The First α-Fluoroallenylphosphonate, the Synthesis of Conjugated Fluoroenynes, and the Stereoselective Synthesis of Vinylfluorophosphonates Using a New Multifunctional Fluorine-Containing Building Block

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Limitations on current methodologies for the introduction of CF_2 and CFH in complex α-fluorophosphonates led to the synthesis of a fluorine-containing building block TIPS-C≡CCFXP(O)$(OEt)_2$, where X = H or F. This multifunctional fluorine synthon reacts with carbonyl compounds under WHE conditions to give high yields of fluorinated conjugated enynes and enediyne. When X = F, trapping of the desilylated anion with an electrophile after TIPS removal provided exclusive access to γ-substituted derivatives of α-fluorophosphonates. When X = H, TBAF deprotection of the silyl group yields H_2C=C=CFP(O)$(OEt)_2$ through an allenyl−propargyl resonance stabilized anion. The allene moiety has been used as template in the stereoselective synthesis of α-fluoro-β,γ-diiodopropenyl phosphonate, via electrophilic iodination, and α-fluoro-γ-amino-α,β-unsaturated phosphonates, including unsaturated phosphononucleosides, by nucleophilic displacement of an allylic iodide. Hydroamination of H_2C=C=CFP(O)$(OEt)_2$ using secondary amines produced (Z)-α-fluoroenaminophosphonates, whereas Diels−Alder cycloaddition with cyclopentadiene provides the corresponding exocyclic vinylfluorophosphonate.

Introduction

The impact and utilization of fluorine span areas as diverse as pharmaceuticals, agrochemicals, and polymers.[1] The presence of fluorine in organic molecules has profound consequences on the physical, chemical, and biological properties of the resulting organofluoro compound. Even though exceptions are known, the implications of replacing a hydrogen atom or a hydroxyl group with fluorine cannot be reliably predicted.[2] A major hurdle in the study of fluorine-containing organic molecules is the limitations posed by current fluorination methodologies. Nowhere are these limitations more evident than in the construction of *gem*-difluoromethylene and fluoromethylene units. Currently, the two most used strategies are (i) substitution of COH, C=O, or active methylene hydrogen by fluorine[3] and (ii) use of small, fluorine-containing building blocks.[4] When it comes to fluorinating complex molecules, the reactivity, thermal instability, hazards, and cost associated with electrophilic and nucleophilic fluorinating agents create a considerable challenge that has contributed to making the fluorine-containing building block approach particularly attractive. Indeed, nonaromatic fluorinated synthons are the focus of current attention because the synthetic handles in them allow the incorporation of fluorine near reactive centers. α-Fluorophosphonates, in which the bridging C−*O*−P phosphate bond has been replaced with either a C−*CFH*−P or a C−CF_2−P bond, constitute an important resource for the study of biological phosphate mimics.[5] For the synthesis of difluorophosphonates, the most widely used building block is $(EtO)_2$P(O)CF_2metal, where metal = Li, ZnBr, Cd, or Ce.[6] With few notable exemptions,[7] the synthesis of monofluorophosphonates using $(EtO)_2$P(O)CFH^-M^+ has yet to reach the same level of notoriety of its difluoro counterpart.

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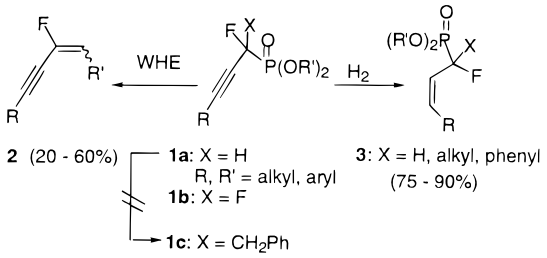
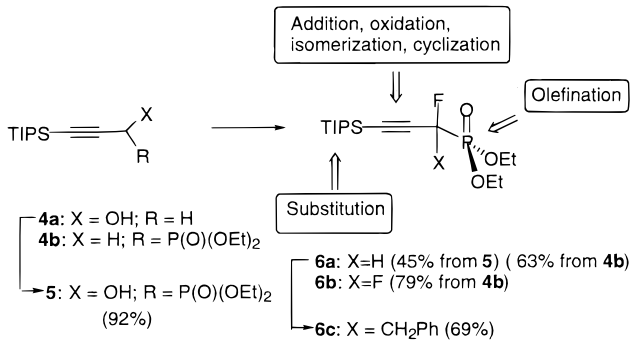
Scheme 1



Numerous literature citations[8] involve the preparation of alkyl-substituted difluorophosphonates using $(EtO)_2P(O)CF_2Br$. In comparison, very few allylic difluorophosphonates have been reported,[9] and, with the exception of our work,[10] no other propargylic analogues have been cited in the literature. Recent theoretical calculations[5,11] have suggested that the presence of one fluorine atom in phosphonates might be sufficient for molecular mimicry. This has fueled interest in the development of monofluorophosphonate building blocks. Our group's contribution to this effort resulted in the synthesis of the first propargylic monofluorophosphonate **1a**[12]—a not so trivial feat using $(EtO)_2P(O)CFHBr$. Very recently, Burton and co-workers[13] utilized $(EtO)_2P(O)CFHBr$ in the preparation of functionalized α-fluorophosphonates. Nonetheless, the inherent lack of fluorine stereocontrol at the α-carbon of $(EtO)_2P(O)CFHBr$ will probably limit its use in the new field of chiral fluorine synthesis.[14]

The synthesis of **1a** enabled us to prepare **2** and **3** via Wadsworth−Horner−Emmons (WHE) olefination and catalytic hydrogenation, respectively[15] (Scheme 1). Two intrinsic disadvantages hinder a wider use of **1** as fluorine synthon: (1) the small pool of commercially available propargyl aldehydes (e.g., RC≡CCHO) needed as starting material and (2) the instability of the α-carbanion of **1a**. The latter presumably accounted for the low yields obtained in the synthesis of **2** and lack of success in alkylation reactions (e.g., **1a** → **1c**).

Scheme 2



It is our postulate that a three-carbon fluorinated scaffold, equipped with functional synthetic handles, possesses important advantages in the preparation of complex and chiral fluorophosphonates, as well as other fluorinated organic molecules. Our pursuit in this direction has led us to report herein the synthesis and chemistry of the first multifunctional fluorophosphonate synthon, namely α-fluoro-γ-silylpropargylphosphonate **6** (Scheme 2). This compound can carry one or two fluorine atoms on a functionalized three-carbon framework. As described below, this fluorine-containing building block has been used in a high-yielding synthesis of fluorinated analogues of conjugated enynes and enediynes; in the first synthesis of α-fluoroallenylphosphonate; and in the stereoselective synthesis of α-fluoro-β,γ-diiodopropenylphosphonate and α-fluoro-γ-amino-α,β-unsaturated phosphonates, including unsaturated phosphononucleosides, α-fluoroenaminophosphonates, and exocyclic vinylfluorophosphonates.

