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A NEW, SHORT SYNTHETIC ROUTE TO α-SUBSTITUTED 5,5-DIFLUORO-4-PENTENOIC ACID ESTERS.

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SUMMARY

The title compounds are prepared in one step from ester enolates and 3,3,3-trifluoropropene. The α-substituted 5,5-difluoro-4-pentenoic acid esters are susceptible to a second deprotonation and, on reaction with an electrophile, give access to the α-disubstituted analogues.

INTRODUCTION

In the course of our work on the design of enzyme inhibitors [1], we required a convenient route to 5,5-difluoro-4-pentenoic acid esters 2 with different subtituents at the α-carbon atom. There are several methods described for the incorporation of a 2,2-difluorovinyl functionality in a given structural environment [2–6], but none was found suitable for our purpose. We initially have

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employed the methodology of Fuqua et al. [2], as this strategy had already been applied to the preparation of some 3,3-difluoroallyl substituted esters [7]; however, in view of the harsh conditions required and the length of the synthetic sequence, we investigated an alternative route.

S_N'-type nucleophilic allylic substitution of one fluorine atom in 3,3,3-trifluoropropene appeared to us as a promising approach to the synthesis of our target compounds. However, this substitution reaction is reported to be restricted to simple alkyl- or aryllithium [6] or trialkylsilyl lithium compounds [8]. 'Softer' carbanionic species, such as Grignard and alkylcopper reagents, do not react in the desired fashion [9].

We now report here the extension of this reaction sequence to lithium ester enolates and one amide enolate and describe a new and short route to α-substituted 5,5-difluoro-4-pentenoic acid derivatives starting from 3,3,3-trifluoropropene.

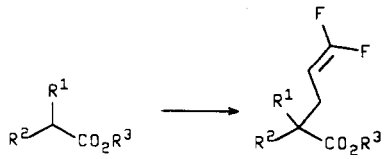
SYNTHESES

Reaction of the ester enolate, generated from the corresponding esters **1** and lithium diisopropylamine in tetrahydrofuran at -78°C, with about 1.5 equivalents of 3,3,3-trifluoropropene first at -78°C and then room temperature affords the 3,3-difluoroallylated analogues **2** (Table 1). The reaction is equally successful for straight-chain esters (**2a,b**) as for the α-branched example **2d**. Branching at the ß-carbon atom gave some lower yield for this difluoroallylation sequence (**2c**). More stabilised enolate anion species, such as those derived from diethyl phenylmalonate (**1e**) or N-benzylidene-phenylalanine methyl ester (**1f**), did not react under these conditions.

In order to increase the scope of possible substituents in the α-position we sought to functionalize the product pentenoic acids **2a–c** further with electrophiles through a second deprotonation sequence. We found that, despite the presence of the difluoroalkene functionality, known to be incompatible with

TABLE

Synthesis of the 3,3-difluoroallylated analogues 2 of esters 1



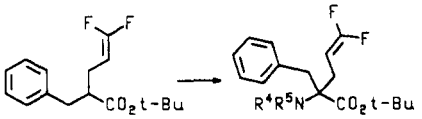
1 2

1	R^1	R^2	R^3	2 Yield(%)
a	$PhCH_2$	H	tBu	66
b	$Ph(CH_2)_2$	H	tBu	85
c	Me_2CH	H	tBu	26
d	$PhCH_2$	Me	tBu	74
e	Ph	CO_2Et	Et	0
f	$PhCH_2$	N=CHPh	Me	0

reaction conditions employing strong bases [10], the enolate of the 3,3-difluoroallylated ester **2a** reacts with methyl iodide to afford the α-methylated analogue **2d** in 71% yield.

Our immediate requirement was for a nitrogen substituent at the 2-position. In the attempt to access these α-amino acid derivatives, two synthetic strategies were investigated, namely electrophilic amination of the 3,3-difluoroallylated species **2** (R^2= H) or electrophilic difluoroallylation of a suitable glycine enolate. In the context of the former approach, we examined different nitrogen electrophiles. Diethyl azodicarboxylate on reaction with the enolate derived from ester **2a** gave the protected α-hydrazino ester **2g** in 44% yield [11], while O-(diphenylphosphinyl)hydroxylamine afforded the α-aminoester **2h** in only

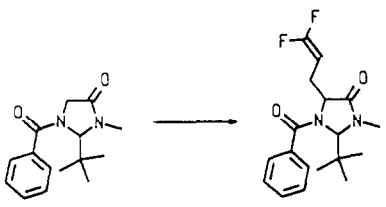
20% [12]. On the other hand, the lithium enolate, which is obtained on treatment of (R,S)-1-benzoyl-2-(*t*-butyl)-3-methyl-1,3-imidazolidin-4-one (**3**) with lithium diisopropylamine [13], reacts with 3,3,3-trifluoropropene under the reaction conditions described for the ester series to give the difluoroallylated analogue **4** in 15%.



