Diallyl (Lithiodifluoromethyl)-phosphonate: A New Reagent for the Introduction of the (Difluoromethylene)phosphonate Functionality

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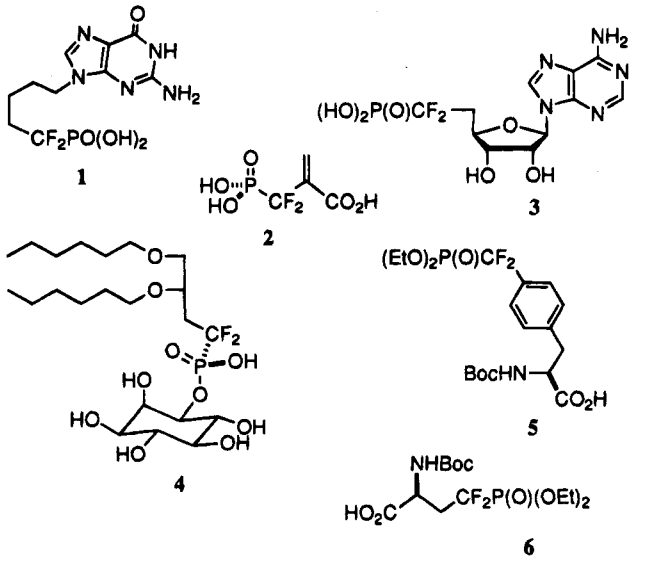
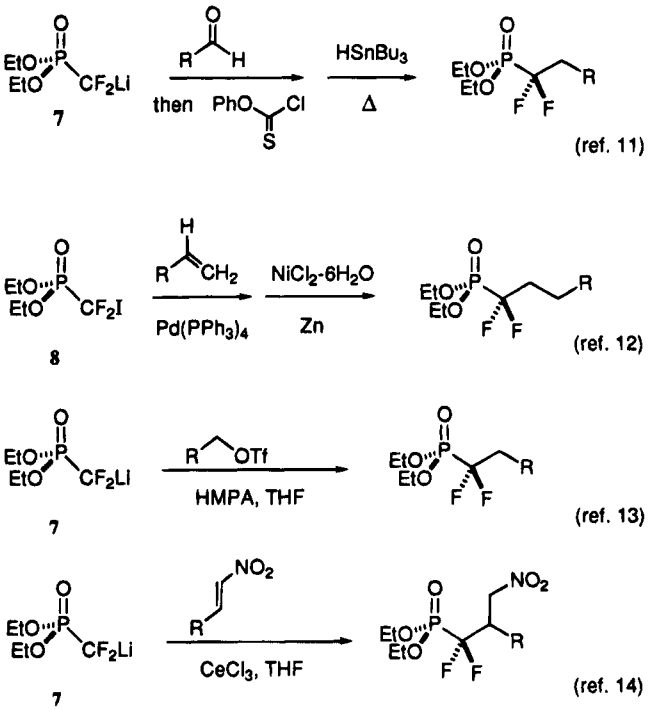
In recent years, an increased focus upon the roles and significance of biological phosphoryl transfer in terms of intracellular signal processing[1] has resulted in a heightened interest in hydrolytically stable and effective phosphate analogues. Several reports suggest that (α,α-difluoroalkyl)phosphonates are particularly effective phosphate mimics, as originally proposed by Blackburn.[2] For example, **1** is a potent bisubstrate analogue inhibitor of purine nucleoside phosphorylase,[3] and **2** is an irreversible inhibitor of EPSP synthase.[4] More recently, a number of more highly functionalized members of this phosphonate family have been synthesized. Among the more interesting of these are the (α,α-difluoroalkyl)-phosphonate analogues of ribonucleoside monophosphates (e.g., **3**),[5] and those of phosphatidylinositol (**4**)[6] and phosphatidylcholine.[7] Of particular interest from the point of view of signal transduction modulation, the (α,α-difluoroalkyl)phosphonate analogues of phosphotyrosine (**5**)[8] and phosphoserine (**6**)[9] have been synthesized in forms appropriate for solid phase peptide synthesis. The former has led to peptides with notable inhibitory activity toward protein phosphotyrosine phosphatases,[10a] and with appreciable binding affinities for SH2 domains.[10b]



Scheme 1

Convergent Approaches to PCF_2-C Bond Formation



The most convergent known approaches to this class of phosphonates involve procedures for fashioning the PCF_2–C bond (Scheme 1). Kondo and co-workers reported that diethyl lithiodifluoromethylphosphonate adds to aldehydes.[11a] Martin et al. noted that the alkoxides thereby formed could be trapped with phenyl chlorothionoformate. Subsequent Barton deoxygenation delivers the desired (α,α-difluoromethylene)phosphonates.[11b] Burton and co-workers described an elegant Pd^0-mediated addition of **8** to monosubstituted alkenes.[12] Reductive deiodination then provides the fluorinated phosphonates.

