alkyl ammonium salts by ^{1}H NMR titration. Taking into account the host employed, important differences were observed in the K_a values of (*R*)-Am and (*S*)-Am for (*S*,*S*)-**1** and (*R*,*R*)-**1** hosts, $K_S/K_R = 5.55$ and $K_R/K_S = 3.65$, $\Delta\Delta G_o = 0.43$ and -0.32 kJ mol^{-1}, respectively. There seems a general tendency for the host to include the guests with the same absolute configuration.

Introduction

Enantiomeric recognition is an essential process in living organisms involving the differentiation of one enantiomer of the guest from the other by a chiral host. Examples of enantiomeric discrimination can be found in many natural processes such as enzyme−substrate interactions, immunological responses, the mechanism of drug action, and the storage and retrieval of genetic information.[1] The development of chiral artificial receptors with the properties chiral recognition has attracted increasing attention because of their high sensitivity and potential applications in pharmaceuticals,[2,3] analysis,[4,5] biology,[6] catalysis,[7−9] and sensing.[10] The chemical and more important biological activities of many chiral substances depend a great deal on the stereochemistry. That is why design, synthesis, and structural activity relationships of enantioselective receptors are still vital areas of research.[11] Recently, much attention has been paid to the development of molecular receptors that recognize chiral molecules.

The study of enantiomeric recognition of amine and protoned amine compounds is of significance because these compounds are basic building blocks of biological molecules. Amino acids are major components of proteins in natural living systems, and their versatile abilities to form complexes with a variety of molecules present various types of interaction modes.[12] Since Cram et al. reported their pioneering research on the use of chiral macrocyclic ligands in enantiomeric recognition,[13] a great number of chiral artificial receptors have been synthesized and studied. Among these, chiral macrocyclic compounds involving

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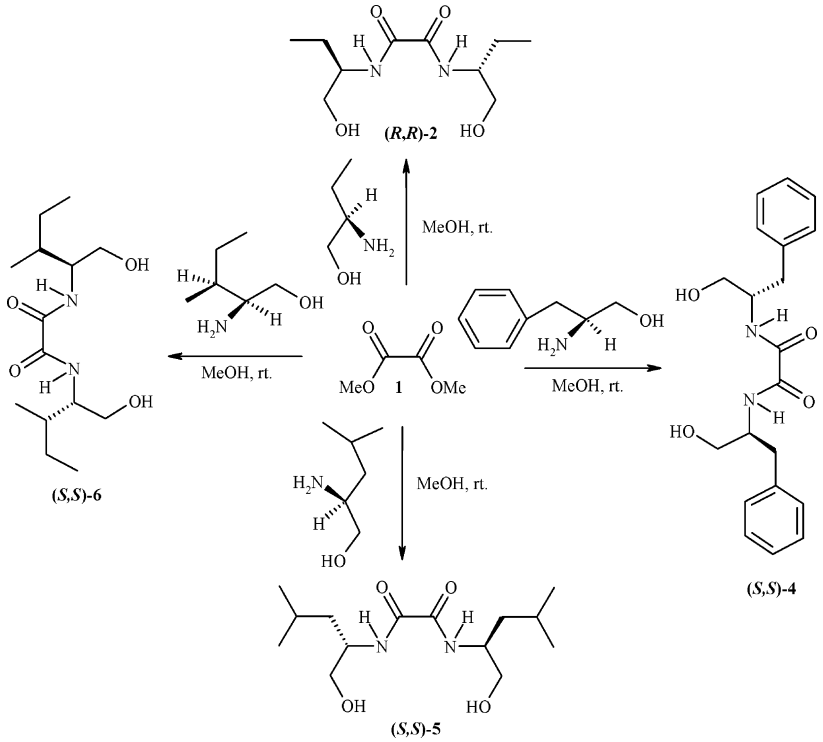
SCHEME 1. The Synthesis of Bis(amino alcohol)oxalamides



cyclophanes,[14] crown ethers,[15] and cyclodextrins[16] are the dominant structures. On the other hand, it is well known that the rigid and C_2-symmetric macrocycles are more selective for protoned amines than the non-rigid and C_2-symmetric molecules.[12]

