85. Chiral 1,1′-Binaphthyl Molecular Clefts for the Complexation of Excitatory Amino-Acid Derivatives

by **Esther Martinborough**[a]), **Tiziana Mordasini Denti**[a]), **Peter P. Castro**[b]), **Tara B. Wyman**[b]), **Carolyn B. Knobler**[b]), and **François Diederich**[a])*

[a]) Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH–8092 Zürich

[b]) Department of Chemistry and Biochemistry, University of California at Los Angeles, Los Angeles, California 90024-1569, USA

(26.IV.95)

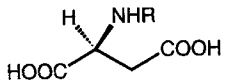
The complexation of *N*-benzyloxycarbonyl (Cbz) derivatives of the excitatory amino acids L-aspartic acid (Asp; **1**), L-glutamic acid (Glu; **3**), and, for the first time, L-kainic acid ((2*S*,3*S*,3*S*)-2-carboxy-4-(1-methylethenyl)pyrrolidine-3-acetic acid; Kai; **5**) was studied in $CDCl_3$ with a diversity of chiral receptors consisting of a 1,1′-binaphthyl spacer with (carboxamido)pyridine (CONH(py)) functionality attached to the 6,6′-positions in the major groove. Receptors of type A possess two *N*-(pyridin-2-yl)carboxamide H-bonding sites (*e.g.* **7**), whereas type B-receptors have two *N*-(pyridine-6,2-diyl)acetamide residues attached (*e.g.* **8** and **9**). Complexes of excitatory amino-acid derivatives and other, achiral α,ω-dicarboxylic acids with these receptors are primarily stabilized by two sets of C=O···H–N and O–H···N H-bonds. Optically active type-A receptors such as (*R*)- and (*S*)-**7** showed a preference for the larger Glu derivative, whereas type-B receptors such as (*R*)- and (*S*)-**8** and (*R*)- and (*S*)-**9** formed more stable complexes with the smaller Cbz-Asp. To improve the poor enantioselectivity shown by **7**–**9**, additional functionality was introduced at the 7,7′-positions of the 1,1′-binaphthyl spacer, and the nature of the H-bonding sites in the 6,6′-positions was varied. Screening the diversity of new racemic receptors for binding affinity, which had been shown in many examples by *Cram* to correlate with enantioselectivity, demonstrated that (±)-**10** and (±)-**11** formed the most stable complexes with dicarboxylic acids, and these receptors were synthesized in enantiomerically pure form. Both are type-B binders and contain additional $PhCH_2O$ (**10**) and MeO (**11**) groups in the 7,7′-positions. By ^{1}H-NMR binding titrations, the complexation of (*R*)- and (*S*)-**10** and (*R*)- and (*S*)-**11** with the excitatory amino-acid derivatives was studied in $CDCl_3$, and association constants K_a between 10^3 and $2 \cdot 10^5$ l mol^{-1} were measured for the 1:1 host-guest complexes formed. Whereas both **10** and **11** formed stable complexes, enantioselective binding was limited to the $PhCH_2O$-substituted receptor **10**, with the (*R*)-enantiomer complexing Cbz-Asp by 0.7 kcal mol^{-1} more tightly than the (*S*)-enantiomer. The structures of the diastereoisomeric complexes were analyzed in detail by experimental methods (complexation-induced changes in ^{1}H-NMR chemical shifts, $^1H\{^1H\}$ nuclear *Overhauser* effect (NOE) difference spectroscopy) and computer modeling. These studies established that an unusual variety of interesting aromatic interactions and secondary electrostatic interactions are responsible for both the high binding affinity ($-\Delta G°$ up to 7.2 kcal mol^{-1}) and the enantioselection observed with (*R*)- and (*S*)-**10**. In an approach to enhance the enantioselectivity by reducing the conformational flexibility of the 1,1′-binaphthyl spacer, an additional crown-ether binding site was attached to the 2,2′-positions in the minor groove of the type-B receptors (*R*)- and (*S*)-**48**. Both the binding affinity and the enantioselectivity ($\Delta(\Delta G°)$ up to 0.7 kcal mol^{-1}) in the complexation of the excitatory amino-acid derivatives by (*R*)- and (*S*)-**48** were not altered upon complexation of $Hg(CN)_2$ at the crown-ether binding site, demonstrating lack of cooperativity between the minor- and major-groove recognition sites.

1. Introduction. – At the heart of biology lies molecular recognition [1]. The unique array of interactions between receptors and substrates determines physical structure and function, and permits the complexity, efficiency, and beauty of biological systems [2].

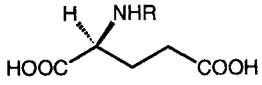
Mimicking biological recognition processes using synthetic receptors is one of the challenging goals of supramolecular chemistry [3].

Much attention has been placed on the design and analysis of receptors for the molecular recognition of biorelevant substrates. Efficient synthetic receptors for the selective complexation of biosubstrates could offer new perspectives for medical technologies such as drug transport, delivery, and slow release [4], specific compound sequestration [5] and detoxification [6], and analytical detection and quantification of traces of ions and molecules in the body [7]. In addition, a profound understanding of molecular-recognition principles, developed in studies with artificial receptors, greatly benefits the rational *de novo* design of small non-peptidic agonists and antagonists for biological receptors targeted in medicinal-chemistry research [8].

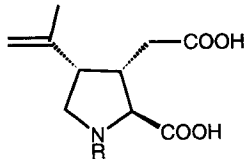
Among the many biosubstrates, amino acids have attracted particularly large interest in synthetic molecular-recognition studies [9–12]. Although amino acids are the universal building blocks for peptides and proteins [13] and regulate numerous physiological functions [14], their recognition and transport properties are not always well understood [15]. The role of amino acids in learning and memory also continues to be the focus of increasing attention [16]. This field is encompassed by the broader neurological questions of how information is encoded, stored, and retrieved in the brain [17]. In the central nervous system, multiple receptors regulate neural synaptic excitation by complexation of transmitters known as excitatory amino acids [16]. It is now widely accepted that long-term memory and learning are controlled by the *N*-methyl-D-aspartate (NMDA) receptor. Memory is built up by an NMDA-regulated synaptic excitation along specific information pathways [17]. L-Aspartic acid (Asp; **1**), L-glutamic acid (Glu; **3**), and L-kainic acid ((2*S*,3*S*,4*S*)-2-carboxy-4-(1-methylethenyl)pyrrolidine-3-acetic acid; Kai; **5**) are among the most potent excitatory amino acids recognized as agonists by the NMDA and related receptors in the brain [16] [17]; thus, in our synthetic molecular-recognition studies, we started focusing on the complexation of α,ω-dicarboxylic acids [18–20] and the *N*-benzyloxycarbonyl (Cbz) derivatives **2**, **4**, and **6** of the excitatory amino acids [20b,c].



1 R = H (Asp)
2 R = $COOCH_2Ph$ (Cbz-Asp)



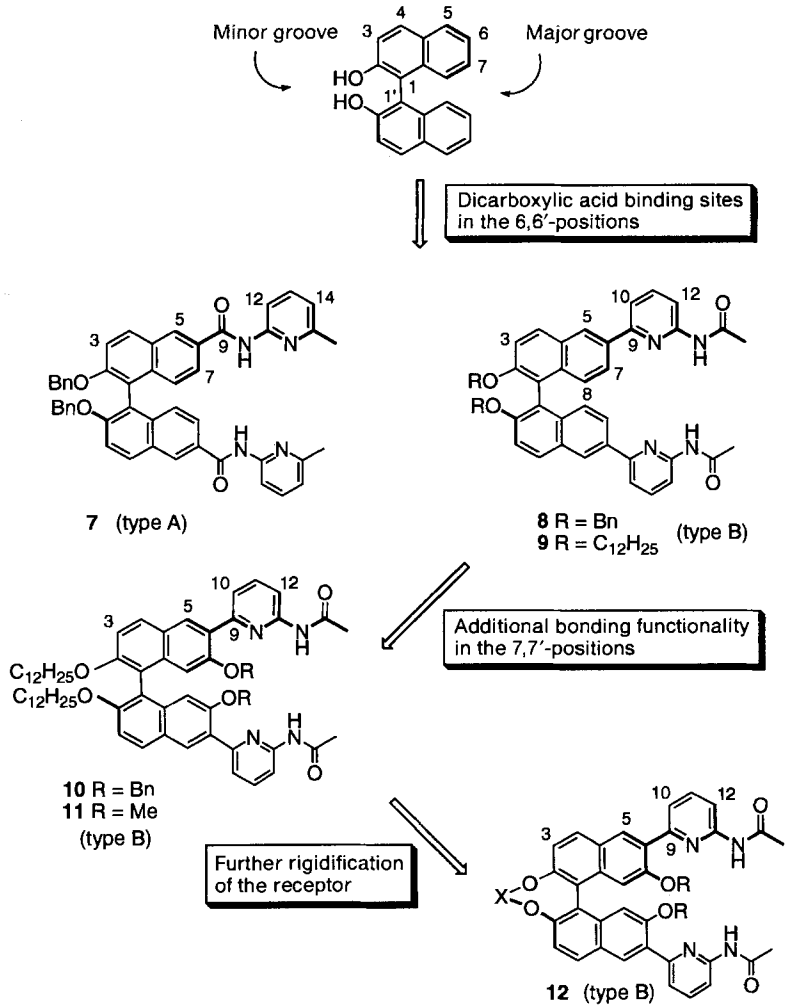
3 R = H (Glu)
4 R = $COOCH_2Ph$ (Cbz-Glu)



5 R = H (L-kainic acid; Kai)
6 R = $COOCH_2Ph$ (Cbz-Kai)

Here we report the design and optimization of cleft-type receptors derived from 1,1′-binaphthyl-2,2′-diol which possess convergent H-bonding sites in the binaphthyl major groove for the specific complexation of excitatory amino-acid derivatives (*Scheme 1*). In the first stage of the project, α,ω-dicarboxylic-acid recognition sites [18] [20] were introduced into the 6,6′-positions of the 1,1′-binaphthyl spacer (see **7–9**). Subsequently, binding efficiency and selectivity were enhanced by introducing additional functionality to the 7,7′-positions (see **10** and **11**) and by variation of the H-bonding edges

Scheme 1. *Sequential Optimization of 1,1′-Binaphthyl Receptors for the Enantioselective Complexation of Derivatives of Excitatory Amino Acids*[1]). Bn = $PhCH_2$.



at the 6,6′-positions. Following optical resolution of the optimized receptors, comprehensive ^{1}H-NMR binding titration studies with the excitatory amino-acid derivatives, complemented by $^1H\{^1H\}$ nuclear *Overhauser* effect (NOE) difference spectroscopy, were conducted in the noncompeting solvent $CDCl_3$. The experimental methods applied to the analysis of the geometries of the complexes and the factors determining binding stability and selectivity were complemented by extensive computer modeling. Finally, initial attempts to bridge the 2,2′-positions at the minor groove of the 1,1′-binaphthyl spacer (→**12**) to enhance the conformational homogeneity [3i] [11a–e] [20b,c] and thus the efficiency and selectivity of the cleft binding site in the major groove are presented.

[1]) The numbering of the substituents at C(6) and C(6′) of **7**–**12** is arbitrary.

2. Results and Discussion. – 2.1. *1,1′-Binaphthyl Receptors with α,ω-Dicarboxylic Acid Recognition Sites in the 6,6′-Positions.* *N*-(Pyridin-2-yl)carboxamide (CONH(py)) moieties, which bind to COOH residues *via* two strong H-bonds (N–H···O=C and N···H–O), can be attached in two different orientations to binaphthyl spacers (*Scheme 1*). The *N*-(6-methylpyridin-2-yl)carboxamide moieties in the previously reported cleft receptor **7** (called a type-A receptor) [20a–c] were initially introduced for carboxylic-acid binding by *Hamilton* and coworkers [18], whereas we had earlier used the *N*-(pyridine-6,2-diyl)acetamide residues in **8** and **9** [20a] (called type-B receptors) as potential recognition sites in a helicopodand receptor [21]. This difference in orientation of the H-bonding moieties with respect to the binaphthyl spacer leads to significant differences in the complexation behavior toward Cbz-Asp (**2**) and Cbz-Glu (**4**). ^{1}H-NMR Binding titrations with (*R*)- and (*S*)-**7** [20b,c] and (*R*)- and (*S*)-**9** were performed in $CDCl_3$ at 298 K and evaluated with a nonlinear least-squares curve-fitting program (*Table 1*) [22]. They showed that (*R*)- and (*S*)-**7** formed the most stable complexes with Cbz-Glu (*Entries 3* and *4*), whereas (*R*)- and (*S*)-**9** preferred complexing the shorter Cbz-Asp (*Entries 5* and *6*). As discussed previously [20b,c], the flexible 1,1′-binaphthyl unit does not provide the conformational homogeneity required for efficient chiral recognition and, therefore, the observed enantioselectivity is very modest with the largest difference in stability between diastereoisomeric complexes $\Delta(\Delta G°) = 0.5$ kcal mol^{-1} measured for the binding of Cbz-Asp by (*R*)- and (*S*)-**9** (*Entries 5* and *6*).

Table 1. *Association Constants* K_a *and Binding Free Energies* $\Delta G°$ (±0.1 kcal mol^{-1}) *for the Complexes Formed between Receptors* (R)- and (S)-**7** *and* (R)- *and* (S)-**9** *with Cbz-Asp* (**2**) *and Cbz-Glu* (**4**) *in* $CDCl_3$ *at 298 K*[a])

Entry	Host	Guest	K_a [l mol^{-1}]	$\Delta G°$ [kcal mol^{-1}]	$\Delta(\Delta G°)$
1	(*R*)-**7**	**2**	2000	–4.5	
2	(*S*)-**7**	**2**	3300	–4.8	0.3
3	(*R*)-**7**	**4**	21000	–5.8[b])	0.1[b])
4	(*S*)-**7**	**4**	19000	–5.7[b])	
5	(*R*)-**9**	**2**	4000	–4.9	
6	(*S*)-**9**	**2**	8900	–5.4	0.5
7	(*R*)-**9**	**4**	3000	–4.7	0.3
8	(*S*)-**9**	**4**	1800	–4.4	

[a]) Evaluated receptor protons in titrations with varying guest concentration: NH, H–C(5), H–C(7), and H–C(12)[1]).

[b]) Reported in [20b, c].

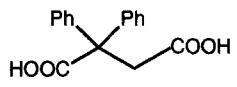
A similar size selectivity had been previously found in binding studies with the racemic receptors (±)-**7** and (±)-**8** and achiral α,ω-dicarboxylic acids of varying lengths: whereas (±)-**7** preferred complexing larger diacids, *e.g.* **14**, receptor (±)-**8**, which is closely related to (±)-**9**, showed a higher complementarity to smaller diacids, *e.g.* **13**, (*Table 2*) [20a].

Another example for size selectivity as a result of the different orientation of the CONH(py) H-bonding sites relative to the molecular cleft was observed with the 9,9′-spirobifluorene receptors **15** and **16** [20a–c]. While **15** complexed carbamate derivatives of Asp (**1**) and Glu (**3**) with K_a values of 10^3–10^4 l mol^{-1} in $CDCl_3$, **16** showed no appreciable binding with either amino acid and only bound smaller acids such as 2,2-diethylmalonic acid (**17**) (K_a = 490 l mol^{-1} in $CDCl_3$, *T* 298 K).

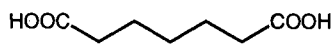
Table 2. *Association Constants* K_a *and Binding Free Energies* $\Delta G°$ (±0.1 kcal mol^{-1}) *for the Complexes Formed between Receptors (±)-***7** *and (±)-***8** *with 2,2-Diphenylsuccinic Acid* (**13**) *and Pimelic Acid* (**14**) *at 293 K*[a])

Entry	Host	Guest	K_a [1 mol^{-1}]	$\Delta G°$ [kcal mol^{-1}]
1	(±)-**7**	**13**	820	−3.9
2	(±)-**7**	**14**	2500	−4.6
3	(±)-**8**	**13**	7300	−5.2
4	(±)-**8**	**14**	470	−3.6

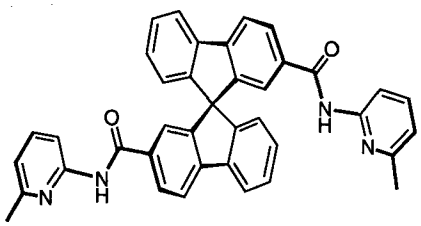
[a]) Reported in [20a].



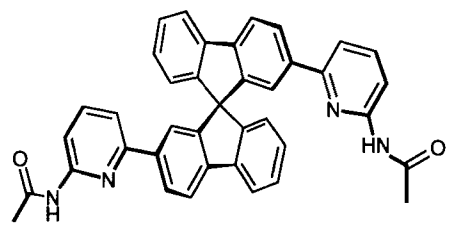
13



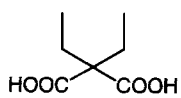
14



15



16



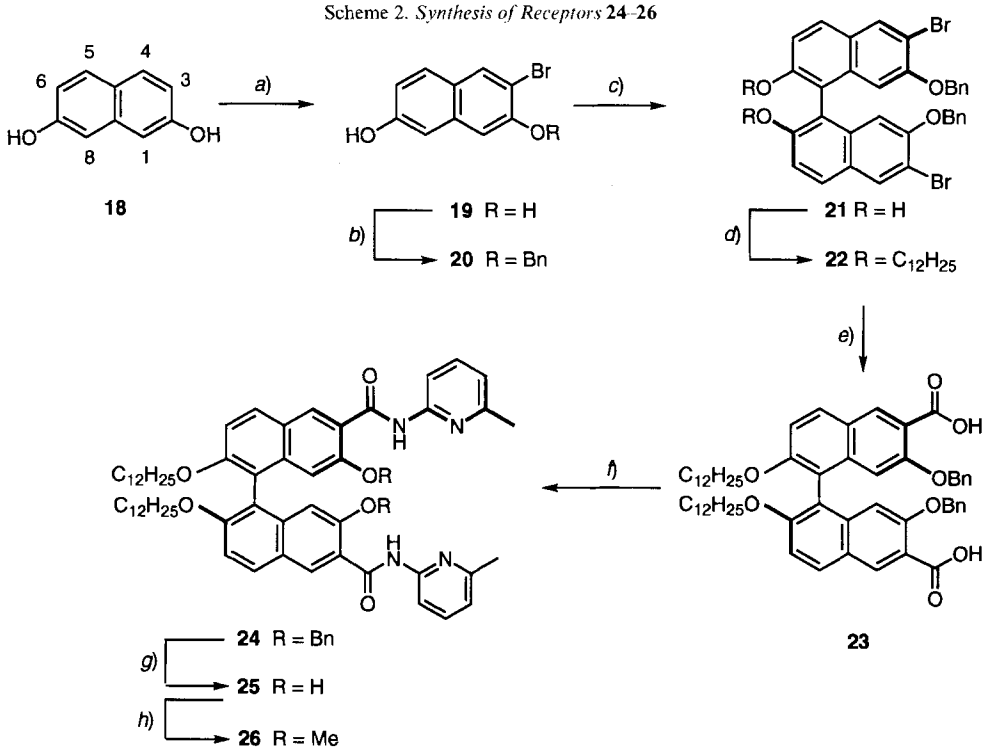
17

In view of the conformational flexibility of the binaphthyl receptors and the substrates, an explanation for the preference of **7** for the longer Cbz-Glu (**4**) and of **8**/**9** for the shorter Cbz-Asp (**2**) is not straightforward. CPK and computer model examinations [23] suggest that, at favorable dihedral angles about the C(1)–C(1′) binaphthyl bond and the C(6)–C(9)[1]) bond between the naphthalene and the CONH(py) moieties, the distance between the two convergent, H-bond-accepting pyridine N-atoms in the receptors may be an important factor in determining the observed size selectivity. In the complexes of these receptors with carboxylic acids, the O–H···N H-bonds are energetically much more important than the C=O···H–N H-bonds [20]. In the favorable all-*anti* (zig-zag) conformation of the C-backbone of the bound diacids, the two OH groups of the Asp derivative are best aligned for strong H-bonding to the pyridine N-atoms in **8** and **9**, whereas those of the Glu derivative interact best with the pyridine N-atoms in **7**.

