DOI: 10.1002/ejoc.201000295

The Grignard Reaction of Cyclodextrin-6-aldehydes Revisited: A Study of the Stereoselectivity Upon Addition of Organometallic Reagents to Aldehydes and Ketones

Emil Lindbäck,[a] You Zhou,[a] Lavinia Marinescu,[a] Christian M. Pedersen,[a] and Mikael Bols*[a]

Keywords: Supramolecules / Carbohydrates / Cyclodextrins / Nucleophilic addition

$2^{A–G},3^{A–G},6^{B–G}$-Icosakis-*O*-benzyl-6^{A}-*O*-oxo-β-cyclodextrin was treated with aromatic and aliphatic Grignard reagents to give diastereomeric mixtures of the secondary alcohols with remarkable difference in polarity. Moderate-to-good yields and selectivity were obtained. By oxidizing the secondary alcohols, followed by a second Grignard reaction, good to excellent yields and selectivity of tertiary alcohols could be obtained. The stereochemistry of the reaction outcome was shown to be dependent on the order of addition of the Grignard reagents and could be efficiently controlled.

Introduction

Cyclodextrins are readily available cyclic amylose oligomers consisting of 6, 7 or 8 glucose units.[1] These compounds are referred to as α-, β-, and γ-cyclodextrins respectively. Because of their ability to bind hydrophobic substrates in their cavity, cyclodextrins are attractive compounds as starting materials for the synthesis of artificial enzymes,[2–4] and other supramolecular devices. Though many interesting enzyme mimics have been made, a limiting factor in this research is probably the difficult and often low yielding methods available for the preparation of modified cyclodextrins.[5] Consequently new and elegant ways of

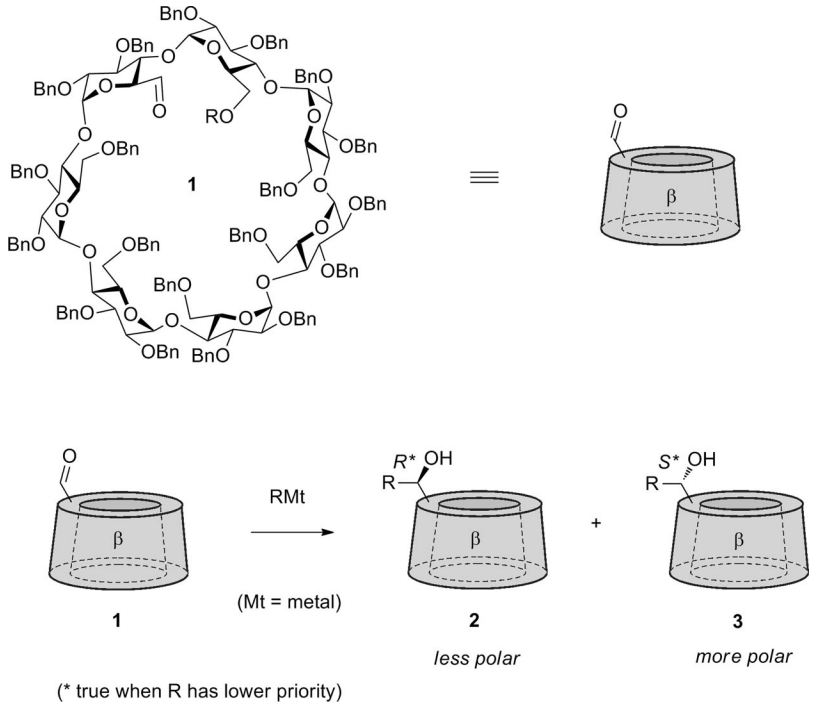

Figure 1. Benzylated β-cyclodextrin-aldehyde and its reaction with organometallic reagents. This leads to two stereoisomers with rather different polarity.

[a] Department of Chemistry, University of Copenhagen, 2100 Copenhagen, Denmark

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000295.

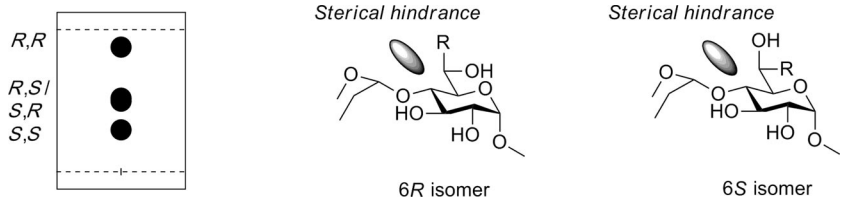

Figure 2. TLC plate showing the different polarity of diastereomeric $6^{A,D}$-di-*C*-allyl-substituted nonadeca-*O*-benzylated β-cyclodextrins in the eluent pentane/ethyl acetate 4:1 (left). Depiction showing how steric hindrance from the subsequent glucose residue prevents substituents at C-6 to enter the *tg* conformation thereby forcing each diastereomer to adopt the shown conformers (right).

modifying these compounds are required and are indeed continuously being developed.[6] One of the very powerful methods with which to modify cyclodextrins is the method developed by Sollogoub and Sinaÿ,[6–8] where perbenzylated cyclodextrins are selectively mono- or di-6-debenzylated with DIBAL-H in high yield. From the resulting alcohols, aldehydes, such as **1** (Figure 1), can readily be obtained from oxidation by Dess–Martin periodane (DMP)[9] or Swern conditions.[10] These are potentially important building blocks for artificial enzymes or molecular machines since C–C bond formation at the oxidized position can be achieved.

The Grignard reaction of perbenzylated β-cyclodextrin derivatives containing one 6-aldehyde group, or two 6-aldehydo groups in the A and D rings, was therefore investigated quite early with aliphatic Grignard reagents.[10] The reaction gave the stereoisomeric secondary alcohols expected for 1,2-addition in diastereomeric ratios of about 1 : 3 ratio for the 6*R*- and 6*S*-isomers. Surprisingly the 6*R*-isomers were consistently found to be much less polar in terms of chromatographic retention times than the 6*S*-isomers. The polarity difference, which disappeared upon acetylation or oxidation, was interpreted as being caused by the presence or absence of intramolecular hydrogen bonding. The configurations of the diastereomers were determined showing that the polar isomer was the *S*-isomer, and the apolar isomer is the *R*-isomer. Modeling studies suggested that 6-*C*-alkylation restricts the conformation around the C5–C6 bond such that the 6*S*-isomer will adopt a *gg* conformation, which has the hydroxy group pointing outwards, while the 6*R*-isomer will adopt a *gt* conformation, which has the OH group pointing towards the inner face of the cyclodextrin (Figure 2).

Recently we wanted to attach other functional groups, particularly pyridine, to the cyclodextrin. This led us to revisit this reaction now using other, predominantly aromatic, organometallic reagents. We have also studied reaction of organometallic reagents to the corresponding ketones, which are readily obtained from oxidation of the Grignard products. We find that the yield and stereoselectivity of these Grignard reactions depend very much on the reagent used.

Results and Discussion

β-Cyclodextrin-aldehyde[11] (**1**) (Figure 1) was treated with Grignard and organolithium reagents (Table 1, entry 1–17). Aliphatic Grignard reagents gave generally a modest yield of product, except methylmagnesium bromide which gave 82% of adducts **2a** and **3a** (entry 1).

Table 1. Results of reaction of organometallic reagents with benzylated β-cyclodextrin-aldehyde **1**, methyl ketone **4a**, phenyl ketone **4b** and phenyl ethynyl ketone **4c** (* ratio may be reversed. *i*Pr = isopropyl).

Entry	Substrate	Reagent	% Yield	Products (ratio)
1	**1**	MeMgBr	82	**2a** and **3a** (1:1)
2	**1**	allylMgBr	31	**2b** and **3b** (3:4)
3	**1**	BnMgBr	<14	–
4	**1**	*i*PrMgCl	<10	–
5	**1**	*c*-pentylMgBr	0	–
6	**1**	propargyl MgBr	82	**2c** and **3c** (1:5)
7	**1**	Ph-ethynylMgBr	70	**2d** and **3d** (5:1)
8	**1**	Ph-ethynylMgBr (+ PhMe)	47	**2d** and **3d** (2:1)
9	**1**	Ph-ethynylLi	60	**2d** and **3d** (8:1)
10	**1**	Ph-ethynyl$CeCl_2$	42	**2d** and **3d** (4:1)
11	**1**	Ph-ethynylZnCl	49	**2d** and **3d** (5:4)
12	**1**	PhMgBr	60	**2e** and **3e** (11:1)
13	**1**	PhLi	0	–
14	**1**	4-F-C_6H_4MgBr	71	**2f** and **3f** (15:1)
15	**1**	4-F-C_6H_4MgBr (+ $MgBr_2$)	57	**2f** and **3f** (5:1)
16	**1**	2-pyridylMgBr	73	**2g** and **3g** (7:1)
17	**1**	2-pyridylLi	0	–
18	**7a**	ethynylMgBr	86	**8a** and **9a** (4:1*)
19	**7a**	PhMgBr	81	**8b** and **9b** (4:1*)
20	**7a**	4-F-C_6H_4MgBr	77	8c and **9c** (4:1*)
21	**7d**	allylMgBr	41	**8d** (>99:1)
22	**7e**	4-F-C_6H_4MgBr	68	**8e** (>99:1)
23	**7f**	Ph-ethynylMgBr	90	**9e** (>99:1)

Benzylmagnesium bromide and isopropylmagnesium chloride (entries 3–4) gave low yield of products that were difficult to purify or separate from the aldehyde, and cyclopentylmagnesium bromide (entry 5) gave no yield. Enolization and possibly reduction of the aldehyde in the latter cases is the most likely reason why these reactions fare so badly. Allyl and propargylmagnesium bromide (entries 2 and 5) gave 33 and 82% of predominantly the polar *S*-isomers **3b** and **3c**. Again the difference in yield is remarkable and is a result of the allyl reagent giving unreacted starting material and possibly side products; presumably enolisation is a bigger problem with allylmagnesium bromide.

The aromatic Grignard reagents, phenyl, 4-fluorophenyl and 2-pyridylmagnesium bromide gave good yields of predominantly the apolar *R*-isomers **2e**, **2f** and **2g** with selec-

tivities up to 11:1 (entries 12, 14 and 16). However none of the aromatic organolithium reagents gave any product and starting material appeared to be present after reaction. It is believed that these strongly basic compounds caused enolization of the aldehyde in **1**. Phenylethynylmagnesium bromide behaved similar to aromatic Grignards giving a 70% yield of **2d** in a 5:1 ratio over **3d** (entry 7). The better yields may be due to the lower reactivity of aryl and alkyl reagents compared with the more reactive alkyl Grignard reagents, which causes more side reactions.[12]

All the stereoisomeric Grignard products had a polarity similar to what had been observed previously, with one C-6 stereoisomer being significantly more polar than the other, and stereochemistry was assigned accordingly. However, to check if aromatic substituents might behave differently we hydrolyzed the apolar, major isomer from the reaction of 4-fluorophenylmagnesium bromide, presumably **2f**, separated the arylated glucose residue from the unmodified glucose residues by chromatography, and subjected it to Fisher glycosylation to give **5a** (Figure 3). Simultaneously the two reference compounds **5a** and **5b** were prepared from methyl 2,3,4-*O*-benzyl-α-D-glucopyran-1,6-diuloside (**4**) by reaction with 4-fluorophenylmagnesium bromide followed by hydrogenolysis (Figure 3). The identity of **5a** and **5b** was established by conversion of the major isomer **5b** to the 4,6-benzylidene derivative **6** with benzaldehyde dimethyl acetal and acid catalysis. In **6** NMR showed a small coupling constant (5.4 Hz) between H-5 and H-6 which is only consistent with the 6*S*-stereochemistry. This confirms that also for aromatic substituents the less polar isomer has *R*-stereochemistry. A TOCSY spectrum of the debenzylated **2f** showed a very small $J_{5,6}$ in the modified glucose residue. This shows that the compound has a fixed conformation around the C-5/C-6 bond and that the 6-H is not in *gg* position. This is consistent with the interpretation that the 6-H is in *tg* position, the aromatic group in *gg* position, thereby on the outside of the cyclodextrin and the hydroxyl group in *gt* position pointing towards the cavity; the only alternative staggered conformer would leave the 4-fluorophenyl group in the space-demanding *tg*-position which is improbable.

In summary aromatic Grignard reagents yield rather selectively the *R*-isomer upon addition to aldehyde **1**, while aliphatic Grignard reagents give a mixture with predominance for *S*-isomer. If empirical stereoselectivity models can be applied here, and assuming that C_4 is a sterically larger group than O^5 (intuitively reasonable), the Felkin–Anh polar model[13] (Figure 5) predict that the *R*-isomer should be the preferred product. In this model a polar α-substituent, here O^5, in the reacting aldehyde or ketone have to be oriented perpendicular to the carbonyl group so that there is a favorable orbital overlap between its π*-orbital and the antibonding orbital of the C^5–O^5 bond. Attack by the nucleophile (Nu) near the smallest group (H5) then result in the observed stereochemistry.

The observation that addition of $MgBr_2$ result in a small lowering of *R*-selectivity (entry 15) supports that chelation is not involved in formation of the major product. Also the experiment with phenethynyllithium, where chelation cannot occur and which gives *R*-product, fits the Felkin–Anh polar model.

Albeit the *S*-selectivity observed with some aliphatic reagents not is large, the difference in selectivity is nevertheless puzzling. It suggests a difference in mechanism or rate-determining step between aliphatic and aromatic reagents.

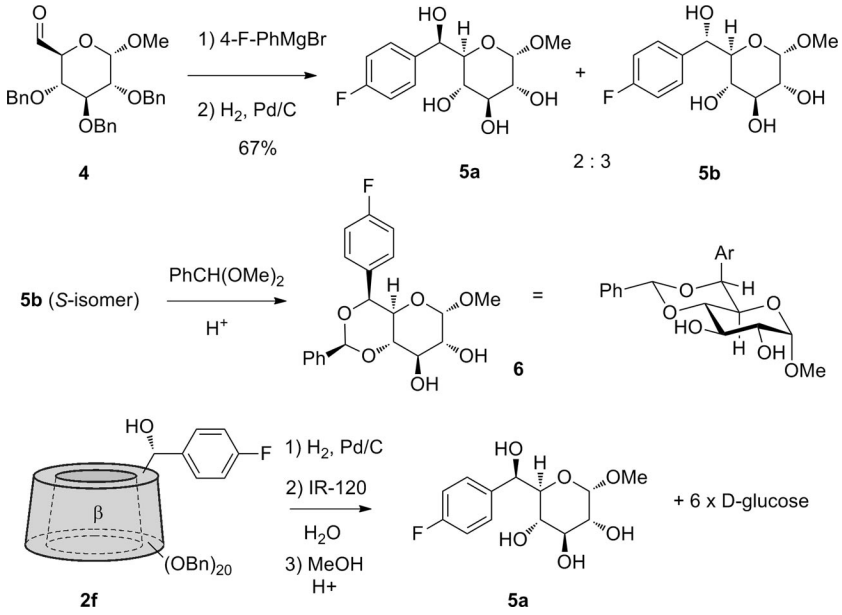

Figure 3. Preparation of two reference monosaccharide derivatives, **5a** and **5b**, that could be used to determine the stereochemistry at C-6. The major isomer **5b** from addition of (4-fluorophenyl)magnesium bromide to glucose-6-aldehyde **4** was converted into the benzylidene derivative **6**. This compound had a small $J_{5,6}$, which is consistent with *S*-stereochemistry only. Hydrolysis of the β-cyclodextrin derivative **2f** and conversion to methyl glycoside led to the minor *R*-isomer **5a**.

