KEYNOTE

Geometrical optimisation of 1,1′-binaphthalene receptors for enantioselective molecular recognition of excitatory amino acid derivatives

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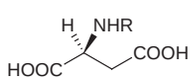
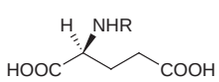
A series of optically active 1,1′-binaphthalene-derived receptors with *N*-(pyridine-2,6-diyl)acetamide [CONH(py)] H-bonding sites in the 6,6′-positions has been prepared for the enantioselective complexation of the *N*-carbobenzyloxy (Cbz)-protected excitatory amino acids aspartic (Asp) and glutamic (Glu) acid *via* two COOH · · · CONH(py) H-bonding arrays and additional secondary bonding interactions. The conformational homogeneity of the receptors is enhanced by locking the dihedral angle θ about the chirality axis through the C(1)–C(1′) bond of the 1,1′-binaphthalene moiety either by bridging the 2,2′-positions or by attaching bulky substituents to these centres. Computer modelling has shown that bridging is more efficient in locking this dihedral angle than the introduction of bulky substituents, and these predictions have been confirmed by ^{1}H NMR binding studies in $CDCl_3$ and in $CDCl_3$–CD_3OD 99.8 : 0.2. Plots of the enantioselectivity $\Delta(\Delta G^\circ)$ (difference in stability between diastereoisomeric complexes) in the recognition by the bridged receptors as a function of the enforced dihedral angle θ are peak-shaped, and the highest values have been measured in $CDCl_3$ (300 K) for the complexation of the enantiomers of *N*-Cbz-Asp [$\Delta(\Delta G^\circ) = 6.9$ kJ mol^{-1}] and *N*-Cbz-Glu [$\Delta(\Delta G^\circ) = 5.2$ kJ mol^{-1}] by (*R*)-21** ($\theta = 86 \pm 4^\circ$). The more stable diastereoisomeric complexes are highly structured, and tight host–guest bonding has been confirmed by the observation of up to five intermolecular NOEs. Enforcing the conformational homogeneity by bridging represents a new general principle for improving the chiral recognition potential of 1,1′-binaphthalene receptors.**

Introduction

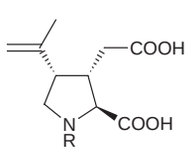
The development of molecular receptors for the selective recognition of amino acids and other biologically relevant mono- and poly-carboxylic acids has attracted major interest in supramolecular chemistry over the past years.[1–19] In our laboratory, we pursued the construction of chiral, cleft-type receptors bearing two convergent H-bonding sites for the complexation of α,ω-dicarboxylic acids and, in particular, derivatives of the excitatory amino acids L-aspartic acid (L-Asp; **1**), L-glutamic acid (L-Glu; **2**), and L-kainic acid (L-Kai; **3**).[1,2b] Excitatory amino



1 R = H (L-Asp)
4 R = COOBn
(*N*-Cbz-L-Asp)



2 R = H (L-Glu)
5 R = COOBn
(*N*-Cbz-L-Glu)

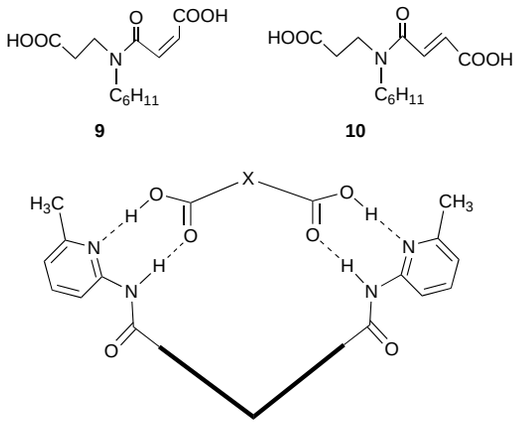


3 R = H (L-Kai)
6 R = COOBn
(*N*-Cbz-L-Kai)

acid derivatives such as *N*-carbobenzyloxy (Cbz)-protected **4**–**6** were selected as target substrates since X-ray crystal structures of neuroreceptors recognising excitatory amino acids still have not been solved[20] and, therefore, the principles governing their selective complexation in biology remain to be explored. Three different classes of synthetic, cleft-type receptors were prepared, namely the helicopodands[1a,b] and two other types of molecular clefts derived from either 9,9′-spirobi[9*H*-fluorene][1c–g] or 1,1′-binaphthalene spacers.[1e,h] They were subsequently tested as receptors in a variety of studies which helped in establishing two important guidelines for efficient chiral recognition: both (*i*) a high degree of conformational homogeneity (preorganisation) of the receptor[1e,h,7b,c,21] and (*ii*) oriented host–guest interactions such as H-bonding are essential for the selective complexation of one substrate enantiomer over the other.[22]

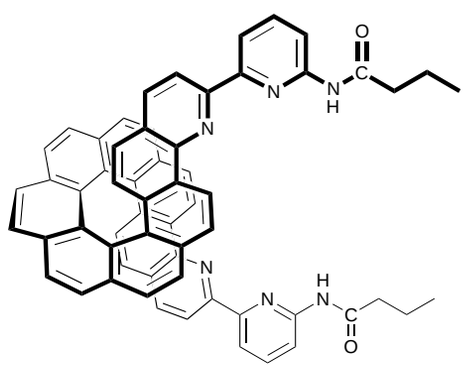
Helicopodands

The helicene derivatives (±)-**7**, with two *N*-(pyridine-2,6-diyl)-butanamide residues,[1a] and (±)-**8**, with two *N*-(6-methyl-2-pyridyl)carboxamide residues,[1b] were prepared in racemic form for the molecular recognition of α,ω-dicarboxylic acids. We named these compounds as 'helicopodands' since they are non-macrocyclic receptors ('podands') and possess a rigid helicene[23] backbone ('helico'). In the productive *in-in*-conformation, in which the two CONH(py) (py = pyridine) groups at the helix termini converge with their NH/N functionality into the binding cleft, receptor (±)-**8** was found to form stable 1 : 1 host–guest complexes with suitably sized α,ω-dicarboxylic acids in $CHCl_3$, a solvent which does not compete for the H-bonding sites of the binding partners. A remarkable diastereoselectivity of $\Delta(\Delta G^\circ) = 6.0$ kJ mol^{-1} was observed by ^{1}H NMR binding titrations at 300 K for the complexation of receptor (±)-**8** with the diastereoisomeric substrates **9** ($K_a = 230 \pm 40$ l mol^{-1}, $\Delta G^\circ = -13.6 \pm 0.5$ kJ mol^{-1}) and **10** ($K_a = 2600 \pm 400$ l mol^{-1}; $\Delta G^\circ = -19.6 \pm 0.5$ kJ mol^{-1}) which differ only by the (*Z*)/(*E*)-configuration at their double bond (Fig. 1). A comprehensive force-field molecular modelling study using MacroModel[24] suggested that only the (*E*)-derivative **10** possesses the correct

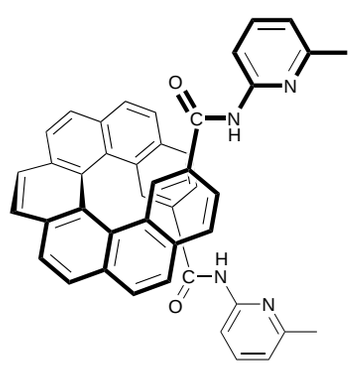


9 **10**

Fig. 1 (*E*)-Isomer **10**, but not the (*Z*)-isomer **9**, can undergo four-fold H-bonding between its two COOH residues and the CONH(py) groups of the receptor



(±)-**7**



(±)-**8**

geometry for a four-fold ditopic H-bonding interaction[6] between its two COOH residues and the two CONH(py) groups of (±)-**8** (Fig. 1) whereas the (*Z*)-derivative **9** cannot adopt a favourable binding orientation under formation of all four host–guest H-bonds.

Although helicopodands (±)-**7** and (±)-**8** displayed desirable binding properties in addition to some spectacular molecular architecture, their low-yielding synthesis *via* photocyclodehydrogenation[25] prevented the preparation of sufficiently large quantities for optical resolution and subsequent comprehensive chiral recognition studies. We therefore decided to construct our chiral molecular cleft receptors starting from the more readily available and chemically more versatile 9,9′-spirobi[9*H*-fluorene][26] and 1,1′-binaphthalene spacers,[3b,21a,27] respectively.

9,9′-Spirobi[9*H*-fluorene] receptors

The receptors **11** and **12** (Fig. 2) were prepared in enantiomerically pure form and shown to form stable 1 : 1 host–guest complexes with *N*-protected Glu and Asp in $CDCl_3$.[1e,f] The major intermolecular interaction in these associations is the H-bonding between the two COOH residues of the substrate and the two heterocyclic carboxamides of the receptors, as depicted in Fig. 1. ^{1}H NMR binding titrations showed that *N*-Cbz-L-Asp (**4**) and *N*-Cbz-L-Glu (**5**) were selectively recognized by the enantiomeric receptors with the differences in stability between diastereoisomeric complexes, *i.e.* the enantioselectivity, amounting to $\Delta(\Delta G^\circ) = 4.0$ kJ mol^{-1} (Table 1). Remarkably, *N*-Cbz-L-Glu binds preferentially to the (*S*)-configured receptors whereas *N*-Cbz-L-Asp prefers association to the (*R*)-configured molecular clefts.[28] As a consequence of the different carbon chain length, which is even-membered in Asp and odd-membered in Glu, the terminal carboxy residues of the substrates bound in the clefts adopt different orientations which ultimately leads to inversion of the favored host configuration.

Table 1 Association constants, K_a, binding free enthalpies,[a] ΔG° and enantioselectivities, $\Delta(\Delta G^\circ)$, determined by ^{1}H NMR titrations[b] for the complexes formed by the enantiomers of **11** (at 293 K) and **12** (at 300 K) with *N*-Cbz-L-Asp and *N*-Cbz-L-Glu

Receptor	Substrate	K_a/1 mol^{-1}	ΔG°/ kJ mol^{-1}	$\Delta(\Delta G^\circ)$/ kJ mol^{-1}
(*S*)-**11**	*N*-Cbz-L-Asp	820	−16.3	
(*R*)-**11**	″	4 200	−20.3	4.0
(*S*)-**12**	″	1 100	−17.5	
(*R*)-**12**	″	2 600	−19.6	2.1
(*S*)-**11**	*N*-Cbz-L-Glu	14 000	−23.3	3.2
(*R*)-**11**	″	3 900	−20.1	
(*S*)-**12**	″	11 650	−23.4	2.8
(*R*)-**12**	″	3 800	−20.6	

[a] Uncertainties: ±0.8 kJ mol^{-1}. [b] In titrations at constant receptor concentration, the complexation-induced downfield shifts of the NH and aromatic protons of the receptor were monitored and evaluated.

Changing the H-bonding sites from pyridinecarboxamide [CONH(py)] in **11** to naphthyridinecarboxamide [CONH(naphthyl)] in **12** did not significantly alter the free enthalpy and enantioselectivity of complexation (Table 1). This initially surprising observation was rationalized with two compensating effects. Binding to cleft **12** should be weakened, since the pK_a value (in H_2O) of naphthyridine (pK_a = 3.39)[29] is significantly lower than that of pyridine (pK_a = 5.23),[30] which makes naphthyridine N-atoms weaker H-bond acceptors. On the other hand, binding to **12** should be strengthened as a result of a more favorable DAA/AD H-bonding pattern (as opposed to DA/AD in **11**; A = H-bond acceptor, D = H-bond donor) which should enable the formation of a bifurcated H-bond between the naphthyridine donor sites and the COOH proton (Fig. 3). In addition, the DAA/AD pattern should also be more favorable in terms of secondary electrostatic interactions.[31]

Variable temperature ^{1}H NMR studies showed that the complexation of the excitatory amino acid derivatives by the enantiomers of both **11** and **12** is strongly enthalpy-driven with the enthalpic driving force being partially compensated by an unfavorable change in entropy.

In a logical extension of the molecular recognition studies in the liquid phase,[2b] the optically active cleft (*S*)-**12** was covalently bound to silica gel, following the procedure of Salvadori and co-workers,[32,33] to provide the novel chiral stationary phase (CSP) (*S*)-**13** (Fig. 2). The subsequent HPLC studies focussed on separating racemic mixtures of compounds that had previously been bound enantioselectively by (*S*)-**12** in $CDCl_3$ (Table 1). With CH_2Cl_2–MeOH 90 : 10 as the eluent, the enantiomers of (±)-*N*-Cbz-Glu were separated with a separation factor $\alpha = 1.18$. The L-enantiomer was eluted last, which correlates with the results in the liquid phase where this enantiomer is bound more strongly by (*S*)-**18** than the D-enantiomer. Other dicarboxylic acids as well as a series of 1,1′-binaphthalene-2,2′-diols could also be separated on this new CSP.

