First Total Synthesis of a Fluorinated Calystegin

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A straightforward chiral pool synthesis for the first fluorinated calystegin is described. Key steps of this synthesis include an ultrasound-assisted Zn-mediated tandem ring opening reaction followed by a Grubbs' catalyst-mediated ring closure metathesis reaction. The target compound is a selective and competitive inhibitor for a β-glycosidase.

Key words: Calystegin, Ring Closure Metathesis, Glucosidase Inhibitor

Introduction

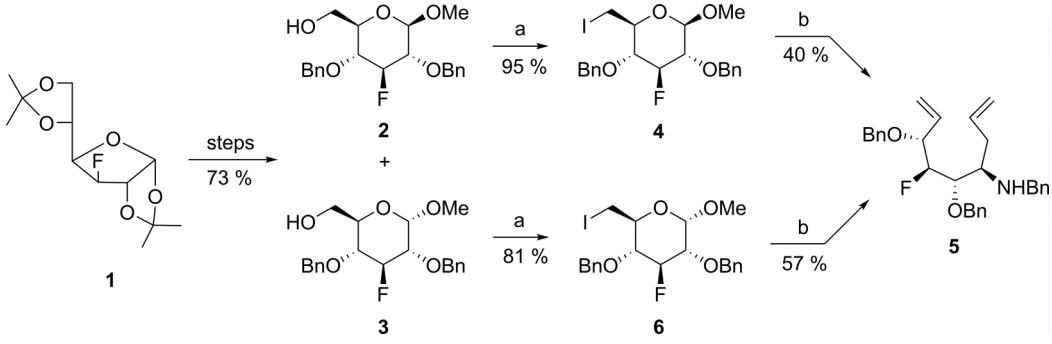
Calystegins [1] are bicyclic alkaloids that hold structural features derived from the nortropane skeleton; they are poly-hydroxylated and represent a group of plant secondary metabolites with structural closeness to sugars. Like iminosugars they display strong and/or specific competitive inhibitory activity [2 – 4], and they have been suggested as chemotherapeutic drugs to treat viral diseases [5, 6] and metabolic disorders [7, 8] (*e. g.* diabetes); quite recently, they have been suggested [9] as pharmacoperones for the treatment of protein folding disorders.

Naturally occurring calystegins have been obtained from their natural sources [1] by more or less tedious extraction processes; only a few of them have become available by total synthesis [10 – 22]. No functional derivatives of calystegins have been prepared so far.

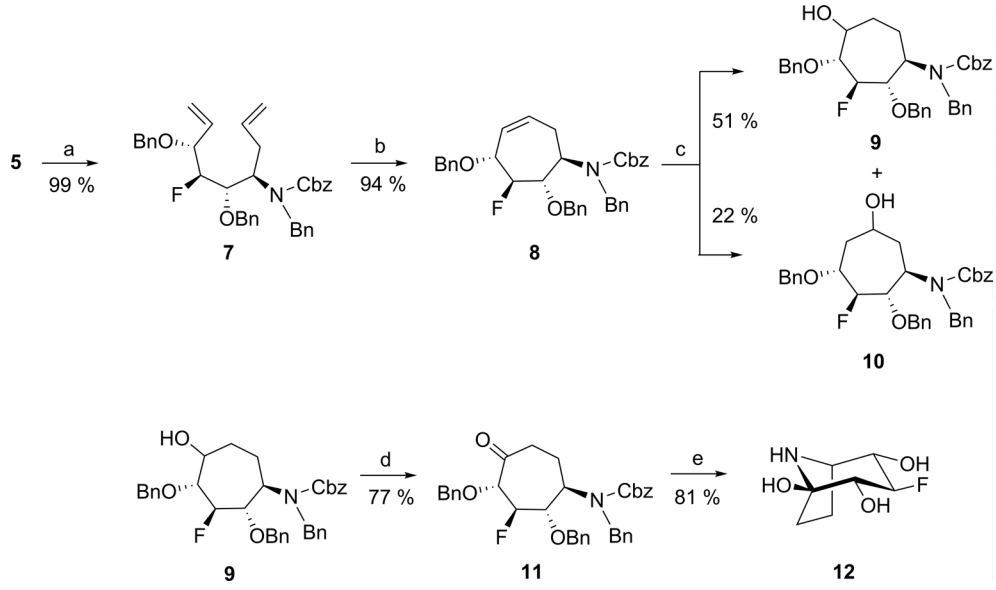
Previously, the incorporation of a fluorine substituent has been shown [23] to be of advantage both for an improved activity, higher bioavailability and a retarded metabolism of several drugs. Therefore, we became interested in the synthesis of a fluorinated calystegin analog. Thus, we report the first total synthesis of fluorinated calystegin.

Results and Discussion

The synthesis of our target molecule, 3-deoxy-3-fluoro-calystegin B_2, was planned as a chiral pool approach starting from the well-known [24, 25] 3-deoxy-3-fluoro-α-D-*gluco*-furanose **1** (Scheme 1) that was easily transformed [26] into the corresponding pyranosidic glycosides **2** and **3**. Treatment of **2** with triphenylphosphane/imidazole/iodine [27] followed by an ultrasound-assisted tandem reaction [28] of **4** gave the diene **5**. In a similar way, from **3** the iodo-compound **6** was obtained that gave **5** in the tandem reaction.



Scheme 1. a) PPh_3, imidazole, I_2, 95 °C; b) Zn^*, THF, ultrasound, then $BnNH_2$, allylbromide.



Scheme 2. a) CbzCl, $NaHCO_3$, 25 °C; b) Grubbs' catalyst, 25 °C; c) BH_3·THF, H_2O_2/NaOH; d) PCC, 25 °C; e) Pd/C, H_2.

Compound **5** was carbobenzoxylated (Scheme 2) in almost quantitative yield to afford **7** which was allowed to react in a Grubbs' (2nd generation) catalyst-mediated ring closure metathesis [28] to afford 94 % of the cycloheptene **8**. Hydroboration [29] of this cycloheptene using BH_3·THF followed by oxidative work-up with sodium hydroxide/hydrogen peroxide provided the cycloheptanols **9** and **10**. PCC-oxidation of **9** gave 77 % of the cycloheptanone **11** which was finally hydrogenated in the presence of Pd/C to yield the 3-fluoro-calystegine B_2 analog **12**.

