Reactive dienophiles containing a difluoromethylenephosphonato group

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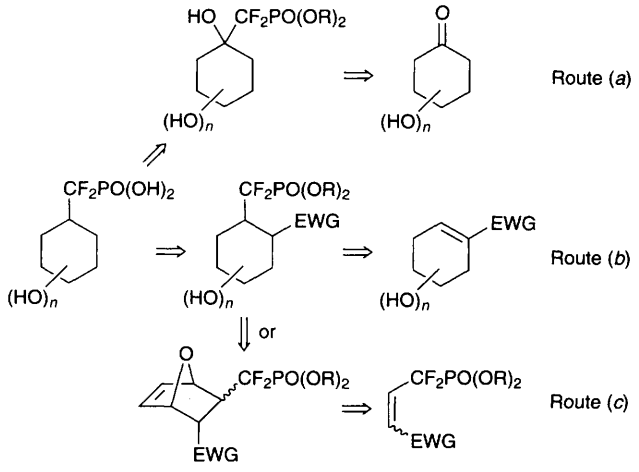
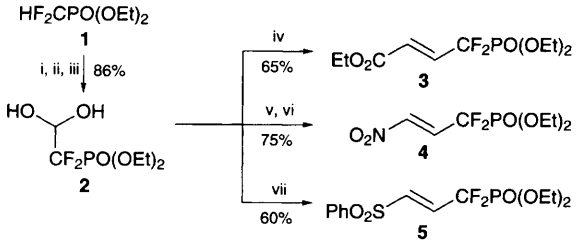
New dienophiles containing the difluoromethylenephosphonato group are synthesised from readily-available starting materials and cycloadditions with reactive dienes are executed successfully.

Difluorophosphonic acids have been used as mimics of phosphate esters in a number of interesting systems.[1] We became interested in the pursuit of metabolically stable analogues of inositol phosphates, critical substrates, products and intermediates in molecular signalling pathways.[2] We were encouraged by the recent reports of structurally-simplified, yet biologically active, congeners[3] and by an early report of a monofluorophosphonate analogue with interesting properties.[4] However, the attachment of the difluoromethylenephosphonato group to a secondary carbon centre within a cyclic array is not a trivial synthetic problem. A classical approach [Scheme 1, route (*a*)] would involve the addition of a lithiophosphonate group to a fully protected cyclitol-derived ketone, followed by Barton–McCombie dehydroxylation of the tertiary alcohol.[5] However, there are no reports of the successful application of the free radical methodology to such weakly nucleophilic and sterically hindered alcohols.[6] An alternative, route (*b*), would involve a conjugate addition of a metallated phosphonate to a nitroalkene[7] or vinylsulfone derived from a cyclitol. We are exploring this strategy *en route* to specific targets. Here we offer a general solution to the problem of attaching the difluoromethylenephosphonato group to a secondary carbon centre within a cyclic array using cycloaddition chemistry. We have synthesised a range of dienophiles **3–5** bearing the difluoromethylenephosphonato group and explored their chemistry in Diels–Alder cycloaddition reactions.



Scheme 1



Scheme 2 *Reagents and conditions*: i, 1.0 LDA, $CeCl_3$, THF, −78 °C; ii, DMF; iii, aq. HCl; iv, $EtO_2CCH_2PO(OEt)_2$, LiBr, Et_3N, THF, room temp., 2 h; v, $MeNO_2$, KF, propan-2-ol, room temp, 18 h; vi, MsCl then Et_3N, CH_2Cl_2; vii, $PhO_2SCH_2PO(OEt)_2$, LiBr, Et_3N, THF, room temp., 2 h.

