the same way, 2-methyl-2,4-pentanediol gave the corresponding acetal, **3d**, in 76% yield. Pinacol also gave acetal, **4d**, in 82% yield, but in this case, the diol must be added after the hydrolysis of **5**. None of these hydroxy acetals were previously reported in the literature.

We varied the amount of water in an effort to optimize the yield of acetal and found that using less water resulted in a lower yield. When one-third to half the amount of water was used, the yield of acetal dropped sharply to 40–50%. More water had no effect.

The hydroxypropyl acetals were readily converted to the chlorides with thionyl chloride and triethylamine, or to the bromides with phosphorus tribromide. The iodide, **4c**, was prepared from the bromide with sodium iodide in refluxing 2-butanone. The usual Finkelstein conditions using refluxing acetone resulted in only a partial conversion to **4c**.

Homologated products made with these reagents should be readily convertible to the free aldehydes by hydrolysis,[14] trans-acetalization,[15] or used directly in the synthesis of heterocycles,[16] as has been done for other aldehydes protected as di- and trimethyldioxanes.

Experimental Section

Organic reagents were purchased from Aldrich. All ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300.075 and 75.46 MHz, respectively.

2-(3-Hydroxypropyl)-5,5-dimethyl-1,3-dioxane (2d). 2,3-Dihydrofuran (9.27 g, 0.132 mol) was added all at once to a solution of concentrated HCl (3 mL), water (30 mL), and 2,2-dimethyl-1,3-propanediol (15.2 g, 0.145 mol) and then stirred for 10 h. At the end of that time, a drop of phenolphthalein solution was added to the reaction mixture, which was then titrated with 4 M NaOH to the pink end point. The organic layer was separated, and the aqueous portion was extracted with $CHCl_3$ (4 × 20 mL). The extracts were combined, dried with $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. Distillation afforded **2d** in 83% yield (19.1 g): bp 85–90 °C (1 mmHg); ^{1}H NMR δ 0.73 (3 H, s), 1.19 (3 H, s), 1.73 (4 H, m), 2.50 (1 H, bs), 3.45 (2 H, d, J = 10.6 Hz), 3.63 (2 H, d, J = 10.6 Hz), 3.65 (2 H, t, J = 5.8 Hz), 4.49 (1 H, t, J = 4.4 Hz); ^{13}C NMR δ 21.82, 22.99, 26.96, 30.11, 31.69, 62.78, 77.25, 101.93.

2-(3-Hydroxypropyl)-4,4,6-trimethyl-1,3-dioxane (3d) was obtained in 76% yield (18.8 g) via the procedure given for **2d**. The hydroxy acetal was sufficiently pure without distillation to be converted to the corresponding halo acetal: ^{1}H NMR δ 1.20 (3 H, d), 1.25 (3 H, s), 1.29 (3 H, s), 1.42 (2 H, d, J = 6.6 Hz), 1.72 (4 H, m), 2.90 (1 H, broad s), 3.64 (2 H, t, J = 5.8 Hz), 3.88 (1 H, m), 4.83 (1 H, t, J = 4.1 Hz); ^{13}C NMR δ 21.66, 22.28, 27.16, 31.56, 32.50, 43.38, 62.83, 68.70, 71.90, 95.15.

2-(3-Hydroxypropyl)-4,4,5,5-tetramethyl-1,3-dioxolane (4d). 2,3-Dihydrofuran (9.27 g, 0.132 mol) was added over 15 min to aqueous HCl (3 mL of concentrated HCl in 30 mL of water), and the resulting solution was stirred for 1 h. Pinacol (18.5 g, 0.157 mol) was dissolved in warm water (30 mL), added dropwise to the solution, and stirred overnight. Isolation according to the method for **2d** afforded 22.0 g (82%) of the crude hydroxy acetal that was then converted directly to the bromo compound: ^{1}H NMR δ 1.21 (12 H, s), 1.70 (4 H, m), 2.69 (1 H, broad s), 3.65 (2 H, t, J = 5.8 Hz), 5.08 (1 H, t, J = 4.7 Hz); ^{13}C NMR δ 22.08, 24.24, 27.58, 33.29, 62.71, 82.01, 100.82.

