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 (CDCl₃) 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 (CDCl₃) 3420, 2940, 2825, 1755, 1655, 1608, 1592, 1455, 1420, 1245, 1215, 1142, 1120, 1055, 1030, 910 cm⁻¹; high-resolution mass spectrum for C₂₈H₂₄O₇ requires 472.152 21, measured 472.152 59.

To a solution of compound 19 (0.078 g, 0.14 mmol) in dry methanol (3 mL) at 0 °C under argon was added 1,l'-carbonyldiimidazole (0.16 mmol) in methylene chloride (20 mL). 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 (CDCl₃) δ 7.34 (d, J = 8 Hz, 2 H), 7.19 (m, 3 H), 6.97 (m, 2 H), 6.90 (d, J = 2 Hz, 2 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 (CDCl₃) 3460, 3550–2650 (br), 2920, 1700, 1620, 1500, 1440, 1250, 1210, 1135, 906, 730 cm⁻¹; high-resolution mass spectrum for C₁₉H₁₈O₇ requires 348.16274; 13C NMR (CDCl₃) δ 176.34, 163.90, 161.83, 159.17, 157.51, 134.89, 129.01, 128.09, 120.12, 119.50, 105.43, 99.41, 92.52, 91.99, 85.86, 83.56, 77.28, 55.65, 55.53, 52.50, 45.04.

Tricyclic Amide 15. To a stirred solution of acid 21 (0.20 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'-carbonyldimidazole (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 Me₃Si ether, 117828-36-1; 5, 117828-32-7; 6, 117828-33-8; 7, 117828-34-9; 9, 117828-37-2; 10, 117828-38-5; 10 demethylated, 117828-39-4; 12, 117828-40-7; 13, 117828-41-8; 14, 117828-42-9; 15, 117828-43-0; 16 (isomer 2), 117828-44-1; 17a, 117828-45-2; 17b, 117828-46-3; 18, 117828-47-4; 18 Me₃Si ether, 117828-48-7; 19, 117828-49-8; 20, 117828-50-9; 21, 117828-51-0; acrylonitrile, 107-13-1; cinnamonic acid, 4380-47-8.

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

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Diastereoselective Crossed Aldol Reactions with Chiral Fluorinated Aldehydes

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Received March 21, 1988

Lewiss 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 Lewiss acid employed. The α-fluoro substituent has little effect on the diastereoselectivity of these Lewis acid catalyzed aldol condensations.

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

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of fluorinated molecules have resulted in their application as "fine chemicals" such as biologically active materials, ferroelectric liquid crystals, 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 when compared to the analogous reaction involving nonfluorinated reactants. This has been one of the most significant factors in preventing the development of reactions when compared to the analogous reaction involving fluorinated molecules have resulted in their application chemistry. However, very recently, Welch and co-workers have disclosed the highly diastereoselective directed aldol condensation with fluorinated ketones or esters. 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. Particularly, enantiomeric 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. It was also found that this molecule could be readily converted to S-(benzyl oxy)-2-fluoro-2-methylpropionaldehyde as either the $S$ or $R$ enantiomer.

Here, we report details of our investigation of the aldol reactions with 2. These studies have involved the

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>Additive</th>
<th>Yield, %</th>
<th>Threo:erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li</td>
<td>-</td>
<td>93</td>
<td>36:67</td>
</tr>
<tr>
<td>2</td>
<td>MgBr</td>
<td>-</td>
<td>54</td>
<td>36:64</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl</td>
<td>-</td>
<td>33</td>
<td>43:57</td>
</tr>
<tr>
<td>4</td>
<td>AlEt$_2$</td>
<td>-</td>
<td>45</td>
<td>29:71</td>
</tr>
<tr>
<td>5</td>
<td>TMS</td>
<td>TBAF</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>TMS</td>
<td>TMSOTY</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>TMS</td>
<td>TiCl$_4$</td>
<td>85</td>
<td>91:9</td>
</tr>
<tr>
<td>8</td>
<td>TMS</td>
<td>EtAlCl$_2$</td>
<td>55</td>
<td>22:78</td>
</tr>
<tr>
<td>9</td>
<td>TMS</td>
<td>BF$_3$-OEt$_2$</td>
<td>62</td>
<td>24:76</td>
</tr>
</tbody>
</table>

*Determined by HPLC analysis.

