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2,3-Di-*O*-methoxymethyl-6-*O*-*tert*-butyldimethylsilyl-γ-cyclodextrin: a new class of cyclodextrin derivatives for gas chromatographic separation of enantiomers

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Abstract

Octakis(2,3-*di*-*O*-methoxymethyl-6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin (2,3-MOM-6-TBDMS-γ-CD) was employed as stationary phase for capillary gas chromatographic separation of enantiomers. Selective introduction of the acetal function at positions 2 and 3 of the glucose units was achieved by reaction of 6-*O*-TBDMS-γ-cyclodextrin with methoxymethyl chloride. 2,3-MOM-6-TBDMS-γ-CD was shown to be a chiral stationary phase suitable for enantiodifferentiation of a broad spectrum of chiral volatiles from various chemical classes. A total of 125 pairs of enantiomers could be separated. Structural influences of the analytes on the enantioseparation were demonstrated. High α values up to 1.8 were observed for the hydroxyketone acetoin and some methyl branched ketones. Pronounced enantioseparations were also determined for cyclic pentenolone and furanone derivatives.

Keywords: Cyclodextrin; Chiral stationary phases; GC; Methoxymethyl side-chain; Enantiomers separation

1. Introduction

Cyclodextrins (CD) belong to the most frequently used chiral stationary phases (CSPs) in gas chromatographic analysis [1–3]. They have found wide application mainly for analysis of chiral flavor and fragrance materials [4,5]. In order to improve the gas chromatographic performance, cyclodextrins have been modified by derivatization of the free hydroxy groups of the glucose units. A wide array of alkylation and acylation strategies have been applied [3]. Blocking the 6 hydroxy position of the glucose unit with a bulky silyl group and subsequent modification of the 2,3-hydroxy groups resulted in useful CSPs [6,7].

Taking into account that the glycosidic bonds are essential structural elements in the cyclodextrin torus, it seemed a reasonable approach to incorporate this feature also in the side-chains at positions 2 and 3 of the glucose units and to investigate their influence on the separation of enantiomers. The use of mixed acetals obtained by proton-catalyzed addition of 2-methoxypropene for protection of hydroxy groups in cyclodextrins has recently been described [8]. In this approach methoxymethyl chloride was applied as acetalization reagent to introduce the methoxymethyl (MOM) moiety at the 2,3-hydroxyl rim of γ-cyclodextrin.

Various silyl groups have been shown to be suitable to block the 6-position of CDs; one successful example is the *t*-hexyldimethylsilyl (THDMS) moiety. However, the experiences gained with this group are limited to a rather small spectrum of substituents (methyl, ethyl and acetyl) at the 2 and 3-positions of the glucose units [9–13]. On the other hand, the general versatility of the *t*-butyldimethylsilyl (TBDMS) group has been demonstrated in combination with a much wider spectrum of substituents at positions 2 and 3 and was therefore selected in the present approach.

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2. Experimental

2.1. Materials

γ-Cyclodextrin was obtained from Wako Pure Chemical Industries (Osaka, Japan). Purification of the crude material was accomplished by column chromatography using silica gel 60 from Merck (Darmstadt, Germany) with toluene and ethanol (95%) as eluting solvent. The effluent was monitored by thin layer chromatography (TLC) on silica gel plates Polygram Sil G/UV_{254} from Macherey Nagel (Düren, Germany) and the spots were detected by dipping the TLC sheets into acidic phosphomolybdic acid and subsequent heating to 105 °C for 5 min. *tert*-Butyldimethylchlorosilane was obtained from Merck-Schuchardt (Hohenbrunn, Germany) and diisopropylethylamine and methoxymethyl chloride from Aldrich (Steinheim, Germany). Polysiloxane OV-1701vi was purchased from Supelco (Bellefonte, PA, USA) and raw fused silica capillary column was obtained from Microquartz (München, Germany). Other commonly used reagents and solvents were obtained from Aldrich and Fluka (Buchs, Switzerland), respectively.

2.2. Instruments

NMR spectra were recorded with a Bruker AC 250 spectrometer (^{1}H 250.133 MHz, ^{13}C 62.896 MHz) with ASPECT 3000 workstation running DISR94 program. The chemical shift values for both ^{1}H and ^{13}C spectra were recorded in part per million and acetone-d_6 was used as solvent and internal chemical shift standard (2.05 ppm and 30.8 ppm, respectively).

Mass spectrometry data were obtained after direct introduction of the derivatized CD (methanol solution) into an Esquire 3000+ (Bruker) instrument. Electron spray ionization was used to ionize the cyclodextrin molecule in positive mode, with source voltage of 4.0 kV, nebulizer gas flow of 5.0 L/min (operating at 69 kPa) and drying temperature of 300 °C.

Gas chromatograms were recorded on Carlo Erba Strumentazione models 4130 and 4160 equipped with flame ionization detectors. The chromatograms were processed by the Chromcard system from Thermoquest (Milan, Italy). Hydrogen was used as carrier gas at an inlet pressure of 100 kPa, and the analyte were introduced via split injection method with a split ratio of 30:1. The injector and the detector temperatures were 220 °C and 230 °C, respectively. The injection volume of the samples was 1 μL and the concentrations of the compounds tested were 0.2 μg/mL in diethyl ether.

