α Fluorination of Ketones. 1.[1] Direct Fluorination of Pyruvic Acid Derivatives by Using Molecular Fluorine[2]

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Direct fluorination of enol-type 3-substituted pyruvates, e.g., those having aromatic and acyl substituents, by using molecular fluorine proceeds smoothly to produce a mixture of keto- and enol-type 3-substituted 3-fluoropyruvates in moderate to good yields, while the reaction with keto-type 3-substituted pyruvates, e.g., those having alkyl substituents, gives complex mixtures of products. The resultant 3-substituted 3-fluoropyruvates have been subsequently converted into silyl enol ether derivatives, which were hydrolyzed under mild conditions to afford the crystalline enol-type 3-substituted 3-fluoropyruvates. The results obtained in this study suggest the feasibility of direct α fluorination of ketones via free enol compounds.

Replacement of hydrogens, in particular those attached to carbon, by fluorine by means of molecular fluorine has been studied over several decades,[3] as the reaction is of potential importance. Nonetheless, the use of molecular fluorine for the selective replacement of individual hydrogen atoms is rather limited, because the reaction proceeds mainly by a free-radical mechanism with little or no selectivity and produces byproducts resulting from cleavage of the organic molecule and recombination of the fragments.[4] Thus, the direct α fluorination of ketones, which was our principal concern in this study had not yet met with the same success as other halogenations using chlorine, bromine, and iodine. For instance, the reactions of some carbonyl compounds such as acetone,[5] methyl ethyl ketone,[6] and butyric acid[7] (acid chloride also) with molecular fluorine have been reported to give complex products besides the desired monofluorinated ones obtained in low yields. Surprisingly, however, hydrogen atoms in the α-position seem to resist replacement in the latter two reactions,[4] apparently being imcompatible with the radical mechanism. Recently, Barton et al.[8] discovered that fluorination of adamantane and steroid derivatives with CF_3OF and molecular fluorine in the presence of certain radical inhibitors occurred selectively at the tertiary centers, which is compelling evidence for electrophilic rather than radical mechanisms for both reactions. Hence, Rozen et al.[9] studied the reaction between fluorine and the enol acetate 5α-androst-3-ene-3,17β-diol diacetate but could not isolate any α-fluoro ketone from the resultant complicated mixture.

Meanwhile, in our previous paper[2] we reported the stereoselective synthesis of *erythro*-3-fluorophenylalanine by the reductive amination of 3-phenyl-3-fluoropyruvic acid. In that study, the starting material, methyl 3-phenyl-3-fluoropyruvate, was successfully prepared by the direct fluorination of methyl 3-phenylpyruvate predominantly existing in the enol but not the keto form. This finding appears to sharply contrast with the reported unsuccessful case with an enol acetate. Thus, aiming at extending our study of fluorinated amino acids as irreversible enzyme inhibitors, we first conducted a detailed study on the direct α fluorination of various pyruvic acid derivatives as the reaction appears to be of both practical and basic importance.

Results and Discussion

In order to obtain substrates for the reaction, we prepared some commercially unavailable 3-substituted pyruvic acids by known methods, e.g., the Claisen condensation[10] or the azlactone method.[11] Free acids were then conveniently converted into esters by using either diazomethane or diazoethane without causing keto–enol isomerization[12] of the starting acids. The compounds studied are shown in Scheme I. Here, those having mesomeric substituents such as para-substituted phenyl (**1a–d**, and **1g–i**), acyl (**1e**), and indole (**1f**) predominantly existed in the enol forms (≥90%) according to the observation of clear NMR vinyl proton signals, while those having nonmesomeric alkyl substituents (**2j–l**) were in the keto form (≥90%) as methylene proton signals were observed instead of vinyl ones. The *o*-nitrophenyl derivative (**2m**), however, predominantly existed in the keto form (≥80%) despite having a mesomeric substituent and sharply contrasted with the *p*-nitrophenyl case (**1d**).

