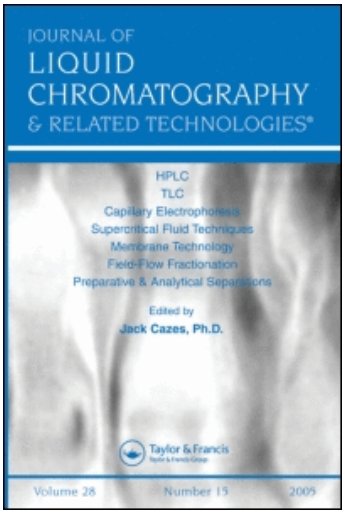

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Chiral HPLC Resolution of the Wieland–Miescher Ketone and Derivatives

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ABSTRACT

The direct HPLC resolution of four structurally related compounds, the Wieland-Miescher ketone, its C(5) homologue, and their C(1) dioxolane derivatives, was studied on commercially available polysaccharide-based chiral stationary phases (CSPs) cellulose *tris*-(3,5-dimethylphenylcarbamate)

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(Chiralcel OD-H), native β-cyclodextrin (Cyclobond I), and acetylated, carboxymethylated and permethylated β-cyclodextrins. The retention, resolution, and elution sequence of the enantiomeric couples were compared using different mobile phases. Baseline enantioseparation of all examined compounds was achieved only on the carboxymethyl-derivatized β-cyclodextrin stationary phase that appeared the most effective chiral selector for this class of compounds. Native, acetylated-, and permethylated-β-cyclodextrin CSPs exhibited specific selectivity providing, in general, partial resolution of the compounds under investigation. On Chiralcel OD-H, only two enantiomeric couples were fully separated. Elution orders depended on CSPs. To optimize chiral separation conditions, the influence of mobile phase composition on column retention and selectivity was also investigated.

Key Words: Wieland-Miescher ketone; HPLC; Chiral separation; β-cyclodextrin derivatives; Cellulose derivatives.

INTRODUCTION

(−)(*R*) **1** and (+)(*S*) **1** Wieland–Miescher ketones[1] and their C(5) homologues, (−)(*R*) **2** and (+)(*S*) **2**[2] (Fig. 1) are key chiral building blocks in natural products synthesis.[3] They can be prepared enantiosynthetically by the Hajos–Parrish methodology[4] or modifications[5] with an e.e. of 68%[6] and 91%,[5] respectively. By a series of crystallizations, compounds **1** and **2** can be then obtained in optically pure form.

To our best knowledge, an HPLC evaluation of the optical purities of compounds **1** and **2** is obtained during the enantiomeric enrichment and during the crystallization process, which has been achieved only for the enantiomeric couple **1** by means of a β-cyclodextrin bonded phase[7] and by means of a Chiralcel OJ chiral stationary phase.[8] Conversely, the HPLC separation of the enantiomeric couple **2** and that of the C(1) dioxolane derivative couples **3** and **4** was never described. The need of a fast and simple method to evaluate the enantiomeric enrichment of **1** → **4** during their enantioselective synthesis, in view of recent improvements in column technology and availability of new chiral stationary phases (CSPs), led us to undertake an investigation on the direct resolution of these compounds by chiral HPLC. This task was by no means trivial, since, up to now, the e.e. compound **2** obtained was evaluated only on a derivative[5] and the enantiomeric couple **4** resolved only by chiral GC.[9]

The present work was carried out using a series of commercially available CSPs based on the following selectors: cellulose *tris*-(3,5-dimethylphenylcarbamate) (Chiralcel OD-H), native β-cyclodextrin (Cyclobond I) and acetylated, carboxymethylated and permethylated β-cyclodextrins. These CSPs were

