Synthesis, NMR Spectroscopic Characterization and Polysiloxane-Based Immobilization of the Three Regioisomeric Monooctenylpermethyl-β-cyclodextrins and Their Application in Enantioselective GC

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$2^{I-VI},3^{I-VII},6^{I-VII}$-Eicosa-*O*-methyl-$2^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose, $2^{I-VII},3^{I-VI},6^{I-VII}$-eicosa-*O*-methyl-$3^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose, and $2^{I-VII},3^{I-VII},6^{I-VI}$-eicosa-*O*-methyl-$6^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose were synthesized by selective introduction of an oct-7-enyl group at one of the *O*-2, *O*-3, or *O*-6 positions of selectively methylated cyclomaltoheptaose (β-cyclodextrin, CD) and, depending on the synthetic route, by a subsequent permethylation step. Each of the regioisomeric mono-oct-7-enylated permethylated β-cyclodextrin derivatives was anchored by hydrosilylation to a hydridomethyldimethylsiloxane copolymer to yield unambiguously *O*-2-, *O*-3-, and *O*-6-bonded chiral stationary phases (CSP) of Chirasil-Dex, which were evaluated in enantioselective gas chromatography (GC). *O*-6-Chirasil-Dex displayed slightly inferior enantioselectivity relative to either *O*-3- or *O*-2-Chirasil-Dex. The statistical synthesis of the CSP by mono-oct-7-enylation of β-CD under varying reactions conditions (base, solvent), without the use of hydroxy group protection chemistry, furnished a mixture of *O*-6- and *O*-2-Chirasil-Dex in dimethylformamide and predominantly the *O*-2-regioisomer in dimethyl sulfoxide. Chirasil-Dex, previously formulated exclusively as the *O*-6 regioisomer, should be revised as an *O*-2- and *O*-6-Chirasil-Dex mixture.

Introduction

Alkylated/acylated cyclodextrins are highly versatile selectors for the separation of enantiomers by gas chromatography (GC).[1−3] A number of different approaches have been developed to prepare the cyclodextrins used in this technique. The first approach utilised undiluted permethylated β-cyclodextrin (β-CD), which was coated on a glass capillary column and used as a chiral stationary phase (CSP) in a supercooled state.[4] *n*-Pentylated CDs, which are fluids at ambient temperatures, are preferred over the use of permethylated CD.[2,5] Moreover, some other derivatives exhibited pronounced enantioselectivities for selected classes of compounds.[6] To overcome the problems of melting points and phase transitions, Schurig and Nowotny dissolved modified CDs in semipolar polysiloxanes, such as OV 1701, thereby combining chemical selectivity with chromatographic efficiency.[7] This strategy is now generally adopted and enantioselective GC fused silica columns are commercially available from major chromatographic suppliers.[8] A logical extension of this approach was to link the modified CDs, e.g., permethylated β-cyclodextrin, via a polymethylene linker to polydimethylsiloxane to yield a chiral polysiloxane-containing cyclodextrin (Chirasil-Dex).[9−11] Chirasil-Dex can be thermally immobilized on the inner capillary wall and used in techniques other than GC (commercially available from Chrompack International-Varian, Middelburg, The Netherlands), such as in open-tubular supercritical fluid chromatography (SFC),[11−14] open-tubular liquid chromatography (LC),[15,16] and open-tubular capillary electrochromatography (CEC),[17,18] as well as in a unified approach thereof.[15,16] Chirasil-Dex can also be utilized in a dual chiral recognition mode in conjunction with another chiral selector added to the mobile phase in CEC leading to compensation[19] or enhancement of overall enantioselectivity.[20] Finally, Chirasil-Dex has been employed to coat silica particles and the CSP can be used in micro-packed LC,[21] packed CEC,[22] as well as sintered[23] or sol-gel-processed monolithic CEC.[24]

The first preparations of Chirasil-Dex contained trimethylene,[9,10] pentamethylene,[10] and octamethylene[10]

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spacers juxtaposed between the permethylated cyclodextrin and the polysiloxane backbone. Recently, an undecamethylene spacer has also been utilized.[25] Based on ^{13}C NMR spectroscopic evidence,[26] the trimethylene spacer was formulated as being attached to the *O*-6 position of the cyclodextrin. It was reasoned that, by employing solid sodium hydroxide in dimethyl sulfoxide, the reaction of higher alkenyl bromides with the more-reactive primary hydroxy groups of β-cyclodextrin at room temperature should also yield the *O*-6-derived ethers.[26] During subsequent modification of the reaction protocols, as well as purification steps, toward obtaining the elongated mono-oct-7-enyl ether of β-cyclodextrin,[27] a competitive *O*-2-alkenylation can be envisioned for Chirasil-Dex preparations employed in various chromatographic applications.[10−24] A detailed GC-MS analysis of the degradation products of permethylated mono-*O*-pent-1-enyl-β-cyclodextrin obtained in DMSO in the presence of sodium hydroxide indicated that 96% of the ether that formed was at the *O*-2 position.[28] No information is available on the synthetic route for the preparation of Chirasil-Dex used for commercial GC capillary columns (Chrompack International-Varian, Middelburg, The Netherlands). It is, therefore, of great importance to probe the three (*O*-2, *O*-3, and *O*-6) regioisomeric Chirasil-Dex preparations for possible differences in their enantioselective gas chromatographic behaviour, i.e., their effects on (i) retention factors, (ii) efficiency, and (iii) selectivity factors, which all govern the final resolution. Previous work in this direction, performed with permethylated cyclodextrins anchored to silica via polymethylene spacers in the enantioselective packed LC mode,[29,30] demonstrated profound differences between the *O*-2- and *O*-6-silica-bonded modified cyclodextrins.[31,32] In GC, the nature of the cyclodextrin selector and its environment play significant roles in determining the enantioselectivity.[33] Thus, it is not only the choice of the diluting matrix that may have a dramatic influence on the enantioselectivity, but different samples of permethylated β-cyclodextrin also display widely varying column performances and enantioselective separation properties (for selected organochlorines) arising from differences in the purity status of the selector.[34] Reversal of the elution order of enantiomers has even been observed for apparently identical modified cyclodextrin chiral stationary phases.[35] Therefore, in the present work, we have exercised great care to synthesize, coat, and immobilize the three positional *O*-2-, *O*-3-, and *O*-6-Chirasil-Dex regioisomers onto fused silica capillaries under identical conditions. We demonstrate that the differences in enantioselective chromatographic behaviour are neither pronounced nor negligible.

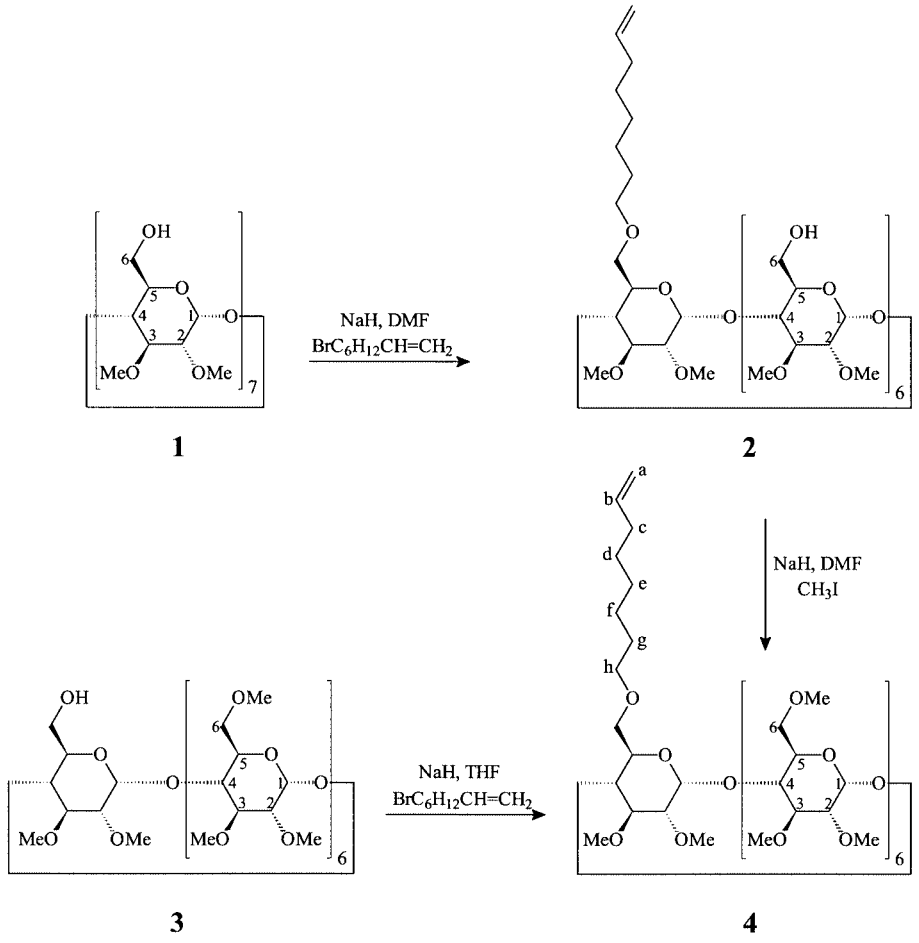
Unfortunately, the selective mono-modification of cyclodextrins is extremely difficult, since the three sets of six (α-cyclodextrin), seven (β-cyclodextrin), or eight (γ-cyclodextrin) hydroxy groups present at the *O*-2-, *O*-3-, and *O*-6-positions compete for the reagents, which favours polysubstitution. Additionally, the hydrophobic cavity often interferes with the syntheses by complexation of the reagent, which can direct the substituent to an unexpected position. Therefore, statistically substituted cyclodextrin derivatives are commonly used as chiral stationary phases. Recent studies have demonstrated, however, that the use of a single isomer of a cyclodextrin derivative has a significant influence on the quality and reproducibility of a chiral separation, because the position of the substituents determines which side of the cone-shaped cyclodextrin molecule becomes accessible to the analyte.[36−38] To obtain single congeneric cyclodextrin derivatives, several strategies have been developed. (i) Statistical derivatization, followed by separation and spectroscopic identification of the congeners. This method is often restricted, however, to a semi-preparative scale because the unambiguous chromatographic separation of large amounts of CD derivatives is difficult, as is the clear interpretation of NMR spectra, which, especially for mono-substituted cyclodextrin derivatives, is extremely complicated because the loss of C_n symmetry results in many signals overlapping. Thus, this approach allows only estimations of the purity and substitution pattern.[36,39,40] (ii) Selective synthesis by protecting-group chemistry, which takes advantage of the different reactivities and accessibilities of the hydroxy groups; those at the C-6 position are more reactive and often most nucleophilic, those at the C-2 position are the more acidic, and those at the C-3 position are the most inaccessible.[41−45]

In the present study, we describe the unambiguous regioselective synthesis of Chirasil-β-Dex CSPs, having the mono-octamethylene spacer in either the *O*-2-, *O*-3-, or *O*-6-position, their complete mass spectrometric and NMR spectroscopic characterization, and their application for enantioselective GC separations. We have developed an HPLC method for the separation of *O*-2-, *O*-3-, and *O*-6-mono-oct-7-enylated permethyl-β-cyclodextrins that permits us to determine which permethylated regioisomers form after the statistical synthesis with isolation by column chromatography.

Results and Discussion

We have chosen two independent strategies for the preparation of $2^{I-VII},3^{I-VII},6^{I-VI}$-eicosa-*O*-methyl-$6^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (**4**, cf. Scheme 1).

