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Diastereoselective synthesis of cyclic α-fluoromethylidenephosphonates using α-fluoroallenephosphonate as dienophile

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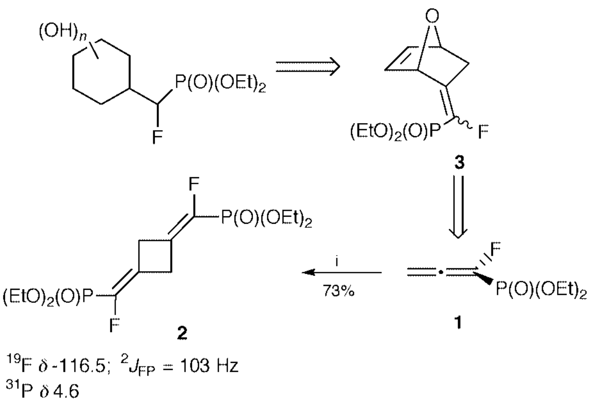
The dimerization of α-fluoroallenephosphonate and its Diels–Alder reaction with various dienes provide a diastereoselective route to cyclic and bicyclic α-fluorovinylphosphonates.

Interest in biological phosphate mimics has spurred the search for new methods to introduce an α-fluoro- or α,α-difluoromethylphosphonyl group in complex organic molecules. A clear majority involve syntheses containing the latter, using $BrCF_2P(O)(OEt)_2$ as a building block.[1] The corresponding monofluoro building block is not amenable to the same synthetic manipulations as its difluoro counterpart, and, therefore, with few exceptions,[2] the synthesis of molecules containing the α-fluoromethylphosphonyl group has been circumscribed to alkyl or aryl substitution on the α-carbon.[3] Cyclic and aromatic systems containing an α-fluoromethylphosphonyl substituent are attractive synthetic targets owing to their critical role as intermediates in molecular signaling processes. To our knowledge, only Percy and coworkers,[4] have addressed this issue by synthesizing cyclic and bicyclic derivatives containing an α,α-difluoromethylphosphonyl group. Percy's strategy relied on a Diels–Alder cyclization using an electron deficient dienophile containing an α,α-difluoromethylphosphonate.

We have recently disclosed the preparation of a multifunctional fluorophosphonate synthon, TIPS-C≡C–CXF–$P(O)(OEt)_2$, where X = H or F.[5] Its building block potential was exemplified by the first synthesis of α-fluoroallenephosphonate **1**, which in turn was used to promote a cascade of stereoselective reactions leading to (*E*)-α-fluoro-β,γ-diiodopropenephosphonate, (*E*)-unsaturated phosphononucleosides and (*Z*)-α-fluoroenaminophosphonates. We postulated that the allene moiety in **1** could serve as a Diels–Alder dienophile,[5,6] thus providing us with a route to hitherto unknown exocyclic α-fluoromethylidenephosphonates (Scheme 1). An added advantage of our strategy is the promise of asymmetry at the α-carbon, provided the stereochemistry of the Diels–Alder adduct can be efficiently controlled.

First, the thermal stability of **1** was studied. Heating **1** in a sealed tube furnished dimer **2** exclusively in 73% yield. Encouraged by this result, we examined the Diels–Alder reaction of **1** with various dienes (Table 1). The reaction of **1** with furan took place under mild conditions providing the heterobicyclic species **3a** in very good yield and in high stereoselective fashion.[7] The structure of **3a** was elucidated by ^1H, ^{19}F, ^{31}P NMR and 2D-COSY spectra. The (*Z*)-stereochemistry of the exocyclic double bond was determined by NOE signal enhancement experiments. We attributed the predominance of the *Z* isomer to the efficient orbital overlap that occurs when the phosphonyl group faces the diene in the transition state leading to **3a** (Fig. 1). The reaction of **1** with cyclopentadiene at room temperature yields **4** exclusively. Anthracene reacts with **1** in refluxing toluene producing **5**. In all cases examined, the only by-product observed corresponded to dimer **2**. As the reaction temperature increases, so does the production of **2**. Dimerization of **1** is unavoidable at higher temperatures.



Scheme 1 *Conditions*: sealed tube, 140 °C, 1.5 h, THF.

Heating a solution of tri(*tert*-butyl)silyloxyvinyl cyclohexene[8] with **1** afforded a 4:1 mixture of α-fluoromethylidenephosphonate **6a** and α-fluoromethylenephosphonate **6b**. Interestingly, prolonged heating reverses the ratio of both isomers but does not alter the isolated yield. Compound **6b** appears to be the thermodynamic product of this reaction, and its formation from **6a** could be explained by invoking a homolytic bond cleavage to give a stabilized bis(allyl) diradical **I**, which can then rearrange to **II** and recombine at the fluorophosphonate terminus to give **6b** (Scheme 2). Other mechanistic explanations such as the intermediacy of an anion/cation pair, or the possibility of a retro-Diels–Alder reaction during prolonged heating cannot be discarded. A retro-Diels–Alder reaction would reform allenephosphonate **1**, which could then react as a dienophile using its proximal olefin, producing **6b**. The Diels–Alder reaction of **1** using Danishefsky's diene (Table 1, entry 5) produced a new compound with a single ^{19}F NMR signal at δ -136. By comparing this signal with the fluorine chemical shift of **6a**, we assumed that the expected cyclic α-fluoromethylidenephosphonate adduct had been formed. Disappointingly, this adduct decomposed during chromatography, most likely as a consequence of the instability of the vinyl TMS ether. In all entries, the regiochemistry shown in the Diels–Alder reaction of **1** is noteworthy because the corresponding allenecarboxylate (without fluorine) undergoes cycloaddition with cyclopentadiene at the proximal olefin[9] rather than at the distant one.