We described the most efficient direct displacement approach to this class of compounds in which primary triflates are subjected to nucleophilic attack by anion **7** at −78 °C in THF–HMPA.[13] This method is quite attractive as it obviates the need for dehalogenation or

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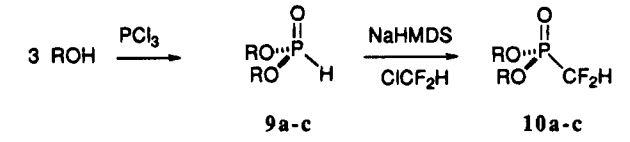
deoxygenation. More recently, this procedure served as the key step in our synthesis of **6**[9a] and in the Keana group's synthesis of **4**.[6] Finally, Lequeux and Percy have reported that anion **7** undergoes conjugate addition to (*E*)-nitroalkenes in the presence of Ce^{III}, providing access to analogues of secondary phosphates in fair to good yields.[14]

It is worthy of note that all of these methods rely upon simple alkyl ester protection for the (α,α-difluoroalkyl)-phosphonate functionality. Deprotection of simple dialkyl phosphonates normally requires the use of TMSBr or relatively harsh, acidic, hydrolytic conditions. Depending upon the molecular context, such conditions sometimes lead to decomposition. For example, with nonfluorinated phosphonates, problems have been encountered in the deprotection of methyl,[15] *n*-butyl,[16] and benzyl esters.[15] As for (α,α-difluoroalkyl)phosphonate protection, ethyl ester protection has proved to be problematic for solid phase peptide synthesis with FMOC cycles.[17] On the other hand, *tert*-butyl ester protecting groups are apparently much too labile to function as practical protecting groups for such fluorinated phosphonates.[18]

We therefore set out to synthesize and evaluate dialkyl (difluoromethyl)phosphonates bearing alternative protecting groups. Once synthesized, these phosphonates would be deprotonated and subjected to our triflate displacement protocol to establish their nucleophilicity and stability to such conditions. All candidates displaying adequate behavior toward triflate displacement would then be screened for efficiency of deprotection. In particular, we sought protecting groups that might be removed under relatively mild, nonacidic conditions, so as to complement the widely used diethyl ester protecting group. For this reason, (2-trialkylsilyl)ethyl and allyl protecting groups were initially targeted. Literature precedents supported these choices. For example, both 2-(trimethylsilyl)ethyl[19] and the more robust 2-(diphenylmethylsilyl)ethyl[20] ester protecting groups have been successfully employed (and deblocked) in phosphate ester synthesis. Allyl ester protecting groups have been applied to both phosphate[21] and nonfluorinated phosphonate ester synthesis.[15,22]

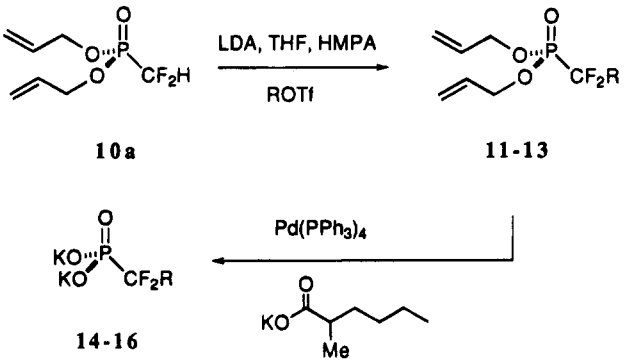
In all three cases, we were able to construct the requisite dialkyl (α,α-difluoromethyl)phosphonates by a modification of the procedure of Soborovskii and Baina, in which the sodium salt of the dialkyl phosphonate is