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

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Lewis acid</th>
<th>Yield, %</th>
<th>Threo:erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>i-Bu</td>
<td>TiCl$_4$</td>
<td>83</td>
<td>78:22</td>
</tr>
<tr>
<td>4</td>
<td>t-Bu</td>
<td>TiCl$_4$</td>
<td>83</td>
<td>95:5</td>
</tr>
<tr>
<td>5</td>
<td>t-Bu</td>
<td>TiCl$_4$</td>
<td>75</td>
<td>9:91</td>
</tr>
<tr>
<td>6</td>
<td>EtAlCl$_2$</td>
<td>68</td>
<td>12:88</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>EtAlCl$_2$</td>
<td>51</td>
<td>15:85</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>BF$_3$-OEt$_2$</td>
<td>50</td>
<td>72:28</td>
<td></td>
</tr>
</tbody>
</table>

*Determined by HPLC. The t-BuMe$_2$Si ketene acetal was used. The relative configuration between C$_r$-C$_s$ stereocenters was not determined. The reaction was performed with siloxy-protected aldehyde (R)-11 instead of (S)-2.

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.

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 $\alpha$ 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 ketone enolates derived from 4-methylpentan-2-one. The results are summarized in Table I. The desired aldol products were produced with only moderate erythro

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

Figure 1. Transition-state model I.

- (anti) selectivity (ca. 2:1) and in moderate to excellent chemical yields (entries 1–4). When the reaction was carried out with the corresponding enol silyl ether, fluoride ion [tetra-n-butylammonium fluoride (TBAF)] or tri-methylsilyl trifluoromethanesulfonate (TMSOTf) did not catalyze the reaction (entries 5 and 6). However, Lewis acids such as TiCl4, EtAlCl2, and BF3- OEt2 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 fluoride-containing aldehyde. Although premixing of α- or β-oxygenated aldehyde and TiCl4 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 TiCl4 would regulate the direction of nucleophilic attack from the sterically less hindered si face to yield the adduct with the three (syn) configuration (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 (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 C2–C4 stereocenters (see Scheme II). Compounds 4t and 4e were individually transformed into their acetones, 10t and 10e, respectively. Examination of their 1H NMR spectra revealed that the coupling constants between H3 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 H3 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 other oxygen and fluorine atoms in (S)-2, which exhibited the stronger ability to undergo bidentate chelation with TiCl4. This could not be solved even after de-

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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. Org. Chem. 1983, 48, 932.


17 Abbreviation in the compound numbers represents the relative stereochemistry of the S-enol ether derived from diethyl ketone, which possesses erythro and threo configurations between the C2–C4 and C3–C4 stereocenters, respectively.
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 accessible 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 to undergo bidentate chelation.

Aldol Reaction of (R)-2 with Nucleophiles with Propionyl Moiety

<table>
<thead>
<tr>
<th>product</th>
<th>R</th>
<th>Lewis acid</th>
<th>yield, %</th>
<th>diastereoselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Et</td>
<td>TiCl4</td>
<td>86</td>
<td>30:8:12:50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EtAIACl2</td>
<td>81</td>
<td>34:7:13:46</td>
</tr>
<tr>
<td>8</td>
<td>OEt</td>
<td>–</td>
<td>90</td>
<td>18:42:11:29</td>
</tr>
<tr>
<td>9</td>
<td>SBu-t</td>
<td>–</td>
<td>90</td>
<td>76:12:2:8</td>
</tr>
</tbody>
</table>

* Isomeric ratios were determined by HPLC, and abbreviations e and t indicate erythro and threo stereochemistry, respectively. The corresponding isomer at C3-C4 was identified in Table I (see Scheme I). This aldehyde was of interest because this type of compound, if fluorine is replaced by a hydrogen atom, is reported to undergo bidentate chelation.

