Synthesis of perfluoroalkylated sugars catalyzed by rabbit muscle aldolase (RAMA)

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Perfluoroalkyl iodides [R_fI: $Cl(CF_2)_4I$, $Cl(CF_2)_6I$, $C_8F_{17}I$] react with acrolein diethyl acetal catalyzed by sulfinatodehalogenation reagents to produce 2-iodo-3-(perfluoroalkyl)propanal diethyl acetal **1**, which is converted into (*E*)-3-(perfluoroalkyl)acrolein diethyl acetals **2** on treatment by base (KOH–MeOH). 3-Perfluoroalkyl-D-glyceraldehyde diethyl acetals **3** are produced through the asymmetric dihydroxylation (AD) of compound **2**. Then **3** are easily hydrolyzed to 3-perfluoroalkyl-D-glyceraldehydes **4**, which could react with DHAP catalyzed by RAMA and further acid phosphatase to form 6-*C*-perfluoroalkyl-D-fructose, which is a novel sugar and surfactant.

Introduction

Perfluoroalkylated monosaccharides[1] which contain the strongly hydrophobic perfluoroalkyl chain and a biocompatible polar head group should be useful surfactants and emulsifiers for biomedical applications.[2] The sugar moiety may allow specific *in vivo* recognition and hence such substances may be capable of drug targeting.[3] On the other hand, such amphiphilic compounds may have interesting liquid-crystalline properties;[1c] however, mesogenic properties of perfluoroalkylated carbohydrate amphiphiles have not been described so far.

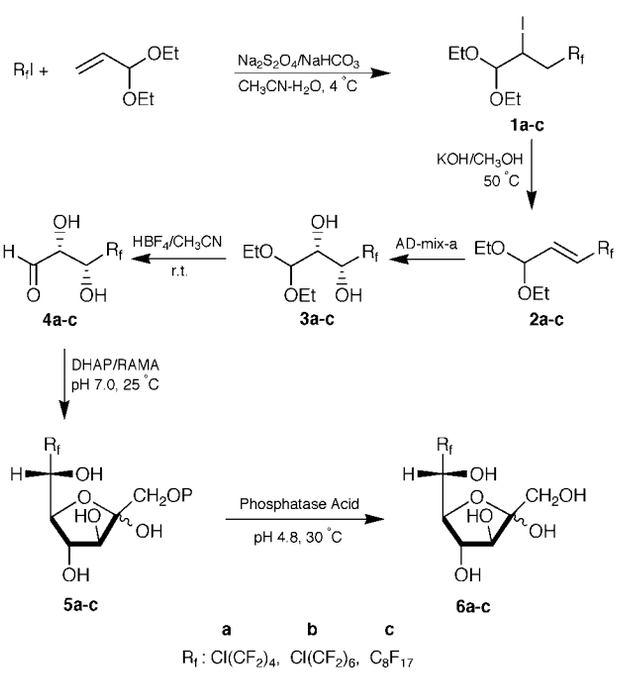
Miethchen and Hein have synthesized 5-*C*-perfluoroalky-D-xylose using a sonochemical Barbier-type reaction.[1c] 2-Perfluoroalkyl-2-deoxy-D-glucose was synthesized by W.-Y. Huang, through the sulfinatodehalogenation reaction.[1e] These amphiphilic perfluoroalkyl-substituted carbohydrates have a stable C–C bond directly between the sugar moiety and the perfluoroalkyl tail. Here we report 6-*C*-perfluoroalkyl-D-fructoses enzymically synthesized based on the principle of enzymic reaction catalyzed by RAMA.

Rabbit muscle fructose-1,6-diphosphate aldolase (EC 4.1.2.13) reversibly catalyzes the production of D-fructose-1,6-diphosphate (FDP) from D-glyceraldehyde 3-phosphate (G3P) and dihydroxyacetone hydrogen cyclic phosphate (DHAP), the equilibrium being in favour of FDP.[4] Whereas the enzyme selectivity is rather high towards the DHAP structure when only minor change are possible,[5] more flexibility is accepted with regard to the G3P analogue. Owing to this feature and also the availability of the enzyme, a large number of syntheses leading to carbohydrates of D-*threo* (3*S*,4*R*) configuration have been developed.[6]

However, the synthesis of perfluoroalkylated sugars catalyzed by RAMA is challenging and interesting work. In the enzymic reaction, DHAP is the nucleophile, and perfluoroalkylated aldehyde acts as the electrophile. As we know, perfluoroalkyl is a hydrophobic group, which retards the solubility of perfluoroalkylated aldehydes in water which is the reaction medium here. Therefore the aldol reaction may be troublesome due to the insolubility of the electrophilic reagent. Furthermore, whether the perfluoroalkylated aldehyde is recognized by FDP aldolase remains a question. Therefore the synthesis of a suitable perfluoroalkylated aldehyde that can be recognized by RAMA is the crucial step in the whole procedure.