2-(3-Bromopropyl)-4,4,6-trimethyl-1,3-dioxane (3b). Phosphorus tribromide (43.0 g, 0.159 mol) was added dropwise to freshly distilled DMF (300 mL) under a nitrogen atmosphere, with mechanical stirring. A dark, thick mixture resulted. The hydroxy acetal, **3d** (20.0 g, 0.106 mol), was then added dropwise to the slurry. The mixture was stirred for 24 h at 50 °C and then poured slowly into 600 mL of saturated aqueous K_2CO_3 solution, which was then extracted with CH_2Cl_2 (6 × 25 mL). The extracts were combined, dried with $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. Distillation afforded 20.6 g (78%) of the bromo acetal: bp 65–67 °C (0.01 mmHg); ^{1}H NMR δ 1.19 (3 H, d, J = 6.3 Hz), 1.23 (3 H, s), 1.27 (3 H, s), 1.40 (2 H, d, J = 7.5 Hz), 1.71 (2 H, m), 1.99 (2 H, m), 3.44 (2 H, t, J = 6.9 Hz), 3.84 (1 H, m), 4.80 (1 H, t, J = 5.1 Hz); ^{13}C NMR δ 21.73, 22.29, 27.67, 31.66, 33.73, 33.91, 43.48, 68.54, 71.51, 94.42. Anal. Calcd for $C_{10}H_{19}BrO_2$: C, 47.82; H, 7.62. Found: C, 48.13; H, 7.66.

2-(3-Bromopropyl)-4,4,5,5-tetramethyl-1,3-dioxolane (4b) was prepared according to the procedure for **3b** (using the same molar amounts). Distillation afforded 20.2 g of the bromo acetal (76%): bp 60–65 °C (0.01 mmHg); ^{1}H NMR δ 1.20 (12 H, s), 1.75 (2 H, m), 1.99 (2 H, m), 3.46 (2 H, t, J = 6.8 Hz), 5.06 (1 H, t, J = 5.0 Hz); ^{13}C NMR δ 22.09, 24.24, 27.85, 33.61, 34.76, 81.85, 100.05. Anal. Calcd for $C_{10}H_{19}BrO_2$: C, 47.82; H, 7.62. Found: C, 48.17; H, 7.65.

2-(3-Iodopropyl)-4,4,5,5-tetramethyl-1,3-dioxolane (4c). Acetal **4b** (1.0 g, 0.0040 mol) was added to a magnetically stirred solution of sodium iodide (0.90 g, 0.0060 mol) in 100 mL of 2-butanone. The solution was heated at reflux overnight, and then the solvent was removed by rotary evaporation. Water (100 mL) was added to the residue, and the resulting mixture was extracted with hexane (3 × 20 mL). The extracts were combined, dried with $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. Distillation afforded 1.1 g (92%) of **4c**: bp 67–68 °C (0.05 mmHg); ^{1}H NMR δ, 1.19 (6 H, s), 1.20 (6 H, s), 1.70 (2 H, m), 1.96 (2 H, m), 3.24 (2 H, t, J = 7.0 Hz), 5.06 (1 H, t, J = 5.0 Hz); ^{13}C NMR δ 6.57, 22.11, 24.26, 28.68, 37.07, 81.81, 99.89. Anal. Calcd for $C_{10}H_{19}IO_2$: C, 40.28; H, 6.42. Found: C, 40.64; H, 6.47.