Oxidation of the secondary alcohols **2** and **3** to the ketone **7** is readily achieved with Dess–Martin periodinane (DMP) or pyridinium dichromate solution (PDC) (Figure 4). This was done on 4 different alcohols giving ketones **7a**,**7d**,**7e**, and **7f**. Addition of Grignard reagents to these ketones proceeded in good yield with both aliphatic and aromatic reagents to give the tertiary alcohols. From the methyl ketone **7a** mixtures of isomers, **8** and **9**, were obtained, but from the other ketones **7d**–**f** only a single isomer of either **8** or **9** was formed. The relative ratio of the two isomers is readily determined by NMR, but the stereochemical identity of the isomers is not, and **8** and **9** have essentially identical chromatographic retention. For **8/9 a**–**c** (Table 1, entries 18–20) the stereochemistry of the isomers was not determined, because the product was mixtures that could not be separated. On the other hand for **8e** and **9e**, which gave pure products, the product was identified by hydrolytic degradation and comparison with reference compounds (see below).

These results show that reaction of **7e** with 4-fluorophenylmagnesium bromide exclusively yields the *S*-isomer **8e** (Table 1, entry 22), while reaction of **7f** with phenethynylmagnesium bromide exclusively yield the *R*-isomer **9e** (Table 1, entry 23). This means that ketones **7e** and **7f** gives stereoselectivity accordance with the Felkin–Anh polar model and thereby with the same mode of reaction as the aldehydes. It also means that the stereochemistry of the tertiary center can be controlled: When starting from aldehyde **1** and reacting with Grignard reagent, oxidizing to ketone and Grignard reaction the order of Grignard reagents determines the stereochemistry, so reversion of the order will generate the antipode.

The single product formed from **7d** has not been specifically determined, but it is assumed to be the *S*-isomer **8d** based on the observed stereoselectivity in the Grignard reactions.

The stereochemistry of **8e** and **9e** was determined as outlined in Figure 5. Cyclodextrin derivative **9e** was hydrogenolyzed and subjected to acidic hydrolysis with IR-120 ion-exchange resin followed by Fischer glycosylation with methanol and acid. The product was a mixture of methyl glycosides from which the C6-modified methyl glycoside was isolated and compared with reference samples using TLC and HPLC. The reference samples were made from **4** by reaction with the corresponding Grignard reagents followed by oxidation to the ketones **11** and **12** respectively (Figure 5). These were then reacted with Grignard reagent and deprotected to give **13*S*** and **13R** with high diastereoselectivity. Reaction of the isomer mixture with dimethoxytoluene and acid gave the 4,6-benzylidene derivatives **10R** and **10*S*** that could be separated by chromatography. The relative stereochemistry of **14R** and **14*S*** could conclusively be determined from NOE experiments: In **14*S*** there is strong NOE between the benzylidene proton and the aromatic protons of the 4-fluorophenyl group, that is not the case in **14*R***, which shows a strong NOE to one of the protons on C7. Acidic hydrolysis of **14*R*** and **14*S*** to reference compounds **10*R*** and **10*S*** was performed (not shown). The hydrolysis product from **9e** was found to be identical with **10*S*** (Figure 5).

Overall it can be concluded that the stereoselectivity of the addition is similar for the reaction of ketones and for the addition of large Grignard reagents to aldehydes: The selectivity follows the one predicted by Felkin–Anh's polar

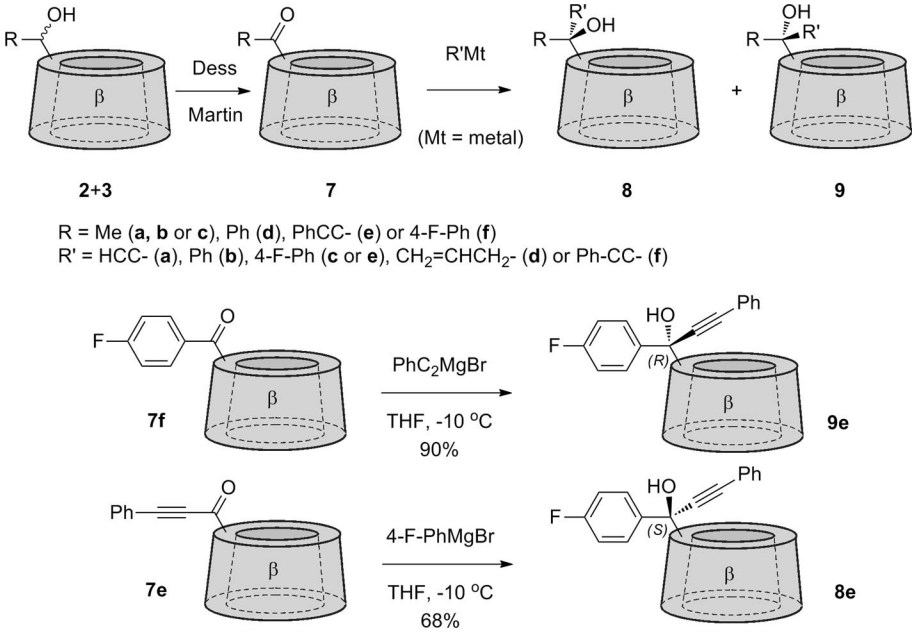

Figure 4. Oxidation of secondary alcohols to the β-cyclodextrin ketone **4**, **7e** and **7f** followed by reaction with organometallic reagents to give tertiary alcohols.

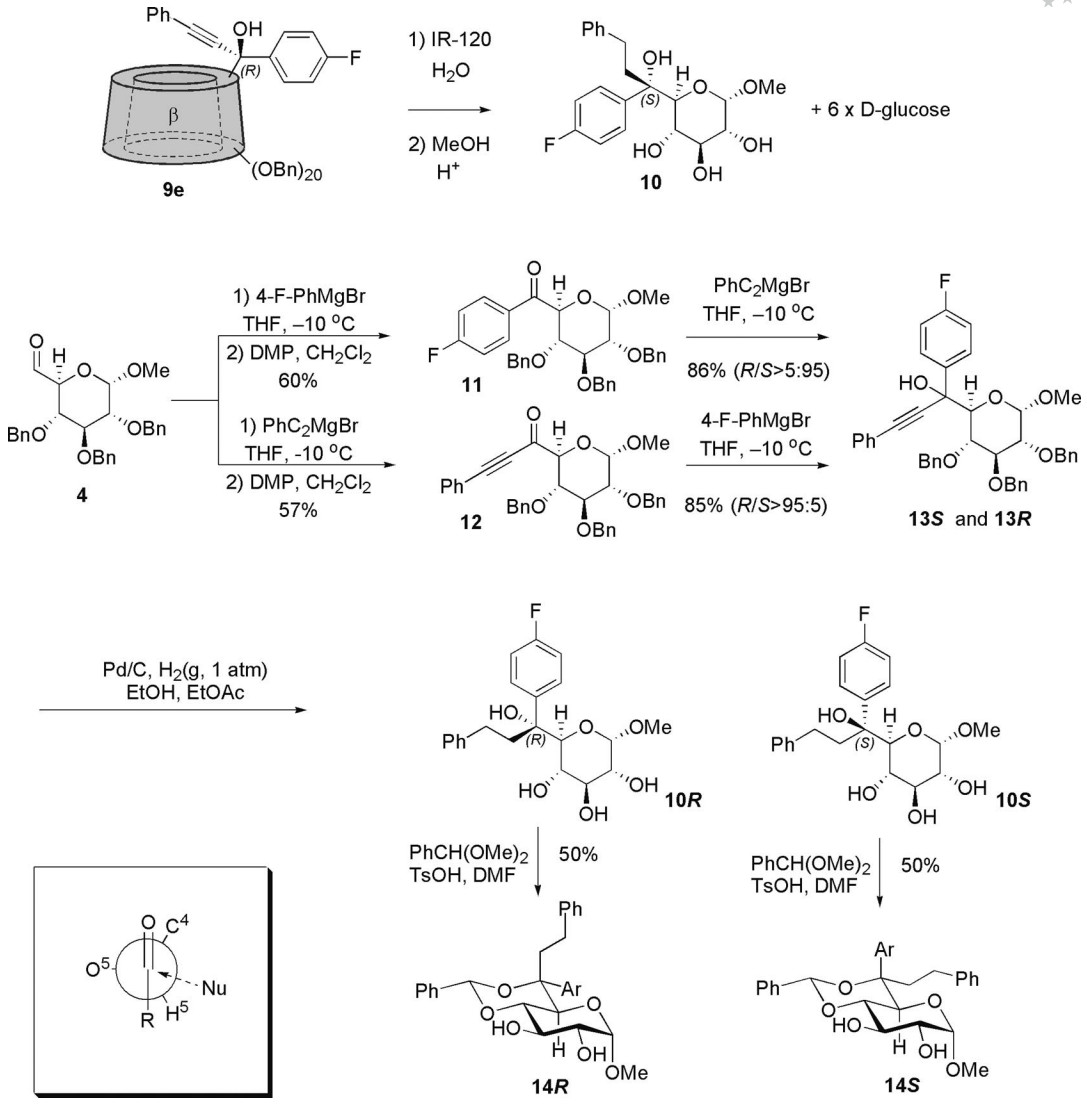

Figure 5. Preparation of two reference monosaccharide derivatives, **10*S*** and **10*R*** that could be used to determine the stereochemistry at C-6 of tertiary alcohols **8e** and **9e**. The mixture of secondary alcohols from the Grignard reaction with **4** was oxidized to the ketones **11** and **12** followed by an additional Grignard reaction. After hydrogenolysis the reference compounds **10*S*** and **10*R*** were obtained. By converting them into the 4,6-benzylidene derivatives **14*S*** and **14*R*** the stereochemistry could be determined by NMR studies. The insert (bottom left) show nucleophilic addition to carbonyl group according to Felkin–Anh's polar model.

model. The selectivity is high and stereoselectivity of the tertiary alcohols can be controlled by the order in which the organometallic reactions are carried out.

Experimental Section

General: Solvents were distilled under anhydrous conditions. All reagents were used as purchased without further purification. Glassware used for water-free reactions was dried for 2 h at 130 °C before use. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. TLC plates (Merck, 60, F_{254}) were visualized by spraying with cerium sulfate (1%) and molybdic acid (1.5%) in 10% H_2SO_4 and heating until colored spots appeared. ^{1}H-, ^{13}C-NMR and COSY experiments were carried out with a Varian Mercury 300 or a Varian Unity 500 instrument. Monoisotopic mass spectra (MALDI-TOF MS) were obtained on a Bruker Daltonics mass spectrometer using ditranol (1,8-dihydroxyanthron) as matrix. Spectra were calibrated using a polymer calibration standard.

$2^{A–G}$,$3^{A–G}$,$4^{A–G}$,$6^{B–G}$-Icosakis-*O*-benzyl-6^A-deoxy-6^A-oxy-6^A-phenyl-β-cyclodextrin (7d): A solution of compound **2e** (706 mg, 0.234 mmol) in DCM (16 mL) was added PDC (793 mg, 2.1 mmol). The reaction mixture was left stirring overnight at room temperature. Then Celite was added and the solvent was removed under reduced pressure. The crude product was added on the top of a silica pad, elution (EtOAc/*n*-pentane: 1/1) afforded compound **7d** (98%, 693.1 mg) as a white foam; R_f = 0.59 (EtOAc/*n*-pentane: 3/5); $[\alpha]_D$ = +41.5 (*c* = 1.0, DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–7.95 (m, 2 H, H arom.), 7.31–6.97 (m, 103 H, H arom.), 5.25–5.16 (m, 5 H), 5.13–5.09 (m, 3 H), 5.05–4.95 (m, 4 H), 4.91 (d, ^2J = 11 Hz, 1 H, CHPh), 4.83–4.75 (m, 5 H), 4.68 (d, ^2J = 11 Hz, 1 H, CHPh), 4.63 (d, ^2J = 11 Hz, 1 H, CHPh), 4.59–4.32 (m, 22 H), 4.26 (d, ^2J = 12 Hz, 1 H, CHPh), 4.16–3.78 (m, 28 H), 3.66–3.35 (m, 15 H), 2.78 [d, ^2J(H,H) = 11 Hz, 1 H,] ppm. ^{13}C

NMR (75 MHz, $CDCl_3$): δ = 194.0 (C=O), 139.7–137.9 (C arom. quat.), 135.6, 133.8 (C arom. quat.), 129.6–127.2 (Carom. tert.), 99.1, 99.0, 98.8, 98.7, 98.5, 98.2, (C-1), 81.5, 81.1, 80.9, 80.8, 80.5, 79.7, 79.6, 79.3, 79.2, 79.0, 78.7, 78.2, 78.1, 77.6, 76.1, 75.8, 75.7, 75.5, 75.2, 73.8, 73.7, 73.5, 73.3, 73.1, 73.0, 72.9, 72.8 71.9, 71.8, 69.9,, 69.6, 68.9, 68.7 (CH, CH_2) ppm. MALDI-TOF-MS: *m/z* calcd. for $C_{188}H_{192}O_{35}Na$ 3034.321 found 3034.398.

$2^{A–G},3^{A–G},4^{A–G},6^{B–G}$-Icosakis-*O*-benzyl-$6^A$-deoxy-$6^A$-(4-fluorophenyl)-$6^A$-oxy-β-cyclodextrin (7f): See experimental part for compound **7d**; yield (98%, 1.62 g); R_f = 0.35 (EtOAc/*n*-pentane: 2/3); $[\alpha]_D$ = +34.4 (*c* = 0.5, DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94 (dd, $^4J_{H,F}$ = 6, $^3J_{H,H}$ = 9 Hz, 2 H, H arom.), 7.26–6.98 (m, 102 H, H arom.), 5.25–5.20 (m, 3 H, 1-H), 5.16 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.14 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.09–5.07 (m, 7 H, 2 1-H, 5CHPh), 5.02 (d, ^2J = 10 Hz, 1 H, CHPh), 4.94 (d, ^2J = 11 Hz, 1 H, CHPh), 4.88 (d, ^2J = 11 Hz, 1 H, CHPh), 4.81–4.75 (m, 4 H), 4.72 (d, ^2J = 11 Hz, 1 H, CHPh), 4.68–4.62 (m, 2 H, 2CHPh), 4.57–4.53 (m, 3 H), 4.51–4.41 (m, 12 H), 4.39–4.33 (m, 6 H), 4.31–4.26 (m, 3 H), 4.18 (br. s, 2 H), 4.11–3.76 (m, 25 H), 3.58–3.44 (m, 11 H), 3.41–3.37 (m, 2 H), 2.90 (d, $^2J_{H,H}$ = 10 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.0 (C=O), 166.1 (d, $^1J_{C,F}$ = 254 Hz, C arom. quat.), 139.7- 138.0 (C arom. quat.), 132.4–132.1 (C arom. quat., C arom. tert.), 128.6–127.2 (C arom. tert.), 116.2 (d, $^2J_{C,F}$ = 21 Hz, C arom. tert.), 99.2, 98.9, 98.7, 98.3, 98.2 (C-1), 81.4, 81.0, 80.8, 80.5, 80.0, 79.8, 79.5, 79.3, 79.1, 78.8, 78.1, 77.6, 75.9, 75.8, 75.4, 75.3, 73.8, 73.7, 73.5, 73.3, 73.1, 73.0, 72.9, 72.8, 72.1, 71.8, 71.7, 69.8, 69.6 69.5, 69.4, 68.9, 68.6 (CH, CH_2) ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –103.67 ppm. MALDI-TOF-MS: *m/z* calcd. for $C_{188}H_{191}FO_{35}Na$ 3052.311, found 3052.307.

