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Short Communication

Direct optical resolution of 3,5-substituted δ-valerolactones and related 3,5-dihydroxyvaleric methyl esters on modified amylose and cellulose chiral stationary phases

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ABSTRACT

The optical resolution of 3,5-disubstituted lactones and related diol esters was carried out by HPLC on chiral stationary phases consisting of cellulose tris(3,5-dimethylphenylcarbamate), cellulose tris(4-chlorophenylcarbamate) and amylose tris(3,5-dimethylphenylcarbamate) derivatives coated on macroporous silica using hexane-Zpropanol and hexane-ethanol mobile phases. In most instances baseline separation could be achieved.

INTRODUCTION

Compactin (Fig. 1) is a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMP-CoA) reductase. A key intermediate of these HMGA-CoA reductase inhibitors is the lactone moiety in an optically pure form. Generally, the target lactone can be directly prepared by cyclization of appropriate 1,3-diol esters, which are obtained by stereoselective reduction of the related aldol [1–3]. Up to now the enantiomeric excesses of these lactones have been determined via diastereomers prepared with (-)-camphanic acid chloride [2,3]. Shibata *et al.* [4] and Francotte and co-workers [5–7] have successfully used chiral chromatography on cellulose triacetate and benzoylcellulose beads for the optical resolution of various lactones and diols.

In this paper we present the first direct determination of the enantiomers of 3,5-substituted δ-valerolactones and related diol esters (Fig. 2) by chiral HPLC on modified amylose and cellulose chiral stationary phases (CSPs). Suitable CSPs were cellulose tris(3,5-dimethylphenylcarbamate) (CDMPC, Chiralcel OD), amylose

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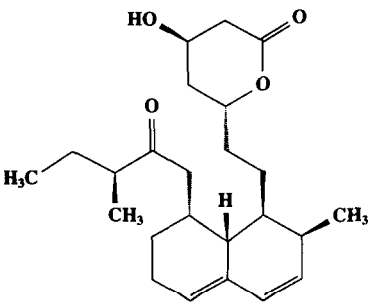

Fig. 1. Structure of compactin A.

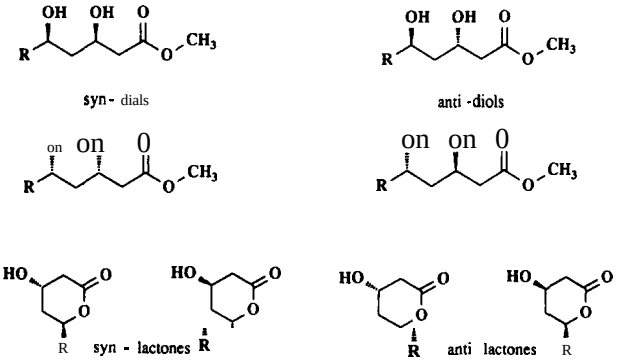

Fig. 2. Structure of solutes. Series 1, R = phenyl; series 2, R = cinnamyl.

tris(3,5-dimethylphenylcarbamate) (ADMPC, Chiralcel AD) and cellulose tris(4-chlorophenylcarbamate) (Cp-ClPC).

EXPERIMENTAL

Chemicals and materials

The synthesis of the title compounds (Fig. 2) has been published elsewhere [8]. Small traces of ***anti-diol*** esters in syn-diol ester samples and vice ***versa*** were separated by HPLC using a silica gel column and hexane-ethyl acetate eluents. Cellulose and amylose carbamate derivatives were prepared by the reaction of the polysaccharide with an excess of corresponding isocyanates in pyridine according to Okamoto and co-workers [9,10].

The Cp-ClPC packing material was obtained by a coating procedure [9] using Nucleosil 4000-7(NH_2) silica gel support and slurry packed in a stainless-steel column (150 *x* 4 mm I.D.).

Chiralcel AD and Chiralcel OD analytical columns (250 x 4.6 mm I.D.) were purchased from J.T. Baker (Gross-Gerau, Germany).

Mobile phase components were carefully dried HPLC-grade 2-propanol, ethanol and hexane and analytical-reagent-grade ethyl acetate (Merck, Darmstadt , Germany).

TABLE I

SEPARATION OF DIOLS

Eluent, hexane-Zpropanol (80:20); flow-rate, 1 ml/min; k_1' = capacity factor of the first-eluting peak; a = separation factor; R_s = resolution.