2.2. *Synthetic Optimization of the Major-Groove Binding Site of the 1,1′-Binaphthyl Clefts.* To enhance the affinity and selectivity in the binding of α,ω-dicarboxylic acids such as the excitatory amino acids, several structural changes at the 1,1′-binaphthyl major groove were investigated. It was planned to first conduct binding studies with a

diversity of racemic receptors to identify the most efficient ones in terms of binding affinity and to subsequently prepare these optimized receptors in enantiomerically pure form for chiral recognition studies. First, OH and alkoxy groups were introduced at the 7,7′-positions to participate in the H-bonding and to reduce the conformational flexibility about the C(6)–C(9) bonds between the binaphthyl spacer and the CONH(py) residues (*Scheme 1*). To synthesize derivatives **24**–**26** of A-type receptor **7**, naphthalene-2,7-diol (**18**) was brominated to give a mixture of 1,3- and 1,6-dibromo derivatives which, by *in situ* hydrogenolysis of the Br–C(1) bond [24], afforded **19** (*Scheme 2*). Selective monobenzylation led to **20** which was oxidatively coupled [25] to the 1,1′-binaphthyl-2,2′-diol **21**.

Scheme 2. *Synthesis of Receptors* **24**–**26**

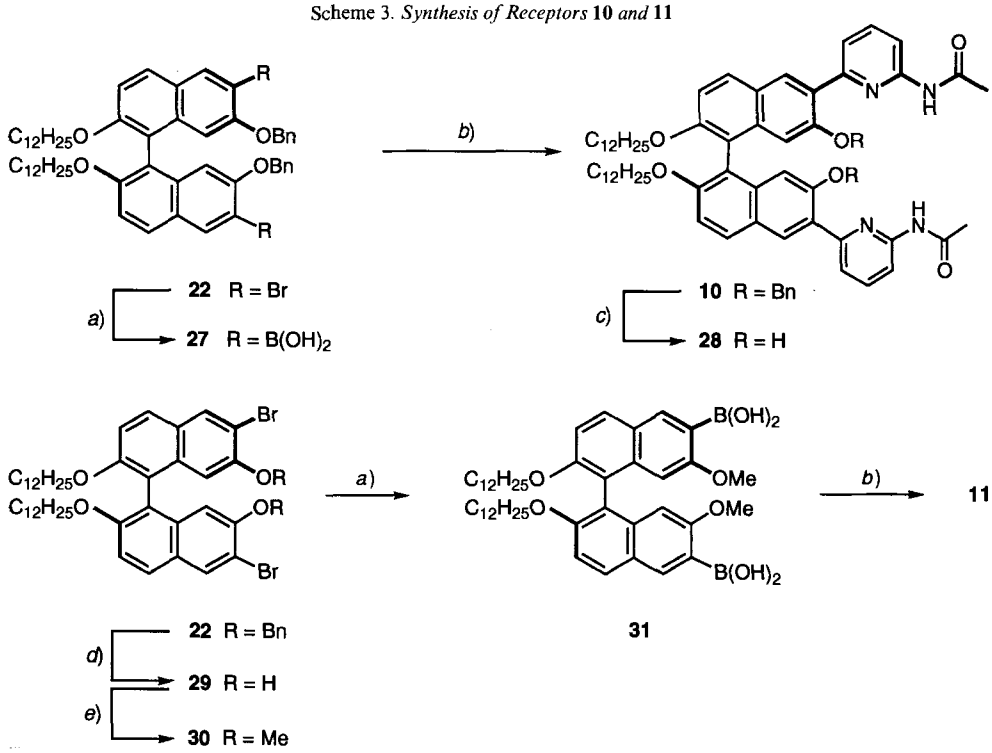


a) 1) Br_2, AcOH; 2) Sn, H_2O, Δ; 91%. *b*) BnCl, K_2CO_3, DMF, Δ; 74%. *c*) $CuCl_2$, *t*-$BuNH_2$, MeOH, Δ; 65%. *d*) $C_{12}H_{25}I$, K_2CO_3, MeCN, Δ; 98%. *e*) BuLi, THF, −78°, then CO_2; 87%. *f*) 1) $(COCl)_2$, benzene; 2) 6-methylpyridin-2-amine, pyridine, Δ; 70%. *g*) 10% Pd/C, $NH_4(HCO_2)$, THF, Δ; 95%. *h*) Me_2SO_4, K_2CO_3, *N*,*N*-dimethylacetamide (DMA); 59%.

After introduction of solubilizing dodecyl chains, the tetraether **22** was metalated with BuLi and reacted with CO_2 [20a] to give the dicarboxylic acid **23**. Amination with 6-methylpyridin-2-amine led to **24** which was debenzylated [26] to the 7,7′-diol **25** and subsequently methylated [27] to give **26**.

To prepare the corresponding derivatives **10**, **11**, and **28** of B-type receptor **9**, dibromide **22** was converted into the bis(boronic acid) **27**, and subsequent *Suzuki* coupling

Scheme 3. *Synthesis of Receptors* **10** *and* **11**

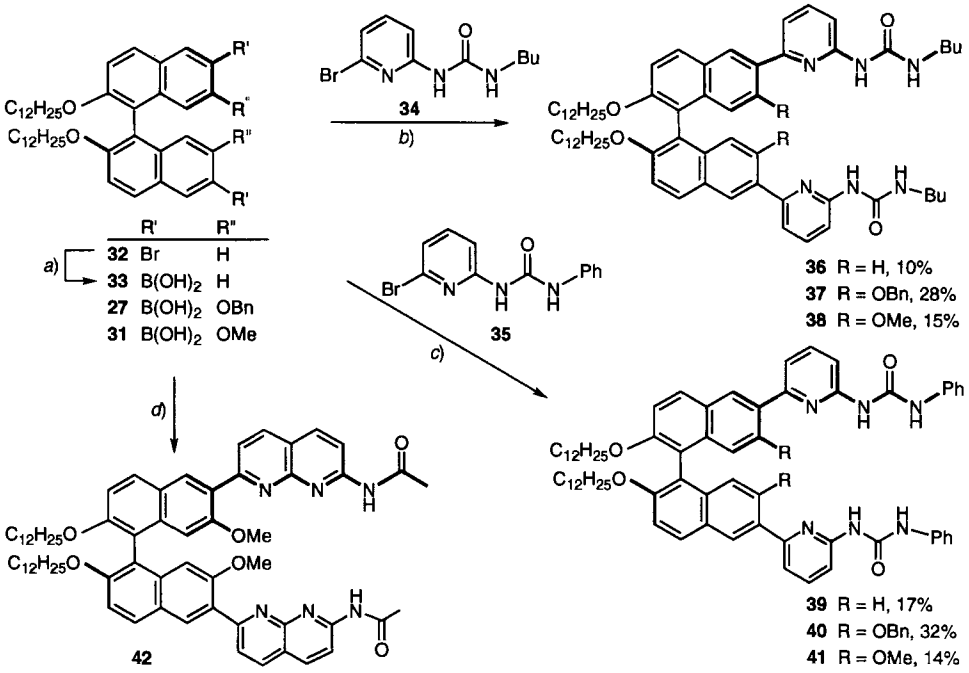


a) BuLi, THF, −78°, then $B(OMe)_3$, Δ. *b*) *N*-(6-Bromopyridin-2-yl)acetamide [28], $[PdCl_2(PPh_3)_2]$, Na_2CO_3, EtOH, benzene, H_2O, Δ; 67% of **10** (from **22**); 52% of **11** (from **30**). *c*) 10% Pd/C, $NH_4(HCO_2)$, THF, Δ; 100%. *d*) BF_3OEt_2, Me_2S, CH_2Cl_2, Δ; 76%. *e*) Me_2SO_4, K_2CO_3, DMA; 100%.

[20a] with *N*-(6-bromopyridin-2-yl)acetamide [28] yielded **10** (*Scheme 3*). Whereas **10** could be debenzylated to give **28**, all attempts of methylating **28** to **11** failed. An alternative route to **11** employed mild debenzylation [29] of **22** to the 7,7′-diol **29** followed by alkylation to **30**. Subsequent transformation into boronic acid **31** and *Suzuki* coupling finally provided **11**.

In a second receptor modification, the CONH(py) units in the 7,7′-positions were changed with the objective to enhance the H-bonding to the C=O groups of the carboxylic-acid substrates. Compounds **36**–**41** bear two *N*-(pyridine-6,2-diyl)urea moieties, whereas compound **42** incorporates two *N*-(1,8-naphthyridine-7,2-diyl)acetamide residues for H-bonding at the major groove. For the *Suzuki* coupling leading to the receptors **36**–**41**, the brominated *N*-(pyridin-2-yl)ureas **34** and **35** were prepared by addition of 6-bromopyridin-2-amine to butyl isocyanate and phenyl isocyanate, respectively [30]. The bis(boronic acids) **27**, **31**, and **33** (obtained from dibromide **32** [20c]) were coupled with **34** to provide clefts **36**–**38** and with **35** to afford clefts **39**–**41** (*Scheme 4*). *Suzuki* coupling of **31** with *N*-(7-chloro-1,8-naphthyridin-2-yl)acetamide [20c] [31] provided the bis(naphthyridine) receptor **42**. The yields of the *Suzuki* reactions leading to the family of racemic hosts **36**–**42** were not optimized.

Scheme 4. *Synthesis of Receptors* **36–42**



a) BuLi, THF, −78°, then $B(OMe)_3$, *Δ*. *b*) **34**, $[PdCl_2(PPh_3)_2]$, Na_2CO_3, EtOH, benzene, H_2O, *Δ*; yields based on **32**, **22**, and **30**, resp. *c*) **35**, $[PdCl_2(PPh_3)_2]$, Na_2CO_3, EtOH, benzene, H_2O, *Δ*; yields based on **32**, **22**, and **30**, resp. *d*) *N*-(7-Chloro-1,8-naphthyridin-2-yl)acetamide [20c] [31], $[PdCl_2(PPh_3)_2]$, Na_2CO_3, EtOH, benzene, H_2O, *Δ*; 20%.

2.3. *Screening of the Binding Affinity of the Racemic Receptors.* The potential of the new receptors to complex α,ω-dicarboxylic acids was investigated in $CDCl_3$ at 300 K by ^{1}H-NMR binding titrations in which the substrate concentration was varied (*Table 3*). The following observations can be made:

1) Introduction of OH and alkoxy functionality at the 7,7′-positions lowers the binding affinity of type-A receptors **24–26** toward Cbz-DL-Glu ((±)-**4**) by 1.5–1.7 kcal mol^{-1} as compared to receptor **7** (*Entries 1–4*). Computer modeling studies, ^{1}H-NMR spectral shifts, and the thermodynamic binding data strongly support that intramolecular H-bonding between the NHs of the CONH(py) moiety and the O-atoms in the 7,7′-positions of **24–26** is responsible for this dramatic reduction in complexation strength (*Fig. 1a*). The amide-NH resonance in the ^{1}H-NMR spectrum of **7** in $CDCl_3$ appears at 8.1 ppm and, upon α,ω-dicarboxylic acid complexation, shifts downfield by 2–3 ppm. In sharp contrast, the amide-NH resonances in unbound **24–26** appear between 10.3 and 11.7 ppm, which is the characteristic spectral region for strongly H-bonded amide NHs. As a result of this intramolecular H-bonding, the NHs in **24–26** are no longer available for the association with the dicarboxylic acids and, upon complexation of these substrates, only small additional downfield shifts (0.1–0.2 ppm) of the NH resonances were observed. Presumably due to the unavailability of the amide NHs for host-guest H-

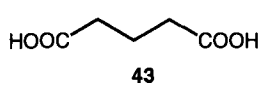
Table 3. *Association Constants* K_a *and Binding Free Energies* $\Delta G°$ (±0.1 kcal mol^{-1}) *of the Complexes Formed between Racemic Binaphthyl Receptors and α,ω-Dicarboxylic Acids in* $CDCl_3$ *at 300 K*[a])

Entry	Host	Guest	K_a [1 mol^{-1}]	$\Delta G°$ [kcal mol^{-1}]
1	**7**	(±)-**4**	20100	−5.8[b])
2	**24**	(±)-**4**	980	−4.1[b])
3	**25**	(±)-**4**	1130	−4.2[b])
4	**26**	(±)-**4**	1430	−4.3[b])
5	**8**	**13**	7300	−5.2[c])
6	**10**	**13**	30000	−6.0
7	**11**	**13**	18000	−5.8
8	**8**	**43**	2500	−4.6[c])
9	**10**	**43**	5300	−5.1
10	**11**	**43**	7400	−5.3
11	**10**	**44**	160	−3.0
12	**8**	**14**	470	−3.6[c])
13	**10**	**14**	2400	−4.6
14	**11**	**14**	3100	−4.8
15	**36**	**14**	770	−4.0
16	**37**	**14**	840	−4.0
17	**38**	**14**	1300	−4.3
18	**39**	**14**	370	−3.5
19	**40**	**14**	440	−3.7
20	**41**	**14**	440	−3.7
21	**42**	**14**	1700	−4.4

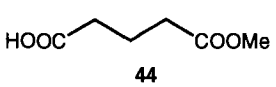
[a]) Evaluated host protons: NH, H–C(5), H–C(7), and, in addition, H–C(10) and H–C(12) for type-B receptors and H–C(12) and H–C(14) for type-A receptors[1]).

[b]) The formation of diastereoisomeric complexes of nearly identical stability and identical complexation-induced changes in chemical shift allows evaluation of their averaged K_a and $\Delta G°$ values in one titration.

[c]) Reported in [20a].

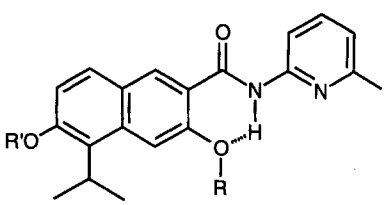


43



44

a)



b)

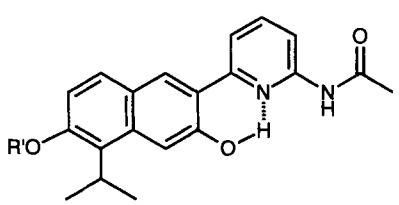


Fig. 1. *Intramolecular H-bonds* a) *in receptors* **24**–**26** *and* b) *in* **28**

bonding, geometrically less suitable diacids such as 2,2-diphenylsuccinic acid (**13**) or pimelic acid (**14**) no longer underwent significant complexation with **24**–**26**.

Conjugate gradient minimizations with the united atom OPLS* force field and the BatchMin v. 4.0 program implemented in MacroModel v. 4.0 [23] predicted for the

intramolecular O···H–N H-bonds in **24**–**26** a short O···H length between 1.75 and 1.80 Å and nonideal bond angles around 140°. Such nonideal angles in H-bonds are frequently observed in the X-ray crystal structures of intramolecularly H-bonded carbohydrates and nucleic acids [32a]. A similar intramolecular O–H···N H-bond is effective in diol **28** (*Fig. 1b*) and presumably prevented the attempted methylation of **28** to give **11** (*Sect. 2.2*). Experimental evidence for this H-bond was obtained in the ^{1}H-NMR spectrum of **28** in $(CD_3)_2SO$, which showed the OH resonance at 12.94 ppm, whereas free phenolic OH protons usually appear somewhere between 9 and 11 ppm in this solvent. In the modeled structures of **24**–**26** and **28**, the six-membered rings formed by the intramolecular H-bonding are nearly planar. Thus the H-bonding centers of the CONH(py) groups no longer converge into the cleft which could also contribute significantly to the lowering of the host-guest association strength.

2) Similar to **8** and **9** (*Sect. 2.1*), the novel, type-B receptors show a preference for complexing to shorter α,ω-dicarboxylic acids. The succinic-acid derivative **13** formed much more stable complexes with **10** or **11** (*Entries 6* and *7*) than glutaric acid (**43**) (*Entries 9* and *10*) or pimelic acid (**14**) (*Entries 13* and *14*). Only weak complexation-induced upfield shifts (up to 0.16 ppm) of the aromatic ^{1}H-NMR resonances of bound **13** were observed at 96% saturation binding ($[\mathbf{10}]_0 \approx 5$ mM, $[\mathbf{13}]_0 \approx 1$ mM), which demonstrates that the complex **10**·**13** is not significantly stabilized by aromatic-aromatic interactions. Also, only a very weak complex ($K_a = 160$ l mol^{-1}, $\Delta G° = -3.0$ kcal mol^{-1}) is formed between **10** and methyl hydrogen glutarate (**44**; *Entry 11*) which demonstrates the necessity for two carboxylate OH groups for efficient bidentate complexation. In general, monocarboxylic acids bind to dicarboxylic-acid receptors such as those investigated in this study with association constants K_a between 100 and 400 l mol^{-1} [18e] [20].

The additional MeO and $PhCH_2O$ groups in the 7,7′-positions make compounds **10** and **11** much better binders than **8** (or **9**) (*Entries 5–14*). Both steric and electronic factors contribute to the enhanced association strength as will be discussed in greater detail in the chiral-recognition studies with the excitatory amino acid derivatives (*Sect. 2.5*). The ether functionality in the 7,7′-positions sterically forces the pyridine rings out of the planes of the 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 ether O-atoms are sufficiently close to the OH groups of the substrates binding to the adjacent pyridine N-atoms, so that additional attractive electrostatic O···H interactions with these OH groups become effective [33] [34] (*Fig. 2*, **A**).

