Conjugate Addition of Diethyl 1-Fluoro-1phenylsulfonylmethanephosphonate to α , β -Unsaturated Compounds

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Supporting Information

ABSTRACT: Diethyl 1-fluoro-1-phenylsulfonylmethanephosphonate (1) in the presence of cesium carbonate undergoes efficient 1,4-addition to Michael acceptors having terminal double bonds such as α,β -unsaturated ketones, esters, sulfones, sulfoxides, and phosphonates to yield the corresponding adducts in good to excellent yields. In the presence of sodium hydride, 1 reacts with α,β -enones to provide γ fluoro- γ -phenylsulfonylenol phosphates arising from 1,4addition followed by phosphonate to phosphate rearrangement.

rganic phosphates are ubiquitous molecules that play important roles in living organisms, ranging from information storage and transfer (DNA, RNA), energy transfer (ATP), to separation of a cell membrane from the environment (phospholipids).¹ Phosphonates, containing nonhydrolyzable C-P bonds, can serve as mimics for natural phosphates in terms of their function and bioactivity. Indeed, many synthetic phosphonates display interesting biological activities.² Moreover, it has been realized that adjunction of electronegative elements such as fluorine atoms to the α -position of a phosphonate enables closer phosphate mimicry.³⁷ α -Fluorinated phosphonates⁴ are often utilized as enzyme inhibitors and metabolic probes.⁵ In recent years, there has been significant progress in studying the chemistry and bioactivity of α, α difluoro phosphonates.⁶ However, the less studied α -monofluoro phosphonates have second pK_a 's more closely correlating with the pK_a of natural phosphates.^{3b,7}

Diethyl 1-fluoro-1-phenylsulfonylmethanephosphonate (1), also known as McCarthỳs reagent, was introduced into organic synthesis in 1987 by Koizumi⁸ and further developed as a fluoromethylene synthon by McCarthy.⁹ Compound 1 reacts under basic conditions with aldehydes, ketones, and α,β unsaturated aldehydes in the course of the Horner–Wadsworth–Emmons reaction to provide 1-fluoro-1-phenylsulfonylalkenes.^{8–10} Furthermore, 1 has been employed as a precursor of α -fluoro phosphonates or α -fluorosulfones. The synthetic strategy is based on alkylation of 1 and further desulfonation or dephosphonylation (Scheme 1).¹¹

Introduction of (poly)fluoroalkyl groups by nucleophilic addition to electrophiles has been extensively studied in recent years. Many strategies and reagents were developed for efficient



Scheme 1. Published HWE and Alkylation Reactions of 1



nucleophilic mono-, di-, and trifluoromethylations as well as perfluoroalkylations and polyfluoroakylations.¹² The reactive species in these processes are α -fluorinated carbanions which are, in comparison to nonfluorinated carbanions, less polarizable and less nucleophilic. As a consequence, unless several electron delocalization groups which increase polarizability (soft character) are present on an α -fluorinated carbanionic center, the reagent behaves as a hard nucleophile. For example, the Ruppert–Prakash reagent (TMSCF₃) is known to undergo 1,2-addition to α , β -unsaturated carbonyl compounds.^{12a,13} The same behavior was observed for diethyl difluoromethylphosphonate in the presence of LDA; however, in the presence of lithium-coordinating HMPA or transmetalation with Ce^{III} salts,

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Table 1. Optimization of the 1,4-Addition of 1 to Methyl Vinyl Ketone $(2a)^a$



^{*a*}Reactions were carried out using **1** (0.20 mmol, 1.0 equiv), **2a** (1.2 equiv), and base in solvent (2.5 mL). ^{*b*19}F NMR yield with PhCF₃ as an internal standard unless noted otherwise. ^{*c*}Isolated yield.

Table 2. 1,4-Addition of 1 to $\alpha_{\beta}\beta$ -Unsaturated Compounds 2^{*a*}

		(EtC) ₂ (O)P、 _3	SO₂Ph ,	A	Cs ₂ CO ₃		(EtO) ₂ (O)P_F	
			τ, Υ F	- +	✓ `EWG	MeC	N, rt	PhO ₂ S	EWG
			1		2			3	
	Entry	2	Michael a (equiv.)	cceptor	Cs ₂ CO ₃ (equiv.)	Time (h)	3	Product	Yield $(\%)^b$
	1	2a	\sim	1.2	0.1	1	3a	(EtO) ₂ (O)P F PhO ₂ S O	95
	2	2b	∭ SO₂Ph	1.0	0.1	1	3b	(EtO) ₂ (O)P_F PhO ₂ S_SO ₂ Ph	95
	3	2c	CO ₂ n-Bu	1.2	0.1	5	3c	(EtO) ₂ (O)P_F PhO ₂ S ⁻ CO ₂ n-Bu	94
	4	2d	──CO ₂ Et	1.2	1.0	4	3d	(EtO) ₂ (O)P F PhO ₂ S CO ₂ Et	$63^{c,d}(E/Z \ 1:1)$
	5	2e	∕sr ^{Ph} ⊓ 0	1.0	1.0	3	3e	(EtO) ₂ (O)P F PhO ₂ S Ph	56 (dr 49:51)
	6	2f	CO ₂ Me	1.2	2.0	21	3f	(EtO) ₂ (O)PF PhO ₂ SCO ₂ Me	48 (dr 22:77)
	7	2g	P(O)(OEt)2	1.0	1.0	25	3g	(EtO) ₂ (O)P_F PhO ₂ S_P(O)(OEt) ₂	69
	8	2h	Ph O Ph	1.0	3.0	24	3h	$(EtO)_2(O)P$ F PhO ₂ S Ph Ph O	0^e
	9	2i	Ph CN CN	1.0	2.0	20	3i	(EtO) ₂ (O)P F CN PhO ₂ S CN Ph	0
	10	2j	PhNO2	1.0	2.0	45	3j	(EtO) ₂ (O)P F PhO ₂ S Ph	0
	11	2k		1.0	3.0	22	3k'	(EtO) ₂ (O)P F SO ₂ Ph PhO ₂ S F	28 ^c

^{*a*}Reactions were carried out using **1** (0.30 mmol, 1.0 equiv), **2**, and Cs_2CO_3 in MeCN (3 mL). ^{*b*}Isolated yield unless noted otherwise. ^{*c*19}F NMR yield using PhCF₃ as a standard. ^{*d*}Pure (*E*)-**3d** was isolated by silica gel chromatorgraphy in 29% yield. ^{*e*}Different products were formed (see discussion below).

significant 1,4-addition to α , β -unsaturated ketones was observed.¹⁴ Similarly, lithium salts of mono- and difluoromethyl phenyl sulfone gave exclusive 1,2-addition to 2-cyclohexenone but showed high 1,4-/1,2-addition ratio in the presence of

HMPA.¹⁵ On the other hand, more delocalized fluoromethyl carbanions of 1-fluorobis(phenylsulfonyl)methane¹⁵ and tetraethyl fluoromethylenebisphosphonate¹⁶ undergo exclusive conjugate addition to $\alpha_{,\beta}$ -enones and other Michael acceptors

without any cation-coordinating additive. The latter reagent is relatively bulky and requires the presence of electrophiles with unsubstituted double bonds. Additionally, α -fluoro- β -keto esters,¹⁷ α -fluoronitroalkanes,¹⁸ and some fluorinated sulfones of the general formula PhSO₂CFR (R = NO₂, CN, CO₂Et)¹⁹ were shown to undergo conjugate additions to various Michael acceptors.

