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Synthesis of α-Fluoro-β,γ-alkenylphosphonates and Conjugated Fluoroenynes From a Common Intermediate (α-Fluoropropargyl) phosphonate

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Abstract

The efficient preparation of α-fluoro-β,γ-alkenylphosphonate **3**, via catalytic hydrogenation of (α-fluoropropargyl)phosphonate ester **1**, is described. Conjugated fluoroenynes **4** have been synthesized using a modified Horner Wadsworth Emmons (HWE) olefination of aldehydes or ketones and **1** in relatively good yields. Yields were lowered because of the formation of α–fluoro-γ-hydroxyallenylphosphonate **5** during the reaction. The nature of the counterion was very important in the outcome of the HWE reaction; better yields of fluoroenynes were obtained when a potassium base was used instead of a lithium base.

Keywords: fluorophosphonates, fluoroenynes, hydrogenation, olefination.

INTRODUCTION

Selective fluorination of organic molecules to enhance biological activity is a successful strategy in bioorganic chemistry. [1-3] Even though exceptions are known, the consequences of replacing a hydrogen atom or a hydroxyl group with fluorine cannot always be reliably predicted.[4,5] Only when more effective partial fluorination methods become available and new, more complex fluorinated analogs of bioactive molecules can be synthesized, will our understanding of fluorine's substituent effects be improved. Fluorine can be introduced in organic molecules directly, using nucleophilic or electrophilic fluorinating agents, or indirectly, using fluorine-containing molecular building blocks.[6] Our group is actively pursuing the development of the latter via a "vicarious fluorination" methodology, in which one or two fluorine atoms, embedded on a reactive carbon framework, can be incorporated selectively in complex organic molecules. With this goal in mind, we have prepared (α-fluoropropargyl) phosphonate **1** and (α,α-difluoropropargyl) phosphonate **2** (R"=F), containing a phosphonate group and an alkyne moiety, suitable for carbon-carbon bond formation and functional group manipulation.[7,8] These intermediates permit the synthesis of α-fluoro- and α-difluoro-β,γ-unsaturated phosphonates, a feat not always possible with $^{+}M^{-}CXF\text{-}P(O)(OEt)_2$--the diethyl ester of mono- or

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difluoromethylenephosphonate (X=H, F)--a fluorine synthon widely used in the synthesis of α-fluoro- and α,α-difluoroalkanephosphonates. Current interest in the synthesis and biological properties of acyclic unsaturated phosphonate nucleosides[9-11] has fostered the synthesis of difluorinated analogs, namely α,α-difluoroallylphosphonate nucleosides.[12-14] Although there have been a number of reports of the synthesis of difluoroallyl phosphonates,[15] the synthesis of the monofluoro counterparts has received less coverage in the literature. Except for an earlier communication from our group[16] on the synthesis of **3**, only one other method has been reported, in preliminary fashion, for the synthesis of α-fluoroallylphosphonate esters using a CuBr-promoted coupling of $(EtO)_2P(O)CFHZnBr$ with a 1-haloalkene.[17] We have now re-examined the conditions leading to the preparation of cis α–fluoroallylphosphonates by hydrogenation of the triple bond present in **1**. A discussion of our findings is described in the following section.

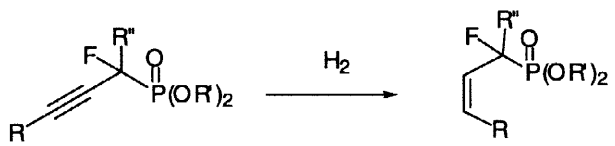
Another synthetically important feature of **1** is the presence of the phosphonate group, capable of undergoing a modified Horner-Wadsworth-Emmons (HWE) olefination with an aldehyde or ketone, to yield conjugated fluoroenyne **4**. The chemistry and biology of conjugated enynes have received extensive coverage in recent years.[18-20] Conjugated enynes are useful building blocks in organic synthesis, providing an efficient means of incorporating high levels of unsaturation.[21,22] Recognizing an opportunity to investigate the effects of fluorine substitution in conjugated enynes, we set out to develop a methodology for the synthesis of fluoroenynes. An inspection of the relevant literature on the preparation of fluorinated enynes revealed less than a handful of palladium-catalyzed cross coupling reactions of fluorinated olefins that ultimately yielded 1,2-difluoro-1-buten-3-ynes.[23-25] The synthesis of monofluoroenynes is even less documented.[6,26,27] Conversely, the synthesis of fluoroalkenes using HWE conditions has been known for some time.[28,29] In an earlier communication,[30] we reported the crystallographic analysis of (*Z*)-**4** (R'=H, R"=C_6H_4-NO_2) obtained in very low yield through a HWE condensation of **1a**. Interestingly, X-ray analysis of (*Z*)-**4** exhibited shorter bond lengths compared to its nonfluorinated counterpart, thus implying a higher degree of conjugation. Herein we report a full account of our improved synthesis of conjugated fluoroenynes from a common precursor, (α-fluoropropargyl) phosphonate **1**, via HWE olefination.

RESULTS AND DISCUSSION

During the course of our hydrogenation studies of **1**, we found that reaction conditions leading to the synthesis of **3** were sensitive to the nature of the starting (α-fluoropropargyl) phosphonate ester. For example, atmospheric pressure hydrogenation of **1a** in methanol using Lindlar catalyst supported on alumina (method A), led to very good yields of **3a**, (entry 1, Table 1). The stereochemistry of the double bond as well as the chemical shift assignment for the vinylic protons were confirmed by NOE experiments. Attempts to use this catalyst with other substrates led to the recovery of starting material (entries 2 and 4). In the case of R^1=TMS, the silyl group on the terminal sp carbon protects the triple bond from hydrogenation, even at 40 psi (entry 3).[31] A search for more effective hydrogenation conditions, led us to a report by Prestwich and Sun[32] on the efficient partial hydrogenation of 11,11-difluorododec-9-inyl acetate to the corresponding *(Z)* -alkene, using quinoline-poisoned $Pd/BaSO_4$ in pyridine. Adoption of this catalyst in our hydrogenation protocol that consisted of bubbling hydrogen, at atmospheric pressure, into an ethanolic solution of aromatic α-fluoroalkynephosphonate (method

B), furnished very good to excellent yields of *(Z)* -alkene (entries 5 and 6). Increasing the degree of substitution on the propargylic carbon (R"=Me), had a deleterious effect on the reduction process (entry 7). This situation could be reversed and the desired alkene obtained in excellent yields, if the hydrogenation was conducted in a solution of pyridine at 40 psi, (method C) using the same catalyst (entry 8). A similar experimental condition was also utilized to partially hydrogenate a non-aromatic (α-fluoropropargyl) phosphonate ester in high yield (entry 9). Replacing pyridine with ethanol slowed the rate of hydrogenation of the non-aromatic (α-fluoropropargyl) phosphonate ester (entry 10). In sum, we have found that quinoline-poisoned $Pd/BaSO_4$ in either pyridine or ethanol at atmospheric pressure or 40 psi are suitable conditions for achieving partial hydrogenations of a wide variety of (α-fluoropropargyl) phosphonates.

