Difluorocyclopentenone Synthesis

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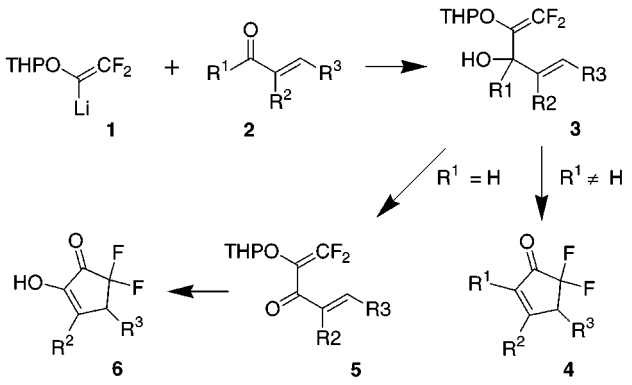
A cyclization for the rapid assembly of *gem*-difluorinated cyclopentenones is described. 2,2,2-Trifluoroethanol is the cheap and convenient source of both fluorine atoms.

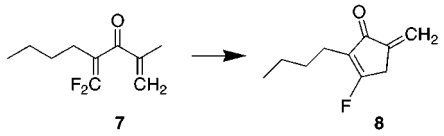
The substitution of hydrogen by fluorine into pharmacologically active organic molecules can often have profound effects on the activity. The *gem*-difluoromethylene group is of particular importance in this regard, as it serves to isosterically replace oxygen in phosphate analogues and to block the metabolic oxidation of methylene groups.[1] There is no direct or convenient synthetic method for cyclization of a linear precursor to a 5,5-difluorocyclopentenone,[2] and there are few methods for simultaneous replacement of the enolizable hydrogens of a ketone by multiple fluorines. Typically, fluorines adjacent to a ketone carbonyl group are introduced stepwise, using one of the reagents for the introduction of electrophilic fluorine.[3] The convergence of our interests in fluorine chemistry[4] and in the synthesis of five-membered rings[5] led us to consider an alternative approach to the problem. The long-term goal of this research is to develop convenient means for the synthesis of fluorinated carbanucleosides.[6]

The general approach is summarized in Scheme 1 (THP = 2-tetrahydropyranyl). Precedent[7] suggested that difluorovinyllithium species **1** would be accessible from cheap 2,2,2-trifluoroethanol. Nucleophilic addition to the carbonyl carbon of **2** ($R_1 \neq H$) would lead to tertiary alcohol **3**, which upon ionization leads to a pentadienyl carbocation that can undergo cyclization to **4** by means

Scheme 1



of a variant of the classical Nazarov cyclization.[8] Loss of the THP group as a stable oxo-cation takes place after the ring-forming step. Several potential obstacles can be recognized in this straightforward approach. In particular, the nucleophilicity of **1** is attenuated by the two fluorine atoms. Consequently, substituents that diminish the electrophilicity of the carbonyl carbon of **2** will interfere with the first step. The effect of the two fluorine atoms on the cationic intermediate and the rate of cyclization were not anticipated to be a problem for the following reasons. 1,1-Difluoroallyl carbocations have been inferred as reactive intermediates.[9] Also, Johnson has demonstrated the beneficial effect of a strategically placed fluorine atom on cation−olefin cyclizations.[10] Furthermore, Ichikawa's results[11] (eq 1) suggest that the



[1]

(1) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619−8683.
(2) However, see: Snegirev, V. F.; Makarov, K. N. *Izv. Akad. Nauk SSR, Ser. Khim.* **1986**, 1331−1340.
(3) (a) Stavber, S.; Zupan, M. *Tetrahedron Lett.* **1996**, *37*, 3591−3594. (b) Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60*, 4730−4737. (c) Xu, Z.-Q.; DesMarteau, D. D.; Gotoh, Y. *J. Fluorine Chem.* **1992**, *58*, 71−79. (d) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595−596. (e) Differding, E.; Ofner, H. *Synlett* **1991**, 187−189.
(4) (a) Tius, M. A.; Kawakami, J. K. *Synth. Commun.* **1992**, *22*, 1461−1471. (b) Tius, M. A.; Kawakami, J. K. *Synlett* **1993**, 207−208. (c) Tius, M. A.; Kawakami, J. K. *Tetrahedron* **1995**, *51*, 3997−4010.
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(6) For example, see: Biggadike, K.; Borthwick, A. D. *J. Chem. Soc., Chem. Commun.* **1990**, 1380−1382.
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(8) Excellent discussions of the Nazarov reaction can be found in the following articles: (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1994; Vol. 45, pp 1−158. (b) Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 751−784. (c) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168−194.
(9) (a) Drakesmith, F. G.; Richardson, R. D.; Stewart, O. J.; Tarrant, P. *J. Org. Chem.* **1968**, *33*, 286−291. (b) Normant, J. F.; Foulon, J. P.; Masure, D.; Sauvêtre, R.; Villieras, J. *Synthesis* **1975**, 122−125. (c) Masure, D.; Sauvêtre, R.; Normant, J. F.; Villieras, J. *Synthesis* **1976**, 761−764.
(10) Fish, P. V.; Johnson, W. S.; Jones, G. S.; Tham, F. S.; Kullnig, R. K. *J. Org. Chem.* **1994**, *59*, 6150−6152 and references cited.
(11) (a) Ichikawa, J.; Miyazaki, S.; Fujiwara, M.; Minami, T. *J. Org. Chem.* **1995**, *60*, 2320−2321. (b) Ichikawa, J.; Fujiwara, M.; Okauchi, T.; Minami, T. *Synlett* **1998**, 927−929.

