Ester Enolate Claisen Rearrangements of Allyl α-Fluoroacetates and α-Fluoropropanoates

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The ester enolate Claisen rearrangement of allyl α-fluoroacetates **1** forms 2-fluoroalkenoic acids **2** in good to excellent yield with good internal asymmetric induction. This selectivity was unexpected as stereoselective deprotonation of fluoroacetates is not normally possible. The selective formation of the required α-fluoro silyl ketene acetal **3** was found to result from the stereoselective rearrangement of the allyl α-fluoro-α-silylacetate isomer. Although silyl ketene acetals derived from α-fluoropropanoates **7** also rearranged, control of internal asymmetric induction was not possible.

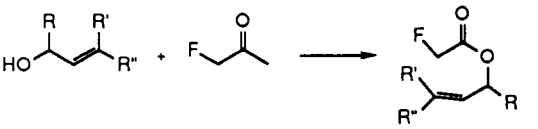
Introduction

The Claisen rearrangement[1] is a powerful synthetic transformation for the stereoselective construction of carbon–carbon bonds. Two new asymmetric centers may be created diastereoselectively with concomitant regio- and stereospecific formation of a new double bond. Because Claisen rearrangements take place through a highly ordered cyclic transition state, chirality in the starting material can be transferred to a new site in the product. Moreover, the most favorable transition-state geometry can ordinarily be predicted from principles of conformational analysis, with the result that the stereochemical outcome of the reaction can often be predicted.

The Ireland ester enolate variant of the Claisen rearrangement has extended the applicability of the rearrangement by facilitating its employment in convergent approaches to the synthesis of new materials.[2-5] The effect of fluorine substitution on sigmatropic rearrangements has been reported in only a few cases,[6] and the effect of the fluoro group on the Claisen rearrangement had been described only in brief communications when this work was begun.[7]

Results and Discussion

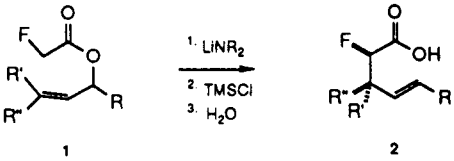
Product Yields and Stereochemistry. The synthesis of allyl fluoroacetates **1** was straight forward and proceeded in high yield. Fluoroacetylation of allyl alcohols was achieved utilizing a 15% excess of the alcohol to fluoroacetyl chloride[8] (freshly distilled) in a 0.3 M solution of pyridine in dichloromethane. The α-fluoro esters were produced in nearly quantitative yields.



(1)

1a R, R' R" = H
1b R, R" = H R' = CH_3
1c R, R' = H R" = CH_3
1d R', R" = H R = CH_3

Allyl fluoroacetates **1** were deprotonated under a variety of conditions with one of three amide bases, lithium diisopropylamide (LDA), lithium tetramethylpiperidide (LTMP), or lithium hexamethyldisilazide (LHMDS). The ester enolate Claisen rearrangement of the resultant silyl ketene acetals demonstrated that good internal asymmetric induction[9] was possible (as high as 20:1) as determined by both ^{13}C and ^{1}H NMR, in good overall yield. The best



(2)

1 **2**

diastereoselectivities and yields were obtained when LDA was used to generate the enolate. When formation of the enolate of allyl fluoroacetates with LHMDS under comparable conditions was attempted, the yields of rearranged products were consistently lower. Excess LDA masked the

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(9) For definition, see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2–73.

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Table I. Ester Enolate Claisen Rearrangement of Allyl Fluoroacetates (See Eq 2)

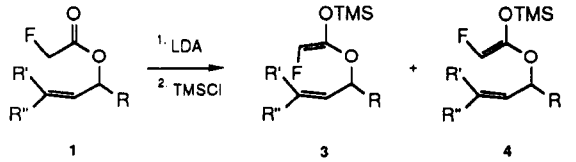
entry	R	R′	R″	base[c]	equiv base	diastereomer ratio	yield, %
1	CH_3	H	H	LDA	3	-	88
2				LDA	0.9	-	23
3	H	H	H	LDA	3	-	72
4	H	CH_3	H	LDA	3	1:1	81
5				LDA	1.1	1:20	43
6	H	H	CH_3	LHMDS	1.2	1:1	43
7				LTMP	1.2	4:1	20
8				LTMP	2	3:1	35
9				LTMP	4	2:1	82
10				LTMP[a]	4	2:1	76
11				LDA	3	2:1	97
12				LDA[a]	1.1	2:1	-
13				LDA[b]	1.1	2:1	-
14				LDA	1.2	4:1	65
15				LDA	0.9	9:1	35

[a] of HMPA (0.5 equiv). [b] 23% by volume HMPA. [c] LDA (lithium diisopropylamide), LTMP (lithium tetramethylpiperidide), or LHMDS (lithium hexamethyldisilazide).

diastereoselectivity of the rearrangement by epimerizing the products. Promotion of the formation of *Z* enolates by hexamethylphosphoramide (HMPA)[10,11] was not observed. The addition of HMPA did degrade the diastereoselectivity of the rearrangement slightly. Although the use of LTMP to effect deprotonation is known to favor formation of *E* enolates under kinetic conditions and *Z* enolates under conditions that favor enolate equilibration, with allyl fluoroacetates there was little difference in the product stereochemistry whether the enolate was generated with LTMP or LDA.[12] Interestingly the use of LHMDS lead to formation of the products with loss of selectivity.

The wide range of yields illustrated in the table reflects the sensitivity of the deprotonation and subsequent rearrangement to the reaction conditions. Control experiments in which the rearrangement was conducted in the presence of excess base demonstrated that the product trimethylsilyl esters are readily epimerized to a thermodynamic mixture. However, with careful control of the optimum conditions, the rearrangement can be reproducibly effected in high yield with good control of the stereochemistry.

Although determination of the diastereoselectivity by ^{13}C and ^{19}F NMR spectroscopy was straightforward, direct determination of which acid diastereomer was being preferentially formed was not possible. Determination of the stereochemistry of the silyl ketene acetal provides an alternative approach to identifying the major diastereomers since the transition state for the rearrangement is most probably chairlike. However our efforts to isolate the *tert*-butyldimethylsilyl and trimethylsilyl ketene acetals after attempted trapping of the enolate with either chlorotrimethylsilane, chloro-*tert*-butyldimethylsilane or *tert*-butyldimethylsilyl triflate failed.



