dried and concentrated in vacuo. The crude product (0.101 g, 97%) was a light yellow foamy solid of high purity, mp 30 °C. It exists as an 80:20 enol ester/keto ester mixture: NMR ($CDCl_3$) δ 10.65 (br, s), 7.42 (d, J = 8 Hz, 2 H), 7.09 (m, 3 H), 6.90 (d, J = 8 Hz, 2 H), 6.79 (m, 2 H), 5.98 (d, J = 2 Hz, 1 H), 5.61 (d, J = 2 Hz, 1 H), 4.67 (s, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.62 (s, 3 H), 3.58 (s, 3 H); IR ($CDCl_3$) 3420, 2940, 2825, 1755, 1655, 1608, 1592, 1455, 1420, 1245, 1212, 1142, 1120, 1055, 1030, 910 cm^{-1}; high-resolution mass spectrum for $C_{28}H_{24}O_7$ requires 472.152 21, measured 472.152 59.

Tricyclic Ester 20. To sodium borohydride (0.081 g, 2.14 mmol) in dry methanol (3 mL) at 0 °C under argon was added a solution of compound **19** (0.078 g, 0.14 mmol) in methanol (5 mL) dropwise. The reaction mixture was stirred at 0 °C for 10 h. It was concentrated in vacuo. The resiude was taken up in ether (25 mL) and treated with dilute HCl solution (2 mL). The organic layer was washed with brine, dried, and concentrated. The crude product was recrystallized in ether/hexanes (3:1) to give ester **20** (0.0706 g, 100%) as a light yellow foamy solid which melts at 78–80 °C: NMR ($CDCl_3$) δ 7.33 (d, J = 8 Hz, 2 H), 7.16 (m, 3 H), 6.94 (m, 2 H), 6.87 (d, J = 8 Hz, 2 H), 6.12 (d, J = 2 Hz, 1 H), 6.05 (d, J = 2 Hz, 1 H), 4.77 (d, J = 11 Hz, 1 H), 4.03 (d, J = 13 Hz, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.60 (s, 3 H), 3.24 (dd, 1 H, J = 11 and 13 Hz); IR ($CDCl_3$) 3472, 2940, 2825, 1720, 1610, 1590, 1450, 1430, 1270, 1175, 1120, 1025, 910 cm^{-1}; high-resolution mass spectrum for $C_{28}H_{28}O_8$ requires 492.178 43, measured 492.178 03; ^{13}C NMR ($CDCl_3$) 172.95, 163.93, 161.89, 159.24, 159.79, 134.84, 128.99, 128.25, 127.82, 127.15, 113.45, 105.03, 99.35, 92.53, 91.23, 88.67, 83.79, 77.25, 55.66, 55.23, 54.70, 52.12, 50.80.

Tricyclic Acid 21. To ester **20** (0.17 g, 0.35 mmol) in a methanol/water mixture (24:4) was added solid potassium hydroxide. The solution was heated at 44 °C for 10 h. It was then neutralized with dilute HCl solution and poured into brine (50 mL). The aqueous layer was extracted three times with diethyl ether. The combined organic layer was treated with brine, dried, and concentrated in vacuo. Recrystallization in chloroform gave acid **21** (0.14 g, 82%) as a white crystalline powder, which melts between 259–261 °C: NMR ($CDCl_3$) δ 7.34 (d, J = 8 Hz, 2 H), 7.19 (m, 3 H), 6.97 (m, 2 H), 6.90 (d, J = 8 Hz, 2 H), 6.14 (d, J = 2 Hz, 1 H), 6.07 (d, J = 2 Hz, 1 H), 4.79 (d, J = 11 Hz, 1 H), 4.00 (d, J = 13 Hz, 1 H), 3.79 (s, 6 H), 3.77 (s, 3 H), 3.24 (dd, J = 11 and 13 Hz, 1 H); IR ($CDCl_3$) 3460, 3550–2650 (br), 2920, 1700, 1620, 1500, 1440, 1250, 1210, 1135, 905, 730 cm^{-1}; high-resolution mass spectrum for $C_{27}H_{26}O_8$ requires 478.162 78, measured 478.162 74; ^{13}C NMR ($CDCl_3$) δ 176.34, 163.90, 161.83, 159.17, 157.81, 134.68, 129.01, 128.90, 128.24, 127.90, 113.43, 104.84, 99.25, 92.52, 91.19, 88.56, 83.56, 77.28, 55.69, 55.55, 55.23, 50.45.

Tricyclic Amide 15. To a stirred solution of acid **21** (90 mg, 0.19 mmol) in methylene chloride (3 mL) at 0 °C under an argon atmosphere was added pyridine (0.076 mL, 0.94 mmol). The solution was stirred for 3 min, and 1,1'-carbonyldiimidazole (0.16 g, 0.94 mmol) in methylene chloride (2 mL) was added. It was stirred at 0 °C for 5 h and then allowed to slowly warm to room temperature. The mixture was quenched with dilute HCl solution and poured into brine. The aqueous layer was extracted twice with methylene chloride (20 mL). The combined organic layer was dried and concentrated in vacuo. Recrystallization in ethyl ether/hexanes (1:5) gave a white crystalline powder (50 mg, 53%) whose physical properties are identical with those of amide **15**.

Registry No. **4**, 117828-35-0; **4** Me_3Si ether, 117828-36-1; **5**, 117828-32-7; **6**, 117828-33-8; **7**, 117828-34-9; **9**, 117828-37-2; **10**, 117828-38-3; **10** detrimethylsilated, 117828-39-4; **12**, 117828-40-7; **13**, 117828-41-8; **14**, 117828-42-9; **15**, 117894-34-5; **16** (isomer 1), 117828-43-0; **16** (isomer 2), 117828-44-1; **17a**, 117828-45-2; **17b**, 117828-46-3; **18**, 117828-48-5; **18** Me_3Si ether, 117828-47-4; **19**, 117828-49-6; **20**, 117828-50-9; **21**, 117828-51-0; acrylonitrile, 107-13-1; cinnamonitrile, 4360-47-8.

Supplementary Material Available: Positional parameters and isotropic temperature factors for compound **18** (1 page). Ordering information is given on any current masthead page.

Diastereoselective Crossed Aldol Reactions with Chiral Fluorinated Aldehydes

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Lewis acid catalyzed crossed aldol reactions were carried out between optically active α-fluoro aldehydes (*S*)- and (*R*)-**2**, prepared from (*S*)-monoethyl 2-fluoro-2-methylmalonate by asymmetric enzymatic hydrolysis, and enol silyl ethers or silyl ketene acetals. Moderate to excellent diastereoselectivity was observed, depending on the nature of the Lewis acid employed. The α-fluoro substituent has little effect on the diastereoselectivity of these Lewis acid catalyzed aldol condensations.

The diastereo- and/or enantioselective construction of molecules is an important current topic in organic chemistry. A wide variety of highly stereoselective reactions have been developed, which seem to afford useful solutions toward this problem.[1] Among these, the crossed aldol reaction has especially attracted the interest of synthetic chemists. Since Mukaiyama's discovery[2] of the Lewis acid mediated reaction of enol silyl ethers with aldehydes, much work has led to the development of methods for the assembly of contiguous stereocenters with high relative as well as absolute stereocontrol.[3]

However, in the field of fluorine chemistry, only a few methods are known for the stereoselective preparation of fluorinated compounds.[4] The exploration of new methodologies is necessary, because the inherent characteristics

(1) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983–1985; Vols. 2–5.

(2) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

(3) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24. (c) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984, Vol. 3. Mukaiyama, T. *Org. React. (N.Y.)* **1982**, *28*, 203. (d) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (e) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

(4) (a) Taguchi, T.; Kawara, A.; Watanabe, S.; Oki, Y.; Fukushima, H.; Kobayash, Y.; Okada, M.; Ohta, K.; Iitaka, Y. *Tetrahedron Lett.* **1986**, *27*, 5117. (b) Scolastico, C.; Conca, E.; Prati, L.; Guanti, G.; Banfi, L.; Berti, A.; Farina, P.; Valcavi, U. *Synthesis* **1985**, 850. (c) Hanzawa, Y.; Kawagoe, K.; Ito, M.; Kobayashi, Y. *Chem. Pharm. Bull.* **1987**, *35*, 1633. (d) Yamazaki, T.; Ishikawa, N.; Iwatsubo, H.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1340.

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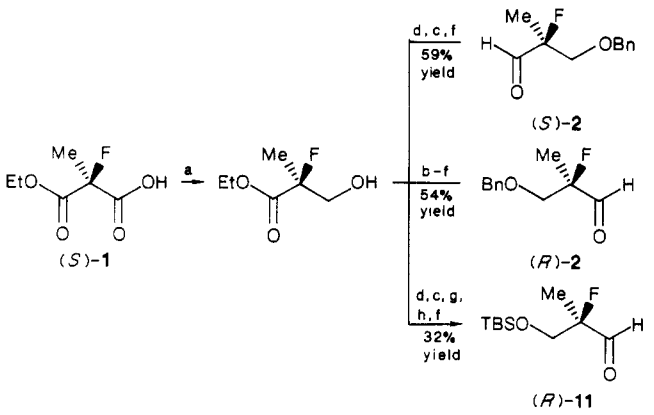
Scheme I.[a] Preparation of Optically Active Fluorinated Aldehydes



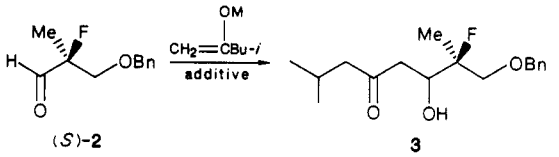
[a] (a) $(COCl)_2$, DMF/$NaBH_4$ (ref 20); (b) dihydropyran/cat. TsOH; (c) $LiAlH_4$; (d) NaH, BnBr; (e) cat. TsOH; (f) Swern oxidation; (g) t-$BuMe_2SiCl$, imidazole; (h) H_2, Pd/C.

of fluorinated molecules have resulted in their application as "fine chemicals" such as biologically active materials,[5] ferroelectric liquid crystals,[6] and so on. But it is also well established that the strongly electronegative nature of this element sometimes interferes with or alters the course of reactions[7] when compared to the analogous reaction involving nonfluorinated reactants. This has been one of the most significant factors in preventing the development of stereoselective procedures in the field of organofluorine chemistry. However, very recently, Welch and co-workers have disclosed the highly diastereoselective directed aldol condensation with fluorinated ketones[8a] or esters.[8b] Considering the success of this process in hydrocarbon chemistry, their method should offer efficient routes for assembling complex molecules containing fluorine.

On the other hand, we have shown the utility of enzymes in the preparation of optically active fluorine-containing molecules bearing appropriate functionalities.[9] Particularly, enantiotopic carbonyl groups in diethyl 2-fluoro-2-methylmalonate were discriminated by lipase-MY (*Candida cylindracea*, Meito Sangyo Co., Ltd., Japan) to produce the corresponding half ester **1** in 91% ee with predominantly the *S* configuration.[10,11] It was also found that this molecule could be readily converted to 3-(benzyloxy)-2-fluoro-2-methylpropionaldehyde **2** as either the *S* or *R* enantiomer.[12]

Here, we report full details of our investigation of the aldol reactions with **2**. These studies have involved the determination of the relative configurations of the aldol procedures, which are formed by the controlled formation of three consecutive stereogenic centers. These compounds should be important building blocks for the synthesis of fluorinated analogues of polyketide natural products.[13]

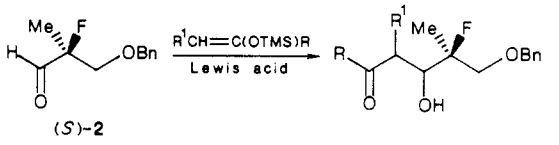
Table I. Reaction of (*S*)-2 with Various Metal Enolates



entry	M	additive	yield, %	threo:erythro[a]
1	Li	–	93	33:67
2	MgBr	–	54	36:64
3	ZnCl	–	33	43:57
4	$AlEt_2$	–	45	29:71
5	TMS	TBAF	0	–
6	TMS	TMSOTf	0	–
7	TMS	$TiCl_4$	85	91:9
8	TMS	$EtAlCl_2$	55	22:78
9	TMS	BF_3-OEt_2	62	24:76

[a] Determined by HPLC analysis.