Upon treatment with molecular fluorine (diluted with N_2 to 10% concentration) in an inert solvent [CH_3CN (1

(1) Our part 2 report entitled "α Fluorination of Ketones by Xenon and Iodobenzene Difluorides" was presented at the 7th Symposium on Fluorine Chemistry, Autumn Annual Meeting of Chemical Society Japan, Okayama, Japan, Oct 1981 (Abstracts pp 14–15), and recently has been accepted for publication in *Tetrahedron Lett.*

(2) (a) Tsushima, T.; Sato, T.; Tsuji, T. *Tetrahedron Lett.* **1980**, *21*, 3591. (b) Tsushima, T.; Nishikawa, J.; Sato, T.; Tanida, H.; Tori, K.; Tsuji, T.; Misaki, S.; Suefuji, M. *Ibid.* **1980**, *21*, 3593.

(3) The first attempt of direct fluorination using molecular fluorine was made by: Moissan, H. *C. R. Hebd. Seances Acad. Sci.* **1905**, *140*, 407.

(4) For details, see: Hudlicky, M. "Chemistry of Organic Fluorine Compounds: A Laboratory Manual"; Ellis Horwood: Chichester, England, 1976; pp 67–73.

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(7) Bockemüller, W. *Justus Liebigs Ann. Chem.* **1933**, *506*, 20.

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(11) Herbst, R. H.; Shemin, D. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, pp 1–3, 519–520.

(12) Stock, A. M.; Donahue, W. E.; Arnstutz, E. D. *J. Org. Chem.* **1958**, *23*, 1840 and references cited therein.

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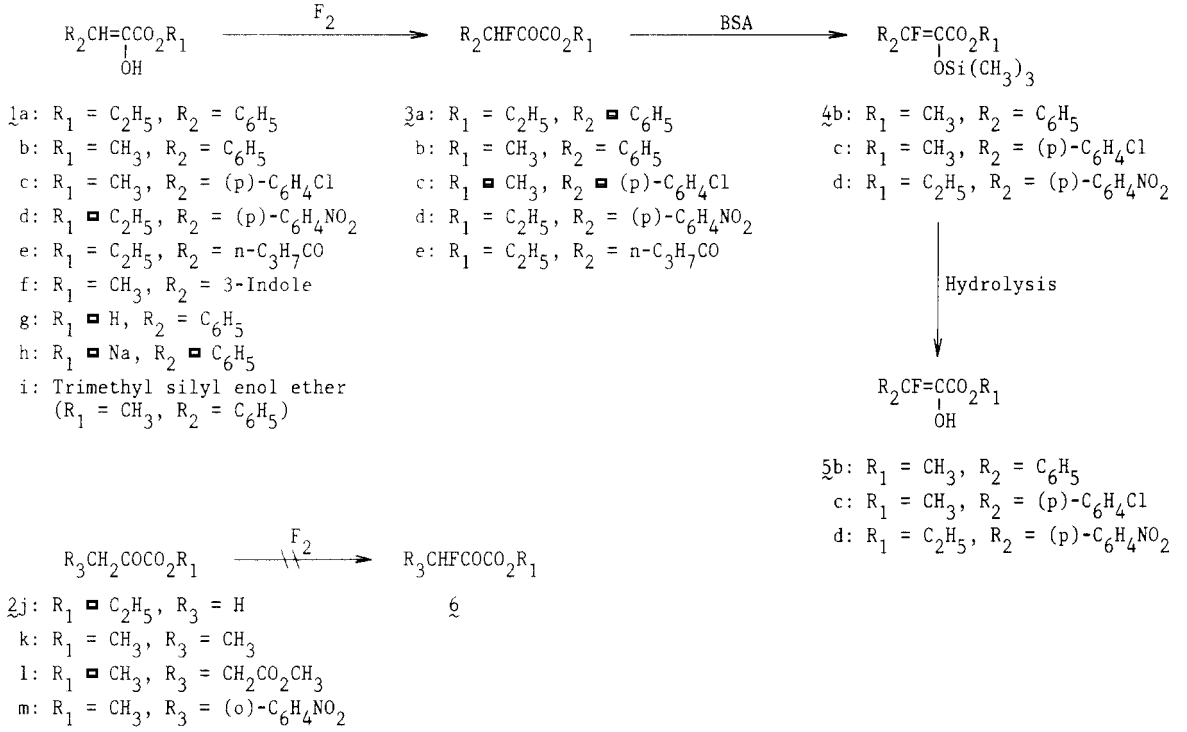
Scheme I. Direct Fluorination of 3-Substituted Pyruvates