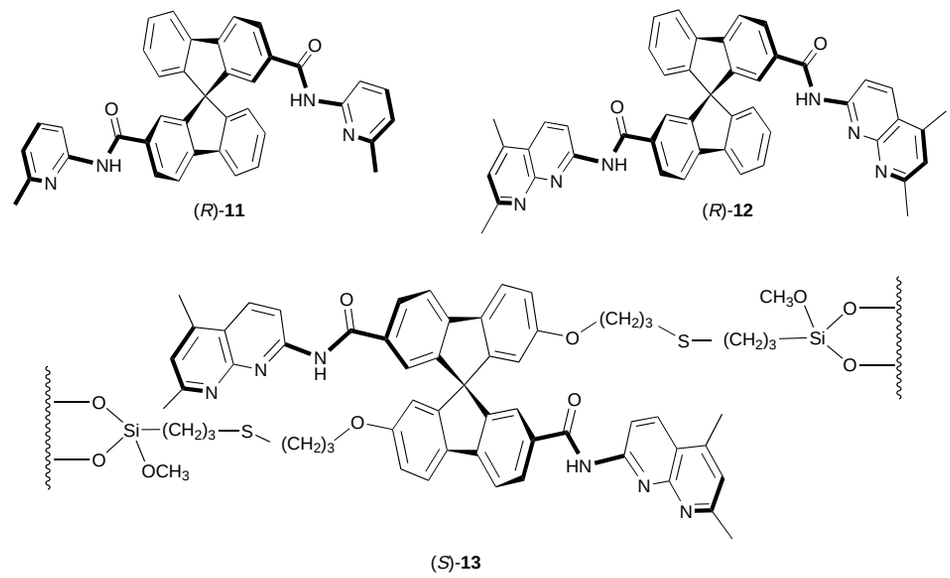


Fig. 2 Cleft-type optically active receptors derived from 9,9′-spirobi[9*H*-fluorene] spacers and a novel, rationally designed chiral stationary phase (CSP) for the HPLC separation of excitatory amino acids and other dicarboxylic acids and diols

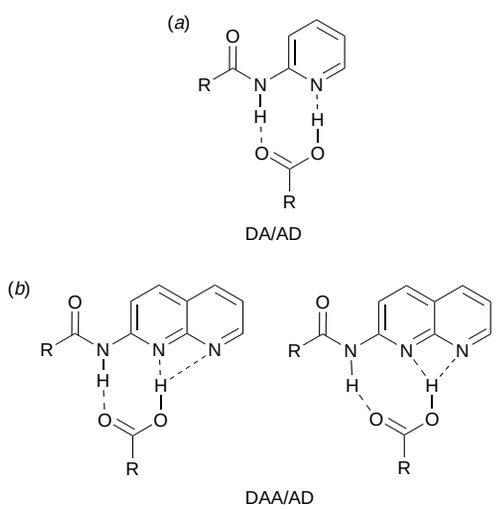


Fig. 3 H-bonding patterns between a COOH residue and (*a*) pyridinecarboxamides in (*R*)-**11** (DA/AD pattern) and (*b*) naphthyridinecarboxamides in (*R*)-**12** (DAA/AD pattern)

1,1′-Binaphthalene receptors

Whereas the spirobi[fluorene] receptors **11** and **12** displayed efficient chiral recognition in the complexation of *N*-Cbz-L-Glu or *N*-Cbz-L-Asp (Table 1), the corresponding enantiomeric 1,1′-binaphthalene-based receptors (*R*)-**14** and (*S*)-**14** (Fig. 4), with CONH(py) H-bonding sites at the 6,6′-positions in the major groove[27a] of the cleft, formed stable diastereoisomeric complexes of similar association strength with the excitatory amino acid derivatives (Table 2).[1e,h] These experimental findings provide impressive support for the hypothesis that a high degree of receptor preorganisation and conformational homogeneity is a requirement for efficient chiral recognition. In contrast to the rigid spirobi[fluorene] cleft with the two fluorene moieties rigidly fixed at an angle of 90° about the spiro centre, the 1,1′-binaphthalene unit is conformationally flexible[21] and conformational analysis revealed that the latter can adopt a variety of energetically similar conformations with dihedral angles θ about the chirality axis through the C(1)–C(1′) bond varying between *ca.* 60 and *ca.* 120° ($\Delta E < 4.18$ kJ mol^{-1}).[34] As a consequence, the 1,1′-binaphthalene receptors are capable of adopting geometries which fit both substrate enantiomers, and diastereoisomeric complexes of similar stability are formed.

In subsequent work, the 1,1′-binaphthalene-derived receptors were incrementally improved and this article describes how

Table 2 Association constants, K_a, binding free enthalpies,[a] $\Delta G°$, and enantioselectivities, $\Delta(\Delta G°)$, determined by ^{1}H NMR titrations[b] for the complexes formed by 1,1′-binaphthalene-derived receptors **14**–**16** (298 K) and **17** (293 K) with *N*-Cbz-Asp, *N*-Cbz-Glu and *N*-Cbz-Kai in $CDCl_3$

Receptor	Substrate	K_a/ 10^3 l mol^{-1}	$\Delta G°$/ kJ mol^{-1}	$\Delta(\Delta G°)$/ kJ mol^{-1}
(*R*)-**14**	*N*-Cbz-L-Asp	2.0	−18.8	
(*S*)-**14**		3.3	−20.1	1.3
(*R*)-**14**	*N*-Cbz-L-Glu	21.0	−24.7	0.3
(*S*)-**14**		19.0	−24.4	
(*R*)-**15**	*N*-Cbz-L-Asp	4.0	−20.6	
(*S*)-**15**		8.9	−22.5	1.9
(*R*)-**15**	*N*-Cbz-L-Glu	3.0	−19.8	1.2
(*S*)-**15**		1.8	−18.6	
(*R*)-**16**	*N*-Cbz-L-Asp	180.0	−30.0	2.7
(*S*)-**16**		60.0	−27.3	
(*R*)-**16**	*N*-Cbz-L-Glu	19.0	−24.4	1.3
(*S*)-**16**		11.0	−23.1	
(*R*)-**16**	*N*-Cbz-L-Kai	4.1	−20.6	1.9
(*S*)-**16**		1.9	−18.7	
(*R*)-**17**	*N*-Cbz-L-Asp	2.9	−19.4	
(*S*)-**17**		8.3	−22.0	2.6
(*R*)-**17**	*N*-Cbz-L-Asp[c]	2.6	−19.2	
(*S*)-**17**		9.1	−22.2	3.0

[a] Uncertainties: ±0.8 kJ mol^{-1}. [b] In titrations at constant receptor concentration, the complexation-induced downfield shifts of the NH and aromatic protons of the receptor were monitored and evaluated. [c] Co-binder $Hg(CN)_2$ (4.98 mM) added.

these systematic developments ultimately led to strong binders which discriminate efficiently between the enantiomers of the excitatory amino acid derivatives. In a first step,[1h] the orientation of the pyridinecarboxamide binding sites in (*R*)-**14** and (*S*)-**14** was changed to yield receptors (*R*)-**15** and (*S*)-**15** in which the pyridine rings, as in helicopodand (±)-**7** had been directly coupled to the spacer *via* the Suzuki cross-coupling reaction (Fig. 4).[35] Although the overall free enthalpy for complexing *N*-Cbz-L-Glu decreased, a modest enhancement in chiral recognition of this substrate was observed (Table 2). Subsequently, additional functional groups were introduced into the 7,7′-positions of the 1,1′-binaphthalene cleft.[1h] The introduction of two benzyloxy residues in (*R*)-**16** and (*S*)-**16** strongly enhanced the overall binding affinity, in particular for *N*-Cbz-L-Asp ($-\Delta G°$ up to 30.0 kJ mol^{-1}) and also provided an improved degree of chiral recognition [up to $\Delta(\Delta G°) = 2.7$ kJ mol^{-1}] (Table 2). The benzyl ether functionality in the 7,7′-positions sterically forces the pyridine rings out of the plane of the

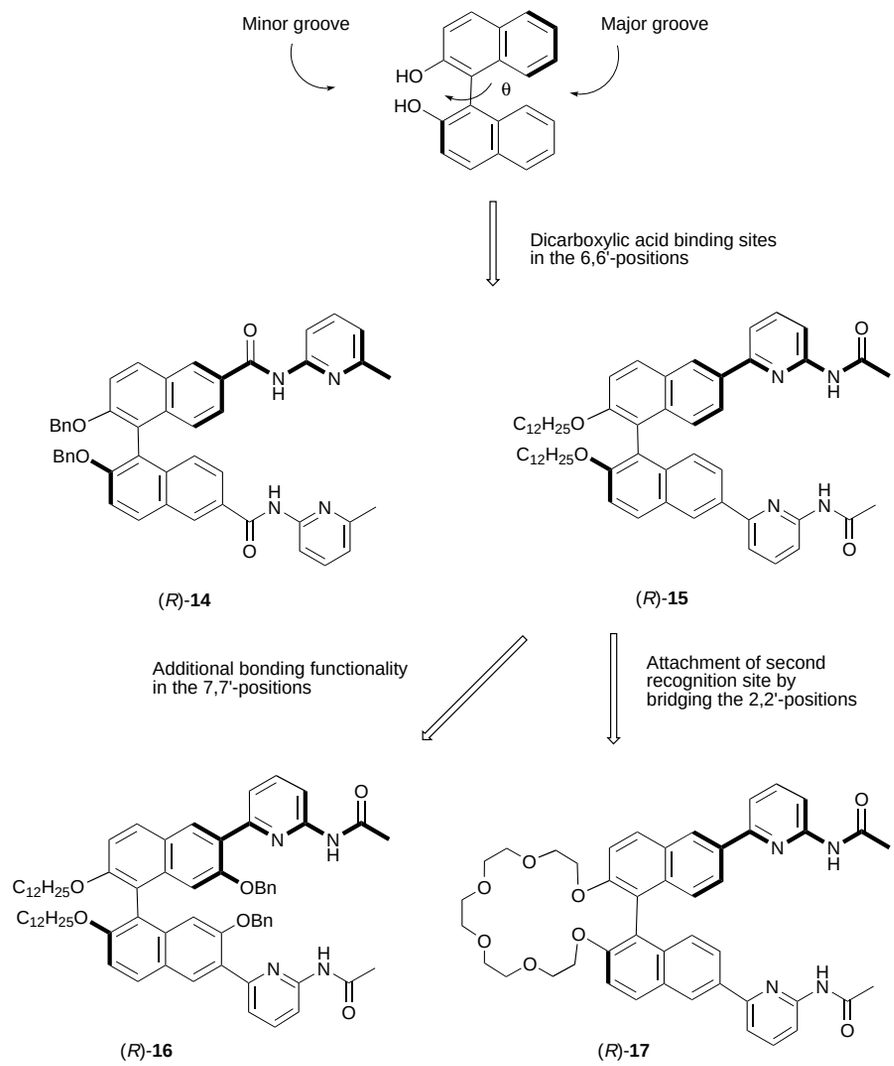


Fig. 4 Sequential optimisation of 1,1′-binaphthalene receptors for the enantioselective complexation of derivatives of excitatory amino acids; Bn = $PhCH_2$

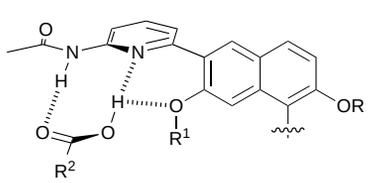


Fig. 5 Secondary electrostatic interactions between the benzyl ether O-atom of receptor **16** and the COOH group of a bound excitatory amino acid derivative

adjacent naphthalene rings and enforces conformations in which the CONH(py) binding sites converge into the cleft for interaction with the dicarboxylic acid guests. Furthermore, the benzyl ether O-atoms are sufficiently close to the COOH groups of the substrates binding to the adjacent pyridine N-atoms, so that additional attractive electrostatic O · · · H interactions with these COOH groups become effective (Fig. 5).[31]

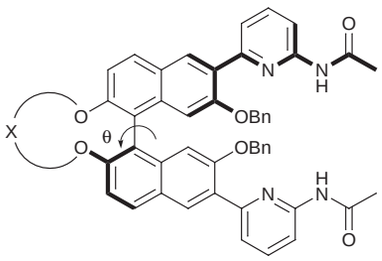
In a first approach to further enhance the preorganisation, a crown ether binding site[3,21] was attached to the minor groove of the receptors (*R*)-**17** and (*S*)-**17** (Fig. 4) by bridging the 2,2′-positions. It was hoped that complexation of a substrate such as $Hg(CN)_2$[36] at the crown ether site would reduce the conformational flexibility about the chirality axis through C(1)–C(1′) and favorably affect, in a cooperative process, the efficiency and enantioselectivity of the excitatory amino acid binding site at the major groove. ^{1}H NMR binding titrations demonstrated, however, that both the binding affinity and enantioselectivity [$\Delta(\Delta G°)$ up to 3.0 kJ mol^{-1}] in the complexation of these substrates by (*R*)-**17** and (*S*)-**17** were not altered upon complexation of $Hg(CN)_2$ at the crown ether binding site (K_a = 350 l mol^{-1}, $\Delta G° = -14.3$ kJ mol^{-1}), demonstrating lack of cooperativity between the minor and major groove recognition sites (Table 2).

In this article, we show that the enantioselectivity of the 1,1′-binaphthalene major groove receptors in the recognition of the excitatory amino acid derivatives can be greatly improved by enforcing the conformational homogeneity of the molecular cleft through tightly bridging the 2,2′-positions in the minor groove. Both the overall association strength and the degree of enantioselection are found to strongly depend on the dihedral angle θ about the chirality axis through C(1)–C(1′), which is locked by the bridging. We also demonstrate that bulky substituents at the 2,2′-positions are inefficient in locking θ and that the corresponding receptors do not display a high degree of chiral recognition.

Results and discussion

Conformational analysis

Two approaches, attaching bulky substituents to the 2,2′-positions in the minor groove and tightly bridging these centres, were pursued to restrict the rotation about the dihedral angle θ of the 1,1′-binaphthalene receptors and to enhance their chiral recognition properties in the major groove. Prior to the synthesis of possible target molecules, computational studies were performed to predict their conformational preferences and, in particular, the preferred dihedral angle θ. We planned to



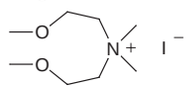
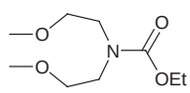
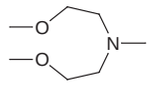
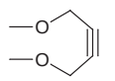
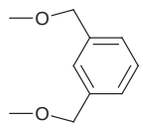
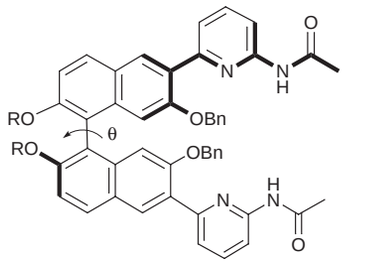
	O—X—O	(θ ± Δθ)/°
(*R*)-**18**		60 ± 5
(*R*)-**19**		72 ± 7
(*R*)-**20**		78 ± 5
(*R*)-**21**		86 ± 4
(*R*)-**22**		91 ± 5
(*R*)-**23**		96 ± 3

Fig. 6 1,1′-Binaphthalene receptors (*R*)-**18**–(*R*)-**23** bridged at the 2,2′-positions and their preferred dihedral angle $\theta \pm \Delta\theta$ determined by computer modelling. The dihedral angle θ is defined by C(8a)–C(1)–C(1′)–C(8a′).

systematically vary θ between values of *ca.* 60 and *ca.* 100° to identify, in correlations with experimental binding affinities, the receptor geometry displaying the highest enantioselectivity in the recognition of individual excitatory amino acids.

