2, olefinic CH), 7.10–7.60 (m, 10, Ar H), 7.63 (s, 2, NH); IR (KBr) 1680 (C=O), 1610 (C=C) cm^{-1}; mass spectrum (20 eV), *m/e* (relative intensity) 472 (1.9, M^+), 236 (37.1, $C_6H_5NHCOCH{=}C(CH_3)OCH_2CH_2S^+$), 117 (100, $HSCH_2CH_2OC(CH_3){=}CH^+$), 93 (96.9, $C_6H_5NH_3^+$). Anal. ($C_{24}H_{28}N_2S_2O_4$) C, H, N, S.

Oxidation of Disulfide 13a to Thiolsulfinate 10a. To an ice-cooled solution of disulfide **13a** (10 mg, 0.02 mmol), obtained from the previous experiment, in chloroform (4 mL) was added a cold solution of MCPBA (80%, 4.6 mg, 0.02 mmol) in chloroform (2 mL). The reaction mixture was stirred at ice-bath temperature for 3 min and poured into ice-cold saturated sodium bicarbonate solution (5 mL). The organic layer was separated, washed with ice-cold water twice, and dried (Na_2SO_4). Evaporation of the solvent gave thiolsulfinate **10a** as an oily residue (9 mg), identical in NMR and IR spectra with the compound prepared by the previous method.

Reaction of Trans Sulfoxide 9b in DMF at 100 °C. A solution of trans sulfoxide **9b** (0.500 g, 2.60 mmol) in DMF (0.25 mL) was heated at 100 °C while stirring for 7 days. The solvent was removed to give an oily residue, which was dissolved in methylene chloride, washed with cold water, and dried (Na_2SO_4). Evaporation of the solvent gave a brown oily residue (316 mg), which was approximately a 5:3:1:1 mixture of respectively isomeric dihydro-1,4-oxathiin **4b**, dihydro-1,4-oxathiin **1b**, disulfide **13b**, and trans sulfoxide **9b** as determined by NMR. These were separated by preparative TLC using 9:9:2 (v/v) methylene chloride–hexane–ethyl acetate as eluant. The first band (R_f 0.8), the second (R_f 0.7), the third (R_f 0.5), and the fourth (R_f 0.3) were respectively extracted with a 1:1 mixture of chloroform and methanol to give **1b** (90 mg), **4b** (148 mg), **13b** (33 mg), and **9b** (11 mg).

For **4b**: bp 93–95 °C (10 mmHg); ^1H NMR (60 MHz) ($CDCl_3$) δ 2.93 (t, J = 4.5 Hz, 5-CH_2), 3.07 (s, 2, CH_2CO), 3.70 (s, 3, OCH_3), 4.30 (t, 2, J = 4.5 Hz, 6-CH_2), 5.05 (s, 1, olefinic CH); IR (NaCl) 1740 (C=O) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 174 (74.8, M^+), 115 (94.0, $M^+ - CO_2CH_3$), 101 (94.5, $M^+ - CH_2CO_2CH_3$). Anal. ($C_7H_{10}O_3S$) C, H, S.

For **13b**: ^1H NMR (60 MHz) ($CDCl_3$) δ 2.30 (s, 6, CH_3), 3.00 (t, 4, J = 6 Hz, CH_2S), 3.67 (s, 6, OCH_3), 4.07 (t, 4, J = 6 Hz, CH_2O), 5.07 (s, 2, olefinic CH). Anal. ($C_{14}H_{22}O_6S_2$) C, H, S.

Oxidation of Disulfide 13b to Thiolsulfinate 10b. To a solution of disulfide **13b** (7 mg, 0.02 mmol), obtained from the foregoing experiment, in chloroform-*d* (0.4 mL) was added a solution of MCPBA (80%, 4.6 mg, 0.02 mmol) in chloroform-*d* (0.2 mL). The reaction mixture was shaken at 34 °C for 5 min and poured into ice-cold saturated sodium bicarbonate solution (5 mL). The organic layer was separated, washed with ice-cold water, and dried (Na_2SO_4). Evaporation of the solvent gave thiolsulfinate **10b** as an oily residue (6 mg), identical in NMR spectrum with that of the compound prepared by the previous method.

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Registry No. **1a**, 5234-68-4; **1b**, 102437-87-6; **2a**, 56537-72-5; **4a**, 102437-90-1; **4b**, 102437-92-3; **7a**, 67980-06-7; **7b**, 80563-95-7; **8a**, 68563-70-2; **8b**, 102437-84-3; **9a**, 68563-71-3; **9b**, 102437-85-4; **10a**, 102437-86-5; **10b**, 102437-88-7; **12a**, 102-01-2; **12b**, 105-45-3; **13a**, 102437-91-2; **13b**, 102437-93-4; **16**, 102437-94-5; **17**, 102437-89-8.