$2^{A–G},3^{A–G},4^{A–G},6^{B–G}$-Icosakis-*O*-benzyl-$6^A$-deoxy-$6^A$-methyl-$6^A$-oxy-β-cyclodextrin (7a): A solution of aldehyde **1** (1.0 g, 0.341 mmol) in THF (5.5 mL) under nitrogen was slowly added MeMgBr (1.14 mL, 3 mol L^{-1} in Et_2O) at room temperature. The reaction mixture was left stirring for 1 h before quenching by slowly addition of saturated aqueous NH_4Cl (15 mL) at 0 °C. Then the phases were separated and the aqueous phase was extracted with DCM (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Then the crude was dissolved in DCM (25 mL) and was added Dess–Martin periodinane (444 mg, 1.02 mmol). The reaction mixture was left stirring overnight under a nitrogen atmosphere. Quenched by adding Et_2O (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) consisting of $Na_2S_2O_3$ (2 g), followed by stirring for 1 h. Then the layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification on a silica column (EtOAc/*n*-pentane: 1/5) afforded ketone **6** (58%, 585 mg) as a white foam; R_f = 0.35 (EtOAc/*n*-pentane: 3/5); $[\alpha]_D$ = +27.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.01 (m, 100 H, H arom.), 5.32 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 5.25 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 5.23–5.17 (m, 4 H, 2 1-H, 2CHPh), 5.13–4.98 (m, 7 H, 3 1-H, 4CHPh), 4.87–4.76 (m, 6 H), 4.71 (d, ^2J = 11 Hz, 1 H, CHPh), 4.66–4.60 (m, 2 H), 4.56–4.28 (m, 24 H), 4.26–4.17 (m, 2 H), 4.12–3.82 (m, 25 H), 3.71–3.68 (m, 1 H), 3.62–3.35 (m, 13 H), 1.98 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.9 (C=O), 139.8–138.1 (C arom. quat.), 128.6–127.2 (C arom. tert.), 99.0, 98.8, 98.6, 98.4, 98.2 (C-1) 81.6, 81.3, 81.1, 80.9, 80.5, 80.2, 79.6, 79.5, 79.3, 79.1, 78.9, 78.8, 77.6, 76.5, 76.1, 75.9, 75.8, 75.5, 75.4, 73.8, 73.7, 73.6, 73.5, 73.1, 73.0, 71.8, 71.6, 69.6, 69.2, 69.0 (CH, CH_2), 26.4 (CH_3) ppm. MALDI-TOF-MS: *m/z* calcd. for $C_{183}H_{190}O_{35}Na$ 2971.302 found 2971.681.

$2^{A–G},3^{A–G},4^{A–G},6^{B–G}$-Icosakis-*O*-benzyl-$6^A$-deoxy-$6^A$-oxy-$6^A$-(phenylethynyl)-β-cyclodextrin (7e): A solution of phenylacetylene (0.95 mL, 8.52 mmol) in THF (2 mL) under nitrogen was cooled down to 0 °C before slowly adding EtMgBr (8.52 mL, 1 mol L^{-1} in THF). Then the reaction mixture was allowed to reach room temperature and stirring for 30 min. The Grignard reagent was added a solution of aldehyde **1** (1.0 g, 0.341 mmol) in THF (7.5 mL) at room temperature. The reaction mixture was left stirring at room temperature for 2 h before quenching by slowly adding saturated aqueous NH_4Cl (15 mL) at 0 °C. Then the layers were separated and the water phase was extracted with DCM (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude was dissolved in DCM (25 mL) and was added Dess–Martin periodinane (444 mg, 1.02 mmol). The reaction mixture was left stirring overnight under nitrogen at room temperature. The reaction was quenched by adding Et_2O (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) and $Na_2S_2O_3$ (2 g), followed by stirring for 1 h. Then the layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Purification on a silica column (EtOAc/*n*-pentane: 1/10 → 1/5) afforded the desired product (70%, 721.6 mg) as a white foam; R_f = 0.37 (EtOAc/*n*-pentane: 4/5); $[\alpha]_D$ = +46.2 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–6.96 (m, 105 H, H arom.), 5.46 (br. s, 2 H, 1-H), 5.30 (d, ^2J = 11 Hz, 1 H, CHPh), 5.21–5.08 (m, 8 H, 5 1-H, 3CHPh) 4.92–4.66 (m, 10 H), 4.50–3.94 (m, 51 H), 3.79–3.59 (m, 5 H), 3.54–3.40 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.5 (C=O), 139.9–138.4 (C arom. quat.), 133.6, 131.3 (C arom. tert.), 129.2–127.3 (C arom. tert.), 119.8 (C arom. quat.), 99.3, 99.1, 98.9, 98.4, 98.1, 97.8 (C-1), 94.8, 86.8 (C_{sp}), 81.9, 81.6, 81.5, 81.4, 81.2, 80.9, 80.4, 80.0, 79.8, 79.6, 79.4, 79.2, 79.1, 78.6, 77.1, 76.3, 76.1, 75.3, 75.2, 73.7, 73.6, 73.5, 73.1, 72.9, 71.8, 71.6, 71.4, 70.0, 69.7, 69.5, 69.3 (CH, CH_2) ppm. MALDI-TOF-MS: *m/z* calcd. for $C_{190}H_{192}O_{35}Na$ 3058.3 found 3058.1.

Preparation of (4-Fluorophenyl)magnesium Bromide (in THF): A suspension of Mg turnings (485 mg, 20.0 mmol) in THF under nitrogen at room temperature was slowly added 1-bromo-4-fluorobenzene (1.57 mL, 14.3 mmol). The reaction mixture was left stirring for 90 min before use.

$2^{A–G},3^{A–G},6^{B–G}$-Icosakis-*O*-benzyl-6^A*R*-(4-fluorophenyl)-β-cyclodextrin (2f) and $2^{A–G},3^{A–G},6^{B–G}$-Icosakis-*O*-benzyl-6^A*S*-(4-fluorophenyl)-β-cyclodextrin (3f)

Method A-1: A freshly prepared solution of (4-fluorophenyl)magnesium bromide (3.17 mL in THF) was slowly added to a solution of aldehyde **1** (559 mg, 0.190 mmol) in THF (7.4 mL) under nitrogen at ambient temperature. The reaction mixture was stirred for 2.5 h before quenching by slowly adding saturated aqueous NH_4Cl (10 mL) at 0 °C. The phases were separated and the water phase was extracted with DCM (4 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification on a silica column (EtOAc/*n*-pentane: 1/10 → 1/5) afforded the monol **2f** (67%, 386.6 mg) as a white foam; R_f = 0.40 (EtOAc/*n*-pentane: 3/5); $[\alpha]_D$ = +35.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 102 H, H arom.), 7.05–6.99 (m, 2 H, H arom.), 5.57 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.38–5.32 (m 3 H, 2 1-H, CHPh), 5.27 (d, ^2J = 11 Hz, 1 H, CHPh), 5.20–5.00 (m, 8 H), 4.93–4.86 (m, 4 H), 4.81 (d, $^3J_{H,H}$ = 5 Hz, 1 H), 4.76–4.41 (m, 30 H), 4.26–3.91 (m, 26 H), 3.78–3.36 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5 (d, $^1J_{C,F}$ = 244 Hz, C arom. quat.), 139.8–137.1 (C arom. quat.), 130.4 (d, $^3J_{C,F}$ = 8 Hz, C arom. tert.), 128.7–127.2 (C arom. tert.), 114.9 (d, $^2J_{C,F}$ = 21 Hz, C arom. tert.), 99.5, 99.4, 99.3, 99.0, 98.7, 97.7 (C-1), 81.5, 81.4, 81.3, 80.9, 80.4, 80.2, 79.8, 79.4, 79.3, 79.2, 76.4, 76.2, 75.9, 75.7,

75.2, 75.0, 74.7, 73.9, 73.8, 73.7, 73.6, 73.4, 73.2, 73.0, 72.9, 72.5, 72.4, 72.0, 71.9, 71.6, 70.1, 69.8, 69.6, 69.1 (CH, CH_2) ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –115.05 ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{188}H_{193}FO_{35}Na$ 3054.327 found 3054.110. Further elution afforded monol **3f** (4%, 23.5 mg) as a white foam; R_f = 0.34 (EtOAc/*n*-pentane: 3/5); $[\alpha]_D$ = +33.4 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.05 (m, 102 H, H arom.), 6.99–6.93 (m, 2 H, H arom.), 5.76 (br. s, 1 H, 1-H), 5.60 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 5.36–5.18 (m, 5 H, 1 1-H, 4CHPh), 5.14 (d, ^2J = 11 Hz, 1 H, CHPh), 4.99 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 4.95 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 4.91–4.72 (m, 11 H), 4.63–4.60 (m, 2 H), 4.58–4.44 (m, 15 H), 4.42–4.37 (m, 2 H), 4.35–4.28 (m, 4 H), 4.23–4.04 (m, 12 H), 4.02–3.85 (m, 11 H), 3.79–3.64 (m, 9 H), 3.59–3.41 (m. 8 H) 3.21–3.02 (m, 3 H), 2.80–2.76 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7 (d, $^1J_{C,F}$ = 277 Hz, C arom. quat.), 139.9–138.6 (C arom. quat.), 138.4 (d, $^4J_{C,F}$ = 4 Hz, C arom. quat.), 138.1, 137.9 (C arom. quat.), 128.7–127.0 (C arom. tert.), 114.9 (d, $^2J_{C,F}$ = 20 Hz, C arom. tert.), 100.4, 100.2, 100.0, 98.8, 98.5, 98.4, 97.7 (C-1), 82.1, 81.6, 81.5, 81.4, 81.2, 81.0, 80.9, 80.7, 80.2, 80.1, 80.0, 79.5, 79.1, 79.0, 78.8, 77.6, 76.8, 76.5, 76.2, 76.1, 75.4, 74.9, 74.7, 74.4, 73.8, 73.7, 73.6, 73.4, 73.3, 73.0, 72.8, 72.7, 72.6, 72.3, 72.1, 72.0, 71.8, 71.5, 70.0, 69.2, 67.9 (CH, CH_2) ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –115.26 ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{188}H_{193}FO_{35}Na$ 3054.327 found 3054.012.

Method A-2: A suspension of $MgBr_2$ [prepared by slowly adding 1,2-dibromoethane (0.49 mL, 5.53 mmol) to a suspension of Mg turnings (134.4 mg, 5.53 mmol) in Et_2O (3.2 mL) under nitrogen at room temperature and stirring for 45 min] under nitrogen at room temperature was slowly added aldehyde **1** (650 mg, 0.221 mmol) dissolved in Et_2O (5.3 mL). Then the mixture was left stirring for 45 min before cooling it down to 0 °C and slowly adding (4-fluorophenyl)magnesium bromide (3.69 mL) [prepared by slowly adding 1-bromo-4-fluorobenzene (1.5 mL, 14.1 mmol) to a suspension of Mg turnings (480 mg, 19.7 mmol) in Et_2O (7.9 mL) under nitrogen at room temperature, and stirring for 1.5 h]. The obtained reaction mixture was left stirring for 10 min before adjusting to room temperature and stirring for 80 min more followed by quenching with saturated aqueous NH_4Cl (10 mL) at 0 °C. Then the phases were separated and the water layer was extracted with DCM (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification on a silica column (EtOAc/*n*-pentane: 1/10→1/5) afforded diastereoisomers **3** (48%, 323 mg) and **7** (9%, 61.7 mg).

$2^{A–G},3^{A–G},6^{B–G}$-Icosakis-*O*-benzyl-6^A*R*-phenyl-β-cyclodextrin (2e) and $2^{A–G},3^{A–G},6^{B–G}$-Icosakis-*O*-benzyl-6^A*S*-phenyl-β-cyclodextrin (3e): A solution of aldehyde **1** (1.0 g, 0.341 mmol) in Et_2O (3 mL) under nitrogen was cooled down to –78 °C and was slowly added PhMgBr (7.57 mL) [prepared by adding a solution of PhBr (1.42 mL, 13.5 mmoL) in Et_2O (10.7 mL) to a suspension of Mg turnings (1.31 g, 54 mmol) in Et_2O (4.3 mL) at room temperature under nitrogen. Then the reaction mixture was stirred for 4 h before use]. The reaction mixture was left stirring for 5 min at –78 °C before increasing the temperature to ambient temperature and stirring for 24 h. The reaction was quenched by adding saturated aqueous NH_4Cl (15 mL) at 0 °C. Then the phases were separated and the water phase was extracted with DCM (4 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification chromatography (EtOAc/*n*-pentane: 1/10→1/5) afforded compound 2e (55%, 561.8 mg) as a white foam; R_f = 0.35 (EtOAc/*n*-pentane: 3/5); $[\alpha]_D$ = +36.8 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.20 (m, 105 H, H arom.), 5.65 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.55 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.41–5.35 (m, 3 H, 1 1-H, 2CHPh), 5.27–5.06 (m, 8 H, 3 1-H, 5CHPh), 4.99–4.87 (m, 5 H, 1 1-H, 4CHPh), 4.83–4.67 (m, 6 H), 4.62–4.48 (m, 20 H), 4.45–4.39 (m, 2 H), 4.34–3.94 (m, 26 H), 3.86–3.71 (m, 8 H), 3.67–3.37 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = ppm. 141.6–138.5 (C arom. quat.), 128.7–127.2 (C arom. tert.) 99.7, 99.6, 99.3, 98.7, 98.4, 97.6 (C-1), 81.5, 81.3, 81.0, 80.8, 80.6, 80.5, 80.0, 79.8, 79.5, 79.4, 79.1, 77.8, 76.5, 76.2, 76.0, 75.9, 75.1 74.9, 74.6, 74.5, 73.8, 73.5, 73.3, 73.1, 72.9, 72.6, 72.5, 72.1, 72.0, 71.8, 71.7, 69.9, 69.6, 69.0 (CH, CH_2). MALDI-TOF-MS: *m*/*z* calcd. for $C_{188}H_{194}O_{35}Na$ 3036.337 found 3036.204.