2-(3-Chloropropyl)-5,5-dimethyl-1,3-dioxane (2a). Acetal **2d** (10.8 g, 0.0620 mol), triethylamine (6.3 g, 0.062 mol), and 100 mL of toluene were added to a flask fitted with a reflux condenser, an addition funnel, and a magnetic stirrer. The temperature of the mixture was then lowered to 0 °C with an ice bath, followed by the dropwise addition of thionyl chloride (7.4 g, 0.062 mol) over 20 min. After the addition, the mixture was heated at reflux for 1 h. It was then cooled and washed successively with water, 10% aqueous HCl, saturated aqueous $NaHCO_3$, and then water. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. Distillation afforded 9.3 g (78%) of **2a**: bp 65–70 °C (0.2 mmHg) (lit.[6] bp 78 °C (0.2 mm)); ^{1}H NMR δ 0.72 (3 H, s), 1.18 (3 H, s), 1.78 (2 H, m), 1.93 (2 H, m), 3.42 (2 H, d, J = 10.7 Hz), 3.56 (2 H, d, J = 10.7 Hz), 3.59 (2 H, t, J = 6.5 Hz), 4.47 (1 H, t, J = 4.7 Hz).

Registry No. **2a**, 65984-84-1; **2d**, 59214-95-8; **3b**, 138923-99-6; **3d**, 59214-99-2; **4b**, 138924-00-2; **4c**, 138924-01-3; **4d**, 138924-02-4; **5**, 1191-99-7; 2,2-dimethyl-1,3-propanediol, 126-30-7; pinacol, 76-09-5.

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Chemistry of Novel Compounds with Multifunctional Carbon Structure. 7.[1] Synthetic Studies of the Potentially Versatile Monofluoro Molecules, α-Functionalized α-Fluoro-β-keto Esters

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Introduction

The chemistry of organofluorine compounds has made rapid progress during the last decade owing to the development of relatively selective methods for fluorination,[2]

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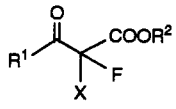
the adaptation of general reaction procedures to fluorinated molecules,[3-5] and the introduction of new building blocks into the field of synthetic fluorine chemistry.[6] However, monofluoro compounds are still difficult to obtain because of low selectivity in fluorination and the inherent high reactivity of the C–F bond when fluorine is located adjacent to other labile groups.[7] With these problems in mind, we sought a general synthesis of monofluorinated structures which would be of interest to basic[3,5,7-10] and biomedicinal[4,11] chemistry research.

The α-fluoro-β-keto ester structure 1 was chosen as an expedient basic skeleton for elaboration on the grounds that the two carbonyl groups would be chemically distinguishable and could be used for derivatization, including C–C bond formation. To increase the versatility of 1 as building blocks, we designed the molecules where the X groups are bromine and some dipolar functional groups such as nitro and sulfonyl because they would serve not only for functionalization at the carbon bearing a fluorine atom but also for steric[8] and electronic[5,9] studies in mechanistic chemistry, e.g., 1,2-asymmetric induction.[10,12]



X : Br, NO_2, SPh, SO_2Ph

1

There have been, however, no multifunctional carbon compounds[13] reported which contain a fluorine atom directly attached to the geminal position to such plural labile groups.[14] Here we present the synthesis of some novel α-functionalized α-fluoro-β-keto esters, which are potentially useful building blocks with wide applicability. Functionalization at the position α to fluorine was investigated because there have been few such studies. Establishing the usefulness and widening the applicability scope of our modified fluorinating procedure using diluted perchloryl fluoride ($FClO_3$)[15] were also our goals since this laboratory-scale fluorination is noteworthy for its safety, convenience, and excellent yield,[16] and therefore, seemed suitable for fluorinating members of this structural family.

Results and Discussion

Synthesis of Bromo Derivatives. Attempts at the fluorination of α-bromo-β-keto esters **2a–e** with $FClO_3$ employing spray-dried KF[17] or Na as a base did not produce the desired bromofluoro derivatives **8a–c**, presumably due to the instability of the bromides **2a–c** toward bases. However, α-fluoro-β-keto esters **3a–c** obtained by fluorination (10% F_2/N_2, 47–69%) of β-keto esters **4a–c** were successfully brominated with Br_2, in CCl_4 at room temperature for 1 h, to produce the new bromofluoro derivatives **8a–c** in 79–94% yield.