Table II. Reaction of (*S*)-2 with Silyl Enol Ethers and Silyl Ketene Acetals



product	R	R^1	Lewis acid	yield, %	threo: erythro[a]
3	*i*-Bu	H	$TiCl_4$	83	78:22
			$EtAlCl_2$	51	9:91
4	*t*-Bu	H	$TiCl_4$	83	95:5
			$EtAlCl_2$	51	29:71
4-Si	*t*-Bu	H	$TiCl_4$[d]	75	9:91
			$EtAlCl_2$[d]	68	12:88
5	OEt	H[b]	$TiCl_4$	58	20:80
			$EtAlCl_2$	24	14:86
			BF_3-OEt_2	51	15:85
7	$(CH_2)_4$[c]		$TiCl_4$	75	52:48
			$EtAlCl_2$	60	77:23

[a] Determined by HPLC. [b] The t-$BuMe_2Si$ ketene acetal was used. [c] The relative configuration between C_2–C_3 stereocenters was not determined. [d] The reaction was performed with siloxy-protected aldehyde (*R*)-11 instead of (*S*)-2.

Results and Discussion

The homochiral fluorinated aldehydes (*S*)-2 and (*R*)-2 were synthesized from the half ester (*S*)-1 in four and six steps, respectively, by using common procedures (see Scheme I). The chirality created by the enzymatic hydrolysis should be retained during the various types of transformations because of the absence of active hydrogens at the position α to the carbonyl moiety.

To investigate the influence of the stereogenic center in (*S*)-2 on the stereoselection of aldol reactions, we first subjected this material to a reaction with a variety of kinetic enolates derived from 4-methylpentan-2-one. The results are summarized in Table I. The desired aldol products were produced with only moderate erythro

(5) (a) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha and Elsevier Biomedical: Amsterdam, 1982. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.

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(7) (a) Hine, J.; Brader, W. H., Jr. *J. Am. Chem. Soc.* **1953**, *75*, 3964. (b) Bordwell, F. G.; Brannen, W. T., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 4645.

(8) (a) Welch, J. T.; Seper, K. W. *Tetrahedron Lett.* **1984**, *25*, 5247. (b) Welch, J. T.; Seper, K. W.; Eswarakrishnan, S.; Samartino, J. *J. Org. Chem.* **1984**, *49*, 4720. Welch, J. T.; Eswakrishnan, S. *J. Chem. Soc., Chem. Commun.* **1985**, 186.

(9) Lin, J.-T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1987**, *52*, 3211 and references cited therein.

(10) (a) Kitazume, T.; Sato, T.; Ishikawa, N. *Chem. Lett.* **1984**, 1811. (b) Kitazume, T.; Sato, T.; Kobayashi, T.; Lin, J.-T. *Nihon Kagaku Kaishi* **1985**, 2116. (c) Kitazume, T.; Sato, T.; Kobayashi, T.; Lin, J.-T. *J. Org. Chem.* **1986**, *51*, 1003.

(11) Although we have also found that (*S*)-2 could be afforded in 99% ee and 94% yield by lipase-MY modified with 2-(trifluoromethyl)acrylic acid, extension to large-scale preparation has not yet been established. See: Kitazume, T.; Murata, K.; Ikeya, T. *J. Fluorine Chem.* **1986**, *32*, 233.

(12) (a) Kitazume, T.; Sato, T.; Lin, J.-T. *Nihon Kagaku Kaishi* **1985**, 2195. (b) Kitazume, T.; Yamamoto, T. *J. Fluorine Chem.* **1987**, *35*, 467. (c) Kitazume, T.; Kobayashi, T. *Synthesis* **1987**, 187.

(13) For example, the synthesis of (8*S*)-8-fluoroerythronolide A and B via fluorination was reported and their stability was also discussed. See: Toscano, L.; Fioriello, G.; Silingardi, S.; Inglesi, M. *Tetrahedron* **1984**, *40*, 2177.

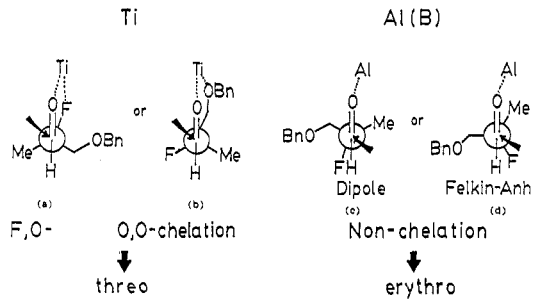


Figure 1. Transition-state model I.

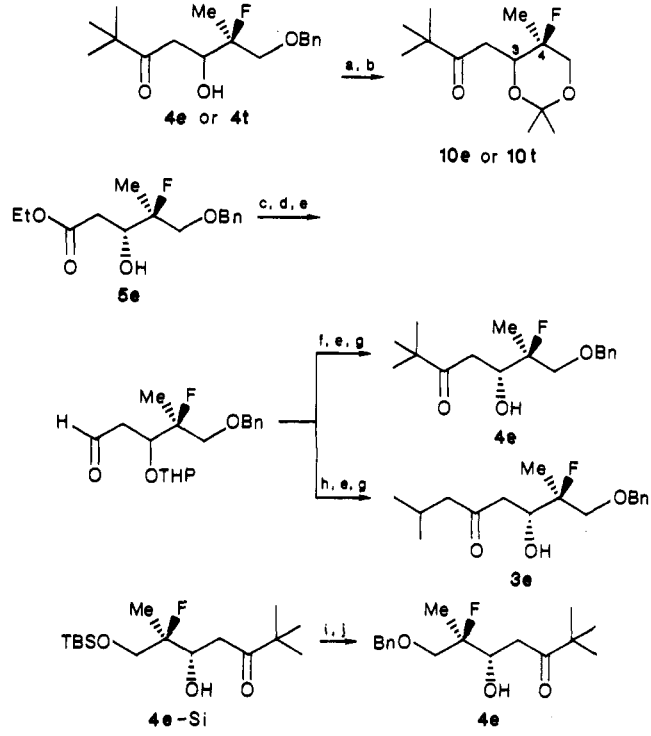
(anti)[14] selectivity (ca. 2:1) and in moderate to excellent chemical yields (entries 1–4). When the reaction was carried out with the corresponding enol sily ether, fluoride ion [tetra-*n*-butylammonium fluoride (TBAF)][15] or trimethylsilyl trifluoromethanesulfonate (TMSOTf) did not catalyze the reaction (entries 5 and 6). However, Lewis acids such as $TiCl_4$, $EtAlCl_2$, and $BF_3{\cdot}OEt_2$ strongly promoted this reaction course to provide the desired aldols **3** in moderate to high yields with moderate to excellent diastereoselectivity (entries 7–9). These results clearly show the importance of the activation of the fluorine-containing aldehyde. Although premixing of α- or β-oxygenated aldehyde and $TiCl_4$ is essential to achieve high levels of stereoselectivity due to rigid bidentate chelation, the sensitivity of (*S*)-**2** under these conditions in the absence of nucleophiles caused us to add the Lewis acid to a mixture containing the enol silyl ether and aldehyde (*S*)-**2**.

Similar stereoselectivities were attained for the reaction of (*S*)-**2** with other enol silyl ethers under similar conditions (see Table II). It is apparent from the table that the diastereomeric ratios are highly dependent on the metals employed as the Lewis acid. The influence of the Lewis acid can be rationalized as follows. The rigidity of the intermediate containing bidentate chelation by $TiCl_4$ would regulate the direction of nucleophilic attack from the sterically less hindered *si* face to yield the adduct with the threo (syn) configuration[16a,b] (see Figure 1, a and b). On the other hand, since the other Lewis acids used here have no ability to interact with two oxygens at the same time, the reaction should proceed through the Felkin model or Cram's dipolar model to afford erythro (anti) selective products[16a,b] (see Figure 1, c and d).

In order to confirm this hypothesis and clarify the stereochemistry of the obtained aldol products, we determined the relative configurations of the newly formed C_3–C_4 stereocenters (see Scheme II). Compounds **4t** and **4e**[17] were individually transformed into their acetonides, **10t** and **10e**, respectively. Examination of their ^1H NMR spectra revealed that the coupling constants between H_3 and F were 26.5 and 7.3 Hz, respectively. This led us to the conclusion that the former compound possessed the threo configuration with an anti relationship between H_3 and F. Consequently, the latter compound was the erythro isomer. The structures of the other products **3t**, **3e**, and **5e** were readily and unambiguously deduced from the results of some chemical transformations. These procedures are described in Scheme II, and their ^1H NMR data as well as the relative configurations are listed in Table III. Compound **5e** was converted in several steps via two independent routes to **3e** and **4e**, and not their diastereomers **3t** and **4t**. This is consistent with our above speculation based on transition-state models.

A question that still remained unanswered was, among the ether oxygen and fluorine atoms in (*S*)-**2**, which exhibited the stronger ability to undergo bidentate chelation with $TiCl_4$?[18] This could not be solved even after de-

Scheme II.[a] **Determination of Relative Configurations**



[a] (a) H_2, Pd/C; (b) 2,2-dimethoxypropane/cat. TsOH; (c) dihydropyran/cat. TsOH; (d) $LiAlH_4$; (e) Swern oxidation; (f) *t*-BuMgCl; (g) cat. TsOH; (h) *i*-BuBgBr; (i) Bu_4NF; (j) NaH, BnBr.

Table III. Coupling Constants and Relative Configurations of Aldols

	coupling constants,[a] Hz		relative confign	
aldol	H_2–H_3	H_3–F	C_2–C_3	C_3–C_4
3t	–	15.70	–	threo
3e	–	7.08	–	erythro
4t	–	15.63 (26.52)	–	threo
4e	–	7.56 (7.32)	–	erythro
5e	–	4.10	–	erythro
6t1	3.05	23.31	–[b]	threo
6t2	3.66	14.89	–[b]	threo
6e1	5.37	8.30	–[b]	erythro
7tt	4.03 (7.92)	14.53	threo	threo
7et	4.80 (1.81)	18.43	erythro	threo
7ee	6.75 (1.73)	7.90	erythro	erythro
8tt	2.94	9.12	threo	threo
8ee	7.08	–[c]	erythro	erythro
9te	4.02	13.26	threo	erythro
9et	4.92	15.12	erythro	threo

[a] Values in parentheses were supported from corresponding acetonides. [b] Not determined. [c] Not analyzed because of multiplicity of the peak obtained by ^1H and ^{19}F NMR.

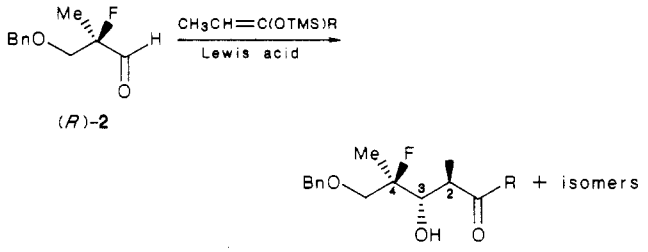
(14) In this text, nomenclature of the relative stereochemistry follows the method proposed by Noyori et al. See: Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598.

(15) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932.

(16) (a) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027. (b) Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.

(17) Abbreviation in the compound numbers represents the relative stereochemistry (erythro (e) or threo (t)) between the C_3–C_4 stereocenters. For molecules with three contiguous asymmetric carbons, the C_2–C_3 stereochemistry was first shown, followed by the C_3–C_4 relationship. Thus, **7et** implies the aldol product from the silyl enol ether derived from diethyl ketone, which possesses erythro and threo configurations between the C_2–C_3 and C_3–C_4 stereocenters, respectively.