2a

2g R^4= CO_2Et, R^5= $NHCO_2Et$

2h R^4=R^5= H



3

4

Overall then, we here describe a reaction sequence by which α-(mono or bis)substituted 5,5-difluoro-4-pentenoic acid derivatives can be prepared in multigram quantities in only one or two operations. The scope of the sequence allows for an α-hetero substituent in both the starting material and the reaction product, as demonstrated by the synthesis of α-nitrogen analogues **2g,h** and **4**.

EXPERIMENTAL

NMR: Varian EM-390 or Bruker AM 360 spectrometer. ^1H chemical shifts are given in ppm relative to internal Me_4Si (δ); ^{19}F NMR shifts in ppm relative to internal C_6F_6 [Θ=0; $\delta(CFCl_3)$= -163ppm]. IR: Perkin-Elmer IR-577 or IR-277 spectrometer. MS: CG/SM Ribermag R10-10 or Finnigan TSQ GC/MS/MS. Solvents and reagents were dried prior to use when deemed necessary. For a detailed description of the experimental techniques refer to the Experimental Section of our earlier work [14]. Chromatography refers to the flash chromatography technique [15] on silica gel. All compounds described are new.

t-Butyl 2-benzyl-5,5-difluoro-4-pentenoate (2a). To a stirred solution of *i*-Pr_2NH (12.4g, 0.12mol) in tetrahydrofuran (THF) (120mL), cooled to -30°C under N_2, is added dropwise n-BuLi (1.6M in hexane, 76mL, 0.12mol). The solution is stirred at -30°C for 20 min, then cooled to -78°C, and a solution of *t*-butyl 3-phenyl propanoate (**1a**, 22.9g, 0.11mol) in THF (120mL) is added dropwise. The solution is stirred for a further 30 min at -78°C, and then 3,3,3-trifluoropropene (4.1L, 0.17mol) is introduced into the reaction flask via a gas syringe. A dry-ice cold finger protects the exit to the N_2 line. The solution is allowed to warm to r.t., and then poured into 1*N* HCl. The mixture is extracted twice with light petroleum, and the combined extracts are washed with H_2O (twice) and brine, dried over Na_2SO_4 / $NaHCO_3$, and concentrated *in vacuo* to give a brown oil (32g). Distillation gives *t*-butyl 2-benzyl-5,5-difluoro-4-pentenoate (**2a**) as a colourless oil, bp 85 - 90°C / 0.5 torr (23.9g), purity 83% by ^1H NMR (remainder starting material), 66% (corrected) yield. When necessary, pure material can be obtained by re-distillation.
^1H NMR ($CDCl_3$) δ 7.2 (m, 5H, Ph-H); 4.15 (dtd, 1H, J= 24, 7, 3Hz, CH=); 3.2 - 2.4 (m, 3H, Ph-CH_2-CH); 2.4 - 2.0 (m, 2H, =C-CH_2); 1.40 (s, 9H, CH_3).
^{19}F NMR ($CDCl_3$, C_6F_6) Θ 74 (br d, J= 50Hz); 72 (dd, J= 50, 24Hz).

t-Butyl 2-phenylethyl-5,5-difluoro-4-pentenoate (2b). Following the experimental procedure described for **2a**, but starting from *t*-butyl 4-phenylbutanoate the ester **2b** was obtained in 85% yield on a 0.01 mol scale.
^1H NMR ($CDCl_3$) δ 7.2 (m, 5H, Ph-H); 4.20 (ddt, 1H, J= 24, 4, 8Hz, =CH); 2.6 (m, 2H, =C-CH_2); 2.2 - 1.9 (m, 5H, CH_2-CH_2-CH); 1.45 (s, 9H, CH_3). IR ($CHCl_3$) 2970, 2930, 2860, 1745, 1725, 1150 cm^{-1}. MS (DCI, NH_3) m/e (rel. intensity) 314 (M + NH_4^+, 100%), 297 (M^+, 10), 258 (20)

t-Butyl 2-(2-propyl)-5,5-difluoro-4-pentenoate (2c). Prepared as described for **2a**, starting from *t*-butyl 3-methyl butanoate: 50% on a 0.009 mol scale.
^1H NMR ($CDCl_3$) δ 4.10 (ddt, 1H, J= 26, 3, 7.5Hz, =CH); 2.1 (m, 3H, CH_2-CH); 1.47 (s, 9H, CH_3); ^{19}F NMR ($CDCl_3$,C_6F_6) Θ 74 (d, J=47Hz); 71 (dd, J= 47, 26Hz).

t-Butyl 2-methyl-2-benzyl-5,5-difluoro-4-pentenoate (2d).

A: Prepared from *t*-butyl 3-phenyl-2-methylpropanoate, as described for 2a: 74% for a 0.015 mol scale. bp 90-95°C/0.5torr.
^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5H, Ph-H); 4.20 (dtd, 1H, J= 24, 8, 3Hz, CH=); 3.00 (d, 1H, J= 14Hz, Ph-CH_A), 2.73 (d, 1H, J= 14Hz, Ph-CH_B); 2.6 - 1.8 (m, 2H, =C-CH_2); 1.40 (s, 9H, CH_3); 1.08 (s, 3H, CH_3). ^{19}F NMR ($CDCl_3$, C_6F_6) Θ 75 (br d, J= 48Hz); 72 (dd, J= 48, 24Hz).

