Pergamon

Tetrahedron Letters 43 (2002) 6249–6253

TETRAHEDRON LETTERS

New type chiral calix[4](aza)crowns: synthesis and chiral recognition

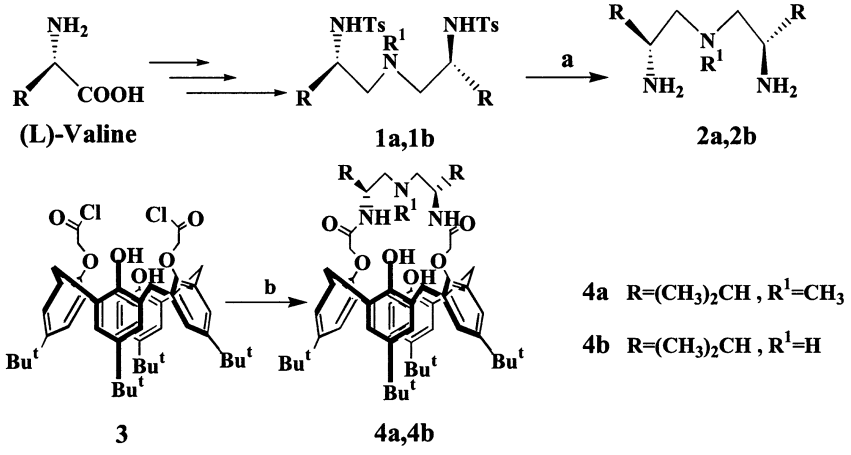
Yongbing He, Yuanjing Xiao, Lingzhi Meng, Zhenya Zeng, Xiaojun Wu and Cheng-Tai Wu*

Department of Chemistry, Wuhan University, Wuhan 430072, PR China

Received 19 March 2002; revised 21 June 2002; accepted 28 June 2002

Abstract—Two new types of chiral calix[4](aza)crowns containing L-valine were synthesized by the reaction of calix[4]arene diacid dichloride with the corresponding chiral diamines derived from C_2-symmetric chiral disulfonamides. Preliminary application of one ligand in chiral recognition was studied by ^1H and ^{13}C NMR, and UV spectroscopy.

The widespread research on molecular recognition of guests by synthetic hosts has stimulated bio(in)organic chemists to design chiral macrocyclic ligands for chiral recognition and chiral catalysis.[1–4] Calixarenes, the third generation of host molecules after crown ethers and cyclodextrin, have been found to be an excellent 'platform' for the design of receptor sites for the specific recognition of guests.[5–8] In this respect, chiral calixarenes, which include those bearing an inherently chiral structure,[9] and those bearing chiral substituents,[10] have attracted considerable attention in the fields of organic, biological and medicinal chemistry since the idea was first proposed by Böhmer et al.[11] Recently, calix[4]azacrowns which combine a calix[4]arene element and aza-crown units in their framework, have received much attention because of their special structures and good complexing properties towards metal cations.[12] The chiral calix(aza) crowns comprising a calixarene and a chiral polyamine derived from an amino acid, could have chiral recognition abilities and could also serve as good anion receptors[13] by co-operation effects. To the best of our knowledge, there is no report on this type of chiral calix(aza)crown. In the present paper, we wish to report the first synthesis and



Scheme 1. *Reagents and reaction conditions*: (a) (i) 33% AcOH/HBr (aq.) (v/v), phenol, 130°C, N_2, 7 days, (ii) 2 M NaOH, $CHCl_3$ extraction, 40% for **2a**, 35% for **2b**; (b) **2a**/**2b**, CH_2Cl_2, NEt_3, rt, 2 days, 25% for **4a**, 12% for **4b**.

Keywords: chiral calix[4](aza)crown; synthesis; L-valine; chiral recognition.

* Corresponding author. Tel.: 86-27-87682922; fax: 86-27-87647617; e-mail: ctwu@public.wh.hb.cn

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01322-9

characterization of the new chiral calix[4](aza)crowns **4a** and **4b** and a preliminary investigation of the chiral recognition properties of **4a**.

