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New Fluorine-containing Building Blocks from Trifluoroethanol. 1.

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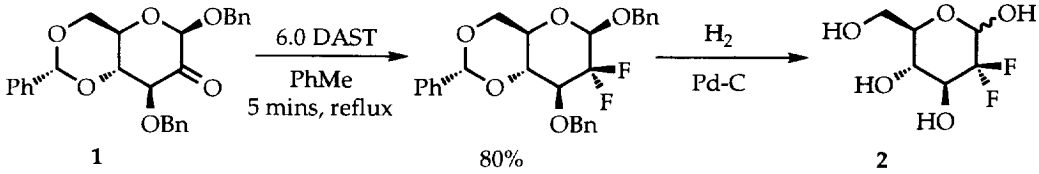
Abstract: A new fluorine containing acyl anion equivalent 1,1-difluoro-2-lithio-2-[(methoxyethoxy)methoxy]ethene **12** has been prepared from trifluoroethanol and trapped with a number of electrophiles in good yield. Effective electrophiles included Group(IV) halides and carbonyl compounds. Attempts to alkylate using iodomethane were unsuccessful.

The synthesis of highly-functionalised molecules containing a limited number of fluorine atoms remains a significant challenge to synthetic organic chemists. A well-tried approach involves the transformation of suitable functional groups by fluorinating agents.[1] For example, a difluoromethylene (CF_2) group can be introduced by the transformation of a ketonic carbonyl group directly by the use of DAST (diethylaminosulfur trifluoride) as shown in **Scheme 1**.[2]



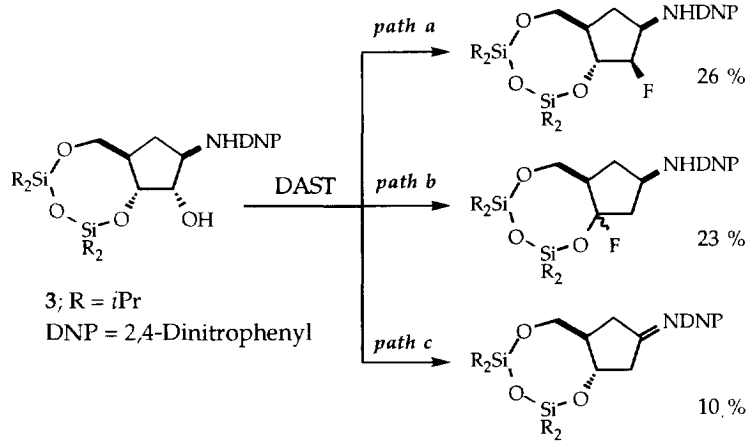
1 80% **2**

Scheme 1

More recent developments have involved the conversions of dithioketals, hydrazones and oximes to CF_2-containing compounds.[3] The fluorination approach is ideal when a ketonic precursor to the CF_2 compound is readily available. In carbohydrate chemistry, protection and functional group manipulation chemistry has advanced to the stage where almost any ketone should be available.

The DAST reagent is compatible with many of the commonly-used protecting groups for the hydroxyl function, and reacts with densely functionalised aliphatic ketones, unlike many of the newer reagents. For example, Castillón and co-workers described a recent synthesis of 2-deoxy-2,2-difluoro-D-glucose **2** in which an efficient fluorination of ulose **1** with DAST was used to install the CF_2 centre (**Scheme 1**).[4] Typically though, the optimised reaction used DAST in excess (6 equivalents) to obtain a good yield of the protected difluorosugar.[5] The orientation of functional groups *adjacent* to the carbonyl group also exerts an influence on the course of the difluorination reaction; the reaction only proceeds cleanly when the substituents are present in

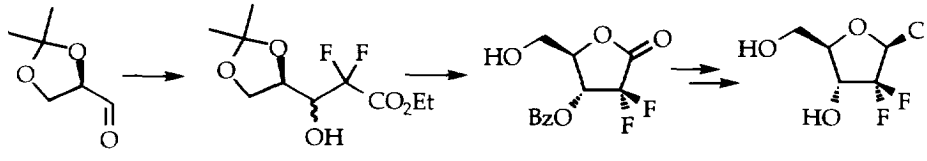
a pseudoequatorial orientation, imposing a significant limitation upon the methodology.[6] In addition, in complex non-carbohydrate molecules, the installation of the appropriate (additional) carbonyl precursor to the CF_2 group may be far from straightforward. There are additional limitations imposed by the nature of the mechanism of the DAST fluorination reaction. Fluorination with DAST and related species occurs *via* pathways in which the development of positive charge on carbon is well advanced. High electron demand or carbenium ion character leads to the activation of pathways involving elimination, rearrangement, 1,2-hydride shifts and neighbouring group participation. The tranformation of **3**, depicted in **Scheme 2** illustrates a number of these pathways.



Scheme 2

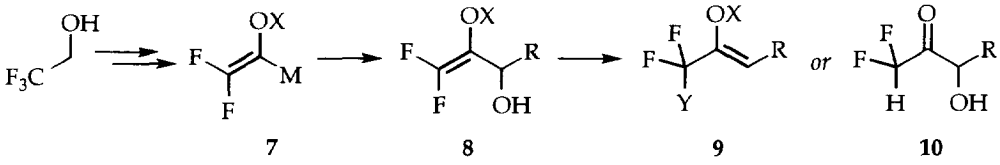
The two significant side reactions involved elimination (*path b*) and 1,2-hydride shift (*path c*). Both competed effectively with the desired fluorination (*path a*). The protection regime chosen for the amino group was critical. More conventional carbamate protecting groups (BOC, Z, *etc.*) led to the formation of products arising from neighbouring group participation.[7] Together with the high cost of the reagent (and the necessity to employ a large excess), these factors have imposed a significant barrier to the large scale use of DAST.

An alternative strategy uses fluorine-containing building blocks. The Lilly synthesis of the anti-tumour compound Gemcitabine **6** (C = cytosine), outlined in **Scheme 3**, illustrates the approach.[8]



Scheme 3

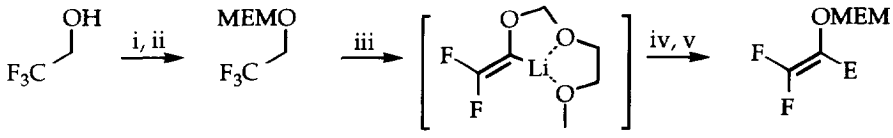
The introduction of the fluorine atoms is achieved *via* carbon-carbon bond formation to a manipulable fluorine-containing starting material or "building block". The key step in the sequence involves the Reformatsky reaction between ethyl bromodifluoroacetate and protected glyceraldehyde which afforded adduct **4** as a mixture of diastereoisomers. Benzoylation of the secondary hydroxyl group, hydrolysis of the ketal and cyclisation afforded a mixture of lactones, from which **5** crystallised in high purity. Nucleoside analogue **6** was elaborated using standard procedures. Indeed, the Reformatsky reagent prepared from ethyl bromodifluoroacetate has been used to prepare a range of biologically-interesting compounds[9] including inhibitors of Renin,[10] Interleukin-1β converting enzyme,[11] human Leukocyte Elastase[12] and an analogue of arginine.[13] Of the two strategies, the building block approach is potentially more versatile. However, for that potential to be realised to the full, general synthetic methods that allow the elaboration of readily-available fluorine-containing starting materials must be developed.[14] A general building block approach to compounds containing a CF_2 group would be required to address targets in which the fluorine-bearing carbon was located in a range of molecular environments. We envisaged a general solution to the problem based on commercially available and inexpensive trifluoroethanol starting material. **Scheme 4** outlines the strategy.



