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Carbohydrate Research 341 (2006) 2641–2652
Carbohydrate RESEARCH

Chlorodifluoromethyl-substituted monosaccharide derivatives—radical activation of the carbon–chlorine-bond☆

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Received 4 July 2006; received in revised form 22 August 2006; accepted 26 August 2006
Available online 20 September 2006

Dedicated to Professor Dr. Dieter Naumann on the occasion of his 65th birthday

Abstract—The dithionite-mediated addition of $BrCF_2Cl$ to 3,4-di-*O*-pivaloyl-D-xylal (**1**) generated preferably 1-CF_2Cl-substituted products, that is, (2-bromo-2-deoxy-3,4-di-*O*-pivaloyl-β-D-xylopyranosyl)-chlorodifluoromethane and (2-deoxy-3,4-di-*O*-pivaloyl-β-D-*threo*-pentopyranosyl)-chlorodifluoromethane. Selected chlorodifluoromethyl-substituted monosaccharide derivatives were hydrodechlorinated or alkylated at the CF_2Cl-group using tin reagents under radical reaction conditions. Thus, hydrodechlorinations of (2,3,4-tri-*O*-acetyl-6-deoxy-α-L-galactopyranosyl)-chlorodifluoromethane and of methyl 3,4-di-*O*-acetyl-2-*C*-chlorodifluoromethyl-2,6-dideoxy-α/β-L-glucopyranoside are reported using tri-*n*-butyltin hydride initiated by AIBN. UV-initiated allylations are reported for reactions of (2-deoxy-3,4-di-*O*-pivaloyl-β-D-*threo*-pentopyranosyl)-chlorodifluoromethane, (2,3,4-tri-*O*-acetyl-6-deoxy-α-L-galactopyranosyl)-chlorodifluoromethane, 1,3,4,6-tetra-*O*-acetyl-2-*C*-chlorodifluoromethyl-2-deoxy-α-D-glucopyranose, 1,3,4,6-tetra-*O*-acetyl-2-*C*-chlorodifluoromethyl-2-deoxy-α-D-mannopyranose and methyl 3,4-di-*O*-acetyl-2-*C*-chlorodifluoromethyl-2-deoxy-α/β-D-rabinopyranoside with allyltri-*n*-butyltin.

Keywords: Glycals; Chlorodifluoromethylation; Fluorinated sugars; C–Cl-bond activation; Radical hydrodechlorination; Radical allylation

1. Introduction

The interest in fluorinated analogues of natural substances is increasing continuously because introduction of fluorine or fluoroalkyl groups may significantly modify the chemical, physical and biological properties of the natural substances.[2–9] 'Organic fluorine' has proven to be valuable and auspicious in bioorganic and medical chemistry, because fluorine can, when strategically positioned, suppress adventitious metabolism, relative to the hydrocarbon analogue. The occurrence of a fluorine substituent in commercial pharmaceutical compounds continues to increase from 2% in 1970 to estimates of more that 18% at present.[10] In view of potential biological properties, new *gem*-difluorinated compounds attract special attention.[11,12] Moreover, a difluoromethylene group introduced instead of an oxygen atom in compounds with a sensitive C–O-bond (e.g., a glycosidic bond) can be used to stabilize such compounds without significantly changing the electronic properties of the parent substance. However, selective methods of fluoroalkylation are fairly rare, especially, in carbohydrate chemistry.[13]

2. Results and discussion

2.1. Chlorodifluoromethylation of glycals

In previous papers,[1,14,15] we reported the introduction of a chlorodifluoromethyl group into 1,2-unsaturated

☆ Organofluorine Compounds and Fluorinating Agents, Part 34; for Part 33 see Ref. 1.

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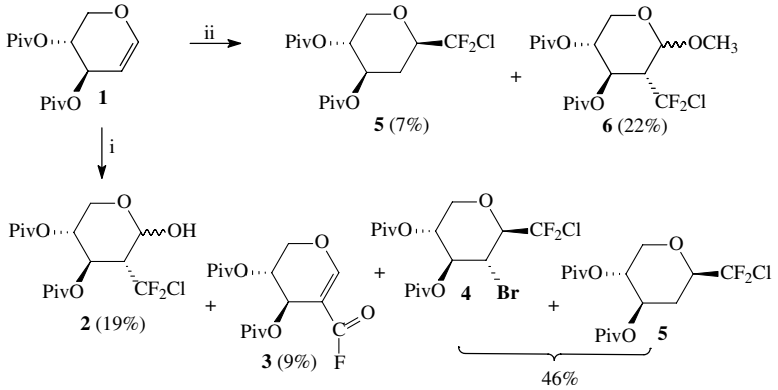
doi:10.1016/j.carres.2006.08.023

carbohydrates by dithionite-mediated addition of $BrCF_2Cl$ to the double bond. The starting materials were the peracetylated D-glucal,[14,15] L-rhamnal,[1,14] D-ribal (D-arabinal)[14] and D-xylal.[14] In all cases, the chlorodifluoromethyl group was predominantly added to the more electron-rich 2-position of the glycals. As radical intermediates are involved in the sodium dithionite-mediated fluoroalkylations of unsaturated substrates,[16,17] transformations of unsaturated carbohydrates lead to different by-products. Thus, 3,4-di-*O*-acetyl-D-xylal reacted with $BrCF_2Cl$ to give 3,4-di-*O*-acetyl-2-*C*-chlorodifluoromethyl-2-deoxy-D-xylopyranose in an isolated yield of 54%, in addition to some unidentified by-products.[14] It could be shown by complete elucidation of the by-products from L-rhamnal and $BrCF_2Cl$ that some of the by-products were compounds with a chlorodifluoromethyl group at the 1-position.[1]

1-Chlorodifluoromethyl derivatives are interesting C-glycosides, which could be suitable precursors for CF_2-bridged glycoside mimetics. Therefore, we focussed our efforts on finding a method that allows regioselective 1-chlorodifluoromethylations. The aim was achieved by modification of the 1,2-unsaturated sugar derivatives. Thus, peracylated 2-hydroxy-glycals, that is, 1,5-anhydro-2,3,4-tri-*O*-pivaloyl-D-*threo*-pent-1-enitol, 2,3,4-tri-*O*-acetyl-1,5-anhydro-6-deoxy-L-*lyxo*-hex-1-enitol and 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol were used as starting materials. The dithionite-mediated additions of $BrCF_2Cl$ to these compounds produced the desired C-glycosides 1,5-anhydro-1-(*S*)-chlorodifluoromethyl-2,3,4-tri-*O*-pivaloyl-D-ribitol, 2,3,4-tri-*O*-acetyl-1,5-anhydro-1-(*R*)-chlorodifluoromethyl-6-deoxy-L-galactitol and 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-1-(*S*)-chlorodifluoromethyl-D-glucitol, respectively, in moderate to good yields.[1]

Although an earlier experiment showed that 3,4,6-tri-*O*-pivaloyl-D-galactal and CF_2Br_2 give the corresponding 2-*C*-bromodifluoromethyl-substituted D-galactose derivative in a dithionite-mediated reaction,[18] we tested three additional models to determine if (compared with acetyl protecting groups) the more bulky pivaloyl groups could direct a $ClCF_2$-group into the 1-position of peracylated glycals. Thus, 3,4-di-*O*-pivaloyl-D-arabinal, 3,4,6-tri-*O*-pivaloyl-D-glucal, and 3,4-di-*O*-pivaloyl-D-xylal (**1**) were reacted with $BrCF_2Cl$ in the presence of sodium dithionite.[19] The result was that the D-arabinal and D-glucal derivatives only produced product mixtures similar to those obtained from the corresponding acetylated analogues[19] (for further reference data see also Refs. 14 and 15). However surprisingly, the pivaloylated D-xylal derivative **1** formed predominantly two 1-fluoroalkylated products (overall yield 46%) as shown in Scheme 1. Although the mixed fraction of these two compounds **4** and **5** could not be separated by flash chromatography, crystals of the pure compounds were obtained from the crystalline mixture of this fraction. Thus, the most important analytical data, including X-ray measurements, could be determined for each of the two compounds. Because the two products show the same configuration at C-1, the mixture was treated with sodium dithionite in DMF/methanol to reduce bromo derivative **4** into the product **5**. By analogy with the procedure described by Constantino et al.[20] for hydrodeiodinations of 2-iodo-2-deoxy-sugars, the dithionite reagent allowed the desired hydrodehalogenation yielding methylene derivative **5** in pure form.

The structure of the 2-bromo-derivative **4** (Fig. 1) shows the equatorial arrangement of the substituents at the 1- and 2-positions. This indicates a trans-addition of the $BrCF_2Cl$ reagent to the D-xylal derivative **1**; the bromine atom was likewise introduced trans to the protective group at the 3-position. The structure of **5** was likewise confirmed by X-ray-analysis.[19] When the radical addition of $BrCF_2Cl$ to 3,4-di-*O*-pivaloyl-D-xylal (**1**) was carried out in dry methanol, the overall yield of the products was only low and the introduction of the CF_2Cl-group was not exclusively introduced at the 1-position. Under these reaction conditions, we obtained the anomeric methyl glycosides **6** in 22% yield



Scheme 1. Reagents and conditions: (i) $BrCF_2Cl$, $Na_2S_2O_4$, $NaHCO_3$, CH_3CN, H_2O, −10 °C → rt, 9 h; (ii) $BrCF_2Cl$, $Na_2S_2O_4$, $NaHCO_3$, MeOH, −10 °C → rt, 9 h.

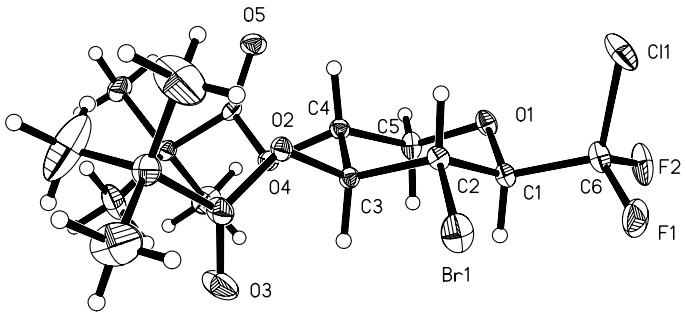


Figure 1. Molecular structure of (2-bromo-2-deoxy-3,4-di-*O*-pivaloyl-β-D-xylopyranosyl)-chlorodifluoromethane (**4**) with 30% probability of the thermal ellipsoids.

and product **5** in 7% yield (Scheme 1); bromo-derivative **4** was not found.

