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Indirect and direct approaches in the synthesis of a new mono-6-*O*-benzyl methylated γ-cyclodextrin as chiral selector for enantioselective gas chromatography

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Abstract—6^{I}-*O*-Benzyl-$2^{I–VIII}$, $3^{I–VIII}$, $6^{II–VIII}$-tricosa-*O*-methyl-γ-cyclodextrin was synthesized using indirect and direct approaches. The first indirect strategy consists of a multi-step sequence including the ring opening of the permethylated α-cyclodextrin, elongation of the chain with a 6-*O*-benzyl methylated disaccharide derivative, and macrocyclization. The direct method deals with a selective mono-6-*O*-TBDMS protection, permethylation, deprotection, and benzylation sequence of γ-cyclodextrin. The results clearly show the higher efficiency of the direct approach but demonstrate the feasibility of the insertion of a modified maltose derivative (indirect method). The new mono-6-O-modified methylated γ-cyclodextrin was used as a selector for the preparation of the new chiral stationary phase. Preliminary enantioselective gas chromatography applications are also reported.
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1. Introduction

The determination of the enantiomeric purity of chiral drugs is essential nowadays and can be efficiently achieved by various enantioselective chromatographic methods: gas chromatography (GC), high performance liquid chromatography (HPLC), and supercritical fluid chromatography (SFC). Among them, gas chromatography using chiral stationary phases (CSPs) based on modified cyclodextrins (CD) is the most commonly used technique for volatile compounds, because of the structure and binding properties of CD.[1,2] The fully methylated cyclodextrin derivatives (α-, β-, or γ-CD) are used the most owing to their easy preparation, thermal stability and ability to recognize a wide range of compounds.

To extend the scope of chiral recognition, new modified cyclodextrins are needed.[1,2] Among them, monofunctionalized asymmetric derivatives have a particular interest due to the loss of the pseudo *n*-axis of symmetry which may strongly modify the shape of the cyclodextrin cavity. New monofunctionalized CD can be obtained from indirect or direct methods. Scheme 1 illustrates both strategies applied to γ-cyclodextrin.

In the indirect method, a great number of modifications are possible since this approach involves the total synthesis of the cyclodextrin ring. This methodology has been used extensively to prepare a large variety of macrocycles,[3] but the most important limitation is the control of the regio- and stereochemistry of each step, especially the final cyclization. An advantageous alternative route consists of the ring opening of a permethylated cyclodextrin derivative by careful cleavage of one interglycosidic bond followed by chain elongation with a selectively modified saccharide unit and, finally, macrocyclization (Scheme 1, indirect method). This 'homologation methodology' was successfully applied to permethylated or peracetylated α-, β-, or γ-CD by Sakairi et al.[4] and by our group.[5] The ability to control the regiochemistry and the relatively easy characterization of the modifications during synthesis are the main advantages of this method.

The direct strategy (Scheme 1, direct method) deals with the use of chemo- and/or regioselective reactions from

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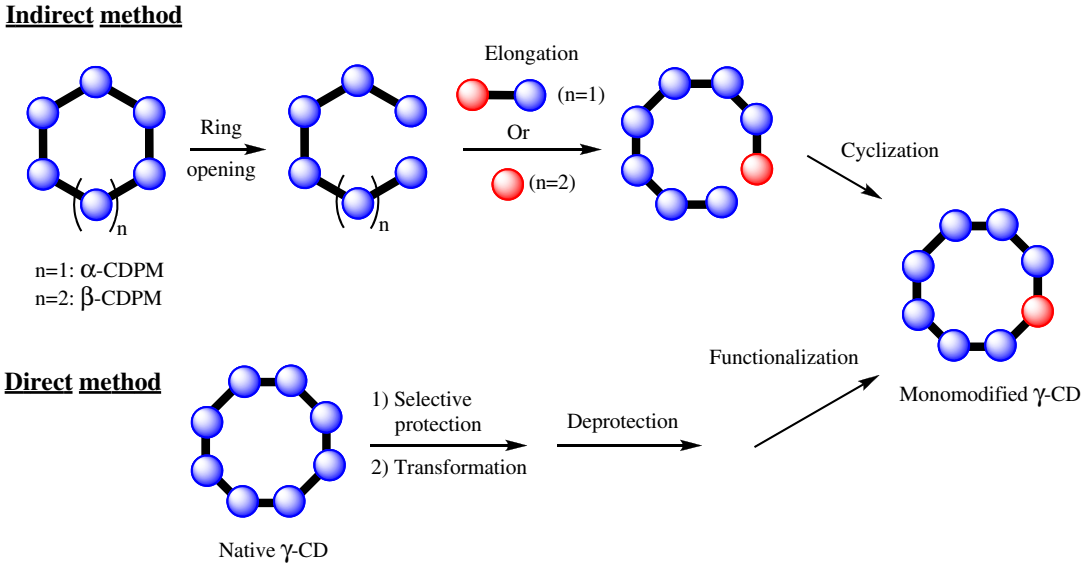


Scheme 1. Indirect and direct strategies for the synthesis of monomodified γ-CD.

native γ-cyclodextrin including four main steps: selective protection of one hydroxyl group, transformation of the remaining ones, deprotection, and finally functionalization. Although it is impossible to summarize all papers in this field, D'Souza et al. have well reviewed the influence of reagent, base, solvent, and temperature to selectively modify the 2-O, 3-O, or 6-O position of cyclodextrins.[6] Concerning the case of mono-6-O-modified CD derivatives, several functionalized methylated α-, β-, or γ-CD were efficiently prepared from mono-6-*O*-(tosyl or arenesulfonyl)[7] or from mono-6-*O*-(*tert*-butyldimethylsilyl)[8] cyclodextrins. Although the direct approach is highly straightforward, the assignment of the modified position of new cyclodextrin derivatives is a rather complicated task.

Although β-cyclodextrin derivatives are usually more enantioselective than their γ-analogs, 6-monomodified permethylated γ-cyclodextrins were chosen to study the original enantioseparations as reported for 3-butyl- (or 3-acetyl-)-2,6-dipentyl-γ-CD.[1]

Herein, we report on the synthesis of 6^{I}-*O*-benzyl-$2^{I–VIII}$, $3^{I–VIII}$, $6^{II–VIII}$-tricosa-*O*-methyl-γ-cyclodextrin from both indirect and direct methods. The first one uses permethylated α-cyclodextrin (α-CDPM) and a suitable maltose derivative, whereas the second one is based on native γ-CD as a starting material.

The introduction of a benzyl group on the CD derivative was performed to modify the conformation of the cyclodextrin cavity (it may induce an additional steric hindrance on the corresponding rim which allows a modification of the CD shape) and to add possible π-stacking interactions with unsaturated analytes. Moreover, the benzyl group can easily be introduced on CD derivatives as well as on maltose ones offering a convenient comparison between indirect and direct strategies. Preliminary results in enantioselective gas chromatography will also be presented.

