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

Michael J. Broadhurst,* Samantha J. Brown,Jonathan M. Percy,** and Michael E. Prime††

*a Roche Discovery Welwyn, 40 Broadwater Road, Welwyn Garden City, Hertfordshire, UK AL7 3AY
*b School of Chemistry, The University of Birmingham, Edgbaston, Birmingham, UK B15 2TT

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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 acetal. 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. The correct location of fluorne atoms within the rearrangement system can result in significant rate enhancements both in neutral [3,3] rearrangements such as Cope, Claisen and oxy-Cope, and in neutral and anionic [2,3] rearrangements. [3,3] Claisen rearrangements of readily available γ,γ-difluorinated allylic alcohols 2 (obtained via the addition of fluorinated vinlymetal 1 to aldehydes or ketones) locate a CF2 centre β to a carboxy carbonyl group (Scheme 1).

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 difluoroalkenolate (making bond a) of the type described by Shi and co-workers7 could be considered, but such additions normally proceed to monodifluorocompounds via addition–elimination mechanisms. Alternatively, McCarthy and co-workers reported8 the synthesis of a Kynureninase inhibitor 4b in which bond b was made from a difluorinated silyl enol ether (Scheme 2).

†Current address: School of Chemistry, University of York, Heslington, York, UK YO10 5DD.

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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
Scheme 3  Reagents and conditions: i, LDA, THF, −78 °C; ii, Me₂SiCl; iii, Δ then work-up.

from esters of lactic⁸ and hydroxybutyric⁹ 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;¹⁰ 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, alkoxycacetates 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 method¹⁹ and methoxy (9), benzyloxy (10) and allyloxy (11) esters were prepared (Scheme 4, Table 1) from the 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.,¹⁹ 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,¹⁹ 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 9g under Eschenmoser conditions (Scheme 7), the major rearrangement product was 21 at the expense of 22.²¹

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

### Table 1  Preparation of esters used for rearrangement

<table>
<thead>
<tr>
<th>R</th>
<th>Alcohol</th>
<th>R’ = Me</th>
<th>Yield (%)</th>
<th>R’ = Bu</th>
<th>Yield (%)</th>
<th>R’ = allyl</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>H</td>
<td>8a</td>
<td>9a</td>
<td>79⁺</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Me</td>
<td>8b</td>
<td></td>
<td></td>
<td>10b</td>
<td>92⁺</td>
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<tr>
<td>Et</td>
<td>8c</td>
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<td>85</td>
<td>10c</td>
<td>82</td>
<td>11c</td>
<td>83</td>
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<tr>
<td>i-Pr</td>
<td>8d</td>
<td>9d</td>
<td>81</td>
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<td>75</td>
<td>11d</td>
<td>80</td>
</tr>
<tr>
<td>t-Bu</td>
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<td>9e</td>
<td>82</td>
<td>10e</td>
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</tr>
<tr>
<td>Ph</td>
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<td>9f</td>
<td>79</td>
<td>10f</td>
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<td></td>
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<tr>
<td>CH₂=CH₂</td>
<td>8g</td>
<td>9g</td>
<td>72</td>
<td></td>
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</tbody>
</table>

* This ester was only moderately stable and could not be characterised fully. ⁺ Esterification started at 0 °C. Obtained in 96% purity and used without purification.

Scheme 4  Reagents and conditions: i, MeOCH₂COCl or BnOCH₂COCl, pyridine, DMAP, DCM, rt, 18 hours then extractive work-up; ii, H₂C=CHCH₂OCH₂CO₂H, EDC, DMAP, DCM; rt, 18 hours then extractive work-up.

Scheme 5  Reagents and conditions: i, LDA, THF, −78 °C; ii, Me₂SiCl; iii, Δ then work-up; iv, SOCl₂, MeOH, 0 °C to rt, 18 hours.

Esters might be occurring intramolecularly, of enolate stability, we explored the less common rearrangement in Scheme 6.

The alcohols compared with their non-rearrangement of the esters derived from 3,3-difluorooallylic esters are located at C-6 and are consistent with the general conclusion of Purrington and Weeks that “no acceleration of rearrangement of the esters derived from 3,3-difluoroallylic alcohol serves as a useful starting material for the preparation of highly functionalised branched acids with moderate stereorecontrol; adequate ester enolate stabilisation by β-alkoxy groups does not appear to be established, whereas β-amino groups have been exploited successfully.