Scheme 4

The whole strategy pivots around metallated difluoroenol derivative **7**; we chose to exploit the well known[15] ability of the MEM group to form a chelate structure including a lithium cation to stabilise our metallated difluoroenol derivative against elimination of lithium fluoride.[16] Trapping **7** with an aldehyde would afford difluoroallylic alcohol[17] **8** with synthetic potential.[18] Allylic transposition *via* a [3,3]-Claisen or [2,3]-Wittig rearrangement[19] would allow us to locate the CF_2 group within a mid-chain position in **9**. Alternatively, removal of the MEM group would release the carbonyl function latent in **9** leading to chain-end difluoroketone **10**.

We now wish to report in full,[20] our studies concerning the generation of a metallated difluoroenol derivative, and its reaction with electrophiles. **Scheme 5** depicts the typical reaction sequence. Acetal **11** was prepared by the slow addition of a THF solution of trifluoroethanol to a suspension of sodium hydride in THF. Alkoxide formation was complete within one hour at 0 °C. The addition of commercial MEM chloride as a solution in THF followed by vigorous stirring of the thick suspension overnight and aqueous work-up afforded the acetal in good yield (80 %). The base of choice for generating the organometallic reagent **12** was LDA.[21] Slow addition of the acetal to a cold (-78 °C) solution of LDA (2 equivalents) in THF resulted in an exothermic reaction.



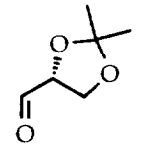
11 **12** **13**; E = H

Reagents and Conditions: i, NaH, THF, 0 °C; ii, MEM-Cl; iii, 2.0 LDA, THF, inverse addition, -78 °C, 30 minutes; iv, 1.1 E^+, -78 °C, 2 hours; v, warm to -30 °C then NH_4Cl/MeOH.

Scheme 5

Slow addition was essential to achieve control of the exotherm. Metallated species **12** was stable at -78 °C but decomposed rapidly at -65 °C or above, leading to the formation of black intractable material. The stability of **12** resembles that displayed by other metallated fluoroalkene derivatives described by the groups of Normant, Nakai, and Alcock.[16] The detailed mechanism of the reaction is unknown though we suspect that dehydrofluorination occurred *via* an E2-mechanism which appeared to determine the rate of the whole sequence. Treatment of **11** with one equivalent of LDA, followed by the addition of methanolic ammonium chloride resulted in the formation of difluoroenol acetal **13** in poor yield, with the recovery of starting material, implying that metallation of **13**, once formed, is rapid with respect to its formation.[22]

A range of electrophiles reacted with **12**. **Table 1** shows the scope of the reaction and the yields of products **13-27**. Quenching a solution of **12** with methanolic ammonium chloride allowed the isolation of volatile difluoroenol acetal **13** in good yield. Silicon and tin electrophiles reacted efficiently.[23] A wide range of carbonyl electrophiles afforded good yields of allylic alcohol products. With aldehydes, alkyl substitution at the α-carbon led to no loss in yield. Unreactive aldehydes such as anisaldehyde were trapped efficiently. Clean, high yielding 1,2-addition occurred with acrolein.



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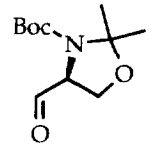

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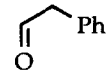

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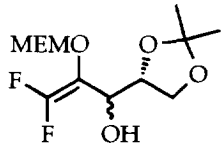

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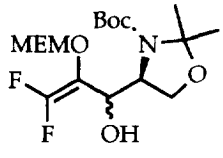

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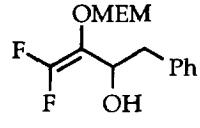

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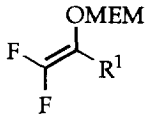
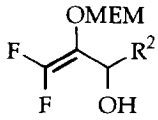
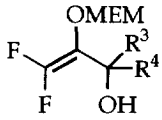
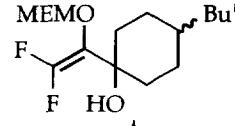
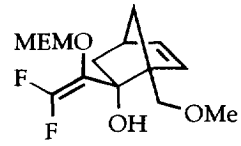
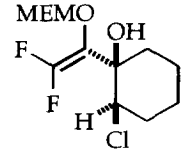
Table 1. Reactions of **12** with Electrophiles

Electrophile	Product		(Yield, %)
$NH_4Cl/MeOH$		**13**; $R^1 = H$	(88)
Me_3SiCl		**14**; $R^1 = SiMe_3$	(79)
Bu_3SnCl		**15**; $R^1 = SnBu_3$	(70)
Formaldehyde		**16**; $R^2 = H$	(61)
Propanal		**17**; $R^2 = CH_2CH_3$	(83)
2-Methylpropanal		**18**; $R^2 = CH(CH_3)_2$	(68)
Trimethylacetaldehyde		**19**; $R^2 = C(CH_3)_3$	(74)
Propenal		**20**; $R^2 = CH{=}CH_2$	(94)
Benzaldehyde		**21**; $R^2 = C_6H_5$	(67)
4-Methoxybenzaldehyde		**22**; $R^2 = C_6H_4OMe$	(74)
Propan-2-one		**23**; $R^3 = R^4 = CH_3$	(68)
Pentan-3-one		**24**; $R^3 = R^4 = CH_2CH_3$	(79)
4-(*t*Butyl)cyclohexanone	 **25**		(50)
1-(Methoxymethyl)-5-norbornen-2-one	 **26**		(56)
2-Chlorocyclohexanone	 **27**		(44)

However, aldehydes **28** and **29** with an α-heteroatom (oxygen or nitrogen-based) substituent afforded low yields of adducts (**30** and **31** respectively) as mixtures of diastereoisomers.[24] Phenylacetaldehyde **32**, an electrophile notorious for the ease with which it forms the enolate conjugate base, reacted with **12** to form a complex mixture of products. Signals arising from the presence of allylic alcohol **33** were observed in the ^{19}F and ^{1}H NMR spectra, but the alcohol could not be obtained in a sufficiently pure state to allow a rigorous characterisation. Clearly, transmetallation of the lithio-species is required for the successful trapping of more complex and demanding electrophiles.[25] Ketones were acceptable electrophiles but the yields were generally lower, reflecting the lower reactivity of the more substituted carbonyl derivatives. However, even with the more hindered electrophiles, nucleophilic attack occurred more rapidly than proton abstraction. Enol acetal **13** was not observed in significant quantities in the ^{19}F NMR spectra of crude product mixtures. It follows that **12** is a well-behaved nucleophile towards simple carbonyl compounds.

Vinyllithium reagents with and without alkoxy substituents at the α-position are known to react efficiently with alkylating agents.[26] However, all attempts to react **12** with iodomethane were unsuccessful. No reaction occurred at low temperature (-78 °C) and allowing the reaction mixture to warm to -30 °C led to decomposition. This result was not entirely unexpected; only one of the metalled fluoroalkenes in the literature has been alkylated.[27] The low reactivity of **12** and related species is probably due to the deactivating electron-withdrawing effect of the two fluorine-atom substituents.

We now have access to a range of allylic alcohols which are useful substrates for further transformation. Allylic transposition by sigmatropic rearrangement allows the CF_2-group to be located mid-chain.[19,28,29] We are now exploring routes to carbocycles containing a CF_2-group based on a rearrangement/cyclisation strategy.

In conclusion, we have shown that trifluoroethanol can function as a precursor to a range of difluoroallylic alcohols and difluoroenol derivatives. The elaboration of these materials to more complex molecules forms the subject of ongoing studies.