part)/$CF_2ClCFCl_2$ (1 part) or CH_3CN only] at −10 to +10 °C for a few hours, the compounds existing in the enol form, **1a–e**, gave the desired monofluorinated products **3a–e** in 40–70% yields, while those existing in the keto form, **2j–m**, gave complex mixtures of products and not the desired ones in more than 5% yields. The free acid **1g**,[13] the sodium salt **1h**, and the trimethylsilyl enol ether **1i** ($R_2 = C_6H_5$, $R_1 = CH_3$), though existing in the enol form, gave unsuccessful results, yielding unidentified complex mixtures of products.

The IR spectra of the crude products obtained from compounds **1a–d** showed C=O absorptions at 1760, 1735, and 1690 (shoulder) cm^{-1} and OH absorption at 3450 cm^{-1}, suggesting that a mixture of keto and enol isomers of 3-substituted 3-fluoropyruvate was produced by the reaction. For characterization,[14] the crude products were converted into volatile silyl enol ether derivatives by treatment with bis(trimethylsilyl)acetamide (BSA) and then distilled under high vacuum free of oxygen. As shown in the Experimental Section, these silyl enol ethers could be well characterized as single products on the basis of mass, IR, and ^{19}F NMR spectroscopic data as well as combustion analysis done with **4c**, unambiguously demonstrating that these reactions proceeded smoothly as desired. Also, the aromatic ring clearly remained intact during the reaction. In addition, the volatile fluorinated product **3e** was easily distilled under oxygen-free conditions to afford a pure sample and was characterized (see Experimental Section).

The silyl enol ethers obtained, **4b–d**, were smoothly hydrolyzed in 70% aqueous methanol under conditions strictly excluding oxygen to afford crystalline enol-type 3-substituted 3-fluoropyruvates **5b–d**, which could be well characterized (see Experimental Section). The enol structure was unambiguously determined for these compounds on the basis of their IR α,β-unsaturated ester carbonyl absorption bands appearing at 1680–1690 cm^{-1} and the singlet ^{19}F NMR signals. These enol derivatives were very sensitive to oxygen and quickly decomposed within a few minutes when exposed to air.[15]

We now discuss the mechanistic features of direct α fluorination of ketones using molecular fluorine. To our knowledge, direct α fluorination of carbonyl compounds remains infeasible in the practical sense as described in the introduction, and the reaction mechanism has not been thoroughly established. Our present results, however, seem to provide some important mechanistic implications. Needless to say, halogenation of carbonyl compounds by halogens other than fluorine has been well established as involving both the rate-determining enolization step and the subsequent electrophilic attack on the resultant enol or enolate intermediate by positively charged halonium ions.[16] The present study clearly showed that direct fluorination proceeded satisfactorily with enol-type compounds but not with keto-type compounds which gave complex mixtures of products. We deduced from this finding that, like other halogenations, direct α fluorination generally involves the rate-determining enolization step after which the electrophilic step can proceed smoothly. However, in the case of keto-type compounds, which have a slow rate-determining enolization step, various rapid side reactions by fluorine such as hydrogen abstraction, carbon–carbon bond breaking, and addition to the carbonyl group may occur in a radical and/or nonradical manner before the rate-determining step and cause the unsuccessful results observed with the keto-type pyruvates. Thus, in order to obtain the desired results, one can see that the enolization step should be completed in advance or promoted to a much quicker process than the side re-

