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Carbohydrate Research 342 (2007) 1689–1703
Carbohydrate RESEARCH

gem-Difluoro-carbasugars, the cases of mannopyranose and galactopyranose

João Sardinha,[a,b] Samuel Guieu,[a] Aurélie Deleuze,[a] M. Carmen Fernández-Alonso,[c] Amelia Pilar Rauter,[b] Pierre Sinaÿ,[a] Jérôme Marrot,[d] Jesús Jiménez-Barbero[c] and Matthieu Sollogoub[a,*]

[a]*Université Pierre et Marie Curie-Paris 6, Institut de Chimie Moléculaire (FR 2769), ENS, UMR CNRS 8642, 75005 Paris, France*
[b]*Departamento de Química e Bioquímica, Faculdade de Ciências da Universidade de Lisboa, Edifício C8, 5º Piso, 1749-016 Lisboa, Portugal*
[c]*Departamento de Estructura y Función de Proteínas, Centro de Investigaciones Biológicas, CSIC, Ramiro de Maeztu 9, 28040 Madrid, Spain*
[d]*Institut Lavoisier, Université de Versailles-Saint-Quentin, 45, Avenue des Etats-Unis, 78035 Versailles Cedex, France*

Received 13 February 2007; received in revised form 7 May 2007; accepted 11 May 2007
Available online 23 May 2007

Abstract—5a-Difluoro-5a-carbamannopyranose (*gem*-difluoro-carbamannopyranose) and 5a-difluoro-5a-carbagalactopyranose (*gem*-difluoro-carbagalactopyranose), close congeners of their respective natural sugars, in which the endocyclic oxygen atom has been replaced by a *gem*-difluoromethylene group, were synthesized from D-mannose and D-galactose, using a rearrangement strategy.

Keywords: Carbasugars; Fluorine; Mimics; Inositol

1. Introduction

Carbasugars are strictly defined as sugar analogues in which the endocyclic oxygen atom has been replaced by a methylene group. This family of sugar mimics has found its application as conformational probes of the bound state of carbohydrates linked to proteins.[1] The conversion of the acetal function of the sugar into an ether, making the glycosidic bond stable to hydrolysis, is the underlying principle of this application. However, it is obvious that these compounds, as *C*-glycosyl compounds,[2] show distinct structural features to those present in natural oligosaccharides, especially regarding the stereoelectronic effects at the anomeric centre.[3] Moreover, the interaction of saccharides with receptors requires the presentation of key polar regions to be recognized by the corresponding proteins,[4] in addition to the frequently found sugar–aromatic interaction.[5] To overcome this disadvantage we envisaged the synthesis of fluorinated analogues, which would hopefully induce conformational bias through stereoelectronic effects as well as provide key polar groups for the interaction with potential receptors.[6] We have first synthesized 5a,5a′-difluoro-5a-carbaglucopyranose (*gem*-difluoro-carbaglucose)[7] and we wish to present herein the synthesis of *gem*-difluoro-carbamannopyranose and *gem*-difluoro-carbagalactopyranose (Fig. 1).

Our strategy is based on a Lewis acid induced rearrangement of an enolether possessing an electron-donating group as illustrated in Scheme 1.[8]

We successfully applied this reaction to the synthesis of carbasugars, carbadisaccharides[9] and more recently to *gem*-difluoro-carbaglucose.[7] In this case, we used an original electron-donating group: a cobalt cluster that is conveniently also a precursor of the CH_2OH

* Corresponding author. Tel.: +33 1 44 32 33 35; e-mail: matthieu.sollogoub@upmc.fr

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doi:10.1016/j.carres.2007.05.021

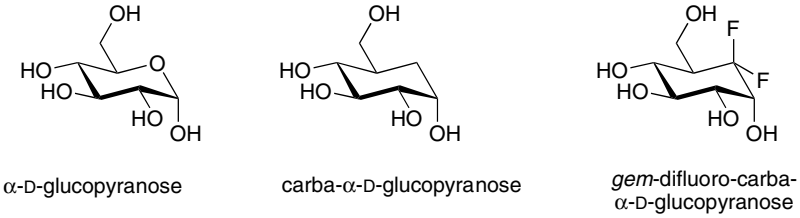
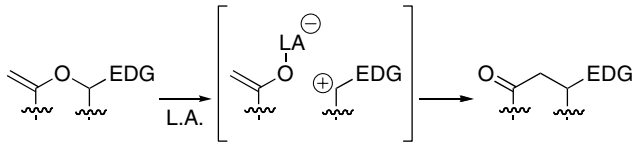


Figure 1. α-D-Glucopyranose and its carbocyclic analogues.



Scheme 1. General scheme for the Lewis acid induced rearrangement.

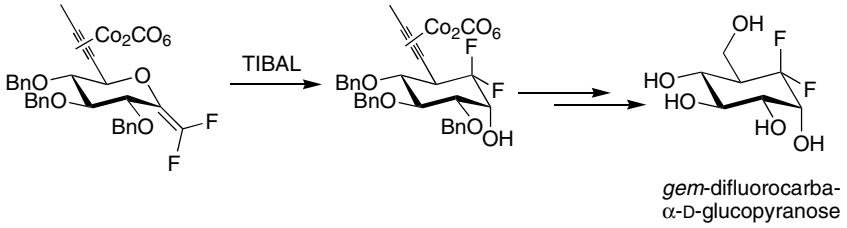
function that will be needed further on in the synthesis. The selected Lewis acid was the triisobutylaluminium (TIBAL), which also conveniently reduces in situ the formed ketone (Scheme 2).

2. Results and discussion

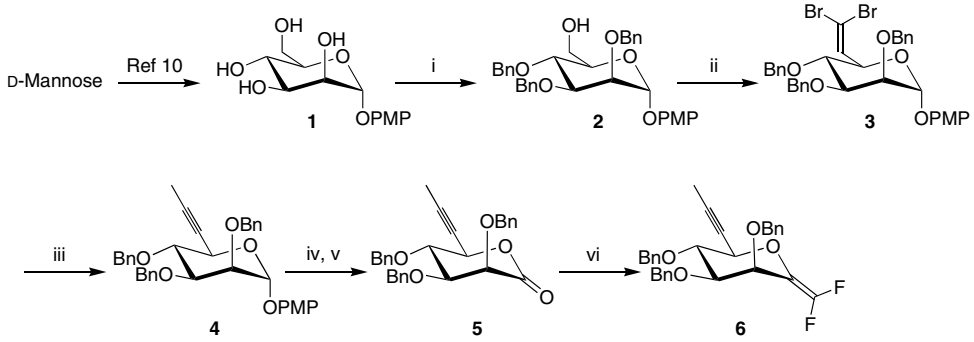
2.1. Synthesis of *gem*-difluoro-α-D-carbamannopyranose

Starting from known *para*-methoxyphenyl mannopyranoside **1**,[10] efficiently synthesized from D-mannose, the protected alcohol **2** was prepared in 68% yield, through a selective silylation, benzylation and desilylation sequence. After Swern oxidation of the primary alcohol of **2**, the triple bond was installed via a Corey–Fuchs reaction[11] and methylation of the alkyne afforded **4**. Cleavage of the *para*-methoxyphenyl (PMP) group and subsequent oxidation allowed the formation of lactone **5**, which was then transformed into the key difluoroalkene **6** in 89% yield (Scheme 3).

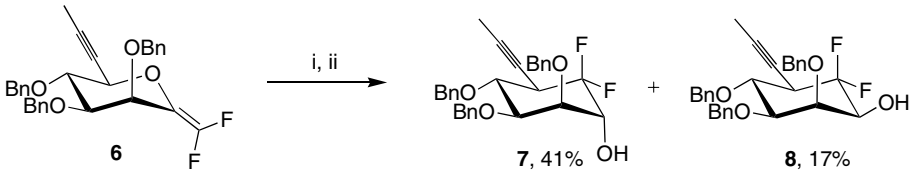
The key intermediate **6** was next engaged in the rearrangement step through cobalt cluster formation, followed by the addition of TIBAL in the same pot. Removal of the cobalt on the transient carbocyclic cluster afforded 58% of rearranged product as a 3:1 mixture of two isomers, **7** and **8**, respectively. The presence of the axial benzyloxy group induces a lower stereoselectivity of the reduction of the transient ketone compared to that obtained in the *gluco* series (Scheme 4).



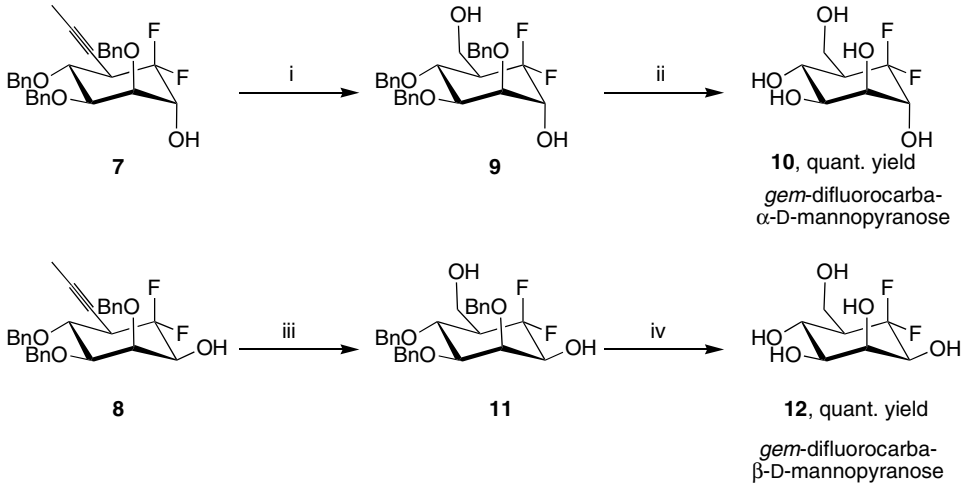
Scheme 2. Rearrangement-based strategy towards *gem*-difluoro-carbasugars.



Scheme 3. Synthesis of difluoroalkene **6**. Reagents and conditions: (i) (1) TBDMSCl, DMAP, pyridine, rt, 150 min; (2) BnBr, NaH, DMF, rt, 16 h; (3) TBAF, THF, rt, 2 h, 68% over three steps; (ii) (1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C to rt, 2 h; (2) CBr_4, PPh_3, CH_2Cl_2, rt, 4 h, 68% over 2 steps; (iii) (1) BuLi, THF, −78 °C to −20 °C, 2 h; (2) MeI, HMPA, −78 °C to rt, 17 h, 79%; (iv) CAN, CH_3CN–H_2O–toluene (1:1:1), 0 °C, 1 h, 70%; (v) PCC, MS 4 Å, CH_2Cl_2, rt, 1 h, 83%; (vi) CBr_2F_2, HMPT, THF, rt, 89%.



Scheme 4. Rearrangement of difluoroalkene **6**. Reagents and conditions: (i) (1) $Co_2(CO)_8$, CH_2Cl_2, 1 h; (2) TIBAL, CH_2Cl_2, rt, 1 h; (ii) CAN, Et_3N, acetone, 2 h, 58% (**7**:**8**, 3:1).



Scheme 5. Synthesis of *gem*-difluoro-α and β-D-carbamannopyranose. Reagents and conditions: (i) (1) Pd–$CaCO_3$, H_2, EtOAc, 2 h; (2) O_3, CH_2Cl_2, −78 °C, 2 min; (3) $NaBH_4$, CH_2Cl_2–EtOH (1:5), rt, 45 min, 38% over three steps; (ii) Pd–C, H_2, MeOH, 3 h, quant. yield; (iii) (1) Pd–$CaCO_3$, H_2, EtOAc, 2 h; (2) O_3, CH_2Cl_2, −78 °C, 2 min; (3) $NaBH_4$, CH_2Cl_2–EtOH (1:5), rt, 30 min, 62% over three steps; (iv) Pd–C, H_2, MeOH, 6 h, quant. yield.

