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Synthesis and evaluation of a copolymeric chiral stationary phase

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Abstract

A copolymer based on a broadly applicable chiral selector has been synthesized by hydrosilylation of an enantiopure diallyl derivative of 4-(3,5-dinitrobenzamido)-3-propyl-1,2,3,4-tetrahydrophenanthrene with a difunctional oligomethylhydrosiloxane. The linear copolymer has alternating selector–oligomer units, providing a well-defined strand. The spacing between the chiral units is controlled by the length of the oligomethylhydrosiloxane units. This new chiral stationary phase shows improved chromatographic performance relative to its brush-type and sidechain-modified polysiloxane analogs, as evidenced by data obtained by high-performance liquid and supercritical fluid chromatography. The copolymeric CSP affords increased enantioselectivity under cryogenic conditions and loses little chromatographic efficiency at optimized flow-rates under these conditions. © 1998 Elsevier Science B.V.

Keywords: Chiral stationary phases, LC; Chiral stationary phases, SFC; Enantiomer separation; Copolymeric chiral stationary phase

1. Introduction

A variety of chiral stationary phases (CSPs) have been developed and optimized for the separation of enantiomers by high-performance liquid chromatography (HPLC) and supercritical fluid chromatography (SFC) [1,2]. The brush-type Whelk-O 1 (CSP 1) was developed using the principle of reciprocity and has been shown to be broadly applicable within its design limits [3]. A sidechain-modified analog, the polyWhelk-O (CSP 2), was obtained by incorporation of the same selector into a polysiloxane backbone. This CSP has a fairly similar application spectrum but exhibits higher selectivity with less retention and efficiency than its brush-type analog [4,5].

In the case of CSPs 1 and 2, the spacing between adjacent selectors can not be controlled. Thus, selector–selector interactions and/or simultaneous bridging interactions of one analyte with adjacent selector units are possible. Since the Whelk-O selector was designed for 1:1 selector–analyte interactions, such bridging would lead to additional retention processes, something which might be detrimental to enantioselectivity. To aid in chromatographic investigation of chiral recognition mechanisms as well as to improve chromatographic performance, a well-defined spacing between adjacent selector units is desirable. Accordingly, chiral copolymers made from achiral α,ω-dihydropolymethylsiloxane oligomers and dienes derived from chiral selectors, such as (1-*R*-*trans*)-N,N′-1,2-cyclohexylenebisbenzamide or (*S*)-naproxen, have been synthesized and used for enantiomer separations by HPLC and SFC [6,7].

Herein, we describe a similar synthetic approach

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to copolymeric CSP 3 employing a diene derived from the Whelk-O selector and report its use for the separation of the enantiomers of test analytes **1**–**5** by HPLC and SFC.

2. Experimental

2.1. Chromatography

HPLC was carried out using an Alcott 760 HPLC pump equipped with a Rheodyne 7125 injector, a Milton Roy UV monitor (254 nm), and an HP 3394A integrating recorder. SubFC and SFC were performed on an HP 1050 supercritical fluid chromatograph equipped with an HP 7673 autosampler, an HP 1050 diode array detector and an HP Chemstation. Carbon dioxide was of SFC grade (Scott Specialty Gases) and 2-propanol, hexanes, dichloromethane and tetrahydrofuran were of HPLC grade (EM Science). All samples were dissolved in ethyl acetate at a concentration of 1 mg/ml. Tri-*tert*.-butylbenzene was used as a void volume marker. The Whelk-O 1 column (250×4.6 mm) used in this study was provided by Regis Technologies.

2.2. Synthesis of the CSPs

Nuclear magnetic resonance (NMR) data were collected on a Varian Unity 400 (^{1}H NMR) and Varian Unity 500 (^{13}C NMR) spectrometer with deuterated chloroform used as the solvent. Chemical shifts are reported in ppm with chloroform used as an internal standard. Elemental analysis was performed by the University of Illinois Microanalytical Service.

Decamethylcyclopentasiloxane was purchased from Gelest, all other reagents were purchased from Aldrich. 1,1,3,3,5,5,7,7,9,9,11,11,13,13-Tetradecamethylheptasiloxane ($^{H}MD_5M^{H}$) was synthesized as described by Uchida et al. [8]. 4-Oxo-1,2,3,4-tetrahydrophenanthrene was synthesized according the procedure described by Huggenberg and Hesse [9].

