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Fragmentation of Carbohydrate Anomeric Alkoxyl Radicals: New Synthesis of Chiral 1-Fluoro-1-halo-1-iodoalditols

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Abstract: A new general methodology for the synthesis of 1,1,1-trihaloalditols by starting from 1,5-anhydro-2-deoxy-hex-1-enitol derivatives (glycals) is described. The halogens are introduced sequentially in each of the three different steps of the process. The fluorine is introduced in the first step by electrophilic fluorination of the starting glycal; next, hydroxyhalogenation of the resulting vinyl fluoride allows the addition of any halogen (F, Cl, Br or I) at will, and finally, an iodine atom is inserted through an alkoxyl radical fragmentation reaction. This methodology allows the preparation of diverse types of 1,1,1-trihalogenated compounds (R−CF_2I, R−CFI_2, R−CFClI and R−CFBrI) under mild conditions compatible with sensitive substituents. In some cases, the diastereomeric mixtures generated from R−CFClI and R−CFBrI can be chromatographically separated, and their configuration determined by X-ray crystallographic analysis. The synthetic usefulness of these compounds has been preliminarily assessed by examining the reactivity of the fluorinated radical generated by rupture of the C−I bond.

Keywords: alditols · asymmetric synthesis · carbohydrates · halogens · radical reactions

Introduction

The field of fluoroorganic chemistry has received considerable attention in recent decades. Extensive research has already been carried out into the incorporation of one or several fluorine atoms into organic substrates, which can lead to profound effects on the physical, chemical and biological properties of the molecules,[1] as exemplified by the growing number of pharmaceutical and plant protection agents that have fluorine incorporated in their structure.[2]

Among them, *gem*-difluoro compounds have become a significant area of research[3] since CH_2/CF_2 transposition has been recognised as a valuable tool in the blockage of metabolic processes,[4] and the difluoromethylene functionality is known to be isostere and isopolar to an oxygen atom.[5] The introduction of a *gem*-difluoromethyl group into bioactive compounds can enhance or alter their activity dramatically.

Recently, fluorinated carbohydrates[6] (fluorosugars) have attracted increased attention from organic chemists. The activity of fluorosugars is mostly attributed to the replacement of a hydroxyl group by fluorine in a carbohydrate residue, which causes electronic effects on neighbouring groups with minimal steric perturbation to the original structure or conformation. Only a few *gem*-difluorinated sugars have been reported,[7] which is probably due to the shortcomings of the existing synthetic methods. Therefore novel and efficient methods to introduce the *gem*-difluoromethyl group into sensitive molecules are still required.

In recent years, we have developed the synthesis of 1-deoxy-1-halo-1-iodoalditols based on the anomeric alkoxyl radical fragmentation (ARF)[8] of 2-deoxy-2-halo-glycofuranoses and pyranoses. The glycopyran-1-*O*-yl and glycofuran-1-*O*-yl radicals were easily generated by reaction of 2-halocarbohydrate anomeric alcohols with hypervalent iodine reagents in the presence of molecular iodine or bromine. Subsequently, alkoxyl-radical-driven fragmentation of the C1−C2 bond afforded a C2 radical that could be trapped intermolecularly by halogen atoms from the medium. In this

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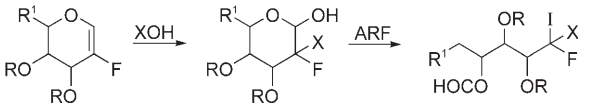
way, 1,1-dihaloalditols with one less carbon atom than the starting sugar were obtained in good yields.[9] 1,1-Dihaloalkanes are versatile compounds in organic synthesis and have attracted much interest as intermediates in C–C bond-forming reactions.[10]

With these results in hand, we turned our attention to a general protocol for the synthesis of 1,1,1-trihaloalditols by starting from a glycal as outlined in Scheme 1, in which the halogens are introduced sequentially in each of the three different steps of the process. The fluorine is introduced in the first step by electrophilic fluorination; next, hydroxyhalogenation of the vinyl fluoride allows the addition of any halogen and finally, the iodine is inserted through a radical ARF reaction.



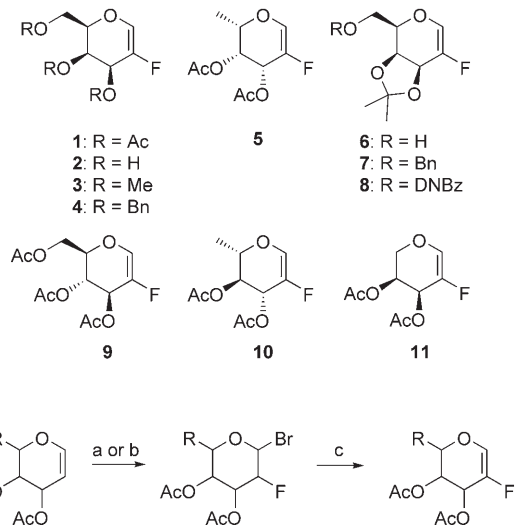
Scheme 1. Synthesis of 1,1,1-trihaloalditols. R = Protective group, R^1 = CH_2OAc, CH_3, H; X = F, Cl, Br, I.

This methodology should prove useful in the synthesis of a number of fluorinated 1,1,1-trihaloalditols of the general structure R–CFIX (X = F, Cl, Br, I). 1,1-Difluoro-1-iodoalditols can be obtained when X = F.[11] These compounds may be of interest as building blocks to introduce a *gem*-difluoromethylene group in target polyhydroxylated chiral molecules. This reaction can also provide useful access to 1,1-diiodo-1-fluoroalditols when X = I.[12] 1,1-Diiodoalkanes are a valuable class of organic compounds that are extensively useful in organic synthesis.[13] Finally, an alditol with three different halogen atoms can also be obtained when X = Br or Cl.[14] Chiral 1,1,1-trihaloalkanes constitute an interesting group of organic compounds that includes chiral trihalomethanes, which is one of the smallest chiral molecules and has been the subject of several studies that deal with important physical and chemical aspects of chirality.[15]

Until now, there appears to be no general methodology directed towards the synthesis of asymmetric carbon atoms that bear three different halogen atoms.[16] For example, one of the simplest compounds of this type is bromochlorofluoromethane, which was first synthesised at the end of the 1800s.[17] Almost a century elapsed before the enantiomers would be even partially resolved and the absolute configuration assigned.[16d,e,18]

Results and Discussion

Synthesis of 2-deoxy-2-fluoro-hex-1-enitols: Vinyl fluorides **1**–**11** (DNBz = 3,5-dinitrobenzoyl) used in this study were synthesised from the corresponding 2-deoxy-hex-1-enitol (glycals) by following the protocols outlined in Scheme 2. Glycals were treated with Selectfluor in dry nitromethane by using magnesium bromide as a nucleophile.[19] Elimination of the anomeric bromide obtained from this reaction with triethylamine in acetonitrile afforded the required vinyl fluoride. By following this methodology (method A), we were able to prepare substrates **1**, **5** and **11**, which are derived from D-galactal,[20] L-fucal and L-arabinal, respectively.



Scheme 2. Synthesis of 1,5-anhydro-2-deoxy-2-fluoro-hex-1-enitols. R = CH_2OAc, CH_3, H. Method A: a) i) Selectfluor (1.5 equiv), nitromethane, 15 h; ii) $MgBr_2$ (2 equiv), reflux, 1 h; c) Et_3N (3 equiv), acetonitrile, reflux, 1.5 h. Method B: b) i) Selectfluor (1.5 equiv), nitromethane/H_2O, RT, 6 h, then reflux 0.5 h; ii) Ac_2O, pyridine; iii) HBr/HOAc, Ac_2O, 2 h; c) Et_3N (3 equiv), acetonitrile, reflux, 1 h.

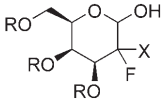
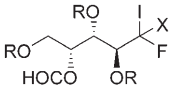
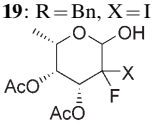
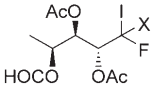
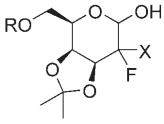
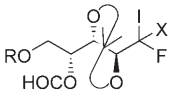
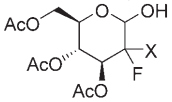
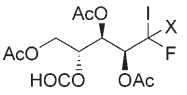
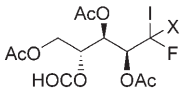
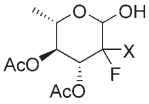
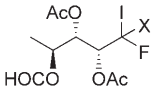
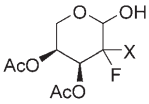
When method A was used, vinyl fluorides derived from D-glucal[20,21] **9** and L-rhamnal **10** resulted in mixtures that were difficult to separate. A somewhat different sequence (method B) was required in these two cases, as exemplified by the reaction of D-glucal. The hex-enitol was also treated with Selectfluor, but in aqueous nitromethane to afford the *mano* and *gluco*-derived fluorohydrin mixtures, which were separated after acetylation. Subsequent substitution of the anomeric acetyl group in the *gluco* derivative by bromide with HBr/HOAc, followed by elimination of the HBr with triethylamine (TEA), gave the desired vinyl fluorides in good yields.

The remainder of the vinyl fluorides **3**, **4**, **7** and **8** were prepared from the 2-deoxy-2-fluoro-D-*arabino*-hex-1-enitol derivative **1**. Hydrolysis of acetate groups with K_2CO_3/MeOH yielded the triol **2**.[19a] Treatment with NaH and MeI or BnBr gave **3** and **4** in moderate yields. Reaction of **1** with dimethoxypropane and subsequent protection of **6** with benzyl bromide or dinitrobenzoyl chloride afforded models **7** and **8**.

In previous communications we have described some preliminary results,[11,14] and now we report the full details of these experiments and their extension to a number of new models.