Deprotection of the C-2 hydroxy group could be achieved by palladium-catalysed hydrostannation of allyl ethers when the chelation effect is weaker.

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.

Kurth used the former esters of simple allylic acetals 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.

**Experimental**

$^1$H 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. $^3$F NMR spectra were recorded on Bruker AC-300 (282.41 MHz) relative to chlorotrifluoromethane as the internal standard.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Ketoesters prepared by rearrangement and methanolation</th>
</tr>
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<tbody>
<tr>
<td>R</td>
<td>R' = Me</td>
</tr>
<tr>
<td>Me</td>
<td>—</td>
</tr>
<tr>
<td>Et</td>
<td>15c</td>
</tr>
<tr>
<td>i-Pr</td>
<td>15d</td>
</tr>
<tr>
<td>t-Bu</td>
<td>15e</td>
</tr>
<tr>
<td>Ph</td>
<td>15f</td>
</tr>
</tbody>
</table>

**Scheme 6** Reagents and conditions: i, LDA–Me$_2$SiCl, 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)$_2$NMe$_2$, PhMe, 60 °C.
rearrangement eucts reveal an AB quartet in which each doublet is further split by J_{HF} coupling (to provide a doublet of doublets). The much larger J_{HF} 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 multipletics using the modification: chemical shift (1D, dd, one half of an AB quartet, 2J_{HF}, 4J_{HF}).

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 (Darmstadt, Germany (silica gel 60 F254, thickness 0.2 mm, Art. 5554). Visualisation was achieved by UV light and/or 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. 78/40–60). Light petroleum refers to the fraction boiling in the range 40–60 °C. Diisopropylalcohols were prepared according to the procedure described below.

4.4-Difluoro-2-[(methoxymethoxy)methoxy]but-3-en-2-ol 8b

2-[(Methoxymethoxy)methoxy]buto-1,1,3-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 DCM (25 ml). Usual work-up and Kugelrohr distillation afforded ester 9c (1.06 g, 81%) as a colourless oil, bp 70 °C/0.05 mmHg; R_f (50% ethyl ether in light petroleum) 0.29; vmax (film/cm^-1) 1748brs (s, C=O); δ_H (300 MHz, CDCl_3) 5.45 (1H, t, J_{HF} 7.3, CH); 4.95 (1H, d, one half of an AB quartet, 2J_{HF} 6.2, OCH_2CH_2O), 4.80 (1H, d, one half of an AB quartet, 2J_{HF} 6.2, OCH_2CH_2O), 4.00 (2H, s, C(OCH_2CH_2O)), 3.90–3.70 (2H, m, OCH_2CH_2O), 3.55 (2H, t, J_{HF} 5.1, OCH_2CH_2O), 3.40 (3H, s, OCH_3), 1.85–1.70 (2H, m, CH_2CH_2O), 0.85 (3H, t, J_{HF} 7.3, CH_2CH_2O); δ_C (125 MHz, CDCl_3) -97.00 (1F, d, J_{HF} 55.3), -105.39 (1F, d, J_{HF} 55.3); δ_F (75 MHz, CDCl_3) 169.3, 155.7 (quat, t, J_{HF} 292.2), 112.9 (quat, J_{HF} 13.1, 14.7), 97.2, 71.7, 71.5, 69.6, 68.4, 59.3, 58.9, 23.9, 9.5 [HRMS (ES, MNa^+) ] Found: 321.1139. Calc. for C_{11}H_{13}F_3O_4Na 321.1126; m/z (CI) 316 (20%, [M + NH_4]^+), 209 (12), 89 (100).

1,1-DiFluoro-2-[(methoxymethoxy)methyl]-1-ethenyl (methoxy)acetate 9d

From 8d (1.0 g, 4.20 mmol), methoxycetyle chloride (0.65 ml, 8.40 mmol) and DMAP (0.4 g, 3.5 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_{10}H_{13}O_4F_4: 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, J_{HF} 3.1, CH), 4.95 (1H, d, one half of an AB quartet, 2J_{HF} 6.2, OCH_2CH_2O), 4.80 (1H, d, one half of an AB quartet, 2J_{HF} 6.2, OCH_2CH_2O), 4.00 (2H, s, C(OCH_2CH_2O)), 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_2CH_2O); δ_F (CDCl_3, 282 MHz) -97.2 (1F, d, J_{HF} 56.4), -105.5 (1F, d, J_{HF} 56.4); δ_C (CDCl_3, 75 MHz) 169.4, 155.9 (t, J_{HF} 297.6).