Synthesis of Nitro Derivatives. We first attempted the preparation of nitro derivative **9** by the electrophilic nitration of **3a** with O_2NOAc[18] and O_2NBF_4,[19] however, mainly resulting in the recovery of the starting material. The failure presumably was due to the difficulty of generating an α-fluoro carbanion.[20] Nucleophilic nitration of **8a** with $NaNO_2$ in dimethylformamide (DMF) did not give **9a**, yielding instead several products including the nitrite **10a**. Introduction of the ester moiety into the fluorinated molecule was also investigated. Fluorination of nitroacetone **13** with $FClO_3$ employing NaH[21] as a base in tetrahydrofuran (THF) gave mono- and difluoro compounds **14** and **15** in 60 and 21% yield, respectively. Treatment of **14** with ClCOOEt/NaH, however, did not produce the desired ester **9a**.

We then switched to the fluorination of the α-nitro-β-keto ester derivative. Compound **5a** obtained by nitration of **4a** with O_2NOAc[18] was treated with spray-dried KF[17] in MeOH to afford the corresponding salt.[22] The salt was subjected to the usual fluorination with $FClO_3$ in THF, but the deacetylation product **19** was obtained in high yield. After extensive investigation of various reaction conditions, we finally overcame this problem. Nitro compound **5a** was treated with 1 equiv of NaH in THF at 0 °C, and the resulting salt was immediately treated, *without isolation*, with diluted $FClO_3$ at 0 °C for 2 h, to give fluoronitro derivative **9a** in almost quantitative yield.[23]

Synthesis of Sulfide and Sulfone Derivatives. Sulfides **6a,b** derived from **4a,b** (PhSCl/NaH/THF, 81–86%) were fluorinated with $FClO_3$ using NaH as a base at 0 °C for 1.5 h to afford the fluorinated derivatives **11a,b** in 76–88% yield. However, oxidation of the sulfide **11a**

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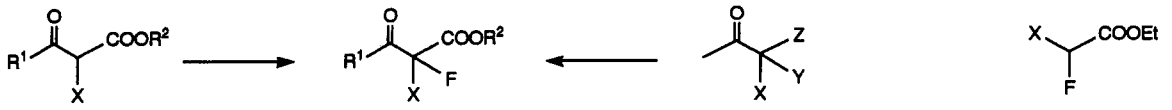
(23) However, compound **9a** was thermally unstable, providing again the deacetylated product **19** when purification by distillation or chromatography was attempted.

Scheme I



2 : X = Br
3 : X = F
4 : X = H
5 : X = NO_2
6 : X = SPh
7 : X = SO_2Ph

8 : X = Br
9 : X = NO_2
10 : X = ONO
11 : X = SPh
12 : X = SO_2Ph

13 : X = NO_2, Y = Z = H
14 : X = NO_2, Y = F, Z = H
15 : X = NO_2, Y = Z = F
16 : X = SO_2Ph, Y = Z = H
17 : X = SO_2Ph, Y = F, Z = H
18 : X = SO_2Ph, Y = Z = F

19 : X = NO_2
20 : X = SO_2Ph
21 : X = SOPh

a : R^1 = Me, R^2 = Et
b : R^1 = Me, R^2 = CH_2Ph
c : R^1 = Ph, R^2 = Et

with various agents[24] usually gave a mixture of deacetylated products **20** and **21**. Nucleophilic sulfonylation of the bromide **8a** with $PhSO_2Na$ in DMF was also attempted; however, mainly the reduced compound **3a** was obtained. The sulfonyl group-containing compound **16** was also used as a precursor. Fluorination of **16**[25] with $FClO_3$/NaH gave mono- and difluorinated products, **17** and **18**, in 59 and 30% yields, respectively. In order to introduce the ester moiety, **17** was treated with ClCOOEt/NaH to provide the target compound **12**, although in poor yield (7%).

We next focused on the α-sulfonyl-β-keto ester structure **7**. Sulfonylation of **4a** with $PhSO_2Cl$/NaH at room temperature yielded **7a** in 52% yield. Attempted fluorination of **7a** with $FClO_3$ or (diethylamino)sulfur trifluoride (DAST),[26] however, resulted in recovery of the starting material. Fluorination of **7a** with 10% F_2/N_2 gave several products of unknown structure. We finally investigated the route involving sulfonylation of the fluoro derivative **3**. Thus, treatment of **3a,c** with $PhSO_2Cl$/NaH at room temperature for 2 h gave the desired compounds **12a,c** in 53–64% yield (Scheme I).