We have synthesised 2,2-dihalohydrins **12**–**39** from 2-deoxy-2-fluoro-hex-1-enitols **1**–**11** as outlined in Table 1. Difluorohydrins (42–76%),[22] chlorofluorohydrins (40–75%),[21] bromofluorohydrins (55–82%)[23] and fluoroiodo-

Table 1. Synthesis of 1,1,1-trihaloalditols.[a]

Entry	Substrate[b]	Product	Yield [%] (dr)[c]
			
1	**12**: R = Ac, X = F	**40**: R = Ac, X = F	75
2	**13**: R = Ac, X = Cl	**41**: R = Ac, X = Cl	67 (1:1)
3	**14**: R = Ac, X = Br	**42**: R = Ac, X = Br	60 (1:1)
4	**15**: R = Ac, X = I	**43**: R = Ac, X = I	81
5	**16**: R = Me, X = F	**44**: R = Me, X = F	57
6	**17**: R = Bn, X = F	**45**: R = Bn, X = F	33
7	**18**: R = Bn, X = Br	**46**: R = Bn, X = Br	46 (1:1)
8	**19**: R = Bn, X = I	**47**: R = Bn, X = I	58
			
9	**20**: X = F	**48** X = F	76
10	**21**: X = Cl	**49**: X = Cl	79 (1:1)
11	**22**: X = Br	**50**: X = Br	72 (1:1)
12	**23**: X = I	**51**: X = I	79
			
13	**24**: R = Bn, X = Br	(*R*/*S*)-**52**: R = Bn, X = Br	46 (3:2)
14[d]	**25**: R = Bn, X = I	**53**: R = Bn, X = I	55
15[e]	**26**: R = DNBz, X = Cl	(*R*/*S*)-**54**: R = DNBz, X = Cl	76 (3:2)
16[f]	**27**: R = DNBz, X = Br	(*R*/*S*)-**55**: R = DNBz, X = Br	66 (2:1)
			
17	**28**: X = F	**56**: X = F	71
18	**29**: X = Cl	**57**: X = Cl	60 (1:1)
19	**30**: X = Br	**58**: X = Br	71 (1:1)
20	**31**: X = I	**59**: X = I	75
			
21	**32**: X = F	**60**: X = F	82
22	**33**: X = Cl	**61**: X = Cl	70 (1:1)
23	**34**: X = Br	**62**: X = Br	80 (1:1)
24	**35**: X = I	**63**: X = I	83
			
25	**36**: X = F	**64**: X = F	77
26	**37**: X = Cl	**65**: X = Cl	84 (1:1)
27	**38**: X = Br	**66**: X = Br	65 (1:1)
28	**39**: X = I	**67**: X = I	94

[a] All reactions were performed in dry CH_2Cl_2 (50 mL mmol^{-1}) under irradiation with two 80 W tungsten filament lamps at room temperature for 1 h and contained 1.5 mmol (diacetoxyiodo)benzene (DIB) and 1.5 mmol I_2 per mmol of substrate. [b] The great majority of dihalohydrins are mixtures at C1 and/or C2, the composition of each one is specified in the Supporting Information section. [c] Isolated yield. [d] The reaction was completed in 0.5 h. [e] DNBz = 3,5-dinitrobenzoyl. [f] The reaction was completed in 0.75 h.

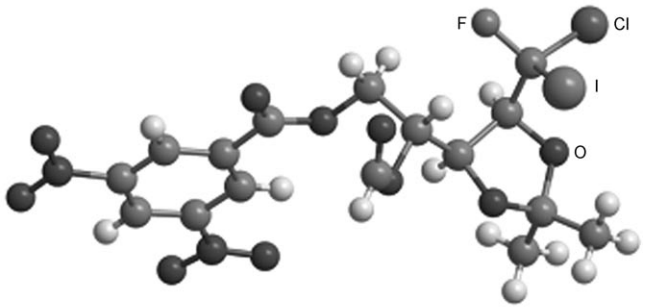
hydrins (66–94%)[21c,24] were prepared by treatment with Selectfluor,[16,25] *N*-chlorosuccinimide,[26] *N*-bromoacetamide[27] and *N*-iodosuccinimide,[28] respectively. Encouraged by the ease of construction of these mixed dihalohydrins, we decided to extend and delineate the scope of our general protocol, particularly in regard to the influence of the stereochemistry of the saccharide on the stereoselectivity of the radical reaction.

The ARF reactions were performed under the conditions stated in the table, with (diacetoxyiodo)benzene (DIB) and iodine in CH_2Cl_2 at room temperature and irradiation with two 80 W tungsten filament lamps. The reactions proceeded smoothly with complete consumption of the starting material and without isomerisation of the adjacent stereogenic centre. No side products were detected in the crude reaction mixtures, even in those with moderate yields.

The first three models shown in entries 1–16 of Table 1 illustrate the transformation of 2-deoxy-2-fluoro-2-halo-galactopyranose derivatives **12**–**27** into 1-deoxy-1-fluoro-1-halo-1-iodo-arabinitols **40**–**55**,[28] with one carbon atom less than the starting material, which proceeded in moderate to good yields. The yields of benzyl-protected carbohydrates (entries 6–8, 13 and 14) are significantly smaller (compare, for example, entries 3 with 7 and 13). This may be attributable to intermolecular reactions since it has been reported that alkoxyl radicals generated under DIB/I_2 conditions can be used to deprotect benzyl ethers in carbohydrate substrates.[30]

As might be expected, neither the chloro (entries 2 and 10) nor bromo (entries 3, 7 and 11) series of mixed trihaloalditols exhibited any significant diastereoselectivity, and in the great majority of cases, they were obtained as inseparable equimolecular mixtures of diastereomers. Notwithstanding, from more sterically demanding substrates (entries 13, 15 and 16), compounds **52**, **54** and **55** were obtained with a slight but significant level of diastereoselection.

Although the diastereomeric mixture **52** could be separated by careful chromatography, unfortunately the crystals obtained of (*S*)-**52** were not suitable for X-ray analysis. We prepared 3,5-dinitrobenzoates **54** and **55** (entries 15 and 16) with the aim to eventually establish the absolute configuration at C1 by X-ray crystallography. The diastereomeric mixtures could be separated by chromatography and their structures were confirmed by ^{1}H, ^{13}C NMR spectroscopies including DEPT, COSY, HMQC and HMBC experiments. Crystallisation of the minor isomers (*S*)-**54** and (*S*)-**55** from *n*-hexane/EtOAc provided colourless crystals suitable for X-ray studies, which permitted the determination of the C1 stereochemistry as stated (Figure 1).[31]



(*S*)-**54**

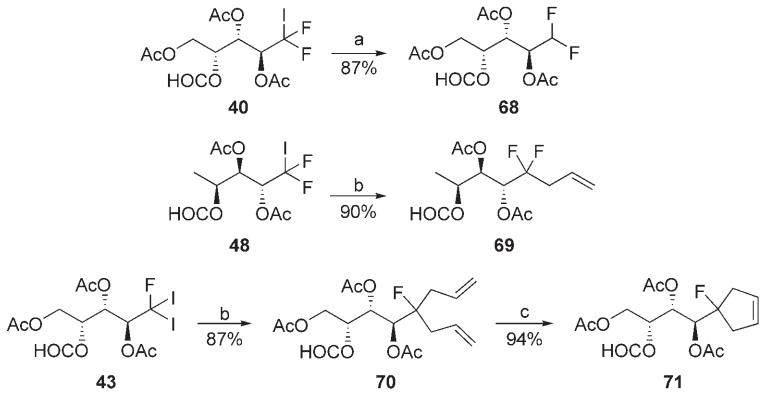
Figure 1. The X-ray structure of (*S*)-**54** showing the *anti* relationships between the C1–F and C2–O bonds.

Some features of the X-ray crystal structures of (*S*)-**54** and (*S*)-**55** deserve brief comment. The F–C1 bond exhibits a nearly antiperiplanar relationship with the C2–O bond with a F-C1-C2-O dihedral angle of 174.6 and 171.8°, respectively. This is quite surprising considering the stereoelectronic preference of two vicinal electronegative atoms to adopt a *gauche* in favour of an *anti* conformation. This counterintuitive *gauche* effect seems to be quite general and has been the subject of numerous synthetic and theoretical studies, particularly with oxygen and fluorine atoms.[32] Furthermore, as a consequence of this *anti* conformation, in both isomers (*S*)-**54** and (*S*)-**55** the voluminous iodine atom is pointing towards the acetal ring plane in an apparently energetically disfavoured arrangement. The conformation of the acetal ring in the crystalline structure was determined as $^{O3}T_3$ with very similar phase angles for both isomers ($P = 103.4$ for (*S*)-**54** and 106.5° for (*S*)-**55**).[33]

Other highlighted features of compounds **54** and **55** are the differences between the $^{1}J_{F,C}$ and $^{3}J_{F,H}$ coupling constants, particularly in the *S* isomers (327 and 14.6 Hz for (*S*)-**54** and 314 and 20.7 Hz for (*S*)-**55**, respectively), which may be attributable to substituent effects and/or conformational changes in solution.[34] Even more surprising is the small but significant difference observed in the $^{3}J_{H,H}$ coupling constant between the protons at C3 and C4 (5.3 Hz for (*S*)-**54** and 2.9 Hz for (*S*)-**55**), most probably due to the flexible nature of the isopropylidene ring in solution.

Next, the reaction was examined with other types of carbohydrates to test the generality and applicability of this methodology. Models derived from D- and L-*arabino*-hexopyranoses (entries 17–24) and L-*erythro*-pentopyranoses (entries 25–28) were used, and the results are summarised in Table 1. As can be observed, the reaction worked very well for all halogen atoms, and the 1,1,1-trihaloalditols **56–67** were obtained in good yields. As well as in the examples of low steric demand discussed before, the radical fragmentation occurs with low diastereoselectivity and trihaloalditols were obtained as equimolecular mixtures of isomers that were difficult to separate by chromatography.

It is necessary to remark that all of the trihaloalditols obtained were quite stable and could be purified by chromatography over silica gel and handled without special precautions apart from avoiding overexposure to light or heat and can be kept for months in the freezer without significant decomposition. The synthetic usefulness of these compounds as building blocks for the preparation of organofluorine compounds has been preliminarily assessed, and the results are summarised in Scheme 3.[35] We were particularly interested in the reactivity of the fluorinated radical generated by rupture of the C–I bond. The reductive deiodination of compound **40** with tributyltin hydride/2,2'-azobisisobutyronitrile (AIBN) led to 1,3,4-tri-*O*-acetyl-5-deoxy-5,5-difluoro-2-*O*-formyl-D-arabinitol (**68**) in excellent yield.[36] Radical intermolecular allylation was also possible by following the Keck and Yates protocol.[37] Reaction of difluoroiodo compound **48** and diiodofluoro compound **43** with allyltributyl stannane in the presence of AIBN gave the expected allyl



Scheme 3. a) Bu_3SnH (5 equiv), AIBN (0.4 equiv), PhH (30 mL), reflux, 0.5 h; b) allyltributylstannane (5 equiv), AIBN (0.4 equiv), PhH (30 mL), reflux, 40 min; c) Grubbs catalyst $[(PCy_3)_2Cl_2Ru{=}CHPh]$ (0.1 equiv), CH_2Cl_2 (40 mL), RT, 1 h.

compound **69** and diallyl compound **70** in good yields.[38] Ring-closing metathesis (RCM) of compound **70** provided the tertiary fluoride compound **71** in 90% yield.[39]

Conclusion

We believe that the reported methodology will be of interest because it permits the facile preparation of mono- or *gem*-difluorinated chiral building blocks for incorporation into important complex target molecules. Also, we report for the first time on the chromatographic resolution of diastereoisomeric mixtures of 1-bromo or 1-chloro-1-deoxy-1-fluoro-1-iodo-alkanes of this type, and the determination of their absolute configuration by X-ray crystallographic analysis. In summary, the ARF reaction of 2-fluoro-2-halohydrins derived from carbohydrates provides a good method of preparing 1,1,1-trihaloalditols with one carbon atom less than the original carbohydrate and offers special advantages, such as ready accessibility of the starting material, experimental simplicity, good yields and mild conditions that are compatible with the stability of the protective groups most commonly used in carbohydrate chemistry. Further exploration of the synthetic potential of these compounds is currently under investigation in our laboratory.