The polyWhelk-O CSP was synthesized as described previously [10].

2.2.1. Preparation of 3-chloropropyldiallylmethylsilane (*6*)

Dichloro-3-chloropropylmethylsilane, 8.3 g (43 mmol), was added dropwise to a 2.0 *M* solution of allylmagnesium chloride in 50 ml of tetrahydrofuran under a nitrogen atmosphere. The suspension was stirred at room temperature for 2 h and at 45°C for another 3 h. The reaction mixture was quenched slowly with 20 ml of 10% ammonium chloride so that the temperature did not rise above 0°C. The two-phase mixture was partitioned between water and dichloromethane, the organic layer was washed with water, and was dried over anhydrous magnesium sulfate. Evaporation of the dried solution at ambient temperature gave 8.3 g (41 mmol, 95% yield) of **6** as a colorless oil.

^{1}H NMR (400 MHz) δ: 0.00 (s, 3H), 0.66 (m, 2H), 1.57 (ddd, 4H, J=1.2 Hz, J=1.2 Hz, J=8.1 Hz), 1.78 (m, 2H), 3.47 (t, 2H, J=6.8 Hz) 4.87 (m, 4H), 5.77 (m, 2H). ^{13}C NMR (125 MHz) δ: −5.72, 10.94, 21.38, 27.56, 48.07, 113.74, 134.53.

2.2.2. Preparation of diallyl-3-iodopropylmethylsilane (*7*)

To a solution of 9.8 g (65 mmol) sodium iodide (dried at 140°C under vacuum for 24 h) in 75 ml dry acetone was added 8.0 g (39.5 mmol) of **6** and the mixture was heated at reflux for 5 h. The reaction mixture was evaporated to dryness and the crude material partitioned between water and several portions of dichloromethane. The combined organic layers were washed with aqueous sodium thiosulfate, water and dried over anhydrous magnesium sulfate. Evaporation of the dichloromethane gave 11.5 g (39 mmol, 98% yield) of **7** as a light yellow oil.

^{1}H NMR (400 MHz) δ: −0.01 (s, 3H), 0.68 (m, 2H), 1.54 (ddd, 4H, J=1.2 Hz, J=1.2 Hz, J=8.1 Hz), 1.82 (m, 2H), 3.16 (t, 2H, J=7.2 Hz) 4.90 (m, 4H), 5.75 (m, 2H). ^{13}C NMR (125 MHz) δ: −5.65, 11.22, 15.31, 21.40, 28.72, 113.78, 134.50.

2.2.3. Preparation of racemic 4-oxo-3-diallylmethylsilylpropyl-1,2,3,4-tetrahydrophenanthrene (*8*)

To a solution of 10.0 g (51 mmol) 4-oxo-1,2,3,4-tetrahydrophenanthrene in 400 ml dry toluene under nitrogen was added 8.6 g (77 mmol) potassium *tert*.-butoxide. This solution was stirred at room

temperature for 30 min and then 10.4 g (35 mmol) of **7** was added in one portion. The reaction mixture was heated to 65°C for 3 h, cooled to room temperature and quenched with 2 *M* hydrochloric acid. The organic phase was washed with water and dried over anhydrous magnesium sulfate. Toluene was removed on a rotary evaporator and the crude material was purified by flash chromatography on silica [dichloromethane–hexane (1:1)]. 7.2 g (20 mmol, 57% yield based on **7**) of **8** as a light yellow oil were obtained and 4.4 g (23 mmol) 4-oxo-1,2,3,4-tetrahydrophenanthrene was recovered.

^{1}H NMR (400 MHz) δ: −0.02 (s, 3H), 0.60 (m, 2H), 1.44 (m, 3H), 1.55 (ddd, 4H, J=1.0 Hz, J=1.0 Hz, J=8.1 Hz), 1.91 (m, 2H), 2.28 (m, 1H), 2.64 (m, 1H), 3.13 (t, 2H, J=6.2 Hz), 4.83 (m, 4H), 5.76 (m, 2H), 7.27 (d, 1H, J=8.3 Hz), 7.46 (ddd, 1H, J=1.0 Hz, J=7.8 Hz, J=8.1 Hz), 7.59 (ddd, 1H, J=1.0 Hz, J=7.8 Hz, J=8.8 Hz), 7.78 (d, 1H, J=8.1 Hz), 7.88 (d, 1H, J=8.3 Hz), 9.26 (d, 1H, J=8.8 Hz). ^{13}C NMR (125 MHz) δ: −5.61, 13.38, 21.49, 21.56, 28.32, 29.92, 34.28, 48.86, 113.36, 125.97, 126.66, 127.02, 127.88, 128.47, 128.78, 131.55, 133.00, 133.92, 134.99, 145.61, 203.51.

