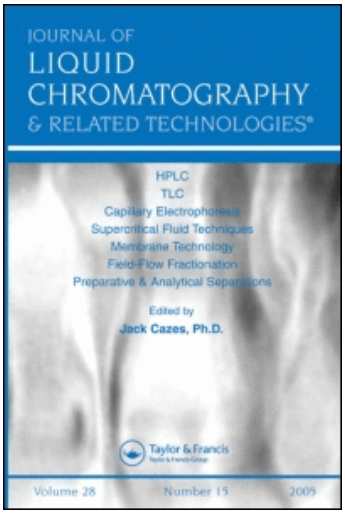

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Preparation and Separation of 1-Methyl-1,2,3,4-tetrahydro-β-carboline Enantiomers by HPLC Using a New Derivatization Reagent

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Preparation and Separation of 1-Methyl-1,2,3,4-tetrahydro-β-carboline Enantiomers by HPLC Using a New Derivatization Reagent

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ABSTRACT

1-Methyl-3,4-dihydro-β-carboline (**1**) was C-acylated with optically active sulfinyl derivatives (**2**) into the 1-methyl group. Reduction of the C═N double bond resulted in diastereomers (**4**, **5**) of different ratios.

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After separation of diastereomers and removal of the chiral sulfinyl moiety, enantiomers of 1-methyl-1,2,3,4-tetrahydro-β-carboline (**6**) were obtained from different enantiomeric excess. The diastereomers were separated by normal phase chromatography. It was proven that the resolution efficiency was much better with this type of separation method compared with very popular reversed phase chromatography. Embedded reversed phase column (Supelcosil ABZ + Plus) gave higher resolution than conventional C-18 stationary phases and monoliths (Chromolith Performance RP-18e), but retention time is high and low solubilities of derivatives caused detection problems and base line noise.

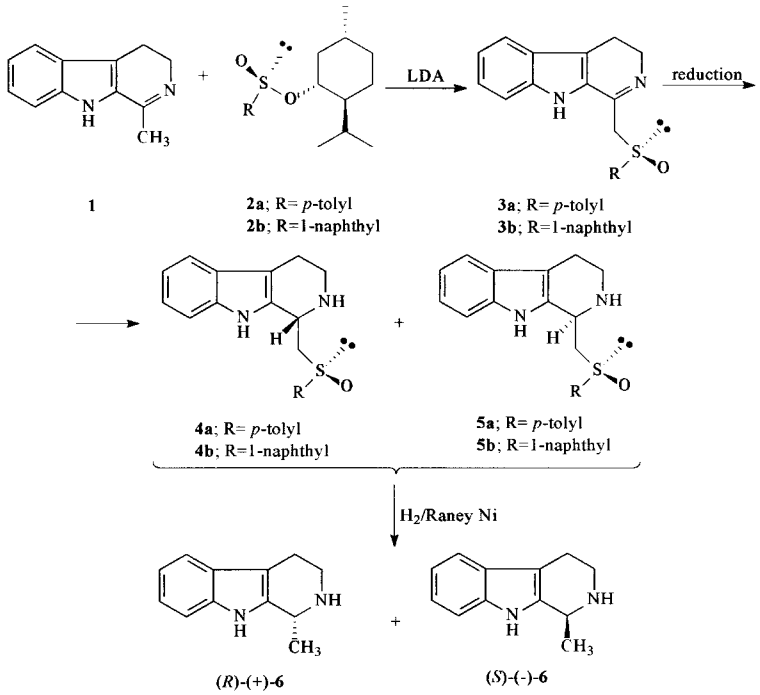
Key Words: Column liquid chromatography; Asymmetric induction; β-Carbolines; Diastereomeric derivatives.

INTRODUCTION

Alkaloids containing the tetrahydro-β-carboline skeleton represent an important class of natural compounds. Since many of these alkaloids are optically active, their stereoselective syntheses is an essential task. In our present paper, we describe the stereoselective synthesis of simple β-carboline derivatives, (*R*)-(+)- and (*S*)-(−)-1-methyl-1,2,3,4-tetrahydro-β-carbolines, (*R*)-(+)-6 and (*S*)-(−)-6, respectively. The stereoselectivity was established by investigation of the diastereomeric derivatives of above-mentioned compounds obtained in the reaction with *p*-tolyl- and naphthylmenthyl sulfinates. Separation of the diastereomers was performed by normal and/or reversed-phase chromatography. Different aspects of this topic are summarized in a series of papers.[1−4] In our previous publication, the effect of flexibility of optically active groups used for derivatization was presented.[5] In this paper, new derivatization reagents were tested, and both reversed- and normal- phase chromatography were used for separation of the diastereomers formed.

