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Tetrahedron Letters 46 (2005) 5659–5663

Tetrahedron Letters

Synthesis, structure and anion binding properties of lower rim α-hydroxyamide calix[4]arene derivatives

Sofiane Ben Sdira, Caroline Felix,* Marie-Béatrice Giudicelli, Francis Vocanson, Monique Perrin and Roger Lamartine

LACE, CNRS UMR 5634, Université Claude Bernard-Lyon 1, 43 bd du 11 Novembre 1918, F-69622 Villeurbanne cedex, France

Received 2 May 2005; revised 16 June 2005; accepted 20 June 2005

Abstract—A new family of *p*-*tert*-butylcalix[4]arenes functionalized at the lower rim with α-ketoamide or α-hydroxyamide functions has been prepared. The ^{1}H and ^{13}C NMR spectra indicate that the macrocycles preferably adopt a cone conformation. X-ray crystal study of the α-ketoamide derivative **4a** shows the *flattened cone* conformation in the solid state. Reduction of α-ketoamide **4ab** has produced the α-hydroxyamide derivatives **6ab**. The introduction of chiral moieties on the lower rim position of the calix[4]arene allowed the synthesis of the chiral derivatives **7** and **8**. Host–guest complexation properties towards various anions of the chiral α-hydroxyamide **8** have been examined by ^{1}H NMR spectroscopy. This new receptor has shown promising selectivity for $H_2PO_4^-$ and *N*-tosyl-(L)-alaninate.

Anion recognition continues to be a very attractive and challenging area of research with the possible application of selective ion receptors in biological and environmental systems. Neutral receptors containing units with hydrogen bond donor capability, which can interact with anionic species have become the focus.[1] Calixarenes are cavity-shaped cyclic molecules made up of phenol units linked via methylene groups.[2] As calixarenes have a cavity-shaped architecture, they are useful building blocks for host–guest type receptors through appropriate modifications. The chemical nature of the cavity and its geometry seem essential for calix[4]arene inclusion complex formation.

In this research field, we have already described the synthesis of chiral lower C-rim peptidocalix[4]arene derivatives.[3,4] We have demonstrated their complexation abilities towards various anions. Calix[4]arenes containing thiourea and amide moieties have been used recently as neutral receptors towards carboxylate anions.[5]

In this work, we report the synthesis of a new family of α-hydroxyamide calix[4]arene derivatives. Two different routes were used. We have attempted the conversion of α-ketoamide calix[4]arene derivatives into the corresponding α-hydroxyamide derivatives via a reduction process. With the aim to synthesize chiral receptors, we have prepared a new calix[4]arene via the introduction of (L)-acetyllactic moieties as chiral auxiliaries on the calixarene core.

All new compounds were characterized by FT-IR, ^{1}H, ^{13}C NMR and ES-MS. The binding ability of the receptor **8** has been shown by ^{1}H NMR spectroscopy.

Di and tetramino calix[4]arenes **2** and **3** have been obtained using known procedures.[6–8] The syntheses of all the α-ketoamide derivatives **4** and **5** were accomplished using a condensation reaction between **2** or **3** and the corresponding α-ketoacid chlorides **1abc** in dry CH_2Cl_2, with Et_3N as the catalyst (Scheme 1). Whereas di-*O*-substituted compounds **4** have been obtained in good yields (39–54%), the tetra-*O*-substituted compound **5a** was obtained in a moderate yield (18%) due to sterical bulk effect of the substituents. Their structure was confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR and ESI data.[9,10]

The ^{1}H NMR spectra of compounds **4** and **5** show the presence of hydrogen-bonds between the amide proton and the calixarene. Indeed, a broad singlet shifted upfield (8.32–8.77 ppm) was observed as a resonance