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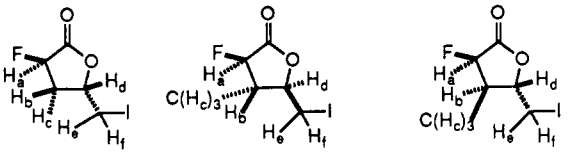
γ-Lactones, more suitable for conformational analysis by NMR spectroscopy, were prepared by conversion of the olefinic acids to the iodo lactones under conditions of thermodynamic control.[13] Iodo lactonization of **2b** yielded

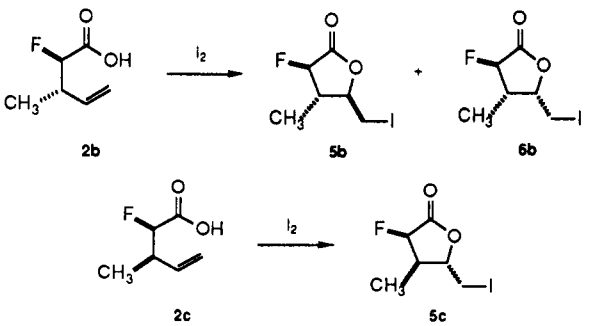
Table II. ^1H NMR Chemical Shifts and Coupling Constants for 5



5a 5b 5c

	lactone		
proton	**5a**	**5b**	**5c**
H_a	δ 5.30 $J_{a,c}$ = 9.1 $J_{a,b}$ = 8.8 $J_{a,F}$ = 51.2	δ 5.28 $J_{a,b}$ = 7.32 $J_{a,F}$ = 50.8	δ 4.89 $J_{a,b}$ = 9.28 $J_{a,F}$ = 51.2
H_b	δ 2.23 $J_{b,F}$ = 26.8 $J_{b,c}$ = 4.99	δ 3.06 $J_{b,c}$ = 6.84 $J_{b,c}$ = 5.0	δ 3.05 $J_{b,c}$ = 6.84 $J_{b,d}$ = 5.0 $J_{b,F}$ = 21.4
H_c	δ 2.97 $J_{c,F}$ = 10.7 $J_{c,d}$ = 7.0	δ 1.03 $J_{c,F}$ = 2.44	δ 1.32
H_d	δ 4.2 $J_{d,e}$ = 4.88 $J_{d,f}$ = 7.99	δ 3.61 $J_{d,e}$ = 9.2 $J_{d,f}$ = 5.86	δ 3.87 $J_{d,e}$ = 5.45
H_e	δ 3.25 $J_{e,f}$ = 10.5	δ 3.39 $J_{e,f}$ = 10.4	δ 3.14 $J_{e,f}$ = 11.4
H_f	δ 3.34	δ 3.39	δ 3.30

a 4:1 mixture of **5b** and **6b**, whereas **2c** preferentially formed only **5c** as determined by ^1H NMR spectroscopy.



2b 5b 6b

2c 5c

The configuration of the lactones was determined by 2D*J*-resolved spectroscopy in conjunction with ^{13}C chemical shift data and ^{19}F–^1H coupling constants. As expected, the ^1H resonance assigned to the methyl in **5b** showed a

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(11) *E* enolates are defined as those in which fluorine is cis relative to the ester alkyl.
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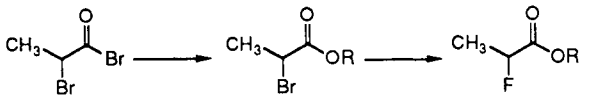
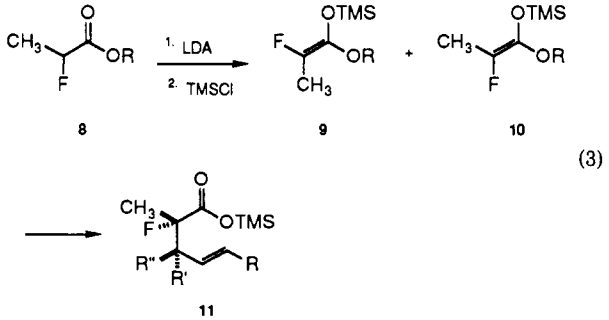
γ coupling to fluorine of 2.4 Hz, whereas in **5c** no γ coupling was observed. In **5b**, $J_{Ha,Hb}$ = 7.32 Hz, and in **5c**, $J_{Ha,Hb}$ = 9.28 Hz, in agreement for the syn and anti relationship of H_a and H_b in **5b** and **5c** respectively. The remainder of the observed proton coupling constants are in agreement with the structures shown. In the ^{13}C NMR spectrum of **5c** the methyl signal (δ 10.12 ppm) appears at higher field than the methyl resonance of **5b** (δ 14.12 ppm) in which the methyl and the fluorine have an anti relationship. Assignment of the structures **2c** and **2b** formed by rearrangement of the *E* and *Z* esters require the rearrangement to proceed from only the *E* silyl ketene acetal if a chairlike transition state is involved.

Allyl α-Fluoropropanoates. In an extension of this study, we prepared α-fluorinated propanoate esters. Since alkylation of the fluoroacetate enolate with methyl iodide or methyl triflate formed complex mixtures, a different approach to the preparation was undertaken. The synthesis of 8 was achieved by preparation of the α-bromo ester **7**, followed by displacement of bromide with fluoride ion using silver fluoride in dry acetonitrile. The use of silver fluoride in these reactions was necessitated by a predominant saponification reaction which occurred when the less expensive potassium fluoride was employed. Exchange was effected at room temperature over several days by portionwise addition of the silver fluoride; efforts to accelerate the displacement by heating only led to decomposition.



7 8

Deprotonation of 8 with LDA was followed by trapping of the enolate with chlorotrimethylsilane. Even though the products could not be epimerized by the excess base, the α-fluoropropanoates 8 exhibited considerably less selectivity on rearrangement than the α-fluoroacetates. The failure of the rearrangement to exhibit the selectivity of either propanoates[2a] or fluoroacetates suggests the possibility of competing pathways for formation of the silyl ketene acetal in the reaction of α-fluoropropanoates in which each pathway leads to a different silyl ketene acetal, **9**, or **10**.



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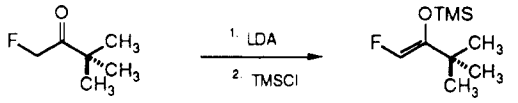
Silyl Ketene Acetal Formation. The stereoselectivity of the kinetic deprotonation of acyclic carbonyl derivatives using lithium dialkylamide bases can be rationalized by the Ireland transition-state model.[14,15] Our earlier studies of fluorinated enolates clearly demonstrated that control of enolate geometry on deprotonation was difficult,[16] except in the case of 1-fluoro-3,3-dimethylbutanone,[17] **12**. Presumably neither steric interactions in the transition state nor differences in the stability of the product enolates are sufficient for selectivity in enolate formation from allyl fluoroacetates. The tendency of fluoroacetate enolates

Table III. Ester Enolate Claisen Rearrangement of Allyl α-Fluoropropanoates 8 (Eq 3)

R	R′	R″	conditions[a]	internal asymmetric induction	yield, %
H	H	H		-	68
H	H	CH_3		1:2.3	69
			b	1:2.4	48
			c	1:1.16	41
H	CH_3	H		1.65:1	69
			b	2.19:1	55
			c	2.07:1	55

[a] Deprotonation was effected with 3 equiv of LDA. [b] Deprotonation in the presence of 25% by volume HMPA. [c] Quenching of the enolate with TMSCl and 25% HMPA.



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to exhibit poor diastereoselectivity in the aldol condensation[18] yet high diastereoselectivities in the ester enolate Claisen rearrangement contrasts with the predictable behavior associated with simple propanoate enolates.

The good internal asymmetric induction in the ester enolate Claisen rearrangement required stereoselective and efficient formation of the ketene silyl acetal. The successful formation of the an α-fluoro silyl ketene acetal may be particularly surprising in light of earlier reports that treatment of enolates with chlorotrimethylsilane could result in significant amounts of C-silylation,[2a,19] in addition to our own findings that fluoroacetamide enolates undergo facile C-silylation.[20] If C-silylated products are formed, they must be converted in high yield to the reactive silyl ketene acetal to achieve the observed yields of rearranged materials.

