Active Heteromethylene Compounds. 3.[1a,b] Synthesis of 4,4-Difluoro-2-azetidinones from α-Haloacetamides and Freon 22

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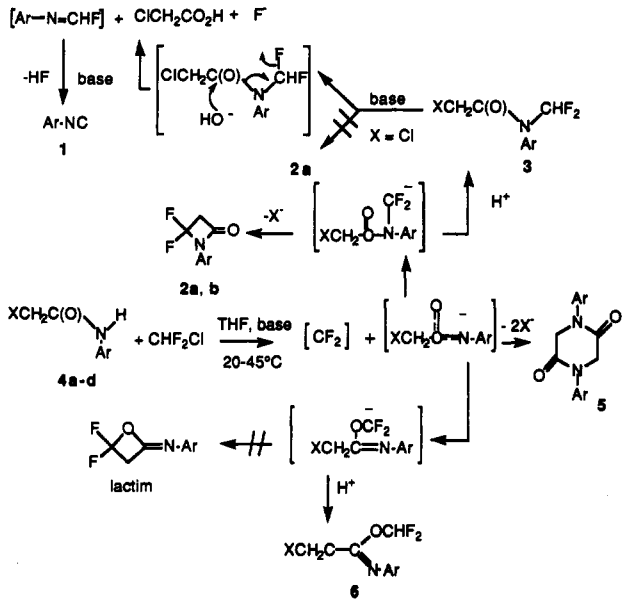
A variety of 4-monofluoro-2-azetidinones have been reported in the literature, many as potential antibiotics, with their preparation generally through sulfur moiety replacement of penicillin-like intermediates by both positive[3] and negative[4,5] fluoride sources. 4,4-Difluoro-2-azetidinones on the other hand are rare, the only examples arising from [2 + 2] cycloaddition from perfluoromethacroyl fluoride[6] or certain perfluoroketenes[7] with isocyanates.

Among the numerous methods for preparing 2-azetidinones (β-lactams)[8] is generation of a carbanion species at the N-substituent of an α-haloacetamide and consequent displacement of halogen. The first example was base treatment of 2-chloroacetanilide, substituted on nitrogen by methylenedicarboxylate (i.e., malonate), to yield 1-phenyl-4,4-bis(ethoxycarbonyl)-2-azetidinone.[9] A number of other similar syntheses have been reported,[10] but as above, with the carbanion generated from a fairly strong carbon acid.

In our continuing studies of N-heteromethylene acetamides, we allowed α-haloacetanilides to react with chlorodifluoromethane (Freon 22) under base conditions (Scheme I). The only previous studies of this reagent reported with amides had not included the α-halo variety.[11] Material **4a**, 2-chloro-*N*-[2-(1,1-dimethylethyl)-6-methylphenyl]acetamide,[12] appeared to completely react, but gave multiple products (**1**, **2a**, **3**, and **6**). GLC/MS revealed a parent molecular ion common to both **3** and **6**. Unfortunately, this isomeric imidate **6** was not purified sufficiently for confirming microanalyses, but NMR and MS make it difficult to assign other than this structure to the material.

Initially, **2a** was isolated only in small amounts and it was unclear whether the material was lactam as shown, or the lactim. A single-crystal X-ray revealed the correct structure. It appears that **3** is not the source of **2a**.

Scheme I[a]



[a] For complete definition of Ar, X, and reagents see Discussion and Experimental Section.

Treatment of the former with strong caustic gave no trace of the lactam; rather the isocyanide **1**[13] was the product isolated. This probably arises from base-promoted deacetylation of **3**, followed by conversion of the remaining "carbyl amine" to isocyanide. Nonnucleophilic strong bases (e.g., LDA) likewise did not effect lactam formation from **3**.

It seems reasonable to believe that both **2** and **3** originate from a common intermediate arising from difluorocarbene attack on the amide anion. The resulting *N*-(difluoromethyl)carbanion then has two options: protonation to form **3**, or cyclization to form **2**. Since this latter process should more effectively compete with protonation if the departing halogen is iodide rather than the less labile chloride,[14] 2-iodo-*N*-[2-(1,1-dimethylethyl)-6-methylphenyl]acetamide, **4b**, was substituted for **4a**. This indeed increased the yield of lactam and gave a cleaner reaction.