*2.2.4. Preparation of racemic 4-amino-3-diallylmethylsilylpropyl-1,2,3,4-tetrahydrophenanthrene (**9**)*

A mixture of 6.0 g (16.6 mmol) of ketone **8**, 40.0 g ammonium acetate and 8.6 g sodium cyanoborohydride in 200 ml of dry 2-propanol was securely closed in a thick-walled Parr bottle and heated to 100°C for 29 h. Approximately 75% of the solvent was removed by rotary evaporation and 1 *M* aqueous sodium hydroxide solution was added until the solution was basic. The mixture was extracted with several portions of dichloromethane, the combined organic layers were washed with water, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The crude amine, **9**, so obtained was not further purified.

*2.2.5. Preparation of racemic cis-4-(3,5-dinitrobenzamido)-3-diallylmethylsilylpropyl-1,2,3,4-tetrahydrophenanthrene (**10**)*

The crude amine **9** was dissolved in 150 ml of dichloromethane and stirred with an excess of 2 *M* potassium hydroxide. To this mixture was added 8.0 g (35 mmol) of 3,5-dinitrobenzoyl chloride and the two-phase system was allowed to stand with periodic agitation for 3 h. The two phases were separated and the organic layer was washed with water and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residual brown oil was flash chromatographed [dichloromethane–hexane (3:1)] to afford 2.4 g (4.3 mmol, 26% yield from **8**) of the *cis* diastereomer, **10**, as pale yellow crystals.

^{1}H NMR (400 MHz) δ: 0.00 (s, 3H), 0.06 (m, 2H), 0.59 (m, 2H), 1.37 (m, 2H), 1.55 (m, 4H), 1.78 (m, 1H), 2.04 (m, 2H), 3.10 (m, 2H), 4.84 (m, 4H), 5.77 (m, 2H), 6.10 (dd, 1H, J=3.6 Hz, J=9.6 Hz), 6.20 (d, 1H, J=9.6 Hz), 7.26 (d, 1H, J=8.3 Hz), 7.42 (dd, 1H, J=7.3 Hz, J=8.1 Hz), 7.50 (ddd, 1H, J=1.2 Hz, J=7.3 Hz, J=8.5 Hz), 7.74 (d, 1H, J=8.3 Hz), 7.79 (d, 1H, J=8.1 Hz), 8.06 (d, 1H, J=8.5 Hz), 8.84 (d, 2H, J=2.0 Hz), 9.09 (dd, 1H, J=2.0 Hz). ^{13}C NMR (125 MHz) δ: −5.59, 13.57, 21.39, 21.57, 23.87, 30.59, 36.49, 39.38, 47.95, 113.39, 121.27, 122.82, 125.76, 127.34, 127.57, 127.90, 128.98, 130.69, 132.20, 132.71, 135.00, 141.02, 141.20, 148.84, 159.41, 160.17.

*2.2.6. Resolution of racemic cis-4-(3,5-dinitrobenzamido)-3-diallylmethylsilylpropyl-1,2,3,4-tetrahydrophenanthrene, **10***

The enantiomers of **10** were separated on a 750 mm×34 mm column containing a naproxen-derived CSP [11] using hexane–tetrahydrofuran (6:1) as the mobile phase.

*2.2.7. Preparation of the ABAB-copolymer (**11**)*

A mixture of 0.98 g (1.76 mmol) of **10** and 0.94 g (1.86 mmol) 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethylheptasiloxane were dissolved in 70 ml of dry toluene under nitrogen, heated to 65°C, and 0.5 mg of hexachloroplatinic acid dissolved in a minimum amount of dry 2-propanol was added. After 3 d, another 0.2 mg of the catalyst in 2-propanol was added. Periodically, the reaction was monitored by ^{1}H NMR spectroscopy to follow the disappearance of vinyl and hydrosiloxane signals. After 6 d, the mixture was cooled to room temperature and the toluene was removed by evaporation. The residue was dissolved in dichloromethane and quickly filtrated through silica gel. Evaporation of the solvent

at ambient temperature gave 1.88 g (98% yield) of **11** as a viscous yellow oil.