^{19}F NMR Studies. Direct examination of the ^{19}F NMR of the lithium enolates at low temperature would avoid complications associated with isolation of reactive silyl ketene acetals and competing O vs C silylation. ^{19}F NMR studies of the lithium enolate of *N,N*-dimethylfluoroacetamide at −85 °C under similar conditions clearly indicated two distinct fluorine resonances, in a 1:1 ratio, at δ −213.15 ppm (δ, $J_{H,F}$ = 85.4 Hz) and δ −214.3 ppm (δ, $J_{H,F}$ = 71.7 Hz) assigned to a mixture of the *E* and *Z* enolates[20] **14** and **15**.

Unfortunately all attempts at the direct observation of the lithium enolate of 2-butenyl fluoroacetate, ethyl fluoroacetate, benzyl fluoroacetate, or 2,6-di-*tert*-butyl-4-

(14) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115.
(15) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando; 1984; Vol. 3, part B, pp 111–212.
(16) (a) Welch, J. T.; Eswarakrishnan, S. *J. Org. Chem.* **1985**, *50*, 5403–5405. (b) Welch, J. T.; Eswarakrishnan, S.; Seper, K.; Samartino, J. S. *Ibid.* **1984**, *49*, 4720–4721. (c) Welch, J. T.; Eswarakrishnan, S. *J. Chem. Soc., Chem. Commun.* **1985**, 186–188. (d) Welch, J. T.; Plummer, J. S. *Synth. Commun.* **1989**, *19*, 1081–1090.
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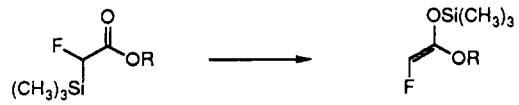
14 15

methylphenyl fluoroacetate, at temperatures between −100 °C and −75 °C, were unsuccessful. No ^{19}F resonances were observable, not even those which could be attributed to undeprotonated starting material. However, a careful ^{19}F NMR study of the ester enolate Claisen rearrangement of α-fluoroacetates did help to elucidate the origin of the diastereoselectivity observed.[7a] At −85 °C treatment of the 2-butenyl fluoroacetate with LDA followed by chlorotrimethylsilane yielded principally the C-silylated ester **16** as determined by low-temperature ^{19}F NMR. As mentioned previously, prior to the addition of chlorotrimethylsilane, it was not possible to measure a ^{19}F NMR signal for the enolate. On warming to 20 °C, resonances assigned to the product of sigmatropic rearrangement (δ −200.37 ppm, $J_{H,F}$ = 49.1 Hz, $J_{H,F}$ = 26.3 Hz) increased while the signal attributed to the C-silylated material (δ −229.9 ppm, $J_{H,F}$ = 48.2 Hz) decreased. At −85 °C there was a signal assigned to fluoro ketene silyl acetal **3** (δ −199.4 ppm, $J_{H,F}$ = 78.6 Hz) whose relative intensity to C-silylated material increased, but decreased relative to the signal attributable to the rearranged products. Presumably the reactive silyl ketene acetal is not formed by direct O-silylation of the fluorinated enolate, rather the initially formed C-silylated material isomerizes in a slow step to form the reactive fluorinated silyl ketene acetal **3** which undergoes sigmatropic rearrangement in a second fast step.



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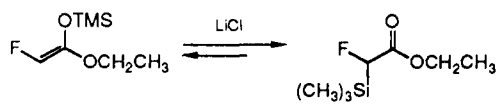
The lability of α-fluoro enol silyl ethers was previously described by Easdon and Burton.[21] These authors reported the formation of C-silylated α-fluoroacetates when α-fluoroacetate enolates, formed by deprotonation with LHMDS, were treated with chlorotrimethylsilane. However, when the enol silyl ether of ethyl α-fluoroacetate, **17**, prepared by other means, was treated with lithium chloride, the lithium chloride promoted isomerization of the enol silyl ether into C-silylated material **18**. Our findings indicate that it is also possible for the α-fluoro-α-silylacetate to undergo a facile rearrangement to the α-fluoro silyl ketene acetal. It is unlikely that the diastereoselectivity observed in the Claisen rearrangement of allyl fluoroacetates could occur without migration of the trimethylsilyl group in a synperiplanar fashion to form an *E* fluoroketene silyl acetal **3**.



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The O to C migration of trialkylsilyl groups has been described.[22] *C*- to *O*-silyl migrations have been proposed to be involved in the reactions of α-trimethylsilyl trimethylsilyl esters under basic conditions.[23] The thermal rearrangement of α-silyl ketones to enol silyl ethers is also known.[24] Although this process required heating and it was thought to be independent of the solvent used, it has been reported that when acetonitrile is used as solvent the rearrangement can be extraordinarily stereoselective.[25] Yet heating of allyl α-diphenylmethylsilyl acetate failed to yield evidence of Claisen rearrangement, even at 200 °C, as would occur on silyl migration.[26] As evidenced by the facility of the *C*- to *O*-silyl migration observed in this work, fluorination is clearly affecting in a profound way the rate of this rearrangement.

It is also clear that fluorine substitution is effective at dramatically modifying the reactivity of the intermediate enolate. The selective C-silylation of lithium ester enolates is generally a difficult transformation, requiring the use of a bulky silylating agent such as α-diphenylmethylchlorosilane.[26,27] The propensity of lithium fluoroacetate enolates to silylate on carbon suggests that I-π destabilization by fluorine decreases the significance of the enolate resonance form in the reactions of deprotonated fluoroacetates. As a practical result of the decreased distribution of electron density onto oxygen, silylation occurs predominantly on carbon.

In conclusion, the successful control of stereochemistry in the α-fluoroacetate ester enolate Claisen rearrangement was the result of the complementary and serendipitous effects of fluorine substitution. First, silylation was directed on carbon, obviating our inability to control the enolate geometry, and second, the selective migration of the trimethylsilyl group from carbon to oxygen resulted in the formation of a *E* fluoro silyl ketene acetal. When a methyl group was introduced, as in the α-fluoropropanoate ester examined, these subtle effects were disturbed and stereochemical control was lost.

Experimental Section

General. ^1H NMR spectra were recorded at either 60 or 300 MHz. ^{13}C NMR spectra were recorded at either 22.63 or 75.429 MHz. ^{19}F NMR spectra were determined in $CDCl_3$ solution at 282.203 MHz. Chemical shifts are reported in ppm upfield from external CCl_3F. Analytical TLC was routinely used to monitor reactions on plates precoated with silica gel 60 F_{254} of 0.20 mm thickness. The chromatograms were visualized under UV light, by staining with iodine or by dipping the plates in a solution of vanillin in absolute ethanol and sulfuric acid and then heating in an oven for 4–5 min at 140 °C. Column chromatography was performed utilizing two methods. Method A: Flash chromatography was performed according to the procedure of W. C. Still[28] using Merck silica gel 60 (230–400 7mesh), Davisil silica gel grade 633 (200–425 mesh) 60 A (Aldrich) or Davisil silica gel 62 (60–200 mesh) 140 A (Aldrich). Method B refers to gravity chromatography using Davisil silica gel grade 62 (60–200 mesh) (Fisher) or Merck silica gel 60 (70–230 mesh). Melting points and boiling points are uncorrected.

