silicone (50 m) capillary column using HP-5890 A gas chromatograph showed a composition of 88.72% *R* and 11.28% *S* isomer, i.e., 77.44% ee in the *R* isomer. Correcting for the optical purity (92% ee) of the ethylapopinene used to prepare the reagent, we obtain an ee of 84.2% in the *R* isomer for the 3-methyl-2-butanol produced in the reaction.

Reduction of other ketones was done under identical conditions. Different ketones had different reaction times, which are summarized in Table III. Workups were as in the case of 3-methyl-2-butanol and analyses were done as MTPA or MCF derivatives on a methylsilicone (50 m), Supelcowax (15 m), or SPB-5 (30 m) capillary column. The % ee obtained for each alcohol is summarized in Table III.

Reduction of Carbonyl Compounds Using ^{d}Ipc-*t*-BuBCl (3). The reductions of cyclohexyl methyl ketone, cyclohexyl ethyl ketone, cyclohexyl *n*-propyl ketone, cyclopentyl methyl ketone, and 2-octanone were conducted at room temperature with ^{d}Ipc-*t*-BuBCl prepared from optically pure (+)-α-pinene by using the procedure reported earlier.[9] For an accurate comparison, the reactions of acetophenone and 3-methyl-2-butanone were repeated at room temperature. Analyses of the alcohols were done as their MTPA esters or MCF derivative on a capillary column. The results are summarized in Table IV.

Reduction of Carbonyl Compounds Using ^{d}Ipc$_2$BCl (2). For a comparative study, the reductions of cyclohexyl ethyl ketone, cyclohexyl *n*-propyl ketone, and cyclopentyl methyl ketone were carried out in THF at −25 °C by using commercially available ^{d}Ipc$_2$BCl. The reactions were carried out by using the procedure reported earlier.[8] The reaction of cyclopentyl methyl ketone took 5 h for completion, whereas, unexpectedly, the reaction of cyclohexyl ethyl ketone took 36 h and the reaction of cyclohexyl *n*-propyl ketone took 144 h for completion. There was no correlation between the rate of the reduction and the % ee realized. Analyses of the alcohols for the % ee were done as their MTPA esters on a methylsilicone (50 m), Supelcowax (15 m), or SPB-5 (30 m) capillary column. The values of % ee for the reduction of acetophenone, 3-methyl-2-butanone, cyclohexyl methyl ketone, 2-cyclohexenone, and 2-octanone were from what we have reported earlier.[8] The results are summarized in Table V.

Acknowledgment. Financial Assistance from the U.S. Army Research Office (DAAL 03-88-K-0107) is acknowledged. We thank Dr. Philip E. Fanwick of our department for the X-ray analysis of 4.

New and Effective Routes to Fluoro Analogues of Aliphatic and Aromatic Amino Acids

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New and efficient syntheses of 4,4,4-trifluorovaline (**1**), 5,5,5-trifluoronorvaline (**2**), 5,5,5-trifluoroleucine (**5**), 6,6,6-trifluoronorleucine (**6**), 4,5,6,7-tetrafluorotryptophan (**25**), and α-(trifluoromethyl)-β-alanine are studied. Trifluorovaline (**1**) and trifluoronorvaline (**2**) are synthesized through amidocarbonylation of 2-(trifluoromethyl)propanal (2-TFMPA) and 3-(trifluoromethyl)propanal (3-TFMPA), respectively, followed by hydrolysis. Trifluoroleucine (**5**) and trifluoronorleucine (**6**) are synthesized by using modified Erlenmeyer's azlactone method from 2-TFMPA and 3-TFMPA, respectively. (*S*)- and (*R*)-trifluoronorvalines ((*S*)-**2** and (*R*)-**2**) and trifluoronorleucines ((*S*)-**6** and (*R*)-**6**) with high enantiomeric purities (95–100% ee) are obtained through enzymatic optical resolution of *N*-acetyltrifluoronorvaline (**4**) and *N*-acetyltrifluoronorleucine (**17**) with the use of a porcine kidney acylase I. Optically active trifluoronorleucine ((*S*)-**6**, 87–89% ee) is also obtained via the asymmetric hydrogenation of (*Z*)-*N*-benzoyldehydrotrifluoroleucine ethyl ester (**10a-Z**) with a chiral rhodium catalyst, [Rh(diPAMP)(NBD)]ClO$_4$, followed by hydrolysis. Unexpectedly high diastereoselectivities (80–87% ee) are observed in the hydrogenation of (*Z*)-*N*-benzoyldehydrotrifluoroleucine ethyl ester (**11b**) and (*Z*)-*N*-benzoyl-4-(pentafluorophenyl)dehydronorvaline (**14-Z**) over palladium/carbon. 4,5,6,7-Tetrafluorotryptophan (**25**) and 4,5,6,7-tetrahydrotryptamine (**30**) are synthesized from 3-formyl-4,5,6,7-tetrafluoroindole (**22a**) in 51% (four steps) and 83% (two steps) overall yields, respectively. 4,5,6,7-Tetrafluoroindoleacetic acid (**28**) is obtained from 1-acetyl-3-(acetoxymethyl)-4,5,6,7-tetrafluoroindole (**23a**) in four steps in 65% overall yield. The 3-formyl- and 1-acetyl-3-(acetoxymethyl)tetrafluoroindoles (**22a**, **23a**) are prepared through selenium dioxide oxidation of 1-acyl-3-methyl-4,5,6,7-tetrafluoroindole (**21**), which is obtained via the cyclization of a Schiff base of 2-(pentafluorophenyl)propanal (2-PFPPA), in good yields.

Introduction

It has been shown that fluorinated analogues of naturally occurring biologically active compounds often exhibit unique physiological activities.[3,4] Recently, there has been an increasing interest in the incorporation of fluoro amino acids into peptides.[5] Accordingly, it is important to de-

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(3) For reviews, see: (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (b) Filler, R., Ed. *Biochemistry Involving Carbon-Fluorine Bonds*, ACS Symp. Series, 28; American Chemical Society, Washington, DC, 1976. (c) Smith, F. A. *CHEMTECH* **1973**, 422. (d) Filler, R. *Ibid.* **1973**, 752.

