A Concise Route to Difluorinated Analogues of Cyclitols and Sugars

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Abstract: Allyl ethers of trifluoroethanol are transformed to difluorinated analogues of deoxysugars via concise sequences involving dehydrofluorination/metallation, [3,3]-Claisen rearrangement, reduction, and RCM, affording cyclohexenediol substrates for dihydroxylation reactions.

Key words: carbasugars, cyclitols, difluorinated, metathesis, dihydroxylation

Selectively fluorinated analogues of cyclitols and saccharides have been used extensively to explore molecular aspects of important cellular transformations. In sugar chemistry, the proximity of one or more fluorine atoms to the anomeric centre can raise the barriers to glycosidic C–O bond cleavage considerably. The high electronegativity of the fluorine atom opposes the molecular aspects of important cellular transformations. In sugar chemistry, the proximity of one or more fluorine atoms to the anomeric centre can raise the barriers to glycosidic C–O bond cleavage considerably. The high electronegativity of the fluorine atom opposes the development of oxacarbenium ion character with some receptors. Also, the electron-withdrawing effect of the fluorine atom opposes the development of oxacarbenium ion character with some receptors.6

The replacement of the pyranose oxygen in saccharides by carbocyclic analogues of pyranoses are hardly a conceptually novel class of glycomimetic, but difluorinated analogues possess certain special and potentially useful features. Their conformations can be read from the size of the 1H,1'H-coupling constants, and they can be seen by 19F NMR spectroscopy against the complex chemical background of a cell. Also, the electron-withdrawing effect of the CF2 may help to ensure that hydroxy group pKα values are not perturbed by the change from oxacyle to carbocycle. One role for difluorinated carbocyclic pyranose mimetics could therefore be found in nonreacting analogues of the reactive NDP sugars (X = ONDP) which nature uses as glycosyl donors; such compounds might find application as probes of the important glycosyltransferase enzymes (Scheme 1).

Fluorination approaches to the target compounds would rely on the isolation of a single hydroxy group from an inositol or other cyclitol precursor, oxidation to the ketone level and transformation with DAST, DeoxoFluor, or another nucleophilic fluorinating agent. These approaches are well preceded and successful; however, a different starting material would be required for each target molecule and nucleophilic fluorination is subject to notoriously capricious stereoelectronic effects.

Sinaÿ and co-workers used a strategically different approach to prepare 2 from D-glucose and dibromodifluoromethane (Scheme 2). Key features of the elegant synthesis include the zinc-mediated difluoromethylation of a sugar lactone followed by a Ferrier rearrangement of 1 to secure the carbocycle; ultimately, 2 was delivered in enantiomerically enriched form in 17 steps. We wished to develop a divergent route, which could be used to prepare small libraries of deoxyhexose analogues in which CF2 replaced the pyranose oxygen. The deoxyhexoses (6-deoxy, 2,6-dideoxy, and 2,3,6-trideoxy sugars) appear in many important antibiotic natural products and there is much to learn about the enzymes which catalyse the biosynthesis of NDP deoxysugars, and add them to their aglycones. The proposed route would allow the fluorine atoms to be delivered from a readily available and sustainable starting material, would be concise, and would

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allow a range of alkylation patterns to be selected from a pattern of accessible fragments; the simplest example is shown (Scheme 3).10

The key sequence is the dehydrofluorination/metallation of allyl ether 3 of trifluoroethanol to afford sensitive metalled enol ether 4.11 Addition to an enal 5 would deliver allylic alcohol product 6, which would then undergo an accelerated Claisen rearrangement12 and the (putatively) sensitive α-hydroxy ketone product 7 would be reduced in situ, with isolation and purification only at the diol stage (8 and 9). Because each reaction could be monitored unambiguously by 19F NMR, we were confident that a reproducible sequence would evolve. Ring-closing metathesis (RCM) and dihydroxylation would afford the tetrols, thereby completing the syntheses. A range of substituted allyl trifluoroethyl ethers 3a–d were synthesised in water according to our scalable procedure. Ultra-low temperature conditions (−100 to −90 °C) were required for the next step, though we were able to secure good yields of products by taking care that reactions were stirred as effectively as possible, by using an efficient dip cooler, by carrying out slow additions, and by ensuring good yields of products by taking care that reactions were stirred as effectively as possible, by using an efficient dip cooler, by carrying out slow additions, and by quenching at low temperature (Scheme 4).

Trapping with cinnamaldehyde and α-methylcinnamaldehyde was efficient (by 19F NMR monitoring of aliquots); we selected these aldehydes rather than the more atom-efficient acrolein to facilitate product isolation. Diols 8aa and 9aa proved rather volatile and difficult to characterise fully) and to ensure that RCM regenerated the original benzylidene precatalyst (vide infra). The crude allylic alcohols products were isolated following an aqueous work-up, but not purified; instead they were taken up in chloroform and heated. Rearrangement occurred smoothly, with evaporation of the solvent returning crude α-hydroxy ketone for the reduction step.

The main scale limitation was imposed by the requirement for good stirring and we found that 25 mmole was the approximate upper limit; only a limited number of reactions were carried out at 70 mmole. In our experience, only metallated difluoroenol derivatives in which chelation of the lithium atom, or stabilisation arising from the presence of an electronegative substituent in the α-position are sufficiently stable at −78 °C for practical trapping reactions to be carried out.

Reduction required a second change of solvent. These changes seem inefficient; we were able to rearrange the allylic alcohol in the THF, but several side-products were also formed in this solvent and we preferred to remove the THF fully. Replacing the chloroform with ethanol allows the inexpensive sodium borohydride to be used; we also explored reducing agents which could be used directly in the chlorinated solvents but no advantages accrued. The reported sequence represents the most practical process in our hands. Table 1 lists the isolated yields (over 3 steps) and reduction stereoselectivities.

The anti-stereoselectivity is typical of the reduction of α-hydroxy ketones by hydride reagents,13 in one case (8bc), the molecular structure in the crystal was determined by X-ray methods (Figure 1). The 19F NMR chemical shift (the minor syn-diastereoisomers have the more negative 19F NMR chemical shifts) was also used to assign the absolute configuration of the major product, with the aid of stereochemical correlation with RCM products.14 Diols 8cc (entry 6) are both anti- with respect to the diol function, differing only in the relative configuration at the tertiary allylic centre; the anti- and syn-prefixes refer to the new 1,3-relationship. We have observed this behaviour of crotol ether 3b before. Using α-methylcinnamaldehyde as the electrophile results in a higher anti-selectivity in the reduction step; in these cases (entries 4–6), none of the syn-diol was observed (by 19F NMR spectroscopy) or isolated.

The sequence tolerates various alkylation patterns; products from ether 3a are most relevant to pentose analogues,
action time was extended to 45 minutes. Reactions were run at the relatively low concentration of 25 mM, with significant quantities of side products forming at higher substrate concentrations. The formation of oligomers seems unlikely given the highly substituted styrene terminus present in all these diols, and six-membered-ring formation is usually efficient, so the presence of side products may arise from reopening of the cyclohexene products at high concentration and oligomerisation via Ru alkylidenes which do not lie on the productive RCM pathway. Unfortunately, we were unable to isolate any of the side products observed in the $^{19}$F NMR spectra of the products of concentrated reaction.

Lowering the precatalyst loading further to 0.25 mol% slowed the reactions significantly (48 h to reach 95% conversion for 8ab). The catalyst loading could be cut to 1 mol% with only a moderate lowering in conversion to 93% over the extended time. The diols from $\alpha$-methylcinnamaldehyde 8ac, 8bc, 8cc were considerably less reactive, requiring 44 hours to react completely, even with 5 mol% of 10. Diols 8bb and 9bb required 4 and 5 mol% of precatalyst respectively to reach 100% conversion, consistent with the more hindered initiation site. At a loading of 2 mol%, 8bb only reached 29% conversion after 48 hours. We were confident that the initial cross metathesis would take place on the least substituted terminal alkenyl group (releasing styrene ultimately), so that the difference in the rate of consumption of 8ab and 8ac reflects steric hindrance of RCM by the internal methyl group in 8ac. The higher precatalyst loading required by 8bc represents a slow initial alkylidene transfer and a hindered RCM. We were pleased to note that 8db and 9db were reactive and underwent RCM in good yields, despite the significant steric hindrance to initial alkylidene transfer.

The Ru catalysts appear to be active throughout these extended reactions because product formation regenerates the original benzylidene catalyst 10, rather than the more fragile methylidene released when terminal $\alpha,\omega$-diienes ring-close.

