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Diels–Alder cycloaddition of novel buta-1,3-diene derivatives possessing a (diethoxyphosphinoyl)difluoromethyl unit

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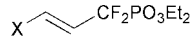
A series of new buta-1,3-diene derivatives possessing a (diethoxyphosphinoyl)difluoromethylene unit at the terminal carbon was prepared to examine the reactivity for Diels–Alder cycloaddition with various representative dienophiles.

(α,α-Difluoromethyl)phosphonic acids (DFMPA) as hydrolytically stable analogues of naturally occurring phosphate esters have attracted much attention because they mimic parental biophosphates more accurately than analogous non-fluorinated phosphonates in their isosteric and isopolar properties.[1] Interest is growing in the development of general methods that allow the synthesis of compounds in which the DFMPA is borne within a functionalised array.[2] While several useful methods have been developed for this purpose,[2] few methods are available for stereoselective installation of DFMPA into a secondary carbon center within a cyclic array.[3]

Diels–Alder reaction of α,β-unsaturated DFMPA-esters **1** having an electron-withdrawing substituent with representative dienes has been applied to construct DFMPA-functionalised cyclohexene derivatives.[4] However, the cycloadditions have met with only limited success due to the low *endo–exo*-selectivity. Such low *endo–exo*-selectivity has hampered practical applications of the Diels–Alder reaction to stereoselective synthesis of DFMPA-functionalised cyclohexane derivatives of biological interest.[5]



1 X = CO_2Et; SO_2Ph; NO_2

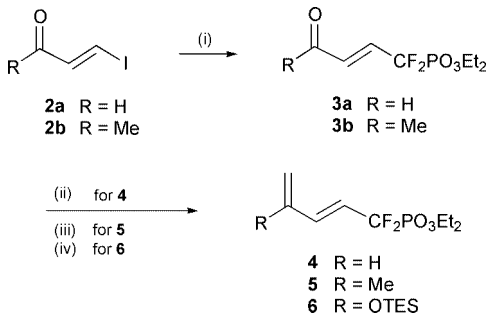
In our efforts directed toward stereoselective synthesis of DFMPA-functionalised cyclohexane derivatives that may act as hydrolytically stable analogues of inositol phosphates,[5] we have pursued an alternative approach to the DFMPA-functionalised cyclohexene derivatives through Diels–Alder cycloaddition of buta-1,3-diene derivatives **4**–**6**. To the best of our knowledge, there is no report on this class of Diels–Alder reaction. Here, we describe preliminary results on the Diels–Alder reaction of dienes **4**–**6** with several representative dienophiles and demonstrate that the approach is quite useful for a stereocontrolled synthesis of poly-functionalised cyclohexane derivatives having a DFMPA-ester.

Treatment of β-iodo-α,β-enal **2a**[6a] and β-iodo-α,β-enone **2b**[6b] with $BrZnCF_2PO_3Et_2$ in DMA in the presence of CuBr according to our procedure described previously[3b,7] gave the corresponding coupling products **3a** and **3b**[3b] in 60 and 79% yield, respectively. Wittig olefination of **3a** and **3b** with $CH_2{=}PPh_3$ in THF gave the dienes **4** and **5** in 63 and 68% yield, respectively. The compound **3b** was transformed to the siloxydiene **6** in 74% yield on treatment with chlorotriethylsilane (TESCl) in benzene in the presence of Et_3N and $ZnCl_2$.[8] All dienes prepared can be stored without decomposition in a freezer for several months.

Diels–Alder reaction of dienes **4** and **5** with maleic anhydride **7** and *N*-phenylmaleimide **8** was first examined to survey the *endo–exo*-selectivity (Table 1). Reaction of **4** with **7** in toluene at reflux for 4 h gave the *endo*-adduct **9a**† in 61% yield (entry 1). The corresponding *exo*-adduct was not detected in the crude mixture. The excellent *endo*-selectivity was also observed upon using *N*-phenylmaleimide **8** as a dienenophile (entry 2). Diene **5** was expected to be more reactive than the diene **4** from calculations of the HOMO-energies. Under the same conditions, the reaction of **5** with **7** and **8** proceeded in a highly *endo*-selective manner to give the *endo*-adducts **9b** and **10b** in higher yield, respectively (entry 1,2 *vs*. 3,4). The stereochemistry of **9a**,**b** and **10a**,**b** was deduced by analysis of the NOESY-spectra (500 MHz, $CDCl_3$).