The conformational analysis was performed using the OPLS* force field[37] implemented in the MacroModel V. 5.0 program.[24,38] All structures were minimized employing the conjugate gradient method[39] and subsequently submitted to a 4000-step pseudo-Monte Carlo Multiple Minimum (MCMM) conformational search *in vacuo* followed by a 2000-step MCMM search in $CHCl_3$ using the GB/SA solvation model.[40] In the simulations, the dihedral angle between the pyridine ring and the attached acetamido function was constrained to 0° in agreement with X-ray crystallographic data for (±)-**16**.[1h] To avoid decomplexed structures, only associations with O–H · · · N and C=O · · · H–N H-bond lengths between 1.5 and 2.1 Å were accepted. Consideration of all conformers found within 10 kJ mol^{-1} above the computed global minimum conformation led to the averaged dihedral angles $\theta \pm \Delta\theta$. The magnitude of $\Delta\theta$ provides an estimate for the residual conformational flexibility about the chirality axis: the larger $\Delta\theta$, the more flexible the receptor. Based on the computational predictions, a total of nine new receptors, six bridged at the 2,2′-positions [(*R*)-**18**–(*R*)-**23**; Fig. 6], and three with bulky substituents at these centres [(*R*)-**24**–(*R*)-**26**; Fig. 7], were selected for synthesis and complexation studies. Their dihedral angle preferences varied in the desired range between $\theta = 60$ and 96°. The ensemble of conformers within 10 kJ mol^{-1} above the computed global minimum conformation for the bridged receptors (*R*)-**18**–(*R*)-**23** is depicted in Fig. 8. Within this series, conformational flexibility with respect to rotation about the dihedral angle θ is lowest in compounds (*R*)-**21** and (*R*)-**23**



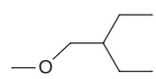
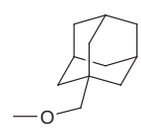
	—OR	(θ ± Δθ)/°
(*R*)-**16**	—$OC_{12}H_{25}$	80 ± 10
(*R*)-**24**		90 ± 10
(*R*)-**25**	—$OSiMe_2Bu^t$	90 ± 10
(*R*)-**26**		70 ± 10

Fig. 7 1,1′-Binaphthalene receptors (*R*)-**16** and (*R*)-**24**–(*R*)-**26** with bulky ether substituents at the 2,2′-positions and their preferred dihedral angle $\theta \pm \Delta\theta$ determined by computer modelling. The dihedral angle θ is defined by C(8a)–C(1)–C(1′)–C(8a′).

(Fig. 8). The molecular modelling showed clearly that bridging the 2,2′-positions in (*R*)-**18**–(*R*)-**23** was more effective ($\Delta\theta = \pm 3$–7°) in enforcing the dihedral angle θ than attaching bulky groups to these centres in (*R*)-(**24**)–(*R*)-**26** ($\Delta\theta = \pm 10$°) (Figs. 6 and 7).

Changes in θ have a profound effect on the dimension of the receptor site at the major groove. When the two pyridine rings adopt the convergent binding orientation seen in Fig. 10 below, the distance between their N-atoms varies from 7.1 Å at $\theta = 60$° to 10.5 Å at $\theta = 96$°.

Synthesis of the optically active receptors

The synthesis of the new receptors (*R*)-**18**–(*R*)-**26** started from the enantiomerically pure 1,1′-binaphthalene derivative (*R*)-**27** (Scheme 1). A protocol for the optical resolution of (±)-**27** by conversion into the corresponding cyclic phosphate, fractional crystallization of the diastereoisomeric salts formed with either quinine or quinidine, and cleavage of the cyclic phosphodiester to give enantiomerically pure (*R*)-**27** and (*S*)-**27**, respectively, has previously been published by our laboratory.[1h] However, the large number of steps involved and the fractional crystallization procedure were found quite tedious for preparing larger quantities of optically pure (*R*)-**27**. A more convenient and quite general method for resolving functionalized (±)-1,1′-binaphthalene-2,2′-diols, *via* column chromatographic separation of the corresponding diastereoisomeric diesters formed with (1*S*)-camphor-10-sulfonyl chloride,† was recently published by Chow and co-workers.[41] With slight modifications, this method was successfully applied to the rapid optical resolution of larger quantities of (±)-**27**. By this protocol, the diastereoisomeric camphorsulfonates (−)-**28** and (+)-**29** were prepared from (±)-**27** and (1*R*)-(−)-camphor-10-sulfonyl chloride (Scheme 1). Flash chromatographic separation of (−)-**28** and (+)-**29** was best achieved on SiO_2 (CH_2Cl_2–AcOEt 99 : 1) with (−)-**28** being eluted first. For both esters, a diastereoisomeric excess (de) higher than 99.5% was determined by HPLC (SiO_2,

† IUPAC name for camphor is 1,7,7-trimethyl-2-oxobicyclo[2.2.1]-heptane.

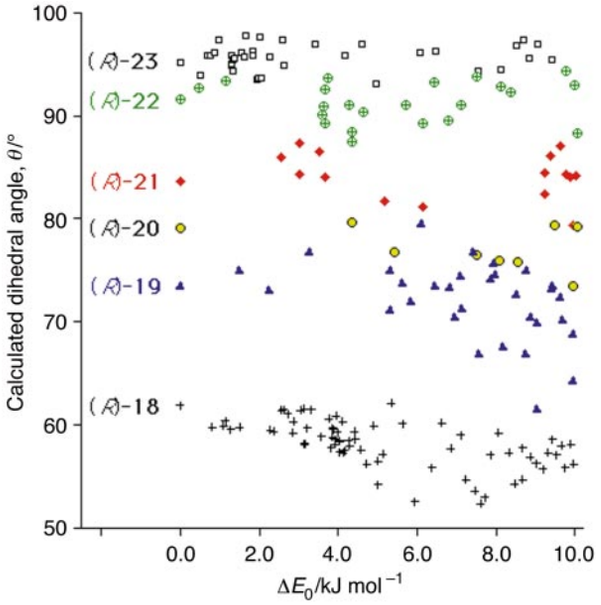


Fig. 8 Dihedral angle θ in the conformers of (*R*)-**18**–(*R*)-**23** within 10 kJ mol^{-1} (ΔE_0) above the computed global minimum conformation as determined by *pseudo*-MCMM-calculations (2000 steps in $CHCl_3$)

CH_2Cl_2–AcOEt gradient). Saponification of (−)-**28** subsequently afforded (*R*)-**27**.

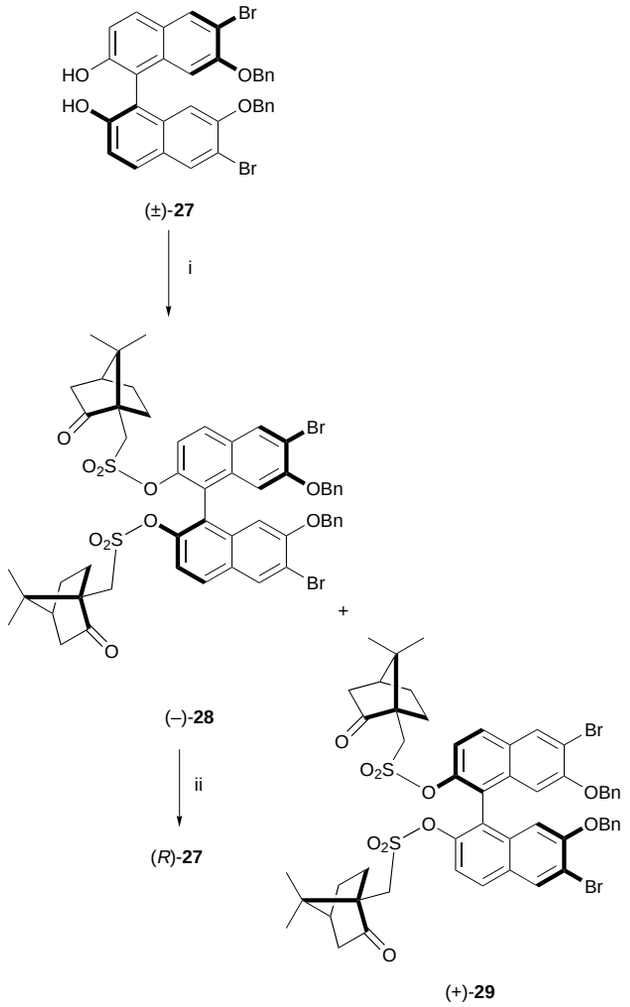
The bridged receptors (*R*)-**18**–(*R*)-**23** were prepared starting from (*R*)-**27** *via* similar routes including a Williamson ether macrocyclization and a Suzuki cross-coupling step (Scheme 2). Protection of the phenolic OH groups in (*R*)-**27** as methoxymethyl (MOM) ethers afforded (*R*)-**30** (82%) to which the H-bonding sites were attached by the Suzuki reaction with *N*-(6-bromo-2-pyridyl)acetamide to give (*R*)-**31** (59%). Cleavage of the MOM ether groups (quant. yield) to (*R*)-**32**, followed by macrocyclization with methylbis(2-chloroethyl)amine hydrochloride or 1,4-dichlorobut-2-yne under high dilution afforded the receptors (*R*)-**21** (50%) and (*R*)-**22** (34%), respectively. Demethylation–acylation reaction[42] of (*R*)-**21** with ethyl chloroformate gave receptor (*R*)-**20** (71%) whereas quaternization of (*R*)-**21** yielded receptor (*R*)-**19** (94%). For further characterization of the strained alkyne (*R*)-**22**, conversion with $Co_2(CO)_8$ readily afforded the stable dicobalt complex (*R*)-**33** (63%).[43]

Macrocyclization of (*R*)-**27** with bromochloromethane or α,α′-dibromo-*m*-xylene yielded (*R*)-**34** (quant. yield) and (*R*)-**35** (83%), respectively, and subsequent Suzuki coupling with *N*-(6-bromo-2-pyridyl)acetamide provided the receptors (*R*)-**18** (57%) and (*R*)-**23** (37%), respectively.

In the series of 1,1′-binaphthalene receptors with bulky substituents in the 2,2′-positions, (*R*)-**24** was prepared by alkylation of **27** to give (*R*)-**36** (quant. yield) followed by Suzuki coupling (45%) (Scheme 3). Compounds (*R*)-**25** and (*R*)-**26** were synthesized *via* silylation or alkylation of (*R*)-**32** in 77 and 67% yield, respectively.

^{1}H NMR binding studies

The complexation of the enantiomers of *N*-Cbz-Asp and *N*-Cbz-Glu by the new receptors (*R*)-**18**–(*R*)-**26** was studied in ^{1}H NMR binding titrations (500 MHz, $T = 300$ K) at constant host concentration in which the complexation-induced change in chemical shift ($\Delta\delta$) of the 1,1′-binaphthalene proton H–C(5) was monitored and subsequently evaluated by a non-linear least-squares curve-fitting procedure.[44] A first set of titration data was collected in pure $CDCl_3$ (dried over molecular sieves 4 Å) (Table 3, entries 1–7; for experimental conditions, see Table 4 in the Experimental section); however, uncertainties in the calculated $\Delta G°$ values for some of the exclusively formed 1 : 1 complexes of the bridged receptors were quite high (±1.0 kJ mol^{-1}) since host–guest exchange on the ^{1}H NMR timescale led

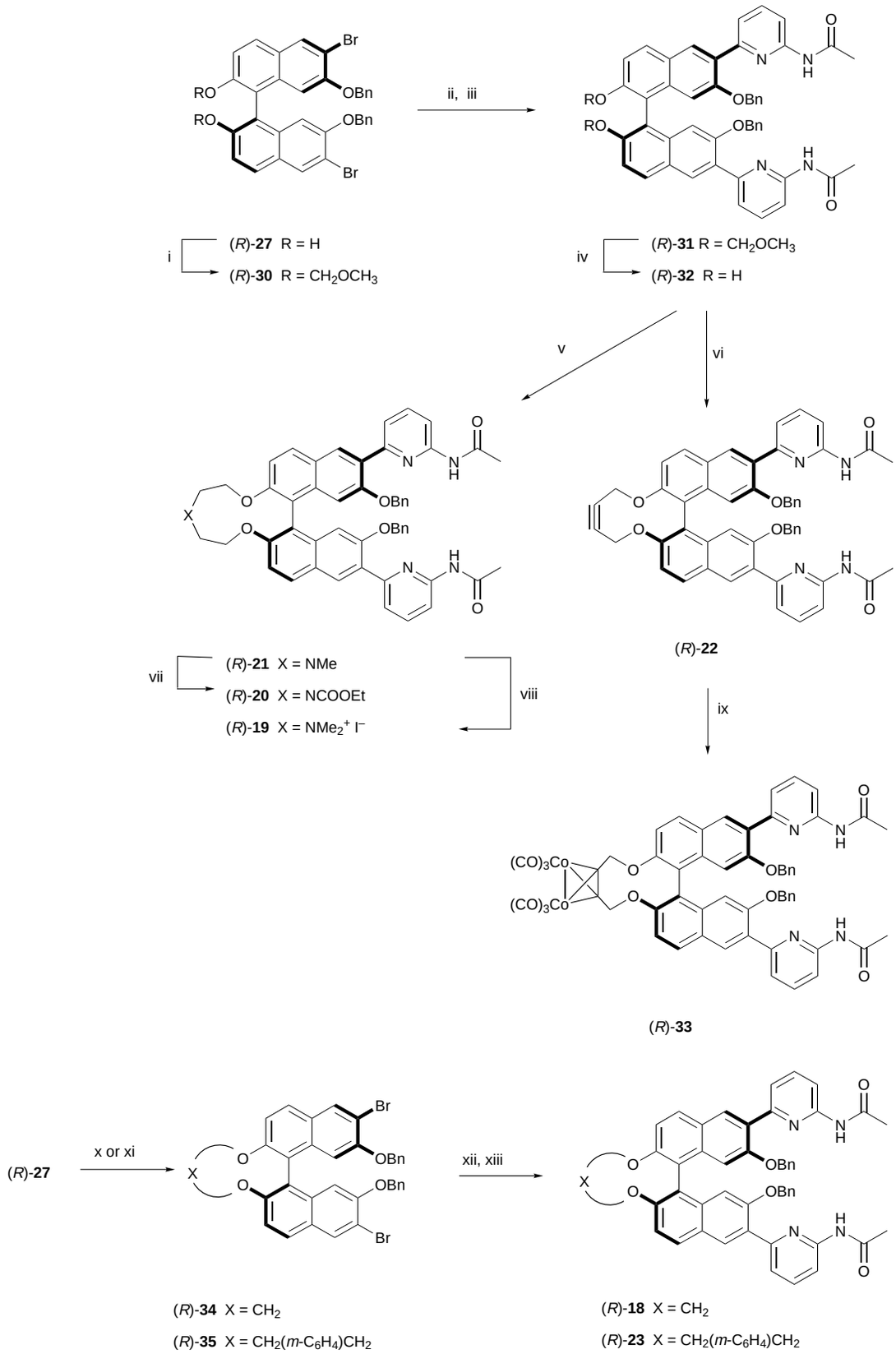


Scheme 1 Optical resolution of (±)-**27**. i, (1*R*)-(−)-Camphor-10-sulfonyl chloride, NEt_3, CH_2Cl_2, 0 °C, 3 h, quant. yield; then flash chromatography (SiO_2, CH_2Cl_2–AcOEt 99 : 1); ii, 1 M NaOH, MeOH, 60 °C, 8 h, quant. yield

to strong broadening of the resonances. Furthermore, the association strength in several runs was too high (K_a > 50 000 l mol^{-1}) to be accurately evaluated in the concentration ranges suitable for ^{1}H NMR titration experiments.[45] Therefore, a second set of titration data yielding more accurate $\Delta G°$ values (±0.4 kJ mol^{-1}) was recorded in $CDCl_3$ containing 0.2% (v/v) of the competitive co-solvent CD_3OD (Table 3, entries 8–12, Table 4).