The first reaction sequence, adapted from a synthesis developed by König and co-workers,[36] started from $2^{I-VII},3^{I-VII}$-tetradeca-*O*-methylcyclomaltoheptaose (**1**) − prepared in three steps from β-cyclodextrin by selective *tert*-butyldimethylsilylation at *O*-6, permethylation of the secondary hydroxy groups, and desilylation[46,47] − which was substituted regioselectively with an octenyl residue using sodium hydride and 8-bromo-1-octene in DMF, producing $2^{I-VII},3^{I-VII}$-tetradeca-*O*-methyl-6^{I}-*O*-(oct-7-enyl)cyclomaltoheptaose (**2**) in 28% yield. After methylation of the residual 6-hydroxy groups, we obtained the desired $2^{I-VII},3^{I-VII},6^{I-VI}$-eicosa-*O*-methyl-$6^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (**4**). The second strategy, which was adapted from a method described by Bradshaw and co-workers,[48] started from $2^{I-VII},3^{I-VII},6^{I-VI}$-eicosa-*O*-methylcyclomalto-



Scheme 1. Synthesis of $2^{I-VII},3^{I-VII},6^{I-VI}$-eicosa-*O*-methyl-$6^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (**4**) by a) mono-octenylation and consecutive per-methylation of $2^{I-VII},3^{I-VII}$-tetradeca-*O*-methylcyclomaltoheptaose **1** and b) octenylation of $2^{I-VII},3^{I-VII},6^{I-VI}$-eicosa-*O*-methylcyclomaltoheptaose (**3**)

heptaose (**3**). Using sodium hydride and a threefold excess of 8-bromo-1-octene in THF, **3**[49,50] was mono-oct-7-enylated in 72% yield. The *O*-6 position of the substituent was confirmed for both products, obtained by the two strategies, by using one- and two-dimensional NMR spectroscopy experiments. Initially, COSY and HMQC experiments allowed the assignment of all the protons and carbon atoms and their correlations. Subsequently, an HMBC experiment (cf. Figure 1) confirmed the attachment of the oct-7-enyl group at the *O*-6 position by the presence of a clear correlation between *C*-6′ and h-H. Mono-oct-7-enylation, rather than a higher degree of substitution, was proved by elemental analysis and MS.

For the preparation of $2^{I-VI},3^{I-VII},6^{I-VI}$-eicosa-*O*-methyl-$2^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (**6**), a method similar to the one described for the second route to compound **4** was used, starting from $2^{I-VI},3^{I-VII},6^{I-VII}$-eicosa-*O*-methylcyclomaltoheptaose (**5**),[52] which resulted in **6** being obtained in 75% yield (cf. Scheme 2).

The *O*-2 attachment of the oct-7-enyl group was also confirmed by using one- and two-dimensional NMR spectroscopy experiments, especially by the HMBC experiment, which permitted highlighting the correlation between 2′-*H* and *C*-h. Mono-oct-7-enylation was proved by elemental analysis and MS.

$2^{I-VII},3^{I-VI},6^{I-VII}$-Eicosa-*O*-methyl-$3^{I}$-*O*-(oct-7-enyl)-cyclomaltoheptaose (**9**, cf. Scheme 3) was prepared starting from $2^{I-VII},6^{I-VII}$-tetradeca-*O*-methylcyclomaltoheptaose **7**, which was commercially available or prepared and purified as described by Lehn et al.[51] Mono-oct-7-enylation was proved by elemental analysis and MS.

The cyclodextrin derivative **7** was oct-7-enylated with 3 equiv. of potassium hydride and 1 equiv. of crown ether in the presence of 2 equiv. of 8-bromo-1-octene in THF. $2^{I-VII},6^{I-VII}$-Tetradeca-*O*-methyl-3^{I}-*O*-(oct-7-enyl)cyclomaltoheptaose (**8**) was obtained in 30% yield after purification. The *O*-3 attachment of the oct-7-enyl chain was proved at this step by NMR spectroscopy. After methylation of the remaining six 3-hydroxy groups, the desired product **9** was obtained in 90% yield after purification. A shorter route to **7** was investigated starting from $2^{I-VII},3^{I-VI},6^{I-VII}$-eicosa-*O*-methylcyclomaltoheptaose, but neither the use of a different base[52] nor the use of 8-iodo-1-octene (prepared starting from 8-bromo-1-octene) were successful. The known low reactivity of the hydroxy group in the *O*-3 position could explain why the reaction does not

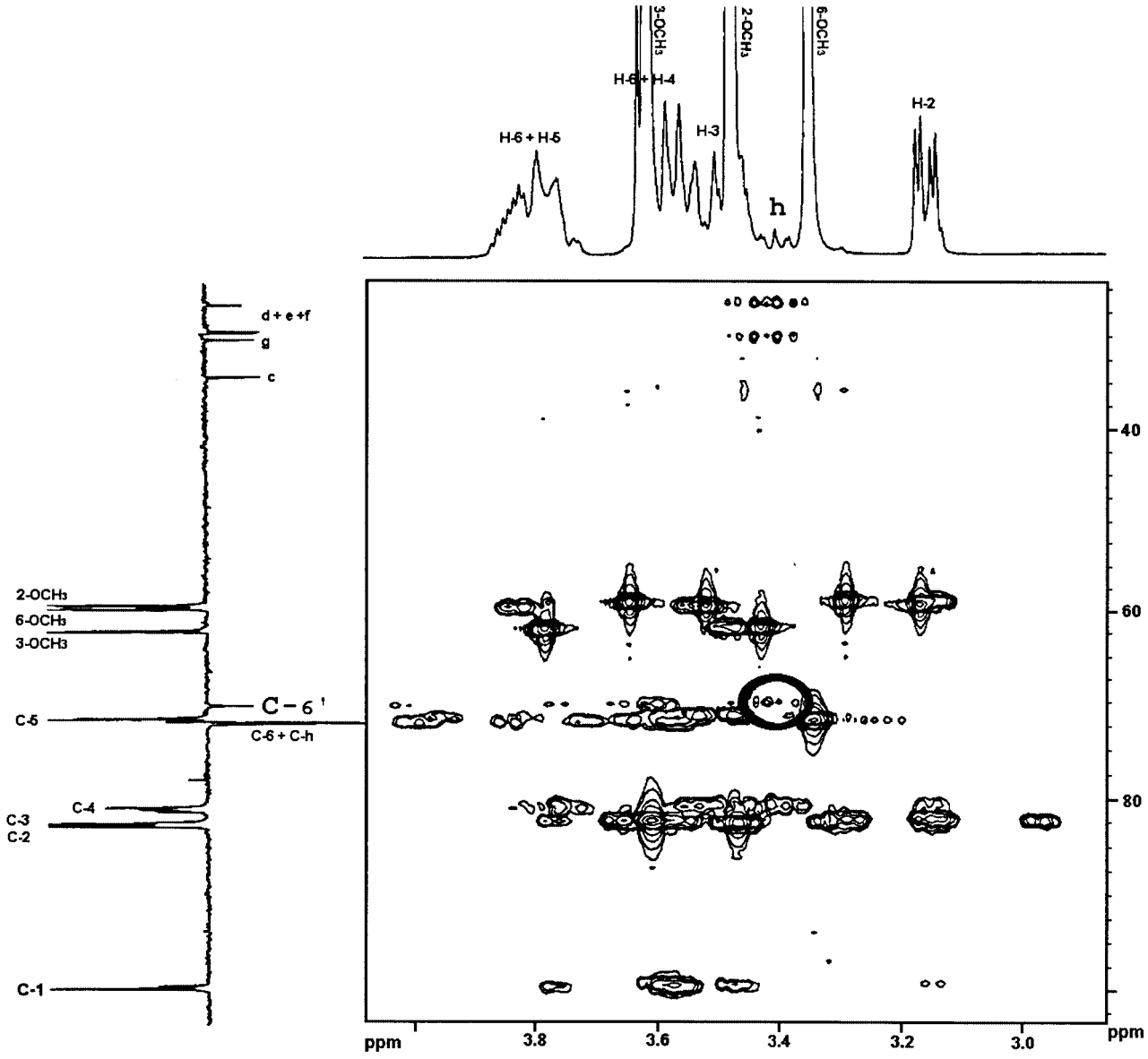
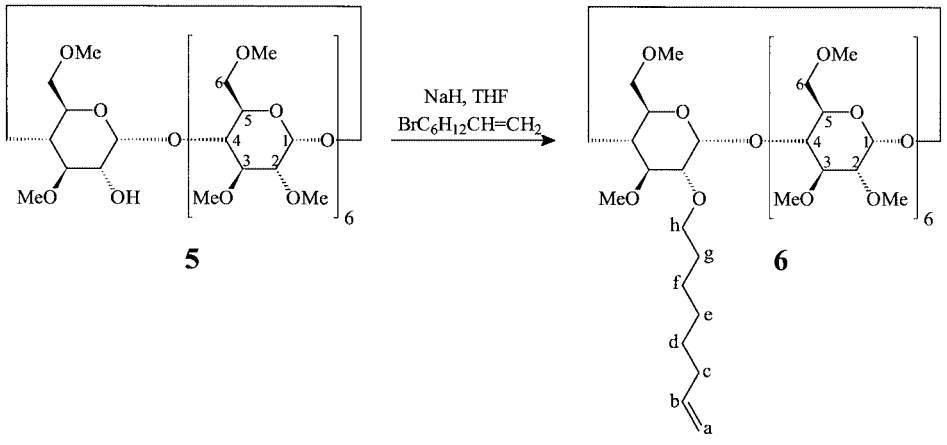
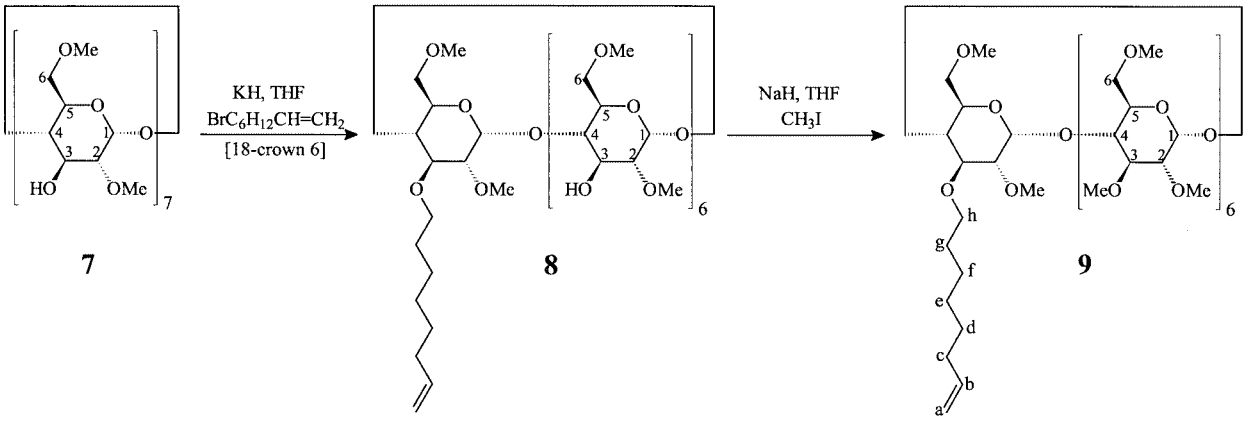


Figure 1. Section of the HMBC long-range correlation spectrum (400 MHz, $CDCl_3$, 25 °C) of $2^{I-VI},3^{I-VII},6^{I-VI}$-eicosa-*O*-methyl-$6^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose **4** showing the correlation between h-H and *C*-6′, which is highlighted by a circle



Scheme 2. Synthesis of $2^{I-VI},3^{I-VII},6^{I-VII}$-eicosa-*O*-methyl-$2^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (**6**) by octenylation of $2^{I-VI},3^{I-VII},6^{I-VII}$-eicosa-*O*-methylcyclomaltoheptaose (**5**)



Scheme 3. Synthesis of $2^{I-VII},3^{I-VI},6^{I-VII}$-eicosa-*O*-methyl-$3^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (**9**) by mono-octenylation and consecutive permethylation of $2^{I-VII},6^{I-VII}$-tetradeca-*O*-methylcyclomaltoheptaose (**7**)

occur. The attachment of the octenyl chain at *O*-3 could not be confirmed by NMR spectroscopy experiments. Indeed, NMR spectroscopy (^{1}H, ^{13}C) shows unambiguously that the octenyl chain is attached to the cyclodextrin and HPLC/ELSD (evaporative light scattering detector) and HPLC/MS analysis (Nucleosil-Phenyl; mobile phase: water/acetonitrile, 1:1) shows that product **9** is different from **4** and **6**. Under these chromatographic conditions, a separation of all three isomeric mono-oct-7-enylated permethyl-β-cyclodextrin derivatives was possible (cf. Figure 2, a), but a separation of the *O*-2 and *O*-3 isomers could not be achieved using C8 or C18 phases (mobile phase: methanol/ water mixtures, 100−50% methanol).