The X-ray crystal structure of **10** (*Fig. 3*) shows a dihedral angle of 77.8° between the two normal planes of the naphthalene rings. The dihedral angle between the planes of the pyridine and the adjacent acetamido group is 0°, whereas the torsional angles C(5)–C(6)–C(9)–N (numbering of *Scheme 1*)[1]) are −40.0 and −25.7°, respectively. The O–CH_2 moieties of the $PhCH_2O$ functions are in plane with the adjacent naphthalene rings, and the lone pairs of the O-atoms are favorably aligned for electrostatic interaction with the H-atoms of the COOH groups of bound dicarboxylic acids. The crystal-packing analysis shows infinite chains of binaphthyl receptors self-associating with their CONH(py) residues to one another. The two $PhCH_2O$ groups in **10** extend the depth of the binding cleft, and ^{1}H{^{1}H}-NOE difference spectroscopy demonstrates their participation in the bonding of suitable guests (*Section 2.5*). In the 1:1 complex of **10** with glutaric acid, intermolecular NOEs are observed between the CH_2 groups of the guest and the H_m

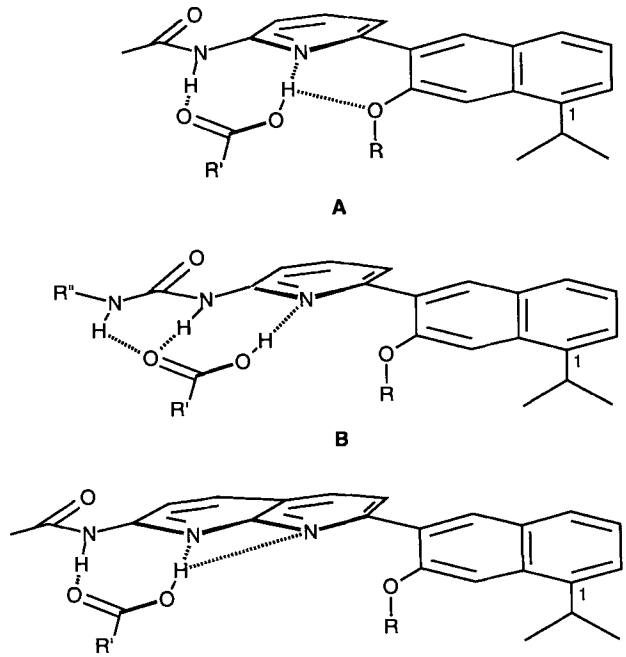


Fig. 2. *Possible H-bonding patterns in complexes of receptors with ether functionality at the 7,7′-positions (* **A***), of urea-receptors (* **B***), and of* **42** *(* **C***)*

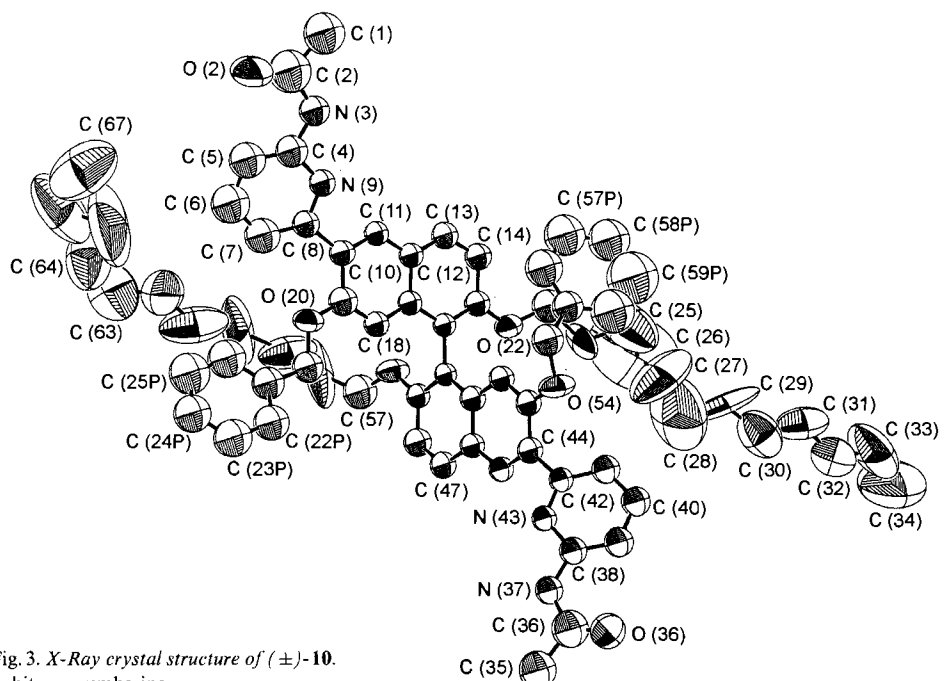


Fig. 3. *X-Ray crystal structure of (±)-* **10**. Arbitrary numbering.

and H_p of the benzylic Ph rings. *Fig. 4* displays a computer-generated model of the complex as obtained by a 1000-step Monte Carlo Multiple Minimum (MC) simulation using the OPLS* force field and the GB/SA solvation model for $CHCl_3$ [35] as implemented in MacroModel v. 4.0 [23]. This model was generated by constraining the dihedral angle between the pyridine ring and the adjacent acetamido function to 0°, *i.e.*, the value seen in the crystal structure, and is in agreement with the experimentally observed intermolecular NOEs (a), b), and c) in *Fig. 4*). 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. All conformations within 12 kcal mol^{-1} of the global minimum energy conformation were stored. A total of 42 structures were found within 2.4 kcal mol^{-1} of the global minimum after the 1000-step MC simulation.

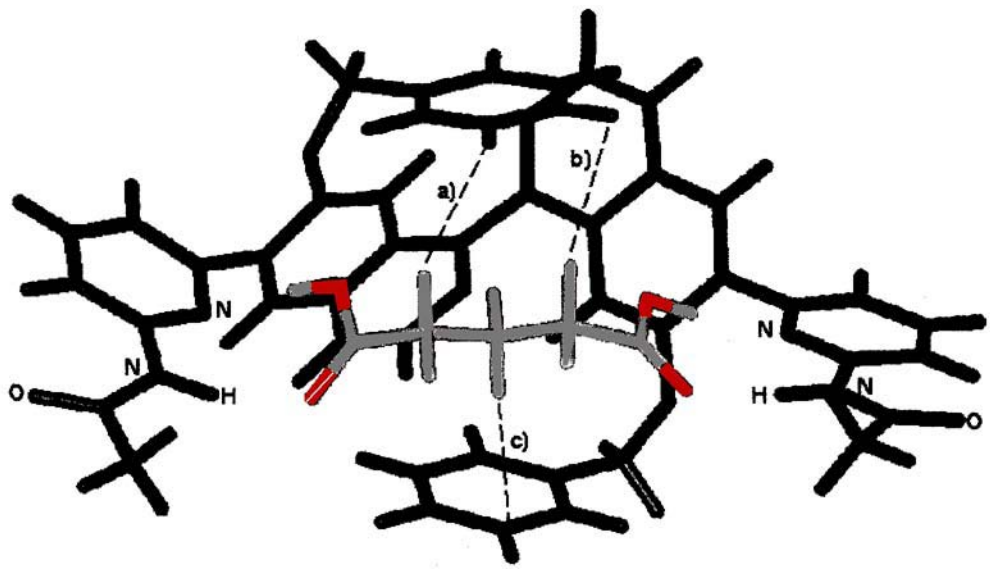


Fig. 4. *Computer-generated model of the complex formed between (±)-***10** *and glutaric acid* (**43**). The observed intermolecular NOEs between the CH_2 protons of **43** and the aromatic protons of (±)-**10** are shown (computer-modeled distances: a) 2.64 Å, b) 2.96 Å, and c) 2.93 Å). The C_{12} chains of (±)-**10** are omitted for clarity.

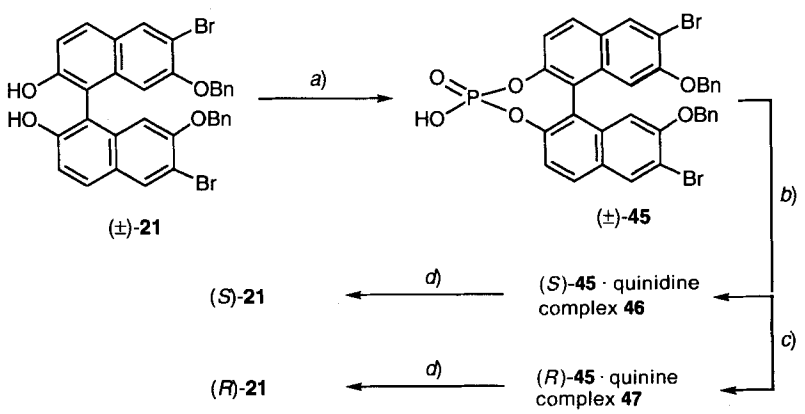
3) When compared to **8**, the phenylurea derivatives **39**–**41** did not provide enhanced binding of pimelic acid (**14**) which was chosen as a reference compound to compare relative complexation strengths (compare *Entry 12* with *18–20*). In contrast, the butylurea receptors **36**–**38** did show improvement over **8** (compare *Entry 12* with *15–17*), although not to the extent observed with **10** and **11**, which clearly are the best binders of pimelic acid (compare *Entries 13* and *14* with *15–21*). Apparently, bifurcated H-bonding between the urea NH groups of **36**–**41** and the C=O groups of the diacid substrate (*Fig. 2*, **B**) is not a very efficient interaction. Experimentally, the complexation-induced changes in ^{1}H-NMR chemical shifts at saturation binding, $\Delta\delta_{sat}$ (see *Table 6* in the *Exper. Part*), suggest a much weaker participation of the more distant urea NH group ($\Delta\delta_{sat} \approx 0.1$–0.2 ppm) in the H-bonding than of the NH group directly attached to the pyridine ring ($\Delta\delta_{sat} \approx 1.8$–2.0 ppm). These findings reiterate that the H-bonds and secondary electro-

static interactions involving the acidic OH groups of the carboxylic acids are much more important for complex stability than the bonding picked up by the C=O groups of the substrates. As noted above, the monomethyl ester **44** of glutaric acid binds to **10** with similar affinity to that of a monocarboxylic acid (*Entry 11*).

The complex between pimelic acid (**14**) and the bis(naphthyridine) receptor **42** is only slightly more stable than the complexes formed by the urea receptors **36**–**41** (compare *Entry 21* with *15–20*). As discussed previously [20c], the additional gain in binding energy from the bifurcated H-bonding between the substrate OH group and the two naphthyridine N-atoms (*Fig. 2*, **C**) is compensated by the weakened H-bonding acceptor ability of the naphthyridine N-atoms. H-Bonding strength correlates at first approximation with the acidity of the donor and the basicity of the acceptor, and the pK_a value of the naphthyridine N-atoms (pK_a 3.39 in H_2O) [36] is significantly reduced as compared to that of pyridine N-atoms (pK_a 5.23) [36].

2.4. *Preparation of the Enantiomerically Pure Receptors (*R*)- and (*S*)-***10*** and (*R*)- and (*S*)-***11***.* Since the screening for binding affinity showed (±)-**10** and (±)-**11** to be clearly superior to the other receptors (*Table 3*), these two compounds were prepared in enantiomerically pure form for chiral-recognition studies with the excitatory amino-acid derivatives. Although high binding affinity is not synonymous to high enantioselection [20c], many examples in the host-guest complexation studies by *Cram* and *Cram* showed a correlation between the two quantities [3a]. For the optical resolution of diol (±)-**21** as a precursor to the two type-B receptors, procedures [26] [37] previously applied to the resolution of 1,1′-binaphthyl-2,2′-diols [38] were followed. The cyclic phosphate (±)-**45** was synthesized from diol (±)-**21** and, upon addition of quinidine to a solution of (±)-**45** in AcOEt, a precipitate was obtained which, after two recrystallizations from AcOEt/hexane 1:1, gave the (*S*)-**45**·quinidine complex **46** (*Scheme 5*). The diastereoisomeric complexes formed by (±)-**45** and quinidine in $CDCl_3$ displayed distinctively different

Scheme 5. *Optical Resolution of Diol* **21**



a) 1) $POCl_3$, NEt_3, CH_2Cl_2; 2) THF, H_2O, Δ; 96%. *b*) Recrystallization with quinidine from AcOEt/hexane 1:1, r.t., 12 h, 66%. *c*) Recrystallization with quinine from AcOEt/hexane 2:1, r.t., 12 h; 23%. *d*) 1) 6M aq. HCl, EtOH, Δ then r.t.; 2) Me_2SO_4, $NaHCO_3$, DMA; 3) $LiAlH_4$, THF, 0°; 78% of (*S*)-**21** and 67% of (*R*)-**21**, based on **46** and **47**, resp.

^{1}H-NMR spectra, which is indicative of distinctively different solution geometries and presumably also stabilities [26]. In a 1.0 mM solution, well separated *singlets* of receptor protons were observed for the two diastereoisomeric complexes at 6.55 and 6.60 ppm (H–C(8)) and at 8.08 and 8.10 ppm (H–C(5)). From the mother liquor of the first precipitation, the (*R*)-enriched binaphthyl cleft was regenerated by decomposing the alkaloid complex with 6M aqueous HCl, and subsequent precipitation with quinine from AcOEt afforded the (*R*)-**45**·quinine complex **47**. Occasionally, the (*R*)-**45**·quinidine complex also crystallized out in pure form. Decomposition of the diastereoisomeric complexes with acid, followed by reduction of the intermediately formed methyl phosphates, gave (*R*)- and (*S*)-**21**. Confirmation of the optical purity and the configurational assignments was obtained by HPLC methods. Using a *Pirkle* chiral stationary phase (CSP; prepared from D-phenylglycine [3h] [39]) and hexane/propan-2-ol 9:1 as the eluent, both (*R*)- and (*S*)-**21** were determined to have e.e. $\geq$ 99.9%. Based on studies of the chromatographic behavior of the enantiomers of 1,1′-binaphthyl-2,2′-diols on this CSP [3h] [26] [39c], the enantiomer with the shorter retention time (t_R 34 min) was assigned the (*S*)-configuration and the one with the longer retention time (t_R 46 min) the (*R*)-configuration. Starting from (*R*)- and (*S*)-**21**, the enantiomers of receptors **10** and **11** were prepared following the procedures for the racemic compounds outlined in *Schemes 2* and *3*.

2.5. *Chiral-Recognition Studies with Excitatory Amino-Acid Derivatives.* Preliminary studies with racemic (±)-**10** or (±)-**11** and Cbz-Asp (**2**) had demonstrated the formation of diastereoisomeric complexes with differential geometries. Almost all aromatic protons, including the benzyl protons of (±)-**10**, showed distinct complexation-induced changes in chemical shift for each diastereoisomeric complex. The degree of chiral recognition in binding the Cbz derivatives Cbz-Asp (**2**), Cbz-D-Asp, Cbz-Glu (**4**), and Cbz-Kai (**6**) by the enantiomerically pure receptors was determined by ^{1}H-NMR titrations in $CDCl_3$ in which the receptor concentration $[H]_o$ was kept constant at 0.10 mM and the substrate concentration $[G]_o$ varied from 0.05 to 0.50 mM. The low concentration ranges were necessary due to the strong binding and, by clustering data points around the curved region of the binding isotherm, association constants $K_a > 10^5$ l mol^{-1}, *i.e.*, at the limit of the applicability range of the NMR method, could be obtained with reproducibilities of ±15–30% (*Table 4*).

Receptors (*R*)- and (*S*)-**10** and (*R*)- and (*S*)-**11** form very stable complexes with the aspartic- and glutamic-acid derivatives (*Table 4*, *Entries 1–5* and *8–12*). In analogy to the recognition by the type-**B** receptors **8** and **9** (*Sect. 2.1*), the complexes of Cbz-Asp (**2**) are more stable than those of Cbz-Glu (**4**). The geometry of the complexes was elucidated based on the observed complexation-induced changes in ^{1}H-NMR chemical shift, NOEs, and computer modeling. For the (*R*)-**10**·**2** complex, which is discussed below in greater detail, a total of 5 strong intermolecular NOEs were observed (*Fig. 5*), and they were crucial in evaluating the quality of the geometries produced by the modeling. In the modeling, a 5000-step Monte Carlo Multiple Minimum (MC) simulation was performed using the OPLS* force field in MacroModel v. 4.0 [23], the GB/SA continuum solvation model for $CHCl_3$ [35], and torsional constraints to keep the pyridines and their acetamido substituents in a plane. 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. All conformations within 12 kcal mol^{-1} of the global-minimum-energy conformation were stored.

Table 4. *Association Constants* K_a *and Binding Free Energies* $\Delta G°$ (± 0.1 kcal mol^{-1}) *of the Complexes Formed between Clefts (R)- and (S)-***10** *and (R)- and (S)-***11** *with Cbz-Asp* (**2**), *Cbz-D-Asp, Cbz-Glu* (**4**), *and Cbz-Kai* (**6**) *in* $CDCl_3$ *at 298 K*

Entry	Host[a])	Guest	K_a [l mol^{-1}]	$\Delta G°$ [kcal mol^{-1}]	$\Delta(\Delta G°)$
1	(*R*)-**10**	**2**	180000	−7.2	0.7 (0.8)
2	(*S*)-**10**	**2**	60000	−6.5	
3	(*R*)-**10**	Cbz-D-Asp	49000	−6.4	
4	(*R*)-**10**	**4**	19000	−5.8	0.3
5	(*S*)-**10**	**4**	11000	−5.5	
6	(*R*)-**10**	**6**	4100	−4.9	0.4
7	(*S*)-**10**	**6**	1900	−4.5	
8	(*R*)-**11**	**2**	120000	−7.0	0.1 (0.2)
9	(*S*)-**11**	**2**	110000	−6.9	
10	(*R*)-**11**	Cbz-D-Asp	98000	−6.8	
11	(*R*)-**11**	**4**	46000	−6.4	0.1
12	(*S*)-**11**	**4**	37000	−6.3	
13	(*R*)-**11**	**6**	4600	−5.0	0.2
14	(*S*)-**11**	**6**	3300	−4.8	

[a]) Evaluated host protons: H–C(5) and H–C(12)[1]).

For the (*R*)-**10**·**2** complex, a total of 62 structures were found within 2.4 kcal mol^{-1} of the computed global minimum. These 62 low-energy conformations fell into two categories. A total of 37 of these structures gave similar conformations which, however, were incongruent with several of the experimentally observed NOEs and were, therefore, rejected in favor of the alternative association mode (*Figs. 5* and *6*), which was represented in the remaining 25 low-energy structures and reproduced the spectroscopic data.

The primary stabilization of the complexes with the Asp and Glu derivatives results from the four-fold H-bonding pattern between the two COOH groups of the substrate and the two CONH(py) groups of the receptors [3g] [18] [20]. In the structure shown in *Fig. 5*, the computed O–H···N and C=O···H–N H-bond distances are 1.9 and 1.7 Å, respectively. The substrate is bound in the preferred *cis*-conformation about the carbamate NH–CO bond [20b]. The association constants are up to two orders of magnitude higher than those measured for the comparable complexes of type-B receptor **9** without functional groups at the 7,7′-positions of the 1,1′-binaphthyl spacer (*Table 1*). The modeling studies provide support for the participation of the ether O-atoms in the 7,7′-positions of **10** and **11** in the bonding event. In the (*R*)-**10**·**2** complex (*Fig. 5*), the OH···O–C(7)[1]) distance is *ca.* 2.9 Å and the O–H···O angle is *ca.* 100° which should lead to a substantial *Coulomb* interaction between the H- and O-atoms of opposite partial charges [32b] [33]. The C(5)–C(6)–C(9)–C(10)[1]) torsional angles range from 60 to 70°.

Aromatic interactions play an important role in providing additional stabilization to the complex between (*R*)-**10** and Cbz-Asp (**2**). Experimentally, the participation of both the $PhCH_2$ groups of receptor and substrate in the association is demonstrated by several characteristic NOEs shown in *Fig. 5*. One Ph ring of the receptor stacks with the *cis*-carbamate bond of the substrate (*Figs. 5* and *6*). A similar stacking interaction between aromatic rings and peptide bonds, in particular those of β-pleated sheets, is commonly observed at aromatic binding sites of proteins [1] [2c, h]. This interaction locates the *o*-protons of this Ph ring in proximity to the benzylic CH_2 protons of the substrate which explains the observed intermolecular NOE (c) in *Fig. 5*) between these protons.