Synthetic Approach to Versatile Chiral Molecules Containing a Fluorine Atom

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Studies of the synthetic tools for the preparation of chiral monofluorinated compounds, involving microbial asymmetric reduction, are described. The preparation and utility of such chiral monofluorinated compounds are reported.

Our studies of the synthetic utility of fluoro olefins have focused on the use of an extremely versatile building block in the preparations of α-fluorinated ketones, a group of compounds which reflect increasing interest in the molecular design concerning the biological activities.[1-4] However, no general stereocontrolled synthetic approach to chiral monofluorinated synthons, for a key process to achieve the above purpose, has been reported except a few approaches to a suicide inactivator.[5-8]

In our previous paper, we have reported that microbial transformation can be a useful synthetic technique for preparing optically active fluorinated compounds.[9-15]

As part of our continuing interest in preparing versatile chiral synthons in fluorine chemistry,[12-15] we now report the use of microorganisms to prepare chiral fluorinated synthons.[16-22]

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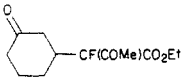
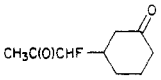
Table I. Michael Addition

RC(O)CHFCO$_2$Et, R =	Michael acceptor	product[a]	reactn time (h)	yield (%)	bp, °C (mmHg)
Me	CH_2=CHC(O)CH_3	$CH_3C(O)CH_2CH_2CF(COMe)CO_2Et$	1	99	95–97 (0.6)
Me	CH_2=CHC(O)CH_2CH_3	$CH_3CH_2C(O)CH_2CH_2CF(COMe)CO_2Et$	1	99	85–87 (0.5)
Me			24	99	117–119 (0.6)
Me	CH_2=CHCO$_2$Et	$CH_3CH_2OC(O)CH_2CH_2CF(COMe)CO_2Et$	1	84	96–97 (0.9)
Me	(*E*)-CH_3CH=CHCO$_2$Me	$CH_3OC(O)CH_2CH_2CF(COMe)CO_2Et$	24	54	95–98 (0.9)
Et	CH_2=CHC(O)CH_3	$CH_3C(O)CH_2CH_2CF(COEt)CO_2Et$	2	89	92–94 (0.7)
Et	CH_2=CHC(O)CH_2CH_3	$CH_3CH_2C(O)CH_2CH_2CF(COEt)CO_2Et$	2	92	88–91 (0.6)
n-Pr	CH_2=CHC(O)CH_3	$CH_3C(O)CH_2CH_2CF(COPr)CO_2Et$	2	78	91–94 (0.4)
n-Pr	CH_2=CHC(O)CH_2CH_3	$CH_3CH_2C(O)CH_2CH_2CF(COPr)CO_2Et$	2	82	86–88 (0.3)
n-Bu	CH_2=CHC(O)CH_3	$CH_3C(O)CH_2CH_2CF(COBu)CO_2Et$	3	86	86–89 (0.3)
n-Bu	CH_2=CHC(O)CH_2CH_3	$CH_3CH_2C(O)CH_2CH_2CF(COBu)CO_2Et$	3	84	98–101 (0.4)

[a] Structures of these products are established from spectral data. For the new compounds the microanalysis was in satisfactory agreement with the calculated values (C, H, N; ±0.5%).

Table II. Preparation of Fluorinated 1,5-Diketones

product[a]	reactn conditn	reactn time (day)	yield (%)	bp, °C (mmHg)
$CH_3C(O)CHFCH_2CH_2C(O)CH_3$	6 N HCl/EtOH	8	76	80–83 (9)
$CH_3C(O)CHFCH_2CH_2C(O)CH_2CH_3$	1 N HCl/EtOH	10	52	81–83 (9)
	6 N HCl/EtOH	14	64	76–79 (3)
$CH_3CH_2C(O)CHFCH_2CH_2C(O)CH_3$	1 N HCl/EtOH	10	56	84–85 (8)
$CH_3CH_2C(O)CHFCH_2CH_2C(O)CH_2CH_3$	6 N HCl/EtOH	6	47	86–88 (8)
$CH_3CH_2CH_2C(O)CHFCH_2CH_2C(O)CH_3$	6 N HCl/EtOH	10	61	79–82 (6)
$CH_3CH_2CH_2C(O)CHFCH_2CH_2C(O)CH_2CH_3$	6 N HCl/EtOH	10	46	82–85 (5)
$CH_3CH_2CH_2CH_2C(O)CHFCH_2CH_2C(O)CH_3$	6 N HCl/EtOH	10	53	78–81 (3)

[a] Structures of these products are confirmed by spectral data. For the new compounds the microanalysis was in satisfactory agreement with the calculated values (C, H, N; ±0.5%).