A multistep route, as shown in Scheme 1, was chosen for the synthesis of these new types of chiral calix[4](aza)crowns. The tosyl groups of compounds **1a** and **1b**[14] were removed by treatment with 33% AcOH/aq. HBr (>40%) (v/v) in the presence of phenol followed by basification with 2 M NaOH to give the chiral amines **2a** and **2b**[15] following the literature method.[16] The reaction of calix[4]arene diacid dichloride **3**[17] with an equimolar amount of **2a** or **2b** in dichloromethane in the presence of excess triethylamine under high dilution conditions gave the new chiral calix[4](aza)crowns **4a** or **4b**[18] after column chromatography (silica gel, with chloroform/ethyl acetate as eluent) in 25 and 12% yields, respectively.

The chiral calix[4](aza)crowns **4a** and **4b** gave satisfactory elemental analyses and FAB-MS spectra indicated that they were '1+1' cyclization products. Compounds **4a** and **4b** are asymmetric due to the formation of the chiral sub-ring on the lower rim of the calix[4]arene. The stereogenic centers disturb the planar symmetry of the phenyl rings, which results in 12 aromatic carbon signals appearing in the ^{13}C NMR spectra of compounds **4a** and **4b**.[18] This pattern is similar to that which has been observed in other chiral calix[4]-arenes.[10b] The ^{1}H NMR spectra of **4a** and **4b**[18] show

