concentrated below 30 °C to give the title compound, 0.79 g (70%).

Cbz-Aep(OLi)-Gly(OLi) [18, $(aa)_1$ = Gly]. An ethanol solution (30 mL) of 11 [$(aa)_1$ = Gly, R = Me, 2.0 g, 5.6 mmol) was mixed with 2 N lithium hydroxide (17 mL). After 24 h at room temperature, the reaction mixture was neutralized with 1 N hydrochloric acid and concentrated below 30 °C. Upon mixing the residue with anhydrous ethanol, the title compound was precipitated as a powder, which was purified by reprecipitation using water and ethanol as dissolving and precipitating solvents, respectively, 1.96 g (52%).

H-Gly-Aep(OLi)-Gly(OLi) (23). The tripeptide diester **16a** (0.24 g, 0.58 mmol) was hydrogenated using Pd/C (10%, 0.12 g) in ethanol (10 mL) at atmospheric pressure and 25 °C for 1 h. After removal of the catalyst with suction filtration, the filtrate was mixed with 2 N lithium hydroxide (1.7 mL) and allowed to stand at room temperature for 20 h. The hydrolysate was then neutralized with 1 N hydrochloric acid and concentrated to afford the residue, which upon triturating with anhydrous ethanol gave amorphous powder, 0.11 g. The ^1H NMR spectrum agreed with the assigned structure of the title compound, but also indicated the presence of a small amount of impurities including glycine. A gel permeation chromatography (Sephadex G-10) was useless to purify the free peptide analogue, since the compound decomposed considerably during the treatment.

The Dilithium Salt of *N*-(Carboxymethyl)-*N'*-(2-(hydroxyethoxyphosphinyl)ethyl)urea (21). To a cooled ethanolic solution (5 mL) of **16b** [$(aa)_1$ = L-Phe, 0.54 g, 1.05 mmol) was added 1 N lithium hydroxide (3.1 mL). Stirring was continued at room temperature for 5 h. The reaction mixture was then neutralized with 1 N hydrochloric acid and concentrated under reduced pressure below 20 °C. The resulting residue was triturated with anhydrous ethanol to give amorphous powder, which was collected with filtration, washed with ethanol, and dried in a desiccator, 0.39 g. The ^1H NMR spectra and the elemental analysis favored the structure of an intermediate [**20**, $(aa)_1$ = L-Phe, R = Et].

The powder was dissolved in water (5 mL), and the pH of the solution was adjusted to ca. 1 by concentrated hydrochloric acid. After 1 h at room temperature, the solution showed the spots of L-phenylalanine (R_f 0.79) and **21** (R_f 0.28) in cellulose TLC with the solvent D. The solvent was evaporated, and the resulting residue was applied to a cation exchange resin (Amberlite 120B, H^+ form, 1 cm × 20 cm). Elution with ca. pH 2 hydrochloric acid gave **21** in the first 50 mL, which was concentrated and recrystallized from a mixture of diethyl ether and ethanol, 0.16 g (overall yield 60%).

Registry No. **1**, 2041-14-7; **2**, 62514-90-3; **4**, 78157-52-5; **5** [$(aa)_1$ = Gly], 78157-53-6; **5** [$(aa)_1$ = Phe], 82155-09-7; **5** [$(aa)_1$ = Ala], 82155-08-6; **6** [$(aa)_1$ = Gly], 82155-18-8; **6** [$(aa)_1$ = Ala], 88981-16-2; **7** [$(aa)_1$ = $(aa)_2$ = Gly], 88981-17-3; **7** [$(aa)_1$ = $(aa)_2$ = Ala], 88981-18-4; **8**, 88981-19-5; **8**·Na, 88981-20-8; **9** (R = Me), 82155-11-1; **10a** (R = Me), 82155-13-3; **10b** (R = Et), 82155-14-4; **10c** (R = bzl), 88981-21-9; **11a** [$(aa)_1$ = Gly], 82155-15-5; **11a** [$(aa)_1$ = Phe], 82155-17-7; **11a** [$(aa)_1$ = Ala], 82155-16-6; **11b** [$(aa)_1$ = Gly], 82168-78-3; **11b** [$(aa)_1$ = Phe], 82168-79-4; **11c** [$(aa)_1$ = Gly], 88981-22-0; **11c** [$(aa)_1$ = Phe], 88981-23-1; **12a** [$(aa)_1$ = Gly], 88981-24-2; **12b** [$(_aa)_1$ = Gly], 82155-18-8; **13** [$(aa)_1$ = Gly], 82155-22-4; **15** [$(aa)_1$ = Gly], 88981-25-3; **16a** [$(aa)_1$ = $(aa)_2$ = Gly], 88981-26-4; **16b** [$(aa)_1$ = $(aa)_2$ = Gly], 82155-20-2; **16b** [$(aa)_1$ = $(aa)_2$ = Phe], 88981-27-5; **17** [R = Me, $(aa)_1$ = Gly, M = Na], 88981-28-6; **18** [$(aa)_1$ = Gly], 82155-23-5; **18** [$(aa)_1$ = Ala], 82155-24-6; **18** [$(aa)_1$ = Phe], 82155-25-7; **19** [$(aa)_1$ = Gly], 88981-29-7; **20**, 88981-30-0; **21** (R = Et), 88981-31-1; **22** (R = Me), 88981-32-2; **23**, 88981-33-3; H-Gly-OEt·HCl, 623-33-6; H-Phe-OEt·HCl, 3182-93-2; Pht-Gly-OH, 4702-13-0; Pht-Ala-OH, 4192-28-3; *N*-(2-bromoethyl)phthalimide, 574-98-1; triethyl phosphite, 122-52-1; carbobenzoxy chloride, 501-53-1; dimethyl (2-carbaminoethyl)phosphonate, 2526-69-4; (carbobenzyloxy)glycine, 1138-80-3; diethyl (2-carbaminoethyl)phosphonate, 2526-67-2.

Supplementary Material Available: Experimental details, full ^1H NMR data, $[\alpha]^{25}_D$, mobilities in TLC, and elemental analyses (14 pages). Ordering information is given on any current masthead page.

Fluorine-Containing Amino Acids and Their Derivatives. 3.[1] Stereoselective Synthesis and Unusual Conformational Features of *threo*- and *erythro*-3-Fluorophenylalanine

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Reductive amination of *p*-substituted 3-fluorophenylpyruvic acids gave *p*-substituted *erythro*-3-fluorophenylalanines with high stereoselectivity. *threo*-3-Fluorophenylalanine was prepared by enzymatic hydrolysis of the *threo*-3-fluorophenylalanine isopropyl ester. NMR spectroscopic population analysis of rotamers of both erythro and threo diastereomers revealed that stabilization interactions (Coulombic attraction and/or hydrogen bonding) between fluorine and the NH_2 group are very important factors for the selection of stable rotational conformations in solution. Based on this information, an explanation is proposed for the remarkably high erythro selectivity observed in the reductive amination reaction. Single-crystal X-ray analysis of both diastereomers showed that the conformations in the solid state are mainly controlled by steric factors of the functional groups involved.

