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Total synthesis of 3,3-difluorinated 1-deoxynojirimycin analogues

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ABSTRACT

Difluorination of 1-deoxynojirimycin at position C(3) creates a competitive inhibitor **15** of 10 times higher activity against an α-glucosidase than the parent compound. Its screening against a panel of human cell lines showed a low cytotoxicity therefore making this compound an interesting candidate for further clinical investigations.

1. Introduction

1-Deoxynojirimycin (DNM, **I**, Fig. 1) and its analogues (cf. miglitol, **II**) have a long history[1] in the in vitro investigation of diabetes and as antiviral agents. To increase the activity of biologically active organic compounds[2] often their fluorinated analogues have been prepared and several procedures are available[3] to introduce a fluorine substituent into a molecule. Interestingly enough, the number of reliable and generally applicable methods for introducing a geminal difluoromethylene group[3] is limited. During our investigations on glucosidase inhibition we became interested in the synthesis of certain geminal difluorinated 1-deoxynojirimycin analogues.

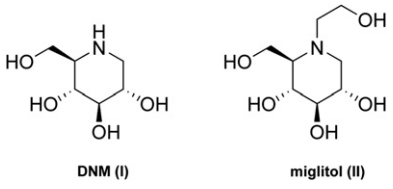
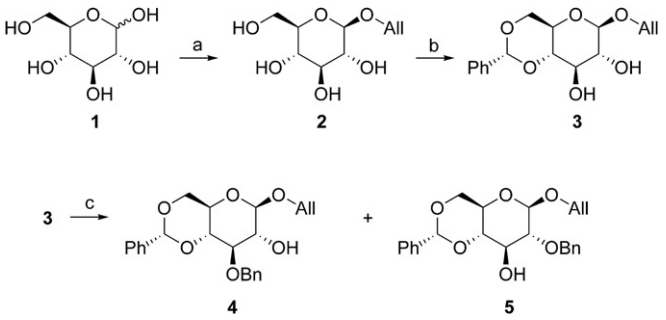


Figure 1. Structure of 1-deoxynojirimycin (**I**) and of miglitol (**II**).

2. Results and discussion

Extensive review of the literature and patents revealed there are only a few reports describing the synthesis of a 4,4-[4,5] and a 6,6-difluorinated 1-deoxynojirimycin[6] analogue. The synthesis and biological evaluation of a 3,3-difluorinated analogue appeared interesting since we expected that this compound might be an inhibitor for an α-glucosidase as well as for an α-galactosidase. We reasoned that the strongly electron-withdrawing geminal difluoromethylene group should affect the binding to the enzyme by changing the pK_a of the iminosugar; also, C(3)-OH in an iminosugar seems critically for a good binding to the enzymes. Since the cleavage of methyl glycosides affords rather harsh conditions we decided to start our approach employing an allyl-glycoside since the allyl protective group can be cleaved off readily[7] under mild conditions.

Thus, glucose (**1**) was allylated[8] (Scheme 1) in water/allylic alcohol at 50 °C in the presence of the β-glucosidase from almonds and 63% of the corresponding allyl β-D-glucopyranoside (**2**)[8,9] was obtained. Its treatment with benzaldehyde dimethylacetal in the



Scheme 1. (a) β-Glucosidase (almonds) (Ref. 8), allyl alcohol/water, 50 °C, 63%; (b) $PhC(OMe)_2$, DMF, $HBF_4 \cdot Et_2O$, 50 °C, 97%; (c) BnBr, NaOH, Bu_4NHSO_4, reflux, combined yield 73%.

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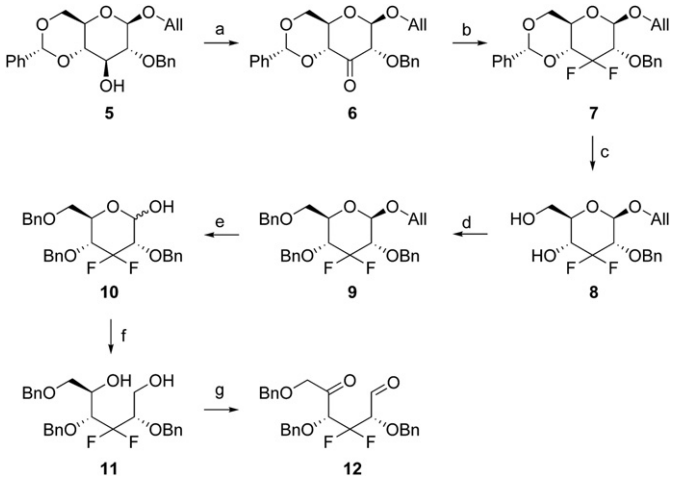
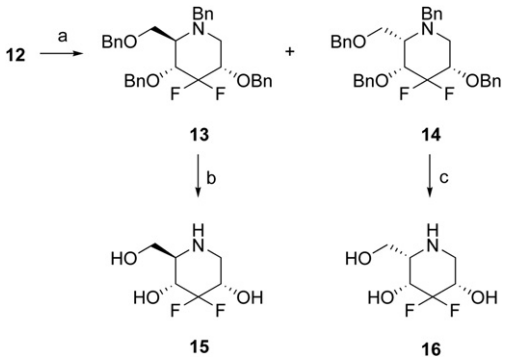
presence of $HBF_4 \cdot Et_2O$ at 50 °C[10,11] for one day gave the 4,6-*O*-benzylidene acetal **3** in an excellent yield of 97%. Compound **3** was benzylated[12] to afford a mixture of the monobenzylated compounds **4** and **5**. This mixture (**4**:**5**=25:48%) was easily separated by chromatography.

Swern-oxidation[13,14] of **5** (Scheme 2) applying DMSO and trifluoroacetic anhydride gave 75% of the hex-3-ulo-pyranoside **6** whose reaction with DAST in anhyd dichloromethane[15] gave 55% of the 3,3-difluorinated pyranoside **7**. Interestingly enough, difluorination of **6** with DAST in refluxing benzene gave only 17% of **7** invariably accompanied by deterioration products. Compound **7** is characterised in its ^{19}F NMR spectrum by the presence of two signals at δ=−119.01 and −132.73 ppm. In the ^{13}C NMR spectrum of **7** the signal for C(3) is found at δ=117.2 ppm; it shows a coupling by the adjacent fluorine substituents of J=250 and 255 Hz being typical for geminal difluorinated carbons.



Scheme 2. (a) DMSO, $(F_3CO_2)_2O$, DCM, −78 °C, then Et_3N, 75%; (b) DAST, DCM, 25 °C, 55%; (c) TFA (30% in DCM), H_2O, 25 °C, 44%; (d) BnBr, NaH, 25 °C, 71%; (e) $PdCl_2$, MeOH, 25 °C, 64%; (f) $LiAlH_4$, THF, 25 °C, 76%; (g) DMSO, $(F_3CO_2)_2O$, DCM, −78 °C, then Et_3N, 57%.

The 4,6-*O*-benzylidene acetal of compound **7** was cleaved off with trifluoroacetic acid in dichloromethane/water[16] to afford **8** that was benzylated[17–19] to yield 71% of 2,4,6-tri-*O*-benzylated compound **9**. Deallylation[20,21] was performed with $PdCl_2$ in MeOH to yield **10** whose reduction with $LiAlH_4$ in THF[14] at room temperature gave the diol **11** in 76% yield. Compound **11** was subject to a double *Swern*-oxidation to yield the corresponding 5-ulose **12** as a mixture of the dicarbonyl compound and its corresponding hydrates. This mixture (Scheme 3) was subjected to a reductive amination[14] to afford a mixture of **13** and **14**. These compounds were easily separated by chromatography and debenzylated[22,23] to afford the target compound **15** and its matching C(5)-epimer **16**.



Scheme 3. (a) $BnNH_2$, MeOH, −78 °C, then $NaBH_3CN$, −78 °C→25 °C→50 °C, combined yield 40%; (b) Pd/C, H_2, MeOH, 35 °C, 87%; (c) Pd/C, H_2, MeOH, 35 °C, 81%.

Compounds **15** and **16** were assayed for their inhibitory activities towards several commercially available glucosidases under ideal enzymatic pH using the well established[24] 4-nitro-phenolate test. The results of these assays are summarised in Table 1.

