Preparation of a New Chiral Stationary Phase Based on (2*S*,3*S*)-*O*,*O'*-Bis-(10-undecenoyl)-*N*,*N'*-bis-(3,5-dinitrobenzoyl)-2,3-diamino-1,4-butandiol and Its Application for the Liquid Chromatographic Resolution of Enantiomers

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A new liquid chromatographic chiral stationary phase based on (2*S*,3*S*)-*O*,*O'*-bis-(10-undecenoyl)-*N*,*N'*-bis-(3,5-dinitrobenzoyl)-2,3-diamino-1,4-butandiol was prepared starting from (2*R*,3*R*)-1,4-bis(benzyloxy)-2,3-butanediol. The new chiral stationary phase was applied to the resolution of racemic anilide derivatives of *N*-acetyl-α-amino acids, 1,1'-bi-2-naphthol and 3,3'-diaryl-1,1'-bi-2-naphthols. The CSP was also applied to the resolution of some chiral drugs including a diuretic, bendroflumethiazide, and non-steroidal anti-inflammatory agents such naproxen and alminoprofen. In every case, the chiral recognition efficiency of the new CSP was quite excellent.

Key Words : Chiral stationary phase, Enantiomer separation, Liquid chromatography

Introduction

Liquid chromatographic chiral stationary phases (CSPs) have been known very effective in the exact determination of enantiomeric composition of chiral compounds. Various chiral selectors bonded to column supporting material such as silica gel have been utilized as liquid chromatographic CSPs. Proteins,[1] cellulose derivatives,[2] cyclodextrins,[3] macrocyclic antibiotics,[4] amino acid derivatives,[5] chiral crown ethers[6] and synthetic low molecular weight optically active chiral molecules[7] have been successfully utilized as chiral selectors for liquid chromatographic CSPs.

C_2 symmetric chiral compounds have also been sparingly utilized as chiral selectors for liquid chromatographic CSPs. For example, C_2 symmetric chiral selectors such as *O*,*O'*-di-*p*-*tert*-butylbenzoyl-*N*,*N'*-diallyl-*L*-tartaramide (**1a**, Figure 1), *O*,*O'*-bis-(3,5-dimethylbenzoyl)-*N*,*N'*-diallyl-*L*-tartardiamide (**1b**, Figure 1) and (+)-trans-9,10-dihydro-9,10-ethano-anthracene-11,12-dicarboxylic acid bis-allylamide (**2**, Figure 1) have been successfully utilized as chiral selectors for liquid chromatographic CSPs.[8] As an effort to develop different type C_2 symmetric chiral selectors, in this study, we first prepared a new chiral selector material, (2*S*,3*S*)-*O*,*O'*-bis-(10-undecenoyl)-*N*,*N'*-bis-(3,5-dinitrobenzoyl)-2,3-diamino-1,4-butandiol (**3**, Figure 1), starting from (2*R*,3*R*)-1,4-bis(benzyloxy)-2,3-butanediol and bonded it to silica gel to get a new liquid chromatographic CSP. Herein, we wish to report the details for the preparation of a new CSP (CSP **4**, Figure 1) based on (2*S*,3*S*)-*O*,*O'*-bis-(10-undecenoyl)-*N*,*N'*-bis-(3,5-dinitrobenzoyl)-2,3-diamino-1,4-butandiol (**3**) and its application to the liquid chromatographic separation of enantiomers.

