Asian Journal of Chemistry Vol. 22, No. 5 (2010), 3923-3928

Synthesis and Enantiomer Separation of 5-(1-(3,5-Dinitrobenzoylamino)pent-4-enyl)acenaphthene

CHAO XU, WEN-FENG LUO, LI-JUN LI, SHUN YAO and HANG SONG*
Department of Pharmaceutical and Biological Engineering, Sichuan University, Sichuan, P.R. China
Tel/Fax: (86)(288)5405221; E-mail: hangsong@scu.edu.cn

A new racemic (±) 5-(1-(3,5-dinitrobenzoylamino)pent-4-enyl)-acenaphthene was synthesized and successfully separated into enantiomers on chiral HPLC. The synthetic approach to the 5-(1-(3,5-dinitrobenzoylamino)pent-4-enyl)acenaphthene is *via* Friedel-Crafts acylation reaction to the acenaphthyl ring, α-H substituent reaction to the ketone, deoxidization reaction to the ketone and amidation reaction to the amidocyanogen. The chemical structure of this compound was characterized by FT-IR and ^{1}H NMR.

Key Words: Amide derivative chiral selector, Synthesis, Chiral separation, 5-(1-(3,5-Dinitrobenzoylamino)pent-4-enyl)acenaphthene.

INTRODUCTION

Enantioselective separation on chiral stationary phases in HPLC is essential in several research fields such as pharmaceutical, agrochemical and food chemistry. A variety of chiral stationary phases have been developed[1-4]. Pirkle type of chiral stationary phases have been proved to be the most practical chiral stationary phases and have been widely used in HPLC enantioseparation[5]. These chiral stationary phases contain a low molecular weight chiral selector covalently linked to the silica gel surface[6]. The chiral selectors contain π-acid or π-base aromatic groups, polar bonds or groups which can form dipole-dipole interaction, atoms or groups which can form hydrogen bond[7,8].

On the basis of resolution mechanism of these chiral stationary phases, we synthesized the racemic 5-(1-(3,5-dinitrobenzoylamino)pent-4-enyl)acenaphthene (**5**) for preparing potential novel chiral selector of chiral stationary phase. The direct enantioseparation of **5** on chiral stationary phase for obtaining single enantiomer **6a** and **6b** were accomplished. In addition, the specific optical rotations of the isolated enantiomers were measured.

EXPERIMENTAL

Nuclear magnetic resonance (NMR) spectra were recorded on an INOVA-400 spectrometer. 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). The HPLC system consisted of an LC-20AT pump and an SPD-M20A diode array detector. Data acquisition was done on Shimadzu

CLASS-VP software. Polarimetric detector (Jasco, Japan) was connected to UV detector in series for identification of the enantiomers. 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. Acetyl chloride and bromopropene were obtained from Fluka. 2-Propanol and *n*-hexane in HPLC level 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.

Synthesis of 5-acetylacenaphthene (2): In a three-neck round flask with condenser, $AlCl_3$ (24 g, 180 mmol), 240 mL dry CH_2Cl_2 and acetyl chloride (8 mL, 112 mmol) were added under ice-bath. The mixture was stirred for 15 min, after which acenaphthene (20.8 g, 135 mmol) dissolved in 120 mL CH_2Cl_2 was dropping into the flask slowly. Then the ice-bath was removed and the mixture was stirred at 20 ºC for 35 min. Ice-water was added into the flask to terminate the reaction, the CH_2Cl_2 layer was isolated and washed two times by saturated Na_2CO_3 solution and water. The combined CH_2Cl_2 layer was dried with anhydrous magnesium sulphate, filtered, evaporated and recrystallized in *n*-hexane to afford **2**. ^{1}H NMR ($CDCl_3$): δ 2.75 (s, 3H), 3.41 (s, 4H), 7.27-8.67 (m, 5H); IR (KBr, ν_{max}, cm^{-1}): 3036, 2921, 1661, 1598, 1496, 1421, 1396, 776, 601.