Transformation of Diels–Alder adducts to highly hydroxylated bioactive derivatives and inositol phosphate analogs are well-known synthetic recourses[10] that we envision for some of the above fluorinated adducts.

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Notes and references

1 For a recent review of fluorinated ylides see: D. J. Burton and L. Lu, *Top. Curr. Chem.*, 1997, **193**, 45. For recent leading references on difluoromethylphosphonates see: K. Uneyama, G. Mizutani, K. Maeda

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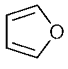
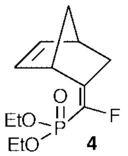
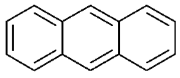
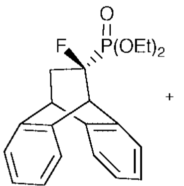
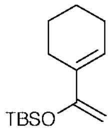
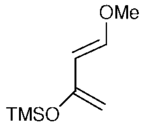
Table 1

Diene	Conditions	Product	Ratio	Yield[a](%)	NMR (ppm)[b]
	r.t., 24 h, neat			No reaction	
	50 °C, 48 h, neat	**3a** + **3b**	95:5	75	$^{19}\mathrm{F}$ δ -130.3; $^{2}J_{\mathrm{FP}} = 105$ Hz $^{31}\mathrm{P}$ δ 5.3
	r.t., 48 h, neat	 **4**	100	78	$^{19}\mathrm{F}$ δ -131.5; $^{2}J_{\mathrm{FP}} = 109$ Hz $^{31}\mathrm{P}$ δ 6.4
	80 °C, 24 h, neat			No reaction	
	120 °C, 48 h, toluene	 **5** + **2** (16%)		43	$^{19}\mathrm{F}$ δ -133.1; $^{2}J_{\mathrm{FP}} = 109$ Hz $^{31}\mathrm{P}$ δ 6.0
 [c]	120 °C, 20 h, toluene	**6a** + **6b**	80:20	50	**6a:** $^{19}\mathrm{F}$ δ -137.7; $^{2}J_{\mathrm{FP}} = 103$ Hz $^{31}\mathrm{P}$ δ 5.6
	120 °C, 5 days, toluene		20:80	43	**6b:** $^{19}\mathrm{F}$ δ -181.2; $^{2}J_{\mathrm{FP}} = 96$ Hz $^{31}\mathrm{P}$ δ 18.2
	80 °C, 24 h, toluene	Mixture of compounds after chromatography			

[a] Isolated yield after chromatography. [b] Solvent: CDCl$_3$. [c] Prepared according to ref. 8.

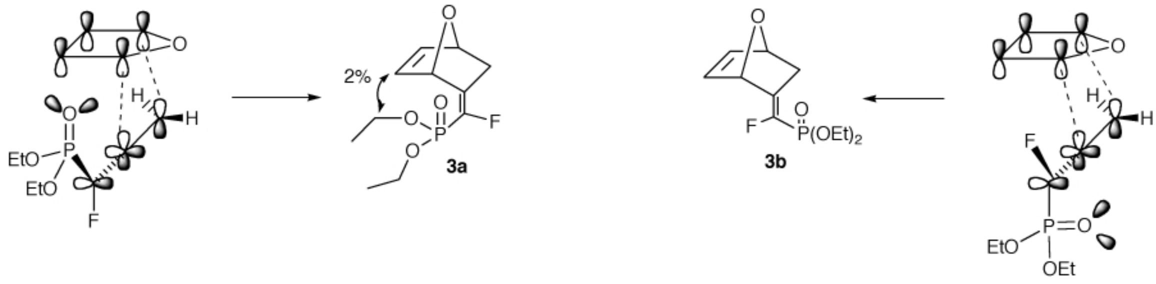
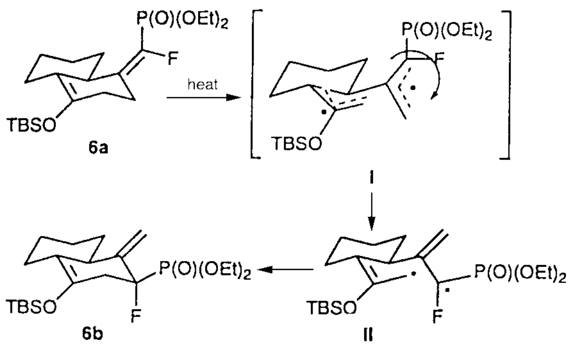


Fig. 1



Scheme 2

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3 Other selected references include: R. Waschbusch, J. Carran and P. Savignac, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1135; R. Waschbusch, J. Carran and P. Savignac, *Tetrahedron*, 1997, **53**, 6391.

4 K. Blades, T. P. Lequeux and J. M. Percy, *Chem. Commun.*, 1996, 1457.

5 A. J. Zapata, Y. Gu and G. B. Hammond, *J. Org. Chem.*, 2000, **65**, 227.

6 A. P. Kozikowski, W. C. Floyd and M. P. Kuniak, *J. Chem. Soc., Chem. Commun.*, 1977, 582.

7 A mixture of **1** (0.090 g, 0.46 mmol) and furan (0.158 g, 2.32 mmol, 5 equiv.) was stirred in a sealed tube at 50 °C for 2 days. The excess furan was evaporated and the residue was purified by flash chromatography (hexane–EtOAc = 1:1) to afford **3a** and **3b** (0.091 g, 75%).

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9 M. Bertrand, H. Monti and K.-C. Huong, *Tetrahedron Lett.*, 1979, 15.

10 C. K. McClure, K. J. Herzog and M. D. Bruch, *Tetrahedron Lett.*, 1996, **37**, 2153; C. K. McClure and K. B. Hansen, *Tetrahedron Lett.*, 1996, **37**, 2149.

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