The inhibitory activity of this fluorodeoxy-calystegin against several β-glycosidases was investigated using a 4-nitrophenyl-D-glucopyranoside assay [30]. In analogy to naturally occurring calystegin B_2, its 3-fluoro analog **12** shows no inhibition against the α-glycosidase from yeast but is a competitive inhibitor of the β-glucosidase from almonds showing a K_i = 82 μM. Its inhibitory activity is lower compared with calystegin B_2 (K_i = 5.9 μM), proving that a hydroxyl group at position C-3 is necessary for a tight binding of the calystegin-based inhibitor into the active site of the β-glycosidases.

Experimental Section

General methods

Melting points are uncorrected (Leica hot stage microscope). Optical rotations were obtained using a Perkin-Elmer 341 polarimeter (1 cm micro cell). NMR spectra were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, J in Hz, internal Me_4Si or internal CCl_3F), IR spectra (film or KBr pellet) on a Perkin-Elmer FT-IR spectrometer Spectrum 1000. Mass spectra were taken on an Intectra GmbH AMD 402 (electron impact, 70eV) or on a Thermo Electron Finnigan LCQ (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument. For elemental analysis a Foss-Heraeus Vario EL instrument was used. TLC was performed on silica gel (Merck 5554, detection by UV absorption or by treatment with a solution of 10 % sulfuric acid, ammonium molybdate and cerium(IV) sulfate) followed by gentle heating. The solvents were dried according to usual procedures.

*Hydrolysis of **1***

A suspension of **1** (3.86 g, 14.7 mmol) in water (25 mL) and concentrated H_2SO_4 (2.0 mL) was stirred for 24 h at 25 °C. After addition of sodium bicarbonate (6.06 g), the solvent was evaporated under reduced pressure, and the remaining solid was suspended in abs. methanol. The slurry was filtered, and the filtrate was concentrated. The resulting mixture of α- and β-pyranoses (colorless solid) was dissolved in abs. methanol and cooled to 0 °C. Methanolic HCl was added dropwise, and the mixture was stirred under reflux for 8 h; the solvent was evaporated, the crude product was dried over potassium hydroxide (desiccator), and then it was dissolved in pyridine (50 mL). Trityl chloride (6.00 g, 21.5 mmol) and DMAP (0.40 g, 3.3 mmol) were added, and the resulting solution was stirred at 25 °C for 16 h. The sol-

vent was evaporated, ether (100 mL) was added, and the organic phase was extracted with water. The aqueous phase was washed with ether (3 × 100 mL), and the combined organic phases were evaporated. The remaining residue was subjected to chromatography (silica gel, *n*-hexane-ethyl acetate = 50:50) to afford an epimeric mixture of the corresponding methyl glycosides (1.4 g). To a solution of this mixture (1.40 g, 3.2 mmol) in dry DMF (50 mL), sodium hydride (55 % in mineral oil, 700 mg, 16.00 mmol) was slowly added, and stirring at 0 °C was continued for 15 min, followed by stirring at 25 °C for 15 min. Then benzyl bromide (2.27 mL, 19.00 mmol) was added and stirring continued at 25 °C for another 3 h. Methanol (30 mL) was carefully added, and the solvents were removed under reduced pressure. The oily residue was dissolved in diethyl ether (150 mL) and washed with water (100 mL). The aqueous phase was extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$), and the solvents were evaporated. The remaining solid was dissolved in methanol (70 mL) and dichloromethane (60 mL), catalytic amounts of *p*-TsOH were added, and the mixture was stirred at 25 °C for 1 d. After neutralization (conc. aqueous ammonium hydroxide), the solvents were removed *in vacuo*. The residue was dissolved in ether (150 mL) and washed with water and brine (100 mL each). After drying ($MgSO_4$), the solvent was removed and the residue subjected to chromatography (silica gel, *n*-hexane-ethyl acetate 5:3) to afford **2** and **3** as colorless oils.

*Methyl 2,4-di-O-benzyl-3-deoxy-3-fluoro-β-D-glucopyranoside (**2**)*

Colorless oil. Yield 2.44 g (44.1 %). – $[\alpha]_D$ = +21.96° (*c* = 0.38, $CHCl_3$). – R_f = 0.14 (*n*-hexane-ethyl acetate 5:3). – IR (film): ν = 3473m, 3089w, 3064w, 3032m, 2932m, 2877m, 1606w, 1497m, 1454s, 1391m, 1309w, 1214m, 1074s, 1027s, 893w, 738s, 698s cm^{-1}. – ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.39 – 7.27 (m, 10 H, Ph), 4.86 (d, 1 H, $^2J_{H,H}$ = 11.2 Hz, CH_2OBn), 4.84 (d, 1 H, $^2J_{H,H}$ = 11.6 Hz, CH_2OBn), 4.74 (d, 1 H, $^2J_{H,H}$ = 11.6 Hz, CH_2OBn), 4.66 (ddd, 1 H, $^2J_{3,F}$ = 51.9, $^3J_{3,2}$ = 8.7, $^3J_{3,4}$ = 8.7 Hz, H-3), 4.62 (d, 1 H, $^2J_{H,H}$ = 11.2, CH_2OBn), 4.31 (d, 1 H, $^3J_{1,2}$ = 7.8 Hz, H-1), 3.88 (d, 1 H, $^2J_{6,6}$ = 11.9 Hz, H-6), 3.74 (dd, 1 H, $^2J_{6',6}$ = 11.9, 10.6, $^3J_{6',5}$ = 4.1 Hz, H-6′), 3.67 (ddd, 1 H, $^3J_{4,3}$ = 8.7, $^3J_{4,5}$ = 9.6, $^3J_{4,F}$ = 13.3 Hz, H-4), 3.55 (s, 3 H, CH_3), 3.42 (ddd, 1 H, $^3J_{2,1}$ = 7.8, $^3J_{2,3}$ = 8.7, $^3J_{2,F}$ = 13.7 Hz, H-2), 3.13 – 3.04 (m, 1 H, H-5). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.0 (C_{ar}), 137.6 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 128.1 (C_{ar}), 128.0 (C_{ar}), 127.9 (C_{ar}), 127.7 (C_{ar}), 127.5 (C_{ar}), 103.7 (d, $^3J_{C,F}$ = 12.3 Hz, C1), 97.8 (d, $^1J_{C,F}$ = 184.5 Hz, C3), 79.7 (d, $^2J_{C,F}$ = 18.0 Hz, C2), 75.6 (d, $^2J_{C,F}$ = 17.3 Hz, C4), 74.4 (*C*H_2OBn), 74.4 (d, $^4J_{C,F}$ = 3.1 Hz, *C*H_2OBn), 73.6 (d, $^3J_{C,F}$ = 9.2 Hz, C5), 61.7 (C6), 57.4 (*C*H_3). – ^{19}F-NMR (188 MHz, $CDCl_3$): δ = −188.94 (ddd, 1 F, $^3J_{F,4}$ = 13.3, $^3J_{F,2}$ = 13.7, $^2J_{F,3}$ = 51.9 Hz, F). – MS (ESI–MeOH+$LiClO_4$): *m/z* (%) = 383.7 (100) $[M+Li]^+$, 759.1 (70) $[M_2+Li]^+$. – $C_{21}H_{25}FO_5$ (376.42): calcd. C 67.01, H 6.69; found C 66.82, H 6.81.

