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# SYNTHESIS OF α,α-DIFLUOROKETONES: NOVEL SYNTHESIS OF α,α-DIFLUOROKETONES FROM α,α-DIFLUOROACYLSILANES

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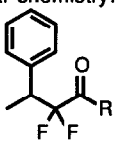
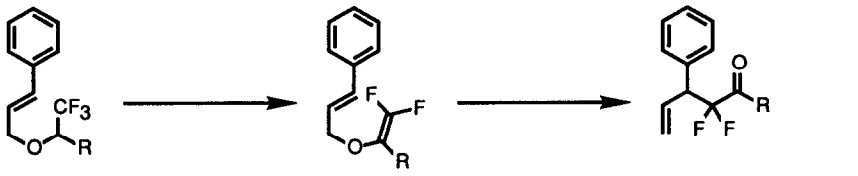
Abstract: α,α-Difluoroketones, targets of interest as potential transition state mimics and enzyme inhibitors, have been synthesized from the corresponding α,α-difluoroacylsilanes by treatment with diazoalkanes.

The specific introduction of fluorine into organic molecules can result in unusual physical and chemical properties, some of which impart interesting biological activity.[1] For instance, ketones with fluorine atoms attached to the α-carbon are unusually susceptible to the formation of hydrates and hemiketals. It is believed that this property allows some fluorinated ketones to mimic the transition states involved in enzymatic acyl hydrolase and transferase reactions.[2] Such a rationale is invoked to explain the remarkable enzyme inhibitory potency such compounds demonstrate.[3] For this reason, fluorinated ketones and their syntheses are of continuing interest in medicinal chemistry.[4]



**1**

Our interest in inhibitors of acyl coenzyme A:cholesterol acyl transferase (ACAT, EC 2.3.1.26)[5] led us to pursue α,α-difluoroketones of the general formula **1** where R is a straight chain alkyl group.[6] When considering synthetic approaches to general formula **1**, we were attracted to a method reported by Jarvi and co-workers[7] which described a synthesis of α,α-difluoroketone **4a**. The synthesis involved a Claisen rearrangement of **3a**, itself prepared by dehydrofluorination of **2a**. By changing the R group of **2a** to an alkyl group, this procedure would provide a direct route to our target compounds. Thus, we sought to make **2b** and carry it through the Claisen rearrangement procedure.

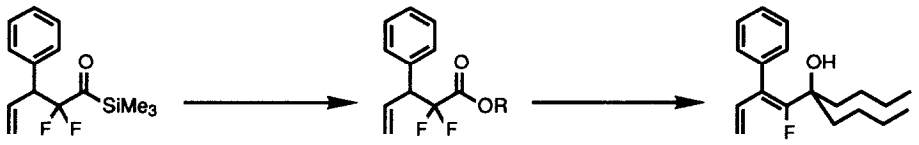


**2a**
**2b**

**3a**
**3b**

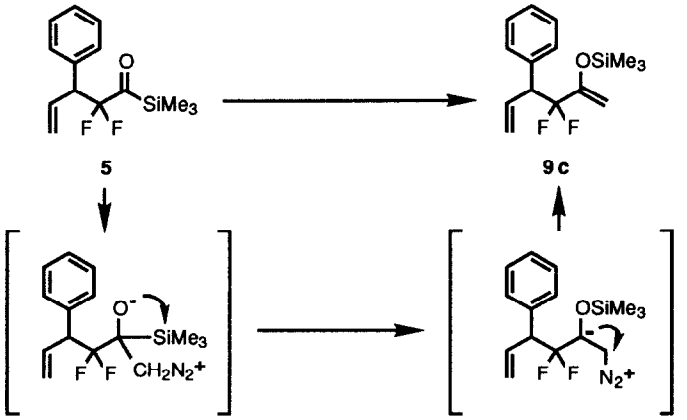
**4a** R = Ph
**4b** R = $(CH_2)_7CH_3$

To synthesize **2b**, we began with the synthesis of 1,1,1-trifluorodecan-2-one from ethyl trifluoroacetate and octylmagnesium bromide.[8] Reduction of this ketone with sodium borohydride gave 1,1,1-trifluorodecan-2-ol. This alcohol was then converted to its sodium salt and coupled with cinnamyl bromide in THF at -78°C to give the desired product. With **2b** in hand, we subjected it to the conditions that were used to convert **2a** to **3a**. To our disappointment, only unchanged starting material was recovered. Longer reaction times, higher temperatures and different bases all failed to convert **2b** to **3b**. This result may be explained by the decreased acidity of the methine proton of **2b** relative to that of **2a**.