Next, the synthesis of less hindered, but more symmetrical **2b** was undertaken. Initially 2-iodo-*N*-(2,6-diethylphenyl)acetamide, **4c**, was used in attempts to duplicate the favorable results the iodo analog furnished in the synthesis of **2a**. However, very little lactam was obtained. Instead, a predominance of 2,5-piperazinedione **5** was produced. Apparently there is little hindrance to the latter's formation by interaction of the anilide nitrogen anion with the α-iodomethylene of a second molecule in contrast to the bulkier **4b**. After a number of trials it was found that **2b** was best prepared by reaction of large excesses of both Freon 22 and the base of choice, sodium hydride, with 2-chloro-*N*-(2,6-diethylphenyl)acetamide, **4d**.

Since lactams **2a,b** are first examples of 4,4-difluoro-2-azetidinones possessing protic ring substituents (i.e., 3-methylene), a brief examination of their chemical properties under both base and acid conditions was carried out as shown in a sequence of alkylation and dehydration reactions, Scheme II. Good yields were generally achieved,

(1) (a) Part 2: Chupp, J. P.; Leschinsky, K. L.; Mischke, D. A. *J. Org. Chem.* **1982**, *47*, 3169. (b) Presented at the 11th Winter Fluorine Conference, St. Petersburg, FL, Jan 25–30, 1993.

(2) Present Address: Great Lakes Chemical Co., Lafayette, IN.

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(9) Sheehan, J. C.; Bose, A. K. *J. Am. Chem. Soc.* **1950**, *72*, 5158.

(10) From ref 8; see refs 240–253 cited therein.

(11) (a) U.S. 3,221,007 to Merck. (b) Japanese patent application to Tokuyama Soda; *Chem. Abstr.* **1992**, *116*, 209745e.

(12) For preparation of hindered *sec*-haloacetanilides see ref 14 and U.S. 3,268,584, U.S. 3,404,976, U.S. 3,442,945, U.S. 3,475,156, U.S. 3,475,157, U.S. 3,547,620 to Monsanto.

(13) Chupp, J. P.; Leschinsky, K. L. *J. Org. Chem.* **1975**, *40*, 66.

(14) For a quantitative comparison of the increased iodo over chloro reactivity in certain hindered α-haloacetanilides, see: Chupp, J. P.; Olin, J. F. *J. Org. Chem.* **1967**, *32*, 2297.

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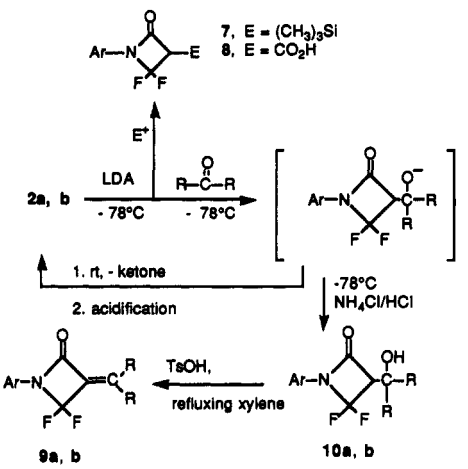
Scheme II[a]



[a] For complete definition of Ar, R, and reagents see Discussion and Experimental Section.

illustrating that in spite of nitrogen attachment to the same carbon bearing geminal fluorine 4,4-difluoro-2-azetidinones appear stable enough perhaps to be prepared and survive as new and unique fluoro analogs of penicillin- or bactam-like antibiotic candidates per their previously cited monofluoro analogs.

Spectral data were collected on these lactams to differentiate between lactam and lactim. The IR showed carbonyl absorption in the 4-membered lactam region at ca. 1800 cm^{-1}, but this was curiously split into two distinct absorption maxima. Further, it was observed that a corresponding strong band at half the frequency was observed (i.e., 900 cm^{-1}). The carbonyl splitting was found in both solid dispersions and solutions, where it was concentration independent. This phenomena is a variation of absorption harmonics called Fermi resonance,[15] not be be confused with simple overtone harmonics, which would be observed with much less intensity (at 1800 cm^{-1}); or two different absorptions arising from rotomeric isomers (but see note on X-ray data in Experimental Section). The hydrogen analogs of **2** did not show Fermi resonance. Neither did several derivatives of **2a,b**, such as **7**, **9**, and **10**, although still exhibiting high frequency absorption at ca. 1800 cm^{-1}.