In a typical procedure, pyridine (0.61 ml, 7.6 mmol), followed by methoxycetyle 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) 0.3; δ_H (CDCl_3, 49.2 (2H, s, OCH_2O), 3.80–3.70 (2H, m, CH_2CH_2), 3.70–3.60 (2H, m, CH_2CH_2O), 3.40–3.30 (3H, s, OCH_3), 3.30 (3H, s, OCH_3); δ_F (282 MHz, CDCl_3) -96.00 (1F, d, J_{HF} 52.2), -106.00 (1F, d, J_{HF} 52.2); δ_C (75 MHz, CDCl_3) 169.8, 155.7 (t, J_{HF} 289.2), 111.5 (dd, J_{HF} 52.3, 16.4), 95.8, 71.4, 69.6, 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.
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); Rf (40% ethyl ether in light petroleum) 0.36; δ(CDC13, 300 MHz) 5.17 (1H, d, J=2.4 Hz, CH), 4.92 (1H, d, one half of an AB quartet, J=2.4 Hz, OCCH2O), 4.82 (1H, d, one half of an AB quartet, J=2.4 Hz, OCH3), 4.05 (1H, d, one half of an AB quartet, J=2.4 Hz, 16.5, C6H5OH), 3.95 (1H, d, one half of an AB quartet, J=2.4 Hz, 16.5, C6H5OH), 3.82–3.71 (2H, m, OCH2CH2O), 5.35–3.49 (2H, m, OCH2CH2O), 3.40 (3H, s, OCH3), 3.35 (3H, s, OCH3), 3.09 (3H, s, C(=O)CH3); δ(CDC13, 282 MHz) –97.4 (1F, d, J=36.4 Hz, J=2.9 Hz, Ph), –104.38 (1F, d, J=56.4 Hz), δ(CDC13, 75 MHz) 169.5, 156.2 (t, J=2.4 Hz, 289.9), 112.6 (dd, J=2.4 Hz, 1.48), 97.7, 76.0, 71.6, 69.6, 68.6, 59.4, 58.9, 53.5, 26.2 (2 signals) [HRMS (ES, M+Na]+ Found: 349.1429. Calc. for C16H13NO4FNa 349.1439; m/z (ES) 349 (60%, [M + Na]+), 257 (100).

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 column chromatography afforded the ester 9f (1.23 g, 79%) as a colourless oil, bp 93°C (0.1 mmHg); Rf (40% ethyl ether in light petroleum) 0.41; δ(CDC13, 176.2Br, s, C(=O), δ 360.0 MHz, CDCl3) 7.40–7.30 (5H, m, Ph), 6.62 (1H, t, J=1.6 Hz, 1.6), 4.90 (1H, d, one half of an AB quartet, J=6.9 Hz, OCH3), 4.70 (1H, d, one half of an AB quartet, J=6.9 Hz, OCH3), 4.20 (2H, s, CH2O), 3.75–3.61 (2H, m, OCH2CH2O), 3.55–3.45 (2H, m, OCH2CH2O), 3.44 (3H, s, OCH3), 3.35 (3H, s, OCH3); δ(CDC13, 282 MHz) –96.4 (1F, d, J=54.5 Hz), –104.7 (1F, d, J=54.5 Hz); δ(CDC13, 75 MHz) 160.9, 155.7 (t, J=286.8 Hz), 153.7, 128.6 (4 signals), 126.5, 112.8 (dd, J=55.2 Hz, 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 C16H15NO4FNa 369.1126; m/z (CI) 364 (42%, [M + Na]+), 254 (33), 106 (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, 75%) as a colourless oil; Rf (50% ethyl ether in light petroleum) 0.38; δ(CDC13, 1738Br, s, C(=O), δ 360.2 MHz, CDCl3) 6.05 (1H, d, J=1.4 Hz, CH3, 0.5 Hz, 5.98–5.85 (1H, m, CCH2CH3), 5.38 (1H, d, J=1.4 Hz, 15.0 Hz, CH2), 5.33 (1H, d, J=9.0 Hz, CH), 4.95 (1H, d, one half of an AB quartet, J=7.5 Hz, CH2O), 4.88 (1H, d, one half of an AB quartet, J=7.5 Hz, CH2O), 4.05 (2H, s, CH2OCH3), 3.72–3.70 (2H, m, OCH2CH2O), 3.50–3.33 (2H, m, OCH2CH2O), 3.35 (3H, s, OCH3), 3.35 (3H, s, OCH3); δ(CDC13, 282 MHz) –96.4 (1F, d, J=53.0 Hz), –104.4 (1F, d, J=53.0 Hz); δ(CDC13, 75 MHz) 268.9, 155.9 (t, J=292.3 Hz), 131.4, 119.2, 113.3 (dd, J=36.2 Hz, 15.3), 97.2, 73.5, 70.6, 69.6, 68.5, 59.3, 59.0 [HRMS (ES, M[+Na]+)] Found: 314.14209. Calc. for C16H13NO4F2 314.141519; m/z (CI) 314 (100%, [M + Na]+).