Table III. Formation of α-Fluoro-α-substituted-β-keto Esters

RC(O)CHFCF$_2$Cl, R =	allylic alcohol	product[a]	yield (%)
Me	CH_2=$CHCH_2OH$	$CH_3C(O)CF(CH_2CH$=$CH_2)CO_2CH_2CH$=CH_2	46
Me	(*E*)-CH_3CH=$CHCH_2OH$	$CH_3C(O)CF(CHCH$=$CH_2)CO_2CH_2CH$=$CHCH_3$ (CH$_3$ on CHCH$_2$)	36
Me	CH_2=$CHCH(OH)CH_3$	$CH_3C(O)CF(CH_2CH$=$CHCH_3)CO_2CH(CH_3)CH$=CH_2	31
Et	CH_2=$CHCH_2OH$	$CH_3CH_2C(O)CF(CH_2CH$=$CH_2)CO_2CH_2CH$=CH_2	54
Et	(*E*)-CH_3CH=$CHCH_2OH$	$CH_3CH_2C(O)CF(CH_2CH$=$CH_2)CO_2CH_2CH$=CH_2 (CH$_3$ on CH$_2$CH)	38
Et	CH_2=$CHCH(OH)CH_3$	$CH_3CH_2C(O)CF(CH_2CH$=$CHCH_3)CO_2CH(CH_3)CH$=CH_2	26
n-Pr	CH_2=$CHCH_2OH$	$CH_3CH_2CH_2C(O)CF(CH_2CH$=$CH_2)CO_2CH_2CH$=$CH_2$	44
n-Bu	CH_2=$CHCH_2OH$	$CH_3CH_2CH_2CH_2C(O)CF(CH_2CH$=$CH_2)CO_2CH_2CH$=$CH_2$	52

[a] Structures were also confirmed by spectral data. For the new compounds the microanalysis was in satisfactory agreement with the calculated values (C, H, N; ±0.5%).

Results and Discussion

Preparation of α-Fluoro 1,5-Diketones with a Fluorine Atom from α-Fluoro-β-keto Esters. The Michael addition reaction between α-fluoro-β-keto esters obtained from trifluoroethene and α,β-unsaturated ketones and/or esters proceeded at room temperature in the presence of spray-dried potassium fluoride.[23]

Although various bases such as NaH, *t*-BuOK, MeONa, EtONa, Et_3N, etc., were examined in this system, only spray-dried potassium fluoride effected the Claisen condensation smoothly (Table I). The data in Table I indicate that the reaction proceeded smoothly, except for acrylonitrile and crotonaldehyde, which produced many compounds.

Table IV. Preparation of α-Fluoro Ketones

product[a]	yield (%)	bp, °C (mmHg)
$CH_3C(O)CHFCH_2CH$=CH_2	56	76–78 (28)
$CH_3C(O)CHFCH(CH_3)CH$=CH_2	52	74–76 (30)
$CH_3C(O)CHFCH_2CH$=$CHCH_3$	58	75–79 (26)
$CH_3CH_2C(O)CHFCH_2CH$=CH_2	61	76–78 (27)
$CH_3CH_2C(O)CHFCH(CH_3)CH$=$CH_2$	47	80–83 (31)
$CH_3CH_2C(O)CHFCH_2CH$=$CHCH_3$	54	79–82 (28)
$CH_3CH_2CH_2C(O)CHFCH_2CH$=$CH_2$	55	84–86 (23)
$CH_3CH_2CH_2CH_2C(O)CHFCH_2CH$=$CH_2$	59	83–86 (21)

[a] Structures were also confirmed by spectral data. For the new compounds the microanalysis was in satisfactory agreement with the calculated values (C, H, N; ±0.5%).

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Table V. Asymmetric Reduction of α-Fluoro Ketones by Bakers' Yeast

product[a]	yield (%)	bp, °C (mmHg)	diastereomeric ratio[b]	enantiomeric % ee	excess
$CH_3CH(OH)CHFCH_2CH{=}CH_2$	58	80–82 (8)	72/28	86	76
$CH_3CH_2CH(OH)CHFCH_2CH{=}CH_2$	64	81–84 (4)	68/32	75	54
$CH_3CH_2CH_2CH(OH)CHFCH_2CH{=}CH_2$	38	86–89 (2)	56/44	79	45
$CH_3CH_2CH_2CH_2CH(OH)CHFCH_2CH{=}CH_2$	42	95–97 (2)	58/42	64	47