Chemistry

1-Methyl-3,4-dihydro-β-carboline (**1**) was C-acylated at the 1-methyl group with chiral *p*-tolyl and 1-naphthylmenthyl sulfinates (**2a**) and (**2b**), respectively (Sch. 1). The *p*-tolylsulfinyl and 1-naphthylsulfinyl 3,4-dihydro-β-carboline derivatives (**3a** and **3b**) were then reduced by different reducing agents generally used in reduction of carbon−nitrogen double bond. The reaction conditions of reduction and the diastereomeric ratios of products (**4a**, **5a**) and (**4b**, **5b**) obtained by HPLC are presented in Table 1. The best results were obtained in the reduction with DIBAL-H in the presence of $ZnBr_2$,



Scheme 1. Acylation of 1-methyl-3,4-dihydro-β-carboline at its 1-methyl group with chiral *p*-tolyl- and 1-naphthylmenthyl sulfinates (**2a**) and (**2b**), respectively.

in this case the ratio of **5a**/**4a** = 76 : 24, and **5b**/**4b** = 74 : 26 were found, respectively, where the C-1 configuration of **5a** proved to be (*S*). Removal of the chiral sulfoxide substituent from the C-1 methyl group of the diastereomeric mixtures of **4a**, **5a** and **4b**, **5b** obtained in this type of reduction, resulted in enantiomeric mixtures of (*R*)- and (*S*)-1-methyl-1,2,3,4-terahydro-β-carbolines (*R*-(+)-6, *S*-(−)-**6**) in different ratios. The configuration of the carbon atom in position 1 of the major diastereomers was determined by measurement of the optical rotation power of their deprotected enantiomeric mixtures.

EXPERIMENTAL

General

Melting points are uncorrected. IR spectra were recorded on Zeiss IR 75 and 80 instruments. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DRX-500

Table 1. Diastereomeric ratios in products obtained by reduction of (3a) and (3b).

	Ratios of diastereomers	
Reduction conditions	**4a : 5a**	**4b : 5b**
$NaBH_4/CH_2Cl_2$–MeOH/0°C	58 : 42	60 : 40
$NaBH_4$/EtOH/ − 70°C	65 : 35	
$NaBH_4$/EtOH–HCl/ − 70°C	58 : 42	
$Na(CN)BH_3$/AcOH–CH_2Cl_2/0°C	63 : 37	
$Na(OAc)_3BH/C_6H_6$/0°C	50 : 50	
Bu_4NBH_4/EtOH/0°C	54 : 46	
DIBAL-H/CH_2Cl_2/ − 48°C	50 : 50	
DIBAL-H/$ZnBr_2/CH_2Cl_2$/ − 48°C	24 : 76	26 : 74
$LiEt_3BH$/THF/rt	65 : 34	
L-Selectride/THF/rt	No reaction	

spectrometer. All mass spectrometric measurements were performed on a VG ZAB-2SEQ mass spectrometer, operating under EI conditions (70 eV, ion source temperature 200°C). Samples were introduced directly into the ion source by a probe. Accurate mass measurements were obtained by the peak-matching technique at 10,000 resolving power (10% valley definition). The measured masses were accurate to ± 0.003 amu. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. TLC was carried out using Kieselgel $60F_{254}$ (Merck) glass plates. The IR, MS, ^{1}H-NMR, and ^{13}C-NMR spectroscopic data of new compounds are in accordance with the presented structures.