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 HCI (100 ml of a 0.1 M aqueous solution) and extracted with ethyl ether (3 x 40 ml) then the combined organic extracts were dried (MgSO4), 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); Rf (50% ethyl ether in light petroleum) 0.42; δ(CDC13, 75 MHz) 7.57–7.28 (5H, m, Ph), 7.53–7.65 (1H, m, CH), 4.97 (1H, d, one half of an AB quartet, J=7.5 Hz, CH2O), 4.90 (1H, d, one half of an AB quartet, J=7.5 Hz, CH2O), 4.63 (1H, d, one half of an AB quartet, J=7.5 Hz, CH2O), 4.58 (1H, d, one half of an AB quartet, J=7.5 Hz, CH2O), 4.20 (2H, s, C(O)CH2O), 3.88–3.73 (2H, m, OCH2CH2O), 3.57–3.52 (2H, m, OCH2CH2O), 3.38 (3H, s, OCH3). 1.44 (3H, d, J=7.3 Hz, CH2CH3); δ(CDC13, 282 MHz) –97.3 (1F, d, J=5.2 Hz, 55.1), –104.7 (1F, d, J=55.1 Hz); δ(CDC13, 75 MHz) 169.3, 155.9 (t, J=292.1 Hz), 137.2, 128.6, 128.4, 114.1 (dd, J=56.2 Hz, 14.7), 97.4, 73.5, 71.5, 68.6, 67.2, 59.2, 24.1, 17.1 (t, J=2.3 Hz); m/z (ES) 360 (78%, M)+, 192 (100).
1,1-Difluoro-2-[methoxythioxy]methoxy]-4,4-dimethylpent-1-en-3-yl (allyloxy)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; Rf (20% ethyl acetate in light petroleum) 0.51 (Found: C, 59.81; H, 6.84. Calc. for C21H21O2NaF: C, 59.69; H, 7.01%; δf (CDCl3, 300 MHz) 7.40–7.21 (5H, m, Ph), 5.25–5.19 (1H, m, CH); 3.93 (1H, d, one half of an AB quartet, JHH = 5.9, OCH2H2O), 4.82 (1H, d, one half of an AB quartet, JHH = 5.9, OCH2H2O), 4.65 (1H, d, one half of an AB quartet, JHH = 11.8, OCH2H2Ph), 4.56 (1H, d, one half of an AB quartet, JHH = 11.8, OCH2H2Ph).

3,3-Difluoro-2-[methoxythioxy]methoxy]-1-phenylprop-2-en-1-yl (allyloxy)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; Rf (40% ethyl ether in light petroleum) 0.41; δf (CDCl3, 300 MHz) 7.49–7.26 (10H, m, Ph), 6.67–6.63 (1H, m, CH); 4.85 (1H, d, one half of an AB quartet, JHH = 5.7, OCH2H2O), 4.67 (1H, d, one half of an AB quartet, JHH = 11.8, OCH2H2Ph), 4.46 (2H, s, OCH2Ph), 4.22 (2H, s, CO2CH2), 3.75–3.61 (2H, m, OCH2CH2O), 3.49–3.42 (2H, m, OCH2CH2O), 3.32 (3H, s, OCH3); δf (CDCl3, 282 MHz) −96.4 (1F, d, JHH = 53.6), −104.6 (1F, d, JHH = 53.6); δc (CDCl3, 75 MHz) 169.1, 155.6 (t, JCF = 289.79), 130.7, 135.7, 128.6, 125.8, 128.0, 113.6 (dd, JCF = 35.7, 15.3); 79.5, 73.4, 71.4, 70.9, 68.5, 67.1, 58.9 [HRMS (ES, M/Na]+ Found: 445.1444. Calc. for C22H21O2F2Na 445.1439; m/z (ES) 423 (100%, [M+Na]+)].