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Solvents were freshly distilled prior to use: tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl; dimethylformamide (DMF) was purified by heating under reflux over barium oxide and was distilled at 5 mm; dichloromethane (CH_2Cl_2) was distilled from anhydrous potassium carbonate; acetonitrile (CH_3CN), chlorotrimethylsilane (TMSCl), methanol, and hexane were distilled from calcium hydride. Lithiated bases were prepared in the following manner: Lithium diisopropylamide (LDA) was prepared by the dropwise addition of 4.0 mL (0.006 mol) of methyllithium (1.5 M solution in diethyl ether) to 0.84 mL (0.006 mol) of dry diisopropylamine dissolved in 25 mL of anhydrous THF under an inert atmosphere at 0 °C. The mixture was allowed to stir at 0 °C for 10 min. Lithium hexamethyldisilazide (LHMDS) was prepared by addition of 20 mL (0.03 mol) of methyllithium (1.5 M solution in diethyl ether) to 6.3 mL (0.03 mol) of hexamethyldisilazane in 50 mL of anhydrous THF under an inert atmosphere. The reaction is complete when methane evolution ceases.

General Method for the Preparation of Fluoroacetates. To 60 mL of a 0.3 M solution of pyridine in dichloromethane, at 0 °C, was added 0.02 mol of the desired alcohol while maintaining the temperature at 0 °C, 1.45 mL (0.017 mol, ca. 1.1 g/mL) of fluoroacetyl chloride[8] [prepared by treatment of sodium fluoroacetate (Sigma, Artel) with phthaloyl chloride, bp 65–71 °C. **Caution**: Sodium fluoroacetate and fluoroacetyl chloride are fatal poisons affecting the central nervous system causing epileptic convulsions. They were handled with extreme caution in an efficient fume hood.] was added dropwise, cautiously. The reaction mixture was allowed to stir at 0 °C for 1 h and then at 25 °C for 12 h. The reaction mixture was washed with saturated $CuSO_4$ (3 × 10 mL), followed by water then brine. The organic extracts were dried ($MgSO_4$), and the solvent was distilled. Distillation of the product at reduced pressure yielded the pure compound.

2-Propenyl fluoroacetate (1a): yield 2.78 g (93%); ^{1}H NMR ($CDCl_3$) δ 5.5–6.1 (m, 2 H), 5.0–5.3 (m, 1 H), 4.7 (d, J_{HF} = 46 Hz, 2 H), 4.5 (d, J = 6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 167.2 ($J_{C,F}$ = 22 Hz, C=O), 131.0 (*C*H=CH$_2$), 118.7 (CH*C*H$_2$), 77.3 (d, $J_{C,F}$ = 180.7 Hz, *C*HF), 65.5 (*C*H$_2$O); ^{19}F NMR ($CDCl_3$) δ −231.38 (t, $J_{H,F}$ = 46.7 Hz).

Anal. Calcd for $C_5H_7FO_2$: C, 50.9; H, 5.97. Found: C, 50.52; H, 6.01.

(*Z*)-Buten-1-yl fluoroacetate (1b): yield 3.08 g (83%); bp 73 °C (55 mm); ^{1}H NMR ($CDCl_3$) δ 6.1–5.2 (m, 2 H), 4.8 (d, J_{HF} = 46 Hz, J = 6 Hz, 2 H), 1.7 (d, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.8 (d, $J_{C,F}$ = 23.2 Hz, C=O), 130.7 (*C*HCH$_2$), 123.24 (*C*HCH$_3$), 77.6 (d, $J_{C,F}$ = 181.8 Hz, *C*HF), 60.84 (*C*H$_2$O), 13.05 (CH$_3$); ^{19}F NMR ($CDCl_3$) δ −233.07 (t, $J_{H,F}$ = 44.8 Hz).

Anal. Calcd for $C_6H_9FO_2$: C, 54.54; H, 6.87. Found: C, 54.49; H, 6.95.

(*E*)-2-Buten-1-yl fluoroacetate (1c): yield 2.06 g (91%); bp 75–78 °C (49 mm); ^{1}H NMR ($CDCl_3$) δ 5.7 (dt, J_{HF} = 21.4 Hz, J = 6.3 Hz, 1 H), 5.5 (dq, J_{HF} = 21.4 Hz, J = 6.4 Hz, 1 H), 4.68 (d, $J_{H,F}$ = 46.7 Hz, 2 H), 4.47 (d, J = 6.0 Hz, 2 H), 1.6 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.57 ($J_{C,F}$ = 21.97 Hz, C=O), 132.8 (*C*HCH$_2$), 124.2 (CH*C*H$_3$), 77.6 ($J_{C,F}$ = 181.9 Hz, *C*HF), 66.0 (*C*H$_2$O), 17.7 (*C*H$_3$); ^{19}F NMR ($CDCl_3$) δ −233.21 (t, $J_{H,F}$ = 48.0 Hz).

Anal. Calcd for $C_6H_9FO_2$: C, 54.54; H, 6.87. Found: C, 54.65; H, 7.02.

3-Buten-2-yl fluoroacetate (1d): yield 2.64 g (87%); bp 70 °C (50 mm); ^{1}H NMR ($CDCl_3$) δ 5.98–4.9 (m, 5 H), 4.9 (d, J_{HF} = 46 Hz, 2 H), 1.6 (d, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.8 ($J_{C,F}$ = 22 Hz, C=O), 136.6 (*C*HCH$_2$), 116.4 (CH*C*H$_2$), 77.4 (d, $J_{C,F}$ = 181.9 Hz, *C*HF), 72.1 (*C*HO), 19.15 (*C*H$_3$).

Anal. Calcd for $C_6H_9FO_2$: C, 54.54; H, 6.87. Found: C, 54.46; H, 6.98.

General Method for the Preparation of 2-Fluoropropanoates. Under an inert atmosphere a solution of 6.5 g (0.030 mol) of 2-bromopropionyl bromide in 30 mL of dichloromethane was stirred magnetically as 0.035 mol of the desired alcohol and 5 mL of pyridine were added at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was allowed to warm to room temperature and to stir overnight. It was washed with saturated $CuSO_4$ (2 × 20 mL), water, and brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by distillation under reduced pressure.

To 0.0058 mol of the purified allyl 2-bromopropanoate in 20 mL of dry acetonitrile was added 1.5 g (0.0012 mol) of silver(I) fluoride (Ozark-Mahoning). The reaction was allowed to stir at room temperature for 10 days, whereupon a second portion of silver fluoride (0.0012 mol) was added. After an additional 5 days, the reaction mixture was distilled and water (20 mL) was added to the distillate. The mixture was extracted with pentane (3 × 20 mL). The pentane extracts were dried ($MgSO_4$) and concentrated in vacuo. Distillation of the residue under reduced pressure yielded the desired 2-fluoropropanoate.

2-Propenyl 2-fluoropropanoate (8a): yield 4.05 g (70%) **7a**; bp 50 °C (7 mm); ^{1}H NMR ($CDCl_3$) δ 5.80 (ddt, J = 16.98 Hz, J = 10.14 Hz, J = 5.43 Hz), 5.27 (dq, J = 17.91 Hz, J = 2.33 Hz, 1 H), 5.15 (dq, J = 10.14 Hz, J = 1.62 Hz, 1 H), 4.53 (m, 2 H), 4.30 (q, J = 6.78 Hz, 1 H), 1.71 (d, J = 6.78 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.35 (C=O), 131.09 (*C*HCH$_2$), 118.35 (CH*C*H$_2$), 65.91 (*O*CH$_2$), 39.65 (*C*HBrCH$_3$), 21.33 (CHBr*C*H$_3$).