Introduction of fluorine into pharmacologically active substances can often lead to the development of more potent agonists or antagonists, as has been widely documented.[3] In the amino acid and peptide field also, a

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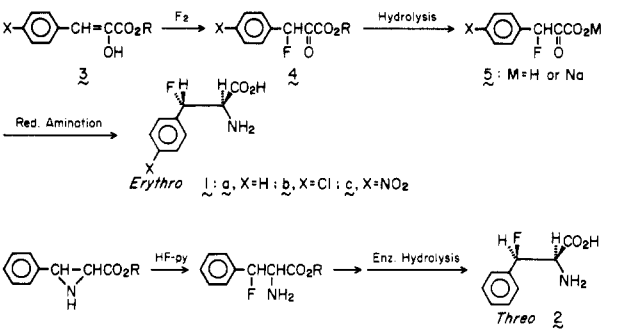
number of fluorine-containing amino acids have been hitherto prepared and examined for their biological activities such as antibacterial, antiviral, antineoplastic, and antihypertensive activities.[4] Particular interest has been attracted by 3-fluoro-D-alanine-2-*d*, which Kollonitsch et al. found to be a very powerful irreversible inhibitor of alanine racemase involved in the cell wall synthesis of microorganisms.[5] This example clearly suggested that substitution of the β-hydrogens of α-amino acids by fluorine significantly affects both their chemical and biological properties with minimal change of steric factors and can lead to medicinally useful compounds. Recently, this type of fluorine substitution has been receiving increasing attention from both mechanistic and synthetic viewpoints as so-called irreversible enzyme inhibitors or suicide enzyme inhibitors.[6] Thus, a number of new β-fluorinated aliphatic amino acids have been synthesized and found to be extremely useful as irreversible enzyme inactivators, particularly, those of alanine racemase,[5a,b,6f,11] dopa decarboxylase,[7] histidine decarboxylase,[7a,d8] ornithine decarboxylase,[7a,9] and serine transhydroxymethylase.[10] However, β-fluorinated aromatic amino acids have not been studied as much.[12] As aromatic amino acids often play important roles in biologically active peptides and proteins (enzymes), synthesis and biological activity evaluations of their fluorine-containing analogues should be worthwhile.

Scheme I



Three different synthetic methods of 3-fluorophenylalanine have been reported recently: the first one involving fluorodehydroxylation by SF_4 in HF solvent was reported by Kollonitsch et al.,[13] the second involved aziridine ring opening in HF–pyridine by Wade et al.,[14] and the third involved the reductive amination of 3-fluorophenylpyruvic acid by us.[1a,b] Interestingly, the fluorodehydroxylation method using DAST (diethylaminosulfur trifluoride) instead of SF_4 nonselectively produced both threo and erythro diastereomers,[1a,13] while the aziridine ring opening and the reductive amination method stereoselectivity yielded the threo and the erythro diastereomer, respectively. Here, we describe a detailed study on the synthesis of fluorine-containing analogues of pharmacologically active *p*-substituted phenylalanines, *p*-substituted *erythro*-3-fluoropheylalanines (**1a–1c**), the remarkable stereochemical effects of fluorine on the reductive amination, and a conformational study of both threo and erythro diastereomers which provides useful information for understanding the observed stereochemical effects.

Results and Discussion

Synthesis. Our synthetic scheme involved direct fluorination[1c] of *p*-substituted phenylpyruvates, mild alkaline hydrolysis of the resulting β-fluorinated *p*-substituted phenylpyruvates under conditions avoiding defluorination, and reductive amination of the fluoropyruvates to the desired *p*-substituted β-fluorophenylalanines (see Scheme I). The two interesting aspects that need to be clarified are the feasibility of direct fluorination and the stereochemistry of reductive amination. The former has already been discussed in a separate paper[1c] and the latter is our principal concern in this work. Here, the reasons for the hydrolysis of fluoropyruvates at an early stage were as follows: (1) An early attempt of Bergmann et al.[15] to prepare β-fluorinated phenylalanine ester failed. (2) even if this ester could be prepared, its hydrolysis to a free amino acid was expected to be difficult, as the literature had shown that alkaline hydrolysis of ω-fluorinated amino esters to free amino acids is sometimes infeasible, resulting in the loss of fluorine.[4a,16] (3) We could not find a proper

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(12) For example, aromatic amino acids with the fluorine substituent at the β-positions had not been prepared until very recently, except those having α-fluoromethyl or α-difluoromethyl groups.

(13) Kollonitsch, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1979**, *44*, 771. Although the authors did not describe the stereochemistry of the product, we think that the 3-fluorophenylalanine obtained by the reported method is a mixture of the erythro and the threo diastereomers, as the phenyl group is a very good carbonium ion stabilizing group.

(14) (a) Wade, T. N.; Gaymard, F.; Guedj, R. *Tetrahedron Lett.* **1979**, *2681*. (b) Wade, T. N.; Gaymard, F.; Guedj, R. *Ibid.* **1979**, 3953.

(15) Bergmann, E. D.; Cohen, A. M. *Israel J. Chem.* **1970**, *8*, 925.

(16) For example, as described below, chemical conversion of *threo*-3-fluorophenfylalanine isopropyl ester into the free amino acid has not yet been successful.

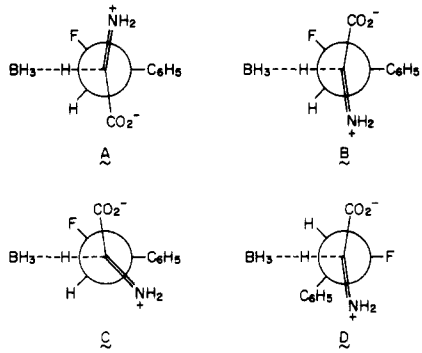

Figure 1. Transition-state models for reduction.

