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Efficient synthesis of lower rim α-hydrazino tetrazolocalix[4]arenes *via* an Ugi-azide multicomponent reaction†

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In this study, we developed an efficient synthesis of α-hydrazino tetrazolocalix[4]arene derivatives in good yields under mild conditions *via* an Ugi-azide multicomponent reaction. Metal ion binding properties of one of the α-hydrazino tetrazolocalix[4]arenes (**7a**) as the model compound were also investigated, revealing that compound **7a** exhibits the highest binding affinity towards Ni(II).

Introduction

Calixarenes, produced by the condensation of *p*-substituted phenols with aldehydes, have been applied in diverse areas.[1] Calixarenes are versatile macromolecules, which can be used for the synthesis of multivalent/multifunctional ligands.[2] The easy accessibility and functionalization at their wide and narrow rims have made them ideal candidates for studying noncovalent interactions involved in many biological processes.[3] Calixarenes can also be used as metal-selective ionophores by virtue of coordinating functional groups at their wide rims.

The presence of nitrogen-rich functional groups such as tetrazole derivatives on the calixarene skeleton has drawn more and more attention in the fields of molecular recognition and host–guest chemistry.

Tetrazoles represent an important class of nitrogen heterocyclic compounds, and their derivatives possess a broad range of biological activities in both medicinal and pharmaceutical fields.[4] Besides their well-known applications in medicinal chemistry, pharmacology, materials chemistry, and organocatalysis, they are also of interest as ligands in coordination chemistry due to the presence of four nitrogen atoms in the tetrazole ring.[5] The ability of two phenolic OH groups to provide more coordination sites and maintain the cone conformation led to the increasing importance of lower rim 1,3-disubstitutedcalix[4]arenes.[6] An interesting example in this respect is the synthesis of tetrazoles and para-substituted phenylazo-coupled calix[4]arenes as highly sensitive chromogenic sensors for Ca^{2+} using the 1,3-dipolar cycloaddition of oxyacetonitrile azocalix[4]arenes activated with trimethylsilyl azide.[7] Another fascinating example is the synthesis of the lower rim 1,3-tetrazole-functionalised calix[4]arene by the reaction of 5,11,17,23-tetra-*tert*-butyl-25,27-dicyanomethoxy-26,28-dihydroxycalix[4]arene with sodium azide and triethylammonium chloride, which acts as an ionophore for lanthaneid cations, forming luminescent complexes.[5b]

As part of our interest in the synthesis of functionalized calixarenes, we reported the synthesis of a number of functionalized calixarenes using multi-component reactions.[8] Multi-component reactions (MCRs) are compelling strategies for the rapid generation of diverse sets of complex molecules.[9] Among MCRs, isocyanide-based multicomponent reactions (IMCRs) by virtue of their synthetic potential, inherent atom efficiency, convergent nature, ease of implementation, and generation of molecular diversity have attracted considerable attention of organic chemists, medicinal chemists and pharmacologists worldwide.[10] Despite their undeniable advantages in the field of combinatorial chemistry, the synthetic utility of IMCRs toward the synthesis of functionalized calixarenes is rather under-represented.[11]

In this study, we propose a versatile synthesis of the lower rim α-hydrazinotetrazolocalix[4]arenes based on the Ugi-azide multicomponent reaction. The presence of numerous nitrogen atoms makes a bidentate bonding mode likely for metal ion complexation.

Results and discussion

The basic precursor of our investigation, calixarene dihydrazide **3**, was prepared in good yield using the previously reported synthetic procedure (Scheme 1).[12]

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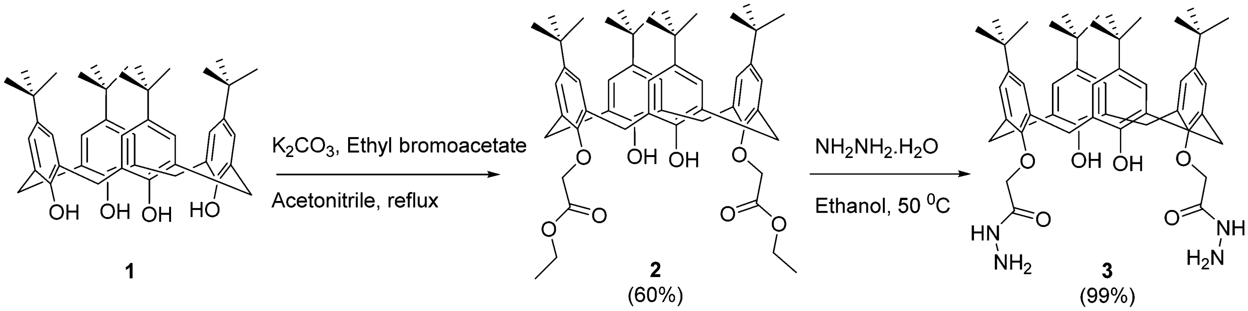


Scheme 1 Synthesis of calixarene dihydrazide **3**.

At the outset of this study, our efforts were focused on finding appropriate reaction conditions to perform the proposed reaction. We commenced our study of the Ugi-azide reaction using calixarene dihydrazide **3**, cyclohexanone, cyclohexyl isocyanide, and trimethylsilyl azide. The results are summarized in Table 1. The use of ethanol, acetonitrile, tetrahydrofuran, and dichloromethane in place of methanol as the reaction solvent decreased the yield of the desired product (entries 2–5).