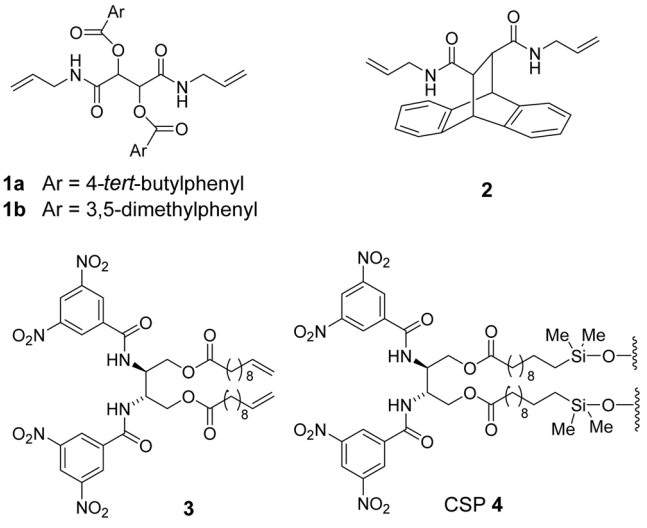


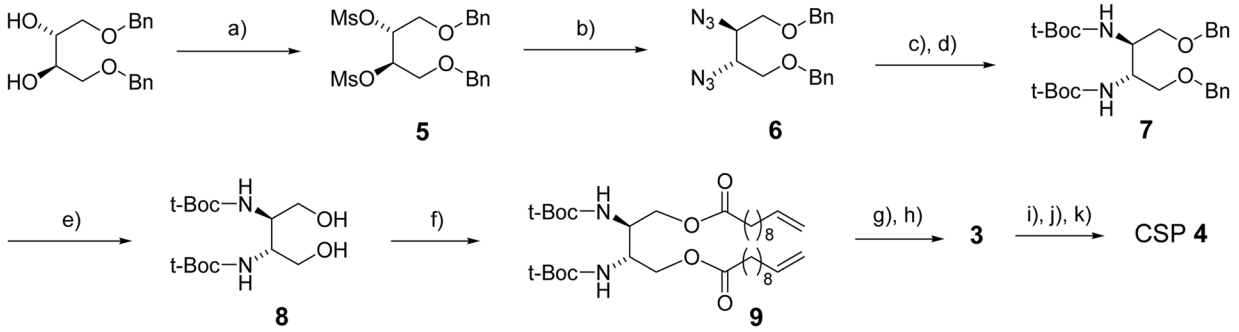
Figure 1. Structures of chiral compounds **1**, **2** and **3** and CSP **4**.

Experimental Section

General. ^{1}H NMR spectra were recorded with a Varian Gemini 200 spectrometer. Chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane as an internal standard. IR spectra were measured with a Jasco FT/IR-300E. Optical rotations were taken on a Rudolph Research Analytical AUTOPOL IV Polarimeter.

Chromatography was performed with an HPLC system consisting of a Waters model 510 HPLC Pump, a Rheodyne model 7725i injector with a 20 μL sample loop, a Waters 484 Tunable Absorbance Detector and a YoungLin Autochro Data Module (Software: YoungLin Autochro-WIN 2.0 plus). The temperature of the chiral column was controlled by using a Julabo F30 Ultratemp 2000 cooling circulator.

Each of racemic samples was available from previous studies or purchased from Aldrich. Optically active 1,1'-bi-2-naphthol and optically active naproxen were available



Scheme 1. (a) methansulfonyl chloride, triethylamine, CH_2Cl_2, 0 °C. (b) sodium azide, DMSO, 80 °C. (c) $LiAlH_4$, THF, 0 °C. (d) di-*tert*-butyl dicarbonate, triethylamine, water/dioxane (1 : 1, v/v), room temperature. (e) Pd/C (10%), H_2 gas, methanol, room temperature. (f) 10-undecenoyl chloride, triethylamine, CH_2Cl_2, room temperature. (g) HCl gas, CH_2Cl_2, room temperature. (h) 3,5-dinitrobenzoyl chloride, triethylamine, CH_2Cl_2, 0 °C. (i) chlorodimethylsilane, Pt/C, THF, reflux. (j) ethanol/triethylamine (1 : 1, v/v), CH_2Cl_2, 0 °C, (k) 5 μm silica gel, toluene, reflux.

from Aldrich. Optically active 3,3'-diary-1,1'-bi-2-naphthols, which have been prepared from optically active 1,1'-bi-2-naphthol by Suzuki coupling reaction, were available from previous study.[9] Optically active bendroflumethiazide and optically active alminoprofen were not available. Each of racemic and optically active samples was dissolved in methylene chloride (usually 2.5 mg/mL) and then used for the resolution on CSP **4**. The usual injection volume was 0.1 μL. However, the elution volume was varied slightly according to the size of the chromatographic peaks corresponding to the two enantiomers.

Preparation of CSP 4. CSP **4** was prepared starting from (2*R*,3*R*)-1,4-bis(benzyloxy)-2,3-butanediol (available from Aldrich) as shown in Scheme 1.

(2*R*,3*R*)-1,4-Bis(benzyloxy)-2,3-butanediol bis(methansulfonate), 5. (2*R*,3*R*)-1,4-Bis(benzyloxy)-2,3-butanediol (3.00 g, 9.93 mmol) and triethylamine (4.1 mL, 29.7 mmol) were dissolved in 70 mL of methylene chloride in 250 mL round bottom flask. To the solution cooled to 0 °C for 30 min was slowly added methansulfonyl chloride (1.8 mL, 23.8 mmol) dissolved in 10 mL of methylene chloride. The whole reaction mixture was stirred at room temperature for 10 h. The mixture was washed with 1.0 M HCl solution and then brine. The organic solution was dried over anhydrous Na_2SO_4 and then evaporated to dryness. The residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane: 1/1) to afford compound **5** (4.05 g, 89% yield). ^{1}H NMR ($CDCl_3$) δ (ppm) 3.30 (s, 6H), 3.74-3.78 (d, 4H), 4.43-4.60 (m, 4H), 4.98-5.01 (m, 2H), 7.25-7.39 (m, 10H).

(2*S*,3*S*)-*O*,*O'*-Dibenzyl-2,3-diazido-1,4-butanediol, 6. Compound **5** (4.05 g, 8.84 mmol) and NaN_3 (2.0 g, 31.0 mmol) were dissolved in 20 mL of dimethylsulfoxide in 100 mL round bottom flask. The reaction mixture was stirred for 18 h at 90 °C and then diluted with 40 mL of brine. The mixture was extracted with 50 mL of methylene chloride three times. The combined organic layer was dried over anhydrous Na_2SO_4 and then evaporated to dryness. The residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane: 1/3) to afford compound **6** (2.89 g, 93% yield). ^{1}H NMR ($CDCl_3$) δ (ppm) 3.65-3.76 (m, 4H), 3.74-3.78 (m, 2H), 4.56 (s, 4H), 7.31-7.36 (m, 10H).