(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) in THF (20 ml) and 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 (MgSO4), filtered and concentrated in vacuo to afford a pale yellow oil. Column chromatography afforded allyloxyacetate 11c (2.37 g, 83%) as a colourless oil; Rf (50% ethyl ether in light petroleum) 0.48; δf (CDCl3, 300 MHz) 8.65–8.61 (1H, m, CH2=CH); 5.50–5.40 (1H, m, CF3CCH); 5.32–5.18 (2H, m, CH2=CH); 4.97 (1H, d, one half of an AB quartet, JHH = 5.9, OCH2H2O), 4.89 (1H, d, one half of an AB quartet, JHH = 5.9, OCH2H2O), 4.10–4.02 (4H, m, OCH2CH2); 3.88–3.79 (2H, m, OCH2CH2O); 3.56–3.51 (2H, m, OCH2CH2O); 3.37 (3H, s, OCH3); 1.83–1.71 (2H, m, CH2=CHCH2); 0.90 (3H, t, JHH = 10.7, CH2CH3); δc (CDCl3, 282 MHz) −83.8 (1F, d, JHH = 54.8), −105.1 (1F, dd, JHH = 54.8, JHH = 1.70); δc (CDCl3, 75 MHz) 169.5, 155.7 (t, JCF = 292.6), 133.7, 118.2, 97.3, 94.1 (dd, JCF = 147.4, 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 C15H15O3FNa 347.1282; m/z (FAB) 347 (90%, [M+Na]+); 229 (100%).}

1,1-Difluoro-2-[methoxythioxy]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; Rf (50% ethyl ether in light petroleum) 0.26; 1H nmr (film) cm−1 176.0 s (C=O); δf (CDCl3, 300 MHz) 5.97–5.78 (1H, m, CH–CH2); 5.36–5.12 (3H, m, CH2CF3, CH2–CH2); 4.93 (1H, d, one half of an AB quartet, JHH = 6.2, OCH2H2O), 4.87 (1H, d, one half of an AB quartet, JHH = 6.2, OCH2H2O), 4.12–4.01 (4H, m, OCH2CH2CH2CH2); 3.87–3.68 (2H, m, OCH2CH2O), 3.57–3.49 (2H, m, OCH2CH2O), 3.46 (3H, s, OCH3), 2.18–2.11 (1H, m, CH–CH=CH2); 0.93 (3H, d, JHH = 6.6, CH3CH2O); 0.90 (3H, d, JHH = 7.0, CH3CH2O); δc (CDCl3, 282 MHz) −97.2 (1F, d, JHH = 55.3), −105.4 (1F, d, JHH = 55.3); δc (CDCl3, 75 MHz) 169.6, 155.9 (t, JCF = 292.3), 133.7, 118.1, 112.1 (dd, JCF = 36.7, 14.7), 97.3, 75.4, 72.4, 71.6, 68.6, 66.9, 59.0, 29.1, 19.2, 18.8 [HRMS (ES, M/Na]+ Found: 361.1429. Calc. for C15H15O3FNa 361.1439; m/z (ES) 361 (30%, [M+Na]+), 284 (40), 243 (100).

Methyl 3,3-difluoro-2-methoxy-4-oxohexanoate 15c

(rearrangement, esterification and enol acetal methanalysis with thioliom chloride)