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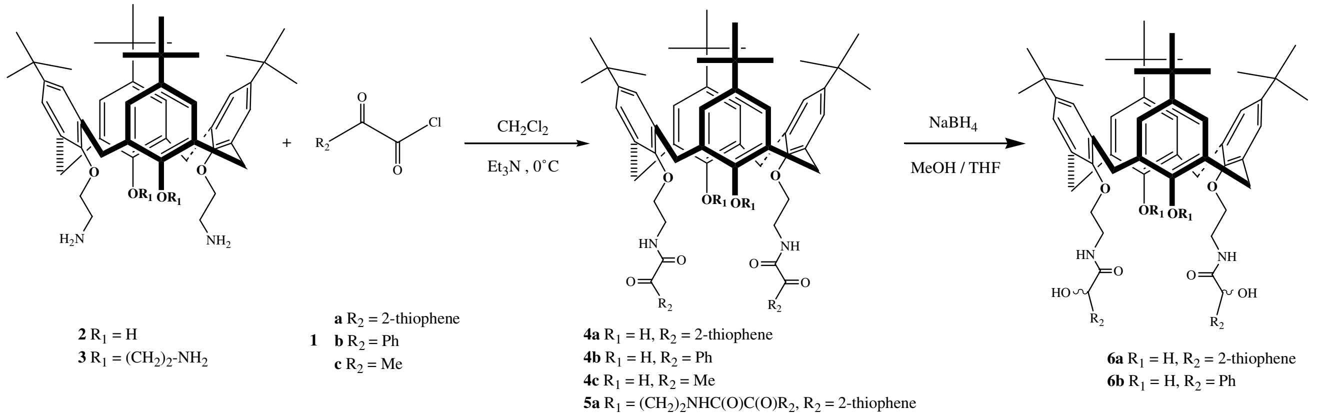
Keywords: Calixarenes; Ketoamide and hydroxyamide moieties; Complexation; Molecular recognition.

* Corresponding author. Tel.: +33 472 44 80 14; fax: +33 472 44 84 38; e-mail: c.felix@cdlyon.univ-lyon1.fr

doi:10.1016/j.tetlet.2005.06.104



Scheme 1. Preparation of α-ketoamide derivatives.

signal of the amide proton. Furthermore, hydroxyl protons of **4a** are shifted upfield too ($\delta = 7.92$ ppm). The hydrogen-bonds generated by amide protons involve the hydroxyl groups of the calixarene, while for the tetrasubstituted derivative hydrogen-bonds are situated between carbonyl groups and amide protons, as already reported.[11] The cone conformation of all compounds **4** and **5** were reflected in the characteristic AB system for the methylene groups bridging the aromatic rings in the ^{1}H and ^{13}C NMR spectra.[12]

Compound **4a** gave crystals (from CH_2Cl_2/EtOH) suitable for X-ray analysis. A summary of the crystallographic data for this compound is listed in Table 1.[13] It confirms that this calix[4]arene adopts a *flattened cone* conformation. This result in the solid state is in accordance with it in the liquid state. The oxygen atoms O256, O276, O254 and O274 of the carbonyl groups (Fig. 1) are in *exo* position, suggesting that the carbonyl groups are anti-periplanar. Concerning hydrogen-bonds, we found three kinds of intramolecular bonds: OH(phenol)···O(ether); O(phenol)···HN(amide) and O(ketone)···HN(amide):

O26–H26···O25 0.82	1.983	2.705 Å	146.44°	
O28–H28···O27 0.82	1.874	2.651 Å	157.73°	
N252–H252···O28	0.923	2.417	3.251 Å	150.27°
N252–H252···O256	0.923	2.158	2.657 Å	112.86°
N272–H272···O26	0.881	2.277	3.145 Å	168.34°
N272–H272···O276	0.881	2.376	2.711 Å	102.77°

The reduction of α-ketoamide derivatives **4ab** was achieved with $NaBH_4$ in a mixture of MeOH and THF (Scheme 1). The resulting α-hydroxyamides **6ab** were obtained in good yields, 55% and 75%, respectively, as a mixture of the two diastereomers.[14]

Compound **6b** gave crystals (from CH_2Cl_2/EtOH) suitable enough for a preliminary X-ray study. However, due to the low quality of the crystals, a well refined structure could not be obtained. The α-hydroxyamide derivative adopts a cone conformation in the solid state in accordance with the results obtained in the liquid state.