Table IV. Reaction of (*R*)-2 with Nucleophiles with Propionyl Moiety



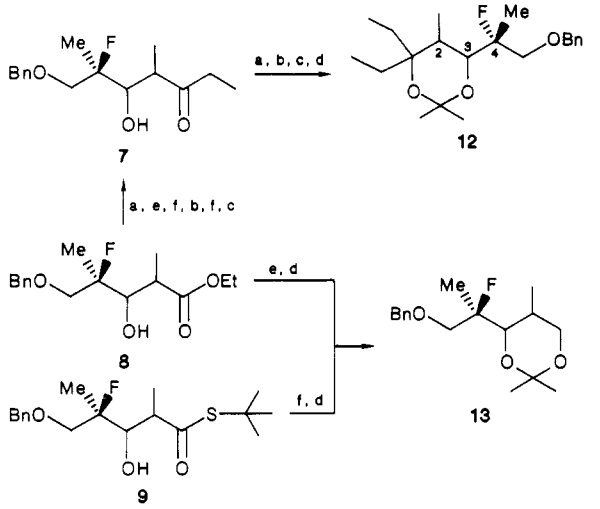
product	R	Lewis acid	yield, %	diastereoselectivity[a] et:ee:te:tt
7[e]	Et	$TiCl_4$[c]	86	30:8:12:50
		$EtAlCl_2$[c]	66	5:33:4:58
	Et	$TiCl_4$[d]	81	34:7:13:46
		$EtAlCl_2$[d]	62	5:34:4:57
8	OEt[b]	–	90	18:42:11:29
		$TiCl_4$	85	2:7:20:71
		$EtAlCl_2$	79	4:24:10:62
		$BF_3{\cdot}OEt_2$	82	5:37:6:52
9	SBu-*t*	$TiCl_4$	94	78:12:2:8
		$BF_3{\cdot}OEt_2$	81	6:12:81:<1

[a] Isomeric ratios were determined by HPLC, and abbreviations e and t indicate erythro and threo configurations between C_2–C_3, C_3–C_4 stereocenters and are arranged in this order. [b] The corresponding lithium enolate was used. [c] The *E*:*Z* ratio of silyl enol ether was 77:23. [d] *E*:*Z* = 14:86. [e] (*S*)-2 was employed instead of the corresponding *R* isomer.

termination of the relative stereochemistry of the products, since both transition-state models (Figure 1, a and b) indicate the same threo preference. Therefore, in order to obtain a more detailed understanding of the reaction pathway, we synthesized the chiral aldehyde (*R*)-11, protected with a *tert*-butyldimethylsilyl (TBS) moiety instead of a benzyl group. This compound was also readily available from the same starting material (*S*)-1 (see Scheme I). This aldehyde was of interest because this type of compound, if fluorine is replaced by a hydrogen atom, is reported not to undergo bidentate chelation.[20] Reaction of (*R*)-11 with the silyl enol ether derived from pinacolone resulted in the predominant formation of the erythro isomer. This explicitly demonstrates that this aldol reaction proceeds mainly through an open transition state, with little or no interaction between the fluorine atom and $TiCl_4$.

These results on the stereoselection of aldol reactions involving the fluorinated chiral aldehyde (*S*)-2 prompted us to develop this crossed aldol procedure for the construction of three contiguous stereogenic centers. For this purpose, we selected nucleophiles containing a propionyl moiety such as the *E* and *Z* enol silyl ethers derived from diethyl ketone, and the *E* and *Z* silyl ketene acetals derived from alkyl propionates. Reaction of (*R*)-2 with the silyl enol ethers gave aldol products **7tt** and **7et** predominantly in a ratio of threo:erythro (chelation:nonchelation) = ca. 8:2 between the C_3–C_4 stereocenters from the *E* isomer and ca. 6:4 from the *Z* isomer. The C_3–C_4 stereoselectivity was threo:erythro = 6:4 irrespective of the nucleophile configuration (Table IV). However, taking into account the fact that these four isomers could be separated into two fractions **7et**–**7ee**, **7te**–**7tt**, reaction of (*R*)-2 with silyl enol

Scheme III.[a] Determination of Relative Configurations



[a] (a) Dihydropyran/cat. TsOH; (b) EtMgBr; (c) cat. TsOH; (d) 2,2-dimethoxypropane/cat. TsOH; (e) $LiAlH_4$; (f) Swern oxidation.

ether provided on purification **7et**, **7ee**, and **7tt** in 79, 87, and 94% diastereomeric purities, respectively.

The lithium enolate prepared from ethyl propionate in turn showed a similarly low selectivity compared with the enolate derived from ethyl acetate. The Lewis acid mediated reaction of the corresponding silyl ketene acetal was shown to provide aldol 8 with an improvement in the isomeric ratio, which was also dependent on the nature of the Lewis acid used. These unsatisfactory results led us to investigate other nucleophiles. Eventually we found that *tert*-butyl thioester derivatives afforded the best diastereoselection in our studies. Thus, the C_3–C_4 stereocenters could be controlled by using $TiCl_4$ to afford the threo configuration predominantly (threo:erythro = 86:14). on the other hand, $BF_3{\cdot}OEt_2$ played a complementary role, affording predominantly the erythro configuration (threo:erythro = 7:93). While problems still remain on the overall selectivity, the isolation of isomerically pure material (**9te**) could be achieved from the $BF_3{\cdot}OEt_2$-catalyzed reaction, due to the readily separable tendency of the above diastereomers.

The stereochemistry of these products was established in basically the same manner as for compound **4**. NMR studies of the acetonides **12** derived from 8 and **9** have led us to determine the relative configurations between both the C_2–C_3 and C_3–C_4 stereocenters as given in Table III. Thus, the latter relationship in **7** is assigned from the fact that the vicinal H_3–F coupling constants differed significantly between acyclic diastereomeric pairs, **3e**–**3t** and **4e**–**4t**. For example, these values for the threo isomers were almost twice those of the erythro compounds. This empirical rule was applied to the three components **7ee**, **7tt**, and **7et**.[21] On this basis, it is concluded that **7tt** and **7et** possessed the threo configuration at C_3–C_4, while **7ee** contained an erythro relationship at this site. The stereochemical sequence between the C_2–C_3 stereocenters, in turn, was clarified after derivatization to the acetonides **12tt**, **12et**, and **12ee**, followed by ^1H NMR analysis (see Table III and Scheme III). Without separation of isomers, aldols 8 were transformed to compounds **7** and, hence, to the acetonides **12**. Their stereochemistry was confirmed by measurement of the ^1H NMR coupling constants of

(18) The fact that fluorine-containing compounds exhibited a higher preference for hydrogen bonding[19] suggested the possibility of the contact of this element with the Lewis acid.

(19) (a) Buckley, P.; Giguere, P. A.; Yamamoto, D. *Can. J. Chem.* **1968**, *46*, 2917. (b) Krueger, P. J.; Mettee, H. D. *Can. J. Chem.* **1964**, *42*, 326.

(20) Keck, G. E.; Catellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847.

(21) For the determination of the relative configuration of these isomers, diastereomerically enriched materials, which were generated by silica gel column chromatography, were employed: they were **7et** with 79% de, **7ee** with 87% de, and **7tt** with 94% de.

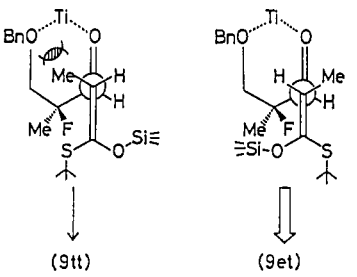


Figure 2. Transition-state model II.

acetonides **12**.[12] The relative configuration of **9** was also confirmed by ^{1}H NMR coupling constants after conversion to their acetonides **13**.[12]

Gennari et al.[16b] have previously reported the highly stereoselective preparation of aldols from the reaction of an aldehyde similar to (*S*)-**2** (fluorine is substituted by hydrogen) with the silyl ketene acetal derived from *tert*-butyl thiopropionate in the presence of a Lewis acid. Predominant formation of the isomers **9et** and **9te** in our reaction is also suggested by their transition-state model based on MNDO calculations, because the fluorine atom would be sterically very similar to hydrogen and therefore not interfere with intramolecular bidentate chelation by $TiCl_4$, as discussed above (Figure 2). For the BF_3·OEt_2-mediated reaction, the repulsion of the methyl group with this Lewis acid would exceed the gauche interaction between the methyl and R groups, favoring the transition state leading to **9te**.

This work has demonstrated the value of our fluorine-containing chiral aldehydes (*R*)- or (*S*)-**2** as substrates for diastereoselective directed aldol condensations. The products provided from these reactions should be versatile and useful molecules for the following reasons: (1) aldols with the desired configuration could be readily prepared with moderate to high levels of diastereoselectivity in around 90% ee, (2) isomeric mixtures should be easily separable by silica gel column chromatography for molecules with three consecutive stereocenters, and (3) they possess three distinguishable functionalities (i.e., alcohol, protected alcohol, and carbonyl moieties), and so on. One application of these products has been the transformation of diastereomerically pure **9te** to alcohol **14te**. This compound contains many of the same structural features as the Prelog–Djerassi lactonic acid (PDLA),[22] which is an important synthetic intermediate for the construction of macrolide antibiotics. Thus, **9te** (synthesized from (*R*)-**2** and the silyl ketene acetal from *tert*-butyl thiopropionate, followed by chromatographic separation) was transformed in five steps to the corresponding alcohol **14te** in 67% overall yield (Figure 3). Asymmetric alkylation of **14te** with a chiral propionamide[23] should afford a C_2-fluorinated PDLA derivative. Other types of aldols could also be employed in this manner for the preparation of fluorinated analogues of naturally occurring compounds and biologically active materials. Although some stereoselectivity problems remain, these should be solved in the near feature by the application of the enormous knowledge base accumulated over the past several years in hydrocarbon chemistry.

In conclusion, it is apparent from these studies that the presence of a fluorine substituent α to the aldehyde group has essentially no impact, either sterically or electronically, on the diastereoselectivity of the aldol condensation.

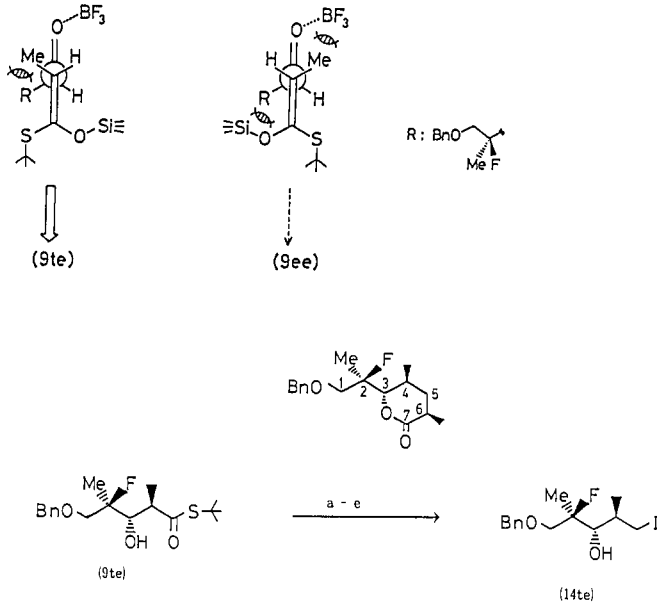


Figure 3. Preparation of the building unit for a fluorinated PDLA derivative. (a) Dihydropyran/cat. TsOH; (b) $LiAlH_4$; (c) TsCl; (d) NaI; (e) cat. TsOH.

Experimental Section

Nuclear magnetic resonance (NMR) spectra were recorded at 90 or 200 MHz for ^{1}H NMR and 56.5 MHz for ^{19}F NMR in carbon tetrachloride (CCl_4) unless otherwise noted. ^{19}F chemical shifts are reported in parts per million (ppm) relative to trifluoroacetic acid (δ 0.00) as an external standard. Optical purities (% ee) are expressed with the same value determined for the starting half ester, because the elimination of fluoride ion from each compound is known not to lead to racemization but to decomposition. Consequently, the obtained fluorine-containing materials were assumed to have retained the absolute stereochemistry of the starting half-ester at the chiral carbon atom. All boiling points were uncorrected. Capillary GLC analyses are obtained (carrier gas helium, flow 20 mL/min, capillary column packed with silicone GEXE-60 Chromosorb W at 200 °C).

