

# Cyclodextrins as Chiral Stationary Phases in Capillary Gas Chromatography

## Part IV: Heptakis(2,3,6-tri-*O*-pentyl)- $\beta$ -cyclodextrin<sup>1)</sup>

W. A. König\*, S. Lutz, M. Hagen, and R. Krebber

Institut für Organische Chemie, Universität Hamburg, D-2000 Hamburg 13, FRG

G. Wenz

Max-Planck-Institut für Polymerforschung, D-6500 Mainz, FRG

K. Baldenius, J. Ehlers, and H. tom Dieck

Institut für Anorganische und Angewandte Chemie, Universität Hamburg, D-2000 Hamburg 13, FRG

### Key Words:

Enantioselective gas chromatography

Cyclodextrin

Alcohols

Hydroxy acids

Carbohydrates

Cyanohydrins

Olefins

Alkyl halides

### Summary

*O*-Perpentylated  $\beta$ -cyclodextrin has been evaluated as chiral stationary phase in capillary gas chromatography. Enantioselectivity is observed towards many chiral hydroxy compounds, including cyanohydrins and carbohydrates. Most importantly, the enantiomers of many olefins and alkyl halides can be resolved on this chiral phase. The thermal stability of the cyclodextrin derivative exceeds 200°C.

### 1 Introduction

In continuation of our investigations on enantioselective gas chromatography using modified cyclodextrins as chiral stationary phases [1-4] we have now studied the properties of heptakis(2,3,6-tri-*O*-pentyl)- $\beta$ -cyclodextrin. As already stated for the 3-*O*-acetylated 2,6-di-*O*-pentylated derivatives of  $\alpha$ - and  $\beta$ -cyclodextrin, we also recognized a striking difference in enantioselectivity of the fully pentylated cyclodextrin derivatives in spite of the close structural relationship. The unique properties with regard to chiral recognition of perpentylated  $\beta$ -cyclodextrin are described in the following.

### 2 Experimental

The preparation of perpentylated  $\beta$ -cyclodextrin proceeded analogously to that of the corresponding  $\alpha$ -cyclodextrin derivative [2]. Pyrex glass capillaries of about 40 m length and 0.2 mm i.d. were coated by the static procedure [5] as described previously [6].

The hydroxy compounds investigated in this study were trifluoroacetylated with trifluoroacetic anhydride (50  $\mu$ l) in dichloromethane (200  $\mu$ l) at room temperature for 10-30 min in screw cap vials with Teflon-lined caps. Carbohydrates were converted into methyl glycosides by heating the samples in 1 ml of 1.5 N methanolic hydrogen chloride for 30 min at 100°C. After removal of the excess reagent in a stream of nitrogen, trifluoroacetylation proceeded as described above, however at 100°C for 30 min. For gas chromatographic investigation the samples were dissolved in dichloromethane after removing the excess reagent. Gas chromatographic investigations were performed on a Carlo Erba Model 2101 apparatus with split injection and flame ionization detection. Hydrogen was used as carrier gas.

### 3 Results and Discussion

Peralkylated and partially alkylated/acetylated cyclodextrin derivatives proved to be highly enantioselective chiral stationary phases for capillary gas chromatography. We have already shown that many hydroxy compounds, including carbohydrates [1,7], polyols [7], diols [4,8] epoxy alcohols [9], and hydroxy acids [2] can be separated as trifluoroacetylated derivatives at low column temperatures. On glass capillaries coated with perpentylated  $\beta$ -cyclodextrin some alcohols are separated which could not be separated before. Two examples are shown in **Figures 1** and **2**. In the case of grandisol, a pheromone of bark beetles [10], the separation of the enantiomers is possible in spite of the fact that the hydroxy group is separated from the chiral center by 2 carbon atoms.

**Figure 3** shows the separation of some cyanohydrins. These compounds can be prepared enzymatically in high enantiomeric excess [11]. The proof of their enantiomeric purity is of great interest since cyanohydrins are important intermediates for the preparation of amino and hydroxy acids.