The host–guest binding studies provided the following results. (*i*) Both the stability of the individual complexes ($\Delta G°$) as well as the binding enantioselectivity [$\Delta(\Delta G°)$] are strongly solvent-dependent. Upon addition of 0.2% (v/v) CD_3OD to the $CDCl_3$ solutions, association constants decrease by a factor of 3–10 (Table 3, entries 1 *vs.* 8 and 3 *vs.* 11) and the highest observed enantioselectivity $\Delta(\Delta G°)$ decreases from 6.9 to 3.6 kJ mol^{-1} (entries 3 and 11). With two exceptions (*N*-Cbz-Asp complexes in entries 4 and 5), the (*R*)-configured receptors all prefer binding the L-enantiomers of the two substrates.

(*ii*) Bulky substituents in the 2,2′-positions of the minor groove in (*R*)-**16** and (*R*)-**24** to (*R*)-**26** are not very effective in enhancing the binding enantioselectivity. The highest $\Delta(\Delta G°)$ value of 2.8 kJ mol^{-1} was measured for the complexation between (*R*)-**16** and the enantiomers of *N*-Cbz-Asp in $CDCl_3$ (Table 3, entry 1),[1h] whereas all other enantioselectivities varied between 0.5 and 1.9 kJ mol^{-1} (entries 5–8). As suggested already by computer modelling, the bulky substituents in the 2,2′-positions are not very effective in enforcing a narrow range of preferred dihedral angles ($\Delta\theta = \pm 10°$, Fig. 7); therefore, the



Scheme 2 Synthesis of the 1,1′-binaphthalene receptors (*R*)-**18**–(*R*)-**23** and (*R*)-**33** bridged at the 2,2′-positions. i, CH_3OCH_2Cl, K_2CO_3, MeCN, r.t., 32 h, 82%; ii, 1.6 M Bu^nLi in hexane, THF, −90 °C, Ar, 2 h, then $B(OMe)_3$, sonicator, 40 °C, 2 h; iii, *N*-(6-bromo-2-pyridyl)acetamide, $[PdCl_2(dppf)]\cdot CH_2Cl_2$ [dppf = 1,1′-bis(diphenylphosphino)ferrocene], Na_2CO_3, EtOH, H_2O, PhH, Δ, 4 h, 59%; iv, conc. aq. HCl, THF, MeOH, Δ, 1 h, quant. yield; v, $MeN(CH_2CH_2Cl)\cdot HCl$, K_2CO_3, MeCN, 80 °C, 48 h, 50%; vi, $ClCH_2C{\equiv}CCH_2Cl$, K_2CO_3, MeCN, 80 °C, 18 h, 34%; vii, ClCOOEt, NEt_3, K_2CO_3, PhMe, 80 °C, 48 h, 71%; viii, MeI, MeCN–THF 1 : 1, 50 °C, 6 h, 94%; ix, $Co_2(CO)_8$, CH_2Cl_2, r.t., 4 h, 63%; x, CH_2BrCl, K_2CO_3, MeCN, 70 °C, 3 d, quant. yield [(*R*)-**34**]; xi, $BrCH_2(m\text{-}C_6H_4)CH_2Br$, K_2CO_3, DMF, 80 °C, 16 h, 83% [(*R*)-**35**]; xii, 1.6 M Bu^nLi in hexane, THF, −78 °C, Ar, 45 min, then $B(OMe)_3$, Δ, 16 h; xiii, *N*-(6-bromo-2-pyridyl)acetamide, $[PdCl_2(PPh_3)_2]$, Na_2CO_3, EtOH, H_2O, PhH, Δ, 20 h, 57% [(*R*)-**18**]; 37% [(*R*)-**23**].

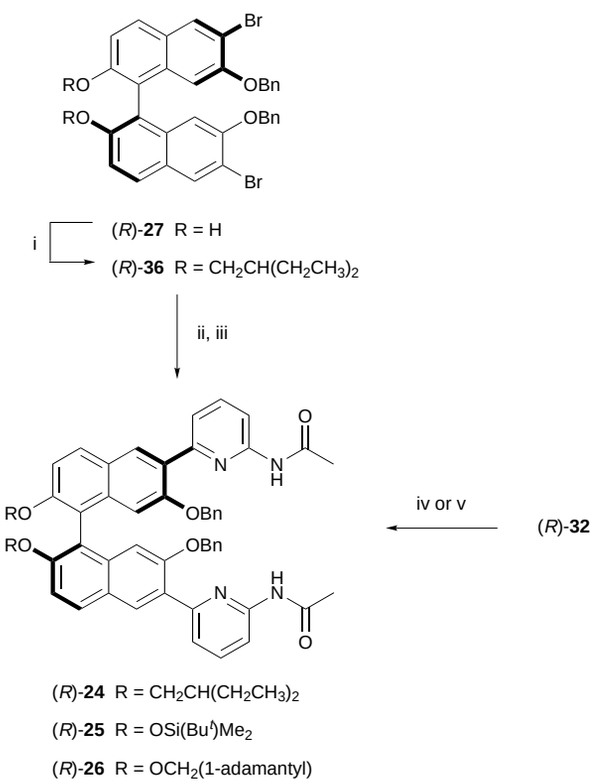
optically active receptors can adopt geometries which fit both substrate enantiomers and form diastereoisomeric complexes of similar stability.

(*iii*) Locking the dihedral angle θ by bridging the 2,2′-positions of the 1,1′-binaphthalene strongly enhances the conformational homogeneity of the receptor. This, in return, has a

Table 3 Association constants, K_a(l mol^{-1}), binding free enthalpies, ΔG^0 (kJ mol^{-1}), and enantioselectivities, $\Delta(\Delta G^0)$ (kJ mol^{-1}), at 300 K for the 1 : 1 complexes of receptors (*R*)-**16** and (*R*)-**18**–(*R*)-**26** with the enantiomers of *N*-Cbz-Asp and *N*-Cbz-Glu. Also shown is the calculated dihedral angle $\theta \pm \Delta\theta$ about the chirality axis of the 1,1′-binaphthalene spacer.

			N-Cbz-L-Asp		*N*-Cbz-D-Asp			*N*-Cbz-L-Glu		*N*-Cbz-D-Glu		
Entry	Receptor	$\theta \pm \Delta\theta$[a]/°	K_a	ΔG^0	K_a	ΔG^0	$\Delta(\Delta G^0)$[b]	K_a	ΔG^0	K_a	ΔG^0	$\Delta(\Delta G^0)$[b]
In $CDCl_3$[c]												
1	(*R*)-**16**	80 ± 10	180 000	−30.2	60 000	−27.4	2.8	19 000	−24.6	11 000	−23.2	1.4
2	(*R*)-**18**	60 ± 5	16 000	−24.1	2800	−19.8	4.3	6 500	−21.9	2 000	−19.0	2.9
3	(*R*)-**21**	86 ± 4	87 000	−28.4	5600	−21.5	6.9	94 000	−28.6	12 000	−23.4	5.2
4	(*R*)-**23**	96 ± 3	31 000	−25.8	37 000	−26.2	−0.4	14 000	−23.8	9 500	−22.8	1.0
5	(*R*)-**24**	90 ± 10	23 000	−25.1	29 000	−25.6	−0.5	23 000	−25.1	13 000	−23.6	1.5
6	(*R*)-**25**	90 ± 10	19 000	−24.6	15 000	−24.0	0.6	13 000	−23.6	7 200	−22.2	1.4
7	(*R*)-**26**	70 ± 10	38 000	−26.3	18 000	−24.4	1.9	12 000	−23.4	—	—	—
In $CDCl_3$–CD_3OD (99.8 : 0.2)[d]												
8	(*R*)-**16**	80 ± 10	18 900	−24.6	13 300	−23.7	0.9	5 500	−21.5	3 100	−20.1	1.4
9	(*R*)-**19**	72 ± 7	6 800	−22.0	2 600	−19.6	2.4	10 100	−23.0	4 900	−21.2	1.8
10	(*R*)-**20**	78 ± 5	15 700	−24.1	4 700	−21.1	3.0	5 500	−21.5	2 000	−19.0	2.5
11	(*R*)-**21**	86 ± 4	9 200	−22.8	2 200	−19.2	3.6	25 000	−25.3	6 900	−22.0	3.3
12	(*R*)-**22**	91 ± 5	7 900	−22.4	6 500	−21.9	0.5	8 000	−22.4	3 400	−20.3	2.1

[a] The dihedral angle θ is defined by C(8a)–C(1)–C(1′)–C(8a′). [b] $\Delta(\Delta G^0) = \Delta G^0$ [(*R*)-host·L-guest] − ΔG^0[(*R*)-host·D-guest]. [c] Uncertainty in ΔG^0 in entries 1–4: ±1.0 kJ mol^{-1}; in entries 5–7: ±0.4 kJ mol^{-1}. [d] Uncertainty in ΔG^0: ±0.4 kJ mol^{-1}.



Scheme 3 Synthesis of 1,1′-binaphthalene receptors (*R*)-**24**–(*R*)-**26** with bulky substituents at the 2,2′-positions. i, 1-Bromo-2-ethylbutane, K_2CO_3, DMF, 80 °C, 16 h, 100%; ii, 1.6 M Bu^nLi in hexane, THF, −78 °C, Ar, 45 min, then $B(OMe)_3$, Δ, 16 h; iii, *N*-(6-bromo-2-pyridyl)acetamide, $[PdCl_2(PPh_3)_2]$, Na_2CO_3, EtOH, H_2O, PhH, Δ, 20 h, 45%; iv, Bu^tMe_2SiCl, imidazole, DMF, 80 °C, 24 h, 77%; v, (1-adamantyl)methyl toluene-*p*-sulfonate, Cs_2CO_3, DMF, 80 °C, 3 d, 67%

pronounced effect on the binding enantioselectivity $\Delta(\Delta G°)$. Plots of the enantioselectivity as a function of θ are peak-shaped in both solvents (Fig. 9). A particularly high enantioselectivity [$\Delta(\Delta G°) = 6.9$ kJ mol^{-1}] was measured in $CDCl_3$ for the complexation of *N*-Cbz-Asp by (*R*)-**21** (Table 3, entry 3), and this receptor also showed the highest enantioselectivity [$\Delta(\Delta G°) = 5.2$ kJ mol^{-1}] in the recognition of *N*-Cbz-Glu in the same solvent. It is also the most efficient enantioselective receptor in the binary solvent mixture (entry 11). Apparently, the dihedral angle $\theta = 86 \pm 4°$ enforces a receptor conformation

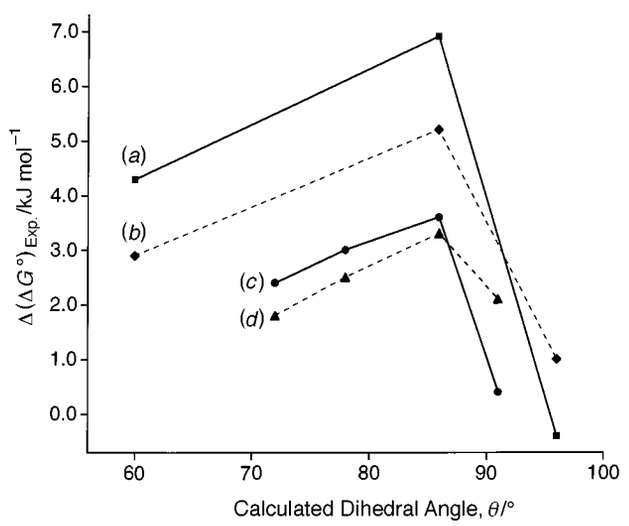


Fig. 9 Enantioselective recognition $\Delta(\Delta G^0)$ of *N*-Cbz-protected excitatory amino acids as a function of the calculated dihedral angle θ in optically active 1,1′-binaphthalene receptors bridged at the minor groove. Complexation by receptors (*R*)-**18**, (*R*)-**21** and (*R*)-**23** in $CDCl_3$ of *N*-Cbz-Asp (*a*) and *N*-Cbz- Glu (*b*). Complexation by receptors (*R*)-**19**, (*R*)-**20**, (*R*)-**21**, and (*R*)-**22** in $CDCl_3$–CD_3OD 99.8 : 0.2 of *N*-Cbz-Asp (*c*) and *N*-Cbz-Glu (*d*).

which is complementary mainly to the L-enantiomer of the two excitatory amino acid derivatives. Enlarging or reducing θ rapidly decreases the degree of enantioselectivity (Table 3, entries 2–4 or 9–12; Fig. 9). Thus, upon changing from the optimal angle $\theta = 86 \pm 4°$ in (*R*)-**21** to $72 \pm 7°$ in (*R*)-**19**, the enantioselectivity $\Delta(\Delta G°)$ for the complexation of *N*-Cbz-Asp in the binary solvent mixture decreases by 1.2 kJ mol^{-1} while it almost vanishes at $91 \pm 5°$ [in (*R*)-**22**]. Interestingly, the enantiomeric binding preference of the (*R*)-configured receptors seems to become reversed at very large dihedral angles (Table 3, entry 4, (*R*)-**23**, $\theta = 96 \pm 3°$).