A glass drying oven (bulb to bulb distillation apparatus) B-580 GKR from Büchi (Flawil, Switzerland) was used to dry the intermediate cyclodextrin derivative.

2.3. Synthesis of octakis(2,3-di-O-methoxylmethyl-6-O-tert-butyldimethylsilyl)-γ-cyclodextrin

Octakis(6-*O*-TBDMS)-γ-cyclodextrin was synthesized according to a procedure described by Fügedi [14]. This intermediate was heated at 100 °C under high vacuum (0.001 mmHg) overnight using a bulb-to-bulb distillation apparatus. The obtained dry octakis(6-*O*-TBDMS)-γ-cyclodextrin (214 mg) was dissolved in dry dichloromethane (10 mL). Diisopropylethylamine (3.6 g) was added at room temperature and stirred. The clear solution was cooled to 0 °C with an ice–water bath and methoxymethyl chloride (1.62 g) was added drop-wise. After stirring at 0 °C for 15 min, the solution was allowed to warm up to room temperature and then stirred overnight at 40 °C. After TLC analysis showed completion of the reaction, the reaction mixture was poured into water/MTBE mixture and extracted with MTBE. The organic phase was washed with 1N HCl aq., water, sodium bicarbonate solution, saturated sodium chloride solution and dried over anhydrous magnesium sulfate, concentrated and purified by column chromatography (Silica gel 60, toluene:ethanol = 9:1, v/v) to yield 186 mg of the titled compound as fine white powder (isolated yield 66%). The structure was checked by means of NMR (^{1}H, ^{13}C, DEPT 135 and double quantum filtered COSY) and MS.

^{1}H NMR: 0.02 (s; 48H; Si(C**H**$_3$)$_2$): 0.87 (s; 72H; Si(C**H**$_3$)$_3$); 3.36 (dd; J = 2.5 Hz, 8.5 Hz; 8H; H_2); 3.39 (s; 24H; –OCH$_2$OC**H**$_3$); 3.44 (s; 24H; –OCH$_2$OC**H**$_3$); 3.64 (d; J = 10.0 Hz; 16H; H_{6a+6b}); 3.87 (t; J = 8.5 Hz; 8H; H_4); 3.94 (t; J = 8.5 Hz; 8H; H_3); 4.25 (d; J = 11.3 Hz; 8H; H_5); 4.69 (d; J = 6.3 Hz; 8H; –OC**H**$_2$OCH$_3$); 4.79 (d; J = 6.5 Hz; 8H; –OC**H**$_2$OCH$_3$); 4.82 (d; J = 6.5 Hz; 8H; –OC**H**$_2$OCH$_3$); 4.99 (d; J = 6.5 Hz; 8H; –OC**H**$_2$OCH$_3$); 5.27 (d; J = 2.5 Hz; 8H; H_1).

^{13}C NMR: −3.6 (Si(**C**H$_3$)$_2$C(CH$_3$)$_3$), −3.2 (Si(**C**H$_3$)$_2$C-(CH$_3$)$_3$), 20.0 (Si(CH$_3$)$_2$**C**(CH$_3$)$_3$), 27.5 (Si(CH$_3$)$_2$C-(**C**H$_3$)$_3$), 57.0 (–OCH$_2$O**C**H$_3$), 57.2 (−OCH$_2$O**C**H$_3$), 64.3 (C6), 74.0, 78.6, 79.7, 80.1 (C2, C3, C4, C5), 99.5 + 100.6 (–O**C**H$_2$OCH$_3$) 100.7 (C1).

MS: m/z = 2938.5 [M + Na + H].

2.4. Preparation of the capillary columns

The cyclodextrin derivative synthesized was diluted in polysiloxane OV-1701vi (33%, w/w) and used as GC stationary phase. Untreated fused-silica capillary column (i.d. 0.25 mm, length 30 m) was deactivated using phenyldimethylsilane at 380 °C (reaction time: 10 h). The deactivated fused-silica column thus prepared was coated with the above-described phase by means of the static coating method according to Grob [15]. A mixture of *n*-pentane and dichloromethane (1:1, v/v) was used as solvent in the coating procedure. The column was coated in stationary phase thickness of 0.25 μm. After coating was completed, the column was mounted on a GC oven and conditioned as follows: 40 °C (initial temperature, 15 min hold), then ramp at rate

of 2 °C/min to 210 °C (final temperature, held for 4 h). The column thus prepared was tested by injecting 1 μL of Grob-I test mixture [15].

2.5. Test of the stability of the stationary phase

Diethyl ether (30 mL) was shaken thoroughly (5 min) with water (20 mL) in a separation funnel and the aqueous layer was discarded. One μL of the water-saturated diethyl ether was injected at 5 min intervals into the GC column (140 °C isothermal) coated with 2,3-MOM-6-TBDMS-γ-CD as stationary phase (total: 3225 injections). At the beginning of the experiment and after every 100 injections, the performance of the column was checked by injecting 1 μl of Grob test mixture I as well as 1 μL of a diethyl ether solution containing 2-pentanol, 2-pentanthiol, limonene, 2-methylbutyl acetate, 2-methylbutanal diethylacetal, 5-methyl-3-heptanone, 1-phenylethanol, 2-methylhexanoic acid and γ-hexalactone (0.2 μL/mL each).

