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Short Communication

Enantiomer separations of secondary alkanols with little asymmetry by high-performance liquid chromatography on chiral columns

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ABSTRACT

Enantiomer separations of secondary alkanols with little asymmetry, $CH_3(CH_2)_nCHOH(CH_2)_{n+1}CH_3$, as their 3,5-dinitrophenylurethane (3,5-DNPU) derivatives were carried out by high-performance liquid chromatography (HPLC) using a chiral column Sumichiral OA-4100 containing N-(*R*)-1-(α-naphthyl)ethylaminocarbonyl-(*S*)-valine chemically bonded to silanized silica. Enantiomer separations (α = 1.06–1.07, R_s = 1.31–1.43) of 2-butanol, 3-hexanol and 4-octanol were obtained by HPLC at low temperature (−20 to −40°C). Enantiomer separation of 5-decanol (α = 1.02, R_s = 0.88) was obtained by HPLC at −20°C after four recyclings. Enantiomer separations (α = 1.07–1.10, R_s = 1.05–1.28) of 2-butanol and 3-hexanol were obtained as 3,5-DNPU derivatives by HPLC using a YMC A-K03 chiral column containing (*R*)-1-(1-naphthyl)ethylamine polymer chemically bonded to spherical silica at ambient temperature.

INTRODUCTION

Enantiomer separations of secondary alcohols are important in analyses of physiologically active materials such as aromas, insect pheromones and products from some enzyme reactions, as described in a review [1].

Diastereomeric (*S*)-(+)-2-phenylpropionate derivatives of secondary alcohols have been separated by gas–liquid chromatography with 5% QF-1 on Gas-Chrom Q. There was no separation of 2-butanol and 4-octanol, and only a very slight separation for the 3-hexanol derivative [2]. As these alcohols of even carbon number have carbinol substituents that differ by only one carbon, they are referred to as secondary alkanols with little asymmetry (**I**) in this paper. The general structure of **I** is

$$CH_3(CH_2)_nCH(OH)(CH_2)_{n+1}CH_3$$

I

This paper presents an HPLC method on a chiral stationary phase for complete separations of **I** with carbon numbers 4, 6 and 8, and a fair separation of **I** of carbon number 10.

EXPERIMENTAL

Samples and reagents

Racemic 2-butanol, 3-hexanol, 4-octanol, 5-decanol and (*S*)-(+)-2-butanol (purities > 99%), 2-

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and 4-decanol (purities > 98%) and 3-decanol (purity > 95%) were obtained from Tokyo Kasei (Tokyo, Japan). 3,5-Dinitrophenyl isocyanate reagent and a Sumichiral OA-4100 chiral column were obtained from Sumika Chemical Analysis (Osaka, Japan). Dehydration of pyridine was carried out with calcium hydride (Tokyo Kasei). Pyridine (500 ml) was preliminarily dehydrated over molecular sieve 4A (50 g) overnight. Pyridine separated by decantation was refluxed with calcium hydride (2 g) for 5 h and then distilled. Toluene was dehydrated on sodium wire.

HPLC

The 3,5-dinitrophenylurethane (3,5-DNPU) derivatives of the secondary alkanols were prepared on the basis of the procedures described for the derivatization of several aromatic and aliphatic chiral alcohols [3]. About 2 mg of 3,5-dinitrophenyl isocyanate was reacted with about 1 mg of the alkanol in dry toluene (4 ml) in the presence of dry pyridine (40 μl) for 1 h.

HPLC separations were carried out with a Shimadzu (Kyoto, Japan) LC-6A instrument equipped with a chiral column. Two columns, Sumichiral OA-4100 (stainless steel, 50 cm × 4 mm I.D.) packed with 5-μm particles of N-(*R*)-1-(α-naphthyl) ethylaminocarbonyl-(*S*)-valine chemically bonded to γ-aminopropylsilanized silica, and YMC A-K03 (stainless steel, 25 cm × 4.6 mm I.D.) packed with 5-μm particles of (*R*)-1-(1-naphthyl)ethylamine polymer phase covalently bonded to 300 Å wide-pore spherical silica, were used as chiral stationary phase columns. *n*-Hexane–1,2-dichloroethane–ethanol (80:20:1, v/v/v) was used as the mobile phase at a constant flow-rate (0.5 ml/min). Peaks were monitored with a Shimadzu SPD-1 UV detector at 254 nm. A Hitachi (Tokyo, Japan) 638-0805 recycle valve was used for recycling. The column was dipped into an ethanol bath, which was kept at a specified low temperature to within about 1.0°C by an immersion cooler with an exclusive controller.