Experimental Section

General methods: Melting points were determined with a hot-stage apparatus and are uncorrected. Optical rotations were measured at the sodium line at ambient temperature in $CHCl_3$ solutions. IR spectra were recorded in CCl_4 solutions unless otherwise stated. NMR spectra were determined at 400 MHz for ^1H, 100.6 MHz for ^{13}C in $CDCl_3$ and 376.5 MHz for ^{19}F in $CDCl_3$ unless otherwise stated, in the presence of TMS as an internal standard. Mass spectra were determined at 70 eV. Merck silica gel 60 PF (0.063–0.2 mm) was used for column chromatography. Circular layers of 1 mm of Merck silica gel 60 PF_{254} were used on a Chromatotron for centrifugally assisted chromatography. Commercially available reagents and solvents were of analytical grade or were purified by standard procedures prior to use. All reactions involving air or moisture-sensitive materials were carried out under a nitrogen atmosphere. TLC plates were visualised by spraying with a solution of 0.5% vanillin in H_2SO_4/EtOH (4:1) and heating until development of colour.

General procedure for the synthesis of 2-deoxy-2,2-difluoropyranoses: F-TEDA-BF_4 (Selectfluor) (1.5 mmol) was added to a solution of the corresponding 2-deoxy-2-fluoro-hex-1-enitol (1 mmol) in nitromethane (10 mL) and H_2O (2 mL) and the mixture was stirred at room temperature until the disappearance of the starting material was observed by TLC (15 h). The mixture was then heated to reflux for 0.5 h, poured into brine and extracted with EtOAc. The organic layer was dried and concentrated in vacuo. Column chromatography of the residue (hexanes/EtOAc mixtures) afforded the required difluorohydrin compounds.

General procedure for the synthesis of 2-deoxy-2,2-chlorofluoropyranoses: A solution of the corresponding 2-deoxy-2-fluoro-hex-1-enitol (1 mmol) in THF (20 mL) and H_2O (10 mL), which contained *N*-chlorosuccinimide (2 mmol) was heated at 50 °C for 6–12 h. The mixture was then poured into H_2O and extracted with EtOAc. The organic layer was dried and concentrated in vacuo. Column chromatography of the residue (hexanes/EtOAc mixtures) afforded the required chlorofluorohydrin compounds.

General procedure for the synthesis of 2-deoxy-2,2-bromofluoropyranoses: A solution of the corresponding 2-deoxy-2-fluoro-hex-1-enitol (1 mmol) in THF (20 mL) and H_2O (5 mL), which contained freshly crystallised *N*-bromoacetamide (1.5 mmol) was stirred at room temperature for 1–7.5 h. The mixture was then poured into H_2O and extracted with EtOAc. The organic layer was dried and concentrated in vacuo. Column chromatography of the residue (hexanes/EtOAc mixtures) afforded the required bromofluorohydrin compounds.

General procedure for the synthesis of 2-deoxy-2,2-fluoroiodopyranoses: A solution of the corresponding 2-deoxy-2-fluoro-hex-1-enitol (1 mmol) in THF (10 mL) and H_2O (5 mL), which contained *N*-iodosuccinimide (2 mmol) was stirred at room temperature (without light exposure) for 1–4 h. The mixture was diluted with EtOAc, poured into H_2O and extracted with EtOAc. The organic layer was washed with aq $Na_2S_2O_3$, dried and concentrated in vacuo. Column chromatography of the residue (hexanes/EtOAc mixtures) afforded the required fluoroiodohydrin compounds.

General procedure for the ARF reaction: A solution of the dihalohydrins (1 mmol) in CH_2Cl_2 (50 mL), which contained (diacetoxyiodo)benzene (1.5 mmol) and I_2 (1.5 mmol) was irradiated with two 80 W tungsten-filament lamps at room temperature. The mixture was then poured into H_2O and extracted with CH_2Cl_2. The organic layer was washed with aq $Na_2S_2O_3$, dried and concentrated in vacuo. Column chromatography of the residue (hexanes/EtOAc mixtures) afforded the halo-fluoro-iodine compounds. No special precautions needed to be taken to exclude light during workup and chromatography, and these compounds could be stored indefinitely under N_2 at −20 °C in the dark.

1,3,4-Tri-*O*-acetyl-5-deoxy-5,5-difluoro-2-*O*-formyl-5-iodo-D-arabinitol (40): Oil (75%); $[\alpha]_D = +23.4$ ($c = 0.73$); ^1H NMR: $\delta = 2.05$ (s, 3H), 2.14 (s, 3H), 2.18 (s, 3H), 3.91 (dd, $J = 7.4$, 11.7 Hz, 1H), 4.31 (dd, $J = 5.0$, 11.7 Hz, 1H), 5.19 (ddd, $J = 8.6$, $^3J_{F,H} = 6.1$, 11.1 Hz, 1H), 5.52 (dddd, $J = 1.0$, 2.1, 5.0, 7.4 Hz, 1H), 5.61 (dd, $J = 2.1$, 8.6 Hz, 1H), 8.00 ppm (brs, 1H); ^{13}C NMR: $\delta = 20.5$ (CH_3), 20.6 (CH_3), 20.8 (CH_3), 61.6 (CH_2), 67.3 (CH), 68.2 (CH), 72.5 (dd, $^2J_{F,C} = 24.4$, 24.4 Hz; CH), 100.4 (dd, $^1J_{F,C} = 314.3$, 314.3 Hz; C), 159.7 (CH), 168.3 (C), 169.1 (C), 170.3 ppm (C); ^{19}F NMR: $\delta = -46.3$ (dd, $^3J_{F,H} = 9.8$, $^2J_{F,F} = 197.3$ Hz, 1F), −50.8 ppm (dd, $^3J_{F,H} = 13.8$, $^2J_{F,F} = 197.3$ Hz, 1F); IR: $\tilde{\nu} = 1762$, 1736, 1230, 1198 cm^{-1}; MS (70 eV, EI): *m/z* (%): 407 (<1) $[M-OCOH]^+$, 393 (3), 325 (33), 283 (100), 263 (86); HRMS (EI): *m/z*: calcd for $C_{11}H_{14}F_2IO_6$: 406.9803 $[M-OCOH]^+$; found: 406.9802; elemental analysis calcd (%) for $C_{12}H_{15}F_2IO_8$ (452.15): C 31.88, H 3.34; found: C 31.95, H 3.31.

1,3,4-Tri-*O*-acetyl-5-deoxy-5-fluoro-2-*O*-formyl-5,5-diiodo-D-arabinitol (43): Crystalline solid (81%); m.p. 103–104 °C (*n*-hexane/EtOAc); $[\alpha]_D = +14.4$ ($c = 0.16$); ^1H NMR (500 MHz): $\delta = 2.03$ (s, 3H), 2.13 (s, 3H), 2.18 (s, 3H), 3.88 (dd, $J = 7.4$, 11.7 Hz, 1H), 4.31 (dd, $J = 4.8$, 11.7 Hz, 1H), 5.24 (dd, $J = 7.4$, $^2J_{F,H} = 7.4$ Hz, 1H), 5.51–5.55 (m, 2H), 8.00 ppm (s, 1H); ^{13}C NMR (125.7 MHz): $\delta = 20.6$ (CH_3), 20.8 (CH_3), 21.1 (CH_3), 27.8 (d, $^1J_{F,C} = 325.1$ Hz; C), 61.8 (CH_2), 67.8 (CH), 70.9 (CH), 76.8 (d, $^2J_{F,C} = 8.8$ Hz; CH), 159.8 (CH), 168.4 (C), 169.2 (C), 170.3 ppm (C); ^{19}F NMR: $\delta = -69.8$ ppm (s, 1F); IR: $\tilde{\nu} = 1760$, 1736, 1370, 1230, 1196 cm^{-1}; MS (70 eV, EI): *m/z* (%): 501 (<1) $[M-OAc]^+$, 433 (<1), 331 (14), 263 (100); HRMS (EI): *m/z*: calcd for $C_{10}H_{12}FI_2O_6$: 500.8707 $[M-OAc]^+$; found: 500.8710; elemental analysis calcd (%) for $C_{12}H_{15}FI_2O_8$ (560.05): C 25.72, H 2.70; found: C 25.89, H 2.73.

5-Deoxy-5,5-difluoro-2-*O*-formyl-5-iodo-1,3,4-tri-*O*-methyl-D-arabinitol (44): Oil (57%); $[\alpha]_D = +9.0$ ($c = 0.10$); ^1H NMR: $\delta = 2.98$ (ddd, $J = 7.9$, $^3J_{F,H} = 6.0$, 8.7 Hz, 1H), 3.41 (s, 3H), 3.52 (s, 3H), 3.53 (dd, $^5J_{F,H} = 0.8$, 1.3 Hz, 3H), 3.58 (d, $J = 6.7$ Hz, 2H), 3.63 (dd, $J = 2.3$, 7.9 Hz, 1H), 5.42 (dddd, $J = 1.0$, 2.3, 6.7, 6.7 Hz, 1H), 8.14 ppm (d, $J = 1.0$ Hz, 1H); ^{13}C NMR: $\delta = 59.0$ (CH_3), 60.8 (d, $^5J_{F,C} = 1.6$ Hz; CH_3), 61.2 (d, $^4J_{F,C} = 2.7$ Hz; CH_3), 69.6 (CH_2), 70.6 (CH), 79.4 (d, $^3J_{F,C} = 4.3$ Hz; CH), 84.8 (dd, $^2J_{F,C} = 19.4$, 20.0 Hz; CH), 107.9 (dd, $^1J_{F,C} = 316.6$, 322.4 Hz; C), 160.1 ppm (CH); ^{19}F NMR: $\delta = -41.7$ (dd, $^3J_{F,H} = 8.8$, $^2J_{F,F} = 200.9$ Hz, 1F), −47.1 ppm (dd, $^3J_{F,H} = 7.8$, $^2J_{F,F} = 200.9$ Hz, 1F); IR: $\tilde{\nu} = 2937$, 1728, 1175, 1224 cm^{-1}; MS (70 eV, EI): *m/z* (%): 353 (1) $[M-CH_3]^+$, 291 (6), 265 (8), 195 (5), 163 (8), 147 (100); HRMS (EI): *m/z*: calcd for $C_8H_{12}F_2IO_5$: 352.9698 $[M-CH_3]^+$; found: 352.9699; elemental analysis calcd (%) for $C_9H_{15}F_2IO_5$ (368.12): C 29.36, H 4.11; found: C 29.47, H 4.09.