It is also well known that the amide group has high affinity for cations with high charge density. Many ionophores with amide ligands are currently employed as chemical sensors that can quantitatively and reversibly measure cationic analytes.[17−19] Macrocyclic diesters and diamides are widely found in nature and constitute an extensive range of natural products with diverse biological activity.[20−22] These natural compounds are complex structures due to the presence of multi-functional groups and their chirality. A number of macrocyclic compounds containing diamide−diester groups have been synthesized.[23] However, few examples have been reported, dealing with the synthesis and chiral recognition studies of chiral macrocyclic containing diamide−diester groups. Herein, we report the synthesis of a series of novel, rigid, and C_2-symmetric macrocycles having two amide and two ester groups in macrocyclic ring by high dilution technique and evaluate enantiomeric recognition properties of these macrocycles toward primary alkyl ammonium salts by ^{1}H NMR titration methods.

Results and Discussion

Synthesis. In the present study, chiral, rigid, and C_2-symmetric macrocycles (*S*,*S*)-**1**, (*S*,*S*)-**2**, (*S*,*S*)-**3**, and (*R*,*R*)-**1** were synthesized from bis(amino alcohol)oxalamides (*S*,*S*)-**4**, (*S*,*S*)-**5**, (*S*,*S*)-**6**, and (*R*,*R*)-**2** as shown in Schemes 1 and 2. Chiral bis(amino alcohol)oxalamides were synthesized from (*R*)-2-amino-1-buthanol, (L)-leucinol, (L)-phenylalanilol, and (L)-isoleucinol reacted with dimethyloxalate in methanol at room temperature, respectively. Chiral bis(amino alcohol)oxalamides were obtained with very high yield (≥97%). Macrocyles were synthesized from corresponding chiral bis(amino alcohol)-oxalamides by high dilution technique. These macrocycles are readily prepared in good yields in short synthetic sequences and allow high modularity by simply changing the amino alcohol moiety. The functionality of amides and esters is not only suitable for binding but also ensures high rigidity. The structures proposed for these new chiral bis(amino alcohol)oxalamides and macrocycles are consistent with data obtained from ^{1}H, ^{13}C NMR, IR, and elemental analyses. All ^{1}H and ^{13}C NMR signals were assigned on the basis of DEPT and ^{1}H−^{13}C correlation experiment.

Enantiomeric Recognition Studies Using NMR Titration Method. The main purpose of synthesizing these macrocycles is to study their enantiomeric recognition for guest molecules. The enantiomeric recognition can be characterized by various spectroscopic methods, such as NMR, ultraviolet visible (UV−

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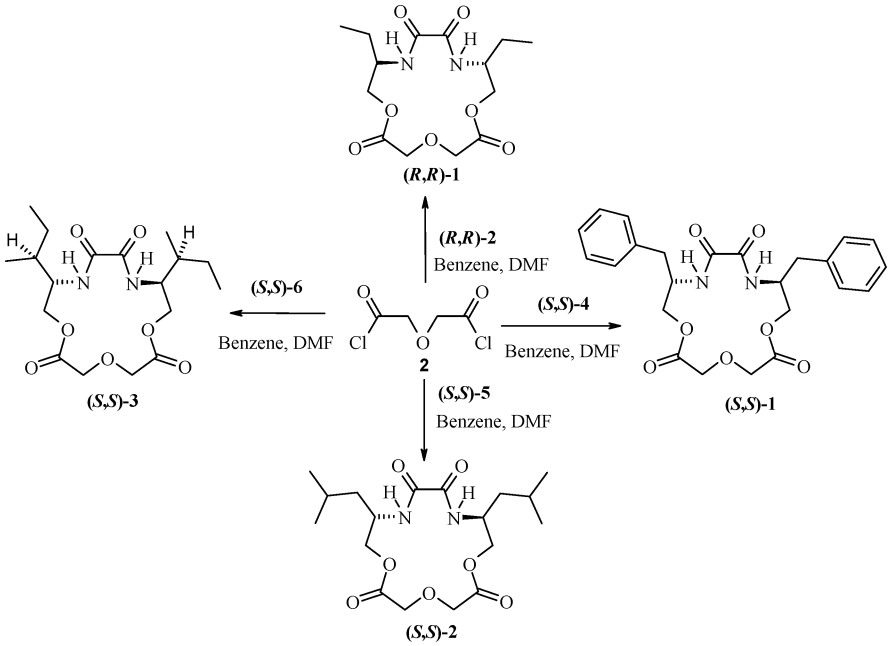
SCHEME 2. The Synthesis of Macrocycle