3. Results and discussion

Octakis(2,3-di-*O*-methoxymethyl-6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin (2,3-MOM-6-TBDMS-γ-CD) was synthesized by reaction of octakis(6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin with methoxymethyl chloride (MOM-Cl) as shown in Fig. 1. The MOM group is widely used in organic chemistry for protection of alcohols. The introduction of this moiety using diisopropylethylamine as proton scavenger is well documented [16]. The reaction proceeded efficiently under homogeneous conditions, did not require extensive purification to remove by-products, and resulted in sufficient and reproducible yield.

The polarity of the newly synthesized CD phase was estimated on the basis of its TLC behavior. Using toluene/ethanol, 90/10 (v/v) as developing solution, the rf value (0.41) determined for 2,3-MOM-6-TBDMS-γ-CD was in the same order of magnitude as that determined for 2,3-di-*O*-acetyl-6-*O*-TBDMS-γ-CD (0.37). Taking into account the reported influence of the polarity of the diluting stationary phase on column efficiency [17], OV-1701vi was selected as polysiloxane solvent. Dissolving CDs in this moderately polar polysiloxane has already been described in 1988 [18].

The column was prepared by coating a fused silica capillary with 33% 2,3-MOM-6-TBDMS-γ-CD in OV-1701vi (film thickness: 0.25 μm). Its general performance was tested

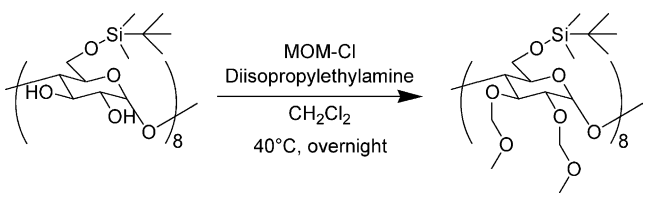


Fig. 1. Synthesis of 2,3-MOM-6-TBDMS-γ-CD.

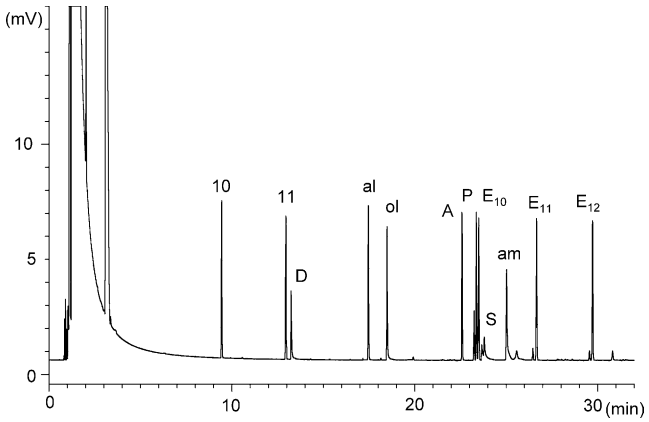


Fig. 2. Grob test chromatogram of a 2,3-MOM-6-TBDMS-γ-CD (33% OV-1701vi) column. Temperature programming: 40 °C initial (2 min hold) then ramp at 4.0 °C/min rate. 10: *n*-decane; 11: undecane; D: (−)-2,3-butanediol; al: 1-nonanal; ol: 1-octanol; A: 2,6-dimethylaniline; P: 2,6-dimethylphenol; E10: methyldecanoate; S: 2-ethylhexanoic acid; am: dicyclohexylamine; E11: methylundecanoate; E12: methyldodecanoate.

using the Grob test mixture I (Fig. 2). The column showed very good performance for all compound classes, except for the acid contained in the mixture. A decreased peak height and tailing was observed for 2-ethylhexanoic acid under the chromatographic conditions of this test. Nevertheless, the use of more suitable parameters (e.g. isothermal runs) allowed the enantioseparation of free acids on this chiral stationary phase (see examples in Table 1).

Repeated heating of the column up to 230 °C, keeping the column temperature at 220 °C for a period of over 12 h as well as repeated injection of solutions of free alkanoic acids did not affect the column performance. In an additional stability test, water-saturated diethyl ether was injected at 5 min intervals (total: 3225 injections). At the beginning of the experiment and after every 100 injections, the performance of the column was checked by injecting Grob test mixture as well as a mixture containing chiral representatives of different compound classes. The repeated injection of water-saturated diethyl ether resulted in significantly reduced peak heights for the two acids tested (2-ethylhexanoic acid and 2-methylhexanoic acid). For all other compounds contained in the Grob test mixture and in the test mixture of chiral compounds the performance of the column in terms of retention times, peak heights and separation factors was not affected. Considering the structure of the side-chain as a mixed acetal of formaldehyde, this stability of the column was rather unexpected. It may be explained by the stabilizing effect of the diluting polysiloxane [19].

The potential of 2,3-MOM-6-TBDMS-γ-CD to separate enantiomers was tested using a broad spectrum of chiral compounds from different classes most of them being used as flavoring and fragrance materials. A total of 125 compounds were investigated. The separation factors α, the resolutions R_S and the retention factors k are listed in Tables 1–6.

