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STEREOSPECIFIC SYNTHESIS OF 1-FLUORO OLEFINS *VIA* (FLUOROVINYL)STANNANES AND AN UNEQUIVOCAL NMR METHOD FOR THE ASSIGNMENT OF FLUORO OLEFIN GEOMETRY

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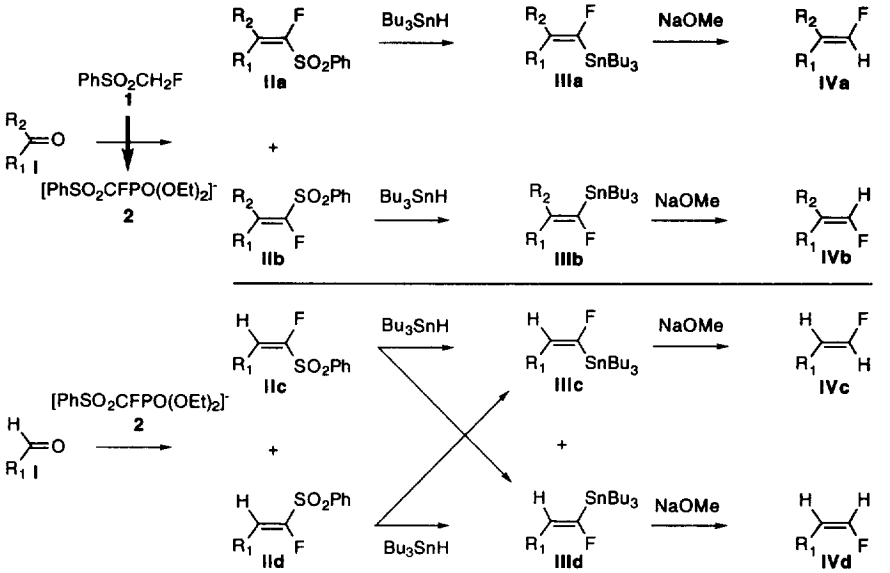
Abstract: (*E*)- and (*Z*)-Fluorovinyl sulfones (**II**) form (fluorovinyl)stannanes (**III**) on treatment with two equivalents of tributyltin hydride and a catalytic amount of AIBN; the free radical catalyzed reaction proceeds with retention of configuration for 2,2-disubstituted fluorovinyl sulfones (**IIa** and **IIb**). Conversion of **III** to 1-fluoro olefins (**IV**) is a stereospecific reaction and provides a general method to (*E*) and (*Z*) fluoro olefins. The utility of this method is exemplified by the synthesis of the deutero fluoro olefin **27**, nucleosides **32** and **34**, and the amino acids **43** and **47**. Proton observe, ^{19}F irradiated (^1H-{^{19}F}) NOE difference specroscopy was used for the first time as an unequivocal method for the assignment of olefin geometry for fluorovinyl sulfones, (fluorovinyl)stannanes and fluoro olefins.

New methods for the synthesis of 1-fluoro olefins have received considerable attention,[1] in part because of their presence in a number of biologically active molecules.[2] This functional group is particulary useful in the design of mechanism-based enzyme inhibitors since the fluorine can mimic a hydrogen atom,[3] but can be activated when the molecule containing the fluoro olefin is a substrate for the enzyme by forming a β-fluoro Michael acceptor that irreversibly alkylates the enzyme. Because the potency of the fluoro olefin inhibitor often depends on its geometry[2a] stereospecific methods to *E* and *Z* isomers are of considerable interest. Schwartz and Lee[1f] reported a stereospecific method to fluoro olefins from acetylenes but the desired products were contaminated with 5-15% of non-fluorinated olefins. Recently, a stereospecific method to 1-fluoro olefins from vinylstannanes and electrophilic fluorinating agents was reported.[1g-1i] However, yields were only moderate and non-fluorinated olefins can form as side products.[1i] Burton has reported a stereoselective method to (*Z*)-1-fluoro-1-olefins, however the *E* isomer can be the major product depending on the substituent on the intermediate fluoroalkenylphosphonium salt.[1e] This is usually the limitation for other stereoselective methods.[2a]

We communicated a stereospecific method to 1-fluoro olefins[4] that was developed for the synthesis of a bioprecursor of a mechanism-based inhibitor of ribonucleotide reductase (compound **34**); this compound has recently entered clinical trials as an antitumor agent. In this article we report several examples of the synthesis of 1-fluoro olefins (see Scheme 1) and illustrate the stereoselectivity of the reaction using aldehydes and ketones as starting materials.[5,6] The utility of the reaction sequence is highlighted with the synthesis of the deutero fluoro olefin **27**, the nucleosides **32**and **34**[7], and the amino acids **43** and **47**. In addition, a method to unequivocally assign the stereochemistry of the intermediate fluorovinyl sulfones (**II**), and (fluorovinyl)stannanes (**III**) is reported using NOE difference spectroscopy.

A key reagent that was utililzed for the development of the stereospecific method to 1-fluoro olefins was fluoromethyl phenyl sulfone (**1**) (see Scheme 1) that is readily prepared by the fluoro-Pummerer (or DAST-Pummerer) reaction.[8,9] It should be noted that the fluoro-Pummerer reaction was initially considered as a direct method for the synthesis of nucleosides **32** and **34**.[10] In previous work, nucleoside sulfoxides were treated with diethylaminosulfur trifluoride (DAST) yielding α-fluorosulfides; the α-fluorosulfides were reoxidized to the corresponding sulfoxides and pyrolyzed to form mixtures of (*E*)- and (*Z*)-fluoro olefins. The method provided a route to a mixture of (*E*)- and (*Z*)-5'-fluoro olefin adenosine analogs that were the first

Scheme 1. Stereospecific conversion of fluorovinyl sulfones (IIa and IIb) and (fluorovinyl)-stannanes (IIIa - IIId) to 1-fluoro olefins (IVa - IVd).



mechanism-based inhibitors of the enzyme S-adenosyl-*L*-homocysteine hydrolase.[11] Attempts to scaleup the synthesis of these compounds was difficult because of the separation of the geometric isomers.

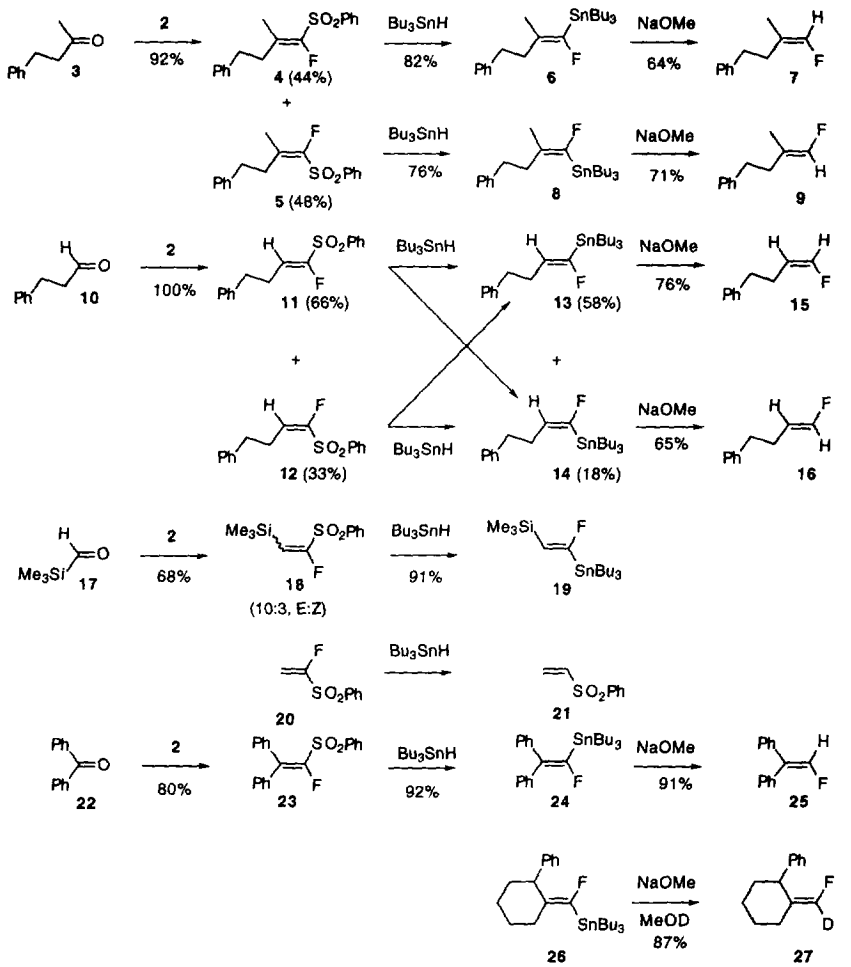
Therefore, the key issue in the synthesis of **32** and **34** was the development of a method that avoided separation of **32** and **34** in the final step of the synthesis; reagent **1** made this possible. The reagent was first reported for the preparation of β-fluorostyrenes from aromatic aldehydes via *II* (R_1 = aryl, R_2 = H or aryl).[9] Subsequently, the utility of the reagent was expanded by the *in situ* conversion of **1** to an Emmons-Wittig reagent (**2**) that was condensed with aromatic and aliphatic aldehydes and ketones to form 1-fluoro-1-(phenylsulfonyl)olefins (**II**) free of the allyl sulfone isomer.[9] The phenylsulfonyl group was removed from **II** with almagated aluminum yielding mixtures of (*E*)- and (*Z*)-fluoro olefins.[9,9] However this reaction gave a multicomponent mixture when attempted during the synthesis of **32** and **34**. This result led to the discovery of the stereospecific replacement of the vinylsulfone group on **IIa** and **IIb** with a tributylstannane group and the subsequent formation of 1-fluoro olefins.[12]