Synthesis of 1-(acenaphthene-5-yl)pent-4-en-1-one (3): In a three-neck round flask with condenser, potassium *tert*-butoxide (8.2 g, 73 mmol), dry toluene (120 mL) and bromopropene (6.3 g, 41 mmol) were added under nitrogen. The mixture was heated to 50 ºC, after which 5-acetylacenaphthene (6 g, 31 mmol) dissolved in 40 mL dry toluene was dropping into the flask. Then the mixture was heated to reflux for 3 h. The toluene layer was isolated and washed three times by distilled water. The combined toluene layer was dried with anhydrous magnesium sulphate, filtered, evaporated to afford **3**. ^{1}H NMR ($CDCl_3$): δ 2.34-2.37 (q, 2H), 2.56-2.60 (t, 2H), 3.43(s, 4H), 4.97-5.08 (q, 1H), 5.08-5.10 (q, 1H), 5.77-5.82 (m, 1H), 7.27-8.51(m, 5H); IR (KBr, ν_{max}, cm^{-1}): 3074, 1669, 1639, 1601, 1440, 995, 916, 780.

Synthesis of 1-(acenaphthene-5-yl)pent-4-en-1-amine (4): In a reaction vessel were mixed 1-(acenaphthene-5-yl)pent-4-en-1-one (1 g, 4.2 mmol), sodium cyanoborohydrie (1.3 g, 21 mmol), ammonium acetate (9.8 g, 127 mmol) and 2-propanol (10 mL). After the reaction vessel was securely closed, the contents were heated to 110 ºC for 24 h. The solvent was removed under reduced pressure; subsequently distilled water was added. The mixture was extracted three times with ether. The combined ethyl acetate layer was dried with anhydrous magnesium sulphate, filtered and evaporated to afford **4**. ^{1}H NMR (DMSO): δ 1.99 (s, 2H), 2.09-2.18 (q, 2H), 3.38 (s, 4H), 5.01 (s, 1H), 5.17 (m, 1H), 5.68 (s, 1H), 7.09-7.50 (m, 5H); IR (KBr, ν_{max}, cm^{-1}): 3289, 2929, 2884, 2413, 2287, 2197, 1662, 1542, 1380, 1262, 1164, 1093, 1036, 919, 801, 662, 607.

Synthesis of 5-(1-(3,5-dinitrobenzoylamino)pent-4-enyl)acenaphthene (5): Triethylamine (0.53 mL, 3.8 mmol) and benzoyl chloride (0.87 g, 3.8 mmol) were added to a solution of 4 (0.6 g, 2.5 mmol) in dry CH_2Cl_2 (50 mL). The mixture was stirred for 2 h at 30 ºC. 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 (petroleum ether: ethyl acetate, 90:10, silica gel column, length: 50 cm, diameter: 2 cm) to afford **3** (0.31 g, 28 %). ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 2H), 2.34 (s, 2H), 3.37 (s, 4H), 5.02-5.06 (q, 1H), 5.11 (d, 1H), 5.23-5.27 (d, 1H), 5.81-5.90 (m, 1H), 5.99-6.08 (m, 1H), 7.10-7.84 (m, 5H), 8.91 (s, 2H), 9.12 (s, 1H); IR (KBr, ν_{max}, cm^{-1}): 3091, 2881, 2675, 2539, 1706, 1629, 1543, 1469, 1415, 1349, 1282, 1174, 1084, 1013, 922, 725, 533.