*Methyl 2,4-di-O-benzyl-3-deoxy-3-fluoro-α-D-glucopyranoside (**3**)*

Colorless oil. Yield 1.61 g (29.1 %). – $[\alpha]_D$ = +58.89° (*c* = 0.25, $CHCl_3$) (lit.: $[\alpha]_D$ = +66.2° [13]). – R_f = 0.38 (*n*-hexane-ethyl acetate 5:3). – IR (film): ν = 3475m, 3064m, 2919m, 1692w, 1572w, 1497m, 1454m, 1369m, 1327w, 1195m, 1074s, 1027s, 905m, 738s, 698s, 606m cm^{-1}. – ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.38 – 7.16 (m, 10 H, Ph), 4.98 (ddd, 1 H, $^2J_{3,F}$ = 53.9, $^3J_{3,2}$ = 8.2, $^3J_{3,4}$ = 9.2 Hz, H-3), 4.88 (d, 1 H, $^2J_{H,H}$ = 11.1 Hz, CH_2OBn), 4.83 (d, 1 H, $^2J_{H,H}$ = 12.3 Hz, CH_2OBn), 4.65 (d, 1 H, $^2J_{H,H}$ = 12.3 Hz, CH_2OBn), 4.62 (d, 1 H, $^2J_{H,H}$ = 11.1 Hz, CH_2OBn), 4.62 (d, 1 H, $^3J_{1,2}$ = 3.8 Hz, H-1), 3.77 (d, 1 H, $^2J_{6,6'}$ = 11.7 Hz, H-6), 3.70 (d, 1 H, $^2J_{6',6}$ = 11.7 Hz, H-6′), 3.65 – 3.60 (m, 2 H, H-4, H-5), 3.54 (ddd, 1 H, $^3J_{2,1}$ = 3.8, $^3J_{2,3}$ = 8.2, $^3J_{2,F}$ = 13.0 Hz, H-2), 3.33 (*s*, 3 H, CH_3). – ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 137.81 (C_{ar}), 131.77 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 128.10 (C_{ar}), 128.0 (C_{ar}), 127.9 (C_{ar}), 98.5 (d, $^3J_{C,F}$ = 10.0 Hz, C1), 96.3 (d, $^1J_{C,F}$ = 182.4 Hz, C3), 77.1 (C2), 75.7 (d, $^2J_{C,F}$ = 16.8 Hz, C4), 74.3 (d, $^4J_{C,F}$ = 3.2 Hz, *C*H_2OBn), 73.3 (d, $^4J_{C,F}$ = 1.6 Hz, *C*H_2OBn), 69.8 (d, $^3J_{C,F}$ = 8.4 Hz, C5), 61.7 (C6), 55.3 (*C*H_3). – ^{19}F-NMR (188 MHz, $CDCl_3$): δ = −192.66 (ddd, 1 F, $^3J_{F,4}$ = 9.3, $^3J_{F,2}$ = 13.0, $^2J_{F,3}$ = 53.9 Hz, F). – MS (ESI–MeOH+$LiClO_4$): *m/z* (%) = 383.7 (100) $[M+Li]^+$. – $C_{21}H_{25}FO_5$ (376.42): calcd. C 67.01, H 6.69; found C 66.87, H 6.73.

*Methyl 2,4-di-O-benzyl-3,6-dideoxy-3-fluoro-6-iodo-β-D-glucopyranoside (**4**)*

To a solution of **4** (1.37 g, 3.72 mmol) in abs. toluene (50 mL) containing triphenylphosphane (2.14 g, 8.32 mmol) and imidazole (1.14 g, 16.75 mmol), iodine (1.89 g, 7.45 mmol) was added in several portions. After stirring at 95 °C for 2 h, the reaction mixture was decanted and the remaining oil washed with ether (3 × 100 mL). The combined organic phases were evaporated, and the remaining residue was subjected to chromatography (silica gel, *n*-hexane-ethyl acetate 85:15) to afford **4** (1.72 g, 95.0 %) as a colorless solid. M. p. 56 – 58 °C. – $[\alpha]_D$ = +29.50° (*c* = 0.49, $CHCl_3$). – R_f = 0.51 (*n*-hexane-ethyl acetate = 85:15). – IR (film): ν = 3441m, 3088w, 3064w, 3032w, 2941w, 2920m, 2880w, 1630w, 1497w, 1454m, 1403w, 1391w, 1370w, 1319w, 1266w, 1246w, 1213w, 1200m, 1173m, 1117s, 1081s, 1040m, 1028m, 1012m, 992m, 912w, 816w, 755m, 736m, 699s, 660w. cm^{-1} – ^{1}H-NMR (500 MHz,