Table 1. Selected crystallographic data for compound **4a**

Chemical formula	$C_{62}H_{72}N_2O_6S_2$
Formula weight	1037.34
Temperature/K	193(2)
Crystal system	triclinic
Space group	$P\bar{1}$
a/Å	12.115(2)
b/Å	13.126(3)
c/Å	18.754(4)
α/°	96.08
β/°	107.94(3)
γ/°	91.32
Volume/Å^3	2016.2(10)
Calculated density/Mg m^3	1.223
Z	2
Absorption coefficient/mm^{-1}	0.151
Final $R1$ [$I > 2\sigma(I)$]	0.0805
Final wR_2	0.1869
Absorption correction	none

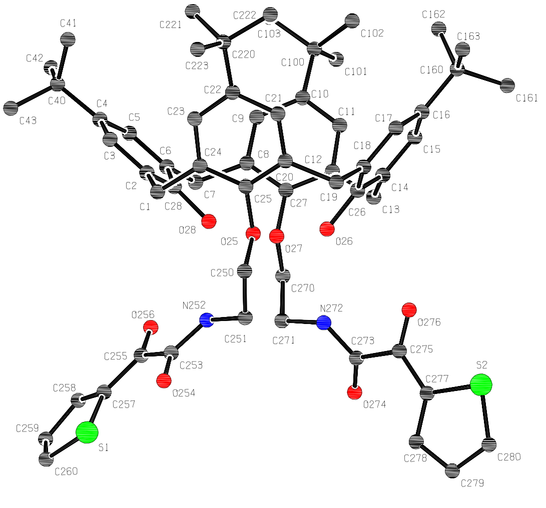


Figure 1. Numbering scheme of compound **4a**.

With the aim to synthesize the pure enantiomer α-hydroxyamide derivative **8**, we have developed a strategy in three steps (Scheme 2), which involves the condensation of the lactic acid chloride with the diamino calix[4]arene **2**, followed by a deprotection step of the hydroxyl groups. The hydroxyl group of the commercially available (L)-lactic acid was protected by acetylation, and the chlorination reaction provided the corresponding chiral acid chloride. The coupling reaction led to the intermediate **7**, which was obtained as a pure enantiomer.[15] The deprotection step has been conducted using the literature procedures.[16,17] This process, which involves metallic sodium and an active resin, gave the pure enantiomer α-hydroxyamide derivative **8** in quantitative yield (92%).[18]

According to ^{1}H NMR in $CDCl_3$, the structure of **7** and **8** derivatives, not only indicates that they possess the cone conformation in the liquid state, but also provides evidence for asymmetric structural features. All of them have two pairs of doublets around 3.40 and 4.20 ppm, which is due to the non-equivalency of the protons of the methylene bridges (Ar–CH_2–Ar). As previously reported in the literature,[3,19] this can be explained by the presence of chiral substituents and indicates a significant degree of structural rigidity. In the ^{1}H NMR spectrum of compound **7**, signals of the aromatic hydroxyl and of the amide proton are shifted upfield, suggesting that hydrogen-bonds involved in the calixarene derivative **7** are more important than in derivative **8**.

Complexation study: The introduction of hydrogen bonding donor and acceptor groups at the lower rim of calixarenes has affected their host–guest properties and has given rise to new possibilities for anions complexation. We report a preliminary study of the complexation properties of various anions such as tetrabutylammonium chloride, bromide, dihydrogen phosphate, hydrogen sulfate and *N*-tosyl-(L)-alaninate. The ^{1}H NMR spectroscopy is a convenient method to determine the binding constant of supramolecular complexes. The recognition properties of the chiral receptor **8** with various anions such as Cl^-, Br^-, HSO_4^-, $H_2PO_4^-$ and *N*-tosyl-(L)-alaninate were monitored by ^{1}H NMR in $CDCl_3$.[20] A large downfield shift of the NH proton of the amide function was observed upon addition of *n*-tetrabutylammonium salts of anions to host derivative. The complexation of anions leads to a more rigid molecular structure as suggested by the enhancement of the broadness of the signals. ^{1}H NMR titration curve of the complexation of anions to the receptor **8** is depicted in Figure 2.

In all cases the stoichiometry is 1:1 as was confirmed by Job plots. The association constants of the anion receptor were determined by the Benesi–Hildebrand method[21] and are summarized in Table 2.

Since it is known that Cl^- and Br^- anions are good hydrogen bond acceptors[22] and the hydrogen bond donor site of the amide group acts as a hard Lewis acid,[23] it was expected that the addition of the hard Lewis bases Cl^- and Br^- would lead to complexation. But, in a recent report,[3] we have demonstrated that the binding properties of C-linked *N*-tosyl peptidocalix[4]arenes towards Cl^- were dependent on the length of the spacer, which links the calixarene to the amide group. We found that, in accordance to the spacer length, no complexation has been observed for halide anions with the α-hydroxylamide ligand **8**.

