A rearrangement-based approach to secondary difluorophosphonates

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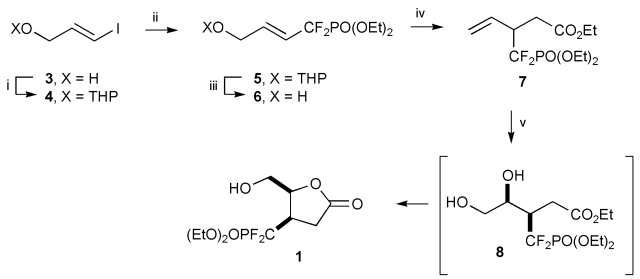
[3,3]-Claisen rearrangements allowed the conversion of a readily available allylic difluorophosphonate to nucleic acid and inositol phosphate-related products *via* epoxide cyclisation or ring closing metathesis respectively.

Secondary hydroxy groups undergo phosphorylation in many of the key molecules of Nature. Inositols undergo phosphorylation and dephosphorylation events that are critical in intracellular signalling pathways while a phosphodiester linkage between primary 5′-hydroxy and secondary 3′-hydroxy groups provides the critical structural backbone of the nucleic acids. Oxygen atom replacement by a CF_2 centre has been used extensively as a mimetic strategy, replacing a scissile O–P bond with a non-scissile C–P bond, in the quest for enzyme inhibitors and molecular probes. A relatively limited range of target types has been synthesised; one of our major interests lies in expanding the range of species accessible using convenient methodology and starting materials. In this communication, we wish to show how a rearrangement-based route affords butyrolactone derivatives **1** (related to building blocks for nucleic acid analogues[1,2]) and cyclohexenone derivatives **2** (related to deoxyinositol phosphate analogues[3]). The approach complements our earlier conjugate addition[4,5] and cycloaddition[6] chemistry which was based upon chlorodifluoromethane as a feedstock.

Known alcohol **3** was prepared according to a modification of the published method[7] and protected as the THP ether **4**. Coupling under the Shibuya–Yokomatsu[8] conditions afforded a good yield of **5** which was deprotected smoothly to afford **6** (Scheme 1). Rearrangement under Johnson–Claisen conditions[9] was uneventful and alkenoate **7** could be isolated and purified rigorously. Overall, this sequence is synthetically equivalent to the selective addition at C_β of a difluoromethylphosphonate anion equivalent to an alkyl α,β,γ,δ-unsaturated dienoate.

To learn about the behaviour of the educt, dihydroxylation of **7** was attempted under a range of conditions, none of which were found to be satisfactory. Though starting material could be converted completely, apparently in a highly stereoselective manner, we were never able to isolate more than 11% of lactone **1**† formed *via* diol **8** (the configuration was inferred from that of **1**). The ^{19}F NMR spectrum of the crude product appeared to be that of a single diastereoisomer (as a racemic modification); the single product was identified as the 5-ring lactone **1** (by gradient HMBC) of *cis*-stereochemistry (by GOESY spectroscopy),



Scheme 1 *Reagents and conditions*: i, dihydropyran, Amberlyst-15, dry hexane, 86%; ii, $BrZnCF_2PO(OEt)_2$, CuBr, DMF, 96%; iii, MeOH, Amberlyst-15, hexane, 82%; iv, triethyl orthoacetate, propionic acid, hydroquinone, 140 °C, 86%; v, 10% OsO_4, 2.0 NMO, acetone–water (2 : 1), rt, 11%.

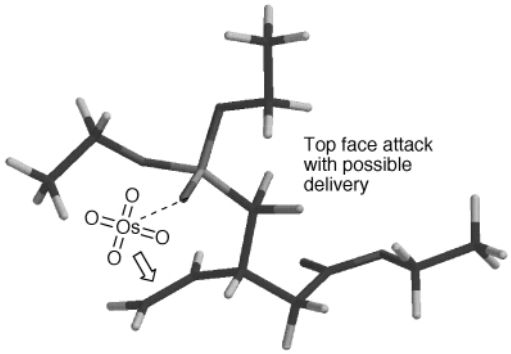


Fig. 1 Possible attack trajectory to explain the formation of lactone **1**.

