A Highly Stereocontrolled Synthetic Approach to Versatile Monofluorinated Molecules

Tomoya Kitazume,* Tadashi Kobayashi, Takeshi Yamamoto, and Takashi Yamazaki

Department of Bioengineering, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152, Japan

Received March 19, 1987

(*R*)-(+)- and (*S*)-(−)-2-fluoro-2-substituted malonic acid monoesters were found to behave as potential synthetic reagents for the acyclic stereoselection of a variety of versatile monofluorinated molecules. (*R*)- and (*S*)-α-fluoro-α-methyl-β-keto esters have been transformed to the stereocontrolled β-hydroxy esters of anti (erythro) or syn (threo) configuration, four diastereomeric products, with hydrosilanes. Especially, highly stereocontrolled synthetic routes to monofluoro amino alcohols were achieved by the transformation of these β-hydroxy esters with 1,3-asymmetric induction via asymmetric Michael addition reaction.

The control of absolute stereochemistry of molecules is of fundamental importance for molecular design concerning the biological activities.[1-5] However, studies on the stereoselective transformations of fluorinated materials giving diasteromeric and/or enantiomeric anti (erythro) or syn (threo) configuration have not been undertaken in detail.[6-9] An objective in the synthesis of bioactive fluorine-containing compounds[10-12] is the development of methodology and/or reagents that will assure unusual selectivity and control for the synthesis of each diastereomeric system.

We recently outlined the synthetic approach to (*R*)-(+)- and/or (*S*)-(−)-2-fluoro-2-substituted-malonic acid monoesters based on the enantiotopic specificity of enzyme, which catalyze the stereospecific hydrolysis of the ester group in monofluorinated malonic acid diesters.[13-15] We describe herein the full details of the synthesis of four diastereomeric α-fluoro-β-hydroxy esters and an acyclic stereoselection in modified molecules possessing a fluorine atom.

Results and Discussion

Diasterocontrolled Reduction of (*S*)-α-Fluoro-α-substituted-β-keto Esters. The utility of organometallic reductive reagents has been generally recognized to be useful in asymmetric synthesis.[16] However, organometallic reductive reagents such as $Zn(BH_4)_2$ and $NaBH_4$ do not reduce (*S*)-ethyl α-fluoro-α-methylacetoacetate[14] to ethyl 2-fluoro-2-methyl-3-hydroxybutyrate with high diastereoselectivity.

We have now found that trisubstituted silanes reduce (*S*)-α-fluoro-α-methyl-β-keto esters to α-fluoro-α-methyl-β-hydroxy esters with high diastereoselectivity in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) in *N*,*N*-dimethylformamide.[17] The TBAF-catalyzed reduction is explained by the Felkin

Table I. Reduction of β-Keto Esters, (*S*)-1, with the $PhMe_2SiH$–TBAF–DMF System

R	reactn condtns[a]	anti:syn ratio	isolated yield (%)
Me	0 °C/12 h	17:83	40
Et	rt/21 h	16:84	75
n-Pr	rt/24 h	16:84	68
i-Pr	rt/50 h	7:93	58
Ph	rt/39 h	5:95	58

[a] rt = room temperature.

Table II[a]

Lewis acid (equiv)	reactn time (h)/rt[b]	anti:syn ratio	isolated yield (%)
$AlCl_3$ (1.5)	2	96:4	65
$AlCl_3$ (1.5)	3	96:4	80
$AlCl_3$ (1.5)	4	98:2	73
$AlCl_3$ (1.0)	4	98:2	51
$EtAlCl_2$ (1.5)	3	97:3	61
$EtAlCl_2$ (1.1)	4	98:2	54
$EtAlCl_2$ (1.1)	10	94:6	68

[a] (*S*)-1 (R = Et) was used in this system as a substrate. [b] rt = room temperature.

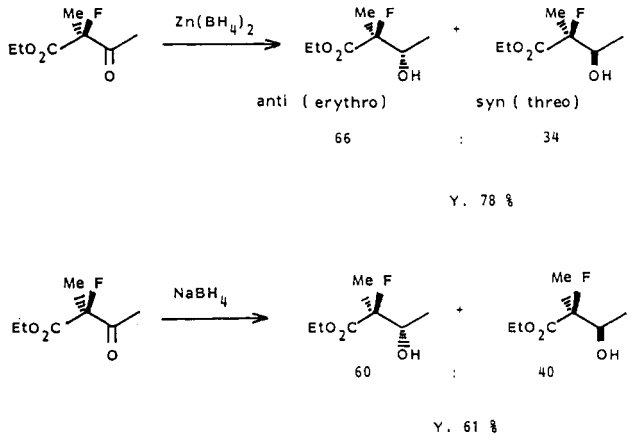
Table III. Reduction of β-Keto Esters, (*S*)-1, with the R_3SiH–$AlCl_3$ System

R	hydrosilane R_3SiH	anti:syn ratio	isolated yield (%)
n-Pr	$PhMe_2SiH$	99:1	65
n-Pr	Ph_3SiH	99:1	74
n-Pr	Et_3SiH	78:22	69
n-Pr	$(EtO)_2MeSiH$	99:1	22
n-Pr	TMCS[a]	94:6	54
Ph	$PhMe_2SiH$	74:26	49
Ph	Ph_3SiH	99:1	65

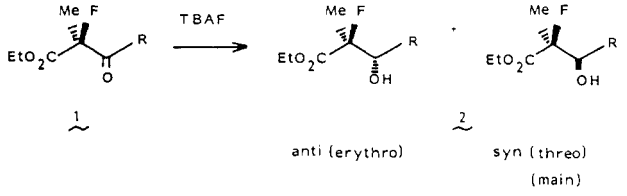
[a] Tetramethylcyclotetrasiloxane.

