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[3,3]-Sigmatropic Rearrangement Routes to β-Fluoro- and β,β-Difluoro-carbonyl Derivatives.

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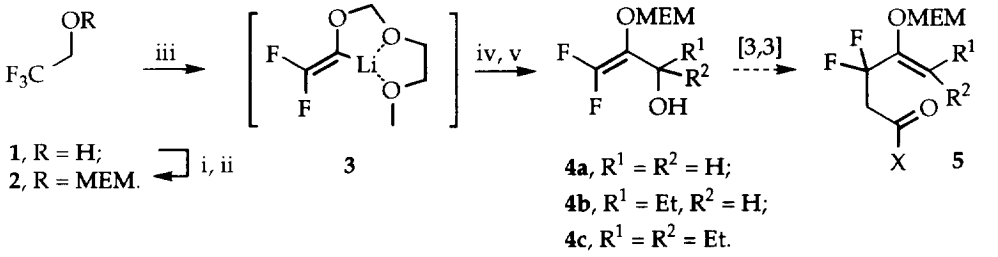
Abstract: Difluoroallylic alcohols prepared in two steps from trifluoroethanol underwent a range of Claisen and related [3,3]-rearrangements in moderate to good yield. In one case, the rearrangement product underwent rapid dehydrofluorination to afford an interesting fluorodienal. Monofluoroallylic alcohols rearranged more slowly but resisted dehydrofluorination.

The synthesis of highly-functionalised molecules containing a limited number of fluorine atoms remains a significant challenge to synthetic organic chemists.[1] We have sought to develop a palette of methods based upon inexpensive and easy-to-handle trifluoroethanol. Conversion of trifluoroethanol **1** to acetal **2** sets the stage for a dehydrofluorination/metallation sequence leading to **3** (**Scheme 1**).[2] A range of allylic alcohols **4** has been prepared upon interception of **3** with electrophiles.



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 R^1CHO, -78 °C, 2 hours; v, warm to -30 °C then NH_4Cl/MeOH.

Scheme 1

Allylic transposition[3] of alcohols **4** *via* a Claisen or related rearrangement would allow the CF_2 group to be relocated from a terminal to a mid-chain position[4] β-to a carbonyl group, as in **5**. As there are very few methods for the location of one or two fluorine atoms in this position, this appeared to be an attractive area for further exploration. Products such as **5** also contain a useful level of functionality for further transformation through either the carbonyl group or the masked ketone at the γ-position.[5]

Transposition methods based on thermal sigmatropic rearrangements are ideal for a number of reasons. Because strong acids or bases are not required, a wide range of functional groups can

be tolerated, and as the reactions are pericyclic rather than involving polar intermediates, potential problems caused by deactivating fluorine atom substituent effects in cationic processes, or by elimination of fluoride ion are avoided. In addition, Dolbier has shown[6] that a significant thermodynamic advantage accrues when the hybridisation state of the fluorine-bearing carbon atom changes from sp^2 to sp^3 during the course of the reaction. This rehybridisation has been identified as a general driving force in the rearrangement reactions of fluorocompounds. Fluorine atom substituents lower the energies of both frontier orbitals of alkenes. Effects of this type may be important in determining the ease with which rearrangements occur.

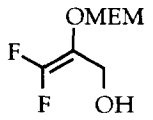
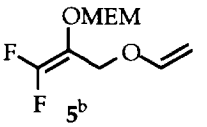
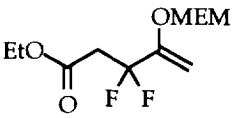
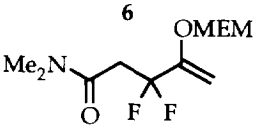
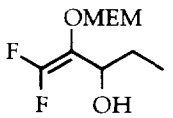
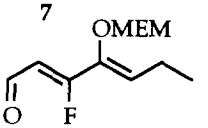
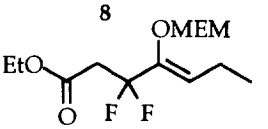
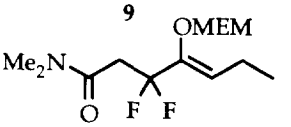
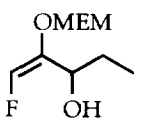
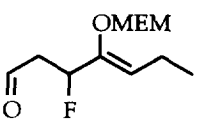
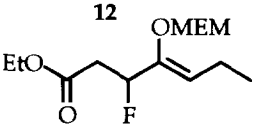
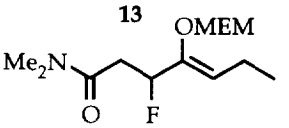
Few authors have exploited [3,3]-rearrangements of difluoroallylic alcohols in target synthetic studies. In a rare example, Metcalf and co-workers[7] described syntheses of HMGCoA Reductase inhibitors *via* [3,3]-Claisen and Ireland silyl ketene acetal rearrangements of 1,1-difluoro-2-(tosyloxy)alken-3-ol derivatives. Both reactions occurred under unusually mild conditions though full details were not reported. Indeed, there are few general procedures or reports of experimental details in this area of synthetic organofluorine chemistry.[8] We have examined the reactivity of a range of mono- and difluoro-allylic alcohols in some of the most important [3,3]-rearrangements from the classical synthetic organic repertoire. The effect of the replacement of one of the fluorine atoms with an hydrogen atom has also been assessed.