(*S*)-Ethyl 3-(Benzyloxy)-2-fluoro-2-methylpropionate. To a suspension of NaH (free from oil, 0.48 g, 20.0 mmol) in freshly distilled THF (15 mL) was added dropwise the previously reported ethyl 3-hydroxy-2-fluoro-2-methylpropionate[8c] (2.70 g, 18.0 mmol) in the same solvent (10 mL) at 0 °C under nitrogen. After 1 h, a catalytic amount of tetra-*n*-butylammonium iodide (TBAI) and benzyl bromide (2.4 mL, 20 mmol) were added, and the whole was stirred overnight at ambient temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O, and this ether layer was washed with water and brine and dried over anhydrous $MgSO_4$. Removal of the solvent afforded the crude product, which was purified by column chromatography on silica gel to give 4.45 g (18.5 mmol) of the benzyloxy ester in 93% yield: $[\alpha]^{20}_D$ −9.79° (*c* 1.13, MeOH); ^{19}F NMR δ 80.0 (ddq); ^{1}H NMR δ 1.29 (3 H, t, $J_{H,H}$ = 7.16 Hz, CH_3CH_2O), 1.46 (3 H, d, $J_{H,F}$ = 21.0 Hz, CH_3CF), 3.53 (1 H, dd, $J_{H,H}$ = 10.1 Hz, $J_{H,F}$ = 18.9 Hz, $PhCH_2OCH_2$), 3.64 (1 H, dd, $J_{H,H}$ = 10.1 Hz, $J_{H,F}$ = 22.1 Hz, $PhCH_2OCH_2$), 4.17 (2 H, q, $J_{H,H}$ = 7.16 Hz, CH_3CH_2O), 4.90 (2 H, s, $PhCH_2$), 7.23 (5 H, s, Ph); IR (neat) 1715 (C=O), 700 (Ph) cm^{-1}.

(*R*)-3-(Benzyloxy)-2-fluoro-2-methylpropanol. To a suspension of $LiAlH_4$ (0.55 g, 14.4 mmol) in 10 mL of freshly distilled Et_2O was added dropwise the benzyloxy ester (5.53 g, 23.0 mmol) at 0 °C under nitrogen, and the whole was stirred for 2 h at that temperature. After the reaction mixture was quenched with saturated aqueous Na_2SO_4, the organic layer was decanted and the precipitate was washed three times with Et_2O. Then the combined ether solution was dried over anhydrous $MgSO_4$, followed by the removal of the solvent. The resulting crude product was chromatographed on silica gel to yield 4.29 g (21.6 mmol) of (*R*)-3-(benzyloxy)-2-fluoro-2-methylpropanol in 94% yield: $[\alpha]^{25}_D$ +1.08° (*c* 1.43, MeOH); ^{19}F NMR δ 82.8 (ddtq); ^{1}H NMR δ 1.27

(22) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.
(23) (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233. (b) Senda, S.; Mori, K. *Agric. Biol. Chem.* **1987**, *51*, 1379.

(3 H, d, $J_{H,F}$ = 21.9 Hz, CH_3CF), 1.83 (1 H, br s, OH), 3.47 (1 H, d, $J_{H,F}$ = 15.1 Hz), 3.58 (1 H, d, $J_{H,F}$ = 14.9 Hz), 3.58 (2 H, d, $J_{H,F}$ = 18.0 Hz), 4.50 (2 H, s, $PhCH_2$), 7.25 (5 H, s, Ph) (the three peaks at δ 3.47, 3.58, and 3.58 were not fully resolved); IR (neat) 3410 (OH), 700 (Ph) cm^{-1}.

Anal. Found: C, 66.84; H, 7.49. Calcd for $C_{11}H_{15}O_2F$: C, 66.65; H, 7.63. Exact mass calcd: 198.237. Found: 198.271.

(*S*)-3-(Benzyloxy)-2-fluoro-2-methylpropionaldehyde 2. To a solution of $(COCl)_2$ (1.3 mL, 14 mmol) in 25 mL of freshly distilled CH_2Cl_2 were added DMSO (2.2 mL, 28 mmol) with 6 mL of CH_2Cl_2 and, after 5 min, the (*R*)-benzyloxy alcohol prepared above (2.26 g, 11.5 mmol) in 10 mL of CH_2Cl_2 at −60 °C under a nitrogen atmosphere. The whole was stirred for 20 min, and then Et_3N (8.9 mL, 64 mmol) was added, followed by 5 min of stirring and removal of the dry ice/acetone bath. After additional stirring for 0.5 h at ambient temperature, the reaction mixture was quenched with water and extracted with CH_2Cl_2, and the organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. Removal of the solvent provided the crude product, which was distilled under reduced pressure to give 1.54 g (7.82 mmol) of (*S*)-**2** in 68% yield: bp 85–87 °C (1.0 mmHg); $[\alpha]^{21}_D$ +13.85° (*c* 1.12, MeOH); ^{19}F NMR δ 85.3 (dddq); ^1H NMR δ 1.34 (3 H, d, $J_{H,F}$ = 21.1 Hz, CH_3CF), 3.58 (1 H, d, $J_{H,F}$ = 20.1 Hz, OCH_2CF), 3.60 (1 H, d, $J_{H,F}$ = 22.8 Hz, OCH_2CF), 4.49 (2 H, s, $PhCH_2$), 7.27 (5 H, s, Ph), 9.74 (1 H, d, $J_{H,F}$ = 4.44 Hz, CHO); IR (neat) 1740 (C=O), 700 (Ph) cm^{-1}.

Anal. Found: C, 67.51; H, 6.46. Calcd for $C_{11}H_{13}O_2F$: C, 67.33; H, 6.68. Exact mass calcd: 196.221. Found: 196.263.

(*S*)-3-(*tert*-Butyldimethylsiloxy)-2-fluoro-2-methyl-1-(benzyloxy)propane. To a solution of the (*R*)-3-(benzyloxy)-2-fluoro-2-methylpropanol prepared above (1.55 g, 7.82 mmol) in 19 mL of DMF were added *tert*-butyldimethylsilyl chloride (1.58 g, 10.5 mmol) with 5 mL of DMF and imidazole (1.40 g, 21 mmol) with 5 mL of DMF at room temperature under a nitrogen atmosphere, and stirring was continued for 1 h. Then the reaction mixture was quenched with 3 mL of 1 N HCl and extracted with diethyl ether, and the organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by column chromatography on silica gel (elution with *n*-hexane/AcOEt = 20/1) to afford 2.18 g (6.98 mmol) of the title silyl ether in 89% yield: $[\alpha]^{25}_D$ +2.03° (*c* 1.06, MeOH); ^{19}F NMR δ 78.7 (m); ^1H NMR (CH_2Cl_2 was employed as an internal standard) δ −0.10 (6 H, s, $(CH_3)_2Si$), 0.72 (9 H, s, $(CH_3)_3Cl$), 1.11 (3 H, d, $J_{H,F}$ = 21.8 Hz, CH_3CF), 3.31–3.69 (4 H, m, $OCH_2CF(CH_3)CH_2O$), 4.36 (2 H, s, $PhCH_2$), 7.14 (5 H, s, Ph); IR (neat) 695 (Ph) cm^{-1}.

(*S*)-3-(*tert*-Butyldimethylsiloxy)-2-fluoro-2-methylpropanol. To a suspension of 10% Pd/C (0.69 g) in 20 mL of MeOH was added (*S*)-3-(*tert*-butyldimethylsiloxy)-2-fluoro-2-methyl-1-(benzyloxy)propane (2.17 g, 6.94 mmol) at room temperature under hydrogen, and stirring was continued for 1 h. Then the mixture was filtered. Removal of the solvent afforded a crude product, which was chromatographed on silica gel (elution with *n*-hexane/AcOEt = 8/1) to produce 1.30 g (5.87 mmol) of the title siloxy alcohol in 85% yield: $[\alpha]^{25}_D$ −0.71° (*c* 1.19, MeOH); ^{19}F NMR δ 78.7 (m); ^1H NMR ($CHCl_3$ was used as an internal standard) −0.09 (6 H, s, $(CH_3)_2Si$), 0.76 (9 H, s, $(CH_3)_3C$), 1.12 (3 H, d, $J_{H,F}$ = 22.3 Hz, CH_3CF), 2.08 (1 H, t, $J_{H,H}$ = 6.06 Hz, OH), 3.23–3.77 (2 H, m, $SiOCH_2$), 3.47 (2 H, dd, $J_{H,H}$ = 6.06 Hz, $J_{H,F}$ = 18.7 Hz, CH_2OH); IR (neat) 3400 (OH) cm^{-1}.

(*R*)-3-(*tert*-Butyldimethylsiloxy)-2-fluoro-2-methylpropionaldehyde (11). To a solution of $(COCl)_2$ (1.3 mL, 15 mmol) in 15 mL of CH_2Cl_2 was added DMSO (2.1 mL, 30 mmol) in 15 mL of CH_2Cl_2 at −60 °C under nitrogen, and stirring was continued for 5 min. Then (*S*)-(*tert*-butyldimethylsiloxy)-2-fluoro-2-methylpropanol prepared above (1.30 g, 5.87 mmol) in 15 mL of CH_2Cl_2 was added. After 20 min, Et_3N (10.5 mL, 75 mmol) was added and the whole was stirred for 5 min at that temperature. Then the cooling bath was removed and stirring was continued for an additional 0.5 h at the ambient temperature. The resulting mixture was quenched with water and extracted with CH_2Cl_2, and the organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. Removal of the solvent provided crude product, which was distilled to afford 0.65 g (3.16 mmol) of (*R*)-**11** in 46% yield: bp 43–44 °C (1.2 mmHg); ^{19}F NMR δ 87.5 (m); ^1H NMR ($CHCl_3$ was used as an internal standard) δ −0.11 (6 H, s, $(CH_3)_2Si$), 0.74 (9 H, s, $(CH_3)_2Si$), 1.17 (3 H, d, $J_{H,F}$ = 22.3 Hz, CH_3CF), 3.65 (1 H, d, $J_{H,F}$ = 19.8 Hz, $SiOCH_2$), 3.68 (1 H, d, $J_{H,F}$ = 23.3 Hz, $SiOCH_2$), 9.73 (1 H, d, $J_{H,F}$ = 4.68 Hz, CHO); IR (neat) 1740 (C=O) cm^{-1}.

Exact mass calcd for $C_{10}H_{21}O_2FSi$: 220.360. Found: 220.346.

General Procedure for the Aldol Reaction. To a solution of (*S*)-**2** (0.193 g, 1.0 mmol) in 1.5 mL of freshly distilled CH_2Cl_2 was added silyl enol ether or silyl ketene acetal (1.5 mmol) in 1 mL of CH_2Cl_2, followed by the addition of the Lewis acid (1.5 mmol) at −78 °C under a nitrogen atmosphere. After 1 h of stirring at the same temperature, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with water and brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by column chromatography on silica gel to afford diastereomerically pure aldol products.

