Summary

In 1988 lipophilic cyclodextrin derivatives were introduced in enantioselective gas chromatography. They belong to the most successfull chiral stationary phases. Since then a great number of acylated and alkylated cyclodextrin derivatives with different enantioselectivities were developed, which allow the enantioseparation of most volatile chiral compounds. The different reactivities of the primary and the secondary hydroxy groups of the cyclodextrins enables a great variety of substitution patterns. Small changes may strongly influence the enantioselectivity. As new structures are evolving on a daily basis by synthesis or as natural products, the pace and development of new cyclodextrin derivatives enantioselective capillary gas chromatography is under increasing pressure. Therefore, in the present study, persubstituted, bifunctionalized and monofunctionalized cyclodextrin derivatives were synthesized and evaluated as polysiloxane diluted chiral stitionary phases in capillary gas chromatography.

For the synthesis of the regioselectively persubstituted 6-TBDMS-2,3-Et-β-CD (**2**) and 6-TBDMS-2,3-MeD_3-β-CD (**3**), 6-TBDMS-β-CD (**1**), prepared by the method of Fügedi[107], was treated with iodoethane or iodotrideuteromethane, respectively. The pentyl substitution of the secondary hydroxyl groups of 6-TBDMS-γ-CD (**10**) and the following desilylation of the primary hydroxyl groups of the glucose units yielded 2,3-Pe-γ-CD (**12**). The treatment with iodotrideuteromethane or iodoethane afforded MeD_3-2,3-Pe-γ-CD (**13**) and 6-Et-2,3-Pe-γ-CD (**14**) (**Fig. 120**).

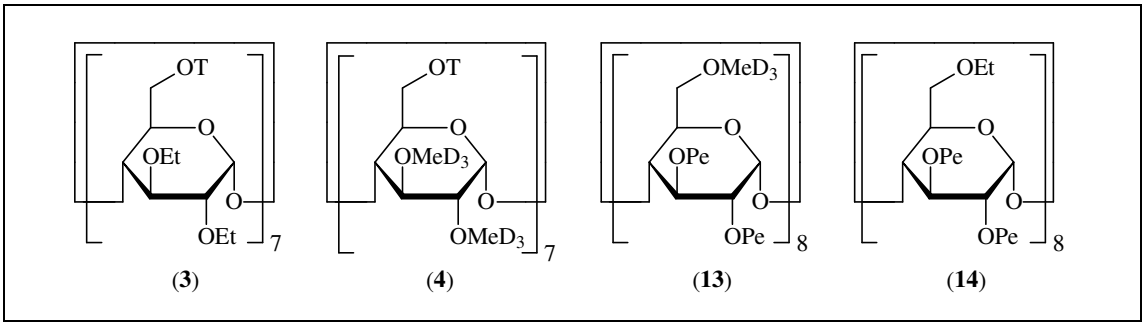

Fig. 120: Persubstituted cyclodextrin derivatives

The newly synthesized chiral selectors displayed different separation capabilities, but the separations on 6-TBDMS-2,3-Et-β-CD (**2**), 6-TBDMS-2,3-MeD_3-β-CD (**3**), 6-MeD_3-2,3-Pe-

γ-CD (**13**) and 6-Et-2,3-Pe-γ-CD (**14**) showed close similarities to the established phases 6-TBDMS-2,3-Me-β-CD and 6-Me-2,3-Pe-γ-CD. Remarkable, that the separations of 2-hydroxyhexanoic acid and linalool on 6-TBDMS-2,3-Et-β-CD (**2**) were improved in comparison with 6-TBDMS-2,3-Me-β-CD.

The substitution of the secondary side with more bulky substituents led to narrowing or deepening the opening at the secondary side. This seemed to be benificial for open-chain compounds, for which improved enantioselectivities were observed. The substitution of the primary side with more voluminous substituents led to narrowing of the opening at the secondary side and simultanously to a deepening of the cyclodextrin cavity because of steric hindrance between these substituents. The decreased enantioselectivity by narrowing the secondary side showed that the discrimination of enantiomers occurred predominantly inside the cyclodextrin cavity and not at the outer surface.