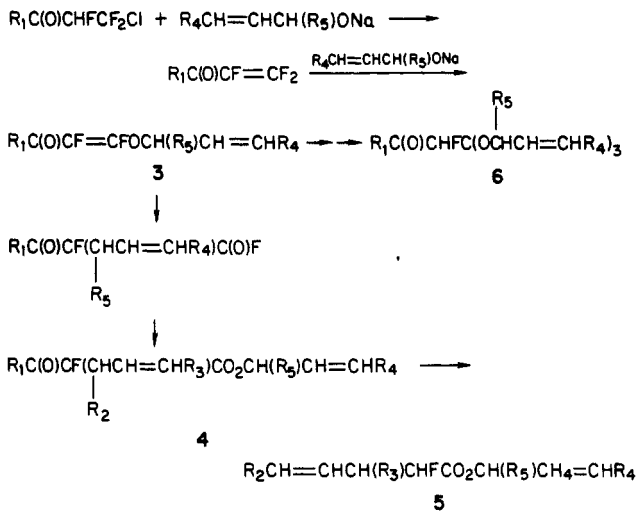
[a] Structures were also confirmed by spectral data. For the new compounds the microanalysis was in satisfactory agreement with the calculated value (C, H, N; ±0.5%). [b] Diastereomeric ratio was determined by ^{19}F NMR signal intensities.

Table VI. Asymmetric Reduction of 1,5-Diketones by Bakers' Yeast

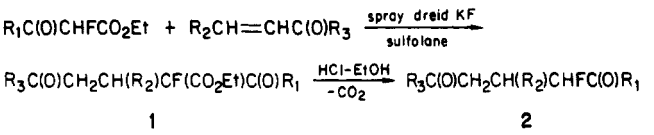
substrate	reactn time (day)	product[a] yield (%) 9	10	diastereomeric ratio[b] 9
$CH_3C(O)CHFCH_2CH_2C(O)CH_3$	1	61	4	73/27
	5	2	65	
$CH_3C(O)CHFCH_2CH_2C(O)CH_2CH_3$	1	58	2	66/34
	5	5	49	
$CH_3CH_2C(O)CHFCH_2CH_2C(O)CH_3$	1	62	7	68/32
	5	2	57	
$CH_3CH_2C(O)CHFCH_2CH_2C(O)CH_2CH_3$	1	54	5	58/42
	5	7	51	
$CH_3CH_2CH_2C(O)CHFCH_2CH_2C(O)CH_3$	1	48	16	71/29
	5	6	52	
$CH_3CH_2CH_2C(O)CHFCH_2CH_2C(O)CH_2CH_3$	1	51	8	63/37
	5	6	46	
$CH_3CH_2CH_2CH_2C(O)CHFCH_2CH_2C(O)CH_3$	1	62	2	55/45
	5	4	48	

[a] Structures were confirmed by spectral data. For the new compounds the microanalysis was satisfactory agreement with the calculated value (C, H, N; ±0.5%). [b] Diastereomeric ratio was determined by ^{19}F NMR signal intensities.

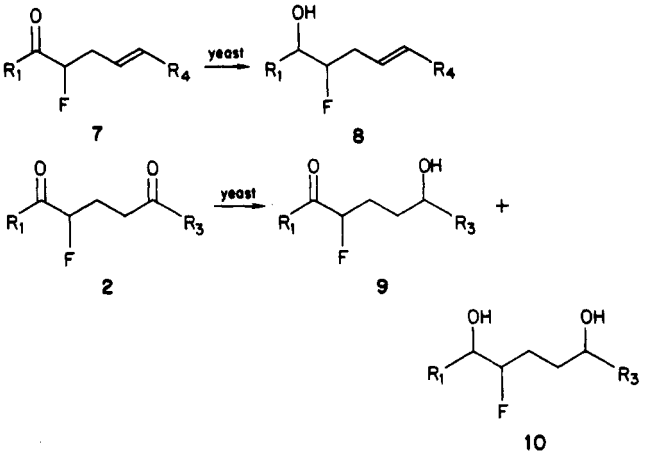
Scheme I



Scheme II



Scheme III



Decarboxylation[24] using the HCl–EtOH system was most effective in forming the desired fluorinated 1,5-diketones. The products were separated and purified by column chromatography on silica gel. The reactions are summarized in Scheme I.

Preparation of α-Fluoro Ketones Using Alkyl Trifluorovinyl Ketones. In a previous paper,[25] we have reported the synthesis of alkyl trifluorovinyl ketones from alkyl 2-chloro-1,2,2-trifluoroethyl ketones. We have now designed a new synthetic route to α-fluoro ketones. Trifluorovinyl ethers, prepared in the first step, rearrange to α-fluoro-α-substituted-β-keto esters by reaction with various types of allylic alcohols. The synthesis proceeds according to the reactions in Scheme II.

This experimental procedure is simple, involving the dropwise addition of alkoxide in diethyl ether solution to the solution of alkyl 2-chloro-1,2,2-trifluoroethyl ketones and ether at 5–10 °C.