As demonstrated for 2-methyl branched compounds (Table 1), the use of 2,3-MOM-6-TBDMS-γ-CD as chiral

Table 1
Separation of the enantiomers of methyl branched compounds

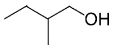
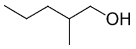
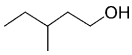
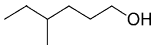
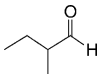
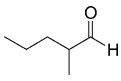
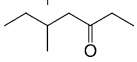
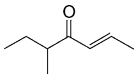
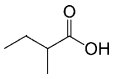
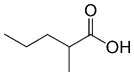
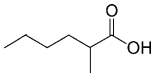
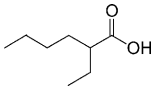
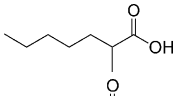
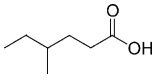
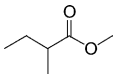
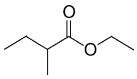
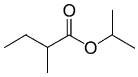
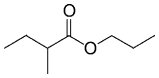
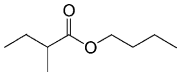
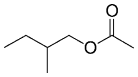
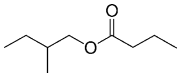
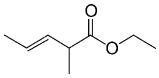
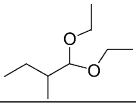
Methyl branched compounds		T (°C)	k	α	R_s
Alcohols					
2-Methylbutanol		40	11.74	1.02	1.17
2-Methylpentanol		55	13.33	1.07	3.88
3-Methylpentanol		50	21.68	1.19	11.43
4-Methylhexanol		65	21.08	1.03	1.69
Aldehydes					
2-Methylbutanal		40	3.33	1.05	1.84
2-Methylpentanal		40	13.06	1.12	6.20
Ketones					
3-Methyl-2-pentanone		40	7.89	1.65	25.89
5-Methyl-3-heptanone		65	13.77	1.29	17.15
5-Methyl-2-hepten-4-one		70	13.56	1.69	37.42
2-Methylcyclohexanone		60	15.16	1.12	10.11
3-Methylcyclohexanone		60	16.83	1.02	1.37
3,3,5-Trimethylcyclohexanone		70	18.02	1.60	33.21
2-Methylcyclopentanone		40	20.27	1.11	6.53
Acids					
2-Methylbutanoic acid		70	17.93	1.01	0.94
2-Methylpentanoic acid		80	22.60	1.08	6.29
2-Methylhexanoic acid		90	25.88	1.09	6.47
2-Ethylhexanoic acid		100	20.40	1.04	2.52
2-Methylheptanoic acid		100	27.69	1.05	4.70
4-Methylhexanoic acid		110	11.73	1.05	4.27
Esters					
Methyl 2-methylbutanoate		40	7.43	1.12	6.07
Ethyl 2-methylbutanoate		40	16.31	1.17	10.1

Table 1 (*Continued*)

Methyl branched compounds		T (°C)	k	α	R_s
iso-Propyl 2-methylbutanoate		40	19.08	1.11	7.05
Propyl 2-methylbutanoate		50	18.25	1.10	6.17
Butyl 2-methylbutanoate		60	20.44	1.04	2.97
2-Methylbutyl acetate		40	21.06	1.07	4.59
2-Methylbutyl butanoate		65	17.31	1.03	2.28
Ethyl 2-methyl-3-pentenoate		50	19.53	1.06	3.94
Acetal					
2-Methylbutanal diethyl acetal		65	6.07	1.07	3.57

stationary phase is suitable for enantiodifferentiation of volatiles containing various functional groups (alcohol, aldehyde, ketone, acid, ester and acetal). The good enantioseparations observed for the esters of 2-methyl branched acids (with an optimum resolution for ethyl 2-methylbutanoate) are remarkable, because esters have been reported to be more poorly separated than the corresponding alcohol compounds on TBDMS-type cyclodextrin stationary phases [20]. Beside 2-methylbutyrates, the esters of 2-methylbutanol such as 2-methylbutyl acetate and 2-methylbutyl butanoate could be baseline-separated into their enantiomers. The latter compound is known to be resolved rather difficultly into enantiomers on TBDMS-CD-type phases [21].

A separation factor of 1.691 was observed for 5-methyl-2-hepten-4-one, the so-called filbertone, a key aroma compound found in hazelnuts [22]. The α value obtained for 3-methyl-2-pentanone (1.648) is in the same order of magnitude. A replacement of the ketone function in this compound by an aldehyde moiety (2-methylbutanal) resulted in a drastic reduction of the separation efficiency. Comparably, the separation factor was decreased significantly by reduction of the ketone to the corresponding secondary alcohol 3-methyl-2-pentanol (Table 2). An exceptionally high separation factor of 1.602 was also determined for the cyclic ketone 3,3,5-trimethylcyclohexanone. The essential role of the carbonyl group for enantiodifferentiation was confirmed by the lowered separation factors determined for 3,3,5-trimethylcyclohexanol (Table 2) obtained by reduction of 3,3,5-trimethylcyclohexanone. When comparing the corresponding chromatograms (Fig. 3) it is noteworthy that the second eluted enantiomer of the ketone (Fig. 3a) is retained stronger than any of the four alcohol stereoisomers (Fig. 3b), indicating the high affinity of the ketone enantiomer towards the CSP.