Synthesis of bifunctional cyclodextrin derivatives was possible by treatment of per-O-benzylated β-cyclodextrin with diisobutylaluminium hydride which resulted in 6A and 6D deprotected $6^A,6^D$-OH-2,3,6*-Bn-β-CD (**16**). The reaction with 1,6-dibromohexane and 1,4-dibromobutane yielded hexylene and butylene bridged derivatives $6^A,6^D$-Hex-2,3,6*-Bn-β-CD (**17**) and $6^A,6^D$-But-2,3,6*-Bn-β-CD (**20**), respectively. Reduction with sodium in liquid ammonia gave the debenzylated products $6^A,6^D$-Hex-β-CD (**18**) and $6^A,6^D$-But-β-CD (**21**) which were substituted to the permethylated capped products $6^A,6^D$-Hex-2,3,6*-Me-β-CD (**19**) and $6^A,6^D$-But-2,3,6*-Me-β-CD (**22**) (**Fig. 121**).

With these capped phases $6^A,6^D$-Hex-2,3,6*-Me-β-CD (**19**) and $6^A,6^D$-But-2,3,6*-Me-β-CD (**22**), not without surprise, a lot of enantiomer separations were achieved. $6^A,6^D$-Hex-2,3,6*-Me-β-CD (**19**) showed higher enantioselectivity than $6^A,6^D$-But-2,3,6*-Me-β-CD (**22**).

The access to the primary side of the cyclodextrin cavity is blocked by the capping. Inclusion and chiral recognition are only possible at the secondary side. The longer AD-hexylene bridge at the primary side of $6^A,6^D$-Hex-2,3,6*-Me-β-CD (**19**) in comparison to the butylene residue at $6^A,6^D$-But-2,3,6*-Me-β-CD (**22**) led to a more flexible cyclodextrin torus. Therefore, conformational changes by guest inclusion are possible which resulted in a stronger interaction between host and guest. But the more rigid conformation of $6^A,6^D$-But-2,3,6*-Me-β-CD (**22**) was more effective for the separation of enantiomers like *trans*-chlordane, mepivacain, methyprylon and ethosuximide which showed improved separations in comparison to $6^A,6^D$-Hex-2,3,6*-Me-β-CD (**19**).