(2*S*,3*S*)-*N*,*N'*-Di-*tert*-Butyloxycarbonyl-1,4-benzyloxy-2,3-butanediamine, 7. $LiAlH_4$ (0.9 g, 24.8 mmol) was dissolved in 70 mL of dry tetrahydrofuran in 250 mL round bottom flask and then stirred at 0 °C for 30 min. To the solution was added compound **6** (2.89 g, 8.21 mmol). The whole mixture was stirred for 2 h at 0 °C and then the reaction was stopped by adding 50 mL of water slowly. The solution was passed through a *Celite* pad and then washed with water. The organic layer was dried over anhydrous Na_2SO_4 and then evaporated to dryness to afford a colorless oily material (2.41 g, 98%), the structure of which was confirmed by ^{1}H NMR as (2*S*,3*S*)-1,4-benzyloxy-2,3-butanediamine [^{1}H NMR ($CDCl_3$) δ (ppm) 1.71 (s, 4H), 2.98-3.02 (m, 2H), 3.37-3.51 (m, 4H), 4.50 (s, 4H), 6.98-7.35 (m, 10H)]. Without further purification, (2*S*,3*S*)-1,4-benzyloxy-2,3-butanediamine (2.4 g, 8.1 mmol) was stirred with triethylamine (3.4 mL, 24.3 mmol) and water (20 mL) at room temperature for 10 min in 100 mL round bottom flask. After adding 20 mL of 1,4-dioxane, the mixture was stirred for 10 min and then di-*tert*-butyl dicarbonate (4.5 mL, 19.5 mmol) was added and the whole solution was stirred at room temperature for 24 h. The reaction mixture was evaporated to dryness. The residue was dissolved in 50 mL of methylene chloride and the resulting solution was washed with 6 M HCl solution. The organic solution was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by flash column chromatography (ethyl acetate/hexane: 1/4) to afford compound **7** (3.57 g, 87%). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.42 (s, 18H), 3.47 (m, 4H), 3.98 (m, 2H), 4.43 (dd, 4H), 5.23 (broad, 2H), 7.25-7.37 (m, 10H).

(2*S*,3*S*)-*N*,*N'*-Di-*tert*-butyloxycarbonyl-2,3-diamino-1,4-butanediol, 8. To the stirred mixture of Pd/C (10%, 0.4 g) in 20 mL of methanol in 100 mL round bottom flask was added compound **7** (4.00 g, 8.00 mmol) and then H_2 gas was bubbled for 48 h. The reaction mixture was passed through a *Celite* pad and evaporated to dryness. The residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane: 2/1) to afford compound **8** (2.07 g, 81%). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.47 (s, 18H), 2.98 (broad, 2H),

3.44-4.86 (m, 4H), 3.85 (m, 2H), 4.93 (broad, 2H).

(2*S*,3*S*)-*O*,*O'*-Bis-(10-undecenoyl)-*N*,*N'*-di-*tert*-butyloxycarbonyl-2,3-diamino-1,4-butanediol, 9. Compound **8** (2.07 g, 6.47 mmol) and triethylamine (2.7 mL, 19.6 mmol) were dissolved in 70 mL of methylene chloride. To the stirred solution was slowly added 10-undecenoyl chloride (3.4 mL, 15.7 mmol). The whole mixture was stirred for 24 h at room temperature. The reaction mixture was washed with 1.0 M HCl solution, 1.0 M NaOH solution and then brine. The organic solution was dried over anhydrous Na_2SO_4 and then evaporated to dryness. The residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane: 1/8) to afford compound **9** (3.84 g, 91%). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.27 (broad, 20 H), 1.41 (s, 18H), 1.56-1.73 (m, 4H), 2.02 (m, 4H), 2.26-2.34 (m, 4H), 3.97 (broad, 2H), 4.13 (m, 4H), 4.86-5.01 (m, 4H), 5.05 (m, 2H), 5.69-5.90 (m, 2H).