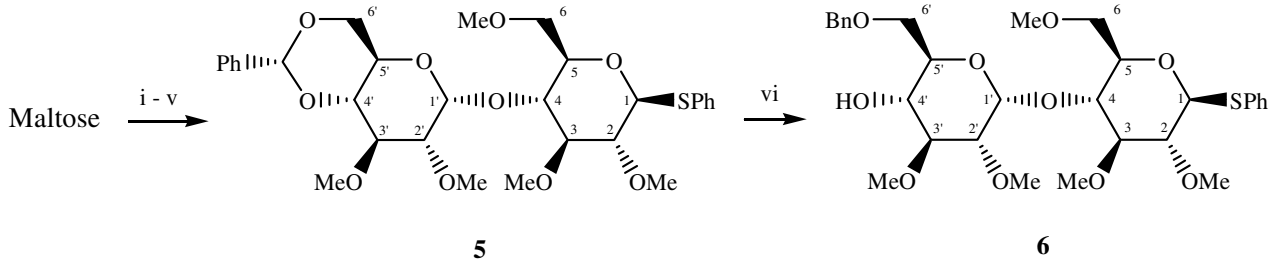
2. Results and discussion

2.1. Indirect method

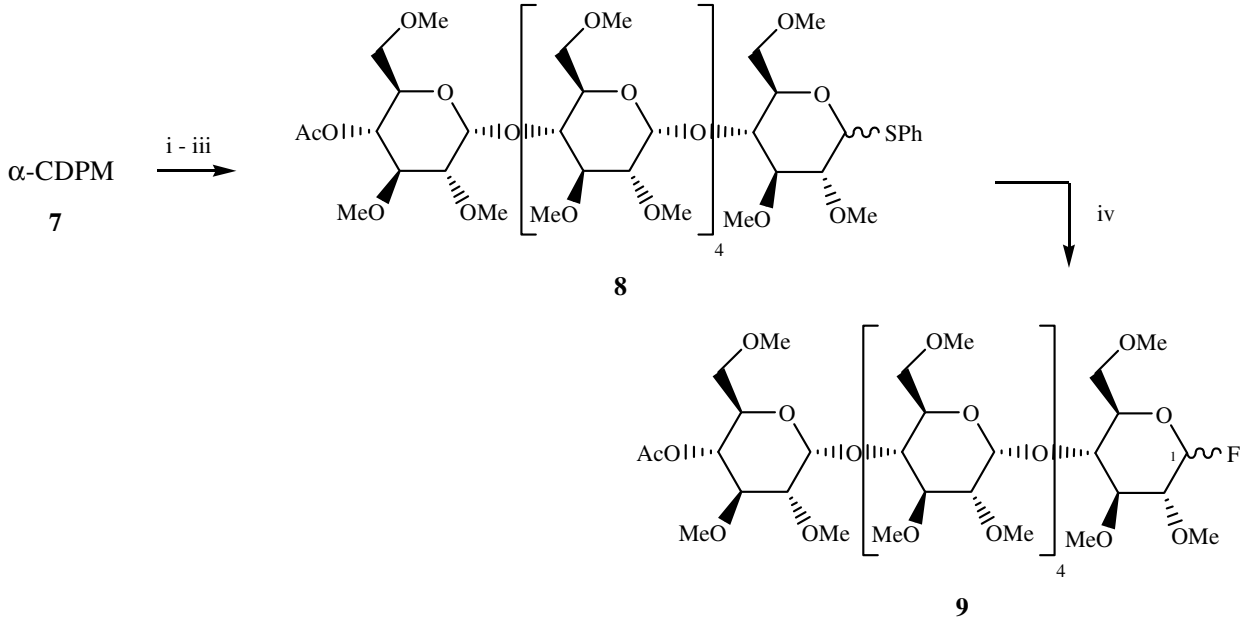
The indirect method is based on our previously reported strategy.[5] The synthesis of disaccharide unit **6** was achieved by a conventional multi-step sequence depicted in Scheme 2. The first five steps involve the transformation of maltose into thioglycoside **5** to differentiate the hydroxyl functions and to activate the anomeric center. The sequence involved peracetylation, thioglycosylation using thiophenol and tin tetrachloride in 1,2-dichloroethane (DCE),[9] hydrolysis of acetyl groups, selective protection of 4′-O and 6′-O positions with benzaldehyde in the presence of zinc dichloride,[10] and permethylation of the remaining free hydroxyl functions in basic conditions (Scheme 2). Compound **5** was then transformed into disaccharide **6** by the selective reduction of the benzyl acetal with sodium cyanoborohydride under acidic conditions.[11] This compound will be used later as a glycosyl donor for the elongation step (see Scheme 4).

The preparation of oligosaccharide **9** was based on the selective cleavage of one glycosidic bond of a permethylated α-cyclodextrin according to Sakairi's method.[12] α-CDPM **7**, prepared according to Schurig's procedure,[13] was treated with phenylthiotrimethylsilane and zinc dibromide[14] in dichloroethane, at room temperature for 5 days (conversion: ~40%) to give a mixture of anomers which was not characterized at this stage. This mixture was first reacted without purification with acetic acid in methanol under reflux to remove the trimethylsilyl group, then the free hydroxyl function was protected by treatment with acetic anhydride and catalytic amounts of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine (DMAP)[15] to give compound **8** in 24% overall yield (Scheme 3).

The phenylsulfanyl group of **8** was converted into the glycosyl fluoride donor **9** (yield: 88%) by treatment with



Scheme 2. Reagents and conditions: (i) Ac_2O, I_2, rt, 1 h (**1**: 85%); (ii) PhSH, $SnCl_4$, DCE, 0 °C to rt, 4 h (**2**: 67%); (iii) MeONa, MeOH, rt, 12 h (**3**: 60%); (iv) PhCHO, $ZnCl_2$, molecular sieves 4 Å, 24 h (**4**: 95%); (v) NaH, DMSO, MeI, rt, 18 h (**5**: 70%); (vi) $NaBH_3CN$, HCl, THF, molecular sieves 4 Å (**6**: 70%).



Scheme 3. Reagents and conditions: (i) $PhSSiMe_3$, $ZnBr_2$, DCE, rt, 5 d; (ii) AcOH, MeOH, reflux (3 h); (iii) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt (three steps, **8**: 24%); (iv) DAST, NBS, DCE, −15 °C (25 min) to rt (1 h) (**9**: 88%).

(diethylamino)sulfur trifluoride (DAST) and *N*-bromosuccinimide (NBS), at −15 °C, according to Nicolaou's procedure[16] (Scheme 3). ^{19}F and ^{1}H NMR spectra, HPLC coupled with ELSD detector, and HPLC–MS analyses confirmed the structure of **9** and showed a (1:1) ratio of α- and β-anomers.

Elongation of the oligosaccharide chain was performed by glycosidation reaction of **6** and **9** in the presence of tin dichloride and silver perchlorate in ether,[11a,17] affording the pure homologated derivative **10** (yield: 30%) as a mixture (∼1:1) of anomers, after preparative silica gel TLC (Scheme 4).