Further elution afforded monol **3e** (5%, 50.6 mg) as a white; R_f = 0.30 (EtOAc/*n*-pentane: 3/5); $[\alpha]_D$ = +35.1 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–6.84 (m, 105 H, H arom.), 5.68 (br. s, 1 H, 1-H), 5.50 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.28–5.23 (m, 2 H, 2CHPh), 5.19–5.09 (m, 3 H, 1 1-H, 2CHPh), 5.04 (d, ^2J = 11 Hz, 1 H, CHPh), 4.86 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 4.82–4.57 (m, 14 H), 4.57–4.51 (m, 2 H), 4.48–4.50 (m,11 H), 4.37–4.25 (m, 8 H), 4.22–3.94 (m, 18 H), 3.92–3.75 (m, 7 H), 3.68–3.54 (m, 10 H), 3.49–3.22 (m, 6 H), 3.06–3.00 (m, 2 H), 2.86 (d, $^2J_{H,H}$ = 17 Hz, 1 H), 2.58 (d, $^2J_{H,H}$ = 17 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.0–138.0 (C arom. quat.), 128.6–126.0 (C arom. tert.) 100.6, 100.0, 99.7, 98.7, 98.4, 97.7 (C-1) 82.1, 82.0, 81.5, 81.4, 81.1, 80.8, 80.7, 80.2, 80.1, 80.0, 79.6, 79.5, 79.0, 78.8, 79.0, 78.8, 77.6, 76.6, 76.5, 76.2, 76.1, 75.4, 74.9, 74.5, 73.8, 73.6, 73.5, 73.4, 73.3, 73.1, 73.0, 72.8, 72.6, 72.2, 72.1, 71.9, 71.7, 71.5, 69.9, 69.7, 69.3, 67.8 (CH, CH_2) ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{188}H_{194}O_{35}Na$ 3036.337 found 3036.152.

6^A*R*-Propargyl-$2^{A–G},3^{A–G},6^{B–G}$-icosakis-*O*-benzyl-β-cyclodextrin (2c) and 6^A*S*-Propargyl-$2^{A–G},3^{A–G},6^{B–G}$-icosakis-*O*-benzyl-β-cyclodextrin (3c): A solution of aldehyde **1** (540 mg, 0.184 mmol) in Et_2O (12 mL) at ambient temperature under nitrogen was slowly added propargylmagnesium bromide solution in Et_2O (12 mL) [prepared by adding a solution of propargyl bromide (0.82 mL, 7.360 mmol) in Et_2O (7 mL) to a suspension of Mg turnings (203.4 mg, 8.464 mmol) and $ZnBr_2$ (82 mg, 0.368 mmol) in Et_2O (5 mL) under nitrogen at room temperature and stirring for 2.5 h before use]. The reaction mixture was left stirring for 3 h before cooling it down to 0 °C and slowly adding saturated aqueous NH_4Cl (30 mL). The two phases were separated and the water phase was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification on a silica column (EtOAc/*n*-pentane: 1/8→1/5) afforded monol **2c** (14%, 76 mg) as a white foam; R_f = 0.44 (EtOAc/petroleum ether: 1/3); $[\alpha]_D$ = +37.7 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–6.99 (m 100 H, H arom.), 5.43 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.38 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.20–5.12 (m, 2 H, 1 1-H, 1CHPh), 5.11–5.02 (m, 3 H, 1 1-H, 2CHPh), 4.98 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 4.96–4.88 (m, 3 H, 1 1-H, 2CHPh), 4.85 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 4.82–4.64 (m, 7 H), 4.55–4.27 (m, 26 H), 4.23 (dd, 1 H), 4.18–3.73 (m, 27 H), 3.73–3.35 (m, 14 H), 3.31 (dd, ^3J = 9, 3 Hz, 1 H, 2-H), 3.13 (s, 1 H, OH), 2.62 (m, 1 H, $CH_2C{\equiv}$), 2.31 (m, 1 H, $CH_2C{\equiv}$), 2.00 (s, 1 H, C≡CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.7–138.1 (C arom. quat.), 128.4–126.8 (C arom. tert.), 99.5, 99.2, 99.1, 99.0, 98.8, 97.7, 97.5 (C-1), 82.2, 81.1, 81.0, 80.9, 80.6, 80.5, 80.0, 79.9, 79.5, 79.0, 78.8, 78.6, 77.3, 76.2, 75.9, 75.5, 75.4, 74.9, 74.8, 73.4, 73.2, 72.9, 72.8, 72.6, 72.4, 72.2, 71.7, 71.6, 71.2, 70.5, 70.2, 70.0, 69.6, 69.4, 69.2, 69.0, 68.7, 68.1, 22.4 ($CH_2C{\equiv}$) ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{185}H_{192}O_{35}Na$ 2996.324 found 2996.252.

Further elution afforded monol **3c** (68%, 370 mg); R_f = 0.30 (EtOAc/petroleum ether: 1/3); $[\alpha]_D$ = +30.7 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–6.96 (m, 100 H, H arom.), 5.67 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 5.42 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.25–

5.18 (m, 2 H, 1 1-H, 1CHPh), 5.10 (m, 1 H, CHPh), 5.07 (m, 1 H, CHPh), 5.00 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 4.91–4.58 (m, 10 H, 2 1-H, 8CHPh), 4.56–4.14 (m, 26 H), 4.12–3.67 (m, 30 H), 3.65–3.33 (m,15 H), 3.15 (br. s, 1 H, OH), 2.35–2.24 (m, 2 H, $CH_2C\equiv$), 2.18 (s, 1 H, C≡CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.8–137.4 (C arom. quat.), 128.4–126.8 (C arom. tert.), 99.7, 99.2, 99.1, 98.5, 98.0, 97.3 (C-1), 82.0, 81.7, 81.3, 81.2, 81.0, 80.9, 80.7, 80.3, 80.2, 80.0, 79.9, 79.6, 79.5, 79.2, 79.1, 78.7, 78.1, 77.3, 76.8, 76.3, 76.0, 76.0, 75.5, 75.3, 75.1, 74.7, 74.4, 74.3, 73.4, 73.3, 73.2, 73.1, 72.9, 72.7, 72.3, 72.0, 71.7, 71.6, 71.4, 71.2, 71.1, 71.0, 69.8, 69.4, 69.3, 68.5, 67.1, 23.9 ($CH_2C\equiv$) ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{185}H_{192}O_{35}Na$ 2996.324 found 2996.121.

6^A*R*-Allyl-2$^{A–G}$,3$^{A–G}$,6$^{B–G}$-icosakis-*O*-benzyl-β-cyclodextrin (2b) and 6^A*S*-Allyl-2$^{A–G}$,3$^{A–G}$,6$^{B–G}$-icosakis-*O*-benzyl-β-cyclodextrin (3b): To a solution of aldehyde 1 (1.0 g, 0.341 mmol) in Et_2O (40 mL) at ambient temperature under nitrogen was slowly added allylmagnesium bromide (5.16 mL) [prepared by adding a solution of allyl bromide (0.685 mL, 7.92 mmol) in Et_2O (8.5 mL) to a suspension of Mg turnings (385.1 mg, 15.84 mmol) in Et_2O (2.8 mL) under nitrogen at room temperature and stirring for 90 min before use]. The reaction mixture was left stirring for 3 h before cooling it down to 0 °C and slowly adding saturated aqueous NH_4Cl (30 mL). The two phases were separated and the water phase was extracted with DCM (3 × 30 mL). The combined organic layers were dried and concentrated under reduced pressure. In order to separate the enolization product from the two diastereoisomers the crude was dissolved in EtOH/THF (2/3, 8 mL) and was added $NaBH_4$ (53.9 mg, 1.36 mmol) at room temperature. The reaction mixture was left stirring overnight before slowly adding aqueous HCl (0.5 mol L^{-1}, 10 mL) and DCM (15 mL). Then the phases were separated and the organic layer was washed with aqueous $NaHCO_3$ (15 mL) and H_2O (15 mL). Then the organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. Purification on a silica column afforded compound 2b (14%, 137 mg) as a white foam; R_f = 0.61 (EtOAc/*n*-pentane: 4/5); $[\alpha]_D$ = +36.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.02 (m 100 H, H arom.), 5.78–6.63 (m, 1 H, CH=CH_2), 5.32 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.29 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 5.21 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.16–4.92 (m, 11 H), 4.79–4.61 (m, 8 H), 4.54–4.25 (m, 26 H), 4.12–3.89 (m, 28 H), 3.61–3.31 (m, 15 H), 2.26–2.02 (m, 2 H, CH_2CH =) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.7–138.2 (C arom. quat.), 135.9 (CH=CH_2), 128.6–127.1 (C arom. tert.), 117.2 (CH=CH_2), 99.31, 99.2, 98.8, 98.5, 98.4, 97.6 (C-1), 81.5, 81.4, 81.2, 80.9, 80.4, 80.3, 79.9, 79.7, 79.4, 79.2, 78.9, 78.4, 78.3, 77.5, 76.2, 76.0, 75.8, 75.7, 75.6, 75.4, 74.8, 74.3, 73.7, 73.6, 73.5, 73.3, 73.1, 73.0, 72.9, 72.8, 72.0, 71.9, 71.8, 71.6, 69.7, 69.5, 69.1 (CH, CH_2), 35.1 (CH_2CH =) ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{185}H_{194}O_{35}Na$ 2998.330 found 2998.169.

Further elution afforded monol **3b** (17%, 177 mg); R_f = 0.54 (EtOAc/*n*-pentane: 4/5); $[\alpha]_D$ = +32.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–6.93 (m, 100 H, H arom.), 5.78–5.64 (m, 1 H, CH=CH_2), 5.57 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 5.48 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 5.26–5.20 (m, 2 H), 5.16, 4.96 (m, 8 H), 4.91–4.59 (m, 12 H), 4.56–4.50 (m, 4 H), 4.46–4.30 (m, 20 H), 4.09–3.71 (m, 30 H), 3.59–3.36 (m,12 H), 2.79 (br. s, 1 H, OH), 2.33–2.23 (m. 1 H, CH_2CH =), 2.12–2.04 (m, 1 H, CH_2CH =) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.7–138.1 (C arom. quat.), 135.9, (CH=CH_2), 128.7 (C arom. tert.), 117.9 (CH=CH_2), 100.1, 99.3, 99.0, 98.6, 98.3, 98.2, 97.9 (C-1), 82.0, 81.8, 81.2, 81.1, 80.9, 80.7, 80.1, 79.8, 79.6, 79.4, 79.2, 79.1, 79.0, 78.9, 76.5, 76.2, 76.1, 76.0, 75.7, 75.4, 75.3, 75.0, 74.9, 73.6, 73.5, 73.2, 73.1, 73.0, 72.9, 72.8, 72.2, 72.1, 71.8, 71.6, 69.9, 69.6, 69.4, 68.7, 68.0 (CH, CH_2), 39.1 (CH_2CH =) ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{185}H_{194}O_{35}Na$ 2998.330 found 2998.268.

6^A*R*-Phenylethynyl-2$^{A–G}$,3$^{A–G}$,6$^{B–G}$-icosakis-*O*-benzyl-β-cyclodextrin (2d) and 6^A*S*-Phenylethynyl-2$^{A–G}$,3$^{A–G}$,6$^{B–G}$-icosakis-*O*-benzyl-β-cyclodextrin (3d)

Method B-1: A solution of phenylacetylene (0.484 mL, 4.32 mmol) in THF (1 mL) at 0 °C under nitrogen was slowly added EtMgBr (4.32 mL, 1 mol L^{-1} in THF). Then the reaction mixture was allowed to reach room temperature and stirring for additional 30 min. Then the solution of Grignard reagent was slowly added a solution of aldehyde **1** (507 mg, 0.173 mmol) in THF (3.8 mL). The reaction mixture was left stirring for 2 h at ambient temperature before quenching the reaction by slowly adding saturated aqueous NH_4Cl (15 mL). After separation of the phases the water layer was extracted with DCM (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by chromatography (EtOAc/*n*-pentane: 1/10→ 1/5) afforded compound **2d** (57%, 300.8 mg) as a white foam; R_f = 0.45 (EtOAc/*n*-pentane: 4/5); $[\alpha]_D$ = +39.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–6.95 (m, 105 H, H arom.), 5.44 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.30 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.21.5.08 (m, 9 H, 5 1-H, 4CHPh), 5.00 (d, ^2J = 11 Hz, 1 H, CHPh), 4.88–4.70 (m, 7 H), 4.63–4.28 (m, 26 H), 4.20–3.87 (m, 28 H), 3.68–3.46 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.7–138.1 (C arom. quat.), 132.2 (C arom. tert.), 128.9–127.3 (C arom. tert.), 122.9 (quat, C arom.), 98.8, 98.5, 98.4, 98.3 (C-1), 87.23, 87.18 (C_{sp}), 81.5, 81.3, 81.1, 81.0, 80.1, 80.0, 79.6, 79.4, 79.2, 78.9, 78.7, 78.5, 76.1, 76.0, 75.7, 75.6, 75.5, 74.1, 73.9, 73.6, 73.3, 73.1, 73.0, 72.9, 72.2, 72.1, 72.0, 71.8, 71.7, 69.7, 69.6, 63.5 (CH, CH_2) ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{190}H_{194}O_{35}Na$ 3060.337 found 3060.281.

Further elution afforde compound **3d** (13%, 66.2 mg); R_f = 0.38 (EtOAc/*n*-pentane: 4/5); $[\alpha]_D$ = +36.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.00 (m, 105 H, H arom.), 5.30 (br. s, 2 H, 2 1-H), 5.23 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.15–4.95 (m, 8 H), 4.91–4.84 (m, 2 H), 4.78–4.60 (m, 8 H), 4.57–4.21 (m, 26 H), 4.14–3.76 (m, 27 H), 3.68–3.38 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.6–138.1 (C arom. quat.), 131.74 (C arom. tert.), 128.6–127.1 (C arom. tert.), 123.0 (C arom. tert.), 99.4, 99.3, 99.0, 98.8, 98.5 (C-1), 89.2, 85.7 (C_{sp}), 81.5, 81.2, 81.1, 80.9, 80.4, 79.9, 79.6, 79.4, 79.3, 79.2, 79.1, 78.9, 78.6, 76.1, 75.9, 75.8, 75.4, 75.2, 74.9, 73.6, 73.5, 73.4, 73.2, 72.9, 72.7, 72.5, 72.1, 72.0, 71.8, 71.6, 69.6, 69.5, 69.3, 68.7 (CH, CH_2) ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{190}H_{194}O_{35}Na$ 3060.337 found 3060.243.

Method B-2: A solution of phenylacetylene (0.11 mL, 0.94 mmol) in PhMe (0.2 mL) under nitrogen at 0 °C was slowly added EtMgBr (0.94 mL, 1 mol L^{-1} in THF). Then the temperature was adjusted to room temperature and stirring for 30 min. Aldehyde **1** (110 mg, 37.5 μmol) dissolved in PhMe (0.9 mL) was slowly added to the Grignard reagent, followed by stirring for 1.5 h at room temperature. Then quenching and workup as described for method B-1 afforded diastereoisomers **2d** (33%, 37.5 mg) and **3d** (15%, 16.5 mg).