Both isomers **7** and **8** were next easily converted into *gem*-difluoro-α- and -β-D-carbamannopyranoses (**10** and **12**) through a partial hydrogenation of the triple bond and then reductive ozonolysis, which afforded **9** and **11** in 38% and 62% yield, respectively. Final deprotective hydrogenolysis of **9** and **11** yielded *gem*-difluoro-α-D-carbamannopyranose **10** and *gem*-difluoro-β-D-carbamannopyranose **12**, respectively (Scheme 5).

2.2. Synthesis of *gem*-difluoro-carba-α and β-D-galactopyranoses

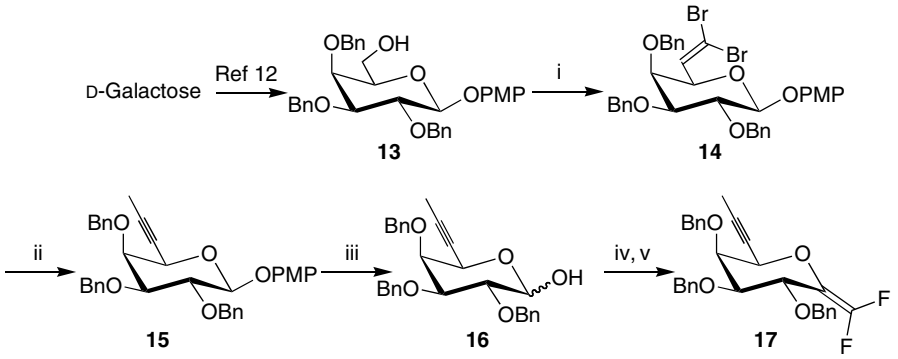
The known primary alcohol **13**, obtained from D-galactose according to the literature,[12] was transformed into the methylated alkyne **15** through Swern oxidation and Corey–Fuchs reaction. The PMP group was cleaved to obtain the corresponding free sugar, oxidation and olefination of the lactone afforded the key *gem*-difluoroalkene **17** (Scheme 6).

Formation of the cluster on **17**, followed by TIBAL induced rearrangement and subsequent removal of the cobalt afforded the carbocyclic products, **18** and **19**, as an almost 1:1 mixture of axial and equatorial alcohols in 64% yield (Scheme 7).

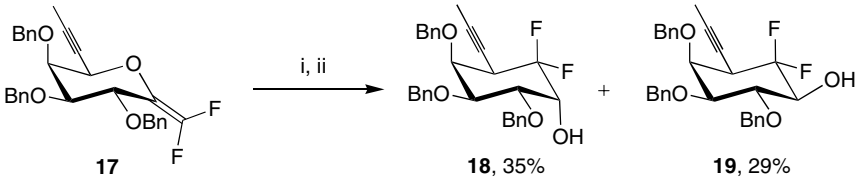
The usual partial hydrogenation and reductive ozonolysis of **18** afforded a diol that was difficult to analyse spectroscopically. We hence isolated its acetylated derivative **20**, which could be fully characterized; its full deprotection afforded *gem*-difluoro-carba-α-D-galactopyranose **21**. The equatorial isomer **19** on the other hand was converted into *gem*-difluoro-carba-β-D-galactopyranose **23** in the usual straightforward manner (Scheme 8).

2.3. Structural studies

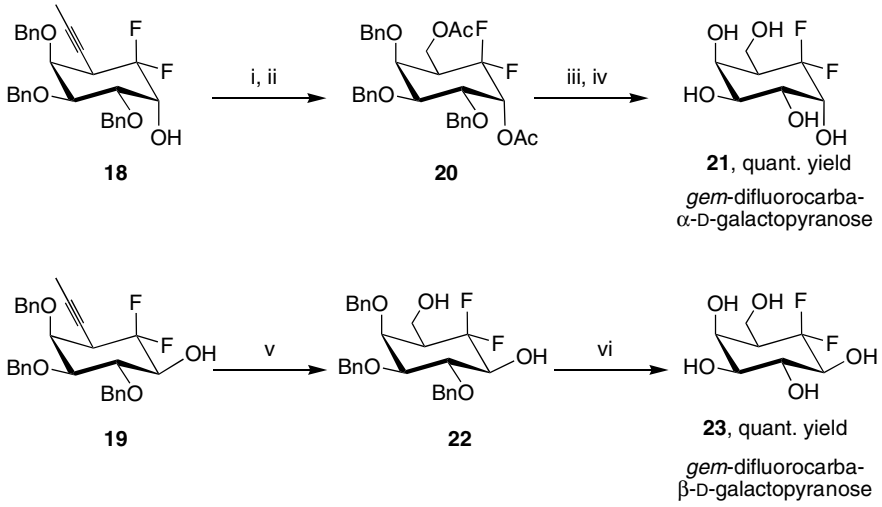
The structure of these molecules was studied by means of X-ray crystallography and ab initio calculations to ascertain the possible steric and stereoelectronic factors associated with the presence of the difluoromethylene group. It is well known that the presence of the anomeric effect strongly modifies the structural properties of pyranose rings, especially in the vicinity of the anomeric centre. Two different levels of theory were employed for comparison purposes. The key structural data for the four compounds are given in Table 1, while the coordinates are gathered in Supplementary data and are available from the authors upon request.



Scheme 6. Synthesis of difluoroalkene **17**. Reagents and conditions: (i) (1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 2 h; (2) CBr_4, PPh_3, CH_2Cl_2, 0 °C→rt, 3 h, 71% over 2 steps; (ii) (1) BuLi, THF, −78 °C to −40 °C, 2 h; (2) MeI, HMPA, −78 °C to rt, 48 h, 78%; (iii) CAN, acetone–H_2O (3:1), 5 min; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt; (v) CBr_2F_2, HMPT, THF, −10 °C to rt, 33%, over 3 steps.



Scheme 7. Rearrangement of difluoroalkene **17**. Reagents and conditions: (i) (1) $Co_2(CO)_8$, CH_2Cl_2, 1 h; (2) TIBAL, CH_2Cl_2, −78 °C to rt, 45 min; (ii) CAN, Et_3N, acetone, 30 min, 64% over three steps.



Scheme 8. Synthesis of *gem*-difluoro-carba-α- and -β-D-galactopyranose. Reagents and conditions: (i) (1) Pd–$CaCO_3$, H_2, EtOAc, 2 h; (2) O_3, CH_2Cl_2, −78 °C, 2 min; (3) $NaBH_4$, CH_2Cl_2–EtOH (1:5), 57% over three steps; (ii) Ac_2O, pyr, 2 h, rt, quant. yield; (iii) MeONa, MeOH, 1 h, rt, quant. yield; (iv) Pd–C, H_2, MeOH, 3 h, quant. yield; (v) (1) Pd–$CaCO_3$, H_2, EtOAc, 2 h; (2) O_3, CH_2Cl_2, −78 °C, 2 min; (3) $NaBH_4$, CH_2Cl_2–EtOH (1:5), 51% over three steps; (vi) Pd–C, H_2, MeOH, 3 h, quant. yield.

According to the interatomic distances, it can be observed that the six-membered ring does not suffer any noticeable distortion. All the C–C bonds range between 1.514 and 1.529 Å, independently of the configuration of the centres or the presence of the *gem*-difluoro moiety, and of the theoretical or experimental method employed. A maximum difference of 0.04 Å is observed for C–C bonds between the X-ray experimental and predicted data. For the C–O distances, the maximum discrepancy amounts to 0.01 Å (MP2) or 0.10 Å (QCISD). According to the calculations, a small decrease of the C1–O1 distance is observed in the two

Table 1. Structural data for the *gem*-difluoro derivatives synthesized in the present work, obtained from X-ray crystallography and theoretical calculations[a]

Bond distance (Å)	Compound							
	α-Man (**10**)		β-Man (**12**)		α-Gal (**21**)			β-Gal (**23**)
	QCISD	MP2	MP2	QCISD	QCISD	MP2	X-ray	MP2
C1–C2	1.533	1.529	1.527	1.530	1.527	1.523	1.525	1.518
C1–CF_2	1.527	1.523	1.527	1.530	1.521	1.517	1.516	1.515
C5–CF_2	1.523	1.518	1.520	1.525	1.521	1.515	1.514	1.521
C2–C3	1.527	1.523	1.519	1.523	1.529	1.525	1.529	1.521
C1–O1	1.423	1.424	1.409	1.408	1.415	1.416	1.421	1.411
C2–O2	1.416	1.417	1.425	1.424	1.422	1.423	1.432	1.422
C3–O3	1.423	1.425	1.422	1.421	1.423	1.424	1.426	1.423
C4–O4	1.433	1.434	1.433	1.432	1.434	1.435	1.433	1.434
F_{ax}–CF	*1.375*	*1.377*	*1.379*	*1.377*	*1.399*	*1.403*	*1.381*	*1.396*
F_{eq}–CF	*1.383*	*1.386*	*1.388*	*1.384*	*1.373*	*1.376*	*1.369*	*1.377*

[a] Geometry optimizations at MP2/6-31G level (MP2 column) with GAUSSIAN98, as well as single-and double-quadratic configuration interaction (QCISD column) theory were used to calculate geometrical parameters. This latter method represents a higher level treatment of electron correlation, which usually provides greater accuracy. Frequency calculations for each conformer were performed to assess their validity as proper minima.[13]

β-OH galactose and mannose derivatives, with respect to the rest of the C–O bonds in the two molecules. Moreover, the distance becomes the usual one (1.42–1.43 Å), when the calculations are performed for the monofluoro analogues (both at axial or equatorial orientations, data not shown). Therefore, it seems that there is an influence of the *gem*-difluoro moiety on the C1–O1 distance for the equatorial derivatives.

The existence of stereoelectronic effects is more evident at the *gem*-difluoro centre, which obviously contains two strongly electronegative atoms attached to one carbon atom.[14] One of the C–F bonds is clearly shorter than the other one, resembling the anomeric centre in regular pyranoses. This fact is also clearly observed in the X-ray structure of **21** (Fig. 2). Nevertheless, the differences are more evident when the QCISD and the MP2 protocols (0.026–0.027 Å) are used than for the X-ray experimental technique (0.012 Å). The C–F distances are 0.003–0.004 Å shorter for the QCISD than for the MP2 method, approaching the experimental distances in the solid state. Regarding the difference between the equatorial and axial C–F bonds, the predicted difference is even more evident for the galactose derivatives. Curiously, the F_{eq}–CF distance is shorter than the F_{ax}–CF one for the galactose derivatives, according to both theoretical and experimental data, while the opposite trend is calculated for the mannose analogues, for which the F_{ax}–CF bond is predicted to be shorter. Previous X-ray analysis of other *gem*-difluoro cyclohexanone-like compounds have shown similar distances for the pseudoaxial and pseudoequatorial C–F linkages (only 0.006 Å).[15] The corresponding distances for the monofluoro analogues are always noticeably larger (between 1.41 and 1.43 Å), thus indicating the existence of stereoelectronic effects at the *gem*-difluoro moiety.

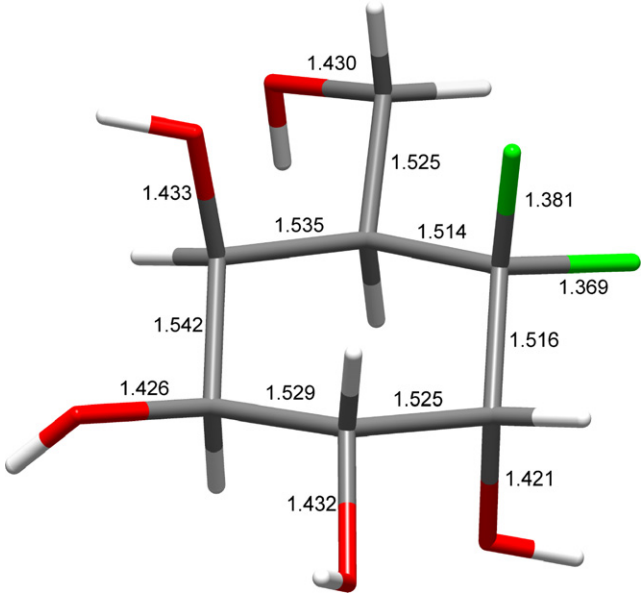


Figure 2. X-ray structure of compound **21**.

