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A Convenient Method for the Determination of the Absolute Configuration of Chiral Amines

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Abstract: A highly useful methodology that allows the determination of the absolute configuration of aliphatic and aromatic chiral amines based on the rationalization of stereoselective three-point interactions during chromatography on a rationally designed chiral stationary phase and conformational analysis of the elutes was developed. This approach is based on the broadly accepted chiral recognition mechanism of the Whelk-O 1 CSP and requires a facile derivatization of the amine and the determination of the lowest energy conformation of the corresponding *t*-Boc- or Z-derived carbamates. The absolute configuration determined by employing chiral structure activity relationships in HPLC analysis was verified by single-crystal X-ray analysis or studies with carbamoyl derivatives of amines of known configuration. The general validity and applicability of this methodology was demonstrated by analysis of seven carbamates derived from aliphatic and aromatic amines. Due to its simplicity and time-efficiency, i.e., ease of derivatization of amines and fast HPLC method development, this approach can be considered a useful supplement to established techniques such as NMR spectroscopy.

The development of new methodologies that allow the determination of the absolute configuration of chiral compounds, in particular amines, alcohols, and carboxylic acids, has attracted considerable attention due to its pivotal role in asymmetric synthesis and structure elucidation of natural products. In addition to X-ray and neutron diffraction analysis,[1] a variety of techniques including NMR spectroscopy[2] and chiroptical methods[3] based on circular dichroism, optical rotary dispersion, or exciton-coupled circular dichroism[4] have been refined during recent years. We report herein an orthogonal approach that allows the convenient determination of the absolute configuration of aromatic and aliphatic chiral amines. This methodology, which is also applicable to amino acids, utilizes a simple model based on three-point interactions between conformationally rigid carbamates and a rationally designed chiral selector to elucidate the absolute configuration of the analytes based on relative stabilities of transient diastereomeric complexes observed in enantioselective chromatography.

Chiral amines have been used as important building blocks in the total synthesis of natural products[5] and employed as enantioselective catalysts in a variety of organic reactions, such as asymmetric organocuprate additions, Baylis−Hillman, and sparteine-mediated reactions.[6] The preparation and determination of the absolute stereochemistry of enantiopure amines is therefore an ongoing challenge in organic synthesis.[7] We have become interested in the synthesis of enantiopure (*R*)- and (*S*)-methyl-(1,2,3,4-tetrahydrophenanthren-4-yl)amine, **1**, since

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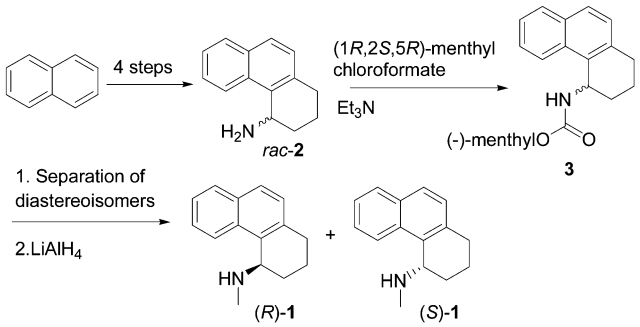
SCHEME 1. Synthesis of Enantiopure Methyl-(1,2,3,4-tetrahydrophenanthren-4-yl)amine, 1



it affords a versatile precursor for the synthesis of amine-derived enantioselective catalysts including quaternary ammonium salts that can be employed in phase-transfer catalysis. Our initial synthetic strategy involved the preparation of racemic 4-amino-1,2,3,4-tetrahydrophenanthrene, **2**, in four steps from naphthalene followed by separation of the enantiomers and subsequent methylation. Since all attempts to resolve the enantiomers of **2** via formation of diastereomeric salts using enantiopure acids, i.e., (2*R*,3*R*)-tartaric acid, (1*R*)-10-camphersulfonic acid, (*R*)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate, and (*R*)-2-phenylpropionic acid, were not successful, we decided to prepare the corresponding (1*R*,2*S*,5*R*)-*N*-menthoxycarbonyl derivative **3**, which, after separation of the diastereomers, could be converted in one step to enantiopure **1** by reductive cleavage, Scheme 1. We were pleased to find that the diastereomers of **3** can be separated through crystallization from methanol/water mixtures or by chromatography on silica gel. Enantiopure amine **1** was obtained from diastereomerically pure carbamate **3** by careful reduction with $LiAlH_4$.[8] The preparative separation of the diastereoisomers of **3** and its reductive cleavage were monitored by chiral HPLC. During the screening of various chiral stationary phases (CSPs), we noticed that the (3*S*,4*R*)-Whelk-O 1 CSP does not provide a baseline separation of the diastereoisomers of **3** but is still able to differentiate between the two isomers.

