Addition of Molecular Fluorine to Azlactones: General Synthetic Method of erythro-β-Fluorinated α-Amino Acids

Chikara Kaneko,* Jun Chiba, Akemi Toyota, and Masayuki Sato

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan.
Received November 21, 1994; accepted January 20, 1995

Reaction of molecular fluorine with unsaturated azlactones derived from appropriate aldehydes (or ketones) and benzoylglycine afforded the difluorinated adducts. The reductive amination reaction of the β-fluorinated α-oxoalanoic acids obtained from the adducts by basic hydrolysis gave erythro-β-fluorinated aliphatic α-amino acids. The same reactions, when applied to methyl 3-phenyl-2-benzoylaminoacrylate, afforded the corresponding aromatic amino acid. Hence, the entire sequence provides a general method for the synthesis of erythro-β-fluorinated α-amino acids.

Key words: fluorination; molecular fluorine; azlactone; β-fluorinated α-amino acid; reductive amination

The addition of molecular fluorine to ethylenes proceeds stereoselectively to give the cis adducts, and this reaction has potential synthetic utility for the preparation of a variety of fluorinated compounds. Using this reaction as the key step, we have disclosed general synthetic methods of 5-fluorinated 1,3-dioxin-4-ones, 5α-fluorinated steroids, and fluoride-containing carbocyclic nucleosides. In this paper, we report the reaction of molecular fluorine with unsaturated azlactones or 3-substituted 2-acylaminoacrylic acids, focusing on the elaboration of a general synthetic method of β-fluorinated α-amino acids. Since the pioneering work on 3-fluoro-D-alanine, a powerful inhibitor of alanine racemase, by Kollonitsch et al., substitution of the β-hydrogen atom of α-amino acids by fluorine has led to a number of irreversible enzyme inhibitors (so-called suicide inhibitors). However, no general synthetic method of β-fluorinated amino acids has so far been reported.

Unsaturated azlactones A are readily prepared by condensation of appropriate aldehydes (or ketones) with acetylglucose. By mild basic hydrolysis, they are converted to the corresponding 3-substituted 2-acylaminoacrylic acids B. Compounds A and B are then used for the synthesis of the corresponding α-amino acids C and α-keto acids D.

Since compounds D are readily converted to C by reductive amination, we planned a general synthetic route to the α-amino acids C starting either from 3-substituted 2-acylaminoacrylic acid derivatives B (method A) or from the corresponding unsaturated azlactones A (method B). In this paper, we present the results.

In order to synthesize β-fluorinated α-amino acid by method A, we chose methyl (Z)-3-phenyl-2-benzoylaminoacrylate (Z-2), readily obtained from benzylidene-2-phenyloxazolin-5-one (I). First, the addition of molecular fluorine to Z-2 was examined at −78°C in 2:1 v/v perchloric acid, ethyl acetate, and water. As a result, the ethoxylated product 3 was obtained in 14% and 20% yields, respectively, together with other minor products. Since all attempts to convert 3 to an appropriate precursor (e.g., the imine 5) of the corresponding amino acid (3-fluorinated phenylalanine) failed, the above fluorination conditions were abandoned. In order to prevent the formation of 3, the solvent was changed to a mixture of CFCl3 and CHCl3 (1:1 v/v). The addition of molecular fluorine to Z-2 in this solvent system followed by silica gel chromatographic separation gave the expected imine 5 (including its hydrated product) and an oxazoline cis-4 as a single stereoisomer in 17.5% and 37.5% yields, respectively.

Chart 1

Chart 2. Strategies for the Synthesis of β-Fluorinated Amino Acids

R = alkyl, aryl.

* To whom correspondence should be addressed.

© 1995 Pharmaceutical Society of Japan
Based on our recent \textit{ab initio} MO calculation using the I RC method on the fluorine addition to ethylene,\textsuperscript{13} we propose the mechanism shown in Chart 4, which involves the \( \pi \)-complex \( E \) as the intermediate and the tight ion pairs \( F \) and \( G \) as the transition states, to account for the formation of \( 4 \) and \( 5 \).

A different result was obtained when \( E-2,\textsuperscript{14} \) which could be prepared from \( Z-2 \) by HBr-catalyzed isomerization, was used in the above reaction. Under these conditions, no oxazoline \( 4 \) was formed and only the imine \( 5 \) and its hydrated product \( 5' \) were obtained in 33\% combined yield. Hence, a more detailed analysis is necessary in order to clarify the reason why the oxazoline \( \textit{cis}-4 \) was formed only from \( Z-2 \).