$CDCl_3$): δ = 7.38 – 7.26 (m, 10 H, Ph), 4.89 (d, 1 H, $^2J_{H,H}$ = 10.8 Hz, CH_2OBn), 4.85 (d, 1 H, $^2J_{H,H}$ = 11.6 Hz, CH_2OBn), 4.74 (d, 1 H, $^2J_{H,H}$ = 11.6 Hz, CH_2OBn), 4.66 (ddd, 1 H, $^2J_{3,F}$ = 51.5, *J* = 7.5, *J* = 8.7 Hz, H-3), 4.63 (d, 1 H, $^2J_{H,H}$ = 10.8 Hz, CH_2OBn), 4.32 (d, 1 H, $^3J_{1,2}$ = 7.5 Hz, H-1), 3.58 (*s*, 3 H, CH_3), 3.52 (d, 1 H, $^2J_{6,6'}$ = 10.8, $^3J_{6,5}$ = 2.1 Hz, H-6), 3.48 – 3.44 (m, 2 H, H-2, H-4), 3.27 (dd, 1 H, $^2J_{6',6}$ = 10.8, $^3J_{6',5}$ = 7.1 Hz, H-6′), 3.12 (m, 1 H, H-5). – ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 138.0 (C_{ar}), 137.4 (C_{ar}), 128.6 (C_{ar}), 128.3 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 128.0 (C_{ar}), 127.8 (C_{ar}), 103.3 (d, $^3J_{C,F}$ = 12.5 Hz, C1), 97.5 (d, $^1J_{C,F}$ = 185.2 Hz, C3), 79.8 – 79.4 (2 × *d*, $^2J_{C,F}$ = 17.8 Hz, C2, $^2J_{C,F}$ = 17.3 Hz, C4), 74.6 (d, $^4J_{C,F}$ = 3.4 Hz, *C*H_2OBn), 74.4 (*C*H_2OBn), 72.3 (d, $^3J_{C,F}$ = 10.6 Hz, C5), 57.3 (*C*H_3), 5.8 (C6). – ^{19}F-NMR (188 MHz, $CDCl_3$): δ = −188.93 (ddd, 1 F, $^3J_{F,4}$ = 13.7, $^3J_{F,2}$ = 13.7, $^2J_{F,3}$ = 51.5 Hz, F). – MS (ESI–MeOH+$LiClO_4$): *m/z* (%) = 493.6 (40) $[M+Li]^+$. – $C_{21}H_{24}FIO_4$ (486.32): calcd. C 51.86, H 4.97; found C 51.71, H 5.10.

*(3R, 4S, 5S, 6R) 6-[(N-Benzyl)amino]-3,5-bis(benzyloxy)-4-fluoro-1,8-nonadiene (**5**)*

From **4**: According to the above procedure using **4** (1.51 g, 3.11 mmol), activated Zn powder (2.03 g, 31.1 mmol), benzylamine (1.70 mL, 15.60 mmol), and allylbromide (0.81 mL, 9.33 mmol), product **5** (819 mg, 57.0 %) was obtained as a colorless oil.

From **6**: To a solution of **6** (920 mg, 1.89 mmol) in dry THF (50 mL), activated Zn powder (1.23 g, 18.90 mmol) was added and the mixture put in an ultrasound cleaning bath for 20 min. At a temperature of 40 °C benzylamine (1.03 mL, 9.46 mmol) was slowly added, and the treatment with ultrasound was continued for another 8 h. Allylbromide (0.49 mL, 5.68 mmol) was added, and ultrasound was applied for another 4 h. The mixture was cooled to 25 °C and filtered over a small layer of silica gel (5 cm). The filtrate was diluted with ethyl acetate (5 × 100 mL) and dried, and the solvents were evaporated. The residue was subjected to chromatography (silica gel, *n*-hexane-ethyl acetate = 85:15) to afford **5** (350 mg, 40.3 %) as a colorless oil. $[\alpha]_D$ = −33.34° (*c* = 0.59, $CHCl_3$). - R_f = 0.55 (*n*-hexane-ethyl acetate = 85:15). – IR (film): ν = 3064w, 3029m, 2964m, 1638w, 1496w, 1454m, 1262s, 1208w, 1089s, 1028s, 914m, 873m, 805s, 735m, 699s cm^{-1}. – ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.41 – 7.24 (m, 15 H, Ph), 5.94 (ddd, 1 H, $^3J_{2,3}$ = 8.1, $^3J_{2,1}$ = 10.4, $^3J_{2,1'}$ = 17.2 Hz, H-2), 5.67 (m, 1 H, H-8), 5.39 (dd, 1 H, $^3J_{1,2}$ = 10.4, $^2J_{1,1'}$ = 1.3 Hz, H-1), 5.26 (d, 1 H, $^3J_{1',2}$ = 17.2 Hz, H-1′), 5.08 (d, 1 H, $^3J_{9,8}$ = 17.1 Hz, H-9), 5.06 (dd, 1 H, $^3J_{9',8}$ = 9.1, $^2J_{9',9}$ = 1.3 Hz, H-9′), 4.92 (ddd, 1 H, $^2J_{4,F}$ = 47.9, $^3J_{4,3}$ = 2.7, $^3J_{4,5}$ = 6.9 Hz, H-4), 4.85 (d, 1 H, $^2J_{H,H}$ = 11.4 Hz, CH_2OBn), 4.56 (d, 1 H, $^2J_{H,H}$ = 11.4 Hz, CH_2OBn), 4.51 (d, 1 H, $^2J_{H,H}$ = 11.8 Hz, CH_2OBn), 4.03 (d, 1 H, $^2J_{H,H}$ = 11.8 Hz, CH_2OBn), 3.90 (ddd, 1 H, $^3J_{5,6}$ = 2.3, $^3J_{5,4}$ = 6.9, $^3J_{5,F}$ = 16.2 Hz, H-5), 3.83 (d, 1 H, $^2J_{H,H}$ = 13.1 Hz, CH_2(NHBn)), 3.76 (ddd, 1 H, $^3J_{3,4}$ = 2.7, $^3J_{3,2}$ = 8.1, $^3J_{3,F}$ = 29.7 Hz, H-3), 3.44 (d, 1 H, $^2J_{H,H}$ = 13.1 Hz, CH_2(NHBn)), 2.54 (m, 1 H, H-7), 2.49 (m, 1 H, H-6), 2.34 (m, 1 H, H-7′), 1.50 (*bs*, 1 H, N*H*Bn). – ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 140.6 (C_{ar}), 138.9 (C_{ar}), 137.7 (C_{ar}), 135.8 (C8), 134.5 (d, $^3J_{C,F}$ = 7.1, C2), 128.5 (C_{ar}), 128.3 (C_{ar}), 128.203 (C_{ar}), 128.195 (C_{ar}), 128.2 (C_{ar}), 127.8 (C_{ar}), 127.6 (C_{ar}), 127.4 (C_{ar}), 126.9 (C_{ar}), 119.4 (C1), 117.1 (C9), 98.2 (d, $^1J_{C,F}$ = 177.4 Hz, C4), 79.2 (d, $^2J_{C,F}$ = 18.2 Hz, C5), 78.4 (d, $^2J_{C,F}$ = 18.2 Hz, C3), 74.0 (d, $^4J_{C,F}$ = 4.1 Hz, *C*H_2OBn), 70.2 (*C*H_2OBn), 56.1 (d, $^3J_{C,F}$ = 7.9 Hz, C6), 50.6 (*C*H_2(NHBn)), 34.6 (C7). – ^{19}F-NMR (188 MHz, $CDCl_3$): δ = −206.61 (ddd, 1 F, $^3J_{F,5}$ = 16.2, $^3J_{F,3}$ = 29.7, $^2J_{F,4}$ = 47.9 Hz, F). – MS (ESI–MeOH): *m/z* (%) = 460.6 (100) $[M+H]^+$. – $C_{30}H_{34}FNO_2$ (459.26): calcd. C 78.40, H 7.46, N 3.05; found C 78.27, H 7.53, N 3.07.

