J. Braz. Chem. Soc., Vol. 21, No. 10, 2005-2011, 2010.
Printed in Brazil - ©2010 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Short Report

Synthesis and Chromatographic Evaluation of the New Phase Heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin

Anderson S. Mallmann, Eduardo M. Ethur, Ubiratan F. da Silva, Ionara I. Dalcol and Ademir F. Morel*

Departamento de Química, NPPN, Universidade Federal de Santa Maria, 97105-900 Santa Maria-RS, Brazil

Neste trabalho uma nova fase estacionária quiral, heptaquis (3-*O*-pentafluoropropionil-2,6-di-*O*-pentil)-β-ciclodextrina, foi sintetizada e avaliada frente uma grande variedade de compostos voláteis quirais. O novo derivado de ciclodextrina foi usado para a separação de componentes de óleos essenciais, como hidrocarbonetos, cetonas, aldeídos, álcoois de cadeia longa, compostos halogenados e compostos contendo nitrogênio e enxofre.

In this work, a new chiral stationary phase heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin was synthesized and evaluated with a wide variety of volatile chiral compounds. As a result, the new cyclodextrin derivative can be applied to the separation of chiral components of essential oils, as hydrocarbons, ketones, aldehydes, alcohols and of various classes of synthetic chiral compounds, as long chain alcohols, halocarbons, nitrogen and sulfur containing compounds.

Keywords*:* enantioselective gas chromatography, heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β- cyclodextrin, pentafluoropropionyl group

Introduction

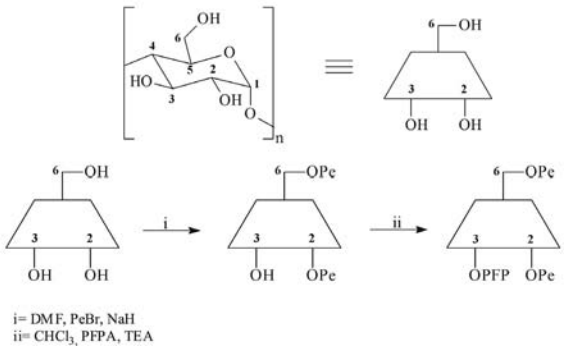
Cyclodextrins (CDs) derivatives, especially those of α-, β- and γ-cyclodextrins, are used widely as chiral stationary phases (CSPs) in gas chromatography (GC) as an efficient method for enantioseparation of a wide variety of volatile compounds of different functionality.[1-11] Various chiral mono and sesquiterpenes common to essential oils and other economically important products could be resolved on columns coated with per-*O*-alkylated/acylated cyclodextrins.[11-16] The number of cyclodextrin derivatives that is prepared and evaluated for enantioselective gas chromatography is still declining in recent years. The most important chiral stationary phases know to data, as octakis (3-*O*-butyryl-2,6-di-*O*-pentyl)-γ-cyclodextrin (Lipodex E)[17], heptakis (3-*O*-pentyl-2,6-di-*O*-methyl)-β-cyclodextrin[18] and octakis (3-*O*-methyl-2,6-di-*O*-pentyl)-γ-cyclodextrin[12], were obtained in the late 80's and 90's. In this work we describe the preparation and the enantioseparation ability of heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin derivative with pentyl groups at the 2 and 6 positions and the pentafluoropropionyl group in the 3 position of their glucose unit. The pentafluoropropionyl group is used as hydroxyl group protection in oligomannoside synthesis,[19] but not used yet as derivatizing agent in CDs. The enantioselectivity of the new phase was evaluated with a number of natural chiral components of essential oils as hydrocarbons, alcohols, ketones and lactones, and determination of enantiomeric composition in asymmetric synthesis. The enantiomers of (+/–)-α-pinene, (+/–)-limonene, alcohols as (+/–)-menthol, (+/–)-*neo*-menthol, (+/–) borneol, (and its acetyl and/or O-trifluoroacetyl derivatives), ketones as (+/–)-carvone, (+/–)-camphor and (+/–)-α-ionone could be resolved. In addition, chiral secondary and tertiary long chain alcohols, halocarbons, nitrogen and sulfur containing compounds may also be resolved.

Results and Discussion

Scheme 1 shows the synthetic route to obtain the new chiral stationary phase heptakis (3-*O*-pentafluoropropionyl-

*e-mail: afmorel@base.ufsm.br

2,6-di-*O*-pentyl)-β-cyclodextrin. The great difference in reactivity of the 2- and 6-OH groups *vs.* the 3-OH groups (low reactivity), allows regioselective pentylation of the positions 2 and 6, followed by acylation with the pentafluoropropionyl group in position 3.



Scheme 1. Synthetic pathway to heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin.

