Design, Synthesis, Resolution, Determination of Absolute Configuration, and Evaluation of a Chiral Naproxen Selector

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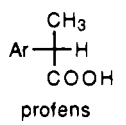
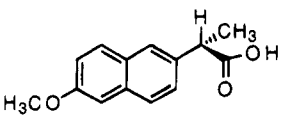
A rigid chiral selector intended to differentiate between the enantiomers of α-arylpropionic acids (profens) has been designed and synthesized. The π-acidic, hydrogen bond donor, and π-basic interaction sites deemed essential to chiral recognition are supported on a [2.2.2]bicyclooctane framework to form a cleft-like "active site" in which enantiodiscrimination occurs. The racemic selector has been resolved chromatographically and the absolute configurations of the enantiomers have been established by a combination of HPLC and NMR methods. Immobilized on silica, this selector affords a chiral stationary phase which shows appreciable levels of enantioselectivity toward the profens, members of an important group of nonsteroidal antiinflammatory drugs. Immobilization has been accomplished in two ways. The selector has been hydrosilylated with either dimethylchlorosilane or with polymethylhydrosiloxane. The former leads to a brush-type CSP whereas the latter leads to a polymeric CSP coated and bonded to the silica support. The polysiloxane-based phase exhibits higher enantioselectivity and shorter retention times than does its brush-type counterpart. A mechanistic hypothesis advanced to account for the enantiodiscrimination observed suggests that relatively simple changes in the structure of the selector might further improve its enantioselectivity.

Introduction

α-Arylpropionic acids (profens), an important group of nonsteroidal antiinflammatory drugs, show stereoselective activity and disposition. (*S*)-Naproxen, used for the treatment of arthritis, is the fifth largest selling drug in the world. Consequently, considerable effort has been devoted to improving methods for its asymmetric synthesis and resolution.



profens



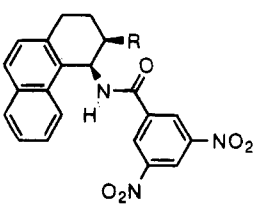
(*S*)-naproxen

We recently described a synthetic chiral selector for naproxen which, when bonded to silica, affords a chiral stationary phase (CSP) capable of separating the enantiomers of profens and a wide range of other compounds as well.[1] The success of this CSP is attributed to the presence of a cleft in which the interactions necessary for chiral recognition occur. Such clefts can be incorporated into other molecular frameworks, one of which is now described.

Results and Discussion

Initially, (*S*)-naproxen, immobilized on silica, was used to evaluate candidates for potential naproxen selectors. Understanding so gained aided in the design of selector **1** used in **CSP 1**. By using this CSP, the effect of analyte structure on enantioselectivity and elution order was systematically studied. The resulting insight into the nature of the available chiral recognition processes suggests structures for other potential useful selectors, some of which have rather rigid structures.

Rigidity can improve the enantioselectivity of a chiral selector if the functional groups essential to chiral recognition are spatially organized so as to allow simultaneous interaction with but one analyte enantiomer. To incorporate greater conformational rigidity into a selector mechanistically similar to **1**, a π-basic substituent and a π-acidic 3,5-dinitrobenzamide substituent have been appended to a bicyclo[2.2.2]octane framework so as to form the cleft-like "active site". A structure such as that of **2** seems, from the use of CPK models, to provide the perpendicular orientation of the π-basic and the π-acidic substituents deemed desirable on the basis of our chiral recognition rationale (Figure 1). The π-acidic substituent, by undergoing a face-to-face π–π interaction with the profen aromatic substituent, causes the latter to present its edge to the face of the selector's π-basic substituent. The resulting face-to-edge π–π interaction and a hydrogen bond between the dinitrobenzamide N–H and the profen's carboxyl group are thought to provide three noncovalent bonding interactions between the selector and the more retained enantiomer of a profen. The results of ^{1}H NMR chemical shift studies as well as a series of ^{1}H{^{1}H} nuclear Overhauser experiments on the 1:1 diastereomeric complexes formed from the enantiomers of a naproxen-derived amide and a chiral selector of this type are consistent with this chiral recognition hypothesis. Accounts of these studies will be reported elsewhere. Emboldened by these results, we undertook the synthesis of a rigid selector expected to be mechanistically similar to selector **1**.



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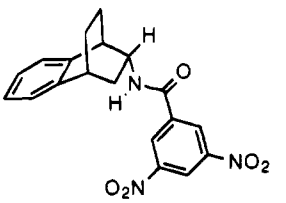

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® Abstract published in *Advance ACS Abstracts,* October 15, 1994.