2.4. Conclusion

In conclusion, we have synthesized, four new *gem*-difluoro-carbasugars analogues of mannose and galactose, and shown that some electronic effects were induced by the CF_2 moiety, slightly modifying interatomic bond distances. We now have to convert these compounds into disaccharide or glycoconjugate mimics, such as lactosamine or psychosine, which will be attractive candidates for probing the capacity of the CF_2 group to mimic the carbohydrate endocyclic oxygen particularly in terms of conformation of the aglycon, an important feature for efficient sugar–protein interactions.[16]

3. Experimental

3.1. General

Optical rotations were measured at 20 ± 2 °C with a Perkin–Elmer Model 241 digital polarimeter, using a 10 cm, 1 mL cell. Mass spectra (CI (ammonia) and FAB) were obtained with a JMS-700 spectrometer. ^{1}H NMR spectra were recorded at 250 MHz with a Brüker AC-250 or at 400 MHz with a Brüker DRX 400 for solns in $CDCl_3$, CD_3OD, C_6D_6 or D_2O at room temperature. Assignments were confirmed by COSY experiments. ^{13}C NMR spectra were recorded at 63 MHz with a Brüker AC-250 or at 100.6 MHz with a Bruker DRX 400 spectrometer. Assignments were confirmed by J-mod technique and HMQC. ^{19}F NMR spectra were recorded at 235 MHz with a Brüker AC-250. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of Silica Gel 60 F_{254} (layer thickness 0.2 mm; E. Merck, Darmstadt, Germany) and detection by charring with H_2SO_4 or with 0.2% w/v cerium sulfate and 5% ammonium molybdate in 2 M H_2SO_4. Flash column chromatography was performed on Silica Gel 60 (230–400 mesh, E. Merck). TIBAL was purchased from Aldrich as 1 M solution in toluene.

3.2. *para*-Methoxyphenyl 2,3,4-tri-*O*-benzyl-α-D-manno-pyranoside (2)

TBDMSCl (1.48 g, 7.70 mmol) and *N*,*N*-dimethylaminopyridine (50 mg, 0.41 mmol) were added to a solution of **1** (2.00 g, 7.00 mmol) in pyridine (11 mL) at 0 °C under argon. After stirring for 3 h at room temperature, the mixture was diluted with EtOAc (10 mL), washed with a satd soln of NH_4Cl (10 mL) and aq $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The product (white solid) was directly engaged in the next step ($R_f = 0.8$, EtOAc/^{i}PrOH/H_2O, 3:3:1). NaH (856 mg, 21.4 mmol) was added to a solution of the product of the previous step (1.90 g, 4.75 mmol) in DMF (40 mL) at 0 °C, and after 15 min BnBr (2.00 mL, 17.1 mmol) was added. After stirring for 16 h at room temperature, MeOH (10 mL) was added and the mixture was concentrated in vacuo. The product (yellow oil) was directly engaged in the next step ($R_f = 0.7$, cyclohexane–EtOAc, 2:1). TBAF (3.00 g, 9.5 mmol) was added to a solution of the product of the previous step (3.18 g, 4.75 mmol) in THF (5 mL). After 2 h, EtOAc (20 mL) and water (30 mL) were added, and the aqueous layer was extracted with EtOAc (2×20 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (cyclohexane–EtOAc, 4:1) of the residue gave **2** (1.79 g, 68% over 3 steps) as a white solid: mp 79–80 °C (cyclohexane–EtOAc); $[\alpha]_D^{20}$ +79.3 (*c* 0.10, $CHCl_3$); $R_f = 0.1$ (cyclohexane–EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46–7.35 (m, 15H, H arom. Bn), 6.96 (d, 2H, $J = 9.1$ Hz, H arom. OPMP), 6.86 (d, 2H, $J = 9.2$ Hz, H arom. OPMP), 5.48 (d, 1H, $J_{1,2} = 1.9$ Hz, H-1), 5.03 (d, 1H, $J = 10.9$ Hz, CHPh), 4.90 (d, 1H, $J = 12.3$ Hz, CHPh), 4.81 (d, 1H, $J = 11.7$ Hz, CHPh), 4.80 (d, 1H, $J = 12.4$ Hz, CHPh), 4.77 (d, 1H, $J = 11.8$ Hz, CHPh), 4.76 (d, 1H, $J = 10.9$ Hz, CHPh), 4.19 (dd, 1H, $J_{2,3} = 2.8$, $J_{3,4} = 9.3$ Hz, H-3), 4.15 (t, 1H, $J_{3,4} = J_{4,5} = 9.2$ Hz, H-4), 4.03 (t, 1H, $J_{1,2} = J_{2,3} = 2.3$ Hz, H-2), 3.85–3.82 (m, 3H, H-5, H-6a, H-6b), 3.81 (s, 3H, OCH_3), 2.04 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.97, 149.94 (2C arom. quat. OPMP), 138.35, 138.27, 138.04 (3C arom. quat. Bn), 128.40–127.62 (15CH arom. Bn), 117.65, 114.58 (4CH arom. OPMP), 97.32 (C-1), 79.87 (C-3), 75.21 (CH_2Ph), 74.71 (C-2), 74.52 (C-4), 73.06 (CH_2Ph), 72.81 (C-5), 72.41 (CH_2Ph), 62.05 (C-6), 55.57 (OCH_3); CIMS *m*/*z*: $[M+NH_4]^+$, 574; CIMS: $[M+NH_4]^+$ calcd for $C_{34}H_{40}O_7N$, 574.2805; found: 574.2808.

3.3. *para*-Methoxyphenyl 2,3,4-tri-*O*-benzyl-7,7-dibromo-6,7-dideoxy-α-D-manno-hept-6-enopyranoside (3)

DMSO (1.13 mL, 15.9 mmol) was added dropwise to a solution of oxalyl chloride (1.18 mL, 13.8 mmol) in CH_2Cl_2 (80 mL) at −60 °C under argon. After 15 min, a mixture of **2** (5.90 g, 10.6 mmol) in CH_2Cl_2 (60 mL) was added dropwise. After 40 min, Et_3N (4.47 mL, 31.8 mmol) was added and the mixture was let warm up to room temperature. After 30 min, water (150 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. The product (yellow oil) was directly engaged in the next step ($R_f = 0.75$ cyclohexane–EtOAc, 1:1). A solution of CBr_4 (7.04 g, 21.2 mmol) in CH_2Cl_2 (60 mL) was added dropwise to a solution of PPh_3 (11.07 g, 42.4 mmol) in CH_2Cl_2 (60 mL) at 0 °C under argon atmosphere. After 20 min, a solution of the product of the previous step (7.23 g, 10.6 mmol) in CH_2Cl_2 (80 mL) was added dropwise and the mixture was let warm up to rt. After 1.5 h, water (150 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (cyclohexane–EtOAc, 6:1) of the residue gave **3** (5.13 g, 68% over 2 steps) as a white solid: mp 82–83 °C (cyclohexane–EtOAc); $[\alpha]_D^{20}$ +66.0 (*c* 0.10, $CHCl_3$); $R_f = 0.7$ (cyclohexane–EtOAc, 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.21 (m, 15H, H arom. Bn), 6.84 (d, 2H, $J = 8.1$ Hz, H arom. OPMP), 6.42 (d, 2H, $J = 9.1$ Hz, H arom. OPMP), 6.37 (d, 1H, $J_{5,6} = 8.7$ Hz, H-6), 5.24 (d, 1H, $J_{1,2} = 1.8$ Hz, H-1), 4.78 (d, 1H, $J = 10.8$ Hz, CHPh), 4.74 (d, 1H, $J = 12.3$ Hz, CHPh), 4.67 (s, 2H, CH_2Ph), 4.62 (d, 1H, $J = 11.6$ Hz, CHPh), 4.60 (d, 1H, $J = 11.0$ Hz, CHPh), 4.41 (t, 1H, $J_{4,5} = J_{5,6} = 9.1$ Hz, H-5), 4.04 (dd, 1H,

$J_{2,3} = 3.0$, $J_{3,4} = 9.4$ Hz, H-3), 3.82 (t, 1H, $J_{3,4} = 9.6$ Hz, H-4), 3.86 (dd, 1H, $J_{1,2} = 1.8$, $J_{2,3} = 3.2$ Hz, H-2), 3.68 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.12, 150.01 (C arom. quat. OPMP), 138.33 (C arom. quat. Bn), 137.92 (2C arom. quat. Bn), 135.67 (C-6), 128.43–127.65 (15CH arom. Bn), 118.08, 114.53 (4CH arom. OPMP), 97.53 (C-1), 95.64 (=CBr_2), 79.42 (C-3), 77.50 (C-4), 75.32 (CH_2Ph), 74.74 (C-2), 73.12 (CH_2Ph), 72.81 (CH_2Ph), 72.63 (C-5), 55.57 (O–CH_3); CIMS *m/z*: $[M+NH_4]^+$, 726.20 (25%), 728.20 (50%), 730.20 (25%); CIMS: $[M+NH_4]^+$ calcd for $C_{35}H_{38}O_6NBr_2$, 726.1066 (49.1%), 728.1049 (100.0%), 730.1038 (55.2%); found, 726.1050 (52.2%), 728.1039 (100.0%), 730.1033 (58.5%).

3.4. *para*-Methoxyphenyl 2,3,4-tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-α-D-manno-octopyranoside (4)

A 2.5 M solution of butyllithium in hexane (3.36 mL, 8.4 mmol) was added dropwise to a solution of **3** (3.00 g, 4.2 mmol) in THF (75 mL) at −70 °C under argon and the mixture was let warm up to 0 °C. After 1 h, iodomethane (5.26 mL, 84.5 mmol) and HMPA (2.94 mL, 16.9 mmol) were added dropwise at −70 °C and the mixture was let warm up to room temperature. After 18 h, diethyl ether (50 mL) and water (100 mL) were added and the aqueous layer was extracted with diethyl ether (3 × 40 mL). The organic layers were combined and washed with a satd soln of $CuSO_4$ (2 × 80 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (cyclohexane–EtOAc, 10:1) of the residue gave **4** (1.878 g, 79%) as a white foam: $[\alpha]_D^{20}$ +66.8 (*c* 1.0, $CHCl_3$); $R_f = 0.4$ (cyclohexane–EtOAc, 4:1); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.46 (m, 15H, H arom. Bn), 6.98 (d, 2H, $J = 9.2$ Hz, H arom. OPMP), 6.86 (d, 2H, $J = 9.2$ Hz, H arom. OPMP), 5.45 (d, 1H, $J_{1,2} = 2.0$ Hz, H-1), 5.02 (d, 1H, $J = 10.6$ Hz, CHPh), 4.95 (d, 1H, $J = 10.6$ Hz, CHPh), 4.87 (d, 1H, $J = 12.5$ Hz, CHPh), 4.83 (d, 1H, $J = 11.7$ Hz, CHPh), 4.82 (d, 1H, $J = 12.4$ Hz, CHPh), 4.74 (d, 1H, $J = 11.7$ Hz, CHPh), 4.51 (dq, 1H, $J_{5,8} = 2.0$, $J_{4,5} = 9.3$ Hz, H-5), 4.11 (dd, 1H, $J_{4,5} = 9.3$, $J_{3,4} = 9.4$ Hz, H-4), 4.05 (dd, 1H, $J_{2,3} = 3.0$, $J_{3,4} = 9.4$ Hz, H-3), 3.97 (dd, 1H, $J_{1,2} = 2.3$, $J_{2,3} = 2.8$ Hz, H-2), 3.82 (s, 3H, OCH_3), 1.93 (d, 3H, $J_{5,8} = 2.2$ Hz, H-8); ^{13}C RMN ($CDCl_3$, 100 MHz): δ 154.98, 149.99 (2C arom. quat. OPMP), 138.47, 138.42, 138.01 (3C arom. quat. Bn), 128.38–127.55 (15CH arom. Bn), 117.50, 114.60 (4CH arom. OPMP), 97.00 (C-1), 81.74 (C alcyn.), 79.10 (C-4), 76.50 (C alcyn.), 78.80 (C-3), 75.50 (CH_2Ph), 74.70 (C-2), 72.90 (CH_2Ph), 72.80 (CH_2Ph), 63.90 (C-5), 55.60 (OCH_3), 3.70 (C-8); CIMS *m/z*: $[M+NH_4]^+$, 582; CIMS: $[M+NH_4]^+$ calcd for $C_{36}H_{40}O_6N$, 582.2856; found, 582.2861. Anal. Calcd for $C_{36}H_{36}O_6$: C, 76.57; H, 6.43. Found: C, 76.13; H, 6.38.