Examples of the synthesis of 1-fluoro olefins from aldehydes and ketones are presented in Scheme 2. Treatment of phenethyl methyl ketone (**3**) with the anion of the Emmons Wittig reagent **2**, generated *in situ* from fluoromethyl phenyl sulfone (**1**), diethyl chlorophosphate and two equivalents of lithium hexamethyldisilizane, provided a 92% combined yield of fluoro vinyl sulfones **4** and **5** in a 9 to 10 ratio that were readily separable by flash chromatography. Similarly, hydrocinamaldehyde (**10**) was treated with **2** to give a quantative yield of **11** and **12**. These isomers could be separated with difficulty but there was no reason since the subsequent free radical catalyzed stannylation did not proceed with retention of stereochemistry (see below). The aldehyde generated *in situ* from 2-trimethylsilylethanol (**17**) by the procedure of Ireland and Norbeck[13] readily reacted with the Emmon-Wittig reagent **2** to give a 10 to 3 *E* to *Z* mixture of the fluoro vinylsilane **18** in 68% yield. The hindered ketone benzophenone (**22**) reacted with **2** to form **23** in 80% yield.[14]

These fluorovinyl sulfones were readily converted to (fluorovinyl)stannanes in good to excellent yields. Treatment of **4** or **5** with two equivalents of tributyltin hydride in benzene or cyclohexane and a catalytic amount of AIBN gave the corresponding (fluorovinyl)stannanes **6** and **8** with only a trace (< 3%) of **6** formed with **8** and *vice versa*. The requirement for two equivalents of tributyltin hydride for the reaction to proceed to completion is consistent with a radical intermediate formed by addition of the tributyltin radical to the fluorovinyl sulfone that collapses to the (fluorovinyl)stannane with the release of a phenylsulfonyl

radical which in turn is trapped by the second equivalent of tributyltin radical. The phenethyl and methyl groups prevent free rotation of the radical intermediate preserving the *E* and *Z* geometry of the product (fluorovinyl)stannanes. Watanabe and co-workers[14] reported this transformation for nonfluorinated vinyl sulfones but did not address the stereoselectivity of the reaction.

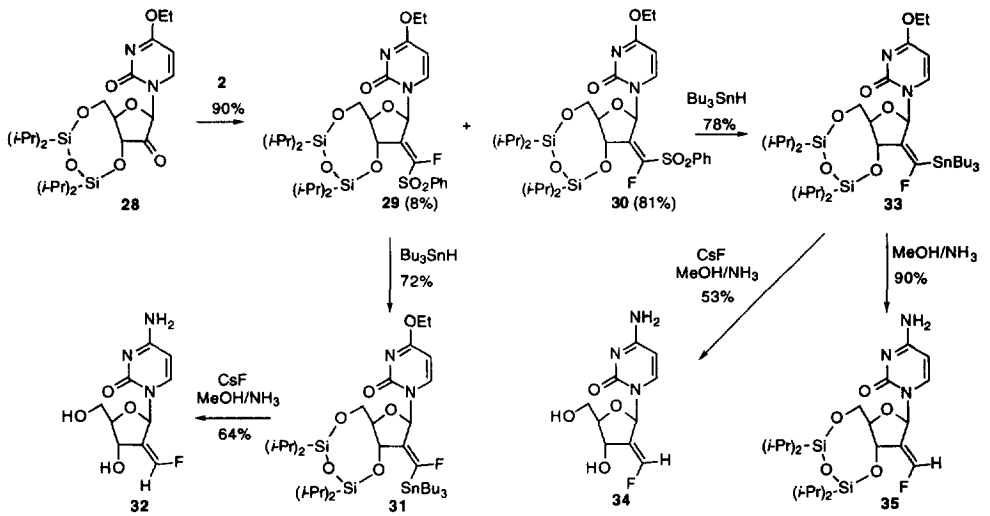
Scheme 2.



In contrast to 2,2-disubstituted fluorovinyl sulfones (**IIa** and **IIb**), the 2-monosubstituted analogs (**IIc** and **IId**) equilibrate to *E* and *Z* mixtures of (fluorovinyl)stannanes (**III**) when treated with tributyltin hydride. For the geometric isomers **11** and **12**, both yielded a 1 to 3 mixture of **13** and **14** in good yields on treatment with tributyltin hydride. The 10 to 3 *E* to *Z* mixture of fluoro phenylsulfonylvinylsilane **18**, was converted exclusively to the *E* isomer **19** in 91% yield. It is important to note that for the unsubstituted fluorvinyl sulfone **20** the only product observed was vinyl phenyl sulfone (**21**). In this case the more stable radical formed by addition of the tributyltin radical to **20** is on the carbon with the fluorine. Collapse of the radical would eliminate tributyltin fluoride forming phenyl vinyl sulfone. Addition of the trimethylsilyl group to the 2-position of the starting material (i.e. **18**) stabilized the radical on the carbon with the trimethylsilyl group and provided an equivalent for the 1-fluoroethene anion.[15]

Cleavage of the vinyl tributylstannane group was accomplished under suprisingly mild conditions with one of three reagents: (1) sodium methoxide in refluxing methanol/THF, (2) cesium fluoride in methanol or ethanol[16] or (3) methanolic ammonia. The preferred reagent is sodium methoxide with the exception of nucleosides where cesium fluoride is preferred (see below). Thus for the synthesis of fluoro olefins **7**, **9**, **15**, **16** and **25** excess (> one equivalent) of sodium methoxide was utilized to replace the tin with hydrogen. To our knowledge cleavage of non-fluorinated vinystannanes under basic conditions requires butyl lithium exchange.[16] A comparison of the cleavage of the vinylstannane group on 2,2-diphenyl tributylvinylstannane (non-fluorinated analog of **24**) and **24** on treatment with refluxing sodium methoxide in methanol for 16 hours showed that **24** was quantatively converted to **25**, but the non-fluorinated analog was unreactive.[17] The methoxide catalyzed cleavage of the tributyltin group on **III** provides a stereospecific method for the introduction of deuterium adjacent to fluorine as illustrated by the synthesis of **27** with CH_3OD and one equivalent of methoxide.

Scheme 3. Synthesis of **32** and **34**.

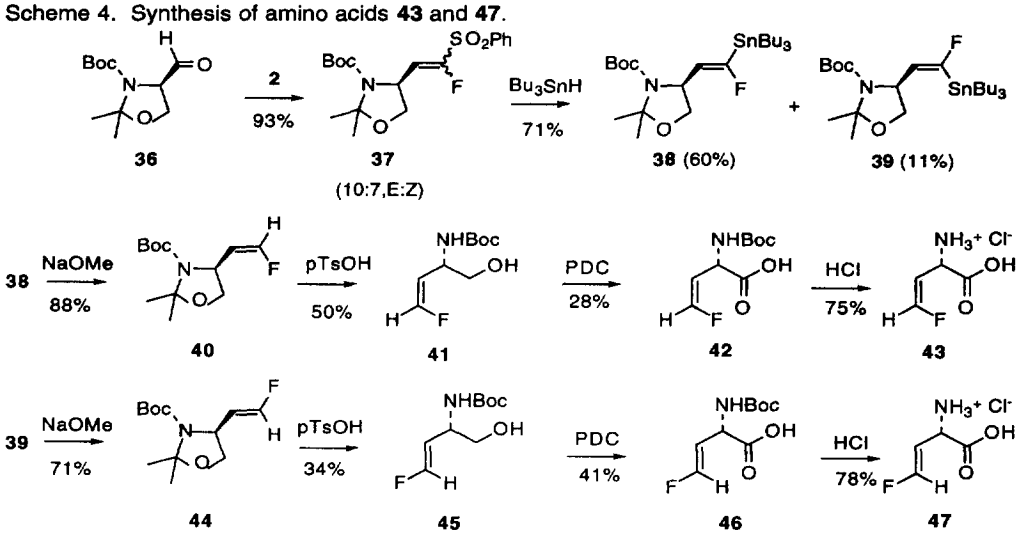


The synthesis of fluoro olefin nucleosides **32** and **34** are outlined in Scheme 3. Ketonucleoside **28**, prepared by the method of Matsuda, Ueda and co-workers[18] was treated with the anion **2** to provide the fluorovinyl sulfones **29** and **30** in a 1 to 10 ratio in a combined yield of 90%. The geometric isomers are readily separated by flash chromatography. Care was taken to avoid the presence of excess base for the generation of anion **2**, otherwise the anomeric hydrogen and the 3' hydrogen of the major product **30** are inverted.[10]. Attempts to reductively remove the phenylsulfonyl group with aluminum amalgum[18] from **29** or **30** gave a multcomponent mixture as judged by TLC.

However, as noted above, a stereospecific route to 1-fluoro olefins was developed as a result of this problem. Treatment of fluorovinyl sulfones **29** and **30** provided (fluorovinyl)stannanes **31** and **33** in 72% and 78%, respectively. This provided a route to the previously unreported (fluorovinyl)stannanes and a stereospecific method to fluoro olefins. For nucleoside **33**, methanolic ammonia cleaved the vinylstannane group and displaced the 4-ethoxy group with an amino group to provide **35** in 90% yield; addition of cesium fluoride to the above reaction resulted in the concominant cleavage of the TIPS protecting group at the 3' and 5' positions (i. e. **33** to **34**). The structure of **34** was confirmed by X-ray crystalography.[19] This same mixture of reagents was used for the synthesis of **32** from **31** in 64 % yield Compound **34** demonstrated broad spectrum antitumor activity against human xenografts either by oral or intravenous administration,[10,20] and is currently undergoing clinical evaluation as an antitumor agent.