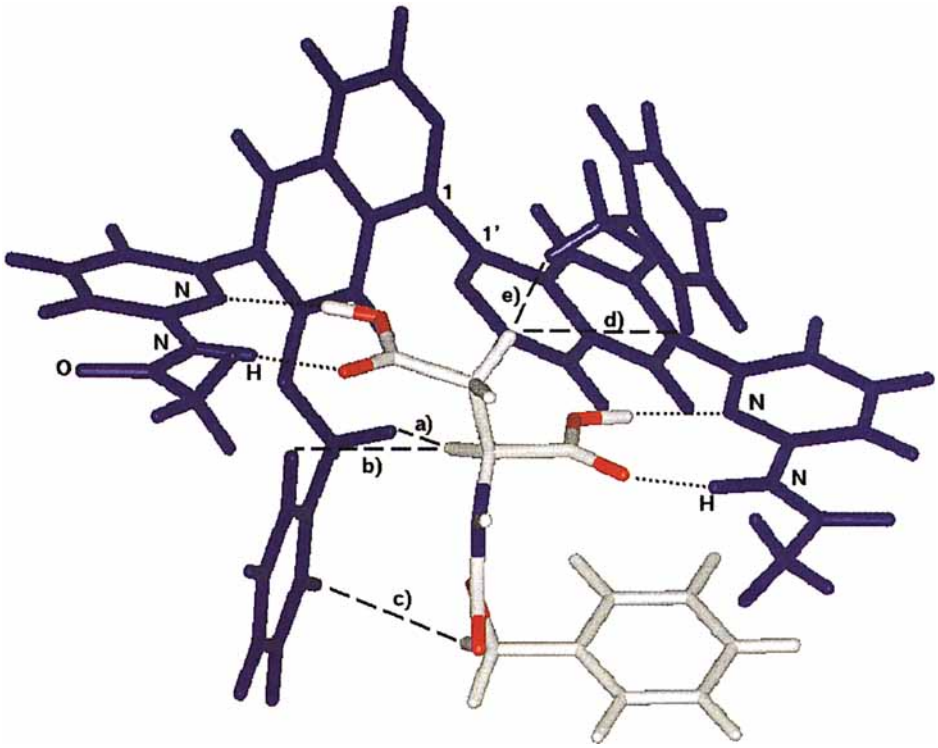


Fig. 5. *Computer-generated model of the complex formed between (R)-***10** *and Cbz-Asp* (**2**). The intermolecular H-bonds (·····) and the observed intermolecular NOEs (– – –) are shown. The computed distances between H-atoms showing intermolecular NOEs are: a) 2.38 Å, b) 2.87 Å, c) 3.21 Å, d) 3.27 Å, e) 2.54 Å. The C_{12} chains of (*R*)-**10** are omitted for clarity.

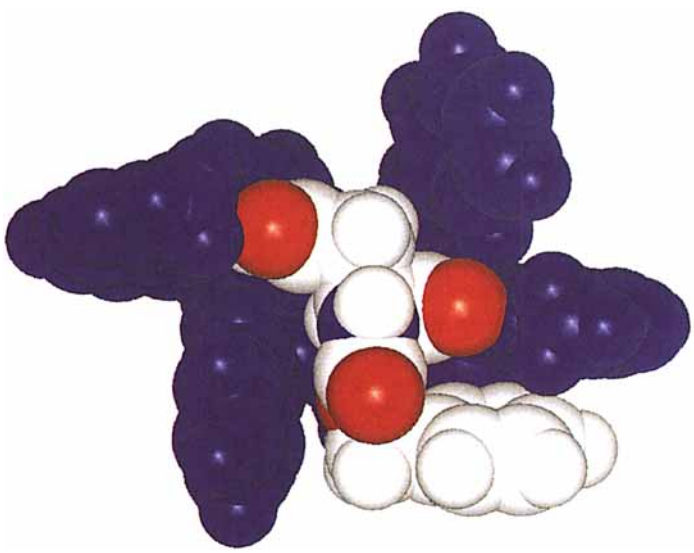


Fig. 6. *Computer-generated space-filling model of the complex formed between (R)-***10** *and Cbz-Asp* (**2**)

Both Ph rings of the receptor participate in interesting T-shaped interactions with the two COOH···CONH(py) H-bond arrays [40]. The Ph ring of the substrate is involved in a face-to-face stacking with one of these host-guest H-binding motifs. This geometry correlates with the atom orientations required for the observed NOEs between the CH_2CO_2H protons of the substrate and the aromatic and aliphatic benzylic protons of (*R*)-**10** (d) and e) in *Fig. 5*). All these host-guest interactions lead to a binding geometry in which H–C(α) of the zig-zag-shaped amino acid points into the cleft, and this is again confirmed by two intermolecular NOEs (a) and b) in *Fig. 5*).

Both the experimental (NOEs and ^{1}H-NMR complexation-induced shifts) and the computational analyses did not show striking differences in host-guest interactions between the diastereoisomeric complexes formed between Cbz-Asp (**2**) and (*R*)- and (*S*)-**10**. Apparently, the observed chiral recognition ($\Delta(\Delta G°) \approx 0.7$–$0.8$ kcal mol^{-1}, *Entries 1–3*, *Table 4*) originates from a series of subtle geometric differences. A comparison of the benzyl-ether receptors (*R*)- and (*S*)-**10** (*Entries 1–3*) with the methyl-ether receptors (*R*)- and (*S*)-**11** (*Entries 8–10*) or **8** and **9** (*Table 1*) without 7,7′-functionality clearly demonstrates that the considerable enantioselection by (*R*)- and (*S*)-**10** is due to the differential interactions provided by its benzylic Ph rings in the two diastereoisomeric complexes. Whereas chiral recognition by (*R*)- and (*S*)-**10** is substantial, the other receptors form diastereoisomeric complexes with **2** of nearly identical stability (*Tables 1* and *4*). Driven by the gain in aromatic interactions (*Figs. 5* and *6*), the $PhCH_2O$ groups shape a more structurally defined, cavity-type binding site, which enables the optically pure receptor to differentiate more efficiently between the enantiomeric substrates. The other receptors lack these $PhCH_2$ groups, and the substrate enantiomers are accommodated equally well in their more cleft-type recognition sites. Although the multiple aromatic interactions provided by (*R*)- and (*S*)-**10** along with the COOH···CONH(py) H-bonding patterns generate more efficient enantioselectivity, the association constants of the complexes are only *ca.* 1.5 times greater than for the complexes of (*R*)- and (*S*)-**11** (compare *Entries 1–3* and *Entries 8–10*). This is a clear indication that much of the enthalpic gains are compensated by entropic losses as a result of the conformational restriction of the $PhCH_2$ groups in the complexes of (*R*)- and (*S*)-**10**.

Since the binding sites of the two enantiomers of MeO-substituted **11** are more open and less structured than those of (*R*)- and (*S*)-**10**, they can better accommodate the larger Glu derivative **4** and form more stable complexes with this substrate (compare *Entries 4* and *5* with *Entries 11* and *12*).

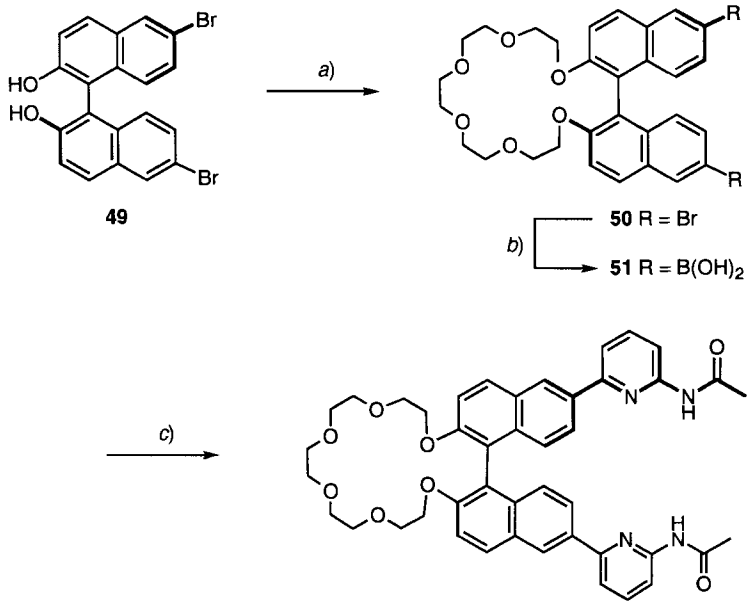
Selective and efficient complexation of Cbz-Kai (**6**) poses a continuing challenge, presumably due to its particular geometry. The two COOH residues connected by a C_3 chain adopt a U-shaped alignment, and the incorporation of this chain into a 5-membered ring reduces the conformational flexibility. Binding of **6** is less efficient than that of the Glu and Asp derivatives (*Entries 6*, *7*, *13*, and *14*) which suggests that the enantiomers of receptors **10** and **11** are unable to adopt a binding geometry with high complementarity to the conformationally more enforced kainic-acid substrate. The orientation of the two terminal COOH residues in the substrates seems to play a role in the binding efficiency (*Table 4*), with the linear alignment in the Asp derivative **2** being preferred over the more W-shaped alignment in the Glu derivative **4**, and the pronounced U-shape alignment in the Kai derivative **6**.

2.6. *Complexation by a 1,1′-Binaphthyl Receptor with an Additional Cation Recognition Site at the Minor Groove.* The 1,1′-binaphthyl unit is flexible [41] and can adopt numerous energetically similar conformations with dihedral angles between the two naphthalene planes varying between 60 and 120° [42]. As a result, binaphthyl receptors such as **7–9** lack the conformational homogeneity required for efficient chiral recognition, and diastereoisomeric complexes of similar stability are formed with chiral dicarboxylic acids (*Table 1*) [20b, c]. Enantiomers of these receptors are capable of adopting geometries which fit both substrate enantiomers, and diastereoisomeric complexes of similar energy are formed. To provide strong association in one diastereoisomeric complex only, the binaphthyl unit needs to be more preorganized and the dihedral angle about the chirality axis constrained. This objective is currently targeted in our laboratory by bridging the 2,2′-positions at the 1,1′-binaphthyl minor groove, and first advances in this direction are presented here.

In receptor **48**, a crown-ether binding site was attached to the 2,2′-positions in the minor groove to reduce the conformational flexibility about the binaphthyl chirality axis [3a] [9] [43a]. Cation complexation by the crown ether was expected to further rigidify the binaphthyl spacer. We were particularly interested in exploring whether cation complexation in the binaphthyl minor groove would alter the efficiency and enantioselectivity of the excitatory amino acid binding site at the major groove [43] [44].

The synthesis of (*R*)- and (*S*)-**48** (*Scheme 6*) started with the enantiomers of 6,6′-dibromide **49** [20c] which were transformed into the crown ethers (*R*)- and (*S*)-**50** [45] and

Scheme 6. *Preparation of Receptor* **48**



48

a) $TosCH_2(CH_2OCH_2)_4CH_2OTos$, NaH, THF; 52%.
b) BuLi, THF, −78°, then $B(OMe)_3$, Δ.
c) *N*-(6-Bromopyridin-2-yl)acetamide, $[PdCl_2(PPh_3)_2]$, Na_2CO_3, EtOH, benzene, H_2O, Δ; 23%.

Table 5. *Association Constants* K_a *and Binding Free Energies* $\Delta G°$ (±0.1 kcal mol^{-1}) *in* $CDCl_3$ *at 293 K of the Complexes Formed between Clefts (R)- and (S)-***48** *with Cbz-Asp* (**2**), *or Cbz-Glu* (**4**) *in the Presence and Absence of* $Hg(CN)_2$ *as a Cobinder* [a][b]

Entry	Host	Guest	Cobinder[c]	K_a [l mol^{-1}]	$\Delta G°$ [kcal mol^{-1}]	$\Delta(\Delta G°)$
1	(*R*)-**48**	**2**	–	2900	−4.6	
2	(*S*)-**48**	**2**	–	8300	−5.2	0.6
3	(*R*)-**48**	**2**	$Hg(CN)_2$	2600	−4.6	
4	(*S*)-**48**	**2**	$Hg(CN)_2$	9100	−5.3	0.7
5	(*R*)-**48**	**4**	–	3200	−4.7	0.4
6	(*S*)-**48**	**4**	–	1700	−4.3	
7	(*R*)-**48**	**4**	$Hg(CN)_2$	3900	−4.8	0.5
8	(*S*)-**48**	**4**	$Hg(CN)_2$	1700	−4.3	

[a]) The association constant of $Hg(CN)_2$ binding to the crown is K_a = 350 l mol^{-1}.
[b]) Evaluated host protons: NH, H–C(5), H–C(7), H–C(10), H–C(11), H–C(12)[1]).
[c]) $[Hg(CN)_2]_0$ = 4.98 mM.

subsequently into the bis(boronic acids) (*R*)- and (*S*)-**51**. *Suzuki* coupling with *N*-(6-bromopyridin-2-yl)acetamide afforded the two enantiomeric receptors which were studied in ^{1}H-NMR binding titrations (*Table 5*).

Since the H-bonding recognition sites in the two type-B receptors **48** and **9** are identical, their complexation properties resemble each other in several ways (*cf. Tables 1* and *5*). Cbz-Asp (**2**) is better bound than Cbz-Glu (**4**), and (*S*)-**48** prefers binding to the shorter Asp derivative, whereas the Glu derivative associates more strongly to (*R*)-**48**. (*R*)- and (*S*)-**48** show a slightly higher degree of chiral recognition than (*R*)- and (*S*)-**9**, presumably as a result of reduced conformational flexibility of the binaphthyl cleft due to the attachment of the cyclic crown-ether moiety. A more rigid, conformationally more enforcing bridging of the 2,2′-positions in the minor groove should enhance more substantially the enantioselection in excitatory amino-acid binding in the major groove of the 1,1′-binaphthyl cleft.

The kinetically slow binding of $Hg(CN)_2$ to the enantiomers of **48** took almost one week to proceed to equilibrium [44] and, from the integration of the ^{1}H-NMR resonances of free and bound receptor, which appeared at different chemical shifts, the association constant for the 1:1 complex was determined as K_a = 350 l mol^{-1}. Disappointingly, no cooperativity between the cation binding at the minor groove and the dicarboxylic-acid binding at the major groove was observed; the complexation of the Hg^{2+} ion neither affected the binding affinity nor the enantioselection in the major groove (*Table 5*).

3. Conclusions. – The chiral molecular clefts **7**–**9** with CONH(py) groups attached in two different ways to the 6,6′-positions of 1,1′-binaphthyls were prepared for the complexation of Cbz derivatives of excitatory amino acids *via* two sets of C=O···H–N and O–H···N H-bonding arrays in $CDCl_3$. Whereas receptor **7** with *N*-(pyridin-2-yl)carboxamide residues (type A) preferred complexing the larger Glu derivative **4**, **8** and **9** with *N*-(pyridine-6,2-diyl)acetamide residues (type B) showed a preference for the shorter Cbz-Asp (**2**). Two synthetic approaches to increase the poor enantioselectivity ($\Delta(\Delta G°)$ between 0.1 and 0.5 kcal mol^{-1}) displayed by the enantiomerically pure **7**–**9** were pursued. One approach consisted of optimizing the recognition site by introducing additional functional groups at the 7,7′-positions of the receptors which could participate

in the substrate recognition and enforce favorable binding conformations of the CONH(py) residues. Based on established correlations between binding free energy and enantioselectivity by *Cram* and coworkers, a diversity of new clefts was first prepared in racemic form and screened for high binding affinity toward α,ω-dicarboxylic acids. The type-B receptors with $PhCH_2O$ or MeO substituents in the 7,7′-positions of the 1,1′-binaphthyl unit, *i.e.*, **10** or **11**, respectively, were found to be the best binders and were subsequently prepared in enantiomerically pure form. The ether substituents in the 7,7′-positions were found to stabilize carboxylic-acid binding *via* substantial secondary electrostatic attractions. Whereas the MeO-substituted receptors (*R*)- and (*S*)-**11** failed to show enantioselectivity in binding the excitatory amino-acid derivatives, the $PhCH_2O$ derivative (*R*)-**10** preferred complexing Cbz-Asp (**2**) by ~ 0.7–0.8 kcal mol^{-1} over Cbz-D-Asp. A comprehensive experimental (^{1}H-NMR complexation-induced changes in chemical shifts, NOEs) and computational analysis demonstrated that the Ph rings of the $PhCH_2O$ groups play an important role in the recognition event. They interact in interesting face-to-face and edge-to-face binding motifs with both the *cis*-carbamate moiety of the substrate and the planar COOH···CONH(py) H-bonding arrays. These additional host-guest interactions, which are lacking in the complexes of **7**–**9** or **11**, are both at the origin of the enantioselectivity observed with (*R*)- and (*S*)-**10** as well as of the high complex stability ($\Delta G^\circ = -7.2$ kcal mol^{-1} for the more stable (*R*)-**10**·**2** complex). For the first time, a derivative of kainic acid was complexed by a synthetic receptor.

In a second approach, an increase in enantioselectivity was targeted by reducing the conformational flexibility of the binaphthyl receptor by attachment of a crown-ether binding site at the 2,2′-positions in the minor groove. Compared to receptors (*R*)- and (*S*)-**9** without such additional functionality, the crown-ether derivatives (*R*)- and (*S*)-**48** showed a very modestly improved enantioselectivity of $\Delta(\Delta G^\circ) \approx 0.6$–$0.7$ kcal mol^{-1} in the binding of Cbz-Asp (**2**). Both binding affinity and selectivity were not altered upon complexation of $Hg(CN)_2$ to the crown-ether moiety of **48**, demonstrating lack of cooperativity between the minor- and major-groove recognition sites. Apparently, both the unbound and bound crown ether do not substantially enforce the conformational homogeneity of the receptor, which is a requirement for strongly enhanced enantioselectivity.

These studies provide a lead toward improved enantioselective binding of excitatory amino acids. Novel receptors should incorporate the optimized major-groove binding site of (*R*)- and (*S*)-**10** and possess significantly more rigid, shorter bridges in the 2,2′-positions of the minor groove. These bridges should enforce a strong preference for specific dihedral angles about the 1,1′-binaphthyl chirality axis and thus enhance the enantioselective recognition capabilities through a higher degree of receptor preorganization.

Experimental Part

General. See [20c]. For optical resolutions, quinine (99%) was purchased from *Fluka* and quinidine (97%) from *Aldrich*. $^1H\{^1H\}$ Nuclear *Overhauser* effect (NOE) difference spectra: *Bruker-AMX-300* spectrometer; all intermolecular NOEs between host and guest in a 1:1 complex were observed by irradiation of the guest and enhancement of the host protons; host-to-guest NOEs were overshadowed by strong intramolecular response of the host. Evaporation and concentration *in vacuo* was done at water-aspirator pressure; drying *in vacuo* at 10^{-2} Torr. DMA = *N*,*N*-Dimethylacetamide.

Complexation Studies. Substrates **2**, Cbz-D-Asp, and **4** for complexation studies were purchased from *Sigma*. All ^{1}H-NMR titration data were acquired on a *Bruker-500-MHz* NMR spectrometer thermostated at 298 ± 0.1 K

if not stated otherwise. The $CDCl_3$ used for diacid binding was dried over molecular sieves (4 Å). Commercially available guests were used without further treatment. For each binding study, ten titration samples were prepared with *Gilson Pipetman* (200 µl and 1000 µl) pipetting from sonicated stock solns. which were obtained by weighing the compounds into 2 or 5-ml volumetric flasks on a *Mettler AT20* microbalance. If not stated otherwise, the host concentration was kept constant at 1.0 mM and the concentration of the guest was varied from 0.5 mM to 5.0 mM to reach saturation values up to 70–90%. In cases of very strong complexation (*Table 4*): $[H]_o = 0.10$ mM and $[G]_o = 0.05$–0.50 mM. For kainic-acid binding: $[H]_o = 0.10$ mM and $[G]_o = 0.5$–5.0 mM.

