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Regiocontrolled fluorination of 2-hydroxyalkyl dihydropyrans and carbonyl derivatives

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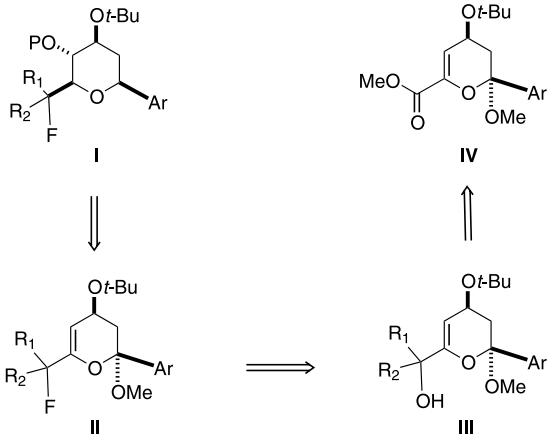
Abstract—Reaction of polysubstituted 2-hydroxyalkyldihydropyrans with DAST led regiospecifically to fluorination at the exocyclic position, except for primary alcohols. Difluorination of carbonylated analogues with deoxo-fluor™ occurred also regioselectively. The unexpected stability and synthetic potential of these new allylic fluorides are discussed.

Selective introduction of fluorine into polyfunctionalized structures is often considered as an important task for the modulation of bioactive molecules.[1] Such manipulation is of particular significance in the field of glycosides,[2] one established feature for *O*-glycosides being the influence of neighbouring C–F bonds on the strength of the glycosidic bond.[2b] Valuable *O*-glycosides[3] of deoxyfluoro sugars[4] have been thus synthesized, mainly through hemisynthetic pathways from carbohydrate natural sources. Concerning de novo approaches,[5] the [4+2] heterocycloaddition of a CF_3–containing heterodiene was successfully employed by Larsen's group as the key step to prepare 6,6,6-trifluorinated *O*-olivosides in racemic,[6] D and L series.[7] In contrast, only unsuccessful access to *C*-aryl glycosides deriving from a fluorine-containing sugar seems to be reported.[6]

We investigated a synthetic plan devoted to the de novo synthesis of (±)-*C*-aryl-2,6-dideoxy-6-fluoro-glycosides **I** (Scheme 1). It is based on the functional modification of type **IV** heteroadducts prepared by a stereoselective route as described recently.[8] The key steps in this strategy involves first dehydroxyfluorination at the 6-position of the allylic alcohols **III**, and then the hydroboration–oxidation and ketal reductive cleavage steps.[9] The present communication discuss the synthesis of type **II** allylic fluorides by DAST-fluorination[10] of the corresponding alcohols (**III**, R_1, R_2 = H or Me) in model series (Ar = 2-naphthyl). It is well established that dehydroxyfluorination of allylic alcohols with DAST is usually neither regio- nor stereocontrolled.[11] However, to the best of our knowledge, there is no example of fluorination on derivatives of this sort bearing an extra vicinal ether function. Therefore the present study is also of interest in order to rationalize the factors controlling the regio- and stereoselectivity in DAST reactions.[12]

In addition, with the aim to define a similar route to 6,6-difluorinated *C*-arylglycosides (compounds **II** with R_1 = H, alkyl, R_2 = F), we report here our preliminary results concerning the bis-fluorination of corresponding



Scheme 1.