(1) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha and Elsevier Biomedical: Amsterdam, 1983.
(2) Smith, F. A. *Handbook of Experimental Pharmacology*; Springer-Verlag: Berlin, 1970; Vol. XX, Part 2, p 166.
(3) Ishikawa, N. *Kagaku to Seibutsu* **1984**, *22*, 93.
(4) Quistad, G. B.; Cerf, D. C.; Schooley, D. A.; Staal, G. B. *Nature (London)* **1981**, *289*, 176.
(5) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice-Hall: Englewood Cliffs, NJ, 1971.
(6) Aranda, G.; Jullien, J.; Martin, J. A. *Bull. Soc. Chim. Fr.* **1966**, 2850.
(7) Kollonitsch, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1979**, *44*, 771.
(8) Groth, U.; Schallkope, U. *Synthesis* **1983**, 673.
(9) (a) Welch, J. T.; Samartino, J. S. *J. Org. Chem.* **1985**, *50*, 3663. (b) Welch, J. T.; Seper, K. W. *Tetrahedron Lett.* **1984**, *25*, 5247. (c) Welch, J. T.; Eswarakrishnan, S.; Seper, K. W.; Samartino, J. S. *J. Org. Chem.* **1984**, *49*, 4720. (d) Welch, J. T.; Eswarakrishnan, S. *J. Chem. Soc., Chem. Commun.* **1985**, *186*. (e) Welch, J. T.; Eswarakrishnan, S. *J. Org. Chem.* **1985**, *50*, 5403.
(10) Souda, K.; Tanizawa, K.; Esaki, N. *Kagaku* **1980** *35*, 97 and references cited therein.
(11) Johnson, M.; Marcotte, P.; Donovan, J.; Walsh, C. *Biochemistry* **1977**, *18*, 1729.
(12) Walsh, C. *Tetrahedron* **1982**, *38*, 871.
(13) Kitazume, T.; Sato, T.; Kobayashi, T.; Lin, J. T. *J. Org. Chem.* **1986**, *51*, 1003.
(14) Kitazume, T.; Kobayashi, T. *J. Fluorine Chem.* **1986**, *31*, 357.
(15) Kitazume, T.; Kobayashi, T. *Synthesis* **1987**, 187.
(16) Rico, I.; Cantacuzene, D.; Wakselman, C. *Tetrahedron Lett.* **1981**, *22*, 3405.
(17) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629 and references cited therein.

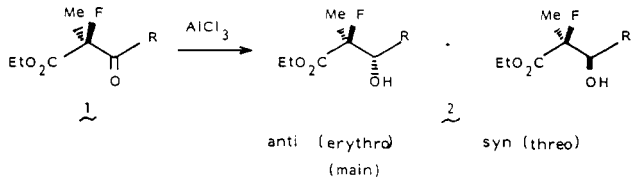
0022-3263/87/1952-3218$01.50/0



model in Figure 1.[18] The reduction of compounds with a bulky group such as phenyl or isopropyl showed remarkable syn selectivity (93–95%), as shown in Table I.



In the next phase of the study,[5,17,21-23] we investigated the diastereocontrolled reduction of α-fluoro-α-methyl-β-keto esters to α-fluoro-α-methyl-β-hydroxy esters of anti configuration, using a variety of Lewis acids or silanes, as shown in Table II or III. The results suggest that triphenylsilane is more than adequate for the high stereoselectivity. Therefore, we examined the diasterocontrolled transformation with triphenylsilane–$AlCl_3$ in dichloromethane. The $AlCl_3$-catalyzed reduction is explained by the chelation model in Figure 2.



The results shown in Table IV demonstrate that the reduction with Ph_3SiH is useful for the design of the desired stereocontrolled α-fluoro-α-methyl-β-hydroxy esters of anti configuration. From the above results, we found that synthetic route to the two diastereomeric products (2*S*,3*R*)- or (2*S*,3*S*)-ethyl 2-fluoro-2-methyl-3-hydroxy-3-substituted-propionate based on (*S*)-(−)-ethyl 2-fluoro-2-methylmalonates.

Using the reduction of the *R* enantiomer of the corresponding α-fluoro-α-methyl-β-keto esters with the hydrosilane, we designed a diastereocontrolled approach to *R* enantiomers with anti and/or syn configuration, such as (2*R*,3*R*)- and (2*R*,3*S*)-ethyl 2-fluoro-2-methyl-3-hydroxy-3-substituted-propionate. The equations in Scheme I indicate how the objective of achieving a stereocontrolled reduction has been achieved.

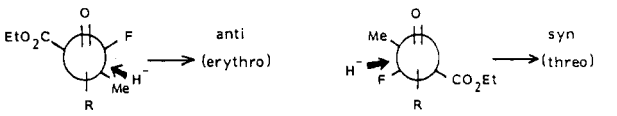


Figure 1.

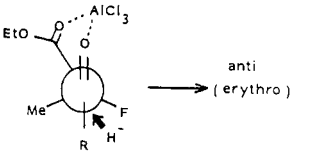


Figure 2.

Table IV. Reduction of (*S*)-β-Keto Esters with the Ph_3SiH–$AlCl_3$ System

R	reactn condtns[a]	anti:syn ratio	isolated yield (%)	$[\alpha]^{24}_D$/MeOH (deg)
Me	0 °C/2 h	98:2	45	−7.60 (*c* 0.24)
Et	rt/2 h	96:4	65	−14.5 (*c* 1.47)
n-Pr	rt/3 h	99:1	74	−21.3 (*c* 1.45)
i-Pr	rt/12 h	98:2	45	−5.00 (*c* 1.60)
n-Bu	rt/3 h	97:3	71	−18.3 (*c* 1.42)
Ph	rt/4 h	99:1	65	−4.30 (*c* 0.77)

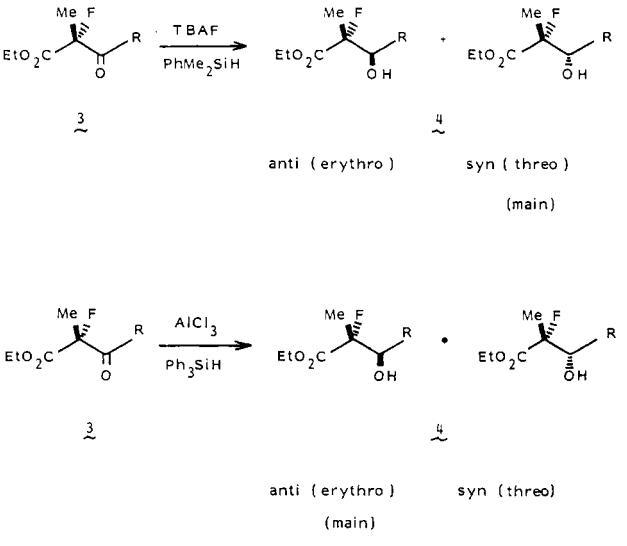
[a] rt = room temperature.