Conjugate addition of the McCarthy's reagent has not been studied. The process would be useful for the synthesis of functionalized monofluoromethylene-containing compounds, which could be further utilized for various transformations such as reductive phenylsulfanyl group removal leading to α fluoro phosphonates. It was also of interest to compare the reactivity of the McCarthy's reagent in conjugate addition with 1-fluorobis(phenylsulfonyl)methane and tetraethyl fluoromethylenebisphosphonate.

Investigation of Michael addition of 1 to methyl vinyl ketone as a model α,β -enone provided the initial focus. Application of conditions optimized for Michael addition of tetraethyl fluoromethylenebisphosphonate provided the required 1,4addition product 3a in good NMR yield; however, a long reaction time was needed and a significant amount of the double addition product 4a was formed (Table 1, entry 1). When the amount of base was reduced to 10 mol %, 3a formed with a short reaction time as a sole product and in high isolated yield (entry 3). The reason for the reactivity difference between 1 and tetraethyl fluoromethylenebisphosphonate¹⁶ could be explained by the steric effect (the phosphonate moiety is bulkier than the phenylsulfonyl group). Addition of 1 to methyl vinyl ketone provides the anionic adduct which is able to deprotonate starting 1. In contrast, high steric crowding of both the fluorobisphosphonate and the product of its addition prevents efficient proton exchange and thus requires the use of excess base. Product 3a was formed in high yields using other solvents than DMF (entries 4 and 5). Finally, although the reaction time was somewhat increased (compared to DMF), it was beneficial to carry out the reaction in low-boiling acetonitrile. Several other bases were tested and it was found that the reaction could be performed with catalytic potassium carbonate at elevated temperature.

Optimized reaction conditions (Table 1, entry 5) were used in the scope and limitation study of the 1,4-addition of 1 to various $\alpha_{,\beta}$ -unsaturated compounds **2** (Table 2). In addition to methyl vinyl ketone (2a), phenyl vinyl sulfone (2b) and butyl acrylate (2c) were found to be very reactive substrates and provided 1,4-addition adducts 3 in high yields (entries 1-3). Ethyl propiolate (2d) reacted with 1 in the presence of catalytic Cs_2CO_3 , but a higher yield of 3d and shorter reaction time was observed with a stoichiometric amount of the base. The ¹⁹F NMR spectrum of the crude reaction mixture indicated the formation of the product 3d in 63% NMR yield as an E/Z 1:1 mixture (entry 4). Phenyl vinyl sulfoxide (2e), methyl methacrylate (2f), and diethyl vinylphosphonate (2g) required the use of at least 1 equiv of the base (entries 5-7). Compounds 3e and 3f were formed as a mixture of diastereomers, and the dr seemed to decrease with increasing distance between the asymmetric centers. Chalcone (2h) did not provide the desired product **3h** (entry 8); however, the use of 3-fold excess cesium carbonate resulted in formation of new products (see discussion below). Benzylidine malononitrile (2i) and β -nitrostyrene (2j) were unreactive in the presence of catalytic amounts of cesium carbonate and an excess of the base gave a range of unidentified fluorinated products in both cases.

Cyclohexenone (2k) did not give the desired product either with a catalytic amount or with excess cesium carbonate. Nevertheless, complete conversion of starting 1 with excess cesium carbonate took place and the formation of 3k' (four isomers) arising from conjugate addition, and HWE reaction was established by HRMS (ESI⁺) and ¹⁹F NMR analyses.

Desulfonation of selected Michael adducts 3 using magnesium in methanol²⁰ gave α -fluorophosphonates in good yields (Scheme 2). During the course of the desulfonation of 3c, transesterification occurred.

Scheme 2. Desulfonation of Adducts 3 to α -Fluorophosphonates 5

(EtO) ₂ (O)P F PhO ₂ S R ¹	Mg (10 equiv.) ► MeOH, rt, 1-2 h	(EtO) ₂ (O)P	\mathbf{A}^{R^2}
3a , R ¹ = Me		5a , $R^2 = Me$ 666	%
3c , R ¹ = O <i>n-</i> Bu		5c , $R^2 = OMe$ 879	%

Reaction of 1 with chalcone (2h) was investigated in more detail (Table 3). With catalytic Cs_2CO_3 , no reaction took place, but the use of an excess of the base gave a new product, enol phosphate 7h, in 31% isolated yield (entries 1 and 2). With LDA in THF a mixture of the HWE product 6h and product 7h formed in low yields (entry 3). Finally, a 2-fold excess of sodium hydride provided 7h in good yield (entry 5). Compound 7h formed as a mixture of separable diastereomers with moderate diastereoselectivity. The relative configuration of 7h was determined by NMR (see Figures SI-1 to SI-4, Supporting Information, for conformational analysis) and X-ray diffraction analysis (see CCDC 906505 and Figure SI-5, Supporting Information) which confirmed that the major (less polar) diasteromer of 7h has the relative configuration as *anti*.

The conditions optimized for the formation of 7h were tested on other $\alpha_{,\beta}$ -unsaturated ketones (Table 4). With methyl vinyl ketone (2a), a mixture of the 1,4-addition product (3a), HWE product (6a), and product 7a was formed (entry 1). Both chalcone 2h and 2l gave compound 7 in good isolated vield (with minor HWE product 6). Ketone 2m provided only product 7m in good yield. On the other hand, isomeric ketone 2n gave only the product of HWE reaction. This reactivity switch could be explained by reversible formation of 1,2adducts. In the reaction with 2n, the 1,2-adduct contains relatively strongly nucleophilic alkoxide which undergoes HWE reaction. For ketones 2h-m, however, the HWE reaction is suppressed and 1,4-addition prevails.²¹ The following phosphonate to phosphate rearrangement to 7 involves the formation of a 6-membered ring. This process was not described before. Related rearrangements of γ -hydroxy phosphonates (involving a 5-membered ring) are known.²²

Surprisingly, the treatment of enol phosphates 7h with magnesium in methanol did not provide the desulfonated product but led to the product of dephosphonylation 8h in low yield (25%) together with some unidentified side products. On the other hand, strongly acidic conditions affect dephosphonylation of 7h, giving the ketone 8h in good yield (Scheme 3). The crude 8h showed the same dr (64:36) as the starting 7h; however, the dr of 8h increased to 90:10 upon isolation using column chromatography. In contrast, Hu and co-workers reported that the addition of fluoromethyl phenyl sulfone to chalcone provided a mixture of 1,2/1,4-addition products in 42:58 ratio.^{15a}

Table 3. Reaction of 1 with Chalcone (2h)^a



^{*a*}Reactions were carried out using **1**, **2h** (0.20 mmol, 1 equiv), and the base in solvent (2 mL). ^{*b*19}F NMR yield using PhCF₃ as an standard. ^{*c*}Isolated yield. ^{*d*}Determined by ¹⁹F NMR of the crude product mixture. ^{*e*}The same conditions as in Table 2, entry 8.