Keywords: fluorination; DAST; deoxo-fluor™; dihydropyran; *C*-glycoside.
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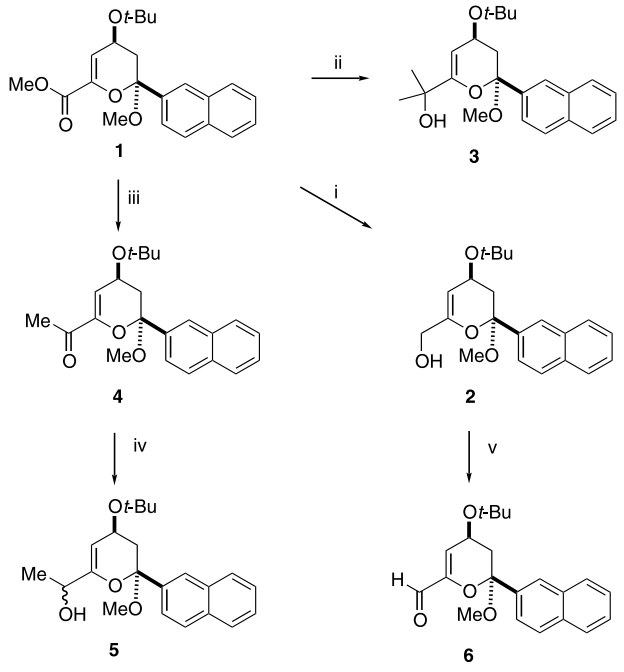


Scheme 2. *Reagents and conditions*: (i) $LiAlH_4$, Et_2O, rt, 87%; (ii) MeLi, THF/Et_2O, −78°C to rt, 71%; (iii) MeLi, TMSCl, THF/Et_2O, −90°C to rt, 64%; (iv) $NaBH_4$, $CeCl_3 \cdot 7\ H_2O$, MeOH, 0°C, 73%; (v) TPAP, NMO, CH_2Cl_2, 0°C to rt, 72%.

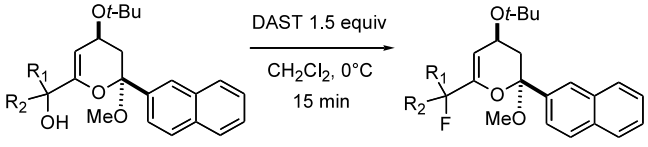
carbonyl derivatives, using deoxo-fluor™ as the reagent.

Starting from the (racemic) dihydropyran **1** (Scheme 2), we prepared various substrates for the allylic fluorination study. $LiAlH_4$-reduction gave the primary alcohol **2**. Tertiary alcohol **3** was prepared by condensation of an excess of methyl lithium on ester **1**, whereas methyl ketone **4** was mainly obtained from the same reactants at low temperature in the presence of TMSCl.[13] A 1:1 epimeric mixture of the secondary alcohol **5** resulted from the Luche reduction of methyl ketone **4**. At last, smooth oxidation of the primary allylic alcohol **2** with tetrapropylammonium perruthenate and NMO furnished the aldehyde **6**.

Nucleophilic fluorination of allylic alcohols **2**, **3** and **5** were next studied with the use of DAST reagent (Table 1).[14] The primary alcohol **2** gave **7** together with **10** resulting from allylic isomerization in a 2:1 ratio. Chromatographic separation of **7** from the 3:1 epimeric mixture of isomeric compounds **10** proved to be difficult and led to modest yields of isolated product. In contrast, secondary and tertiary alcohols **5** and **3** underwent a clean dehydroxyfluorination with DAST without any trace of isomerization side-product.

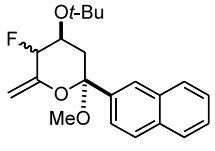
The secondary and tertiary fluorides **8** and **9** proved to be stable under standard chromatographic conditions, and thus were obtained in 55 and 75% yield, respectively, after purification. Location of the fluorine substituent on each of the products **7**–**9** and **10** was unambiguously established by ^1H and ^{19}F NMR data (Table 1). For the secondary alcohol **8** there is no stereoselectivity during the fluorination step: the same 2:1 mixture of diastereomeric fluorides was obtained starting either from the 1:1 mixture of **5** or from mixtures enriched in one of the alcohols. A positive result was the fair stability observed for the compounds **7**–**9**: after one month-storage in freeze or even at room temperature, NMR of these allylic fluorides showed no