Table 1.
Catalytic Hydrogenation of (α-Fluoropropargyl) phosphonate Esters **1**



1 R" = H, Me **3** a - e

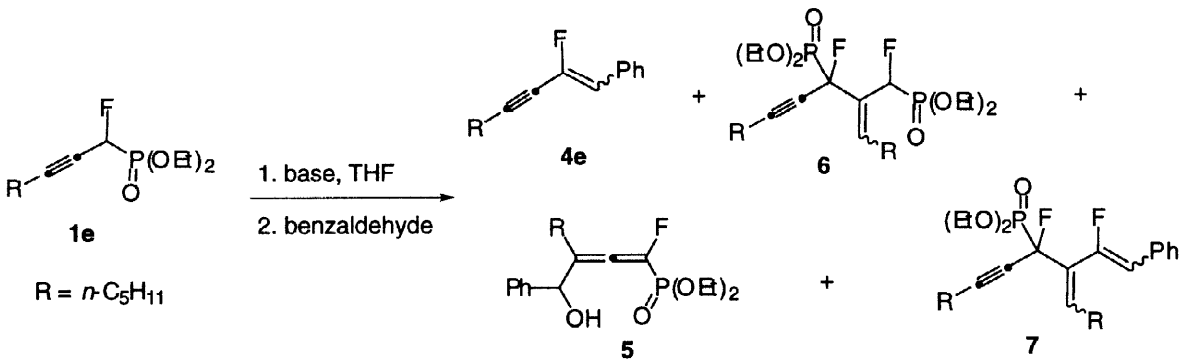
Entry	R	R'	R"	Method[a]	Time (h)	Solvent	Yield[b] of 3 (%)
1	Me	Et	H	A	4	MeOH	**3a** (89)
2	TMS	Et	H	A	6.5	MeOH	NR[c]
3	TMS	Et	H	A[d]	10	MeOH	NR
4	Ph	Et	H	A	3.5	MeOH	<40[e]
5	Ph	Et	H	B	3.5	EtOH	**3b** (75)
6	Ph	2-ethylhexyl	H	B	5.5	EtOH	**3c** (90)
7	Ph	Et	Me	B	3	EtOH	NR
8	Ph	Et	Me	C	48	pyridine	**3d** (99)
9	C_5H_{11}	Et	H	C	7	pyridine	**3e** (85)
10	C_5H_{11}	Et	H	C	10	EtOH	<10[e]

[a]method A: atmospheric hydrogenation using Lindlar catalyst supported on alumina; method B: atmospheric hydrogenation using quinoline-poisoned $Pd/BaSO_4$; method C: Parr hydrogenation at 40 psi using quinoline-poisoned $Pd/BaSO_4$. [b]after catalyst filtration and solvent removal. [c]NR=no reaction. [d]Parr hydrogenation at 40 psi. [e]yield was determined by GC-MS.

The search for optimal conditions for the synthesis of fluoroenyne **4**, starting from fluorophosphonate **1**, using a HWE olefination,[33] was laborious, due to the inherent instability of the α-carbanion of **1**. In the presence of a traditional strong base such as NaH, the reaction of **1** and benzaldehyde led repeatedly to an intractable mixture, or minimal yields of fluoroenyne. Use of milder basic conditions such as K_2CO_3 in CH3CN

at 25°C,[34] BaOH in aqueous THF,[35] or LiOH in THF at room temperature[36] afforded enyne **4** (1:1 *E/Z*), in less than 10% yield. A similar result was obtained in the presence of DBU/LiCl in CH_3CN at 0°C.[37] Interestingly, the presence of an alkali metal salt was essential for the success of the reaction. Use of DBU alone in CH_3CN at 0°C led to an unidentified mixture of products as did a combination of DBU and $CeCl_3$ under the same conditions. Whether the stabilizing effect imparted by an alkali metal cation was due to interaction with the initial anion or a betaine-like intermediate was not known at first. Use of lithium bis(trimethylsilyl)amide ($LiNTMS_2$) the conditions described in entry 1, Table 2, produced some surprising results.

Table 2.
Reaction of (α-Fluoropropargyl) phosphonate **1e** with benzaldehyde.