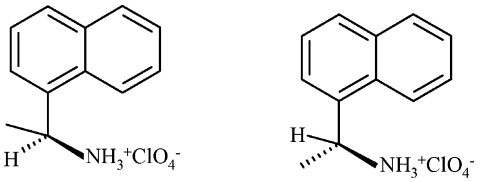
vis), fluorescence, and infrared (IR), which are powerful tools used for the examination of the recognition ability of new chiral macrocycles.[24−30] NMR has become a routine tool for the study of host−guest supramolecular chemistry, and there are now hundreds of reports of studies where NMR titration was used to measure intermolecular association.[25,31,32]

When the macrocycles absorb light at different frequency in free and complexed states, the differences of chemical shifts in the NMR spectra may suffice for the estimation of enantiomeric recognition of thermodynamics. In NMR titration experiments, the addition of varying concentration of guest molecules results gradually in shifting of some chemical signals upfield or downfield. The complexation of ammonium cations [G] with chiral macrocycle [H] is expressed by eq 1:

$$H + G \overset{K}{\rightleftharpoons} H{\cdot}G \qquad (1)$$

Under the condition employed herein, chiral α-(1-napthyl) ethylamine perchlorate salts ((*R*)-Am and (*S*)-Am) were selected as the guest molecules (Scheme 3). The association constant of the supramolecular systems formed was calculated according to the modified Benesi−Hildebrand equation (eq 2), where $[H]_o$ and $[G]_o$ refer to total concentration of macrocycles and organic ammonium salts, respectively. The original Benesi−Hildebrand experiment was an optical spectroscopy study of the association of iodine with aromatic hydrocarbons.[33] The key feature of this

SCHEME 3. Ammonium Perchlorate Salts Used as the Guest



method is that by working with a large excess of component H, the concentration of uncomplexed H can be set equal to the initial concentration, $[H] = [H]_0$. Relationships between known quantities (initial concentrations) and experimental observations can now be derived, Mathur et al.[34] and Hannah and Ashbaugh[35] have independently derived the NMR version of the Benesi−Hildebrand equation. For all of the guests examined, plots of calculated $1/\Delta\delta$ values as a function of $1/[G]_o$ values give a linear relationship with a slope $1/K_a{\cdot}\Delta\delta_{max}$ and intercept $1/\Delta\delta_{max}$, supporting the 1:1 complex formation.

$$1/\Delta\delta = 1/(K_a{\cdot}\Delta\delta_{max}{\cdot}[G]_o) + 1/\Delta\delta_{max} \qquad (2)$$

where $\Delta\delta = (\delta_G - \delta_{obs})$, and $\Delta\delta_{max} = (\delta_G - \delta_{H{\cdot}G})$.