(1) (a) Pirkle, W. H.; Welch, C. J.; Lamm, B. *J. Org. Chem.* **1992**, *57*, 3854–3860. (b) Pirkle, W. H.; Welch, C. J. *J. Liquid Chromatogr.* **1992**, *15*, 1947–1955.

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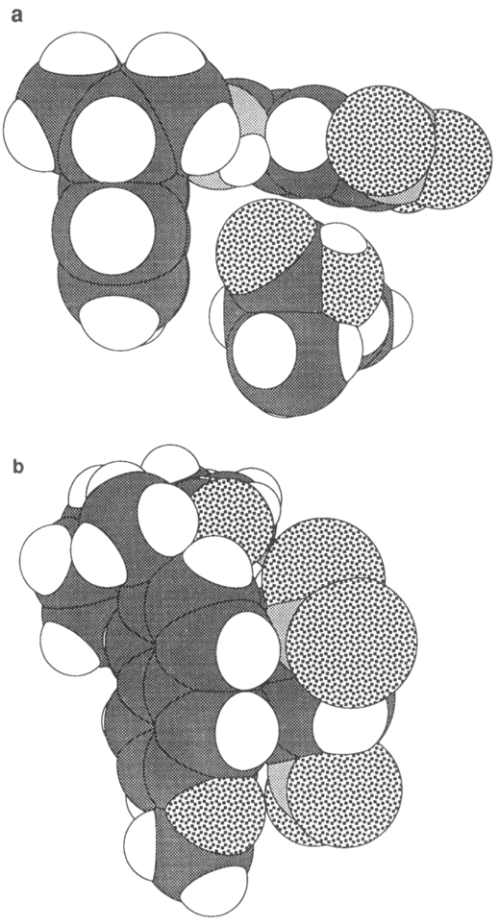


Figure 1. Two views from different perspectives of how the more retained (*R*)-enantiomer of naproxen is thought to fit into the cleft of the selector used in **CSP 2**. Three simultaneous noncovalent bonding interactions: (i) a hydrogen bond; (ii) a face-to-face $\pi-\pi$ interaction; (iii) a face-to-edge $\pi-\pi$ interaction, are thought to be present in this complex.

In designing a chiral selector, one should not incorporate any structural elements which can afford attractive interactions with the analytes except those which are essential to the chiral recognition process. This improves enantioselectivity by eliminating those interactions which retain but do not distinguish between the analyte enantiomers. To understand this point, one should be aware that the enantioselectivity, expressed as the separation factor (α), is determined by the weighted time-average of the energetic consequences of all interactions that the analyte enantiomers experience during chromatography. Interactions which retain but do not differentiate between enantiomers reduce the magnitude of the observed separation factor. To expedite the preparation of the rigid prototype, we knowingly ignored this precept. The imide functionality employed in the tether of **CSP 2** was used for convenience and is, in all likelihood, unnecessary for the chiral recognition process. It may, however, serve to impede the approach of an analyte to the *exo*-face (with respect to the DNB system) of the π-basic aromatic substituent, a desirable feature.

Synthesis. The selector for **CSP 2** can be prepared from inexpensive commercial reagents as shown in Scheme 1. Diels–Alder addition of maleic anhydride to β-naphthol, reaction of the resulting keto anhydride[2] with an alkenyl amine to afford the keto imide, reductive amination of the ketone,[3] and acylation of the resulting amine with 3,5-dinitrobenzoyl chloride affords the racemic precursor of **CSP 2**. After purification, the precursor was resolved chromatographically using a preparative naproxen-derived CSP. The terminal double bond was hydrosilylated with dimethylchlorosilane to enable the chiral selector to be immobilized on 5 μm silica gel particles. These were slurry-packed into a 4.6 × 250 mm stainless steel column by conventional techniques. Elemental analysis indicates the surface coverage of the silica to be 0.12 mmol/g, somewhat lower than that usually achieved. Typically, low surface coverages reduce enantioselectivity owing to the presence of residual silanol groups. These increase the retention of the analyte enantiomers without differentiating between them.[4] Endcapping with hexamethyldisilazane alleviates but does not eliminate this effect.