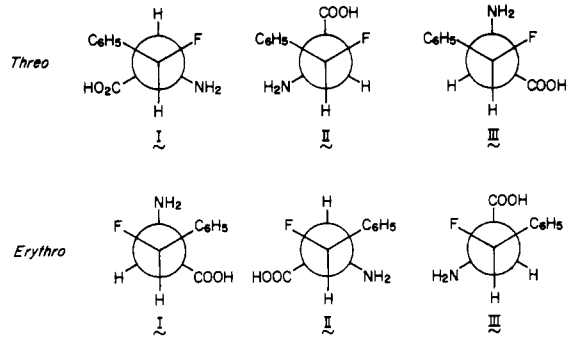

Figure 2. Staggered conformations of rotamers.

carboxyl protecting group which could survive the conditions of direct fluorination and be easily hydrolyzed under acidic conditions at the final stage.[17]

We found that the starting materials, *p*-substituted 3-fluorophenylpyruvates, could be conveniently prepared in 50–80% yields by direct fluorination of methyl or ethyl esters of *p*-substituted phenylpyruvic acids.[1c] Hydrolysis of the resulting fluoropyruvates in 50% 2-propanol in the presence of sodium bicarbonate proceeded smoothly without defluorination to give sodium *p*-substituted 3-fluorophenylpyruvates in good yields. As these sodium salts were very oxygen sensitive, they were subjected, without purification, to reductive amination using either sodium borohydride[18] or cyanoborohydride as a reducing agent.[19] Both reductive amination procedures gave the fluorinated amino acid **1a** in an isolated yield of 52% and 20%, respectively, the former being superior to the latter. The configuration of product **1a** was determined to be erythro by X-ray diffraction analysis and NMR spectroscopic measurement (see latter sections). Thus, the reactions were shown to be stereoselective, producing this isomer in more than 95% ratio. Both reductive amination procedures, even though carried out under different pH conditions, showed almost the same stereoselectivity. Next, we studied reductive amination of the other *p*-substituted derivatives **5b** and **5c** using the sodium borohydride method in order to confirm the observed stereoselectivity. Like the unsubstituted case, the erythro products **1b** and **1c** were obtained with stereoselectivity higher than 95% with not more than 5% of the threo isomers. Their conversion yields were 60% and 25% yield, respectively. The yield was relatively low with the nitro case, probably because the nitro group might have been partially reduced under the reaction conditions employed and caused side reactions. Nevertheless, the erythro stereoselectivity was unambiguously disclosed in these substituted cases as well. Coincidently, Pandit et al.[20] have observed the same stereoselectivity in the sodium borohydride reduction of β-fluoro-α-aminomaleic or fumaric acids. Thus, we conclude that the erythro selectivity is a common feature with this type of reduction.

According to the Felkin model, which has been commonly accepted as the most satisfactory explanation for the asymmetric reduction of carbonyl compounds, both transition states (A and B) can rationally account for the formation of the erythro and the threo product, respectively (see Figure 1).[21] In general, transition state A is more favored than B for steric reasons. However, when the molecule bears polar substituents, the rule of assymmetric induction usually requires modification, as proposed by Cornforth et al.[21c] (transition state C) or Cherest and Felkin[21d] (transition state D). In this case, the configuration of the favored products was threo and thus opposite from the one derived from transition state A. Thus, our case is clearly different from the halo ketone case and transition state A can well account for the observed erythro selectivity. However, it is inconceivable here that the steric factors of the substituents involved can distinguish the transition states so well, as the Van der Waals radii of fluorine and hydrogen are not very different. Previously, Pandit et al.[20] pointed out the Coulombic repulsion between fluorine and the incoming nucleophile as the key factor. We propose here an alternative explanation. As is described in detail in the following section, our NMR spectroscopic conformational study of both *threo*- and *erythro*-3-fluorophenylalanine showed a striking stabilization effect between the NH_3^+ and F group to control the equilibria of rotamers. This factor overcomes, especially under acidic conditions, steric factors in the selection of rotamers and becomes a dominant factor in deciding the ground-state conformations of these fluoro amino acids. We propose here that a similar stabilization factor exists between the neighboring fluorine and the imino group, especially when the latter is protonated or complexed with sodium ion, and affects the ground-state conformation of the imine intermediate so that transition state A becomes more favored compared to transition state B.[22]

The other diastereomer, *threo*-3-fluorophenylalanine (**2a**) was prepared as follows. Wade et al.[14a] have reported a convenient method for synthesizing 3-fluorophenylalanine ester using the aziridine ring-opening reaction in HF–pyridine. However, two problems remain with this methods: determination of the product configuration and conversion of the fluorine-containing amino ester into free amino acid without loss of fluorine. We determined the configuration to be threo by means of X-ray analysis as shown in the last section. The second problem was overcome in the present work not by chemical methods but by an enzymatic one. The conventional method we employed here involves *tert*-butyloxycarbonylation of the amino group and chymotrypsine-catalyzed hydrolysis of the resulting carbamate ester in aqueous DMF under pH

(17) Although use of the tertiary butyl protecting group may be promising, we did not use it since *tert*-butyl esters of these enol-type α-keto acids could hardly be obtained. Use of the benzhydryl group was also unsuccessful.

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(21) See references and arguments cited in (a) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972, pp 54–58. (b) Cherest, M. Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (c) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. (d) Cherest, M.; Felkin, H. *Ibid.* **1968**, 2205. (e) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367.

(22) An electrostatic repulsion force between fluorine and carboxylate anion may also be a reinforcing factor for the favored transition state (A).

Table I. NMR Spectroscopic Data for Population Analysis

compd	pD value	coupling constant[a] $^3J^{HH}$	temperature[b] effect	coupling constant[a] $^3J^{HF}$	temperature[b] effect	rotamer population[d] p_I	p_{II}	p_{III}
erythro-1a	basic (pD 12.7)	5.4_4	+	13.3_7	±[c]	0.515	0.274	0.211
(isomer A)	neutral (pD 5.1)	3.3_6	+	16.3_1	+	0.567	0.139	0.294
	acidic (3 M DCl)	3.3_8	+	18.4_5	+	0.500	0.145	0.355
threo-2	basic (pD 12.7)	4.2_6	+	27.5_2	−	0.273	0.152	0.611
(isomer B)	neutral (pD 5.1)	4.2_8	+	27.2_5	−	0.297	0.116	0.587
	acidic (3 M DCl)	4.0_0	+	26.9_2	−	0.274	0.132	0.594

[a] The calculated average values of $^3J^{HH}$ and $^3J^{HF}$ were as follows: $^3J^{HH}_{av}$ = 5.5 Hz under acidic and neutral conditions; $^3J_{av}^{HH}$ = 6.0 Hz under basic conditions; $^3J_{av}^{HF}$ = 17.7 Hz. [b] Temperature effects were measured at several different temperatures between 5 and 95 °C. The positive sign means an increase of coupling constants with increasing temperature and the negative sign, the opposite effect. [c] No significant temperature effect was observed in this case. [d] Rotamer populations were calculated using eq 1-4 and the literature values;[25] 41.3 Hz for $^3J^{FH}$(t) and 5.9 Hz for $^3J^{FH}$(g).

values between 6.7 and 7.0. The hydrolysis product obtained, *N*-(*tert*-butoxycarbonyl)-3-fluorophenylalanine, was treated sequentially with trifluoroacetic acid and an acidic ion exchange resin, Dowex-50W X8, and gave the desired *threo*-3-fluorophenylalanine (the enantiomeric ratio was not determined). We used this sample for the NMR spectroscopic study of population analysis of rotamers.