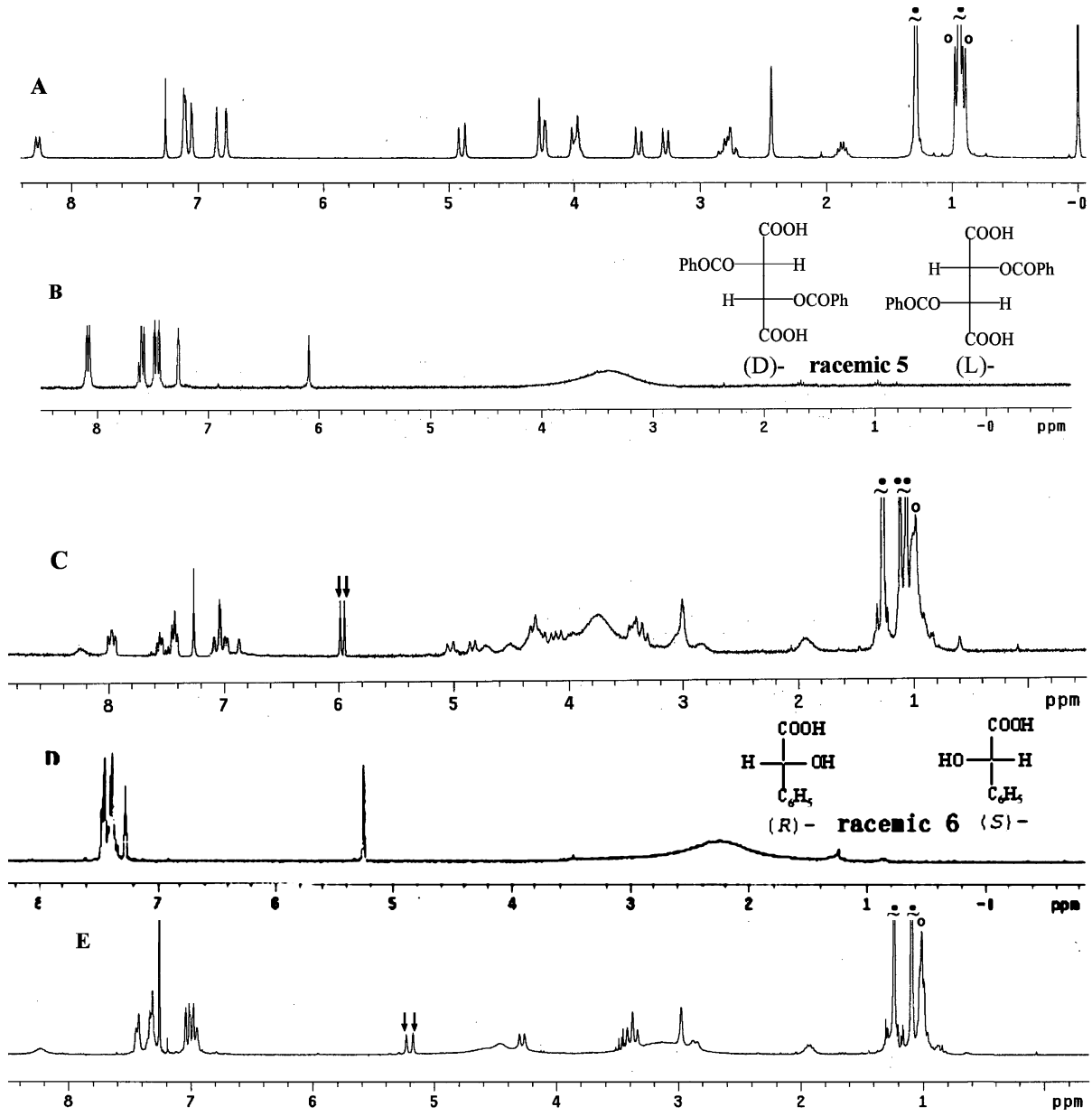


Figure 1. ^{1}H NMR spectra of the host and its guest complex at 25°C in $CDCl_3$ at 300 MHz. (A) [**4a**]=4.0×10^{-3} M; (B) [**5**]=4.0×10^{-3} M; (C) [**4a**]=[**5**]=4.0×10^{-3} M; (D) [**6**]=4.0×10^{-3} M; (E) [**4a**]=[**6**]=4.0×10^{-3} M. The small circles indicate the (CH)C**H**$_3$ methyl protons of the isopropyl groups of host **4a**, the small circle points indicate the protons in the *p-tert*-butyl groups of host **4a** and the arrow indicates the CH proton of racemic **5** and **6**.

two sets of doublets for the bridging methylene protons. This demonstrated that the two compounds are in the cone conformation. The ^{1}H NMR spectra of **4a** and **4b** also exhibit two sets of doublets for the aromatic protons and one set of doublets for the ArOC**H**$_2$ protons. This splitting pattern may relate to the presence of the chiral moieties in the molecules, as seen in other chiral calix[4]arenes.[10]

Preliminary experiments[19] were undertaken to assess the chiral recognition properties of ligand **4a** by ^{1}H NMR. The dibenzoate of racemic tartaric acid **5** (Fig. 1B) and racemic amygdalic acid **6** (Fig. 1D) were chosen as probes, The ^{1}H NMR spectra of host **4a** and its complex with equimolar amounts of racemic **5** and **6** are shown in Fig. 1. Two singlet resonances (δ 6.03 and 5.99) due to the CH proton of racemic **5** were observed in the presence of equimolar amounts of **4a**, and their intensity ratio is 1:1, the separation between the two peaks is 12 Hz (Fig. 1C). However, as shown in Fig. 1B, only one singlet (δ 6.13) for the CH proton resonance of racemic **5** was observed in the absence of host **4a**. ^{1}H NMR titration experiments showed that the singlet for the CH protons of the L- or D-forms as guests exhibited a gradual upfield shift with increasing concentration of the guest until the guest/host mole ratio reached 1:1; $\Delta\delta$ is 0.10 and 0.14 ppm towards the L- and D-form guest, respectively. This indicates that the interactions of host **4a** with the L- and D-forms of the tartaric acid derivative are different, resulting in two singlet resonances for the racemic C**H** proton. The results of the ^{1}H NMR titration experiments also suggested the formation of a 1:1 complex between the host and the D- or L-forms of the guest, on the basis of the molar ratio method.[19] In comparison with Fig. 1A, in the presence of racemic **5**, Fig. 1C shows a significant difference for the signals of the *p-tert*-butyl groups on the upper-rim of the host **4a**: these changed from two singlets (ratio 1:1) to three singlets (ratio 2:1:1), however, this interesting phenomenon did not occur between host **4a** and racemic amygdalic acid **6**. Fig. 1E clearly shows that the ^{1}H NMR resonances of the protons in the *p-tert*-butyl groups of host **4a** still show two singlets (ratio 1:1), but two singlet peaks (δ 5.23