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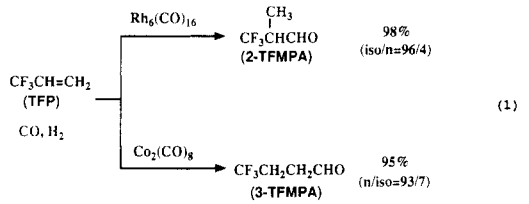
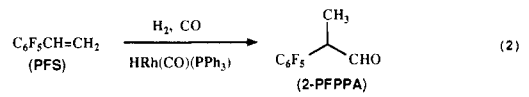
0022-3263/89/1954-4511$01.50/0

velop new and effective methods for the synthesis of fluoro amino acids.

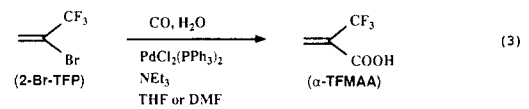
In the course of our study on the synthesis of versatile intermediates for biologically active organofluorine compounds via functionalization of readily available fluoro chemicals,[6] we developed efficient and practical methods (i) for the synthesis of 2- and 3-(trifluoromethyl)propanals (2-TFMPA and 3-TFMPA) as well as 2-(pentafluorophenyl)propanal (2-PFPPA) based on the extremely regioselective hydroformylation of 3,3,3-trifluoropropene (TFP) (eq 1) and pentafluorostyrene (PFS) (eq 2)[7,9] and (ii) for the synthesis of 2-(trifluoromethyl)acrylic acid (TFMAA) through the carboxylation of 2-bromo-3,3,3-trifluoropropene (2-Br-TFP) (eq 3).[8,9]



(1)



(2)



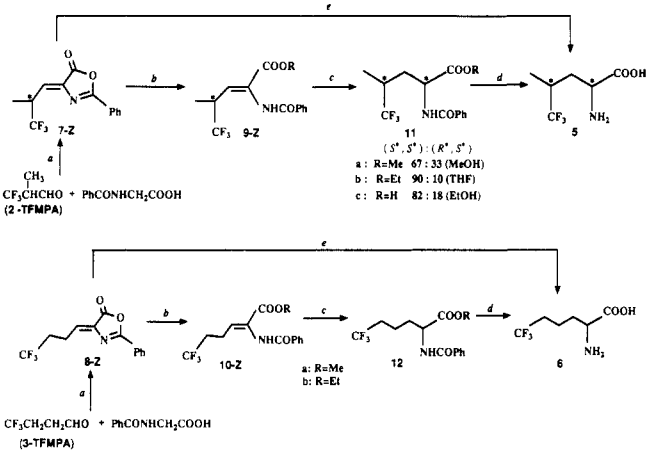
(3)

We found that the fluoro aldehydes and fluoro acrylic acid thus obtained serve as excellent intermediates for the synthesis of fluoro amino acids. We describe here new and efficient syntheses of 4,4,4-trifluorovaline (1), 5,5,5-trifluoronorvaline (2), 5,5,5-trifluoroleucine (5), 6,6,6-trifluoronorleucine (6), 4,5,6,7-tetrafluorotryptophan (25), α-(trifluoromethyl)-β-alanine (α-TFM-β-Ala), and related compounds.

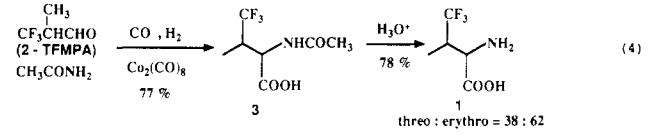
Results and Discussion

4,4,4-Trifluorovaline (1) and 5,5,5-Trifluoronorvaline (2). Recently, we reported the direct synthesis of 1 and 2 from TFP through hydroformylation–amidocarbonylation of TFP catalyzed by $Co_2(CO)_8$ and $Rh_6(CO)_{16}$–$Co_2(CO)_8$, which gave 1 with 96% purity and 2 with 94% purity, respectively.[10] In order to obtain pure 1 and 2, the recrystallization of crude products was necessary. In this work, trifluorovaline (1) and trifluoronorvaline (2) were synthesized via amidocarbonylation of 2-TFMPA and 3-TFMPA, respectively. Since the present syntheses of 1 and 2 start from pure 2-TFMPA and 3-TFMPA, respectively, the products obtained are regiochemically pure. The amidocarbonylation of 2-TFMPA and 3-TFMPA with acetamide catalyzed by cobalt carbonyl at 120 °C and 100 atm of carbon monoxide/hydrogen (1/1) gave *N*-acetyltrifluorovaline (3) and *N*-acetyltrifluoronorvaline (4), respectively, in good yields, which were further hydrolyzed to the corresponding free amino acids (eq 4 and 5). Trifluorovaline (1) thus obtained was a mixture of two diastereomers (threo/erythro = 38/62).

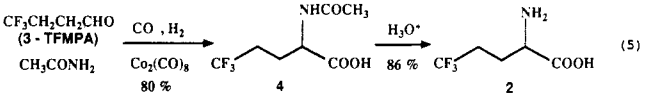
Scheme I[a]



[a] (a) Ac_2O/THF/$Pb(OAc)_2$; (b) ROH/base; (c) H_2/Pd-C; (d) H_3O^+; (e) HI/P.



(4)



(5)

The kinetic optical resolution of *N*-acetyltrifluoronorvaline (4) was carried out by using porcine kidney acylase I (25 °C, pH 7.0) to give (*S*)-trifluoronorvaline ((*S*)-2) and (*R*)-*N*-acetyltrifluoronorvaline ((*R*)-4) with high enantiomeric purities, which were readily separated (see Experimental Section) (eq 6). The latter was further hydrolyzed to (*R*)-trifluoronorvaline ((*R*)-2) with 3 N hydrochloric acid. The optical purities of (*S*)-2 and (*R*)-2 determined by the Mosher's MTPA method[11] (^1H and ^{19}F NMR) were >99% ee (the other diastereomer was not detected) and 95% ee, respectively.