The RCM tolerated a reasonable level of steric hindrance allowing a small library of cyclohexenediols to be prepared (Table 2). The products adhered strongly to Ru residues from the RCM, and sublimination of the diols out of the crude products in the Kugelrohr, followed by minimal column chromatography, provided analytically pure material. Stereochemical assignment was carried out on the basis of precedent; a range of diols had crystallised well and the molecular structures in the crystals had been determined.

We also examined the effect of protecting the diol before RCM by preparing cyclic carbonate 15 from anti-diol 8ab; the RCM was slower than for 8a requiring 39 hours and delivering 16 in only moderate yield (56% based on recovered starting material) (Scheme 6). Cyclic boronate 18 was prepared in 43% yield from 17 via a faster RCM (3 h, complete conversion). While cyclic diol protection freezes a rotatable bond (reducing $\Delta S$ and favouring cycli-

### Table 1 Diols 8 and 9 Prepared

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ether</th>
<th>Enal</th>
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<th>Yield (%)</th>
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<th>Yield (%)</th>
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<td>8aa</td>
<td>11</td>
<td>9aa</td>
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<tr>
<td>2</td>
<td>3a</td>
<td>5b</td>
<td>8ab</td>
<td>57</td>
<td>9ab</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>3b</td>
<td>5b</td>
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<tr>
<td>4</td>
<td>3a</td>
<td>5c</td>
<td>8ac</td>
<td>56</td>
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<td>–</td>
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<tr>
<td>5</td>
<td>3b</td>
<td>5c</td>
<td>8bc</td>
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<td>–</td>
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<tr>
<td>6</td>
<td>3c</td>
<td>5c</td>
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<td>–</td>
<td>syn-8cc</td>
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<tr>
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<td>3d</td>
<td>5b</td>
<td>8db</td>
<td>57</td>
<td>9db</td>
<td>8</td>
</tr>
</tbody>
</table>

$^a$ Isolated purified yield from ether 3 over 3 steps.
$^b$ Product purified directly by crystallisation.
$^c$ Products anti-8cc and syn-8cc are both anti-diols; the prefix refers to the 1,3-relationship with the allylic C-Me.

![Figure 1 ORTEP representation of 8bc](image)

**Figure 1** ORTEP representation of 8bc

while those from 3c and 3d relate to 6-deoxyhexoses and 5-methyl-6-deoxyhexoses (noviose, for example), respectively, and the alkylation pattern in 8cc is found in mycarose. It follows that a wide range of interesting templates is available from this concise sequence.

With the diols in hand, we began to investigate RCM reactions (Scheme 5). Diols derived from 3a have an unhindered terminal alkene, which is a reactive locus for alkylidene transfer.

Diol 8ab was exposed to Grubbs’ second-generation precatalyst 10 at 5 mol%; starting material was consumed rapidly (within 15 min) and precatalyst loading could be lowered to 0.5 mol% with no drop in conversion if the re-

![Scheme 5 RCM of unprotected diols](image)

**Scheme 5** RCM of unprotected diols
sation), the formation of the 5,6-ring fusion may introduce enough strain to slow RCM down.

Dihydroxylation was carried out under either Upjohn 20 [catalytic Os(VIII), NMO reoxidant or stoichiometric Os(VIII)/TMEDA]21 conditions (Table 3). With one exception (23bb), the tetrol products were water-soluble and very difficult to free from osmium residues even from the catalytic procedures, so in most cases, the crude products were peracetylated and purified rigorously. Tertiary hydroxy groups did not acetylate under the conditions used, but tri- and diacetates were purifiable by column chromatography. The yields over two steps range from excellent to poor; our priority here was to secure pure materials, uncontaminated by heavy metal residues and the low yields reflect the rigour of the procedures employed.

The reactions show the anticipated pattern of stereoselectivity with a modest preference for the Kishi22 product under Upjohn conditions, 23 and higher selectivities under stoichiometric conditions, except in the cases of 13 and

| Table 2 Cyclic Diols 11 and 12 Prepared |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Diol            | R1 | R2 | R3 | R4 | % 10 | Time* (h) | Product Yield (%) |
| 8ab             | H  | H  | H  | H  | 0.5 | 0.75     | 11ab 76          |
| 9ab             | H  | H  | H  | H  | 0.5 | 0.75     | 12ab 81          |
| 8bb             | Me | H  | H  | H  | 4   | 30       | 11bb 79          |
| 9bb             | Me | H  | H  | H  | 5   | 48       | 12bb 90          |
| 8ac             | H  | H  | H  | Me | 2.5 | 48       | 11ac 77          |
| 8bc             | Me | H  | H  | Me | 8.5 | 48       | 11bc 81          |
| 8db             | H  | Me | Me | H  | 5   | 5        | 11db 83          |
| 9db             | H  | Me | Me | H  | 5   | 18       | 12db 80          |
| anti-8cc        | H  | H  | Me | Me | 8.5 | 48       | 13 61            |
| syn-8cc         | H  | Me | H  | Me | 8.5 | 48       | 14 20            |

* Time taken for 100% conversion of acyclic diol.

b Yield of isolated purified material.

c An inseparable mixture of diastereoisomers.

Scheme 6 RCM of protected diols. Reagents and conditions: (a) Cl2C=O, pyridine, toluene; (b) PhB(OH)2, THF, then evaporation; (c) 10 (5 mol%), 25 mM in CH2Cl2, reflux (see text).

| Table 3 Compounds 19–25 Prepared |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Diol            | Method* | Major product | dr | Time (h) | Yield (%) |
| 11ab A          | 19ab      | F F OAc        | 5:1 | 7        | 58          |
|                 | B         | F F OAc        | 11:1 | 1.5 | 48          |
| 12ab A          | 21ab      | F F OAc        | 2.5:1 | 24 | 57          |
|                 | B         | F F OAc        | 16:1 | 1.5 | 42          |
| 11bb A          | 23bb      | F F OAc        | 1:0 | 48       | 95          |
| 11ac A          | 19ac      | F F OAc        | 2.2:1 | 48 | 23          |
|                 | B         | F F OAc        | 11:1 | 1.0 | 56          |
| 11bc A          | 19bc      | F F OAc        | 5:1 | 48       | 33          |
| 13 A            | 24        | F F OAc        | 1:0 | 48       | 79          |
|                 | B         | F F OAc        | 1:0 | 1.5 | 42          |
| 14 A            | 25        | F F OAc        | 1:0 | 48       | 41          |

*Method A = OsO4, NMO, r-BuOH, acetone, H2O; Method B = OsO4, TMEDA, CH2Cl2.
In the former case, both sets of conditions led to the formation of the all-cis product (a reversal of the normal Kishi selectivity), while the cis,trans,cis or Kishi product formed exclusively in the latter case. A full discussion of the factors influencing the stereoselectivity of these reactions lies outside the scope of this manuscript but the results for 13 and 14 may be informative. Donohoe noted that an allylic hydroxy group must be equatorial if it is to direct dihydroxylation under the stoichiometric Os(VIII) conditions. If 13b (Figure 2) is the most favoured conformer, the allylic hydroxy is equatorial and should direct effectively, consistent with the exclusive formation of 24. However, 14b looks destabilised by a pseudo-1,3-diaxial repulsion; the axial allylic hydroxy now exerts no influence on the dihydroxylation and both reactions deliver the Kishi product.

Figure 2  Conformation and hydroxy group directing ability

Full 2D assignment of the 1H NMR spectra allowed stereochemical outcomes to be inferred from vicinal 1H and 19F NMR coupling constants, supported by precedent and by stereochemical correlation with molecular structures in the crystal, obtained for 24 and 25 (Figure 3). These structures also confirm the identity of the 8cc diols unambiguously.