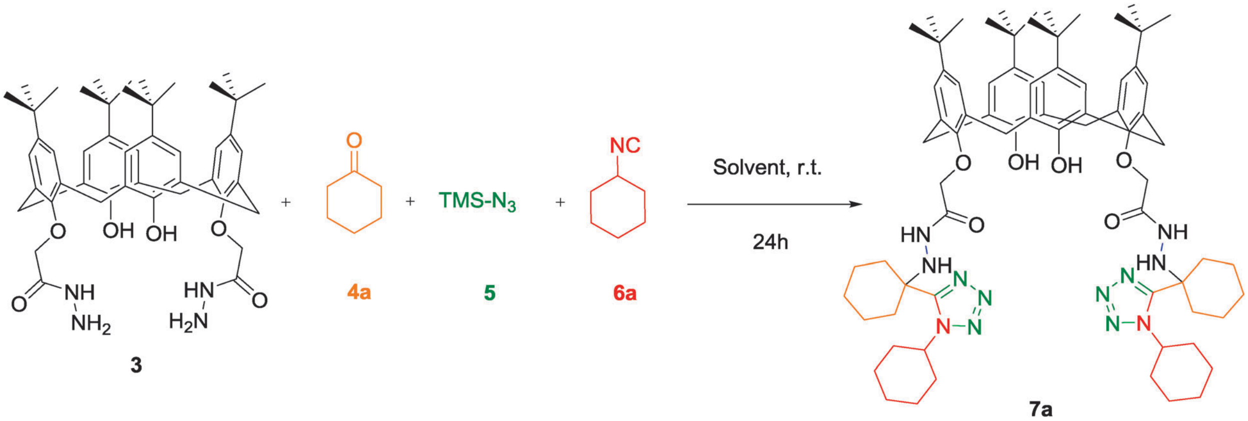
Furthermore, when TMS-N$_3$ in the reaction was replaced by NaN$_3$, we could isolate only 30% of **7a**. To further demonstrate the efficiency of the Ugi-azide reaction based on calixarene dihydrazide **3**, the scope of the reaction with various ketones and isocyanides was explored and the results obtained are summarized in Table 2.

The products have been characterized using spectroscopic techniques, and the IR, ^{1}H NMR, ^{13}C NMR, and UHPLC–TOFMS spectroscopic data confirm the proposed structures. All the synthesized compounds exist in the cone conformation as the signals of all bridging methylene carbons appear at about 31 ppm in their ^{13}C NMR spectra.[13]

Due to the presence of two chiral centers in compounds **7g–7j**, diastereomeric products are possible. The structure of one of the compounds, **7g**, has also been established by single crystal X-ray diffraction analysis (Fig. 1). The crystal structure of compound **7g** shows the presence of both the diastereomers in a 60 : 40 ratio. In 60% of the molecules in this specific crystal, the configuration of the asymmetric carbon atom C85 is the same as for the asymmetric carbon C55. In 40% of the molecules it is the opposite one, which means that there are indeed different stereoisomers.

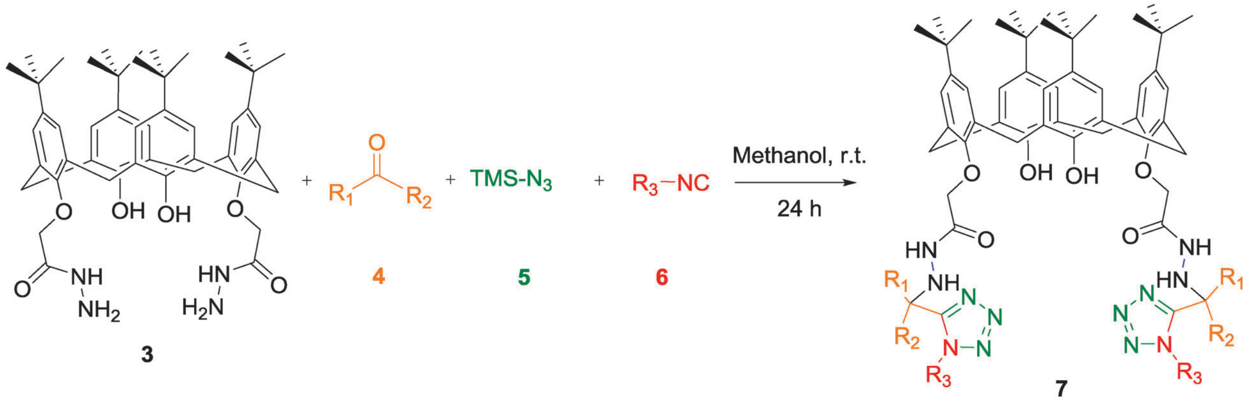
The strength of this process lies in the simple one-step synthesis of bidentate nitrogen rich calixarene ligands through an Ugi-azide multicomponent reaction with easy workup and purification procedures. To gain some insights into the intramolecular hydrogen bonding occurring in these compounds, the ^{1}H NMR spectra of **7a** as the model compound in CDCl$_3$ and DMSO-d_6 were obtained. Significant downfield shifts of the CH proton directly attached to the nitrogen of the tetrazole ($\sim$0.5 ppm) and OH protons ($\sim$1.65 ppm) indicate that both the tetrazole and OH groups participate in significant hydrogen-bonding interactions in a nonpolar solvent (Fig. 2).

