Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: Org. Biomol. Chem., 2014, 12, 4211

Improved hemicryptophane hosts for the stereoselective recognition of glucopyranosides†

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Received 21st January 2014,
Accepted 10th March 2014

DOI: 10.1039/c4ob00156g

www.rsc.org/obc

Four new enantiomerically and diastereomerically pure hemicryptophane hosts (*M*-*SSS*-**2**/*P*-*SSS*-**2** and *M*-*RRR*-**2**/*P*-*RRR*-**2** pairs) were designed for the recognition of sugar derivatives. Their absolute configuration was determined from the circular dichroism spectra and DFT calculations. The host molecules were then used for the stereoselective recognition of glucopyranosides. Binding constants were obtained from ^{1}H NMR titration experiments showing an increase of affinity for this class of receptors, associated with an improved diastereo- and enantio-differentiation.

Introduction

Carbohydrate recognition is involved in numerous biological processes such as protein folding,[1] cell–cell recognition,[2] infection by pathogens[3] or tumour metastasis.[4] Thus, there is great interest in mimicking biological receptors of carbohydrates such as lectins.[5–7] However, these guests are challenging for supramolecular chemists as they possess complex three-dimensional structures, which often present subtle changes (such as the configuration of a single stereogenic centre) so that a large selectivity is difficult to achieve. Consequently, a great deal of effort has been devoted to the development of new synthetic hosts for the recognition of carbohydrates.[7–14] Some examples have shown good β/α diastereoselectivities[10d,11b,c] but significant progress has to be made to increase enantiodifferentiation.[15–22]

Among the different classes of molecular receptors, the chiral hemicryptophane host molecules were found to be efficient in molecular recognition[23–27] and in supramolecular catalysis,[28,29] and have been used as molecular switches.[30] Enantiopure hemicryptophanes have been obtained following two main strategies: the resolution of racemic mixtures using chiral semi-preparative HPLC[31] or the introduction of stereogenic centers to form diastereomers.[27,32,33] The resulting enantiopure hosts were efficient in the stereoselective recognition of chiral guests including carbohydrates,[25b] ammoniums, such as ephedrine and norephedrine,[31c] and zwitterions such as carnitine.[27] In particular, we previously resolved the racemic mixture of hemicryptophane **1** and studied its binding abilities toward *n*-octyl-β-D-glucopyranoside (OctβGlc) and *n*-octyl-α-D-glucopyranoside (OctαGlc) in $CDCl_3$ (Fig. 1).[25b] Good stereoselectivities were obtained, and interestingly, OctβGlc was exclusively bound to the *M*-configurated host. Thus, we decided to synthesize new enantiomerically pure hemicryptophanes containing additional stereogenic groups in order (i) to avoid the use of a semi-preparative HPLC to separate the stereoisomers, (ii) to get a deeper understanding of the role of the cyclotribenzylene (CTB) moiety on the stereoselectivity, and (iii) to improve the binding constants. The introduction of stereogenic centers should modify the shape of the inner space of the cavity, which may induce an improvement of the binding properties of the receptor.

Herein, we report the synthesis of four enantiopure hemicryptophanes, corresponding to the four C_3-symmetric stereoisomers of host **2**, which contain three asymmetric carbons with a controlled stereochemistry (Fig. 1). The absolute configuration of the hemicryptophanes was assigned from the CD spectra and DFT calculations. The binding abilities of these enantiomerically pure receptors toward OctαGlc and OctβGlc were investigated in $CDCl_3$ solution.

