Enantioselective recognition with C_3-symmetric cage-like receptors in solution and on a stationary phase

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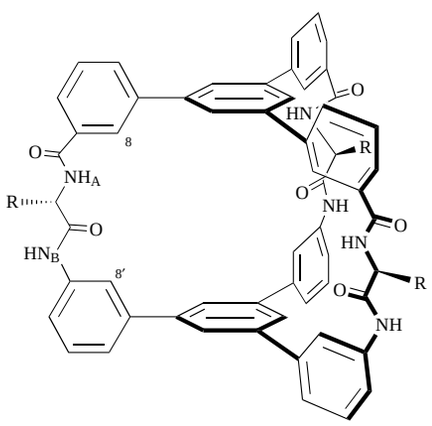
The chiral C_3-symmetric, cage-like receptors (*S*,*S*,*S*)-(+)-1 and (*S*,*S*,*S*)-(+)-2 with convergent, helically oriented amide hydrogen bonding sites have been prepared by a short, modular synthetic route. They are found to complex *N*-protected amino acid derivatives and, in particular, dicarboxylic acids in non-competitive solvents. Enantioselectivity is observed in the binding of *N*-Cbz-Glu (*N*-carbobenzyloxy-protected glutamic acid), and differences in stability of the diastereoisomeric complexes [$\Delta(\Delta G)$ of up to 4.6 kJ mol^{-1}] have been measured by ^{1}H NMR binding titrations in $CDCl_2CDCl_2$. The geometries of free and bound receptor (*S*,*S*,*S*)-(+)-1 have been analysed by computer molecular modelling. Receptor (*S*,*S*,*S*)-(+)-2 is covalently linked to thiol-functionalised silica gel, yielding the novel chiral stationary phase (CSP) (*S*,*S*,*S*)-14. In analytical HPLC (high performance liquid chromatography) runs, the new CSP is found to be effective for the optical resolution of (±)-1,1′-binaphthyl-2,2′-diol derivatives, but not for the separation of enantiomeric amino acid derivatives.

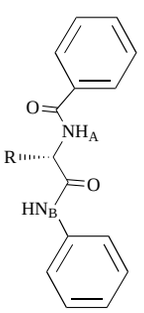
In living systems, molecular recognition phenomena are at the origin of highly selective chemical reactions and transport phenomena, as well as the formation of functional supramolecular assemblies. The study of synthetic model systems contributes to the understanding of these processes and, at the same time, offers new perspectives for controlling reactivity and specificity in chemistry.[1] One area that has proven especially challenging is the creation of enantioselective artificial receptors.[2] Nature's selective binding sites are often characterised by a large degree of encapsulation of the targeted substrate.[3] We have taken this lesson to heart in the design of receptors with a cage-like molecular architecture.[4] Systems like these[5] have mostly been developed for hydrophobic binding in aqueous solution or for the complexation of metal ions. In contrast, our cage-like receptors are internally functionalised with H-bonding sites and were designed to select guests complementary with respect to H-bonding[6] as well as size and shape. Most successful enantioselective synthetic receptors feature a high degree of conformational homogeneity and the presence of multiple hydrogen bonding sites.[7] It is generally appreciated that for the recognition of a single stereogenic centre three contact points, either repulsive or attractive, are required.[2,6a,8] These criteria combined led us to the design of C_3-symmetric cage-like receptors. Chiral shapes with this symmetric group have in the past been successfully applied to both molecular recognition[7a,9] and asymmetric catalysis studies.[10]

An emerging application of enantioselective artificial receptors is their use as chiral selectors in chromatographic optical resolutions.[8,11] The specific host–guest interactions at the origin of chiral recognition in the liquid phase should translate into differential retention times for substrate enantiomers eluted on stationary phases containing the immobilised optically active receptor. Such correlations between solution affinity and chromatographic separation have recently been demonstrated.[12–14]

Here we report on the synthesis of the cage-like C_3-symmetric receptors (*S*,*S*,*S*)-(+)-**1** and (*S*,*S*,*S*)-(+)-**2**, their conformations in the free and bound state, and their selective complexation properties in non-competitive (aprotic) solvents, as evaluated by ^{1}H NMR titration and solubilisation studies. The receptors contain 1,3,5-triarylbenzene moieties as both the 'floor' and 'ceiling' of the cavity, and these units are linked by three amino acid spacers through peptide bonds. Substrates in the liquid phase binding studies were *N*-protected amino acid derivatives[15] and, in particular, derivatives of the excitatory amino acids aspartic acid (Asp) and glutamic acid (Glu).[16,17] In addition, a close analogue of (*S*,*S*,*S*)-(+)-**2** was immobilised on silica gel and the resulting material evaluated as a chiral stationary phase (CSP) in HPLC studies. Derivatives of (±)-1,1′-binaphthyl-2,2′-diol were successfully resolved on this new CSP.



(*S*,*S*,*S*)-(+)-**1** R = $CH_2CH(CH_3)_2$
(*S*,*S*,*S*)-(+)-**2** R = CH_2Ph

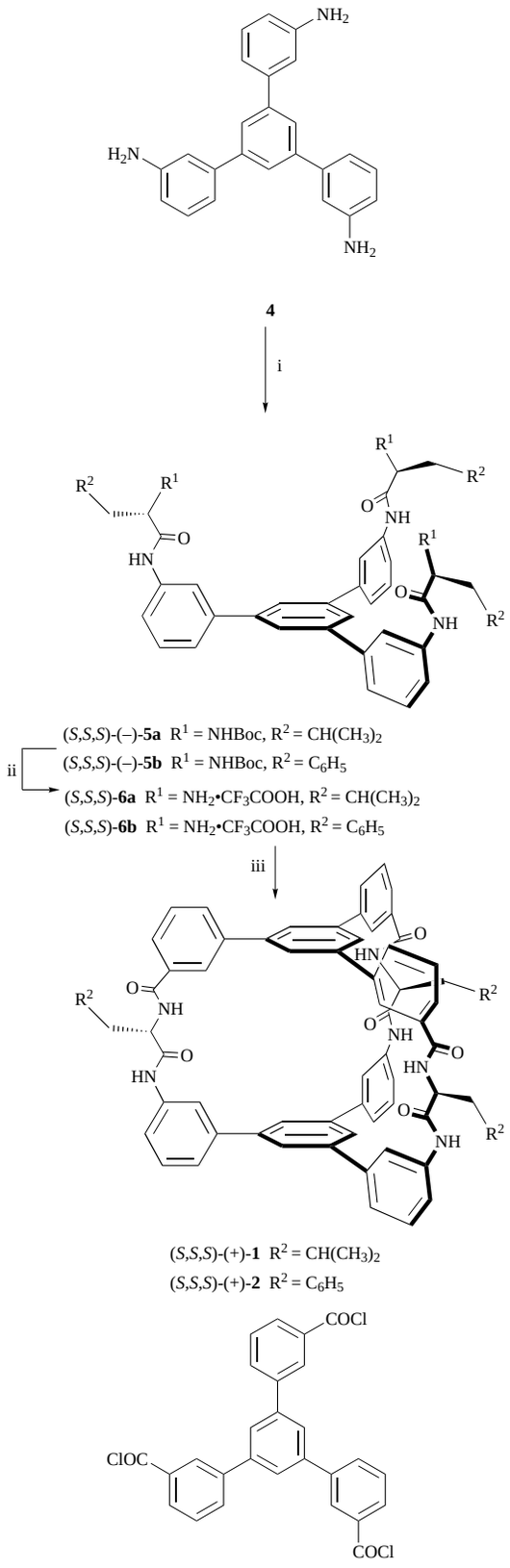


(*S*)-(+)-**3** R = $CH_2CH(CH_3)_2$

Results and discussion

Synthesis of the optically active receptors

Receptors (*S*,*S*,*S*)-(+)-**1** and (*S*,*S*,*S*)-(+)-**2** were prepared *via* a short route and in a modular fashion from triamine **4**[18,19] and



Scheme 1 Synthesis of receptors (*S*,*S*,*S*)-(+)-**1** and (*S*,*S*,*S*)-(+)-**2**. i *N*-Boc-L-Leu·H_2O or *N*-Boc-L-Phe, EDC·HCl, cat. DMAP, THF, 14 h, 60% [(*S*,*S*,*S*)-**5a**], 68% [(*S*,*S*,*S*)-**5b**]. ii CF_3COOH–CH_2Cl_2 1:1, 1 h, quant. yield. iii **7**, NEt_3, THF, 14 h, 10% [(*S*,*S*,*S*)-(+)-**1**], 3% [(*S*,*S*,*S*)-(+)-**2**].

acyl halide **7**[20] (Scheme 1). The triamine **4** was coupled to the *tert*-butoxycarbonyl (Boc)-protected L-amino acids leucine (Leu) or phenylalanine (Phe) by using 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (EDC·HCl) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in tetrahydrofuran (THF) to give (*S*,*S*,*S*)-(−)-**5a** and (*S*,*S*,*S*)-(−)-**5b**, respectively. Deprotection with trifluoroacetic acid (TFA) provided the ammonium salts (*S*,*S*,*S*)-**6a** and (*S*,*S*,*S*)-**6b**, which were cyclised with tris(acyl halide) **7** to give receptors (*S*,*S*,*S*)-(+)-**1** (10% yield) and (*S*,*S*,*S*)-(+)-**2** (3% yield), respectively. Reference compound (*S*)-(+)-**3** was prepared from aniline, *N*-Boc-L-Leu, and benzoyl chloride by following a similar protocol.