Table 1
Inhibitory activities (IC_{50}, mM) of several compounds against glycosidases. The values are the average from at least three independent experiments; variation was 5%; n.i.: no inhibition

Compound	α-Glucosidase (baker's yeast)	β-Glucosidase (almonds)	α-Galactosidase (green coffee beans)	β-Galactosidase (*E. coli*)
Miglitol	9.88	0.21	13.93	0.19
15	0.84	0.82	3.30	n.i.
16	2.24	1.40	9.12	8.90

3. Conclusions

Compound **15** is an excellent competitive inhibitor for the α-glucosidase from baker's yeast showing an approx. 10-fold increased inhibition compared to standard miglitol. It is also a stronger inhibitor than miglitol for the α-galactosidase from green coffee beans. Less inhibitory activity can be detected for the epimeric compound **16** although its inhibitory activity for the α-glucosidase from baker's yeast is approx four times enhanced compared to miglitol. For both compounds a reduced or no activity at all is observed when tested with a β-galactosidase (from *Escherichia coli*). Their screening against a panel of human cell lines showed a low cytotoxicity therefore making these compound interesting candidates for further investigations.

4. Experimental

4.1. General

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, MS spectra were taken on a Intectra GmbH AMD 402 (electron impact, 70 eV) 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.

4.2. Allyl (*R*)-4,6-*O*-benzylidene-β-D-*gluco*-pyranoside (3)

A solution of allyl β-D-*gluco*-pyranoside (**2**) (10.00 g, 45.41 mmol) in benzaldehyde dimethylacetal (50.0 ml, 334.05 mmol) was stirred at 50 °C for 10 min, then $HBF_4 \cdot Et_2O$ (3.00 ml) was added and stirring was continued at 50 °C for another 24 h. After neutralisation with triethylamine, the solvent was removed in vacuo and the remaining residue subjected to chromatography (silica gel, methanol/ethyl acetate=10:90) to afford **3** (13.64 g, 97.4%) as colourless crystals; mp 146–147 °C (lit.[25] 146–148 °C); $[\alpha]_D$ −51.68 (*c* 0.45, $CHCl_3$) [lit.[25] $[\alpha]_D$ −57.6 (*c* 1.02, $CHCl_3$)]; R_f (hexane/ethyl acetate=50:50) 0.29; R_f (methanol/ethyl acetate=10:90) 0.84; IR (KBr): ν=3511s, 2925m, 1647w, 1453w, 1374m, 1267w, 1172m, 1087m, 1043m, 1004m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.49–7.48 (m, 2H, Ph), 7.37–7.33 (m, 3H, Ph), 5.93 (dddd, 1H, $^3J_{2',1''}$=5.4, $^3J_{2',1'}$=6.4, $^3J_{2',3'}$=10.4, $^3J_{2',3''}$=17.0, H-2′), 5.52 (s, 1H, C*H*-benzylidene), 5.32 (dddd, 1H, $^4J_{3'',1'}$=1.2, $^2J_{3'',3'}$=1.2,

$^4J_{3'',1''}$=1.2, $^3J_{3'',2'}$=17.0, H-3″), 5.23 (dddd, 1H, $^4J_{3',1'}$=1.2, $^4J_{3',1''}$=1.4, $^2J_{3',3''}$=1.2, $^3J_{3',2'}$=10.4, H-3′), 4.44 (d, 1H, $^3J_{1,2}$=7.7, H-1), 4.37 (dddd, 1H, $^4J_{1'',3''}$=1.4, $^4J_{1'',3'}$=1.4, $^3J_{1'',2'}$=5.4, $^2J_{1'',1'}$=12.6, H-1″), 4.33 (dd, 1H, $^3J_{6B,5}$=4.9, $^2J_{6B,6A}$=10.4, H-6$_B$), 4.14 (dddd, 1H, $^4J_{1',3'}$=1.2, $^4J_{1',3''}$=1.2, $^3J_{1',2'}$=6.4, $^2J_{1',1''}$=12.6, H-1′), 3.81 (dd, 1H, $^3J_{2,1}$=7.7, $^3J_{2,3}$=9.1, H-2), 3.78 (dd, 1H, $^3J_{6A,5}$=10.2, $^2J_{6A,6B}$=10.4, H-6$_A$), 3.55 (dd, 1H, $^3J_{4,3}$=9.1, $^3J_{4,5}$=9.4, H-4), 3.52 (dd, 1H, $^3J_{3,2}$=9.1, $^3J_{3,4}$=9.1, H-3), 3.44 (ddd, 1H, $^3J_{5,6B}$=4.9, $^3J_{5,4}$=10.2, $^3J_{5,6A}$=9.4, H-5) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=136.9 (C_{ar}), 133.4 (C2′), 129.3 (C_{ar}), 128.3 (C_{ar}), 126.3 (C_{ar}), 118.3 (C3′), 102.1 (C1), 101.9 (*C*H-benzylidene), 80.5 (C4), 74.5 (C3), 73.2 (C2), 70.6 (C1′), 68.6 (C6), 66.4 (C5) ppm; MS (ESI-MeOH): *m*/*z* (%)=309.2 ([M+H]$^+$, 10), 331.3 ([M+NH$_4$]$^+$, 18), 482.2 ([M$_3$+K, H]$^{2+}$, 4), 639.0 ([M$_2$+Na]$^+$, 100); analysis for $C_{16}H_{20}O_6$ (308.33): calcd: C, 62.33; H, 6.54; found: C, 62.09; H, 6.71.

4.3. Allyl 3-*O*-benzyl-(*R*)-4,6-*O*-benzylidene-β-D-*gluco*-pyranoside (4) and allyl 2-*O*-benzyl-(*R*)-4,6-*O*-benzylidene-β-D-*gluco*-pyranoside (5)

To a solution of **3** (8.44 g, 27.27 mmol) and tetrabutylammonium hydrogen sulfate (1.63 g, 4.80 mmol) in dichloromethane (315.0 ml) an aq sodium hydroxide solution (1.3 M, 31.6 ml) was added and the mixture was heated to reflux. Benzylbromide (4.91 ml, 41.06 mmol) was added dropwise under vigorous stirring. After stirring under reflux for 96 h and cooling to 25 °C, water (80 ml) was added, the phases were separated and the aq phase was extracted with dichloromethane (3×100 ml). The combined organic phases were evaporated and the remaining residue was subjected to chromatography (silica gel, hexane/ethyl acetate=85:15) to afford **4** (2.71 g, 25.0%) and **5** (5.22 g, 48.1%). Data for **4**: colourless crystals; mp 139–140 °C (lit.[26] 140–141 °C); $[\alpha]_D$ −18.96 (*c* 0.42; $CHCl_3$) [lit.[26] $[\alpha]_D$ +39.9 (*c* 1; $CHCl_3$)]; R_f (hexane/ethyl acetate=5:3) 0.53; IR (KBr): ν=3364s, 3067m, 3034m, 2971m, 2931m, 2907m, 2860s, 1966w, 1735s, 1643m, 1586m, 1498m, 1452s, 1400m, 1367s, 1303m, 1283m, 1264m, 1209m, 1173s, 1093s, 1066s, 1030s, 1008s, 964s, 932s, 876m, 753s, 697s, 665m, 629m, 593m, 450m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.48–7.46 (m, 2H, Ph), 7.39–7.26 (m, 8H, Ph), 5.93 (dddd, 1H, $^3J_{2',1''}$=6.4, $^3J_{2',1'}$=5.3, $^3J_{2',3'}$=10.5, $^3J_{2',3''}$=17.2, H-2′), 5.56 (s, 1H, C*H*-benzylidene), 5.32 (dddd, 1H, $^2J_{3'',3'}$=1.4, $^3J_{3'',2'}$=17.2, H-3″), 5.22 (dddd, 1H, $^2J_{3',3''}$=1.4, $^3J_{3',2'}$=10.5, H-3′), 4.95 (d, 1H, $^2J_{H'',H'}$=11.7, C*H*″$_2$(OBn)), 4.79 (d, 1H, $^2J_{H'',H'}$=11.7, C*H*″$_2$(OBn)), 4.44 (d, 1H, $^3J_{1,2}$=7.6, H-1), 4.36 (dddd, 1H, $^3J_{1'',2'}$=5.3, $^2J_{1'',1'}$=12.8, H-1″), 4.33 (dd, 1H, $^3J_{6B,5}$=4.9, $^2J_{6B,6A}$=10.5, H-6$_B$), 4.14 (dddd, 1H, $^3J_{1',2'}$=6.4, $^2J_{1',1''}$=12.7, H-1′), 3.79 (dd, 1H, $^3J_{6A,5}$=10.1, $^2J_{6A,6B}$=10.5, H-6$_A$), 3.67 (m, 2H, H-3, H-4), 3.58 (dd, 1H, $^3J_{2,1}$=7.6, $^3J_{2,3}$=9.5, H-2), 3.43 (ddd, 1H, $^3J_{5,6B}$=4.9, $^3J_{5,4}$=9.1, $^3J_{5,6A}$=10.1, H-5) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=138.3 (C_{ar}), 137.2 (Ph), 133.5 (C2′), 129.0 (C_{ar}), 128.4 (C_{ar}), 128.2 (C_{ar}), 128.0 (C_{ar}), 127.8 (C_{ar}), 126.0 (C_{ar}), 118.2 (C3′), 102.2 (C1), 101.3 (*C*H-benzylidene), 81.4 (C3), 80.2 (C4), 74.6 (*C*H$_2$(OBn)), 74.3 (C2), 70.5 (C1′), 68.7 (C6), 66.4 (C5) ppm; MS (ESI-MeOH): *m*/*z* (%)=399.2 ([M+H]$^+$, 18), 416.1 ([M+NH$_4$]$^+$, 30), 421.3 ([M+Na]$^+$, 22), 433.9 ([M$_2$+K, HMeOH]$^{2+}$, 3), 617.2 ([M$_3$+K, H]$^{2+}$, 16), 818.9 ([M$_2$+Na]$^+$, 100); analysis for $C_{23}H_{26}O_6$ (398.45): calcd: C, 69.33; H, 6.58; found: C, 69.17; H, 6.71.