For secondary alcohols (Table 2) a comparison of the α values for 2-hexanol/3-hexanol and 2-heptanol/3-heptanol demonstrates that there is no consistent influence of the position of the hydroxy group on the separation efficiency. As shown for 3-octanol, 1-octen-3-ol and 1-octyn-3-ol the insertion of a double bond improves the separation whereas a triple bond has a negative impact on the separation of

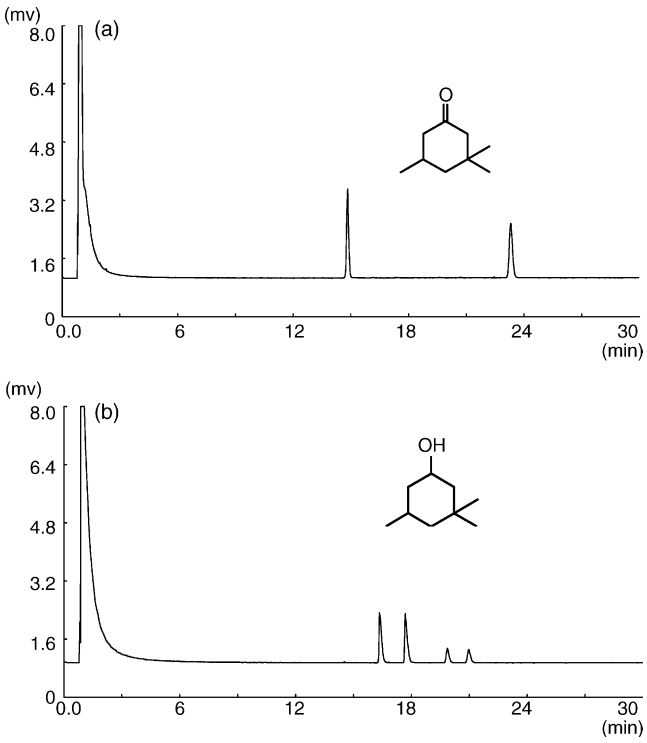
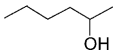
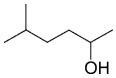
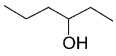
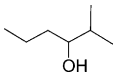
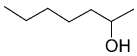
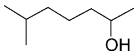
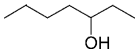
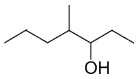
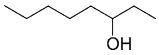
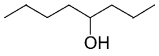
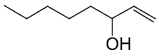
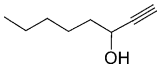
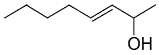


Fig. 3. Separation of 3,3,5-trimethylcyclohexanone (a) and 3,3,5-trimethylcyclohexanol (b). Temperature: 70 °C isothermal.

Table 2
Separation of the enantiomers of secondary alcohols

Secondary alcohols		T (°C)	k	α	R_s
2-Butanol[a]		40	3.79	1.05	2.11
3-Methyl-2-butanol		30	8.90	1.08	4.59
2-Pentanol		40	11.70	1.10	5.63
threo-3-Methyl-2-pentanol		40	16.40	1.07	3.89
erythro-3-Methyl-2-pentanol		40	16.91	1.21	11.0
2-Hexanol		50	17.06	1.11	7.31
5-Methyl-2-hexanol		60	10.69	1.08	5.31
3-Hexanol		50	13.53	1.06	3.47
2-Methyl-3-hexanol		60	9.85	1.12	7.05
2-Heptanol		60	22.76	1.05	3.96
6-Methyl-2-heptanol		65	16.47	1.02	1.68
3-Heptanol		60	13.49	1.08	5.02
erythro-4-Methyl-3-heptanol		70	13.22	1.39	22.10
threo-4-Methyl-3-heptanol		70	14.36	1.03	1.77
3-Octanol		70	17.78	1.04	2.90
4-Octanol		70	16.27	1.04	2.62
3-Buten-2-ol[a]		30	6.92	1.10	4.92
1-Penten-3-ol		40	10.65	1.09	4.81
1-Octen-3-ol		70	16.71	1.09	6.05
1-Octyn-3-ol		80	18.13	1.03	2.24
3-Octen-2-ol		70	22.83	1.04	3.43
trans-3,3,5-Trimethylcyclohexanol		70	19.96	1.09	5.66
cis-3,3,5-Trimethylcyclohexanol		70	24.47	1.06	3.97

[a] Analysis performed at 50 kPa inlet pressure.

enantiomers. An analogous effect has been observed for the C4 homologues: 3-buten-2-ol is separated better than 2-butanol whereas no separation could be achieved for 3-butyn-2-ol (not listed in the table). The α values obtained for 2-hexanol/5-methyl-2-hexanol and 2-heptanol/6-methyl-2-heptanol demonstrate that the insertion of a methyl group at a position distant from the chiral center bearing the hydroxy group results in a decrease of the separation efficiency. On the other hand insertion of a methyl group in adjacent position to the chiral center (2-butanol/3-methyl-2-butanol and 3-hexanol/2-methyl-3-hexanol) improves the separation. If the presence of such an adjacent methyl group results in an additional chiral center (2-pentanol/3-methyl-2-pentanol and 3-heptanol/4-methyl-3-heptanol) the pair of *trans* enantiomers was resolved better.

