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AN IMPROVED CYCLISATION PROTOCOL FOR THE SYNTHESIS OF δ,δ-DIFLUORO-δ-LACTONES.

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SUMMARY

An improved procedure for the synthesis of δ,δ-difluoro-δ-lactones from 5,5-difluoro-4-pentenoic acids is described. The method is illustrated for 2-benzyl-5,5-difluoro-4-pentenoic acid (2), which upon treatment with first mercury(II)acetate and then tri-n-butyltin hydride affords α-benzyl δ,δ-difluoro-δ-lactone (5).

INTRODUCTION

Morikawa *et al.* have reported the synthesis of 3,3-difluoro-isochroman-1-on via an iodolactonisation protocol, starting from methyl difluorovinyl benzoate 1 [1]. In the context of our work on enzyme inhibitors, we were interested in the

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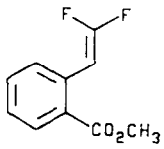
synthesis of lactones with fluorine substituents next to the ring oxygen functionality in general.

Recently we have described a new and short route to 5,5-difluoro-4-pentenoic acids, such as compound **2** [2], suitable starting materials for the above purpose. In our hands, however, the synthesis of the δ,δ-difluoro-δ-lactones, e.g. **5**, from the corresponding fluorinated pentenoic acid esters via the above described iodolactonisation protocol [1] generated a considerable quantity of dark tar, from which the lactones could be isolated only by tedious chromatography. In addition, the intermediate iodolactones **3** were not very stable; even the purified material darkened within a few hours.

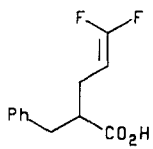
SYNTHESIS

Our investigation implied the use of 5,5-difluoro-4-pentenoic acids, in particular 2-benzyl-5,5-difluoro-4-pentenoic acid **2** as starting material and focused on the inspection of the utility of other electrophiles in this cyclisation step. As a first approach, reagents which would give a more stable intermediate cyclized product were sought.

Initially we attempted to cyclize model compound **1** with (tosyloxy)iodosobenzene [3]. Some evidence for cyclization was observed (^{19}F NMR) but results were not very encouraging in terms of yield. Also proto-lactonisation was possible, but again only in low yield.



1



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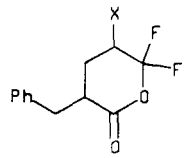

3 X = I
4 X = HgOAc
5 X = H

We then turned to mercurilactonisation [4]. The difluorovinyl acid **2** was treated with mercury (II) acetate, and the progress of the reaction was monitored by ^{19}F NMR. When iodine was added to trap the organo-mercurial **4** [5]. only a 1:2 mixture of the iodolactone **3** [^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5H, Ph); 4.25 (structured m, 1H, C*H*-I); 3.4 ("d", 1H, J= 9Hz, Ph-CHH_A); 2.9 (m, 2H, Ph-CHH_B-C*H*); 2.3 (m, 2H, CH_2). ^{19}F NMR ($CDCl_3$, C_6F_6) Θ 96 (dd, J= 14, 4Hz, CFF_A); 95 (dd, J= 7, 3Hz, CFF_B)] and the mercurilactone **4** was isolated. However, treatment of the crude mercurilactone with tri-n-butyltin hydride [6] cleanly removed the mercury from the intermediate lactone **4** and afforded the desired target structure **5** in a satisfying 50% overall yield, after chromatography.

The total process for the synthesis of δ,δ-difluoro-δ-lactones is then reduced to a simple one-pot reaction, which is complete in short time and requires no heating and no aqueous work up of the water-sensitive product material. Thus, this improved cyclization procedure of 5,5-difluoro-4-pentenoic acids together with their synthesis, reported recently by us [2], allows to obtain these fluorinated lactones with a broad substitution pattern in a straightforward reaction sequence.

EXPERIMENTAL

NMR: Varian EM-390 or Bruker AM 360 spectrometer. ^{1}H and ^{13}C 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. 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 [7]. Chromatography refers to the flash chromatography technique [8] on silica gel.

α-Benzyl δ,δ-difluoro-δ-lactone (5). A mixture of 2-benzyl 5,5-difluoro-4-pentenoic acid (**2**, 0.46g, 2.17mmol), obtained from *t*-butyl 2-benzyl-5,5-difluoro-4-pentenoate [2] on treatment with trifluoroacetic acid at r. t. for 14h, and $Hg(OAc)_2$ (0.69g, 2.1mmol) in acetonitrile (5mL) is stirred for *ca.* 45 min, until

it becomes homogeneous. ^{19}F NMR indicates the complete consumption of starting material [**2**: ^{19}F NMR ($CDCl_3$, C_6F_6) Θ 75 (broad d, J= 44Hz, CFF_A); 73 (ddt, J= 44, 24, 3Hz, CFF_B), **4**: ^{19}F NMR ($CDCl_3$, C_6F_6) Θ 113 (dd, J= 153, 31Hz, CFF_A); 105 (dt, J= 153, 3Hz, CFF_B)]. n-BuSnH (1.89g, 1.75mL, 6.51mmol) is added and stirring is continued for a further 10 min. The mixture is diluted with Et_2O, the precipitate is removed by filtration through celite and washed with Et_2O. The filtrate is concentrated to give the crude δ,δ-difluoro-δ-lactone product **5**, a new compound which is purified by flash chromatography (eluant: Et_2O / hexane, 1:4).

^1H NMR ($CDCl_3$, 360 MHz) δ 7.3 and 7.2 (2 struct'd m, 5H, 3:2, Ph); 3.47 (struct'd m, 1H, Ph-CHH_A); 2.85 (struct'd m, 1H, CH); 2.80 (struct'd m, 1H, Ph-CHH_B); 2.35 (struct'd m, 1H, CF_2-CHH_A); 2.1 (struct'd m, 1H, CF_2-CHH_B); 1.9 (struct'd m, 1H, CHH_A); 1.7 (struct'd m, 1H, CHH_B). ^{13}C NMR ($CDCl_3$, 90.5 MHz) δ 168 (*C*O), 138, 129, 128.5, 127.5 (Ph), 124.5 (t, J_{CF}= 249Hz, CF_2), 42 (*C*H), 38.5 (Ph-*C*H_2), 30 (t, J_{CF}= 28Hz, *C*-CF_2), 21 (*C*H_2). ^{19}F NMR ($CDCl_3$, C_6F_6) Θ 98 (narrow ABX_2). IR ($CHCl_3$) 2920, 1780, 1440, 1380, 1265, 1080 cm^{-1}.

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