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Incremental development of chiral selectors for underivatized profens

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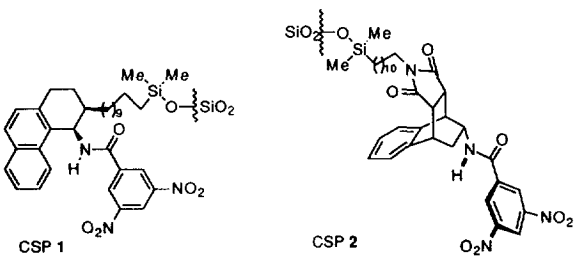
Abstract

Using a previously advanced mechanistic hypothesis, a conformationally rigid, [2.2.2]-bicyclooctane-based, selector intended to differentiate between the enantiomers of underivatized profens, an important group of non-steroidal anti-inflammatory drugs, was designed, synthesized, resolved, and immobilized on silica. The resulting chiral stationary phase effectively discriminates between the enantiomers of the various profens. The discriminating ability of this selector is ascribed to a 'preorganized' cleft which provides an active site in which but one enantiomer of a profen can undergo simultaneous hydrogen bonding, $\pi-\pi$ face-to-face stacking, and $\pi-\pi$ face-to-edge interaction while in a relatively low energy conformation. The multi-step synthesis of the racemic selector is relatively efficient and employs inexpensive starting materials. The racemic selector is easily resolved on a preparative chiral column derived from the diallyl amide of (*S*)-naproxen.

Keywords: Enantiomer separation; Chiral stationary phases, LC; Profens; Anti-inflammatory drugs, non-steroidal

1. Introduction

Several years ago, CSP **1** (Scheme 1), a rather broad spectrum brush-type chiral stationary phase, since commercialized, was developed from a mechanistic hypothesis entailing face-to-edge and face-to-face $\pi-\pi$ interactions acting in concert with a hydrogen bond [1,2]. These interactions occur in a cleft which serves as an 'active site' for chiral recognition. Similar clefts are to be found in selectors **2** and **3** (Scheme 2). The synthesis, resolution, and determination of absolute configuration of **2** has been reported, as has the evaluation of a CSP derived from this selector [3]. The ability of CSPs **1** and **2** to discriminate between many enantiomers is ascribed to the fact that the π-basic and π-acidic interaction sites are appended to a rigid bicyclo[2.2.2]octane framework so as to form the 'floor' and 'wall',



Scheme. 1.

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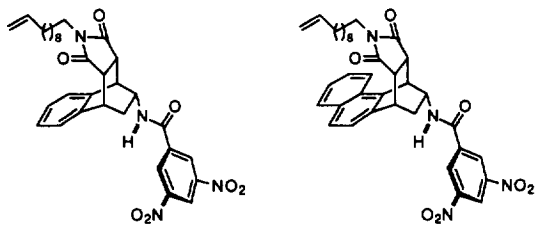


(1*R*, 2*R*, 4*S*, 9*R*, 10*S*)-(+)-**2** (1*S*, 3*R*, 4*R*, 11*S*, 12*R*)-(+)-**3**

Scheme. 2.

respectively, of a cleft. In this cleft, one enantiomer of a suitable analyte can more readily undergo simultaneous hydrogen bonding, face-to-face and face-to-edge $\pi-\pi$ interactions while in a low energy conformation. Because the naphthyl portion of **3** is a better π-base than the benzo portion of **2**, the former was expected to have a greater ability to differentiate between the enantiomers of suitable analytes. Usually, compounds having π-basic and hydrogen bond acceptor groups on or near a stereogenic center will be suitable analytes. In this paper, we describe the synthesis and resolution of **3** and report the preliminary evaluation of a CSP afforded by immobilizing one enantiomer of **3** on silica.

2. Experimental

2.1. General

All reagents used were of reagent grade. ^{1}H NMR spectra were recorded either on a Varian XL-200 or a Unity 400 NMR instrument. Chemical shifts are reported in ppm relative to internal standard tetramethylsilane. Elemental analyses were performed by T. McCarthy and associates of the University of Illinois microanalytical service. Chromatography was performed at room temperature using a Rainin HPX Rabbit pump, a Rheodyne Model 7125 injector with a 20-μl sample loop, a Milton Roy-LDC UV detector (254 nm), and a Shimadzu CR1A integrating recorder.