The enantiomers of the homologous series of both γ-lactones and δ-lactones, important flavor compounds, could be separated (Table 3). Optimum resolutions were obtained

Table 3
Separation of the enantiomers of lactones

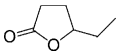
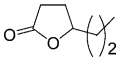
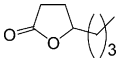
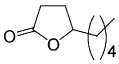
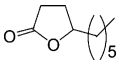
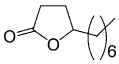
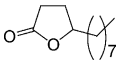
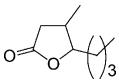
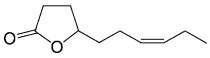
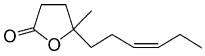
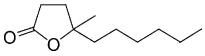
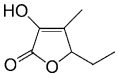
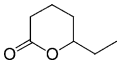
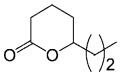
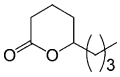
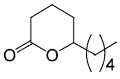
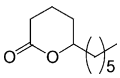
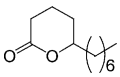
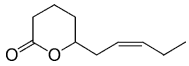
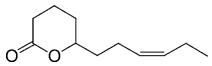
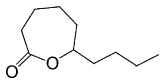
Lactones		T (°C)	k	α	R_s
γ-Lactones					
γ-Hexalactone		120	6.28	1.15	9.59
γ-Heptalactone		130	6.31	1.14	9.16
γ-Octalactone		140	6.17	1.07	5.13
γ-Nonalactone		150	6.60	1.03	2.38
γ-Decalactone		160	7.07	1.02	1.26
γ-Undecalactone		170	7.72	1.01	1.00
γ-Dodecalactone		170	11.85	1.01	1.13
trans-Whiskey lactone		130	8.97	1.20	13.80
cis-Whiskey lactone		130	11.08	1.04	3.12
(*Z*)-Dec-7-en-4-olide		150	15.93	1.03	1.99
4-Methyl-(*Z*)-dec-7-en-4-olide		145	11.24	1.04	2.97
4-Methyl-4-decanolide		140	14.26	1.06	4.96
Sotolone		120	11.01	1.15	9.35
Pantolactone		110	10.72	1.03	2.00
5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone		130	10.86	1.28	16.91
δ-Lactones					
δ-Heptalactone		120	11.94	1.04	2.86
δ-Octalactone		130	10.93	1.13	8.91
δ-Nonalactone		140	10.72	1.05	3.74
δ-Decalactone		150	11.02	1.02	1.69
δ-Undecalactone		150	17.50	1.02	1.77
δ-Dodecalactone		150	27.89	1.02	1.90

Table 3 (*Continued*)

Lactones		T (°C)	k	α	R_s
(*Z*)-Dec-7-en-5-olide		140	17.62	1.04	3.04
(*Z*)-Undec-7-en-5-olide		150	16.09	1.03	1.95
Mevalonic acid lactone		140	21.82	1.02	1.78
ε-Lactone					
ε-Decalactone		150	8.33	1.11	7.99

for the homologues C6 and C7 (γ-lactones) and C8 (δ-lactones). Representatives containing alkyl chains of 2–3 carbons attached to the ring are preferentially resolved. The enantiomers of a lactone with a larger ring system (ε-decalactone) and of γ-lactones exhibiting a branched ring structure (e.g. whiskey lactones) or other additional functional groups (e.g. sotolone and 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone) were also well separated. The α values obtained for γ-octalactone and the whiskey lactones demonstrate that the creation of an additional chiral center by a methyl substituent adjacent to the carbon bearing the alkyl chain results in improved separation of one pair of enantiomers (*trans*-whiskey lactone) and a worse separation for the other pair (*cis*-whiskey lactone), comparable to the data described for the secondary alcohols (Table 2).

A broad spectrum of aromatic compound classes including the ethyl methylphenylglycidates could be separated (Table 4). For the 1-phenylethyl esters a significant impact of the length of the alkyl chain of the acid moiety was observed.

Enantiomers of sulfur-containing compounds from different classes could be separated (Table 5). A comparison of the α values obtained for 2-pentanethiol/2-pentanol and 2-methylbutane-thiol/2-methylbutanol demonstrates that the replacement of the hydroxy group by a thiol group had no significant impact on the separation of the enantiomers. For the sulfur-containing whiskey lactone-derivatives (5-butyldihydro-4-methyl-2(3H)-thiophenone; 5-butyldihydro-4-methyl-2(3H)-furanthione; 5-butyldihydro-4-methyl-3(3H)-thiophenthione) the improved separation observed for the *trans*-configured stereoisomers (Table 3)

Table 4
Separation of the enantiomers of aromatic compounds

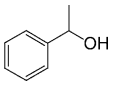
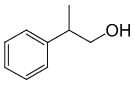
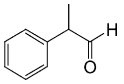
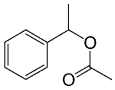
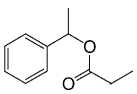
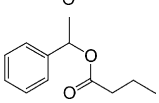
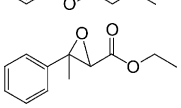
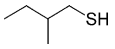
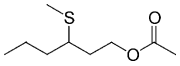
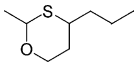
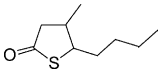
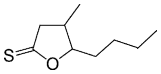
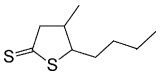
Aromatic compounds		T (°C)	k	α	R_s
1-Phenylethanol		100	14.79	1.14	11.08
Hydratropalcohol		110	12.75	1.09	6.36
Hydratropaldehyde		90	23.26	1.04	3.56
1-Phenylethyl acetate		90	23.88	1.06	4.56
1-Phenylethyl propionate		100	22.79	1.09	7.75
1-Phenylethyl butyrate		110	17.44	1.02	1.79
cis-Ethyl methylphenylglycidate		120	20.39	1.02	1.68
trans-Ethyl methylphenylglycidate		130	23.45	1.06	4.90