The stereochemistry of these products was established in basically the same manner as for compound 4. NMR studies of the acetones 12 derived from 8 and 9 have led us to determine the relative configurations between both the C2-C3 and C3-C4 stereocenters as given in Table III. Thus, the C2-C3 stereocenters could be controlled by using TiCl4 to afford the three configuration predominantly (threo:erythro = 86:14). Then, the reaction of (R)-2 with the silyl enol ether derived from pinacolone was transformed to the corresponding aldol 8 with an improvement in the diastereomeric purity.

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

Gennari et al.$^{25b}$ 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 9e and 9t 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 future 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.$^{22}$

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**Figure 2.** Transition-state model II.

**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.

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**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 (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).

(3)-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$^{26}$ (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$_4$Cl and extracted with Et$_2$O, and the resulting crude product was chromatographed on silica gel to yield 4.45 g (15.5 mmol) of the benzylxy ester in 95% yield: [α]$^{20}_{D}$ = -9.75$^o$ (c 1.15, MeOH); $^{19}$F NMR δ 80.0 (ddq); $^1$H NMR δ 5.19 (3 H, t, $J_{	ext{HH}}$ = 7.16 Hz, CH$_2$(CH$_3$O)), 1.46 (3 H, d, $J_{	ext{HH}}$ = 21.0 Hz, CH$_3$CF), 3.53 (1 H, dd, $J_{	ext{HH}}$ = 10.1 Hz, $J_{	ext{HF}}$ = 18.9 Hz, PhCH$_2$OCH$_2$), 3.64 (1 H, dd, $J_{	ext{HH}}$ = 10.1 Hz, $J_{	ext{HF}}$ = 22.1 Hz, PhCH$_2$OCH$_2$), 4.17 (2 H, q, $J_{	ext{HH}}$ = 7.16 Hz, CH$_2$CH$_2$O), 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-methylpropional. To a suspension of LiAlH$_4$ (0.55 g, 14.4 mmol) in 10 mL of freshly distilled Et$_2$O was added dropwise the benzylxy ester (6.55 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$_2$SO$_4$, the organic layer was decanted and the precipitate was washed three times with Et$_2$O. 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-methylpropional in 94% yield: [α]$^{20}_{D}$ +1.08$^o$ (c 1.43, MeOH); $^{19}$F NMR δ 82.8 (ddtq); $^1$H NMR δ 1.27$^o$.
was quenched with water and extracted with CH$_2$Cl$_2$, and the product, which was distilled under reduced pressure to give 1.54 anhydrous MgSO$_4$. Removal of the solvent provided the crude

stirring and removal of the stirring for 0.5 h at ambient temperature, the reaction mixture


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

IR (neat) 1740 (C=O), 700 (Ph) cm$^{-1}$.

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solvent, the crude product was purified by column chromatography on silica gel to afford diastereomERICally pure aldo products.

(6S,7S)-8-(Benzyloxy)-7-fluoro-2,7-dimethyl-6-hydroxy-4-octanone (3t). The silyl ether derived from isobutyl methyl ketone with TiCl$_4$ as the Lewis acid was used: [a]$_D$ = -2.57° (c 1.26, MeOH, 89% ee); [c]$_D$ = +12.80° (c 1.26, MeOH, 86% ee); [f]$_D$ NMR δ 80.7 (dddq); [c]$_D$ NMR δ 79.0 (dddd); [h] NMR (CDCl$_3$ with D$_2$O) δ 1.83 (9 H, s, Ph), 7.33 (3 H, s, Ph); IR (neat) 3480 (OH), 1710 (C=O), 700 (Ph) cm$^{-1}$.