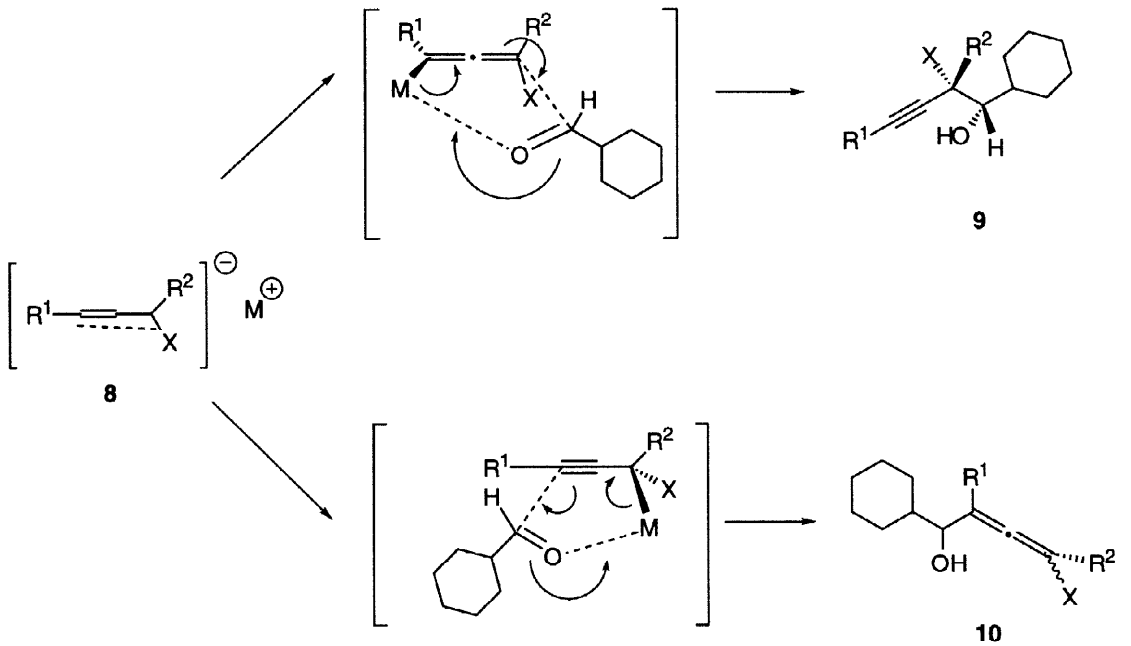


Entry	Reaction Conditions	4e	5	6	7
1	$LiNTMS_2$ (1 equiv) added to substrate at -80°C, stirring for 1 h; addition of benzaldehyde; warm up to RT	traces	–	>21%	>2%
2	$LiNTMS_2$ (1 equiv) added to substrate at -110°C, stirring for 10 min; addition of benzaldehyde; warm up to RT	31%	30%	traces	2%
3	Substrate added to LDA at -110°C, benzaldehyde added inmediately; warm up to RT	38%	29%	traces	traces
4	$KNTMS_2$ (1.1 equiv) added to a mixture of substrate and benzaldehyde at -80°C and warm up to RT	54%	20%	traces	–

While only traces of the desired enyne **4e** were observed, under two other spots of lower Rf in TLC caught our attention. After their separation by column chromatography, it was noticed by ^{19}F NMR that two distinct fluorine atoms were present in each one of the two unknowns. Mass spectrum (FAB) and two dimensional NMR analysis (HMBC and HMQC) helped to identify them as the fluorophosphonate dimer **6** and its olefinic derivative **7**. When the reaction was repeated at lower temperature (-110°C), only trace amounts of **6**

and **7** were detected. This time, enyne **4** was obtained in 31% yield accompanied by 30% α-fluoro-δ-hydroxyallenylphoshonate **5** (entry 2). Use of lithium diisopropylamide (LDA) under inverse addition conditions improved the ratio of **4** to **5** slightly (entry 3). Our results are in line with Yamamoto and coworkers[38] who found that the lithio reagent **8** (M=Li, R^1=Me, X=H, R^2=H), (Scheme 1) gave approximately equimolar mixtures of β-acetylenic alcohol **9** and α-allenic alcohol **10** upon condensation with cyclohexylcarbaldehyde.

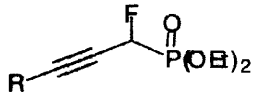
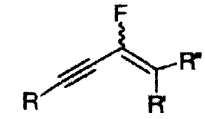
Scheme 1.
The regioselectivity of the reaction of propargylic anion **8** with cyclohexylcarbaldehyde.

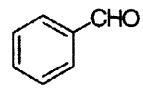
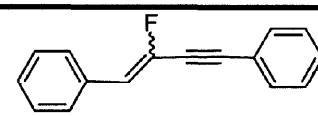
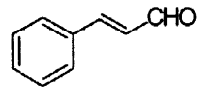
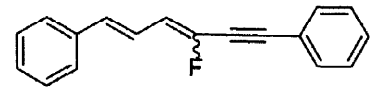
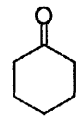
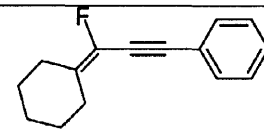
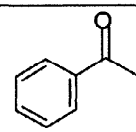
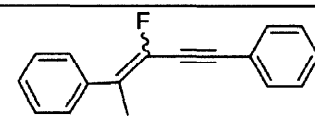
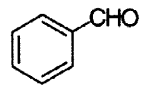
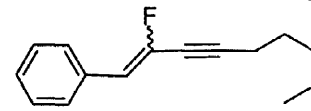
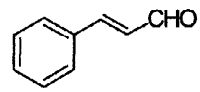
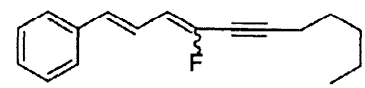
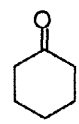
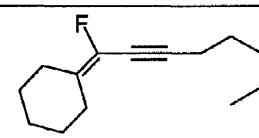
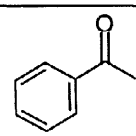
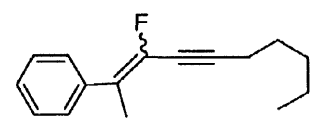
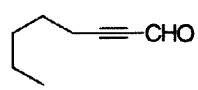
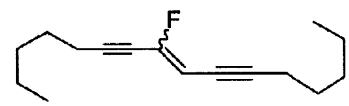
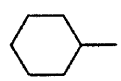
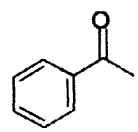
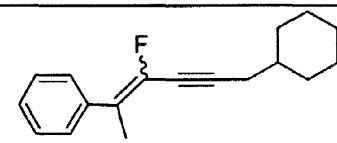


The structure and reactivity of ambident anions such as **8**, are highly dependent on the nature of the countercation and the solvent. In the present work, changing from M=Li to M=K will presumably disrupt the coordinating ability of the metal ion, leading to the operation of an acyclic transition state involving a relatively naked propargylic carbanion. Indeed, use of $KN(TMS)_2$ in THF provided superior results, affording enyne **4e** in almost 3 to 1 ratio with respect to allene **5** (entry 4). Differding and coworkers[39] also noted the importance of the alkali metal countercation in the electrophilic fluorination of alkylphosphonate anions. For example, deprotonation of CH_3-CHF-P(O)$(OEt)_2$ using LDA, and reaction of the resulting anion with N-fluorobenzenesulfonimide (NFSI) afforded the corresponding difluoro derivative in only 20% yield. However, when lithium was replaced by potassium, the yield increased to 66%.

Our modified conditions have proven readily compatible with both aldehydes and ketones, providing a simple route to a variety of linear and exocyclic fluorinated conjugated enynes in approximately 1:1 ratio of *cis*

Table 3.
Synthesis of Conjugated Fluoroenyne **4**

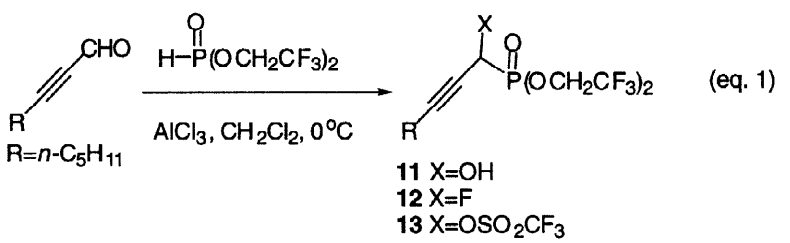
1b,e,f  1) $KN(TMS)_2$, THF, -80°C to rt; 2) R'-C(O)-R"  **4 a - j**

Entry	R	R'-C(O)-R"	4	Yield[a]	E/Z[b]
1	 **(1b)**			**4a** (28 %)	75/25
2				**4b** (35 %)	36/64
3				**4c** (40 %)	–
4				**4d** (21 %)	57/43
5	 **(1e)**			**4e** (54 %)	61/39
6				**4f** (58 %)	48/52
7				**4g** (58 %)	–
8				**4h** (50 %)	42/58
9				**4i** (4%)[c]	47/53
10	 **(1f)**			**4j** (58 %)	48/52

[a] Isolated yields. [b] Based on NMR. [c] LDA was used as the base.

and *trans* isomers (Table 3). For reasons that are still unclear, when R=phenyl, the yields of conjugated enynes were consistently lower (entries 1-4) than for other (α-fluoropropargyl) phosphonate derivatives, and the reaction of fluorophosphonate **1e** with 2-octynal produced only minimal yields of enediyne **4i** (entry 9).

