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3-Methyl-4*H*-[1,2,4]-oxadiazol-5-one: a versatile synthon for protecting monosubstituted acetamidines

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Abstract—The utilization of 3-methyl-4*H*-[1,2,4]-oxadiazol-5-one as a versatile protected acetamidine is demonstrated through employment in a variety of synthetic sequences. The potassium salt (**2a**) or the neutral form (**2b**) is alternatively shown to be superior for various synthetic reactions (i.e., alkylation, Michael addition, Mitsunobu) to incorporate side chains for further synthesis. The 3-methyl-4*H*-[1,2,4]-oxadiazol-5-one moiety was found to be stable to acid or base under non-aqueous conditions. It was also found to be stable to many reagents commonly used for organic synthesis. Despite this stability, the free acetamidine may be released by mild reduction including Lindlar hydrogenation or dissolving metal reductions. Alternatively, the hydroxyl amidine may be formed via alkaline hydrolysis.

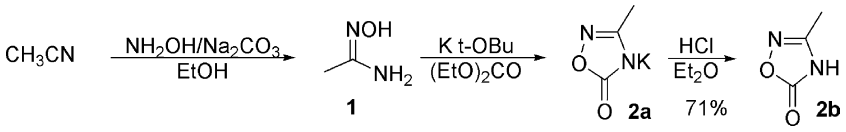
1. Introduction

Amidine groups are found in many medicinal drugs, for example, cardiovascular, anti-diabetic, antibacterial, anti-protozoal, anthelmintic, anti-inflammatory, central nervous system, antineoplastic and others.[1,2] N-monosubstituted acetamidines have been useful as arginine mimetics and they have been utilized in nitric oxide synthase (NOS) inhibitors in particular.[3,4] The basic nature of the amidine and its facile hydrolysis to the corresponding amide makes the synthesis and purification of compounds containing them troublesome. For our needs we sought a versatile method to prepare highly functionalized N-monosubstituted acetamidines. This investigation led to the introduction of the acetamidine in a protected form that enabled facile synthetic manipulations.

A survey of the literature revealed that oxadiazol-5-ones have been previously described as precursors to amidines.[5a–c,6a–d] These prior investigations did not explore the utility of this conversion as a component of a synthetic sequence. The work described here explores the synthetic utility of the use of 3-methyl-4*H*-[1,2,4]-oxadiazol-5-one as a protected acetamidine. We have found this heterocycle to be stable to many synthetic conditions and have used it in extended synthetic schemes. The mild reaction conditions for the selective generation of acetamidines and hydroxy-acetamidines is described as well.

2. Results and discussion

The utility of 3-methyl-4*H*-[1,2,4]-oxadiazol-5-one is dependent upon a consistent route for preparation. We utilized a procedure described by Hett et al. (Scheme 1), which is suitable for the kilogram scale synthesis of the potassium salt **2a**.[7] A simple bubbling of HCl through an ether suspension of **2a** affords the protonated form of the heterocycle **2b**.



Scheme 1.

Keywords: Protected amidine; 3-Methyl-4*H*-[1,2,4]-oxadiazol-5-one.
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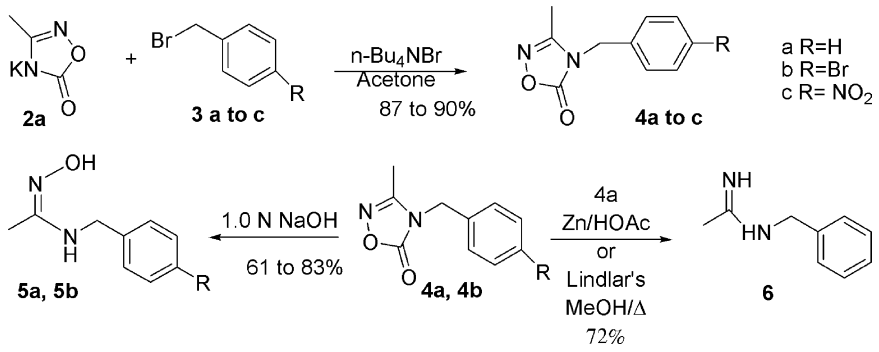


Scheme 2.

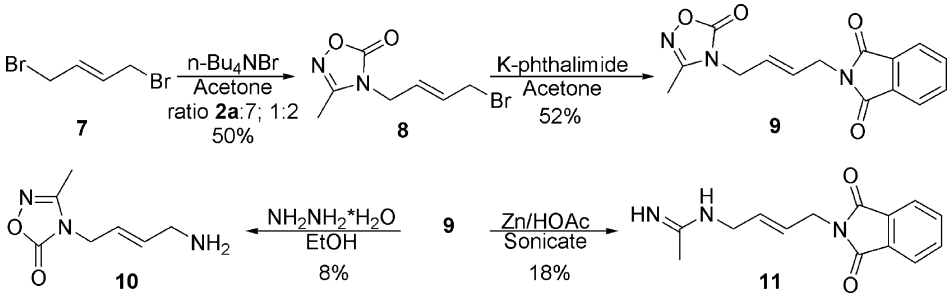
Schemes 2–4 examine the reactivity of the potassium salt **2a** with activated halides. These schemes also show the feasibility of unmasking the acetamidine in the presence of other sensitive groups and the stability of the oxadiazolone ring to further synthetic manipulations.

The potassium salt **2a** readily reacts with benzyl bromides to form the benzyl adducts (Scheme 2). The heterocycles **4a** and **4b** were subsequently hydrolyzed in aqueous hydroxide to afford the *N*-hydroxy amidines **5a** and **5b**. Heating **4a** with Lindlar's catalyst in MeOH at reflux or with zinc in HOAc at 60 °C reduced the N–O bond to afford the acetamidine.

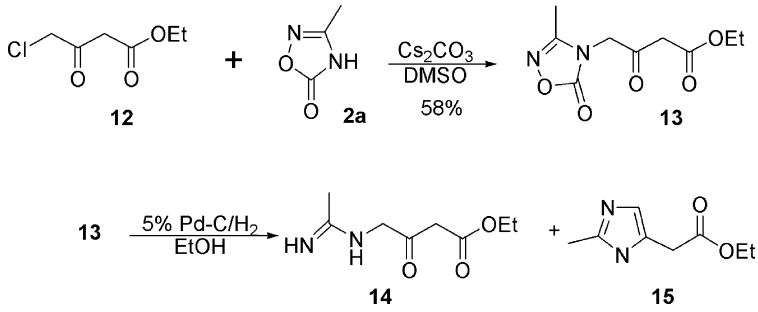
Mono-alkylation of the allylic dibromide **7** was accomplished by limiting the amount of **2a** (Scheme 3). This produced a mixture favoring the mono-alkylated derivative **8**, along with a small amount of the di-alkylated derivative that was separable by chromatography. The oxadiazolinone **8** was further elaborated to the phthalimide protected amino derivative **9** using potassium phthalimide. The phthalimide was removed with hydrazine to yield the free amine while retaining the protected amidine **10**. Alternatively, sonication of **9** in the presence of zinc and HOAc released the acetamidine **11** without altering the phthalimide. In both deprotections the double bond was retained.