Yield 0.83 g (69%) **8a**: bp 74–75 °C (75 mm); ^{1}H NMR ($CDCl_3$) δ 5.87 (ddt, J = 17.15 Hz, J = 10.54 Hz, J = 5.89 Hz), 5.27 (dq, J = 17.09 Hz, J = 1.52 Hz, 1 H), 5.18 (dq, J = 11.13 Hz, J = 1.57 Hz, 1 H), 4.95 (dq, $J_{H,F}$ = 48.2 Hz, J = 7.0 Hz, 1 H), 4.6 (dt, J = 15.87 Hz, J = 1.33 Hz, 2 H), 1.50 (dd, J_{HF} = 23.34 Hz, J = 7.25 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.99 ($J_{C,F}$ = 22.9 Hz, C=O), 131.23 (*C*HCH$_2$), 118.95 (CH*C*H$_2$), 85.5 ($J_{C,F}$ = 181.1 Hz, *C*FCH$_3$), 65.74 (CH$_2$O), 18.18 ($J_{C,F}$ = 22.0 Hz, CF*C*H$_3$); ^{19}F NMR ($CDCl_3$) δ −186.2 (dq, $J_{H,F}$ = 50.2 Hz, $J_{H,F}$ = 25.1 Hz).

Anal. Calcd for $C_6H_9FO_2$: C, 54.54; H, 6.86. Found: C, 54.56; H, 6.97.

(*Z*)-2-Buten-1-yl 2-fluoropropanoate (8b): yield 4.8 g (77%) **7b**; bp 52–54 °C (4 mm); ^{1}H NMR ($CDCl_3$) δ 5.75 (m, 1 H), 5.55 (m, 1 H), 4.69 (d, J = 6.72 Hz, 2 H), 4.34 (q, J = 6.78 Hz, 1 H), 1.79 (d, J = 6.84 Hz, 3 H), 1.69 (dm, J = 5.62 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.4 (C=O), 129.89 (*C*HCH$_2$), 123.09 (*C*HCH$_3$), 60.90 (*C*H$_2$O), 39.68 (*C*HBrCH$_3$), 21.19 (CHBr*C*H$_3$), 12.71 (CH*C*H$_3$).

Yield 1.02 g (83%) **8b**: bp 75 °C (35 mm); ^{1}H NMR ($CDCl_3$) δ 5.78 (m, 1 H), 5.56 (m, 1 H), 5.01 (dq, $J_{H,F}$ = 48.1 Hz, J = 6.78 Hz, 1 H), 4.75 (d, J = 7.33 Hz, 1 H), 1.72 (dm, J = 6.94 Hz, 3 H), 1.58 (dd, $J_{H,F}$ = 24.1 Hz, J = 6.73 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.1 ($J_{C,F}$ = 23.1 Hz, *C*=O), 130.3 (*C*HCH$_2$), 123.4 (*C*HCH$_3$), 85.5 ($J_{C,F}$ = 181.2 Hz, *C*FCH$_3$), 60.5 (*C*H$_2$O), 18.1 ($J_{C,F}$ = 21.9 Hz, CF*C*H$_3$), 12.9 (CH*C*H$_3$); ^{19}F NMR ($CDCl_3$) δ −186.5 (dq, $J_{H,F}$ = 48.5 Hz, $J_{H,F}$ = 24.2 Hz).

Anal. Calcd for $C_7H_{11}FO_2$: C, 57.52; H, 7.59. Found: C, 57.30; H, 7.42.

(*E*)-2-Buten-1-yl 2-fluoropropanoate (8c): yield 4.9 g (80%) **7c**; bp 68 °C (4 mm); ^{1}H NMR ($CDCl_3$) δ 5.65 (m, 1 H), 5.41 (m, 1 H), 4.39 (d, J = 7.17 Hz), 4.19 (q, J = 6.72 Hz, 2 H), 1.62 (d, J = 6.73 Hz, 1 H), 1.54 (dm, J = 6.18 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.31 (C=O), 131.40 (*C*HCH$_2$), 124.01 (*C*HCH$_3$), 65.93 (*C*H$_2$O), 39.73 (*C*HBrCH$_3$), 21.17 (CHBr*C*H$_3$), 17.29 (CH$_2$*C*H$_3$).

Yield 0.91 g (77%) **8c**; bp 78–80 °C (55 mm); ^{1}H NMR ($CDCl_3$) δ 5.80 (m, 1 H), 5.59 (m, 1 H), 4.99 (dq, $J_{H,F}$ = 48.8 Hz, J = 6.81 Hz, 1 H), 4.60 (dd, J = 6.30 Hz, J = 2.00 Hz), 1.72 (dm, J = 6.30 Hz, 3 H), 1.56 (dd, $J_{H,F}$ = 23.41 Hz, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.9 ($J_{C,F}$ = 24.4 Hz), 132.1 (*C*HCH$_2$), 124.1 (*C*HCH$_3$), 85.4 ($J_{C,F}$ = 181.3 Hz, *C*HFCH$_3$), 65.7 (*C*H$_2$O), 17.4 (CH$_2$*C*H$_3$), 17.9 ($J_{C,F}$ = 23.8 Hz, CHF*C*H$_3$); ^{19}F NMR ($CDCl_3$) δ −185.6 (dq, $J_{H,F}$ = 24.4 Hz, $J_{H,F}$ = 48.8 Hz).

Anal. Calcd for $C_7H_{11}FO_2$: C, 57.52; H, 7.59. Found: C, 57.45; H, 7.68.

2-Fluoropent-4-enoic Acid (2a). A solution of 0.009 mol of LDA in 30 mL of THF under an inert atmosphere was magnetically stirred and cooled to −100 °C, and 0.4 g (0.003 mol) of **2a** was added followed by 1.14 mL (0.009 mol) of chlorotrimethylsilane (TMSCl). The solution was warmed to room temperature and heated at 40 °C for 2 h. The reaction was quenched with methanol and basicified with 5% NaOH; the basic layer was washed with ether. The organic washings were discarded. The extracted, basic phase was acidified with concentrated HCl. The acidic layer was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine (1 × 20 mL), dried ($MgSO_4$), and evaporated in vacuo to yield 0.25 g (70%) of **2a**: ^{1}H NMR ($CDCl_3$) δ 10.2 (br s, 1 H), 5.00–6.05 (m, 3 H), 4.73 (dt, J_{HF} = 48 Hz, J = 6 Hz, 1 H), 2.55 (dt, J_{HF} = 24 Hz, J = 6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 174.70 (d, $J_{C,F}$ = 24.4 Hz, C=O), 130.5

(d, $J_{C,F}$ = 3.7 Hz, $CHCH_2$), 119.0 ($CHCH_2$), 87.7 (d, $J_{C,F}$ = 186.8 Hz, CHF), 36.4 (d, $J_{C,F}$ = 20.8 Hz, CH_2CFH).

Anal. Calcd for $C_5H_7FO_2$: C, 50.85; H, 5.95. Found: C, 51.29; H, 6.75.

2-Fluoro-3-methylpent-4-enoic Acid (2b). Deprotonation at −100 °C, followed by reaction, and workup in the usual manner yielded 0.27 g (70%) of **2b**: ^{1}H NMR ($CDCl_3$) δ 10.25 (br s, 1 H), 5.66 (ddd, J = 17.58 Hz, J = 10.25 Hz, J = 8.3 Hz, 1 H), 5.06 (d, J = 17.58 Hz, 1 H), 5.03 (d, J = 10.25 Hz, 1 H), 4.67 (dd, $J_{H,F}$ = 48.72 Hz, J = 4.12 Hz, 1 H), 2.7 (dm, J_{HF} = 26 Hz, 1 H), 1.06 (d, J = 7.65 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.38 (d, $J_{C,F}$ = 25.0 Hz, C=O), 136.22 ($CH=CH_2$), 116.70 ($CH=CH_2$), 91.69 (d, $J_{C,F}$ = 188.3 Hz, CHF), 40.39 ($J_{C,F}$ = 20.2 Hz), 15.65 (d, $J_{C,F}$ = 4.4 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −201.08 (dd, $J_{H,F}$ = 48.9 Hz, $J_{H,F}$ = 27.5 Hz).