Results and discussion

In our research, a succinct route was performed to achieve the goal (Scheme 1).



Scheme 1

2-Iodo-3-(perfluoroalkyl)propanal diethyl acetal **1** was formed by the addition of a perfluoroalkyl iodide R_fI to acrolein diethyl acetal promoted by sulfinatodehalogenation reagents with high yields (>90%).[7] This was a radical reaction. The reaction should be run at low temperature. When the temperature was higher than 40 °C, the yield of by-product (perfluoroalkanesulfinate) was improved. The purpose of the addition of sodium hydrogen carbonate was to decrease the loss of sodium dithionite which acted as the radical initiator. However, the ratio of acetonitrile to water was a very important factor. Acetonitrile was added to improve the mutual solubility in the reaction system. In this reaction, the ratio of acetonitrile to water should be 1.2–1.8 : 1. Of course, this value was based

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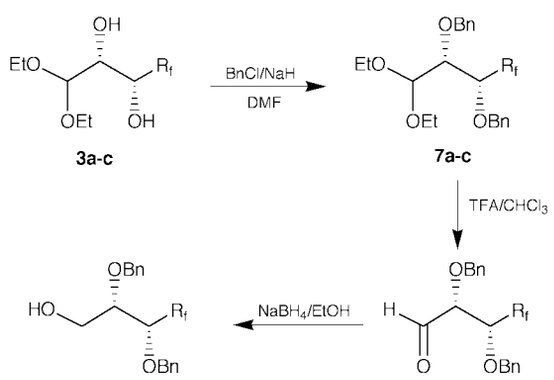
on the properties of R_fI. The smaller R_fI [$Cl(CF_2)_4I$] required the lower ratio (1.2). As for $C_8F_{17}I$, the best ratio was 1.8 : 1 and the optimum temperature was 15 °C, since this reagent is a solid at low temperature and difficult to dissolve.

Because of the high electronegativity of perfluoroalkyl groups of compounds **1**, the adjacent proton was easily removed by base,[8] and the iodide ion was sequentially eliminated to produce the corresponding (*E*)-3-perfluoroalkylacrolein diethyl acetal **2**. A number of bases could accomplish the elimination reaction. Potassium hydroxide in warm methanol led to completion of the reaction with quantitative transformation. The *E*-olefin analyzed by ^{19}F NMR spectroscopy was the only product in this reaction: the CF_2 group α to the double bond exhibited two signals, at δ_F 29.1–29.5 and δ_F 33.8–34.4 ppm (TFA as external standard) corresponding to the *Z* and *E* isomers,[1d] respectively, while the CF_2 group α to the double bond of compounds **2** exhibited signals at δ_F 35.3–36.1, without any signals at δ_F 29–30.

Probably due to the R_f group, the asymmetric dihydroxylation of compounds **2** using AD-mix-α to 3-perfluoroalkyl-D-glyceraldehyde diethyl acetals **3** was slow.[9] (The 3.01 g AD-mix-α, necessary for conversion of 1 mmol of olefin, contains 2 g of $K_3Fe(CN)_6$ (6.0 mmol), 1 g of K_2CO_3 (7.3 mmol), 10 mg of $(DHQ)_2$-PHAL (0.013 mmol), and 2 mg of $K_2OsO_2(OH)_4$ (0.0054 mmol).) The yields reached only 60–70% after 10 days. Fortunately the enantiomeric excesses (ees) of diols **3** were good (90–92%). The ee-values of **3** were determined by chiral HPLC of benzyl derivatives (Scheme 2).