Attempts to expand this protocol to aliphatic aldehydes possessing α-protons met with failure. In all cases, the major product isolated corresponded to a self-aldol condensation of the aldehyde. In an effort to improve the stereoselectivity of the newly formed double bond, we examined the effects of the phosphonate ester substituent on the stereochemistry of the HWE olefination. Substituting the OCH_2CH_3 group with a bulkier group such as $OCH_2CH(Et)(n\text{-}Bu)$ (i.e., **1c**) did not improve the ratio of *E/Z* isomers. An alternate strategy, pioneered by Still,[40] was to increase the electron-withdrawing nature of the phosphonate group by replacing the OCH_2CH_3 group with the OCH_2CF_3 moiety. This substituent would accelerate the final elimination step of the oxyphosphonate anion intermediate, thus allowing the (initial) nucleophilic attack by the phosphonate anion on the C=O group to become rate-determining and irreversible. Hence, the initially (kinetically) favored oxyphosphonate eliminates to give the (*Z*) alkene. To this end, we decided to synthesize **11** and convert it to its (α-fluoropropargyl) phosphonate derivative **12** by substituting the hydroxy group with fluorine. The presence of six fluorine atoms in $H\text{-}P(O)(OCH_2CF_3)_2$ drastically reduced the nucleophilic nature of the phosphorus atom, and so it was not surprising when no reaction took place upon mixing 2-octynal and bis(trifluoroethyl)phosphite under basic conditions. We chose to enhance the electrophilic nature of the carbonyl group in 2-octynal by using one equivalent of a Lewis acid such as $AlCl_3$ in CH_2Cl_2 (eq. 1). Under these conditions, we obtained the desired (α-hydroxypropargyl) phosphonate **11** in 60 % yield. The next step, conversion of **11** to **12**, did not proceed as expected. DAST fluorination failed to produce **12**. Rather, it yielded an unidentified mixture of compounds. We were able to convert the hydroxy group into a better leaving group such as triflate **13** (89%) but all our attempts to displace it with a source of F^- (CsF, TBAF) yielded either starting material or unidentified mixtures.



(eq. 1)

CONCLUSION

We have begun to demonstrate the potential building block properties of (α-fluoropropargyl) phosphonate esters by developing experimental conditions leading to the preparation of *cis*-(α-fluoroallyl) phosphonates via catalytic hydrogenation; and *cis* and *trans* isomers of conjugated fluoroenynes, via HWE olefination. We are currently exploring the synthetic repercussions of preparing stable α-anions of **1** mediated by the functionalization of the γ-carbon.

EXPERIMENTAL SECTION

Materials and Methods. For general details regarding instrumentation, reaction conditions, spectral parameters and the preparation of (α-fluoropropargyl)phosphonate ester **1, see reference** [7].

Method A. *(Z)* Diethyl 1-Fluorobut-2-enylphosphonate (3a). Hydrogen was bubbled slowly during 4 h into a stirred solution of **1a** (0.30 g, 1.4 mmol) in methanol (20 mL), in the presence of Lindlar's catalyst supported on alumina (2.5 g, 1% Pd). The mixture was filtered through a Celite pad and concentrated to give **3a** (0.26 g, 89%) as a colorless oil. An analytically pure sample was obtained by flash column chromatography (silica gel, hexane:ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.36 (td, J_{HH}= 7.07 Hz, J_{HP}=2.66 Hz, 6H, CH_3), 1.77 (m, 3H, CH_3), 4.21 (m, 4H, OCH_2), 5.48 (dm, J_{HF}= 46.3 Hz, 1H, CHF), 5.65 (m, 1H, CH=), 5.97 (m, 1H, CH=); ^{31}P NMR δ 16.9 (d, J_{PF} = 83.84 Hz); ^{19}F NMR δ −199.7 (d, J_{FP}= 83.84Hz); GC-MS 210 (M^+, 0.2), 138 (19), 109 (77), 91 (30), 81 (100), 53 (73). Anal Calcd. for $C_8H_{16}FO_3P$: C, 45.71; H, 7.67. Found: C, 45.64; H, 7.72.

Method B. Representative Procedure for *(Z)* Bis(2-ethylhexyl) 1-Fluoro-3-phenylprop-2-enylphosphonate (3c). Catalytic amounts of quinoline-poisoned Pd/$BaSO_4$ (5% Pd, reduced) were added to a solution of **1c** (0.16 g, 36 mmol) in ethanol (15 mL) and the mixture was placed in a bottle housed in a Parr hydrogenation apparatus shaker but left open to the atmosphere. Hydrogen was bubbled under vigorous agitation for 5.5 h at room temperature after which the catalyst was filtered off with the aid of Celite and the solvent was removed. Neutralization of the residue using 20% aq HCl was followed by extraction with CH_2Cl_2 (3X20mL). The combined organic layers were dried over $MgSO_4$ and concentrated to yield **3c** (0.14 g, 90%). An analytical sample was obtained using preparative TLC (silica gel, hexane: ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.88 (t, J_{HH}=7.1 Hz, 12H, CH_3) 1.34 (m, 16H, $-C(CH_2)CH_2CH_2CH_2$) 1.60 (m, 2H, CH), 4.09 (m, 4H, OCH_2), 5.62 (ddd, J_{HF}=46.8 Hz, J_{HP}=12.2 Hz, J_{HH}=6.5 Hz, 1H, CHF), 5.94 (ddd, J_{HF}=21.6 Hz, J_{HH}=10.8 Hz, J_{HH}=6.5 Hz, 1H, CH=), 7.00 (dd, J_{HH}=10.8 Hz, J_{HF}=5.0 Hz, 1H, PhCH=), 7.37 (m, 5H, phenyl); ^{31}P NMR δ 17.00 (d, J_{PF}=83.67 Hz); ^{19}F NMR δ −190.75 (d, J_{FP}=81.87 Hz); GC-MS 217 (39), 197 (18), 35 (100), 15 (49), 71 (99). Anal Calcd. for $C_{25}H_{42}FO_3P$: C, 68.18; H, 9.55. Found: C: 68.38, H, 9.72.

