69. Molecular Recognition and Enantiomer Separations on a Novel Chiral Stationary Phase Based on a 9,9′-Spirobi[9*H*-fluorene]-Derived Molecular Cleft

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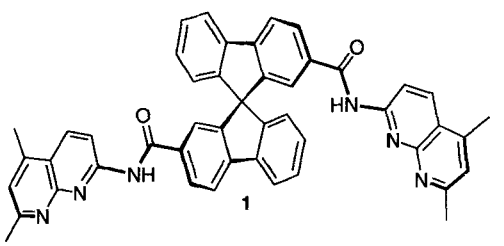
An optically active molecular cleft incorporating a 9,9′-spirobi[9*H*-fluorene] spacer and two *N*-(5,7-dimethyl-1,8-naphthyridin-2-yl)carboxamide (CONH(naphthyr)) moieties as H-bonding sites was covalently bound to silica gel to provide the new chiral stationary phase (CSP) (*R*)-**16** (*Scheme 2*). Previous solution-binding studies in $CDCl_3$ had shown that the anchored molecular cleft was capable of complexing optically active dicarboxylic acids with differences in free energy of the formed diastereoisomeric complexes ($\Delta(\Delta G^0)$) between 0.5 and 1.6 kcal mol^{-1} ($T \approx 300$ K). The optical resolution of racemic dicarboxylic acids, that are bound with a high degree of enantioselectivity in the liquid phase, was now achieved by HPLC on the CSP (*R*)-**16**. The order of enantiomer elution was as predicted from the solution studies, and the separation factor α varied between 1.18 and 1.24. A series of 1,1′-binaphthalene-2,2′-diol derivatives were also resolved on the new CSP, in some cases with baseline separation. The order of enantiomer elution under normal-phase chromatographic conditions was rationalized by computer modeling of the association between the solute enantiomers and the immobilized molecular cleft. HPLC Separations with eluents of different polarity suggested that the attractive interactions between solute and immobilized chiral selector are a combination of H-bonding, which prevails in apolar eluents, and aromatic $\pi-\pi$ stacking, which dominates in polar eluents.

1. Introduction. – The development of new chiral stationary phases (CSPs) for the chromatographic separation of enantiomers is an area of substantial interest in supramolecular chemistry [1–12]. Chiral recognition mechanisms of efficient CSPs have often been rationalized afterwards by investigating the molecular recognition properties of model systems in the liquid phase by ^{1}H-NMR techniques [13] [14]. More recently, CSPs were developed *via* attachment of optically active receptors, which had previously been shown to exhibit strong chiral-selector properties in the liquid phase, to chromatographic supports. Thus, *Gasparrini*, *Still*, and coworkers attached an optically active, C_3-symmetrical macrotricyclic receptor to SiO_2 [15]. This receptor had shown a high degree of enantioselectivity in the complexation of *N*-Boc-amino acid methylamides (*t*-BuOCONHCH(R)CONHMe) in the liquid phase, and its chiral-selector properties were successfully transferred to the solid phase, thus enabling the chromatographic resolution of the racemic amino-acid derivatives. Immobilization of efficient solution receptors to the solid phase also opened up interesting binding studies [16]. *Zimmerman et al.* determined binding enthalpies (ΔH^0) for host-guest complexes on chemically bonded stationary phases by HPLC, and the thermodynamic quantities measured on the solid phase correlated well with those obtained in solution [17].

In this paper, we describe the preparation and separation properties of a new CSP obtained by immobilization on SiO_2 of the molecular cleft-type, C_2-symmetrical recep-

tor **1** [18]. This receptor consists of a 9,9′-spirobi[9*H*-fluorene] spacer [19] bearing two *N*-(5,7-dimethyl-1,8-naphthyridin-2-yl)carboxamide (CONH(naphthyr)) moieties as H-bonding sites [20]. In $CDCl_3$ at 300 K, (*R*)-**1** and (*S*)-**1** [18] formed diastereoisomeric complexes of differential stability with a variety of optically active dicarboxylic acids such as *N*-benzyloxycarbonyl(Cbz)-L-aspartic acid ((+)-**2**; difference in free energy of formation of the diastereoisomeric complexes $\Delta(\Delta G^0) = 0.5\ kcal\,mol^{-1}$), *N*-Cbz-L-glutamic acid ((−)-**3**; $\Delta(\Delta G^0) = 0.7\ kcal\,mol^{-1}$), or 9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxylic acid ((+)-**5**; $\Delta(\Delta G^0) = 1.6\ kcal\,mol^{-1}$). A variety of pyranosides bind to (*R*)-**1** and (*S*)-**1** in $CDCl_3$ ($-\Delta G^0 = 3.1-4.3\ kcal\,mol^{-1}$), and an enantioselectivity of $0.4\ kcal\,mol^{-1}$ for octyl-α-D-glucopyranoside ((+)-**6**) was measured. In other recent work, CSPs were developed by immobilizing C_2-symmetrical cleft-type chiral selectors such as 1,1′-biphenyl [21a], 1,1′-binaphthyl [21b–d], and 1,1′-bianthracene [21e] derivatives without elaborate H-bonding sites. In pioneering work, *Cram* and coworkers had developed a CSP based on a 1,1′-binaphthyl-derived crown ether for the optical resolution of chiral ammonium ions [21f–h].



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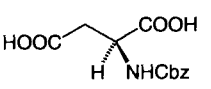

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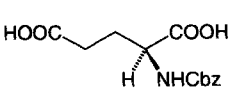

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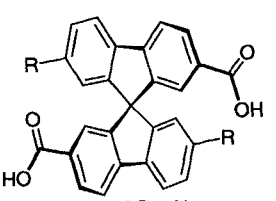
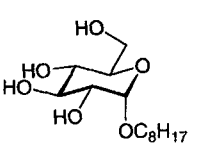


4 R = H
5 R = COC_7H_{15}



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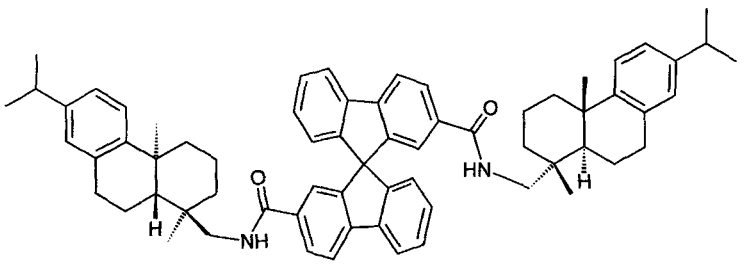
2. Results and Discussion. – 2.1. *Synthesis of the New CSP.* The preparation of the cleft-type receptor (+)-(*R*)-**7** for attachment as a chiral selector to SiO_2 started from dicarboxylic acid (+)-(*R*)-**4** (*Scheme 1*), which was obtained in optically pure form by a modification of the procedure initially developed by *Prelog* and coworkers [22]. By this method, the diastereoisomeric diamides **8** obtained from (+)-dehydroabietylamine (2 equiv.) and the bis(acyl halide) prepared *in situ* from (±)-**4** were partially separated by tedious medium-pressure liquid chromatography (MPLC). Amide hydrolysis yielded enantiomerically enriched dicarboxylic acid ($\approx$ 68% enantiomeric excess (*ee*) for (*R*)-**4** and 60% *ee* for (*S*)-**4**), and fractional crystallization afforded first remaining (±)-**4**, then the pure enantiomers (+)-(*R*)-**4** or (−)-(*S*)-**4**, respectively.