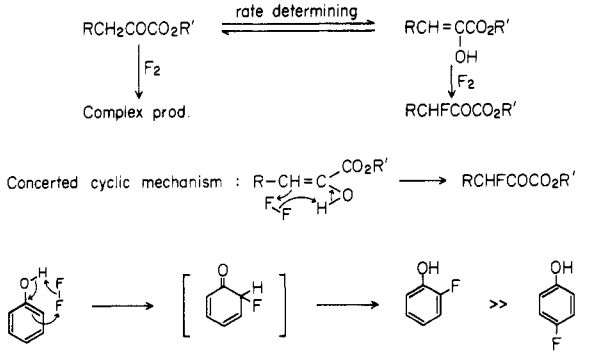
(13) Treatment of free carboxylic acids or their alkali salts with molecular fluorine has been known to lead to decarboxylation: (a) Menefee, A.; Cady, G. H. *J. Am. Chem. Soc.* **1954**, *76*, 2020. (b) Grakauskas, V. *J. Org. Chem.* **1969**, *34*, 2446.

(14) At first, we tried to separate small amounts of pure samples of **3a,c,d** by preparative VPC using 5% SE-30 column, as TLC was found to be unsuitable for the separation of these labile compounds. Although the obtained samples gave the correct compositions on combustion analysis, they were found to be mixtures containing a large amount of the keto isomer and minor enol isomers (see Experimental Section).

(15) When exposed to air (oxygen), **5c** decomposed quickly within 5 min to produce an unidentified crystalline product, mp 85–87 °C.

(16) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; pp 459–479.

Scheme II. Possible Mechanism of Direct Fluorination



actions by choosing the proper reaction conditions. Unfortunately, however, the use of both a silyl enol ether and an enol acetate[9a] has been unsuccessful, although more studies are needed before drawing any definite conclusions. The use of a metal enolate may be another choice.

Two interesting mechanistic implications were found in this present study. One is that as far as the fluorination of enol-type compounds is concerned, the possibility of radical involvement in the reaction may be excluded by the success of the reaction with the *p*-nitrophenyl case, **1d**, as nitrobenzene has been often used as a radical inhibitor.[8] The other is that, as one of the present authors[17] found previously, in the direct fluorination of phenol derivatives, a very high ortho regioselectivity is obtained, showing an ortho/para product ratio of 22/1 (see Scheme II). This regioselectivity appeared to be unusually high, compared with those of the reactions with anisole and toluene which had ratios less than 3/1.[17] This finding may support the concerted cyclic mechanism of the direct fluorination of enol compounds, as shown in Scheme II.

In conclusion, we have shown in this study that α fluorination of ketones using molecular fluorine is feasible as far as free enol compounds are concerned. The compounds prepared here appear to be potential irreversible enzyme inactivators,[18] in particular, those for pyridoxal-dependent enzymes.[19] As an extension of this work, we are currently conducting synthetic and biochemical studies of fluoro amino acids,[20] and the results will be reported in due course.

Experimental Section

General Methods. Unless otherwise stated, the uncorrected melting points were determined by using a Yanagimoto hot-stage apparatus. ^1H and ^{19}F NMR were taken on a Varian EM-360 spectrometer for solutions in $CDCl_3$ containing 1% Me_4Si and 3% C_6F_6 as an internal standard, respectively, and IR spectra were recorded on a Hitachi 215 grating spectrometer for solutions in $CHCl_3$. Mass spectra were obtained with a Hitachi RMU-6 spectrometer and GC/MS were performed on a Shimazu LKB-900 GC/MS spectrometer. Preparative and analytical VPC were carried out on a 5% silicone SE-30 column (support 80–100-mesh Chromosorb WAW DMCS) by using a Shimazu GC-RIA gas chromatograph. As most of the enol-type compounds prepared here were extremely air-sensitive (with lifetimes less than 5 min) and difficult to handle without decomposition, elementary analysis was done only with a few typical compounds.