With the same HPLC method and having the single *O*-2, *O*-3, and *O*-6 regioisomers (**4**, **6**, and **9**) in hand, we were able to make an assignment of the products obtained by the non-regioselective statistical introduction of the oct-7-enyl spacer followed by permethylation (described in detail elsewhere),[27] whereby the peaks were identified by coinjection (cf. Figure 2, b). The statistical synthesis of oct-7-enylated permethyl-β-cyclodextrin leads to mixtures of the *O*-2- and *O*-6-mono-oct-7-enylated products in DMF, and mainly *O*-2-mono-oct-7-enylated product in DMSO in addition to higher or non-oct-7-enylated cyclodextrin derivatives. The composition of this mixture is strongly dependent on the reaction conditions, i.e., the solvent (DMF or DMSO) and the base (sodium hydroxide, sodium hydride), and varies from batch to batch. We found that, under certain column chromatography conditions[27] for the purification of the mono-oct-7-enylated β-cyclodextrin mixture, the almost-pure *O*-2-substituted product **6** can be obtained after permethylation, with the *O*-6 product being separated together with the higher oct-7-enylated derivatives. Removing higher-order and non-oct-7-enylated derivatives is necessary at this stage to prevent cross polymerization by any multifunctional groups during the bonding process and to guarantee reproducible amounts of the desired product for hydrosilylation.

To obtain the regioselectively bonded chiral stationary phases, Chirasil-β-Dex (*O*-6-Chirasil-β-Dex **11**, *O*-2-Chirasil-β-Dex **12**, and *O*-3-Chirasil-β-Dex **13**), $2^{I-VI},3^{I-VII},6^{I-VII}$-eicosa-*O*-methyl-$2^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose, $2^{I-VII},3^{I-VI},6^{I-VII}$-eicosa-*O*-methyl-$3^{I}$-*O*-(oct-7-enyl)-cyclomaltoheptaose and $2^{I-VII},3^{I-VII},6^{I-VI}$-eicosa-*O*-methyl-$6^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose were bonded via the oct-7-enyl spacer to a hydridomethyldimethylsiloxane copolymer **10** — having a ratio of $Si(O)(CH_3)H/Si(O)(CH_3)_2$ of 14.1:100 [total content of 12.3% $Si(O)(CH_3)H$], prepared by a modification of the method described by Schomburg et al.[53] — by hydrosilylation with hexachloroplatinic(IV) acid as catalyst (cf. Scheme 4).

By integration of signals of the $Si(O)(CH_3)H$ and $Si(O)(CH_3)_2$ units in the ^{1}H NMR spectrum, the degree of bonded permethyl-β-cyclodextrin was determined to be approximately 9.3:100 [total residual content of $Si(O)(CH_3)H \approx 8.5\%$]. From this ratio, the permethyl-β-cyclodextrin content was calculated to be ca. 44% (w/w). The residual $Si(O)(CH_3)H$ groups are required for immobilization by irreversible bonding of the CSP to the glass wall of the fused silica open-tubular capillaries.

In Figure 3 and Table 1, we compare the performance of the three columns coated with *O*-2-, *O*-3-, and *O*-6-Chirasil-Dex toward a mixture of enantiomeric menthol, menthyl acetate, menthyl propionate, and menthyl butyrate (isothermal at 100 °C).

This mixture had been resolved previously on a commercial Chirasil-Dex-column with remarkable enantioselectivities in one of our laboratories. Despite an effort to produce three columns with nearly identical characteristics − such as capillary surface deactivation, ratio of cyclodextrin selector to polysiloxane matrix (molality), purity status of Chirasil-Dex (e.g., residual platinum catalyst), film thickness, coating efficiency, degree of immobilization, and fluctuations in capillary dimensions − differences in column performance were clearly apparent. For the sake of a better empirical comparison of the chromatograms, the total retention times t_R of the inert reference standards *n*-undecane (C_{11}) and *n*-dodecane (C_{12}) were closely approximated by adjusting the carrier gas flow. This process required a higher inlet pressure for the *O*-2 column since the retention

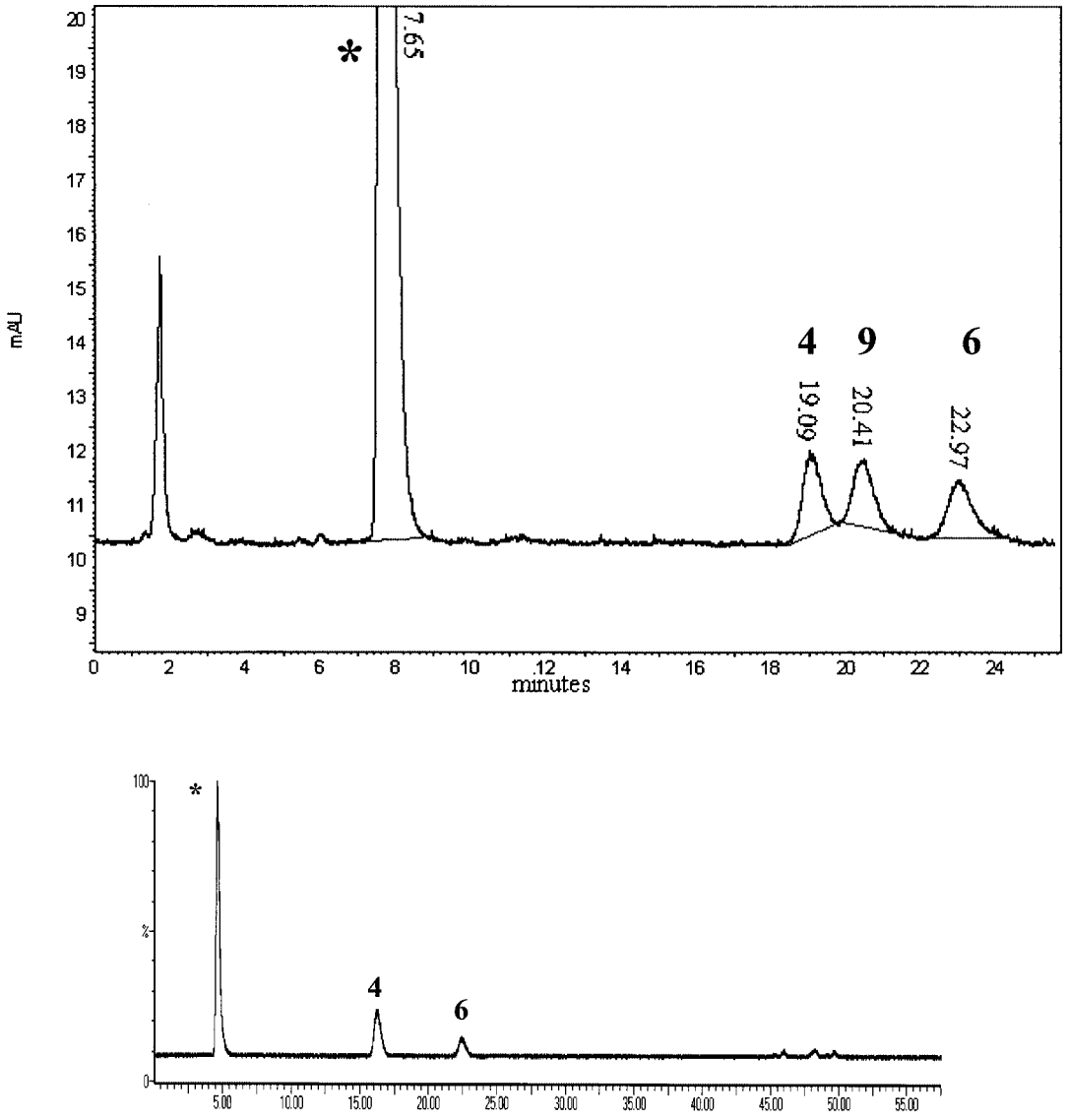
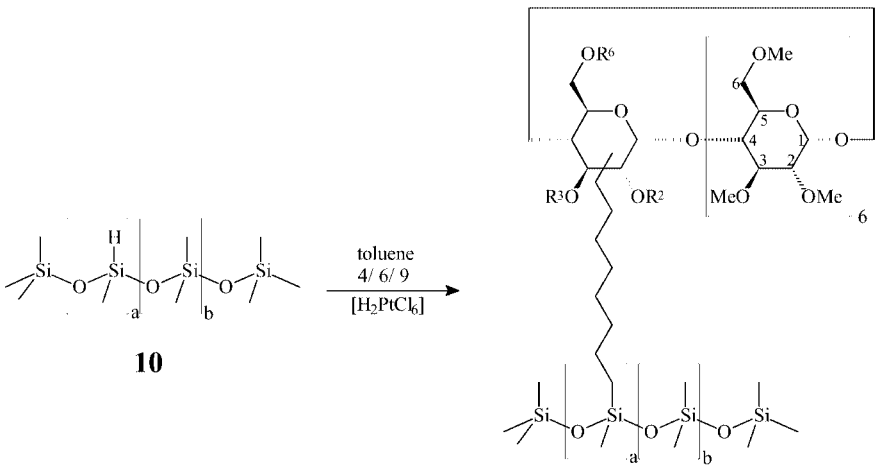


Figure 2. (a) Separation of $2^{I-VII},3^{I-VII},6^{I-VI}$-eicosa-*O*-methyl-$6^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (**4**), $2^{I-VI},3^{I-VII},6^{I-VII}$-eicosa-*O*-methyl-$2^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (**6**), $2^{I-VII},3^{I-VI},6^{I-VII}$-eicosa-*O*-methyl-$3^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (**9**), and heptakis(2,3,6-tri-*O*-methyl)cyclomaltoheptaose (*) by liquid chromatography [column: Nucleosil-Phenyl, 7−100, 4.6 mm (i.d.) × 250 mm; mobile phase: water/acetonitrile, 1:1, flow rate: 1 mL/min; Evaporative Light Scattering Detector (ELSD)]; (b) separation of the crude reaction product obtained by the non-regioselective statistical introduction of the oct-7-enyl spacer followed by permethylation of cyclomaltoheptaose [column Zorbax Phenyl, 7−100, 4.6 mm (i.d.) × 250 mm; mobile phase: water/acetonitrile, 1:1, flow rate: 1 mL/min; after 30 min solvent gradient to 100% acetonitrile within 30 min, ELSD]

factor of the standards, as well as that of all analytes, were higher than for the *O*-3 and *O*-6 columns, probably because of an accidental higher loading of the stationary phase. An important finding is the observation that all analytes *i* show very close relative retentions $r_i = t_i / t_{standard}$ in regard to both reference standards C_{11} and C_{12}, which indicates an almost equal concentration (molality) of the selector in the polysiloxane matrix for all three columns. Yet the enantioselectivity α is smaller for *O*-6-Chirasil-Dex, relative to *O*-3- and *O*-2-Chirasil-Dex (the latter two being nearly identical), although the enantiomers undergo nearly the same molecular association with the selector in all three cases as judged from the similar mean values of r_i. This important finding implies that enantioselectivity is impaired when the mono-octamethylene spacer originates from the smaller rim of the cyclodextrin torus. No dramatic influence of regioisomerism on enantioselectivity can be discerned between *O*-2- and *O*-3-Chirasil-Dex.