Data for **5**: colourless crystals; mp 124–125 °C (lit.[27] 124 °C); $[\alpha]_D$ −17.70 (*c* 0.93; $CHCl_3$); R_f (hexane/ethyl acetate=5:3) 0.63; IR (KBr): ν=3477s, 3288s, 3063m, 3030m, 2978m, 2877s, 1736w, 1645m, 1497m, 1454s, 1400m, 1384s, 1366m, 1348m, 1306m, 1266m, 1216m, 1180s, 1099s, 1046s, 1028s, 986s, 934s, 911m, 877m, 761s, 750s, 734s, 697s, 658m, 601m, 568m, 512m, 461m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.47–7.45 (m, 2H, Ph), 7.37–7.26 (m, 8H, Ph), 5.93 (dddd, 1H, $^3J_{2',1''}$=5.2, $^3J_{2',1'}$=5.7, $^3J_{2',3'}$=10.8, $^3J_{2',3''}$=17.3, H-2′), 5.50 (s, 1H, C*H*-benzylidene), 5.34 (dd, 1H, $^2J_{3'',3'}$=1.5, $^3J_{3'',2'}$=17.3, H-3″), 5.22 (dd, 1H, $^2J_{3',3''}$=1.5, $^3J_{3',2'}$=10.8, H-3′), 4.94 (d, 1H, $^2J_{H'',H'}$=12.0, C*H*″$_2$(OBn)), 4.72 (d, 1H, $^2J_{H',H''}$=12.0, C*H*′$_2$(OBn)), 4.56 (d, 1H, $^3J_{1,2}$=7.7, H-1), 4.40 (dd, 1H, $^3J_{1'',2'}$=5.2, $^2J_{1'',1'}$=12.7, H-1″), 4.32 (dd, 1H, $^3J_{6B,5}$=4.9, $^2J_{6B,6A}$=10.5, H-6$_B$), 4.14 (dd, 1H, $^3J_{1',2'}$=5.7, $^2J_{1',1''}$=12.7, H-1′), 3.82 (dd, 1H, $^3J_{3,2}$=9.1, $^3J_{3,4}$=9.1, H-3), 3.76 (dd, 1H, $^3J_{6A,5}$=10.2, $^2J_{6A,6B}$=10.5, H-6$_A$), 3.53 (dd, 1H, $^3J_{4,3}$=9.1, $^3J_{4,5}$=9.6, H-4), 3.41 (ddd, 1H, $^3J_{5,6B}$=4.9, $^3J_{5,4}$=9.6, $^3J_{5,6A}$=10.2, H-5), 3.37 (dd, 1H, $^3J_{2,1}$=7.7, $^3J_{2,3}$=9.1, H-2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=138.3 (C_{ar}), 137.0 (Ph), 133.6 (C2′), 129.2 (C_{ar}), 128.5 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 128.1 (C_{ar}), 128.0 (C_{ar}), 127.9 (C_{ar}), 126.3 (C_{ar}), 126.0 (C_{ar}), 117.7 (C3′), 102.9 (C1), 101.8 (*C*H-benzylidene), 81.8 (C2), 80.4 (C4), 74.8 (*C*H$_2$(OBn)), 73.2 (C3), 70.7 (C1′), 68.7 (C6), 66.1 (C5) ppm; MS (ESI-MeOH): *m*/*z* (%)=399.1 ([M+H]$^+$, 7), 416.1 ([M+NH$_4$]$^+$, 8), 421.3 ([M+Na]$^+$, 9), 617.2 ([M$_3$+K, H]$^{2+}$, 7), 818.9 ([M$_2$+Na]$^+$, 100); analysis for $C_{23}H_{26}O_6$ (398.45): calcd: C, 69.33; H, 6.58; found: C, 69.19; H, 6.80.

4.4. Allyl 2-*O*-benzyl-(*R*)-4,6-*O*-benzylidene-β-D-*ribo*-hexo-3-ulo-pyranoside (6)

To a mixture of dry DMSO (8.41 g, 107.64 mmol) and anhyd dichloromethane (72.0 ml) at −78 °C a solution of trifluoroacetic anhydride (16.05 g, 76.41 mmol) in anhyd dichloromethane (18.0 ml) was added dropwise under argon and the mixture was stirred at this temperature for 45 min. Then a solution of **5** (14.67 g, 36.82 mmol) in dry dichloromethane (40.0 ml) was added dropwise, maintaining the temperature at −78 °C during this addition. The mixture was stirred for 2 h at −78 °C, then a solution of Et_3N (13.0 ml, 93.27 mmol) in anhyd dichloromethane (30.0 ml) was added dropwise and the mixture was allowed to warm to 25 °C. Dichloromethane (300 ml) and water (100 ml) were added, the phases were separated and the organic phase was extracted with water (4×100 ml). The combined organic phases were evaporated under reduced pressure and the remaining residue was subjected to chromatography (silica gel, hexane/ethyl acetate=50:50) to afford **6** (10.90 g, 74.7%) as colourless crystals; mp 125–127 °C; $[\alpha]_D$ −64.84 (*c* 0.49, $CHCl_3$); R_f (hexane/ethyl acetate=5:3) 0.73; IR (KBr): ν=3426m, 3066m, 3032m, 2882m, 1746s, 1645m, 1497m, 1452m, 1401m, 1384m, 1370m, 1362m, 1327m, 1276m, 1251m, 1216m, 1176s, 1162m, 1148m, 1128s, 1093s, 1074s, 1043s, 1030s, 1011s, 979s, 936m, 753s, 729m, 696s, 668w, 654m, 630w, 569m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.49–7.47 (m, 2H, Ph), 7.41–7.39 (m, 2H, Ph), 7.36–7.26 (m, 6H, Ph), 5.93 (dddd, 1H, $^3J_{2',1''}$=5.3, $^3J_{2',1'}$=5.6, $^3J_{2',3'}$=10.8, $^3J_{2',3''}$=17.2, H-2′), 5.52 (s, 1H, C*H*-benzylidene), 5.36 (dddd, 1H, $^4J_{3'',1'}$=1.5, $^2J_{3'',3'}$=1.5, $^4J_{3'',1''}$=1.5, $^3J_{3'',2'}$=17.2, H-3″), 5.24 (dddd, 1H, $^4J_{3',1'}$=1.4, $^4J_{3',1''}$=1.5, $^2J_{3',3''}$=1.5, $^3J_{3',2'}$=10.8, H-3′), 4.89 (d, 1H, $^2J_{H'',H'}$=11.9, C*H*″$_2$(OBn)), 4.75 (d, 1H, $^2J_{H',H''}$=11.9, C*H*′$_2$(OBn)), 4.72 (d, 1H, $^3J_{1,2}$=7.4, H-1), 4.45 (dd, 1H, $^3J_{6B,5}$=4.9, $^2J_{6B,6A}$=10.4, H-6$_B$), 4.40 (dddd, 1H, $^4J_{1'',3''}$=1.5, $^4J_{1'',3'}$=1.4, $^3J_{1'',2'}$=5.3, $^2J_{1'',1'}$=12.7, H-1″), 4.24–4.18 (m, 2H, H-4, H-1′), 4.00 (dd, 1H, $^3J_{2,1}$=7.4, $^4J_{2,4}$=1.5, H-2), 3.85 (dd, 1H, $^3J_{6A,5}$=9.9, $^2J_{6A,6B}$=10.4, H-6$_A$), 3.57 (ddd, 1H, $^3J_{5,6B}$=4.9, $^3J_{5,4}$=9.9, $^3J_{5,6A}$=9.9, H-5) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=196.4 (*C*=O (3)), 137.1 (C_{ar}), 136.3 (Ph), 133.2 (C2′), 129.3 (C_{ar}), 128.8 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 128.3 (C_{ar}), 128.4 (C_{ar}), 128.2 (C_{ar}), 128.1 (C_{ar}), 128.0 (C_{ar}), 127.9 (C_{ar}), 127.3 (C_{ar}), 126.3 (C_{ar}), 126.1 (C_{ar}), 118.1 (C3′), 104.1 (C1), 101.7 (*C*H-benzylidene), 82.8 (C2), 81.8 (C4), 73.6 (*C*H$_2$(OBn)), 71.0 (C1′), 69.2 (C6), 66.5 (C5) ppm; MS (ESI-MeOH): *m*/*z* (%)=397.0 ([M+H]$^+$, 6), 414.1 ([M+NH$_4$]$^+$, 14), 446.1 ([M+NH$_4$, MeOH]$^+$, 34), 451.3 ([M+Na, MeOH]$^+$, 38), 815.0 ([M$_2$+Na]$^+$, 100), 846.9 ([M$_2$+Na, MeOH]$^+$, 60), 878.9 ([M$_2$+Na, (MeOH)$_2$]$^+$, 52); analysis for $C_{23}H_{24}O_6$ (396.43): calcd: C, 69.43; H, 6.10; found: C, 69.31; H, 6.28.