It is a well-known fact that crown ethers form very stable complexes with ammonium salts by means of a hydrogen-bonding network, thus making them useful in many applications;[36−38]

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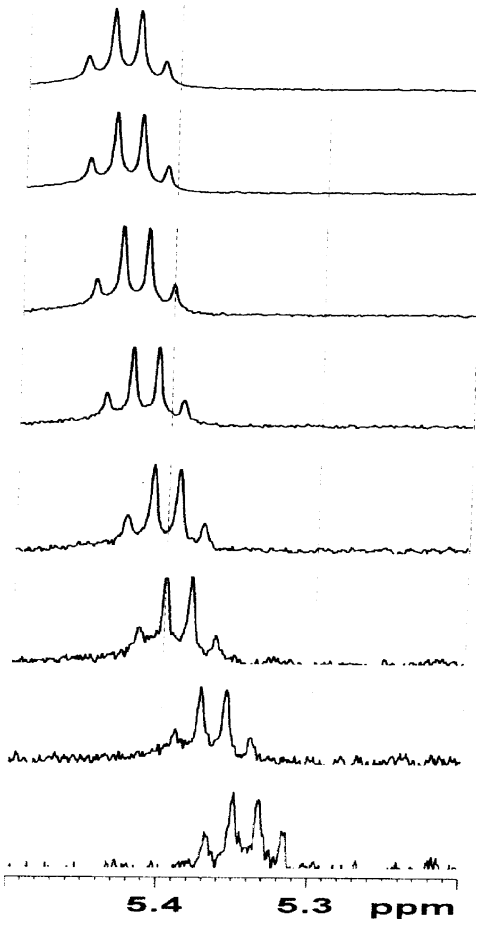

FIGURE 1. Typical NMR spectrum of guest's CH (methine) proton, and changes upon the addition of constant concentration of guest ((*R*)-Am) molecule (1.33×10^{-3} M) to the (*S*,*S*)-**3** host molecule at various concentrations ($0-6.55 \times 10^{-3}$ M).

in particular, those bearing chiral centers on their rings core are of great interest in their usage in stereoselective applications.[12] The model compounds, easily synthesized as compared to crown ethers, might be considered to be cyclic esters possessing crown ether-like rings, and are predicted to behave in a similar mode to accommodate ammonium salts. In addition, because they hold carbonyl and amide functions on their rings, they are expected to be superior to crown ethers. These functions are thought to make the ring more rigid, which is a preferential prerequisite for a host to include a guest more tightly.

We first examined the binding properties of novel diamide−diester macrocycles (*R*,*R*)-**1**, (*S*,*S*)-**1**, (*S*,*S*)-**2**, and (*S*,*S*)-**3** toward (*R*)-Am and (*S*)-Am by using ^{1}H NMR titration. The concentration of guest was fixed at 1.33×10^{-3} M in CD_3CN. The NMR spectrum of CH (methine) at guest was monitorized, with addition of various concentrations ($0-6.55 \times 10^{-3}$ M) of host. For the guest CH, ^{1}H NMR signal (quartet) gradually shifted downfield upon addition of the hosts (Figure 1). The Job's plot based on the chemical shift changes supported the 1:1 stoichiometry of host−guest complexes (Figure 2). Typical plots for the complexation of (*S*,*S*)-**3** host with α-(1-napthyl)ethylamine perchlorate salt (guest) are shown in Figure 3.

The determination of K_a values for chiral host−guest interaction provides information about the capability of the chiral host to recognize enantiomers of the chiral guest under given sets of condition. The correlation of degree of recognition with the

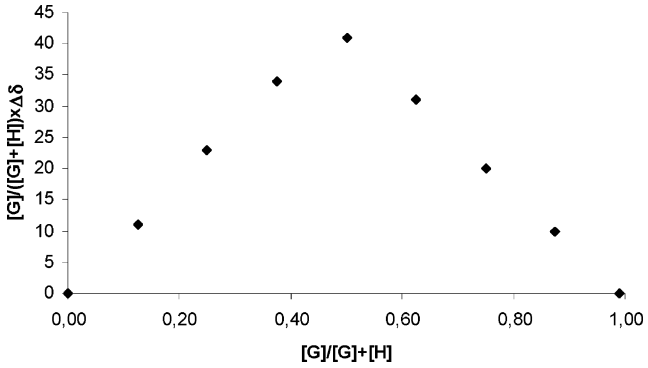

FIGURE 2. Job plot for macrocycle (*S*,*S*)-**3** with (*R*)-Am.