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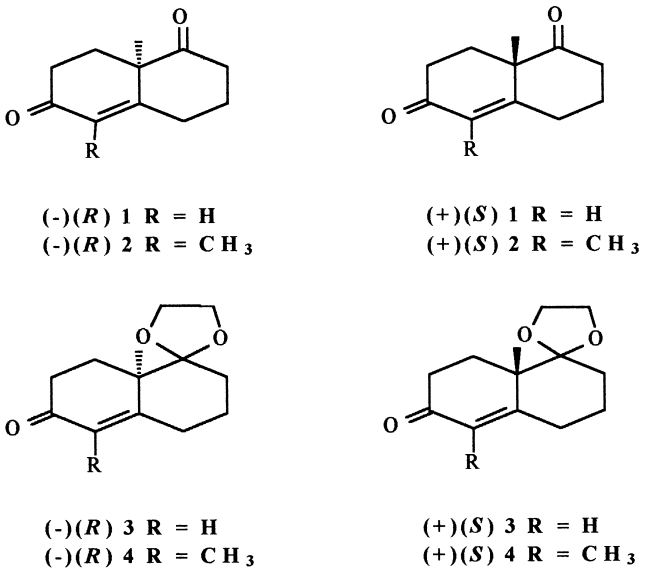

Figure 1. Chemical structure of the examined compounds.

selected on the basis of the size and structure of the compounds under study, as well as of the type of sites of possible interactions with the selector molecules. In order to achieve best column selectivity, the effect of the mobile phase composition was also investigated.

EXPERIMENTAL

Materials

(±), (−)(*R*), and (+)(*S*) 1,6(2H,7H)-naphtalenedione, 3,4,8,8a-tetrahydro-8a-methyl **1** were purchased by Aldrich. (±) 1,6(2H,7H)-naphtalenedione, 3,4,8,8a-tetrahydro-5,8a-dimethyl **2** and (+)(*S*) **2** were obtained according to the method of McMurry[10] and Hagiwara and Uda,[5] respectively.

(±) Spiro[1,3-dioxolane-2,1′(2′H)-naphtalene]-6′(7′H)-one, 3′, 4′, 8′, 8′ a-tetrahydro-8′ a-methyl **3** and (−)(*R*) **3** were synthesized according to the method of Demnitz[11] from commercial (±) **1** and (−)(*R*) 1, respectively.

(±) Spiro[1,3-dioxolane-2,1′(2′H)-naphtalene]-6′(7′H)-one, 3′, 4′, 8′, 8′ a-tetrahydro-5′, 8′ a-dimethyl **4** was synthesized from (±) **2** by a standard

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acetalization procedure (ethylene glycol and catalytic TsOH in refluxing benzene, Dean-Stark apparatus). Spiro [1,3-dioxolane-2,1′(2′H)-naphtalene]-6′(7′H)-one, 3′, 4′, 8′, 8′ a-tetrahydro-5′, 8′ a-dimethyl (+)(*S*) **4** was obtained from (+)(*S*) **2** by the Demnitz acetalization procedure.[11]

Chromatographic Procedures

The HPLC apparatus consisted of a Series 410 Model (Perkin Elmer, Norwalk, CT) solvent delivery pump, equipped with a Rheodyne 7125 Model (10 μL sample loop) injection valve, and connected to a 2550 Model (Varian, Walnut Creek, CA) variable wavelength detector. Chromatographic data were collected and processed by ChromCard software (Fisons, Milano, Italy). HPLC experiments were performed at room temperature.

A polarimetric HPLC detector (Büchi, Milano, Italy), which utilized a Xe–Hg lamp as a light source at full 350–900 nm range with the strong mercury line emission at 365 nm, a flow cell pathlength 0.25 dm, and volume 40 μL, was also used. The output from the polarimetric detector was recorded on a 3396 Series II Model (Agilent Technologies, Waldbronn, Germany) integrator.

The following pre-packed columns were used:

Chiralcel OD-H [150 × 4.6 mm I.D., silica gel (5 μm) coated with cellulose *tris*-(3,5-dimethylphenylcarbamate)] (Daicel Chemical Industries, Baker, Holland).

Cyclobond I 2000 [250 × 4.6 mm I.D., silica (5 μm) bonded with native *β*-cyclodextrin] (Astec, Alltech Italia, Milan, Italy).

Orpak CDBS-453, [150 × 4.6 mm I.D., silica (5 μm) bonded with carboxymethyl-*β*-cyclodextrin (CM-b-CD)] (Shodex, Japan).

MN EC 200/4 Nucleodex *β*-PM [200 × 4.0 mm I.D., silica (5 μm) bonded with permethyl-*β*-cyclodextrin) (PM-b-CD)] (Chemtek Analytica, Bologna, Italy).