^{1}H NMR (400 MHz) δ: −0.06 (s, 3H), 0.04 (m, 43H), 0.58 (m, 8H), 1.17 (dd, 2H, J=2.0 Hz, J=6.1 Hz), 1.32 (m, 4H), 1.52 (m, 2H), 1.61 (m, 1H), 1.80 (m, 1H), 2.05 (d, 2H, J=9.8 Hz), 3.08 (m, 2H), 6.09 (d, 1H, J=9.3 Hz), 6.25 (m, 1H), 7.23 (m, 1H), 7.40 (m, 1H), 7.48 (m, 1H), 7.73 (m, 2H), 8.06 (m, 1H), 8.82 (m, 2H), 9.06 (m, 1H). ^{13}C NMR (125 MHz) δ: −4.82, 0.50, 1.24, 1.28, 1.39, 14.74, 18.03, 18.61, 21.73, 23.28, 25.84, 30.62, 36.59, 39.44, 48.13, 121.21, 122.85, 125.72, 127.33, 127.55, 127.88, 128.95, 130.79, 132.21, 132.70, 135.62, 138.21, 148.80, 162.05.

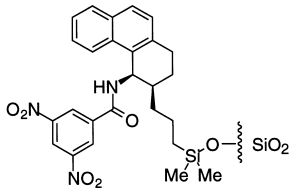
2.3. Immobilization, packing and endcapping of the chiral polymers

Each of the chiral polymers (CSP 2 and CSP 3) was coated onto silica gel (5 μm, 300 Å pore size) and immobilized by heating at 120°C for 24 h under reduced pressure. After extensive washing of each CSP with dichloromethane and methanol, each was a slurried in dichloromethane and packed into a stainless steel column (250×4.6 mm). Endcapping of remaining silanols was performed for each of the three columns used by passing a solution of 2% (v/v) hexamethyldisilazane in dichloromethane through the column at a flow of 1 ml/min for 2 h.

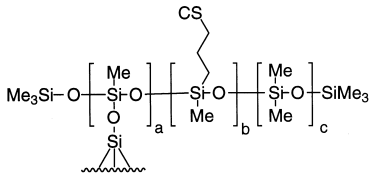
3. Results and discussion

In contrast to CSP 1 and CSP 2, the synthesis of a chiral ABAB-copolymer, such as CSP 3, which consists of alternating chiral (A) and achiral (B) units allows one to control the spacing between the selectors (Fig. 1). In accordance with HPLC studies on (*S*)-naproxen-derived copolymeric CSPs [7], CSP 3 was expected to provide higher enantioselectivity than its brush-type and sidechain-modified analogs, possibly as a result of less significant simultaneous interactions between one analyte and two selector units.

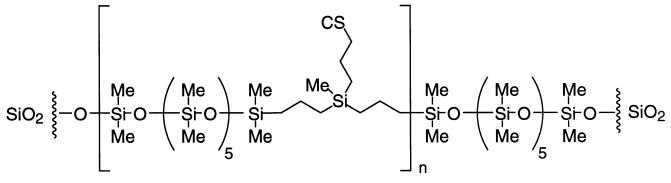
The chiral copolymer **11** was synthesized by hydrosilylation of a diallyl derivative of the Whelk-O selector, **10**, using an α,ω-dihydropolymethylsiloxane oligomer (Scheme 1). 1,1,3,3,5,5,7,7,9,9,11,11,13,13 - Tetradecamethylheptasiloxane (^{H}MD$_5$M^H) was chosen as the achiral moiety because it was expected to provide sufficient spacing between the selector units. Additionally, this spacer had already been shown to be effective in a copolymeric (*S*)-naproxen phase [7]. Grignard reaction of dichloro-3-chloropropylmethylsilane using allylmagnesium chloride followed by Finkelstein reaction of silane **6** provided the iodo derivative, **7**, in high yield. α-Alkylation of 4-oxo-1,2,3,4-tetrahydrophenanthrene with **7** affords ketone **8** which was converted to the chiral moiety **10** by reductive