A facile reaction of the α-chloroketoester **12** with **2a** afforded the α-ketoester **13** (Scheme 4). Deprotection of **13** via hydrogenation with Lindlar's catalyst in MeOH yielded the acetamidine **14** and a small amount of the imidazole **15**. The mixture was separated and it was determined that **14** slowly cyclizes to form the imidazole **15**.

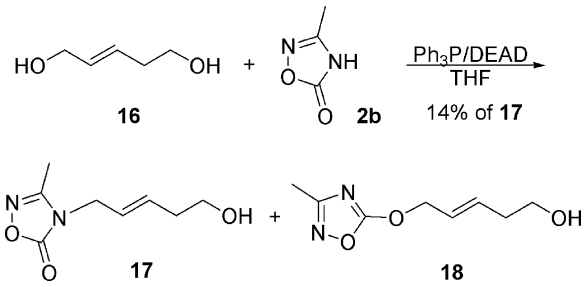
The protonated form of the heterocycle, **2b**, was found to undergo the Mitsunobu reaction with dihydroxy-olefinic alcohol **16** in a preferential reaction of the allylic alcohol to the alkyl alcohol (Scheme 5). The reaction afforded a mixture of N and O-alkylated products **17** and **18**. These isomers were separable by chromatography and the structures confirmed by NMR. Only the protonated form **2b** was successful in this reaction. Attempts to use the potassium salt **2a** directly or via in situ generation of **2b**, failed to afford the Mitsunobu product. Although the alkyl



Scheme 3.



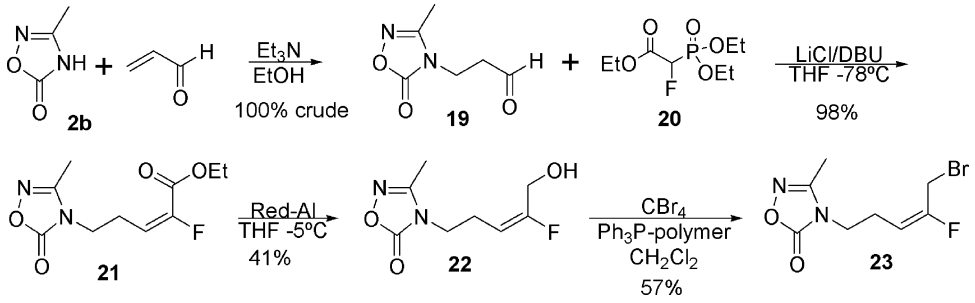
Scheme 4.



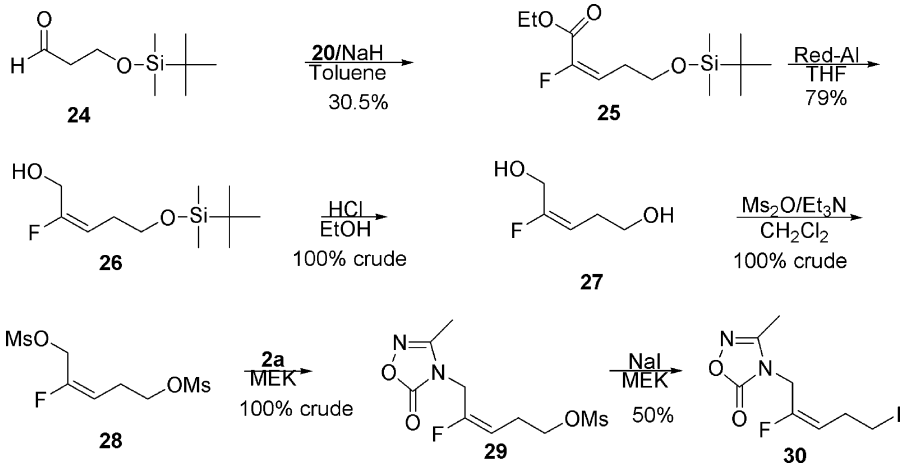
Scheme 5.

alcohols were found to be much less reactive than allylic alcohols, a mixture of O and N- alkylated products of the alkyl alcohol was observed when a large excess of Mitsunobu reagents were utilized along with extended reaction time.

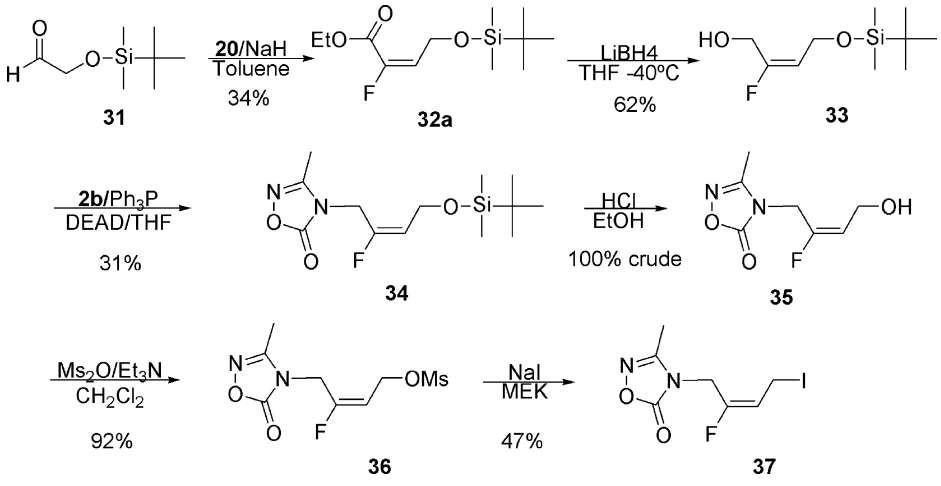
After exploring the reactivity of **2a** and **2b**, several fluoroolefins were synthesized to demonstrate the flexibility and chemical stability of the oxadiaxolinone when incorporated into a synthetic sequence. Schemes 6–8 exemplify the use of a Michael addition, alkylation and Mitsunobu reaction, respectively.