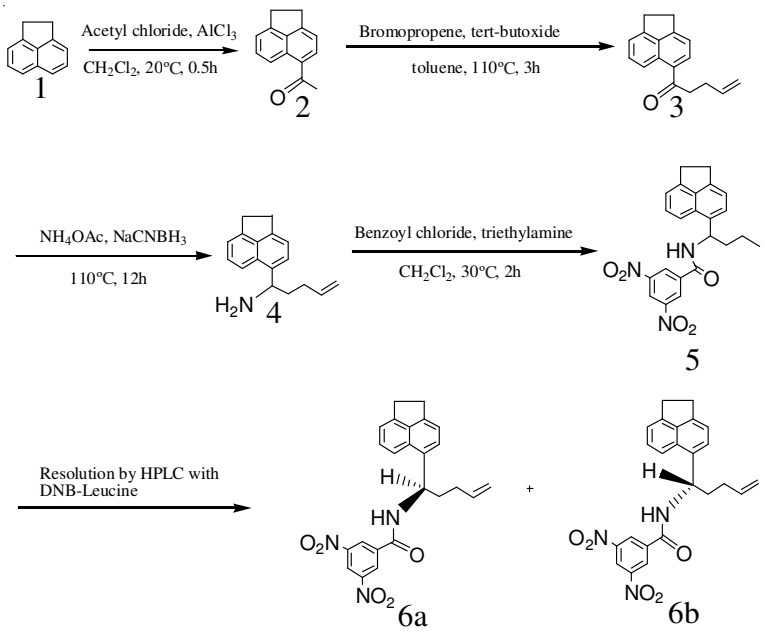
Resolution of 5 with different chiral stationary phases: The resolution and retention of compound **5** on four different chiral columns, DNB-leucine, DNB-PG, Whelk-O1 and SH-1, was investigated. The HPLC operation conditions: the mobile phase: *n*-hexane to 2-propanol = 90: 10 (v/v), the flow rate: 1 mL/min, the wavelength: 254 nm, the column temperature: 25 ºC, the injection volume: 20 µL. A polarimetric detector was connected to UV detector in series for identification of the enantiomers.

Preparation of 6a and 6b: The enantiomers of compound **5** were chromatographically separated on a DNB-leucine using 10 % 2-propanol in *n*-hexane as the eluent. And 40 mg of compound **5** was dissolved in 10 mL toluene. The solution was repeatedly injected to the HPLC system. The chromatographic conditions were as same as given for resolution of compound **5**. Fractions containing the same isomer were combined and the solvent removed on a rotavapor. With the above mentioned process, 10 mg of (R)-(+)-5-(1-(3, 5-dinitrobenzoylamino)pent-4-enyl)-acenaphthene (**6a**), $[\alpha]_{20}$ D= +12.00 (c 1, C_2H_5OH) and 10 mg of (S)-(-)-5-(1-(3,5-dinitrobenzoylamino)pent-4-enyl)acenaphthene (**6b**), $[\alpha]_{20}$ D = -12.06 (c 1, C_2H_5OH), were obtained (**Scheme-I**).

RESULTS AND DISCUSSION

Synthesis of 5-acetyl acenaphthene (2): The results showed that both 5-acetyl acenaphthene and 3-acetyl acenaphthene can be generated in the reaction. The synthesis was carried out according to the Friedel-Craft acylation reaction, which involves the acylation of acenaphthene with acetyl chloride in the presence of $AlCl_3$. After the recrystallization with the mixture of *n*-hexane and ether as eluent, compound **2** was obtained in 75 % yield, 99 % purity and the by-product 3-acetyl acenaphthene can be removed almost completely. The composition of **2** was verified by ^{1}H NMR and IR.

Synthesis of 1-(acenaphthene-5-yl)pent-4-en-1-one (3): Compound **3** was prepared according to the α-carbonyl nucleophilic substituted reaction, which involves the substituted reaction of 5-acetyl acenaphthene with bromopropylene catalyzed by potassium *tert*-butoxide. Compound **3** was obtained in 76 % yield. The composition of **3** was verified by ^{1}H NMR and IR.