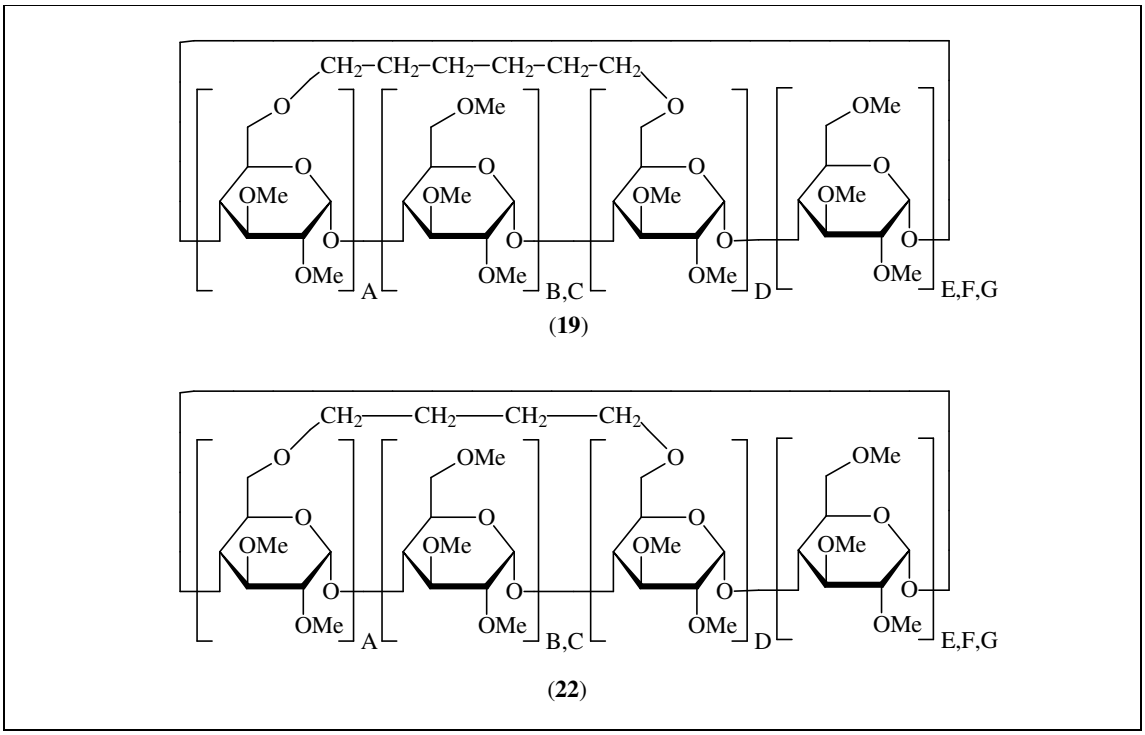

Fig. 121: Capped bifunctionalized cyclodextrin derivatives

Pentylation of $6^A,6^D$-OH-2,3,6*-Bn-β-CD (**16**),following reduction with sodium in liquid ammonia yielded $6^A,6^D$-Pe-β-CD (**24**), alkylated only in position 6A and 6D, which was methylated to $6^A,6^D$-Pe-2,3,6*-Me-β-CD (**25**). Silylation of the remaining five primary hydroxy groups of $6^A,6^D$-Pe-β-CD (**24**) with *tert*-butyldimethylsilyl chloride in pyridine[107] led to $6^A,6^D$-Pe-6*-TBDMS-β-CD (**26**). Methylation of the secondary hydroxy groups gave $6^A,6^D$-Pe-6*-TBDMS-2,3-Me-β-CD (**28**). Further silylation of $6^A,6^D$-Pe-6*-TBDMS-β-CD (**26**) yielded $6^A,6^D$-Pe-2' ,6*-TBDMS-β-CD (**27**) with only one silylated hydroxy group in position 2. Methylation of the remaining secondary hydroxyl groups gave $6^A,6^D$-Pe-3' ,6*-TBDMS-2,3*-Me-β-CD (**29**). As expected, migration of the single silyl group from position 2 to 3 took place. Silylation of both deprotected hydroxyl groups in $6^A,6^D$-OH-2,3,6*-Bn-β-CD (**16**) with *tert*-butyldimethylsilyl chloride led to $6^A,6^D$-TBDMS-2,3,6*-Bn-β-CD (**30**). After reduction and methylation of the nineteen debenzylated primary and secondary hydroxy groups $6^A,6^D$-TBDMS-2,3,6*-Me-β-CD (**32**) was obtained (**Fig. 122**).

