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Novel C_1-symmetric chiral crown ethers bearing rosin acids groups: synthesis and enantiomeric recognition for ammonium salts

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ABSTRACT

Four types of novel C_1-symmetric chiral crown ethers including 28-crown-8, 20-crown-6, 17-crown-5 and 14-crown-3 (**9a**–**m**) were synthesized and their enantiodiscriminating abilities with protonated primary amines (**10**–**14**) were examined by ^{1}H NMR spectroscopy. 20-crown-6 crown ethers exhibited good chiral recognition properties toward these guests and showed different complementarity to some chiral guests, indicating that 20-crown-6 crown ethers could be used as a chiral NMR solvating agent to determine the enantiopurity of these guests. In addition, the binding model and binding site between the hosts and guests were also studied by the computational modeling and experimental calculation.

1. Introduction

The development of chiral artificial receptors that are capable of differentially binding enantiomeric amine or protonated amine compounds is of great significance because these substrates are basic building blocks of biological molecules and a number of them are major components of proteins in natural living systems.[1] Since the pioneering research on the application of macrocyclic ligands in chiral recognition was reported by Cram et al., a great number of novel chiral cavity compounds have been designed and synthesized.[2] As chiral selectors, chiral crown ethers have attracted increasing attention owing to their superior selectivity in the enantiomers complexation with racemic-amino acids and primary amines.[3]

Chiral crown ethers possessing C_2, C_3, and D_2-symmetry usually show high enantioselectivity because of their interaction in a complementary way between substrates and chiral macrocycles.[1a] In contrast, chiral macrocycles possessing C_1-symmetry always show low or no enantioselectivity due to the 'sidedness' problems as described by Naemura, K.[4] It has been believed that the chiral recognition in C_1-symmetry environments may not be feasible and have received less attention. However, in contrast to C_2, C_3, and D_2-symmetry chiral crown ethers, C_1-symmetry selectors have some significant advantages. First, it is simple and convenient to prepare the C_1-symmetry chiral macrocycles by introducing numbers of chiral structures into crown, avoiding tedious multistep synthesis and purification, particularly for the asymmetric reaction, which would be difficult (or impossible) to obtain the compounds with perfect optical purity. Second, they can easier be selectively functionalized to synthesize various crown derivatives. Therefore, it is very important to develop a new method for the synthesis of the C_1-symmetry chiral macrocycles with high selectivity in the enantiomer separation, which can expand the type of receptors and find more different complex models in the host–guest system.

Generally, the bulkiness of substituents, the rigidity and the symmetry of the molecular frame, and the structural complementarity are all expected to play an important role in enantioselective recognition.[5] For C_1-symmetry chiral crown ethers, when the substrates interact with the C_1-symmetry selectors from one side, the chiral barrier would protrude to the other sides, which minimize the role of the chiral barrier, thus resulting in a low degree of the chiral recognition. But if a suitable chiral structure (especial the large natural chiral structure) is introduced into crown, it might lead to complementarity between the host and guest.[1a] Naturally occurring enantiomeric levopimaric acid, including unique three-dimensional

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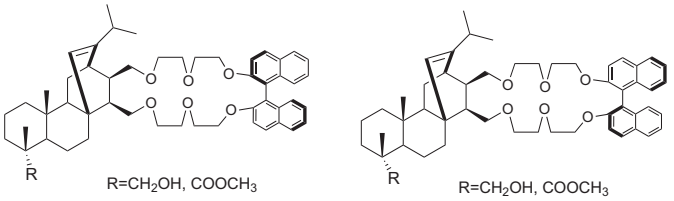
structure with more than one chiral centers, promises to be a better structural complementarity with bio-supermolecular and an excellent material for chiral reagents.[6] Recently, some derivatives of levopimaric acid have been applied in catalytic asymmetric reaction.[7] In our prior works, it has been reported to use levopimaric acid derivatives in the separations of D/L-amino acids by capillary electrophoresis.[8] Apparently, attempt to design the C_1-symmetry chiral crown ethers with enantioselectivity and enantiomer separation from natural products, levopimaric acid or its derivative, is one of the best choice as the chiral substituents. As it turned out, a series of novel C_1-symmetry chiral 22-crown-6 ethers bearing maleopimaric acid (the Diels–Alder adduct of levopimaric acid with maleic anhydride, Scheme 1) we synthesized, exhibited good chiral recognition and showed different complementarity towards the chiral guests in UV–vis spectroscopy.[9] However, this method is not suitable for determining the enantiomeric purity of chiral guests. Thus we synthesized another four types of novel C_1-symmetric chiral crown ethers including 28-crown-8, 20-crown-6, 17-crown-5 and 14-crown-3 from maleopimaric acid, and studied their enantiodiscriminating abilities towards protonated primary amines and amino acid methyl ester salts by ^{1}H NMR spectroscopy.

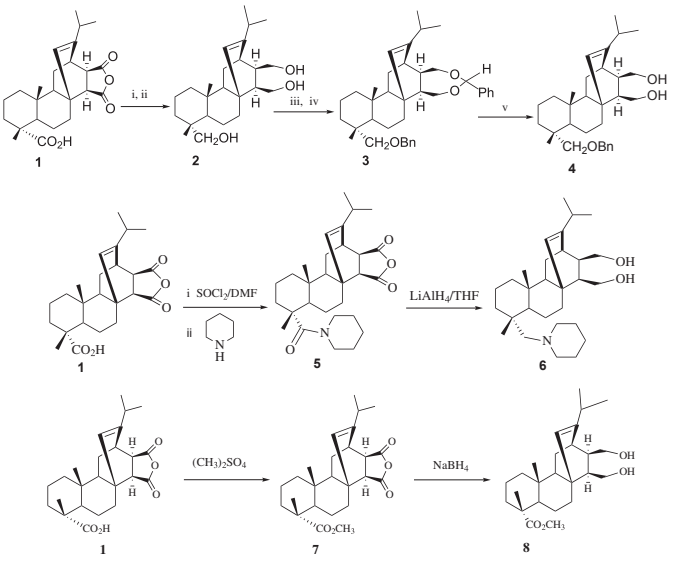


Scheme 1. Structure of four novel C_1-symmetry chiral 22-crown-6 ethers.

2. Results and discussion

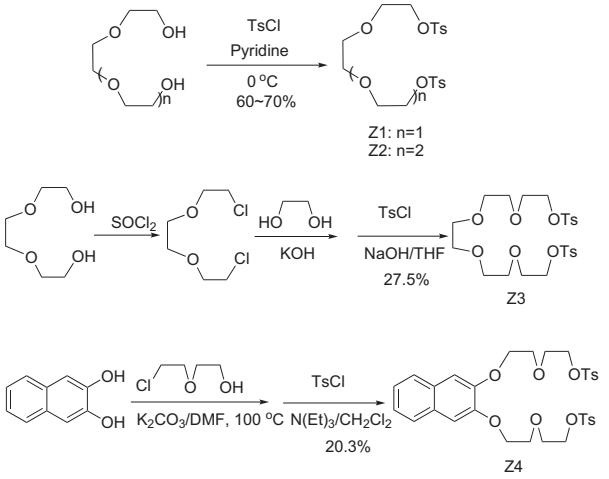
2.1. Synthesis

The different substituent maleopimaric acid (**2**, **4**, **6**, and **8**), possessing two hydroxyl groups served as linkage part of host molecular in present crown ether synthesis, were prepared according to the synthetic strategy shown in Scheme 2. Compound **1** was prepared according to the reported procedure,[10] followed by reaction with pyridine and dimethyl sulfate afforded the compounds **5** and **7**, respectively. Subsequently, the reaction of these intermediates with $LiAlH_4$ or $NaBH_4$ in the presence of THF provided the compounds **6** and **8**. Synthesis of the other alcohol **4** began with the treatment of compound **1** with PCl_3, then reduction with $LiAlH_4$ to afford triol **2** in an 83% yield. Compound **3** was produced by Williamson reaction of alcohol-protected **2** with benzyl chloride. Subsequent deprotection of the benzyl group gave alcohol **4** in an 80% yield.

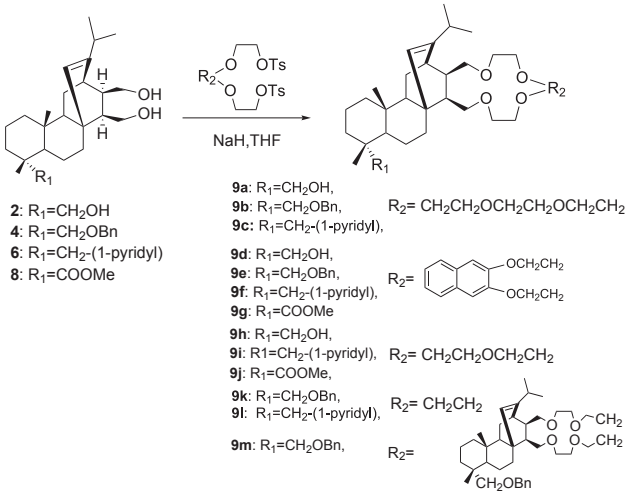


Scheme 2. Synthesis of the glycol derivatives **4**, **6**, and **8**: (i) PCl_3, MeOH, reflux, 4 h; (ii) $LiAlH_4$, Et_2O, reflux, 8 h; (iii) $TsOH\cdot H_2O$, $PhCH(OMe)_2$, rt, 1 h; (iv) $(n\text{-}Bt)_4NBr$, BnCl, 5 h; (v) PPTS, Me_2CO, 65 °C, 5 h.