Figure 3  ORTEP representations for 24 and 25

Deacetylation was achieved simply and effectively using Mulholland’s conditions (100 wt% Dowex-50, 100 °C, 10 min) to return the tetrols in excellent yields (Table 4). We also dihydroxylated the diol 8ac under Narasaka conditions; the reaction reached completion with a low (0.2 mol%) loading of osmium oxidant and returned a single diastereoisomer 23ac (as a racemic modification), in contrast to the Upjohn which afforded only a 2.2:1 mixture from 8ac (Scheme 7). However, the tetrol product was disappointingly difficult topurify and a low (37%) yield accrued over the two steps and unfortunately, we were unable to generalise this procedure to other diols. The main difficult lay in removing boronic acid residues from the

<p>| Table 4  Tetrols 23, 26, and 27 Prepared |
|-------------------------------|-------------------|------------------|</p>
<table>
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<th>Entry</th>
<th>Precursor</th>
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<th>Yield (%)</th>
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</tr>
<tr>
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<td>26ac</td>
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</tr>
<tr>
<td>5</td>
<td>24</td>
<td>27</td>
<td>75</td>
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</tbody>
</table>

Scheme 7  Dihydroxylation of 8ac. Reagents and conditions: (a) PhB(OH)2, CH2Cl2; (b) OsO4 (0.2 mol%), NMO; (c) H2O2, EtOAc, acetone.

- **Table 4**: Tetrols 23, 26, and 27 Prepared
- **Figure 2**: Conformation and hydroxy group directing ability
- **Figure 3**: ORTEP representations for 24 and 25
- **Scheme 7**: Dihydroxylation of 8ac. Reagents and conditions: (a) PhB(OH)2, CH2Cl2; (b) OsO4 (0.2 mol%), NMO; (c) H2O2, EtOAc, acetone.
tetrol products, which is disappointing given the excellent stereocontrol afforded by these procedures.

The sequences described in this manuscript deliver a range of carbasugars in which CF_2 replaces the pyranose oxygen. The sequences are short and effective; the main limitations arise from the requirement for an ultra-low temperature reaction involving t-BuLi and the formation of racemic products. Subsequent-generation syntheses will be required to challenge these limitations.

NMR spectra were recorded on 300 or 400 MHz spectrometers. ^1H and ^13C NMR spectra were recorded using the deuterated solvent as the lock and the residual solvent as the internal reference. ^19F NMR spectra were recorded relative to chlorotrifluoromethane as the external standard. The appearance of complex signals is indicated by app (apparent). Homocouplings (H-H, F-F) are given in hertz and specified by J; the nuclei involved in heteronuclear couplings are defined with the observed nucleus given first. Unless stated otherwise, all refer to ^1J couplings. Chemical ionisation mass spectra were recorded using ammonia as the reagent gas. GC-MS was carried out on a 30 m m PE-5 column running a 20–350 °C ramp over 27 min. High-resolution mass spectrometry measurements were carried out using peak matching to suitable reference spectra.

Threo-Three Step Diol Synthesis: (1E,3S,4S*)-5,5-Difluoro-1-phenylolita-1,7-diene-3,4-diol (8ab) and (1E,3R,4S*)-5,5-Difluoro-1-phenylolita-1,7-diene-3,4-diol (9ab); Typical Procedure

Note: Checking this reaction sequence at each stage by ^19F NMR of an aliquot is strongly recommended.

Dehydrofluorination/Metallation and Addition: t-BuLi was obtained from Sigma-Aldrich and was used directly for the next step without further purification; R_f = 0.4 (hexanes–EtOAc, 5:2).

IR (film): 3405, 1746, 1670, 1249, 1124, 1071, 969 cm⁻¹.

^1H NMR (300 MHz, CDCl₃): δ = 2.28 (br s, 1 H), 2.76–2.91 (m, 1 H), 5.17–5.26 (m, 2 H), 5.26–5.30 (m, 1 H), 5.69 (dd, J = 16.8, 10.4, 7.2 Hz, 1 H), 6.17 (dddd, J = 15.8, 6.4 Hz, J_{H,F} = 1.3, 0.9 Hz, 1 H), 6.84 (dd, J = 15.8 Hz, J = 1.5 Hz, 1 H), 7.21–7.43 (m, 5 H).

^19F NMR (282 MHz, CDCl₃): δ = -104.3 (dt, J_{F,F} = 273.9 Hz, J_{F,H} = 16.1 Hz, 1 F), -105.5 (dt, J_{F,F} = 273.9 Hz, J_{F,H} = 18.0 Hz, 1 F).

MS (EL, 70 eV): mz (%) = 131 (100), 214 (1), 232 (2), 252 (2, [M⁺]).

Claisen Rearrangement: Crude dienol 6ab (10 mmol) was taken up in CHCl₃ (30 mL). The solution was stirred at 60 °C for 25 min to afford the crude hydroxy ketone 7ab, which was used directly for the next step without further purification; R_f = 0.64 (hexanes–EtOAc, 5:2).

IR (film): 3405, 1746, 1670, 1249, 1124, 1071, 969 cm⁻¹.

^1H NMR (300 MHz, CDCl₃): δ = 2.28 (br s, 1 H), 2.76–2.91 (m, 1 H), 5.17–5.26 (m, 2 H), 5.26–5.30 (m, 1 H), 5.69 (dd, J = 16.8, 10.4, 7.2 Hz, 1 H), 6.17 (dddd, J = 15.8, 6.4 Hz, J_{H,F} = 1.3, 0.9 Hz, 1 H), 6.84 (dd, J = 15.8 Hz, J = 1.5 Hz, 1 H), 7.21–7.43 (m, 5 H).

^19F NMR (282 MHz, CDCl₃): δ = -104.3 (dt, J_{F,F} = 273.9 Hz, J_{F,H} = 16.1 Hz, 1 F), -105.5 (dt, J_{F,F} = 273.9 Hz, J_{F,H} = 18.0 Hz, 1 F).

MS (EL, 70 eV): mz (%) = 131 (100), 214 (1), 232 (2), 252 (2, [M⁺]).

Reduction: NaBH₄ (30.0 mmol, 1.13 g) was added in 3 portions over 30 min at r.t. to a crude solution of the hydroxy ketone 7ab (ca. 10 mmol) in EtOH (30 mL). The suspension was stirred overnight at r.t. The mixture was quenched with conc HCl (4 mL) and concentrated in vacuo. The residue was taken up in brine (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), and concentrated in vacuo to afford a 5:1 mixture of crude diols as a pale yellow solid.

Flash column chromatography (9:1 hexanes–EtOAc) gave the diols 8ab (1.44 g, 57%) and 9ab (0.28 g, 11%) separately as colourless solids.

8ab

Mp 59–60 °C; R_f = 0.4 (hexanes–EtOAc, 3:2).

IR (KBr): 3346, 3245, 1066, 972 cm⁻¹.

^1H NMR (300 MHz, CDCl₃): δ = 2.20 (br s, 1 H), 2.47 (br s, 1 H), 2.60–2.80 (m, 2 H), 3.87 (ddd, J_{H,F} = 16.5, 6.6 Hz, J = 4.3 Hz, 1 H), 4.55 (dd, J = 6.6, 4.3 Hz, 1 H), 5.20–5.30 (m, 2 H), 5.70–5.93 (m, 1 H), 6.37 (ddd, J = 16.0, 6.6 Hz, J = 2.0 Hz, J = 1.3 Hz, 1 H), 6.71 (d, J = 16.0 Hz, 1 H), 7.15–7.34 (m, 5 H).

^13C NMR (75 MHz, CDCl₃): δ = 38.7 (ddd, J_{C,F} = 25.1, 23.3 Hz), 71.7 (ddd, J_{C,F} = 3.0, 1.2 Hz), 74.3 (dd, J_{C,F} = 28.6, 25.0 Hz), 120.8, 122.9 (dd, J_{C,F} = 247.7, 245.3 Hz), 126.5, 126.7, 128.1, 128.6, 128.7, 133.1, 136.2.

^19F NMR (282 MHz, CDCl₃): δ = -106.6 (ddd, J_{F,F} = 252.1 Hz, J_{F,H} = 19.9, 19.9 Hz, 1 F), -108.5 (ddd, J_{F,F} = 252.1 Hz, J_{F,H} = 16.5, 13.4 Hz, 1 F).

MS (EL, 70 eV): mz (%) = 133 (100), 145 (8), 216 (5), 234 (33), 254 (30, [M⁺]).


9ab

Mp 75–77 °C; R_f = 0.56 (hexanes–EtOAc, 3:2).

IR (KBr): 3348, 3240, 1063, 969 cm⁻¹.

^1H NMR (300 MHz, CDCl₃): δ = 2.68–2.87 (m, 3 H), 3.42 (br s, 1 H), 3.69 (dd, J_{H,F} = 18.0, 10.0 Hz, J = 5.4 Hz, 1 H), 4.59–4.68 (m, 1 H), 5.18–5.28 (m, 2 H), 5.81 (ddd, J = 17.0, 10.4, 7.0 Hz, 1 H), 6.25 (dd, J = 15.9, 6.6 Hz, 1 H), 6.65 (dd, J = 15.9 Hz, 1 H), 7.39–7.18 (m, 5 H).