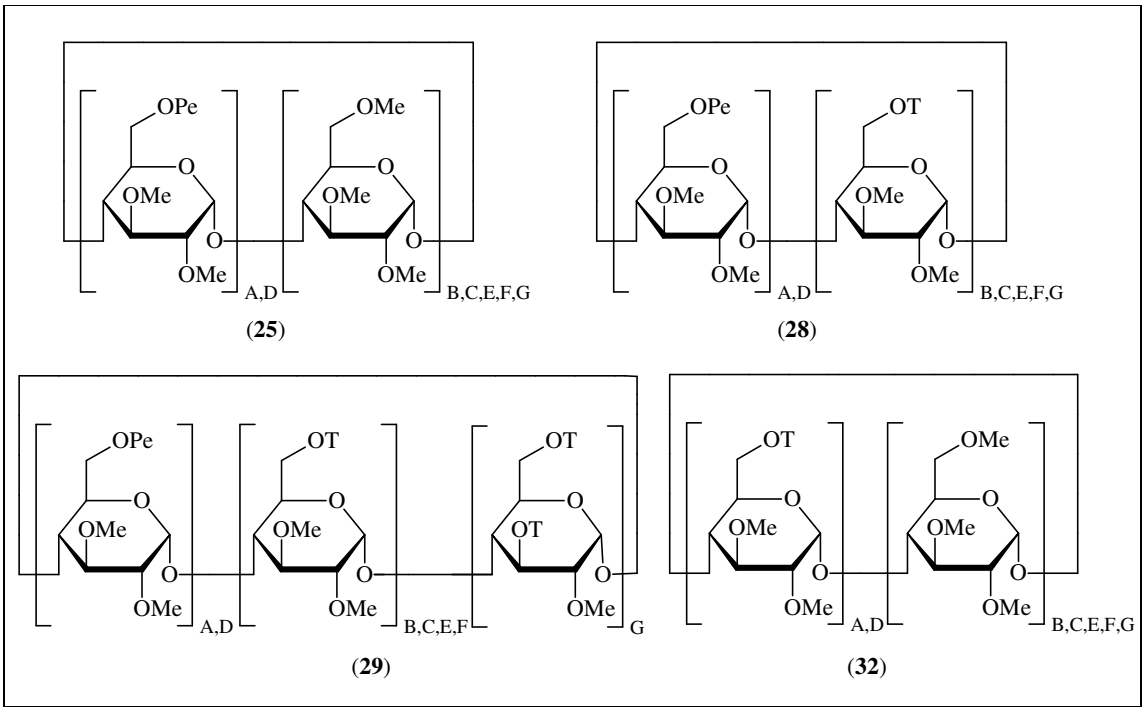

Fig. 122: Bifunctionalized cyclodextrin derivatives

$6^A,6^D$-Pe-2,3,6-Me-β-CD (**25**) and $6^A,6^D$-TBDMS-2,3,6-Me-β-CD (**32**) were also suitable for enantioselective gas chromatography and showed specifically high enantioselectivities for 2-hydroxy- and 2-halogenated carboxylic acids. Using $6^A,6^D$-TBDMS-2,3,6-Me-β-CD (**32**) separations of *trans*-heptachloroepoxide and *trans*-chlordane were achieved, while the same separations failed when position 6 was completely silylated to 6-TBDMS-2,3-Me-β-CD. $6^A,6^D$-TBDMS-2,3,6-Me-β-CD (**32**) showed interconversion of the enantiomers of Troeger's base in the stationary phase[262]. In comparison to 6-TBDMS-2,3-Me-β-CD on this phase the separation of metaxalone was highly improved. At $6^A,6^D$-Pe-6*-TBDMS-2,3-Me-β-CD (**28**) the separation of some alcohols and derivatives of carboxylic acids showed good results. The additional TBDMS group in position 3' of $6^A,6^D$-Pe-3',6*-TBDMS-2,3*-Me-β-CD (**29**) resulted in a nearly complete loss of enantioselectivity. Here only separations of camphor and menthol which could not be separated on $6^A,6^D$-Pe-6*-TBDMS-2,3-Me-β-CD (**28**) showed increased separation factors.

It appears that the substituents of the primary side show a strong influence on the dimensions of the secondary side and are of crucial importance for chiral recognition. In comparison to 6-TBDMS-2,3-Me-β-CD the synthesized bifunctionalized derivatives showed decreased enantioselctivity. Because of their smaller size the pentyl substitution at the primary side of $6^A,6^D$-Pe-2,3,6*-Me-β-CD (**25**) resulted in a wider opening at the secondary side in

comparison to the TBDMS groups of 6^A,6^D-TBDMS-2,3,6*-Me-β-CD (**32**). The molecular dimensions of 6^A,6^D-Pe-6-TBDMS-2,3-Me-β-CD (**28**) are nearly the same as in 6-TBDMS-2,3-Me-β-CD and thus, these stationary phases showed comparable enantioselectivities.

For monofunctionalization of 6-TBDMS-2,3-Me-β-CD at position 2, 2' ,6-TBDMS-β-CD (**33**) with one single silyl group in position 2 was treated under basic conditions with iodomethane, which induced a migration of the single silyl group from position 2' to 3' (ref.) to the rearranged 3' ,6-TBDMS-2,3*-Me-β-CD (**34**). After complete desilylation and resilylation of the primary hydroxy groups, 3'-OH-6-TBDMS-2,3*-Me-β-CD (**36**) was obtained with one single hydroxy group in position 3' . Alkylation with iodopentane or acylation with acetic anhydride yielded 3'-pentyl-substituted 3'-Pe-6-TBDMS-2,3*-Me-β-CD (**37**) and acetylated 3'-Ac-6-TBDMS-2,3*-Me-β-CD (**38**), respectively. Methylation of 2' ,6-TBDMS-β-CD (**33**) under weak basic conditions with methyl trifluoromethanesulfonate and 2,6-di-*tert*-butylpyridine in dichloromethane[248] led to 2' ,6-TBDMS-2*,3-Me-β-CD (**41**). Desilylation and introduction of the TBDMS-groups in position 6 gave 2'-OH-6-TBDMS-2*,3-Me-β-CD (**43**) with one single hydroxy group in position 2' . Alkylation with iodopentane or acylation with acetic anhydride yielded in position 2' pentyl-substituted 2'-Pe-6-TBDMS-2*,3-Me-β-CD (**44**) and acetylated 2'-Ac-6-TBDMS-2*,3-Me-β-CD (**45**), respectively (**Fig. 123**).