*Methyl 2,4-di-O-benzyl-3,6-dideoxy-3-fluoro-6-iodo-a-D-glucopyranoside (**6**)*

To a solution of **3** (950 mg, 2.52 mmol) in abs. toluene (50 mL) containing triphenylphosphane (1.44 g, 5.55 mmol) and imidazole (1.27 g, 18.66 mmol), iodine (1.27 g, 5.01 mmol) was added in several portions. After stirring at 95 °C for 2 h the reaction mixture was decanted, and the remaining oil washed with ether (3 × 100 mL). The combined organic phases were evaporated, and the remaining residue was subjected to chromatography (silica gel, *n*-hexane-ethyl acetate 85:15) to afford **6** (995 mg, 81.0 %) as a colorless solid. M. p. 69 – 71 °C. – $[\alpha]_D$ = +61.46° (*c* = 0.48, $CHCl_3$). – R_f = 0.41 (*n*-hexane-ethyl acetate = 85:15). – IR (film): ν = 3442m, 3089w, 3066w, 3031w, 2991w, 2914m, 2833w, 1629w, 1497w, 1454m, 1410w, 1372m, 1329w, 1274w, 1198m, 1153m, 1133s, 1103s, 1065s, 1030s, 993s, 944m, 910w, 892w, 745s, 697s, 635w cm^{-1}. – ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.36 – 7.29 (m, 10 H, Ph), 5.02 (ddd, 1 H, $^2J_{3,F}$ = 55.0, $^3J_{3,4}$ = 8.3, $^3J_{3,2}$ = 8.7 Hz, H-3), 4.91 (d, 1 H, $^2J_{H,H}$ = 10.8 Hz, CH_2OBn), 4.83 (d, 1 H, $^2J_{H,H}$ = 12.4 Hz, CH_2OBn), 4.65 (d, 1 H, $^2J_{H,H}$ = 12.4 Hz, CH_2OBn), 4.65 (d, 1 H, $^2J_{H,H}$ = 10.8 Hz, CH_2OBn), 4.65 (d, 1 H, $^3J_{1,2}$ = 3.6 Hz, H-1), 3.56 (ddd, 1 H, $^3J_{2,1}$ = 3.6, $^3J_{2,3}$ = 8.7, $^3J_{2,F}$ = 12.9 Hz, H-2), 3.48 (d, 1 H, $^2J_{6,6'}$ = 10.5 Hz, H-6), 3.49 – 3.41 (m, 2 H, H-4, H-5), 3.37 (*s*, 3 H, CH_3), 3.29 (dd, 1 H, $^2J_{6',6}$ = 10.5, $^3J_{6',5}$ = 3.3 Hz, H-6′). – ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 137.7 (C_{ar}), 137.5 (C_{ar}), 128.41 (C_{ar}), 128.37 (C_{ar}), 128.2 (C_{ar}), 128.1 (C_{ar}), 127.94 (C_{ar}), 127.89 (C_{ar}), 127.87 (C_{ar}), 98.3 (d, $^3J_{C,F}$ = 11.1 Hz, C1), 95.8 (d, $^1J_{C,F}$ = 182.6 Hz, C3), 79.9 (d, $^2J_{C,F}$ = 16.9 Hz, C2), 77.1 (d, $^2J_{C,F}$ = 16.1 Hz, C4), 74.6 (d, $^4J_{C,F}$ = 3.5 Hz, *C*H_2OBn), 73.3 (d, $^4J_{C,F}$ = 1.9 Hz, *C*H_2OBn), 68.2 (d, $^3J_{C,F}$ = 8.8 Hz, C5), 55.6 (*C*H_3), 7.2 (C6). – ^{19}F-NMR (188 MHz, $CDCl_3$): δ =

−192.50 (ddd, 1 F, $^3J_{F,4}$ = 10.7, $^3J_{F,2}$ = 12.9, $^2J_{F,3}$ = 55.0 Hz, F). – MS (ESI–MeOH+$LiClO_4$): *m/z* (%) = 493.7 (100) $[M+Li]^+$. – $C_{21}H_{24}FIO_4$ (486.32): calcd. C 51.86, H 4.97; found C 51.63, H 5.17.

*(3R, 4S, 5S, 6R)-6-[(N-Benzyl-N-(benzyloxycarbonyl))-amino]-3,5-bis(benzyloxy)-4-fluoro-1,8-nonadiene (**7**)*