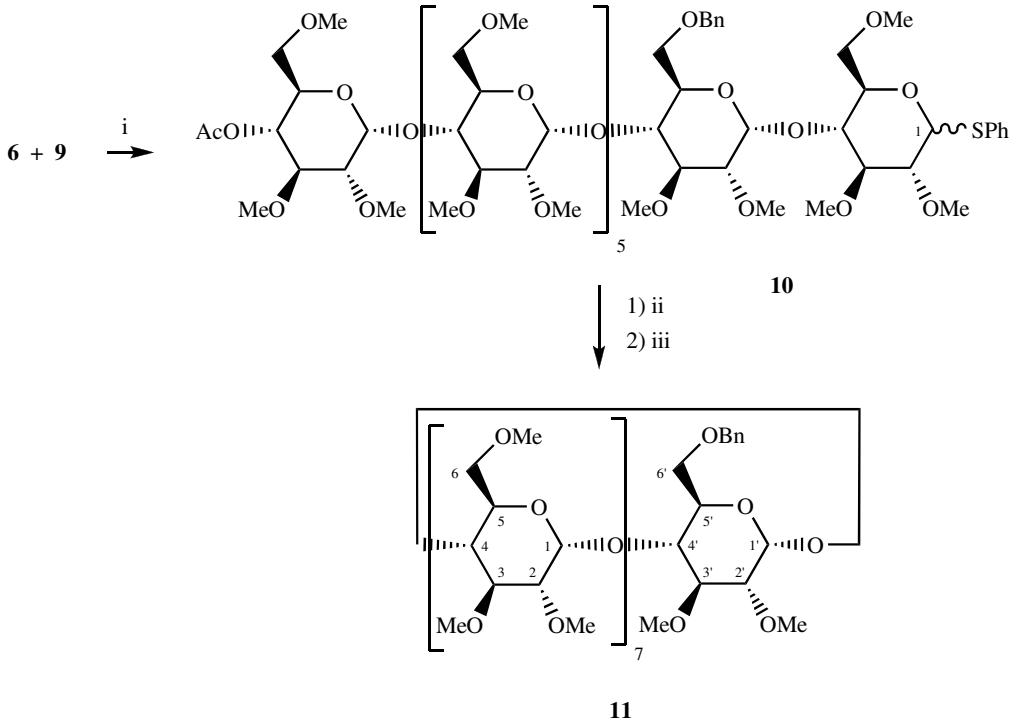
Quantitative deprotection of the acetyl group in basic conditions[18] and cycloglycosilation (macrocyclization) in the presence of methyl trifluoromethanesulfonate (MeOTf) via a high dilution technique[19] were performed, giving the new γ-cyclodextrin **11** (Scheme 4).

Due to the small quantity of final compound **11** and to the overlapping of the anomeric protons (5.27–5.19 ppm, multiplet, 8H) at 300 MHz, we could not assign the α-glycosidic bond at this stage. Nevertheless, ^{1}H NMR data, HPLC, and HRMS analyses of **11** are the same as those of γ-CD derivative, which was obtained from the direct method (see Scheme 5).

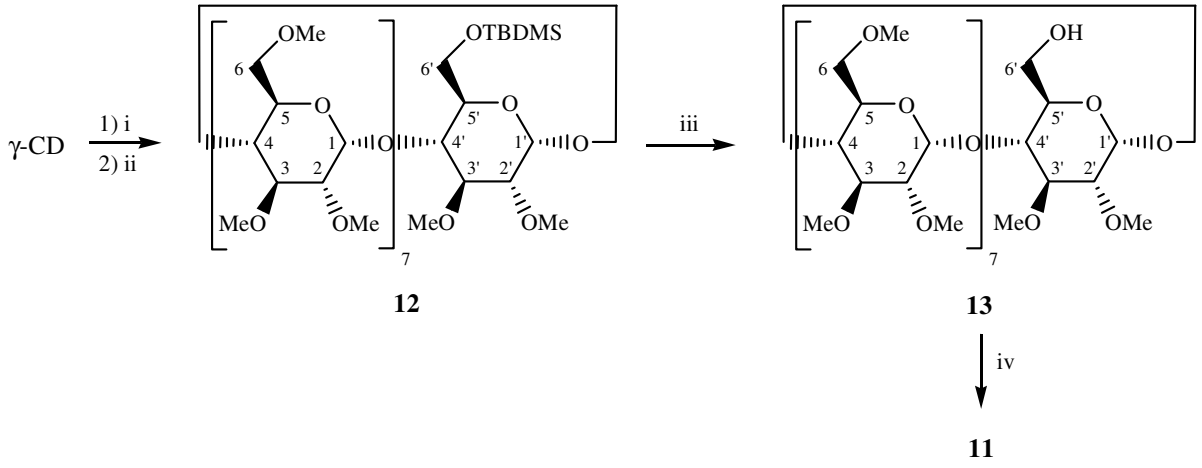
2.2. Direct method

The preparation of γ-CD **11** was also performed using a direct methodology (Scheme 1, direct method) to decrease the number of steps and to obtain a suitable quantity of the chiral selector for a GC application. A similar protection/deprotection strategy that Bradshaw and co-workers[20] used for β-CD was chosen (Scheme 5).

The 6-OH groups of 'native' γ-CD are the more reactive ones; consequently they were easily transformed into silyl ethers using imidazole and *tert*-butyldimethylsilyl (TBDMS) chloride as a moderate electrophile. The stoichiometry and reaction conditions were chosen to favor the selective mono-6-*O*-TBDMS silylation.[20] Nevertheless, careful HPLC analysis of the crude product revealed a



Scheme 4. Reagents and conditions: (i) $SnCl_2$, $AgClO_4$, Et_2O, −15 °C (2 h) to rt (12 h) (**10**: 30%); (ii) MeONa, MeOH; (iii) MeOTf, molecular sieves 4 Å, 0 °C to rt, 2 d (two steps, **11**: 35%).



Scheme 5. Reagents and conditions: (i) TBDMSCl, imidazole, DMF, rt (24 h); (ii) NaH, DMF, 0 °C (30 min) to rt (2 h) then MeI, 0 °C (1 h) to rt (24 h) (two steps, **12**: 30%); (iii) Bu_4NF, THF, rt (12 h) (**13**: 54%); (iv) NaH, THF, Δ (2 h) then BnCl, 0 °C (1 h) to reflux (12 h) (**11**: 76%).

mixture of the starting material as the major product, the mono-6-*O*-TBDMS compound, and small amounts of bis- and tris-6-O-protected derivatives. Thus, the conversion of the reaction did not exceed ~55%. The mono-6-*O*-TBDMS derivative was not purified at this stage due to its pronounced polar character.

The reaction mixture was then subjected to the methylation of the free remaining hydroxyl groups using sodium hydride and methyl iodide. The crude material was purified by silica gel column chromatography, giving 30% overall yield of the pure cyclodextrin **12** (Scheme 5). Normal phase chromatography was chosen due to the better selectivity between cyclodextrin **12** and the by-products, and to the higher volatility of eluent (toluene/acetone).

The TBDMS group was removed using tetrabutylammonium fluoride in THF at room temperature. The yield of this step reached 54% after purification on silica gel. This deprotection step would need further improvement as CD derivative **13** seemed difficult to extract from the aqueous phase.

Finally, the benzyl substituent was introduced using sodium hydride and 10-fold excess of benzyl chloride in refluxing THF to give the final compound **11** after purification by column chromatography on grafted C18 silica gel. This direct strategy was straightforward (only three steps) and afforded the final compound **11** in ~12% overall yield.