Table V. Reduction of (*R*)-β-Keto Esters, (*R*)-3, with the $PhMe_2SiH$–TBAF–DMF System

R	reactn condtns[a]	anti:syn ratio	isolated yield (%)
Me	0 °C/10 h	21:79	51
Et	rt/21 h	14:86	67
n-Pr	rt/24 h	17:83	74
Ph	rt/40 h	4:96	49

[a] rt = room temperature.

Scheme I



These transformations, based on the diasterotopic specificity of reductive reagents, appear to be the most convenient process for preparing the four monofluorinated diastereomeric products.

Stereostructural Assignments. The stereochemistry of anti or syn configuration was confirmed by NMR coupling constants after conversion of the corresponding optically active β-hydroxy esters to their acetonides.[6,24-26] A

(18) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.
(19) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.
(20) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245.
(21) Tramomtini, M. *Synthesis* **1982**, 605.
(22) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265 and references cited therein.
(23) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641.
(24) Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1066.
(25) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876 and references cited therein.
(26) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975.

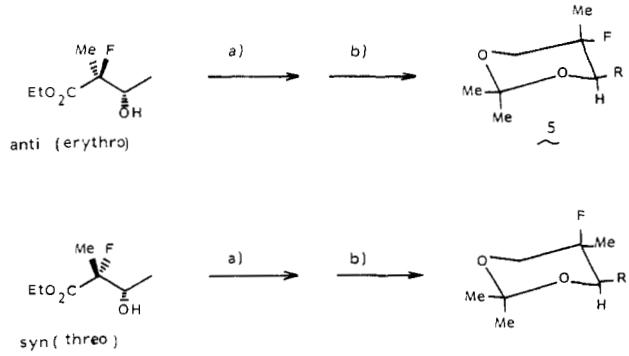
Table VI. Reduction of (*R*)-β-Keto Esters, (*R*)-3, with the Ph_3SiH–$AlCl_3$ System

R	reactn condtns[a]	anti:syn ratio	isolated yield (%)
Me	0 °C/2 h	97:3	57
Et	rt/2 h	98:2	64
n-Pr	rt/4 h	99:1	77
n-Bu	rt/3 h	98:2	63
Ph	rt/5 h	99:1	68

[a] rt = room temperature.

brief outline of the synthetic strategies is required to achieve the desired structures shown in Scheme II. The optically active ethyl 2-fluoro-2-methyl-3-hydroxybutanoate derived from (*S*)-ethyl α-fluoro-α-methylacetoacetate was selectively reduced with lithium aluminum hydride in diethyl ether to give good yields of the optically pure 2-fluoro-2-methyl-3-hydroxybutanol. Treatment of the 3-hydroxybutanol with acetone dimethyl ketal gave the corresponding acetonide with the coupling constant J_{CH_3-CF} = 15 Hz. Similarly, the diastereomer,

Scheme II[a]

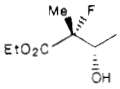
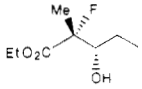
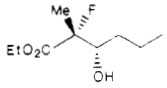
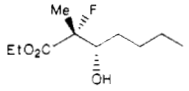
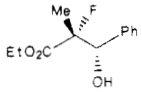


[a] (a) $LiAlH_4/Et_2O$; (b) $Me_2C(OMe)_2$/toluene/TsOH.

derived from (*R*)-ethyl α-fluoro-α-methylacetoacetate, was also transformed to its acetonide with the coupling constant J_{CH_3-CF} = 25.3 Hz.

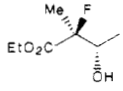
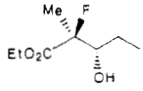
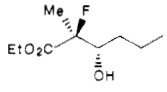
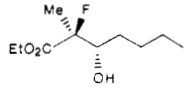
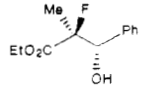
Diastereoselective Amination via an Intramolecu-

Table VII. ^1H and ^{19}F NMR Spectral Data of α-Fluoro-α-methyl-β-hydroxy Esters with the Syn (Threo) Configuration

product[a]	^{19}F NMR ($CDCl_3$), ppm	^1H NMR ($CDCl_3$), δ
	+90.4 (qd)	1.19 (d, 3 H, J_{CH_3-CH} = 6.3 Hz), 1.33 (t, 3 H, $J_{CH_3-CH_2}$ = 7.4 Hz), 1.49 (d, 3 H, J_{CH_3-CF} = 22 Hz), 2.80 (s, 1 H), 4.03 (dq, 1 H, J_{CF-CH} = 17.4 Hz), 4.27 (q, 2 H)
	+85.8 (qd)	1.02 (t, 3 H, $J_{CH_3-CH_2}$ = 7.1 Hz), 1.15–1.80 (m, 2 H), 1.33 (t, 3 H, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.51 (d, 3 H, J_{CH_3-CF} = 21 Hz), 2.39 (br, 1 H), 3.33–3.79 (m, 1 H), 4.22 (q, 2 H)
	+87.3 (qd)	0.95 (t, 3 H, $J_{CH_3-CH_2}$ = 6.2 Hz), 1.34 (t, 3 H, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.14–1.84 (m, 4 H), 1.51 (d, 3 H, J_{CH_3-CF} = 21 Hz), 2.34 (br, 1 H), 3.43–3.98 (m, 1 H), 4.27 (q, 2 H)
	+87.5 (qd)	0.93 (t, 3 H, $J_{CH_3-CH_2}$ = 6.0 Hz), 1.24 (t, 3 H, $J_{CH_3-CH_2}$ = 7.3 Hz), 1.30–1.71 (m, 6 H), 1.56 (d, 3 H, J_{CH_3-CF} = 21 Hz), 2.35 (br, 1 H), 3.45–3.90 (m, 1 H), 4.25 (q, 2 H)
	+84.5 (qd)	1.11 (t, 3 H, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.45 (d, 3 H, J_{CH_3-CF} = 22 Hz), 3.30 (d, 1 H, J_{OH-CH} = 4.5 Hz), 4.07 (q, 2 H), 4.86 (dd, 1 H, J_{CH-CF} = 15.6 Hz), 7.32 (Ar H)