The complexation-induced changes in chemical shifts $\Delta\delta$ of host protons were plotted against the guest concentration. Quantitative binding numbers (K_a, $\Delta G°$, $\Delta\delta_{sat}$) were obtained by using a nonlinear least-squares curve-fitting program [22]. The K_a and $\Delta G°$ values reported are averages calculated from the complexation-induced changes in chemical shift of all observed protons of multiple runs. *Table 6* shows the maximum observed complexation-induced changes in chemical shift ($\Delta\delta_{max}$(obs.)) and the calculated changes in chemical shift at saturation binding ($\Delta\delta_{sat}$) for the proton resonances monitored during exemplary binding titrations. *Job* plots [46] were performed by keeping the sum of host and guest concentration at 1.0 mM. *Job* plots of receptors **7** and **8** with several diacids had previously been performed [20a, b] and confirmed the 1:1 stoichiometry for complexes of this type. *Job* plots of receptor **10** binding to pimelic acid (**14**) proved the 1:1 stoichiometry for complexes formed by the new receptors.

Table 6. *Evaluated Host Protons in Selected ^{1}H-NMR Binding Titrations in $CDCl_3$*

Host	Guest	Evaluated host protons; $\Delta\delta_{sat}$[a]); $\Delta\delta_{max}$(obs.)[b])			
		NH	H–C(5)	H–C(10)[1])	H–C(12)[1])
10	**13**	br.[c])	−0.171; −0.164	−0.140; −0.136	–
11	**13**	br.	−0.143; −0.137	–	br.
10	**43**	2.688; 2.630	−0.316; −0.309	−0.355; −0.348	0.206; 0.202
11	**43**	2.681; 2.630	−0.334; −0.331	–	0.192; 0.188
10	**14**	1.821; 1.680	−0.218; −0.201	−0.230; −0.228	0.130; 0.121
11	**14**	2.046; 1.964	−0.250; −0.240	−0.218; −0.214	0.142; 0.136
37	**14**	0.196; 0.159 (Bu-N*H*CO) 1.997; 1.638 (CON*H*(py))	−0.029; −0.023	–	0.156; 0.125
40	**14**	0.094; 0.071 (Bu-N*H*CO) 1.785; 1.214 (CON*H*(py))	−0.026; −0.021	–	0.122; 0.085
42	**14**	1.761; 1.462	−0.096; −0.093	–	–
(*R*)-**10**	**2**[d])	br.	−0.380; −0.376	–; −0.342	0.299; 0.293
(*S*)-**10**	**2**[e])	br.	−0.294; −0.285	–; −0.309	0.169; 0.166

[a]) Change in chemical shift at saturation binding. [b]) Maximum observed change in chemical shift during the titration, [c]) Due to very strong broadening, the peak could not be followed during the entire titration. [d]) Additional $\Delta\delta_{max}$(obs.) values: −0.101 (H–C(8)); 0.181 (H–C(11)[1])); 0.03 (H_o); 0.02 (H_m, H_p). [e]) Additional $\Delta\delta_{max}$(obs.) values: +0.038 (H–C(8)); 0.226 (H–C(11)[1])); 0.08 (H_o); 0.02 (H_m, H_p).

Complexation of $Hg(CN)_2$ to the crown-ether site in **48** was a very slow process which required a week to reach equilibrium. Typically, samples of the optically pure receptor and $Hg(CN)_2$ were stirred at *ca.* 295 K in $CDCl_3$ and stored in the dark during the complexation process. Progress was determined by ^{1}H-NMR integration of signals for bound and unbound receptor. The resonance of H–C(8) appeared 0.11 ppm upfield in the complex (δ 7.23 ppm) and the signals for Naph–O–CH_2CH_2, which in the free crown appeared as two *m*'s (*AA'BB'*) at δ 4.22 and 4.08 ppm, shifted downfield in the complex and converged to a *t* at 4.68 ppm. From the integration of the resonances for bound and unbound receptor at $[H]_0 = 4.73$ mM and $[G]_o = 8.07$ mM, the association constant for the 1:1 binding was determined as $K_a = 350$ l mol^{-1} ($\Delta G° = -3.5$ kcal mol^{-1}).

Crystallographic Data. Crystals of (±)-**10** were obtained by slow evaporation from a MeCN soln. The resulting colorless material crystallized in the triclinic space group $P\bar{1}$ with $a = 12.802$ (3), $b = 15.362$ (3), $c = 18.764$ (4) Å, $\alpha = 105.499$ (6), $\beta = 106.777$ (7), $\gamma = 98.777$ (7) °, $V = 3308$ Å^3, and $Z = 2$. *Syntex-P1* diffractometer modified by Prof. *C. E. Strouse*, UCLA, CuK_α radiation, $\lambda = 1.5418$ Å. The structure was solved by statistical methods (SHELX86). Only the O-atoms and some C-atoms were refined anisotropically, all other

Table 7. *Selected Bond Lengths* [Å] *and Bond Angles* [°] *of* (±)-**10**. For numbering, see *Fig. 10*.

C(1)–C(2)	1.52 (4)	C(10)–C(11)	1.34 (2)	C(1)–C(2)–O(2)	127 (3)
C(2)–O(2)	1.18 (3)	C(10)–C(19)	1.48 (2)	C(1)–C(2)–N(3)	107 (2)
C(2)–N(3)	1.43 (3)	C(11)–C(12)	1.40 (2)	O(2)–C(2)–N(3)	124 (2)
N(3)–C(4)	1.41 (2)	C(12)–C(13)	1.39 (2)	C(2)–N(3)–C(4)	120.4 (16)
C(4)–C(5)	1.35 (3)	C(12)–C(17)	1.46 (2)	N(3)–C(4)–C(5)	129 (2)
C(4)–N(9)	1.38 (2)	C(15)–O(22)	1.37 (2)	N(3)–C(4)–N(9)	108.8 (14)
C(5)–C(6)	1.41 (3)	C(16)–C(50)	1.53 (2)	C(5)–C(4)–N(9)	122.5 (17)
C(6)–C(7)	1.43 (3)	O(20)–C(21)	1.41 (2)	C(4)–C(5)–C(6)	121 (2)
C(7)–C(8)	1.37 (2)			N(9)–C(8)–C(10)	112.2 (12)
C(8)–N(9)	1.35 (2)			C(8)–C(10)–C(11)	118.5 (13)
				C(14)–C(15)–O(22)	120.5 (13)
				C(15)–C(16)–C(50)	120.1 (12)
				C(19)–O(20)–C(21)	116.7 (12)
				O(20)–C(21)–C(21P)	109.7 (12)

non-H-atoms were refined isotropically; H-positions based on configurational considerations. Final $R(I) = 0.143$, $wR(I) = 0.169$ for 445 variables and 9059 unique reflections with $I > 3\sigma(I)$ and $2\theta < 115°$. The molecular geometry is given in *Table 7*. Further details of the crystal structure investigations are available on request from the Director of the *Cambridge Crystallographic Centre*, 12 Union Road, Cambridge CB2 1EZ, UK.

(2S,3S,3S)-N-(Benzyloxycarbonyl)-2-carboxy-4-(1-methylethenyl)pyrrolidine-3-acetic Acid (**6**). To a soln. of L-kainic acid monohydrate (**5**; 100 mg, 0.43 mmol) in H_2O (21.5 ml) was added KOH (48 mg, 0.860 mmol), Na_2CO_3 (91 mg, 0.860 mmol), and benzyl chloroformate (0.073 ml, 0.52 mmol). The mixture was stirred at r.t. for 16 h, cooled to 0°, and acidified with 2M aq. HCl. The product was extracted with Et_2O (25 ml) and the org. soln. washed with H_2O (3 × 25 ml), dried ($MgSO_4$), and evaporated: **6** (119 mg, 80%) as a white glassy oil which slowly solidified. M.p. 53–55°. $[\alpha]_D^{22} = -61.57$ ($c = 0.055$, $CHCl_3$). IR ($CHCl_3$): 3090, 2952, 1714, 1415, 1133. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.22 (*s*, 3 H); 2.18–2.30 (*m*, 1 H); 2.32–2.44 (*m*, 1 H); 2.98–3.06 (*m*, 2 H); 3.47–3.59 (*m*, 2 H); 3.69–3.80 (*m*, 2 H); 4.33–4.75 (*m*, 2 H); 4.97 (*s*, 1 H); 5.20 (*s*, 2 H); 7.31–7.47 (*m*, 5 H). FAB-MS: 347 (M^+). Anal. calc. for $C_{18}H_{21}NO_6 \cdot 0.25\ H_2O$ (351.6): C 61.38, H 6.11, N 3.98; found: C 61.61, H 6.19, N 3.73.

3-Bromonaphthalene-2,7-diol (**19**). To naphthalene-2,7-diol (**18**; 40 g, 0.25 mol) in AcOH (586 ml) at 10–15°, Br_2 (26 ml, 0.50 mol) in AcOH (195 ml) was added dropwise within 4 h. Then, H_2O (160 ml) and Sn powder (325 mesh; 62 g, 0.52 mol) were added, and the mixture was placed for 1.5 h in an oil bath warmed to 80°. The mixture was cooled to 10°, diluted with ice-cold H_2O (1.5 l), and extracted with AcOEt (2 × 2 l). The org. layers were dried ($MgSO_4$) and evaporated to produce a purple solid which was stirred for 1 h in H_2O (600 ml), filtered, suction-dried, and recrystallized from toluene (1 l) to provide **19** (54.6 g, 91%). Pink solid. M.p. 190–191°. IR (KBr): 3218, 1200. ^{1}H-NMR (500 MHz, $(CD_3)_2CO$): 6.96 (*dd*, $J = 9.0, 2.3$, 1 H); 6.99 (*d*, $J = 2.3$, 1 H); 7.04 (*s*, 1 H); 7.63 (*d*, $J = 9.0$, 1 H); 7.98 (*s*, 1 H); 8.64 (br. *s*, 1 H); 9.01 (br. *s*, 1 H). FAB-MS: 240 (M^+). Anal. calc. for $C_{10}H_7BrO_2$ (239.1): C 50.24, H 2.95, Br 33.42, O 13.38; found: C 50.27, H 2.75, Br 33.18, O 13.24.

7-(Benzyloxy)-6-bromonaphthalen-2-ol (**20**). To **19** (20 g, 0.083 mol) in DMF (440 ml) under Ar was added K_2CO_3 (23.3 g, 0.169 mol). The mixture was stirred for 15 min and then heated to 80°. Benzyl chloride (8.6 ml, 0.075 mol) was added *via* syringe pump within 5 h. The resulting green soln. was filtered through *Celite*, the solvent removed by distillation, and the residue diluted with MeOH (1 l). Cooling precipitated the dibenzylated side-product. The mother liquor was evaporated and the residue passed through a plug of SiO_2 (400 g) with CH_2Cl_2. Evaporation and recrystallization from toluene/hexane 1:1 gave **20** (20.4 g, 74%). Off-white platelets. M.p. 140–142°. IR (KBr): 3518, 1540, 1218. ^{1}H-NMR (360 MHz, $(CD_3)_2CO$): 5.29 (*s*, 2 H); 7.02 (*dd*, $J = 9.0, 2.3$, 1 H); 7.13 (*d*, $J = 2.3$, 1 H); 7.30–7.45 (*m*, 4 H); 7.55–7.60 (*m*, 2 H); 7.67 (*d*, $J = 9.0$, 1 H); 8.04 (*s*, 1 H); 8.71 (br. *s*, 1 H). FAB-MS: 328 (M^+). Anal. calc. for $C_{17}H_{13}BrO_2$ (329.2): C 62.03, H 3.98, Br 24.27; found: C 62.33, H 4.26, Br 24.34.

7,7'-Bis(benzyloxy)-6,6'-dibromo-1,1'-binaphthyl-2,2'-diol (**21**). To **20** (10 g, 30.4 mmol) under Ar in degassed MeOH (1 l) was added $CuCl_2$ (8.4 g, 62.5 mmol), and Ar was bubbled through the soln. for 15 min. *t*-$BuNH_2$ (13.9 ml, 132.3 mmol) in degassed MeOH (100 ml) was added within 30 min and the mixture refluxed for 2.5 h and then cooled to 0°. After addition of 6N aq. HCl (440 ml), the brown suspension was diluted with CH_2Cl_2 (3 × 250 ml) and the org. phase washed with H_2O (2 × 500 ml), dried ($MgSO_4$), and evaporated. The resulting brown foam was

passed through a plug of SiO_2 (150 g) with CH_2Cl_2. Evaporation and recrystallization from toluene/hexane provided **21** (6.5 g, 65%). M.p. 168–170°. IR (KBr): 3277, 1580, 1220. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.74 (*q*, *AB*, *J* = 12.5, 4 H); 4.92 (*s*, 2 H); 6.24 (*s*, 2 H); 7.00–7.05 (*m*, 4 H); 7.10–7.15 (*m*, 6 H); 7.22 (*d*, *J* = 9.0, 2 H); 7.82 (*d*, *J* = 9.0, 2 H); 8.11 (*s*, 2 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 70.28; 105.41; 109.60; 111.72; 116.17; 125.24; 126.70; 127.66; 128.33; 130.17; 132.61; 133.57; 135.75; 153.26; 153.63. FAB-MS: 656 (M^+). Anal. calc. for $C_{34}H_{24}Br_2O_4$ (656.4): C 62.22, H 3.69, Br 24.35; found: C 62.25, H 3.57, Br 24.60.

Optical Resolution of (±)-**21**. To (±)-**21** (4.38 g, 6.7 mmol) in CH_2Cl_2 (50 ml) was added dropwise over 15 min $POCl_3$ (1.58 ml, 17.2 mmol) followed by NEt_3 (2.45 ml, 17.6 mmol). The mixture was stirred for 3 h and then quenched with ice-cold H_2O (150 ml). The org. layer was dried ($MgSO_4$) and evaporated to produce the intermediate chlorophosphate as an orange foam. The crude chlorophosphate was dissolved in THF/H_2O 2:1, (35 ml) and refluxed for 4 h. The cooled mixture was partitioned between AcOEt (3 × 300 ml) and H_2O (250 ml) and the combined org. phase dried ($MgSO_4$) and evaporated: (±)-**45** (4.6 g, 96%). White crystals. M.p. 208–210°.

Crude (±)-**45** (4.6 g, 6.67 mmol) was heated to reflux in AcOEt (200 ml), and quinidine (2.2 g, 6.67 mmol) was added. Additional AcOEt (200 ml) was added to dissolve all material. Hexane was added slowly (350 ml) to the refluxing soln. until it became turbid. Diastereoisomerically pure seed crystals (obtained by recrystallization of 500 mg of (±)-**45** with 230 mg of quinidine from hexane/AcOEt 5:1 (100 ml) and collected after 10 d) were added, and the soln. was cooled to r.t. for 12 h. The light-brown crystals were collected by filtration, and a second recrystallization from AcOEt/hexane 1:1 (500 ml) along with seed-crystal addition afforded the (*S*)-45·quinidine complex **46** (2.4 g, 66%, $[\alpha]_D^{23} = +396.6$ (*c* = 1.00, $CHCl_3$)) as cream-colored crystals.

Complex **46** (2.4 g) was stirred at reflux with EtOH (6.8 ml) and 6M aq. HCl (3.4 ml) for 15 min and then at r.t. overnight. Extraction with AcOEt (3 × 300 ml), washing with 2M aq. HCl (300 ml) and sat. aq. NaCl soln. (300 ml), drying ($MgSO_4$), and evaporation produced 1.58 g (100%) of (*S*)-**45**, $[\alpha]_D^{22} = +240.5$ (*c* = 1.00, $CHCl_3$).

To (*S*)-**45** (1.580 g, 2.2 mmol) in DMA (49 ml) was added Me_2SO_4 (0.389 ml, 4.0 mmol) followed by $NaHCO_3$ (0.386 g, 4.6 mmol) and the mixture was stirred at r.t. overnight. The clear soln. was diluted with Et_2O (100 ml) and washed successively with sat. aq. $NaHCO_3$ soln. (100 ml), H_2O (100 ml), and sat. aq. NaCl soln. (100 ml). The org. layer was dried ($MgSO_4$) and evaporated to produce the corresponding methyl (*S*)-phosphate (1.55 g, 96%) as a brown oil.

To the crude methyl (*S*)-phosphate (1.55 g, 2.11 mmol) in dry THF (75 ml) under Ar at 0° was added 1.0M $LiAlH_4$ in hexane (4.6 ml, 4.6 mmol). The mixture was stirred at 0° for 20 min before quenching cautiously and successively with H_2O (4.6 ml), 15% aq. NaOH soln. (4.6 ml), and then H_2O (13.8 ml). After stirring overnight, the resulting soln. was filtered and the filtrate extracted with (2 × 25 ml). The org. layers were dried ($MgSO_4$) and evaporated: (*S*)-**21** (1.13 g, 82%). $[\alpha]_D^{23} = +296.6$ (*c* = 1.00, $CHCl_3$).

The mother liquor from the recrystallization of (±)-**45** with quinidine was evaporated and the residue dissolved in refluxing AcOEt (20 ml). Hot 6M aq. HCl (20 ml) was added and the mixture heated for 15 min and then stirred at r.t. overnight. The org. layer was washed with 6M aq. HCl and sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated to produce (*R*)-enriched **45** (2.7 g).

The crude (*R*)-enriched **45** (2.7 g, 3.75 mmol) was heated in AcOEt (150 ml), and quinine (1.2 g, 3.75 mmol) was added to give a clear soln. Hexane (100 ml) was added and the resulting mixture left at r.t. overnight. The precipitated complex was collected by filtration, and recrystallization from AcOEt (200 ml) and hexane (100 ml) produced the (*R*)-**45**·quinine complex **47** (0.44 g, 23%; $[\alpha]_D^{23} = -399.7$ (*c* = 1.00, $CHCl_3$)) as white crystals. Decomposition of the complex and dephosphorylation was done in a similar manner as described above to provide (*R*)-**21** (0.11 g, 67%, from **47**), $[\alpha]_D^{23} = -296.7$ (*c* = 1.01, $CHCl_3$).

Occasionally, after the initial addition of quinidine to (±)-**45**, a white, insoluble precipitate would have to be removed by filtration before the addition of hexane. The precipitate in many cases was 100% diastereoisomerically pure (*R*)-**45**·quinidine complex ($[\alpha]_D^{23} = -286.1$ (*c* = 1.01, $CHCl_3$)). This complex could also be decomposed and dephosphorylated to provide (*R*)-**21**.

(±)-7,7'-Bis(benzyloxy)-6,6'-dibromo-2,2'-bis(dodecyloxy)-1,1'binaphthyl (**22**). To a soln. of **21** (1.0 g, 1.52 mmol) in MeCN (50 ml) was added K_2CO_3 (0.9 g, 6.51 mmol), and the mixture was stirred for 10 min before the addition of 1-iodododecane (1.0 ml, 4.05 mmol). After refluxing for 12 h, the mixture was filtered through a pad of *Celite*, evaporated, and chromatographed (100 g of SiO_2, hexane→hexane/AcOEt 3:2): **22** (1.47 g, 98%). Yellow semi-solid. M.p. 60–62°. IR (KBr): 2927, 1638, 1241. ^{1}H-NMR (360 MHz, $CDCl_3$): 0.84–1.40 (*m*, 46 H); 3.65–3.75 (*m*, 2 H); 3.80–3.90 (*m*, 2 H); 4.68 (*q*, *AB*, *J* = 12.7, 4 H); 6.29 (*s*, 2 H); 6.95–7.00 (*m*, 4 H); 7.10–7.15 (*m*, 6 H); 7.20 (*d*, *J* = 9.0, 2 H); 7.75 (*d*, *J* = 9.0, 2 H); 8.06 (*s*, 2 H). FAB-MS: 992 (M^+). Anal. calc. for $C_{58}H_{72}Br_2O_4$ (993.0): C 70.15, H 7.31, Br 16.09; found: C 70.23, H 7.05, Br 15.91.

