are listed in Table II; Table III lists the crystallographically determined bond distances and angles (Tables I–II) (listings of observed and calculated structure factors amplitudes are available from the authors); a figure which shows a computer-generated stereodrawing with anisotropic thermal ellipsoids of the compound (5 pages). Ordering information is given on any current masthead page.

Preparation of α-Fluoro Enolates and Their Use in the Directed Aldol Reaction

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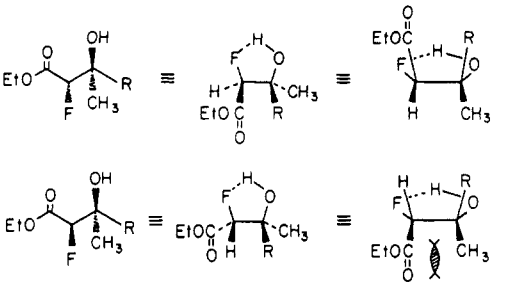
Although the directed aldol reaction has been the subject of much investigation,[1] surprisingly little has been reported about the stereochemistry of α-heteroatom substituted enolates and their utilization in directed aldol reactions. The stereoselective formation of olefins by the aldol products of silyl-substituted enolates[2] on warming has engendered speculation that formation of the aldol product is itself diastereoselective.[2d] Stereoselectively formed α-amino enolates[1a,3] may react with high diastereoselectivity.[4] In contrast, neither the stereochemistry of monohalogenated enolates[5] nor their diastereoselectivity in aldol reactions has been reported.

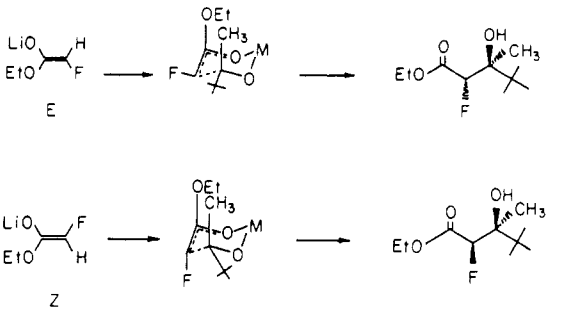
Results and Discussion

We have found that the lithium enolate of ethyl fluoroacetate may be readily prepared and efficiently utilized in the directed aldol reaction[6] (Table I). The utility of the fluoroacetate residue in compounds such as γ-fluoroglutamic acid or fluorocitric acid in discerning biochemical pathways has been limited by the difficulty of constructing the fluorinated molecules. We are currently exploring the use of this anion in the stereoselective synthesis of such specifically fluorinated natural products, where substitution by fluorine has a little steric effect but a pronounced electronic effect on the properties of the molecule. Much early work has been reported on the use of ethyl fluoroacetate in synthesis but with no indication of stereochemistry and often under conditions where the fluorohydrin would not survive.[7] Previously ethyl bromofluoroacetate,

Scheme I



Scheme II



in a Reformatsky reaction, and the lithium enolate of *tert*-butyl fluoroacetate were used in the preparation of fluorocitrate[8] and fluorohomocitric acid,[9] respectively. In both reports, difficulty in the preparation of the lithium enolate of ethyl fluoroacetate or very low yields in the attempted directed aldol reaction of the lithium enolate were described. For the introduction of the fluoroacetate residue, commercially available ethyl fluoroacetate where the ester function can be easily manipulated further is the reagent of choice.

In contrast to the low yields of aldol product reported upon enolate formation with lithium diisopropylamide (LDA) at −78 °C in the presence of 1 equiv of hexamethylphosphoric triamide (HMPA), generation of the enolate with lithium hexamethyldisilazide (LHMDS) at −78 °C resulted in consistently higher yields of aldol products (eq 1 and 2). Furthermore it was observed that

$$CH_2FCO_2CH_2CH_3 + \text{LHMDS} \rightarrow LiCHFCO_2CH_2CH_3 \quad (1)$$

$$LiCHFCO_2CH_2CH_3 + RR'CO \rightarrow RR'COHCHFCO_2CH_2CH_3 \quad (2)$$

generation of the base with methyllithium–lithium bromide complex in diethyl ether resulted in higher yields than when the base was isolated in the conventional manner.[10] Success in the generation of the enolate with LHMDS led to our reexamination of the reaction with LDA. Comparable yields of aldol products were isolated when the enolate was formed with LDA at −105 °C in the presence of HMPA. The enolate may be trapped with chlorotrimethylsilane to form the corresponding silyl enol ether (eq 3). The ratio of the *E*:*Z* enolate was found to be 1:1 by

$$LiCHFCO_2CH_2CH_3 + (CH_3)_3SiCl \rightarrow CHF{=}C(OCH_2CH_3)(OSi(CH_3)_3) \quad (3)$$