Further trials involving enantiomers exhibiting reduced separation factors, which make up most applications in enantioselective gas chromatography, revealed that the differences in enantioselectivity between the three columns is less pronounced and that some bias occurs also between *O*-3- and *O*-2-Chirasil-Dex. Thus, for the enantiomers of 1-(pentafluorophenyl)ethanol (cf. Figure 4, Table 2), the values of α are 1.13, 1.24, and 1.14 for *O*-6-, *O*-3-, and *O*-2-



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11, **12**, **13**

Scheme 4. Synthesis of the selectively bonded CSPs Chirasil-β-Dex-6 **11** [from $2^{I-VII},3^{I-VII},6^{I-VI}$-eicosa-*O*-methyl-$6^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (**4**), $2^{I-VI},3^{I-VII},6^{I-VII}$-eicosa-*O*-methyl-$2^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (**6**)] and Chirasil-β-Dex-3 **12** [from $2^{I-VII},3^{I-VI},6^{I-VII}$-eicosa-*O*-methyl-$3^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (**9**)] by hydrosilylation with hydridomethyldimethylsiloxane copolymer **10**

Chirasil-Dex, respectively, whereas for *N*-(trifluoroacetyl)-proline ethyl ester (cf. Figure 5, Table 3), they are 1.03, 1.05, and 1.04, respectively. For the enantiomers of diastereomeric 3-menthanols (neomenthol, menthol, isomenthol; cf. Figure 6, Table 4), *O*-6- exhibits slightly reduced values of α relative to *O*-3- and *O*-2-Chirasil-Dex.

The Schurig test mixture[54,55] (cf. Figure 11 in ref.[56]) is frequently used in a temperature program for the evaluation of commercial columns coated with permethylated β-cyclodextrin dissolved in CP-Sil 19 (CP-Cyclodex beta 236 M) or coated with Chirasil-Dex (Chrompack International-Varian, Middelburg, The Netherlands). The mixture covers the whole polarity range of enantiomers and it is comprised of α-pinene, *trans*- and *cis*-pinane, *rac*- and *meso*-2,3-butanediol, γ-valerolactone, 1-phenylethylamine, 1-phenylethanol, and 2-ethylhexanoic acid. In Figure 7 and Table 5 it is evident that the polar analytes, 2,3-butanediol and 1-phenylethylamine, are not eluted, probably because of the absence of the deactivation procedure prior to coating of the fused silica capillaries, whereas with a commercial Chirasil-Dex column (Chrompack International-Varian, Middelburg, The Netherlands), it is not only 2,3-butanediol and 1-phenylethylamine that are not eluted, but also 2-ethylhexanoic acid.

The remainder of the test mixture shows a very similar elution pattern on all three columns coated with *O*-2-, *O*-3-, and *O*-6-Chirasil-Dex. The most remarkable feature is the good peak performance for the most critical polar analyte, 2-ethylhexanoic acid. Because of the temperature program, determining the chiral separation factor α is inappropriate and the resolution R_s may be obscured by different efficiencies, as is clearly evident for 1-phenylethanol on *O*-6-Chirasil-Dex. From inspection of Figure 7, however, it is obvious that an inferior separability of the enantiomers of the first eluted apolar hydrocarbons occurs on the *O*-6-Chirasil-Dex column.

An important criterion for probing different chiral selectors consists of the correlation of the absolute configuration and the order of elution of the enantiomers. Figure 8 depicts a number of secondary 1-phenylalkanols that are resolved on regioselective *O*-6-, *O*-3-, and *O*-2-Chirasil-Dex, and statistical Chirasil-Dex containing an undecamethylene spacer[25]. An inversion of the elution order between (*R*) and (*S*) enantiomers is observed for compounds **1**, **2** vs. compounds **3**−**6** on all CSPs. Moreover, with the exception of *O*-6-Chirasil-Dex, which displays lower retention factors for the alcohols and, hence, lower separation factors,[57] the gas chromatograms resemble each other to a great extent, which reinforces the notion that enantioselectivity is independent of the length and position of the polymethylene spacer. Since inversion of the elution order may readily occur as the result of minute changes in the selector composition and its purity status (vide supra), the position of the spacer has no influence on the mode of chiral recognition in the present example.

Since the regioselective *O*-2-Chirasil-Dex columns showed the best separation factors α for almost all enantiomers tested, the non-regioselective Chirasil-Dex columns — formulated as *O*-6, but now revised as a mixture of *O*-2- and *O*-6-Chirasil-Dex with a preponderance of *O*-2-Chirasil-Dex — are most likely operating at optimum enantioselectivities in various applications of different chromatographic techniques.[10−24] Furthermore, in regard to the practice of contemporary chiral separation, the differences between the *O*-2, *O*-3, and *O*-6-Chirasil-Dex regioisomers appear not to be pronounced enough to warrant the rather tedious synthetic pathways to selected regioisomers, and so the conventional access to Chirasil-Dex by statistical syn-

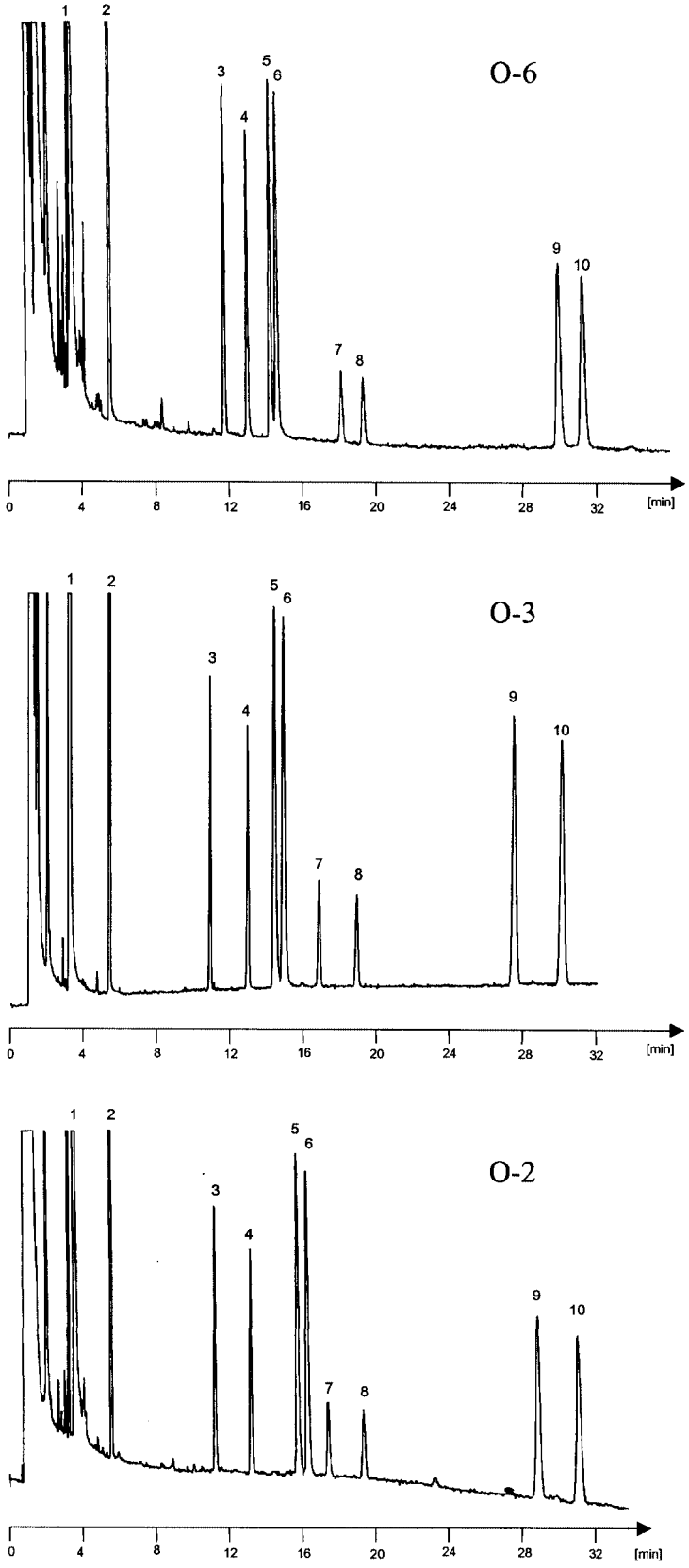

Figure 3. Gas chromatographic separation of the enantiomers of menthyl acetate (3, 4), menthol (5, 6), menthyl propionate (7, 8), and menthyl buryrate (9, 10) in the presence of the reference standards *n*-undecane (1) and *n*-dodecane (2) at 100 °C; fused silica columns [25 m × 0.25 mm (i.d.)] coated and immobilized with 0.25 μm of *O*-6-Chirasil-β-Dex (top), *O*-3-Chirasil-β-Dex (center), and *O*-2-Chirasil-β-Dex (bottom) (carrier gas: dihydrogen; for additional gas chromatographic data, see Table 1)

Table 1. Data of the gas chromatographic separation of the enantiomers of menthyl acetate, menthol, menthyl propionate and menthyl buryrate in the presence of the reference standards *n*-undecane and *n*-dodecane at 100 °C; fused silica columns [25 m × 0.25 mm (i.d.)] coated and immobilized with 0.25 μm of *O*-6-Chirasil-β-Dex, *O*-3-Chirasil-β-Dex, and *O*-2-Chirasil-β-Dex