Scheme 2

In our research, the racemates of 2,3-di-*O*-benzyl-3-perfluoroalkyl-D-glyceraldehyde diethyl acetals **7** directly from the benzylation of compounds **3** could not be separated on chiral columns, probably because of the presence of two large groups (R_f and diethyl acetal). When compounds **7** were further converted into 1,2-di-*O*-benzyl-1-(perfluoroalkyl)glycerols **9** after two more steps, chiral HPLC could separate the racemates of **9**. Since no racemization occurred during the conversion processes, the ee-values of **9** represented the ee-values of **3**

Deprotection of the diethyl acetal group of compounds **3** could be run in acetonitrile at room temperature and was catalyzed by fluoroboric acid. The products, 3-perfluoroalkyl-D-glyceraldehydes **4**, should be good acceptor substrates for FDP aldolase as analogues of D-glyceraldehyde 3-phosphate (G3P). However, compounds **4** were prone to hydration forming dimers and polymers[6c] (exhibited from ^1H NMR spectra), that are in equilibrium with monomers. Then the monomers reacted with DHAP catalyzed by RAMA in buffer (pH 7.0) at 25 °C for 2 days to produce compounds **5**, which were hydrolyzed catalyzed by acid phosphatase (EC 3.1.3.2) to remove the phosphate group, leading to the obtainment of the goal compounds 6-*C*-perfluoroalkyl-D-fructoses **6**. The total yields of the last two steps were 30–35%.

Conclusions

6-*C*-Perfluoroalkyl-D-fructoses **6** were enzymically synthesized through a succinct route. This is important and significant not only for the aldol reaction catalyzed by RAMA but also for the synthetic method of perfluoroalkylated sugars. Physicochemical and biological tests of compounds **6** including surface activity, emulsion stabilization, and toxicity will be performed next.

Experimental

The commercially available reagents were used as received without further purification. ^1H NMR spectra were recorded on a Bruker AMX-300 (300 MHz) spectrometer at room temperature. ^{19}F NMR spectra were recorded on a Varian EM-360L (56.4 MHz) spectrometer using TFA as external standard. Chemical shifts in ppm were positive for upfield shifts. IR spectra were recorded neat or in KBr and measured in cm^{-1}, using a Shimadzu IR-440 IR spectrophotometer. Mass spectra were taken using a HP5989A spectrometer. High-resolution mass spectra were obtained on a Fourier transform ion cyclotron resonance mass spectrometer (APEX II, Bruker Co. USA). Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter for solutions in acetone. Acid phosphatase (EC 3.1.3.2) was purchased from Sigma. RAMA was prepared by ourselves. Petroleum spirit was the fraction with distillation range 60–90 °C.

The preparation of RAMA[10]

The ground skeletal muscle of a rabbit was extracted in a cold room at 5 °C with two equal portions of cold water (or cold 0.03 M NaOH, or KOH) and strained through gauze. The cold extract (1200 ml) was first brought to pH 7.5 with dil. NaOH and then to 0.45 saturation by the addition of solid $(NH_4)_2SO_4$. The solution was cooled to 0 °C and the precipitate was removed by centrifugation (4 °C; 5000 rpm; 30 min). To the clear supernatant was added enough $(NH_4)_2SO_4$ to make the saturation 0.55. The precipitate was obtained by centrifugation (4 °C; 5000 rpm; 30 min), containing 2.72 g of protein (2.49 u mg^{-1} specific activity).

