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Synthesis of α-hydroxy-β,β-difluoro-γ-ketoesters *via* [3,3]sigmatropic rearrangements

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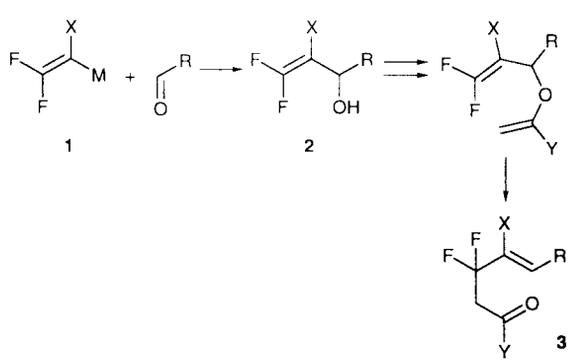
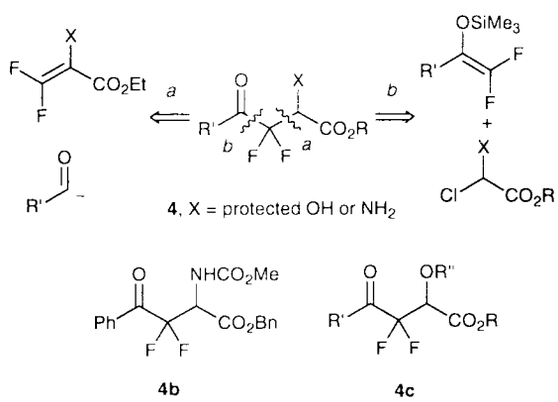
Readily available γ,γ-difluorinated allylic alcohols obtained from trifluoroethanol were esterified efficiently. Exposure to strong base (LDA) afforded the ester enolates, in which chelation both controlled configuration and stabilised against fragmentation, which were trapped as their silyl ketene acetals. Rearrangement occurred to afford base-sensitive acid products. Esterification under mild conditions afforded the purifiable methyl esters in which the masked ketone had been released. Educts with either a benzyloxy or an allyloxy group at the α-position could be deprotected releasing the alcohols.

Sigmatropic rearrangements provide an extremely powerful way of transforming simple fluorinated species into more complex substrates, and for the elaboration of readily available fluorinated building blocks.[1] The correct location of fluorine atoms within the rearrangement system can result in significant rate enhancements both in neutral [3,3] rearrangements such as Cope,[2] Claisen[3] and oxy-Cope,[4] and in neutral[5] and anionic[6] [2,3] rearrangements. [3,3] Claisen rearrangements of readily available γ,γ-difluorinated allylic alcohols **2** (obtained *via* the addition of fluorinated vinylmetals **1** to aldehydes or ketones) locate a CF_2 centre β to a carboxy carbonyl group (**3** in Scheme 1).



Scheme 1 Outline route to masked β,β-difluoro-γ-oxocarboxylic acid derivatives.

In analysis, disconnections of targets that contain this functionality pattern along bonds *a* or *b* could be considered (Scheme 2). The addition of an acyl anion equivalent to an α-alkoxy difluoroalkenoate (making bond *a*) of the type described by Shi and co-workers[7] could be considered, but such additions normally proceed to monofluorocompounds *via* addition–elimination mechanisms. Alternatively, McCarthy and co-workers reported[8] the synthesis of a Kynureninase inhibitor **4b** in which bond *b* was made from a difluorinated silyl enol ether (Scheme 2).



Scheme 2 Possible disconnections from the target molecules.

Given the generality of the difluoroenol ether synthesis reported by Portella and co-workers,[9] this looks like an attractive reaction. Though aldol and related[10] reactions have been reported, electrophiles of the level of functionality used by McCarthy have not been used to our knowledge. Alternatively, rearrangements of alkoxyacetates of γ,γ-difluorinated allylic alcohols derived from trifluoroethanol have been used to synthesise novel difluorinated ketoamino acids **4b**;[11] here we wish to show how rearrangement chemistry can be used to synthesise α-hydroxy-β,β-difluoro-γ-ketoesters[12] on 1–22 mmol scales from trifluoroethanol.

Results and discussion

The generation of enolates from alkoxyacetate esters of allylic alcohols occurs stereoselectively (Scheme 3).[13] Coordination of the metal counterion (usually lithium) between two oxygen atoms controls the configuration of the developing enolate **5**. Trapping as a silyl ketene acetal **6** then locks this stereochemical information in place and the rearrangement can be used to transcribe the information into a vicinal pair of stereogenic centres (in **7**), or to effect chirality transfer or asymmetric induction. Recent applications have been made in natural product synthesis,[14] while attractive combinations with ring-closing metathesis procedures afford interesting heterocycles.[15] The reaction is not limited to alkoxyacetate esters; enolates

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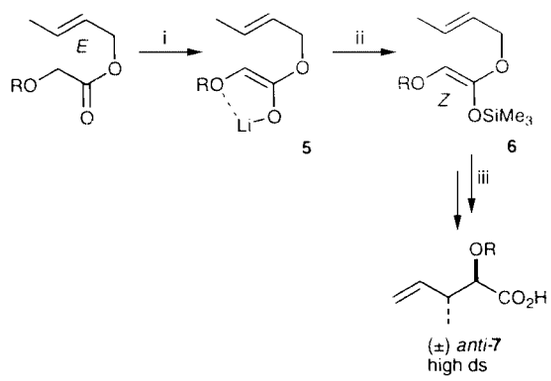
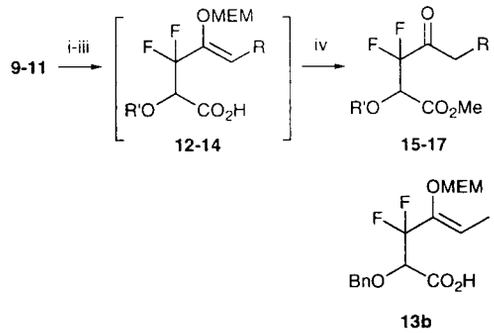
Table 1 Preparation of esters used for rearrangement

R	Alcohol	R′ = Me	Yield (%)	R′ = Bn	Yield (%)	R′ = allyl	Yield (%)
H	**8a**	**9a**	79[a]	—	—	—	—
Me	**8b**	—	—	**10b**	92[b,c]	—	—
Et	**8c**	**9c**	85	**10c**	82	**11c**	83
i-Pr	**8d**	**9d**	81	**10d**	75	**11d**	80
t-Bu	**8e**	**9e**	82	**10e**	85	—	—
Ph	**8f**	**9f**	79	**10f**	79	—	—
$CH{=}CH_2$	**8g**	**9g**	72	—	—	—	—

[a] This ester was only moderately stable and could not be characterised fully. [b] Esterification started at 0 °C. [c] Obtained in 96% purity and used without purification.



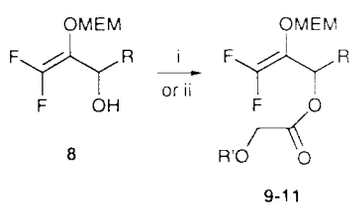
Scheme 3 *Reagents and conditions*: i, LDA, THF, −78 °C; ii, Me_3SiCl; iii, Δ then work-up.



Scheme 5 *Reagents and conditions*: i, LDA, THF, −78 °C; ii, Me_3SiCl; iii, Δ then work-up; iv, $SOCl_2$, MeOH, 0 °C to rt, 18 hours.

from esters of lactic[16] and hydroxybutyric[17] acids have also proved sufficiently stable for trapping and rearrangement though the range of examples is more limited. The main limitation to the method arises from the tendency of ester enolates to fragment to the corresponding ketene–alkoxide pair;[18] trapping with the silicon electrophile must therefore be efficient at low temperature. When a difluoroallylic ester is deprotonated, elimination appears to be particularly facile and we were not able to perform simple Ireland ester enolate Claisen rearrangements. However, alkoxyacetates could be deprotonated and trapped successfully, presumably because the chelation of the lithium atom stabilises the enolates against fragmentation as well as controlling their configuration.

Difluoroallylic alcohols **8** were synthesised according to our published method[19] and methoxy (**9**), benzyloxy (**10**) and allyloxy (**11**) esters were prepared (Scheme 4, Table 1) from the



Scheme 4 *Reagents and conditions*: i, $MeOCH_2COCl$ or $BnOCH_2COCl$, pyridine, DMAP, DCM, rt, 18 hours then extractive work-up; ii, $H_2C{=}CHCH_2OCH_2CO_2H$, EDC, DMAP, DCM, rt, 18 hours then extractive work-up.

commercial acid chlorides in the first two cases, and from allyloxyacetic acid in the last using a diimide coupling. Chromatography was not always necessary; for example, ester **10b** was obtained direct from the work-up in 96% purity (by GC) on a 20 g scale.

Rearrangements were executed cleanly (Scheme 5) when the esters were added slowly to freshly generated LDA in THF at −78 °C. The silicon electrophile was added five minutes after the end of the addition, then the mixture was allowed to warm to room temperature over one hour and quenched with methanol. Prior to quenching, the ester was no longer visible by TLC, and NMR of the crude acid after work-up indicated (in each case) the presence of a single fluorinated compound **12**–**14**.

In the case of **13b** (from **10b**), the crude product also exhibited satisfactory NMR spectra (though most products were esterified directly, see later). Procedures using other bases were less successful; the same procedure with LTMP (TMP = 2,2,6,6-tetramethylpiperidine) returned the starting ester, while mostly starting material (*ca.* 75%) was recovered when LiHMDS was used, along with a small amount (*ca.* 25%) of rearranged material and a number of unidentified minor products. The Lewis acid-mediated procedure described by Oh *et al.*[20] led to the recovery of starting material and fragmentation product only. No advantage in yield accrued when more than one equivalent of silicon electrophile was added (we tried up to a six-fold excess).

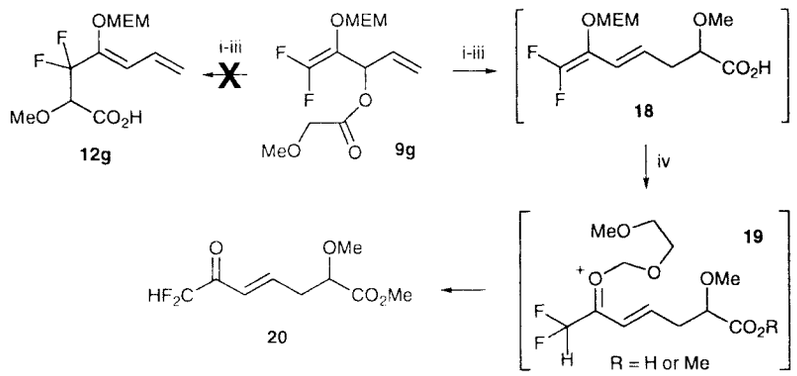
We were not able to purify the acids and instead investigated the preparation of the esters directly. Treatment with diazomethane (generated *in situ*) resulted in decomposition; we were not able to isolate any identifiable products from the reaction mixtures. The observation of a similar pattern of behaviour under the iodomethane–*N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) conditions used by Kocienski and co-workers,[21] suggested a decarboxylative pathway involving β-fluoride elimination. However, esterification was successful under acidic conditions;[22] simply taking the crude acid into cold (0 °C) methanol and adding thionyl chloride led to the formation of the methyl esters **15**–**17** (Table 2), from which the MEM-group had been cleaved.