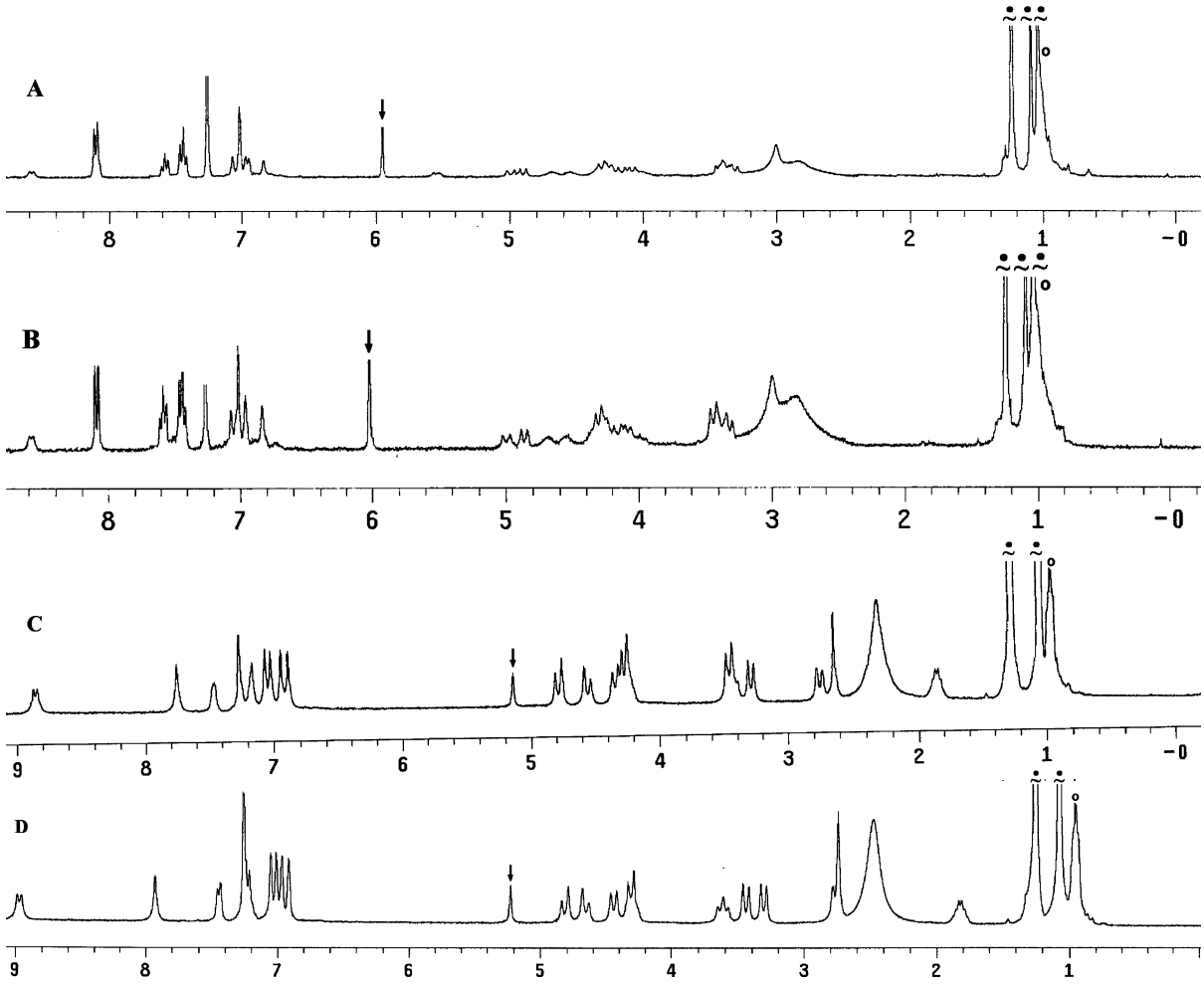


Figure 2. ^{1}H NMR spectra of the complexes of individual enantiomers of the guests **5** and **6** with host **4a** at 25°C in $CDCl_3$ at 300 MHz. The small circles indicate the (CH)C**H**$_3$ methyl protons of the isopropyl groups of host **4a**, the small circle points indicate the protons in the *p-tert*-butyl groups of host **4a** and the arrow indicates the CH proton of individual enantiomers of the guests **5** and **6**. (A) [**4a**]=[(D)-**5**]=4.0×10^{-3} M; (B) [**4a**]=[(L)-**5**]=4.0×10^{-3} M; (C) [**4a**]=[(*R*)-**6**]=4.0×10^{-3} M; (D) [**4a**]=[(*S*)-**6**]=4.0×10^{-3} M.

and 5.17) for the CH proton of racemic enantiomer **6** were also observed in the presence of an equimolar amount of host **4a**, and their intensity ratio is 1:1, the separation between two peaks is 18 Hz whereas only a singlet peak (δ 5.26) for the CH proton resonance of racemic amygdalic acid **6** was observed in the absence of host **4a** as Fig. 1D shows. From Fig. 1C, we can deduce that interaction between the host **4a** and guest **5** results in a partial cone conformation of **4a** in the complex,[20] because an appropriate conformational environment is beneficial to the complexation of the relatively larger molecular skeleton of guest **5** in comparison with guest **6**.[21] Additional support for this conclusion was obtained from the ^{13}C NMR spectra of the complex of host **4a** and guest **5** in which two signals at δ 37.2 and 31.8 ppm were present due to the bridging methylene carbons, however, there was no signal at δ 37.0 ppm in the ^{13}C NMR spectrum of pure host **4a**.[18] This suggests that the predominant conformation of host **4a** in the complex was a partial cone conformation.[22]

Further ^1H NMR experiments were conducted by adding the individual enantiomers of the guests instead of the racemic mixture. The ^1H NMR spectra of the complex of the individual enantiomers of the guests with equimolar amounts of host **4a** are shown in Fig. 2. This also shows a significant difference for the signals of the *p-tert*-butyl groups on