To a solution of **5** (1.10 g, 2.40 mmol) in dichloromethane (50 mL) water (10 mL) containing sodium bicarbonate (1.20 g, 17.60 mmol), benzyl chloroformate (1.00 mL, 7.09 mmol) was added dropwise, and stirring at 25 °C was continued for 14 h. The layers were separated, the organic layer was washed with water (100 mL), and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvents evaporated under reduced presure. The remaining residue was subjected to chromatography (silica gel, *n*-hexane-ethyl acetate = 85:15) to afford **7** (1.35 g, 99.6 %) as a colorless oil. $[\alpha]_D$ = −1.51° (*c* = 0.52, $CHCl_3$). – R_f = 0.60 (*n*-hexane-ethyl acetate = 85:15). – IR (film): ν = 3065w, 3032m, 2942w, 1747w, 1694s, 1642w, 1606w, 1497m, 1455s, 1415m, 1370w, 1327m, 1250s, 1102s, 1028m, 995m, 920w, 771m, 735s, 698s, 597w, 458w cm^{-1}. – ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.37 – 7.17 (m, 20 H, Ph), 5.79 (m, 1 H, H-2), 5.42 (m, 1 H, H-8), 5.29 (d, 1 H, $^3J_{H,H}$ = 10.2 Hz, H-1), 5.23 – 5.07 (m, 3 H, H-1′, CH_2OBn, CH_2OBn, CH_2CBz), 4.87 (m, 2 H, H-9, H-9′), 4.70 (m, 2 H, CH_2OBn, CH_2OBn), 4.59 (m, 1 H, CH_2OBn), 4.45 (m, 2 H, CH_2OBn, CH_2NBn), 4.43 – 4.07 (m, 5 H, H-3, H-4, H-5, H-6, CH_2NBn), 2.38 (m, 1 H, H-7), 2.28 (m, 1 H, H-7′). – ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 157.0 (*C*=O, CBz), 138.4 (C_{ar}), 138.1 (C_{ar}), 137.4 (C_{ar}), 136.30 (C_{ar}), 134.5 (C8), 133.9 (C2), 128.6 (C_{ar}), 128.5 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 128.2 (C_{ar}), 128.0 (C_{ar}), 127.9 (C_{ar}), 127.6 (C_{ar}), 127.53 (C_{ar}), 127.46 (C_{ar}), 126.8 (C_{ar}), 119.8 (C1), 117.5 (C9), 79.3 (d, $^2J_{C,F}$ = 18.1 Hz, C3 or C5), 79.0 (d, $^2J_{C,F}$ = 18.1 Hz, C3 or C5), 75.2 (*C*H_2OBn), 70.9 (*C*H_2OBn), 67.4 (*C*H_2CBz), 56.8 (C6), 46.2 (*C*H_2NBn), 34.9 (C7). – ^{19}F-NMR (188 MHz, $CDCl_3$): δ = −207.37 (m, 1 F, F). – MS (ESI–MeOH+$LiClO_4$): *m/z* (%) = 601.0 (100) $[M+Li]^+$, 1193.1 (5) $[M_2+Li]^+$. – $C_{38}H_{40}FNO_4$ (593.73): calcd. C 76.87, H 6.79, N 2.36; found C 76.69, H 6.92, N 2.41.

*(3R, 4S, 5S, 6R)-6-[(N-Benzyl)amino]-3,5-bis(benzyloxy)-4-fluoro-cycloheptene (**8**)*

To a solution of **7** (1.02 g, 1.72 mmol) in dry dichloromethane (50 mL) under argon Grubbs' catalyst (second generation, 20 mg) was added, and stirring at 25 °C was continued for 30 h. The mixture was filtered through a short pad of silica gel (5 cm), the filtrate was evaporated, and the remaining residue was subjected to chromatography (silica gel, *n*-hexane-ethyl acetate = 80:20) to afford **8** (910 mg, 94.0 %) as a colorless oil. $[\alpha]_D$ = −2.40° (*c* = 0.61, $CHCl_3$). – R_f = 0.38 (*n*-hexane-ethyl acetate = 85:15). – IR (film): ν = 3088w, 3064w, 3032m, 2937w, 2869w, 1953w, 1698s, 1606w, 1586w, 1496m, 1455s, 1357m, 1315m, 1230s, 1121s, 1073s, 1028m, 1000m, 942w, 914w, 821w, 736s, 698s cm^{-1}. – ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.39 – 7.16 (m, 20 H, Ph), 5.66 (m, 2 H, H-1, H-2), 5.20 (d, 1 H, $^2J_{H,H}$ = 12.2 Hz, CH_2CBz), 5.10 (d, 1 H, $^2J_{H,H}$ = 12.2 Hz, CH_2CBz), 4.90 (d, 1 H, $^2J_{H,H}$ = 15.6 Hz, CH_2NBn), 4.85 (d, 1 H, $^2J_{H,H}$ = 10.6 Hz, CH_2OBn), 4.73 (d, 1 H, $^2J_{H,H}$ = 11.7 Hz, CH_2OBn), 4.66 (d, 1 H, $^2J_{H,H}$ = 11.7 Hz, CH_2OBn), 4.49 – 4.28 (m, 4 H, H-3, H-4, H-5, CH_2OBn), 4.02 (d, 1 H, $^2J_{H,H}$ = 15.6 Hz, CH_2NBn), 3.08 (m, 1 H, H-6), 2.84 (m, 1 H, H-7), 1.92 (m, 1 H, H-7′). – ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 155.2 (*C*=O CBz), 138.3 (C_{ar}), 138.0 (C_{ar}), 137.7 (C_{ar}), 136.6 (C_{ar}), 131.4 (C1), 129.1 (C2), 128.4 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 128.1 (C_{ar}), 128.1 (C_{ar}), 127.8 (C_{ar}), 127.5 (C_{ar}), 127.3 (C_{ar}), 96.5 (d, $^1J_{C,F}$ = 184.1 Hz, C4), 82.7 (d, $^2J_{C,F}$ = 18.5 Hz, C5), 75.8 (*C*H_2OBn), 75.6 (d, $^2J_{C,F}$ = 17.5 Hz, C3), 72.7 (*C*H_2OBn), 67.0 (*C*H_2CBz), 61.0 (d, $^3J_{C,F}$ = 9.1 Hz, C6), 54.1 (*C*H_2NBn), 29.7 (C7). – ^{19}F-NMR (188 MHz, $CDCl_3$): δ = −181.68 (m, 1 F, F). – MS (ESI–MeOH+$LiClO_4$): *m/z* (%) = 572.5 (100) $[M+Li]^+$. – $C_{36}H_{36}FNO_4$ (565.67): calcd. C 76.44, H 6.41, N 2.48; found C 76.31, H 6.57, N 2.54.

*Hydroboration of **8***

To a stirred solution of **8** (910 mg, 1.57 mmol) in anhydrous THF (60 mL) at −78 °C under argon BH_3·THF (5.0 mL of a 1 M solution in THF, 5.0 mmol) was added dropwise. The mixture was stirred for 12 h, during which time it warmed to 25 °C. 2 N aqueous NaOH (7.5 mL) and 30 % aqueous H_2O_2 (1.5 mL) were added. After stirring for 5 h at 25 °C the phases were separated, the aqueous phase was extracted with ether (3 × 50 mL), the combined organic phases were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was subjected to chromatography (silica gel, *n*-hexane-ethyl acetate = 5:3) to afford **9** (472 mg, 51.5 %) and **10** (200 mg, 21.8 %).