Anal. Calcd for $C_6H_9FO_2$: C, 54.54; H, 6.87. Found: C, 54.49; H, 6.95.

2-Fluoro-3-methylpent-4-enoic Acid (2c). Deprotonation at −100 °C with 0.0028 mol of LDA and 0.5 g (0.0037 mol) of **1c** was followed by the addition of 0.0028 mol of TMSCl. After being heated to 40 °C for 2 h the reaction was quenched and worked up in the usual manner to yield 0.24 g (66%) of **2c**: ^{1}H NMR ($CDCl_3$) δ 10.1–10.6 (br s, 1 H), 5.84 (ddd, J = 17.58 Hz, J = 10.26 Hz, J = 7.33 Hz, 1 H), 5.34 (d, J = 17.09 Hz, 1 H), 5.14 (d, J = 10.26 Hz, 1 H), 4.88 (dd, $J_{H,F}$ = 48.34 Hz, J = 3.42 Hz, 1 H), 2.64 (dm, J_{HF} = 26.86 Hz, 1 H), 0.94 (d, J = 7.33 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.18 (d, $J_{C,F}$ = 24.41 Hz, C=O), 137.76 ($CH=CH_2$), 116.24 ($CH=CH_2$), 91.23 (d, $J_{C,F}$ = 189.6 Hz, CHF), 40.16 (d, $J_{C,F}$ = 20 Hz, $CHCH_3$), 13.40 (d, $J_{C,F}$ = 6.1 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −200.73 (dd, J_{HF} = 48.8 Hz, J_{HF} = 28.1 Hz).

Anal. Calcd for $C_6H_9FO_2 \cdot {}^1/_3H_2O$: C, 52.22; H, 7.00. Found: C, 52.53; H, 7.20.

2-Fluorohex-4-enoic Acid (2d). Deprotonation at −95 °C with 0.0027 mol of LDA and 0.44 g (0.0030 mol) of **1d** was followed by the addition of 0.0027 mol of TMSCl. After being heated to 40 °C for 2 h the reaction was quenched and worked up in the usual manner to yield 0.25 g (70%) of **2d**: ^{1}H NMR ($CDCl_3$) δ 10.19 (br s, 1 H), 5.2–5.6 (m, 2 H), 4.7 (dt, J_{HF} = 48 Hz, J = 6 Hz, 1 H), 2.53 (dm, J_{HF} = 22 Hz, 2 H), 1.7 (d, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.1 (d, $J_{C,F}$ = 24.4 Hz, C=O), 130.5 ($CHCHCH_3$), 122.9 (d, $J_{C,F}$ = 3.7 Hz, $CHCHCH_3$), 88.1 (d, $J_{C,F}$ = 186.8 Hz, CHF), 35.3 (d, $J_{C,F}$ = 20.8 Hz, $CHFCH_2$), 17.90 (CH_3).

Anal. Calcd for $C_6H_9FO_2$: C, 54.54; H, 6.87. Found: C, 53.61; H, 6.74.

2-Fluoro-2-methyl-pent-4-enoic Acid (11a). Deprotonation at −100 °C with 0.0028 mol of LDA and 0.132 g (0.001 mol) of **8a** was followed by the addition of 0.003 mol of TMSCl. After being heated to 40 °C for 2 h the reaction was quenched and worked up in the usual manner to yield 0.089 g (68%) of **11a**: ^{1}H NMR ($CDCl_3$) δ 6.9 (br, 1 H), 5.8 (m, 1 H), 5.18 (dd, $J_{H,F}$ = 14.3 Hz, J = 4.84 Hz, 2 H), 2.62 (m, 2 H), 1.59 (d, $J_{H,F}$ = 21.65 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.5 ($J_{C,F}$ = 25.6 Hz, C=O), 130.6 ($J_{C,F}$ = 4.0 Hz, $CHCH_2$), 119.3 ($CHCH_2$), 94.0 ($J_{C,F}$ = 24.1 Hz, $CFCH_3$); ^{19}F NMR ($CDCl_3$) δ −157.7 (m, $J_{H,F}$ = 21.8 Hz).

Anal. Calcd for $C_6H_9FO_2 \cdot {}^1/_2H_2O$: C, 51.06; H, 7.14. Found: C, 50.89; H, 7.03.

2-Fluoro-2,3-dimethylpent-4-enoic Acid (11b and 11c) from 8c. Deprotonation at −100 °C with 0.0028 mol of LDA and 0.146 g (0.001 mol) of **8c** was followed by the addition of 0.003 mol of TMSCl. After being heated to 40 °C for 2 h the reaction was quenched and worked up in the usual manner to yield 0.070 g (48%) of **11b and 11c**: ^{1}H NMR ($CDCl_3$) (**11c**) δ 10.4 (br, 1 H), 5.73 (ddd, $J_{H,H}$ = 10.1 Hz, $J_{H,H}$ = 8.52 Hz, $J_{H,H}$ = 6.1 Hz, 1 H), 5.082 (d, $J_{H,H}$ = 8.52 Hz, 1 H), 5.16 (d, $J_{H,H}$ = 10.14 Hz, 1 H), 1.52 (d, $J_{H,F}$ = 22.3 Hz, 3 H), 1.09 (d, $J_{H,H}$ = 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 176.2 ($J_{C,F}$ = 26.4 Hz, C=O), 96.4 ($J_{C,F}$ = 188.4 Hz, $CFCH_3$), 44.8 ($J_{C,F}$ = 20.6 Hz, $CHCH_3$), 137.4 ($J_{C,F}$ = 3.2 Hz, $CHCH_2$), 116.9 ($CHCH_2$), 21.1 ($J_{C,F}$ = 25.3 Hz, $CFCH_3$), 13.5 ($J_{C,F}$ = 4.3 Hz, $CHCH_3$), 176.5 ($J_{C,F}$ = 24.0 Hz, C=O), 96.6 ($J_{C,F}$ = 189.4 Hz, $CFCH_3$), 44.7 ($J_{C,F}$ = 21.2 Hz, $CHCH_3$), 136.6 ($J_{C,F}$ = 4.8 Hz, $CHCH_2$), 117.7 ($CHCH_2$), 21.8 ($J_{C,F}$ = 23.9 Hz, $CFCH_3$), 14.9 ($J_{C,F}$ = 2.2 Hz, $CHCH_3$); ^{19}F NMR ($CDCl_3$) δ −168.26 (m, $J_{H,F}$ = 21.3 Hz), −164.37 (m, $J_{H,F}$ = 22.5 Hz).

Anal. Calcd for $C_7H_{11}FO_2 \cdot {}^1/_4H_2O$: C, 55.80; H, 7.69. Found: C, 55.60; H, 7.67.