Conclusions

We have succeeded in developing some routes to members of the novel α functionalized α-fluoro-β-keto ester family, which are versatile building blocks of potentially wide utility and interest. We also demonstrated that our modified fluorination procedure is very useful for adding fluorine to a functionalized active-methylene moiety. Studies of C–C bond formation at the fluorine-bearing carbon atom and some mechanistic studies employing the novel monofluoro molecules are in progress.

Experimental Section

General. IR spectra were recorded on JASCO A-102 and Perkin-Elmer 1600 spectrometers. ^1H NMR spectra and ^{13}C NMR spectra were measured with $SiMe_4$ as internal standard and were recorded on a JEOL GX-270 (270 MHz) and a Varian XL-200 (50 MHz) spectrometer, respectively. ^{19}F NMR spectra were measured with $CFCl_3$ as internal standard and were taken with a JEOL GX-270 (254 MHz) spectrometer. Upfield shifts are quoted as negative δ values. EI mass spectra (including high-resolution mass spectra) were taken with a JEOL JMS-D300 spectrometer. Column chromatography and preparative TLC were performed on Kieselgel 60 (Merck, Art. 9385 and 7748, respectively). Combustion analytical data were provided for all new compounds except for **8a** which is too volatile for combustion analysis and for **9a** which decomposes on attempted distillation. The purity of both compounds was judged to be ≥95% by ^1H and ^{13}C NMR spectral determinations.

Typical Procedure for Fluorination with Diluted $FClO_3$ at the α-Position of α-Functionalized Ketones. A 200-mL two-necked flask was fitted with a $FClO_3$ gas-outlet tube and a condenser, the upper end of which was attached to a gas-inlet tube for N_2 from a cylinder. A mixture of FSO_3H (80 mL) and $KClO_4$ (10 g) was placed in the flask, stirred vigorously, and heated gently (the bath temperature should not exceed 100 °C) under a slow stream of N_2 gas. The evolved $FClO_3$ gas was diluted with N_2 gas and passed twice over a solution of aqueous 10% NaOH containing 5% $Na_2S_2O_3$ and then bubbled through the reaction vessel at 0 °C or room temperature which contained a suspension of the sodium salt of the α-functionalized ketones (0.03 mol) in dry THF (50 mL). The sodium salt was prepared by mixing the α-functionalized ketone (0.03 mol) and NaH (60% dispersion in mineral oil, 0.03 mol) in MeOH (100 mL) followed by the evaporation of the solvent after the ceasing of the evolution of hydrogen gas. The salt was sometimes prepared in situ in THF and subjected to fluorination without isolation. This fluorination involving the slow generation of $FClO_3$ and entrainment as a dilute gas in N_2 was continued for 0.5–2 h (reaction mixture monitored by TLC). After reaction was complete, precipitates were removed by filtration and the filtrate was concentrated in vacuo to give the fluorinated products usually in excellent yield and in an almost pure state.

General Procedure for Preparation of α-Bromo-α-fluoro-β-keto Esters (8a–c). A 50-mL three-necked flask was fitted with a dropping funnel, a gas-inlet tube connected to a N_2 gas cylinder, and a gas-outlet tube connected to an efficient hydrogen bromide absorption trap. A solution of α-fluoro-β-keto esters (**3a–c**) (5 mmol) in dry CCl_4 (15 mL) was placed in the flask which was then immersed in an ice bath and stirred vigorously. A solution of Br_2 (0.28 mL, 5.5 mmol) in CCl_4 (5 mL) was added from the dropping funnel over a period of 20 min under a slow N_2 gas stream. The ice bath was removed and the solution was stirred at room temperature for 1 h. Water (25 mL) was added to the solution, and the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2), and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent gave a yellow oil which was purified by silica gel chromatography to give **8a–c**.