The ditosylates **Z1**–**Z4** were prepared according to the synthetic strategy shown in Scheme 3. Finally, four novels types of C1-symmetric macrocycles **9a**–**m** such as 28-crown-8, 20-crown-6, 17-crown-5 and 14-crown-3(Scheme 4) were synthesized from **Z1**–**Z4** with compounds **2**, **4**, **6**, and **8** via a regioselective ring formation reaction in the presence of NaH in THF under high dilution conditions in 10.3%–9.3% yields, respectively. The products were characterized by a combination of ^{1}H NMR, ^{13}C NMR, MS, IR and elemental analysis.



Scheme 3. Synthesis of the diethylene glycol tosylate derivatives **Z1**–**Z4**.

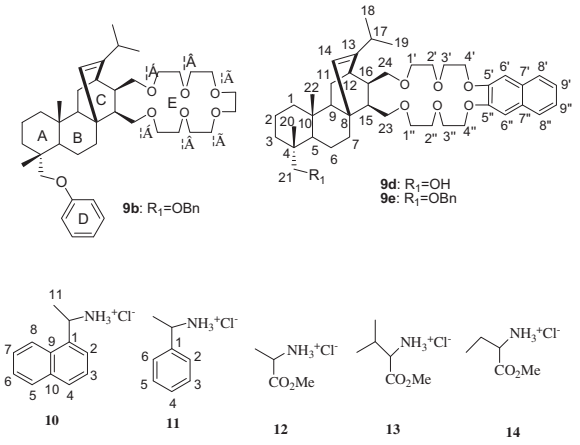


Scheme 4. Synthesis of four types of novel C_1-symmetric chiral crown ethers **9a**–**m**.

2.2. ^{1}H NMR spectroscopy

In our previous report, we have known that rosin-based 22-crown-6 ethers have excellent ability to form host–guest complexes and distinguish chiral primary amines. 20-crown-6 are the

analogue as 22-crown-6, in which they possess a similar distribution of the oxygen atoms or coordination site of the cavity. Thus we chose this type receptor to study their chiral recognition properties. ^{1}H NMR spectroscopy is a convenient and widely used method for the study of chiral recognition. Discrimination occurs when the addition of an optically pure chiral discriminating agent associates with a pair of enantiomers to produce diastereomeric complexes that exhibit different shifts in the NMR spectrum. ^{1}H NMR spectra of solutions of **9b**, **9d**, and **9e** were recorded in the absence and presence of various racemic ammonium salts (Scheme 5), such as racemic α-(1-naphthyl)ethylamine HCl (**10**), racemic α-phenylethylamine HCl (**11**), D,L-alanine methyl ester HCl (**12**), D,L-valine methyl ester HCl (**13**) and D,L-serine methyl ester HCl (**14**). Considering the solubility of all the guests and hosts in different solvents and the chemical shift changes (ΔΔδ) of methyl protons (see Supplementary data: Fig. S66 and Table S1), $CDCl_3/CD_3OD$ (*v*/*v*=2:1) were chosen as the best solvent in which receptors had good chiral recognition abilities.



Scheme 5. Structures of 20-crown-6 macrocycles and primary ammonium salts guests.

Fig. 1 showed the ^{1}H NMR spectra for racemic naphthylethylammonium chloride **10** (5 mM) in the absence and presence of the chiral crown ether **9e** in different concentrations in a mixed solvent of $CDCl_3/CD_3OD$ (2:1). The protons signals CH_3, CH, H_4, H_5 and H_8 of **10** were shifted to high field and the peaks except H_8 were slip into two sets in 1:1 integration ratio, which nearly no change even the crown/substrate ratio increased to 4:1. In combination with the sharpening of all the resonances, indicating that the exchange rate of crown–substrate complexes was fast on the NMR time scale. The splitting of the resonances in the spectrum of **10** was the result of enantiomeric discrimination under fast exchange rather than separate bound forms of **10** with **9e**, in agreement with the literature[3i] reporting the chiral recognition properties of (18-crown-6)-2,3,11,12-tetracarboxylic acid. These results clearly indicated that chiral crown ether **9e** could be used as a chiral NMR solvating agent to determine the enantiopurity of **10** at ambient temperature. The significant enantiomeric discrimination was observed for the resonances of the methyl (0.082 ppm), methine (0.013 ppm) and H_4 hydrogen (0.023 ppm) at a 4:1 crown/substrate ratio. In particular, the greatest enantiomeric discrimination ΔΔδ for the resonances of H_5 was up to 0.135 ppm (Table 1).

Table 1
Enantiomeric discrimination [ΔΔδ (ppm)] between enantiomers in the ^{1}H NMR spectra (500 MHz) of guests (5 mM) in the presence of chiral crown ethers (20 mM) in $CDCl_3/CD_3OD$ (2/1)

Guest	Proton	**9b** (ΔΔδ, ppm)	**9d**(ΔΔδ, ppm)	**9e** (ΔΔδ, ppm)
10	CH_3	0.025	0.0726	0.082
	CH	0.027	0.0153	0.013
	H_4	0.164	0.0233	0.023
	H_5	0.031	0.0181	0.135
	H_8	0.009	0.0259	0
11	CH_3	0.014	0.0145	0.026
	CH	Overlap	0	0.013
12	CH	0.005	Overlap	Overlap
	CH_3	0.001	0.01495	0.008
	OCH_3	0.008	0.0018	0.004
13	N–CH	0.018	0.0030	Overlap
	CH_3	0.010	Overlap	0.010
	OCH_3	0.006	0.0027	0.000
14	N–CH	0.004	Overlap	Overlap
	OCH_3	0.003	0.000	0.003

ΔΔδ (ppm)=$|\Delta\delta^R-\Delta\delta^S|$, Δδ=(Chemical shift values of the protons specified in bold in the presence of chiral crown ethers)−(chemical shift values in the absence of chiral crown ethers).

Furthermore, ^{1}H NMR studies of the chiral crown ether **9e** with different molar ratios of (*R*)- or (*S*)-**10** were examined (Fig. 2). The methyl doublets of **10** separated into two doublet peaks with an upfield shift. The methyl proton of (*R*)-**10** appeared at lower field

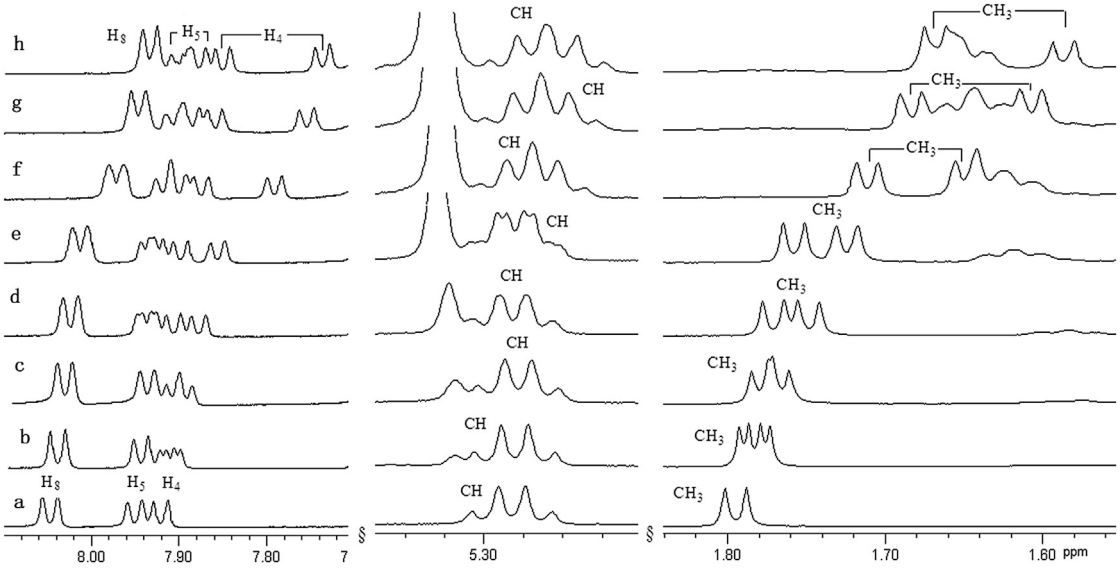


Fig. 1. Partial ^{1}H NMR spectrum of (+/−)-**10** (5 mM) with **9e** at (a) 0 mM, (b) 0.5 mM, (c) 1 mM, (d) 2.5 mM, (e) 5 mM, (f) 10 mM, (g) 15 mM and (h) 20 mM in $CDCl_3/CD_3OD$ (2/1).