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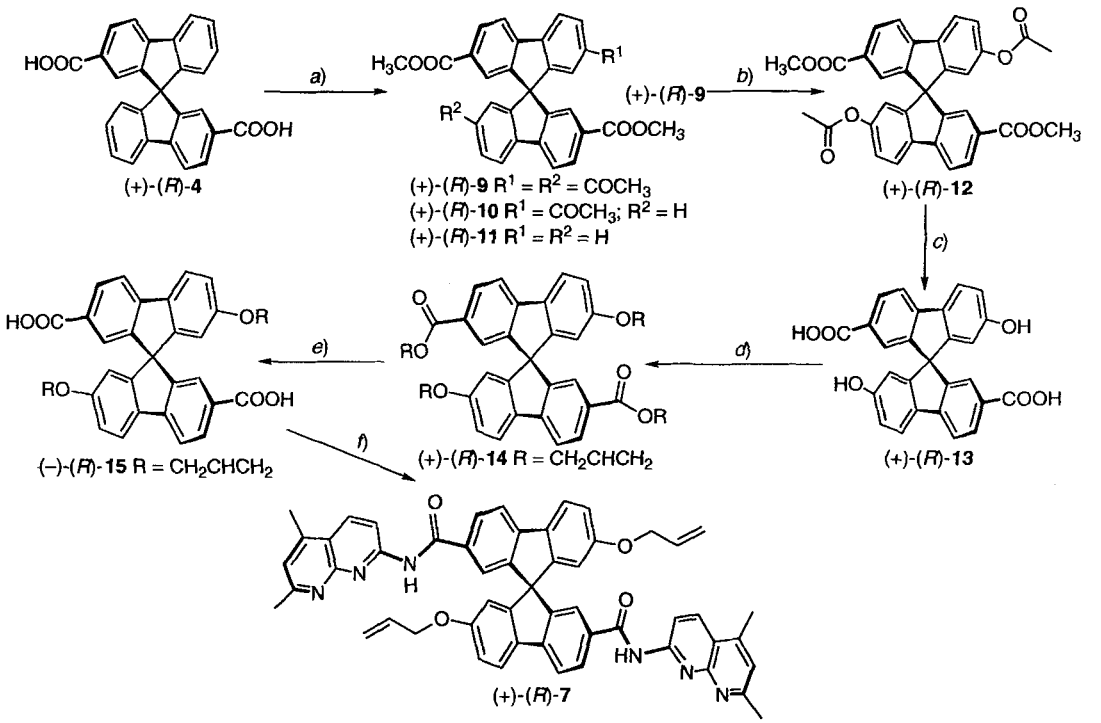
Starting from (+)-(*R*)-**4**, *Friedel-Crafts* acylation followed by esterification yielded (+)-(*R*)-**9** in addition to (+)-(*R*)-**10** and (+)-(*R*)-**11** as isolable side-products (*Scheme 1*). *Baeyer-Villiger* oxidation of (+)-(*R*)-**9** gave tetraester (+)-(*R*)-**12**, which was hydrolyzed to the dicarboxylic acid (+)-(*R*)-**13**. Reaction of (+)-(*R*)-**13** with allyl bromide and K_2CO_3 in DMF afforded (+)-(*R*)-**14**, and subsequent ester hydrolysis provided dicar-

Scheme 1

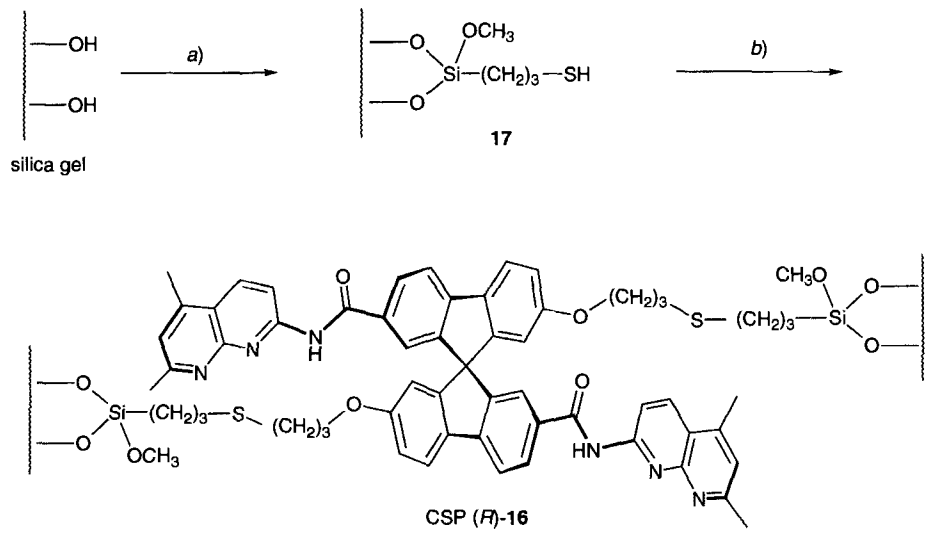


a) 1) CH_3COCl, $AlCl_3$, CS_2, 14 h; 2) MeOH, H_2SO_4, 2 d, Δ, 76% (+)-(*R*)-(**9**), 15% (+)-(*R*)-(**10**), 1% (+)-(*R*)-(**11**). *b*) *meta*-Chloroperbenzoic acid, $CHCl_3$, 5 d, 95%. *c*) NaOH, MeOH, H_2O, 12 h, Δ, 94%. *d*) Allyl bromide, K_2CO_3, DMF, 15 h, Δ, 89%. *e*) aq. NaOH, THF, 12 h, 95%. *f*) 1) *N*-Hydroxysuccinimide, DCC, THF; 2) 2-Amino-5,7-dimethyl-1,8-naphthyridine, Et_3N, THF, 3 d, Δ, 85%.

boxylic acid (−)-(*R*)-**15**. Formation of the corresponding bis(*N*-succinimidyl ester) and treatment with 2-amino-5,7-dimethyl-1,8-naphthyridine finally led to the molecular cleft (+)-(*R*)-**7**.

Attachment of (+)-(*R*)-**7** to SiO_2 (*Lichrosorb Si60*, particle size 5 μm, *E. Merck*) under formation of the novel CSP (*R*)-**16** was achieved following a procedure of *Salvadori* and coworkers [23] [24] (*Scheme 2*). First, the surface of the solid support was functionalized with 3-(mercaptopropyl)trimethoxysilane to give **17**, then the chiral selector was bound by radical-chain addition of the thiol group in **17** to the allyl ether moieties of (+)-(*R*)-**7**. The modified SiO_2 was characterized by elemental analysis according to *Berendsen* and *de Galan* [25], which revealed an attachment of 1.3 mmol (2.6 μmol/m^2) thiol groups/g SiO_2 for **17** and of 0.25 mmol (0.50 μmol/m^2) receptor/g SiO_2 for CSP (*R*)-**16**.

Scheme 2



a) (3-Mercaptopropyl)trimethoxysilane, toluene, pyridine, Δ, 20 h. *b*) (+)-(*R*)-**7**, AIBN, $CHCl_3$, Δ, 20 h, 47%.