(6*S*,7*S*)-8-(Benzyloxy)-7-fluoro-2,7-dimethyl-6-hydroxy-4-octanone (3t). The silyl enol ether derived from isobutyl methyl ketone with $TiCl_4$ as the Lewis acid was employed: $[\alpha]^{22}_D$ −2.37° (*c* 1.26, MeOH, 82% de); ^{19}F NMR δ 80.5 (dddq); ^1H NMR ($CDCl_3$ with D_2O) δ 1.19 (6 H, d, $J_{H,H}$ = 6.59 Hz, $CH(CH_3)_2$), 1.35 (3 H, d, $J_{H,F}$ = 22.2 Hz, CH_3CF), 2.14 (1 H, t of sep, $J_{H,H}$ = 6.84, 6.59 Hz, $CH(CH_3)_2$), 2.32 (2 H, d, $J_{H,H}$ = 6.84 Hz, $C(O)CH_2CH(CH_3)_2$), 2.63 (2 H, d, $J_{H,H}$ = 6.10 Hz, $CH(OH)CH_2C(O)$), 3.59 (1 H, dd, $J_{H,H}$ = 10.7 Hz, $J_{H,F}$ = 29.3 Hz, CH_2OCH_2Ph), 3.68 (1 H, dd, $J_{H,H}$ = 10.7 Hz, $J_{H,F}$ = 28.6 Hz, CH_2OCH_2Ph), 4.25 (1 H, dt, $J_{H,F}$ = 15.7 Hz, $J_{H,H}$ = 6.10 Hz, CH(OH)), 4.57 (2 H, s, CH_2Ph), 7.33 (5 H, s, Ph); IR (neat) 3480 (OH), 1710 (C=O), 700 (Ph) cm^{-1}.

Anal. Found: C, 68.64; H, 8.31. Calcd for $C_{17}H_{25}O_3F$: C, 68.89; H, 8.50. Exact mass calcd: 296.382. Found: 296.347.

(6*R*,7*S*)-8-(Benzyloxy)-7-fluoro-2,7-dimethyl-6-hydroxy-4-octanone (3e). The silyl enol ether derived from isobutyl methyl ketone with $EtAlCl_2$ as the Lewis acid was used. $[\alpha]^{22}_D$ +13.20° (*c* 1.26, MeOH, 56% de); ^{19}F NMR δ 79.0 (dddq); ^1H NMR ($CDCl_3$ with D_2O) δ 0.92 (6 H, d, $J_{H,H}$ = 6.59 Hz, $CH(CH_3)_2$), 1.31 (3 H, d, $J_{H,F}$ = 22.2 Hz, CH_3CF), 2.16 (1 H, t of sep, $J_{H,H}$ = 6.84, 6.59 Hz, $CH(CH_3)_2$), 2.33 (2 H, d, $J_{H,H}$ = 6.84 Hz, $C(O)CH_2CH(CH_3)_2$), 2.55 (1 H, dd, $J_{H,H}$ = 17.34, 9.77 Hz, $CH(OH)CH_2C(O)$), 2.71 (1 H, dd, $J_{H,H}$ = 17.3, 2.28 Hz, $CH(OH)CH_2C(O)$), 3.61 (1 H, d, $J_{H,F}$ = 21.5 Hz, CH_2OCH_2Ph), 3.61 (1 H, d, $J_{H,F}$ = 19.1 Hz, CH_2OCH_2Ph), 4.37 (1 H, ddd, $J_{H,H}$ = 2.28, 9.77 Hz, $J_{H,F}$ = 7.08 Hz, CH(OH)), 4.59 (2 H, s, CH_2Ph), 7.34 (5 H, s, Ph); IR (neat) 3480 (OH), 1710 (C=O), 700 (Ph) cm^{-1}.

Anal. Found: C, 68.73; H, 8.19. Calcd for $C_{17}H_{25}O_3F$: C, 68.89; H, 8.50. Exact mass calcd: 296.382. Found: 296.336.

(5*S*,6*S*)-7-(Benzyloxy)-6-fluoro-2,2,6-trimethyl-3-heptanone (4t). The silyl enol ether derived from pinacolone with $TiCl_4$ as the Lewis acid was used: $[\alpha]^{25}_D$ −17.08° (*c* 1.21, MeOH, 90% de); ^{19}F NMR δ 80.7 (dddq); ^1H NMR ($CDCl_3$ with D_2O) δ 1.14 (9 H, s, $(CH_3)_3C$), 1.37 (3 H, d, $J_{H,F}$ = 22.2 Hz, CH_3CF), 2.75 (2 H, d, $J_{H,H}$ = 5.98 Hz, $CH_2C(O)$), 3.66 (1 H, d, $J_{H,F}$ = 16.4 Hz, CH_2OCH_2Ph), 3.66 (1 H, d, $J_{H,F}$ = 20.5 Hz, CH_2OCH_2Ph), 4.22 (1 H, dt, $J_{H,H}$ = 5.98 Hz, $J_{H,F}$ = 15.6 Hz, CH(OH)), 4.58 (2 H, s, CH_2Ph), 7.33 (5 H, s, Ph); IR (neat) 3490 (OH), 1700 (C=O), 700 (Ph) cm^{-1}.

Anal. Found: C, 68.59; H, 8.43. Calcd for $C_{17}H_{25}O_3F$: C, 68.89; H, 8.50. Exact mass calcd: 296.382. Found: 296.378.

(5*R*,6*S*)-7-(Benzyloxy)-6-fluoro-2,2,6-trimethyl-3-heptanone (4e). The silyl enol ether derived from pinacolone with $EtAlCl_2$ as the Lewis acid was used: $[\alpha]^{25}_D$ +17.88° (*c* 1.11, MeOH, 89% ee, 42% de); ^{19}F NMR δ 79.1 (dddq); ^1H NMR ($CDCl_3$ with D_2O) δ 1.15 (9 H, s, $(CH_3)_3C$), 1.32 (3 H, d, $J_{H,F}$ = 22.5 Hz, CH_3CF), 2.61 (2 H, dd, $J_{H,H}$ = 17.6, 10.0 Hz, $CH_2C(O)$), 2.86 (2 H, dd, $J_{H,H}$ = 17.58, 1.71 Hz, $CH_2C(O)$), 3.62 (1 H, d, $J_{H,F}$ = 19.8 Hz, CH_2OCH_2Ph), 3.63 (1 H, d, $J_{H,F}$ = 22.0 Hz, CH_2OCH_2Ph), 4.34 (1 H, ddd, $J_{H,H}$ = 10.0, 1.71 Hz, $J_{H,F}$ = 7.56 Hz, CH_2OCH_2Ph), 4.60 (2 H, s, CH_2Ph), 7.34 (5 H, s, Ph); IR (KBr) 3470 (OH), 1700 (C=O), 700 (Ph) cm^{-1}.

Exact mass calcd for $C_{17}H_{25}O_3F$: 296.382. Found: 296.402.

(3*S*,4*S*)-Ethyl 5-(Benzyloxy)-4-fluoro-4-methyl-3-hydroxypentanoate (5e). The silyl ketene acetal derived from ethyl acetate with $BF_3{\cdot}OEt_2$ as the Lewis acid was used: $[\alpha]^{25}_D$ +6.90° (*c* 1.26, MeOH, 88% ee, 70% de); ^{19}F NMR δ 79.2 (dddq); ^1H NMR ($CDCl_3$) δ 1.26 (3 H, t, $J_{H,H}$ = 7.08 Hz, CH_3CH_2O), 1.31 (3 H, d, $J_{H,F}$ = 22.6 Hz, CH_3C), 2.43 (1 H, dd, $J_{H,H}$ = 16.3 Hz, $J_{H,F}$ = 8.94 Hz, $CH_2C(O)$), 2.64 (1 H, dd, $J_{H,H}$ = 16.3 Hz, $J_{H,F}$ =

3.90 Hz, $CH_2C(O)$), 3.14 (1 H, d, $J_{H,H}$ = 3.96 Hz, O*H*), 3.60 (2 H, d, $J_{H,F}$ = 19.8 Hz, CH_2OCH_2Ph), 4.16 (2 H, d, $J_{H,H}$ = 7.08 Hz, CH_3CH_2O), 4.32 (1 H, m, C*H*(OH)), 4.57 (2 H, s, CH_2Ph), 7.35 (5 H, s, Ph); IR (neat) 3490 (OH), 1735 (C=O), 700 (Ph) cm^{-1}.

Anal. Found: C, 63.74; H, 7.27. Calcd for $C_{15}H_{21}O_4F$: C, 63.37; H, 7.45. Exact mass calcd: 284.327. Found: 284.351.

2-((1*R*,2*S*)-3-(Benzyloxy)-2-fluoro-2-methyl-1-hydroxypropyl)cyclohexanone (6t1). The silyl enol ether derived from cyclohexanone and $TiCl_4$ as the Lewis acid were used: $[\alpha]^{22}_D$ −11.21° (*c* 1.02, MeOH, 89% ee); ^{19}F NMR δ 82.5 (dddq); ^1H NMR ($CDCl_3$ with D_2O) δ 1.36 (3 H, d, $J_{H,F}$ = 22.2 Hz, CH_3CF), 1.57–2.69 (9 H, m, cyclohexanone ring), 3.62 (1 H, dd, $J_{H,H}$ = 10.0 Hz, $J_{H,F}$ = 28.8 Hz, CH_2OCH_2Ph), 3.69 (1 H, dd, $J_{H,H}$ = 10.0 Hz, $J_{H,F}$ = 29.5 Hz, CH_2OCH_2Ph), 4.35 (1 H, dd, $J_{H,H}$ = 3.05 Hz, $J_{H,F}$ = 23.3 Hz, C*H*OH), 4.56 (2 H, s, CH_2Ph), 7.33 (5 H, s, Ph); IR (neat) 3470 (OH), 1700 (C=O), 700 (Ph) cm^{-1}.

Anal. Found: C, 68.99; H, 7.68. Calcd for $C_{17}H_{23}O_3F$: C, 69.37; H, 7.88. Exact mass calcd: 294.366. Found: 294.344.

2-((1*S*,2*S*)-3-(Benzyloxy)-2-fluoro-2-methyl-1-hydroxypropyl)cyclohexanone (6e). The silyl enol ether derived from cyclohexanone and $TiCl_4$ as the Lewis acid were used: ^{19}F NMR δ 77.2 (dddq); ^1H NMR ($CDCl_3$ with D_2O) δ 1.29 (3 H, d, $J_{H,F}$ = 22.2 Hz, CH_3CF), 1.53–2.76 (9 H, m, cyclohexanone ring), 3.57 (1 H, dd, $J_{H,H}$ = 11.0 Hz, $J_{H,F}$ = 19.1 Hz, CH_2OCH_2Ph), 3.67 (1 H, dd, $J_{H,H}$ = 11.0 Hz, $J_{H,F}$ = 25.4 Hz, CH_2OCH_2Ph), 3.96 (1 H, dd, $J_{H,H}$ = 5.37 Hz, $J_{H,F}$ = 8.30 Hz, C*H*OH), 4.60 (2 H, s, CH_2Ph), 7.34 (5 H, s, Ph); IR (neat) 3470 (OH), 1700 (C=O), 700 (Ph) cm^{-1}.

Exact mass calcd for $C_{17}H_{23}O_3F$: 294.366. Found: 294.381.

2-((1*R*,2*S*)-3-(Benzyloxy)-2-fluoro-2-methyl-1-hydroxypropyl)cyclohexanone (6t2). The silyl enol ether derived from cyclohexanone and $EtAlCl_2$ as the Lewis acid were used: $[\alpha]^{26}_D$ +38.61° (*c* 1.00, MeOH, 89% ee); ^{19}F NMR δ 81.2 (dtq); ^1H NMR ($CDCl_3$ with D_2O) δ 1.41 (3 H, d, $J_{H,F}$ = 22.5 Hz, CH_3CF), 1.53–2.71 (9 H, m, cyclohexanone ring), 3.55 (2 H, d, $J_{H,F}$ = 18.1 Hz, CH_2OCH_2Ph), 4.42 (1 H, dd, $J_{H,H}$ = 3.66 Hz, $J_{H,F}$ = 14.9 Hz, C*H*OH), 4.56 (2 H, s, CH_2Ph), 7.34 (5 H, s, Ph); IR (neat) 3460 (OH), 1700 (C=O), 700 (Ph) cm^{-1}.

Exact mass calcd for $C_{17}H_{23}O_3F$: 294.366. Found: 294.325.