Results and Discussion

Synthesis of TIPS-fluoropropargylphosphonate 6 and Fluoroenynes. The TIPS group, critical to the success of **6**, was chosen because of its remarkable electronic and steric properties, compared with other silyl groups.[16] Hydroxyphosphonate **5**, prepared in two steps from **4a**,[17] produced the desired **6a** after DAST dehydroxyfluorination[18] (Scheme 2). An alternate, one-step synthesis of **6** involves an electrophilic fluorination of TIPS propargyl phosphonate **4b**[19] using *N*-fluorobenzenesulfonimide (NFSI).[20] The synthesis of difluoro **6b** was readily accomplished in 79% yield from **4b** employing 2 molar equiv of NFSI.

The phosphonate present in **6a** provides an opportunity for the synthesis of conjugated enynes and enediynes via WHE olefination.[21] The chemistry and biology of conju-

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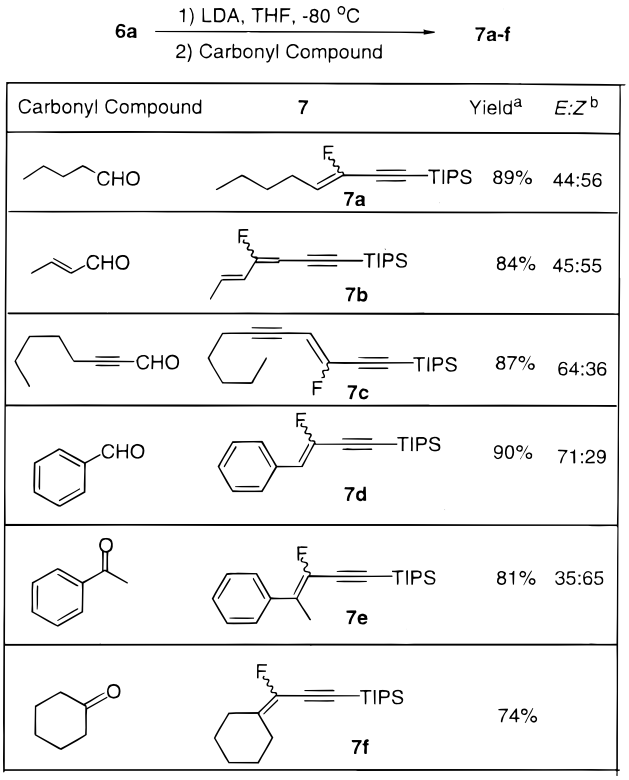
Table 1. Synthesis of Fluoro-1,3-enynes and Fluoroenediynes

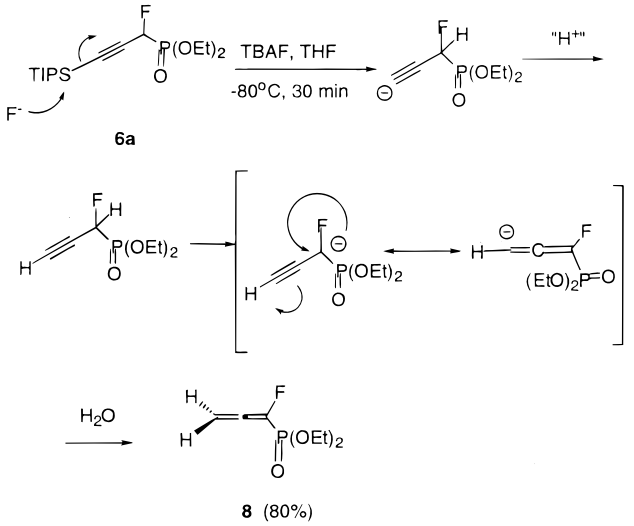


[a] Isolated. [b] Determined by ^{1}H and ^{19}F NMR analysis.

gated enynes and enediynes have received extensive coverage in recent years.[22] Fluorine substitution of a vinyl hydrogen should impart interesting properties to the resulting fluoroenyne and fluoroenediyne. However, their synthesis remains elusive. In total, less than a handful of syntheses have been reported, all low yielding.[15] As Table 1 shows, the merit of silylfluoropropargylphosphonate **6a** as a building block is obvious in the synthesis of fluorolefins under WHE conditions. For example, saturated and unsaturated aldehydes, as well as ketones, reacted with **6a**, and in all cases very good to excellent yields of fluoroenynes and fluoroenediynes **7a**−**f** were obtained. In stark contrast, **1a** produced trace amounts of enediynes, and its reaction with pentanal and other saturated aldehydes gave exclusively aldol condensation products.[15] Along the same lines, the synthesis of α-alkyl substituted fluoropropargylphosphonate **6c**, an impossible task using **1a**,[23] was easily accomplished with **6a**. The efficiency of this reaction is probably the consequence of an increase in the stability of the α-carbanion through a cumulene-type resonance with the silicon atom.

With an aim of optimizing the *Z*/*E* ratio in **7**, we modified the nature of the phosphorus ester substituent. Replacement of Et by CF_3CH_2, a strategy pioneered by Still,[24] and employed by other workers[25] to boost the olefinic ratio of the less favored *Z* isomer, did not improve the *Z*/*E* isomer ratio of **7**. To examine whether TIPS-C≡CCHFTIPS, a nonphosphonate analogue of **6a**, could yield **7** with greater stereoselectivity, Corey's variation of the Peterson olefination was attempted.[26] TIPS-C≡CCHFTIPS was prepared in 50% yield by electrophilic fluorination and was reacted with pentanal following LDA deprotonation. Unexpectedly, the reaction yielded defluoroenyne TIPS-C≡CCH=CH$(CH_2)_3CH_3$ and recovered starting material. Other bases [LDA-Ti(*i*-PrO)$_4$, *n*-BuLi, *t*-BuLi) and solvent systems (THF−HMPA) did not modify the initial outcome of this reaction. This result has served to underscore the importance of the phoshonate group in the synthesis of **7**.

Scheme 3



Synthesis of α-Fluoroallenylphosphonate 8. Attention was then turned to the silyl group. We speculated that if tetrabutylammonium fluoride (TBAF, 1 M solution in THF) was used to cleave the C−Si bond, the resulting anion (Scheme 3) could abstract a proton, perhaps from trace amounts of water present in commercial TBAF, to form α-fluoropropynephosphonate. Under the existing basic conditions, α-fluoropropynephosphonate would undergo deprotonation at the α-carbon to give a resonance-stabilized allenyl−propargyl anion. Aqueous workup will then produce **8**. Indeed, when the experiment was carried out, **6a** was exclusively converted to **8** after 30 min at −80 °C.