<sup>1)</sup> Part III: HRC & CC 11 (1988) 621.

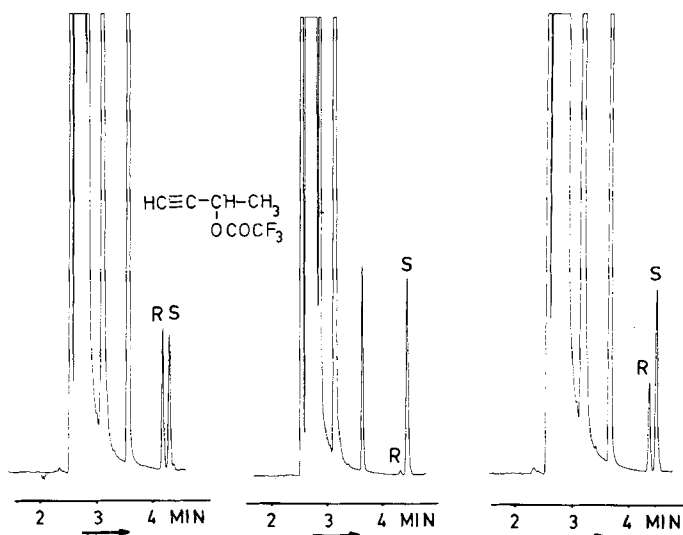


Figure 1

Enantiomer separation of 1-butyn-3-ol after trifluoroacetylation (the samples were obtained from *K. Weber, Universität Hamburg*). 42 m glass capillary column with perpentyl- $\beta$ -cyclodextrin. Column temperature 20°C; carrier gas 1 bar hydrogen.

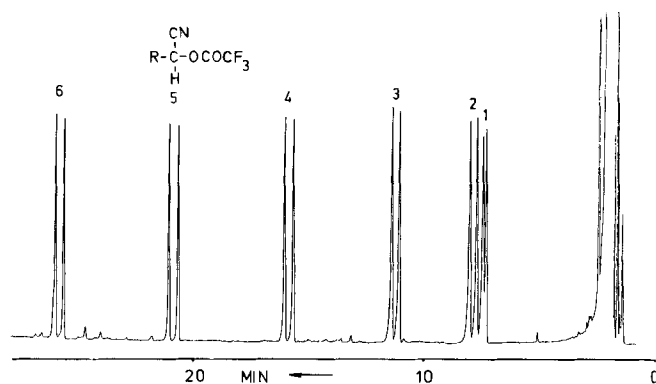


Figure 3

Enantiomer separation of cyanohydrins after trifluoroacetylation [ $R = n$ -propyl (1), isobutyl (2),  $n$ -butyl (3),  $n$ -pentyl (4),  $n$ -hexyl (5),  $n$ -heptyl (6)]. ( $R$ )-enantiomers are eluted before ( $S$ )-enantiomers. 40 m glass capillary column with perpentyl- $\beta$ -cyclodextrin. Column temperature 50°C; 2°/min to 180°C = carrier gas 1 bar hydrogen.