1,3,4-Tri-*O*-benzyl-5-deoxy-5,5-difluoro-2-formyl-5-iodo-D-arabinitol (45): Crystalline solid (46%); m.p. 52.5–53.6°C (*n*-hexane/EtOAc); $[\alpha]_D = -38.5$ ($c = 0.14$); ^{1}H NMR: $\delta = 3.44$ (ddd, $J = 7.1$, $^3J_{F,H} = 7.1$, 8.2 Hz, 1H), 3.60 (dd, $J = 6.9$, 9.8 Hz, 1H), 3.64 (dd, $J = 5.8$, 9.8 Hz, 1H), 4.02 (dd, $J = 2.6$, 7.1 Hz, 1H), 4.47 (d, $J = 11.8$ Hz, 1H), 4.51 (d, $J = 11.8$ Hz, 1H), 4.53 (d, $J = 10.8$ Hz, 1H), 4.57 (d, $J = 10.8$ Hz, 1H), 4.76 (d, $J = 10.6$ Hz, 1H), 4.87 (d, $J = 10.6$ Hz, 1H), 5.47 (dddd, $J = 0.8$, 2.6, 5.8, 6.9 Hz, 1H), 7.25–7.39 (m, 15H), 8.00 ppm (dd, $J = 0.8$, 0.8 Hz, 1H); ^{13}C NMR: $\delta = 67.2$ (CH_2), 70.9 (CH), 73.3 (CH_2), 74.6 (CH_2), 75.1 (CH_2), 77.1 (d, $^3J_{F,C} = 4.3$ Hz; CH), 82.8 (dd, $^2J_{F,C} = 19.3$, 20.3 Hz; CH), 104.4 (dd, $^1J_{F,C} = 324.5$, 366.4 Hz; C), 127.8 (2×CH), 127.9 (CH), 128.0 (CH), 128.1 (2×CH), 128.3 (CH), 128.4 (2×CH), 128.46 (4×CH), 128.5 (2×CH), 136.3 (C), 137.2 (C), 137.4 (C), 160.2 ppm (CH); ^{19}F NMR: $\delta = -40.9$ (d, $^2J_{F,F} = 183.5$ Hz, 1F), -46.4 ppm (d, $^2J_{F,F} = 183.5$ Hz, 1F); IR: $\tilde{\nu} = 3018$, 2930, 1727, 1455, 1178, 1115 cm^{-1}; MS (70 eV, EI): *m/z* (%): 505 (1) $[M-Bn]^+$, 399 (1), 309 (1), 271 (1), 91 (100); HRMS (EI): *m/z* calcd for $C_{20}H_{20}F_2IO_5$: 505.0324 $[M-Bn]^+$; found: 505.0347; elemental analysis calcd (%) for $C_{27}H_{27}F_2IO_5$ (596.41): C 54.37, H 4.56; found: C 54.14, H 4.40.

1,3,4-Tri-*O*-benzyl-5-deoxy-5-fluoro-2-formyl-5,5-diiodo-D-arabinitol (47): Oil (58%); $[\alpha]_D = -11.2$ ($c = 0.34$); ^{1}H NMR: $\delta = 3.62$ (dd, $J = 1.1$, 6.4 Hz, 2H), 3.78 (dd, $J = 5.6$, $^3J_{F,H} = 8.5$ Hz, 1H), 4.07 (dd, $J = 2.9$, 5.6 Hz, 1H), 4.44 (d, $J = 11.9$ Hz, 1H), 4.49 (d, $J = 11.9$ Hz, 1H), 4.57 (d, $J = 11.1$ Hz, 1H), 4.78 (d, $J = 10.9$ Hz, 1H), 4.86 (d, $J = 11.1$ Hz, 1H), 5.06 (d, $J = 10.9$ Hz, 1H), 5.51 (ddd, $J = 2.6$, 6.4, 6.4 Hz, 1H), 7.26–7.43 (m, 15H), 7.96 ppm (s, 1H); ^{13}C NMR: $\delta = 36.6$ (d, $^1J_{F,C} = 328.5$ Hz; C), 67.6 (CH_2), 71.3 (CH), 73.2 (CH_2), 74.1 (CH_2), 75.7 (CH_2), 78.2 (CH), 88.6 (d, $^2J_{F,C} = 17.7$ Hz; CH), 127.8–128.6 (15×CH), 136.6 (C), 137.3 (C), 137.5 (C), 160.3 ppm (CH); ^{19}F NMR: $\delta = -64.1$ ppm (d, $^3J_{F,H} = 6.2$ Hz, 1F); IR: $\tilde{\nu} = 3067$, 3033, 2929, 1732, 1456, 1172, 1098 cm^{-1}; MS (70 eV, EI): *m/z* (%): 613 (1) $[M-Bn]^+$, 507 (1), 303 (1), 289 (1), 254 (4), 181 (12), 91 (100); HRMS (EI): *m/z*: calcd for $C_{20}H_{20}FI_2O_5$: 612.9384 $[M-Bn]^+$; found: 612.9378; elemental analysis calcd (%) for $C_{27}H_{27}FI_2O_5$ (704.32): C 46.02, H 3.87; found: C 46.02, H 4.05.

3,4-Di-*O*-acetyl-1,5-dideoxy-5,5-difluoro-2-*O*-formyl-5-iodo-L-arabinitol (48): Crystalline solid (76%); m.p. 76.5–78°C (*n*-hexane/EtOAc); $[\alpha]_D = -14.9$ ($c = 0.22$); ^{1}H NMR: $\delta = 1.23$ (d, $J = 6.2$ Hz, 3H), 2.16 (s, 3H), 2.17 (s, 3H), 5.18 (ddd, $J = 8.8$, $^3J_{F,H} = 6.0$, 11.2 Hz, 1H), 5.32 (dddd, $J = 2.1$, 6.2, 6.2, 6.2 Hz, 1H), 5.42 (dd, $J = 2.1$, 8.8 Hz, 1H), 7.96 ppm (s, 1H); ^{13}C NMR: $\delta = 16.1$ (CH_3), 20.5 (CH_3), 20.7 (CH_3), 66.9 (CH), 71.1 (CH), 72.8 (dd, $^2J_{F,C} = 23.0$, 24.0 Hz; CH), 100.8 (dd, $^1J_{F,C} = 314.0$, 318.0 Hz; C), 159.9 (CH), 168.2 (C), 169.4 ppm (C); ^{19}F NMR: $\delta = -46.0$ (d, $^2J_{F,F} = 192.0$ Hz, 1F), -50.7 ppm (dd, $^3J_{F,H} = 13.4$, $^2J_{F,F} = 192.0$ Hz, 1F); IR: $\tilde{\nu} = 2940$, 1760, 1731, 1371, 1201, 1170 cm^{-1}; MS (70 eV, EI): *m/z* (%): 267 (14) $[M-I]^+$, 249 (16), 225 (100), 205 (91); HRMS (EI): *m/z*: calcd for $C_{10}H_{13}F_2O_6$: 267.0680 $[M-I]^+$; found: 267.0692; elemental analysis calcd (%) for $C_{10}H_{13}F_2IO_6$ (394.11): C 30.48, H 3.32; found: C 30.68, H 3.14.

3,4-Di-*O*-acetyl-1,5-dideoxy-5-fluoro-2-*O*-formyl-5,5-diiodo-L-arabinitol (51): Crystalline solid (79%); m.p. 90–91°C (*n*-hexane/EtOAc); $[\alpha]_D = -16.9$ ($c = 0.42$); ^{1}H NMR: $\delta = 1.23$ (d, $J = 6.4$ Hz, 3H), 2.17 (s, 3H), 2.19 (s, 3H), 5.23 (dd, $J = 8.0$, $^3J_{F,H} = 6.0$ Hz, 1H), 5.30–5.35 (m, 2H), 7.95 ppm (s, 1H); ^{13}C NMR: $\delta = 16.4$ (CH_3), 20.9 (CH_3), 21.1 (CH_3), 28.7 (d, $^1J_{F,C} = 324.0$ Hz; C), 67.4 (CH), 74.0 (CH), 76.8 (d, $^2J_{F,C} = 24.0$ Hz; CH), 160.0 (CH), 168.2 (C), 169.4 ppm (C); ^{19}F NMR: $\delta = -69.1$ ppm (s, 1F); IR: $\tilde{\nu} = 2991$, 1759, 1730, 1370, 1199, 1171 cm^{-1}; MS (70 eV, EI): *m/z* (%): 457 (<1) $[M-OCOH]^+$, 287 (11), 273 (6), 205 (100); HRMS (EI): *m/z*: calcd for $C_9H_{12}FI_2O_4$: 456.8809 $[M-OCOH]^+$; found: 456.8800; elemental analysis calcd (%) for $C_{10}H_{13}FI_2O_6$ (502.02): C 23.93, H 2.61; found: C 23.93, H 2.31.

(5*R*)-1-*O*-Benzyl-5-bromo-5-deoxy-5-fluoro-2-*O*-formyl-3,4-*O*-isopropylidene-5-iodo-D-arabinitol ((*R*)-52): Oil (28%); $[\alpha]_D = +12.7$ ($c = 0.49$); ^{1}H NMR: $\delta = 1.44$ (s, 3H), 1.63 (s, 3H), 3.68 (d, $J = 6.1$ Hz, 2H), 4.54 (d, $J = 11.9$ Hz, 1H), 4.55 (dd, $J = 6.1$, $^3J_{F,H} = 23.4$ Hz, 1H), 4.58 (d, $J = 11.9$ Hz, 1H), 4.67 (dd, $J = 3.4$, 6.1 Hz, 1H), 5.58 (ddd, $J = 3.4$, 6.1, 6.1 Hz, 1H), 7.29 –7.36 (m, 5H), 8.05 ppm (s, 1H); ^{13}C NMR (125.7 MHz): $\delta = 25.4$ (CH_3), 26.3 (CH_3), 59.6 (d, $^1J_{F,C} = 333.7$ Hz; C), 67.9 (CH_2), 68.2 (CH), 73.3 (CH_2), 74.3 (CH), 86.4 (d, $^2J_{F,C} = 17.2$ Hz; CH), 109.9 (C), 127.7 (2×CH), 127.9 (CH), 128.5 (2×CH), 137.5 (C), 159.9 ppm (CH); ^{19}F NMR: $\delta = -67.7$ ppm (d, $^3J_{F,H} = 22.9$ Hz, 1F); IR: $\tilde{\nu} = 3030$, 2931, 1735, 1455, 1383, 1218, 1172, 1110 cm^{-1}; MS (70 eV, EI): *m/z* (%): 518/516 (<1) $[M]^+$, 503/501 (1/1), 460/458 (<1), 273 (1), 227/225 (11/11), 183/181 (12/14), 91 (100); HRMS (EI): *m/z* calcd for $C_{16}H_{19}{}^{79}BrFIO_5$: 515.9445 $[M]^+$; found: 515.9449; elemental analysis calcd (%) for $C_{16}H_{19}BrFIO_5$ (517.13): C 37.16, H 3.70; found: C 37.15, H 3.84.