Ethyl 2-bromo-2-fluoro-3-oxobutyrate (8a): pale yellow oil, 81% yield; bp 83–85 °C (2 mmHg); IR (neat) 1765, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (3 H, t, J = 7.08 Hz, CH_2CH_3), 2.50 (3 H, q, J = 2.93 Hz, $COCH_3$), 4.38 (2 H, q, J = 7.08 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ 13.81 (CH_2CH_3), 24.06 ($COCH_3$), 64.38 (CH_2), 94.17 (d, J_{C-F} = 274.5 Hz, CF), 162.78 (d, J_{C-F} = 25.6 Hz, COO), 193.65 (d, J_{C-F} = 28.5 Hz, $COCH_3$); ^{19}F NMR ($CDCl_3$) δ −125.63 (q, J = 2.76 Hz); mass spectrum (EI mode), m/z 186, 184 ($M^+ - CH_2CO$), 155, 153 ($M^+ - COOEt$), 43 (CH_3CO^+); HRMS calcd

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for $C_4H_6BrFO_2$ ($M^+ - CH_2CO$) m/z 183.9536, found 183.9559.

Benzyl 2-bromo-2-fluoro-3-oxobutyrate (8b): colorless oil, in 79% yield; bp 82 °C (5×10^{-3} mmHg); IR (neat) 1760, 1750, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (3 H, d, J = 2.69 Hz, CH_3), 5.31 (2 H, s, CH_2), 7.36 (5 H, s, Ph); ^{19}F NMR ($CDCl_3$) δ −125.68 (br s); mass spectrum (EI mode), m/z 290, 288 (M^+), 209 (M^+ − Br), 91 ($PhCH_2^+$), 43 (CH_3CO^+); HRMS calcd for $C_{11}H_{10}Br^*FO_3$ (M^+) m/z 289.9777, found 289.9710. Calcd for $C_{11}H_{10}BrFO_3$ (M^+) m/z 287.9797, found 287.9695. Anal. Calcd for $C_{11}H_{10}BrFO_3$: C, 45.70; H, 3.49. Found: C, 45.61; H, 3.55.

Ethyl 2-bromo-2-fluoro-3-oxo-3-phenylpropionate (8c): colorless oil, 94% yield; bp 95 °C (1×10^{-2} mmHg); IR (neat) 1770, 1715, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (3 H, t, J = 7.08 Hz, CH_3), 4.37 (2 H, q, J = 7.08 Hz, CH_2), 7.45–8.10 (5 H, m, Ph); ^{19}F NMR ($CDCl_3$) δ −118.86 (br s); mass spectrum (EI mode), m/z 290, 288 (M^+), 245, 243 (M^+ − OEt), 217, 215 (M^+ − COOEt), 209 (M^+ − Br), 105 ($PhCO^+$); HRMS calcd for $C_{11}H_{10}Br^*FO_3$ (M^+) m/z 289.9777, found 289.9693. Calcd for $C_{11}H_{10}BrFO_3$ (M^+) m/z 287.9797, found 287.9736. Anal. Calcd for $C_{11}H_{10}BrFO_3$: C, 45.70; H, 3.49. Found: C, 45.45; H, 3.52.

Ethyl 2-Fluoro-2-nitro-3-oxobutyrate (9a). To an ice-cooled suspension of NaH (60% in mineral oil, 0.096 g, 2.4 mmol) in dry THF (30 mL) was syringed a solution of ethyl 2-nitro-3-oxobutyrate (**5a**) (0.462 g, 2.4 mmol) in dry THF (10 mL), and the resultant suspension was stirred at room temperature for 2 h. The suspension was subjected to fluorination with $FClO_3$ in the usual manner (0 °C, 2 h). Insoluble materials were removed by filtration and the filtrate was concentrated in vacuo to give **9a** in an almost pure state (100%) as a pale yellow oil: IR (neat) 1760, 1710, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (3 H, t, J = 7.08 Hz, CH_2CH_3), 2.45 (3 H, d, J = 2.68 Hz, $COCH_3$), 4.45 (2 H, q, J = 7.08 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ 13.78 (CH_2CH_3), 24.79 ($COCH_3$), 65.55 (CH_2), 109.31 (d, J_{C-F} = 260.7 Hz, CF), 158.56 (d, J_{C-F} = 25.2 Hz, COO), 189.32 (d, J_{C-F} = 26.5 Hz, $COCH_3$); ^{19}F NMR ($CDCl_3$) δ −128.48 (br s); mass spectrum (EI mode), m/z 194 ($M + H^+$), 178 (M^+ − CH_3), 150 (M^+ − $COCH_3$), 73 (COOEt); HRMS calcd for $C_6H_9FNO_5$ ($M + H^+$) m/z 194.0463, found 194.0422.