Results and discussion

Synthesis

The *P* and *M* stereoisomers of hemicryptophane *SSS*-**2** have been synthesized from (*S*)-4-methoxy-α-methylbenzylamine

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†Electronic supplementary information (ESI) available: NMR spectra, experimental details for ^{1}H NMR titrations, Job's plot and CD spectra. See DOI: 10.1039/c4ob00156g

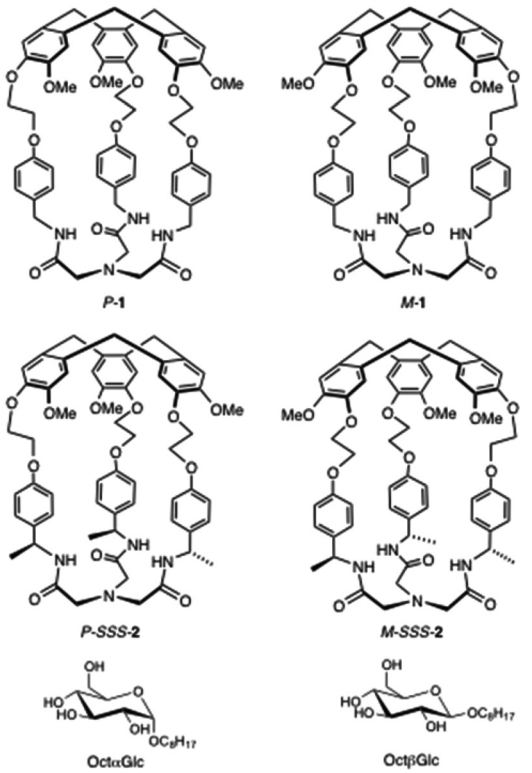
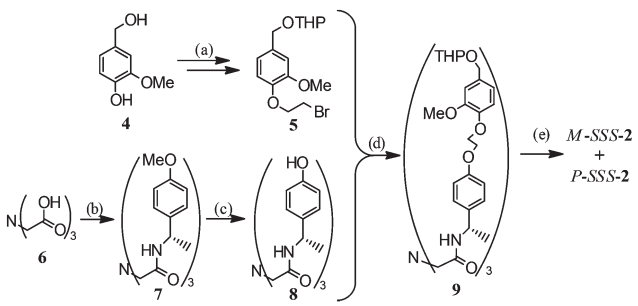


Fig. 1 Structures of the stereoisomers of hemicryptophanes **1**, *SSS*-**2**, and octyl-α-D-glucopyranoside (OctαGlc) and octyl-β-D-glucopyranoside (OctβGlc).

according to Scheme 1. Starting from vanillyl alcohol **4**, compound **5** was obtained according to the known two-step sequence (a): nucleophilic substitution with dibromoethane and protection with THP.[34,35] (b) Nitrilotriacetic acid **6** was condensed with (*S*)-4-methoxy-α-methylbenzylamine in the presence of $P(OPh_3)_3$ in pyridine to give **7**. (c) Deprotection with BBr_3 in dichloromethane afforded **8**, which reacted under basic conditions with **5** (d) to give the precursor **9**. (e) Cyclization was then performed in pure formic acid ([**9**] < 1 mM) to give diastereomers *M*-*SSS*-**2** and *P*-*SSS*-**2**, which were separated by column chromatography. The same procedure was followed from (*R*)-4-methoxy-α-methylbenzylamine to give the *M*-*RRR*-**2** and *P*-*RRR*-**2** isomers.



Scheme 1 (a) (1) $BrCH_2CH_2Br$, K_2CO_3, EtOH, 50 °C, 6 h, (2) DHP, pyridinium *p*-toluenesulfonate, THF–CH_2Cl_2, rt, 3 h, 46% over two steps; (b) (*S*)-4-methoxy-α-methylbenzylamine, $P(OPh)_3$, pyridine, 110 °C, 24 h, 74%; (c) BBr_3, CH_2Cl_2, –78 °C → rt, 18 h, 80%; (d) Cs_2CO_3, DMF, 80 °C, 24 h, 65%; (e) HCOOH, rt, 24 h, 35%.

The ^1H NMR spectra of the diastereomers of hemicryptophane **2** indicate that both molecules are, on average, of C_3 symmetry in solution (Fig. 2). Both spectra display the usual features of the structures of the CTB unit, *i.e.* two singlets for the aromatic protons, one singlet for the OCH_3 groups, and the characteristic AB system for the $ArCH_2$ bridges. The aromatic protons of the linkers and the multiplets for the OCH_2 and NCH_2 groups were also easily assigned.