the upper-rim of the host **4a**, the same as Figs. 1C and E show. However, only one singlet for the CH proton resonance of the individual enantiomers of the guests **5** and **6** was observed in the presence of the host **4a**, thus, we can conclude that the splitting of the CH is due to the different binding of the enantiomers and not to two different binding modes.

A series of UV-absorption experiments was undertaken to investigate a possible interaction between the host and guest **5**, as shown in Fig. 3. In the plot, A_H+A_D or A_H+A_L denotes the algebraic addition of the individual absorbances of the D- or L-forms of guests at different concentrations with the absorbances of host **4a**; plot A_{H-D} or A_{H-L} shows the UV absorbance of a mixture of the D- or L-forms of the guests at different concentrations with host **4a**. These clearly indicate that interactions between the host and guest do indeed occur, which could be due to the formation of hydrogen bonds or π–π interactions between host and guest. Fig. 4 shows a Benesi–Hildebrand plot[19,23] for a mixture of host **4a** and the D- or L-forms of **5** in $CHCl_3$ at 25°C: the plot is linear, supporting the 1:1 stoichiometry of the complex as shown in ^1H NMR experiments. The association constant *K*, calculated from the slope, was $(9.83\pm0.43)\times10^3$ M^{-1} and $(5.04\pm0.28)\times10^3$ M^{-1} for the D- and L-form guests, respectively. It also indicates that the host **4a** exhibits relatively good complexing ability towards the D-form of the tartaric acid derivative.

In summary, we have synthesized two new types of chiral calix[4](aza)crowns (**4a** and **4b**). Their structure was confirmed by elemental analysis, MS, ^1H and ^{13}C NMR spectroscopy. Chiral recognition by host **4a** was studied by ^1H and ^{13}C NMR, and UV spectroscopy. It was found that host **4a** exhibited different recognition ability towards the D- and L-forms of a tartaric acid derivative and had different recognition conformations with different guest species. Recognition ability for such acidic molecules has been reported only rarely.