2.2. *HPLC Studies.* Analytical HPLC columns (25 cm × 4.6 mm ID) were packed with either **17** or CSP (*R*)-**16**. The focus of the studies was put on separating racemic mixtures of compounds that had previously been enantioselectively bound by (*R*)-**1** and (*S*)-**1** in $CDCl_3$ (*Table 1*) [18]. Under conditions identical to those used for the separations on CSP (*R*)-**16**, columns packed with the thiol-functionalized SiO_2 **17** showed only weak affinity for the employed solutes. Therefore, the retentions on CSP (*R*)-**16** are attributed mainly to interactions with the covalently bound chiral selector.

2.2.1. *Separation of Dicarboxylic Acids.* The optical resolution of the dicarboxylic acids (±)-**2**, (±)-**3**, (±)-**4**, and (±)-**5** on CSP (*R*)-**16** was attempted with $MeOH/CH_2Cl_2$ mixtures as eluents. The enantiomers of (±)-*N*-Cbz-Asp ((±)-**2**) (*Table 2, Entry 1*), the dicarboxylic acid substrate bound with the lowest degree of enantioselectivity in the liquid phase by (*R*)-**1** or (*S*)-**1** (*Table 1, Entries 1* and *2*), were not separable on CSP (*R*)-**16** as the stationary phase, independent on eluent composition. The enantiomers of

Table 1. *Association Constants* K_a *and Binding Free Energies* ΔG^0 (uncertainties ± 0.2 kcal mol^{-1}) *of the Complexes Formed with* **1** *in* $CDCl_3$ *at 300 K*

Entry	Host	Guest	K_a [l mol^{-1}]	ΔG^0 [kcal mol^{-1}]
1	(*R*)-**1**	(+)-**2**	1100	−4.2
2	(*S*)-**1**	(+)-**2**	2600	−4.7
3	(*R*)-**1**	(−)-**3**	11650	−5.6
4	(*S*)-**1**	(−)-**3**	3800	−4.9
5	(*R*)-**1**	(+)-(*S*)-**5**	650	−3.9
6	(*S*)-**1**	(+)-(*S*)-**5**	9400	−5.5
7	(*R*)-**1**	(+)-**6**	180	−3.1
8	(*S*)-**1**	(+)-**6**	360	−3.5

(±)-*N*-Cbz-Glu ((±)-**3**) were separable with a separation factor $\alpha = 1.18$ (*Table 2, Entry 2*; for the definition of α, see the *Footnote* to *Table 2*). The (−)-L-enantiomer was eluted last, which correlates with the results in the liquid phase where this enantiomer is bound more strongly by (*R*)-**1** (*Table 1, Entry 3*). The enantiomers of the 9,9′-spirobi-[9*H*-fluorene]-2,2′-dicarboxylic acid (±)-**4** and its derivative (±)-**5** were also separable, with $\alpha = 1.24$ and 1.19, respectively (*Fig. 1*; *Table 2, Entries 3* and *4*). Thus, the CSP can potentially be used to optically resolve the precursor ((±)-**4**) to both its chiral selector (+)-(*R*)-**7** and the molecular clefts (*R*)-**1** and (*S*)-**1** for liquid-phase recognition. The order of elution followed the order of binding strength seen in solution (*Table 1, Entries 5* and *6*), with the (*R*)-CSP forming the most stable association with the (+)-(*R*)-**4** and (−)-(*R*)-**5** enantiomers, respectively. In view of the difficult, tedious enantiomer separation of (±)-**4** *via* the diastereoisomeric amides (*Sect. 2.1*), chromatography on CSP (*R*)-**16** provides an attractive alternative to the resolution of this chiral building block.

Table 2. *HPLC Resolution of Dicarboxylic Acids on CSP* (R)-**16**. Flow rate = 1.0 ml/min; retention time of non-retained solute $t_0 = 2.83$ min; $T = 295$ K; UV (254 nm) detection.

Entry	Solute	K_1'[a])	α[b])	$\Delta\Delta G^{0}$[c]) [kcal mol^{-1}]	Eluent (*v*/*v*)
1	(±)-**2**	3.28	1.0	0.00	MeOH/CH_2Cl_2 15:85
2	(±)-**3**[d])	2.04	1.18	0.10	MeOH/CH_2Cl_2 10:90
3	(±)-**4**	10.58	1.24	0.13	MeOH/CH_2Cl_2 5:95
4	(±)-**5**	5.82	1.19	0.10	MeOH/CH_2Cl_2 5:95

[a]) Capacity factor of the first eluted enantiomer ($(t_R - t_0)/t_0$), where t_R is the retention time.
[b]) Separation factor (K_2'/K_1').
[c]) $\Delta\Delta G^0 = -RT\ln\alpha$.
[d]) $t_0 = 3.10$ min on a differently packed (second) column.

These first results demonstrated that well-understood recognition properties of the cleft-type receptor (*R*)-**1** in the liquid phase could be transferred to the solid phase containing the analogous chiral selector (*R*)-**7**. The degree of separation, however, was weaker than expected. The difference in stability of the diastereoisomeric associations, $\Delta(\Delta G^0) = RT\ln\alpha$, formed between the enantiomers of the solutes (±)-**3** or (±)-**5** and

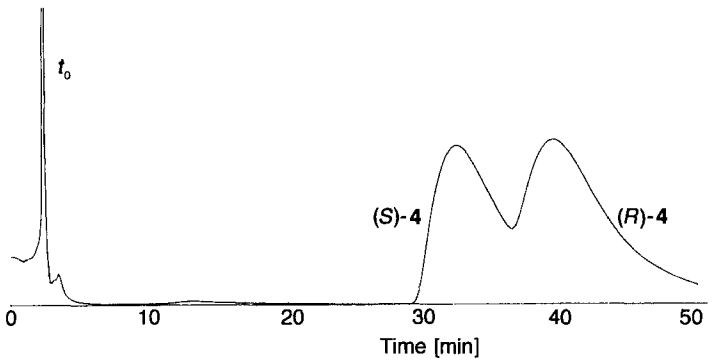
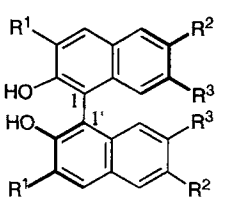


Fig. 1. *HPLC Resolution of (±)-4 on CSP (R)-16* ($MeOH/CH_2Cl_2$ 5:95 (*v/v*); 1 ml/min; UV (254 nm) detection)

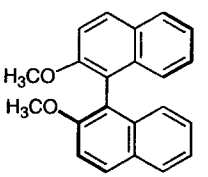
CSP (*R*)-**16** was only 0.10 kcal mol^{-1} in the HPLC studies, whereas the corresponding $\Delta(\Delta G^0)$ values were 0.7 and 1.6 kcal mol^{-1}, respectively, in the binding studies with receptor **1** in the liquid phase. This is likely due to the drastic change in solvent polarity, from $CDCl_3$ in the liquid phase to 5–10% MeOH in CH_2Cl_2 in the HPLC studies. The addition of MeOH, which strongly competes for the H-bonding centers of solute and chiral selector, is necessary to elute the polar dicarboxylic acids from the CSP. Since the differential interactions between solute enantiomers and the chiral selector of CSP (*R*)-**16** are nearly exclusively based on H-bonding [18], addition of MeOH is particularly detrimental to the chromatographic resolution process. A drop in the separation factor α with increasing amount of alcohol in the eluent and corresponding weakening of the H-bonding association was also observed by *Okamoto* and coworkers [13] in optical resolutions on phenylcarbamate-derived cellulose. However, this drop was not as dramatic, since the association of solutes with this CSP not only involves H-bonding but also apolar (π-π and CH-π) interactions as well as hydrophobic desolvation. These latter bonding forces become strengthened with increasing eluent polarity.