In a typical procedure, ester 9e (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 (estimated) of concentrated HCl before being extracted with ether (3 × 25 ml). The organic extracts were combined, dried (MgSO4), filtered and concentrated in vacuo to afford the crude carboxylic acid as a yellow oil (0.49 g, 82%). Thiouyl 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 (MgSO4), filtration and concentration in vacuo afforded a yellow oil. Column chromatography afforded ketero 15e (0.20 g, 54%) as a colourless oil; Rf (10% ethyl acetate in light petroleum) 0.32; νmax (film/cm−1) 1721 (C=O) (Found: C, 48.32; H, 6.19. Calc. for C14H14O2F: C, 48.21; H, 6.19%; δf (CDCl3, 300 MHz) 4.30 (1H, dd, JH-JH = 10.3, 9.9, CH(OCH3)), 3.80 (3H, s, OCH3) (3H, s, OCH3), 2.65 (2H, t, JH-JH = 9.9, CH2CH2CH3), 1.70–1.50 (2H, m, CH2CH2CH2CH3), 0.90 (3H, t, JH-JH = 7.3, CH3CH2CH3); δf (CDCl3, 282 MHz) −113.6 (1F, dd, one half of an AB quartet, J1J2 = 270.5, J1F = 10.3), −118.7 (1F, dd, one half of an AB quartet, J1J2 = 113.0, J1F = 9.9) δf (CDCl3, 75 MHz) 198.0 (t, Jff = 26.6, C=O), 166.7, 113.8 (t, Jff = 259.3), 79.1 (t, Jff = 24.9), 60.0, 52.7, 39.3, 15.8, 13.2; m/z (CI) 242 (100%, [M + Na]+)].

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 thiouyl chloride (0.09 ml, 1.34 mmol) in methanol (20 ml) followed by the usual work-up and column chromatography afforded ketero 15d (0.16 g, 56%) as a colourless oil; Rf (10% ethyl acetate in light petroleum) 0.35 (Found: C, 50.48; H, 6.78. Calc. for C13H14F2O2Si: C, 50.42; H, 6.77%; δf (CDCl3, 300 MHz) 4.34 (1H, dd, JH-JH = 14.1, 9.9, CH(OCH3)), 3.82 (3H, s, OCH3) (3H, s, OCH3), 2.59 (2H, d, JH-JH = 9.0, CH2CH2CH3), 2.36–2.10 (2H, m, CH2CH2CH3), 0.95 (6H, d, JH-JH = 8.7, CH3CH2); δf (CDCl3, 282 MHz) −113.6 (1F, dd, one half of an AB quartet, J1J2 = 270.5, J1F = 10.3), −118.7 (1F, dd, one half of an AB quartet, J1J2 = 113.0, J1F = 9.9) δf (CDCl3, 75 MHz) 198.0 (t, Jff = 26.6, C=O), 166.7, 113.8, 114.4 (t, Jff = 259.3), 79.1 (t, Jff = 24.9), 60.0, 52.7, 39.3, 15.8, 13.2; m/z (CI) 242 (100%, [M + Na]+)].