Ethyl 2-Fluoro-2-(phenylthio)-3-oxobutyrate (11a). Fluorination of ethyl 2-(phenylthio)-3-oxobutyrate (**6a**) with $FClO_3$ in the usual manner (0 °C, 1.5 h) gave **11a** in 76% yield as a colorless oil after purification by silica gel chromatography: bp 106 °C (5×10^{-3} mmHg); IR (neat) 1760, 1740, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (3 H, t, J = 7.08 Hz, CH_2CH_3), 2.21 (3 H, d, J = 3.42 Hz, $COCH_3$), 4.20 (2 H, q, J = 7.08 Hz, CH_2), 7.33–7.59 (5 H, m, Ph); ^{19}F NMR ($CDCl_3$) δ −135.30 (q, J = 3.76 Hz); mass spectrum (EI mode), m/z 257 ($M + H^+$), 256 (M^+), 214 (M^+ − CH_2CO), 109 (SPh); HRMS calcd for $C_{12}H_{13}FO_3S$ (M^+) m/z 256.0568, found 256.0533. Anal. Calcd for $C_{12}H_{13}FSO_3$: C, 56.24; H, 5.11. Found: C, 56.28; H, 5.24.

Benzyl 2-Fluoro-2-(phenylthio)-3-oxobutyrate (11b). Fluorination of benzyl 2-(phenylthio)-3-oxobutyrate (**6b**) with $FClO_3$ in the usual manner (0 °C, 1.5 h) gave **11b** in 88% yield as a colorless oil after purification by silica gel chromatography: bp 148 °C (5×10^{-3} mmHg); IR (neat) 1760, 1740, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (3 H, d, J = 12.2 Hz, CH_3), 5.14 (2 H, AB q, J = 12.2 Hz, $\Delta\delta$ = 7.45 Hz, CH_2), 7.21–7.59 (10 H, m, Ph × 2); ^{19}F NMR ($CDCl_3$) δ −135.43 (br s); mass spectrum (EI mode), m/z 319 ($M + H^+$), 318 (M^+), 276 (M^+ − CH_2CO), 91 ($PhCH_2^+$); HRMS calcd for $C_{17}H_{15}FO_3S$ (M^+) m/z 318.0724, found 318.0694, calcd for $C_{15}H_{13}FO_2S$ (M^+ − CH_2CO) m/z 276.0619, found 276.0618. Anal. Calcd for $C_{17}H_{15}FO_3S$: C, 64.14; H, 4.75. Found: C, 64.42; H, 4.78.

General Procedure for Preparation of α-Fluoro-α-(benzenesulfonyl)-β-keto Esters (12a,c). To a stirred suspension of NaH (60% dispersion in mineral oil, 0.04 g, 1 mmol) in dry THF (15 mL) was syringed a solution of α-fluoro-β-keto esters (**3a,c**) (1 mmol) in THF (5 mL) under an argon atmosphere with stirring at room temperature for 0.5 h. To the mixture was added dropwise $PhSO_2Cl$ (0.177 g, 1 mmol) over 10 min, and the resultant mixture was stirred at room temperature for 2 h. The solvent was evaporated, Et_2O (5 mL) and water (10 mL) were added to the residue, and the organic layer was separated. The aqueous layer was extracted with Et_2O (5 mL × 3), and the combined ethereal layer was dried on $MgSO_4$. Evaporation of the solvent gave a pale yellow oil which was purified by preparative TLC to produce **12a,c**.