2-Iodo-3-(perfluoroalkyl)propanal diethyl acetals 1

A mixture of sodium dithionite (3.5 g, 20 mmol) and sodium hydrogen carbonate (1.8 g, 21 mmol) was added to a stirred solution of R_fI (20 mmol, ClC_4F_8I: 7.3 g; $ClC_6F_{12}I$: 9.3 g; $C_8F_{17}I$: 10.9 g), acrolein diethyl acetal (2.9 g, 22 mmol), acetonitrile (15 ml) and water (10 ml) at 5–10 °C. The mixture was stirred for 2 h, diluted with water (30 ml), and extracted with diethyl ether (3 × 25 ml). The combined organic layer was dried with anhydrous magnesium sulfate. After removal of the solvent, the crude product was purified by flash column chromatography using petroleum spirit and ethyl acetate (50 : 1) as eluent to give the corresponding pure product **1** (**1a**: 9.46 g, 96%; **1b**: 11.14 g, 94%; **1c**: 12.17 g, 90%), ν_{max}(neat)/cm^{-1} 3000, 2890, 1240, 1200, 1150, 1060; δ_H(300 MHz, $CDCl_3$) 1.21–1.27 (m, 6H, 2 × CH_3), 2.65–3.15 (m, 2H, CH_2CF_2), 3.53–3.77 (m, 4H, 2 × CH_2O), 4.21 (m, 1H, CHI), 4.36 (d, *J* 3.2 Hz, 1H); **1a**: δ_F(56.4 MHz, $CDCl_3$) −8.0 (s, 2F, $ClCF_2$), 38.3 (m, 2F, CF_2CH_2), 43.4 (s, 2F, CF_2), 46.6 (s, 2F, CF_2); MS (EI) *m*/*z* 447, 449 (M^+ − EtO), 103 [$CH(OEt)_2$] (Calc. for $C_{11}H_{14}ClF_8IO_2$: C, 26.82; H, 2.86; F, 30.86. Found: C, 26.85; H, 2.83; F, 32.00%). **1b**: δ_F(56.4 MHz, $CDCl_3$) −8.2 (s, 2F, $ClCF_2$), 37.2, 43.9, 45.0, 47.3 (m, 10F, 5 × CF_2); MS (EI) *m*/*z* 547, 549 (M^+ − EtO), 103 [$CH(OEt)_2$] (Calc. for $C_{13}H_{14}ClF_{12}IO_2$: C, 26.35; H, 2.38; F, 38.47. Found: C, 26.70; H, 2.32; F, 38.12%). **1c**: δ_F(56.4 MHz, $CDCl_3$) 3.2 (s, 3F, CF_3), 36.4 (m, 2F, CF_2CH_2), 44.2, 45.9, 48.5 (m, 12F, 6 × CF_2); MS (EI) *m*/*z* 676 (M^+) (Calc. for $C_{15}H_{14}F_{17}IO_2$: C, 26.65; H, 2.09; F, 47.77; I, 18.77. Found: C, 26.67; H, 1.94; F, 48.09; I, 18.24%).

(*E*)-3-(Perfluoroalkyl)acrolein diethyl acetals 2

Potassium hydroxide (1.12 g, 20 mmol) was added to a stirred solution of a compound **1** (17 mmol) in methanol (20 ml) at room temperature. Then, the mixture was warmed to 50 °C. The solid potassium hydroxide slowly dissolved. Soon after a white solid (KI) precipitated from the solution. About 1 h later, the reaction was complete (detected by TLC). After the removal of methanol, the residue was diluted with water (20 ml) and extracted with diethyl ether (3 × 15 ml). The combined organic layer was dried with anhydrous magnesium sulfate. Solvent was evaporated off, and the crude product was purified by column chromatography (petroleum spirit–ethyl acetate 50:1) to give the corresponding pure product **2** (100% yield), ν_{max}(neat)/cm^{-1} 2900, 1660, 1600, 1440, 1370, 1150; δ_H(300 MHz; $CDCl_3$) 1.14–1.26 (m, 6H, 2 × CH_3), 3.46–3.71 (m, 4H, 2 × CH_2O), 5.06 [m, 1H, C*H*$(OEt)_2$], 6.03 (m, 1H), 6.34 (m, 1H, $CHCF_2$); **2a**: δ_F(56.4 MHz, $CDCl_3$) −8.1 (t, *J* 13.5 Hz, 2F, $ClCF_2$), 35.7 (d, *J* 12.4 Hz, 2F, CF_2CH), 43.3 (s, 2F, CF_2), 46.3 (s, 2F, CF_2); MS (EI) *m*/*z* 364, 366 (M^+) (Calc. for $C_{11}H_{13}ClF_8O_2$: C, 36.23; H, 3.59; Cl, 9.72; F, 41.68. Found: C, 35.92; H, 3.56; Cl, 9.65; F, 41.95%). **2b**: δ_F(56.4 MHz, $CDCl_3$) −8.2 (s, 2F, $ClCF_2$), 36.1 (s, 2F, CF_2CH), 44.1, 45.1, 47.1 (m, 8F, 4 × CF_2); MS (EI) *m*/*z* 419, 421 (M^+ − EtO) (Calc. for $C_{13}H_{13}ClF_{12}O_2$: C, 33.60; H, 2.82; Cl, 7.63; F, 49.06. Found: C, 33.10; H, 2.63; Cl, 7.89; F, 49.10%). **2c**: δ_F(56.4 MHz, $CDCl_3$) 4.0 (s, 3F, CF_3), 35.3 (s, 2F, CF_2CH), 44.6, 46.0, 49.1 (m, 12F, 6 × CF_2); MS (EI) *m*/*z* 548 (M^+) (Calc. for $C_{15}H_{13}F_{17}O_2$: C, 32.86; H, 2.39; F, 58.91. Found: C, 32.69; H, 2.32; F, 58.95%).