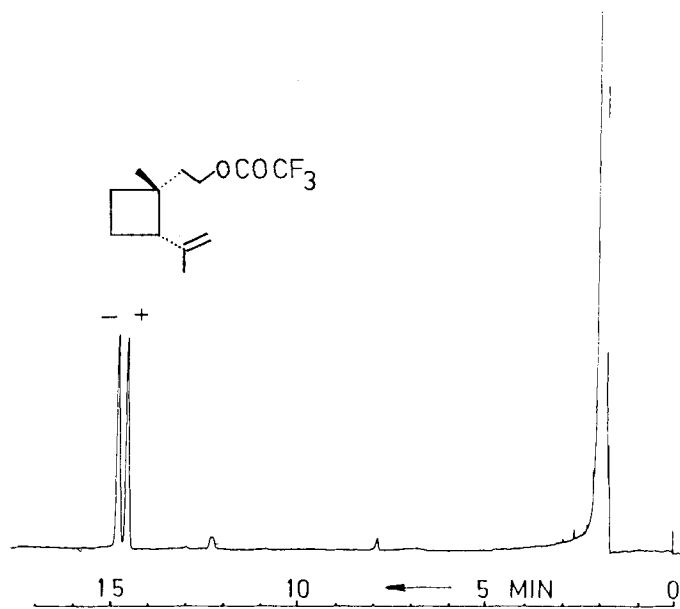


Figure 2

Enantiomer separation of grandisol after trifluoroacetylation (the sample was obtained from *Prof. W. Francke, Universität Hamburg*). Column as in Figure 1. Column temperature 90°C; carrier gas 1 bar hydrogen.

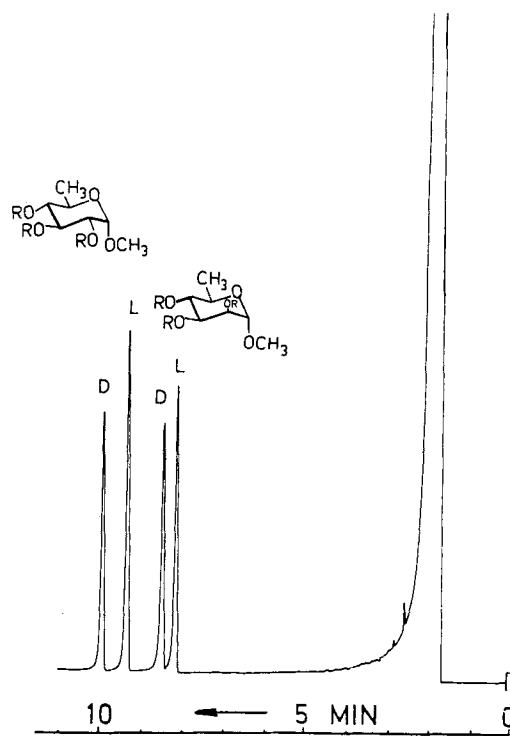


Figure 4

Enantiomer separation of  $\alpha$ -methyl rhamnoside and  $\alpha$ -methyl quinovoside after trifluoroacetylation. Column as in Figure 1. Column temperature 90°C; carrier gas 1 bar hydrogen.

Although trifluoroacetylated carbohydrates could be separated on any of the cyclodextrin derivatives investigated so far the best separation of 6-deoxy sugars was obtained on perpentylated  $\beta$ -cyclodextrin (Figure 4). It should be mentioned that the *D*-enantiomer of rhamnose was only recently identified for the first time as a constituent of a bacterial polysaccharide [12], while the *L*-enantiomer is very common as a constituent of plants and microorganisms.

Unlike the isopropyl urethanes of  $\alpha$ -hydroxy acid esters which can be very well separated on chiral polysiloxane phases as XE-60-*L*-valine-*(S)*- $\alpha$ -phenylethylamide [13] or Chirasil-val [14], only the lower homologues of trifluoroacetylated  $\alpha$ -hydroxy acid methyl esters can be separated on alkylated cyclodextrins. As shown in Figure 5 the optimum of enantioselective interaction differs for pentylated  $\alpha$ - and  $\beta$ -cyclodextrins. This clearly indicates that the dimension of the cavity of the macrocyclic