Conformations of the receptors

In the ^{1}H NMR spectra ($CDCl_3$, c = 1 mM), the chemical shifts of protons NH_A and NH_B of (*S*,*S*,*S*)-(+)-**1** (6.55 and 8.68 ppm, respectively) and those of the corresponding protons in (*S*,*S*,*S*)-(+)-**3** (6.50 and 8.32 ppm, respectively) are very similar, indicating that no collapse of the cavity of the macrobicyclic receptor during formation of intramolecular H-bonds had occurred. Similarly, the chemical shifts of the aromatic protons of the two compounds did not significantly differ; the absence of aromatic–aromatic interactions in (*S*,*S*,*S*)-(+)-**1** further supports the absence of any collapse of the cavity. Additional support for an open cavity in the macrobicyclic receptor was derived from molecular modelling studies. A Monte Carlo (MC) multiple minimum conformational search[21] within MacroModel/Batchmin V. 5.0[22] (>5000 steps) using the AMBER force field[23] and the GB/SA (generalised born solvent accessible surface area) solvation model for $CHCl_3$[24] found only low-energy conformations with open cavities for (*S*,*S*,*S*)-(+)-**1**. A few of them, still with open cavities, contained an intramolecular C=O · · · H–N hydrogen bond (seven-membered ring) within one or more spacer arms, but as mentioned above no experimental evidence supports the relevance of such an H-bond in (*S*,*S*,*S*)-(+)-**1**.[25] The lowest energy conformation found, a structure with no intramolecular H-bond, is shown in Fig. 1. It can be clearly seen, especially from the top view onto one of the 1,3,5-triarylbenzene moieties, that the molecule has an overall chiral twist introduced by the amino acid spacers. This twist transfers chirality, which at first glance seems to reside only on the periphery, to the interior of the cavity where the hydrogen bonding sites become aligned in a helical orientation.

^{1}H NMR complexation studies

A series of ^{1}H NMR binding titrations at a constant receptor concentration were undertaken in the non-competitive solvent $CDCl_3$. Initially, a group of *N*-protected amino acids was investigated as substrates; they all formed moderately stable 1:1 host–guest complexes with (*S*,*S*,*S*)-(+)-**1** for which very similar binding free energies ($-\Delta G$ = 10.9–12.1 kJ mol^{-1}) were measured (Table 1, entries 2–5). A similar association mode seems likely in these associations. The large downfield shift of the NH_A resonance suggests as the major binding mode bidentate H-bonding of one spacer arm of the receptor to the COOH moiety of the substrate (Fig. 2), possibly complemented by a minor contribution from H-bonding between the carbamate protecting group and a second spacer arm.

Consistent with the proposed binding mode, α,ω-dicarboxylic acids proved to be higher affinity guests. The excitatory amino acid derivative *N*-Cbz-L-Asp (Cbz = benzyloxycarbonyl) was complexed by (*S*,*S*,*S*)-(+)-**1** in $CDCl_3$ with a binding free energy of 14.6 kJ mol^{-1} (Table 1, entry 6). From a 'reverse' titration experiment at varying concentrations of (*S*,*S*,*S*)-(+)-**1**, upfield shifts at saturation binding between 0.5 and 0.7 ppm were calculated for the CH and CH_2COOH resonances, respectively, of the amino acid derivative. These shifts support the notion that complexation takes place inside the cavity, especially since no such shifts were observed with 2,2-diphenylsuccinic acid, which is too large to fit inside the macrobicyclic binding site.

Examining the interaction of (*S*,*S*,*S*)-(+)-**1** with both enantiomers of *N*-Cbz-Glu in $CDCl_3$ showed that the ^{1}H NMR resonances of the sample containing the L-enantiomer were

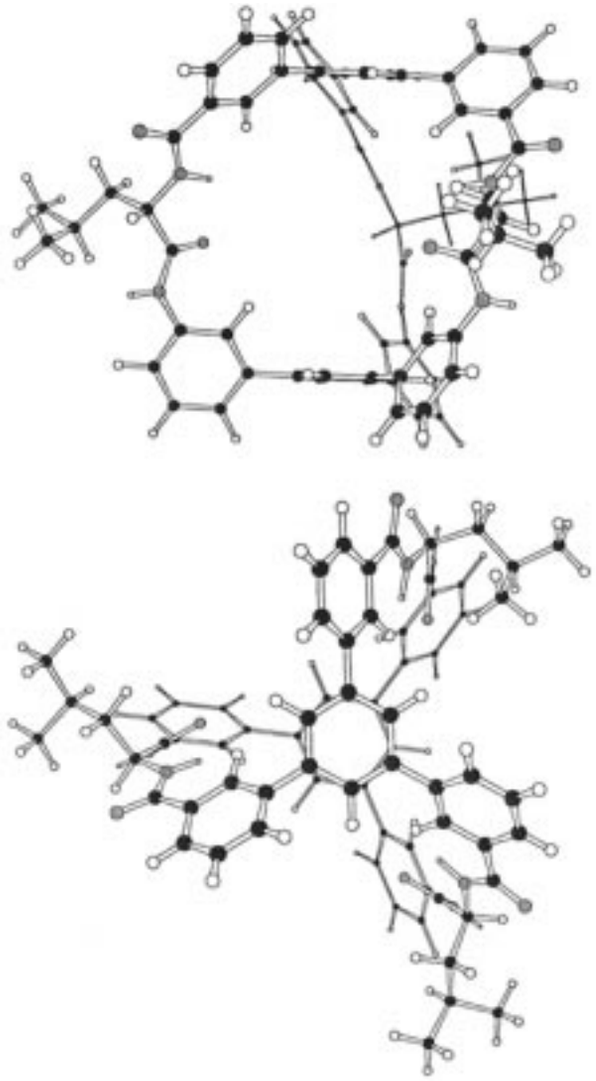


Fig. 1 View into the cavity (top) and onto the CO-substituted 1,3,5-triaryl moiety (bottom) of the lowest energy conformer of (*S*,*S*,*S*)-(+)-**1** as found by molecular modelling

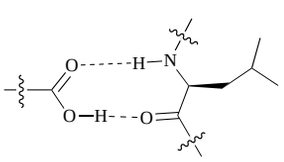


Fig. 2 Major interaction in the binding of *N*-protected amino acids to (*S*,*S*,*S*)-(+)-**1** and (*S*,*S*,*S*)-(+)-**2**

dramatically broadened at 300 K, whereas no such broadening was seen with the D-enantiomer. This is indicative of significant enantioselectivity in complexation, which could not be quantified due to slow exchange. This problem was overcome by changing the solvent from $CDCl_3$ to $CDCl_2CDCl_2$. In this solvent, association free energies were somewhat lower, as shown in studies with *N*-Cbz-L-Asp and glutaric acid (Table 1, entries 6 and 7), and ^{1}H NMR signals remained sufficiently sharp throughout the titration for evaluation of the binding strength. This is similar to the results of Whitlock and Whitlock,[26] who also observed a lower binding affinity with cyclophane receptors in $CDCl_2CDCl_2$ as compared to $CDCl_3$, but contrasts with the findings of Chapman and Still.[27] The latter observed a large increase in association strength with a H-bonding macrobicyclic receptor upon changing from the smaller ($CHCl_3$) to the larger solvent ($CDCl_2CDCl_2$). Clearly, there exists no general linear relationship between solvent size and binding strength, but rather the size of an individual cyclophane cavity determines whether one or more solvent molecules are complementary and will inhibit complexation through efficient solvation. In $CDCl_2CDCl_2$, the enantioselectivity (*i.e.* the difference in stability between the diastereoisomeric complexes) in the recognition of *N*-Cbz-protected L- and D-Glu by (*S*,*S*,*S*)-(+)-**1** amounted to $\Delta(\Delta G) = 4.2$ kJ mol^{-1} (entries 8 and 9). Dilution studies established that the free host is present in a monomeric, non-aggregated state and that the (aggregation) state of the free carboxylic acid substrates does not change under the titration conditions. Thus, the ^{1}H NMR resonance of the NH proton of the *N*-Cbz-L-Glu appeared at a nearly identical value ($\Delta\delta = 0.06$) in the concentration range 1–21 mM.

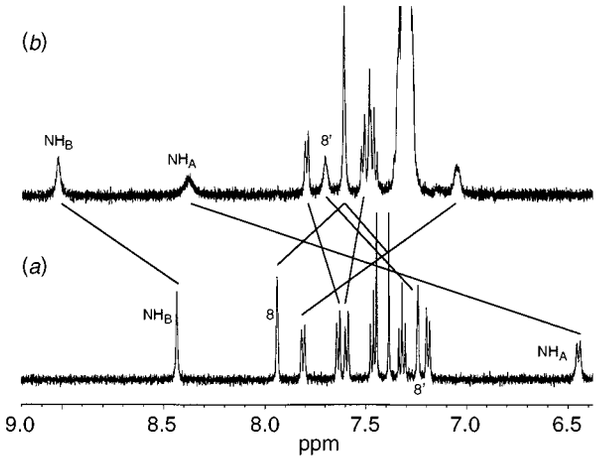


Fig. 3 Aromatic region of the ^{1}H NMR spectra (500 MHz, $CDCl_2CDCl_2$) of (*a*) (*S*,*S*,*S*)-(+)-**1** (1.0 mM) and (*b*) (*S*,*S*,*S*)-(+)-**1** (1 mM) + *N*-Cbz-L-Glu (15 mM, 80% saturation)

Fig. 3 shows the changes in the ^{1}H NMR spectrum that occur upon complexation of *N*-Cbz-L-Glu to (*S*,*S*,*S*)-(+)-**1** at 80% saturation binding. The large downfield shift (2 ppm) of the signal of NH_A, a proton expected (based on the computer modelling) to point into the macrobicyclic binding site, is indicative of strong intracavity hydrogen bonding. This is in contrast to the much smaller shift of the resonance of the more externally directed proton NH_B. In addition, sizeable differential up- and down-field shifts of the signals of the aromatic protons of the receptor are seen. They result both from anisotropic shielding and deshielding effects of the guest as well as from possible conformational changes of the receptor upon binding, although the latter are expected to be minor (see below). No shifts in the aromatic resonances were observed in the association of reference (*S*)-(+)-**3** to *N*-Boc-Gly (Table 1, entry 1).