Trifluoronorvaline (2) inhibits the growth of *Escherichia coli* and may be used as a growth regulatory factor in microbiology.[12] Although no significant biological activity of trifluorovaline (1) has been reported to date, 1 may serve as a modifier of biologically active peptides.

5,5,5-Trifluoroleucine (5) and 6,6,6-Trifluoronorleucine (6). Trifluoroleucine (5) and trifluoronorleucine (6) were synthesized via azlactones starting from 2-

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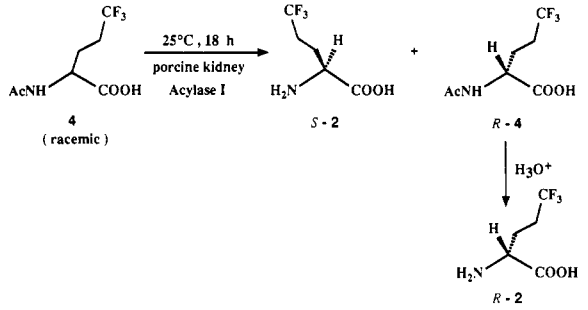


(6)

TFMPA and 3-TFMPA, respectively (Schemes I and II). For the preparation of the azlactones, *the use of lead acetate, N-benzoylglycine, and acetic anhydride in tetrahydrofuran (THF) was crucial to obtain the azlactones in good yields*,[13] since the usual reaction conditions for Erlenmyer's method, *N*-acetylglycine and sodium acetate in acetic anhydride, did not give the desired azlactones at all. The azlactones thus formed were a mixture of *E* and *Z* isomers (*E*/*Z* = 13/87 for **7**; *E*/*Z* = 12/88 for **8**). Pure *Z* isomers, **7-Z** and **8-Z**, were obtained by recrystallization in 70% and 71% yields, respectively. Pure *E* isomers, **7-E** and **8-E**, were isolated through chromatography on silica gel. The azlactones were subjected to alcoholysis to give the corresponding dehydroamino acid esters **9** and **10**. A (*Z*)-dehydro amino acid (**9c**) was obtained by hydrolysis of **7-Z**. Then, the (*Z*)-dehydro amino acid and esters (**9** and **10**) were hydrogenated over palladium/carbon followed by hydrolysis to give the corresponding amino acids **5** and **6**. The azlactones (**7-Z** and **8-Z**) were also treated with hydriodic acid/red phosphorus to give directly the final amino acids (**5** and **6**). The stereochemistry of the dehydro amino acid esters **9** and **10** was confirmed on the basis of a substantially large difference in the chemical shifts of *C*-alkyl protons[14,15] as well as olefin protons between *E* and *Z* isomers and by NOE experiments (see Experimental Section). The results elucidated the stereochemistry of the azlactones **7** and **8** as well.

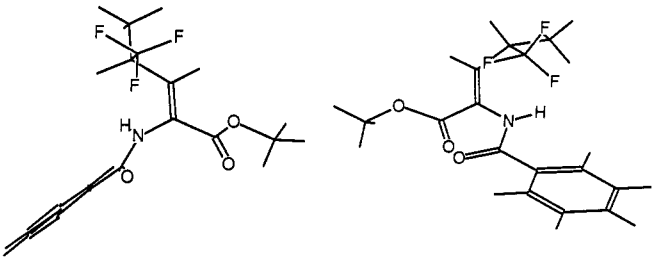
Stereoselective Hydrogenation of *N*-Benzoyldehydrotrifluoroleucine (9c) and Its Esters (9a, 9b). It is worth mentioning that in the hydrogenation of **9** over palladium/carbon yielding **11**, a trifluoroisopropyl group that has a chiral carbon serves as an effective stereogenic center. Thus, the reductions of **9a**, **9b**, and **9c** in THF at ambient temperature and pressure gave **11a** (70% de), **11b** (80% de), and **11c** (64% de), respectively. The major diastereomers of **11**, thus formed, were found to be *S**,*S** isomers on the basis of the ^{1}H NMR analysis of trifluoroleucine (**5**) obtained by hydrolysis of **11**: It has been shown that (*S**,*S**)-**11** and (*R**,*S**)-**11** are clearly distinguished on their ^{1}H NMR spectra.[16] It is surprising that the "chiral isopropyl group" can induce a relatively high degree of stereoselectivity. The solvent effect on the stereoselectivity of the reaction was examined with **9a** by using methanol, ethanol, 2-propanol, THF, and ether under the standard conditions. While methanol gave the worst selectivity (38% de), other solvents gave similar selectivities, i.e., EtOH, 68% de; *i*-PrOH, 72% de; THF, 70% de; Et_2O, 70% de.

Table I. Asymmetric Hydrogenation of *N*-Benzoyldehydrotrifluoronorleucine Methyl Ester (10a-Z)[a]

chiral ligand	conditions	enantioselectivity (% ee)	configrtn
diPAMP[18]	1 atm, 40 °C, 12 h	89	*S*
	5 atm 30 °C, 16 h	52	*S*
Degphos[19]	5 atm, 25 °C, 12 h	67	*S*
Chiraphos[20]	5 atm, 30 °C, 16 h	54	*R*
(+)-BPPM[21]	1 atm, 25 °C, 12 h	22	*S*
(*S*)-BINAP[22]	5 atm, 25 °C, 48 h	18	*R*

[a] All reactions were run with 1 mmol of **10a-Z**, 2 mol % of chiral rhodium catalyst in ethanol (10 mL). Enantiomeric purity of the product (**12a**) was determined based on specific optical rotation (see Experimental Section).

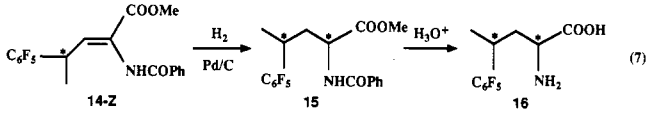
A molecular modeling study was performed in order to accommodate the observed *S**,*S** selectivity. For the possible ground state conformers of **9a**, the MM2 calculations suggest the two low energy structures (**9a-A** and **9a-B**) and **9a-A** is 1.17 kcal/mol more stable than **9a-B**.