2-Fluoro-2,3-dimethylpent-4-enoic Acid (11b and 11c) from 8b. Deprotonation at −100 °C with 0.0028 mol of LDA and 0.146 g (0.001 mol) of **8b** was followed by the addition of 0.003 mol of TMSCl. The reaction warmed to room temperature and was heated to 40 °C for 2 h. The reaction was quenched and worked up in the usual manner yielding 0.080 g (55%) of **11b and 11c**: ^{1}H NMR ($CDCl_3$) (**11b**) δ 10.4 (br, 1 H), 5.81 (ddd, $J_{H,H}$ = 10 Hz, $J_{H,H}$ = 5 Hz, $J_{H,H}$ = 7 Hz, 1 H), 5.13 (d, $J_{H,H}$ = 10 Hz, 1 H), 5.09 (d, $J_{H,H}$ = 5 Hz, 1 H), 1.55 (d, $J_{H,F}$ = 21.4 Hz, 3 H), 1.12 (d, $J_{H,H}$ = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.3 ($J_{C,F}$ = 25.7 Hz, C=O), 96.2 ($J_{C,F}$ = 187.5 Hz, $CFCH_3$), 44.8 ($J_{C,F}$ = 21.2 Hz, $CHCH_3$), 137.2 ($J_{C,F}$ = 2.9 Hz, $CHCH_2$), 117.3 ($CHCH_2$), 15.0 ($J_{C,F}$ = 4.7 Hz, $CHCH_3$), 22.0 ($J_{C,F}$ = 23.9 Hz, $CFCH_3$), 172.9 ($J_{C,F}$ = 22.9 Hz, C=O), 96.5 ($J_{C,F}$ = 186.3 Hz, $CFCH_3$), 44.8 ($J_{C,F}$ = 22.3 Hz, $CHCH_3$), 137.9 ($J_{C,F}$ = 5.1 Hz, $CHCH_2$), 116.4 ($CHCH_2$), 13.7 ($J_{C,F}$ = 4.2 Hz, $CHCH_3$), 21.3 ($J_{C,F}$ = 23.9 Hz, $CFCH_3$); ^{19}F NMR ($CDCl_3$) δ −169.2 (m, $J_{H,F}$ = 25.4 Hz), −163.5 (m, $J_{H,F}$ = 21.2 Hz).

Anal. Calcd for $C_7H_{11}FO_2 \cdot H_2O$: C, 51.21; H, 7.98. Found: C, 51.25; H, 7.71.

4,5-Dihydro-3-fluoro-5-(iodomethyl)-2(3*H*)-furanone (5a). A mixture of 0.090 g (0.00084 mol) of **2a** and 0.64 g (0.0025 mol) of solid iodine in 5 mL of acetonitrile was stirred in the dark, under nitrogen at 0 °C for 5 h. The product solution was partitioned between 25 mL of ether and saturated aqueous $NaHCO_3$. The organic layer was washed with 10% aqueous $Na_2S_2O_3$ until colorless and then with water and brine. It was dried ($MgSO_4$) and concentrated in vacuo to yield 0.180 g (87%) of the lactone as a thick oil. Purification by chromatography afforded sufficiently pure lactones for NMR analysis: TLC R_f = 0.69 (10% acetone/CH_2Cl_2); ^{13}C NMR ($CDCl_3$) major isomer δ 170.51 (d, $J_{C,F}$ = 20.1 Hz, C=O), 85.69 (d, $J_{C,F}$ = 191.0 Hz, CHF), 74.63 (d, $J_{C,F}$ = 7.2 Hz, CHO), 35.16 (d, $J_{C,F}$ = 18.8 Hz, CH_2CHF), 6.34 (CH_2I); ^{19}F NMR ($CDCl_3$) δ −194.3 (ddd, $J_{C,F}$ = 50.4 Hz, $J_{C,F}$ = 24.4 Hz, $J_{C,F}$ = 6.1 Hz).

Anal. Calcd for $C_5H_6FIO_2$: C, 24.61; H, 2.48. Found: C, 24.40; H, 2.41.

4,5-Dihydro-3-fluoro-5-(iodomethyl)-4-methyl-2(3*H*)-furanone, (5b). A mixture of 0.150 g (0.0011 mol) of **2b** and 0.864 g (0.0024 mol) of solid iodine in 5 mL of acetonitrile was stirred in the dark at 0 °C for 5 h. Workup as described above gave 0.110 g (42.6%) of the lactone **5b** as a 4:1 mixture with **6b**: ^{13}C NMR ($CDCl_3$) δ 87.82 ($J_{C,F}$ = 189.3 Hz, CHF), 77.68 ($J_{C,F}$ = 7.5 Hz, OCH), 40.11 ($J_{C,F}$ = 19 Hz, $CHCH_3$), 14.12 ($J_{C,F}$ = 10 Hz, CCH_3), 5.23 (CH_2I); ^{19}F NMR ($CDCl_3$) δ −195.91 (dd, J_{HF} = 52.3 Hz, J_{HF} = 26.1 Hz).

Anal. Calcd for $C_6H_8FIO_2$: C, 27.93; H, 3.125. Found: C, 27.99; H, 3.06.

4,5-Dihydro-3-fluoro-5-(iodomethyl)-4-methyl-2(3*H*)-furanone (5c). To a solution of 10 mL of 50% aqueous 1,2-dimethoxyethane was added 0.230 g (0.0017 mol) of **2c**; to this was added 0.89 g (0.0035 mol) of solid iodine at room temperature. The mixture was allowed to stir in the dark at room temperature overnight. The solution as diluted with ether, washed with saturated aqueous sodium thiosulfate ($Na_2S_2O_3$) solution (1 × 20 mL) and with $NaHCO_3$ followed with brine, and dried ($MgSO_4$). The $Na_2S_2O_3$ solution was back-extracted with ether (2 × 10 mL). The combined ether extracts were washed with saturated $NaHCO_3$ (1 × 20 mL) and brine (1 × 20 mL). After drying ($MgSO_4$), the ether was removed in vacuo to yield 0.33 g (73%) of **5c** as a single isomer. Purification by chromatography afforded sufficiently pure lactone for NMR analysis: ^{13}C NMR ($CDCl_3$) δ 169.62 (d, $J_{C,F}$ = 19.1 Hz, C=O), 91.14 (d, $J_{C,F}$ = 196.7 Hz, CHF), 79.34 (d, $J_{C,F}$ = 9.1 Hz, OCH), 42.9 (d, $J_{C,F}$ = 19.3 Hz, CCH_3), 10.12 (CH_3), 4.68 (CH_2I); ^{19}F NMR ($CDCl_3$) δ −199.83 (dd, J_{HF} = 52.6 Hz, J_{HF} = 21.7 Hz).

Anal. Calcd for $C_6H_8FIO_2$: C, 27.93; H, 3.125. Found: C, 28.16; H, 3.54.

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Registry No. **1a**, 406-23-5; **1b**, 98064-42-7; **1c**, 98064-43-8; **1d**, 98064-41-6; **2a**, 3885-23-2; **2b**, 98064-45-0; **2c**, 98064-46-1; **2d**,

98064-44-9; **5a**, 129731-39-1; **5b**, 98064-47-2; **5c**, 98064-49-4; **7a**, 87129-38-2; **7b**, 129731-40-4; **7c**, 129731-41-5; **8a**, 129731-42-6; **8b**, 129731-43-7; **8c**, 125573-09-3; **11a**, 129731-44-8; **11b**, 129731-45-9; **11c**, 129731-46-0; H_2C=$CHCH_2OH$, 107-18-6; (*Z*)-H_3CCH=$CHCH_2OH$, 4088-60-2; (*E*)-H_3CCH=$CHCH_2OH$, 504-61-0; H_3C-$CH(OH)CH$=CH_2, 598-32-3; $H_3CCHBrCPBr$, 563-76-8; fluoroacetyl chloride, 359-06-8; sodium fluoroacetate, 62-74-8; phthloyl chloride, 88-95-9.