(*iv*) The more stable diastereoisomeric complexes are much more structured in solution than the less stable counterparts. This was clearly demonstrated by $^1H\{^1H\}$ nuclear Overhauser effect (NOE) difference spectroscopy. A total of five intermolecular NOEs were measured for the complex between (*R*)-**21** and *N*-Cbz-L-Asp, whereas only two intermolecular NOEs were observed for the diastereoisomeric complex formed by *N*-Cbz-D-Asp. Computer simulation of the more stable complex

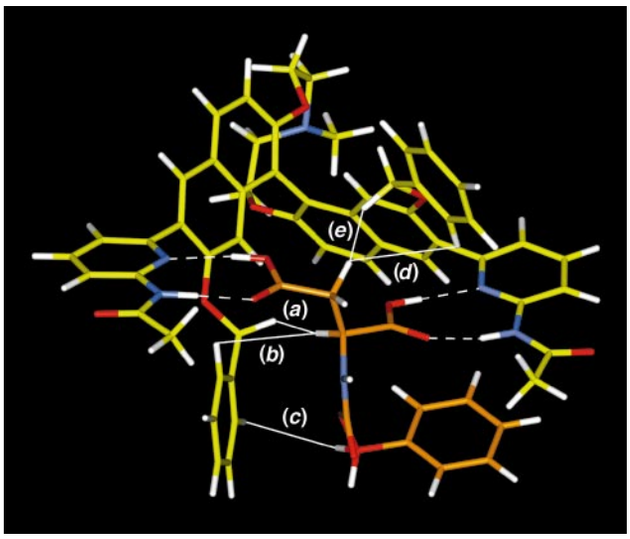


Fig. 10 Computer-generated model of the complex formed between (*R*)-**21** and *N*-Cbz-L-Asp in $CDCl_3$. The four COOH···CONH(py) H-bonds (– – –) are shown as well as the five observed intermolecular NOEs (—) at computed distances of 2.39 Å (*a*), 2.83 Å (*b*), 3.25 Å (*c*), 3.26 Å (*d*) and 2.53 Å (*e*). Secondary electrostatic interactions between the substrate COOH groups and the benzyl ether O-atoms of the receptor are effective at H···O distances of 2.94 (O–H···O angle of 104.0°) and 3.03 Å (O–H···O) angle of 104.4°).

(MacroModel V. 5.0, OPLS* force field, 2000-step pseudo-MCMM search in $CDCl_3$) yielded a total of eight structures within 10 kJ mol^{-1} of the computed global minimum (Fig. 10) which were all congruent with the experimentally observed NOEs. The torsional angles between the pyridyl and adjacent naphthalene moieties of the receptor were found to be 70°, and the dihedral angle θ was computed to be *ca.* 86°. The substrate binds in the *cis*-carbamate conformation. Characteristic host–guest interactions in the tight complex are the two COOH···CONH(py) H-bonding motifs[6] with nearly perfectly linear O–H···N H-bonds of *ca.* 1.9 Å and C=O···H–N H-bonds of *ca.* 1.7 Å length. The bound COOH groups further participate in attractive secondary electrostatic H-bonding interactions[31] C(O)O–H···O–C(7), with O···O distances between 3.3 and 3.4 Å and O–H···O angles of 105°. Aromatic interactions also play an important role in the stabilization of the complex: one phenyl ring of the receptor stacks with the *cis*-carbamate bond of the substrate, both phenyl rings of the receptor participate in T-shaped interactions with the two COOH···CONH(py) H-bond arrays,[46] and the phenyl ring of the substrate is involved in a face-to-face stacking with one of these host–guest H-bonding motifs. A much poorer host–guest complementarity with a smaller number of intermolecular contacts was found in the compound structures of the less stable diastereoisomeric complex between (*R*)-**21** and *N*-Cbz-D-Asp, for which only two NOEs were observed experimentally. Furthermore, the two COOH···CONH(py) H-bonding arrays in this complex are strongly distorted out of planarity.

Note that the complex of the flexible receptor (*R*)-**16** with *N*-Cbz-L-Asp (Table 3, entry 1)[1h] resembles closely in its geometry the complex of (*R*)-**21** with this guest, as shown in Fig. 10. The same five intermolecular NOEs are observed for both complexes in $CDCl_3$, and the calculated lowest-energy structures, which are in agreement with the experimental NOEs, are nearly identical. The dihedral angle θ in the complex of (*R*)-**16** was computed to be *ca.* 85° and, therefore, is identical to the corresponding angle in the complex of (*R*)-**21** ($\theta = 86°$). The complex formed by the flexible receptor and *N*-Cbz-L-Asp is even more stable (by 1.8 kJ mol^{-1}; Table 3, entry 1) than the association formed by the bridged receptor (*R*)-**21** (entry 3); however, the enantioselectivity displayed by the two receptors differs greatly, with the difference in stability between the diastereoisomeric complexes of the bridged receptor (*R*)-**21** being 4.1 kJ mol^{-1} higher. This comparison illustrates in an impressive way the importance of preorganisation and conformational homogeneity of a receptor for efficient chiral recognition. The bridge in the minor groove of (*R*)-**21** enforces a geometry of the recognition site which fits the L-Asp derivative much better than the D-Asp derivative; hence, the latter is only weakly bound. The more flexible receptor (*R*)-**16** adopts a similar, favorable geometry for complexing the L-Asp derivative; however, its greater flexibility also allows geometrical adjustment of its recognition site to the other substrate enantiomer and, therefore, stable diastereoisomeric complexes with both optical antipodes are formed (Table 3, entry 1).

Conclusions

This report describes the successful completion of a systematic development of optically active 1,1′-binaphthalene receptors with H-bonding sites located in the major groove for efficient chiral recognition of excitatory amino acid derivatives. In a first step, described in a previous article[1h] and summarised in the introduction to this paper, the major groove H-bonding sites had been systematically optimized for binding strength. In the subsequent study reported here, the conformational homogeneity and, as a consequence, the enantioselectivity of the receptors were strongly enhanced by enforcing the dihedral angle about the chirality axis through C(1)–C(1′). This was achieved by tightly bridging the 2,2′-positions in the minor groove, whereas attachment of bulky substituents at these centres proved to be less efficient. Plots of the enantioselectivity $\Delta(\Delta G°)$ in the recognition by the bridged receptors as a function of the enforced dihedral angle θ displayed a pronounced peak-shape, and the highest enantioselectivities were measured in $CDCl_3$ (300 K) for the complexation of the enantiomers of *N*-Cbz-Asp [$\Delta(\Delta G°) = 6.9$ kJ mol^{-1}] and *N*-Cbz-Glu [$\Delta(\Delta G°) = 5.2$ kJ mol^{-1}] by (*R*)-**21** ($\theta = 86 \pm 4°$); these are remarkably high numbers for flexible substrates. In contrast, the more flexible optically active receptors without a bridge in the minor groove are capable of forming stable diastereoisomeric complexes with both substrate enantiomers; hence, the degree of chiral recognition is low. We conclude from this and previous studies[1e,h,7b,c,21] that conformational homogeneity is even more important for efficient chiral recognition [$\Delta(\Delta G°)$] than for binding strength ($\Delta G°$).

This molecular recognition study with excitatory amino acid derivatives illustrates a new, general principle for improving the chiral recognition potential of 1,1′-binaphthalene receptors. Locking the dihedral angle θ about their C(1)–C(1′)-axis by bridging either the minor or the major groove should in the future provide access to a variety of tailor-made, enantioselective receptors for diverse classes of chiral substrates. Furthermore, it should also provide an attractive protocol for developing new generations of preorganised 1,1′-binaphthalene ligands for transition-metal mediated asymmetric catalysis.[47]

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. $CHCl_3$ was purified by washing with H_2O and then distilling over P_2O_5. Evaporation *in vacuo* was carried out at water aspirator pressure; drying of products occurred at 10^{-2} Torr. 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 rt = 295 ± 1 K, unless stated otherwise). 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. FABMS: VG ZAB 2 SEQ instrument, 3-nitrobenzyl alcohol as matrix, positive mode. Elemental analysis: Mikrolabor des Laboratoriums für Organische Chemie at ETHZ.

Optical resolution of (±)-7,7′-bis(benzyloxy)-6,6′-dibromo-1,1′-binaphthalene-2,2′-diol, (±)-27

To (±)-**27** (4.0 g, 6.1 mmol) and NEt_3 (2.12 ml, 1.54 g; 15.2 mmol) in abs. CH_2Cl_2 (180 ml) was added (1*R*)-(−)-camphor-10-sulfonyl chloride (3.44 g, 13.7 mmol) at 0 °C under Ar, and the mixture was stirred for 3 h at this temperature. Water (180 ml) was added, the phases were separated, and the organic phase was washed with sat. aq. NaCl solution, dried ($MgSO_4$) and evaporated *in vacuo* to give, after drying, 6.62 g (quant. yield) of the mixture of diastereosiomers (−)-**28** and (+)-**29**. Chromatography (SiO_2, CH_2Cl_2–AcOEt 99:1) provided (−)-**28** (3.13 g, 47%) as a white foam, together with 3.31 g of enriched (+)-**29**. Chromatography of an analytical sample (500 mg) yielded optically pure (+)-**29** (425 mg) as a white foam.

(−)-7,7′-Bis(benzyloxy)-6,6′-dibromo-2,2′-bis[(7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methylsulfonyloxy]-1,1′-binaphthalene, (−)-28

R_f 0.21 (CH_2Cl_2–AcOEt 98:2) [Found: C, 59.71; H, 4.97; Br, 14.65; S, 5.93. Calc. for $C_{54}H_{52}Br_2O_{10}S_2$ (1084.94): C, 59.78; H, 4.83; Br, 14.72; S, 5.91%]; $[\alpha]_D^{23}$ −154.9 (*c* 1.00, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3440m, 2958m, 1748s, 1615m, 1489s; δ_H(300 MHz, $CDCl_3$) 0.54 (6 H, s), 0.78 (6 H, s), 1.22–1.38 (4 H, m), 1.77–2.12 (8 H, m), 2.15–2.26 (2 H, m), 2.43 (2 H, d, J_{AB} 14.8), 2.84 (2 H, J_{AB} 14.8), 4.59 (2 H, d, J_{AB} 12.9), 4.93 (2 H, d, J_{AB} 12.9), 6.33 (2 H, s), 6.95–7.18 (10 H, m), 7.62 (2 H, d, *J* 9.0), 7.89 (2 H, d, *J* 9.0), 8.16 (2 H, s); δ_C(75 MHz, $CDCl_3$) 19.25, 19.42, 24.88, 26.79, 42.31, 42.78, 47.71, 49.09, 57.71, 70.52, 107.34, 115.29, 120.21, 122.15, 126.71, 127.76, 127.82, 128.54, 129.46, 132.57, 133.47, 135.98, 146.53, 153.94, 213.49; *m/z* (FABMS) 1084 (M^+, 100%), 870 [$(M - C_{10}H_{14}O_3S)^+$, 81%].

(+)-7,7′-Bis(benzyloxy)-6,6′-dibromo-2,2′-bis[(7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methylsulfonyloxy]-1,1′-binaphthalene, (+)-29

R_f 0.10 (CH_2Cl_2–AcOEt 98:2); [Found: C, 59.94; H, 4.86; Br, 14.55; S, 5.92. Calc. for $C_{54}H_{52}Br_2O_{10}S_2$ (1084.94): C, 59.78; H, 4.83; Br, 14.72; S, 5.91%]; $[\alpha]_D^{23}$ +130.9 (*c* 1.00, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3439m, 2958m, 1748s, 1615m, 1583w, 1489s; δ_H(300 MHz, $CDCl_3$) 0.49 (6 H, s), 0.68 (6 H, s), 1.18–1.35 (4 H, m), 1.77–1.97 (8 H, m), 2.16 (2 H, d, J_{AB} 14.9), 2.20–2.28 (2 H, m), 3.27 (2 H, d, J_{AB} 14.9), 4.59 (2 H, d, J_{AB} 12.8), 4.89 (2 H, d, J_{AB} 12.8), 6.31 (2 H, s), 6.93–7.16 (10 H, m), 7.63 (2 H, d, *J* 9.0), 7.89 (2 H, d, *J* 9.0), 8.16 (2 H, s); δ_C(75 MHz, $CDCl_3$) 19.11, 19.22, 24.61, 26.76, 42.31, 42.66, 47.58, 49.14, 57.71, 70.56, 107.51, 115.21, 120.12, 122.28, 126.66, 127.79, 127.84, 128.55, 129.43, 132.55, 133.55, 135.87, 146.35, 153.76, 213.63; *m/z* (FABMS) 1085 [$(MH)^+$, 100], 870 [$(M - C_{10}H_{14}O_3S)^+$, 57%].

(*R*)-7,7′-Bis(benzyloxy)-6,6′-dibromo-1,1′-binaphthalene-2,2′-diol, (*R*)-27

To (−)-**28** (2.00 g, 1.86 mmol) in abs. THF (30 ml) and MeOH (40 ml) was added 1 M aq. NaOH solution (25 ml), and the mixture was heated to 60 °C for 8 h, then stirred at room temp. for 12 h. After concentration *in vacuo* and neutralization with 2 M aq. HCl solution, the mixture was extracted with CH_2Cl_2 (3 × 120 ml) and the combined organic layers were washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl solutions, dried ($MgSO_4$) and evaporated *in vacuo*. Plug filtration (SiO_2, CH_2Cl_2) afforded (−)-(*R*)-**27** (1.217 g, quant. yield) as a white foam; $[\alpha]_D^{23}$ −304.4 (*c* 1.00, $CHCL_3$) [lit.,[1h] $[\alpha]_D^{23}$ −296.7 (*c* 1.00, $CHCl_3$)].