Evaluation. The column containing **CSP 2** was used to chromatograph a series of profens using 20% 2-propanol in hexane containing 1 g/L of ammonium acetate as a mobile phase. These data appear in Table 1 along with similar data obtained using a column containing **CSP 1** having a surface coverage (0.11 mmol/g) similar to that of **CSP 2**. It is known that higher surface coverages increase the enantioselectivity of **CSP 1**.[1] Higher surface coverages reduce the number of residual silanol groups. As demonstrated previously,[5,6] residual silanol groups appear to be masked when the chiral selector is incorporated into a polysiloxane coated onto the silica surface.[5] Following a procedure previously reported from these laboratories,[6] **CSP 3**, a polysiloxane variation of **CSP 2**, was prepared by incorporating the chiral selector, (+)-**11**, into polymethylhydrosiloxane. The resulting chiral polysiloxane was then coated and immobilized on 5 μm/300 Å silica. This material was packed into a 4.6 × 250 mm column and endcapped and its performance compared to that of **CSP 2** using identical chromatographic conditions for both.

Inspection of Table 1 reveals that, at similar surface coverages, **CSP 2** shows enantioselectivity equal to or exceeding that shown by **CSP 1**. Polysiloxane-based **CSP 3**, when compared to its brush-type counterpart, **CSP 2**, demonstrates reduced retention and increased enantioselectivitiy in every case. The reduced retention is to be expected owing to the reduced surface area of the large pore silica although this may not be the only factor involved. In one sense, the ability of **CSP 2** and **CSP 3** to equal or exceed the enantioselectivity of **CSP 1** is encouraging, for the rigid selector has polar functionality which may be deleterious to the chiral recognition process. Although the imide functionality serves as a convenient means of tethering the selector to silica, it may also serve as a site at which nonenantiodiscriminating interactions occur with the analyte, thus reducing enantioselectivity.[4b] Moreover, **CSP 2** has a π-basic site inferior to that of **CSP 1**. Hence, one must conclude that the conformational rigidity of the [2.2.2]bicyclooctane framework is beneficial for enantiodiscrimination of profens. It is expected that enantioselectivity can be

(2) Cookson, R. C.; Wariyar, N. S. *J. Chem. Soc.* **1956**, 2302–2311.

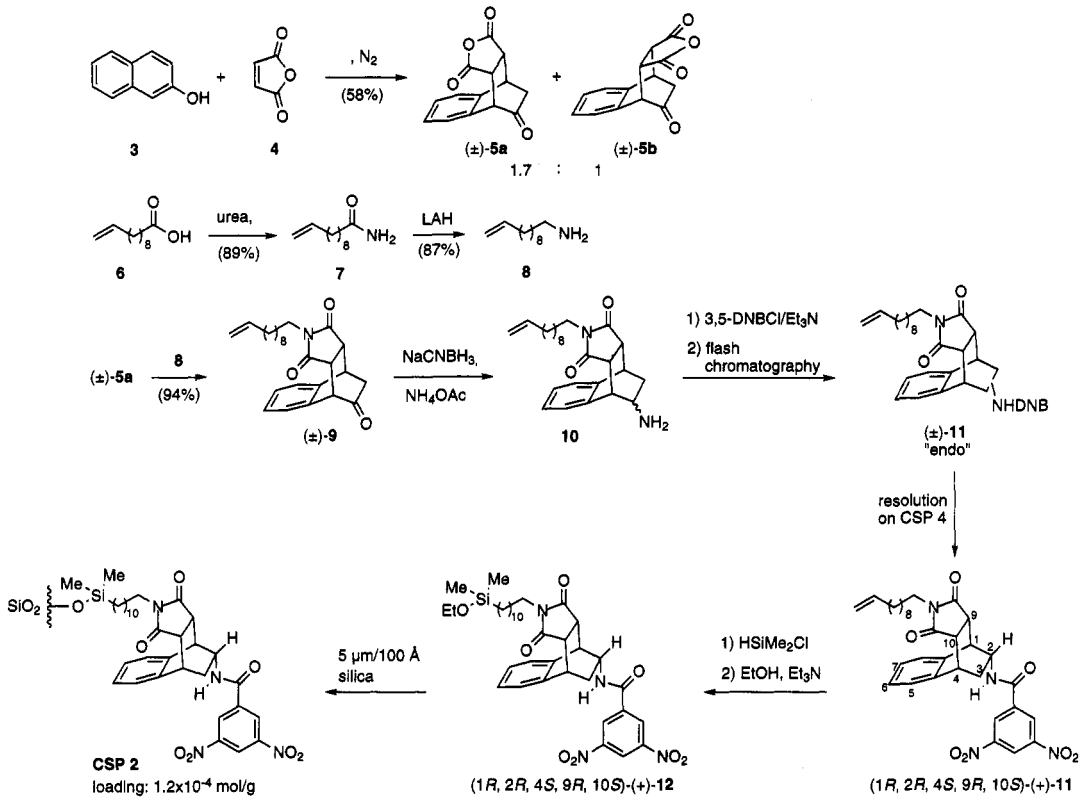
(3) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.