Receptor (*S*,*S*,*S*)-(+)-**2** showed similar enantioselective binding of *N*-Cbz-protected L- and D-Glu, although the measured association free energies were somewhat lower (Table 1, entries 12 and 13). Replacing the Cbz by the smaller butyl carbamate group led to a reduced enantioselectivity (entries 10 and 11). The possible interaction between the carbamate moiety and the receptor was confirmed by a ^{1}H{^{1}H}-ROESY spectrum ($CDCl_2CDCl_2$)[28] of the solution of (*S*,*S*,*S*)-(+)-**1** (14 mM) and *N*-Cbz-L-Glu (82 mM) which showed cross peaks between the resonances of the Cbz methylene protons of the guest and the Leu side-chain protons of the receptor.

Extraction and solubilisation studies

To confirm the enantioselective recognition of *N*-Cbz-L-Glu by (*S*,*S*,*S*)-(+)-**1**, solubilisation studies were undertaken. To this end, a solvent mixture was chosen in which pure *N*-Cbz-L-Glu was not soluble, *i.e.* no signals were visible in the ^{1}H NMR spectrum of a sonicated sample after a reasonable acquisition time (128 scans). A $CDCl_3$–CCl_4 1:3 mixture proved satisfactory for this purpose. When a mixture of solid (*S*,*S*,*S*)-(+)-**1** and an excess of solid *N*-Cbz-L-Glu was briefly sonicated, a 1:1.1 (±0.1) host–guest complex was solubilised, whereas the same experiment with *N*-Cbz-D-Glu yielded hardly any detect-

Table 1 Binding free energies $-\Delta G$ (kJ mol^{-1})[a] and, in parentheses, calculated (downfield) changes in chemical shift of receptor proton NH_A at saturation binding, determined by ^{1}H NMR titrations at 300 K[b]

Entry	Host	Guest	$-\Delta G$ ($\Delta\delta_{sat}$) $CDCl_3$	$-\Delta G$ ($\Delta\delta_{sat}$) $CDCl_2CDCl_2$	$\Delta(\Delta G)$[c]
1	(*S*)-(+)-**3**	*N*-Boc-Gly	8.8 (1.1)		
2	(*S*,*S*,*S*)-(+)-**1**	*N*-Boc-Gly	12.1 (0.8)		
3	(*S*,*S*,*S*)-(+)-**1**	*N*-Boc-L-Ser	12.1 (0.8)		
4	(*S*,*S*,*S*)-(+)-**1**	*N*-Boc-L-Phe	10.9 (0.8)		
5	(*S*,*S*,*S*)-(+)-**1**	*N*-Boc-L-Ala-L-Ala	11.7 (0.8)		
6	(*S*,*S*,*S*)-(+)-**1**	*N*-Cbz-L-Asp	14.6 (1.1)	13.0 (1.3)	
7	(*S*,*S*,*S*)-(+)-**1**	Glutaric acid	13.4 (1.9)	11.3 (2.1)	
8	(*S*,*S*,*S*)-(+)-**1**	*N*-Cbz-L-Glu		14.6 (2.4)	
9	(*S*,*S*,*S*)-(+)-**1**	*N*-Cbz-D-Glu		10.5 (2.0)	4.2
10	(*S*,*S*,*S*)-(+)-**1**	*N*-BuOCO-L-Glu		13.8 (2.5)	
11	(*S*,*S*,*S*)-(+)-**1**	*N*-BuOCO-D-Glu		11.3 (2.1)	2.5
12	(*S*,*S*,*S*)-(+)-**2**	*N*-Cbz-L-Glu		13.4 (2.5)	
13	(*S*,*S*,*S*)-(+)-**2**	*N*-Cbz-D-Glu		8.8 (2.4)	4.6

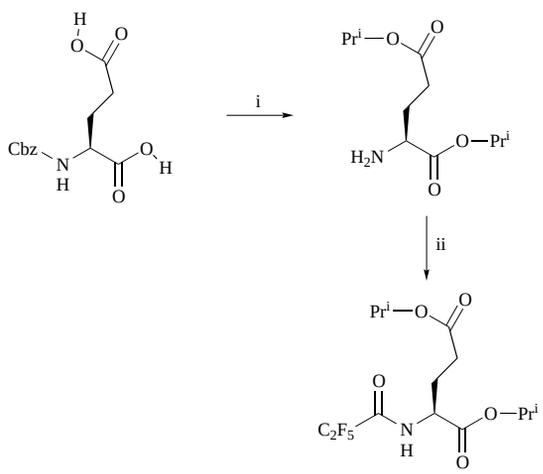
[a] Apparent binding free energies obtained from fitting the titration data to a 1:1 model, based on the evaluation of several aromatic protons of the receptor and proton NH_A. Estimated error in ΔG: ±0.6 kJ mol^{-1}. The non-linear least-squares curve fittings of the experimental data were not always fully in support of exclusive 1:1 host–guest complexation, due to additional weak external association. [b] [Host] = 5 mM (entry 1) or 0.5–1.0 mM (entries 2–13); [guest] = 0.5–50 mM. [c] Enantioselectivity, *i.e.* difference in stability between diastereoisomeric complexes (kJ mol^{-1}).

able solubilisation of either host or guest. Thus, *N*-Cbz-L-Glu and (*S*,*S*,*S*)-(+)-**1** solubilise each other, since they are both insoluble in this solvent mixture but their complex is soluble. In the ^{1}H NMR spectrum of the complex in $CDCl_3$–CCl_4 1:3, each of the three spacer arms of the receptor now gives a separate signal, because host–guest exchange is slow on the ^{1}H NMR timescale, whereas it was fast in $CDCl_2CDCl_2$ (Fig. 3). In $CDCl_3$, the exchange was at an intermediate rate resulting in only extremely broad signals, as mentioned earlier. These observations show that the host–guest exchange kinetics parallel the thermodynamic association strength in the various solvents: with increasing binding free energy, complexation–decomplexation rates become increasingly reduced.

Solubilisation was also observed when an excess of racemic (±)-*N*-Cbz-Glu was employed. The racemic substrate employed here represents a 1:1 mixture of pure crystalline enantiomers (*i.e.* an artificial conglomerate[29]) rather than crystals of racemic (±)-*N*-Cbz-Glu, prepared by protecting (±)-Glu, which is a racemic compound.[29] The latter has a melting point 7–8 °C higher than that of the individual crystalline enantiomers and is much less efficiently solubilised.

The observed solubilisation using the 1:1 mixture of enantiomers prompted us to determine the solubilisation efficiency as well as the enantioselectivity. First the efficiency was determined by ^{1}H NMR integration with the help of an internal standard [2,7-bis(benzyloxy)-3-bromonaphthalene[17]]. It was determined that 80 (±15)% of (*S*,*S*,*S*)-(+)-**1** was solubilised, even when its amounts as a solid varied from 1–4 mg per ml of solvent (keeping at least a seven-fold excess of racemic substrate). This means that the solubility of the complex is at least ≈2.6 mM, which is considerable since it consists of two insoluble (solubilities lower than ≈0.2 mM) components.

To determine the enantiomer ratio of the solubilised substrate, an established derivatisation protocol combined with gas chromatographic (GC) analysis on a chiral stationary phase was utilised.[30] This derivatisation normally starts from the free amino acid, but worked here for Cbz-protected glutamic acid because in the first step, an acid-catalysed esterification of the two COOH groups with Pr^{i}OH, the Cbz group was also cleaved (Scheme 2). In the second step, reaction of the amino group of the formed diisopropyl glutamate with pentafluoropropionic anhydride yielded the volatile pentafluoropropylamide, whose enantiomers were separated on a chiral GC capillary column. The enantiomeric ratio of the solubilised *N*-Cbz-Glu, as determined by this procedure, was found to be around 5:1 in favour of the L-enantiomer, consistent with the titration results. The actual selectivity of the cavity binding site is probably even



Scheme 2 Derivatisation of *N*-Cbz-Glu for determination of its enantiomer ratio by GC analysis on a chiral column; only one enantiomer is shown.[30] i HCl, Pr^{i}OH, 110 °C, 80 min. ii $(C_2F_5CO)_2O$, CH_2Cl_2, 110 °C, 15 min.

higher, because in the solubilisation generally a little more than one equivalent of *N*-Cbz-Glu is solubilised (up to 1.2 equiv.) and this extra material is probably non-selectively associated to the exterior of the receptor.

Molecular modelling of the complex between (*S*,*S*,*S*)-(+)-1 and *N*-Cbz-L-Glu

A Monte Carlo (MC) multiple minimum conformational search[21] within MacroModel/Batchmin V. 5.0[22] (>15 000 steps) using the AMBER* force field[23] of the complex between (*S*,*S*,*S*)-(+)-**1** and *N*-Cbz-L-Glu was undertaken. The search yielded a series of eight closely related conformations within 12.6 kJ mol^{-1}, the lowest of which is shown in Fig. 4. They all contain five short hydrogen bonds, two from each of the COOH groups of the guest to two of the spacer arms of the host, according to the binding mode shown in Fig. 2. The fifth hydrogen bond is formed between the carbonyl group of the *cis*-carbamate to the amide proton NH_A of the third spacer arm. Also, in seven of the eight low energy conformers the protons of the Cbz methylene group of the guest are in close proximity (<3.0 Å) to those of one Leu side-chain of the receptor, consistent with the ^{1}H{^{1}H}-ROESY spectrum of the complex (see above).

Preparation of chiral stationary phases for HPLC separations

Chiral stationary phases derived from the new receptors were

prepared from the tris(tyrosine) analogue of (*S*,*S*,*S*)-(+)-**2**, using the extra OH groups as points of attachment to the solid phase. For reference, an open-faced analogue, lacking a 1,3,5-triarylbenzene 'ceiling' was prepared.