The α-hydroxylamide derivative **8** shows a relatively strong association with $H_2PO_4^-$ ($K_{ass} = 5413\ M^{-1}$) and no complexation with HSO_4^-. While both anions $H_2PO_4^-$ and HSO_4^- are tetrahedral and their size is quite similar, the selectivity of the ligand cavity (which is large enough to bind $H_2PO_4^-$) seems to be more complex. It has been demonstrated that there is a marked difference

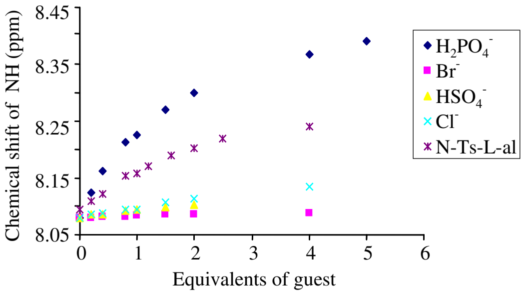
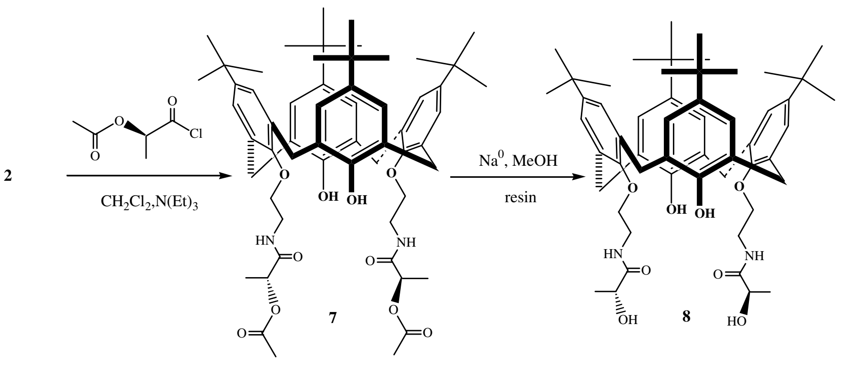


Figure 2. Titration curve of calix[4]arene **8** with Bu_4NCl, Bu_4NBr, Bu_4NHSO_4, $Bu_4NH_2PO_4$ and Bu_4N–*N*-Ts-L-alaninate in $CDCl_3$. Concentration host is 10^{-2} M.

Table 2. K_{ass} Values (M^{-1}) of **8**

Compd	Cl^-	Br^-	HSO_4^-	$H_2PO_4^-$	*N*-Tosyl-(L)-alaninate
8	—	—	—	5413	1590



Scheme 2. Preparation of chiral α-hydroxyamide derivative **8**.

in the stereochemistry of bonding of hydrogen to sulfate and to phosphate, and it may be possible that a stereochemically defined hydrogen bonding network would be able to differentiate between sulfate and phosphate at biomolecular receptor sites.[24]

The *N*-tosyl-(L)-alaninate guest is weakly complexed by the ligand **8**. The complexation may take place from H-bonding provided both by the amide and/or hydroxyl protons. According to recent studies carried out in our group,[3,4] recognition of such carboxylates anions could be enhanced using a longer spacer and increasing hydrophobicity of the ligand.

In conclusion, new α-ketoamide calix[4]arene derivatives have been prepared using the condensation reaction of α-ketoacid chloride with amino calix[4]arene derivatives. These derivatives adopt a *flattened cone* conformation. The corresponding α-hydroxyamide derivatives have been obtained by a reduction reaction. The introduction of a chiral auxiliary on the calix[4]arene core allowed the synthesis of the chiral receptor **8**. Host–guest complexation properties towards various anions of this ligand have been studied by ^{1}H NMR spectroscopy. This new receptor binds $H_2PO_4^-$ and *N*-tosyl-(L)-alaninate in a 1:1 stoichiometry and shows promising ability for a good selectivity and for chiral discrimination.