Series[a]	Column	Diol[b]					
		syn form			*anti* form		
		k_1'	a	R_s	k_1'	α	R_s
1	CDMPC	2.67	1.08	0.75	1.43	1.07	0.67
2		4.16	4.08	7.96	2.88	1.29	1.56
1	ADMPC	1.61	*ca.* 1	0	1.26	*ca.* 1	0
2		*2.14*	*ca.* 1	0	1.87	*ca.* 1	0
1	Cp-ClPC	6.92	1.77	4.55	4.66	1.24	1.47
2		6.36	1.19	1.29	5.20	*ca.* 1	0

[a] Series 1, R = phenyl; series *2,* R = cinnamyl (Fig. 2).
[b] See Fig. 2 for structures.

TABLE II

SEPARATION OF LACTONES

Eluent, hexane–2-propanol (80:20); flow-rate, 1 ml/min; k_1' = capacity factor of the first-eluting peak; α = separation factor; R, = resolution.

Series[a]	Column	Lactone[b]					
		syn form			*anti* form		
		k_1'	a	R_s	k_1'	a	R_s
1	CDMPC	2.81	1.07	0.60	3.90	1.32	2.95
2		2.20	1.09	0.80	3.11	1.14	1.37
1	ADMPC	1.54	1.05	0.45	1.77	1.14	1.05
2		1.76	1.16	1.17	2.40	1.15	1.50
1	Cp-ClPC	8.64	*ca.* 1	0	9.86	1.19	1.48
2		8.75	1.43	2.68	12.30	*ca.* 1	0

[a,b] See Table I.

Apparatus and chromatographic conditions

The liquid chromatographic system consisted of a Merck-Hitachi L 6200 pump (Merck), a Rheodyne RH 7125 injection valve (20-μl loop), a variable-wavelength spectrophotometer (Knauer, Berlin, Germany) and an Auswert 2

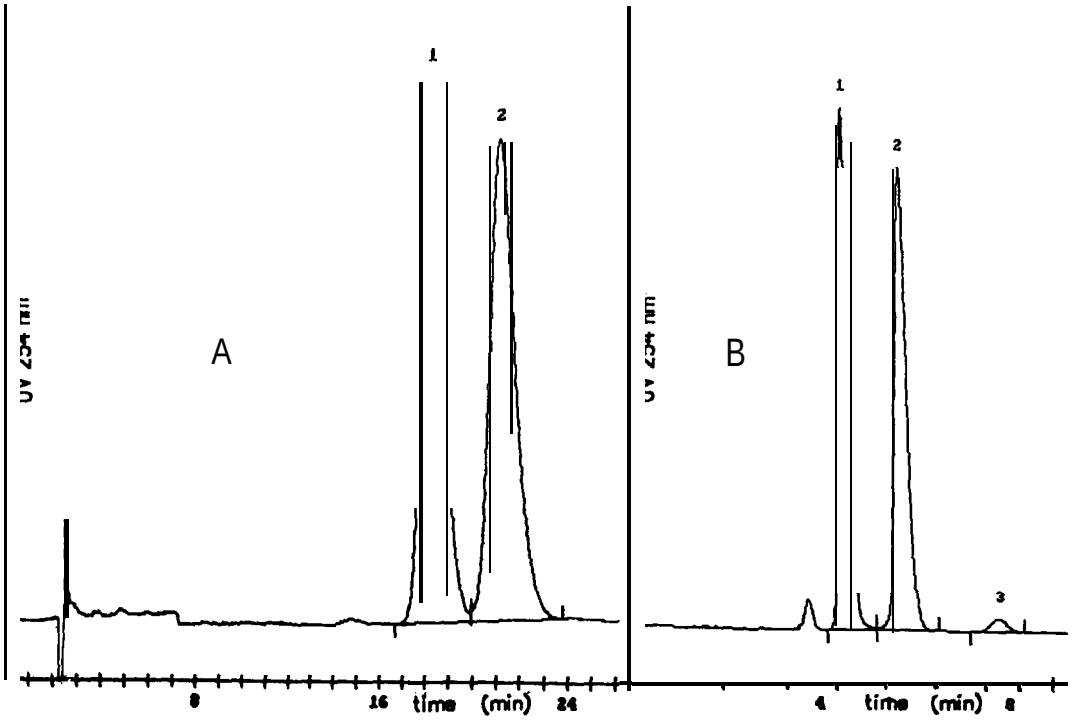

Fig. 3. Separation of the series 2 diols. (A) *syn* form; column, Cp-ClPC; eluent, hexane–2-propanol (80:20); flow-rate, 0.5 ml/min. (B) *anti* form; column, CDMPC; eluent as in (A); flow-rate, 2 ml/min.