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

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 thiouyl chloride (0.06 ml, 0.84 mmol) in methanol (15 ml) followed by usual work-up and column chromatography afforded ketero 15c (0.12 g, 56%) as a colourless oil; Rf (10% ethyl acetate in light petroleum) 0.47; δf (CDCl3, 300 MHz) 4.32 (1H, dd, JH-JH = 14.7, 9.9, CH(OCH3)), 3.83 (3H, s, OCH3) (3H, s, OCH3), 2.60 (2H, s, CH2CH2F), 1.06 (9H, s, C(CH3)3); δf (CDCl3, 282 MHz) −113.6 (1F, dd, one half of an AB quartet, J1J2 = 268.8, J1F = 9.9), −118.6 (1F, dd, one half of an AB quartet, J1J2 = 270.5, J1F = 10.3); δf (CDCl3, 199.2 MHz) 252.9, 78.7, 58.5, 52.2, 48.7, 46.1, 23.2, 11.1 [HRMS (FAB, M[+Na]+) Found: 261.0971]. Calc. for C12H16F2O3Na 261.094135; m/z (CI) 256 (5%, [M + Na]+); 240 (51%, [M + 2Na]+); 224 (29%, [M + 3Na]+); 208 (17%, [M + 4Na]+); 192 (10%, [M + 5Na]+); 176 (5%, [M + 6Na]+).
Treatment of crude 13b was washed with diethyl ether (3 × 20 ml). The organic fraction was discarded and the pH was lowered to ca. 10 with concentrated NaOH (5 M aqueous solution) and the solution was washed with diethyl ether (3 × 20 ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated in vacuo to afford acid 13b as a pale yellow oil (2.02 g, 75%); vₐₜₜ, (film/cm⁻¹) 3620–3680 (m, COOH-H), 2922s, 1722s (C=O), δ₁₉ (CDCl₃, 300 MHz) 8.37–8.17 (1H, br s, COH), 7.40–7.27 (5H, m, Ph), 5.68 (1H, dq, J₁₉–H₁₇ = 7.1, J₁₉–H₁₉ = 1.29, CH₃CH), 4.95 (1H, d, one half of an AB quartet, J₇–H₅ = 5.9, OCH₂H₅Ph), 4.91 (1H, d, one half of an AB quartet), J₇–H₅ = 5.9, OCH₂H₅Ph), 4.40 (1H, dd, J₁₉–H₁₇ = 14.7, J₁₉–H₁₈ = 8.1, CH–(OBr)CO₂H), 3.89–3.73 (2H, m, OCH₂CH₂OCH₂), 3.55 (2H, t, J₁₉–H₁₇ = 6.0, OCH₂CH₂OCH₂), 3.36 (3H, s, OCH₃), 1.71 (3H, dt, J₁₉–H₁₇ = 7.1, J₁₉–H₁₈ = 2.8, CH₃CH₂), δ₁₉ (CDCl₃, 75 MHz) 170.0, 145.1 (29.7, 25.1), 125.6, 121.1, 120.3, 113.9 (t, J₁₉–F₁₁ = 25.7), 98.2, 76.8 (2t, J₁₉–F₁₁ = 29.7), 73.6, 71.6, 68.7, 59.0, 10.9, δ₁₉ (CDCl₃, 282 MHz) –111.5 (1F, dd, J₁₉–F₁₁ = 25.6, J₁₉–F₁₁ = 14.7), –106.3 (1F, dd, J₁₉–F₁₁ = 25.6, 60.0) [HRMS (E, M+Na⁺)] Found: 337.1279. Calcd. For C₂₄H₂₄O₂F₂Na 338.1282; 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 ¹H and ¹³C and ¹⁹F NMR spectra.

Methyl 2-benzoxyl-3,3-difluoro-4-oxoheptanoate 16b

Treatment of crude 13b (0.34 g, 0.83 mmol) with thionyl chloride (0.07 ml, 0.94 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); R₁ (40% ethyl acetate in light petroleum) 0.61; δ₁₉ (CDCl₃, 300 MHz) 7.39–7.26 (5H, m, Ph), 4.77 (1H, d, one half of an AB quartet, J₇–H₅ = 11.4, OCH₂H₅Ph), 4.57 (1H, d, one half of an AB quartet, J₇–H₅ = 11.4, OCH₂H₅Ph), 4.55 (2H, dd, J₁₉–H₁₇ = 14.3, 10.3, CHF₂CO₂), 3.80 (3H, s, OCH₃), 2.73 (2H, q, J₁₉–H₁₇ = 7.3, CH₂CH₃), 1.09 (3H, t, J₁₉–H₁₇ = 7.3, CH₃CH₂), δ₁₉ (CDCl₃, 75 MHz) 200.1 (t, J₁₉–F₁₁ = 27.6), 165.0, 137.8, 128.5, 114.2 (t, J₁₉–F₁₁ = 261.2), 76.9 (t, J₁₉–F₁₁ = 24.7), 52.8, 31.3, 6.3; δ₁₉ (CDCl₃, 282 MHz) –113.4 (1F, dd, one half of an AB quartet, J₁₉–F₁₁ = 269.6, J₁₉–F₁₁ = 10.2), –118.1 (1F, dd, one half of an AB quartet, J₁₉–F₁₁ = 269.7, J₁₉–F₁₁ = 15.3) [HRMS (ES, M+Na⁺)] Found: 309.0919. Calc. for C₂₁H₂₁O₄F₂Na 309.0914; m/z (ES) 309 (100%, [M + Na⁺]), 123 (10), 91 (100), 71 (28).