4.5. Allyl 2-*O*-benzyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-3,3-difluoro-β-D-*ribo*-hexopyranoside (7)

To a solution of **6** (300 mg, 0.72 mmol) in anhyd dichloromethane (6.0 ml), DAST (417 μl, 3.03 mmol) was added dropwise

under argon and the mixture was stirred at 25 °C for 5 days. Methanol (5.0 ml) was carefully added and the solvents were removed under diminished pressure. The oily residue was dissolved in dichloromethane (90 ml) and washed with water (50 ml). The aq phase was extracted with dichloromethane (3×100 ml); the organic phases were combined and the solvent was evaporated. The remaining residue was subjected to chromatography (silica gel, hexane/ethyl acetate=5:3) to afford **7** (167 mg, 55.2%) as a white foam; $[\alpha]_D$ −27.89 (*c* 0.39; $CHCl_3$); R_f (hexane/ethyl acetate=5:3) 0.67; IR (film): ν=2927m, 1736m, 1454m, 1384m, 1252m, 1093s, 745w, 698m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.50–7.48 (m, 2H, Ph), 7.41–7.28 (m, 8H, Ph), 5.93 (dddd, 1H, $^3J_{2',1''}$=0.7, $^3J_{2',1'}$=5.8, $^3J_{2',3'}$=10.5, $^3J_{2',3''}$=17.2, H-2′), 5.53 (s, 1H, C*H*-benzylidene), 5.35 (dddd, 1H, $^4J_{3'',1'}$=1.5, $^2J_{3'',3'}$=1.5, $^4J_{3'',1''}$=1.5, $^3J_{3'',2'}$=17.2, H-3″), 5.24 (dddd, 1H, $^4J_{3',1'}$=1.3, $^4J_{3',1''}$=1.5, $^2J_{3',3''}$=1.3, $^3J_{3',2'}$=10.5, H-3′), 4.89 (d, 1H, $^2J_{H'',H'}$=11.5, C*H*″$_2$(OBn)), 4.86 (d, 1H, $^2J_{H',H''}$=11.5, C*H*′$_2$(OBn)), 4.70 (dd, 1H, $^3J_{1,2}$=7.8, $^4J_{1,F'}$=1.1, H-1), 4.42–4.37 (m, 2H, H-6_B, H-1″), 4.18 (dddd, 1H, $^4J_{1',3''}$=1.3, $^4J_{1',3''}$=1.5, $^3J_{1',2''}$=5.8, $^2J_{1',1''}$=12.7, H-1′), 3.79–3.68 (m, 3H, H-4, H-5, H-6_A), 3.55 (ddd, 1H, $^3J_{2,1}$=7.8, $^3J_{2,F''}$=4.7, $^3J_{2,F}$=18.9, H-2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=137.1 (C_{ar}), 136.4 (Ph), 133.3 (C2′), 129.3 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 128.3 (C_{ar}), 128.0 (C_{ar}), 128.0 (C_{ar}), 127.8 (C_{ar}), 126.2 (C_{ar}), 117.9 (C3′), 117.2 (dd, $^1J_{3,F}$=250.0, $^1J_{3,F}$=255.5, C3), 101.9 (*C*H-benzylidene), 101.6 (d, $^3J_{1,F}$=5.7, C1), 78.5 (dd, $^2J_{2,F}$=18.3, $^2J_{2,F}$=18.5, C2), 77.9 (dd, $^2J_{4,F}$=18.5, $^2J_{4,F}$=18.9, C4), 75.1 (*C*H$_2$(OBn)), 71.0 (C1′), 68.7 (C6), 64.3 (d, $^3J_{5,F}$=6.9, C5) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ=−119.01 (ddd, 1F, $^3J_{F'',2}$=4.7, $^3J_{F'',4}$=4.7, $^2J_{F'',F'}$=243.6, F″), −132.73 (dddd, 1F, $^4J_{F',1}$=1.1, $^3J_{F',4}$=17.8, $^2J_{F',2}$=18.9, $^2J_{F',F''}$=243.6, F′) ppm; MS (ESI-MeOH): *m*/*z* (%)=419.1 ($[M+H]^+$, 56), 436.1 ($[M+NH_4]^+$, 52), 441.3 ($[M+Na]^+$, 53), 647.1 ($[M_3+K, H]^{2+}$, 18), 853.8 ($[M_2+NH_4]^+$, 35), 858.7 ($[M_2+Na]^+$, 100); analysis for $C_{23}H_{24}F_2O_5$ (418.43): calcd: C, 66.02; H, 5.78; found: C, 65.86; H, 5.92.