3.5. 2,3,4-Tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-D-manno-octono-1,5-lactone (5)

To a solution of **4** (1.74 g, 3.08 mmol) in a 1:1:1 mixture of H_2O/acetonitrile/toluene, ammonium cerium(IV) nitrate (16.90 g, 30.80 mmol) was added at 0 °C. After 45 min, the mixture was washed with a satd aq $NaHCO_3$ (100 mL), and the aqueous layer was extracted with EtOAc (3 × 40 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. Filtration on silica gel (cyclohexane–EtOAc, 10:1) of the residue gave the lactol as an orange oil (982 mg, 70%). This product was directly engaged in the next step ($R_f = 0.3$ cyclohexane–EtOAc, 2:1). Molecular sieve 4 Å (1.74 g) was added to a solution of the product of the previous step (1.23 g, 2.69 mmol) in CH_2Cl_2 (100 mL). After 30 min, PCC (1.74 g, 8.07 mmol) was added. After 1 h, diethyl ether (100 mL) was added, the mixture filtered through silica gel and concentrated in vacuo. Column chromatography (cyclohexane–EtOAc, 4:1) of the residue gave **5** (820 mg, 67%) as a white solid: mp 94–95 °C (cyclohexane–EtOAc); $[\alpha]_D^{20}$ +10.9 (*c* 1.00, $CHCl_3$); $R_f = 0.5$ (cyclohexane–EtOAc, 2:1); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.44–7.26 (m, 15H, H arom.), 5.08 (d, 1H, $J = 11.9$ Hz, CHPh), 4.84 (d, 1H, $J = 12.3$ Hz, CHPh), 4.81 (qd, 1H, $J_{5,8} = 2.2$, $J_{4,5} = 7.0$ Hz, H-5), 4.68 (d, 1H, $J = 12.3$ Hz, CHPh), 4.63 (d, 1H, $J = 11.9$ Hz, CHPh), 4.56 (d, 1H, $J = 11.7$ Hz, CHPh), 4.51 (d, 1H, $J = 11.7$ Hz, CHPh), 4.34 (d, 1H, $J_{2,3} = 2.8$ Hz, H-2), 4.06 (dd, 1H, $J_{3,4} = 1.7$, $J_{2,3} = 2.4$ Hz, H-3), 3.98 (dd, 1H, $J_{3,4} = 1.2$, $J_{4,5} = 7.2$ Hz, H-4), 1.89 (d, 3H, $J_{5,8} = 2.1$ Hz, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.45 (C-1), 137.58, 137.11, 136.75 (3C arom. quat. Bn), 128.52–127.79 (15CH arom. Bn), 84.86 (C alcyn.), 80.57 (C-4), 77.15 (C-3), 74.97 (C-2), 74.20 (C alcyn.), 72.87 (CH_2Ph), 72.80 (CH_2Ph), 72.50 (CH_2Ph), 69.54 (C-5), 3.67 (C-8); CIMS *m/z*: $[M+NH_4]^+$, 474; CIMS: $[M+NH_4]^+$ calcd for $C_{29}H_{32}O_5N$, 474.2280; found, 474.2283. Anal. Calcd for $C_{29}H_{28}O_5$: C, 76.30; H, 6.18. Found: C, 76.02; H, 5.99.

3.6. 2,6-Anhydro-3,4,5-tri-*O*-benzyl-7,7,8,8-tetradehydro-1,7,8,9-tetradeoxy-1,1-difluoro-D-manno-non-1-enitol (6)

CBr_2F_2 (107 μL, 1.17 mmol) and HMPT (213 μL, 1.17 mmol) were added to a solution of **5** (107 mg, 235 μmol) in THF (10 mL) at −20 °C. The reaction mixture was slowly warm up to 10 °C and a white precipitate appeared, then HMPT (640 μL, 3.52 mmol) was added and the mixture was warm up to room temperature. After 1 h, diethyl ether (10 mL) was added; the mixture was washed with satd soln of $CuSO_4$ (3 × 10 mL), and the organic layer was dried ($MgSO_4$), filtered and concen-

trated in vacuo. Column chromatography (cyclohexane–EtOAc, 6:1) of the residue gave **6** (103 mg, 89%) as a white solid: mp 133–134 °C (cyclohexane–EtOAc); $[\alpha]_D^{20}$ +27.2 (*c* 0.1, $CHCl_3$); $R_f = 0.6$ (cyclohexane–EtOAc, 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45–7.30 (m, 15H, H arom.), 4.97 (s, 2H, CH_2Ph), 4.79 (d, 1H, $J = 12.6$ Hz, CHPh), 4.63 (d, 1H, $J = 11.9$ Hz, CHPh), 4.59 (d, 1H, $J = 11.9$ Hz, CHPh), 4.38 (d, 1H, $J = 12.6$ Hz, CHPh), 4.17–4.12 (m, 2H, H-2, H-5), 4.35 (dd, 1H, $J_{3,4} = 3.0$, $J_{2,3} = 6.1$ Hz, H-3), 3.52 (dd, 1H, $J_{3,4} = 3.7$, $J_{4,5} = 9.1$ Hz, H-4), 1.96 (s, 3H, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.91 (dd, $^1J_{C,F} = 282.3$, $^1J_{C,F'} = 295.7$ Hz, CF_2), 138.24, 137.80, 137.28 (3C arom. quat. Bn), 128.34–127.68 (15CH arom. Bn), 111.75 (dd, $^2J_{C,F} = 13.7$, $^2J_{C,F'} = 41.3$ Hz, C-1), 83.43 (C alcyn.), 80.17 (dd, $^5J_{C,F} = 1.4$, $^5J_{C,F'} = 3.0$ Hz, C-4), 78.26 (C-5), 75.91 (CH_2Ph), 75.38 (C alcyn.), 72.49 (t, $^3J_{C,F} = 2.2$ Hz, C-2), 71.76 (CH_2Ph), 69.87 (CH_2Ph), 67.61 (t, $^4J_{C,F}$ 2.9 Hz, C-3), 3.74 (C-8); ^{19}F NMR ($CDCl_3$, 250 MHz): δ −111.76 (dd, 1F, J 2.4, $J_{F,F'}$ 61.2 Hz), −96.01 (dd, J 2.4, $J_{F,F'}$ 61.2 Hz, Hz) ; CIMS *m/z*: $[M+NH_4]^+$, 508; CIMS: $[M+NH_4]^+$ calcd for $C_{30}H_{32}F_2O_4N$, 508.2299; found, 508.2302.

3.7. Rearrangement of (6) into 2,3,4-tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-5a-difluoro-5a-carba-α-D-manno-octopyranose (7) and 2,3,4-tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-5a-difluoro-5a-carba-β-D-manno-octopyranose (8)

$Co_2(CO)_8$ (50 mg, 0.15 mmol) was added to a solution of difluoroalkene **6** (50 mg, 0.10 mmol) in CH_2Cl_2 (6 mL) under argon. After stirring at room temperature for 1 h, TLC (cyclohexane–EtOAc, 4:1) indicated completely complexation of the starting material. A 1 M solution in toluene of TIBAL (1.5 mL, 1.5 mmol) was added dropwise over a period of 30 min. After 1 h the mixture was diluted with CH_2Cl_2 (15 mL) and washed with a satd aq $NaHCO_3$ (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was dissolved in acetone (10 mL) and Et_3N (0.014 mL, 0.10 mmol) and CAN (550 mg, 1.0 mmol) were added. After stirring at room temperature for 1 h, TLC (cyclohexane–EtOAc, 4:1) indicated completion of the reaction and the formation of two products. The mixture was concentrated in vacuo and chromatographed (cyclohexane–EtOAc, 8:1) to afford **7** (20.6 mg, 41%) as a colourless oil and **8** (8.3 mg, 17%) as a colourless oil.

3.7.1. 2,3,4-Tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-5a-difluoro-5a-carba-α-D-manno-octopyranose (7).

Compound **7**: $[\alpha]_D^{20}$ +15.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.30 (m, 15H, H arom.), 4.87 (d, 1H, $J = 10.8$ Hz, CHPh), 4.78 (d, 1H, $J = 10.7$ Hz, CHPh), 4.75 (d, 1H, $J = 11.8$ Hz, CHPh), 4.72 (d, 1H, $J = 12.0$ Hz, CHPh), 4.69 (d, 1H, $J = 12.1$ Hz, CHPh), 4.59 (d, 1H, $J = 11.9$ Hz, CHPh), 4.26–4.21 (m, 1H, H-1), 4.08 (t, 1H, $J_{3,4} = J_{4,5}$ 8.0 Hz, H-4), 3.94–3.91 (m, 1H, H-2), 3.85 (dd, 1H, $J_{2,3} = 3.2$, $J_{3,4} = 7.9$ Hz, H-3), 3.34 (ddq, 1H, $J_{5,8} = 2.3$, $J_{4,5} = 8.8$, $J_{5,Fax} = 23.1$Hz, H-5), 2.27 (t, 1H, $J = 1.5$ Hz, OH), 1.85 (d, 3H, $J_{5,8} = 2.4$ Hz, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.30, 138.17, 137.95 (3C arom. quat.), 128.51–127.59 (15CH arom. Bn), 120.42 (t, $^1J_{C,F} = 250.6$ Hz, CF_2), 80.16 (C alcyn.), 78.34, 77.26, 75.91 (C-2, C-3, C-4), 74.84 (C alcyn.), 72.93 ($2CH_2Ph$), 72.86 (CH_2Ph), 68.77 (t, $^2J_{C,F} = 24.4$ Hz, C-1), 38.96 (t, $^2J_{C,F} = 21.8$ Hz, C-5), 3.65 (C-8); ^{19}F NMR ($CDCl_3$, 250 MHz): δ −108.35 (d, 1F, $J_{F,F'} = 255.1$ Hz), −105.60 (d, 1F, $J_{F,F'} = 259.6$ Hz); CIMS *m/z*: $[M+NH_4]^+$; CIMS: $[M+NH_4]^+$ calcd for $C_{30}H_{34}F_2O_4N$, 510.2456; found, 510.2449.

3.7.2. 2,3,4-Tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-5a-difluoro-5a-carba-β-D-manno-octopyranose (8).

Compound **8**: $[\alpha]_D^{20}$ +18.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.29 (m, 15H, H arom.), 5.12 (d, 1H, $J = 11.7$ Hz, CHPh), 4.93 (d, 1H, $J = 10.4$ Hz, CHPh), 4.85 (d, 1H, $J = 11.9$ Hz, CHPh), 4.84 (d, 1H, $J = 10.3$ Hz, CHPh), 4.75 (d, 1H, $J = 11.8$ Hz, CHPh), 4.64 (d, 1H, $J = 11.7$ Hz, CHPh), 4.08 (t, 1H, $J_{3,4} = J_{4,5} = 9.4$ Hz, H-4), 4.02 (br d, 1H, $J = 3.0$ Hz, H-2), 3.74–3.66 (m, 1H, H-1), 3.54 (dd, 1H, $J_{2,3} = 2.5$, $J_{3,4} = 9.1$ Hz, H-3), 2.95–2.86 (m, 2H, H-5, OH), 1.88 (d, 3H, $J_{5,8} = 2.3$ Hz, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.56, 138.54, 138.45 (3C arom. quat.), 128.94–127.92 (15CH arom. Bn), 81.79 (C-3), 81.09 (C alcyn.), 78.34, 77.95 (C-2, C-4), 76.12 (C alcyn.), 75.42 (CH_2Ph), 74.13 ($2CH_2Ph$), 70.65 (br s, C-1), 4.13 (C-8); ^{19}F NMR ($CDCl_3$, 250 MHz): δ −102.13 (d, 1F, $J_{F,F'} = 248.4$ Hz), −116.21 (br s, 1F); CIMS *m/z*: $[M+NH_4]^+$; CIMS: $[M+H]^+$ calcd for $C_{30}H_{31}F_2O_4$, 493.2190; found, 493.2181.