Cyclobond I 2000 Ac [250 × 4.6 mm I.D., silica (5 μm) bonded with acetyl-*β*-cyclodextrin (AC-*β*-CD)] (Astec, Alltech Italia, Milan, Italy).

The average substitution degree of the *β*-cyclodextrin (CD) derivatives is not declared by the column producers.

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Mobile phase elution was made isocratically using binary *n*-hexane/2-propanol or water/methanol mixtures, depending on the chiral column type. Water/methanol mixtures were degassed under He pressure before use. Mobile phase specific compositions are given in the text.

HPLC grade solvents were purchased by Carlo Erba (Milan, Italy). Water was filtered through Millipore (Bedford, MA) type GS (0.22 μm) filter disks.

Enantiomers elution orders were verified on all the selected chiral columns by injecting mixtures of racemates **2**, **3**, **4** (1 μL, 0.5 nmoles, each) and (+)(*S*) **2**, (−)(*R*) **3** and (+)(*S*) **4** (1 μL, 0.3 nmoles, each), respectively. The elution order of the enantiomers (−)(*R*) **1** and (+)(*S*) **1** was determined by injecting a mixture of (+)(*S*) **1** (1 μL, 0.3 nmoles) and commercial racemate **1** (1 μL, 0.5 nmoles). Sample solutions were prepared by dissolving the analyte in 2-propanol (IPA).

RESULTS AND DISCUSSION

Chiralcel OD-H

Chiralcel OD-H consists of macroporous spherical silica gel particles coated with cellulose *tris*-(3,5-dimethylphenylcarbamate). It has been assumed, that chiral recognition on this stationary phase is due to the formation of complexes between the solute and the chiral cavities within the high ordered structure of the selector: hydrogen bonding and/or insertion of an unsaturated portion of the solute into the cavities (π–π interaction) might concur to stabilize the complexes, while chiral discrimination between the enantiomers is due to the degree of their fitting into the chiral cavity.[12–15] Therefore, the urethane groups of the CSP should interact by hydrogen bonding with the C═O group at C(6) present in all compounds **1** → **4**, with the C═O group at C(1) in the case of compounds **1** and **2**, and with the dioxolane group at C(1) in compounds **3** and **4**. Dipole-dipole interactions should also be operating.

Table 1 summarizes the chromatographic data obtained on Chiralcel OD-H. Actually, only compounds **1** and **3** were baseline resolved, showing a separation factor α value of 1.12 and 1.37, respectively. Compound **2** showed an insignificant value of resolution; no separation was observed for compound **4**. Therefore, it might be assumed, that hydrogen bonding interaction between the carbonyl function at C(6) and the urethane group of the selector represents the more stabilizing interaction in the formation of inclusion complexes for this class of compounds, and that the dioxolane ring in compound **3**, when compared to the carbonyl group in compound **1**, determines a preferential steric inclusion into the helix structure of the modified cellulose. This is

Table 1. Enantiomeric separation of the Wieland–Miescher ketone and derivatives on Chiracel OD-H[a].

Compound	k'	α	R_s	Elution order
(±) **1**	5.55	1.12	1.20	(+)(*S*), (−)(*R*)
(±) **2**	2.99	1.02	—	—
(±) **3**	4.54	1.37	2.97	(−)(*R*), (+)(*S*)
(±) **4**	1.75	1.0	—	—

[a]Chromatographic conditions: mobile phase, *n*-hexane–2-propanol (94 : 6 v/v); flow-rate, 0.6 mL/min; void time, 2.16 min. UV detector: 230 nm. Room temperature. Retention factor of the more retained enantiomer (k'); separation factor (α); resolution ($R_s = 2[\Delta t_R/w_a + w_b)]$.

evidenced, also, by the different elution sequence of the two enantiomer pairs (Table 1, column 5).

On the other hand, the presence in compounds **2** and **4** of a methyl group at C(5) seems to inhibit the stabilizing hydrogen bonding interaction with the adjacent C=O and the results are, consequently, detrimental for the enantioseparation. Decreased interaction ability of C=O group at C(6) to interact with the stationary phase is also observed in terms of decreased retention, with compounds **2** and **4** being less retained than **1** and **3**.