Chemicals

(1*R*,2*S*,5*R*)-(−)-Menthyl (*S*)-*p*-toluenesulfinate (**2a**) was purchased from Aldrich. 1-Methyl-3,4-dihydro-β-carboline or harmalan[6] (**1**) and (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-1-naphthalenesulfinate[7] (**2b**) were prepared by literature methods. *p*-Tolylsulfinyl derivative (**3a**) was synthesized according to reported procedure.[8]

Synthesis

Synthesis of Naphthylsulfinyl Derivative (**3b**)

The naphthylsulfinyl derivative (**3b**) was synthesized by the method[8] used for preparation of (**3a**). Yield: 0.20 g (69.0%), $R_f = 0.48$

(CH_2Cl_2–MeOH 10 : 1), mp 168–170°C (decomp.), $[\alpha]_D^{26} = +616.8°$ (*c* 1.0, CH_2Cl_2). IR (KBr) 3176, 1604, 1528, 1328, 1024, 799, 744 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H (ppm): 2.74 (m, 2H, CH_2), 3.41 (m, 1H, CH_2), 3.69 (m, 1H, CH_2), 4.21 (d, $J = \sim$13.3 Hz, 1H, CH_2), 4.36 (d, $J = \sim$13.3 Hz, 1H, CH_2), 7.15 (t, $J = \sim$7.5 Hz, 1H, Ar), 7.32 (t, $J = \sim$7.5 Hz, 1H, Ar), 7.49 (d, $J = \sim$8.2 Hz, 1H, Ar), 7.52 (m, 1H, Ar), 7.55 (m, 1H, Ar), 7.56 (m, 1H, Ar), 7.62 (t, $J = \sim$7.5 Hz, 1H, Ar), 7.91 (d, $J = \sim$8.1 Hz, 1H, Ar), 7.94 (m, 1H, Ar), 7.96 (m, 1H, Ar), 7.98 (m, 1H, Ar), 10.30 (s, 1H, NH). ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C (ppm): 19.25 (CH_2), 48.20 (CH_2), 61.59 (CH_2), 112.68 (–CH═), 118.44 (–C═), 119.87 (–CH═), 120.12 (–CH═), 121.17 (–CH═), 122.86 (–CH═), 124.70 (–C═), 124.86 (–CH═), 124.94 (–CH–), 126.64 (–CH═), 127.59 (–CH═), 128.35 (–C═), 128.45 (–C═), 128.64 (–CH═), 131.57 (–CH═), 133.01 (–C═), 136.19 (–C═), 137.60 (–C═), 153.89 (–C═). HRMS: Calcd for $C_{22}H_{18}N_2SO$: 358.1140, found: 358.1138.

Reduction of Sulfinyl Derivatives (**3a**) and (**3b**); Preparation of **4a**/**5a**, and **4b**/**5b** Diastereomeric Mixtures

Reduction of (**3a**) was carried out according to known literature methods. Reaction conditions and diastereomeric ratios of products (**4a** : **5a**) are presented in Table 1. Spectroscopic data of products (**4a**, **5a**) are in accordance with compounds prepared by another way reported previously.[9] In the course of reduction of (**3b**) the procedure presented above for reduction of *p*-tolylsulfinyl derivative (**3a**) was used. For diastereomeric ratios of (**4b** : **5b**) see Table 1. IR (KBr) 3216, 1652, 1504, 1112, 1032, 804, 728 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H (ppm): 2.16 (b, 1H, NH), 2.66 (m, 1H, CH_2), 2.72 (m, 1H, CH_2), 2.90 (m, 1H, CH_2), 3.09 (m, 1H, CH_2), 3.25 (dd, $J = 2\sim$14.1 Hz, $J = \sim$2.2 Hz, 1H, CH_2), 3.71 (dd, $J = \sim$14.1 Hz, $J = \sim$8.6 Hz, 1H, CH_2), 4.31 (d, $J = \sim$7.7 Hz, CH), 7.08 (t, $J = \sim$7.5 Hz, 1H, Ar), 7.17 (t, $J = \sim$7.5 Hz, 1H, Ar), 7.41 (d, $J = \sim$ 8.0 Hz, 1H, Ar), 7.46 (d, $J = \sim$7.7 Hz, 1H, Ar), 7.60 (m, 2H, Ar), 7.67 (t, $J = \sim$7.7 Hz, 1H, Ar), 7.91 (m, 1H, Ar), 7.97 (m, 1H, Ar), 8.01 (d, $J = \sim$8.1 Hz, 1H, Ar), 8.20 (d, $J = \sim$7.2 Hz 1H, Ar), 9.92 (s, 1H, NH). ^{13}C-NMR (500 MHz, $CDCl_3$) δ_C (ppm): 22.14 (CH_2), 42.46 (CH_2), 47.74 (CH), 56.58 (CH_2), 108.33 (–C═), 111.20 (–CH═), 117.74 (–CH═), 118.83 (–CH═), 121.07 (–CH═), 121.45 (–CH═), 123.93 (–CH═), 125.04 (–CH═), 126.60 (–CH═), 126.71 (–C═), 127.36 (–CH═), 128.21 (–C═), 128.94 (–CH═), 131.51 (–CH═), 132.56 (–C═), 133.34 (–C═), 135.38 (–C═), 135.97 (–C═). HRMS: Calcd for $C_{22}H_{20}N_2OS$: 360.1296, found: 360.1286.