Results and Discussion

Difluoroallylic alcohols were prepared following a published procedure.[2] Three types of [3,3]-rearrangement were examined; the results are summarised in **Table 1**. The reactions were monitored easily by ^{19}F NMR and were run until the conversion of starting material was complete. The yields in the Table refer to isolated yields after purification. The classical allyl vinyl ether Claisen rearrangements were performed using the method described by Dauben and Dietsch.[9] Alcohols were refluxed in ethyl vinyl ether containing mercuric acetate until the consumption of starting material was complete (conditions A). The four alcohols behaved in very different ways. Propenol derivative **4a** was converted through to the allyl vinyl ether **5** in moderate yield but attempts to achieve rearrangement under thermal conditions, for example using sealed tube procedures led only to decomposition.

The effect of replacing one of the hydrogen atoms by an ethyl group was dramatic. After refluxing **4b** in ethyl vinyl ether for 16 hours, dienal **8** was obtained in 67% yield.[10] The result implies that the allyl vinyl ether, once formed, rearranges rapidly. Indeed formation of the precursor to rearrangement may be the rate determining step. Elimination of HF occurs *in situ*, presumably catalysed by acetic acid formed in the reaction. Aldehydes enolise readily, and the presence of the two fluorine atoms at the β-position is likely to facilitate that process. When we attempted the reaction with the tertiary allylic alcohol **4c**, we were unable to form any of the allyl vinyl ether. Monofluoroalcohol **11** was synthesised by Red-Al reduction of **4b** following a modification of the method described by Burton and co-workers[11] and isolated as a mixture of alkene diastereoisomers. The mixture of isomers rearranged slowly,[12] apparently without dehydrofluorination, though the isolated yield of **12** was moderate. The presence of only one

Table 1. Attempted [3,3]-Rearrangements of Fluoroallylic Alcohols.

Alcohol	Conditions	T (°C)	Time (Hours)	Product	Yield (%)[a]
 **4a**	A	40	18	 **5**[b]	41
	B	140	18	 **6**	50
	C	115	4	 **7**	59
 **4b**	A	40	18	 **8**	67
	B	140	0.75	 **9**	64
	C	60	2	 **10**	61
 **11**	A	40	140	 **12**	43
	B	140	48	 **13**	41
	C	60	2	 **14**	55

[a]Yields refer to isolated yields of chromatographically pure products.

[b]5 Failed to rearrange and decomposed at more elevated temperatures (> 150 °C).

fluorine atom lowers the rate of rearrangement but also reduces the acidity of the product aldehyde so that dehydrofluorination does not occur.

The Eschenmoser Claisen rearrangement occurs under mild, neutral conditions, allowing the transposition of acid- or base-sensitive substrates.[13] Heating a solution of **4b** and dimethylacetamide dimethyl acetal in toluene (conditions C) resulted in smooth rearrangement to the β,β-difluoroamide **10**. None of the dehydrofluorination product was detectable by TLC, or in the ^{19}F NMR spectrum, reflecting the neutrality of the reaction conditions and the lower acidity of amides. The less substituted **4a** also rearranged cleanly though a higher reaction temperature (115 °C) was required to achieve the conversion. Tertiary alcohol **4c** failed to react, even when the mixture was refluxed for a prolonged period in the presence of powdered molecular sieves, or indeed, when heated to 150 °C overnight in a sealed tube. Johnson and co-workers have reported the low reactivity of a tertiary allylic alcohol during syntheses of polyene precursors to steroid (±)-β-Amyrin.[14] Presumably, the extreme difficulty of the reaction arises because of steric hindrance around the hydroxyl group of the allylic alcohol. In our case, the presence of the two fluorine atom substitutents is expected to depress the nucleophilicity still further. Claisen-Johnson rearrangements were performed by heating in triethylorthoacetate containing propionic acid and hydroquinone (conditions B)[15] and followed a similar pattern. Alcohol **4b** reacted rapidly, while **4a** rearranged more slowly. Again, **4c** failed to rearrange under Claisen-Johnson conditions. Monofluoroalcohol **11** underwent both Eschenmoser and Claisen-Johnson rearrangements in moderate yield.