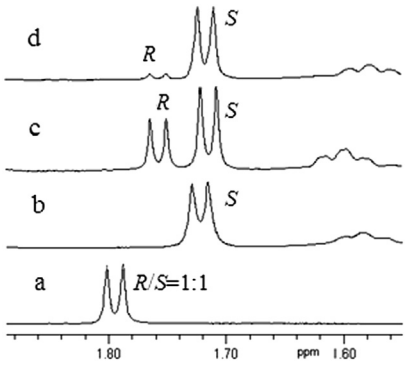


Fig. 2. The methyl resonance in the ^{1}H NMR of **10** (5 mM) with various enantiomeric ratios in the presence of **9e** (5 mM) in $CDCl_3/CD_3OD$ (2/1) (a) 50% *S*-enantiomer, (b) 100% *S*-enantiomer, (c) 63.2% *S*-enantiomer, and (d) 93% *S*-enantiomer.

than that of (*S*)-**10**, which was confirmed by an increase of the methyl proton signal of (*S*)-**10** that was added into the complex of racemic guests with **9e**. This indicated that the interactions of host **9e** with the (*R*)- and (*S*)-forms of **10** were different, resulting in two doublet resonances for the CH_3 protons. The degree of signal separation of (*R*)- and (*S*)-**10** depended greatly on the molar ratio of **9e**/**10** (Fig. 1a–h). The value ($\Delta\Delta\delta$) of the signals of methyl proton gradually raised with an increase in the concentration of **9e**, suggesting that increasing the concentration of chiral solvating agents could promote the formation of the diastereomeric complexes and enhance the extent of enantiomeric discrimination in the ^{1}H NMR spectrum.

Chiral recognition between **10** and **9b** that contains softer cavity compared with **9e**, has also been investigated. More excellent enantiomeric discrimination was observed based on the larger chemical shift changes ($\Delta\Delta\delta$ of CH, H_4, H_5 and H_8 protons at a 4:1 **9b**/**10** ratio). These values were up to 0.027, 0.164, 0.031 and 0.009 ppm, respectively. Importantly, the greatest enantiomeric discrimination observed for proton was at the 4-position or 5-position on **10** in the **9b**–**10** or **9e**–**10** systems, respectively. As far as we know, 18-crown-6 unit can form 1:1 complex with NH_3^+ by the interaction of three hydrogen bonds. In general, the closer the substrate's stereogenic center is to the binding cavity, the larger enantiomeric discrimination will be shown. According to the significant enantiomeric discrimination for the signals of H_8 on guest **10** in different hosts **9b** and **9e**. We could conclude that the cavity size of **9b** was more suitable to complex **10** and therefore showed greater excellent chiral recognition. The possible reason was that the soft cavity of **9b** was easier to self-control its size to the slightly larger guest molecular such as **10**, but difficulty for **9e** because of its larger naphthalene group making the cavity greater rigidity. However, when the guest structure was smaller, the rigidity cavity would generate more effective enantiomeric discrimination. To confirm this hypothesis, we studied the chiral recognition of **9b** and **9e** with the model primary ammonium salt guest **11**. As expected, **9e** gave a larger chemical shift change and discrimination of the methyl signal of **11** than **9b**. Its value of $\Delta\Delta\delta$ was up to 0.026 ppm at a 4:1 crown/substrate ratio, suggesting the better chiral recognition property for **9e** with **11**.

Interestingly, compared to **9b**, the 20-crown-6 ether **9e** showed greater enantiomeric discrimination of the methyl protons for both of the guests **10** and **11**. Considering the minimal interference from other protons in the spectrum, 20-crown-6 ether **9d**, bearing the same cavity as **9e** but different side chain on the maleopimaric acid group, was studied for its chiral recognition ability toward the guests **10** and **11**. The results showed that its chiral recognition abilities were not as efficient and sensitive as **9e** based on the less chemical shift change of guests. For example, the enantiomeric discrimination in the spectrum of **10** in the presence of **9e** was large for the proton H_5 resonances ($\Delta\Delta\delta$=0.135 ppm), but the small nonequivalence of this hydrogen resonances when the host was instead by **9d**. And its values $\Delta\Delta\delta$ decreased sharply to 0.0181 ppm. It was shown that the binding properties of 20-crown-6 ether were significantly influenced by the different side chain. For **9d**, there were two binding sites (polyether ring and hydroxyl group) towards **10** driven by hydrogen-bonding interactions. This competition would reduce the enantiomeric discrimination, and require much higher concentrations of **9d** to achieve any distinction.

In the light of these results, we can say the 20-crown-6 ethers have good chiral recognition properties with primary ammonium salts. To examine the influence of the different guests on the binding interaction, we studied the complexation of these three 20-crown-6 ethers and the other primary ammonium salts **12**, **13**, and **14**. Table 1 showed the ^{1}H NMR up-field shift $\Delta\Delta\delta$ of guests in host-guest system. All guests exhibited some degree of enantiomeric discrimination. It is noteworthy that these three chiral crown ethers showed remarkable $\Delta\Delta\delta$ towards protonated primary amines, especially naphthylethylammonium chloride, but weak for amino acid methyl ester salts. Their $\Delta\Delta\delta$ increased in the order of (**12**, **13**, and **14**)<**11**<**10**. In addition, the 1:1 stoichiometry of the complexes between all receptors and guests were determined by ESI-MS or APCI-MS (Supplementary data: Figs. S67–79).

2.3. Chiral recognition model

It is well-known that molecular structure plays an important role in determining the chiral recognition properties of hosts. Planar molecule, large chiral barrier and rigid cavity usually show good enantiomeric recognition for chiral macrocyclic receptors. In order to investigate the spatial structure with the aim of forecasting the chiral recognition model of title compound, we optimized the geometry of compound **9b** and **9e** with the HF method at the 6-31G/ level of GAUSSIAN 09.[11] The optimized molecular structures are shown in Fig. 3. Some selected geometric parameters are listed in Table 2. The chiral barrier contains four crystallographically unique rings: three cyclohexane rings A, B and C, and an aromatic ring D (labeled in Scheme 5).

For **9b**, Torsion angles show that ring A, B and C exhibit boat

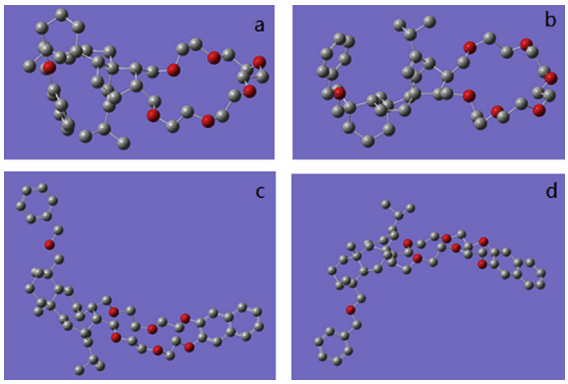


Fig. 3. Equilibrium structures calculation of **9b** (a and b) and **9e** (c and d).

configurations. A and B form cis ring junction with two methyl groups (C(17) and C(18)) in the axis positions. In addition, benzyl and isopropyl was in the cis position between ring A, B and C. On the basis of the torsion angles of (Oα–Oβ–Oγ–Oα′), the cavity of crown is slightly twisted. As a result, the host can complex guest through the up or down cavity of the crown (Fig. 4a).

Table 2
Selected bond lengths (Å) and torsion angles (°)

	9b	9e
Bond lengths (Å)		
C1–C4	3.090	3.000
C2–C5	2.830	2.950
C3–C10	2.880	3.010
C5–C8	2.850	2.870
C6–C9	3.000	3.020
C7–C10	2.890	3.340
C8–C12	2.570	2.580
C9–C16	2.870	3.100
C11–C15	3.010	2.800
Oα–Oα′	8.310	7.290
Oα–Oβ′	6.540	5.500
Oβ–Oβ′	6.465	4.630
Oβ–Oγ′	5.542	5.960
Oγ–Oβ′	4.520	3.830
Oγ–Oγ′	5.440	6.980
Torsion angles (°)		
C2–C1–C10–C5	36.86	53.39
C5–C4–C3–C2	24.28	−53.68
C7–C6–C5–C10	36.36	−34.86
C10–C9–C8–C7	34.99	−35.98
C9–C11–C12–C16	51.67	76.59
C16–C15–C8–C9	59.78	66.68
Oα–Oβ–Oγ–Oα′	−15.73	122.92

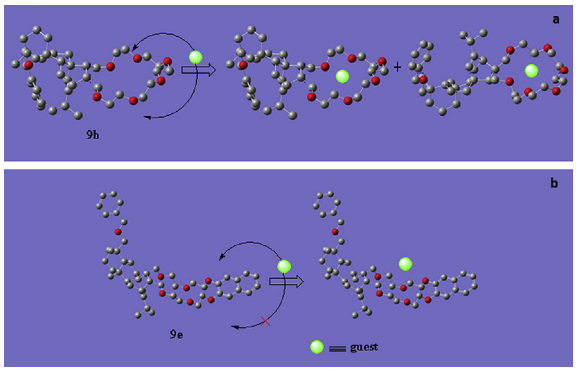


Fig. 4. The binding model of **9b** (a) and **9e** (b) with guest.

