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The reaction of pyranoside 2-uloses with DAST revised. Synthesis of 1-fluoro-ketofuranosyl fluorides and their reactivity with alcohols

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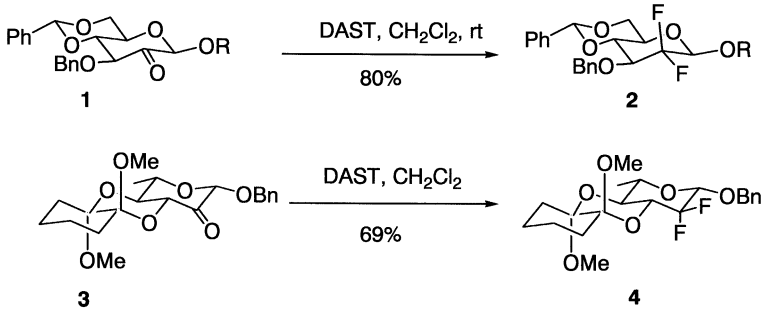
Abstract—We have reinvestigated the reaction of α-pyranosides-2-uloses **13**, **14**, **19** and **24** with DAST and shown that the 1,2-difluorinated compounds **17**, **18** and **25** are produced by a ring-contraction reaction. The reaction of **18** with benzyl alcohol gives the tri-benzyl derivative **26** or compound **27**, depending on the reaction conditions. Treating **17** with 2-naphthol produced the spiranic compounds **29**–**31**. The reaction of **17** with bis(trimethylsilyl)uracil produced the mononucleoside **28**, which preserves the fluorine atom in the more substituted carbon. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Diethylaminosulfur trifluoride (DAST) has been widely used in the fluorination of sugars.[1] The reaction is usually carried out starting from alcohols and involves inversion of configuration. However, there are some cases in which the configuration is retained,[2] and others that involve 1,2-migration.[3] Over the last ten years we have studied the reaction of uloses with DAST and established the structural requirements for obtaining *gem*-difluoro carbohydrates[4] without secondary reactions.[5–9] Thus, for 2-uloses the anomeric substituent must be equatorial and the conformational mobility must be restricted (see, for instance, difluorination of uloses **1** and **3**, Scheme 1).[7] This is usually achieved by forming *trans*-fused bicycles. When the anomeric substituent is *axial*, such as in ulose **5** (Scheme 2) or the molecule is conformationally flexible, rearrangements usually occur.[5,7]

Recently, Cabrera-Escribano et al.[10] showed that treatment with DAST of 2-hydroxy-pyranoside **7**, whose anomeric substituent and 2-hydroxyl group are in relative *trans diaxial* disposition, affords compounds **8a/8b**, which is generated by a 1,2-migration with concomitant stereoselective fluorination of the anomeric position. However, when these substituents are *cis* (**9**) the reaction leads to



Scheme 1.

Keywords: carbohydrates; uloses; fluorination; diethylaminosulfur trifluoride; glycosylation; spiroacetals.

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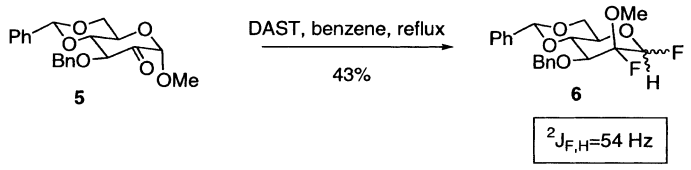
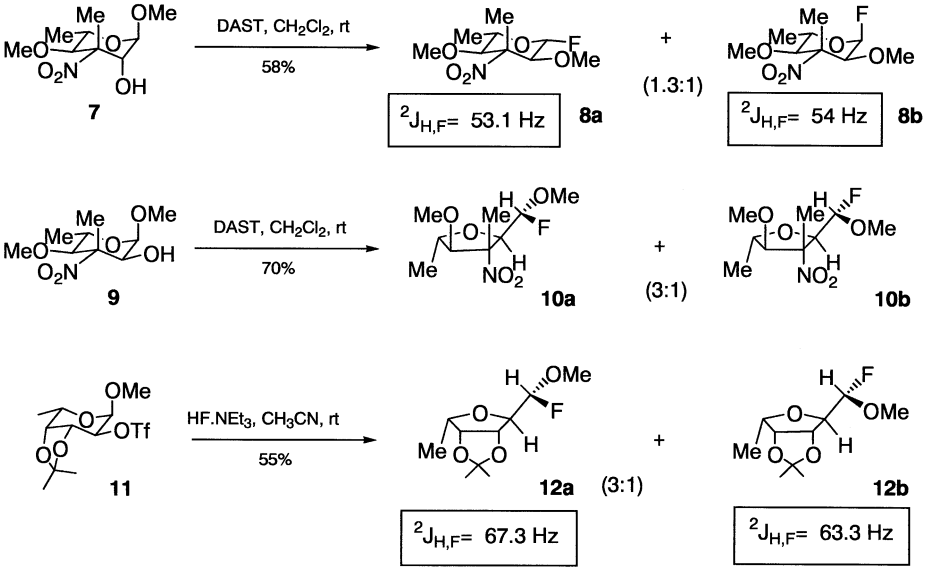


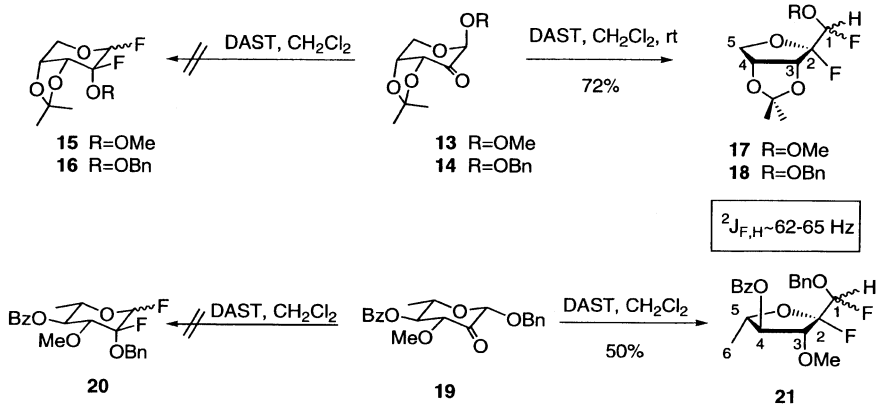
Scheme 2.

the ring-contraction products **10a/10b**. There is a similar ring contraction in the reaction of 2-*O*-triflyl-pyranosides **11** with conventional nucleophilic fluorination reagents, and this leads to products **12a/12b**.[11] In compounds **9** and **11** the leaving groups (OSF_2NEt_2 and OTf) are *equatorial* and the ring contraction reaction takes place independently of the configuration of the anomeric position. Other ring-contraction reactions have also been observed in the reaction of partially protected carbohydrates with DAST.[12] In a very recent review, Dax et al. systematized the reactions that can take place in the fluorination of the various positions of the sugar ring.[12] The $^2J_{H1,F}$ values are spectroscopic data with diagnostic value, with which we can differentiate between ring contraction products (Scheme 3) and 1,2 migration products (Schemes 2 and 3).

We had explored the reaction of 2-uloses **13**, **14** and **19** with DAST to obtain products which we initially assigned to structures **15**, **16** and **20**, as a result of a 1,2-migration and difluorination.[5,7] However, the $^2J_{H1,F}$ values for these (Scheme 4) compounds were identical to those of compounds **10** and **12** but very different from those of compounds **6** and **8** (Schemes 2 and 3). Actually, Dax' review anticipated the suspicion of these compounds to be



Scheme 3.



Scheme 4.

Table 1. Selected spectroscopic ^{1}H- and ^{13}C NMR data, δ (ppm) and J (Hz), for compounds **17**, **18**, **21** and **25**

	$^2J_{H1,F1}$	$^3J_{H1,F2}$	$^3J_{H3,F2}$	$^3J_{H3,H4}$	$^4J_{H4,F2}$	$^4J_{H1,H3}$	δ C1	δ C2	$^1J_{C2,F2}$	$^2J_{C2,F1}$	$^1J_{C1,F1}$	$^2J_{C1,F2}$	$^2J_{C3,F2}$	$^3J_{C5,F2}$
17a[a]	64.4	0.6	10.6		2.0	0.8	109.1	112.1	234.8	32.0	223.8	45.4	19.8	
17a[b]	64.4	–	12	6.0			110.7	113.6	234.8	26.5	223.8	46.2	19.8	1.2
17b[a]	63.4	2.3					109.5	112.2	236.8	32.4	223.8	45.8	20.4	
17b[c]	64.4	2.0	11.4	6.4			110.3	113.6	236.8	31.3	224.3	45.7	19.4	1.1
18a	63.6	–					106.8	112.2	237.3	28.2	222.8	45.4	19.4	
18b	63.8	2.0					107.1	112.4	237.3	34.0	224.9	45.1	19.7	
21a	63.8	1.6	14.1				105.4	112.3	211.7	32.3	224.7	45.0	20.4	2.4
21b	63.5	1.8	14.1				105.3	–[d]	–[d]	–[d]	225.3	43.8	20.6	2.8
25[e]	62.4	1.2	20.4	10.2			106.2	110.3	223.3	25.8	224.2	46.2	20.2	2.4

a/b denotes major and minor epimers at C-1 (**17a/17b**, **18a/18b** and **21a/21b** ratios are 2:1, 3:1 and 2:1, respectively).
[a] $CDCl_3$.
[b] C_6D_6, $J_{F1,OMe}$=1.6 Hz, $J_{F2,Me}$=0.4 Hz, $J_{CH3(iPr),F}$=1.5 Hz.
[c] C_6D_6, $J_{OCH3,F1}$=1.6 Hz, $J_{C3,F1}$=1.1 Hz.
[d] $^3J_{C4,F2}$=1.6 Hz.
[e] For the minor isomer, signals are not detected.

ring contracted products.[12] All these facts prompted us to reconsider the structural elucidation of the products obtained from reaction of uloses **13**, **14** and **19** with DAST.