The main features of indirect and direct strategies could be summarized as follows:

- On one hand, the main advantage of *indirect method* consists of the possible insertion of a wide variety of maltose derivatives (to obtain new CSP–solute interactions) or other sugar units, whereas the very poor overall yields of **11** (2.2% from modified derivative **6** and α-CDPM **7**) and the 11-steps sequence (from maltose and α-CDPM) are the most important drawbacks.
- On the other hand, the *direct method* is more straightforward (three steps) and efficient (12.3% overall yields from commercially available γ-CD). The main problem of this approach remains the regioselective mono-6-*O*-TBDMS protection (low conversion, rather difficult separation of **12** and by-products).

The final compound **11** was fully characterized by HPLC, HRMS, ^{1}H and ^{13}C (1D and 2D) NMR spectroscopies.

2.3. Chromatographic study

Mono-6-*O*-benzyl methylated γ-cyclodextrin **11** was evaluated as a chiral selector for enantioselective gas chromatography. This CD derivative was diluted at 15% (w/w) in OV 1701 (86% methyl, 7% phenyl, 7% cyanopropyl polysiloxane) and coated in a fused silica column (10 m × 0.25 mm) according to the static method previously described.[21] The film of the stationary phase was about 0.25 μm thickness. Column efficiency was determined by measuring the number of theoretical plates/m at 20 °C intervals in the temperature range of 60–180 °C (Table 1).

Table 1. The efficiency and retention factor for various *n*-alkanes in the temperature range of 60–180 °C on mono-6-*O*-benzyl methylated γ-cyclodextrin **11** coated column

T (°C)	*k*	Efficiency (plates/m)	Solute
60	11.0	1790	*n*-Undecane
80	4.7	1830	*n*-Undecane
100	3.9	2780	*n*-Dodecane
120	3.2	3300	*n*-Tridecane
140	3.4	3600	*n*-Tetradecane
160	3.3	3720	*n*-Hexadecane
180	3.6	3820	*n*-Octadecane

The column possesses good efficiency, which is constant and up to 2500 plates/m on a wide range of temperatures. However, a decrease in efficiency was observed below 100 °C, which is probably due to the poor solubility of mono-6-*O*-benzyl methylated γ-cyclodextrin **11** in OV1701. Nevertheless, the efficiencies measured above 100 °C were suitable for a first evaluation of the enantioselective capability of this new chiral selector. Therefore, some racemic mixtures of alcohols, ester, and 5-alkyl-5-methylhydantoins were injected.

The stationary phase presents generally low resolution values for the solutes tested, and only linalool and α-terpineol enantiomers were not separated (Table 2). The best values of enantioselectivities were observed for phenylethan-1-ol derivatives. This result might be the consequence of additional π-stacking interactions between these solutes and the benzyl group of the CD derivative. A study concerning the confirmation of this hypothesis and the choice of polysiloxane (used for the dilution of CD selector) is currently under investigation to enhance the column efficiency below 80 °C.

Table 2. Separation of the enantiomers of alcohols, methyl mandelate, and 5-alkyl-5-methylhydantoins

	T (°C)	k_1[a]	α	R_s
Menthol	100	9.6	1.019	0.5
Phenylethan-1-ol	100	8.0	1.023	0.7
p-Fluorophenylethan-1-ol	100	10.4	1.035	1.3
p-Chlorophenylethan-1-ol	100	40.1	1.066	1.9
Pentan-2,4-diol	110	2.2	1.025	0.7
Linalool	110	3.4	1.000	0.0
α-Terpineol	110	7.1	1.000	0.0
Methyl mandelate	130	8.9	1.011	0.6
5-Methyl-5-propylhydantoin	170	27.8	1.013	0.6
5-Methyl-5-pentylhydantoin	170	41.6	1.010	0.5
5-Hexyl-5-methylhydantoin	170	62.7	1.010	0.5
5-Heptyl-5-methylhydantoin	170	95.2	1.010	0.5

[a] k_1 is the retention factor for the first eluted enantiomer.

3. Conclusion

In conclusion, we have developed two new routes to asymmetric γ-cyclodextrin **11** starting from suitable modified disaccharide **6** and permethylated α-cyclodextrin **7** (*indirect method*) and from 'native' γ-cyclodextrin (*direct method*). The advantages and drawbacks of each approach have been discussed and compared leading to the following conclusion: the *direct strategy* was more efficient, offering 12.3% of the final compound **11** after only three steps. Although the global yield is quite poor, compound **11** was used as a selector for the preparation of GC capillary column which requires only a few mg of a chiral derivative. The preliminary chromatographic results showed that mono-6-*O*-benzyl methylated γ-cyclodextrin **11** could be suitable for gas chromatographic enantioseparations. The full enantioselective GC study is currently under investigation.

4. Experimental

4.1. General methods

α-CDPM and γ-CD were dried at 80 °C under vacuum for 48 h. Dimethylsulfoxide (DMSO), dimethylformamide

(DMF) and diethyl ether (ether) were dried over calcium hydride and fractionally distilled. Tetrahydrofuran (THF) was distilled over sodium/benzophenone. Dichloromethane (DCM) and 1,2-dichloroethane (DCE) were dried over calcium chloride and distilled. Other commercially available reagents were used without further purification. Reactions were followed by thin layer chromatography (TLC) on silica gel (Merck, Darmstadt, Germany) and revealed with a 10% solution of H_2SO_4 in ethanol. Purifications were carried out using flash column chromatography with silica gel (70–200 μm, Chromagel, SDS Val de Reuil, France), or grafted C18 silica gel (60–200 μm, Chromagel, SDS Peypin, France).

The purity of the synthetic products was established by HPLC/ELSD analysis and confirmed by NMR spectroscopy data and HPLC/MS analysis. HPLC: ThermoQuest P1500, Detector: Evaporative Light Scattering Detector (ELSD), Polymer Laboratories, PL-ELS 2100, PM = 600 mV, Evaporator 40 °C, Nebullisor 70 °C, N_2 Flow 1.3 L min^{-1}. HPLC columns used are the following: HYPERSIL® H5C18.25F, 25 cm × 4.6 mm × 5 μm, flow = 1 mL/min; XTerra RP 18, 25 cm × 2.1 mm × 5 μm, flow = 0.20 mL/min; ALLTIMA® C18 EPS, 25 cm × 2.1 mm × 5 μm, flow = 0.30 mL/min. MS: Thermo Finnigan, LCQ Advantage Max, Electrospray Ionization, Source heater $T = 220$ °C, cone voltage = 33 V. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Brucker Advance DMX 500 instrument. The assignment of ^1H and ^{13}C signals was supported by one- and two-dimensional NMR (CPD, DEPT, ^1H–^1H COSY, ^1H–^{13}C HSQC, and HMBC) experiments. All the experiments were recorded using $CDCl_3$ as solvent. The TMS signal was taken as the internal reference for ^1H and ^{13}C spectra. Approximately 20 mg of sample was dissolved in 0.5 mL of solvent. The numbers of protons and carbons of the modified glucosyl unit will be indicated as follows: H-1′, C-1′, … High Resolution Mass Spectra (HRMS) were recorded with a Q-TOF Micromass Instrument in the positive ESI (CV = 30 V) mode.