Figure 2 shows the direct enantioseparation on Chiralcel OD-H of compounds **1** (a) and **3** (b) with UV detection, and of compound **3** with polarimetric detection. Since chiral separation of compounds **1** → **4** has not been previously attempted on Chiralcel OD-H, it was necessary to identify, in each resolved couple, the *R* and *S* enantiomers. This implied, in addition to the synthesis of racemic compounds **2** → **4**, the preparation of enantiopure (+)(*S*) **2**, (−)(*R*) **3**, and (+)(*S*) **4** (as reported in the Experimental section). By comparing the chromatograms of the resolved racemates **1** and **3** with the same racemates enriched with one pure enantiomer, the elution sequence of the two resolved enantiomers could be established.

Figure 3 shows the influence of IPA concentration on the retention and enantioseparation of compound **3**. Up to a concentration of about 18% IPA, the retention of the two enantiomers rapidly decreases owing to the competition of the alcohol modifier in hydrogen bond formation with the selector; over this concentration, the retention and selectivity factors remain almost constant and the enantiodiscriminative effect due to the chiral cavities on the selector might be evidenced.[12]

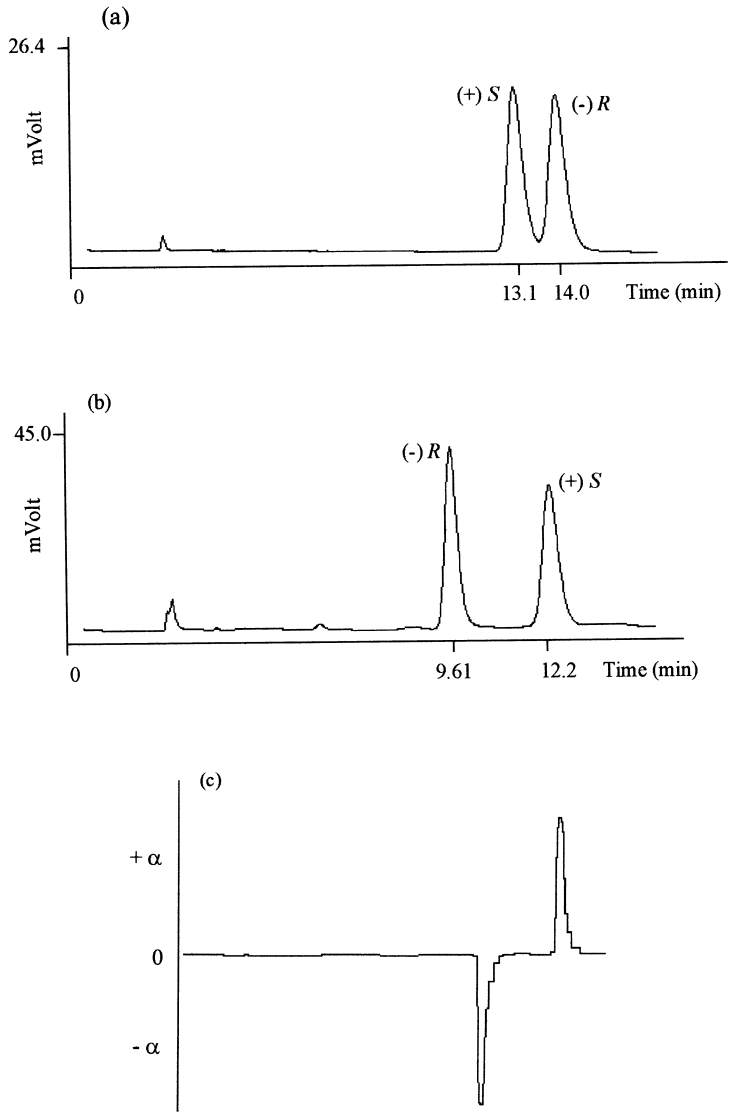

Figure 2. Enantioseparation of compounds (a) **1** and (b) **3** with UV detector and (c) **3** with polarimetric detector on Chiracel ODH using *n*-hexane–IPA (94/6 v/v) as the mobile phase. Other chromatographic conditions as in Table 1.