4.6. Allyl 2-*O*-benzyl-3-deoxy-3,3-difluoro-β-D-*ribo*-hexopyranoside (8)

To a solution of **7** (2.25 g, 5.68 mmol) in dichloromethane (14.7 ml), water (0.3 ml) and a solution of trifluoroacetic acid in dichloromethane (30%, 8.0 ml) were added at 25 °C and stirring was continued for another hour. Dichloromethane (60 ml) and water (40 ml) were added, the phases were separated and the aq phase was extracted with water (3×100 ml). The aq phase was extracted with dichloromethane (3×100 ml) and the combined organic layers were dried ($MgSO_4$). The solvents were evaporated under reduced pressure and the remaining residue was subjected to chromatography (silica gel, hexane/ethyl acetate=50:50) to afford **8** (830 mg, 44.3%) as a colourless oil; $[\alpha]_D$ −20.67 (*c* 0.53, $CHCl_3$); R_f (hexane/ethyl acetate=5:3) 0.06; R_f (methanol/ethyl acetate=10:90) 0.75; IR (film): ν=3396s, 3033m, 2883m, 1677m, 1498m, 1455m, 1407m, 1351m, 1237s, 1070s, 930m, 854m, 745m, 699s, 552w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.33–7.22 (m, 5H, Ph), 5.86 (dddd, 1H, $^3J_{2',1''}$=5.4, $^3J_{2',1'}$=5.8, $^3J_{2',3'}$=10.5, $^3J_{2',3''}$=17.2, H-2′), 5.27 (dddd, 1H, $^4J_{3'',1'}$=1.3, $^2J_{3'',3'}$=1.5, $^4J_{3'',1''}$=1.6, $^3J_{3'',2'}$=17.2, H-3″), 5.16 (dddd, 1H, $^4J_{3',1'}$=1.3, $^4J_{3',1''}$=1.4, $^2J_{3',3''}$=1.5, $^3J_{3',2'}$=10.5, H-3′), 4.81 (d, 1H, $^2J_{H'',H'}$=11.5, C*H*″$_2$(OBn)), 4.76 (d, 1H, $^2J_{H',H''}$=11.5, C*H*′$_2$(OBn)), 4.57 (dd, 1H, $^4J_{1,F'}$=1.4, $^3J_{1,2}$=7.9, H-1), 4.31 (dddd, 1H, $^4J_{1'',3''}$=1.3, $^4J_{1'',3'}$=1.4, $^3J_{1'',2'}$=5.4, $^2J_{1'',1'}$=12.8, H-1″), 4.10 (dddd, 1H, $^4J_{1',3'}$=1.3, $^4J_{1',3''}$=1.3, $^3J_{1',2'}$=5.8, $^2J_{1',1''}$=12.8, H-1′), 3.86 (m, 1H, H-6_B), 3.76 (dd, 1H, $^3J_{6A,5}$=4.0, $^2J_{6A,6B}$=12.0, H-6_A), 3.73 (ddd, 1H, $^3J_{4,F''}$=4.3, $^3J_{4,5}$=9.9, $^3J_{4,F'}$=17.9, H-4), 3.42 (m, 1H, H-5), 3.38 (ddd, 1H, $^3J_{2,F''}$=4.4, $^3J_{2,1}$=7.9, $^3J_{2,F'}$=17.9, H-2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=137.2 (Ph), 133.4 (C2′), 128.3 (C_{ar}), 128.2 (C_{ar}), 128.0 (C_{ar}), 119.5 (dd, $^1J_{3,F}$=245.3, $^1J_{3,F}$=253.1, C3), 117.8 (C3′), 100.9 (d, $^3J_{1,F}$=10.1, C1), 77.8 (dd, $^2J_{2,F}$=19.0, $^2J_{2,F}$=18.1, C2), 74.9 (*C*H$_2$(OBn)), 73.7 (d, $^3J_{5,F}$=6.5, C5), 70.9 (C1′), 68.5 (dd, $^2J_{4,F}$=20.1, $^2J_{4,F}$=20.1, C4), 61.6 (C6) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ=−116.08 (ddd, 1F, $^3J_{F'',2}$=4.4, $^3J_{F'',4}$=4.3, $^2J_{F'',F'}$=243.5, F″), −133.69 (dddd, 1F, $^4J_{F',1}$=1.4, $^3J_{F',2}$=17.9, $^3J_{F',4}$=17.9, $^2J_{F',F''}$=243.5, F′) ppm; MS (ESI-MeOH): *m*/*z* (%)=331.1 ($[M+H]^+$, 4), 348.3 ($[M+NH_4]^+$, 52), 353.3 ($[M+Na]^+$, 100), 515.0 ($[M_3+K, H]^{2+}$, 46), 672.0 ($[M_4+Na, H]^{2+}$, 26), 682.8 ($[M_2+Na]^+$, 74); analysis for $C_{16}H_{20}F_2O_5$ (330.32): calcd: C, 58.18; H, 6.10; found: C, 57.94; H, 6.35.

4.7. Allyl 2,4,6-tri-*O*-benzyl-3-deoxy-3,3-difluoro-β-D-*ribo*-hexopyranoside (9)

To an ice-cold solution of **8** (2.79 g, 8.45 mmol) in dry DMF (40 ml), sodium hydride (80% in mineral oil, 1.01 g, 33.79 mmol) was slowly added in several portions. Stirring at 0 °C followed by stirring at 25 °C was continued for another hour, then benzylbromide (3.03 ml, 25.34 mmol) was slowly added at 0 °C. After stirring at 25 °C for another 4 h, methanol (30 ml) was carefully added and the solvents were removed under diminished pressure. The oily residue was dissolved in diethylether (200 ml), washed with water and brine (100 ml each) and dried ($MgSO_4$). The solvents were evaporated and the remaining residue was subjected to chromatography (silica gel, hexane/ethyl acetate=85:15) to afford **9** (3.08 g, 71.4%) as a colourless oil; $[\alpha]_D$ +11.32 (*c* 0.38, $CHCl_3$); R_f (hexane/ethyl acetate=85:15) 0.74; R_f (hexane/ethyl acetate=5:3) 0.79; IR (film): ν=3356m, 3032m, 2921m, 1723m, 1497m, 1454m, 1404m, 1351m, 1239m, 1061s, 860w, 739m, 698m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.40–7.23 (m, 15H, Ph), 5.93 (dddd, 1H, $^3J_{2',1''}$=5.1, $^3J_{2',1'}$=6.1, $^3J_{2',3'}$=10.5, $^3J_{2',3''}$=17.3, H-2′), 5.32 (dddd, 1H, $^4J_{3'',1'}$=1.5, $^2J_{3'',3'}$=1.5, $^4J_{3'',1''}$=1.6, $^3J_{3'',2'}$=17.3, H-3″), 5.19 (dddd, 1H, $^4J_{3',1'}$=1.3, $^4J_{3',1''}$=1.5, $^2J_{3',3''}$=1.5, $^3J_{3',2'}$=10.5, H-3′), 4.88 (d, 1H, $^2J_{H'',H'}$=11.5, C*H*″$_2$(OBn)), 4.84 (d, 1H, $^2J_{H'',H'}$=11.1, C*H*″$_2$(OBn)), 4.82 (d, 1H, $^2J_{H',H''}$=11.5, C*H*′$_2$(OBn)), 4.58 (d, 1H, $^2J_{H'',H'}$=12.2, C*H*″$_2$(OBn)), 4.56 (dd, 1H, $^4J_{1,F'}$=1.5, $^3J_{1,2}$=7.9, H-1), 4.53 (d, 1H, $^2J_{H',H''}$=11.1, C*H*′$_2$(OBn)), 4.50 (d, 1H, $^2J_{H',H''}$=12.2, C*H*′$_2$(OBn)), 4.39 (dddd, 1H, $^4J_{1'',3''}$=1.6, $^4J_{1'',3'}$=1.5, $^3J_{1'',2'}$=5.1, $^2J_{1'',1'}$=12.9, H-1″), 4.13 (dddd, 1H, $^4J_{1',3'}$=1.3, $^4J_{1',3''}$=1.4, $^3J_{1',2'}$=6.1, $^2J_{1',1''}$=12.9, H-1′), 3.74 (ddd, 1H, $^3J_{4,F''}$=3.4, $^3J_{4,5}$=9.8, $^3J_{4,F'}$=19.3, H-4), 3.68–3.65 (m, 2H, H-6_B, H-6_A), 3.58 (m, 1H, H-5), 3.49 (ddd, 1H, $^3J_{2,F''}$=4.4, $^3J_{2,1}$=7.9, $^3J_{2,F'}$=20.0, H-2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=137.9 (Ph), 137.4 (Ph), 137.2 (Ph), 133.7 (C2′), 128.7 (C_{ar}), 128.5 (C_{ar}), 128.5 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 128.1 (C_{ar}), 128.0 (C_{ar}), 127.9 (C_{ar}), 127.8 (C_{ar}), 127.7 (C_{ar}), 127.6 (C_{ar}), 122.5 (dd, $^1J_{3,F}$=248.1, $^1J_{3,F}$=252.8, C3), 117.4 (C3′), 100.9 (d, $^3J_{1,F}$=10.2, C1), 78.1 (dd, $^2J_{2,F}$=18.2, $^2J_{2,F}$=18.7, C2), 74.9 (*C*H$_2$(OBn)), 74.9 (*C*H$_2$(OBn)), 74.8 (*C*H$_2$(OBn)), 73.5 (C4), 72.9 (d, $^3J_{5,F}$=8.2, C5), 70.5 (C1′), 68.1 (C6) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ=−112.16 (ddd, 1F, $^3J_{F'',4}$=3.4, $^3J_{F'',2}$=4.4, $^1J_{F'',F'}$=246.6, F″), −130.80 (dddd, 1F, $^4J_{F',1}$=1.5, $^3J_{F',4}$=19.3, $^3J_{F',2}$=20.0, $^1J_{F',F''}$=246.6, F′) ppm; MS (ESI-MeOH): *m*/*z* (%)=528.3 ($[M+NH_4]^+$, 52), 533.3 ($[M+Na]^+$, 46), 565.1 ($[M+Na, MeOH]^+$, 24), 597.1 ($[M+Na, (MeOH)_2]^+$, 16), 631.0 ($[M+Na, (MeOH)_3]^+$, 8), 1042.7 ($[M_2+Na]^+$, 100), 1074.7 ($[M_2+Na, MeOH]^+$, 20), 1106.5 ($[M_2+Na, (MeOH)_3]^+$, 10), 1140.7 ($[M_2+Na,(MeOH)_4]^+$, 3) analysis for $C_{30}H_{32}F_2O_5$ (510.57): calcd: C, 70.57; H, 6.32; found: C, 70.41; H, 6.54.