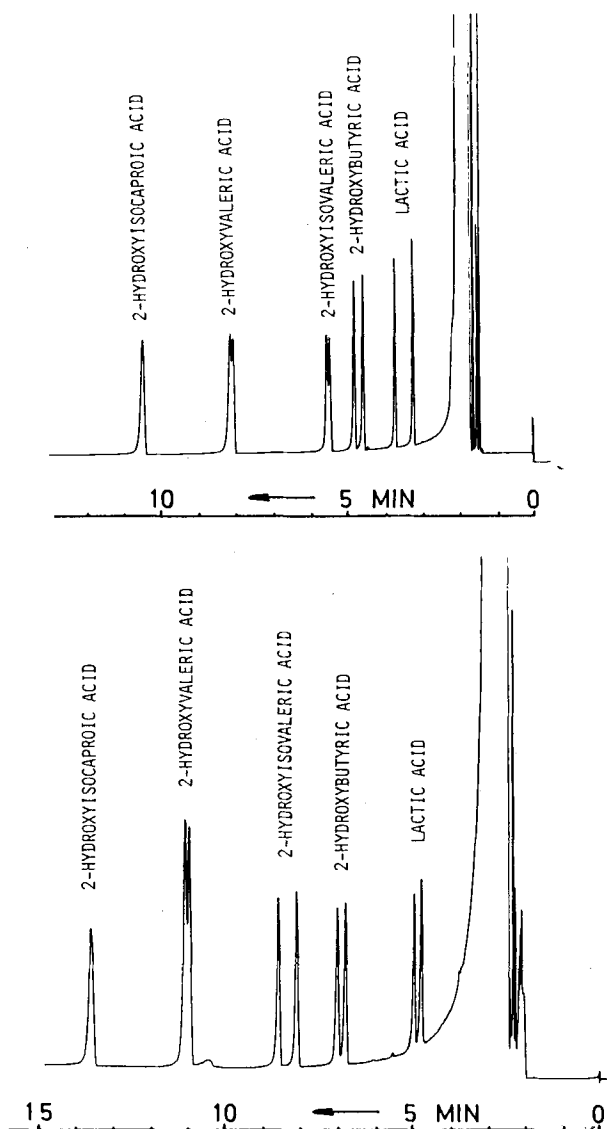


Figure 5

Enantiomer separation of 2-hydroxy acid methyl esters after trifluoroacetylation. Upper part: 40 m glass capillary column with perpentyl- $\alpha$ -cyclodextrin, 50°C; lower part: 40 m glass capillary with perpentyl- $\beta$ -cyclodextrin, 50°C. Carrier gas 1 bar Hz.

system plays an important role in the enantioselective inclusion of the chiral substrates.

**Figure 6** shows the separation of the enantiomers of mandelic acid. In this case substitution of the 3- and 4-position of the aromatic ring with hydroxy- or methoxy groups does not interfere with the inclusion. Both of the 3,4-disubstituted isomers are separated very well.

Enantioselective interaction of unmodified  $\alpha$ -cyclodextrin with olefins and even saturated hydrocarbons was already observed by *Sybiliska et al.* [15] in an investigation of  $\beta$ -pinene and its hydrogenation products. *Schurig* and *Nowotny* [16] recently reported the separation of  $\alpha$ -pinene and incomplete separation of limonene on glass capillaries coated with permethylated  $\beta$ -cyclodextrin diluted with the polysiloxane OV-1701. We found