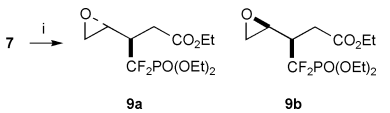
which showed a strong transfer of magnetisation from H-3 to H-4. Attack from the face occupied by the bulky (diethoxyphosphoryl)difluoromethyl group (Fig. 1) appears to have led to the observed product, suggesting a possible role for the phosphoryl P=O oxygen atom in delivering the reagent.[10]

We then tried to reverse the stereochemical relationship and obtain the *trans*-lactone by forming epoxide **9b** which would undergo nucleophilic ring-opening under acid catalysis, either intramolecularly with the ester carbonyl, or intermolecularly by traces of water in the medium (followed by cyclisation) to form the *trans*-lactone (Scheme 2).

Both reactions would involve a single inversion of configuration at the epoxide stereogenic centre. Epoxidation was very slow indeed under MCPBA or methyl trioxorhenium[11] conditions but the *in situ* dioxirane method of Yang[12] proved most effective and both epoxides **9a** and **9b** were obtained as an inseparable mixture in good (91%, **9a**:**9b** 1:2) yield.

However, treatment with Amberlyst-15 in dry dichloromethane[13] (Scheme 3) resulted in the isolation of only *cis*-lactone **1** in good (78%) yield.

A lower facial selectivity for oxidation with the smaller dioxirane reagent (which cannot coordinate to the phosphoryl oxygen either) was no surprise, but the convergence of the epoxides was unexpected. One epoxide (we believe **9a**) reacted considerably more quickly than the other and we were able to recover the less reactive species as a pure compound by careful ^{19}F NMR monitoring of the consumption of **9a**. The stereochemical convergence may involve neighbouring group participation by the phosphoryl oxygen in a double inversion mechanism *via* **10**; effectively, the all *cis*-epoxide **9b** must be opened with overall retention at the secondary carbon for the *cis*-lactone to form. Interestingly, an NMR sample of the less reactive epoxide in untreated $CDCl_3$ was converted to **1** and a trace of **11** upon standing. Neighbouring group participation by *thio*phosphoryl oxygen has been exploited to control glycosylation stereochemistry[14] but we are not aware of examples of a phosphoryl group exerting such an influence. Further under-



Scheme 2 *Reagents and conditions*: i, CF_3COCH_3, Oxone, $NaHCO_3$, Na_2EDTA, MeCN, H_2O, 91%.

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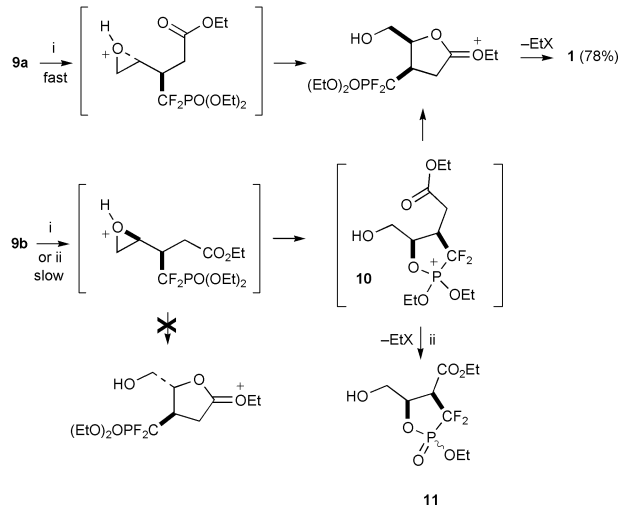
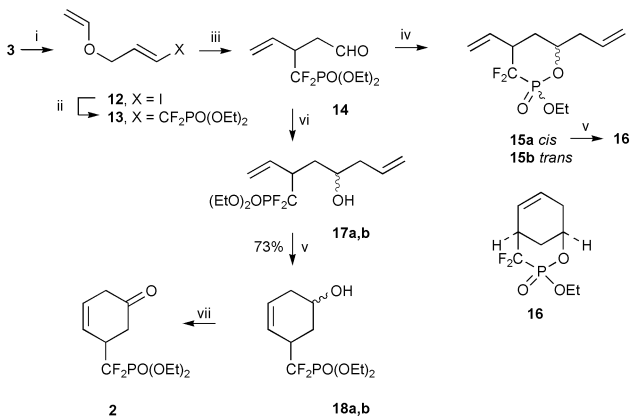