(*R*)-7,7′-Bis(benzyloxy)-6,6′-dibromo-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene, (*R*)-30

To (*R*)-**27** (4.0 g, 6.1 mmol) in CH_3CN (160 ml) under Ar was added K_2CO_3 (5.0 g, 36.0 mmol), and the mixture was stirred for 15 min at 0 °C after which chloromethyl methyl ether (MOMCl, 1.8 ml, 24.0 mmol) was added dropwise. The solution was stirred at room temp. for 16 h, quenched with MeOH (30 ml) and stirred for an additional 16 h. Filtration (×2) through a pad of Celite, evaporation *in vacuo* and recrystallization [AcOEt–hexane 3:1 (60 ml)] afforded (*R*)-**30** (3.7 g, 82%) as white crystals; mp 124–125 °C [Found: C, 61.20; H, 4.40; Br, 21.23. Calc. for $C_{38}H_{32}O_6Br_2$ (744.5): C, 61.31; H, 4.33; Br 21.47%]; $[\alpha]_D^{22}$ −148.5 (*c* 1.23, $CHCl_3$); ν_{max}($CDCl_3$)/cm^{-1} 2927, 1638, 1241; δ_H(500 MHz, $CDCl_3$) 3.11 (6 H, s), 4.64 (2 H, d, J_{AB} 12.8), 4.74 (2 H, d, J_{AB} 12.8), 4.86 (2 H, d, J_{AB} 6.8), 4.96 (2 H, d, J_{AB} 6.8), 6.27 (2 H, s), 6.90–7.20 (10 H, m), 7.41 (2 H, d, *J* 9.0), 7.80 (2 H, d, *J* 9.0), 8.10 (2 H, s); δ_C(125.8 MHz, $CDCl_3$) 55.78, 70.15, 94.92, 106.31, 111.97, 115.53, 119.69, 125.85, 126.59, 127.52, 128.10, 128.29, 132.12, 133.86, 135.99, 152.65, 153.23; *m/z* (FABMS) 744 (M^+, 23), 713 (4), 669 (3), 634 (2), 91 (100%).

(*S*)-**30** {$[\alpha]_D^{22}$ +148.1 (*c* 1.23, $CHCl_3$)} was prepared in a similar manner to (*S*)-**27** which was obtained as previously described.[1h]

(*R*)-6,6′-Bis(6-acetamido-2-pyridyl)-7,7′-bis(benzyloxy)-2,2′-bis-(methoxymethoxy)-1,1′-binaphthalene, (*R*)-31

To (*R*)-**30** (800 g, 1.1 mmol) in dry THF (30 ml) at −90 °C under Ar was added dropwise 2.5 M BuLi in hexane (2.2 ml, 5.4 mmol), and the mixture was stirred at −90 °C for 2 h. Trimethyl borate (1.2 ml, 10.7 mmol) was added rapidly, and the mixture was warmed to room temp., then sonicated at 40 °C for 2 h. Removal of the solvent *in vacuo*, partitioning of the residue between CH_2Cl_2 (100 ml) and sat. aq. $NaHCO_3$ solution (40 ml), washing of the organic layer with sat. aq. NaCl solution (50 ml), and evaporation *in vacuo* yielded the crude bis(boronic acid) as a yellow oil. To the crude bis(boronic acid) in EtOH (6 ml), PhH (22 ml) and H_2O (5 ml) was added *N*-(6-bromo-2-pyridyl)acetamide (460 mg, 2.1 mmol) and Na_2CO_3 (228 mg, 2.1 mmol), and the mixture was heated to reflux under Ar. After addition of $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (24 mg, 0.03 mmol), heating was continued for 4 h. Removal of the solvent *in vacuo* gave a brown oil which was dissolved in CH_2Cl_2 (100 ml), washed with sat. aq. $NaHCO_3$ solution (30 ml) and sat. aq. NaCl solution (30 ml), dried ($MgSO_4$) and evaporated *in vacuo* to produce a yellow oil. Chromatography ($SiO_2CH_2Cl_2$–AcOEt–NEt_3 97.5:2:0.5→49.75:49.75:0.50) afforded colorless (*R*)-**31** (545 mg, 59%): mp 243–244 °C [Found: C, 72.65; H, 5.73; N, 6.40. Calc. for $C_{52}H_{46}N_4O_8$ (855.0): C, 73.05; H, 5.42; N, 6.55%]; $[\alpha]_D^{22}$ −152.5 (*c* 1.00, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3350, 1692, 1625; δ_H(200 MHz, $CDCl_3$) 2.25 (6 H, s), 3.16 (6 H, s), 4.69 (2 H, d, J_{AB} 12.4), 4.72 (2 H, d, J_{AB} 12.4), 4.90 (2 H, d, J_{AB} 6.7), 4.98 (2 H, d, J_{AB} 6.7), 6.55 (2 H, S), 6.92–7.36 (10 H, m), 7.44 (2 H, d, *J* 9.0), 7.60–7.80 (4 H, m), 7.96 (2 H, d, *J* 9.0), 8.04 (2 H, s), 8.15 (2 H, d, *J* 8.0), 8.24 (2 H, s); δ_C(125.8 MHz, $CDCl_3$) 24.76, 55.84, 69.81, 95.05, 105.76, 111.96, 115.28, 121.36, 125.23, 126.92, 127.45, 128.25, 129.72, 130.80, 135.16, 136.47, 138.10, 150.84, 153.65, 154.48; *m/z* (FABMS) 855 (M^+, 11), 460 (6), 391 (13), 371 (5), 307 (38), 154 (100%).

(*S*)-**31** {$[\alpha]_D^{22}$ +152.1 (*c* 1.00, $CHCl_3$)} was prepared in a similar manner to (*S*)-**30**.

(*R*)-6,6′-Bis(6-acetamido-2-pyridyl)-7,7′-bis(benzyloxy)-1,1′-binaphthalene-2,2′-diol, (*R*)-32

To (*R*)-**31** (0.47 g, 0.55 mmol) in THF (32.0 ml) and MeOH (18.0 ml) was added conc. aq. HCl solution (0.6 ml), and the resulting green solution was heated to reflux for 1 h. The mixture was diluted with H_2O (10 ml), neutralized with 15% aq. NaOH solution (1.5 ml) and extracted with AcOEt (3 × 60 ml). The combined organic layers were washed with H_2O (60 ml), dried ($MgSO_4$) and evaporated *in vacuo* to produce 422.0 mg

(100%) of colorless (*R*)-**32**: mp 272–275 °C [Found: C, 71.16; H, 5.27; N, 6.70. Calc. for $C_{48}H_{38}N_4O_6 \cdot 2.5\ H_2O$ (811.9): C, 70.95; H, 5.30; N, 6.89%]; $[\alpha]_D^{22}$ −241.2 (*c* 0.434, $CHCl_3$); $\nu_{max}(CDCl_3)/cm^{-1}$ 3677, 3289, 1689, 1600, 1572; δ_H(200 MHz, $CDCl_3$) 2.24 (6 H, s), 4.72 (2 H, d, J_{AB} 12.2), 4.80 (2 H, d, J_{AB} 12.2), 5.11 (2 H, br s), 6.54 (2 H, s), 6.90–7.30 (10 H, m), 7.26 (2 H, d, *J* 9.0), 7.30–7.80 (4 H, m), 7.99 (2 H, d, *J* 9.0), 8.09 (2 H, s), 8.15 (2 H, d, *J* 8.0), 8.25 (s, 2 H); *m*/*z* (FABMS) 767 (M^+, 31), 675 (3), 391 (8), 307 (27), 154 (100%).

(*S*)-**32** {$[\alpha]_D^{22}$ +242.1 (*c* 0.436, $CHCl_3$)} was prepared in a similar manner to (*S*)-**31**.

(*R*)-3,17-Bis(6-acetamido-2-pyridyl)-2,18-bis(benzyloxy)-10-methyl-9,10,11,12-tetrahydro-8*H*-dinaphtho[2,1-*h*:1,2-*j*][1,7,4]dioxazacycloundecine, (*R*)-21

To a slurry of K_2CO_3 (108 mg, 0.782 mmol) in MeCN (50 ml) at 80 °C under Ar were simultaneously added a solution of (*R*)-**32** (75 mg, 0.098 mmol) in THF (5 ml) and methylbis(2-chloroethyl)amine hydrochloride (22.6 mg, 0.117 mmol) in MeCN (5 ml) over 14 h using a syringe pump. Additional methylbis-(2-chloroethyl)amine hydrochloride (20 mg, 0.103 mmol) was added, and the mixture was stirred at 80 °C for 34 h. Cooling to room temp., filtration over Celite and evaporation *in vacuo* followed by chromatography (SiO_2, CH_2Cl_2–AcOEt–NEt_3 79.5:20:0.5→74.5:25:0.5) afforded (*R*)-**21** (42 mg, 50%) as a white foam: mp 148–149 °C; $[\alpha]_D^{23}$ −272.0 (*c* 0.10, $CHCl_3$); $\nu_{max}(CDCl_3)/cm^{-1}$ 3417, 1694, 1625; δ_H(200 MHz, $CDCl_3$) 2.21 (9 H, br s), 2.68–2.78 (4 H, m), 4.03–4.19 (2 H, m), 3.37–4.43 (2 H, m), 4.58 (2 H, d, J_{AB} 12.0), 4.71 (2 H, d, J_{AB} 12.0), 6.55 (2 H, s), 6.95–7.07 (4 H, m), 7.09–7.12 (6 H, m), 7.30 (2 H, d, *J* 8.7), 7.61–7.75 (4 H, m), 7.94 (2 H, d, *J* 9.1), 8.10–8.16 (4 H, m), 8.23 (2 H, s); δ_C(50.0 MHz, $CDCl_3$) 24.80, 42.03, 56.54, 67.66, 69.82, 105.74, 112.06, 114.35, 119.90, 121.66, 124.91, 127.32, 127.67, 128.19, 128.45, 129.78, 131.20, 135.77, 136.78, 138.29, 151.17, 154.69, 154.97, 155.39, 168.51; *m*/*z* (FABMS) 850 (MH^+, 100%); *m*/*z* (HR-FABMS) 849.3529 (M^+, $[C_{53}H_{47}N_5O_6]^+$; calc. 849.3526).

(*R*)-3,17-Bis(6-acetamido-2-pyridyl)-2,18-bis(benzyloxy)-10-(ethoxycarbonyl)-9,10,11,12-tetrahydro-8*H*-dinaphtho[2,1-*h*:1,2-*j*][1,7,4]dioxazacycloundecine, (*R*)-20

A slurry of K_2CO_3 (397 mg) in toluene (30 ml) was degassed with Ar, then (*R*)-**21** (55 mg, 0.065 mmol) and NEt_3 (1.5 ml) were added, and the mixture was heated to 80 °C. After addition of ethyl chloroformate (2.0 ml, 2.27 g, 20.9 mmol), the mixture was heated to 80 °C for 48 h, then cooled to room temp. The residue obtained by evaporation *in vacuo* was partitioned between CH_2Cl_2 (150 ml) and sat. aq. $NaHCO_3$ solution (3 × 50 ml), the organic phase was dried ($MgSO_4$) and evaporated *in vacuo*, and chromatography (SiO_2, CH_2Cl_2–AcOEt 95:5→85:15) yielded (*R*)-**20** (42 mg, 71%) as a white solid: decomp. >154 °C; $[\alpha]_D^{23}$ −347.4 (*c* 0.10, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3426w, 2922w, 1697s, 1624m, 1573m, δ_H(200 MHz, $CDCl_3$) 1.28 (3 H, t, *J* 7.1), 2.26 (6 H, s), 3.35–3.75 (4 H, m), 4.17 (2 H, q, *J* 7.1), 4.35–4.55 (4 H, m), 4.56 (2 H, d, J_{AB} 12.2), 4.66 (2 H, d, J_{AB} 12.2), 6.61 (2 H, s), 6.94–7.12 (10 H, m), 7.20–7.30 (2 H, m), 7.64–7.77 (4 H, m), 8.00 (2 H, d, *J* 9.1), 8.04 (2 H, s), 8.15 (2 H, d, *J* 7.5), 8.29 (2 H, s); δ_C(50 MHz, $CDCl_3$) 14.56, 24.66, 50.60, 51.70, 61.54, 68.33, 69.83, 105.60, 111.50, 111.95, 117.44, 117.91, 121.44, 124.58, 126.99, 127.53, 127.91, 128.04, 128.29, 128.67, 130.01, 131.18, 132.07, 132.26, 134.90, 135.06, 136.52, 138.10, 150.99, 154.04, 154.26, 154.54, 155.02, 156.45, 168.7; *m*/*z* (FABMS) 908 (M^+, 100), 818 (12%); *m*/*z* (HR-FABMS) 907.3564 (M^+, $[C_{55}H_{49}N_5O_8]^+$; calc. 907.3581).

(*R*)-3,17-Bis(6-acetamido-2-pyridyl)-2,18-bis(benzyloxy)-10,10-dimethyl-9,10,11,12-tetrahydro-8*H*-dinaphtho[2,1-*h*:1,2-*j*][1.7.4]dioxazacycloundecinium iodide, (*R*)-19

A solution of (*R*)-**21** (20 mg, 0.023 mmol) in THF–MeCN 1:1 (5 ml) and methyl iodide (29 µl, 66.8 mg; 0.470 mmol) was stirred at 50 °C for 6 h. Evaporation *in vacuo* and chromatography (neutral Al_2O_3 containing 1% H_2O, MeCN) afforded (*R*)-**19** (22 mg, 94%) as a cream-colored solid: mp 175–176 °C; $[\alpha]_D^{23}$ −263.4 (*c* 0.10, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3433m, 3244w, 2922w, 1683m, 1622s, 1572s; δ_H(300 MHz, $CDCl_3$) 2.24 (6 H, s), 3.14 (6 H, br s), 3.42–3.76 (4 H, m), 4.30–4.45 (2 H, m), 4.51 (4 H, br s), 4.71–4.76 (2 H, m), 6.43 (2 H, s), 6.76–6.99 (10 H, m), 7.20 (2 H, d, *J* 9.0), 7.62–7.72 (4 H, m), 7.95 (2 H, d, *J* 8.7), 8.18 (2 H, d, *J* 7.5), 8.35 (2 H, s), 8.65 (2 H, br s); δ_C(75 MHz, $CDCl_3$) 24.82, 53.52, 60.99, 62.37, 70.05, 105.65, 112.36, 112.71, 119.01, 121.39, 125.22, 127.10, 127.91, 128.55, 129.07, 130.91, 131.85, 134.91, 136.25, 138.41, 151.61, 152.43, 153.55, 155.49, 169.55; *m*/*z* (FABMS) 864 [$(M - I)^+$, 100], 774 (8), 663 (18), 530 (82%); *m*/*z* (HR-FABMS) 864.3911 [$(M - I)^+$, $[C_{54}H_{50}N_5O_6]^+$, calc. 864.3761].