In contrast, compound **9e** contains a naphthalene ring on the other side of 20-crown-6. Its optimized structure show that ring B and C exhibit boat configurations, while A and B form cis ring junction with two methyl groups as **9b**. The ring A exhibit chair configuration. In addition, benzyl and isopropyl was in the *trans* position between ring A, B, and C, which not like **9b**. Furthermore, oxygen atoms in cavity E are coplanar. The torsion angle (Oα–Oβ–Oγ–Oα′) between rosin skeleton and naphthalene moiety is 122.9°. It showed that the cavity of crown is greatly twisted attributing to the steric hindrance of rosin skeleton and naphthalene moiety. The whole structure of chiral macrocyclic receptor looks like an arch bridge (Fig. 3c and d), which resulting that host-guest complex can firm only on one side of the cavity (Fig. 4b).

In order to further understand the chiral recognition mechanism, two model complexes **9e-(*R*)-10** and **9e-(*S*)-10** (in Fig. 5) are calculated using the same theory level and basis set as the parent uncomplexed crown **9e**. By inspection of the data obtained, it is believed that hydrogen bonding interactions between the oxygen atoms of **9e** and ammonium ion formed base on their N–O bond length (see Supplementary data: Table S1) in these two complexes. Symmetric cavity and planar molecular frame of model complexes is much better compared to the parent free crown. The main difference between **9e-(*R*)-10** and **9e-(*S*)-10** is that the recognized **(*S*)-10** and isopropyl group was in the opposite direction between cavity. Furthermore, the methyl and naphthalene group of **(*S*)-10** are closer to naphthalene moiety or the cavity of crown **9e** whose shielding effect was stronger, indicating that these protons of **(*S*)-10** appeared at upper field than that of **(*R*)-10** in agreement with the previous analysis by experiment. This result well explained the excellent chiral recognition properties of **9e** toward **10**. The chiral recognition model of **9e** might be as Fig. 6.

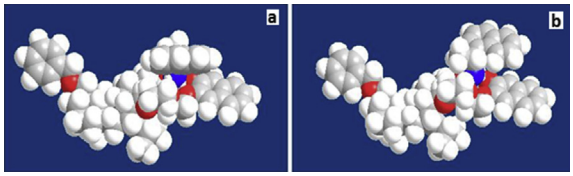


Fig. 5. The complexes model of **9e-(*R*)-10** (a) and **9e-(*S*)-10** (b).

3. Conclusions

Four types of novel C_1-symmetric chiral crown ethers including 28-crown-8, 20-crown-6, 17-crown-5, and 14-crown-3 (**9a**–**m**) were synthesized and their enantiodiscriminating abilities with protonated primary amines (**10**–**14**) were examined by ^{1}H NMR spectroscopy. Complexation studies revealed that 20-crown-6 crown ethers exhibited good chiral recognition properties toward these guests and showed different complementarity to some chiral guests. It was observed that changes in the side chain on maleopimaric acid unit as well as insertion of the naphthyl group into the ring influence both binding model and enantiodiscrimination ability of macrocyclic compounds against protonated primary amines and amino acid methyl ester salts. The significant information gained in this study will help to further understand the molecular recognition in the biological processes. More importantly, the chiral crown ether **9d** possessing a hydroxyl group in the side chain can easily be used as linkage group covalently bound to silica gel in the preparing chiral stationary phases or membranes.

4. Experimental

4.1. General information

Optical rotations were measured using polarimeter at ambient temperature and $[\alpha]_D$-values were given in units of 10^{-1} deg cm^2 g^{-1}. NMR spectra were measured in $CDCl_3$ using TMS as the internal standard. IR spectra were recorded on FTIR instrument. HR-ESI-MS were recorded in TOF. All the other chemicals and organic solvents used in this work were of analytical grade unless otherwise specified.

4.2. Enantiomeric separation in the ^{1}H NMR spectra

The racemic ammonium salts (5 mM) and chiral crown ether (5 mM) were dissolved in 0.4 mL of $CDCl_3/CD_3OD$ (2/1, *v*/v), and were assessed by ^{1}H NMR at 500 MHz. Differences in the chemical shifts between the enantiomers were then recorded. All chemical shift values were referenced to the internal tetramethylsilane standard.

4.3. Synthesis

Compound **2** and **Z1**–**Z2** were prepared according to the reported procedure.[12]

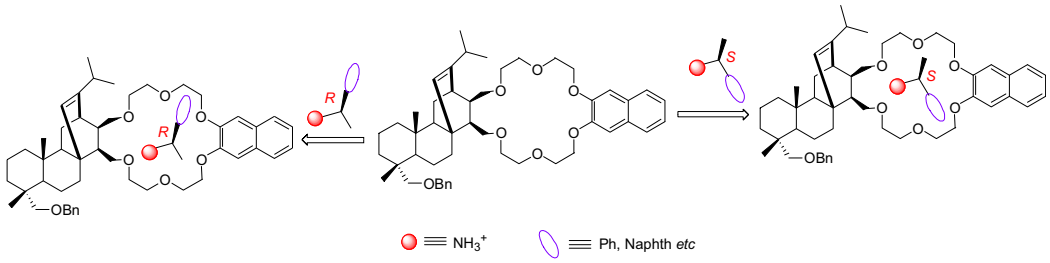


Fig. 6. A representative interaction of the macrocycle **9e** with *R*- and *S*-protonated primary amines.

4.3.1. Compound ***2***. Yield: 92.2%; mp 172.9–173.6 °C (ref: mp 170 °C[13]); $[\alpha]_D^{25}$ +4.2 (*c* 1.50, CH_3OH); ^1H NMR (CD_3OD, 500 MHz): 0.59 (3H, s), 0.73 (3H, s), 0.783–0.86 (1H, m), 0.99, 1.00 (6H, dd, *J*=6.8 Hz), 1.07–1.17 (1H, m), 1.16–1.24 (2H, m), 1.31–1.34 (1H, m), 1.37–1.52 (7H, m), 1.65 (1H, ddd, *J*=13.1, 11.4, 2.6 Hz), 1.83 (1H, dt, *J*=9.9, 2.3 Hz), 2.02–2.03 (1H, m), 2.18–2.22 (2H, m), 2.35 (1H, br s), 3.07 (1H, d, *J*=10.9 Hz), 3.41 (1H, d, *J*=10.6 Hz), 3.45 (1H, d, *J*=10.9 Hz), 3.51 (1H, dd, *J*=11.4, 3.7 Hz) 3.58 (1H, t, *J*=10.1 Hz), 3.76 (1H, dd, *J*=11.3, 1.9 Hz), 5.35 (1H, s).

4.3.2. Compound ***3***. To the solution of triol **2** (5.6 g, 14.8 mmol) in CH_2Cl_2 (160 mL), dimethyl benzaldehyde (3.4 g, 22.4 mmol), and *p*-toluenesulfonic acid (0.2 g, 1.17 mmol) were added. After stirring at room temperature (1 h), the reaction mixture was washed with $NaHCO_3$ solution (5%, 2×150 mL) and water (2×150 mL). The organic layer was separated, dried over Na_2SO_4, and evaporated. The residue was crystallized from EtOAc to give hydroxyl groups protected derivative 4.6 g as a white solid. To the solution of this compound (4.6 g, 10 mmol) in CH_2Cl_2 (5 mL), 50% aqueous NaOH (5 mL), tetrabutylammonium hydrosulfate (0.17 g, 0.5 mmol), and benzyl chloride (7 mL, 61 mmol) were added. After stirring at 50 °C (5 h), the reaction mixture was washed with water to pH=7. The organic layer was separated, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (petroleum ether: ethyl acetate, 4:1) giving compound **3** as a colorless oil (4.2 g, 56%): ^1H NMR ($CDCl_3$, 500 MHz) δ 0.62 (3H, s), 0.78 (3H, s), 0.89 (1H, m), 1.07 (3H, d, *J*=6.8 Hz), 1.07 (3H, d, *J*=6.8 Hz), 1.17 (1H, m), 1.33–1.42 (8H, m), 1.56 (2H, m), 1.67 (1H, m), 1.94 (1H, m), 2.19 (1H, m), 2.25 (1H, sept. d, *J*=6.7, 1.2 Hz), 2.32 (1, m), 2.48 (1H, m), 2.94 (1H, d, *J*=8.8 Hz), 3.23 (1H, d, *J*=8.8 Hz), 3.51 (2H, t, *J*=12.3 Hz), 4.01 (1H, dd, *J*=12.5, 4 Hz), 4.28 (1, dd, *J*=12.5, 4 Hz), 4.47 (1H, d, *J*=12.4 Hz), 4.57 (1H, d, *J*=12.4 Hz), 5.25 (1H, s), 5.45 (1H, s), 7.28–7.42 (8H, m), 7.47 (2H, m).