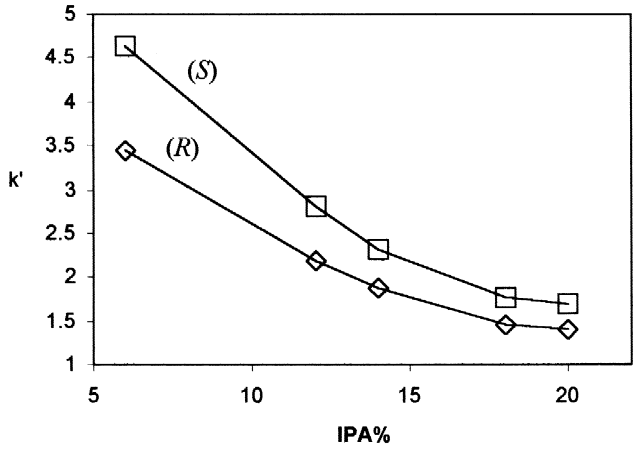

Figure 3. Influence of IPA content in the mobile phase on the retention factor k' for the two enantiomers of compound **3** on Chiralcel OD-H (□) = (+) (*S*) enantiomer, (◆) = (−) (*S*) enantiomer. Chromatographic conditions, as in Table 1.

β-Cyclodextrin Based Chiral Stationary Phases

Cyclodextrins (CDs) are cyclic oligosaccharides, which can be represented as a truncated cone consisting of 6, 7, and 8 D-glycopyranose α-1,4 linked units, respectively. In the presence of water, the inner part of the CDs cavity is relatively hydrophobic. Thus, lipophilic molecules or parts of a molecule can form inclusion complexes, while the secondary hydroxyls oriented towards the outside region of the selector, can form hydrogen bonding or dipole–dipole interaction with the polar moieties of the solute. The stability of inclusion complexes depends on the shape and polarity of the host CD molecule and on how the guest solute fits into the CD cavity.[16] If enantiomers form inclusion complexes and if interactions between the chiral center (or substituents near the chiral center) and the mouth of the CD cavity are established, chiral recognition may occur.[17] Owing to the suitable cavity size for inclusion complexes to be formed with a large number of racemic solutes and the wide availability of chemically bonded β-CD stationary phases,[18–23] most HPLC chiral separations reported in the literature were performed with β-CD based CSPs.

On the basis of the structure of the compounds studied in the present work, it may be hypothesized that both the enone moiety (Fig. 4A) or the dioxolane ring (Fig. 4B) can participate in the inclusion into the β-CD cavity.

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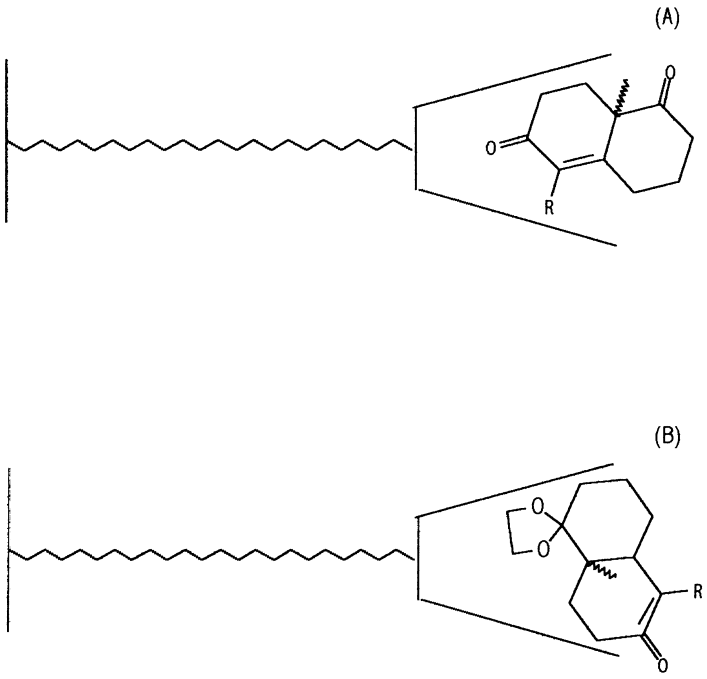

Figure 4. Proposed inclusion orientation of the Wieland–Miescher ketone and derivatives into the β-cyclodextrin cavity.

The direct chiral separation of racemates **1** → **4** was then investigated on a series of chemically bonded β-CDs CSPs. Chromatographic data are summarized in Table 2.