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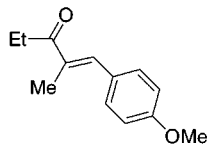
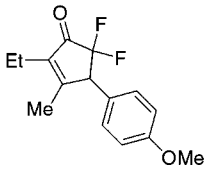
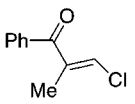
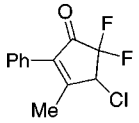
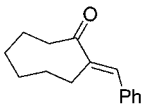
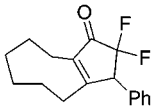
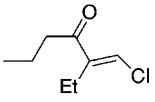
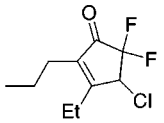
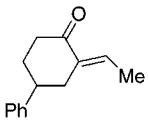
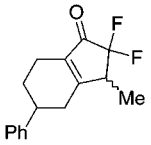
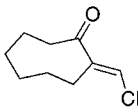
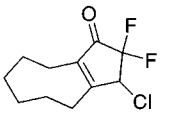
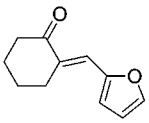
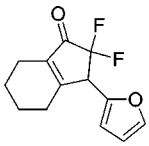
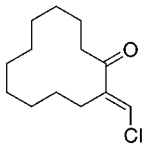
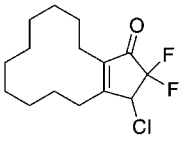
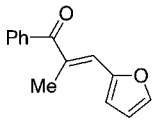
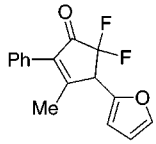
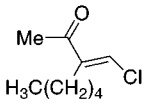
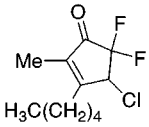
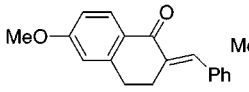
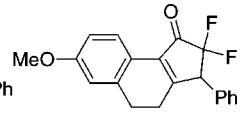
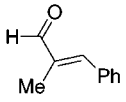
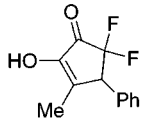
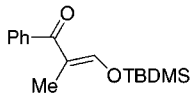
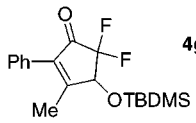
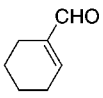
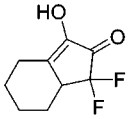
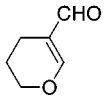
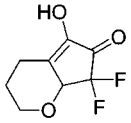
Table 1. 1,1-Difluorocyclopentenones from Enones and Enals

Enone or Enal	Cyclopentenone (yield[a])	Enone or Enal	Cyclopentenone (yield[a])
2a 	 **4a** (63%)	**2h** 	 **4h** (63%)
2b 	 **4b** (90%)	**2i** 	 **4i** (50%)
2c 	 **4c** (50%)	**2j** 	 **4j** (48%)
2d 	 **4d** (61%)	**2k** 	 **4k** (56%)
2e 	 **4e** (48%)	**2l** 	 **4l** (51%)
2f 	 **4f** (60%)	**2m** 	 **6m** (51%)
2g 	 **4g** (36%)[b]	**2n** 	 **6n** (42%)
		2o 	 **6o** (45%)

[a] Overall yield from enone or enal following purification by flash column chromatography. [b] Overall yield from hydroxymethylene ketone.

ionization of **3** will lead to the requisite pentadienyl cation; exposure of **7** to trimethylsilyl triflate led to monofluorocyclopentenone **8** through a Nazarov cyclization. A potentially complicating factor in Scheme 1 is the fact that the ionization of tertiary alcohol **3** is irreversible and must compete with acid-catalyzed processes that lead to the destruction of the sensitive enol ether function.