Anal. Found: C, 68.73; H, 8.19. Calculated for C$_{17}$H$_{26}$_O$_3$F: C, 68.89; H, 8.50. Exact mass calcld. 394.382. Found: 394.378.

(6S,7S)-7-(Benzyloxy)-6-fluoro-2,2,6,6-tetramethyl-3-heptanone (4t). The silyl ether derived from pinacolone with TiCl$_4$ as the Lewis acid was used: [a]$_D$ = -17.08° (c 1.21, MeOH, 90% de); [f]$_D$ NMR δ 80.7 (ddd); [c]$_D$ NMR (CDCl$_3$ with D$_2$O) δ 1.14 (9 H, s, (CH$_3$)$_3$C), 1.37 (9 H, s, (CH$_3$)$_3$C), 2.22 (H, s, CH$_2$CH$_3$C(O)), 2.55 (H, d, J$_{HH}$ = 13.4 Hz, C=O), 2.75 (H, d, J$_{HH}$ = 13.4 Hz, C=O), 3.58 (H, d, J$_{HH}$ = 16.4 Hz, CH(OH)CH$_2$Ph), 3.59 (H, d, J$_{HH}$ = 16.5 Hz, CH(OH)CH$_2$Ph), 4.22 (1 H, dt, J$_{HH}$ = 16.4 Hz, CH(OH)CH$_2$Ph), 4.85 (2 H, s, (CH$_3$)$_3$C), 7.33 (5 H, s, Ph); IR (neat) 3480 (OH), 1710 (C=O), 700 (Ph) cm$^{-1}$.

Anal. Found: C, 68.73; H, 8.19. Calculated for C$_{17}$H$_{26}$_O$_3$F: C, 68.89; H, 8.50. Exact mass calcld. 394.382. Found: 394.378.

(5S,6S)-7-(Benzyloxy)-6-fluoro-2,2,6,6-tetramethyl-3-heptanone (4e). The silyl ether derived from pinacolone with TiCl$_4$ as the Lewis acid was used: [a]$_D$ = -17.08° (c 1.21, MeOH, 90% de); [f]$_D$ NMR δ 80.7 (ddd); [c]$_D$ NMR (CDCl$_3$ with D$_2$O) δ 1.14 (9 H, s, (CH$_3$)$_3$C), 1.37 (9 H, s, (CH$_3$)$_3$C), 2.22 (H, s, CH$_2$CH$_3$C(O)), 2.55 (H, d, J$_{HH}$ = 13.4 Hz, C=O), 2.75 (H, d, J$_{HH}$ = 13.4 Hz, C=O), 3.58 (H, d, J$_{HH}$ = 16.4 Hz, CH(OH)CH$_2$Ph), 3.59 (H, d, J$_{HH}$ = 16.5 Hz, CH(OH)CH$_2$Ph), 4.22 (1 H, dt, J$_{HH}$ = 16.4 Hz, CH(OH)CH$_2$Ph), 4.85 (2 H, s, (CH$_3$)$_3$C), 7.33 (5 H, s, Ph); IR (neat) 3480 (OH), 1710 (C=O), 700 (Ph) cm$^{-1}$.

Anal. Found: C, 68.73; H, 8.19. Calculated for C$_{17}$H$_{26}$_O$_3$F: C, 68.89; H, 8.50. Exact mass calcld. 394.382. Found: 394.378.
3.90 Hz, CH₂CO(O)), 3.14 (1 H, d, J₉H = 3.56 Hz, OH), 3.60 (2 H, d, J₉H = 19.8 Hz, CH₂OCH₂Ph), 4.16 (2 H, d, J₉H = 7.08 Hz, CH₂OCH₂Ph), 6.57-7.05 (5 H, s, Ph); IR (neat) 3490 (OH), 1753 (C=O), 700 (Ph) cm⁻¹.