Method B-3: A solution of phenylacetylene (61 μL, 0.511 mmol) in THF (0.55 mL) under nitrogen at –78 °C was slowly added *n*BuLi (0.32 mL, 1.6 mol L^{-1} in *n*-hexane). Then stirring for 30 min before slowly adding **1** (100 mg, 34.1 μmol) dissolved in THF (1 mL). The reaction mixture was left stirring for 1.5 h before increasing to room temperature and stirring for 30 min more. Then quenching and workup as described for method B-1 afforded the diastereoisomers **2d** (53%, 55.3 mg) and **3d** (7 mg, 7%).

Method B-4: A suspension of $CeCl_3$ (210 mg 0.853 mmol) in THF (2.6 mL) was left stirring for 2 h. Then the suspension was cooled down to –78 °C and was slowly added a solution of Ph-ethynylLi [prepared by mixing phenylacetylene (90 μL, 0.80 mmol) in THF (0.8 mL) with *n*BuLi (0.49 mL, 1.6 mol L^{-1} in *n*-hexane) at –78 °C, for 30 minn]. The mixture was left stirring for 30 min before adding **5** (100 mg, 34.1 μmol) dissolved in THF (1 mL). Then the mixture was stirred at –78 °C for 1.5 h and room temperature for 30 min. Then quenching and workup as described for method B-1 afforded diastereoisomers **2b** (33%, 34.6 mg) and **3b** (9%, 9.1 mg).

Method B-5: A suspension of $ZnCl_2$ (116.2 mg, 0.85 mmol) in Et_2O (1.7 mL) was cooled down to 0 °C and was added Ph-ethynylLi [prepared by mixing phenylacetylene (97 μL, 0.87 mmol) in Et_2O (3.3 mL) and *n*BuLi (0.54 mL, 1.6 mol L^{-1} in *n*-hexane) at –78 °C, for 30 min] followed by stirring for 45 min. Then a solution of **1** (100 mg, 34.1 μmol) in Et_2O (3.3 mL) was added and the temperature was adjusted to room temperature and the reaction stirred for 2 h. Quenching and workup as described for method B-1 afforded diastereoisomers **2d** (27%, 28.2 mg) and **3d** (22%, 23.2 mg).

6^A*R*-Methyl-$2^{A–G}$,$3^{A–G}$,$6^{B–G}$-icosakis-*O*-benzyl-β-cyclodextrin (2a) and 6^A*S*-Methyl-$2^{A–G}$,$3^{A–G}$,$6^{B–G}$-icosakis-*O*-benzyl-β-cyclodextrin (3a): A solution of aldehyde 1 (443 mg, 0.151 mmol) in THF (2.4 mL) under nitrogen at room temperature was slowly added MeMgBr (0.503 mL, 3 mol L^{-1} in Et_2O). The reaction mixture was left stirring for 2 h at room temperature before slowly adding saturated aqueous NH_4Cl (15 mL) at 0 °C. Then the phases were separated and the water layer was extracted with DCM (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification on a silica column (EtOAc/*n*-pentane: 1/4) afforded compound 2a (40%, 180.2 mg) as a white foam; R_f = 0.30 (EtOAc/*n*-pentane: 3/5); $[\alpha]_D$ = +36.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.13 (m, 100 H, H arom.), 5.39 5.37 (m, 2 H, 2 1-H), 5.35 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 5.27–5.07 (m, 9 H), 5.02 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 4.88–4.73 (m, 9 H) 4.64–4.37 (m, 25 H), 4.19–3.98 (m, 27 H), 3.73–3.51 (m, 13 H), 3.42 (dd, $^3J_{2,1}$ = 4, $^3J_{2,3}$ = 9 Hz, 1 H, 2-H), 1.05 (d, $^3J_{7,6}$ = 6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.7–138.3 (C arom. quat.), 128.6–127.2 (C arom. tert.), 99.3, 98.9, 98.7, 98.6, 98.0 (C-1), 81.5, 81.4, 81.1, 80.4, 80.3, 80.0, 79.7, 79.5, 79.4, 79.2, 78.8, 78.2, 78.0, 76.2, 76.0, 75.6, 74.9, 74.4, 73.8, 73.6, 73.4, 73.1, 72.9, 72.7, 71.2, 72.0, 71.9, 71.8, 71.7, 71.2, 69.5, 69.3, 66.8 (CH, CH_2); 17.1 (CH_3) ppm. MALDI TOF-MS: *m*/*z* calcd. for $C_{183}H_{192}O_{35}K$ 2988.3 found 2988.2.

Further elution afforded compound **3a** (41%, 183.7 mg); R_f = 0.23 (EtOAc/*n*-pentane: 3/5); $[\alpha]_D$ = +34.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 ppm. 7.01 (m, 100 H, H arom.), 5.54–5.49 (m, 2 H, 2 H-1), 5.29–5.08 (m, 5 H), 4.97–4.88 (m, 4 H), 4.79–4.67 (m, 7 H), 4.64–4.30 (m, 26 H), 4.16–3.78 (m, 28 H), 3.70–3.39 (m, 15 H), 2.72–2.65 (m, 2 H), 1.06 (d, 3 H, $^3J_{7,6}$ 6 Hz, CH_3), ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.7–139.1 (C arom. quat.), 128.6–127.1 (C arom. tert.), 99.9, 98.9, 98.7, 98.5, 98.2, 97.8, 97.5 (C-1), 82.1, 81.6, 81.4, 81.0, 80.8, 79.8, 79.6, 79.5, 78.9, 78.8, 77.5, 76.0, 75.8, 75.2, 75.0, 73.7, 73.6, 73.5, 73.1, 73.0, 72.8, 72.0, 71.7, 71.6, 69.7, 69.6, 69.4, 69.2, 68.6, 63.9 (CH, CH_2); 20.7 (CH_3) ppm. MALDI TOF-MS: *m*/*z* calcd. for $C_{183}H_{192}O_{35}K$ 2988.288 found 2988.423.

6^A*R*-(2-Pyridyl)-$2^{A–G}$,$3^{A–G}$,$6^{B–G}$-icosakis-*O*-benzyl-β-cyclodextrin (2 g) and 6^A*S*-(2-Pyridyl)-$2^{A–G}$,$3^{A–G}$,$6^{B–G}$-icosakis-*O*-benzyl-β-cyclodextrin (3g): A solution of 2-pyridylMgBr was prepared by slowly adding *i*PrMgCl (4.40 mL, 2 mol L^{-1} in THF) to a solution of 2-bromopyridine (0.848 mL, 8.806 mmol) in THF (7.3 mL) under nitrogen at room temperature. The obtained reaction mixture was left stirring for 14 h at this temperature. Then the solution of Grignard reagent was cooled down to –78 °C and was slowly added a solution of aldehyde 1 (1.62 g, 0.550 mmol) in THF (5.5 mL). The reaction mixture was stirred at –78 °C for 1 h before increasing to room temperature and stirring for 2 h before quenching by slowly adding H_2O (25 mL) at 0 °C. Then the layers were separated and the water phase was extracted with DCM (3 × 40 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude product on a silica column (EtOAc/*n*-pentane: 1/9 → 1/4) afforded compound **2g** (64%, 1.06 g) as a white foam; R_f = 0.26 (EtOAc/*n*-pentane: 1/3); $[\alpha]_D$ = +40.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.81 (d, $^3J_{H,H}$ = 5 Hz, 1 H, H arom.), 7.61–7.55 (m, 1 H, H arom.), 7.49–7.46 (m, 1 H, H arom.), 7.34–7.13 (m, 101 H, H arom.), 5.84 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.47 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.36 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.30 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.26–5.03 (m, 9 H), 4.95 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 4.88–4.71 (m, 8 H), 4.62–4.27 (m, 28 H), 4.21–4.01 (m, 25 H), 3.81 (d, $^2J_{H,H}$ = 12 Hz, 1 H), 3.71–3.46 (m, 11 H), 3.23 (dd, $^3J_{2,1}$ = 3, $^3J_{2,3}$ = 9 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6 (C arom. quat.), 148.1 (C arom. tert.), 139.7–138.3 (C arom. quat.), 136.3 (C arom. tert.), 128.6–127.2 (C arom. tert.), 122.5, 122.4 (C arom. tert.), 99.1, 99.0, 98.9, 98.7, 98.3, 97.6 (C-1), 81.5, 81.3, 80.8, 80.4, 80.0, 79.7, 79.4, 79.3, 78.9, 78.8, 78.7, 78.3, 78.0, 77.6, 76.3, 75.8, 75.7, 75.3, 73.6, 73.5, 73.4, 73.1, 73.0, 72.4, 72.0, 71.8, 71.7, 69.8, 69.6, 69.5, 69.1 (CH, CH_2) ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{187}H_{193}NO_{35}Na$ 3014.342 found 3014.910.

Further elution afforded an 85% pure mixture of **3g** (9%, 150 mg); R_f = 0.18 (EtOAc/*n*-pentane: 1/3). MALDI-TOF-MS: *m*/*z* calcd. for $C_{187}H_{193}NO_{35}Na$ 3014.3 found 3014.7.

6^A(*R*)-(4-Fluorophenyl)-β-cyclodextrin: Compound **2f** (392.2 mg, 0.129 mmol) and TFA (cat) were dissolved in 2-methoxyethanol (85 mL) under nitrogen. Palladium on carbon (10%, 200 mg) was added, and a hydrogen atmosphere (1 atm) was introduced. Then the reaction mixture was left stirring for 20 h at room temperature before filtration through a pad of Celite. Concentration of the filtrate afforded the desired product (74%, 117 mg) as a white solid; R_f = 0.69 (*i*PrOH/MeOH/H_2O: 5/4/3); $[\alpha]_D$ = +151.8 (*c* = 0.5, MeOH). ^{1}H NMR [300 MHz, $(CD_3O)_2SO_2$]: δ = 7.52 (dd, $^4J_{H,F}$ = 6, $^3J_{H,H}$ = 8 Hz, 2 H, H arom.), 7.08–7.02 (m, 2 H, H arom.), 6.08 (d, $^3J_{H,H}$ = 5 Hz, 1 H), 5.81- 5.63 (m, 10 H), 5.48 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 5.13 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 4.92–4.77 (m, 7 H), 4.59–4.40 (m, 5 H), 4.03–3.93 (m, 2 H), 3.63–3.21 (m, 40 H), 3.01–2.94 (m, 1 H), 2.71–2.65 (m, 1 H) ppm. ^{13}C NMR [75 MHz, $(CD_3O)_2SO_2$]: δ = 162.0 (d, $^1J_{C,F}$ = 220 Hz, C arom. quat.), 137.3 (d, $^4J_{C,F}$ > = 0 Hz, C arom. quat.), 131.3 (d, $^3J_{C,F}$ = 8 Hz, C arom. tert.), 114.6 (d, $^2J_{C,F}$ = 21 Hz, C arom. tert.), 102.7, 102.5, 102.4, 101.9 (C-1), 82.4, 82.3, 82.2, 81.9, 81.7, 74.6, 74.5, 73.8, 73.6, 73.5, 73.4, 73.3, 73.1, 73.0, 72.8, 72.7, 72.4, 70.3, 60.6, 60.4 (CH) ppm. Ms (ES) *m*/*z* calcd. $C_{48}H_{73}FO_{35}Na$ 1251.4 found 1251.7.

$2^{A–G}$,$3^{A–G}$,$6^{B–G}$-Icosakis-*O*-benzyl-6^A*R*-(4-fluorophenyl)-(phenylethynyl)-β-cyclodextrin (9e): A solution of phenylacetylene (0.66 mL, 5.85 mmol) in THF (1.3 mL) under nitrogen at 0 °C was slowly added EtMgBr (5.73 mL, 1 mol L^{-1} in THF). Then the temperature was adjusted to room temperature and the stirring was continued for 30 min. Then the solution of Grignard reagent was cooled down to –10 °C and a solution of ketone (709 mg, 0.243 mmol) in THF (7 mL) was slowly added. The reaction mixture was left stirring at this temperature for 2 h before increasing to room temperature and stirring for 1 h more. The reaction was quenched at 0 °C by slowly adding saturated aqueous NH_4Cl (15 mL). Then the phases were separated and the water phase was extracted with DCM

(3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product on a silica column (EtOAc/*n*-pentane: 1/9→1/3) afforded compound **9e** (90%, 659.4 mg) as a light yellow foam; R_f = 0.39 (EtOAc/*n*-pentane: 2/3); $[\alpha]_D$ = +36.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (dd, $^4J_{H,F}$ = 5, $^3J_{H,H}$ = 8 Hz, 2 H, H arom.), 7.49–7.46 (m, 2 H, H arom.), 7.37–6.87 (m, 105 H, H arom.), 5.98 (br. s, 1 H, OH), 5.81 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 5.43–5.28 (m, 4 H, 4CHPh), 5.07 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.01 (d, ^2J = 12 Hz, 1 H, CHPh), 4.95–4.54 (m, 16 H), 4.50–3.91 (m, 40 H), 3.87–3.79 (m, 5 H), 3.76–3.73 (m, 2 H), 3.68–3.54 (m, 8 H), 3.46–3.28 (m, 5 H), 3.10 (d, $^2J_{H,H}$ = 10 Hz, 1 H), 2.82 (d, $^2J_{H,H}$ = 11 Hz, 1 H), 2.60–2.49 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3 (d, $^1J_{C,F}$ = 245 Hz, C arom. quat.), 140.6 (d, $^4J_{C,F}$ = 2 Hz, C arom. quat.), 140.2–138.1 (C arom. quat.), 132.6 (C arom. tert.), 129.5 (d, $^3J_{C,F}$ = 7 Hz, C arom. tert.), 129.2–126.8 (C arom. tert.), 123.7 (C arom. quat.), 114.9 (d, $^2J_{C,F}$ = 20 Hz, C arom. tert.), 101.2, 100.7, 100.1, 98.5, 97.5 (C-1), 88.9 (C_{sp}), 82.4, 82.0, 81.6, 81.4, 81.2, 80.8, 80.4, 79.9, 79.6, 79.0, 78.5, 76.6, 76.4, 76.2, 76.8, 75.2, 74.2, 73.8, 73.6, 73.5, 73.4, 73.3, 73.1, 73.0, 72.5, 72.4, 72.2, 72.0, 71.4, 71.1, 69.8, 69.7, 69.3, 67.5 (CH, CH_2) ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –114.04 ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{196}H_{197}FO_{35}Na$ 3154.4 found 3154.3.