Acknowledgements

The authors wish to thank the EPSRC, Keele University, ICI Chemicals and Polymers, Zeneca Specialties Strategic Research Fund and the Royal Society for financial support.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AC-300 (300.13 and 75.47 MHz respectively) and Bruker AMX-400 (400.14 and 100.6 MHz respectively) spectrometers. All spectra were recorded relative to tetramethylsilane as the internal standard. ^{19}F-NMR spectra were recorded on JEOL GX-90 (89.70 MHz) or Bruker AMX-400 (376.45 MHz) spectrometers relative to chlorotrifluoromethane as the internal standard. ^{13}C NMR spectra were recorded using the JMOD pulse sequence unless otherwise stated. Mass spectra were recorded on a Kratos MS-80 mass spectrometer with a DS-55 data system or a Kratos MS-580 RF mass

spectrometer. Chemical ionisation (CI^+) methods used ammonia as the carrier gas. Microanalyses were performed on a Perkin Elmer 240 Elemental Analyser. Fluorine analysis could not be obtained locally. For TLC, precoated aluminium-backed silica gel plates were supplied by E. Merck, A.G. Darmstadt, Germany. (Silica gel 60 F_{254}, thickness 0.2 mm). Anisaldehyde staining was employed for visualisation, unless otherwise stated. Column chromatography was performed using silica gel (E. Merck A. G. Kieselgel 60, Art. 9385). Column fractions were collected and monitored by thin layer chromatography.

Gas chromatographic analyses were carried out on a Pye Unicam series 304 chromatograph, fitted with a Pye Unicam computing integrator or on a Carlo-Erba 8000 series chromatograph. The chromatograph was fitted with a wall-coated fused silica capillary column, type CP-SIL-19 CB (50 m). Infra red spectra were obtained from a Perkin Elmer 1600 series FTIR spectrophotometer, in the region 4000-625 cm^{-1}. The samples were run as films.

Tetrahydrofuran was dried by refluxing with sodium metal and benzophenone under dry nitrogen, until a deep purple colour persisted. The solvent was then collected by syringe as required. MEM chloride was purchased from the Aldrich Chemical Company and used without further purification. Trifluoroethanol was purchased from Fluorochem. All electrophiles were purchased from the Aldrich Chemical Company and distilled before use, or freshly prepared by literature procedures.

Products **13-15** could be stored for extended periods in the freezer. However, the stabilities of the allylic alcohol products were variable and some decomposed upon storage producing HF. All products were purified to >98% purity by Kugelrohr distillation or flash column chromatography and analysed immediately. In some cases, product instability prevented satisfactory microanalyses from being obtained.

Preparation of acetal (**11**). 1,1,1-Trifluoroethanol (34.5 ml, 47.4 g, 0.474 mol) in dry THF (45 ml) was added dropwise over 1 hour to sodium hydride (18.7 g at 60 % dispersion from which the oil had been removed with toluene) in dry THF (45 ml) at 0 °C. The olive green suspension was stirred for 1 hour, then MEMCl (71.2 ml, 0.568 mol assuming 90 % purity) in dry THF (75 ml) was added dropwise over 90 minutes at 0 °C. The white suspension was allowed to warm to room temperature, and stirred overnight. Cautious addition of water (450 ml) and extractive workup with diethyl ether (3 x 200 ml) followed. The combined ether extracts were washed with water (2 x 250 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The *acetal* **11** (71.2 g, 80 %) was isolated as a colourless liquid, b.p. 110 °C/100 mmHg; (Found: C, 38.60; H, 6.02. Calc. for $C_6H_{11}F_3O_3$: C, 38.30; H, 5.89 %); ν_{max} ($CHCl_3$)/cm^{-1} 3422 ; δ_H(300 MHz; $CDCl_3$) 4.70 (2H, *s*, OCH_2O), 3.80 (2H, *q*, $^3J_{H\text{-}F}$ 9.0, CF_3CH_2O), 3.67-3.62 (2H, *m*, $OCH_2CH_2OCH_3$), 3.50-3.44 (2H, *m*, $OCH_2CH_2OCH_3$), 3.30 (3H, *s*, OCH_3); δ_F(90 MHz; $CDCl_3$) -77.4 (3F, *t*, $^3J_{H\text{-}F}$ 9.0); δ_C(300 MHz; $CDCl_3$) 123.9 (*q*, $^1J_{C\text{-}F}$ 277.8), 95.4, 71.4, 67.3, 64.6 (*q*, $^2J_{C\text{-}F}$ 34.6), 58.6; *m/z* 206 (100, $[M+NH_4]^+$), 189 (20, $[M+H]^+$), 188 (1 %, M^+), 89 (90, $CH_2OCH_2CH_2OCH_3^+$).

Preparation of (**13**). In a typical procedure, acetal **11** (0.94 g, 5.0 mmol) was added slowly to a stirred solution of LDA (generated from slow addition of *n*-butyllithium (7.0 ml of a 1.5 M

solution in hexane) to diisopropylamine (1.3 ml, 10.5 mmol) in dry THF (5.0 ml)) at -78 °C. The dark orange suspension was stirred at -78 °C for half an hour then treated with methanolic ammonium chloride (5.0 ml). The mixture was allowed to warm to room temperature and poured into water (50 ml). The mixture was extracted with diethyl ether (3 x 50 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated cautiously *in vacuo* (not less that 100 mmHg). Kugelrohr distillation afforded *alkene* **13** (0.73 g, 88 %) as a colourless oil, b.p. 70-72 °C/20 mmHg; (Found: C, 42.71; H, 5.73. Calc. for $C_6H_{10}F_2O_3$: C, 42.86; H, 5.99 %); δ_H(300 MHz; $CDCl_3$) 5.82 (1H, *dd*, $^3J_{H\text{-}Ftrans}$ 16.0, $^3J_{H\text{-}Fcis}$ 3.0, CF_2=CH(OMEM)), 4.82 (2H, *s*, OCH_2O), 3.75-3.71 (2H, *m*, $OCH_2CH_2OCH_3$), 3.57-3.52 (2H, *m*, $OCH_2CH_2OCH_3$), 3.37 (3H, *s*, OCH_3); δ_F(90 MHz; $CDCl_3$) -100.6 (1F, *dd*, $^2J_{F\text{-}F}$ 76.3, $^3J_{H\text{-}Ftrans}$ 16.0, $^3J_{H\text{-}Fcis}$ 3.0), -119.7 (1F, *d*, $^2J_{F\text{-}F}$ 76.3); δ_C(300 MHz; $CDCl_3$) 155.4 (*dd*, $^1J_{C\text{-}F}$ 287.8, 275.6), 105.3 (*dd*, $^2J_{C\text{-}F}$ 15.8, 15.4), 96.1, 71.5, 67.8, 58.9; *m/z* 186 (35 %, $[M+NH_4]^+$), 169 (5, $[M+H]^+$), 89 (95, $OCH_2OCH_2CH_2OCH_3^+$), 59 (100, $CH_2CH_2OCH_3^+$).

Preparation of (**14**). As for **13** but trimethylsilyl chloride (0.75 ml, 6.0 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (5 mmol). The mixture was allowed to warm to -30 °C over 2 hours then quenched with aqueous ammonium chloride (10 ml).[30] Work-up in the usual way followed by Kugelrohr distillation afforded *vinyl silane* **14** (0.95 g, 79 %) as a colourless oil, b.p. 87-89 °C/11 mmHg; (Found: C, 45.04; H, 7.68. Calc. for $C_9H_{18}F_2O_3Si$: C, 44.98; H, 7.55 %); δ_H(300 MHz; $CDCl_3$) 4.77 (2H, *s*, OCH_2O), 3.79-3.74 (2H, *m* , $OCH_2CH_2OCH_3$), 3.55-3.51 (2H, *m*, $OCH_2CH_2OCH_3$), 3.36 (3H, *s*, OCH_3), 0.16 (9H, *s*, 3 x $Si(CH_3)_3$); δ_F(90 MHz; $CDCl_3$) -82.3 (1F, *d*, $^2J_{F\text{-}F}$ 51.9), -119.7 (1F, *d*, $^2J_{F\text{-}F}$ 51.9); δ_C(300 MHz; $CDCl_3$) 161.2 (*dd*, $^1J_{C\text{-}F}$ 312.7, 282.3), 110.3 (*dd*, $^2J_{C\text{-}F}$ 16.3, 15.7), 96.9, 71.6, 68.0, 58.9, -1.8; *m/z* 258 (73, $[M+NH_4]^+$), 241 (22, $[M+H]^+$), 240 (0.2 %, M^+), 89 (100, $OCH_2OCH_2CH_2OCH_3$), 59 (97, $CH_2CH_2OCH_3^+$).