Head pressure	*O*-6 0.64 bar H_2	*O*-3 0.60 bar H_2	*O*-2 0.84 bar H_2
$t_{M(methane)}$	61 s	61 s	50 s
k_{C11}	2.21	2.17	2.87
k_{C12}	4.39	4.27	5.67
$k_{menthyl\ acetate1}$	10.49	9.66	12.48
$k_{menthyl\ acetate2}$	11.74	11.68	14.86
$k_{menthol1}$	12.95	13.05	17.90
$k_{menthol2}$	13.29	13.53	18.57
$k_{menthyl\ propionate1}$	16.74	15.45	19.94
$k_{menthyl\ propionate2}$	17.92	17.49	22.27
$k_{menthyl\ butyrate1}$	28.36	25.93	33.76
$k_{menthyl\ butyrate2}$	29.67	28.48	36.46
$r_{menthyl\ acetate1/C11}$	4.75	4.45	4.35
$r_{menthyl\ acetate2/C11}$	5.31	5.38	5.18
$r_{menthyl\ acetate1/C12}$	2.39	2.26	2.20
$r_{menthyl\ acetate2/C12}$	2.67	2.74	2.62
$r_{menthol1/C11}$	5.86	6.01	6.24
$r_{menthol2/C11}$	6.01	6.24	6.47
$r_{menthol1/C12}$	2.95	3.06	3.16
$r_{menthol2/C12}$	3.03	3.17	3.28
$r_{menthyl\ propionate1/C11}$	7.57	7.12	6.95
$r_{menthyl\ propionate2/C11}$	8.11	8.06	7.76
$r_{menthyl\ propionate1/C12}$	3.81	3.61	3.52
$r_{menthyl\ propionate2/C12}$	4.08	4.10	3.93
$r_{menthyl\ butyrate1/C11}$	12.83	11.95	13.76
$r_{menthyl\ butyrate2/C11}$	13.43	13.12	12.70
$r_{menthyl\ butyrate1/C12}$	6.45	6.07	5.95
$r_{menthyl\ butyrate2/C12}$	6.76	6.66	6.43
$\alpha_{menthyl\ acetate}$	1.12	1.21	1.19
$\alpha_{menthol}$	1.02	1.04	1.04
$\alpha_{menthyl\ propionate}$	1.07	1.13	1.12
$\alpha_{menthyl\ butyrate}$	1.05	1.10	1.08

thesis,[27] which is devoid of the cumbersome protective functional group chemistry, should be accepted.

Experimental Section

General: 8-Bromo-1-octene, hexamethyldisiloxane, octamethylcyclotetrasiloxane, and polyhydridomethylsiloxane were purchased from Aldrich (Steinheim, Germany). Hexachloroplatinic(IV) acid was obtained from Degussa (Hanau, Germany). Anhydrous DMF, *n*-heptane, methanol, iodomethane, and sodium hydride were obtained from Fluka (Buchs, Switzerland). $2^{I-VII},6^{I-VII}$-Tetradeca-*O*-methylcyclomaltoheptaose (**7**) was purchased from Cyclolab (Budapest, Hungary). Prior to use, THF and toluene were distilled from Na/paraffin suspension, and DCM from CaH_2. All reactions were carried out under nitrogen. Purification steps were carried out using flash column chromatography with silica (63−200 mesh, Normasil Prolabo, Fontenay-sous-bois, France, or E. Merck, Darmstadt, Germany), or preparative TLC using 2-mm glass-backed precoated silica gel plates (E. Merck, Darmstadt, Germany). NMR spectra (^1H, 400.13 MHz; ^{13}C, 100.75 MHz) were recorded with a Bruker Avance DMX 500 or Bruker Avance WM 400 instrument, respectively. The assignment of ^1H and ^{13}C signals was supported by one- and two-dimensional ^1H-^1H COSY, DEPT,

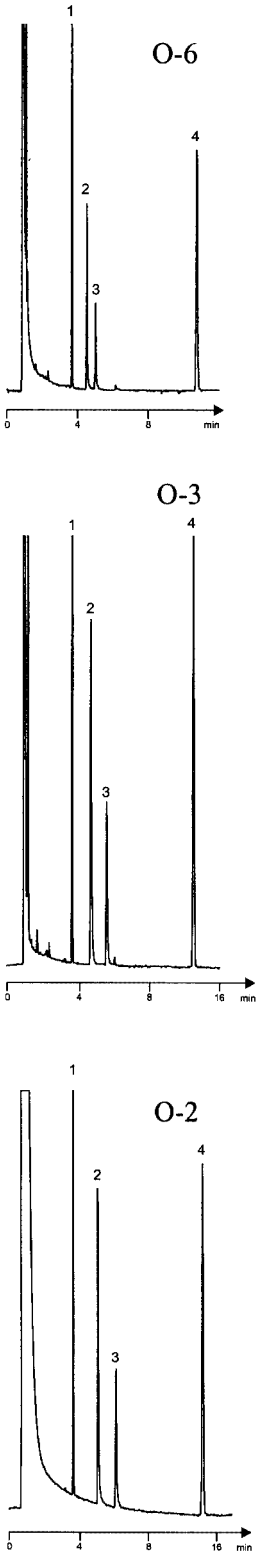

Figure 4. Gas chromatographic separation of the enantiomers of 1-(pentafluorophenyl)ethanol (2, 3) in the presence of the reference standards *n*-dodecane (1) and *n*-tetradecane (4) at 110 °C; fused silica columns [25 m × 0.25 mm (i.d.)] coated and immobilized with 0.25 μm of *O*-6-Chirasil-β-Dex (top), *O*-3-Chirasil-β-Dex (center), and *O*-2-Chirasil-β-Dex (bottom) (carrier gas: dihydrogen; for additional gas chromatographic data, see Table 2)

Table 2. Data of the gas chromatographic separation of the enantiomers of 1-(pentafluorophenyl)ethanol in the presence of the reference standards *n*-dodecane and *n*-tetradecane at 110 °C; fused silica columns [25 m × 0.25 mm (i.d.)] coated and immobilized with 0.25 μm of *O*-6-Chirasil-β-Dex, *O*-3-Chirasil-β-Dex, and *O*-2-Chirasil-β-Dex

Head pressure	*O*-6 0.84 bar H_2	*O*-3 0.66 bar H_2	*O*-2 1.0 bar H_2
$t_{M(methane)}$	48 s	60 s	48 s
k_1	4.59	3.72	5.39
k_2	5.20	4.63	6.70
k_{C12}	3.51	2.65	3.56
k_{C14}	12.39	9.60	13.06
$r_{peak1/C12}$	1.31	1.40	1.51
$r_{peak2/C12}$	1.48	1.75	1.88
$r_{peak1/C14}$	0.37	0.39	0.41
$r_{peak2/C14}$	0.42	0.48	0.51
α	1.13	1.24	1.14

^1H-^{13}C HMQC, and HMBC experiments. All the experiments were recorded using $CDCl_3$ as solvent. The sample (ca. 30 mg) was directly dissolved into the NMR tube in the solvent (0.6 mL). Diastereotopic protons are designated by α and β. Carbon and hydrogen atoms of the substituted units are designated 1′, 2′, 3′, etc. Carbon and hydrogen atoms of the substituents are designated a, b, c, etc. The purity of synthetic products was established by NMR spectroscopy, HPLC/MS and HPLC/ELSD [HPLC: ThermoQuest P1500 and a Nucleosil-Phenyl, 7−100, 4.6 mm (i.d.), 250 mm (Macherey−Nagel, Düren, Germany) column, mobile phase: water/acetonitrile 1:1, flow: 1 mL/min; MS: Finnigan Navigator, APCI, Source Heater 150 °C and APCI Heater 550 °C, cone voltage 25 V; ELSD: Evaporative Light Scattering Detector, Eurosep instrument DDL31, T = 45 °C] and Thin Layer Chromatography (TLC) on silica gel (E. Merck, Darmstadt, Germany) with H_2SO_4 (10% in EtOH) as spray reagent. High-resolution mass spectra were recorded with an APEX-II-FTICR mass spectrometer (4.7 T, Bruker, Bremen, Germany) in the positive-ion mode with ES-ionization (0.1% solution of the analyte in methanol, 0.1% NaCl was added). Elementary analyses were carried out with an EA 1110 (CE instruments).

Gas Chromatography: Gas chromatography was performed with Carlo−Erba HRGC Mega 5300 Series instruments and Shimadzu C-R6A integrators. Highly purified dihydrogen was used as the carrier gas. The split was adjusted to 50 mL/min. The temperature of both injector and detector (FID) was set at 250 °C. Additional chromatographic conditions are listed in the Tables and Figures. Fused silica tubing [25 m × 0.25 mm (i.d.); Micro-Quartz, Munich, Germany] was dehydrated in a gentle stream of dihydrogen at 250 °C for 24 h. Without further deactivation of the inner surface, the columns were coated with Chirasil-Dex (12 mg) dissolved in diethyl ether (3 mL; 0.4% solution yielding approximately a 0.25-μm film thickness) by the static method[58] in a water bath at room temperature. After conditioning the columns by a temperature program (30−220 °C at 1 °C/min at a very low gas flow), the stationary phase was immobilized at 220 °C for 48 h.

$2^{I-VII},3^{I-VII}$-Tetradeca-*O*-methyl-6^I-*O*-(oct-7-enyl)cyclomaltoheptaose (2): A solution of $2^{I-VII},3^{I-VII}$-tetradeca-*O*-methylcyclomaltoheptaose (**1**) (4.0 g, 3 mmol), prepared by a method previously described,[48,49] in anhydrous DMF (10 mL) was added at 0 °C to a stirred suspension of sodium hydride (0.72 g, 30 mmol, washed with petroleum ether) in anhydrous DMF (30 mL). After

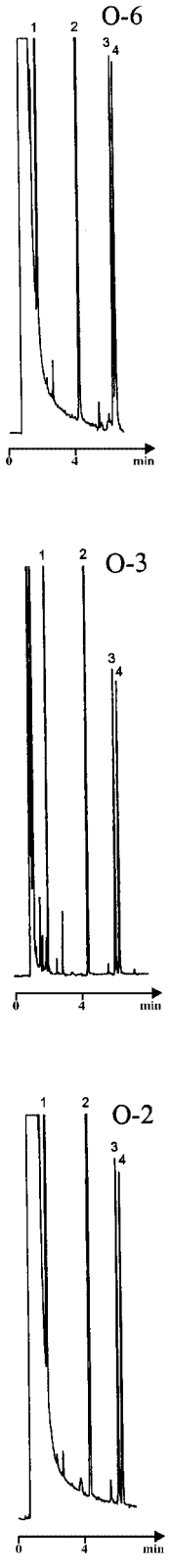

Figure 5. Gas chromatographic separation of the enantiomers of *N*-(trifluoroacetyl)proline ethyl ester (3, 4) in the presence of the reference standards *n*-undecane (1) and *n*-tridecane (2) at 120 °C; fused silica columns [25 m × 0.25 mm (i.d.)] coated and immobilized with 0.25 μm of *O*-6-Chirasil-β-Dex (top), *O*-3-Chirasil-β-Dex (middle), and *O*-2-Chirasil-β-Dex (bottom) (carrier gas: dihydrogen; for additional gas-chromatographic data, see Table 3)

Table 3. Data of the gas chromatographic separation of the enantiomers of *N*-(trifluoroacetyl)proline ethyl ester in the presence of the reference standards *n*-undecane and *n*-tridecane at 120 °C; fused silica columns [25 m × 0.25 mm (i.d.)] coated and immobilized with 0.25 μm of *O*-6-Chirasil-β-Dex, *O*-3-Chirasil-β-Dex, and *O*-2-Chirasil-β-Dex