^{1}H NMR spectroscopy.[11] Not unexpectedly, the enol silyl ether–fluoroketene acetal was observed to decompose

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(11) Chemical shifts are reported in ppm from Me_4Si in carbon tetrachloride solution: 6.2, $J_{H,F}$ = 77 Hz; 6.32, $J_{H,F}$ = 74 Hz.

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Table I. Products of the Directed Aldol Reaction of Lithium Enolate of Ethyl Fluoroacetate

$LiCHFCO_2CH_2CH_3 + RR'CO \rightarrow RR'COHCHFCO_2CH_2CH_3$

	R	R′	yield, %	diastereoselectivity
1	CH_3	$(CH_3)_3C$	95	1:3.8[a]
2	CH_3	CH_2CH_3	82	1:1
3	CH_3	Ph	96	1:1.6[a]
4	CH_3	C_5H_{11}	93	1:1.1[a]
5	Ph	Ph	70	
6	2-adamantyl		75	
7	2-norbornyl		91	
8	H	$(CH_3)_3C$	85	1:3
9	H	C_6H_{13}	20	1:2
10	H	Ph	93	1:2
11	H	3,3-dimethyl-2,4-dioxol-1-yl	55	1:1.2

[a] Syn to anti.

above 50 °C. The relative ratio of *E*:*Z* enol ether differs significantly from the 95:5 ratio formed by enolization and trapping of methyl propionate under similar conditions.[12]

The relative configuration of the aldol adducts was determined by ^{13}C NMR spectroscopy employing the observations of Heathcock.[13] Fluorohydrins may be expected to exhibit a highly favored conformational preference for hydrogen bonding between fluorine and hydroxylic proton (Scheme I). Energy of the stabilization of the favored conformation has been determined to be as much as 2 kcal/mol in fluoroethanol.[14] Gauche interactions of the methyl group from methyl ketone coupling partners and the ester function of the enolate component result from this strong conformational preference. When products having the syn[15] configuration are formed, this gauche interaction may be predicted to result in an upfield shift of the methyl resonance in the ^{13}C NMR spectrum. The determination of the configuration of the major product of reaction with pinacolone as anti is in agreement with the product stereochemistry predicted for the reaction of an *E* enolate with the ketone if the Zimmerman chair-preferred transition state is applied (Scheme II). The failure to observe better diastereoselection is in agreement with our failure to observe selectivity in enolate formation. Extension of this method to aldehyde condensation products by correlation of the chemical shift of the carbon bearing fluorine and the carbinol carbon with the assignments determined for methyl ketones is not possible because no consistent chemical shift trend is observed.[13]

Single-crystal X-ray diffraction studies of the products, as well as the synthesis of appropriate derivatives of the products, are in progress to confirm relative stereochemical assignments made by NMR. Additional experiments to confirm that kinetic stereoselectivity is important in controlling product formation are also under way. The synthesis of fluorinated biologically active materials using these methods will be reported shortly.

Experimental Section

Ethyl fluoroacetate (Sigma)[6] was used without further purification. Aldehydes and ketones were purified by fractional distillation from calcium sulfate. THF was purified by distillation from sodium benzophenone ketyl. Hexamethyldisilazane and HMPA were purified by distillation from calcium hydride. Infrared spectra were recorded on a Perkin-Elmer Model 283 or 710B infrared spectrometer. ^1H magnetic resonance spectra were determined on a Varian EM-360A and a Bruker WH 90D spectrometer. ^{13}C magnetic resonance spectra were measured on a Bruker WH 90D. Analytical samples were prepared by preparative thin-layer chromatography on silica gel $F_{254,366}$ (E. Merck). Combustion analyses were performed by Galbraith Laboratories (Knoxville, TN).