3.8. 2,3,4-Tri-*O*-benzyl-5a-difluoro-5a-carba-α-D-manno-pyranose (9)

Pd–$CaCO_3$ (10%, 2 mg) was added to a solution of **7** (8.0 mg, 0.02 mmol) in EtOAc (1 mL). Three purges of vacuo/argon were performed, followed by five purges of vacuo/H_2. After stirring for 2 h at room temperature under hydrogen (2 atm), the mixture was filtered through a Rotilabo® Nylon 0.45 μm filter, the solvent evaporated and the product was directly engaged in the next step. Ozone gas was bubbled through a solution of the product of the previous step (8.0 mg, 0.02 mmol) in CH_2Cl_2 (15 mL) at −78 °C until the solution obtained a blue colouration. Oxygen was then bubbled through the solution for 1 min and then DMS (3 drops) was added. The solution was allowed to warm to room temperature over a period of 30 min and the solvent was

removed in vacuo. The product obtained was dissolved in a mixture of 5:1 ethanol–CH_2Cl_2 (3.5 mL) and $NaBH_4$ (2.0 mg, 0.05 mmol) was added carefully. After stirring for 45 min at room temperature, TLC (cyclohexane–EtOAc, 2:1) showed no trace of starting material. MeOH (10 mL) was added, the solvent removed, the residue coevaporated with MeOH (3 × 10 mL), and then purified by flash chromatography (cyclohexane–EtOAc, 3:1) to yield **9** (3.0 mg, 38%) as a colourless oil; $[\alpha]_D^{20}$ +8.3 (*c* 0.2, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.29 (m, 15H, H arom. Bn), 4.84 (d, 1H, $J = 11.2$ Hz, CHPh), 4.73–4.64 (m, 5H, 5 CHPh), 4.16–4.12 (m, 1H, H-1), 4.10 (t, 1H, $J_{3,4} = J_{4,5} = 8.1$ Hz, H-4), 3.97–3.94 (m, 4H, H-2, H-3, H-6a, H-6b), 2.56–2.45 (m, 2H, H-5, OH), 2.31 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.32, 138.27, 138.25 (3C arom. quat. Bn), 128.96–128.18 (15CH arom. Bn), 123.30 (dd, $^1J_{C,F} = 245.3$, $^1J_{C,F'} = 248.7$ Hz, CF_2), 79.50 (C-3), 76.94 (dd, $^3J_{C,F} = 1.9$, $^3J_{C,F'} = 6.3$ Hz, C-4), 76.36 (br s, C-2), 74.75 (CH_2Ph), 73.60 (CH_2Ph), 73.54 (CH_2Ph), 69.94 (dd, $^2J_{C,F} = 22.0$, $^2J_{C,F'} = 26.8$ Hz, C-1), 59.80 (t, $^3J_{C,F} = 4.5$ Hz, C-6), 46.98 (t, $^2J_{C,F} = 20.1$ Hz, C-5); ^{19}F NMR ($CDCl_3$, 235 MHz): δ −103.28 (d, 1F, $J_{F,F'} = 258.2$ Hz), −109.84 (d, 1F, $J_{F,F'} = 257.8$ Hz); CIMS: $[M+NH_4]^+$ calcd for $C_{28}H_{34}O_5NF_2$, 502.2405; found, 502.2426.

3.9. 5a-Difluoro-5a-carba-α-D-mannopyranose (10)

Pd–C (10%, 2 mg) was added to a solution of **9** (3.0 mg, 4 μmol) in MeOH (1 mL). Three purges of vacuo/argon were performed, followed by five purges of vacuo/H_2. After stirring for 2 h at room temperature under hydrogen (2 atm), the mixture was filtered through a Rotilabo® Nylon 0.45 μm filter and the solvent evaporated to afford *gem*-difluoro-carba-α-D-mannopyranose **10** (0.8 mg, 100%); $[\alpha]_D^{20}$ −4.4 (*c* 0.27, MeOH) ^{1}H NMR (CD_3OD, 400 MHz): 4.01–3.96 (m, 3H, H-2, H-6a, H-6b), 3.91–3.84 (m, 2H, H-1, H-4), 3.78 (dd, 1H, $J_{2,3} = 3.5$, $J_{3,4} = 8.7$ Hz, H-3), 2.27 (dddt, 1H, $J_{5,6a} = J_{5,6b}$ 5.0, $J_{5,Feq} = 6.3$, $J_{4,5} = 9.7$, $J_{5,Fax} = 25.8$ Hz, H-5); ^{13}C NMR (CD_3OD, 100 MHz): δ 123.25 (t, $^1J_{C,F} = 247.0$ Hz, CF_2), 72.47 (C-3), 71.97 (d, $^3J_{C,F} = 5.9$ Hz, C-2), 71.36 (dd, $^2J_{C,F} = 21.9$, $^2J_{C,F'} = 28.2$ Hz, C-1), 69.47 (d, $^3J_{C,F} = 7.8$ Hz, C-4), 58.19 (dd, $^3J_{C,F} = 3.5$, $^3J_{C,F'} = 4.7$ Hz, C-6), 47.05 (t, $^2J_{C,F} = 19.7$ Hz, C-5); ^{19}F NMR (CD_3OD, 235 MHz): δ −106.35 (dd, 1F, $J_{5,Feq} = 5.9$, $J_{Feq,Fax} = 260.9$ Hz, F_{eq}), −111.80 (ddd, 1F, $J = 6.0$, $J_{5,Fax} = 25.8$, $J_{Feq,Fax} = 260.1$ Hz, F_{ax}); CIMS: $[M+NH_4]^+$ calcd for $C_7H_{16}O_5NF_2$, 232.0997; found, 232.0991.

3.10. 2,3,4-Tri-*O*-benzyl-5a-difluoro-5a-carba-β-D-mannopyranose (11)

Pd–$CaCO_3$ (10%, 5 mg) was added to a solution of **8** (9.5 mg, 0.02 mmol) in EtOAc (3 mL). Three purges of vacuo/argon were performed, followed by five purges of vacuo/H_2. After stirring for 2 h at room temperature under hydrogen (2 atm), the mixture was filtered through a Rotilabo® Nylon 0.45 μm filter, the solvent evaporated and the product was directly engaged in the next step. Ozone gas was bubbled through a solution of the product of the previous step (9.9 mg, 0.02 mmol) in CH_2Cl_2 (15 mL) at −78 °C until the solution obtained a blue colouration. Oxygen was then bubbled through the solution for 1 min and then DMS (2 drops) was added. The solution was allowed to warm to room temperature over a period of 30 min and the solvent was removed in vacuo. The product obtained was dissolved in a mixture of ethanol/CH_2Cl_2 (4:1, 5 mL) and $NaBH_4$ (5.0 mg, 0.05 mmol) was added carefully. After stirring for 30 min at room temperature, TLC (cyclohexane–EtOAc, 2:1) showed no trace of starting material. MeOH (10 mL) was added, the solvent removed, the residue coevaporated with MeOH (3 × 10 mL), and then purified by flash chromatography (cyclohexane–EtOAc, 5:1) to yield **11** (6.0 mg, 62%) as a colourless oil; $[\alpha]_D^{20}$ +12.6 (*c* 0.3, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.29 (m, 15H, H arom. Bn), 5.14 (d, 1H, $J = 11.7$ Hz, CHPh), 5.01 (d, 1H, $J = 10.7$ Hz, CHPh), 4.83 (d, 1H, $J = 11.7$ Hz, CHPh), 4.79 (d, 1H, $J = 11.7$ Hz, CHPh), 4.77 (d, 1H, $J = 10.7$ Hz, CHPh), 4.65 (d, 1H, $J = 11.7$ Hz, CHPh), 4.22 (t, 1H, $J_{3,4} = J_{4,5} = 10.1$ Hz, H-4), 4.08 (br d, 1H, $J_{1,2} = J_{2,3} = 3.3$ Hz, H-2) 4.05–4.02 (m, 2H, H-6a, H-6b), 3.75–3.64 (m, 1H, H-1), 3.64 (dd, 1H, $J_{2,3} = 2.5$, $J_{3,4} = 9.4$ Hz, H-3), 2.81 (d, 1H, $J_{1,OH} = 11.2$ Hz, OH), 2.23 (br s, 1H, OH), 1.99 (ddt, 1H, $J = 4.5$, $J_{4,5} = 10.1$ Hz, $J_{5,Fax} = 28.2$ Hz, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.50, 138.12, 138.02 (3C arom. quat. Bn), 129.05–127.93 (15CH arom. Bn), 122.07 (t, $^1J_{C,F} = 247.4$ Hz, CF_2), 83.22 (d, $^4J_{C,F} = 1.5$ Hz, C-3), 76.89 (d, $^3J_{C,F} = 9.2$ Hz, C-2), 76.47 (d, $^3J_{C,F} = 8.7$ Hz, C-4), 76.02 (CH_2Ph), 75.61 (CH_2Ph), 73.79 (CH_2Ph), 70.77 (dd, $^2J_{C,F} = 19.4$, $^2J_{C,F'} = 23.5$ Hz, C-1), 58.73 (dd, $^3J_{C,F} = 3.6$, $^3J_{C,F} = 4.8$ Hz, C-6), 48.42 (t, $^2J_{C,F} = 20.4$ Hz, C-5); ^{19}F NMR ($CDCl_3$, 235 MHz): δ −103.76 (d, 1F, $J_{Feq,Fax} = 251.9$ Hz), −120.13 (d, 1F, $J_{Feq,Fax} = 251.3$ Hz); FABMS: $[M+Na]^+$ calcd for $C_{28}H_{30}O_5F_2Na$, 507.1959; found, 507.1960.

3.11. 5a,5a′-Difluoro-5a-carba-β-D-mannopyranose (12)

Pd–C (10%, 3 mg) was added to a solution of **11** (6.0 mg, 12 μmol) in MeOH (3 mL). Three purges of vacuo/argon were performed, followed by five purges of vacuo/H_2. After stirring for 6 h at room temperature under hydrogen (2 atm), the mixture was filtered through a Rotilabo® Nylon 0.45 μm filter and the solvent evaporated to afford *gem*-difluoro-carba-α-D-mannopyranose

12 (2.7 mg, 100%); $[\alpha]_D^{20}$ −9.1 (*c* 0.2, MeOH) ^{1}H NMR (D_2O, 400 MHz): δ 4.09–4.06 (m, 1H, H-2) 3.99–3.84 (m, 3H, H-1, H-6a, H-6b), 3.68 (t, 1H, $J_{3,4} = J_{4,5} = 10.4$ Hz, H-4), 3.54 (dd, 1H, $J_{2,3} = 3.2$, $J_{3,4} = 9.9$ Hz, H-3), 1.91 (br d, 1H, $J_{5,Fax} = 28.4$ Hz, H-5); ^{13}C NMR (D_2O, 100 MHz): δ 122.82 (t, $^1J_{C,F} = 249.7$ Hz, CF_2), 73.08 (d, $^4J_{C,F} = 1.8$ Hz, C-3), 71.25 (d, $^3J_{C,F} = 9.1$ Hz, C-2), 69.81 (dd, $^2J_{C,F} = 18.0$, $^2J_{C,F'} = 21.3$ Hz, C-1), 67.46 (d, $^3J_{C,F} = 9.7$ Hz, C-4), 56.43 (dd, $^3J_{C,F} = 1.8$, $^3J_{C,F'} = 4.8$ Hz, C-6), 47.50 (t, $^2J_{C,F} = 19.9$ Hz, C-5); ^{19}F NMR (D_2O, 235 MHz): δ −104.37 (dq, 1F, $J_{5,Feq} = J_{1,Feq} = 5.5$, $J_{Feq,Fax} = 247.6$ Hz, F_{eq}), −120.86 (ddd, 1F, $J_{1,Fax} = 23.1$, $J_{5,Fax}$ 28.8, $J_{Feq,Fax} = 247.6$ Hz, F_{ax}); CIMS: $[M+H]^+$ calcd for $C_7H_{13}O_5F_2$, 215.0731; found, 215.0728.