The most interesting feature of the sequence is the direct formation of α-fluoro-α-substituted-β-keto esters **5**, whose structures were assigned by analytical and spectroscopic data. The intermediate difluorovinyl ether, which is known to be an unstable material, could not be isolated. The transformation of α-fluoro-α-substituted-β-keto esters **4** to the corresponding α-fluoro ketones **7** by decarboxylation proceeded readily under the conditions described earlier.

$$R_1C(O)CF(CHR_3CH{=}CHR_2)CO_2CH(R_5)CH{=}CHR_4 \quad \mathbf{4}$$

$$\xrightarrow{HCl/EtOH} R_1C(O)CHFCH(R_5)CH{=}CHR_4 \quad \mathbf{7}$$

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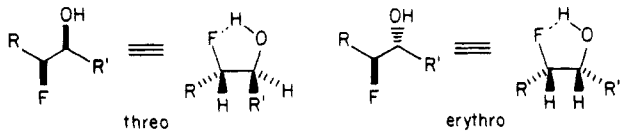
Table VII. NMR Spectra of Compounds 8

product	^{19}F NMR	^{1}H NMR
$CH_3CH(OH)CHFCH_2CH{=}CH_2$		
threo	92.5 (m, $J_{F\text{-}H_{gem}}$ = 49 Hz, $J_{F\text{-}H_{vic}}$ = 18 Hz, $J_{F\text{-}CH_2}$ = 14 Hz)	1.25 (CH_3, d, $J_{CH_3\text{-}CH}$ = 7.1 Hz), 2.64 (CH_2, m), 4.25 (CHF, m), 4.54 (CHOH, m, $J_{CH\text{-}CH}$ = 6.5 Hz), 4.89–5.10 (m, 2 × H), 5.82 (m, 2 × H)
erythro	94.0 (m, $J_{F\text{-}H_{vic}}$ = 16 Hz)	1.26 (CH_3, d), 2.65 (CH_2, m), 4.25 (CHF, m), 4.76 (CHOH, m, $J_{CH\text{-}CH}$ = 4.1 Hz), 4.87–5.09 (m, 2 × H), 5.82 (m, 2 × H)
$CH_3CH_2CH(OH)CHFCH_2CH{=}CH_2$		
threo	92.6 (m, $J_{F\text{-}H_{gem}}$ = 42 Hz, $J_{F\text{-}H_{vic}}$ = 19 Hz, $J_{F\text{-}CH_2}$ = 13 Hz)	1.12 (CH_3, t, $J_{CH_3\text{-}CH_2}$ = 7.5 Hz), 2.53–2.67 (m, 4 × H), 4.28 (CHF, m), 4.57 (CHOH, m, $J_{CH\text{-}CH}$ = 6.7 Hz), 4.86–5.16 (m, 2 × H), 5.87 (m, 2 × H)
erythro	94.5 (m, $J_{F\text{-}H_{vic}}$ = 17 Hz)	1.12 (CH_3, t), 2.50–2.69 (m, 4 × H), 4.27 (m, CHF), 4.78 (CHOH, m, $J_{CH\text{-}CH}$ = 4.0 Hz), 4.85–5.16 (m, 2 × H), 5.87 (m, 2 × H)
$CH_3CH_2CH_2CH(OH)CHFCH_2CH{=}CH_2$		
threo	93.1 (m, $J_{F\text{-}H_{gem}}$ = 44 Hz, $J_{F\text{-}H_{vic}}$ = 17 Hz, $J_{F\text{-}CH_2}$ = 13 Hz)	1.08 (CH_3, t, $J_{CH_3\text{-}CH_2}$ = 6.8 Hz), 2.12–2.89 (6 × H), 4.31 (CHF, m), 4.61 (CHOH, m, $J_{CH\text{-}CH}$ = 6.7 Hz), 4.85–5.14 (m, 2 × H), 5.82 (m, 2 × H)
erythro	95.4 (m, $J_{F\text{-}H_{vic}}$ = 15 Hz)	1.09 (CH_3, t), 2.13–2.92 (6 × H), 4.29 (CHF, m), 4.79 (CHOH, m, $J_{CH\text{-}CH}$ = 4.2 Hz), 4.86–5.13 (m, 2 × H), 5.86 (m, 2 × H)
$CH_3CH_2CH_2CH_2CH(OH)CHFCH_2CH{=}CH_2$		
threo	92.5 (m, $J_{F\text{-}H_{gem}}$ = 40 Hz, $J_{F\text{-}H_{vic}}$ = 17 Hz, $J_{F\text{-}CH_2}$ = 12 Hz)	0.98 (CH_3, t, $J_{CH_3\text{-}CH_2}$ = 6.9 Hz), 2.31–2.72 (8 × H), 4.27 (CHF, m), 4.54 (CHOH, m, $J_{CH\text{-}CH}$ = 6.7 Hz), 4.81–5.09 (m, 2 × H), 5.79 (2 × H)
erythro	94.3 (m, $J_{F\text{-}H_{vic}}$ = 14 Hz)	0.98 (CH_3, t), 2.32–2.74 (8 × H), 4.29 (CHF, m), 4.75 (CHOH, m, $J_{CH\text{-}CH}$ = 4.2 Hz), 4.82–5.07 (m, 2 × H), 5.82 (2 × H)

Asymmetric Induction with Bakers' Yeast. Our stereocontrolled route to fluorinated synthons led to a search for a new approach to versatile chiral monofluorinated materials from the achiral ones, as shown in Scheme III.