Gas chromatographic analyses were performed on Hewlett–Packard HP 5890 series II or HP 6890 chromatographs, equipped with Flame Ionization Detector and split–splitless injector both operating at 250 °C. Helium was used as a carrier gas at an average linear velocity of 35 cm/s. Intermediate polarity-fused silica capillary tube (0.25 mm i.d., length 10 m) was purchased from Supelco (Saint Quentin Fallavier, France).

4.2. Indirect method

4.2.1. 1,2,3,6-Tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-α-D-glucopyranose 1[22] (Scheme 2). This compound was prepared according to a reported procedure[23] starting from maltose (10.10 g, 29.5 mmol), acetic anhydride (50 mL, 0.53 mol), and iodine (0.52 g, 2.03 mmol) giving 17.00 g (yield: 85%) of a white powder. R_f (EtOAc) = 0.58. HPLC/MS: column HYPERSIL® H5C18.25F; from CH_3OH/H_2O (50/50) to CH_3OH (35 min); rt = 12.06 min; m/z ($[M+Na]^+$) = 701.2.

4.2.2. Phenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranose 2[24] (Scheme 2). This compound was prepared according to a reported procedure[9] starting from per *O*-acetyl maltose **1** (7.00 g, 10.3 mmol), thiophenol (1.3 mL, 12.8 mmol), and tin tetrachloride (0.9 mL, 7.8 mmol) to give 5.03 g (yield: 67%) of the desired compound after purification by silica gel column chromatography (CH_2Cl_2/EtOAc 90/10). R_f (CH_2Cl_2/EtOAc 90/10) = 0.29. HPLC/MS: column HYPERSIL® H5C18.25F; from CH_3OH/H_2O (50/50) to CH_3OH (35 min); rt = 20.43 min; m/z ($[M+Na]^+$) = 751.5.

4.2.3. Phenyl 4-*O*-(α-D-glucopyranosyl)-1-thio-β-D-glucopyranose 3[25] (Scheme 2). This compound was prepared according to a reported procedure[18] starting from compound **2** (3.92 g, 5.38 mmol) and a solution of sodium methanolate (250 mL, conc: 0.01 mol L^{-1}) in methanol to give 1.40 g (yield: 60%) of the desired compound after purification by silica gel column chromatography (EtOAc then EtOAc/MeOH 50/50). R_f (EtOAc/MeOH 50/50) = 0.78. HPLC/MS: column HYPERSIL® H5C18.25F; from CH_3OH/H_2O (50/50) to CH_3OH (35 min); rt = 3.28 min; m/z ($[M+Na]^+$) = 457.4.

4.2.4. Phenyl 4-*O*-(4,6-*O*-benzylidene-α-D-glucopyranosyl)-1-thio-β-D-glucopyranose 4[26] (Scheme 2). This compound was prepared according to a reported procedure[10] starting from compound **3** (0.70 g, 1.61 mmol), zinc dichloride (0.37 g, 1.64 mmol), and benzaldehyde (3 mL, 29.5 mmol) to give 0.80 g (yield: 95%) of the desired compound after purification by silica gel column chromatography (CH_2Cl_2/EtOAc 50/50). R_f (EtOAc) = 0.30. HPLC/MS: column HYPERSIL® H5C18.25F; from CH_3OH/H_2O 50/50 to CH_3OH (35 min); rt = 11.45 min; m/z ($[M+Na]^+$) = 545.2.

4.2.5. Phenyl 2,3,6-tri-*O*-methyl-4-*O*-(4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranose 5 (Scheme 2). A suspension of sodium hydride (0.50 g, 20.8 mmol) in dimethylsulfoxide (50 mL) was heated at 60 °C for 2 h under a nitrogen atmosphere. After cooling at room temperature, compound **4** (0.69 g, 1.32 mmol) was added portionwise (5 min). Methyl iodide (1.75 g, 12.3 mmol) was added and the resulting solution was stirred for 18 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and the organic phase was washed successively with a 10% aqueous solution of hydrochloric acid (2 × 150 mL), a saturated aqueous solution of sodium hydrogenocarbonate (150 mL), and brine (150 mL). The resulting solution was dried over Na_2SO_4 and concentrated under reduced pressure to give 0.50 g (yield: 70%) of the desired compound **5**. White powder. R_f (Et_2O/CH_2Cl_2 50/50) = 0.60. HPLC/MS: column HYPERSIL® H5C18.25F; from CH_3OH/H_2O 50/50 to CH_3OH (35 min); rt = 10.12 min; m/z ($[M+Na]^+$) = 559.4. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.34–7.26 (m, 4H, H-aro), 7.25–7.19 (m, 6H, H-aro), 5.58 (d, 1H, $^3J_{H1,H2}$ = 3.8 Hz, H-1), 5.46 (s, 1H, PhC*H*O_2), 4.47 (d, 1H, $^3J_{H1',H2'}$ = 9.7 Hz, H-1′), 4.21 (m, 1H), 3.84–3.60 (m, 5H, H-5′, H-6 or H-6′), 3.60–3.45 (m, 19H, 5 × OCH_3 and H-3,3′ and H-4,4′), 3.20 (dd, 1H, $^3J_{H2,H3}$ = 7.8 Hz, $^3J_{H1,H2}$ = 3.7 Hz, H-2), 3.07 (dd, 1H, $^3J_{H1',H2'}$ = 9.7 Hz, $^3J_{H2',H3'}$ = 6.6 Hz, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$) δ:

135.7, 134.7, 131.5, 129.4, 127.9, 127.2, 126.4, 125.0 (C-aro), 100.3 (Ph*C*HO$_2$), 96.0 (C-1′), 87.8 (C-1), 86.6, 82.2 (C-3, C-3′), 81.2, 80.5 (C-2, C-2′), 78.9, 76.8 (C-4, C-4′), 70.1, 70.0 (C-5, C-5′), 68.0, 64.8 (C-6, C-6′), 61.9, 59.9, 59.6, 59.2, 58.4, (2,2′-OCH$_3$, 3,3′-OCH$_3$, 6-OCH$_3$).