Population Analysis of Rotamers by NMR Spectroscopy. β-Fluoro-α-amino acids exist as two distinct diastereomers, the erythro and the threo, and each of them can take three staggered rotational conformation[23] (I-III) in solution, as shown in Figure 2. NMR spectroscopic determination of the configurations of these diastereomers have remained ambiguous, as no study has yet provided detailed data of the H–F and the H–H coupling constants requisite for the structural elucidation of both diastereomers.[24] Thus, other information, such as X-ray analysis and mechanistic consideration of reactions employed, is required. In order to overcome this situation, an interesting study on the use of ^{19}F NMR spectroscopy for the configurational determination of β-fluoro-α-amino acids through complexation by 18-crown-6 ether has recently been devised by Beguin et al.[25] Before the report of this work, we had taken another approach of measuring the pH dependence of rotamer populations of both diastereomers of 3-fluorophenylalanine.[1a,b] As we briefly reported in our preliminarly communication, stabilization interactions (Coulombic attraction and/or hydrogen bonding) between fluorine and the NH group affect the equilibria of rotational conformations more than steric factors of the functional groups involved. We also found some useful information for the determination of configurations of β-fluoro-α-amino acids by NMR spectroscopy. The detailed findings are reported here.

Table I summarizes the H–H and H–F vicinal coupling constants observed at the different pH values together with the signs of the temperature effects. Both coupling constants can be theoretically expressed, for example for the erythro isomer, by eq 1 and 2 in terms of the population-

$$^3J^{FH} = p_I{}^3J_I^{FH}(g) + p_{II}{}^3J_{II}^{FH}(g) + p_{III}{}^3J_{III}^{FH}(t) \quad (1)$$

$$^3J^{HH} = p_I{}^3J_I^{HH}(g) + p_{II}{}^3J_{II}^{HH}(t) + p_{III}{}^3J_{III}^{HH}(g) \quad (2)$$

$$p_I + p_{II} + p_{III} = 1 \quad (3)$$

weighted coupling constants of individual rotamers, where p and J(g) and J(t) denote the population of each component rotamer and the coupling constants of rotamers existing in both gauche and trans conformations, respectively.

In order to solve these equations, we assumed that the H–H coupling constants of each rotamer can be estimated, as previously done by Jorgensen and Weinkam[26] using eq 4. Δx_i, Δx_j, and Δx_k denote the electronegativity difference

$$^3J^{HH} = p_I(1 + a\Delta s_i^I + b\Delta x_j^I)(B_1{}^u \cos^2 \phi_{HH}{}^I) + p_{II}(1 + c\Delta x_k^{II})(B_2{}^u \cos^2\phi_{HH}{}^{II}) + p_{III}(1 + a\Delta x_i^{III} + b\Delta x_j^{III})(B_1{}^u \cos^2 \phi_{HH}{}^{III}) \quad (4)$$

of substituents gauche to a gauche HCCH unit, trans to a gauche HCCH unit, and gauche to a trans HCCH unit, respectively, and the following values are used: a = 0.13, b = −0.35, c = −0.06, $B_1{}^u$ = 13.2 Hz, $B_2{}^u$ = 17.4 Hz. We also assumed that the H–F coupling constants were the same values used in the population analysis by Beguin et al.: $^3J^{FH}$(t) = 41.3 Hz, $^3J^{FH}$(g) = 5.9 Hz.[27]

The conformational populations thus calculated for both diastereomers are also given in Table I. The significant features of the experimental results can be summarized as follows: (1) $^3J^{HF}$ values of isomer A were markedly larger than those of isomer B. $^3J^{HH}$ values of isomers A and B were nearly the same. (2) $^3J^{HF}$ values of isomer A were larger than the average value of 17.7 Hz (see Table I, footnote a) and the temperature effect of $^3J^{HF}$ was negative. Other coupling constants, $^3J^{HH}$ of isomer A, $^3J^{HF}$ and $^3J^{HH}$ of isomer B were slightly smaller than the corresponding average values ($^3J_{av}^{HH}$ = 5.5 Hz under acidic and neutral conditions, $^3J_{av}^{HH}$ = 6.0 Hz under basic conditions), and the temperature effects on these coupling constants were positive. (3) The pH effects on the observed J values were small with isomer A but relatively large with isomer B. These facts strongly suggest that isomer A mostly takes the trans H–F and gauche H–H rotamer III conformation while isomer **B** takes the gauche H–F and gauche H–H rotamer I conformation.

We deduced from these facts that isomer A can be tentatively assigned as the threo diastereomer and isomer B as the erythro one. This assignment has been unambiguously confirmed by the results of population analysis given in Table I, as follows. Four major electrostatic or

(23) Gaudemer, A. In "Stereochemistry: Fundamentals and Methods"; Kagan, H. B., Ed.; Georg Thieme Publishers: Stuttgart, 1977; pp 62–116 and references cited therein.
(24) See references cited in ref 25.
(25) Hamman, S.; Salon, M. C.; Beguin, C. *Org. Magn. Reson.* **1982**, *20*, 78.
(26) Jorgensen, E. C.; Weinkam, R. J. *J. Am. Chem Soc.* **1973**, *95*, 6084. See this paper for details for the calculation of coupling constants, $^3J^{HH}$(t) and $^3J^{HH}$(g).
(27) Before ref 25 appeared, we used in our earlier population analysis the values 8 Hz and 44 Hz for $^3J^{HH}$(g) and $^3J^{HH}$(t), respectively, which were taken from literature: Birdsall, M. J. M.; Partington, P. *J. Chem. Soc. Perkin Trans. 2* **1980**, 1415. However, in order to conveniently compare our data with those of Beguin et al., we used their values in the present study.

steric interactions are conceivable: (1) steric repulsion between two bulky C_6H_5 and COOH groups; (2) stabilization interaction between F and NH_3^+ groups, which are probably ascribed to hydrogen bonding and/or the electrostatic attraction force; (3) dipole–dipole repulsion between two negatively charged F and COO^- groups; and (4) hydrogen bonding between C_6H_5 and NH_3^+ groups. In view of these interactions, rotamer III of the threo isomer is understandable as the most stable one, provided that interactions (1 and 2) are dominant compared to the other two factors. This assumption is supported by the observation of no significant pH dependence and a negative temperature effect on the coupling constants. Thus, in the threo isomer, two major factors, steric repulsion (1) and stabilization interaction (2), reinforce each other to make rotamer III the most stable one independent of the pH conditions.