Deprotection of Sulfinyl Diastereomers (**4a**, **5a**) and (**4b**, **5b**)

p-Tolylsulfinyl substituted diastereomeric mixture (**4a**, **5a**) obtained by reduction with DIBAL-H in the presence of $ZnBr_2$ was purified by preparative TLC. Isolated diastereomer **5a** was obtained with de = 80%. Desulfoxylation of this diastereomeric mixture was carried out by hydrogenation in the presence of Raney nickel analogously with reported procedure.[10] The optical rotatory power of product proved to be $[\alpha]_D^{23} = -40^\circ$ (*c* 0.45, EtOH). This value means 77% enantiomeric excess (ee) for (*S*)-(−)-1-methyl-1,2,3,4-tetrahydro-β-carboline (*S*–(−)-**6**); *lit.* $[\alpha]_D^{24} = -51.7^\circ$ (*c* 1, EtOH).[11] After desulfoxylation of naphthylsulfonyl diastereomers (**4b**, **5b**) similar results were obtained. In this way, the configuration of C-1 in diastereomeric mixtures presented in Table 1 could be identified.

Chromatographic Experiments

Solvents

Hexane, methanol, and tetrahydrofuran were of chromatographic grade (Merck, Darmstadt, FRG). Water of high purity was from Milli Q equipment (Millipore, USA). Phosphoric acid (85%) was from Reanal, Budapest, Hungary. Triethylamine was purchased from Aldrich.

Chromatographic Separations

Normal Phase Chromatography

Pump: Hitachi (Merck, Darmstadt, FRG), sampling: Rheodyne 7125, equipped with 20 μL loop (Rheodyne Inc., Cotati, CA, USA); detector: PE (Perkin-Elmer Corp., Norwalk, CT, USA); data system: Turbo Chrom 4.1 (Perkin-Elmer Corp., Norwalk, CT, USA); column: BST SI-100S 10 μm, 250 × 4.0 mm^2; wavelength: 260 nm; flowrate: 2 mL min^{-1}. (List of eluents, t_R for each diastereomeric pairs: see Table 2.)

Reversed Phase Chromatography

Pump: Perkin-Elmer 200 quaternary gradient pump; sampler: ISS 200 automatic sampler; detector: 235C diode-array detector; data system and controller: Turbo Chrom NT version (Perkin-Elmer Corp., Norwalk, CT,

Table 2. Chromatographic conditions and results of diastereomeric separations of *p*-tolyl- (**4a**, **5a**) and 1-naphthyl derivatives (**4b**, **5b**) by normal phase and reversed phase LC.