Table 4. Formation of Enol Phosphates 7 by the Addition of 1 to Unsaturated Ketones $(2)^{a}$

		$R^{1} \xrightarrow{O} R^{2} \xrightarrow{1, \text{ NaH, THF}} \xrightarrow{(EtO)_{2}(O)P} PhO_{2}S \xrightarrow{F} O + R^{1} \xrightarrow{F_{2}} SO_{2}Ph \xrightarrow{R^{1}} OP(O)(OEt)_{2}$						
		2		3	6	7		
entry	2	\mathbb{R}^1	R ²	yield ^{b} (%) of 3	yield ^{b} (%) of 6	yield ^{c} (%) of 7	dr^d of 7	
1	2a	Н	Me	30	22	18^{b}		
2	2h	Ph	Ph	0	7	72	64:36	
3	21	<i>p</i> -Tol	Ph	0	12	68	58:42	
4	2m	Me	Ph	0	0	68	71:29	
5	2n	Ph	Me	0	34, 70 ^e	0		

^{*a*}Reactions were carried out using 1 (2 equiv), 2 (0.20 mmol, 1 equiv), and NaH (2 equiv) in THF (3 mL). ^{*b*19}F NMR yield using PhCF₃ as a standard. ^{*c*}Isolated yield unless noted otherwise. ^{*d*}Determined by ¹⁹F NMR of the crude product mixture. ^{*e*}Using 1 (0.4 mmol, 1 equiv), 2n (4 equiv), and NaH (1.2 equiv) in THF (3 mL) at -70 to 0 °C for 1 h. *E/Z* ratio of **6n** was 62:38.

Scheme 3. Formation of γ -Fluoro Ketone 8h by Dephosphonylation of 7h



In summary, efficient conjugated addition of 1 to Michael acceptors was accomplished using catalytic or equimolar amounts of cesium carbonate. The adducts can be desulfonated using magnesium in methanol to yield α -fluoro phosphonates. Reaction of 1 with chalcones and related ketones in the presence of sodium hydride resulted in formation of unexpected γ -fluoro- γ -phenylsulfonylenol phosphates which can be hydrolyzed to γ -fluoro- γ -phenylsulfonyl ketones.

EXPERIMENTAL SECTION

Compounds **2h**, **2l**, and **2n** were prepared according to literature procedure.²³ HRMS (ESI) analyses were recorded using an ion trap MS analyzer.

General Procedure for the Synthesis of Compounds 3. Cs_2CO_3 (0.03–0.90 mmol, 0.1–3.0 equiv) was placed in a Schlenk flask, and MeCN (3 mL) and 1 (93.1 mg, 0.3 mmol, 1.0 equiv) were added followed by addition of 2 (0.30–0.36 mmol, 1.0–1.2 equiv). The reaction mixture was stirred at rt, followed by addition of saturated NH₄Cl (15 mL), extraction with Et₂O (3 × 15 mL), drying, and removal of solvents under reduced pressure. Purification by silica gel column chromatography using hexane/EtOAc as eluent provided compounds 3.

3a. Prepared from Cs₂CO₃ (10 mg, 0.03 mmol), 1 (93.1 mg, 0.3 mmol) and 2a (26 mg, 0.36 mmol) in 1 h at rt giving 3a (112 mg, 95%) as a colorless liquid: R_f 0.30 (hexane–EtOAc, 1:1); ¹H NMR (400 MHz, CDCl₃) δ 1.26 (t, 3H, J = 7.1 Hz), 1.30 (t, 3H, J = 7.1 Hz), 2.14 (s, 3H), 2.37–2.65 (m, 2H), 2.78–3.04 (m, 2H), 4.09–4.26 (m, 4H), 7.53–7.59 (m, 2H), 7.65–7.72 (m, 1H), 7.92–7.97 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 16.2 (d, ³_{JCP} = 4.3 Hz), 16.3 (d, ³_{JCP} = 4.3 Hz), 25.4 (dd, ²_{JCF} = 19.6 Hz, ²_{JCP} = 7.1 Hz), 64.9 (d, ²_{JCP} = 6.8 Hz), 106.9 (dd, ¹_{JCF} = 228.6 Hz, ¹_{JCP} = 164.7 Hz), 128.7, 130.7, 134.7, 135.3, 205.7; ¹⁹F NMR (376 MHz, CDCl₃) δ –164.5 (ddd, ²_{JFP} = 80.5 Hz, ³_{JFH} = 23.4, 16.7 Hz); ³¹P NMR (162 MHz, CDCl₃) δ 8.8 (d, ²_{JFF} = 80.5 Hz); HRMS (ESI) calcd for C₁₅H₂₃FO₆PS [M + H]⁺ 381.0932, found 381.0931.

3b. Prepared from Cs₂CO₃ (10 mg, 0.03 mmol), **1** (93 mg, 0.3 mmol), and **2b** (40 mg, 0.30 mmol) in 1 h at rt giving **3b** (139 mg, 95%) as a colorless liquid: R_f 0.22 (hexane–EtOAc, 1:1); ¹H NMR (400 MHz, CDCl₃) δ 1.23 (t, 3H, *J* = 7.1 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 2.54–2.68 (m, 2H), 3.39–3.48 (m, 1H), 3.61–3.72 (m, 1H), 4.06–4.23 (m, 4H), 7.52–7.59 (m, 4H), 7.64–7.73 (m, 2H), 7.86–7.90 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 16.1 (d, ³*J*_{CP} = 5.6 Hz), 16.2 (d, ³*J*_{CP} = 5.6 Hz), 25.4 (dd, ²*J*_{CF} = 20.5 Hz, ²*J*_{CP} = 2.2 Hz), 50.1 (dd, ³*J*_{CF} = 6.0 Hz, ³*J*_{CP} = 2.5 Hz), 65.0 (d, ²*J*_{CP} = 7.1 Hz), 65.2 (d, ²*J*_{CP} = 6.8 Hz), 105.3 (dd, ¹*J*_{CF} = 230.7 Hz, ¹*J*_{CP} = 164.3 Hz), 128.0, 128.8, 129.4, 130.7 (d, ³*J*_{CF} = 1.2 Hz), 133.9, 134.6, 135.0, 138.3; ¹⁹F NMR (376 MHz, CDCl₃) δ –164.4 (ddd, ²*J*_{FP} = 78.8 Hz, ³*J*_{FH} = 18.9, 18.9 Hz); ³¹P NMR (162 MHz, CDCl₃) δ 7.8 (d, ²*J*_{FF} = 78.8 Hz); HRMS (ESI) calcd for C₁₉H₂₄FNaO₇PS₂ [M + Na]⁺ 501.0577, found 501.0577.