Native β-Cyclodextrin

The HPLC resolution of the Wieland–Miescher ketone **1** on native β-CD CSP has first been reported by Armstrong et al.[7] more than 10 years ago. Since that time, a variety of new stationary phases based on β-CD have been synthesized.[24–27] As shown in Table 2 on Cyclobond I, compounds **1** → **4** showed different retention because of the influence exerted by the dioxolane ring and, to a lesser extent, by the carbonyl group at C(1). On the other hand, the methyl group at C(5) seems to inhibit hydrogen bonding interactions between the adjacent carbonyl group and the secondary hydroxyl groups of the

Table 2. Retention (k') and enantioselectivity (α) factors, and resolution (R_s) values of the Wieland–Miescher ketone and derivatives on β-cyclodextrin based CSPs[a].

	β-CD[b]			AC-β-CD[c]			CM-β-CD[d]			PM-β-CD[e]		
Compound	$k'_{(-)S}$	α	R_s	$k'_{(-)R}$	α	R_s	$k'_{(-)R}$	α	R_s	$k'_{(-)R}$	α	R_s
(±) **1**	3.47	1.06	0.75	3.06	1.09	1.04	4.48	1.17	1.76	4.20[b]	1.06	0.59
(±) **2**	1.66	1.04	0.43	1.51	1.08	0.78	2.74	1.21	1.59	2.97	1.11	0.96
(±) **3**	7.87	1.10	0.98	4.44	1.0	—	9.26	1.10	1.13	4.15	1.07	0.80
(±) **4**	4.33	1.0	—	3.38	1.11	0.54[f]	4.96	1.20	1.86	6.39	1.18	1.46

Note: Flow-rate, 0.6 mL/min; UV detector, 230 nm; room temperature. k', retention factor of the more retained enantiomer; $R_s = 2[\Delta t_R/w_a + w_b)]$.

[a]Pre-packed chromatographic columns: native β-cyclodextrin (β-CD); acetyl-β-cyclodextrin (AC-β-CD); carboxymethyl-β-cyclodextrin (CM-β-CD); permethyl-β-cyclodextrin (PM-β-CD) silica bonded CSPs. Mobile phase, methanol–water mixtures.

[b]20%.

[c]30%.

[d]25%.

[e]40% methanol.

[f]Enantiomers eluted as two broad partially resolved peaks.

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selector. Compounds **1** → **4** seem to be retained according to the model proposed in Fig. 4B. In terms of enantioselectivity, such a model reflects the full resolution of **3** ($R_s = 0.98$), but not that of **4**, which is not resolved at all, even using a larger amount of water in the mobile phase. Under our experimental conditions, only partial resolution was obtained for compounds **1** and **2**, showing a R_s value of 0.75 and 0.43, respectively. Therefore, the requisites for enantiodiscrimination on native β-CD in this class of compounds are the fitting of dioxolane groups into the selector cavity, and the presence of a carbonyl group suitably set on the analyte frame to establish stabilizing interactions with the β-CD secondary hydroxyls. On this CSP, the enantiomer with absolute configuration (*S*) was more retained than the corresponding isomer (*R*).

Derivatized-β-Cyclodextrins

Because of derivatization of hydroxyls on the rim of the β-CD ring, these CSPs may exhibit different separation characteristics and chiral recognition with respect to the native form. In the acetylated-β-CD (AC-β-CD) derivative, the mouth of the selector molecule is extended by the acetylated 2-hydroxyls.[19] This modification has, in principle, the effect of enlarging the cavity, providing further binding sites with the guest analyte.[23] Data in Table 2 show that this CSP retained the samples with a trend similar to that observed on native β-CD, but with a different chiral recognition. On AC-β-CD, the C═O groups seem responsible for a larger stabilizing effect in the formation of the inclusion complexes than that exhibited by the dioxolane groups, probably because of a less tight fit of the latter into the CD cavities. Ketones **1** and **2** are more resolved ($\alpha = 1.09$ and 1.08) than dioxolanes **3** (not resolved) and **4** (partially resolved and eluted as two broaded peaks). On this CSP, the methyl group at C(5) does not show inhibiting effects on the enantioseparation. With respect to native β-CD, AC-β-CD promotes an opposite enantiodiscriminative process, which may be caused by the decrease of the hydrogen bonding sites of the cyclodextrin or by steric reason. As a matter of fact, on this CSP the (*R*) enantiomer is more retained than the (*S*) one.