(3*R*)-3-Perfluoroalkyl-D-glyceraldehyde diethyl acetals 3

A 250-ml round-bottomed flask, equipped with a big magnetic stirrer, was charged with *tert*-butyl alcohol (50 ml), water (50 ml), $K_3Fe(CN)_6$ (20 g, 61 mmol), K_2CO_3 (10 g, 73 mmol), $(DHQ)_2$-PHAL (100 mg, 0.13 mmol), $K_2OsO_2(OH)_4$ (20 mg, 0.054 mmol), and methanesulfonamide (1 g, 10.5 mmol); stirring at room temperature produced two clear phases. The mixture was cooled to 4 °C whereupon some of the dissolved salts precipitated. A compound **2** (10 mmol) was added, and the heterogeneous slurry was stirred vigorously at 4 °C for 10 days. Solid sodium sulfite (35 g) was added and the mixture was allowed to warm to room temperature and stirred for 2 h. Ethyl acetate (50 ml) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with ethyl acetate (3 × 40 ml). The combined organic extracts were washed with 1 M hydrochloric acid (20 ml) to recover the chiral ligand from the organic solvent, and subsequently washed successively with 1 M aq. sodium hydroxide (30 ml) and brine (2 × 20 ml), and dried with anhydrous sodium sulfate. After removal of solvent, the crude product was purified by flash chromatography (silica gel; hexane–ethyl acetate 20:1–10:1) to afford the corresponding compound **3** (**3a**: 2.79 g, 70% yield, 92% ee; **3b**: 3.39 g, 68% yield, 91% ee; **3c**: 3.67 g, 63% yield, 90% ee); ν_{max}(neat)/cm^{-1} 3360, 2940, 2900, 1390, 1200, 1140; δ_H(300 MHz, $CDCl_3$) 1.21–1.27 (m, 6H, 2 × CH_3), 3.32 (br, 2H, 2 × CH), 3.57–3.85 (m, 4H, 2 × CH_2O), 3.95 (dd, 1H, J_1 6.4 Hz, J_2 1.5 Hz), 4.32–4.40 (m, 1H, $CHCF_2$), 4.58 [d, 1H, *J* 6.4 Hz, C*H*$(OEt)_2$]; **3a**: $[\alpha]_D^{22}$ 5.56; δ_F(56.4 MHz, $CDCl_3$) −8.6 (s, 2F, $ClCF_2$), 43.4, 43.8, 44.7, 47.6 (m, 6F, 3 × CF_2); MS (EI) *m*/*z* 352, 354 (M^+ − EtOH), 103 [$CH(OEt)_2$] (Calc. for $C_{11}H_{15}ClF_8O_4$: C, 33.14; H, 3.79; Cl, 8.89; F, 38.12. Found: C, 33.38; H, 3.89; Cl, 8.66; F, 38.40%). **3b**: $[\alpha]_D$ 8.63; δ_F(56.4 MHz, $CDCl_3$) −8.4 (s, 2F, $ClCF_2$), 43.8, 45.0, 45.5, 48.1 (m, 10F, 5 × CF_2); MS (EI) *m*/*z* 453, 455 (M^+ − EtOH), 103 [$CH(OEt)_2$] (Calc. for $C_{13}H_{15}ClF_{12}O_4$: C, 31.31; H, 3.03; Cl, 7.11; F, 45.72. Found: C, 31.94; H, 3.28; Cl, 7.00; F, 45.75%). **3c**: $[\alpha]_D^{17}$ 2.65 × 10^{-1} deg cm^2 g^{-1}; δ_F(56.4 MHz, $CDCl_3$) 3.0 (s, 3F, CF_3), 44.1, 48.3 (m, 14F, 7 × CF_2); MS (EI) *m*/*z* 537 (M^+ − EtO) (Calc. for $C_{15}H_{15}F_{17}O_4$: C, 30.94; H, 2.60; F, 55.47. Found: C, 30.82; H, 2.44; F, 55.92%).