(4*R*,5*S*,6*S*)-7-(Benzyloxy)-6-fluoro-4,6-dimethyl-5-hydroxy-3-heptanone (7tt). The silyl enol ether derived from diethyl ketone and $EtAlCl_2$ as the Lewis acid were used: $[\alpha]^{27}_D$ +9.33° (*c* 1.24, MeOH, 34% de (with the C_2–C_3 isomer)); ^{19}F NMR δ 77.6 (dddq); ^1H NMR ($CDCl_3$ with D_2O) δ 1.02 (3 H, t, $J_{H,H}$ = 7.21 Hz, CH_3CH_2), 1.24 (3 H, d, $J_{H,H}$ = 7.12 Hz, $CH_3CHC(O)$), 1.32 (3 H, d, $J_{H,F}$ = 22.5 Hz, CHCF), 2.53 (2 H, q, $J_{H,H}$ = 7.21 Hz, CH_3CH_2), 2.95 (1 H, dq, $J_{H,H}$ = 4.03, 7.12 Hz, $CH_3CHC(O)$), 3.56 (1 H, d, $J_{H,F}$ = 17.6 Hz, CH_2OCH_2Ph), 3.56 (1 H, d, $J_{H,F}$ = 20.5 Hz, CH_2OCH_2Ph), 3.85 (1 H, dd, $J_{H,H}$ = 4.03 Hz, $J_{H,F}$ = 14.5 Hz, C*H*OH), 4.60 (2 H, s, CH_2Ph), 7.34 (5 H, s, Ph); IR (neat) 3450 (OH), 1700 (C=O), 700 (Ph) cm^{-1}.

Anal. Found: C, 72.42; H, 8.96. Calcd for $C_{16}H_{23}O_2F$: C, 72.15; H, 8.70. Exact mass calcd: 266.356. Found: 266.327.

(4*R*,5*R*,6*S*)-7-(Benzyloxy)-6-fluoro-4,6-dimethyl-5-hydroxy-3-heptanone (7ee). The silyl enol ether derived from diethyl ketone and $EtAlCl_2$ as the Lewis acid were used: $[\alpha]^{27}_D$ +5.88° (*c* 0.29, MeOH, 89% ee, 74% de (with **7ee**:**7et**)); ^{19}F NMR δ 77.5 (dtq); ^1H NMR ($CDCl_3$ with D_2O) δ 1.03 (3 H, t, $J_{H,H}$ = 7.20 Hz, CH_3CH_2), 1.18 (3 H, d, $J_{H,H}$ = 7.08 Hz, $CH_3CHC(O)$), 1.37 (3 H, d, $J_{H,F}$ = 22.7 Hz, CH_3CF), 2.49 (2 H, dq, $J_{H,F}$ = 3.67 Hz, $J_{H,H}$ = 7.20 Hz, CH_3CH_2), 2.87 (1 H, dq, $J_{H,H}$ = 6.75, 7.08 Hz, $CH_3CHC(O)$), 3.58 (2 H, d, $J_{H,F}$ = 18.6 Hz, CH_2OCH_2Ph), 4.16 (1 H, dd, $J_{H,H}$ = 6.75 Hz, $J_{H,F}$ = 7.90 Hz, C*H*OH), 4.57 (2 H, m, CH_2Ph), 7.33 (5 H, s, Ph); IR (neat) 3470 (OH), 1710 (C=O), 700 (Ph) cm^{-1}.

Exact mass calcd for $C_{16}H_{23}O_2F$: 266.356. Found: 266.375.

(4*S*,5*S*,6*S*)-7-(Benzyloxy)-6-fluoro-4,6-dimethyl-5-hydroxy-3-heptanone (7et). The silyl enol ether derived from diethyl ketone and $EtAlCl_2$ as the Lewis acid were used: $[\alpha]^{27}_D$ +15.49° (*c* 1.24, MeOH, 89% ee); ^{19}F NMR δ 81.5 (dddq); ^1H NMR ($CDCl_3$ with D_2O) δ 1.04 (3 H, t, $J_{H,H}$ = 7.21 Hz, CH_3CH_2), 1.21 (3 H, d, $J_{H,H}$ = 7.12 Hz, $CH_3CHC(O)$), 1.38 (3 H, d, $J_{H,F}$ = 22.7 Hz, CH_3CF), 2.51 (2 H, dq, $J_{H,F}$ = 5.86 Hz, $J_{H,H}$ = 7.21 Hz, CH_3CH_2), 2.84 (1 H, dq, $J_{H,H}$ = 4.80, 7.12 Hz, $CH_3CHC(O)$), 3.58 (1 H, dd, $J_{H,H}$ = 10.1 Hz, $J_{H,F}$ = 15.5 Hz, CH_2OCH_2Ph), 3.72 (1 H, dd, $J_{H,H}$ = 10.1 Hz, $J_{H,F}$ = 15.4 Hz, CH_2OCH_2Ph), 4.06 (1 H, dd, $J_{H,H}$ = 4.80 Hz, $J_{H,F}$ = 18.4 Hz, C*H*OH), 4.57 (2 H, s, CH_2Ph), 7.33 (5 H, s, Ph); IR (neat) 3490 (OH), 1710 (C=O), 700 (Ph) cm^{-1}.

Exact mass calcd for $C_{16}H_{23}O_2F$: 266.356. Found: 266.394.

(2*S*,3*R*,4*R*)-Ethyl 5-(Benzyloxy)-4-fluoro-2,4-dimethyl-3-hydroxypentanoate (8tt). The silyl ketene acetal derived from ethyl propionate and $EtAlCl_2$ as the Lewis acid were used: $[\alpha]^{22}_D$ −7.75° (*c* 1.25, MeOH, 90% ee, 72% de (with the C_3–C_4 isomer)); ^{19}F NMR δ 81.0 (dtq); ^1H NMR ($CDCl_3$) δ 1.23 (3 H, d, $J_{H,H}$ = 7.20 Hz, $CH_3CHC(O)$), 1.25 (3 H, t, $J_{H,H}$ = 7.30 Hz, CH_3CH_2O), 1.29 (3 H, d, $J_{H,F}$ = 22.7 Hz, CH_3CF), 2.71 (1 H, dq, $J_{H,H}$ = 2.94, 7.32 Hz, $CH_3CHC(O)$), 3.53 (2 H, d, $J_{H,F}$ = 19.2 Hz, CH_2OCH_2Ph), 3.64 (1 H, d, $J_{H,H}$ = 3.66 Hz, O*H*), 3.76 (1 H, ddd, $J_{H,H}$ = 3.66, 2.94 Hz, $J_{H,F}$ = 9.12 Hz, C*H*OH), 4.13 (2 H, q, $J_{H,H}$ = 7.30 Hz, CH_3CH_2O), 4.57 (2 H, m, CH_2Ph), 7.34 (5 H, s, Ph); IR (neat) 3470 (OH), 1730 (C=O), 700 (Ph) cm^{-1}.

Anal. Found: C, 64.61; H, 8.03. Calcd for $C_{16}H_{23}O_4F$: C, 64.41; H, 7.77. Exact mass calcd: 298.354. Found: 298.395.

(2*S*,3*S*,4*R*)-Ethyl 5-(Benzyloxy)-4-fluoro-2,4-dimethyl-3-hydroxypentanoate (8ee). The silyl ketene acetal derived from ethyl propionate and $EtAlCl_2$ as the Lewis acid were used: $[\alpha]^{22}_D$ −7.06° (*c* 0.83, MeOH, 90% ee, 71% de (with the C_3–C_4 isomer)); ^{19}F NMR δ 78.3 (dddq); ^1H NMR ($CDCl_3$) δ 1.19 (3 H, d, $J_{H,H}$ = 7.14 Hz, $CH_3CHC(O)$), 1.23 (3 H, t, $J_{H,H}$ = 7.22 Hz, CH_3CH_2O), 1.34 (3 H, d, $J_{H,F}$ = 22.7 Hz, CH_3CF), 2.63 (1 H, dq, $J_{H,H}$ = 7.14, 7.08 Hz, $CH_3CHC(O)$), 2.80 (1 H, br d, $J_{H,H}$ = 4.80 Hz, O*H*), 3.54 (1 H, d, $J_{H,F}$ = 17.6 Hz, CH_2OCH_2Ph), 3.55 (1 H, d, $J_{H,F}$ = 19.7 Hz, CH_2OCH_2Ph), 3.93–4.20 (1 H, m, C*H*OH), 4.11 (2 H, q, $J_{H,H}$ = 7.22 Hz, CH_3CH_2O), 4.57 (2 H, s, CH_2Ph), 7.34 (5 H, s, Ph); IR (neat) 3470 (OH), 1730 (C=O), 700 (Ph) cm^{-1}.

Exact mass calcd for $C_{16}H_{23}O_4F$: 298.354. Found: 298.303.

(2*R*,3*S*,4*R*)-*tert*-Butyl 5-(Benzyloxy)-4-fluoro-2,4-dimethyl-3-hydroxythiopentanoate (9te). The silyl ketene acetal derived from *tert*-butyl thiopropionate was used: $[\alpha]^{19}_D$ −20.61° (*c* 1.06, MeOH, 89% ee, 99% de); ^{19}F NMR δ 78.8 (dtq); ^1H NMR ($CDCl_3$) δ 1.31 (3 H, d, $J_{H,F}$ = 22.4 Hz, CH_3CF), 1.32 (3 H, d, $J_{H,H}$ = 7.26 Hz, $CH_3CHC(O)$), 1.46 (9 H, s, $(CH_3)_3CS$), 2.80 (1 H, dq, $J_{H,H}$ = 4.02, 7.26 Hz, $CH_3CHC(O)$), 3.41 (1 H, d, $J_{H,H}$ = 9.84 Hz, O*H*), 3.54 (2 H, d, $J_{H,F}$ = 18.3 Hz, CH_2OCH_2Ph), 3.72 (1 H, ddd, $J_{H,H}$ = 4.02, 9.84 Hz, $J_{H,F}$ = 13.3 Hz, C*H*OH), 4.57 (2 H, s, CH_2Ph), 7.32 (5 H, s, Ph); IR (neat) 3480 (OH), 1660 (C=O), 700 (Ph) cm^{-1}.

(2*R*,3*R*,4*R*)-*tert*-Butyl 5-(Benzyloxy)-4-fluoro-2,4-dimethyl-3-hydroxythiopentanoate (9et). The silyl ketene acetal derived from *tert*-butyl thiopropionate was used: 34% de; ^{19}F NMR δ 78.6 (m); ^1H NMR ($CDCl_3$) δ 1.23 (3 H, dd, $J_{H,H}$ = 7.20 Hz, $J_{H,F}$ = 1.08 Hz, $CH_3CHC(O)$), 1.33 (3 H, d, $J_{H,F}$ = 22.9 Hz, CH_3CF), 1.44 (9 H, s, $(CH_3)_3CS$), 2.50 (1 H, dd, $J_{H,H}$ = 5.58 Hz, $J_{H,F}$ = 1.26 Hz, O*H*), 2.77 (1 H, dq, $J_{H,H}$ = 4.92, 7.14 Hz, $CH_3CHC(O)$), 3.53 (1 H, dd, $J_{H,H}$ = 10.3 Hz, $J_{H,F}$ = 13.9 Hz, CH_2OCH_2Ph), 3.69 (1 H, dd, $J_{H,H}$ = 10.3 Hz, $J_{H,F}$ = 16.4 Hz, CH_2OCH_2Ph), 4.06 (1 H, ddd, $J_{H,H}$ = 4.92, 5.58 Hz, $J_{H,F}$ = 15.1 Hz, C*H*OH), 4.56 (2 H, s, CH_2Ph), 7.33 (5 H, s Ph); IR (neat) 3470 (OH), 1660 (C=O), 700 (Ph) cm^{-1}.