In the case of **9g**, rearrangement is possible at either of two vinylic termini; the dienyl ester fragmented when exposed to LDA at −78 °C so we carried out the deprotonation under trapping conditions at −100 °C and isolated crude material that contained only **18** in an estimated yield of 71%, and *none* of the product (**12g**) of rearrangement through the fluorinated terminus (Scheme 6). When we rearranged **8g** under Eschenmoser conditions (Scheme 7), the major rearrangement product was **21** at the expense of **22**.[23]

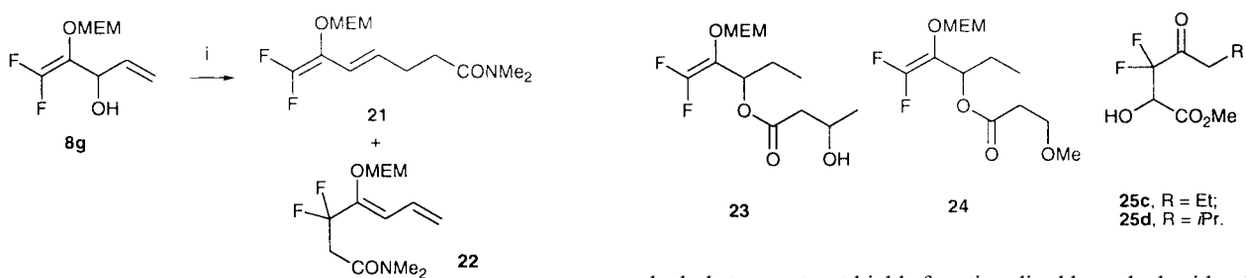
These observations suggest that Claisen and related rearrangements occur more slowly when fluorine atom sub-

Table 2 Ketoesters prepared by rearrangement and methanolysis

R	R′ = Me	Yield (%)	R′ = Bn	Yield (%)	R′ = allyl	Yield (%)
Me	—	—	**16b**	74	—	—
Et	**15c**	54	**16c**	58	**17c**	63
i-Pr	**15d**	56	**16d**	54	**17d**	60
t-Bu	**15e**	65	**16e**	76	—	—
Ph	**15f**	61	—	—	—	—



Scheme 6 *Reagents and conditions*: i, LDA–Me_3SiCl, THF, −100 °C, inverse addition; ii, warm to rt; iii, aqueous work-up; iv, $TMSCHN_2$, MeOH.



Scheme 7 *Reagents and conditions*: i, $HC(OMe)_2NMe_2$, PhMe, 60 °C.

stituents are located at C-6 and are consistent with the general conclusion of Purrington and Weeks[24] that "no acceleration of rearrangement of the esters derived from 3,3-difluoroallyl alcohols compared with their non-fluorinated analogs was observed," whereas the effect of fluorination at C-1 and C-2 is unambiguously accelerative, as documented by Normant,[25] Gelb[26] and Gerhart[27] *inter alia*. In contrast, Dauben–Dietsch rearrangement of **8c** occurred at 40 °C, an unusually low temperature,[28] and was followed by dehydrofluorination. However, we are not able to rule out the possibility that this unusually facile rearrangement is mercury(II)-catalysed or -mediated.[29] Burkhart and co-workers concluded that [3,3] Claisen rearrangements of γ,γ-difluoroallylic (C-6-difluorination) alcohols are *accelerated* relative to the non-fluorinated congeners, though the systems described in their paper lack control experiments and were not capable of competitive reactions. We suggest that the observations of Schemes 6 and 7 reinforce strongly the conclusion of Purrington and Weeks.

Cleavage of the MEM-group of **18** occurred upon standing in $CDCl_3$; we speculated that C-protonation of the enol acetal might be occurring intramolecularly,[30] so the acid was esterified with TMS-diazomethane. However, column chromatography of the product returned enone **20** in 50% yield; presumably, the increased conjugation increases the reactivity of the system towards C-protonation through stabilisation of the conjugate acid **19** implying a mechanism for MEM cleavage as described in Scheme 6.

Though suspicious that we were operating close to the limit of enolate stability, we explored the less common rearrangements of 3-hydroxybutyrate[17] and 3-methoxypropionate[13] esters **23** and **24**. Kurth used the former esters of simple allylic alcohols to construct highly functionalised branched acids with moderate stereocontrol; adequate ester enolate stabilisation by β-alkoxy groups does not appear to be established, whereas β-amino groups have been exploited successfully.[31] In any case, the conditions described by Kurth led only to decomposition and a number of attempts using trapping conditions met with a similar fate. We suggest that the difluoroallylic alkoxides are too competent as leaving groups for the derived enolates to persist when the chelation effect is weaker.

Deprotection of the C-2 hydroxy group could be achieved by palladium-catalysed hydrostannation of allyl ethers[32] **17c** and **17d**, but debenzylations[33] (H_2/20 wt% $Pd(OH)_2$–C, MeOH, 1 atm) of **16c** and **16d** were cleaner reactions and afforded pleasing yields of the alcohols **25c** and **25d** respectively. Studies of the relative propensities for hydration of 2-alkoxy and 2-hydroxy ketoesters are in progress. Once again, trifluoroethanol serves as a useful starting material for the preparation of highly functionalised difluorocompounds. In this case, the CF_2 centre is surrounded by three oxygen functions differentiated by their oxidation states. The sequences are short, the chemistry is scalable and the penultimate educts **15**–**17** can be isolated with a minimum of chromatography. The route complements the well-known and often used Reformatsky[34] entry to highly functionalised difluorocompounds.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 (300.13 and 75.47 MHz respectively) spectrometer. 500 MHz NMR spectra were recorded on a Bruker DRX500 spectrometer. All spectra were recorded relative to tetramethylsilane as the internal standard. ^{19}F NMR spectra were recorded on Bruker AC-300 (282.41 MHz) relative to chlorotrifluoromethane as the internal standard. The ^{19}F NMR spectra of

rearrangement educts reveal an AB quartet in which each "doublet" is further split by $^3J_{H-F}$ coupling (to provide a doublet of doublets). The much larger $^2J_{F-F}$ coupling (greater than 25 times) means that the overall appearance of these is one of an AB quartet. This descriptor is therefore retained in describing these more complex multiplicities using the modification: chemical shift (1F, dd, one half of an AB quartet, $^2J_{F-F}$, $^3J_{H-F}$). Chemical ionisation (CI) and electron impact (EI) mass spectra were recorded on a Kratos MS-80 mass spectrometer or a VG ProSpec mass spectrometer with a DS-90 data system. Chemical ionisation (CI) methods used ammonia as the reagent gas. Fast atom bombardment (FAB) mass spectra were recorded using a VG Zabspec instrument. A Micromass LCT mass spectrometer was used for both low resolution (ES-TOF) mass spectra (using a methanol mobile phase) and HRMS measurements (using a lockmass incorporated into the mobile phase). HRMS measurements were also obtained from either the VG ProSpec spectrometer or a VG Autospec instrument. Elemental analyses were performed at the University of North London. Thin layer chromatography was performed on precoated aluminium-backed silica gel plates supplied by E. Merck, A. G. Darmstadt, Germany (silica gel 60 F254, thickness 0.2 mm, Art. 5554). Visualisation was achieved by UV light and/or an anisaldehyde–sulfuric acid or potassium permanganate stain. Flash column chromatography was performed using an air compressor on silica gel (E. Merck A. G. Kieselgel 60, Art. 9385). THF was dried by refluxing with benzophenone over sodium wire until a deep purple colour developed. It was then distilled and collected by dry syringe as required. Dichloromethane was dried by refluxing with calcium hydride, subsequently distilled and collected by dry syringe as required. Methanol was dried by refluxing with iodine and magnesium turnings for 3 hours, and subsequently distilled onto 3 Å molecular sieves. *n*-Butyllithium was titrated before use against 1,3-diphenylpropan-2-one *p*-tolylsulfonylhydrazone. Thionyl chloride was distilled from 10% triphenyl phosphite (w/w) under an atmosphere of nitrogen. Diisopropylamine was distilled from calcium hydride and stored over calcium hydride under an atmosphere of nitrogen. DCC and EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] were used as supplied by the Aldrich Chemical Co. Ltd. All organic extracts were dried using oven-dried magnesium sulfate. Light petroleum refers to the fraction boiling in the range 40–60 °C. Difluoroallylic alcohols were prepared according to our published procedure,[19] except for **8b** which was prepared as described below.

4,4-Difluoro-3-[(methoxyethoxy)methoxy]but-3-en-2-ol 8b

2-[(Methoxyethoxy)methoxy]-1,1,1-trifluoroethane (18.8 g, 0.1 mol) was added slowly to a stirred solution of LDA (generated from *n*-butyllithium (140 ml of a 1.43 M solution in hexanes, 0.20 mol) and dry diisopropylamine (26 ml, 0.205 mmol)) in THF (100 ml) at −78 °C. The dark orange suspension was stirred at −78 °C for 30 minutes, then freshly fractionated acetaldehyde (4.4 g, 0.1 mol) was added in a thin stream. The mixture was allowed to warm to −30 °C over 2 hours then quenched with methanolic ammonium chloride (100 ml) and allowed to warm to room temperature. The mixture was then poured into water (800 ml) and extracted with ethyl ether (3 × 100 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated at reduced pressure (> 40 mmHg). Reduced pressure short path distillation afforded **8b** as a colourless oil (13.2 g, 74%, 97% pure by GC) bp 57 °C/0.15 mmHg; δ_H (300 MHz, $CDCl_3$) 5.00 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.6, OCH_aH_bO), 4.88 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.6, OCH_aH_bO), 4.51–4.39 (1H, br s, O*H*), 3.99–3.90 (2H, m, OCH_2CH_2O), 3.82–3.73 (2H, m, OCH_2CH_2O), 3.58–3.52 (1H, m, C*H*OH), 3.48 (3H, s, OCH_3), 1.35 (3H, d, $^3J_{H-H}$ 7.3, $CHCH_3$); δ_F (282 MHz, $CDCl_3$) −100.9 (1F, d, $^2J_{F-F}$ 64.9), −109.6 (1F, d, $^2J_{F-F}$ 64.9); δ_C (75 MHz, $CDCl_3$) 154.0 (dd, $^1J_{C-F}$ 291.3, 285.7), 118.9 (td, $^2J_{C-F}$ 36.5, 9.9), 97.9, 71.4, 68.4, 63.0 (dd, $^3J_{C-F}$ 3.9, 1.7), 58.9, 20.1 (t, $^4J_{C-F}$ 2.3). The alcohol was taken on to the ester without further characterisation.