2.2.2. *Separation of 1,1′-Binaphthalene-2,2′-diols and Modeling Studies.* 1,1′-Binaphthalene-2,2′-diols are widely used chiral spacers in stereoselective catalysts [26] and molecular receptors [27–29]. In early work, *Pirkle* and *Schreiner* separated a variety of 1,1′-binaphthalene-2,2′-diols on a *N*-(3,5-dinitrobenzoyl)phenylglycine-derived CSP [30]. They rationalized the order of enantiomer elution with a plausible interaction model and used this chromatographic method for determining the absolute configuration of a wide range of these solutes. In the following, 1,1′-binaphthalene-2,2′-diols were optically resolved on a variety of CSPs [7–10] [13] [21 b,d,e] [31]. As shown in *Table 3*, many of these chiral solutes could also be resolved by HPLC on CSP (*R*)-**16** and, in some cases, baseline separation of the enantiomers was achieved (*Fig. 2*). Again, elution of the solutes required addition of various amounts of polar cosolvent (i-PrOH in $ClCH_2CH_2Cl$).

In these separations, the (*R*)-enantiomers of **18a**, **18c**, and **18d** were eluted later under the conditions displayed in *Table 3*. For compound **18b**, it was shown that the order of elution of the enantiomers changed upon increasing the polarity of the eluent. With an eluent containing up to 15% (*v/v*) i-PrOH in CH_2ClCH_2Cl, the (*R*)-enantiomer was eluted later, whereas a further increase in solvent polarity inverted the order of



18	R^1	R^2	R^3
a	H	H	H
b	H	Br	BnO
c	H	Br	H
d	Br	H	BnO
e	H	Br	MeO



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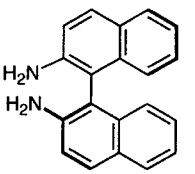

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elution. Furthermore, the capacity factor (*K'*, for a definition see *Footnote* to *Table 3*) of **18b** increased at very polar eluent mixtures (*Table 3, Entries 2–6*). These unexpected phenomena were studied in more detail, and the dependency of *K'* on the polarity of the eluent was found to give a U-shaped curve for both diastereoisomeric associations (*Fig. 3*). As expected for apolar chromatographic ('normal phase') conditions, *K'* decreases upon increasing the amount of i-PrOH in CH_2ClCH_2Cl up to 40% (*v/v*), since the complex-forming H-bonds become weaker. Upon further increasing the amount of i-PrOH in the eluent, however, *K'* increases again. This suggests that apolar interactions, such as the aromatic interactions between the CONH(naphthyr) moieties of the receptor and the naphthyl rings of the guest, are now becoming more important under the polar chromatographic ('reversed phase') conditions. Under apolar conditions, the observed enantioselectivity probably results from differential H-bonding interactions in the diastereoisomeric associations, whereas apolar aromatic interactions are the major discriminating force under the polar conditions. A similar U-shaped curve has previously been reported by *Armstrong et al.* with CSPs based on cyclodextrins or CSPs with antibiotics and proteins as immobilized chiral selectors [8].

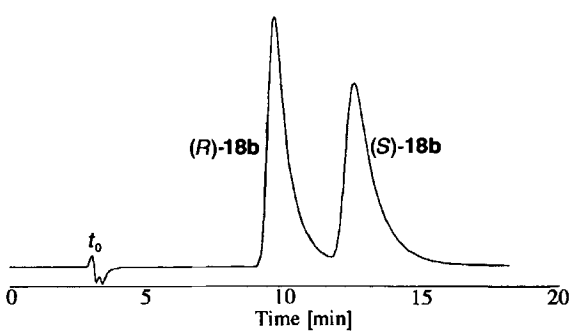


Fig. 2. *HPLC Resolution of (±)-***18b** *on CSP (R)-***16** (i-PrOH/CH_2ClCH_2Cl 1:1 (*v/v*); 1 ml/min; UV (254 nm) detection)

Table 3. *HPLC Resolution of Diols on CSP* (R)-**16**. Flow rate = 1.0 ml/min; retention time of non-retained solute t_0 = 3.10 min; T = 295 K; UV (254 nm) detection.

Entry	Solute	K'_1 [a])	α [b])	$\Delta\Delta G^{0}$ [c]) [kcal mol^{-1}]	Eluent (v/v; % i-PrOH in CH_2ClCH_2Cl)
1	(±)-**18a**	2.32	1.10	0.06	10
2	(±)-**18b**	6.05	1.15	0.08	10
3	(±)-**18b**	2.41	1.28	0.15	20
4	(±)-**18b**	2.11	1.45	0.22	50
5	(±)-**18b**	4.41	1.55	0.26	70
6	(±)-**18b**	8.32	1.68	0.31	80
7	(±)-**18c**	3.16	1.09	0.05	30
8	(±)-**18d**	2.15	1.18	0.10	30
9	(±)-**18e**	3.53	1.25	0.13	30
10	(±)-**19**	<0.1	1.0	0.00	0
11	(±)-**19**	3.83	1.0	0.00	[d])
12	(±)-**19**	0.51	1.0	0.00	80
13	(±)-**20**	1.28	1.0	0.00	0
14	(±)-**21**	1.19	1.11	0.06	15

[a]) Capacity factor of the first eluted enantiomer ($(t_R - t_0)/t_0$), where t_R is the retention time.
[b]) Separation factor (K'_2/K'_1).
[c]) $\Delta\Delta G^0 = -RT\ln\alpha$.
[d]) Hexane/CH_2ClCH_2Cl 90:10 (v/v).

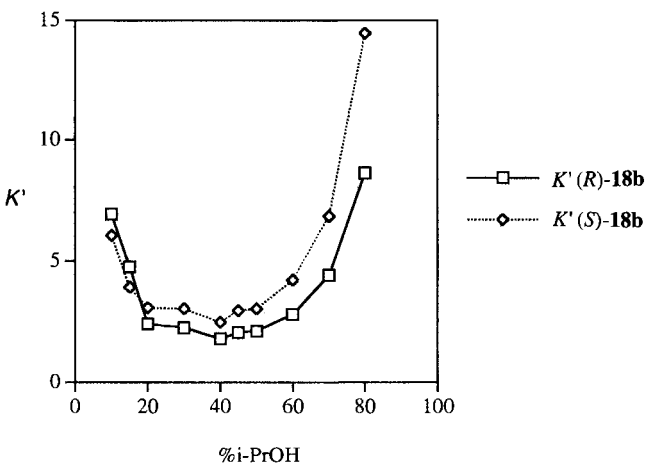


Fig. 3. *Capacity factors (K') of* (R)-**18b** *and* (S)-**18b** *on CSP* (R)-**16** *as a function of solvent polarity* (mixtures of i-PrOH/CH_2ClCH_2Cl (v/v); 1 ml/min; UV (254 nm) detection)