2. Results and discussion

We reacted uloses **13**, **14** and **19** with DAST. Structures of the products obtained were unequivocally established by ^{1}H- and ^{13}C NMR spectroscopy, using one- and two-dimensional techniques. The methodology used involved the full assignment of the ^{1}H spectra by gCOSY, TOCSY and NOESY experiments and the ^{13}C spectra by gHSQC, and gHMBC experiments. Relevant ^{1}H- and ^{13}C spectra data are gathered in Table 1. Thus, δ ~106–110 ppm ($^1J_{C,F}$ ~223 Hz, $^2J_{C,F}$=44 Hz) for C-1 and δ ~112–114 ppm ($^1J_{C,F}$ ~236–241 Hz, $^2J_{C,F}$=28–34 Hz) for C-2 indicate that a fluorine atom is bonded to each of these carbons. The C-3, the OMe carbon and the carbon of one of the isopropylidene methyl groups appear as doublets with coupling constants of 19.8, 1.5, 1.5 Hz, respectively. ^{19}F NMR spectra also support the presence of two neighboring fluorine atoms in secondary and tertiary carbons with similar environments. However, these data are compatible with 1,2-migration products **15**, **16** and **20**, as well as with the ring contraction products **17**, **18** and **21** (Scheme 4).

The $^2J_{H1,F}$ values of these products were 62–65 Hz, which is as expected for ring-contraction products. Moreover, the gHMBC experiment, with which we can detect protons and carbons separated by two or three bonds, shows that there is a correlation between H-1 and O*C*H$_3$ (**17**), or H-1 and *C*H$_2$Ph (**18**, **21**), which confirms a five-membered structure for these compounds.

To determine the configuration at C-2 we considered $^3J_{H3,F2}$ and $^2J_{C3,F2}$, because they are reported to depend on the relative configuration of the carbon atoms involved in the coupling.[13] In the bibliography there is a wide range of values for vicinal F/H coupling constants. In furanosyl fluorides, values of $^3J_{H2,F1}$ are >15 Hz for a *trans* relationship and <8 Hz for a *cis* relationship.[13–16] For both isomers of compounds **17**, **18** and **21**, the coupling constants $^3J_{H3,F2}$=10–14 Hz (see Table 1) are closer to *trans* than to *cis* values. The presence of strong electronegative atoms at C-1 may explain these small values. Actually, the structure of natural nucleoside nucleocidine is very related to that of compounds **17** and **18**, and 2,3-isopropylidene derivatives with a H_3,F_4 *trans* disposition have $^3J_{H,F}$ coupling constants of the same order of those observed for **17** and **18** (Fig. 1).[17] All these data suggest that F-2/H-3 have a *trans* relationship in these compounds.

The values of $^2J_{C3,F2}$=19–21 Hz for compounds **17**, **18** and **21** agree with a *gauche* or *syn* relationship of the fluorine atom relative to the electronegative substituent (the oxygen) on C-3, i.e. a *trans* H-3/F-2 relationship.[13,18] This value confirms the C-2 configuration of compounds **17**, **18** and **21**.

For the C-1 configuration, the small $^3J_{H1,F2}$ values for all isomers of compounds **17**, **18** and **21** indicate a preferred rotameric disposition with a *gauche* H-1/F-2 arrangement. Besides, the high value of $^2J_{C1,F2}$>40 Hz, also for all isomers of compounds **17**, **18** and **21**, suggest an *anti* orientation of F-2 and the electronegative group (OMe) bonded to C-1. The small differences in the values of $J_{C2,F1}$ for the major and minor isomers in **17**, **18** and **21** do not allow, however, the assignation of the configuration at C-1 for each of the isomers.

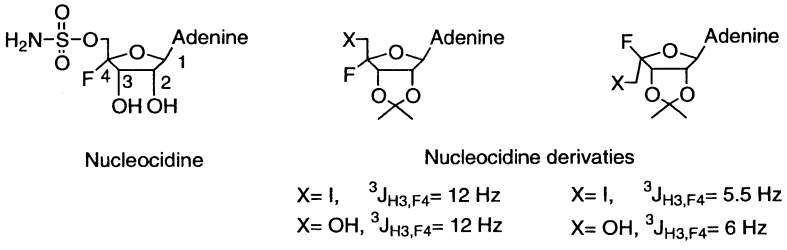
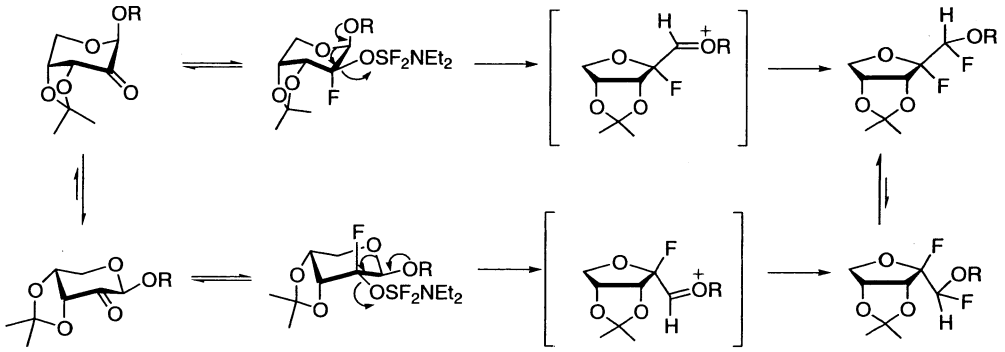


Figure 1.



Scheme 5.

2.1. Mechanistic considerations

The reaction of 2-OH unprotected pyranosides with DAST depends on the stereochemisty at positions 1 and 2 and has the following general trends: (a) when 2-OH is *axial*, the substitution or elimination reaction takes place independently if the anomeric group is *equatorial* or *axial*; however, in the latter case 1,2-migration usually competes. (b) When 2-OH is *equatorial* substitution competes with ring contraction and 1,2-migration. Ring contraction is favored when the anomeric group is *cis* and in 3,4-*O*-isopropyledene derivatives and, in general, it is restricted in 4,6-*O*-benzyledene derivatives. 1,2-Migration may take place when the anomeric substituent is *trans* to the 2-OH.

The reaction of 2-uloses with DAST is more complex. It involves at least two reactions and all the processes mentioned above can compete.

In the case of compound **1**, the difluorination product may be justified by the initial attack of fluorine from both sides of the carbonyl group. The ring-contraction product, which might be the result of fluorine attacking from the top of the ring (leaving group *equatorial*), is probably limited by the presence of the 4,6-*O*-benzylidene group. A similar explanation must also account for compound **3**. In compound **5**, whose anomeric group is *axial*, the configuration at position 2 is due to 1,2-migration taking place first.

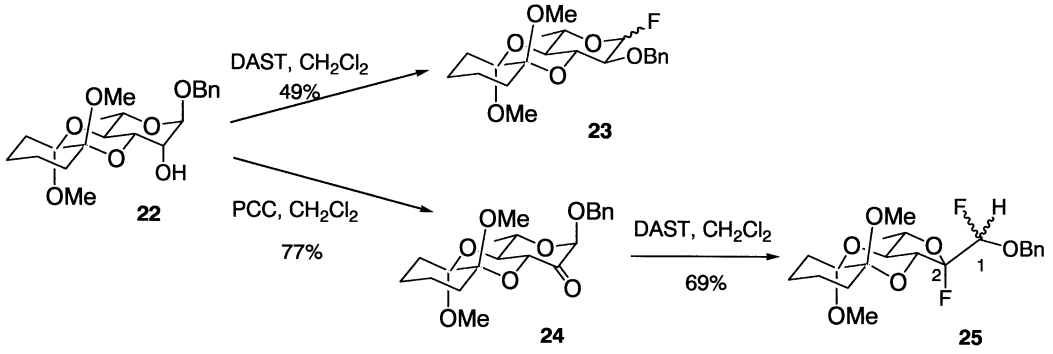
In compounds **13**, **14** (whose main conformation is $^4C_1$) and **19**, fluorine is expected to attack initially from the upper side. However, this would lead to ring contraction products having a configuration at C-2 that it is not the actually obtained in compounds **17**, **18** and **21**. The stereochemistry observed may be due to an equilibrium process between intermediates such that the ring contraction takes place faster from the intermediate resulting from the attack of fluorine from the bottom, or through epimerization of the final product (Scheme 5).