(2*S*,3S)-*O*,*O'*-Bis-(10-undecenoyl)-*N*,*N'*-bis-(3,5-dinitrobenzoyl)-2,3-diamino-1,4-butandiol, 3. Compound **9** (3.84 g, 5.89 mmol) was dissolved in 30 mL of methylene chloride in 100 mL round bottom flask. Through the solution was bubbled HCl gas, which was slowly produced by adding concentrated H_2SO_4 (20 mL) to NaCl (80 g), and then the whole mixture was stirred for 8 h at room temperature. The reaction mixture was evaporated ant the residue was dissolved in 70 mL of methylene chloride in 250 mL round bottom flask. Triethylamine (3.4 mL, 24.3 mmol) was added to the solution. The whole mixture was cooled to 0 °C and then 3,5-dinitrobenzoyl chloride (3.4 g, 14.6 mmol) was added. The whole mixture was stirred for 1 h at room temperature and then washed with 1.0 M HCl solution, 1.0 M NaOH solution and then brine. The organic solution was dried over anhydrous Na_2SO_4 and then evaporated to dryness. The residue was purified by flash column chromatography on silica gel (ethyl acetate/methylene chloride: 1/9) to afford compound **3** (3.96, g, 80%) as a brownish sticky solid. $[\alpha]_D^{25}$ +0.53 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.27 (s, 20H), 1.58-1.68 (m, 4H), 1.96-2.05 (m, 4H), 2.43 (m, 4H), 4.44-4.60 (m, 4H), 4.60 (m, 2H), 4.87-5.02 (m, 4H), 5.68-5.88 (m, 2H), 8.06 (d, 2H), 8.96-9.13 (m, 6H); IR (KBr, cm^{-1}) 3290, 3088, 2926, 2855, 1738, 1647, 1545, 1460.

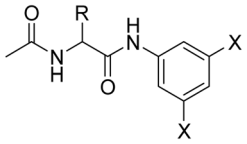
Preparation of CSP 4 and column packing. Compound **3** (2.34 g, 2.79 mmol) and Pt/C (5 mg) was added to 50 mL of tetrahydrofuran in 250 mL round bottom flask and the heterogeneous solution was stirred for 30 min. To the heterogeneous solution was added chlorodimethylsilane (11 mL, 20 eq.). The whole mixture was refluxed for 6 h under an argon atmosphere. The reaction mixture was evaporated and the residue was dissolved in 10 mL of methylene chloride. To the solution was slowly added 10 mL of the mixed solution of ethyl alcohol/triethylamine (1 : 1, v/v). The whole mixture was stirred at room temperature for 30 min and then evaporated. The residue was purified by flash column chromatography on silica gel to afford hydrosilylated compound (1.56 g, 55%) as a white sticky material [^{1}H NMR ($CDCl_3$) δ(ppm) 0.1 (s, 12H), 0.5 (m, 4H), 1.12-1.33 (m, 34H), 1.54-1.68 (m, 4H), 2.47 (m, 4 H), 3.64 (q, 4H), 4.44-4.61 (m, 6H), 8.07 (broad, 2H), 9.13-9.15 (m, 6H)]. The hydrosilylated compound was used for the preparation of CSP **4**. For the preparation of CSP **4**, a 250 mL flask equipped with a Dean-Stark trap, a condenser and a magnetic stirring bar was charged with Kromasil silica gel (4.2 g, 5 μm, 100 Å available from Eka Chemicals.) and toluene (100 mL). The mixture was heated to reflux until the complete azeotropic removal of water. To the heterogeneous solution was added the hydrosilylated compound (1.56 g, 1.53 mmol) dissolved in 10 mL of toluene. The whole mixture was heated to reflux for 72 h and then cooled to room temperature. The modified silica gel was collected by filtering and then washed successively with toluene, methanol, acetone, ethyl acetate, methylene chloride, hexane and diethyl ether. Finally, the modified silica gel was dried under high vacuum. Elemental analysis of the modified silica gel (Found: C, 7.37%; H, 1.22%; N, 0.80%) showed a loading of 0.14 mmol of selector (based on C) or 0.10 mmol of selector (based on N) per gram of stationary phase. The modified silica gel was slurried in methanol and packed into a 250 mm × 4.6 mm I.D. stainless-steel HPLC column using a conventional slurry packing method with an Alltech slurry packer.

Results and Discussion

CSP **4** prepared *via* the method described in Scheme 1 contains two strong π-acidic 3,5-dinitrobenzoyl groups. Previously, Pirkle-type CSPs have been known to resolve racemic compounds through the enantioselective π-π donor-acceptor interaction between the CSP and analytes.[10] In this instance, the two strong π-acidic 3,5-dinitrobenzoyl groups of CSP **4** are expected to be utilized as effective π-acceptor sites for the resolution of racemic π-basic analytes.

CSP **4** was applied to the resolution of various π-basic compounds. First of all, CSP **4** was applied to the resolution of anilide derivatives **10** of *N*-acetyl-α-amino acids. The chromatographic results for the resolution of anilide derivatives **10** of *N*-acetyl-α-amino acids on CSP **4** are summarized in Table 1. As shown in Table 1, anilide derivatives **10** of *N*-acetyl-α-amino acids are resolved quite well on CSP **4**. The chromatographic results for the resolution of anilide derivatives **10** of *N*-acetyl-α-amino acids on CSP **4** are also graphically illustrated in Figure 2. The representative chromatograms for the resolution of simple anilide (X = H), 3,5-dimethylanilide (X = CH_3) and 3,5-dimethoxyanilide (X = OCH_3) derivative of a certain *N*-acetyl-α-amino acid (**10b**, R = CH_2CH_3) on CSP **4** are shown in Figure 3. As the π-basicity of the anilide derivatizing group of *N*-acetyl-α-amino acids increases, the retention (k) and the separation factors (α) increase as shown in Table 1, Figure 2 and Figure 3. Among the simple anilide, 3,5-dimethylanilide and 3,5-dimethoxyalinide derivatives of *N*-acetyl-α-amino acids, 3,5-dimethoxyalinide derivatives were resolved best with the longest retention times. From these results, the π-π donor acceptor interaction between the 3,5-dinitrobenzoyl group of