(5*S*)-1-*O*-Benzyl-5-bromo-5-deoxy-5-fluoro-2-*O*-formyl-3,4-*O*-isopropylidene-5-iodo-D-arabinitol ((*S*)-52): Crystalline solid (18%); m.p. 84.0–85.3°C (*n*-hexane/EtOAc); $[\alpha]_D = +14.0$ ($c = 0.10$); ^{1}H NMR: $\delta = 1.44$ (s, 3H), 1.65 (s, 3H), 3.69 (d, $J = 5.3$ Hz, 2H), 4.54 (d, $J = 11.9$ Hz, 1H), 4.59 (d, $J = 11.9$ Hz, 1H), 4.65 (dd, $J = 5.0$, 6.2 Hz, 1H), 4.66 (dd, $J = 6.2$, $^3J_{F,H} = 16.7$ Hz,1H), 5.69 (dddd, $J = 1.1$, 5.0, 5.3, 5.3 Hz, 1H), 7.30–7.37 ppm (m, 5H), 8.07 ppm (brs, 1H); ^{13}C NMR (125.7 MHz): $\delta = 25.4$ (CH_3), 26.3 (CH_3), 60.3 (d, $^1J_{F,C} = 325.9$ Hz; C), 67.8 (CH_2), 68.3 (CH), 73.4 (CH_2), 75.6 (CH), 86.2 (d, $^2J_{F,C} = 23.3$ Hz; CH), 110.4 (C), 127.7 (2×CH), 127.9 (CH), 128.5 (2×CH), 137.5 (C), 159.9 ppm (CH); ^{19}F NMR: $\delta = -67.6$ ppm (brs, 1F); IR: $\tilde{\nu} = 3030$, 2938, 1735, 1383, 1218, 1172, 1112 cm^{-1}; MS (70 eV, EI): *m/z* (%): 518/516 (<1) $[M]^+$, 503/501 (1/1), 460/458 (<1), 285 (<1), 273 (2), 227/225 (10/10), 91 (100); HRMS (EI): *m/z*: calcd for $C_{16}H_{19}{}^{81}BrFIO_5$: 517.9424 $[M]^+$; found: 517.9427; elemental analysis calcd (%) for $C_{16}H_{19}BrFIO_5$ (517.13): C 37.16, H 3.70; found: C 37.47, H 3.34.

5-Deoxy-1-*O*-benzyl-5-fluoro-2-*O*-formyl-3,4-*O*-isopropylidene-5,5-diiodo-D-arabinitol (53): Oil (55%); $[\alpha]_D = +4.9$ ($c = 0.51$); ^{1}H NMR: $\delta = 1.45$ (s, 3H), 1.65 (s, 3H), 3.66 (dd, $J = 5.5$, 9.8 Hz, 1H), 3.69 (dd, $J = 6.7$, 9.8 Hz, 1H), 4.56 (d, $J = 11.9$ Hz, 1H), 4.58 (d, $J = 11.9$ Hz, 1H), 4.64 (dd, $J = 6.1$, $^3J_{F,H} = 22.6$ Hz, 1H), 4.72 (dd, $J = 3.3$, 6.1 Hz, 1H), 5.61 (m, 1H), 7.29–7.36 (m, 5H), 8.05 ppm (brs, 1H); ^{13}C NMR (125.7 MHz): $\delta = 22.3$ (d, $^1J_{F,C} = 335.5$ Hz; C), 25.4 (CH_3), 26.5 (CH_3), 67.8 (CH_2), 68.3 (CH), 73.3 (CH_2), 74.7 (CH), 87.3 (d, $^2J_{F,C} = 20.7$ Hz; CH), 109.9 (C), 127.7 (2×CH), 127.8 (CH), 128.4 (2×CH), 137.6 (C), 159.9 ppm (CH); ^{19}F NMR: $\delta = -74.1$ ppm (s, 1F); IR: $\tilde{\nu} = 3018$, 2935, 1732, 1549, 1383, 1215, 1170 cm^{-1}; MS (70 eV, EI): *m/z* (%): 564 (<1) $[M]^+$, 549 (<1), 273 (11), 229 (22), 91 (100); HRMS (EI): *m/z*: calcd for $C_{16}H_{19}FI_2O_5$: 563.9306 $[M]^+$; found: 563.9297; elemental analysis calcd (%) for $C_{16}H_{19}FI_2O_5$ (564.13): C 34.07, H 3.39; found: C 34.18, H 3.02.

(5*R*)-5-Chloro-5-deoxy-1-*O*-(3,5-dinitrobenzoyl)-5-fluoro-2-*O*-formyl-3,4-*O*-isopropylidene-5-iodo-D-arabinitol ((*R*)-54): Crystalline solid (46%); m.p. 120.4–122.0°C (hexane/EtOAc); $[\alpha]_D = +30$ ($c = 0.05$); ^{1}H NMR: $\delta = 1.48$ (s, 3H), 1.66 (s, 3H), 4.55 (dd, $J = 2.4$, 6.1 Hz, 1H), 4.58 (dd, $J = 6.8$, 11.9 Hz, 1H), 4.71 (dd, $J = 6.1$, $^3J_{F,H} = 24.4$ Hz, 1H), 4.79 (dd, $J = 3.7$, 11.9 Hz, 1H), 5.81 (ddd, $J = 2.4$, 3.7, 6.8 Hz, 1H), 8.10 (s, 1H), 9.13 (d, $J = 2.1$ Hz, 2H), 9.23 ppm (dd, $J = 2.1$, 2.1 Hz, 1H); ^{13}C NMR (C_6D_6): $\delta = 25.2$ (CH_3), 26.1 (CH_3), 66.0 (CH_2), 67.2 (CH), 74.0 (d, $^1J_{F,C} = 324.5$ Hz; C), 74.9 (CH), 86.6 (d, $^2J_{F,C} = 20.7$ Hz; CH), 110.5 (C), 122.5 (CH), 128.8 (2×CH), 132.5 (C), 148.3 (2×C), 159.6 (CH), 162.3 ppm (C); ^{19}F NMR: $\delta = -66.7$ ppm (s, 1F); IR: $\tilde{\nu} = 3102$, 2929, 1737, 1549, 1461, 1342, 1273 cm^{-1}; MS (70 eV, EI): *m/z* (%): 563/561 (5/15) $[M-CH_3]^+$, 483 (18), 385 (9), 295/293 (3/7), 293 (7), 195 (100); HRMS (EI): *m/z*: calcd for $C_{15}H_{12}{}^{35}ClFIN_2O_{10}$: 560.9209 $[M-CH_3]^+$; found: 560.9212; elemental analysis calcd (%) for $C_{16}H_{15}ClFIN_2O_{10}$ (576.66): C 33.33, H 2.62, N 4.86; found: C 33.49, H 2.52, N 4.84.

(5*S*)-5-Chloro-5-deoxy-1-*O*-(3,5-dinitrobenzoyl)-5-fluoro-2-*O*-formyl-3,4-*O*-isopropylidene-5-iodo-D-arabinitol ((*S*)-54): Crystalline solid (30%); m.p. 134.5–135.5°C (hexane/EtOAc); $[\alpha]_D = 0$ ($c = 0.15$); ^{1}H NMR: $\delta = 1.48$ (s, 3H), 1.68 (s, 3H), 4.56 (dd, $J = 5.3$, 6.1 Hz, 1H), 4.58 (dd, $J = 6.6$, 12.0 Hz, 1H), 4.78 (dd, $J = 3.9$, 12.0 Hz, 1H), 4.88 (dd, $J = 6.1$, $^3J_{F,H} = 14.6$ Hz, 1H), 5.90–5.93 (m, 1H), 8.16 (brs, 1H), 9.14 (d, $J = 2.1$ Hz, 2H), 9.24 ppm (dd, $J = 2.1$, 2.1 Hz, 1H); ^{13}C NMR (C_6D_6): $\delta = 25.1$ (CH_3), 26.3 (CH_3), 65.6 (d, $^3J_{F,C} = 3.2$ Hz; CH), 67.0 (CH_2), 76.29 (d, $^1J_{F,C} = 314.8$ Hz; C), 76.3 (CH), 86.2 (d, $^2J_{F,C} = 24.7$ Hz; CH), 111.2 (C), 122.2 (CH), 128.8 (2×CH), 132.4 (C), 148.3 (2×C), 159.4 (CH), 162.2 ppm (C); ^{19}F NMR: $\delta = -68.0$ ppm (brs, 1F); IR: $\tilde{\nu} = 3102$, 2939, 1740, 1548, 1343, 1275, 1173 cm^{-1}; MS (70 eV, EI): *m/z* (%): 563/561 (4/13) $[M-CH_3]^+$, 483 (24), 385 (7), 295/293 (2/6), 195 (100); HRMS (EI): *m/z*: calcd for $C_{15}H_{12}{}^{35}ClFIN_2O_{10}$: 560.9209 $[M-CH_3]^+$; found: 560.9213; elemental analysis calcd (%) for $C_{16}H_{15}ClFIN_2O_{10}$ (576.66): C 33.33, H 2.62, N 4.86; found: C 33.51, H 2.52, N 4.74.