9a-A **9a-B**

Thus, it is reasonable to assume that **9a-A** represents the predominant species on the palladium surface. In this conformation, molecular hydrogen can add across the olefin bond either from the methyl side or trifluoromethyl side, and the *S**,*S** isomer should be formed through the methyl-side attack. Judging from the relatively high stereoselectivities observed, it is suggested that the trifluoromethyl group is not only a bulkier substituent than methyl but also has a unique electronic effect against the palladium surface.

In a similar manner the hydrogenation of (*Z*)-*N*-benzoyl-4-pentafluorodehydronorvaline methyl ester (**14-Z**), which was synthesized from 2-PFPPA via an azlactone (**13-Z**), was carried out under the standard conditions (eq 7). The reaction gave *N*-benzoyl-4-(pentafluorophenyl)-norvaline methyl ester (**15**) with 87% de, i.e., *S**,*S**:*R**,*S** = 93.5:6.5, which was further hydrolyzed to 4-(pentafluorophenyl)norvaline (**16**).[17]



(7)

Preparation of Optically Active Trifluoronorleucine. Optically active (*S*)-*N*-benzoyltrifluoronorleucine methyl ester ((*S*)-**12a**, 87–89% ee) was obtained quantitatively by asymmetric hydrogenation of **10a-Z** by using a rhodium catalyst with diPAMP[18] as the chiral ligand, [(diPAMP)Rh(NBD)]ClO_4 (NBD = norbornadiene) (eq 8). The optical purity was determined on the basis of the

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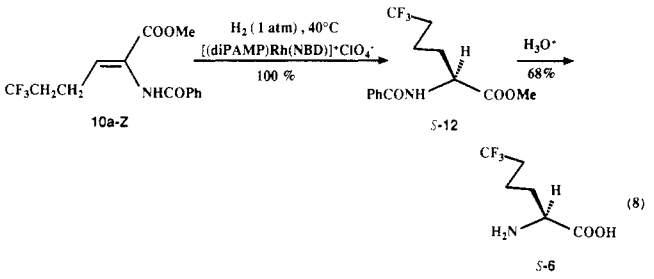
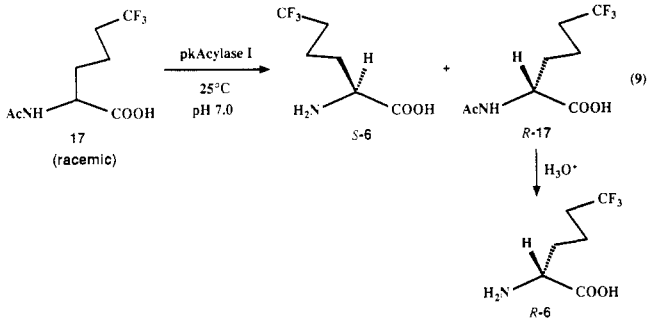
(17) Although the stereochemical assignment of two diastereomers should wait further elucidation, the ^{1}H NMR patterns of the ester (**15**) and the acid (**16**) suggest that the mode of stereodifferentiation for **14** is the same as that for **9a**.
(18) diPAMP = (1*R*,2*R*)-1,2-bis[(*o*-anisylphenyl)phosphino]ethane: Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567.

specific rotation and confirmed by ^1H and ^{19}F NMR analyses of the corresponding MTPA–amino acid methyl ester, i.e., by Mosher's method.[11] Other chiral ligands such as Degphos,[19] Chiraphos,[20] (+)-BPPM,[21] and (*S*)-BINAP[22] did not give better results. The results are listed in Table I.



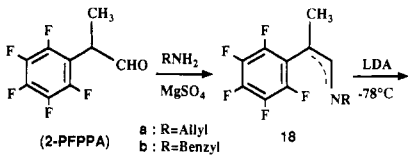
(*S*)- and (*R*)-trifluoronorleucines (**6**) with ≥98% ee were obtained through enzymatic resolution of *N*-acetyltrifluoronorleucine (**17**) by using porcine kidney acylase I in a manner similar to that for *N*-acetyltrifluoronorvaline (**4**) (eq 9). The optical purities were confirmed by the MTPA method.

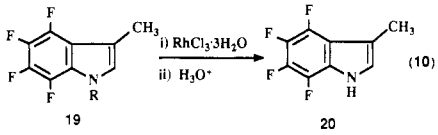


4,5,6,7-Tetrafluorotryptophan and Related Compounds.[23] Because of the importance of biologically active compounds containing the indole ring such as tryptophan, tryptamine, indoleacetic acid, and alkaloids, tetrafluoro analogues of indoles were synthesized from 2-PFPPA.

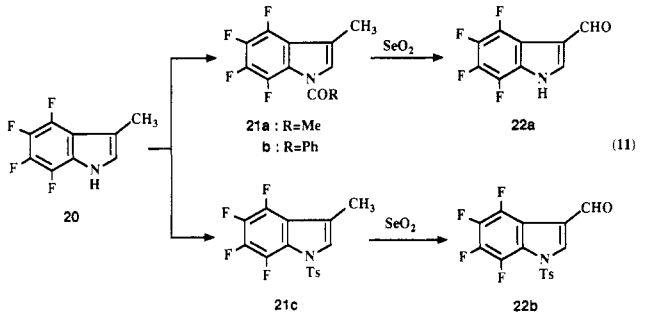
Reaction of 2-PFPPA with allylamine followed by cyclization using lithium diisopropylamide (LDA) as a base and deprotection of the indole nitrogen gave 3-methyl-4,5,6,7-tetrafluoroindole (**20**) (72% from 2-PFPPA) (eq 10).