(4*S*,5*S*)-2,2,5-Trimethyl-4-(3,3-dimethyl-2-oxo-1-butyl)-5-fluoro-1,3-dioxane (10t). To a suspension of 10% Pd/C (0.80 g) in 5 mL of MeOH was added aldol **4t** (0.23 g, 0.74 mmol) with 3 mL of MeOH at room temperature under a hydrogen atmosphere. After 0.5 h of stirring, the mixture was filtered. The solvent was evaporated in vacuo, and the crude product was purified by column chromatography on silica gel to afford 0.13 g (0.65 mmol) of the corresponding diol in 83% yield: ^{19}F NMR δ 74.8 (m); ^1H NMR ($CDCl_3$) δ 0.99 (3 H, s, $(CH_3)_3C$), 1.16 (6 H, s, $(CH_3)_3C$), 1.33 (3 H, d, $J_{H,F}$ = 20.4 Hz, CH_3CF), 1.76 (2 H, br s, O*H*), 2.32–2.83 (2 H, m, $CH_2C(O)$), 3.45–3.94 (2 H, m, CH_2OH), 4.12–4.45 (1 H, m, C*H*OH); IR (neat) 3400 (OH), 1700 (C=O) cm^{-1}.

Then, to a solution of this diol (115 mg, 0.56 mmol) and 2,2-dimethoxypropane (0.2 mL, 1.6 mmol) was added a catalytic amount of *p*-toluenesulfonic acid in 4 mL of dry acetone, which was stirred for 20 min at room temperature, followed by quenching with saturated aqueous $NaHCO_3$ and extraction with Et_2O. The organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by column chromatography on silica gel to afford 124 mg (0.53 mmol) of acetonide **10t** in 95% yield: $[\alpha]^{25}_D$ −36.92° (*c* 0.73, MeOH, 91% ee, 98% de); ^{19}F NMR δ 89.8 (dddq); ^1H NMR δ 1.13 (9 H, s, $(CH_3)_3C$), 1.15 (3 H, d, $J_{H,F}$ = 19.62 Hz, CH_3CF), 1.29, 1.36 (3 H each, s, CH_3), 2.23 (1 H, dd, $J_{H,H}$ = 16.8, 3.60 Hz, $CH_2C(O)$), 2.68 (1 H, dd, $J_{H,H}$ = 16.8, 8.10 Hz, $CH_2C(O)$),

3.62 (1 H, d, $J_{H,F}$ = 22.4 Hz, CH_2O), 3.82 (1 H, d, $J_{H,F}$ = 19.0 Hz, CH_2O), 4.40 (1 H, ddd, $J_{H,H}$ = 8.10, 3.60 Hz, $J_{H,F}$ = 26.5 Hz, C*H*O); IR (neat) 1710 (C=O) cm^{-1}.

Exact mass calcd for $C_{13}H_{20}O_3F$: 243.298. Found: 243.329.

(4*R*,5*S*)-2,2,5-Trimethyl-4-(3,3-dimethyl-2-oxo-1-butyl)-5-fluoro-1,3-dioxane (10e). The same procedure as for the preparation of **10t** was employed to afford protected erythro diol **10e** in 79% yield for two steps. Physical properties for the intermediate diol: ^{19}F NMR δ 75.9 (m); ^{1}H NMR ($CDCl_3$) δ 0.99 (3 H, s, $(CH_3)_3$), 1.19 (6 H, s (CH_3)$_3$), 1.36 (3 H, d, $J_{H,F}$ = 22.1 Hz, CH_3CF), 1.94 (2 H, br s, O*H*), 2.79 (1 H, d, $J_{H,H}$ = 6.60 Hz, CH_2C(O)), 2.80 (1 H, d, $J_{H,H}$ = 4.92 Hz, CH_2C(O)), 3.43 (2 H, d, $J_{H,F}$ = 17.8 Hz, CHOH), 4.20 (1 H, ddd, $J_{H,H}$ = 6.60, 4.92 Hz, $J_{H,F}$ = 14.9 Hz, C*H*OH); IR (neat) 3400 (OH), 1700 (C=O) cm^{-1}.

For **10e**: $[\alpha]^{25}_D$ +45.02° (*c* 0.54, MeOH, 91% ee, >99% de); ^{19}F NMR δ 80.7 (dddq); ^{1}H NMR δ 1.09 (9 H, s, $(CH_3)_3$C), 1.22, 1.43 (3 H each, s, CH_3), 1.33 (3 H, d, $J_{H,F}$ = 20.9 Hz, CH_3CF), 2.29 (1 H, dd, $J_{H,H}$ = 16.2, 2.28 Hz, CH_2C(O)), 2.68 (1 H, dd, $J_{H,H}$ = 16.2, 9.60 Hz, CH_2C(O)), 3.52 (1 H, dd, $J_{H,H}$ = 11.4 Hz, $J_{H,F}$ = 4.86 Hz, CH_2O), 3.82 (1 H, dd, $J_{H,H}$ = 11.4 Hz, $J_{H,F}$ = 11.2 Hz, CH_2O), 4.40 (1 H, ddd, $J_{H,H}$ = 16.2, 9.60 Hz, $J_{H,F}$ = 7.32 Hz, C*H*O); IR (neat) 1710 (C=O) cm^{-1}.

Exact mass calcd for $C_{13}H_{20}O_3F$: 243.298. Found: 243.276.

(5*R*,6*S*)-4,4-Diethyl-2,2,5-trimethyl-6-((2*S*)-2-fluoro-1-(benzyloxy)prop-2-yl)-1,3-dioxane (12tt). A mixture of aldol **7tt** (366 mg, 0.130 mmol), dihydopyran (0.20 mL, 0.22 mmol), and a catalytic amount of TsOH in 3 mL of benzene was stirred for 30 min at room temperature. The mxiture was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O, and the organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. Evaporation afforded 538 mg of crude THP ether, which was dissolved in 4 mL of freshly distilled THF and added to a solution of EtMgBr (7 mmol) in 4 mL of the same solvent at 0 °C under nitrogen. After 1 h of stirring at that temperature, the mxture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O, and the organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to afford 544 mg of crude material. This was dissolved in 8 mL of MeOH with a catalytic amount of TsOH and was stirred overnight at room temperature. Then a few drops of Et_3N were added, and removal of the volatiles provided a crude product. This was purified by column chromatography on silica gel to afford 182 mg of the corresponding diol. A mixture of this diol (182 mg, 0.58 mmol), 2,2-dimethoxypropane (0.3 mL, 2.4 mmol), and a catalytic amount of TsOH in 5 mL of dry acetone was stirred for 0.5 h at room temperature. Then the reaction mixture was quenched with a few drops of Et_3N. The removal of the solvent afforded a crude oil, which was chromatographed to afford 92 mg (0.26 mmol) of acetonide **12tt** in 20% total yield: ^{19}F NMR δ 77.9 (m); ^{1}H NMR ($CDCl_3$) δ 0.88 (3 H, t, $J_{H,H}$ = 7.14 Hz, CH_3CH$_2$), 0.89 (3 H, t, $J_{H,H}$ = 7.14 Hz, CH_3CH$_2$), 1.15 (3 H, dd, $J_{H,H}$ = 9.12 Hz, $J_{H,F}$ = 1.36 Hz, CH_3CH), 1.21–1.66 (4 H, m, CH$_3$CH_2), 1.31 (3 H, d, $J_{H,F}$ = 21.7 Hz, CH_3CF), 1.32 and 1.40 (3 H each, s, $(CH_3)_2$C), 2.01 (1 H, dq, $J_{H,H}$ = 7.92, 9.18 Hz, CH$_3$C*H*), 3.50 (1 H, dd, $J_{H,H}$ = 7.90 Hz, $J_{H,F}$ = 19.2 Hz, CH_2OCH$_2$Ph), 3.55 (1 H, dd, $J_{H,H}$ = 7.90 Hz, $J_{H,F}$ = 18.6 Hz, CH_2OCH$_2$Ph), 4.00 (1 H, dd, $J_{H,H}$ = 7.92 Hz, $J_{H,F}$ = 9.18 Hz, C*H*O), 4.58 (2 H, s, CH_2Ph), 7.32 (5 H, s, Ph); IR (neat) 700 (Ph) cm^{-1}.

Exact mass calcd for $C_{21}H_{33}O_3F$: 352.490. Found: 352.436.

Compounds **12ee** and **12et** were prepared by an analogous procedure.

(5*R*,6*R*)-4,4-Diethyl-2,2,5-trimethyl-6-((2*S*)-2-fluoro-1-(benzyloxy)prop-2-yl)-1,3-dioxane (12ee): ^{19}F NMR δ 82.3 (m); ^{1}H NMR ($CDCl_3$) δ 0.71 (3 H, t, $J_{H,H}$ = 7.42 Hz, CH_3CH$_2$), 0.88 (3 H, t, $J_{H,H}$ = 7.37 Hz, CH_3CH$_2$), 1.04 (3 H, dd, $J_{H,H}$ = 6.80 Hz, $J_{H,F}$ = 1.59 Hz, CH_3CH), 1.24–1.62 (4 H, m, CH$_3$CH_2), 1.49 (3 H, d, $J_{H,F}$ = 21.3 Hz, CH_3CF), 1.52 (6 H, s, $(CH_3)_2$C), 1.98 (1 H, dq, $J_{H,H}$ = 1.73, 6.80 Hz, CH$_3$C*H*), 3.53 (1 H, dd, $J_{H,H}$ = 8.95 Hz, $J_{H,F}$ = 14.7 Hz, CH_2OCH$_2$Ph), 3.55 (1 H, dd, $J_{H,H}$ = 8.95 Hz, $J_{H,F}$ = 14.9 Hz, CH_2OCH$_2$Ph), 4.19 (1 H, dd, $J_{H,H}$ = 1.73 Hz, $J_{H,F}$ = 21.4 Hz, C*H*O), 4.51 (1 H, d, $J_{H,H}$ = 11.4 Hz, CH_2Ph), 4.62 (1 H, d, $J_{H,H}$ = 11.4 Hz, CH_2Ph), 7.33 (5 H, s, Ph); IR (neat) 700 (Ph) cm^{-1}.

Exact mass calcd for $C_{21}H_{33}O_3F$: 352.490. Found: 352.474.

(5*S*,6*S*)-4,4-Diethyl-2,2,5-trimethyl-6-((2*R*)-2-fluoro-1-(benzyloxy)prop-2-yl)-1,3-dioxane (12et): ^{19}F NMR δ 82.8 (m); ^{1}H NMR ($CDCl_3$) δ 0.75 (3 H, t, $J_{H,H}$ = 7.37 Hz, CH_3CH$_2$), 0.88 (3 H, t, $J_{H,H}$ = 7.37 Hz, CH_3CH$_2$), 1.07 (3 H, dd, $J_{H,H}$ = 8.0 Hz, $J_{H,F}$ = 1.93 Hz, CH_3CH), 1.28–1.62 (4 H, m, CH$_3$CH_2), 1.39 and 1.41 (3 H each, s, $(CH_3)_2$C), 1.40 (3 H, d, $J_{H,F}$ = 21.2 Hz, CH_3CF), 1.99 (1 H, dq, $J_{H,H}$ = 1.81, 8.0 Hz, CH$_3$C*H*), 3.46 (1 H, dd, $J_{H,H}$ = 9.29 Hz, $J_{H,F}$ = 11.5 Hz, CH_2OCH$_2$Ph), 3.72 (1 H, dd, $J_{H,H}$ = 9.29 Hz, $J_{H,F}$ = 11.9 Hz, CH_2OCH$_2$Ph), 4.21 (1 H, dd, $J_{H,H}$ = 1.81 Hz, $J_{H,F}$ = 25.8 Hz, C*H*O), 4.53 (2 H, m, CH_2Ph), 7.32 (5 H, s, Ph); IR (neat) 700 (Ph) cm^{-1}.

Exact mass calcd for $C_{21}H_{33}O_3F$: 352.490. Found: 352.524.