The Whelk-O 1 CSP was developed by Pirkle and co-workers to resolve enantiomers of compounds that exhibit a hydrogen bond acceptor and an aromatic moiety close to the stereogenic center.[9] This CSP exhibits an amide hydrogen, an electron-deficient 3,5-dinitrobenzoyl group, and an electron-rich naphthyl moiety, Figure 1. The cleftlike structure is considered to be essential for the chiral recognition mechanism. Both enantiomers of a racemic compound can diffuse into the cleft, but only one is capable of participating in simultaneous hydrogen-bonding, $\pi-\pi$ interactions with the electron-deficient 3,5-dinitrobenzoyl group and CH/π interactions with the

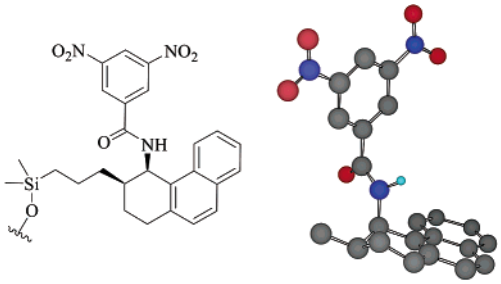


FIGURE 1. Structure and 3-dimensional view of the (3*S*,4*R*)-Whelk-O 1 CSP. For clarity, hydrogens bonded to carbon are omitted and the anchor of the CSP is simplified as a methyl group in the 3-dimensional view.

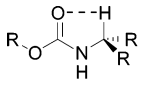


FIGURE 2. Preferentially populated conformation of carbamates and carbinyl hydrogen bonding.

electron-rich naphthyl moiety of the selector while maintaining a low energy conformation. This chiral recognition model has been verified by chromatographic structure−activity relationships, crystallographic data, and NMR studies.[10] Determination of the most stable and thus predominant conformation of a given chiral analyte should thus allow one to predict the elution order of the stereoisomers on this CSP, which would provide a means to determine the absolute configuration of the elutes.

It is important to note that the heavily populated conformations of carbamates while adsorbed on a stationary phase are generally expected to be similar to those in solution.[11] Carbamates preferentially populate conformations exhibiting a time-averaged planar carbamoyl scaffold that affords conformational control and rigidity as a consequence of intramolecular carbinyl hydrogen bonding. This conformation is further stabilized since repulsive interactions between the carbonyl oxygen of the carbamoyl group and α-substituents of the amine moiety are minimized, Figure 2.[12] Based on the well-defined chiral recognition mechanism of the Whelk-O 1 CSP and the conformational rigidity inherent to carbamates, we decided to determine the absolute configuration of chiral carbamate **3** and its related amine **1** by utilizing the aforementioned chromatographic rationale.[13]

The conformation of each stereoisomer of carbamate **3** was optimized by PM3 calculations to predict which isomer would form the more stable diastereomeric complex with the (3*S*,4*R*)-Whelk-O selector while avoiding significant spatial reorientations of the functional groups involved in the three-point interaction. Accordingly,

(8) Attempts to cleave the carbamate using concentrated HCl, 48% HBr in glacial acetic acid, or DIBAH were not successful. Treatment of diastereomerically pure **3** with $LiAlH_4$ in THF under reflux conditions for 12 h resulted in considerable racemization of **1**. Careful monitoring of the reductive cleavage by TLC showed that the reaction can be quenched within 4−6 h to avoid racemization of **1** without compromising the yield.

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(13) The stereoisomeric composition of **1** and **3** were determined by HPLC using Chiralcel OD, which provides baseline separations of the stereoisomers for both compounds.

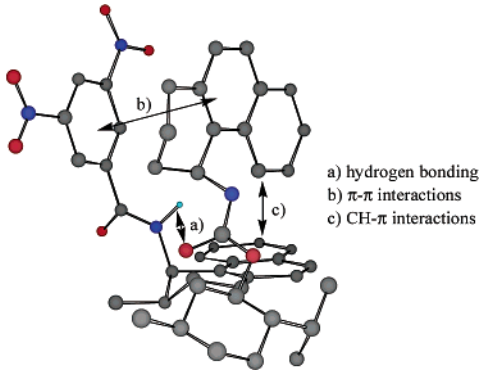

FIGURE 3. Enantioselective recognition model for the favored diastereomeric complex between the (3*S*,4*R*)-Whelk-O selector and (1*R*,2*S*,4′*S*,5*R*)-*N*- menthoxycarbonyl-4′-(1′,2′,3′,4′-tetrahydrophenanthryl)amine, **3a**. For clarity, hydrogens bonded to carbon are omitted and the anchor in position 3 of the tetrahydrophenanthrene ring that is required for the immobilization of the selector on silica gel is simplified as a methyl group.