Head pressure	*O*-6 0.84 bar H_2	*O*-3 0.66 bar H_2	*O*-2 1.0 bar H_2
$t_{M(methane)}$	50 s	54 s	42 s
k_1	6.75	5.63	7.64
k_2	6.92	5.90	7.99
k_{C11}	1.18	1.18	1.55
k_{C13}	4.19	3.83	5.19
$r_{peak1/C11}$	5.72	4.77	4.93
$r_{peak2/C11}$	5.86	5.00	5.15
$r_{peak1/C13}$	1.61	1.40	1.47
$r_{peak2/C13}$	1.65	1.54	1.54
α	1.03	1.05	1.04

1 h, 8-bromo-1-octene (1.25 mL, 7.5 mmol) was added dropwise over 4 h and then stirring was continued at 0 °C for 2 h, then at room temperature for 24 h. Excess sodium hydride was decomposed by adding methanol to the reaction mixture. The reaction mixture was then neutralized with dilute acetic acid and concentrated under reduced pressure (10^{-2} Torr, 24 h). Purification of the residue by column chromatography (silica gel, *n*-heptane/EtOAc, 4:1) gave **2** (1.21 g, 0.84 mmol) in 28% yield. TLC (toluene/acetone, 1:1): R_f = 0.35. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.73 (ddt, $^3J_{b,a(E)}$ = 16.9, $^3J_{b,a(Z)}$ = 10.6, $^3J_{b,c(Z)}$ = 6.7 Hz, 1 H, b-H), 5.03 (m, 6 H, 6-OH), 4.97−4.86 (m, 9 H, 1-,a-H), 3.80−3.73 (m, 14 H, $6_α$-,5-H), 3.64 (s, 21 H, 3-OCH_3), 3.61 (m, 1 H, $h_α$-H), 3.57−3.48 (m, 21 H, $6_β$-H, 4-,3-H), 3.46 (s, 21 H, 2-OCH_3), 3.43 (m, 1 H, $h_β$-H), 3.18 (dd, $^3J_{2,3}$ = 9.8, $^3J_{2,1}$ = 3.3 Hz, 7 H, 2-H), 1.98 (m, 2 H, c-H), 1.54 (m, 2 H, g-H), 1.34−1.26 (m, 6 H, d-,e-,f-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 138.7 (C-b), 114.7 (C-a), 99.4, 98.7 (C-1), 82.5, 82.2, 81.8 (C-2,-3), 80.8, 80.7, 80.5, 80.4, 80.3 (C-4), 71.9 (C-6,-h), 71.2 (C-5), 69.8 (C-6′), 61.8 (3-O-CH_3), 58.9 (2-O-CH_3), 34.1 (C-c), 30.1, 29.2, 29.2, 26.3 (C-d,-e,-f,-g) ppm. MS: *m*/*z* = 1463.3 [M + Na^+], 1479.4 [M + K^+]. $C_{64}H_{112}O_{35}$ (1441.6): calcd. C 53.32, H 7.83, found C 53.28, H 7.80.

2^{I-VII},3^{I-VII},6^{I-VI}-Eicosa-*O*-methyl-6^I-*O*-(oct-7-enyl)cyclomaltoheptaose (4). a) A solution of 2^{I-VII},3^{I-VII}-tetradeca-*O*-methyl-6^I-*O*-(oct-7-enyl)cyclomaltoheptaose (**2**) (1.0 g, 0.7 mmol) in anhydrous DMF (10 mL) was added at 0 °C to a stirred suspension of sodium hydride (1.0 g, 42 mmol, washed with petroleum ether) in anhydrous DMF (10 mL). After 1 h, a solution of methyl iodide (3.12 mL, 50 mmol) in DMF (10 mL) was added dropwise over 12 h, and then stirring was continued at 0 °C for 6 h and at room temperature for 24 h. Excess sodium hydride was decomposed by adding methanol to the reaction mixture. The reaction mixture was then neutralized with dilute acetic acid and concentrated under reduced pressure (10^{-2} Torr, 24 h). Purification of the residue by column chromatography (silica gel, toluene/acetone, 4:1) and recrystallization from *n*-heptane gave **4** (920 mg, 0.60 mmol) in 87% yield. TLC (toluene/acetone 1:1): R_f = 0.64. **b)** A solution of 2^{I-VII},3^{I-VII},6^{I-VI}-eicosa-*O*-methylcyclomaltoheptaose (**3**) (500 mg, 0.35 mmol), which was prepared by adapting the procedure of Bradshaw and co-workers,[50,52] in anhydrous THF (20 mL) was added dropwise to a stirred mixture of sodium hydride (17 mg, 0.70 mmol, washed with THF) in anhydrous THF (10 mL). The

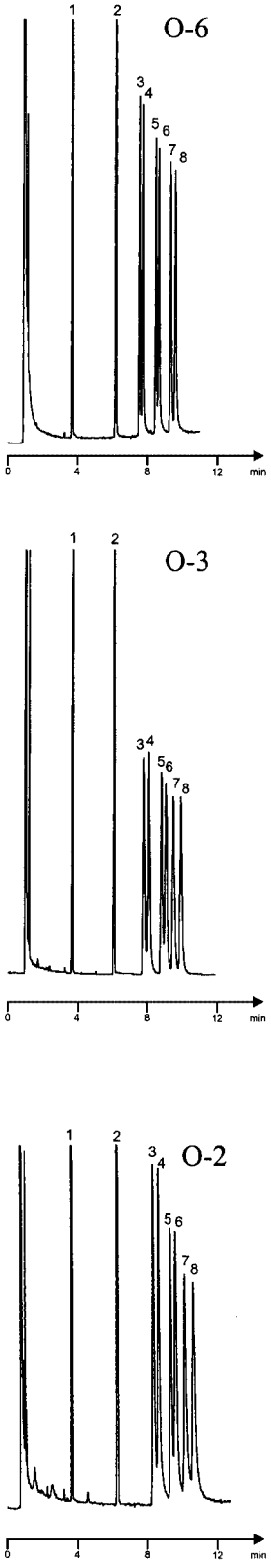

Figure 6. Gas chromatographic separation of the enantiomers of neomenthol (3, 4), menthol (5, 6), and isomenthol (7, 8) in the presence of the reference standards *n*-dodecane (1) and *n*-tridecane (2) at 110 °C; fused silica columns [25 m × 0.25 mm (i.d.)] coated and immobilized with 0.25 μm of *O*-6-Chirasil-β-Dex (top), *O*-3-Chirasil-β-Dex (center), and *O*-2-Chirasil-β-Dex (bottom) (carrier gas: dihydrogen; for additional gas chromatographic data, see Table 4)

Table 4. Data of the gas chromatographic separation of the enantiomers of neomenthol, menthol, and isomenthol in the presence of the reference standards *n*-dodecane and *n*-tridecane at 110 °C; fused silica columns [25 m × 0.25 mm (i.d.)] coated and immobilized with 0.25 μm of *O*-6-Chirasil-β-Dex, *O*-3-Chirasil-β-Dex, and *O*-2-Chirasil-β-Dex

Head pressure	*O*-6 0.84 bar H_2	*O*-3 0.66 bar H_2	*O*-2 1.0 bar H_2
$t_{M(methane)}$	48s	52 s	48s
k_{C12}	3.59	3.22	3.56
k_{C13}	6.74	5.99	6.86
$k_{neomenthol1}$	8.41	7.95	9.40
$k_{neomenthol2}$	8.65	8.25	9.80
$k_{menthol1}$	9.55	9.22	10.66
$k_{menthol2}$	9.79	9.39	11.04
$k_{isomenthol1}$	10.64	9.89	11.71
$k_{isomenthol2}$	10.99	10.39	12.30
$r_{neomenthol1/C12}$	2.34	2.47	2.64
$r_{neomenthol2/C12}$	2.41	2.56	2.75
$r_{neomenthol1/C13}$	1.25	1.33	1.37
$r_{neomenthol2/C13}$	1.28	1.38	1.43
$r_{menthol1/C12}$	2.66	2.86	2.99
$r_{menthol2/\ C12}$	2.73	2.92	3.10
$r_{menthol1/C13}$	1.42	1.54	1.55
$r_{menthol2/C13}$	1.45	1.57	1.61
$r_{isomenthol1/C12}$	2.96	3.07	3.29
$r_{isomenthol2/C12}$	3.06	3.23	3.46
$r_{isomenthol1/C13}$	1.58	1.65	1.71
$r_{isomenthol2/C13}$	1.63	1.73	1.79
$\alpha_{neomenthol}$	1.03	1.04	1.04
$\alpha_{menthol}$	1.02	1.02	1.04
$\alpha_{isomenthol}$	1.03	1.05	1.05

resulting mixture was stirred and heated under reflux for 2 h. After cooling to 0 °C, 8-bromo-1-octene (130 mg, 0.70 mmol) was added dropwise and then stirring was continued at 0 °C for 1 h and then the mixture was heated under reflux overnight. After cooling the reaction mixture to 0 °C, the excess of sodium hydride was decomposed by the addition of methanol (1 mL). The solvent was evaporated under reduced pressure and then the residue was dissolved in $CHCl_3$ and washed with water and brine. After drying with $MgSO_4$ and filtration, the solvent was evaporated under vacuum. The crude product was purified by column chromatography (silica gel, toluene/acetone, 4:1) yielding **4** (388 mg, 0.25 mmol, 72%). TLC (toluene/acetone, 1:1): R_f = 0.64. Both synthetic pathways [a) and b)] led to materials with the same physical and spectroscopic properties. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.76 (ddt, $^3J_{b,a(E)}$ = 17.0, $^3J_{b,a(Z)}$ = 10.8, $^3J_{b,c}$ = 6.6 Hz, 1 H, b-H), 5.12−5.07 (m, 7 H, 1-H), 4.96 (dd, $^2J_{a(E),a(Z)}$ = 1.7 Hz, 1 H, a$^{(E)}$-H), 4.89 (dd, 1 H, a$^{(Z)}$-H), 3.81−3.75 (m, 14 H, 6$_α$-,5-H), 3.63 (m, 1 H, h$_α$-H), 3.61 (s, 21 H, 3-OCH_3), 3.57−3.53 (m, 14 H, 6$_β$-,4-H), 3.49−3.48 (m, 7 H, 3-H), 3.47 (s, 21 H, 2-OCH_3), 3.40 (m, 1 H, h$_β$-H), 3.34 (m, 18 H, 6-OCH_3), 3.15 (dd, $^3J_{2,3}$ = 9.6, $^3J_{2,1}$ = 3.6 Hz, 7 H, 2-H), 1.98 (m, 2 H, c-H), 1.55 (m, 2 H, g-H), 1.35−1.27 (m, 6 H, d-,e-,f-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 138.9 (C-b), 114.3 (C-a), 99.0, 98.7 (C-1), 82.1, 81.9, 81.8 (C-2,-3), 80.6, 80.4, 80.3, 80.2, 80.1 (C-4), 71.5 (C-6, C-h), 70.9 (C-5), 69.6 (C-6′), 61.4 (3-O-CH_3), 59.0 (6-O-CH_3), 58.6 (2-O-CH_3), 33.7 (C-c), 29.7, 29.0, 28.9, 26.1 (C-d,-e,-f,-g) ppm. HPLC/MS (ACN/H_2O, 1:1): t_R = 19.09 min; *m*/*z* = 1547.3 [M + Na^+], 1563.5 [M + K^+]. FTICR-MS: *m*/*z* (%) = 785.3940 (100) [M^{2+} + Na^+], 785.8940 (66.0), 786.3978 (31.2), 1547.8116 (100.0), 1548.8221 (76.4), 1549.8402