Scheme-I: The chemical process

Synthesis of 1-(acenaphthene-5-yl)pent-4-en-1-amine (4): Compound **4** can be obtained from **3** according to a literature method[9] 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 **4** was obtained in 60 % yield after 24 h when the mole ratio of 1-(acenaphthene-5-yl)pent-4-en-1-one, sodium cyanoborohydride and ammonium acetate was 1:5:30. After chromatographic purification with the mixture of petroleum ether and ethyl acetate as eluent, compound **4** was obtained in 41 % yield, 98 % purity. The composition of **4** was verified by ^{1}H NMR and IR.

Synthesis of 5-(1-(3, 5-dinitrobenzoylamino)pent-4-enyl)acenaphthene (5): Racemic **5** was prepared by coupling of compound **4** and benzoyl chloride using triethylamine in CH_2Cl_2. The reaction was monitored by TLC. When no compound **4** was observed, the solid was filtered out and the filtrate was evaporated under reduced pressure. Water was added to the CH_2Cl_2 solution of residue to remove any water-soluble impurity. After chromatographic purification with the mixture of petroleum ether and ethyl acetate as eluent, compound **5** was obtained in 28 % yield, 99 % purity. The composition of **5** was verified by ^{1}H NMR and IR.

Resolution of 5-(1-(3,5-dinitrobenzoylamino)pent-4-enyl)-acenaphene (5): The selectivity of four columns, DNB-leucine, DNB-PG, Whelk-O1 and SH-1, which structures are shown in Fig. 1, on the resolution and retention of compound **5** was investigated. The results suggest that compound **5** 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 **5**.

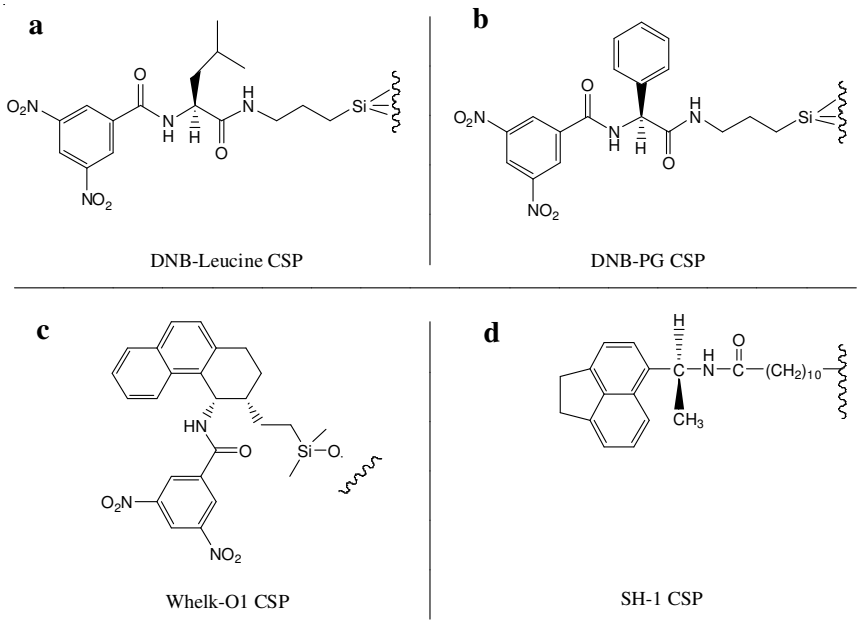


Fig. 1. Structure of the chiral stationary phases

TABLE-1
ENANTIOSELECTIVE HPLC RESOLUTION OF COMPOUND **5**
ON DNB-LEUCINE, DNB-PG AND WHELK-O1

CSPs	k_1'	k_2'	α	R
DNB-Leucine	10.584	15.620	1.47	3.39
DNB-PG	11.075	17.303	1.56	2.56
Whelk-O1	4.221	7.735	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 mL/min, the wavelength: 254 nm, the column temperature: 30 ºC, the injection volume: 20 µL.