Table 1. Resolution of anilide derivatives 10 of *N*-acetyl-α-amino acids on CSP **4**[a]



10

	R	X	k_1	k_2	α
10a	CH_3	H	4.10	4.72	1.15
		CH_3	4.83	6.15	1.27
		OCH_3	12.69	19.74	1.56
10b	CH_2CH_3	H	2.65	3.34	1.26
		CH_3	3.44	4.86	1.41
		OCH_3	8.41	14.84	1.77
10c	$CH_2CH_2CH_3$	H	2.23	2.84	1.28
		CH_3	3.12	4.49	1.44
		OCH_3	7.28	13.54	1.86
10d	$(CH_2)_5CH_3$	H	2.03	2.60	1.28
		CH_3	2.75	3.92	1.42
		OCH_3	6.19	11.37	1.84
10e	$CH(CH_3)_2$	H	1.85	2.68	1.45
		CH_3	2.42	4.14	1.71
		OCH_3	5.64	12.14	2.15
10f	$CH_2C_6H_5$	H	3.24	4.95	1.53
		CH_3	4.48	8.28	1.85
		OCH_3	10.32	27.65	2.68
10g	C_6H_5	H	5.69	6.12	1.08
		CH_3	6.99	11.07	1.58
		OCH_3	15.45	25.67	1.66

[a]Mobile phase: 20% isopropyl alcohol in hexane. Flow rate: 2.0 mL/min. Detection: 254 nm UV. Temperature: 20 °C. k_1: Retention factor of the first eluted enantiomer. k_2: Retention factor of the second eluted enantiomer. α: Separation factor.

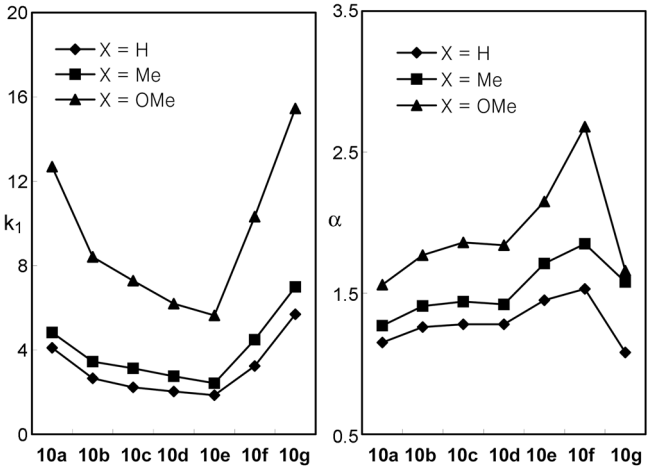


Figure 2. Chromatographic trends for the resolution of anilide derivatives (**10a-10g**) of α-amino acids on CSP **4**. For the chromatographic condition, see the footnote to Table 1.

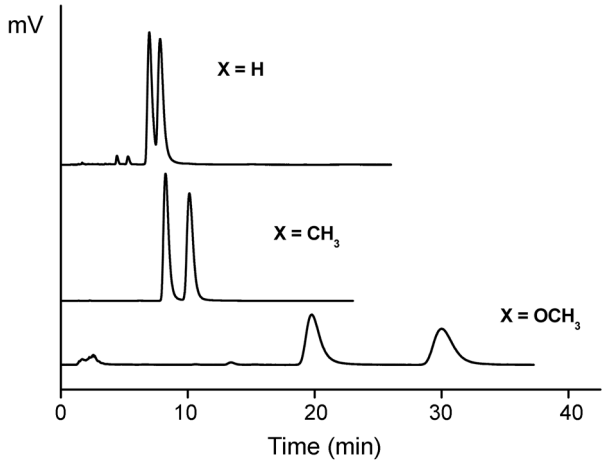


Figure 3. Comparison of the chromatograms for the resolution of anilide derivatives **10b** of *N*-acetyl-α-propanoic acid on CSP **4**. For the chromatographic condition, see the footnote to Table 1.

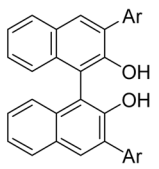
the CSP and the anilide group of analytes is expected to play an important role for the chiral recognition.