Condition		t_R (min)		k		A_s			N				
Phase	Eluant (ratio)	**4a**	**5a**	**4a**	**5a**	**4a**	**5a**	α	**4a**	**5a**	R_s	log P **4a**, **5a**	pK_a **4a**, **5a**
NP	Hex–THF–MeOH–TEA (171 : 43 : 11 : 1)	9.88	12.77	6.06	8.12	0.95	1.27	1.34	3,950	4,666	3.32	2.06	8.36
RP-Ch	MeOH–H_2O–85%H_3PO_4 (8 : 12 : 0.1)	7.85	8.82	4.61	5.30	2.00	3.21	1.15	2,634	2,693	1.46		
RP-P	MeOH–H_2O–85%H_3PO_4 (8 : 12 : 0.1)	6.67	7.46	9.11	10.30	1.25	0.83	1.13	698	683	0.67		
RP-S	MeOH–H_2O–85%H_3PO_4 (8 : 12 : 0.1)	4.46	4.32	1.74	1.65	2.00	2.33	1.05	6,771	3,784	0.56		
		4b	**5b**	**4b**	**5b**	**4b**	**5b**		**4b**	**5b**		**4b**, **5b**	**4b**, **5b**
NP	Hex–THF–MeOH–TEA (171 : 43 : 11 : 1)	7.88	9.92	4.84	6.35	1.63	1.31	1.31	3,580	3,584	3.02	3.03	8.25
RP-Ch	MeOH–H_2O–85%H_3PO_4 (8 : 12 : 0.1)	19.09	17.15	12.08	10.95	1.80	2.68	1.10	2,102	2,423	1.24		
RP-P	MeOH–H_2O–85%H_3PO_4 (8 : 12 : 0.1)	20.46	18.24	25.92	23.00	1.20	1.43	1.13	765	852	0.81		
RP-S	MeOH–H_2O–85%H_3PO_4 (8 : 12 : 0.1)	9.95	8.16	5.03	3.94	1.09	1.00	1.28	6,094	5,457	3.28		

Note: t_R, retention time; k, retention factor; A_s, symmetry factor; α, relative retention (selectivity); N, theoretical plate number; R_s, resolution factor; log P, partition constant between octanol and water; pK_a, acidic dissociation constant; Hex, hexane; THF, tetrahydrofuran; MeOH, methanol; TEA, triethylamine; NP, normal phase; RP, reversed phase—Ch, Chromolith performance; P, Purospher RPe; S, Supelcosil^{TM} ABZ + Plus.

USA); columns: Chromolith Performance RP-18e, 100 × 4.6 mm; Purospher, RP-18e, 5 μm, 125 × 3.0 mm; SUPELCOSIL™ ABZ + Plus, 3 μm, 150 × 4.6 mm; wavelength: 260 nm; flowrate: 1 mL min^{-1}. (List of eluents, t_R for each diastereomeric pairs: see Table 2.)

Calculations

All column characteristics, retention factor (k), number of theoretical plates (N), relative retention (selectivity factor, α), resolution factor (R_s), and asymmetry factor (A_s), were calculated according to European Pharmacopoeia.[12] The log P, pK_a values were calculated by Pallas 3.0 intelligent software package (CompuDrug International Institute, Inc.: Budapest, Hungary.)

RESULTS

Separation of Diastereomers

Base line separation was achieved by normal phase chromatography, both the 1-naphthyl-(**4b**, **5b**) and *p*-tolylsulfinyl derivatives (**4a**, **5a**) (Fig. 1). To reduce the silanol activity, triethylamine must be added to the mobile phase. The optimized mobile phase composition was hexane : tetrahydrofuran : methanol : triethylamine 171 : 43 : 11 : 1, respectively.

For reversed phase separation different stationary phases were used. All alkyl-silica were prepared from high purity silica (type-B) with low metal content. Physico-chemical properties of selected columns chromatographic behavior differs widely. The Chromolith RP-18e is a new generation monolith column, Purospher RPe is a polar end-capped column with amino end group, Supelcosil amide C-16 is an embedded one.

To reduce further the silanol group effects, acidic mobile phase was applied. All mobile phase contained 0.5% v/v con. H_3PO_4. The retention times, relative retention, and separation are summarized in Table 2. The highest value for separation was obtained on a Supelcosil amide C-16 column. Unfortunately, the solubility of naphthyl derivatives was very low in methanol : water : con. phosphoric acid 40 : 60 : 0.5 v/v/v (near to the detection limit), and the baseline was very noisy and drifting (see Fig. 2). The peaks are symmetrical ones. All other reversed phase columns gave unsatisfactory separation and asymmetrical peak shapes.