[a] Products were purified by column chromatography. Structures were confirmed by spectral data. For the new compounds the microanalysis was in satisfactory agreement with the calculated value (C, H, N: ±0.4%).

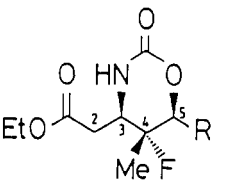
Table VIII. ^1H and ^{19}F NMR Spectral Data of α-Fluoro-α-methyl-β-hydroxy Esters with the Anti (Erythro) Configuration

product[a]	^{19}F NMR ($CDCl_3$), ppm	^1H NMR ($CDCl_3$), δ
	+87.4 (qd)	1.20 (d, 3 H, J_{CH_3-CH} = 6.6 Hz), 1.37 (t, 3 H, $J_{CH_3-CH_2}$ = 7.4 Hz), 1.57 (d, 3 H, J_{CH_3-CF} = 21 Hz), 3.03 (s, 1 H), 4.03 (dq, 1 H, J_{CH-CF} = 17 Hz), 4.35 (q, 2 H)
	+86.4 (qd)	1.00 (t, 3 H, $J_{CH_3-CH_2}$ = 6.9 Hz), 1.12–1.63 (m, 2 H), 1.32 (t, 3 H, $J_{CH_3-CH_2}$ = 7.3 Hz), 1.52 (d, 3 H, J_{CH_3-CF} = 21 Hz), 2.63 (br, 1 H), 3.64 (ddd, 1 H, J_{CH-CF} = 16 Hz, J_{CH-CH_2} = 6.6 Hz), 4.25 (q, 2 H)
	+86.8 (qd)	0.96 (t, 3 H, $J_{CH_3-CH_2}$ = 6.2 Hz), 1.35 (t, 3 H, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.17–1.82 (m, 4 H), 1.52 (d, 3 H, J_{CH_3-CF} = 21 Hz), 2.50 (br, 1 H), 3.55–3.93 (m, 1 H), 4.27 (q, 2 H)
	+86.6 (qd)	0.92 (t, 3 H, $J_{CH_3-CH_2}$ = 6.0 Hz), 1.25 (t, 3 H, $J_{CH_3-CH_2}$ = 7.3 Hz), 1.10–1.71 (m, 6 H), 1.54 (d, 3 H, J_{CH_3-CF} = 21 Hz), 2.36 (br, 1 H), 3.53–3.89 (m, 1 H), 4.24 (q, 2 H)
	+84.5 (qd)	1.11 (t, 3 H, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.45 (d, 3 H, J_{CH_3-CF} = 22 Hz), 3.30 (d, 1 H, J_{OH-CH} = 4.5 Hz), 4.07 (q, 2 H), 4.86 (dd, 1 H, J_{CH-CF} = 15.6 Hz), 7.32 (Ar H)

[a] Products were purified by column chromatography. Structures were confirmed by spectral data. For the new compounds the microanalysis was satisfactory agreement with the calculated value (C, H, N: ±0.4%).

J_{H^3-F} 12.9 Hz (Me)

J_{H^5-F} 2.9 Hz (Me)