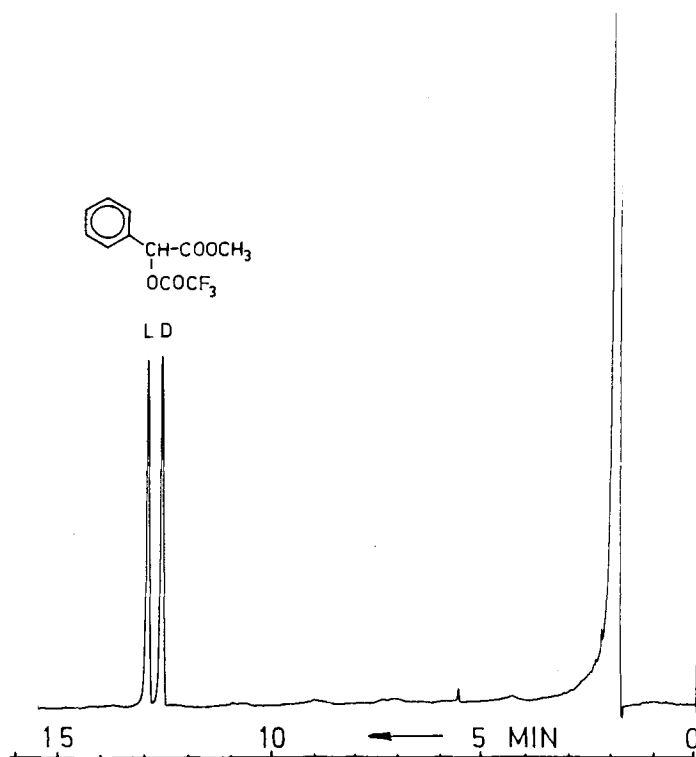


Figure 6

Enantiomer separation of mandelic acid methyl ester after trifluoroacetylation. Column as in Figure 1. Column temperature 115°C; carrier gas 1 bar Hz.

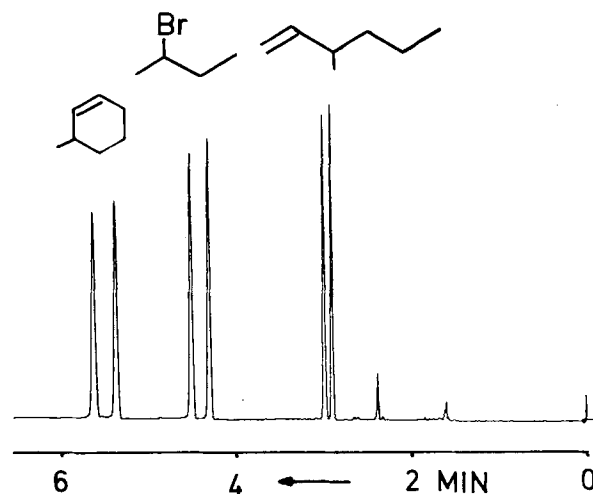


Figure 7

Enantiomer separation of 3-methyl-1-hexene, 2-bromobutane, and 3-methyl-cyclohexene. Column as in Figure 1. Column temperature 30°C; headspace injection; carrier gas 1 bar Hz.

that many different chiral olefins and dienes can be resolved on perpentylated  $\beta$ -cyclodextrin. In a previous communication [17] we have already demonstrated the use of this phase for the determination of the enantiomeric excess of olefins prepared by chiral catalysis. In **Figure 7** the separation of 3-methyl-1-hexene and 3-methyl-cyclohexene is shown, while **Figure 8**

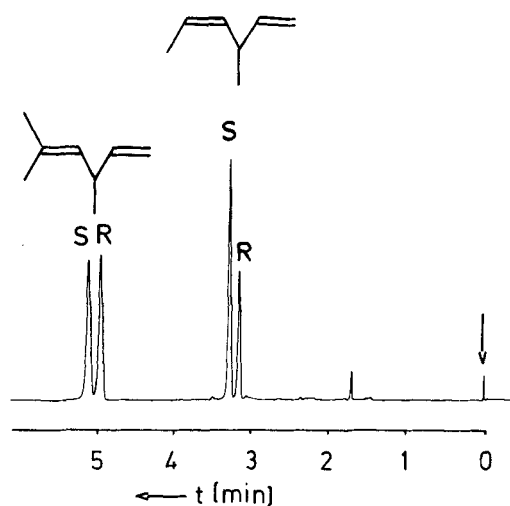


Figure 8

Enantiomer separation of 3-methyl-1,4(Z)-hexadiene and 3,5-dimethyl-1,4-hexadiene. Column as in Figure 1. Column temperature 30°C; headspace injection; carrier gas 1 bar Hz.