These considerations can be applied to the erythro case as well. Population analysis with the erythro isomer clearly shows that this isomer takes an increasing amount of both rotamers I and III in going from basic to acidic conditions. The population of rotamer I is the largest of three despite the existence of large steric repulsion between C_6H_5 and COOH in this conformation. These unusual results can be rationalized by invoking the increasing amount of the stabilization interaction (2) in going from basic to acidic conditions, as the protonation of the NH_2 group becomes predominant. However, the contribution of rotamer III becomes relatively significant, especially under acidic conditions, as shown by the increasing $^3J^{HF}$ value in going from basic to acidic conditions. Here, concerning the relative importance of rotamers I and III, two stabilizing factors (2 and 4) and only one destabilizing factor (1) exist with rotamer I, whereas only one stabilizing factor (2) and two destabilizing factors (1 and 3) exist with rotamer III.[28] This difference may decide the relative importance of both rotamers I and III. Surprisingly, the sterically most favorable rotamer II makes the least contribution to rotational conformation, particularly under both neutral andd acidic conditions. This is in accordance with the sharp decrease of the $^3J^{HH}$ value in going from basic to neutral conditions. Thus, the erythro case clearly demonstrated, as cited at the beginning of this section, that stabilization interaction (2) can bring about stronger effects on the equilibria of rotational conformations than the steric factors of the functional groups involved.

Single-Crystal X-ray Analysis of *threo*-*N*-Acetyl-3-fluorophenylalanine Isopropyl Ester (6) and *erythro*-*N*-Acetyl-3-fluorophenylalanine (7). The configuration of the product of the aziridine ring-opening reaction was determined by single-crystal X-ray analysis of its *N*-acetyl derivative (6). Crystals for the analysis were prepared by acetylation of the reaction product (2) followed by recrystallization from hexane–ether mixed solvent. The analysis revealed that the configuration of fluorine was threo [see Figure 3A and Table 2A (supplemental material)]. The fluorination had little effect on the bond distance and angle about the C(3) atom as shown in Table 2. The torsional angles ϕ, x^1, and x^2 were similar to those observed in *N*-acetyl-DL-phenylalanine *N*-methylamide.[29] The shortest intermolecular contacts were found in C(2)–H(C2)···F [(2)···F, 3.206 (3); H(C2)···F, 2.31 (2) Å] and N–H(N)···O(3) [N···O(3), 3.212 (3); H(N)···O(3), 2.34 (2) Å]. The latter was longer than the usual interchain N–H···O hydrogen bonds in peptide.

(28) The electrostatic repulsion force may also be an important factor in the selection of these two rotamers, especially under basic conditions.
(29) Harada, Y.; Iitaka, Y. *Acta Crystallogr., Sect. B* **1974**, *B-30* 726.

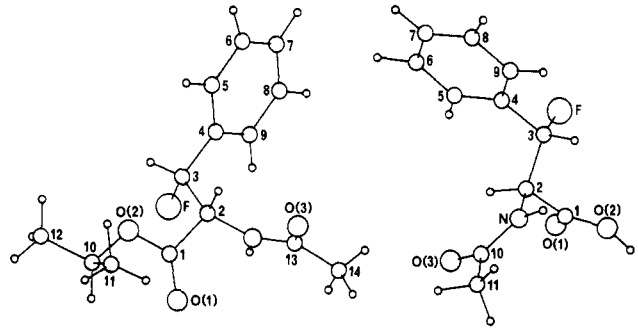

Figure 3. (a) A perspective view of the molecule 6. (b) A perspective view of the molecule 7.

The configuration of the product of the reductive amination reaction was also determined on its *N*-acetyl derivative (7) as for the product (6). Crystals for the analysis were prepared by acetylation of the obtained free amino acid (1a) followed by recrystallization from methanol. The analysis revealed that the configuration of fluorine was erythro [see Figure 3B and Table 2B (supplemental material)]. The region near fluorine had a bond distance and angle similar to those found in the threo case. Two intermolecular hydrogen bonds are found: N–H(N)···O(1) [N···O(1), 2.981 (4); H(N)···O(1), 2.11 (4) Å] and O(2)–H(O2)···O(3), [O(2)···O(3), 2.543 (3); H(O2)···O(3), 1.56 (5) Å].

In view of the structures determined with both cases, rotational conformations under freezing conditions appeared to be mainly controlled by steric factors. Thus, the stabilization interaction which is a dominant factor controlling conformations in solution may be of no significant importance for solid-state conformations.

The present study has clarified, for the first time, that introduction of β-fluorine into pyruvic acid derivatives strikingly affects the stereochemistry of reductive amination as well as the conformations of the product, β-fluoro-α-amino acids. This information should contribute to the understanding of different biological activities or metabolic behaviors, in particular those of the transamination reaction of both threo and erythro diastereomers of β-fluoro-α-amino acids. As an extended study of this series, we carried out stereocontrolled chemical conversions of these diastereomers into dehydroxylated *threo*- and *erythro*-1-fluorochloramphenicols and will report the results in the near future.[33]

Experimental Section

General Methods. Unless otherwise stated, the uncorrected melting points were determined using a Yanagimoto hot-stage apparatus. ^1H and ^{19}F NMR were taken as described below. IR spectra were recorded on a Hitachi 215 grating spectrometer as KBr discs. Mass spectra were measured on a Hitachi RMU-8GN and M-68 spectrometer either by the usual method or by the SIMS technique using xenon as the primary ion gas. Fluoro amino acids were purified, when necessary, by elution chromatography on dry cellulose column [packed with Whatman cellulose powder CG31; eluent consisting of 1-PrOH (3 parts), H_2O (1 part), and NH_4OH (a 0.5 N concentration of the final solution)] followed by recrystallization from aqueous 2-propanol.

NMR spectroscopic measurements for population analysis were carried out as follows. ^1H and ^{19}F NMR were taken on a Varian EM-360 spectrometer for solutions in D_2O with the same sample concentration (10 mg/0.4 mL D_2O) using a capillary tube containing TMS or C_6F_6, respectively, as an external standard. Observed proton chemical shifts were then converted into the chemical shifts from the internal DSS standard by calculation. Measurements were made for three different pH conditions with 12 runs each. Both coupling constants, $^3J^{HH}$ and $^3J^{HF}$, were determined as the average value of 12 runs. For the

pH adjustment, 40% NaOD and 20% DCl aqueous solutions were used. Temperature variation experiments were done at eight different points between 5 and 95 °C.