Fluoroallenylphosphonate **8** was thermally stable and easily purified by chromatography. The synthesis of **8** was slower using other fluoride sources such as CsF and TASF,[27] probably as a result of the decreased concentration of F^-. Given the moderate to poor solubility of these reagents in THF, the result is not surprising. Difluoro **6b**, lacking an α-hydrogen, yielded **9a** in near quantitative yield following treatment with TBAF (eq 1). Compound **9a** possesses a terminal acetylene moiety suitable for Sonogashira-type coupling[28] or Schwartz hydrozirconation.[29] In the presence of an electrophilic trap[30] such as benzaldehyde, **6b** produced the γ-substituted hydroxyfluorophosphonate **9b** in 92% yield.

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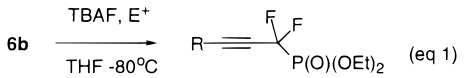
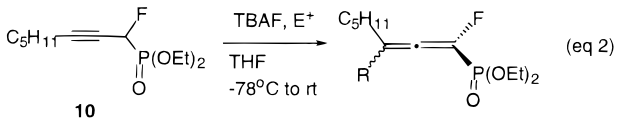


(eq 1)

	E^+	R	%
9a	H_2O	H	97
9b	PhCHO		92

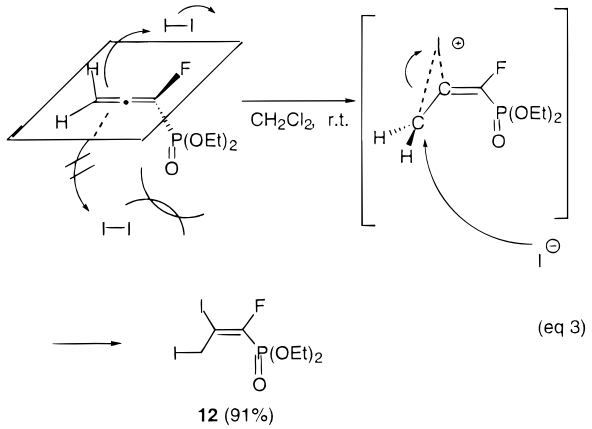
Interestingly, when **10**, the alkyl analogue of **6a**, was treated with TBAF in the presence of benzaldehyde, the allene **11b** was obtained in 72% yield as a 12:5 mixture of diastereomers (eq 2). Without benzaldehyde, the same experimental conditions led to the slow formation of α-fluoroallenylphosphonate **11a** in moderate yield.



(eq 2)

	E^+	R	%
11a	H_2O	H	40
11b	PhCHO		72

Iodination of α-Fluoroallenylphosphonate. The allene unit itself is a versatile synthetic handle,[31] and recently, its chiral nature has been used advantageously in asymmetric synthesis.[32] α-Fluoroallenylphosphonate **8** is a hitherto unknown fluorinated molecule endowed with excellent building block attributes for the construction of a variety of fluorophosphonates. To investigate the chemistry of fluoroallenylphosphonate **8**, the electrophilic addition of iodine was initially examined. Generally speaking, 1,1-disubstituted allenes regioselectively add I_2 across the C2−C3 bond to afford the more highly substituted olefin.[33] In the case of **8**, it was predicted that the electrophile would approach the α-fluoroallenylphosphonate from above the plane of the C2−C3 double bond, on the less hindered fluorine side (eq 3). In the transition



(eq 3)

12 (91%)

state, the resulting iodonium intermediate would be expected to have a stronger, shorter bond to C2 and a weaker, longer bond to C3 because of the added stability conferred by the sp^2 allylic character of the latter (versus an sp vinylic character in C2). Therefore, the C3−I bond would be expected to open up upon iodide attack on the iodonium intermediate (eq 3). Indeed, when the iodination of **8** was conducted at ambient room light, it furnished exclusively (*E*)-diiodo **12** in excellent yield. At room temperature, **12** darkened over a period of days and decomposed at temperatures above 50 °C. The stereospecificity observed in the iodination of **8** was a pleasant surprise, given the lack of stereocontrol reported by other workers during the halogenation of allenylphosphonates.[34] The iodination of **8** represents the first stereoselective synthesis of a α-fluorovinylphosphonate unit equipped with two valuable synthetic handles: allyl- and vinyliodine.

Synthesis of Fluorinated Vinylphosphonates. Vinylphosphonates find wide applications as intermediates in organic synthesis.[35] Research groups interested in the asymmetric synthesis of α-monofluoroalkylphosphonates have targeted the preparation of stereoisomerically pure α-fluorovinylphosphonates. Prior to our investigation, the syntheses of α-fluorovinylphosphonates using WHE condensation,[36] Peterson olefination[37] or palladium-coupling methodologies[38] produced mixtures of *E* and *Z* isomers. Our synthesis of **12** does provide a stereoselective point of entry into a wide variety of α-fluorovinylphosphonates because it contains a vinyl iodide capable of further manipulation through transition metal catalyzed coupling reactions. In addition, nucleophilic displacement of the allylic iodide in **12** could provide access to (*E*)-γ-substituted-α-fluoroalkenylphosphonates. Thus, **12** can be envisioned as a building block for the synthesis of allylamines and α-fluorophosphononucleosides,[39] in which the nitrogen atom is attached to the γ-carbon of a phosphonate moiety. Although α-monofluoro derivatives of vinylphosphononucleosides have never been reported, β,γ-unsaturated phosphonucleosides have provided important leads in anti-HIV therapy,[40] partly as a spin-off of phosphate mimicry research. The synthesis of allylamines[41] was examined first using an aliphatic amine

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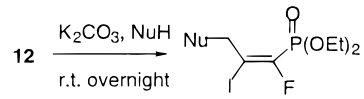
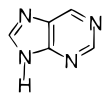
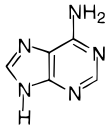
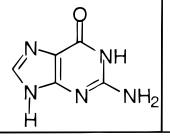
Table 2. Synthesis of 13



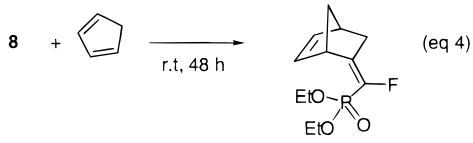
	NuH	Solvent	Yield (%)	IC_{50} (Molar)[a]
13a	$HNEt_2$	CH_2Cl_2	85	NT[b]
13b		DMF	68	9.97×10^{-5}
13c		DMF	60%	1.46×10^{-4}
13d		DMF	No Reaction	

[a] See ref 46. [b] Not tested.

to displace the allylic iodide in **12**. Before running this experiment, it was of concern to us that under basic conditions the S_N2 reaction might promote a simultaneous deiodination of **12** and concomitant regeneration of allene **8**, thereby limiting the utility of the allylic iodine. However, to our satisfaction, the nucleophilic displacement of **12** at room temperature, using Et_2NH and K_2CO_3 as base, yielded solely the allylamine **13a**. Nucleoside bases such as purine and adenine produced fluorinated acyclic phosphononucleosides **13b** and **13c** in 68 and 60% yield after recrystallization, respectively. Results of their in vitro anti-HIV activity are shown in Table 2. Failure to obtain **13d** under these reaction conditions is probably due to the decreased nucleophilicity of guanine. Crystallographic analysis of both **13b** and **13c**[42] served to elucidate their olefin stereochemistry and to confirm our proposed mechanism on the iodination of allene **8**.