3-formyl-4,5,6,7-tetrafluoroindoles **22** and 3-(acetoxymethyl)-4,5,6,7-tetrafluoroindoles **23** are key intermediates for the synthesis of tetrafluoro analogues of tryptophan, tryptamine, and indoleacetic acid. The synthesis of **22** was realized through selenium dioxide oxidation of 3-methyltetrafluoroindoles **21**. As direct oxidation of **20** with selenium dioxide[24] resulted in the decomposition of indole

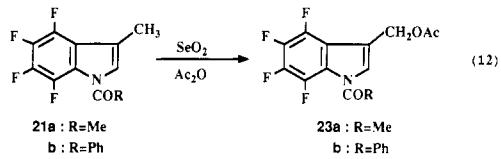




skeleton, the 1-position was protected by an acetyl, benzoyl, or tosyl group, giving **21a–c**. The selenium dioxide oxidation of **21a** and **21b** gave 3-formyl-4,5,6,7-tetrafluoroindole (**22a**) in 86% and 74% yields, respectively, i.e., the acetyl and benzoyl protecting groups were removed during the reaction (eq 11). On the other hand, the 1-tosyl group was tolerant of the reaction condition; thus the reaction of **21c** gave 1-tosyl-3-formyl-4,5,6,7-tetrafluoroindole (**22b**) in 81% yield.



Oxidation of **21** in the presence of acetic anhydride gave 1-acetyl- or 1-benzoyl-3-(acetoxymethyl)-4,5,6,7-tetrafluoroindole (**23a** or **23b**) in 50–60% yield after chromatographic separation to remove a small amount of **22a**, which was formed as side product (eq 12).



Usefulness of **22** and **23** is demonstrated by the following examples: (i) the reaction of **23** with piperidine (a large excess) at room temperature for 20 h gave 3-(piperidinomethyl)-4,5,6,7-tetrafluoroindole (**24**)[25] in 97% yield, which is a known key intermediate for the synthesis of 4,5,6,7-tetrafluorotryptophan (**25**) (eq 13), (ii) the reaction of N-methylated 3-[(*N*-methylpiperidiniumyl)methyl]-4,5,6,7-tetrafluoroindolylmethyl sulfate (**26**)[26] with potassium cyanide (4 equiv) in aqueous dimethylformamide (DMF) under reflux for 2 h gave 3-(cyanomethyl)-4,5,6,7-tetrafluoroindole (**27**) in 96% yield, which is an excellent precursor of 4,5,6,7-tetrafluoroindoleacetic acid (**28**)[25a] (eq 14), (iii) 4,5,6,7-tetrafluorotryptamine (**30**)[25a] was obtained from **22a** through condensation with nitromethane followed by $LiAlH_4$ reduction in 83% overall yield (eq 15), and (iv) 4,5,6,7-tetrafluorotryptophan (**25**) was obtained from **22a** through Erlenmeyer's azlactone method[27] in four

(19) Degphos = (3*R*,4*R*)-1-benzyl-3,4-bis(diphenylphosphino)-pyrrolidine: (a) Nagel, U. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 435. (b) Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. *Chem. Ber.* **1986**, *119*, 3326.

(20) Chiraphos = (2*S*,3*S*)-2,3-bis(diphenylphosphino)butane: Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262.

(21) (+)-BPPM = (2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-2-[(diphenylphosphino)methyl]-4-(diphenylphosphino)pyrrolidine: (a) Ojima, I.; Kogure, T.; Yoda, N.; Suzuki, T.; Yatabe, M.; Tanaka, T. *J. Org. Chem.* **1982**, *47*, 1329. (b) Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *Ibid.* **1981**, *46*, 2954.

(22) (*S*)-BINAP = (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl: (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245.

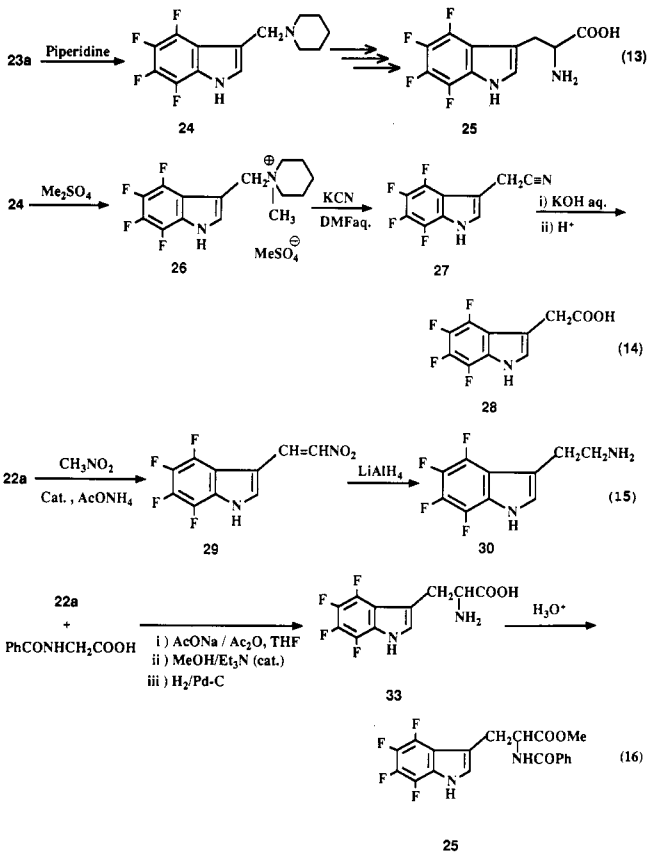
(23) As a preliminary communication, see: Fujita, M.; Ojima, I. *Tetrahedron Lett.* **1983**, *24*, 4573.

(24) For a review on selenium dioxide oxidation, see: Rabjohn, N. *Org. React.* **1976**, *24*, 261.

(25) (a) Petrova, T. D.; Savchenko, T. I.; Ardyukova, T. F.; Yakobson, G. G. *Khim. Geterotsikl. Soedin.* **1971**, *2*, 213. (b) Rajh, H. M.; Uitzetter, J. H.; Westerhuis, L. W.; Dries, C. L.; Tesser, G. I. *Peptide Protein Res.* **1979**, *14*, 68.

(26) Petrova, T. D.; Savachenko, T. I.; Shchegoleva, L. N.; Ardyukova, T. F.; Yakobson, G. G. *Khim. Geterotsikl. Soedin.* **1970**, *10*, 1344.

(27) For samples: Herbst, R. M.; Shemin, D. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. 2, p 1.



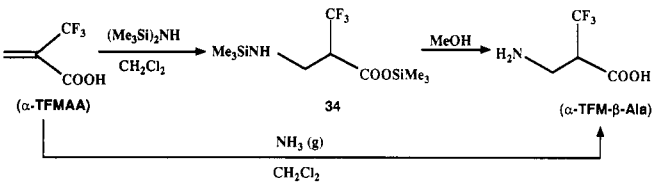
steps in 51% overall yield (eq 16).