*(1RS, 2R, 3R, 4S, 5R) 5-[(N-Benzyl-N-(benzyloxycarbonyl))-amino]-2,4-bis(benzyloxy)-3-fluoro-cycloheptanol (**9**)*

Colorless oil. – $[\alpha]_D$ = −12.54° (*c* = 0.80, $CHCl_3$). – R_f = 0.46 (*n*-hexane-ethyl acetate = 5:3). – IR (film): ν = 3455m, 3064w, 3031m, 2933m, 1694s, 1606w, 1496m, 1455s, 1360m, 1309m, 1235s, 1113s, 1028m, 1004m, 913w, 736s, 698s cm^{-1}. – ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.37 – 7.18 (m, 20 H, Ph), 5.08 (m, 2 H, CH_2CBz, CH_2CBz), 4.88 (d, 1 H, $^2J_{H,H}$ = 11.4 Hz, CH_2OBn), 4.80 (d, 1 H, $^2J_{H,H}$ = 10.9 Hz, CH_2OBn), 4.75 (d, 1 H, $^2J_{H,H}$ = 15.8 Hz, CH_2NBn), 4.66 (m, 1 H, H-3), 4.52 (d, $^2J_{H,H}$ = 10.9 Hz,

CH_2OBn), 4.43 (d, $^2J_{H,H}$ = 10.9 Hz, CH_2OBn), 4.33 (m, 1 H, H-2), 3.99 (d, 1 H, $^2J_{H,H}$ = 15.8 Hz, CH_2NBn), 3.53 (m, 2 H, H-1, H-4), 3.13 (m, 1 H, H-5), 1.59 – 1.25 (m, 4 H, H-6, H-6′, H-7, H-7′). – ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 155.4 (*C*=O, CBz), 138.3 (C_{ar}), 137.9 (C_{ar}), 137.8 (C_{ar}), 136.4 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 127.9 (C_{ar}), 127.5 (C_{ar}), 127.2 (C_{ar}), 98.7 (d, $^1J_{C,F}$ = 176.1 Hz, C3), 83.0 (d, $^2J_{C,F}$ = 16.5 Hz, C4), 79.9 (d, $^2J_{C,F}$ = 16.5 Hz, C2), 75.3 (CH_2, Ph), 75.0 (CH_2, Ph), 69.2 (C1), 67.0 (CH_2, Cbz), 60.2 (C5), 53.5 (CH_2, Ph), 28.3 (C7), 25.3 (C6). – ^{19}F-NMR (188 MHz, $CDCl_3$): δ = −184.60 (m, 1 F, F). – MS (ESI–MeOH+$LiClO_4$): *m/z* (%) = 590.5 (100) $[M+Li]^+$, 696.4 (10) $[M+Li,LiClO_4]^+$, 1173.3 (22) $[M_2+Li]^+$. – $C_{36}H_{38}FNO_5$ (583.69): calcd. C 74.08, H 6.56, N 2.40; found C 73.86, H 6.67, N 2.51.

*(1RS, 3R, 4S, 5S, 6R) 6-[(N-Benzyl-N-(benzyloxycarbonyl))-amino]-3,5-bis(benzyloxy)-4-fluoro-cycloheptanol (**10**)*

Colorless oil. – $[\alpha]_D$ = −42.10° (*c* = 0.52, $CHCl_3$). – R_f = 0.30 (*n*-hexane-ethyl acetate = 5:3). – IR (film): ν = 3444m, 3030m, 2927m, 1694s, 1496m, 1455s, 1233m, 1071s, 735m, 697s cm^{-1}. – ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.33 – 7.13 (m, 20 H, Ph), 5.11 (m, 2 H, CH_2CBz, CH_2CBz), 4.70 (d, 1 H, $^2J_{H,H}$ = 11.4 Hz, CH_2OBn), 4.65 (m, 1 H, H-4), 4.63 – 4.38 (m, 4 H, CH_2OBn, CH_2OBn, CH_2OBn, CH_2NBn), 4.24 (m, 1 H, H-3), 3.97 (d, 1 H, $^2J_{H,H}$ = 16.0 Hz, CH_2NBn), 3.85 (m, 1 H, H-5), 3.66 (m, 1 H, H-1), 3.36 (m, 1 H, H-6), 2.10 – 1.51 (m, 4 H, H-2, H-2′, H-7, H-7′. – ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 155.6 (*C*=O CBz), 138.3 (C_{ar}), 138.0 (C_{ar}), 137.8 (C_{ar}), 136.5 (C_{ar}), 128.4 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 127.9 (C_{ar}), 127.9 (C_{ar}), 127.8 (C_{ar}), 127.63 (C_{ar}), 127.57 (C_{ar}), 127.5 (C_{ar}), 127.2 (C_{ar}), 97.0 (d, $^1J_{C,F}$ = 178.2, C4), 81.4 (d, $^2J_{C,F}$ = 22.5 Hz, C5), 74.5 (d, $^2J_{C,F}$ = 24.9 Hz, C3), 74.3 (C1), 72.6 (*C*H_2OBn), 71.9 (*C*H_2OBn), 66.9 (CH_2CBz), 65.7 (C6), 40.2 (*C*H_2NBn), 35.9 (C2), 35.5 (C7). – ^{19}F-NMR (188 MHz, $CDCl_3$): δ = −176.94 (m, 1 F, F). – MS (ESI–MeOH+$LiClO_4$): *m/z* (%) = 590.9 (100) $[M+Li]^+$, 1173.2 (15) $[M_2+Li]^+$. – $C_{36}H_{38}FNO_5$ (583.69): calcd. C 74.08, H 6.56, N 2.40; found C 73.91, H 6.70, N 2.50.