The newly synthesized cyclodextrin phase has demonstrated good selectivity for a wide variety of chiral compounds of various chemical classes, as hydrocarbons, ketones, alcohols, lactones, halocarbons, nitrogen and sulfur containing compounds. Figure 1 shows the GC separation of (+/–)-α-pinene and (+/–)-limonene. Figure 2 illustrate the GC separation of (+/–)-carvone, (+/–)-camphor and (+/–)-α-ionone, respectively. Figure 3 shows the GC of (–)-menthylacetate. This clearly indicates an adulteration with their enantiomer (+)-menthylacetate. On this phase, not only can be underivatized alcohols be resolved, but also the correspondent acetates and trifluoroacetates. The chromatogram presented in Figure 4 illustrates the separations of the enantiomers of (+/–)-borneol, (+/–)-borneol-*O*-Ac, (+/–)-borneol-*O*-TFA. This phase can be applied to the separation of racemates of secondary and tertiary long chain alcohols. Figure 5 illustrates the separation of (+/–)-decanol-*O*-Ac, (+/–)-decanol-*O*-TFA, (+/–)-undecanol-*O*-Ac and (+/–)-undecanol-*O*-TFA, respectively. One example of discrimination being affected by structural properties is the separation of tertiary acetyl alcohols. Figure 6 shows the separation of (+/–)-2-phenylbutanol-*O*-Ac, (+/–)-2-phenylpentanol-*O*-Ac, (+/–)-2-phenylhexanol-*O*-Ac and (+/–)-2-phenylheptanol-*O*-Ac, respectively. In this case, the increased size of the alcohol causes a decrease in separation efficiency. The efficiency of this phase for the separation of nitrogen and sulfur containing compounds is of particular interest. Figure 7 shows the separation of D,L-alanine-*O*-Et and of *R*,*S*-(*E*)-ethyl-2-(4-oxopent-2-en-2-ylamino) propanoate, compound obtained synthetically from alanine. Finally, Figures 8 and 9 illustrated the use of this phase for the separation of sulfur-containing compounds. The enantiomers (+/–)-cyclohexylbenzenesulfinate and (+/–)-1-chloro-3-(ethylsulfinyl) benzene (Figure 8) and of (+/–)-cyclohexylbenzenesulfinate,

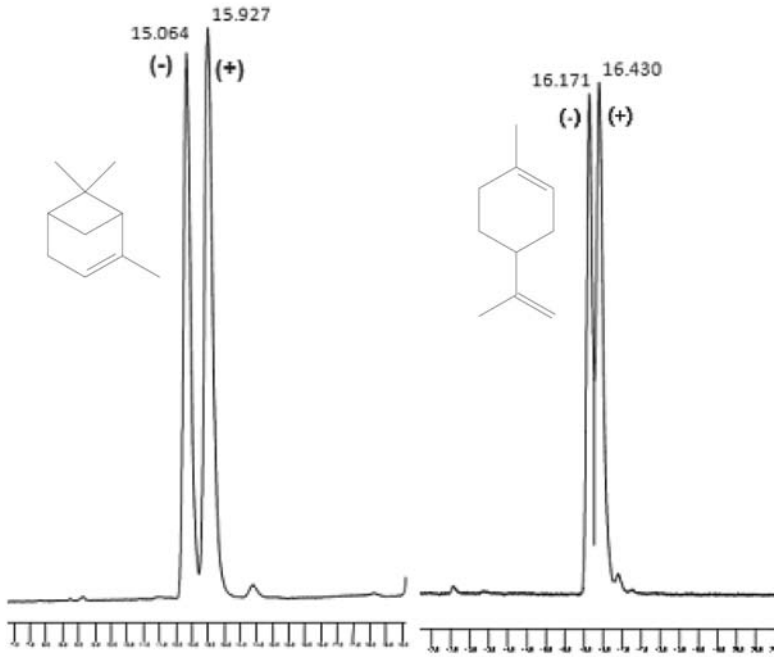


Figure 1. Enantiomeric separation of (+/–)-α-pinene: 30 °C (20 min) and 30-180 °C (1° min^{-1}) and (+/–)-limonene: 35-180 °C (1° min^{-1}), on a 25 m × 0.25 mm CCSF coated with heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin in OV 1701; carrier gas, hydrogen 7 psi.