Scheme 2



a	R = $CH_2CH{=}CH_2$	(93%)	(51%)
b	R = $CH_2CH_2SiMe_3$	(77%)	(50%)
c	R = $CH_2CH_2SiPh_2Me$	(81%)	(65%)

Scheme 3



treated with chlorodifluoromethane (Scheme 2).[23] The dialkyl phosphites themselves could be readily obtained by reaction of the corresponding alcohols with phosphorus trichloride.[15]

Unfortunately, all attempts to displace primary triflates with the lithium anions derived from the bis(2-trialkylsilyl)ethyl (difluoromethyl)phosphonates **10b** and **10c** were without success.[24] However, we are pleased to report that diallyl (lithiodifluoromethyl)phosphonate displaced primary triflates derived from D-ribofuranose, D-glucopyranose, and serinol in good yields (Scheme 3 and Table 1).

Furthermore, the fluorinated phosphonates thereby obtained, **11**–**13**, could be smoothly deprotected under Pd^0 catalysis.[25] In this undertaking, the choice of allyl acceptor proved to be of considerable importance, with the organic-soluble salt, potassium 2-methylhexanoate, reported by Jeffrey and McCombie[26] performing most efficiently. In this way, the dipotassium salts of these (α,α-diflouroalkyl)phosphonates (**14**–**16**) were obtained in respectable (56–91%) yields. These salts were also

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(19) (a) Sawabe, A.; Filla, S. A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 7685–7686. (b) Chao, H.-G.; Bernatowicz, M. S.; Klimas, C. E.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3377–3380. (c) Wada, T.; Sekine, M. *Tetrahedron Lett.* **1994**, *35*, 757–760.
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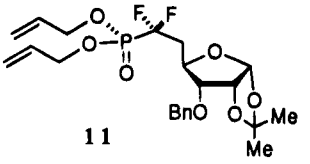
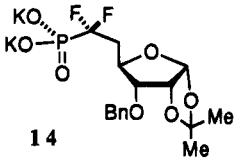
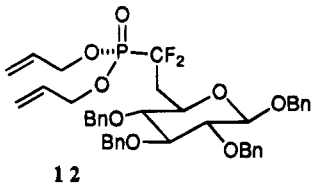
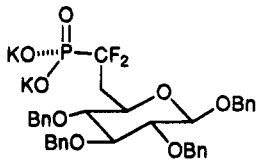
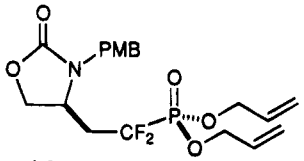
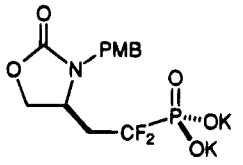
(23) Soborovskii, L. Z.; Baina, N. F. *J. Gen. Chem. U.S.S.R. (Engl. Trans.)* **1959** *29*, 1115–1117.
(24) In several trial runs, **10b** or **10c** (3.5 equiv) was treated with LDA (3.5 equiv) at −78 °C for 30 min, followed by addition of benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(trifluoromethanesulfonyl)-β-D-glucopyranoside. Analogous triflate displacements with the title compound (the lithium salt of **10a**) or its diethyl congener are typically complete within 5–10 min at −78 °C (ref 13 and this work). In these reactions, however, even after 1 h, TLC analysis revealed either largely **10b** or exclusively **10c**, unreacted starting triflate. Upon concentration of the organic layer following aqueous workup (saturated NH_4Cl), ^1H NMR analysis revealed that most of the (difluoromethylene)phosphonate (**10b** or **10c**) was also recovered unchanged.
(25) Pd catalysis has previously been employed to deprotect both allyl phosphates[21] and simple allyl phosphonates.[15,22] To our knowledge, α-fluorinated phosphonates bearing allyl protection have not been previously reported. Kamber and Just report the use of diallyl phosphite for nucleophilic P–C bond formation.[15] However, we are not aware of previous examples in which carbanions derived from *allyl-protected* alkyl phosphonates have been employed for C–C bond formation.
(26) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587–590. As these authors note, Pd^0-catalyzed allyl transfer produces allyl 2-methylhexanoate as the coproduct.