***(Z)* Diethyl 1-Fluoro-3-phenylprop-2-enylphosphonate (3b).** A solution of **1b** (0.19 g, 0.71 mmol) in ethanol (10 mL) was hydrogenated following method B, yielding **3b** (0.15 g, 75%). An analytical sample was obtained using preparative TLC (silica gel, hexane:ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.39 (m, 6H, CH_3), 4.25 (m, 4H, OCH_2), 5.60 (ddd, J_{HF}=46.00 Hz, J_{HP}=10.31 Hz, J_{HH}=5.52 Hz, 1H, CHF), 5.95 (ddd, J_{HF}=21.92 Hz, J_{HH}=10.82 Hz, J_{HH}=6.03 Hz, 1H, CH=), 7.01 (dd, J_{HH}=11.46 Hz, J_{HF}=4.60 Hz, 1H, PhCH=), 7.40 (m, 5H, phenyl); ^{31}P NMR δ 16.95 (d, J_{PF}=83.27 Hz); ^{19}F NMR δ −191.14 (d, J_{FP}=82.58 Hz); GC-MS 272 (M^+, 10), 135 (100), 15 (79), 09 (52), 81 (38). Anal Calcd. for $C_{13}H_{18}FO_3P$: C, 57.35; H, 6.62. Found: C: 57.60, H, 6.73.

Method C. Representative Procedure for *(Z)* Diethyl 1-fluorooct-2-enylphosphonate (3e). Catalytic amounts of quinoline-poisoned $Pd/BaSO_4$ (5% Pd, reduced), **1e** (0.49 g, 1.9 mmol) and pyridine (10 mL) were placed under a hydrogen atmosphere in a bottle in a Parr hydrogenation apparatus at 40 psi and vigorously agitated for 7 h, after which the solution was neutralized with 20% aq HCl and the catalyst was filtered with the aid of Celite. The aqueous layer was extracted with CH_2Cl_2 (3X20mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated to give **3e** (0.42 g, 85%). An analytical sample was obtained via column chromatography (acidic Al_2O_3, 150 mesh, hexane: ethyl acetate 8:2). ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.88 (t, J_{HH}=6.1 Hz, 3H, CH_3) 1.34 (m, 12H, CH_3 and $CH_2CH_2CH_2$), 2.14 (m, 2H, CH_2), 4.18 (m, 4H, OCH_2), 5.44 (ddd, J_{HF}=49.4 Hz, J_{HP}=13.7 Hz, J_{HH}=6.8 Hz, 1H, CHF), 5.62 (ddd, J_{HF}=25.4 Hz, J_{HH}=10.3 Hz, J_{HH}=6.8 Hz, 1H, CH=), 5.88 (dd, J_{HH}=10.3 Hz, J_{HF}=4.1 Hz, 1H, CH=); ^{31}P NMR δ 17.11 (d, J_{PF}=84.63 Hz); ^{19}F NMR δ −197.58 (d, J_{FP}=88.08 Hz); GC-MS 217 (22), 152 (13), 38 (39), 11 (100), 91 (24), 81 (83). Anal Calcd. for $C_{12}H_{24}FO_3P$: C, 54.13; H, 9.02. Found: C: 54.35, H, 9.13.

***(Z)* Diethyl 1-Fluoro-1-methyl-3-phenylprop-2-enylphosphonate (3d).** A solution of **1d** (0.05 g, 0.16 mmol) in pyridine (10 mL) was hydrogenated following method C, yielding **3d** (0.04 g, 99%). An analytical sample was obtained via preparative TLC (silica gel 60, hexane:ethyl acetate 8:2). ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.34 (t, J_{HH}=7.2 Hz, 6H, CH_3), 1.71 (dd, J_{HF}=23.5 Hz, J_{HP}=16.2 Hz, 3H, CH_3), 4.21 (m, 4H, OCH_2), 5.73 (ddd, J_{HF}=27.94 Hz, J_{HH}=12.96 Hz, J_{HH}=3.91 Hz, 1H, CH=), 6.70 (d, J_{HH}=12.95 Hz, 1H, PhCH=), 7.34 (m, 5H, phenyl); ^{31}P NMR δ 18.47 (d, J_{PF}=85.87 Hz); ^{19}F NMR δ −163.10 (d, J_{FP}=88.76 Hz); GC-MS 286 (M^+, 6), 149 (100), 29 (59), 09 (22), 81 (28). Anal Calcd. for $C_{14}H_{20}FO_3P$: C, 58.74; H, 6.99. Found: C: 58.75, H, 7.05.

Reaction of 1e with Lithium Bis(trimethylsilyl)amide [$LiN(TMS)_2$] (entry 1, Table 2). Diethyl 1,3-Difluoro-2-hexenylidene-3-(diethoxyphosphoryl)dec-4-ynylphosphonate (6).

$LiN(TMS)_2$ (1.0 mL of a 1 M solution in THF, 1.0 mmol) was added dropwise to a cold solution (-80°C) of **1e** (0.2423 g, 0.92 mmol) in THF (5 mL). After 1 h, benzaldehyde (0.09 mL, 0.89 mmol) was added and the resulting reaction mixture was allowed to warm up to room temperature. Then, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ether (3x10 mL). The combined organic extracts were dried over MgSO4 and concentrated. The crude product was purified by flash chromatography (silica gel, hexane: ethyl acetate 2:3) afforded a non-polar fraction and **6** (0.050 g, 21%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.85-0.92 (m, 6H, CH_3), 1.28-1.68 (m, 24H, CH_3 and $CH_2CH_2CH_2$), 2.27-2.39 (m, 2H, CH_2), 2.54 (broad multiplet, 2H, CH_2), 4.11-4.35 (m, 8H, OCH_2), 5.59 (dd, J_{HF}=43.5 Hz, J_{HP}=11.5 Hz, 1H of the major isomer, CHF), 5.70 (dd, J_{HF}=43.4 Hz, J_{HP}=11.5 Hz, 1H of the minor isomer, CHF), 6.34-6.41 (m, 1H of the major isomer, CH=), 6.45-6.51 (m, 1H of the minor isomer, CH=). ^{19}F NMR δ -151 (apparent d, J_{FP}=95.0 Hz), -154 (apparent dd, J_{FP}=96.6 Hz, J =12 Hz), -196 (apparent d, J_{FP}=91.6 Hz), -200 (apparent dd, J_{FP}=90.8 Hz, J =12 Hz). ^{31}P NMR major isomer δ 12.02 (apparent d, J_{PF}=97.41 Hz), δ 16.78 (apparent d, J_{PF}=94.50 Hz), minor

isomer δ 12.66 (apparent d, J_{PF}=98.84 Hz), δ 16.51 (apparent d, J_{PF}=88.75 Hz); IR (neat, NaCl) ν 2930, 2235, 1270, 1130, 980 cm^{-1}. Anal. Calcd for $C_{24}H_{44}F_2O_6P_2$: C, 54.54; H, 8.39. Found: C, 54.69; H, 8.36.