When the substituent group (R) at the chiral center of anilide derivatives **10** of *N*-acetyl-α-amino acids was changed from methyl to ethyl and then to propyl, the separation factor (α) increases. With the further increase in the length of the substituent R-group at the chiral center to hexyl, the separation factor (α) does not increase. The initial increase of the separation factors (α) shown in Figure 2 might be a consequence of conformational factors. As the alkyl substituent (R) at the chiral center of analytes **10** changes from methyl to ethyl and then to propyl, a significant change in steric bulkiness is experienced and consequently, the conformational preferences should be altered for the chiral recognition.[11] However, the conformational preferences may not be altered any more by further increasing the length of the alkyl substituent because the changes in the structure occur at sites remote from the stereogenic center and do not affect the conformation.[11] The substituent group (R) at the chiral center of analytes **10** was changed to isopropyl or to benzyl group, the separation factor (α) increases quite much. The sterically bulky group such as isopropyl or benzyl group at the chiral center of the analytes seems to provide the conformational preferences more significantly for the chiral recognition.

When the substituent group (R) at the chiral center of analytes **10** was changed to phenyl, the separation factor (α) was quite low. Probably, the competition of the phenyl group at the chiral center and the anilide group of the analyte for the π-π interaction with the 3,5-dinitrobenzoyl group of CSP **4** might be responsible for the low chiral recognition as rationalized previously for the relatively low chiral recognition for the resolution of anilide derivative of *N*-acetylphenylglycine or anilide derivative of *N*-tert-Boc-phenylglycine on a CSP based on *N*-(3,5-dinitrobenzoyl)leucine.[12]

The retention factors (k) for the resolution of anilide derivatives **10** of *N*-acetyl-α-amino acids generally decrease as the length of the alkyl substituent (R) at the chiral center of analytes **10** as shown in Table 1 and Figure 2. As the length of the alkyl substituent (R) at the chiral center of analytes **10** increases, the lipophilic interaction between the analytes and the mobile phase increases and consequently,

Table 2. Resolution of 1,1'-bi-2-naphthol (**11a**), 2,2'-diaryl-1,1'-bi-2-naphthols (**11b-h**) and 1,1'-bi-2-naphthol dimethyl ether (**11i**) on CSP **4**[a]



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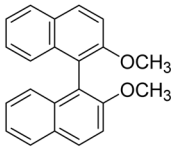

11i

	Analytes (Ar)	k_1	k_2	α
11a	H	3.64 (R)	5.71 (S)	1.57
11b	C_6H_5	3.71 (R)	4.27 (S)	1.15
11c	4-*tert*-butyl-C_6H_4	2.13 (R)	3.11 (S)	1.46
11d	4-(C_6H_5)-C_6H_4	12.88 (R)	17.26 (S)	1.34
11e	3,4-dimethyl-C_6H_3	5.80 (R)	8.70 (S)	1.50
11f	2,6-dimethyl-C_6H_3	0.67 (R)	1.07 (S)	1.60
11g	1-naphthyl	11.76 (R)	18.23 (S)	1.55
11h	2-naphthyl	12.00 (R)	18.00 (S)	1.50
11i		0.78 (S)	0.84 (R)	1.07

[a]Mobile phase: 20% isopropyl alcohol in hexane. Flow rate: 2.0 mL/min. Detection: 254 nm UV. Temperature: room temperature. k_1: Retention factor of the first eluted enantiomer. The absolute configuration of the first eluted enantiomer is presented in the parenthesis. k_2: Retention factor of the second eluted enantiomer. The absolute configuration of the second eluted enantiomer is presented in the parenthesis. α: Separation factor.

the analytes should be eluted fast. In the resolution of anilide derivatives of *N*-acetylphenylalanine (**10f**, R = $CH_2C_6H_4$) and *N*-acetylphenylglycine (**10g**, R = C_6H_5), however, the retention factors (k) are quite large as shown in Figure 2 even though the substituent at the chiral center of the analyte is quite large and lipophilic. The additional π-π interaction between the phenyl or benzyl group at the chiral center of the analytes and the 3,5-dinitrobenzoyl group of the CSP might be responsible for the long retention of analytes **10f** and **10g**.

CSP **4** was also applied to the resolution of 1,1'-bi-2-naphthol (**11a**) and 3,3'-diaryl-1,1'-bi-2-naphthols (**11b-h**). The chromatographic results for the resolution of 1,1'-bi-2-naphthol (**11a**) and 3,3'-diaryl-1,1'-bi-2-naphthols (**11b-h**) on CSP **4** are summarized in Table 2. The representative chromatogram for the resolution of 1,1'-bi-2-naphthol (**11a**) on CSP **4** is illustrated in Figure 4a. As shown in Table 2 and Figure 4a, the chiral recognition efficiency for the resolution of 1,1'-bi-2-naphthol (**11a**) and 3,3'-diaryl-1,1'-bi-2-naphthols (**11b-h**) on CSP **4** is quite excellent. Especially, the chromatographic results for the resolution of 1,1'-bi-2-naphthol (**11a**) and 3,3'-diaryl-1,1'-bi-2-naphtols (**11c-h**) on CSP **4** are turned out to be even greater than those reported previously on a well known Pirkle-type CSP based on *N*-(3,5-dinitrobenzoyl)leucine or based on *N*-(3,5-dinitrobenzoyl)phenylglycine.[9] When the two hydroxyl group of 1,1'-bi-2-naphthol (**11a**) was changed into dimethoxy group (compound **11i** in Table 2), the retention (k) and the separation factor (α) were diminished quite much with the inversion of elution order. Consequently, the two hydroxyl group of compounds **11** seems to do some important role for the chiral recognition.