The synthesis of the chiral selectors (Scheme 3) for attachment to the solid phase started from the *N*-Boc-protected tyrosine derivative (*S*)-**8**,[31] which was coupled (EDC·HCl, DMAP) with triamine **4** to yield triamide (*S*,*S*,*S*)-(+)-**9**. The Boc groups were removed with TFA to afford (*S*,*S*,*S*)-(+)-**10**. The open-faced chiral selector (*S*,*S*,*S*)-(+)-**11** was obtained by reaction of (*S*,*S*,*S*)-(+)-**10** with acetyl chloride, whereas macrobicyclic (*S*,*S*,*S*)-(−)-**12** was isolated in 20% yield from the reaction with tris(acyl halide) **7**.

The chiral selectors were each attached to silica gel, following a previously published procedure.[14,32,33] For this purpose, silica gel (Lichrosorb Si60, particle size 5 μm) was reacted with (3-mercaptopropyl)trimethoxysilane to introduce the thiol functions (Scheme 4). This modified silica gel **13** was then coupled to (*S*,*S*,*S*)-(−)-**12** or (*S*,*S*,*S*)-(+)-**11** *via* a radical chain reaction to give the CSPs (*S*,*S*,*S*)-**14** and (*S*,*S*,*S*)-**15**, respectively. Characterisation of the modified silica gels was carried out by elemental analysis according to the method of Berendsen and de Galan.[34] The degree of functionalisation with chiral selector was 0.06 mmol g^{-1} (0.12 μmol m^{-2}) for both CSPs (*S*,*S*,*S*)-**14** and (*S*,*S*,*S*)-**15**, based on carbon analysis.

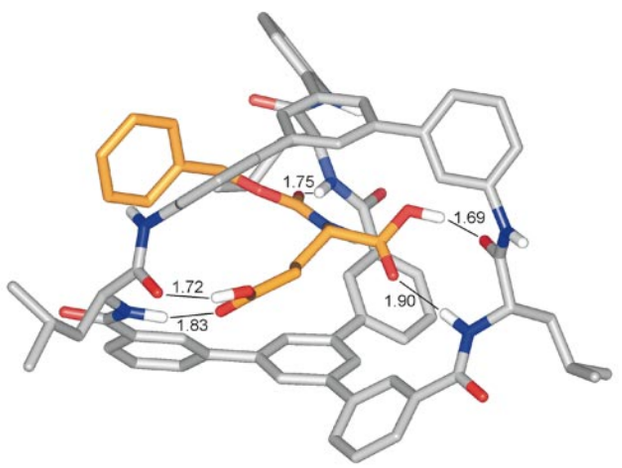
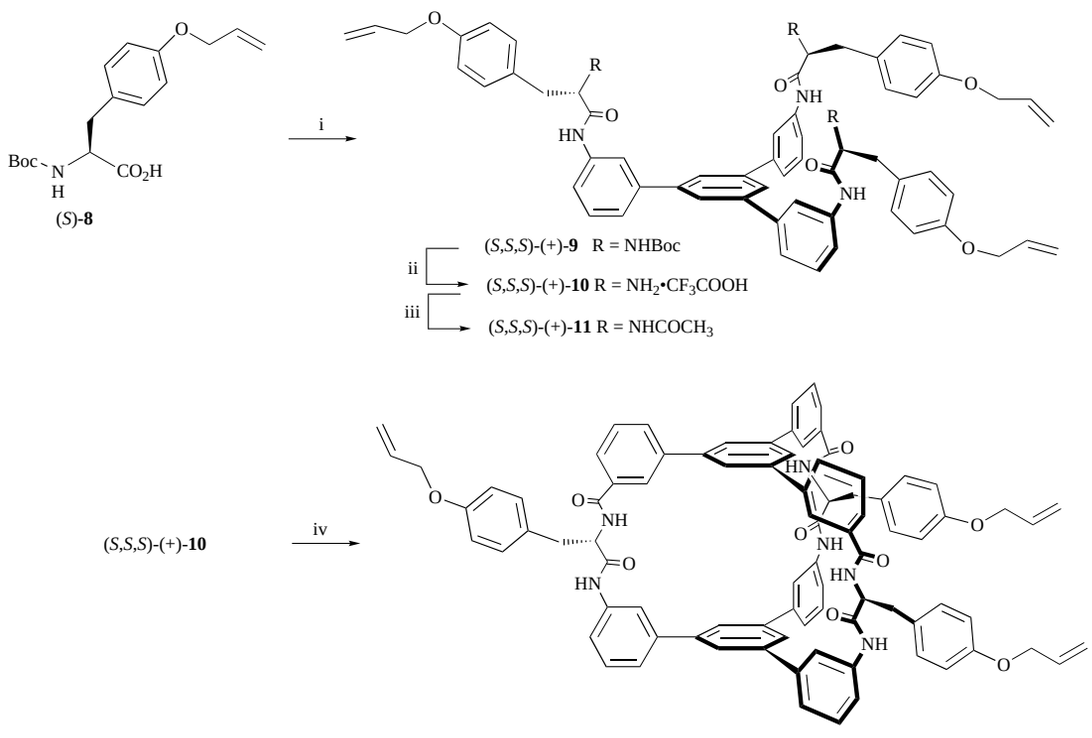


Fig. 4 Lowest energy conformer of the complex between (*S*,*S*,*S*)-(+)-**1** and *N*-Cbz-L-Glu, as found by molecular modelling. The five host–guest hydrogen bonds (in Å) are shown.

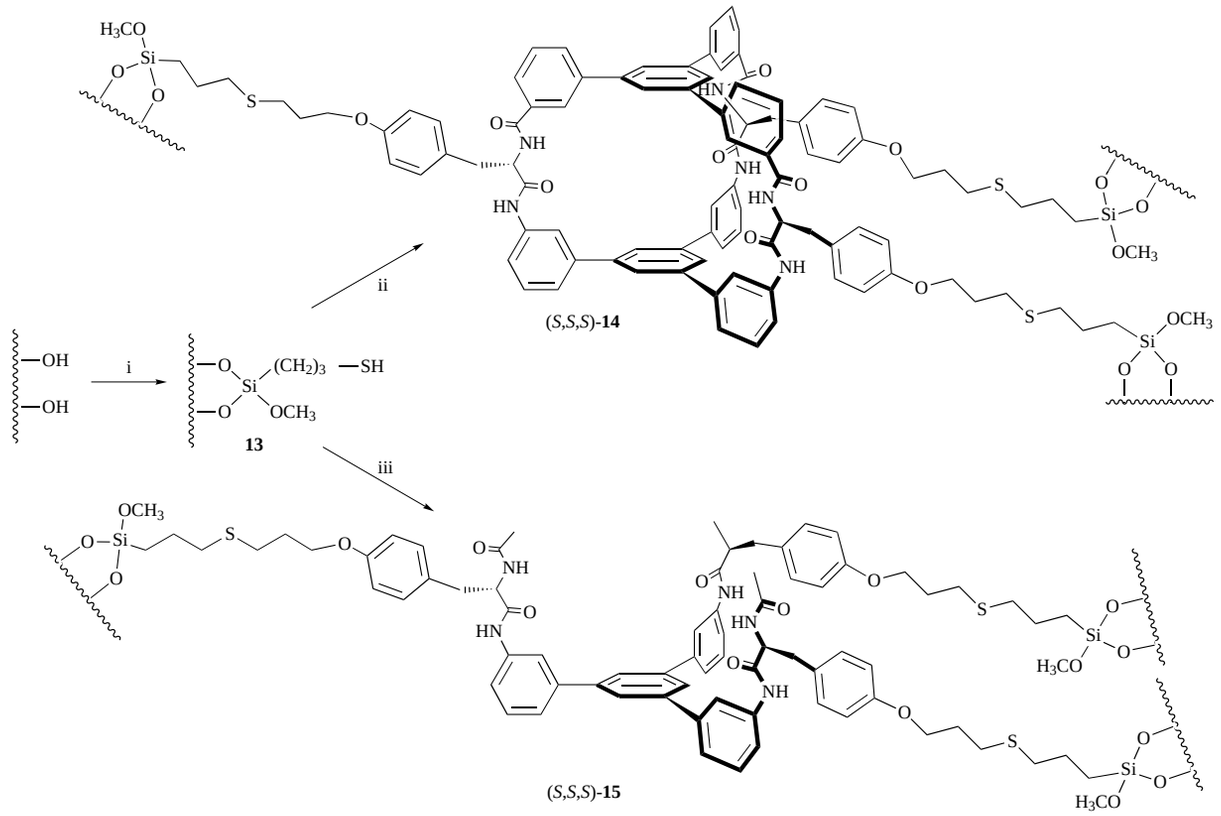
HPLC separations of 1,1′-binaphthyl-2,2′-diol on CSPs (*S*,*S*,*S*)-14 and (*S*,*S*,*S*)-15

The initial focus of the HPLC studies was to separate the enantiomers of the *N*-Cbz-protected excitatory amino acids Glu and Asp and to correlate the results obtained on the solid phases with those of the solution studies described above (Table 1). All attempts, however, to resolve the excitatory amino acid derivatives or other amino acid derivatives such as *N*-Boc-protected Phe failed on both CSPs. One likely explanation why the results from the liquid phase did not translate to the solid phase is the fact that different solvents were employed. The liquid phase studies were conducted in $CDCl_2CDCl_2$, whereas the eluent in the HPLC studies was CH_2Cl_2 containing various amounts of MeOH (1–5% v/v), which was required for the elution of the polar substrates. However, MeOH competes effectively for the complex-forming hydrogen bonds which determine the differential stability of the diastereoisomeric associations between the solute enantiomers and the chiral selector.