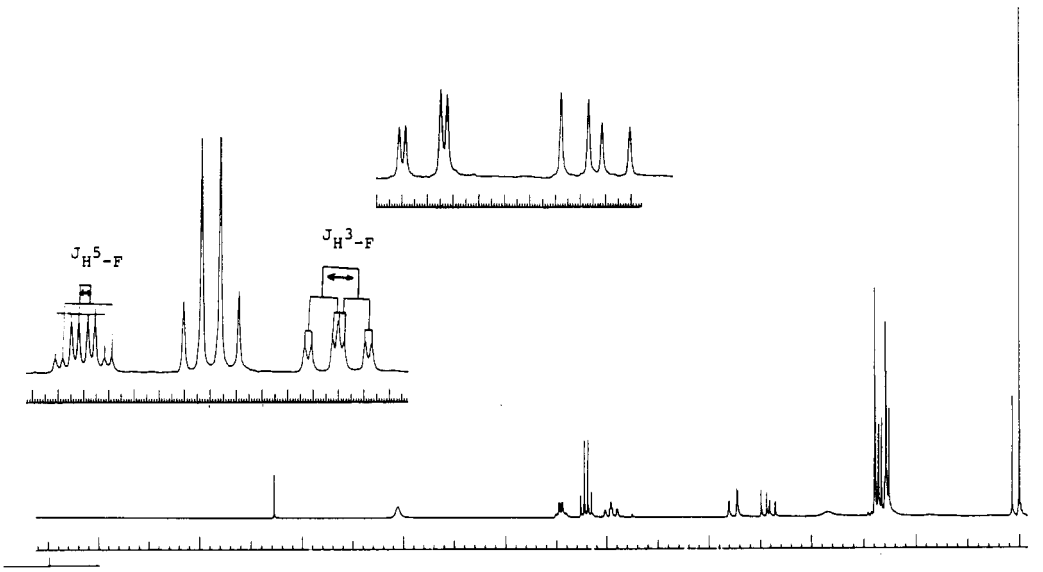


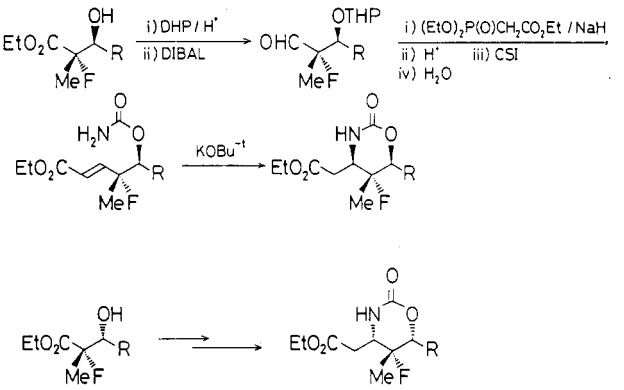
Figure 3.

lar Michael Addition Reaction.[27] The next stereocontrolled transformation studied was 1,3-asymmetric induction,[28-33] which efficiently provides important functionalities such as fluoroamino acids derivatives, which are of interest as irreversible enzyme inhibitors.[34-43]

Until now, no reports of acyclic stereoselection, such as triply stereocontrolled synthesis, have been published except for the aldol condensation reaction of monofluoroacetic acid derivatives.

In this study, we have shown that it is possible to control the stereochemistry of fluorinated molecules with functionalization of acyclic olefinic systems, such as an intramolecular Michael addition reaction of *O*-carbamates to γ,δ-unsaturated esters. Four diastereomeric δ-hydroxy-α,β-unsaturated esters were treated with chlorosulfonyl isocyanate to yield *O*-carbamates by a known procedure.[44] The cyclic carbamates were then obtained on treatment with potassium *tert*-butoxide (Scheme III).

Scheme III



The stereochemistry of 1,3-asymmetric induction was determined by the ^1H NMR (200 MHz) coupling constant (J_{F-H}) as shown in Figures 3 and 4. The results from the ^1H NMR data show that the vicinal couplings (J_{F-H}) of the cyclic carbamate derived from the threo isomer, (2*S*,3*R*)-ethyl 2-fluoro-2-methyl-3-hydroxybutanoate, are larger than those of the cyclic carbamate derived from the erythro isomer, (2*S*,3*S*)-ethyl 2-fluoro-2-methyl-3-hydroxybutanoate. The other stereochemistry in (2*R*,3*S*)-**4** and/or (2*R*,3*R*)-**4** was determined in the same manner.

Experimental Section

General Procedures. All microbial transformations were carried out in the Jarfermentor. Commercially available reagents were used without purification. Infrared spectra were obtained by using a JASCO A-102 spectrometer and KBr pellets. The ^1H (internal Me_4Si) and ^{19}F (external CF_3CO_2H) NMR spectra were

(27) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797.
(28) Hirama, M.; Uei, M. *Tetrahedron Lett.* **1982**, *23*, 5307.
(29) Hirama, M.; Iwashita, M.; Yamazaki, Y.; Ito, S. *Tetrahedron Lett.* **1984**, *25*, 4963.
(30) Kobayashi, S.; Isobe, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 5079.
(31) Georges, M.; MacKay, D.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1982**, *104*, 1101.
(32) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *Tetrahedron Lett.* **1982**, *23*, 619.
(33) Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654.
(34) Loncrini, D. F.; Filler, R. *Advances in Fluorine Chemistry*; Butterworths: London, 1972; Vol. 6.
(35) Kollonitsch, J. *Isr. J. Chem.* **1978**, *17*, 53.
(36) Rando, R. R. *Acc. Chem. Res.* **1975**, *8*, 281.
(37) Abeles, R. H.; Maycock, A. L. *Acc. Chem Res.* **1976**, *9*, 313.
(38) Kollonitsch, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1979**, *44*, 771.
(39) Wade, T. N.; Gaymard, F.; Guedj, R. *Tetrahedron Lett.* **1979**, 2681.
(40) Tsushima, T.; Sato, T.; Tsuji, T. *Tetrahedron Lett.* **1980**, *21*, 3591.
(41) Tsushima, T.; Nishikawa, J.; Sato, T.; Tanida, H.; Tori, K.; Tsuji, T.; Misaki, S.; Suefuji, M. *Tetrahedron Lett.* **1980**, *21*, 3593.
(42) Tsushima, T.; Kawada, K.; Shiratori, O.; Uchida, N. *Heterocycles* **1985**, *23*, 45.
(43) Douglas, A. W.; Reider, P. J. *Tetrahedron Lett.* **1984**, *25*, 2851.
(44) Graf, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 172.