A rationalization of the preferred elution of (*S*)-1,1′-binaphthalene-2,2′-diol ((*S*)-**18a**) under apolar conditions was attempted by computer modeling. For this purpose, a 5000-step Monte Carlo (MC) conformational search using MacroModel v. 5.0 [32] with the AMBER* force field [33] and the GB/SA solvation model for $CHCl_3$ [34] was conducted for the diastereoisomeric complexes formed by (*R*)-**18a** and (*S*)-**18a** with

(*R*)-**1**, the chiral selector of CSP (*R*)-**16**. In this search, full rotation about the C(1)–C(1′) bond of **18a**, including a change in absolute configuration, was permitted. Of the 25 complex conformers within 3 kcal mol^{-1} of the global minimum, 19 corresponded to the (*R*)-**1** · (*R*)-**18a** complex, including the 16 structures of lowest energy, and the other six conformers corresponded to the diastereoisomeric (*R*)-**1** · (*S*)-**18a** complex. The computed lowest-energy structure of the more stable (*R*)-**1** · (*R*)-**18a** complex is shown in *Fig. 4*. Both OH groups of the guest form H-bonds to naphthyridine N-atoms, and the complex is additionally stabilized by aromatic $\pi-\pi$ stacking interactions between the naphthyl rings of the substrate and the heterocyclic rings of the receptor. Similar interactions are seen in the other low-energy conformers of the (*R*)-**1** · (*R*)-**18a** complex. In contrast, the six lowest-energy conformers of the (*R*)-**1** · (*S*)-**18a** complex all displayed only one OH · · · N H-bond, which could explain its shorter retention time under apolar ('normal phase') conditions. Some experimental evidence for the aromatic $\pi-\pi$ stacking interactions, suggested by the modeling for both diastereoisomeric complexes, was obtained by ^{1}H-NMR spectroscopy. In *ca.* 5 mM solutions of both binding partners (*R*)-**1**, and (*R*)-**18** or (*S*)-**18a** in $CDCl_3$, their aromatic resonances were shifted upfield by 0.02–0.07 ppm as compared to those in the solutions of the individual components.

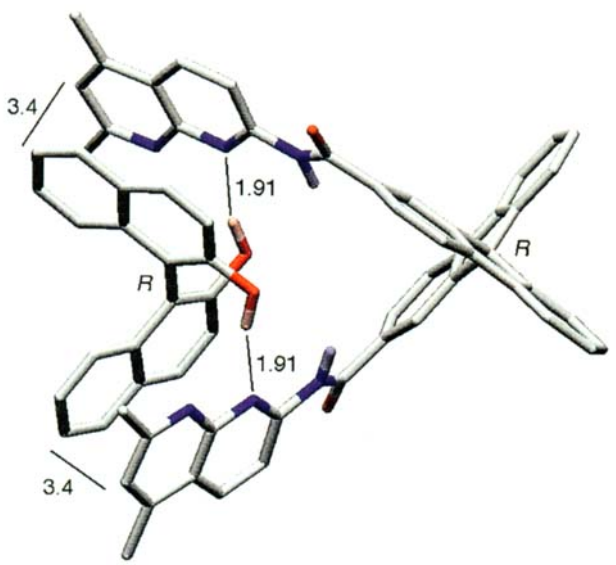
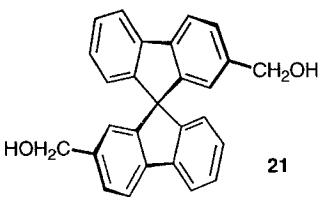


Fig. 4. *Lowest-energy structure of the complex formed between* (R)-**1** *and* (R)-**18a** *in* $CDCl_3$, *generated by a Monte-Carlo search of conformational space.* H-Atoms are omitted for clarity. Distances are in Å.

Attempts to rationalize the reversal of the elution order under polar ('reversed phase') conditions in a 5000-step Monte Carlo (MC) search of conformational space as described above, but with the GB/SA solvation model for H_2O [34], were not successful. Among the eight conformers found within 3 kcal mol^{-1} of the global minimum, the four lowest-energy structures corresponded to the (*R*)-**1** · (*R*)-**18a** complex.

The importance of H-bonding for the enantiomer separation on CSP (*R*)-**16** was confirmed by control experiments. Bis(methyl ether) (±)-**19**, is not capable of forming strong H-bonds to the CSP and is, therefore, eluted faster than the corresponding diol (±)-**18a**, with no separation of enantiomers (*Table 3, Entries 10–12*). A similar behavior was observed with (±)-1,1′-binaphthalene-2,2′-diamine ((±)-**20**), which is a much weaker H-bond donor than (±)-**18a** (*Entry 13*).

Finally, attempts to separate the enantiomers of pyranoside (±)-**6**, which are bound with a small degree of enantioselectivity by (*R*)-**1** or (*S*)-**1** in $CDCl_3$ (*Table 1, Entries 7* and *8*), were not successful. A variety of 2,2′-substituted (±)-9,9′-spirobi[9*H*-fluorene] derivatives (R=R′=OH, OAc, COMe, CO_2Me, CH_2OAc, or CH_2OH) were also used as solutes, but only the enantiomers of diol (±)-**21** were separable with $\alpha = 1.11$ (*Table 3, Entry 14*).



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3. Conclusion. – A new chiral stationary phase (CSP) (*R*)-**16** was prepared by immobilizing the chiral selector (+)-(*R*)-**7** on functionalized silica gel. The optical resolution of chiral dicarboxylic acids such as (±)-*N*-Cbz-glutamic acid ((±)-**3**) and the (±)-9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxylic acids (±)-**4** and (±)-**5** was achieved under normal phase conditions on CSP (*R*)-**16**. Efficient chiral recognition of these substrates had previously been observed in liquid phase studies ($CDCl_3$) with the molecular cleft-type receptors (*R*)-**1** and (*S*)-**1**, which are close analogs of the immobilized chiral selector (+)-(*R*)-**7**. As expected, the elution order in the chromatographic enantiomer separation correlated with the differences in stability of the diastereoisomeric complexes formed in solution: the enantiomer that was more strongly bound in solution was eluted later. The results show that it is possible to transfer binding results, obtained with optically active receptors in liquid phase studies, to the solid phase.

Enantiomers of 1,1′-binaphthalene-2,2′-diols were separated with α up to 1.68 ($\Delta(\Delta G^0) = 0.31$ kcal mol^{-1}) by HPLC on the new CSP (*R*)-**16**. Under normal phase conditions, the (*R*)-enantiomer was eluted later, which was rationalized by computer modeling studies. The models suggested that (*R*)-1,1′-binaphthalene-2,2′-diol (**18a**) interacts by two O–H···N H-bonds with (*R*)-**1**, whereas the (*S*)-enantiomer forms only one H-bond. The separation of the enantiomers of the 1,1′-binaphthalene-2,2′-diol derivative **18b** showed an interesting solvent dependency. At low solvent polarity, the (*R*)-enantiomer was eluted later, whereas at higher polarity, the order of elution was inverted. Also, upon increasing the solvent polarity, the retention times first decreased, then showed a strong increase. This U-shaped-curve-type dependency of the capacity factor from solvent polarity suggests that different intermolecular forces are predominant: under apolar ('normal phase') conditions, solute association and retention times are mainly controlled by H-bonding, whereas under polar ('reversed phase') conditions, apolar contacts such as aromatic $\pi-\pi$ stacking interactions are more effective.