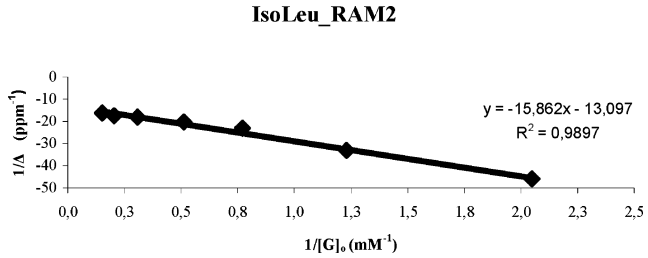

FIGURE 3. Typical plot of $1/\Delta\delta$ versus $1/[G]_o$ for host−guest complexation of (*S*,*S*)-**3** and (*R*)-(−)α-(1-napthyl)ethylamine perchlorate salt ((*R*)-Am).

structural features of the host−guest complexes is essential in understanding the origin of the chiral recognition. The choice of these macrocycles was based on the fact that rigid and C_2-symmetric generally form more stable complexes than the non-rigid and C_2-symmetric. The binding constant, K_a, of the complexes of the macrocyles (*S*,*S*)-**1**, (*S*,*S*)-**2**, (*S*,*S*)-**3**, and (*R*,*R*)-**1** with α-(1-napthyl)ethylamine perchlorate salts [(*R*)-Am, (*S*)-Am] were determined by the Benesi−Hildebrand equation on the basis of the NMR spectrum of the complexes in CD_3CN collected at 25 ± 0.1 °C. Binding constant (K_a) and the Gibbs free energy changes ($-\Delta G_o$) of these hosts with guest molecules obtained from usual curve-fitting analyses ($R > 0.9897$) of the observed chemical shift changes are summarized in Table 1, along with enantioselectivity K_R/K_S or $\Delta\Delta G_o$ calculated from $-\Delta G_o$ for the complexation of (*R*/*S*)-α-(1-napthyl)ethylamine perchlorate salts by these hosts.

Important differences were observed in the K_a values of (*R*)-Am and (*S*)-Am for (*S*,*S*)-**1** and (*R*,*R*)-**1** hosts, $K_S/K_R = 5.55$ and $K_R/K_S = 3.65$, $\Delta\Delta G_o = 0.43$ and -0.32 kJ mol^{-1}, respectively, as shown in Table 1. On the other hand, differences in K_a values of (*R*)-Am and (*S*)-Am for (*S*,*S*)-**2** and (*S*,*S*)-**3** hosts were moderate, $K_R/K_S = 0.94$ and 1.23, $\Delta\Delta G_o = -0.02$ and -0.05 kJ mol^{-1}, respectively. There seems a general tendency for the host to include the guests with the same absolute configuration. The host bearing benzyl group with (*S*)-configuration forms a more stable binding of complexes with the enantiomer of guest with (*S*)-configuration. This observation can be confirmed by an ERF (enantiomer recognition factor) of 5.55 (K_S/K_R), which corresponds to approximately 70% ee. This can be seen for the complex of the host with two enantiomers as seen in Figure 4. It is clearly indicated that the former **1** is more stable than the latter **2** because it is quite apparent that the enantiomer with (*S*)-configuration fits better than the one with (*R*)- as the bulky naphthyl group in the former is placed opposite the benzyl side chain in the cavity of the

TABLE 1. Binding Constant (K_a), the Gibbs Free Energy Changes ($-\Delta G_o$), and Enantioselectivities K_R/K_S or $\Delta\Delta G_o$ for the Inclusion of *R*/*S* Guest with the Chiral Host Macrocycles in CD_3CN at 25 °C