Scheme 3 *Reagents and conditions*: i, Amberlyst-15, dry DCM, rt; ii, $CDCl_3$, rt, 18 h.

standing of this process is sought currently, but clearly the direct cyclisation of **9b** *via* nucleophilic attack involving the ester carbonyl group is highly unfavourable.[15]

A change of tactics allowed access to an attractively functionalised cyclohexenone (Scheme 4); vinylation of **3** protected the hydroxy group as **12** for the Shibuya–Yokomatsu coupling allowing Dauben–Dietsche rearrangement[16] to proceed affording enal **14**.



Scheme 4 *Reagents and conditions*: i, ethyl vinyl ether, $Hg(OAc)_2$, reflux, 70%; ii, $BrZnCF_2PO(OEt)_2$, CuBr, DMF, 84%; iii, 140 °C, xylene, 75%; iv, allylmagnesium bromide, ethyl ether, 60% (1:1 ratio); v, Grubbs' catalyst, DCM, reflux, 48 h; vi, allyltrimethylsilane, $BF_3{\cdot}OEt_2$, DCM, rt, 83% (7:2 ratio); vii, PDC, DCM, rt.

Allylation under Grignard conditions afforded a pair (in a 1:1 ratio) of diastereoisomeric phosphodiesters **15a** and **15b**; slow (48 h) RCM under standard Grubbs' conditions[17] then closed the *cis* congener to yield **16** (64% by NMR) leaving the *trans* isomer **15b** unchanged. We inferred that cyclisation with loss of ethanol had occurred after Grignard addition. Boron trifluoride-catalysed (Sakurai) allylation with allyltrimethylsilane[18] afforded homoallyl alcohols **17a** and **17b** in a 7:2 ratio (unassigned) then RCM afforded a 7:2 mixture of cyclohexenols **18a** and **18b** which were converged by oxidation to **2**‡ with PDC. Enone **2** contains a pattern of functional groups from which four contiguous hydroxylated positions could be developed and we will explore its chemistry further.

The appeal of this strategy lies in the possibility of asymmetric catalysis of the [3,3] rearrangement controlling the absolute configuration of the mimetic-bearing carbon atom and the potential for a high degree of subsequent stereocontrol on the cyclohexene template. The products of this study are under evaluation as components for novel nucleoside and inositol phosphate analogues as we learn more about the steric and electronic effects of the mimetic group.