(4) (a) Pirkle, W. H.; Readnour, R. S. *Chromatographia* **1991**, *31*, 129–132. (b) Pirkle, W. H.; Welch, C. J. *J. Chromatogr.* **1992**, *584*, 45–51.

(5) Röder, W.; Ruffing, F.-J.; Schomburg, G.; Pirkle, W. H. *HRC & CC, J. High Resolut. Chromatogr. Chromatogr. Commun.* **1987**, *10*, 665–667.

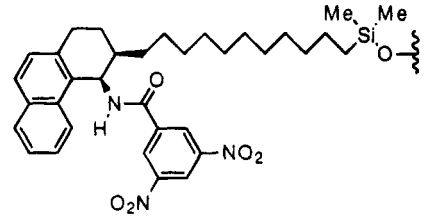
(6) Schleimer, M.; Pirkle, W. H.; Schurig, V. *J. Chromatogr.*, in press.

Scheme 1



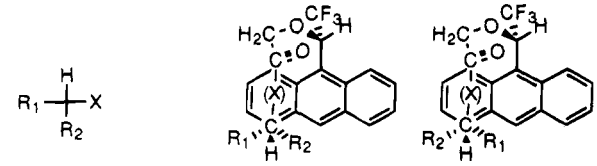
improved by relatively simple changes in the structure of this type of selector. For example, the use of a tether without superfluous polar functionality and/or the use

CSP 1:



of a more efficacious π-basic aryl substituent would be expected to afford greater enantioselectivity.

Determination of Absolute Configuration. Although the chiral recognition rationale can be used to relate the absolute configurations of the enantiomers of selector **2** to their elution orders from an (*S*)-naproxen-derived CSP, an assignment made on this basis would not be universally accepted. Accordingly, an NMR method employing (*S*)-α-[1-(9-anthryl)-2,2,2-trifluoroethoxy]acetyl chloride (ATEA) as a chiral derivatizing agent

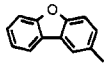
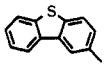
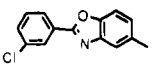


(CDA) was used. Diastereoisomers derived from this CDA and chiral primary amines, secondary alcohols, or thiols are known to have differences in their NMR spectra which can be related to stereochemistry.[7] For example, the signals arising from the protons in the R_1 group of diastereomer **14A** will occur downfield of the corresponding protons in diastereomer **14B** owing to the greater shielding effect of the anthryl group in **14B**. Conversely, the signals arising from the R_2 group in **14A** will occur upfield of those in the R_2 group of diastereomer **14B**. This CDA has been applied similarly for the determination of the absolute configuration of the selector used in **CSP 1**.[8]

Treatment of racemic *endo*-amine **10** (obtained by hydrolysis of racemic dinitrobenzamide **11**) with the CDA affords a 1:1 mixture of the diastereomeric amides shown in Scheme 2. The NMR signals arising from protons H_1 to H_4, H_9, and H_{10} were unambiguously assigned from multiplicities, coupling constants, and decoupling experiments for both diastereomers and for dinitrobenzamide **11**. The chemical shift differences noted between the various sets of diastereotopic protons are greatest for those protons at positions 1 and 3 since these positions flank position 2, the point of attachment of the CDA (see Table 2). Because H_1, H_{3a}, and H_{3b} are nearer the anthryl system, their chemical shifts are more influenced by their *syn* versus *anti* positions relative to the anthryl group than are those of the more distant H_4, H_9, or H_{10}. H_2, being in essentially the same position relative to the anthryl group in both diastereomers, is not expected to show much dependence of its chemical shift on stereochemistry nor does it. Hydrolysis of a portion of (+)-**11**, the enantiomer most retained on the (*S*)-naproxen-derived CSP, affords a single enantiomer of *endo*-amine **10**. Treatment of this amine with the CDA affords a single diastereomer which, when spiked into the mixture of

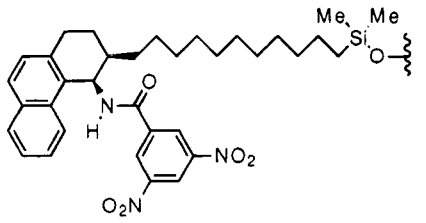
(7) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1981**, *46*, 3239–3246.
(8) Pirkle, W. H.; Welch, C. J. *Chirality*, in press.