3,3-Difluoro-2-[(methoxyethoxy)methoxy]prop-2-en-1-yl (methoxy)acetate 9a

In a typical procedure, pyridine (0.61 ml, 7.6 mmol), followed by methoxyacetyl chloride (1.18 ml, 7.6 mmol), was added to a stirred solution of **8a** (1.5 g, 7.6 mmol) in DCM (20 ml) containing DMAP (0.35 g, 3.04 mmol). The mixture was stirred at room temperature and followed by TLC. After 18 hours, all of the starting material had been converted to a new product (R_f = 0.33, 50% ethyl ether in light petroleum). The solution was then concentrated *in vacuo* and the residue taken up in DCM. The solution was washed with HCl (20 ml, 0.1 M) then water (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. Kugelrohr distillation afforded ester **9a** (1.62 g, 79%) as a colourless oil; bp 85 °C/0.05 mmHg; R_f (50% ethyl ether in light petroleum) 0.33; δ_H (300 MHz, $CDCl_3$) 4.92 (2H, s, OCH_2O), 4.80 (2H, t, $^4J_{H-F}$ 2.6, CCH_2O), 4.05 (2H, s, CH_2OCH_3), 3.85–3.78 (2H, m, OCH_2CH_2O), 3.55–3.50 (2H, m, OCH_2CH_2O), 3.45 (3H, s, OCH_3), 3.35 (3H, s, OCH_3); δ_F (282 MHz, $CDCl_3$) −96.0 (1F, d, $^2J_{F-F}$ 52.2), −106.0 (1F, d, $^2J_{F-F}$ 52.2); δ_C (75 MHz, $CDCl_3$) 169.8, 155.7 (t, $^1J_{C-F}$ 289.2), 111.5 (dd, $^2J_{C-F}$ 52.3, 16.4), 95.8, 71.4, 69.4, 68.1, 59.2, 58.8, 58.5; mass spectra and microanalysis could not be obtained, as surprisingly, the compound is unstable and decomposes upon storage. Further transformations of this compound were not pursued.

1,1-Difluoro-2-[(methoxyethoxy)methoxy]pent-1-en-3-yl (methoxy)acetate 9c

From **8c** (2.0 g, 8.85 mmol), methoxyacetyl chloride (0.9 ml, 8.85 mmol), pyridine (0.71 ml, 8.85 mmol) and DMAP (0.4 g, 3.5 mmol) in DCM (50 ml). Usual work-up then Kugelrohr distillation afforded ester **9c** (2.23 g, 85%) as a colourless oil, bp 80 °C/0.05 mmHg; R_f (50% ethyl ether in light petroleum) 0.29; ν_{max} (film)/cm^{-1} 1748br s (C=O); δ_H (300 MHz, $CDCl_3$) 5.45 (1H, t, $^4J_{H-F}$ 7.3, C*H*), 4.95 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.2, OCH_aH_bO), 4.80 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.2, OCH_aH_bO), 4.00 (2H, s, $C(O)CH_2OCH_3$), 3.90–3.70 (2H, m, OCH_2CH_2O), 3.55 (2H, t, $^3J_{H-H}$ 5.1, OCH_2CH_2O), 3.40 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 1.85–1.70 (2H, m, CH_2CH_3), 0.85 (3H, t, $^3J_{H-H}$ 7.3, CH_2CH_3); δ_F (282 MHz, $CDCl_3$) −97.00 (1F, d, $^2J_{F-F}$ 55.3), −105.39 (1F, d, $^2J_{F-F}$ 55.3); δ_C (75 MHz, $CDCl_3$) 169.3, 155.7 (quat, t, $^1J_{C-F}$ 292.2), 112.9 (quat, dd, $^1J_{C-F}$ 53.1, 14.7), 97.2, 71.7, 71.5, 69.6, 68.4, 59.3, 58.9, 23.9, 9.5 [HRMS (ES, M[Na]$^+$) Found: 321.1139. Calc. for $C_{12}H_{20}O_6F_2Na$ 321.1126]; *m*/*z* (CI) 316 (20%, $[M + NH_4]^+$), 209 (12), 89 (100).

1,1-Difluoro-2-[(methoxyethoxy)methoxy]-4-methylpent-1-en-3-yl (methoxy)acetate 9d

From **8d** (1.0 g, 4.20 mmol), methoxyacetyl chloride (0.65 ml, 4.20 mmol), pyridine (0.34 ml, 4.20 mmol) and DMAP (0.2 g, 1.70 mmol) in DCM (25 ml). Usual work-up and Kugelrohr distillation afforded ester **9d** (1.06 g, 81%) as a colourless oil, bp 80 °C/0.05 mmHg (Found: C, 50.20; H, 7.14. Calc. for $C_{13}H_{22}O_6F_2$: C, 50.00; H, 7.10%); R_f (40% ethyl ether in light petroleum) 0.3; δ_H ($CDCl_3$, 300 MHz) 5.17 (1H, d, $^3J_{H-H}$ 3.1, C*H*), 4.95 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.2, OCH_aH_bO), 4.80 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.2, OCH_aH_bO), 4.00 (2H, s, CH_2), 3.88–3.65 (4H, m, OCH_2CH_2O), 3.35 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 2.20–2.00 (1H, m, $CH(CH_3)_2$), 0.95–0.80 (6H, d, $^3J_{H-H}$ 12.0, $CH(CH_3)_2$); δ_F ($CDCl_3$, 282 MHz) −97.2 (1F, d, $^2J_{F-F}$ 56.4), −105.5 (1F, d, $^2J_{F-F}$ 56.4); δ_C ($CDCl_3$, 75 MHz) 169.4, 155.9 (t, $^1J_{C-F}$ 297.6),

114.2 (dd, $^2J_{C-F}$ 57.1, 14.3), 97.2, 75.4, 71.5, 65.6, 59.5, 59.3, 59.0, 29.1, 18.2 [HRMS (CI, M[NH_4]$^+$) Found: 330.174323. Calc. for $C_{13}H_{26}NO_6F_2$ 330.172819]; *m/z* (CI) 330 (100%, [M + NH_4]$^+$).

1,1-Difluoro-2-[(methoxyethoxy)methoxy]-4,4-dimethylpent-1-en-3-yl (methoxy)acetate 9e

From **8e** (0.6 g, 2.45 mmol), methoxyacetyl chloride (0.40 ml, 2.45 mmol), pyridine (0.20 ml, 2.45 mmol) and DMAP (0.11 g, 0.98 mmol) in DCM (20 ml). Usual work-up and purification by Kugelrohr distillation afforded the ester **9e** (0.64 g, 82%) as a colourless oil, bp 82 °C/0.1 mmHg; R_f (40% ethyl ether in light petroleum) 0.36; δ_H ($CDCl_3$, 300 MHz) 5.17 (1H, d, $^4J_{H-F}$ 2.9, C*H*), 4.92 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 5.9, OCH_aH$_b$O), 4.82 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 5.9, OCH$_a$$H_b$O), 4.05 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 16.5, CH_aH$_b$OCH$_3$), 3.95 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 16.5, CH_aH$_b$OCH$_3$), 3.82–3.71 (2H, m, OCH_2CH$_2$O), 3.55–3.49 (2H, m, OCH$_2$CH_2O), 3.40 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 0.90 (9H, s, C(CH_3)$_3$); δ_F ($CDCl_3$, 282 MHz) −97.4 (1F, dd, $^2J_{F-F}$ 56.4, $^4J_{H-F}$ 2.9), −104.8 (1F, d, $^2J_{F-F}$ 56.4); δ_C ($CDCl_3$, 75 MHz) 169.5, 156.2 (t, $^1J_{C-F}$ 289.9), 112.6 (dd, $^2J_{C-F}$ 54.8, 14.8), 97.7, 76.0, 71.6, 69.6, 68.6, 59.4, 58.9, 35.3, 26.2 (3 signals) [HRMS (ES, M[Na]$^+$) Found: 349.1429. Calc. for $C_{14}H_{24}O_6F_2Na$ 349.1439]; *m/z* (ES) 349 (60%, [M + Na]$^+$), 257 (100).

3,3-Difluoro-2-[(methoxyethoxy)methoxy]-1-phenylprop-2-en-1-yl (methoxy)acetate 9f

From **8f** (1.23 g, 4.48 mmol), methoxyacetyl chloride (0.56 ml, 4.48 mmol), pyridine (0.36 ml, 4.48 mmol) and DMAP (0.21 g, 1.80 mmol) in DCM (35 ml). Usual work-up and purification by Kugelrohr distillation afforded the ester **9f** (1.23 g, 79%) as a colourless oil, bp 93 °C/0.1 mmHg; R_f (40% ethyl ether in light petroleum) 0.41; ν_{max} (film)/cm^{-1} 1762br s (C=O); δ_H (300 MHz, $CDCl_3$) 7.40–7.30 (5H, m, Ph), 6.62 (1H, t, $^4J_{H-F}$ 1.6, C*H*), 4.90 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.9, OCH_aH$_b$O), 4.70 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.9, OCH$_a$$H_b$O), 4.20 (2H, s, C$H_2OCH_3$), 3.75–3.61 (2H, m, OC$H_2CH_2$O), 3.55–3.45 (2H, m, OCH$_2$CH_2O), 3.44 (3H, s, OCH_3), 3.35 (3H, s, OCH_3); δ_F (282 MHz, $CDCl_3$) −96.4 (1F, d, $^2J_{F-F}$ 54.5), −104.7 (1F, d, $^2J_{F-F}$ 54.5); δ_C (75 MHz, $CDCl_3$) 169.0, 155.7 (t, $^1J_{C-F}$ 288.6), 135.7, 128.6 (4 signals), 126.5, 112.8 (dd, $^2J_{C-F}$ 55.2, 14.6), 97.5, 71.5, 71.0, 69.7, 68.5, 59.5, 59.0 [HRMS (ES, M[Na]$^+$) Found: 369.1151. Calc. for $C_{16}H_{20}O_6F_2Na$ 369.1126]; *m/z* (CI) 364 (42%, [M + NH_4]$^+$), 254 (33), 108 (76), 59 (100).

1,1-Difluoro-2-[(methoxyethoxy)methoxy]penta-1,4-dien-3-yl (methoxy)acetate 9g

From **8g** (2.0 g, 8.9 mmol), methoxyacetyl chloride (1.38 ml, 8.9 mmol), pyridine (0.72 ml, 8.9 mmol) and DMAP (0.43 g, 1.80 mmol) in DCM (35 ml). Usual work-up and purification by column chromatography afforded the ester **9g** (1.89 g, 72%) as a colourless oil; R_f (50% ethyl ether in light petroleum) 0.38; ν_{max} (film)/cm^{-1} 1738s (C=O); δ_H (300 MHz, $CDCl_3$) 6.05 (1H, d, $^3J_{H-H}$ 6.0, C*H*), 5.98–5.85 (1H, m, CC*H*CH$_2$), 5.38 (1H, d, $^3J_{H-H}$ 15.0, C*H*′), 5.33 (1H, d, $^3J_{H-H}$ 9.0, C*H*′), 4.95 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 7.5, OCH_aH$_b$O), 4.88 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 7.5, OCH$_a$$H_b$O), 4.05 (2H, s, C$H_2OCH_3$), 3.72–3.70 (2H, m, OC$H_2CH_2$O), 3.50–3.33 (2H, m, OCH$_2$CH_2O), 3.45 (3H, s, OCH_3), 3.35 (3H, s, OCH_3); δ_F (282 MHz, $CDCl_3$) −96.4 (1F, d, $^2J_{F-F}$ 53.0), −104.2 (1F, d, $^2J_{F-F}$ 53.0); δ_C (75 MHz, $CDCl_3$) 168.9, 155.5 (t, $^1J_{C-F}$ 292.3), 131.4, 119.2, 113.3 (dd, $^2J_{C-F}$ 36.2, 15.3), 97.2, 71.5, 70.6, 69.6, 68.5, 59.3, 59.0 [HRMS (CI, M[NH_4]$^+$) Found: 314.142009. Calc. for $C_{12}H_{22}NO_6F_2$ 314.141519]; *m/z* (CI) 314 (100% [M + NH_4]$^+$.