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Notes and references

† *Selected data* for **1**: ν_{max} (film)/cm^{-1} 3434br s, 1786s; δ_H($CDCl_3$, 300 MHz) 4.88–4.79 (m, 1H), 4.32–4.20 (m, 4H), 3.95 (dd, 1H, $^2J_{H\text{-}H}$ 12.5, $^3J_{H\text{-}H}$ 2.2), 3.65 (dd, 1H, $^2J_{H\text{-}H}$ 12.5, $^3J_{H\text{-}H}$ 2.6), 3.5 (br s, 1H, OH), 3.44–3.20 (m, 2H), 2.85 (dd, 1H, $^2J_{H\text{-}H}$ 18.8, $^3J_{H\text{-}H}$ 9.2), 2.77 (dd, 1H, $^2J_{H\text{-}H}$ 18.4, $^3J_{H\text{-}H}$ 7.0), 1.38 (t, 6H, $^3J_{H\text{-}H}$ 7.0); ^{13}C δ_C($CDCl_3$, 75 MHz) 175.2 (s), 119.4 (td, $^1J_{C\text{-}F}$ 263.4, $^1J_{C\text{-}P}$ 214.8), 78.8 (q, $^3J_{C\text{-}F=C\text{-}P}$ 4.5), 65.4 (d, $^2J_{C\text{-}P}$ 6.8), 65.2 (d, $^2J_{C\text{-}P}$ 6.8), 63.4 (s), 40.3 (td, $^2J_{C\text{-}F}$ 20.9, $^2J_{C\text{-}P}$ 15.3), 29.1 (td, $^3J_{C\text{-}F}$ 5.1, $^3J_{C\text{-}P}$ 2.3), 16.4 (d, $^3J_{C\text{-}P}$ 5.7); δ_F($CDCl_3$, 282 MHz) −116.8 (ddd, $^2J_{F\text{-}F}$ 342.1, $^2J_{F\text{-}P}$ 105.5, $^3J_{F\text{-}H}$ 16.5). −117.99 (ddd, $^2J_{F\text{-}F}$ 343.3, $^2J_{F\text{-}P}$ 104.3, $^3J_{F\text{-}H}$ 17.8); δ_P($CDCl_3$, 121 MHz) 5.6 (t, $^2J_{P\text{-}F}$ 103.9 Hz); *m/z* (ES) 325 (M + Na, 100) HRMS calc. for $C_{10}H_{17}O_6F_2NaP$ 325.0629, found 325.0632. Anal. Calcd for $C_{10}H_{17}O_6F_2P$: C, 39.74, H, 5.70; found: C, 39.55, H, 5.45%.

‡ *Selected data* for **2**: ν_{max} (film)/cm^{-1} 2987m, 1725s, 1684m; δ_H($CDCl_3$, 300 MHz) 6.10–5.89 (m, 2H), 4.25–4.10 (m, 4H), 3.39–3.19 (m, 1H), 2.89 (d, 1H, $^2J_{H\text{-}H}$ 22.4), 2.77 (d, 1H, $^2J_{H\text{-}H}$ 22.6), 2.71 (dd, 1H, $^2J_{H\text{-}H}$ 14.7, $^3J_{H\text{-}H}$ 6.6), 2.55 (dd, 1H, $^2J_{H\text{-}H}$ 15.1, $^3J_{H\text{-}H}$ 6.3), 1.28 (t, 6H, $^3J_{H\text{-}H}$ 6.3); δ_C($CDCl_3$, 75 MHz) 206.5 (s), 128.7 (s), 122.2–122.0 (m), 120.4 (td, $^1J_{C\text{-}F}$ 264.5, $^1J_{C\text{-}P}$ 211.9), 64.7 (t, $^3J_{C\text{-}F}$ 7.4), 41.9 (td, $^2J_{C\text{-}F}$ 21.5, $^2J_{C\text{-}P}$ 15.8), 39.1 (s), 37.5 (q, $^3J_{CF=CP}$ 5.1), 16.3 (d, $^3J_{C\text{-}P}$ 5.7); δ_F($CDCl_3$, 282 MHz) −114.1 (ddd, $^2J_{F\text{-}F}$ 300.1, $^2J_{F\text{-}P}$ 105.5, $^3J_{F\text{-}H}$ 15.3), −115.8 (ddd, $^2J_{F\text{-}F}$ 300.1, $^2J_{F\text{-}P}$ 109.8, $^3J_{F\text{-}H}$ 17.8); δ_P($CDCl_3$, 121 MHz) 6.0 (t, $^2J_{F\text{-}P}$ 106.8); *m/z* (ES) 305 (M + Na, 100); HRMS calc. for $C_{11}H_{17}O_4F_2P$ 305.0730, found 305.0722.

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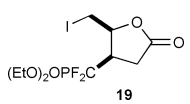

GOESY); this process must follow a trajectory similar to that of the closure of **9a** to **1**.
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