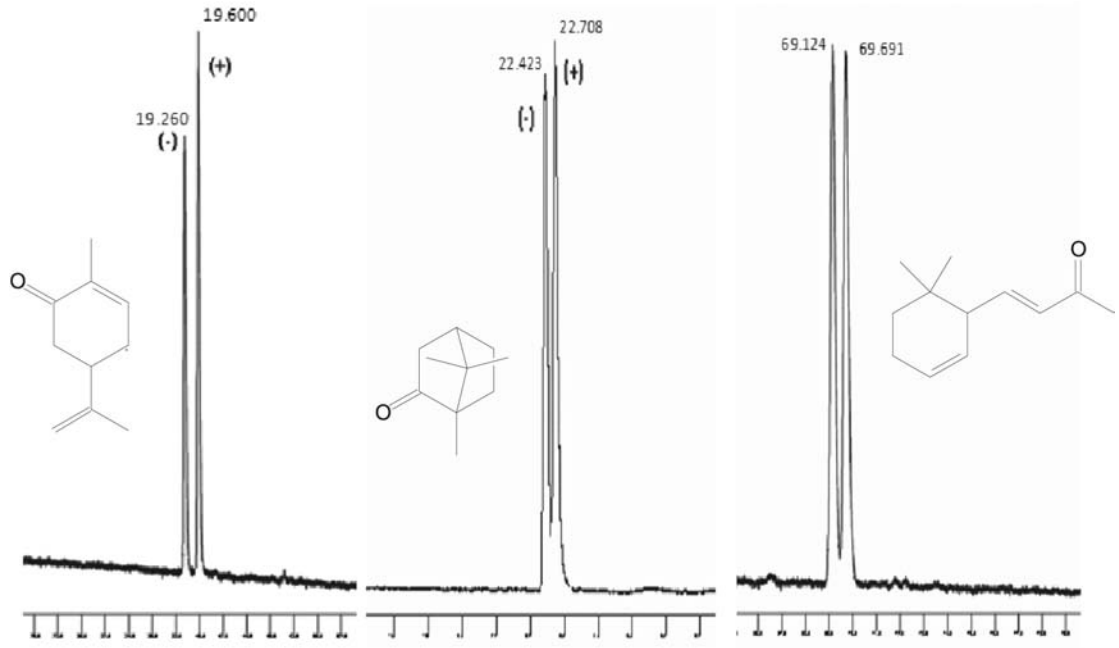


Figure 2. Enantiomeric separation of (+/–)-carvone: 40-180 °C (2° min^{-1}), (+/–)-camphor: 50-180 °C (1° min^{-1}), and (+/–)-α-ionone: 40-180 °C (1° min^{-1}) on a 25 m × 0.25 mm CCSF coated with heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin in OV 1701; carrier gas, hydrogen 7 psi.

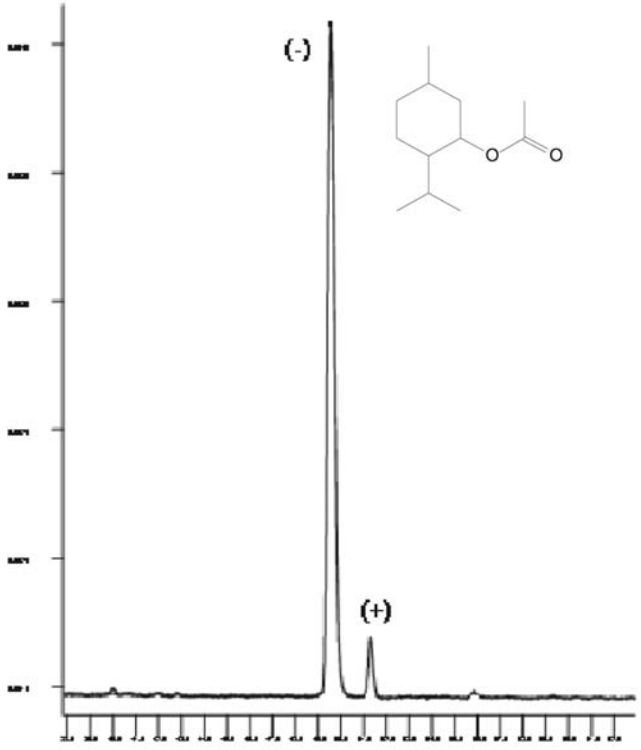


Figure 3. Enantiomeric separation of (+/–)-menthol-*O*-Ac: 35-180 °C (1° min^{-1}) on a 25 m × 0.25 mm CCSF coated with heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin in OV 1701; carrier gas, hydrogen 7 psi.

(+/–)-methylsulfinylbenzene, (+/–)-ethylsulfinylbenzene, (+/–)-1-methyl-4-(methylsulfinyl)benzene and (+/–)-1-ethyl-4-(methylsulfinyl)benzene, respectively (Figure 9) have been resolved.