2.2. β-(Hydroxymethylene)-α-tetralone (5)

A mixture of 3.2 g of 60% sodium hydride dispersed in mineral oil (washed with hexane prior to use), 160 ml of anhydrous diethyl ether and 0.4 ml of ethanol was placed in a 500-ml three-necked round-bottom flask equipped with a stirrer and a dropping funnel. A solution of 11.6 g of tetralone-1 and 8.8 g of ethyl formate in 30 ml of anhydrous ethyl ether was added at 0°C under nitrogen over 30 min. Stirring was continued at room temperature for 6 h and the reaction mixture was then allowed to stand overnight. After the addition of 2 ml of ethanol, the mixture was stirred for 40 min, 20 ml of water was added and the mixture was extracted repeatedly with 1 *M* potassium carbonate solution. The aqueous layers were combined, acidified to pH<1 with 6 *M* HCl solution, and extracted with ether repeatedly. The combined organic layers were washed with water, brine, and dried over $MgSO_4$. Evaporation of the solvent gave 12.5 g of the crude product as a light brown oil. This oil was carried on directly to the next step without further purification.

2.3. 3-Keto-1,2,3,9,10,10a-hexahydrophenanthrene (6)

The 12.5 g of the crude β-(hydroxymethylene)-α-tetralone was mixed with 8.0 g of methyl vinyl ketone and cooled to 0°C. Twenty-five drops of triethylamine was added and the mixture was maintained at 0°C for 1 h, then allowed to stand at room temperature for three days. The reaction mixture was taken up in 200 ml of ether and washed repeatedly with 1 *M* potassium carbonate to remove any unreacted starting material. Evaporation of the solvent gave 16.5 g of a crude oily product, which was dissolved in 900 ml of 50% aqueous methanol containing 9.0 g of potassium hydroxide. This mixture was heated to reflux under nitrogen overnight. After cooling and dilution with water, the reaction mixture was extracted with ether. After evaporation of the ethereal extracts, the residue was crystallized from methanol to afford 12.4 g (79% from **4**) of **6** as a yellowish crystalline solid, mp 86–87°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (1H, d J=8.1 Hz), 7.33 (1H, dd, J=7.6 Hz, 7.3 Hz), 7.24 (1H, dd, J=8.1 Hz, 7.3 Hz), 7.19 (1H, d, J=7.6 Hz), 6.66 (1H, d, J=2.0 Hz), 3.04–2.89 (2H, m), 2.66 (1H, m), 2.07 (1H, m), 1.83 (1H, m), 1.62 (1H, m). Analysis: Calculated for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.79; H, 7.11.

2.4. 3-Hydroxyphenanthrene (7)

To a solution of 8.0 g of 3-keto-1,2,3,9,10,10a-hexahydrophenanthrene in 100 ml of α-methylnaphthalene was added 4.0 g of 5% palladium on carbon. This mixture was heated to reflux under nitrogen overnight, cooled, filtered to recover the catalyst, concentrated under reduced pressure, and chromatographed on a short silica gel column using first hexane then dichloromethane as eluent to afford 7.3 g of **7** (93% yield) as a light brown crystalline solid, mp 118–120°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.53 (1H, d, J=9.5 Hz), 8.03 (1H, d, J=2.6 Hz), 7.89–7.58 (6H, aromatic), 7.16 (1H, dd, J=8.6 Hz, 2.5 Hz), 5.21 (1H, s). Analysis: Calculated for $C_{14}H_{10}O$: C, 86.57; H, 5.19. Found: C, 86.52; H, 5.18.