CSP 1



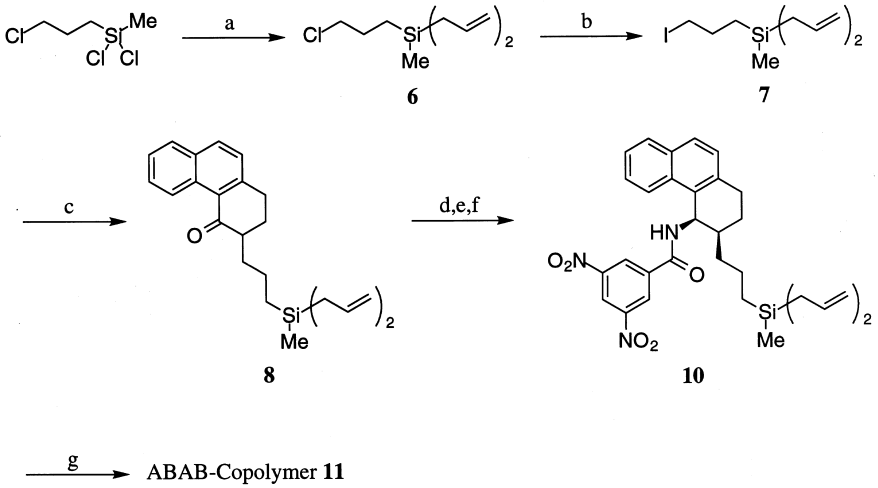
CSP 2



CSP 3

Fig. 1. Chiral stationary phases used in this study. CS=Whelk-O selector.

Scheme 1



Conditions: a) allylmagnesium chloride, THF. b) NaI, acetone.

c)  , *tert.*-butoxide, toluene. d) $NaCNBH_3$, NH_4OAc, 2-propanol.

e) 3,5-DNBCl, KOH, CH_2Cl_2. f) Preparative enantioseparation on a naproxen-derived CSP.

g) $^{H}MD_5M^{H}$, H_2PtCl_6, toluene.

Scheme 1. Synthesis of the chiral copolymer **11**.

amination, acylation with 3,5-dinitrobenzoyl chloride, and preparative separation of the enantiomers by HPLC on a naproxen-derived CSP. Copolymer **11** was coated on silica gel (5 μm, 300 Å), immobilized by heating, and CSP 3 was packed into an HPLC column. The CSPs investigated were endcapped with hexamethyldisilazane prior to evaluation.

Representing a variety of compounds, analytes **1**–**5** (see Fig. 2) were used to study the chromatographic performance of CSPs 1–3. Different amounts of 2-propanol were used as a polar modifier in hexanes or carbon dioxide for HPLC and SFC, respectively (Tables 1 and 2). Because of greater diffusivity, modified carbon dioxide affords higher column efficiency with all CSPs than was observed by HPLC. It should be noted that the use of a modifier presumably alters the subcritical–supercritical transition point but no chromatographic discontinuities accompany this transition. Interestingly,

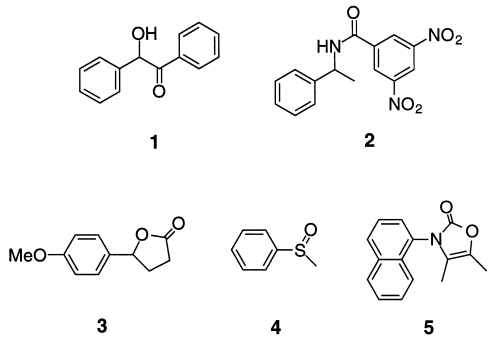


Fig. 2. Structure of the analytes **1**–**5**.

Table 1
SFC enantioseparations of **1**–**5** on CSPs 1, 2 and 3

	CSP 1				CSP 2				CSP 3			
Entry	k_1	α	N_1	R_s	k_1	α	N_1	R_s	k_1	α	N_1	R_s
1	0.63	2.56	7200	10.31	0.23	2.74	2300	3.71	0.41	2.73	9300	9.96
2	6.09	2.14	9500	16.24	2.61	2.15	3200	8.53	4.51	2.16	11 800	17.95
3	1.99	1.52	7800	6.58	0.70	1.57	2800	2.85	1.16	1.64	8400	6.85
4	1.55	1.34	6500	3.85	0.83	1.34	1300	1.33	1.18	1.41	5000	3.74
5	3.62	2.93	11 300	22.76	1.81	2.98	3400	11.47	2.92	3.22	10 500	24.25

Conditions: 10% (**1**, **2**, **4**), 5% (**3**) and 20% (**5**) 2-propanol in carbon dioxide, 2 ml/min, 200 bar back pressure, 30.0°C.