**PAPER**

Diffinuorinated Analogues of Cyclitols and Sugars 3090

1H C NMR (75 MHz, DMSO-d$_6$): $\delta = 38.2$ (dd, $^2J_{CF} = 25.7, 23.3$ Hz), 69.8 (dd, $^2J_{CF} = 3.6, 20.7$ Hz), 73.3 (dd, $^2J_{CF} = 29.9, 25.7$ Hz), 120.8, 123.3 (dd, $^2J_{CF} = 247.5, 245.9$ Hz), 126.7, 127.7, 128.1, 128.7, 128.8 (dd, $^2J_{CF} = 7.8, 3.6$ Hz), 132.4, 136.2.

19F NMR (282 MHz, CDCl$_3$): $\delta = -106.3$ (dddd, $^2J_{CF} = 251.1$ Hz, $^3J_{HF} = 21.8, 19.0, 5.2$ Hz, 1 F), $-110.4$ (dd, $^2J_{CF} = 251.1$ Hz, $^3J_{HF} = 18.0, 12.3$ Hz, 1 F).

MS (EI, 70 eV): $m/z$ (%) = 133 (100), 145 (18), 216 (2), 234 (53), 254 (40, [M]+).

HRMS-EI: $m/z$ calcd for C$_8$H$_8$F$_2$O$_2$ [M + H]+: 254.11184; found: 254.11187.

Anal. Calc. for C$_8$H$_8$F$_2$O$_2$: C, 66.13; H, 6.34. Found: C, 66.26; H, 6.27.

**(1E,3S*,4S*)-5,5-Difluoro-7-methyl-1-phenylocta-1,7-diene-3,4-diol (8bb) and (1E,3S*,4S*)-5,5-Difluoro-7-methyl-1-phenylocta-1,7-diene-3,4-diol (9bb)**

8bb: From ether 3b (11 mmol, 1.75 g) and cinnamaldehyde (5b; 10 mmol, 1.34 g).

1H NMR (400 MHz, CDCl$_3$): $\delta = 2.63–2.84$ (m, 2 H), 3.96 (dt, 3 H, $J = 6.5, 2.0$ Hz, 1 H), 4.93–4.96 (m, 1 H), 5.00–5.03 (m, 1 H), 6.27 (dd, $^2J = 15.8, 6.5$ Hz, 1 H), 6.72 (dd, $J = 15.8, 5.7$ Hz, 1 H), 7.23–7.41 (m, 5 H),

13C NMR (100.6 MHz, CDCl$_3$): $\delta = 23.6$ (dd, $^2J_{CF} = 2.4, 1.6$ Hz, 1 H), 41.3 (dd, $^2J_{CF} = 24.8, 22.4$ Hz), 69.6 (dd, $^2J_{CF} = 4.0, 1.6$ Hz), 73.4 (dd, $^2J_{CF} = 31.2, 24.8$ Hz), 117.0, 123.8 (t, $^2J_{CF} = 248.5$ Hz), 126.6, 127.7, 128.0, 128.6, 132.4, 136.2, 137.5 (d, $^2J_{CF} = 6.4$ Hz).

IR (KBr): 3364, 3279, 1449, 1193, 1059 cm$^{-1}$.

HRMS-EI: $m/z$ calcd for C$_8$H$_8$F$_2$O$_2$ [M + H]+: 254.11187; found: 254.11187.

**8ac**: From ether 3a (11 mmol, 1.75 g) and $\alpha$-methylenecyclomaldehyde (5c; 10 mmol, 1.49 g).

1H NMR (282 MHz, CDCl$_3$): $\delta = -99.1$ (dt, $^2J_{CF} = 69.0$ Hz, $^3J_{HF} = 1.6$ Hz, 1 F), $-109.9$ (dd, $^2J_{CF} = 69.0$ Hz, $^3J_{HF} = 3.3$ Hz, 1 F).

7bc: Crude dienol 6bb (10 mmol) was taken up in CHCl$_3$ (30 mL). The solution was stirred at 60 °C for 150 min to afford the hydroxy ketone 7bb.

19F NMR (282 MHz, CDCl$_3$): $\delta = -102.6$ (dt, $^2J_{CF} = 272.0$ Hz, $^3J_{HF} = 16.6$ Hz, 1 F), $-103.6$ (dt, $^2J_{CF} = 272.0$ Hz, $^3J_{HF} = 18.5$, 1 F).

8bb and 9bb: The crude hydroxy ketone 7bb (10 mmol) was reduced directly without further purification to afford diols 8bb (1.34 g, 48%) and 9bb (0.12 g, 4%) after flash column chromatography (hexanes–EtOAc, 4:1).

**8bb**

Mp 86–87 °C; $R_f = 0.44$ (hexanes–EtOAc).

IR (KBr): 3408, 3215, 1449, 1193, 1059 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta = 1.84$ (s, 3 H), 2.23 (br s, 1 H), 2.48 (br s, 1 H), 2.63–2.84 (m, 2 H), 3.96 (dd, $^2J_{HF} = 17.6$ Hz, $^3J_{HF} = 4.3$ Hz, 1 H), 4.65 (dddd, $^2J = 6.5, 4.3$ Hz, $^3J_{HF} = 1.2$, 0.5 Hz, 1 H), 4.91–4.93 (m, 1 H), 4.99–5.02 (m, 1 H), 6.37 (dddd, $^2J = 16.0, 6.5$ Hz, $^3J_{HF} = 2.0$, 1.2 Hz, 1 H), 6.73 (dd, $^2J = 16.0$, $^3J_{HF} = 0.8$ Hz, 1 H), 7.23–7.42 (m, 5 H).

**9bb**

Mp 87–89 °C; $R_f = 0.6$ (hexanes–EtOAc, 3:2).

IR (KBr): 3408, 3215, 1449, 1118, 1062 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta = 1.85$ (s, 3 H), 2.21 (br s, 1 H), 2.66–2.87 (m, 2 H), 2.99 (br s, 1 H), 3.70 (dd, $^2J_{HF} = 19.2$ Hz, 1 H), 4.73 (ddd, $^2J = 6.5$, $^3J_{HF} = 1.2$ Hz, 1 H).

8ec: The crude hydroxy ketone 7ec (10 mmol) was reduced directly without further purification to afford after column chromatography (hexanes–EtOAc, 5:1) an inseparable 3:1 mixture of diols anti-8ec and syn-8ec as a white solid (2.2 g, 78% over 3 steps); mp 71–73 °C; Rf = 0.62 (hexanes–EtOAc, 3:2).

IR (KBr): 3587, 3404, 1183, 1017, 977 cm⁻¹.

1H NMR (300 MHz, CDCl₃); δ (major diastereoisomer) = 1.21 (d, J = 7.2 Hz, 3 H), 1.95 (d, J = 1.4 Hz, 3 H), 2.12 (br, s, 2 H), 2.96–3.18 (m, 1 H), 3.88–4.05 (m, 1 H), 4.49 (d, J = 7.2, 0.9 Hz, 1 H), 5.17–5.31 (m, 2 H), 5.99 (d, J = 17.1, 10.5, 8.0 Hz, 1 H), 6.58 (br s, 1 H), 7.19–7.38 (m, 5 H); δ (minor diastereoisomer) = 1.18 (d, J = 7.2 Hz, 3 H), 1.94 (d, J = 1.4 Hz, 3 H, 1 H), 1.99 (br s, 2 H), 2.96–3.18 (m, 1 H), 3.88–4.05 (m, 1 H), 4.51 (d, J = 7.0, 0.7 Hz, 1 H), 5.17–5.31 (m, 2 H), 5.82 (d, J = 17.2, 10.2, 8.8 Hz, 1 H), 6.58 (br s, 1 H), 7.19–7.38 (m, 5 H).