Flash chromatography (silica gel, hexane: ethyl acetate 7:3) of the non-polar fraction afforded an unidentified compound (0.0168 g) and **7** (0.0039 g, 2%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.84-0.97 (m, 6H, CH_3), 1.26-1.58 (m, 18H, CH_3 and $CH_2CH_2CH_2$), 2.32-2.40 (m, 4H, CH_2), 4.10-4.31 (m, 4H, OCH_2), 5.30-5.35 (m, 1H, CH=), 6.32 (d, J_{HF}=41.0 Hz, 1H major isomer, PhCH=), 6.45 (d, J_{HF}=19.73 Hz, 1H minor isomer, PhCH=), 7.18-7.37 (m, 3H, phenyl), 7.56-7.59 (m, 2H, phenyl). ^{31}P NMR δ 16.0 (d, J_{PF}=109.2 Hz, minor isomer), 16.6 (d, J_{PF}=112.6 Hz, major isomer). ^{19}F NMR δ -105 (s), -118 (s), -167 (d, J_{FP}=109.2 Hz), -170 (d, J_{FP}=113.0 Hz).

Reaction of 1e with $LiN(TMS)_2$ (entry 2, Table 2). 2-Fluoro-1-phenylnon-1-ene-3-yne (4e) and Diethyl 1-Fluoro-4-hydroxy-3-pentyl-4-phenyl-buta-1,2-dienylphosphonate (5).

To a solution of $LiN(TMS)_2$ (0.40 mL of a 1 M solution in THF, 0.40 mmol) in THF (2 mL) at -110°C was added dropwise a solution of **1e** (0.0966 g, 0.36 mmol) in THF (1 mL). After stirring for 10 min, benzaldehyde (0.040 mL, 0.39 mmol) was added neat and the reaction was allowed to reach room temperature. The reaction was poured into saturated aqueous NH_4Cl (10 mL) and extracted with ether (3x15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, hexane: ethyl acetate 3:2) to afford **4e** (0.0247 g, 31%) as a 3:2 *Z*:*E* mixture, and **5** (0.0409 g, 30 %).

4e : ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.92 (m, 3H, CH_3), 1.40 (m, 6H, *(Z)*-$CH_2CH_2CH_2$), 1.61 (m, 6H, *(E)*-$CH_2CH_2CH_2$), 2.39 (td, J_{HF} = 4.96 Hz, J_{HH}=7.08 Hz, 2H *(Z)*-≡CCH_2), 2.48 (td, J_{HF} = 5.35 Hz, J_{HH}=7.01 Hz, 2H *(E)*-≡CCH_2), 5.93 (d, J_{HF} = 35.19 Hz, 1H, *(Z)*-CH=), 6.49 (d, J_{HF} = 17.06 Hz, 1H, *(E)*-CH=), 7.28 (m, 3H, phenyl), 7.48 (m, 2H, *(Z)*-phenyl), 7.62 (m, 2H, *(E)*-phenyl); ^{19}F NMR δ -102.00 (s, *(Z)*-isomer), -99.66 (s, *(E)*-isomer); IR (NaCl, neat) ν 3045, 3025, 2960, 2930, 2865, 2230, 1640, 1450, 1150, 755, 695 cm^{-1}; EIMS 216 (M^+, 41), 173 (12), 159 (100), 146 (46), 133 (83), 109 (17), 91(25). Anal. Calcd for $C_{15}H_{17}F$: C, 83.29; H, 7.92. Found: C, 83.53; H, 8.01.

5 : ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.81-0.86 (m, 3H, CH_3), 1.21-1.46 (m, 12H, CH_3 and $CH_2CH_2CH_2$), 2.02-2.10 (m, 2H, =CCH_2), 4.07-4.22 (m, 4H, OCH_2), 5.31 (dd, J_{HF}=7.25 Hz, J_{HP}=2.13 Hz, 1H, CH), 7.26-7.47 (m, 5H, phenyl); ^{19}F NMR δ -150.74 (d, J_{FP}= 121.97 Hz); ^{31}P NMR ($CDCl_3$) δ 7.22(d, J_{PF}= 121.80 Hz); IR (NaCl, neat) ν 3350, 2925, 2860, 1955, 1250, 1080, 1020, 970, 700 cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_4FP$: C, 61.61; H, 7.62. Found: C, 61.77; H, 7.61.

Representative Procedure for the Preparation of Fluoroenyne 4. Synthesis of 2-Fluoro-1-phenylnon-1-ene-3-yne (4e)

To a solution of **1e** (0.1419 g, 0.54 mmol) and benzaldehyde (0.11 mL, 1.08 mmol) in THF (5 mL) at -80°C was added potassium bis(trimethylsilyl)amide [$KN(TMS)_2$] (0.1256 g, 0.63 mmol) in one portion. After the addition, the reaction was allowed to reach room temperature, poured into saturated aqueous NH_4Cl (20 mL) and extracted with ether (3x20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated.

The crude product was separated by flash chromatography (silica gel, hexane: ethyl acetate 3:2) to afford **4e** (0.0622 g, 54%) as a 3:2 *Z:E* mixture and **5** (0.0396 g, 20 %).

2-Fluoro-1,4-diphenylbut-1-en-3-yne (4a)

$KN(TMS)_2$ (0.0899 g, 0.44 mmol) was added to a stirred solution of **1b** (0.0997 g, 0.37 mmol) and benzaldehyde (0.06 mL, 0.56 mmol) in THF (5 mL). The colored solution was allowed to stir for 1 h at -80°C and then for an additional 19.5 h at ambient temperature after which water (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (3 x 25 mL). Combined organic phases were washed with sat. $NaHSO_3$ solution (2 x 25 mL) to remove excess aldehyde, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, hexane: ethyl acetate 8:2) to afford **4a** (0.0230 g, 28%) as a 75:25 *Z:E* mixture. ^{1}H NMR ($CDCl_3$, 300MHz) δ 6.15 (d, J_{HF}= 34.5 Hz, 1H, *(Z)*-CH=), 6.67 (d, J_{HF}= 15.4 Hz, 1H, *(E)*-CH=), 7.25 - 7.75 (m, 10H, phenyl); ^{19}F NMR δ -102.63 (s, *(Z)*-isomer), -104.39 (s, *(E)*-isomer); EIMS 223 (M+1, 18), 222 (M+, 100), 221 (85), 220 (87), 219 (11), 202 (17), 111 (9), 110 (22), 98 (13). Anal calcd. for $C_{16}H_{11}F$: C, 86.46; H, 4.99. Found: C, 86.22; H, 5.08.