host	guest[a]	K_a (M^{-1})	K_R/K_S	$-\Delta G_o$ (kJ mol^{-1})	$\Delta\Delta G_o$ (kJ mol^{-1})[b]
(*R*,*R*)-1	(*R*)-Am	7752.9 ± 0.019	3.65	2.22	−0.32
(*R*,*R*)-**1**	(*S*)-Am	2122.9 ± 0.028		1.90	
(*S*,*S*)-**1**	(*R*)-Am	1230.7 ± 0.011	0.18 (K_S/K_R = 5.55)	1.76	+0.43
(*S*,*S*)-**1**	(*S*)-Am	6835.7 ± 0.021		2.19	
(*S*,*S*)-**2**	(*R*)-Am	2507.4 ± 0.036	0.94 (K_S/K_R = 1.07)	1.94	0.02
(*S*,*S*)-**2**	(*S*)-Am	2669.4 ± 0.026		1.96	
(*S*,*S*)-**3**	(*R*)-Am	1211.2 ± 0.029	1.23	1.76	−0.05
(*S*,*S*)-**3**	(*S*)-Am	988.6 ± 0.041		1.71	

[a] $NapEtHClO_4$: α-(1-napthyl)ethylamine perchlorate salts. [b] $\Delta\Delta G_o = -\Delta G_{o(R)} - \Delta G_{o(S)}$.

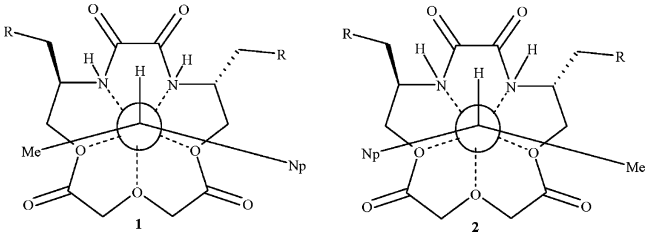

FIGURE 4. Schematic diagram of the enantiomeric recognition mode of amine salts by hosts.

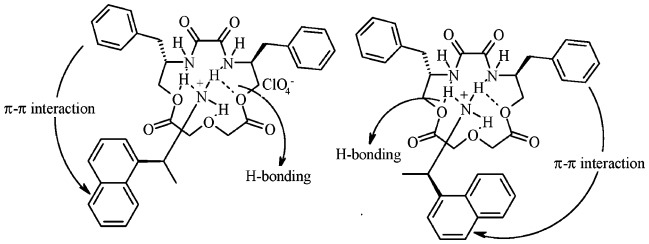

FIGURE 5. Schematic diagram of binding interaction between amine salts and host (*S*,*S*)-**1**.

host, whereas in the latter, these two groups are located in the same face, causing unfavorable steric interactions. One may argue that in the former model, location of two aromatic rings facing opposite may give rise to favorable $\pi-\pi$ interaction and H-bonding (Figure 5), thus accounting for the relative stability of the complex. As to the binding ability of the host possessing ethyl side chains with (*R*)-configuration, it was observed that it has the highest binding affinity among the host, preferably accommodating the enantiomer with (*R*)-configuration with ERF of 3.65 (K_R/K_S), hence resulting in approximately 57% ee. Higher binding tendency and lower ERF as compared to the host with benzyl side chains could be ascribed to the fact that methyl−ethyl interaction is expected to be less energetic than that of methyl−benzyl interaction, thus making the complex of the host bearing ethyl more stable than the benzyl bearing one. As to the difference in ERF, this may be explained in a similar manner. This may be attributed to favorable hydrophobic interaction between naphthyl ring and ethyl. However, the NMR shifts in ethyl group were not quite significant upon changes in the concentration of guest (*R*)-Am to be accounted for in the most stable complex. The relatively lower binding ability and possible consequence of smaller ERF of hosts bearing iso- and sec-buthyl groups toward guests remain to be answered. It is possible that there should be an unfavorable steric interaction between these groups and the naphthyl group of the guest.

Conclusion

We have synthesized a series of novel macrocycles having diamide−diester groups (*S*,*S*)-**1**, (*S*,*S*)-**2**, (*S*,*S*)-**3**, and (*R*,*R*)-**1**, derived from dimethyloxalate and amino alcohols by high dilution technique, and evaluated enantiomeric recognition properties of these macrocycles toward primary alkyl ammonium salts by ^1H NMR titration. These macrocycles are readily prepared in short synthetic sequences and allow high modularity by simply changing the amino alcohol moiety. The functionality of amides and esters is not only suitable for binding but also ensures high rigidity. The macrocycles have shown a considerable binding affinity and consequently enantiomeric discrimination against amine salts.