Compound **3** (Scheme 1) produced the difluoroderivative **4** when treated with DAST. We considered that ulose **24** and its precursor, alcohol **22** (Scheme 6), were good models for confirming the structural requirements for ring-contraction and 1,2-migration in the reaction with DAST. Effectively, the reaction of alcohol **22** with DAST led to the glycosyl fluoride **23**, which resulted from a 1,2-migration ($J_{H1,F}$ ~52 Hz, see Schemes 2 and 3). However, the reaction of ulose **24** with DAST led to the ring-contraction product **25**. Spectroscopic data of **25** agree with those of ring-contraction products **17**, **18** and **21** (Table 1).

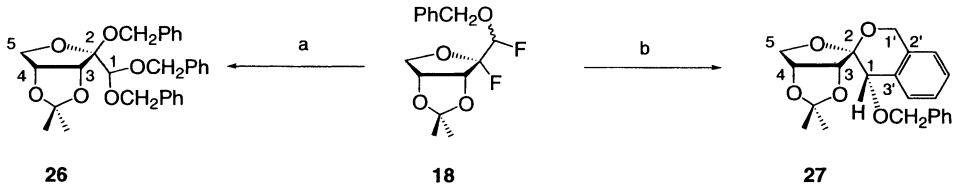
2.2. Reactivity of difluorinated compounds with alcohols

We had studied the reactivity of the difluorinated compounds with alcohols. Actually, we showed that those compounds behaved as 1,2-dielectrophilic synthons when allowed to react with benzyl alcohol or naphthol derivatives.[19–22] As we corrected the structure of starting difluorinated compounds, we revised the structure of glycosylation products. Also, we reinvestigated the more significant reactivity of difluoroderivatives **17** and **18**.

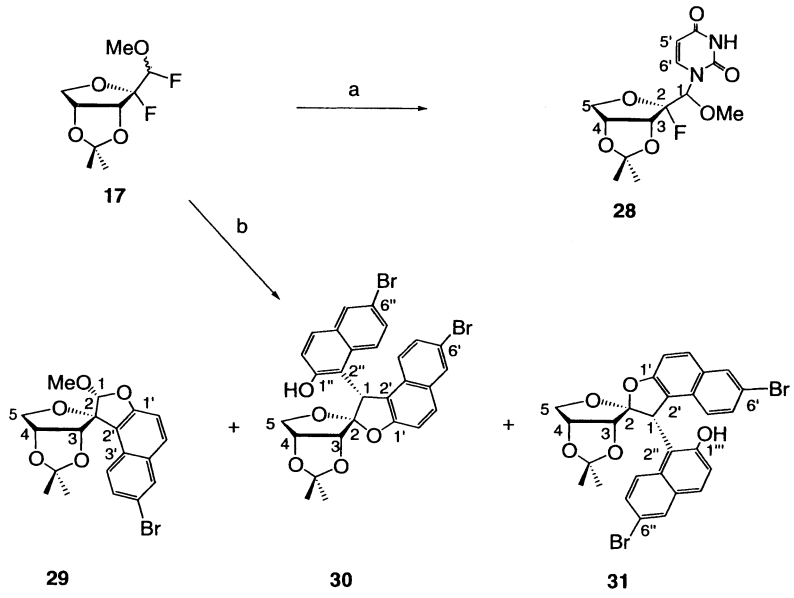
Therefore, when compound **18** was treated with a 10-fold excess of benzyl alcohol in the presence of Cp_2HfCl_2/AgOTf (difluorinated sugar/alcohol/Cp_2HfCl_2/AgOTf ratio= 1:10:1:2) at −50°C in dry dichloromethane, compound **26** was obtained in a 66% yield (Scheme 7).



Scheme 6.



Scheme 7. a: difluorinated sugar/benzyl alcohol/Cp_2HfCl_2/AgOTf ratio=1/10/1/2, DCM, −50°C–rt; b: difluorinated sugar/benzyl alcohol/Cp_2HfCl_2/AgOTf ratio=1/2/1/2, DCM, −50°C–rt.



Scheme 8. a: sugar/bis(trimethylsilyl)uracil/Cp_2HfCl_2/AgOTf ratio=1/2/1/2, benzene, rt; b: sugar/6-bromo-2-naphthol/Cp_2HfCl_2/AgOTf ratio=1/1.7/1/2, DCM, −50°C–rt.

Treatment of **18** with two equivalents of benzyl alcohol under similar conditions produced compound **27** in 70% yield. A similar reaction of **17** with an excess of 6-bromo-β-naphthol led to a 1:1.3:1.9 mixture of compounds **29**, **30** and **31** in an overall yield of 47%[23] (Scheme 8).

We extended our study of the glycosylation reaction to the synthesis of nucleoside analogues. When compound **17** was allowed to react with bis(trimethylsilyl)uracil in the presence of Cp_2HfCl_2/AgOTf, the nucleoside analogue **28** was obtained as a mixture in 85% yield with excellent stereoselectivity (87:13), and from which we were able to isolate the major isomer in pure form. Interestingly, only one fluorine atom was substituted in the presence of bis-(trimethylsilyl)uracil.

2.3. Structural elucidation of compounds 26–31

^{1}H- and ^{13}C NMR spectra of compounds **26–31** were unequivocally assigned by one- and two-dimensional experiments (gCOSY, TOCSY, NOESY, gHSQC and gHMBC). Relevant ^{13}C NMR data are collected in Table 2.

Table 2. Selected spectroscopic ^{13}C NMR data, δ (ppm) for compounds **26**, **27**, **28, 29, 30** and **31** ($CDCl_3$)

	C1	C2	C3	C4	C5	C1′	C2′	C1″	C2″
26	100.7	106.8	84.7	79.2	71.3				
27	71.8	107.7	84.3	80.2	72.9	62.6			
28	83.6	112.5	80.7	77.2	71.6				
29	106.2	92.6	83.3	79.3	72.2	154.9	114.2		
30	42.8	118.1	84.3	78.6	71.8	153.2	119.2	152.1	115.8
31	42.3	118.9	83.9	78.4	72.0	153.2	118.1	153.8	115.4

Compounds **26–31** keep the same sugar backbone of their difluorinated precursors, including the isopropylidene group.[24] There are no fluorine atoms, except for compound **28**, which has only one.

The NMR spectra of compound **26** showed the presence of three benzyl groups and two acetalic carbon atoms (apart from the isopropylidene group) attributed to C-1 (tertiary, 100.7 ppm) and C-2 (quaternary, 106.8 ppm). gHMBC correlations confirmed the presence of two benzyl groups bonded to C-1 and one to C-2. The configuration at C-1 and C-2 was established by NOESY experiments (Fig. 2).

The NMR spectra for **27** show the following features: C-2 (quaternary, 107.7 ppm) is acetalic, C-1 (71.8 ppm) is a tertiary carbon bonded to one oxygen, and there are two benzyl groups. The protons of one of the benzylic groups show a ^2J=11.1 Hz and correlate with C-1 in the gHMBC spectrum, whereas the ones of the other benzyl group show a ^2J=15.3 Hz, which indicates that they are part of a cycle[25] and correlate with C-1 in the HMBC spectrum. Moreover, one aromatic quaternary carbon (134 ppm) shows an HMBC correlation with H-1 (4.5 ppm) and with protons of the endocyclic benzyl CH_2 group. All these data indicate that the benzyl group at C-2 has undergone a Friedel–Crafts