4-Fluoro-1,6-diphenylhexa-1,3-dien-5-yne (4b)

$KN(TMS)_2$ (0.0598 g, 0.30 mmol), **1b** (0.0682 g, 0.25 mmol) and cinnamaldehyde (0.38 mL, 0.30 mmol) in THF (4 mL) were mixed as above and stirred for 20 h at -78°C. After work up and concentration an orange oil (0.0429) was obtained, which was purified by flash chromatography (silica gel, hexane: ethyl acetate 8:2) to afford **4b** (0.0153 g, 35 %) as 36:64 *Z:E* mixture. ^{1}H NMR ($CDCl_3$, 300MHz) δ 6.09 (dd, J_{HH}= 11.37 Hz, J_{HF} = 30.94 Hz, 1H, *(Z)*-CH=), 6.45 (apparent t, J_{HF} = 11.95 Hz, 1H, *(E)*-CH=) , 6.66 (d, J_{HH}= 16.76 Hz, 1H, *(Z)*- and *(E)*-PhCH=), 6.97 (ddd, J_{HF}= 1.68 Hz, J_{HH}= 11.40 Hz, J_{HH}= 15.85 Hz,. 1H, *(Z)*-CH=), 7.14 (dd, J_{HH}= 16.00 Hz, J_{HH}= 11.31 Hz, 1H, *(E)*-CH=), 7.25 - 7.62 (m, 10H, phenyl); ^{19}F NMR δ -107.07 (s, *(Z)*-isomer), -108.45 (s, *(E)*-isomer); EIMS 248 (M+1, 78), 247 (M+, 100), 246 (50), 245 (18), 244 (20), 233 (51), 228 (29), 227 (31), 226 (50), 220 (24), 171 (21), 170 (39), 146 (24), 115 (15), 113 (16), 101 (11), 63 (20), 51 (31), 50 (16), 39 (24). HRMS calcd for $C_{18}H_{13}F$: 248.1001, Found: 248.1000.

3-Cyclohexylidene-3-fluoro-1-propynylbenzene (4c)

$KN(TMS)_2$ (0.2416 g, 1.2 mmol), **1b** (0.2643 g, 1 mmol) and cyclohexanone (0.12 mL, 1.2 mmol) in THF (14 mL) were mixed and stirred for 10 min at -78°C. After workup, concentration and chromatography (silica gel, hexane), **4c** (0.0876 g, 40 %) was obtained as a pale-green oil. ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.02 - 1.26 (m, 2H, CH_2), 1.56 - 1.62 (m, 4H, CH_2), 2.31 - 2.37 (m, 4H, CH_2), 7.26 - 7.49 (m, 5H, phenyl); ^{19}F NMR δ -119.82 (s); EIMS 215 (M+1, 9), 214 (M+, 60), 185 (31), 171 (26), 170 (20), 165 (26), 159 (21), 146 (100), 133 (30), 115 (14), 81 (13), 63 (13), 51 (14), 39 (29). HRMS calcd for $C_{15}H_{15}F$: 214.1158, Found: 214.1162.

3-Fluoro-2,4-diphenylpent-2-ene-4-yne (4d)

$KN(TMS)_2$ (0.1199g, 0.6mmol), **1b** (135 mg, 0.5 mmol), acetophenone (0.069 ml, 0.06mmol) in THF (5 mL) were mixed and stirred following the general method described for **4e.** The resulting yellow oil was purified by column chromatography (silica gel, hexane: ethyl acetate 4:1) to give **4d** (0.025g, 21%) as 57:43 *Z:E* mixture. ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.19 (d, J_{HF}= 4.02 Hz, 3H, *(E)*-CH_3), 2.27 (d, J_{HF}= 3.32 Hz, 3H, *(Z)*-CH_3), 7.2-7.7 (m, 10H, phenyl); ^{19}F NMR δ -107.8 (s, *(Z)*-isomer), -111.6 (s, *(E)*-isomer); EIMS 236 (39), 159

(17), 133 (26), 107 (21), 89 (20), 63 (52), 51 (100). Anal. Calcd for $C_{17}H_{13}F$: C, 84.37; H, 8.20. Found: C, 84.13; H, 8.40.

4-Fluoro-1-phenylundeca-1,3-diene-5-yne (4f)

Following the general protocol described above, $KN(TMS)_2$ (0.1199g, 0.6mmol), **1e** (132 mg, 0.5 mmol) and trans-cinnamaldeyde (0.16 ml, 1.25mmol) in THF (5 mL) afforded, after column chromatography (silica gel, hexane: ethyl acetate 4:1) **4f** (0.070g, 58%) as 48:52 *Z:E* mixture. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.90 (t, J_{HH} = 7 Hz, 3H, CH_3), 1.20-1.72 (m, 6H, $CH_2CH_2CH_2$), 2.42 (q, J_{HH}= 7 Hz, 2H, *(Z)*-≡CCH_2), 2.52 (q, J_{HH}= 7 Hz, 2H, *(E)*-≡CCH_2), 5.89 (dd, J_{HF}= 30.83 Hz, J_{HH}= 11.26 Hz, 1H, *(Z)*-CH=), 6.31 (t, J_{HF}=J_{HH}= 11.80 Hz, 1H, *(E)*-CH=), 6.59 (dd, J_{HH}= 21.11 Hz, J_{HH}= 15.8 Hz, 1H, *(Z)*- and *(E)*-PHCH=), 6.88 (ddd, J_{HH}= 15.71 Hz, J_{HH}= 11.19 Hz, J_{HF}=1.67 Hz, 1H, *(Z)*-CH=), 7.08 (dd, J_{HH}= 15.81 Hz, J_{HH}= 11.17 Hz, 1H, *(E)*-CH=), 7.22-7.48 (m, 5H, phenyl); ^{19}F NMR δ -104.59 (s, *(Z)*-isomer), -105.92 (s, *(E)*-isomer); EIMS 242 (M^+, 37), 199 (22), 165 (69), 160 (35), 115 (24), 91 (26), 55 (30), 29 (100). Anal. Calcd for $C_{17}H_{19}F$: C, 84.29; H, 7.85. Found: C, 84.29; H, 7.91.