Since 4,5,6,7-tetrafluorotryptophan (**25**) strongly inhibits both the tryptophanyl hydroxamate and aminoacyl t-RNA formation,[28] the tetrafluoro analogues of tryptamine, indoleacetic acid, and other indole derivatives are expected to have interesting physiological activities.

α-(Trifluoromethyl)-β-alanine (α-TFM-β-Ala). Addition of gaseous ammonia to 2-(trifluoromethyl)acrylic acid (TFMAA) at 0–5 °C in dichloromethane gave a new β-amino acid, α-(trifluoromethyl)-β-alanine (α-TFM-β-Ala), in excellent yield.[29] Use of hexamethyldisilazane in an attempt to protect the C-terminus of TFMAA with a trimethylsilyl (TMS) group resulted in an addition of mono(trimethylsilyl)amine, probably generated in situ, to *O*-TMS-TFMAA, giving *N,O*-bis-TMS-α-TFM-β-Ala (**34**) in quantitative yield. *No trace of N,N,O-tris-TMS-α-TFM-β-Ala was detected.* Michael addition of HMDS to the methyl and benzyl esters of TFMAA did not proceed at all, which is reasonable since HMDS is well known as a bulky nonnucleophilic amine. Accordingly, this silylation–Michael addition process is noteworthy. The *N,O*-bis-TMS-α-TFM-β-Ala (**34**) thus obtained was treated with methanol to give α-TFM-β-Ala in nearly quantitative yield (Scheme II).

α-TFM-β-Ala did not have any antibacterial activity. However, an enkephalin analogue bearing α-TFM-β-Ala, Tyr-D-Ala-(α-TFM-β-Ala)-Phe-Met, has shown fairly strong analgesic effects.[30] Detailed results will be published elsewhere. This suggests that the new fluoro β-amino acid can serve as a modifier for a variety of peptide hormones and other physiologically active peptides.

Scheme II



Experimental Section

General Method. Melting points were measured with a Thomas-Hoover Unimelt and are uncorrected. ^{1}H NMR spectra were measured with a General Electric QE-300 spectrometer using Me_4Si (TMS) for organic solvents and 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propanoic acid sodium salt (TSP) for D_2O as the internal standards. ^{19}F NMR spectra were measured with a Nicolet NT-300 spectrometer using $CFCl_3$ for organic solvents and CF_3COOH for D_2O as the internal standards. The IR spectra were recorded on Perkin-Elmer Model 1310 or 1430 or JASCO A-202 spectrophotometers using samples as neat liquid or KBr disks. Optical rotations were measured with Perkin-Elmer Model 241 polarimeter. Microanalyses were performed at the M-H-W Laboratories, Phoenix, AZ.

Materials. 3,3,3-Trifluoropropene (TFP) was obtained from Japan Halon Co., Ltd., and Halocarbon Co. and used as obtained. Pentafluorostyrene (PFS) was commercially available from SCM Chemicals Inc. and used as purchased. Fluoro aldehydes, 2-methyl-3,3,3-trifluoropropanal (2-TFMPA), 4,4,4-trifluorobutanal (3-TFMPA), and 2-(pentafluorophenyl)propanal (2-PFPPA), were prepared by the hydroformylation of TFP and PFS catalyzed by tetrarhodium dodecacarbonyl and dicobalt octacarbonyl as reported.[7] Porcine kidney acylase I was purchased from Sigma Chemical Co. Inc. and used as purchased. A cationic rhodium complex, $[Rh(NBD)]ClO_4$, was prepared by the literature method. Chiraphos[20] and (*S*)-BINAP[22] were purchased from Strem Chemicals Inc. and Aldrich Chemical Co., respectively. (+)-BPPM[21] was prepared by the literature method. A chiral ligand, diPAMP, and a chiral catalyst, $[Rh(Degphos)(NBD)]BF_4$,[19] were obtained from Monsanto Co. and Degussa Co., respectively. 2-(Trifluoromethyl)acrylic acid (TFMAA) was obtained from Japan Halon Co., Ltd., and also prepared by the carboxylation of 2-bromo-3,3,3-trifluoropropene catalyzed by $PdCl_2(PPh_3)_2$.[8] Silica gel used for chromatography, MN-Kieselgel 60 (silica gel 60), was purchased from Brinkmann Instruments, Inc. All other chemicals were purchased from Aldrich Chemical Co., Inc.

***N*-Acetyl-4,4,4-trifluorovaline (3).** A 300-mL autoclave was charged with 2-TFMPA (1.26 g, 10 mmol), acetamide (885 mg, 15 mmol), $Co_2(CO)_8$ (171 mg, 0.5 mmol), and dioxane (10 mL). The atmosphere was replaced by carbon monoxide and pressurized to 1500 psi with carbon monoxide and hydrogen ($CO:H_2$ = 1:1) at room temperature. The autoclave was heated at 120 °C with stirring for 12 h. Then, the gases were purged out carefully at 0 °C. To the reaction mixture were added 5% Na_2CO_3 (50 mL) and ethyl acetate (30 mL) with stirring. The aqueous layer was separated and the organic layer was further extracted with water. The combined aqueous solution was acidified with phosphoric acid and extracted with ethyl acetate. The extract was dried over anhydrous $MgSO_4$ and Norit. After filtration and removal of the solvent, **3** was obtained as a white solid (1.64 g, 77% yield). The ^{1}H and ^{19}F NMR analyses showed that **3**, thus obtained, was a 38:62 (threo:erythro) mixture of two diastereomers. The stereochemical assignment of the threo and the erythro isomers were unambiguously made through hydrolysis of **3** to 4,4,4-trifluorovaline (**1**) whose stereochemistry has been well established[31] (vide infra).