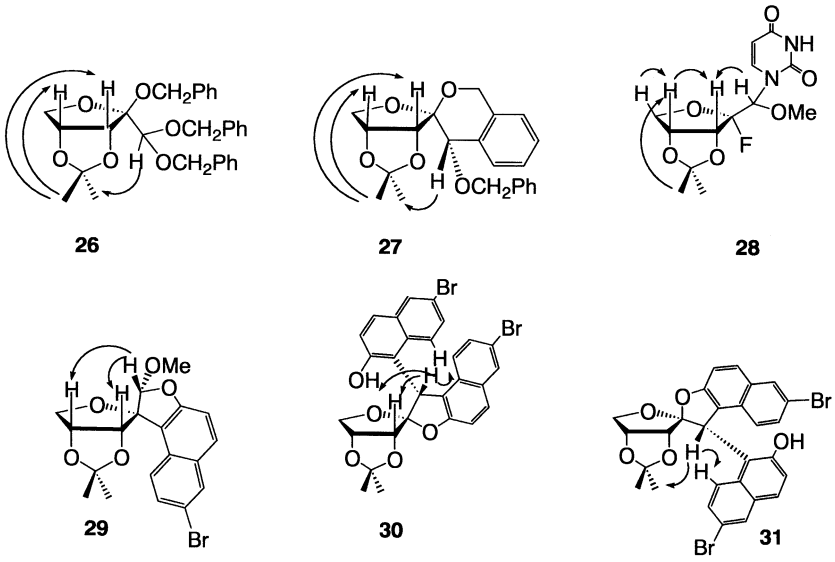


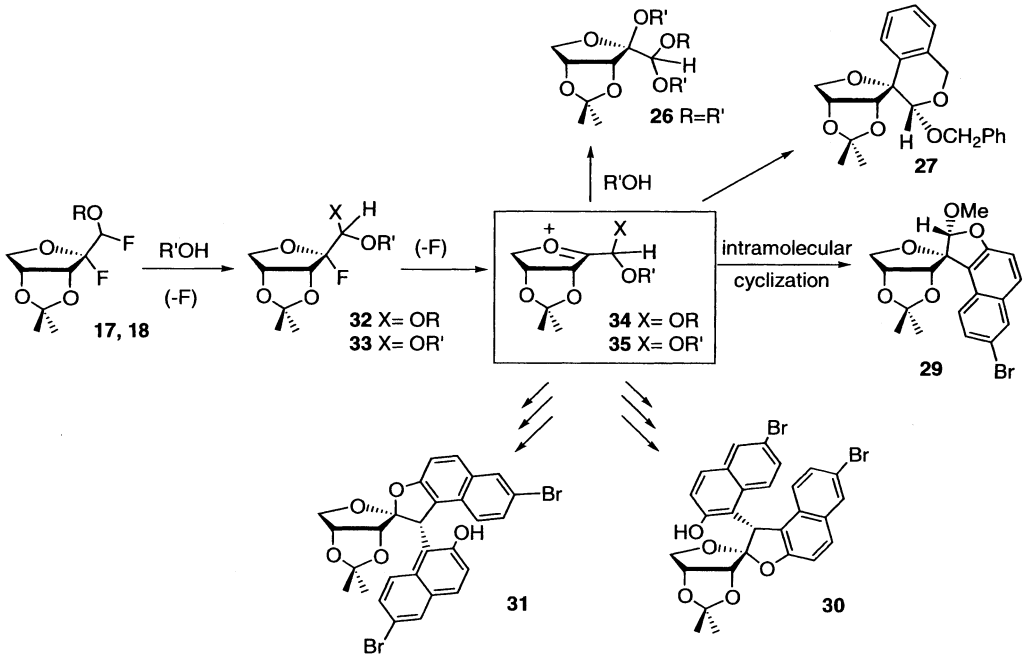
Figure 2.

cyclization involving C-1. The configuration at C1 and C2 was established by NOESY experiments.

NMR data for compounds **29**–**31** were comparatively studied. Compound **29** shows the following features: one naphthol unit, an OMe group, a tertiary acetalic carbon attributed to C-1, and a quaternary nonacetalic carbon corresponding to C-2. The gHMBC correlation between H-1 and two aromatic carbons at 154.9 ppm (C-1′) and 114.3 ppm (C-2′) indicates that the naphthol unit bonded to C-1 via its oxygen has undergone an electrophilic substitution and is bonded to C-2 via its Cα. The configuration at C-1 and C-2 was established by NOESY experiments.

The spectra for compounds **30** and **31** are very similar and show that C-2 (118.1 and 118.9 ppm, respectively) is acetalic and quaternary and C-1 (42.8 and 42.3 ppm, respectively) is a tertiary carbon not bonded to oxygen. The presence of eleven protons in the aromatic region (one of which is due to an OH group) indicates the presence of two naphthol units, one of them bonded to C-1 via its Cα, and the other one cyclized via its oxygen and its Cα. All these data are consistent with the spiroacetal structures proposed and show that compounds **30** and **31** are epimers at C-2, as confirmed by NOESY experiments.

The spectra of compound **28** show the presence of one fluorine atom at C-2 (112.5 ppm), and an OMe group and a uracil moiety bonded to C-1 (83.6 ppm). Configuration of C-2 is determined by the values of $^{3}J_{3,F}$=12.8 Hz and



Scheme 9.

$^2J_{C3,F}$=21.9 Hz, which indicate a *trans* disposition between H-3 and fluorine, and by a NOE enhancement in H_3 when H_1 was irradiated.

2.4. Mechanistic consideration of the reaction of difluorinated compounds with alcohols

Scheme 9 shows a possible mechanism to explain how compounds **26**–**31** are formed. The reaction starts with the abstraction of fluorine at C_1, followed by acetal formation to give **32** (R=methyl, benzyl, R′=benzyl, naphthyl). A trans-acetalization can be produced at this stage to give the intermediate **33**. The activation of the fluorine in **32** produces the oxonium cation **34**, from which compound **26** (R=R′=benzyl) is formed by the attack by a second molecule of benzyl alcohol on the *exo* face. An intramolecular Friedel–Crafts reaction from **34** (R=methyl, R′=benzyl or 6-bromo-2-naphthyl) gives the spiro compounds **27** or **29**. Compounds **30** and **31** are probably formed from **35**. A series of processes must be involved, including OR′ migration, the attack by a second molecule of R′OH, isomerization, the departure of an R′OH molecule and Friedel–Crafts cyclization. However, the sequence of events cannot be precised.

In conclusion, the reaction of α-pyranside-2-uloses **13**, **14**, **19** and **24** with DAST gives 2,5-anhydro-1,2-difluorofuranoses **17**, **18**, **21** and **25**, respectively, as a result of a ring-contraction reaction with concomitant entry of fluorine at positions 1 and 2. These 2,5-anhydro-1,2-difluoro sugars behave like 1,2-dielectrophilic synthons. Therefore, they react with benzyl alcohol or naphthols to give products of fluorine substitution (**26**) or spiroacetalic compounds resulting from fluorine substitution and intramolecular Friedel–Crafts reaction (**27**, **29**–**31**). Isomerization is also possible under the reaction conditions. When 1,2-difluorosugar **17** was allowed to react with bis(trimethylsilyl)uracil, fluoronucleoside **28** was obtained due to the substitution of one fluorine atom.

3. Experimental

Melting points are uncorrected. Optical rotations were measured at 25°C in 10 cm cells. ^{1}H- and ^{13}C NMR spectra were recorded on a Varian INOVA-400 and VARIAN Unity-400 spectrometers operating at 399.93 MHz (^{1}H) and 99.98 MHz (^{13}C), respectively, using $CDCl_3$ as solvent at 30°C with TMS as internal standard. ^{19}F spectra were recorded either on a Varian Gemini 300 MHz spectrometer operating at 282.3 MHz or on a Varian 400 MHz spectrometer operating at 376.4 MHz, using $CDCl_3$ as solvent at 30°C. Monodimensional ^{1}H-, ^{13}C- and ^{19}F spectra were obtained using standard conditions. Homonuclear 2D spectra (COSY, TOCSY and NOESY) were acquired in the phase-sensitive mode. Elemental analyses were determined at the Servei de Recursos Cientifics (Universitat Rovira I Virgili). Flash column chromatography was performed using silica gel 60 A CC (40–63 μm). Preparative layer chromatography was performed on silicagel 60. Radial chromatography was performed on 1, 2 or 4 mm plates of silica gel, depending on the amount of product. Medium-pressure chromatography (MPLC) was performed using silica gel 60 A CC (6–35 μm). Band separation was monitored by UV. TLC plates were prepared with Kieselgel 60 PF254. Solvents for chromatography were distilled at atmospheric pressure prior to use. Reaction solvents were purified and dried by using standard procedures.

3.1. Synthesis of difluorocarbohydrate 17

DAST (0.54 ml, 4 mmol) was added dropwise at room temperature to a solution of ulose **13** (0.202 g, 1 mmol) in dichloromethane (5 ml). After 8 h, the reaction mixture was poured into a cold saturated aqueous $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and evaporated to give a crude oil, which was chromatographed (ethyl acetate/hexane=1:4) to produce compound **17** (0.161 g, 72%) as a diastereoisomeric mixture.