SFC provides less retention and higher enantioselectivity than HPLC, indicating that the nature of the mobile phase plays an important role in the chiral recognition mechanism. It should be noted that the substitution of a supercritical fluid for a liquid eluent changes the physical and chemical properties of the mobile phase and also affects the nature of the stationary phase. Unsurprisingly, similar comparisons of the chromatographic performance in HPLC and SFC have been reported for a variety of CSPs [2].

Comparison of the chromatographic properties of CSP 1 and CSP 2 in SFC and HPLC shows that the sidechain-modified CSP usually exhibits higher selectivity. This was attributed to a better shielding of residual silanol groups and consequently less achiral interaction [7]. In contrast, decreased accessibility of the selector and reduced diffusivity in the sidechain-modified polysiloxane might be responsible for the lower efficiency of CSP 2.

The loading of selector per gram of CSP was determined by elemental analysis to be 0.08 mmol/g for CSP 2 and as 0.09 mmol/g for CSP 3. A loading of 0.2 mmol/g was reported for original CSP 1 [12] and the commercial version used in this study has a loading of ca. 0.25 mmol/g [13]. Accordingly, analytes are much stronger retained on CSP 1 than on CSP 2 and CSP 3. Note too that the 100 Å silica used in CSP 1 has greater surface area than the 300 Å silica used in CSPs 2 and 3.

Copolymeric CSP 3 does indeed show a chromatographic performance superior to that of CSP 1 and CSP 2 in both SFC and HPLC. In general, CSP 3 combines the high efficiency of CSP 1 with the high enantioselectivity of CSP 2 (Tables 1 and 2). The former may result from reduction of possible bridging effects and more effective shielding of remaining silanols while the latter must result from more favorable mass transfer kinetics.

We recently reported the use of CSP 1 and CSP 2 for subcritical fluid chromatographic (SubFC) separations of the enantiomers of several ketones and secondary alcohols [5]. The term SubFC is used to clearly indicate that the carbon dioxide mobile phase is not supercritical, i.e., one works below the supercritical temperature. Both CSPs provide high enantioselectivity and reasonable column efficiency at cryogenic temperatures. As is shown with analyte **3**, CSP 3 also affords good chromatographic performance at cryogenic temperatures. As the temperature is decreased, greater enantioselectivity and resolution is observed without a significant loss in efficiency at

Table 2
HPLC enantioseparations of **1**–**5** on CSPs 1, 2 and 3

	CSP 1				CSP 2				CSP 3			
Entry	k_1	α	N_1	R_s	k_1	α	N_1	R_s	k_1	α	N_1	R_s
1	0.98	2.18	1600	5.67	0.36	2.22	1500	2.85	0.65	2.29	3400	6.56
2	9.35	2.34	3400	11.70	4.59	2.04	1200	6.50	9.18	1.98	3900	11.91
3	2.21	1.34	4800	3.91	1.01	1.40	1700	2.10	1.69	1.47	4000	4.39
4	4.26	1.30	4500	3.89	1.81	1.34	900	1.53	2.88	1.40	3600	4.41
5	5.34	2.78	5200	15.00	2.30	2.72	2800	11.01	4.19	2.99	5800	17.80

Conditions: 10% (**1**, **2**, **4**), 5% (**3**) and 20% (**5**) 2-propanol in hexane, 2 ml/min, 25.0°C.

Table 3
SubFC and SFC separations of the enantiomers of **3** on CSP 3

Temperature (°C)	Method	Flow (ml/min)	k_1	α	N_1	R_s
−33.0	A	1.50	0.41	2.47	7600	8.76
−33.0	B	1.50	0.63	2.41	7000	8.63
0.0	B	1.75	0.92	1.86	7500	7.23
27.0	B	2.00	1.06	1.65	8400	6.78
60.0	B	2.50	1.32	1.46	8500	5.42

Conditions: 5% methanol (A) or 2-propanol (B) in carbon dioxide, 200 bar back pressure.

optimized flow-rates. At a flow-rate of 1.5 ml/min, 7000 plates per column were observed even at −33.0°C (Table 3). A comparison of van Deemter plots shows a shift of the minimum theoretical plate height, *h*, to higher flow-rates with increasing temperature (Fig. 3). This presumably results from the increasing influence of mass transfer characteristics and axial diffusion on column efficiency at higher temperatures, i.e., an increase in the rate of adsorption and desorption and higher diffusivity of the mobile phase. Interestingly, substitution of methanol for 2-propanol as the organic modifier in SubFC at cryogenic conditions increases selectivity, efficiency and resolution and also shortens the time required for analysis (Fig. 4, Table 3).