We consider that in the case of formation of the oxazoline \( \textit{cis}-4 \) from \( Z-2 \), the addition is completed when the singly halogenated transition state (the tight ion pair: \( F-1 \)) reacts “with its own tail.” Note that the second step, the attack by the oxygen of the benzoyl group is a Walden inversion. Though the fluorination does not proceed \textit{via} the corresponding halonium ions (\( \overset{\ddagger}{\overset{\ddagger}{X}}^+ \)), the stereochemical demand in this reaction (the preference for anti-addition) is the same as that of other halogenation reactions. That is, because of the presence of the outer fluorine (\textit{cf.} \( F^- \) in \( F-1 \)), only the rear side attack of the entering nucleophile (the oxygen in the benzoyl group) is possible. In accordance with this explanation, the \(^1\text{H}-\text{NMR} \) spectrum of \( \textit{cis}-4 \) clearly demonstrated the \textit{trans} relationship between \( H(5) \) and \( F \) by a large coupling constant (\( J_{H-F}=25.3\text{Hz} \)).\textsuperscript{15} The same mechanism, if applied to the fluorination of \( E-2 \), predicts the formation of the \textit{trans} oxazoline (\( \textit{trans}-4 \)). However, this pathway seems to be difficult due to steric hindrance between the phenyl and methoxycarbonyl groups (\textit{cf.} \( F-2 \)).

Among the two products thus obtained, the oxazoline \( \textit{cis}-4 \) was stable and could be well characterized, whereas the imine \( 5 \) and its hydrated product \( 5' \) were too unstable to isolate in pure forms. Hence, the mixture of \( 5 \) and \( 5' \) was treated with sodium cyanoborohydride in methanol in order to convert them to the corresponding amino acid derivative \( 7 \). As a result, methyl 3-fluoro-2-hydroxy-3-phenylpropionate (\( 6 \)) was obtained as a mixture (\textit{ca.} 5:1) of two diastereomers in a quantitative yield. The \(^1\text{H}-\text{NMR} \) spectrum of the mixture revealed that the \textit{erythro
diastereomer 6-erythro was the major product. The reason for this selectivity will be discussed later. The formation of 6 from 5 (and 5') in the above reaction indicates that methyl 3-fluoro-3-phenylpyruvate (13) was formed before the reduction occurred. Hence, it is expected that, if treated under reductive amination conditions, 5 would afford 3-fluorophenylalanine methyl ester (8). Reductive amination of 5, however, gave only a small amount (less than 5% yield) of 6 and none of 8 was obtained. The reason for this failure is most probably intrinsic instability of this ester 8, as demonstrated by Bergmann and Cohen. A survey of the literature revealed that Tsushima et al. had synthesized erythro 3-fluorophenylalanine (11-erythro) by the reductive amination of sodium 3-fluoro-3-phenylpyruvate (9), using sodium borohydride as the reducing reagent.

Thus, in order to utilize the above reaction for the present case, the imine 5 was hydrolyzed with aqueous NaHCO₃ at room temperature to give crude sodium 3-fluoro-3-phenylpyruvate (9). The reductive amination reaction of 9 using sodium borohydride as a reducing reagent then afforded 3-fluorophenylalanine (11) in 60% yield from the crude imine (the mixture of 5 and 5'). As reported by Tsushima et al., the erythro isomer was obtained with high stereoselectivity (ratio of erythro/threo: 95:5).

Extension of the above method (method A) to the synthesis of 3-fluorinated aliphatic amino acids was then investigated, taking 3-fluoroleucine (18a) as the target compound. The dehydroamino acid derivatives 15 (R = isopropyl and methyl), however, did not react with fluorine under the same conditions as in the case of 2 to 5, and

![Chemical structures and reactions](chart6.png)

**Chart 6**

![Chemical structures and reactions](chart7.png)

**Chart 7**
the starting materials were recovered quantitatively. Hence, we employed method B. It was found that, when the same reaction was applied to the azlactone 14a itself, the fluorination proceeded smoothly to give the expected addition product 16a. Since both 16a and its hydrolysis product 17a are too unstable to isolate in pure forms, the reactions were carried out successively without isolating any intermediate. Overall yield of the amino acid 18a-erythro was 30% and none of the three isomer was detected in the final product.

Application of the same reaction sequence to 14b afforded 18b-erythro as a sole product in 14% yield. By the same one-pot procedure, the azlactone 19 derived from hippuric acid and acetone was converted to the corresponding amino acid 21 in 23% yield.