(5*R*)-5-Bromo-5-deoxy-1-*O*-(3,5-dinitrobenzoyl)-5-fluoro-2-*O*-formyl-3,4-*O*-isopropylidene-5-iodo-D-arabinitol ((*R*)-55): Crystalline solid (44%); m.p. 128.7–130.3°C (*n*-hexane/EtOAc); $[\alpha]_D = +19.3$ ($c = 0.14$); ^{1}H NMR: $\delta = 1.49$ (s, 3H), 1.67 (s, 3H), 4.58 (dd, $J = 6.5$, 11.8 Hz, 1H), 4.61 (dd, $J = 1.9$, 6.1 Hz, 1H), 4.77 (dd, $J = 3.9$, 11.8 Hz, 1H), 4.80 (dd, $J = 6.1$, $^3J_{F,H} = 25.6$ Hz, 1H), 5.83 (ddd, $J = 1.9$, 3.9, 6.5 Hz, 1H), 8.08 (s, 1H), 9.15 (d, $J = 2.1$ Hz, 2H), 9.24 ppm (dd, $J = 2.1$, 2.1 Hz, 1H); ^{13}C NMR: $\delta = 25.5$ (CH_3), 26.3 (CH_3), 55.9 (d, $^1J_{F,C} = 331.7$ Hz; C), 65.8 (CH_2), 67.4 (CH), 74.8 (CH), 86.9 (d, $^2J_{F,C} = 20.0$ Hz; CH), 110.7 (C), 122.6 (CH), 129.6 (2×CH), 133.2 (C), 148.7 (2×C), 159.8 (CH), 162.2 ppm (C); ^{19}F NMR: $\delta = -69.3$ ppm (br s, 1F); IR: $\tilde{\nu} = 3111$, 2950, 1738, 1550, 1343, 1275, 1175, 1154 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 607/605 (9/9) $[M-CH_3]^+$, 483 (27), 437/435 (7/7), 385 (11), 195 (100); HRMS (EI): *m*/*z*: calcd for $C_{15}H_{12}{}^{79}BrFIN_2O_{10}$: 604.8704 $[M-CH_3]^+$; found: 604.8721; elemental analysis calcd (%) for $C_{16}H_{15}BrFIN_2O_{10}$ (621.11): C 30.94, H 2.43, N 4.51; found: C 30.95, H 2.46, N 4.26.

(5*S*)-5-Bromo-5-deoxy-1-*O*-(3,5-dinitrobenzoyl)-5-fluoro-2-*O*-formyl-3,4-*O*-isopropylidene-5-iodo-D-arabinitol ((*S*)-55): Crystalline solid (22%); m.p. 142.7–143.8°C (*n*-hexane/EtOAc); $[\alpha]_D = -21.0$ ($c = 0.10$); ^{1}H NMR: $\delta = 1.49$ (s, 3H), 1.69 (s, 3H), 4.57 (dd, $J = 6.6$, 11.7 Hz, 1H), 4.64 (ddd, $J = 2.9$, 6.4, $^4J_{F,H} = 0.8$ Hz, 1H), 4.77 (dd, $J = 4.0$, 11.7 Hz, 1H), 4.90 (dd, $J = 6.4$, $^3J_{F,H} = 20.7$ Hz, 1H), 5.88 (ddd, $J = 2.9$, 4.0, 6.6 Hz, 1H), 8.10 (s, 1H), 9.16 (d, $J = 2.1$ Hz, 2H), 9.24 ppm (dd, $J = 2.1$, 2.1 Hz, 1H); ^{13}C NMR: $\delta = 25.5$ (CH_3), 26.4 (CH_3), 57.2 (d, $^1J_{F,C} = 326.7$ Hz; C), 65.5 (CH_2), 67.2 (CH), 76.1 (CH), 86.6 (d, $^2J_{F,C} = 21.3$ Hz; CH), 111.4 (C), 122.7 (CH), 129.6 (2×CH), 133.2 (C), 148.7 (2×C), 159.7 (CH), 162.2 ppm (C); ^{19}F NMR: $\delta = -70.6$ ppm (br s, 1F); IR: $\tilde{\nu} = 3098$, 2984, 1740, 1550, 1342, 1275, 1175 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 607/605 (7/7) $[M-CH_3]^+$, 483 (15), 437/435 (6/6), 385 (13), 195 (100); HRMS (EI): *m*/*z*: calcd for $C_{15}H_{12}{}^{81}BrFIN_2O_{10}$: 606.8684 $[M-CH_3]^+$; found: 606.8685; elemental analysis calcd (%) for $C_{16}H_{15}BrFIN_2O_{10}$ (621.11): C 30.94, H 2.43, N 4.51; found: C 31.06, H 2.41, N 4.48.

2,3,5-Tri-*O*-acetyl-1-deoxy-1,1-difluoro-4-*O*-formyl-1-iodo-D-arabinitol (56): Crystalline solid (71%); m.p. 70–71°C (*n*-hexane/EtOAc); $[\alpha]_D = +38.5$ ($c = 0.15$); ^{1}H NMR: $\delta = 2.08$ (s, 3H), 2.12 (s, 3H), 2.23 (s, 3H), 4.16 (dd, $J = 5.0$, 12.7 Hz, 1H), 4.27 (dd, $J = 2.9$, 12.7 Hz, 1H), 5.17 (dddd, $J = 0.8$, 2.9, 5.0, 8.5 Hz, 1H), 5.56 (ddd, $J = 1.8$, $^3J_{F,H} = 10.8$, 12.8 Hz, 1H), 5.87 (dd, $J = 1.8$, 8.5 Hz, 1H), 8.01 ppm (d, $J = 0.8$ Hz, 1H); ^{13}C NMR: $\delta = 20.5$ (CH_3), 20.6 (2×CH_3), 61.0 (CH_2), 65.8 (CH), 67.8 (CH), 73.6 (dd, $^2J_{F,C} = 23.0$, 23.0 Hz; CH), 97.7 (dd, $^1J_{F,C} = 317.6$, 322.5 Hz; C), 159.2 (CH), 168.8 (C), 168.9 (C), 170.4 ppm (C); ^{19}F NMR: $\delta = -50.6$ (dd, $^3J_{F,H} = 12.0$, $^2J_{F,F} = 191.5$ Hz, 1F), −51.2 ppm (dd, $^3J_{F,H} = 10.0$, $^2J_{F,F} = 191.5$ Hz, 1F); IR: $\tilde{\nu} = 1766$, 1744, 1201, 1150 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 407 (2) $[M-OCOH]^+$, 393 (1), 325 (23), 283 (100), 263 (83); HRMS (EI): *m*/*z*: calcd for $C_{11}H_{14}F_2IO_6$: 406.9803 $[M-OCOH]^+$; found: 406.9804; elemental analysis calcd (%) for $C_{12}H_{15}F_2IO_8$ (452.15): C 31.88, H 3.34; found: C 31.84, H 3.26.

2,3,5-Tri-*O*-acetyl-1-deoxy-1-fluoro-4-*O*-formyl-1,1-diiodo-D-arabinitol (59): Oil (75%); $[\alpha]_D = +30.0$ ($c = 0.09$); ^{1}H NMR: $\delta = 2.08$ (s, 3H), 2.11 (s, 3H), 2.27 (s, 3H), 4.17 (dd, $J = 5.0$, 12.4 Hz, 1H), 4.29 (dd, $J = 2.9$, 12.4 Hz, 1H), 5.13 (ddd, $J = 2.9$, 5.0, 8.2 Hz, 1H), 5.50 (dd, $J = 1.4$, $^2J_{F,H} = 18.5$ Hz, 1H), 6.15 (dd, $J = 1.4$, 8.2 Hz, 1H), 8.04 ppm (s, 1H); ^{13}C NMR: $\delta = 20.6$ (CH_3), 20.8 (CH_3), 20.9 (CH_3), 25.8 (d, $^1J_{F,C} = 329.9$ Hz; C), 61.0 (CH_2), 66.8 (CH), 68.7 (CH), 77.2 (d, $^2J_{F,C} = 19.4$ Hz; CH), 159.3 (CH), 168.9 (2×C), 170.4 ppm (C); ^{19}F NMR: $\delta = -70.7$ ppm (d, $^3J_{F,H} = 9.0$ Hz, 1F); IR: $\tilde{\nu} = 2978$, 1742, 1374, 1239, 1201, 1151 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 515 (1) $[M-OCOH]^+$, 501 (<1), 433 (1), 373 (1), 330 (10), 263 (100); HRMS (EI): *m*/*z*: calcd for $C_{11}H_{14}FI_2O_6$: 514.8864 $[M-OCOH]^+$; found: 514.8884; elemental analysis calcd (%) for $C_{12}H_{15}FI_2O_8$ (560.05): C 25.74, H 2.70; found: C 25.80, H 2.56.

2,3-Di-*O*-acetyl-1,5-dideoxy-1,1-difluoro-4-*O*-formyl-1-iodo-L-arabinitol (60): Syrup (82%); $[\alpha]_D = -51.1$ ($c = 0.62$); ^{1}H NMR: $\delta = 1.28$ (d, $J = 6.4$ Hz, 3H), 2.13 (s, 3H), 2.23 (s, 3H), 5.05 (dddd, $J = 6.4$, 6.4, 6.4, 6.4 Hz, 1H), 5.56 (ddd, $J = 2.0$, $^3J_{F,H} = 10.0$, 12.0 Hz, 1H), 5.64 (dd, $J = 2.0$, 6.4 Hz, 1H), 8.00 ppm (s, 1H); ^{13}C NMR: $\delta = 15.9$ (CH_3), 20.5 (CH_3), 20.6 (CH_3), 67.2 (CH), 69.3 (CH), 73.5 (dd, ^2J(CH) = 21.8, 24.5 Hz; CH), 98.2 (dd, $^1J_{F,C} = 314.6$, 315.1 Hz; C), 159.6 (CH), 168.8 (C), 169.3 ppm (C); ^{19}F NMR: $\delta = -50.4$ (dd, $^3J_{F,H} = 8.8$, $^2J_{F,F} = 188.1$ Hz, 1F), −51.1 ppm (dd, $^3J_{F,H} = 10.0$, $^2J_{F,F} = 188.1$ Hz, 1F); IR: $\tilde{\nu} = 1767$, 1736, 1203, 1161 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 349 (36) $[M-OCOH]^+$, 267 (9), 225 (97), 205 (100); HRMS (EI): *m*/*z*: calcd for $C_9H_{12}F_2IO_4$: 348.9748 $[M-OCOH]^+$; found: 348.9737; elemental analysis calcd (%) for $C_{10}H_{13}F_2IO_6$ (394.11): C 30.48, H 3.32; found: C: 30.53, H 3.30.

2,3-Di-*O*-acetyl-1,5-dideoxy-1-fluoro-4-*O*-formyl-1,1-diiodo-L-arabinitol (63): Oil (83%); $[\alpha]_D = -52.8$ ($c = 1.0$); ^{1}H NMR: $\delta = 1.30$ (d, $J = 6.4$ Hz, 3H), 2.13 (s, 3H), 2.26 (s, 3H), 5.02 (dddd, $J = 6.4$, 6.4, 6.4, 7.2 Hz, 1H), 5.51 (dd, $J = 2.0$, $^3J_{F,H} = 18.0$ Hz, 1H), 5.92 (dd, $J = 2.0$, 7.2 Hz, 1H), 8.00 ppm (s, 1H); ^{13}C NMR: $\delta = 15.8$ (CH_3), 20.8 (CH_3), 20.9 (CH_3), 26.7 (d, $^1J_{F,C} = 327.8$ Hz; C), 68.1 (CH), 70.2 (CH), 77.1 (d, $^2J_{F,C} = 21.2$ Hz; CH), 159.6 (CH), 168.9 (C), 169.4 ppm (C); ^{19}F NMR: $\delta = -70.2$ ppm (d, $^3J_{F,H} = 17.4$ Hz, 1F); IR: $\tilde{\nu} = 2939$, 1764, 1736, 1371, 1202, 1166 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 457 (1) $[M-OCOH]^+$, 287 (5), 249 (4), 205 (100); HRMS (EI): *m*/*z*: calcd for $C_9H_{12}FI_2O_4$: 456.8809 $[M-OCOH]^+$; found: 456.8813; elemental analysis calcd (%) for $C_{10}H_{13}FI_2O_6$ (502.02): C 23.93, H 2.61; found: C 24.00, H 2.53.