Hydroamination of α-Fluoroallenylphosphonate. The hydroamination of α-fluoroallenylphosphonate **8** can serve as a conduit to the preparation of fluoroanalogues of enamines[43] and *β*-enaminophosphonate, a key component in the synthesis of pyrimidone ring systems.[44] Prior to this work, *β*-fluoroenaminephosphonates were unknown. At ambient temperature, the *(E)*-isomer **14** was found to be the major product when primary amines were used (entries 1 and 2 in Table 3). The extensive long-range coupling existing between neighboring fluorine and phosphorus atoms, and lack of background NMR data on fluoroenaminephosphonates, prevented us, in the beginning, from accurate stereochemical assignments of *E* and *Z* isomers using NMR. Fortunately, the growth of crystals of *(E)*-**14a**, suitable for X-ray crystallography,[42] was achieved by recrystallization from hexane, thus permitting the determination of its relative stereochemistry. With a secondary amine (Table 3, entry 3), where enamine−imine tautomerization is not possible, only the (*Z*)-isomer was produced. The stereochemical assignment was facilitated by comparing the coupling constant $^2J_{FP}$ of **14b** and **14c** with that of **14a**. Repeated attempts to purify **14** by silica chromatography met with failure as it was readily hydrolyzed to the corresponding *β*-ketofluorophosphonate during this operation.

Diels−Alder Cyclization. Allenes in general and fluoroallenes in particular are highly regarded dienophiles in cycloaddition reactions.[45] Using a Diels−Alder reaction, the allenyl moiety present in **8** could serve as framework for the construction of functionalized cyclic systems containing an exocyclic $=CFP(O)(OEt)_2$. To probe this, allene **8** was stirred at room temperature with cyclopentadiene furnishing solely the endo adduct **15**. By assuming maximum *π* electron overlap in the transition state, the endo adduct offers a favorable interaction of the oxygen lone pair orbital of the phosphonate moiety and the incoming diene. This interaction may be responsible for the stereospecificity of the reaction.



(eq 4)

15 (78%)

Summary. A new, multifunctional fluorine-containing building block has been presented, and its synthetic usefulness has been demonstrated with the regiospecific synthesis of fluorinated analogues of enynes, enediynes, and α-fluoroallenylphosphonate and the stereoselective synthesis of fluorinated derivatives of cyclic and acyclic vinylphosphonates. Furthermore, the synergism resulting from the juxtaposition of neighboring silyl, alkynyl, and phosphoryl groups in **6** should facilitate other synthetic manipulations such as silicon-mediated electrophilic activation, transition metal-catalyzed coupling reactions, and solid-phase synthesis, some of which are presently under investigation.

Experimental Section

All moisture-sensitive reactions were performed using flame-dried glassware flushed with argon, magnetic stirring, and dry, freshly distilled solvents. THF was distilled from Na/benzophenone. Toluene and methylene chloride (CH_2Cl_2) were distilled from calcium hydride. Other solvents were HPLC grade and were used without purification. Benzaldehyde was distilled prior to use. All other reagents were used as received. $MgSO_4$ was used to remove water contamination from the organic layer in the final phase of reaction workups. All reactions were monitored using one of the following techniques: TLC, GC−MS, or ^{31}P and/or ^{19}F NMR. Preparative TLC was performed using E. Merck silica gel 60 F254.

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(42) For details regarding the X-ray crystal structure of **13b**,**c** and **14a**, see the Supporting Information.

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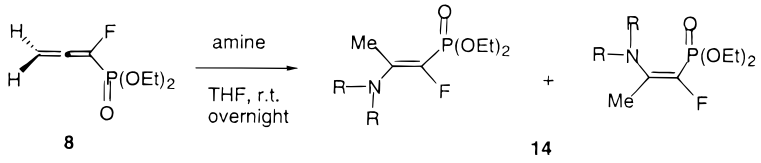
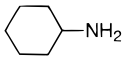
Table 3. Hydroamination of 8



8 **14**

Entry	Amine	Yield (NMR)	*E*	:	*Z*
1	Ph-CH_2-NH_2	80%	67 ^{19}F NMR δ -172 ^{31}P NMR δ +11.5 *J* = 84 Hz		33 ^{19}F NMR δ -183.5 ^{31}P NMR δ +13.1 *J* = 91 Hz
2		81%	70 ^{19}F NMR δ -174 ^{31}P NMR δ +12.1 *J* = 85 Hz		30 ^{19}F NMR δ -184 ^{31}P NMR δ +13.4 *J* = 91.5 Hz
3	Et_2NH	75%	0		100 ^{19}F NMR δ -166 ^{31}P NMR δ +14.6 *J* = 91.5 Hz

Analytical TLC was performed using Macherey-Nagel Polygram Sil G/UV254 precoated plates. Flash chromatography was performed using silica gel 230−400 mesh, 40−63 microns (Lagand Chemicals). Dry-column chromatography was performed using Florisil, 60−100 mesh. Solid-phase extraction was performed using Extract-Clean columns (silica gel, 60 Å). Melting points are uncorrected. Infrared spectra were recorded on neat liquids. Unless otherwise noted, ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded in $CDCl_3$ at 300, 282, and 121 MHz, respectively. ^{19}F NMR spectra are referenced against external $CFCl_3$, ^{1}H and ^{13}C NMR spectra against internal $(CH_3)_4Si$, and ^{31}P NMR spectra against 85% H_3PO_4. ^{31}P, ^{13}C, and ^{19}F NMR spectra were broadband decoupled from hydrogen nuclei. *J* values are given in hertz (Hz). Low-resolution EI mass spectra were recorded with an ionization voltage of 70 eV; peaks are reported as *m/e* (% intensity relative to base peak). Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Diethyl 1-Hydroxy-3-triisopropylsilyl-2-propynephosphonate 5. A solution of **4a**[17](10.32 g, 49 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a solution of Dess−Martin periodinane (22.63 g, 53.35 mmol) in CH_2Cl_2 (200 mL). A mildly exothermic reaction ensued, and the mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with a mixture of aqueous NaOH (500 mL, 1 M) and ether (900 mL). The organic phase was dried and concentrated. Distillation of the crude product afforded TIPS-propargyl aldehyde bp 70−3 °C/0.45 Torr (9.82 g, 96%): ^{1}H NMR δ1.10 (m, 21 H), 9.21 (s, 1H); IR (neat, NaCl) 2950, 2870, 2150, 1670 cm^{-1}. Anal. Calcd for $C_{12}H_{22}OSi$: C, 68.51; H, 10.54. Found: C, 68.26; H, 10.45.