Typical Procedure for Enolate Formation and Aldol Reaction. To a stirred round-bottomed flask containing 50 mL of anhydrous THF and 6.1 mL (0.03 mol) of hexamethyldisilazane was added 20 mL (0.03 mol) of a 1.5 M solution of methyllithium in diethyl ether. After methane evolution ceased the temperature was lowered to −85 °C, and 1.79 g (0.010 mol) of HMPA and 0.97 mL (0.010 mol) of ethyl fluoroacetate were added dropwise as rapidly as possible while not allowing the temperature to rise above −85 °C. After 5 additional min 0.005–0.01 mol of the carbonyl compound was added quickly. The mixture was allowed to stir 10 additional min and then was quenched at −85 °C with 5 mL of saturated ammonium chloride. On warming to room temperature the mixture was diluted with 60 mL of distilled hexanes. Separation followed by washing with four 100-mL portions of water, drying over anhydrous magnesium sulfate, and evaporation of the solvent in vacuo yielded the crude product.

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Registry No. $CH_2FC(O)OEt$, 459-72-3; $LiCHFC(O)OEt$, 83192-17-0; (*E*)-$CHF{=}C(OEt)OSiMe_3$, 92397-82-5; (*Z*)-$CHF{=}C(OEt)OSiMe_3$, 92397-83-6; (*R**,*R**)-*t*-$BuC(CH_3)(OH)CHFC(O)OEt$, 92397-84-7; (*R**,*S**)-*t*-$BuC(CH_3)(OH)CHFC(O)OEt$, 92397-85-8; (*R**,*R**)-$CH_3CH_2C(CH_3)(OH)CHFC(O)OEt$, 92397-86-9; (*R**,*S**)-$CH_3CH_2C(CH_3)(OH)CHFC(O)OEt$, 92397-87-0; (*R**,*R**)-$PhC(CH_3)(OH)CHFC(O)OEt$, 92397-88-1; (*R**,*S**)-$PhC(CH_3)(OH)CHFC(O)OEt$, 92397-89-2; (*R**,*R**)-$CH_3(CH_2)_4C(CH_3)(OH)CHFC(O)OEt$, 92397-90-5; (*R**,*S**)-$CH_3(CH_2)_4C(CH_3)(OH)CHFC(O)OEt$, 92397-91-6; $Ph_2C(OH)CHFC(O)OEt$, 427-31-6; (*R**,*R**)-*t*-$BuCH(OH)CHFC(O)OEt$, 92397-94-9; (*R**,*S**)-*t*-$BuCH(OH)CHFC(O)OEt$, 92397-95-0; (*R**,*R**)-$CH_3(CH_2)_5CH(OH)CHFC(O)OEt$, 92397-96-1; (*R**,*S*,*)-$CH_3(CH_2)_5CH(OH)CHFC(O)OEt$, 92397-97-2; (*R**,*R**)-$PhCH(OH)CHFC(O)OEt$, 50778-15-9; (*R**,*S**)-$PhCH(OH)CHFC(O)OEt$, 50778-16-0; $CH_3C(O)C(CH_3)_3$, 75-97-8; $CH_3C(O)CH_2CH_3$, 78-93-3; $CH_3C(O)Ph$, 98-86-2; $CH_3C(O)(CH_2)_4CH_3$, 110-43-0; $PhC(O)Ph$, 119-61-9; $(CH_3)_3CCHO$, 630-19-3; $CH_3(CH_2)_5CHO$, 111-71-7; PhCHO, 100-52-7; ethyl 2-hydroxy-α-fluoro-2-adamantaneacetate, 92397-92-7; ethyl 2-methyl-α-fluoro-2-norbornaneacetate, 92397-93-8; 2-adamantanone, 700-58-3; 2-norbornanone, 497-38-1.

Supplementary Material Available: Complete spectral and analytical data for all new compounds (4 pages). Ordering information is given on any current masthead page.

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(15) When the main chain of the molecule is drawn in a zig–zag fashion and the two substituents, fluorine and hydroxyl, are on the same side of plane defined by the main chain, the molecule has been described as having a syn relationship. When fluorine and hydroxyl lie on opposite sides of this plane, the relationship has been denoted as anti.

Complexation of *ent*-8,13β-Epoxylabdane-12,14-diols with Boric Acid. A Method for Establishing the C(14) Configuration[1]

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Among natural substances of the diterpene type there exist some compounds containing a vicinal glycol unit in

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