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9. Selected data for compounds **4abc**:
   Compound **4a**. Yield = 54%; R_f = 0.23 (AcOEt/hexane 1/4); mp = 230–232 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 0.98 (s, 18H), 1.18 (s, 18H), 3.29 (AB, 4H, J_{AB} = 13.0 Hz), 3.96–4.00 (m, 4H), 4.13–4.17 (m, 4H), 4.18 (AB, 4H, J_{AB} = 13.0 Hz), 6.85 (s, 4H), 6.95 (s, 4H), 7.03–7.06 (dd, 2H, *J* = 4.89 Hz), 7.66 (d, 2H, *J* = 6.2 Hz), 7.92 (s, 2H), 8.23 (d, 2H, *J* = 5.1 Hz), 8.77 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 31.46, 32.05, 32.51, 34.23, 34.57, 40.09, 74.81, 125.74, 126.30, 127.78, 128.42, 133.27, 137.50, 138.11, 138.35, 142.28, 143.46, 148.09, 149.32, 162.20, 178.75. IR: 1638 (CONH), 1683 (CO(O)), 3354 (NH). ES-MS(+): *m*/*z* = 1033.30 $[M+Na]^+$ (calcd 1033.45), 1011.30 $[M+H]^+$ (calcd 1011.47).
   Compound **4b**. Yield = 47%; R_f = 0.26 (AcOEt/petroleum ether 1/4); mp = 173–176 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.09 (s, 18H), 1.25 (s, 18H), 3.36 (AB, 4H, J_{AB} = 13.2 Hz), 4.08–4.10 (m, 4H), 4.19–4.24 (m, 8H), 6.96 (s, 4H), 7.00 (s, 4H), 7.40 (t, 4H, *J* = 7.5 Hz), 7.58 (t, 2H, *J* = 7.7 Hz), 8.16–8.21 (m, 6H), 8.86 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 30.11, 31.47, 32.02, 34.22, 34.54, 39.75, 75.11, 125.79, 126.37, 127.68, 128.79, 131.14, 133.72, 134.38, 142.55, 148.25, 149.10, 150.26, 164.07, 189.10. IR: 1675 (COPh), 1723 (CONH). ES-MS(+): *m*/*z* = 1021.5 $[M+Na]^+$ (calcd 1021.27), 999.6 $[M+H]^+$ (calcd 999.29).
   Compound **4c**. Yield = 39%; R_f = 0.76 (AcOEt/petroleum ether 1/1); mp = 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.06 (s, 18H), 1.28 (s, 18H), 2.50 (s, 6H), 3.38 (AB, 4H, J_{AB} = 13.0 Hz), 3.97–4.08 (m, 4H), 4.16–4.25 (m+d, 8H), 4.94 (s, 4H), 7.06 (s, 4H), 7.87 (s, 2H), 8.54 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 25.21, 31.46, 32.05, 32.38, 34.24, 34.51, 38.88, 74.62, 125.76, 126.28, 127.60, 133.18, 142.38, 148.13, 149.15, 150.64, 161.59, 197.11. IR: 1677 ($COCH_3$), 1736 (CONH), 3335 (NH). ES-MS(+): *m*/*z* = 897.4 $[M+Na]^+$ (calcd 897.5), 875.45 $[M+H]^+$ (calcd 875.52).
10. Compound **5a**. Yield = 18%; R_f = 0.49 (AcOEt/hexane 3/7); mp = 133–135 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.09 (s, 36H), 3.22 (AB, 4H, J_{AB} = 12.8 Hz), 4.01–4.05 (m, 8H), 4.17–4.22 (m, 8H), 4.35 (AB, 4H, J_{AB} = 12.6 Hz), 6.80 (s, 8H), 7.07 (t, 4H, *J* = 4.7 Hz), 7.70 (d, 4H, *J* = 6.0 Hz), 8.28 (d, 4H, *J* = 5.1 Hz), 8.32 (br s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 31.26, 31.78, 34.28, 40.34, 73.16, 120.33, 125.76, 128.42, 138.31, 138.67, 132.24, 133.71, 136.12, 137.28, 145.69, 153.22, 162.00, 178.70. IR: 1638 (CO-thiophene), 1683 (CONH), 3354 (NH). ES-MS(+): *m*/*z* = 1395.4 $[M+Na]^+$ (calcd 1395.49).
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13. Single crystals of **4a** were obtained from a saturated mixture of CH_2Cl_2 and ethanol solution. Data were collected at 293 K on a Nonius Kappa CCD with Mo-Kα radiation (λ = 0.71073 Å). Final unit cell parameters were by means of a least-squares refinement. The structure has been solved by direct methods using SHELXS 97 (SHELX97 includes SHELXS97, SHELXL97)—*Programs for Crystal Structure Analysis* (release 97-2) : G. M. Sheldrick, Institüt für Anorganische Chemie der Universität, Göttingen, Germany, 1998. CCDC number 239 881.
14. Selected data for the α-hydroxyamides **6ab**:
    Compound **6a** (obtained as a mixture of the two diastereomers). Yield = 55%; R_f = 0.53 (AcOEt/hexane 7/3); mp = 188–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 0.95 (s, 36H), 1.20 (s, 36H), 3.16 (d, 2H, AB, J_{AB} = 13.4 Hz), 3.27 (d, 2H, AB, J_{AB} = 13.4 Hz), 3.31 (d, 4H, AB, J_{AB} = 13.4 Hz), 3.27–3.38 (m, 2H), 3.33 (d, 2H, AB, J_{AB} = 13.4 Hz), 3.51–3.64 (m, 2H), 3.68–3.84 (m, 6H), 3.89 (d, 2H, AB, J_{AB} = 13.4 Hz), 3.98 (d, 2H, AB, J_{AB} = 13.4 Hz), 4.07 (d, 2H, AB, J_{AB} = 13.4 Hz), 4.08–4.19 (m, 6H), 4.13 (d, 2H, AB, J_{AB} = 13.4), 4.52 (d, 2H, *J* = 4.5 Hz), 4.80 (d, 2H, *J* = 4.5 Hz), 5.27 (d, 2H, *J* = 4.5 Hz), 5.29 (d, 2H, *J* = 4.5 Hz), 6.72 (d, 2H, *J* = 4.5 Hz), 6.73 (d, 2H, *J* = 4.5 Hz), 6.78–6.81 (m, 2H), 6.82–6.84 (m, 2H), 6.89–7.0 (m, 16H), 7.13 (d, 2H, *J* = 5.0 Hz), 7.18 (d, 2H, *J* = 5.0 Hz), 7.85 (s, 2H), 7.90 (s, 2H), 8.25 (t, 2H, *J* = 6.0 Hz), 8.31 (t, 2H, *J* = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 31.41, 32.00, 34.33, 34.37, 39.51, 39.81,