3c. Prepared from Cs₂CO₃ (10 mg, 0.03 mmol), **1** (93 mg, 0.3 mmol), and **2c** (46 mg, 0.36 mmol) in 5 h at rt giving **3c** (124 mg, 94%) as a colorless liquid: R_f 0.52 (hexane–EtOAc, 1:1); ¹H NMR (400 MHz, CDCl₃) δ 0.93 (t, 3H, J = 7.4 Hz), 1.30 (t, 3H, J = 7.0 Hz), 1.33 (t, 3H, J = 7.1 Hz), 1.33–1.42 (m, 2H), 1.55–1.64 (m, 2H), 2.50–2.66 (m, 2H), 2.67–2.74 (m, 1H), 2.80–2.90 (m, 1H), 4.07 (t,

3H, J = 6.7 Hz), 4.15–4.30 (m, 4H), 7.56–7.61 (m, 2H), 7.69–7.75 (m, 1H), 7.97–8.01 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 13.6, 16.2 (d, ${}^{3}J_{CP} = 4.4$ Hz), 16.3 (d, ${}^{3}J_{CP} = 4.4$ Hz), 19.0, 26.8 (dd, ${}^{2}J_{CF} = 19.6$ Hz, ${}^{2}J_{CP} = 2.0$ Hz), 28.0 (dd, ${}^{3}J_{CF} = 6.6$ Hz, ${}^{3}J_{CP} = 2.7$ Hz), 30.5, 64.6, 64.7 (d, ${}^{2}J_{CP} = 7.0$ Hz), 64.9 (d, ${}^{2}J_{CP} = 6.8$ Hz), 106.6 (dd, ${}^{1}J_{CF} = 229.4$ Hz, ${}^{1}J_{CP} = 164.9$ Hz), 128.7, 130.8 (d, ${}^{3}J_{CF} = 1.2$ Hz), 134.7, 135.3, 171.9; 19 F NMR (376 MHz, CDCl₃) δ –165.5 (ddd, ${}^{2}J_{FP} = 80.1$ Hz, ${}^{3}J_{FH} = 22.3$, 16.8 Hz); 31 P NMR (162 MHz, CDCl₃) δ 8.7 (d, ${}^{2}J_{PF} = 80.5$ Hz); HRMS (ESI) calcd for C₁₈H₂₈FNaO₇PS [M + Na]⁺ 461.1170, found 461.1169.

3d. Prepared from Cs₂CO₃ (100 mg, 0.30 mmol), 1 (93 mg, 0.3 mmol), and 2d (35 mg, 0.36 mmol) in 4 h at rt giving 3d (63% ¹⁹F NMR yield). (*E*)-3d (36 mg, 29%) a colorless liquid: R_f = 0.50 (hexane-EtOAc, 1:1); ¹H NMR (400 MHz, CDCl₃) δ 1.28 (t, 3H, *J* = 7.1 Hz), 1.36 (t, 3H, *J* = 7.1 Hz), 1.37 (t, 3H, *J* = 7.1 Hz), 4.15–4.23 (m, 2H), 4.24–4.40 (m, 4H), 5.97 (dd, 1H, *J* = 15.7 Hz, ⁴*J*_{FH} = 4.1 Hz), 7.15 (ddd, 1H, ³*J*_{FH} = 24.3 Hz, *J* = 15.7 Hz, ³*J*_{PH} = 3.1 Hz), 7.59 (m, 2H), 7.68–7.74 (m, 1H), 7.89–7.93 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 14.1, 16.2, 16.3, 61.1, 65.6 (d, ²*J*_{CP} = 7.2 Hz), 65.7 (d, ²*J*_{CP} = 6.9 Hz), 106.0 (dd, ¹*J*_{CF} = 238.8 Hz, ¹*J*_{CP} = 165.1 Hz), 125.6 (dd, ²*J*_{CF} = 10.5 Hz, ²*J*_{CP} = 7.8 Hz), 128.1, 130.1, 133.5, 133.6, 134.5, 163.5; ¹⁹F NMR (376 MHz, CDCl₃) δ –168.5 (dd, ²*J*_{FP} = 74.2 Hz, ³*J*_{FH} = 24.3 Hz); ³¹P NMR (162 MHz, CDCl₃) δ 5.2 (d, ²*J*_{FP} = 74.2 Hz); HRMS (ESI) calcd for C₁₆H₂₃FO₇PS [M + H]⁺ 409.0881, found 409.0880.

3e. Prepared from Cs₂CO₃ (100 mg, 0.30 mmol), 1 (93 mg, 0.3 mmol), and 2e (46 mg, 0.30 mmol) in 3 h at rt giving a 1:1 mixture of diastereomers of 3e (78 mg, 56%) as a colorless liquid: $R_{\rm f}$ 0.48 (EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 1.26 (t, 6H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.3 Hz), 1.31 (t, 3H, J = 7.1 Hz), 2.17–2.41 (m, 2H), 2.59–2.81 (m, 2H), 2.99 (ddd, 1H, ${}^{2}J_{HH} = 16.5$ Hz, ${}^{3}J_{HH} = 13.5$, 4.8 Hz), 3.17 (ddd, 1H, ${}^{2}J_{HH} = 16.5$ Hz, ${}^{3}J_{HH} = 13.5$, 4.7 Hz), 3.34 (ddd, 1H, ${}^{2}J_{HH} = 16.6$ Hz, ${}^{3}J_{HH} = 13.6$, 4.6 Hz), 3.52 (ddd, 1H, ${}^{2}J_{HH} = 16.1$ Hz, ${}^{3}J_{HH} = 13.5, 4.4$ Hz), 4.07–4.28 (m, 8H), 7.48–7.61 (m, 14H), 7.68–7.73 (m, 2H), 7.85–7.93 (m, 4H); ${}^{13}C$ NMR (100 MHz, 100 MHz) CDCl₃) δ 16.1 (d, ${}^{3}J_{CP}$ = 3.3 Hz), 16.2 (d, ${}^{3}J_{CP}$ = 3.1 Hz), 16.2 (d, ${}^{3}J_{CP}$ = 2.4 Hz), 16.3 (d, ${}^{3}J_{CP}$ = 3.6 Hz), 23.9 (dd, ${}^{2}J_{CF}$ = 20.4 Hz, ${}^{2}J_{CP}$ = 2.4 Hz), 23.9 (dd, ${}^{2}J_{CF}$ = 20.0 Hz, ${}^{2}J_{CP}$ = 2.3 Hz), 49.0 (dd, ${}^{3}J_{CF}$ = 7.0 Hz, ${}^{3}J_{CP} = 3.7 \text{ Hz}), 49.1 \text{ (dd, } {}^{3}J_{CF} = 6.6 \text{ Hz}, {}^{3}J_{CP} = 2.5 \text{ Hz}), 64.9 \text{ (d, } {}^{2}J_{CP} = 2.5 \text{ Hz})$ 7.1 Hz), 65.0 (d, ${}^{2}J_{CP} = 7.1$ Hz), 65.0 (d, ${}^{2}J_{CP} = 7.2$ Hz), 65.1 (d, ${}^{2}J_{CP} = 6.5$ Hz), 106.2 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CF} = 230.1$ Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, {}^{1}J_{CF} = 230.1 Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, {}^{1}J_{CF} = 230.1 Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, {}^{1}J_{CF} = 230.1 Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, {}^{1}J_{CF} = 230.1 Hz, ${}^{1}J_{CP} = 164.5$ Hz), 106.3 (dd, {}^{1}J_{CP} = 164.5 Hz), 106.5 = 229.7 Hz, ¹J_{CP} = 163.8 Hz), 124.0, 124.0, 128.8, 128.8, 129.2, 129.2, 130.7, 130.7, 131.0, 131.0, 134.8, 134.8, 134.8, 134.9, 142.4, 142.6; ¹⁹F NMR (376 MHz, CDCl₃) δ –164.1 (ddd, ²J_{FP} = 79.3 Hz, ³J_{FH} = 23.6, 16.5 Hz), -163.6 (ddd, ${}^{2}J_{\text{FP}}$ = 79.2 Hz, ${}^{3}J_{\text{FH}}$ = 23.9, 15.2 Hz); ${}^{31}\text{P}$ NMR (162 MHz, CDCl₃) δ 8.0 (d, ²J_{PF} = 79.3 Hz), 8.1 (d, ²J_{PF} = 79.2 Hz); HRMS (ESI) calcd for C₁₉H₂₅FO₆PS₂ [M + H]⁺ 463.0809, found 463.0809