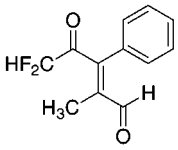
These issues have been addressed. A series of α,β-unsaturated ketones **2a**−**f** (Table 1) were prepared by standard methods.[12] 2,2,2-Trifluoroethanol was converted to the tetrahydropyranyl derivative and then treated with 2 equiv of LDA in THF to produce lithio carbanion **1**. Addition of **1** to **2a**−**f** took place cleanly to produce tertiary alcohols following aqueous workup. The low nucleophilicity of **1** was evident from the fact that it was necessary to warm the addition reaction from −78 to 0 °C, or even to room temperature, to ensure the complete consumption of the enone. A modest excess (ca. 1.7 equiv) of **1** was used; some darkening of the solution was noted as the temperature was allowed to rise, presumably due to slow decomposition of the anion. Because the alcohols appeared to undergo some decomposition during purification, crude materials were used for the cyclization reaction. A variety of conditions[13] were explored for the cyclization reaction. In all cases, cyclized material was detected in the product; however, $BF_3{\cdot}Et_2O$ in dichloromethane consistently resulted in the best yield of product. The results of this study are summarized in Table 1. Overall yields varied from 48% to 90% for **2a**−**f**.

Our first attempt to introduce functionality during cyclization led us to prepare vinylogous silyl ester **2g**.[14] Addition of **1**, followed by treatment with $BF_3{\cdot}Et_2O$ as previously described, led to **4g** in 36% yield following flash column chromatography on silica gel. Byproducts

(12) Gairaud, C. B.; Lappin, G. R. *J. Org. Chem.* **1953**, *18*, 1−3.

(13) The following conditions were examined: TFAA, 2,6-lutidine, CH_2Cl_2; TFAA, 2,6-lutidine, CH_2Cl_2, silica gel; TFAA, DMAP, CH_2Cl_2; TFAA, 2,6-lutidine, $MeNO_2$; MsCl, Et_3N, CH_2Cl_2; $BF_3{\cdot}Et_2O$, CH_2Cl_2.

9 ((*E*)-5,5-difluoro-2-methyl-4-oxo-3-phenyl-2-pentenal, 7% yield) and **10** (7% yield)[15] were also isolated from this



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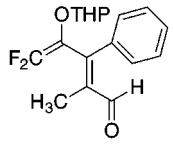
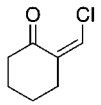


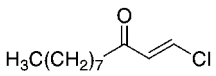
10

reaction, along with larger amounts of hydroxymethylene ketone from protodesilylation of **2g**. The low yield of **4g** can therefore be attributed to the lower electrophilicity of the vinylogous silyl ester **2g** as compared to **2a**−**f**. Premature cleavage of the silyl group during the ionization step leads to the observed byproducts. Replacement of the TBDMS group in **2g** by methyl led to no improvement in the yield of cyclic product, which indicates that vinylogous esters are unsuitable substrates for the addition reaction.

We predicted that the problems that were encountered with **2g** could be overcome by replacing the OTBDMS group by chlorine. This proved to be the case. The greater reactivity of *β*-chloroenone[16] **2h** was reflected in a higher yield for the addition of **1**. The addition reaction of **1** to **2h**−**l** was cleaner when **1** was generated at −78 °C with 2 equiv of *tert*-butyllithium, rather than LDA. Addition of diisopropylamine to the *β*-chloroenones, followed by elimination of chloride, may compete with the desired addition of **1**. Cyclopentenone **4h** was isolated in 63% overall yield from **2h** following $BF_3{\cdot}Et_2O$-catalyzed cyclization (Table 1). We were surprised to find that the same conditions failed in the case of **4i**. The difference in reactivity between the tertiary alcohols derived from **2h** and **2i** is likely due to the stabilizing effect of the phenyl on the cationic intermediate leading to **4h**. Premature loss of the THP group was responsible for the low yield of **4i**. From other work we were aware that ethylene ketals are stable to prolonged treatment with anhydrous trifluoroacetic acid (TFA); therefore, the cyclization of **2i** was catalyzed by TFA in dichloromethane. These conditions worked well; a further improvement in yield was obtained by performing the cyclization with trifluoroacetic anhydride in dichloromethane, and these conditions were used in all subsequent reactions. Two limitations of the cyclization process are apparent from the failure of *β*-chloroenones **11** and **12** to provide cyclic



11



12

products. In both cases, addition of **1** to **11** and **12** took place uneventfully, whereas cyclization could not be induced to take place under a variety of reaction conditions. In the case of **11**, it is likely that the *Z* geometry of the exocyclic double bond inhibits close approach of the terminal carbon atoms of the pentadienyl cation. In the case of **12**, the absence of a substituent at the α vinylic carbon inhibits the cyclization.[17]