Conclusions

All of the chromatograms presented above have shown that heptakis (3-*O*-pentafluoropropionyl-2,6-di-

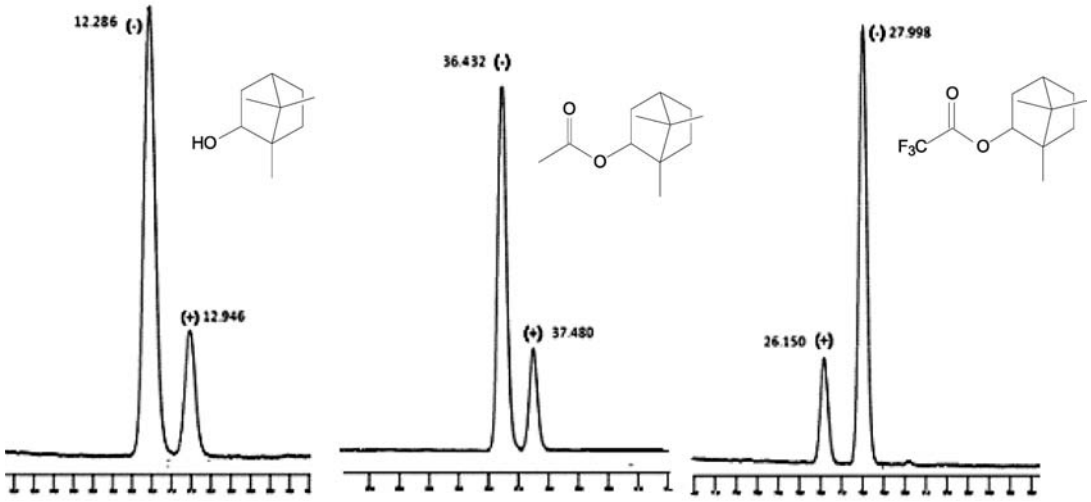


Figure 4. Enantiomeric separation of (+/–)-borneol, (+/–)-borneol-*O*-Ac and (+/–)-borneol-*O*-TFA: 40-180 °C (2° min^{-1}) on a 25 m × 0.25 mm CCSF coated with heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin in OV 1701; carrier gas, hydrogen 7 psi.

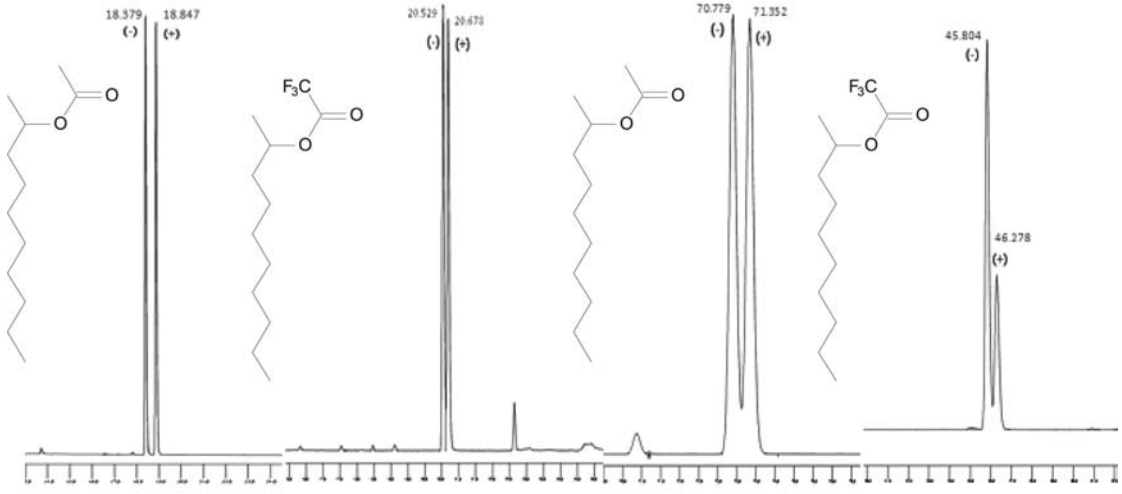


Figure 5. Enantiomeric separation of (+/–)-decanol-*O*-Ac: 50-180 °C (4° min^{-1}), (+/–)-decanol-*O*-TFA: 50 °C (10 min) and 50-180 °C (4° min^{-1}), (+/–)-undecanol-*O*-Ac: 30-180 °C (1° min^{-1}), and (+/–)-undecanol-*O*-TFA: 40-180 °C (1° min^{-1}) on a 25 m × 0.25 mm CCSF coated with heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin in OV 1701; carrier gas, hydrogen 7 psi.