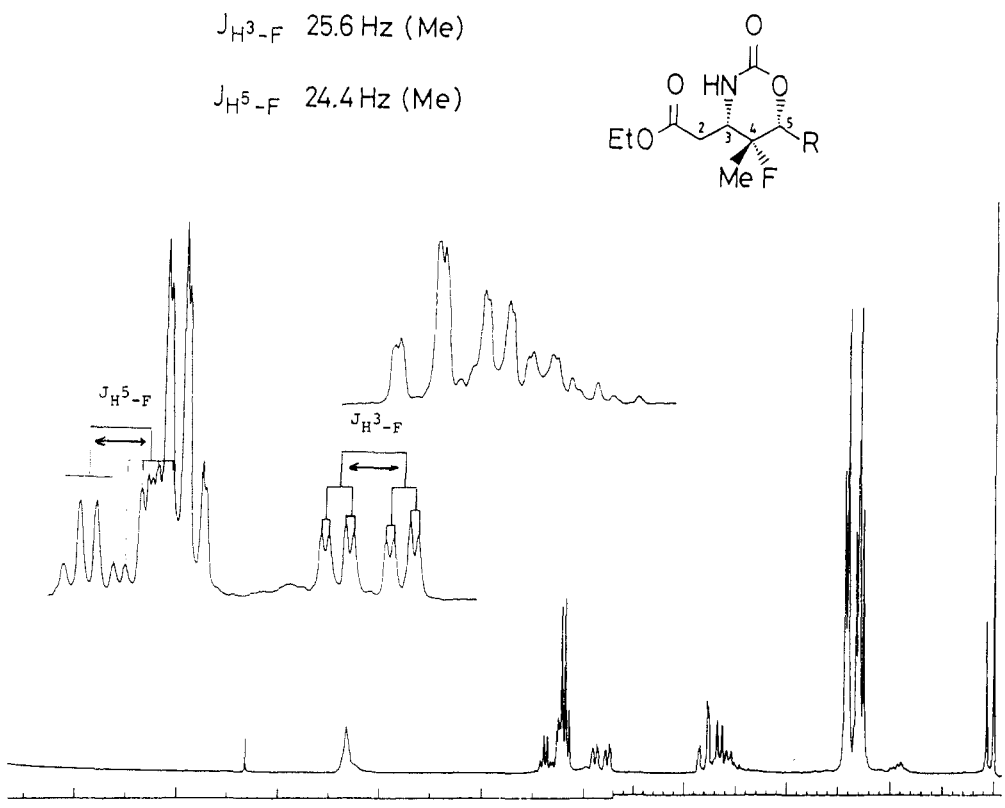


Figure 4.

recorded by using a Varian EM-390 spectrometer. Mass spectra were obtained by using a Hitachi M-52 spectrometer at 20 eV. Specific rotations were recorded on a JASCO DIP-140 digital polarimeter. Yields were those of the products actually isolated. Solvents were dried over molecular sieves.

Preparation of β-Keto Esters. (*S*)-Ethyl α-Fluoro-α-methylacetoacetate. Lithium dimethylcuprate (15 mmol) was added to a mixture of acid chloride (10 mmol) and freshly dried diethyl ether (30 mL) at −60 °C. After 5 h of stirring, the reaction mixture was poured onto 1 N HCl solution and oily materials were extracted with diethyl ether. The ethereal extract was dried over magnesium sulfate and the solvent removed. Distillation gave (*S*)-ethyl α-fluoro-α-methylacetoacetate in a yield of 77%, bp 59–61 °C/20 mmHg.

Other β-keto esters were prepared in the same manner.[14]

Diastereocontrolled Reduction of β-Keto Esters with Hydrosilane. TBAF-Catalyzed Reduction. To a magnetically stirred mixture of dimethylphenylsilane (3.24 g, 24 mmol) and tetrabutylammonium fluoride (0.9 mmol in hexane) in freshly dried *N,N*-dimethylformamide (20 mL) at 0 °C under an argon was added (*S*)-ethyl α-fluoro-α-methylacetoacetate (4.0 g, 18 mmol) over 5 min. The mixture was stirred at 0 °C for 3 h and then was allowed to warm to room temperature. After 30 h of stirring at that temperature, the mixture was quenched with aqueous NH_4Cl and extracted with diethyl ether. The organic extract was dried over anhydrous magnesium sulfate and concentrated in vacuo. The resulting crude product was flash chromatographed over silica gel (1:1, hexane/ether) to give β-hydroxy esters in the yields shown in Table I.

TFA-Catalyzed Reduction. Dimethylphenylsilane (1.67 mmol) was added to a trifluoroacetic acid (1.3 mL) solution of (*S*)-ethyl α-fluoro-α-methylacetoacetate (0.27 g, 1.23 mmol) at 0 °C. After 6 h of stirring, the mixture was allowed to warm to room temperature and then the whole was stirred for 8 h at that temperature. The reaction mixture was neutralized with saturated $NaHCO_3$ solution andd subsequently worked up. The product, purified by column chromatography on silica gel, was a mixture of syn (threo) and anti (erythro) β-hydroxy ester.

(2*S*,3*S*)-2-Fluoro-2-methyl-3-hydroxybutanol. Into a mixture of lithium aluminum hydride (0.40 g, 14 mmol) in freshly dried diethyl ether (10 mL) was added (2*S*,3*S*)-ethyl 2-fluoro-2-methyl-3-hydroxybutanoate (1.0 g, 0.6 mmol) at 0 °C. After 1 h of stirring at that temperature, the reaction mixture was allowed to warm to room temperature, stirred for 8 h, and worked up. The product was purified by column chromatography on silica gel (1:1, hexane/diethyl ether) to give the corresponding 3-hydroxybutanol.

Acetonide 5. (A) A mixture of *anti*(*erythro*)-(2*S*,3*S*)-2-fluoro-2-methyl-3-hydroxypentanol, which was obtained by reduction of (2*S*,3*S*)-ethyl 2-fluoro-2-methyl-3-hydroxypentanate (1.1 g, 6 mmol) with $LiAlH_4$ (0.04 g) in dry Et_2O (15 mL) at 0 °C, acetone dimethyl acetal (1.56 g, 15 mmol), and *p*-toluenesulfonic acid (0.1 g) in toluene (10 mL), was heated for 4 h at 90 °C. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and then the oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate and the solvent was removed. The product was separated by column chromatography on silica gel using *n*-hexane–diethyl ether (10:1) as eluent. ^{19}F NMR (Et_2O): 78.1 (m) ppm from external CF_3CO_2H. ^1H NMR (CCl_4): δ 0.95 (t, 3 H, $J_{CH_3-CH_2}$ = 7.0 Hz), 1.23 (m, 2 H), 1.31 (d, 3 H, J_{CH_3-CF} = 22.5 Hz), 1.30 (s, 3 H), 1.39 (s, 3 H), 3.49 (dd, 1 H), 3.35 (dt, 1 H, J_{CH-CF} = 15.2 Hz, J_{CH-CH_2} = 4.1 Hz), 3.72 (dd, 1 H).

