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Conformational effects on the enantioselective recognition of 4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene derivatives by a Naproxen-derived chiral stationary phase

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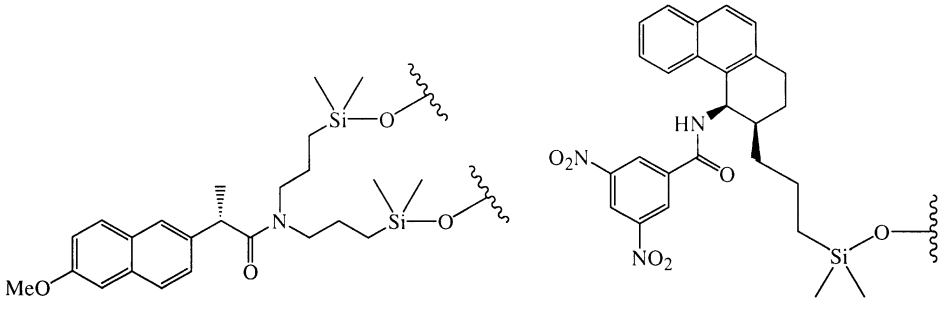
Abstract—4-(3,5-Dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene and derivatives having methyl groups in various positions on the tetrahydro ring were synthesized and resolved on an (*S*)-Naproxen-derived chiral stationary phase. The difference in the Gibbs free energy, $\Delta\Delta G$, of the transient diastereomeric adsorbates was determined from the chromatographic data. The highest enantioselectivity was observed for *cis*-4-(3,5-dinitrobenzamido)-3-methyl-1,2,3,4-tetrahydrophenanthrene. Introducing methyl groups into other positions of the tetrahydrophenanthrene ring proved to be detrimental to enantioselectivity. Prior studies indicate that, in the 4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene used in the Whelk-O chiral HPLC columns, the 3,5-dinitrobenzamide group occupies a pseudoaxial position, thus forming one wall of a binding cleft owing to its spatial relationship with the naphthyl portion of the selector. The effect of the methyl substituents on enantioselectivity is attributed to their ability to both influence the 'psuedoaxiality' of the dinitrobenzamido group and to their ability to sterically hinder the presentation of the 'back face' of this group to the Naproxen-derived selector.

1. Introduction

The concept of reciprocity in chiral recognition allows a rational development of a chiral stationary phase (CSP) for a given target group of compounds.[1] First, a CSP derived from the ultimate target compound is used to chromatographically screen racemic CSP candidates. Then, one enantiomer of an analyte that affords high enantioselectivity is immobilized on silica gel to afford a new CSP. Assuming reciprocity in stereoselective interactions, one would expect that the new CSP would be effective in separating the enantiomers of compounds that are structurally similar to the target compound. This is how the 4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene selector used in the Whelk-O-1 CSP was developed to separate the enantiomers of arylpropionic acids such as Naproxen (Fig. 1).[2] This approach can be further utilized to develop improved selectors and to refine one's understanding of the subtleties of the chiral recognition processes.

A chiral recognition model which accounts for the ability of the Whelk-O selector to differentiate between enantiomers



(*S*)-Naproxen-derived CSP (3*S*,4*R*)-Whelk-O 1 CSP

Figure 1. Chiral stationary phases exhibiting reciprocal behavior.

Keywords: diastereomeric adsorbates; enantioselectivity; chiral stationary phase.
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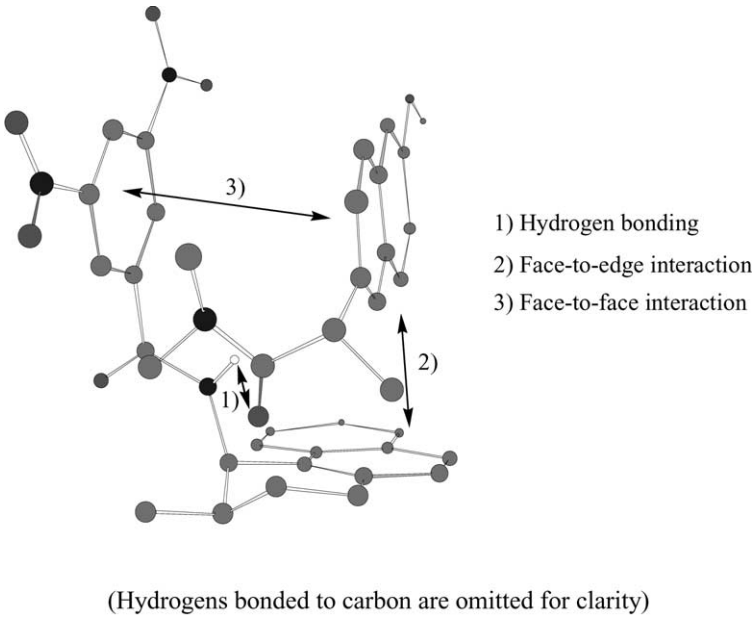