Table 5
Separation of the enantiomers of sulfur-containing compounds

Sulfur-containing compounds		T (°C)	k	α	R_s
2-Methylbutanethiol		30	14.28	1.06	3.44
2-Pentanthiol		40	8.15	1.10	5.31
erythro-2-Mercapto-3-butanol		55	19.43	1.20	12.28
threo-2-Mercapto-3-butanol		55	21.94	1.05	3.12
3-Methylthio-1-hexylacetate		105	19.72	1.02	1.45
cis-2-Methyl-4-propyl-1,3-oxathiane		90	14.10	1.19	13.68
trans-2-Methyl-4-propyl-1,3-oxathiane		90	17.70	1.21	14.20
trans-5-Butyldihydro-4-methyl-2(3H)-thiophenone		130	11.71	1.15	10.89
cis-5-Butyldihydro-4-methyl-2(3H)-thiophenone		130	13.76	1.09	6.59
trans-5-Butyldihydro-4-methyl-2(3H)-furanthione		130	18.06	1.07	5.67
cis-5-Butyldihydro-4-methyl-2(3H)-furanthione		130	21.28	1.02	1.34
trans-5-Butylhydro-4-methyl-2(3H)-thiophenthione		140	17.69	1.09	6.87
cis-5-Butylhydro-4-methyl-2(3H)-thiophenthione		140	20.80	1.04	3.55

remained unchanged independent from the insertion of sulfur at various positions of the lactone ring.

The potential of 2,3-di-MOM-6-TBDMS-γ-CD to separate enantiomers of monoterpenes was demonstrated for different structural classes (the hydrocarbon limonene, the acyclic and cyclic alcohols citronellol and menthol, and the cyclic ketone carvone; Table 6). The separation of the C13-norisoprenoid compounds α-ionone, dihydro-α-ionone and α-damascone and of the cyclic propylene glycol acetals are other examples for the usefulness of this chiral stationary phase for separation of important flavor substances.

The highest separation factor among the compounds tested was found for acetoin. The α value of 1.805 decreased drastically by either esterification of the hydroxy moiety (acetoin *n*-butanoate) or by reduction of the keto group (2,3-butanediol). This apparent importance of the hydroxycarbonyl structure for enantioseparation was also confirmed for the cyclic enols 3,5-dimethyl-2-hydroxy-2-cyclopentenone and 2,5-dimethyl-4-hydroxy-3(2H)-furanone. Shifting of the methyl group (3,4-dimethyl-2-hydroxy-2-cyclopentenone) or esterification of the hydroxy group (2,5-dimethyl-4-acetyl-3(2H)-furanone) resulted in significant decrease of the α value.

In conclusion, 2,3-MOM-6-TBDMS-γ-CD proved to be a CSP suitable for enantioseparation of a very broad spectrum of volatiles comprising various functional groups. Compound classes which turned out to be not accessible to enantiodifferentiation on this phase are tertiary alcohols (e.g. linalool, α-terpineol) and their esters, bicyclic compounds (e.g. camphene, camphor, borneol, fenchol) and less volatile esters (e.g. hexyl 2-methylbutanoate, β-phenylethyl 2-methylbutanoate, benzyl 2-methylbutanoate).

An extraordinary feature of 2,3-MOM-6-TBDMS-γ-CD are the high separation factors α exhibited for the hydroxyketone (acetoin), for cyclic enolones (3,5-dimethyl-2-hydroxy-2-cyclopentenone and 2,5-dimethyl-4-hydroxy-3(2H)-furanone), for acyclic methyl branched ketones (3-methyl-2-pentanone and 5-methyl-2-hepten-4-one), and for the cyclic ketone 3,3,5-trimethylcyclohexanone. The gas chromatographic separation exemplarily shown in Fig. 4 demonstrates the suitability of 2,3-MOM-6-TBDMS-γ-CD for this type of compound classes. So far, α values higher than 1.5 have been mainly reported for compounds containing halo-atoms such as 2-halopropanoates and fluoroethers [23–26]. An impressive example is a separation factor of 10 observed on Lipodex E for 2-(fluoromethoxy)-3-methoxy-1,1,1,3,3-pentafluoropropane, a minor decomposition product of the inhalational anesthetic sevoflurane [27].