3: mp 134–139 °C (a mixture of diastereomers: threo/erythro = 38/62); ^{1}H NMR (DMSO-d_6/TMS) δ 1.10 (d, J = 7.2 Hz, 3 H), 1.89 (s, 3 H), 2.80–3.06 (m, 1 H), [4.61 (dd, J = 8.8, 5.6 Hz) (threo), 4.86 (dd, J = 9.5, 3.5 Hz) (erythro)] (1 H), 8.29 (bd, J = 9.5, 8.8

(28) (a) Knorre, D. G.; Lavrik, O. I.; Petrova, T. D.; Savachenko, T. I.; Yakobson, G. G. *FEBS Lett.* **1971**, *12*, 204. (b) Nevinsky, G. A.; Favorova, O. O.; Lavrik, O. I.; Petrova, T. D.; Kochkina, L. L.; Savachenko, T. I. *Ibid.* **1974**, *43*, 135.

(29) The reaction sometimes gives double and triple Michael addition products, i.e., $NH[CH_2CH(CF_3)COOH]_2$ and $N[CH_2(CF_3)COOH]_3$, depending on the experimental conditions.

(30) Ojima, I.; Nakahashi, K. Jpn. Pat., Kokai Tokkyo Koho, **1986**, S61-286353.

(31) Babb, R. M.; Bollinger, F. W. *J. Org. Chem.* **1970**, *35*, 1438.

Hz, 1 H); ^{19}F NMR (DMSO-d_6/$CFCl_3$) δ −67.8 (dd, J = 9.3, 2.3 Hz) (threo), −69.5 (dd, J = 9.0, 2.6 Hz) (erythro); IR (KBr disk) 3360 (νNH), 1735 (νC=O), 1625 (νC=O) cm^{-1}. Anal. Calcd for $C_7H_{10}F_3NO_3$: C, 39.44; H, 4.73; N, 6.57. Found: C, 39.15; H, 4.89; N, 6.78.

***N*-Acetyl-5,5,5-trifluoronorvaline (4).** The amidocarbonylation of 3-TFMPA was carried out in the same manner as described for 2-TFMPA. *N*-Acetyl-5,5,5-trifluoronorvaline (4) was obtained as a white solid in 80% yield.

4: mp 119–122 °C; ^{1}H NMR (DMSO-d_6/TMS) δ 1.86 (s, 3 H), 1.70–2.00 (m, 2 H), 2.20–2.40 (m, 2 H), 4.27 (m, 1 H), 8.21 (d, J = 7.8 Hz, 1 H); ^{19}F NMR (DMSO-d_6/$CFCl_3$) δ −64.5 (t, J = 9.7 Hz); IR (KBr disk) 3365 (νNH), 1720 (νC=O), 1610 (νC=O), 1550 (δNH). Anal. Calcd for $C_7H_{10}F_3NO_3$: C, 39.44; H, 4.73; N, 6.57. Found: C, 39.17; H, 4.73; N, 6.82.

4,4,4-Trifluorovaline (1). *N*-Acetyltrifluorovaline (3), threo/erythro = 34/66) (500 mg, 2.4 mmol), was refluxed in 6 N hydrochloric acid (5 mL) for 20 h. The reaction mixture was neutralized with concentrated aqueous ammonia. The mixture was concentrated until some precipitate came out. Then, methanol (1 mL) was added to the mixture and kept in a refrigerator overnight. The resulting precipitate was collected on a glass filter to give crystalline 1 (313 mg, 78% yield). The assignment of stereochemistry is based on the ^{1}HMR data reported by Babb and Bollinger.[31]

1 (a mixture of two diastereomers: threo/erythro = 34/66): mp 227–230 °C subl [lit.[31] mp 252 °C (threo/erythro = 75/25)]; ^{1}H NMR (D_2O/TSP) δ [1.23 (d, J = 7.4 Hz) (erythro), 1.32 (d, J = 7.3 Hz) (threo)] (3 H), [3.00–3.20 (m) (threo), 3.15–3.27 (m) (erythro)] (1 H), [3.91 (d, J = 4.6 Hz) (threo), 4.13 (d, J = 2.5 Hz) (erythro)] (1 H); ^{19}F NMR (D_2O/CF_3COOH) δ 4.81 (d, J = 8.7 Hz) (erythro) (−72.19 from $CFCl_3$), 6.46 (d, J = 9.4 Hz) (threo) (−70.54 from $CFCl_3$); IR (KBr disk) 3500–2400 (νNH), 1650 (δNH), 1575 (νC=O), 1500 (δNH) cm^{-1}.

5,5,5-Trifluoronorvaline (2). *N*-Acetyltrifluoronorvaline (4) was hydrolyzed in the same manner as described for 3 and 5,5,5-trifluoronorvaline was obtained as colorless crystals in 86% yield.

2: mp 254–256 °C dec [lit.[12] 258 °C]; ^{1}H NMR (CD_3OD/TMS) δ 2.02–2.13 (m, 2 H), 2.20–2.54 (m, 2 H), 3.60 (t, J = 6.2 Hz, 1 H); ^{19}F NMR (CD_3OD/$CFCl_3$) δ −66.6 (t, J = 10.7 Hz); IR (KBr disk) 3500–2500 (νNH), 1610 (δNH), 1585 (νC=O), 1520 (δNH) cm^{-1}.

Optical Resolution of *N*-Acetyl-5,5,5-trifluoronorvaline (4) with an Acylase. A solution of 4 (5.00 g, 23.5 mmol) in water (20 mL) was adjusted to pH 7 and porcine kidney acylase I (45 mg, 850 unit/mg) was added at 25 °C. The reaction mixture was kept at 25 °C for 14 h with stirring. The resulting precipitate was collected on a glass filter, redissolved in water, and purified by being passed through a Waters reversed phase filter, Sep-Pak C_{18} (eluent: water). The removal of water in vacuo to dryness gave (*S*)-5,5,5-trifluoronorvaline ((*S*)-2) (1.61 g, 40%): $[\alpha]^{20}_D$ +7.2° (*c* 1.5, H_2O).