(3*R*)-3-Perfluoroalkyl-D-glyceraldehydes 4

Fluoroboric acid (48 wt-% solution in water, 1 ml) was added to a stirred solution of a compound **3** (5 mmol) in acetonitrile (15 ml) at room temperature. Then the mixture was stirred for 10 h. Sodium hydrogen carbonate (0.6 g) was added to neutralize the mixture. After the removal of most acetonitrile, the residue was diluted with water (15 ml), and extracted with diethyl ether (3 × 15 ml). The combined organic layer was dried with anhydrous magnesium sulfate. Solvent was evaporated off, and the crude product was purified by column chromatography (petroleum spirit–ethyl acetate 5:1) to give the pure product **4** (**4a**:1.40 g, 86%; **4b**: 1.77 g, 83%; **4c**: 2.00 g, 79%); ν_{max}(KBr)/cm^{-1} 3453, 2930, 1750, 1200, 1150; δ_H[300 MHz, $(CD_3)_2CO$] 3.58 (2H, br), 3.70–4.25 (1H, m), 4.37–4.54 (1H, m), 4.96–5.64, 9.75 (1H, m); **4a**: δ_F(56.4 MHz, $(CD_3)_2CO$) −8.3 (2F, s, $ClCF_2$), 43.6, 43.9, 44.8, 47.7 (6F, m, 3 × CF_2); MS (EI) *m*/*z* 325, 327 (M^+ + 1), 295, 297 (M^+ − CHO). **4b**: δ_F[56.4 MHz, $(CD_3)_2CO$] −7.8 (2F, s, $ClCF_2$), 44.1, 45.5 (10F, m, 5 × CF_2); MS (EI) *m*/*z* 425, 427 (M^+ + 1); 395, 397 (M^+ − CHO). **4c**: δ_F[56.4 MHz, $(CD_3)_2CO$] 4.7 (3F, s, CF_3), 45.5, 46.4, 49.8 (14F, m, 7 × CF_2); MS (EI) *m*/*z* 509 (M^+ + 1), 479 (M^+ − CHO).

(6*R*)-6-*C*-Perfluoroalkyl-D-fructose 6

A compound **4** (3 mmol) was added to 20 ml of a solution containing 4 mmol of DHAP[11] prepared from 1,3-dihydroxyacetone hydrogen cyclic phosphate dimer by chemical phosphorylation, and the solution was adjusted to pH 7 with 1 M NaOH. RAMA (1000 u) was added. After the mixture had been stirred under nitrogen at room temperature for 2 days, the pH of the mixture was adjusted to 4.8 with 1 M HCl and 100 mg (36 u) of acid phosphatase was added. The mixture was stirred at 30 °C for 48 h, neutralized and freeze-dried. The residue was extracted with methanol (3 × 30 ml). After removal of solvent, the resultant syrup was purified by column chromatography (*n*-hexane–acetone 4:1) to give the corresponding product **6** (**6a**: 0.44 g, 35%; **6b**: 0.48 g, 31%; **6c**: 0.54 g, 30%) as syrups; ν_{max}(KBr)/cm^{-1} 3409, 2970, 1214, 1139; δ_H[300 MHz, $(CD_3)_2CO$] 3.41–4.03 (5H, m), 4.14–4.22 (1H, m); **6a**: δ_F[56.4 MHz, $(CD_3)_2CO$] −9.5 (2F, s, $ClCF_2$), 43.6, 44.0, 44.8 (6F, m, 3 × CF_2); MS (FAB) *m*/*z* 437, 439 (M^+ + Na); HR-SIMS $C_{10}H_{11}ClF_8NaO_6$ requires *m*/*z*, 437.0009. Found: *m*/*z*, 437.0004. **6b**: δ_F[56.4 MHz, $(CD_3)_2CO$] −8.1 (2F, s, $ClCF_2$), 43.8, 45.3, 46.9 (10F, m, 5 × CF_2); MS (FAB) *m*/*z* 537, 539 (M^+ + Na). HR-SIMS $C_{12}H_{11}ClF_{12}NaO_6$ requires *m*/*z*, 536.9945. Found: *m*/*z*, 536.9940. **6c**: δ_F[56.4 MHz, $(CD_3)_2CO$] 5.0 (3F, s, CF_3), 45.7, 46.5, 50.1 (14F, m, 7 × CF_2); MS (FAB) *m*/*z* 621 (M^+ + Na). HR-SIMS $C_{14}H_{11}F_{17}NaO_6$ requires *m*/*z*, 621.0176. Found: *m*/*z*, 621.0182.