4.8. 2,4,6-Tri-*O*-benzyl-3-deoxy-3,3-difluoro-D-*ribo*-hexopyranose (10)

To a solution of **9** (2.84 g, 5.56 mmol) in methanol (30.0 ml), $PdCl_2$ (400 mg, 2.26 mmol) was slowly added under argon and stirring was continued for another 24 h. The suspension was filtrated and the remaining residue was washed with methanol (4×100 ml). The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The remaining residue was subjected to chromatography (silica gel, hexane/ethyl acetate=5:3) to afford **10** (2.61 g, 99.7%) as a mixture of equilibrating anomers; colourless crystals; mp 128–130 °C; $[\alpha]_D$

+27.17 (*c* 0.43, $CHCl_3$); R_f (hexane/ethyl acetate=85:15) 0.08 and 0.04; R_f (hexane/ethyl acetate=5:3) 0.51 and 0.41; IR (KBr): ν=3442m, 3031m, 2919m, 2864m, 1734w, 1497w, 1454m, 1405w, 1362m, 1265m, 1237m, 1187m, 1094s, 1073m, 1049m, 1029m, 1003m, 914w, 864w, 788w, 756m, 734m, 699m, 649w, 620w, 523w cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.40–7.21 (m, 30H, Ph), 5.20 (m, 1H), 4.90–4.80 (m, 6H), 4.72 (d, 1H, $^2J_{H'',H'}$=12.1, CH_2(OBn)), 4.57–4.51 (m, 4H), 4.47 (d, 1H, $^2J_{H'',H'}$=12.0, CH_2(OBn)), 4.45 (d, 1H, $^2J_{H'',H'}$=12.2, CH_2(OBn)), 4.10 (ddd, 1H, *J*=1.6, *J*=3.3, *J*=5.8), 3.81 (ddd, 1H, *J*=4.5, *J*=9.7, *J*=19.4), 3.77–3.62 (m, 7H), 3.42 (ddd, *J*=4.2, *J*=7.7, *J*=19.9) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=137.6 (Ph), 137.3 (Ph), 137.3 (Ph), 137.2 (Ph), 137.2 (Ph), 137.1 (Ph), 128.6 (C_{ar}), 128.4 (C_{ar}), 128.4 (C_{ar}), 128.4 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 128.1 (C_{ar}), 128.0 (C_{ar}), 128.0 (C_{ar}), 128.0 (C_{ar}), 128.0 (C_{ar}), 127.9 (C_{ar}), 127.9 (C_{ar}), 127.8 (C_{ar}), 121.4 (m, C3), 120.8 (m, C3), 95.6 (d, $^3J_{1,F}$=10.6, C1), 91.3 (d, $^3J_{1,F}$=8.5, C1), 78.9 (m), 75.1–74.0 (m, CH_2(OBn)), 73.6 (CH_2(OBn)), 73.0 (d, $^3J_{5,F}$=8.2, C5), 68.3 (d, $^3J_{5,F}$=7.2, C5), 68.2 (6), 67.7 (6) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ=−107.81 (d, 1F, $^1J_{F'',F'}$=247.6, F″), −111.89 (d, 1F, $^1J_{F',F''}$=247.1, F″), −125.74 (ddd, 1F, $J_{F',H}$=20.3, $J_{F',H}$=20.3, $^1J_{F'',F'}$=247.6, F′), −130.83 (ddd, 1F, $J_{F',H}$=19.4, $J_{F',H}$=19.4, $^1J_{F',F''}$=247.1, F′) ppm; MS (ESI-MeOH): *m*/*z* (%)=488.3 ($[M+NH_4]^+$, 15), 493.3 ($[M+Na]^+$, 15), 725.5 ($[M_3+K, H]^{2+}$, 3), 962.8 ($[M_2+Na]^+$, 100); source CID: *m*/*z* (%)=488.5 ($[M+NH_4]^+$, 2), 493.4 ($[M+Na]^+$, 100), 962.7 ($[M_2+Na]^+$, 2); analysis for $C_{27}H_{28}F_2O_{5\times}$ (470.51): calcd: C, 68.92; H, 6.00; found: C, 68.77; H, 6.29.

4.9. 2,4,6-Tri-*O*-benzyl-3-deoxy-3,3-difluoro-D-*ribo*-hexitol (11)

To an ice-cold solution of **10** (1.99 g, 4.23 mmol) in abs THF (150.0 ml), lithium aluminium hydride (642 mg, 16.92 mmol) was added in several portions and the suspension was stirred for 12 h at 25 °C. Methanol (30 ml) was carefully added and stirring was continued for another 30 min. The solvents were evaporated under reduced pressure. The remaining residue was subjected to chromatography (silica gel, hexane/ethyl acetate=5:3) to afford **11** (1.52 g, 76.1%) as a colourless oil; $[\alpha]_D$ +5.28 (*c* 0.40, $CHCl_3$); 3R_f (hexane/ethyl acetate=5:3) 0.36; IR (film): ν=3453s, 3090m, 3065m, 3032m, 2926m, 1732m, 1644m, 1497m, 1454s, 1360s, 1211m, 1102s, 1028s, 912m, 822m, 738s, 699s, 605m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.37–7.22 (m, 15H, Ph), 4.78 (d, 1H, $^2J_{H'',H'}$=11.3, CH''_2(OBn)), 4.74 (d, 1H, $^2J_{H'',H'}$=11.0, CH''_2(OBn)), 4.69 (d, 1H, $^2J_{H',H''}$=11.3, CH'_2(OBn)), 4.63 (d, 1H, $^2J_{H',H''}$=11.0, CH'_2(OBn)), 4.54 (d, 1H, $^2J_{H'',H'}$=11.8, CH''_2(OBn)), 4.48 (d, 1H, $^2J_{H',H''}$=11.8, CH'_2(OBn)), 4.14–3.97 (m, 3H, H-2, H-4, H-5), 3.85 (dd, 1H, $^3J_{1B,2}$=2.0, $^2J_{1B,1A}$=11.5, H-1_B), 3.78 (dd, 1H, $^3J_{1A,2}$=5.7, $^2J_{1A,1B}$=11.5, H-1_A), 3.68–3.61 (m, 2H, H-6_B, H-6_A) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=137.8 (Ph), 137.4 (Ph), 137.2 (Ph), 128.6 (C_{ar}), 128.5 (C_{ar}), 128.5 (C_{ar}), 128.4 (C_{ar}), 128.4 (C_{ar}), 128.2 (C_{ar}), 128.2 (C_{ar}), 128.1 (C_{ar}), 128.1 (C_{ar}), 127.9 (C_{ar}), 127.9 (C_{ar}), 127.8 (C_{ar}), 122.7 (dd, $^1J_{3,F}$=253.4, $^1J_{3,F}$=250.5, C3), 79.4 (dd, $^3J_{4,F}$=24.4, $^3J_{4,F}$=26.4, C4), 77.9 (dd, $^3J_{2,F}$=22.5, $^3J_{2,F}$=24.9, C2), 75.4 (CH_2(OBn)), 74.2 (CH_2(OBn)), 73.5 (CH_2(OBn)), 70.5 (C6), 69.7 (C5), 60.6 (dd, $^4J_{1,F}$=4.4, $^4J_{1,F}$=4.8, C1) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ=−112.78 (ddd, 1F, $^3J_{F'',4}$=12.2, $^3J_{F'',2}$=12.2, $^1J_{F'',F'}$=269.9, F″), −114.80 (ddd, 1F, $^3J_{F',4}$=12.0, $^3J_{F',2}$=12.0, $^1J_{F',F''}$=269.9, F′) ppm; MS (ESI-MeOH): *m*/*z* (%)=473.3 ($[M+H]^+$, 6), 490.3 ($[M+NH_4]^+$, 28), 495.4 ($[M+Na]^+$, 36), 728.6 ($[M_3+K, H]^{2+}$, 7), 966.9 ($[M_2+Na]^+$, 100); analysis for $C_{27}H_{30}F_2O_5$ (472.52): calcd: C, 68.63; H, 6.40; found: C, 68.45; H, 6.63.