data system (ZIOC, Berlin, Germany). Optical rotation was followed in a flow cell (40 μl) using a Polar monitor (IBZ Messtechnik, Hannover, Germany) and two-channel recorder (Kipp & Zonen, Delft, Netherlands).

The detection wavelength of the spectrophotometer and the flow-rate were set at 254 nm and 1 ml/min, respectively. Chromatograms were taken at room temperature (23 ± 1°C). The eluents used were hexane-2-propanol (80:20, v/v) and hexane-ethanol (90:10, v/v), respectively. The solutes were dissolved in the eluent as usual at a concentration of 0.5 mg/ml.

UV and circular dichroism (CD) spectra of CDMPC and ADMPC solutions were recorded at room temperature using a JASCO Uvidec-610 C and a Jasco J-500 P spectrophotometer.

RESULTS AND DISCUSSION

The structures of the chiral 3,5-dihydroxy valeric methyl esters and related δ-valerolactones investigated are shown in Fig. 2. The chromatographic parameters obtained are given in Tables I and II. Solutes investigated include two series, (1) with a phenyl group at the C-5 position and (2) with a corresponding cinnamyl substituent.

Examples of chromatograms of the diols 2 are shown in Fig. 3 and chromatograms of the lactones 2 in Figs. 4 and 5. The results indicate that almost all the solutes investigated could be separated sufficiently using CDMPC, ADMPC and Cp-ClPC CSPs. However, large differences in capacity factors, chiral recognition ability and efficiency of optical resolution were observed.

Retention (k'_1) depends on the stereochemical behaviour of the solutes used. In all instances the *syn*-diols showed longer retention times than the corresponding anti forms, whereas the lactones gave longer retentions for the appropriate anti forms. These findings, however. do not affect the optical resolution. Solutes on the Cp-ClPC column show comparatively high capacity fac-