The pattern of reactivity is interesting and requires some explanation. We suggest that the following qualitative treatment may be applied. Rapid rearrangement arises from a balance between the nucleophilicity of the hydroxyl group of the allylic alcohol (which consists of electronic and steric components), and the level of substitution upon the double bond formed in the transposition step. The former parameter depresses the rate at which the rearrangement precursor is reached, whether the precursor is an allyl vinyl ether, ketene aminal or acetal. An increase in the latter variable would be expected to accelerate the product-like[16] [3,3]-rearrangements because alkene stability increases with alkyl substitution on the double bond. We are applying semi-empirical and *ab initio* methods to allow us to validate this hypothesis and exploring the chemistry of the enol acetal functionality in the transposed products.[17]

Acknowledgements

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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 or pendant 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. 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, Art. 5554). 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 and a wall-coated fused silica capillary column, type CP-SIL-19CB (50 m) or on a Carlo-Erba 9000 series chromatograph containing a DB-5 column (15 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 (90%, tech.) was purchased from the Aldrich Chemical Company and used without further purification. Trifluoroethanol was purchased from Fluorochem and used as supplied. Ethyl vinyl ether, sodium *bis*(methoxyethoxy)aluminium hydride, triethyl orthoacetate and *N,N*-dimethylacetamide dimethyl acetal were purchased from the Aldrich Chemical Company and were used as supplied. Mercuric (II) acetate was also purchased from the Aldrich Chemical Company, and was recrystallised prior to use.

Dauben-Dietsch-modified Claisen Rearrangements.

Preparation of 3-Fluoro-4-([methoxyethoxy]methoxy)hepta-2,4-dienal (8)

Alcohol (**4b**) (0.86 g, 3.80 mmol), ethyl vinyl ether (3.63 ml, 38.00 mmol) and mercuric (II) acetate (0.036 g, 0.11 mmol) were mixed together at room temperature and heated to reflux overnight. A 10% aqueous solution of sodium carbonate (10 ml) was added and the resultant mixture was extracted with diethyl ether (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a brown oil. Purification by flash column chromatography, using 20% ethyl acetate/hexane as eluant, gave **dienal (8)** as a yellow oil (0.64 g, 67%), (R_f = 0.25); ν_{max} (Film) 1654, 1604 and 1423 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.05 (1H, d, $^3J_{H-H}$ = 6.5 Hz, CHO), 6.04 (1H, td, $^3J_{H-H}$ = 7.5 Hz, $^4J_{H-F}$ = 3.5 Hz, C=C**H**CH_2CH_3), 5.78 (1H, dd, $^3J_{H-H}$ = 6.5 Hz, $^3J_{H-Ftrans}$ = 33.0 Hz, CH=CF), 4.94 (2H, s, OCH_2O), 3.89-3.84 (2H, m, OCH_2CH_2O), 3.58-3.53 (2H, m, OCH_2CH_2O), 3.38 (3H, s, OCH_3), 2.37-2.25 (2H, m, CH_2CH_3), 1.05 (3H, t, $^3J_{H-H}$ = 7.0 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 188.6, 169.4 (d, $^1J_{C-F}$ = 274.0 Hz), 143.9, 128.4, 107.1, 98.2, 71.6, 69.4, 59.1, 19.7, 10.6; δ_F (90 MHz, $CDCl_3$) –117.1 (1F, d, $^3J_{H-F}$ = 33.0 Hz); m/z (CI, NH_3) 250 (0.5%, $[M+NH_4]^+$), 233 (7, $[M+H]^+$), 232 (0.5, M^+), 213 (1, $[M-F]^+$), 89 (100, $CH_2OCH_2OCH_3^+$), 59 (43, $CH_2CH_2OCH_3^+$).