The NMR spectra of the compounds were examined, and are given in detail with moiety identification in the Experimental Section under each respective compound. However, it may be instructive to note here certain rationales regarding the nuclear multiplicities observed. Rotomers arising from hindered rotation about the N-C(O) bond are shown in **3**, and indeed help serve as structure proof for this compound. The ratio of isomers deduced from the spectra are about the same as observed for comparable NCH_3 anilides.[14] Moreover, the CF_2- group fluorine atoms in either chloroacetanilides or lactams show diastereotopic properties (nonequivalence, with different chemical shifts, and coupling to each other), providing there is at least one asymmetric center in the molecule. The latter type center can arise in these molecules from the presence of an asymmetric carbon atom, or from hindered rotation about an *unsymmetrically* 2,6-substituted anilide or lactam phenyl-N bond. The combination of these phenomena with appreciable geminal ^1H coupling in **3** causes a total of 16 observed ^{19}F peaks. If the phenyl ring is symmetrically substituted, this center of asymmetry vanishes. This effect of structure on the lactam CF_2 NMR properties is thus manifested by the collapse of the paired doublets observed in chiral lactam **2a** to a singlet in symmetrical lactam **2b**.

As the lactams are substituted on the 3-carbon, another chiral center is introduced. From lactam **2a**, **8** and **10a** were prepared, for instance; this translates into two asymmetric centers in these materials, with unequal amounts of diastereomers. The latter, overlaid with diastereotopic CF_2, leads to two unequal sets of paired doublets (eight peaks in all) in the ^{19}F NMR spectra. In contrast, **7** and **10b** from achiral **2b** produce only one chiral center, inducing only two doublets (similar to an AB quartet) in their ^{19}F NMR spectra representing a typical diastereotopic CF_2 group. Removing chirality at the 3-carbon in **9a** and **9b** restores the CF_2 absorption to only one set of paired doublets and a singlet, respectively.

Experimental Section

Melting points were determined on a Haake Buchler apparatus and are uncorrected. ^{13}C, ^1H, and ^{19}F NMR spectra were recorded on an XL300 (300 MHz), XL360 (360 MHz), or XL400 (400 MHz) with instruments referenced internally. Mass spectra were measured by a direct probe EI or isobutane chemical ionization (CI) and GC MS. Parent molecular ion (*m/e*) is expressed in all cases as molecular weight. Liquid chromatography purification was achieved on a Rainin reversed-phase, C-18 Prep LC with variable UV detector, or by Chromatotron (rotary TLC) on silica plates. Unless otherwise noted, boiling and sublimation points are recorded as oven temperatures during bulb-to-bulb (Kugelrohr) distillations. All microanalyses were performed by Atlantic Microlab Inc., P.O. Box 2288, Norcross, GA 30091.

1-[2-(1,1-Dimethylethyl)-6-methylphenyl]-4,4-difluoro-2-azetidinone (2a). The title compound was first seen in the GC MS and isolated in fraction 8 from the chromatography described below for the preparation of **3** from **4a**.