3f. Prepared from Cs₂CO₃ (200 mg, 0.60 mmol), 1 (93 mg, 0.3 mmol), and 2f (36 mg, 0.36 mmol) in 21 h at rt giving a 3:1 mixture of diastereomers of 3f (59 mg, 48%) as a colorless liquid: R_f 0.34 (hexane-EtOAc, 1:1); ¹H NMR (400 MHz, CDCl₃) δ 1.20–1.40 (m, 9H, major), 1.20-1.40 (m, 9H, minor), 2.20-2.37 (m, 1H, major), 2.20-2.37 (m, 1H, minor), 2.80-2.96 (m, 1H, major), 2.96-3.08 (m, 1H, minor), 3.11-3.21 (m, 1H, major), 3.11-3.21 (m, 1H, minor), 3.59 (s, 3H, major), 3.69 (s, 3H, minor), 4.12-4.35 (m, 4H, major), 4.12-4.35 (m, 4H, minor), 7.55-7.64 (m, 2H, major), 7.55-7.64 (m, 2H, minor), 7.69-7.75 (m, 1H, major), 7.69-7.75 (m, 1H, minor), 7.97–8.05 (m, 2H, major), 7.97–8.05 (m, 2H, minor); ¹³C NMR (100 MHz, CDCl₃) δ 16.2 (d, ${}^{3}J_{CP}$ = 2.1 Hz, major), 16.2 (d, ${}^{3}J_{CP}$ = 2.1 Hz, minor), 16.3 (d, ${}^{3}J_{CP} = 2.1$ Hz, major), 16.3 (d, ${}^{3}J_{CP} = 2.1$ Hz, minor), 18.9 (minor), 19.5 (major), 33.7 (dd, ${}^{2}J_{CF} = 18.2$ Hz, ${}^{2}J_{CP} = 2.1$ Hz, minor), 34.3 (dd, ${}^{2}J_{CF}$ = 18.5 Hz, ${}^{2}J_{CP}$ = 2.1 Hz, major), 34.7 (dd, ${}^{3}J_{CF}$ = 4.2 Hz, ${}^{3}J_{CP}$ = 2.0 Hz, major), 34.8 (dd, ${}^{3}J_{CF}$ = 4.2 Hz, ${}^{3}J_{CP}$ = 2.2 Hz, minor), 51.7 (major), 51.9 (minor), 64.6 (d, ${}^{2}J_{CP} = 6.9$ Hz, minor), 64.8 (d, ${}^{2}J_{CP}$ = 7.0 Hz, major), 64.8 (d, ${}^{2}J_{CP}$ = 6.9 Hz, minor), 64.9 (d, ${}^{2}J_{CP}$ = 6.8 Hz, major), 107.0 (dd, ${}^{1}J_{CF}$ = 231.3 Hz, ${}^{1}J_{CP}$ = 165.0 Hz, major), 107.2 (dd, ${}^{1}J_{CF} = 231.3$ Hz, ${}^{1}J_{CP} = 165.9$ Hz, minor), 128.6 (major), 129.1 (minor), 130.8 (d, ${}^{3}J_{CF} = 1.4$ Hz, major), 130.9 (d, ${}^{3}J_{CF}$ = 1.3 Hz, minor), 134.6 (major), 134.9 (minor), 135.2 (major), 135.4

(minor), 175.6 (major), 175.9 (minor); ¹⁹F NMR (376 MHz, CDCl₃) δ –167.5 (ddd, ²*J*_{FP} = 81.7 Hz, ³*J*_{FH} = 20.9, 20.9 Hz, minor), –167.9 (ddd, ²*J*_{FP} = 81.0 Hz, ³*J*_{FH} = 30.8, 12.8 Hz, major); ³¹P NMR (162 MHz, CDCl₃) δ 8.5 (d, ²*J*_{PF} = 81.8 Hz, minor), 8.9 (d, ²*J*_{PF} = 81.0 Hz, major); HRMS (ESI) calcd for C₁₆H₂₄FNaO₇PS [M + Na]⁺ 433.0857, found 433.0855.

3g. Prepared from Cs₂CO₃ (100 mg, 0.30 mmol), **1** (93 mg, 0.3 mmol), and **2g** (49 mg, 0.30 mmol) in 25 h at rt giving **3g** (98 mg, 69%) as a colorless liquid: R_f 0.18 (EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 1.30 (t, 3H, J = 7.1 Hz), 1.32 (t, 6H, J = 7.1 Hz), 1.33 (t, 3H, J = 7.1 Hz), 2.05–2.16 (m, 1H), 2.23–2.37 (m, 1H), 2.45–2.63 (m, 2H), 4.05–4.15 (m, 4H), 4.16–4.30 (m, 4H), 7.56–7.62 (m, 2H), 7.70–7.75 (m, 1H), 7.97–8.01 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 16.2 (d, ³ J_{CP} = 3.7 Hz), 16.3 (d, ³ J_{CP} = 3.9 Hz), 16.4 (d, ³ J_{CP} = 6.2 Hz), 16.5 (ddd, ¹ J_{CP} = 142.7 Hz, ³ J_{CF} = 6.0 Hz, ³ J_{CP} = 2.4 Hz), 25.3 (ddd, ² J_{CF} = 20.1 Hz, ² J_{CP} = 2.0, 2.0 Hz), 61.7 (d, ² J_{CP} = 1.8 Hz), 61.8 (d, ³ J_{CP} = 1.8 Hz), 64.7 (d, ² J_{CP} = 7.0 Hz), 65.0 (d, ² J_{CP} = 6.7 Hz), 106.4 (ddd, ¹ J_{CF} = 229.9 Hz, ¹ J_{CP} = 164.9 Hz, ³ J_{CP} = 18.9 Hz), 128.7, 130.8 (d, ³ J_{CF} = 1.2 Hz), 134.7, 135.1; ¹⁹F NMR (376 MHz, CDCl₃) δ –165.0 (ddd, ² J_{FF} = 80.4 Hz, ³ J_{FH} = 19.8, 19.5 Hz); ³¹P NMR (162 MHz, CDCl₃) δ 8.5 (d, ² J_{FF} = 80.4 Hz), 29.4 (d, ⁴ J_{FF} = 3.6 Hz); HRMS (ESI) calcd for C₁₇H₃₀FO₈P₂S [M + H]⁺ 475.1115, found 475.1113.

General Procedure for the Synthesis of Compounds 5. Mg turnings (48 mg, 2 mmol, 10 equiv) were placed in a Schlenk flask followed by addition of MeOH (1.5 mL) and a solution of 3 (0.2 mmol, 1.0 equiv) in MeOH (0.3 mL). The reaction mixture was stirred at rt, followed by addition of 1 M HCl (10 mL) and extraction into Et_2O (3 × 15 mL). The combined organic phase was washed with brine (10 mL) and dried, and solvent was removed under reduced pressure. Purification by silica gel column chromatography using hexane/EtOAc as eluent gave products 5.