Finally CSP **4** was applied to the resolution of chiral drugs including a diuretic, bendroflumethiazide (**12**, Figure 5), and non-steroidal anti-inflammatory agents such as naproxen and alminoprofen (**13** and **14** respectively, Figure 5). All of

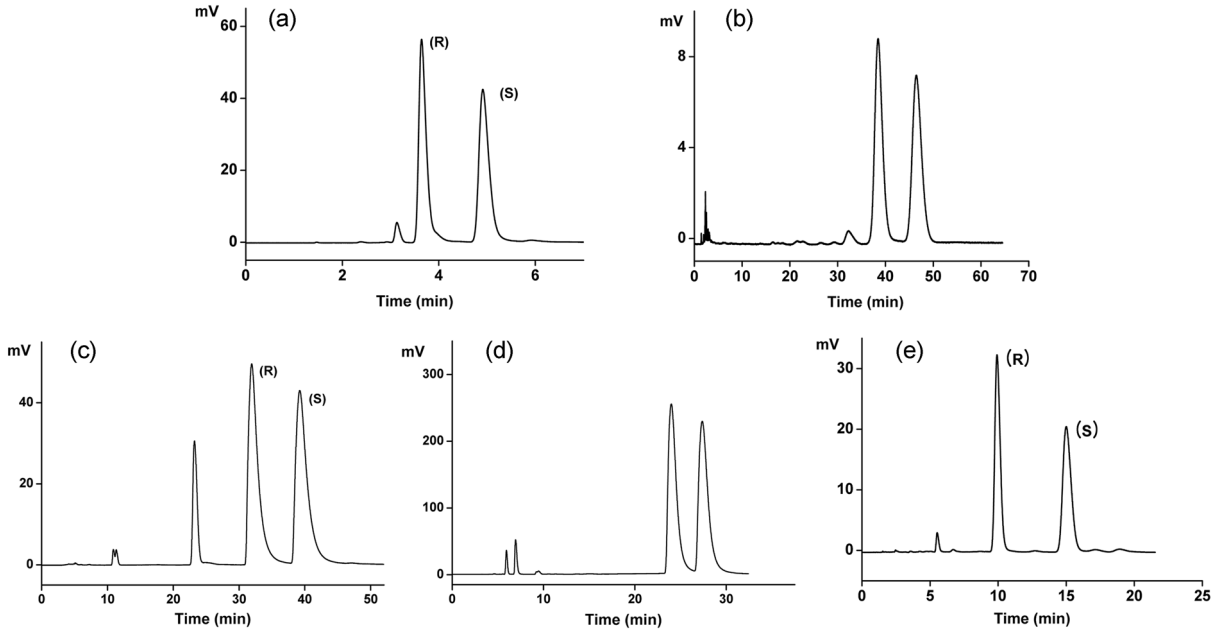

Figure 4. Chromatograms for the resolution of (a) 1,1'-bi-2-naphthol (**11a**) (for the chromatographic condition, see the footnote to Table 2), (b) bendroflumethiazide (**12**) (mobile phase: 20% isopropyl alcohol in hexane, flow rate: 2.0 mL/min, detection: 254 nm UV, 20 °C). (c) naproxen (**13**) (mobile phase: 2% isopropyl alcohol in hexane, flow rate: 1.0 mL/min, detection: 254 nm UV, 20 °C). (d) alminoprofen (**14**) (mobile phase: 2% isopropyl alcohol in hexane, flow rate: 1.0 mL/min, detection: 254 nm UV, 20 °C). and (e) *N*-methyl-3,5-dimethylanilide derivative **15** of naproxen (mobile phase: 20% isopropyl alcohol in hexane, flow rate: 2.0 mL/min, detection: 254 nm UV, 20 °C) on CSP **4**. In the case of (b) and (d), optically active analytes were not available and consequently, the elution orders were not determined.

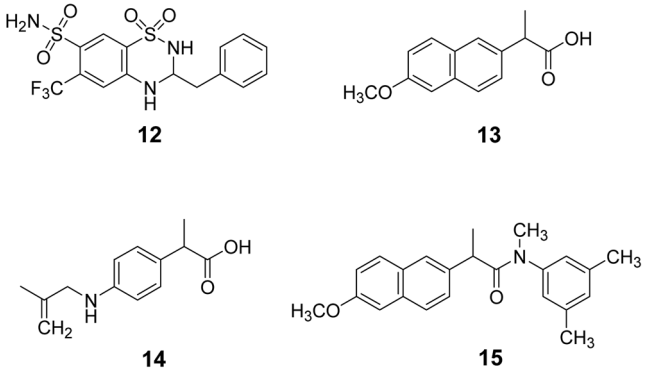

Figure 5. Structures of bendroflumethiazide (**12**), naproxen (**13**), alminoprofen (**14**) and *N*-methyl-3,5-dimethylanilide derivative **15** of naproxen.

these chiral drugs contain π-basic aromatic groups. Consequently, these chiral drugs were expected to be resolved on CSP **4**. As shown in Figure 4b, bendroflumethiazide (**12**) was indeed resolved quite well on CSP **4** (α = 1.22). Non-steroidal anti-inflammatory drugs such as naproxen (**13**) and alminoprofen (**14**) were also resolved quite well on CSP **4** with reasonable separation factors (α for **13** = 1.25, α for **14** = 1.16) as shown in Figure 4c and 4d. When naproxen (**14**) was converted to its *N*-methyl-3,5-dimethylanilide derivative **15** (Figure 5), the chiral resolution (α = 1.60) was improved even more as shown in Figure 4e.