3.12. *para*-Methoxyphenyl 2,3,4-tri-*O*-benzyl-7,7-dibromo-6,7-dideoxy-β-D-*galacto*-hept-6-enopyranoside (14)

To a solution of oxalyl chloride (0.6 mL, 7.2 mmol) in anhydrous CH_2Cl_2 (30 mL), DMSO (1.0 mL, 14.4 mmol) was added dropwise at −78 °C under argon. After 15 min a solution of 4-methoxyphenyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranoside **13** (2.0 mg, 3.6 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise. After 1 h, Et_3N (2.8 mL, 19.8 mmol) was added and the reaction mixture was allowed to reach room temperature. After 45 min, water was added (80 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude aldehyde was azeotroped with toluene and used without further purification. A solution of tetrabromomethane (2.4 g, 7.2 mmol) in dry CH_2Cl_2 (15 mL) was added to a solution of triphenylphosphane (3.8 g, 14.4 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C under argon. The mixture was stirred at room temperature for 15 min. The resulting bright orange slurry was cooled to 0 °C, the solution of the aldehyde (2.0 g, 3.6 mmol) in anhydrous CH_2Cl_2 (15 mL) was added and the resulting mixture was stirred for 2 h at room temperature. Water (80 mL) and CH_2Cl_2 (100 mL) were added. The organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed (cyclohexane–EtOAc, 15:1) to afford **14** (1.8 g, 71% over two steps) as a yellow oil; $[\alpha]_D^{20}$ −43.4 (*c* 1.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.36 (m, 15H, H arom. Bn), 7.08 (d, 2H, $J = 9.1$ Hz, H arom. OPMP), 6.88 (d, 2H, $J = 9.0$ Hz, H arom. OPMP), 6.71 (d, 1H, $J_{5,6} = 7.1$ Hz, H-6), 5.08 (d, 1H, $J = 10.9$ Hz, CHPh), 5.03 (d, 1H, $J = 11.8$ Hz, CHPh), 4.93 (d, 1H, $J_{1,2} = 7.5$ Hz, H-1), 4.92 (d, 1H, $J = 11.3$ Hz, CHPh), 4.88 (d, 1H, $J = 11.8$ Hz, CHPh), 4.80 (d, 1H, $J = 11.8$ Hz, CHPh), 4.76 (d, 1H, $J = 11.8$ Hz, CHPh), 4.14 (dd, 1H, $J_{1,2} = 7.7$, $J_{2,3} = 9.7$ Hz, H-2), 4.11 (dd, 1H, $J_{4,5} = 0.9$, $J_{5,6} = 7.2$ Hz, H-5), 3.94 (dd, 1H, $J_{4,5} = 0.8$, $J_{3,4} = 2.8$ Hz, H-4), 3.82 (s, 3H, OCH_3), 3.67 (dd, 1H, $J_{3,4} = 2.9$, $J_{2,3} = 9.7$ Hz, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.29, 151.41 (2C arom. quat. OPMP), 138.45, 138.15, 137.77 (3C arom. quat. Bn), 135.57 (C-6), 128.46–127.60 (15CH arom. Bn), 118.55, 114.61 (4CH arom. OPMP), 102.88 (C-1), 91.89 (=CBr_2), 81.59 (C-3), 78.80 (C-2), 75.42 (C-5), 75.35 (CH_2Ph), 74.58 (CH_2Ph), 74.00 (C-4), 73.39 (CH_2Ph), 55.59 (OCH_3); CIMS: $[M+NH_4]^+$ calcd for $C_{35}H_{31}O_6NBr_2$, 726.1066 (49.1%), 728.1049 (100.0%), 730.1038 (55.2%); found, 726.1079 (53.9%), 728.1056 (100.0%), 730.1069 (54.9%). Anal. Calcd for $C_{35}H_{34}O_6Br_2$: C, 59.17; H, 4.82. Found: C, 58.91; H, 4.85.

3.13. *para*-Methoxyphenyl 2,3,4-tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-β-D-*galacto*-octopyranoside (15)

A 2.5 M solution of butyl lithium in hexane (2.0 mL, 5.1 mmol) was added dropwise to a solution of **14** (1.8 g, 2.5 mmol) in THF (50 mL) at −78 °C under argon. The solution was stirred for 2 h at −40 °C and then cooled to −78 °C. MeI (1.6 mL, 25.0 mmol) was added dropwise followed by the HMPA (4.4 mL, 25.0 mmol). The mixture was allowed to reach room temperature, and stirred for 48 h. The reaction mixture was concentrated under reduced pressure, the crude dissolved in ether (200 mL) washed with water (100 mL) and then with a satd soln of $CuSO_4$ (2 × 75 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane–EtOAc, 10:1) to give **15** (1.1 g, 78%) as a syrup; $[\alpha]_D^{20}$ −29.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56–7.34 (m, 15H, H arom. Bn), 7.12 (d, 2H, $J = 9.0$ Hz, H arom. OPMP), 6.87 (d, 2H, $J = 9.0$ Hz, OPMP), 5.09 (d, 1H, $J = 11.7$ Hz, CHPh), 5.07 (d, 1H, $J = 10.3$ Hz, CHPh), 5.03 (d, 1H, $J = 12.0$ Hz, CHPh), 4.92 (d, 1H, $J = 10.8$ Hz, CHPh), 4.87 (d, 1H, $J_{1,2} = 7.7$ Hz, H-1) 4.76 (d, 1H, $J = 12.0$ Hz, CHPh), 4.71 (d, 1H, $J = 11.9$ Hz, CHPh), 4.21 (dd, 1H, $J_{4,5} = 0.8$, $J_{5,8} = 2.0$ Hz, H-5), 4.13 (dd, 1H, $J_{1,2} = 7.8$, $J_{2,3} = 9.7$ Hz, H-2), 3.93 (dd, 1H, $J_{4,5} = 0.6$, $J_{3,4} = 3.0$ Hz, H-4), 3.82 (s, 3H, OCH_3), 3.58 (dd, 1H, $J_{3,4} = 3.0$, $J_{2,3} = 9.7$ Hz, H-3), 1.90 (d, 3H, $J_{5,8} = 2.2$ Hz, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.20, 151.62 (2C arom. quat. OPMP), 138.52, 138.38, 138.21 (3C arom. quat. Bn), 128.39–127.46 (15CH arom. Bn), 118.70, 114.38 (4CH arom. OPMP), 102.97 (C-1), 82.61 (C alcyn.), 80.96 (C-3), 78.72 (C-2), 75.75 (C-4), 75.33 (CH_2Ph), 74.81 (C alcyn.) 74.55 (CH_2Ph), 72.74 (CH_2Ph), 65.97 (C-5), 55.56 (OCH_3), 3.67 (C-8); CIMS: $[M+NH_4]^+$ calcd for $C_{36}H_{40}O_6N$, 582.2856; found, 582.2858. Anal. Calcd for $C_{36}H_{36}O_6$: C, 76.57; H, 6.43. Found: C, 76.64; H, 6.45.

3.14. 2,3,4-Tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-α-β-D-*galacto*-octopyranose (16)

To a solution of **15** (45.0 mg, 0.08 mmol) in a 3:1 mixture of acetone/H_2O (2 mL) was added ammonium cerium(IV) nitrate (310.0 mg, 0.56 mmol). The resulting clear orange solution was stirred at room temperature for 5 min. The mixture was partially concentrated under reduced pressure, diluted with dichloromethane (10 mL) and washed with water (5 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (cyclohexane–EtOAc, 4:1) to give **16** (26.1 mg, 71%) as an orange oil and as a 3:1 mixture of α and β anomers; extracted data for α anomer; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49–7.30 (m, 15H, H arom. Bn), 5.33 (d, 1H, $J_{1,2} = 3.5$ Hz, H-1), 4.99 (d, 1H, $J = 11.9$ Hz, CHPh), 4.93 (d, 1H, $J = 11.9$ Hz, CHPh), 4.85 (d, 1H, $J = 11.7$ Hz, CHPh), 4.75–4.70 (m, 4H, 3CHPh, H-5), 4.44 (dd, 1H, $J_{1,2} = 3.5$, $J_{2,3} = 9.5$ Hz, H-2), 3.94 (dd, 1H, $J_{4,5} = 1.6$, $J_{3,4} = 2.9$ Hz, H-4), 3.89 (dd, 1H, $J_{3,4} = 2.9$, $J_{2,3} = 9.6$ Hz, H-3), 3.03 (br s, 1H, OH), 1.87 (d, 3H, $J_{5,8} = 2.2$ Hz, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.43, 138.38, 138.02 (3C arom. quat. Bn), 128.40–127.49 (15CH arom. Bn), 91.87 (C-1), 82.42 (C alcyn.), 77.41 (C-3), 76.63 (C-4), 75.93 (C-2), 75.27 (C alcyn.), 74.63 (CH_2Ph), 73.60 (CH_2Ph), 72.74 (CH_2Ph), 62.60 (C-5), 3.64 (C-8); extracted data for β anomer; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49–7.30 (m, 15H, H arom. Bn), 5.01–4.90 (m, 3H, 3CHPh), 4.81 (d, 1H, $J = 11.1$ Hz, CHPh), 4.77 (d, 1H, $J = 11.9$ Hz, CHPh), 4.75–4.70 (m, 2H, CHPh, H-1), 4.27 (quintet, 1H, $J_{4,5} = J_{5,8} = 2.0$ Hz, H-5), 3.90–3.87 (m, 1H, H-4), 3.80 (dd, 1H, $J_{1,2} = 6.8$, $J_{2,3} = 9.0$ Hz, H-2), 3.58 (dd, 1H, $J_{3,4} = 2.9$, $J_{2,3} = 9.0$ Hz, H-3) 3.53 (br s, 1H, OH), 1.87 (d, 3H, $J_{5,8} = 2.2$ Hz, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.43–138.02 (3C arom. quat. Bn), 128.40–127.49 (15CH arom. Bn), 97.21 (C-1), 82.42 (C alcyn.), 80.36 (C-3), 79.87 (C-2), 75.50 (C-4), 75.27 (C alcyn.), 74.74 (CH_2Ph), 74.35 (CH_2Ph), 72.86 (CH_2Ph), 65.61 (C-5), 3.60 (C-8); CIMS: $[M+NH_4]^+$ calcd for $C_{29}H_{34}O_5N$, 476.2437; found, 476.2442.