The monofunctionalized derivatives of 6-TBDMS-2,3-Me-β-CD with TBDMS groups in position 2 and 3 showed a loss of enantioselectivity which was much higher for the derivative with 2-silyl-substitutionewhere only a few separations were possible. Enantioselectivities of 3'-Pe-6-TBDMS-2,3*-Me-β-CD (**37**) and 2'-Pe-6-TBDMS-2*,3-Me-β-CD (**44**) were comparable to those of 6-TBDMS-2,3-Me-β-CD. In comparison to 6-TBDMS-2,3-Me-β-CD and 6-TBDMS-2,3-Ac-β-CD, 3'-Ac-6-TBDMS-2,3*-Me-β-CD (**38**) in general showed enhanced selectivity as shown the separations of γ-lactones and α-HCH. Separations were also possible in the case of 4-methyl-1-phenyl-1,3-pentanediol and *trans*-chlordane which could neither be separated by 6-TBDMS-2,3-Me-β-CD nor 6-TBDMS-2,3-Ac-β-CD. The synthesis of 3'-Ac-6-TBDMS-2,3*-Me-β-CD (**38**) combined the positive characteristics of 6-TBDMS-2,3-Me-β-CD and 6-TBDMS-2,3-Ac-β-CD. The separations of bromocyclene, oxychlordane, α-damascone, β-elemene, hexobarbital and gluthetimide are possible with 6-TBDMS-2,3-Me-β-CD but not with 6-TBDMS-2,3-Ac-β-CD. The separation of α-ionone showed the same elution order at 3'-Ac-6-TBDMS-2,3*-Me-β-CD (**38**) and 6-TBDMS-2,3-Me-β-CD while 6-TBDMS-2,3-Ac-β-CD showed opposite elution order. The separations of

linalyl acetate, citronellal and phenylalanine showed the contribution of enantioselectivity of 6-TBDMS-2,3-Ac-β-CD. These enantiomers could not be separated on 6-TBDMS-2,3-Me-β-CD. 2'-Ac-6-TBDMS-2*,3-Me-β-CD (**45**) and a 1:1 mixture of 6-TBDMS-2,3-Me-β-CD and 6-TBDMS-2,3-Ac-β-CD resulted in a significant loss of enantioselectivity.