2.2. Transformation of the chlorodifluoromethyl group

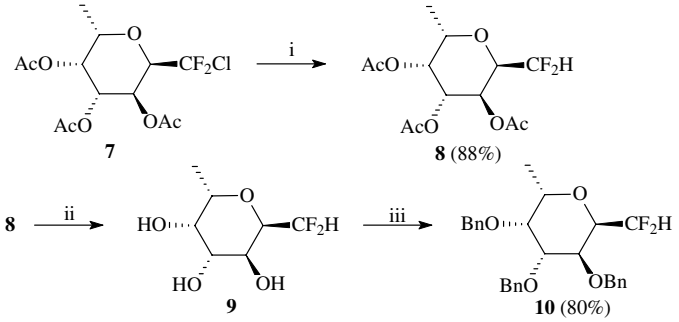
Chlorodifluoromethylated sugars open new possibilities for consecutive reactions by activation of the C–Cl-bond. Previously, the transformation of a chlorodifluoromethyl group into a trifluoromethyl group was reported.[15] However, because of the lower reactivity of the CF_2–Cl bond compared to a CF_2–Br bond of bromodifluoromethylated sugars,[18] the transformation required a more active fluorination reagent (TBAF/CsF).[15]

gem-Difluorinated compounds are of particular interest in view of their potential biological properties.[11,12] Therefore, we studied some possibilities to activate the carbon–chlorine bond of the chlorodifluoromethyl group. At first, compound **7**[1] was hydrodechlorinated by treatment with tri-*n*-butyltin hydride and AIBN in toluene. The isolated yield of product **8** was 88% (Scheme 2). In a second experiment, the possibility of a selective deprotonation of the CF_2H moiety was investigated as a prerequisite for the following C–C-bond formations with selected electrophiles. Initially, compound **8** was transformed into a benzyl derivative **10** as shown in Scheme 2 (overall yield of **10** via two steps: 80%). Subsequent treatment of **10** with lithium diisopropylamide did not result in deprotonation of the CF_2H-group, but instead deprotonation of the likewise acidified proton at C-1 occurred. The unsaturated product, formed in very poor yields under HF-elimination, has an exocyclic fluoromethylene group at C-1.

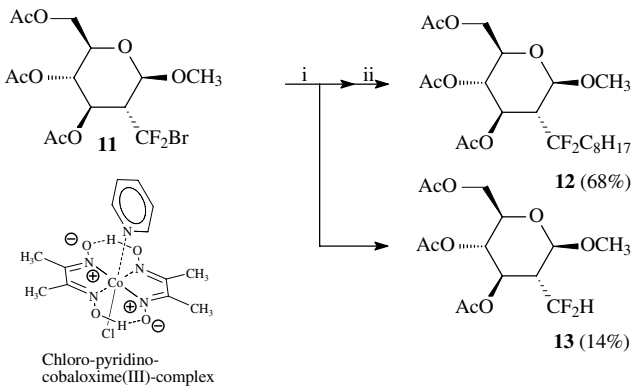
Subsequently, radical activation of the CF_2X-group was investigated. First, a chloro-pyridino-cobaloxime(I)-complex[21] was used to activate the CF_2Br-group of compound **11**[18] and simultaneously reacted with 1-octene. The column chromatographic separation of the product mixture gave a pure fraction of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*C*-difluoromethyl-β-D-glucopyranoside[18] in 14% isolated yield and a mixed fraction of a saturated and at least two unsaturated products, probably compound **12** and *E*/*Z*-mixtures of products containing a double bond in the side chain. The latter was reduced with Pd/C and H_2 yielding exclusively product **12** in 68% overall yield (Scheme 3).

The application of this procedure on the reaction of chlorodifluoromethyl derivative **7** with 1-octene resulted in a complex product mixture containing only small amounts of the desired product of C–C-coupling. The major component was the CF_2H-derivative **8**.

Similarly, the reaction of the anomeric chlorodifluoromethyl derivatives **14** with the more reactive ethyl vinyl ether yielded only products of hydrodechlorination (Scheme 4). In this case the reaction was carried out in the presence of *n*-Bu_3SnH/AIBN for the radical generation. Following the procedure described in Section 4.10, the α-anomer **15** was isolated in 32% yield. When the



Scheme 2. Reagents and conditions: (i) *n*-Bu_3SnH, AIBN, toluene, argon, reflux, 3 h; (ii) cat. *t*-BuOK, CH_3OH, rt, 12 h; (iii) BnBr, NaH, DMF, rt, 6 h.



Scheme 3. Reagents and conditions: (i) 1-octene, Al, I_2, chloro-pyridino-cobaloxime(III)-complex, CH_3OH, 0 °C–rt, 4–5 h; (ii) H_2 (1 atm), Pd/C, EtOAc, rt, 3 d.

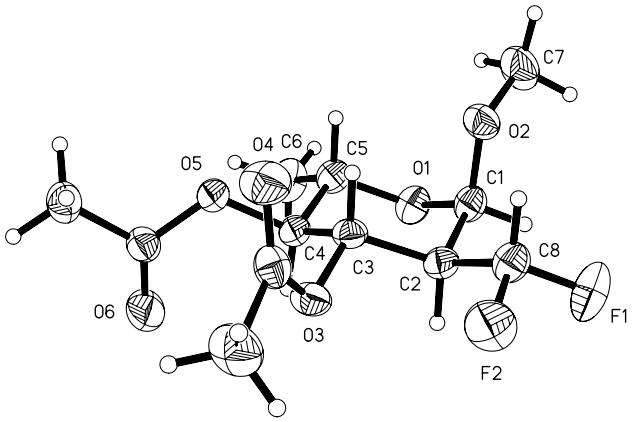


Figure 2. Molecular structure of methyl 3,4-di-*O*-acetyl-2-*C*-difluoro-methyl-2,6-dideoxy-α-L-glucopyranoside (**15**) with 50% probability of the thermal ellipsoids.

procedure was modified in such a way, that solutions of *n*-Bu_3SnH and AIBN were simultaneously added drop by drop, no significant change of the product spectrum was observed. β-Configurated products could not be identified in the product mixtures, however, decomposition was observed. Consequently, only some small fractions of fluorine-free (not identified) compounds could be separated beside product **15**. The ^{19}F NMR spectra of these fractions did not show any signals related to a CF_2H-group or to the expected CF_2–C-group.

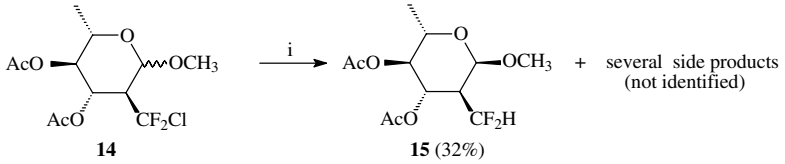
Compound **15** crystallized from *n*-heptane and EtOAc in single crystals. Its molecular structure shows that the α-L-*gluco*-configured ring adopts a $^1C_4$-chair-conformation. All substituents with the exception of the methoxy group are equatorially arranged (Fig. 2).

The following experiment is based on a strategy of Arnone et al.[22] Under radical reaction conditions, the authors cyclized different allyl ethers of 1-chloro-1,1-difluoro-3-(*p*-tolylsulfonyl)propan-2-ols leading to five-membered carbocyclic rings. We started with allyl derivative **17**, prepared from **16**[14] analogous to Refs. 23 and 24 (Scheme 5). However, because the CF_2Cl-group of **17** is linked to a sp^2-hybridized carbon, a radical cyclization would lead to a sp^2-hybridized bridging carbon in a system of condensed rings, that is, the formation of the bicyclic compound (**I**) (5-*exo*-trig reaction) is not expected. Nevertheless, the bicyclic byproduct **18** with a fused six-membered ring (6-*endo*-trig reaction) was formed in 11% yield. However, the major product (isolated yield 80%) was also in this case, a hydrodechlorinated CF_2H-derivative, compound **19**, with intact allyl group at C-1 (Scheme 5).

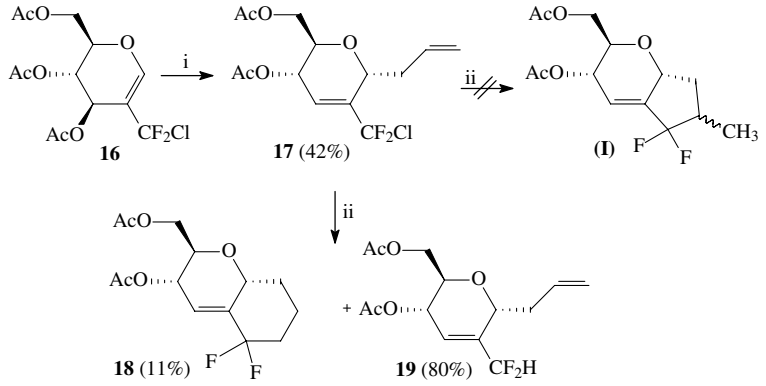
The ^{19}F NMR spectrum of compound **18** shows two doublets at −93.8 and −106.5 ppm with a fluorine–fluorine coupling of 242 Hz. These chemical shifts and coupling indicate the replacement of the chlorine atom by a carbon atom. The corresponding ^1H and ^{13}C NMR spectra contain appropriate signals for three new CH_2-groups, whereas a new signal for a CH_3-group, required for product (**I**), was not found. The fact that C-2 of compound **18** is quaternary and C-3 is tertiary proves that the product is 2,3-unsaturated. The ^{13}C NMR signal for C-3 has a chemical shift of 119.3 ppm, which is typical for carbon atoms in double bonds.

The radical activations with AIBN/tri-*n*-butyltin hydride have shown that this reagent system induces predominantly the reduction of a F_2C–X-bond to a F_2C–H-bond. Therefore, we tested finally the allyltri-*n*-butyltin reagent,[25,26] which was already used for radical allylations of a CF_2Br-group[27,28] and of chlorodifluoro-acetic acid,[29] respectively. The reactions of the CF_2Cl-substituted sugars **5**, **7**, **22**,[14,15] **24**[15] and **26α,β** with allyltri-*n*-butyltin in EtOAc, carried out in a quartz tube, were initiated by UV-irradiation ($\lambda = 254$ nm). Scheme 6 shows the results of these CF_2-allylations. The products **20**, **21**, **23**, **25** and **27α,β** were isolated with yields between 48% and 73%.