4.10. 2,4,6-Tri-*O*-benzyl-3-deoxy-3,3-difluoro-D-*erythro*-hexos-5-ulose (12)

To a mixture of dry DMSO (1.23 g, 15.86 mmol) and anhyd dichloromethane (11.0 ml) at −78 °C a solution of trifluoroacetic anhydride (2.29 ml, 11.26 mmol) in anhyd dichloromethane (2.0 ml) was added dropwise under argon and the mixture was stirred for 45 min at −78 °C. A solution of **11** (660 mg, 1.40 mmol) in anhyd dichloromethane (11 ml) was added dropwise and stirring was continued at −78 °C for 2 h followed by a solution of Et_3N (2.9 ml, 20.94 mmol) in anhyd dichloromethane (11.0 ml). After stirring at −78 °C for 30 min and 1 h at 25 °C, followed by usual aq work-up, the remaining residue was subjected to chromatography (silica gel, hexane/ethyl acetate=5:3) to afford **12** (370 mg, 56.5%) as a mixture of dicarbonyl compound and its corresponding hydrates; white foam; $[\alpha]_D$ −13.22 (*c* 0.25, MeOH); R_f (hexane/ethyl acetate=5:3) 0.35; IR (KBr): ν=3418s, 2919s, 1732s, 1583w, 1454m, 1384m, 1268s, 1097s, 738w, 712m cm^{-1}; MS (ESI-MeOH): *m*/*z* (%)=504.3 ($[M+NH_4, H_2O]^+$, 43), 509.5 ($[M+Na, H_2O]^+$, 76), 518.3 ($[M+NH_4, MeOH]^+$, 58), 523.4 ($[M+Na, MeOH]^+$, 100), 567.3 ($[M+NH_4, (MeOH)_2, H_2O]^+$, 58), 599.4 ($[M+NH_4, (MeOH)_3, H_2O]^+$, 30), 994.9 ($[M_2+Na, (H_2O)_2]^+$, 58), 1008.9 ($[M_2+NH_4, (H_2O)_2]^+$, 44).

4.11. *N*-Benzyl-2,4,6-tri-*O*-benzyl-1,3,5-trideoxy-3,3-difluoro-1,5-imino-D-*ribo*-hexitol (13) and *N*-benzyl-2,4,6-tri-*O*-benzyl-1,3,5-trideoxy-3,3-difluoro-1,5-imino-L-*lyxo*-hexitol (14)

To a solution of **12** (370 mg, 0.79 mmol) in abs methanol (7.0 ml), sodium sulfate (1.00 g) was added and the solution cooled to −78 °C. A solution of benzylamine (103 μl, 0.95 mmol) and acetic acid (135 μl, 2.34 mmol) in abs methanol (7.0 ml) was added and the mixture was stirred for 2 h at this temperature. Sodium cyanobohydride (109 mg, 1.74 mmol) was added in small portions and the suspension was stirred for another 2 h. The solution was allowed to warm to 25 °C and stirring was continued for additional 24 h followed by 48 h at 50 °C. Methanol (30 ml) was added and the suspension was filtered through a thin layer of silica gel. The solvents were evaporated, the remaining residue was dissolved in dichloromethane (50 ml) and was washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution (20 ml each). The organic layer was dried (Na_2SO_4), the solvents were evaporated and the remaining residue was subjected to chromatography (silica gel, hexane/ethyl acetate=85:15) to afford **13** (100 mg, 23.3%) and **14** (70 mg, 16.3%). Data for **13**: colourless oil; $[\alpha]_D$ −33.47 (*c* 0.30, $CHCl_3$); R_f (hexane/ethyl acetate=85:15) 0.51; R_f (hexane/ethyl acetate=5:3) 0.86; IR (film): ν=3088m, 3063m, 3030m, 2922m, 2872m, 2360w, 1953w, 1875w, 1812w, 1737w, 1604w, 1586w, 1496s, 1454s, 1368s, 1321m, 1238s, 1207m, 1070s, 1028s, 1002s, 909w, 853w, 736s, 698s, 607w, 464w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.30–7.12 (m, 20H, Ph), 4.68 (d, 1H, $^2J_{H'',H'}$=11.9, CH''_2(OBn)), 4.67 (d, 1H, $^2J_{H',H''}$=11.9, CH'_2(OBn)), 4.60 (d, 1H, $^2J_{H'',H'}$=12.0, CH''_2(OBn)), 4.50 (d, 1H, $^2J_{H',H''}$=11.9, CH'_2(OBn)), 4.44 (d, 1H, $^2J_{H'',H'}$=12.0, CH''_2(OBn)), 4.40 (d, 1H, $^2J_{H',H''}$=11.9, CH'_2(OBn)), 3.91 (d, 1H, $^2J_{H'',H'}$=13.9, CH''_2(NBn)), 3.85 (dd, 1H, $^3J_{6B,5}$=4.07, $^2J_{6B,6A}$=10.8, H-6_B), 3.70 (dd, 1H, $^3J_{6A,5}$=1.6, $^2J_{6A,6B}$=10.8, H-6_A), 3.67 (m, 1H, H-4), 3.61 (d, 1H, $^2J_{H',H''}$=13.9, CH'_2(NBn)), 3.49 (dddd, 1H, $^3J_{2,F''}$=5.4, $^3J_{2,1B}$=5.2, $^3J_{2,1A}$=10.4, $^3J_{2,F}$=19.5, H-2), 3.37 (m, 1H, H-5), 2.65 (ddd, 1H, $^4J_{1B,F}$=2.2, $^3J_{1B,2}$=5.2, $^2J_{1B,1A}$=11.7, H-1_B), 2.57 (dd, 1H, $^3J_{1A,2}$=10.4, $^2J_{1A,1B}$=11.7, H-1_A) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=139.1 (Ph), 138.4 (Ph), 137.7 (Ph), 137.5 (C(ar(*ipso*; NBn))), 128.8 (C_{ar}), 128.7 (C_{ar}), 128.4 (C_{ar}), 128.7 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 128.0 (C_{ar}), 127.9 (C_{ar}), 127.8 (C_{ar}), 127.7 (C_{ar}), 127.7 (C_{ar}), 127.6 (C_{ar}), 127.5 (C_{ar}), 127.0 (C_{ar}), 121.1 (dd, $^1J_{3,F}$=251.5, $^1J_{3,F}$=251.0, C3), 75.8 (dd, $^3J_{4,F}$=18.7, $^3J_{4,F}$=18.7, C4), 74.5 (dd, $^3J_{2,F}$=18.7, $^3J_{2,F}$=19.2, C2), 73.4 (CH_2(OBn)), 73.4 (CH_2(OBn)), 73.1 (CH_2(OBn)), 66.8 (C6), 60.6 (d, $^4J_{5,F}$=6.3, C5), 58.9 (CH_2(NBn)), 46.9 (C1) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ=−114.02 (d, 1F, $^1J_{F'',F'}$=245.6, F″), −130.10 (dd, 1F, $^3J_{F',H}$=15.9, $^1J_{F',F''}$=245.6, F′) ppm; MS (ESI-MeOH): *m*/*z* (%)=544.3 ($[M+H]^+$, 100), 566.4 ($[M+Na]^+$, 4); analysis for $C_{34}H_{35}F_2NO_3$ (543.64): calcd: C, 75.12; H, 6.49; N, 2.58; found: C, 75.01; H, 6.62; N, 2.41.

