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Synthesis and enantiomer separation of 5-(10-undecenthylamido)-acenaphthene

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ABSTRACT

(±)-5-(10-Undecenethylamido)-acenaphthene was synthesized and successfully separated into enantiomers using chiral HPLC. The chemical structure of this compound was characterized by FT-IR, ^{1}H NMR, MS spectra, and elemental analyses.

1. Introduction

Resolution of racemic synthetic compounds is one of the most interesting challenges for a synthetic chemist and is essential in several research fields such as pharmaceutical, agrochemical, and food chemistry.[1,2] Enantiomers can be effectively separated using high-performance liquid chromatography (HPLC) with chiral stationary phases (CSPs).[3–5] Pirkle type CSPs have been proved to be the most practical CSPs and have been widely used in HPLC enantioseparation.[6] These CSPs contain a low molecular weight chiral selector covalently linked to the silica gel surface.[7] The chiral selectors contain π-acid or π-base aromatic groups, polar bonds or groups which can form dipole–dipole interaction, and atoms or groups which can form hydrogen bonds.[8,9]

Based on the resolution mechanism of these CSPs, racemic 5-(10-undecenethylamido)-acenaphthene **3**, a chiral compound with potential as a novel chiral selector of CSP, was synthesized starting from acenaphthene. The direct enantioseparation of **3** on CSP for preparing single enantiomers of **4a** or **4b** is described. In addition, the specific rotations of the isolated enantiomers were measured. The chemical process is shown in Scheme 1.

2. Results and discussion

2.1. Synthesis of 2

Compound **2** can be obtained from **1** according to a literature method[10] with some modifications. The yield of the target product was strongly affected by the amount of sodium cyanoborohydride and ammonium acetate. The results of the experiment suggest that compound **2** was obtained in 78% yield after 12 h when the mole ratio of 5-acetylacenaphthene, sodium cyanoborohydride and ammonium acetate was 1:2.9:40. In order to purify compound **2**, hydrochloric acid was added to form a water-soluble ammonium salt. Then, compound **2** was recovered by adding sodium hydroxide to neutralize the solution of ammonium salt. The composition of **2** was verified by ^{1}H NMR and elemental analyses. Analytical data are summarized in Section 4.

2.2. Synthesis of racemic 3

Racemic **3** was prepared by coupling of compound **2** and 10-undecenoyl chloride using triethylamine in THF. The reaction was monitored by TLC. When no compound **2** was observed, the solid was filtered out and the filtrate was evaporated under reduced pressure. Water was added to the dichloromethane solution of residue to remove any water-soluble impurity. After chromatographic purification with the mixture of dichloromethane and methanol as eluent, compound **3** was obtained in 84.4% yield. The composition of **3** was verified by FT-IR, ^{1}H NMR, MS and elemental analyses; analytical data are summarized in Section 4.

2.3. Resolution of racemic 3

The selectivity of five columns, Chiralcel OD-H, DNB-Leucine, DNB-PG, Whelk-O1 and CHI-DMB, which structures are shown in Figure 1, on the resolution and retention of compound **3** was investigated. The results suggest that compound **3** can be separated on DNB-Leucine, DNB-PG and Whelk-O1, as shown in Table 1. Among the CSPs, DNB-Leucine has the highest resolution which is suitable for separating two enantiomers of compound **3**.

Experiments indicate that compound **3** cannot only be separated by π-acid types of CSPs such as DNB-Leucine CSP and DNB-PG CSP, but also be separated by a CSP in which both π-acid and π-basic groups are present, such as Whelk-O1. This is a benefit from the molecular structure of compound **3**. The push-electronic methylene on the acenaphthylene ring can enhance the π–π interaction in the process of chiral recognition. Amide hydrogen atoms