4.3.3. Compound ***4***. To a solution of compound **3** (5.5 g, 10 mmol) in 150 mL propanone/water=4:1 (*v*:*v*) was added pyridinum *p*-toluenesulfonate (0.6 g, 2 mmol). The reaction mixture was stirred for 5 h at 65 °C. After concentration under reduced pressure, water (30 mL) was added to the residue, and then extracted with dichloromethane (30 mL×3). The combined organic layer was dried over Na_2SO_4 and the dichloromethane was evaporated off. The crude product was purified by column chromatography (petroleum ether: ethyl acetate=3:1) to give 4 (2.8 g, 6.1 mmol) as a colorless oil. Yield 60.6%, $[\alpha]_D^{25}$ +13.7 (*c* 1.65, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.58 (3H, s), 0.76 (3H, s), 0.85 (1H, m), 0.99 (3H, d, *J*=6.8 Hz), 1.01 (3H, d, *J*=6.8 Hz), 1.07 (1H, m), 1.21–1.52 (10H, m), 1.62 (1H, ddd, *J*=12.6, 9.8, 2.8 Hz), 1.83 (1H, m), 1.94 (1H, dd, *J*=9, 2 Hz), 2.19–2.22 (2H, m), 2.35 (1H, m), 2.95 (1, d, *J*=8.9 Hz), 3.22 (1H, d, *J*=8.9 Hz), 3.45 (1H, t, *J*=10.5 Hz), 3.52 (1H, dd, *J*=11.0, 3.5 Hz), 3.58 (1H, t, *J*=10.5 Hz), 3.77 (1H, dd, *J*=10.5, 2.2 Hz), 4.49 (1H, d, *J*=12.5 Hz), 4.54 (1H, d, *J*=12.5 Hz), 5.35 (1H, s), 7.28–7.39 (5H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.0, 17.4, 18.2, 19.6, 20.5, 21.1, 30.4, 33.2, 36.1, 36.3, 37.0, 38.0, 38.2, 38.8, 40.0, 45.8, 48.3, 54.1, 55.0, 61.1, 65.5, 73.2, 79.8, 125.0, 127.3, 128.2, 139.1, 147.9. *m*/*z*: 467 $[M+H]^+$.

4.3.4. Compound ***5***. To a solution of compound 1 (4.0 g, 10 mmol) in 20 mL $SOCl_2$ was added 1 mL DMF. The reaction mixture was stirred for 6 h at 79 °C. After concentration under reduced pressure, 1,4-diethylene dioxide (40 mL) was added to the residue under ice bath. A mixture solution of 1-oxa-4-azacyclohexane (2.0 mL), triethylamine (1.6 mL) and 1,4-diethylene dioxide (7.0 mL) was added slowly. The solution was stirred for 8 h and then poured into cold hydrochloric acid solution (6 mol/L). The precipitate was filtered, dried and recrystallized from toluene to give 5 (4.4 g, 9.4 mmol) as white crystals. Yield 94.2%, mp 254.3–256.7 °C, IR (KBr, ν, cm^{-1}): 2940 (CH_2), 1836, 1770 (C=C), 1611 (C=C), 1085 (C–O); MS (ESI) *m*/*z*: 468 $(M+H^+)$.

4.3.5. Compound ***6***. To a solution of compound 5 (4.0 g, 8.6 mmol) in 150 mL anhydrous tetrahydrofuran was added $LiAlH_4$ (2.0 g, 52.6 mmol) under ice-bath. Then the reaction solution was stirred for 16 h at refluxing temperature. After cooling to room temperature, 20 mL EtOAc and 40 mL hydrochloric acid solution (1 mol/L) were added slowly to the solution, respectively, and then extracted with EtOAc (50 mL×3). The combined organic layer was dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. The crude product was recrystallized from EtOAc to give 6 (2.2 g, 5.0 mmol) as white crystals. Yield 58.1%, mp 177.5–178.0 °C, $[\alpha]_D^{25}$ +11.9 (*c* 1.003, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.58 (3H, s), 0.70 (3H, s), 0.83 (1H, m), 1.00 (3H, d, *J*=6.6 Hz), 1.01 (3H, d, *J*=6.7 Hz), 1.06–1.55 (17H, m), 1.65 (1H, ddd, *J*=9.8, 9.8, 2.5 Hz), 1.80 (1H, d, *J*=14.0 Hz), 1.84 (1H, m), 2.00 (1H, m), 2.16 (1H, d, *J*=14.2 Hz), 2.20 (2H, m), 2.33 (1H, s), 2.42 (4H, s), 3.43 (1H, t, *J*=10.5 Hz), 3.52 (1H, d, *J*=11.0 Hz), 3.57 (1H, t, *J*=10.3 Hz), 3.75 (1H, d, *J*=10.8 Hz), 3.99 (1H, s), 4.33 (1H, s), 5.35 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.1, 17.8, 19.2, 19.8, 20.5, 21.1, 24.2, 26.6, 30.5, 33.1, 36.5, 36.6, 38.0, 38.2, 38.4, 38.9, 40.1, 45.6, 48.7, 54.3, 55.1, 57.5, 61.0, 65.5, 69.8, 125.2, 147.7; IR (KBr, ν, cm^{-1}): 3325, 2925, 1638, 1110, 1040; MS (ESI) *m*/*z*: 444 $(M+H^+)$.

4.3.6. Compound ***7***. To a solution of compound 1 (30 g, 75 mmol) and K_2CO_3 (10 g, 72 mol) in 150 mL acetone was added dimethyl sulfate (10.7 g, 85 mol). The reaction mixture was stirred for 6 h at refluxing temperature. After cooling to room temperature, the solution was filtered through Celite, and concentrated under reduced pressure. The crude product was recrystallized from acetic acid to give 7 (26.4 g, 63.7 mmol) as white crystals. Yield 85%, mp 216–219 °C (mp 211–213 °C[14]), $[\alpha]_D^{25}$ −29.8 (*c* 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.59 (3H, s), 0.94 (1H, m), 0.99 (3H, d, *J*=6.7 Hz), 1.00 (3H, d, *J*=6.8 Hz), 1.16 (3H, s), 1.20–1.28 (2H, m), 1.37–1.55 (7H, m), 1.65–1.78 (3H, m), 2.26 (1H, sept. d, *J*=6.6, 1.3 Hz), 2.51 (1H, dt, *J*=13.9, 3.2 Hz), 2.72 (1H, d, *J*=8.7 Hz), 3.09 (1H, dd, *J*=8.7, 3.0 Hz), 3.12 (1H, m), 3.68 (3H, s), 5.53 (1H, s).

4.3.7. Compound ***8***. To a solution of compound **7** (4.0 g, 10 mmol) in 100 mL anhydrous tetrahydrofuran was added $NaBH_4$ (1.51 g,

37.6 mmol) under ice-bath. Then the reaction solution was stirred for 16 h at refluxing temperature. After cooling to room temperature, 20 mL EtOAc and 40 mL hydrochloric acid solution (1 mol/L) were added slowly to the solution, respectively, and then extracted with EtOAc (50 mL×3). The combined organic layer was dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. The crude product was recrystallized from EtOAc/petroleum ether to give 8 (2.1 g, 5.3 mmol) as white crystals. Yield 53.1%, mp 163–165 °C (mp 163–164 °C[15]), $[\alpha]_D^{25}$ +33.1 (*c* 1.50, EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.59 (3H, s), 0.92 (1H, m), 0.99 (3H, d, *J*=6.7 Hz), 1.00 (3H, d, *J*=6.7 Hz), 1.07–1.15(5H, m), 1.35–1.55 (7H, m), 1.62–1.73 (3H, m), 1.84 (1H, dt, *J*=9.8, 2.7 Hz), 1.98 (1H, m), 2.20 (2H, m), 2.37 (1H, s), 3.43 (1H, t, *J*=10.4 Hz), 3.49–3.60 (2H, m), 3.67 (3H, s), 3.71–3.81 (2H, m), 5.33 (1H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.8, 16.9, 17.2, 20.5, 21.2, 22.3, 30.1, 33.2, 36.1, 36.9, 37.7, 38.2, 38.2, 40.3, 45.8, 47.2, 49.4, 51.9, 54.1, 55.2, 61.1, 65.5, 124.9, 148.1, 179.6; IR (KBr, ν, cm^{-1}): 3224, 2928, 2867, 1719; MS (APCI) *m*/*z*: 405($M+H^+$).

*4.3.8. Compound **Z3**.* Triglycol dichloride (10.8 g, 57.8 mmol) was added to a stirred mixture of KOH (7.8 g, 139.3 mmol) in ethylene glycol (60 mL) at room temperature under N_2. The reaction mixture was stirred at refluxing temperature for 36 h. After cooling to room temperature, the reaction mixture was filtered and concentrated under reduced pressure to yield a viscous oil.