Amino acids **43** and **47** (see Scheme 4) were targeted because of their potential antibacterial activity as alanine racemase inhibitors.[21] Aldehyde **36**[22] was converted to a 10 to 7 *E* to *Z* mixture of fluorovinyl sulfones **37** that can be separated by flash chromatography. However, treatment of either geometric isomer or the mixture with tributytin hydride gave a 11 to 2 mixture of **38** and **39**. Stannanes **38** and **39** were separated by flash chromatography and treated with one equivalent of sodium methoxide in methanol for 2 hours to provide **40** and **44** in 88 and 71% yields, respectively, with no apparent isomerization of the allylic hydrogens. The isopropylildene group was removed with *p*-toluenesulfonic acid monohydrate in methanol to give **41** as a white crystalline solid in 50% yield and **45** as an oil in 34% yield. Oxidization of the alcohols to the carboxylic acids were accomplished with pyridium dichromate in acetic acid at room termperature and the Boc protecting group were removed with HCl/dioxane or trifluoroacetic acid:water (9:1) to give amino acids **43**, $[\alpha]_D^{25}$ = +108 (*C* 0.976, H_2O) and **47**, $[\alpha]_D^{20}$ = +111 (*C* 0.04, H_2O).

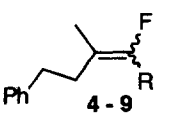
Scheme 4. Synthesis of amino acids **43** and **47**.



Initial attempts to determine the olefin geometry of the fluorovinyl sulfoxides (**II**) and (fluorovinyl)stannanes (**III**) were made using ^{19}F-^{13}C and $^{117/119}Sn$-^{13}C vicinal coupling constants. It is generally accepted that, similar to ^{1}H-^{1}H coupling constants, *trans* heteronuclear olefin couplings are larger than *cis*. For the fluorovinyl sulphones and (fluorovinyl)stannanes this was not always found to be true. This is best exemplified for compounds **4-9**. The three-bond ^{19}F-^{13}C and $^{117/119}Sn$-^{13}C coupling constants are given in Table 1.

Table 1. Vicinal ^{19}F-^{13}C and $^{117/119}Sn$-^{13}C Coupling Constants for **4-9**.

R	X	J_{X,CH_3} (Hz)		J_{X,CH_2} (Hz)	
-SO_2Ph(**4,5**)	F	*cis*	9.1	*cis*	6.7
		trans	(not observed)	*trans*	3.1
-Sn(Bu)$_3$(**6,8**)	F	*cis*	16.6	*cis*	14.4
		trans	12.7	*trans*	11.6
-Sn(Bu)$_3$(**6,8**)	Sn	*cis*	9.9	*cis*	9.8
		trans	19.0	*trans*	18.8
-H(**7,9**)	F	*cis*	6.2	*cis*	4.8
		trans	7.9	*trans*	6.8



With both the sulfones and (fluorovinyl)stannanes the *cis* ^{19}F-^{13}C coupling constants are larger than the *trans* coupling constants. In these cases the steric effect of the sulfone or tributyltin group reduces the magnitude of the *trans* coupling while not affecting *cis* couplings, similar to observations made for *cis-trans* ^{1}H-^{13}C couplings.[23] The variance in magnitudes between the stannanes and sulfones is explained by the differences in electronegativity. The electropositive tin group increases both *cis* and *trans* couplings, again analogous to ^{1}H-^{13}C couplings.[23] When the bulky sulphone and tributyltin groups were replaced with a hydrogen the expected *trans* > *cis* relationship was observed. The $^{117/119}Sn$-^{13}C vicinal coupling constants were also measured for **6** and **8** and the *trans* coupling constants observed were larger than the corresponding *cis* couplings. In both cases the magnitudes of the coupling constants were greatly reduced compared to expectations. In (Z)-1-(tributylstannyl)-1-propene the *cis* tin to methyl carbon coupling constant is 49 Hz while in the *trans* isomer a 78 Hz coupling is observed.[24] The smaller values observed for **6** and **8** are because of the effect of the electronegative fluorine which decreases both *cis* and *trans* couplings.

Because of the large variations in coupling constants due to the steric and electronegativity effects vicinal coupling constants were not a viable means of determining olefin geometry for the sulfones or stannanes. Instead, proton observe, ^{19}F-irradiated (^{1}H-{^{19}F}) NOE difference spectroscopy was used to make definative olefin geometry assignments. While ^{1}H-^{19}F NOE experiments are not new[25] limited applications have been reported,[26-28] especially for small molecules.[29] This is presumably due to hardware limitations for many spectrometers. For the ^{1}H-{^{19}F} NOE difference experiments used for olefin geometry assignments two hardware requirements are worthy of discussion. First, since our spectrometer is a single broadbanded system it was necessary to run these experiments in the "reverse" mode. That is, the ^{1}H decoupler was used as the observe transmitter and the broadband transmitter as the decoupler transmitter. Second, this experiment requires a probe which is capable of being tuned to both ^{1}H and ^{19}F at the same time. The four-nuclei probes which are becoming popular have a double tuned circuit for ^{1}H and ^{19}F and are ideal for this purpose.

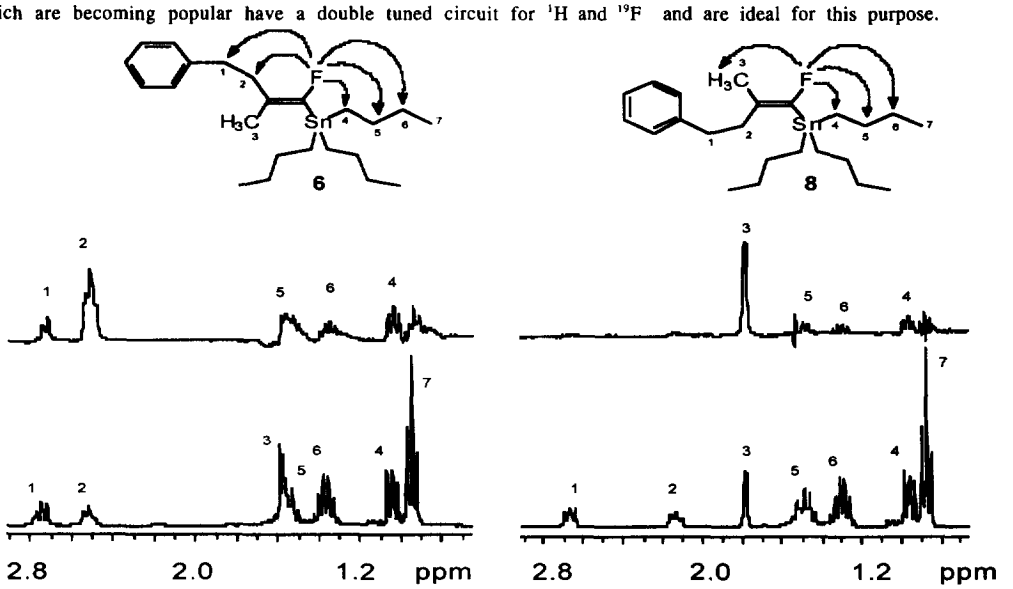


Fig. 1. ^{1}H-{^{19}F} NOE difference spectra of **6** and **8** (top spectra), with reference ^{1}H spectra shown below. Arrows with structures indicate NOE's observed.

Typical ^{1}H-{^{19}F} NOE difference spectra obtained for **6** and **8** are shown in Figure 1. Like ^{1}H-{^{1}H} NOE's, ^{1}H-{^{19}F} NOE's can be large (maximum enhancement 53%[25]) but typically are much smaller due to environmental, instrumental, and sample considerations. Unlike ^{1}H-{^{1}H} NOE's, with ^{1}H-{^{19}F}experiments there are no problems with incomplete saturation since nearby signals are typically not an issue. In Fig. 1 for **6** large enhancements are observed to methylene protons 1 and 2 while no enhancement is observed to the

methyl signal. Conversely, for **8** a strong enhancement is observed to the methyl protons and not to methylene protons 1 and 2. In both compounds the expected NOE's to the butyl protons are observed. It should also be noted that these spectra were obtained in *ca.* 15 min each demonstrating the simplicity of these experiments. These experiments unequivocally establish the olefin geometry of **6** is *E* and for **8** is *Z*. Similar experiments with other compounds in this paper gave NOE's which allowed for definitive proof of olefin geometry.

In summary, a new method for the synthesis of (*E*)- and (*Z*)-1-fluoro olefins from aldehydes and ketones was developed and used for the preparation of 1-deudero-1-fluoro olefin **27**, nucleosides **32** and **34**, the amino acids **43** and **47** as well as **7**, **9**, **15**, **16**, and **25**. The synthetic route is stereospecific for the conversion of 2,2-disubstituted sulfones (**IIa** and **IIb**) to 2,2-disubstituted-1-fluoro olefins and for the conversion of 2-monosubstituted (fluorovinyl)stannanes (**IIIc** and **IIId**) to 2-monosubstituted-1-fluoro olefins. Assignment of stereochemistry for the fluorvinyl sulfones (**II**) and (fluorovinyl)stannanes (**III**) were established for the first time by proton observe, ^{19}F irriadiated (^1H-{^{19}F}) NOE difference specroscopy.

Experimental

General. All melting points are uncorrected. The IR spectra were recorded with a Perkin-Elmer Model 710B spectrophotometer. The NMR spectra were recorded at 25 °C on Varian VXR-300 and Unity-300 spectrometers. The chemical shifts are reported in parts per million versus internal tetramethylsilane for ^1H, external tetramethylsilane for ^{13}C, and external fluorotrichloromethane for ^{19}F. The ^1H-{^{19}F} NOE difference spectra were obtained on the Unity-300 equiped with a 4-nucleus Auto-nmr™ probe using a standard steady-state NOE difference pulse sequence (D1 = 5 sec, not optimized). Mass spectra were obtained on a Finnigan MAT TSQ-700 mass spectrometer system. Elemental analysis data were obtained using a Perkin-Elmer Mode 12400 elemental analyzer. Thin-layer chromatography (TLC) (silica gel plates) was visualized by UV or by staining with alkaline potassium permanganate and heating.