Preparation of *erythro*-3-Fluorophenylalanine (1a). The starting material, methyl 3-fluorophenylpyruvate, was prepared by a slightly improved procedure of our previously reported one. In a 1-L cylindrical stainless steel vessel equipped with a mechanical stirrer, a gas inlet tube, and a thermometer holder, the enol-type methyl phenylpyruvate (39.3 g, 0.221 mol) was dissolved in 450 mL of acetonitrile. The resulting solution was cooled to −5 °C, then fluorine gas (1.58 molar equiv) diluted with nitrogen to 10% concentration was introduced over 3 h with vigorous stirring. The reaction mixture was treated with 22.5 g of sodium fluoride and filtered, and then the solvent was removed under reduced pressure, leaving 51.3 g of an oily crude product. VPC analysis of this product showed that the starting material had been completely consumed and a large amount of the desired product had been formed. As the product, methyl 3-fluorophenylpyruvate, was easily decomposed by oxygen, the unpurified crude product was added to the nitrogen-flashed 50% aqueous 2-propanol solution (650 mL each of H_2O and 2-PrOH) together with 55.6 g of sodium bicarbonate and kept for hydrolysis at 40 °C overnight under nitrogen. At this stage, the first fraction of the hydrolysis product was isolated as follows. After adding ethyl acetate and saline to the reaction mixture, the aqueous layer was separated from the organic one containing a large amount of unreacted starting material. The separated aqueous layer was then acidified with 36% HCl and extracted with ethyl acetate. The organic layer was then dried over magnesium sulfate and the solvent was removed under reduced pressure, affording 19.33 g of the first fraction of the hydrolysis product. Again, hydrolysis was repeated in the same way with the starting material recovered from the first separated organic layer. After the same workup, 11.05 g of additional acidic hydrolysis product was obtained. The combined hydrolysis product was 30.3 g, indicating an approximate total yield of 75.5% for the two steps of fluorination and hydrolysis. The acid product obtained was then converted into sodium salt by treatment with 14.01 g of sodium bicarbonate in water and concentrated under vacuum almost to dryness. All operations were carried out as much as possible under nitrogen. Next, reductive amination was carried out by the two different methods described below.

Reductive Amination (Method A). The resulting sodium salt (30.38 g, 0.186 mol) was dissolved into 380 mL of 25% aqueous ammonia and maintained at 37 °C for 3 h to allow the imine formation to reach complete equilibrium. The brown solution was cooled to 10 °C and sodium borohydride (5.37 g, 0.56 mol) was added to this solution, while vigorously introducing nitrogen gas under reduced pressure. The reaction mixture was gradually warmed up to 30 °C over 2.0 h to complete the reduction. After complete removal of ammonia under reduced pressure, the reaction mixture was again cooled in an ice bath and acidified to pH 1–2 using 2.5 N HCl solution. Precipitates coming out of the solution were dissolved by adding 2-propanol. The clear solution thus obtained was then treated with 1 L of acidic ion exchange resin (AG 50W-X8) by sequentially using 50% aqueous 2-propanol, water, and 1 N aqueous ammonia as eluents. Removal of the solvent from the last eluate at 25 °C under reduced pressure gave 13.48 g of **1a** (44% from **5a**, another run showed a slightly higher yield of 51.8% than this case). Both ^1H and ^{19}F NMR spectra of this crude product showed no formation of byproducts or the threo diastereoisomer in more than 5% yield. Recrystallization of the crude product from aqueous 2-PrOH afforded 9.6 g of the pure sample: mp 168–169 °C dec; IR ν 3420–2400 (br s, NH_3^+ and aromatic), 1660–1550 (br s, COO^- and C_6H_6), 1520 (s, NH_3^+ and aromatic), 1450 (m), 1410, 1390 (m, COO^-), 1370 (s), 1330 (m), 1135 (w), 1029 (s), 708 (s) cm^{-1}; ^1H NMR δ 4.33 (dd, 1 H, H_α, $J_{H_\alpha-F}$ = 16.3 Hz, $J_{H_\alpha-H\beta}$ = 3.4 Hz), 6.17 (dd, 1 H, H_β, $J_{H_\beta-F}$ = 44 Hz), 7.44 (m, 5 H, aromatic H); ^{19}F NMR (D_2O) δ −21.3 (J = 44 Hz, 16.3 Hz); mass spectrum, m/z 276 (M + H^+ + glycerin), 184 (M + H^+), 164 (M^+ − F).

Anal. Calcd for $C_9H_{10}O_2NF$: C, 59.01; H, 5.50; N, 7.65; F, 10.37. Found: C, 59.29; H, 5.40; N, 7.73; F, 10.15.

Reductive Amination (Method B). Into 6 mL of dry methanol was added 3 mmol (204 mg) of the sodium salt (**5a**), 15 mmol of dry ammonium bromide, and 6 mmol (300 mg) of sodium cyanoborohydride at room temperature with vigorous stirring for 48 h under nitrogen atmosphere. Next, the reaction mixture was acidified with 15 mL of 36% HCl and stirring was continued at room temperature for 1 h. After removal of the solvent under reduced pressure, the residue obtained was diluted with 9 mL of water and then treated with acidic ion exchange resin (AG 50W-X8) as described above. The desired product (**1a**) was obtained in 17.9% yield (98.2 mg) from **5a**–Na. Both ^1H and ^{19}F NMR spectra of the crude product were identical with those obtained from method A, suggesting that the threo diastereoisomer was not present in more than 5% yield.

Preparation of *erythro*-3-Fluoro-*p*-chlorophenylalanine (1b). By the same method employed in the preparation of **1a**, methyl 3-fluoro-*p*-chlorophenylpyruvate (**4b**) was obtained in an estimated yield of more than 80%. This sample (39.5 g) was hydrolyzed as described above and gave 30.0 g of the free acid which was subjected, after conversion into 33.2 g of the sodium salt, to reductive amination (method A). In this case, however, the solubility of the sodium salt in both H_2O and organic solvents was so low that the workup procedure of the hydrolysis and the volume of the 25% aqueous ammonia solution for the reductive amination had to be adjusted. Finally, 18.0 g of the desired product was obtained in a yield of 60% from the sodium salt **5b**–Na after the workup described above. Both ^1H and ^{19}F NMR of this crude product showed the formation of neither notable amounts of byproducts nor the threo diasteroisomer in more than 5% yield. Recrystallization of the crude product from aqueous 2-PrOH afforded 11.4 g of the pure sample: mp 180–182 °C dec; IR ν 3420–2400 (br s, NH_3^+ and aromatic), 1640–1550 (br s, COOH), 1520 (s, NH_3^+ and aromatic), 1495 (s), 1475–1400 (s, COO^-), 1325 (s), 1090 (m), 1015 (m), 855 (m) cm^{-1}; ^1H NMR (D_2O–NaOD, pH ≥ 10) δ (external Me_4Si) 4.25 (dd, 1 H, H_β, $J_{H_\beta-F}$ = 13.5 Hz, $J_{H_\alpha-H_\beta}$ = 5.0 Hz), 6.27 (dd, 1 H, H_α, $J_{H_\alpha-F}$ = 47.0 Hz), 7.90 (m, 4 H, aromatic H); ^{19}F NMR (D_2O–NaOD, pH ≥ 10) δ −14.25 (J = 47.0 Hz, J = 13.5 Hz); mass spectrum, m/z 310 (M + H^+ + glycerin), 218 (M + H^+), 198 (M − F).