Preparation of (**15**). As for **13** but tributyltin chloride (1.95 g, 6.0 mmol) in THF (2.0 ml) was added to a cold (-78 °C) solution of the organometallic reagent (5 mmol). The mixture was allowed to warm to -30 °C over 2 hours then quenched with aqueous ammonium chloride (10 ml). Work-up in the usual way followed by filtration of the oily product through a short column of alumina (Brockmann, Activity 1) with toluene as eluant afforded *stannane* **15** (1.59 g, 70 %) as a colourless oil; (Found: C, 47.61; H, 7.68. Calc. for $C_{18}H_{36}F_2O_3Sn$: C, 47.29; H, 7.94 %); δ_H(300 MHz; $CDCl_3$) 4.73 (2H, *s*, OCH_2O), 3.76-3.72 (2H, *m*, $OCH_2CH_2OCH_3$), 3.55-3.51 (2H, *m*, $OCH_2CH_2OCH_3$), 3.37 (3H, *s*, OCH_3), 1.60-0.90 (27H, *envelope*, 3 x $CH_2CH_2CH_2CH_3$); δ_F(90 MHz; $CDCl_3$) -85.6 (1F, *d*, $^2J_{F\text{-}F}$ 64.1), -110.1 (1F, *d*, $^2J_{F\text{-}F}$ 64.1); δ_C(300 MHz; $CDCl_3$) 159.7 (*dd*, $^1J_{C\text{-}F}$ 317.1, 267.2), 116.3 (*dd*, $^2J_{C\text{-}F}$ 15.8, 15.4), 96.1, 71.6, 67.7, 58.9, 28.7, 27.1, 13.5, 10.2; *m/z* 458 (0.5 %, $[M+H]^+$), 89 (57, $OCH_2OCH_2CH_2OCH_3^+$).

Preparation of difluoroallylic alcohols (**16-31**).

Preparation of (**16**). As for **6** but an approximately 0.6 M solution of monomeric formaldehyde[31] (8.86 ml, 5.32 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (2.66 mmol). The reaction mixture was allowed to warm to room temperature overnight. Work-up

in the usual way followed by Kugelrohr distillation afforded *alcohol* **16** (0.32 g, 61%) as a colourless oil, b.p. 85-90 °C/0.1 mmHg; (Found: C, 42.58; H, 6.22. Calc. for $C_7H_{12}F_2O_4$: C, 42.43; H, 6.10 %); $\nu_{max.}$ (Film)/ cm^{-1} 3422, 1759, 1644; δ_H (300 MHz; $CDCl_3$) 4.86 (2H, *s*, OCH_2O), 4.10 (1H, *d*, one half of an AB quartet, $^2J_{Ha\text{-}Hb}$ 2.5, OCH_aH_bOH), 4.09 (1H, *d*, one half of an AB quartet, $^2J_{Ha\text{-}Hb}$ 2.5, OCH_aH_bOH), 3.80-3.73 (2H, *m*, $OCH_2CH_2OCH_3$), 3.53-3.47 (2H, *m*, $OCH_2CH_2OCH_3$), 3.30 (3H, *s*, OCH_3), OH not observed; δ_F (90 MHz; $CDCl_3$) -111.3 (1F, *d*, $^2J_{F\text{-}F}$ 61.0), -101.2 (1F, *d*, $^2J_{F\text{-}F}$ 61.0); δ_C (300 MHz; $CDCl_3$) 154.5 (*dd*, $^1J_{C\text{-}F}$ 291.6, 284.1), 116.6 (*dd*, $^2J_{C\text{-}F}$ 39.0, 11.4), 96.4, 71.4, 67.9, 58.8, 56.6; m/z 216 (92% $[M+NH_4]^+$), 89 (100, $CH_2OCH_2CH_2OCH_3^+$), 59 (41, $CH_2CH_2OCH_3^+$); HRMS calculated for $C_7H_{16}F_2NO_4$ 216.10474, found 216.10484.

Preparation of (**17**). As for **13** but propanal (64 ml, 0.6 mol) was added to a cold (-78 °C) solution of the organometallic reagent (0.3 mol). The mixture was allowed to warm up to -30 °C. Work-up in the usual way and Kugelrohr distillation afforded *alcohol* **17** (56.2 g, 83 %) as a clear oil, b.p. 75 °C/0.05 mmHg; (Found: C, 48.05; H, 7.20. Calc. for $C_9H_{16}F_2O_4$: C, 47.78; H, 7.13 %); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3434, 1752; δ_H(300 MHz; $CDCl_3$) 4.96 (1H, *d*, one half of an AB quartet, $^2J_{Ha\text{-}Hb}$ 7.6, OCH_aH_bO), 4.83 (1H, *d*, one half of an AB quartet, $^2J_{Ha\text{-}Hb}$ 7.6, OCH_aH_bO), 4.15-4.05 (1H, *m*, CH(OH)Et), 3.96-3.70 (2H, *m*, $OCH_2CH_2OCH_3$), 3.60-3.45 (3H, *m*, $OCH_2CH_2OCH_3$ + OH), 3.25 (3H, *s*, OCH_3), 1.78-1.52 (2H, *m*, CH_2Me), 0.85 (3H, *t*, $^3J_{H\text{-}H}$ 7.0, CH_3); δ_F(90 MHz; $CDCl_3$) -100.9 (1F, *d*, $^2J_{F\text{-}F}$ 61.0), -110.9 (1F, *d*, $^2J_{F\text{-}F}$ 61.0); δ_C(300 MHz; $CDCl_3$) 154.8 (*dd*, $^1J_{C\text{-}F}$ 291.9, 285.5), 117.8 (*dd*, $^2J_{C\text{-}F}$ 47.9, 47.8), 97.9, 71.4, 68.6, 68.4, 58.9, 27.0, 9.9; *m/z* 244 (17 %, $[M+NH_4]^+$), 226 (5, M^+), 209 (76, $[M\text{-}OH]^+$), 89 (100, $CH_2OCH_2CH_2OCH_3^+$).

Preparation of (**18**). As for **13** but *iso*butyraldehyde (0.109 ml, 1.2 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (1.0 mmol). Work-up in the usual way and Kugelrohr distillation afforded *alcohol* **18** (0.16 g, 68 %) as a clear oil, b.p. 85 °C/0.1 mmHg; (Found: C, 50.04; H, 7.68. Calc. for $C_{10}H_{18}F_2O_4$: C, 49.99; H, 7.55 %); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3410, 1636; δ_H(300 MHz; $CDCl_3$) 4.98 (1H, *d*, one half of an AB quartet, $^2J_{HaHb}$, 7.0, OCH_aH_bO), 4.83 (1H, *d*, one half of an AB quartet, $^2J_{HaHb}$, 7.0, OCH_aH_bO), 3.98-3.89 (1H, *m*, $CCH(OH)CH(Me)_2$), 3.79-3.69 (2H, *m*, $OCH_2CH_2OCH_3$), 3.61-3.50 (2H, *m*, $OCH_2CH_2OCH_3$), 3.38 (3H, *s*, OCH_3), 3.45 (1H, *br. s*, OH), 1.93-1.80 (1H, *m*, $CH(OH)CH(Me)_2$), 1.02 (3H, *d*, $^3J_{H\text{-}H}$ 7.5, $(CH_3)CH(CH_3)$), 0.70 (3H, *d*, $^3J_{H\text{-}H}$ 7.5, $(CH_3)CH(CH_3)$); δ_F(90 MHz; $CDCl_3$) -101.1 (1F, *d*, $^2J_{F\text{-}F}$ 64.1), -111.0 (1F, *d*, $^2J_{F\text{-}F}$ 64.1); δ_C(300 MHz; $CDCl_3$) 155.1 (*dd*, $^1J_{C\text{-}F}$ 291.8, 285.0), 119.6 (*dd*, $^2J_{C\text{-}F}$ 34.4, 10.7), 98.0, 73.0, 71.4, 68.5, 59.0, 31.6, 19.1, 18.7; *m/z* 258 (4 %, $[M+NH_4]^+$), 241 (2, $[M+H]^+$), 240 (1, M^+), 223 (50, $[M\text{-}OH]^+$), 59 (100, $CH_2CH_2OCH_3^+$).