The dienes **4** and **5** did not react with ethyl crotonate and crotonaldehyde, respectively, under the thermal conditions and were recovered. The siloxydiene **6** decomposed to **3b** under the conditions; no adduct was obtained by the reaction with maleic anhydride **7**. However, the siloxydiene **6** reacted slowly with methyl propiolate to give adduct **11** in 57% yield, upon heating the toluene solution (1 M) at 150 °C in a sealed tube for 22 h (Scheme 2). The regiochemical outcome for the cycloaddition was consistent with that predicted. The adduct **11** gradually isomerized to the conjugated diene **13** upon standing at room temperature. Under the same conditions, dimethyl acetylenedicarboxylate reacted with **6** rather rapidly (1 h) to give **12** in 57% yield. The yield was significantly improved to 74% when the reaction was conducted in refluxing benzene for 23 h.

Aiming at a synthesis of highly functionalised cyclohexane derivatives of a DFMPA-ester, we examined selective discrimination of the anhydride carbonyls of **9a** (Scheme 3). Upon treatment of **9a** in ethanol at reflux, solvolysis occurred exclusively at the less-hindered carbonyl to give the half-ester **14** as crystals (mp 96–98 °C) in 90% yield.[9] The structure of **14** was confirmed after its transformation to a phenylseleno lactone. Phenylseleno lactonisation of **14** with PhSeCl in CH_2Cl_2 gave the phenylseleno δ-lactone **15**‡ in 51% yield.[10] In the lactonisation, the corresponding γ-lactone **A** was not detected.§ The structure of **15** was deduced by GRASP-COSY as well as NOESY experiments (500 MHz, $CDCl_3$). The diagnostic NOESY-correlations are depicted in Fig. 1. The structure of **15** was further confirmed by oxidative removal of



2a R = H
2b R = Me
3a R = H
3b R = Me
4 R = H
5 R = Me
6 R = OTES

Scheme 1 *Reagents and conditions*: (i) $BrZnCF_2PO_3Et_2$, CuBr, DMA, ultrasound, 25 °C; (ii) Ph_3PCH_3Br, *n*-BuLi, THF, −78 to 0 °C; (iii) Ph_3PCH_3Br, *tert*-BuOK, THF, 0 °C; (iv) TESCl, Et_3N, $ZnCl_2$, benzene, 40 °C.

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the phenyselenyl group to give the unsaturated lactone **16**¶ in good yield (87%).

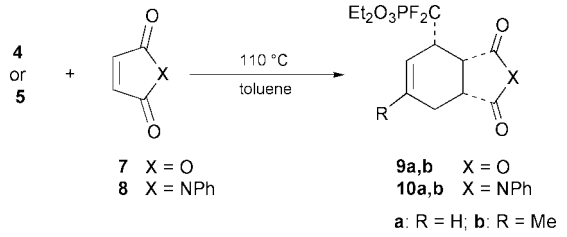
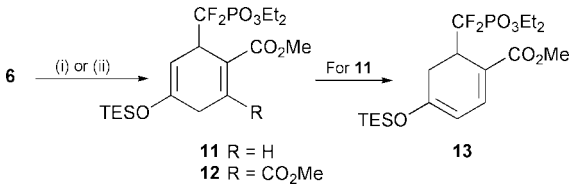


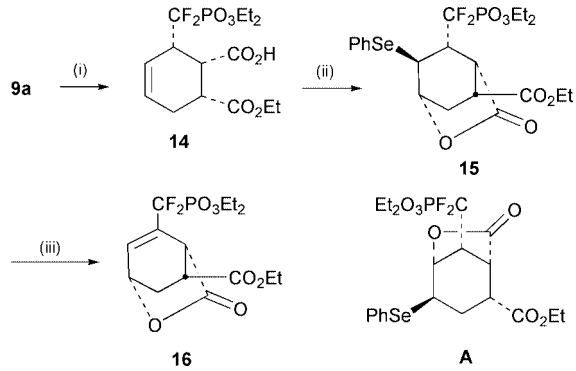
Table 1 Diels–Alder reaction of **4** and **5** with maleic anhydride and *N*-phenylmaleimide

Entry[a]	Diene	Dienophile	Product	Yield (%)[b]	*Endo–exo*[c]
1	**4**	**7**	**9a**	61	>99:1
2	**4**	**8**	**10a**	56	>99:1
3	**5**	**7**	**9b**	81	>99:1
4	**5**	**8**	**10b**	67	>99:1

[a] All reactions were carried out in 1 M solution of toluene for 4 h. [b] Unoptimised isolated yield after column chromatography. [c] The ratio was determined by ^{1}H NMR (300 MHz, $CDCl_3$).



Scheme 2 *Reagents and conditions*: (i) methyl propiolate, toluene, 150 °C, 22 h; (ii) dimethyl acetylenedicarboxylate, toluene, 150 °C, 1 h or benzene, 80 °C, 23 h.