Anal. Calcd for $C_9H_9O_2NFCl$: C, 49.67; H, 4.17; N, 6.44; F, 8.73. Found: C, 49.44; H, 4.47; N, 6.63; F, 8.46.

Preparation of *erythro*-3-Fluoro-*p*-nitrophenylalanine (1c). Ethyl 3-fluoro-*p*-nitrophenylpyruvate (**4c**) was prepared by direct fluorination of 30 g of ethyl *p*-nitrophenylpyruvate (**3c**) by the method employed in the preparation of **1a**. The crude product was hydrolyzed, without purification, and afforded 23.9 g of the free acid which was subjected, after conversion into 26.4 g of the sodium salt, to reductive amination (method A). The reaction was carried out as for **1a** except a slightly longer reaction time was used to give 4.46 g of the desired product in 18.5% yield. Another run showed a higher yield of 25.7% than the yield in this case. Like other cases of **1a** and **1b**, this product did not show formation of the threo diastereomer in more than 5% yield on NMR spectra. After column chromatography over cellulose [Whatmann CC31, 2-PrOH (5 parts)–0.2 N aqueous NH_3 (1 part) as an eluent], recrystallization of the product from aqueous 2-PrOH afforded 1.50 g of the pure hygroscopic sample: mp 172–174 °C dec; IR ν 3420–2400 (br s, NH_2 and COOH), 1640–1550 (br s, COOH), 1520 (s, aromatic, NO_2 and NH_3^+), 1400 (m, COO^-), 1350 (s, NO_2), 1320 (s), 1110 (w), 1015 (w), 865, 850 (both m) cm^{-1}; ^1H NMR D_2O–NaOD, pH ≥ 10) δ (external Me_4Si) 4.29 (dd, 1 H, H_β, $J_{H_\beta-F}$ = 16.9 Hz, $J_{H_\alpha-H_\beta}$ = 5.0 Hz), 6.35 (dd, 1 H, H_α, $J_{H_\alpha-F}$ = 45.2 Hz), 8.00, 8.74 (m, 2 H each, aromatic H); ^{19}F NMR (D_2O–NaOD, pH ≥ 10) δ −19.68 (J = 45.2 Hz, J = 16.9 Hz); mass spectrum, m/z 321 (M + H^+ + glycerin), 329 (M + H^+).

Anal. Calcd for $C_9H_9N_2O_4F \cdot H_2O$: C, 43.90; H, 4.50; N, 11.38; F, 7.72. Found: C, 44.34; H, 4.84; N, 11.44; F, 7.48.

Preparation of *threo*-3-Fluorophenylalanine (2a). *threo*-3-Fluorophenylalanine isopropyl ester was prepared by the method reported by Wade et al. Next, 225 mg (1 mmol) of the ester was treated, in the presence of 101 mg (1 mmol) of triethylamine, with 240 mg (1 mmol) of *S*-(*tert*-butoxycarbonyl)-4,6-dimethyl-2-mercaptopyrimidine overnight at room temperature in 2 mL of DMF solvent. This reaction mixture was poured into water and extracted with ether. The organic layer was separated and dried over magnesium sulfate, and then the solvent was evaporated under reduced pressure, leaving an oily residue. Silica gel chromatography of the residue gave the desired N-protected amino ester, *threo*-*N*-(*tert*-butyloxycarbonyl)-3-

fluorophenylalanine isopropyl ester: mp 39–40 °C; IR ($CHCl_3$) ν 3450 (m, NH), 2970, 2930 (m, CH), 1740–1710 (s, two C=O), 1495 (s), 1375 (s), 1280–1170 (br s, COO), 1110 (s), 1070 (m), 1040 (m), 985 (m), 920 (m), 865 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ (Me_4Si) 1.15–1.53 (m, 16 H, 2-C_3H_7, t-C_4H_9), 4.40–5.40 (overlapping m, 3 H, H_α, NH, -$CHMe_2$), 5.90 (dd, 1 H, H_β, J = 45 Hz, $J_{H_\alpha-H_\beta}$ = 3.7 Hz), 7.27 (m, 5 H, aromatic H); mass spectrum, m/z 326 (M^+ + H), 325 (M^+), 269 ($M^+ - C_4H_8$), 215 ($M^+ - C_6H_7F$), 182 ($C_9H_9O_2NF$), 138 (C_8H_9NF), 116 ($NHCO_2C_4H_9$), 109 (C_7H_6F), 73 (C_4H_9OH), 57 (C_4H_9).

Anal. Calcd for $C_{17}H_{24}O_4NF$: C, 62.75; H, 7.43; N, 4.30; F, 5.84. Found: C, 63.06; H, 7.66; N, 4.29; F, 5.98.

Enzymatic hydrolysis of the esster to *threo*-*N*-(*tert*-butyloxycarbonyl)-3-fluorophenylalanine was carried out as follows. Into the DMF solution of the N-protected amino ester [975 mg (3 mmol)/145 Ml of DMF] were sequentially added 145 mL of water and the enzyme, chymotrypsine dissolved in 5 mL of water just prior to use, with vigorous stirring at room temperature. As soon as the enzyme was added, the pH meter monitoring the progress of hydrolysis showed a quick shfit toward the acidic value of 6.0. Aqueous hydroxide solution (0.5 N) was immediately added to adjust the pH value of the solution to 7.2–7.5. This operation was repeated for 6 h until the rate of hydrolysis became markedly sluggish when half of the starting material had been hydrolyzed. At this stage, 3.16 mL of 0.5 N aqueous sodium hydroxide solution had been consumed to neutralize the acidic product liberated. Next, aqueous sodium hydroxide was added to the solution to change its pH value to 11.0. After the 500 mg of unreacted material was removed from the solution with ether extraction for three times, the aqueous layer was acidified with 0.5 N hydrogen chloride to a pH value of around 1.5. From this aqueous solution, the desired acidic hydrolysis product was removed by extraction three times with ethyl acetate using the salting out technique. The organic layer was dried over magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure, leaving 203 mg of the oily product in 48.7% yield. After recrystallization from hexane–ether, the product gave the following data: mp 141–142 °C; $[\alpha]^{21.5}_D$ 0.0 (c 0.547, $CHCl_3$–1% EtOH); $[\alpha]^{365}_{21.5}$ +9.9 ± 0.9 (c 0.547, $CHCl_3$–1% EtOH); ^1H NMR ($CDCl_3$ + D_2O) δ (Me_4Si) 1.28 (s, 9 H, C_4H_9), 4.58 (m, 1 H, H_α, $J_{H_\beta-F}$ = ca. 29 Hz), 6.02 (q, 1 H, H_β, $J_{H_\beta-H_\alpha}$ = ca. 3.5 Hz, $J_{H_\beta-F}$ = 46 Hz), 7.35 (m, 5 H, aromatic H).