4.2.6. Phenyl 2,3,6-tri-*O*-methyl-4-*O*-(6-*O*-benzyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-1-thio-β-D-gluco-pyranose 6 (Scheme 2). Sodium cyanoborohydride (295 mg, 4.70 mmol) was added portionwise to a suspension of compound **5** (278 mg, 0.47 mmol) and 4 Å (50 mg) molecular sieves in THF (5 mL). A saturated solution (~10 mL) of hydrochloric acid in ether was added dropwise to the reaction mixture until the disappearance of the starting material (monitoring by TLC). After dilution with CH_2Cl_2 (50 mL), the reaction mixture was filtered, washed successively with aqueous solution of 3% (20 mL) ammonia and water (20 mL). The resulting organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc) to give 0.20 g (yield: 70%) of the desired compound **6**. R_f (EtOAc) =0.19. HPLC/MS: column HYPERSIL® H5C18.25F; CH_3OH/H_2O (90/10); rt = 4.06 min; *m*/*z* ([M+Na]$^+$) = 617.10. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54–7.50 (m, 2H, H-aro), 7.34–7.26 (m, 8H, H-aro), 5.60 (d, 1H, $^3J_{H1,H2} = 3.6$ Hz, H-1), 4.62 (d, 1H, $^2J_{a,b} = 12.0$ Hz, CH_aH$_b$Ph), 4.53 (d, 1H, $^2J_{a,b} = 12.0$ Hz, CH$_a$$H_b$Ph), 4.51 (d, 1H, $^3J_{H1',H2'} = 9.7$ Hz, H-1′), 3.88–3.64 (m, 6H, H-5, H-5′, H-6, H-6′), 3.64, 3.62, 3.59, 3.54 (s, 3H, 3-OCH$_3$), (s, 3H, 3′-OCH$_3$), (s, 3H, 2-OCH$_3$), (s, 3H, 2′-OCH$_3$), 3.59 (m, 1H, H-4), 3.54 (m, 1H, H-4′), 3.37 (dd, 1H, $^3J_{H3,H4} = {}^3J_{H3,H2} = 7.9$ Hz, H-3), 3.41 (dd, 1H, $^3J_{H3',H4'} = {}^3J_{H3',H2'} = 6.6$ Hz, H-3′), 3.29 (s, 3H, 6-OCH$_3$), 3.22 (dd, 1H, $^3J_{H1,H2} = 3.6$ Hz, $^3J_{H2,H3} = 7.9$ Hz, H-2), 3.13 (dd, 1H, $^3J_{H1',H2'} = 9.7$ Hz, $^3J_{H2',H3'} = 6.6$ Hz, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.2, 132.7, 130.8, 127.8, 127.4, 127.1, 126.9, 126.4 (C-aro), 95.4 (C-1′), 87.7 (C-1), 86.3 (C-3, C-3′), 82.6 (C-2′), 82.1 (C-2), 77.1 (*C*H$_2$Ph), 70.5, 70.3 (C-4, C-4′), 67.5 (C-5, C-5′), 60.7, 60.6 (C-6, C-6′), 60.0, 59.6 (3-OCH$_3$, 3′-OCH$_3$), 59.2 (6-OCH$_3$), 58.8, 58.5 (2-OCH$_3$, 2′-OCH$_3$).

4.2.7. Phenyl 4-*O*-acetyl-2,3,6-tri-*O*-methyl-α-D-glucopyranosyl-[(1→4)-2,3,6-tri-*O*-methyl-α-D-gluco-pyranosyl]4-(1→4)-2,3,6-tri-*O*-methyl-1-thio-D-glucopyranose 8 (Scheme 3). Zinc dibromide (1.02 g, 4.52 mmol) and phenylthiotrimethylsilane (0.86 mL, 4.54 mmol) were added to a solution of compound **7**[13] (1.38 g, 1.13 mmol) in 1,2-dichloroethane (DCE, 30 mL), under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 5 days (orange-brown color) then poured into a mixture ice water (~100 mL). The aqueous phase was extracted with $CHCl_3$ (2 × 30 mL). The combined organic layers were washed successively with a saturated solution of sodium hydrogenocarbonate (2 × 10 mL) and brine (2 × 10 mL). After drying over Na_2SO_4, the solvents were removed under reduced pressure. The crude product was used without purification and characterization for the deprotection step.

Next it was dissolved in MeOH (10 mL) and acetic acid (0.86 mL, 14.69 mmol) was added, after which the resulting solution was refluxed for 3 h. After evaporation under reduced pressure, the residue (colorless oil) was used without purification for the acetylation step.

Acetic anhydride (1.17 mL, 11.65 mmol), catalytic amounts of triethylamine (17 μL) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 6 mg) were successively added to a CH_2Cl_2 solution (10 mL) of the crude product. The resulting mixture was stirred at room temperature for 4 h, then was diluted with CH_2Cl_2 (10 mL). The organic phase was successively washed with 3 M aqueous solution of hydrochloric acid (2 × 5 mL), saturated aqueous solution of sodium hydrogenocarbonate (2 × 5 mL) and brine (2 × 5 mL). After drying over Na_2SO_4 and evaporation under reduced pressure, the crude product was purified by silica gel column chromatography (toluene/acetone 80/20) to give 0.37 g (yield: 24% for the three steps) of the desired compound **8**. R_f (toluene/acetone 50/50) = 0.57. HPLC/MS: column HYPERSIL® H5C18.25F; CH_3OH/H_2O 80/20; rt = 17.04 min; calculated *m*/*z* 1399.62, found *m*/*z* ([M+Na]$^+$) = 1399.12. Selected ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.39 (m, 2H, H-aro), 7.20–7.15 (m, 3H, H-aro), 5.60 (m, 1H), 5.50–5.37 (m), 5.00 (d, 1H, *J* = 3.7 Hz), 4.20 (d, 1H, *J* = 9.7 Hz), 3.03–3.92 (m), 2.02 (s, 3H, Ac). Selected ^{13}C NMR (75 MHz, $CDCl_3$): 170.2 (*C*OCH$_3$), 134.2 (C$_q$, Ph), 131.8 (2 × CH, Ph), 129.1 (2 × CH, Ph), 127.2 (CH, Ph), 97.4, 96.9, 96.7, 95.5, 88.1, 87.0, 84.2, 83.4, 82.4, 82.1, 82.0, 80.2, 80.0, 73.5, 73.0, 72.8, 72.7, 71.3, 71.1, 70.8, 70.3, 70.0, 69.9, 69.8, 62.8, 62.6, 62.3, 62.2, 61.7, 61.6, 60.9, 60.7, 60.4, 60.1, 22.1 (*C*H$_3$CO).

4.2.8. 4-*O*-Acetyl-2,3,6-tri-*O*-methyl-α-D-glucopyranosyl-[(1→4)-2,3,6-tri-*O*-methyl-α-D-glucopyranosyl]4-(1→4)-1-deoxy-1-fluoro-2,3,6-tri-*O*-methyl-D-glucopyranose 9 (Scheme 3). (Diethylamino)sulfur trifluoride (DAST, 47 μL, 0.38 mmol) was added to a solution of compound **8** (372 mg, 0.27 mmol) in 1,2-dichloroethane (25 mL), at −15 °C, under nitrogen atmosphere. After 2 min, *N*-bromosuccinimide (NBS, 63 mg, 0.35 mmol) was added and the resulting mixture was stirred at −15 °C for 25 min. After warming at room temperature (1 h), the same work-up as described for compound **8** (last step) was used. The crude product was purified by silica gel column chromatography (toluene/acetate 50/50) to give 306 mg (yield: 88%) of the desired compound **9** as a mixture (1:1) of α- and β-anomers. R_f (toluene/acetone 50/50) = 0.49. HPLC/MS: column HYPERSIL® H5C18.25F; from CH_3OH/H_2O (50/50) to CH_3OH (35 min); rt = 20.84 min (anomer 1) and 21.57 min (anomer 2); calculated *m*/*z* 1309.61, found *m*/*z* ([M+Na]$^+$) = 1310.01. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −149.9 (dd, $^2J_{F,H1} = 53.0$, $^3J_{F,H2} = 26.2$ Hz), −136.8 (dd, $^2J_{F,H1} = 53.0$, $^3J_{F,H2} = 12.1$ Hz). Selected ^{1}H NMR data (300 MHz, $CDCl_3$) δ: 5.67 (d, 1H, $^3J_{H1,H2} = 3.8$ Hz, H-1), 5.56–5.41 (m, 4H, H-1), 5.30 (dd, 0.5H, $^2J_{H1,F} = 53.0$ Hz, $^3J_{H1,H2} = 6.3$ Hz, H-1), 5.00 (dd, 0.5H, $^2J_{H1,F} = 53.0$ Hz, $^3J_{H1,H2} = 3.7$ Hz, H-1), 4.22 (m, 1H, H-5), 3.87–3.61 (m, 18H, H-4, H-5, H-6), 3.58–3.48 (m, 36H, 3-OCH$_3$, 2-OCH$_3$), 3.45–3.42 (m, 6H, H-3), 3.40–3.31 (m, 18H, 6-OCH$_3$), 2.09 (s, 3H, C*H*$_3$CO). Selected ^{13}C data (75 MHz, $CDCl_3$) δ: 170.0 (CH$_3$*C*O), 97.5, 96.9, 96.7, 95.5 (C-1), 88.1, 87.0, 84.2, 83.7, 82.4, 82.1, 82.0,