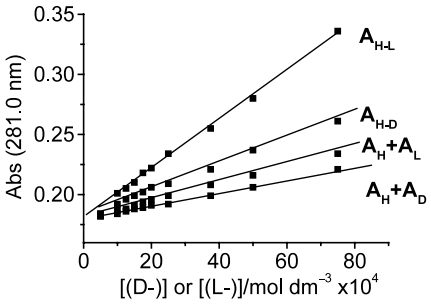


Figure 3. UV spectra absorbance plot upon addition of the D- or L-forms of the tartaric acid derivative to host **4a** ($CHCl_3$ solution, 2.5×10^{-5} mol dm^{-3} at 25°C).

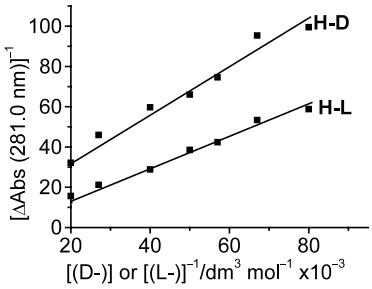


Figure 4. Benesi–Hildebrand plot for a mixture of host **4a** and the D- or L-forms of the tartaric acid derivative, [**4a**]= 2.5×10^{-5} mol dm^{-3}, $CHCl_3$, at 25°C.

Acknowledgements

Financial support from the National Natural Science Foundation of China (No. 20072029) is gratefully acknowledged.

References

1. Lehn, J. M. *Superamolecular Chemistry*: *Concepts and Perspectives*; VCH: Weinheim, 1995.
2. Webb, T. H.; Wilcox, C. S. *Chem. Soc. Rev.* **1993**, *22*, 383.
3. Wenzel, T. J.; Thurston, J. E. *Tetrahedron Lett.* **2000**, *41*, 3769.
4. Tejeda, A.; Oliva, A. I.; Simón, L.; Grande, M.; Caballero, M.-C.; Morán, J. R. *Tetrahedron Lett.* **2000**, *41*, 4563.
5. Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989.
6. Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713.
7. Molenveld, P.; Engbersen, J. F.; Reinhoudt, D. N. *Chem. Soc. Rev.* **2000**, *29*, 75.
8. Memon, S.; Yilmaz, M. *J. Mol. Struct.* **2001**, *595*, 101.