A mixture of TIPS-propargyl aldehyde (9.82 g, 47 mmol), diethyl phosphite (6.2 mL, 48.13 mmol), and potassium fluoride dihydrate (11.0 g, 116.8 mmol) was stirred overnight. The reaction was taken up in ether and washed with water. The ethereal extract was dried and concentrated to afford **5** (15.61 g, 96%) as a thick oil that changed to a waxy solid upon storage at low temperature. This material was judged homogeneous by analytical TLC (50% ethyl acetate/hexanes): ^{1}H NMR δ 1.09 (s, 21H), 1.35 (m, 6H), 4.23 (m, 4H), 4.71 (d, *J* = 15.9 Hz, 1H); ^{31}P NMR δ 17.9. Anal. Calcd for $C_{16}H_{33}O_4PSi$: C,55.14; H, 9.54. Found: C, 54.87; H, 9.65.

Diethyl 1-Fluoro-3-triisopropylsilyl-2-propynephosphonate 6a from 5. A solution of **5** (3.144 g, 9.02 mmol) in CH_2Cl_2 (50 mL) was added dropwise via cannula to a solution of diethylaminosulfur trifluoride (DAST) (6.6 mL, 48.5 mmol) in CH_2Cl_2 (100 mL) at −80 °C, and the resulting reaction mixture was allowed to reach room temperature slowly overnight. The reaction was quenched carefully with saturated $NaHCO_3$ (100 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give a dark red oil. Purification of the crude product by flash chromatography (hexane/EtOAc = 9:1 to 7:3 + 4% triethylamine) afforded **5** (1.303 g, 41%): ^{1}H NMR δ 1.09 (s, 21H), 1.37 (t, *J* = 7.1 Hz, 6H), 4.28 (m, 4H), 5.35 (dd, *J* = 47.0, 12.5 Hz, 1H); ^{19}F NMR δ −196 (d, *J* = 79 Hz); ^{31}P NMR δ 11.4 (d, *J* = 79 Hz); IR (neat, NaCl) 2950, 2870, 2180, 1460 cm^{-1}. Anal. Calcd for $C_{16}H_{32}FO_3PSi$: C, 54.83; H, 9.20. Found: C, 54.77; H, 9.23.

Diethyl 1-Fluoro-3-triisopropylsilyl-2-propynephosphonate 6a from 4b. To a solution of **4b** (0.197 g, 0.59 mmol) in THF (5 mL) was added sodium bis(trimethysilyl)amide (0.70 mL of a 1 M solution in THF) at −80 °C. After the addition, the reaction was warmed to −50 °C over 1 h and then cooled to −80 °C. NFSI (0.186 g, 0.59 mmol) in THF (3 mL) was added, and the reaction mixture was allowed to warm to room temperature, poured into saturated NH_4Cl, and extracted with ether. The combined organic extracts were dried and concentrated. The residue was triturated with hexane, filtrated, and concentrated. The resulting oil was purified by flash chromatography (hexane/EtOAc=7:3) to afford the desired **6a** (0.130 g, 63%): ^{1}H NMR δ 1.09 (s, 21H), 1.37 (t, *J* = 7.1 Hz, 6H), 4.28 (m, 4H), 5.35 (dd, *J* = 47.0, 12.5 Hz, 1H); ^{19}F NMR δ −196 (d, *J* = 79 Hz); ^{31}P NMR δ 11.4 (d, *J* = 79 Hz); IR (neat, NaCl) 2950, 2870, 2180, 1460 cm^{-1}. Anal. Calcd for $C_{16}H_{32}FO_3PSi$: C, 54.83; H, 9.20. Found: C, 54.77; H, 9.23.

Diethyl 1,1-Difluoro-3-triisopropylsilylpropynephosphonate 6b. To a solution of **4b** (0.126 g, 0.38 mmol) in THF (5 mL) was added sodium bis(trimethylsilyl)amide (2.2 equiv, 0.834 mL, 1 M in THF) at −60 °C. After the solution was stirred at that temperature for 15 min, *N*-fluorobenzenesulfonimide (2.4 equiv, 0.287 g) in THF (5 mL) was added dropwise to the reaction, and the resulting reaction mixture was warmed to room temperature slowly. The reaction was quenched with saturated NH_4Cl, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were dried and concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 8:2) affording **4b**

(0.1107 g, 79%) as a light yellow oil: ^{1}H NMR δ 1,11 (s, 21H), 1.39 (t, J = 7.0 Hz, 6H), 4.32 (m, 4H); ^{19}F NMR δ −96.8 (d, J = 109 Hz); ^{31}P NMR δ 4.2 (t, J = 109 Hz); IR (neat, NaCl) ν 2950, 2870, 2170, 1465 cm^{-1}; GC−MS m/z 325 (M^+ − 43, 89), 297 (39), 269 (100), 153 (13), 109 (20), 81 (40). Anal. Calcd for $C_{16}H_{31}O_3F_2SiP$: C, 52.15; H, 8.48. Found: C, 52.22; H, 8.37.

Diethyl 1-Fluoro-1-benzyl-3-triisopropylsilyl-2-propynephosphonate 6c. A solution of diisopropylamine (0.05 mL, 0.36 mmol) in THF (10 mL) was cooled to 0 °C, BuLi (0.22 mL, 1.6M in hexane) and HMPA (0.06 mL) were added into the solution, the resulting LDA solution was stirred at 0 °C for 15 min, then cooled to −78 °C. The solution of 6a in THF (0.5 mL) was added into the LDA solution and stirred at that temperature for 1 h. Benzyl bromide (0.072 g, 0.42 mmol) was added into the reaction solution, and the resulting mixture was allowed to reach room temperature slowly overnight. The reaction was quenched with saturated NH_4Cl, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were dried and concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 8:2) affording **6c** (0.059 g, 69%): ^{1}H NMR δ 1.01 (s, 21H), 1.36 (m, 6H), 3.36 (m, 2H), 4.28 (m, 4H) 7.26−7.35 (m, 5H); ^{19}F NMR δ −160(d, J = 90.1 Hz); ^{31}P NMR δ 13.6 (d, J = 88.7 Hz); GC−MS m/z 440 (M^+, 2), 397 (100), 321 (17), 213 (12), 77 (17). Anal. Calcd for $C_{23}H_{38}O_3FSiP$: C, 62.70; H, 8.69. Found: C, 62.46; H, 8.58.