Found: C, 63.74; H, 7.27. Calcd for C₁₉H₂₃O₅F: C, 63.73; H, 7.45. Exact mass calcld: 284.327. Found: 284.351.

(1R,2S)-3-(Benzyloxy)-2-fluoro-2-methyl-1-hydroxypropyl)cyclohexane (61). The silyl enol ether derived from cyclohexanone and TiCl₄ as the Lewis acid were used: [α]D²⁻ = -7.75° (c 1.25, MeOH, 90% ee, 72% de (with the C₅⁻C isomer)); [19F NMR δ 81.0 (dtq); 'H NMR (CDCl₃) δ 7.13 (3 H, d, J₉H = 7.0 Hz, CH₂CO(O)), 1.25 (3 H, t, J₈H = 7.0 Hz, CH₃CH₂O), 1.29 (3 H, d, J₉H = 22.7 Hz, CH₃CF), 2.71 (1 H, dq, J₈H = 2.94, 7.28 Hz, CH₂CO(O)), 3.55 (2 H, dq, J₈H = 19.3 Hz, CH₂OCH₂Ph), 3.61 (2 H, d, J₉H = 20.4 Hz, CH₂OCH₂Ph), 3.69 (1 H, dd, J₇H = 15.8 Hz, CH₃CF), 4.57 (2 H, s, CH₂Ph), 7.24 Hz, CH₂OCH₂Ph), 1.24 (3 H, t, J₈H = 7.0 Hz, CH₂CO(O)), 1.42 (2 H, s, CH₃Ph), 7.35 (5 H, s, Ph); IR (neat) 3470 (OH), 1730 (C=O), 700 (Ph) cm⁻¹.

Found: C, 64.61; H, 8.03. Calcd for C₁₉H₂₃O₅F: C, 64.41; H, 7.77. Exact mass calcld: 298.354. Found: 298.395.

(1R,2S,4R)-Ethyl-1-(Benzyloxy)-4-fluoro-2,4-dimethyl-3-hydroxypropionate (86). The silyl ketene acetal derived from ethyl propionate and EtAlCl₃ as the Lewis acid were used: [α]D²⁻ = -7.06° (c 0.83, MeOH, 90% ee, 71% de (with the C₅⁻C isomer)); [19F NMR δ 78.3 (dddq); 'H NMR (CDCl₃) δ 1.19 (3 H, t, J₈H = 7.14 Hz, CH₃CH₂O), 1.23 (3 H, t, J₈H = 7.22 Hz, CH₃CH₂O), 1.34 (3 H, d, J₉H = 22.7 Hz, CH₃CF), 2.83 (1 H, dq, J₈H = 7.14, 7.08 Hz, CH₂CO(O)), 2.80 (1 H, br d, J₉H = 4.80 Hz, OH), 3.54 (1 H, d, J₉H = 17.6 Hz, CH₂OCH₂Ph), 3.55 (1 H, d, J₉H = 19.7 Hz, CH₂OCH₂Ph), 4.93 (2 H, s, CH₂Ph), 7.32 (5 H, s, Ph); IR (neat) 3490 (OH), 1730 (C=O), 700 (Ph) cm⁻¹.

Exact mass calcld for C₁₉H₂₃O₅F: 298.354. Found: 298.303.

(2R,3S,4R)-tert-Butyl-5-(Benzyloxy)-4-fluoro-2,4-dimethyl-3-hydroxythiopentanoate (98e). The silyl ketene acetal derived from tert-butyl thiopropionate was used: [α]D²⁻ = -20.61° (c 1.06, MeOH, 89% ee, 98% de); [19F NMR δ 78.8 (dtq); 'H NMR (CDCl₃) δ 1.93 (3 H, t, J₈H = 7.08 Hz, CH₂CO(O)), 1.46 (9 H, s, (CH₃)₂C), 2.80 (1 H, dq, J₉H = 4.02, 7.26 Hz, CH₂CO(O)), 3.41 (1 H, J₉H = 9.84 Hz, OH), 3.54 (2 H, d, J₉H = 18.3 Hz, CH₂OCH₂Ph), 3.72 (1 H, dd, J₉H = 4.02, 9.84 Hz, J₈H = 13.3 Hz, CH₂OHO), 4.57 (2 H, s, CH₂Ph), 7.32 (5 H, s, Ph); IR (neat) 3480 (OH), 1660 (C=O), 700 (Ph) cm⁻¹.