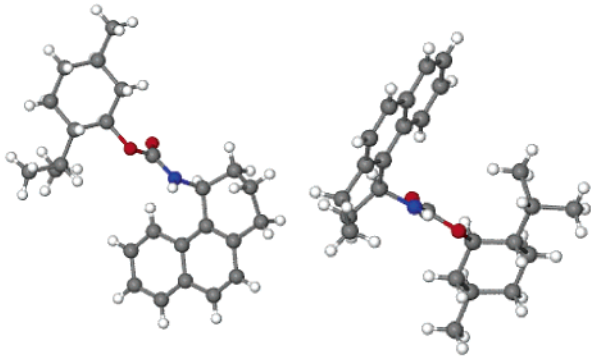

FIGURE 4. Crystal structure of (1*R*,2*S*,4′*S*,5*R*)-*N*-menthoxycarbonyl-4′-(1′,2′,3′,4′-tetrahydrophenanthryl)amine, **3a**.

(1*R*,2*S*,4′*S*,5*R*)-*N*-menthoxycarbonyl-4′-(1′,2′,3′,4′-tetrahydrophenanthryl)amine, **3a**, is capable of participating in all three aforementioned interactions with the chiral selector without undergoing significant conformational changes and should be more strongly retained on this CSP than its (1*R*,2*S*,4′*R*,5*R*)-diastereoisomer, Figure 3. We were thus able to deduce the absolute stereochemistry of the two diastereomeric carbamates **3** and of the corresponding enantiomers of secondary amine **1**.

Our chromatographic studies were followed by successful attempts to grow single crystals of carbamate **3a**, which was more strongly retained on the (3*S*,4*R*)-Whelk-O CSP. The crystallographic data confirmed the (*S*)-configuration of the chiral center of the 4-amino-1,2,3,4-tetrahydrophenanthryl moiety. Furthermore, X-ray analysis of **3a** reveals that its solid-state structure is quite similar to the conformation expected to be dominant in solution, Figure 4.[14]

Encouraged by these results, we decided to further investigate the applicability and validity of this concept to other chiral carbamates derived from aromatic and aliphatic amines. Since enantiodifferentiation by the

(14) See the Supporting Information for more crystallographic data of **3a**.

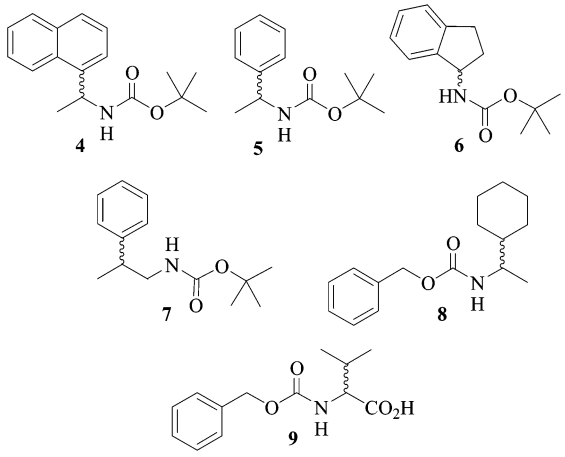

FIGURE 5. Structure of carbamates **4**−**9**

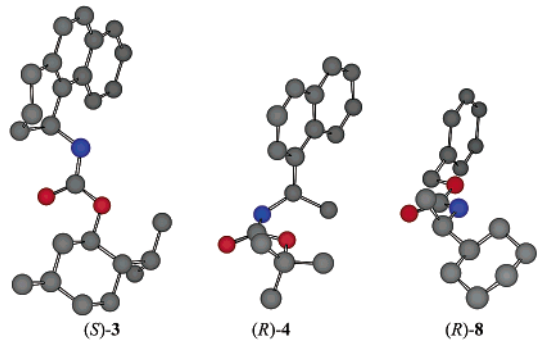

FIGURE 6. Optimized conformations of the enantiomers of carbamates **3**, **4**, and **8** capable of undergoing simultaneous hydrogen bonding, $\pi-\pi$ interactions, and CH$-\pi$ interaction with (3*S*,4*R*)-Whelk-O 1. Hydrogens are omitted for clarity.