Table 1. Fluorination of alcohols **2**, **3** and **5** with DAST

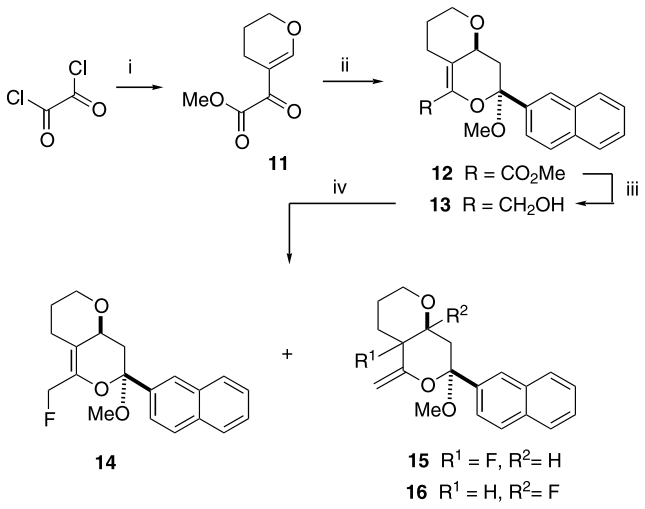


2 ; 3 ; 5 **7 ; 8 ; 9**

Starting alcohol	Products (isomeric ratio)	Yield (%)	^{19}F NMR δ, J_{F-H}
2	**7**	30	−216.1 (tdd, *J* 47.7, 8.3, 4.5)
	10a		−195.4 (dm, *J* 51.2)
	10b		−192.1 (dddd, *J* 51.5, 28.0, 5.6, 2.5)
	(68:24:8)		
3	**8**	75	−142.1 (septd, *J* 21.8, 2.9)
5	**9a**	55	−171.6 (dqd, *J* 47.5, 23.5, 8.3)
	9b		−174.9 (dqd, *J* 47.7, 24.2, 4.4)
	(2:1)		



10



Scheme 3. *Reagents and conditions*: (i) (a) DHP, −10°C to rt, (b) NEt_3, MeOH, rt, 69%; (ii) 2-(α-methoxy-vinyl)-naphthalene, $SnCl_4$ (cat.), CH_2Cl_2, 0°C, 59%; (iii) $LiAlH_4$, Et_2O, rt, 100%; (iv) DAST, CH_2Cl_2, rt, 40%.

significant loss of purity or formation of decomposition products.

It appeared of interest to evaluate the effect of an extra substituent on the double bond with regard to the regioselectivity of the fluorination. For that purpose the bicyclic derivative **13** was prepared by the route indicated in Scheme 3. Under the same reaction conditions as before, DAST afforded a (19:24:57) mixture of fluorides **14**, **15** and **16**.[15] By SiO_2 chromatography it was possible to isolate **16** in a pure form and mixtures of **14** and **15**. The structure of these derivatives has been established by extensive 1D and 2D NMR experiments, as in the previous examples. In the case of **15** and **16** only one stereoisomer was detected in the crude reaction mixture but its stereochemistry could not be unambiguously established at this stage. Like for primary alcohol **2** there is a competition between fluorination without allylic isomerization, leading to **14**, and with isomerization giving **15**. Furthermore it is possible to propose a mechanism for the formation of **16**: starting from a first allylic cation intermediate a 1,2 hydrogen shift occurs leading to an oxonium ion which is trapped by F^-, thus affording **16**.

Then we extended our study to carbonyl compounds **4** and **6**: in this case the reagent of choice was deoxo-fluor™ (neat with a few drops of ethanol).[16] The expected allylic *gem* bis-fluorides (**17**–**18**) were obtained selectively and in good yields (Table 2).[17] These derivatives were purified by chromatography and were also found to be stable on storage. Bis-fluorination of **4** and **6** appears of special interest since enals and enones usually have, at most, a very low reactivity towards DAST and deoxo-fluor™.[18] Therefore the preparation of corresponding *gem*-difluoro derivatives has generally to be performed via propargylic intermediates.[19] Thus, the presence of the vinyl ether function in **4** and **6** induces a higher reactivity of the carbonyls towards these reagents.