3.1.1. Spectroscopic data of 17a (maj) extracted from the spectrum of mixture. ^{1}H NMR (C_6D_6, 400 MHz) δ 5.08 (d, 1H, $J_{1,F1}$=64.4 Hz, H_1), 4.74 (dd, 1H, $J_{3,F2}$=12.0 Hz, $J_{3,4}$=6.0 Hz, H_3), 4.06–4.18 (m, 2H, H_{5a}, H_{5b}), 3.68 (ddd, 1H, $J_{4,5a}$=10.4 Hz, $J_{4,3}$=6.0 Hz, $J_{4,5b}$=4.4 Hz, H_4), 3.06 (d, 3H, $J_{Me,F1}$=1.6 Hz, OCH_3), 1.57 (s, 3H, CH_3), 1.14 (d, 3H, $J_{Me,F2}$=0.4 Hz, CH_3). ^{13}C NMR (C_6D_6, 100 MHz) δ 115.8 ($C(CH_3)_2$), 113.6 (dd, $J_{2,F2}$=234.8 Hz, $J_{2,F1}$=26.5 Hz, C_2), 110.7 (dd, $J_{1,F1}$=223.8 Hz, $J_{1,F2}$=45.8 Hz, C_1), 80.4 (d, $J_{3,F2}$=20.4 Hz, C_3), 79.3 (C_4), 73.0 (d, $J_{5,F2}$=1.2 Hz, C_5), 57.8 (OCH_3), 26.8 (CH_3), 26.3 (d, $J_{Me,F2}$=1.5 Hz, CH_3). ^{19}F NMR (C_6D_6, 376.4 MHz) δ −124.3 (td, $J_{F2,H3}$=12.0 Hz, $J_{F2,F1}$=$J_{F2,H5}$=4.6 Hz, F_2), −145.2 (dd, $J_{F1,H1}$=64.4 Hz, $J_{F1,F2}$=4.6 Hz, F_1).

3.1.2. Spectroscopic data of 17b (min) extracted from the spectrum of mixture. ^{1}H NMR (C_6D_6, 400 MHz) δ 5.03 (dd, 1H, $J_{1,F1}$=64.4 Hz, $J_{1,F2}$=2.0 Hz, H_1), 4.81 (dd, 1H, $J_{3,F2}$=11.4 Hz, $J_{3,4}$=6.4 Hz, H_3), 4.06–4.18 (m, 2H, H_{5a}, H_{5b}), 3.62 (ddd, 1H, $J_{4,5a}$=10.0 Hz, $J_{4,3}$=6.4 Hz, $J_{4,5b}$=4.4 Hz, H_4), 3.03 (d, 3H, $J_{Me,F1}$=1.6 Hz, OCH_3), 1.59 (s, 3H, CH_3), 1.16 (d, 3H, $J_{Me,F2}$=0.4 Hz, CH_3). ^{13}C NMR (C_6D_6, 100 MHz) δ 115.8 ($C(CH_3)_2$), 113.6 (dd, $J_{2,F2}$=236.8 Hz, $J_{2,F1}$=31.3 Hz, C_2), 110.3 (dd, $J_{1,F1}$=224.3 Hz, $J_{1,F2}$=45.7 Hz, C_1), 80.2 (dd, 1H, $J_{3,F2}$=19.4 Hz, $J_{3,F1}$=1.1 Hz, C_3), 79.1 (C_4), 73.0 (d, $J_{5,F2}$=1.1 Hz, C_5), 58.5 (d, $J_{Me,F1}$=0.2 Hz, OCH_3), 26.8 (d, $J_{Me,F2}$=1.5 Hz, CH_3), 26.3 (CH_3). ^{19}F NMR (C_6D_6, 376.4 MHz) δ −125.2 (td, $J_{F2,F1}$=$J_{F2,H3}$=11.4 Hz, $J_{F2,H5}$=5.3 Hz, F_2), −144.4 (dd, $J_{F1,H1}$=64.4 Hz, $J_{F1,F2}$=11.4 Hz, F_1).

3.2. Synthesis of difluorocarbohydrate 18

DAST (0.53 ml, 3.9 mmol) was added dropwise at room temperature to a solution of ulose **14** (0.5 g, 1.8 mmol) in anhydrous benzene (5 ml). After 24 h, standard work-up as described for synthesis of **17** rendered a crude oil that was purified by column chromatography (ethyl acetate/hexane=1:2) to give a diastereoisomeric mixture of compound **18** (0.420 g, 78%) as a colorless oil.

3.2.1. Spectroscopic data of 18a (maj) extracted from the spectrum of mixture. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.12 (m, 5H, Ph), 5.27 (dd, 1H, $J_{1,F1}$=63.6 Hz, $J_{1,F2}$=0.9 Hz,

H_1), 4.91 (m, 1H, CH_2Ph), 4.83 (m, 1H, H_3), 4.78 (m, 1H, H_4), 4.72 (m, 1H, CH_2Ph), 4.22 (m, 1H, H_{5a}), 4.12 (m, 1H, $J_{5b,F2}$=4.6 Hz, H_{5b}), 1.52 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.7 (C_{Ar}), 129.0–128.0 (C_{Ar}), 115.4 ($C(CH_3)_2$), 112.2 (dd, $J_{2,F2}$=237.3 Hz, $J_{2,F1}$=28.2 Hz, C_2), 106.8 (dd, $J_{1,F1}$=222.8 Hz, $J_{1,F2}$=45.4 Hz, C_1), 79.3 (d, $J_{3,F2}$=19.4 Hz, C_3), 78.3 (C_4), 72.4 (C_5), 71.6 (CH_2Ph), 25.9 (CH_3), 25.6 (CH_3). ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −123.5 (m, F_2), −143.7 (dd, $J_{F1,H1}$=63.6 Hz, $J_{F1,F2}$=3.1 Hz, F_1).

3.2.2. Spectroscopic data of 18b (min) extracted from the spectrum of mixture. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45–7.20 (m, 5H, Ph), 5.32 (dd, 1H, $J_{1,F1}$=63.8 Hz, $J_{1,F2}$=2.0 Hz, H_1), 4.88 (m, 1H, CH_2Ph), 4.84 (m, 1H, H_3), 4.78 (m, 1H, H_4), 4.66 (m, 1H, CH_2Ph), 4.22 (m, 1H, H_{5a}), 4.10 (m, 1H, $J_{5b,F2}$=4.7 Hz, H_{5b}), 1.52 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.1 (C_{Ar}), 129.0–128.0 (C_{Ar}), 116.5 ($C(CH_3)_2$), 112.4 (dd, $J_{2,F2}$=237.3 Hz, $J_{2,F1}$=34.0 Hz, C_2), 107.1 (dd, $J_{1,F1}$=224.9 Hz, $J_{1,F2}$=45.1 Hz, C_1), 79.2 (d, 1H, $J_{3,F2}$=19.7 Hz, C_3), 78.3 (C_4), 72.5 (C_5), 71.8 (CH_2Ph), 25.9 (CH_3), 25.6 (CH_3). ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −123.3 (td, $J_{F2,F1}$=$J_{F2,H3}$=13.0 Hz, $J_{F2,H5'}$=5.3 Hz, F_2), −141.6 (dd, $J_{F1,H1}$=63.8 Hz, $J_{F1,F2}$=13.0 Hz, F_1).

3.3. Synthesis of difluorocarbohydrate 21

DAST (0.14 ml, 1 mmol) was added dropwise to a solution of compound **19** (0.048 g, 0.13 mmol)) in anhydrous CH_2Cl_2 (1 ml). After 24 h, standard work up gave an oil, which was purified by preparative thin layer chromatography (ethyl acetate/hexane=1:7), to yield the difluoro compound **21** (0.029 g, 61%) as an diastereoisomeric mixture.

3.3.1. Spectroscopic data of 21a (maj) extracted from the spectrum of mixture. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.00–7.25 (m, 10H, H_{Ar}), 5.34 (dd, 1H, $J_{1,F1}$=63.8 Hz, $J_{1,F2}$=1.6 Hz, H_1), 5.24 (dd, 1H, $J_{4,3}$=5.4 Hz, $J_{4,5}$=4.8 Hz, H_4), 4.95 (d, 1H, J_{AB}=12.0 Hz, CH_2Ph), 4.73 (dd, 1H, J_{AB}=12.0 Hz, $J_{H,F1}$=1.7 Hz CH_2Ph), 4.32 (dd, 1H, $J_{3,F2}$=14.1 Hz, $J_{3,4}$=5.4 Hz, H_3), 4.22 (m, 1H, $J_{5,6}$=6.8 Hz, $J_{5,4}$=4.8 Hz, H_5), 3.45 (s, 3H, OCH_3), 1.48 (d, 3H, $J_{6,5}$=6.8 Hz, H_6). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6 (CO), 133.5–128.0 (12C_{Ar}), 112.3 (dd, $J_{2,F2}$=211.7 Hz, $J_{2,F1}$=32.3 Hz, C_2), 105.4 (dd, $J_{1,F1}$=224.7 Hz, $J_{1,F2}$=45.0 Hz, C_1), 82.9 (d, $J_{3,F2}$=20.4 Hz, C_3), 80.7 (C_4), 79.6 (d, $J_{5,F2}$=2.4 Hz, C_5), 71.0 (CH_2Ph), 58.4 (d, $J_{Me,F2}$=2.4 Hz, OCH_3), 19.4 (C_6). ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −140.89 (dd, $J_{F1,H1}$=63.8 Hz, $J_{F1,F2}$=9.0 Hz, F_1), −119.15 (m, F_2).