The fact that the treatment of the fluorination product with sodium methoxide in methanol gave the product 22 having a methoxy group at the 2-position indicates the intermediacy of the difluorinated adduct 20.

Finally, the possible reason for high erythro-selectivity in the reductive amination reactions seems worthy of comment. In order to account for the predominant formation of 11-erythro from 3-fluoro-3-phenylpyruvic acid (9), Tsushima et al. proposed that, owing to the stabilizing interaction between fluorine and the neighboring imine (or more probably the corresponding iminium ion), the conformer (H: R = Ph) is the more stable of the two possible conformers (H and I: R = Ph) predicted from the Felkin model. Therefore, the reduction is predicted to occur on H from the less hindered side to give the erythro diastereomer (J-erythro: R = Ph). However, that explanation is not applicable to the predominant formation of 6-erythro from 5 via 13 by the same reduction as demonstrated in the present study (cf. Chart 6). In this reaction, one can not expect the same stabilizing interaction between C(2)=O and fluorine in 13. Hence, preference for the conformer corresponding to H (the precursor of 11-erythro) to that corresponding to I (the precursor of 11-three) would not be predicted.

Pandit et al. have observed the same stereoselectivity in sodium cyanoborohydride reduction of β-fluoro-α-amino maleic or fumaric acid. They explained this stereoselectivity in terms of the Felkin-Anh model. Thus, by assuming two conformers (H and I) as the stable ones, the obtuse trajectory of the attacking nucleophile (H⁻ or BH₄⁻) to the C=O bond according to Anh’s transition state model suggests that the transition state I is destabilized by Coulombic repulsion between the hydride (or the charged borohydride complex: BH₄⁻) and the fluorine atom. Hence, the formation of the three isomer K is suppressed compared with that of the erythro isomer derived via the transition state H', in which no such repulsion exists. Since this explanation is consistent with the predominant formation of 6-erythro from 13, we support the Pandit’s proposal as the most reasonable mechanism for the erythro preference observed in the present study. The rather low selectivity (erythro/threo = ca. 5) in the reduction of 13 to 6 as compared to those (erythro/threo = 20—100) of the imines to the fluorinated amino acids indicates that the different stability of the two possible conformers (cf. H and I) may play a minor role.

In any event, it can be concluded from the present study that the erythro selectivity is a common feature in these reductive amination reactions, irrespective of the kind of substituents on C(3) of 3-fluoro-2-oxopropanoic acid. The same erythro preference also holds for the reduction of 3-fluorinated 2-oxoalanoic acids.

Conclusion

The transformation from unsaturated azlactones A to β-fluorinated β-amino acids C reported in this paper seems to have wide applicability. Thus, for the synthesis of fluorinated aliphatic amino acids the fluorination is applied to A, while for that of aromatic ones the same fluorination is applied not to A but to B, which can be obtained readily from A. Though the reductive amination step has precedent, this method is superior to other existing methods in the following respects: a) use of unsaturated azlactones which are not only readily synthesized but also can have all kinds of functionalities on the exo methylene moiety, b) the fluorination reagent is molecular fluorine, which is easiest to handle and cheapest among the known fluorinating reagents and c) this method is superior to the method elaborated by Tsushima et al. because, while the present transformation should be applicable to all kinds of azlactones, Tsushima’s method is only applicable to pyruvates which can exist in enol forms and hence, is not applicable to the synthesis of fluorinated aliphatic amino acids.

Experimental

All melting points were determined on a Yanagimoto microhot stage and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. 1H-NMR spectra were recorded with a Hitachi R-300 spectrometer with tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra (MS) were obtained on a JEOL JMS-DX303 or JEOL JMS-AX500 mass spectrometer. Silica gel used for column chromatography was Wako gel C-200. Merck Kieselgel 60 F-254 was employed for thin layer chromatography (TLC).

Materials Azlactones 1a, 14a, 14b and 19 and methyl 3-phenyl-2-benzoylaminoacrylates Z-21 and E-21 were prepared according to the literature.