9. (a) Shinkai, S.; Arimura, T.; Kawabata, H.; Murakami, H.; Iwamoto, K.; Matsuda, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1734; (b) Caccamese, S.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Principato, G. *Tetrahedron* **1999**, *55*, 5505; (c) Morohashi, N.; Iki, N.; Onodera, T.; Kabuto, C.; Miyano, S. *Tetrahedron Lett.* **2000**, *41*, 5093.
10. (a) Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 522; (b) Yuan, H. S.; Huang, Z.-T. *Tetrahedron: Asymmetry* **1999**, *10*, 429; (c) Hu, X. B.; He, J. Q.; Chan, A. S. C.; Han, X. X.; Cheng, J.-P. *Tetrahedron: Asymmetry* **1999**, *10*, 2685; (d) Hu, X. B.; Chan, A. S. C.; Han, X. X.; He, J. Q.; Cheng, J.-P. *Tetrahedron Lett.* **1999**, *40*, 7115; (e) Biserka, K.-p.; Mladen, Z. *Chem. Eur. J.* **2000**, *6*, 442; (f) Dondoni, A.; Hu, X. B.; Marra, A.; Banks, H. D. *Tetrahedron Lett.* **2001**, *42*, 3259.
11. Wolff, A.; Böhmer, V.; Vogt, W.; Vgozzoli, F; Andreetti, G. D. *J. Org. Chem.* **1990**, *55*, 5665.
12. (a) Oueslati, I.; Abidi, R.; Thuery, P.; Nierlich, M.; Asfari, Z.; Harrowfield, J.; Vicens, J. *Tetrahedron Lett.* **2000**, *41*, 8263; (b) Kim, J. S.; Lee, W. K.; No, K.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **2000**, *41*, 3345; (c) Abidi, R.; Oueslati, I.; Amri, H.; Thuéry, P.; Nierlich, M.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **2001**, *42*, 1685; (d) Kim, J. S.; Yang, S. H.; Rim, J. A.; Kim, J. Y.; Vicens, J.; Shinkai, S. *Tetrahedron Lett.* **2001**, *42*, 8047.
13. Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609.
14. Wang, J.-q.; Zhong, M.; Lin, G.-q. *Chin. J. Chem.* **1998**, *16*, 65.
15. Analytical data for compound **2a**: yellowish thick liquid; *m*/*z* (%): 202 (M^+, 90); δ_H ($CDCl_3$ 300 MHz): 2.50–2.57 (m, 2H, $2NH_2C\mathbf{H}$), 2.09 (s, 3H, N-$C\mathbf{H}_3$), 2.06–2.11 (m, 4H, $2C\mathbf{H}_2NCH_3$), 1.60 (br, s, 4H, $2N\mathbf{H}_2$, after addition of D_2O, this peak disappeared), 1.35–1.42 (m, 2H, $2C\mathbf{H}(CH_3)_2$), 0.77 (d, $J=6.9$ Hz, 12H, $2CH(C\mathbf{H}_3)_2$).
Compound **2b**: yellowish thick liquid; *m*/*z* (%): 188 (M^+, 80); δ_H 2.56–2.61 (m, 2H, $2NH_2C\mathbf{H}$), 2.25–2.54 (m, 2H, $CHC\mathbf{H}_2NH$), 2.32–2.39 (m, 2H, $CHC\mathbf{H}_2NH$), 1.49–1.57 (m, 2H, $2C\mathbf{H}(CH_3)_2$), 1.50 (br, s, 5H, $2N\mathbf{H}_2$+N**H**, after addition of D_2O, this peak disappeared), 0.87 (d, $J=4.2$ Hz, 6H, $CH(C\mathbf{H}_3)_2$), 0.84 (d, $J=4.2$ Hz, 6H, $CH(C\mathbf{H}_3)_2$).
16. Liu, Y.; Xue, G.-P.; Wu, Ch.-T. *Chin. J. Chem.* **1998**, *16*, 538.
17. Collins, E. M.; McKervey, M. A.; Madigan, E.; Moran, M. B.; Owens, M.; Ferguson, G.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, *12*, 3137.