3.3.2. Spectroscopic data of 21b (min) extracted from the spectrum of mixture. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.00–7.25 (m, 10H, H_{Ar}), 5.33 (dd, 1H, $J_{1,F1}$=63.5 Hz, $J_{1,F2}$=1.8 Hz, H_1), 5.22 (dd, 1H, $J_{4,3}$=5.0 Hz, $J_{4,5}$=4.3 Hz, H_4), 4.23 (dd, 1H, $J_{3,F2}$=14.1 Hz, $J_{3,4}$=5.0 Hz, H_3), 4.23 (m, 1H, $J_{5,6}$=6.8 Hz, $J_{5,4}$=4.3 Hz, H_5), 3.45 (s, 3H, OCH_3), 1.47 (d, 3H, $J_{6,5}$=6.8 Hz, H_6). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6 (CO), 133.5–128.0 (C_{Ar}), (C_2) not observed, 105.3 (dd, $J_{1,F1}$=225.3 Hz, $J_{1,F2}$=43.8 Hz, C_1), 83.2 (d, $J_{3,F2}$=20.6 Hz, C_3), 80.8 (C4), 79.7 (d, $J_{5,F2}$=2.8 Hz, C_5), 70.81 (CH_2Ph), 58.5 (OCH_3), 19.3 (C_6). ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −144.4 (dd, $J_{F1,H1}$=63.5 Hz, $J_{F1,F2}$=7.0 Hz, F_1), −119.00 (m, F_2).

3.4. Synthesis of glycopyranosyl fluoride 23

A solution of alcohol **22** (0.118 g, 0.3 mmol) in dry DCM (2 ml) was treated with DAST (0.3 ml, 0.360 g, 2.2 mmol) dropwise under argon atmosphere at room temperature and the resulting mixture was stirred for a period of 4 h and then refluxed for 3 h. After cooling and standard work up, the crude residue was purified over silica gel chromatography in ethyl acetate/hexane=1:9 to give compound **23** (0.060 g, 49%) as a 1:1 anomeric mixture (colorless oil).

3.4.1. Spectroscopic data of 23a (β) extracted from the spectrum of mixture. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.20 (m, 5H, Ph), 5.20 (dd, 1H $J_{1,F}$=52.4 Hz, $J_{1,2}$=6.3 Hz, H_1), 4.84 (d, 1H, J=11.4 Hz, OCH_2Ph), 4.78 (d, 1H, J=11.4 Hz, OCH_2Ph), 3.94 (td, 1H, $J_{3,2}$=$J_{3,4}$=10.2 Hz, $J_{3,F}$=0.9 Hz, H_3), 3.67 (dq, 1H, $J_{5,4}$=9.6, $J_{5,6}$=6.0 Hz, H_5) 3.60 (ddd, 1H, $J_{2,F}$=13.7 Hz, $J_{2,3}$=10.4 Hz, $J_{2,1}$=6.0 Hz, H_2), 3.54 (t, 1H, $J_{4,3}$=$J_{4,5}$=10 Hz, H_4), 3.25 (s, 3H, OMe), 3.22 (s, 3H, OMe), 1.85–1.36 (m, 8H, $(CH_2)_4$), 1.33 (d, 3H, $J_{6,5}$=6.0 Hz, H_6). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2 (C_{Ar}), 128.3, (CH_{Ar}), 127.6 (CH_{Ar}), 109.4 (d, $J_{1,F}$=213.2 Hz, C_1), 98.4 (C_{acetal}), 98.2 (C_{acetal}), 78.9 (d, $J_{2,F}$=23.2 Hz, C_2), 74.4 (OCH_2Ph), 71.9 (d, $J_{3,F}$=12.2 Hz, C_3), 70.8 (C_4), 70.5 (d, $J_{5,F}$=5.5 Hz, C_5), 48.8 (OMe), 46.7 (OMe), 27.0 (CH_2), 26.9 (CH_2), 21.4 (CH_2), 21.3 (CH_2), 16.7 (C_6). ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −139.6 (dd, $J_{H1,F}$=51.8 Hz and $J_{H2,F}$=13.5 Hz).

3.4.2. Spectroscopic data for 23b (α) extracted from spectrum of mixture. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.26 (m, 5H, Ph), 5.50 (dd, 1H, $J_{1,F}$=52.8 Hz, $J_{1,H2}$=2.8 Hz, H_1), 4.86 (m, 2H), 4.29 (t, 1H, $J_{3,2}$=$J_{3,4}$=10.4 Hz, H_3), 3.5–3.7 (m, 3H, H_2, H_4, H_5), 3.22 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 2.20–1.47 (m, 8H, $(CH_2)_4$), 1.26 (d, 3H, $J_{6,5}$=6.4 Hz, H_6). ^{13}C NMR ($CDCl_3$, 100 MHz) 138.1, 128.3, 127.7, 127.4, 105.2 (d, $J_{1,F}$=226.7 Hz, C_1), 96.7 (C_{acetal}), 96.5 (C_{acetal}), 76.3 (d, J=23.5 Hz, C2), 74.4 (OCH_2Ph), 71.2, 69.9, 68.0 (d, J=2.1 Hz), 46.7 (OMe), 46.5 (OMe), 27.0 (CH_2), 26.9 (CH_2), 21.3(CH_2), 21.2 (CH_2), 16.6 (C_6). ^{19}F NMR ($CDCl_3$, 282.3 MHz): −146.65 (dd, $J_{H1,F}$=51.8 Hz, $J_{H2,F}$=22.9 Hz).

3.5. Synthesis of the ulose 24

A mixture of alcohol **22** (0.197 g, 0.5 mmol), PCC (0.431 g, 2.0 mmol), sodium acetate (0.164 g, 2.0 mmol) and 4 Å activated molecular sieves (1.0 g) was placed in a light-protected flask under argon atmosphere and DCM (5 ml) was added. After 1 h, the solvent was evaporated to dryness and the residue was purified by column chromatography in chloroform to afford pure product **24** (0.150 g, 77%).

3.5.1. Compound 24. $[\alpha]_D$=−79.0 (c=0.45, $CDCl_3$); IR 1727 cm^{-1} (ν_{CO}) ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.29 (m, 5H, Ph), 4.93 (d, 1H, J=10.4 Hz, H_3), 4.78 (s, 1H, H_1), 4.69 (d, 1H, J=11.8 Hz, CH_2Ph), 4.53 (d, 1H, J=11.8 Hz, CH_2Ph), 4.22 (m, 1H, H_5), 3.67 (t, 1H, $J_{4,3}$=$J_{4,5}$=10.4 Hz, H_4), 3.16 (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 1.82–1.30 (m, 8H, $(CH_2)_4$), 1.23 (d, 3H,

$J_{6,5}$=6.4 Hz, H_6). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.6 (CO), 136.2, 128.5, 128.3, 128.2, 99.4 (C_1), 99.1 (C_{acetal}), 98.5 (C_{acetal}), 74.3 (C_4), 73.4 (C_3), 70.1 (OCH_2Ph), 66.9 (C_5), 47.3 (OCH_3), 46.6 (OCH_3), 26.9 (CH_2), 26.8 (CH_2), 21.2 ($2CH_2$), 16.1 (C_6). Anal. Calcd. for $C_{21}H_{28}O_7$: C, 64.28; H, 7.14. Found; C, 64.18; H, 7.43.

3.6. Synthesis of difluorocarbohydrate 25

A solution of ketone **24** (0.100 g, 0.25 mmol) in dry DCM (4 ml) was treated with DAST (0.7 ml, 0.84 g, 5.2 mmol) under argon atmosphere and the mixture was refluxed for 16 h. After cooling and the standard work up, the residue was chromatographed on silica gel in ethyl acetate/hexane=1:9 to ethyl acetate/hexane=1:1 to give compound **25** as a diastereoisoeric mixture (0.020 g, 19% yield, conversion 50%) and unreacted ketone **24** (0.050 g).

3.6.1. Spectroscopic data for 25a (maj) extracted from spectrum of mixture. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.26 (m, 5H, Ph), 5.32 (dd, 1H, $J_{1,F1}$=62.4 Hz, $J_{1,F2}$=1.2 Hz, H_1), 4.90 (d, 1H, J=12.9 Hz, OCH_2Ph) 4.68 (dd, 1H, J=12.0 Hz, $J_{CH2,F1}$=1.2 Hz, OCH_2Ph), 4.32 (dd, 1H, $J_{3,F2}$=20.4 Hz, $J_{3,4}$=10.2 Hz, H_3), 4.14–3.97 (m, 2H, H_4, H_5), 3.15 (s, 3H, OMe), 3.05 (s, 3H, OMe). 1.95–1.40 (m, 8H, $(CH_2)_4$), 1.33 (d, 3H, $J_{6,5}$=6 Hz, H_6). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.6, 128.4, 128.2, 127.9, 110.3 (dd, $J_{2,F2}$=223.3 Hz, $J_{2,F1}$=25.8 Hz, C_2), 106.2 (dd, $J_{1,F1}$=224.2 Hz, $J_{1,F2}$=46.2 Hz, C_1), 100.4 (C_{acetal}), 99.8 (C_{acetal}), 74.9 (d, $J_{5,F2}$=2.4 Hz, C_5), 72.9 (d, $J_{4,F2}$=1.6Hz, C_4), 71.6 (OCH_2Ph), 70.3 (d, $J_{3,F2}$=20.2 Hz, C_3), 46.7 (OMe), 46.6 (OMe), 27.3 (CH_2), 27.2 (CH_2), 21.3 ($2CH_2$), 18.9 (C_6). ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −118.9 (m, F_2), −144.3 (dd, $J_{F1,H1}$=62.4 Hz, $J_{F1,F2}$=6.0 Hz, F_1).