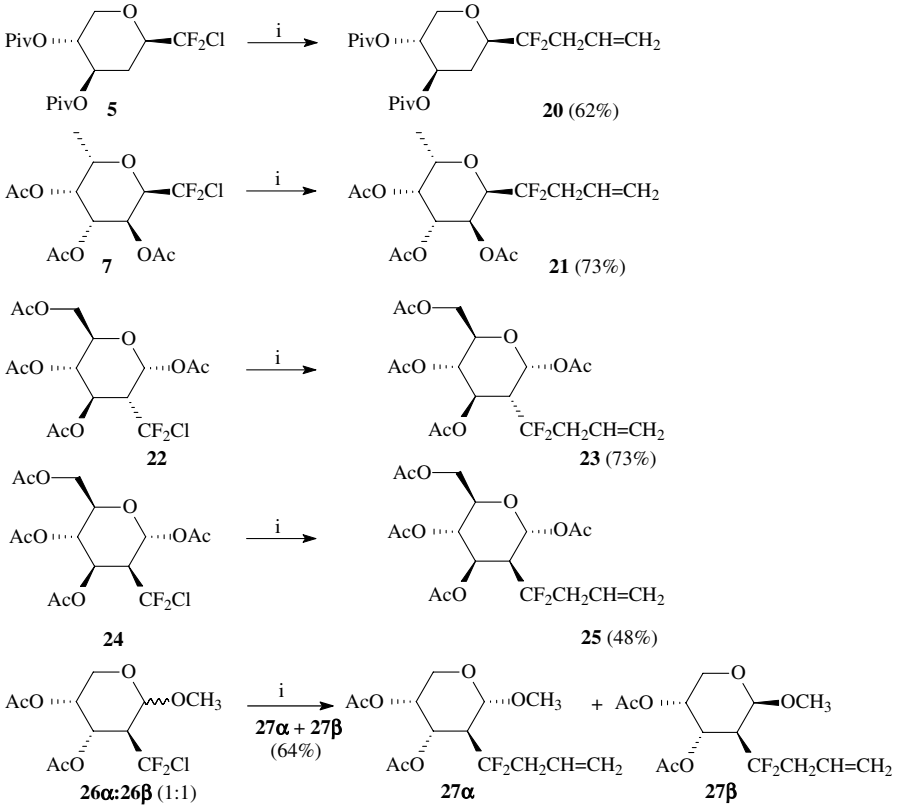
The reactions were uniformly stopped after 2–3 h, although the conversion of the starting materials was not completed in each case. However, an extension of



Scheme 4. Reagents and condition: *n*-Bu_3SnH, AIBN, ethyl vinyl ether, benzene, reflux, 12 h.



Scheme 5. Reagents and conditions: (i) $AllSiMe_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C → rt, 24 h; (ii) AIBN, *n*-Bu_3SnH, benzene, reflux, 4 h.



Scheme 6. Reagents and conditions: allyltri-*n*-butyltin, EtOAc, $\lambda = 254$ nm, 2–3 h.

the reaction time by 15–30 min led to larger amounts of by-products but not to higher yields of the desired products. Ethyl acetate was selected as the solvent for the photoreaction, after the evaluation of solvents of a range of polarities as it yielded the best results at relatively short reaction times.

3. Conclusion

For the first time, a CF_2Cl-group was preferentially introduced into the 1-position of an 1,2-unsaturated monosaccharide derivative without an acyloxy group in 2-position (see Ref. 1). However, this dithionite-mediated addition of $BrCF_2Cl$ to the starting material 3,4-di-*O*-pivaloyl-D-xylal (**1**) requires the use of acetonitrile/water as the solvent system to produce the major products (2-bromo-2-deoxy-3,4-di-*O*-pivaloyl-β-D-xylopyranosyl)-chlorodifluoromethane (**4**) and (2-deoxy-3,4-di-*O*-pivaloyl-β-D-*threo*-pentopyranosyl)-chlorodifluoromethane (**5**).

Activation of CF_2Cl-groups may be achieved by radical reaction conditions. Tri-*n*-butyltin hydride/AIBN leads to satisfying results with reference to a reduction

of this group to a CF_2H-moiety. Under UV irradiation ($\lambda = 254$ nm), reaction with allyltri-*n*-butyltin leads to allylation of the CF_2Cl-group yielding a CF_2-allyl unit. The allylations with allyltri-*n*-butyltin are the first examples of radical substitution at CF_2Cl-groups of carbohydrates. The *C*-glycosides, available in this way, are very interesting unsaturated building blocks for novel potentially bioactive substances.

4. Experimental

4.1. General methods

Column chromatography: Particle size for silica gel 63–200 μm; thin layer chromatography (TLC): E. Merck Silica Gel 60 F_{254} foils; NMR: Bruker instruments AC 250 and ARX 300; internal standard $(CH_3)_4Si$. Melting points were measured using a polarising microscope Leitz (Laborlux 12 Pol) equipped with a hot stage (Mettler FP 90). Chemicals: $Na_2S_2O_4$ (85%, Fluka), tri-*n*-butyltin hydride (96%, Fluka), allyltri-*n*-butyltin (ABCR), AIBN (98%, Fluka), allyltrimethylsilane (97%, Fluka), $BF_3{\cdot}Et_2O$ (Fluka).

For the X-ray structure determination of **4**, **5**[19] and **15**, an X8 Apex with CCD area detector with Mo-K_α-radiation ($\lambda = 0.71073$ Å) and graphite monochromator was used. The structures were solved by direct methods (Bruker SHELXTL, 1990, SHELXS-97[30]). The refinement was done in all cases by the full matrix least-squares method of Bruker SHELXTL, Vers.5.10, Copyright 1997, Bruker Analytical X-ray Systems. All nonhydrogen atoms were refined anisotropically. The hydrogen atoms were put into theoretical positions and refined using the riding model. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 612996 (**4**), 612997 (**5**),[19] 612998 (**15**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.2. Dithionite-initiated radical addition of $BrCF_2Cl$ to glycals

A solution of protected glycal (10 mmol) in CH_3CN and H_2O (2:1, 30 mL) (or 30 mL dry CH_3OH) was stirred for 1 h at rt under an argon atmosphere. After cooling to −10 °C, $NaHCO_3$ (1.5 equiv) was suspended with vigorous stirring and then $BrCF_2Cl$ (about 5 mL) was introduced (install an dry ice/acetone-cooled trap for condensation of Freon vapor). Subsequently, $Na_2S_2O_4$ (1.5 equiv) was added and the mixture was warmed to ~25 °C. At about 4 °C, Freon 12a reaches reflux. After 8 h, the cold trap is removed and stirring is continued for further 12 h at ~25 °C. Finally, Et_2O (50 mL) and H_2O (30 mL) were added. The organic phase was separated, washed with H_2O (2×30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography.

4.3. Photochemical allylation of carbohydrates with a CF_2Cl-group

The CF_2Cl containing derivative (0.3 mmol) was dissolved in 4 mL of dry EtOAc in a quartz tube ($d = 1$ cm, $l = 25$ cm) under argon. Allyltri-*n*-butyltin (5 equiv) was added and the solution degassed with argon for 30 min. The quartz tube was closed with a septum and the reaction mixture was irradiated for 2–3 h at $\lambda = 254$ nm in a Rayonet apparatus. Afterwards, the solvent was removed under reduced pressure and the syrupy residue was purified by column chromatography.

4.4. 2-*C*-Chlorodifluoromethyl-2-deoxy-3,4-di-*O*-pivaloyl-D-xylopyranose (2), 1,5-anhydro-2-*C*-fluoroformyl-1,2-dideoxy-3,4-di-*O*-pivaloyl-D-*threo*-pent-1-enitol (3), (2-bromo-2-deoxy-3,4-di-*O*-pivaloyl-β-D-xylopyranosyl)-chlorodifluoromethane (4) and (2-deoxy-3,4-di-*O*-pivaloyl-β-D-*threo*-pentopyranosyl)-chlorodifluoromethane (5)

3,4-Di-*O*-pivaloyl-D-xylal (**1**)[31] (0.57 g, 2.0 mmol) was reacted as described in Section 4.2. The syrupy residue (0.7 g) was separated by column chromatography (heptane/EtOAc, 10:1 v/v) yielding successively 0.15 g (19%) of **2**, 0.34 g of **4** and **5** together (46%) and 0.06 g (9%) of **3**.

Compound **2**: $R_f = 0.40$ (heptane/EtOAc, 2:1 v/v), colourless syrup; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.85 (dd, 1H, $^3J_{2,3} = 11.0$, $^3J_{3,4} = 9.4$ Hz, H-3), 5.60 (d, 1H, $^3J_{1,2} = 3.2$ Hz, H-1), 4.94 (ddd, 1H, $^3J_{3,4} = 9.4$, $^3J_{4,5a} = 10.5$, $^3J_{4,5b} = 6.3$ Hz, H-4), 3.88 (t, 1H, $^2J_{5a,5b} = 10.9$ Hz, H-5a), 3.79 (dd, 1H, $^3J_{4,5b} = 6.3$, $^2J_{5a,5b} = 10.9$ Hz, H-5b), 3.04 (br s, 1H, OH, HO-1), 2.95–2.81 (m, 1H, $^3J_{1,2} = 3.2$, $^3J_{2,3} = 11.0$ Hz, H-2), 1.15, 1.15 (2s, 18H, $2 \times C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9, 176.6 ($2 \times C{=}O$), 127.7 (t, $^1J_{C,F} = 297$ Hz, CF_2Cl), 90.9 (t, $^4J_{C,F} = 5$ Hz, C-1), 70.1 (C-4), 66.7 (C-3), 58.6 (C-5), 53.9 (t, $^2J_{C,F} = 22$ Hz, C-2), 38.9, 38.8 ($2 \times C(CH_3)_3$), 27.2, 27.2 ($2 \times C(CH_3)_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ −47.6 (d, $^2J_{Fa,Fb} = 172$ Hz, F_a), −48.8 (d, $^2J_{Fa,Fb} = 172$ Hz, F_b); Anal. Calcd for $C_{16}H_{25}ClF_2O_6$ (386.82): C, 49.68; H, 6.51. Found: C, 50.30; H, 6.49.

Compound **3**: $R_f = 0.56$ (heptane/EtOAc, 2:1 v/v), colourless syrup, $[\alpha]_D^{22}$ −111.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.90 (s, 1H, H-1), 5.48 (t, 1H, $^3J_{2,3} = {}^3J_{3,4} = 2.3$ Hz, H-3), 4.95–4.91 (m, 1H,

H-4), 4.48 (dt, 1H, $^2J_{5a,5b} = 12.7$, $^3J = 2.1$, $^3J = 4.1$ Hz, H-5a), 4.07–4.00 (m, 1H, $^2J_{5a,5b} = 12.7$ Hz, H-5b), 1.19, 1.17 (2s, 18H, $2 \times C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.0, 176.7 ($2 \times C{=}O$), 163.1 (d, $^3J_{C,F} = 6$ Hz, C-1), 156.6 (d, $^1J_{C,F} = 335$ Hz, COF), 100.0 (d, $^2J_{C,F} = 60$ Hz, C-2), 65.3 (C-5), 64.9 (C-4), 60.9 (C-3), 39.0, 38.8 ($2 \times C(CH_3)_3$), 27.2, 27.0 ($2 \times C(CH_3)_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ +13.4 (s, COF); HRMS-ESI: Calcd $[M+Na]^+$: 353.1382. Found: 353.1376.