An improved procedure, producing a higher yield of **2a** and lesser amounts of side products utilized 2-iodo-*N*-[2-(1,1-dimethylethyl)-6-methylphenyl]acetamide, **4b**.[12] Material **4b** (1.1 g, 3.3 mmol) was dissolved in 15 mL of THF followed by ca. 5 g of Freon 22. Then 1.5 g of 50% NaOH was added and the mixture stirred while feeding in Freon 22 at 0.5–1 g per min. The temperature increased to 30 °C. The dark solution (containing ca. 60% of **2a** as observed in the GC) was treated with water and methylene chloride, the latter phase was separated and evaporated, and the residue was bulb-to-bulb distilled to 120 °C (1 mmHg). The distillate was recrystallized from heptane in dry ice to give 100 mg (12% yield) of 98% assay **2a**, mp 67.5–69 °C. ^1H NMR ($CDCl_3$) δ (exclusive of fine structure due to remote coupling with ^{19}F) 1.43 (s, 9 H, $C(CH_3)_3$), 2.29 (s, 3 H, $ArCH_3$), 3.51 (AB multiplet, 2 H, diastereotopic CH_2), 7.13 and 7.35 (2d, 2 H, 3- and 5-ArH), 7.23 (t, 1 H, 4-ArH); ^{19}F δ -92.6 (d, J = 149 Hz, 1 F, diastereotopic CF), -88.35 (d, J = 149 Hz, 1 F, diastereotopic CF); GC MS *m/e* = 253; IR (CCl_4) $\nu_{C=O}$ 1815 and 1795, 900 cm^{-1}. Fermi resonance at this last absorption frequency causes splitting of the carbonyl absorption at double this frequency (see Discussion with references). Single-crystal X-ray analysis is as follows: single crystals of $C_{14}H_{17}F_2NO$ are, at 20 ± 1°, monoclinic, space group $P2_1/c$-C^5_{2h} (no. 14) with a = 12.875 (2) Å, b = 11.694 (3) Å, c = 9.128 (2) Å, β = 101.97 (1)°, V = 1344.4 (4) Å^3, and Z = 4 [d_{calcd} = 1.251 g cm^{-3}; μ_a(Mo K$\bar{\alpha}$) = 0.09 mm^{-1}]. A total of 2445 independent reflections having 2θ(Mo K$\bar{\alpha}$) < 50.7° (the equivalent of 0.8 limiting Cu K$\bar{\alpha}$ spheres) were collected on a computer-controlled Nicolet autodiffractometer using full (0.90 ° wide) ω scans and graphite-monochromated Mo K$\bar{\alpha}$ radiation. The structure was solved using "direct methods" techniques with the Siemens SHELXTL-PLUS software package

(15) (a) Colthup, N. B.; Daly, C. H.; Wiberly, S. E. *Introduction to Infrared and Raman Spectroscopy*, 3rd ed.; Academic Press: New York, 1990; p 31. (b) Jones, R. N.; Angell, C. L.; Ito, T.; Smith, R. J. D. *Can. J. Chem.* **1959**, *37*, 2007. (c) Nyquist, R. A.; Settineri, S. E. *Appl. Spectrosc.* **1990**, *44*, 791.

as modified at Crystalytics Company. The resulting structural parameters have been refined to convergence [R_1 (unweighted, based on F) = 0.048 for 1290 independent reflections having 2θ(Mo K$\bar{\alpha}$ < 50.7° and $I > 3\sigma(I)$] using counter-weighted full-matrix least-squares techniques and a structural model which incorporated anisotropic thermal parameters for all non-hydrogen atoms and isotropic thermal parameters for all hydrogen atoms. The four methyl groups were refined as rigid rotors with sp^3-hybridized geometry and a C–H bond length of 0.96 Å. The refined positions for the rigid rotor methyl groups gave C–C–H angles which ranged from 104° to 114°. The lactam ring appears to be nonstatistically disordered in the lattice with two preferred orientations about the C_{1a}–N bond. The major (84%) conformation is specified by (only) nonprimed atoms and the minor (16%) by both primed and nonprimed atoms (see supplementary material). The sites occupied by C_1, C_2, or C_3 will therefore always be occupied by a carbon atom. Anal. Calcd for $C_{14}H_{17}F_2NO$: C, 66.39; H, 6.77, N, 5.53. Found: C, 66.46; H, 6.79; N, 5.58.