Scheme 6.



Scheme 7.



Scheme 8.

The Michael addition was successful with **2b** to afford the saturated aldehyde **19** (Scheme 6). As with the Mitsunobu reaction only the protonated form successfully produced product. The aldehyde **19** was further elaborated using Wittig conditions to the fluoro-olefinic ester **21** in high yield with no alteration of the heterocycle. The oxadiazolinone was further shown to be stable during reduction of the ester group in **21** with Red-Al to afford the alcohol **22**. The alcohol **22** was then converted to the bromide **23**, using PPh_3/CBr_4 in CH_2Cl_2, to set up for further potential elaboration.

A selective alkylation of an allyl mesylate in the presence the alkyl mesylate utilizing the potassium salt **2a** afforded **29** (Scheme 7). Further elaboration to the iodo-olefin **30** afforded an analog of **23** where the amidine precursor is transposed in relation to the halide.

The one carbon shorter homolog of **29** was prepared using a Mitsunobu reaction to yield **36** (Scheme 8). Further elaboration as for **30** afforded the corresponding homolog **37**.

3. Conclusions

3-Methyl-4*H*-[1,2,4]-oxadiazol-5-one **2** was demonstrated to be selective and versatile for the incorporation of the acetamidine in a protected form. The oxadiazolone ring was stable and robust, through multiple synthetic manipulations. Furthermore, the incorporated oxadiazolone produced products, which could be purified by silica chromatography and often by recrystallization. Catalytic reduction using Lindler's catalyst or zinc/HOAc selectively reduced the N–O bond, releasing the acetamidine in the presence of olefins and other reducible groups. The released acetamidine was often isolated pure. When purification was required, simple reverse-phase chromatography afforded clean product.

Only the protonated form of the oxadiazolone **2b** participated in Michael additions and Mitsunobu reactions while the salt **2a** participated in alkylation reactions. Both the Mitsunobu and alkylation reactions were selective for the allylic versus alkyl sites. Weak nucleophilic hydrides reduced a distal carbonyl to an alcohol without altering the oxadiazolinone. The oxadiazolinone ring was found to be stable to mild acidic conditions, but was hydrolyzed to afford the *N*-hydroxyamidine in 1 N NaOH. Hydrazine reacted with phthalimide **8** to release the amine **34** in the presence of the oxadiazolone ring.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on either a Varian Unity Plus 300 (300 MHz) or a Varian Unity Inova 400 (400 MHz) spectrometer. All NMR spectra are 400 MHz unless stated otherwise. All proton chemical shifts are recorded in ppm (δ) relative to trimethylsilane. All fluorine chemical shifts are recorded in ppm (δ) relative to a reference of $C_6H_5CF_3$ in benzene (Varian standard sample), which has a ^{19}F chemical shift of -64 ppm, with an error of <1 ppm. Column chromatography was performed using either Biotage Flash 40 or 12 system. Reverse phase chromatography was performed on a Gilson semi-preparative HPLC with a YMC Combiprep ODS-A semi-prep column eluting with acetonitrile/water (0.01% TFA) at 20 mL/min. Mass spectra were obtained on a HP series 1100MSD, and high-resolution mass spectra were obtained with a PerSeptive Biosystems Mariner TOF. All solvents and reagents were purchased from Sigma-Aldrich.

4.1.1. Preparation of 3-methyl-1,2,4-oxadiaxolin-5-one (2b). Oxadiazolone **2a**[7] (30.0 g, 0.217 mol) was suspended in Et_2O (150 mL) and cooled in an ice bath. HCl gas was bubbled through the slurry until the exotherm ceased. The mixture was stirred for 2 h, the solid filtered and the filtrate concentrated. The residue was dried under high vacuum to yield 15.5 g (71.4%) of **2b**. ^{1}H NMR (DMSO-d_6): δ 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 11.8, 162.5, 168.2; MS(CI) calcd for $C_3H_4N_2O_2$: [M+H] 101. Found: [M+H] 101; Anal. calcd for $C_3H_4N_2O_2$: C, 36.01; H, 4.03; N, 27.99. Found: C, 35.76; H, 3.99; N, 28.26.

4.1.2. 4-Benzyl-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (4a). Benzyl bromide (1.13 g, 6.59 mmol) in acetone (15 mL) was added at ambient temperature to a suspension of **2a** (1 g, 7.25 mmol), and tetrabutylammonium bromide (0.21 g, 0.66 mmol) in acetone (20 mL). The mixture was stirred 18 h, then quenched with brine and EtOAc. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated and the product was dried under vacuum to yield 1.12 g (89%) **4a** as a white solid, mp 64–65 °C. ^{1}H NMR ($CDCl_3$): δ 2.12 (s, 3H), 4.74 (s, 2H), 7.26 (m, 2H), 7.36 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 10.9, 46.0, 127.6, 129.0, 129.5, 134.2, 156.8, 159.9; HRMS calcd for $C_{10}H_{10}N_2O_2$: [M+H] 191.0821. Found: [M+H]191.0822; Anal. calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.39; N, 14.73. Found: C, 63.22; H, 5.36; N, 14.79.

4.1.3. 4-(4-Bromobenzyl)-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (4b). 4-Bromobenzyl bromide (1.65 g, 6.59 mmol) was allowed to react as in **4a** to yielded 1.60 g (90%) of **4b** as a white solid, mp 108–109 °C. ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H), 4.69 (s, 2H), 7.13 (d, 2H), 7.50 (d, 2H); ^{13}C NMR ($CDCl_3$): δ 10.9, 45.4, 123.5, 129.3, 132.7, 132.8, 149.5, 160.1; HRMS calcd for $C_{10}H_9N_2O_2Br$: [M+H] 268.9926. Found: [M+H] 268.9923; Anal. calcd for $C_{10}H_9N_2O_2Br$: C, 44.63; H, 3.37; N, 10.41. Found: C, 44.76; H, 3.40; N, 10.37.

4.1.4. 3-Methyl-4-(4-nitrobenzyl)-1,2,4-oxadiazol-5(4*H*)-one (4c). 4-Nitrobenzyl bromide (1.42 g, 6.59 mmol) was allowed to react as in **4a** to yielded 1.35 g (87%) of **4c** as a white solid, mp 150–152 °C. ^{1}H NMR ($CDCl_3$): δ 2.17 (s, 3H), 4.85 (s, 2H), 7.45 (d, 2H), 8.25 (d, 2H); ^{13}C NMR ($CDCl_3$): δ 10.9, 45.2, 124.8, 128.5, 141.7, 156.2; HRMS calcd for $C_{10}H_9N_3O_4$: [M+H] 236.1963. Found: [M+H] 236.1959; Anal. calcd for $C_{10}H_9N_3O_4$: C, 51.07; H, 3.86; N, 17.87. Found: C, 51.19; H, 3.88; N, 17.83.