Our final goal was to extend the method to the preparation of α-hydroxyenones **6** (Scheme 1). Addition of **1** to the Weinreb or morpholino amides[18] of α,*β*-unsaturated carboxylic acids failed to take place at low temperature or even at room temperature, where decomposition of the anion **1** occurs fairly rapidly.[7c] In light of the failure of **1** to add to vinylogous silyl ester **2g**, this is not surprising. Consequently, the indirect approach that is indicated in Scheme 1 was followed.[19] Addition of **1** to an enal produced alcohol **3**, which was oxidized to ketone **5** and cyclized to **6**. The addition reaction to form the intermediate secondary allylic alcohols took place in nearly quantitative yield; however, the oxidation step failed to provide ketone **5** under a variety of conditions. Of the oxidants which were examined,[20] only IBX[21] and DDQ[22] were effective, and of the two, IBX consistently gave the best yields. The difficulty of this step is not due to any resistance of **3** (R_1 = H) to undergo oxidation (in no case was any starting material recovered) but rather is attributed to the instability of the product **5**, which can undergo multiple, rapid addition−elimination processes in the presence of weak nucleophiles.[23] Ketones **5** were best used immediately after preparation. Cyclization to the difluorocyclopentenone products was successful with $FeCl_3$ under Denmark's conditions.[24] Overall yields for the cyclization varied from 42% to 51% (**6m**−**o**).

Conclusion

We have demonstrated a direct synthesis of substituted difluorocyclopentenones starting with cheap 2,2,2-trifluoroethanol. Our work complements that of Ichikawa,[11] which is the only other report we are aware of in which a Nazarov cyclization is used to prepare fluorinated cyclopentenones. Our method provides a set of fluorocyclopentenones that are not available through his method. Based on a limited number of experiments, it has been shown that α-hydroxycyclopentenones **6m**−**o** are also available through our method. *β*-Chloroenones lead to the unusual chlorodifluorocyclopentenones **4h**−**l** in good overall yield. These materials cannot be obtained directly in any other way and offer a large number of options for functional group transformation. Some of these options

(14) Hydrolytically labile vinylogous silyl ester **2g** was prepared from the hydroxymethylene derivative by treatment with *tert*-butyldimethylsilyl chloride and triethylamine and was allowed to react with an excess of **1** directly, without isolation. See: Tius, M. A.; Kannangara, G. S. K. *Org. Synth.* **1993**, *71*, 158−166.

(15) Aldehyde **10** was isolated as a single geometrical isomer of undetermined stereochemistry.

(16) *β*-Chloroenones were prepared according to: Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 636−643.

(17) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219−4222.

(18) Martin, R.; Romea, P.; Tey, C.; Urpi, F.; Vilarassa, J. *Synlett* **1997**, 1414−1416.

(19) We considered using acid chlorides instead of morpholino amides; however, all attempts to add the (simple) Gilman cuprate derived from **1** to α-methyl-*trans*-cinnamoyl chloride led to very complicated reaction mixtures.

(20) The following oxidations were examined: Swern, DMSO/TFAA/Et_3N, DMSO/$SO_3{\cdot}Py/Et_3N$, NiO_2, MnO_2, PCC/molecular sieves, $BaMnO_4$, Ag_2CO_3/Celite, Magtrieve (Lee, R. A.; Donald, D. S. *Tetrahedron Lett.* **1997**, *38*, 3857−3860), Dess−Martin reagent, and cat. *n*-$Pr_4N(RuO_4)$/NMO.

(21) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272−7276.

(22) McKittrick, B. A.; Ganem, B. *J. Org. Chem.* **1985**, *50*, 5897−5898. Best results were obtained in 10/1 hexanes/CH_2Cl_2.

(23) Ichikawa, J.; Kobayashi, M.; Yokota, N.; Noda, Y.; Minami, T. *Tetrahedron* **1994**, *50*, 11637−11646.

(24) (a) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2377−2396. (b) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2397−2411.