Determination of the absolute configurations

The absolute configurations of the chiral hosts were determined from the circular dichroism (CD) spectra recorded in $CHCl_3$ at 298 K (Fig. 3). We observe a classical behaviour for hemicryptophanes, which consists of two exciton patterns roughly centred on the isotropic absorption of the ^1L_B (290 nm) and ^1L_A (240 nm) transitions. As shown previously by Collet and co-workers, the CD spectra of chiral C_3 derivatives of cyclotriveratrylene can be analyzed in terms of exciton coupling between the transition moments of the three aryl chromophores.[36–38] In such compounds bearing two different alkoxy groups (the ethoxy linkers and the methoxy groups in our case), the spectroscopic moment of the bulkier group is greater than that of the smaller one, which implies that the *P* stereoisomer (respectively *M*) displays a positive (respectively negative) Cotton effect in the region of the ^1L_A transition

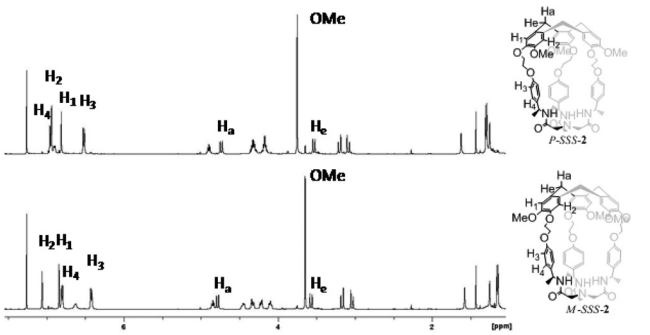


Fig. 2 ^1H NMR spectra (500.1 MHz, $CDCl_3$, 298 K) of hemicryptophanes **2**.

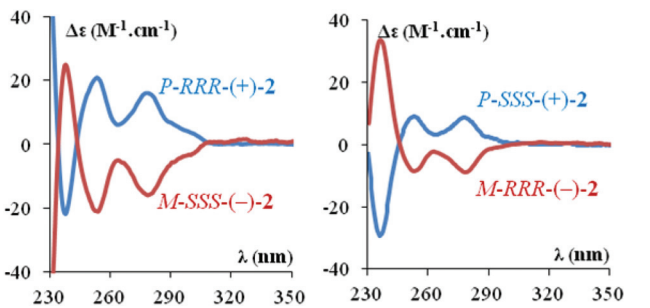


Fig. 3 Experimental CD spectra ($CHCl_3$, 298 K) of the isomers of **2** (left: first eluted compounds; right: second eluted compounds).

(240–245 nm).[39] Thus, observation of the CD spectra allowed us to assign the different configurations as shown in Fig. 3: the first eluted compounds (respectively the second) correspond to the *P-RRR* and *M-SSS* enantiomers (respectively the *P-SSS* and *M-RRR* enantiomers).

Calculations of the CD spectra of enantiopure hosts were performed using the TD-DFT method, performing a scan of different hybrid functionals (B3LYP, CAM-B3LYP, BH&LYP) with the SVP basis set. Fig. 4 compares the results obtained with the different functionals used to compute the CD spectra for the two diastereomers of **2**. Two of the functionals (CAM and BH&HLYP) agree very well, while B3LYP strongly underestimates the rotational strengths of most transitions and also redshifts them by about 20 nm. Nonetheless, the sign sequence is the same for all of them. The match with the experiment is extremely good for CAM and BH&HLYP and ultimately confirms the configurational assignment. We note that for the *M-SSS* isomer at longer wavelengths, TD-DFT calculations systematically overestimate the rotational strength of a low-lying charge transfer transition, which is not apparent in the experimental spectrum.