O-pentyl)-β-cyclodextrin represents a versatile stationary phase for the enantioseparation of different classes of compounds by high-resolution gas chromatography. The separation of sulfur containing compounds in Figure 8 and 9 are only two examples of the contribution of the new heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin to this class of chiral synthetic compounds. Another important property is the capability of this phase to resolve the enantiomers of a wide range of secondary and tertiary long chain alcohols (in its acetyl and/or *O*-trifluoroacetyl derivatives), as show in Figure 5 and 6. Moreover, the new phase showed a good performance in the resolution of chiral compounds commonly found in many essential oils, as hydrocarbons, alcohols and ketones.

Experimental

Instrumentation

Capillary GC was performed on a Varian CP 3800 equipped with FID, using capillary column (25 m) of fused silica. Hydrogen was used as carrier gas. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400/100 MHz, with deuterochloroform and tetramethylsilane as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz.

Synthesis of heptakis (2,6-di-O-pentyl)-β-cyclodextrin[2]

Bromopentane (14.56 g; 92.02 mmol) was added to a stirred solution of β-CD (3.20 g; 2.83 mmol), sodium

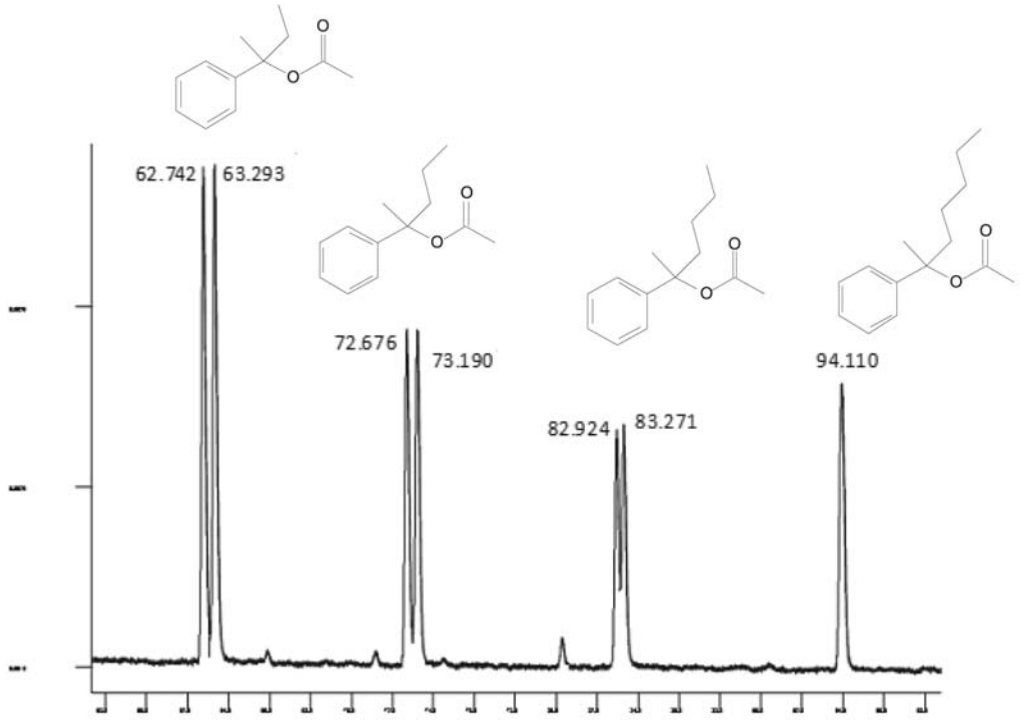


Figure 6. Enantiomeric separation of (+/–)-2-phenylbutanol-*O*-Ac, (+/–)-2-phenylpentanol-*O*-Ac, (+/–)-2-phenylhexanol-*O*-Ac, and (+/–)-2-phenylheptanol-*O*-Ac: 30 °C (10 min) and 30-180 °C (1° min^{-1}) on a 25 m × 0.25 mm CCSF coated with heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin in OV 1701; carrier gas, hydrogen 7 psi.