General Procedure of Fluorine Addition Reaction with Molecular Fluorine (5% F₂/N₂) in CFCl₃–CHCl₃, Exemplified by the Synthesis of 3-Fluorophenylalanine by Method A A solution of Z-2 (1.12 g, 4 mmol) in a mixture of CFCl₃–CHCl₃ (1:1 v/v, 100 ml) was cooled to −78°C. At this temperature, 5% F₂/N₂ was passed into the solution under vigorous stirring until 8.0 mmol (2 mol eq) of F₂ had passed through the flowmeter (ca. 40 min). After the reaction, nitrogen was passed through the solution for 5 min and 100 ml of water was added. Saturated NaHCO₃
solution was added slowly to this solution under stirring, until the pH of the aqueous layer became 7—8. The organic layer was separated and washed with water. After reextraction of the aqueous layers with CHCl₃ (50 ml × 3), the combined organic layer was dried over MgSO₄ and evaporated in vacuo. The residue thus obtained was chromatographed over silica gel with hexane-AcOEt (5:1 v/v) to give the starting material Z-2 (233.9 mg, 1.19 mmol, 29.7%), cis-4 (315.4 mg, 1.05 mmol, 26%), and a mixture (155.8 mg, 0.49 mmol, 12.3%) of 5 and its hydrolyzed compound 5' (ratio of 5 and 5' = ca. 3:2 as judged from the ¹H-NMR spectrum). The yields based on the consumed Z-2 were 37.5% for cis-4 and 17.5% for the mixture of 5 and 5'.

cis-4: oil. IR (CHCl₃): 1745, 1629 cm⁻¹. ¹H-NMR (CDCl₃): δ: 3.95 (3H, s), 6.18 (1H, d, J = 25.3 Hz), 7.36—7.65 (8H, m), 8.14—8.17 (2H, m). MS m/z: 299 (M⁺), 279 (M⁺—H). High-resolution MS m/z: Found 299.0953 [Calcd for C₁₄H₁₂F₂NO (M⁺) 299.0958].

5: oil. ¹H-NMR (CDCl₃): δ: 3.82 (3H, s), 6.46 (1H, d, J = 47.2 Hz), 7.39—7.57 (8H, m), 7.76—7.83 (2H, m).

5': oil. ¹H-NMR (CDCl₃): δ: 3.83 (3H, s), 5.70 (1H, d, J = 44.7 Hz), 7.39—7.57 (8H, m), 7.85—7.87 (2H, m).

The high-resolution mass spectrum was measured for the mixture of 5 and 5'. MS m/z: Found 299.0953 [Calcd for C₁₄H₁₂F₂NO (M⁺) 299.0958].

Application of the same reaction to E-2 gave, along with the starting material E-2, a mixture of 5 and 8 in 33% yield based on the consumed E-2.

Fluorine Addition Reaction to Z-2 with Molecular Fluorine (5% F₂/N₂) in CFCl₃—CHCl₃—EtOH—MeOH. A solution of Z-2 (281 mg, 1.11 mol) in a mixture of CFCl₃—CHCl₃—EtOH (5:4:1 v/v, 50 ml) was cooled to —78 °C. At this temperature, 5% F₂/N₂ was passed under vigorous stirring into the solution until 4.0 mmol (2 mol equiv) of F₂ had passed through the flask (ca. 20 min). The products were treated in the same manner as above to give the recovered Z-2 (39 mg), 4 (45 mg) and 3 (39 mg). The yields based on the consumed Z-2 were 19.0% for cis-4 and 14.2% for 3, which consisted predominantly of one diastereomer. The spectra of the oxazoline were identical with those of cis-4 obtained as above.

3: ¹H-NMR (CDCl₃): δ: 1.20 (3H, t, J = 7.3 Hz), 3.53 (2H, q, J = 7.3 Hz), 3.78 (3H, s), 6.02 (1H, d, J = 44.3 Hz), 7.36—7.59 (8H, m), 7.71—7.81 (2H, m). MS m/z: Found 299.0953 [Calcd for C₁₄H₁₂F₂NO (M⁺—EtOH) 299.0958].