(*R*)-2,7-Bis(6-acetamido-2-pyridyl)-3,6-bis(benzyloxy)-13,14-didehydro-12,15-dihydrodinaphtho[2,1-*b*:1,2-*d*][1,6]dioxecine, (*R*)-22

To a slurry of K_2CO_3 (72.08 mg, 0.522 mmol) in 50 ml MeCN at 80 °C under Ar were simultaneously added a solution of (*R*)-**32** (50 mg, 0.065 mmol) in THF (5 ml) and 1,4-dichlorobut-2-yne (7.6 µl, 9.6 mg, 0.078 mmol) in MeCN (5 ml) over 14 h using a syringe pump. Additional dichlorobut-2-yne (7.9 µl, 10 mg, 0.081 mmol) was added, and the mixture was stirred at 80 °C for 4 h, then cooled to room temp. Filtration over Celice and evaporation *in vacuo*, followed by chromatography (SiO_2, CH_2Cl_2–AcOEt–NEt_3 79.5:20:0.5→74.5:25:0.5) gave (*R*)-**22** (18 mg, 34%): decomp. >135 °C; $[\alpha]_D^{23}$ −208.5 (*c* 0.10, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3400w, 2992w, 1697m, 1623m, 1572m; δ_H(300 MHz, $CDCl_3$) 2.18 (6 H, s), 4.44–4.59 (4 H, m), 4.72 (2 H, d, J_{AB} 11.8), 4.86 (2 H, d, J_{AB} 11.8), 6.71 (2 H, s), 7.02–7.16 (10 H, m), 7.30 (2 H, d, *J* 8.7), 7.62–7.75 (4 H, m), 8.00 (2 H, d, *J* 8.7), 8.15 (2 H, d, *J* 7.8), 8.21 (2 H, br s), 8.24 (2 H, s); δ_C(75 MHz, $CDCl_3$) 24.76, 62.37, 70.05, 88.29, 106.84, 112.36, 119.56, 121.64, 126.74, 126.82, 127.47, 127.78, 128.50, 129.77, 130.75, 131.08, 135.40, 136.64, 138.37, 151.25, 153.89, 154.41, 155.02, 169.00; *m*/*z* (FABMS) 817 (MH^+, 100%); *m*/*z* (HR-FABMS) 817.3029 [$(MH)^+$, $[C_{52}H_{41}N_4O_6]^+$; calc. 817.3026].

(*R*)-µ-(6,7-η:6,7-η′)[2,7-Bis(6-acetamido-2-pyridyl)-3,6-bis(benzyloxy)-13,14-didehydro-12,15-dihydrodinaphtho[2,1-*b*:1,2-*d*][1,6]dioxecine]-bis(tricarbonylcobalt) (*Co*–*Co*), (*R*)-33

To a degassed solution of (*R*)-**22** (14 mg, 0.017 mmol) in CH_2Cl_2 (4 ml) was added $Co_2(CO)_8$ (13.0 mg, 0.034 mmol), and the mixture was stirred at room temp. for 4 h. Chromatography (SiO_2, $CHCl_3$) followed by precipitation with hexane gave (*R*)-**33** (12 mg, 63%) as an orange foam: decomp. >115 °C; ν_{max}(KBr)/cm^{-1} 3423w, 2092m, 2058s, 2025s, 1699m, 1623m, 1586m, 1572m; δ_H(500 MHz, $CDCl_3$) 2.24 (6 H, s), 4.55 (2 H, d, *J* 12.2), 4.71 (2 H, d, *J* 12.2), 5.30 (2 H, d, *J* 14.5), 5.59 (2 H, d, *J* 14.5), 6.49 (2 H, s), 6.95–6.98 (4 H, m), 7.06–7.25 (6 H, m), 7.41 (2 H, d, *J* 9.0), 7.62 (2 H, d, *J* 8.0), 7.70 (2 H, t, *J* 8.3), 7.98 (2 H, d, *J* 8.0), 8.00 (2 H, s), 8.13 (2 H, d, *J* 8.3), 8.24 (2 H, s); δ_C(125.8 MHz, $CDCl_3$) 24.78, 69.77, 71.65, 90.29, 105.63, 112.00, 116.30, 120.44, 121.43, 125.57, 127.00, 127.51, 128.23, 128.72, 130.33, 130.96, 135.35, 136.30, 138.05, 150.88, 154.02, 154.57, 155.01, 168.50, 198.60, 213.70, 223.72; *m*/*z* (FABMS) 1103 (MH^+, 100), 1075 [$(MH - CO)^+$, 9%], 990 (69), 883 (41), 791 (37%); *m*/*z* (HR-FABMS) 1103.1391 [$(MH)^+$, $[C_{58}H_{41}Co_2N_4O_{12}]^+$; calc. 1103.1384].

(*R*)-8,11-Bis(benzyloxy)-7,12-dibromodinaphtho[2,1-*d*:1,2-*f*][1,3]dioxepine, (*R*)-34

To (*R*)-**27** (330.0 mg, 0.5 mmol) in CH_3CN (16.5 ml) was added K_2CO_3 (1.2 g, 8.0 mmol), and the mixture was stirred for 15 min at 70 °C after which bromochloromethane (0.15 ml, 2.3 mmol) was added. After stirring at 70 °C for 3 d, filtration through a pad of Celite, evaporation *in vacuo*, and chromatography

(SiO_2, cyclohexane–CH_2Cl_2 3:2) afforded (*R*)-**34** (334.5 mg, 100%) as a white solid: mp 112–113 °C [Found: C, 62.90; H, 3.65. Calc. for $C_{35}H_{24}O_4Br_2$ (668.4): C, 62.90; H, 3.62%]; $[\alpha]_D^{23}$ −724.2 (*c* 0.521, $CHCl_3$); $\nu_{max}(CDCl_3)/cm^{-1}$ 1618, 1500; δ_H(500 MHz, $CDCl_3$) 4.59 (2 H, d, J_{AB} 12.8), 4.65 (2 H, d, J_{AB} 12.8), 5.92 (s, 2 H), 6.71 (2 H, s), 7.00–7.10 (4 H, m), 7.15–7.24 (6 H, m), 7.34 (2 H, d, *J* 9.0), 7.85 (2 H, d, *J* 9.0), 8.18 (2 H, s); δ_C(125.8 MHz, $CDCl_3$) 70.57, 102.93, 107.43, 113.22, 119.54, 124.74, 126.41, 127.86, 128.43, 129.09, 131.81, 132.68, 135.89, 151.92, 153.01; *m*/*z* (DCIMS) 668 (M^+, 100), 588 (10), 469 (16), 181 (24%).

(*R*)-2,18-Bis(benzyloxy)-3,17-dibromo-8,12-dihydrobenzo[*hi*]-dinaphtho[2,1-*b*:1,2-*d*][1,6]dioxacycloundecine, (*R*)-35

To (*R*)-**27** (200.0 mg, 0.30 mmol) in DMF (6.0 ml) was added K_2CO_3 (664.0 mg, 4.80 mmol) and the mixture was stirred for 15 min at 80 °C after which α,α′-dibromo-*m*-xylene (119.0 mg, 0.48 mmol) in DMF (4.0 ml) was slowly added *via* syringe pump over 16 h. Filtration through a pad of Celite, evaporation *in vacuo* and chromatography (SiO_2, CH_2Cl_2–cyclohexane 1:1) afforded (*R*)-**35** (191.4 mg, 83%) as a white solid: mp 210–212 °C [Found: C, 66.56; H, 4.02. Calc. for $C_{42}H_{30}O_4Br_2$ (758.5): C, 66.51; H, 3.99%]; $[\alpha]_D^{23}$ −1562.2 (*c* 0.522, $CHCl_3$); $\nu_{max}(CDCl_3)/cm^{-1}$ 2927, 1638, 1241; δ_H(500 MHz, $CDCl_3$) 4.76 (2 H, d, J_{AB} 12.3), 4.90 (2 H, d, J_{AB} 12.3), 4.99 (2 H, d, J_{AB} 12.4), 5.18 (2 H, d, J_{AB} 12.4), 6.45 (2 H, s), 6.87–6.98 (2 H, m), 6.93–6.96 (1 H, m), 7.05–7.15 (10 H, m), 7.24 (2 H, d, *J* 9.0), 7.46 (1 H, s), 7.71 (2 H, d, *J* 9.0), 8.01 (2 H, s); *m*/*z* (DCIMS) 758 (M^+, 33), 679 (12), 588 (5), 181 (5), 91 (100%).

(*R*)-7,12-Bis(6-acetamido-2-pyridyl)-8,11-bis(benzyloxy)-dinaphtho[2,1-*d*:1,2-*f*][1,3]dioxepine, (*R*)-18

To dry THF (15 ml) at −78 °C under Ar was added 1.6 M BuLi in hexane (0.9 ml, 1.5 mmol). A solution of (*R*)-**34** (210.0 mg, 0.3 mmol) in dry THF (3 ml) was added dropwise and the mixture was stirred at −78 °C for 45 min. Trimethyl borate (8.3 ml) was added rapidly, and the mixture was warmed to room temp., then heated to reflux for 16 h under Ar. Removal of the solvent *in vacuo*, partitioning of the residue between 2 M aq. HCl solution (40 ml) and Et_2O (80 ml), drying ($MgSO_4$) and evaporation *in vacuo* produced the crude bis(boronic acid) as a yellow oil. To the crude bis(boronic acid) in EtOH (6 ml) and PhH (22 ml) was added *N*-(6-bromo-2-pyridyl)acetamide (175.0 mg, 0.8 mmol), a solution of Na_2CO_3 (85 mg, 0.6 mmol) in H_2O (10 ml) and $[PdCl_2(PPh_3)_2]$ (23 mg, 0.03 mmol). The resulting two-phase mixture was heated to reflux for 20 h, then cooled, diluted with AcOEt (25 ml), washed with sat. aq. $NaHCO_3$ solution (2 × 25 ml) and sat. aq. NaCl solution (2 × 25 ml), dried ($MgSO_4$) and evaporated *in vacuo* to produce an oil which was chromatographed (SiO_2, AcOEt–hexane 3:2) to yield yellowish (*R*)-**18** (139.0 mg, 57%): mp 136–137 °C [Found: C, 73.45; H, 5.34; N, 6.42. Calc. for $C_{49}H_{38}N_4O_6$·AcOEt (867.0): C, 73.43; H, 5.35; N, 6.46%]; $[\alpha]_D^{23}$ −258.7 (*c* 0.032, $CHCl_3$); $\nu_{max}(CDCl_3)/cm^{-1}$ 3344, 1661, 1615, 1480; δ_H(500 MHz, $CDCl_3$) 2.22 (6 H, s), 4.67–4.68 (4 H, m), 5.70 (2 H, s), 6.98–6.99 (4 H, m), 7.03 (2 H, s), 7.11–7.14 (6 H, m), 7.38 (2 H, d, *J* 9.0), 7.67–7.72 (4 H, m), 8.00 (2 H, d, *J* 9.0), 8.17 (4 H, m), 8.37 (2 H, s); δ_C(125.8 MHz, $CDCl_3$) 24.72, 70.48, 103.11, 107.57, 112.27, 119.24, 121.43, 124.72, 126.86, 127.23, 128.34, 128.95, 129.19, 130.65, 131.34, 132.86, 136.24, 138.14, 151.00, 152.40, 153.61, 154.73, 168.51; *m*/*z* (FABMS) 779 [$(MH)^+$, 24], 397 (24), 375 (14), 136 (74), 91 (13%).

(*R*)-3,7-Bis(6-acetamido-2-pyridyl)-2,18-bis(benzyloxy)-8,12-dihydrobenzo[*hi*]dinaphtho[2,1-*b*:1,2-*f*][1,3]dioxepine, (*R*)-23

To dry THF (15 ml) at −78 °C under Ar was added 1.6 M BuLi in hexane (0.8 ml, 1.3 mmol). A solution of (*R*)-**35** (200.0 mg, 0.26 mmol) in dry THF (3 ml) was added dropwise and the mixture was stirred at −78 °C for 45 min. Trimethyl borate (7.2 ml) was added rapidly and the mixture was warmed to room temp., then heated to reflux for 16 h under Ar. Removal of the solvent *in vacuo* and partitioning of the residue between 2 M aq. HCl solution (40 ml) and Et_2O (80 ml), drying ($MgSO_4$) and evaporation *in vacuo* gave the crude bis(boronic acid) as a yellow oil. To the crude bis(boronic acid) in EtOH (6 ml) and PhH (22 ml) was added *N*-(6-bromo-2-pyridyl)acetamide (145 mg, 0.67 mmol), a solution of Na_2CO_3 (95 mg, 0.67 mmol) in H_2O (10 ml) and $[PdCl_2(PPh_3)_2]$ (23 mg, 0.03 mmol). The resulting two-phase mixture was heated to reflux for 20 h, cooled, diluted with AcOEt (25 ml), washed with sat. aq. $NaHCO_2$ solution (2 × 25 ml) and sat. aq. NaCl solution (2 × 25 ml), dried ($MgSO_4$) and evaporated *in vacuo* to produce an oil which was chromatographed (SiO_2, AcOEt–EtOH 24:1) to yield (*R*)-**23** (85.8 mg, 37%) as a white foam: $[\alpha]_D^{23}$ −1326.2 (*c* 0.001, $CHCl_3$); $\nu_{max}(CDCl_3)/cm^{-1}$ 3354, 1669; δ_H(500 MHz, $CDCl_3$) 2.18 (6 H, s), 4.72 (2 H, d, J_{AB} 12.1), 4.88 (2 H, d, J_{AB} 12.1), 5.03 (2 H, d, J_{AB} 12.6), 5.23 (2 H, d, J_{AB} 12.6), 6.68 (2 H, s); 6.89–6.97 (3 H, m), 7.07–7.09 (4 H, m), 7.11–7.16 (6 H, m), 7.26–7.27 (2 H, m), 7.45–7.48 (1 H, m), 7.55 (2 H, br s), 7.62 (2 H, d, *J* 8.0), 7.65–7.69 (2 H, m), 7.85 (2 H, d, *J* 9.0); 8.08–8.13 (4 H, m); δ_C(125.8 MHz, $CDCl_3$) 24.66, 69.82, 74.92, 106.68, 111.97, 118.50, 121.32, 124.55, 125.32, 127.21, 127.34, 127.44, 128.19, 128.43, 128.52, 129.53, 130.10, 130.48, 132.04, 132.11, 135.50, 136.53, 138.05, 138.26, 150.84, 154.48, 154.74; *m*/*z* (FABMS) 869 (MH^+, 59), 136 (75%); *m*/*z* (HR-FABMS) 869.3420 $[(MH)^+$, $[C_{56}H_{45}N_4O_6]^+$; calc. 869.3338].