On the other hand, the enantiomers of 1,1′-binaphthyl-2,2′-diol derivatives, which are among the most useful chiral shapes in stereoselective catalysis[35] and supramolecular chemistry,[17,36] could be separated on both CSPs (*S*,*S*,*S*)-**14** and (*S*,*S*,*S*)-**15** using a non-competitive solvent mixture as eluent (Table 2). As illustrated by Fig. 5, the (*S*)-enantiomer of (±)-**17** [as well as of (±)-**16**] was eluted first, showing that it undergoes the weaker association with the chiral selectors. The optical resolution of (±)-1,1′-binaphthyl-2,2′-diols on CSP (*S*,*S*,*S*)-**14** is surprising in the sense that these solutes only partially fit into the cavity of the chiral selector. The enantiomer separation must therefore mostly be due to external association by a combination of hydrogen bonding and aryl–aryl interactions.



Scheme 3 Synthesis of the chiral selectors (*S*,*S*,*S*)-(+)-**11** and (*S*,*S*,*S*)-(−)-**12**. i **4**, EDC·HCl, cat. DMAP, THF, 24 h, 82%. ii CF_3COOH–CH_2Cl_2 1:1, 1 h, 99%. iii CH_3COCl, NEt_3, 12 h, 80%. iv **7**, NEt_3, THF, 16 h, 20%.

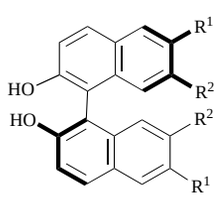


Scheme 4 Synthesis of the new CSPs (*S*,*S*,*S*)-**14** and (*S*,*S*,*S*)-**15**. i (3-Mercaptopropyl)trimethoxysilane, PhMe, pyridine, Δ, 20 h. ii (*S*,*S*,*S*)-(−)-**12**, α,α′-azobis(isobutyronitrile) (AIBN), $CHCl_3$, Δ, 25 h, 75%. iii (*S*,*S*,*S*)-(+)-**11**, AIBN, $CHCl_3$, Δ, 25 h, 83%.

Table 2 HPLC separation of enantiomers of 1,1′-binaphthyl-2,2′-diols on CSPs (*S*,*S*,*S*)-**14** and (*S*,*S*,*S*)-**15** [flow rate = 1.0 ml min^{-1}; retention time of non-retained solute t_O = 2.89 and 2.67 min, respectively; *T* = 295 K; UV (254 nm) detection]

Entry	CSP	Solute	$K_1'^a$	α^b	Eluent (v/v)
1	**14**	(±)-**16**	3.40	1.08	Hexane–CH_2Cl_2 50:50
2	**14**	(±)-**17**	8.46	1.12	Hexane–CH_2Cl_2 50:50
3	**15**	(±)-**16**	7.82	1.04	Hexane–CH_2Cl_2 80:20
4	**15**	(±)-**17**	2.18	1.32	Hexane–CH_2Cl_2 50:50

[a] Capacity factor of the first eluted enantiomer $[(t_R - t_O)/t_O]$, where t_R is the retention time. [b] Selectivity (K_2'/K_1').



16 $R^1 = R^2 = H$

17 R^1 = Br; R^2 = BnO

Conclusions

New cage-like chiral, C_3-symmetric receptors (*S*,*S*,*S*)-(+)-**1** and (*S*,*S*,*S*)-(+)-**2** were prepared by a short, convergent synthesis. They contain open, non-collapsed cavities with hydrogen bonding sites in a chiral (helical) orientation and associate with carboxylic acids *via* hydrogen bonding in non-competitive solvents. ^{1}H NMR titrations in $CDCl_2CDCl_2$ revealed that the two optically active receptors bound *N*-Cbz-protected L- and D-Glu enantioselectively with differences in formation free energy between the diastereoisomeric complexes [Δ(Δ*G*)] of up to 4.6 kJ mol^{-1}. The more stable diastereoisomeric complex formed between (*S*,*S*,*S*)-(+)-**1** and *N*-Cbz-L-Glu was efficiently solubilised in $CDCl_3$–CCl_4 1:3, a solvent mixture in which neither component had a significant solubility. No such solubilisation was observed when the weaker binding *N*-Cbz-D-Glu was used. When a racemic mixture of *N*-Cbz-Glu was employed, the L-enantiomer was solubilised over its antipode by a >5:1 ratio. Compounds (*S*,*S*,*S*)-(+)-**1** and (*S*,*S*,*S*)-(+)-**2** are selective receptors although their affinity for the guests is relatively moderate. We believe that this high selectivity is due to the cage-like architecture of the system, which creates specific size and shape requirements for guests and imposes specific constraints for the three-dimensional orientation of their hydrogen bonding groups. Immobilisation of the optically active receptors as chiral selectors on modified silica gel led to the new chiral stationary phases (CSPs) (*S*,*S*,*S*)-**14** and (*S*,*S*,*S*)-**15**. Racemic *N*-protected amino acids could not, however, be optically resolved on these phases due to incompatibility of the HPLC conditions, which require the use of MeOH as co-solvent for elution of the polar solutes, with efficient host–guest association *via* hydrogen bonding. In contrast, enantiomers of 1,1′-binaphthyl-2,2′-diols could be readily separated on the two CSPs by eluting with non-competitive hexane–CH_2Cl_2 mixtures. The results from the solid phase studies, which are now continued with other classes of substrates, further corroborate the important role of hydrogen bonding in the enantioselective recognition by the new cage-type receptors.

Experimental

General

Reagent-grade chemicals were purchased from Fluka or Aldrich and used without further purification unless otherwise stated. THF was freshly distilled from sodium benzophenone ketyl. $CHCl_3$ was purified by washing with H_2O and then distilling over P_2O_5. Compound (*S*)-**8** was synthesized according to a published procedure.[31] Thin layer chromatography: E. Merck plates precoated with silica gel F_{254}. Column chromatography: E. Merck silica gel 60 (0.040–0.063 mm). Mp: Büchi Smp-20 apparatus, uncorrected. Optical rotation: Perkin-Elmer-241 polarimeter (at room temp. = 295 ± 1 °C, unless stated other-

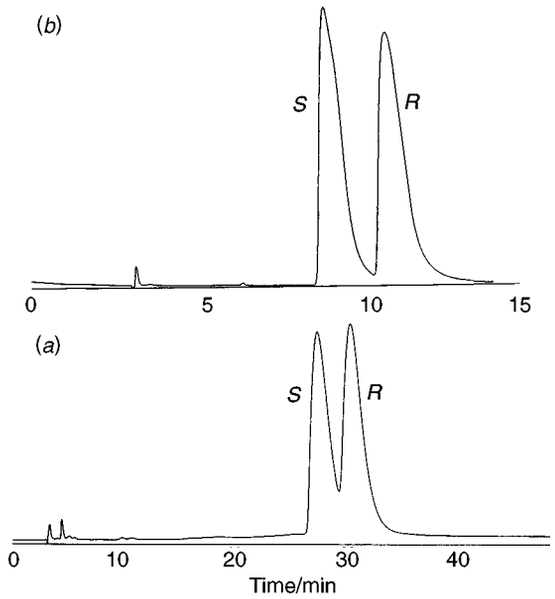


Fig. 5 Optical resolution of (±)-**17** by HPLC on CSPs (*S*,*S*,*S*)-**14** (*a*) and (*S*,*S*,*S*)-**15** (*b*); eluent hexane–CH_2Cl_2 50:50 (v/v); flow rate 1 ml min^{-1}; UV (254 nm) detection

wise). IR spectra: Perkin-Elmer 1600-FTIR instrument. ^{1}H- and ^{13}C-NMR spectra: Bruker AMX 500, Varian Gemini 200 or Varian Gemini 300 spectrometers, *J* values are given in Hz. GC-analysis: Carlo Erba Series 4160 gas chromatograph. FABMS: VG ZAB 2 SEQ instrument, 3-nitrobenzyl alcohol as matrix, positive mode. Elemental analysis: Mikrolabor des Laboratoriums für Organische Chemie at ETHZ.

(*S*,*S*,*S*)-(−)-1,3,5-Tris{3-[2-(*tert*-butoxycarbonylamino)-4-methylpentanoylamino]phenyl}benzene, (*S*,*S*,*S*)-(−)-5a

To **4** [18,19] (300 mg, 0.855 mmol) in THF (50 ml) was added Boc-L-leucine monohydrate (661 mg, 2.65 mmol), DMAP (31 mg, 0.256 mmol) and EDC·HCl (820 mg, 4.27 mmol), and the mixture was stirred for 14 h at room temp. After evaporation, CH_2Cl_2 (150 ml) was added and the resulting solution was washed with 1% aq. HCl solution (60 ml), sat. aq. $NaHCO_3$ solution (60 ml) and sat. aq. NaCl solution (60 ml). After drying (Na_2SO_4) and evaporation, the residue was purified by column chromatography over SiO_2 (CH_2Cl_2–MeOH 19:1) to give (*S*,*S*,*S*)-(−)-**5a** (510 mg, 60%) as an off-white solid; mp 170 °C (decomp.) [Found: C, 68.82; H, 7.95; N, 8.51. Calc. for $C_{57}H_{78}N_6O_9$ (991.3): C, 69.07; H, 7.93; N, 8.48]; $[a]_D^{23} = -3$ (*c* = 0.62, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3313m, 2958m, 1670s, 1497m, 1367m, 1165s, 1048w, 870w, 785w, 698w; δ_H[500 MHz, $(CD_3)_2SO$] 9:1 carbamate rotamer mixture,[37] major rotamer: 0.89 (9 H, d, *J* 6.5), 0.90 (9 H, d, *J* 6.5), 1.37 (27 H, s), 1.40–1.50 (3 H, m), 1.51–1.59 (3 H, m), 1.61–1.70 (3 H, m), 4.11–4.18 (3 H, m), 7.03 (3 H, d, *J* 8.0), 7.45 (3 H, t, *J* 7.5), 7.51 (3 H, d, *J* 7.5), 7.75 (3 H, d, *J* 7.5), 7.79 (3 H, s), 7.97 (3 H, s), 10.07 (3 H, s); separate signals minor rotamer: 1.31 (27 H, s), 4.00 (3 H, br s), 6.62 (3 H, br s), 9.98 (3 H, br s); δ_C[125.76 MHz, $(CD_3)_2SO$] (only major rotamer visible): 21.49, 22.92, 24.32, 28.16, 40.63, 53.58, 77.98, 117.60, 118.61, 121.90, 124.20, 129.44, 139.67, 140.36, 141.59, 155.42, 171.91; *m/z* (FABMS) 691 [(M − 3 Boc + H)$^+$, 100%], 578 (17%).