Recognition of glucopyranosides

Binding constants were determined from ^{1}H NMR titration experiments in $CDCl_3$ using *n*-octyl-β-D-glucopyranoside (OctβGlc) and *n*-octyl-α-D-glucopyranoside (OctαGlc) as soluble glycosidic guests, and the stereoisomers of **2** as enantiopure receptors. In all cases only one set of signals was observed for the complex and for the receptor, showing that host–guest exchange is fast on the NMR time scale. Complexation induced shifts of either the aromatic or NH protons of the linkers were plotted as a function of the guest/host ratio (Fig. 5). Indeed, all these protons displayed sharp signals and no overlapping region. As for host **1**,[25b] fitting these curves with the HypNMR2008 software[40] allowed us to obtain the 1 : 1 binding constants K_a, which are reported in Table 1. The Job's plot experiment performed with *M-SSS*-**2** and OctβGlc (see ESI†) confirms the 1 : 1 host–guest association as observed with host **1**.[25b]

From the data in Table 1, several conclusions can be drawn. Firstly, we can see that binding abilities have been improved compared to host **1** since K_a values are up to one order of magnitude larger. Secondly, the trend in diastereoselectivity previously observed with **1** is contrary to **2**: OctβGlc shows larger binding constants than its α anomer with a ratio going from 2.8 to exclusive binding of the β isomer. As binding sites are similar in hosts **1** and **2**, conformational changes induced by addition of the methyl groups could account for both the improvement of the binding constant and the change in selectivity. This could result in a larger cavity more suitable for the glucopyranoside guest.

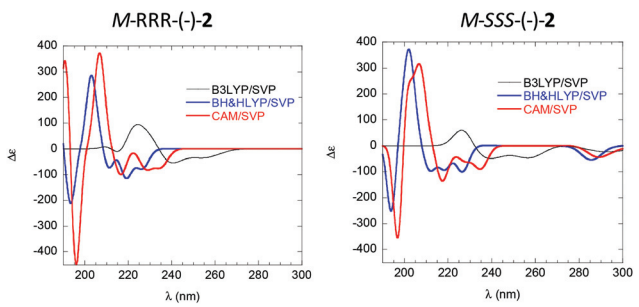


Fig. 4 TD DFT computed CD spectra of the isomers of **2** using three different functionals.

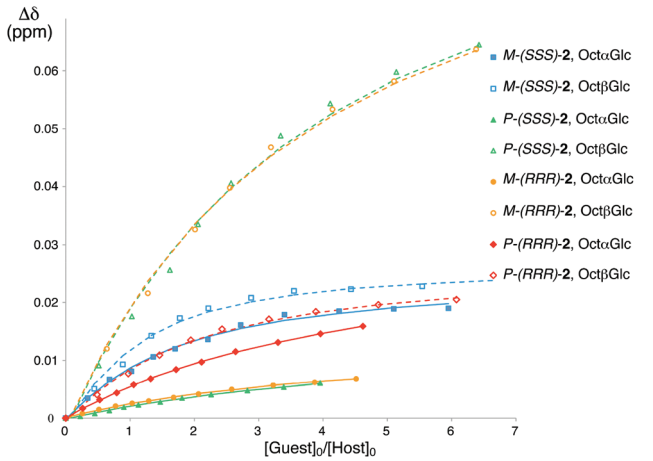


Fig. 5 Plots of the experimental chemical shift variations of the aromatic protons of the linker as a function of the ratio [sugar]/[**2**]. The curves are those obtained after modelling with HypNMR2008 software.

Table 1 Association constants K_a for enantiopure hemicryptophanes with *n*-octylglucopyranosides in $CDCl_3$ [a]

	M-SSS-**2**	*P-SSS*-**2**	*P-RRR*-**2**	*M-RRR*-**2**	*M*-**1**	*P*-**1**
OctαGlc	595	—[b]	34	56	216	31
OctβGlc	1660	183	384	192	64	—[b]

[a] K_a determined by fitting ^{1}H NMR titration curves ($CDCl_3$, 500 MHz, 298 K) on aromatic protons with HypNMR2008; estimated error 10%. [b] No complexation detected.