Table 1. Enantioselective Separation of Underivatized Profens (mobile phase: 20% 2-propanol in hexane with 1 g/L of NH_4OAc; flow rate: 2.00 mL/min)

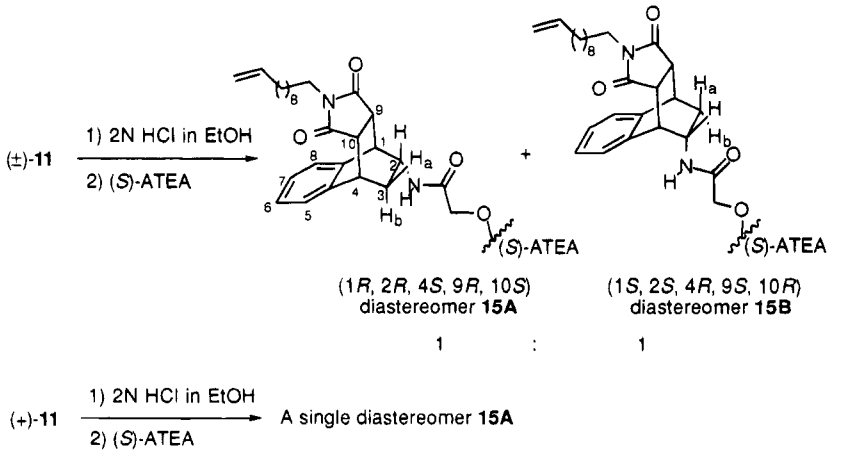
$ArCHCOOH$ (Profens:)	CSP 1[a]			CSP 2			CSP 3		
	k_1'	k_2'	α	k_1'	k_2'	α	k_1'	k_2'	α
Naproxen	1.99	3.00	1.51	1.80	3.60	2.00	1.29	3.30	2.56
Carprofen	4.93	6.15	1.25	2.99	5.39	1.80	1.83	3.88	2.12
Cicloprofen	1.95	2.75	1.41	1.39	1.95	1.40	0.92	1.57	1.71
Ketoprofen	2.06	2.81	1.08	1.40	1.67	1.19	1.20	1.68	1.40
Fenoprofen	0.53	0.61	1.15	0.55	0.69	1.25	0.33	0.55	1.67
Pirprofen	1.38	1.70	1.23	0.95	1.33	1.40	0.78	1.47	1.89
	1.51	2.15	1.42	1.04	1.69	1.63	0.80	1.78	2.23
	2.20	3.37	1.53	1.53	3.12	2.04	1.10	3.07	2.79
	2.80	3.33	1.19	1.09	1.36	1.25	0.87	1.31	1.51
Ibuprofen	0.45	0.45	1.00[b]	0.23	0.23	1.00	0.16	0.22	1.38

[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]Values as high as 1.45 have been observed on the WHELKO I, a commercial version of CSP 1 having greater surface coverage and a short tether.[1b]

CSP 1:



Scheme 2



diastereomeric derivatives, enhances the signals of the diastereomer that has its H_1 and H_9 signals downfield and its H_{3a}, H_{3b}, H_4, and H_{10} signals upfield of those of its diastereomeric counterpart. This indicates that (+)-**11** leads to **15A**. Hence, **CSP 2** has the 1*R*,2*R*,4*S*,9*R*,-10*S* configuration as expected from the observed elution orders and the mechanistic argument.

Experimental Section

All reagents used were of reagent grade. All ^1H NMR spectra were recorded on a 200 MHz NMR instrument. Chemical shifts were reported in ppm relative to internal tetramethylsilane. Elemental analyses were performed by the University of Illinois microanalytical service. Chromatography was performed at room temperature using a Rainin HPX

Table 2. ^{1}H NMR Diastereotopic Nonequivalences for the (*S*)-ATEA Derivatives

	observed nonequivalences for **15**, $\Delta\delta$ (ppm)	observed chemical shifts, $\Delta\delta$ (ppm)	
		15A	**15B**
R_1: H_1	+0.21	3.65	3.44
H_9	+0.03	3.14	3.11
R_2: H_{3a}	−0.21	2.28	2.49
H_{3b}	−0.43	0.83	1.26
H_4	−0.08	3.53	3.61
H_{10}	−0.03	2.96	2.99

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.