5a. Prepared from **3a** (76 mg, 0.2 mmol) in 1 h at rt giving **5a** (32 mg, 66%) as a colorless liquid: R_f 0.30 (hexane–EtOAc, 1:2); ¹H NMR (400 MHz, CDCl₃) δ 1.33 (t, 6H, J = 7.1 Hz), 2.07–2.28 (m, 2H), 2.14 (s, 3H), 2.59–2.78 (m, 2H), 4.15 (q, 2H, J = 7.1 Hz), 4.19 (q, 2H, J = 7.1 Hz), 4.73 (dddd, 1H, ² J_{FH} = 46.6 Hz, ² J_{PH} = 9.5 Hz, ³ J_{HH} = 4.2, 3.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 16.3 (d, ³ J_{CP} = 2.9 Hz), 16.4 (d, ³ J_{CP} = 3.0 Hz), 24.1 (dd, ² J_{CF} = 20.3 Hz, ² J_{CP} = 1.5 Hz), 29.9, 38.2 (dd, ³ J_{CF} = 11.1 Hz, ³ J_{CP} = 4.2 Hz), 62.8 (d, ² J_{CP} = 6.7 Hz), 63.2 (d, ² J_{CP} = 6.9 Hz), 87.7 (dd, ¹ J_{CF} = 179.4 Hz, ¹ J_{CP} = 170.9 Hz), 206.8; ¹⁹F {¹H} NMR (376 MHz, CDCl₃) δ -210.8 (d, ² J_{PF} = 75.8 Hz); ³¹P NMR (162 MHz, CDCl₃) δ 17.5 (d, ² J_{PF} = 75.7 Hz); HRMS (ESI) calcd for C₉H₁₈FO₄P [M]⁺ 240.0927, found 240.0925.

5c. Prepared from **3c** (88 mg, 0.2 mmol) in 2 h at rt giving **5c** (45 mg, 87%) as a colorless liquid: R_f 0.44 (hexane–EtOAc, 1:3); ¹H NMR (400 MHz, CDCl₃) δ 1.37 (t, 6H, J = 7.1 Hz), 2.16–2.34 (m, 2H), 2.49–2.66 (m, 2H), 3.70 (s, 3H), 4.20 (q, 2H, J = 7.1 Hz), 4.23 (q, 2H, J = 7.1 Hz), 4.80 (dddd, 1H, ² $J_{FH} = 46.8$ Hz, ² $J_{PH} = 8.2$ Hz, ³ $J_{HH} = 5.6$, 3.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 16.3 (d, ³ $J_{CP} = 2.7$ Hz), 16.4 (d, ³ $J_{CP} = 2.7$ Hz), 25.5 (d, ² $J_{CP} = 20.2$ Hz), 29.1 (dd, ³ $J_{CP} = 12.7$ Hz), 87.5 (dd, ¹ $J_{CF} = 180.0$ Hz, ¹ $J_{CP} = 171.2$ Hz), 172.6; ¹⁹F {¹H} NMR (376 MHz, CDCl₃) δ 1-211.5 (d, ² $J_{PF} = 75.2$ Hz); ³¹P NMR (162 MHz, CDCl₃) δ 17.3 (d, ² $J_{PF} = 75.2$ Hz); HRMS (ESI) calcd for C₉H₁₈FNaO₅P [M + Na]⁺ 279.0768, found 279.0768.

General Procedure for the Synthesis of Compounds 6 and 7. NaH (10 mg, 0.40 mmol, 2 equiv) and THF (2 mL) were placed in a Schlenk flask. The resulting suspension was cooled to 0 °C, and a solution of 1 (128 mg, 0.40 mmol, 2 equiv) in THF (0.5 mL) was added. The color of the solution became yellow, and after a few minutes a solution of 2 (0.20 mmol, 1 equiv) in THF (0.5 mL) was added. The reaction mixture was allowed to warm to rt, and after 1–2 h a solution of saturated NH₄Cl (20 mL) was added. The product was extracted into Et_2O (3 × 20 mL) and dried, and solvent was removed under reduced pressure. Purification by silica gel column chromatography using hexane/EtOAc as eluent gave products 6 and 7.

7h. Prepared from 2h (42 mg, 0.2 mmol) in 1 h giving 7h as a colorless oil (74 mg, 72%). Silica gel column chromatography and crystallization gave *anti*-7h (37 mg) as colorless crystals: mp 90–91 °C

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(Et₂O-pentane); R_f 0.60 (hexane-EtOAc, 1:1); ¹H NMR (400 MHz, CDCl₃) δ 1.17 (td, 3H, J = 7.1 Hz, ⁴J_{PH} = 1.1 Hz), 1.31 (td, 3H, J = 7.1 Hz, ${}^{4}J_{PH} = 1.1$ Hz), 3.91–4.29 (m, 4H), 4.94 (ddd, 1H, ${}^{3}J_{HF} = 28.4$ Hz, ${}^{3}J_{HH} = 10.1$, 4.5 Hz), 5.69 (dd, 1H, ${}^{2}J_{HF} = 46.4$ Hz, ${}^{3}J_{HH} = 4.5$ Hz), 5.89 (dd, 1H, ${}^{3}J_{HH}$ = 10.1 Hz, ${}^{4}J_{PH}$ = 1.9 Hz), 7.22–7.27 (m, 3H), 7.31–7.39 (m, 5H), 7.42–7.48 (m, 2H), 7.51–7.55 (m, 2H), 7.56–7.61 (m, 1H), 7.78–7.82 (m, 2H); 13 C NMR (100 MHz, CDCl₃) δ 15.9 (d, ${}^{3}J_{CP}$ = 6.9 Hz), 16.1 (d, ${}^{3}J_{CP}$ = 6.9 Hz), 42.0 (dd, ${}^{2}J_{CF}$ = 18.2 Hz, ${}^{4}J_{CP} = 1.2$ Hz), 64.7 (d, ${}^{2}J_{CP} = 6.0$ Hz), 64.8 (d, ${}^{2}J_{CP} = 5.9$ Hz), 104.0 (dd, ${}^{1}J_{CF} = 225.2$ Hz, ${}^{5}J_{CP} = 2.4$ Hz), 113.4 (dd, ${}^{3}J_{CP} = 7.1$ Hz, ${}^{3}J_{CF} = 4.7$ Hz), 126.1, 127.7, 128.3, 128.5, 128.9, 129.1, 129.2, 129.3, 134.0, 134.7 (d, ${}^{3}J_{CF} = 1.2 \text{ Hz}$), 136.0 (d, ${}^{3}J_{CF} = 0.9 \text{ Hz}$), 136.6, 147.4 (d, ${}^{2}J_{CP} = 8.7 \text{ Hz}$); ¹⁹F NMR (376 MHz, CDCl₃) δ –185.0 (dd, ${}^{2}J_{HF} = 1.2 \text{ Hz}$) 46.4 Hz, ${}^{3}J_{\text{HF}} = 28.4$ Hz); ${}^{31}P$ NMR (162 MHz, CDCl₃) δ -5.7 (s); HRMS (ESI) calcd for $C_{26}H_{28}FNaO_6PS [M + Na]^+$ 541.1221, found 541.1219. syn-7h (26 mg) as colorless oil: Rf 0.56 (hexane-EtOAc 1:1); ¹H NMR (400 MHz, CDCl₃) δ 1.17–1.22 (m, 6H), 3.92–4.13 (m, 4H), 5.10 (ddd, 1H, ${}^{3}J_{HF} = 30.0$ Hz, ${}^{3}J_{HH} = 9.5$, 2.3 Hz), 5.34 (dd, 1H, ${}^{2}J_{HF} = 46.6$ Hz, ${}^{3}J_{HH} = 2.5$ Hz), 5.87 (dd, 1H, ${}^{3}J_{HH} = 9.5$ Hz, ${}^{4}J$ _{PH}= 1.5 Hz), 7.25–7.36 (m, 6H), 7.38–7.46 (m, 4H), 7.47–7.53 (m, 2H), 7.57–7.62 (m, 1H), 7.93–7.97 (m, 2H); $^{13}\mathrm{C}$ NMR (100 MHz, CDCl₃) δ 16.0 (d, ${}^{3}J_{CP} = 6.8 \text{ Hz}$), 16.0 (d, ${}^{3}J_{CP} = 6.8 \text{ Hz}$), 41.3 (d, ${}^{2}J_{CF} = 17.4 \text{ Hz}$), 64.5 (d, ${}^{2}J_{CP} = 6.0 \text{ Hz}$), 64.6 (d, ${}^{2}J_{CP} = 6.0 \text{ Hz}$), 104.5 (d, ${}^{1}J_{CF} = 227.3 \text{ Hz}$), 110.4 (dd, ${}^{3}J_{CP} = 7.2 \text{ Hz}$, ${}^{3}J_{CF} = 7.1 \text{ Hz}$), 126.1, 127.6, 128.1, 128.3, 128.9, 129.0, 129.2, 129.6, 134.3, 134.8 (d, $^3\!J_{\rm CF}=$ 1.3 Hz), 136.4, 138.7 (d, ${}^{3}J_{CF}$ = 1.9 Hz), 148.4 (d, ${}^{2}J_{CP}$ = 9.2 Hz); ${}^{19}F$ NMR (376 MHz, CDCl₃) δ –186.3 (dd, ²J_{HF} = 46.5 Hz, ³J_{HF} = 30.0 Hz); ³¹P NMR (162 MHz, CDCl₃) δ –6.4 (s); HRMS (ESI) calcd for C₂₆H₂₈FNaO₆PS [M + Na]⁺ 541.1221, found 541.1219.