RESULTS AND DISCUSSION

Enantiomer separations of racemates of 2-butanol, 3-hexanol, 4-octanol and 5-decanol were carries out as their 3,5-DNPUs by HPLC on Sumichiral OA-4100. At room temperature, each racemate of 3-hexanol and 4-octanol was partially resolved into enantiomers, but 2-butanol and 5-decanol did not show any separation. In previous studies [4,5], we observed that mono- and diacylglycerols were better resolved into enantiomers at low temperature. The chiral phase HPLC of the alkanols was also carried out at low temperature. The results are shown in Fig. 1 and Table I (A).

At −20 to −40°C, clear enantiomer separations were obtained for 2-butanol, 3-hexanol and 4-octanol, but the separation of 5-decanol enantiomers was poor. The separation of 5-decanol enantiomers was much improved by recycling, as shown in Fig. 2 and Table I (B). Enantiomer separations of second-

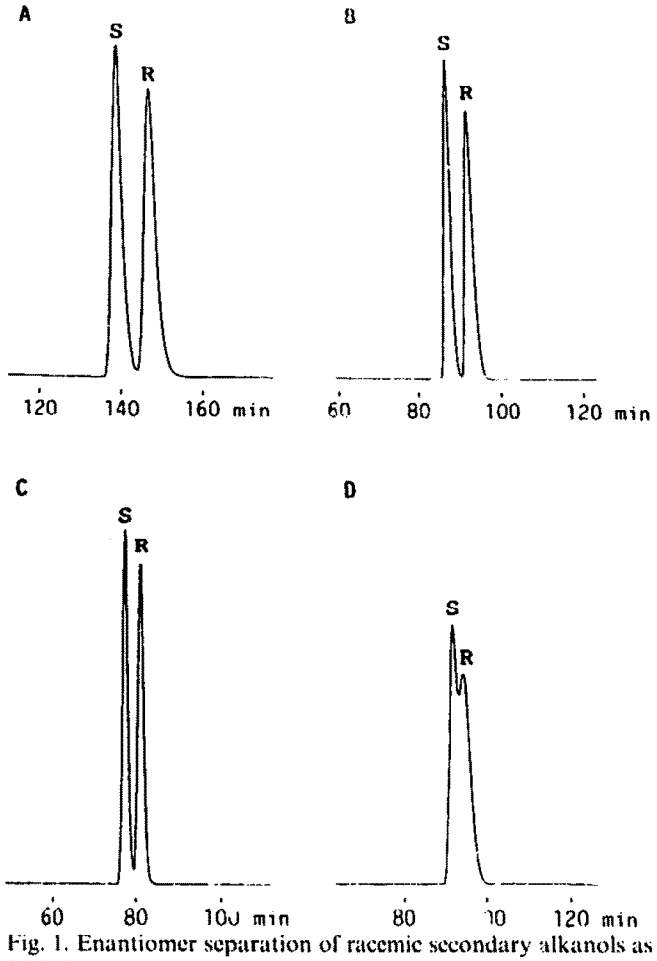

Fig. 1. Enantiomer separation of racemic secondary alkanols as 3,5-DNPU derivatives on an OA-4100 chiral column at low temperature. Mobile phase, *n*-hexane–1,2-dichloroethane–ethanol (80:20:1, v/v/v); flow-rate, 0.5 ml/min; detection at 254 nm. Samples and column temperature: (A) 2-butanol, −40°C; (B) 3-hexanol, −30°C; (C) 4-octanol, −20°C; (D) 5-decanol, −20°C.

TABLE I

ENANTIOMER SEPARATIONS OF CHIRAL SECONDARY ALKANOLS BY HPLC ON CHIRAL COLUMNS

Column	Alcohol	Configuration	Column temperature (°C)	V_r^b (ml)	α^c	R_s^d
(A) OA-4100	2-Butanol	*S*	−40	63.47	1.06	1.43
		R		67.53		
	3-Hexanol	*S*	−30	37.87	1.07	1.39
		R		39.85		
	4-Octanol	*S*	−20	32.82	1.06	1.31
		R		34.66		
	5-Decanol	*S*	−20	38.40	1.02	0.34
		R		39.35		
(B) OA-4100	5-Decanol[a]	*S*	−20	218.88	1.02	0.88
		R		223.71		
(C) A-K03	2-Butanol	*S*	26	41.52	1.07	1.05
		R		44.37		
	3-Hexanol	*S*	26	25.43	1.10	1.28
		R		27.86		
	4-Octanol	*S*	26	18.25	1.04	0.48
		R		19.02		
	5-Decanol	*R,S*	26	14.74	Not separated	