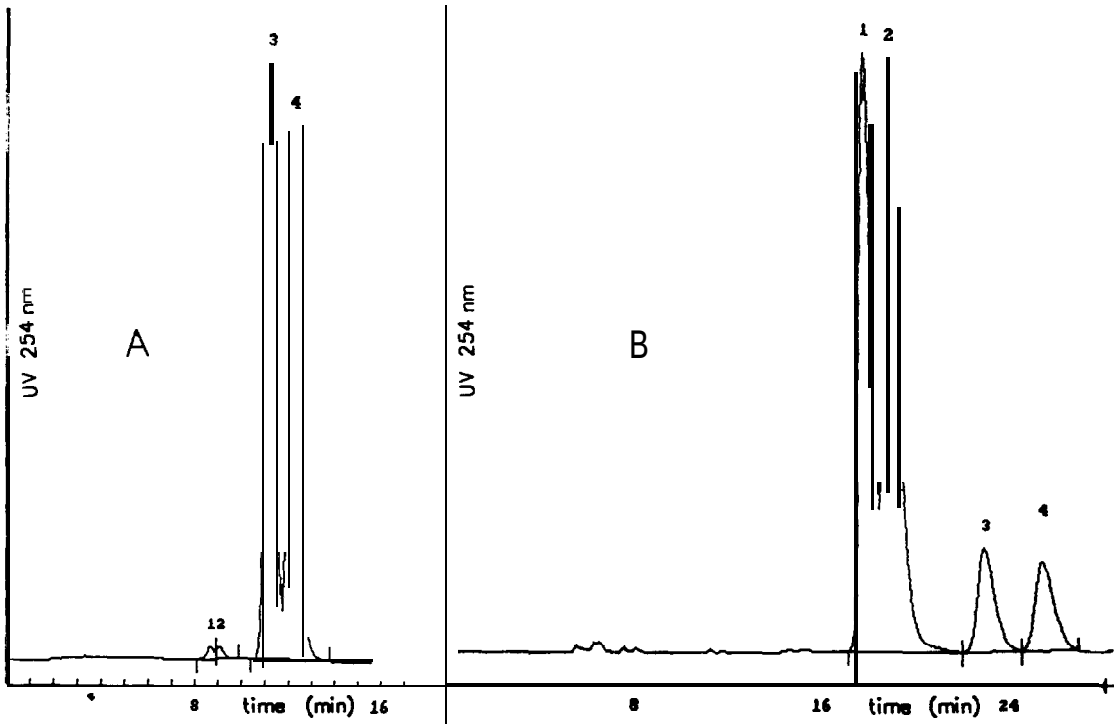

Fig. 4. Separation of the series 2 lactones on a CDMPC column. Eluent, hexane–2-propanol (80:20); flow-rate, (A) 1 and (B) 0.5 ml/min. Peaks: 1 and 2 = *syn* enantiomers; 3 and 4 = ***anti*** enantiomers.

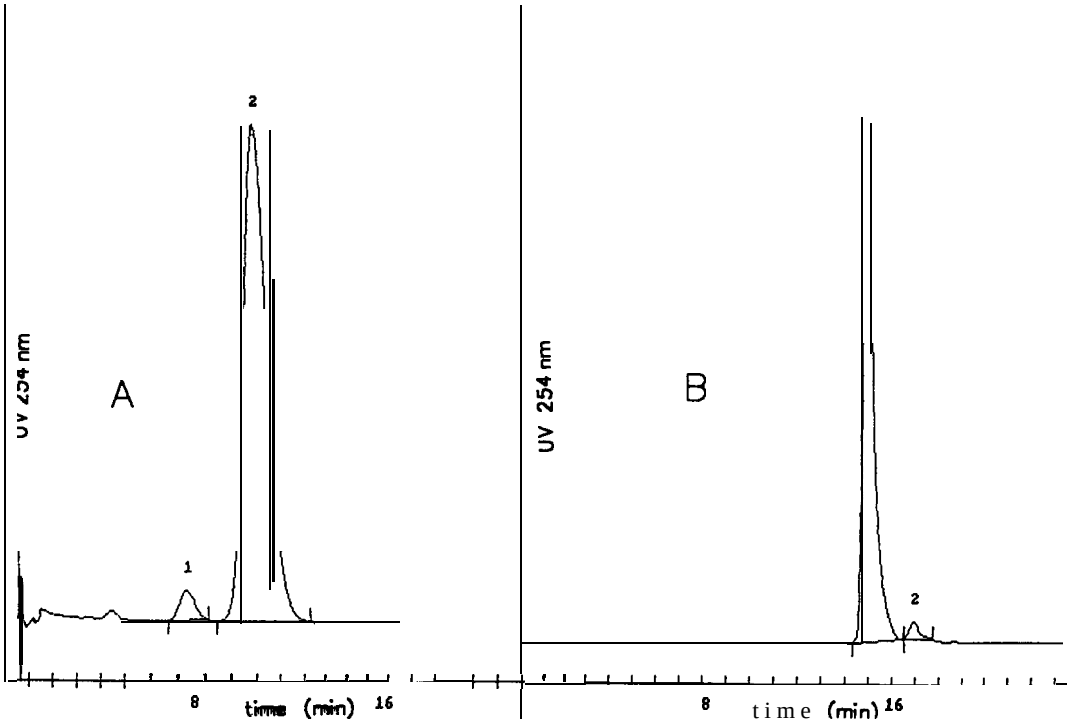

Fig. 5. Separation of an enriched series 2 (3*R*,5*S*)-(+)-*syn*-lactone. Eluent, hexane–2-propanol (80:20). (A) column, Cp-ClPC; flow-rate, 2 ml/min. Peak 1 = (-)-enantiomer. (B) column, ADMPC; flow-rate, 0.5 ml/min. Peak 1 = (+)-enantiomer.

tors, indicating a strong influence of the electron-withdrawing chloro substituent on the retention interactions, taken as the sum of chiral and achiral elements. The best resolutions of the racemic diols were obtained with the Cp-ClPC column, except for the anti-diol 2, which was well separated on a CDMPC column (Table I, Fig. 3B). In some instances a better resolution could be obtained by reducing the flow-rate to 0.5 ml/min (Fig. 3A), but the separation of *syn*-lactone 1 on CDMPC remained poor even at lower flow-rates. Changing the eluent from hexane-Zpropanol (80:20) to hexane-ethanol (90:10) gave a successful resolution. The capacity factor (k_1') increased from 2.81 to 2.99, the separation factor from 1.08 to 1.12 and the resolution from 0.75 to 1.38.