4,4-Difluoro-3-[(methoxyethoxy)methoxy]but-3-en-2-yl (benzyloxy)acetate 10b

Pyridine (5.22 ml, 64.6 mmol), followed by benzyloxyacetyl chloride (11.93 g, 64.6 mmol), was added slowly (over 20 minutes) to a stirred solution of **8b** (11.56 g, 64.6 mmol) in DCM (100 ml) containing DMAP (2.7 g, 22 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight; TLC then showed the reaction to be complete. The solution was poured into cold HCl (100 ml of a 0.1 M aqueous solution) and extracted with ethyl ether (3 × 40 ml) then the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford **10b** as a pale yellow oil (20.72 g, 92%) which was used without further purification (96% pure by GC); R_f (50% ethyl ether in light petroleum) 0.42; ν_{max} (film)/cm^{-1} 2921br s, 1761br s (C=O), 1604w, 1496s, 1454s, 1248br s, 1194br s, 1128br s, 1044br s, 942s, 855m, 733s, 697s; δ_H ($CDCl_3$, 300 MHz) 7.37–7.28 (5H, m, Ph), 5.73–5.65 (1H, m, C*H*), 4.97 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.3, OCH_aH$_b$O), 4.90 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.3, OCH$_a$$H_b$O), 4.63 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 11.8, OCH_aH$_b$Ph), 4.58 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 11.8, OCH$_a$$H_b$-Ph), 4.06 (2H, s, C(O)C$H_2$O), 3.88–3.73 (2H, m, OC$H_2CH_2$O), 3.57–3.52 (2H, m, OCH$_2$CH_2O), 3.38 (3H, s, OCH_3), 1.44 (3H, d, $^3J_{H-H}$ 7.3, CHCH_3); δ_F ($CDCl_3$, 282 MHz) −97.3 (1F, d, $^2J_{F-F}$ 55.1), −104.7 (1F, d, $^2J_{F-F}$ 55.1); δ_C ($CDCl_3$, 75 MHz) 169.3, 155.9 (t, $^1J_{C-F}$ 292.1), 137.2, 128.6, 128.2, 114.1 (dd, $^2J_{C-F}$ 36.2, 14.7), 97.4, 73.5, 71.5, 68.6, 67.2, 59.2, 24.1, 17.1 (t, $^4J_{C-F}$ 2.3); *m/z* (ES) 360 (78%, M$^+$), 192 (100).

1,1-Difluoro-2-[(methoxyethoxy)methoxy]pent-1-en-3-yl (benzyloxy)acetate 10c

From **8c** (0.9 g, 3.89 mmol) in DCM (20 ml), pyridine (0.31 ml, 4.28 mmol), benzyloxyacetyl chloride (0.48 ml, 4.28 mmol) and DMAP (0.20 g, 1.56 mmol). Usual work-up and column chromatography afforded ester **10c** (1.16 g, 82%) as a colourless oil; R_f (50% ethyl ether in light petroleum) 0.45 (Found: C, 58.03; H, 6.50. Calc. for $C_{18}H_{24}O_6F_2$: C, 57.75; H, 6.46%); δ_H ($CDCl_3$, 300 MHz) 7.48–7.32 (5H, m, Ph), 5.50–5.42 (1H, m, C*H*), 4.98 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 5.9, OCH_aH$_b$O), 4.88 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 5.9, OCH$_a$$H_b$O), 4.64 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 11.8, OCH_aH$_b$Ph), 4.58 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 11.8, OCH$_a$$H_b$-Ph), 4.05 (2H, s, C(O)C$H_2$O), 3.88–3.70 (2H, m, OC$H_2CH_2$O), 3.55–3.52 (2H, m, OCH$_2$CH_2O), 3.35 (3H, s, OCH_3), 1.85–1.70 (2H, m, CH_2CH$_3$), 0.91 (3H, t, $^3J_{H-H}$ 7.3, CH$_2$CH_3); δ_F ($CDCl_3$, 282 MHz) −96.70 (1F, d, $^2J_{F-F}$ 54.9), −105.1 (1F, d, $^2J_{F-F}$ 54.9); δ_C ($CDCl_3$, 75 MHz) 169.6, 155.9 (t, $^1J_{C-F}$ 292.1), 137.2, 128.6, 128.2, 113.2 (dd, $^2J_{C-F}$ 15.5, 36.8), 97.4, 73.5, 71.9, 71.5, 68.6, 67.2, 59.2, 24.1, 9.7; *m/z* (CI) 392 (26%, [M + NH_4]$^+$), 300 (36), 242 (76), 184 (87), 91 (100).

1,1-Difluoro-2-[(methoxyethoxy)methoxy]-4-methylpent-1-en-3-yl (benzyloxy)acetate 10d

From alcohol **8d** (1.0 g, 4.16 mmol), benzyloxyacetyl chloride (0.71 ml, 4.60 mmol), pyridine (0.37 ml, 4.60 mmol) and DMAP (0.2 g, 1.70 mmol) in DCM (25 ml). Usual work-up and column chromatography afforded **10d** (1.22 g, 75%) as a colourless oil; R_f (20% ethyl acetate in light petroleum) 0.57; ν_{max} (film)/cm^{-1} 1761 (C=O) (Found: C, 58.92; H, 6.88. Calc. for $C_{19}H_{26}O_5F_2$: C, 58.75; H, 6.75%); δ_H ($CDCl_3$, 300 MHz) 7.40–7.25 (5H, m, Ph), 5.25–5.15 (1H, m, C*H*), 4.95 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.2, OCH_aH$_b$O), 4.85 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.2, OCH$_a$$H_b$O), 4.66 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 11.8, OCH_aH$_b$Ph), 4.61 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 11.8, OCH$_a$$H_b$Ph), 4.10 (2H, s, C(O)C$H_2$O), 3.85–3.70 (2H, m, OC$H_2CH_2$O), 3.65–3.45 (2H, m, OCH$_2$CH_2O), 3.35 (3H, s, OCH_3), 2.25–2.05 (1H, m, C*H*(CH$_3$)$_2$), 0.95 (3H, d, $^3J_{H-H}$ 6.6, CH(CH_3)$_2$), 0.91 (3H, d,

$^2J_{H–H}$ 6.6, CH(CH_3)$_2$); δ_F ($CDCl_3$, 282 MHz) −97.1 (1F, d, $^2J_{F–F}$ 55.9), −105.4 (1F, d, $^2J_{F–F}$ 55.9); δ_C ($CDCl_3$, 75 MHz) 169.6, 155.9 (t, $^1J_{C–F}$ 292.0), 137.2, 128.6, 128.1, 112.8 (dd, $^2J_{C–F}$ 36.2, 14.9), 97.3, 75.5, 73.4, 71.6, 68.5, 67.1, 59.1, 29.2, 18.9, 18.3; *m/z* (CI) 406 (55%, [M + NH_4]$^+$), 184 (65), 108 (82), 59 (100).

1,1-Difluoro-2-[(methoxyethoxy)methoxy]-4,4-dimethylpent-1-en-3-yl (benzyloxy)acetate 10e

From **8e** (0.80 g, 3.16 mmol), benzyloxyacetyl chloride (0.54 ml, 3.50 mmol), pyridine (0.28 ml, 3.50 mmol) and DMAP (0.11 g, 1.26 mmol) in DCM (25 ml). Usual work-up and column chromatography afforded **10e** (1.30 g, 85%) as a colourless oil; R_f (20% ethyl acetate in light petroleum) 0.51 (Found: C, 59.81; H, 6.84. Calc. for $C_{18}H_{24}O_6F_2$: C, 59.69; H, 7.01%); δ_H ($CDCl_3$, 300 MHz) 7.40–7.21 (5H, m, Ph), 5.25–5.19 (1H, m, C*H*), 4.93 (1H, d, one half of an AB quartet, $^2J_{Ha–Hb}$ 5.9, OCH_aH$_b$O), 4.82 (1H, d, one half of an AB quartet, $^2J_{Ha–Hb}$ 5.9, OCH$_a$$H_b$O), 4.65 (1H, d, one half of an AB quartet, $^2J_{Ha–Hb}$ 11.8, OCH_aH$_b$Ph), 4.56 (1H, d, one half of an AB quartet, $^2J_{Ha–Hb}$ 11.8, OCH$_a$$H_b$Ph), 4.12 (2H, s, C(O)C$H_2$O), 3.80–3.68 (2H, m, OC$H_2CH_2$O), 3.50–3.41 (2H, m, OCH$_2$CH_2O), 3.30 (3H, s, OCH_3), 1.00 (9H, s, C(CH_3)$_3$); δ_F ($CDCl_3$, 282 MHz) −97.4 (1F, d, $^2J_{F–F}$ 56.4), −104.7 (1F, dd, $^2J_{F–F}$ 56.4, $^4J_{H–F}$ 1.97); δ_C ($CDCl_3$, 75 MHz) 169.7, 156.3 (t, $^1J_{C–F}$ 296.2), 137.3, 128.6, 128.1, 112.8 (dd, $^2J_{C–F}$ 35.7, 15.0), 97.9, 76.3, 73.5, 71.7, 68.7, 67.2, 59.2, 35.5, 26.4; *m/z* (CI) 420 (26%, [M + NH_4]$^+$), 252 (15), 184 (55), 106 (100).

3,3-Difluoro-2-[(methoxyethoxy)methoxy]-1-phenylprop-2-en-1-yl (benzyloxy)acetate 10f

From alcohol **8f** (1.23 g, 4.48 mmol), benzyloxyacetyl chloride (0.56 ml, 4.48 mmol), pyridine (0.36 ml, 4.48 mmol) and DMAP (0.21 g, 1.80 mmol) in DCM (35 ml). Usual work-up and column chromatography afforded **10f** (1.56 g, 79%) as a colourless oil; R_f (40% ethyl ether in light petroleum) 0.41; δ_H ($CDCl_3$, 300 MHz) 7.49–7.26 (10H, m, Ph), 6.67–6.63 (1H, m, C*H*), 4.88 (1H, d, one half of an AB quartet, $^2J_{Ha–Hb}$ 5.7, OCH_aH$_b$O), 4.67 (1H, d, one half of an AB quartet, $^2J_{Ha–Hb}$ 5.7, OCH$_a$$H_b$O), 4.46 (2H, s, OC$H_2$Ph), 4.22 (2H, s, C(O)C$H_2$), 3.75–3.61 (2H, m, OC$H_2CH_2$O), 3.49–3.42 (2H, m, OCH$_2$CH_2O), 3.32 (3H, s, OCH_3); δ_F ($CDCl_3$, 282 MHz) −96.4 (1F, d, $^2J_{F–F}$ 53.6), −104.6 (1F, d, $^2J_{F–F}$ 53.6); δ_C ($CDCl_3$, 75 MHz) 169.1, 155.6 (t, $^1J_{C–F}$ 289.9), 137.0, 135.7, 128.6, 128.5, 128.0, 113.6 (dd, $^2J_{C–F}$ 35.7, 15.3), 97.5, 73.4, 71.4, 70.9, 68.5, 67.1, 58.9 [HRMS (ES, M[Na]$^+$) Found: 445.1444. Calc. for $C_{22}H_{24}O_6F_2Na$ 445.1439]; *m/z* (ES) 423 (100%, [M + H]$^+$).