Starting Materials for Direct Fluorination. Compounds **1d** and **1e** were prepared by the known Claisen condensation method and **1c** by the azlactone procedure. Other compounds, mostly as free acids or sodium salts, were purchased from Sigma Chemical Co. Free pyruvic acids were esterified under ice cooling by using either diazomethane or diazoethane and gave the corresponding esters without causing keto–enol isomerization of the starting acid. The resultant esters were roughly and quickly recrystallized from ether–hexane, carefully avoiding keto–enol isomerization, and used for the direct fluorination. Their ^1H NMR spectra clearly showed characteristic features of both enol- and keto-type pyruvates, respectively. The methylene proton of the keto isomer and the vinyl proton of the enol one appeared as separate signals, suggesting that both steps in the equilibrium are slow. All the compounds prepared were classified as either the keto or enol type as shown in Scheme I on the basis of their NMR and IR spectroscopic data.

Direct Fluorination. Ethyl 3-phenyl-3-fluoropyruvate (3a) was prepared as follows. In a 1-L cylindrical stainless-steel vessel equipped with a mechanical stirrer, a gas-inlet tube, and a thermometer holder, was dissolved 10 g of ethyl 3-phenylpyruvate (**1a**, 0.052 mol) in a mixture of acetonitrile (60 g) and Freon 113 (410 g), and the resulting solution was cooled to −10 °C. Next, fluorine gas (0.067 mol) diluted with nitrogen to 10% concentration was introduced over a period of 2.5 h with vigorous stirring. After the reaction mixture was treated with sodium fluoride (2 g), the solvent was removed under reduced pressure, leaving an oily residue. VPC analysis of the residue on a 5% SE-30 column showed that a large amount of a new compound had been formed and that the starting material had been completely consumed. Fractional distillation of the residue afforded ethyl 3-phenyl-3-fluoropyruvate (**3a**): 4.37 g (40%); bp 90–95 °C (1 mmHg). Preparative VPC gave the analytically pure sample: mass spectrum, *m/e* 210 (M^+), 182 (M^+ − CO), 162 (M^+ − CO − HF), 109 (C_7H_6F); IR (oxygen-free $CHCl_3$) 3450 (w, enolic OH), 1760 (s, ketone C=O), 1735 (s, ester C=O), 1690 (m, α,β-unsaturated ester C=O) cm^{-1}. Anal. Calcd for $C_{11}H_{11}O_3F$: C, 61.58; H, 5.24; F, 9.05. Found: C, 61.18; H, 5.23; F, 9.00. The IR data showed a mixture of keto (main component) and enol (minor one) isomers. Crude product **3a** was converted into a stable *erythro*-3-fluorophenylalanine which was fully characterized as reported[2] previously.

Methyl 3-Phenyl-3-fluoropyruvate (3b) and the Trimethylsilyl Enol Ether Derivative (4b). Compound **3b** was similarly prepared in approximately 50–60% yield as determined by VPC analysis. The crude reaction product obtained was dissolved in CH_2Cl_2, treated under nitrogen with a 1.5 equimolar amount of bis(trimethylsilyl)acetamide for 4 h at room temperature, and then fractionally distilled to afford **4b**: bp 93–95 °C (1–2 mmHg); IR (oxygen-free CH_3Cl) 1720 (s, ester C=O), 1630 (w, C=O), 1260–1200 (s), 1100 (m, CF) cm^{-1}; ^{19}F NMR (oxygen-free $CDCl_3$) δ 31.5 (s); mass spectrum, *m/e* 268 (M^+), 253 (M^+ − CH_3), 136 (C_8H_5OF), 109 (C_7H_6F), 108 (C_7H_5F), 89 (C_3H_9Si), 73 (C_3H_9Si).