Table 1

Displacement Product	Yield	Deprotected Phosphonate	Yield
 11	(64%)	 14	(77%)
 12	(56%)	 15	(91%)
 13	(50%)[a]	 16	(56%)

[a] This yield is for two steps (triflate synthesis and displacement) from the corresponding alcohol.

convenient vehicles for phosphonate purification, via trituration or recrystallization, where necessary.

In conclusion, the displacement of primary triflates with diallyl (lithiodifluoromethyl)phosphonate, followed by allyl ester deprotection [$Pd(PPh_3)_4$, potassium 2-methylhexanoate], is a practical method for the synthesis of (α,α-diflouroalkyl)phosphonates. This approach is complementary to the most convergent existing procedures for the synthesis of these phosphate mimics, all of which rely upon ethyl ester protection for the fluorinated phosphonate functionality.

Experimental Section

General. All reactions were conducted under argon atmosphere using oven-dried glassware. Diisopropylamine was distilled from CaH_2. THF and Et_2O were distilled from sodium benzophenone ketyl. HMPA was distilled from Na.

Diallyl (α,α-Difluoromethyl)phosphonate (10a). To diallyl phosphonate (**9a**)[15] (1.01 g, 6.23 mmol) in THF (3.5 mL) at rt was added sodium bis(trimethylsilyl)amide (6.9 mL of a 1 M solution in THF, 6.85 mmol) and stirring continued for 40 min. Excess chlorodifluoromethane (Freon 22) was bubbled into the solution for 20 min, and the reaction mixture was stirred for an additional 12 h under a balloon atmosphere of HCF_2Cl. Precipitated NaCl was removed by filtration through Celite, and the solvent was evaporated. The resulting liquid was distilled to yield **10a** (677 mg, 51%, bp 60 °C at 0.2 Torr) as a colorless liquid (stored at −20 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (m, 4 H), 5.27−5.31 (br dd, J = 10 Hz, 2 H), 5.35−5.42 (app dq, J = 17 Hz, 2 H), 5.71−6.12 (dt, $J_{F,H}$ = 49 Hz, $J_{P,H}$ = 28 Hz, 1 H), 5.89−6.00 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.3, 108.3−114.2 (dt, $J_{C,P}$ = 215 Hz, $J_{C,F}$ = 259 Hz), 119.1, 131.7; ^{31}P NMR (202 MHz, $CDCl_3$) δ 4.5−5.4 (t, $J_{P,F}$ = 92 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ −135.5 (dd, $J_{H,F}$ = 49, $J_{P,F}$ = 92 Hz); HRMS (FAB, 3-NOBA) calcd for $C_7H_{12}O_3F_2P$ $(M + H)^+$ 213.0492, obsd 213.0484. Anal. Calcd for $C_7H_{11}O_3F_2P$: C, 39.63; H, 5.23. Found: C, 39.74; H, 5.25.

Typical Triflate Displacement Procedure. 3-*O*-Benzyl-5-deoxy-5-[(diallylphosphono)difluoromethyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (11). All solutions were deoxygenated by being frozen (liquid nitrogen) and subjected to five cycles of evacuation and purging with argon. To a solution of diisopropylamine (684 μL, 4.88 mmol) and HMPA (849 μL, 4.88 mmol) in THF (5.60 mL) at −78 °C was added *n*-butyllithium (3.05 mL of a 1.6 M solution in hexane, 4.88 mmol). The resulting solution was stirred for 30 min at 0 °C and then cooled to −78 °C. To this solution were added, via cannula, a cooled (−78 °C) solution of **10a** (1.04 mL, 4.88 mmol) in THF (2.8 mL) and then, 2 min later, a cooled (−78 °C) solution of the corresponding triflate[13] (575 mg, 1.39 mmol) in THF (5.6 mL). After 10 min at −78 °C, the reaction was quenched [NH_4Cl (aqueous, 5 mL)/Et_2O (10 mL)]. The aqueous layer was further extracted with EtOAc (2 × 20 mL), and the combined extracts were dried ($MgSO_4$), filtered, and evaporated. Flash chromatography (50% EtOAc−hexanes) yielded **11** (422 mg, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3 H), 1.58 (s, 3 H), 2.08−2.28 (m, 1 H), 2.30−2.56 (m, 1 H), 3.42 (dd, J = 4, 9 Hz, 1 H), 4.37 (app t, J = 9 Hz, 1 H), 4.51−4.54 (app t, J = 4 Hz, 1 H), 4.51−4.55 (d, J = 12 Hz, 1 H), 4.67 (br app t, J = 7 Hz, 4 H), 4.88 (d, J = 12 Hz), 5.26 (br d, J = 11 Hz, 2 H), 5.37 (br d, J = 17 Hz, 2 H), 5.74 (d, J = 4 Hz, 1 H), 5.89−6.00 (m, 2 H), 7.30−7.36 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 26.6, 36.4−37.0 (m, 1 C), 68.5 (app t, J = 7 Hz, 2 C), 71.7 (m, 1 C), 76.2, 81.6, 104.3, 113.0, 116.6−122.4 (dt, $J_{C,P}$ = 216 Hz, $J_{C,F}$ = 256 Hz), 118.79, 118.85, 127.97, 128.03, 128.4, 132.0 (app t, J = 7 Hz, 2C), 137.3; HRMS (FAB, 3-NOBA/NaI) calcd for $C_{22}H_{29}O_7F_2PNa$ $(M + Na)^+$ 497.1517, obsd 497.1523.