(11*S*,31*S*,48*S*)-11,31,48-Tris(2-methylpropyl)-9,12,30,33,46,49-hexaazadecacyclo[19.19.15.1^{3,39}.1^{4,8}.1^{14,18}.1^{19,23}.1^{24,28}.1^{34,38}.1^{41,45}.1^{51,55}]trihexaconta-1,3(58),4(63),5,7,14(62),15,17,19,21,23(61),24(60),25,27,34,36,38(59),39,41,43,45(57),51(56),52,54-tetracosaene-10,13,29,32,47,50-hexone, (*S*,*S*,*S*)-(+)-1

Tricarbamate (*S*,*S*,*S*)-(−)-**5a** (1.16 g, 1.17 mmol) was stirred for 1 h in CH_2Cl_2–TFA 1:1 (20 ml), after which the mixture was concentrated and dried at high vacuum to give (*S*,*S*,*S*)-**6a** (1.21 g, 100%) as a light brown salt which was used as such in the next step; δ_H[200 MHz, $(CD_3)_2SO$] 0.94 (18 H, d, *J* 4.7), 1.60–1.80 (9 H, m), 3.90–4.04 (3 H, m), 7.51 (3 H, t, *J* 7.8), 7.60 (3 H, d, *J* 7.8), 7.75 (3 H, d, *J* 7.8), 7.82 (3 H, s), 7.99 (3 H, s), 8.30 (9 H, br s), 10.75 (3 H, s). The crude salt (*S*,*S*,*S*)-**6a** together with **7** (598 mg, 1.211 mmol) and NEt_3 (1.01 ml, 7.27 mmol) were stirred in THF (1.2 l) for 2 h at 0 °C, then for 14 h at room temp. The solvent was evaporated and the residue purified by column chromatography (SiO_2, CH_2Cl_2–MeOH 19:1), followed by radial chromatography (SiO_2, CH_2Cl_2–MeOH 19:1) to give (*S*,*S*,*S*)-(+)-**1** (121 mg, 10%) as a white solid; mp >300 °C (Found: $[M + H]^+$, 1075.5135. $C_{69}H_{67}N_6O_6^+$ requires 1075.5122); $[a]_D^{23} = +78$ (*c* = 0.42, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3318m, 2956m, 1653s, 1584s, 1540s, 1490s, 1303m, 789w, 698m; δ_H(500 MHz, $CDCl_3$, 1 mM) 1.01 (9 H, d, *J* 6.5), 1.04 (9 H, d, *J* 6.5), 1.70–1.80 (6 H, m), 1.95–2.05 (3 H, m), 4.87–4.92 (3 H, m), 6.55 (3 H, d, *J* 9.7), 7.15 (3 H, s), 7.20 (3 H, d, *J* 7.8), 7.34 (3 H, t, *J* 7.8), 7.44 (3 H, s), 7.46 (3 H, t, *J* 8.1), 7.48 (3 H, s), 7.59 (3 H, d, *J* 8.1), 7.65 (3 H, d, *J* 8.1), 7.99 (3 H, d, *J* 7.8), 8.09 (3 H, s), 8.68 (3 H, s); δ_C(125.76 MHz, $CDCl_3$–CD_3OD 5:1) 21.95, 22.48, 24.72, 38.62, 52.36, 118.39, 120.42, 122.90, 125.90, 126.15, 126.63, 128.27, 128.72, 128.97, 130.43, 133.25, 138.13, 142.01, 142.30, 142.39, 142.62, 167.88, 170.49.

(*S*,*S*,*S*)-(−)-1,3,5-Tris{3-[2-(*tert*-butoxycarbonylamino)-3-phenylpropanoylamino]phenyl}benzene, (*S*,*S*,*S*)-(−)-5b

A mixture of **4** (1.000 g, 2.849 mmol), Boc-L-phenylalanine (2.343 g, 8.832 mmol), EDC·HCl (2.731 g, 14.245 mmol) and DMAP (104 mg, 0.855 mmol) in THF (100 ml) was stirred overnight. After evaporation, AcOEt (200 ml) was added to the residue, the insoluble part was filtered off and the residual solution was washed with a sat. aq. $NaHCO_3$ solution (75 ml), aq. HCl solution (2 × 75 ml) and sat. aq. NaCl solution (75 ml). Drying (Na_2SO_4) and evaporation yielded (*S*,*S*,*S*)-(−)-**5b** (2.130 g, 68%) as an off-white solid; mp 160 °C (decomp.) [Found: C, 72.29; H, 6.52; N, 7.80. Calc. for $C_{66}H_{72}N_6O_9$ (1093.3): C, 72.49; H, 6.64; N, 7.69]; $[a]_D^{23} = -11$ (*c* = 0.63, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3309m, 2977w, 1668s, 1497s, 1367m, 1165s, 785w, 698m; δ_H[500 MHz, $(CD_3)_2SO$] 8:1 carbamate rotamer mixture, major rotamer: 1.31 (27 H, s), 2.86 (3 H, dd, *J* 13.5, 10.3), 3.03 (3 H, dd, *J* 13.5, 4.5), 4.32–4.39 (3 H, m), 7.12 (3 H, d, *J* 8.2), 7.19 (3 H, t, *J* 7.3), 7.26 (6 H, t, *J* 7.3), 7.32 (6 H, d, *J* 7.3), 7.47 (3 H, t, *J* 7.6), 7.53 (3 H, d, *J* 7.6), 7.73 (3 H, d, *J* 7.6), 7.81 (3 H, s), 7.94 (3 H, s), 10.17 (3 H, s); separate signals minor rotamer: 1.23 (27 H, s), 4.23 (3 H, br s), 6.68 (3 H, br s), 10.12 (3 H, br s); δ_C[125.76 MHz, $(CD_3)_2SO$] (only major rotamer visible): 28.11, 37.47, 56.57, 78.08, 117.74, 118.78, 122.04, 124.25, 126.25, 128.01, 129.19, 129.48, 137.88, 139.52, 140.38, 141.59, 155.35, 170.91; *m/z* (FABMS) 793 [(M − 3 Boc + H)$^+$, 80%], 646 (15%), 120 (100%).

(11*S*,31*S*,48*S*)-11,31,48-Tris(phenylmethyl)-9,12,30,33,46,49-hexaazadecacyclo[19.19.15.1^{3,39}.1^{4,8}.1^{14,18}.1^{19,23}.1^{24,28}.1^{34,38}.1^{41,45}.1^{51,55}]trihexaconta-1,3(58),4(63),5,7,14(62),15,17,19,21,23(61),24(60),25,27,34,36,38(59),39,41,43,45(57),51(56),52,54-tetracosaene-10,13,29,32,47,50-hexone, (*S*,*S*,*S*)-(+)-2

Tricarbamate (*S*,*S*,*S*)-(−)-**5b** (1.831 g, 1.675 mmol) was stirred for 1 h in CH_2Cl_2–TFA 1:1 (20 ml), after which the mixture was evaporated and dried at 10^{-2} Torr to give (*S*,*S*,*S*)-**6b** (1.91 g, 100%) as a light brown salt which was used as such in the next step; δ_H[200 MHz, $(CD_3)_2SO$] 3.00–3.25 (6 H, m), 4.22 (3 H, br s), 7.17–7.38 (18 H, m), 7.45–7.58 (6 H, m), 7.79 (3 H, s), 7.88 (3 H, s), 8.38 (9 H, br s), 10.65 (3 H, s). To a stirred mixture of (*S*,*S*,*S*)-**6b** (1.305 g, 1.00 mmol) and NEt_3 (0.98 ml, 7.0 mmol) in THF (750 ml) at 0 °C, **7** (494 mg, 1.00 mmol) in THF (250 ml) was added dropwise over a period of 1 h, and the mixture was stirred for a further 12 h at room temp. After filtration, the residual solution was evaporated and purified twice by column chromatography (SiO_2, CH_2Cl_2–MeOH 19:1) to give (*S*,*S*,*S*)-(+)-**2** (32 mg, 3%) as a white solid; mp

275 °C (decomp.) (Found: $[M + H]^+$, 1177.4651. $C_{78}H_{61}N_6O_6^+$ requires 1177.4652); $[\alpha]_D^{23} = +22$ ($c = 0.35$, $CHCl_3$–MeOH 5:1); ν_{max}(KBr)/cm^{-1} 3333m, 3027w, 1654s, 1583s, 1522s, 1490s, 1303m, 788w, 749w, 697s; δ_H(500 MHz, $CD_2Cl_2CD_2Cl_2$, 1 mM) 3.16 (3 H, dd, *J* 14.3, 7.5), 3.35 (3 H, dd, *J* 14.3, 7.5), 4.93 (3 H, ddd, *J* 7.5, 7.5, 7.5), 6.50 (3 H, d, *J* 7.5), 7.17 (3 H, d, *J* 7.2), 7.18 (3 H, s), 7.23 (3 H, t, *J* 6.9), 7.28–7.35 (18 H, m), 7.38–7.45 (9 H, m), 7.60 (3 H, d, *J* 6.5), 7.73 (3 H, d, *J* 8.5), 7.84 (3 H, s), 8.21 (3 H, s); δ_C(125.76 MHz, $CDCl_3$–CD_3OD 5:1) 36.11, 55.19, 118.43, 120.53, 123.01, 125.91, 126.19, 126.60 (2×), 128.12, 128.38, 128.76, 128.95, 129.00, 130.44, 133.32, 136.83, 137.92, 141.98, 142.24, 142.44, 142.58, 167.86, 169.62.