Preparation of 7 via WHE Olefination. General Procedure. To a solution of diisopropylamine (0.130 mL, 0.93 mmol) in THF (5 mL) at 0 °C was added dropwise *n*-butyllithium (0.60 mL of a 1.53 M solution in hexanes, 0.92 mmol). After 5 min, the solution was cooled to −80 °C, and a solution of **6a** (0.286 g, 0.82 mmol) in THF (1 mL) was added dropwise. After the addition was completed, the carbonyl compound (1.1 equiv) was added neat, and the reaction was allowed to reach room temperature. The reaction was poured into saturated aqueous ammonium chloride and extracted with ether. The combined organic extracts were dried and concentrated. Products were purified by flash chromatography using silica gel and hexanes containing 4% of triethylamine as eluent.

6-Fluoro-8-triisopropylsilyloct-5-ene-7-yne 7a. Obtained in 89% yield as a 44:56 *E*/*Z* mixture of isomers. Two isomers were separated by flash chromatography.

Isomer *E*: ^{1}H NMR δ 0.90 (t, J = 7.1 Hz, 3H), 1.10 (m, 21H), 1.29−1.42 (m, 4H), 2.12−2.19 (m, 2H), 5.61 (dt, J = 14.7, 8.2 Hz, 1H); ^{19}F NMR δ −109 (s).

Isomer *Z*: ^{1}H NMR δ 0.90 (t, J = 7.1 Hz, 3H), 1.09 (m, 21H), 1.33−1.39 (m, 4H), 2.15−2.18 (m, 2H), 5.24 (dt, J = 33.5, 7.8 Hz, 1H); ^{19}F NMR δ −112 (s).

Mixture: IR (neat, NaCl) 2950, 2870, 2160, 1655 cm^{-1}. Anal. Calcd for $C_{17}H_{31}FSi$: C, 72.27; H, 11.06. Found: C, 72.37; H, 11.04.

5-Fluoro-7-triisopropylsilylhept-2,4-dien-6-yne 7b. Obtained in 84% yield as a 45:55 *E*/*Z* mixture of isomers: ^{1}H NMR δ 1.09 (m, 21H, (*Z*)-isopropyl), 1.13 (m, 21H, *(E)*-isopropyl) 1.79 (m, 3H, *(Z)*-CH_3) 1.80 (m, 3H, *(E)*-CH_3), 5.71−5.86, 6.16−6.20 and 6.30−6.40 (three multiplets, 3H, *(Z)*- and *(E)*-CH═); ^{19}F NMR δ −111.9 (s, *(E)*-isomer) and −112.4 (s, *(Z)*-isomer); IR (neat, NaCl) 3040, 2950, 2870, 2150, 1610 cm^{-1}.

3-Fluoro-1-triisopropylsilyl-undeca-3-en-1,5-diyne 7c. Obtained in 87% yield as a 64:36 *E*/*Z* mixture of isomers: ^{1}H NMR δ 0.87−0.92 (m, 3H), 1.07−1.19 (m, 21H), 1.25−1.39 (m, 4H), 1.48−1.57 (m, 2H), 2.29−2.39 (m, 2H), 5.32 (dt, J = 28.8, 2.4 Hz, 1H, *(Z)*-CH═), 5.67 (dt, J = 8.0, 2.5 Hz, 1H *(E)*-CH═); ^{19}F NMR δ −97 (s, *(Z)*-isomer) and −102 (s, *(E)*-isomer); IR (neat, NaCl) 2940, 2870, 2220, 2150, 1615 cm^{-1}. Anal. Calcd for $C_{20}H_{33}FSi$: C, 74.94; H, 10.38. Found: C, 74.95; H, 10.31.

2-Fluoro-1-phenyl-4-triisopropylsilylbut-1-en-3-yne 7d. Obtained in 90% yield as a 71:29 *E*/*Z* mixture of isomers: ^{1}H NMR δ 1.09−1.20 (m, 21H), 6.06 (d, J = 34.9 Hz, *(Z)*-CH═), 6.59 (d, J = 17.1 Hz, *(E)*-CH═), 7.25−7.36 (m, 3H), 7.50 (d, J = 7.4 Hz, 2H, *(Z)*-phenyl), 7.70 (d, J = 6.9 Hz, 2H, *(E)*-phenyl); ^{19}F NMR δ −102 (s, *(E)*-isomer) and −105 (s, *(Z)*- isomer); IR (neat, NaCl) 3060, 3030, 2950, 2870, 2150, 1690 cm^{-1}. Anal. Calcd for $C_{19}H_{27}FSi$: C, 75.44; H, 9.00. Found: C, 75.52; H, 8.89.

3-Fluoro-2-phenyl-5-triisopropylsilylpent-2-en-4-yne 7e. Obtained in 81% yield as a 35:65 *E*:*Z* mixture of isomers: ^{1}H NMR δ 1.00 (m, 21H, *(Z)*-isopropyl), 1.14 (m, 21H, *(E)*-isopropyl), 2.11 (d, J = 4.0 Hz, 3H, *(Z)*-CH_3), 2.20 (d, J = 3.4 Hz, 3H, *(E)*-CH_3), 7.23−7.36 (m, 3H), 7.41−7.50 (m, 2H); ^{19}F NMR δ −108 (s, *(Z)*-isomer) and −112 (s, *(E)*-isomer); IR (film, NaCl) 3060, 3030, 2950, 2870, 2150, 1645 cm^{-1}. Anal. Calcd for $C_{20}H_{29}FSi$: C, 75.89; H, 9.23. Found: C, 75.88; H, 9.28.

3-Cyclohexylidene-3-fluoro-1-triisopropylsilyl-1-propyne 7f. Obtained in 74% yield: ^{1}H NMR δ 1.10 (apparent s, 21H), 1.68−1.73 (m, 4H,), 2.38−2.45 (m, 4H); ^{19}F NMR δ −114 (s); IR (neat, NaCl) 2960, 2865, 2145, 1675 cm^{-1}.