2$^{A–G}$,3$^{A–G}$,6$^{B–G}$-Icosakis-*O*-benzyl-6^A*S*-(4-fluorophenyl)-(phenylethynyl)-β-cyclodextrin (8e): To a solution of the ketone (438 mg, 0.144 mmol) in THF (5.6 mL) at –10 °C under nitrogen atmosphere was slowly added (4-fluorophenyl)magnesium bromide (2.4 mL in THF). Then the reaction mixture was left stirring for 1.5 h before adjusting to 0 °C and slowly adding saturated aqueous NH_4Cl (10 mL). The layers were separated and the water phase was extracted with DCM (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (EtOAc/*n*-pentane: 1/9→1/4) afforded compound **8e** (68%, 308.1 mg) as alight yellow foam; R_f = 0.39 (EtOAc/*n*-pentane: 2/3); $[\alpha]_D$ = +36.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (dd, $^4J_{H,F}$ = 5, $^3J_{H,H}$ = 8 Hz, 2 H, H arom.), 7.78–7.73 (m, 1 H, H arom.), 7.58–7.55 (m, 2 H, H arom.), 7.45–6.96 (m, 104 H, H arom.), 6.07 (br. s, 1 H, 1-H), 5.89 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 5.52–5.37 (m, 4 H), 5.16 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 5.10 (d, ^2J = 12 Hz, 1 H, CHPh), 4.59–4.37 (m, 76 H), 3.32 (d, $^2J_{H,H}$ = 10 Hz, 1 H), 2.91 (d, $^2J_{H,H}$ = 11 Hz, 1 H), 2.69–1.42 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3 (d, $^1J_{C,F}$ = 245 Hz, C arom. quat.), 140.7 (d, $^4J_{C,F}$ = 2 Hz, C arom. quat.), 140.2–138.1 (C arom. quat.), 132.4 (C arom. tert.), 129.5 (d, $^3J_{C,F}$ = 7 Hz, C arom. tert.), 129.2–126.8 (C arom. tert.), 122.8 (C arom. quat.), 114.9 (d, $^2J_{C,F}$ = 20 Hz, C arom. tert.), 101.2, 100.8, 100.1, 98.6, 97.6, 97.3, (C-1); 88.9 (C_{sp}), 82.4, 82.1, 81.6, 81.5, 81.3, 80.8, 80.5, 80.0, 79.6, 79.0, 78.5, 76.6, 76.4, 76.3, 75.9, 75.3, 74.5, 74.2, 73.8, 73.7, 73.5, 73.3, 73.2, 73.1, 73.0, 72.5, 72.4, 72.2, 72.1, 71.5, 71.4, 71.2, 69.8, 69.7, 69.3, 69.0, 67.5 (CH, CH_2) ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –114.03 ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{196}H_{197}FO_{35}Na$ 3154.358 found 3154.390.

2$^{A–G}$,3$^{A–G}$,6$^{B–G}$-Icosakis-*O*-benzyl-6^A-(4-fluorophenyl)methyl-β-cyclodextrin (8c and 9c): To a solution of the ketone (399 mg, 0.135 mmol) in THF (5.3 mL) under nitrogen atmosphere at room temperature was slowly added (4-fluorophenyl)magnesium bromide (2.3 mL in THF). The reaction mixture was left stirring for 3 h adjusting the temperature to 0 °C followed by slowly addition of saturated NH_4Cl (10 mL). Then the phases were separated and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude product on a silica column (EtOAc/*n*-pentane: 1/10→1/7) afforded compound **9c** (15%, 65.1 mg) as a white foam; R_f = 0.48 (EtOAc/*n*-pentane: 1/2). MALDI-TOF-MS: *m*/*z* calcd. for $C_{189}H_{195}F5_{35}Na$ 3066.3 found 3066.4.

Further elution afforded compound **8c** (61%, 252.3 mg); R_f = 0.46 (EtOAc/*n*-pentane: 1/2); $[\alpha]_D$ = +30.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–6.98 (m, 102 H, H arom.), 6.87–6.81 (m, 2 H, H arom.), 5.73 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 5.32–5.37 (m, 2 H, 2CHPh), 5.12 (d, $^3J_{1,2}$ = 3 Hz, 1 H, 1-H), 4.99–4.90 (m, 2 H, 2CHPh), 4.84–4.70 (m, 10 H), 4.61–4.52 (m, 7 H), 4.48–4.28 (m, 19 H), 4.23–4.80 (m, 28 H), 3.71–3.25 (m, 17 H), 1.39 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7 (d, $^1J_{C,F}$ = 243 Hz, C arom. quat.), 140.1–138.5 (C arom. quat.), 138.4 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 128.8–126.9 (C arom. tert.), 114.6 (d, $^2J_{C,F}$ = 20 Hz, C arom. tert.), 100,6, 100.4, 99.9, 99.1, 98.7, 97.6 (C-1), 82.1, 82.0, 81.4, 81.1, 81.0, 80.8, 80.4, 79.5, 79.2, 79.0, 77.6, 77.2, 76.5, 76.3, 76.1, 75.7, 75.2, 74.1, 73.7, 73.6, 73.3, 73.1, 72.4, 72.2, 72.1, 71.4, 71.2, 69.8, 69.4, 69.3, 69.1, 69.0, 67.9 (CH, CH_2); 32.3 (CH_3) ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –116.07 ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{189}H_{195}FO_{35}Na$ 3068.343 found 3068.387.

6^A-Allylphenyl-2$^{A–G}$,3$^{A–G}$,6$^{B–G}$-icosakis-*O*-benzyl-β-cyclodextrin (8d): A solution of ketone **7d** (210 mg, 69.7 μmol) in Et_2O (3.1 mL) at room temperature under nitrogen was slowly added allylmagnesium bromide (1.59 mL) [prepared by adding a solution of allyl bromide (286 μL, 3.3 mmol) in Et_2O (3.5 mL) to a suspension of Mg turnings (160.4 mg, 6.6 mmol) in Et_2O (1.2 mL) under nitrogen at room temperature, then stirring for 90 min before use]. The reaction mixture was left stirring for 3 h at room temperature before adjusting the temperature to 0 °C and slowly adding saturated aqueous NH_4Cl (10 mL). Then the phases were separated and the water phase was extracted with DCM (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification on a silica gel (EtOAc/*n*-pentane: 1/10→1/5) afforded compound **8d** (41%, 86.2 mg) as a pure diastereoisomer; R_f = 0.28 (EtOAc/*n*-pentane: 3/5); $[\alpha]_D$ = +28.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–6.89 (m, 105 H, H arom.) 5.76 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 5.63–5.54 (m, 1 H, CH=CH_2), 5.34–5.28 (m, 2 H, 2CHPh), 5.15–4.95 (m, 7 H), 4.87–4.72 (m, 8 H), 4.68–4.58 (m, 5 H), 4.53–4.25 (m, 25 H), 4.14–3.94 (m, 23 H), 3.76–3.32 (m, 17 H), 2.93–2.86 (m, 1 H, CH_2CH =), 2.76–2.69 (m, 1 H, CH_2CH =) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.4 (C arom. quat.), 139.9–138.3 (C arom. quat.), 134.7 (CH=CH_2), 128.6–126.9 (C arom. tert.), 117.5 (CH=CH_2), 100.2, 99.8, 98.7, 98.3, 98.1 (C-1), 82.1, 81.8, 81.2, 81.0, 80.8, 80.5, 80.3, 79.5, 79.3, 78.9, 76.4, 76.1, 75.8, 74.7, 74.3, 73.5, 73.4, 73.0, 72.5, 72.2, 71.9, 71.7, 71.6, 71.2, 69.9, 69.6, 69.4, 69.3, 68.9 (CH, CH_2) ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{191}H_{198}FO_{35}Na$ 3075.4 found 3075.4.

2$^{A–G}$,3$^{A–G}$,6$^{B–G}$-Icosakis-*O*-benzyl-6^A-(ethynylmethyl)-β-cyclodextrin (8a and 9a): To a solution of the ketone **7a** (100 mg, 33.9 μmol) in THF (0.2 mL) under nitrogen at –78 °C was slowly added ethynylmagnesium bromide (1.69 mL, 0.5 mol L^{-1} in THF). The reaction mixture was left stirring at this temperature for 3 h before increasing to room temperature and stirring for additional 1 h. The reaction was quenched by adjusting the temperature to 0 °C and slowly adding saturated aqueous NH_4Cl (5 mL). Then the phases were separated and the water phase was extracted with DCM (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification on a silica gel (EtOAc/*n*-pentane: 1/3) afforded compounds **8a** an **9a** (86%, 86.7 mg) as a mixture of diastereoisomers (4/1); R_f = 0.38 (EtOAc/*n*-pentane: 3/5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–6.93 (m, H arom.), 5.62 (d, $^3J_{1,2}$ = 3 Hz, 1-H), 5.53 (d, $^3J_{1,2}$ = 3 Hz, 1-H), 5.32 (d, $^3J_{1,2}$ = 3 Hz,

1-H), 5.26 (d, ^2J = 11 Hz, CHPh), 5.22–5.04 (m), 5.02 (d, $^3J_{1,2}$ = 3 Hz, 1-H), 4.98 (d, $^3J_{1,2}$ = 3 Hz, 1-H), 4.90–4.71 (m), 4.66–4.55 (m), 4.52–4.29 (m), 4.25–3.94 (m), 3.91–3.71 (m), 3.67–3.35 (m), 2.42 (s, OH), 2.08 (s, OH), 1.47 (s, CH_3), 1.31 (s, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9–138.0 (C arom. quat.), 128.6–127.0 (C arom. tert.), 99.8, 99.3, 98.9, 98.7, 98.4, 98.3, 98.1, 97.7, 97.6, 97.3 (C-1), 87.5, 85.4 (C_{sp}), 82.1, 81.6, 81.4, 81.2, 81.1, 80.6, 80.3, 80.0, 79.3, 79.2, 79.1, 76.4, 76.3, 76.1, 75.7, 75.5, 73.7, 73.4, 73.2, 73.0, 72.7, 72.5, 72.2, 72.1, 71.9, 71.6, 71.5, 71.3, 70.2, 70.0, 69.9, 69.6, 69.3, 69.0 (CH, CH_2, C_{sp}), 29.2, 26.0 (CH_3) ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{185}H_{192}O_{35}Na$ 2996.314 found 2996.364.

$2^{A–G}$,$3^{A–G}$,$6^{B–G}$-Icosakis-*O*-benzyl-6^A-(methylethynyl)-β-cyclodextrin (8b and 9b): To a solution of the ketone **7a** (258 mg, 87.4 μmol) in THF (1.5 mL) under nitrogen atmosphere at room temperature was slowly added PhMgBr (3.3 mL) [prepared by adding a solution of PhBr (0.7 mL, 6.60 mmol) in THF (7 mL) to a suspension of Mg turnings (481 mg, 19.8 mmol) in THF (2.3 mL) under nitrogen at room temperature, then stirring for 3 h before use]. The reaction mixture was left stirring at the same temperature for 2 h before quenching by slowly adding saturated aqueous NH_4Cl (5 mL). Then the phases were separated and the aqueous phase was extracted with DCM (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification on silica gel (EtOAc/*n*-pentane: 1/10→1/3) afforded compounds **8b** and **9b** (81%, 213.1 mg) as a mixture of diastereoisomers (4/1); R_f = 0.34 (EtOAc/*n*-pentane: 3/5). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–6.97 (m, H arom.), 5.75 (d, $^3J_{1,2}$ = 4 Hz, 1-H), 5.48 (d, $^3J_{1,2}$ = 3 Hz, 1-H), 5.33–5.16 (m), 5.12 (d, $^3J_{1,2}$ = 3 Hz, 1-H), 5.03–4.90 (m), 4.83–4.69 (m), 4.63–4.30 (m), 4.26–4.14 (m), 4.12–3.92 (m), 3.81–3.67 (m), 3.61–3.50 (m), 3.46–3.20 (m), 1.58 (s, CH_3), 1.43 (s, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6, 146.4 (C arom. quat.), 139.9–130.1 (C arom. quat.), 128.5–126.7 (C arom. tert.), 100.7, 100.1, 99.5, 99.1, 98.9, 98.8, 98.6, 98.4, 97.3, 97.2 (C-1), 82.5, 81.7, 81.3, 81.2, 80.9, 80.7, 80.6, 80.4, 80.2, 79.8, 79.5, 79.2, 79.0, 78.8, 78.6, 77.9, 77.3, 76.2, 76.1, 75.9, 75.8, 75.5, 75.3, 74.7, 74.6, 74.5, 73.8, 73.5, 73.4, 73.3, 73.0, 72.9, 72.8, 72.5, 72.2, 72.1, 71.9, 71.7, 71.4, 71.3, 71.1, 71.0, 69.6, 69.5, 69.1, 69.0, 68.8, 68.5, 67.5 (CH, CH_2), 31.2, 30.4 (CH_3) ppm. MALDI-TOF-MS: *m*/*z* calcd. for $C_{189}H_{196}O_{35}Na$ 3048.3 found 3048.31.

(*S*)-(4-Fluorophenyl)[(2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxy-tetrahydro-2*H*-pyran-2-yl]methanol and (*R*)-(4-Fluorophenyl)[(2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxy-tetrahydro-2*H*-pyran-2-yl]methanol: To a solution of aldehyde **4** (296 mg, 0.64 mmo) in THF (5.1 mL) under nitrogen at room temperature was slowly added (4-fluorophenyl)magnesium bromide (3.4 mL in THF). The reaction mixture was left stirring at this temperature for 1 h before adjusting the temperature to 0 °C and slowly adding saturated aqueous NH_4Cl (10 mL). The two phases were separated and the water phase was extracted with DCM (4 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification on a silica column (EtOAc/*n*-pentane: 1/20→1/12) afforded the *R*-isomer (41%, 146 mg) as a yellow syrup; R_f = 0.45 (EtOAc/*n*-pentane: 1/3); $[\alpha]_D$ = +20.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 17 H, H arom.), 7.00–6.93 (m, 2 H, H arom.), 5.01–4.94 (m, 3 H, 6-H, 2CHPh), 4.84 (d, ^2J = 11 Hz, 1 H, CHPh), 4.76 (d, ^2J = 12 Hz, 1 H, CHPh), 4.73 (d, ^2J = 11 Hz, 1 H, CHPh), 4.62 (d, ^2J = 12 Hz, 1 H, CHPh), 4.47 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 4.02–3,96 (m, 1 H, 3-H), 3.75–3.65 (m, 2 H, 4-H, 5-H), 3.52 (dd, $^3J_{2,1}$ = 4, $^3J_{2,3}$ = 10 Hz, 1 H, 2-H), 2.84 (s, 3 H, OCH_3), 2.33 (br. s, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.0 (d, $^1J_{C,F}$ = 243 Hz, C arom. quat.), 138.7, 138.3, 138.1 (C arom. quat.), 137.7 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 128.6–127.5 (C arom. tert.), 114.6 (d, $^2J_{C,F}$ = 21 Hz, C arom. tert.), 98.1 (C-1), 82.4 (C-3), 79.9 (C-2), 77.7, 75.9, 75.2, 73.53, 73.46, 70.3 (CH, CH_2), 54.8 (OCH_3) ppm. Ms (ES) *m*/*z* calcd. for $C_{34}H_{35}FO_6Na$ 581.2 found 581.2. Further elution afforded the *S*-isomer (26%, 94 mg) as a light yellow syrup; R_f = 0.30 (EtOAc/*n*-pentane: 1/3); $[\alpha]_D$ = +37.9 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 17 H, H arom.), 7.00–6.93 (m, 2 H, H arom.), 5.02 (d, ^2J = 11 Hz, 1 H, CHPh), 5.01 (d, ^2J = 11 Hz, 1 H, CHPh), 4.79–4.76 (m, 3 H, 6-H, 2CHPh), 4.61 (d, ^2J = 12 Hz, 1 H, CHPh), 4.60 (d, ^2J = 12 Hz, 1 H, CHPh), 4.48 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 4.07–4.01 (m, 3 H, 3-H), 3.82–3.74 (m, 2 H, 5-H, OH), 3.49–3.43 (m, 2 H, 2-H, 4-H), 3.08 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (d, $^1J_{C,F}$ = 244 Hz, C arom. quat.), 138.5, 138.0, 137.6 (C arom. quat.), 136.6 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 129.2 (d, $^3J_{C,F}$ = 8 Hz, C arom. tert.), 128.7–127.8 (C arom. tert.), 114.6 (d, $^2J_{C,F}$ = 21 Hz, C arom. tert.), 97.7 (C-1), 82.4, 81.1, 80.4, 75.7, 75.1, 74.9, 73.4, 71.6 (CH, CH_2), 55.1 (OCH_3) ppm. Ms (ES) *m*/*z* calcd. for $C_{34}H_{35}FO_6Na$ 581.2 found 581.3.