(*R*)-**22** ($[\alpha]_D^{23} = -82.80$ (*c* = 1.01, $CHCl_3$)) and (*S*)-**22** ($[\alpha]_D^{23} = +82.43$ (*c* = 1.02, $CHCl_3$)) were prepared in a similar manner.

7,7'-Bis(benzyloxy)-2,2'-bis(dodecyloxy)-1,1'-binaphthyl-6,6'-dicarboxylic Acid (**23**). To THF (74 ml) under Ar at −78° was added 1.6M BuLi in hexane (11.5 ml, 18.5 mmol), and the mixture was stirred for 15 min. A soln. of **22** (4.6 g, 4.6 mmol) in THF (16 ml) was added dropwise over 15 min and the resulting bright-yellow soln. stirred at −78° for 45 min. Pieces of dry ice were added rapidly to approximately double the volume, then the mixture was warmed to r.t. and CO_2 gas was bubbled through overnight at a moderate rate. The resulting yellow soln. was concentrated *in vacuo*, diluted with H_2O (200 ml), and washed with Et_2O (3 × 300 ml). The aq. phase was acidified with conc. aq. HCl soln. and extracted with Et_2O (2 × 300 ml). The org. layers were dried ($MgSO_4$) and evaporated. Recrystallization from benzene (10 ml) and hexane (120 ml) afforded **23** (3.70 g, 87%). Off white solid. M.p. 106–107°. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.85–1.53 (*m*, 46 H); 3.80–3.94 (*m*, 4 H); 4.81 (*q*, *AB*, *J* = 12.0, 4 H); 6.40 (*s*, 2 H); 6.93–7.21 (*m*, 10 H); 7.30 (*d*, *J* = 9.0, 2 H); 8.01 (*d*, *J* = 9.0, 2 H); 8.81 (*s*, 2 H); 10.90 (br. *s*, 2 H). FAB-MS: 923 (M^+). Anal. calc. for $C_{60}H_{74}O_8$ (923.3): C 78.06, H 8.08, O 13.86; found: C 78.19, H 7.92, O 13.64.

*7,7'-Bis(benzyloxy)-2,2'-bis(dodecyloxy)-*N,N'*-bis(6-methylpyridin-2-yl)-1,1'-binaphthyl-6,6'-dicarboxamide* (**24**). To **23** (1.00 g, 1.1 mmol) in dry benzene (2.75 ml) was added dropwise oxalyl chloride (1.15 ml, 13.0 mmol). Evolution of HCl gas was observed for 10 min, and the mixture was stirred at r.t. for an additional 15 min. Evaporation with heating (50°) afforded the bis(acyl chloride). Dry benzene (4 × 10 ml) was successively added and distilled off to ensure the complete removal of oxalyl chloride. To the crude bis(acyl chloride) in pyridine (6.6 ml) was added 6-methylpyridin-2-amine (0.36 g, 3.3 mmol), and the mixture was stirred at r.t. for 3 h and then at 60–70° for 16 h. The yellow soln. was quenched with ice-cold H_2O (100 ml), and the aq. soln. was decanted from the resulting yellow solid. The solid was washed with 1.0M aq. NaOH (50 ml), dissolved in $CHCl_3$ (50 ml), dried ($MgSO_4$), and evaporated. The orange oil was passed through a plug of SiO_2 (20 g) with hexane/AcOEt 4:1→3:2: **24** (838 mg, 70%). Yellow solid. M.p. 91–92°. IR (KBr): 3344, 1661, 1611, 1450. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.82–1.48 (*m*, 46 H); 2.41 (*s*, 6 H); 3.75–4.10 (*m*, 4 H); 4.85 (*q*, *AB*, *J* = 12.0, 4 H); 6.48 (*s*, 2 H); 6.85 (*d*, *J* = 8.0, 2 H); 7.10–7.24 (*m*, 10 H); 7.27 (*d*, *J* = 9.0, 2 H); 7.59 (*t*, *J* = 8.0, 2 H); 8.01 (*d*, *J* = 9.0, 2 H); 8.24 (*d*, *J* = 8.0, 2 H); 8.86 (*s*, 2 H); 10.45 (*s*, 2 H). FAB-MS: 1103 (MH^+). Anal. calc. for $C_{72}H_{86}N_4O_6$ (1103.5): C 78.37, H 7.86, N 5.08, O 8.70; found: C 78.55, H 8.07, N 5.06, O 8.44.

*2,2'-Bis(dodecyloxy)-7,7'-dihydroxy-*N,N'*-bis(6-methylpyridin-2-yl)-1,1'-binaphthyl-6,6'-dicarboxamide* (**25**). To **24** (100 mg, 0.09 mmol) in THF (4.5 ml) was added $NH_4(HCO_2)$ (215 mg, 3.40 mmol) followed by 10% Pd/C (37 mg, 0.04 mmol), and the mixture was refluxed for 1 h. The cooled soln. was filtered through a plug of *Celite*, the plug washed with hot AcOEt, and the filtrate evaporated: **25** (87.6 mg, 95%). White foam. M.p. 267–268°. IR ($CHCl_3$): 3677, 1661, 1600, 1450. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.56–1.55 (*m*, 46 H); 2.46 (*s*, 6 H); 3.90–3.96 (*m*, 4 H); 6.58 (br. *s*, 2 H); 6.73 (*s*, 2 H); 6.93–6.99 (*m*, 2 H); 7.23 (*d*, *J* = 9.0, 2 H); 7.65 (*t*, *J* = 8.0, 2 H); 7.85 (*d*, *J* = 9.0, 2 H); 8.13 (*m*, 2 H); 8.26 (*s*, 2 H); 11.70 (*s*, 2 H). FAB-MS: 923 (MH^+). Anal. calc. for $C_{58}H_{74}N_4O_6$ (923.3): C 75.46, H 8.08, N 6.07, O 10.40; found: C 75.54, H 8.25, N 5.88, O 10.66.

*2,2'-Bis(dodecyloxy)-7,7'-dimethoxy-*N,N'*-bis(6-methylpyridin-2-yl)-1,1'-binaphthyl-6,6'-dicarboxamide* (**26**). To **25** (46 mg, 0.049 mmol) in DMA (3.5 ml) was added Me_2SO_4 (0.017 ml, 0.180 mmol) followed by K_2CO_3 (29 mg, 0.21 mmol), and the mixture was stirred overnight. Addition of ice-cold H_2O (3.5 ml) precipitated **26** (27.4 mg, 59%). White solid. M.p. 99–100°. IR ($CHCl_3$): 3344, 1661, 1611, 1450. ^{1}H-NMR (500 MHz $CDCl_3$): 0.86–1.56 (*m*, 46 H); 2.47 (*s*, 6 H); 3.71 (*s*, 6 H); 3.96–4.04 (*m*, 4 H); 6.59 (*s*, 2 H); 6.90 (*d*, *J* = 8.0, 2 H); 7.34 (*d*, *J* = 9.0, 2 H); 7.63 (*t*, *J* = 8.0, 2 H); 8.03 (*d*, *J* = 9.0, 2 H); 8.27 (*d*, *J* = 8.0, 2 H); 8.86 (*s*, 2 H); 10.29 (*s*, 2 H). FAB-MS: 951 (MH^+). HR-FAB-MS: 951.6010 (M^+, $C_{60}H_{78}N_4O_6^+$; calc. 950.5921).

(±)-6,6'-Dibromo-2,2'-bis(dodecyloxy)-1,1'-binaphthyl-7,7'-diol (**29**). To a soln. of **22** (5.0 g, 5.0 mmol) in CH_2Cl_2 (64 ml) was added $BF_3 \cdot OEt_2$ (7.0 ml, 57.0 mmol) followed by Me_2S (64 ml), and the mixture was refluxed for 16 h. Solvent and Me_2S were removed by distillation. The remaining orange oil was dissolved in Et_2O (500 ml) and the soln. washed with cold H_2O (5 × 1 l), dried ($MgSO_4$), and evaporated: **29** (3.1 g, 76%). Light-pink oil. IR ($CHCl_3$): 3240, 1614, 1253. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.88–1.46 (*m*, 46 H); 3.87–3.98 (*m*, 4 H); 5.39 (*s*, 2 H); 6.66 (s, 2 H); 7.25 (*d*, *J* = 9.0, 2 H); 7.76 (*d*, *J* = 9.0, 2 H); 8.01 (*s*, 2 H). FAB-MS: 812 (M^+). Anal. calc. for $C_{44}H_{60}Br_2O_4$ (812.8): C 65.02, H 7.44, Br 19.66; found: C 65.24, H 7.34, Br 19.64.

(*R*)-**29** ($[\alpha]_D^{23}$ = −36.22 (*c* = 1.00, $CHCl_3$)) and (*S*)-**29** ($[\alpha]_D^{23}$ = +36.62 (*c* = 1.00, $CHCl_3$)) were prepared in a similar manner.

(±)-6,6'-Dibromo-2,2'-bis(dodecyloxy)-7,7'-dimethoxy-1,1'-binaphthyl (**30**). To a soln. of **29** (2.2 g, 2.7 mmol) in DMA (192 ml) was added Me_2SO_4 (1.0 ml, 10.8 mmol) followed by K_2CO_3 (1.6 g, 11.6 mmol). The mixture was stirred ar r.t. for 16 h, then diluted with H_2O (250 ml) and extracted with CH_2Cl_2 (4 × 250 ml). The combined org. layer was dried ($MgSO_4$) and evaporated and the residue passed through a plug of SiO_2 (100 g), with hexane/AcOEt 9:1: **30** (2.3, g, 100%). Light yellow solid. M.p. 55–56°. IR ($CHCl_3$): 1615, 1495, 1258. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.88–1.44 (*m*, 46 H); 3.55 (*s*, 6 H); 3.86–3.99 (*m*, 4 H); 6.47 (*s*, 2 H); 7.23 (*d*, *J* = 9.0, 2 H); 7.77 (*d*, *J* = 9.0,

2 H); 8.05 (*s*, 2 H). FAB-MS: 840 (M^+). Anal. calc. for $C_{46}H_{64}Br_2O_4$ (840.8): C 65.71, H 7.67, Br 19.01, O 7.61; found: C 65.67, H 7.55, Br 19.04, O 7.70.

(*R*)-**30** ($[\alpha]_D^{23} = -29.65$ (*c* = 0.800, $CHCl_3$)) and (*S*)-**30** ($[\alpha]_D^{23} = +29.77$ (*c* = 0.890, $CHCl_3$)) were prepared in a similar manner.

(±)-22,27-Dibromo-4,5,7,8,10,11,13,14,16,17-decahydrodinaphtho[2,1-q:1′,2′-s][1,4,7,10,13,16]hexaoxacycloicosin (**50**). Pentaethyleneglycol bis(toluene-4-sulfonate) (14.86 g, 27.2 mmol) and **49** [20c] (10.00 g, 22.5 mmol) were each dissolved in separate aliquots of THF (100 ml) and added under N_2 simultaneously *via* syringe pumps over 24 h to a vigorously stirred soln. of NaH (2.68 g, 0.11 mol) in THF (250 ml). The mixture was stirred for 3 d at r.t., quenched with MeOH, and evaporated. The residue was dissolved in CH_2Cl_2, the soln. washed with deionized H_2O and sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated, and the residue chromatographed (400 g SiO_2, AcOEt): **50** (8.60 g, 52%). White solid. M.p. 134–136° ([45]: 133–137°). ^{1}H-NMR (360 MHz, $CDCl_3$): 3.46 (*m*, 16 H); 4.06, 4.19 (*m*, 4 H); 6.95 (*d*, *J* = 9.0, 2 H); 7.27 (*dd*, *J* = 9.0, 1.4, 2 H); 7.49 (*d*, *J* = 9.0, 2 H); 7.86 (*d*, *J* = 9.0, 2 H); 8.01 (*d*, *J* = 9.0, 2 H).

(*R*)-**50** ($[\alpha]_D^{25} = +8.42$ (*c* = 1.01, THF)) and (*S*)-**50** ($[\alpha]_D^{20} = -9.54$ (*c* = 0.597, THF)) were prepared in a similar manner.

Bis(boronic Acid) Formation: General Procedure A. To dry THF (15 ml) at −78° under Ar was added 1.6M BuLi in hexane (3.0 ml, 5.0 mmol). A soln. of the 6,6′-dibromo-1,1′-binaphthyl derivative (1.0 mmol) in dry THF (3 ml) was added dropwise, and the mixture was stirred at −78° for 45 min. Trimethyl borate (27 ml) was added rapidly. The mixture was warmed to r.t., then refluxed for 16 h under Ar, and evaporated. Partitioning between 2M aq. HCl (40 ml) and Et_2O (80 ml), drying ($MgSO_4$), and evaporation produced a quantitative yield of a yellow oil which was a mixture of bis(boronic acid), mono(boronic acid), and material where the Br-atoms had been exchanged by H-atoms. This crude mixture was used directly in the *Suzuki* coupling.

2,2′-Bis(dodecyloxy)-1,1′-binaphthyl-6,6′-bis(boronic Acid) (**33**). From **32** (3.5 g, 4.5 mmol) [20c] using the *General Procedure A*: crude **33** (3.7 g). Yellow oil.

(±)-7,7′-Bis(benzyloxy)-2,2′-bis(dodecyloxy)-1,1′-binaphthyl-6,6′-bis(boronic Acid) (**27**). From **22** (2.0 g, 2.0 mmol), using the *General Procedure A*: crude **27** (2.0 g). Yellow oil.

(*R*)-**27** and (*S*)-**27** were prepared in a similar manner.

(±)-2,2′-Bis(dodecyloxy)-7,7′-dimethoxy-1,1′-binaphthyl-6,6′-bis(boronic Acid) (**31**). From **30** (2.2 g, 2.6 mmol), using the *General Procedure A*: crude **31** (1.9 g). Yellow oil.

(*R*)-**31** and (*S*)-**31** were prepared in a similar manner.

(±)-4,5,7,8,10,11,13,14,16,17-Decahydrodinaphtho[2,1-q:1′,2′-s][1,4,7,10,13,16]hexaoxacycloicosin-22,27-bis(boronic Acid) (**51**). From **50** (2.74 g, 3.74 mmol), using the *General Procedure A*: crude **51** (2.49 g). Yellow oil.

(*R*)-**51** and (*S*)-**51** were prepared in a similar manner.

'Suzuki *Couplings*': *General Procedure B.* To the crude bis(boronic acid) (1.0 mmol) in EtOH (6 ml) and benzene (22 ml) was added the aryl halide (2.0 mmol), a soln. of Na_2CO_3 (218 mg, 2.0 mmol) in H_2O (10 ml), and $[PdCl_2(PPh_3)_2]$ (102 mg, 0.1 mmol). The resulting two-phase mixture was refluxed for 16–20 h. The cooled mixture was diluted with AcOEt (25 ml) and washed with sat. aq. $NaHCO_3$ soln. (2 × 25 ml) and sat. aq. NaCl soln. (2 × 25 ml). The org. phase was dried ($MgSO_4$) and evaporated and the oily residue purified by chromatography. Recrystallization first from MeCN (→yellow crystals), then from AcOEt/hexane produced the desired target compounds, generally as white solids.

(±)-N,N′-{[2,2′-Bis(dodecyloxy)-1,1′-binaphthalene-6,6′-diyl]dipyridine-6,2-diyl}bis[acetamide] (**9**). From **33** (711 mg, 1.0 mmol) and *N*-(6-bromopyridine-2-yl)acetamide [28] (430 mg, 2.0 mmol) using the *General Procedure B.* Chromatography (SiO_2, hexane/AcOEt 4:1→3:2) afforded **9** (650 mg, 73% overall yield from **32**). Brown foam. M.p. 76–78°. IR ($CHCl_3$): 3418, 1691, 1575, 1449. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.87–1.45 (*m*, 46 H); 2.25 (*s*, 6 H); 3.81–4.02 (*m*, 4 H); 7.25 (*d*, *J* = 9.0, 2 H); 7.46 (*d*, *J* = 9.0, 2 H); 7.56 (*dd*, *J* = 7.0, 1.0, 2 H); 7.77 (*m*, 4 H); 7.95 (*s*, 2 H); 8.05 (*d*, *J* = 9.0, 2 H); 8.13 (*d*, *J* = 9.0, 2 H); 8.47 (*d*, *J* = 2.0, 2 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 14.10; 22.67; 24.79; 25.66; 29.14; 29.36; 29.34; 29.50; 29.61; 29.63; 31.90; 69.60; 111.71; 116.04; 116.33; 120.26; 124.47; 126.02; 126.29; 129.10; 129.97; 133.56; 134.53; 139.05; 150.99; 155.32; 155.91. FAB-MS: 892 (MH^+). Anal. calc. for $C_{58}H_{74}N_4O_4$ (891.3): C 78.16, H 8.37, N 6.29; found: C 78.23, H 8.48, N 6.13.

(*R*)-**9** ($[\alpha]_D^{23} = -96.4$ (*c* = 1.01, $CHCl_3$)) and (*S*)-**9** ($[\alpha]_D^{23} = +96.4$ (*c* = 1.00, $CHCl_3$)) were prepared in a similar manner.

(±)-N,N′-{[7,7′-Bis(benzyloxy)-2,2′-bis(dodecyloxy)-1,1′-binaphthalene-6,6′-diyl]dipyridine-6,2-diyl}bis[acetamide] (**10**). From **27** (742 mg, 0.8 mmol) and *N*-(6-bromopyridin-2-yl)acetamide (344 mg, 1.6 mmol) using the *General Procedure B.* Chromatography (SiO_2, hexane/AcOEt 4:1→3:2) afforded **10** (591 mg, 67% overall yield from **22**). The subsequent recrystallizations gave an off-white solid. M.p. 132–133°. IR (KBr): 3350, 1692, 1625. ^{1}H-NMR (360 MHz, $CDCl_3$): 0.88 (*t*, *J* = 7.2, 6 H); 1.00–1.50 (*m*, 40 H); 2.24 (*s*, 6 H); 3.70–3.75 (*m*, 2 H);

3.85–3.95 (*m*, 2 H); 4.69 (*q*, *AB*, *J* = 4.6, 4 H); 6.55 (*s*, 2 H); 6.95–7.05 (*m*, 4 H); 7.10–7.15 (*m*, 6 H); 7.25 (*d*, *J* = 9.0, 2 H); 7.60–7.75 (*m*, 4 H); 7.93 (*d*, *J* = 9.0, 2 H); 8.03 (*s*, 2 H); 8.14 (*d*, *J* = 9.0, 2 H); 8.22 (*s*, 2 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 14.11; 22.68, 24.77; 25.69; 29.20; 29.35; 29.37; 29.54; 29.63; 29.66; 31.91; 69.39; 69.70; 105.60; 111.73; 113.65; 119.10; 121.41; 124.62; 126.99; 127.38; 127.63; 128.21; 129.42; 130.73; 135.39; 136.69; 137.97; 150.79; 154.30; 154.47; 155.53. FAB-MS: 1104 (MH$^+$). Anal. calc. for $C_{72}H_{86}N_4O_6 \cdot H_2O$ (1121.5): C 77.11, H 7.91, N 5.00; found: C 76.90, H 7.78, N 4.97.