Thus, these hosts present a good recurrent diastereoselectivity in discriminating OctβGlc from OctαGlc. However, it is also interesting to compare each of the different hosts' isomers. From Table 1 it appears that the *M-SSS* host bound much more strongly carbohydrates than the other stereoisomer receptors. This indicates that the combination of both, stereogenic centres and the CTB unit, with respectively the *SSS* and *M* configurations corresponds to the match case. Indeed, other combinations result in a drop in the binding constant either for the β or α anomer. From this trend, we can conclude that selectivity is not only controlled by the chirality of the CTB unit or by that of the benzylic carbons; the whole structure of the hemicryptophane is involved. This is consistent with previous observations that the chirality of both the CTB moiety and the second binding unit are strongly involved.[30] Therefore, higher diastereoselectivity is obtained with the *M-SSS* stereoisomer. For instance, *M-SSS*-**2** is able to

recognize the OctαGlc anomer whereas no complexation is observed with the *P-SSS*-**2** diastereomer. This selectivity is probably based on a structural change of the host compounds. As mentioned above, one possible explanation could be that both stereogenic units match in the first case to form a suitable cavity able to encapsulate the guest, whereas they mismatch in the second one, involving a less appropriate conformation of the hosts.

Finally, we observed a marked enantioselectivity in favour of the *M*-configurated hosts, particularly with OctαGlc. This is consistent with our previous results, which showed that *M* hemicryptophane enantiomers present better binding abilities toward carbohydrates than their *P*-configurated counterparts. In particular, for the OctαGlc guest the ratio $K_{M\text{-}SSS\text{-}2}/K_{P\text{-}RRR\text{-}2}$ reaches a 17 : 1 value. Concerning the other enantiomeric pair, OctαGlc is exclusively recognized by *M-RRR*-**2** and no complexation is observed with the *P-SSS*-**2** enantiomer. This highlights the remarkable enantiomeric discrimination properties of hemicryptophane **2** in the recognition of carbohydrates.

Conclusions

We have reported the synthesis of four new enantiopure hemicryptophane hosts and the assignment of their absolute configuration thanks to the study of their CD spectra associated with DFT calculations. These four hemicryptophane hosts were used for the stereoselective complexation of carbohydrates. They specifically recognize the β anomer of a D-glucose derivative, and the host bearing the *M*-CTB combined with the *SSS*-stereogenic centres presents a much higher binding constant for sugar derivatives than the other isomers. Therefore remarkable diastereoselectivity and enantioselectivity were achieved. Moreover, in comparison with previous hemicryptophane receptors used for the recognition of glucopyranosides, the association constants measured with hosts **2** are up to one order of magnitude higher, highlighting the relevance of such structures for efficient and selective recognition of carbohydrates.

Experimental section

General methods

All reactions were carried out under argon by means of inert gas/vacuum double manifold and standard Schlenk techniques. Dichloromethane was dried and degassed on a solvent station by passage through an activated alumina column followed by an argon flush. Other solvents were dried prior to use over molecular sieves. ^{1}H and ^{13}C spectra were recorded at 500.1 MHz and 125.7 MHz, respectively, and are reported relative to the residual protonated solvent signal (^{1}H, ^{13}C). Mass spectra were recorded by the Centre de Spectrométrie de Masse, Institute of Chemistry, Lyon. Compound **5** was prepared according to the published procedure.[41]