(B) The preparation of the acetonide of *syn*(*threo*)-(2*R*,3*S*)-2-fluoro-2-methyl-3-hydroxypentanol was carried out in the same manner. ^{19}F NMR (Et_2O): 89.6 (m) ppm from external CF_3CO_2H. ^1H NMR (CCl_4): δ 0.94 (t, 3 H, $J_{CH_3-CH_2}$ = 7.5 Hz), 1.16 (d, 3 H, J_{CH_3-CF} = 19.8 Hz), 1.32 (s, 6 H), 1.43–1.75 (m, 2 H), 3.20–3.76 (m, 2 H), 3.46 (dt, 1 H, J_{CH-CF} = 25.3 Hz, J_{CH-CH_2} = 6.5 Hz).

1,3-Asymmetric Induction. (a) Protection of Dihydropyran. A mixture of (2*S*,3*S*)-ethyl 2-fluoro-2-methyl-3-hydroxybutanoate (6.0 g, 6 mmol), dihydropyran (1.4 g, 20 mmol), and *p*-toluenesulfonic acid (20 mg) in diethyl ether (65 mL) was stirred for 24 h at room temperature. After removing the solvent, the product was purified by silica gel.

(b) Reduction by Diisobutylaluminum Hydride. Into the reaction vessel was placed 6 mmol of the above compound, freshly dried hexane (30 mL) was added with a syringe under an atmosphere of argon, and diisobutylaluminum hydride (10 mmol, 1 M in hexane) was added at −70 °C. After adding the reagent, the reaction mixture was stirred for 1 h at room temperature, and then the mixture was quenched with saturated NH_4Cl solution. Oily materials were extracted with diethyl ether and the ethereal extract was dried over anhydrous magnesium sulfate. On removal of the solvent, distillation gave the corresponding aldehyde.

(c) Into a mixture of sodium hydride (0.52 g, 8 mmol) and toluene (10 mL), under an atmosphere of nitrogen, was added

triethyl phosphonoacetate (2.4 g, 8 mmol) in toluene (10 mL) with a syringe at 0 °C. After 30 min of stirring, the aldehyde (vide supra) (1.3 g, 6 mmol) was added at 0 °C, the reaction mixture was stirred for 2.5 h at room temperature, and then the mixture was quenched with saturated NH_4Cl solution. Oily materials were extracted with ethyl acetate. After removing the solvent, the crude product obtained was mixed with methanol (15 mL) and *p*-toluenesulfonic acid (10 mg), stirred for 24 h at room temperature, and subsequently worked up. The product was purified by silica gel to give the γ-fluoro-γ-methyl-δ-hydroxy-α,β-unsaturated esters.

Erythro isomer (R = Me): $[\alpha]^{24}_D$ −8.17° (*c* 1.25; MeOH). ^{19}F NMR ($CDCl_3$): 80 (ddqq) ppm. ^1H NMR ($CDCl_3$): δ 1.16 (CH_3CHOH, dd, J_{CH_3-CH} = 6.5, J_{CH_3-F} = 1.2 Hz), 1.30 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.43 (CH_3CF, d, J_{CH_3-F} = 21 Hz), 3.00 (OH), 4.00 (CH, dq, J_{H-F} = 22.6 Hz), 4.16 (CH_3CH_2, q), 5.96 (CH=, d, $J_{H-H_{trans}}$ = 16.5 Hz), 6.86 (=CHCF, dd, J_{H-F} = 21 Hz).

Threo isomer (R = Me): $[\alpha]^{24}_D$ +8.34° (*c* 1.24; MeOH). ^{19}F NMR ($CDCl_3$): 78.5 (ddqq) ppm. ^1H NMR ($CDCl_3$): δ 1.13 (CH_3CHOH, dd, J_{CH_3-CH} = 6.6, J_{CH_3-F} = 1.2 Hz, 1.30 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.45 (CH_3CF, f, J_{CH_3-F} = 22.4 Hz), 3.10 (OH), 4.00 (CH, dq, J_{H-F} = 13.7 Hz), 4.14 (CH_3CH_2, q), 6.00 (=CH, d, $J_{H-H_{trans}}$ = 16.2 Hz), 6.88 (=CHCF, dd, J_{H-F} = 21.6 Hz).

Erythro isomer (R = Ph): $[\alpha]^{24}_D$ +8.00° (*c* 0.92; MeOH). ^{19}F NMR ($CDCl_3$): 76 (ddq) ppm. ^1H NMR ($CDCl_3$): δ 1.20 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.34 (CH_3CF, d, J_{CH_3-F} = 21 Hz), 3.30 (OH), 4.10 (CH_3CH_2, q), 4.97 (CH, d, J_{H-F} = 12 Hz), 5.91 (CH=, d, $J_{H-H_{trans}}$ = 15 Hz), 6.83 (=CHCF, dd, J_{H-F} = 19.5 Hz), 7.20 (Ar H).

Threo isomer (R = Ph): $[\alpha]^{24}_D$ −41.5° (*c* 1.20; MeOH). ^{19}F NMR ($CDCl_3$): 77 (ddq) ppm. ^1H NMR ($CDCl_3$): δ 1.20 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.5 Hz), 1.40 (CH_3CF, d, J_{CH_3-F} = 21.0 Hz), 3.32 (OH), 4.10 (CH_3CH_2, q), 4.67 (CH, d, J_{H-F} = 12.0 Hz), 5.90 (CH=, d, $J_{H-H_{trans}}$ = 15.0 Hz), 6.80 (=CHCF, dd, J_{H-F} = 21.0 Hz), 7.27 (Ar H).

(d) *O*-Carbamates of δ-Hydroxy-α,β-unsaturated Esters. Into a solution of chlorosulfonyl isocyanate (0.87 g, 8 mmol) and methylene chloride (20 mL) was added (−)-δ-hydroxy-α,β-unsaturated ester (4.6 mmol) at −78 °C, and then the mixture was allowed to warm to room temperature. After 30 min of stirring, water was added and then the whole was heated at 70 °C for 5 h. Oily materials were extracted with ethyl acetate, the extract was dried over anhydrous magnesium sulfate, and the solvent was removed. The *O*-carbamate was purified by column chromatography using *n*-hexane–ethyl acetate (5:1).