Compound **4**: $R_f = 0.62$ (heptane/EtOAc, 2:1 v/v), Mp 143–144 °C (*i*-PrOH); ^1H NMR (250 MHz, $CDCl_3$): δ 5.39 (t, 1H, $^3J_{2,3} = {}^3J_{3,4} = 9.6$ Hz, H-3), 4.93 (dd, 1H, $^3J_{3,4} = 9.6$, $^3J_{4,5a} = 5.6$ Hz, H-4), 4.25 (dd, 1H, $^3J_{4,5a} = 5.6$, $^2J_{5a,5b} = 11.8$ Hz, H-5a), 4.01–3.94 (m, 2H, H-1, H-2), 3.43 (t, 1H, $J = 11.0$ Hz, H-5b), 1.15, 1.14 (2s, 18H, $2 \times C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.2, 176.8 ($2 \times C{=}O$), 127.0 (t, $^1J_{C,F} = 296$ Hz, CF_2Cl), 81.5 (t, $^3J_{C,F} = 27$ Hz, C-1), 73.9 (C-3), 68.9 (C-4), 67.0 (C-5), 43.3 (C-2), 38.9, 38.8 ($2 \times C(CH_3)_3$), 27.3, 27.2 ($2 \times C(CH_3)_3$); ^{19}F NMR (235 MHz, $CDCl_3$): $\delta = -54.3$ (d, $^2J_{Fa,Fb} = 176$ Hz, F_a), -57.5 (d, $^2J_{Fa,Fb} = 176$ Hz, F_b); HRMS-ESI: Calcd $[M+Na]^+$: 471.0356. Found: 471.0349.

Compound **5**: $R_f = 0.62$ (heptane/EtOAc, 2:1 v/v), Mp 122.0–122.6 °C (Et_2O), $[\alpha]_D^{23}$ −34.3 (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 5.09 (dd, 1H, $^3J_{2a,3} = 5.0$, $^3J_{3,4} = 10.0$ Hz, H-3), 5.02 (dd, 1H, $^3J_{3,4} = 10.0$, $^3J_{4,5a} = 5.4$ Hz, H-4), 4.24 (dd, 1H, $^3J_{4,5a} = 5.4$, $^2J_{5a,5b} = 11.2$ Hz, H-5a), 3.94–3.87 (m, 1H, $^3J_{1,2a} = 2.1$, $^3J_{1,2b} = 11.8$ Hz, H-1), 3.33 (dd, 1H, $^3J_{4,5b} = 10.0$, $^2J_{5a,5b} = 11.2$ Hz, H-5b), 2.39 (m, 1H, $^3J_{1,2a} = 2.1$, $^3J_{2a,3} = 5.0$, H-2a), 1.77 (m, 1H, $^3J_{1,2b} = 11.8$ Hz, H-2b), 1.20, 1.18 (2s, 18H, $2 \times C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7, 177.5 ($2 \times C{=}O$), 127.2 (t, $^1J_{C,F} = 294$ Hz, CF_2Cl), 78.2 (t, $^3J_{C,F} = 29$ Hz, C-1), 70.0 (C-3), 68.7 (C-4), 67.2 (C-5), 38.9, 38.9 ($2 \times C(CH_3)_3$), 30.2 (C-2), 27.2, 27.0 ($2 \times C(CH_3)_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ −62.7 (d, $^2J_{Fa,Fb} = 169$ Hz, F_a), −64.7 (d, $^2J_{Fa,Fb} = 169$ Hz, F_b); Anal. Calcd for $C_{16}H_{25}ClF_2O_5$: C, 51.82; H, 6.80. Found: C, 51.80; H, 7.11.

4.5. Methyl 2-*C*-chlorodifluoromethyl-2-deoxy-3,4-di-*O*-pivaloyl-α-D-xylopyranoside (6α) and methyl 2-*C*-chlorodifluoromethyl-2-deoxy-3,4-di-*O*-pivaloyl-β-D-xylopyranoside (6β)

3,4-Di-*O*-pivaloyl-D-xylal (**1**)[31] (0.32 g, 1.13 mmol) was dissolved in dry CH_3OH (10 mL) and converted as described in Section 4.2. The syrupy residue (0.5 g) was separated by column chromatography (heptane/EtOAc, 20:1 v/v) yielding 0.17 g (22%) of an anomeric mixture of **6α/β** (α:β = 1:0.65).

Compound **6α**: $R_f = 0.60$ (heptane/EtOAc, 2:1 v/v), colourless syrup.

^1H NMR (250 MHz, $CDCl_3$): δ 5.75 (dd, 1H, $^3J_{2,3} = 11.1$, $^3J_{3,4} = 9.3$ Hz, H-3), 4.90 (ddd, 1H, $^3J_{3,4} = 9.3$, $^3J_{4,5a} = 6.1$, $^3J_{4,5b} = 10.8$ Hz, H-4), 5.00 (d, 1H, $^3J_{1,2} = 3.3$ Hz, H-1), 3.75 (dd, 1H, $^3J_{4,5a} = 6.1$, $^2J_{5a,5b} = 10.8$ Hz, H-5a), 3.58 (t, 1H, $^3J_{4,5b} = {}^2J_{5a,5b} = 10.8$ Hz, H-5b), 3.39 (s, 3H, OCH_3), 2.92–2.78 (m, 1H, $^3J_{1,2} = 3.3$, $^3J_{2,3} = 11.1$ Hz, H-2), 1.13, 1.12 (2s, 18H, $2 \times C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ 177.7, 177.4 ($2 \times C{=}O$), 128.6 (t, $^1J_{C,F} = 296$ Hz, CF_2Cl), 97.6 (C-1), 69.9, 66.9, (C-3, C-4), 63.8 (C-5), 55.7 (OCH_3), 53.8 (t, $^2J_{C,F} = 22$ Hz, C-2), 38.9, 38.8 ($2 \times C(CH_3)_3$), 27.2, 27.1 ($2 \times C(CH_3)_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ −46.9 (d, $^2J_{Fa,Fb} = 168$ Hz, F_a), −49.0 (d, $^2J_{Fa,Fb} = 168$ Hz, F_b); HRMS-ESI: Calcd $[M+Na]^+$: 423.1362. Found: 423.1356.

Compound **6β**: $R_f = 0.60$ (heptane/EtOAc, 2:1 v/v), colourless syrup; ^1H NMR (250 MHz, $CDCl_3$): δ 5.50 (t, 1H, $^3J_{2,3} = {}^3J_{3,4} = 8.3$ Hz, H-3), 4.92–4.85 (m, 1H, H-4), 4.76 (d, 1H, $^3J_{1,2} = 4.5$ Hz, H-1), 4.23–4.13 (m, 2H, H-5a, H-5b), 3.41 (s, 3H, OCH_3), 2.75–2.62 (m, 1H, $^3J_{1,2} = 4.5$, $^3J_{2,3} = 8.3$ Hz, H-2), 1.14, 1.13 (2s, 18H, $2 \times C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ 177.9, 177.6 ($2 \times C{=}O$), 128.5 (t, $^1J_{C,F} = 296$ Hz, CF_2Cl), 98.8 (C-1), 70.0, 70.0, (C-3, C-4), 63.6 (C-5), 56.2 (OCH_3), 53.8 (t, $^2J_{C,F} = 22$ Hz, C-2), 38.9, 38.7 ($2 \times C(CH_3)_3$), 27.2, 27.1 ($2 \times C(CH_3)_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ −49.9 (d, $^2J_{Fa,Fb} = 170$ Hz, F_a), −50.8 (d, $^2J_{Fa,Fb} = 170$ Hz, F_b); HRMS-ESI: Calcd $[M+Na]^+$: 423.1362. Found: 423.1356.

4.6. (2,3,4-Tri-*O*-acetyl-6-deoxy-α-L-galactopyranosyl)-difluoromethane (8)

Compound **7**[1] (0.75 g, 2.09 mmol) was dissolved in dry toluene (20 mL). Under argon, 0.76 g of *n*-Bu_3SnH (2.61 mmol) and 0.01 g of AIBN (0.06 mmol) were added. The reaction mixture was heated under reflux for 3 h. Then, the reaction was quenched by the addition of an aq KF solution (10% in H_2O, 10 mL) and stirred for one hour at rt. The heterogenic solution was filtered over Kieselguhr and the filter cake washed with toluene. The toluene phase was washed with H_2O (2×20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The syrupy residue (1.60 g) was separated by column chromatography (heptane/EtOAc, 4:1v/v) yielding 0.58 g (88%) of **8**.

Compound **8**: $R_f = 0.55$ (heptane/EtOAc, 1:2 v/v), colourless syrup; ^1H NMR (250 MHz, $CDCl_3$): δ 5.94 (ddd, 1H, $^2J_{H,Fa,b} = 54.1$, $^2J_{H,Fa,b} = 56.7$, $^3J_{H,1} = 2.6$ Hz, CF_2H), 5.38–5.33 (m, 2H, H-2, H-3), 5.29 (t, 1H, $^3J_{3,4} = {}^3J_{4,5} = 2.6$ Hz, H-4), 4.41–4.24 (m, 1H, H-1), 4.24–4.14 (m, 1H, $^3J_{5,6} = 6.7$ Hz, H-5), 2.13, 2.06, 1.99 (3s, 9H, $3 \times CH_3$), 1.17 (d, 3H, $^3J_{5,6} = 6.7$ Hz, CH_3-6); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.4, 170.1, 169.9 ($3 \times C{=}O$), 115.8 (dd, $^1J_{C,Fa} = 246$, $^1J_{C,Fb} = 248$ Hz, CF_2H), 70.4 (t, $^2J_{C,F} = 22$ Hz, C-1), 69.8

(C-4), 69.7 (C-5), 68.6 (t, $^3J_{C,F} = 2$ Hz, C-2), 66.3 (C-3), 20.8, 20.7, 20.7 ($3 \times CH_3$), 16.1 (C-6); ^{19}F NMR (235 MHz, $CDCl_3$): δ −121.6 (d, $^2J_{Fa,Fb} = 297$ Hz, F_a), −125.4 (d, $^2J_{Fa,Fb} = 297$ Hz, F_b); HRMS-ESI: Calcd $[M+Na]^+$: 347.0918. Found: 347.0926.

4.7. (2,3,4-Tri-*O*-benzyl-6-deoxy-α-L-galactopyranosyl)-difluoromethane (10)

To a solution of compound **8** (0.47 g, 1.45 mmol) in dry CH_3OH (10 mL), *t*-BuOK (0.01 g, 0.087 mmol) was added, and the solution was stirred for 12 h at rt. Monitoring of the reaction by TLC indicated the complete conversion of **8**. The reaction mixture was filtered through Kieselguhr and the CH_3OH was evaporated under reduced pressure. The syrupy residue **9** (0.35 g) was at once dissolved in dry DMF (15 mL). At 0 °C, 0.19 g of NaH (60% in paraffin wax, 4.8 mmol) was added. With a syringe, benzyl bromide (0.53 mL, 4.45 mmol) was quickly added to the reaction mixture. The solution was stirred for about 6 h at rt until complete conversion of the starting material **9** (TLC). Five millilitres of CH_3OH and 5 mL of H_2O were added and the aqueous phase was extracted with toluene (3×20 mL). The organic phase was washed with satd aq $NaHCO_3$-soln, brine and H_2O (each 3×50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The syrupy residue (0.90 g) was separated by column chromatography (heptane/EtOAc, 4:1 v/v) yielding successively 0.54 g of **10**. This corresponds to a yield of 80% after two steps from **8**.