(*E*)- and (*Z*)-2-Methyl-2-(2-phenylethyl)-1-fluoro-1-(phenylsulfonyl)ethene (**4**) and (**5**). Under nitrogen in a 3-neck 250 mL flask, a solution of fluoromethyl phenyl sulfone (**1**)[8b] (3.5 g, 20 mmol) in THF (40 mL) was cooled to -60 °C. Diethyl chlorophosphate (3.6 g, 20 mmol) was added followed immediately by 1*M* lithium hexamethyldisilazane (40 mL). After 0.5 h, benzylacetone (**3**) (1.48 g, 10 mmol) in THF (10 mL) was added and the dry-ice bath was removed. After stirring overnight at room temperature, the reaction was quenched with saturated NH_4Cl and the product extracted into CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated to give 11 g crude material. Purification by flash chromatography (200 g silica gel, 1/15 Et_2O/hexane) yielded 1.31 g **4** as the first elutant and 1.48 g **5** for an overall yield of 92%. **4**: colorless oil; ^1H NMR ($CDCl_3$) δ 1.85 (d, 3H, *J* = 4.4 Hz), 2.81-2.97 (m, 4H), 7.23-7.84 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 148.77 (d, $^1J_{F-C}$ = 277.5 Hz), 140.59, 138.83, 134.00, 129.76 (d, $^2J_{F-C}$ = 7.8 Hz), 129.20, 128.55, 128.52, 128.11, 126.77, 34.68 (d, $^3J_{F-H}$ = 3.1 Hz), 32.85, 16.71 (d, $^3J_{F-H}$ = 9.1 Hz); ^{19}F NMR ($CDCl_3$) δ -121.14 (d, *J* = 3.9 Hz); MS (CI/CH_4) m/z 305 (MH^+). Anal. Calcd for $C_{17}C_{17}FO_2S$: C, 67.08, H, 5.63. Found: C, 66.77; H, 5.73. **5**: colorless oil; ^1H NMR ($CDCl_3$) δ 2.16 (d, 3H, *J* = 3.4 Hz), 2.45-2.51 (m, 2H), 2,70-2.75 (m, 2), 7.04-7.88 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 148.55 (d, $^1J_{F-C}$ = 276.7 Hz), 139.97, 139.06, 133.94, 129.44 (d, $^2J_{F-C}$ = 5.9 Hz), 129.27, 129.20, 128.37, 128.15, 127.88, 126.25, 34.08 (d, $^3J_{F-H}$ = 6.7 Hz), 32.87 (d, $^4J_{F-H}$ = 1.9 Hz), 15.57, ^{19}F NMR ($CDCl_3$), δ -121.28 (d, *J* = 3.1 Hz); MS (CI/CH_4) m/z 305 (MH^+). Anal. Calcd for $C_{17}H_{17}FO_2S$: C, 67.08; H, 5.63. Found: C, 66.84; H, 5.81.

(*E*)-2-Methyl-2-(phenylethyl)-1-fluoro-1-(tributylstannyl)ethene (**6**). A mixture of **4** (200 mg, 0.66 mmol), tributyltin hydride (421 mg, 1.45 mmol), AIBN (ca. 10 mg) and benzene (25 mL) was refluxed for 6.5 h and the solution was concentrated. Analysis by ^{19}F NMR showed a major peak (>97%) at -104.44 ppm and a minor (<3%) peak at -105.88 ppm. Purfication by flash chromatography (20 g silica gel/hexane) gave 227 mg (76%) **6** as a colorless oil. ^1H NMR ($CDCl_3$) δ 0.88 (t, 9H, *J* = 7 Hz), 0.94-0.99 (m, 6H), 1.24-1.36 (m, 6H), 1.44-1.54 (m, 6H), 1.79 (d, 3H, *J* = 4.0 Hz), 2.09-2.17 (m, 2H), 2.65-2.70 (m, 2H), 7.14-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 165.72 (d, $^1J_{F-C}$ = 303.4 Hz), 141.80, 130.16, 128.40, 128.30, 125.96, 35.72 (d, $^3J_{F-H}$ = 11.6 Hz), 35.39, (d, $^4J_{F-CH2}$ = 3.1 Hz), 28.96, 27.23, 13.65, 12.64, (d, $^3J_{F-H}$ = 16.6 Hz), 10.31; ^{19}F NMR ($CDCl_3$) δ -104.44 (84%, s), (16%, d, J_{F-Sn} = 282 Hz); MS (CI, CH_4) m/z 435 (MH^+-HF). Anal. Calcd for $C_{23}H_{39}FSn$: C, 60.95; H, 8.67. Found: C, 61.23; H, 9.00.

(*Z*)-1-Fluoro-2-methyl-4-phenyl-1-butene (**7**). A mixture of **6** (454 mg, 1 mmol), 1*M* methanolic sodium methoxide (1.5 mL, 1,5 mmol) and THF (4 mL) was heated at reflux and the progress of the reaction was

monitored by glc. After 12 hr the reaction was cooled to room temp, diluted wiht hexane (10 mL) and washed with water (3x5 mL). The colorless hexane solution was dried ($MgSO_4$), and evaporated to an oil *in vacuo* (25 °C bath temp). Purification by flash chromatography (hexane) gave **7** (105 mg, 64%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.32-7.15 (m, 5H), 6.36 (dm, 1H, J = 86.5 Hz), 2.71 (m, 2H), 2.41 (m, 2H), 1.53 (dd, 3H, J = 4.5 and 1.5 Hz); ^{19}F NMR ($CDCl_3$) δ -135.8 (dm, J = 87 Hz); ^{13}C NMR ($CDCl_3$) δ 143.3 (d, $^1J_{F,C}$ = 249.5 Hz), 141.7, 128.4, 128.3, 125.9, 117.6 (d, $^2J_{F,C}$ = 7.0 Hz), 33.5 (d, $^4J_{F,C}$ = 2.0 Hz), 29.9 (d, $^3J_{F,C}$ = 5.0 Hz), 15.1 (d, $^3J_{F,C}$ = 7.9 Hz); MS (EI, 70ev) m/z, %: 164 (M^+, 15), 91 (100). Anal. Calcd for $C_{11}H_{13}F$: C, 80.45; H, 7.98. Found: C, 80.83; H, 8.15.

(*Z*)-2-Methyl-2-(phenylethyl)-1-fluoro-1-(tributylstannyl)ethene (**8**). Prepared by the same procedure as **6**. ^{19}F NMR analysis of the crude product showed a major peak (>97%) at -105.88 ppm and a minor (<3%) peak at -104.44 ppm. After purification by flash chromatography (hexane), 224 mg (82%) **8** was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 9H, J = 7 Hz, 0.96-1.02 (m, 6H), 1.25-1.37 (m, 6H), 1.45-1.56 (m, 6H), 1.53 (d, 3H, J = 4.2 Hz), 2.43-2.50 (m, 2H), 2.67,-2.74 (m, 2H), 7.13-7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 165.09 (d, $^1J_{F-C}$ = 305.6 Hz), 142.06, 130.12, 128.39, 128.18, 125,69, 34.25, 31.08 (d, $^1J_{F-H}$ = 14.4 Hz), 28.92, 27.18, 17.04 (d, $^3J_{F-H}$ = 12.7 Hz), 13.67, 10.19; ^{19}F NMR ($CDCl_3$) δ -105.88 (84%, s), (16%, d, J_{F-Sn} = 282 Hz); MS (CI/CH_4) m/z 435 (MH^+-HF). Anal. Calcd for $C_{23}H_{39}FSn$: C, 60.95: H, 8.67. Found C, 61.06; H, 8.98.

(*E*)-1-Fluoro-2-methyl-4-phenyl-1-butene (**9**). Prepared by the same procedure as **7** to provide **9** as a colorless oil in 71% yield. ^{1}H NMR ($CDCl_3$) δ 7.32-7.13 (m, 5H), 6.37 (dm, 1H, J = 86.5 Hz), 2.69 (m, 2H), 2.18 (m, 2H), 1.69 (dd, 3H, J = 3.2, 1.5 Hz); ^{19}F NMR ($CDCl_3$) δ -137.0 (dm, J = 87 Hz); ^{13}C NMR ($CDCl_3$) δ 144.0 (d, $^1J_{F,C}$ = 250.5 Hz), 141.5, 128.4, 128.3, 126.0, 117.4 (d, $^2J_{F,C}$ = 6.0 Hz), 34.1 (d, $^4J_{F,C}$ = 3.0 Hz), 33.6 (d, $^3J_{F,C}$ = 7.0 Hz), 12.0 (d, $^3J_{F,C}$ = 6.0 Hz); MS (CI/CH_4, 70 ev) m/z, %: 165 (MH^+, 10), 164 (15), 145 (90), 91 (100).

(*E*)- and (*Z*)-2-(2-Phenylethyl)-1-fluoro-1-(phenylsulfonyl)ethene (**11** and **12**). The reaction was run by the same procedure as for the synthesis of **4** and **5** and the crude reaction mixture contained **11** and **12** in a 2 to 1 ratio by glc. Purification by filtration through a flash silica gel column (1/5 EtOAc/hexane) provided **11** and **12** in quantative yield. The two isomers were separated by flash chromatography (1/10 Et_2O/hexane). **11**: mp 61-63 °C (hexane); ^{1}H NMR δ 2.49-2.61 (m, 2H), 2.72-2.81 (m, 2H), 6.26 (dt, 1H, J = 32 Hz), 7.09-7.88 (m, 5H); ^{19}F NMR δ -128.07 (d, J = 32 Hz); MS (CI/CH_4) m/z 291 (MH^+). Anal. Calcd for $C_{16}H_{15}FO_2S$: C, 66.19; H, 5.21. Found: C, 65.98; H, 5.09. **12**: Colorless oil; ^{1}H NMR δ 2.74-2.83 (m, 2H), 2.92-3.05 (m, 2H), 5.84 (dt, 1H, J = 22 Hz), 7.18-7.84 (m, 5H); ^{19}F NMR δ -116.25 (d, J = 22 Hz); MS (CI/CH_4) m/z 291 (MH^+). Anal. Calcd for $C_{16}H_{15}FO_2S$: C, 66.19; H, 5.21. Found: C, 65.96; H, 5.29.