will be explored in future work directed toward the synthesis of fluorinated carbanucleosides.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded at 300 (^{1}H) or 75 (^{13}C) MHz in deuteriochloroform ($CDCl_3$) with chloroform as an internal reference, unless noted otherwise. ^{1}H and ^{13}C chemical shift assignments are based on detailed analysis of two-dimensional NMR spectra when necessary. ^{19}F NMR spectra were recorded on Varian Unity Inova 400 WB operating at 376 MHz (^{19}F) with trifluoroacetic acid (−76.54 ppm, ^{19}F) as the external standard. IR spectra were recorded neat. MS data are reported in the form of *m*/*z*. TLC was performed on Sigma-Aldrich precoated silica gel 60 F-254 analytical plates (0.25 mm). Normal-phase flash column chromatography was performed on ICN silica gel (0.032−0.063 mm). Purity and homogeneity of all materials was determined chromatographically and from ^{1}H and ^{13}C NMR or combustion analysis. THF and ethyl ether were distilled from sodium−benzophenone ketyl. Methylene chloride was distilled from phosphorus pentoxide, and hexane was distilled from CaH_2. Triethylamine and diisopropylamine were distilled from CaH_2 and stored over potassium hydroxide. Benzene, 2,6-lutidine, and nitromethane were distilled from CaH_2 and stored over activated 4 Å molecular sieves. $BF_3{\cdot}Et_2O$ was distilled from CaH_2, and TFAA was distilled from phosphorus pentoxide. Other reagents were obtained commercially and used as received, unless otherwise specified. All reactions were performed under a static nitrogen or argon atmosphere in flame-dried glassware. Elemental analyses were performed by Desert Analytics, Inc.

Tetrahydro-2-(2,2,2-trifluoroethoxy)-2*H*-pyran. To a solution of 2,2,2-trifluoroethanol (26 mL, 0.36 mmol) and 28 mg (0.16 mmol) of *p*-toluenesulfonic acid in 55 mL of CH_2Cl_2 at 0 °C was added 11.88 g (141.2 mmol) of 3,4-dihydro-2*H*-pyran. The reaction mixture was warmed to ambient temperature and stirred for 22 h. The reaction was diluted with ether, washed once with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). Distillation from $CaCO_3$ (water aspirator, ca. 22−25 Torr, 100−110 °C) produced 20.83 g of tetrahydro-2-(2,2,2-trifluoroethoxy)-2*H*-pyran as a colorless oil (80% yield): R_f = 0.34 (5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (t, J = 2.9 Hz, 1H), 4.05−3.76 (m, 3H), 3.53 (m, 1H), 1.90−1.50 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.1 (q, $^1J_{C-F}$ = 277.6 Hz), 98.6, 64.0 (q, $^2J_{C-F}$ = 34.4 Hz), 61.7, 29.9, 25.2, 18.5.

General Procedure. 2-Ethyl-5,5-difluoro-4-(4-methoxyphenyl)-3-methyl-2-cyclopenten-1-one 4a. To a solution of 480 μL of diisopropylamine (3.42 mmol) in 4 mL of THF at −78 °C was added *n*-BuLi (1.06 mL, 3.38 mmol, 3.19 M in hexanes). After 30 min, a solution of tetrahydro-2-(2,2,2-trifluoroethoxy)-2*H*-pyran (287 mg, 1.56 mmol) in 2 mL of THF was added. After 30 min, a solution of **2a** (189 mg, 0.925 mmol) in 4 mL of THF was added. The reaction mixture was quenched after 1 h with saturated NH_4Cl and was diluted with ether and water. The reaction mixture was partitioned between ether and water, washed with brine, dried (Na_2SO_4), and concentrated to give the crude adduct. The crude adduct was dissolved in 13 mL of CH_2Cl_2 and cooled to 0 °C, and $BF_3{\cdot}Et_2O$ (645 μL, 1.01 mmol, 1.58 M in CH_2Cl_2) was added. After 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ and diluted with ether. The aqueous phase was extracted with ether, and the combined extracts were washed with saturated $NaHCO_3$ and brine and dried (Na_2SO_4). Purification by flash column chromatography on SiO_2 (10% EtOAc/hexanes) produced 156 mg (63% yield) of **4a** as a white solid: mp 61−62 °C; R_f = 0.14 (10% EtOAc in hexanes); IR 1725, 1630, 1610, 1205 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.02 (ddm, $^3J_{H-F}$ = 17.1, 2.2 Hz, 1H), 3.79 (s, 3H), 2.37 (q, J = 7.6 Hz, 2H), 1.94 (s br, 3H), 1.10 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7 (t, $^2J_{C-F}$ = 26.2 Hz), 169.2, 159.5, 141.0, 130.2, 124.7, 114.3, 114.1 (t, $^1J_{C-F}$ = 257.0 Hz), 56.2 (dd, $^2J_{C-F}$ = 25.6, 22.0 Hz), 55.2, 16.4, 15.7, 12.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.6 (dd, $^2J_{F-F}$ = 277.1, $^3J_{H-F}$ = 17.1 Hz, 1F), −119.0 (dd, $^2J_{F-F}$ = 277.2, $^3J_{H-F}$ = 2.7 Hz, 1F); mass spectrum *m*/*z* 266 (M^+, 100), 251 (55), 237 (18); exact mass calcd for $C_{15}H_{16}F_2O_2$ 266.1119, found 266.1110. Anal. Calcd for $C_{15}H_{16}F_2O_2$: C, 67.66; H, 6.06. Found: C, 67.54; H, 6.16.