(Allyloxy)acetic acid

A solution of allyl alcohol (5.80 ml, 0.09 mol) in THF (20 ml) was added dropwise to a cool (0 °C) solution of sodium hydride (5.16 g, 0.13 mol, of a 60% dispersion from which the oil had been washed with hexane) in THF (30 ml). The grey coloured suspension was stirred at 0 °C for an hour, then a solution of chloroacetic acid (4.06 g, 0.04 mol) in THF (20 ml) was added dropwise. Upon completion of the addition, the reaction mixture was heated to reflux and maintained there for a further two hours before being cooled and quenched (**CAUTION**) with HCl (20 ml, of a 1 M aqueous solution). The reaction mixture was then extracted with NaOH (3 × 20 ml, of a 2 M aqueous solution), and the aqueous layers were combined and carefully re-acidified (with a minimum volume of concentrated HCl) to pH 3 before being extracted with diethyl ether (3 × 50 ml). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford allyloxyacetic acid (7.01 g, 70%) as a pale yellow oil; δ_H ($CDCl_3$, 300 MHz) 10.82 (1H, br s, CO_2H), 5.91–5.79 (1H, m, H_2C=C*H*), 5.20–5.11 (2H, m, H_2C=CH), 4.18–4.00 (4H, m, 2 × CH_2); δ_C ($CDCl_3$, 75 MHz) 175.8, 133.3, 118.8, 72.4, 66.5; *m/z* (CI) 134 (100%, [M + NH_4]$^+$) which was used without further characterisation or purification.

1,1-Difluoro-2-[(methoxyethoxy)methoxy]pent-1-en-3-yl (allyloxy)acetate 11c

In a typical procedure, EDC (1.99 g, 9.73 mmol) was added to a cool (0 °C) solution of the alcohol **8c** (2.0 g, 8.85 mmol), DMAP (0.41 g, 3.54 mmol) in dry DCM (20 ml). The mixture was stirred until all of the EDC had dissolved, then allyloxyacetic acid (1.13 g, 9.73 mmol) was added and the reaction mixture was left to stir overnight. The mixture was then concentrated *in vacuo* and the residue taken up in a mixture of ethyl acetate (30 ml) and HCl (10 ml of a 1 M aqueous solution). The aqueous layer was removed and the organic layer washed with water (20 ml), saturated sodium bicarbonate (20 ml) and brine (20 ml) before being dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a pale yellow oil. Column chromatography afforded allyloxyacetate **11c** (2.37 g, 83%) as a colourless oil; R_f (50% ethyl ether in light petroleum) 0.48; δ_H ($CDCl_3$, 300 MHz) 5.98–5.81 (1H, m, C*H*=CH$_2$), 5.50–5.40 (1H, m, CF$_2$CC*H*), 5.32–5.18 (2H, m, CH=CH_2), 4.97 (1H, d, one half of an AB quartet, $^2J_{Ha–Hb}$ 5.9, OCH_aH$_b$O), 4.89 (1H, d, one half of an AB quartet, $^2J_{Ha–Hb}$ 5.9, OCH$_a$$H_b$O), 4.10–4.02 (4H, m, C(O)CH_2, OCH_2CH), 3.88–3.49 (2H, m, OCH_2CH$_2$O), 3.56–3.51 (2H, m, OCH$_2$CH_2O), 3.37 (3H, s, OCH_3), 1.83–1.71 (2H, m, CHCH_2-CH$_3$), 0.90 (3H, t, $^3J_{H–H}$ 10.7, CH$_2$CH_3); δ_F ($CDCl_3$, 282 MHz) −96.8 (1F, d, $^2J_{F–F}$ 54.8), −105.1 (1F, dd, $^2J_{F–F}$ 54.8, $^4J_{H–F}$ 1.70); δ_C ($CDCl_3$, 75 MHz) 169.5, 155.7 (t, $^1J_{C–F}$ 292.6), 133.7, 118.2, 97.3, 94.1 (dd, $^2J_{C–F}$ 14.7, 36.7), 72.3, 71.7, 71.5, 68.5, 67.0, 59.0, 23.9, 9.51 [HRMS (ES, M[Na]$^+$) Found: 347.1289. Calc. for $C_{14}H_{22}O_6F_2Na$ 347.1282]; *m/z* (FAB) 347 (90%, [M + Na]$^+$), 229 (100).

1,1-Difluoro-2-[(methoxyethoxy)methoxy]-4-methylpent-1-en-3-yl (allyloxy)acetate 11d

From **8d** (1.50 g, 6.30 mmol), DMAP (0.29 g, 2.52 mmol), EDC (1.41 g, 6.90 mmol) and allyloxyacetic acid (0.80 g, 6.90 mmol) in DCM. Usual work-up and column chromatography afforded allyloxyacetate **11d** (1.5 g, 80%) as a colourless oil; R_f (50% ethyl ether in light petroleum) 0.26; ν_{max} (film)/cm^{-1} 1760br s (C=O); δ_H ($CDCl_3$, 300 MHz) 5.97–5.78 (1H, m, C*H*=CH$_2$), 5.36–5.12 (3H, m, C*H*CF$_2$, CH=CH_2), 4.93 (1H, d, one half of an AB quartet, $^2J_{Ha–Hb}$ 6.2, OCH_aH$_b$O), 4.87 (1H, d, one half of an AB quartet, $^2J_{Ha–Hb}$ 6.2, OCH$_a$$H_b$O), 4.12–4.01 (4H, m, C(O)CH_2, CH_2CHCH$_2$), 3.87–3.68 (2H, m, OCH_2CH$_2$O), 3.57–3.49 (2H, m, OCH$_2$CH_2O), 3.46 (3H, s, OCH$_3$), 2.18–2.11 (1H, m, C*H*(CH$_3$)$_2$), 0.93 (3H, d, $^3J_{H–H}$ 6.6, CH(CH_3)$_2$), 0.90 (3H, d, $^3J_{H–H}$ 7.0, CH(CH_3)$_2$); δ_F ($CDCl_3$, 282 MHz) −97.2 (1F, d, $^2J_{F–F}$ 55.3), −105.4 (1F, d, $^2J_{F–F}$ 55.3); δ_C ($CDCl_3$, 75 MHz) 169.6, 155.9 (t, $^1J_{C–F}$ 292.0), 133.7, 118.1, 112.1 (dd, $^2J_{C–F}$ 36.7, 14.7), 97.3, 75.4, 72.4, 71.6, 68.4, 66.9, 59.0, 29.1, 19.2, 18.8 [HRMS (ES, M[Na]$^+$) Found: 361.1429. Calc. for $C_{15}H_{24}O_6F_2Na$ 361.1439]; *m/z* (ES) 361 (30%, [M + Na]$^+$), 284 (40), 243 (100).

Methyl 3,3-difluoro-2-methoxy-4-oxoheptanoate 15c (rearrangement, esterification and enol acetal methanolysis with thionyl chloride)

In a typical procedure, ester **9c** (0.60 g, 2.0 mmol) was added to a stirred solution of freshly prepared LDA (2.0 mmol) in THF (25 ml) at −78 °C. Approximately five minutes after the addition of the ester was complete, chlorotrimethylsilane (0.3 ml, 2.2 mmol) was added to the yellow solution in one portion and the reaction mixture was allowed to warm to room temperature with stirring over one hour. After this time, TLC indicated that consumption of the starting material was complete, and methanol (3 ml) was added and the mixture was stirred for a further 15 mins before being poured onto NaOH (20 ml of a

2 M aqueous solution). The aqueous layer was removed and the organic layer was extracted with NaOH (2 × 20 ml, 2 M). The aqueous layers were combined and carefully re-acidified to pH 3 using a minimum amount (*ca*. 5 ml) of concentrated HCl before being extracted with ether (3 × 25 ml). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude carboxylic acid as a yellow oil (0.49 g, 82%). Thionyl chloride (0.14 ml, 1.91 mmol) was added slowly to a cool (0 °C) solution of the crude acid (0.49 g, 1.64 mmol) in methanol (25 ml). The reaction mixture was then allowed to stir overnight at room temperature. The methanol was then removed *in vacuo* and water (25 ml) was added. Extractive work-up with ethyl acetate followed by drying of the organic extracts ($MgSO_4$), filtration and concentration *in vacuo* afforded a yellow oil. Column chromatography afforded ketoester **15c** (0.20 g, 54%) as a colourless oil; R_f (10% ethyl acetate in light petroleum) 0.32; ν_{max} (film)/cm^{-1} 1721 (C=O) (Found: C, 48.32; H, 6.19. Calc. for $C_9H_{14}O_4F_2$: C, 48.21; H, 6.19%); δ_H ($CDCl_3$, 300 MHz) 4.30 (1H, dd, $^3J_{H-F}$ 10.3, 9.9, C*H*(OCH$_3$)), 3.80 (3H, s, OC*H*$_3$), 3.50 (3H, s, OC*H*$_3$), 2.65 (2H, t, $^3J_{H-H}$ 6.9, C*H*$_2$CH$_2$CH$_3$), 1.70–1.50 (2H, m, CH$_2$C*H*$_2$CH$_3$), 0.90 (3H, t, $^3J_{H-H}$ 7.3, CH$_2$CH$_2$C*H*$_3$); δ_F ($CDCl_3$, 282 MHz) −113.6 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 270.5, $^3J_{H-F}$ 10.3), −118.7 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 270.5, $^3J_{H-F}$ 9.9); δ_C ($CDCl_3$, 75 MHz) 198.0 (t, $^2J_{C-F}$ 26.6, C-4), 166.7, 113.8 (t, $^1J_{C-F}$ 259.3), 79.1 (t, $^2J_{C-F}$ 24.9), 60.0, 52.7, 39.3, 15.8, 13.2; *m*/*z* (CI) 242 (100%, [M + NH$_4$]$^+$).

Methyl 3,3-difluoro-2-methoxy-4-oxo-6-methylheptanoate 15d

From **9d** (0.5 g, 1.6 mmol), LDA (1.6 mmol) and chlorotrimethylsilane (0.23 ml, 1.8 mmol) in THF (20 ml) which afforded crude carboxylic acid **12d** as a yellow oil [0.38 g, 76% (estimated)]. Treatment of this material with thionyl chloride (0.09 ml, 1.34 mmol) in methanol (20 ml) followed by the usual work-up and column chromatography afforded ketoester **15d** (0.16 g, 56%) as a colourless oil; R_f (10% ethyl acetate in light petroleum) 0.35 (Found: C, 50.48; H, 6.78. Calc. for $C_{10}H_{16}O_4F_2$: C, 50.42; H, 6.77%); δ_H ($CDCl_3$, 300 MHz) 4.34 (1H, dd, $^3J_{H-F}$ 14.1, 9.9, C*H*(OCH$_3$)), 3.82 (3H, s, OC*H*$_3$), 3.49 (3H, s, OC*H*$_3$), 2.59 (2H, d, $^3J_{H-H}$ 9.0, C*H*$_2$CH(CH$_3$)$_2$), 2.30–2.10 (1H, m, C*H*(CH$_3$)$_2$), 0.95 (6H, d, $^3J_{H-H}$ 8.7, CH(C*H*$_3$)$_2$); δ_F ($CDCl_3$, 282 MHz) −113.6 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 270.8, $^3J_{H-F}$ 9.9), −118.8 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 270.8, $^3J_{H-F}$ 14.1); δ_C ($CDCl_3$, 75 MHz) 199.4 (t, $^2J_{C-F}$ 27.1), 166.7, 113.6 (t, $^1J_{C-F}$ 261.6), 79.0 (t, $^2J_{C-F}$ 27.1), 59.9, 52.6, 46.1, 23.2, 11.1 [HRMS (FAB, M[Na]$^+$) Found: 261.091703. Calc. for $C_{10}H_{16}O_4F_2Na$ 261.091435]; *m*/*z* (CI) 256 (5%, [M + NH$_4$]$^+$), 239 (7), 85 (100), 57 (47).