Attempted Claisen rearrangement of (4a); preparation of 3-Ethenyloxy-1,1-difluoro-2-([methoxyethoxy]methoxy)prop-1-ene (5)

As for (**8**) except alcohol (**4a**) was used and the reaction was heated to reflux overnight. Work-up as for (**8**) and purification by flash column chromatography, using 20% ethyl acetate/hexane as eluant, gave only starting material and unrearranged **ether (5)** as a yellow oil (0.093 g, 41%), (R_f = 0.39); ν_{max} (Film) 1761, 1639, 1618 and 1457 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.42 (1H, dd, $^3J_{H\text{-}Htrans}$ = 14.5 Hz, $^3J_{H\text{-}Hcis}$ = 7.0 Hz, C**H**=CH_2), 4.94 (2H, s, OCH_2O), 4.32 (1H, d, $^2J_{H\text{-}H}$ = 2.0 Hz, $CH_2OCH{=}CH_2$), 4.31 (1H, d, $^2J_{H\text{-}H}$ = 2.0 Hz, $CH_2OCH{=}CH_2$), 4.22 (1H, dd, $^2J_{H\text{-}H}$ = 2.5 Hz, $^3J_{H\text{-}Htrans}$ = 14.5 Hz, CH=C$H_a$$H_b$), 4.06 (1H, dd, $^2J_{H\text{-}H}$ = 2.5 Hz, $^3J_{H\text{-}Hcis}$ = 7.0 Hz, CH=C$H_a$$H_b$), 3.82-3.77 (2H, m, OCH_2CH_2O), 3.57-3.51 (2H, m, OCH_2CH_2O), 3.36 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 155.7 (t, $^1J_{C\text{-}F}$ = 286.0 Hz), 151.0, 111.8 (dd, $^2J_{C\text{-}F}$ = 38.6, 15.3 Hz), 96.1, 88.1, 71.7, 68.4, 62.7, 59.1; δ_F (90 MHz, $CDCl_3$) –98.2 (1F, d, $^2J_{F\text{-}F}$ = 58.0 Hz), –108.4 (1F, d, $^2J_{F\text{-}F}$ = 58.0); m/z (CI, NH_3) 242 (0.5%, $[M+NH_4]^+$), 181 (2, $[M–OCH{=}CH_2]^+$), 89 (58, $CH_2OCH_2OCH_3^+$), 59 (100, $CH_2CH_2OCH_3^+$); HRMS calcd for $C_9H_{18}F_2NO_4$ ($[M+NH_4]^+$) 242.12039, found 242.11988.

Preparation of (*E*) and (*Z*)-1-Fluoro-3-hydroxy-2-([methoxyethoxy]methoxy)pent-1-ene (11)

Alcohol (**4b**) (4.00 g, 17.70 mmol) and sodium *bis*(methoxyethoxy)aluminium hydride (65% solution in toluene) (13.27 ml, 68.0 mmol) were heated to reflux in ^{n}pentane (40 ml) over 3 hours. The reaction mixture was cooled and poured onto an ice-water mixture (80 ml). The resultant white suspension was acidified to *ca.* pH 3 with concentrated hydrochloric acid, and the mixture was extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were washed with a saturated aqueous solution of brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography, using 40% ethyl acetate/hexane as eluant, gave **alcohol (11)** as a mixture of alkene diastereoisomers as a colourless oil (2.65 g, 72%), (R_f = 0.15); Isomer ratio = 10 : 1 (*E* :*Z*); ν_{max} (Film) 3434, 1650 and 1462 cm^{-1}; δ_H (300 MHz, $CDCl_3$) Major (*E*) isomer: 6.85 (1H, d, $^2J_{H\text{-}F}$ = 80.0 Hz, HFC=C), 4.90 (1H, d, $^2J_{H\text{-}H}$ = 6.5 Hz, OC$H_a$$H_b$O), 4.86 (1H, d, $^2J_{H\text{-}H}$ = 6.5 Hz, OC$H_a$$H_b$O), 4.46 (1H, m, CHOH), 3.77-3.61 (2H, m, OCH_2CH_2O), 3.53-3.47 (2H, m, OCH_2CH_2O), 3.32 (3H, s, OCH_3), 2.52 (1H, br. s, OH), 1.73-1.47 (2H, m, CH_2CH_3), 0.85 (3H, t, $^3J_{H\text{-}H}$ = 7.4 Hz, CH_2CH_3); Minor (*Z*) isomer: distinct signals at 6.40 (1H, d, $^2J_{H\text{-}F}$ = 77.0 Hz, HFC=C), 0.84 (3H, t, $^3J_{H\text{-}H}$ = 7.4 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) Major (*E*) isomer: 146.4 (d, $^2J_{C\text{-}F}$ = 26.3 Hz), 138.9 (d, $^1J_{C\text{-}F}$ = 249.0 Hz), 95.4, 71.5, 67.7, 67.4, 58.9, 27.2, 9.7; Minor (*Z*) isomer: distinct signals at 96.4, 71.6, 68.5, 27.0, 10.0; δ_F (90 MHz, $CDCl_3$) Major (*E*) isomer: –172.8 (1F, d, $^2J_{H\text{-}F}$ = 80.0 Hz); Minor (*Z*) isomer: –157.8 (1F, d, $^2J_{H\text{-}F}$ = 77.0 Hz); m/z (CI, NH_3) 226 (55%, $[M+NH_4]^+$), 209 (8, $[M+H]^+$), 208 (20, M^+), 191 (72, $[M–OH]^+$), 89 (100, $CH_2OCH_2OCH_3^+$), 59 (78, $CH_2CH_2OCH_3^+$); HRMS calcd for $C_9H_{21}FNO_4$ ($[M+NH_4]^+$) 226.14546, found 226.14501.