The amino group was deprotected by sequentially adding 0.308 mL (20 molar equiv) of trifluoroacetic acid and 0.30 mL of anisol with stirring at 0 °C to the dichloromethane solution of the acid obtained above [114 mg (0.40 mmol)/1.5 mL of CH_2Cl_2]. The reaction temperature was gradually raised to room temperature and maintained for 4 h to complete the reaction. Concentration of this reaction mixture under reduced pressure left a crude oily product, the trifluoroacetic acid salt of *threo*-3-fluorophenylalanine. This salt was converted into the desired free amino acid *threo*-3-fluorophenylalanine by treatment with acidic ion exchange resin, Dowex 50W-X8, as in the case of the erythro diastereomer. After recrystallization from aqueous 2-propanol, the pure product was obtained: mp 150–152 °C dec. with evolution of gas; IR ν 3400–2400 (br s, NH_3^+ and aromatic), 1640–1560 (three peaks s, COO^- and C_6H_5), 1500 (m, NH_3^+ and aromatic), 1475 (w), 1405 (m, COO^-), 1345 (m), 1255 (w), 1223 (w), 1150 (w), 1130 (w), 990 (s) cm^{-1}; ^1H NMR δ 4.14 (dd, 1 H, H_α, $J_{H_\alpha-F}$ = 27.3 Hz, $J_{H_\alpha-H_\beta}$ = 4.3 Hz), 6.14 (dd, 1 H, H_β, $J_{H_\beta-F}$ = 45 Hz), 7.47 (m, 5 H, aroamtic H); ^{19}F NMR δ –25.3 (J = 45 Hz, J = 27.3 Hz); mass spectrum, m/z 276 (M + H^+ + glycerin), 184 (M + H^+), 164 (M^+ – F).

Single-Crystal X-ray Analysis. Crystal Data for *threo*-*N*-Acetyl-3-fluorophenylalanine Isopropyl Ester (6). $C_{14}H_{18}NO_3F$, monoclinic, $P2_1/c$, a = 5.167 (1) Å, b 22.089 (2) Å, c = 12.856 (1) Å, β = 103.85 (1)°, Z = 4. A crystal, with dimensions of 0.15 × 0.15 × 0.15 mm, was used for data collection on a Rigaku diffractometer (monochromated Cu K_α radiation) and 2130 independent reflections were measured in the range $\theta \leq 60°$. No absorption correction was made. The structure was solved by direct methods (MULTAN76).[30] After a few cycles of anisotropic block diagonal least-squares refinement, difference synthesis showed all the hydrogen atoms, which were included in the refinement with isotropic temperature factors. The final R value was 0.041 for 1768 reflections. The atomic scattering factors were taken from the International Table for X-ray Crystallography (1974).[31] The weighting scheme employed was $w = 1/\sigma^2(F_o)$ for $|F_c| \geq \sigma(F_o)$ and $w = 0$ for $|F_c| < \sigma(F_o)$ or $|\Delta F| > 3\sigma(F_o)$. $\sigma(F_o)$ was estimated by the relation $\sigma(F_o) = [\sigma_1^2(F_o) + 0.00082|F_o|^2]^{1/2}$, where $\sigma_1(F_o)$ is the esd based on the counting errors.[32]

Crystal Data for *erythro*-*N*-Acetyl-3-fluorophenylalanine (7). $C_{11}H_{12}NO_3F$, orthorhombic, $P2_12_12_1$, a = 11.899 (7) Å, b = 16.714 (8) Å, c = 5.615 (2) Å, Z = 4. A crystal, with dimensions of 0.10 × 0.10 × 0.20 mm, was used for data collection and 1250 independent reflections were measured in the range $\theta \leq 70°$. The crystal structure was solved and refined as described above. The final R value was 0.044 for 1033 reflections.

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Registry No. **1a**, 79617-87-1; **1b**, 80817-87-4; **1c**, 80817-88-5; **2**, 76582-49-5; **3a** (X = H, R = Me), 80540-55-2; **3b** (X = Cl, R = Me), 80540-56-3; **3c** (X = NO_2, R = Et), 80540-57-4; **4a** (X = H, R = Me), 76532-83-7; **4b** (X = Cl, R = Me), 79547-04-9; **4c** (X = NO_2, R = Me), 88867-08-7; **5a** (X = H, M = Na), 76532-84-8; **5b** (X = Cl, M = H), 88867-09-8; **5b** (X = Cl, M = Na), 88867-10-1; **5c** (X = NO_2, M = H), 88867-11-2; **5c** (X = NO_2, M = Na), 88867-12-3; **6**, 88928-87-4; **7**, 88867-13-4; *threo*-3-fluorophenylalanine isopropyl ester, 79617-86-0; *threo*-*N*-(*tert*-butyloxycarbonyl)-3-fluorophenylalanine isopropyl ester, 88867-14-5; *threo*-*N*-(*tert*-butyloxycarbonyl)-3-fluorophenylalanine, 88867-15-6; *threo*-3-fluorophenylalanine·trifluoroacetic acid salt, 88867-16-7.

Supplementary Material Available: Table 2A and 2B, interatomic distances, angles and torsion angles; Table 3A and 3B, final positional and isotropic thermal parameters; Table 4A and 4B, anisotropic thermal parameters (10 pages). Ordering informations is given on a current masthead page.

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Total Synthesis of 2,6-Epoxy-1(2*H*)-benzoxocin Sugar Analogues

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An expedient route for construction of sugar analogues of 2,6-epoxy-1(2*H*)-benzoxocins is described.

The anthracycline antibiotic nogalamycin (**1a**) is the only known example of a glycosidic natural product containing a perhydroxylated epoxyoxocin ring system.[2] Conceptually this fragment originates from the dual at-

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