(*E*)- and (*Z*)-2-(Phenylethyl)-1-(tributylstannyl)-1-fluoroethene (**13** and **14**). A 2 to 1 mixture of **11** and **12** (6.1 g, 21 mmol), tributyltin hydride (12.8g, 44 mmol) and 1,1-azobis(cyclohexanecarbonitrile) (ACN) (200 mg) was added to benzene (200 mL) and heated at 80 °C (bath temp). The progress of the reaction was monitored by GC MS and additional aliquots of ACN were added after 6, 20, and 27 hr. After 36 hr the reaction was evaporated to a colorless oil. ^{19}F NMR ($CDCl_3$) analysis of the oil showed the formation of **13** and **14** in a 3 to 1 ratio. Purification by flash chromatography (1800 mL silica gel, 24 x 10 cm) (hexane) gave 5.3 g (58%) of **13** and 1.7 g (18%) of **14**. Fractions containing **13** (R_f = 0.34, hexane) and **14** (R_f = 0.25, hexane) were visualized by iodine staining on TLC plates. (*E*)-Vinylfluoro sulfone **11** was converted to the vinyl stannane as described above to give a 3/1 *E/Z* mixture of vinyl stannanes **13** and **14** as a colorless oil. In a third experiment, an identical mixture of *E/Z* isomers was obtained from pure (*Z*)-fluoro sulfone **12**. **13**: ^{1}H NMR ($CDCl_3$) δ 0.84-1.02 (m, 15H), 1.26-1.38 (m, 6H), 1.45-1.58 (m, 6H) 2.42-2.53 (m, 2H), 2.60-2.71 (m, 2H), 5.82 (dt, 1H, J = 54 Hz), 7.12-7.33 (m, 5H): ^{19}F NMR δ -103.68 (d, J = 54 Hz, 84%), (dd, J_{Sn-F} = 246 Hz, 16%). **14**: ^{1}H NMR ($CDCl_3$) δ 0.84-1.02 (m, 15H), 1.26-1.38 (m, 6H), 1.45-1.58 (m, 6H), 2.12-2.33 (m, 2H), 2.60-2.71 (m, 2H), 5.93 (dt, 1H, J = 36 Hz), 7.12-7.33 (m, 5H); ^{19}F NMR δ -99.68 (d, J = 37 Hz, 84%), (dd, J_{Sn-F} = 257 Hz, 16%). As the mixture MS (CI/CH_4) m/z 383 (MH^+-Bu). Anal. Calcd for $C_{72}H_{37}FSn$: C, 60.16; H, 8.49. Found: C, 60.18; H, 8.83, for the 3 to 1 mixture of **13** and **14**.

(*Z*)-1-Fluoro-4-phenyl-1-butene (**15**). To a solution of (fluorovinyl)stannane **13** (5.0 g, 11.4 mmol) in dry THF (25 mL) was added 1*M* sodium methoxide in methanol (14 mL, 14 mmol). The solution was heated at 60 °C (bath temp) and the progress of the reaction was monitored by GC MS. After 12 hr., the reaction was partioned between hexane (25 mL) and water (25 mL). The aqueous layer was extracted with additional hexane (25 mL) and the combined organic layers were washed with water (3x25 mL). The organic layer was dried ($MgSO_4$) and concentrated on a rotary evaporator (25 °C bath temp) to give a colorless oil. Purification by flash chromatography (hexane) gave 1.3 g (76%) **15** as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.47 (m, 2H); 2.69 (m, 2H);

4.76 (dm, 1H, J = 43.6 Hz), 6.43 (dm, 1H, J = 85.6 Hz), 7.17-7.33 (m, 5H); ^{19}F NMR ($CDCl_3$) δ -130.8 (dd, J = 43.6, 85.7 Hz); MS (EI) m/z 150 (M^+). HRMS Calcd for $C_{10}H_{11}F$: 150.0845 (M^+). Found: 150.0847.

(*E*)-1-Fluoro-4-phenyl-1-butene (16). (Fluorovinyl)stanne **14** (1.6 g, 3.6 mmol) was treated by the procedure as for the synthesis of **15** to provide the colorless liquid **16** (350 mg, 65%). ^{1}H NMR ($CDCl_3$) δ 2.25 (m, 2H); 2.69 (m, 2H), 5.39 (dm, 1H, J = 26.6 Hz), 6.50 (dd, 1H, J = 11.1, 85.7 Hz), 7.17-7.36 (m, 5); ^{19}F NMR ($CDCl_3$) δ -130.48 (dd, J = 19.2 Hz, 85.7 Hz); MS (EI) m/z 150 (M^+). HRMS Calcd for $C_{10}H_{11}F$: 150.0845 (M^+). Found: 150.0844.

(*E*) and (*Z*)-2-Trimethylsilyl-1-fluoro-1(phenylsulfonyl)ethene (18). To a solution of 18.45 g (106 mmol) fluoromethyl phenyl sulfone[8b] in 400 mL of THF at -78 °C under a nitrogen atmosphere was added 191 mL of a 1.0 *M* solution of LDA followed by 15.3 mL (106 mmol) of diethyl chlorophosphate and the mixture stirred at -78 °C for 1.5 h to provide **2**. In a separate round bottomed flask, a solution of 13.9 mL (159 mmol) oxalyl chloride in 500 mL of CH_2Cl_2 was cooled to -78 °C under a nitrogen atmosphere and treated with 12.8 mL (180 mmol) of dimethyl sulfoxide in 250 mL of CH_2Cl_2 over 20 min. The mixture was stirred for an additional 10 min and to this solution was added 13.9 mL (110 mmol) of trimethylsilylmethanol in 150 mL of CH_2Cl_2 and the mixture stirred for 15 min at -78 °C. Then 55 mL (392 mmol) of triethylamine was added and the mixture stirred at -78 °C for 20 min. To this solution was added the solution of **2** *via* cannula and the mixture stirred at -78 °C for 1 h, allowed to warm to ambient temperature and stirred one additional hour. The reaction was quenched with a saturated aq. ammonium chloride solution. The organic phase was separated, the aqueous phase extracted (3 x $CHCl_3$) and the combined organic phases dried ($MgSO_4$). The crude product was purified by flash chromatography (silica gel, 1/5 ethyl acetate/hexanes) affording 21.1 g (77%) of fluorovinyl sulfone **18** as a 10:3 mixture of *E/Z* isomers used directly in the synthesis of **19**..

(*E*)-2-Trimethylsilyl-1-fluoro-1-(tributylstannyl)ethene (19)[15] To 21.2 g (82 mmol) of fluorovinyl sulfone **18** in 400 ml of toluene under a nitrogen atmosphere was added 670 mg (4.1 mmol) AIBN and 48.5 ml (180 mmol) of tributyltin hydride. This mixture was refluxed for 24 hr, cooled, and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (silica gel, hexane) affording 30.4 g (91%) of fluorovinyl stanane **19** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.85-1.68 (m, 36H); 4.92 (dm, 1H, J = 86.6 Hz); ^{19}F NMR δ -61.4 (d, J = 86.6 Hz). Anal. Calcd for $C_{17}H_{37}FSiSn$: C, 50.14; H, 9.16. Found: C, 50.21; H, 9.25.

2,2-Diphenyl-1-(tributylstannyl)-1-fluoroethene (24). A mixture of 1,1-diphenyl-2-(phenylsulfonyl)-2-fluoroethylene (**23**) (1.2 g, 3.55 mmol), tributyltin hydride (2.1 g, 7.1 mmol), AIBN (50 mg) and benzene (100 mL) was reluxed for 18 h. After cooling and concentration, 5 g colorless oil was obtained. Purification by flash chromatography (350 g silica gel/hexane) gave 1.56 g (92%) **24** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.72-0.78 (t, 9H), 0.81-0 91 (m, 6H), 1.18-1.32 (m, 6H), 1.36-1.95 (m, 6H), 7.17-7.36 (m, 10H); ^{19}F NMR ($CDCl_3$) δ -94.37 (84%, s) (16%, d, J_{Sn-F} = 255 Hz); MS (CI/CH_4) m/z 489 (MH^+). Anal. Calcd for $C_{26}H_{37}FSn$: C, 64.09; H, 7.65. Found: C, 64.46; H, 7.64.

1,1-Diphenyl-2-fluoroethene (25). A mixture of **24** (135 mg, 0.28 mmol) in CH_3OH (10 mL) was treated with 1*M* sodium methoxide in CH_3OH (0.34 mL, 0.34 mmol). The solution was heated at reflux for 16 h. Concentration and subsequent purification by flash chromatography (50 g silica gel/hexane) gave 50 mg (91%) **25** as a colorless oil, identical with an authentic sample.[9] ^{1}H NMR ($CDCl_3$) δ 6.98 (d, 1H, J_{HF} = 81 Hz), 7.21-7.39 (m, 10H); ^{19}F NMR ($CDCl_3$) δ -128.72 (d, J_{HF} = 83.5 Hz); MS (EI) m/z 198 (M^+).

(*Z*)-1-(Deuterofluoromethylene)-2-phenylcyclohexane (27). Fluorovinylstannane **26**[6] (4.8 g, 10 mmol) was dissolved in THF (25 mL), and 1*M* sodium methoxide in methyl alcohol-d_4 (99.5+ atom % D, Aldrich) (25 mL) and heated at reflux under a nitrogen atmosphere. The progress of the reaction was followed by GC and after 24 h, the cooled reaction was poured into water (100 mL). The colorless solution was extracted with hexane (3 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to a colorless oil. Purification by flash chromatography (hexane) gave 1.65 g (87%) of **27**; ^{1}H NMR ($CDCl_3$) δ 1.27-2.02 (m, 7H), 2.37 (d, 1H, J = 13.1 Hz), 4.22 (dd, 1H, J = 2.7, 5.4 Hz), 7.19 (m, 1H), 7.26-7.35 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 141.88 (d, $^1J_{F-C}$ = 250.2 Hz), 141.58, 128.30, 127.52, 125.73, 123.0, 36.11 (d, $^3J_{F-C}$ = 5.2 Hz), 29.74, 27.71 (d, $^4J_{F-C}$ = 2.9 Hz), 25.04 (d, $^3J_{F-C}$ = 6.8 Hz), 21.72; ^{19}F NMR ($CDCl_3$) δ -140.27 (dt, J = 2.8, 13.5 Hz) plus 5% of the peak at -139.64 ppm for the hydrogen analog; MS (CI/CH_4) m/z 192 (MH^+). Anal. Calcd for $C_{13}H_{14}DF$: C, 81.63; H+D, 8.43. Found: C, 81.85; H+D, 8.04.