The microbial transformation of α-fluoro ketones proceeded smoothly to give the corresponding α-fluoro carbinols with high diastereoselectivity. After separating the diastereomers by GLC, the diastereomeric and/or enantiomeric ratios were determined by ^{19}F NMR signal intensities after conversion of the hydroxy compound to its diastereomeric ester with optically active MTPA and/or optically active perfluorocarboxylic acids.[25]

The diastereomeric erythro and/or threo configurations of 4-fluoro-5-hydroxy-1-heptene exhibited a diastereoselectivity of 72/28 threo/erythro, which was determined by the coupling constant [$J_{H\text{-}H_{vic}}$(threo) > $J_{H_{vic}}$(erythro)] of the ^{1}H NMR spectrum. The fluorohydrins have been suggested to exhibit a highly favored conformational preference for hydrogen bonding between fluorine and the hydroxylic proton.[26-29]



However, when the reduction was applied to some 1,5-diketones containing a fluorine atom, bakers' yeast was found to reduce those diketones to produce mainly the diols **10**, along with minor amounts optically active carbinols **9**, after fermenting for 5 days.

This newly developed microbial approach to chiral monofluorinated synthons offers a convenient practical synthetic route to asymmetric induction with high enantio- and/or diastereoselection. The microbial approach developed here may open up a new avenue for biologically active compounds containing fluorine.

Experimental Section

General Procedures. All commercial reagents were used without purification. Solvents, e.g., ether and sulfolane, were purified by distillation. Infrared spectra were obtained by using a Jasco A-102 spectrometer and KBr pellets. The ^{1}H (internal Me_4Si) and ^{19}F (external CF_3CO_2H) NMR spectra were recorded by using a Varian EM-390 spectrometer. Mass spectra were obtained with a Hitachi M-52 spectrometer at 20 eV. All microbial transformations were carried out in the Jarfermentor. Yields were those of the products actually isolated.

Ethyl 2-Fluoro-2-acetyl-5-oxohexanoate. Into a flask (100 mL) was stirred a suspension of spray-dried potassium fluoride (1.8 g, 30 mmol), ethyl 2-fluoroacetoacetate (1.48 g, 10 mmol), and methyl vinyl ketone (1.05 g, 15 mmol) in freshly dried sulfolane (10 mL) at room temperature. After 10 h of stirring, the mixture was poured into water and the oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate and the solvent was removed. Distillation gave ethyl 2-fluoro-2-acetyl-5-oxohexanoate in quantitative yield. The molecular ion (M^+, m/e 218) and other appropriate fragment peaks appeared in the mass spectrum.

3-Fluoro-2,6-heptanedione. A mixture of ethyl 2-fluoro-2-acetyl-5-oxohexanoate (2.2 g, 10 mmol) and 6 N HCl (20 mL) in ethanol (20 mL) was stirred at room temperature. After 8 days of stirring, the reaction mixture was poured into water, and then the oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate and the solvent was removed. Distillation gave 3-fluoro-2,6-heptadione in 76% yield. In the mass spectrum, the molecular ion (M^+, m/e 146) appeared.

Reaction of 4-Chloro-3,4,4-trifluoro-2-butanone with Allylic Alcoholates. Into a solution of 4-chloro-3,4,4-trifluoro-2-butanone (1.6 g, 10 mmol) in freshly dried diethyl ether (20 mL), cooled in an ice–water bath, was added slowly over 30 min. A solution of sodium allyl alcoholate, which was prepared from allyl alcohol (2 g, 34 mmol) and sodium hydride (0.86 g, 36 mmol) in freshly dried diethyl ether (20 mL), so that the reaction temperature remained below 10 °C. After the mixture was stirred for 1 h at that temperature, the whole was quenched by 1 N HCl below 10 °C. Oily material was extracted with diethyl ether, and

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(28) Welch, J. T.; Seper, K.; Eswarakrishnan, S.; Samartino, J. *J. Org. Chem.* **1984**, *49*, 4720.
(29) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

then the ethereal layer was dried over anhydrous magnesium sulfate. After the solvent was removed, the residue was purified by column chromatography using a mixture of *n*-hexane–diethyl ether (5:1) as eluent (yield 46%).