Compound **10**: $R_f = 0.59$ (heptane/EtOAc, 1:2 v/v), colourless syrup, $[\alpha]_D^{22}$ −15.18 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.42–7.22 (m, 15H, $3 \times$ Ph), 5.91 (ddd, 1H, $^2J_{H,Fa,b} = 55.7$, $^2J_{H,Fa,b} = 61.3$, $^3J_{H,1} = 5.4$ Hz, CF_2H), 4.79–4.57 (m, 4H, $2 \times CH_2Ph$), 4.56–4.52 (m, 2H, CH_2Ph), 4.33–4.20 (m, 1H, $^3J_{5,6} = 6.8$ Hz, H-5), 4.16–4.03 (m, 1H, H-1), 3.91–3.84 (m, 3H, H-2, H-3, H-4), 1.43 (d, 3H, $^3J_{5,6} = 6.8$, CH_3-6); ^{13}C NMR (63 MHz, $CDCl_3$): δ 138.5, 138.4, 137.7 ($3 \times$ qC–Ph), 128.6, 128.6, 128.2, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7 ($3 \times$ Ph), 115.7 (dd, $^1J_{C,Fa} = 240$, $^1J_{C,Fb} = 244$ Hz, CF_2H), 75.3 (C-3), 75.2 (C-2), 74.5 (C-4), 73.4, 73,4, 72.4 ($3 \times CH_2Ph$), 71.3 (C-5), 68.8 (dd, $^2J_{C,F} = 23$, 27 Hz, C-1), 14.2 (C-6); ^{19}F NMR (235 MHz, $CDCl_3$): δ −126.1 (d, $^2J_{Fa,Fb} = 295$ Hz, F_a), −127.8 (d, $^2J_{Fa,Fb} = 295$ Hz, F_b). Anal. Calcd for $C_{28}H_{30}F_2O_4$ (468.54): C, 71.78; H, 6.45. Found: C, 72.27; H, 6.61.

4.8. Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*C*-(1,1-difluorononyl)-β-D-glucopyranoside (12) and methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*C*-difluoromethyl-β-D-glucopyranoside (13)

Aluminium powder (0.2 g, 7.41 mmol) was suspended in dry CH_3OH (15–20 mL) and iodine (10–20 mg) was added under argon. The reaction mixture was irradiated with ultrasound for 2–3 min (until the brownish colour disappeared) and afterwards again 10–20 mg of iodine was added and activated by ultrasound. The mixture was cooled to 0 °C under argon. With vigorous stirring, chloro-pyridino-cobaloxime(III)-complex[21] (50 mg, 0.12 mmol), 1-octene (1 mL, 6.42 mmol) and compound **11**[18] (340 mg, 0.78 mmol) were added. The reaction mixture was warmed to rt within 2 h and was stirred for another 2–3 h at rt. The mixture was diluted with EtOAc (20–30 mL), filtered over Kieselguhr and concentrated under reduced pressure. The syrupy residue was separated by column chromatography (heptane/EtOAc, 3:1 → 2:1 v/v) yielding 260 mg of a major fraction; $R_f = 0.30$ (heptane/EtOAc, 3:1 v/v), which consisted of at least three compounds and, as well 40 mg (14%) of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*C*-difluoromethyl-β-D-glucopyranoside (**13**);[18] $R_f = 0.15$ (heptane/EtOAc, 3:1 v/v).

The syrupy residue of the major fraction (260 mg) was dissolved in dry EtOAc (20 mL) and hydrogenated with H_2 (1 atm) and 20 mg of Pd/C (10%) for 48–72 h. After filtration of the reaction mixture over Kieselguhr and concentration of the solution under reduced pressure, 250 mg (68%) of almost pure product **12** could be obtained.

Compound **12**: Colourless syrup; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.45 (dd, 1H, $^3J_{3,4} = 8.9$, $^3J_{2,3} = 9.8$ Hz, H-3), 5.03 (dd, 1H, $^3J_{4,5} = 10.1$ Hz, H-4), 4.46 (d, 1H, $^3J_{1,2} = 7.6$ Hz, H-1), 4.26 (dd, 1H, $^3J_{5,6a} = 4.9$ Hz, H-6a), 4.07 (dd, 1H, $^2J_{6a,6b} = 12.3$ Hz, H-6b), 3.66 (ddd, 1H, $^3J_{5,6b} = 2.6$ Hz, H-5), 3.47 (s, 3H, OCH_3), 2.44 (dddd, 1H, $^3J_{2,Fa,b} = 19.1$, 6.1 Hz, H-2), 2.04, 1.98, 1.96 (all s, 9H, 3 acetyl CH_3), 1.72–2.09 (m, 2H, α-CH_2), 1.13–1.54 (m, 12H, $6CH_2$), 0.84 (t (br), 3H, $^3J_{H,H} = 6.6$ Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.6, 169.8, 169.7 (all s, 3CO), 123.8 (dd, $^1J_{C,Fa,b} = 247.5$, 245.6 Hz, CF_2), 100.5 (t, $^3J_{C\text{-}1,Fa,b} = 6.7$, 6.7 Hz, C-1), 71.1 (s, C-5), 69.4 (s, C-4), 68.7 (dd, $^3J_{C\text{-}3,Fa,b} = 4.0$, 2.6 Hz, C-3), 62.3 (s, C-6), 56.7 (s, OCH_3), 50.4 (dd, $^2J_{C\text{-}2,Fa,b} = 21.9$, 20.5 Hz, C-2), 36.7 (t, $^2J_{C,Fa,b} = 23.8$, 23.8 Hz, α-CH_2), 31.7, 29.2, 29.2, 29.0, 22.6 (all s, $5CH_2$), 21.7 (dd, $^3J_{C,Fa,b} = 5.7$, 3.8 Hz, β-CH_2), 20.7, 20.7, 20.6 (all s, 3 acetyl-CH_3), 14.0 (s, CH_3); ^{19}F NMR (235 MHz, $CDCl_3$): δ −99.8 (d, $^2J_{Fa,Fb} = 256$ Hz, Fa), −101.7 (d, Fb); Anal. Calcd for $C_{22}H_{36}F_2O_8$ (466.52): C, 56.64; H, 7.78. Found: C, 56.77; H, 7.78.

4.9. Methyl 3,4-di-*O*-acetyl-2-*C*-chlorodifluoromethyl-2,6-dideoxy-α-L-glucopyranoside (14α) and methyl 3,4-di-*O*-acetyl-2-*C*-chlorodifluoromethyl-2,6-dideoxy-β-L-glucopyranoside (14β)

3,4-Di-*O*-acetyl-L-rhamnal[32,33] (2.14 g, 10 mmol) was dissolved in dry CH_3OH (30 mL) and converted like

described in Section 4.2. After purification by column chromatography (toluene/EtOAc, 10:1), the two anomers **14α** and **14β** were separated (**14α**: 49%, **14β**: 24%).

Compound **14α**: $R_f = 0.48$ (toluene/EtOAc, 5:1), Mp 85.8 °C (Et_2O), $[\alpha]_D^{19}$ −139.9 (*c* 1.1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 5.65 (dd, 1H, $^3J_{3,4} = 9.2$, $^3J_{2,3} = 11.2$ Hz, H-3), 4.99 (d, 1H, $^3J_{1,2} = 3.4$ Hz, H-1) 4.80–4.70 (m, 1H, H-4), 3.98–3.85 (m, 1H, $^3J_{5,6} = 6.3$ Hz, H-5), 3.39 (s, 3H, OCH_3), 2.97–2.82 (m, 1H, $^3J_{1,2} = 3.4$, $^3J_{2,3} = 11.2$ Hz, H-2), 2.04, 2.00 (2s, 6H, $2 \times CH_3$), 1.19 (d, 3H, $^3J_{5,6} = 6.3$ Hz, CH_3-6); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.1, 169.6 ($2 \times C{=}O$), 127.0 (t, $^1J_{C,F} = 281$, CF_2Cl), 97.1 (dd, $^3J_{C,Fa} = 3.9$, $^3J_{C,Fb} = 5.8$ Hz, C-1), 74.5 (C-3), 67.8 (C-4), 65.2 (C-5), 55.4 (OCH_3), 53.9 (t, $^2J_{C,F} = 22$ Hz, C-2), 20.8, 20.7 ($2 \times CH_3$), 17.3 (C-6); ^{19}F NMR (235 MHz, $CDCl_3$): δ −48.3 (d, $^2J_{Fa,Fb} = 168$ Hz, F_a), −50.6 (d, $^2J_{Fa,Fb} = 168$ Hz, F_b); Anal. Calcd for $C_{12}H_{17}ClF_2O_6$ (330.71): C, 43.58; H, 5.18. Found: C, 43.31; H, 5.23.

Compound **14β**: $R_f = 0.41$ (toluene/EtOAc, 5:1), colourless syrup, $[\alpha]_D^{19}$ −28.3 (*c* 1.1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 5.49–5.40 (m, 1H, $^3J_{3,4} = 9.8$ Hz, H-3), 4.83 (dd, 1H, $^3J_{3,4} = 9.8$, $^3J_{4,5} = 9.9$ Hz, H-4), 4.59 (d, 1H, $^3J_{1,2} = 7.4$ Hz, H-1), 3.60 (ddd, 1H, $^3J_{5,6} = 6.2$, $^3J_{4,5} = 9.9$ Hz, H-5), 2.81–2.72 (m, 1H, $^3J_{1,2} = 7.4$ Hz, H-2), 2.04, 2.01 (2s, 6H, $2 \times CH_3$), 1.25 (d, 3H, $^3J_{5,6} = 6.2$ Hz, CH_3-6); ^{13}C NMR (63 MHz, $CDCl_3$): δ 169.8, 169.6 ($2 \times C{=}O$), 128.1 (t, $^1J_{C,F} = 283$ Hz, CF_2Cl), 100.7 (d, $^3J_{C,F} = 5$ Hz, C-1), 74.0 (t, $^3J_{C,F} = 34$ Hz, C-3), 69.7 (C-4), 68.9 (C-5), 57.1 (OCH_3), 55.1 (dd, $^2J_{C,Fa} = 22$, $^2J_{C,Fb} = 18$ Hz, C-2), 20.9, 20.8 ($2 \times CH_3$), 17.7 (C-6); ^{19}F NMR (235 MHz, $CDCl_3$): δ −45.9 (d, $^2J_{Fa,Fb} = 174$ Hz, F_a), −49.5 (d, $^2J_{Fa,Fb} = 174$ Hz, F_b); Anal. Calcd for $C_{12}H_{17}ClF_2O_6$ (330.71): C, 43.58; H, 5.18. Found: C, 43.77; H, 5.38.