JH,F

3.62 (1 H, d, JH,F = 22.4 Hz, CH2OH), 3.82 (1 H, d, JH,F = 19.0 Hz, CH2O), 4.40 (1 H, d, JH,F = 8.10 Hz, CH2OH), JH,F = 26.5 Hz, CHO); IR (neat) 1710 (C=O) cm⁻¹.


(4R,5S)-2,2,5,5-T trimethyl-4-(3,3-dimethyl-2-oxo-1-buty1)-5-fluoro-1,3-dioxane (10e).

The same procedure as for the preparation of 18t was employed to afford protected erythro diol 10e in 79% yield for two steps. Physical properties for the intermediate diol: ¹H NMR δ 75.9 (m); ¹H NMR (CDCl₃) δ 0.89 (3 H, s, CH₃), 1.19 (6 H, s, CH₃), 1.36 (3 H, d, JH,F = 21.2 Hz, CH₂CF₃), 1.94 (2 H, br, s, OH), 2.79 (1 H, d, JH,F = 6.60 Hz, CH₂C(O)), 2.80 (1 H, d, JH,F = 4.92 Hz, CH₂C(O), 3.45 (2 H, d, JH,F = 17.8 Hz, CHOH), 4.20 (1 H, d, dd, JH,F = 6.60, 4.92 Hz, JH,H = 10.7 Hz, CH(OH)), 4.47 (1 H, d, JH,F = 10.7 Hz, CHO); IR (neat) 3400 (CH₂, CHOH), 1700 (C=O) cm⁻¹.

For the 18t diastereomer: ¹H NMR δ 80.7 (ddqq); ¹H NMR (CDCl₃) δ 1.98, 1.32 (3 H each, s, CH₃), 1.21-1.66 (4 H, m, CH₂CH₂), 1.31 (3 H, d, JH,F = 13.0 Hz, CH₂Ph), 7.04 (5 H, s, Ph); IR (neat) 700 (Ph) cm⁻¹.

Acknowledgment. We gratefully acknowledge Professor Yoshiharu Ishido for obtaining the 200-MHz ¹H NMR spectra.

Registry No. (S)-2, 117581-75-8; (R)-2, 117581-99-4; 3t, 117581-77-8; 3e, 117581-75-8; 4t, 117581-79-0; 4t (diol), 117582-06-6; 4t-Si, 117582-00-0; 4e, 117581-80-3; 4e (diol), 117582-07-7; 4t-2-Si, 117582-00-0;
Germacranes are a ubiquitous class of sesquiterpenoid natural products that possess a variety of biological activities, including cytotoxic activity. Over 30 germacranolides have demonstrated cytotoxic behavior. In analogy with the work of Smith and co-workers on vinyl-3(2H)-furanones it would seem therefore plausible that C-5 is the electrophilic center responsible for this contention was garnered for this contention was garnered.

A synthesis of the 11-oxabicyclo[6.2.1]undecane ring system found in the furanoheliangolide and abstinane classes of natural products is described. The key reaction involves the ozonolysis of an oxa-bridged \( \Delta^8 \)-octalin to yield an oxa-bridged 1,6-cyclohexanedione. Selective reduction of the dione with sodium borohydride yielded a hemiketal, 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 2,6-divinyl-1,3-cyclohexadiene failed and instead produced cyclopentenes via a palladium-catalyzed cyclization.