The development of novel chiral stationary phases such as CSP (*R*)-**16** is a logical extension of molecular recognition studies with chiral receptors in the liquid phase. It is safe to expect that, with further refinement of the understanding of weak intermolecular interactions and of rational receptor design, a great diversity of novel made-to-order chiral stationary phases will become commercially available. This development should, therefore, benefit the efforts in the pharmaceutical industry which is required to produce chiral drugs in enantiomerically pure form only.

Experimental Part

General. All reactions were carried out under N_2. Reagent-grade chemicals were purchased from *Fluka* or *Aldrich* and used without further purification unless otherwise stated. THF was freshly distilled from sodium benzophenone ketyl. $CHCl_3$ was purified by washing with H_2O and then distilling over P_2O_5. TLC: *E. Merck* plates precoated with SiO_2 F_{254}. Column chromatography (CC): *E. Merck* SiO_2 *60* (0.040–0.063 mm). MPLC: *Büchi 688* chromatography pump, *Büchi 686* peak detector, *Büchi 687* gradient former, *Knauer Wavelength Monitor* UV/VIS detector. *E. Merck* SiO_2 (0.016–0.040 mm). M.p.: *Büchi Smp-20*, uncorrected. Optical rotation: *Perkin-Elmer-Polarimeter 241* (at r.t. = 295 ± 1°). IR Spectra (cm^{-1}): *Perkin-Elmer 1600-FTIR*. ^{1}H-NMR and ^{13}C-NMR spectra: at 300 K with a *Bruker AMX 500* or *Varian Gemini 300* if not stated otherwise. FAB-MS (*m/z*, %): *m*-nitrobenzyl alcohol as matrix; EI-MS (*m/z*, %) at 70 eV. Elemental analyses: Mikrolabor des Laboratoriums für Organische Chemie at ETHZ.

HPLC Studies. For HPLC studies, the diacids (±)-**2** and (±)-**3** were purchased from *Sigma*, and pyranoside (±)-**6** and the 1,1′-binaphthyl derivatives (±)-**18a** and (±)-**20** from *Fluka*. Compounds (±)-**5** [18], **17** [23], (±)-**18b–e** [18] [28] [29], (±)-**19** [35], and (±)-**21** [22] were synthesized according to published procedures. *HPLC Instrumentation*: *Knauer HPLC Pump 64* high-pressure gradient pumps with anal. pump heads and vacuum on-line degasser, electrical injection valve, *Variable Wavelength Monitor* UV/VIS detector from *Knauer*. Samples of 20 µl were injected. Two anal. columns (250 mm × 4 mm I.D.) were packed with CSP (*R*)-**16**, showing slightly different retention times: retention time of non-retained solute (t_0): 2.83 min and 3.10 min, resp. The columns were packed using the slurry method.

*Optical Resolution of (±)-9,9′-Spirobi[9*H*-fluorene]-2,2′-dicarboxylic Acid* ((±)-**4**). Compound (±)-**4** (30 g, 75 mmol) was refluxed in $SOCl_2$ (300 ml) with three drops of pyridine for 3 h. After evaporation, the residue was dissolved in pyridine (80 ml), a soln. of (+)-dehydroabietylamine (44 g, 154 mmol) in pyridine (30 ml) was added, and the mixture was stirred at r.t. for 30 h. The solvent was evaporated, H_2O (400 ml) added, and the mixture was extracted with Et_2O. The org. phase was dried ($MgSO_4$) and evaporated to give a mixture of two diastereoisomers of **8** (66 g). This crude product (40 g) was chromatographed by MPLC (SiO_2, hexane/Et_2O 5:2; flow rate: 100 ml/min). After repeated chromatography, 17 g of enriched diastereoisomer **8** derived from (+)-(*R*)-**4** (R_f 0.39 (hexane/Et_2O 1:1)) and 14 g of enriched diastereoisomer **8** derived from (−)-(*S*)-**4** (R_f 0.32 (hexane/Et_2O 1:1)) were isolated. Either enriched diastereoisomer of **8** (9 g, 9.6 mmol) and KOH (18 g, 320 mmol) were refluxed in 2-methoxymethanol (30 ml) for 14 h. The solvent was distilled off, and H_2O (100 ml) was added. The aq. phase was first acidified with 3M HCl and then extracted with AcOEt. Drying ($MgSO_4$) and evaporation yielded the respective enantiomerically enriched **4**. Optically pure material was obtained by fractional crystallization from toluene/EtOH, from which the racemate crystallized out first. This afforded (+)-(*R*)-**4** (2.4 g; $[\alpha]_D^{r.t.} = +63.9$ ($c = 0.635$, acetone)) and (−)-(*S*)-**4** (2.1 g; $[\alpha]_D^{r.t.} = -63.6$ ($c = 0.525$, acetone) ([22]: −63°)), resp.

*Dimethyl (+)-(*R*)-7,7′-Diacetyl-9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxylate* ((*R*)-**9**), *Dimethyl (+)-(*R*)-7-Acetyl-9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxylate* ((*R*)-**10**), *and Dimethyl (+)-(*R*)-9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxylate* ((*R*)-**11**). To (+)-(*R*)-**4** (6.8 g, 16.8 mmol) in CS_2 (40 ml) was added $AlCl_3$ (27.0 g, 200 mmol), and, after stirring for 10 min at r.t., a brown suspension was obtained. A soln. of AcCl (4.7 ml, 5.2 g, 67 mmol) in CS_2 (10 ml) was added dropwise over 10 min, and the resulting yellow-greenish mixture was stirred at r.t. for 12 h, refluxed for 2 h, cooled, and evaporated. After addition of ice (100 g) and acidification with 2M HCl (80 ml), the formed precipitate was filtered off and heated for 2 d under reflux in MeOH (500 ml) in the presence of conc. H_2SO_4 (1.0 ml). The soln. was then concentrated to 100 ml under reduced pressure, ice (100 g) was added, and the aq. phase was extracted with $CHCl_3$. After drying ($MgSO_4$), the solvent was evaporated and the residue chromatographed (hexane/Et_2O 2:1 → 1:1) to give three products. Recrystallization of the most polar product (R_f 0.23 (Et_2O/hexane 2:1)) from $CHCl_3$/hexane and drying (12 h, 80°/0.05 Torr) afforded (+)-(*R*)-**9** (6.6 g, 76%). White powder. M.p. > 300°. $[\alpha]_D^{r.t.} = +0.42$ ($c = 0.875$, $CHCl_3$). IR (KBr): 3420*m*, 1716*s*, 1682*s*, 1606*m*,

1437*m*, 1357*w*, 1287*s*, 1244*s*, 760*w*, 609*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.47 (*s*, 6H); 3.78 (*s*, 6H); 7.30 (*d*, *J* = 1.5, 2H); 7.36 (*d*, *J* = 1.5, 2H); 8.00 (*d*, *J* = 8.1, 2H); 8.01 (*d*, *J* = 8.1, 2H); 8.05 (*dd*, *J* = 8.1, 1.5, 2H); 8.15 (*dd*, *J* = 8.1, 1.5, 2H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 26.69; 52.12; 65.57; 121.18; 121.20; 123.78; 125.36; 129.46; 130.31; 130.82; 137.71; 144.94; 145.23; 148.42; 148.56; 166.43; 197.25. FAB-MS: 1033.5 (38, M_2H^+), 517.2 (100, MH^+), 485.2 (99, $[M - MeO]^+$). Anal. calc. for $C_{33}H_{24}O_6 \cdot 0.25\,H_2O$ (521.05): C 76.07, H 4.74; found: C 76.19, H 4.81.