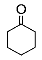
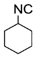
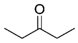
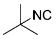
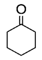
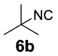
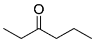
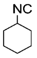
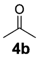
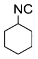
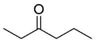
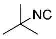
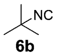
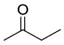
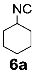
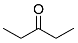
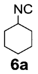
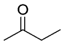
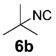
Table 1 Optimization of the reaction conditions



Entry	Solvents	Yield of **7a** (%)
1	Methanol	80
2	Ethanol	72
3	Acetonitrile	54
4	Tetrahydrofuran	40
5	Dichloromethane	30

Table 2 Scope of the Ugi-azide reaction of calixarene dihydrazide **3**



Entry	Ketones	Isocyanides	Yield of 7 (%)	Entry	Ketones	Isocyanides	Yield of 7 (%)
1	 **4a**	 **6a**	**7a**, 80	6	 **4c**	 **6b**	**7f**, 65
2	 **4a**	 **6b**	**7b**, 72	7	 **4d**	 **6a**	**7g**, 76
3	 **4b**	 **6a**	**7c**, 68	8	 **4d**	 **6b**	**7h**, 67
4	 **4b**	 **6b**	**7d**, 58	9	 **4e**	 **6a**	**7i**, 70
5	 **4c**	 **6a**	**7e**, 73	10	 **4e**	 **6b**	**7j**, 61

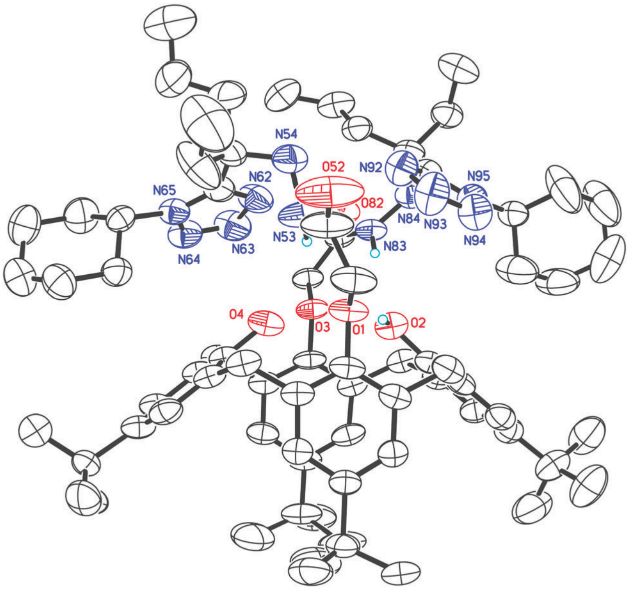


Fig. 1 ORTEP view of the major diastereomer of compound **7g**.

The metal-binding sites on the synthesized compounds are the nitrogen and oxygen atoms. Therefore, we further investigated the metal cation binding properties of the newly synthesized receptor **7a** as the model compound by fluorescence titration with cations as metal perchlorates (Li^+, Na^+, K^+, Ba^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and Hg^{2+}), and the desired compound demonstrated the highest binding affinity toward Ni(II) to form a Ni(II)-**7a** complex, resulting in prominent fluorescence quenching, as shown in Fig. 3 and 4.

The fluorescence spectrum of **7a** (λ_{ex} = 280 nm, molar extinction coefficient ε = 9340.66 M^{-1} cm^{-1}) in CH_3CN exhibited two characteristic emission bands at 309 nm and 612 nm. The strong band at 390 nm is a characteristic of the aromatic core of the calixarene.[14]

As shown, the fluorescence of compound **7a** was almost completely quenched by $Ni(ClO_4)_2$. The binding constant of compound **7a** with Ni^{2+} was calculated by non-linear least squares curve fitting (SigmaPlot Version 10.0), and the corresponding association constant K_a was found to be 1.70×10^7 M^{-1} (Table 3).[15]

Job plot analysis and ESI-MS spectra show that **7a** and Ni(II) form a 1 : 1 Ni(II)-**7a** complex (Fig. 5). Peaks in the ^1H NMR spectra of compound **7a** with Ni^{2+} (1 : 1) decreased in signal intensities, culminating in a substantial broadening and subsequent disappearance of the resonances ascribable to the compound **7a**. These results provide evidence that **7a** and Ni(II) form a 1 : 1 Ni(II)-**7a** complex.

To test the highest binding affinity of compound **7a** with Ni^{2+}, competition experiments were carried out in the presence of Ni^{2+} at 1 equiv. mixed with Li^+, Na^+, K^+, Ba^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and Hg^{2+} at 1 equiv. and no significant variation was found by comparison with and without the other

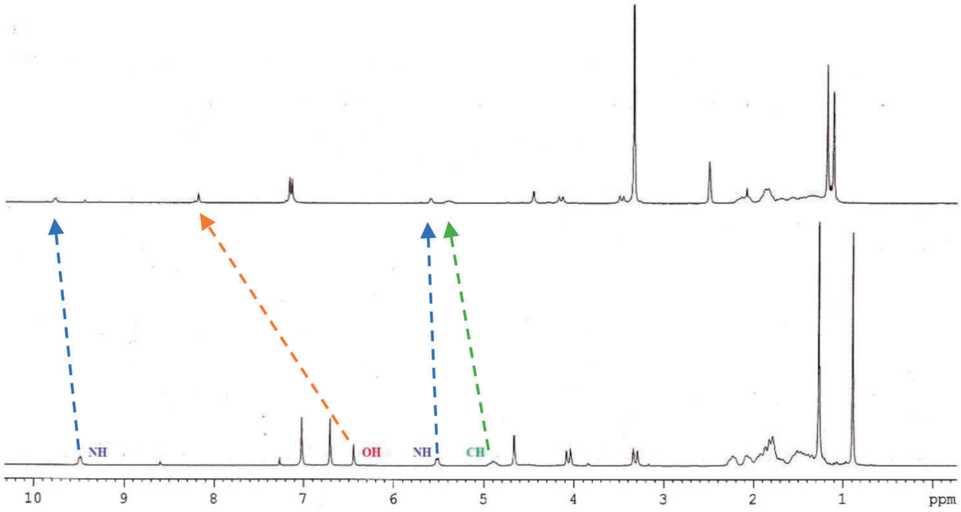


Fig. 2 Comparison of ^1H NMR spectra of compound **7a** in DMSO-d_6 (above) and $CDCl_3$ (below).