Masked aldehyde **2** was prepared *via* a high yielding (80%) cerium(III)-mediated reaction between **1** and LDA, followed by quenching with DMF and an acidic work-up.[8]

Treatment of **2** with triethylphosphonoacetate under the conditions described by Rathke[9] afforded **3** as the *E*-isomer alone in good (65%) yield. The masked aldehyde also underwent a Henry reaction with nitromethane in propan-2-ol containing potassium fluoride (84%). Dehydration with methanesulfonyl chloride and triethylamine followed, allowing the isolation of **4** in 90% yield.† Sulfone **5** was prepared (60%) by the reaction of the lithium salt of (phenylsulfonyl)methyl phosphonate with **2**.‡ The results of the cycloaddition reactions are summarised in Table 1.

As expected, all the dienophiles reacted smoothly with cyclopentadiene; indeed, the reaction between **4** and cyclopentadiene was particularly facile, reaching completion in 5 min at room temperature (15 °C). The stereoselectivity was low in all cases, reflecting the steric bulk of the difluoromethylenephosphonato group.§ Useful yields of cycloadducts were obtained upon reaction with Danishefsky's diene. With furan, the full spectrum of dienophile reactivity was revealed more clearly. Nitroalkene **4** and sulfonyl congener **5** underwent thermal cycloadditions in sealed tubes,¶ while **3** failed to react at all, even after extended periods. However, when zinc iodide was added to the reaction mixture, cycloaddition occurred under very mild conditions.[10]

An extensive repertoire exists concerning the elaboration of furan Diels–Alder adducts to highly hydroxylated natural and unnatural products.[11] To date we have dihydroxylated (cat. OsO_4, H_2O_2, Bu^tOH, 40 °C) and epoxidised (*m*CPBA, CH_2Cl_2, 40 °C) **10** and **11**, establishing encouraging precedents for further elaboration; as expected, both reactions occurred exclusively on the *exo*-face of the double bond. Work in progress seeks to elaborate these, and other, cycloadducts to analogues of the inositol phosphates.

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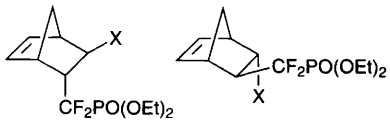
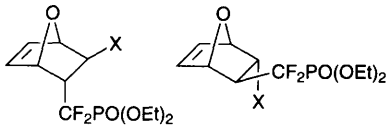
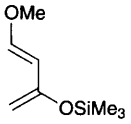
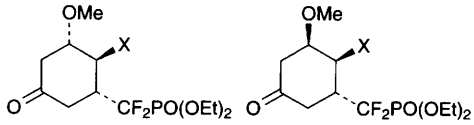
Footnotes

† Nitromethane (4.16 ml, 0.077 mol) and anhydrous potassium fluoride (0.50 g) were added in one portion to a solution of **2** (6.0 g, 0.026 mol) in propan-2-ol (100 ml). The mixture was stirred at room temperature (18 h) then evaporated *in vacuo*. The residue was diluted with ether (100 ml), washed with brine (50 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue chromatographed (3:2 hexane–ethyl acetate) to afford the β-nitroalcohol (6.0 g, 84%) as a clear oil, δ_H(300 MHz; $CDCl_3$) 5.55 (1 H, d, *J* 7 Hz), 4.90–4.70 (1 H, m), 4.65 (1 H, dd, *J* 14, 2.5 Hz), 4.55 (1 H, d, *J* 14, 9.5 Hz), 4.26 (2 H, q, *J* 7 Hz), 4.24 (2 H, q, *J* 7 Hz), 1.32 (6

Table 1

Diene	Dienophile	Conditions[a]	Yield (%)[b]	Products			Ratio (**a** : **b**)
							
	3	room temp., 120 h	81	**6a**	**6b**	(X = CO_2Et)	(4 : 1)
	4	room temp., 5 min	95	**7a**	**7b**	(X = NO_2)	(2 : 3)
	5	room temp., 5 d	93	**8a**	**8b**	(X = SO_2Ph)	(2 : 3)
							
	3	40 °C, 18 h[c]	83	**9a**	**9b**	(X = CO_2Et)	(1 : 1)
	4	80 °C, 2 h	92	**10a**	**10b**	(X = NO_2)	(3 : 7)
	5	80 °C, 18 h	60	**11a**	**11b**	(X = SO_2Ph)	(2 : 3)
							