Figure 2. Enantioselective recognition model for the more stable diastereomeric complex between (*S*)-Naproxen dimethylamide and the soluble Whelk-O-1 analog (3*R*,4*R*)-**1**.

that possess a hydrogen bond acceptor and an aromatic moiety close to the stereogenic center has been developed and is based on chromatographic structure–activity relationships, crystallographic data, and NMR studies in solution.[3] In this model, the amide proton participates in hydrogen bonding whereas the electron-deficient 3,5-dinitrobenzoyl (3,5-DNB) group and the electron-rich naphthyl portion of the tetrahydrophenanthrene ring participate in face-to-face and face-to-edge interactions, respectively, with the aryl group in the preferentially retained enantiomer of the analyte. The cleft-like structure of the WhelkO-1 selector appears to be essential to enantiodifferentiation. While both enantiomers of a given racemate can diffuse into the cleft, only one can undergo all three of the aforementioned interactions simultaneously while maintaining a heavily populated low energy conformation. This chiral recognition model is consistent with the elution order observed from the Whelk-O column for the enantiomers of a number of classes of compounds including Naproxen-derived amides. Moreover, it agrees with the elution order observed for the enantiomers of a number of configurationally established analogs of the Whelk-O selector when these are chromatographed on the Naproxen-derived columns. Because of the consistent pattern between relative configuration and relative stability of the diastereomeric adsorbates, the absolute configuration shown for **3**–**6** (here to fore configurationally unassigned) is taken to be that which, for each of these compounds, will be the enantiomer

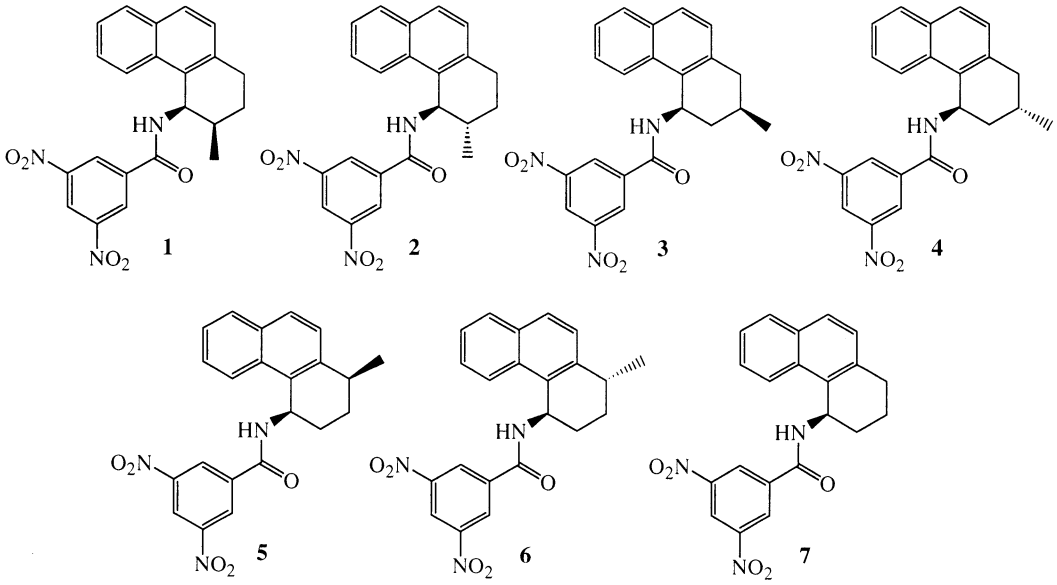

Figure 3. Structures of the 4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrenes studied. The stereochemistry shown is that of the enantiomers more strongly retained on the (*S*)-Naproxen-derived CSP shown in Fig. 1.