In conclusion we have reported a flexible route to mono- and *gem*-difluorinated type-**II** dihydropyrans. Starting from these key intermediates the preparation of fluorinated *C*-aryl glycosides of type **I** is under investigation and will be reported in due course.

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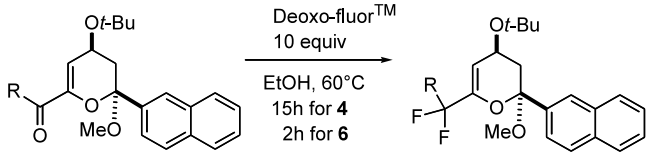
Table 2. *Gem*-difluorination of carbonyl compounds **4** and **6** with deoxo-fluor™



4 : R= Me; **6** : R=H **17; 18**

Starting compound	Product	Yield (%)	^{19}F NMR δ, J_{F-F}, J_{F-H}
4	**17**	61	−93.6 (dqdd, *J* 252.1, 18.3, 4.5, 1.6) −98.5 (dqdd, *J* 252.1, 18.5, 1.4, 3.8)
6	**18**	42	−121.5 (ddd, *J* 299.8, 54.3, 3.8) −123.0 (ddd, *J* 299.8, 54.3, 4.2)

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14. General procedure for DAST fluorination of alcohols **2**, **3**, **5** and **13**: To a solution of DAST (1.5 equiv.) in CH_2Cl_2 was added, under nitrogen at 0°C, a solution of allylic alcohol in CH_2Cl_2. Then the mixture was stirred for 10 min, solid Na_2CO_3 was added first, then a saturated Na_2CO_3 solution. After filtration and decantation, the organic phase was dried ($MgSO_4$) and concentrated. The allylic fluorides were purified by flash chromatography on silica gel. Selected data for fluoride **7** (R_f 0.26 (PE/ethyl acetate 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–8.05 (m, 7H), 5.18 (bs, 1H), 4.94 (dd, 1H, J=47.7, 10.7 Hz), 4.82 (dd, 1H, J=47.7, 10.7 Hz), 4.62 (m, 1H) 3.14 (s, 3H), 2.42 (ddd, 1H, J=13.5, 6.8, 1.5 Hz), 1.86 (dd, 1H, J=13.5, 10.3 Hz), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9 (d, J=15 Hz), 138–123 (Ar), 109.0 (d, J=8.8 Hz), 103.4, 83.5 (d, J=168 Hz), 74.6, 62.1, 50.7, 42.8, 28.7; HRMS (EI) calcd for $C_{21}H_{25}FO_3$ $[M]^+$: 344.1788; found: 344.1791. Fluoride **8**: R_f 0.47 (PE/ethyl acetate 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.97 (m, 7H), 5.13 (t, 1H, J=1.7 Hz), 4.58 (dddd, 1H, J_{HF}= 2.9, J=10.4, 6.7, 1.9 Hz), 3.13 (s, 3H), 2.37 (ddd, 1H, J=13.4, 6.7, 1.9 Hz), 1.80 (dd, 1H, J=13.4, 10.4 Hz), 1.67 (d, 3H, J_{HF}=21.7 Hz), 1.64 (d, 3H, J_{HF}=21.7 Hz); 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0 (d, J=24.4 Hz), 138–123 (Ar), 102.8, 100.9 (d, J=6.8 Hz), 93.0 (d, J=169.4 Hz), 74.1, 61.8, 50.4, 42.5, 28.3, 26.1 (d, J=25.3 Hz); 25.7 (d, J=24.3 Hz); HRMS (EI) calcd for $C_{23}H_{29}FO_3$ $[M]^+$: 373.2101; found: 373.2105. Fluorides **9a**,**b**: R_f 0.39 (PE/ethyl acetate 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–8.00 (m, 7H), 5.11 (bs, 1H), 