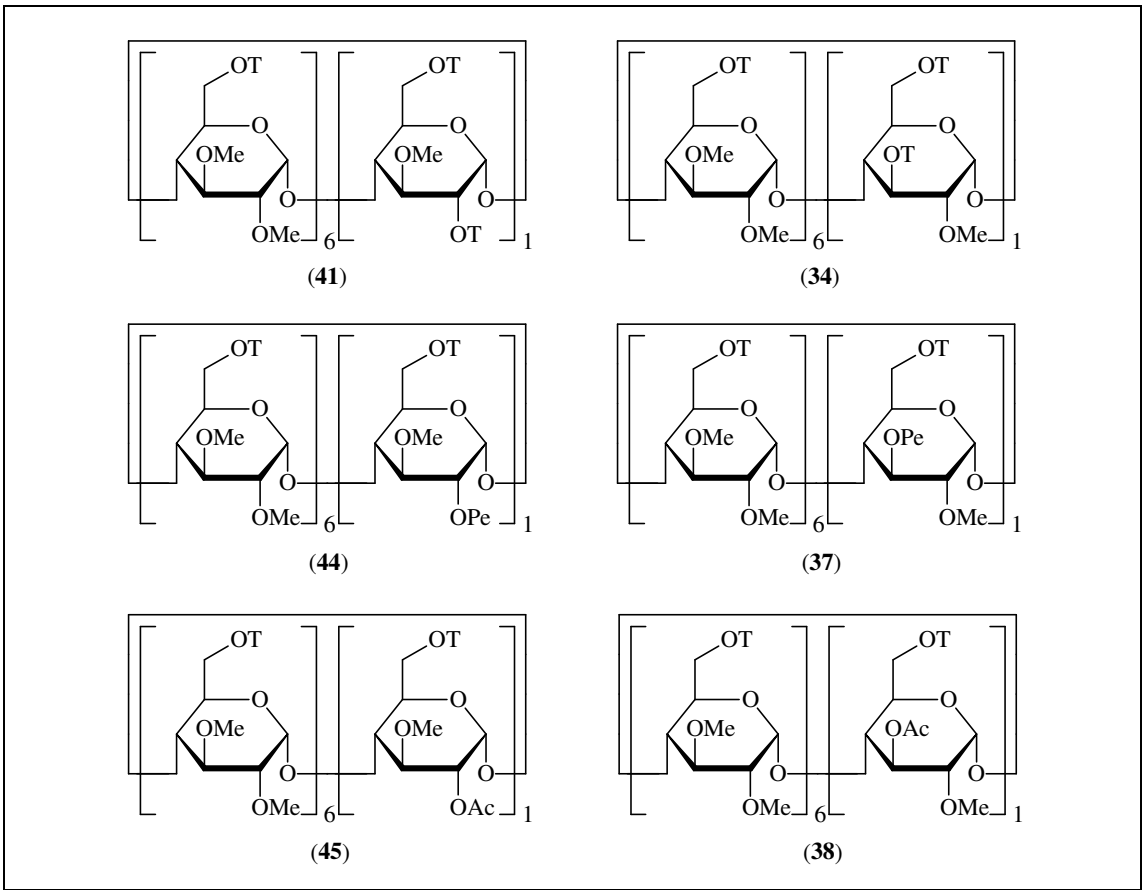

Fig. **123**: Monofunctionalized derivatives of 6-TBDMS-2,3-Me-β-CD

3'-monofunctionalization in comparison to that in 2'-position resulted in a predominantly positive influence on enantioselectivity. The more flexible pentyl substituents caused only minor differences in the enantioselective behaviour. Possibly steric and electrosterical effects result in different orientations of the TBDMS and acetyl residues in 3'- and 2'-position, respectively. While the TBDMS group in position 2 blocked the entrance to the cyclodextrin cavity the *tert*-butyl residue of the 3'-TBDMS group is orientated to the outer side. The inclusion of enantiomers, although lower in comparison to 6-TBDMS-2,3-Me-β-CD, was possible.

Monofunctionalized permethylated β-cyclodextrins with one pentyl or acetyl residue were obtained by two different strategies. The synthesis of 3'-Pe-2,3*,6-Me-β-CD (**40**) was achieved starting from 3'-Pe-6-TBDMS-2,3*-Me-β-CD (**37**) after desilylation and the following methylation of the primary hydroxyl groups. The synthesis of 3'-Ac-2,3*,6-Me-β-CD (**56**) was performed starting from 2,6-Me-β-CD (**49**) through monofunctionalization in position 3' with *tert*-butyldimethylsilyltrifluoromethane sulfonate and 2,6-lutidine in dichloromethane[249] to yield 3'-TBDMS-2,6-Me-β-CD (**50**). Methylation and desilylation gave permethylated 3'-OH-2,3*,6-Me-β-CD (**55**) with one single hydroxyl group in position 3' . Reaction with acetic anhydride afforded 3'-Ac-2,3*,6-Me-β-CD (**56**) (**Fig. 124**).

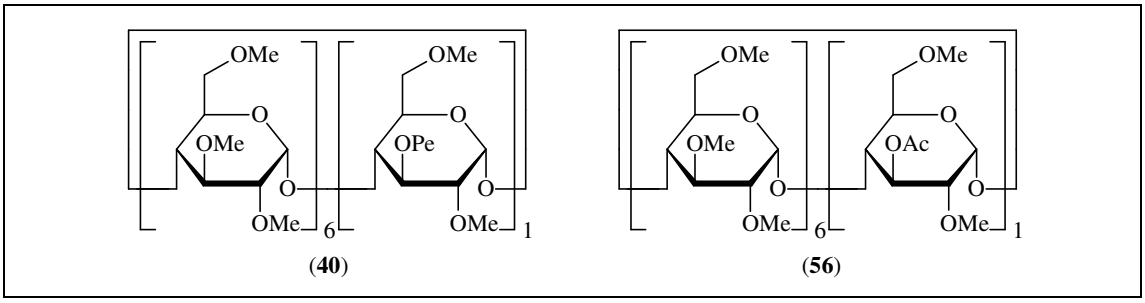

Fig. 124: Monofunctionalized derivatives of 2,3,6-Me-β-CD

3'-Pe-2,3*,6-Me-β-CD (**40**) and 3'-Ac-2,3*,6-Me-β-CD (**56**) were suitable for enantiomer separations. It showed that 3'-Pe-2,3*,6-Me-β-CD (**40**) were more suitable for unpolar agrochemicals, alcohols and phenyl carboxylic acids than 3'-Ac-2,3*,6-Me-β-CD (**56**) which showed better separation capabilities for polar amino acids, amines and 2-hydroxy carboxylic acids.