4.10. Methyl 3,4-di-*O*-acetyl-2-*C*-difluoromethyl-2,6-dideoxy-α-L-glucopyranoside (15)

A mixture of **14α/14β** (0.3 g, 0.91 mmol) was dissolved in dry benzene (5 mL) in a Schlenk flask under argon. After ethylvinyl ether (0.4 mL, 5 equiv) and a catalytic amount of AIBN (ca. 3–5 mg) were added, the reaction mixture was heated to 75 °C. At this temperature, a solution of 0.26 mL (0.91 mmol) *n*-Bu_3SnH in dry benzene (5 mL) was slowly added within 3 h. After complete conversion of the starting material (TLC), the solution was concentrated under reduced pressure. The syrupy residue was treated with an aq KF-soln (10% in H_2O, 10 mL) and stirred for 30 min. The aq phase was extracted with EtOAc (3×50 mL) and afterwards the organic phase was washed with H_2O (2×50 mL) and brine (1×50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The syrupy residue (0.7 g) was separated by column chromatography (heptane/EtOAc, 5:1 v/v) yielding 85 mg (32%) of **15**. There was another fraction (230 mg, $R_f = 0.53$) containing traces of compound **15** and various other products, but none of them contained a new CF_2–C-bond.

Compound **15**: $R_f = 0.56$ (heptane/EtOAc, 1:2 v/v), Mp 105.0–106.5 °C (heptane/EtOAc), $[\alpha]_D^{22}$ −162.5 (*c* 1.1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 5.82 (dt, 1H, $^3J_{H,2} = 7.3$, $^2J_{H,Fa,b} = 55.5$ Hz, CF_2H), 5.44 (dd, 1H, $^3J_{3,4} = 9.5$, $^3J_{2,3} = 11.2$ Hz, H-3), 4.79 (d, 1H, $^3J_{1,2} = 3.6$ Hz, H-1), 4.77 (t, 1H, $^3J = 9.7$ Hz, H-4), 3.86 (ddd, 1H, $^3J_{5,6} = 6.3$, $^3J_{4,5} = 9.9$ Hz, H-5), 2.46–2.28 (m, 1H, $^3J_{1,2} = 3.6$, $^3J_{H,2} = 7.3$, $^3J_{2,3} = 11.2$ Hz, H-2), 2.03, 1.99 (2s, 6H, $2 \times CH_3$), 1.18 (d, 3H, $^3J_{5,6} = 6.3$ Hz, CH_3-6); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.6, 170.0 ($2 \times C{=}O$), 116.3 (t, $^1J_{C,Fa,b} = 243$ Hz, CF_2H), 97.1 (t, $^3J_{C,F} = 8$ Hz, C-1), 73.8 (C-4), 67.8 (t, $^3J_{C,F} = 4$ Hz, C-3), 65.6 (C-5), 55.3 (OCH_3), 49.0 (t, $^2J_{C,F} = 19$ Hz, C-2), 20.8, 20.7, ($2 \times CH_3$), 17.7 (C-6); ^{19}F NMR (235 MHz, $CDCl_3$): δ −119.8 (s, CF_2H); Anal. Calcd for $C_{12}H_{18}F_2O_6$ (296.27): C, 48.65; H, 6.12. Found: C, 48.07; H, 6.14.

4.11. 3-(4,6-Di-*O*-acetyl-2-*C*-chlorodifluoromethyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-propene (17)

To a solution of compound **16**[14] (2.0 g, 5.61 mmol) in dry CH_2Cl_2, allyltrimethylsilane (2.6 mL, about 3 equiv) and $BF_3{\cdot}Et_2O$ (3.5 mL, about 5 equiv) were added at 0 °C with stirring. The reaction mixture was then allowed to warm to rt. After 24 h, allyltrimethylsilane (1.3 mL) and $BF_3{\cdot}Et_2O$ (1.75 mL) were added. After further 5 h stirring at rt, the reaction mixture was worked up. The CH_2Cl_2 phase was washed with a satd aq $NaHCO_3$ (3×20 mL) and brine (3×20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The syrupy residue was separated by column chromatography (heptane/EtOAc, 2:1 v/v) yielding successively 0.76 g (42%) of **17**.

Compound **17**: $R_f = 0.56$ (heptane/EtOAc, 1:3 v/v), colourless syrup, $[\alpha]_D^{22}$ +93.6 (*c* 1.2, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 6.36–6.30 (m, 1H, H-3), 5.97–5.79 (m, 1H, H-2-allyl), 5.35–5.27 (m, 1H, H-4), 5.21–5.10 (m, 2H, CH_2-allyl), 4.61–4.52 (m, 1H, H-1), 4.20–4.15 (m, 2H, H-6a, H-6b), 3.99–3.91 (m, 1H, H-5), 3.62–2.53 (m, 2H, CH_2-allyl), 2.11, 2.08 (2s, 6H, $2 \times CH_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.1, 170.0 ($2 \times C{=}O$), 139.2 (t, $^2J_{C,F} = 25$ Hz, C-2), 133.7 (C-allyl), 131.3 (t, $^1J_{C,F} = 290$ Hz, CF_2Cl), 127.7 (dd, $^3J_{C,Fa} = 6$, $^3J_{C,Fb} = 8$ Hz, C-3), 117.9 (CH_2-allyl), 71.3 (C-1), 67.6 (C-5), 64.5 (C-4), 63.1 (C-6), 36.3 (CH_2-allyl), 21.0, 20.9 ($2 \times CH_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ −45.8 (d, $^2J_{Fa,Fb} = 170.2$ Hz, F_a), −52.8 (d, $^2J_{Fa,Fb} = 170$ Hz, F_b). Anal. Calcd for $C_{14}H_{17}ClF_2O_5$ (338.74): C, 49.64; H, 5.06. Found: C, 49.51; H, 5.06.

4.12. (2*R*,3*S*,8a*R*)-2-Acetoxymethyl-3-acetoxy-5,5-difluoro-3,5,6,7,8,8a-hexahydro-2*H*-benzopyrane (18) and 3-(4,6-di-*O*-acetyl-2,3-dideoxy-2-*C*-difluoromethyl-α-D-*erythro*-hex-2-enopyranosyl)-propene (19)

To a solution of compound **17** (0.21 g, 0.62 mmol) in 2 mL of dry benzene, AIBN (3 mg, 0.018 mmol) was added under argon at rt (Schlenk flask). After the reaction mixture was heated to 75 °C, a solution of *n*-Bu_3SnH (0.18 mL, 0.62 mmol) in dry benzene (10 mL) was slowly added within 3 h. When the conversion of the starting material was completed (TLC control), the solution was concentrated under reduced pressure. The syrupy residue was treated with and aq KF-soln (10% in H_2O, 10 mL) and stirred for 30 min. The aq phase was extracted with EtOAc (3 × 50 mL) and afterwards the combined organic phases were washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The syrupy residue was separated by column chromatography (heptane/EtOAc, 4:1 v/v) yielding successively 0.15 g (80%) of **19** ($R_f = 0.36$) and 0.02 g of **18** (11%).

Compound **18**: $R_f = 0.32$ (heptane/EtOAc, 1:2 v/v), colourless syrup, $[\alpha]_D^{22}$ +76.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.13–6.06 (m, 1H, H-4), 5.24–5.16 (m, 1H, H-3), 4.37–4.27 (m, 1H, H-8a), 4.27 (dd, 1H, $^3J_{2,9a} = 6.0$, $^2J_{9a,9b} = 12.0$ Hz, H-9a), 4.17 (dd, 1H, $^3J_{2,9b} = 3.8$, $^2J_{9a,9b} = 12.0$ Hz, H-9b), 3.90 (ddd, 1H, $^3J_{2,3} = 9.6$, $^3J_{2,9a} = 6.0$, $^3J_{2,9b} = 3.8$ Hz, H-2), 2.32–2.18 (m, 1H, H-6a), 2.16–2.11 (m, 1H, H-8a), 1.92–1.82 (m, 1H, H-7a), 1.79–1.69 (m, 1H, H-6b), 1.43–1.31 (m, 1H, H-7b), 1.31–1.23 (m, 1H, H-8b), 2.10, 2.09 (2s, 6H, 2 × CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.4, 170.3, (2 × C=O), 138.7 (dd, $^2J_{C,Fa} = 21$, $^2J_{C,Fb} = 24$ Hz, C-4a), 119.9 (dd, $^1J_{C,Fa} = 235$, $^1J_{C,Fb} = 250$ Hz, CF_2), 119.3 (dd, $^3J_{C,Fa} = 7$, $^3J_{C,Fb} = 9$ Hz, C-4), 71.1 (C-8a), 70.5 (C-2), 64.7 (C-3), 62.6 (C-9), 35.3 (dd, $^2J_{C,Fa} = 22$, $^2J_{C,F} = 27$ Hz, C-6), 31.4 (C-8), 21.1, 20.9 (2 × CH_3), 18.3 (C-7); ^{19}F NMR (235 MHz, $CDCl_3$): δ −93.8 (d, $^2J_{Fa,Fb} = 242$ Hz, F_a), −106.5 (d, $^2J_{Fa,Fb} = 242$ Hz, F_b); HRMS-ESI: Calcd $[M+Na]^+$: 327.1020. Found: 327.1015.

Compound **19**: $R_f = 0.34$ (heptane/EtOAc, 1:2 v/v), colourless syrup, $[\alpha]_D^{22}$ +94.3 (*c* 1.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.09 (br s, 1H, H-3), 6.06 (t, 1H, CF_2H), 5.98–5.79 (m, 1H, CH-allyl), 5.29–5.20 (m, 1H, H-4), 5.21–5.07 (m, 2H, CH_2-allyl), 4.53–4.40 (m, 1H, H-1), 4.19–4.15 (m, 2H, H-6a, H-6b), 4.01–3.95 (m, 1H, H-5), 2.56–2.49 (m, 2H, CH_2-allyl), 2.09, 2.08 (2s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 170.3 (2 × C=O), 137.9 (dd, $^2J_{C,F} = 21$, $^2J_{C,F} = 22$ Hz, C-2), 133.9 (C-allyl), 127.7 (t, $^3J_{C,Fa} = {}^3J_{C,Fb} = 10$ Hz, C-3), 117.8 (CH_2-allyl), 114.4 (t, $^1J_{C,F} = 239$ Hz, CF_2H), 70.6 (C-1), 68.1 (C-5), 64.6 (C-4), 63.1 (C-6), 36.5 (CH_2-allyl), 20.9, 20.8 (2 × CH_3); ^{19}F NMR (235 MHz, $CDCl_3$): δ −111.3 (d, $^2J_{Fa,Fb} = 304$ Hz, F_a), −119.9 (d, $^2J_{Fa,Fb} = 304$ Hz, F_b); HRMS-ESI: Calcd $[M+Na]^+$: 327.1020. Found: 327.1015.