2.5. 1,4-Ethano-3-oxo-1,2,3,4-tetrahydrophenanthrene-11,12-endo-dicarboxylic anhydride ((±)-8)

A mixture of 4.0 g of 3-hydroxyphenanthrene and 4.0 g of maleic anhydride was melted under nitrogen and transferred into a 15-ml PTFE bottle which was then filled with hexane. The bottle was capped, placed in a high-pressure reactor and maintained at 25 000 p.s.i. (1.72×10^8 Pa) at 200°C for 8 h. After cooling and depressurization, 3.8 g (63%) of (±)-**8** was isolated as a yellow solid by crystallization of the crude product from ethyl acetate, mp 293–295°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.03 (1H, d, J=8.9 Hz), 7.87 (2H, d, J=8.2 Hz), 7.61 (1H, dd, J=8.9 Hz, 8.3 Hz), 7.55 (1H, dd, J=8.3 Hz, 8.2 Hz), 7.42 (1H, d, J=8.2 Hz), 4.97 (1H, d, J=3.7 Hz), 4.19 (1H, m), 3.88 (1H, dd, J=9.1 Hz, 3.1 Hz), 3.76 (1H, dd, J=9.1 Hz, 3.2 Hz), 2.55 (1H, dd, J=17.1 Hz, 2.6 Hz), 2.41 (1H, dd, J=17.1 Hz, 3.6 Hz). Analysis: Calculated for $C_{18}H_{12}O$: C, 73.97; H, 4.14. Found: C, 73.99; H, 4.12.

2.6. 1,4-Ethano-3-oxo-1,2,3,4-tetrahydrophenanthrene-11,12-endo-ω-undecenylimide ((±)-9)

In a 250-ml round-bottomed flask equipped with a Dean–Stark trap and a condensor was added 8.0 g of (±)-**8** in 140 ml of anhydrous benzene, 5.3 g of ω-undecenylamine, and 3.1 g of triethylamine. The resulting mixture was heated to reflux for 5 h, diluted with ether, and washed with water and brine. Evaporation of the organic layer and crystallization of the residue from ethonal gave 8.8 g of (±)-**9** as a white solid. The mother liquid was chromatographed on a short silica gel column with ethyl acetate–hexane (1:1) to afford an additional 2.2 g of (±)-**9** for a total yield of 91%, mp 115–117°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.04 (1H, d, J=8.3 Hz), 7.81 (1H, d, J=6.4 Hz), 7.76 (1H, d, J=8.3 Hz), 7.57 (1H, dd, J=8.3 Hz, 7.2 Hz), 7.46 (1H, dd, J=7.2 Hz, 6.4 Hz), 7.37 (1H, d, J=8.3 Hz), 5.82 (1H, m), 5.06–4.90 (3H, m), 4.12 (1H, m), 3.53 (1H, dd, J=8.6 Hz, 3.7 Hz), 3.39 (1H, dd, J=8.6 Hz, 3.6 Hz), 2.96 (2H, m), 2.53 (1H, dd, J=18.7 Hz, 2.1 Hz), 2.41 (1H, dd, J=18.7 Hz, 3.1 Hz), 2.03 (2H, m), 1.38–1.06 (6H), 0.90–0.67 (4H), 0.46–0.35 (4H). Analysis: Calculated for $C_{29}H_{33}NO_3$: C, 78.52; H, 7.50; N, 3.16. Found: C, 78.57; H, 7.54; N, 3.17.

2.7. 1,4-Ethano-3-oximo-1,2,3,4-tetrahydrophenanthrene-11,12-endo-ω-undecenylimide ((±)-10)

A solution of 6.5 g of the keto imide, (±)-**9**, 1.2 g of hydroxylamine hydrochloride, and 1.5 g of sodium acetate in 175 ml of ethanol–water (4:1) was refluxed for 2 h. When cool, the reaction mixture was diluted with water and extracted repeatedly with ether. The combined organic layers were washed with water, brine, and dried over $MgSO_4$. Evaporation of the solvent gave 6.7 g of (±)-**10** as a white crystalline solid, mp 102–104°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.09 (1H, d, J=8.3 Hz), 7.78 (1H, d, J=8.4 Hz), 7.73 (1H, d, J=8.2 Hz), 7.55–7.44 (2H, aromatic), 7.34 (1H, d, J=8.3 Hz), 5.82 (1H, m), 5.16 (1H, d, J=3.5 Hz), 5.05–4.91 (2H, m), 4.04 (1H, m), 3.44 (1H, dd, J=8.8 Hz, 3.6 Hz), 3.24 (1H, dd, J=8.8 Hz, 3.2 Hz), 2.94 (2H, m), 2.78 (1H, dd, J=14.3 Hz, 2.2 Hz), 2.56 (1H, dd, J=14.3 Hz, 3.6 Hz), 2.03 (2H, m), 1.42–1.01 (6H), 0.95–0.62 (4H), 0.48–0.35 (4H).