Experimental Section

Macrocyclic (*S*,*S*)-1. This experiment was conducted under high dilution technique. A 2 L, four-necked, round-bottomed flask, fitted with a mechanical stirrer and two-faced condenser, was charged with 1 L of benzene and tritely amine equivalent to the produced HCl. The solution was refluxed vigorously while (*S*,*S*)-**4** (1.5 g, 4.2 mmol) in dry THF/DMF (w:w,70/30 = 100 mL) and diacide dichloride **2** (0.86 g, 5mmol) in dry benzene (100 mL) were added dropwise at the same rate. After the addition was complete, the reaction mixture was refluxed for further 5 days. The solution was cooled to room temperature, filtered, and solvent was evaporated under vacuum. The white solid resulting was crystallized from an ethanol−acetonitrile mixture (2:1). Macrocyclic (*S*,*S*)-**1**: yield (1.26 g, 63%); mp 289−290 °C; IR (KBr) ν 3298 (N−H), 3086 (Ar−H), 3059 (Ar−H), 3028 (Ar−H), 1759 (C═O, ester), 1731 (C═O, ester), 1659 (C═O, first amide band), 1516 (C═O, second amide band), 1130 (C−O−C), 1053 (C−O−C) cm^{-1}; $[\alpha]^{34}_D = -58$ (*c* 0.04, CH_3CN); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.75−2.87 (m, 4H, CH_2Ar), 3.75−3.88 (m, 6H, CH_2O and CH−N), 4.25−4.57 (m, 4H, O−CH_2−C═O), 7.17−7.26 (m, 10H, ArH), 8.60 (d, J = 10 Hz, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 35.04 (t, CH_2Ar), 50.70 (d, CH−N), 65.77 (t, CH−CH_2O), 65.82 (t, OCH_2C═O), 126.71, 128.69, 129.33 (d, aromatic CH), 138.42 (s, quaternary aromatic), 160.12 (s, C═O amide), 169.56 (s, C═O ester). Anal. Calcd (%) for $C_{24}H_{26}N_2O_7$: C, 63.42; H, 5.77; N, 6.16. Found: C, 63.41; H, 5.78; N, 6.15.

Macrocyclic (*S*,*S*)-2. The reaction was carried out by the high dilution technique as described above. Macrocyclic (*S*,*S*)-**2**: yield (0.98 g, 49%); mp 278−279 °C; IR (KBr) ν 3297 (N−H), 1751 (C═O, ester), 1728 (C═O, ester), 1659 (C═O, first amide band), 1520 (C═O, second amide band), 1277 (O═C−O−C), 1130 (C−O−C) cm^{-1}; $[\alpha]^{33}_D = -62.0$ (*c* 0.1, CH_3CN); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 0.84 (d, J = 7.2 Hz, 6H, CH_3 (a)), 0.86 (d, J = 7.2 Hz, 6H, CH_3 (b)), 1.12−1.20 (m, 2H, $CH(CH_3)_2$), 1.49−1.60 (m, 4H,$NCHCH_2CH$), 3.79−4.66 (m, 10H,CHN, CHN−CH_2−C═O and O−CH_2−C═O), 8.50 (d, J = 10 Hz, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 21.91 (q, CH_3 (a)), 23.54 (q, CH_3

(b)), 24.76 (d, $CH(CH_3)_2$), 37.77 (t, $CH_2CH(CH_3)_2$), 47.75 (d, CH−N), 65.81 (t, CH−CH_2−O), 66.31 (t, O−CH_2−C═O), 160.43 (s amide C═O), 169.52 (s, ester C═O). Anal. Calcd (%) for $C_{18}H_{30}N_2O_7$: C, 55.95; H, 7.83; N, 7.25. Found: C, 55.93; H, 7.81; N, 7.24.