(*R*)-**10** ($[\alpha]_D^{23} = -100.98$ (*c* = 0.0551, $CHCl_3$)) and (*S*)-**10** ($[\alpha]_D^{23} = +100.29$ (*c* = 0.0558, $CHCl_3$)) were prepared in a similar manner.

*(±)-*N,N′-*{[2,2′-Bis(dodecyloxy)-7,7′-dimethoxy-1,1′-binaphthalene-6,6′-diyl]dipyridine-6,2-diyl}bis[acetamide]* (**11**). From **31** (618 mg, 0.8 mmol) and *N*-(6-bromopyridin-2-yl)acetamide (344 mg, 1.6 mmol) using the *General Procedure B*. Chromatography (SiO_2, hexane/AcOEt 4:1→3:2) afforded **11** (396 mg, 52% overall yield from **30**). The subsequent recrystallizations gave an off-white solid. M.p. 176–177°. IR ($CHCl_3$): 3417, 1694, 1625, 1573, 1449. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.86 (*t*, *J* = 7.2, 6 H); 0.98–1.44 (*m*, 40 H); 2.21 (*s*, 6 H); 3.47 (*s*, 6 H); 3.8–4.0 (*m*, 4 H); 6.56 (*s*, 2 H); 7.27 (*d*, *J* = 9.0, 2 H); 7.53 (*dd*, *J* = 8.0, 1.0, 2 H); 7.70 (*t*, *J* = 8.0, 2 H); 7.89 (*d*, *J* = 9.0, 2 H); 7.95 (*s*, 2 H); 8.10 (*d*, *J* = 8.0, 2 H); 8.13 (*s*, 2 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 14.09; 22.67; 24.75; 25.74; 29.21; 29.34; 29.41; 29.51; 29.53; 29.62; 29.63; 31.09; 55.20; 69.41; 103.93; 113.34; 121.23; 124.57; 129.55; 130.67; 138.03; 150.76; 151.91; 154.52; 155.50. FAB-MS: 952 (MH$^+$). Anal. calc. for $C_{60}H_{78}N_4O_6$ (951.3): C 75.76, H 8.26, N 5.89; found: C 75.76, H 8.07, N 5.73.

(*R*)-**11** ($[\alpha]_D^{23} = -74.53$ (*c* = 0.0475, $CHCl_3$)) and (*S*)-**11** ($[\alpha]_D^{23} = +74.10$ (*c* = 0.0478, $CHCl_3$)) were prepared in a similar manner.

N,N′-*{[2,2′-Bis(dodecyloxy)-7,7′-dihydroxy-1,1′-binaphthalene-6,6′-diyl]dipyridine-6,2-diyl}bis[acetamide]* (**28**). To **10** (150 mg, 0.13 mmol) in THF (6.8 ml) was added $NH_4(HCO_2)$ (320 mg, 5.07 mmol) followed by 10% Pd/C (55 mg, 0.06 mmol), and the mixture was refluxed for 1 h. The cooled soln. was filtered through a plug of *Celite*, the plug washed with hot AcOEt, and the filtrate evaporated: **28** (120.0 mg, 100%). White solid. M.p. 267–268°. IR ($CHCl_3$): 3677, 3289, 1689, 1600, 1572. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 1.21 (*t*, *J* = 7.0, 6 H); 1.33–1.77 (*m*, 40 H); 3.60 (*s*, 6 H); 4.27–4.41 (*m*, 4 H); 6.82 (*s*, 2 H); 7.62 (*d*, *J* = 9.0, 2 H); 8.20–8.23 (*m*, 4 H); 8.29 (*d*, *J* = 9.0, 2 H); 8.35–8.37 (*m*, 2 H); 8.79 (*s*, 2 H); 10.98 (*s*, 2 H); 12.94 (*s*, 2 H). FAB-MS: 923 (MH$^+$). Anal. calc. for $C_{58}H_{74}N_4O_6$ (923.3): C 75.46, H 8.08, N 6.07, O 10.40; found: C 75.36, H 8.15, N 5.90, O 10.37.

N-*(6-Bromopyridin-2-yl)*-N′-*butylurea* (**34**). To a soln. of 6-bromopyridin-2-amine [28] (2.0 g, 12.0 mmol) in warm *p*-xylene (6 ml), butyl isocyanate (1.3 ml, 12.0 mmol) was added. The mixture was heated to 80° for 2 h. Evaporation, purification by plug filtration (SiO_2, AcOEt/hexane 4:1), and recrystallization from pentane produced **34** (2.0 g, 55%). Yellow needles. M.p. 74–76°. IR ($CHCl_3$): 3206, 1672, 1583. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.99 (*m*, 3 H); 1.49–1.63 (*m*, 4 H); 3.24–3.46 (*m*, 2 H); 6.74 (*d*, *J* = 8.0, 1 H); 7.03 (*d*, *J* = 8.0, 1 H); 7.43 (*t*, *J* = 8.0, 1 H); 8.05 (br. *s*, 1 H); 8.78 (br. *s*, 1 H). ^{13}C-NMR (500 MHz, $CDCl_3$): 13.76; 20.13; 31.72; 39.65; 110.50; 120.05; 137.79; 140.07. FAB-MS: 272 (M^+). Anal. calc. for $C_{10}H_{14}BrN_3O$ (272.2): C 44.13, H 5.19, N 15.44; found: C 44.34, H 5.26, N 15.41.

N,N′-*{[2,2′-Bis(dodecyloxy)-1,1′-binaphthalene-6,6′-diyl]dipyridine-6,2-diyl}bis[*N′,N‴-*butylurea]* (**36**). From **33** (711 mg, 1.0 mmol) and **34** (430 mg, 2.0 mmol) using the *General Procedure B*. Chromatography (SiO_2, hexane/AcOEt 3:2 → AcOEt) afforded **36** (101 mg, 10% overall yield from **32**). The subsequent recrystallizations gave a white solid. M.p. 159–160°. IR ($CHCl_3$): 3233, 1672, 1589. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.81–1.66 (*m*, 60 H); 3.37–3.41 (*m*, 4 H); 3.91–4.02 (*m*, 4 H); 6.53 (*d*, *J* = 8.0, 2 H); 7.03 (br. *s*, 2 H); 7.24 (*m*, 2 H); 7.34 (*d*, *J* = 8.0, 2 H); 7.46 (*d*, *J* = 9.0, 2 H); 7.61 (*t*, *J* = 8.0, 2 H); 7.67 (*dd*, *J* = 9.0, 2.0, 2 H); 8.00 (*d*, *J* = 9.0, 2 H); 8.35 (*d*, *J* = 2.0, 2 H); 9.62 (br. *s*, 2 H). FAB-MS: 1005 (MH$^+$). Anal. calc. for $C_{64}H_{88}N_6O_4 \cdot 2\ H_2O$ (1041.5): C 73.81, H 8.90, N 8.07; found: C 73.71, H 8.71, N 7.62.

N,N″-*{[7,7′-Bis(benzyloxy)-2,2′-bis(dodecyloxy)-1,1′-binaphthalene-6,6′-diyl]dipyridine-6,2-diyl}bis-[N′,N‴-butylurea]* (**37**). From **27** (1.39 g, 1.5 mmol) and **34** (0.65 g, 3 mmol) using the *General Procedure B*. Chromatography (SiO_2, hexane/AcOEt 7:3→AcOEt) afforded **37** (0.51 g, 28% overall yield from **22**). The subsequent recrystallizations gave a light orange solid. M.p. 146–148°. IR ($CHCl_3$): 3233, 1672, 1583. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.84–1.66 (*m*, 60 H); 3.37–3.42 (*m*, 4 H); 3.79–3.97 (*m*, 4 H); 4.73 (*q*, *AB*, *J* = 12.0, 4 H); 6.58 (*d*, *J* = 8.0, 2 H); 6.60 (*s*, 2 H); 6.94 (*s*, 2 H); 6.97–7.12 (*m*, 10 H); 7.27 (*m*, 2 H); 7.56 (*dd*, *J* = 8.0, 1.0, 2 H); 7.61 (*t*, *J* = 8.0, 2 H); 7.92 (*d*, *J* = 9.0, 2 H); 8.21 (*s*, 2 H); 9.81 (br. *s*, 2 H). FAB-MS: 1218 (MH$^+$). Anal. calc. for $C_{78}H_{100}N_6O_6$ (1217.7): C 76.94, H 8.28, N 6.90, O 7.64; found: C 77.11, H 8.30, N 6.80, O 7.64.

N,N″-*{[2,2′-Bis(dodecyloxy)-7,7′-dimethoxy-1,1′-binaphthalene-6,6′-diyl]dipyridine-6,2-diyl}bis[*N′,N‴-*butylurea]* (**38**). From **31** (618 mg, 0.8 mmol) and **34** (344 mg, 1.6 mmol) using the *General Procedure B*. Chromatography (SiO_2, hexane/AcOEt 3:2→AcOEt) afforded **38** (128 mg, 15% overall yield from **30**). The subsequent recrystallizations gave a white solid. M.p. 99–100°. IR ($CHCl_3$): 3223, 1676, 1590. ^{1}H-NMR (500 MHz,

$CDCl_3$): 0.79 (*t*, *J* = 7.3, 6 H); 0.85 (*t*, *J* = 7.0, 6 H); 1.01–1.60 (*m*, 48 H); 3.35–3.39 (*m*, 4 H); 3.51 (*s*, 6 H); 3.92–4.01 (*m*, 4 H); 6.51 (*d*, *J* = 8.0, 2 H); 6.62 (*s*, 2 H); 6.75 (*s*, 2 H); 7.29 (*d*, *J* = 9.0, 2 H); 7.40 (*d*, *J* = 8.0, 2 H); 7.58 (*t*, *J* = 8.0, 2 H); 7.88 (*d*, *J* = 9.0, 2 H); 8.11 (*s*, 2 H); 9.73 (br. *s*, 2 H). FAB-MS: 1066 (MH$^+$). Anal. calc. for $C_{66}H_{92}N_6O_6$ (1065.5): C 74.40, H 8.70, N 7.89; found: C 74.39, H 8.81, N 7.66.

N-(6-Bromopyridin-2-yl)-N′-phenylurea (**35**). To a soln. of 6-bromopyridin-2-amine (1.0 g, 6.0 mmol) in warm *p*-xylene (3 ml), phenyl isocyanate (0.630 ml, 6.0 mmol) was added, and the mixture was stirred at r.t. for 1 h. The formed solid was collected by filtration and recrystallized from EtOH (125 ml): **35** (1.1 g, 63%). White material. M.p. 189–190°. IR ($CHCl_3$): 3204, 1690, 1594, 1560. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.78 (*d*, *J* = 8.0, 1 H); 7.11–7.15 (*m*, 3 H); 7.37 (*m*, 2 H); 7.52 (*t*, *J* = 8.0, 1 H); 7.62 (*dd*, *J* = 8.0, 1.0, 1 H); 7.74 (*s*, 1 H); 11.15 (*s*, 1 H). FAB-MS: 293 (MH$^+$). Anal. calc. for $C_{12}H_{10}BrN_3O$ (292.1): C 49.34, H 3.45, N 14.38; found: C 49.42, H 3.63, N 14.09.

N,N″-{*[2,2′-Bis(dodecyloxy)-1,1′-binaphthalene-6,6′-diyl]dipyridine-6,2-diyl*}*bis[* N′,N‴-*phenylurea]* (**39**). From **33** (711 mg, 1.0 mmol) and **35** (430 mg, 2.0 mmol) using the *General Procedure B*. Chromatography (SiO_2, hexane/AcOEt 7:3→1:1) afforded **39** (178 mg, 17% overall yield from **32**). M.p. 168–170°. IR (KBr): 3433, 1689, 1622, 1589. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.87 (*t*, *J* = 7.0, 6 H); 0.99–1.49 (*m*, 40 H); 3.98–4.09 (*m*, 4 H); 6.65 (br. *s*, 2 H); 7.00–7.06 (*m*, 4 H); 7.27 (*m*, 4 H); 7.35 (*d*, *J* = 8.0, 2 H); 7.44 (*d*, *J* = 8.0, 2 H); 7.52 (*d*, *J* = 9.0, 2 H); 7.66 (*d*, *J* = 8.0, 4 H); 7.71 (*m*, 2 H); 7.77 (*d*, *J* = 8.0, 2 H); 8.08 (*d*, *J* = 9.0, 2 H); 8.51 (*d*, *J* = 2.0, 2 H); 12.32 (br. *s*, 2 H). FAB-MS: 1046 (MH$^+$). Anal. calc. for $C_{68}H_{80}N_6O_4$ (1045.4): C 78.13, H 7.71, N 8.04; found: C 77.85, H 7.78, N 7.76.

N,N″-{*[7,7′-Bis(benzyloxy)-2,2′-bis(dodecyloxy)-1,1′-binaphthalene-6,6′-diyl]dipyridine-6,2-diyl*}*bis-[* N′,N‴-*phenylurea]* (**40**). From **27** (927 mg, 1.0 mmol) and **35** (430 mg, 2.0 mmol) using the *General Procedure B*. Chromatography (SiO_2, hexane/AcOEt 7:3→1:1) afforded **40** (402 mg, 32% overall yield from **22**). The subsequent recrystallizations gave a white solid. M.p. 105–108°. IR (KBr): 3434, 1689, 1623, 1585. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.80–1.50 (*m*, 46 H); 3.75–4.00 (*m*, 4 H); 4.71 (*s*, 4 H); 6.63 (*s*, 2 H); 6.64 (*d*, *J* = 8.0, 2 H); 6.91–7.19 (*m*, 14 H); 7.19 (*s*, 2 H); 7.23–7.30 (*m*, 4 H); 7.60–7.67 (*m*, 8 H); 7.96 (*d*, *J* = 9.0, 2 H); 8.34 (*s*, 2 H); 12.55 (br. *s*, 2 H). FAB-MS: 1258 (MH$^+$). Anal. calc. for $C_{82}H_{92}N_6O_6$ (1257.7): C 78.31, H 7.37, N 6.68; found: C 78.04, H 7.33, N 6.66.

N,N″-{*[2,2′-Bis(dodecyloxy)-7,7′-dimethoxy-1,1′-binaphthalene-6,6′-diyl]dipyridine-6,2-diyl*}*bis[* N′,N‴-*phenylurea]* (**41**). From **31** (464 mg, 0.6 mmol) and **35** (258 mg, 1.2 mmol) using the *General Procedure B*. Chromatography (SiO_2, hexane/AcOEt 4:1→3:2) afforded **41** (93 mg, 14% overall yield from **30**). The subsequent recrystallizations gave an off-white solid. M.p. 184–185°. IR ($CHCl_3$): 3430, 1689, 1620, 1583. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.87 (*t*, *J* = 7.0, 6 H); 1.03–1.54 (*m*, 40 H); 3.52 (*s*, 6 H); 3.98–4.10 (*m*, 4 H); 6.65 (*d*, *J* = 8.0, 2 H); 6.71 (*s*, 2 H); 7.01–7.12 (*m*, 4 H); 7.12 (*s*, 2 H); 7.26 (*m*, 2 H); 7.36 (*d*, *J* = 8.0, 2 H); 7.54 (*dd*, *J* = 8.0, 1.0, 2 H); 7.60 (*dd*, *J* = 9.0, 1.0, 4 H); 7.69 (*t*, *J* = 8.0, 2 H); 7.97 (*d*, *J* = 9.0, 2 H); 8.29 (*s*, 2 H); 12.49 (br. *s*, 2 H). FAB-MS: 1106 (MH$^+$). Anal. calc. for $C_{70}H_{84}N_6O_6$ (1105.5): C 76.06, H 7.66, N 7.60; found: C 76.08, H 7.90, N 7.41.

N,N′-{*[2,2′-Bis(dodecyloxy)-7,7′-dimethoxy-1,1′-binaphthalene-6,6′-diyl]di(1,8-naphthyridine-2,7-diyl)*}*bis-[acetamide]* (**42**). From **31** (387 mg, 0.5 mmol) and *N*-(7-chloro-1,8-naphthyridin-2-yl)acetamide [20c] [31] (221 mg, 1.0 mmol) using the *General Procedure B*. Chromatography (SiO_2, AcOEt/hexane 3:2→4:1) afforded **42** (105 mg, 20% overall yield from **30**). The subsequent recrystallizations gave a yellow solid. M.p. 145–146°. IR ($CHCl_3$): 3156, 1670, 1467. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.86 (*t*, *J* = 7.0, 6 H); 1.05–1.53 (*m*, 40 H); 2.30 (*s*, 6 H); 3.56 (*s*, 6 H); 3.96–4.04 (*m*, 4 H); 6.65 (*s*, 2 H); 7.31 (*d*, *J* = 9.0, 2 H); 8.00 (*d*, *J* = 9.0, 2 H); 8.10 (*d*, *J* = 1.2, 4 H); 8.21 (*d*, *J* = 9.0, 2 H); 8.34 (*s*, 2 H); 8.50 (*d*, *J* = 9.0, 2 H); 8.67 (*s*, 2 H). FAB-MS: 1053 (MH$^+$). Anal. calc. for $C_{66}H_{80}N_6O_6$ (1053.4): C 75.25, H 7.65, N 7.98; found: C 75.54, H 7.53, N 7.85.

(±)-N,N′-{*(4,5,7,8,10,11,13,14,16,17-Decahydrodinaphtho[2,1-q:1′,2′-s][1,4,7,10,13,16]hexaoxacyclo-icosin-22,27-diyl)dipyridine-6,2-diyl*}*bis[acetamide]* (**48**). From **51** (3.94 g, 5.92 mmol) and *N*-(6-bromopyridin-2-yl)acetamide (2.45 g, 11.30 mmol) using the *General Procedure B*. Chromatography (SiO_2, AcOEt) afforded **48** (1.21 g, 23% overall yield from **50**). Subsequent recrystallization from CH_2Cl_2/Et_2O gave an off-white solid. M.p. 149–152°. IR (KBr): 3365, 1700, 1540, 1100. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.23 (*s*, 6 H); 3.55 (*m*, 16 H); 4.08, 4.22 (2*m*, 4 H); 7.23 (*d*, *J* = 9.0, 2 H); 7.52 (*d*, *J* = 9.0, 2 H); 7.60 (*d*, *J* = 8.0, 2 H); 7.70 (*t*, *J* = 8.0, 2 H); 7.77 (*dd*, *J* = 9.0, 2.0, 2 H); 7.99 (*s*, 2 H); 8.05 (*d*, *J* = 9.0, 2 H); 8.12 (*d*, *J* = 8.0, 2 H); 8.46 (*d*, *J* = 2.0, 2 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 24.76; 69.74, 70.63; 70.82; 111.87; 116.40; 120.15; 124.71; 126.01; 126.34; 129.30; 130.16; 133.87; 134.37; 139.14; 151.06; 155.23; 155.78; 168.76. HR-FAB-MS: 757.3237 (MH$^+$, $C_{44}H_{45}N_4O_8^+$; calc. 757.3237). Anal. calc. for $C_{44}H_{44}N_4O_8 \cdot 2\,H_2O$ (792.9): C 66.65, H 6.10, N 7.07; found: C 66.88, H 5.80, N 6.79.