2.8. 3-Amino-1,4-ethano-1,2,3,4-tetrahydrophenanthrene-11,12-endo-ω-undecenylimide ((±)-11)

To 6.7 g of (±)-**10** in 300 ml of methanol was added 3.2 g of molybdenium oxide and 5.6 g of

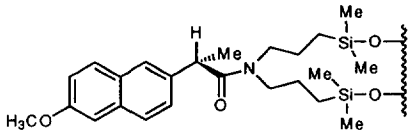
sodium borohydride with stirring at 0°C. The mixture was allowed to warm to room temperature, stirred overnight and 500 ml of 0.8 *M* sodium hydroxide was added. The solution was extracted several times with 50-ml portions of dichloromethane and the combined extracts were dried over $MgSO_4$, then concentrated at reduced pressure to afford 5.7 g of crude amine (±)-**11** which was carried on to the next step without further purification.

2.9. 3-Endo-(3,5-dinitrobenzamido)-1,4-ethano-1,2,3,4-tetrahydrophenanthrene-11,12-endo-ω-undecenylimide ((±)-3)

Crude racemic amine **11** from the previous reaction was dissolved in 100 ml of dichloromethane and 1.5 g of triethylamine and 2.9 g of 3,5-dinitrobenzoyl chloride in 10 ml of dichloromethane were added. The reaction was allowed to proceed at room temperature for 1 h. Flash chromatography of the mixture on silica with ethyl acetate–hexane (1:1) afforded 3.4 g (36% from **9**) of the desired product, (±)-**3**, as a yellow crystalline solid, mp 99–101°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.98 (1H, t, J=1.8 Hz), 8.39 (1H, d, J=1.8 Hz), 8.03 (1H, d, J=8.3 Hz), 7.81 (1H, d, J=8.4 Hz), 7.78 (1H, d, J=8.2 Hz), 7.57–7.41 (2H, aromatic), 7.38 (1H, d, J=8.3 Hz), 5.82 (1H, m), 5.48 (1H, amide proton, d, J=7.8 Hz), 5.05–4.91 (2H, m), 4.82 (2H), 3.89 (1H, m), 3.37 (1H, dd, J=9.0 Hz, 3.5 Hz), 3.18 (1H, dd, J=9.0 Hz, 3.2 Hz), 2.95 (2H, m), 2.62 (1H, m), 2.03 (2H, m), 1.50–1.01 (7H), 0.92–0.60 (4H), 0.48–0.35 (4H). Analysis: Calculated for $C_{36}H_{38}N_4O_7$: C, 67.71; H, 5.96; N, 8.78. Found: C, 67.75; H, 5.97; N, 8.75.

2.10. (1S,3R,4R,11S,12R)-(+)-3-Endo-(3,5-dinitrobenzamido)-1,4-ethano-1,2,3,4-tetrahydrophenanthrene-11,12-endo-ω-undecenylimide ((+)-3)

Resolution of racemic dinitrobenzamide **3** was achieved readily on a 900×25 mm preparative chiral stationary phase containing (*S*)-naproxen-derived CSP **12** (Scheme 3) [9] bonded to 40-μm irregular silica using 20% 2-propanol in hexane as a mobile phase. The second eluted enantiomer, (+)-**3**, assigned the (1*S*,3*R*,4*R*,11*S*,12*R*) absolute cconfiguration by a combination of HPLC and NMR methods, was used to prepare CSP **3**.



CSP 12

Scheme. 3.