1,4-Ethano-2-oxo-1,2,3,4-tetrahydronaphthalene-9,10-*endo*-dicarboxylic Anhydride (5a). A modified literature procedure[2] was used to prepare **5a**. To a 100 mL three-neck round-bottom flask, equipped with a thermometer and a magnetic stirrer, was added 10.0 g of 2-hydroxynaphthalene and 7.5 g of maleic anhydride. After the mixture was melted and stirred under N_2 at 195−200 °C for 40 min, 40 mL of ethyl acetate was carefully added to the cooled reaction mixture. On standing overnight, 9.7 g (58%) of *endo* and *exo* adducts in a ratio of 1.7:1 crystallized from solution. Six grams (36%) of *endo*-isomer **5a** was isolated as a white crystalline solid by fractional crystallization of the mixed isomers from ethyl acetate, mp 195−196 °C.

ω-Undecenamide (7).[9] A literature procedure[10] was followed for the preparation of **6**.

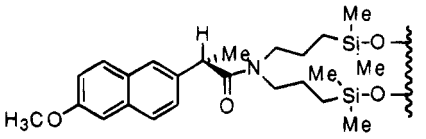
ω-Undecenylamine (8).[11] Into a 500 mL round-bottom flask containing 100 mL of anhydrous tetrahydrofuran (THF) was placed 4.6 g of lithium aluminum hydride (LAH). The resulting suspension was heated at reflux for 30 min under N_2. Heating was stopped and 10.0 g of undecenamide (**7**) in 200 mL of anhydrous THF was introduced with stirring at such a rate that the reaction mixture was maintained at gentle reflux. Reflux was continued under nitrogen with stirring for an additional 24 h. The reaction was then quenched by dropwise addition of 16 mL of water to destroy the excess LAH. The resulting white precipitate was removed by filtration and washed with three 30 mL portions of ethyl acetate. After the combined organic phases were dried over anhydrous Na_2SO_4, evaporation of the solvent followed by vacuum distillation (80−82 °C at 0.06 torr) gave 8.1 g (87%) of **8** as a colorless oil.

1,4-Ethano-2-oxo-*N*-ω-undecenyl-1,2,3,4-tetrahydronaphthalene-9,10-*endo*-dicarboximide (9). To a 250 mL round-bottom flask, equipped with a condenser and a Dean−Stark trap, was added 5.5 g of keto anhydride **5a** in 60 mL of anhydrous benzene, 4.1 g (1.05 equiv) of undecenylamine (**8**) and 2.3 g (1 equiv) of triethylamine. The resulting mixture was allowed to reflux for 4 h. Rotary evaporation of the solvent left an oily crude product which was purified by flash chromatography on silica gel with ethyl acetate/dichloromethane (1:4) to yield 8.5 g (94%) of **9** as a white crystalline solid, mp 75−76 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.36−7.18 (4H, aromatic), 5.80 (1H, m), 5.02 (1H, m), 4.92 (1H), 4.10 (1H, d, J = 2.8 Hz), 3.94 (1H, m), 3.59 (1H, dd, J = 9.3 Hz, 4.1 Hz), 3.27 (1H, dd, J = 9.3 Hz, 4.4 Hz), 3.08 (2H, m), 2.46 (1H, dd, J = 17.1 Hz, 3.4 Hz), 2.31 (1H, dd, J = 17.1 Hz, 3.9 Hz), 2.01 (2H, m), 1.52−0.92 (10H), 0.80 (4H). Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.33; H, 7.89; N, 3.56. Found: C, 76.42; H, 7.91; N, 3.52.

1,4-Ethano-2-amino-*N*-ω-undecenyl-1,2,3,4-tetrahydronaphthalene-9,10-*endo*-dicarboximide (10). To a round-bottom flask was added 5.0 g of keto imide **9** in 100 mL of anhydrous methanol, 3.2 g of sodium cyanoborohydride, and 9.8 g of ammonium acetate. The mixture was heated to reflux under nitrogen with stirring for 48 h. After the mixture was cooled, it was made basic with 2 N potassium hydroxide solution and the methanol was removed under reduced pressure. Diethyl ether was added and the ether layer was collected, washed with water, and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent afforded 4.5 g of crude amine which was carried on to the next step without further purification. The aqueous layer was treated with Chlorox and allowed to stand 24 h to destroy residual cyanide before disposal.