Ethyl 2-(benzenesulfonyl)-2-fluoro-3-oxobutyrate (12a): colorless oil, 53% yield: bp 100–102 °C (0.5 mmHg); IR (neat) 1760, 1735, 1385, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (3 H, t, J = 7.08 Hz, CH_2CH_3), 2.44 (3 H, d, J = 4.64 Hz, $COCH_3$), 4.24 (2 H, q, J = 7.08 Hz, CH_2), 7.55–7.80 (5 H, m, Ph); ^{19}F NMR ($CDCl_3$) δ −132.86 (q, J = 4.64 Hz); mass spectrum (EI mode), m/z 284 ($M + H^+$), 244 ($M + H^+$ − OEt), 216 ($M^+ + 1$ − COOEt), 141 ($PhSO_2$), 77 (Ph); HRMS calcd for $C_9H_9FO_3S$ ($M + H^+$ − COOEt) m/z 216.0256, found 216.0226. Anal. Calcd for $C_{11}H_{13}FO_5S$: C, 50.00; H, 4.54. Found: C, 49.92; H, 4.52.

Ethyl 2-(benzenesulfonyl)-2-fluoro-3-oxo-3-phenylpropionate (12c): colorless needles (Et_2O/hexane), 64% yield: mp 97.0–97.5 °C; IR (KBr) 1731, 1381, 1073 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (3 H, t, J = 7.08 Hz, CH_3), 4.39 (2 H, q, J = 7.08 Hz, CH_2), 7.1–7.70 (10 H, m, Ph × 2); ^{19}F NMR ($CDCl_3$) δ −140.94 (s); mass spectrum (EI mode), m/z 350 (M^+), 305 (M^+ − OEt), 141 ($PhSO_2$), 77 (Ph); HRMS calcd for $C_{17}H_{15}FO_5S$ (M^+) m/z 350.0623, found 350.0596. Anal. Calcd for $C_{17}H_{15}FO_5S$: C, 58.28; H, 4.32. Found: C, 58.23; H, 4.47.

1-(Benzenesulfonyl)-1-fluoropropan-2-one (17). Fluorination of 1-(benzenesulfonyl)propan-**2-one (16)** as a usual manner gave **17** in 59% yield as a colorless oil after purification by preparative TLC: bp 98 °C (5×10^{-3} mmHg); IR (neat) 1743, 1580, 1340, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (3 H, d, J = 3.91 Hz, CH_3), 5.47 (1 H, J = 49.07 Hz, CH), 7.61–7.98 (5 H, m, Ph); ^{19}F NMR ($CDCl_3$) δ −180.21 (dq, J = 49.64, 3.68 Hz); mass spectrum (EI mode), m/z 217 ($M + H^+$), 216 (M^+), 141 ($PhSO_2^+$), 77 (Ph^+); HRMS calcd for $C_9H_9FO_3S$ (M^+) m/z 216.0255, found 216.0240. Anal. Calcd for $C_9H_9FO_3S$: C, 49.99; H, 4.20. Found: C, 49.92; H, 4.21.

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On the Search for Diastereoselective Bisepoxidation of Template-Bound 1,5-Dienes

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We report here our efforts toward a novel template-based approach to the stereoselective bisepoxidation of 1,5-unsaturated hydrocarbon chains. This system attempts to exploit the conformational biases imposed on a hydrocarbon chain bearing distal sp^2 (alkene) centers by a large, rigid organic molecule. In broad terms, the strategy consists of coupling of template diol with a bisunsaturated diacid to provide a sterically biased macrocyclic bislactone.[1] Face-selective functionalization of the unsaturated moieties in the chain may then be possible as an external reagent should add from the less hindered peripheral face of the olefins. To the extent that the template imposes conformational restrictions on the attached diene-containing chain, high levels of remote relative asymmetric induction may be observed for the diacid substrate. Stereochemical control in bisepoxidations forms the basis for several

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