Pentylation of 2',6-TBDMS-β-CD (**33**) led to the rearranged 3',6-TBDMS-2,3*-Pe-β-CD (**46**). After desilylation and complete methylation with iodomethane 3',6-Me-2,3*-Pe-β-CD (**48**) was obtained. For the monofunctionalization of 2,6-Me-3-Pe-β-CD in position 3' the six hydroxy groups of 3'-TBDMS-2,6-Me-β-CD (**50**) were alkylated with iodopentane. After deprotecting the single TBDMS group in 3-position, 3'-OH-2,6-Me-3-Pe-β-CD (**52**) reacted with acetic anhydride to 3'-Ac-2,6-Me-3-Pe-β-CD (**53**).

For the monofunctionalization of 3-Bc-2,6-Pe-γ-CD (Lipodex E®) 2,6-Pe-γ-CD (**57**) was applied to obtain three different analogues. Pentylation of one single hydroxy group in position 3' followed by treatment with butyric acid and butyric acid anhydride yielded 3-Bc-2,3',6-Pe-γ-CD (**59**). Silylation of one single hydroxy group in position 3' with *tert*-

butyldimethylsilyltrifluoromethane sulfonate[249] led to 3'-TBDMS-2,6-Pe-γ-CD (**60**). Acylation of the free hydroxy groups resulted in 3'-TBDMS-3*-Bc-2,6-Pe-γ-CD (**61**). Desilylation to 3'-OH-3*-Bc-2,6-Pe-γ-CD (**62**) was followed by acetylation to 3'-Ac-3*-Bc-2,6-Pe-γ-CD (**63**). After silylation of the primary hydroxy groups in native γ-cyclodextrin and regioselective pentyl-substitution of the C-2 hydroxy groups 6-TBDMS-2-Pe-γ-CD (**64**) was obtained. Desilylation and regioselective methylation of the primary hydroxy groups led to 6-Me-2-Pe-γ-CD (**66**) which was treated with *tert*-butyldimethylsilyltrifluoromethane sulfonate to for successful monofunctionalization in position 3' . Pentylation of the position 3 and desilylation gave 3'-OH-6-Me-2,3*-Pe-γ-CD (**69**) which was treated with acetic anhydride to obtain 3'-Ac-6-Me-2,3*-Pe-γ-CD (**70**) (**Fig. 125**).