4-(*tert*-Butyldimethylsilyloxy)-5,5-difluoro-3-methyl-2-phenyl-2-cyclopenten-1-one 4g. To a mixture of 137 mg of 2-(hydroxymethylene)propiophenone (0.845 mmol), triethylamine (170 μL, 1.22 mmol), and catalytic DMAP at room temperature was added via cannula a solution of *tert*-butyldimethylchlorosilane (167 mg, 1.11 mmol) in 3 mL of THF. To a second flask at −78 °C was added 5 mL of THF, diisopropylamine (735 μL, 531 mg, 5.24 mmol), and *n*-BuLi (1.52 mL, 5.24 mmol, 3.45 M in hexanes). After 30 min, a solution of tetrahydro-2-(2,2,2-trifluoroethoxy)-2*H*-pyran (460 mg, 2.50 mmol) in 2 mL of THF at −78 °C was added via cannula. After 30 min, a solution of the protected hydroxymethylene ketone was added via cannula at −78 °C, and after 20 min, the reaction mixture was quenched with saturated $NaHCO_3$, diluted with ether, and partitioned between ether and water. The combined extracts were washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The crude product was dissolved in 13 mL of CH_2Cl_2 and cooled to −25 °C, and $BF_3{\cdot}Et_2O$ (120 μL, 0.947 mmol) was added. After 15 min, the reaction mixture was quenched with saturated $NaHCO_3$ and partitioned between ether and water. The organic phase was washed with brine and dried (Na_2SO_4). Purification by flash column chromatography on SiO_2 (EtOAc gradient in hexanes) produced 103 mg (36% yield) of **4g** as a white solid. Aldehydes **9** and **10** were also isolated as a mixture (56 mg, ca. 1:1 by ^{1}H NMR integration of the formyl hydrogen, 7% yield each) that was separated by flash column chromatography on SiO_2 (50% CH_2Cl_2/hexanes). **4g**: mp 93−94 °C; R_f = 0.30 (5% EtOAc/hexanes); IR 1740, 1630, 1240, 1100, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.39 (m, 3H), 7.35 (dt, J = 6.6, 1.4 Hz, 2H), 4.74 (dm, $^3J_{H-F}$ = 13.1 Hz, 1H), 2.24 (s, 3H), 0.99 (s, 9H), 0.25 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.6 (t, $^2J_{C-F}$ = 26.7 Hz), 168.7 (d, $^3J_{C-F}$ = 9.8 Hz), 139.2, 129.1, 129.0, 128.9, 128.5, 112.8 (dd, $^1J_{C-F}$ = 261.1, 256.2 Hz), 74.1 (dd, $^2J_{C-F}$ = 28.8, 18.3 Hz), 25.6, 18.3, 15.2, −4.8, −5.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −118.4 (dd, $^2J_{F-F}$ = 279.3, $^3J_{H-F}$ = 12.8 Hz, 1F), −123.2 (d br, $^2J_{F-F}$ = 278.8 Hz, 1F); mass spectrum *m*/*z* 281 (61), 77 (100); exact mass calcd for $C_{17}H_{21}F_2O_2Si$ ($M^+ - CH_3$) 323.1279, found 323.1279. Anal. Calcd for $C_{18}H_{24}F_2O_2Si$: C, 63.88; H, 7.15. Found: C, 63.93; H, 7.17. **9**: R_f = 0.31 (50% CH_2Cl_2 in hexanes); IR 1730, 1680, 1215, 1100, 1065 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.52−7.43 (m, 3H), 7.30 (dd, J = 7.6, 2.0 Hz, 2H), 5.82 (t, $^2J_{H-F}$ = 53.3 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5 (t, $^2J_{C-F}$ = 26.3 Hz), 192.1, 149.6, 139.6, 130.1, 129.2, 128.7 (t, $^3J_{C-F}$ = 8.8 Hz), 128.5, 108.5 (t, $^1J_{C-F}$ = 252.4 Hz), 13.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −127.8 (d, $^2J_{H-F}$ = 53.4 Hz, 2F). **10**: R_f = 0.13 (50% CH_2Cl_2 in hexanes); IR 1730, 1670, 1225, 1115, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.41−7.30 (m, 5H), 4.82 (s br, 1H), 3.86 (t br, J = 10.6 Hz, 1H), 3.61 (dm, J = 11.5 Hz, 1H), 2.02 (s, 3H), 1.85−1.48 (m, 6H).