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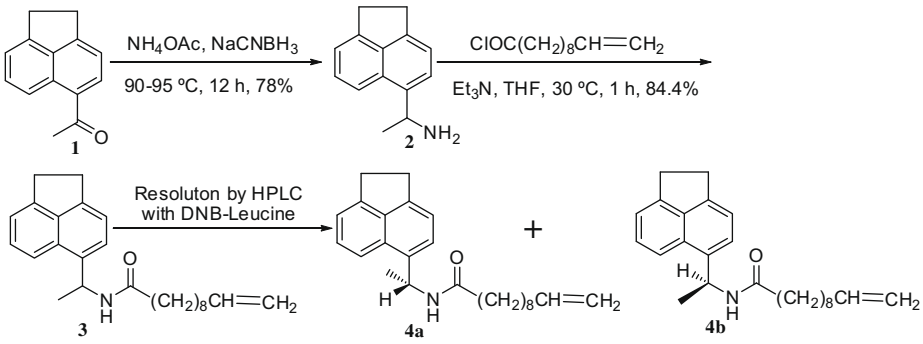

Scheme 1. The chemical process.

can form hydrogen bonding interaction with the CSPs, which is important for chiral recognition. Based on the notion of reciprocity in chiral recognition,[10] the single isomer of compound **3** may be developed as a chiral selector for CSP. The proposed CSP may be used to separate the enantiomers with only π-acid groups as well as with both π-acid and π-basic groups, and will have a wider scope when applied in chiral separation.

A polarimetric detector was connected to a UV detector in series for identification of **4a** and **4b**. The chromatographic separation is shown in Figure 2. The specific rotation of **4a** and **4b** was measured with an automatic polarimeter. The absolute configurations of **4a** and **4b** were deduced with the help of Brewster's model.[11]

2.4. Preparation of 4a and 4b

DNB-Leucine with the highest R value was selected to isolate the enantiomers of compound **3**. This was accomplished by repeating 50 μL injections (0.2 mg) of racemic **3** (30 mg) in the eluent and collecting the eluates corresponding to the two major chromatographic peaks to obtain 7.8 mg of each compound. Analytical HPLC identified 100% enantiomeric excess (ee) of the eluates. Specific rotation $[\alpha]_D^{30} = +46.7$ (*c* 1.0, C_2H_5OH) was measured for the first-eluted sample of compound **3**, while the second afforded an experimental $[\alpha]_D^{30} = -46.7$ (*c* 1.0, C_2H_5OH).

3. Conclusion

In summary, we have prepared a racemic sample of 5-(10-undecenethylamido)-acenaphthene. The compound was separated on chiral HPLC, and the CSP of these single enantiomeric compounds is currently underway and will be reported in due course.

4. Experimental

4.1. General

Elemental analyses were carried out on a Carlo erba-1106 analyzer. Nuclear magnetic resonance (NMR) spectra were recorded