4.13. 4,4-Difluoro-4-(2-deoxy-3,4-di-*O*-pivaloyl-β-D-*threo*-pentopyranosyl)-butene (20)

Compound **5** (0.11 g, 0.29 mmol) dissolved in dry EtOAc (3 mL) was converted as described in Section 4.3. The syrupy residue (0.6 g) was separated by column chromatography (heptane/EtOAc, 20:1 v/v) yielding 0.07 g (62%) of **20**; $R_f = 0.63$ (heptane/EtOAc, 5:1 v/v), colourless syrup; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.88–5.65 (m, 1H, CH-allyl), 5.28–5.14 (m, 2H, CH_2-allyl), 5.08–4.86 (m, 2H, H-3, H-4), 4.15 (dd, 1H, $^3J_{4,5a} = 5.4$, $^2J_{5a,5b} = 11.2$ Hz, H-5a), 3.68–3.52 (m, 1H, $^3J_{1,2a} = 2.1$, $^3J_{1,2b} = 11.8$ Hz, H-1), 3.20 (dd, 1H, $^3J_{4,5b} = 10.0$, $^2J_{5a,5b} = 11.2$ Hz, H-5b), 2.85–2.57 (m, 2H, CH_2-allyl), 2.28 (ddd, 1H, $^3J_{1,2a} = 2.1$, $^3J_{2a,3} = 5.0$, $J = 12.7$ Hz, H-2a), 1.69 (dd, 1H, $^3J_{1,2b} = 11.8$, $J = 23.9$ Hz, H-2b) 1.16, 1.14 (2s, 18H, 2 × C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7, 177.5 (2 × C=O), 128.7 (dd, $^3J_{C,F} = 3$, $^3J_{C,F} = 8$ Hz, CH-allyl), 127.1 (t, $^1J_{C,F} = 245$ Hz, CF_2), 121.0 (CH_2-allyl), 75.6 (dd, $^2J_{C,F} = 27$, $^2J_{C,F} = 34$ Hz, C-1), 70.7 (C-3), 69.2 (C-4), 67.4 (C-5), 38.9, 38.8 (2 × *C*(CH_3)$_3$), 37.9 (dd, $^2J_{C,F} = 24$, $^2J_{C,F} = 26$ Hz, CH_2-allyl), 28.8 (t, $^3J_{C,F} = 4$ Hz, C-2), 27.2, 27.1 (2 × C(*C*H_3)$_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ −107.9 (d, $^2J_{Fa,Fb} = 255$ Hz, F_a), −111.6 (d, $^2J_{Fa,Fb} = 255$ Hz, F_b); HRMS-ESI: Calcd $[M+Na]^+$: 399.1959. Found: 399.1962.

4.14. 4,4-Difluoro-4-(2,3,4-tri-*O*-acetyl-6-deoxy-α-L-galactopyranosyl)-butene (21)

Compound **7** (0.15 g, 0.42 mmol) dissolved in dry EtOAc (3 mL) was converted as described in Section 4.3. The syrupy residue (0.9 g) was separated by column chromatography (heptane/EtOAc, 10:1 v/v) yielding 0.11 g (73%) of product **21**; $R_f = 0.27$ (heptane/EtOAc, 1:1 v/v); colourless syrup; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.87–5.68 (m, 1H, CH-allyl), 5.48 (dd, 1H, $^3J_{2,3} = 9.8$, $^3J_{3,4} = 3.3$ Hz, H-3), 5.32 (dd, 1H, $^3J_{2,3} = 9.8$, $^3J_{1,2} = 6.2$ Hz, H-2), 5.30 (dd, 1H, $^3J_{4,5} = 1.8$, $^3J_{3,4} = 3.3$ Hz, H-4), 5.27–5.18 (m, 2H, CH_2-allyl), 4.46–4.29 (m, 1H, $^3J_{1,2} = 6.2$ Hz, H-1), 4.14–4.01 (m, 1H, $^3J_{5,6} = 6.4$ Hz, H-5), 2.77–2.57 (m, 2H, CH_2-allyl), 2.12, 2.04, 1.99, (3s, 9H, 3 × CH_3), 1.16 (d, 3H, $^3J_{5,6} = 6.4$ Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.6, 170.4, 169.8 (3 × C=O), 128.3 (t, $^3J_{C,F} = 5$ Hz, CH-allyl), 124.4 (t, $^1J_{C,F} = 250$ Hz, CF_2), 121.3 (CH_2-allyl), 70.9 (dd, $^2J_{C,F} = 25$, $^2J_{C,F} = 28$ Hz, C-1), 69.9 (C-4), 68.8 (C-5), 68.5 (C-2), 66.4 (C-3), 39.7 (t, $^2J_{C,F} = 25$ Hz, CH_2-allyl), 20.8, 20.7, 20.6 (3 × CH_3), 16.2 (C-6); ^{19}F NMR (235 MHz, $CDCl_3$): δ −98.7 (d,

$^2J_{Fa,Fb} = 258$ Hz, F_a), −100.0 (d, $^2J_{Fa,Fb} = 258$ Hz, F_b); HRMS-ESI: Calcd $[M+H]^+$: 365.1412. Found: 365.1415.

4.15. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-*C*-(4,4-difluorobutene-4-yl)-α-D-glucopyranose (23)

1-*O*-Acetyl derivative **22**[14,15] (0.27 g, 0.65 mmol) dissolved in dry EtOAc (5 mL) was converted as described in procedure 2. The syrupy residue (1.3 g) was separated by column chromatography (heptane/EtOAc, 8:1 v/v) yielding 0.20 g (73%) of **23**; $R_f = 0.34$ (heptane/EtOAc, 1:1 v/v); colourless syrup; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.35 (d, 1H, $^3J_{1,2} = 3.2$ Hz, H-1), 5.82–5.74 (m, 1H, CH-allyl), 5.65 (dd, 1H, $^3J_{2,3} = 11.5$, $^3J_{3,4} = 9.3$ Hz, H-3), 5.28–5.13 (m, 2H, CH_2-allyl), 5.02 (t, 1H, $^3J_{3,4} = {}^3J_{4,5} = 9.3$ Hz, H-4), 4.35–4.20 (m, 2H, H-6a, H-6b), 4.07–3.94 (m, 1H, H-5), 2.80–2.46 (m, 3H, H-2, CH_2-allyl), 2.11, 2.02, 1.99, 1.98 (4s, 12H, $4 \times CH_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.6, 169.7, 169.6, 168.4 ($4 \times$ C=O), 128.1 (t, $^3J_{C,F} = 5$ Hz, CH-allyl), 121.7 (CH_2-allyl), 121.1 (t, $^1J_{C,F} = 248$ Hz, CF_2), 88.7 (t, $^3J_{C,F} = 6$ Hz, C-1), 79.5 (C-5), 67.7 ($^3J_{C,F} = 4$ Hz, C-3), 66.5 (C-4), 61.7 (C-6), 47.6 (t, $^2J_{C,F} = 22$ Hz, C-2), 41.3 (t, $^2J_{C,F} = 25$ Hz, CH_2-allyl), 21.1, 20.8, 20.7, 20.6 ($4 \times CH_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ −98.2 (d, $^2J_{Fa,Fb} = 248$ Hz, F_a), −99.2 (d, $^2J_{Fa,Fb} = 248$ Hz, F_b) HRMS-ESI: Calcd $[M+Na]^+$: 445.1286. Found: 445.1294.

4.16. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-*C*-(4,4-difluorobutene-4-yl)-α-D-mannopyranose (25)

1-*O*-acetyl derivative **24**[15] (0.29 g, 0.69 mmol) dissolved in dry EtOAc (5 mL) was converted as described in Section 4.3. The syrupy residue (1.4 g) was separated by column chromatography (heptane/EtOAc, 8:1 v/v) yielding 0.17 g of a mixture of **25** and starting material (ratio 1:0.2) corresponding to a yield of 48% for compound **25**; $R_f = 0.32$ (heptane/EtOAc, 1:1 v/v), colourless syrup; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.43 (d, 1H, $^3J_{1,2} = 3.3$ Hz, H-1), 5.82–5.63 (m, 1H, CH-allyl), 5.43–5.33 (m, 1H, H-3), 5.27–5.13 (m, 3H, H-4, CH_2-allyl), 4.12 (d, 2H, $^3J_{5,6} = 3.2$ Hz, H-6a, H-6b), 4.02–3.92 (m, 1H, H-5), 2.86–2.62 (m, 3H, H-2, CH_2-allyl), 2.09, 2.02, 2.02, 2.01 (4s, 12H, $4 \times CH_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.5, 169.8, 169.3, 168.6 ($4 \times$ C=O), 128.3 (t, $^3J_{C,F} = 6$ Hz, CH-allyl), 122.3 (t, $^1J_{C,F} = 248$ Hz, CF_2), 121.3 (CH_2-allyl), 89.6 (t, $^3J_{C,F} = 5$ Hz, C-1), 70.3 (C-5), 67.9 (C-3), 66.9 (C-4), 62.6 (C-6), 45.2 (t, $^2J_{C,F} = 23$ Hz, C-2), 40.9 (t, $^2J_{C,F} = 26$ Hz, CH_2-allyl), 20.9, 20.8, 20.6, 20.5 ($4 \times CH_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ −94.7 (d, $^2J_{Fa,Fb} = 258$ Hz, F_a), −96.2 (d, $^2J_{Fa,Fb} = 258$ Hz, F_b). HRMS-ESI: Calcd $[M+Na]^+$: 445.1286. Found: 445.1295.

4.17. Methyl 3,4-di-*O*-acetyl-2-*C*-chlorodifluoromethyl-2-deoxy-α-D-arabinopyranoside (26α) and methyl 3,4-di-*O*-acetyl-2-*C*-chlorodifluoromethyl-2-deoxy-β-D-arabinopyranoside (26β)

3,4-Di-*O*-acetyl-D-arabinal[34] (2.5 g, 12.5 mmol) dissolved in dry CH_3OH (30 mL) was converted as described in Section 4.2. The syrupy residue (3.30 g) was separated by column chromatography (heptane/EtOAc, 6:1 v/v) yielding 2.88 g (72%) of an anomeric mixture of **26α/26β** (α:β = 1:1).

Compound **26α**: $R_f = 0.20$ (heptane/EtOAc, 3:1 v/v), colourless syrup; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.40 (dd, 1H, $^3J_{2,3} = 8.8$, $^3J_{3,4} = 3.8$ Hz, H-3), 5.26–5.19 (m, 1H, H-4), 4.67 (d, 1H, $^3J_{1,2} = 5.2$ Hz, H-1), 3.97 (dd, 1H, $^3J_{4,5a} = 4.6$, $^2J_{5a,5b} = 12.3$ Hz, H-5a), 3.74 (dd, 1H, $^3J_{4,5b} = 3.4$, $^2J_{5a,5b} = 12.3$ Hz, H-5b), 3.47 (s, 3H, OCH_3), 2.98–2.84 (m, 1H, $^3J_{1,2} = 5.2$, $^3J_{2,3} = 8.8$ Hz, H-2), 2.10, 2.04 (2s, 6H, $2 \times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 169.8 ($2 \times$ C=O), 128.6 (t, $^1J_{C,F} = 297$ Hz, CF_2Cl), 99.5 (C-1), 66.7 (C-3), 66.1 (C-4), 61.8 (C-5), 56.7 (OCH_3), 51.7 (t, $^2J_{C,F} = 22$ Hz, C-2), 21.0, 20.8 ($2 \times CH_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ −47.5 (d, $^2J_{Fa,Fb} = 170$ Hz, F_a), −48.7 (d, $^2J_{Fa,Fb} = 170$ Hz, F_b); Anal. Calcd for $C_{11}H_{15}ClF_2O_6$ (316.69): C, 41.72; H, 4.77. Found: C, 41.59; H, 4.51.