1-Cyclohexylidene-1-fluoro-2-octyne (4g)

$KN(TMS)_2$ (0.1199g, 0.6mmol), **1e** (132 mg, 0.5 mmol), cyclohexanone (0.062 ml, 0.6mmol) in THF (5 mL) were mixed and stirred following the general procedure described for **4e**. The resulting yellow oil was purified by column chromatography (silica gel, hexane: ethyl acetate 4:1) to give **4g** (0.060g, 58%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.90 (t, J_{HH}= 7 Hz, 3H, CH_3), 1.20-1.72 (m, 12H, $CH_2CH_2CH_2$), 2.24 (m, 4H, =CCH_2), 2.40 (q, J_{HH}= 7 Hz, 2H, ≡CCH_2), ^{19}F NMR δ -118.03 (s); EIMS 208 (M^+, 16), 153 (6), 123 (16), 109 (45), 91 (33), 67 (42), 29 (100). HRMS calcd for $C_{14}H_{21}F$ 208.1627 Found 208.1629.

3-Fluoro-2-phenyldec-2-ene-4-yne (4h)

$KN(TMS)_2$ (0.1199g, 0.6mmol), **1e** (132 mg, 0.5 mmol), acetophenone (0.069 ml, 0.6mmol) in THF (5 mL) were mixed and stirred following the general method described for **4e**. The resulting yellow oil was purified by column chromatography (silica gel, hexane: ethyl acetate 4:1) to give **4h** (0.058g, 50%) as 42:58 *Z:E* mixture. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.86 (t, J_{HH}=7 Hz, 3H, *(E)*-CH_3), 0.92 (t, J_{HH} = 7 Hz, 3H, *(Z)*-CH_3), 1.20-1.72 (m, 6H, $CH_2CH_2CH_2$), 2.10 (d, J_{HF}= 3.97 Hz, 3H, *(E)*-CH_3), 2.15 (d, J_{HF}= 3.28 Hz, 3H, *(Z)*-CH_3), 2.28 (q, J_{HH}= 7 Hz, 2H, *(E)*-≡CCH_2), 2.44 (q, J_{HH}= 7 Hz, 2H, *(Z)*-≡CCH_2), 7.2-7.5 (m, 5H, phenyl); ^{19}F NMR δ -105.15 (s, *(Z)*-isomer), -109.55 (s, *(E)*-isomer); EIMS 230 (14), 159 (44), 152 (24), 127 (10), 83 (26), 55 (48), 29 (100). HRMS calcd for $C_{16}H_{19}F$ 230.1470, Found 230.1469.

8-Fluorohexadec-8-ene-6,10-diyne (4i)

To a solution of diisopropylamine (0.54 mL, 3.85 mmol) in THF (10 mL) at 0°C was added *n*-butyllithium (2.4 mL of a 1.6 M solution in hexanes, 3.84 mmol) dropwise with stirring. After 5 min the resulting solution was cooled down to -80°C, hexamethylphosphoramide (0.67 mL, 3.85 mmol) was added and stirring continued. After 15 min, a solution of **1e** (0.9294 g, 3.52 mmol) in THF (5 mL) was added dropwise. After 1 h at -80°C, 2-octynal was added (0.50 mL, 3.51 mmol) and the reaction mixture was allowed to warm up to room temperature followed by quenching with saturated aqueous NH_4Cl (20 mL). The two layers were separated, the aqueous

layer was extracted with ether (2x10 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated. Isolation of the non-polar, UV-active component by flash chromatography (silica gel, hexane) afforded **4i** (0.0332 g, 4%) as a 53:47 *E:Z* mixture of isomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88-0.94 (m, 6H, CH_3), 1.26-1.45 (m, 8H, CH_2), 1.47-1.65 (m, 4H, CH_2), 2.33-2.46 (m, 4H, $\equiv CCH_2$), 5.19 (dt, J_{HF}= 29.22 Hz, J_{HH}= 2.33 Hz, 1H, *(Z)*-CH=), 5.58 (dt, J_{HF}= 8.21 Hz, J_{HH}= 2.36 Hz, 1H, *(E)*-CH=); ^{19}F NMR δ -93.93 (s, *(Z)*-isomer), -98.98 (s, *(E)*-isomer). Anal. Calcd for $C_{16}H_{23}F$: C, 82.00; H, 9.89. Found: C, 82.10; H, 9.78.

3-Fluoro-2-phenyl-6-cyclohexylhex-2-ene-4-yne (4j)

$KN(TMS)_2$ (0.1199g, 0.6mmol), **1f** (145 mg, 0.5 mmol), acetophenone (0.069 ml, 0.6mmol) in THF (5 mL)were mixed and stirred following the general method described for **4e**. The resulting yellow oil was purified by column chromatography (silica gel, hexane: ethyl acetate 4:1) to give **4j** (0.074g, 58%) as 48:52 *Z:E* mixture. ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.2-1.9 (m, 13H, cyclohexanyl and CH_2), 2.10 (d, J_{HF}= 3.89 Hz, 3H, *(E)*-CH_3), 2.16 (d, J_{HF}= 3.16 Hz, 3H, *(Z)*-CH_3), 7.2-7.5 (m, 5H, phenyl); ^{19}F NMR δ -105.20 (s, *(Z)*-isomer), -109.46 (s, *(E)*-isomer); EIMS 256 (2), 159 (10), 152 (5), 109 (4), 83 (16), 55 (100). Anal. Calcd for $C_{18}H_{21}F$: C, 84.37; H, 8.20. Found: C, 84.13; H, 8.40.

Bis(2,2,2-trifluoroethyl) 1-Hydroxyoct-2-ynylphosphonate (11).

2-Octynal (0.29 mL, 2 mmol) in CH_2Cl_2 (4 mL) and mixed with $AlCl_3$ (2 mL, 1M solution in nitrobenzene) was stirred at 0°C while bis(2,2,2-trifluoroethyl)phosphite (0.4 mL, 1.2 eq) was added slowly. After 2 h. the reaction mixture was poured into water and extracted with CH_2Cl_2 The combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated. The crude product was separated by column chromatography (silica gel, hexane: ethyl acetate 8:2) to afford **11** (0.444 g, 60%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.9 (t, J_{HH}=7 Hz, 3H, CH_3), 1.25-1.45 (m, 6H, $CH_2CH_2CH_2$), 2.2-2.3 (m, 2H, $\equiv CCH_2$), 4.15 (br s, 1H, OH), 4.4-4.6 (m, 4H, OCH_2), 4.80 (br d, J_{HP} = 15 Hz, 1H, CHP); ^{19}F NMR (CDCl3) δ -75.75 (s) and -75.79 (s); ^{31}P NMR (CDCl3) δ 20.25 (s). Anal. Calcd for $C_{12}H_{17}O_4F_6P$: C, 38.91; H, 4.59. Found: C, 38.96; H, 4.66.

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