Scheme 3 *Reagent and conditions*: (i) EtOH, reflux, 12 h; (ii) PhSeCl, CH_2Cl_2, −78 to 25 °C, 12 h; (iii) 30% H_2O_2, THF, 0 to 25 °C, 12 h.

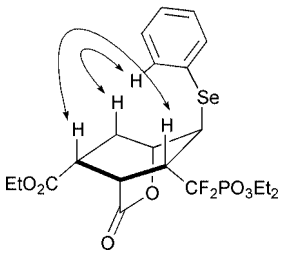


Fig. 1 NOESY correlations of **15**.

In summary, we have developed a facile method for stereoselective introduction of a DFMPA-ester unit to functionalised cyclohexanes based on a novel Diels–Alder reaction with the DFMPA-functionalised buta-1,3-dienes.

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Notes and references

† *Spectroscopic data* for **9a**: δ_H (400 MHz, $CDCl_3$) 6.18 (2H, broad s), 4.39–4.27 (4H, m), 3.78 (1H, dd, J = 10.0, 5.7 Hz), 3.52 (1H, ddd, J = 2.5, 8.5, 10.0 Hz), 3.27–3.13 (1H, m), 2.82 (1H, ddd, J = 2.3, 5.4, 16.6 Hz), 2.57 (1H, dd with small splits, J = 8.3, 16.6 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.39 (3H, t, J = 7.0 Hz); δ_P (162 MHz, $CDCl_3$) 5.63 (t, J_{PF} = 104.6 Hz); δ_F (376 MHz, $CDCl_3$, benzotrifluoride) −48.07 (1F, ddd, J_{FF} = 303.1 Hz, J_{FP} = 104.6 Hz, J_{FH} = 9.8 Hz), −50.0 (1F, ddd, J_{FF} = 303.1 Hz, J_{FP} = 104.6 Hz, J_{FH} = 25.6 Hz); EI MS m/z 339 (M^+ + 1).

‡ *Spectroscopic data* for **15**: ν_{max} (film)/cm^{-1} 1772, 1735; δ_H (400 MHz, $CDCl_3$) 7.64 (2H, d with small splits, J = 7.6 Hz), 7.37–7.32 (3H, m), 4.46 (1H, broad t, J = 5.3 Hz), 4.39–4.29 (4H, m), 4.23–4.14 (2H, m), 3.89–3.84 (1H, m), 3.43 (1H, broad s), 2.94 (1H, ddd , J = 2.0, 5.9, 10.9 Hz), 2.84 (1H, ddd, J = 1.4, 11.0, 12.4 Hz), 2.71–2.60 (1H, m), 2.39–2.32 (1H, m), 1.44 (3H, t, J = 7.2 Hz), 1.41 (3H, t, J = 7.1 Hz), 1.26 (3H, t, J = 7.1 Hz); δ_P (162 MHz, $CDCl_3$) 4.98 (dd, J_{PF} = 100.8, 105.5 Hz); δ_F (376 MHz, $CDCl_3$, benzotrifluoride) −50.7 (1F, ddd, J_{PF} = 309.4 Hz, J_{FF} = 105.5 Hz, J_{HF} = 11.3 Hz), −53.4 (1F, ddd, J_{PF} = 309.4 Hz, J_{FF} = 100.8 Hz, J_{HF} = 20.7 Hz); FABMS m/z 541 (MH^+).

§ An unidentified phenylseleno lactone was isolated in 19% yield from the reaction. The compound is not consistent with lactone **A** or the lactones that will be derived in a normal way[10] from the positional isomer of **14**, on the 2D-spectrum.

¶ *Spectroscopic data* for **16**: ν_{max} (film)/cm^{-1} 1770, 1734; δ_H (400 MHz, $CDCl_3$) 6.93–6.83 (1H, m), 5.32 (1H, broad t, J = 4.0 Hz), 4.32–4.21 (4H, m), 4.21–4.15 (2H, m), 3.97 (1H, t, J = 1.9 Hz), 2.84 (1H, ddd, J = 2.3, 5.5, 10.8 Hz), 2.53 (1H, dt, J = 4.4, 13.9 Hz), 1.97 (1H, ddd, J = 1.4, 10.8, 13.7 Hz), 1.37 (3H, t, J = 6.9 Hz), 1.35 (3H, t, J = 6.9 Hz), 1.24 (3H, t, J = 7.1 Hz); δ_P (162 MHz, $CDCl_3$) 5.33 (t, J_{PF} = 110.5Hz); δ_F (376 MHz, $CDCl_3$, benzotrifluoride) −48.1 (1F, dd, J_{PF} = 110.5, J_{FF} = 306.4 Hz), −50.0 (1F, dd, J_{PF} = 110.5 HZ, J_{FF} = 306.4 Hz), EIMS m/z 383 (M^+ + 1).

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