18. Analytical data for compound **4a**: mp 180–182°C; $[\alpha]_D^{24}=+82$ (*c* 0.65, $CHCl_3$); IR (cm^{-1}) 3363 (NH), 1680 (C=O, amide); δ_H ($CDCl_3$, 300 MHz): 8.27 (d, $J=8.7$ Hz, 2H, 2N**H**C=O, after addition of D_2O, this peak disappeared), 7.11 (d, $J=1.5$ Hz, 2H, Ar**H**), 7.09 (s, 2H, ArO**H**, after addition of D_2O, this peak disappeared), 7.05 (d, $J=2.1$ Hz, 2H, Ar**H**), 6.85 (d, $J=2.1$ Hz, 2H, Ar**H**), 6.77 (d, $J=1.5$ Hz, 2H, Ar**H**), 4.90 (d, $J=15.3$ Hz, 2H, $ArOC\mathbf{H}_2$), 4.26 (d, $J=12.6$ Hz, 2H, $ArC\mathbf{H}_2Ar$), 4.25 (d, $J=15.3$ Hz, 2H, $ArOC\mathbf{H}_2$), 3.99 (d, $J=13.5$ Hz, 2H, $ArC\mathbf{H}_2Ar$), 3.90–4.01 (m, 2H, $2CHC\mathbf{H}CH_2NCH_3$), 3.50 (d, $J=13.5$ Hz, 2H, $ArC\mathbf{H}_2Ar$), 3.28 (d, $J=12.6$ Hz, 2H, $ArC\mathbf{H}_2Ar$), 2.72–2.80 (m, 4H, $2CHC\mathbf{H}_2NCH_3$), 2.48 (s, 3H, N-$C\mathbf{H}_3$), 1.86–1.92 (m, 2H, $2C\mathbf{H}(CH_3)_2$), 1.29 (s, 18H, Bu^t), 0.97 (d, $J=6.6$ Hz, 6H, $CH(C\mathbf{H}_3)_2$), 0.95 (s, 18H, Bu^t), 0.92 (d, $J=6.6$ Hz, 6H, $CH(C\mathbf{H}_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 19.3, 19.9, 30.7, 30.8, 31.6, 31.7, 33.9, 34.0, 44.8, 55.0, 60.4, 74.9, 125.2, 125.4, 126.1, 126.9, 127.1, 128.2, 131.9, 132.6, 143.3, 148.6, 149.3, 149.9, 168.5; *m*/*z* (%): 930 (M^+, 100). Anal. calcd for $C_{59}H_{83}N_3O_6$: C, 76.17; H, 8.99; N, 4.52. Found: C, 75.89; H, 9.12; N, 4.29%.
Analytical data for **4b**: mp 218–220°C; $[\alpha]_D^{24}=+74$ (*c* 0.67, $CHCl_3$); IR (cm^{-1}) 3366 (NH), 1679 (C=O, amide); δ_H (300 MHz, $CDCl_3$): 8.30 (d, $J=9.0$ Hz, 2H, 2N**H**C=O, after addition of D_2O, this peak disappeared), 7.10 (d, $J=2.4$ Hz, 2H, Ar**H**), 7.07 (d, $J=2.1$ Hz, 2H, Ar**H**), 6.79 (d, $J=2.1$ Hz, 2H, Ar**H**), 6.74 (d, $J=2.4$ Hz, 2H, Ar**H**), 6.72 (s, 2H, ArO**H**, after addition of D_2O, this peak disappeared), 4.84 (d, $J=15.9$ Hz, 2H, $ArOC\mathbf{H}_2$), 4.29 (d, $J=13.2$ Hz, 2H, $ArC\mathbf{H}_2Ar$), 4.24 (d, $J=15.9$ Hz, 2H, $ArOC\mathbf{H}_2$), 4.03 (d, $J=13.5$ Hz, 2H, $ArC\mathbf{H}_2Ar$), 3.82–3.90 (m, 2H, $2NHC\mathbf{H}CH_2$), 3.48 (d, $J=13.5$ Hz, 2H, $ArC\mathbf{H}_2Ar$), 3.26 (d, $J=13.2$ Hz, 2H, $ArC\mathbf{H}_2Ar$), 2.89–3.01 (m, 5H, $2CHC\mathbf{H}_2$+N**H**), 1.84–1.94 (m, 2H, $2C\mathbf{H}(CH_3)_2$), 1.29 (s, 18H, Bu^t), 0.93 (d, $J=7.2$ Hz, 6H, $CH(C\mathbf{H}_3)_2$), 0.90 (d, $J=7.2$ Hz, 6H, $CH(C\mathbf{H}_3)_2$), 0.89 (s, 18H, Bu^t); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.1, 30.5, 31.2, 31.7, 32.0, 34.3, 51.5, 56.4, 75.1, 125.0, 125.2, 125.9, 126.1, 126.8, 128.3, 131.5, 132.3, 142.9, 148.1, 149.0, 149.7, 168.3; *m*/*z* (%): 917 ($M+1^+$, 20). Anal. calcd for $C_{58}H_{81}N_3O_6$: C, 76.03; H, 8.91; N, 4.59. Found: C, 75.76; H, 9.13; N, 4.31%.
19. Tsukube, H.; Furuta, H.; Odani, A.; Takeda, Y.; Kudo, Y.; Inoue, Y.; Liu, Y.; Sakamoto, H.; Kimura, K. In *Comprehensive Supramolecular Chemistry*; Lehn, J. M.; Davies, J. E. D.; Ripmeester, J. A., Eds. Determination of stability constants. Pergamon: New York, 1996; Vol. 8, p. 426.
20. Gutsche, C. D.; Dhawan, B.; Levine, J. A. *Tetrahedron* **1983**, *39*, 409.
21. Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *97*, 3313.
22. Jaime, C.; De Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372.
23. Benesi, H.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.