Methyl 3,3-difluoro-2-methoxy-4-oxo-6,6-dimethylheptanoate 15e

From **9e** (0.3 g, 0.92 mmol), LDA (0.92 mmol) and chlorotrimethylsilane (0.13 ml, 1.0 mmol) in THF (15 ml) which afforded crude carboxylic acid **12e** as a yellow oil [0.24 g, 81% (estimated)]. Treatment of this material with thionyl chloride (0.06 ml, 0.84 mmol) in methanol (15 ml) followed by usual work-up and column chromatography afforded ketoester **15e** (0.12 g, 65%) as a colourless oil; R_f (10% ethyl acetate in light petroleum) 0.47; δ_H ($CDCl_3$, 300 MHz) 4.32 (1H, dd, $^3J_{H-F}$ 14.7, 9.9, C*H*(OCH$_3$)), 3.83 (3H, s, OC*H*$_3$), 3.49 (3H, s, OC*H*$_3$), 2.60 (2H, s, C*H*$_2$C(CH$_3$)$_3$), 1.06 (9H, s, C(C*H*$_3$)$_3$); δ_F ($CDCl_3$, 282 MHz) −113.6 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 268.8, $^3J_{H-F}$ 9.9), −118.6 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 268.8, $^3J_{H-F}$ 14.7); δ_C ($CDCl_3$, 75 MHz) 199.2 (t, $^2J_{C-F}$ 32.1), 163.3, 113.8 (t, $^1J_{C-F}$ 241.5), 79.1 (t, $^2J_{C-F}$ 27.3), 59.9, 52.6, 46.9, 30.6, 29.1 [HRMS (CI, M[NH$_4$]$^+$) Found: 270.150694. Calc. for $C_{11}H_{22}O_4F_2N$ 270.151690]; *m*/*z* (CI) 270 (34%, [M + NH$_4$]$^+$), 233 (25), 97 (52), 70 (100).

Methyl 3,3-difluoro-2-methoxy-4-oxo-5-phenylpentanoate 15f

From **9f** (0.8 g, 2.30 mmol), LDA (2.30 mmol) and chlorotrimethylsilane (0.32 ml, 2.53 mmol) in THF (35 ml) which afforded crude carboxylic acid **12f** as a yellow oil [0.71 g, 88% (estimated from mass recovery)]. This material was treated with thionyl chloride (0.17 ml, 2.31 mmol) in methanol (25 ml). Usual work-up and column chromatography afforded ketoester **15f** (0.35 g, 61%) as a colourless oil; R_f (10% ethyl acetate in light petroleum) 0.45 (Found: C, 57.60; H, 5.27. Calc. for $C_{13}H_{14}O_4F_2$: C, 57.35; H, 5.27%); δ_H ($CDCl_3$, 300 MHz) 7.39–7.15 (5H, m, Ph), 4.37 (1H, dd, $^3J_{H-F}$ 13.8, 10.6, C*H*CF$_2$), 4.05 (2H, s, C(O)C*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 3.51 (3H, s, OC*H*$_3$); δ_F ($CDCl_3$, 282 MHz) −113.4 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 268.8, $^3J_{H-F}$ 10.6), −117.7 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 268.8, $^3J_{H-F}$ 13.8); δ_C ($CDCl_3$, 75 MHz) 197.5 (t, $^2J_{C-F}$ 26.1), 166.9, 131.8, 129.9, 128.7, 127.5, 114.4 (t, $^1J_{C-F}$ 261.8), 79.5 (t, $^2J_{C-F}$ 26.5), 60.4, 53.0, 44.3; *m*/*z* (CI) 290 (26%, [M + NH$_4$]$^+$), 186 (72), 84 (100).

Attempted preparation of 12g: 7,7-difluoro-6-[(methoxyethoxy)-methoxy]-2-methoxyhepta-4,6-dienoic acid 18

Ester **9g** (1.0 g, 3.38 mmol) was added dropwise to a cold (−100 °C) solution of LDA (3.38 mmol) and chlorotrimethylsilane (0.47 ml, 3.71 mmol) in THF (25 ml). The solution was stirred at this temperature for a further 5 minutes before being warmed to room temperature and stirred for an hour, after which time TLC indicated complete consumption of the starting material. The reaction was stopped by addition of HCl (10 ml of a 1 M solution) before being poured on to NaOH (20 ml of a 2 M solution). The aqueous layer was removed and the organic layer was extracted with NaOH (2 × 20 ml of a 2 M solution). The aqueous layers were combined and carefully re-acidified to pH 3 using a minimum (*ca*. 5 ml) amount of concentrated HCl before being extracted with ether (3 × 25 ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude acid **18** as a yellow oil [0.71 g, 71% (estimated)]; δ_H ($CDCl_3$, 300 MHz) 9.46 (1H, br s, CO$_2$*H*), 6.00 (1H, dd, one half of an AB quartet, $^3J_{H-H}$ 15.8, $^4J_{H-F}$ 1.5, CF$_2$C(OMEM)C*H*$_a$CH$_b$), 5.87–5.78 (1H, m including d, $^3J_{H-H}$ 15.8, CF$_2$C(OMEM)CH$_a$C*H*$_b$), 4.89 (2H, s, OC*H*$_2$O), 3.90–3.81 (2H, m, OC*H*$_2$CH$_2$O), 3.61–3.53 (2H, m, OCH$_2$-C*H*$_2$O), 3.42 (3H, s, OC*H*$_3$), 3.49 (3H, s, OC*H*$_3$), 2.70–2.52 (3H, m, C*H*(OCH$_3$)CO$_2$H, C*H*$_2$CH(OCH$_3$)CO$_2$H); due to the onset of acetal cleavage (during the acquisition time of a ^{13}C NMR spectrum), the acid was esterified directly without further characterisation.

Methyl (*E*)-7,7-difluoro-2-methoxy-6-oxohept-4-enoate 20

Trimethylsilyldiazomethane (1.28 ml, 2.56 mmol) was added slowly to a cool (0 °C) solution of acid **18** (0.69 g, 2.33 mmol) in methanol (10 ml) and the solution stirred at this temperature for 10 minutes before being warmed to room temperature and stirred overnight. The methanol was removed *in vacuo* to afford an orange oil. Purification by column chromatography afforded enone **20** (0.37 g, 50%) as a colourless oil; R_f (40% ethyl ether in light petroleum) 0.19; δ_H ($CDCl_3$, 300 MHz) 7.24–7.10 (1H, m, C(O)CHC*H*CH$_2$), 6.49 (1H, d, $^3J_{H-H}$ 15.8, C(O)C*H*CHCH$_2$), 5.83 (1H, t, $^2J_{H-F}$ 54.0, C*H*F$_2$), 3.93 (1H, d, $^3J_{H-H}$ 5.1, C*H*(OCH$_3$)CO$_2$CH$_3$), 3.80 (3H, s, OC*H*$_3$), 3.42 (3H, s, OC*H*$_3$), 2.79–2.69 (2H, m, C(O)CHCHC*H*$_2$); δ_F ($CDCl_3$, 282 MHz) −126.3 (2F, d, $^2J_{H-F}$ 54.0); δ_C ($CDCl_3$, 75 MHz) 171.6, 147.8, 125.0, 110.3 (t, $^1J_{C-F}$ 252.9), 78.7, 58.5, 52.2, 36.2 (one carbon, believed to be C-6 could not be observed) [HRMS (ES, M[Na]$^+$) Found: 245.0603. Calcd. for $C_9H_{12}O_4F_2Na$ 245.0601]; *m*/*z* (CI) 240 (100%, [M + NH$_4$]$^+$).

2-Benzyloxy-3,3-difluoro-4-[(methoxyethoxy)methoxy]hex-4-enoic acid 13b (rearrangement only)

A solution of LDA was generated from *n*-butyllithium (3.86 ml

of a 2.2 M solution in hexanes, 8.49 mmol) and diisopropylamine (1.2 ml, 8.6 mmol) in THF (10 ml). The solution was diluted with THF (10 ml) then ester **10b** (3.0 g, 8.3 mmol) was added dropwise. After 5 minutes, chlorotrimethylsilane (1.62 ml, 12.8 mmol) was added dropwise and the reaction was allowed to warm to room temperature over one hour. The reaction was quenched with cold HCl (17 ml of a 1 M aqueous solution) and stirred for 3 minutes. The pH was adjusted to *ca.* 10 with concentrated NaOH (5 M aqueous solution) and the solution was washed with diethyl ether (3 × 20 ml). The organic washings were discarded and the pH was lowered to *ca.* 1 by the careful dropwise addition of concentrated HCl (10 M), then the aqueous phase was extracted further with diethyl ether (3 × 25 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford acid **13b** as a pale yellow oil (2.02 g, 75%); ν_{max} (film)/cm^{-1} 3620–2680br m (COO-H), 2922s, 1722s (C=O); δ_H ($CDCl_3$, 300 MHz) 8.37–8.17 (1H, br s, CO_2H), 7.40–7.27 (5H, m, Ph), 5.68 (1H, dq, $^3J_{H-H}$ 7.1, $^4J_{H-F}$ 1.29, CHCH$_3$), 4.95 (1H, d, one half of an AB quartet, $^2J_{H-H}$ 5.9, OCH_aH$_b$Ph), 4.91 (1H, d, one half of an AB quartet, $^2J_{H-H}$ 5.9, OCH$_a$$H_b$Ph), 4.40 (1H, dd, $^3J_{H-F}$ 14.7, $^3J_{H-F}$ 8.1, CH-(OBn)CO$_2$H), 3.89–3.73 (2H, m, OCH_2CH$_2$OCH$_3$), 3.55 (2H, t, $^3J_{H-F}$ 4.6, OCH$_2$CH_2OCH$_3$), 3.36 (3H, s, OCH_3), 1.71 (3H, dt, $^3J_{H-H}$ 7.1, $^5J_{H-F}$ 2.8, CHCH_3); δ_C ($CDCl_3$, 75 MHz) 170.0, 145.1 (t, $^2J_{C-F}$ 25.5), 136.2, 128.5, 128.3, 116.8 (t, $^1J_{C-F}$ 251.2), 115.8, 98.2, 76.8 (t, $^2J_{C-F}$ 29.7), 73.6, 71.6, 68.7, 59.0, 10.9; δ_F ($CDCl_3$, 282 MHz) −111.5 (1F, dd, $^2J_{F-F}$ 256.6, $^3J_{H-F}$ 14.7), −106.3 (1F, d, $^2J_{F-F}$ 256.6) [HRMS (ES, M[Na]$^+$) Found: 383.1279. Calcd. For $C_{17}H_{22}O_6F_2Na$ 383.1282]; *m/z* (ES) 383 (100%, [M + Na]$^+$). The reaction could also be performed on 22 mmol of **10b** affording **13b** in 60% crude yield with acceptable ^{1}H, ^{13}C and ^{19}F NMR spectra.