Preparation of 3-Fluoro-4-([methoxyethoxy]methoxy)hepta-4-enal (12)

As for (**8**) except the mixture of diastereoisomeric alcohols (**11**) was used and the reaction was heated to reflux for 5 days. Work-up as for (**8**) and purification by flash column chromatography, using 20% ethyl acetate/hexane as eluant, gave **enal (12)** as a yellow oil (0.045 g, 43%), (R_f = 0.30); ν_{max} (Film) 1715, 1684 and 1456 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.53 (1H, t, $^3J_{H\text{-}H}$ = 5.0 Hz, CHO), 5.47 (1H, ddd, $^2J_{H\text{-}F}$ = 47.3 Hz, $^3J_{H\text{-}H}$ = 8.5 Hz, $^3J_{H\text{-}H}$ = 4.0 Hz, CH_2CHF), 5.16 (1H, td, $^3J_{H\text{-}H}$ = 7.5 Hz, $^4J_{H\text{-}F}$ = 3.5 Hz, C=C**H**CH_2CH_3), 4.91 (2H, s, OCH_2O), 3.89-3.84 (2H, m,

OCH_2CH_2O), 3.58-3.53 (2H, m, OCH_2CH_2O), 3.35 (3H, s, OCH_3), 2.37-2.25 (2H, m, CH_2CH_3), 1.40-1.00 (2H, m, CH_2CHF), 0.90 (3H, t, $^3J_{H-H}$ = 7.0 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 167.4, 149.4 (d, $^2J_{C-F}$ = 25.6 Hz), 121.5, 98.5, 91.3 (d, $^1J_{C-F}$ = 173.4 Hz), 71.4, 67.6, 54.7, 34.8, 18.4, 14.7; δ_F (90 MHz, $CDCl_3$) –117.1 (1F, dddd, $^2J_{H-F}$ = 47.2 Hz, $^3J_{H-F}$ = 32.0 Hz, $^3J_{H-F}$ = 16.0 Hz, $^4J_{H-F}$ = 3.5 Hz); m/z (CI, NH_3) 252 (5%, $[M+NH_4]^+$), 235 (1, $[M+H]^+$), 191 (30, $[M-C(O)CH_2]^+$), 89 (86, $CH_2OCH_2OCH_3^+$), 59 (100, $CH_2CH_2OCH_3^+$).

Claisen-Johnson Rearrangements.

Preparation of Ethyl[3,3-difluoro-4-([methoxyethoxy]methoxy)]hepta-4-enoate (9)