In conclusion, the CSP (CSP **4**) developed in this study has been demonstrated to be useful for the resolution of various racemic π-basic analytes including various anilide derivatives of α-amino acids, 1,1'-bi-2-naphthol and 3,3'-diaryl-1,1'-bi-2-naphthols. CSP **4** was also very successful in the resolution of racemic π-basic chiral drugs including a diuretic, bendroflumethiazide, and non-steroidal anti-inflammatory drugs such as naproxen and alminoprofen. The enantioselective π-π donor-acceptor interaction between the 3,5-dinitrobenzoyl group of CSP **4** and the π-basic aromatic groups of analytes seems to play an important role for the chiral recognition. However, the exact chiral recognition mechanism is not clear yet and needs further study. Application of CSP **4** to the resolution of other racemic compounds is underway in our laboratory.

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References

1. (a) Miwa, T.; Ichikawa, M.; Tsuno, M.; Hattori, T.; Miyakawa, T.; Kayano, M.; Miyake, Y. *Chem. Pharm. Bull.* **1987**, *35*, 682. (b) Allenmark, S. *J. Liq. Chromatogr.* **1986**, *9*, 425.
2. Okamoto, Y.; Kawashima, M.; Hatada, K. *J. Am. Chem. Soc.* **1984**, *106*, 5357.
3. Ward, T. J.; Armstrong, D. W. *J. Liq. Chromatogr.* **1986**, *9*, 407.
4. (a) Armstrong, D. W.; Tang, Y.; Chen, S.; Zhou, Y.; Bagwill, C.; Chen, J. R. *Anal. Chem.* **1994**, *66*, 1473. (b) Ward, T. J.; Farris, A. B. *J. Chromatogr. A* **2001**, *906*, 73.
5. (a) Hyun, M. H.; Kang, M. H.; Han, S. C. *J. Chromatogr. A* **2000**, *868*, 31. (b) Hyun, M. H.; Cho, Y. J.; Choi, H. J.; Lee, K. W. *Bull. Kor. Chem. Soc.* **2004**, *25*, 1977. (c) Hyun, M. H.; Cho, Y. J.; Kim, J. A. *Bull. Kor. Chem. Soc.* **2005**, *26*, 823.
6. (a) Hyun, M. H. *J. Sep. Sci.* **2003**, *26*, 242. (b) Hyun, M. H. *Bull. Kor. Chem. Soc.* **2005**, *26*, 1153. (c) Hyun, M. H. *J. Sep. Sci.* **2006**, *29*, 750.
7. (a) Pirkle, W. H.; Welch, C. J.; Lamm, B. *J. Org. Chem.* **1992**, *57*, 3854. (b) Gasparrini, F.; Misiti, D.; Villani, C. *J. Chromatogr. A* **2001**, *906*, 35. (c) Hyun, M. H.; Kim, J. I.; Cho, Y. J.; Ryoo, J.-J. *Bull. Kor. Chem. Soc.* **2004**, *25*, 1707.
8. (a) Allenmark, S.; Andersson, S.; Moller, P.; Sanchez, D. *Chirality* **1995**, *7*, 248. (b) Thunberg, L.; Allenmark, S. *Chirality* **2003**, *15*, 400.
9. Hyun, M. H.; Kim, K. S.; Cho, Y. J. *J. Liq. Chromatogr. Rel. Technol.* **2005**, *28*, 527.
10. (a) Finn, J. M. In *Chromatographic Chiral Separations*; Zief, M., Crane, L. J., Eds.; Marcel Dekker: New York, 1988; p 53. (b) Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347. (c) Taylor, D. R.; Maher, K. *J. Chromatogr. Sci.* **1992**, *30*, 67. (d) Welch, C. J. *J. Chromatogr.* **1994**, *666*, 3.
11. (a) Hyun, M. H.; Cho, S. M.; Ryoo, J. J.; Kim, M. S. *J. Liq. Chromatogr.* **1994**, *17*, 317. (b) Hyun, M. H.; Hwang, S.-R.; Han, S. C. *Bull. Kor. Chem. Soc.* **1999**, *20*, 1309.
12. (a) Hyun, M. H.; Lee, G. S.; Han, S. C.; Cho, Y. J.; Baik, I. K. *Chirality* **2002**, *14*, 503. (b) Hyun, M. H.; Cho, Y. J.; Baik, I. K. *Bull. Kor. Chem. Soc.* **2002**, *23*, 1291.