Methyl 2-benzyloxy-3,3-difluoro-4-oxohexanoate 16b

Treatment of crude **13b** (0.34 g, 0.83 mmol) with thionyl chloride (0.07 ml, 0.91 mmol) in methanol (15 ml) followed by the usual work-up and column chromatography afforded ketoester **16b** as a pale yellow oil (0.17 g, 74%, 98% pure by GC); R_f (40% ethyl acetate in light petroleum) 0.61; δ_H ($CDCl_3$, 300 MHz) 7.39–7.26 (5H, m, Ph), 4.77 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 11.4, OCH_aH$_b$Ph), 4.57 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 11.4, OCH$_a$$H_b$Ph), 4.55 (2H, dd, $^3J_{H-F}$ 14.3, 10.3, CHCF$_2$), 3.80 (3H, s, OCH_3), 2.73 (2H, q, $^3J_{H-H}$ 7.3, CH_2CH$_3$), 1.09 (3H, t, $^3J_{H-H}$ 7.3, CH$_2$CH_3); δ_C ($CDCl_3$, 75 MHz) 200.1 (t, $^2J_{C-F}$ 27.6), 167.0, 135.8, 128.5, 114.2 (t, $^1J_{C-F}$ 261.2), 76.9 (t, $^2J_{C-F}$ 24.7), 52.8, 31.3, 6.3; δ_F ($CDCl_3$, 282 MHz) −113.4 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 269.6, $^3J_{H-F}$ 10.2), −118.1 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 269.7, $^3J_{H-F}$ 15.3) [HRMS (ES, M[Na]$^+$) Found: 309.0919. Calc. for $C_{14}H_{16}O_4F_2Na$ 309.0914]; *m/z* (ES) 309 (100%, [M + NH$_4$]$^+$), 123 (10), 91 (100), 71 (28).

Methyl 2-benzyloxy-3,3-difluoro-4-oxoheptanoate 16c

From **10c** (0.55 g, 1.50 mmol), LDA (1.50 mmol) and chlorotrimethylsilane (0.21 ml, 1.65 mmol) in THF (20 ml) which afforded crude carboxylic acid **13c** as a yellow oil [0.43 g, 78% (estimated)]. Treatment of this material with thionyl chloride (0.09 ml, 1.26 mmol) in methanol (25 ml) followed by the usual work-up and column chromatography afforded ketoester **16c** (0.20 g, 58%) as a colourless oil; R_f (20% ethyl acetate in light petroleum) 0.36; δ_H ($CDCl_3$, 300 MHz) 7.30–7.18 (5H, m, Ph), 4.77 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 9.9, OCH_aH$_b$-Ph), 4.58 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 9.9, OCH$_a$$H_b$Ph), 4.53 (2H, dd, $^3J_{H-F}$ 14.1, 10.2, CHCF$_2$), 3.80 (3H, s, OCH_3), 2.66 (2H, t, $^3J_{H-H}$ 6.0, CH_2CH$_2$CH$_3$), 1.70–1.51 (2H, m, CH$_2$CH_2CH$_3$), 0.99 (3H, t, $^3J_{H-H}$ 9.6, CH$_2$CH$_2$CH_3); δ_C ($CDCl_3$, 75 MHz) 200.1 (t, $^2J_{C-F}$ 27.6), 167.0, 135.8, 128.5, 114.2 (t, $^1J_{C-F}$ 261.2), 76.9 (t, $^2J_{C-F}$ 24.5), 74.3, 52.8, 39.4, 15.9, 13.4) [HRMS (CI, M[NH$_4$]$^+$) Found: 318.151582. Calc. for $C_{15}H_{22}NO_4F_2$ 318.151690]; *m/z* (CI) 318 (57%, [M + NH$_4$]$^+$), 123 (10), 91 (100), 71 (28).

Methyl 2-benzyloxy-3,3-difluoro-4-oxo-6-methylheptanoate 16d

From **10d** (0.43 g, 1.11 mmol), LDA (1.11 mmol) and chlorotrimethylsilane (0.16 ml, 1.22 mmol) in THF (20 ml) which afforded crude carboxylic acid **13d** as a yellow oil [0.33 g, 77% (estimated)]. Treatment of this material with thionyl chloride (0.07 ml, 0.94 mmol) in methanol (20 ml) followed by usual work-up and column chromatography afforded ketoester **16d** (0.15 g, 54%) as a colourless oil; R_f (20% ethyl acetate in light petroleum) 0.51; ν_{max} (film)/cm^{-1} 1744.5 (C=O); δ_H ($CDCl_3$, 300 MHz) 7.40–7.24 (5H, m, Ph), 4.76 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 9.7, OCH_aH$_b$Ph), 4.58 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 9.7, OCH$_a$$H_b$Ph), 4.51 (1H, dd, $^3J_{H-F}$ 14.4, 10.2, CHCF$_2$), 3.78 (3H, s, OCH_3), 2.57 (2H, d, $^3J_{H-H}$ 7.50, CH_2CH(CH$_3$)$_2$), 2.25–2.09 (1H, m, CH(CH$_3$)$_2$), 0.94 (6H, d, $^3J_{H-H}$ 8.0, CH(CH_3)$_2$); δ_F ($CDCl_3$, 282 MHz) −113.5 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 270.3, $^3J_{H-F}$ 10.2), −118.0 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 270.3, $^3J_{H-F}$ 14.4); δ_C ($CDCl_3$, 75 MHz) 199.6 (t, $^2J_{C-F}$ 26.6), 167.0, 135.7, 128.5, 113.9 (t, $^1J_{C-F}$ 261.6), 76.3 (t, $^2J_{C-F}$ 23.6), 74.3, 52.8, 46.3, 23.4, 22.4 [HRMS (ES, M[Na]$^+$) Found: 337.1217. Calc. for $C_{16}H_{20}O_4F_2Na$ 337.1227]; *m/z* (ES) 337 (100%, [M + Na]$^+$).

Methyl 2-benzyloxy-3,3-difluoro-4-oxo-6,6-dimethylheptanoate 16e

From **10e** (0.62 g, 1.55 mmol), LDA (1.55 mmol) and chlorotrimethylsilane (0.22 ml, 1.70 mmol) in THF (25 ml) which afforded crude carboxylic acid **13e** as a yellow oil [0.48 g, 78% (estimated)]. Treatment of this material with thionyl chloride (0.10 ml, 1.32 mmol) in methanol (25 ml) followed by the usual work-up and column chromatography afforded ketoester **16e** (0.31 g, 76%) as a colourless oil; R_f (20% ethyl acetate in light petroleum) 0.48 (Found: C, 62.14; H, 6.57. Calc. for $C_{17}H_{22}O_4F_2$: C, 62.18; H, 6.75%); δ_H ($CDCl_3$, 300 MHz) 7.41–7.28 (5H, m, Ph), 4.76 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 11.0, OCH_aH$_b$Ph), 4.57 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 11.0, OCH$_a$$H_b$Ph), 4.52 (1H, dd, $^3J_{H-F}$ 9.2, 10.7, CHCF$_2$), 3.80 (3H, s, OCH_3), 2.60 (2H, s, CH_2C(CH$_3$)$_3$), 1.02 (9H, s, C(CH_3)$_3$); δ_F ($CDCl_3$, 282 MHz) −113.3 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 268.6, $^3J_{H-F}$ 10.7), −117.9 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 268.6, $^3J_{H-F}$ 9.2); δ_C ($CDCl_3$, 75 MHz) 199.2 (t, $^2J_{C-F}$ 28.1), 166.9, 135.5, 128.4, 113.6 (t, $^1J_{C-F}$ 261.1), 76.5 (t, $^2J_{C-F}$ 28.2), 74.1, 52.6, 49.1, 29.2, C-6 was not visible [HRMS (ES, M[Na]$^+$) Found: 351.1376. Calc. for $C_{17}H_{22}O_4F_2Na$ 351.1384]; *m/z* (FAB) 328 (17%, [M]$^+$), 181 (19), 91 (100).

Methyl 2-allyloxy-3,3-difluoro-4-oxoheptanoate 17c

From **11c** (0.93 g, 2.88 mmol), LDA (3.20 mmol) and chlorotrimethylsilane (0.41 ml, 3.20 mmol) in THF (30 ml) which afforded crude carboxylic acid **14c** as a yellow oil [0.76 g, 82% (estimated)]. This material was treated with thionyl chloride (0.17 ml, 2.58 mmol) in methanol (25 ml) followed by usual work-and column chromatography to afford ketoester **17c** (0.34 g, 63%) as a colourless oil; R_f (50% ethyl ether in light petroleum) 0.59 (Found: C, 52.74; H, 6.70. Calc. for $C_{13}H_{16}O_4F_2$: C, 52.80; H, 6.45%); δ_H ($CDCl_3$, 300 MHz) 5.90–5.78 (1H, m, CH$_2$CHCH$_2$O), 5.31–5.20 (2H, m, CH$_2$CHCH$_2$O), 4.50 (1H, dd, $^3J_{H-F}$ 14.1, 10.3, CHCF$_2$), 4.23 (1H, dd, one half of an AB quartet, $^3J_{H-H}$ 5.9, $^2J_{Ha-Hb}$ 12.5, CH$_2$CHCH_aH$_b$O), 4.05 (1H, dd, one half of an AB quartet, $^3J_{H-H}$ 5.1, $^2J_{Ha-Hb}$ 12.5, CH$_2$CH-CH$_a$$H_b$O), 3.80 (3H, s, OC$H_3$), 2.70 (2H, t, $^3J_{H-H}$ 7.0, CH_2-CH$_2$CH$_3$), 1.71–1.60 (2H, m, CH$_2$CH_2CH$_3$), 0.95 (3H, t, $^3J_{H-H}$ 7.73, CH$_2$CH$_2$CH_3); δ_F ($CDCl_3$, 282 MHz) −113.7 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 270.0, $^3J_{H-F}$ 10.3), −118.1 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 270.0, $^3J_{H-F}$ 14.1); δ_C ($CDCl_3$,

75 MHz) 201.1 (t, $^2J_{C-F}$ 28.5), 167.1, 132.5, 119.7, 114.0 (t, $^1J_{C-F}$ 261.3), 76.4 (t, $^2J_{C-F}$ 25.3), 73.3, 52.8, 39.5, 15.9, 13.4; *m/z* (ES) 273 (100%, $[M + Na]^+$).