1-(2,6-Diethylphenyl)-4,4-difluoro-2-azetidinone (2b). Sodium hydride (60% dispersion in mineral oil, 6.4 g active 0.27 mol) (3× washed with hexanes) in 100 mL of THF was treated dropwise with 15 g (66.5 mmol) of 2-chloro-*N*-(2,6-diethylphenyl)acetamide,[12] **4d**, in 95 mL of THF over 1 h. After the initial neutralization reaction, Freon 22 was sparged in with the temperature permitted to reach 50 °C. After 17 g of Freon 22 was added, GC showed 28% **4d**, 38% **2b**, and 12% **5**. After a total of 27 g of Freon was added GC showed 49% **2b** with no starting material and 19% **5**. The reaction mixture was cooled, *n*-butanol added to quench the remaining sodium hydride, then 30 mL water very cautiously added (dropwise at first) to further quench the reaction. The mixture was extracted with 200 mL of CH_2Cl_2, washed with water, and dried over $MgSO_4$. After filtering and solvent removal the residue was bulb-to-bulb distilled to 160 °C (1.5 mmHg) to give 12 g of distillate and 5.5 g of residue. This material was then distilled again through a short-path Vigreux column, followed by final purification with C-18 LC (water/acetonitrile) and bulb-to-bulb distillation at 125–135 °C (1 mmHg) to give 3.0 g (19% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (t, 6 H, CH_2CH_3), 2.63 (sym m [including coupling with F_2], 4 H, CH_2CH_3), 3.58 (t, J = 2.46 Hz [coupling to F_2], 2 H, CH_2CF_2), 7.10 (d, 2 H, 3, 5-ArH), 7.33 (t, 1 H, 4-ArH); ^{19}F δ −92.31 (s [excluding coupling to CH_2], CF_2); GC MS m/e = 239. Anal. Calcd for $C_{13}H_{15}F_2NO$: C, 65.26; H, 6.32; N, 5.85. Found: C, 64.84; H, 6.3; N, 5.67.

2-Chloro-*N*-(difluoromethyl)-*N*-[2-(1,1-dimethylethyl)-6-methylphenyl]acetamide (3). 2-Chloro-*N*-[2-(1,1-dimethylethyl)-6-methylphenyl]acetamide, **4a**[12] (2.4 g, 0.01 mol), was placed in 30 mL of THF containing 2.5 mL of 50% caustic and then Freon 22 sparged in. Approximately 18 g of the gas was introduced over 1–2 h, with initial exotherm to 45 °C. The reaction mixture was permitted to stand over the weekend, with no change in the GC and GC MS. The mixture was made up of several components, including the following [GC t_R, parent m/e (material), relative peak area]: 2.4, 173 (**1**), 19%; 3.46, 289 (1 Cl) (**6**), 15%; 3.57, 253 (**2a**), 8%; 4.36, 289 (1 Cl) (**3**), 51%. Workup consisted of decanting the THF phase and washing the remaining tarry solid and water phase 2× with fresh THF. Evaporation of the combined organic solvents gave 2.9 g dark oil, with odor characteristic of isocyanide (the latter compound, 2-(1,1-dimethylethyl)-6-methylphenyl isocyanide, **1**, was isolated from one of the chromatographic fractions and identified by comparison to an authentic sample[13]). The oil was dissolved in 2% ethyl acetate contained in cyclohexane, filtered, and then chromatographed by the Chromatotron with 2% ethyl acetate in cyclohexane. Fractions 4–6 contained **3**, which was recrystallized from heptane to give 0.8 g (28% yield) white solid, mp 84–85 °C: ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9 H, $C(CH_3)_3$), 2.27 (s, 3 H, $ArCH_3$), 3.78 (AB q, 2 H, diastereotopic $ClCH_2$), 7.30 (t, J_{H-F} = 62.8 Hz, 1 H, CHF_2), 7.23 and 7.49 (2d, 2 H, 3- and 5-ArH), 7.30 (t, 1 H, 4-ArH); ^{19}F δ −108.46 (d of d, J_{F-F} = 228 Hz, and J_{F-H} = 60.3 Hz, diastereotopic CF), −98.55 (d of d, J_{F-F} = 228 Hz, and J_{F-H} = 65.4 Hz, diastereotopic CF); characteristic of this type of *tertiary* anilide, evidence for ca. 10% rotomer was the presence also of an $ArCH_3$ singlet at δ 2.16 and a $ClCH_2$ AB q at δ 4.48 constituting ca. 10% of the total peak area for each function; this observation was repeated in the ^{19}F NMR where ca. 10% of the absorption was noted for CF_2 in two sets of d (i.e., eight peaks), centered at δ −86.5 and −89.4; GC MS m/e 289 (1 Cl). Anal. Calcd for $C_{14}H_{18}ClF_2NO$: C, 58.03; H, 6.26; N, 4.83. Found: C, 58.25; H, 6.33, N, 5.02.