Preparation of (**19**):- As for **13** but trimethylacetaldehyde (0.65 ml, 6 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (5 mmol). Work-up in the usual way followed by flash column chromatography afforded *alcohol* **19** (0.94 g, 74 %) as a clear oil, R_f (0.35, 1:5 EtOAc/Hexane); (Found: C, 51.6; H, 7.97. Calc. for $C_{11}H_{20}F_2O_4$: C, 51.9; H 7.93 %); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3454, 1748; δ_H(300 MHz; $CDCl_3$) 4.98 (1H, *d*, one half of an AB quartet, $^2J_{HaHb}$ 7.0, OCH_aH_bO), 4.79 (1H, *d*, one half of an AB quartet, $^2J_{HaHb}$ 7.0, OCH_aH_bO), 3.94-3.85 (1H, *br. s*,

CH(OH)C(Me)$_3$), 3.90-3.67 (2H, *m*, OC**H$_2$**CH$_2$OCH$_3$), 3.55-3.50 (2H, *m*, OCH$_2$C**H$_2$**OCH$_3$), 3.30 (3H, *s*, OCH$_3$), 3.20 (1H, *br. s*, OH), 0.90 (9H, *s*, 3 x CH$_3$); δ_F(90 MHz; CDCl$_3$) -101.4 (1F, *d*, $^2J_{F\text{-}F}$ 67.1), -109.3 (1F, *d*, $^2J_{F\text{-}F}$ 67.1); δ_C(300 MHz; CDCl$_3$) 155.1 (*dd*, $^1J_{C\text{-}F}$ 291.3, 285.1), 117.6 (*dd*, $^2J_{C\text{-}F}$ 35.1, 9.9), 98.5, 73.9, 71.6, 69.0, 59.0, 36.1, 26.2; *m/z* 272 (2 %, [M+NH$_4$]$^+$), 255 (1, [M+H]$^+$), 254 (0.5, M$^+$), 237 (10, [M-OH]$^+$), 59 (100, CH$_2$CH$_2$OCH$_3^+$).

Preparation of (**20**). As for **13** but propen-2-al (2.0 ml, 30 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (25 mmol). Work-up in the usual way followed by flash column chromatography afforded *alcohol* **20** (5.25 g, 94 %), R$_f$ (0.35, 1:5 EtOAc/Hexane); $\nu_{max.}$ (CHCl$_3$)/cm^{-1} 3418, 1752; δ_H(300 MHz; CDCl$_3$) 5.92 (1H, *dddd*, $^3J_{H\text{-}Hd}$ 15.0, $^3J_{H\text{-}Hc}$ 10.0, $^3J_{H\text{-}H}$ 5.0, $^5J_{H\text{-}F}$ 1.0, CH(OH)C**H**=CH$_c$H$_d$), 5.37 (1H, *dt*, $^3J_{trans}$ 15.0, $^2J_{Hc\text{-}Hd}$ 2.5, $^4J_{H\text{-}Hd}$ 2.5, CH=CH$_c$**H$_d$**), 5.22 (1H, *dt*, $^3J_{cis}$10.0, $^2J_{Hc\text{-}Hd}$ 2.5, $^4J_{H\text{-}Hc}$ 2.5, CH=C**H$_c$**H$_d$), 4.95 (1H, *d*, one half of an AB quartet, $^2J_{HaHb}$ 7.0, OC**H$_a$**H$_b$O), 4.85 (1H, *d*, one half of an AB quartet, $^2J_{HaHb}$ 7.0, OCH$_a$**H$_b$**O), 4.80 (1H, *br. s*, OH), 3.96-3.70 (2H, *m*, OC**H$_2$**CH$_2$OCH$_3$), 3.69-3.62 (1H, *m*, C**H**(OH)CH=CH$_2$), 3.56 (2H, *t*, $^3J_{H\text{-}H}$ 5.0, OCH$_2$C**H$_2$**OCH$_3$), 3.40 (3 H, *s*, OCH$_3$); δ_F(90 MHz; CDCl$_3$) -100.4 (1F, *d*, $^2J_{F\text{-}F}$ 61.0), -109.6 (1F, *d*, $^2J_{F\text{-}F}$ 61.0); δ_C(300 MHz; CDCl$_3$) 154.6 (*dd*, $^1J_{C\text{-}F}$ 292.4, 286.7), 136.5, 117.6 (*dd*, $^2J_{C\text{-}F}$ 35.1, 9.9), 116.2, 97.9, 71.4, 68.5, 67.7, 59.0; *m/z* 242 (10, [M+NH$_4$]$^+$), 224 (2 %, M$^+$), 207 (30, [M-OH]$^+$), 59 (100, CH$_2$CH$_2$OCH$_3^+$). A satisfactory microanalysis could not be obtained for this compound, which decomposed on storage at room temperature.

Preparation of (**21**). As for **13** but benzaldehyde (1.22 ml, 12 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (10 mmol). Work-up in the usual way afforded *alcohol* **21** as a colourless oil (1.89 g, 67 %), R$_f$ (0.50, 1:5 EtOAc/hexane); (Found: C, 57.08; H, 6.14. Calc. for C$_{13}$H$_{16}$F$_2$O$_4$: C, 56.93; H, 5.88 %); $\nu_{max.}$ (CHCl$_3$)/cm^{-1} 3449; δ_H(300 MHz; CDCl$_3$) 7.50-7.20 (5H, *m*, 5 x aromatic H), 5.40 (1H, *s*, CH(OH)Ar), 4.91 (1H, *d*, one half of an AB quartet, $^2J_{HaHb}$ 7.0, OC**H$_a$**H$_b$O), 4.77 (1H, *d*, one half of an AB quartet, $^2J_{HaHb}$ 7.0, OCH$_a$**H$_b$**O), 4.10 (1H, *br. s*, OH), 3.73-3.57 (2H, *m*, OC**H$_2$**CH$_2$OCH$_3$), 3.46 (2H, *t*, $^3J_{H\text{-}H}$ 3.5, OCH$_2$C**H$_2$**OCH$_3$), 3.30 (3H, *s*, OCH$_3$); δ_F(90 MHz; CDCl$_3$) -100.7 (1F, *d*, $^2J_{F\text{-}F}$ 61.0), -109.5 (1F, *d*, $^2J_{F\text{-}F}$ 61.0); δ_C(300 MHz; CDCl$_3$) 154.9 (*dd*, $J_{C\text{-}F}$ 291.5, 284.2), 137.3, 129.2, 128.3, 126.5, 117.9 (*dd*, $J_{C\text{-}F}$ 35.9, 10.5), 98.1, 71.4, 68.5, 68.4, 58.9; *m/z* 292 (5 %, [M+NH$_4$]$^+$), 275 (2, [M+H]$^+$), 274 (0.5, M$^+$), 59 (100, CH$_2$CH$_2$OCH$_3^+$).