To a stirred solution of the above viscous oil and NaOH (4.8 g, 120 mmol) in THF/H_2O (v/v=1/1 40 mL) cooled to 0 °C under N_2 was slowly added portions of *p*-toluenesulfonyl chloride (22 g, 115 mmol). After stirring for 3 h, water (100 mL) was added to the reaction mixture. The product was extracted with CH_2Cl_2 (20 mL×3) and washed with brine (20 mL×3). The combined organic layer was dried over $MgSO_4$ and the CH_2Cl_2 was evaporated off. The crude product was purified by column chromatography (petroleum ether: ethyl acetate=3:1) to give pure product (8.1 g) as yellow oil. Yield 27.5%, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.44 (3H, s), 3.57 (4H, s), 3.59 (2H, s), 3.67 (2H, t, *J*=4.8 Hz), 4.14 (2H, t, *J*=4.8 Hz), 7.33 (2H, d, *J*=8.1 Hz), 7.78 (2H, d, *J*=8.2 Hz).

*4.3.9. Compound **Z4**.* Solid 2,3-dihydroxynaphthalene (3.2 g, 20 mmol) was added to a stirred mixture of K_2CO_3 (8.3 g, 60.1 mmol) in dry DMF (20 mL) at room temperature under N_2. The mixture was stirred at 90 °C for 1 h before addition of 2-(2-chloroethoxy) ethanol (4.3 mL, 43.8 mmol) and KI (6.8 g, 40.1 mmol). The reaction mixture was stirred at 100 °C for 48 h. After cooling to room temperature, the reaction mixture was dissolved in CH_2Cl_2 (100 mL) and filtered to remove potassium salts. The organics were dried over $MgSO_4$ and concentrated under reduced pressure to yield a viscous red oil.

To a stirred solution of the above viscous red oil and Et_3N (4 mL) in dry CH_2Cl_2 (20 mL) cooled to 0 °C under N_2 was slowly added portions of *p*-toluenesulfonyl chloride (5.5 g). After stirring at room temperature for 24 h, water (20 mL) was added to the reaction mixture. The product was extracted with CH_2Cl_2 (20 mL×3) and washed with brine (20 mL×3). The combined organic layer was dried over $MgSO_4$ and the CH_2Cl_2 was evaporated off. The crude product was purified by column chromatography (petroleum ether: ethyl acetate=2:1) to give pure product (2.6 g) as a white solid. Yield 20.3%, mp 93.2–93.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (3H, s), 3.82 (2H, t, *J*=4.8 Hz), 3.87 (2H, t, *J*=4.8 Hz), 4.18 (2H, t, *J*=4.7 Hz), 4.22 (2H, t, *J*=4.7 Hz), 7.13 (1H, s), 7.26 (2H, d, *J*=8.1 Hz), 7.36 (2H, m), 7.68 (2H, m), 7.79 (2H, d, *J*=8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 68.5, 69.0, 69.5, 69.7, 108.6, 108.6, 124.4, 124.4, 126.4, 126.4, 127.9, 127.9, 129.4, 129.8, 129.8, 133.1, 144.8, 148.9.

*4.3.10. General experimental procedure for the preparation of chiral crown ethers (**9a**–**m**).* To a suspension of NaH (0.96 g, 24 mmol 60% in paraffin oil) in dry THF (75 mL) was slowly added dropwisely a mixture of **2** or **4** (6 mmol) and pentaethylene glycol ditosylate or 2,3-bis{2-[2-(*p*-tolylsulfonyl)ethoxy]ethoxy}naphthalene (6 mmol) in dry THF (75 mL) at 45 °C. The suspension was stirred for 50 h at refluxing temperature. After cooling to room temperature, a small portion of water was add to the mixture in order to deactivate the excess NaH and the mixture was filtered and concentrated in vacuo. Water (20 mL) was added to the residue, and then extracted with dichloromethane (50 mL×3). The combined organic layer was dried over $MgSO_4$ and the dichloromethane was removed. The residue was purified by chromatography over silica (petroleum ether/ethyl acetate=4:1) to give crown ether derivatives.

*4.3.11. Compound **9a**.* Light yellow oil. Yield: 9.3%, $[\alpha]_D^{25}$ −4.4 (*c* 9.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.56 (3H, s), 0.70 (3H, s), 0.76 (1H, m), 0.98 (6H, t, *J*=6.8 Hz), 1.08 (1H, m), 1.20–1.58 (11H, m), 1.75 (1H, dt, *J*=9.3, 2.7 Hz), 1.93 (1H, m), 2.10 (1H, m), 2.18 (1H, sept. d, *J*=6.5, 1.2 Hz), 2.63 (1H, s), 2.93 (1H, t, *J*=9.4 Hz), 2.97 (1H, t, *J*=9.6 Hz), 3.07 (1H, d, *J*=10.8 Hz), 3.32 (1H, d, *J*=10.8 Hz), 3.35–3.65 (22H, m), 5.31 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.4, 16.7, 17.1, 18.8, 19.6, 20.4, 28.8, 32.6, 34.8, 35.2, 35.5, 36.6, 37.4, 38.2, 39.2, 41.6, 47.6, 50.1, 55.2, 68.9, 69.5, 69.6, 69.9, 69.9, 70.0, 70.1, 70.1, 70.1, 70.2, 71.4, 71.2, 71.5, 124.4, 146.9; IR (KBr, ν, cm^{-1}): 3466, 2925, 1643, 1110; MS (APCI) *m*/*z*: 535.37 ($M+H^+$). Anal. Calcd for $C_{34}H_{58}O_7$: C, 70.55; H, 10.10. Found: C, 70.70; H, 10.21.

*4.3.12. Compound **9b**.* Colorless oil. Yield: 10.3%, $[\alpha]_D^{25}$ −1.0 (*c* 0.933, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.58 (3H, s), 0.75 (3H, s), 0.83 (1H, m), 1.01 (3H, d, *J*=6.5 Hz), 1.03 (3H, d, *J*=6.5 Hz), 1.13 (1H, m), 1.27–1.43 (8H, m), 1.50–1.58 (3H, m), 1.80 (1H, d.t, *J*=9.7, 2.7 Hz), 1.94 (1H, m), 2.15 (1H, m), 2.22 (1H, sept. d, *J*=6.5, 1.2 Hz), 2.68 (1H, s), 2.92 (1H, d, *J*=8.9 Hz), 2.95 (1H, t, *J*=9.5 Hz), 3.01 (1H, t, *J*=8.9 Hz), 3.19 (1H, d, *J*=9.5 Hz), 3.41–3.80 (22H, m), 4.47 (1H, d, *J*=12.5 Hz), 4.52 (1H, d, *J*=12.5 Hz), 5.35 (1H, s), 7.28–7.38 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.0, 17.4, 18.2, 19.5, 20.3, 21.0, 29.4, 33.3, 35.8, 36.1, 36.1, 37.0, 38.0, 38.7, 39.8, 42.2, 48.5, 50.7, 55.8, 69.7, 70.2, 70.3, 70.6, 70.7, 70.7, 70.7, 70.8, 70.8, 70.9, 71.1, 71.7, 73.1, 79.9, 125.0, 127.3, 127.3, 127.3, 128.2, 128.2, 139.2, 147.6; IR (KBr, ν, cm^{-1}): 3082, 3062, 3028, 1496, 1455, 1641, 1112; MS (APCI) *m*/*z*: 669 ($M+H^+$). Anal. Calcd for $C_{41}H_{64}O_7$: C, 73.61; H, 9.64. Found: C, 73.77; H, 10.13.

*4.3.13. Compound **9c**.* Light yellow oil. Yield: 10.6%, $[\alpha]_D^{25}$ −10.2 (*c* 1.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.59 (s, 3H), 0.69 (3H, s), 0.81 (1H, m), 1.01 (3H, d, *J*=6.6 Hz), 1.03 (3H, d, *J*=6.5 Hz), 1.09–1.58 (18H, m), 1.75–1.81 (2H, m), 1.94 (1H, m), 2.09–2.16 (2H, m), 2.22 (1H, sept., *J*=6.6 Hz), 2.41 (4H, br s), 2.69 (1H, s), 2.92 (1H, t, *J*=9.5 Hz), 2.98 (1H, t, *J*=9.5 Hz), 3.37–3.72 (22H, m), 5.34 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 17.6, 19.2, 19.8, 20.3, 21.0, 24.2, 26.6, 29.5, 33.3, 35.6, 36.3, 36.5, 38.0, 38.1, 38.4, 38.9, 39.9, 42.1, 48.8, 50.8, 55.8, 57.6, 69.8, 69.8, 69.9, 69.9, 70.0, 70.5, 70.6, 70.7, 71.6, 125.3, 147.7; IR (KBr, ν, cm^{-1}): 2928, 2867, 1642, 1110; MS (ESI) *m*/*z*: 646 ($M+H^+$). Anal. Calcd for $C_{39}H_{67}O_6N$: C, 72.52; H, 10.45; N, 2.17. Found: C, 72.33; H, 10.58; N, 2.07.