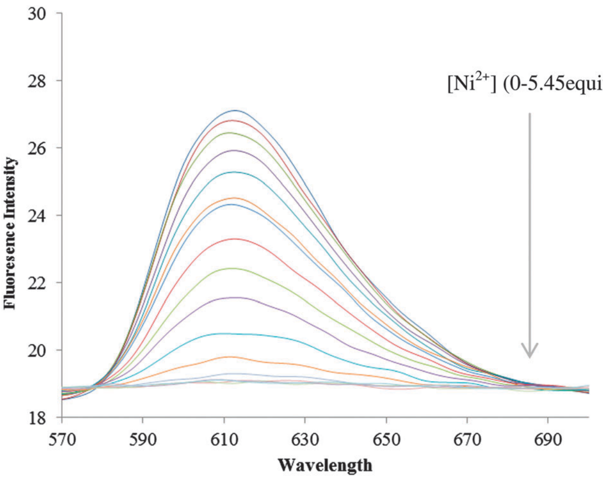
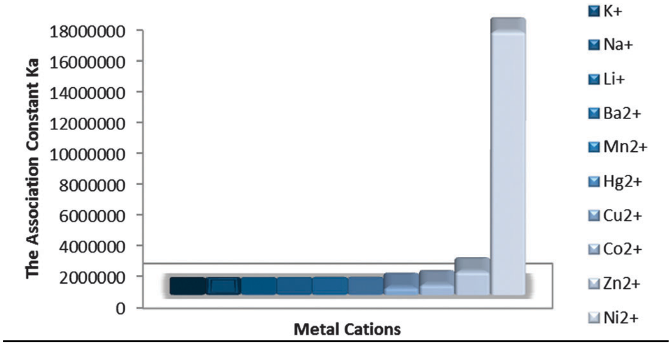


Fig. 3 Fluorescence spectra of **7a** in response to the presence of Ni^{2+} ions (0 to 5.45 equiv.) in MeCN; λ_{ex} = 280 nm.

Table 3 The association constants of **7a** with metal cations (1 : 1 binding model) in CH_3CN



Cation	K_a (M^{-1})	Cation	K_a (M^{-1})
K^+	1560	Hg^{2+}	15 100
Na^+	1640	Cu^{2+}	422 000
Li^+	2480	Co^{2+}	599 000
Ba^{2+}	4290	Zn^{2+}	1 430 000
Mn^{2+}	7767	Ni^{2+}	17 000 000

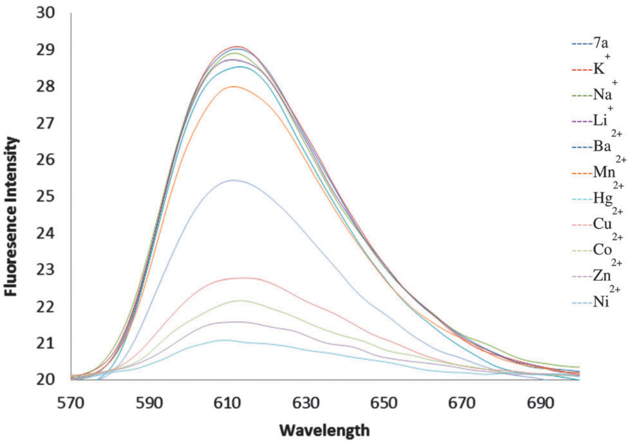


Fig. 4 Fluorescence intensity changes of compound **7a** in MeCN upon addition of 1 equiv. of various metal perchlorates; λ_{ex} = 280 nm.

metal ions besides Ni^{2+}. This means that compound **7a** has the highest binding affinity for Ni^{2+} ions.

In contrast to many fluorescent sensors used for the detection of heavy and transition metal ions like Hg^{2+}, Ag^+, Cd^{2+}, Pb^{2+}, and Cr^{3+}, reports concerning fluorescent sensors for Ni^{2+} detection are scarce.[16] Fluorescent sensors for Ni^{2+} detection are often based on small molecules and encounter serious interference problems from other heavy and transition metal ions.[17] This study opens up new opportunities for the design of an efficient, fast and inexpensive synthesis of fluorescent sensor libraries based on the calixarene unit.