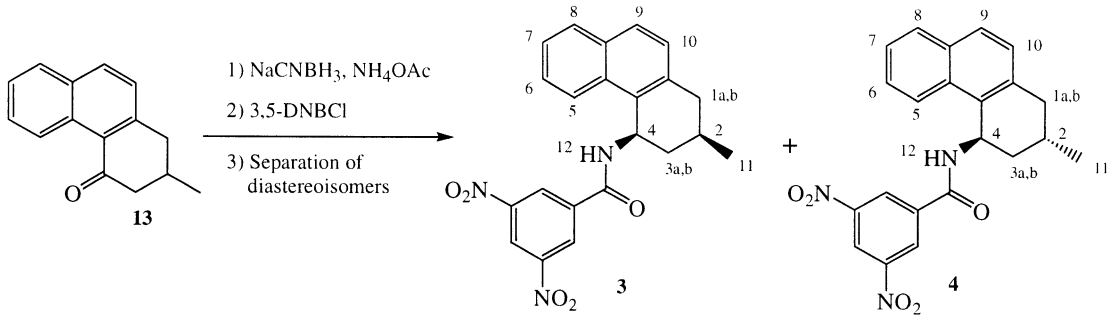

Figure 4. Synthesis of racemic 4-(3,5-dinitrobenzamido)-2-methyl-1,2,3,4-tetrahydrophenanthrene derivatives **3** and **4**.

which forms the more stable diastereomeric complex (Fig. 2) with the Naproxen-derived selector used in this study. Hence, these will be the enantiomers preferentially retained by this CSP (Fig. 1).

Immobilization of the Whelk-O selector on silica gel requires a tether that, in principle, can be incorporated into positions 1, 2, or 3 of the tetrahydrophenanthrene ring. It is known that tether length influences enantioselectivity as does its stereochemistry relative to the dinitrobenzamido group. It was hoped that investigation of the influence that the tether position has on enantioselectivity would improve the understanding of the chiral recognition mechanism and possibly allow further optimization of the Whelk-O CSP. We envisioned that introducing methyl groups into the tetrahydro ring of the selector would, from the stand point of reciprocity, enable us to study the influence that the location of the tether would have on the performance of a Whelk-O-like CSP without actually having to prepare the CSP. The racemic Whelk-O selector analogs, **1**–**7**, (Fig. 3) were chromatographed on an (*S*)-Naproxen-derived CSP to determine the effect these methyl substituents would have on enantioselectivity.

2. Results and discussion

Racemic methyl-4-oxo-1,2,3,4-tetrahydrophenanthrene, **13**, was prepared as described by Haworth et al.[4] Reductive amination using sodium cyanoborohydride and ammonium acetate followed by acylation with 3,5-dinitrobenzoyl chloride affords a 1:1 mixture of racemic *cis*- and *trans*-4-(3,5-dinitrobenzamido)-2-methyl-1,2,3,4-tetrahydrophenanthrene, **3** and **4**, respectively. The diastereoisomers were separated on a racemic phenylglycine-derived stationary phase[5] and their relative configuration was assigned by NOE experiments (Fig. 4).

Racemic 5-methyl-5-(2-naphthyl)dihydrofuran-2-one, **10**, was synthesized following a procedure reported by Robinson et al.[6] Hydrogenolysis of lactone **10** yields 4-(2-naphthyl)pentanoic acid, **11**, which was converted to ketone **12**. Reductive amination and acylation produced a 1:1 mixture of racemic *cis*- and *trans*-4-(3,5-dinitrobenzamido)-1-methyl-1,2,3,4-tetrahydrophenanthrene, **5** and **6**. Chromatographic separation of racemic diastereoisomers **5** and **6** and structure elucidation were accomplished as described for **3** and **4** (Fig. 5). 4-Oxo-1,2,3,4-tetrahydrophenanthrene, **8**, was prepared following a procedure reported by Huggenberg et al.[7] and converted to amine **9** by reductive amination. Acylation using 3,5-dinitrobenzoyl chloride affords 4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene, **7** (Fig. 6). The racemic *cis* and *trans* diastereoisomers of 4-(3,5-dinitrobenzamido)-3-methyl-1,2,3,4-tetrahydrophenanthrene, **1** and **2**, were available from previous studies.

Compounds **1**–**7** each have a 3,5-DNB group in the benzylic 3-position of the tetrahydrophenanthrene moiety. The two conformational extremes would place this benzylic substituent in either a pseudoaxial or a pseudoequatorial position. It is known that electronegative groups in an allylic