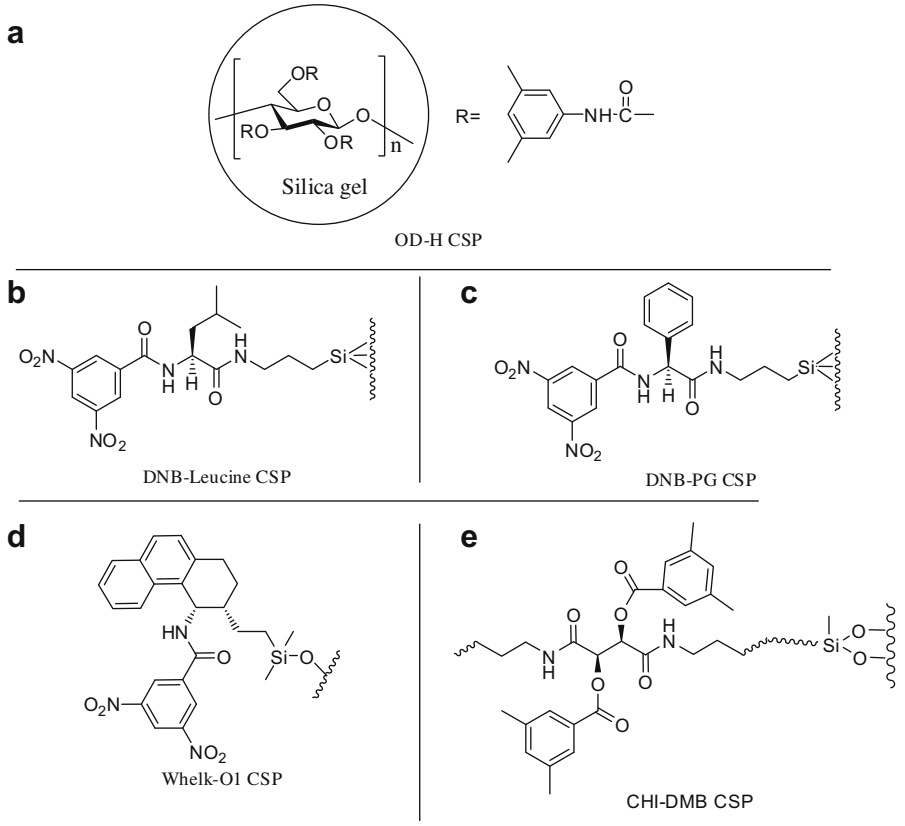

Figure 1. Structure of the CSPs.

Table 1
Enantioselective HPLC resolution of compound **3** on DNB-Leucine, DNB-PG and Whelk-O1

CSPs	k'_1	k'_2	α	R
DNB-Leucine	10.58	15.62	1.47	3.39
DNB-PG	11.08	17.30	1.56	2.56
Whelk-O1	4.22	7.74	1.83	1.58

k'_1: capacity factor for the first-eluted enantiomer; k'_2: capacity factor for the second-eluted enantiomer; α: separation factor; R: resolution; operation conditions: the mobile phase: *n*-hexane to 2-propanol = 90:10 (*v*/*v*), the flow rate: 1.5 mL/min, the wavelength: 254 nm, the column temperature: 30 °C, the injection volume: 20 μL.

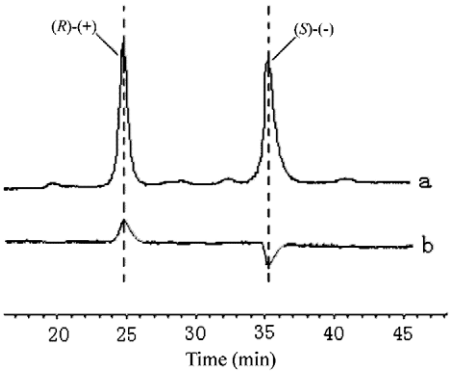

Figure 2. Chromatogram of compound **3** detected by UV detector (a) and OR detector (b).

on an INOVA-400 spectrometer. EI mass spectra were acquired on a ABI API 3000 instrument and are reported as mass/charge ratio (*m*/*z*). IR data were obtained on a Bruker Tensor 27 FT-IR spectrometer. The specific rotation was determined with a Polarimeter Autopol IV automatic polarimeter (Rudolph, America). Melting points were determined on YRT-3 melting point measuring apparatus (Precision Instrument Plant, Tianjin University). The HPLC system consisted of an LC-20AT pump and an SPD-M20A diode array detector. Data acquisition was done on a Shimadzu CLASS-VP software. Polarimetric detector (JASCO, Japan) was connected to UV detector in series for identification of the enantiomers. Chiralcel OD–H (250 mm × 4.6 mm; particle size 5 μm), DNB-Leucine (250 mm × 4.6 mm; particle size 5 μm), L-PG (250 mm × 4.6 mm; particle size 5 μm),Whelk-O1 (250 mm × 4.6 mm; particle size 5 μm) (Regis Technologies, USA), and Kromasil CHI-DMB (250 mm × 4.6 mm; particle size 5 μm) (Akzo Nobel, Sweden) were used for separation.

Acenaphthene and $NaCNBH_3$ were purchased from Sigma. 10-Undecenoyl chloride was obtained from Fluka. *n*-Hexane and 2-propanol of HPLC grade were was purchased from Merck. Other reagents supplied by Bodi Chemical Co., Ltd (Tianjin, China) were all of analytical grade. The solvents were dried according to common methods, distilled, and stored under argon.