Mobile phases used in normal phase chromatography, highly dissolves the solutes and separation efficiency for *p*-tolyl (**4a**, **5a**)- and 1-naphthyl

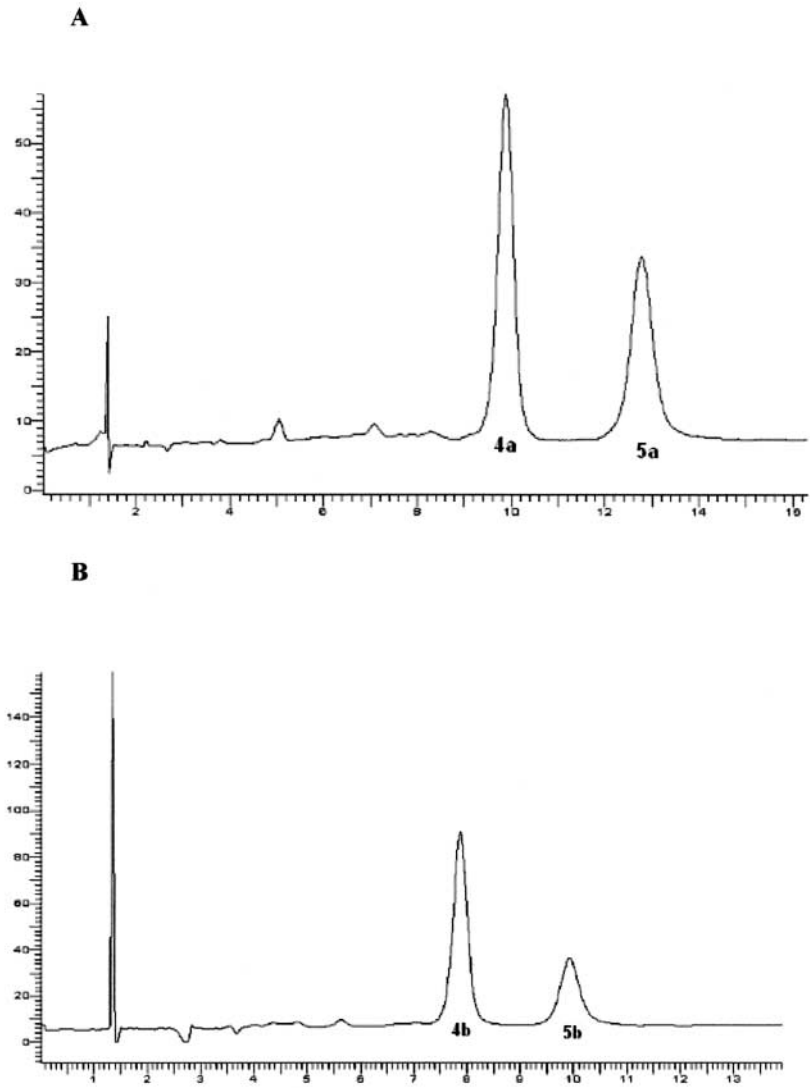


Figure 1. Separation of diastereomers (**4a**, **5a**, **4b**, **5b**) by NP-HPLC, column: 25 cm × 4.0 mm, 10 μm; stationary phase: Chromasil; mobile phase: hexane : tetrahydrofuran : methanol : triethylamine (171 : 43 : 11 : 1). (A), *p*-tolyl- and (B), 1-naphthyl derivatives of 1-methyl-1,2,3,4-tetrahydro-β-carboline, flow rate is 2 mL min^{-1}.