Benzyl 6-Deoxy-6-[(diallylphosphono)difluoromethyl]-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (12). From the corresponding triflate (107 mg, 160 μmol),[13] following the displacement procedure described for the synthesis of **11**, was obtained **12** (66.3 mg, 56%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13−2.27 (m, 1 H), 2.48−2.64 (m, 1 H), 3.28 (app t, J = 9 Hz, 1 H), 3.51 (app t, J = 8.5 Hz, 1 H), 3.66 (app t, J = 9 Hz, 1 H), 3.75 (app t, J = 10 Hz, 1 H), 4.50 (d, J = 8 Hz, 1 H), 4.58−4.77 (m, 8H), 4.89−4.99 (m, 4 H), 5.26 (br d, J = 10 Hz, 2 H), 5.34−5.40 (br d, J = 17 Hz, 2 H), 5.85−5.99 (m, 2 H), 7.24−7.38 (m, 20 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.3 (m, 1 C), 69.2, 69.5, 71.5, 75.4, 75.6, 76.4, 81.1, 83.0, 85.4, 102.5, 119.7, 128.29, 128.32, 128.45, 128.53, 128.57, 128.65, 128.79, 128.88, 128.98, 129.04, 129.12, 132.7, 138.0, 138.5, 139.10, 139.13; HRMS (FAB, 3-NOBA/NaI) calcd for $C_{41}H_{45}O_8F_2PNa$ $(M + Na)^+$ 757.2718, obsd 757.2735.

(*S*)-4-[2′-[1′-(Diallylphosphono)-1′,1′-difluoroethyl]-3-(4″-methoxybenzyl)oxazolidin-2-one (13). To a solution of al-

cohol **18** (109 mg, 459 μmol) and 2,6-di-*tert*-butyl-4-methylpyridine (104 mg, 505 μmol) in CH_2Cl_2 (4.6 mL) at −50 °C was added triflic anhydride (85 μL, 505 μmol). After 0.5 h at −50 °C, the reaction was quenched by the addition of $NaHCO_3$ (saturated, aqueous, 5 mL) and Et_2O (10 mL). The aqueous layer was extracted twice more with Et_2O, and the combined organics were dried ($MgSO_4$), filtered, and evaporated. The crude triflate thereby obtained was treated with **10a** (300 mg, 1.42 mmol), after deprotonation, as described for the synthesis of **11**, to provide phosphonate **13** (101 mg, 50% over two steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07−2.16 (m, 1 H), 2.18−2.66 (m, 1 H), 3.79 (s, 3 H), 3.96−4.10 (m, 2 H), 4.02 (d, J = 15 Hz, 1 H), 4.41 (app t, J = 9 Hz, 1 H), 4.60−4.66 (m, 4 H), 4.70 (d, J = 15 Hz, 1 H), 5.32−5.40 (m, 4 H), 5.84−5.97 (m, 2 H), 6.86 (d, J = 9 Hz, 2 H), 7.20 (d, J = 9 Hz, 2 H); HRMS (FAB, 3-NOBA/NaI) calcd for $C_{19}H_{24}NO_6F_2PNa$ $(M + Na)^+$ 454.1207, obsd 454.1214.