4.2. Synthesis of 5-ethylaminoacenaphthene 2

Compound **2** was synthesized according to a literature method[10] with some modifications. In a reaction vessel were mixed 5-acetylacenaphthene (2.5 g, 12.8 mmol), prepared from acenaphthene,[12,13] sodium cyanoborohydride (2.3 g, 37.1 mmol), ammonium acetate (39.5 g, 512 mmol), and 2-propanol (100 mL). After the reaction vessel was securely closed, the contents were heated to 90–95 °C for 12 h. The solvent was removed under reduced pressure; subsequently distilled water (100 mL) was added. The mixture was extracted three times with ether (3 × 50 mL). Hydrochloric acid (1 mol/L, 50 mL) was added to the combined ether layer and stirred. The aqueous phase was washed two times with ether (2 × 50 mL), separated and neutralized to pH 7 with sodium hydroxide (1 mol/L). The mixture was extracted three times with ethyl acetate (3 × 50 mL). The combined ethyl acetate layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to afford **2** (1.95 g, 78%). ^{1}H NMR ($CDCl_3$): δ 1.54 (d, 3H), 1.92 (s, 2H), 3.38 (s, 4H), 4.84 (q, 1H), 7.25–7.81 (m, 5H). Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10. Found: C, 84.92; H, 7.93; N, 7.15.

4.3. Synthesis of 5-(10-undecenethylamido)-acenaphthene 3

Triethylamine (0.8 mL, 5.8 mmol) and 10-undecenoyl chloride (1.1 mL, 5.1 mmol) were added to a solution of **2** (1.0 g, 5.1 mmol) in dry tetrahydrofuran (20 mL). The mixture was stirred for 1 h at 30 °C. The solid was filtered out and the filtrate was evaporated under reduced pressure. Dichloromethane (20 mL) was added to the residue and the solution was washed with water (3 × 20 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give a crude product, which was purified by column chromatography (dichloromethane: methanol, 98:2, silica gel column, length: 50 cm, diameter: 2 cm) to afford **3** (1.56 g, 84.4%): mp 87.5–88.5 °C; IR(KBr): 3267, 3053, 2975, 2923, 2852, 1731, 1628, 1459, 1546, 1423, 1370, 1252, 1178, 1110, 995, 91,838, 785, 643 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 10H), 1.58 (d, 2H), 1.64 (d, 3H), 2.00 (d, 1H), 2.14 (d, 2H), 2.16 (s, 2H), 3.37 (s, 4H), 4.91 (d, 1H), 5.00 (d, 1H), 5.64 (d, 1H), 5.72–5.86 (m, 1H), 7.21–7.77 (m, 5H); MS(EI) *m*/*z*: 262 [M^+]. Anal. Calcd for $C_{25}H_{33}NO$: C, 82.64; H, 9.09; N, 3.86. Found: C, 82.57; H, 9.12; N, 3.79.

4.4. Resolution of 3 with different columns

The selectivity of five different columns, Chiralcel OD-H, DNB-Leucine, DNB-PG, Whelk-O1 and Kromasil CHI-DMB, on resolution and retention of compound **3** was studied. The operation conditions: the mobile phase: *n*-hexane to 2-propanol = 90:10 (v/v), the flow rate: 1.5 mL/min, the wavelength: 254 nm, the column temperature: 30 °C, the injection volume: 20 μL. A polarimetric detector was connected to UV detector in series for identification of the enantiomers.

4.5. Preparation of 4a and 4b

The enantiomers of compound **3** were chromatographically separated on a DNB-Leucine using 10% 2-propanol in *n*-hexane as the eluent. Therefore, 30 mg of compound **3** was dissolved in 7.5 mL eluent. The solution was repeatedly injected to the HPLC system. The chromatographic conditions were as same as indicated in Section 4.4. Fractions containing the same isomer were combined and the solvent removed on a rotavapor. With the above mentioned process, 7.8 mg (26%) of (*R*)-(+)-5-(10-undecenethylamido)-acenaphthene **4a**, $[\alpha]_D^{30} = +46.7$ (*c* 1.0, C_2H_5OH), and 7.8 mg (26%) of (*S*)-(−)-5-(10-undecenethylamido)-acenaphthene **4b**, $[\alpha]_D^{30} = -46.7$ (*c* 1.0, C_2H_5OH), were obtained.

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