(*E*)-1-[2-Deoxy-2-[fluoro(phenylsulfonyl)methylene]-3,5-O-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-*D-erythro*-pentofuranosyl]-4-ethoxy-2(1H)-pyrimidinone (**29**) and (*Z*)-1-[2-Deoxy-2-[fluoro(phenylsulfonyl)methylene]-3,5-O-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-*D-erythro*-pentofuranosyl]-4-ethoxy-2(1H)-pyrimidinone (**30**). Under argon, a solution of fluromethyl phenyl sulfone (**1**) (4.1 g, 23.5 mmol) in THF (200 mL) was cooled to -78 °C. Diethyl chlorophosphate (freshly distilled, 3.4 mL, 23.5 mmol) was added *via* syringe followed by slow addition of lithium hexamethyldisilazane (1 *M*, 46 mL, 46 mmol). The progress of formation of the anion of diethyl 1-fluoro-1-phenylsulfonylmethanephosphonate (**2**) was followed by GC by quenching a small aliquot with saturated NH_4Cl/EtOAc. After 15 min, GC showed approximately 80% conversion. The reaction was allowed to warm to 0 °C and a THF (120 mL) solution of oven dried ketone **28**[17] (5.0 g, 9.8 mmol) added. After 2 h at 0 °C, TLC (1/3 EtOAc/hexane) showed no remaining ketone. The reaction was quenched with saturated NH_4Cl, the THF removed under reduced pressure and the product extracted into EtOAc (2 x 200 mL). The solution was dried ($MgSO_4$) and concentrated to give 10.3 g crude product. ^{19}F NMR of the crude product shows a 1 to 6 ratio of **29** to **30**. Flash chromatography (800 g silica gel; 1/3 EtOAc/hexane) gave 5.3 g (81%) **30** eluting first and 560 mg (8.5%) geometric isomer **29** eluting second. **29**: ^1H NMR ($CDCl_3$) δ 1.02-1.15 (m, 28H), 1.33 (t, 3H, J = 7 Hz), 3.94-4.06 (m, 2H), 4.31 (m, 1H), 4.39 (q, 2H, J = 7 Hz), 5.83 (d, 1H, J = 7.5 Hz), 5.86 (m, 1H), 6.80 (m, 1H), 7.22 (d, 1H, J = 7.6 Hz), 7.52-7.99 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 171.47, 154.86, 150.85 (d, $^1J_{F\text{-}C}$ = 300.2 Hz), 143.07, 136.80, 134.82, 130.28 (d, $^2J_{F\text{-}C}$ = 5.6 Hz), 129.37, 128.94, 97.39, 88.31, 86.30, 73.52 (d, $^3J_{F\text{-}C3}$ = 3.4 Hz), 64.46, 63.55, 17.52, 17.48, 17.30, 17.28, 17.20, 17.12, 16.98, 14.06, 13.97, 13.35, 13.32, 13.23; ^{19}F NMR ($CDCl_3$) δ -114.95 (s); MS (CI/CH_4) m/z 669 (MH^+). HRMS Calcd for $C_{30}H_{45}FN_2O_8SSi_2$: 669.2494 (MH^+). Found: 669.2457. **30**: ^1H NMR ($CDCl_3$) δ 0.98-1.10 (m, 28H), 1.37 (t, 3H, J = 7 Hz), 3.94-4.02 (m, 2H), 4.16 (m, 1H), 4.36-4.43 (q, 2, J = 7 Hz), 5.80 (m, 1H), 5.89 (d, 1H, J = 7.4 Hz), 6.47 (m, 1H), 7.45-7.67 (m, 5H), 7.56 (d, 1H, J = 7.5Hz); ^{13}C NMR ($CDCl_3$) δ 172.15, 154.53, 148.50 (d, $^1J_{F\text{-}C}$ = 301.4 Hz), 148.46, 137.56, 134.88, 133.61 (d, $^2J_{F\text{-}C}$ = 9.9 Hz), 129.58, 127.90, 95.39, 88.99, (d, $^3J_{F\text{-}C}$ = 5.0 Hz), 76.06,63.88, 63.29, 17.22, 17.14, 17.08, 17.05, 16.80, 16.76, 16.58, 16.52, 13.88, 13.00, 12.86, 12.38, 12.30; ^{19}F NMR ($CDCl_3$) δ -118.80 (s); MS (CI/isobutane) m/z 669 (MH^+). HRMS Calcd for $C_{30}H_{45}FN_2O_8SSi_2$: 669.2494 (MH^+). Found: 669.2483.

(*E*)-1-[2-Deoxy-2-[fluoro(tributylstannyl)methylene]-3,5-O-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-*D-erythro*-pentofuranosyl]-4-ethoxy-2(1H)-pyrimidinone (**31**). A mixture of **29** (520 mg, 0.78 mmol), tributyltin hydride (0.53 mL, 2.0 mmol), AIBN (10 mg) and benzene (15 mL) was heated at 80 °C for 18 h. TLC (1/5 EtOAc/hexane) showed that no starting material remained and the reaction mixture was concentrated. Analysis by ^{19}F NMR showed the presence of a single isomer (δ -87.74 ppm). Purification by flash chromatography (1/5 EtOAc/hexane) on 60 g silica gel (15 mL fractions collected) and combining fraction 5 and 6 gave 460 mg (72%) **31** as an oil that rapidly crystallized after drying under high vacuum; ^1H NMR ($CDCl_3$) δ 0.89 (t, 9H, J = 7 Hz), 1.05-1.11 (m, 37H), 1.24-1.37 (m, 6H), 1.45-1.56 (m, 6H), 3.74 (m, 1H), 4.08 (m, 1H), 4.23 (m, 1H), 4.43 (q, 2H, J = 7 Hz), 5.06 (m, 1H), 5.80 (d, 1H, J = 7.5 Hz), 6.96 (m, 1H), 7.28 (d, 1H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 176.19 (d, $^1J_{F\text{-}C}$ = 320.8 Hz) 171.20, 155.72, 143.14, 134.75, 96.29, 85.46, 85.07 (d, $^3J_{F\text{-}C}$, = 12.8 Hz) 74.40 (d, $^3J_{F\text{-}C}$, = 11.3 Hz), 64.37, 63.26, 28.86, 27.15, 17.62, 17.51, 17.43, 17.37, 17.31, 17.26, 17.16, 14.63, 14.46, 14.17, 13.68, 13.19, 13.06, 10.38; ^{19}F NMR ($CDCl_3$) δ -89.74 (84%, s), (16%, d, $J_{Sn\text{-}F}$ = 218 Hz); MS m/z (CI/CH_4) 819 (MH^+). HRMS Calcd for $C_{36}H_{67}FN_2O_6Si_2Sn$: 819.3622 ($MH^+$). Found: 819.3690.

(*Z*)-1-[2-Deoxy-2-(fluoromethylene)-β-*D-erythro*-pentofuranosyl]cytosine (**32**). A methanolic (10 mL) solution of **31** (210 mg, 0.26 mmol) was cooled to 0 °C and saturated with NH_3. The tube was sealed and heated overnight at 50 °C. TLC (90/10/1 CH_2Cl_2/MeOH/NH_4OH) showed that no starting material remained. The reaction was concentrated and the residue re-dissolved in MeOH. Solid CsF (600 mg, 3.9 mmol) was added and the solution was stirred at room temperature. After 3 days, ~20% **31** remained and more CsF (100 mg, 0.67 mmol) was added. After another 3 days, the reaction was concentrated and purified by flash chromatography (50 g) (upper layer of 4/1/2 EtOAc/n-PrOH/H_2O). Fractions 5-13 were concentrated to give 82 mg **32** as a viscous oil. The product was repurified on 50 g silica gel to give 43 mg (64%) **32** as an off-white solid, mp 166-168°C; ^1H NMR (DMSO-d_6) δ 3.51 (m, 1H), 3.59-3.68 (m, 2H), 4.67 (m, 1H), 4.86 (t, 1H, J = 5.4 Hz), 5.67 (d, 1H, J = 6.4 Hz), 5.71 (d, 1H, J = 7.6 Hz) 6.75 (m, 1H), 6.88 (dt, 1H, J_{HF} = 80, 2.3 Hz) 7.22 (br d, 2H), 7.45 (d, 1H, J = 7.4 Hz); ^{13}C NMR (DMSO-d_6) δ 165.62, 154.71, 146.72 (d, $^1J_{F\text{-}C}$ = 258.2 Hz), 125.13 (d, $^2J_{F\text{-}C}$ = 3.2 Hz), 94.80, 85.19, 82.07 (d, $^3J_{F\text{-}C}$ = 2.1 Hz), 68.57 (d, $^3J_{F\text{-}C}$ = 6.3 Hz), 60.55; ^{19}F NMR (DMSO-d_6) δ -130.54 (d, J_{HF} = 81 Hz); MS m/z 257 (NEG CI/CH_4). HRMS Calcd for $C_{10}H_{12}FN_3O_4$: 258.0890 (MH^+). Found: 258.0898.