*(2R, 3S, 4S, 5R) 5-[(N-Benzyl)amino]-2,4-bis(benzyloxy)-3-fluoro-cycloheptanone (**11**)*

To a solution of **9** (472 mg, 0.81 mmol) in dry dichloromethane (100 mL), PCC (200 mg, 0.93 mmol) was added, and stirring at 25 °C was continued for another 12 h; more PCC (200 mg, 0.93 mmol) was added, and after 10 h of stirring at 25 °C one fourth of the solvent was evaporated under reduced pressure, and ethyl acetate (100 mL) was added. The mixture was filtered over a small layer of silica gel (5 cm) and diluted with ethyl acetate (5 × 100 mL). The solvents were evaporated, and the remaining residue was subjected to chromatography (silica gel, *n*-hexane-ethyl acetate = 80:20) to afford **11** (360 mg; 77.0 %) as a colorless oil. $[\alpha]_D$ = −8.58° (*c* = 0.80, $CHCl_3$). – R_f = 0.69 (*n*-hexane-ethyl acetate = 5:3). – IR (KBr): ν = 3064m, 3031m, 2942m, 1694s, 1496m, 1455s, 1360m, 1227s, 1115s, 1028m, 736s, 698s cm^{-1}. – ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.36 – 7.11 (m, 20 H, Ph), 5.12 (m, 2 H, CH_2CBz, 4.77 (m, 2 H, CH_2OBn), 4.67 (m, 1 H, H-3), 4.62 – 4.48 (m, 3 H, CH_2OBn, CH_2OBn, CH_2NBn), 4.38 – 4.29 (m, 2 H, H-2, H-4), 4.07 (m, 1 H, CH_2NBn), 3.42 (m, 1 H, H-5), 2.39 – 2.11 (m, 2 H, H-7, H-7′), 1.74 – 1.59 (m, 2 H, H-6, H-6′). – ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 205.9 (*C*=O), 155.3 (*C*=O, CBz), 137.8 (C_{ar}), 136.8 (C_{ar}), 136.3 (C_{ar}), 128.6 (C_{ar}), 128.5 (C_{ar}), 128.4 (C_{ar}), 128.2 (C_{ar}), 128.0 (C_{ar}), 127.9 (C_{ar}), 127.8 (C_{ar}), 127.6 (C_{ar}), 127.4 (C_{ar}), 127.3 (C_{ar}), 95.1 (d, $^1J_{C,F}$ = 183.1, C3), 82.6 (d, $^2J_{C,F}$ = 20.1 Hz, C4), 80.7 (d, $^2J_{C,F}$ = 21.1 Hz, C2), 74.6 (*C*H_2OBn), 72.7 (*C*H_2OBn), 67.2 (CH_2CBz), 59.8 (C5), 53.1 (*C*H_2NBn), 39.0 (C7), 26.3 (C6). – ^{19}F-NMR (188 MHz, $CDCl_3$): δ = −182.91 (m, 1 F, F). – MS (ESI–MeOH+$LiClO_4$): *m/z* (%) = 588.5 (100) $[M+Li]^+$, 694.6 (24) $[M+Li,LiClO_4]^+$, 1168.8 (10) $[M_2+Li]^+$– $C_{36}H_{36}FNO_5$ (581.26): calcd. C 74.33, H 6.24, N 2.41; found C 74.19, H 6.29, N 2.48.

*(+)(1R, 2R, 3R, 4S, 5R) 8-Azabicyclo[3.2.1]octane-3-fluoro-1,2,4-triol (**12**)*

A solution of **11** (300 mg, 0.52 mmol) in abs. ethyl acetate (20 mL) and acetic acid (66 % in water, 80 mL) was hydrogenated in the presence of palladium on charcoal (200 mg, 10 % Pd) at a pressure of 2.38 atm for 5 d. The suspension was filtered, the solvents were removed under reduced pressure, and the residue was subjected to chromatography (silica gel, methanol-water-conc. ammonium hydroxide = 95:5:1) to afford **12** (75 mg, 80.6 %) as a colorless glass. – $[\alpha]_D$ = +65.4° (*c* = 0.2 H_2O). – R_f = 0.45 (MeOH-ethyl acetate = 50:50). – IR (KBr): ν = 3441s, 2925m, 2851m, 1717w, 1570w, 1405w, 1340w, 1295w, 1265w, 1020w, 810w, 657w cm^{-1}. – ^{1}H-NMR (500 MHz, CD_3OD): δ = 4.12 (ddd, 1 H, $^2J_{3,F}$ = 51.9, $^3J_{3,4}$ = 7.9, $^3J_{3,2}$ = 8.2 Hz, H-3), 3.75 (dddd, 1 H, $^3J_{4,H}$ = 0.9, $^3J_{4,5}$ = 4.3, $^3J_{4,3}$ = 7.9, $^3J_{4,F}$ = 16.5 Hz, H-4), 3.61 (ddd, 1 H, $^3J_{2,3}$ = 8.2, $^3J_{2,F}$ = 16.8, $^4J_{2,7'}$ = 1.9 Hz, H-2), 3.28 (ddd, 1 H, $^3J_{5,4}$ = 4.3, $^3J_{5,6}$ = 5.0, $^4J_{5,F}$ = 4.5 Hz, H-5), 2.04 (ddd, 1 H, $^2J_{7,7'}$ = 13.2, $^3J_{7,6'}$ = 4.9, $^3J_{7,6}$ = 9.8 Hz, H-7), 1.91 (dddd, 1 H, $^2J_{6,6'}$ = 13.9, $^3J_{6,5}$ = 5.0, $^3J_{6,7'}$ = 5.1, $^3J_{6,7}$ = 9.8 Hz, H-6), 1.85 (ddd, 1 H, $^2J_{6',6}$ = 13.9, $^3J_{6',7}$ = 4.9, $^3J_{6',7'}$ = 12.8 Hz, H-6′), 1.52 (dddd, $^2J_{7',7}$ = 13.2, $^3J_{7',6}$ = 5.1, $^3J_{7',6'}$ = 12.8, $^4J_{7,2}$ = 1.9 Hz, H-7′). – ^{13}C-NMR (125 MHz, CD_3OD): δ = 98.6 (d, $^1J_{C,F}$ = 180.9 Hz, C3), 92.0 (d, $^3J_{C,F}$ = 11.1 Hz, C1), 77.5 (d, $^2J_{C,F}$ = 17.3 Hz, C2), 74.5 (d, $^2J_{C,F}$ = 17.5 Hz, C4), 57.4 (d, $^3J_{C,F}$ = 10.1 Hz, C5), 30.1 (C7), 23.2 (C6). – ^{19}F-NMR (188 MHz, CD_3OD): δ = −198.41 (dddd, 1 F, $^4J_{F,5}$ = 4.5, $^3J_{F,4}$ =

16.5, $^3J_{F,2}$ = 16.8, $^2J_{F,3}$ = 51.9 Hz, F). – MS (ESI–MeOH): *m/z* (%) = 178.2 (100) $[M+H]^+$. – $C_7H_{12}FNO_3$ (177.17): calcd. C 47.45, H 6.83, N 7.91; found C 47.38, H 6.94, N 8.02.

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