70.59, 70.87, 74.91, 75.28, 126.02, 126.11, 126.27, 126.47, 126.70, 127.05, 127.10, 128.03, 128.47, 128.55, 132.78, 133.00, 133.09, 133.15, 142.60, 143.49, 143.77, 143.85, 148.46, 148.51, 148.78, 148.83, 149.16, 149.43, 172.43, 172.58. IR: 1656 (CONH), 3336 (NH and OH). ES-MS(+): *m*/*z* = 1037.30 $[M+Na]^+$ (calcd 1037.48), 1015.30 $[M+H]^+$ (calcd 1015.5).

Compound **6b** (obtained as a mixture of the two diastereomers). Yield = 75%; $R_f = 0.39$ (AcOEt/hexane 7/3); mp = 123–126 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 1.09 (s, 36H), 1.30 (s, 36H), 3.18 (d, 2H, AB, J_{AB} = 13.2 Hz), 3.35 (d, 2H, AB, J_{AB} = 13.2 Hz), 3.42 (d, 2H, AB, J_{AB} = 13.2 Hz), 3.45 (d, 2H, AB, J_{AB} = 13.2 Hz), 3.47–3.54 (m, 4H), 3.62–4.17 (m, 12H), 3.89 (d, 2H, AB, J_{AB} = 13.2 Hz), 4.05 (d, 2H, AB, J_{AB} = 13.2 Hz), 4.18 (d, 2H, AB, J_{AB} = 13.2 Hz), 4.22 (d, 2H, AB, J_{AB} = 13.2 Hz), 5.04 (s, 2H), 5.05 (s, 2H), 6.90–7.65 (m, 36H), 8.11 (s, 2H), 8.14 (s, 2H), 8.23 (s, 1H), 8.25 (s, 2H), 8.31 (s, 1H), 8.34 (t, 2H, *J* = 6.0 Hz), 8.38–8.44 (m, 2H). RMN ^{13}C (75 MHz, $CDCl_3$, ppm):31.46, 31.99, 32.22, 32.38, 32.60, 32.72, 34.34, 34.37, 34.58, 39.36, 39.74, 74.53, 74.59, 75.41, 75.66, 126.06, 126.10, 126.17, 126.28, 126.46, 126.48, 126.51, 126.90, 127.42, 127.48, 127.80, 127.90, 128.41, 128.50, 128.72, 129.12, 132.94, 133.19, 133.31, 133.40, 139.88, 143.58, 143.80, 143.88, 148.61, 148.67, 148.70, 148.76, 149.04, 149.13, 149.46, 173.31, 173.45. IR: 1662 (CONH), 3319 (NH and OH). ES-MS(+): *m*/*z* = 1025.4 $[M+Na]^+$ (calcd 1025.57), 1003.4 $[M+H]^+$ (calcd 1003.59).