4.1.5. (1*Z*)-*N*-Benzyl-*N*′-Hydroxyethanimidamide (5a). **4a** (190 mg, 1.0 mmol) was suspended in 5% NaOH

(2 mL) at 60 °C for 3 h. The mixture was neutralized with 1 N HCl to pH 7–8. The solid was collected, washed with cold water several times and air dried to yield 100 mg (61%) of **5a** as a white solid, mp 138–139 °C. ^{1}H NMR (CD_3OD): δ 1.76 (s, 3H), 4.35 (s, 2H), 7.26 (m, 5H); ^{13}C NMR (CD_3OD): δ 13.5, 45.5, 114, 126.5, 127.2, 128.4; HRMS calcd For $C_9H_{12}N_2O$: [M+H] 165.1028. Found: [M+H] 165.0987; Anal. calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.05. Found: C, 65.83; H, 7.39; N, 17.06.

4.1.6. (1*Z*)-*N*-(4-Bromobenzyl)-*N'*-hydroxyethanimidamide (5b). 4b (270 mg, 1.0 mmol) was allowed to react as in **5a** to give 200 mg (83%) of **5b** as a white solid, mp 129–130 °C. ^{1}H NMR (CD_3OD): δ 1.74 (s, 3H), 4.31 (s, 2H), 7.22 (d, 2H), 7.47 (d, 2H); ^{13}C NMR (CD_3OD): δ 13.5, 44.5, 120.1, 120.5, 128.4, 131.5; Anal. calcd for $C_9H_{11}BrN_2O$: C, 44.47; H, 4.56; N, 11.52. Found: C, 44.69; H, 5.59; N, 11.66.

4.1.7. Preparation of (iminoethyl)benzylamine (6). Method A: Oxadiazolone **4a** (380 mg, 2.0 mmol) was combined with MeOH (2 mL), HOAc (2 mL), water (2 mL) and zinc dust (570 mg, 8.7 mmol). The mixture was heated at 60 °C for 4 h. LCMS indicated product formation with no starting material. The reaction mixture was filtered and the filtrate concentrated. The crude product was purified by Reverse phase HPLC (0–100% acetonitrile with 0.01% HOAc) isolated as the HOAc salt to yield 300 mg (72%) of **6** as a clear oil. ^{1}H NMR (CD_3OD): δ 1.86 (s, 3H), 4.46 (s, 2H), 7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 17.7, 46.0, 127.6, 127.9, 128.2, 128.8, 134.7, 164.0; HRMS calcd for $C_9H_{12}N_2$: [M+H] 149.1079. Found: [M+H] 149.1041.

Method B: Oxadiazolone **4a** (190 mg, 1.0 mmol) and Lindlar's catalyst Pd–$CaCO_3$ (290 mg) were combined in MeOH (10 mL). The mixture was heated at 60 °C for 2 h. LCMS indicated a new product with **4a** consumed. The reaction mixture was filtered and washed with MeOH. The filtrate was concentrated to dryness to yield **6** quantitively.

4.1.8. 4-[(2*E*)-4-Bromobut-2-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (8). *Trans*-1,4-dibromo-2-butene (**7**) (50 g, 0.23 mol) was dissolved in acetone (500 mL). Oxadiazolone **2a** (16 g, 0.12 mol) was added, followed by tetrabutylammonium bromide (3.9 g, 0.012 mol). The reaction mixture was stirred at ambient temperature for 18 h, diluted with brine and the product was extracted into EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to a yellow semi-solid residue. The product **8** was extracted from the residue into CH_2Cl_2 and concentrated to an oily residue. This residue was triturated with hot hexane to remove unreacted **7**, then chromatographed on silica, eluting with EtOAc/hexane to yield 14.2 g (50%) of **8** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H), 3.9 (d, 2H), 4.2 (d, 2H), 5.7 (d of t, 1H), 5.9 (d of t, 1H).

4.1.9. 2-[(2*E*)-4-(3-Methyl-5-oxo-1,2,4-oxadiazol-4(5*H*)-yl)but-2-enyl]-1*H*-isoindole-1,3(2*H*)-dione (9). Bromide **8** (2 g, 8.58 mmol), tetrabutylammonium bromide (0.26 g, 0.86 mmol) and potassium phthalimide (1.9 g, 10.3 mmol) were dissolved in acetone (20 mL) and stirred for 2 h at ambient temperature. The solid was filtered and washed with H_2O (50 mL), and the filtrate was extracted with EtOAc. The organic layer was dried over $MgSO_4$, and concentrated to yield 1.32 g (52%) of **9** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H), 4.06 (d, 2H), 4.32 (d, 2H), 5.59 (m, 2H), 7.71 (m, 2H) 7.89 (m, 2H); LC–MS calc for $C_{15}H_{13}N_3O_4$: [M+H] 300. Found: [M+H] 300; Anal calcd for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04. Found: C, 59.98; H, 4.34; N, 14.10.

4.1.10. *N*-Benzylethanimidamide (10). Phthalimide **9** (150 mg, 0.5 mmol) was dissolved/suspended in EtOH (3.0 mL). Hydrazine hydrate (50 mg, 1.0 mmol) was added and the mixture was stirred at reflux for 30 min. The reaction mixture was concentrated and the residue dissolved in dilute K_2CO_3. The insoluble material was filtered and the filtrate was chromatographed using reverse phase to yield 10 mg of **10** (7.5%) isolated as the TFA salt. ^{1}H NMR (MeOD): δ 2.25 (s, 3H), 3.55 (dd, J=6.4, 1.2 Hz, 2H), 4.29, 4.28 and 4.27, 4.270 (d of d, J=5.2, 1.2 Hz, 2H), 5.78–5.71 (m, 1H), 5.97–5.90 (m, 1H); ^{19}F NMR (MeOD): δ −77.37; HRMS calcd for $C_7H_{11}N_3O_2$: [M+H] 170.0924. Found: [M+H] 170.0916.