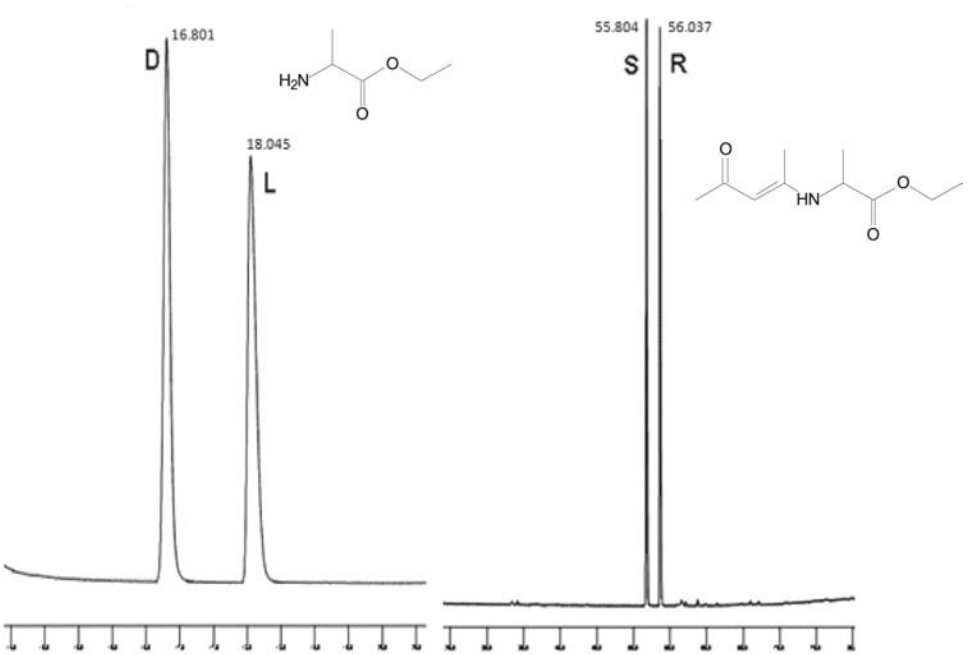


Figure 7. Enantiomeric separation of D,L-alanine-*O*-Et and *R*,*S*-(*E*)-ethyl-2-(4-oxopent-2-en-2-ylamino) propanoate: 50-180 °C (1.5° min^{-1}) on a 25 m × 0.25 mm CCSF coated with heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin in OV 1701; carrier gas, hydrogen 7 psi.

hydroxide (5.0 g; 125.0 mmol), and dry dimethylsulfoxide at 0 °C. Stirring was continued for 4 days, at room temperature, protected from light. The mixture was taken up in diisopropyl ether and washed with water. The organic layer was dried over anhydrous magnesium and concentrate under vacuum. The crude product was purified by column chromatography on silica gel (230-400 mesh) with ethyl acetate/hexane (4:1), yielding 2.40g (40%) of heptakis (2,6-di-*O*-pentyl)-β-cyclodextrin. The purity of the product was monitored by TLC and ^{1}H and ^{13}C NMR.

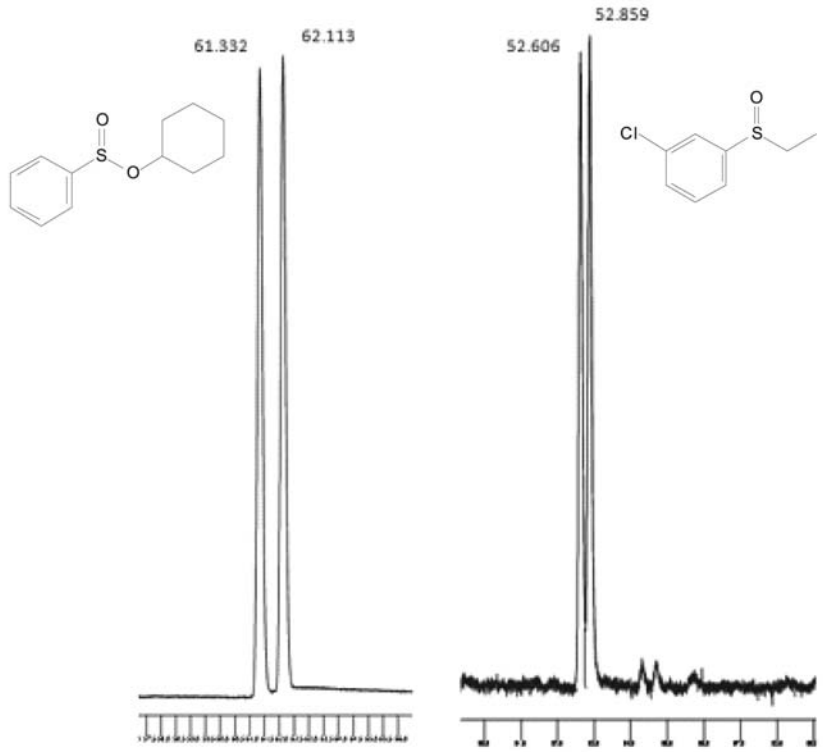


Figure 8. Enantiomeric separation of (+/–)-cyclohexylbenzenesulfinate: 35-180 °C (1° min^{-1}) and (+/–)-1-chloro-3-(ethylsulfinyl)benzene: 40-180 °C (2° min^{-1}) on a 25 m × 0.25 mm CCSF coated with heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin in OV 1701; carrier gas, hydrogen 7 psi.

