α,α-Difluoro β-Lactones and Their Thermal Decarboxylation to 1,1-Difluoroalkenes

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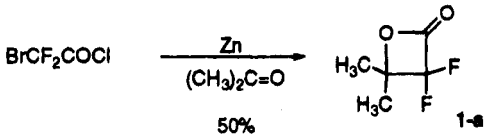
β-Lactones have been known for more than 100 years,[1] and they are readily prepared by a number of methods,[2] perhaps the most generally useful being Adam's method of cyclization of β-hydroxy acids via treatment with benzenesulfonyl chloride in pyridine.[3] This method, and others, have been used to prepare β-lactones of widely diverse structural types.[2] However, to our knowledge, there has been but one mention of a β-lactone which bears fluorine as a substituent on the ring, and that was within England and Krespan's report of the preparation of difluoroketene in 1968 wherein they claimed evidence for the intermediacy of difluoroketene by virtue of their ability to trap it with acetone to form α,α-difluoro-β,β-dimethylpropiolactone, **1a** (eq 1).



(1)

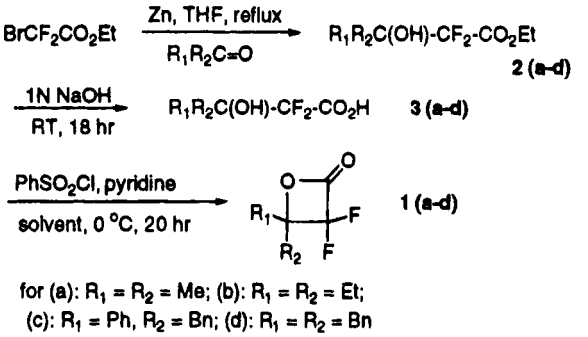
Because of the presence of geminal fluorine substituents α to the carbonyl function, one would expect β-lactones such as **1a** to be very reactive, particularly with respect to nucleophilic acyl substitution. Moreover, it is likely that such α,α-difluoro β-lactones will act as excellent precursors to 1,1-difluoroalkenes, via their thermal decarboxylation. We wish to report at this time, using a modified Adam procedure, the first general method for the preparation of α,α-difluoro-β,β-dialkyl β-lactones (3,3-difluoro-4,4-dialkyl-2-oxetanones). We will also present initial observations regarding their reactivity, including the finding that they do indeed act as useful synthetic precursors to 1,1-difluoroalkenes.

The overall synthetic scheme, starting from a broad assortment of ketones, is depicted below. The procedure involves initial Reformatsky reactions with the ketones using ethyl bromodifluoroacetate to form β-hydroxy esters, **2**.[5] Hydrolysis under mild basic conditions then converts these esters to the respective β-hydroxy acid precursors, **3**.

In the conversion of these β-hydroxy acids to the desired β-lactones, a strict adherence to the Adam procedure leads to poor yields of impure lactones. For the most part this is due to the great sensitivity of the α,α-difluoro-β-lactones to the aqueous workup. Modification of the Adam procedure in a manner so as to both avoid aqueous workup and to optimize the ease of isolation of the highly labile products has allowed us to successfully prepare and isolate the series of 3,3-difluoro-2-oxetanones indicated above. Table 1 gives the yields which were obtained for each step in taking each of the ketones through to their respective β-lactones, **1a-d**.

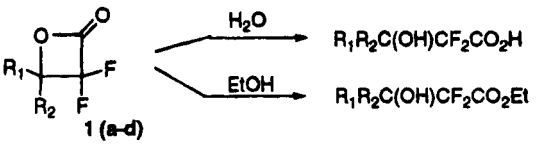
Table 1. Yields of Esters, Acids, Lactones, and 1,1-Difluoroalkenes

			yields (%)			
compd	R_1	R_2	2	3	1	$CF_2=CR_1R_2$
a	Me	Me	77	80	89	87
b	Et	Et	74	99	95	98
c	Ph	Bn	95	93	100	100
d	Bn	Bn	88	97	100	95



A typical procedure for preparation of nonvolatile β-lactones, **1c, d**, involves slow addition of 1.0 equiv of benzenesulfonyl chloride to a stirred solution of β-hydroxy acid and 2 equiv of pyridine in $CHCl_3$ at 0 °C. After 20 h, the mixture is evaporated and the residue extracted with hexane. Evaporation of the hexane, followed by recrystallization of the impure lactone from hexane, gave, for example, 95% of pure 4,4-dibenzyl-3,3-difluoro-2-oxetanone, **1d**.[6,7]

As we suspected, the 3,3-difluoro-2-oxetanones proved to be very labile with respect to nucleophilic acyl substitution, each undergoing rapid reaction at room temperature with both water and ethanol to reform the respective carboxylic acids or ethyl esters.



Each of these α,α-difluoro β-lactones was also found to decarboxylate smoothly in solution at 150–180 °C. Excellent yields of the respective 1,1-difluoroalkenes were obtained, as indicated in the last column of Table 1. Thus, this overall sequence provides a new and poten-

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(6) Esters **2**, acids **3**, and lactones **1** were fully characterized, if not known, by ^1H, ^{19}F, and ^{13}C NMR, while the lactones were also characterized by HRMS and elemental analysis. For example, **1c**: mp 83–88 °C dec; ^1H NMR δ 3.15 (d, J = 15.3 Hz, 2H), 3.23 (d, J = 15.3 Hz, 2H), 7.06–7.33 ppm (m, 10H); ^{19}F NMR, δ −118.4 ppm; ^{13}C NMR δ 36.9 (bs), 92.5 (t, J = 20 Hz), 120.2 (t, J = 293.0 Hz), 127.5, 128.6, 130.3, 132.8, 161.0 (t, J = 32.4); IR 1857.7 cm^{-1}. Anal. Calcd for $C_{17}H_{14}O_2F_2$: C, 70.83; H, 4.89. Found: C, 70.56; H, 5.06.

(7) In the synthesis of relatively *volatile* β-lactones, **1a, b**, the reactions are carried out the same way except that dry tetraglyme is utilized as solvent and the volatile β-lactones are subsequently vacuum transferred out of the reaction mixture (at 0.05 mmHg) over a 2 h period as the mixture is warmed. (No limitation was noted for the scale of the lactonization reaction, although the largest scale attempted used 4 g of starting hydroxy acid.)

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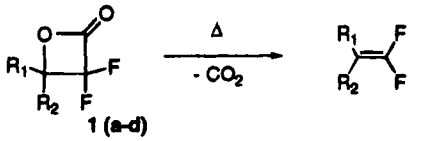
tially useful alternative to the ylide and other methodologies currently available for the synthesis of 1,1-difluoroalkenes.[8]



1 (a-d)

As would be expected for the assumed polar transition state for decarboxylation,[9] the fluorinated lactones had somewhat slower rates of decarboxylation than their hydrocarbon counterparts.[2,10] For example, **1a** was converted to 1,1-difluoro-2-methylpropene with a rate constant of 4.58×10^{-5} s^{-1} at 170 °C, which is a factor of 12.3 slower than the rate of the analogous decarboxylation of 4,4-dimethyl-2-oxetanone as determined by Frey and Pidgeon (5.62×10^{-4} s^{-1} at 170 °C).[11]

Work continues in order to find an equally good synthetic procedure for the use of aldehydes in this synthetic scheme, as well as to fully define the reactivity of such lactones, including obtaining kinetic parameters for their decarboxylative processes.

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Supporting Information Available: Characterization data for all β-lactones and a kinetic plot for decarboxylation of **1a** (10 pages).

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