4.1.11. *N*-[(2*E*)-4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)but-2-enyl]ethanimidamide (11). Phthalimide **9** (150 mg, 0.5 mmol) and zinc (101 mg; 1.5 mmol) were dissolved/suspended in HOAc (10 mL) and sonicated for 10 min. The resulting mixture was filtered and concentrated. The residue was chromatographed using reverse phase chromatography to yield 96 mg (18%) of **11** isolated as the TFA salt. ^{1}H NMR (MeOD): δ 2.23 (s, 3H), 4.04 (dd, J= 11.2, 6.4 Hz, 1H), 4.23 (dd, J=5.2, 1.2 Hz, 2H), 4.31 (d of d, J=16.0, 4.8 Hz, 1H), 5.83–5.69 (m, 2H), 7.73–7.51 (m, 4H); ^{19}F NMR (MeOD): δ −77.38; HRMS calcd for $C_{14}H_{15}N_3O_2$: [M+H] 258.1164. Found: [M+H] 258.1152.

4.1.12. Ethyl 4-(3-methyl-5-oxo-1,2,4-oxadiazol-4(5*H*)-yl)-3-oxobutanoate (13). Chloroester **12** (5.0 g, 0.03 mol) was added drop wise to a mixture of Cs_2CO_3 (13 g, 0.04 mol), NaI (50 mg) and **2a** (6 g, 0.04 mol) dissolved/suspended in DMSO (40 mL), and stirred for 3 h at ambient temperature. The reaction was quenched with NH_4Cl solution and the product extracted into EtOAc. The residue was chromatographed over silica, eluting with EtOAc/hexane to yield 5.3 g (58%) of **13** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.33, (t, J=9.6 Hz, 3H), 2.20 (s, 3H), 3.60 (s, 2H), 4.25 (q, J=9.2 Hz, 2H), 4.63 (s, 2H); MS(CI) calcd for $C_9H_{12}N_2O_5$: [M+H] 229. Found: [M+H] 229; Anal. calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.40; H, 5.46; N, 11.86.

4.1.13. Ethyl 4-(ethanimidoylamino)-3-oxobutanoate (14) and ethyl (2-methyl-1*H*-imidazol-5-yl)acetate (15). Ester **13** (80 mg; 0.35 mmol) was added to 5% Pd–C (10 mg) in EtOH (20 mL) and placed under 40 psi hydrogen gas for 4 h. The reaction mixture was filtered and concentrated at ambient temperature. The residue was chromatographed using reverse phase. Two products were isolated:

Ester **14** was the first component off the column. ^{1}H NMR (MeOD): δ 1.25 (t, J=7.2 Hz, 3H), 2.35 (s, 3H), 3.59

(s, 2H), 4.15 (q, $J=9.6$ Hz, 2H), 4.91 (s, 2H); HRMS calcd for $C_8H_{14}N_2O_3$: 187.1083, found: 187.1064.

Imidazole **15** was the second component off the column. ^{1}H NMR (MeOD): δ 1.24 (t, $J=7.2$ Hz, 3H), 2.35 (s, 3H), 3.58 (s, 2H), 4.14 (q, $J=6.0$ Hz, 2H), 6.70 (s, 1H); HRMS calcd for $C_8H_{12}N_2O_2$: [M+H] 169.0977. Found: [M+H] 169.0933.

Heating converted **14** to **15**.

4.1.14. 4-[(2*E*)-5-Hydroxypent-2-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (17) and (3*E*)-5-[(3-methyl-1,2,4-oxadiazol-5-yl)oxy]pent-3-en-1-ol (18). Dihydroxy-olefin **16** (109 mg, 1.0 mmol), Ph_3P (262 mg, 1.0 mmol) and **2b** (100 mg, 1.0 mmol) were dissolved in THF (5.0 mL). The reaction mixture was cooled in an ice bath before adding DEAD (174 mg, 1.0 mmol) drop wise. TLC (EtOAc) indicated that **16** was consumed and two new products were present. The reaction mixture was concentrated and chromatographed, eluting with EtOAc/hexane. The first compound to elute was identified as the O-alkylated derivative **18**, 13 mg (7%). ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H), 2.32 (q, $J=15$ Hz, 2H), 3.68 (t, $J=12.4$ Hz, 2H), 4.15 (dd, $J=6$, 1.2 Hz, 2H), 5.55, (pent. $J=5.6$ Hz, 1H), 5.73, (pent, Hz, $J=8.4$ Hz, 1H); MS(CI) calcd for $C_8H_{12}N_2O_3$: [M+H] 185. Found: [M+H] 185; Anal. calcd for $C_8H_{12}N_2O_3$: C, 36.01; H, 4.03; N, 27.99. Found: C, 35.76; H, 3.99; N, 28.26.

The second product to elute was the N-alkylated derivative **17**, 26 mg (14%). ^{1}H NMR ($CDCl_3$): δ 2.25 (s, 3H), 2.36 (q, $J=6.4$ Hz, 2H), 3.70 (t, $J=6.0$ Hz, 2H), 4.89 (dd, $J=6.0$, 0.8 Hz, 2H), 5.80 (pent, $J=6.4$ Hz, 1H), 5.94 (pent, $J=7.2$ Hz, 1H); MS(CI) calcd for $C_8H_{12}N_2O_3$: [M+H] 185. Found: [M+H] 185; Anal. calcd for $C_8H_{12}N_2O_3$: C, 36.01; H, 4.03; N, 27.99. Found: C, 36.18; H, 4.14; N, 27.86.

Dihydroxy-olefin **16** (109 mg, 1.0 mmol) and **2b** (100 mg, 1 mol) were dissolved in THF (5.0 mL). Ph_3P–polymer (3.0 mmol/g) (500 mg, 1.5 mmol) was added and the mixture was slowly stirred while adding DEAD (174 mg, 1.0 mmol). The products were identical to the reaction with unbound Ph_3P: O-alkylated 34 mg (18%) of **18**, and N-alkylated 50 mg (27%) of **17**.

4.1.15. 3-(3-Methyl-5-oxo-1,2,4-oxadiazol-4(5*H*)-yl)propanal (19). Oxadiazolone **2b** (729 mg, 7.24 mmol) was dissolve in ethanol (15 mL) then combined with acrolein (0.53 mL, 7.24 mmol) and triethylamine (0.10 mL, 0.723 mmol) and stirred for 18 h. The reaction mixture was partitioned between H_2O/EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated producing 1.3 g of **19** (100% crude) as a pale orange oil. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 3.04 (t, $J=6$ Hz, 2H), 3.80 (t, $J=6$ Hz, 2H), 9.73 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 18.6, 40.8, 58.6, 95.1, 157.0, 198.9; MS(CI) calcd for $C_6H_8N_2O_3$: [M+H] 157. Found: [M+H] 157.