80.2, 80.0 (C-2, C-3), 73.5, 73.0, 72.8, 72.7, 71.3, 71.2, 70.7, 70.1, 70.0, 69.9, 69.8 (C-4, C-5, C-6), 62.8, 62.6, 62.5, 62.2, 61.7 (3-OCH_3, 6-OCH_3), 60.8, 60.7, 60.3, 60.1 (2-OCH_3), 22.0 (CH_3CO).

4.2.9. Phenyl 4-*O*-acetyl-2,3,6-tri-*O*-methyl-α-D-glucopyranosyl-[(1→4)-2,3,6-tri-*O*-methyl-α-D-gluco-pyranosyl]5-(1→4)-6-*O*-benzyl-2,3-di-*O*-methyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-methyl-1-thio-D-glucopyranose 10 (Scheme 4). Compound **9** (94 mg, 0.073 mmol) and alcohol **6** (63 mg, 0.106 mmol) were azeotropically dried with benzene. After the evaporation of the solvent, the mixture was dried under high vacuum (5×10^{-2} mbar) for 1 h. Then, the dried compounds were diluted with Et_2O (1 mL) and 4 Å (25 mg) molecular sieves were added. The resulting mixture was stirred at room temperature for 20 min, then cooled to −15 °C. A solution of silver perchlorate (18 mg, 0.087 mmol) and tin dichloride (17 mg, 0.090 mmol) in ether (1 mL) was added. The mixture was stirred at −15 °C for 2 h, then the temperature was allowed to reach 25 °C (stirring for 12 h). After dilution with EtOAc (15 mL), the organic phase was successively washed with saturated solution of sodium hydrogenocarbonate (2 × 10 mL) and with brine (2 × 10 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by a preparative silica gel thin layer chromatography (CH_2Cl_2) to give 42 mg (yield: 30%) of the desired compound **10** as a mixture (~1:1) of anomers. R_f (CH_2Cl_2) = 0.14. HPLC/MS: column HYPERSIL® H5C18.25F; from CH_3OH/H_2O (50/50) to CH_3OH (35 min); rt = 30.48 min (anomer 1) and rt = 30.81 min (anomer 2); calculated *m/z* 953.4, found *m/z* ($[M+2Na]^{2+}$) = 953.9. Selected ^1H NMR data (300 MHz, $CDCl_3$) δ: 7.5–7.2 (m, 10H, 2 × Ph), 4.58 (d, 0.5H, $^3J_{H1,H2}$ = 9.8 Hz, H-1), 4.31 (d, 0.5H, $^3J_{H1,H2}$ = 4.9 Hz, H-1), 2.15 (s, 3H, CH_3CO). Selected ^{13}C NMR data (75 MHz, $CDCl_3$) δ: 167.7 (CH_3CO), 132.7 (C_q, Ph), 129.4–126.4 (C-aro), 101.6, 95.8, 95.5 (C-1), 88.3, 85.2, 83.6, 83.3, 82.6, 82.5, 81.5, 80.7 (C-2, C-3), 70.5–69.1 (C-4), 67.9–65.5 (C-5, C-6), 62.5, 61.7, 61.4, 61.3 (3-OCH_3, 6-OCH_3), 60.1–58.3 (2-OCH_3), 22.3 (CH_3CO).

4.2.10. 6^{I}-*O*-Benzyl-2$^{I–VIII}$, 3$^{I–VIII}$, 6$^{II–VIII}$-tricosa-*O*-methylcyclomaltooctaose 11 (Scheme 4). Compound **10** (17 mg, 0.009 mmol) was deprotected according to a reported procedure[18] to give 25 mg of a crude product, which was used without further purification. The crude product was dissolved in diethyl ether (5 mL) and 4 Å molecular sieves (500 mg) were added. After cooling at 0 °C, methyl trifluoromethanesulfonate (23.7 μL, 0.210 mmol) was added and the resulting mixture was stirred at room temperature for 2 days. The reaction was quenched by the addition of methanol (3 mL), then diluted with $CHCl_3$ (15 mL). The resulting solution was washed with aqueous solution of 3 M (2 × 5 mL) hydrochloric acid, saturated aqueous solution of sodium bicarbonate (2 × 5 mL), then finally with brine (2 × 5 mL). The organic phase was separated, dried over Na_2SO_4, and concentrated in vacuo to give the desired γ-cyclodextrin **11** (5.5 mg, yield for the two steps: 35%), which was analyzed without further purification. For complete analyses of compound **11**, see *direct method* (Scheme 5).

4.3. Direct method

4.3.1. 6^{I}-*O*-*tert*-Butyldimethylsilyl-2$^{I–VIII}$, 3$^{I–VIII}$, 6$^{II–VIII}$-tricosa-*O*-methylcyclomaltooctaose 12 (Scheme 5). A solution of *tert*-butyldimethylsilyl chloride (464 mg, 3.08 mmol) in DMF (5 mL) was added dropwise, at room temperature under a nitrogen atmosphere, to a solution of anhydrous γ-CD (2.00 g, 1.54 mmol) and imidazole (262 mg, 3.86 mmol) in DMF (40 mL). The mixture was stirred at rt for 24 h. In another flask, a suspension of 60% sodium hydride in mineral oil (4.00 g, 100 mmol) in DMF (10 mL) was prepared. After cooling at 0 °C, the reaction mixture was added to the sodium hydride suspension and was stirred at 0 °C for 30 min and at rt for 2 h. After cooling to 0 °C, methyl iodide (6.71 mL, 108 mmol) was added dropwise. The mixture was kept for 1 h at 0 °C, then at rt for 24 h. An excess of sodium hydride was decomposed by the addition of MeOH (10 mL). The resulting mixture was poured into 100 mL of ice water and extracted with chloroform (3 × 70 mL). The combined organic layers were washed successively with aqueous solution of sodium thiosulfate (2 × 30 mL), 10% aqueous hydrochloric acid solution (30 mL), and brine (3 × 30 mL). After drying over $MgSO_4$, filtration, and evaporation in vacuo, the crude product was purified by silica gel column chromatography (toluene/acetone 75/25) yielding 30% (760 mg) of pure compound **12**. R_f (toluene/acetone 50/50) = 0.70. HPLC: column XTerra RP 18; CH_3OH/H_2O (80/20); rt = 12.03 min. HRMS (ESI+) calcd $C_{77}H_{140}O_{40}NaSi$ *m/z* = 1755.8601, found 1755.8588. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.26–5.07 (m, 8H, H-1,1′), 4.00–3.81 (m, 16H, H-5,5′, H-6α), 3.75–3.56 (m, 8H, H-4,4′), 3.70–3.38 (m, 8H, H-3,3′), 3.65–3.64 (m, 24H, 3,3′-OCH_3), 3.58–3.51 (m, 24H, 2,2′-OCH_3), 3.49–3.25 (m, 8H, H-6β), 3.36–3.35 (m, 21H, 6-OCH_3), 3.23–3.11 (m, 8H, H-2,2′), 0.88 (s, 9H, $SiMe_2^tBu$), 0.05 (m, 6H, $SiMe_2^tBu$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 98.4, 98.3, 98.2, 98.1, 98.0, 97.6 (C-1), 82.3, 82.1, 82.0, 81.9 (C-2, C-3), 79.0, 78.8, 78.7, 78.5, 78.3, 78.2, 78.0 (C-4), 72.4 (C-5), 71.3 (C-6), 71.0, 70.0 (C-5), 62.7 (C-6′), 61.7, 61.6, 61.55, 61.51, 61.46 (3-OCH_3), 59.14, 59.13, 59.09 (6-OCH_3), 58.9, 58.8, 58.7 (2-OCH_3), 26.1 ($SiMe_2(C(CH_3)_3)$), 18.6 ($SiMe_2(C(CH_3)_3)$), −4.9, −5.1 ($SiMe_2^tBu$).