71. Prepared from 21 (44 mg, 0.2 mmol) in 1.5 h giving 71 as a pale yellow oil (72 mg, 68%). major-7l, a colorless oil: Rf 0.55 (hexane-EtOAc 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.17 (td, 3H, ³J_{HH} = 7.0 Hz, ${}^{4}J_{PH} = 1.1$ Hz), 1.32 (td, 3H, ${}^{3}J_{HH} = 7.0$ Hz, ${}^{4}J_{PH} = 1.1$ Hz), 2.29 (s, 3H), 3.91–4.28 (m, 4H), 4.91 (ddd, 1H, ${}^{3}J_{HF} = 28.8$ Hz, ${}^{3}J_{HH} = 10.1$, 4.4 Hz), 5.68 (dd, 1H, ${}^{2}J_{\rm HF}$ = 46.4 Hz, ${}^{3}J_{\rm HH}$ = 4.4 Hz), 5.87 (dd, 1H, ${}^{3}J_{\rm HH}$ = 10.1 Hz, ${}^{4}J_{\rm HP}$ = 1.9 Hz), 7.04–7.09 (m, 2H), 7.23–7.27 (m, 2H), 7.34 (m, 3H), 7.42-7.47 (m, 2H), 7.50-7.54 (m, 2H), 7.58-7.61 (m, 1H), 7.78–7.82 (m, 2H); 13 C NMR (125 MHz, CDCl₃) δ 15.9 (d, ${}^{3}J_{CP} = 6.9 \text{ Hz}$), 16.0 (d, ${}^{3}J_{CP} = 6.9 \text{ Hz}$), 21.1, 41.6 (dd, ${}^{2}J_{CF} = 18.2 \text{ Hz}$, ${}^{4}J_{CP} = 1.3 \text{ Hz}$), 64.6 (d, ${}^{2}J_{CP} = 6.0 \text{ Hz}$), 64.8 (d, ${}^{2}J_{CP} = 6.0 \text{ Hz}$), 64.8 (d, ${}^{2}J_{CP} = 6.0 \text{ Hz}$) Hz), 104.2 (dd, ${}^{1}J_{CF} = 224.9$ Hz, ${}^{5}J_{CP} = 2.4$ Hz), 113.6 (dd, ${}^{3}J_{CP} = 6.9$ Hz, ${}^{3}J_{CF} = 4.6$ Hz), 126.1, 128.2, 128.9, 129.1, 129.1, 129.2, 129.3, 132.9 (d, ${}^{3}J_{CF} = 1.1$ Hz), 133.9, 134.7 (d, ${}^{3}J_{CF} = 1.3$ Hz), 136.7, 137.3, 147.2 (d, ${}^{2}J_{CP} = 8.7$ Hz); ${}^{19}F$ NMR (470 MHz, CDCl₃) δ –185.4 (dd, ${}^{2}J_{\rm HF}$ = 46.4 Hz, ${}^{3}J_{\rm HF}$ = 28.9 Hz); 31 P NMR (203 MHz, CDCl₃) δ –5.7 (s); HRMS (ESI) calcd for C₂₇H₃₁FO₆PS [M + H]⁺ 533.1558, found 533.1559. minor-7l, a pale yellow oil: $R_f 0.50$ (hexane-EtOAc, 1:1); ¹H NMR (500 MHz, CDCl₃) δ 1.19 (td, 3H, ${}^{3}J_{HH} = 7.1$ Hz, ${}^{4}J_{PH} = 1.1$ Hz), 1.21 (td, 3H, ${}^{3}J_{HH} = 7.0$ Hz, ${}^{4}J_{PH} = 1.1$ Hz), 2.31 (s, 3H), 3.93– 4.16 (m, 4H), 5.05 (ddd, 1H, ${}^{3}J_{HF} = 29.5$ Hz, ${}^{3}J_{HH} = 9.6$, 2.6 Hz), 5.33 (dd, 1H, ${}^{2}J_{HF} = 46.6$ Hz, ${}^{3}J_{HH} = 2.7$ Hz), 5.84 (dd, 1H, ${}^{3}J_{HH} = 9.6$ Hz, ${}^{4}J_{\rm HP}$ = 1.5 Hz), 7.11–7.15 (m, 2H), 7.27–7.33 (m, 5H), 7.41–7.45 (m, 2H), 7.47-7.52 (m, 2H), 7.56-7.62 (m, 1H), 7.92-7.96 (m, 2H); ¹⁹F NMR (470 MHz, CDCl₃) δ –185.9 (dd, ²J_{HF} = 46.6 Hz, ³J_{HF} = 29.5 Hz); ³¹P NMR (203 MHz, CDCl₃) δ -6.3 (s).