Conclusion

In summary, an operationally simple Ugi-azide multicomponent reaction protocol was developed for the preparation of

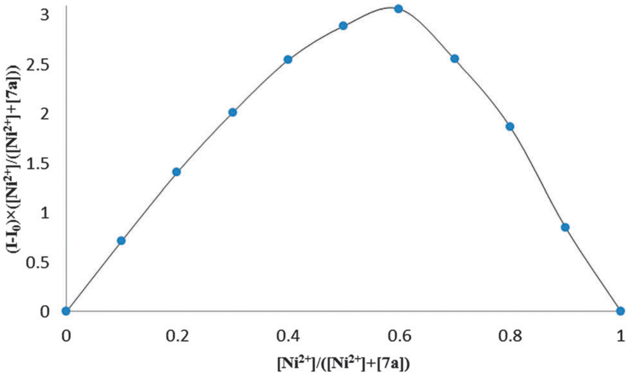


Fig. 5 The Job plot for the complexation of **7a** with Ni^{2+} in CH_3CN.

lower rim α-hydrazino tetrazolocalix[4]arene derivatives in good yields under mild conditions. The scope of this reaction was expanded to include various ketones and isocyanides. A detailed investigation of the metal ion binding properties of the model compound **7a** is performed mainly by the fluorometric titration approach, revealing that compound **7a** exhibits the highest binding toward Ni(II). Future efforts in our laboratories are aimed to develop new and efficient multicomponent reaction protocols for the rapid synthesis of large libraries of functionalized calixarene derivatives and will be reported in due course.

Experimental section

All solvents and reagents were commercially sourced. NMR spectra were obtained on a Bruker DRX-300 AVANCE 300 MHz spectrometer. All chemical shifts are reported in the standard δ notation of parts per million. UHPLC-TOF mass spectra using electrospray ionisation were acquired with an Agilent 1290 Infinity UHPLC and an Agilent 6550 iFunnel Q-TOF. Fluorescence emission spectra were obtained on an A JASCO FP-6500 spectrofluorometer. UV/Vis spectra were measured on a PerkinElmer LAMBDA 35 UV/Vis spectrophotometer.

General procedure for the synthesis of lower rim α-hydrazino tetrazolocalix[4]arenes

A solution of calixarene dihydrazide 3 (0.2 mmol) and ketone 4 (0.5 mmol) in 2 mL MeOH was stirred for 2 h and trimethylsilyl azide 3 (0.5 mmol) and isocyanide 4 (0.5 mmol) were then added. The mixture was stirred for 24 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 1 : 3), the solvent was removed under vacuum, and the residue was precipitated by addition of 3 mL of EtOH and 1 mL of H_2O. The precipitate was filtered off and then recrystallized from ethanol.

7a. Yield: 80%, mp: 223–225 °C; IR (KBr, ν, cm^{-1}): 3056, 2953, 2863, 1673, 1549, 1482, 1425, 1266, 1194, 1104, 1036, 896, 749; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, *t*-Bu, 18H); 1.27 (s, *t*-Bu, 18H); 1.44 (m, CH_2, 12H); 1.81 (m, CH_2, 20H); 2.06 (m, CH_2, 4H); 2.24 (m, CH_2, 4H); 3.32 (d, *J* = 13.4 Hz, $ArCH_2Ar$, 4H); 4.06 (d, *J* = 13.4 Hz, $ArCH_2Ar$, 4H); 4.66 (s, OCH_2, 4H); 4.90 (m, CH, 2H); 5.52 (d, *J* = 5.7 Hz, NH, 2H); 6.45 (s, OH, 2H); 6.71 (s, ArH, 4H); 7.02 (s, ArH, 4H); 9.49 (d, *J* = 5.5 Hz, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 21.9, 24.8, 24.9, 25.3, 25.5, 30.8, 31.6, 31.8, 33.0, 33.2, 33.4, 33.6, 33.8, 33.9, 57.9, 58.7, 59.4, 74.5, 125.3, 125.9, 127.3, 131.9, 142.9, 147.9, 149.2, 149.6, 155.7, 167.5; UHPLC–TOFMS (ESI) *m*/*z*: calcd for $C_{74}H_{105}N_{12}O_6$: 1257.8275 $[M + H]^+$; found 1257.8297, calcd for $C_{74}H_{104}N_{12}NaO_6$: 1279.8094 $[M + Na]^+$; found 1279.8117.

7b. Yield: 72%, mp: 161–163 °C; IR (KBr, ν, cm^{-1}): 3320, 3056, 2963, 2864, 1685, 1544, 1481, 1427, 1266, 1196, 1120, 1039, 898, 743; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, *t*-Bu, 18H); 1.27 (s, *t*-Bu, 18H); 1.37–1.41 (m, CH_2, 2H); 1.58 (m, CH_2, 6H); 1.63 (s, *t*-Bu, 18H); 1.94–1.98 (m, CH_2, 4H); 2.12–2.16 (m, CH_2, 4H); 2.34–2.37 (m, CH_2, 4H); 3.30 (d, *J* = 13.4 Hz, $ArCH_2Ar$, 4H); 4.11 (d, *J* = 13.4 Hz, $ArCH_2Ar$, 4H); 4.71 (s, OCH_2, 4H); 5.55 (d, *J* = 5.9 Hz, NH, 2H); 6.35 (s, OH, 2H); 6.68 (s, ArH, 4H); 7.00 (s, ArH, 4H); 9.27 (d, *J* = 5.7 Hz, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 25.3, 30.8, 30.9, 31.6, 33.8, 33.7, 34.7, 60.4, 63.5, 74.6, 76.6, 125.2, 125.8, 127.2, 131.9, 142.6, 147.7, 149.4, 149.5, 158.1, 167.7; UHPLC–TOFMS (ESI) *m*/*z*: calcd for $C_{70}H_{100}N_{12}NaO_6$: 1227.7781 $[M + Na]^+$; found 1227.7803.