15. Compound **7**. Yield = 50%; $R_f = 0.29$ (AcOEt/hexane 1/1); mp = 213–215 °C. $[\alpha]_D^{20}$ +33.3 (*c* 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.25 (s, 18H), 1.47 (s, 18H), 1.52 (d, 6H, *J* = 6.8 Hz), 1.86 (s, 6H), 3.36–3.47 (dd, 2H, *J* = 12.2 Hz, *J* = 13.2 Hz, 2H), 3.86–4.29 (m+d, 12H), 5.28 (q, 2H, *J* = 6.8 Hz), 7.03–7.05 (dd, 8H, *J* = 7.3 Hz), 8.35 (s large, 2H), 8.59 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 18.46, 20.89, 31.53, 31.93, 32.52, 32.82, 34.29, 34.63, 39.73, 70.86, 74.21, 126.07, 126.46, 128.26, 133.6, 143.53, 148.5, 149.72, 170.50, 171.35. IR: 1664 (CONH), 1736 (CO(O)), 3262 (NH). ES-MS(+): *m*/*z* = 985.5 $[M+Na]^+$ (calcd 985.56), 1007.6 $[M+2Na-H]^+$ (calcd 1007.54), 963.5 $[M+H]^+$ (calcd 963.58).
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18. **8**. Yield = 92%; $R_f = 0.12$ (AcOEt/hexane 4/1); mp = 225–227 °C. $[\alpha]_D^{20}$ −92.7 (*c* 0.52, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 0.93 (s, 18H), 1.32 (s, 18H), 1.46 (d, 6H, *J* = 6.6 Hz), 3.35–3.40 (dd, 4H, AB, J_{AB} = 13.2 Hz), 3.84–3.97 (m, 6H), 4.13–4.23 (dd, 4H, AB, J_{AB} = 13.5 Hz, J_{AB} = 13.2 Hz), 4.29–4.33 (m, 4H), 4.42 (d, 2H, *J* = 4.9 Hz), 6.78 (s, 4H), 7.11 (d, 4H, *J* = 1.1 Hz), 7.29 (s, 2H), 8.11 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 20.97, 31.32, 31.70, 32.05, 34.34, 39.36, 69.64, 74.21, 125.87, 126.21, 128.41, 132.49, 143.49, 148.03, 149.02, 149.48, 176.28. IR: 1651 (CONH), 3371 (NH). ES-MS(+): *m*/*z* = 901.5 $[M+Na]^+$ (calcd 901.53), 923.5 $[M+2Na-H]^+$ (calcd 923.51), 879.5 $[M+H]^+$ (calcd 879.55).
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20. ^{1}H NMR titrations: A 10 mM solution of the host in $CDCl_3$ was prepared. To 0.5 mL of this solution 0–5 equiv of tetrabutylammonium salts were added in the ^{1}H NMR tube and the spectra were recorded. The chemical shifts of the NH proton were followed and plotted against the equivalents of guest added.

    Job plot: Stick solution for the host (10 mM) and for the tetrabutylammonium salts (10 mM) in $CDCl_3$ were prepared. The ^{1}H NMR tubes were filled with 500 μL solutions of the host and guest in the following volume ratios: 50:450, 100:400, 150:350, 200:300, 250:250, 300:200, 400:100, 450:50.
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