2,3-Di-*O*-acetyl-4-deoxy-4,4-difluoro-1-*O*-formyl-4-iodo-D-erythritol (64): Oil (77%); $[\alpha]_D = -17.5$ ($c = 0.27$); ^{1}H NMR (500 MHz): $\delta = 2.08$ (s, 3H), 2.20 (s, 3H), 4.29 (dd, $J = 6.2$, 12.4 Hz, 1H), 4.47 (dd, $J = 2.4$, 12.4 Hz, 1H), 5.42 (ddd, $J = 6.2$, $^3J_{F,H} = 7.6$, 13.2 Hz, 1H), 5.50 (ddd, $J = 2.4$, 6.2, 6.2 Hz, 1H), 8.03 ppm (s, 1H); ^{13}C NMR (125.7 MHz): $\delta = 20.6$ (2×CH_3), 60.7 (CH_2), 68.4 (CH), 74.4 (dd, $^2J_{F,C} = 21.4$, 24.5 Hz; CH), 98.6 (dd, $^1J_{F,C} = 314.3$, 320.4 Hz; C), 160.1 (CH), 168.2 (C), 169.4 ppm (C); ^{19}F NMR: $\delta = -48.7$ (dd, $^3J_{F,H} = 9.2$, $^2J_{F,F} = 192.8$ Hz, 1F), −51.1 ppm (dd, $^3J_{F,H} = 13.8$, $^2J_{F,F} = 192.8$ Hz, 1F); IR: $\tilde{\nu} = 2940$, 1762, 1737, 1371, 1228, 1201, 1168 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 335 (1) $[M-OCOH]^+$, 321 (1), 253 (9), 211 (97), 191 (100); HRMS (EI): *m*/*z*: calcd for $C_8H_{10}F_2IO_4$: 334.9592 $[M-OCOH]^+$; found: 334.9600; elemental analysis calcd (%) for $C_9H_{11}F_2IO_6$ (380.08): C 28.44, H 2.92; found: C 28.64, H 2.73.

2,3-Di-*O*-acetyl-4-deoxy-4-fluoro-1-*O*-formyl-4-diiodo-D-erythritol (67): Oil (94%); $[\alpha]_D = -20.0$ ($c = 0.23$); ^{1}H NMR: $\delta = 2.09$ (s, 3H), 2.24 (s, 3H), 4.27 (dd, $J = 6.8$, 12.3 Hz, 1H), 4.53 (ddd, $J = 1.4$, 2.8, 12.3 Hz, 1H), 5.46 (dd, $J = 4.7$, $^3J_{F,H} = 17.2$ Hz, 1H), 5.69 (ddd, $J = 2.8$, 4.7, 6.8 Hz, 1H), 8.04 ppm (br s, 1H); ^{13}C NMR (125.7 MHz): $\delta = 20.8$ (2×CH_3), 24.6 (d, $^1J_{F,C} = 327.7$ Hz; C), 60.9 (CH_2), 70.0 (CH), 78.7 (d, $^2J_{F,C} = 20.2$ Hz; CH), 160.2 (CH), 168.4 (C), 169.5 ppm (C); ^{19}F NMR: $\delta = -69.7$ ppm (d, $^3J_{F,H} = 17.5$ Hz, 1F); IR: $\tilde{\nu} = 1759$, 1737, 1371, 1226, 1200, 1170 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 361 (<1) $[M-I]^+$, 254 (22), 191 (100); HRMS (EI): *m*/*z*: calcd for $C_9H_{11}FIO_6$: 360.9584 $[M-I]^+$; found: 360.9567; elemental analysis calcd (%) for $C_9H_{11}FI_2O_6$ (487.99): C 22.15, H 2.27; found: C 22.34, H 2.33.

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[1] a) R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell, Oxford, **2004**; b) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**; c) T. Hiyama, K. Kanie, T. Kusumoto, Y. Morizawa, M. Shimizu, *Organofluorine Compounds: Chemistry and Applications*, Springer, Berlin, **2000**; d) V. A. Soloshonok, *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*, Wiley, Chichester, **1999**.

[2] a) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) T. Mori, N. Matsuo, *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 620–625; c) T. Mori, K. Ujihara, O. Matsumoto, K. Yanagi, N. Matsuo, *J. Fluorine Chem.* **2007**, *128*, 1174–1181; d) J. C. Pastre, C. R. D. Correia, *Org. Lett.* **2006**, *8*, 1657–1660; e) Y. L. Ding, *Chem. Lett.* **2006**, *35*, 952–953; f) P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589; g) T. Hiyama, K. Kanie, T. Kusumoto, Y. Morizawa, M. Shimizu, *Organo-*

fluorine Compounds: Chemistry and Applications, Springer, Berlin **2000**, Chapter 5, pp. 137–182.

[3] For selected papers and review, see: a) S. Murakami, T. Fuchigami, *Synlett* **2006**, *7*, 1015–1020; b) T. Furuya, T. Fukuhara, S. Hara, *J. Fluorine Chem.* **2005**, *126*, 721–725; c) J. M. Percy, *Chim. Oggi* **2004**, *22*, 18–20; d) W. Peng, P. He, S. Zhu, Z. Li, *Tetrahedron Lett.* **2004**, *45*, 3677–3680; e) Y. Wang, S. Zhu, *Tetrahedron Lett.* **2001**, *42*, 5741–5744; f) C. R. Bulkholder, W. R. Dolbier, M. Medebielle, *J. Fluorine Chem.* **2001**, *109*, 39–48; g) M. J. Tozer, T. F. Herpin, *Tetrahedron* **1996**, *52*, 8619–8683.

[4] a) H. Wang, S. Zhu, C. Xing, W. Pang, Q. Deng, S. Zhu, *J. Fluorine Chem.* **2006**, *127*, 1195–1203; b) A. Guerrero, G. Rosell, *Curr. Med. Chem.* **2005**, *12*, 461–469; c) D. Shirlin, S. Baltzer, J. M. Altenburger, C. Tarnus, J. M. Remy, *Tetrahedron* **1996**, *52*, 305–318.

[5] a) G. K. Surya Prakash, Y. Wang, J. Hu, G. A. Olah, *J. Fluorine Chem.* **2005**, *126*, 1361–1367; b) G. M. Blackburn, D. Brown, S. J. Martin, M. J. Parrat, *J. Chem. Soc. Perkin Trans. 1* **1987**, 181–186; c) G. M. Blackburn, D. E. Kent, *J. Chem. Soc. Perkin Trans. 1* **1986**, 913–917; d) G. M. Blackburn, D. A. England, F. Kollmann, *J. Chem. Soc. Chem. Commun.* **1981**, 930–932.

[6] a) X.-H. Xu, Z.-W. You, X. Zhang, F.-L. Qing, *J. Fluorine Chem.* **2007**, *128*, 535–539; b) X. Yue, Y.-Y. Wu, F.-L. Qing, *Tetrahedron* **2007**, *63*, 1560–1567; c) C. Audouard, J. Fawcett, G. A. Griffith, E. Kérourédan, A. Miah, J. M. Percy, H. Yang, *Org. Lett.* **2004**, *6*, 4269–4272; d) S. Marcotte, B. Gérard, X. Pannecoucke, C. Feasson, J.-C. Quirion, *Synthesis* **2001**, *6*, 929–933; e) K. Dax, M. Albert, J. Ortner, B. J. Paul, *Carbohydr. Res.* **2000**, *327*, 47–86; f) A. A. E. Penglis, *Adv. Carbohydr. Chem. Biochem.* **1981**, 38, 195–285.

[7] a) B. Moreno, C. Quehen, M. Rose-Hélène, E. Leclerc, J.-C. Quirion, *Org. Lett.* **2007**, *9*, 2477–2480, and references therein; b) L. R. Cox, G. A. DeBoos, J. J. Fullbrook, J. M. Percy, N. S. Spencer, M. Tolley, *Org. Lett.* **2003**, *5*, 337–339, and references therein.

[8] a) C. G. Francisco, R. Freire, C. C. González, E. I. León, C. Riesco-Fagundo, E. Suárez, *J. Org. Chem.* **2001**, *66*, 1861–1866; b) C. G. Francisco, C. G. Martín, E. Suárez, *J. Org. Chem.* **1998**, *63*, 8092–8093; c) C. G. Francisco, C. G. Martín, E. Suárez, *J. Org. Chem.* **1998**, *63*, 2099–2109; d) P. Armas, C. G. Francisco, E. Suárez, *J. Am. Chem. Soc.* **1993**, *115*, 8865–8866.

[9] a) C. C. González, A. R. Kennedy, E. I. León, C. Riesco-Fagundo, E. Suárez, *Angew. Chem.* **2001**, *113*, 2388–2390; *Angew. Chem. Int. Ed.* **2001**, *40*, 2326–2328; b) C. C. González, A. R. Kennedy, E. I. León, C. Riesco-Fagundo, E. Suárez, *Chem. Eur. J.* **2003**, *9*, 5800–5809; c) C. C. González, E. I. León, C. Riesco-Fagundo, E. Suárez, *Tetrahedron Lett.* **2003**, *44*, 6347–6350.

[10] a) T. Fujiwara, M. Odaira, T. Takeda, *Tetrahedron Lett.* **2001**, *42*, 3369–3372; b) K. Oshima, *J. Organomet. Chem.* **1999**, *575*, 1–20; c) A. B. Smith, S. A. Kozmin, D. V. Paone, *J. Am. Chem. Soc.* **1999**, *121*, 7423–7424; d) C. J. Kowalski, R. E. Reddy, *J. Org. Chem.* **1992**, *57*, 7194–7208; e) P. Helquist in *Comprehensive Organic Synthesis*, (Eds.: B. Trost, I. Fleming), Pergamon Press, New York, **1991**.

[11] C. G. Francisco, C. C. González, N. R. Paz, E. Suárez, *Org. Lett.* ***2003****, 5*, 4171–4173.