The product of intermediate polarity (R_f 0.17 (Et_2O/hexane 1:1)) was dried (12 h, 80°/0.05 Torr) to give (+)-(*R*)-**10** (1.2 g, 15%). White powder. M.p. 170–172°. $[\alpha]_D^{r.t.} = +1.29$ (*c* = 0.695, $CHCl_3$). IR (KBr): 3415*w*, 1716*s*, 1681*m*, 1606*w*, 1436*m*, 1284*s*, 1245*s*, 1096*w*, 756*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.47 (*s*, 3H); 3.78 (*s*, 3H); 3.79 (*s*, 3H); 6.71 (*dd*, *J* = 7.5, 1.3, 1H); 7.18 (*td*, *J* = 7.5, 1.3, 1H); 7.31 (*d*, *J* = 1.3, 1H); 7.34 (*d*, *J* = 1.3, 1H); 7.39 (*d*, *J* = 1.3, 1H); 7.44 (*td*, *J* = 7.5, 1.3, 1H); 7.95 (*d*, *J* = 8.0, 2H); 7.98 (*d*, *J* = 8.0, 1H); 7.99 (*d*, *J* = 8.0, 1H); 8.05 (*dd*, *J* = 8.0, 1.3, 1H); 8.13 (*dd*, *J* = 8.0, 1.3, 1H); 8.14 (*dd*, *J* = 8.0, 1.3, 1H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 26.68; 51.98; 52.06; 65.65; 120.17; 120.90; 120.95; 121.28; 123.95; 124.03; 125.20; 125.42; 128.49; 129.07; 129.25; 129.65; 130.06; 130.19; 130.72; 137.66; 140.72; 144.83; 145.13; 146.55; 147.16; 148.04; 149.33; 149.44; 166.52; 166.70; 197.30. FAB-MS: 949.3 (70, M_2H^+), 474.2 (79, M^+), 443.1 (100, $[M - MeO]^+$). Anal. calc. for $C_{31}H_{22}O_5$ (474.51): C 78.47, H 4.67; found: C 78.43, H 4.91.

The least polar product (R_f 0.45 (Et_2O/hexane 1:1)) was dried (12 h, 80°/0.05 Torr) to afford (+)-(*R*)-**11** (0.1 g, 1%) [22]. White powder. M.p. 225–227° (m.p. 217–219° for (±)-**11** [22]). $[\alpha]_D^{r.t.} = +83.2$ (*c* = 0.475, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 3.78 (*s*, 6H, 2Me); 6.74 (*d*, *J* = 7.5, 2H); 7.18 (*t*, *J* = 7.5, 2H); 7.39 (*s*, 2H); 7.42 (*t*, *J* = 7.5, 2H); 7.93 (*m*, 4H); 8.12 (*d*, *J* = 7.5, 2H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 52.00; 65.70; 120.00; 121.09; 124.17; 125.32; 128.24; 129.18; 129.55; 130.00; 140.61; 146.52; 148.06; 149.01; 166.84.

*Dimethyl (+)-(*R*)-7,7'-Diacetoxy-9,9'-spirobi[9*H*-fluorene]-2,2'-dicarboxylate* ((*R*)-**12**). Compound (+)-(*R*)-**9** (5.6 g, 10.8 mmol) and *meta*-chloroperbenzoic acid (60%, 20.0 g, 114 mmol) were stirred in $CHCl_3$ (150 ml) at r.t. for 5 d. $CHCl_3$ (150 ml) was then added, and the org. phase was washed with 20% aq. $Na_2S_2O_5$ soln. (100 ml) and 1M aq. $KHCO_3$ soln. (150 ml). The solvent was evaporated, and the residue dried (12 h, 80°/0.05 Torr) to give (+)-(*R*)-**12** (5.3 g, 95%). White solid. M.p. 114–116° ($CHCl_3$). $[\alpha]_D^{r.t.} = +13.8$ (*c* = 0.708, $CHCl_3$). IR (KBr): 3422*w*, 1761*s*, 1715*s*, 1611*m*, 1434*m*, 1369*m*, 1289*s*, 1208*s*, 1094*m*, 1006*w*, 905*w*, 760*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.16 (*s*, 6H); 3.78 (*s*, 6H); 6.49 (*d*, *J* = 2.1, 2H); 7.20 (*dd*, *J* = 8.3, 2.1, 2H); 7.36 (*d*, *J* = 1.5, 2H); 7.86 (*d*, *J* = 8.0, 2H); 7.89 (*d*, *J* = 8.3, 2H); 8.11 (*dd*, *J* = 8.0, 1.5, 2H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 20.94; 51.95; 65.54; 117.48; 119.87; 121.63; 122.09; 125.29; 129.61; 130.26; 138.10; 145.48; 147.61; 149.93; 151.46; 166.60; 168.92. FAB-MS: 1097.3 (5, M_2H^+), 548.2 (67, M^+), 517.1 (100, $[M - MeO]^+$). Anal. calc. for $C_{33}H_{24}O_8 \cdot 0.5\,CHCl_3$ (608.24): C 66.15, H 4.06; found: C 66.20, H 4.14.

*(+)-(*R*)-7,7'-Dihydroxy-9,9'-spirobi[9*H*-fluorene]-2,2'-dicarboxylic Acid* ((*R*)-**13**). A mixture of (+)-(*R*)-**12** (5.2 g, 10.1 mmol) and NaOH (4.3 g, 108 mmol) was stirred in MeOH/H_2O 3:1 (150 ml) for 12 h at r.t. and then heated under reflux for 1 h. The soln. was concentrated to 40 ml and acidified with 1M HCl. The formed precipitate was filtered off and dried (12 h, 80°/0.05 Torr) to give (+)-(*R*)-**13** (4.2 g, 94%). White powder. M.p. > 300°. $[\alpha]_D^{r.t.} = +13.1$ (*c* = 0.352, acetone). IR (KBr): 3311*s* (br.), 1689*s*, 1600*m*, 1442*w*, 1283*m*, 1200*m*, 822*w*. ^{1}H-NMR (500 MHz, $(CD_3)_2CO$): 6.25 (*d*, *J* = 2.3, 2H); 6.97 (*dd*, *J* = 8.3, 2.3, 2H); 7.33 (*d*, *J* = 1.5, 2H); 7.94 (*d*, *J* = 8.3, 2H); 7.98 (*d*, *J* = 8.0, 2H); 8.09 (*dd*, *J* = 8.0, 1.5, 2H). ^{13}C-NMR (125.8 MHz, $(CD_3)_2CO$): 65.31; 110.56; 115.83; 119.08; 122.49; 124.61; 128.39; 130.10; 132.24; 146.76; 147.95; 151.45; 158.84; 166.43. EI-MS: 436.2 (48, M^+), 156.0 (63), 139.0 (100). HR-EI-MS: 436.0946 (M^+, $C_{27}H_{16}O_6^+$; calc. 436.0947).