7c. Yield: 68%, mp: 228–230 °C; IR (KBr, ν, cm^{-1}): 3394, 3305, 3056, 2961, 2863, 1690, 1549, 1485, 1426, 1359, 1267, 1190, 1102, 1039, 894, 743; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, *t*-Bu, 18H); 1.24–1.27 (m, CH_2, 4H); 1.27 (s, *t*-Bu, 18H), 1.68–1.71 (bs, CH_3, CH_2, 14H); 1.78 (m, CH_2, 14H); 3.31 (d, *J* = 13.3 Hz, $ArCH_2Ar$, 4H); 4.11 (d, *J* = 13.3 Hz, $ArCH_2Ar$, 4H); 4.72 (s, OCH_2, 4H); 4.72–4.78 (m, CH, 2H); 5.45 (d, *J* = 5.1 Hz, NH, 2H); 6.40 (s, OH, 2H); 6.69 (s, ArH, 4H); 7.02 (s, ArH, 4H); 9.50 (d, *J* = 4.9 Hz, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 24.8, 25.4, 30.8, 31.5, 31.6, 33.0, 33.8, 33.9, 56.4, 59.2, 74.4, 76.6, 125.2, 125.8, 127.3, 131.9, 142.7, 147.8, 149.4, 149.5, 157.0, 168.3; UHPLC–TOFMS (ESI) *m*/*z*: calcd for $C_{68}H_{97}N_{12}O_6$: 1177.7649 $[M + H]^+$; found 1177.7665, calcd for $C_{68}H_{96}N_{12}NaO_6$: 1199.7468 $[M + Na]^+$; found 1199.7488.

7d. Yield: 58%, mp: 162–164 °C; IR (KBr, ν, cm^{-1}): 3312, 3056, 2968, 2867, 1684, 1546, 1482, 1429, 1357, 1268, 1190, 1123, 1039, 895, 746; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, *t*-Bu, 18H); 1.27 (s, *t*-Bu, 18H); 1.59 (s, *t*-Bu, 18H); 1.75 (s, CH_3, 12H); 3.27 (d, *J* = 13.3 Hz, $ArCH_2Ar$, 4H); 4.14 (d, *J* = 13.3 Hz, $ArCH_2Ar$, 4H); 4.76 (s, OCH_2, 4H); 5.51 (bs, NH, 2H); 6.26 (s, OH, 2H); 6.66 (s, ArH, 4H); 7.01 (s, ArH, 4H); 9.45 (s, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.1, 27.7, 30.6, 30.8, 31.4, 31.6, 33.8, 58.7, 63.3, 74.6, 76.6, 125.1, 125.7, 127.3, 131.7, 142.6, 147.8, 149.4, 149.5, 159.0, 168.4; UHPLC–TOFMS (ESI) *m*/*z*: calcd for $C_{64}H_{93}N_{12}O_6$: 1125.7336 $[M + H]^+$; found 1125.7328, calcd for $C_{64}H_{92}N_{12}NaO_6$: 1147.7155 $[M + Na]^+$; found 1147.717.

7e. Yield: 73%, mp: 220–222 °C; IR (KBr, ν, cm^{-1}): 3310, 3051, 2936, 2865, 1702, 1594, 1549, 1480, 1356, 1296, 1269, 1198, 1125, 1098, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, CH_3, 12H); 0.89 (s, *t*-Bu, 18H); 1.29 (s, *t*-Bu, 18H); 1.35–1.39 (m, CH_2, 4H); 1.68–1.72 (m, CH_2, 4H); 1.72–1.83 (m, CH_2, 10H); 2.00–2.07 (m, CH_2, 6H); 2.14–2.19 (m, CH_2, 4H); 3.33 (d, *J* = 13.4 Hz, $ArCH_2Ar$, 4H); 4.08 (d, *J* = 13.4 Hz, $ArCH_2Ar$, 4H); 4.65 (s, OCH_2, 4H); 5.02 (m, CH, 2H); 5.53 (d, *J* = 4.7 Hz, NH, 2H); 6.50 (s, OH, 2H); 6.72 (s, ArH, 4H); 7.04 (s, ArH, 4H); 9.40 (d, *J* = 4.7 Hz, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.7, 25.0, 25.5, 26.3, 30.8, 31.6, 33.1, 33.8, 33.9, 59.6, 62.9, 74.6, 76.6, 125.3, 125.9, 127.2, 131.8, 142.9, 148.0, 149.3, 155.1, 167.5; UHPLC–TOFMS (ESI) *m*/*z*: calcd for $C_{72}H_{105}N_{12}O_6$: 1233.8275 $[M + H]^+$; found 1233.8293, calcd for $C_{72}H_{104}N_{12}NaO_6$: 1255.8094 $[M + Na]^+$; found 1255.8112.

7f. Yield: 65%, mp: 161–163 °C; IR (KBr, ν, cm^{-1}): 3310, 3057, 2965, 2865, 1682, 1542, 1480, 1427, 1268, 1268, 1190, 1121, 1036, 896, 745; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84–0.89 (t, CH_3, 12H); 0.87 (s, *t*-Bu, 18H); 1.29 (s, *t*-Bu, 18H); 1.64 (s, *t*-Bu, 18H); 2.21 (q, CH_2, 8H); 3.31 (d, J = 13.4 Hz, $ArCH_2Ar$, 4H); 4.12 (d, J = 13.4 Hz, $ArCH_2Ar$, 4H); 4.72 (s, OCH_2, 4H); 5.61 (d, J = 5.4 Hz, NH, 2H); 6.22 (s, OH, 2H); 6.68 (s, ArH, 4H); 7.03 (s, ArH, 4H); 9.26 (d, J = 5.2 Hz, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.1, 27.9, 30.8, 30.9, 31.5, 31.6, 33.8, 64.2, 64.7, 74.6, 76.6, 125.2, 125.8, 127.4, 131.7, 142.8, 147.8, 149.4, 149.6, 156.8, 167.5; UHPLC–TOFMS (ESI) *m*/*z*: calcd for $C_{68}H_{100}N_{12}NaO_6$: 1203.7781 $[M + Na]^+$; found 1203.7803.