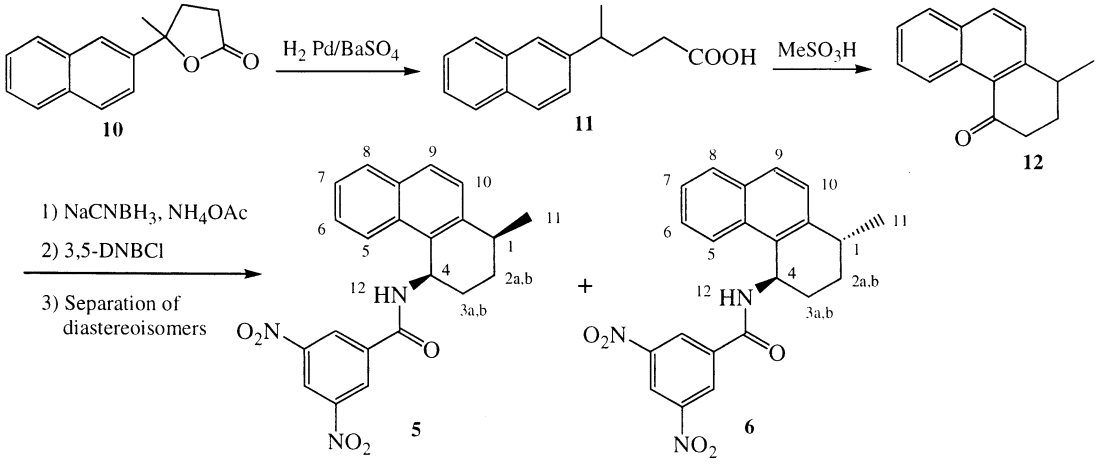

Figure 5. Synthesis of racemic 4-(3,5-dinitrobenzamido)-1-methyl-1,2,3,4-tetrahydrophenanthrene derivatives **5** and **6**.

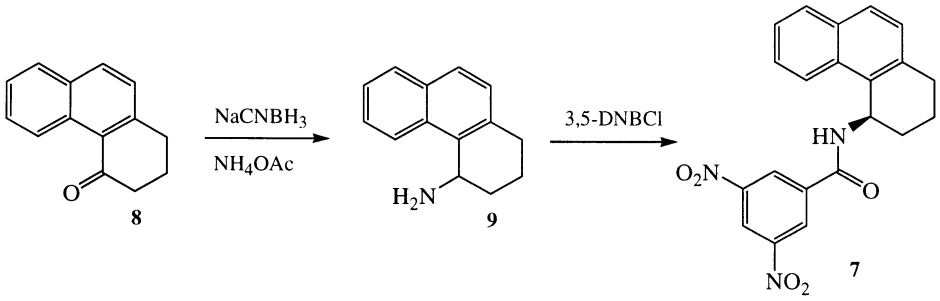

Figure 6. Synthesis of racemic 4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene, **7**.

position on cyclohexenes prefer the pseudoaxial position.[8] Similar to the anomeric effect observed with carbohydrates, this might be attributed to an overlap of a π-orbital of the double bond and an antibonding orbital of the allylic σ-bond (Fig. 7).

Based on the similarity of an allylic position in cyclohexene

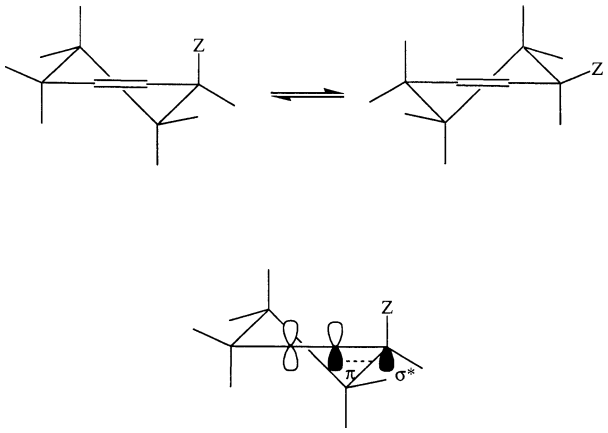

Figure 7. Half-chair conformation of cyclohexenes and overlap of the π-orbital of the double bond and the σ*-orbital of the C–Z bond.

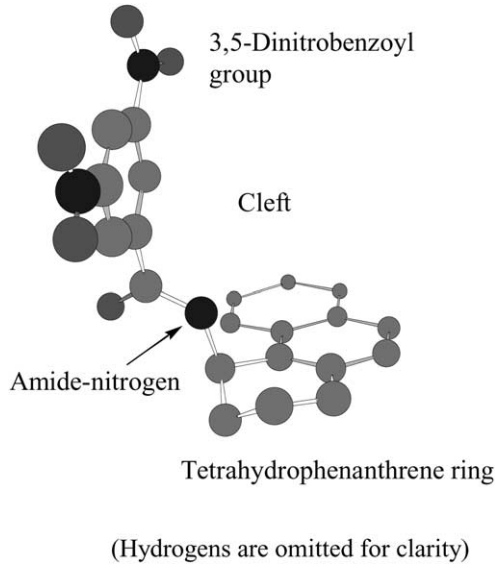

Figure 8. Main conformation of **7** exhibiting the 3,5-DNB group in the pseudoaxial position.

to a benzylic position in tetrahydrophenanthrene, one would expect the most stable conformer of **7** to have the DNB group in the pseudoaxial position. Thus, **7** forms a cleft in which the π-acidic 3,5-dinitrobenzamide moiety can be viewed as a 'wall' which is nearly perpendicular to the π-basic naphthyl 'floor'of the cleft (Fig. 8). This geometry has been verified by X-ray crystal structure determinations, both in the absence[3a] and presence[9] of an associated 'guest'.