*4.3.14. Compound **9d**.* White solid, Yield: 11%, $[\alpha]_D^{25}$ −14.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.57 (3H, s), 0.72 (3H, s), 0.76 (1H, m), 0.97 (3H, d, *J*=6.7 Hz), 0.98 (3H, d, *J*=6.7 Hz), 1.07 (1H, m), 1.20–1.38 (8H, m), 1.43–1.55 (3H, m), 1.73 (1H, dt), 1.94 (1H, m), 2.10 (1H, m), 2.19 (1H, sept. d, *J*=6.5, 1.2 Hz), 2.63 (1H, s), 3.01 (1H, t, *J*=9.4 Hz), 3.06 (1H, t, *J*=9.4 Hz), 3.09 (1H, d, *J*=10.7 Hz), 3.35 (1H, d, *J*=10.7 Hz), 3.39–3.69 (5H, m), 3.70–3.81 (5H, m), 3.90–4.03 (4H, m), 4.16–4.28 (4H, m), 5.31 (1H, s), 7.09 (1H, s), 7.12 (1H, s), 7.30 (2H, m), 7.64 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.0, 17.3, 17.7, 19.5, 20.2, 21.0, 29.5, 33.3, 35.3, 36.0, 36.1, 36.1, 37.2, 38.0, 38.7, 39.8, 42.4, 48.3, 50.8, 55.7, 68.9, 69.0, 69.7, 70.0, 70.4, 70.5, 70.6, 71.1, 71.7,

72.3, 108.2, 109.1, 124.1, 124.2, 125.0, 126.3, 126.3, 129.4, 129.5, 147.5, 149.2, 149.4; IR (KBr, ν, cm^{-1}): 3440, 2930, 1601, 1509, 1486, 1451, 1628, 1111; MS (APCI) *m/z*: 677.44 ($M+H^+$). HRMS (ESI) 699.4220 $[M+Na]^+$, calcd for $C_{42}H_{60}O_7Na$: 699.4232.

4.3.15. Compound ***9e***. Colorless oil. Yield: 9.3%, $[\alpha]_D^{25}$ −6.1 (*c* 1.45, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.56 (3H, s), 0.73 (3H, s), 0.79 (1H, m), 0.97 (3H, d, *J*=6.5 Hz), 0.98 (3H, d, *J*=6.5 Hz), 1.07 (1H, m), 1.21−1.43 (8H, m), 1.46−1.54 (3H, m), 1.75 (1H, dt, *J*=9.7, 2.7 Hz), 1.94 (1H, m), 2.10 (1H, m), 2.19 (1H, sept. d, *J*=6.5, 1.2 Hz), 2.64 (1H, s), 2.90 (1H, d, *J*=8.9 Hz), 2.98 (1H, t, *J*=9.5 Hz), 3.05 (1H, t, *J*=9.5 Hz), 3.14 (1H, d, *J*=8.9 Hz), 3.41−3.70 (5H, m), 3.71−3.82 (5H, m), 3.91−4.04 (4H, m), 4.20−4.29 (4H, m), 4.48 (1H, d, *J*=12.5 Hz), 4.53 (1H, d, *J*=12.5 Hz), 5.31 (1H, s), 7.09 (1H, s), 7.12(1H, s), 7.26−7.36 (7H, m), 7.65(2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.0, 17.4, 18.2, 19.6, 20.3, 21.0, 29.5, 33.3, 35.9, 36.1, 37.0, 38.0, 38.7, 39.8, 42.3, 48.5, 50.8, 55.6, 68.9, 69.0, 69.7, 69.8, 70.1, 70.4, 70.5, 70.6, 71.2, 71.7, 73.2, 79.9, 108.0, 109.0, 124.1, 124.2, 125.1, 126.3, 126.4, 127.3, 127.4, 127.5, 128.1, 128.3, 129.3, 129.5, 139.2, 147.5, 149.2, 149.4; IR (KBr, ν, cm^{-1}): 3081, 3062, 3028, 1602, 1509, 1487, 1453, 1628, 1115; MS (APCI) *m/z*: 767 ($M+H^+$). Anal. Calcd for $C_{49}H_{66}O_7$: C, 76.73; H, 8.67. Found: C, 76.91; H, 8.64.

4.3.16. Compound ***9f***. Yellow solid, Yield: 9.4%, mp 85−86 °C, $[\alpha]_D^{25}$ −16.0 (*c* 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.60 (3H, s), 0.72 (3H, s), 0.81 (1H, m), 1.00 (3H, d, *J*=6.7 Hz), 1.01 (3H, d, *J*=6.7 Hz), 1.08−1.57 (18H, m), 1.78 (1H, dt, *J*=9.3, 2.3 Hz), 1.81 (1H, m), 1.97 (1H, m), 2.11 (1H, m), 2.18 (1H, m), 2.23 (1H, sept., *J*=6.7 Hz), 2.44 (4H, s), 2.67 (1H, s), 2.99 (1H, t, *J*=9.5 Hz), 3.08 (1H, t, *J*=9.5 Hz), 3.48−3.72 (5H, m), 3.73−3.81 (5H, m), 3.95−4.03 (4H, m), 4.25−4.28 (4H, m), 5.34 (1H, s), 7.15 (1H, s), 7.12 (1H, s), 7.34 (2H, m), 7.67 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 17.6, 19.2, 19.8, 20.3, 21.0, 24.3, 26.7, 29.7, 33.3, 35.9, 36.3, 36.5, 38.1, 38.4, 38.9, 39.9, 42.2, 48.8, 51.0, 55.7, 57.6, 68.9, 69.1, 69.7, 69.8, 69.8, 70.1, 70.4, 70.6, 71.2, 71.6, 108.1, 109.1, 124.1, 124.2, 125.2, 126.3, 126.3, 129.3, 129.5, 147.5, 149.2, 149.4; IR (KBr, ν, cm^{-1}): 3056, 1600, 1511, 1489, 1456, 1627, 1110; MS (APCI) *m/z*: 744 ($M+H^+$). Anal. Calcd for $C_{47}H_{69}O_6N$: C, 75.87; H, 9.35; N, 1.88. Found: C, 75.68; H, 9.43; N, 1.79.

4.3.17. Compound ***9g***. White solid, Yield: 9.5%, $[\alpha]_D^{25}$ −17.5 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.56 (3H, s), 0.87 (1H, m), 0.97 (3H, d, *J*=6.5 Hz), 0.98 (3H, d, *J*=6.5 Hz), 1.09 (1H, m), 1.13 (3H, s), 1.21−1.43 (8H, m), 1.46−1.54 (3H, m), 1.75 (1H, dt, *J*=9.6, 2.9 Hz), 1.92 (1H, m), 2.10 (1H, m), 2.19 (1H, sept. d, *J*=6.5, 1.2 Hz), 2.65 (1H, s), 3.00 (1H, t, *J*=9.5 Hz), 3.05 (1H, t, *J*=9.3 Hz), 3.39−3.70 (8H, m), 3.71−3.82 (5H, m), 3.91−4.04 (4H, m), 4.20−4.29 (4H, m), 5.30 (1H, s), 7.09 (1H, s), 7.13 (1H, s), 7.32 (2H, m), 7.65 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.8, 16.8, 17.2, 20.2, 21.0, 22.3, 29.2, 33.3, 35.9, 36.0, 36.9, 37.7, 38.2, 40.1, 42.5, 47.3, 49.5, 50.7, 51.9, 55.9, 69.0, 69.1, 69.7, 69.8, 70.1, 70.5, 70.5, 70.6, 71.2, 71.7, 108.2, 109.1, 124.2, 124.3, 124.9, 126.3, 126.4, 129.4, 129.6, 147.6, 149.2, 149.4, 179.6; IR (KBr, ν, cm^{-1}): 2926, 1602, 1508, 1486, 1451, 1723, 1629, 1116; MS (APCI) *m/z*: 705.33 ($M+H^+$). Anal. Calcd for $C_{43}H_{60}O_8$: C, 73.26; H, 8.58. Found: C, 73.19; H, 8.66.