Better separations were accomplished on carboxymethylated β-CD (CM-β-CD) based CSP. As in the case of the previously studied CSPs, also on CM-β-CD, the dioxolane derivatives were more retained than the diketones. The most striking difference is that CM-β-CD fully resolved all the enantiomeric couples **1** → **4** (Fig. 5). The reason for this wide enantioselectivity has to be ascribed to the electronic nature of the derivatizing group and to its proton acceptor–donator property. In fact, under the used mobile phase conditions

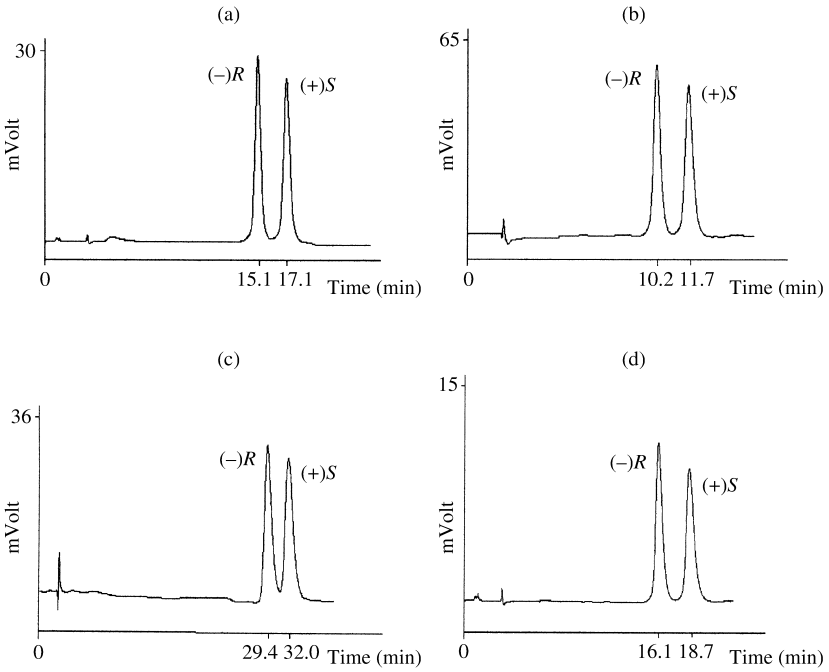

Figure 5. Chiral separations of compounds **1** (a); **2** (b); **3** (c); **4** (d), on carboxymethyl-β-cyclodextrin column 150×4.6 mm I.D.). Chromatographic conditions mobile phase, methanol/water (3 : 7 v/v), flow-rate, 0.6 mL/min. UV detector, 230 nm. Room temperature.

(water – methanol mixtures), the carboxylic function of the selector remains practically undissociated. This allows the solute to fit the selector in such a way, that at least one of the carbonyl groups can form hydrogen bonds with the polar groups at the edges of the cavity, whereas the non polar moiety interacts with the hydrophobic inner surface of the β-CD. These stabilizing interactions are exploited by all the investigated compounds. In particular, the interaction involving the carbonyl group at C(1) adjacent to the analyte stereogenic center seems to be influential for chiral recognition (compounds **1** and **2** showed α values of 1.17 and 1.21, respectively). When the carbonyl group at C(1) is substituted by the less polar dioxolane group (compound **3**), chiral recognition results are weaker, as reflected by the decrease of the enantioselectivity factor (1.10). Compound **4**, on the other hand, is resolved with an $\alpha = 1.20$.

The reason for this apparently anomalous behavior is not clear, and a definite recognition model cannot be derived from the results obtained. NMR spectroscopy of modified CDs-solute complexes has proven to be a valuable tool to study the molecular mechanisms and recognition processes in solution occurring in capillary zone electrophoretic (CZE) separations.[28] In this concern, chiral CZE separation of the Wieland–Miescher ketone and related compounds using carboxymethylated β-cyclodextrin as the selector is presently under study.