2.11. (1S,3R,4R,11S,12R)-CSP 3

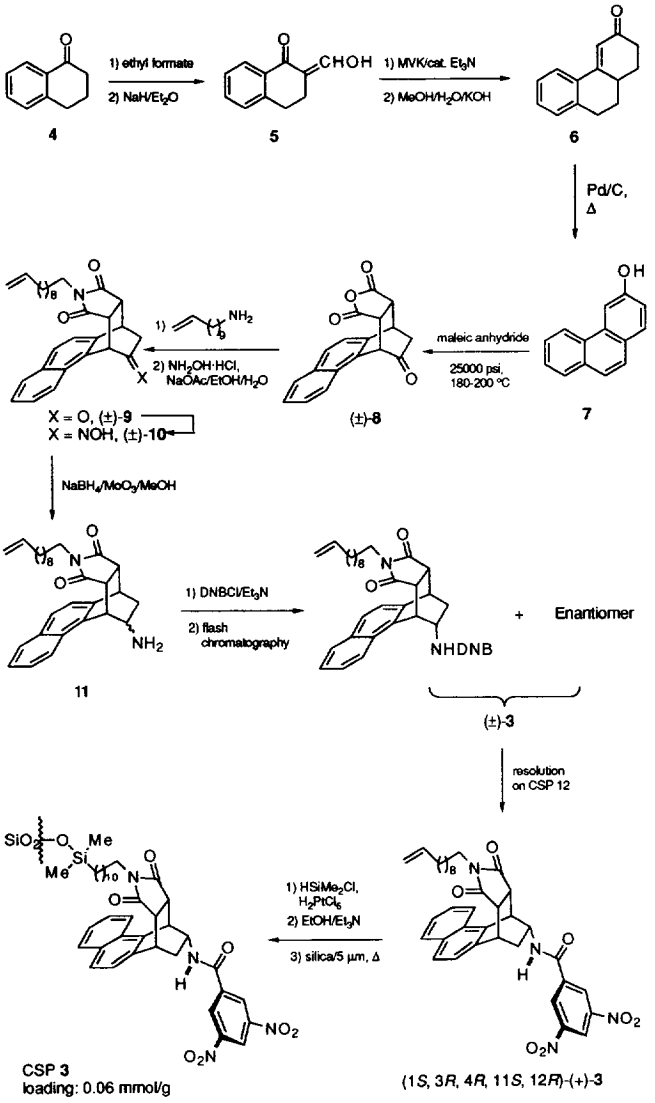
To a 50-ml round-bottomed flask containing 1.1 g of (+)-**3** in 15 ml of dry dichloromethane was added 15 ml of dimethylchlorosilane and 15 mg of chloroplatinic acid which had been dissolved in 40 μl of 2-propanol and diluted with 1 ml of dry dichloromethane. After the reaction mixture had been heated to reflux under N_2 for 2 h, the excess dimethylchlorosilane was evaporated under vacuum and similarly chased with three successive small portions of dichloromethane. A solution of 7 ml of absolute ethanol, 7 ml of triethylamine, and 7 ml of diethyl ether was added to the crude chlorosilane. The precipitated triethylamine hydrochloride was removed by filtration. Concentration of the filtrate and chromatography on a silica gel column using methylene chloride–acetonitrile (5:1) afforded 0.8 g of the corresponding ethoxyorganosilane as a pale yellow oil, which was carried on directly to the next step without further purification.

To 0.8 g of the organosilane in 8 ml of anhydrous tetrahydrofuran was added 4.0 g of previously dried 5-μm, 100-Å spherical silica. The resulting slurry was carefully evaporated to dryness using a rotary evaporator and then heated at 110°C at 1 Torr in a Kügelrohr apparatus for 28 h. The modified silica was washed thoroughly with methanol and slurry packed into a 250×4.6 mm stainless-steel column. From elemental analysis (C, 3.18; H, 0.53; N, 0.29), the surface coverage of the silica is 0.06 mmol/g. Residual silanol groups were endcapped by passing a solution of 2 ml of hexamethyldisilazane in 50 ml of dichloromethane through this column at a flow-rate of 1 ml/min after the column had been flushed with dichloromethane.