Derivatization of 3 (the racemates of 3 were derived from the same reactions)

(3*R*)-2,3-Di-*O*-benzyl-3-perfluoroalkyl-D-glyceraldehyde diethyl acetals 7. NaH (120 mg, 5 mmol) was added to a solution of a diol **3** (2 mmol) in DMF (10 ml) at ambient temperature with magnetic stirring. After 15 min benzyl chloride (0.6 ml, 5.2 mmol) was added and stirring was continued for 10 h. The reaction mixture was added to crushed ice (≈20 g) and extracted with diethyl ether (3 × 10 ml). The organic layer was washed successively with water (10 ml) and brine (10 ml), then dried and concentrated to dryness. Flash chromatography on silica gel (petroleum spirit–ethyl acetate 50:1) provided the corresponding compound **7** (**7a**: 1.11 g, 96%; **7b**: 1.29 g, 95%; **7c**: 1.48 g, 97%) as colorless oils, ν_{max}(neat)/cm^{-1} 3020, 2980, 2900, 1495, 1450, 1350, 1220, 1140, 730, 695; δ_H(300 MHz, $CDCl_3$) 1.32 (6H, t, *J* 7.0 Hz, 2 × CH_3), 3.47–3.86 (4H, m, 2 × CH_2), 3.96–3.98 (1H, m, C*H*OBn), 4.51–4.58 (1H, m, C*H*OBnCF_2), 4.67 [1H, d, *J* 5.8 Hz, C*H*$(OEt)_2$], 4.86, 4.89 (4H, 2s, 2 × C*H*$_2$Ph), 7.36–7.49 (10H, m, 2 × C_6H_5). **7a**: δ_F(56.4

MHz, $CDCl_3$) −9.3 (2F, s, CF_2Cl), 41.0, 42.8, 43.3, 43.6 (6F, m, 3 × CF_2); MS (EI) *m*/*z* 577, 579 ($M^+ - 1$) (Calc. for $C_{25}H_{27}ClF_8O_4$: C, 51.87; H, 4.70; F, 26.25; Cl, 6.12. Found: C, 52.16; H, 4.55; F, 26.27; Cl, 6.13%). **7b**: δ_F(56.4 MHz, $CDCl_3$) −8.1 (2F, s, CF_2Cl), 41.5, 43.9, 44.8 (10F, m, 5 × CF_2); MS (EI) *m*/*z* 633, 635 ($M^+ - OEt$), 103 [$CH(OEt)_2$], 91 (Bn) (Calc. for $C_{27}H_{27}ClF_{12}O_4$: C, 47.77; H, 4.01; F, 33.58; Cl, 5.22. Found: C, 48.11; H, 3.92; F, 33.44; Cl, 5.15%). **7c**: δ_F(56.4 MHz, $CDCl_3$) 3.6 (3F, s, CF_3), 41.1, 42.6 (2F, AB, CF_2CH), 44.5, 49.0 (12F, m, 6 × CF_2); MS (EI) *m*/*z* 762 (M^+), 103 [$CH(OEt)_2$], 91 (Bn) (Calc. for $C_{29}H_{27}F_{17}O_4$: C, 45.68; H, 3.57; F, 42.36. Found: C, 45.74; H, 3.72; F, 41.78%).

(3*R*)-2,3-Di-*O*-benzyl-3-perfluoroalkyl-D-glyceraldehydes 8. Trifluoroacetic acid (0.5 ml) was added to a solution of an acetal **7** (**7a**: 1.01 g, **7b**: 1.05 g, **7c**: 1.26 g) in $CHCl_3$ (1 ml) at 10 °C with magnetic stirring. After the removal of TFA and $CHCl_3$ *in vacuo* after 2 h, the residue was neutralized with saturated aq. sodium hydrogen carbonate (5 ml) and extracted with diethyl ether (3 × 10 ml). The organic layer was dried and concentrated to dryness. Flash chromatography on silica gel (petroleum spirit–ethyl acetate 20 : 1) provided the corresponding aldehyde **8** (**8a**: 0.78 g, 89%; **8b**: 0.87 g, 93%; **8c**: 1.04 g, 91%); ν_{max}(neat)/cm^{-1} 3000, 2990, 1720, 1500, 1450, 1200, 730, 700; δ_H(300 MHz, $CDCl_3$) 4.13 (1H, d, *J* 3.2 Hz, C*H*OBn), 4.36–4.44 (1H, m, $CHCF_2$), 4.56, 4.64 (2H, AB, *J* 10.9 Hz, CH_2Ph), 4.66, 4.79 (2H, AB, *J* 11.6 Hz, CH_2Ph), 7.25–7.37 (10H, m, 2 × C_6H_5), 9.60 (1H, s, CHO). **8a**: δ_F(56.4 MHz, $CDCl_3$) −8.9 (2F, s, CF_2Cl), 41.2, 42.9, 43.3, 43.7 (6F, m, 3 × CF_2); MS (EI) *m*/*z* 503, 505 ($M^+ - 1$), 413, 415 ($M^+ - Bn$). **8b**: δ_F(56.4 MHz, $CDCl_3$) −8.1 (2F, s, CF_2Cl), 41.0, 42.3, 44.0, 44.8 (10F, m, 5 × CF_2); MS (EI) *m*/*z* 513, 515 ($M^+ - Bn$), 91 (Bn). **8c**: δ_F(56.4 MHz, $CDCl_3$) 2.8 (3F, s, CF_3), 39.4, 40.9 (2F, AB, CF_2CH), 43.7, 44.6, 48.2 (12F, m, 6 × CF_2); MS (EI) *m*/*z* 688 (M^+), 597 ($M^+ - Bn$), 91 (Bn).