1,4-Bis(diethylphenyl)-2,5-piperazinedione (5). Initial attempts at synthesis of **2b** from 2-iodo-*N*-(2,6-diethylphenyl)-acetamide, **4c**, per the procedure described for **2a** gave mainly (53.4%) **5** in the GC MS, isolated after vacuum removal of THF, followed by water washing and trituration with ether. Upon filtering the ether slurry a white solid was obtained, mp 150–152 °C: ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 12 H, CH_2CH_3), 2.56 (m, 8 H, CH_2CH_3), 4.25 (s, 4 H, CH_2N), 7.14–7.29 (m's, 6 H, ArH); GC MS m/e 378. Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99, N, 7.40. Found: C, 76.03; H, 7.99, N, 7.37.

***N*-[2-Chloro-1-(difluoromethoxy)ethylidene]-2-(1,1-dimethylethyl)-6-methylbenzeneamine (6).** Fraction 2 from the chromatography described in **3** contained isocyanide **1** admixed with a material assigned structure **6** based on spectra as follows: ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H, $C(CH_3)_3$), 2.35 (s, 2 H, $ClCH_2$), 7.09 (t, 1 H, CHF_2O), 6.9–7.6 (m's, 3 H, ArH); GC MS m/e = 289 (1 Cl).

1-(2,6-Diethylphenyl)-4,4-difluoro-3-(trimethylsilyl)-2-azetidinone (7). In a suitable multineck flask, containing 11.5 mmol (10% excess) of LDA in 50 mL of THF, was added dropwise over 5 min 2.5 g of **2b** (10.5 mmol) in 20 mL of THF at −78 °C, with stirring continued for 10 min. A 5% molar excess of trimethylsilyl chloride was added all at once, the dry ice bath removed, and the reaction mixture allowed to warm to room temperature over 1 h. The mixture was quenched with water and extracted with ethyl acetate, dried over $MgSO_4$, and then heated with warm water on the vacuum rotovap to give 2.98 g as residue. Bulb-to-bulb distillation at 110–120 °C (0.7 mmHg) gave 2.62 g, with GC showing 90% product and 8.3% starting material. This material was subjected to LC C-18 preparative chromatography with 80% acetonitrile in water at 20 mL per min. The second component was product. This was bulb-to-bulb distilled at 115–130 °C (0.7 mmHg) to give 1.6 g (49% yield) of colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 9 H, $(CH_3)_3Si$), 1.11 (2 t, 6 H, CH_2CH_3), 2.55 (m's, 4 H, CH_2CH_3), 3.24 (2 d, J = ca. 3.65 Hz [coupling to 2 different ^{19}F], 1 H, CHSi), 7.049 and 7.20 (several m's, 3 H, ArH); ^{19}F δ −91.9 (d, J = 149 Hz, 1 F, diastereotopic CF), −88.2 (d, J = 149 Hz, 1 F, diastereotopic CF); GC MS m/e = 311. Anal. Calcd for $C_{16}H_{23}F_2NOSi$: C, 61.7; H, 7.44; N, 4.50. Found: C, 62.1; H, 7.47; N, 4.59.

Sodium 1-[2-(1,1-Dimethylethyl)-6-methylphenyl]-2,2-difluoro-4-oxo-3-azetidinecarboxylate (8). Material **2a** (1.25g, 0.005 mmol) was added to LDA, made from 2.3 mL of 2.5 M *n*-butyllithium and 0.63 mL of diisopropylamine in 35 mL of THF, over 5 min. The mixture was allowed to stir for 10 additional min, and then several grams of dry ice was added at −78 °C. While still cold the mixture was added to a mixture of ice, hydrochloric acid, and ether. The ether layer after 2× washes with aqueous acid was dried over $MgSO_4$, filtered, and treated under vacuum to remove solvent. The gummy residue was taken up in concentrated sodium bicarbonate, whereby lustrous white plates crystallized from the aqueous solution. This material was washed with ether and air dried. A total of 0.6 g (38% yield) was thus obtained, mp 170–173 °C. It was found expedient to record a definitive NMR spectra of this material by its conversion to the free acid. The material then proved to be a 80/20 diastereomeric mixture as follows: ^{1}H NMR ($CDCl_3$) δ 1.35 and 1.38 (2s, 0.8 and 0.2 × 9 H respectively, $C(CH_3)_3$), 2.21 and 2.31 (2s, 0.2 and 0.8 × 3 H respectively, $ArCH_3$), 4.46 and 4.55 (2 d of d, 0.8 and 0.2 × 1 H respectively, $CHCF_2$), 7.08, 7.22, and 7.35 (d, t, d respectively, 1 H each, ArH); ^{19}F δ −96.5 and −84.8 (2 d [J = 146 Hz each], 0.8 × 2 F, diastereotopic and diastereomeric CF_2), −89 and −91 (2 d [J = 146 Hz each], 0.2 × 2 F, diastereotopic and diastereomeric CF_2); direct probe MS (as acid) m/e = 297. Anal. Calcd for $C_{15}H_{16}F_2NO_3Na \cdot 0.1H_2O$: C, 56.11; H, 5.09; N, 4.36. Found: C, 55.94; H, 5.32; N, 4.48.