3.15. 2,6-Anhydro-3,4,5-tri-*O*-benzyl-7,7,8,8-tetradehydro-1,7,8,9-tetradeoxy-1,1-difluoro-D-*galacto*-non-1-enitol (17)

To a solution of oxalyl chloride (0.16 mL, 1.92 mmol) in anhydrous CH_2Cl_2 (10 mL), DMSO (0.27 mL, 3.84 mmol) was added dropwise at −78 °C under argon. After 15 min a solution of **16** (0.44 mg, 0.96 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise. After 1 h, Et_3N (0.74 mL, 5.28 mmol) was added and the reaction mixture was allowed to reach room temperature. After 45 min, water was added (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude lactone was azeotroped with toluene and used without further purification. To a solution of 2,3,4-tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-D-*galacto*-octono-1,5-lactone (0.44 g, 0.96 mmol) in anhydrous THF (25 mL) was added, with a cooled syringe, CBr_2F_2 (0.9 mL, 9.60 mmol) at −10 °C under argon. HMPT (1.7 mL, 9.60 mmol) was added dropwise and the mixture was allowed to reach room temperature. After 1 h HMPT (3.5 mL, 19.20 mmol) was added and the reaction mixture stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure and then was diluted with ether (100 mL) and water (50 mL). The organic layer was separated, washed with a satd soln of $CuSO_4$ (2 × 30 mL), dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The residue was purified by flash chromatography (cyclohexane–EtOAc, 25:1) to afford **17** (155.9 mg, 33%) as a colourless oil; $[\alpha]_D^{22}$ +36.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.30 (m, 15H, H arom. Bn), 4.93–4.91 (m, 1H, H-5), 4.89 (d, 1H, $J = 12.3$ Hz, CHPh), 4.74 (d, 1H, $J = 12.1$ Hz, CHPh), 4.70 (d, 1H, $J = 10.5$ Hz, CHPh), 4.67 (d, 1H, $J = 12.2$ Hz, CHPh), 4.61 (d, 1H, $J = 11.8$ Hz, CHPh), 4.35 (d, 1H, $J = 11.8$ Hz, CHPh), 4.31 (dd, 1H, $^4J_{2,F} = 3.4$, $J_{2,3} = 5.7$ Hz, H-2), 4.09 (dd, 1H, $J_{4,5} = 2.8$, $J_{3,4} = 5.5$ Hz, H-4), 4.00–3.98 (m, 1H, H-3), 1.85 (d, 3H, $J_{5,8} = 2.2$ Hz, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.20 (dd, $^1J_{C,F} = 280.2$, $^1J_{C,F'} = 293.5$ Hz, CF_2) 139.11, 138.28, 137.85 (3C arom. quat. Bn), 128.83–127.60 (15CH arom. Bn), 84.73 (C alcyn.), 75.57 (d, $^4J_{C,F} = 1.6$ Hz, C-3), 75.00 (C alcyn.), 73.89 (C-4), 73.10 (CH_2Ph), 72.43 (CH_2Ph), 71.57 (t, $^3J_{C,F} = 3.3$ Hz, C-2), 70.70 (CH_2Ph), 68.45 (t, $^4J_{C,F} = 1.6$ Hz, C-5), 4.45 (C-8); ^{19}F NMR ($CDCl_3$, 235 MHz): δ −97.22 (d, 1F, $J_{F,F'}$ 67.5 Hz), −111.64 (dd, 1F, $J_{2,F} = 2.4$, $J_{F,F'}$ 61.1 Hz); FABMS: $[M+Na]^+$ calcd for $C_{30}H_{28}O_4F_2Na$, 513.1853; found, 518.1849.

3.16. Rearrangement of (17) into 2,3,4-tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-5a-difluoro-5a-carba-α-D-*galacto*-octopyranose (18) and 2,3,4-tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-5a-difluoro-5a-carba-β-D-*galacto*-octopyranose (19)

$Co_2(CO)_8$ (0.15 g, 0.45 mmol) was added to a solution of difluoroalkene **17** (0.15 g, 0.30 mmol) in CH_2Cl_2 (15 mL) under argon. After stirring at room temperature for 1 h, TLC (cyclohexane–EtOAc, 4:1) indicat completely complexation of the starting material. The reaction mixture was cooled to −78 °C and a 1 M solution in toluene of TIBAL (2.40 mL, 2.40 mmol) was added dropwise over a period of 15 min. The mixture was allowed to reach room temperature and stirred for 1 h. The mixture was diluted with CH_2Cl_2 (20 mL) and

washed with a satd aq $NaHCO_3$ (15 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was dissolved in acetone (10 mL) and Et_3N (0.03 mL, 0.30 mmol) and CAN (0.82 g, 1.5 mmol) were added. After stirring at room temperature for 30 min, TLC (cyclohexane–EtOAc, 4:1) indicated completion of the reaction and the formation of two products. The mixture was concentrated in vacuo and chromatographed (cyclohexane–EtOAc, 8:1) to afford **18** (52 mg, 35%) as a colourless oil and **19** (42 mg, 29%) as a colourless oil.

3.16.1. 2,3,4-Tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-5a-difluoro-5a-carba-α-D-*galacto*-octopyranose (18). Compound **18**: $[\alpha]_D^{20}$ +33.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz): δ 7.37–7.20 (m, 15H, H arom. Bn), 4.80–4.55 (m, 6H, 6CHPh), 4.13 (dt, 1H, $J_{1,2} = J_{1,Feq} = 3.0$, $J_{1,Fax} = 7.1$ Hz, H-1), 4.01 (dd, 1H, $J_{1,2} = 3.2$, $J_{2,3} = 8.9$ Hz, H-2), 3.93 (t, 1H, $J_{3,4} = J_{4,5} = 2.8$ Hz, H-4), 3.74 (dd, 1H, $J_{3,4} = 3.0$, $J_{2,3} = 8.9$ Hz, H-3), 3.16 (br d, 1H, $J_{5,Fax} = 28.5$ Hz, H-5), 2.51 (br s, 1H, OH); ^{13}C NMR (C_6D_6, 63 MHz): δ 139.42, 139.26, 138.54 (3C arom. quat. Bn), 128.62–127.66 (15CH arom. Bn), 120.32 (t, $^1J_{C,F} = 251.5$ Hz, CF_2), 80.59 (C alcyn.), 78.29 (C-3), 77.50 (br s, C-2), 76.35 (d, $^3J_{C,F} = 6.5$ Hz, C-4), 75.66 (CH_2Ph), 73.35 ($2CH_2Ph$), 72.78 (C alcyn.), 70.36 (br s, C-1), 36.94 (t, $^2J_{C,F} = 20.8$ Hz, C-5), 3.41 (C-8); ^{19}F NMR (C_6D_6, 235 MHz): δ −102.44 (d, 1F, $J_{Feq,Fax} = 247.8$ Hz), −107.53 (d, 1F $J_{Feq,Fax} = 248.9$ Hz); CIMS: $[M+NH_4]^+$ calcd for $C_{30}H_{34}O_4NF_2$, 510.2456; found, 510.2441.

3.16.2. 2,3,4-Tri-*O*-benzyl-6,6,7,7-tetradehydro-6,7,8-trideoxy-5a-difluoro-5a-carba-β-D-*galacto*-octopyranose (19). Compound **19**: $[\alpha]_D^{20}$ −15.1 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.29 (m, 15H, H arom. Bn), 4.92 (br d, 3H, $J = 10.3$ Hz, 3CHPh), 4.79 (d, 1H, $J = 11.1$ Hz, CHPh), 4.75 (d, 3H, $J = 12.0$ Hz, CHPh), 4.71 (d, 1H, $J = 11.9$ Hz, CHPh), 4.07–4.02 (m, 2H, H-2, H-4) 3.74 (ddd, 1H, $J_{1,Feq} = 6.8$, $J_{1,2} = 8.7$, $J_{1,Fax} = 15.3$ Hz, H-1), 3.53 (dd, 1H, $J_{3,4} = 2.0$, $J_{2,3} = 8.7$ Hz, H-3), 2.90 (br d, 1H, $J_{5,Fax} = 23.6$ Hz, H-5), 1.84 (d, 3H, $J_{5,8} = 2.4$ Hz H-8); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.83, 138.56, 138.32 (3C arom. quat. Bn), 128.92–127.89 (15CH arom. Bn), 119.50 (dd, $^1J_{C,F} = 245.1$, $^1J_{C,F'} = 255.4$ Hz, CF_2), 81.50 (C alcyn.), 81.17 (C-3), 79.36 (d, $^3J_{C,F} = 6.3$ Hz, C-2 or C-4), 75.87 (d, $^3J_{C,F} = 6.8$ Hz, C-2 or C-4), 75.81 (CH_2Ph), 75.09 (CH_2Ph), 74.22 (br s, C-1), 73.41 (CH_2Ph), 71.48 (C alcyn.), 38.72 (t, $^2J_{C,F} = 21.0$ Hz, C-5), 4.15 (C-8); ^{19}F NMR ($CDCl_3$, 235 MHz): δ −102.08 (d, 1F, $J_{Feq,Fax} = 247.0$ Hz), −117.05 (br s, 1F); CIMS: $[M+NH_4]^+$ calcd for $C_{30}H_{34}O_4NF_2$, 510.2456; found, 510.2463.

3.17. 1,6-Di-*O*-acetyl-2,3,4-tri-*O*-benzyl-5a-difluoro-5a-carba-α-D-galactopyranose (20)

Pd–$CaCO_3$ (10%, 2 mg) was added to a solution of **18** (51 mg, 0.10 mmol) in EtOAc (4 mL). Three purges of vacuo/argon were performed, followed by five purges of vacuo/H_2. After stirring for 2 h at room temperature under hydrogen (2 atm), the mixture was filtered through a Rotilabo® Nylon 0.45 μm filter, the solvent evaporated and the product was directly engaged in the next step. Ozone gas was bubbled through a solution of the product of the previous step (51 mg, 0.10 mmol) in CH_2Cl_2 (40 mL) at −78 °C until the solution obtained a blue colouration (typically 2 min). Oxygen was then bubbled through the solution for 1 min and then DMS (5 drops) was added. The solution was allowed to warm to room temperature over a period of 30 min and the solvent was removed in vacuo. The product obtained was dissolved in a mixture of 4:1 ethanol/CH_2Cl_2 (5 mL) and $NaBH_4$ (26 mg, 0.70 mmol) was added carefully. After stirring for 45 min at room temperature, TLC (cyclohexane–EtOAc, 2:1) indicated complete consumption of starting material ($R_f = 0.33$) and the formation of a major product ($R_f = 0.19$). MeOH (10 mL) was added, the solvent removed, and the residue coevaporated with MeOH (3×10 mL). The crude product was dissolved in pyridine (1 mL), Ac_2O (0.5 mL) was added dropwise and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure (azeotroped with toluene) and purified by flash chromatography (cyclohexane–EtOAc, 2:1) to yield **20** (32.4 mg, 57%), as a colourless oil; $[\alpha]_D^{20}$ +39.4 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.29 (m, 15H, H arom. Bn), 5.68 (dt, 1H, $J_{1,2} = 3.2$, $J_{1,F} = 6.9$ Hz, H-1) 5.01 (br d, 1H, $J = 10.8$ Hz, CHPh), 4.91 (d, 1H, $J = 11.7$ Hz, CHPh), 4.76 (d, 1H, $J = 11.7$ Hz, CHPh), 4.74 (d, 1H, $J = 11.1$ Hz, CHPh), 4.61 (d, 1H, $J = 11.6$ Hz, CHPh), 4.60 (d, 1H $J = 11.0$ Hz, CHPh), 4.45 (dd, 1H, $J_{5,6a} = 4.8$, $J_{6a,6b} = 11.2$ Hz, H-6a) 4.31–4.22 (m, 2H, H-2 and H-6b), 4.07 (ddd, 1H, $J = 2.6$, $J = 3.0$, $J = 5.7$ Hz, H-4), 3.84 (dd, 1H, $J_{3,4} = 2.8$, $J_{2,3} = 9.9$ Hz, H-3), 2.52 (br d, 1H, $J_{5,Fax} = 27.0$ Hz, H-5), 2.16 (s, 3H, OAc), 2.00 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.01, 169.58 (2C quat. OAc) 138.90, 138.75, 138.08 (3C arom. quat. Bn), 128.81–127.90 (15CH arom. Bn), 120.16 (dd, $^1J_{C,F} = 249.0$, $^1J_{C,F'} = 251.2$ Hz, CF_2), 79.49 (C-3), 75.72 (d, $^3J_{C,F} = 5.7$ Hz, C-2), 75.46 (CH_2Ph), 74.37 (CH_2Ph), 73.12 (CH_2Ph), 73.11 (d, $^3J_{C,F} = 9.5$ Hz, C-4), 69.53 (dd, $^2J_{C,F} = 20.6$, $^2J_{C,F'} = 36.5$ Hz, C-1), 58.92 (C-6), 42.50 (br s, C-5), 21.26 (CH_3, OAc), 21.24 (CH_3, OAc); ^{19}F NMR ($CDCl_3$, 235 MHz): δ −105.11 (d, 1F, $J_{Feq,Fax} = 260.9$ Hz), −109.21 (d, 1F, $J_{Feq,Fax} = 260.9$ Hz); CIMS: $[M+NH_4]^+$ calcd for $C_{32}H_{38}O_7NF_2$, 586.2616; found, 586.2610.