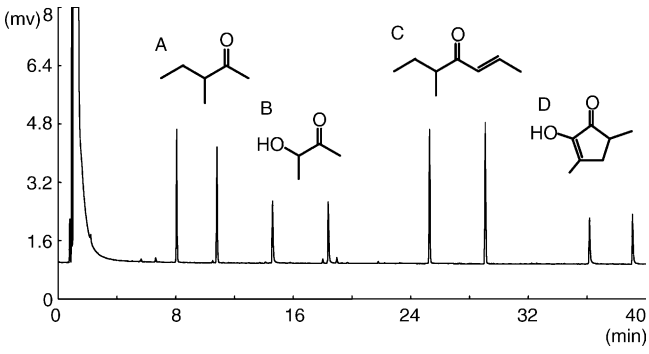


Fig. 4. Separation of: (A) 3-methyl-2-pentanone; (B) acetoin; (C) 5-methyl-2-hepten-4-one (filbertone); (D) 2-hydroxy-3,5-dimethyl-2-cyclopentenone (coronol®). Temperature programming: 30 °C (initial, 2 min hold) then ramp at 2 °C/min rate.

Table 6
Separation of compounds from miscellaneous structural classes

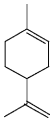
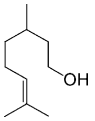
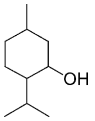
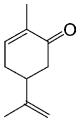
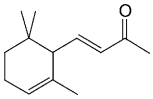
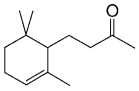
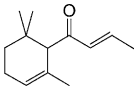
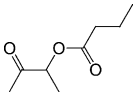
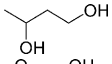
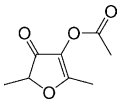
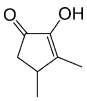
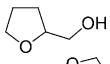
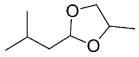
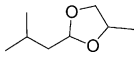
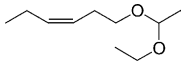
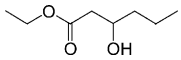
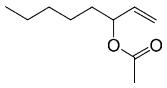
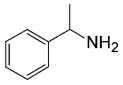
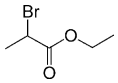
Miscellaneous		T (°C)	k	α	R_s
Limonene		50	19.39	1.06	3.85
Citronellol		100	21.62	1.02	1.79
Menthol		100	13.24	1.04	3.27
Carvone		110	8.82	1.04	2.76
α-Ionone		110	25.01	1.02	2.08
Dihydro-α-ionone		120	14.15	1.04	2.69
α-Damascone		110	18.83	1.02	1.490
Acetoin		50	12.44	1.81	36.73
Acetoin *n*-butanoate		80	22.92	1.18	15.10
threo-2,3-Butanediol		70	10.32	1.10	5.85
Propylene glycol		65	11.70	1.05	2.50
trans-1,2-Cyclohexanediol		95	17.82	1.03	1.93
1,3-Butanediol		80	15.19	1.05	3.77
3,5-Dimethyl-2-hydroxy-2-cyclo-pentenone (Coronol®)		100	12.10	1.37	22.01
2,5-Dimethyl-4-hydroxy-3(2H)-furanone (Furaneol®)		110	12.35	1.31	24.79
2,5-Dimethyl-4-acetyl-3(2H)-furanone (Acetyl furaneol)		110	19.16	1.02	2.00
3,4-Dimethyl-2-hydroxy-2-cyclo-petenone (Methyl Corylone®)		90	16.39	1.11	7.35

Table 6 (*Continued*)

Miscellaneous		T (°C)	k	α	R_s
2-Methyltetrahydrofuran-3-one		40	7.43	1.09	5.77
Tetrahydrofurfuryl alcohol		60	18.94	1.04	2.50
cis-4-Methyl-2-(2-methylpropyl)-1,3-dioxolane		55	10.67	1.09	5.22
trans-4-Methyl-2-(2-methylpropyl)-1,3-dioxolane		55	12.78	1.07	4.15
Acetaldehyde ethyl *cis*-3-hexenyl acetal		70	16.03	1.08	5.56
Ethyl 3-hydroxyhexanoate		100	12.56	1.03	2.26
1-Octen-3-yl acetate		70	19.78	1.22	17.50
1-Phenylethylamine		100	7.74	1.03	1.95
2-Bromobutane[a]		40	4.83	1.08	3.63
2-Iodobutane		40	7.93	1.04	2.01
Ethyl 2-bromopropionate		70	15.30	1.26	14.97

[a] Analysis performed at 50 kPa inlet pressure.

The data observed for 2,3-MOM-6-TBDMS-γ-CD are also interesting from a preparative point of view, because it should eventually be possible to isolate the separated enantiomers at large scale, as described for a fluorinated chiral compound, 2-chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane (enflurane) using Lipodex E [28]. In addition, they should be useful for mechanistic considerations. In accordance with former considerations [29], the fact that the chiral separation factors α are significantly higher than 1.3 should qualify these substances as useful candidates to determine thermodynamic data and to broaden the knowledge on the mechanisms underlying their enantioseparations.

In general, the results obtained for 2,3-MOM-6-TBDMS-γ-CD demonstrate that the acetalization of cyclodextrins is a useful approach to obtain modified cyclodextrins suitable for gas chromatographic enantioseparations. Studies on the incorporation of MOM groups into cyclodextrin rings of other sizes (α, β) as well as the introduction of acetal moieties with different structures at the 2,3 positions are in progress. First data show that the introduction of MOM groups in TBDMS-β-CD results in a stationary phase exhibiting enantioseparation efficiencies comparable to 2,3-MOM-6-TBDMS-γ-CD, whereas the corresponding α-CD-derivative is of limited use.

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