Alcohol (**4b**) (0.25 g, 1.20 mmol), triethyl orthoacetate (2.20 ml, 12.00 mmol), propionic acid (4 μl) and hydroquinone (5 mg) were mixed together at room temperature and heated to 140 °C for 45 minutes. Ethanol and excess triethyl orthoacetate were removed *in vacuo* to afford a pale yellow oil. Purification by flash column chromatography, using 20% ethyl acetate/hexane as eluant, gave **γ,δ-unsaturated ester (9)** as a colourless oil (0.16 g, 64%), (R_f = 0.25); ν_{max} (Film) 1755, 1682 and 1462 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.52 (1H, t, $^3J_{H-H}$ = 7.5 Hz, C=C**H**CH_2CH_3), 4.96 (2H, s, OCH_2O), 4.15 (2H, q, $^3J_{H-H}$ = 7.5 Hz, OCH_2CH_3), 3.85-3.81 (2H, m, OCH_2CH_2O), 3.56-3.54 (2H, m, OCH_2CH_2O), 3.37 (3H, s, OCH_3), 3.06 (2H, t, $^3J_{H-F}$ = 15.3 Hz, CH_2CF_2), 2.32-2.11 (2H, m, CH_2CH_3), 1.24 (3H, t, $^3J_{H-H}$ = 7.5 Hz, OCH_2CH_3), 0.99 (3H, t, $^3J_{H-H}$ = 7.0 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 166.5, 145.5 (t, $^2J_{C-F}$ = 28.2 Hz), 120.5, 117.4 (t, $^1J_{C-F}$ = 244.9 Hz), 98.3, 71.6, 68.8, 61.0, 58.9, 40.9 (t, $^2J_{C-F}$ = 28.2 Hz), 18.6, 14.0, 13.6; δ_F (90 MHz, $CDCl_3$) –98.4 (2F, t, $^3J_{H-F}$ = 15.3 Hz); m/z (CI, NH_3) 297 (100%, $[M+H]^+$), 296 (3, M^+), 89 (47, $CH_2OCH_2OCH_3^+$), 59 (100, $CH_2CH_2OCH_3^+$); HRMS calcd for $C_{13}H_{23}F_2O_5$ ($[M+H]^+$) 297.15021, found 297.15070.

Preparation of Ethyl-[3,3-difluoro-4-([methoxyethoxy]methoxy)]penta-4-enoate (6)

As for (**9**) except alcohol (**4a**) was used and the reaction mixture was heated at 140 °C overnight. Ethanol and excess triethyl orthoacetate were removed *in vacuo* to afford an orange oil. Purification by flash column chromatography, using 30% ethyl acetate/petroleum ether (40:60) as eluant, gave **γ,δ-unsaturated ester (6)** as an orange oil (0.14 g, 50%), (R_f = 0.56); ν_{max} (Film) 1744, 1654 and 1458 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.10 (2H, s, OCH_2O), 4.79 (1H, d, $^2J_{H-H}$ = 3.0 Hz, C(OMEM)=CH_aH_b), 4.71-4.63 (1H, m, C(OMEM)=CH_aH_b) 4.12 (2H, q, $^3J_{H-H}$ = 7.0 Hz, OCH_2CH_3), 3.81-3.71 (2H, m, OCH_2CH_2O), 3.59-3.51 (2H, m, OCH_2CH_2O), 3.36 (3H, s, OCH_3), 3.06 (2H, t, CH_2CF_2, $^3J_{H-F}$ = 15.3 Hz), 1.23 (3H, t, $^3J_{H-H}$ = 7.2 Hz, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 166.3, 152.7 (t, $^2J_{C-F}$ = 28.0 Hz), 116.1 (t, $^1J_{C-F}$ = 244.1 Hz), 93.5, 88.7, 71.5, 68.0, 61.2, 59.0, 40.7 (t, $^2J_{C-F}$ = 27.9 Hz), 14.1; δ_F (90 MHz, $CDCl_3$) –99.9 (2F, t, $^3J_{H-F}$ = 15.3 Hz); m/z (CI, NH_3) 286 (100%, $[M+NH_4]^+$), 268 (2, M^+), 89 (28, $CH_2OCH_2OCH_3^+$), 59 (33, $CH_2CH_2OCH_3^+$); HRMS calcd for $C_{11}H_{22}F_2NO_5$ ($[M+NH_4]^+$) 286.14660, found 286.14615.