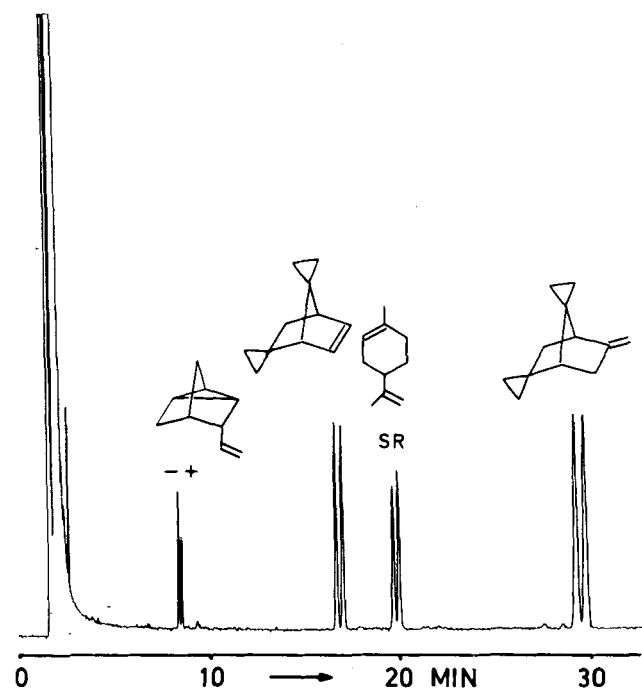


Figure 9

Enantiomer separation of some cyclic olefins (the cyclopropane anelated compounds were obtained from Prof. A. de Meijere [19], Universität Hamburg). Column as in Figure 1. Column temperature 70°C; carrier gas 1 bar hydrogen.

gives an example for the separation of dienes, one of which was prepared by enantioselective synthesis [17]. Due to the high volatility of these compounds the headspace injection technique had to be used in these examples. **Figure 9** demonstrates the resolution of some cyclic olefins including limonene. Apparently chiral recognition or enantioselective inclusion of chiral

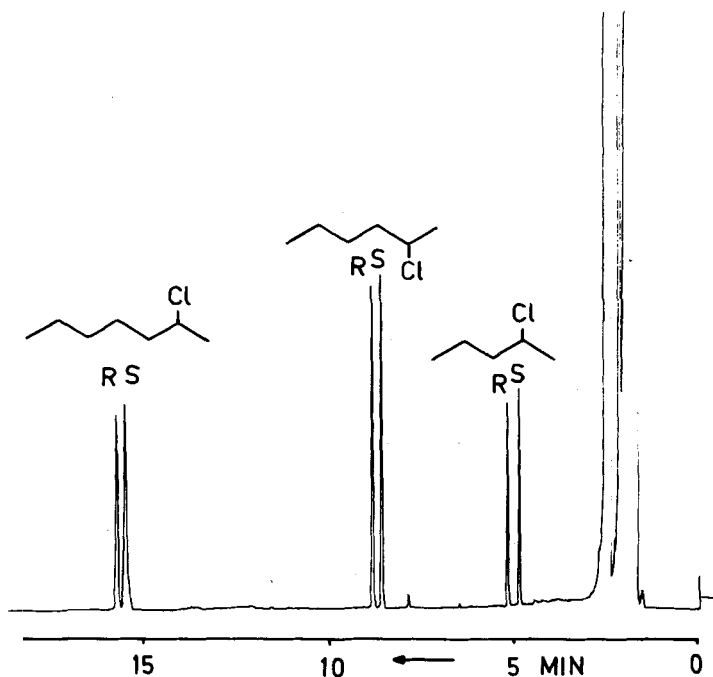


Figure 10

Enantiomer separation of 2-chloroalkanes [(S)-enantiomers are eluted before (R)-enantiomers]. Column as in Figure 1. Column temperature 60°C; carrier gas 1 bar Hz.

olefins is very sensitive to structural changes. 4-Methyl-1-hexene and 4-methylcyclohexene could not be resolved.

Finally, we found that perpentylated  $\beta$ -cyclodextrin is highly enantioselective towards chiral chloro- and bromo-alkanes. The enantiomers of 2-chlorobutane to 2-chlorooctane are completely separated with slightly decreasing separation factors ( $\alpha$ -values) with increasing chain length (**Figure 10**). The (S)-enantiomers are eluted prior to the (R)-enantiomers, provided that the conversion of 2-alkanols to 2-chloroalkanes with thionyl chloride in dioxane proceeds under retention of configuration as described by Bartlett and Herbrandson [18].