4.1.16. Ethyl (2*E*)-2-fluoro-5-(3-methyl-5-oxo-1,2,4-oxadiazol-4(5*H*)-yl)pent-2-enoate (21). Triethylfluorophosphonate (**20**) (52.9 g, 0.218 mol) and LiCl (10.1 g, 0.238 mol) were dissolved in THF (100 mL). DBU (33.2 g, 0.218 mol) was added drop wise over a 20 min. period. After stirring 1 h a deep orange-red color developed, where the mixture was cooled to −78 °C. Aldehyde **19** (31.2 g, 0.199 mol) dissolved in THF (60 mL) was added to the reaction mixture over a 45 min period. The mixture was stirred 4 h at −78 °C then quenched with saturated NH_4Cl solution. After warming to ambient temperature the mixture was diluted with H_2O (100 mL) and the product extracted into EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to yield 47.9 g (98%) of **21** as a dark amber oil. ^{1}H NMR ($CDCl_3$): δ 1.285 (t, $J=6.8$ Hz, 3H), 2.26 (s, 3H), 2.85 (q, $J=6.4$ Hz, 2H), 3.64 (t, $J=7.2$ Hz, 2H), 4.24 (q, $J=7.2$ Hz, 2H), 5.85 (dt, $J=19.6$, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 10.46, 14.21, 24.97, 25.02, 41.10, 41.14, 62.11, 117.01, 117.21, 148.11, 150.70, 156.55, 159.34, 160.46, 160.81; ^{19}F NMR ($CDCl_3$): δ −117.43 (d, $J=20.4$ Hz); MS(CI) calcd for $C_{10}H_{13}FN_2O_4$: [M+H] 245. Found: [M+H] 245.

4.1.17. 4-[(3*E*)-4-Fluoro-5-hydroxypent-3-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (22). Ester **21** (6.2 g, 25.4 mmol) was dissolved in THF (100 mL) and cooled to −5 °C. Red-Al 68% in toluene (8.5 mL, 27.9 mmol) was added drop wise to the cooled solution. The reaction mixture was monitored by TLC every 0.5 h until the starting material was consumed. The reaction was quenched with 75 mL of saturated Rochelle's salt. The product was extracted into CH_2Cl_2 (2×150 mL), dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica, eluting with EtOAc/hexane to yield 2.1 g (41%) of **22** as an oil. ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H), 2.43 (q, $J=8.0$ Hz, 2H), 3.62–3.56 (m, 2H), 4.12 (d, $J=20$ Hz, 2H), 5.14–5.05 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 10.66, 14.38, 24.16, 24.25, 42.35, 57.50, 60.63, 103.54, 103.77, 156.55, 159.80, 162.32, 171.46; ^{19}F NMR ($CDCl_3$): δ −106.69 (dd, $J=42.0$, 30.4 Hz); MS(CI) calcd for $C_8H_{11}FN_2O_3$: [M+H] 203. Found: [M+H] 203; Anal. calcd for $C_8H_{11}FN_2O_3\cdot 0.1\,H_2O$: C, 47.10; H, 5.53; N, 13.73. Found: C, 46.96; H, 5.41; N, 13.40.

4.1.18. 4-[(3*E*)-5-Bromo-4-fluoropent-3-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (23). Alcohol **22** (800 mg, 3.98 mmol) and CBr_4 (3.28 g, 9.9 mmol) were dissolved in CH_2Cl_2 and cooled to −5 °C. Ph_3P–polymer (3.0 mmol/g) (3.98 g, 12.0 mmol) was added to the reaction mixture and stirred for 18 h. The reaction mixture was filtered and concentrated. The residue was chromatographed over silica, eluting with EtOAc/hexane to yield 600 mg (57%) of **23** as an oil. ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H), 2.46 (q, $J=12.0$ Hz, 2H), 3.68 (t, $J=6.8$ Hz, 2H), 4.10 (d, $J=22.8$ Hz, 2H), 5.35–5.26 (m, 1H);); ^{13}C NMR ($CDCl_3$): δ 10.67, 25.13, 27.85, 31.97, 41.66, 41.92, 105.47, 105.70, 156.25, 169.32; ^{19}F NMR ($CDCl_3$): δ −105.27 (dd, $J=44.0$, 22.4 Hz); MS(CI) calcd for $C_8H_{10}BrFN_2O_2$: [M+H] 265 and 267. Found: [M+H] 265 and 267; Anal. calcd for $C_8H_{10}BrFN_2O_2\cdot 0.05$ EtOAc: C, 36.55; H, 3.89; N, 10.40; F, 7.05; Br, 29.65. Found: C, 36.92; H, 3.89; N, 10.35; F, 6.69: Br, 29.75.

4.1.19. Ethyl (2*E*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-2-fluoropent-2-enoate (25a) and ethyl (2*Z*)-5-{[*tert*-butyl-(dimethyl)silyl]oxy}-2-fluoropent-2-enoate (25b). NaH (60% suspension in mineral oil) (1.7 g, 72.0 mmol) was

washed with hexane to remove the mineral oil, toluene (200 mL), **20** (17.2 g, 71.0 mmol) and **24**[8] (13.2 g; 0.07 mol) dissolved in toluene (50 mL) was reacted at 0 °C as described for Compound **21** to yield 5.9 g (30.5%) of **25a**. ^{1}H NMR ($CDCl_3$): δ 0.04 (s, 6H), 0.87 (s, 9H), 1.33 (t, J=7.2 Hz, 3H), 2.75–2.69 (m, 2H), 3.68 (dt, J=0.8, 6.0 Hz, 2H), 4.28 (q, J=7.2 Hz, 2H), 6.19 (dt, J=33.6, 7.6 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −121.67 (d, J=23.2 Hz); MS(CI) calcd for $C_{13}H_{25}O_3FSi$: [M+H] 277. Found: [M+H] 277.

A minor component was isolated and purified and identified as **25b** the *Z*-isomer: ^{1}H NMR ($CDCl_3$): δ 0.037 (s, 6H), 0.87 (s, 9H), 1.330 (t, J=7.2 Hz, 3H), 2.47–2.42 (m, 2H), 3.68 (dt, J=0.8, 8.0 Hz, 2H), 4.28 (q, J=7.2 Hz, 2H), 6.00 (dt, J=21.2, 8.0 Hz, 1H). ^{19}F NMR ($CDCl_3$): δ −129.79 (d, J=33.2 Hz); MS(CI) calcd for $C_{13}H_{25}O_3FSi$: [M+H] 277. Found: [M+H] 277.