	3	80 °C, 18 h[d]	41	**12a**	**12b**	(X = CO_2Et)	(1 : 1)
	4	−78 °C to room temp., 2 h[e]	57	**13a**	**13b**	(X = NO_2)	(3 : 7)
	5	80 °C, 18 h[f]	50	**14a**	**14b**	(X = SO_2Ph)	(—)

[a] All reactions were performed neat in sealed tubes unless stated otherwise. [b] Isolated yields after chromatography are reported. [c] Zinc iodide was present (0.5 equiv.) and the tube was stirred. [d] Starting material **3** was recovered (35%). [e] The cycloaddition was performed in dichloromethane. [f] The cyclohexenone was isolated, after the elimination of methanol *in situ*.

H, *J* 7 Hz); δ_C(75 MHz; $CDCl_3$) 118.5 (dt, *J* 267, 211 Hz), 75.1, 68.9 (dt, *J* 23, 15 Hz), 65.4 (d, *J* 6 Hz), 16.2; δ_F(84 MHz; $CDCl_3$) −124.1 (1 F, ddd, *J* 308, 98, 16 Hz), −115.7 (1 F, ddd, *J* 308, 98, 6 Hz); δ_P(36 MHz; $CDCl_3$) 4.6 (t, *J* 98 Hz); MS (CI): *m/z* 295 ($[M + NH_4]^+$, 100%), 278 ($[M + H]^+$, 36).

Methanesulfonyl chloride (5.0 ml, 0.065 mol) was added in one portion to a stirred cold (0 °C) solution of the β-nitroalcohol (6.0 g, 0.021 mol) in dry dichloromethane (100 ml). The mixture was stirred for 30 min, then triethylamine (8.92 ml, 0.065 mol) was added dropwise over 15 min. Stirring was continued for a further 30 min, then water (30 ml) was added. The mixture was extracted with diethyl ether (3 × 50 ml) and the combined ether extracts were washed with brine (50 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (20% EtOAc in hexane) afforded the *E*-nitroalkene **4** (4.89 g, 90%) as a clear oil; δ_H(300 MHz; $CDCl_3$) 7.30 (1 H, tdd, *J* 12, 13.5, 2.5 Hz), 7.10 (1 H, tdd, *J* 12, 13.5, 2 Hz), 4.26 (2 H, q, *J* 7 Hz), 4.24 (2 H, q, *J* 7 Hz), 1.35 (6 H, *J* 7 Hz); δ_C(75 MHz; $CDCl_3$) 144.2 (br s), 130.2 (dt, *J* 23, 14 Hz), 115.1 (dt, *J* 270, 217 Hz), 65.6 (d, *J* 7 Hz), 16.3 (d, *J* 7 Hz); δ_F(84 MHz, $CDCl_3$) −112.1 (1 F, dd, *J* 103, 12 Hz), −115.7 (1 F, ddd, *J* 308, 98, 6 Hz); δ_P(36 MHz; $CDCl_3$) 3.6 (t, *J* 103 Hz); MS (CI): *m/z* 277 ($[M + NH_4]^+$, 100%), 260 ($[M + H]^+$, 36), 259 ($[M]^+$, 18).

‡ The (phenylsulfonyl)methanephosphonate was prepared by the oxidation (*m*CPBA) of commercial (Lancaster) diethyl phenylthiomethylphosphonate.

§ Diels–Alder reactions involving *E*-nitroalkenes are relatively rare, though the *endo* adduct is normally formed with low selectivity. In the furan cycloaddition reactions, we were able to separate the *endo*- and *exo*-isomers by column chromatography. All cycloadducts were characterised fully by NMR (^1H, ^{13}C, ^{19}F and ^{31}P) and mass spectrometric methods.

¶ Typical cycloaddition reactions were perfomed in Ace Pressure tubes (8648B) fitted with plunger valve.

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