Syntheses

Hemicryptophanes *P-SSS*-2 and *M-SSS*-2. Precursor (*SSS*)-**9** (2.50 g, 1.86 mmol) was dissolved in formic acid (2.5 L). The mixture was stirred for one day at room temperature and then the formic acid was removed under vacuum. The brown residue was dissolved in chloroform (100 mL), and aqueous K_2CO_3 (10%, 50 mL) was added. The organic layer was washed with aqueous K_2CO_3 (10%, 50 mL) and the aqueous phases were extracted with chloroform (2 × 100 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel (dichloromethane–diethyl ether–methanol 60/40/5 then 60/40/10) to give a mixture of *M-SSS*-**2** and *P-SSS*-**2** (674 mg, 35%). Both diastereomers were separated on an alumina preparative TLC (*m* = 30 mg, chloroform–diethyl ether–methanol 70/30/5). The two residues were precipitated in $CHCl_3$–cyclohexane and the solvent was removed under vacuum to obtain two white solids. Hemicryptophane *M-SSS*-**2** (1st eluted): ^{1}H NMR ($CDCl_3$, 298 K, 497.8 MHz) δ 7.04 (s, 3H, ArH); 6.82 (s, 3H, ArH); 6.79 (d, 6H, J = 8.5 Hz, ArH); 6.59 (d, 3H, J = 5.5 Hz, CONH); 6.41 (d, 6H, J = 8.5 Hz, ArH); 4.85 (m, 3H, NCH); 4.78 (d, 3H, J = 13.8 Hz, $ArCH_2Ar$); 4.43–4.47 (m, 3H, $O(CH_2)_2O$); 4.31–4.35 (m, 3H, $O(CH_2)_2O$); 4.19–4.23 (m, 3H, $O(CH_2)_2O$); 4.07–4.11 (m, 3H, $O(CH_2)_2O$); 3.63 (s, 9H, OMe); 3.55 (d, 3H, J = 13.8 Hz, $ArCH_2Ar$); 3.15 (d, 3H, J = 16.0 Hz, $COCH_2$); 3.02 (d, 3H, J = 16.0 Hz, $COCH_2$); 1.14 (d, 9H, J = 6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 298 K, 125.2 MHz) δ 168.7 (CONH); 157.9 ($C_{Ar}O$); 148.6 ($C_{Ar}O$); 146.7 ($C_{Ar}O$); 135.7 (C_{Ar}); 133.2 (C_{Ar}); 131.9 (C_{Ar}); 127.2 (C_{Ar}); 117.2 (C_{Ar}); 115.3 (C_{Ar}); 113.9 (C_{Ar}); 68.1 (OCH_2); 67.9 (OCH_2); 59.9 (NCH_2); 55.9 (OMe); 48.1 (NCH); 36.6 (ArCAr); 21.0 (CH_3). ESI-MS *m*/*z*: 1035.4730 $[M + H]^+$ (calculated: 1035.4750 for $C_{60}H_{67}N_4O_{12}$). IR (KBr) 3300, 3058, 1656 cm^{-1}. $[\alpha]_D^{25}$ = −128 (*c* = 0.1; CH_2Cl_2).

Hemicryptophane *P-SSS*-**2** (2nd eluted): ^{1}H NMR ($CDCl_3$, 298 K, 497.8 MHz) δ 6.94 (m, 9H, ArH); 6.89 (d, 3H, J = 7.9 Hz, CONH); 6.81 (s, 3H, ArH); 6.52 (d, 6H, J = 8.5 Hz, ArH); 4.89 (m, 3H, NCH); 4.73 (d, 3H, J = 13.8 Hz, $ArCH_2Ar$); 4.27–4.35 (m, 6H, $O(CH_2)_2O$); 4.14–4.21 (m, 6H, $O(CH_2)_2O$); 3.75 (s, 9H, OMe); 3.53 (d, 3H, J = 13.8 Hz, $ArCH_2Ar$); 3.20 (d, 3H, J = 16.0 Hz, $COCH_2$); 3.08 (d, 3H, J = 16.0 Hz, $COCH_2$); 1.29 (d, 9H, J = 6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 298 K, 125.2 MHz) δ 169.0 (CONH); 157.8 ($C_{Ar}O$); 149.0 ($C_{Ar}O$); 146.8 ($C_{Ar}O$); 135.9 (C_{Ar}); 133.5 (C_{Ar}); 132.2 (C_{Ar}); 127.1 (C_{Ar}); 117.6 (C_{Ar}); 115.4 (C_{Ar}); 114.3 (C_{Ar}); 68.8 (OCH_2); 67.4 (OCH_2); 59.9 (NCH_2); 56.5 (OMe); 48.3 (NCH); 36.5 (ArCAr); 21.9 (CH_3). ESI-MS *m*/*z*: 1035.4728 $[M + H]^+$ (calculated: 1035.4750 for $C_{60}H_{67}N_4O_{12}$). IR (KBr) $\bar{\nu}$ = 3305, 3055, 1654 cm^{-1}. $[\alpha]_D^{25}$ = +22 (*c* = 0.1; CH_2Cl_2).