3.7. General procedure for the reaction of difluorocarbohydrates 17 and 18 with alcohols

A mixture of Cp_2HfCl_2 (0.5 mmols), AgOTf (1 mmol) and powered 4 Å molecular sieves (440 mg) in dichlorometane (1.5 ml) was stirred for 10 min. at room temperature. The alcohol (1 mmol) in dichlorometane (0.5 ml) was then added and, after 5 minutes at room temperature, the mixture was cooled to −50°C. Difluoride **17** or **18** (0.5 mmol) was then added and the temperature was left to reach room temperature. When the reaction was finished, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution, and filtered through a Celite pad. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×10 ml). The combined layers were dried ($MgSO_4$) and evaporated. The crude oil was purified by flash or thin-layer chromatography.

3.8. Reaction of difluorocarbohydrate 18 with benzyl alcohol

3.8.1. Synthesis of compound 26. Ratio **18**/$PhCH_2OH$ 1:10. The general procedure was followed with Cp_2HfCl_2 (0.124 g, 0.33 mmol), AgOTf (0.171 g, 0.66 mmol) and 4Å molecular sieves (0.300 g), benzyl alcohol (0.350 g, 3.3 mmol) and compound **18** (0.050 g, 0.17 mmol) for 3 h. The standard work up gave a crude oil which was purified by thin layer chromatography (ethyl acetate/hexane=1:3) to afford compound **26** (0.101 g, 66%) as a colorless oil. Compound **26**: $[\alpha]_D$=−51.3 (c=0.97, $CHCl_3$), ^1H NMR ($CDCl_3$, 400 MHz), δ 7.33–7.08 (m, 15H, Ph), 4.96 (d, 1H, J_{AB}=12.1 Hz, CH_2Ph), 4.90 (s, 1H, H_1), 4.76 (d, 1H, J_{AB}=12.0 Hz, CH_2Ph), 4.75 (dd, 1H, $J_{4,3}$=5.8 Hz, $J_{4,5a}$=4.0 Hz, H_4), 4.75 (d, 1H, J_{AB}=12.3 Hz, CH_2Ph), 4.72 (d, 1H, J_{AB}=12.1 Hz, CH_2Ph), 4.62 (d, 1H, J_{AB}=12.3 Hz, CH_2Ph), 4.61 (d, 1H, J_{AB}=12.0 Hz, CH_2Ph), 4.51 (d, 1H, $J_{3,4}$=5.8 Hz, H_3), 3.95 (d, 1H, $J_{5b,5a}$=10.5 Hz, H_{5b}), 3.79 (dd, 1H, $J_{5a,5b}$=10.5 Hz, $J_{5a,4}$=4.0 Hz, H_{5a}), 1.33 (s, 3H, CH_3), 1.21 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 138.1 (C_{Ar}), 137.0 (C_{Ar}), 136.9 (C_{Ar}), 127.8–125.8 ($15CH_{Ar}$), 111.3 ($C(CH_3)_2$), 106.8 (C_2), 100.7 (C_1), 84.7 (C_3), 79.2 (C_4), 71.3 (C_5), 71.0 (CH_2Ph), 68.9 (CH_2Ph), 64.5 (CH_2Ph), 25.3 (CH_3), 23.9 (CH_3). Anal. Calcd for $C_{29}H_{32}O_6$: C, 73.08; H, 6.76. Found: C, 73.04, H, 6.79.

3.8.2. Synthesis of compound 27. Ratio **18**/$PhCH_2OH$ 1:2. The general procedure was followed with Cp_2HfCl_2 (0.120 g, 0.32 mmol), AgOTf (0.166 g, 0.64 mmol) and 4Å molecular sieves (0.320 g), benzyl alcohol (0.69 g, 0.64 mmol) and compound **18** (0.050 g, 0.17 mmol) for 90 min. Standard work up gave a crude oil which was purified by column chromatography (ethyl acetate/hexane=2:3) to produce compound **27** (0.046 g, 70%) as a colorless oil. Compound **27**: $[\alpha]_D$=−149.6 (c=0.84, $CHCl_3$), ^1H NMR ($CDCl_3$, 400 MHz), δ 7.41–7.03 (m, 9H, Ph), 4.96 (dd, 1H, $J_{4,3}$=6.2 Hz, $J_{4,5a}$=3.8 Hz, H_4), 4.89 (d, 1H, $J_{1a',1b'}$=15.3 Hz, $H_{1a'}$), 4.82 (d, 1H, $J_{3,4}$=6.2 Hz, H_3), 4.76 (d, 1H, J_{AB}=11.1 Hz, CH_2Ph), 4.75 (d, 1H, $J_{1b',1a'}$=15.3 Hz, $H_{1b'}$), 4.64 (d, 1H, J_{AB}=11.1 Hz, CH_2Ph), 4.50 (s, 1H, H_1), 4.00 (d, 1H, $J_{5b,5a}$=10.2 Hz, H_{5b}), 3.92 (dd, 1H, $J_{5a,4}$=3.8 Hz, $J_{5a,5b}$=10.2 Hz, H_{5a}), 1.49 (s, 1H, CH_3), 1.39 (s, 1H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 138.2 (C_{Ar}), 134.0 (C_{Ar}), 130.9 (C_{Ar}), 130.2 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 128.1 (CH_{Ar}), 127.5 (CH_{Ar}), 126.3 (CH_{Ar}), 124.2 (CH_{Ar}), 112.7 ($C(CH_3)_2$), 107.7 (C_2), 84.3 (C_3), 80.2 (C_4), 72.9 (C_5), 71.8 (C_1), 70.8 (CH_2), 62.6 ($C_{1'}$), 26.4 (CH_3), 25.1 (CH_3). Anal. Calcd for $C_{22}H_{24}O_5$: C, 73.08; H, 6.76. Found: C, 73.04, H, 6.79.

3.9. Reaction of difluorocarbohydrate 17 with uracil(TMS)$_2$

3.9.1. Synthesis of compounds 28. A mixture of Cp_2HfCl_2 (0.460 mmol), AgOTf (0.92 mmol) and 4 Å molecular sieves in 1.5 ml of benzene was stirred for 10 min under inert atmosphere. To this reaction mixture, a solution of bis(trimethylsilyl)uracil (0.92 mmol) in benzene (0.5 ml) and after 5 min, a solution of compound **17** (0.46 mmol) in benzene (1 ml) was added. The reaction mixture was stirred for 24 h, then poured into cold saturated aqueous $NaHCO_3$ solution, and filtered through a Cellite pad. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated. The crude residue was purified by flash chromatography to afford 0.124 g of **28** (85%) as an epimeric 87/13 mixture. A pure sample of the major isomer was isolated by repetitive chromatography of a small sample of the mixture to afford a white solid. mp=183–185°C; $[\alpha]_D$=+53.2 (c=0.74, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz), δ 9.70 (bs, 1H, NH), 7.45 (dd, 1H, $J_{6',5'}$=8.2 Hz, $J_{6',F}$=1.7 Hz, $H_{6'}$), 5.72 (d, 1H, $J_{5',6'}$=

8.2 Hz, $H_{5'}$), 5.61 (d, 1H, $J_{1,F}$=13.3 Hz, H_1), 4.84 (dd, 1H, $J_{4,5a}$=5.4 Hz, $J_{4,5b}$=2.8 Hz, H_4), 4.67 (dd, 1H, $J_{3,4}$=6.5 Hz, $J_{3,F}$=12.8 Hz, H_3), 4.19 (m, 1H, $J_{5a,4}$=5.4 Hz, $J_{5a,5b}$= 10.4 Hz, $J_{5a,F}$=2.8 Hz, H_{5a}), 4.14 (dd, 1H, $J_{5b,5a}$=10.4 Hz, $J_{5b,4}$=2.8 Hz, H_{5b}), 3.39 (s, 3H, OCH_3), 1.51 (s, 3H, CH_3), 1.33 (s, 1H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz), δ 161.9 ($C_{4'}$), 150.3 ($C_{2'}$), 139.2 (d, $J_{6',F}$=5.4 Hz, $C_{6'}$), 115.4 ($C(CH_3)_2$), 112.5 (d, $J_{2,F}$=245.1 Hz, C_2), 101.9 ($C_{5'}$), 83.6 (d, $J_{1,F}$=27.2 Hz, C_1), 80.7 (d, $J_{3,F}$=21.9 Hz, C_3), 77.2 (C_4), 71.6 (C_5), 56.4 (OCH_3), 24.9 (CH_3), 24.5 (CH_3). ^{19}F NMR ($CDCl_3$, 282.3 MHz), δ −127.8 (t, $J_{F,H1}$=$J_{F,H3}$=13.0 Hz). Anal. Calcd for $C_{13}H_{17}FN_2O_6$: C, 49.37; H, 5.42. Found: C, 49.58, H, 5.07.