Methyl groups are known to prefer pseudoequatorial and equatorial positions in cyclohexene rings. Introducing a methyl group into positions 1, 2, or 3 of **7** generates a second stereogenic center and should affect the equilibrium between the two conformers, the position of which, for analogs **1**–**6,** will be determined by an energetic compromise between the preference of the 3,5-DNB group for the pseudoaxial position and the preference of the methyl group for an equatorial (**1**–**4**) or pseudoequatorial (**5**, **6**) position. From the model, one would expect that, if a methyl substituent, by tending to occupy a pseudoequatorial position, increases the 'pseudoaxiality' of the dinitrobenzamido group, this would stabilize the cleft-like conformation and increase the enantioselectivity shown by that Whelk-O analog. Conversely, a methyl substituent that diminishes the pseudoaxiality of the dinitrobenzamido group would be expected to reduce the enantioselectivity shown by that analog. The concept of reciprocity provides a simple means to study the stereodynamics of **1**–**7**. The enantiomers of racemic analytes **1**–**7** were separated on the (*S*)-Naproxen-derived CSP using hexanes/2-propanol (4:1) as the mobile phase at 25°C. Differences in the Gibbs free energy, $\Delta\Delta G^0$, of the transient diastereoisomeric complexes formed from each racemate were calculated from the observed chromatographic separation factor, α, for the enantiomers according to Eq. 1.[10]

$$\Delta\Delta G^0 = RT \ln(\alpha) \quad (1)$$

The difference in the Gibbs free energies of the diastereomeric adsorbates formed from the (*S*)-Naproxen-derived selector and each of the enantiomers of nonmethylated **7** was determined to be 3.87 kJ/mol (Table 1). The high stereoselectivity is likely to be a consequence of stabilization of the pseudoaxial conformation by stereoelectronic effects. Notably, a slight increase in enantioselectivity is observed for *cis*-3-methyl analog **1** whereas a slight decrease is noted for *trans*-3-methyl **2.** Note also that, for the 1-methylated analogs, *cis*-methyl **5** shows greater enantioselectivity than *trans*-methyl **6**. Finally, for the

Table 1. Differences of Gibbs enthalpies of transient diastereomeric complexes determined by separation of enantiomers of compounds **1**–**7** on an (*S*)-Naproxen-derived CSP

Compound	Configuration	$\Delta\Delta G^0$ (kJ/mol)
1	*cis*	4.05
2	*trans*	3.77
3	*cis*	1.52
4	*trans*	3.02
5	*cis*	3.56
6	*trans*	1.92
7	–	3.87

2-methylated analogs, *cis*-methyl **3** shows less enantioselectivity than *trans*-methyl **4**. These differences in enantioselectivity are ascribed to the influence of the methyl group on the dynamic equilibrium between the two major conformations of the tetrahydro ring. Compounds **1**, **4**, and **5** each more extensively populate the stable conformer having the 3,5-DNB group in the pseudoaxial position and the methyl group in either a pseudoequatorial or an equatorial position. More extensive population of the cleft thus formed (Fig. 9) increases enantioselectivity. In contrast, the cleft is less populated in isomers **2**, **3**, and **6** since the methyl group would have to occupy an axial or a pseudoaxial position.

The greater enantioselectivity shown by *cis*-3-methyl **1** relative to *cis*-1-methyl **5** is believed to stem largely to the ability of the vicinal methyl to impede presentation of the back face of the 3,5-DNB group to the Naproxen-derived selector. This 'out of cleft' mode of approach would be utilized primarily by the less retained enantiomer so that it might simultaneously utilize both its amide hydrogen and the 3,5-DNB group to interact with the Naproxen-derived selector. By discouraging this mode of approach, the vicinal *cis*-3-methyl further reduces the retention of the less retained enantiomer and, consequently, enantioselectivity is increased.