The difference between compounds **1**–**2** and **3**–**4** lies in the methyl group at C(5). As shown in Fig. 6, this structural change is responsible for the different pattern of α plots vs. the methanol content in the mobile phase. As it is generally observed for native β-CD, the higher the concentration of the organic modifier in the mobile phase, the easier it is for the solute to be displaced from the cyclodextrin cavity.[29] Within the range 30–50% of organic modifier in the eluent, α plots of compounds **1**, **2**, and **4** show a similar trend; over 50%, the enantioselectivity decreases gently for **1**, whereas it drops rapidly for compounds **2** and **4**, indicating a different effect of methanol on the enantioseparation of these compounds. The behavior of compound **3** is

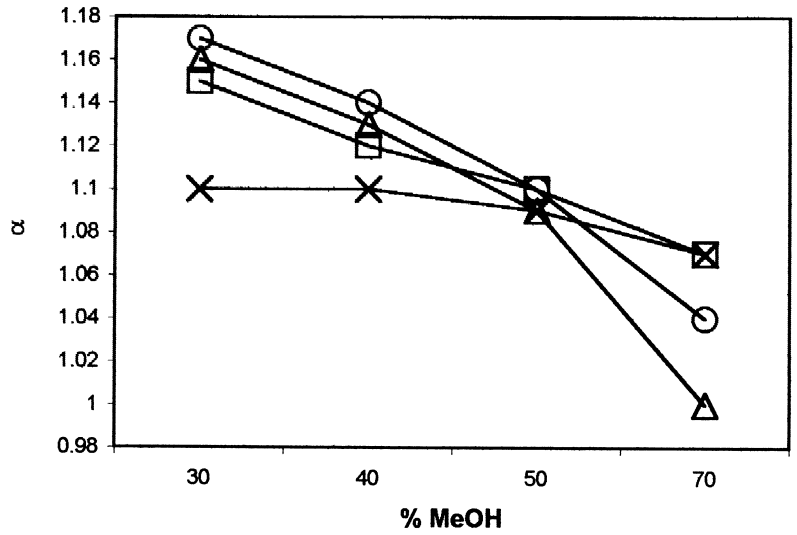

Figure 6. Influence of the organic modifier content in the mobile phase on the enantioselectivity factor (α) for compounds **1** → **4** on carboxymethyl-β-cyclodextrin based stationary phase. Samples: **1** (□), **2**(△), **3** (×), and **4** (○). Chromatographic conditions, as in Table 2.

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apparently anomalous, the α factor remaining almost constant within the overall studied mobile phase composition. However, at low methanol percentages, structural changes in the chiral analyte do not cause strong differences in enantioseparation, being compounds **1**, **2**, and 4 resolved with similar α values, with the only exception of **3**. According to the method described in the Experimental section, all the studied enantiomeric couples eluted on CM-β-CD with the same elution sequence, the $(-)(R)$ enantiomer being more retained than the $(+)(S)$ enantiomer.

Since the hydroxyl groups on the rim of the cyclodextrin cavity are substituted by methoxy groups, permethylated β-CD is expected to exhibit different retention and enantiodiscrimination in comparison to the previously studied CD-based CSPs. In fact, retention depended on the non polar moieties of the solute molecule, the dioxolane derivatives being more retained than the diketones, and compound **2** more retained than **1**. As a consequence, dioxolane **4**, which is fully resolved, and, to a lesser extent, enedione **2**, are the compounds that fit the selector cavity with the highest efficiency. It is remarkable that on permethylated CD, the methyl group at C(5) contributes more than in any other case to the chiral separation. Likewise native β-CD and AC-β-CD, PM-β-CD resulted in a more restricted enantiodiscrimination than CM-β-CD.

In conclusion, the potential of carboxymethylated β-cyclodextrin-based chiral stationary phase for the direct resolution of the Wieland-Miescher ketone **1**, its C(5) homologue **2**, as well as their C(1)-dioxolane derivatives **3** and **4**, is demonstrated. On the other CSPs used, minor structural changes of the solutes can greatly affect enantioselectivity and resolution. Among the various CSPs used, CM-β-CD appeared the most effective. Thus, the present paper provides a fast and simple method to evaluate, by HPLC, the optical purity of compounds **1** $\rightarrow$ **4**, which are obtained by enantiomeric enrichment during the crystallization processes.

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