7g. Yield: 76%, mp: 225–227 °C; IR (KBr, ν, cm^{-1}): 3305, 3054, 2981, 2867, 1696, 1546, 1476, 1354, 1267, 1196, 1099, 1038, 897, 819, 744, 560; ^1H NMR (300 MHz, $CDCl_3$, mixture of two diastereomers (60 : 40)) δ 0.83–0.96 (m, CH_3, 12H, mixture); 0.88 (s, *t*-Bu, 18H, major); 0.89 (s, *t*-Bu, 18H, minor); 1.04–1.09 (m, CH_2, 4H, mixture); 1.29 (s, *t*-Bu, 18H, mixture); 1.34–1.40 (m, CH_2, 4H, mixture); 1.67–1.83 (m, CH_2, 16H, mixture); 1.91–2.09 (m, CH_2, 6H, mixture); 2.21–2.25 (m, CH_2, 2H, mixture); 3.30–3.35 (m, $ArCH_2Ar$, 4H, mixture); 4.07–4.12 (m, $ArCH_2Ar$, 4H, mixture); 4.56–4.76 (m, OCH_2, 4H, mixture); 5.01 (m, CH, 2H, mixture); 5.46 (d, J = 5.0 Hz, NH, 2H, mixture); 6.34 (s, OH, 1H, minor); 6.44 (s, OH, 2H, major); 6.49 (s, OH, 1H, minor); 6.71 (s, ArH, 4H, mixture); 7.04 (s, ArH, 4H, mixture); 9.30 (d, J = 5.0 Hz, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6, 7.7, 14.3, 16.8, 16.9, 24.9, 25.4, 26.6, 30.8, 31.5, 31.6, 33.0, 33.3, 33.8, 33.9, 36.3, 59.5, 62.6, 62.7, 74.5, 76.6, 125.3, 125.8, 125.9, 127.2, 127.3, 131.7, 131.8, 142.7, 142.8, 142.9, 147.9, 149.3, 149.4, 155.3, 155.4, 167.6, 167.7; UHPLC–TOFMS (ESI) *m*/*z*: calcd for $C_{74}H_{109}N_{12}O_6$: 1261.8588 $[M + H]^+$; found 1261.8604, calcd for $C_{74}H_{108}N_{12}NaO_6$: 1283.8407 $[M + Na]^+$; found 1283.8426.

Crystallographic analysis. A colourless crystal (polyhedron), dimensions 0.110 × 0.080 × 0.050 mm^3, crystal system triclinic, space group *P*, *Z* = 2, *a* = 15.0078(8) Å, *b* = 15.5458(8) Å, *c* = 18.4958(10) Å, alpha = 99.5345(15) deg, beta = 101.1917(16) deg, gamma = 113.0196(14) deg, *V* = 3754.1(3) $Å^3$, rho = 1.116 g cm^{-3}, *T* = 200(2) K, Thetamax = 22.464 deg, radiation Mo Kalpha, lambda = 0.71073 Å, 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 4.95 and a completeness of 99.9% to a resolution of 0.93 Å, 48 309 reflections measured, 9743 unique (R(int) = 0.0512), 6476 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS1 based on the Laue symmetry of the reciprocal space, μ = 0.07 mm^{-1}, T_{min} = 0.95, T_{max} = 1.00, structure refined against F^2 with a Full-matrix least-squares algorithm using the SHELXL (Version 2014-3) software 2980 parameters refined, hydrogen atoms were treated using appropriate riding models, except those at the hetero atoms, which were refined isotropically (except H54 at N54, that could not be considered at all), goodness of fit 1.06 for observed reflections, final residual values $R_1(F)$ = 0.088, $wR(F_2)$ = 0.255 for observed reflections, residual electron density from −0.37 to 0.78 e $Å^{-3}$. CCDC 1025095.

7h. Yield: 67%, mp: 163–165 °C; IR (KBr, ν, cm^{-1}): 3318, 3050, 2960, 2860, 1682, 1541, 1479, 1427, 1260, 1190, 898, 743; ^1H NMR (300 MHz, $CDCl_3$, mixture of two diastereomers (52 : 48)) δ 0.73–0.75 (m, CH_3, 6H, mixture); 0.86 (s, *t*-Bu, 18H, major); 0.87 (s, *t*-Bu, 18H, minor); 0.92–0.98 (m, CH_2, 4H, mixture); 1.17–1.28 (m, CH_3, 6H, mixture); 1.28 (s, *t*-Bu, 18H, mixture); 1.64 (s, *t*-Bu, 18H, major); 1.66 (s, *t*-Bu, 18H, minor); 1.91–1.99 (m, CH_2, 2H, mixture); 2.06–2.19 (m, CH_2, 4H, mixture); 2.29–2.34 (m, CH_2, 2H, mixture); 3.28–3.34 (m, $ArCH_2Ar$, 4H, mixture); 4.09–4.31 (m, $ArCH_2Ar$, 4H, mixture); 4.59–4.84 (m, OCH_2, 4H, mixture); 5.56 (s, NH, 2H, major); 5.57 (s, NH, 2H, minor); 6.03 (s, OH, 1H, minor); 6.24 (s, OH, 2H, major); 6.30 (s, OH, 1H, minor); 6.66 (s, ArH, 4H, minor); 6.72 (s, ArH, 4H, major); 7.01 (s, ArH, 4H, minor); 7.03 (s, ArH, 2H, major); 7.04 (s, ArH, 2H, major); 9.30 (m, NH, 2H, mixture); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.0, 8.2, 14.1, 17.2, 28.6, 29.7, 30.7, 30.8, 31.4, 31.6, 33.8, 37.9, 64.0, 64.5, 74.7, 76.6, 125.1, 125.2, 125.7, 127.0, 127.2, 127.3, 127.5, 131.6, 131.6, 131.7, 147.8, 149.3, 149.5, 156.8, 156.9, 167.6; UHPLC–TOFMS (ESI) *m*/*z*: calcd for $C_{70}H_{104}N_{12}NaO_6$: 1231.8094 $[M + Na]^+$; found 1231.8115.