Preparation of (**22**). As for **13** but 4-methoxybenzaldehyde (1.46 ml, 12 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (10 mmol). Work-up in the usual way followed by flash column chromatography afforded *alcohol* **22** (2.31 g, 76 %) as a clear oil, R$_f$ (0.45, 1:5 EtOAc/hexane); (Found: C, 54.97; H, 6.09. Calc. for C$_{14}$H$_{18}$F$_2$O$_5$: C, 55.26; H, 5.96 %); $\nu_{max.}$ (CHCl$_3$)/cm^{-1} 3446; δ_H(300 MHz; CDCl$_3$) 7.30 (2H, *d*, $^3J_{H\text{-}H}$ 8.5, 2 x aromatic H), 6.85 (2H, *d*, $^3J_{H\text{-}H}$ 8.5, 2 x aromatic H), 5.40 (1H, *s*, CH(OH)ArOMe), 4.91 (1H, *d*, one half of an AB quartet, $^2J_{HaHb}$ 7.0, OC**H$_a$**H$_b$O), 4.77 (1H, *d*, one half of an AB quartet, $^2J_{HaHb}$ 7.0, OCH$_a$**H$_b$**O), 4.10 (1H, *br. s*, OH), 3.75 (3H, *s*, ArOCH$_3$), 3.73-3.57 (2H, *m*, OC**H$_2$**CH$_2$OCH$_3$), 3.46 (2H, *t*, $^3J_{H\text{-}H}$ 3.5, OCH$_2$C**H$_2$**OCH$_3$), 3.30 (3H, *s*, OCH$_3$); δ_F(90 MHz; CDCl$_3$) -100.3 (1F, *d*, $^2J_{F\text{-}F}$ 61.0), -109.6 (1F, *d*, $^2J_{F\text{-}$

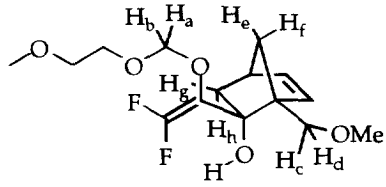
$_F$ 61.0); δ_C(300 MHz; $CDCl_3$) 154.9 (*dd*, J_{C-F} 292.6, 286.2), 132.4, 131.9, 129.9, 127.1, 117.9 (*dd*, J_{C-F} 35.9, 10.5), 97.8, 71.3, 68.5, 68.1, 58.9, 55.6; *m/z* 322 (1 %, $[M+NH_4]^+$), 89 (89, $CH_2OCH_2CH_2OCH_3^+$).

Preparation of (**23**). As for **13** but acetone (7.8 ml, 106.0 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (10.6 mmol).[32] The reaction mixture was allowed to warm to room temperature overnight. Work-up in the usual way followed by Kugelrohr distillation afforded *alcohol* **23** (1.63 g, 68%) as a pale yellow oil, b.p. 65-70 °C/0.05 mmHg; $\nu_{max.}$ (Film)/ cm^{-1} 3450, 1740, 1655; δ_H (300 MHz; $CDCl_3$) 4.90 (2H, *s*, OCH_2O), 3.86-3.81 (2H, *m*, $OCH_2CH_2OCH_3$), 3.57-3.52 (2H, *m*, $OCH_2CH_2OCH_3$), 3.51 (1H, *br. s*, OH), 3.35 (3H, *s*, OCH_3), 1.37 (6H, *d*, $^4J_{H-H}$ 3.2, $C(OH)(CH_3)_2$); δ_F (90 MHz; $CDCl_3$) -104.0 (1F, *d*, $^2J_{F-F}$ 70.2), -99.5 (1F, *d*, $^2J_{F-F}$ 70.2); δ_C (300 MHz; $CDCl_3$) 154.2 (*t*,$^1J_{C-F}$ 288.4), 122.5 (*dd*, $^2J_{C-F}$ 32.6, 11.3), 99.0, 71.5, 69.4, 68.9, 58.9, 27.7; m/z 244 (5% $[M+NH_4]^+$), 227 (2, $[M+H]^+$), 209 (8, $[M-OH]^+$), 89 (47, $CH_2OCH_2CH_2OCH_3^+$), 59 (86, $CH_2CH_2OCH_3^+$); HRMS calculated for $C_9H_{20}F_2NO_4$ 244.13604, found 244.13476. The acetone adduct decomposed at room temperature; satisfactory microanalysis could not be obtained.

Preparation of (**24**). As for **13** but pentan-3-one (1.21 ml, 12 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (10 mmol). Work-up in the usual way and Kugelrohr distillation afforded *alcohol* **24** (2.02 g, 79 %) as a clear oil, b.p. 80 °C/0.04 mmHg; (Found: C, 52.0; H, 7.94. Calc for $C_{11}H_{20}F_2O_4$: C, 51.9; H, 7.93 %); ν_{max} ($CHCl_3$)/cm^{-1} 3472, 1738; δ_H(300 MHz; $CDCl_3$) 4.85 (2H, *s*, OCH_2O), 3.83-3.76 (2H, *m*, $OCH_2CH_2OCH_3$), 3.53-3.47 (2H, *m*, $OCH_2CH_2OCH_3$), 3.25 (3H, *s*, OCH_3), 3.00 (1H, *br. s*, OH), 1.65-1.55 (4H, *m*, 2 x CH_2Me), 0.80 (6H, *t*, $^3J_{H-H}$ 7.5, 2 x CH_3); δ_F(90 MHz; $CDCl_3$) -99.2 (1F, *d*, $^2J_{F-F}$ 70.2), -105.6 (1F, *d*, $^2J_{F-F}$ 70.2); δ_C(300 MHz; $CDCl_3$) 155.1 (*t*, $^1J_{C-F}$ 290.5, 287.5), 119.6 (*dd*, $^2J_{C-F}$ 34.4, 10.9), 98.8, 75.0, 71.7, 69.1, 59.0, 30.8, 7.9; *m/z* 272 (4, $[M+NH_4]^+$) , 255 (3, $[M+H]^+$), 254 (10 %, M^+), 59 (100, $CH_2CH_2OCH_3^+$).

Preparation of (**25**). As for **13** but 4-*tert*-butylcyclohexanone (0.93 g, 6 mmol) in THF (1 ml) was added to a cold (-78 °C) solution of the organometallic reagent (5 mmol). Work-up in the usual way and flash column chromatography afforded an inseparable mixture of the *cis* and *trans* isomers of *alcohol* **25** (0.81 g, 50 %) as a clear oil, R_f (0.40, 1:5 EtOAc/hexane); (Found: C, 59.99; H, 8.77. Calc. for $C_{16}H_{28}F_2O_4$: C, 59.61; H, 8.75 %); *Isomer 1* (60 %) δ_H(300 MHz; $CDCl_3$) 4.92 (2H, *s*, OCH_2O), 3.89-3.84 (2H, *m*, $OCH_2CH_2OCH_3$), 3.60-3.55 (2H, *m*, $OCH_2CH_2OCH_3$), 3.39 (3H, *s*, OCH_3), 3.10 (1H, *br. s*, OH), 2.30-1.00 (8H, *envelope*, 4 x CH_2), 0.90 (9H, *s*, 3 x CH_3); δ_F(90 MHz; $CDCl_3$) -99.3 (1F, *d*, $^2J_{F-F}$ 64.1), -104.3 (1F, *d*, $^2J_{F-F}$ 64.1); δ_C(300 MHz; $CDCl_3$) 154.5 (*dd*, $^1J_{C-F}$ 290.6, 288.5), 123.2 (*dd*, $^2J_{C-F}$ 35.1, 10.8), 98.9, 71.5, 70.0, 68.8, 58.9, 47.5, 35.2, 27.5, 21.9; *Isomer 2* (40 %) δ_H(300 MHz; $CDCl_3$) 4.95 (2H, *s*, OCH_2O), 3.89-3.84 (2H, *m*, OCH_2CH_2O), 3.66 (1H, *br. s*, OH), 3.60-3.55 (2H, *m*, OCH_2CH_2O), 3.37 (3H, *s*, OCH_3), 2.30-1.40 (8H, *m*, 4 x CH_2), 0.83 (9H, *s*, 3 x CH_3); δ_F(90 MHz; $CDCl_3$) -96.4 (1F, *d*, $^2J_{F-F}$ 61.0), -102.9 (1F, *d*, $^2J_{F-F}$ 61.0); δ_C(300 MHz; $CDCl_3$) 155.5 (*dd*, $^1J_{C-F}$ 290.6, 288.5), 119.9 (*dd*, $^2J_{C-F}$ 35.1, 10.8), 98.9, 72.6, 71.4, 68.8, 58.9, 36.5, 32.2, 27.5, 24.5; *m/z* 322 (2 %, M^+), 59 (100, $CH_2CH_2OCH_3^+$).