4.3.2. 2$^{I–VIII}$, 3$^{I–VIII}$, 6$^{I–VII}$-Tricosa-*O*-methylcyclomaltooctaose 13 (Scheme 5). The protected compound **12** (570 mg, 0.33 mmol) was stirred for 12 h with a 1 M THF solution of Bu_4NF (333 μL, 3.33 mmol) in THF (6 mL). The solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate (4 mL) and the resulting solution was filtered through Celite. The filtrate was then concentrated in vacuo. The crude product was purified by silica gel column chromatography (toluene/acetone 70/30) giving pure white product **13** (289 mg, yield: 54%). R_f (toluene/acetone 50/50) = 0.12. HPLC: column XTerra RP 18; CH_3OH/H_2O (80/20); rt = 5.14 min. HRMS (ESI+) calcd $C_{71}H_{126}O_{40}Na$ *m/z* = 1641.7729, found 1641.7723. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.26–5.07 (m, 8H, H-1,1′), 3.93–3.75 (m, 8H, H-6α), 3.90–3.70 (m, 8H, H-4,4′), 3.71–3.62 (m, 8H, H-6β), 3.63–3.59 (m, 24H, 3,3′-OCH_3), 3.59–3.39 (m, 8H, H-3,3′), 3.50–3.39 (m, 8H, H-5,5′), 3.51–3.42 (m, 24H, 2,2′-OCH_3), 3.34–3.33 (m, 21H, 6-OCH_3), 3.20–3.15 (m, 8H, H-2,2′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 98.5, 98.3,

98.2, 98.15, 98.06, 97.9, 97.8 (C-1), 82.3, 82.1, 82.0, 81.9, 81.8, 81.6 (C-2, C-3), 79.8, 79.1, 79.0, 78.9, 78.2 (C-4), 71.6, 71.4, 71.3, 71.2, 71.1 (C-6), 71.7, 71.0, 70.9, 70.8 (C-5), 61.5, 61.4, 61.1, 61.0 (3-OCH_3), 59.4, 59.2, 59.13, 59.06, 59.0, 58.8, 58.7, 58.6, 58.5 (6-OCH_3, 2-OCH_3).

4.3.3. 6^{I}-*O*-Benzyl-$2^{I–VIII}$, $3^{I–VIII}$, $6^{II–VIII}$-tricosa-*O*-methyl-cyclomaltooctaose 11 (Scheme 5). A solution of cyclodextrin **13** (192 mg, 0.12 mmol) in THF (5 mL) was added dropwise to a stirred suspension of sodium hydride (28 mg, 1.18 mmol) in THF (2 mL). The resulting mixture was heated at reflux for 2 h. After cooling to 0 °C, benzyl chloride (136 μL, 1.18 mmol) was added dropwise and the resulting solution was stirred first at 0 °C for 1 h, then was refluxed overnight. The reaction mixture was quenched by the addition of methanol (2 mL). The solvent was evaporated under reduced pressure, then the residue was dissolved in CH_2Cl_2 (10 mL) and washed with brine (2 × 5 mL). After drying over $MgSO_4$ and filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography on grafted C18 silica gel (methanol/water 90/10) yielding 76% (153 mg) of pure cyclodextrin **11**. White powder. R_f (toluene/acetone 50/50) = 0.49. $[\alpha]_D = +0.3$ (*c* 1.64, EtOH, 589 nm). HPLC: column ALLTIMA® C18 EPS; CH_3OH/H_2O (80/20); rt = 11.35 min. HRMS (ESI+) calcd $C_{78}H_{132}O_{40}Na$ $m/z = 1731.8193$, found 1731.8204. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.32–7.31 (m, 5H, Ph), 5.27–5.19 (m, 8H, H-1,1′), 4.62 (d, 1H, $^2J_{a,b} = 12.3$ Hz, CH_aH_bPh), 4.53 (d, 1H, $^2J_{a,b} = 12.3$ Hz, CH_aH_bPh), 3.98 (m, 1H, H-6′α), 3.92–3.81 (m, 8H, H-6α,6′β), 3.81 (m, 1H, H-5′), 3.77–3.71 (m, 8H, H-4,4′), 3.72 (m, 8H, H-3,3′), 3.66–3.51 (m, 7H, H-6β), 3.66–3.63 (m, 24H, 3,3′-OCH_3), 3.52–3.50 (m, 24H, 2,2′-OCH_3), 3.37–3.31 (m, 21H, 6-OCH_3), 3.23–3.19 (m, 8H, H-2,2′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.4 (C_q, Ph), 128.4 (CH-meta), 127.6 (CH-ortho and para), 98.3, 98.24, 98.18, 98.06, 97.98 (C-1), 82.2, 82.1, 82.0 (C-2, C-3), 79.5, 79.0, 78.9, 78.7, 78.3, 78.1, 77.4 (C-4), 73.3 (CH_2Ph), 71.3 (C-6), 71.1 (C-5′), 71.0 (C-5), 69.0 (C-6′), 61.7, 61.6, 61.5, 61.4 (3-OCH_3), 59.14–59.11 (6-OCH_3), 58.9–58.7 (2-OCH_3).

4.4. Column preparation

An intermediate polarity-fused silica capillary tube was statically coated with a solution containing a mixture (15/85, w/w) of CD derivative **11** and OV 1701 (86% methyl, 7% phenyl, 7% cyanopropyl polysiloxane) dissolved in a mixture of pentane/dichloromethane (50/50, v/v) to produce a 0.25 μm thick film of stationary phase. Before any test, the column was conditioned under helium as described: 40 °C (initial temperature, 10 min hold), then ramp at a rate of 1 °C/min to 190 °C (final temperature, 4 h hold).

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