(*Z*)-1-[2-Deoxy-2-[fluoro(tributylstannyl)methylene]-3,5-O-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-*D-erythro*-pentofuranosyl]-4-ethoxy-2(1H)-pyrimidinone (**33**). Under argon, a mixture of **30** (4.6 g, 6.9 mmol), tributyltin hydride (6.0 g, 20.7 mmol), AIBN (400 mg) and benzene (200 mL) was heated

to reflux. After 3 h, TLC (1.5 EtOAc/hexane) showed that no starting material remained. The reaction was concentrated to give 10.6 g crude product; ^{19}F NMR showed the presence of a single isomer at δ - 82.41 ppm. The product was purified by flash chromatography (700 g silica gel; 1/5 EtOAc/hexane). After concentration of the fractions containing **33** and drying under high vacuum, 4.39 g **33** (78%) was obtained as a viscous colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 9H, J = 7 Hz), 0.95-1.11 (m, 28H), 1.21-1.47 (m, 18H), 1.35 (t, 3H, J = 7 Hz), 3.81-3.91 (m, 2H), 4.00 (m, 1H), 4.44 (q, 2H, J = 7 Hz), 5.19 (m, 1H), 5.85 (d, 1H, J = 7.4 Hz), 6.75 (m, 1H), 7.42 (d, 1H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 176.88 (d, $^1J_{F-C}$ = 326.1 Hz), 171.55, 156.20, 143.51, 133.61 (d, $^2J_{F-C}$ = 2.8 Hz), 96.97, 84.60, 84.16, (d, $^3J_{F-C'}$ = 16.5 Hz), 72.46 (d, $^3J_{F-C'}$ = 6.6 Hz), 63.29, 62.05, 28.55, 26.83, 17.16, 17.08, 17.03, 26,70, 16.58, 16.50, 16.46, 13.84, 13.26, 12.92, 12.64, 12.25, 9.74; ^{19}F NMR ($CDCl_3$) δ -82.41 (82.4%, s) (16%, d, J_{Sn-F} = 218 Hz); MS (CI/CH_4), m/z 819 (MH^+). HRMS Calcd for $C_{36}H_{67}FN_2O_6Si_2Sn$: 819.3622 ($MH^+$). Found: 819.3632.

(E)-1-[2-Deoxy-2-(fluoromethylene)-β-*D-erythro*-pentofuranosyl]cytosine (**34**). A mixture of **33** (14.9 g, 18 mmol), CsF (13.7 g, 90 mmol) in CH_3OH (200 mL) was cooled to 0 °C and saturated with NH_3. The vessel was sealed and then heated at 50 °C for 24 h. After cooling and concentration, **34** was purified by flash chromatography (1/1 EtOAc hexane) to give 4.7 g white solid. Recrystallization (EtOAc, CH_3OH added to point of solution) gave 2.5 g (53%) **33** as white crystals, mp 166-168 °C (foamed and turned yellow); ^{1}H NMR (DMSO-d_6) δ 3.48-3.62 (m, 2H), 3.75 (m, 1H), 4.75 (m, 1H), 4.95 (t, 1H, J = 5.6 Hz), 5.65 (d, 1H, J = 6.9 Hz), 5.73 (d, 1H, J = 7.6 Hz), 6.66 (m, 1H) 6.77 (dt, 1H, J = 81.3, 2.0 Hz), 7.25 (br s, 1H), 7.54 (d, 1H, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 165.58, 155.08, 147.48 (d, $^1J_{F-C}$ = 259.7 Hz), 141.73, 125.39 (d, $^2J_{F-C}$ = 8.8 Hz), 94.94, 86.14, 82.25 (d, $^3J_{F-C}$ = 10.2 Hz), 68.05, 60.89; ^{19}F NMR (DMSO-d_6) δ -130.05 (d, J = 80.9 Hz); MS (NEG CI/CH_4) 257 (M^+). Anal. Calcd for $C_{10}H_{12}FN_3O_4$: C, 46.70; H, 4.70; N, 16.34. Found: C, 46.62; H, 4.75; N, 16.23.

(E)-1-[2-Deoxy-2-(fluoromethylene)-3,5-0-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-*D-erythro*-pentofuranosyl]cytosine (**35**). In a Carius tube was placed **33** (4.0 g, 4.89 mmol) in CH_3OH (30 mL) and the solution cooled to 0°C. After saturation with NH_3, the tube was sealed and warmed to room temperature and then heated to 50°C. After 18 h, TLC (90/10/1 $CHCl_3$/CH_3OH/NH_4OH) showed the disappearance of **33**. Purification by flash chromatography (500 g silica gel) (90/7/0.7 $CHCl_3$/CH_3OH/NH_4OH) gave 2.2 g (90%) crude **35** as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.03-1.11 (m, 28H), 3.91 (m, 1H), 4.04-4.08 (m, 2H), 4.98-5.04 (br s, 2H), 5.69 (d, 1H, J = 7.5 Hz), 6.80 (dt, 1H, J = 80.8, 1.9 Hz), 6.85 (m, 1H), 6.97 (m, 1H), 7.71 (d, 1H, J = 7.5 Hz); ^{19}F NMR δ -130.04 (d, 1H, J = 80.4 Hz) major and -131.26 (d, J = 82.3 Hz) minor from partial cleavage of TIPDSi group; MS (CI/CH_4), m/z 500 (MH^+). HRMS Calcd for $C_{22}H_{39}N_3O_5Si_2F$: 500.2412 (MH^+). Found: 500.2404.

(S)-(E) and (Z)-4-[2-Fluoro-2(phenylsulfonyl)ethenyl]-2,2-dimethyl-3-oxazolidine-carboxylic acid 1,1-dimethylethyl ester (**37**). To a solution of fluoromethylphenyl sulfone (**1**) (12.79 g, 72.92 mmol) in dry THF (180 mL) under a nitrogen atmosphere at -78 °C was added, dropwise, diethyl chlorophosphate (10.76 mL, 72.92 mmol). The mixture was stirred at -78 °C for 10 min and then a solution of lithium bis(trimethylsilyl)amide (145.8 mL of 1.0 *M* solution in THF, 145.8 mmol) was added, followed by a solution of 1,1-dimethylethyl (*D*)-4-formyl-2,2-dimethyl-3-oxazolidine-carboxylate (**36**)[22] (8.36 g, 36.4 mmol) in THF (20 mL), with the temperature maintained at -78°C. The reaction mixture was allowed to warm to room temperature and was stirred overnight. Saturated ammonium chloride solution was added, and the reaction mixture was extracted with diethyl ether. The combined extracts were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give a viscous, brown residue. Flash chromatography on silica gel (10% ethyl acetate in hexane) gave *E* isomer of **37** (7.46 g, 53%) R_f 0.72 (ethyl acetate:hexane, 1:1) and *Z* isomer of **37** (5.33 g, 40%) R_f 0.77 (ethyl acetate:hexane, 1:1) as white solids. (*E*)-**37**: mp 128-129 °C; ^{1}H NMR (DMSO-d_6, 55 °C) δ 1.20 (s, 9H), δ 1.44 (s, 3H), δ 1.53 (s, 3H) δ 3.85 (dd, 1H, J = 2.4 and 9.4 Hz), δ 4.09 (dd, 1H, J = 6.2 and 9.4 Hz), δ 4.63-4.70 (m, 1H), δ 6.23 (dd, 1H, J = 9.3 and 32.1 Hz), δ 7.70-7.98 (m, 5H). ^{19}F NMR ($CDCl_3$) δ conformational isomer 1 (80%): -126.9 (d, J = 32 Hz); conformational isomer 2 (20%): -125.7 (d, J = 30 Hz); MS (CI/CH_4) m/z 386 (MH^+). Anal. Calcd for $C_{18}H_{24}FNO_5S$: C, 56.09; H, 6.28; N, 3.63. Found: C, 56.19; H, 6.49; N, 3.86. (*Z*)-**37**: mp 105-106 °C; ^{1}H NMR (DMSO-d_6, 75 °C) δ 1.37 (s, 9H), 1.50 (s, 3H), 1.55 (s, 3H), 3.82 (ddd, 1H, J = 0.7, 3.5 and 9.3 Hz), 4.23 (ddd, 1H, J = 1.8, 6.6 and 9.3 Hz), 5.26 (br m, 1H), 6.25 (dd, 1H, J = 8.8 and 21.6 Hz), 7.70-8.04 (m, 5H). ^{19}F NMR ($CDCl_3$), δ conformational isomer 1 (50%): -117.4 (d, J = 20 Hz); conformational isomer 2 (50%): -118.2 (d, J = 20 Hz); MS (CI/CH_4) m/z 386 (MH^+). Anal. Calcd for $C_{18}H_{24}FNO_5S$: C, 56.09; H, 6.28; N, 3.63. Found: C, 56.31; H, 6.42; N, 3.45.

(*S*)-(*E*)-and(*Z*)-4-[2-Fluoro-2-(tributylstannyl)ethenyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid 1,1-dimethylethylester (**38**) and (**39**). A mixture of the two isomers of **37** (15.34 g, 39.80 mmol), tributyltin hydride (21.5 mL, 79.6 mmol) and a catalytic amount of 2, 2'-azobis(2-methylpropionitrile) in benzene (400 mL) was refluxed under a nitrogen atmosphere and the reaction was monitored by TLC (ethyl acetate:hexane, 1:9). After 3 h, additional tributyltin hydride (21.5 mL, 79.6 mmol) was added, and reflux continued for an additional 2 h, at which time TLC indicated the reaction to be complete. The reaction mixture was concentrated under reduced pressure to give a colorless viscous liquid, which was chromatographed on silica gel eluting with 1% ethyl acetate in hexane to afford 2.41 g (11%) of *Z* isomer **39**, R_f 0.81 (ethyl acetate:hexane, 1:9) and 12.68 g (60%) of *E* isomer **38**, R_f 0.71 (ethyl acetate:hexane, 1:9) as colorless viscous liquids. **38**: ^{1}H NMR (DMSO-d_6) δ 0.85 (t, 9H), 0.95-1.41 (m, 27H), 1.48-1.64 (m, 6H), 3.60 (dd, 1H, *J* = 2.2 and 9.0 Hz), 4.02 (dd, 1H, *J* = 6.1 and 8.9 Hz), 4.73-4.82 (m, 1H), 4.94 (dd, 1H, *J* = 8.8 and 53.0 Hz). ^{19}F NMR (DMSO-d_6) δ conformational isomer 1 (95%): for ^{118}Sn: -102.4 (d, *J* = 53 Hz); for ^{117}Sn and ^{119}Sn: -102.4 (dd, *J* = 53 Hz and 182 Hz); conformational isomer 2 (5%): for ^{118}Sn: -101.0 (d, J = 53.0 Hz); for ^{117}Sn and ^{119}Sn peaks undetectable; MS (CI/CH_4) m/z 536 (MH^+). Anal. Calcd for $C_{24}H_{46}FNO_3Sn$: C, 53.95; H. 8.68; N, 2.62. Found: C, 54.10; H, 8.97; N, 2.33. **39**: ^{1}H NMR (DMSO-d_6) δ 0.85 (t, 9H), 1.01-1.45 (m, 27H), 1.46-1.63 (m, 6H), 3.62 (d, 1H, *J* = 9.3 Hz), 4.02 (t, 1H, *J* = 7.2 and 7.6 Hz), 4.11 (br s, 1H), 5.81 (dd, 1H, *J* = 10.2 and 36.0 Hz). ^{19}F NMR (DMSO-d_6) δ -95.4 (d, *J* = 36 Hz); MS (CI/CH_4) m/z 536 (MH^+). Anal. Calcd for $C_{24}H_{46}FNO_3Sn$: C, 53.95; H, 8.68; N, 2.62. Found: C, 54.15; H, 8.92; N, 2.65.