The electron-donating groups -CH_2 on the acenaphthyl ring and electron withdrawing group -NO_2 on the benzoyl chloride can enhance π-π interaction in the process of chiral recognition. Amide hydrogen atom can form hydrogen bonding interaction with the CSPs which is important for chiral recognition. Basing on the notion of reciprocity in chiral recognition[9], the single isomer of compound **5** may be developed as chiral selector of CSP. The proposed CSP would 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 apply in chiral separation.

A polarimetric detector was connected to UV detector in series for identification of **6a** and **6b**. The chromatographic separation is shown in Fig. 2. The specific rotation of **6a** and **6b** were measured with an automatic polarimeter. The absolute configurations of **6a** and **6b** were deduced with the help of Brewster's model[10].

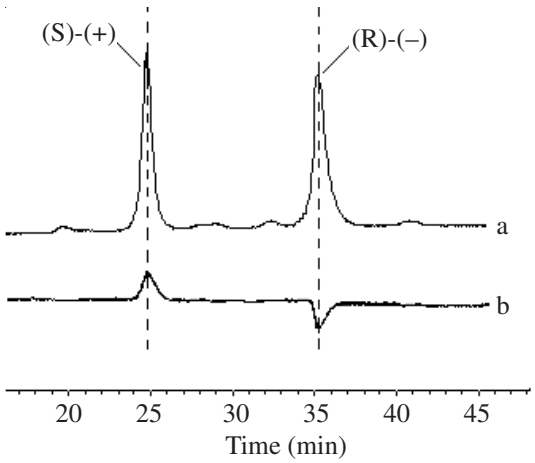


Fig. 2. Chromatogram of compound **5** detected by UV detector (a) and OR detector (b)

Preparation of 6a and 6b: DNB-Leucine with highest R value was selected to isolate the enantiomers of compound **5**. This was accomplished by repeating 25 µL injections of racemic **5** (40 mg) in the eluent and collecting the eluates corresponding to the two major chromatographic peaks to obtain 10 mg of each compound. Analytical HPLC identified 100 % enantiomeric excess (e.e) of the eluates. Specific rotation $[\alpha]_{20}$ D = +12.06 (c 1, C_2H_5OH) was measured for the first eluted sample of compound **5**, while the second afforded an experimental $[\alpha]_{20}$ D = -12.06 (c 1, C_2H_5OH).

Conclusion

In summary, we have prepared a racemic sample of 5-(1-(3,5-dinitrobenzoylamino)pent-4-enyl)acenaphthene. The compound was separated on chiral HPLC and the chiral stationary phase of the single enatiomeric compounds is currently underway and will be reported in due course.

REFERENCES

1. W. Lao and J. Gan, *Chromatogr. A*, **1216**, 5020 (2009).
2. W. Bicker, I. Chiorescu and V.B. Arion, *Tetrahedron: Asym.*, **19**, 97 (2008).
3. C. Moiteiro, N. Fonseca and J.M. Maria, *Tetrahedron: Asym.*, **17**, 3248 (2006).
4. I. Ali, L. Naimb, A. Ghanemc and H.Y. Aboul-Enein, *Talanta*, **69**, 1013 (2006).
5. X.L. Tan, S.C. Hou, Q.H. Bian and M. Wang, *Chin. Chem. Lett*., **18**, 461 (2007).
6. W.H. Pirkle and T.C. Pochapsky, *Chem. Rev*., **89**, 347 (1989).
7. J.J. Ryoo, T.H. Kim, S.H. Im, Y.H. Jeong, J.Y. Park, S.-H. Choi, K.-P. Lee and J.H.J. Park, *Chromatogr. A*, **987**, 429 (2003).
8. C. Wolf and W.H. Pirkle, *Tetrahedron*, **58**, 3597 (2002).
9. W.H. Pirkle, C.J. Welch and B. Lamm, *J. Org. Chem*., **57**, 3854 (1992).
10. J.H. Brewster, *J. Am. Chem. Soc*., **81**, 5475 (1959).

(*Received*: 24 August 2009; *Accepted*: 23 January 2010) AJC-8354