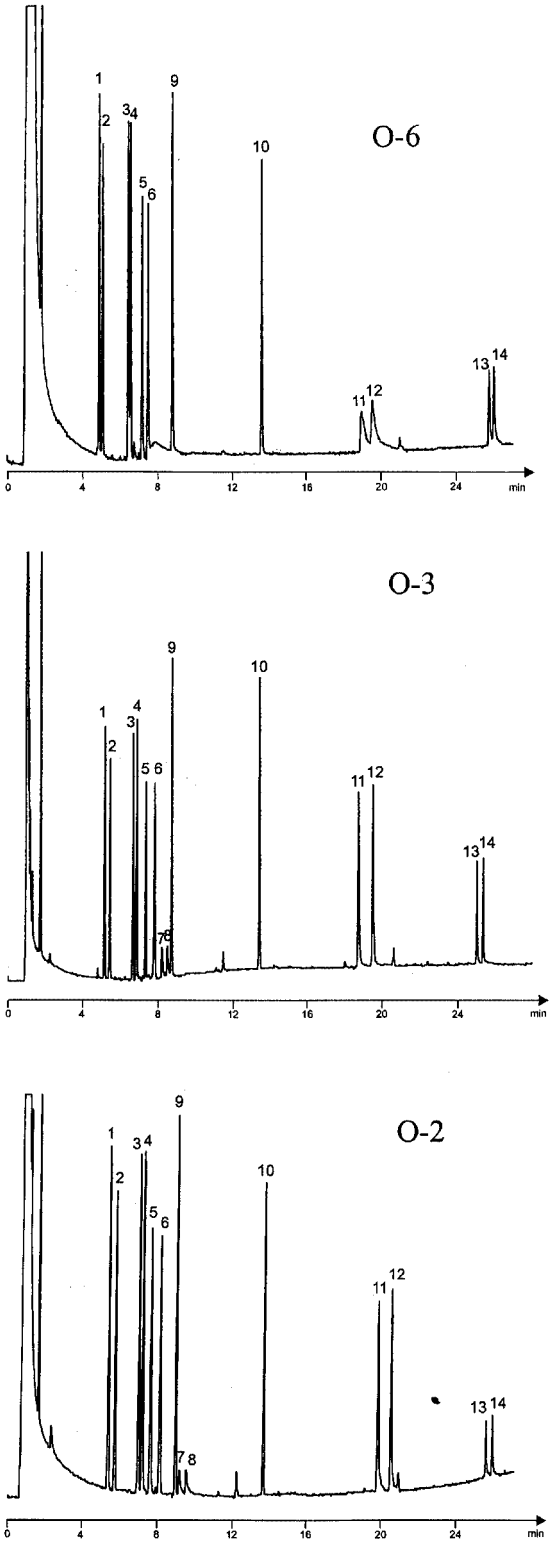

Figure 7. Gas chromatographic separation of the enantiomers of α-pinene (1, 2), *trans*-pinane (3, 4), *cis*-pinane (5, 6), γ-valerolactone (7, 8), 1-phenylethanol (11, 12), and 2-ethylhexanoic (13, 14) in the presence of the reference standards *n*-undecane (9) and *n*-dodecane (10) at 70 °C/5 min//3 °C/min//160 °C; fused silica columns [25 m × 0.25 mm (i.d.)] coated and immobilized with 0.25 μm of *O*-6-Chirasil-β-Dex (top), *O*-3-Chirasil-β-Dex (middle), and *O*-2-Chirasil-β-Dex (bottom) (carrier gas: dihydrogen; for additional gas chromatographic data, see Table 5)

Table 5. Data of the gas chromatographic separation of the enantiomers of α-pinene, *trans*-pinane, *cis*-pinane, γ-valerolactone, 1-phenylethanol, and 2-ethylhexanoic acid in the presence of the reference standards *n*-undecane and *n*-dodecane at a temperature program of 70 °C/5 min//3 °C/min//160 °C; fused silica columns [25 m × 0.25 mm (i.d.)] coated and immobilized with 0.25 μm of *O*-6-Chirasil-β-Dex, *O*-3-Chirasil-β-Dex, and *O*-2-Chirasil-β-Dex

Head pressure	*O*-6 0.7 bar H_2	*O*-3 0.61 bar H_2	*O*-2 1.0 bar H_2
$t_{M(methane)}$	54 s	55 s	46 s
k_{C11}	8.82	8.57	10.62
k_{C12}	14.20	13.62	16.71
$k_{\alpha\text{-pinene1}}$	4.50	4.66	5.95
$k_{\alpha\text{-pinene2}}$	4.70	4.99	6.42
$k_{trans\text{-pinane1}}$	6.23	6.35	8.03
$k_{trans\text{-pinane2}}$	6.37	6.55	8.29
$k_{cis\text{-pinane1}}$	7.04	7.08	8.86
$k_{cis\text{-pinane2}}$	7.40	7.58	9.49
$k_{\gamma\text{-pentalacton1}}$	–	8.01	10.86
$k_{\gamma\text{-pentalacton2}}$	–	8.32	11.35
$k_{1\text{-phenylethanol1}}$	20.12	19.43	24.66
$k_{1\text{-phenylethanol2}}$	20.77	20.27	25.58
$k_{2\text{-ethylhexanoic acid1}}$	27.72	26.29	32.21
$k_{2\text{-ethylhexanoic acid2}}$	28.02	26.65	32.65

(34.0). $C_{70}H_{124}O_{35}$ (1525.7): calcd. C 54.29, H 8.01, found C 54.24, H 8.04.

$2^{I-VI},3^{I-VII},6^{I-VII}$-Eicosa-*O*-methyl-$2^{I}$-*O*-(oct-7-enyl)cyclomaltoheptaose (6): This compound was obtained as described for **4** according to reaction path b). $2^{I-VI},3^{I-VII},6^{I-VII}$-Eicosa-*O*-methylcyclomaltoheptaose (**5**), prepared by adapting a method described previously,[52] was used instead of $2^{I-VII},3^{I-VII},6^{I-VI}$-eicosa-*O*-methylcyclomaltoheptaose (**3**). The crude product was purified by column chromatography (toluene/acetone, 4:1) yielding **6** (75%). TLC (toluene/acetone, 1:1): R_f = 0.61. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.73 (ddt, $^3J_{b,a(E)}$ = 17.2, $^3J_{b,a(Z)}$ = 11.2, $^3J_{b,c}$ = 6.5 Hz, 1 H, b-H), 5.07 (m, 6 H, 1-H), 4.99 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 4.92 (dd, $^2J_{a(E),a(Z)}$ = 1.8 Hz, 1 H, a_α-H), 4.86 (dd,, 1 H, a_β-H), 3.88−3.70 (m, 14 H, 6_α-,5-H), 3.68 (m, 1 H, h_α-H), 3.68 (s, 21 H, 3-OCH_3), 3.65−3.48 (m, 7 H, 4-H), 3.56−3.45 (m, 7 H, 6_β-H), 3.50−3.38 (m, 7 H, 3-H), 3.43 (s, 18 H, 2-OCH_3), 3.40 (m, 1 H, h_β-H), 3.32 (s, 21 H, 6-OCH_3), 3.19 (dd, 1 H, $^3J_{2,3}$ = 10.0 Hz, 2-H), 3.12 (dd, $^3J_{2,3}$ = 10.0 , 6 H, 2-H), 1.97 (m, 2 H, c-H), 1.54 (m, 2 H, g-H), 1.30 (m, 6 H, d-,e-,f-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 138.11 (C-b), 113.16 (C-a), 97.92 (C-1), 81.08, 81.01, 80.82, 80.72, 80.70, 80.55 (C-2,-3,-2′), 79.47, 79.41, 79.18, 79.07, 79.02, 78.86 (C-4), 70.47, 70.40, 70.30 (C-6), 70.05 (C-h), 69.96, 69.87, 69.80 (C-5), 60.54, 60.43, 60.39, 60.36 (3-OCH_3), 57.95 (6-OCH_3), 57.69, 57.63, 57.53, 57.45, 57.38

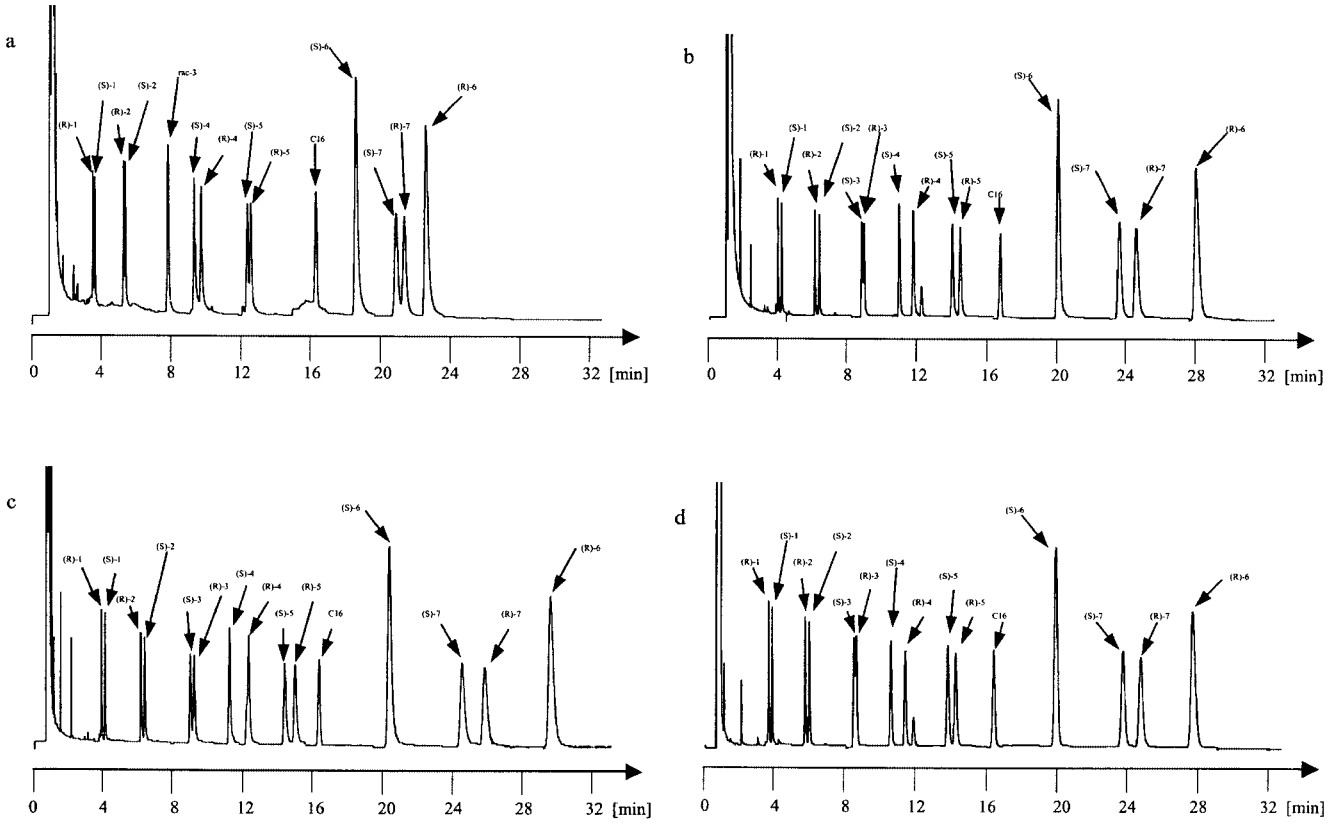

Figure 8. Gas chromatographic separation of the enantiomers of 1-phenylethanol (1), 1-phenyl-1-propanol (2), 1-phenyl-1-butanol (3), 1-(2-methoxy)phenylethanol (4), 1-phenyl-1-pentanol (5), 1-(2-methoxy)phenyl-1-butanol (6), 1-phenyl-1-hexanol; *n*-hexadecane (C16); fused silica columns [25 m × 0.25 mm (i.d.)] coated and immobilized with (a) *O*-6-Chirasil-Dex, (b) *O*-3-Chirasil-Dex, (c) *O*-2-Chirasil-Dex, and (d) statistically derivatized Chirasil-Dex having an undecamethylene spacer.[25] Oven temperature: 120 °C; injector temperature: 200 °C; FID temperature: 250 °C; head pressure (KPa): (a) 72.5, (b) 70, (c) 100, and (d) 70

(2-OCH_3), 32.73 (C-c), 29.00 (C-g), 27.97, 27.87, 24.81 (C-d,-e,-f) ppm. HPLC/MS (ACN/H_2O, 1:1): t_R = 22.97 min; *m/z* = 1547.6 [M + Na^+], 1563.4 [M + K^+]. $C_{70}H_{124}O_{35}$ (1525.7): calcd. C 54.29, H 8.01, found C 54.34, H 7.96.