1,2-Di-*O*-benzyl-1-(perfluoroalkyl)glycerol 9. $NaBH_4$ (40 mg, 1 mmol) was added to a solution of an aldehyde **8** (**8a**: 0.65 g, **8b**: 0.69 g, **8c**: 0.81 g) in ethanol (5 ml). The reaction mixture was treated with 10% aq. NH_4Cl (10 ml) after 2 h and extracted with diethyl ether (3 × 10 ml). The organic layer was dried and concentrated to dryness. Flash chromatography on silica gel (petroleum spirit–ethyl acetate 10 : 1) provided the corresponding compound **9** (**9a**: 0.55 g, 84%; **9b**: 0.59 g, 86%; **9c**: 0.66 g, 81%); ν_{max}(KBr)/cm^{-1} 3477, 3038, 2954, 1500, 1457, 1369, 1201, 745, 697; δ_H(300 MHz, $CDCl_3$) 2.06 (1H, br, OH), 3.64 (1H, dd, *J* 11.8, 5.3 Hz), 3.78 (1H, dd, *J* 11.8, 3.1 Hz), 3.87–3.93 (1H, m, C*H*OBn), 4.18–4.28 (1H, m, $CHCF_2$), 4.58, 4.79 (2H, AB, *J* 11.5 Hz, CH_2Ph), 4.74, 4.81 (2H, AB, *J* 10.7 Hz, CH_2Ph), 7.27–7.40 (10H, m, 2 × C_6H_5). **9a**: $[\alpha]_D^{19}$ −1.59; δ_F(56.4 MHz, $CDCl_3$) −8.6 (2F, s, CF_2Cl), 41.4, 43.0, 43.3, 43.8 (6F, m, 3 × CF_2); MS (EI) *m*/*z* 505, 507 ($M^+ - 1$), 415, 417 ($M^+ - Bn$) (Calc. for $C_{21}H_{19}ClF_8O_3$: C, 49.77; H, 3.78; F, 29.99; Cl, 7.00. Found: C, 49.74; H, 3.78; F, 29.79; Cl, 6.98%). **9b**: $[\alpha]_D^{21}$ −1.51; δ_F(56.4 MHz, $CDCl_3$) −8.1 (2F, s, CF_2Cl), 41.4, 43.6, 44.7 (10F, m, 5 × CF_2); MS (EI) *m*/*z* 605, 607 ($M^+ - 1$), 515, 517 ($M^+ - Bn$), 91 (Bn) (Calc. for $C_{23}H_{19}ClF_{12}O_3$: C, 45.52; H, 3.16; F, 37.57; Cl, 5.84. Found: C, 45.99; H, 3.24; F, 37.53; Cl, 5.66%). **9c**: $[\alpha]_D^{26}$ −1.47; δ_F(56.4 MHz, $CDCl_3$) 3.5 (3F, s, CF_3), 40.6, 42.3 (2F, AB, CF_2CH), 44.4, 48.7 (12F, m, 6 × CF_2); MS (EI) *m*/*z* 690 (M^+), 91 (Bn) (Calc. for $C_{25}H_{19}F_{17}O_3$: C, 43.49; H, 2.77; F, 46.78. Found: C, 43.89; H, 2.81; F, 47.15%).

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