Preparation of Ethyl-[3-fluoro-4-([methoxyethoxy]methoxy)]hepta-4-enoate (13)

As for (**9**) except alcohol (**11**) was used and the reaction mixture was heated at 140 °C for 2 days. Ethanol and excess triethyl orthoacetate were removed *in vacuo* to afford a pale yellow oil. Purification by flash column chromatography, using 20% ethyl acetate/hexane as eluant, gave **γ,δ-unsaturated ester (13)** as a colourless oil (0.055 g, 41%), (R_f = 0.35); ν_{max} (Film) 1745, 1656 and 1453 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.30 (1H, ddd, $^2J_{H-F}$ = 47.1 Hz, $^3J_{H-H}$ = 8.5 Hz, $^3J_{H-H}$ = 4.0 Hz, $CHFCH_2$), 5.16 (1H, td, $^3J_{H-H}$ = 8.0 Hz, $^4J_{H-F}$ = 3.0 Hz, C=C**H**CH_2CH_3), 4.93 (2H, s, OCH_2O), 4.18

(2H, q, $^3J_{H-H}$ = 7.5 Hz, OCH_2CH_3), 3.89-3.75 (2H, m, OCH_2CH_2O), 3.59-3.54 (2H, m, OCH_2CH_2O), 3.36 (3H, s, OCH_3), 2.88-2.68 (2H, m, $CHFCH_2$), 2.19-2.05 (2H, m, CH_2CH_3), 1.39 (3H, t, $^3J_{H-H}$ = 7.5 Hz, OCH_2CH_3), 0.96 (3H, t, $^3J_{H-H}$ = 7.0 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 166.5, 145.5 (d, $^2J_{C-F}$ = 17.5 Hz), 120.5, 117.4 (d, $^1J_{C-F}$ = 189.5 Hz), 98.4, 71.7, 68.6, 61.0, 58.9, 36.8 (d, $^2J_{C-F}$ = 25.8 Hz), 18.6, 13.9, 13.7; δ_F (90 MHz, $CDCl_3$) –179.9 (1F, ddd, $^2J_{H-F}$ = 47.1 Hz, $^3J_{H-F}$ = 32.0 Hz, $^3J_{H-F}$ = 16.0 Hz); m/z (CI, NH_3) 279 (100%, $[M+H]^+$), 278 (3, M^+), 89 (47, $CH_2OCH_2OCH_3^+$), 59 (100, $CH_2CH_2OCH_3^+$).

Eschenmoser Rearrangements.

Preparation of N,N-dimethyl-[3,3-Difluoro-4-([methoxyethoxy]methoxy)]hepta-4-enamide, (10)

Alcohol (**4b**) (1.12 g, 5.00 mmol) was dissolved in toluene (2 ml) and stirred at room temperature for 10 minutes. *N, N*-Dimethylacetamide dimethyl acetal (3.60 ml, 5.00 mmol) was added dropwise and the mixture was heated to 60 °C for 2 hours. The toluene was removed *in vacuo* to afford a brown oil. Purification by flash column chromatography, using 50% ethyl acetate/hexane as eluant, gave **amide (10)** as an orange oil (0.90 g, 61%), (R_f = 0.05); ν_{max} (Film) 1651 and 1460 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.50 (1H, t, $^3J_{H-H}$ = 6.5 Hz, $C=CHCH_2CH_3$), 4.95 (2H, s, OCH_2O), 3.84-3.78 (2H, m, OCH_2CH_2O), 3.56-3.50 (2H, m, OCH_2CH_2O), 3.34 (3H, s, OCH_3), 3.12 (2H, t, $^3J_{H-F}$ = 15.4 Hz, CH_2CF_2), 3.10 (3H, s, NCH_3), 2.91 (3H, s, NCH_3), 2.21-2.08 (2H, m, CH_2CH_3), 0.75 (3H, t, $^3J_{H-H}$ = 7.0 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 165.8, 145.9 (t, $^2J_{C-F}$ = 26.6 Hz), 129.8, 129.6, 118.5, 118.4 (t, $^1J_{C-F}$ = 244.9 Hz), 98.4, 71.6, 68.8, 58.9, 39.2 (t, $^2J_{C-F}$ = 27.0 Hz), 37.9, 35.5; δ_F (90 MHz, $CDCl_3$) –97.9 (2F, t, $^3J_{H-F}$ = 15.4 Hz); m/z (CI, NH_3) 313 (4%, $[M+NH_4]^+$), 296 (100, $[M+H]^+$), 295 (3, M^+), 208 (95, $[M-CH_3C(O)NMe_2]^+$), 89 (47, $CH_2OCH_2OCH_3^+$), 59 (100, $CH_2CH_2OCH_3^+$); HRMS calcd for $C_{13}H_{24}F_2NO_4$ ($[M+H]^+$) 296.16734, found 296.16669.