4.1.20. (2*E*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-fluoropent-2-en-1-ol (26). Ester **25a** (6.0 g, 21.7 mmol) dissolved in THF (70 mL), Red-Al 68% in toluene (9.2 mL, 30.0 mmol) was reacted at −5 °C as described for Compound **22** to yield 4.0 g (79%) of **26**. ^{1}H NMR ($CDCl_3$): δ 0.04 (s, 6H), 0.87 (s, 9H), 2.29–2.21 (m, 3H, 1 exchangeable), 3.63 (dt, J=1.2, 8.0 Hz, 2H), 4.20 (d, J=26.0 Hz, 2H), 5.20 (dt, J=26.0, 12.0 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −109.63 (q, 28.4 Hz); MS(CI) calcd for $C_{11}H_{23}FO_2Si$: [M+H] 235. Found: [M+H] 235; Anal. calcd for $C_{11}H_{23}FO_2Si$: C, 56.37; H, 9.89. Found: C, 56.38; H, 10.19.

4.1.21. (2*E*)-2-Fluoropent-2-ene-1,5-diol (27). Alcohol **26** (131.0 g, 0.56 mol) was dissolved in EtOH (1.5 l) and concn HCl (15 mL) was added and the mixture was stirred for 0.25 h. TLC (20% EtOAc/hexane) indicated that the starting material was consumed. The mixture was concentrated and the residue was azeotroped twice with toluene (500 mL) to produce 71.8 g (100% crude) of **27** as an oil. ^{1}H NMR ($CDCl_3$): δ 2.30–2.23 (m, 2H), 3.64 (dt, J=0.8, 8.0 Hz, 2H), 4.18 (d, J=29.6 Hz, 2H), 5.21 (dt, J=27.0, 11.6 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ−108.16 (q, J=30.8 Hz); MS(CI) calcd for $C_5H_9O_2F$: [M+H] 121. Found: [M+H] 121.

4.1.22. (2*E*)-2-Fluoro-5-[(methylsulfonyl)oxy]pent-2-enyl methanesulfonate (28). Dihydroxyolefin **27** (71.8 g, 0.56 mol) and Et_3N (141.4 g/195 mL, 1.4 mol) were dissolved in CH_2Cl_2 (1.0 l) and cooled in an ice bath. Ms_2O (243.4 g, 1.4 mol) was dissolved in CH_2Cl_2 (0.5 l) and added drop wise. The reaction mixture was stirred 15 min when TLC (60% EtOAc/hexane) indicated that the starting material was consumed. The reaction mixture was partitioned between H_2O/CH_2Cl_2. The organic layer was washed with H_2O, dried over $MgSO_4$ and concentrated to yield 164.9 g (100% crude) of **28** as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 2.55 (q, J=10.0 Hz, 2H), 3.02 (s, 3H), 3.07 (s, 3H), 4.25 (dt, J=1.2, 8.4 Hz, 2H), 4.82 (d, J=27.6 Hz, 2H), 5.50 (dt, J=24.8, 11.2 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −107.91 (q, J=27.2 Hz); MS(CI) calcd for $C_7H_{13}O_6S_2F$: [M+NH_4] 294. Found: [M+NH_4] 294.

4.1.23. (3*E*)-4-Fluoro-5-(3-methyl-5-oxo-1,2,4-oxadiazol-4(5*H*)-yl)pent-3-enyl methanesulfonate (29). Dimesylate **28** (164.9 g, 0.55 mol) dissolved in MEK (0.6 l) was added to a slurry of **2a** (84.8 g, 0.61 mol) in MEK (0.6 l) and heated at reflux 6.0 h where TLC (60% EtOAc/hexane) indicated that **28** was still present. Additional **2a** (17 g) was added and the mixture was stirred at reflux for an additional 2.0 h at which time the starting material was consumed. The reaction mixture was cooled and filtered and the solid washed with MEK. The filtrate was concentrated to yield 204 g (100% crude) of **29** as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H), 2.63 (q, J=6.4 Hz, 2H), 3.01 (s, 3H), 4.26 (dt, J=0.8, 6.4 Hz, 2H), 4.31 (d, J=19.6 Hz, 2H), 5.409 (dt, J=19.6, 8.4 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −106.89 (q, J=21.2 Hz); MS(CI) calcd for $C_9H_{13}N_2O_5SF$: [M+H] 281. Found: [M+H] 281.

4.1.24. 4-[(2*E*)-2-Fluoro-5-iodopent-2-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (30). Mesylate **29** (204.8 g, 0.56 mol) was dissolved in MEK (1.2 l) and solid NaI (167 g, 1.12 mol) was added to the mixture and stirred 18 h at which time TLC (60% EtOAc/hexane) indicated that the starting material was consumed. The reaction mixture was partitioned between an equal volume of H_2O and the aqueous layer was washed with Et_2O then CH_2Cl_2 (500 mL each). The combined organic layers were washed with 1% $Na_2S_2O_3$, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica, eluting with EtOAc/hexane to yield 87.4 g (50%) of **30** as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H), 2.74 (q, J=7.2 Hz, 2H), 3.20 (dt, J=0.8, 6.8 Hz, 2H), 4.31 (d, J=19.6 Hz, 2H), 5.39 (dt, J=19.6, 8.4 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −108.31 (q, J=21.2 Hz); MS(CI) calcd for $C_8H_{10}FIN_2O_2$: [M+H] 313. Found: [M+H] 313; Anal. calcd for $C_8H_{10}FIN_2O_2$; C, 30.79; H, 3.23; N, 8.98; I, 40.66. Found: C, 30.75; H, 2.99; N, 8.92; I, 40.41.

4.1.25. Ethyl (2*E*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-fluorobut-2-enoate (32a) and ethyl (2*Z*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-fluorobut-2-enoate (32b). NaH (60% suspension in mineral oil) (3.9 g, 0.10 mol), THF (300 mL), **20** (25 g, 0.10 mol) and **31**[9] (17.4 g; 0.1 mol) was reacted at 0 °C as described for Compound **21** to yield 8.9 g (34%) of **32a**. ^{1}H NMR ($CDCl_3$): δ 0.08 (s, 6H), 0.88 (s, 9H), 1.25 (t, J=7.2 Hz, 3H), 4.28 (q, J=7.2 Hz, 2H), 4.64 (dd, J=3.6, 5.6 Hz, 2H), 6.01 (dt, J=19.6, 5.6 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −123.95 (dt, J=20.8, 3.2 Hz); MS(CI) calcd for $C_{12}H_{23}O_3FSi$: [M+H] 263. Found: [M+H] 263.