(*R*)-6,6′-Bis(6-acetamido-2-pyridyl)-7,7′-bis(benzyloxy)-2,2′-bis(*tert*-butyldimethylsiloxy)-1,1′-binaphthalene, (*R*)-25

To (*R*)-**32** (50.0 mg, 0.065 mmol) in DMF (0.4 ml) was added imidazole (35.4 mg, 0.520 mmol) followed by Bu^tMe_2SiCl (58.0 mg, 0.390 mmol), and the mixture was heated to 80 °C for 24 h, then quenched with sat. aq. $NaHCO_3$ solution (1 ml) and extracted with CH_2Cl_2 (2 × 2 ml). The combined organic layers were evaporated *in vacuo*, and chromatography (SiO_2, AcOEt–hexane 3:2) afforded (*R*)-**25** (50.0 mg, 77%) as a white solid: mp 120–121 °C [Found: C, 72.49; H, 6.86; N, 5.35. Calc. for $C_{60}H_{66}N_4O_6Si_2$ (995.4): C, 72.40; H, 6.68; N, 5.63%]; $[\alpha]_D^{23}$ −982.3 (*c* 0.523, $CHCl_3$); $\nu_{max}(CDCl_3)/cm^{-1}$ 3204, 1690; δ_H(500 MHz, $CDCl_3$) −0.21 (6 H, s), 0.35 (6 H, s), 0.55 (18 H, s), 2.21 (6 H, s), 4.70 (2 H, d, J_{AB} 12.2), 4.72 (2 H, d, J_{AB} 12.2), 6.64 (2 H, s), 6.99–7.01 (4 H, m), 7.07 (2 H, d, *J* 9.0), 7.10–7.12 (6 H, m), 7.71–7.72 (4 H, m), 7.84 (2 H, d, *J* 9.0), 8.02 (2 H, br s), 8.12–8.14 (2 H, m), 8.24 (2 H, s); δ_C(125.8 MHz, $CDCl_3$) −4.46, −4.22, 18.10, 24.78, 25.09, 70.10, 106.44, 111.75, 118.88, 121.43, 124.65, 126.93, 127.46, 128.24, 129.20, 130.62, 137.97, 150.82, 152.30, 154.39, 154.42; *m*/*z* (FABMS) 995 (MH^+, 50), 937 (9), 903 (5), 91 (71), 73 (100%).

(*S*)-**25** {$[\alpha]_D^{22}$ +983.5 (*c* 0.032, $CHCl_3$)} was prepared in a similar manner to (*S*)-**32**.

(*R*-)6,6′-Bis(6-acetamido-2-pyridyl)-2,2′-bis(1-adamantylmethoxy)-7,7′-bis(benzyloxy)-1,1′-binaphthalene, (*R*)-26

To (*R*)-**32** (30.0 mg, 0.04 mmol) in DMF (0.12 ml) was added Cs_2CO_3 (120.0 mg, 0.37 mmol) followed by (1-adamantyl)-methyl-*p*-toluenesulfonate (120.0 ml, 0.37 mmol), and the mixture was stirred for 3 d. Filtration through a pad of Celite, evaporation *in vacuo*, and chromatography (SiO_2, hexane–AcOEt 2:3→3:2) afforded (*R*)-**26** (41.6 mg, 67%) as a brown foam: $[\alpha]_D^{23}$ −57.7 (*c* 0.531, $CHCl_3$) [Found: C, 78.71; H, 6.66; N, 5.20. Calc. for $C_{70}H_{70}N_4O_6$ (1063.4): C, 79.07; H 6.64; N, 5.27%]; $\nu_{max}(CDCl_3)/cm^{-1}$ 3223, 1676; δ_H(500 MHz, $CDCl_3$) 1.47–1.48 (12 H, m), 1.57–1.68 (12 H, m), 1.96 (6 H, br s), 2.21 (6 H, s), 3.56–3.85 (4 H, m), 4.72 (4 H, br s), 6.68 (2 H, s), 7.00–7.26 (12 H, m), 7.63–7.81 (4 H, m), 7.91 (2 H, d, *J* 9.0), 8.56 (2 H, br s), 8.10–8.15 (2 H, m), 8.20 (2 H, s); *m*/*z* (FABMS) 1063 (MH^+).

(*S*)-**26** {$[\alpha]_D^{22}$ +58.0 (*c* 0.500, $CHCl_3$)} was prepared in a similar manner to (*S*)-**32**.

(*R*)-7,7′-Bis(benzyloxy)-2,2′-bis(2-ethylbutoxy)-6,6′-dibromo-1,1′-binaphthalene, (*R*)-36

To (*R*)-**27** (150.00 mg, 0.23 mmol) in DMF (4 ml) was added K_2CO_3 (252.0 mg, 1.80 mmol), and the mixture was stirred for 10 min at 80 °C after which 1-bromo-2-ethylbutane (0.13 ml, 0.90 mmol) was added. Heating to 80 °C for 16 h, filtration through a pad of Celite, evaporation *in vacuo* and chromatography (SiO_2, gradient hexane to hexane–AcOEt 19:1) gave (*R*)-**36** (188.20 mg, 100%) as a clear oil: $[\alpha]_D^{23}$ −1144.1 (*c* 0.527, $CHCl_3$) [Found: C, 66.97; H, 6.12; O, 7.92. Calc. for $C_{46}H_{48}Br_2O_4$ (824.7): C, 67.00; H, 5.87; O, 7.76%]; ν_{max}(KBr)/cm^{-1} 2927, 1638; δ_H(360 MHz, $CDCl_3$) 0.96 (12 H, t, *J* 7.5), 1.47–1.53 (8 H, m), 1.49–1.54 (2 H, m), 3.95 (4 H, d, *J* 6.0), 5.26 (4 H, s), 7.01–7.04 (4 H, m), 7.13 (2 H, s), 7.35–7.41 (2 H, m), 7.43–7.44 (4 H, m), 7.53–7.59 (4 H, m), 7.99 (2 H, s); *m*/*z* (FABMS) 824 (MH^+, 2%), 498 (10), 414 (22), 220 (15), 91 (100).

(*R*)-6,6′-Bis(6-acetamido-2-pyridyl)-7,7′-bis(benzyloxy)-2,2′-bis(2-ethylbutoxy)-1,1′-binaphthalene, (*R*)-24

To dry THF (15 ml) at −78 °C under Ar was added 1.6 M BuLi in hexane (0.7 ml, 1.1 mmol). A solution of (*R*)-**36** (168 mg, 0.2 mmol) in dry THF (3 ml) was added dropwise, and the mixture was stirred at −78 °C for 45 min. After rapid addition of trimethyl borate (5.5 ml), the mixture was warmed to room temp., then heated to reflux for 16 h under Ar. Removal of the solvent *in vacuo*, partitioning of the residue between 2 M aq. HCl solution (40 ml) and Et_2O (80 ml), drying ($MgSO_4$) and evaporation *in vacuo* produced the crude bis(boronic acid) as a yellow oil. To the crude bis(boronic acid) in EtOH (6 ml) and PhH (22 ml) was added *N*-(6-bromo-2-pyridyl)acetamide (76.0 g, 0.3 mmol), a solution of Na_2CO_3 (42 mg, 0.4 mmol) in H_2O (10 ml) and [$PdCl_2(PPh_3)_2$] (79 mg, 0.1 mmol). The resulting two-phase reaction mixture was heated to reflux for 20 h. The cooled mixture was diluted with AcOEt (25 ml), washed with sat. aq. $NaHCO_3$ solution (2 × 25 ml) and sat. aq. NaCl solution (2 × 25 ml), dried ($MgSO_4$) and concentrated *in vacuo* to produce an oil which was chromatographed (SiO_2, hexane–AcOEt 4:1→3:2) to provide (*R*)-**24** (84.3 mg, 45%) as a white solid: $[\alpha]_D^{23}$ −1025.9 (*c* 0.025, $CHCl_3$) [Found: C, 76.26; H, 6.92; N, 6.17. Calc. for $C_{60}H_{62}O_6N_4 \cdot 0.5\ H_2O$ (944.2): C, 76.33; H, 6.72; O, 5.93%]; ν_{max}($CDCl_3$)/cm^{-1} 3344, 1661, 1611; δ_H(360 MHz, $CDCl_3$) 0.40–0.52 (12 H, m), 0.80–1.12 (8 H, m), 1.60 (2 H, s), 2.25 (6 H, m), 3.61–3.65 (4 H, m), 4.60–4.78 (4 H, m), 6.61 (2 H, s), 6.92–7.08 (10 H, m), 7.20–7.24 (2 H, m), 7.42 (2 H, d, *J* 9.0), 7.65–7.71 (4 H, m), 8.13 (2 H, s), 8.15–8.18 (4 H, m); *m*/*z* (FABMS) 935 (MH^+, 100), 845 (7), 91 (100%).

Computational studies

All calculations were performed on Silicon Graphics Crimson Elan or Indigo workstations. The conformational analysis was performed using the OPLS* force field[37] implemented in the MacroModel V. 5.0 program.[24,38] All structures were minimized employing the conjugate gradient method[39] and subsequently submitted to a 4000-step *pseudo*-Monte Carlo Multiple Minimum (MCMM) conformational search *in vacuo* followed by a 2000-step MCMM search in $CHCl_3$ using the GB/SA solvation model.[40] In the simulations of the 1,1′-binaphthalene major groove receptors, the dihedral angle between the pyridine ring and the attached acetamido function was constrained to 0° in agreement with X-ray crystallographic data for (±)-**16**.[1h] To avoid decomplexed structures, only associations with O–H···N and C=O···H–N H-bond lengths between 1.5 and 2.1 Å were accepted. Consideration of all conformers found within 10 kJ mol^{-1} above the computed global minimum conformation led to the averaged dihedral angles $\theta \pm \Delta\theta$.

Complexation studies

The substrates for the complexation studies were purchased from Sigma. The solvent $CDCl_3$ was dried over molecular sieves (4 Å). For each binding study, 10 titration samples were prepared by pipetting with Gilson Pipetman (200 µl and 1000 µl) from sonicated stock solutions obtained by weighing the compounds into 2 or 5 ml volumetric flasks on a Mettler AT20 microbalance. All ^{1}H NMR titration data were acquired on a Bruker 500 MHz NMR spectrometer thermostatted at 300 ± 0.1 K if not stated otherwise. For titrations in $CDCl_3$, the host concentration was kept constant at 1.0×10^{-4} M and the concentration of the guest was varied from 5.0×10^{-5} to 5.0×10^{-4} M to reach saturation values up to 70–90%. For titrations in $CDCl_3$–CD_3OD 99.8:0.2 the host concentration was kept constant at 2.0×10^{-4} M and the concentration of the guest varied from 8.0×10^{-5} to 8.0×10^{-4} M (Table 4). The complexation-induced change in chemical shift $\Delta\delta$ of host proton H–C(5) on the 1,1′-binaphthalene core was plotted against the guest concentration. Quantitative binding numbers (K_a, $\Delta G°$, $\Delta\delta_{sat}$) were obtained by using the non-linear least-squares curve-fitting program Associate 1.6.[44] The K_a and $\Delta G°$ values reported are averages calculated from multiple runs. Table 4 shows the maximum observed complexation-induced changes in chemical shift ($\Delta\delta_{max}$) and the calculated changes in chemical shift at saturation binding ($\Delta\delta_{sat}$) for selected binding titrations.

Table 4 Experimental data for selected ^{1}H NMR binding titrations (500 MHz, 300 K). Shown are the host concentration [H_o], the guest concentration [G_o], the calculated change in chemical shift of proton H–C(5) on the 1,1′-binaphthalene core at saturation binding $\Delta\delta_{sat}$ and the maximum change in chemical shift $\Delta\delta_{max\ obs}$ observed during the titration

	Host ([H_o]/10^{-4} M)	Guest ([G_o]/10^{-5} M)	$\Delta\delta_{max\ obs}$ ($\Delta\delta_{sat}$)
a	(*R*)-**25**	*N*-Cbz-L-Asp	0.366 (86%)[c]
	(1.00)	(5.0–50)	(0.427)
a	(*R*)-**24**	*N*-Cbz-L-Asp	0.369 (91%)[c]
	(1.04)	(5.2–52)	(0.408)
a	(*R*)-**18**	*N*-Cbz-L-Glu	0.153 (74%)[c]
	(1.01)	(5.0–50)	(0.206)
a	(*R*)-**23**	*N*-Cbz-D-Asp	0.275 (93%)[c]
	(0.99)	(5.5–55)	(0.294)
b	(*R*)-**21**	*N*-Cbz-L-Asp	0.189 (85%)[c]
	(1.99)	(8.1–81)	(0.223)
b	(*R*)-**20**	*N*-Cbz-D-Asp	0.189 (83%)[c]
	(1.91)	(13–130)	(0.226)
b	(*R*)-**33**	*N*-Cbz-L-Glu	0.217 (83%)
	(2.07)	(7.3–73)	(0.263)

[a] In $CDCl_3$. [b] In $CDCl_3$–CD_3OD (99.8:0.2). [c] Percentage of saturation binding reached.

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