Synthesis of 1-erythro. The mixture of 5 and 5' (45.9 mg, 0.15 mmol) obtained as above was dissolved in 5 ml of 1,4-dioxane—H₂O (1:1 v/v) and the pH of this solution was adjusted to 10 by addition of saturated NaHCO₃ solution. The resultant solution was stirred vigorously for 24 h at room temperature. After acidification (pH, ca. 2) by addition of 10% HCl solution, the product was extracted with AcOEt. The organic layer was separated and dried over MgSO₄. By evaporation of the solvent in vacuo, 3-fluoro-3-phenylpyruvic acid [identified by ¹H-NMR showing H3 (a) (doublet, 6 = 6.47, J = 48.8 Hz) was obtained (26 mg, 0.143 mmol, 99%)]. Since this acid is unstable in air, it was used in the following reaction without further purification. By addition of 2 ml of H₂O and 12 mg (0.143 mmol) of NaHCO₃, a solution of the sodium salt 9 was prepared. To this solution, MeOH (3 ml) and 25% NH₄OH solution (0.3 ml) were added and the mixture was maintained at 40 °C for 6 h to allow imine formation to reach equilibrium. After cooling of the solution to 0 °C, NaBH₄ (16.3 mg, 0.429 mmol) was added and the mixture was gradually warmed to room temperature, then kept standing for 24 h. After evaporation of ammonia in vacuo, the reaction mixture was acidified under ice cooling to pH 2 by the addition of 5% HCl solution. The precipitates were dissolved completely by adding 2-propanol. The clear solution thus obtained was treated with 30 ml of acidic ion exchange resin (AG 50W-X8) by sequential using 50% aqueous 2-propanol, water, and 1% aqueous ammonia as eluents. Removal of the solvent from the last eluate at room temperature in vacuo gave 3-fluoro-3-phenylalanine HCl (12 mg, 0.066 mmol). The ¹H-NMR spectrum (CD₃OD) of this product revealed that it consists of the erythro- and threo-diastereomers in a ratio of ca. 95:5.

1-erythro: ¹H-NMR (CD₃OD): δ: 4.21 (1H, dd, J = 14.1, 3.3 Hz), 6.19 (1H, dd, J = 43.6, 3.3 Hz), 7.40 (5H, s).

1-threo: ¹H-NMR (CD₃OD): δ: 4.12 (1H, dd, J = 25.0, 4.3 Hz), 6.14 (1H, dd, J = 45.0, 4.3 Hz), 7.36 (2H, s).

The spectra are identical with those of authentic samples. Recrystallization of the crude HCl from 2-propanol gave pure 1-erythro, mp 167—169 °C (dec.); lit., mp 168—169 °C. Anal. Calcd for C₁₄H₁₁F₂NO·HCl: C, 59.01; H, 5.50; N, 7.65. Found: C, 59.30; H, 5.60; N, 7.42.

Reduction of the Imine 5 (and the Hydroxylated Product 5) to 6 by Sodium Cyanoborohydride. A solution of the crude imine 5 (and 5') (14.0 mg, 0.47 mmol) in MeOH (5 ml) was cooled to 0 °C. At this temperature, NaBH₄·CN (0.147 mg, 0.234 mmol) was added slowly to the solution and then the mixture was warmed gradually to room temperature. The reaction mixture was stirred for 24 h and adjusted to pH 3—4 by addition of saturated NH₄Cl. After evaporation of methanol in vacuo, the product was extracted with ether (5 ml × 3) and the organic layer was dried over MgSO₄. The residue obtained after evaporation of the solvent was purified by preparative TLC (hexane-AcOEt, 2:1 v/v) to give 9.7 mg (quantitative yield) of 6. The structure of each diastereomer and the ratio of erythro/threo (ca. 5:1) were determined by comparison of the ¹H-NMR spectra with those of authentic samples.

6-erythro (the Major Diastereomer): δ: 3.76 (3H, s), 4.62 (1H, dd, J = 16.0, 3.0 Hz), 5.72 (1H, dd, J = 45.1, 3.0 Hz), 7.29—7.51 (5H, m).

6-threo (the Minor Diastereomer): δ: 3.86 (3H, s), 4.44 (1H, dd, J = 13.0, 2.0 Hz), 5.79 (1H, dd, J = 45.2, 2.0 Hz), 7.29—7.51 (5H, m).

One-Pot Synthesis of β-Fluorinated Aliphatic Amino Acids (Method B). A Typical Procedure: Synthesis of 3-Fluoroalanine (18a). 1) Fluorination (Step 1). According to the general procedure for the fluorination reaction with 3-fluorophenylalanine as the target molecule, the azadectone 14a (215 mg, 1 mmol) was fluorinated by using 2 mol equiv of F₂ (5% F₂/N₂). The reaction mixture was washed with aqueous NaHCO₃ solution and then water. The organic layer was dried over MgSO₄ and the solvent was evaporated off in vacuo. This product was used, without further purification, in the following reaction.

2) Basic Hydrolysis of the Fluorine Adduct (Step 2). The imine obtained as above was dissolved in 5 ml of 1,4-dioxane—H₂O (1:1 v/v) and the pH of this solution was adjusted to 10 by addition of saturated NaHCO₃ solution. The resultant solution was stirred vigorously for 24 h at room temperature. After acidification (pH, ca. 2) by the addition of 10% HCl.