3. Results and discussion

3.1 Synthesis of CSP 3

3-Hydroxyphenanthrene was prepared using the reported procedure, which, as shown in Scheme 4, begins with condensation of α-tetralone, **4**, and ethyl formate [4] to give β-(hydroxymethylene)-α-tetralone, **5**. Subsequent Michael reaction with methyl vinyl ketone in the presence of catalytic amount of triethylamine [5] affords 3-keto-1,2,3,9,10,10a-hexahydrophenanthrene, **6**, in high yield upon treatment with base. Subsequent aromatization of **6** occurs smoothly with over palladium to afford 3-hydroxyphenanthrene, **7**, in excellent yield (93%). Diels–Alder addition of maleic anhydride to **7** proceeds under high pressure, affording the desired *endo*-keto anhydride, (±)-**8**, in 63% yield. Transformation of keto anhydride (±)-**8** to keto imide (±)-**9** occurs on heating with 10-undecenylamine. Reductive amination via oxime (±)-**10** [6] and acylation of the resulting mixture of epimeric amines, (±)-**11**, with



Scheme. 4.

3,5-dinitrobenzoyl chloride affords a mixture of the corresponding 3,5-dinitrobenzamides. Chromatography on silica affords the desired epimer, (±)-**3**, the racemic selector. Resolution of racemic **3** is easily accomplished using a preparative column containing a CSP derived from the diallyl amide of (*S*)-naproxen. The more retained enantiomer, (+)-**3**, is assigned the (1*S*, 3*R*, 4*R*, 11*S*, 12*R*) absolute configuration based on the correspondence of its sign of optical rotation and its elution order from several different CSPs with those of the rigorously assigned benzo analog [3]. After characterization, (+)-**3** was hydrosilylated with dimethylchlorosilane, converted to the corresponding ethoxysilane for purposes of purification and characterization, then immobilized on 5-μm, 100-Å silica gel particles. These were slurry packed into a 250×4.6 mm stainless-steel column by conventional techniques to afford CSP **3**. Elemental analysis of the modified silica indicates a surface coverage of 0.06 mmol/g, a lower coverage than is normally achieved. This is attributed to the size and rigidity of the selector.

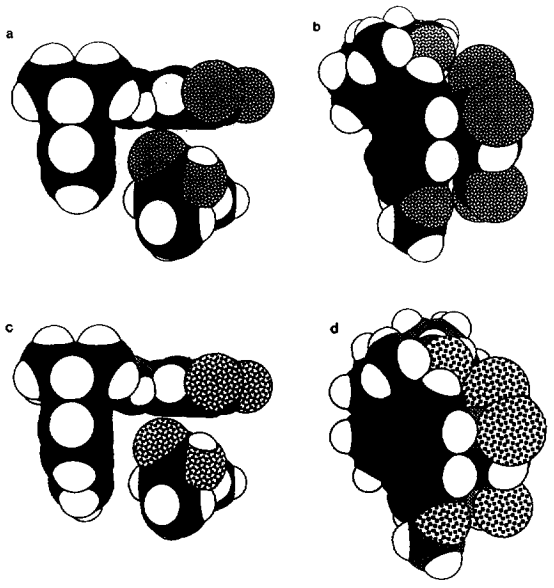


Fig. 1. Computer-generated CPK molecular representations of the more stable diastereomeric complex of **2** (a and b) or **3** (c and d) with the (*R*)-enantiomer of naproxen. The distance between the selector and naproxen is exaggerated for clarity.

3.2. Evaluation of CSP 3

In previous papers, the efficacy of CSPs **1** and **2** was attributed to the presence of preorganized clefts in which enantiodiscrimination occurs. Shown in Fig. 1 are computer-generated CPK molecular representations of how the (*R*)-enantiomer of naproxen is expected to fit into the clefts of **2** (a and b in Fig. 1) and **3** (c and d in Fig. 1) to form the more stable of the possible diastereomeric complexes.

Three simultaneous bonding interactions are proposed: a hydrogen bond between the carboxyl group of naproxen and the dinitrobenzoyl amide proton, a $\pi-\pi$ face-to-face interaction between the naphthyl ring of naproxen and the dinitrobenzoyl ring, and a $\pi-\pi$ face-to-edge interaction between the edge of the naphthyl group of naproxen and the face of the π-basic group (the benzo group in the case of **1**). Since a more efficacious π-basic aryl substituent should strengthen this latter interaction, CSP **3** was expected to show greater enantioselectivity towards the profens than its predecessor, CSP **2**.