Whelk-O CSP requires a hydrogen-bonding site and an aromatic group in close proximity of the chiral center of the analytes, we chose to prepare the racemate and one enantiopure form of *t*-Boc-derived aromatic amines **4**−**7** and Z-derived aliphatic amines **8** and **9**, Figure 5. The conformation of each enantiomer was optimized by PM3 calculations for comparison of its ability to undergo simultaneous hydrogen bonding, $\pi-\pi$ interactions, and CH$-\pi$ interactions with the (3*S*,4*R*)-Whelk-O selector. The preferentially populated conformations of the enantiomers of carbamates **3**, **4**, and **8** that can be expected to form stronger transient diastereomeric complexes during chromatography on the (3*S*,4*R*)-Whelk-O 1 than their enantiomers are depicted in Figure 6.

We were very pleased to find that the elution order and absolute configuration of the more retained enantiomers predicted by the chiral recognition model are in excellent agreement with experimentally obtained results, Table 1. The CSP was found to be able to differentiate between the stereoisomers of all analytes employed in this study. The difference of the Gibbs energy of the transient diastereoisomers, $\Delta\Delta G°$, was calculated from the observed enantioselectivity, α. Notably, small selectivities such as 70 J/mol proved to be sufficient for the determination of the absolute configuration of chiral amine **7** exhibiting a chiral center in β-position. Moreover, the introduction of a benzyloxycarbonyl moiety allows elucidation of the absolute

TABLE 1. Chiral Recognition of Carbamates 3−9 by the (3*S*,4*R*)-Whelk-O 1 CSP

carbamate	predicted abs config of the favored stereoisomer	abs config of the stereoisomer forming the stronger diastereomeric complex[a]	ΔΔ*G*° (kJ/mol)[b]
3	*S*	*S*	0.10[c]
4	*R*	*R*	2.23[d]
5	*R*	*R*	0.71[d]
6	*S*	*S*	0.12[e]
7	*R*	*R*	0.07[e]
8	*R*	*R*	0.23[f]
9	*R*	*R*	0.17[g]

[a] Determined by HPLC on (3*S*,4*R*)-Whelk-O 1 CSP by co-injection of an enantiopure carbamate of known absolute configuration and the related racemate. [b] Differences in the Gibbs energy, ΔΔ*G*°, of the transient diastereomeric complexes were calculated from the observed HPLC enantioseparation factor, α, according to $\Delta\Delta G^\circ = RT \ln(\alpha)$. [c] Hexanes/*i*-PrOH = 98:2. [d] Hexanes/EtOH = 95:5. [e] Hexanes/*i*-PrOH = 97:3. [f] Hexanes/*i*-PrOH = 9:1. [g] Hexanes/*i*-PrOH/AcOH = 95:5:0.2.

stereochemistry of simple aliphatic amines, such as **8**, and amino acids, such as **9**.

In conclusion, we have prepared enantiopure methyl-(1,2,3,4-tetrahydrophenanthren-4-yl)amine and determined the absolute configuration of its (1*R*,2*S*,5*R*)-menthyl-derived carbamate utilizing a commercially available CSP that exhibits a well-understood chiral recognition mechanism. The absolute configuration was elucidated on the basis of stereoselective three-point interactions in conjunction with conformational analysis of the analytes and was verified by single-crystal X-ray analysis of (1*R*,2*S*,4′*S*,5*R*)-*N*-menthoxycarbonyl-4′-(1′,2′,3′,4′-tetrahydrophenanthryl)amine. Furthermore, we have developed a highly useful methodology that allows the determination of the absolute configuration of chiral amines by enantioselective HPLC. This concept is based on the broadly accepted chiral recognition mechanism of the Whelk-O 1 CSP and requires a facile derivatization of the amine and the determination of the lowest energy conformation of the corresponding *t*-Boc- or Z-carbamates. The general validity and applicability of this chromatographic model has been demonstrated by analysis of seven carbamates derived from aliphatic and aromatic amines. Due to its simplicity and time-efficiency, i.e., ease of derivatization of amines and fast HPLC method development, the chromatographic analysis of the absolute configuration of chiral amines can be considered a useful supplement to established methodologies including NMR spectroscopy using chiral derivatizing reagents. The studies with Z-protected valine imply that our methodology is compatible with amines carrying additional functionalities such as carboxyl groups. However, the determination of the absolute stereochemistry of complex amines exhibiting more than one chiral center or other functional groups that undergo strong interactions with the CSP might not be feasible.