4-Chloro-5,5-difluoro-3-methyl-2-phenyl-2-cyclopenten-1-one 4h. To a solution of 263 μL (313 mg, 1.7 mmol) of tetrahydro-2-(2,2,2-trifluoroethoxy)-2*H*-pyran in 6 mL of THF, 2.2 mL of *t*-BuLi (1.6 M in pentane, 3.52 mmol) was added dropwise. After the addition, stirring was continued for 1 h at −78 °C and was followed by the dropwise addition of 1 mL of a 1 M solution of chloroketone **2h** (181 mg) in hexane. The resulting mixture was stirred at −78 °C for 3 h, then quenched with aqueous $NaHCO_3$, and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), evaporated, and then redissolved in 15 mL of CH_2Cl_2. The solution was cooled to −50 °C and 135 μL (1 mmol, 1 equiv) of $BF_3{\cdot}Et_2O$ was added dropwise. Warming to −15 °C over 30 min was followed by quenching with aqueous $NaHCO_3$ and ether extraction. The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash column chromatography on SiO_2 (5% EtOAc/hexanes) to produce 153 mg (63% yield) of **4h** as a colorless

oil: IR 1756, 1630, 1200 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.50 (m, 3H), 7.34 (dd, J = 8.1, 1.9 Hz, 2H), 5.00 (d, $^3J_{H-F}$ = 12.9 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.1 (t, $^2J_{C-F}$ = 25.4 Hz), 164.9 (d, $^3J_{C-F}$ = 6.0 Hz), 140.2 (t, $^3J_{C-F}$ = 2.7 Hz), 129.5, 129.0, 128.7, 128.3, 111.4 (dd, $^1J_{C-F}$ = 263.5, 255.4 Hz), 60.3 (dd, $^2J_{C-F}$ = 32.1, 20.1 Hz), 16.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.2 (dd, $^2J_{F-F}$ = 278.5 Hz, $^3J_{H-F}$ = 12.9 Hz, 1F), −116.4 (d, $^2J_{F-F}$ = 278.5 Hz, 1F); mass spectrum *m*/*z* 242/244 (M^+, 42/15), 207 (100); exact mass calcd for $C_{12}H_9ClF_2O$ 242.0311, found 242.0311. Anal. Calcd for $C_{12}H_9ClF_2O$: C, 59.40; H, 3.74. Found: C, 59.22; H, 3.94.

4-Chloro-5,5-difluoro-3-ethyl-2-propyl-2-cyclopenten-1-one 4i. The addition step was carried out as in the preceding example, proceeding from 1 mmol (161 mg) of **2i**. The crude product from the addition was dissolved in 2 mL of CH_2Cl_2 and cooled to 0 °C, and 282 μL (2 mmol) of TFAA was added in 3 min. After 30 min at 0 °C, the reaction was quenched by careful addition of aqueous $NaHCO_3$. The resulting mixture was extracted with ether, washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash column chromatography on SiO_2 (5% EtOAc/hexanes) to produce 111 mg (50% yield) of **4i** as a colorless oil: IR 1749, 1640, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.95 (d, $^3J_{H-F}$ = 13.3 Hz, 1H), 2.68 (dq, J = 14.3, 7.5 Hz, 1H), 2.58 (dq, J = 14.3, 7.5 Hz, 1H), 2.27 (t, J = 7.7 Hz, 2H), 1.48 (qt, J = 7.5, 7.5 Hz, 2H), 1.21 (t, J = 7.7 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4 (t, $^2J_{C-F}$ = 26.7 Hz), 169.2 (d, $^3J_{C-F}$ = 5.4 Hz), 141.3 (t, $^3J_{C-F}$ = 2.7 Hz), 111.4 (dd, $^1J_{C-F}$ = 263.5, 255.4 Hz), 58.1 (dd, $^2J_{C-F}$ = 32.1, 20.1 Hz), 25.2, 21.5, 21.2, 13.8, 11.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.0 (dd, $^2J_{F-F}$ = 277.7, $^3J_{H-F}$ = 13.0 Hz, 1F), −117.0 (d, $^2J_{F-F}$ = 277.0 Hz, 1F); mass spectrum *m*/*z* 222/224 (M^+, 27/9), 187 (60); exact mass calcd for $C_{10}H_{13}ClF_2O$ 222.0624, found 222.0614. Anal. Calcd for $C_{10}H_{13}ClF_2O$: C, 53.94; H, 5.88. Found: C, 54.12; H, 5.71.