3-Fluoro-5-heptan-2-one. A mixture of the compound (2.0 g, 10 mmol), prepared from the reaction of 4-chloro-3,4,4-trifluoro-2-butanone with sodium allyl alcoholate, and 1 N NaOH solution (20 mL) in ethanol (20 mL) was stirred at room temperature. After 1 h of stirring, the reaction mixture was acidified by 6 N HCl, and then the whole solution was stirred for 2 h at room temperature. The mixture was poured into water and oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate. After removing the solvent, distillation gave 3-fluoro-5-heptan-2-one in 56% yield. The molecular ion (M^+, m/e 116) and other appropriate fragment peaks appeared in the mass spectrum.

4-Fluoro-5-hydroxy-1-heptene. A suspension of active fermenting bakers' yeast (Oriental Yeast Co. Ltd.) (50 g) and soluble starch (Wako's 1st grade, 75 g) in a buffer solution [600 mL, pH 7.3; prepared from $^1/_{15}$ M aqueous Na_2HPO_4 solution (460.8 mL) and $^1/_{15}$ M aqueous KH_2PO_4 solution (139.2 mL)] was stirred for 1 h at 35–36 °C in Jarfermentor (M-100, Tokyo Rikakikai Co. Ltd.). Into the mixture was added 3-fluoro-5-heptan-2-one (5 g), and then the whole mixture was stirred at 35–36 °C. After 3 days of stirring, the flocculant (200 ppm solution prepared from p-713, Dai-ichi Kogyo Seiyaku, 100 mL) was added into the stirring mixture for a few minutes. After standing for 1 h, the mixture was acidified with 1 N HCl solution, and then the precipitates were separated by filtration. The oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate and the solvent was removed. Distillation gave 4-fluoro-5-hydroxy-1-heptene in 58% yield.