(*S*)-(*Z*)-4-(2-Fluoroethenyl)-2,2-dimethyl-3-oxazolidinecarboxylic acid 1,1-dimethylethyl ester (**40**). To a solution of sodium methoxide in MeOH (0.12 g of Na, 5.2 mmol, in 20 mL of MeOH) was added **38** (2.63 g, 4.92 mmol) in 10 mL of MeOH. The mixture was heated to 50 °C under a nitrogen atmosphere for 2 h and concentrated under reduced pressure. The residue was chromatographed on silica gel (10% ethyl acetate in hexane) to give 1.10 g (88%) of **40** as a colorless viscous liquid: ^{1}H NMR (DMSO-d_6) δ 1.40 (m, 12H), 1.50 (s, 3H), 3.66 (dd, 1H, *J* = 2.9 and 8.8 Hz), 4.05 (dd, 1H, *J* = 7.0 and 9.0 Hz), 4.66-4.75 (m, 1H), 4.95 (ddd, 1H, *J* = 4.3, 8.7 and 43.1 Hz), 6.75 (dd, 1H, *J* = 3.9 and 85.2 Hz). ^{19}F NMR (DMSO-d_6) δ conformational isomer 1 (70%): -129.6 (dd, *J* = 42 and 84 Hz); conformational isomer 2 (30%): -128.5 (dd, *J* = 43 and 84 Hz); MS (CI/CH_4) m/z 246 (MH^+). Anal Calcd for $C_{12}H_{20}FNO_3$: C, 58.76; H, 8.22; N, 5.71. Found: C, 58.75; H, 8.33; N, 5.43.

Conversion of (S)-**40** to (S)-**41**: A mixture of **40** (1.46 g, 5.95 mmol), *p*-toluenesulfonic acid monohydrate (0.11 g, 0.59 mmol) and MeOH (20 mL) was heated to 60 °C under a nitrogen atmosphere and the reaction was monitored by TLC (ethyl acetate:hexane, 1:9). After 48 h, the reaction mixture was concentrated and purified by flash chromatography (5% MeOH in CH_2Cl_2) to give 0.61 g (50%) of **41** as a white solid: mp 53-55 °C; ^{1}H NMR (DMSO-d_6) δ 1.37 (s, 9H), 3.22-3.40 (m, 2H), 4.30-4.42 (m, 1H), 4.74 (m, 1H, OH), 4.82 (ddd, 1H, *J* = 5.0, 10.0, and 45.0 Hz), 6.70 (dd, 1H, *J* = 5.0 and 85.0 Hz), 6.77 (br d, 1H). ^{19}F NMR (DMSO-d_6) δ -127.3 (dd, *J* = 45 and 85 Hz); MS (CI/CH_4) m/z 206 (MH^+). Anal. Calcd for $C_9H_{16}FNO_3$: C, 52.67; H, 7.86; N, 6.82. Found: C, 52.67; H, 7.93; N, 6.90.

(*S*)-(*Z*)-2-[[1,1-Dimethylethoxylcarbonyl]amino]-4-fluoro-3-butenoic acid (**42**). A mixture of **41** (0.1 g, 0.49 mmol) and pyridinium dichromate (1.88 g, 5 mmol) in acetic acid (25 mL) was stirred at room temperature for 4 h. The reaction mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and extracted with saturated $NaHCO_3$ (3 x 50 mL). The combined $NaHCO_3$ layers were taken to pH = 2 with 1 *N* HCl and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **42** (0.03 g, 28%) as a colorless viscous liquid, which was homogeneous by TLC. The product was used in the following reaction without further purification: MS (CI/CH_4) m/z 220 (MH^+).

(*S*)-(*Z*)-2-Amino-4-fluoro-3-butenoic acid hydrochloride (**43**). Boc-protected compound **42** (0.080 g, 0.36 mmol) was dissolved in a solution of anhydrous 4 *N* HCl/dioxane (1 mL). The reaction mixture was stirred at room temperature for 1 h, and the solvent was removed under reduced pressure. Diethyl ether was added to the clear syrup and the product precipitated as a white solid. The product was chromatographed on an ion exchange column (3.5 x 15 cm, AG 500W x 8, hydrogen form) using water (300 mL) followed by 1 *M* NH_4OH (500 mL) as eluents. Lyophilization of the appropriate fractions collected afforded 0.042 g (75%) of **43** as a white solid, MP 202-204 °C (dec) (darkens at 180 °C), $[\alpha]_D^{25}$ = +108 (*C* 0.976, H_2O): ^{1}H NMR (D_2O) δ 4.82 (d, 1H, *J* = 9.7 Hz), 5.18 (ddd, 1H, *J* = 4.4, 9.4, and 38.8 Hz), 6.90 (dd, 1H, *J* = 4.5 and 82.0 Hz). ^{19}F NMR (D_2O) δ -120.5 (dd, *J* = 39 and 81 Hz); HRMS Calcd for $C_4H_7FNO_2$: 120.1032 (MH+). Found: 120.0461. Anal Calcd for $C_4H_7ClFNO_2$: C, 30.89; H, 4.545, N, 9.00. Found: C, 30.80; H, 4.39; N, 9.16.

Isomers **44**, **45**, **46** and **47** were prepared in similar manner and have the following spectral and physical properties. S-(E)-4-(2-Fluoroethenyl)-2,2-dimethyl-3-oxazolidinecarbo-xylic acid 1,1-dimethylethyl ester (**44**). Starting with 1.88 g (3.52 mmol) of **38** 0.61 g (71%) of **44** was isolated as a colorless viscous liquid; ^{1}H NMR (DMSO-d_6) δ 1.40 (m, 12H), 1.50 (s, 3H), 3.70 (dd, 1H, J = 2.1 and 8.9 Hz), 3.95-4.05 (ddd, 1H, J = 2.0, 5.9, and 9.0 Hz), 4.28 (brs, 1H), 5.42 (ddd, 1H, J = 9.0, 11.0, and 19.0 Hz), 6.88 (dd, 1H, J = 11.0 and 84.0 Hz). ^{19}F NMR (DMSO-d_6) δ conformational isomer 1 (70%): -129.6 (dd, J = 19 and 84 Hz); conformational isomer 2 (30%): -129.3 (dd, J = 19 and 84 Hz); MS (CI/CH_4) m/z 246 (MH^+). Anal. Calcd for $C_{12}H_{20}FNO_3$: C, 58.76; H, 8.22; H, 5.71. Found: C, 58.72; H, 8.51; N, 5.54.

Conversion of **44** to **45**. Starting with 0.32 g (1.30 mmol) of **44** , 0.09 g (34%) of **45** was isolated as a colorless viscous liquid; ^{1}H NMR (DMSO-d_6) δ 1.39 (s, 9H), 3.23-3.40 (m, 2H), 3.85-3.97 (m, 1H), 4.76 (t, 1H), 5.33 (ddd, 1H, J = 9.0, 11.0, and 20.0 Hz), 6.80 (br d, 1H), 6.81 (dd, 1H, J = 11.0 and 86.0 Hz). ^{19}F NMR (DMSO-d_6) δ -129.2 (dd, J = 20 and 86 Hz); MS (CI/CH_4) m/z 206 (MH^+). Anal. Calcd for $C_9H_{16}FNO_3$: C, 52.67; H, 7.86; N, 6.82. Found: C, 52.31; H, 7.84; N, 6.80.

(*S*)-(*E*)-2-[[1,1-Dimethylethoxylcarbonyllamino]-4-fluoro-3-butenoic acid (**46**). Starting with 55 mg (0.27 mmol) of **45**, 25.4 mg (41%) of **46** was isolated as a colorless viscous liquid; MS (CI/CH_4) m/z 220 (MH^+).

(*S*)-(*E*)-2-Amino-4-fluoro-3-butenoic acid hydrochloride (**47**). Starting with 25.4 mg (0.11 mmol) of **46**, 13.3 mg (78%) of **47** was isolated as a white solid; $[\alpha]_0^{20}$ = +111 (*C* 0.04, H_2O); ^{1}H NMR (CD_3OD) δ 4.03 (d, 1H, J = 9.8 Hz), 5.50 (ddd, 1H, J = 9.8, 11.3, and 16.6 Hz), 6.89 (ddd, 1H, J = 0.5, 11.1 and 81.7 Hz). ^{19}F NMR (CD_3OD) δ -121.0 (dd, J = 17 and 82 Hz). MS exact mass Calcd for $C_4H_7FNO_2$: 120.1032 (MH^+). Found: 120.0461.

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