Enantiomers M-RRR-2 and P-RRR-2 have been synthesized following the same procedure from the precursor enantiomer (*RRR*)-**9**. ^{1}H, ^{13}C NMR, ESI-MS and IR spectroscopy gave the same results. Specific rotation analysis gave $[\alpha]_D^{25}$ = −29 and +137 (*c* = 0.1; CH_2Cl_2) for *M-RRR*-**2** and *P-RRR*-**2** respectively.

2,2′,2″-Nitrilotris{*N*-[(*S*)-1-(4-methoxyphenyl)ethyl]-acetamide} (7). To a solution of nitrilotriacetic acid **6** (10.7 g, 56 mmol) in

pyridine (120 mL) was added under inert atmosphere (*S*)-4-methoxy-alpha-methylbenzylamine (25 g, 165 mmol). The solution was warmed to 50 °C and triphenylphosphite (55 mL, 203 mmol) was added. The mixture was heated at 110 °C and stirred for one day and then the pyridine was removed under vacuum. The orange residue was dissolved in chloroform (400 mL) and was successively washed with 10% aq. $NaHCO_3$ (2 × 200 mL) and distilled water (1 × 200 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane with 0 to 10% methanol) to give **7** as a beige powder (23.3 g, 74%). ^{1}H NMR ($CDCl_3$, 298 K, 497.8 MHz) δ 7.60 (d, 3H, J = 7.6 Hz, CONH); 7.19 (d, 6H, J = 8.5 Hz, ArH); 6.79 (d, 6H, J = 8.5 Hz, ArH); 5.04 (m, 3H, ArCHN); 3.75 (s, 9H, OMe); 3.16 (s, 6H, $COCH_2$); 1.40 (d, 9H, J = 7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 298 K, 125.2 MHz) δ 169.4 (CONH); 158.5 ($C_{Ar}O$); 135.5 (C_{Ar}); 127.5 ($C_{Ar}H$); 114.1 ($C_{Ar}H$); 60.9 (NCH_2CO); 55.4 (OCH_3); 48.5 ($NHCH_2Ar$); 22.1 (CH_3). ESI-MS m/z: 591.3156 $[M + H]^+$ (calculated: 591.3177 for $C_{33}H_{43}N_4O_6$). IR (KBr) 3068, 2981, 2931, 2833, 1650, 1546, 1512, 1245 cm^{-1}. $[\alpha]_D^{25}$ = −90 (c = 0.06; CH_2Cl_2).

2,2′,2″-Nitrilotris{*N*-[(*S*)-1-(4-hydroxyphenyl)ethyl]-acetamide} (8). A 1 M boron tribromide solution in CH_2Cl_2 (200 mL, 200 mmol) was added dropwise at −78 °C under inert atmosphere to a well-stirred solution of **7** (20.0 g, 33.8 mmol) in CH_2Cl_2 (200 mL). The mixture was allowed to warm to room temperature and stirred for 18 hours. The solution was cooled to 0 °C and quenched by slow addition of methanol. 10% aqueous solution of $NaHCO_3$ was added to achieve pH ~ 7–8. The aqueous phase was extracted with ethyl acetate (3 × 500 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure to give **8** as a white solid (15 g, 80%). ^{1}H NMR (DMSO-d_6, 298 K, 497.8 MHz) δ 9.23 (s, 3H, ArOH); 8.47 (d, 3H, J = 7.6 Hz, CONH); 7.09 (d, 6H, J = 8.5 Hz, ArH); 6.67 (d, 6H, J = 8.5 Hz, ArH); 4.86 (m, 3H, ArCHN); 3.24 (s, 6H, $COCH_2$); 1.29 (d, 9H, J = 7.0 Hz, CH_3). ^{13}C NMR (DMSO-d_6, 298 K, 125.2 MHz) δ 168.6 (CONH); 158.2 ($C_{Ar}O$); 134.7 (C_{Ar}); 126.8 ($C_{Ar}H$); 113.4 ($C_{Ar}H$); 60.1 (NCH_2); 47.8 (NCH); 21.4 (CH_3). ESI-MS m/z: 549.2688 $[M + H]^+$ (calculated: 549.2708 for $C_{30}H_{37}N_4O_6$). IR (KBr) 3313, 2973, 2933, 1654, 1542, 1515, 1240 cm^{-1}. $[\alpha]_D^{25}$ = −138 (c = 0.1; CH_2Cl_2).