Methyl 3-(*p*-chlorophenyl)-3-fluoropyruvate (3c) was prepared in 65% yield and characterized as follows. The sample obtained by preparative VPC had the correct analytical values, but IR spectra showed it to be a mixture containing a large amount of the keto isomer and minor amounts of enol isomers: IR (film) 3450 (m, enolic OH), 1760 (s, ketone C=O), 1740 (s, ester C=O), 1695 (m, α,β-unsaturated ester C=O), 1260–1210 (s, ester) cm^{-1}; ^1H NMR (acetone-d_6) δ 3.70 (s, 3 H, CH_3), 6.33 (d, 1 H, CHF, J = 47.9 Hz), 7.33 (s, 5 H, aromatic); ^{19}F NMR (acetone-d_6, from external CF_3COOH) δ −106.0 (d, J = 47.9 Hz); mass spectrum, *m/e* 232 and 230 (M^+), 145 and 143 (C_7H_5FCl), 107 (C_7H_4Cl). Anal. Calcd for $C_{10}H_8O_3FCl$: C, 52.06; H, 3.47; F, 8.24. Found: C, 51.81; H, 3.40; F, 8.21.

Silyl enol ether (4c) was characterized as follows: bp 130–132 °C (1 mmHg); IR (oxygen-free $CHCl_3$) 1720 (s, ester C=O), 1630 (w, C=C), 1260–1200 (s), 1105 (m, CF) cm^{-1}; ^{19}F NMR (oxygen-free $CDCl_3$) δ 29.8 (s); mass spectrum, *m/e* 304 and 302 (M^+), 289 and 287 (M^+ − CH_3), 172 and 170 (C_8H_4ClOF), 144 and 142 (C_7H_4ClF), 89 (C_3H_9OSi), 73 (C_3H_9Si). Anal. Calcd for $C_{13}H_{16}O_3FClSi$: C, 51.56; H, 5.32; Cl, 11.71; F, 6.27. Found: C, 51.04; H, 5.65; Cl, 11.24; F, 6.25.

Ethyl 3-(*p*-nitrophenyl)-3-fluoropyruvate (3d) was prepared in 46% yield and characterized as follows. The sample obtained by preparative VPC had the correct analytical values

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(18) Rando, R. R. *Acc. Chem. Res.* **1975**, *8*, 281. (b) Abeles, R. H.; Maycock, A. L. *Acc. Chem. Res.* **1976**, *9*, 313.
(19) Bey, P. *Chem. Ind. (London)* **1981**, 139.
(20) (a) Loncrini, D. F.; Filler, R. In "Advances in Fluorine Chemistry"; Butterworths: London, 1972; Vol. 6, pp 43–67. (b) Kollonitsch, J. *Isr. J. Chem.* **1978**, *17*, 58 and references cited therein.

but was found to be a mixture containing a large amount of the keto isomer and probably minor amounts of enol isomers as suggested by the IR data: IR (film) 3450 (m, enolic OH), 1760 (s, 2 C=O), 1740 (s, ester C=O), 1695 (m, α,β-unsaturated C=O), 1610 (m), 1530 and 1350 (s, NO_2), 1260–1210 (s, ester) cm^{-1}; ^1H NMR (acetone-d_6) δ 1.30 (t, 3 H, CH_3, J = 6.3 Hz), 4.50 (q, 2 H, CH_2, J = 6.3 Hz), 6.62 (d, 1 H, CHF, J = 43.2 Hz), 7.60–8.40 (m, 4 H, aromatic); ^{19}F NMR (acetone-d_6, from external CF_3COOH) δ −108.8 (d, J = 43.2 Hz); mass spectrum, m/e 255 (M^+), 183 ($M^+ - CO_2C_2H_5 + H$), 181 ($M^+ - CO_2C_2H_5 - H$), 155 ($C_7H_5NO_2F$), 154 ($C_7H_4NO_2F$), 108 (C_7H_5F), 107 (C_7H_4F). Anal. Calcd for $C_{11}H_{10}O_5N$: C, 51.76; H, 3.92; N, 5.49; F, 7.49. Found: C, 51.53; H, 3.80; N, 5.53; F, 7.25.