Preparation of (**26**). As for **13** but 1-methoxymethyl-5-norbornen-2-one[33] (0.72 ml, 5 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (5 mmol). Work-up in the usual way and flash column chromatography afforded *alcohol* **26** (0.99 g, 56 %) as a clear oil, R_f (0.45, 1:5 EtOAc/hexane); (Found: C, 56.13; H, 7.00. Calc. for $C_{15}H_{22}F_2O_5$: C, 56.24; H, 6.92 %); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3525, 1728; δ_H(300 MHz; $CDCl_3$) 6.42-6.38 (1H, *m*, CCH=C**H**CH(CH_2)), 6.10 (1H, *d*, $^3J_{H\text{-}H}$ 5.0, C**C**H=CHCH(CH_2)), 5.00 (1H, *d*, one half of an AB quartet, $^2J_{HaHb}$ 6.0, OC$\mathbf{H_a}$$\mathbf{H_b}$O), 4.93 (1H, *d*, one half of an AB quartet, $^2J_{HaHb}$ 6.0, OC$\mathbf{H_a}$$\mathbf{H_b}$O), 3.88-3.75 (2H, *m*, OC$\mathbf{H_2}$$CH_2OCH_3$), 3.68



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(1H, *d*, one half of an AB quartet, $^2J_{HcHd}$ 9.0, CC$\mathbf{H_c}$$\mathbf{H_d}$OMe), 3.58 (1H, *d*, one half of an AB quartet, $^2J_{HcHd}$ 9.0, CC$\mathbf{H_c}$$\mathbf{H_d}$OMe), 3.55 (2H, *t*, $^3J_{H\text{-}H}$ 4.0, OC$\mathbf{H_2}$$CH_2OCH_3$), 3.30 (3H, *s*, OCH_3), 3.29 (3H, *s*, OCH_3), 3.10 (1H, *br. s*, OH), 2.77 (1H, *br. s*, bridgehead CH), 2.45 (1H, *dd*, $^2J_{He\text{-}Hf}$ 12.0, $^3J_{He\text{-}H}$ 4.0, CCH=CHCH(C$\mathbf{H_e}$$\mathbf{H_f}$)), 1.55 (1H, *br. d*, $^2J_{Hg\text{-}Hh}$ 9.0, CHC$\mathbf{H_g}$$\mathbf{H_h}$), 1.45-1.35 (1H, *m*, CHC$\mathbf{H_g}$$\mathbf{H_h}$), 1.35-1.25 (1H, *m*, CCH=CHCH(C$\mathbf{H_e}$$\mathbf{H_f}$)); δ_F(90 MHz; $CDCl_3$) -95.0 (1F, *d*, $^2J_{F\text{-}F}$ 58.0), -110.5 (1F, *d*, $^2J_{F\text{-}F}$ 58.0); δ_C(300 MHz; $CDCl_3$) 155.8 (*dd*, $^1J_{C\text{-}F}$ 290.5, 286.6), 140.0, 135.2, 119.9 (*dd*, $^2J_{C\text{-}F}$ 24.3, 13.0), 99.1, 81.1, 72.9, 71.6, 69.1, 62.7, 59.6, 59.3, 48.6, 41.5, 41.2; *m/z* 320 (1 %, M^+), 303 (90, $[M\text{-}OH]^+$), 59 (100, $CH_2CH_2OCH_3^+$).

Preparation of (**27**). As for **13** but 2-chlorocyclohexanone[34] (264 mg, 2 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (2 mmol). Work-up in the usual way followed by flash column chromatography afforded *alcohol* **27** (0.13 g, 44 %) as a clear oil; δ_H(300 MHz; $CDCl_3$) 4.95 (2H, *s*, OCH_2O), 3.87-3.83 (2H, *m*, OC$\mathbf{H_2}$$CH_2OCH_3$), 3.60 (2H, *m*, OCH_2C$\mathbf{H_2}$$OCH_3$), 3.38 (3H, *s*, OCH_3), 2.92 (1H, *br. s*, OH), 2.80-0.80 (9H, *envelope*, $C_6\mathbf{H_9}$); δ_F(90 MHz; $CDCl_3$) -97.2 (1F, *d*, $^2J_{F\text{-}F}$ 71.7), -104.4 (1F, *d*, $^2J_{F\text{-}F}$ 71.7); δ_C(300 MHz; $CDCl_3$) 155.2 (*dd*, $^1J_{C\text{-}F}$ 290.4, 283.3), 120.0 (*dd*, $^2J_{C\text{-}F}$ 37.9, 36.8), 98.7, 77.5, 73.7, 71.6, 65.2, 59.0, 36.4, 31.9, 25.5, 20.0; *m/z* 318 (4, $[M+NH_4]^+$), 301 (3, $[M+H]^+$), 300 (10 %, M^+), 59 (100, $CH_2CH_2OCH_3^+$). Satisfactory microanalysis could not be obtained for this compound.

Preparation of (**30**). As for **13** but freshly prepared(*R*)-2,3-O-isopropylidene-D-glyceraldehyde (0.758 g, 5.8 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (5.0 mmol). Work-up in the usual way and flash column chromatography gave *alcohol* **28** as an inseparable mixture of two diasteroisomers (0.79 g, 26 %) as a clear oil, R_f (0.20, 1:5 EtOAc/hexane); *Diastereoisomer 1* (60 %): δ_H(300 MHz; $CDCl_3$) 4.99 (1H, *d*, one half of an AB quartet, $^2J_{Ha\text{-}Hb}$ 6.0, OC$\mathbf{H_a}$$\mathbf{H_b}$O), 4.88 (1H, *d*, one half of an AB quartet, $^2J_{Ha\text{-}Hb}$ 6.0, OC$\mathbf{H_a}$$\mathbf{H_b}$O), 4.28 (1H, *dt*, $^3J_{H\text{-}H}$ 7.5, 7.0, CH(OH)C**H**CH_2O), 4.21-4.14 (1H, *m*, C(OMEM)C**H**(OH)) 4.01 (2H, *d*,

$^3J_{H-H}$ 8.5, CH(OH)CHC**H$_2$**O), 3.96-3.60 (2H, *m*, OC**H$_2$**CH$_2$OCH$_3$), 3.56-3.51 (2H, *m*, OCH$_2$**CH$_2$**OCH$_3$), 3.35 (3H, *s*, OCH$_3$), 1.41 (3H, *s*, (**CH$_3$**)C(CH$_3$)), 1.33 (3H, *s*, (CH$_3$)C(**CH$_3$**)), OH not observed; δ_F(90 MHz; $CDCl_3$) -98.0 (1F, *d*, $^2J_{F-F}$ 61.0), -108.4 (1F, *d*, $^2J_{F-F}$ 61.0); δ_C(300 MHz; $CDCl_3$) 155.5 (*dd*, $^1J_{C-F}$ 291.8, 285.5), 114.9 (*dd*, $^2J_{C-F}$ 36.3, 12.3), 110.2, 98.1, 75.1, 71.5, 69.1, 68.7, 66.0, 59.0, 26.8, 25.4; *m/z* 298 (1 %, M^+), 316 (65, $[M+NH_4]^+$). *Diastereoisomer 2* (40 %): δ_H(300 MHz; $CDCl_3$) 4.96 (1H, *d*, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.0, OC**H$_a$**H$_b$O), 4.85 (1H, *d*, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.0, OCH$_a$**H$_b$**O), 4.11 (1H, *dt*, $^3J_{H-H}$ 7.5, 7.0, CH(OH)C**H**CH$_2$O), 4.13-4.05 (1H, *m*, C(OMEM)C**H**(OH)) 3.98 (2H, *d*, $^3J_{H-H}$ 8.5, CH(OH)CHC**H$_2$**O), 3.96-3.60 (2H, *m*, OC**H$_2$**CH$_2$OCH$_3$), 3.58-3.50 (2H, *m*, OCH$_2$**CH$_2$**OCH$_3$), 3.30 (3H, *s*, OCH$_3$), 1.34 (3H, *s*, (**CH$_3$**)C(CH$_3$)), 1.30 (3H, *s*, (CH$_3$)C(**CH$_3$**)), OH not observed; δ_F($CDCl_3$) -98.4 (1F, *d*, $^2J_{F-F}$ 61.0), -109.9 (1F, *d*, $^2J_{F-F}$ 61.0); δ_C(300 MHz; $CDCl_3$) 155.5 (*dd*, $^1J_{C-F}$ 291.8, 285.5), 116.3 (*dd*, $^2J_{C-F}$ 36.3, 12.3), 109.6, 98.1, 77.0, 71.4, 68.6, 68.3, 67.0, 58.9, 26.9, 25.3; *m/z* 298 (1 %, M^+), 316 (65, $[M+NH_4]^+$). The adduct was not sufficiently stable to allow a satisfactory microanalysis to be obtained.