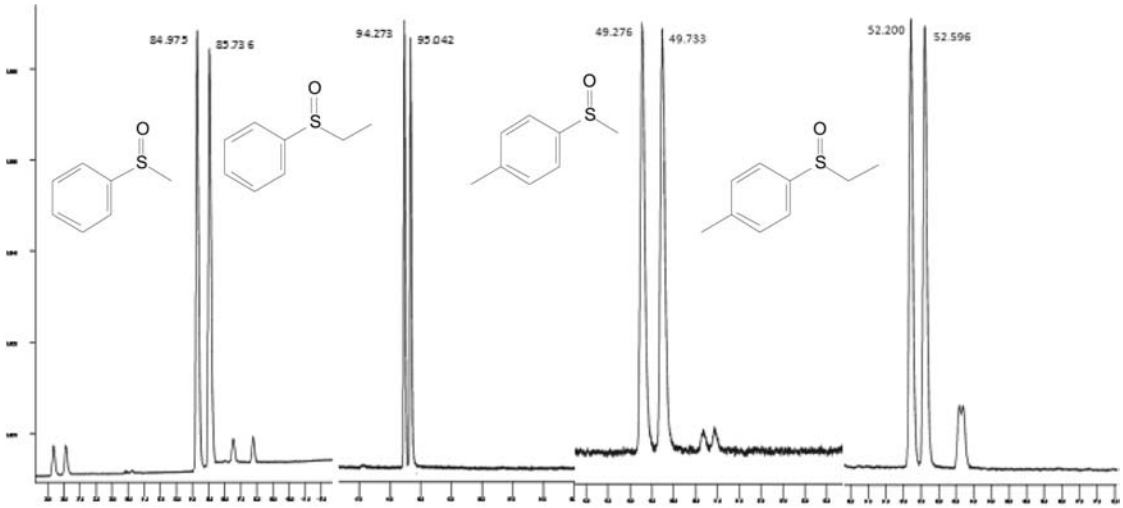


Figure 9. Enantiomeric separation of (+/–)-methylsulfinylbenzene and (+/–)-ethylsulfinylbenzene: 35-180 °C (1° min^{-1}), (+/–)-1-methyl-4-(methylsulfinyl) benzene and (+/–)-1-ethyl-4-(methylsulfinyl)benzene: 40-180 °C (2° min^{-1}) on a 25 m × 0.25 mm CCSF coated with heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin in OV 1701; carrier gas: hydrogen 7 psi.

Synthesis of heptakis (3-O-pentafluoropropionyl-2,6-di-O-pentyl)-β-cyclodextrin

Heptakis (2,6-di-*O*-pentyl)-β-cyclodextrin (100 mg; 47.25 μmol) was dissolved in dry mixture of chloroform (3.0 mL) and triethylamine (1.0 mL) and stirred by 5 min at room temperature. Pentafluoropropionic anhydride (146.46 mg; 0.47 mmol) was added at room temperature. After stirring for 1 h, 100 mL of cold water was added and extracted with dichloromethane. The organic layer

was washed with 100 mL of 5% HCl solution, 100 mL of $NaHCO_3$ saturated solution and 100 mL of water. After dry over anhydrous sodium sulfate the organic layer was concentrated. The crude product was chromatographed on silica gel column with ethyl acetate/hexane 1:9 (v/v), to give heptakis (3-*O*-pentafluoropropionyl-2,6-di-*O*-pentyl)-β-cyclodextrin (2,6-Pe-3-PFP-β-CD; 116 mg, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (t, 6H, *J* 6.36 Hz; 2 × ε-CH_3); 1.17-1.30 (m, 8H, 2 × δ-CH_2; 2 × γ-CH_2); 1.44-1.57 (m, 4H, 2 × β-CH_2); 3.33-3.47 (m, 6H, H-2, 2 × α-CH_2; H-6'); 3.87-3.99 (m, 3H, H-4, H-5, H-6); 5.01(d, 1H, *J* 2.80 Hz; H-1); 5.37 (t, 1H, *J* 8.24 Hz; H-3); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz): δ 13.7, 13.9 (2 × ε-CH_3); 22.3, 22.5 (2 × δ-CH_2); 27.6, 27.9 (2 × γ-CH_2); 28.3, 29.1 (2 × β-CH_2); 69.1 (C-6); 71.2 (C-5); 71.8, 71.9 (2 × α-CH_2); 75.9 (C-4); 76.7 (C-3); 77.4 (C-2); 97.9 (C-1); 105.87 (CF_2, J^1 264.9 Hz, J^3 38.4 Hz); 117.7 (CF_3, J^1 285.3 Hz, J^3 34.2 Hz); 115.4 (C=O, J^3 29.1 Hz). Peak assignments were made with the aid of two-dimensional ^{1}H-^{1}H and ^{1}H-^{13}C correlation (COSY and HMQC) techniques.