1,4-Ethano-2-*endo*-(3,5-dinitrobenzamido)-*N*-ω-undecenyl-1,2,3,4-tetrahydronaphthalene-9,10-*endo*-dicarboximide [(±)-11)]. After the crude amine **10** from the previous reaction was dissolved in 50 mL of dichloromethane, 4.6 g of triethylamine and 3.7 g of 3,5-dinitrobenzoyl chloride in 10 mL of dichloromethane were added. After 2 h at room temperature, the reaction mixture was washed with water and brine. The organic layer was dried and evaporated to afford a mixture of racemic *endo*- and *exo*-dinitrobenzamide diastereomers in about a 1:1 ratio. Separation of the diastereomers by flash chromatography on silica using 1:1 ethyl acetate/hexane gave 1.9 g (25% from **9**) of *endo* (±)-**11** as pale yellow solid, mp 85−86 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.07 (1H, t, J = 1.6 Hz), 8.72 (2H, d, J = 1.6 Hz), 7.32−7.16 (4H, m), 6.06 (1H, amide NH, d, J = 9.6 Hz), 5.80 (1H, m), 5.00 (1H), 4.90 (1H), 4.70 (1H, m), 3.80 (1H, m), 3.69 (1H, m), 3.25 (1H, dd, J = 9.3 Hz, 4.4 Hz), 3.08 (1H, dd, J = 9.3 Hz, 4.4 Hz), 3.01 (2H, m), 2.60 (1H, m), 2.02 (2H, m), 0.90−1.63 (11H), 0.73 (4H). Anal. Calcd for $C_{32}H_{36}N_4O_7$: C, 65.28; H, 6.18; N, 9.52. Found: C, 65.31; H, 6.19; N, 9.51.

(1*R*,2*R*,4*S*,9*R*,10*S*)-(+)-1,4-Ethano-2-*endo*-(3,5-dinitrobenzamido)-*N*-ω-undecenyl-1,2,3,4-tetrahydronaphthalene-9,10-*endo*-dicarboximide [(+)-11]. Racemic dinitrobenzamide **11** was resolved on a 25 × 900 mm preparative chiral column containing (*S*)-naproxen-derived **CSP 4**[12] using 10%



CSP 4

2-propanol in hexane as a mobile phase. The second eluted enantiomer, (+)-**11**, determined by analytical HPLC on **CSP 4** to be of 99+% ee {mp 90−91 °C, $[\alpha]^{25}_D$ = 128.4° (10 mg/mL in THF)}, and to have the (1*R*,2*R*,4*S*,9*R*,10*S*) absolute configuration, was used to prepare **CSP 2**.

(1*R*,2*R*,4*S*,9*R*,10*S*)-(+)-Ethoxyorganosilane (12). To a 50 mL round-bottom flask containing 1.6 g of (+)-**11** in 15 mL of dry dichloromethane were added 15 mL of dimethylchlorosilane and 5.6 mg of chloroplatinic acid which had been dissolved in 20 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 3 h, and the excess dimethylchlorosilane was evaporated under vacuum and successively chased with three small portions of dichloromethane. A solution of 7 mL of absolute ethanol, 7 mL of triethylamine, and 7 mL of diethyl ether was then added to the crude chlorosilane and, after 5 min, the precipitated triethylamine hydrochloride was removed by filtration. Concentration of the filtrate and chromatography on a silica gel column using 5:1 methylene chloride/acetonitrile afforded 1.4 g of (+)-**12** as a pale yellow oil in 75% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.08 (1H, t, J = 1.6 Hz), 8.71 (2H, d, J = 1.6 Hz), 7.34−7.17 (4H, m), 5.81 (1H, amide NH, d, J = 9.3 Hz), 4.70 (1H, m), 3.80 (1H, dd, J = 4.3 Hz, 3.9 Hz), 3.69 (1H, m), 3.64 (2H, quart, J = 7.1 Hz), 3.25 (1H, dd, J = 9.3 Hz, 4.4 Hz), 3.09 (1H, dd, J = 9.3 Hz, 4.3 Hz), 3.06 (2H, m), 2.60 (1H, ddd, J = 15.1 Hz, 10.4 Hz, 2.6 Hz), 1.41 (1H, ddd, J = 15.1 Hz, 4.2 Hz, 2.9 Hz), 1.32−0.92 (14H), 0.74 (4H), 0.59 (2H, t, J = 7.1 Hz), 0.08 (6H, s). Anal. Calcd for $C_{36}H_{48}N_4O_8Si$: C, 62.43; H, 6.94; N, 8.09. Found: C, 62.60; H, 7.08; N, 8.07.