In addition to 2-chloro- and 2-bromo-alkanes (Figure 7) 1,2-dibromohexane could be separated. In this case the higher homologues 1,2-dibromoheptane and 1,2-dibromooctane were no longer resolved.

#### 4 Conclusion

Enantiomeric resolution of different types of trifluoroacetylated hydroxy compounds is demonstrated using perpentylated  $\beta$ -cyclodextrin as a chiral stationary phase. This phase shows a remarkable enantioselectivity towards chiral olefins and alkyl halides. In spite of the great structural resemblance with the corresponding  $\alpha$ -cyclodextrin derivative the pentylated  $\beta$ -cyclodextrin exhibits unique properties with regard to enantioselectivity. In the case of  $\alpha$ -hydroxy acid esters, the dependence of substrate specificity upon the dimensions of the cavity of the cyclodextrin derivatives can be demonstrated.

### Acknowledgment

This work was in part supported by the Bundesminister für Forschung und Technologie (Project No. 0319134A).

### References

- [1] W. A. König, S. Lutz, P. Mischnick-Lübbecke, B. Brassat, and G. Wenz, *J. Chromatogr.* **447** (1988) 193.
- [2] W. A. König, S. Lutz, and G. Wenz, *Angew. Chem.* **100** (1988) 989; *Angew. Chem. Int. Ed. Engl.* **27** (1988) 979.
- [3] W. A. König, S. Lutz, G. Wenz, and E. von der Bey, *HRC & CC* **11** (1988) 506.
- [4] W. A. König, S. Lutz, C. Colberg, N. Schmidt, G. Wenz, E. von der Bey, A. Mosandl, C. Günther, and A. Kustermann, *HRC & CC* **11** (1988) 621.
- [5] J. Bouche and M. Verzele, *J. Gas Chromatogr.* **6** (1968) 501.
- [6] W. A. König and K. Ernst, *J. Chromatogr.* **280** (1983) 135.
- [7] W. A. König, P. Mischnick-Lübbecke, B. Brassat, S. Lutz, and G. Wenz, *Carbohydr. Res.* **183** (1988) 11.
- [8] W. A. König, S. Lutz, P. Mischnick-Lübbecke, B. Brassat, E. von der Bey, and G. Wenz, *Starch/Stärke* **40** (1988) 472.
- [9] W. A. König, S. Lutz, G. Wenz, G. Görgen, C. Neumann, A. Gäbler, and W. Boland, *Angew. Chem.* (in press).
- [10] W. Francke, M.-L. Pan, W. A. König, K. Mori, P. Puapoomchareon, H. Heuer, and J. P. Vite, *Naturwiss.* **74** (1987) 343.
- [11] F. Effenberger, Th. Ziegler, and S. Förster, *Angew. Chem.* **99** (1987) 491; *Angew. Chem. Int. Ed. Engl.* **26** (1987) 458.
- [12] R. J. Stack, Poster abstract No. A 109, XIVth Intern. Carbohydr. Symposium, Stockholm, 1988.
- [13] W. A. König, I. Benecke, and S. Sievers, *J. Chromatogr.* **238** (1983) 427.
- [14] H. Frank, J. Gerhardt, G. J. Nicholson, and E. Bayer, *J. Chromatogr.* **270** (1983) 159.
- [15] T. Koscielski, D. Sybilska, S. Belniak, and J. Jurczak, *Chromatographia* **21** (1986) 413.
- [16] V. Schurig and H.-P. Nowotny, *J. Chromatogr.* **441** (1988) 155.
- [17] J. Ehlers, W. A. König, S. Lutz, G. Wenz, and H. tom Dieck, *Angew. Chem.* **100** (1988) 164; *Angew. Chem. Int. Ed. Engl.* **27** (1988) 1556.
- [18] P. D. Bartlett and H. F. Herbrandson, *J. Amer. Chem. Soc.* **74** (1952) 5971.
- [19] A. de Meijere, K. Michelsen, R. Gleiter, and J. Spanget-Larsen, *Israel J. Chem.* (in press).

Ms received: November 10, 1988

Accepted: December 1, 1988