Experimental Section

Reactions were carried out under nitrogen atmosphere and under anhydrous conditions. NMR spectra were obtained at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm relative to TMS. Flash chromatography was performed on silica gel (Merck, Kieselgel 60, particle size: 32−63 μm). All HPLC chromatograms were obtained using a flow rate of 1 mL/min and UV detection at 254 nm. Samples were dissolved in hexanes/EtOH = 1:1 at a concentration of 1 mg/mL. Enantioselectivity, α, on (3*S*,4*R*)-Whelk-O 1 CSP: 1.04 (**3**), 2.36 (**4**), 1.32 (**5**), 1.05 (**6**), 1.03 (**7**), 1.09 (**8**), 1.07 (**9**). Racemic 4-amino-1,2,3,4-tetrahydrophenanthrene, **2**, was prepared as described in the literature.[15] Racemic and enantiopure carbamates **4**−**9** were commercially available or prepared according to standard procedures.

(1*R*,2*S*,5*R*)-*N*-Menthoxycarbonyl-4′-(1′,2′,3′,4′-tetrahydrophenanthryl)amine, 3. To a solution of amine **2** (1.6 g, 8.1 mmol) and triethylamine (1.7 mL, 12.2 mmol) in 25 mL of anhydrous ether was added a solution of (1*R*,2*S*,5*R*)-(−)-menthyl chloroformate (2.6 mL, 12.2 mmol) in 3 mL of anhydrous Et_2O at 0 °C. The mixture was allowed to stir at room temperature for 2 h. Upon completion of the reaction, the etheral solution was washed with aqueous NaOH, dried over $MgSO_4$, and evaporated to give a reddish yellow oil. Purification by column chromatography (3:1 hexane/CH_2Cl_2) yielded 3.0 g of a white powder (7.9 mmol, 98%). Separation of diastereoisomers: Method A: flash chromatography (6:1 hexane/CH_2Cl_2). The first eluted isomer exhibits (1*R*,2*S*,4′S,5*R*)-configuration and the second eluted carbamate is derived from (4*R*)-4-amino-1,2,3,4-tetrahydrophenanthrene. Method B: crystallization. (1*R*,2*S*,4′*S*,5*R*)-*N*-menthoxycarbonyl-4′-(1′,2′,3′,4′-tetrahydrophenanthryl)amine, **3a**, was crystallized from a saturated solution of racemic **3** in MeOH/H_2O = 8:1. The de of the isolated diastereoisomers was determined by HPLC on Chiralcel OD (hexanes/*i*-PrOH = 98:2) as 100%.

^{1}H NMR of **3a**: δ 0.78−0.97 (m, 9H), 1.05−1.25 (m, 2H), 1.45−1.78 (m, 4H), 1.85−2.02 (m, 5H), 2.10 (m, 1H), 2.29 (m, 1H), 2.90−2.98 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.42−7.47 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.78 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR of **3a** δ 22.7, 23.9, 26.3, 30.2, 30.4, 31.8, 34.7, 42.0, 45.1, 48.0, 74.7, 123.5, 125.4, 126.7, 127.2, 128.0, 128.3, 128.6. Anal. Calcd for $C_{25}H_{33}NO_2$: C, 79.11; H, 8.76; N, 3.69. Found: C, 79.41; H, 9.00; N, 3.57.

(*S*)-Methyl-(1,2,3,4-tetrahydrophenanthren-4-yl)-amine, 1. To a solution of **3a** (300 mg, 0.8 mmol) in anhydrous THF was added a 1 M solution of $LiAlH_4$ in THF (0.9 mL, 0.9 mmol), and the reaction mixture was allowed to reflux at 70 °C for 4 h. The reaction was cooled to 0 °C and quenched with 1 N HCl. The acidic layer was made basic with 6 N NaOH. The aqueous phase was extracted three times with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. The organic solvent was evaporated to afford 140 mg of a light reddish oil (0.7 mmol, 83%). The enantiomeric excess of (*S*)-**1** was determined by HPLC on Chiralcel OD (hexanes/*i*-PrOH = 98:2) as 99.7%: ^{1}H NMR δ 1.34 (s, 1H), 1.65 (m, 1H), 1.82 (m, 1H), 2.08 (m, 1H), 2.31 (m, 1H), 2.64 (s, 3H), 2.87−2.93 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.41 (m, 1H), 7.52 (m, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H): ^{13}C NMR δ 17.2, 25.7, 30.4, 34.8, 53.1, 122.5, 124.6, 126.3, 127.1, 128.0, 128.6, 132.0, 132.3, 133.1, 135.0. Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.42; H, 7.88; N, 6.45.

Supporting Information Available: X-ray crystallographic data of (1*R*,2*S*,4′*S*,5*R*)-*N*-menthoxycarbonyl-4′-(1′,2′,3′,4′-tetrahydrophenanthryl)amine, **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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