Column preparation

Fused silica columns (25 m × 0.25 mm i.d.) were prepared by static coating.[18] The inner surface of the fused silica tubing was submitting to a mild leaching with HCl. The 25% of the capillary is filled with a 2% aqueous HCl (0.5 mL). After the liquid has left the capillary both ends are sealed with a high temperature flame (microflame gas torch). The capillary is treated for 6 h at 220 °C in a GC oven. Then small pieces at the end of the capillary are cut of, 1mL of 2% aqueous HCl solution and subsequently 1 mL of methanol are filled into and pushed through the column with nitrogen (30 min) until the column appears dry. The column is again installed in a GC oven and conditioned for 2 h at 250 °C under nitrogen flow to ensure dehydratation of the surface. Columns were deactivated with diphenyltetramethyldisilazane (50% in pentane). For this, the solution is slowly pushed through the column and the ends are sealed immediately. Then the column is heated for 6 h in a GC oven at 330 °C. After cutting off the ends of the capillary its volume is filled with MeOH (1 mL) and followed by diethyl ether (1 mL). The solvent was removed by a nitrogen flow and the capillary is flushed 1 h with nitrogen. The capillary is then filled with a 0.2% solution of the cyclodextrine derivative and OV 1701 (1:1; m m^{-1}) according to the procedure described previously.[2]

Acknowledgements

Financial support for this work was provided by the CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico-Brazil). The authors thank Prof. Anita J. Marsaioli at the Chemistry Institute of the State University of Campinas, Brazil, to supply the racemic sulfur compounds.

References

1. Hedges, R. A.; *Chem. Rev.* **1998**, *98*, 2035.
2. König, W. A.; *Gas Chromatographic Enantioseparation with Modified Cyclodextrins*; Heidelberg: Huethig Verlag, Germany, 1992.
3. Schurig, V.; Nowotny, P.; *Angew. Chem., Int. Ed.* **1990**, *29*, 939.
4. Schurig V.; *J. Chromatogr*., *A* **2002**, *965*, 315.
5. Schurig, V.; Schmidt, R.; *J. Chromatogr*., *A* **2003**, *1000*, 311.
6. Singh, M.; Sharma, R.; Banerjee, U. C.; *Biotechnol. Adv.* **2002**, *20*, 341.
7. Spanik, I.; Krupcik, J.; Scacani, I.; Sandra, P.; Armstrong, D. W.; *J. Chromatogr*., *A* **2005**, *1071*, 59.
8. Szetjli, J.; *Chem. Rev*. **1998**, *98*, 1743.
9. Ward, T. J.; *Anal. Chem.* **2002**, *74*, 2863.
10. Grisales, J. O.; Lebed, P. J.; Keunchkarian, S.; González, F. R.; Castells, C. B.; *J. Chromatogr*., *A* **2009**, *1216*, 6844.
11. Bicchi, C.; Cagliero, C.; Liberto, E.; Sgorbini, B.; Martina, K.; Cravotto, G.; Rubiolo, P.; *J. Chromatogr*., *A* **2010**, *1217*, 1106.
12. König, W. A.; Gehrcke, B.; Icheln, D.; Evers, P.; Dönnecke, J.; Wang, W.; *HRC- J. High. Resolut. Chromatogr.* **1992**, *15*, 367.
13. Bicchi, C.; Artuffo, G.; D'Amato, A.; Manzin, V.; Galli, A.; Galli, M.; *HRC- J. High. Resol. Chromatogr.* **1993**, *16*, 209.
14. Bicchi, C.; D'Amato, A.; Manzin, V.; Galli, A.; Galli, M.; *J. Chromatogr*., *A* **1994**, *666*, 137.
15. König, W. A.; Hochmuth, D. H.; *J. Chromatogr. Sci*. **2004**, *42*, 402.
16. Bicchi, C.; Blumberg, L.; Cagliero, C.; Cordero, C.; Rubiolo, P.; Liberto, E.; *J. Chromatogr*., *A* **2010**, *1217*, 1530.
17. König, W. A.; Krebber R.; Wenz, G.; *HRC- J. High. Resolut. Chromatogr.* **1989**, *12*, 641.
18. König, W. A.; Icheln, D.; Runge, T.; Pforr, I.; Krebs, A.; *HRC- J. High. Resolut. Chromatogr.* **1990**, *13*, 702.
19. Takatani, M.; Matsuo, I.; Ito, Y.; *Carbohydr. Res*. **2003**, *338*, 1073.
20. Grob, K.; *Making and Manipulating Columns for Gas Chromatography*, Heidelberg: Huethig Verlag, Germany, 1986.

Submitted: September 17, 2009
Published online: July 1, 2010