[12] A few references concerning the formation of these compounds as side products or intermediates during different types of reaction in the field of perfluorinated chemistry are found in the literature, but no general synthetic methodology has been described. a) G. Maier, T. Preiss, H. P. Reisenauer, *Chem. Ber.* **1994**, *127*, 779–782; b) D. J. Burton, I. H. Jeong, *J. Fluorine Chem.* **1993**, *60*, 93–100; c) R. E. Banks, M. G. Barlow, R. N. Haszeldine, W. D. Morton, *J. Chem. Soc. Perkin Trans. 1* **1974**, 1266–1271.

[13] R. A. Hill in *Comprehensive Organic Functional Group Transformations, Vol. 4* (Eds.: A. R. Katrizky, O. Meth-Cohn, C. W. Rees), Pergamon, Oxford, **1995**, pp. 2–40.

[14] C. G. Francisco, C. C. González, A. R. Kennedy, N. R. Paz, E. Suárez, *Tetrahedron: Asymmetry* **2004**, *15*, 11–14.

[15] a) J. Crassous, F. Monier, J.-P. Dutasta, M. Ziskind, C. Daussy, C. Grain, C. Chardonnet, *ChemPhysChem* **2003**, *4*, 541–548; b) I. Novak, D. B. Li, A. W. Potts, *J. Phys. Chem. A* **2002**, *106*, 465–468; c) J. Crassous, A. Collet, *Enantiomer* **2000**, *5*, 429–438; d) C. Daussy, T. Marrel, A. Amy-Klein, C. T. Nguyen, C. J. Bordé, C. Chardonnet, *Chem. Phys. Lett.* **1999**, *83*, 1554–1557.

[16] a) J. Crassous, Z. Jiang, V. Schurig, P. L. Polavarapu, *Tetrahedron: Asymmetry* **2004**, *15*, 1995–2001; b) P. R. Schereiner, A. A. Fokin, O. Lauenstein, Y. Okamoto, T. Wakita, C. Rinderspacher, G. H. Robinson, J. K. Vohs, C. F. Campana, *J. Am. Chem. Soc.* **2002**, *124*, 13348–13349; c) D. B. Li, S.-C. Ng, I. Novak, *Tetrahedron* **2002**, *58*, 5923–5926; d) J. Costante, L. Hecht, P. L. Polavarapu, A. Collet, L. D. Barron, *Angew. Chem.* **1997**, *109*, 917–919; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 885–887; e) T. R. Doyle, O. Vogl, *J. Am. Chem. Soc.* **1989**, *111*, 8510–8511; f) J. Hine, F. P. Prosser, *J. Am. Chem. Soc.* **1958**, *80*, 4282–4285; g) R. N. Haszeldine, *J. Chem. Soc.* **1952**, 4259–4268.

[17] F. Swarts, *Bull. Acad. R. Med. Belg.* **1893**, *26*, 102–106.

[18] a) H. Grosenick, V. Schurig, J. Costante, A. Collet, *Tetrahedron: Asymmetry* **1995**, *6*, 87–88; b) J. Canceill, L. Lacombe, A. Collet, *J. Am. Chem. Soc.* **1985**, *107*, 6993–6996.

[19] M. Albert, K. Dax, J. Ortner, *Tetrahedron* **1998**, *54*, 4839–4848.

[20] a) E. C. K. Lai, S. A. Morris, I. P. Street, S. G. Withers, *Bioorg. Med. Chem.* **1996**, *4*, 1929–1937; b) J. D. McCarter, M. J. Adam, C. Braun, M. Namchuck, D. Tull, S. G. Withers, *Carbohydr. Res.* **1993**, *249*, 77–90.

[21] a) R. Zhang, J. D. McCarter, C. Braun, W. Yeung, G. D. Brayer, S. G. Withers, *J. Org. Chem.* **2008**, *73*, 3070–3077; b) E. Boyd, R. V. H. Jones, P. Quayle, A. J. Waring, *Tetrahedron Lett.* **2006**, *47*, 7983–7986; c) M. J. Adam, *J. Labelled Compd. Radiopharm.* **1999**, 42, 809–814; d) J. D. McCarter, M. J. Adam, S. G. Withers, *Carbohydr. Res.* **1995**, *266*, 273–278; e) J. Adamson, A. B. Foster, J. H. Westwood, *Carbohydr. Res.* **1971**, *18*, 345–347.

[22] For other syntheses of 2-deoxy-2,2-difluoro-saccharides using different methodologies, see: a) Y. Li, M. G. B. Drew, E. V. Welchman, R. K. Shirvastava, S. Jiang, R. Valentine, G. Singh, *Tetrahedron* **2004**, *60*, 6523–6531; b) M. I. Barrena, M. I. Matheu, S. Castillon, *J. Org. Chem.* **1998**, *63*, 2184–2188. See also references [20b], [21c,d] and [24].

[23] To our knowledge the mixed dihalohydrins, 2-chloro-2-fluoro- and 2-bromo-2-fluoro-glycopyranoses have not been described previously. For a related methyl 2-bromo-2-deoxy-2-fluoro-D-*erythro*-pentopyranoside, see: a) M. Bobek, S.-H. An, D. Skrinscosky, E. De Clerq, R. J. Bernacki, *J. Med. Chem.* **1989**, *32*, 799–807; b) S.-H. An, M. Bobek, *Tetrahedron Lett.* **1986**, *27*, 3219–3222.

[24] M. J. Adam, D. M. Lyster, G. Matte, *J. Labelled Compd. Radiopharm.* **1999**, *42*, 698–700.

[25] a) M. D. Burkart, Z. Zhang, S.-C. Hung, C.-H. Wong, *J. Am. Chem. Soc.* **1997**, *119*, 11743–11746; b) S. P. Vincent, M. D. Burkart, C.-Y. Tsai, Z. Zhang, C.-H. Wong, *J. Org. Chem.* **1999**, *64*, 5264–5279.

[26] J. Rodriguez, J.-P. Dulcère, *Synthesis* **1993**, 1177–1205.

[27] C. H. Marzadabi, C. D. Spilling, *J. Org. Chem.* **1993**, *58*, 3761–3766.

[28] M. Smietana, V. Gourverneur, C. Mioskowski, *Tetrahedron Lett.* **2000**, *41*, 193–195.

[29] Throughout this section, the numbering of the trihaloalditols has always begun at the carbon atom bearing the halogens, although the correct IUPAC systematic nomenclature has been used in the Experimental Section and Supporting Information.

[30] J. Madsen, C. Viuf, M. Bols, *Chem. Eur. J.* **2000**, *6*, 1140–1146.

[31] CCDC-679904 ((*S*)-**54**) and 219090 ((*S*)-**55**) contain the supplementary crystallographic data (excluding structure factors) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal data and structure refinements

*Compound (S)-**54***: $C_{16}H_{15}ClFIN_2O_{10}$; $M_r = 576.65$; monoclinic; space group = C_2; $a = 29.7995(13)$, $b = 6.5809(3)$, $c = 10.4310(3)$ Å; $\beta = 96.422(2)°$; $V = 2032.76(15)$ Å^3; $Z = 4$; $\rho_{calcd} = 1.884$ mg cm^{-3}; $\mu(Mo_{K\alpha}) = 0.71073$ Å; $F(000) = 1136$; $T = 123(2)$ K; colourless crystal, $0.18 \times 0.18 \times 0.07$ mm, collected reflections 21338. The structure was solved by direct methods, all hydrogen atoms were refined anisotropically by using full-matrix least-squares-based F^2 to give $R_1 = 0.0367$, $wR_2 = 0.0688$ for 4857 independently observed reflections

($|F_o| > 2\sigma(|F_o|)$) and 286 parameters. Selected structural data: O-C2-C1-I = −64.7, O-C2-C1-Cl = 58.0, O-C2-C1-F = 174.6°. *Compound* (S)-***55***: $C_{16}H_{15}BrFIN_2O_{10}$; $M_r = 621.11$; monoclinic; space group = C_2; $a = 29.7108(8)$, $b = 6.5966(2)$, $c = 10.5583(3)$ Å; $\beta = 97.414(1)°$; $V = 2052.02(10)$ Å^3; $Z = 4$; $\rho_{calcd} = 2.010$ mg cm^{-3}; $\mu(Mo_{K\alpha}) = 0.71073$ Å; $F(000) = 1208$; $T = 123(2)$ K; colourless crystal; $0.30 \times 0.12 \times 0.05$ mm; collected reflections 19723. The structure was solved by direct methods, all hydrogen atoms were refined anisotropically by using full-matrix least-squares-based F^2 to give $R_1 = 0.0329$, $wR_2 = 0.0606$ for 4534 independently observed reflections ($|F_o| > 2\sigma(|F_o|)$) and 284 parameters. Selected structural data: O-C2-C1-I = −66.6, O-C2-C1-Br = 56.8, O-C2-C1-F = 171.8°.

[32] a) A. G. Myers, J. K. Barbay, B. Zhong, *J. Am. Chem. Soc.* **2001**, *123*, 7207–7219; b) C. R. S. Briggs, D. O'Hagan, H. S. Rzepa, A. M. Z. Slawin, *J. Fluorine Chem.* **2004**, *125*, 19–25; c) L.-S. Sonntag, S. Schweizer, C. Ochsenfeld, H. Wennemers, *J. Am. Chem. Soc.* **2006**, *128*, 14697–14703, and references therein.

[33] C. Altona, M. Sundaralingam, *J. Am. Chem. Soc.* **1972**, *94*, 8205–8212.

[34] It has been demonstrated that $^3J_{F,H}$ coupling constants are highly sensitive to dihedral angles and substituent effects, see C. Thibaudeau, J. Plavec, J. Chattopadhyaya, *J. Org. Chem.* **1998**, *63*, 4967–4984, and references therein. For a review on NMR spectra of fluorinated carbohydrates, see: M. Michalik, M. Hein, M. Frank, *Carbohydr. Res.* **2000**, *327*, 185–218.

[35] For a review on building block approaches to aliphatic organofluorine compounds, see: J. M. Percy, in *Topics in Current Chemistry, Vol. 193*, (Ed.: R. D. Chambers), Springer, Berlin, **1997**, pp. 131–195.

[36] H. Wang, S. Zhu, C. Xing, W. Pang, Q. Deng, S. Zhu, *J. Fluorine Chem.* **2006**, *127*, 1195–1203.

[37] a) G. E. Keck, E. J. Enholm, J. B. Yates, M. R. Wiley, *Tetrahedron* **1985**, *41*, 4079–4094; b) G. E. Keck, J. B. Yates, *J. Am. Chem. Soc.* **1982**, *104*, 5829–5831.

[38] For a radical methodology in the synthesis of tertiary alkyl fluorides, see: Y. Takeuchi, A. Kanada, S. Kawahara, T. Koizumi, *J. Org. Chem.* **1993**, *58*, 3483–3485.

[39] *Handbook of Metathesis, Vol. 1–3* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**.

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