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

From 10c (0.55 g, 1.50 mmol), LDA (1.50 mmol) and chloro-trimethylsilane (0.21 ml) 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 (0.07 ml, 0.94 mmol) in methanol (20 ml) followed by usual work-up and column chromatography afforded ketoester 16c (0.43 g, 0.91 mmol) as an oil which afforded crude carboxylic acid 13c 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) 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) 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) 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) which afforded crude carboxylic acid 13d as a yellow oil [0.33 g, 77% (estimated)].
Methyl 2-allyloxy-3,3-difuoro-4-oxo-6-methylheptanoate 17d

From 11d (1.22 g, 3.62 mmol), LDA (0.41 g, 4.4 mmol) and benzylalcohol (0.88 g, 56%) as a colourless oil; \( \delta \) (CDCl\(_3\), 75 MHz) 199.7; \( J_{\text{HF}} \) 14.1; \( \delta_c \) (CDCl\(_3\), 75 MHz) 200.1 (1F, \( J_{\text{HF}} \) 27.7), 169.2, 113.7 (t, \( J_{\text{HF}} \) 27.4), 53.6, 39.4, 15.8, 13.4; m/z (CI) 228 (100%, [M + NH\(_4\)]\(^+\)).

Methyl 2-hydroxy-3,3-difuoro-4-oxoheptanoate 25c (dechloration)

Zinc(II) chloride (0.1 g, 0.78 mmol) was added to a solution of allyloxyketone 17e (0.15 g, 0.6 mmol) in dry THF (10 ml) and the reaction mixture was stirred at room temperature for 15 minutes. Tetrakis(triphenylphosphine) 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 HC1 (10 ml of a 1 M aqueous solution) was added and then the solution extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were dried (MgSO\(_4\)) and concentrated by column chromatography to afford the hydroxyketone 25c (0.07 g, 56%) as a colourless oil; \( \delta \) (CDCl\(_3\), 75 MHz) 0.56 (0.076 g, 56.9%).

Methyl 2-hydroxy-3,3-difuoro-4-oxoheptanoate 25d

From ZnCl\(_2\) (0.12 g, 0.92 mmol), 17d (0.18 g, 0.77 mmol), Pd(PPh\(_3\))\(_2\)Cl\(_2\) (0.09 g, 0.08 mmol) and Bu\(_4\)N\(_2\) (0.38 ml, 1.4 mmol) in dry THF (15 ml). Usual work-up and column chromatography afforded hydroxyketone 25d as a colourless oil; \( \delta \) (CDCl\(_3\), 75 MHz) 0.56 (0.69 mmol) in light petroleum) 0.78; \( \delta_c \) (CDCl\(_3\), 75 MHz) 201.0 (1F, \( J_{\text{HF}} \) 27.7), 169.2, 113.7 (t, \( J_{\text{HF}} \) 27.4), 53.6, 39.4, 15.8, 13.4; m/z (CI) 228 (100%, [M + NH\(_4\)]\(^+\)).

Methyl 2-hydroxy-3,3-difuoro-4-oxo-6-methylheptanoate 25f

From ZnCl\(_2\) (0.12 g, 0.92 mmol), 17d (0.18 g, 0.77 mmol), Pd(PPh\(_3\))\(_2\)Cl\(_2\) (0.09 g, 0.08 mmol) and Bu\(_4\)N\(_2\) (0.38 ml, 1.4 mmol) in dry THF (15 ml). Usual work-up and column chromatography afforded hydroxyketone 25f as a colourless oil; \( \delta \) (CDCl\(_3\), 75 MHz) 0.56 (0.69 mmol) in light petroleum) 0.78; \( \delta_c \) (CDCl\(_3\), 75 MHz) 201.0 (1F, \( J_{\text{HF}} \) 27.7), 169.2, 113.7 (t, \( J_{\text{HF}} \) 27.4), 53.6, 39.4, 15.8, 13.4; m/z (CI) 228 (100%, [M + NH\(_4\)]\(^+\)).

Methyl 2-hydroxy-3,3-difuoro-4-oxoheptanoate 25g (debenzylation)

Pearlman's catalyst (0.10 g, 20 wt% Pd) was added to a solution of benzoxoyletoester 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 hydroxyketone 25g (0.26 g, 92%) as a colourless oil.

Methyl 2-hydroxy-3,3-difuoro-4-oxo-6-methylheptanoate 25h

From Pearlman's catalyst (0.21 g, 20 wt% Pd) and benzoxoyletoester 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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References

12 There is a known route from the Kobayashi laboratory involving difluoromethylation and rearrangement, in which ozonolysis was used to cleave an allenyl group and reveal a ketone, but this chemistry has not been reported in full and is, we believe, less convenient than that described herein. See: T. Taguchi, T. Morikawa, O. Kitagawa, T. Mishima and Y. Kobayashi, Chem. Pharm. Bull., 1985, 33, 5137.
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