Macrocyclic (*S*,*S*)-3. The reaction was carried out by the high dilution technique as described above. Macrocyclic (*S*,*S*)-**3**: yield (0.88 g, 44%); mp 280−282 °C; IR (KBr) ν 3282 (N−H), 1763 (C═O, ester), 1736 (C═O, ester), 1659 (C═O, first amide band), 1524 (C═O, second amide band), 1284 (O═C−O−C), 1149 (C−O−C) cm^{-1}; $[\alpha]^{34}_D$ = +153.0 (*c* 0.03, CH_3CN); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 0.85 (t, *J* = 3.8 Hz, 6H, CH_2CH_3), 0.89 (d, *J* = 4.0 Hz, 6H, $CHCH_3$), 1.04−1.11 (m, 2H, CH_2CH_3 (a)), 1.38−1.40 (m, 2H, CH_2CH_3 (b)), 1.68−1.70 (m, 2H, $CHCH_3$), 3.81−3.93 (m, 2H, CH−N), 3.97−4.65 (m, 8H, $NCHCH_2O$ and OCH_2C═O), 8.44 (d, *J* = 12 Hz, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 10.76 (q, CH_2CH_3), 15.84 (q, $CHCH_3$), 25.78 (t, $CHCH_2CH_3$), 34.66 (d, $CHCH_3$), 53.42 (d, N−CH−), 64.95 (t, CH_2O), 66.22 (t, OCH_2C═O), 160.72 (s, amide C═O), 169.61 (s, ester C═O). Anal. Calcd (%) for $C_{18}H_{30}N_2O_7$: C, 55.95; H, 7.83; N, 7.25. Found: C, 55.94; H, 7.84; N, 7.23.

Macrocyclic (*R*,*R*)-1. The reaction was carried out by the high dilution technique as described above. Macrocyclic (*R*,*R*)-**1**: yield (1.14 g, 57%); mp 266.5−268 °C; IR (KBr) ν 3282 (N−H), 1767 (C═O, ester), 1735 (C═O, ester), 1659 (C═O, first amide band), 1520 (C═O, second amide band), 1296 (O═C−O−C), 1149 (C−O−C) cm^{-1}; $[\alpha]^{34}_D$ = +96.0 (*c* 0.2, CH_3CN); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 0.84 (t, *J* = 7.4 Hz, 6H, CH_3), 1.46−1.52 (m, 4H, $CH\mathbf{CH_2}CH_3$), 3.82−4.66 (m, 10H, CH−N, CH_2O and O−CH_2−C═O), 8.45 (d, *J* = 10 Hz, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 10.99 (q, CH_3), 22.39 (t, CH_2CH_3), 51.15 (d, CH−N), 65.87 (t, CH−CH_2−O), 65.97 (t, O−CH_2−C═O), 160.73 (s, amide C═O), 169.56 (s, ester C═O). Anal. Calcd (%) for $C_{14}H_{22}N_2O_7$: C, 50.91; H, 6.71; N, 8.48. Found: C, 50.88; H, 6.72; N, 8.46.

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Supporting Information Available: Synthesis of aminoalcohols and diamidediols (*S*,*S*)-**4**, (*S*,*S*)-**5**, (*S*,*S*)-**6**, (*R*,*R*)-**2**, and also ^{1}H and ^{13}C NMR spectra for compounds (*R*,*R*)-**1**, (*S*,*S*)-**1**, (*S*,*S*)-**2**, (*S*,*S*)-**3**, (*R*,*R*)-**2**, (*S*,*S*)-**4**, (*S*,*S*)-**5**, (*S*,*S*)-**6**, and furthermore ^{1}H−^{13}C correlation NMR spectra for compounds (*R*,*R*)-**1**, (*S*,*S*)-**1**, (*S*,*S*)-**2**, (*S*,*S*)-**3**.[39] This material is available free of charge via the Internet at http://pubs.acs.org.

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