Methyl 2-allyloxy-3,3-difluoro-4-oxo-6-methylheptanoate 17d

From **11d** (1.22 g, 3.62 mmol), LDA (3.62 mmol) and chlorotrimethylsilane (0.51 ml, 3.98 mmol) in THF (30 ml) which afforded crude carboxylic acid **14d** as a yellow oil [1.15 g, 94% (estimated)]. This material was treated with thionyl chloride (0.28 ml, 3.80 mmol) in methanol (20 ml) and usual work-up and column chromatography afforded ketoester **17d** (0.58 g, 60%) as a colourless oil; R_f (40% ethyl acetate in light petroleum) 0.61 (Found: C, 54.49; H, 6.90. Calc. for $C_{14}H_{18}O_4F_2$: C, 54.54; H, 6.87%); δ_H ($CDCl_3$, 300 MHz) 5.89–5.71 (1H, m, C*H*CH_2), 5.30–5.20 (2H, m, CHC*H*$_2$), 4.46 (1H, dd, $^3J_{H-F}$ 14.1, 10.2, C*H*CF_2), 4.18 (1H, dd, one half of an AB quartet, $^2J_{Ha-Hb}$ 12.1, $^3J_{H-H}$ 5.9, OC*H*$_a$H$_b$CHCH$_2$), 4.02 (1H, dd, one half of an AB quartet, $^2J_{Ha-Hb}$ 12.1, $^3J_{H-H}$ 6.2, OCH$_a$*H*$_b$CHCH$_2$), 3.78 (3H, s, OC*H*$_3$), 2.57 (2H, d, $^3J_{H-H}$ 6.6, C*H*$_2$CH(CH$_3$)$_2$), 2.26–2.10 (1H, m, C*H*(CH$_3$)$_2$), 0.91 (3H, d, $^3J_{H-H}$ 1.5, CH(C*H*$_3$)$_2$), 0.89 (3H, d, $^3J_{H-H}$ 1.5, CH(C*H*$_3$)$_2$); δ_F ($CDCl_3$, 282 MHz) −113.7 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 269.7, $^3J_{H-F}$ 10.2), −118.3 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 269.7, $^3J_{H-F}$ 14.1); δ_C ($CDCl_3$, 75 MHz) 199.7 (t, $^2J_{C-F}$ 27.1), 167.1, 132.6, 119.7, 113.9 (t, $^1J_{C-F}$ 260.9), 76.3 (t, $^2J_{C-F}$ 25.2, 73.2, 52.8, 46.3, 23.4, 22.3; *m/z* (CI) 282 (45%, $[M + NH_4]^+$), 265 (12), 85 (100), 58 (29).

1,1-Difluoro-2[(methoxyethoxy)methoxy]pent-1-en-3-yl 3-hydroxybutyrate 23

The procedure for **11c** was followed using alcohol **8c** (1.0 g, 4.42 mmol), DMAP (0.21 g, 1.77 mmol), DCC (1.0 g, 4.86 mmol) and 3-hydroxybutyric acid (0.41 ml, 4.42 mmol) in DCM. Usual work-up and column chromatography afforded hydroxybutyrate **23** (0.88 g, 64%) as a colourless oil; R_f (20% ethyl acetate in light petroleum) 0.30; δ_H ($CDCl_3$, 300 MHz) 5.42–5.35 (1H, m, C*H*), 4.98 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 5.8, OC*H*$_a$H$_b$O), 4.90 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 5.8, OCH$_a$*H*$_b$O), 3.90–3.72 (2H, m, OC*H*$_2$CH$_2$O), 3.69–3.59 (2H, m, OCH$_2$C*H*$_2$O), 3.55 (2H, t, $^3J_{H-H}$ 3.7, CH$_2$C*H*$_2$-OCH$_3$), 3.40 (3H, s, OC*H*$_3$), 3.35 (3H, s, OC*H*$_3$), 2.54 (2H, t, $^3J_{H-H}$ 3.7, C*H*$_2$CH$_2$OCH$_3$), 1.86–1.71 (2H, m, C*H*$_2$CH$_3$), 0.89 (3H, t, $^3J_{H-H}$ 9.6, CH$_2$C*H*$_3$); δ_F ($CDCl_3$, 282 MHz) −97.2 (1F, d, $^2J_{F-F}$ 55.9), −105.6 (1F, d, $^2J_{F-F}$ 55.9); δ_C ($CDCl_3$, 75 MHz) 168.6, 154.8 (t, $^1J_{C-F}$ 291.5), 117.7 (dd, $^2J_{C-F}$ 36.8, 11.5), 97.9, 71.4, 68.6, 68.4, 58.9, 58.6, 56.6, 39.1, 26.9, 9.9 [HRMS (CI, M[NH$_4$]$^+$) Found: 330.172838. Calc. for $C_{13}H_{26}O_6NF_2$ 330.172819]; *m/z* (ES) 335 (100%, $[M + Na]^+$). This material was not characterised further as all attempts at rearrangement under the conditions used for **12**–**14** or **18** were completely unsuccessful, returning only a low yield of **8c**.

1,1-Difluoro-2-[(methoxyethoxy)methoxy]pent-1-en-3-yl 3-methoxypropionate 24

β-Butyrolactone (0.35 ml, 4.33 mmol) was added dropwise to a solution of alcohol **8c** (1.0 g, 3.94 mmol) in DCM (25 ml) and the solution was stirred for 18 hours. The DCM was then removed *in vacuo* to afford a pale yellow oil. Column chromatography afforded propionate **24** (1.1 g, 82%); R_f (50% ethyl ether in light petroleum) 0.55; δ_H ($CDCl_3$, 300 MHz) 4.99 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.6, OC*H*$_a$H$_b$O), 4.80 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 6.6, OCH$_a$*H*$_b$O), 4.71–4.60 (2H, m, C*H*, CH$_2$C*H*(OH)CH$_3$), 3.92–3.65 (2H, m, OC*H*$_2$-CH$_2$O), 3.56–3.49 (2H, m, OCH$_2$C*H*$_2$O), 3.33 (3H, s, OC*H*$_3$), 3.18 (1H, br s, O*H*), 3.05 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 4.4, C*H*$_a$H$_b$CH(OH)CH$_3$), 3.00 (1H, d, one half of an AB quartet, $^2J_{Ha-Hb}$ 4.4, CH$_a$*H*$_b$CH(OH)CH$_3$), 1.53 (3H, d, $^3J_{H-H}$ 5.9, CH$_2$CH(OH)C*H*$_3$), 1.15 (9H, s, C(C*H*$_3$)$_3$); δ_F ($CDCl_3$, 282 MHz) −100.7 (1F, d, $^2J_{F-F}$ 66.1), −108.6 (1F, d, $^2J_{F-F}$ 66.1); δ_C ($CDCl_3$, 75 MHz) 168.1, 154.9 (t, $^1J_{C-F}$ 285.3), 117.4 (dd, $^2J_{C-F}$ 31.2, 8.7), 98.4, 73.8, 71.5, 68.9, 67.9, 59.0, 44.3, 36.1, 26.1, 20.6. This material was not characterised further as all attempts at rearrangement under the conditions used for **12**–**14** or **18** were completely unsuccessful returning only a low yield of **8c**.

Methyl 2-hydroxy-3,3-difluoro-4-oxoheptanoate 25c (deallylation)

Zinc(II) chloride (0.1 g, 0.78 mmol) was added to a solution of allyloxyketoester **17c** (0.15 g, 0.6 mmol) in dry THF (10 ml) and the reaction mixture was stirred at room temperature for 15 minutes. Tetrakis(triphenylphosphino)palladium(0) (0.13 g, 0.15 mmol) was added and the mixture was stirred for a further 10 minutes. Tributyltin hydride (0.32 ml, 1.2 mmol) was added cautiously to the yellow coloured solution over a period of 10 minutes. Upon completion of the addition, the reaction mixture was stirred at room temperature for 30 minutes when TLC indicated that the starting material had been consumed completely. The reaction mixture was diluted with ethyl acetate (20 ml) and HCl (10 ml of a 1 M aqueous solution) was added then the mixture extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and purified by column chromatography to afford the hydroxyketoester **25c** (0.07 g, 56%) as a colourless oil; R_f (50% ethyl ether in light petroleum) 0.56 (Found: C, 45.60; H, 5.89. Calc for $C_8H_{12}O_4F_2$: C, 45.72; H, 5.75%); δ_H ($CDCl_3$, 300 MHz) 4.66–4.57 (1H, m, CF_2C*H*), 3.90 (3H, s, OC*H*$_3$), 3.38 (1H, d, $^3J_{H-H}$ 6.7, O*H*), 2.60 (2H, t, $^3J_{H-H}$ 6.2, C*H*$_2$CH$_2$CH$_3$), 1.72–1.59 (2H, m, CH$_2$C*H*$_2$CH$_3$), 0.95 (3H, t, $^3J_{H-H}$ 7.7, CH$_2$CH$_2$C*H*$_3$); δ_F ($CDCl_3$, 282 MHz) −114.0 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 272.2, $^3J_{H-F}$ 8.5), −119.4 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 272.2, $^3J_{H-F}$ 14.7); δ_C ($CDCl_3$, 75 MHz) 200.1 (t, $^2J_{C-F}$ 27.7), 169.2, 113.7 (t, $^1J_{C-F}$ 261.6), 70.3 (t, $^2J_{C-F}$ 27.4), 53.6, 39.4, 15.8, 13.4; *m/z* (CI) 228 (100%, $[M + NH_4]^+$).

Methyl 2-hydroxy-3,3-difluoro-4-oxo-6-methylheptanoate 25d

From $ZnCl_2$ (0.12 g, 0.92 mmol), **17d** (0.18 g, 0.7 mmol), $Pd(PPh_3)_4$ (0.09 g, 0.08 mmol) and Bu_3SnH (0.38 ml, 1.4 mmol) in dry THF (15 ml). Usual work-up and column chromatography afforded hydroxyketoester **25d** as a colourless oil (0.10 g, 63%); R_f (40% ethyl ether in light petroleum) 0.67; δ_H ($CDCl_3$, 300 MHz) 4.62 (1H, dd, $^3J_{H-F}$ 8.5, 14.3 CF_2C*H*), 3.90 (3H, s, OC*H*$_3$), 3.30 (1H, br s, O*H*), 2.60 (2H, d, $^3J_{H-H}$ 6.6, C*H*$_2$CH-(CH$_3$)$_2$), 2.28–1.95 (1H, m, CH$_2$C*H*(CH$_3$)$_2$), 0.95 (6H, d, $^3J_{H-H}$ 6.6, CH$_2$CH(C*H*$_3$)$_2$); δ_F ($CDCl_3$, 282 MHz) −114.0 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 273.4, $^3J_{H-F}$ 8.5), −119.0 (1F, dd, one half of an AB quartet, $^2J_{F-F}$ 273.4, $^3J_{H-F}$ 14.7); δ_C ($CDCl_3$, 75 MHz) 199.6 (t, $^2J_{C-F}$ 28.2), 169.3, 113.7 (t, $^1J_{C-F}$ 261.8), 70.7 (t, $^2J_{C-F}$ 12.3), 53.7, 46.3, 23.5, 22.4 [HRMS (ES, M[Na]$^+$) Found: 247.0756. Calc. for $C_9H_{14}O_4F_2Na$ 247.0758]; *m/z* (CI) 242 (100%, $[M + NH_4]^+$).

Methyl 2-hydroxy-3,3-difluoro-4-oxoheptanoate 25c (debenzylation)

Pearlman's catalyst (0.10 g, 20 wt% Pd) was added to a solution of benzyloxyketoester **16c** (0.41 g, 1.44 mmol) in dry methanol (15 ml) and the reaction mixture was stirred under a hydrogen atmosphere at room temperature for 2 hours at which time TLC indicated that starting material had been consumed completely. The catalyst was removed by filtration through Celite and the solvent removed *in vacuo* to afford the pure hydroxyketoester **25c** (0.26 g, 92%) as a colourless oil.

Methyl 2-hydroxy-3,3-difluoro-4-oxo-6-methylheptanoate 25d

From Pearlman's catalyst (0.21 g, 20 wt% Pd) and benzyloxyketoester **16d** (0.85 g, 2.6 mmol) in dry methanol (30 ml) which

afforded pure hydroxyketoester **25d** (0.57 g, 91%) as a colourless oil.

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