It is widely understood that the enantioselectivity of a CSP almost invariably increases as the column temperature is reduced. However, retention typically increases as well and the kinetics of mass transfer are usually slowed so that, despite the increased enantioselectivity, resolution, R_s, is reduced. The ability of the copolyWhelk-O to maintain its chromatographic efficiency at cryogenic temperatures is an unusual and very desirable characteristic.

4. Conclusions

A chiral copolymer was synthesized by hydrosilylation of a diallyl derivative of the chiral selector with a difunctional α,ω-dihydropolymethylsiloxane oligomer. Immobilization of the polymer on silica support provides a stable CSP with improved chromatographic performance relative to its brush-type and sidechain-modified analogs. In general, the copolymeric CSP combines high selectivity with high efficiency in SubFC, SFC and HPLC. With all three CSPs investigated, SFC was superior to HPLC with respect to enantioselectivity, efficiency and time analysis.

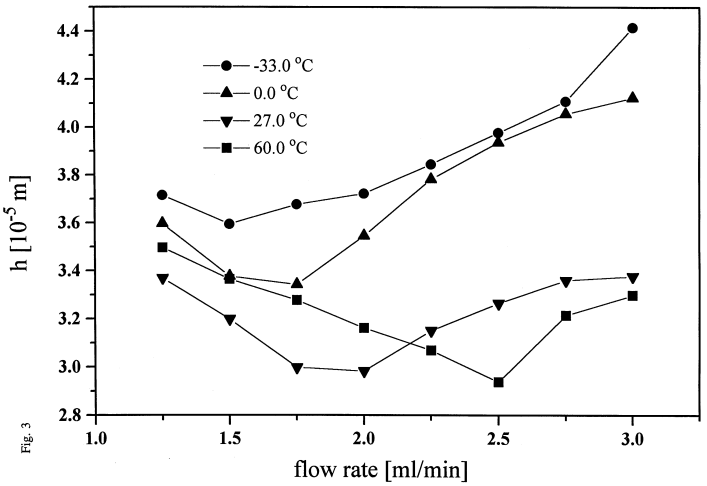


Fig. 3. Van Deemter plots for the less retained enantiomer of **3** using CSP 3 at different temperatures. For conditions see Table 3.

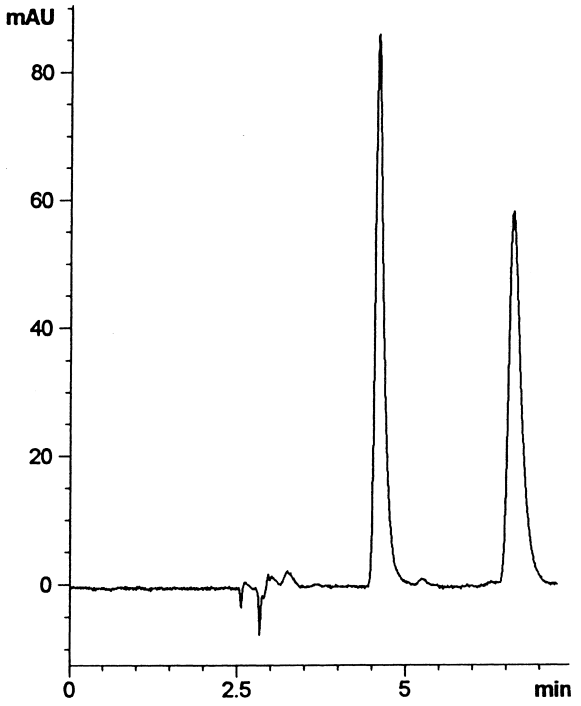


Fig. 4. SubFC enantioseparation of **3** on CSP 3 at −33.0°C. For conditions see Method A in Table 3.

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