5,5-Difluoro-2-hydroxy-3-methyl-4-phenyl-2-cyclopenten-1-one 6m. A solution of **1** was prepared from 256 mg (1.39 mmol) of tetrahydro-2-(2,2,2-trifluoroethoxy)-2*H*-pyran and 2.90 mmol of LDA in 4 mL of THF at −78 °C. Dropwise addition of a solution of 146 mg (1 mmol) of 2-methyl-*trans*-cinnamaldehyde **2m** in 2 mL of THF was followed by stirring at −78 °C for 4 h. The reaction was quenched with aqueous $NaHCO_3$ and extracted with ether, and the combined organic extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded crude adduct in quantitative yield based on aldehyde (310 mg). The crude product was used for the next step without purification. A portion of the crude product (217 mg) was dissolved in 10 mL of DMSO at room temperature, and 299 mg of IBX (1.07 mmol, 1.5 equiv) was added in one portion. The resulting mixture was stirred for 1 h, 150 mg of IBX (0.54 mmol) was added, stirring was continued for 15 min, and an additional 148 mg (0.53 mmol) of IBX was added. After 15 min, the mixture was diluted with 50 mL of ether/hexane (1/1), and 50 mL of aqueous $NaHCO_3$ was added. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated to afford 150 mg of crude ketone as a yellow oil (∼70% yield). The crude ketone was dissolved in 10 mL of CH_2Cl_2 and cooled to −20 °C, and 80 mg (0.49 mmol, 1 equiv) of $FeCl_3$ was added in one portion. The mixture was allowed to warm slowly to −10 °C during 30 min and was quenched by the addition of 1 M aqueous HCl. The resulting mixture was extracted with ether, and the combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash column chromatography on SiO_2 (10% EtOAc/hexanes) to afford **6m** as a waxy white solid (80 mg, 51% overall yield **2m**): IR 3390, 1737, 1650, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.35 (m, 3H), 7.15 (dd, J = 7.7, 2.1 Hz, 2H), 6.60 (br s, 1H), 4.14 (dd, $^3J_{H-F}$ = 16.4, 1.3 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.8 (t, $^2J_{C-F}$ = 28.1 Hz), 148.0 (t, $^3J_{C-F}$ = 4.0 Hz), 147.0 (d, $^3J_{C-F}$ = 5.4 Hz), 132.7, 129.3, 128.9, 128.5, 112.8 (dd, $^1J_{C-F}$ = 259.5, 256.8 Hz), 54.8 (dd, $^2J_{C-F}$ = 25.4, 22.8 Hz), 13.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.2 (dd, $^2J_{F-F}$ = 278.5 Hz, $^3J_{H-F}$ = 16.0 Hz, 1F), −117.7 (d, $^2J_{F-F}$ = 278.5 Hz, 1F); mass spectrum *m*/*z* 224 (M^+, 100), 209 (26); exact mass calcd for $C_{12}H_{10}F_2O_2$ 224.0649, found 224.0650. Anal. Calcd for $C_{12}H_{10}F_2O_2$: C, 64.28; H, 4.50. Found: C, 64.23; H, 4.35.

7,7-Difluoro-9-hydroxy-8-oxobicyclo[4.3.0]undec-1(9)-ene 6n. The addition of **1** to 110 mg (1 mmol) of cyclohexene carboxaldehyde **2n** was accomplished as in the case of **6m** to produce 275 mg of crude alcohol. The oxidation step was performed on 137 mg of the alcohol in 15 mL of DMSO with 182 mg (0.65 mmol, 1.3 equiv) of IBX. After stirring for 1 h, TLC showed that the reaction had gone to completion. Cyclization of the crude product (96 mg) was performed as in the case of **6m** to produce 40 mg of **6n** as a white waxy solid following flash column chromatography (10% EtOAc/hexane) on SiO_2 (42% overall yield from **2n**): IR 3380, 1735, 1650, 1208 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (br s, 1H), 3.07 (dd, $^3J_{H-F}$ = 13.8, 3.3 Hz, 1H), 2.84 (m, 1H), 2.20−1.92 (m, 4H), 1.55−1.25 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.2 (t, $^2J_{C-F}$ = 28.1 Hz), 150.9 (t, $^3J_{C-F}$ = 4.0 Hz), 143.4 (t, $^3J_{C-F}$ = 4.0 Hz), 113.5 (dd, $^1J_{C-F}$ = 256.8, 255.5 Hz), 44.9 (dd, $^2J_{C-F}$ = 24.1, 22.8 Hz), 26.4 (d, $^4J_{C-F}$ = 8.0 Hz), 25.6, 25.3, 24.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.1 (dd, $^2J_{F-F}$ = 283.8 Hz, $^3J_{H-F}$ = 16.8 Hz, 1F), −125.5 (d, $^2J_{F-F}$ = 283.8 Hz, 1F); mass spectrum *m*/*z* 188 (M^+, 100); exact mass calcd for $C_9H_{10}F_2O_2$ 188.0649, found 188.0651.

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Supporting Information Available: Copies of ^1H, ^{13}C, and ^{19}F NMR spectra, IR spectra, mass spectra, and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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