Diethyl 1-Fluoro-1,2-propadienephosphonate 8. To a stirred solution of **6a** (0.930 g, 2.65 mmol) in THF (10 mL) was added dropwise TBAF (2.92 mL, 1.0M in THF) at −80 °C. The reaction mixture was stirred at −80 °C for 30 min. The reaction was quenched with H_2O, the organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried and concentrated to give a dark red oil. Purification of the crude product by flash chromatography (hexane/EtOAc = 7:3−1:1) afforded α-fluoroallenylphosphonate **8** as a yellow oil (0.3864 g, 75%): ^{1}H NMR δ 1.38 (t, J = 7.1 Hz, 6H), 4.21 (m, 4H), 5.84 (dd, 2H, J = 9.97, 1.24 Hz); ^{19}F NMR δ −162 (d, J = 104 Hz); ^{31}P NMR δ 6.2 (d, J = 108 Hz); IR (neat, NaCl) 3040, 2990, 1955 cm^{-1}; GC−MS 194 (M^+, 6), 166 (17), 138 (100), 109 (16), 91 (10), 81 (45), 65 (52). Anal. Calcd for $C_7H_{12}O_3FP$: C, 43.31; H, 6.23. Found: C, 43.11; H, 6.41.

Diethyl 1,1-Difluoropropynephosphonate 9a. To a stirred solution of **6b** (0.054 g, 0.147 mmol) in THF (5 mL), was added dropwise TBAF (0.15 mL, 1.0 M in THF) at −80 °C. The reaction mixture was stirred for 40 min. The reaction was quenched with saturated NH_4Cl, the organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried and concentrated. Purification of the crude product by flash chromatography (hexane/EtOAc = 7:3) afforded of **9a** as a yellow oil (30 mg, 97%): ^{1}H NMR δ 1.39 (t, J = 7.1 Hz, 6H), 3.06 (td, J = 6.1, 3.1 Hz, 1H) 4.32 (m, 4H); ^{19}F NMR δ −99.1 (d, J = 105 Hz); ^{31}P NMR δ 3.5 (t, J = 104 Hz); GC−MS 211 (M^+-1, 0.6), 156 (42), 137 (29), 109 (100), 91 (42), 81 (94), 65 (29); IR (neat, NaCl) 3260, 2170 cm^{-1}. Anal. Calcd for $C_7H_{11}O_3F_2P$: C, 39.62; H, 5.19. Found: C, 39.87; H, 5.31.

Diethyl 1,1-Difluoro-4-hydroxy-4-phenylbutynephosphonate 9b. To a mixture of **6b** (0.063 g, 0.172 mmol) and benzaldehyde (0.0398 g, 0.375 mmol) in THF (5 mL) at −80 °C was added dropwise tetrabutylammonium fluoride (TBAF) (0.18 mL, 1.0 M in THF). The reaction mixture was stirred at −80 °C for 30 min. The reaction was quenched with saturated NH_4Cl, the organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried and concentrated. Purification of the crude product by flash chromatography (hexane/EtOAc = 7:3) afforded **9b** as a yellow oil (0.050 g, 92%): ^{1}H NMR δ 1.37 (t, J = 7.1 Hz, 6H), 3.04 (bs, 1H), 4.31 (m, 4H), 5.58 (d, J = 1.9 Hz, 1H), 7.35−7.54 (m, 5H); ^{19}F NMR δ −98.3 (d, J = 104 Hz); ^{31}P NMR δ 3.9 (t, J = 106 Hz); GC−MS 298 (M^+ − 20, 7), 270 (17), 242 (35), 212 (46), 164 (100), 133 (54), 109 (75), 81 (63), 65 (30). Anal. Calcd for $C_{14}H_{17}O_4F_2P$: C, 52.84; H, 5.38. Found: C, 52.05; H, 5.53.

Diethyl 1-Fluoro-4-hydroxy-4-phenyl-3-*n*-pentyl-1,2-butadienephosphonate 11b. To a mixture of **10** (0.176 g, 0.67 mmol) and benzaldehyde (0.068 mL, 0.67 mmol) in THF (5 mL) at −80 °C was added dropwise tetrabutylammonium fluoride (1.33 mL of a 1 M solution in THF, 1.33 mmol). After the addition, the reaction was allowed to reach room temperature. After 1 h, the reaction was poured into saturated NH_4Cl and extracted with ether. The combined organic extracts were dried and concentrated. The crude product was separated by flash chromatography (hexane/EtOAc = 9:1−4:6) to afford of **11b** (0.179 g, 72%) as a 12:5 mixture of diastereomers.

Major diastereomer of allenol **11b**: ^{1}H NMR δ 0.81−0.86 (m, 3H), 1.21−1.46 (m, 12H), 2.02−2.10 (m, 2H), 4.07−4.22 (m, 4H), 5.31 (dd, J = 7.0, 2.1 Hz, 1H), 7.26−7.47 (m, 5H); ^{19}F NMR δ −151 (d, J = 122 Hz); ^{31}P NMR δ 7.2 (d, J = 122 Hz); IR (NaCl, neat) 3350, 2925, 2860, 1955 cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_4FP$: C, 61.61; H, 7.62. Found: C, 61.77; H, 7.61.

Minor diastereomer of allenol **11b**: ^{1}H NMR δ 0.81−0.86 (m, 3H), 1.22−1.47 (m, 12H), 2.04−2.13 (m, 2 H), 4.03−4.20 (m, 4H), 5.21 (dd, J = 7.0, 3.0 Hz, 1H), 7.27−7.43 (m, 5H); ^{19}F NMR δ −155 (d, J = 123 Hz); ^{31}P NMR δ 6.9 (d, J = 123 Hz).

***(E)*-Diethyl 1-Fluoro-2,3-diiodo-1-propenephosphonate 12.** To a stirred solution of **8** (0.221 g, 1.14 mmol) was added a solution of iodine (0.304 g, 1.20 mmol) in CH_2Cl_2 (15 mL), and the mixture was stirred at room temperature for 1 h. The reaction was quenched with 5% $Na_2S_2O_3$ (25 mL), the organic layer was separated, and then the aqueous layer was washed with diethyl ether. The combined organic layers were dried and concentrated to give an orange oil. The crude product was purified by flash chromatography (hexane/EtOAc = 8:2) affording **12** as a yellow oil (0.465 g, 91%): ^{1}H NMR δ 1.39 (t, J = 7.3 Hz, 6H), 4.21 (m, 4H), 5.06 (dd, J = 2.2, 1.7 Hz, 2H); ^{19}F NMR δ −83.6 (d, J = 103 Hz); ^{31}P NMR δ −0.9 (d, J = 101 Hz); GC−MS 321 (M^+ − 127, 31), 265 (56), 156 (29), 138 (100), 109 (23), 65 (88).