*Di(prop-2-en-1-yl) (+)-(*R*)-7,7'-Bis(prop-2-en-1-yloxy)-9,9'-spirobi[9*H*-fluorene]-2,2'-dicarboxylate* ((*R*)-**14**). A mixture of (+)-(*R*)-**13** (4.2 g, 9.6 mmol), allyl bromide (4.8 ml, 6.8 g, 56 mmol), and K_2CO_3 (13.8 g, 100 mmol) in DMF (100 ml) was stirred for 12 h at r.t., then heated to 60° for 3 h. The solvent was removed, 1M aq. HCl (100 ml) was added, and the aq. phase was extracted with Et_2O. The solvent was evaporated and the residue dried (12 h/0.05 Torr) to give (+)-(*R*)-**14** (5.1 g, 89%) as a yellow oil that was used without further purification. $[\alpha]_D^{r.t.} = +10.6$ (*c* = 0.502, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 4.36 (*m*, 4H); 4.71 (*m*, 4H); 5.20 (*m*, 4H); 5.30 (*m*, 4H); 5.94 (*m*, 4H); 6.26 (*d*, *J* = 2.4, 2H); 6.97 (*dd*, *J* = 8.5, 2.4, 2H); 7.36 (*d*, *J* = 1.5, 2H); 7.80 (*d*, *J* = 8.0, 2H); 7.81 (*d*, *J* = 8.5, 2H); 8.10 (*dd*, *J* = 8.0, 1.5, 2H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 65.51; 65.57; 68.93; 110.31; 114.96; 117.80; 118.24; 119.02; 121.93; 125.26; 128.35; 130.09; 132.33; 132.72; 133.48; 146.56; 147.71; 151.15; 159.89; 166.13. FAB-MS: 596.2 (100, M^+).

*(*R*)-(−)-7,7'-Bis(prop-2-en-1-yloxy)-9,9'-spirobi[9*H*-fluorene]-2,2'-dicarboxylic Acid* ((*R*)-**15**). The crude compound (+)-(*R*)-**14** (5.0 g, 8.4 mmol) was dissolved in THF (150 ml), 1M NaOH (50 ml) was added, and the mixture was stirred at r.t. for 12 h. The soln. was then acidified with 1M HCl and extracted with Et_2O. The org. phase was dried ($MgSO_4$) and evaporated to give a residue that was dried (12 h, 80°/0.05 Torr): (−)-(*R*)-**15** (4.1 g, 95%). White powder. M.p. 235° (dec.). $[\alpha]_D^{r.t.} = -2.14$ (*c* = 0.515, acetone). IR (KBr): 3078*m* (br.), 1683*s*, 1606*s*,

1494*w*, 1422*m*, 1269*s*, 1204*m*, 998*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.36 (*m*, 4H); 5.11 (*m*, 2H); 5.24 (*m*, 2H); 5.89 (*m*, 2H); 6.23 (*d*, *J* = 2.4, 2H); 7.03 (*dd*, *J* = 8.5, 2.4, 2H); 7.21 (*d*, *J* = 1.5, 2H); 7.92 (*d*, *J* = 8.1, 2H); 7.93 (*d*, *J* = 8.5, 2H); 8.07 (*dd*, *J* = 8.1, 1.5, 2H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 65.45; 68.56; 109.52; 115.28; 116.18; 118.89; 121.91; 124.39; 128.65; 129.92; 133.01; 133.41; 146.41; 147.95; 150.89; 160.13; 168.23. EI-MS: 516.2 (100, M^+), 475.2 (72), 434.1 (68). Anal. calc. for $C_{33}H_{24}O_6 \cdot 1.5\ H_2O$ (543.58): C 72.92, H 5.01; found: C 73.57, H 4.68.

*(+)-(*R*)-N,N'-Bis(5,7-dimethyl-1,8-naphthyridin-2-yl)-7,7'-bis(prop-2-en-1-yloxy)-9,9'-spirobi[9H-fluorene]-2,2'-dicarboxamide* ((*R*)-**7**). A soln. of (−)-(*R*)-**15** (4.0 g, 7.8 mmol), *N*-hydroxysuccinimide (2.0 g, 17 mmol), and DCC (5.6 g, 27 mmol) in THF (50 ml) was stirred at r.t. for 4 h. The precipitate was removed by filtration, 2-amino-5,7-dimethyl-1,8-naphthyridine (5.4 g, 31 mmol) and Et_3N (2.0 ml, 1.5 g, 15 mmol) were added to the soln., and the mixture heated for 3 d under reflux. Evaporation followed by chromatography (AcOEt → AcOEt/THF 1:1) yielded (+)-(*R*)-**7** (5.5 g, 85%). R_f 0.1 (AcOEt). White powder. M.p. 198° (dec.). $[\alpha]_D^{r.t.} = +115.9$ (*c* = 0.643, $CHCl_3$). IR (KBr): 3322*w*, 2927*m*, 2845*w*, 1677*m*, 1600*s*, 1508*s*, 1405*w*, 1310*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.59 (*s*, 6H); 2.66 (*s*, 6H); 4.39 (*m*, 4H); 5.19 (*m*, 2H); 5.30 (*m*, 2H); 5.93 (*m*, 2H); 6.31 (*d*, *J* = 2.3, 2H); 7.01 (*dd*, *J* = 8.5, 2.3, 2H); 7.06 (*s*, 2H); 7.32 (*d*, *J* = 1.5, 2H); 7.86 (*d*, *J* = 8.5, 2H); 7.92 (*d*, *J* = 8.1, 2H); 8.11 (*dd*, *J* = 8.1, 1.5, 2H); 8.26 (*d*, *J* = 9.0, 2H); 8.50 (*d*, *J* = 9.0, 2H); 8.93 (br. *s*, 2H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 17.95; 25.15; 65.63; 68.98; 110.40; 113.60; 115.22; 117.83; 118.50; 119.87; 122.19; 122.63; 128.33; 131.78; 132.74; 133.46; 135.48; 145.43; 146.26; 148.33; 150.80; 153.24; 154.34; 156.90; 160.04; 162.76; 165.49. FAB-MS: 827.3 (100, MH^+). HR-FAB-MS: 826.3274 (M^+, $C_{53}H_{42}N_6O_4^+$; calc. 826.3267).

Chiral Stationary Phase (CSP) ((*R*)-**16**). A mixture of γ-mercaptopropyl silica gel **17** [23] (4.5 g; C 5.14, H 1.32), (+)-(*R*)-**7** (2.0 g, 2.4 mmol), and 2,2'-azobis(2-methylpropionitrile) (AIBN; 200 mg, 1.2 mmol) was stirred in freshly distilled $CHCl_3$ (25 ml) for 20 h under reflux. After cooling to r.t., the suspension was centrifuged (5000 rpm) for 1 h. The modified silica gel was separated from the liquid and washed thoroughly with MeOH. Drying (4 h/0.05 Torr) afforded 5.5 g of CSP (*R*)-**16**. Anal. calc.: C 18.32, H 1.99, N 1.97, S 2.62. Loading density [25]: 0.25 mmol receptor/g silica gel **17**, based on C, *i.e.*, 47% of the employed receptor was attached. The rest could be recovered.

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