Supplementary Material Available: IR spectral data for compounds **1a-d**, **2a-d**, **5b,c**, **7a-c**, **8a-c**, and **11a-c** (2 pages). Ordering information is given on any current masthead page.

Carboxyl-Mediated Pictet-Spengler Reaction. Direct Synthesis of 1,2,3,4-Tetrahydro-β-carbolines from Tryptamine-2-carboxylic Acids†

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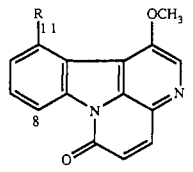
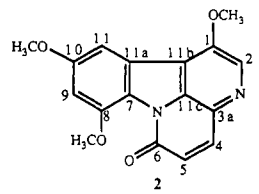
The Pictet-Spengler condensation of various tryptamine-2-carboxylic acids **9a-f** with carbonyl compounds in benzene/dioxane/trifluoroacetic acid (Table I) with simultaneous loss of carbon dioxide afforded directly the corresponding 1,2,3,4-tetrahydro-β-carbolines **14a-j** in good to excellent yields. This reaction greatly enhances the use of the Abramovitch-Shapiro method for the synthesis of highly oxygenated ring A substituted 1,2,3,4-tetrahydro-β-carbolines (THBC). The lactams **14f,g** and **14h** are key intermediates for the synthesis of ring A substituted 1-methoxycanthin-6-one analogues.

In recent years an increasing number of β-carboline alkaloids that contain an oxygen substituent at position 4 have been isolated.[1a,b,2] The 4-methoxy-β-carbolines[1a,b] and canthin-6-ones,[1b,2a] as well as several bisindoles,[3] serve as representative examples. The alkaloids 1-methoxycanthin-6-one (**1a**) 1,11-dimethoxycanthin-6-one (**1b**) and their congeners have been shown to exhibit cytotoxic, antileukemic activity via their inhibitory effects on DNA synthesis in GPK epithelial cells.[2c,4] Oxygenation of the



1a, R=H
1b, R=OCH_3



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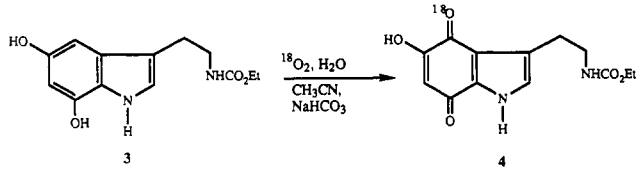
canthin-6-one skeleton either at position 1 (C-4 in the β-carboline numbering system) and/or ring A greatly enhances the cytotoxic, antileukemic activity of these bases. Recently, while studying the mechanism of action of 5,7-dihydroxytryptamine **3** (5,7-DHT), a selective serotonergic neurotoxin, Borchardt[5] proposed two possible modes of autoxidation of 5,7-DHT **3** to the quinone **4** (Scheme I). He demonstrated, experimentally, that a derivative of 5,7-DHT underwent autoxidation in the presence of $^{18}O_2$ to incorporate ^{18}O at the C-4 position of the indole ring system (eq 1). It is possible that the canthin-6-one alkaloids may also undergo autoxidation of ring A in a related fashion in vivo to furnish quinone intermediates which elicit the cytotoxic activity.

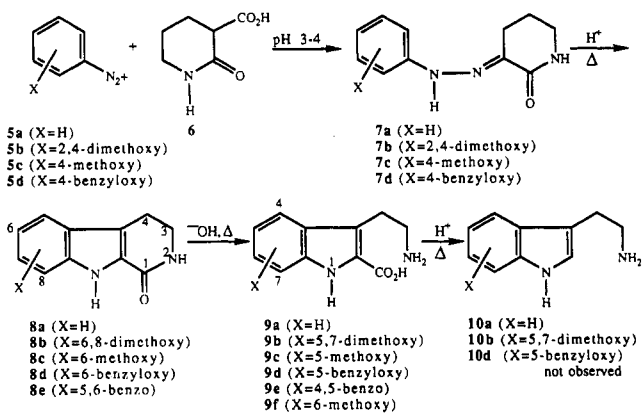
Although **1a** has recently been prepared in our laboratory,[6] current efforts have centered on the synthesis of "unnatural products" such as 1,8,10-trimethoxycanthin-6-one (**2**) to investigate the mode of action in vivo of these unique oxygenated canthin-6-ones.[2c,4] The approach requires a simple route to oxy-substituted tryptamines, the most straightforward of which was reported earlier by Abramovitch and Shapiro.[7] These authors employed a

Scheme I



3 **4**

Scheme II



5a (X=H)
5b (X=2,4-dimethoxy)
5c (X=4-methoxy)
5d (X=4-benzyloxy)

6

7a (X=H)
7b (X=2,4-dimethoxy)
7c (X=4-methoxy)
7d (X=4-benzyloxy)

8a (X=H)
8b (X=6,8-dimethoxy)
8c (X=6-methoxy)
8d (X=6-benzyloxy)
8e (X=5,6-benzo)

9a (X=H)
9b (X=5,7-dimethoxy)
9c (X=5-methoxy)
9d (X=5-benzyloxy)
9e (X=4,5-benzo)
9f (X=6-methoxy)

10a (X=H)
10b (X=5,7-dimethoxy)
10d (X=5-benzyloxy) not observed

† This paper is dedicated to Professor Gilbert Koch on the occasion of his 77th birthday.

(1) (a) For a list of structures of these alkaloids, see: Hagen, T. J. Ph.D. Thesis, University of Wisconsin—Milwaukee, Milwaukee, WI, 1988, p 164. (b) Sung, Y.-i.; Koike, K.; Nikaido, T.; Ohmoto, T.; Sankawa, U. *Chem. Pharm. Bull.* **1984**, *32*, 1872. Ohmoto, T.; Nikaido, T.; Koike, K.; Kohda, K.; Sankawa, U. *Chem. Pharm. Bull.* **1988**, *36*, 4588. Pavanand, K.; Yonganitchit, K.; Webster, H. K.; Dechatiwongse, T.; Nutakul, W.; Jewvachdamrongkul, Y.; Bansiddhi, J. *Phytother. Res.* **1988**, *2*, 33. Arbain, D.; Sargent, M. V. *Aust. J. Chem.* **1987**, *40*, 1527. Ohmoto, T.; Koike, K.; Higuchi, T.; Ikeda, K. *Chem. Pharm. Bull.* **1985**, *33*, 3356. Ohmoto, T.; Tankaka, R.; Nikado, T. *Chem. Pharm. Bull.* **1976**, *24*, 1532. Ohmoto, T.; Koike, K.; Sakamoto, Y. *Chem. Pharm. Bull.* **1981**, *29*, 390. Ohmoto, T.; Koike, K. *Chem. Pharm. Bull.* **1983**, *31*, 3198. Ohmoto, T.; Koike, K. *Chem. Pharm. Bull.* **1986**, *34*, 2090. Lassak, E. V.; Polonsky, J.; Jacquemin, H. *Phytochemistry* **1977**, *16*, 1126-27. Bowiguignon-Zylber, N.; Polonsky, J. *Chim. Ther.* **1970**, *5*, 396. Joshi, B. S.; Kamat, V. N.; Gawad, D. H. *Heterocycles* **1977**, 193.

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