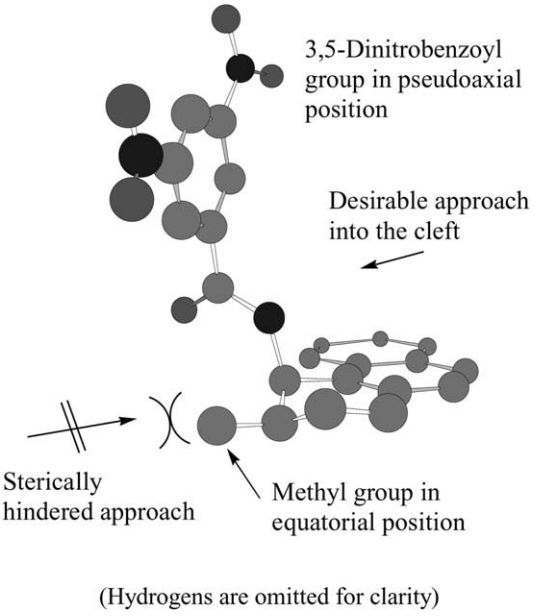

Figure 9. Main conformation of **1** exhibiting the 3,5-DNB moiety in the pseudoaxial position and the methyl group in the equatorial position.

3. Conclusion

The ability of analogs of the Whelk-O-1 CSP to differentiate between enantiomers of arylpropionic acids was investigated using the concept of reciprocity. The enantiomers of 4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene and six of its methyl derivatives were separated on an (*S*)-Naproxen-derived CSP. The highest enantioselectivity was observed for *cis*-4-(3,5-dinitrobenzamido)-3-methyl-1,2,3,4-tetrahydrophenanthrene, **1**. Introduction of a methyl substituent into other positions of the tetrahydrophenanthrene ring is detrimental to enantioselectivity. This is attributed to destabilization of a cleft-like conformation. In addition, it was found that *cis*-3-substitution slightly improves enantioselectivity, presumably by impeding an out of cleft approach of the less retained enantiomer to the Naproxen-derived selector.

4. Experimental

HPLC was carried out using an Alcott 760 HPLC pump equipped with a Rheodyne 7125 injector, a Milton Roy UV monitor (254 nm), and an HP 3394A integrating recorder. 2-Propanol, hexanes, dichloromethane, and tetrahydrofuran were of HPLC grade (EM Science). Tri-*tert*-butylbenzene was used as a void volume marker. ^{1}H Nuclear magnetic resonance (NMR) spectra were collected on a Varian Unity 400 spectrometer with deuterated chloroform used as the solvent. Chemical shifts are reported in ppm with TMS used as internal standard. All NOE experiments were recorded on a Varian Unity 500 using a CycleNOE macro. The samples were exhaustively degassed by five freeze–pump–thaw cycles and sealed. Percent NOEs are shown in parentheses and were calculated by setting the integral for the saturated signal to −100.

4.1. Preparation of racemic *cis*- and *trans*-4-(3,5-dinitrobenzamido)-2-methyl-1,2,3,4-tetrahydrophenanthrene, 3 and 4

The reductive amination of 0.35 g (1.67 mmol) of racemic 2-methyl-4-oxo-1,2,3,4-tetrahydrophenanthrene, **13**, and acylation with 3,5-dinitrobenzoyl chloride was performed as described for **7** and **9** and provided 0.27 g (0.68 mmol, 41% yield) of a 1:1 mixture of the *cis* and *trans* diastereoisomers of 4-(3,5-dinitrobenzamido)-2-methyl-1,2,3,4-tetrahydrophenanthrene. The *cis* and *trans* diastereoisomers were separated on a racemic phenylglycine-derived stationary phase using hexanes/2-propanol (3:1) as the mobile phase.

4.1.1. Racemic *cis*-4-(3,5-dinitrobenzamido)-2-methyl-1,2,3,4-tetrahydrophenanthrene, 3. ^{1}H NMR (400 MHz) δ: 1.18 (d, 3H, J=6.8 Hz), 1.85 (m, 1H), 2.14 (m, 2H), 3.23 (m, 2H), 5.28 (m, 1H), 6.52 (d, 1H, J=8.8 Hz), 7.33 (d, 1H, J=8.7 Hz), 7.49 (ddd, 1H, J=1.2, 6.9, 7.8 Hz), 7.54 (ddd, 1H, J=1.6, 6.9, 8.4 Hz), 7.67 (d, 1H, J=8.7 Hz), 7.79 (d, 1H, J=7.8 Hz), 7.99 (d, 1H, J=8.3 Hz), 8.93 (d, 2H, J=2.2 Hz), 9.10 (t, 1H, J=2.2 Hz). NOE: Irradiation at H-2: H-3a (27); irradiation at H-11: H-3a (1), H-4 (1). Mass spectrum (70 eV) *m*/*z* (relative intensity): 405 (7),

346 (1), 208 (6), 194 (100), 179 (88), 168 (20), 141 (10), 75 (16).