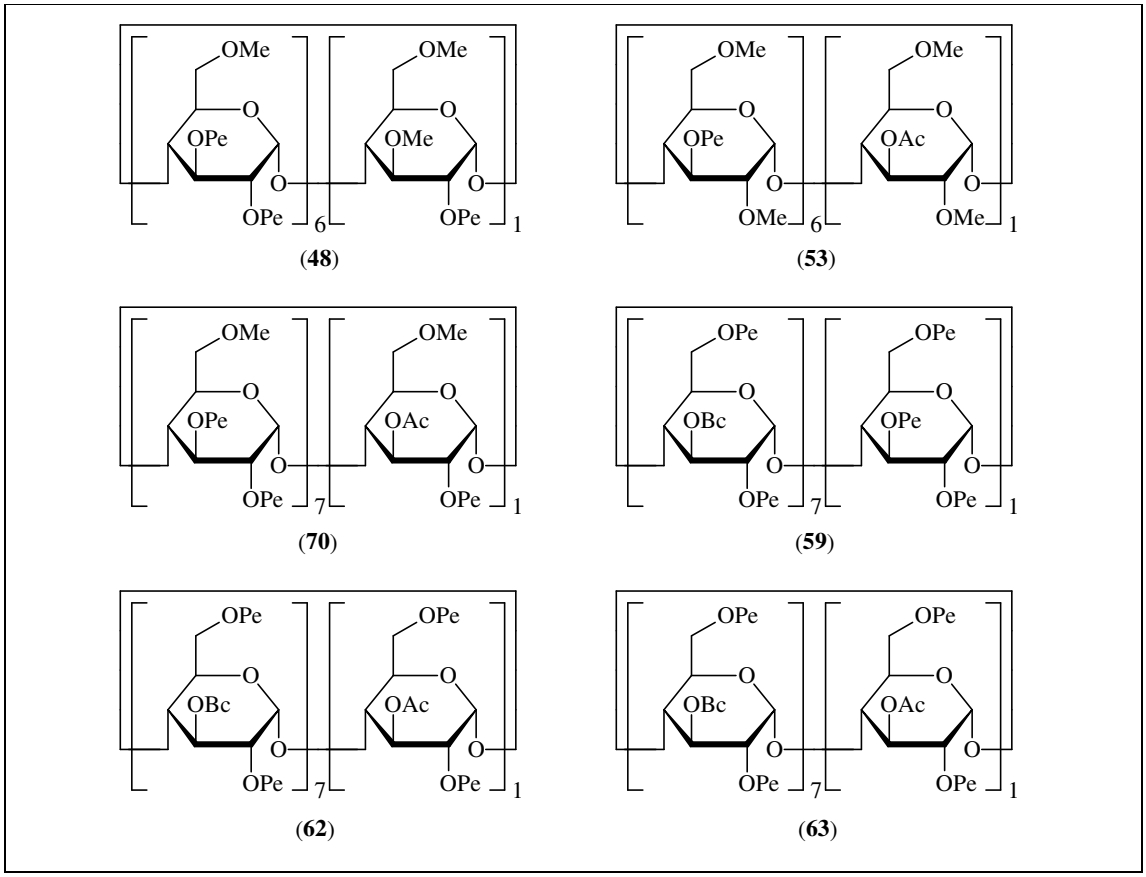

Fig. 125: Monofunctionalized derivatives of 6-Me-2,3-Pe-β-CD, 2,6-Me-3-Pe-β-CD, Lipodex E and 6-Me-2,3-Pe-γ-CD

3' ,6Me-2,3*-Pe-β-CD (**48**), 3'-Ac-3*-Pe-2,6-Me-β-CD (**53**) and 3'-Ac-6-Me-2,3*-Pe-γ-CD (**70**) were also suitable as chiral stationary phases, however as compared to the "mother phases" a significant loss of enantioselctivity was observed. Only the separations of 2-

hydroxy carboxylic acids were possible on 3'-Ac-3*-Pe-2,6-Me-β-CD (**53**) and 3'-Ac-3*-Pe-2,6-Me-β-CD (**53**) with comparable results.

3*-Bc-2,3' ,6-Pe-γ-CD (**59**), 3'-OH-3*-Bc-2,6-Pe-γ-CD (**62**) and 3'-Ac-3*-Bc-2,6-Pe-γ-CD (**63**) exhibuted some enantioselective capabilities. But these cyclodextrin derivatives showed differences in comparison to Lipodex E®. While the separations on 3*-Bc-2,3' ,6-Pe-γ-CD (**59**) were comparable, the selectivities on 3'-Ac-3*-Bc-2,6-Pe-γ-CD (**63**) were mostly decreased. In some cases a total loss of enantioselectivity was observed. The separations of alcohols and halogenated carboxylic acids were improved at using 3*-Bc-2,3' ,6-Pe-γ-CD (**59**) and for amino acids comparable with Lipodex E.

The 3'-monofunctionalization could result in an irregular distribution of the remaining C-2 and C-3 substituents at the opening of the secondary side. This irregular distribution could be caused by narrowing of the secondary side because of resulting attractive and repulsive interactions. As a result, the inclusion and discrimination of enantiomers were disturbed. The absence of one substituent or the introduction of one longer substituent seemed to result in a more regular distribution of the substituents at the opening of the secondary side. The enantioselectivity changed dramatically.

In the present work it could be shown that chiral recognition of enantiomers is mainly caused by inclusion in the cyclodextrin cavity on the secondary side. Adsorption at the outer surface of the cyclodextrin does not seem to make any difference. For the discrimination of enantiomers a conformational change and a change in the dimensions of the secondary side are of importance. Different substitution patterns at the primary side changed the enantioselectivity and confirmed the influence of these substituents. The substituents in position 2 and 3 showed unpredictable influences on the selectivity. Monofunctionalizations demonstrated that a chiral separation could be positively influenced by 3'-substituents in comparison to 2'-substituents.

With 3'-Ac-6-TBDMS-2,3*-Me-β-CD (**38**) a stationary phase was synthesized where the separation capabilities of 6-TBDMS-2,3-Me-β-CD and 6-TBDMS-2,3-Ac-β-CD are combined. This new chiral selector displayed considerably improved and new enantioselectivities for different compound classes.