Compound **26β**: $R_f = 0.26$ (heptane/EtOAc, 3:1 v/v), colourless syrup (anomeric mixture).

^{1}H NMR (250 MHz, $CDCl_3$): δ 5.55 (dd, 1H, $^3J_{2,3} = 11.5$, $^3J_{3,4} = 3.2$ Hz, H-3), 5.24–5.17 (m, 1H, H-4), 5.06 (d, 1H, $^3J_{1,2} = 3.2$ Hz, H-1), 3.95 (dd, 1H, $^3J_{4,5a} = 1.4$, $^2J_{5a,5b} = 13.0$ Hz, H-5a), 3.69 (dd, 1H, $^3J_{4,5b} = 2.1$, $^2J_{5a,5b} = 13.0$ Hz, H-5b), 3.39 (s, 3H, OCH_3), 3.19–3.03 (m, 1H, $^3J_{1,2} = 3.2$, $^3J_{2,3} = 11.5$ Hz, H-2), 2.13, 1.99 (2s, 6H, $2 \times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.4$, 169.7 ($2 \times$ C=O), 128.7 (t, $^1J_{C,F} = 298$ Hz, CF_2Cl), 97.9 (C-1), 66.6 (C-3), 66.1 (C-4), 60.8 (C-5), 55.8 (OCH_3), 49.4 (t, $^2J_{C,F} = 22$ Hz, C-2), 21.1, 20.8 ($2 \times CH_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ −48.2 (d, $^2J_{Fa,Fb} = 170$ Hz, F_a), −49.7 (d, $^2J_{Fa,Fb} = 170$ Hz, F_b); Anal. Calcd for $C_{11}H_{15}ClF_2O_6$ (316.69): C, 41.72; H, 4.77. Found: C, 41.59; H, 4.51.

4.18. Methyl 3,4-di-*O*-acetyl-2-*C*-(4,4-difluorobutene-4-yl)-2-deoxy-α-D-arabinopyranoside (27α) and methyl 3,4-di-*O*-acetyl-2-*C*-(4,4-difluorobutene-4-yl)-2-deoxy-β-D-arabinopyranoside (27β)

The 1:1 anomeric mixture of **26α/26β** (1.6 g, 5.05 mmol) dissolved in dry EtOAc (10 mL) was converted as described in Section 4.3. The syrupy residue (9.2 g) was separated by column chromatography (heptane/EtOAc, 6:1 v/v) yielding 0.97 g (64%) of the anomeric mixture **27α/27β** (α:β = 1:1); HRMS-ESI of the α/β mixture: Calcd $[M+Na]^+$: 345.1126. Found: 345.1118.

Compound **27α**: $R_f = 0.43$ (heptane/EtOAc, 1:1 v/v), colourless syrup; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.89–5.69 (m, 1H, CH-allyl), 5.37 (dd, 1H, $^3J_{2,3} = 8.4$, $^3J_{3,4} = 3.7$ Hz, H-3), 5.28–5.16 (m, 3H, CH_2-allyl, H-4), 4.55 (d, 1H, $^3J_{1,2} = 5.8$ Hz, H-1), 3.96 (dd, 1H, $^3J_{4,5a} = 5.0$, $^2J_{5a,5b} = 12.3$ Hz, H-5a), 3.60 (dd, 1H, $^3J_{4,5b} = 3.0$, $^2J_{5a,5b} = 12.3$ Hz, H-5b), 3.45 (s, 3H, OCH_3), 2.93–2.62 (m, 1H, $^3J_{1,2} = 5.8$, $^3J_{2,3} = 8.4$ Hz, H-2), 2.62–2.44 (m, 2H, CH_2-allyl), 2.07, 2.00 (2s, 6H, $2 \times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 169.8 ($2 \times$ C=O), 128.9 (t, $^3J_{C,F} = 5$ Hz, CH-allyl), 122.9 (t, $^1J_{C,F} = 248$ Hz, CF_2), 121.1 (CH_2-allyl), 99.2 (t, $^3J_{C,F} = 6$ Hz, C-1), 66.4 (C-4), 66.1 (t, $^3J_{C,F} = 4$ Hz, C-3), 61.2 (C-5), 56.4 (OCH_3), 47.1 (t, $^2J_{C,F} = 22$ Hz, C-2), 41.7 (t, $^3J_{C,F} = 25$ Hz, CH_2-allyl), 20.9, 20.9 ($2 \times CH_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ −97.6 (d, $^2J_{Fa,Fb} = 258$ Hz, F_a), −98.3 (d, $^2J_{Fa,Fb} = 258$ Hz, F_b).

Compound **27β**: $R_f = 0.45$ (heptane/EtOAc, 3:1 v/v), colourless syrup.

^{1}H NMR (250 MHz, $CDCl_3$): δ 5.89–5.69 (m, 1H, CH-allyl), 5.43 (dd, 1H, $^3J_{2,3} = 12.0$, $^3J_{3,4} = 3.4$ Hz, H-3), 5.27–5.16 (m, 3H, CH_2-allyl, H-4), 4.93 (d, 1H, $^3J_{1,2} = 3.2$ Hz, H-1), 3.91 (dd, 1H, $^3J_{4,5a} = 1.3$, $^2J_{5a,5b} = 13.0$ Hz, H-5a), 3.65 (dd, 1H, $^3J_{4,5b} = 2.0$, $^2J_{5a,5b} = 13.0$ Hz, H-5b), 3.36 (s, 3H, OCH_3), 2.93–2.73 (m, 1H, $^3J_{1,2} = 3.2$, $^3J_{2,3} = 12.0$ Hz, H-2), 2.75–2.35 (m, 2H, CH_2-allyl), 2.11, 1.98 (2s, 6H, $2 \times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 169.7 ($2 \times$ C=O), 129.1 (t, $^3J_{C,F} = 5$ Hz, CH-allyl), 122.4 (t, $^1J_{C,F} = 248$ Hz, CF_2), 120.5 (CH_2-allyl), 97.8 (t, $^3J_{C,F} = 7$ Hz, C-1), 67.6 (C-4), 65.7 (t, $^3J_{C,F} = 4$ Hz, C-3), 60.7 (C-5), 55.3 (OCH_3), 45.0 (t, $^2J_{C,F} = 25$ Hz, C-2), 40.0 (t, $^3J_{C,F} = 25$ Hz, CH_2-allyl), 20.9, 20.8 ($2 \times CH_3$); ^{19}F NMR (235 MHz, $CDCl_3$): δ −93.9 (d, $^2J_{Fa,Fb} = 258$ Hz, F_a), −98.3 (d, $^2J_{Fa,Fb} = 258$ Hz, F_b).

Acknowledgements

The authors are grateful to Professor Dr. Manfred Michalik (Leibniz-Institut für Organische Katalyse Rostock) for recording the NMR spectra and, to Claudia Vinke (Universität Rostock) and Dominique Harakat (Université de Reims Champagne-Ardenne, France) for technical assistance.

References

1. Wegert, A.; Miethchen, R.; Hein, M.; Reinke, H. *Synthesis* **2005**, 1850–1858.
2. Tsuchiya, T. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 91–277.
3. Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991.
4. Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993.
5. *Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards*; Resnati, G., Soloshonok, V. A., Eds.; Pergamon Press: Oxford, 1996.
6. Yamamoto, H. *Organofluorine Compounds—Chemistry and Applications*; Springer: Berlin, 2000.
7. *Carbohydr. Res., Special Issue, Fluoro Sugars*; Miethchen, R., Defaye, J., Eds.; Elsevier: Amsterdam, 2000; Vol. 327, pp 1–218.
8. Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004.
9. Jäckel, C.; Koksch, B. *Eur. J. Org. Chem.* **2005**, 4483–4503.
10. Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303–319, and references cited therein.
11. Tozer, M. J.; Herpin, T. *Tetrahedron* **1996**, *52*, 8619–8683, and references cited therein.
12. Burkholder, C. R.; Dolbier, W. R.; Medebielle, M. *J. Fluorine Chem.* **2001**, *109*, 39–48, and references cited therein.
13. Hein, M.; Miethchen, R. In *Advances in Organic Synthesis, Modern Organofluorine Chemistry—Synthetic Aspect*; Laali, K. K., Ed.; Bentham Science Publ. Ltd, 2006; Vol. 2, pp 381–430, and references cited therein.
14. Tews, S.; Miethchen, R.; Reinke, H. *Synthesis* **2003**, 707–716 (Erratum: *Synthesis* **2003**, 1136) and references cited therein.
15. Wegert, A.; Reinke, H.; Miethchen, R. *Carbohydr. Res.* **2004**, *339*, 1833–1837.
16. Huang, W.-Y. *J. Fluorine Chem.* **1992**, *58*, 1–8.
17. Plenkiewicz, H.; Dmowski, W.; Lipinski, M. *J. Fluorine Chem.* **2001**, *111*, 227–232.
18. Miethchen, R.; Hein, M.; Reinke, H. *Eur. J. Org. Chem.* **1998**, 919–923.
19. Wegert, A. Dissertation, University of Rostock, 2006.
20. Constantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *Tetrahedron Lett.* **2002**, *43*, 9047–9050.
21. Schrauzer, G. N. *Inorg. Synth.* **1968**, *11*, 61–70.
22. Arnone, A.; Bernardi, R.; Bravo, P.; Cardillo, R.; Ghiringhelli, D.; Cavicchio, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1887–1891.
23. Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082–2089.
24. Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *Tetrahedron Lett.* **1994**, *35*, 5673–5676.
25. Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829–5831.
26. Russell, G. A.; Herold, L. L. *J. Org. Chem.* **1985**, *50*, 1037–1040.
27. Katagiri, T.; Handa, M.; Matsukawa, Y.; Dileep Kumar, J. S.; Uneyama, K. *Tetrahedron: Asymmetry* **2001**, *12*, 1303–1311.
28. Kirihara, M.; Takuwa, T.; Okumura, M.; Wakikawa, T.; Takahata, H.; Momose, T.; Takeuchi, Y.; Nemoto, H. *Chem. Pharm. Bull.* **2000**, *48*, 885–888.
29. Yoshida, M.; Morinaga, Y.; Iyoda, M. *J. Fluorine Chem.* **1994**, *68*, 33–38.
30. Sheldrick, G. M. Universität Göttingen, 1997.
31. Cook, M. J.; Fletcher, M. J. E.; Gray, D.; Lovell, P. J.; Gallagher, T. *Tetrahedron* **2004**, *60*, 5085–5092.
32. Fischer, E.; Zach, C. *Sitzber. Kgl. Preuss. Akad. Wiss.* **1913**, *16*, 311–317.
33. Roth, W.; Pigman, W. *Methods Carbohydr. Chem.* **1963**, *2*, 405–408.
34. Smiatacz, Z.; Myszka, H. *Carbohydr. Res.* **1988**, *172*, 171–182.