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(1*R*,2*R*,4*S*, 9*R*,10*S*)-CSP 2. To 1.4 g of (+)-**12** in 8 mL of anhydrous THF was added 4.5 g of previously dried 5 μm silica. The resulting slurry was carefully evaporated to dryness using a rotary evaporator and then heated at 110 °C (1 torr) in a Kügelrohr apparatus for 28 h. This modified silica was washed thoroughly with methanol and slurry packed into a 4.6 × 250 mm stainless steel column. From elemental analysis (C, 5.28; H, 0.90; N, 0.60.), the surface coverage of the silica is 0.12 mmol/g. Residual silanol groups were endcapped by passing a solution of 2 mL of hexamethyldisilazane in 50 mL of dichloromethane at a flow rate of 1 mL/min through this column which had been washed previously with dichloromethane.

(1*R*,2*R*,4*S*,9*R*,10*S*)-CSP 3. **CSP 3** was prepared using a procedure developed by Roder *et al.*[5] and used recently by Schleimer *et al.*[6] Chiral selector (+)-**11** was incorporated into polymethylhydrosiloxane, and the modified polymer was coated onto silica (5 μm, 300 Å) and immobilized by heating. The modified silica was washed successively with dichloromethane and methanol and then slurry-packed into a 4.6 × 250 mm stainless steel column. The surface coverage of the silica is 0.10 mmol/g based on elemental analysis (C, 7.44; H, 1.50; N, 0.54). A solution of 2 mL of hexamethyldisilazane in 50 mL of dichloromethane was pumped through the column at 1 mL/min to endcap residual silanols.

1,4-Ethano-2-*endo*-(α-(1-(9-anthryl)-2,2,2-trifluoroethoxy)acetamido)-*N*-ω-undecenyl-1,2,3,4-tetrahydronaphthalene-9,10-*endo*-dicarboximide (15). To a solution of 100 mg of (±)-**11** in 20 mL of ethanol was added 5 mL of concentrated hydrochloric acid. The resultant mixture was heated to reflux until the starting material had disappeared by TLC. The reaction mixture was concentrated to dryness, the residue was washed with several three mL portions of diethyl ether at 0 °C. Saturated sodium bicarbonate solution was added to the solid residue and the mixture was extracted repeatedly with dichloromethane. The combined organic extracts were dried over sodium sulfate and then concentrated to give 60 mg of (±)-*endo*-amine **10** as a colorless oily liquid.

To a solution of 60 mg of (±)-**10** in 5 mL of dichloromethane was added 65 mg of (*S*)-ATEA (1.1 equiv) and two drops of triethylamine. The reaction mixture was stirred at room temperature for 30 min. Evaporation of the solvent and purification on a small silica gel column, using first dichloromethane and then 1:1 ethyl acetate/hexane as the eluent, afforded 45 mg of the diastereomeric mixture **15** (42% from **11**) as a pale yellow viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.53 (1H, s), 8.32 (1H, d, J = 9.2 Hz), 8.10–7.95 (3H), 7.68–6.90 (8H), 6.04 (1H, q, J = 8.2 Hz), 6.00 (1H, amide NH), 5.82 (1H, m), 5.04 (1H), 4.92 (1H), 4.39 (1H, m), 4.00 (1H, d, J = 16.0 Hz), 3.84 (1H, d, J = 16.0 Hz), 3.65 (1H, dd, J = 4.3 Hz, 3.9 Hz), 3.61 (1H, m), 3.53 (1H, m), 3.44 (1H, dd, J = 4.3 Hz, 3.9 Hz), 3.14 (1H, dd, J = 9.3 Hz, 4.4 Hz), 3.11 (1H, dd, J = 9.3 Hz, 4.4 Hz), 3.07 (2H, m), 2.99 (1H, dd, J = 9.3 Hz, 4.3 Hz), 2.96 (1H, dd, J = 9.3 Hz, 4.3 Hz), 2.49 (1H, ddd, J = 15.1 Hz, 10.4 Hz, 2.6 Hz), 2.28 (1H, ddd, J = 15.1 Hz, 10.4 Hz, 2.6 Hz), 2.04 (2H, m), 1.46–0.94 (11H), 1.26 (1H, dd, J = 15.1 Hz, 4.2 Hz, 2.9 Hz), 0.83 (1H, dd, J = 15.1 Hz, 4.2 Hz, 2.9 Hz), 0.76 (4H). MS (HR-FAB) calcd for $C_{43}H_{46}N_2O_4F_3$ (M + 1) 711.3410, found 711.3412.

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