[a] At fourth recycle.
[b] Retention volume.
[c] Separation factor.
[d] Peak resolution.

ary decanol isomers as 3,5-DNPUs on OA-4100 at room temperature are shown in Table II (A). The separation of 5-decanol was very difficult in comparison with those of 2-, 3- and 4-decanols. In general, enantiomer separations of the secondary decanols decreased in the order of 2-, 3-, 4- and 5-isomers, *i.e.*, with decreasing asymmetry of the molecule. Enantiomer separararation of 5-decanol was first achieved using an OA-4100 column after several recycles at low temperature. This difficulty is attributable to the low asymmetry of 5-decanol.

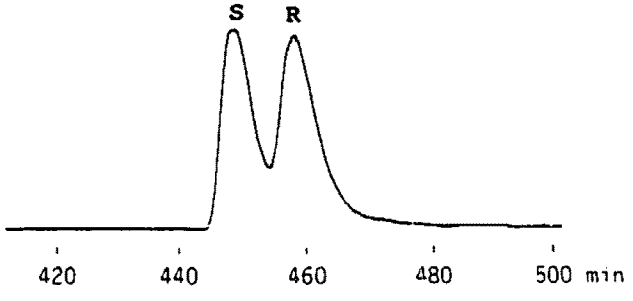

Fig. 2. Enantiomer separation of racemic 5-decanol as 3,5-DNPU derivatives on an OA-4100 column. Peaks were monitored at the fourth recycle. Column temperature, −20°C; other conditions as in Fig. 1.

The configurations of peak components were assigned on the basis of the results obtained with co-injection of (*S*)-2-butanol and racemic 2-butanol. The (*S*)-2-butanol peak emerged earlier than the (*R*)-2-butanol peak. This indicates that the retention time of the *S* enantiomer is shorter than that of the *R* isomer in the HPLC of the secondary alkanols with little asymmetry on the chiral phase under the conditions used in this study.

The secondary alkanols were also separated as 3,5-DNPUs by HPLC on a YMC A-K03 chiral column at ambient temperature [Tables I (C) and II (B)]. In this instance, the enantiomers of 2-butanol, 3-hexanol and 2-, 3- and 4-decanol were resolved even at room temperature, whereas 4-octanol enantiomers were partially resolved, and 5-decanol was not resolved at all. As individual peaks obtained on the YMC A-K03 column were broad with peak tailing, recycling and low-temperature tech-

TABLE II

ENANTIOMER SEPARATION OF SECONDARY DECANOLS BY HPLC ON CHIRAL COLUMNS AT ROOM TEMPERATURE[a]

Column	Alcohol	Configuration	V_r^b (ml)	α^c	R_s^d
(A) OA-4100	2-Decanol	*S*	19.73	1.09	2.23
		R	21.40		
	3-Decanol	*S*	17.73	1.09	2.32
		R	19.39		
	4-Decanol	*S*	17.64	1.06	1.31
		R	18.58		
	5-Decanol	*R,S*	21.82	Not separated	
(B) A-K03	2-Decanol	*S*	17.40	1.24	3.37
		R	21.61		
	3-Decanol	*S*	16.46	1.15	2.17
		R	18.96		
	4-Decanol	*S*	15.48	1.05	0.72
		R	16.31		
	5-Decanol	*R,S*	14.74	Not separated	

[a] Room temperature = 26°C.
[b] Retention volume.
[c] Separation factor.
[d] Peak resolution.

niques could not be applied for separation on the A-K03 column. The YMC A-K03 column is useful for enantiomer separations of 2-butanol and 3-hexanol at room temperature.

In Fig. 1A–C, the peak-area ratios of the *S* to the *R* enantiomer are 0.98–0.99. This shows that the methods in this paper can be applied to the determination of enantiomer ratios and examination of the optical purity of secundary alkanols. The peak-area ratios of the *S* to the *R* enantiomers in Fig. 2 are 0.86–0.90. The smaller peak area for the *S* enantiomer seems to be caused by counting the tailing part of the *S* enantiomer peak as part of the *R* enantiomer peak. In this case, the enantiomer ratios are approximately determined by the HPLC method.

To achieve the separation of 5-decanol enantiomers on OA-4100, as shown in this study, an extremely long elution time was required in comparison with the enantiomer separations of the other secondary alkanols. The method presented here must be improved for complete separation of 5-decanol in a shorter time, and for separations of higher homologues of the secondary alkanols with little asymmetry.

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