Silyl enol ether (4d) was characterized as follows: bp 120 °C (0.05–0.08 mmHg); IR (oxygen-free $CHCl_3$) 1720 (s, ester C=O), 1520 and 1340 (s, NO_2), 1260–1200 (s, ester) cm^{-1}; ^{19}F NMR (oxygen-free $CDCl_3$) δ 26.2 (s); mass spectrum, m/e 327 (M^+), 312 ($M^+ - CH_3$), 284 ($M^+ - CH_3 - C_2H_4$), 224 ($C_{10}H_7O_4NF$), 220 ($C_{11}H_9NO_4 + H$), 181 ($C_8H_4NO_3F$), 147 ($C_7H_4NO_2F$), 73 (C_3H_9Si).

Ethyl 3-butyryl-3-fluoropyruvate (3e) was prepared in a yield higher than 70% and characterized as follows: bp 72–78 °C (2 mmHg); IR (oxygen-free $CHCl_3$) 1760–1720 (s, probably three C=O peaks), 1650 (m, C=C of enol isomer), 1260–1200 (s, ester) cm^{-1}; mass spectrum, m/e 222 (M^+), 174 ($M^+ - CO - HF$), 131 ($M^+ - CO_2C_2H_5$), 71 (C_4H_7O), 29 (C_2H_5); ^{19}F NMR ($CDCl_3$) δ −34.2 (dt, J = 49.0 Hz, J = 3.0 Hz), 3.0 (t, J = 3.0 Hz), 47.3 (s). Anal. Calcd for $C_9H_{13}O_4F$: C, 52.94; H, 6.42; F, 9.30. Found: C, 52.65; H, 6.28; F, 9.10.

Conversion of Silyl Enol Ethers 4b–d into Enol-Type 3-Substituted 3-Fluoropyruvates 5b–d. All the experiments described here were carried out in a nitrogen drybox in order to eliminate oxygen. The silyl enol ether **4b** (200 mg) was hydrolyzed in 4 mL of oxygen-free 75% aqueous methanol at room temperature for 50–30 min, and then water was added to facilitate the precipitation of crystalline product **5b** from the solution. The resultant precipitate was collected by filtration, dried under vacuum, and recrystallized from ether–hexane to afford a pure sample in good yield (50–70%).

Compound 5b thus prepared was characterized as follows: mp (under N_2) 64–66 °C; IR (oxygen-free $CHCl_3$) 3450 (m, enolic OH), 3030 (w), 2950 (w), 1690 (s, C=O), 1580 (w), 1440 (s), 1380 (s), 1260–1180 (s, ester), 1100 (m, CF) cm^{-1}; ^{19}F NMR (oxygen-free $CDCl_3$) δ 22.7 (s), clearly suggesting that no isomer was involved; mass spectrum, m/e 196 (M^+), 134 ($M^+ - CO_2CH_3 - H$), 108 (C_7H_5F); all the spectroscopic data suggested no contamination by impurities.

Compound 5c was similarly prepared and characterized as follows: mp (under N_2) 115–120 °C (gradually decomposed from 110 °C); IR (oxygen-free $CHCl_3$) 3440 (m, enolic OH), 3030 (w), 2950 (w), 1685 (s, α,β-unsaturated ester C=O), 1590 (w), 1490 (m), 1440 (s), 1370 (s), 1100 (m, CF) cm^{-1}; ^{19}F NMR (oxygen-free $CDCl_3$) δ 21.6 (s), suggesting that no isomer was involved; mass spectrum, m/e 232 and 230 (M^+), 172 and 170 ($M^+ - CO_2CH_3 - H$), 145 and 143 (C_7H_5FCl), 144 and 142 (C_7H_4FCl), 107 (C_7H_4F). Anal. Calcd for $C_{10}H_8O_3FCl$: C, 52.08; H, 3.50; F, 8.24. Found: C, 51.93; H, 3.41; F, 8.54.