$2^{I-VII},6^{I-VII}$-Tetradeca-*O*-methyl-3^I-*O*-(oct-7-enyl)cyclomaltoheptaose (8): $2^{I-VII},6^{I-VII}$-Tetradeca-*O*-methylcyclomaltoheptaose (**7**) (5.00 g, 3.75 mmol), dissolved in anhydrous THF (100 mL), was added to a stirred solution of potassium hydride (0.75 g, 18.7 mmol, washed three times with THF) and 18-crown-6 (200 mg, 1 mmol) in anhydrous THF (40 mL). The mixture was stirred at room temp. for 30 min and then under reflux for 2 h. After cooling to room temp., 8-bromo-1-octene (2.21 g, 8.3 mmol) in THF (20 mL) was added dropwise and the mixture was stirred at room temp. for 1 h and then under reflux overnight. The reaction mixture was cooled to 0 °C and then quenched by addition of methanol. The solvent was evaporated under vacuum and then the residue was dissolved in $CHCl_3$ (300 mL) and washed with water (50 mL) and brine (2 × 50 mL). After drying with $MgSO_4$, filtration, and concentration, the crude product was purified by column chromatography (toluene/acetone, 7:3) yielding **8** (1.00 g, 0.69 mmol, 18%) as a white powder. TLC (toluene/acetone, 2:3): R_f = 0.33. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.78 (ddt, $^3J_{b,a(E)}$ = 16.8, $^3J_{b,a(Z)}$ = 10.4, $^3J_{b,c}$ = 6.8 Hz, 1 H, b-H), 5.02 (m, 6 H, 3-OH), 4.98−4.91 (m, 9 H, 1-H, a-H), 4.01 (m, 1 H, $h_α$-H), 3.99−3.85 (m, 5 H, 3-H), 3.96 (m, 7 H, $6_α$-H), 3.83 (m, 1 H, 3-H), 3.78−3.65 (m, 7 H, 5-H), 3.60 (m, 7 H, $6_β$-H), 3.59 (m, 21 H, 2-OCH_3), 3.46 (m, 1 H, $h_β$-H), 3.45 (m, 1 H, 3-H), 3.44−3.32 (m, 7 H, 4-H), 3.34 (m, 21 H, 6-OCH_3), 3.25 (dd, $^3J_{2,3}$ = 9.8, $^3J_{1,2}$ = 3.2 Hz, 6 H, 2-H), 3.15 (dd, $^3J_{1,2}$ = 3.2 Hz, 1 H, 2-H), 2.01 (m, 2 H, c-H), 1.58 (m, 2 H, g-H), 1.40−1.15 (m, 6 H, d-,e-,f-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 139.2 (C-b), 114.2 (C-a), 101.6, 101.5, 101.3, 101.2, 101.1, 100.0 (C-1), 84.4, 83.8, 83.5, 83.3 (C-4), 82.8 (C-2), 82.2 (C-4), 82.1, 81.0 (C-2), 80.1 (C-3′), 74.9 (C-h), 73.2, 72.0 (C-3), 71.6, 70.9 (C-6), 70.3, 70.0 (C-5), 60.7, 60.6, 60.4, 60.3 (6-OCH_3), 59.0, 58.9, 58.7 (2-OCH_3), 33.8 (C-c), 30.4, 29.7, 26.0 (C-d,-e,-f,-g) ppm. HPLC/MS (methanol/H_2O, 9:1): t_R = 10.87 min; *m/z* = 1463.6 [M + Na^+], 1479.5 [M + K^+]. $C_{64}H_{112}O_{35}$ (1441.6): calcd. C 53.33, H 7.78, found C 53.40, H 7.80.

$2^{I-VII},3^{I-VI},6^{I-VII}$-Eicosa-*O*-methyl-$3^I$-*O*-(oct-7-enyl)cyclomaltoheptaose (9): $2^{I-VII},6^{I-VII}$-Tetradeca-*O*-methyl-3^I-*O*-(oct-7-enyl)cyclomaltoheptaose (**8**) (1.00 g, 0.7 mmol) in anhydrous THF (20 mL) was added to a stirred solution of sodium hydride (160 mg, 6.9 mmol, washed three times with THF) in anhydrous THF (5 mL). The mixture was stirred at room temp. for 30 min and then under reflux for 2 h. After cooling to room temp., methyl iodide (0.98 g, 6.9 mmol) in anhydrous THF (3 mL) was added dropwise and then the mixture was stirred at room temp. for 1 h and under reflux overnight. The reaction mixture was cooled to 0 °C and then quenched by addition of methanol. The solvent was evaporated under vacuum and then the residue was dissolved in $CHCl_3$ (80 mL) and washed with water (15 mL) and brine (2 × 15 mL). After drying with $MgSO_4$, filtration, and concentration, the crude product was purified by column chromatography (toluene/acetone, 4:1) yielding **9** (0.85 g, 0.56 mmol, 80%) as a white powder. TLC (toluene/acetone, 1:1): R_f = 0.57. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.76 (ddt, $^3J_{b,a(E)}$ = 16.8, $^3J_{b,a(Z)}$ = 10.4, $^3J_{b,c}$ = 6.4 Hz, 1 H, b-H), 5.11 (m, 7 H, 1-H), 4.94 (dd, $^2J_{a(E),a(Z)}$ = 1.2 Hz, 1 H, $a_α$-H), 4.88 (dd, $^2J_{a(E),a(Z)}$ = 1.2 Hz, 1 H, $a_β$-H), 3.90−3.70 (m, 14 H, $6_α$-,5-H), 3. 89 (m, 1 H, $h_α$-H), 3.72−3.35 (m, 14 H, 4-,3-H), 3.63 (m, 18 H, 3-OCH_3), 3.60 (m, 1 H, $h_β$-H), 3.55 (m, 7 H, $6_β$-H), 3.46 (s, 21 H, 2-OCH_3), 3.34 (s, 21 H, 6-OCH_3), 3.15 (dd, $^3J_{2,3}$ = 9.6, $^3J_{1,2}$ = 3.2 Hz, 7 H, 2-H), 2.00 (m, 2 H, c-H), 1.58 (m, 2 H, g-H), 1.35 (m, 6 H, d-,e-,f-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.1 (C-b), 114.2 (C-a), 99.0, 98.5 (C-1), 82.1, 82.0, 81.8, 81.7 (C-4,-2), 80.5, 80.3, 80.2, 80.1, 80.0, 79.9 (C-2), 74.0 (3-O-C-h), 71.4, 71.3 (C-6), 71.0, 70.9, 70.8 (C-5), 61.5, 61.4 (3-OCH_3), 58.9, 58.9 (6-OCH_3), 58.7, 58.5, 58.4 (2-OCH_3), 33.8 (C-c), 30.3, 29.2, 29.0, 26.0 (C-d,-e,-f,-g) ppm. HPLC/MS (ACN/H_2O, 1:1): t_R = 20.41 min; *m/z* = 1548.2 [M + Na^+], 1564.5 [M + K^+]. $C_{70}H_{124}O_{35}$ (1525.7): calcd. C 54.29, H 8.01, found C 54.31, H 7.99.

Hydridomethyldimethylsiloxane Copolymer 10: A mixture of hexamethyldisiloxane (9.6 g, 116 mmol), polyhydridomethylsiloxane (28 g, 0.46 mol), octamethylcyclotetrasiloxane (140 g, 1.89 mol), China clay (2 g), and sulfuric acid (1 mL) was stirred at 100 °C under gentle reflux for 5 d. During this time the reaction mixture became increasingly more viscous. After cooling the reaction mixture to room temp., the catalyst was removed by extraction with water and filtration. Water and other volatile constituents of the filtrate were removed by evaporation at 120 °C under an oil-pump vacuum to give **10** (167.5 g, 94.3%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = −0.02−0.25 [m, 97.8 H, $Si(CH_3)_n$ (*n* = 1−3)], 4.61 (s, 2.2 H, Si-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = −2.3, 1.3, 1.6 ppm. By integration of the signals of the ^{1}H NMR spectrum, the ratio of $Si(O)(CH_3)H/Si(O)(CH_3)_2$ was determined to be 14.1:100 [total content 12.3% $Si(O)(CH_3)H$].[59]

Chemical Bonding of the Isomeric Monooctenylpermethyl-β-cyclodextrins 4, 6, and 9 to Hydridomethyldimethylsiloxane Copolymer 10 To Give 11, 12, 13: A mixture of hydridomethyldimethylsiloxane copolymer **10** (1.02 g, ca. 0.33 mmol), hexachloroplatinic(IV) acid [0.5 mg, dissolved in THF (1 mL), added in several portions], toluene (40 mL) and either $2^{I-VII},3^{I-VII},6^{II-VII}$-eicosa-*O*-methyl-$6^I$-*O*-(oct-7-enyl)cyclomaltoheptaose (**4**), $2^{II-VII},3^{I-VII},6^{I-VII}$-eicosa-*O*-methyl-$2^I$-*O*-(oct-7-enyl)cyclomaltoheptaose (**6**), or $2^{I-VII},3^{II-VII},6^{I-VII}$-eicosa-*O*-methyl-$3^I$-*O*-(oct-7-enyl)cyclomaltoheptaose (**9**) (0.56 g, 0.37 mmol) was stirred under reflux for 24 h. The solvent was evaporated in vacuo with a rotary evaporator and the residue was taken up in anhydrous methanol (20 mL), separated from the catalyst and the solvent was removed under reduced pressure[62] to give **11**, **12**, or **13**, respectively (1.2 g, 76%). By integration of the signals of the ^{1}H NMR spectrum, the ratio of $Si(O)CH_3$-H/$Si(O)(CH_3)_2$ was determined to be ca. 9.3:100 [total residual content of $Si(O)(CH_3)H$ ≈ 8.5%]. From this ratio, the cyclodextrin content was calculated to be ca. 44%.

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[61] $[Si(O)(CH_3)H]/[Si(O)(CH_3)_2] = 6/(I_{Si-CH}/I_{Si-H} - 3)$, with integrals I taken from the ^1H NMR spectrum.
[62] Combining the solvent evaporation with heating (60 °C) results in an indissoluble gum.

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