Preparation of *N,N*-dimethyl-[3,3-Difluoro-4-([methoxyethoxy]methoxy)]penta-4-enamide (7)

As for (**10**) except alcohol (**4a**) was used and the reaction mixture was heated to reflux (115 °C) for 4 hours. Removal of toluene *in vacuo* afforded a brown oil. Purification by flash column chromatography, using 40% ethyl acetate/petroleum ether (40:60) as eluant, gave **amide (7)** as an orange oil (0.08 g, 59%), (R_f = 0.05); ν_{max} (Film) 1721, 1651, 1592 and 1455 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.03 (2H, s, OCH_2O), 4.71 (1H, d, $^2J_{H-H}$ = 3.0 Hz, $C(OMEM)=CH_aH_b$), 4.60-4.54 (1H, m, $C(OMEM)=CH_aH_b$), 3.77-3.62 (2H, m, OCH_2CH_2O), 3.53-3.42 (2H, m, OCH_2CH_2O), 3.29 (3H, s, OCH_3), 3.07 (2H, t, $^3J_{H-F}$ = 15.0 Hz, CH_2CF_2), 2.97 (3H, s, NCH_3), 2.85 (3H, s, NCH_3); δ_C (75 MHz, $CDCl_3$) 165.6, 153.1 (t, $^2J_{C-F}$ = 28.3 Hz), 117.3 (t, $^1J_{C-F}$ = 243.0 Hz), 93.5, 88.3, 71.5, 68.0, 59.0, 38.9 (t, $^2J_{C-F}$ = 26.6 Hz), 37.9, 35.4; δ_F (90 MHz, $CDCl_3$) –98.8 (2F, t, $^3J_{H-F}$ = 15.3 Hz); m/z (CI, NH_3) 285 (5%, $[M+NH_4]^+$), 268 (75, $[M+H]^+$), 180 (100, $[M-CH_3C(O)NMe_2]^+$), 89 (34, $CH_2OCH_2OCH_3^+$), 59 (9, $CH_2CH_2OCH_3^+$); HRMS calcd for$C_{11}H_{20}F_2NO_4$ ($[M+H]^+$) 268.13604, found 268.13646.

Preparation of *N,N*-dimethyl-[3-Fluoro-4-([methoxyethoxy]methoxy)]hepta-4-enamide (14)

As for (**10**) except alcohol (**11**) was used. Removal of toluene *in vacuo* afforded a brown oil. Purification by flash column chromatography, using 40% ethyl acetate/hexane as eluant, gave **amide (14)** as an orange oil (0.21 g, 55%), (R_f = 0.10); ν_{max} (Film) 1650 and 1454 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.40 (1H, ddd, $^3J_{H-H}$ = 8.5 Hz, $^3J_{H-H}$ = 4.0 Hz, $^2J_{H-F}$ = 47.1 Hz, $CHFCH_2$), 5.15 (1H, td, $^3J_{H-H}$ = 8.0 Hz, $^4J_{H-F}$ = 2.5 Hz, $C=CHCH_2CH_3$), 4.97 (2H, s, OCH_2O), 3.86-3.76 (2H, m, OCH_2CH_2O), 3.59-3.54 (2H, m, OCH_2CH_2O), 3.36 (3H, s, OCH_3), 3.04-2.57 (2H, m, $CHFCH_2$), 3.00

(3H, s, NCH_3), 2.93 (3H, s, NCH_3), 1.75-1.53 (2H, m, CH_2CH_3), 0.96 (3H, t, $^3J_{H-H}$ = 7.0 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 169.2, 149.4 (d, $^2J_{C-F}$ = 17.5 Hz), 120.0, 97.3, 90.7 (d, $^1J_{C-F}$ = 170.5 Hz), 71.7, 68.6, 58.9, 36.8 (d, $^2J_{C-F}$ = 25.8 Hz), 37.3, 35.5, 18.6, 13.9; δ_F (90 MHz, $CDCl_3$) –175.0 (1F, dddq, $^2J_{H-F}$ = 47.1 Hz, $^3J_{H-F}$ = 32.0 Hz, $^3J_{H-F}$ = 16.0 Hz, long range J_{H-F} = 3.0 Hz); m/z (CI, NH_3) 278 (53%, $[M+H]^+$), 277 (1, M^+), 258 (100, $[M-F]^+$), 190 (10, $[M-CH_3C(O)NMe_2]^+$), 89 (36, $CH_2OCH_2OCH_3^+$), 59 (17, $CH_2CH_2OCH_3^+$); HRMS calcd for $C_{13}H_{25}FNO_4$ ($[M+H]^+$) 278.17676, found 278.17813.

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