(*R*)-**48** ($[\alpha]_D^{25} = -134.5$ (*c* = 0.505, THF)) and (*S*)-**48** ($[\alpha]_D^{25} = +134.1$ (*c* = 0.507, THF)) were prepared in a similar manner.

This work was supported by the 'Chiral-2- Program' of the *Swiss National Science Foundation*, by *F. Hoffmann-La Roche AG*, and, in its initial stages, by the *U.S. National Institutes of Health (NIH)*. We are especially grateful to Ms. *Brigitte Brandenberg* for NOE measurements and to Dr. *Bernhard Jaun* for assistance with variable-temperature ^{1}H-NMR experiments.

REFERENCES

[1] 'Chemical Recognition in Biology', 'Molecular Biology, Biochemistry and Biophysics', Eds. F. Chapeville and A. L. Haenni, Springer, Berlin, 1980, Vol. 32.

[2] a) W. Saenger, 'Principles of Nucleic Acid Structure', Ed. C.R. Cantor, Springer-Verlag, Berlin, 1984; b) 'Proteins: Structure, Dynamics and Design', Eds. V. Renugopalakrishnan, P.R. Carey, I.C.P. Smith, S.-G. Huang, and A.C. Storer, Escom Science Publishers, Leiden, 1991; c) E. Katchalski-Katzir, 'Some General Considerations on the Recognition by and of Proteins', in 'Affinity Chromatography and Biological Recognition', Eds. I.M. Chaiken, M. Wilchek, and I. Parikh, Academic Press, New York, 1983, pp. 7–26; d) J. Kraut, *Science (Washington, D.C.)* **1988,** *242,* 533; e) 'Structure and Activity of Enzymes', *Faraday Discussions Chem. Soc.* **1992,** *93,* 1; f) A. Fersht, 'Enzyme Structure and Mechanism', W.H. Freeman and Company, New York, 1985; g) A.G. Amit, R.A. Mariuzza, S.E.V. Phillips, R.J. Poliak, *Science (Washington, D.C.)* **1988,** *233,* 747; h) 'Peptides: Chemistry, Structure, Biology', Eds. R.S. Hodges and J.A. Smith, Escom Science Publishers, Leiden, 1994; i) 'Structural Aspects of Recognition and Assembly in Biological Macromolecules', Ed. M. Balaban, Balaban International Science Service, 1981, Vol. 1.

[3] a) D.J. Cram, J.M. Cram, 'Container Molecules and Their Guests', 'Monographs in Supramolecular Chemistry', Ed. J.F. Stoddart, The Royal Society of Chemistry, Cambridge, 1994; b) J. Rebek, Jr., *Angew. Chem.* **1990,** *102,* 261; *ibid. Int. Ed.* **1990,** *29,* 245; c) B. Dietrich, P. Viout, J.-M. Lehn, 'Macrocyclic Chemistry: Aspects of Organic and Inorganic Supramolecular Chemistry', VCH, Weinheim, 1993; d) F. Diederich, 'Cyclophanes', 'Monographs in Supramolecular Chemistry', Ed. J.F. Stoddart, The Royal Society of Chemistry, Cambridge, 1991; e) 'Tetrahedron Symposium in Print on Molecular Recognition', Ed. A.D. Hamilton, *Tetrahedron* **1995,** *51,* 343; f) A. Eschenmoser, *Angew. Chem.* **1994,** *106,* 2455; *ibid. Int. Ed.* **1994,** *33,* 2363; g) H.-J. Schneider, *Angew. Chem.* **1991,** *103,* 1419; *ibid. Int. Ed.* **1991,** *30,* 1417; h) W.H. Pirkle, T.C. Pochapsky, *Chem. Rev.* **1989,** *89,* 347; i) T.H. Webb, C.S. Wilcox, *Chem. Soc. Rev.* **1993,** *22,* 383; j) P.C. Kearney, L.S. Mizoue, R.A. Kumpf, J.E. Forman, A. McCurdy, D.A. Dougherty, *J. Am. Chem. Soc.* **1993,** *115,* 9907; k) S.C. Zimmermann, *Topics Curr. Chem.* **1993,** *165,* 71.

[4] C. Andreu, A. Galán, K. Kobiro, J. de Mendoza, T.K. Park, J. Rebek, Jr., A. Salmerón, N. Usman, *J. Am. Chem. Soc.* **1994,** *116,* 5501; B.F. Grotjohn, A.W. Czarnik, *Tetrahedron Lett.* **1989,** *30,* 2325; J.F.G.A. Jansen, E.M.M. de Brabander van den Berg, E.W. Meijer, *Science (Washington, D.C.)* **1994,** *266,* 1226.

[5] B.R. Peterson, F. Diederich, *Angew. Chem.* **1994,** *106,* 1688; *ibid. Int. Ed.* **1994,** *33,* 1625; F. Djedaini, B. Perly, *J. Pharm. Sci.* **1991,** *80,* 1157; S. Kubik, G. Wulff, *Macromol. Chem. Phys.* **1994,** *195,* 1719.

[6] S.-K. Chang, A.D. Hamilton, *J. Am. Chem. Soc.* **1988,** *110,* 1318.

[7] K.R.A.S. Sandanayake, I.O. Sutherland, *Tetrahedron Lett.* **1993,** *34,* 3165; R.C. Helgeson, B.J. Selle, I. Goldberg, C.B. Knobler, D.J. Cram, *J. Am. Chem. Soc.* **1993,** *115,* 11506; D.J. Cram, *Nature (London)* **1992,** *356,* 29; D. Ammann, W.E. Morf, P. Anker, P.C. Meier, E. Pretsch, W. Simon, *Ion-Selective Electrode Rev.* **1983,** *5,* 3; A.W. Czarnik, *Acc. Chem. Res.* **1994,** *27,* 302; 'Host-Guest Molecular Interactions: From Chemistry to Biology', '*Ciba* Foundation Symposium', Vol. 158, Eds. D.J. Chadwick and K. Widdows, Wiley-Interscience, Chichester, 1991.

[8] U. Obst, V. Gramlich, F. Diederich, L. Weber, D. Banner, *Angew. Chem.*, in press; P.Y.S. Lam, P.K. Jadhav, C.J. Eyermann, C.N. Hodge, Y. Ru, L.T. Bacheler, J.L. Meek, M.J. Otto, M.M. Rayner, Y.N. Wong, C.-H. Chang, P.C. Weber, D.A. Jackson, T.R. Sharpe, S. Erickson-Viitanen, *Science (Washington, D.C.)* **1994,** *263,* 380; R. Hirschmann, K.C. Nicolaou, S. Pietranico, E.M. Leahy, J. Salvino, B. Arison, M.A. Cichy, P.G. Spoors, W.C. Shakespeare, P.A. Sprengeler, P. Hamley, A.B. Smith III, T. Reisine, K. Raynor, L. Maechler, C. Donaldson, W. Vale, R.M. Freidinger, M.R. Cascieri, C.D. Strader, *J. Am. Chem. Soc.* **1993,** *115,* 12550

[9] G.W. Gokel, 'Crown Ethers and Cryptands', 'Monographs in Supramolecular Chemistry', Ed. J.F. Stoddart, The Royal Society of Chemistry, Cambridge, 1991; D.J. Cram, J.M. Cram, *Acc. Chem. Res.* **1978,** *11,* 8.

[10] J. Rebek, Jr., B. Askew, D. Nemeth, K. Parris, *J. Am. Chem. Soc.* **1987,** *109,* 2432; A. Galán, D. Andreu, A.M. Echavarren, P. Prados, J. De Mendoza, *ibid.* **1992,** *114,* 1511; L.K. Mohler, A.W. Czarnik, *ibid.* **1993,** *115,* 7037; M.T. Reetz, J. Huff, J. Rudolph, K. Töllner, A. Deege, R. Goddard, *ibid.* **1994,** *116,* 11588;

K. Maruyama, H. Tsukube, T. Araki, *ibid.* **1982,** *104,* 5502; Y. Aoyama, M. Asakawa, A. Yamagishi, H. Toi, H. Ogoshi, *ibid.* **1990,** *112,* 3145.

[11] a) R. Liu, P.E.J. Sanderson, W.C. Still, *J. Org. Chem.* **1990,** *55,* 5184; b) S.D. Erickson, J.A. Simon, W.C. Still, *ibid.* **1993,** *58,* 1305; c) J.-I. Hong, S.K. Namgoong, A. Bernardi, W.C. Still, *J. Am. Chem. Soc.* **1991,** *113,* 5111; d) W.C. Still, J.D. Kilburn, P.E.J. Sanderson, R. Liu, M.R. Wiley, F.P. Hollinger, R.C. Hawley, M. Nakajima, A. Bernardi, J.-I. Hong, S.K. Namgoong, *Isr. J. Chem.* **1992,** *32,* 41; e) R. Liu, W.C. Still, *Tetrahedron Lett.* **1993,** *34,* 2573; f) S.S. Yoon, W.C. Still, *ibid.* **1994,** *35,* 2117; g) H.P. Nestler, P.A. Barlett, W.C. Still, *J. Org. Chem.* **1994,** *59,* 4723; h) R. Boyce, G. Li, H.P. Nestler, T. Suenaga, W.C. Still, *J. Am. Chem. Soc.* **1994,** *116,* 7955; i) S.S. Yoon, W.C. Still, *ibid.* **1993,** *115,* 823.

[12] P.B. Savage, S.H. Gellman, *J. Am. Chem. Soc.* **1993,** *115,* 10448; E.A. Gallo, S.H. Gellman, *ibid.* **1993,** *115,* 9774.

[13] 'Proteins – Structural and Molecular Properties', Ed. T.E. Creighton, W.H. Freeman and Company, New York, 1993.

[14] 'Chemistry and Biochemistry of Amino Acids', Ed. G.C. Barrett, Chapman and Hall, London, 1985.

[15] 'Amino Acids, Chemistry, Biology, and Medicine', Eds. G. Lubec and G.A. Rosenthal, Escom Science Publishers, Leiden, 1990.

[16] 'Excitatory Amino Acid Receptors: Design of Agonists and Antagonists', Eds. P. Krogsgaard-Larsen and J.J. Hansen, Ellis Horwood, New York, 1992; 'Frontiers in Excitatory Amino Acid Research', Eds. E.A. Cavalheiro, J. Lehmann and L. Turski, Alan R. Liss, Inc., New York, 1988.

[17] 'The NMDA Receptor', Eds. J.C. Watkins and G.L. Collingridge, Oxford University Press, Oxford, 1989.

[18] a) F. Garcia-Tellado, J. Albert, A.D. Hamilton, *J. Chem. Soc., Chem. Commun.* **1991,** 1761; b) F. Garcia-Tellado, S. Goswami, S.-K. Chang, S.J. Geib, A.D. Hamilton, *J. Am. Chem. Soc.* **1990,** *112,* 7393; c) E. Fan, S.A. Van Arman, S. Kincaid, A.D. Hamilton, *ibid.* **1993,** *115,* 369; d) E. Fan, C. Vincent, S.J. Geib, A.D. Hamilton, *Chem. Mater.* **1994,** *6,* 1113; e) M.S. Goodman, J. Weiss, A.D. Hamilton, *Tetrahedron Lett.* **1994,** *35,* 8943.

[19] J. Rebek, Jr., D. Nemeth, P, Ballester, F.-T. Lin, *J. Am. Chem. Soc.* **1987,** *109,* 3474; Y. Tanaka, Y. Kato, Y. Aoyama, *ibid.* **1990** *112,* 2807; A. Bencini, A. Bianchi, M.I. Burguete, E. García-España, S.V. Luis, J.A. Ramirez, *ibid.* **1992,** *114,* 1919; R. Breslow, R. Rajagopalan, J. Schwarz, *ibid.* **1981,** *103,* 2905; E. Kimura, A. Sakonaka, T. Yatsunami, M. Kodama, *ibid.* **1981,** *103,* 3041; M.W. Hosseini, J.M. Lehn, *ibid.* **1982,** *104,* 3525; P. Schiessl, F.P. Schmidtchen, *Tetrahedron Lett.* **1993,** *34,* 2449; S.S. Flack, J.-L. Chaumette, J.D. Kilburn, G.J. Langley, M. Webster, *J. Chem. Soc., Chem. Commun.* **1993,** 399; L. Szente, J. Szejtli, J. Szemán, L. Kató, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1993,** *16,* 339; T. Mizutani, T. Ema, T. Yoshida, Y. Kuroda, H. Ogoshi, *Inorg. Chem.* **1993,** *32,* 2072; V. Král, A. Andrievsky, J.L. Sessler, *J. Am. Chem. Soc.* **1995,** *117,* 2953; E. Kimura, T. Ikeda, M. Shionoya, M. Shiro, *Angew. Chem.* **1995,** *107,* 711; *ibid. Int. Ed.* **1995,** *34,* 663.

[20] a) V. Alcazar, J.R. Morán, F. Diederich, *Isr. J. Chem.* **1992,** *32,* 69; b) V. Alcazar, F. Diederich, *Angew. Chem.* **1992,** *104,* 1503; *ibid. Int. Ed.* **1992,** *31,* 1521; c) J. Cuntze, L. Owens, V. Alcazar, P. Seiler, F. Diederich, *Helv. Chim. Acta* **1995,** *78,* 367; d) L. Owens, C. Thilgen, F. Diederich, C.B. Knobler, *ibid.* **1993,** *76,* 2757.

[21] K. Deshayes, R.D. Broene, I. Chao, C.B. Knobler, F. Diederich, *J. Org. Chem.* **1991,** *56,* 6787.

[22] Associate V. 1.6, *Blake Peterson,* Ph. D. Dissertation, University of California at Los Angeles, 1994.

[23] W.C. Still, 'MacroModel v. 4.0', Columbia University, New York; F. Mohamadi, N.G.J. Richards, W.C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W.C. Still, *J. Comput. Chem.* **1990,** *11,* 440; W.C. Still, 'BatchMin v. 4.0', Columbia University, New York, 1993.

[24] C.F. Koelsch, in 'Organic Synthesis', Ed. E.C. Horning, John Wiley, New York, 1965, Coll. Vol. 3, p. 132.

[25] M. Hovorka, J. Günterová, J. Závada, *Tetrahedron Lett.* **1990,** *31,* 413.

[26] P.P. Castro, T.M. Georgiadis, F. Diederich, *J. Org. Chem.* **1989,** *54,* 5835; J. Reeder, P.P. Castro, C.B. Knobler, E. Martinborough, L. Owens, F. Diederich, *ibid.* **1994,** *59,* 3151.

[27] L.K. Truesdale, *Org. Synth.* **1988,** *67,* 13.

[28] F. Johnson, J.P. Panella, A.A. Carlson, D.H. Hunneman, *J. Org. Chem.* **1962,** *27,* 2473.

[29] K. Fuji, K. Ichikawa, M. Node, E. Fujita, *J. Org. Chem.* **1979,** *44,* 1661.

[30] H. Ogura, S. Mineo, K. Nakagawa, *Chem. Pharm. Bull.* **1981,** *29,* 1518.

[31] G.R. Newkome, S.J. Garbis, V.K. Majestic, F.R. Fronczek, G. Chiari, *J. Org. Chem.* **1981,** *46,* 833.

[32] a) G.A. Jeffrey, W. Saenger, 'Hydrogen Bonding in Biological Structures', Springer, Berlin, 1991, pp. 147–165; b) *ibid.* pp. 15–24.

[33] W.L. Jorgensen, *Chemtracts: Org. Chem.* **1991,** 91; W.L. Jorgensen, J. Pranata, *J. Am. Chem. Soc.* **1990,** *112,* 2008.

[34] T.J. Murray, S.C. Zimmermann, *J. Am. Chem. Soc.* **1992,** *114,* 4010; S.C. Zimmerman, T.J. Murray, *Tetrahedron Lett.* **1994,** *35,* 4077.

[35] W.C. Still, A. Tempczyk, R.C.Hawley, T. Hendrickson, *J. Am. Chem. Soc.* **1990,** *112,* 6127.

[36] A.J.Boulton, A. McKillop, in 'Comprehensive Heterocyclic Chemistry', Eds. A.J. Boulton and A. McKillop, Pergamon, Oxford, 1984, Vol. 2, p. 34; P.A. Lowe, *ibid.*, Vol. 2, p. 587.

[37] D.J. Cram, R.C. Helgeson, S.C. Peacock, L.J. Kaplan, L.A. Domeier, P. Moreau, K. Koga, J.M. Mayer, Y. Chao, M.G. Siegel, D.H. Hoffman, G.D.Y. Sogah, *J. Org. Chem.* **1978,** *43,* 1930; J. Jacques, C. Fouquey, *Org. Synth.* **1988,** *67,* 1.

[38] F. Toda, K. Tanaka, T.C.W. Mac, *Chem. Lett.* **1984,** 2085; J. Jacques, C. Fouquey, *Tetrahedron Lett.* **1971,** 4617; F. Toda, K. Tanaka, *J. Org. Chem.* **1988,** *53,* 3607; F. Toda, K. Tanaka, *ibid.* **1994,** *59,* 5748; T.D. Nelson, A.I. Meyers, *ibid.* **1994,** *59,* 2655; J.-M. Brunel, G. Buono, *ibid.* **1993,** *58,* 7313; K. Tanaka, T. Okada, F. Toda, *Angew. Chem.* **1993,** *105,* 1266; *ibid. Int. Ed.* **1993,** *32,* 1147; M. Smrcina, M. Lorenc, V. Hanus, P. Sedmera, P. Kocovsky, *J. Org. Chem.* **1992,** *57,* 1917; J. Brussee, J.L.G. Groenendijk, J.M. Koppele, A.C.A. Jansen, *Tetrahedron* **1985,** *41,* 3313; G. Bringmann, R. Walter, R. Weirich, *Angew. Chem.* **1990,** *102,* 1006; *ibid. Int. Ed.* **1990,** *29,* 977.

[39] a) W.H. Pirkle, D.W. House, *J. Org. Chem.* **1979,** *44,* 1957; b) W.H. Pirkle, D.W. House, J.M. Finn, *J. Chromatogr.* **1980,** *192,* 143; c) W.H. Pirkle, J.L. Schreiner, *J. Org. Chem.* **1981,** *46,* 4988.

[40] A.V. Muehldorf, D. Van Engen, J.C. Warner, A.D. Hamilton, *J. Am. Chem. Soc.* **1988,** *110,* 6561.

[41] M. Kranz, T. Clark, P. von R. Schleyer, *J. Org. Chem.* **1993,** *58,* 3317, and ref. cit. therein.

[42] D.J. Cram, K.N. Trueblood, *Topics Curr. Chem.* **1981,** *98,* 43; R.E. Carter, T. Liljefors, *Tetrahedron* **1976,** *32,* 2915; W.R. Busing, *J. Am. Chem. Soc.* **1982,** *104,* 4829.

[43] a) F. Diederich, M.R. Hester, M.A. Uyeki, *Angew. Chem.* **1988,** *100,* 1775; *ibid. Int. Ed.* **1988,** *27,* 1705; b) M.R. Hester, M.A. Uyeki, F. Diederich, *Isr. J. Chem.* **1989,** *29,* 201.

[44] J. Rebek, Jr., S.V. Luis, L.R. Marshall, *J. Am. Chem. Soc.* **1986,** *108,* 5011.

[45] M.G. Siegel, Ph. D. Dissertation, University of California at Los Angeles, 1973.

[46] M.T. Blanda, J.H. Horner, M. Newcomb, *J. Org. Chem.* **1989,** *54,* 4626.