<table>
<thead>
<tr>
<th>Amino acid (Comp.)</th>
<th>Overall yield (%)</th>
<th>Melting point (°C)</th>
<th>¹H-NMR (CD₃OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₂COH</td>
<td>30.1</td>
<td>162—163 (dec.)</td>
<td></td>
</tr>
<tr>
<td>FeCO₂H</td>
<td>14.7</td>
<td>197—198 (dec.)</td>
<td></td>
</tr>
<tr>
<td>Me₂COH</td>
<td>23.0</td>
<td>196—197 (dec.)</td>
<td></td>
</tr>
</tbody>
</table>

a) The erythro isomer. b) MS m/z: 140.0819 [Calcd for C₁₄H₁₂F₂NO (M⁺) 140.0985]. c) See reference 24. d) See reference 22.
solution, the product was extracted with AcOEt. The organic layer was separated and dried over MgSO4. Evaporation of the solvent in vacuo afforded 3-fluoro-4-methyl-2-oxo-4-pentanone [17a] identified by 1H-NMR showing H3 as a doublet (δ 6.47, J = 4.8 Hz). This crude acid was used in the following reaction without further purification.

3) Reductive Amination (Step 3): The crude acid 17a (45 mg (0.30 mmol)) obtained as above was dissolved in 3 ml of H2O containing 51 mg (0.60 mmol) of NaHCO3. To this solution, MeOH (10 ml) and 25% NH2OH solution (0.6 ml) were added and the mixture was maintained at 40 °C for 6 h to allow the imine formation to reach equilibrium. After cooling of the solution to 0 °C, NaBH4 (34.2 mg, 0.90 mmol) was added and the mixture was gradually warmed up to room temperature, then kept standing for 24 h. After evaporation of ammonia in vacuo, the reaction mixture was acidified, under ice cooling, to pH 2 by the addition of 5% HCl solution. The precipitates were dissolved completely by adding 2-propanol.

4) Isolation Step of erythro-3-Fluorouracil (18a): The clear solution obtained as above was treated with 30 ml 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 room temperature in vacuo afforded erythro-3-fluorouracil (18a) as a sole product. Recrystallization from methanol gave an analytically pure sample.

The yields, melting points, 1H-NMR data and elemental analyses (and/or high-resolution mass spectral data) of 18a and other β-fluorinated amino acids (18b and 21) are shown in Table 1.

Methyl 2-Benzoylamino-3-fluoro-2-methoxy-3-methylbutanoate (22)
According to the general procedure for the fluorination reaction (method A), the azlactone 19 (105 mg, 0.50 mmol) was fluorinated by 5% F2/N2 (2 mol eq). The reaction mixture was washed with aqueous NaHCO3 and then water. The organic layer was dried over MgSO4 and the solvent was evaporated in vacuo. The crude residue thus obtained was dissolved in 20 ml of methanol. The solution was basified by addition of sodium methoxide until the pH reached 9, then stirred at room temperature for 24 h. Water (10 ml) was added to this mixture and methanol was evaporated in vacuo. The resultant solution was extracted with AcOEt (30 ml x 3) and the combined organic layer was dried over MgSO4. The residue obtained was subjected to TLC (hexane-AcOEt, 3:1 v/v) to give 22 (34 mg, 0.12 mmol), along with methyl 2-benzoylamino-3-methylacrylate (47 mg, 0.20 mmol) derived from the unreacted azlactone 19. The yield of 22 based on the consumed 19 was 40.3%.

Methyl 2-benzoylamino-3-methylacrylate: mp 135–137 °C (lit. 318 mp 138 °C).

References and Notes
8) The most common method for the synthesis of β-fluorohydroxamic acids so far reported is fluorodehydration by SF4 in HF of the corresponding β-hydroxyxamic acids. The reagent is costly and the method proceeds with low stereoselectivity, giving a mixture of the erythro and threo diastereomers.
15) Concerning the 19F-1H coupling constants of fluorinated cycloalkanes, it was reported that a cis vicinal F-H coupling was small (J = cu 4 Hz), whereas a trans vicinal coupling was large (J = 20–25 Hz). See: Hall L. D., Manville J. F., Chem. Ind., 1965, 991; White O. F., Anal. Chem., 37, 403 (1965); Williamson K., Li Y. F., Hall F. H., Sawyer S. J., J. Am. Chem. Soc., 88, 5676 (1966).