3-(Dicyclopropylmethylene)-1-[2-(1,1-dimethylethyl)-6-methylphenyl]-4,4-difluoro-2-azetidinone (9a). Material **10a** (0.49 g, 1.35 mmol) was dissolved in 20 mL of mixed xylenes and 0.1 g of *p*-toluenesulfonic acid added, and then the mixture was refluxed under a Dean Stark trap. The reaction appeared to go to completion with this amount of acid (lesser amounts did not

effect complete dehydration). The cooled organic solution was washed with saturated $NaHCO_3$ solution and then water. The organic phase was dried over $MgSO_4$. After vacuum rotovap treatment, the residue was bulb-to-bulb distilled to 200 °C (0.7 mmHg). The distillate was recrystallized from cold hexane to give 150 mg (32% yield), mp 107–110 °C: ^1H NMR ($CDCl_3$) δ 0.94, 1.01, and 1.14 (3 m's, 8 H, cyclopropylCH_2), 1.38 and 2.01 (2 m's, 1 H each, cyclopropyl CH), 1.41 (s, 9 H, $C(CH_3)_3$), 7.13, 7.22, and 7.39 (3 m's, 1 H each, ArH); ^{19}F δ −94.0 (d, J = ca. 149 Hz, 1 F, diastereotopic CF), −87.0 (d, J = ca. 149 Hz, 1 F, diastereotopic CF); GC MS m/e = 345; IR (CCl_4) $\nu_{C=O}$ 1819 cm^{-1}. Anal. Calcd for $C_{21}H_{25}F_2NO$: C, 73.02; H, 7.30; N, 4.05. Found: C, 72.66; H, 7.30; N, 4.19.

3-(Dicyclopropylmethylene)-1-(2,6-diethylphenyl)-4,4-difluoro-2-azetidinone (9b). Material **10b** (1.44 g, 4.13 mmol) was placed in 50 mL of xylene with 0.2 g of *p*-toluenesulfonic acid. The material was heated at reflux for 10 min. The GC was deceptive in that the same t_R was evident for **9b** as well as **10b**. TLC, however, showed no starting material remaining. The xylene solution (with ethyl acetate added) was washed with aqueous $NaHCO_3$ solution and then vacuum treated to remove solvent to give 1.3 g of oil, which by GC proved to be ca. 80% assay. Bulb-to-bulb distillation at 100–150 °C (0.7 mmHg) gave 0.7 g (90% assay) and 0.4 g of residue. The distillate was recrystallized from cold hexanes to give 0.47 g (34% yield) of white solid, 96% GC assay, mp 78–82 °C: ^1H NMR ($CDCl_3$) δ 0.95, 99, 1.13 (3 m's, 8 H, cyclopropyl CH_2), 1.23, and 2.05 (2 m's, 2 H, cyclopropyl CH), 1.21 (t, 6 H, CH_2CH_3), 2.59, and 2.67 (2 m's [coupling to CH_3 and F], 4 H, CH_2CH_3), 7.16 (d, 2 H, ArH), 7.31 (d of d, 1 H, *p*-ArH); ^{19}F δ −92.06 (s, 2 F, CF_2). Anal. Calcd for $C_{20}H_{23}F_2NO$: C, 72.49; H, 7.00; N, 4.23. Found: C, 72.48; H, 7.05; N, 4.28.