13C NMR (75 MHz, CDCl₃); δ (major diastereoisomer) = 13.5, 13.7 (dd, J = 6.0, 4.8 Hz), 42.1 (t, J = 23.0 Hz), 71.2 (dd, J₁C₁ = 28.1, 24.5 Hz, C-4), 77.15 (t, J = 24.5 Hz), 118.1, 124.6 (dd, J₁C₁ = 250.1 Hz), 127.1, 128.3, 129.2, 129.7, 135.7 (dd, J = 5.4 Hz, J₁C₁), 136.7; δ (minor diastereoisomer) = 12.6 (t, J₁C₁ = 5.4 Hz), 137.4, 42.2 (dd, J₁C₁ = 23.9, 22.7 Hz), 71.0 (dd, J₁C₁ = 28.1, 25.7 Hz), 77.15 (t, J = 24.5 Hz), 118.4, 124.7 (dd, J₁C₁ = 235.2, 250.1 Hz), 127.0, 128.3, 129.2, 129.5, 136.4 (dd, J₁C₁ = 6.6, 4.2 Hz), 136.6, 136.8.

IR (KBr): 3658, 3527, 2927, 1716, 1597, 1464, 1363, 1161, 793 cm⁻¹.

MS (ES-MS, 70 eV); m/z (%) = 129 (82), 147 (100), 244 (22), 262 (20), 285 (5, [M⁺]).

HRMS-El: m/z calculated for C₁₉H₁₇F₂O₂ [M⁺]: 282.13414; found: 282.13430.


Crystal Structure

C₂₁H₂₁F₂O₂, crystal size 0.25 × 0.21 × 0.10 mm, M = 282.32, crystalline system monoclinic, cell unit dimensions a = 29.670(6), b = 5.2539(11), c = 9.158(2) Å, α = 90°, β = 95.393(4)°, γ = 90°, U = 1416.4(5) Å³, T = 150(2) K, space group P2₁/c, absorption coefficient μ (Mo-Kα) = 0.103 mm⁻¹, 8200 reflections collected 2030 unique [R(int) = 0.0332], which were used in all calculations. Final R indices [I > 2σ(I)] R1 = 0.0409, wR2 = 0.0997; R indices (all data) R1 = 0.0463, wR2 = 0.1032.

(1E,3S*,4S*,8S*)-5,5-Difluoro-6,6-dimethyl-1-phenyl-1,7-diene-3,4-diol (8db) and (1E,3S*,4S*,6R*)-5,5-Difluoro-6,6-dimethyl-1-phenyl-1,7-diene-3,4-diol (8hd) from ether 3d (5.5 mmol, 1.00 g) and cinnamaldehyde (5b; 5.6 mmol, 0.74 g).

19F NMR (282 MHz, CDCl₃); δ = −100.4 (d, J₁F₁ = 70.1 Hz, 1 F), −111.6 (dd, J₁F₁ = 70.1 Hz, J₁F₂ = 3.3 Hz, 1 F).

7db: Crude dienol 6db (10 mmol) was taken up in CHCl₃ (30 mL). The solution was stirred at 60 °C for 150 min to afford the hydroxy ketone 7db.

[1H]¹⁹F NMR (282 MHz, CDCl₃); δ = −111.6 (d, J₁F₁ = 264.0 Hz, 1 F), −115.2 (d, J₁F₁ = 264.0 Hz, 1 F).

The crude hydroxy ketone 7db (5.6 mmol) was reduced directly without further purification to afford, after flash column chromatography (5:1 hexanes–EtOAc) diols 8db (0.89 g, 57%) and 9db (0.13 g, 8%).

8db

Mp 61–62 °C; Rf = 0.49 (hexanes–EtOAc, 3:2).

IR (KBr): 3453, 3389, 1066, 966 cm⁻¹.

1H NMR (400 MHz, CDCl₃); δ = 1.21 (s, 3 H), 1.23 (s, 3 H), 2.39 (br s, 2 H), 4.15 (dd, J₁F₁ = 22.1, 15.4 Hz, J = 2.2 Hz, 1 H), 4.65 (s, 1 H), 5.17 (dd, J = 10.7 Hz, J₁F₁ = 0.9 Hz, 1 H), 5.20 (d, J = 17.5 Hz, 1 H), 6.01 (dd, J = 17.5, 10.7 Hz, 1 H), 6.38 (dd, J₁F₁ = 16.1, 5.6 Hz, J = 2.8 Hz, J₁F₂ = 1.3 Hz, 1 H), 6.71 (dd, J = 16.1 Hz, J₁F₁ = 0.9 Hz, 1 H), 7.21–7.42 (m, 5 H).

13C NMR (75 MHz, CDCl₃); δ = 21.0 (dd, J₁C₁ = 5.4, 3.6 Hz), 21.5 (t, J₁C₂ = 4.8 Hz), 44.4 (t, J₁C₂ = 22.3 Hz), 71.6 (d, J₁C₁ = 5.4 Hz), 73.1 (d, J₁C₂ = 31.7, 22.1 Hz), 115.1, 123.7 (dd, J₁C₁ = 257.9, 251.3 Hz), 126.6 (dd, J₁C₂ = 24.2, 1.2 Hz), 128.0, 126.8, 132.6, 128.7, 136.6, 141.2 (t, J₁C₁ = 4.2 Hz).

19F NMR (282 MHz, CDCl₃); δ = −113.3 (d, J₁F₁ = 256.8 Hz, 1 F), −121.9 (dd, J₁F₁ = 256.8 Hz, J₁F₂ = 22.1 Hz, 1 F).

MS (ES-MS); m/z (%) = 133 (100), 262 (21), 282 (6, [M⁺]).

HRMS-El: m/z calculated for C₁₉H₁₇F₂O₂ [M⁺]: 282.13414; found: 282.13451.
9db

Mp 68–70 °C; Rf = 0.67 (hexanes–EtOAc, 3:2).

IR (KBr): 3562, 3409, 1046 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.23 (s, 3 H), 1.26 (s, 3 H), 2.24 (br s, 1 H), 2.93 (br s, 1 H), 3.86 (dd, J₁,F = 23.5, 9.4 Hz, 1 H), 4.78 (d, J = 6.4 Hz, 1 H), 5.17 (d, J = 10.8 Hz, 1 H), 5.18 (d, J = 17.5 Hz, 1 H), 6.06 (dd, J = 17.5, 10.8 Hz, 1 H), 6.27 (ddd, J = 15.9, 6.4 Hz, J' = 0.9 Hz, 1 H), 6.70 (dd, J = 15.9 Hz, J' = 0.7 Hz, 1 H), 7.21–7.42 (m, 5 H). No H⁻⁻H coupling constant was visible in the 1H NMR spectrum.

13C NMR (75 MHz, CDCl₃): δ = 21.0 (dd, J₁,C-F = 4.8 Hz, 21.7 (t, J₁,C = 4.8 Hz), 44.3 (t, J₂,C-F = 22.3 Hz), 70.3 (dd, J₁,C-F = 5.4, 1.2 Hz), 72.7 (dd, J₂,C = 33.5, 22.7 Hz), 114.8, 124.5 (dd, J₁,C-F = 258.5, 251.3 Hz), 126.7, 127.9, 128.1, 128.7, 132.3, 136.4, 141.4 (t, J₁,C-F = 4.2 Hz).

19F NMR (282 MHz, CDCl₃): δ = −111.6 (dd, J₁,F = 253.5 Hz, 1 F), −123.8 (dd, J₁,F = 253.5 Hz, 1 F), −21.7 (dd, J₁,F = 23.7 Hz, 1 F).

HRMS-EI: m/z calc'd for C₁₀H₁₉F₂O₂ [M⁺]: 282.14314; found: 282.14309.


(4S*,5S*)-4-[(1,1-Difluorobut-3-enyl)-5-[(E)-2′-phenylvinyl]-1,3-dioxolane-2-one (15)
Phosgene (6.5 mmol, 3.25 mL of a 2.0 M solution in toluene) was added at 0 °C to a solution of the diol 8ab (4.3 mmol, 1.1 g) and pyridine (26.0 mmol, 2.1 mL) in toluene (40 mL). The mixture was stirred at 0 °C for 60 min, then was washed successively with H₂O (20 mL), aq 5% citric acid (20 mL) and aq sat. Na₂CO₃ (20 mL). The combined organic extracts were dried (MgSO₄) and concentrated to afford the cyclic diol 15 in 65% yield as a colourless oil (mp 80–82 °C; from diol 9ab). 9ab

1H NMR (300 MHz, CDCl₃): δ = 2.74–2.88 (m, 2 H), 4.77 (ddd, J₁,F = 21.0 Hz, J = 8.3 Hz, J' = 3.3 Hz, 1 H), 5.26–5.35 (m, 2 H), 5.43 (1 H, t, J = 8.3 Hz), 5.76 (dd, 1 H, J = 18.0, 9.2 Hz), 6.39 (ddt, 1 H, J = 15.8, 8.3 Hz, J₁,F = 3.1 Hz), 6.80 (d, J₁,F = 15.8 Hz, 1 H), 7.29–7.45 (SH, m).