3.10. Reaction of difluorocarbohydrate 17 with 6-bromo-2-naphthol. Synthesis of compounds 29, 30 and 31

A mixture of Cp_2HfCl_2 (0.822 g, 2.16 mmols), AgOTf (1.113 g, 4.32 mmol) and 4 Å molecular sieves (1.9 g) in dichloromethane (11 ml) was stirred for 10 min at room temperature. 6-bromo-2-naphthol (0.820 g, 3.67 mmol) in dichloromethane (6.5 ml) was then added and, after 5 min at room temperature, the mixture was cooled to −50°C. Compound **17** (0.486 g, 2.16 mmol) in 11 ml of dichloromethane was added and the temperature was then left to reach room temperature. After the reaction was completed (4 h) standard work up gave a crude oil, which was purified to afford compound **29** (0.131 g, 15%) as a colorless oil, and compounds **30** (0.275 g, 21%) and **31** (0.145 g, 11%) as white solids.

3.10.1. Compound 29. $[\alpha]_D$=−113.0 (c=0.8, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz), δ 8.16 (d, 1H, $J_{4',5'}$=9.3 Hz, $H_{4'}$), 7.82 (d, 1H, $J_{7',5'}$=2.1 Hz, $H_{7'}$), 7.60 (d, 1H, $J_{9',10'}$=9.0 Hz, $H_{9'}$), 7.38 (dd, 1H, $J_{5',4'}$=9.3 Hz, $J_{5',7'}$=2.1 Hz, $H_{5'}$), 7.05 (d, 1H, $J_{10',9'}$=9.0 Hz, $H_{10'}$), 5.06 (s, 1H, H_1), 4.94 (dd, 1H, $J_{4,3}$=5.9 Hz, $J_{4,5a}$=4.2 Hz, H_4), 4.72 (d, 1H, $J_{3,4}$=5.9 Hz, H_3), 4.28 (d, 1H, $J_{5b,5a}$=11.0 Hz, H_{5b}), 3.76 (dd, 1H, $J_{5a,5b}$=11.0 Hz, $J_{5a,4}$=4.2 Hz, H_{5a}), 3.47 (s, 3H, OCH_3), 1.45 (s, 3H, CH_3), 1.19 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 154.9 ($C_{1'}$), 130.3 ($C_{8'}$), 129.9 ($C_{9'}$) 129.6 ($C_{3'}$), 128.9 ($C_{7'}$), 128.1 ($C_{5'}$),?126.4 ($C_{4'}$), 116.2 ($C_{6'}$), 114.2 ($C_{2'}$), 112.2 ($C_{10'}$), 111.9 ($C(CH_3)_2$), 106.2 (C_1), 92.6 (C_2), 83.3 (C_3), 79.3 (C_4), 72.2 (C_5), 55.1 (OCH_3), 24.5 (CH_3), 22.5 (CH_3). Anal. Calcd for $C_{19}H_{19}BrO_5$: C, 56.03; H, 4.70. Found: C, 55.85, H, 4.78.

3.10.2. Compound 30. Mp=204–206°C, $[\alpha]_D$=−177.0 (c=0.3, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.78 (d, 1H, $J_{7',5'}$=2.1 Hz, $H_{7'}$), 7.70 (d, 1H, $J_{7'',5''}$=2.1 Hz, $H_{7''}$), 7.63 (s, 1H, OH), 7.58 (d, 1H, $J_{9'',10''}$=8.7 Hz, $H_{9''}$), 7.56 (d, 1H, $J_{9',10'}$=9.0 Hz, $H_{9'}$), 7.26 (d, 1H, $J_{10'',9''}$=8.7 Hz, $H_{10''}$), 7.13 (d, 1H, $J_{4'',5''}$=9.0 Hz, $H_{4''}$), 7.10 (d, 1H, $J_{10',9'}$=9.0 Hz, $H_{10'}$), 6.93 (dd, 1H, $J_{5',4'}$=9.0 Hz, $J_{5',7'}$= 2.1 Hz, $H_{5'}$), 6.83 (dd, 1H, $J_{5'',4''}$=9.0 Hz, $J_{5'',7''}$=2.1 Hz, $H_{5''}$), 6.45 (d, 1H, $J_{4',5'}$=9.0 Hz, $H_{4'}$), 5.76 (s, 1H, H_1), 5.00–4.90 (m, 2H, H_3, H_4), 4.10 (dd, 1H, $J_{5a,5b}$=10.8 Hz, $J_{5a,4}$=3.3 Hz, H_{5a}), 3.87 (d, 1H, $J_{5b,5a}$=10.8 Hz, H_{5b}), 1.35 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 153.2 ($C_{1'}$), 152.1 ($C_{1''}$), 131.5 ($C_{3''}$), 130.1 ($C_{8''}$), 129.7 ($C_{8'}$), 129.5 ($C_{7'}$), 129.1 ($C_{7''}$), 129.0 ($C_{5'}$), 128.5 ($C_{9'}$), 128.1 ($C_{9''}$), 127.4 ($C_{5''}$), 127.4 ($C_{3'}$), 126.1 ($C_{4''}$), 122.5 ($C_{4'}$), 120.0 ($C_{10''}$), 119.2 ($C_{2'}$), 118.1 (C_2), 116.1 ($C_{6'}$), 114.6 ($C_{6''}$), 115.8 ($C_{2''}$), 112.7 ($C(CH_3)_2$), 84.3 (C_3), 78.6 (C_4), 71.8 (C_5), 42.8 (C_1), 24.3 (CH_3), 23.6 (CH_3). Anal. Calcd for $C_{28}H_{22}Br_2O_5$: C, 56.21; H, 3.68. Found: C, 55.90, H, 3.64.

3.10.3. Compound 31. Mp=224–226°C, $[\alpha]_D$=+7.1 (c=1.21, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz), δ 8.36 (d, 1H, $J_{4'',5''}$=9.3 Hz, $H_{4''}$), 7.96 (d, 1H, $J_{7'',5''}$=2.1 Hz, $H_{7''}$), 7.86 (d, 1H, $J_{7',5'}$=2.1 Hz, $H_{7'}$), 7.60 (d, 1H, $J_{9',10'}$= 9.0 Hz, $H_{9'}$), 7.60 (d, 1H, $J_{9'',10''}$=8.7 Hz, $H_{9''}$), 7.56 (dd, 1H, $J_{5'',4''}$=9.3 Hz, $J_{5'',7''}$=2.1 Hz, $H_{5''}$), 7.12 (d, 1H, $J_{10',9'}$= 9 Hz, $H_{10'}$), 7.03 (dd, 1H, $J_{5',4'}$=9.3 Hz, $J_{5',7'}$=2.1 Hz, $H_{5'}$), 6.98 (d, 1H, $J_{10'',9''}$=8.7 Hz, $H_{10''}$), 6.63 (s, 1H, OH), 6.43 (d, 1H, $J_{4',5'}$=9.3 Hz, $H_{4'}$), 6.15 (s, 1H, H_1), 5.02–4.98 (m, 2H, H_3, H_4), 4.23 (dd, 1H, $J_{5a,5b}$=10.2 Hz, $J_{5a,4}$=3.0 Hz, H_{5a}), 4.09 (d, 1H, $J_{5b,5a}$=10.2 Hz, H_{5b}), 1.28 (s, 3H, CH_3), 0.76 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.8 ($C_{1''}$), 153.2 ($C_{1'}$), 130.2 ($C_{8'}$), 129.9 ($C_{8''}$), 118.09 ($C_{2'}$), 129.7 ($C_{7'}$), 129.6 ($C_{7''}$), 120.7 ($C_{10''}$), 128.4 ($C_{9'}$), 128.2 ($C_{9''}$), 128.1 ($C_{5''}$), 131.06 ($C_{3''}$), 124.6 ($C_{4''}$), 122.6 ($C_{4'}$), 118.9 (C_2), 127.7 ($C_{3'}$, 129.2 ($C_{5'}$, 116.1 ($C_{6'}$), 115.9 ($C_{6''}$), 115.4 ($C_{2''}$), 112.4 ($C(CH_3)_2$), 111.7 ($C_{10'}$), 83.9 (C_3), 78.4 (C_4), 72.0 (C_5), 42.3 (C_1), 24.4 (CH_3), 23.8 (CH_3). Anal. Calcd for $C_{28}H_{22}Br_2O_5$: C, 56.21; H, 3.68. Found: C, 55.94, H, 3.83.

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