4.1.2. Racemic *trans*-4-(3,5-dinitrobenzamido)-2-methyl-1,2,3,4-tetrahydrophenanthrene, 4. ^{1}H NMR (400 MHz) δ: 1.16 (d, 3H, J=6.8 Hz), 1.69 (m, 1H), 2.05 (m, 1H), 2.31 (m, 1H), 3.10 (m, 1H), 3.42 (m, 1H), 5.61 (m, 1H), 6.33 (d, 1H, J=8.5 Hz), 7.36 (d, 1H, J=8.5 Hz), 7.50 (dd, 1H, J=6.6, 8.3 Hz), 7.55 (dd, 1H, J=6.6, 8.5 Hz), 7.68 (d, 1H, J=8.5 Hz), 7.80 (d, 1H, J=8.5 Hz), 8.01 (d, 1H, J=8.3 Hz), 8.90 (m, 2H), 9.12 (m, 1H). NOE: Irradiation at H-2: H-1a (7), H-3a (23), H-12 (11); irradiation at H-11: H-3b (3), H-4 (3), H-12 (1). Mass spectrum (70 eV) *m/z* (relative intensity): 405 (8), 346 (1), 208 (6), 194 (100), 179 (54), 168 (13), 141 (7), 75 (12).

4.2. Preparation of racemic *cis*- and *trans*-4-(3,5-dinitrobenzamido)-1-methyl-1,2,3,4-tetrahydrophenanthrene, 5 and 6

The reductive amination of 0.15 g (0.71 mmol) of racemic 1-methyl-4-oxo-1,2,3,4-tetrahydrophenanthrene, **12**, and acylation with 3,5-dinitrobenzoyl chloride was performed as described for **7** and **9** and afforded 0.15 g (0.39 mmol, 54% yield) of a 1:1 mixture of the *cis* and *trans* diastereoisomers of 4-(3,5-dinitrobenzamido)-1-methyl-1,2,3,4-tetrahydrophenanthrene. The *cis* and *trans* diastereoisomers were separated on a racemic phenylglycine-derived stationary phase using hexanes/2-propanol (3:1) as the mobile phase.

4.2.1. Racemic *cis*-4-(3,5-dinitrobenzamido)-1-methyl-1,2,3,4-tetrahydrophenanthrene, 5. ^{1}H NMR (400 MHz) δ: 1.36 (d, 3H, J=7.1 Hz), 1.81 (m, 1H), 2.15 (m, 1H), 2.25 (m, 2H), 3.22 (m, 1H), 5.94 (m, 1H), 6.56 (d, 1H, J=7.6 Hz), 7.31 (d, 1H, J=8.5 Hz), 7.42 (dd, 1H, J=6.9, 9.1 Hz), 7.47 (dd, 1H, J=6.9, 8.3 Hz), 7.77 (d, 1H, J=8.5 Hz), 7.79 (d, 1H, J=8.1 Hz), 7.87 (d, 1H, J=8.3 Hz), 8.84 (d, 2H, J=2.0 Hz), 9.08 (t, 1H, J=2.0 Hz). NOE: Irradiation at H-2a: H-1 (10), H-2b (23), H-4 (2), H-12 (5); irradiation at H-2b: H-1 (4), H-2a (29), H-11 (4), H-12 (−1). Mass spectrum (70 eV) *m/z* (relative intensity): 405 (1), 194 (100), 179 (37), 178 (11), 165 (6), 75 (14).

4.2.2. Racemic *trans*-4-(3,5-dinitrobenzamido)-1-methyl-1,2,3,4-tetrahydrophenanthrene, 6. ^{1}H NMR (400 MHz) δ: 1.50 (d, 3H, J=6.8 Hz), 1.63 (m, 1H), 2.08 (m, 2H), 2.40 (m, 1H), 3.07 (m, 1H), 5.97 (m, 1H), 6.61 (m, 1H), 7.45 (m, 2H), 7.53 (d, 1H, J=8.8 Hz), 7.81 (d, 2H, J=8.8 Hz), 7.88 (d, 1H, J=8.3 Hz), 8.86 (m, 2H), 9.09 (m, 1H). NOE: Irradiation at H-2a: H-1 (1), H-2b,3b (19), H-12 (4); irradiation at H-3a: H-2b,3b (31), H-4 (6), H-12 (1). Mass spectrum (70 eV) *m/z* (relative intensity): 405 (7), 194 (100), 179 (34), 165 (10), 152 (5), 75 (7).