3.18. 5a-Difluoro-5a-carba-α-D-galactopyranose (21)

To a solution of **20** (25 mg, 0.043 mmol) in MeOH, was added dropwise a 1 M solution of NaOMe (1 mL) and the mixture was stirred for 6 h at rt. The reaction mixture was neutralized with acid resin Amberlite IR 120 (H^+), filtered and concentrated under reduced pressure. The product was directly engaged in the next step. Pd–C (10%, 2 mg) was added to a solution of the diol (21 mg, 0.043 mmol) in MeOH (1.5 mL). Three purges of vacuo/argon were performed, followed by five purges of vacuo/H_2. After stirring for 3 h at room temperature under hydrogen (2 atm), the mixture was filtered through a Rotilabo® Nylon 0.45 μm filter and the solvent evaporated to afford *gem*-difluoro-carba-α-D-galactopyranose **21** (9.3 mg, 100%) as a white crystalline solid; mp 232 °C (MeOH); $[\alpha]_D^{20}$ +1.8 (*c* 0.8, MeOH); ^{1}H NMR (CD_3OD, 400 MHz): δ 4.18 (ddd, 1H, $J = 3.0$, $J_{3,4} = 3.2$, $J = 6.0$ Hz, H-4) 4.00–3.85 (m, 4H, H-1, H-2, H-6a, H-6b), 3.78 (dd, 1H, $J_{3,4} = 3.3$, $J_{2,3} = 9.8$ Hz, H-3), 2.36 (ddq, 1H, $J = 4.4$, $J = 8.1$, $J_{5,Fax} = 31.4$ Hz, H-5); ^{13}C NMR (CD_3OD, 100 MHz): δ 123.07 (dd, $^1J_{C,F} = 246.1$, $^1J_{C,F'} = 258.5$ Hz, CF_2), 72.53 (dd, $^2J_{C,F} = 20.4$, $^2JC_{,F'} = 33.1$ Hz, C-1), 70.64 (C-3), 68.78 (d, $^3J_{C,F} = 7.3$ Hz, C-2), 67.35 (d, $^3J_{C,F} = 10.1$ Hz, C-4) 55.72 (dd, $^3J_{C,F} = 2.2$, $^3J_{C,F'} = 3.5$ Hz, C-6), 43.70 (t, $^2J_{C,F} = 19.7$ Hz, C-5); ^{19}F NMR (CD_3OD, 235 MHz): δ −107.23 (dd, 1F, $J_{5,Feq} = 5.0$, $J_{Feq,Fax} = 256.3$ Hz, F_{eq}), −111.19 (dd, 1F, $J_{5,Fax} = 31.0$, $J_{Feq,Fax} = 255.7$ Hz, F_{ax}); CIMS: $[M+NH_4]^+$ calcd for $C_7H_{16}O_5NF_2$, 232.0997; found, 232.1002.

3.19. 2,3,4-Tri-*O*-benzyl-5a-difluoro-5a-carba-β-D-galactopyranose (22)

Pd–$CaCO_3$ (10%, 2 mg) was added to a solution of **19** (30 mg, 0.06 mmol) in EtOAc (3 mL). Three purges of vacuo/argon were performed, followed by five purges of vacuo/H_2. After stirring for 2 h at room temperature under hydrogen (2 atm), the mixture was filtered through a Rotilabo® Nylon 0.45 μm filter, the solvent evaporated and the product was directly engaged in the next step. Ozone gas was bubbled through a solution of the product of the previous step (30 mg, 0.06 mmol) in CH_2Cl_2 (40 mL) at −78 °C until the solution obtained a blue colouration (typically 2 min). Oxygen was then bubbled through the solution for 1 min and then DMS (4 drops) was added. The solution was allowed to warm to room temperature over a period of 30 min and the solvent was removed in vacuo. The product obtained was dissolved in a mixture 4:1 ethanol/CH_2Cl_2 (5 mL) and $NaBH_4$ (20 mg, 0.42 mmol) was added carefully. After stirring for 30 min at room temperature, TLC (cyclohexane–EtOAc, 2:1) indicated complete consumption of starting material ($R_f = 0.40$) and the formation of a major product ($R_f = 0.27$). MeOH (10 mL) was added, the solvent removed, the residue coevaporated with MeOH (3 × 10 mL), and then purified by flash chromatography (cyclohexane–EtOAc, 3:1) to yield **22** (14.8 mg, 51%), as a colourless oil; $[\alpha]_D^{20}$ −19.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.28 (m, 15H, H arom. Bn), 5.02 (d, 1H, $J = 11.9$ Hz, CHPh), 4.96 (d, 1H, $J = 11.1$ Hz, CHPh), 4.82 (d, 3H, $J = 11.3$ Hz, 3CHPh), 4.68 (d, 1H, $J = 11.9$ Hz, CHPh), 4.17 (d, 1H, $J_{3,4} = 3.0$ Hz, H-4) 4.06 (t, 1H, $J_{1,2} = J_{2,3} = 9.0$ Hz, H-2), 3.99 (dd, 1H, $J_{5,6a} = 4.3$, $J_{6a,6b} = 10.9$ Hz, H-6), 3.87 (t, 1H, $J_{5,6b} = J_{6a,6b} = 10.5$ Hz, H-6b), 3.76 (dt, 1H, $J_{1,2} = J_{1,Feq} = 8.5$, $J_{1,Fax} = 16.7$ Hz, H-1), 3.58 (dd, 1H, $J_{3,4} = 2.6$, $J_{2,3} = 9.1$ Hz, H-3), 2.70 (br s, 1H, OH), 2.04 (br d, 1H, $J_{5,Fax} = 24.5$ Hz, H-5), 1.64 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.87, 138.61, 138.24 (3C arom. quat. Bn), 128.98–127.09 (15CH arom. Bn), 121.55 (dd, $^1J_{C,F} = 244.0$, $^1J_{C,F'} = 252.7$ Hz, CF_2), 82.53 (C-3), 79.67 (d, $^3J_{C,F} = 7.9$ Hz, C-2), 75.97 (CH_2Ph), 74.83 (CH_2Ph), 74.63 (br s, C-1), 73.73 (CH_2Ph), 72.12 (d, $^3J_{C,F} = 9.0$ Hz, C-4), 56.73 (dd, $^3J_{C,F} = 2.6$, $^3J_{C,F'} = 4.3$ Hz, C-6), 46.47 (t, $^2J_{C,F} = 19.8$ Hz, C-5); ^{19}F NMR ($CDCl_3$, 235 MHz): δ −104.79 (br d, 1F, $J_{Feq,Fax} = 251.0$ Hz), −119.52 (br d, 1F, $J_{Feq,Fax} = 256.7$ Hz); CIMS: $[M+H]^+$ calcd for $C_{28}H_{31}O_5F_2$, 485.2140; found, 485.2143.

3.20. 5a-Difluoro-5a-carba-β-D-galactopyranose (23)

Pd–C (10%, 2 mg) was added to a solution of **22** (18 mg, 0.04 mmol) in MeOH (3 mL). Three purges of vacuo/argon were performed, followed by five purges of vacuo/H_2. After stirring for 2 h at room temperature under hydrogen (2 atm), the mixture was filtered through a Rotilabo® Nylon 0.45 μm filter and the solvent evaporated to afford *gem*-difluoro-carba-β-D-galactopyranose **23** (7.2 mg, 91%) as a colourless oil; $[\alpha]_D^{20}$ −16.2 (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD, 400 MHz): δ 4.17 (ddd, 1H, $J = 2.6$, $J_{3,4} = 3.0$, $J = 5.3$ Hz, H-4) 4.01–3.95 (m, 2H, H-6a, H-6b), 3.76 (dt, 1H, $J_{2,F} = 1.2$, $J_{1,2} = J_{2,3} = 9.8$ Hz, H-2), 3.55 (ddd, 1H, $J_{1,Feq} = 6.4$, $J_{1,2} = 9.8$, $J_{1,Fax} = 20.1$ Hz, H-1), 3.44 (dd, 1H, $J_{3,4} = 3.2$, $J_{2,3} = 9.7$ Hz, H-3), 2.06 (br d, 1H, $J_{5,Fax} = 27.4$ Hz, H-5); ^{13}C NMR (CD_3OD, 100 MHz): δ 122.17 (dd, $^1J_{C,F} = 243.2$, $^1J_{C,F'} = 250,0$ Hz, CF_2), 74.64 (t, $^2J_{C,F} = 20.4$ Hz, C-1), 73.89 (d, $^4J_{C,F} = 1.8$ Hz, C-3), 71.29 (d, $^3J_{C,F} = 9.0$ Hz, C-2), 67.68 (d, $^3J_{C,F} = 9.8$ Hz, C-4) 55.49 (dd, $^3J_{C,F} = 2.4$, $^3J_{C,F'} = 4.7$ Hz, C-6), 46.18 (t, $^2J_{C,F} = 19.4$ Hz, C-5); ^{19}F NMR (CD_3OD, 235 MHz): δ −108.52 (ddd, 1F, $J_{1,Feq} = 5.2$, $J_{5,Feq} = 10.5$, $J_{Feq,Fax} = 247.0$ Hz, F_{eq}), −123.80 (ddd, 1F, $J_{1,Fax} = 20.1$, $J_{5,Fax} = 29.8$, $J_{Feq,Fax} = 247.0$ Hz, F_{ax}); CIMS: $[M+NH_4]^+$ calcd for $C_7H_{16}O_5NF_2$, 232.0997; found, 232.0988.

3.21. Ab initio calculations

The calculations were performed on HP Cluster Superdome computer, at the Supercomputing Centre of Galicia, Spain (CESGA). Full geometry optimizations were performed with GAUSSIAN98[13] for α,β-*gem*-difluoro-carbagalactopyranose, α,β-*gem*-difluoro-carbamannopyranose, α,β-*gem*-difluoro-carbaglucopyranose and the corresponding mono-fluorinated analogues using Møller-Plesset calculations, specifically, at the MP2/6-31G(d,p) level of theory. Vibrational frequency calculations were performed to characterize the nature of each conformer.

3.22. X-ray crystal structure

Crystal of dimensions, $0.35 \times 0.20 \times 0.01\ mm^3$, was mounted with Paratone-N oil (Hampton Research) coating and immediately placed in a nitrogen cold stream. X-ray intensity data were collected at 100 K on a Bruker-Nonius X8-APEX2 CCD area-detector diffractometer using Mo-K_α radiation ($\lambda = 0.71073$ Å). Six sets of narrow data frames (30 s per frame) were collected at different values of θ, for six initial values of ϕ, using 0.5° increments of ϕ. Data reduction was accomplished using SAINT V7.03 (APEX2 version 2.0–2; Bruker AXS: Madison, WI, 2003). The redundancy (14.64) in data allowed a semi-empirical absorption correction (SADABS V2.10)[1] to be applied, on the basis of multiple measurements of equivalent reflections. The structure was solved by direct methods, developed by successive difference Fourier syntheses, and refined by full-matrix least-squares on all F^2 data using SHELXTL V6.14 (SHELXTL version 6.14; Bruker AXS: Madison, WI, 2001). Crystal structure analysis: monoclinic, space group $P2(1)$; dimensions $a = 5.1332(5)$ Å, $b = 6.6770(7)$ Å, $c = 12.1193(13)$ Å, $\beta = 99.694(5)°$, $V = 409.45(7)$ Å^3; $Z = 2$; total reflections collected: 25,587; independent reflections: 1308 (1239 $F_o > 4\sigma(F_o)$); data were collected up to a 2θ max value of 60.52° (98.7% coverage). Number of variables: 175; $R_1 = 0.0245$, $wR_2 = 0.0636$, $S = 1.088$; highest residual electron density 0.346 e Å^{-3}. CCDC 641966 contains the crystallographic data for the structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB12EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.

Acknowledgements

The authors thank Fundação para a Ciência e Tecnologia (FCT Portugal) for research grant (João Sardinha) and the Franco Spanish program PICASSO for useful travel money.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.05.021.

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