B: Prepared from *t*-butyl 2-benzyl-5,5-difluoro-4-pentenoate (2a): To a cooled (-20°C external temp.) solution of *i*-Pr_2NH (1.68mL, 0.012mol) in THF (20mL) is added n-BuLi (1.4M in hexane, 7.8mL, 0.011mol), the solution is stirred at -20°C for 15 min and then cooled to -78°C. A solution of *t*-butyl 2-benzyl-5,5-difluoro-4-pentenoate (**2a**, 2.82g, 0.010mol) in THF (20mL) is added dropwise and the mixture is stirred at -78°C for 30 min, to afford a solution of *t*-butyl 2-benzyl-5,5-difluoro-2-lithio-4-pentenoate. MeI (1.25mL, 0.02mol) is added, the mixture is stirred at -78°C for a further 10 min, allowed to warm to room temperature, and poured into 10% aq. $NaHSO_4$. The mixture is extracted twice with pentane. The combined extracts are washed with H_2O, satd. $KHCO_3$, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue is distilled to give *t*-butyl 2-benzyl-5,5-difluoro-2-methyl-4-pentenoate (**2d**, 2.11g, 71%) as a colourless oil; spectroscopical and analytical data are identical to those, obtained for the material prepared from *t*-butyl 3-phenyl 2-methylpropionate, described above under A.

t-Butyl 2-benzyl-2-[N-(ethoxycarbonyl-ethoxycarbonylamino)amino]-5,5-difluoro-4-pentenoate (2g). Prepared at a 0.01 mol scale as described above for **2d** under B, using diethyl azodicarboxylate as electrophile to quench the enolate species at -78°C. After 3 min acetic acid (1.2mL, 0.02mol) is added. Work-up gives crude **2g**, purified by column chromatography (eluant: pentane/Et_2O, 3:2). Yield 44%.
^{1}H NMR ($CDCl_3$) δ 7.3 and 7.1 (2m, 3:2, 5H, Ph-H); 4.20 (d, 4H, J=7.5 Hz, O-CH_2); 4.1 (m, 1H, =CH); 3.3 and 2.9 (AB, 2H, J= 15 Hz, Ph-CH_2); 2.5 (broad t, 2H, J= 7Hz, =C-CH_2); 1.43 (s, 9H, CH_3); 1.33 and 1.23 (2t, 6H, J= 7Hz, CH_3). ^{19}F NMR ($CDCl_3$, C_6F_6) Θ 76 (d, J= 47 Hz); 74 (dd, J= 47, 26Hz). MS (DCI, NH_3) m/e (rel. intensity) 474 (M + NH_4^+, 100%), 457 (M^+, 20), 418 (40), 401 (20), 300 (20), 194 (20).

t-Butyl 2-amino-2-benzyl-5,5-difluoro-4-pentenoate (**2h**). Prepared as described above for **2d** under B. After adding the cold enolate solution to cold (-78°C) O-(diphenylphosphinyl)hydroxylamine [12], stirring is continued for 30 min, and the reaction mixture is then allowed to warm to room temperature. Work-up (Et_2O / aq.$KHCO_3$) and column chromatography of the crude material (eluant: hexane / Et2O, 1:1) gave in 20% yield the target α-amino ester **2h.**

^1H NMR ($CDCl_3$) δ 7.3 (s, 5H, Ph-H); 4.23 (ddt, 1H, J= 24, 3, 7.5Hz, =CH); 3.15 (d, 1H, J= 13Hz, Ph-CH_A); 2.77 (d, 1H, J= 13Hz, Ph-CH_B), 2.6 - 2.0 (structured m, 2H, =C-CH_2); 1.5 (broad s, 2H, NH_2); 1.47 (s, 9H, CH_3). ^{19}F NMR ($CDCl_3$, C_6F_6) Θ 76 (dm, J= 45Hz); 73 (ddt, J= 45, 26, 15Hz).

(R,S) 1-Benzoyl-2-(*t*-butyl)-5-(3,3-difluoroallyl)-3-methyl-1,3-imidazolidin-4-one (2j). Prepared as described for 2a from 3,3,3-trifluoropropene and (R,S)-2-(*t*-butyl)-3-methyl-1,3-imidazolidin-4-one [13]. Yield 15% after column chromatography (eluant: hexane / EtOAc, 3:1).

^1H NMR ($CDCl_3$) δ 7.6 (m 5H, Ph-H); 5.7 (s, 1H, N-CH-N); 4.7 (m, 1H, N-CH-CO); 3.73 (ddt, 1H, J= 24, 3, 7.5Hz, =CH); 3.07 (s, 3H, CH_3); 2.5 (m, 2H, =C-CH_2); 1.03 (s, 9H, CH_3). ^{19}F NMR ($CDCl_3$, C_6F_6) Θ 78 (d, J= 46Hz); 76 (dd, J= 46, 26Hz).

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