For practical use, CDMPC and ADMPC columns are suitable for the optical resolution of racemic lactones (Table II). As with racemic diols, a better resolution was obtained using lower flow-rates (Fig. 4A and B). As can be seen from the molecular structural models, the rotational freedom of the phenyl group in lactone molecules of series 1 is somehow restricted to one enantiomer owing to the Van der Waals force interactions, which are particularly strong with the anti form. This might support enantiomeric discrimination from a stereochemical point of view. The chromatographic results in Table II, however, show sufficient optical resolution of the anti form lactones 1 on all columns used.

The elution order of enantiomers was checked by following the optical rotation in a polarimetric detector for the lactones 2. For both the racemic *syn-* and anti-lactones, the enantiomers eluted first exhibit the same sign of optical rotation. Using CDMPC and Cp-ClPC columns the (−)-enantiomer is eluted first, whereas the ADMPC column gave the (+)-enantiomer first. These findings could also be proved by optical resolution of an enriched (3*R*,5*S*)-(+)-*syn*-lactone 2 (Fig. 5). The enantiomeric excess was found to be 96%.

Such an inversion of the elution order between carbamate phases of cellulose and amylose

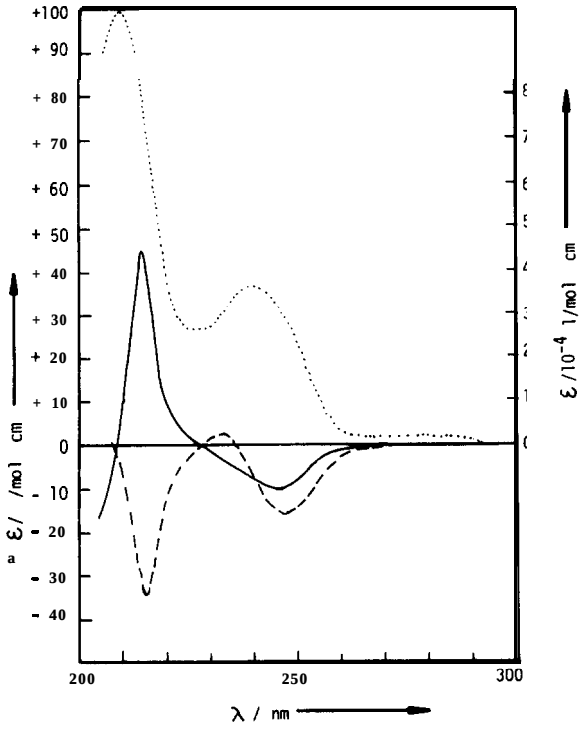

Fig. 6. UV and CD spectra of CDMPC and ADMPC solutions. Dotted line, UV spectrum of CDMPC solution (solvent, tetrahydrofuran). Solid and dashed lines, CD spectra of CDMPC and ADMPC solution, respectively.

stationary phases has been observed in many instances [11]. One reason might be the difference in conformation and helicity of appropriate polymer chains, which can be proved by CD spectrometry. Fig. 6 shows the UV and CD spectra of CDMPC and ADMPC solutions (ca. 1 mg/ml polymer in tetrahydrofuran). The CD curves of CDMPC and ADMPC exhibit a Cotton effect of opposite direction at a wavelength of 215 nm. Although CD spectra were measured in low-concentration solutions, the observed differences in polymer chain conformation were assumed to be fixed in the packing material during the coating process.

CONCLUSIONS

CDMPC, ADMPC and Cp-ClPC CSPs are suitable for the optical resolution of 3,5-disubstituted S-valerolactones and related 3,5-dihydroxyvaleric methyl esters. Large differences in capacity factors, chiral recognition ability and elution order of the enantiomers and also the efficiency of optical resolution were observed. Significant differences in chiral recognition between *syn* and *anti* forms of solutes could not be found.

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