5.01 (m, 1H), 4.61 (m, 1H), 3.14 (s, 3H), 2.37 (m, 1H), 1.82 (dd, 1H, J=13.3, 10.3 Hz), 1.66 (dd, 3H, dia **9a**, J_{HF}=23.9 Hz, 6.6 Hz), 1.62 (dd, 3H, dia **9b**, J_{HF}=23.9 Hz, J=6.6 Hz), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) **9a**: δ 148.9 (d, J=18.3 Hz), 138–124, 105.9 (d, J=8.2 Hz), 102.7, 89.4 (d, J=168 Hz), 74.2, 61.7, 50.4, 42.5, 28.4, 18.5 (d, J=25.1 Hz); **9b**: δ 149.3 (d, J=18.9 Hz), 104.5 (d, J=7.0 Hz), 88.1 (d, J=168 Hz), 18.7 (d, J=23.9 Hz); HRMS (EI) calcd for $C_{22}H_{27}FO_3$ $[M]^+$: 358.1944; found: 358.1948.
15. Ratios were determined by ^{19}F NMR (376 MHz, $CDCl_3$) δ ($CFCl_3$) −114.3 (dt, J=30.4 and 23.2 Hz, **16**, 57%), −170.9 (ddt, J=37.4, 23.6 and 5.4 Hz, **15**, 24%), −212.9 (tt, J=48.7 and 8.1 Hz, **14**, 19%). Fluorides **14**–**16** gave other satisfactory spectral data.
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17. General procedure for deoxo-fluor™ fluorination: the carbonyl compound (**4** or **6**, 0.3 mmol) was dissolved under N_2 in deoxo-fluor™ (600 μL≈10 equiv.). After addition of ethanol (20 μL), the mixture was stirred at 60°C (15 h for the ketone, 2 h for the aldehyde). The cooled solution was then treated with saturated Na_2CO_3 solution. The organic layers were extracted with CH_2Cl_2, washed with water, dried ($MgSO_4$) and concentrated. The allylic difluorides were purified by flash chromatography on silica gel. Selected data for difluoride **17**: R_f 0.4 (PE/diethyl ether 14/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5–7.97 (m, 7H), 5.41 (bs, 1H), 4.61 (dddd, 1H, J_{HF}=4.5, J=10.3, 6.7, 1.9 Hz), 3.14 (s, 3H), 2.42 (ddd, 1H, J= 13.5, 6.8, 1.5 Hz), 1.91 (t, 3H, J_{HF}=18.4 Hz), 1.86 (dd, 1H, J=13.5 Hz, 10.5 Hz), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3 (dd, J=27.6, 31.5 Hz), 138–123 (Ar), 118.2 (t, J=238.5 Hz), 104.7 (t, J=5.6 Hz), 103.6, 74.5, 61.5, 50.5, 42.3, 28.3, 26.4 (t, J=29.7 Hz); HRMS (EI) calcd for $C_{22}H_{26}O_3F_2$ $[M]^+$: 376.1850; found: 376.1871. Difluoride **18**: R_f 0.29 (PE/diethyl ether 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5–8.02 (m, 7H), 6.07 (t, 1H, J=54.4 Hz), 5.38 (bs, 1H), 4.62 (m, 1H), 3.14 (s, 3H), 2.41 (ddd, 1H, J=13.6, 6.9, 1.4 Hz), 1.87 (dd, 1H, J=13.6 Hz, 10.4 Hz) 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0 (t, J=21.7 Hz), 137.4–124.0 (Ar), 111.8 (t, J=238.5 Hz), 108.8 (t, J=6.4 Hz), 104.0, 74.9, 61.7, 50.9, 42.8, 28.7; HRMS (EI) calcd for $C_{21}H_{24}O_3F_2$ $[M]^+$: 362.1693; found: 362.1686.
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