IR (film): 1807, 1347, 1074, 967 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 2.74–2.88 (m, 2 H), 4.77 (ddd, J₁,F = 21.0 Hz, J = 8.3 Hz, J' = 3.3 Hz, 1 H), 5.26–5.35 (m, 2 H), 5.43 (1 H, t, J = 8.3 Hz), 5.76 (dd, 1 H, J = 18.0, 9.2 Hz), 6.39 (ddt, 1 H, J = 15.8, 8.3 Hz, J₁,F = 3.1 Hz), 6.80 (d, J₁,F = 15.8 Hz, 1 H), 7.29–7.45 (SH, m).

Anal. Caled for C₂₀H₁₉BF₂O₂: C, 66.50; H, 4.98; F, 14.08. Found: C, 66.50; H, 5.00; F, 14.08.

HRMS-EI: m/z calc'd for C₂₀H₁₉BF₂O₂ [M⁺]: 454.16354; found: 454.16267.

Difluorinated Analogues of Cyclitols and Sugars

1H NMR (125 MHz, CDCl3; δ = 1.12 (3H, s)), 3.35 (2H, s), 4.02 (2H, d, J = 6.2 Hz), 6.78 (2H, d, J = 9.2 Hz) affording the cyclic diols 10ac (0.351 g, 77%) as an oil; Rf = 0.37 (hexanes–EtOAc, 3:2).

IR (KBr): 3516, 3307, 1595, 1475, 1381, 1238, 1094 cm⁻¹. 13C NMR (100 MHz, CDCl3; δ = 13.1 (3H, s), 35.9 (2H, s), 140.7 (1H, d, J = 18.7 Hz), 157.3 (1H, s)). HRMS-EI: m/z calc for C6H10F2O2 [M⁺]: 150.04926; found: 150.04927.


(1S,2S*)-6,6-Difluoro-3,5-dimethylcyclohex-3-ene-1,2-diol (11ac)

From diol 10ac (2.8 mmol, 745 mg), purified by Kugelrohr (bp 65 °C/0.025 mmHg), then column chromatography (hexanes–EtOAc, 3:2) affording 11ac (0.351 g, 77%) as an oil; Rf = 0.37 (hexanes–EtOAc, 3:2).
Hz, 3 H), 2.53–2.69 (m, 1 H), 3.03 (br s, 1 H), 3.88 (dddd, 3 J = 10.2 Hz, 5 J = 7.3 Hz, 3 H), 4.08 (dddd, J = 10.7, 5.2, 4.7 Hz, 1 H), 5.24–5.29 (m, 1 H).

13C NMR (75 MHz, CDCl3): δ = 12.3 (d, JCF = 7.2, 12.2 Hz, 1 H), 20.4 (d, JCF = 1.2 Hz, 1 H), 57.13 (d, JCF = 4.8 Hz, 37.6 (t, JCF = 23.9 Hz, 70.0 (t, JCF = 20.0 Hz), 122.2 (dd, JCF = 247.7, 243.5 Hz), 127.0 (d, JCF = 9.3 Hz), 133.5 (d, JCF = 2.0 Hz).

19F NMR (282 MHz, CDCl3): δ = -114.2 (dd, JCF = 244.5 Hz, JCF = 0.0 Hz, 1 F), 4.80 (dd, JCF = 244.5 Hz, JCF = 25.9, 20.9 Hz, 4 JCF = 4.2, 0.9 Hz, 1 F).

MS (EL 70 eV): m/z (%) = 86 (100), 97 (14), 143 (6), 160 (1), 163 (4), 178 (3, [M]+).


(3aS*,7aS*)-4,4-Difluoro-3a,4,5,7a-tetrahydro-1,3-benzodioxol-2-one (16)

From diol 18 (0.7 mmol, 199 mg), purified by column chromatography (hexanes–EtOAc, 1:4) affording 16 (150 mg, 55%, 57% based on recovered starting material, 98% by GC) as a pale yellow oil: Rf = 0.44 (hexanes–EtOAc, 4:1).

IR (film): 1796, 1347, 1074 cm–1.

HRMS-EI: m/z (%) = 172 (100), 236 (37, [M]+).

HRMS-EL: m/z calc'd for C12H11BF2O2 [M]+: 236.08202; found: 236.08210.

Anal. Calcd for C12H11BF2O2: C, 47.60; H, 3.8.

(3aS*,7aS*)-4,4-Difluoro-2-phenyl-3a,4,5,7a-tetrahydro-1,3,2-benzodioxaborole (18)

From cyclic boronate 17 (0.12 mmol, 41 mg), purified by column chromatography (hexanes–EtOAc, 4:1) affording 18 (12 mg, 43%) as a colourless oil: Rf = 0.05 (hexanes–EtOAc, 3:1).

IR (film): 1815, 1359, 1213, 1084 cm–1.

HRMS-EI: m/z (%) = 172 (100), 236 (37, [M]+).


(15a,2R*)-6,6-Difluoro-5,5-dimethylcyclohex-3-ene-1,2-diol (11b)

From diol 9db (0.12 mmol, 350 mg), purified by column chromatography (hexanes–EtOAc, 3:2) affording 11b (103 mg, 83%) as a colourless solid; mp 70–71 °C; Rf = 0.34 (hexanes–EtOAc, 3:2).

IR (KBr): 3351, 3233, 1475, 1083 cm–1.

HRMS-EI: m/z (%) = 86 (100), 97 (14), 143 (6), 160 (1), 163 (4), 178 (31, [M]+).


(3aS*,7aS*)-4,4-Difluoro-3a,4,5,7a-tetrahydro-1,3-benzodioxol-2-one (16)

From diol 18 (0.7 mmol, 199 mg), purified by column chromatography (hexanes–EtOAc, 1:4) affording 16 (150 mg, 55%, 57% based on recovered starting material, 98% by GC) as a pale yellow oil: Rf = 0.44 (hexanes–EtOAc, 4:1).

IR (film): 1796, 1347, 1074 cm–1.

HRMS-EI: m/z (%) = 172 (100), 236 (37, [M]+).

HRMS-EL: m/z calc'd for C12H11BF2O2 [M]+: 236.08202; found: 236.08210.

Anal. Calcd for C12H11BF2O2: C, 47.60; H, 3.8.

(3aS*,7aS*)-4,4-Difluoro-2-phenyl-3a,4,5,7a-tetrahydro-1,3,2-benzodioxaborole (18)

From cyclic boronate 17 (0.12 mmol, 41 mg), purified by column chromatography (hexanes–EtOAc, 4:1) affording 18 (12 mg, 43%) as a colourless oil: Rf = 0.05 (hexanes–EtOAc, 3:1).

IR (film): 1815, 1359, 1213, 1084 cm–1.

HRMS-EI: m/z (%) = 172 (100), 236 (37, [M]+).


19ab

Mp 121–122 °C; Rf = 0.39 (hexanes–EtOAc, 3:2).

IR (KBr): 1743, 1370, 1218, 1181, 1028 cm–1.  
1H NMR (400 MHz, CDCl3): δ = 2.05, 2.07, 2.09, 2.15 (4 s, 3 H each), 2.35–2.45 (m, 2 H), 5.22 (dd, J = 9.2, 3.3 Hz, 1 H), 5.40–5.47 (m, 2 H), 5.53 (JHF = 7.6 Hz, JHF = 3.2 Hz, 1 H).

13C NMR (100.6 MHz, CDCl3): δ = 20.6, 20.7, 20.9, 32.8 (t, JCF = 23.5 Hz), 65.3 (t, JCF = 5.4 Hz), 67.0 (t, JCF = 3.0 Hz, JCF = 6.9 Hz), 67.6 (t, JCF = 28.3 Hz), 118.7 (t, JCF = 248.5 Hz), 169.1, 169.5, 169.9, 170.1.

19F NMR (376.5 MHz, CDCl3, 328 K): δ = −100.1 (dt, JFF = 266.8 Hz, JHF = 17.8 Hz, 1 F), −102.9 to −104.5 (m, incl. app d d JFF = 266.8 Hz, 1 F).

MS (EI, 70 eV); m/z (%) = 190 (100), 232 (70), 250 (21), 268 (7), 268, 268, 273, 293 (4), 310 (18), 352 (10, [M]+*).