Typical Diallyl Phosphonate Deprotection Procedure. 3-*O*-Benzyl-5-deoxy-5-(difluorophosphonomethyl)-1,2-*O*-isopropylidene-α-D-Ribofuranose, Dipotassium Salt (14). A solution of **11** (61 mg, 0.129 mmol), potassium 2-methylhexanoate (44 mg, 0.26 mmol), and $Pd(PPh_3)_4$ (30 mg, 29 μmol) in CH_2Cl_2 (1.5 mL) was stirred at 25 °C in the dark for 4 h. The solvent was evaporated, and the residue was dissolved in 50% H_2O/MeOH (2 mL) and extracted with Et_2O (2 × 2 mL). Evaporation of the aqueous layer, followed by thorough drying in vacuo, provided **14** (47 mg, 77%): ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.24 (s, 3 H), 1.40 (s, 3 H), 1.9−2.05 (m, 1 H), 2.2−2.35 (m, 1 H), 3.35−3.42 (m, 1 H), 4.11 (app t, J = 9 Hz, 1 H), 4.46 (d, J = 11 Hz, 1 H), 4.60 (d, J = 11 Hz, 1 H), 4.61 (br s, 1 H), 5.67 (d, J = 3.2 Hz, 1 H), 7.25−7.32 (m, 5 H); HRMS (FAB, triethanolamine) calcd for $C_{16}H_{20}O_7F_2P$ $(M - H)^-$ 393.0915, obsd 393.0922.

Benzyl 6-Deoxy-6-(difluorophosphonomethyl)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside, Dipotassium Salt (15). This phosphonate (153 mg, 0.208 mmol) was deprotected using the same procedure as for **11** and purified by recrystallization from 2-propanol to yield **15** (138 mg, 91%) as a white solid: ^{1}H NMR (500 MHz, *d*-MeOD) δ 2.27−2.39 (m, 1 H), 2.71−2.83 (m, 1 H), 3.27 (app t, J = 9 Hz, 1 H), 3.42 (app t, J = 8 Hz, 1 H), 3.61 (appt, J = 9 Hz, 1 H), 3.83 (appt, J = 10 Hz, 1 H), 4.49 (d, J = 8 Hz, 1 H), 4.64−4.91 (m, 8 H), 7.20−7.37 (m, 20 H); HRMS (FAB, triethanolamine) calcd for $C_{35}H_{36}O_8F_2P$ $(M - H)^-$ 653.2116, obsd 653.2136.

(*S*)-4-[2′-(1′,1′-Difluoro-1′-phosphonoethyl)]-3-(4″-methoxybenzyl)oxazolidin-2-one, Dipotassium Salt (16). This phosphonate (35.0 mg, 81 μmol) was deprotected using the same procedure as for **11** and purified by trituration with *tert*-butyl alcohol to yield **6** (20 mg, 56%): ^{1}H NMR (500 MHz, *d*-MeOD) δ 2.20−2.32 (m, 1 H), 2.69−2.81 (m, 1 H), 3.76 (s, 3 H), 4.06−4.11 (m, 1 H), 4.14 (d, J = 15 Hz,1 H), 4.24 (app t, J = 8 Hz, 1 H), 4.47 (app t, J = 8 Hz, 1 H), 4.61 (d, J = 15 Hz, 1 H), 6.87 (d, J = 8 Hz, 1 H), 7.27 (d, J = 8Hz, 1 H); HRMS (FAB, triethanolamine) calcd for $C_{13}H_{15}O_6NF_2P$ $(M - H)^-$ 350.0605, obsd 350.0617.

***Bis*[2-(diphenylmethylsilyl)ethyl] Phosphonate (9c).** To a solution of 2-(diphenylmethylsilyl)ethanol (10.0 g, 41.3 mmol)[20a] in Et_2O (1.4 mL) was added, dropwise, a solution of PCl_3 in Et_2O (6 mL). An Ar stream was used to remove HCl. Once the reaction had reached completion, as judged by ^{1}H NMR, the reaction was quenched with anhydrous NH_3. Filtration (of NH_4Cl) through Celite, evaporation of the volatiles, and flash chromatography (80% hexane−EtOAc) gave **8** (5.90 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.58 (s, 6 H), 1.63 (m, 4 H), 4.15 (m, 4 H), 5.50−7.80 (d, $J_{P,H}$ = 691 Hz, 1 H), 7.31−7.51 (m, 20 H).