2-Benzamido-4-methylpentananilide, (*S*)-(+)-3

A mixture of aniline (140 μl, 1.53 mmol), Boc-L-leucine monohydrate (421 mg, 1.69 mmol), EDC·HCl (500 mg, 2.608 mmol) and DMAP (19 mg, 0.15 mmol) in THF (30 ml) was stirred for 6 h. The solvent was evaporated, AcOEt (100 ml) was added and the insoluble part was removed by filtration. The residual solution was washed with 1% aq. HCl solution (50 ml), sat. aq. $NaHCO_3$ solution (50 ml) and sat. aq. NaCl solution (50 ml). Drying (Na_2SO_4) and evaporation yielded *N*-Boc-L-Leu-NHPhe (340 mg, 72%); δ_H(200 MHz, $CDCl_3$) 0.96 (3 H, d, *J* 2.8), 0.99 (3 H, d, *J* 3.2), 1.46 (9 H, s), 1.65–1.85 (2 H, m), 4.15–4.30 (1 H, m), 4.96 (1 H, d, *J* 8.3), 7.09 (1 H, t, *J* 7.5), 7.31 (2 H, t, *J* 7.5), 7.51 (2 H, d, *J* 7.5), 8.31 (1 H, br s). A solution of this material in CH_2Cl_2–TFA 1:1 (8 ml) was stirred for 1.5 h, evaporated, and dried. The resulting crude amine·TFA salt was dissolved in THF (25 ml) along with benzoyl chloride (129 μl, 1.11 mmol) and NEt_3 (308 μl, 2.22 mmol), and the mixture was stirred at room temp. for 3 h. The resulting precipitate was removed by filtration, and the filtrate was evaporated to dryness. The residue was redissolved in CH_2Cl_2 and washed with 10% aq. HCl solution (30 ml), sat. aq. $NaHCO_3$ solution (30 ml) and sat. aq. NaCl solution (30 ml). Drying (Na_2SO_4) and evaporation yielded (*S*)-(+)-**3** (230 mg, 48% starting from aniline) as a white solid; mp 200–203 °C (Found: C, 72.24; H, 6.86; N, 8.95. Calc. for $C_{19}H_{22}N_2O_2$·0.25 H_2O (314.9): C, 72.46; H, 7.21; N, 8.90); $[\alpha]_D^{22} = +57$ ($c = 0.42$, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3304m, 2958m, 1671m, 1634s, 1558m, 1445m, 1308m, 1252m, 752w, 688m; δ_H[500 MHz, $(CD_3)_2SO$] 0.92 (3 H, d, *J* 6.5), 0.94 (3 H, d, *J* 6.5), 1.57 (1 H, ddd, *J* 13.3, 8.6, 4.9), 1.69–1.84 (2 H, m), 4.66 (1 H, ddd, *J* 10.3, 7.9, 4.9), 7.03 (1 H, t, *J* 7.5), 7.29 (2 H, t, *J* 7.5), 7.46 (2 H, t, *J* 7.3), 7.53 (1 H, t, *J* 7.3), 7.62 (2 H, d, *J* 7.5), 7.91 (2 H, d, *J* 7.3), 8.57 (1 H, d, *J* 7.9), 10.09 (1 H, s); δ_C[125.76 MHz, $(CD_3)_2SO$] 21.45, 23.00, 24.53, 40.29, 52.73, 119.26, 123.21, 127.53, 128.14, 128.63, 131.27, 133.99, 139.02, 166.48, 171.39; *m/z* (FABMS) 311.2 [$(M + H)^+$, 100%].

(*S*,*S*,*S*)-(+)-1,3,5-Tris(3-{2-(*tert*-butoxycarbonylamino)-3-[4-(prop-2-enyloxy)phenyl]propanoylamino}phenyl)benzene, (*S*,*S*,*S*)-(+)-9

A mixture of (*S*)-**8** (1.47 g, 4.42 mmol),[31] **4** (500 mg, 1.42 mmol), DMAP (50 mg, 0.40 mmol) and EDC·HCl (1.37 g, 7.13 mmol) in THF (50 ml) was stirred at room temp. for 24 h. The solvent was evaporated, AcOEt was added to the residue and the formed precipitate was removed by filtration. The filtrate was washed with sat. aq. $NaHCO_3$ solution, 1 M aq. HCl, and sat. aq. NaCl solution. Drying (Na_2SO_4) and evaporation followed by drying (12 h, 0.05 Torr) afforded (*S*,*S*,*S*)-(+)-**9** (1.47 g, 82%) as a beige solid; mp 105 °C [Found: C, 71.25; H, 6.93; N, 6.53. Calc. for $C_{75}H_{84}N_6O_{12}$ (1261.52): C, 71.41; H, 6.71; N, 6.66]; $[\alpha]_D^{r.t.} = +16.3$ ($c = 1.00$, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3311br m, 2977w, 1668s, 1612s, 1511s, 1366s, 1244s, 1164s, 1023w, 765w, 697w; δ_H[500 MHz, $(CD_3)_2SO$] 1.32 (27 H, s) 2.77–2.98 (6 H, m), 4.29–4.30 (3 H, m), 4.47–4.49 (6 H, m), 5.20 (3 H, ddd, *J* 10.5, 3.1, 1.6), 5.34 (3 H, ddd, 17.3, 3.5, 1.6), 5.95–6.03 (3 H, m), 6.85 (6 H, d, *J* 8.5), 7.07 (3 H, d, *J* 8.2), 7.23 (6 H, d, *J* 8.5), 7.47 (3 H, t, *J* 7.7), 7.53 (3 H, d, *J* 7.7), 7.74 (3 H, d, *J* 7.7), 7.82 (3 H, s), 7.95 (3 H, s), 10.15 (3 H, s); δ_C[125.8 MHz, $(CD_3)_2SO$] 28.60, 37.09, 57.30, 68.51, 78.55, 114.71, 117.65, 118.19, 119.24, 122.49, 124.72, 129.96, 130.36, 130.66, 134.26, 140.01, 140.86, 142.07, 155.85, 157.21, 171.49; *m/z* (FABMS) 961.4 [$(M - 3\ Boc + H)^+$, 63%], 921.4 (5%), 813.3 (7%), 758.3 (11%), 216.1 (12.6%).

(*S*,*S*,*S*)-(+)-1,3,5-Tris(3-{2-ammonio-3-[4-(prop-2-enyloxy)-phenyl]propanoylamino}phenyl)benzene tris(trifluoroacetate), (*S*,*S*,*S*)-(+)-10

A solution of (*S*,*S*,*S*)-(+)-**9** (1.0 g, 0.8 mmol) in TFA–CH_2Cl_2 1:1 (50 ml) was stirred at room temp. for 1 h, then the solvent was evaporated. EtOH was added, and, after evaporation, drying (12 h, 0.05 Torr) afforded (*S*,*S*,*S*)-(+)-**10** (1.17 g, 99%) as a colourless product containing 1.5 equiv. of TFA; mp 85 °C [Found: C, 55.97; H, 4.68; N, 5.60. Calc. for $C_{66}H_{63}N_6O_{12}F_9$·1.5 CF_3CO_2H (1474.28): C, 56.21; H, 4.41; N, 5.70]; $[\alpha]_D^{r.t.} = +65.1$ ($c = 1.00$, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2925br m, 1675s, 1512s, 1202.6s, 798m, 722m; δ_H[500 MHz, $(CD_3)_2SO$] 3.02–3.16 (6 H, m), 4.15–4.17 (3 H, m), 4.46–4.48 (6 H, m), 5.17–5.19 (3 H, m), 5.29–5.33 (3 H, m), 5.92–5.95 (3 H, m), 6.89 (6 H, d, *J* 8.5), 7.18 (6 H, d, *J* 8.5), 7.51 (3 H, t, *J* 8.0), 7.58 (3 H, d, *J* 8.0), 7.65 (3 H, d, *J* 8.0), 7.80 (3 H, s), 7.90 (3 H, s), 8.35 (9 H, br s), 10.67 (3 H, s); δ_C[125.8 MHz, $(CD_3)_2SO$] 36.66, 59.94, 68.54, 115.19, 115.70, 117.76, 118.66, 119.65, 123.39, 124.84, 127.08, 130.17, 131.02, 134.08, 139.02, 140.96, 141.92, 157.89, 158.66, 167.45; *m/z* (FABMS) 961.3 [$(M - 3\ CF_3CO_2H)^+$, 100%], 813.3 (19%), 372.2 (29%), 332.2 (56%).

(*S*,*S*,*S*)-(+)-1,3,5-Tris(3-{2-(ethanoylamino)-3-[4-(prop-2-enyloxy)phenyl]propanoylamino}phenylbenzene, (*S*,*S*,*S*)-(+)-11

A mixture of (*S*,*S*,*S*)-(+)-**10** (0.5 mmol, 700 mg), acetyl chloride (0.13 ml, 140 mg, 1.8 mmol) and NEt_3 (0.5 ml, 350 mg, 3.5 mmol) in THF (20 ml) was stirred at room temp. for 12 h. Evaporation and column chromatography (SiO_2, CH_2Cl_2–MeOH 96:4) gave (*S*,*S*,*S*)-(+)-**11** (450 mg, 80%) as a white product; mp 148 °C (Found: C, 70.70; H, 6.18; N, 7.13. Calc. for $C_{66}H_{66}N_6O_9$·2H_2O (1123.33): C, 70.57; H, 6.28; N, 7.48); $[\alpha]_D^{r.t.} = +40.7$ ($c = 0.62$, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3284m, 1653s, 1610m, 1554m, 1510s, 1223m, 786w; δ_H[500 MHz, $(CD_3)_2SO$] 2.49 (9 H, s), 2.78–2.99 (6 H, m), 4.47–4.49 (6 H, m), 4.59–4.61 (3 H, m), 5.19–5.21 (3 H, m), 5.32–5.36 (3 H, m), 5.95–6.00 (3 H, m), 6.84 (6 H, d, *J* 8.6), 7.20 (6 H, d, *J* 8.6), 7.45 (3 H, t, *J* 8.1), 7.52 (3 H, d, *J* 8.1), 7.69 (3 H, d, *J* 8.1), 7.79 (3 H, s), 7.96 (3 H, s), 8.25 (3 H, d, *J* 8.0), 10.21 (3 H, s); δ_C(75.5 MHz, $CDCl_3$) 22.94, 37.94, 56.56, 68.83, 115.00, 115.01, 117.83, 118.91, 119.20, 122.54, 124.14, 128.96, 129.28, 130.35, 133.50, 138.36, 140.53, 141.03, 157.88, 171.43; *m/z* (FABMS) 1087.6 [$(M + H)^+$, 9%], 651.3 (22%), 391.3 (76%), 176.1 (100%).