7m. Prepared from 2m (29 mg, 0.2 mmol) in 1 h giving 7m as a pale yellow oil (62 mg, 68%). *major*-7m (46 mg), a pale yellow liquid: R_f 0.71 (hexane–EtOAc, 1:1); ¹H NMR (400 MHz, CDCl₃) δ 1.15 (t, 3H, J = 7.1 Hz), 1.32 (t, 3H, J = 7.1 Hz), 1.41 (d, 3H, J = 6.8 Hz), 3.80–4.30 (m, 5H), 5.44 (dd, 1H, ² J_{HF} = 47.5 Hz, ³ J_{HH} = 3.3 Hz), 5.52 (dd, 1H, ³ J_{HH} = 9.4 Hz, ⁴ J_{HP} = 2.0 Hz), 7.31–7.36 (m, 3H), 7.50–7.54 (m, 2H), 7.55–7.61 (m, 2H), 7.65–7.70 (m, 1H), 7.97–8.01 (m, 2H), C_{Ar}H); ¹³C NMR (100 MHz, CDCl₃) δ 14.1 (d, ³ J_{CF} = 5.3 Hz), 15.8 (d, ³ J_{CP} = 7.1 Hz), 16.0 (d, ³ J_{CP} = 7.0 Hz), 30.9 (d, ² J_{CF} = 19.4 Hz), 64.5 (d, ³ J_{CP} = 6.7 Hz, ³ J_{CF} = 2.7 Hz), 103.7 (d, ¹ J_{CF} = 223.7 Hz), 115.8 (dd, ³ J_{CP} = 6.7 Hz, ³ J_{CF} = 2.7 Hz), 126.0, 128.2, 129.0, 129.1, 129.2, 134.2, 134.8, 137.2, 146.9 (d, ² J_{CP} = 8.5 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ –191.3 (dd, ² J_{HF} = 47.0 Hz, ³ J_{HF} = 27.6 Hz); ³¹P NMR (162 MHz, CDCl₃) δ –5.6 (s); HRMS (ESI) calcd for

 $\begin{array}{l} C_{21}H_{26}\text{FNaO}_6\text{PS} \ [M + \text{Na}]^+ 479.1064, \text{ found } 479.1062. \textit{ minor-7m} \ (16 mg), a pale yellow oil: R_{f} 0.48 (hexane-EtOAc, 1:1); 1 H NMR (400 MHz, CDCl_3) δ 1.21 (t, 3H, $J = 7.1 Hz), 1.28 (t, 3H, $J = 7.1 Hz), 1.42 (d, 3H, $J = 7.0 Hz), 3.78-3.92 (m, 1H), 3.95-4.22 (m, 4H), 5.16 (dd, 1H, $^{2}_{J_{\text{HF}}} = 46.5 Hz, $^{3}_{J_{\text{HH}}} = 3.9 Hz), 5.49 (dd, 1H, $^{3}_{J_{\text{HH}}} = 9.9 Hz, $^{4}_{J_{\text{HF}}} = 1.5 Hz), 7.29-7.34 (m, 3H), 7.43-7.47 (m, 2H), 7.47-7.53 (m, 2H), 7.56-7.62 (m, 1H), 7.92-7.96 (m, 2H); $^{13}\text{C} NMR (100 MHz, CDCl_3) δ 15.9 (d, $^{3}_{J_{\text{CF}}} = 7.0 Hz), 16.0 (d, $^{3}_{J_{\text{CP}}} = 7.0 Hz), 16.9 (d, $^{3}_{J_{\text{CP}}} = 4.4 Hz), 64.6 (d, $^{2}_{J_{\text{CP}}} = 6.5 Hz), 104.5 (dd, $^{1}_{J_{\text{CF}}} = 22.36 Hz, $^{5}_{J_{\text{CP}}} = 1.3 Hz), 113.7 (dd, $^{3}_{J_{\text{CP}}} = 6.6 Hz, $^{3}_{J_{\text{CF}}} = 6.6 Hz), 125.9, 128.1, 128.8, 129.1, 129.4, 134.2, 134.9, 136.7, 147.4 (d, $^{2}_{J_{\text{CP}}} = 9.1 Hz); 19 F NMR (376 MHz, CDCl_3) δ -183.4 (dd, $^{2}_{J_{\text{HF}}} = 46.4 Hz, $^{3}_{J_{\text{HF}}} = 22.8 Hz); $^{3}_{\text{P}}$ NMR (162 MHz, CDCl_3) δ -6.0 (s); HRMS (ESI) calcd for $C_{21}H_{26}\text{FNaO}_6\text{PS} [M + Na]^+ 479.1064, found 479.1063. \\ \end{array}$

8h. A mixture of 7h (52 mg, 0.1 mmol) and 36% aqueous HCl (2 mL) was heated at 70 °C for 20 h. A saturated solution of NaHCO₃ (10 mL) was added, and the product was extracted into Et_2O (3 × 10 mL). The combined organic phase was washed with brine (10 mL) and dried (MgSO₄), and solvent was removed under reduced pressure. Purification by silica gel column chromatography using hexane/EtOAc gave 8h as a pale yellow liquid (28 mg, 75%). major-8h (12 mg), a pale yellow oil: Rf 0.49 (hexane-EtOAc, 4:1); ¹H NMR (400 MHz, CDCl₃) δ 3.68 (dd, 1H, ²J_{HH} = 18.0 Hz, ³J_{HH} = 10.2 Hz), 3.94 (dd, 1H, ²J_{HH} = 17.9 Hz, ³J_{HH} = 2.9 Hz), 4.53 (dddd, 1H, ³J_{HF} = 30.4 Hz, ${}^{3}J_{\rm HH} = 10.1, 2.7, 2.0 \text{ Hz}), 5.30 \text{ (dd, 1H, } {}^{2}J_{\rm HF} = 47.6 \text{ Hz}, {}^{3}J_{\rm HH} = 1.9 \text{ Hz}),$ 7.20-7.31 (m, 3H), 7.34-7.38 (m, 2H), 7.41-7.46 (m, 2H), 7.51-7.61 (m, 3H), 7.66-7.72 (m, 1H), 7.90-7.97 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 38.5 (d, ${}^{3}J_{CF}$ = 5.0 Hz), 39.2 (d, ${}^{2}J_{CF}$ = 17.6 Hz), 104.5 (d, ${}^{1}J_{CF} = 226.1$ Hz), 127.7, 128.0, 128.2, 128.6, 128.9, 129.3, 129.4, 133.2, 134.6, 136.3, 136.6, 139.6, 196.2; ¹⁹F NMR (376 MHz, CDCl₃) δ –185.1 (dd, ²J_{HF} = 47.6 Hz, ³J_{HF} = 30.3 Hz); HRMS (ESI) calcd for C₂₂H₁₉FNaO₃S [M + Na]⁺ 405.0931, found 405.0932. minor-8h (isolated in a mixture with major-8h 65:35, 16 mg): Rf 0.44 (hexane-EtOAc, 4:1).

ASSOCIATED CONTENT

S Supporting Information

Conformational analysis of *syn-* and *anti-*7**h**. Copies of ¹H, ¹³C, ¹⁹F, and ³¹P NMR spectra of newly synthesized products. This material is available free of charge via the Internet at http:// pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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