***Bis*[2-(diphenylmethylsilyl)ethyl] (α,α-Difluoromethyl)-phosphonate (10c).** From **9c** (5.90 g, 11.1 mmol), following the general procedure described for the synthesis of **10a**, was obtained **10c** (4.2 g, 65%) after purification by flash chromatography (90% hexane−EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.58 (s, 6 H), 1.65 (m, 4 H), 4.28 (m, 4 H), 5.49−5.91 (dt, J = 27, 49 Hz, 1 H),7.31−7.50 (m, 20 H); HRMS (FAB, 3-NOBA/NaI) calcd for $C_{31}H_{35}O_3F_2PNa$ $(M + Na)^+$ 603.1728, obsd 603.1720.

***Bis*[2-(trimethylsilyl)ethyl] Phosphonate (9b).** From 2-(trimethylsilyl)ethanol (5.00 mL, 34.9 mmol) and PCl_3 (1.01 mL, 11.6 mmol), following the procedure used for the synthesis of **9c**, was obtained **9b** (2.52 g, 77%) of sufficient purity for direct use in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 18 H), 1.06−1.12 (m, 4 H), 4.11−4.21 (m, 4 H), 5.64−7.93 (d, J = 688 Hz, 1 H).

***Bis*[2-(trimethylsilyl)ethyl] (α,α-Difluoromethyl)phosphonate (10b).** From **9b** (2.52 g, 8.92 mmol), following the general procedure described for the synthesis of **10a**, was obtained **10b** (1.51 g, 50%) after purification by kugelrohr distillation: bp 140−145 °C at 0.5 Torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 18 H), 1.11−1.16 (m, 4 H), 4.26−4.35 (m, 4 H), 5.67−6.08 (dt, J = 27, 49 Hz, 1 H).

(*R*)-4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]oxazolidin-2-one (17). To a solution of the (hydroxymethyl)oxazolidin-2-one[27] in DMF (10 mL) at 0 °C were added *tert*-butyldimethylsilyl chloride (1.36 g, 9.05 mmol) and imidazole (1.23 g, 18.1 mmol). Upon completion, the reaction was quenched with $NaHCO_3$(aq) 50 mL and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Flash chromatography (50% Hex−EtOAc) provided **17** (1.10 g, 58%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.88 (s, 9 H), 3.58 (dd, J = 6, 10 Hz, 1 H), 3.62 (dd, J = 5, 10 Hz, 1 H), 3.93 (m, 1 H), 4.14 (dd, J = 5, 9 Hz, 1 H), 4.45 (app t, J = 9 Hz, 1 H), 5.25 (br s, 1 H).

(*S*)-4-(Hydroxymethyl)-3-(4″-methoxybenzyl)oxazolidin-2-one (18). To a solution of **17** (1.10 g, 4.76 mmol) in DMF (15 mL) at −40 °C were added NaH (60% dispersion, 305 mg, 7.62 mmol) and PMBBr (1.34 g, 6.66 mmol). The reaction was warmed to rt over 3 h and quenched with H_2O (20 mL) prior to extraction with EtOAc (2 × 30 mL). Following drying ($MgSO_4$) and evaporation of the solvent, the crude residue was taken up in THF (20 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 5.0 mL, 5 mmol) was added and the resulting reaction mixture allowed to warm to rt over 2 h. The reaction was quenched by addition of $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were dried ($MgSO_4$), filtered, evaporated, and subjected to flash chromatography (50% Hex−EtOAc) to yield **18** (830 mg, 73% for two steps): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.95 (br s, 1 H), 3.54 (m, 1 H), 3.71 (m, 2 H), 3.79 (s, 3 H), 4.23 (dd, J = 6, 9 Hz, 1 H), 4.28 (d, J = 15 Hz, 1 H), 4.29 (app t, J = 9 Hz, 1 H), 4.57 (d, J = 15 Hz, 1 H), 6.87 (d, J = 8.5 Hz, 2 H), 7.24 (d, J = 8.5 Hz, 2 H); HRMS (FAB, 3-NOBA/LiI) calcd for $C_{12}H_{15}NO_4Li$ $(M + Li)^+$ 244.1161, obsd 244.1160.

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Supporting Information Available: ^{1}H NMR spectra for compounds **9b,c**, **10a−c**, and **11−18** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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