(11*S*,31*S*,48*S*)-11,31,48-Tris[4-(prop-2-enyloxy)phenylmethyl]-9,12,30,33,46,49-hexaazadecacyclo[19.19.15.1^{3,39}.1^{4,8}.1^{14,18}.1^{19,23}.1^{24,28}.1^{34,38}.1^{41,45}.1^{51,55}]trihexaconta-1,3(58),4(63),5,7,14(62),15,17,19,21,23(61),24(60),25,27,34,36,38(59),39,41,43,45(57),51(56),52,54,55-tetracosaene-10,13,29,32,47,50-hexone, (*S*,*S*,*S*)-(−)-12

A mixture of **7** (494 mg, 1.0 mmol), NEt_3 (1.0 ml, 7.0 mmol) and (*S*,*S*,*S*)-(+)-**10** (1.3 g, 1.0 mmol) in THF (1 l) was stirred at 0 °C for 2 h and then at room temp. for 14 h. After evaporation, the residue was first purified by column chromatography (SiO_2, CH_2Cl_2–MeOH 19:1) then by prep. thin layer chromatography (SiO_2, CH_2Cl_2–MeOH 97:3) to afford (*S*,*S*,*S*)-(−)-**12** (275 mg, 20%) as a colourless product; mp 260 °C; $[\alpha]_D^{r.t.} = -27.0$ ($c = 0.10$, CH_2Cl_2–MeOH 95:5); ν_{max}(KBr)/cm^{-1} 3280br s, 2360m, 1611s, 1510s, 1242s, 1178m, 998w, 791w, 697m; δ_H(500 MHz, $CDCl_3$–CD_3OD 95:5): 3.01–3.05 (3 H, m), 3.26–3.31 (3 H, m), 4.42 (6 H, dt, *J* 5.3, 1.5), 4.96–4.99 (3 H, m), 5.17 (3 H, dd, *J* 10.5, 1.5); 5.30 (3 H, dd, *J* 17.3, 1.5), 5.92–5.97 (3 H, m), 6.79 (6 H, d, *J* 8.7), 7.17 (3 H, d, *J* 7.8), 7.20 (6 H, d, *J* 8.7), 7.24 (3 H, t, *J* 7.8), 7.35 (3 H, d, *J* 7.8), 7.37 (3 H, s), 7.40 (3 H, t, *J* 7.8), 7.48 (3 H, s), 7.61 (3 H, d, *J* 7.8), 7.66 (3 H, s), 7.70 (3 H, d, *J* 7.8),

7.97 (3 H, s); δ_C(125.8 MHz, $CDCl_3$–CD_3OD 95:5) 35.29, 55.39, 68.70, 114.72, 117.38, 118.44, 120.51, 123.00, 125.92, 126.20, 126.61, 128.14, 128.78, 128.95, 129.08, 130.06, 130.45, 133.10, 133.32, 137.97, 141.99, 142.26, 142.45, 142.61, 157.29, 167.80, 169.68; *m/z* (FABMS) 1345.6 [$(M + H)^+$, 100%], 1031.6 (21%).

Chiral stationary phase (*S*,*S*,*S*)-14

A mixture of 3-mercaptopropyl silica gel **13**[32,33] (4.0 g; Anal. found: C, 5.24; H, 1.41), (*S*,*S*,*S*)-(−)-**12** (430 mg, 0.32 mmol) and AIBN (60 mg, 0.37 mmol) was stirred in freshly distilled $CHCl_3$ (25 ml) for 20 h under reflux. After cooling to room temp., further AIBN (30 mg, 0.18 mmol) was added and the mixture was heated to reflux for 5 h. The suspension was centrifuged (5000 rpm) for 1 h, then the silica gel was separated from the liquid phase and washed thoroughly (MeOH). Drying (4 h, 0.05 Torr) yielded CSP (*S*,*S*,*S*)-**14** (4.3 g); Anal. found: C, 11.29; H, 1.58; N, 0.71, corresponding to a loading density[34] of 0.06 mmol g^{-1} based on C. This means 75% of the employed receptor was attached. A steel HPLC column (25 cm × 4.6 mm id) was packed with this material using the slurry method (CCl_4).

Chiral stationary phase (*S*,*S*,*S*)-15

A mixture of 3-mercaptopropyl silica gel **13** (2.5 g; Anal. found: C, 5.14; H, 1.32), (*S*,*S*,*S*)-(+)-**11** (200 mg, 0.18 mmol) and AIBN (60 mg, 0.37 mmol) was stirred in freshly distilled $CHCl_3$ (15 ml) for 20 h under reflux. After cooling to room temp., further AIBN (20 mg, 0.12 mmol) was added and the mixture was heated to reflux for 5 h. The suspension was centrifuged (5000 rpm) for 1 h, then the silica gel was separated from the liquid phase and washed thoroughly (MeOH). Drying (4 h, 0.05 Torr) afforded (*S*,*S*,*S*)-**15** (2.7 g); Anal. found: C, 9.62; H, 1.56; N, 0.60, corresponding to a loading density of 0.06 mmol g^{-1} based on C. This means 83% of the employed receptor was attached. A steel HPLC column (25 cm × 4.6 mm id) was packed with this material using the slurry method (CCl_4).

^{1}H NMR binding titrations

Most *N*-protected amino acid derivatives for binding studies were purchased from Fluka or Aldrich; *N*-Boc-L-Ala-L-Ala was purchased from Bachem. *N*-Boc-D-Glu as well as both enantiomers of *N*-BuOCO-Glu were prepared according to the procedure for the synthesis of *N*-Bu^{n}OCO-L-Glu.[7c] All ^{1}H NMR titration data were acquired on a Bruker 500 MHz NMR spectrometer thermostatted to ±0.1 K at 300 K. The solvents $CDCl_3$ and $CDCl_2CDCl_2$ used in the titrations were dried over molecular sieves (4 Å); their water content after drying was estimated by ^{1}H NMR integration to be smaller than 1 mM. Hosts and guests were dried at high vacuum (10^{-5} Torr) and stored in a vacuum desiccator. The titrations in $CDCl_3$ were performed by preparing 10 NMR samples with the same concentration of the host (typically 0.5–1 mM), and varying guest concentrations (range 0.5–50 mM, depending on guest), generally achieving saturation values of 70% or higher. The titrations in $CDCl_2CDCl_2$ were carried out by incremental additions of a guest solution to a solution of the host, where the guest solution also contains host at such a concentration as to keep its concentration constant throughout the titration (at 1.0 mM). Additions were continued until a satisfactory degree of saturation was achieved, again generally at least 70%. The changes in chemical shift of host protons were monitored and evaluated. The binding free energies $-\Delta G$ were calculated from the titration curves by a non-linear least-squares treatment using the program Associate V. 1.6.[38] Titrations were duplicated and results were averaged.

Extraction and solubilisation studies

To (*S*,*S*,*S*)-(+)-**1** (0.8 mg) and *N*-Cbz-Glu (4.0 mg, 1:1 mixture of pure crystalline D- and L-enantiomers) was added CCl_4–$CDCl_3$ 3:1 (0.4 ml) containing 2,7-di(benzyloxy)-3-bromonaphthalene[17] (1.0 mM) as an internal standard and the mixture was sonicated for 5 min. After filtration, the sample was split into two portions. With one portion, the extraction efficiency was determined. The solvent was removed and the residue was dissolved in $(CD_3)_2SO$. Integration of the ^{1}H NMR signals of the benzylic protons of the internal standard (s at 5.29 and s at 5.20 ppm), the Cbz methylene protons of the solubilised *N*-Cbz-Glu (s at 5.00 ppm) and H_α of the amino acid in the spacer arms of (*S*,*S*,*S*)-(+)-**1** (m, 4.56–4.63 ppm) gave the ratio of these compounds in solution. The other portion was derivatised to determine the enantiomeric composition of the extracted *N*-Cbz-Glu as follows. The solvent was removed, the residue was dissolved in 2.7 M HCl in Pr^{i}OH (made by mixing acetyl chloride and Pr^{i}OH), and the mixture was heated in a closed screw-cap vial at 110 °C for 80 min. The insoluble (*S*,*S*,*S*)-(+)-**1** was filtered off, after which the solvent was removed from the filtrate under a stream of nitrogen. To the residue were added CH_2Cl_2 (100 μl) and pentafluoropropionic anhydride (60 μl), and the mixture was heated again in a screw-cap vial to 110 °C for 15 min, after which the solvent was removed under a stream of nitrogen. The residue was dissolved in Et_2O and analysed by GC using the Chirasil-Val (25 m × 0.25 mm) chiral capillary column from Alltech.

HPLC studies

For HPLC separations, compound **16** was purchased from Fluka and compound **17** was synthesized according to the published procedure.[17] HPLC instrumentation: Knauer HPLC Pump 64 high pressure gradient pumps with analytical pump heads and vacuum on-line degasser, electrical injection valve, Variable Wavelength Monitor UV–VIS-detector from Knauer. Samples of 20 μl were injected.

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