Precursor (*SSS*)-9. Compounds **8** (15 g, 27.3 mmol) and **5** (31.1 g, 89.9 mmol) and Cs_2CO_3 (35 g, 108 mmol) were dissolved in DMF (85 mL). The solution was heated at 80 °C and stirred for one day. The mixture was cooled to room temperature and distilled water (250 mL) was added. The aqueous mixture was then extracted with ethyl acetate (4 × 150 mL). The combined organic layers were washed with distilled water (2 × 150 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (dichloromethane with 0 to 4% methanol) to give **9** as a brown oil (24 g, 65%). ^{1}H NMR ($CDCl_3$, 298 K, 497.8 MHz) δ 7.59 (d, 3H, J = 8.0 Hz, CONH); 7.16 (d, 6H, J = 8.5 Hz, ArH); 6.86–6.90 (m, 9H, ArH); 6.80 (d, 6H, J = 8.5 Hz, ArH); 5.01 (m, 3H, ArCHN); 4.69 (d, 3H, J = 11.7 Hz, $ArCH_2O$); 4.66 (m, 3H, OTHP); 4.41 (d, 3H, J = 11.7 Hz, $ArCH_2O$); 4.20–4.32 (m, 12H, $O(CH_2)_2O$); 3.90 (m, 3H, OTHP); 3.79 (s, 9H, OMe); 3.52 (m, 3H, OTHP); 3.12 (s, 6H, $COCH_2$); 1.68–1.86 (m, 18H, OTHP); 1.26 (d, 9H, J = 7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 298 K, 125.2 MHz) δ 169.6 (CONH); 158.03 ($C_{Ar}O$); 149.8 ($C_{Ar}O$); 147.7 ($C_{Ar}O$); 135.9 (C_{Ar}); 132.0 (C_{Ar}); 127.6 (C_{Ar}); 120.7 (C_{Ar}); 114.9 (C_{Ar}); 114.3 (C_{Ar}); 112.3 (C_{Ar}); 97.8 (OCO); 68.9 (CH_2O); 68.0 (CH_2O); 66.7 (CH_2O); 62.5 (CH_2O); 60.0 (NCH_2); 56.0 (OMe); 48.5 (NCH); 30.8 (OTHP); 25.6 (OTHP); 22.1 (CH_3); 19.7 (OTHP). ESI-MS m/z: 1341.6754 $[M + H]^+$ (calculated: 1341.6792 for $C_{75}H_{97}N_4O_{18}$). IR (KBr) 3058, 2937, 2871, 1645, 1610, 1511 cm^{-1}. $[\alpha]_D^{25}$ = −27 (c = 0.1; CH_2Cl_2).

*Enantiomers (RRR)-7, (RRR)-**8** and (RRR)-**9*** were obtained similarly starting from (*R*)-4-methoxy-alpha-methylbenzylamine.

^{1}H NMR titrations

Solutions of hosts (2.0 mM in $CDCl_3$, 500 μL) were titrated in NMR tubes with small aliquots of concentrated solutions (10 or 20 mM in $CDCl_3$) of guests. At these concentrations, no self-aggregation of the hosts was observed.[42] Complexation induced shifts $\Delta\delta$ of the aromatic protons or the NH protons of the host were measured after each addition and plotted as a function of the guest/host ratio. Mathematical analysis of data and graphical representation of results were performed using the HypNMR 2008 program,[43] handling general host–guest association equilibria under the fast exchange regime on the NMR time scale. This allows obtaining the binding constant K_a (see ESI† section). Experimental and modeled titration plots are shown in Fig. 5.

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