HRMS-EI: m/z calc for C14H18F2O8 [M]+: 352.09679; found: 352.09671.

Anal. Calcd for C14H18F2O8: C, 47.73; H, 5.15. Found: C, 47.80; H, 4.93.

20ab

Rf = 0.32 (hexanes–EtOAc, 3:2).

IR (film): 1739, 1368, 1215, 1182, 1031 cm–1.  
1H NMR (400 MHz, CDCl3): δ = 2.05, 2.07, 2.10, 2.16 (4 s, 3 H each), 2.25–2.35 (m, 1 H), 2.54 (dddd, JHF = 30.8 Hz, JHF = 13.2 Hz, JHF = 5.3 Hz, JHF = 1 H), 5.09 (dd, JHF = 12.2, 4.8, 3.1 Hz), JHF = 0.4 Hz, 1 H), 5.15 (td, JHF = 3.1 Hz, JHF = 1.3 Hz, 1 H), 5.43–5.48 (m, 1 H), 5.55 (t, JHF = 3.1 Hz, 1 H).

13C NMR (100.6 MHz, CDCl3): δ = 20.5, 20.6, 20.7, 20.8, 30.8 (t, JCF = 23.2 Hz), 65.6 (dd, JCF = 13.2, 5.4 Hz), 66.3 (dd, JCF = 9.6, 1.8 Hz), 67.6, 68.9 (dd, JCF = 36.8, 24.1 Hz), 119.1 (dd, JCF = 255.6, 240.5 Hz), 169.1, 169.2, 169.5, 170.0.

19F NMR (376.5 MHz, CDCl3): δ = −102.9 (dddd, JFF = 266.8 Hz, JFF = 30.8, 9.5, 5.3 Hz, JHF = 1.3 Hz, 1 F), −101.9 (ddd, JFF = 266.8 Hz, JHF = 12.3, 6.6 Hz, 1 F).

MS (EL, 70 eV); m/z (%) = 131 (100), 140 (84), 232 (41), 250 (45), 268 (8), 293 (7), 310 (36), 352 (3, [M]+*).

HRMS-EI: m/z calc for C14H18F2O8 [M + H]+: 352.09697; found: 352.09694.

(1R,2R,3S,4S*)-5,5-Difluoro-2,3,4-tri(acetoxyl)cyclohex-1-yl Acetate (19ab) and (1S*,2S*,3R*,4S*)-5,5-Difluoro-2,3,4-tri(acetoxyl)cyclohex-1-yl Acetate (20ab); Typical Upjohn/Peracetylation Procedure

OsO4 (68 μL of a 2.5 wt% solution in t-BuOH, 6.7 μmol, 2 mol%) was added to a solution of diol 11ab (0.33 mmol, 50.0 mg) and NMO·H2O (0.67 mmol, 92.8 mg, 2.0 equiv) in a mixture of acetone (0.3 mL), H2O (0.3 mL), and t-BuOH (0.15 mL) precooled to 0 °C. The mixture was stirred at rt for 7 h, then quenched with Na2SO4 (100 mg) and stirred for a further 3 h. The mixture was filtered through Celite; the solid residue was washed at the pump with MeOH (15 mL) and the filtrate and washings were concentrated in vacuo to leave a black oil. The residue was taken up in pyridine (2 mL) and Ac2O (2.0 mmol, 0.2 mL) was added. The mixture was stirred overnight at rt. The solution was concentrated in vacuo to leave a black solid. The residue was taken up in acq 5% HCl (10 mL), then extracted with CH2Cl2 (3 × 10 mL). The combined organic extracts were washed with acq sat. K2CO3 (15 mL) and brine (15 mL), dried (MgSO4), and concentrated in vacuo to deliver the crude tetraacetates as a (5:1) mixture of diastereoisomers affording 19ab (56 mg, 48%) and 20ab (11 mg, 10%) after flash chromatography (hexanes–EtOAc, 2:1).

Peracetylation Procedure

NMO·H2O (0.67 mmol, 92.8 mg, 2.0 equiv) in a mixture of acetone (6.7 mL) and Ac2O (2.0 mmol, 0.2 mL) was added. The mixture was stirred overnight at rt. The solution was concentrated in vacuo to leave a black solid. The residue was taken up in acq 5% HCl (10 mL), then extracted with CH2Cl2 (3 × 10 mL). The combined organic extracts were washed with acq sat. K2CO3 (20 mL) and brine (20 mL), dried (MgSO4), and concentrated in vacuo to deliver the crude tetraacetates as a (1:11) mixture of diastereoisomers affording 19ab (6 mg, 4%) and 20ab (66 mg, 44%) after flash chromatography (hexanes–EtOAc, 2:1). The data were in agreement with those reported above.

Abstract

A freshly prepared solution of OsO4 (0.44 mmol, 113 mg, 1.05 equiv) in CH2Cl2 (1 mL) was added to a solution of diol 11ab (0.42 mmol, 63.4 mg) and TMEDA (0.465 mmol, 70 μL, 1.1 equiv) in CH2Cl2 (42.2 mL, 0.01 M) at −78 °C. The solution rapidly turned deep red and then brown-black. The solution was stirred until the starting material was consumed (by TLC, ca. 1.25 h) before being allowed to warm to rt. The solvent was removed in vacuo and the residue was taken up in THF (15 mL) andaq Na2SO4 (sat, 15 mL). This mixture was heated at reflux for 3 h and the product filtered through Celite. The filter bed was washed with MeOH (40 mL) and the combined initial filtrate and washings were concentrated in vacuo to leave a black oil. The residue was taken up in pyridine (2 mL) and Ac2O (4.2 mmol, 0.4 mL) was added, then the mixture was stirred overnight at rt, then concentrated in vacuo to leave a black solid. The residue was taken up in acq 5% HCl (10 mL), then extracted with CH2Cl2 (3 × 15 mL). The combined organic extracts were washed with acq sat. K2CO3 (20 mL) and brine (20 mL), dried (MgSO4), and concentrated in vacuo to deliver the crude tetraacetates as a (1:11) mixture of diastereoisomers affording 19ab (6 mg, 4%) and 20ab (66 mg, 44%) after flash chromatography (hexanes–EtOAc, 2:1).

Acknowledgments

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From diol 11ac (0.38 mmol, 63.5 mg) via Upjohn procedure afford-
ing the triacetates 19ac (19 mg, 16%) and 20ac (8 mg, 7%) after flash chromatography (hexanes–EtOAc, 3:2).

**19ac**

Mp 134–136 °C; Rf = 0.32 (hexanes–EtOAc, 3:2).

IR (KBr): 3478, 3387, 1743, 1318, 1225, 1017 cm–1.

1H NMR (400 MHz, CDCl3): δ = 1.24 (s, 3 H), 2.09, 2.13, 2.14 (3 s, 3 H each), 2.28–2.53 (m, 3 H), 5.11 (dd, J = 11.2, 1.5, 1 H), 5.30 (dd, J_H2 = 5.3 Hz, J = 3.9 Hz, J_H2 = 0.8 Hz, 1 H), 5.53 (dd, J_H2 = 21.3, 5.3 Hz, J = 3.9 Hz, 1 H).

13C NMR (100.6 MHz, CDCl3): C-F = 20.8 Hz, 69.0 (dd, J_CF = 24.8 Hz, 1 F), 110.6 (dd, J_CF = 4.7 Hz, 1 F), 174.6 (1 F).

MS (FAB+, 70 eV): m/z calc for C_{14}H_{21}F_2O_7: 296.10721; found: 296.10714.

HRMS-FAB+: m/z calc for C_{14}H_{19}F_2O_7 [M + H]^+: 325.10480; found: 325.10478.

HRMS-EI: m/z = 87 (100), 113 (78), 156 (72), 176 (25), 194 (17), 216 (8), 236 (4), 254 (3), 296 (1, [M]+*).

HRMS-El cals for C_{14}H_{19}F2O7 [M]: 296.10715; found: 296.10714.

Anal. Caled for C_{14}H_{19}F_2O_7: C, 48.15; H, 5.59. Found: C, 48.10; H, 5.70.

20bc

Mp 142–144 °C; Rf = 0.10 (hexanes–EtOAc, 3:2).

IR (KBr): 3478, 3387, 1743, 1318, 1225, 1017 cm–1.