Erythro isomer (R = Me): $[\alpha]^{24}_D$ +6.36° (*c* 1.09; MeOH). ^{19}F NMR ($CDCl_3$): 81 (ddqq) ppm. ^1H NMR ($CDCl_3$): δ 1.26 (CH_3CHOH, dd, J_{CH_3-CH} = 6.6, J_{CH_3-F} = 1.0 Hz), 1.32 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.0 Hz), 1.45 (CH_3CF, d, J_{CH_3-F} = 21.7 Hz), 4.22 (CH_3CH_2, q), 4.90 (CH, dq, J_{H-F} = 21.4 Hz), 4.98 (NH_2), 6.10 (CH=, d, $J_{H-H_{trans}}$ = 15.9 Hz), 6.90 (=CHCF, dd, J_{H-F} = 20.4 Hz).

Threo isomer (R = Me): $[\alpha]^{24}_D$ +18.9° (*c* 1.12; MeOH). ^{19}F NMR ($CDCl_3$): 79 (ddqq) ppm. ^1H NMR ($CDCl_3$): δ 1.29 (CH_3CHOH, dd, J_{CH_3-H} = 6.6, J_{CH_3-F} = 1.0 Hz), 1.33 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.50 (CH_3CF, d, J_{CH_3-F} = 21.7 Hz), 4.21 (CH_3CH_2, q), 4.91 (CH, dq, J_{H-F} = 12.6 Hz), 5.04 (NH), 6.10 (=CH, d, $J_{H-H_{trans}}$ = 15.9 Hz), 6.90 (=CHCF, dd, J_{H-F} = 20.9 Hz).

Erythro isomer (R = Ph): $[\alpha]^{24}_D$ −10.7° (*c* 1.12; MeOH). ^{19}F NMR ($CDCl_3$): 75.5 (ddq) ppm. ^1H NMR ($CDCl_3$): δ 1.25 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.43 (CH_3CF, d, J_{CH_3-F} = 21.6 Hz), 4.17 (CH_3CH_2, q), 4.96 (NH_2), 5.73 (CH=, d, $J_{H-H_{trans}}$ = 15.6 Hz), 5.95 (CH, d, J_{H-F} = 16.2 Hz), 6.92 (=CHCF, dd, J_{H-F} = 20.3 Hz), 7.31 (Ar H).

Threo isomer (R = Ph): $[\alpha]^{24}_D$ −31.4° (*c* 1.02; MeOH). ^{19}F NMR ($CDCl_3$): 79.5 (ddq) ppm. ^1H NMR ($CDCl_3$): δ 1.26 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.0 Hz), 1.43 (CH_3CF, d, J_{CH_3-F} = 21.5 Hz), 4.17 (NH_2), 6.01 (CH, d, J_{H-F} = 13.2 Hz), 5.71 (CH=, d, $J_{H-H_{trans}}$ = 16.5 Hz), 6.91 (=CHCF, dd, J_{H-F} = 21.5 Hz), 7.34 (Ar H).

(e) Cyclic Carbamate. A mixture of the *O*-carbamate (1 mmol) and potassium *tert*-butoxide (1.1 mmol) in tetrahydrofuran (3 mL) was stirred for 5 min at 0 °C and the mixture was quenched with water. Oily materials were extracted with diethyl ether, and the product was isolated after workup.

Asymmetric Microbial Reduction of Prochiral 2,2-Disubstituted Cycloalkanediones

Dee W. Brooks,*† Hormoz Mazdiyasni,‡ and Paul G. Grothaus‡

Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, Illinois 60064, and Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received April 1, 1987

Asymmetric microbial reduction of a series of 2,2-disubstituted 1,3-cycloalkanediones with bakers' yeast was examined as an example of an enzyme-catalyzed distinction of a substrate containing two trigonal carbonyl centers with stereoheterotropic faces and one prochiral tetrahedral carbon center where monoreduction generates two chiral centers. Synthetically useful yeast-mediated reductions were achieved for cyclopentanoid and cyclohexanoid diones with a variety of substituents at C2 providing chiral intermediates for enantioselective syntheses. For each case studied, the ketol products had >98% ee, and the hydroxy configuration was consistently of the *S* configuration. For the cyclopentanoids, the major product of yeast reduction was the (2*S*,3*S*) diastereomer, whereas for the cyclohexanoids, the major product was the (2*R*,3*S*) diastereomer. The relative stereoselectivity of the yeast-mediated reduction of each substrate was compared with that of reduction with $NaBH_4$.

The discovery and development of applications of enzyme-catalyzed processes to effect asymmetric reactions on synthetic substrates to provide optically pure intermediates for enantioselective syntheses is an alternative complementary strategy to methods involving resolution of racemates, chiral pool templates, and asymmetric synthetic reagents.[1] The organic chemist can consider microorganisms as a microscopic reaction vessel containing numerous enzymes complete with cofactors that can potentially react with a synthetic substrate. However, most enzymes have specific requirements for substrate binding and catalytic activity that limits the versatility of this approach as compared with a synthetic reagent that offers a wider range of substrate opportunities. This lack of

† Abbott Laboratories.
‡ Purdue University.

(1) For pertinent reviews of this topic, refer to: (a) *Enzymes in Organic Synthesis*; Ciba Foundation Symposium 111; Pitman: London, 1985. (b) Whitesides, G. M.; Wong, C. H. *Aldrichimica Acta* **1983**, *16*, 27. (c) Sih, C. J.; Rosaza, J. P. In *Applications of Biochemical Systems in Organic Chemistry*; Jones, J. B., Sih, C. J., Perlman, D., Eds.; Wiley: New York, 1976; Part I, Chapter III. (d) Kieslich, K. *Microbial Transformations of Chemical Compounds Excluding Steroids and Noncyclic Structures*; G. Thieme Verlag: Stuttgart, 1976.

0022-3263/87/1952-3223$01.50/0