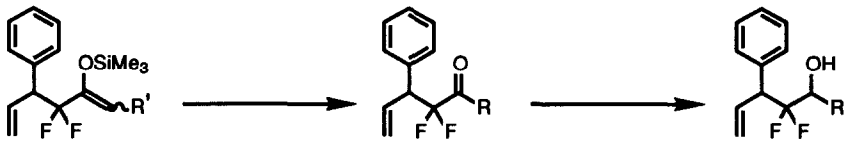



**5** **6** R = H
**7** R = $CH_3$ **8**

This result led us to consider another approach based on the Jarvi precedent. In the same publication, the synthesis of α,α-difluoroacylsilane **5** was reported. Treatment of **5** with hydrogen peroxide[9] and methanol gave **6** which could be converted to **7** by treatment with diazomethane in ether. With **7** in hand, we were poised to repeat the procedure which we had successfully used earlier to synthesize 1,1,1-trifluorodecan-2-one. However, treatment of **7** with n-butyllithium in THF at -78°C produced only diene **8**. Typically, α-fluorinated esters only suffer single additions of nucleophiles because the fluorine atoms stabilize the tetrahedral intermediate.[8,3b] In this case, however, dehydrofluorination removed the stabilizing group, allowing the tetrahedral intermediate to collapse to the ketone and suffer a second addition of n-butyllithium.



As an alternative to this route, we decided to explore additions to **5** as a route to general formula **1**. Addition of naked anions to **4** appeared unattractive, not only because of possible dehydrofluorination, but also because of potential Brook rearrangement[10] of the tetrahedral intermediate followed by fluoride elimination. Upon further consideration, it appeared that advantage might be made of such a Brook rearrangement by using an anion stabilized by a moiety which was a better leaving group than fluoride. A search of the literature provided support for this rationale,[11] thus we explored the reaction of diazoalkanes with **5**. Treatment of **5** with diazomethane in ether resulted in rapid reaction producing fluorinated silyl enol ether **9c** in 95% yield. Although we have not pursued any studies, the mechanistic rationale illustrated above does explain the results.




**9c** R = H **4c** R = $CH_3$ **10c** R = $CH_3$
**9d** R = $(CH_2)_3CH_3$ **4d** R = $(CH_2)_4CH_3$ **10d** R = $(CH_2)_4CH_3$

Brief treatment of **9c** with HF in acetonitrile provides the desired α,α-difluoroketone **4c** in 60% yield. Treatment of this ketone with sodium borohydride provides an 83% yield of the corresponding fluorinated alcohol **10c**[12] which is also of potential medicinal interest. In terms of the scope of the reaction, treatment of **5** with 1-diazopentane[13a] followed by workup produces **4d**, but we have been unable to detect any reaction with 2-diazopropane.[13b] Attempts to extend this procedure to other anions stabilized by leaving groups (i.e. sulfones and nitriles[14]) have been unsuccessful, in some case because of dehydrofluorination. Thus, in this system, this procedure appears to be limited to the addition of primary diazoalkanes.

In summary, we have investigated methods to synthesize compounds of general formula **1**. Only a novel method involving the reaction of α,α-difluoroacylsilane **5** with primary diazoalkanes provided the desired products. Together with existing Claisen rearrangement methodology for making α,α-difluoroacylsilanes, this work provides a novel pathway to α,α-difluoroketones. Ketones **4c** and **4d** and alcohols **10c** and **10d** have demonstrated modest ACAT inhibitory activity ($IC_{50}$'s ≥ 50 μM). Further refinement may lead to compounds of greater potency, and studies along these lines will be reported in due course.

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12. Spectral data: **9c**: $^1$H NMR ($CDCl_3$) δ (ppm): 7.32 (m, 5H); 6.24 (ddd, 10, 12, 20 Hz, 1H); 5.28 (d, 12 Hz, 1H); 5.17 (d, 20 Hz, 1H); 4.66 (d, 2 Hz, 1H); 4.29 (d, 2 Hz, 1H); 4.05 (dt, 10, 16 Hz, 1H); 0.22 (s, 9H). **4c**: $^1$H NMR ($CDCl_3$) δ (ppm): 7.32 (m, 5H); 6.18 (ddd, 10, 12, 20 Hz, 1H); 5.34 (d, 12 Hz, 1H); 5.26 (d, 20 Hz, 1H); 4.08 (dt, 1, 16 Hz, 1H); 2.13 ( t, 2 Hz, 3H). $^{19}$F NMR ($CDCl_3$) Φ* (ppm, $CFCl_3$ = 0 ppm): 68.28 (dd, 15, 261 Hz), 65.24 (dd, 16, 261 Hz). **10c**: (mixture of diastereomers) $^1$H NMR ($CDCl_3$) δ (ppm): 7.38 (m, 10H); 6.30 (ddd, 10, 12, 20 Hz, 1H); 6.24 (ddd, 10, 12, 20 Hz, 1H); 5.35 (d, 12 Hz, 1H); 5.32 (d, 20 Hz, 1H); 1.80 (br s, 2 H); 1.33 (s, 3H). $^{19}$F NMR ($CDCl_3$) Φ* (ppm, $CFCl_3$ = 0 ppm): 60.52 (ddd, 11, 22, 250 Hz); 59.48 (dd, 25, 248 Hz), 57.26 (ddd, 111, 16, 249 Hz); 56.59 (ddd, 9, 18, 249 Hz).

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