2,2,5-Trimethyl-4-((2*R*)-1-(benzyloxy)-2-fluoroprop-2-yl)-1,3-dioxane (13). To a solution of 50 mg of $LiAlH_4$ (1.31 mmol) in 5 mL of freshly distilled Et_2O was added at 0 °C a diastereomer mixture of **8** in 2 mL of the same solvent, and stirring was continued for 3 h at that temperature. The reaction mixture was quenched with saturated aqueous Na_2SO_4, followed by decantation and washing of the precipitate three times with Et_2O. The combined ether solution was dried over anhydrous $MgSO_4$. The removal of the volatiles in vacuo afforded the crude diol, which was then dissolved in 3 mL of dry acetone. After addition of 0.2 mL of 2,2-dimethoxypropane (1.6 mmol) and a catalytic amount of *p*-TsOH at 0 °C, the whole was stirred for 10 min, followed by the addition of a few drops of Et_3N. Evaporation of the volatiles afforded the crude acetonide **13**, which was subjected to GLC analysis (PEG 20M at 200 °C).

Exact mass calcd for $C_{17}H_{25}O_3F$: 296.382. Found: 296.340.

(2*R*,3*S*,4*R*)-5-(Benzyloxy)-4-fluoro-2,4-dimethyl-3-hydroxypentyl Iodide (14te). A mixture of aldol **9te** (1.44 g, 4.20 mmol), dihydropyran (0.57 mL, 6.3 mmol), and a catalytic amount of TsOH in 3.5 mL of Et_2O was stirred for 1 h at room temperature. After the mixture was quenched with a few drops of Et_3N, removal of the volatiles afforded 1.91 g of crude THP ether, which was dissolved in 6 mL of freshly distilled Et_2O and added at 0 °C to a suspension of $LiAlH_4$ (120 mg, 3.15 mmol) in 6 mL of the same solvent under a nitrogen atmosphere. After being stirred for 2 h at room temperature, the mixture was quenched with saturated aqueous Na_2SO_4 and decanted. The precipitate was washed with Et_2O, and the combined organic layer was dried over anhydrous $MgSO_4$. The evaporation afforded 1.51 g of crude alcohol, which was employed without further purification for the next reaction. To a suspension of TsCl (1.27 g, 6.65 mmol) in 8 mL of CH_2Cl_2 was added pyridine (3.6 mL, 44 mmol) in 7 mL of CH_2Cl_2 at 0 °C under nitrogen, and the whole was stirred overnight at ambient temperature. Then the mixture was quenched with saturated aqueous NH_4Cl and 1 H HCl and extracted with CH_2Cl_2, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over anhydrous $MgSO_4$. Removal of the solvent afforded the crude product, which was added to a suspension of sodium iodide (2.95 g, 19.6 mmol) in 20 mL of acetone at room temperature under a nitrogen atmosphere. After being refluxed for 20 h, the reaction mixture was quenched with water and extracted with Et_2O. This ether layer was washed with water and brine and dried over anhydrous $MgSO_4$. Evaporation afforded the crude product, which was dissolved in 40 mL of MeOH, and a catalytic amount of TsOH was added. The whole was stirred for 3 h at room temperature. Then the mixture was quenched with a few drops of Et_3N. Removal of the solvent afforded a crude product, which was chromatographed to yield 1.03 g (2.81 mmol) of iodide **14te** in 67% total yield: $[\alpha]^{18}_D$ −13.93° (*c* 1.36, MeOH, 89% ee, >99% de); ^{19}F NMR δ 73.0 (m); ^{1}H NMR δ 1.06 (3 H, dd, $J_{H,H}$ = 6.66 Hz, $J_{H,F}$ = 3.48 Hz, CH_3CH), 1.31 (3 H, d, $J_{H,F}$ = 22.4 Hz, CH_3CF), 1.32–1.68 (1 H, m, CH$_3$C*H*), 2.59 (1 H, dd, $J_{H,H}$ = 5.04 Hz, $J_{H,F}$ = 1.44 Hz, O*H*), 3.40 (2 H, d, $J_{H,H}$ = 4.56 Hz, CH_2I), 3.56 (1 H, d, $J_{H,F}$ = 17.6 Hz, CH_2OCH$_2$Ph), 3.58 (1 H, d, $J_{H,F}$ = 21.5 Hz, CH_2OCH$_2$Ph), 3.66 (1 H, ddd, $J_{H,H}$ = 5.04, 8.16 Hz, $J_{H,F}$ = 16.6 Hz, C*H*OH), 4.51 (1 H, d, $J_{H,H}$ = 13.0 Hz, CH$_2$Ph), 4.69 (1 H, d, $J_{H,H}$ = 13.0 Hz, CH$_2$Ph), 7.04 (5 H, s, Ph); IR (neat) 3470 (OH), 700 (Ph) cm^{-1}.

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Registry No. (*S*)-**2**, 117581-75-6; (*R*)-**2**, 117581-99-4; **3t**, 117581-77-8; **3e**, 117581-78-9; **4t**, 117581-79-0; **4t** (diol), 117582-06-6; **4t**-Si, 117582-00-0; **4e**, 117581-80-3; **4e** (diol), 117582-07-7;

4e-Si, 117582-01-1; **5t**, 117676-80-9; **5e**, 117581-81-4; [2*S*-(1*R*,2*S*)]-**6t**, 117676-81-0; [2*R*-(1*R*,2*S*)]-**6t**, 117581-82-5; **6e**, 117676-76-3; **7et**, 117676-79-6; **7ee**, 117676-78-5; **7te**, 117581-83-6; **7tt**, 117676-77-4; **7tt** (THP ether), 117582-08-8; **8et**, 117582-02-2; **8et** (1,3-diol), 117676-87-6; **8ee**, 117581-85-8; **8ee** (1,3-diol), 117676-85-4; **8te**, 117582-03-3; **8te** (1,3-diol), 117676-86-5; **8tt**, 117581-84-7; **8tt** (1,3-diol), 117582-11-3; **9et**, 117581-87-0; **9ee**, 117582-04-4; **9te**, 117581-86-9; **9te** (THP ether), 117582-12-4; **9te** (1,3-diol; 3-THP ether), 117582-13-5; **9te** (1,3-diol; 1-tosylate, 3-THP ether), 117582-14-6; **9tt**, 117582-05-5; **10t**, 117581-88-1; **10e**, 117581-89-2; (*R*)-**11**, 117581-76-7; **12et**, 117581-92-7; **12ee**, 117581-91-6; **12tt**, 117581-90-5; **12tt** (diol), 117582-10-2; **13et**, 117676-84-3; **13ee**, 117676-82-1; **13te**, 117676-83-2; **13tt**, 117581-93-8; **14te**, 117581-94-9; (*S*)-$BnOCH_2CF(CH_3)COOEt$, 117581-95-0; (*S*)-$HOCH_2CF(CH_3)COOEt$, 105314-05-4; BnBr, 100-39-0; (*R*)-$BnOCH_2CF(CH_3)CH_2OH$, 117581-96-1; (*S*)-$BnOCH_2CF(CH_3)CH_2OSiMe_2Bu$-*t*, 117581-97-2; (*S*)-$HOCH_2CF(CH_3)CH_2OSiMe_2Bu$-*t*, 117581-98-3; (4*R*,5*S*,6*S*)-$BnOCH_2CF(CH_3)CH(OTHP)CH(CH_3)CEt_2OH$, 117582-09-9; $CH_2=C(OLi)Bu$-*i*, 76638-96-5; $CH_2=C(OMgBr)Bu$-*i*, 117582-15-7; $CH_2=C(OZnCl)Bu$-*i*, 117582-16-8; $CH_2=C(OAlEt_2)Bu$-*i*, 117582-17-9; $CH_2=C(OTMS)Bu$-*i*, 59417-87-7; $CH_2=C(OTMS)Bu$-*t*, 17510-46-2; $CH_2=C(OTMS)OEt$, 42201-84-3; (*E*)-$CH_3CH=C(OTMS)Et$, 51425-53-7; (*Z*)-$CH_3CH=C(OTMS)Et$, 51425-54-8; $CH_3CH=C(OLi)OEt$, 81355-01-3; (*E*)-$CH_3CH=C(OTMS)SBu$-*t*, 76943-95-8; (*Z*)-$CH_3CH=C(OTMS)SBu$-*t*, 76943-94-7; TiCl4, 7550-45-0; $EtAlCl_2$, 563-43-9; BF_3·OEt, 109-63-7; cyclohexanone trimethylsilyl enol ether, 6651-36-1.

Synthesis of the Furanoheliangolide Ring Skeleton

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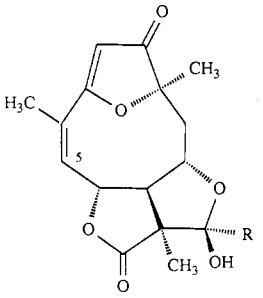
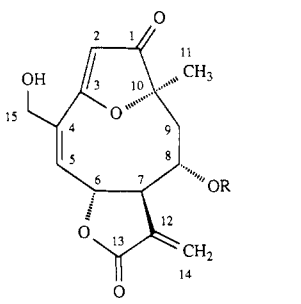
A synthesis of the 11-oxabicyclo[6.2.1]undecane ring system found in the furanoheliangolide and abestinane classes of natural products is described. The key reaction involves the ozonolysis of an oxa-bridged Δ^9-octalin (**28**) to yield an oxa-bridged 1,6-cyclodecanedione (**29**). Selective reduction of the dione with sodium borohydride yielded a hemiketal **30**, whose structure was determined by an X-ray analysis. Attempts to synthesize the above ring system via a palladium(II)-catalyzed Cope rearrangement of a 2,3-divinyl-7-oxanorborane (**19**) failed and instead produced cyclopentenes **21a** and **21b** via a palladium-catalyzed cyclization.

Germacranes are a ubiquitious class of sesquiterpenoid natural products that possess a variety of biological activities, including cytotoxic activity.[1] Over 30 germacranolides have demonstrated either in vitro or in vivo antineoplastic activity. Many of the active compounds belong to a subgroup of the germacranes sometimes referred to as the furanoheliangolides. These compounds have an oxygen atom bridging C-3 and C-10. The resulting tetrahydrofuran ring is usually further oxidized and is often found as a 3(2*H*)-furanone as in the eremantholides (**1**) and lynchnophorolides (**2**). Several representative examples of this compound class are listed below.[2,3] All these particular substances have demonstrated cytotoxic behavior.

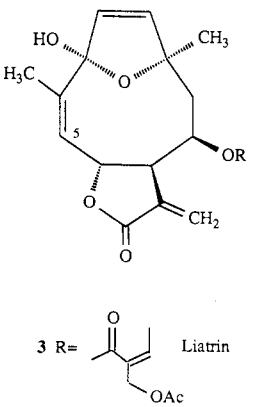
Unfortunately all the active germacranolides, except for the eremantholides **1**, contain an α-methylene lactone. This structural unit, while consistently identified with cytotoxic activity, has proven to be too toxic for clinical use.[4] That the eremantholides maintain cytotoxic activity despite the absence of an α-methylene lactone may therefore be significant. In analogy with the work of Smith and co-workers on vinyl-3(2*H*)-furanones[5] it would seem



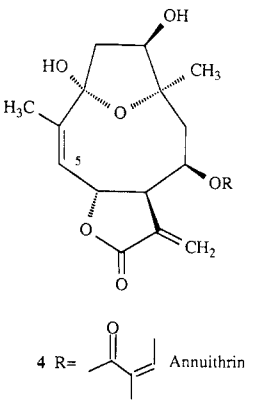
1a R=i-Pr Eremantholide A
1b R=s-Bu Eremantholide B
1c R= Eremantholide C



2a R= Lychnophorolide A
2b R= Lychnophorolide B



3 R= Liatrin



4 R= Annuithrin

plausible that C-5 is the electrophilic center responsible for the activity of the eremantholides. Further support for this contention was garnered by LeQuesne who found that eremantholide A (**1a**) undergoes clean thiol addition at C-5.[2a] Interestingly all the cytotoxic furanoheliangolides

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(3) A number of structural misassignments have persisted in this class of compounds. For correct structures, see: Herz, W.; Goeden, V. L. *J. Org. Chem.* **1982**, *47*, 2798.

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(5) Smith, A. B., III; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M., Jr.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501.

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