Data for **14**: colourless oil; $[\alpha]_D$ +5.00 (*c* 0.35 g, $CHCl_3$); R_f (hexane/ethyl acetate=85:15) 0.43; R_f (hexane/ethyl acetate=5:3) 0.84; IR (film): ν=3063m, 3031m, 2920m, 1738w, 1604w, 1496m, 1454s, 1365m, 1318m, 1241s, 1107s, 1028s, 1004m, 844m, 737s, 698s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.36–7.18 (m, 20H, Ph), 4.89 (d, 1H, $^2J_{H'',H'}$=10.9, C*H*″$_2$(OBn)), 4.74 (d, 1H, $^2J_{H'',H'}$=12.0, C*H*″$_2$(OBn)), 4.57 (d, 1H, $^2J_{H',H''}$=12.0, C*H*′$_2$(OBn)), 4.51 (d, 1H, $^2J_{H',H''}$=10.9, C*H*′$_2$(OBn)), 4.44 (d, 1H, $^2J_{H'',H'}$=12.1, C*H*″$_2$(OBn)), 4.38 (d, 1H, $^2J_{H',H''}$=12.1, C*H*′$_2$(OBn)), 4.02 (d, 1H, $^2J_{H'',H'}$=13.6, C*H*″$_2$(NBn)), 3.79 (ddd, 1H, $^3J_{4,F''}$=3.8, $^3J_{4,5}$=9.9, $^3J_{4,F'}$=19.9, H-4), 3.77 (dd, 1H, $^3J_{6B,5}$=1.8, $^2J_{6B,6A}$=10.7, H-6$_B$), 3.72 (dd, 1H, $^3J_{6A,5}$=3.3, $^2J_{6A,6B}$=10.7, H-6$_A$), 3.63 (m, 1H, $^3J_{2,F}$=19.9, H-2), 3.33 (d, 1H, $^2J_{H',H''}$=12.6, C*H*′$_2$(NBn)), 2.88 (ddd, 1H, $^4J_{1B,F}$=3.58, $^3J_{1B,2}$=4.6, $^2J_{1B,1A}$=11.2, H-1$_B$), 2.55 (ddd, 1H, $^3J_{5,6B}$=1.8, $^3J_{5,4}$=9.9, $^3J_{5,6A}$=3.3, H-5), 2.26 (dd, 1H, $^3J_{1A,2}$=1.2, $^2J_{1A,1B}$=11.2, H-1$_A$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=137.9 (Ph), 137.7 (Ph), 137.6 (Ph), 137.5 (Ph), 128.9 (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}), 127.1 (C_{ar}), 121.7 (dd, $^1J_{3,F}$=246.1, $^1J_{3,F}$=246.1, C3), 76.0 (m, C4), 75.4 (*C*H$_2$(OBn)), 74.1 (dd, $^3J_{2,F}$=17.3, $^3J_{2,F}$=18.7, C2), 73.3 (*C*H$_2$(OBn)), 73.3 (*C*H$_2$(OBn)), 65.5 (C6), 62.7 (d, $^4J_{5,F}$=6.3, C5), 56.1 (*C*H$_2$(NBn)), 52.3 (d, $^4J_{1,F}$=3.0, C1) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ=−113.95 (d, 1F, $^1J_{F'',F'}$=238.1, F″), −135.63 (ddd, 1F, $^3J_{F',4}$=19.9, $^3J_{F',2}$=19.9, $^1J_{F',F''}$=238.1, F′) ppm; MS (ESI-MeOH): *m*/*z* (%)=544.3 ($[M+H]^+$, 100), 566.3 ($[M+Na]^+$, 10); analysis for $C_{34}H_{35}F_2NO_3$ (543.64): calcd: C, 75.12; H, 6.49; N, 2.58; found: C, 74.98; H, 6.69; N, 2.38.

4.12. 3,3-Difluoro-1,3-dideoxynojirimycin (15)

A solution of **13** (170 mg, 0.31 mmol) in dry methanol (22.0 ml) containing palladium on charcoal (10%; 120 mg) was hydrogenated (35 °C, 4.43 atm, 72 h). The solution was filtered through a Celite pad and this pad was washed with methanol (2×30 ml). The combined organic phases were dried ($MgSO_4$), the solvent was removed and the residue subjected to chromatography (silica gel, methanol/ethyl acetate=20:80) to afford **15** (50 mg, 87.3%) as a white foam; $[\alpha]_D$ +3.71 (*c* 0.59, MeOH); R_f (methanol/ethyl acetate=10:90) 0.10; R_f (methanol/ethyl acetate=20:80) 0.32; IR (film): ν=3257s, 2010w, 1822w, 1457s, 1363s, 1317s, 1274s, 1242s, 1110w, 1058m, 977s, 935s, 708w, 541w, 491w cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ=4.00 (m, 2H, H-2, H-4), 3.77 (m, 2H, H-6$_B$, H-6$_A$), 2.80 (m, 1H, H-1$_B$), 3.15–3.10 (m, 2H, H-1$_A$, H-5) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ=116.4 (dd, $^1J_{3,F}$=242.4, $^1J_{3,F}$=260.6, C3), 67.9–66.7 (m, C2, C4), 59.5 (C6), 59.3 (d, $^4J_{5,F}$=5.7, C5), 47.1 (d, $^4J_{1,F}$=5.3, C1) ppm; ^{19}F NMR (188 MHz, CD_3OD): δ=−114.81 (d, 1F, $^1J_{F'',F'}$=261.0, F″), −119.80 (d, 1F, $^1J_{F',F''}$=261.0, F′) ppm; MS (ESI-MeOH): *m*/*z* (%)=184.3 ($[M+H]^+$, 100), 194.9 ($[M_2+H, Na]^{2+}$, 24); analysis for $C_6H_{11}F_2NO_3$ (183.15): calcd: C, 39.35; H, 6.01; N, 7.65; found: C, 39.21; H, 6.18; N, 7.48.

4.13. 3,3-Difluoro-1,3-dideoxy-L-idonojirimycin (16)

Hydrogenation of **14** (110 mg, 0.20 mmol) in the presence of palladium on charcoal (10%, 200 mg) as described above afforded **16** (30 mg, 81.0%) as a colourless oil; $[\alpha]_D$ +13.19 (*c* 0.35, MeOH); R_f (methanol/ethyl acetate=10:90) 0.08; R_f (methanol/ethyl acetate=20:80) 0.23; IR (film): ν=3264m, 2019w, 1806w, 1570w, 1455m, 1319m, 1242m, 1140m, 1010m, 944s, 912s, 850s, 705m, 604w, 540w, 491w cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ=3.86–3.75 (m, 3H, H-6$_B$, H-6$_A$, H-2), 3.68 (ddd, 1H, $^3J_{4,F''}$=4.1, $^3J_{4,5}$=10.5, $^3J_{4,F'}$=21.1, H-4), 3.20 (ddd, 1H, $^3J_{5,6B}$=4.8, $^3J_{5,4}$=10.5, $^3J_{5,6A}$=4.53, H-5), 2.85 (ddd, 1H, $^4J_{1B,F}$=3.9, $^3J_{1B,2}$=3.4, $^2J_{1B,1A}$=11.3, H-1$_B$), 2.78 (dd, 1H, $^3J_{1A,2}$=11.9, $^2J_{1A,1B}$=11.3, H-1$_A$) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ=119.5 (dd, $^1J_{3,F}$=249.1, $^1J_{3,F}$=246.2, C3), 67.8–66.4 (m, C2, C4), 59.1 (C5), 59.0 (C6), 46.7 (d, $^4J_{1,F}$=6.3, C1) ppm; ^{19}F NMR (188 MHz, CD_3OD): δ=−121.98 (d, 1F, $^1J_{F'',F'}$=237.7, F″), −141.67 (ddd, 1F, $^3J_{F',4}$=21.1, $^3J_{F',2}$=21.1, $^1J_{F',F''}$=237.7, F′) ppm; MS (ESI-MeOH): *m*/*z* (%)=184.3 ($[M+H]^+$, 100), 194.9 ($[M_2+H, Na]^{2+}$, 40); analysis for $C_6H_{11}F_2NO_3$ (183.15): calcd: C, 39.35; H, 6.01; N, 7.65; found: C, 39.28; H, 6.21; N, 7.59.

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