***(E)*-Diethyl 1-Fluoro-2-iodo-3-diethylamino-1-propenephosphonate 13a.** A mixture of **12** (0.049 g, 0.11 mmol), diethylamine (0.013 mL, 0.12 mmol), and potassium carbonate (0.0152 g, 0.11 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 1 day. The reaction was quenched with H_2O, the organic layer was separated, and the aqueous layer was washed with diethyl ether. The combined organic layers were dried and concentrated. The crude product was purified by chromatotron (hexane/EtOAc = 8:2) affording **13a** (0.037 g, 85%): ^{1}H NMR δ 1.07 (t, J = 7.1 Hz, 6H), 1.39 (t, J = 7.1 Hz, 6H), 2.57 (q, J = 7.1 Hz, 4H), 3.64 (dd, J = 1.7, 2.8 Hz, 2H), 4.20 (m, 4H); ^{19}F NMR δ −83.4 (d, J = 107 Hz); ^{31}P NMR δ −0.3 (d, J = 107 Hz); GC−MS 379 (M^+ − 14, 0.4), 266 (35), 246 (34), 190 (27), 110 (100), 56 (42). Anal. Calcd for $C_{11}H_{22}NO_3FPI$: C, 33.60; H, 5.64. Found: C, 33.43; H, 5.67.

***(E)*-Diethyl 3-(Purin-9-yl)-1-fluoro-2-iodo-1-propenephosphonate 13b.** A mixture of **12** (0.116 g, 0.26 mmol), purine (0.031 g, 0.26 mmol), and potassium carbonate (0.053 g, 0.39 mmol) in DMF (10 mL) was stirred at room temperature overnight. The reaction was quenched with H_2O, the organic layer was separated, and the aqueous layer was washed with CH_2Cl_2. The combined organic layers were dried and concentrated. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH = 9:1) affording **13b** (0.076 g, 67%) as pale yellow powder. The product was recrystallized from benzene/hexane yielding white crystals: mp 130−132 °C; ^{1}H NMR δ 1.45 (t, J = 7.0 Hz, 6H), 4.36 (m, 4H), 5.90 (dd, J = 1.7, 2.1 Hz, 2H), 8.25, 8.99, and 9.18 (3s, H_2, H_6 and H_8, purine, 3H); ^{19}F NMR δ −80.0 (d, J = 100 Hz); ^{31}P NMR δ −1.6 (d, J = 101 Hz). Anal. Calcd for $C_{12}H_{15}N_4O_3FPI$: C, 32.75; H, 3.43. Found: C, 32.76; H, 3.39.

***(E)*-Diethyl 3-(Adenin-9-yl)-1-fluoro-2-iodo-1-propenephosphonate 13c.** A mixture of **12** (0.112 g, 0.25 mmol), adenine (0.0338 g, 0.25 mmol), and potassium carbonate (0.0518 g, 0.375 mmol) in DMF (10 mL) was stirred at room temperature for 1 day. The reaction was quenched with H_2O, the organic layer was separated, and the aqueous layer was washed with CH_2Cl_2. The combined organic layers were dried and concentrated.The crude product was purified by flash chromatography (CH_2Cl_2/MeOH = 8:2) affording the **13c** (0.068 g, 60%) as pale yellow powder. The product was recrystallized from benzene yielding pale yellow crystals: mp 159−161 °C; ^{1}H NMR δ 1.44 (t, J = 7.2 Hz, 6H), 4.34 (m, 4H), 5.68 (s, NH_2), 5.78 (dd, J = 1.7, 2.2 Hz, 2H), 7.93 and 8.36 (2 s, H_2 and H_8, adenine, 2H); ^{19}F NMR δ −80.7 (d, J = 100 Hz); ^{31}P NMR δ −1.4 (d, J = 101 Hz). Anal. Calcd for $C_{12}H_{16}N_5O_3FPI$: C, 31.67; H, 3.54. Found: C, 31.95; H, 3.49.

General Procedure for the Preparation of Enaminophosphonate 14. The mixture of the **8** (0.194 g, 1.0 mmol) and excess amine (2 equiv) in THF (10 mL) was stirred at room temperature for 18−24 h.

***(Z)*- and *(E)*-diethyl *β*-*N*-benzylamino-1-fluoro-1-propenephosphonate 14a:** ^{19}F NMR δ −172 (d, J = 84 Hz, *E*-isomer), −183.5 (d, J = 91 Hz, *(Z)*-isomer); ^{31}P NMR δ 11.5 (d, J = 84 Hz, *(E)*-isomer), 13.1 (d, J = 91 Hz, *(Z)*-isomer).

***(Z)*- and *(E)*-diethyl *β*-N-cyclohexanylamino-1-fluoro-1-propenephosphonate 14b:** ^{19}F NMR δ −174 (d, J = 85 Hz, *(E)*-isomer), −184 (d, J = 91.5 Hz, *(Z)*-isomer); ^{31}P NMR δ 12.1 (d, J = 85 Hz, *(E)*-isomer), 13.4 (d, J = 91.5 Hz, *(Z)*-isomer).

***(Z)*-Diethyl *β*-*N*,*N*-Diethylamino-1-fluoro-1-propenephosphonate 14c:** ^{1}H NMR δ 1.14 (t, J = 6.9 Hz, 6H), 1.35 (t, J = 7.0 Hz, 6H), 2.17 (dd, J = 3.6, 2.0 Hz, 3H), 3.25 (q, J = 1.7 Hz, 4H), 4.11 (m, 4H); ^{19}F NMR δ −166 (d, J = 91.5 Hz); ^{31}P NMR δ 14.6 (d, J = 91.5 Hz).

5-Fluorodiethoxyphosphorylmethylidinebicyclo[2.2.1]-hept-2-ene 15. The mixture of **8** (0.136 g, 0.70 mmol) and cyclopentadiene (0.069 g, 1.05 mmol, 1.5 equiv) was stirred in a sealed tube at room temperature for 2 days. The residue was purified by flash chromatography (hexane/EtOAc = 9:1−7:3) to afford the bicycloheptene **15** (0.142 g, 78%): ^{1}H NMR δ 1.36 (m, 6H), 1.63−1.66 (m, 2H), 2.15 (ddd, J = 16.0, 3.2, 2.9 Hz, 1H), 2.57 (ddd, J = 16.0, 3.1, 2.7 Hz, 1H), 3.10 (broad s, 1H), 3.90 (broad s, 1H), 4.10 (m, 4H), 6.05 (dd, J = 5.4, 3.1 Hz, 1H), 6.27 (dd, J = 5.5, 3.0 Hz, 1H); ^{19}F NMR δ −132 (d, J = 109 Hz); ^{31}P NMR δ 6.4 (d, J = 110 Hz); IR (neat, NaCl) 3492, 3065, 2984, 2867, 1673 cm^{-1}; GC−MS m/z 260 (M^+, 87), 232 (18), 204 (100), 123(38), 103 (43), 65 (43). Anal. Calcd for $C_{12}H_{18}O_3FP$: C, 55.38; H, 6.97. Found: C, 54.93; H, 7.07.

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Supporting Information Available: Tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **13a**,**b** and (*E*)-**14a** (PDF). ^{1}H and ^{13}C NMR spectra of **7b**,**f** and **12.** This material is available free of charge via the Internet at http://pubs.acs.org.

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