3-(Dicyclopropylhydroxymethyl)-1-[2-(1,1-dimethylethyl)-6-methylphenyl]-4,4-difluoro-2-azetidinone (10a). In a suitable multineck flask, containing 6.5 mmol of LDA in 30 mL THF, was added dropwise over 5 min 1.6 g (6.3 mmol) of **2a** in 10 mL THF. After the mixture was stirred for an additional 10 min, 0.74 mL of dicyclopropyl ketone (6.6 mmol) was added, keeping the temperature below −72 °C. It was found at this time that if an aliquot was allowed to warm to room temperature before acidification, the reaction was reversible, and mostly starting material was recovered. However, if the reaction mixture was treated with 4 mL of saturated NH_4Cl and/or hydrochloric acid solution at −78 °C, then on warming to room temperature **10a** was largely recovered. The mixture after acidification and warming to room temperature was treated with water and extracted with CH_2Cl_2, followed by a second water wash. The organic phase was dried over $MgSO_4$, treated on the rotovap, with the residue bulb-to-bulb vacuum distilled to give 1.25 g of crude. This material was then treated on the Chromatotron with 3% ethyl acetate in cyclohexane to give material having 92.1% GC assay with 2.7% starting lactam. A second preparation using the same proportions was carried out to give a combined weight of purified material of 1.6 g (35% yield) as a mixture of two diastereomers, mp 109–111 °C: ^1H NMR ($CDCl_3$) δ 0.48 (m's, 8 H, cyclopropyl CH_2), 1.1 and 1.2 (2m's, 2 H, cyclopropyl CH), 1.35 and 1.38 (2 s, 9 H, diastereomeric $C(CH_3)_3$), 2.21 and 2.30 (2 s, 3 H, diastereomeric $ArCH_3$), 3.71 and 3.84 (2d of d [coupled to ^{19}F], 1 H, diastereomeric C*H*COH), 7.07, 7.18, and 7.35 (3 m's, 1 H each, ArH); ^{19}F δ −86 and −91 (2 d [J = ca. 150 Hz each], ca. 0.6 and 0.4 F respectively, diastereomeric and diastereotopic CF), −92.8 and −99.2 (2 d, [J = ca. 150 Hz each], ca. 0.4 and 0.6 F respectively, diastereomeric and diastereotopic CF); GC MS m/e = 363; IR (CCl_4) ν_{OH} 3600 cm^{-1}, $\nu_{C=O}$ 1809 cm^{-1}. Anal. Calcd for $C_{21}H_{27}F_2NO_2$: C, 69.40; H. 7.49; N, 3.85. Found: C, 69.42; H, 7.52; N, 3.84.

3-(Dicyclopropylhydroxymethyl)-1-(2,6-diethylphenyl)-4,4-difluoro-2-azetidinone (10b). In substantially the same manner as given above for **10a**, material **2b** (2.1 g, 8.8 mmol) was converted to crude product that was subjected to the Chromatotron with elution by 3% ethyl acetate in cyclohexane, fractions 7–9 containing 1.74 g (57% yield) of **10b**. Final purification of a portion was by recrystallization from cold hexanes, mp 74–75 °C: ^1H NMR ($CDCl_3$) δ 0.39 and 0.56 (2 m's, 8 H, cyclopropyl CH_2), 1.13 and 1.16 (2t, 6 H, CH_3CH_2), 1.12 and 1.17 (d of d or q, 2 H, cyclopropyl CH), 2.6 and 2.77 (2 uneven m's, 4 H, CH_3CH_2), 3.84 (d of d, 1 H, C*H*CF_2), 7.10 (d, 2 H, ArH), 7.26 (d of d, 1 H, *p*-ArH); ^{19}F δ −88.80 (d, J = 158 Hz, 1 F, diastereotopic CF), −99.0 (d, J = 158 Hz, 1 F, diastereotopic CF); GC MS m/e = 349. Anal. Calcd for $C_{20}H_{25}F_2NO_2$: C, 68.75; H, 7.21; N, 4.01. Found: C, 68.69; H, 7.24; N, 4.03.

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Supplementary Material Available: Complete X-ray crystallographic data for material **2a** (26 pages). This material is contained in libraries on microfiche, immediately follows this paper in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.