Direct comparison of the chiral recognition abilities of the selectors used in CSPs **1**–**3** is complicated by the fact that the bulk of the latter selectors has thus far prevented the attainment of surface coverages comparable to those attainable with selector **1**. In the case of selector **1**, enantioselectivity increases with surface coverage (at least up to 0.25 mmol/g). Surface coverages of 0.12 and 0.06 mmol/g were attained for CSPs **2** and **3**, respectively. As an approximate comparison of the innate chiral recognition abilities of the three selectors, data obtained [3] from chromatographing a series of underivatized profens on the aforementioned CSP **2** column and on a low surface coverage (0.11 mmol/g) version of CSP **1** is presented in Table 1 along with similar data obtained from the present CSP **3** column and from a commercial Whelko-1 column having a higher surface coverage and a trimethylene tether. All columns utilize the same 5-μm, 100-Å spherical silica support, and the same mobile phase (20% 2-propanol in hexane containing 1 g/l of ammonium acetate) was used in all cases. Generally, lower surface coverage reduces

Table 1
Comparison of the separation of the enantiomers of underivatized profens on CSP **1**, CSP **2**, CSP **3** and the Whelko-1

Profens	CSP **1**[a]		CSP **2**[b]		CSP **3**		Whelko-1[c]	
	k_1'	α	k_1'	α	k_1'	α	k_1'	α
Naproxen	1.99	1.51	1.80	2.00	1.00	3.81	5.39	3.91
Ibuprofen	0.45	1.00	0.23	1.00	0.10	1.36	0.69	1.54
Carprofen	4.93	1.25	2.99	1.80	1.40	2.02	5.58	2.37
Cicloprofen	1.95	1.41	1.39	1.40	1.15	1.80	3.70	2.18
Pirprofen	1.38	1.23	0.95	1.40	0.20	1.60	2.80	2.07
Ketoprofen	2.06	1.08	1.40	1.19	0.81	1.34	4.62	1.40
Fenoprofen	0.53	1.15	0.55	1.25	0.23	1.65	1.29	1.84

Mobile phase: 20% 2-propanol in hexane with 1 g/l of NH_4OAc; flow-rate: 2.00 ml/min; k_1': capacity factor for the first eluted enantiomer; α: separation factor.
[a]This version of CSP **1** has a surface coverage of 0.11 mmol/g and shows less enantioselectivity than versions of higher surface coverage.
[b]The surface coverage for CSP **2** is 0.12 mmol/g.
[c]The Whelko-1 is a commercial version of CSP **1** having greater surface coverage and a short tether.

enantioselectivity due to the greater number of residual silanols on the surface of the silica [7,8]. Endcapping reduces but does not eliminate the effects of these silanol groups.

Despite its lower surface coverage, CSP **3** shows greater enantioselectivity for the profens than does CSP **1** or CSP **2**. For example, separation factors of 3.81 and 1.36 are observed for the enantiomers of naproxen and ibuprofen, respectively, whereas no enantioseparations of ibuprofen are seen on CSP **1** or CSP **2** *under these conditions*. These results suggest that selector **3** does indeed have greater innate chiral recognition ability than selector **2** and, possibly, selector **1** as well. When these racemic selectors are chromatographed on a naproxen-derived CSP, the enantiomers of **3** show the largest separation factor, those of **2** show the smallest. Even so, the present CSP **3** column does not equal the performance of the Whelko-1, a commercial version of CSP **1**. One might hope that the enantioselectivity of future CSPs derived from selector **3** could be improved by increasing the surface coverage or by using a different method of immobilizing the selector. For example, higher enantioselectivity is achieved when selector **2** is tethered to a polydimethylhydrosiloxane backbone which is immobilized on silica. This approach possibly could overcome the steric difficulties encountered in attempts to produce a brush-type CSP from bulky selector **3**. Such work is underway.

4. Conclusion

It has been demonstrated that a cleft having an electron-deficient aromatic group as a 'wall' and an electron-rich aromatic group as a 'floor' can serve as an 'active site' for the discrimination of profen enantiomers. Once the fundamentals of a chiral recognition process are understood, one has a rational basis for modifying the structure in ways fully expected to enhance enantioselectivity. Although the full potential of the chiral selector used in CSP **3** has not yet been fully realized, it is evident that this conformationally rigid selector deserves further investigation in terms of its mode of immobilization.

Acknowledgments

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