4.3.18. Compound ***9h***. Light yellow oil. Yield: 11.2%, $[\alpha]_D^{25}$ −3.0 (*c* 3.98, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.60 (3H, s), 0.74 (3H, s), 0.80 (1H, m), 1.01 (3H, d, *J*=6.5 Hz), 1.03 (3H, d, *J*=6.5 Hz), 1.10 (1H, m), 1.23−1.40 (8H, m), 1.48−1.58 (3H, m), 1.81 (1H, dt, *J*=9.8, 2.4 Hz), 1.96 (1H, m), 2.13 (1H, m), 2.23 (1H, sept. d, *J*=6.7, 1.3 Hz), 2.71 (s, 1H), 2.92 (2H, t, *J*=9.7 Hz), 3.09 (1H, d, *J*=10.8 Hz), 3.35 (1H, d, *J*=10.8 Hz), 3.37−3.73 (18H, m), 5.34 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3, 16.7, 17.1, 18.8, 19.6, 20.4, 28.8, 32.6, 34.7, 34.8, 35.5, 36.5, 37.3, 38.1, 39.1, 41.4, 47.5, 50., 55.2, 68.9, 69.1, 69.4, 69.7, 69.9, 70.0, 70.4, 70.7, 71.2, 124.2; IR (KBr, ν, cm^{-1}): 3443, 2925, 1636, 1113; MS (APCI) *m/z*: 535.37 ($M+H^+$). Anal. Calcd for $C_{32}H_{54}O_6$: C, 71.87; H, 10.18. Found: C, 71.79; H, 10.25.

4.3.19. Compound ***9i***. Light yellow oil. Yield: 36.8%, $[\alpha]_D^{25}$ −8.3 (*c* 1.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.60 (3H, s), 0.69 (3H, s), 0.79 (1H, m), 1.02 (3H, d, *J*=6.6 Hz), 1.04 (3H, d, *J*=6.7 Hz), 1.10−1.58 (18H, m), 1.78−1.83 (2H, m), 1.96 (1H, m), 2.14 (2H, m), 2.23 (1H, sept. d, *J*=6.7, 1.3 Hz), 2.41 (4H, br s), 2.73 (1H, s), 2.89 (1H, t, *J*=10.0 Hz), 2.92 (1H, t, *J*=10.0 Hz), 3.39−3.99 (18H, m), 5.35 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 17.8, 19.2, 19.8, 20.3, 21.0, 24.2, 26.6, 29.5, 33.3, 35.4, 36.4, 36.5, 38.1, 38.4, 38.9, 39.8, 41.9, 48.7, 51.0, 55.8, 57.5, 69.7, 69.7, 69.9, 70.1, 70.4, 70.7, 70.8, 71.0, 71.5, 125.1, 147.8; IR (KBr, ν, cm^{-1}): 2929, 2867, 1641, 1112; MS (APCI) *m/z*: 602 ($M+H^+$). Anal. Calcd for $C_{37}H_{63}O_5N$: C, 73.83; H, 10.55; N, 2.33. Found: C, 73.63; H, 10.66; N, 2.20.

4.3.20. Compound ***9j***. Light yellow oil. Yield: 10.8%, $[\alpha]_D^{25}$ −2.5 (*c* 0.8, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.58 (3H, s), 0.90 (1H, m), 1.02 (6H, t, *J*=6.3 Hz), 1.08−1.15 (4H, m), 1.31−1.56 (8H, m), 1.61−1.72 (3H, m), 1.82 (1H, dt, *J*=9.8, 2.5 Hz), 1.92 (1H, m), 2.14 (1H, m), 2.22 (1H, sept. d, *J*=6.7, 1.3 Hz), 2.74 (1H, s), 2.88 (1H, t, *J*=9.4 Hz), 2.90 (1H, t, *J*=9.6 Hz), 3.37−4.06 (21H, m), 5.32 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.8, 16.8, 17.2, 20.2, 21.0, 22.3, 29.1, 33.3, 35.4, 36.0, 36.8, 37.7, 38.2, 40.1, 42.1, 47.2, 49.4, 50.6, 55.9, 66.0, 69.6, 69.9, 70.1, 70.4, 70.7, 70.8, 71.0, 71.5, 124.66, 147.9, 178.9; IR (KBr, ν, cm^{-1}): 2930, 1638, 1116. MS (APCI) *m/z*: 507 ($M+H^+$). Anal. Calcd for $C_{31}H_{54}O_5$: C, 73.47; H, 10.74. Found: C, 73.31; H, 10.88.

4.3.21. Compound ***9k***. Colorless oil. Yield: 8.6%, $[\alpha]_D^{25}$ −2.72 (*c* 6.85, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.59 (3H, s), 0.76 (3H, s), 0.84 (1H, m), 1.03 (3H, d, *J*=6.4 Hz), 1.06 (3H, d, *J*=6.4 Hz), 1.14 (1H, m), 1.27−1.44 (8H, m), 1.48−1.58 (3H, m), 1.82 (1H, dt, *J*=9.7, 2.7 Hz), 1.93 (1H, m), 2.11 (1H, m), 2.24 (1H, sept. d, *J*=6.5, 1.3 Hz), 2.71 (1H, s), 2.91−2.96 (3H, m), 3.18 (1H, d, *J*=8.9 Hz), 3.37−3.80 (14H, m), 4.49 (1H, d, *J*=12.5 Hz), 4.52 (1H, d, *J*=12.5 Hz), 5.35 (1H, s), 7.29−7.38 (5H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.0, 17.4, 18.1, 19.6, 20.3, 21.0, 29.4, 33.4, 35.7, 36.1, 36.2, 37.0, 38.1, 38.7, 39.8, 42.4, 48.5, 51.1, 55.9, 69.1, 69.5, 69.6, 70.0, 70.2, 70.3, 71.3, 72.5, 73.2, 79.9, 124.9, 127.3, 128.2, 139.1, 147.9; IR (KBr, ν, cm^{-1}): 3081, 3062, 3027, 1496, 1454, 1638, 112; MS (FAB) *m/z*: 603 ($M+Na^+$). Anal. Calcd for $C_{37}H_{56}O_5$: C, 76.51; H, 9.72. Found: C,76.63; H, 9.83.

4.3.22. Compound ***9l***. Light yellow oil. Yield: 15.3%, $[\alpha]_D^{25}$ −13.1 (*c* 1.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.60 (3H, s), 0.70 (3H, s), 0.82 (1H, m), 1.04 (3H, d, *J*=6.5 Hz), 1.05 (3H, d, *J*=6.4 Hz), 1.09−1.59 (18H, m), 1.81 (1H, dt, *J*=9.7, 2.7 Hz), 1.95 (1H, m), 2.05−2.12 (2H, m), 2.17 (1H, d, *J*=14.1 Hz), 2.24 (1H, sept. d, *J*=6.5, 1.3 Hz3), 2.43 (4H, br s), 2.71 (1H, s), 2.88−2.94 (2H, m), 3.36−4.33 (14H, m), 5.35 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.1, 17.3, 18.9, 19.9, 20.3, 21.0, 24.5, 26.4, 29.7, 33.4, 35.7, 36.2, 36.3, 38.1, 38.3, 38.4, 39.8, 42.3, 49.4, 51.1, 55.8, 57.1, 69.1, 69.5, 69.6, 70.0, 70.2, 70.3, 71.3, 72.5, 125.1, 147.8; IR (KBr, ν, cm^{-1}): 2928, 2866, 1641, 1122; MS (ESI) *m/z*: 658 ($M+H^+$). Anal. Calcd for $C_{35}H_{59}O_4N$: C, 75.36; H, 10.66; N, 2.51. Found: C, 75.23; H, 10.79; N, 2.37.

4.3.23. Compound ***9m***. Colorless oil. Yield: 10.7%, $[\alpha]_D^{25}$ −6.78 (*c* 9.73, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.60 (3H, s), 0.77 (3H, s), 0.85 (1H, m), 1.03 (3H, d, *J*=6.8 Hz), 1.06 (3H, d, *J*=6.8 Hz), 1.13 (1H, m), 1.28−1.45 (8H, m), 1.50−1.60 (3H, m), 1.79 (1H, dt, *J*=9.7, 2.8 Hz), 1.95 (1H, m), 2.14 (1H, m), 2.24 (1H, sept. d, *J*=6.7, 1.3 Hz), 2.68 (1H, s), 2.95 (1H, d, *J*=8.9 Hz), 2.99 (1H, t, *J*=9.5 Hz), 3.04 (1H, t, *J*=9.5 Hz), 3.20 (1H, d, *J*=8.9 Hz), 3.38−3.79 (14H, m), 4.49 (1H, d, *J*=12.5 Hz), 4.53 (1H, d, *J*=12.5 Hz), 5.35 (1H, s), 7.29−7.38 (5H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.0, 17.4, 18.2, 19.6, 20.3, 21.0, 29.5, 33.3, 35.9, 36.1, 36.2, 37.1, 38.1, 38.7, 39.9, 42.4, 48.6, 50.7, 55.8, 69.7, 70.1, 70.2, 70.6, 70.7, 70.8, 71.8, 73.2, 80.0, 125.1, 127.3, 128.2, 139.2,

147.4; IR (KBr, ν, cm^{-1}): 3082, 3063, 3027, 1496, 1454, 1641, 1108; MS (FAB) m/z: 1183 ($M+Na^+$). Anal. Calcd for $C_{80}H_{112}O_{10}$: C, 77.88; H, 9.15. Found: C, 77.67; H, 9.28.

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Supplementary data

Supplementary data available: copies of ^1H NMR and ^{13}C NMR spectra. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.10.050.

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