4.2.3. Preparation of racemic 4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene, 7. The crude amine **9** was dissolved in 40 ml of dichloromethane and stirred with an excess of 2 M potassium hydroxide. To this mixture was added 2.3 g (10 mmol) of 3,5-dinitrobenzoyl chloride and the two-phase system was allowed to stand with periodic agitation for 3 h. The two phases were separated and the organic layer was washed with water and dried over anhydrous magnesium sulfate. After evaporation of the solvent, a brown oil was obtained. Flash chromatography using dichloromethane as the mobile phase and crystallization from dichloromethane/hexanes 5:1 yielded 1.6 g (4.1 mmol, 80% yield from **9**) of pale yellow crystals.

^{1}H NMR (400 MHz) δ: 1.93 (m, 1H), 2.03 (m, 2H), 2.43 (m, 1H), 3.03 (m, 2H), 5.99 (m, 1H), 6.56 (d, 1H, J=7.3 Hz), 7.27 (d, 1H, J=8.5 Hz), 7.43 (ddd, 1H, J=1.5, 6.8, 7.8 Hz), 7.48 (ddd, 1H, J=1.7, 6.8, 8.3 Hz), 7.76 (d, 1H, J=8.5 Hz), 7.81 (dd, 1H, J=1.5, 7.8 Hz), 7.87 (d, 1H, J=8.3 Hz), 8.86 (d, 2H, J=1.8 Hz), 9.10 (t, 1H, J=1.8 Hz). Mass spectrum (70 eV) *m/z* (relative intensity): 391 (4), 195 (4), 180 (100), 165 (21), 141 (4), 75 (7).

4.3. Preparation of racemic 4-amino-1,2,3,4-tetrahydrophenanthrene, 9

A mixture of 1.0 g (5.1 mmol) 4-oxo-1,2,3,4-tetrahydrophenanthrene, **8**, 16.0 g ammonium acetate, and 2.2 g sodium cyanoborohydride in 60 ml of dry 2-propanol was heated at reflux for 44 h. Approximately 75% of the solvent was removed by rotary evaporation and 1N aqueous sodium hydroxide solution added until the solution was basic. The mixture was extracted with several portions of dichloromethane and the combined organic layers were washed with water, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The crude amine **9** so obtained was not further purified.

4.4. Preparation of racemic 4-(2-naphthyl)pentanoic acid, 11

A mixture of 0.4 g (1.8 mmol) racemic 5-methyl-5-(2-naphthyl)dihydrofuran-2-one, **10**, and 0.5 g of 5% Pd/$BaSO_4$ in 30 ml methanol/tetrahydrofuran (1:1) was placed in a thick-walled Parr bottle under a hydrogen atmosphere (50 psi) for 6 h. The reaction mixture was filtrated through celite and the solvents removed on a rotary evaporator. The residue was dissolved in dichloromethane and extracted with 5N sodium hydroxide. The aqueous phase was acidified and extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and dichloromethane evaporated to give an orange oil that was not further purified.

4.4.1. Preparation of racemic 1-methyl-4-oxo-1,2,3,4-tetrahydrophenanthrene, 12. The crude acid **11** was dissolved in 5 ml of methanesulfonic acid under nitrogen and heated to 90°C for 1 h. The mixture was allowed to cool to room temperature and slowly poured onto ice. The mixture was extracted with dichloromethane and the organic layer was washed with water and saturated sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The dichloromethane was removed at the rotary evaporator and the residue purified by flash chromatography using dichloromethane as the mobile phase to give 0.16 g (0.76 mmol, 43% yield based on **10**) of a yellow oil.

^{1}H NMR (400 MHz) δ: 1.44 (d, 3H, J=7.1 Hz), 1.97 (m, 1H), 2.35 (m, 1H), 2.71 (ddd, 1H, J=5.6, 5.6, 17.1 Hz), 2.93 (ddd, 1H, J=5.3, 10.9, 17.1 Hz), 3.23 (ddq, 1H, J=5.1, 7.1, 10.0 Hz), 7.38 (d, 1H, J=8.5 Hz), 7.47 (ddd, 1H, J=1.0, 6.8,

8.1 Hz), 7.60 (ddd, 1H, J=1.5, 6.8, 8.8 Hz), 7.78 (dd, 1H, J=1.5, 8.1 Hz), 7.94 (d, 1H, J=8.5 Hz), 9.33 (dd, 1H, J=1.0 Hz J=8.8 Hz). Mass spectrum (70 eV) m/z (relative intensity): 210 (100), 195 (29), 182 (79), 168 (34), 167 (28), 165 (28), 154 (57), 153 (49), 152 (35), 139 (15), 128 (11), 115 (9), 76 (14).

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10. The separation factor, α, is the ratio of the retention times of the enantiomers (after correction for t_0, the time required for the elution of a nonretained substance) and is the ratio of the partition coefficients of the enantiomers between the chiral stationary phase and the achiral mobile phase.