7i. Yield: 70%, mp: 221–223 °C; IR (KBr, ν, cm^{-1}): 3394, 3309, 3056, 2960, 2863, 1689, 1547, 1483, 1426, 1360, 1267, 1194, 1099, 1040, 899, 741; ^1H NMR (300 MHz, $CDCl_3$, mixture of two diastereomers (54 : 46)) δ 0.86 (s, *t*-Bu, 18H, major); 0.87 (s, *t*-Bu, 18H, minor); 0.87 (s, CH3, 6H, mixture); 1.15–1.4 (m, CH_3, CH_2, 8H, mixture); 1.27 (s, *t*-Bu, 18H, minor); 1.28 (s, *t*-Bu, 18H, major); 1.52–1.67 (m, CH_2, 4H, mixture); 1.71 (br, CH_2, 4H, mixture); 1.78–1.87 (m, CH_2, 10H, mixture); 1.92–2.07 (m, CH_2, 4H, mixture); 3.24–3.51 (m, $ArCH_2Ar$, 4H, mixture); 4.03–4.18 (m, $ArCH_2Ar$, 4H, mixture); 4.32–4.89 (m, CH, OCH_2, 6H, mixture); 5.45 (br, NH, 2H, minor); 5.53 (br, NH, 2H, minor); 6.08 (s, OH, 1H, minor); 6.26 (s, OH, 2H, major); 6.35 (s, OH, 1H, minor); 6.66 (s, ArH, 4H, major); 6.68 (s, ArH, 4H, minor); 6.98 (s, ArH, 4H, major); 7.02 (s, ArH, 4H, major); 9.38 (br, NH, 2H, major); 9.45 (br, NH, 2H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3, 8.4, 21.8, 21.9, 24.8, 25.4, 30.8, 31.6, 32.8, 33.0, 33.8, 59.2, 59.3, 59.8, 59.9, 74.6, 76.6, 125.0, 125.2, 125.6, 125.7, 125.8, 125.9, 127.0, 127.2, 127.4, 127.6, 131.7, 131.9, 142.6, 142.9, 147.7, 147.8, 149.5, 149.5, 149.6, 155.9, 156.2, 168.2, 168.3; UHPLC–TOFMS (ESI) *m*/*z*: calcd for $C_{70}H_{101}N_{12}O_6$: 1205.7962 $[M + H]^+$; found 1205.7976, calcd for $C_{70}H_{100}N_{12}NaO_6$: 1227.7781 $[M + Na]^+$; found 1227.7795.

7j. Yield: 61%, mp: 160–162 °C; IR (KBr, ν, cm^{-1}): 3309, 3055, 2967, 2866, 1687, 1546, 1476, 1357, 1269, 1193, 1121, 1039, 902, 820, 739, 583; ^1H NMR (300 MHz, $CDCl_3$, mixture of two diastereomers (52 : 48)) δ 0.76–0.85 (m, CH_3, 6H, mixture); 0.85 (s, *t*-Bu, 18H, mixture); 1.28 (m, *t*-Bu, 18H, mixture); 1.27–1.30 (m, CH_3, 3H, mixture); 1.57 (s, *t*-Bu, 18H, major) 1.58 (s, *t*-Bu, 18H, minor); 1.77–1.84 (m, CH_3, 3H, mixture); 1.98–2.20 (m, CH_2, 4H, mixture); 3.20–3.49 (m, $ArCH_2Ar$, 4H, mixture); 3.96–4.24 (m, $ArCH_2Ar$, 4H, mixture); 4.45–4.94 (m, OCH_2, 4H, mixture); 5.07–5.68 (br, NH, 2H, mixture); 5.99 (s, OH, 1H, minor); 6.19 (s, OH, 2H, major); 6.35 (s, OH, 1H, minor);

6.64 (s, ArH, 4H, major); 6.65 (s, ArH, 4H, minor); 6.91–7.06 (m, ArH, 4H, mixture); 9.38 (s, NH, 2H, mixture); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3, 8.4, 24.1, 24.3, 27.7, 29.8, 30.7, 30.8, 31.3, 31.4, 31.6, 32.1, 32.3, 33.8, 61.7, 63.5, 63.6, 74.6, 76.6, 125.0, 125.1, 125.2, 125.4, 125.7, 125.8, 125.9, 126.9, 127.1, 127.4, 127.6, 131.5, 131.6, 131.8, 142.6, 147.7, 149.2, 149.4, 149.5, 149.6, 157.7, 157.9, 168.1, 168.3; UHPLC–TOFMS (ESI) *m/z*: calcd for $C_{66}H_{96}N_{12}NaO_6$: 1175.7468 $[M + Na]^+$; found 1175.7486.

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