A minor component was isolated and purified and identified as the *Z*-isomer **32b**: ^{1}H NMR ($CDCl_3$): δ 0.08 (s, 6H), 0.88 (s, 9H), 1.25 (t, J=7.2 Hz, 3H), 4.28 (q, J=7.2 Hz, 2H), 4.41 (dd, J=6.4, 1.2 Hz, 2H), 6.19 (dt, J=33.6, 6.4 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −127.28 (dt, J=35.2, 3.6 Hz); MS (CI) calcd for $C_{12}H_{23}O_3FSi$: [M+H] 263. Found: [M+H] 263.

4.1.26. (2*E*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-fluorobut-2-en-1-ol (33). Ester **32a** (8.7 g, 33.0 mmol) was dissolved in THF (100 mL) and cooled in an ice bath. $LiBH_4$ 2.0 M in THF (33 mL, 66.0 mmol) was added and the mixture stored at −40 °C for 18 h. The reaction was quenched with H_2O. A solid formed which was filtered and washed with THF. The filtrate was concentrated and chromatographed over silica, eluting with EtOAc/hexane to yield 4.5 g (62%) of **33**. ^{1}H NMR ($CDCl_3$): δ 0.08 (s, 6H),

0.88 (s, 9H), 4.20 (dd, J=6.8, 2.4 Hz, 2H), 4.24 (d, J=19.6 Hz, 2H), 5.38 (dt, J=20.4, 7.2 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −109.28 (q, J=22.0 Hz); MS(CI) calcd for $C_{10}H_{21}O_2FSi$: [M+H] 221. Found: [M+H] 221; Anal. calcd for $C_{10}H_{21}O_2FSi$: C, 54.51; H, 9.61. Found: C, 54.44; H, 9.78.

4.1.27. 4-((2*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-fluorobut-2-enyl)-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (34). Alcohol **33** (25.5 g, 0.115 mol), **2b** (11.3 g, 0.1 mol) and triphenylphosphine (29.7 g, 0.11 mol) were dissolved in THF (500 mL) and cooled in an ice bath. DEAD (19.1 g/17.3 mL, 0.11 mol) was added drop wise to the reaction mixture. The reaction progress was monitored by TLC (60% EtOAc/hexane). When **33** was consumed the reaction mixture was concentrated and the residue triturated with Et_2O. The filtrate was concentrated and chromatographed over silica, eluting with EtOAc/hexane to yield 10.4 g (31%) of **34**. ^{1}H NMR ($CDCl_3$): δ 0.08 (s, 6H), 0.88 (s, 9H), 2.28 (s, 3H), 4.31 (dd, J=6.4, 2.8 Hz, 2H), 4.44 (d, J=19.2 Hz, 2H), 5.53 (dt, J=20.0, 6.4 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −109.06 (q, J=20.8 Hz); MS(CI) calcd for $C_{13}H_{23}N_2O_3FSi$: [M+H] 303. Found: [M+H] 303; Anal calcd for $C_{13}H_{23}N_2O_3FSi$: C, 51.63; H, 7.67; N, 9.26. Found: C, 51.84; H, 7.82; N, 8.95.

4.1.28. 4-[(2*E*)-2-Fluoro-4-hydroxybut-2-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (35). Oxadiazolone **34** (10.4 g, 34.0 mmol) was dissolved in EtOH (100 mL) and concn HCl (1.0 mL) was added and the mixture stirred for 1 h. TLC (60% EtOAc/hexane) indicated that **34** was consumed. The mixture was concentrated to dryness to yield 6.9 g (100% crude) of **35**. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 4.25 (dd, J=6.8, 2.8 Hz, 2H), 4.44 (d, J=21.2 Hz, 2H), 5.65 (dt, J=20.0, 7.2 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −107.88 (q, J=21.6 Hz); MS(CI) calcd for $C_7H_9FN_2O_3$: [M+H] 189. Found: [M+H] 189.

4.1.29. (2*E*)-3-Fluoro-4-(3-methyl-5-oxo-1,2,4-oxadiazol-4(5*H*)-yl)but-2-enyl methanesulfonate (36). Alcohol **35** (6.9 g, 34.0 mmol) and Et_3N (4.0 g/5.5 mL, 40.0 mmol) were dissolved in CH_2Cl_2 (100 mL). Ms_2O (6.9 g, 40.0 mol) was added drop wise 30 min. TLC (60% EtOAc/hexane) indicated that **35** was consumed. The reaction mixture was poured into H_2O and the layers separated. The organic layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to yield 8.3 g (92%) of **36** as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 3.06 (s, 3H), 4.42 (d, J=20.0 Hz, 2H), 4.92 (dd, J=8.0, 1.2 Hz, 2H), 5.67 (dt, J=8.7, 8.0 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −101.10 (q, J=19.6 Hz); MS(CI) calcd for $C_8H_{11}FN_2O_5S$: [M+H] 267. Found: [M+H] 267; Anal. calcd for $C_8H_{11}FN_2O_5S$: C, 36.09; H, 4.16; N, 10.52. Found: C, 36.43; H, 4.06; N, 10.41.

4.1.30. 4-[(2*E*)-2-Fluoro-4-iodobut-2-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (37). Mesylate **36** (8.3 g, 32.0 mmol) and NaI (9.8 g, 65.0 mmol) were stirred for 30 min in MEK. TLC (40% EtOAc/hexane) indicated that **36** was consumed. The reaction mixture was partitioned between Et_2O/H_2O. The aqueous layer was washed with Et_2O and the combined organic layers were washed with 1% $Na_2S_2O_3$, dried over $MgSO_4$ and concentrated. Chromatographed over silica eluting with EtOAc/hexane to yield 4.5 g (47%) of **37** as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 3.98 (dd, J=9.6, 0.8 Hz, 2H), 4.34 (d, J=19.6 Hz, 2H), 5.78 (dt, J=16.8, 7.6 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ−106.08 (q, J=19.2 Hz); MS(CI) calcd for $C_7H_8FIN_2O_2$: [M+H] 299. Found: [M+H] 299; Anal. calcd for $C_7H_8FIN_2O_2$: C, 28.21; H, 2.71; N, 9.40. Found: C, 28.36; H, 3.04; N, 9.37.

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