Preparation of (**31**):- As for **13** but 1,1-dimethyl *(S)*-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate[24].(0.275 ml, 1.2 mmol) was added to a cold (-78 °C) solution of the organometallic reagent (1 mmol). Work-up in the usual way followed by flash column chromatography afforded *alcohol* **29** (0.13 g, 33 %) as a colourless oil, R_f (0.15, 1:5 EtOAc/Hexane); *Diastereoisomer 1* (75 %): δ_H(300 MHz; $CDCl_3$) 5.10 (1H, *d*, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.0, OC**H$_a$**H$_b$O), 4.98 (1H, *d*, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.0, OCH$_a$**H$_b$**O), 4.42-4.38 (1H, *m*, CH$_2$C**H**N), 4.29-4.25 (1H, *m*, C**H**(OH)CHCH$_2$O), 3.96-3.60 (2H, *envelope*, OC**H$_2$**CH$_2$OCH$_3$), 3.65 (1H, *dd*, $^3J_{Hc-H}$ 8.7, $^2J_{Hc-Hd}$ 2.9, OC**H$_c$**H$_d$CHN), 3.55-3.53 (2H, *m*, OCH$_2$**CH$_2$**OCH$_3$), 3.52 (1H, *dd*, $^3J_{Hd-H}$ 8.7, $^2J_{Hc-Hd}$ 2.9, OCH$_c$**H$_d$**CHN), 3.35 (3H, *s*, OCH$_3$), 1.59 (3H, *br. s*, (**CH$_3$**)C(CH$_3$)), 1.41 (3H, *br. s*, (CH$_3$)C(**CH$_3$**)), 1.5 (9H, *s*, OC(CH$_3$)$_3$), OH not observed; δ_F(90 MHz; $CDCl_3$) -98.7 (1F, *d*, $^2J_{F-F}$ 61.0), -110.3 (1F, *d*, $^2J_{F-F}$ 61.0); *m/z* 397 (1 %, M^+), 59 (70, [^{t}BuCO$_2^+$]). *Diastereoisomer 2* (25 %): δ_H(300 MHz; $CDCl_3$) 5.10 (1H, *d*, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.0, OC**H$_a$**H$_b$O), 4.98 (1H, *d*, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.0, OCH$_a$**H$_b$**O), 4.37-4.35 (1H, *m*, CH$_2$C**H**N), 4.27-4.24 (1H, *m*, C**H**(OH)CHCH$_2$O), 3.96-3.60 (2H, *m*, OC**H$_2$**CH$_2$OCH$_3$), 3.65 (1H, *dd*, $^3J_{Hc-H}$ 8.7, $^2J_{Hc-Hd}$ 2.9, OC**H$_c$**H$_d$CHN), 3.55-3.53 (2H, *m*, OCH$_2$**CH$_2$**OCH$_3$), 3.52 (1H, *dd*, $^3J_{Hd-H}$ 8.7, $^2J_{Hc-Hd}$ 2.9, OCH$_c$**H$_d$**CHN), 3.33 (3H, *s*, OCH$_3$), 1.59 (3H, *br. s*, (**CH$_3$**)C(CH$_3$)), 1.50 (9H, *s*, C(CH$_3$)$_3$O), 1.41 (3H, *br. s*, (CH$_3$)C(**CH$_3$**)), OH not observed; δ_F(90 MHz; $CDCl_3$) -99.4 (1F, *d*, $^2J_{F-F}$ 61.0), -110.7 (1F, *d*, $^2J_{F-F}$ 61.0); *m/z* 397 (1 %, M^+), 59 (70, [^{t}BuCO$_2^+$]). The adduct was not sufficiently stable to allow a satisfactory microanalysis to be obtained.

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22. We are unable to distinguish between $E1_CB$ and E2 mechanisms for the initial dehydrofluorination.
23. Though all attempts to use stannane **15** in palladium catalysed (Stille) coupling have failed, the stannane can be remetallated efficiently in THF (1.0 nBuLi, -78 °C, 15 minutes) providing an amine-free source of **12**. Silane **14** underwent addition/elimination upon treatment with n-butyllithium in TMEDA at -45 °C to afford an alkylated monofluoroenol silane as a mixture of *E*- and *Z*-diastereoisomers. Treatment of a mixture of **14** and propanal at -30 °C with redried TBAF afforded a respectable (72%) yield of **17**: Patel, S.T.; Percy, J.M.; unpublished results. For similar results involving an enol carbamate, see 17a.
24. The ratio of diastereoisomers were determined by integration of the ^1H and ^{19}F NMR spectra. Diastereoselective additions of vinylmetals to Garner's aldehyde **29** form the subject of a recent report: Coleman, R.S.; Carpenter, A.; *Tetrahedron Lett.*, **1992**, *33*, 1697-1700. The most selective additions occurred with vinylzinc chloride. The aldehyde was prepared according to the standard procedure, Garner, P.; Park, J.M.; *Org. Synth.*, **1992**, *70*, 18-28. However, a superior small-scale procedure was reported recently: Roush, W.R.; Hunt, J.A.; *J. Org. Chem.*, **1995**, *60*, 798-806.
25. The vinylzinc reagent derived from **12** is a very weak nucleophile though we have successfully trapped it with iodine to afford the iodoalkene in good yield. However, the reaction is slow.
26. Knight, D.W.; in Comprehensive Organic Syntheses, Ed. by Fleming, I.; Trost, B.M.; Pergamon, Oxford, **1994**, *3*, Chapter 1.6, 241-270.
27. Primary alkyl triflates were the successful electrophiles; see 17a.

28. Patel, S.T.; Percy, J.M.; Wilkes, R.D.; manuscript in preparation for submission to *J. Org. Chem.*.
29. Patel, S.T.; Percy, J.M.; Wilkes, R.D.; manuscript submitted to *Tetrahedron*.
30. Careful temperature control is important during these reaction sequences. If discoloured material is obtained, from the reaction, filtration through a short column of alumina is recommended prior to distillation.
31. Schlosser, M.: Jenny, T.; Guggisberg, Y; *Synlett*, **1990**, 704.
32. A good yield of alcohol **23** could only be obtained by treating **12** with a ten-fold excess of acetone. The reasons for this unusual observation are unclear. Alcohol **23** was also unstable in storage.
33. Additions to bicyclo[2.2.1]heptenones that lack substituents at the 7-position usually occur in an *exo*-mode. The single racemic diastereoisomer that we were able to detect in the NMR of **26** has therefore been assigned as an *exo*-product.
34. Paquette and Shi reported that vinylmagnesium bromide added to 2-chlorocyclohexanone to afford the product in which the C-Cl and C-O bonds are *cis*. We have therefore assigned the relative configuration of **27** accordingly. See Paquette, L.A.; Shi, Y-J.; *J. Am. Chem. Soc.*, **1990**, *112*, 8478-8489.

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