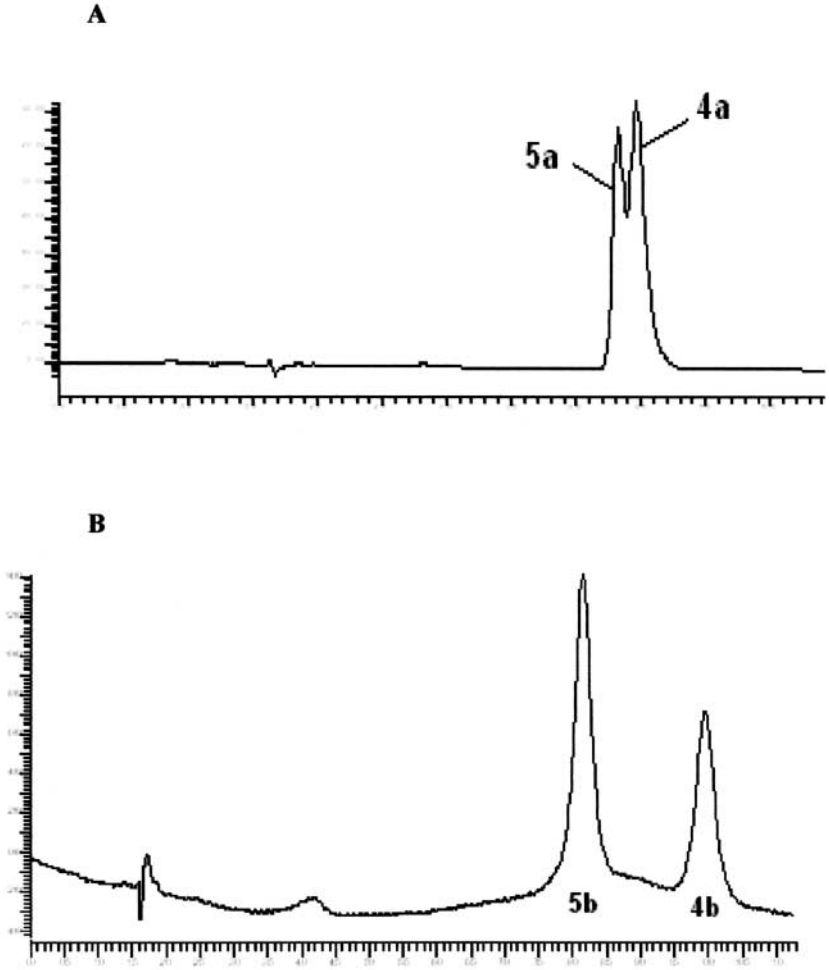


Figure 2. Separation of diastereomers (**4a**, **5a**, **4b**, **5b**) by RP-HPLC on Supelcosil^{TM} ABZ + Plus embedded column. Column is 150 cm × 4.6 mm I.D, 3 μm particle size, mobile phase is methanol : water : cc.phosphoric acid (8 : 12 : 0.1). (A), *p*-tolyl-, (B), 1-naphthyl derivatives of 1-methyl-1,2,3,4-tetrahydro-*β*-carboline, flow rate is 1 mL min^{-1}.

derivatives (**4b**, **5b**) (see Fig. 1) is high. The separation between the diastereomers is above 2.

Interaction of compounds investigated with silica was found to be very high. To reduce the high interaction in order to reduce the retention and improve the peak symmetry, methanol, and triethylamine had to be added to the mobile phase. The mobile phase composition is presented in Table 2.

In spite of different polarity of substituents the resolution was about the same, only the retention times decreased in the case of the 1-naphthyl derivatives (**5a**, **5b**). The log *P* values of two kinds of derivatives were 2.06 (**4a**, **5a**) and 3.03 (**4b**, **5b**), respectively (see Table 2). The retention times and the log *P* values were in good agreement, the higher the log *P* the lower the retention times.

In our earlier publication,[5] we found the rigid, enantiomerically pure reactants gave high resolution factors in normal phase chromatography; this was supported using these new derivatives. With the rigid molecular geometry, it seems that the basic needs for good diastereomer separation, in most cases, involve normal phase chromatography.

CONCLUSION

In this work, the usefulness of chiral sulfoxides (**2a**, **2b**) as new auxiliaries were demonstrated. Moreover, this type of chiral sulfoxide substituents had an important influence in diastereomeric selectivity in the course of stereoselective reduction of the dihydro derivatives (**3a**, **3b**), which are important intermediates for synthesis of optically-active 1-methyl-1,2,3,4-tetrahydro-β-carboline enantiomers (*R*-(+)-**6** and *S*-(−)-**6**).

Separation of both the derivatives can be done by normal phase chromatography. The embedded reversed phase (Supelcosil amide C-16) and stationary phase also gave some selectivity for the two different derivatives, but the solubility of the solutes is too low and the qualitative work would be difficult. In this respect, normal phase chromatography has a distinct advantage; there is no difficulty with solubility and resolution factors are higher than 1.5 and analysis time is a relatively short one (less than 15 min). Last but not least, according to the earlier suggestion in the literature, the rigid reactants containing aromatic ring(s) are the preferable reactants for separation of enantiomers by indirect methods. In our work, we have pointed out the perfect choice of reagent(s) to contol an enantiomeric synthesis.

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