Compound 5d was similarly prepared and characterized as follows: mp (under N_2) 106–108 °C (gradually decomposed from 100 °C); IR (oxygen-free $CHCl_3$) 3430 (m, enolic OH), 3030 (w), 2950 (w), 1690 (s, α,β-unsaturated ester C=O), 1595 (w), 1520 and 1340 (s, NO_2), 1260–1200 (s, ester), 1100 (s, CF) cm^{-1}; ^{19}F NMR (oxygen-free $CDCl_3$) δ 19.8 (s), clearly suggesting that no isomer was involved; mass spectrum, m/e 255 (M^+), 181 ($M^+ - CO_2C_2H_5 - H$), 155 ($C_7H_5NO_2F$), 154 ($C_7H_4NO_2F$), 153, 107 (C_7H_4F).

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Registry No. 1a, 6362-56-7; **1b**, 80540-55-2; **1c**, 80540-56-3; **1d**, 80540-57-4; **1e**, 80540-58-5; **3a**, 79547-03-8; **3b**, 76532-83-7; **3c**, 79547-04-9; **3d**, 79547-06-1; **3e**, 79555-08-1; **4b**, 80540-59-6; **4c**, 80540-60-9; **4d**, 80540-61-0; **5b**, 80540-62-1; **5c**, 80540-63-2; **5d**, 80540-64-3; F_2, 7782-41-4.

Synthesis of the Enantiomeric Bay-Region Diol Epoxides of Benz[*a*]anthracene and Chrysene

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Both *trans*-3,4-dihydroxy-3,4-dihydrobenz[*a*]anthracene and *trans*-1,2-dihydroxy-1,2-dihydrochrysene are known proximate carcinogens of their respective hydrocarbons. The present study describes the synthesis of their (+)- and (−)-enantiomers as well as the diastereomeric pair of bay-region diol epoxides formed from each enantiomer when the double bond of the dihydrodiol ring is epoxidized either cis (isomer-1 series) or trans (isomer-2 series) to the benzylic hydroxyl group. For both hydrocarbons, (i) the tetrahydro analogues of the dihydrodiols were resolved by chromatographic separation of their diastereomeric bis esters with (−)-menthoxyacetic acid, and the resultant tetrahydrodiols were converted to the requisite dihydrodiols, and (ii) the (+)-tetrahydrodiols led to the (−)-dihydrodiols, both with (*R*,*R*) absolute configuration. Assignment of absolute configuration in the chrysene series was achieved through application of the exciton chirality circular dichroism technique to the bis[*p*-(dimethylamino)benzoate] of (−)-*trans*-1,2-dihydroxy-1,2,3,4-tetrahydrochrysene. NMR coupling patterns of the $OCOCH_2O$ hydrogens in the bis[methoxyacetic acid esters] of these vicinal trans diols were found to be diagnostic of their absolute configuration. An interesting correlation was observed upon conversion of the enantiomerically pure dihydrodiols to their diastereomeric pairs of bay-region diol epoxides; as was previously the case for (−)-*trans*-(7*R*,8*R*)-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene, the (−)-(*R*,*R*)-dihydrodiols in the chrysene and benz[*a*]anthracene series led to the (−)-diol epoxide **1** and (+)-diol epoxide **2** isomers. Of the four metabolically possible bay-region diol epoxides for each of the three hydrocarbons, tumor studies now indicate that the (+)-(*R*,*S*)-diol (*S*,*R*)-epoxide **2** isomers (designated from the carbon bearing the benzylic hydroxyl group toward the epoxide) have practically all of the tumorigenic activity.

The polycyclic aromatic hydrocarbons benz[*a*]anthracene (a) and chrysene (b) are weakly carcinogenic environmental contaminants.[1] In accord with predictions of the bay-region theory,[2] their tumorigenic activity is due