(2*R*,3*S*,4*S*,5*R*,6*S*)-2-[(*S*)-4(-Fluorophenyl)(hydroxy)methyl]-6-methoxy-tetrahydro-2*H*-pyran-3,4,5-triol (5b): To a solution of the benzylated sugar (160 mg, 0.286 mmol) in MeOH (10 mL) under nitrogen was added Pd/C (10%, 96 mg) before degassing the mixture and introducing a hydrogen atmosphere (1 atm). The reaction mixture was left stirring at room temperature for 7 h before filtering the mixture through a pad of Celite. Concentration of the filtrate and purification on a pad of silica (EtOAc/MeOH: 20/1) afforded compound **5b** (99%, 82 mg) as a white solid; R_f = 0.18 (EtOAc/MeOH: 20/1). ^1H NMR (300 MHz, CD_3OD): δ = 7.45 (dd, $^4J_{H,F}$ = 6, $^3J_{H,H}$ = 8 Hz, 2 H, H arom.), 7.07–7.01 (m, 2 H, H arom.), 5.07 (br. s, 1 H, 6-H), 4.59 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 3.68–3.58 (m, 2 H, 3-H, 4-H), 3.53–3.50 (m, 1 H, 5-H), 3.46–3.42 (m, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 163.3 (d, $^1J_{C,F}$ = 242 Hz, C arom. quat.), 140.2 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 129.2 (d, $^3J_{C,F}$ = 8 Hz, C arom. tert.), 115.3 (d, $^2J_{C,F}$ = 22 Hz, C arom. tert.), 101.2 (C-1), 76.0, 75.5,73.4, 71.5, 70.9 (CH), 54.9 (OCH_3) ppm. MS (ES) *m*/*z* calcd. for $C_{13}H_{17}FO_6Na$ 311.1 found 311.1.

(2*R*,3*S*,4*S*,5*R*,6*S*)-2-[(*R*)-(4-Fluorophenyl)(hydroxy)methyl]-6-methoxy-tetrahydro-2*H*-pyran-3,4,5-triol (5a): The benzylated sugar (74 mg, 0.132 mmol) was debenzylated in the same way as for **5b** to afford **5a** (100%, 38 mg); R_f = 0.18 (EtOAc/MeOH: 20/1). ^1H NMR (300 MHz, CD_3OD): δ = 7.47–7.43 (m, 2 H, H arom.), 7.06–7.02 (m, 2 H, H arom.), 4.87 (d, $^3J_{6,5}$ = 5 Hz, 1 H, 6-H), 4.57 4.59 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 3.73 (dd, $^3J_{5,6}$ = 5, $^3J_{5,4}$ = 10 Hz, 1 H; 5-H), 3.64–3.58 (m, 1 H, 3-H), 3.23–3.19 (m, 4 H, 2-H, OCH_3), 3.13–3.06 (m, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 163.3 (d, $^1J_{C,F}$ = 242 Hz, C arom. quat.), 138.3 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 130.8 (d, $^3J_{C,F}$ = 8 Hz, C arom. tert.), 115.3 (d, $^2J_{C,F}$ = 22 Hz, C arom. tert.), 101.2 (C-1), 75.2, 75.1, 74.4, 74.3, 73.3 (CH), 55.7 (OCH_3) ppm. MS (ES) *m*/*z* calcd. for $C_{13}H_{17}FO_6Na$ 311.1 found 311.1.

(2*R*,4*S*,4a*R*,6*S*,7*R*,8*R*,8a*S*)-4-(4-Fluorophenyl)-6-methoxy-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxine-7,8-diol (6): To a solution of **5b** (68 mg, 0.236 mmol) and *p*-toluenesulfonic acid monohydrate (4.49 mg, 23.6 μmol) in DMF (3 mL) under nitrogen was added $PhCH(OMe)_2$ (0.248 mL, 1.65 mmol). The reaction mixture was heated to 100 °C and left stirring for 18 h. Then an additional amount of $PhCH(OMe)_2$ (0.48 mL, 3.304 mmol) was added and the reaction was allowed continue at the same temperature for 24 h. The reaction mixture was then added $PhCH(OMe)_2$ (0.248 mL, 1.625 mmol) and the reaction mixture was stirred for 5 h more at 100 °C before cooling it down to room temperature and neutralized

by adding Et_3N. The solvent was removed under reduced pressure. Purification of the crude product on a silica column (EtOAc/*n*-pentane: 1/3→1/1) afforded the benzylidene **6** (27%, 23.8 mg) as a white solid; R_f = 0.68 (EtOAc); $[\alpha]_D$ = +37.5 (*c* = 0.27, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD): δ = 7.83–7.79 (m, 2 H, H arom.), 7.49–7.46 (m, 2 H, H arom.), 7.36–7.33 (m, 3 H, H arom.), 7.17–7.11 (m, 2 H, H arom.), 5.60 (s, 1 H, $CHPhO_2$), 5.40 (d, $^3J_{6,5}$ = 5 Hz, 1 H,, 6-H), 4.89 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 4.41–4.36 (m, 1 H, 5-H), 3.93–3.82 (m, 2 H, 4-H, 3-H), 3.62–3.58 (m, 1 H, 2-H), 3.51 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8 (d, $^1J_{C,F}$ = 246 Hz, C arom. quat.), 138.7 (C arom. quat.), 133.8 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 131.8 (d, $^3J_{C,F}$ = 8 Hz, C arom. tert.), 130.8, 130.0, 127.9 (C arom. tert.), 117.1 (d, $^2J_{C,F}$ = 22 Hz, C arom. tert.), 101.3, 97.1 ($CHPhO_2$, C-1), 76.8, 75.2, 74.1, 74.0, 69.2 (CH), 57.4 (OCH_3) ppm. MS (ES) *m*/*z* calcd. for $C_{20}H_{21}FO_6Na$ 399.1 found 399.1.

(4-Fluorophenyl)[(2*S*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-methoxy-tetrahydo-2*H*-pyran-2-yl]methanone (11): Dess–Martin periodinane (720 mg, 1.70 mmol) was added to a solution of the alcohol (621.2 mg, 1.11 mmol) in DCM (30 mL) under nitrogen. The reaction mixture was left stirring overnight at room temperature. The reaction was quenched by adding Et_2O (50 mL) and saturated aqueous $NaHCO_3$ (30 mL) consisting of $Na_2S_2O_3$ (3 g) and stirring for 1 h at room temperature. Then Et_2O (50 mL) was added and the phases were separated. The organic layer was washed with $NaHCO_3$ (40 mL) and H_2O (40 mL). Then the organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (EtOAc/*n*-pentane: 1/9) afforded ketone **11** (89%, 552 mg) as a light yellow syrup; R_f = 0.58 (EtOAc/*n*-pentane: 1/4); $[\alpha]_D$ = +40.7 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.04 (dd, $^4J_{H,F}$ = 5, $^3J_{H,H}$ = 9 Hz, 2 H, H arom.), 7.38–7.26 (m, 10 H, H arom.), 7.16–7.05 (m, 5 H, H arom.), 6.93–6.90 (m, 2 H, H arom.), 5.07–4.99 (m, 2 H, 5-H, CHPh), 4.88–4.81 (m, 2 H, 2CHPh), 4.73 (d, ^2J = 10 Hz, 1 H, CHPh), 4.68–4.64 (m, 2 H, 1-H, CHPh), 4.43 (d, ^2J = 11 Hz, 1 H, CHPh), 4.15–4.09 (m, 1 H, 3-H), 3.93–3.86 (m, 1 H, 4-H), 3.63 (dd, $^3J_{2,1}$ = 4, $^3J_{2,3}$ = 10 Hz, 1 H, 2-H), 3.46 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.7 (C=O), 166.3 (d, $^1J_{C,F}$ = 255 Hz, C arom. quat.), 138.9, 138.3, 137.9 (C arom. quat.), 132.9 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 132.1 (d, $^3J_{C,F}$ = 9 Hz, C arom. tert.), 128.8–128.0 (C arom. tert.), 116.0 (d, $^2J_{C,F}$ = 22 Hz, C arom. tert.), 99.7 (C-1), 82.0, 79.83, 79.75, 76.2, 72.5, 74.0, 70.0 (CH, CH_2), 56.7 (OCH_3) ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –104.20 ppm. MS (ES) *m*/*z* calcd. for $C_{34}H_{33}FO_6Na$ 579.2 found 579.2.

3-Phenyl-1-[(2*S*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxy-tetrahydro-2*H*-pyran]prop-2-yn-1-one (12): A solution of phenylacetylene (1.60 mL, 14.0 mmol) in THF (3.5 mL) under nitrogen was cooled down to 0 °C. Then EtMgBr (12.76 mL, 1 mol L^{-1} in THF) was slowly added and the temperature was adjusted to room temperature and stirring for 30 min. The solution of Grignard reagent was cooled down to –10 °C and was slowly added a solution of aldehyde **4** (2.95 g, 6.38 mmol) in THF (30 mL). The stirring was continued at the same temperature for 1 h before increasing to room temperature and stirring for additional 5 min followed by quenching by slowly adding saturated aqueous NH_4Cl (30 mL) at 0 °C. The phases were separated and the water phase was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The concentrate was purified by chromatography (Et_2O/*n*-pentane: 1/5) affording a mixture if diastereoisomers. Then the mixture was dissolved in DCM (120 mL) under nitrogen atmosphere and Dess–Martin periodinane (2.7 g, 6.38 mmol) was added, followed by stirring overnight at room temperature. The reaction was quenched by adding Et_2O (150 mL) and saturated aqueous $NaHCO_3$ (250 mL) containing $Na_2S_2O_3$ (12 g) followed by stirring for 1 h. The phases were separated and the organic layer was washed with $NaHCO_3$ (2 × 150 mL) and H_2O (150 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography (Et_2O/*n*-pentane: 1/5) afforded ketone **12** (57%, 2.05 g) as a light yellow syrup; R_f = 0.59 (EtOAc/*n*-pentane: 2/3); $[\alpha]_D$ = +3.6 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.41 (m, 4 H, H arom.), 7.39–7.29 (m, 11 H, H arom.), 7.27–7.19 (m, 5 H, H arom.), 4.99 (d, ^2J = 11 Hz, 1 H, CHPh), 4.85 (d, ^2J = 11 Hz, 1 H, CHPh), 4.84 (d, ^2J = 11 Hz, 1 H, CHPh), 4.82 (d, ^2J = 12 Hz, 1 H, CHPh), 4.72–4.65 (m, 3 H, 1-H, 2CHPh), 4.35 (d, $^3J_{5,4}$ = 10 Hz, 1 H, 5-H), 4.11–4.05 (m, 1 H, 3-H), 3.83 (dd, $^3J_{4,3}$ = 9, $^3J_{4,5}$ = 10 Hz, 1 H, 4-H), 3.62 (dd, $^3J_{2,1}$ = 4, $^3J_{2,3}$ = 10 Hz, 1 H, 2-H), 3.54 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.2 (C=O), 138.6, 138.0, 137.8 (C arom. quat.), 133.4, 131.1 (C arom. tert.), 128.7–127.8 (C arom. tert.), 119.6 (C arom. quat.), 98.8 (C-1), 94.2, 87.3 (C_{sp}), 81.7, 79.5, 79.1 (CH), 76.1 (CH_2), 75.6 (CH), 75.3, 73.7 (CH_2), 55.7 (OCH_3) ppm. HRMS (ES) *m*/*z* calcd. for $C_{36}H_{34}O_6Na$ 585.2253 found 585.2286.

(*R*)-1-(4-Fluorophenyl)-3-phenyl-[(2*S*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxy-tetrahydro-2*H*-pyran-2-yl]prop-2-yn-ol (13*R*): A solution of ketone 12 (866 mg, 1.54 mmol) in THF (9 mL) under nitrogen at –10 °C was slowly added (4-fluorophenyl)magnesium bromide (6.2 mL in THF). The reaction mixture was left stirring at this temperature for 30 min before increasing to room temperature followed by stirring for 30 min more. The reaction was quenched by adjusting adding saturated aqueous NH_4Cl (20 mL) at 0 °C. Then the phases were separated and the water phase was extracted with DCM (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The concentrate was purified on a silica column (Et_2O/*n*-pentane: 1/3) affording compound **13*R*** (85%, 862.3 mg) as a light yellow syrup; R_f = 0.55 (EtOAc/*n*-pentane: 2/3); $[\alpha]_D$ = +50.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (dd, $^4J_{H,F}$ = 5, $^3J_{H,H}$ = 9 Hz, 2 H, H arom.), 7.4–7.21 (m, 18 H, H arom.), 7.00–6.91 (m, 4 H, H arom.), 4.96 (d, ^2J = 11 Hz, 1 H, CHPh), 4.90 (d, ^2J = 11 Hz, 1 H, CHPh), 4.77 (d, ^2J = 12 Hz, 1 H, CHPh), 4.70–4.66 (m, 2 H, 1-H, CHPh), 4.62 (d, ^2J = 12 Hz, 1 H, CHPh), 4.49 (s, 1 H, OH), 4.43 (d, ^2J = 11 Hz, 1 H, CHPh), 4.18 (d, $^3J_{4,5}$ = 10 Hz, 1 H, 5-H), 4.10–4.04 (m, 1 H, 3-H), 3.56–4.47 (m, 2 H, 2-H, 4-H) 3.47 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5 (d, $^1J_{C,F}$ = 245 Hz, C arom. quat.), 138.2, 138.0, 137.6 (C arom. quat.), 136.9 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 131.7 (C arom. tert.), 128.6–127.9 (C arom. tert.), 127.6 (d, $^3J_{C,F}$ = 8 Hz, C arom. tert.), 127.1 (C arom. tert.), 122.3 (C arom. quat.), 114.7 (d, $^2J_{C,F}$ = 21 Hz, C arom. tert.), 97.9 (C-1), 89.7, 86. 4 (C_{sp}), 82.4, 80.1 79.3 (CH), 75.8 (CH_2), 74.4 (CH), 74.3 (C-6), 74.2, 73.3 (CH_2), 55.4 (OCH_3) ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –115.05 ppm. HRMS (ES) *m*/*z* calcd. for $C_{42}H_{39}FO_6Na$ 681.2628 found 681.2646.