Registry No. 1 (R_1 = R^3 = Me, R_2 = H), 88100-62-3; 1 (R_1 = Me, R_2 = H, R_3 = Et), 88100-63-4; 1 (R_1 = Me, R_2 = H, R_3 = OEt), 2586-30-3; 1 (R_1 = Me, R_2 = H, R_3 = OMe), 88100-69-0; 1 (R_1 = Et, R_2 = H, R_3 = Me), 102283-24-9; 1 (R_1 = Et, R_2 = H, R_3 = Et), 102283-25-0; 1 (R_1 = Pr, R_2 = H, R_3 = Me), 102283-26-1; 1 (R_1 = Pr, R_2 = H, R_3 = Et), 102283-27-2; 1 (R_1 = Bu, R_2 = H, R_3 = Me), 102283-28-3; 1 (R_1 = Bu, R_2 = H, R_3 = Et), 102434-48-0; 2 (R_1 = Et, R_2 = H, R_3 = Me), 102283-30-7; 2 (R_1 = R_3 = Et, R_2 = H), 102283-31-8; 2 (R_1 = Pr, R_2 = H, R_3 = Me), 102283-32-9; 2 (R_1 = Pr, R_2 = H, R_3 = Et), 102283-33-0; 2 (R_1 = Bu, R_2 = H, R_3 = Me), 102283-34-1; 2 (R_1 = R^3 = Me, R_2 = H), 88100-72-5; 2 (R_1 = Me, R_2 = H, R_3 = Et), 88100-64-5; 4 (R_1 = Me, R_2 = R_3 = R_4 = R_5 = H), 102283-35-2; 4 (R_1 = R_2 = R_4 = Me, R_3 = R_5 = H), 102283-36-3; 4 (R_1 = R^3 = R_5 = Me, R_2 = R_4 = H), 102283-37-4; 4 (R_1 = Et, R_2 = R_3 = R_4 = R_5 = H), 102283-38-5; 4 (R_1 = Et, R_2 = Me, R_3 = R_4 = R_5 = H), 102283-39-6; 4 (R_1 = Et, R_2 = R_4 = H, R_3 = R_5 = Me), 102283-40-9; 4 (R_1 = Pr, R_2 = R_3 = R_4 = R_5 = H), 102283-41-0; 4 (R_1 = Bu, R_2 = R_3 = R_4 = R_5 = H), 102283-42-1; 7 (R_1 = Me, R_4 = R_5 = H), 2021-74-1; 7 (R_1 = R_5 = Me, R_4 = H), 102283-45-4; 7 (R_1 = R_4 = Me, R_5 = H), 102283-46-5; 7 (R_1 = Et, R_4 = R_5 = H), 102283-47-6; 7 (R_1 = Et, R_4 = H, R_5 = Me), 102283-48-7; 7 (R_1 = Et, R_4 = Me, R_5 = H), 102283-49-8; 7 (R_1 = Pr, R_4 = R_5 = H), 102283-50-1; 7 (R_1 = Bu, R_4 = R_5 = H), 102283-51-2; *threo*-8 (R_1 = Me, R_4 = H), 102283-52-3; *erythro*-8 (R_1 = Me, R_4 = H), 102283-53-4; *threo*-8 (R_1 = Et, R_4 = H), 102283-54-5; *erythro*-8 (R_1 = Et, R_4 = H), 102283-55-6; *threo*-8 (R_1 = Pr, R_4 = H), 102283-56-7; *erythro*-8 (R_1 = Pr, R_4 = H), 102283-57-8; *threo*-8 (R_1 = Bu, R_4 = H), 102283-58-9; *erythro*-8 (R_1 = Bu, R_4 = H), 102283-59-0; *threo*-9 (R_1 = R_3 = Me), 102283-60-3; *erythro*-9 (R_1 = R_3 = Me), 102283-74-9; *threo*-9 (R_1 = Me, R_3 = Et), 102283-62-5; *erythro*-9 (R_1 = Me, R_3 = Et), 102305-62-4; *threo*-9 (R_1 = Et, R_3 = Me), 102283-64-7; *erythro*-9 (R_1 = Et, R_3 = Me), 102283-75-0; *threo*-9 (R_1 = R_3 = Et), 102283-66-9; *erythro*-9 (R_1 = R_3 = Et), 102283-76-1; *threo*-9 (R_1 = Pr, R_3 = Me), 102283-68-1; *erythro*-9 (R_1 = Pr, R_3 = Me), 102283-77-2; *erythro*-9 (R_1 = Pr, R_3 = Et), 102283-70-5; *erytrho*-9 (R_1 = Pr, R_3 = Et), 102305-82-8; *threo*-9 (R_1 = Bu, R_3 = Me), 102283-72-7; *erythro*-9 (R_1 = Bu, R_3 = Me), 102283-78-3; 10 (R_1 = R_3 = Me), 102283-61-4; 10 (R_1 = Me, R_3 = Et), 102283-63-6; 10 (R_1 = Et, R_3 = Me), 102283-65-8; 10 (R_1 = R_3 = Et), 102283-67-0; 10 (R_1 = Pr, R_3 = Me), 102283-69-2; 10 (R_1 = Pr, R_3 = Et), 102283-71-6; 10 (R_1 = Bu, R_3 = Me), 102283-73-8; $MeC(O)CHFCO_2Et$, 1522-41-4; $EtC(O)CHFCO_2Et$, 759-67-1; *n*-$PrC(O)CHFCO_2Et$, 76435-44-4; *n*-$BuC(O)CHFCO_2Et$, 102283-29-4; $CH_2{=}C(O)CH_3$, 78-94-4; $CH_2{=}CHC(O)CH_2CH_3$, 1629-58-9; $CH_2{=}CHCO_2Et$, 140-88-5; (*E*)-$CH_3CH{=}CHCO_iMe$, 623-43-8; $MeC(O)CHFCF_2Cl$, 684-05-9; $EtC(O)CHFCF_2Cl$, 102283-43-2; *n*-$PrC(O)CHFCF_2Cl$, 76435-55-7; *n*-$BuC(O)CHFCF_2Cl$, 102283-44-3; $CH_2{=}CHCH_2OH$, 107-18-6; (*E*)-$CH_3CH{=}CHCH_2OH$, 504-61-0; $CH_2{=}CHCH(OH)CH_3$, 598-32-3; ethyl α-acetyl-α-fluoro-3-oxocyclohexaneacetate, 88100-70-3; 3-(1-fluoro-2-oxoprpyl)cyclohexanone, 102283-79-4; cyclohex-2-en-1-one, 930-68-7.

Synthesis of Polyether-Type Tetrahydrofurans via Hydroperoxide Cyclization

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Isomerization of an unsaturated hydroperoxy ester to the epoxy alcohol and thence to the tetrahydrofuran, as depicted in Scheme I, was investigated as a method for the stereocontrolled construction of ethers with a substitution pattern appropriate for polyether synthesis. This sequence is highly stereoselective in the case of the secondary hydroperoxides **11**, both with respect to the tetrahydrofuran stereochemistry as well as the acyclic relationship. With tertiary hydroperoxides (**18**, **21**, or **28**), little stereocontrol is seen over the ring stereochemistry. In the case of **28**, for example, the trans,cis and trans,trans bis ethers **29c** and **29t** are formed in a 1.4:1 ratio. Tertiary hydroperoxide **28** can be generated stereospecifically from **27mb** by a ring contraction process; however, when this method is applied in the related secondary system **27hi**, hydroperoxytetrahydropyran **31** is the major product. Cyclization of **31** affords a mixture of the fused bis ether isomers **32** and **33**.

The stereocontrolled construction of α,α′-substituted tetrahydrofurans and -pyrans is a necessary element in synthetic approaches to polyether natural products such as nigericin (**1**) and septamycin (**2**). Whereas the cyclization of olefinic hydroxyl compounds is a straightforward way to generate cyclic ethers, in a number of instances more complex strategies must be employed to ensure the desired sense and degree of stereocontrol.[1] A goal of our

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