1H NMR (400 MHz, CDCl3): δ = 1.27–1.29 (m, 6 H), 2.13–2.15 (m, 6 H), 2.08–2.22 (m, 1 H), 2.48 (dd, J_H2 = 31.3 Hz, J = 14.9 Hz, 1 H), 3.02 (br s, 2 H), 5.21 (dd, J = 3.9 Hz, J_H2 = 1.6 Hz, 1 H), 5.32–5.40 (m, 1 H).

13C NMR (100.6 MHz, CDCl3): C-F = 2.4 Hz, 68.9 (dd, J_CF = 26.8 Hz, 1 F), 104.2–105.1 (m, J_F = 254.6 Hz, 1 F), 104.2–105.1 (m, J_F = 254.6 Hz, 1 F); δ (minor conformer) = –101.3 (d, J_F = 256.3 Hz, 1 F); δ (minor conformer) = –101.3 (d, J_F = 265.3 Hz, 1 F), 172.5 (t, J_CF = 3.2 Hz), 73.3 (t, J_CF = 4.8 Hz), 75.2, 119.2 (dd, J_CF = 250.1, 245.3 Hz), 169.5, 170.4.


**19bc**

Mp 116–118 °C; Rf = 0.19 (hexanes–EtOAc, 3:2).

IR (KBr): 3468, 3431, 1704, 1325, 1217, 1021 cm–1.

1H NMR (400 MHz, CDCl3): δ = 1.28 (s, 3 H), 1.38 (s, 3 H), 2.10 (s, 3 H), 2.18–2.41 (m, 2 H), 2.57 (br s, 1 H), 2.90 (br s, 1 H), 5.38 (t, J_H2 = 3.9 Hz, J = 3.9 Hz, 1 H), 5.48–5.58 (m, 1 H).
The stereochemistry and identity of 25 were confirmed by XRD analysis: C14H20F2O7, crystal size 0.26 x 0.16 x 0.12 mm, M = 338.30, crystal system monoclinic, unit cell dimensions a = 20.454(5), b = 8.329(2), c = 9.502(3) Å, β = 90°, β = 101.455(4)°, γ = 90°, U = 1586.4(7) Å³, T = 150(2) K, space group P2(1)/c, absorption coefficient μ (Mo-Kα) = 0.121 mm⁻¹, 11017 reflections collected 2787 unique [R(int) = 0.0588], which were used in all calculations. Final R indices [I > 2σ(I)] R1 = 0.0488, wR2 = 0.1086; R indices (all data) R1 = 0.0685, wR2 = 0.1172.

(15R,25S,3R,4S*,6R*)-5,5-Difluoro-2,6-dimethyl-1,3,4-triacyclohexanol-2-ol (25)

From diol 14 (0.16 mmol, 29 mg) via Upjohn procedure affording 25 (22 mg, 41% over 2 steps) after flash chromatography (hexanes–EtOAc, 3:2) as colourless plates; mp 124–125 °C; found: C 73 (100), 128 (7), 144 (5), 166 (2, [M – H2O]+).

HRMS-FAB+: m/z calcd for C14H20F2O7 [M + H]+: 339.1255; found: 339.1242.

Anal. Calcd for C14H20F2O7: C, 49.70; H, 5.96. Found: C, 49.78; H, 5.92.

X-ray Crystal Structure

The stereochemistry and identity of 25 were confirmed by XRD analysis: C14H20F2O7, crystal size 0.26 x 0.16 x 0.12 mm, M = 338.30, crystal system monoclinic, unit cell dimensions a = 20.454(5), b = 8.329(2), c = 9.502(3) Å, β = 90°, β = 101.455(4)°, γ = 90°, U = 1586.4(7) Å³, T = 150(2) K, space group P2(1)/c, absorption coefficient μ (Mo-Kα) = 0.121 mm⁻¹, 11017 reflections collected 2787 unique [R(int) = 0.0588], which were used in all calculations. Final R indices [I > 2σ(I)] R1 = 0.0488, wR2 = 0.1086; R indices (all data) R1 = 0.0685, wR2 = 0.1172.
(1R,2R,3S,4S)-5,5-Difluoro-2-methylcyclohexane-1,2,3,4-tetrol (23ac)

From 19ac (48 mmol, 17 mg) affording 23ac (9.9 mg, 95%, 100% by GC) as a colourless solid; mp 57–59 °C; Rf = 0.32 (EtOAc).

IR (KBr): 3503, 3335, 1289, 1029, 1021 cm⁻¹.

1H NMR (400 MHz, CD3OD): δ = 1.16 (d, J = 6.7 Hz, 3 H), 1.30 (s, 3 H), 2.37 (dddd, J1,2 = 29.5 Hz, J1,3 = 11.0 Hz, J2,3 = 6.7 Hz, J3,4 = 3.3 Hz, 1 H)), 3.02 (dt, J = 11.0 Hz, J1,2 = 1.0 Hz, 1 H), 3.37 (dd, J2,3 = 2.3 Hz, J1,2 = 2.2 Hz, 1 H), 3.86 (ddd, J3,4 = 7.5 Hz, 4.4 Hz, J = 3.3 Hz, 1 H).

13C NMR (100 MHz, CD3OD): δ = 22.7 (dd, J = 8.7, 6.0 Hz, 2 H), 31.7 (d, J = 12.3 Hz, 1 H), 50.3 (d, J = 12.8 Hz, 1 H), 69.1 (dd, J = 1.9 Hz, 1 H), 101.2 (d, J1,2 = 2.2 Hz, 1 H), 121.1 (d, J1,2 = 2.2 Hz, 1 H), 123.7 (d, J1,2 = 2.2 Hz, 1 H).

HRMS-FAB: m/z calced for C4H13F2O4 [M + Na]⁺: 221.10729; found: 221.10702.


Direct Upjohn Oxidation with Teflon Isolation;

(1R,2S,3S,4S)-5,5-Difluoro-1-methylcyclohexane-1,2,3,4-tetrol (23bb)

OsO4 (61 mL of a 2.5 wt% solution in t-BuOH, 6.1 μmol, 2 mol%) was added to a cooled (0 °C) solution of diol 11bb (0.30 mmol, 50 mg) and NMO·H2O (0.61 mmol, 84 mg, 2 equiv) in a mixture of acetone (0.3 mL), H2O (0.3 mL), and t-BuOH (0.15 mL). The mixture was stirred at r.t. for 2 d. The reaction was quenched with solid Na2SO4 (100 mg) and stirred overnight. Solid Na2SO4 (ca. 10 g) was added followed by EtOAc (5 mL). The mixture was filtered through silica gel, and the filter cake was rinsed with EtOAc (30 mL). The combined filtrate and washings were concentrated in vacuo, then freeze-dried to afford the tetrol 23bb (57 mg, 95%, 100% by GC) as a single diastereoisomer; white solid; mp 90–92 °C; Rf = 0.55 (CH2Cl2–MeOH, 4:1).

IR (KBr): 3487, 3356, 3297, 3221, 1289, 1191, 1048, 1031 cm⁻¹.

1H NMR (400 MHz, CD3OD): δ = 1.28 (s, 3 H), 1.96–2.11 (m, 1 H), 2.15 (dddd, J1,2 = 33.6 Hz, J2,3 = 14.9 Hz, J3,4 = 6.6 Hz, 1 H), 3.56 (d, J = 9.8 Hz, 1 H), 3.76–3.85 (m, incl. app d, J = 9.8 Hz, 1 H), 3.85–3.93 (m, 1 H).

13C NMR (100 MHz, CD3OD): δ = 21.7, 34.3 (t, J1,2 = 22.4 Hz), 70.8 (d, J1,2 = 11.2 Hz), 70.9 (d, J1,2 = 8.7 Hz), 74.2 (dd, J1,2 = 32.8, 21.6 Hz), 77.1, 127.2 (dd, J1,2 = 251.7, 237.3 Hz).

19F NMR (376.5 MHz, CD3OD): δ = 104.2 to 105.0 (m, incl. app d, J1,2 = 257.5 Hz, J1,3 = 6.6 Hz, 1 F), −106.4 to −107.3 (m, incl. app ddd, J1,2 = 257.5 Hz, J1,3 = 36.5, 10.4 Hz, 1 F).

MS (EI, 70 eV): m/z (%) = 114 (100), 177 (10), 197 (15, [M – H]–).

HRMS-FAB: m/z calced for C16H21F4O7 [M + H]⁺: 397.09383; found: 397.09378.

Anal. Calcd for C16H21F4O7: C, 42.83; H, 5.69; F, 20.44. Found: C, 42.82; H, 5.68; F, 20.39.

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