(*S*)-1-(4-Fluorophenyl)-3-phenyl-[(2*S*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxy-tetrahydro-2*H*-pyran-2-yl]prop-2-yn-ol (13*S*): A solution of phenylacetylene (0.27 mL, 2.37 mmol) in THF (0.6 mL) under nitrogen was cooled to 0 °C. To the solution was slowly added EtMgBr (2.30 mL, 1 mol L^{-1} in THF) and the temperature was adjusted to room temperature. The reaction mixture was stirred at this temperature for 30 min before cooling it down to –10 °C and slowly adding a solution of ketone **11** (426 mg, 0.765 mmol) in THF (8 mL). Then the reaction mixture was left stirring for 1 h before increasing to 0 °C and slowly adding saturated aqueous NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined

organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification of the concentrate by chromatography (EtOAc/*n*-pentane: 1/25) afforded compound **13*S*** (85%, 430.5 mg) as a light yellow syrup; R_f = 0.36 (EtOAc/*n*-pentane: 1/3); $[\alpha]_D$ = +57.3 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = (dd, $^4J_{H,F}$ = 6, $^3J_{H,H}$ = 9 Hz, 2 H, H arom.), 7.55–7.52 (m, 2 H, H arom.), 7.39–7.24 (m, 18 H, H arom.), 7.03–6.97 (m, 2 H, H arom.), 5.39 (s, 1 H, OH), 5.18 (d, ^2J = 10 Hz, 1 H, CHPh), 5.06 (d, ^2J = 11 Hz, 1 H, CHPh), 4.93 (d, ^2J = 10 Hz, 1 H, CHPh), 4.85 (d, ^2J = 11 Hz, 1 H, CHPh), 4.74 (d, ^2J = 12 Hz, 1 H, CHPh), 4.60 (d, ^2J = 12 Hz, 1 H, CHPh), 4.40 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 4.24–4.18 (m, 1 H, 4-H), 4.12–4.06 (m, 1 H, 3-H), 3.71 (d, $^3J_{5,4}$ = 9 Hz, 1 H, 5-H), 3.60 (dd, $^3J_{2,1}$ = 4, $^3J_{2,3}$ = 9 Hz, 1 H, 2-H), 2.70 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5 (d, $^1J_{C,F}$ = 245 Hz, C arom. quat.), 138.3, 137.93 (C arom. quat.), 137.3 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 136.9 (C arom. quat.), 131.9 (C arom. tert.) 128.8–127.9 (C arom. tert.), 122.9 (C arom. quat.), 114.4 (d, $^2J_{C,F}$ = 21 Hz, C arom. tert.), 97.9 (C-1), 89.2, 87.9 (C_{sp}), 82.5, 82.1, 80.5 (CH), 76.31, 75.9 (CH_2), 75.2 (C-6), 73.8 (CH), 73.6 (CH_2), 54.8 (OCH_3) ppm. HRMS (ES) *m*/*z* calcd. for $C_{42}H_{39}FO_6Na$ 681.2628 found 681.2571. Further elution afforded compound other isomer (1%, 5 mg).

(2*S*,3*S*,4*S*,5*R*,6*S*)-2-[(*R*)-1-(4-Fluorophenyl)-1-hydroxy-3-phenylpropyl]-6-methoxy-tetrahydro-2*H*-pyran-3,4,5-triol: To a solution of **13*R*** (425 mg, 0.647 mmol) and TFA (cat) in EtOH/EtOAc (2/1, 60 mL) under nitrogen at room temperature was added Pd/C (10%, 260 mg). The mixture was degassed and a hydrogen atmosphere (1 atm) was introduced. Then the reaction mixture was left stirring for 48 h before filtering it through Celite. Concentration of the filtrate afforded the product (90%, 228 mg) as a white solid; R_f = 0.49 (EtOAc/MeOH: 12/1); $[\alpha]_D$ = +9.3 (*c* = 0.25, MeOH). ^1H NMR (300 MHz, CD_3OD): δ = 7.65–7.60 (m, 2 H, H arom.), 7.27–7.22 (m, 2 H, H arom.), 7.15–7.05 (m, 5 H, H arom.), 4.57 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 3.69–3.57 (m, 2 H, 3-H, 4-H), 3.50 (d, $^3J_{5,4}$ = 9 Hz, 1 H, 5-H), 3.38 (dd, $^3J_{2,1}$ = 4, $^3J_{2,3}$ = 9 Hz, 1 H, 2-H), 2.82 (s, 3 H, OCH_3), 2.77–2.68 (m, 1 H), 2.54–2.45 (m, 1 H), 2.35–2.16 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 163.0 (d, $^1J_{C,F}$ = 242 Hz, C arom. quat.), 144.1 (C arom. quat.), 141.0 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 129.9 (d, $^3J_{C,F}$ = 8 Hz, C arom. tert.), 129.3, 129.2, 126.6 (C arom. tert.), 114.0 (d, $^2J_{C,F}$ = 21 Hz, C arom. tert.), 100.8 (C-1), 78.6 (C-6), 75,5, 73.2, 73.1 (CH), 55.0 (OCH_3), 38.6, 30.6 (CH_2) ppm. ^{19}F NMR (300 MHz, CD_3OD): δ = –118.89 ppm. HRMS (ES) *m*/*z* calcd. for $C_{21}H_{25}FO_6Na$ 415.1533 found 415.1541.

(2*S*,3*S*,4*S*,5*R*,6*S*)-2-[(*S*)-1-(4-Fluorophenyl)-1-hydroxy-3-phenylpropyl]-6-methoxy-tetrahydro-2*H*-pyran-3,4,5-triol: To a solution of **13*S*** (496 mg, 0.753 mmol) and TFA (cat) in MeOH/EtOAc (2/1, 60 mL) under nitrogen at room temperature was added Pd/C (10%, 300 mg). The mixture was degassed and a hydrogen atmosphere (1 atm) was introduced. The reaction mixture was left stirring for 48 h before filtering it through a pad of Celite. Concentration of the filtrate afforded the desired product (95%, 281 mg) as a white solid; R_f = 0.56 (EtOAc/MeOH: 12/1); $[\alpha]_D$ = +80.7 (*c* = 0.3, MeOH) ^1H NMR (300 MHz, CD_3OD): δ = 7.67–7.63 (m, 2 H, H arom.), 7.24–7.19 (m, 2 H, H arom.), 7.14–7.06 (m, 5 H, H arom.), 4.72 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 3.80 (d, $^3J_{5,4}$ = 10 Hz, 1 H, 5-H), 3.69–3.63 (m, 1 H, 3-H), 3.43 (s, 3 H, OCH_3), 3.20 (d, $^3J_{2,1}$ = 4, $^3J_{2,3}$ = 10 Hz, 1 H, 2-H), 3.03–2.97 (m, 1 H, 4-H), 2.79–2.71 (m, 1 H), 2.48–2.39 (m, 1 H), 2.30–2.13 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 162.2 (d, $^1J_{C,F}$ = 242 Hz, C arom. quat.), 142.9 (C arom. quat.), 139.3 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 128.5 (d, $^3J_{C,F}$ = 8 Hz, C arom. tert.), 114.2 (d, $^2J_{C,F}$ = 21 Hz, C arom. tert.), 100.3 (C-1) 78.4 (C-6), 74.2, 73.9, 72.7, 72.0 (CH), 55.2 (OCH_3), 42.2, 29.2 (CH_2) ppm. ^{19}F NMR (300 MHz, CD_3OD): δ = –119.03 ppm. HRMS (ES) *m*/*z* calcd. for $C_{21}H_{25}FO_6Na$ 415.1533 found 415.1554.

(2*S*,4*S*,4a*S*,6*S*,7*R*,8*R*,8a*S*)-4-(4-Fluorophenyl)-6-methoxy-4-phenethyl-2-phenyl-hexahydropyrano[3,2-*d*][1,3]dioxine-7,8-diol (14*S*): To a solution of the triol (15 mg, 38.2 μmol) and $PhCH(OMe)_2$ (40 μL, 268 μmol) in DMF (0.3 mL) under nitrogen was added *p*-toluenesulfonic acid monohydrate (2.23 mg, 11.5 μmol). The obtained reaction mixture was left stirring overnight at room temperature before neutralizing it by adding Et_3N. The solvent was removed and the crude product was purified by column chromatography. (EtOAc/*n*-pentane: 1/2 → 3/1) afforded compound **15*S*** (50%, 9.1 mg) with minor impurities; R_f = 0.57 (EtOAc). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.77 (dd, $^4J_{H,F}$ = 5, $^3J_{H,H}$ = 9 Hz, 2 H, H arom.), 7.55–7.72 (m, 2 H, H arom.), 7.43–7.34 (m, 3 H, H arom.), 7.23–7.21 (m, 2 H, H arom.), 7.17–7.05 (m, 5 H, H arom.), 5.75 (s, 1 H, $CHPhCO_2$), 5.01 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 4.24 (d, $^3J_{5,4}$ = 10 Hz, 1 H, 5-H), 3.98–3.92 (m, 1 H, 3-H), 3.74 (dd, $^3J_{4,3}$ = 9, $^3J_{4,5}$ = 10 Hz, 1 H, 4-H), 3.68–3.64 (m, 1 H, 2-H), 2.58 (s, 3 H, OCH_3), 2.77–2.56 (m, 2 H), 2.27–2.21 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.1 (d, $^1J_{C,F}$ = 246 Hz, C arom. quat.), 141.9, 137.5 (C arom. tert.), 135.7 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 129.6 (d, $^3J_{C,F}$ = 8 Hz, C arom. tert.), 129.2–125.9 (C arom. tert.), 115.4 (d, $^2J_{C,F}$ = 21 Hz, C arom. tert.), 99.7 (C-1), 96.3 ($CHPhCO_2$), 80.4 (C-6), 75.8, 72.4, 72.2, 71.7 (CH), 56.2 (OCH_3), 44.7, 29.5 (CH_2) ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –115.05 ppm. HRMS (ES) *m*/*z* calcd. for $C_{28}H_{29}FO_6Na$ 503.1846 found 503.1866.

(2*S*,4*R*,4a*S*,6*S*,7*R*,8*R*,8a*S*)-4-(4-Fluorophenyl)-6-methoxy-4-phenethyl-2-phenyl-hexahydropyrano[3,2-*d*][1,3]dioxine-7,8-diol (14*R*): The benzylidene **14*R*** was prepared in the same way as benzylidene (14S). (50%, 6.0 mg); R_f = 0.66 (EtOAc); $[\alpha]_D$ = +4.3 (*c* = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71 (dd, $^4J_{H,F}$ = 6, $^3J_{H,H}$ = 9 Hz, 2 H, H arom.), 7.64–7.61 (m, 2 H, H arom.), 7.49–7.42 (m, 3 H, H arom.), 7.29–7.24 (m, 2 H, H arom.), 7.20–7.15 (m, 1 H, H arom.), 7.12–7.05 (m, 4 H, H arom.), 6.01 (s, 1 H, $CHPhO_2$), 4.78 (d, $^3J_{1,2}$ = 4 Hz, 1 H, 1-H), 3.93–3.80 (m, 2 H, 3-H, 4-H), 3.63–3.58 (m, 2 H, 2-H, 5-H), 3.01 (s, 3 H, OCH_3), 2.83–2.73 (m, 1 H, 7-H), 2.62–2.38 (m, 2 H, 7-H, 8-H), 2.28–2.19 (m, 1 H, 8-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2 (d, $^1J_{C,F}$ = 246 Hz, C arom. quat.), 140.1 (C arom. quat.), 139.1 (d, $^4J_{C,F}$ = 3 Hz, C arom. quat.), 137.7 (C arom. quat.), 129.5, 128.7, 128.6, 128.4 (C arom. tert.), 127.6 (d, $^3J_{C,F}$ = 8 Hz, C arom. tert.), 126.6, 126.1 (C arom. tert.), 114.9 (d, $^2J_{C,F}$ = 21 Hz, C arom. tert.), 99.6 (C-1), 95.5 ($CHPhO_2$), 79.2 (C-6), 75.7, 72.84, 72.77, 70.8 (CH), 55.4 (OCH_3), 30.2 (C-7), 28.7 (C-8) ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –116.07 ppm. HRMS (ES) *m*/*z* calcd. for $C_{28}H_{29}FO_6Na$ 503.1846 found 503.1868.

Degradation of 2f: A solution of the debenzylated **9e** (117 mg, 95 μmol) in H_2O (35 mL) was added Amberlite IR-120 (H^+) and the mixture was refluxed for 48 h. The resin was removed by filtration and the filtrate was neutralized by adding Amberlite (OH^-). The resin was removed and the filtrate was concentrated. The filtrate was dissolved in MeOH (35 mL) and was added Amberlite IR-120 (H^+) followed by reflux for 24 h. Then the resin was removed and the filtrate was concentrated. Purification by chromatography (EtOAc/DCM: 4/1) afforded a mixture (6.5 mg) consisting of **10** as the major component.

Degradation of 8e: The *S*-isomer (**8e**) (300 mg,9.6 μmol) was debenzylated in the same way as **2f**. The crude product was dissolved in methanolic HCl (0.3 mol L^{-1} in MeOH, 34 mL) [prepared by mixing MeOH (34 mL) and AcCl (0.74 mL, 10.5 mmol) for 10 min] and refluxed for 10 h. Then the reaction mixture was allowed to

reach room temperature and concentrated under reduced pressure. Purification on a silica column (EtOAc/DCM: 4/1) afforded a mixture (14.7 mg) consisting of mainly **10*R***.

Degradation of 9e: Compound **9e** (610 mg, 0.194 mmol) was debenzylated in the same way as **2f** followed by degradation and methyl glycosylation following the same procedure as for **9e**. Affording a mixture (7 mg) consisting of mostly **10*S***.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra of all new compounds.

[1] K. L. Larsen, H. J. Christensen, F. Mathiesen, L. H. Pedersen, W. Zimmermann, *Appl. Microbiol. Biotechnol.* **1998**, *50*, 314–317.
[2] I. Tabushi, *Acc. Chem. Res.* **1982**, *15*, 66–72.
[3] R. Breslow, S. D. Dong, *Chem. Rev.* **1998**, *98*, 1997–2011.
[4] J. Bjerre, C. Rousseau, L. Marinescu, M. Bols, *Appl. Microbiol. Biotechnol.* **2008**, *81*, 1–11.
[5] A. R. Khan, P. Forgo, K. J. Stine, V. T. D'Souza, *Chem. Rev.* **1998**, *98*, 1977–1996.
[6] M. Sollogoub, *Eur. J. Org. Chem.* **2009**, 1295–1303.
[7] A. Pearce, P. Sinaÿ, *Angew. Chem. Int. Ed.* **2000**, *39*, 3610–3612.
[8] T. Lecourt, A. Herault, A. J. Pearce, M. Sollogoub, P. Sinaÿ, *Chem. Eur. J.* **2004**, *10*, 2960–2971.
[9] C. Rousseau, N. Nielsen, M. Bols, *Tetrahedron Lett.* **2004**, *45*, 8709–8711.
[10] T. Hardlei, M. Bols, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2880–2885.
[11] D. Horton, A. E. Luetzow, O. Theander, *Carbohydr. Res.* **1973**, *26*,2 1.
[12] L. I. Zakharkin, V. V. Gavrilenko, B. A. Palei, *Zh. Obshch. Khim.* **1970**, *40*, 2669–2676.
[13] N. T. Anh, O. Eisenstein, *Nouv. J. Chim.* **1977**, *1*, 61.

Received: March 3, 2010
Published Online: May 27, 2010