The filtrate of the reaction mixture was acidified with 1 N hydrochloric acid to pH 3.0 and extracted with ethyl acetate. After drying over anhydrous $MgSO_4$, the solvent was removed to give (*R*)-4 as a white solid (1.25 g, 25%): $[\alpha]^{20}_D$ −0.6° (*c* 5.25, EtOAc). The hydrolysis of (*R*)-4 (1.00 g, 4.69 mmol) with 3 N hydrochloric acid under reflux for 3 h followed by neutralization with concentrated aqueous ammonia and the same workup as described above gave (*R*)-2 (669 mg, 83.4% yield) as a white solid: $[\alpha]^{20}_D$ −6.8° (*c* 0.58, H_2O).

Determination of Optical Purity. Typically, methanol (1.0 mL) and $SOCl_2$ (0.45 mL, 6.2 mmol) were mixed at −10 °C (ice–acetone bath) with stirring for 15 min and to this solution was added slowly (*S*)-2 (86 mg, 0.5 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for 24 h. The removal of methanol and excess $SOCl_2$ in vacuo gave 5,5,5-trifluoronorvaline methyl ester hydrochloride (103 mg, 92% yield) as colorless needles: mp 159.5–160.5 °C; ^{1}H NMR (D_2O/TSP) δ 2.10–2.55 (m, 4 H), 3.87 (s, 3 H), 4.23 (t, J = 5.3 Hz, 1 H); ^{19}F NMR (D_2O/CF_3COOH) δ 9.04 (t, J = 10.5 Hz); IR (KBr disk) 3400–2500 (νNH), 1750 (νC=O), 1580 (δNH) cm^{-1}.

A solution of the methyl ester hydrochloride (56.8 mg, 0.24 mmol) in THF (5 mL) was treated with *N*-methylmorpholine (25.9 mg, 0.26 mmol) at 0 °C, and to this solution were added (*R*)-(+)-methoxy(trifluoromethyl)phenylacetic acid (MTPA) (60 mg, 0.26 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) (58.1 mg, 0.28 mmol). The mixture was stirred at 0 °C for 3 h and then at room temperature for 24 h. The resulting *N*,*N*′-dicyclohexylurea was removed by filtration and the solvent was evaporated. The residue thus obtained was dissolved in ethyl acetate and washed with 10% citric acid, 5% $NaHCO_3$, and brine and concentrated in vacuo to give *N*-[(*R*)-MTPA]-(*S*)-trifluoronorvaline methyl ester (88.9 mg, 87% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 1.90–2.32 (m, 4 H), 3.36 (q, J = 1.3 Hz, 3 H), 3.80 (s, 3 H), 4.70 (td, J = 8.4, 4.9 Hz, 1 H), 7.41–7.50 (m, 6 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −66.00 (t, J = 10.4 Hz, 3 F), −68.92 (bs, 3 F). The optical purity of (*S*)-2 was determined to be >99% ee on the basis of ^{19}F NMR analysis.

In the same manner, *N*-[(*R*)-MTPA]-(*R*)-trifluoronorvaline methyl ester was prepared from (*R*)-2: ^{1}H NMR ($CDCl_3$/TMS) δ 1.90–2.35 (m, 4 H), 3.53 (q, J = 1.6 Hz, 3 H), 3.80 (s, 3 H), 4.71 (td, J = 7.7, 5.2 Hz, 1 H), 7.24 (d, J = 7.7 Hz, 1 H), 7.41–7.59 (m, 5 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −66.02 (t, J = 10.7 Hz, 3 F), −68.62 (bs, 3 F). The optical purity of (*R*)-2 was determined to be 95% ee on the basis of ^{19}F NMR analysis.

2-Phenyl-4-[2-(trifluoromethyl)propylidene]-5-oxazolone (7). A mixture of 2-TFMPA (1.74 g, 13.8 mmol), hippuric acid (2.06 g, 11.5 mmol), lead (II) acetate trihydrate (2.18 g, 5.8 mmol), and acetic anhydride (3.52 g, 34.5 mmol) in THF (26 mL) was refluxed for 4 h. The reaction mixture was concentrated and water (100 mL) was added. The resulting yellow precipitate (3.1 g) was collected on a glass filter, dissolved in ethyl acetate, and washed with water. After being dried over $MgSO_4$, the solvent was evaporated to give 7 as a yellow solid: *E*/*Z* = 13/87 based on NMR analysis.

Recrystallization of the *E*/*Z* mixture of 7 thus obtained from hexane yielded the pure *Z* isomer (**7-Z**) as a white solid (2.06 g, 70% yield). The *E* isomer (**7-E**) was obtained from the mother liquor of the recrystallization by a column chromatography on silica gel. Thus, 500 mg of a 1:1 mixture of *E* and *Z* isomers was recovered from the mother liquor, and 100 mg of pure **7-E** was obtained as a white solid by the chromatographic separation.

7-Z: mp 74–75 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.40 (d, J = 7.1 Hz, 3 H), 3.98 (m, 1 H), 6.49 (d, J = 9.9 Hz, 1 H), 7.53 (m, 2 H), 7.64 (m, 1 H), 8.11 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −71.2 (d, J = 7.5 Hz); IR (KBr disk) 1815 (νC=O), 1680 (νC=O) cm^{-1}; MS (*m*/*e*) 269 (15, M^+), 105 (100). Anal. Calcd for $C_{13}H_{10}F_3NO_2$: C, 58.00; H, 3.74; N, 5.20. Found: C, 57.83; H, 3.77; N, 5.16.

7-E: mp 68–69.5 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.37 (d, J = 7.0 Hz, 3 H), 4.38 (m, 1 H), 6.62 (d, J = 10.5 Hz, 1 H), 7.51 (m, 2 H), 7.61 (m, 1 H), 8.05 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −71.8 (d, J = 8.1 Hz); IR (KBr disk) 1800 (νC=O), 1675 (νC=C) cm^{-1}. Anal. Calcd for $C_{13}H_{10}F_3NO_2$: C, 58.00; H, 3.74; N, 5.20. Found: C, 57.91; H, 3.86; N, 5.19.

2-Phenyl-4-(4,4,4-trifluorobutylidene)-5-oxazolone (8). In a similar manner, a mixture of 3-TFMPA (15.0 g, 0.12 mol), hippuric acid (17.75 g, 0.10 mol), lead(II) acetate trihydrate (18.8 g, 50 mmol), and acetic anhydride (30.5 g) in THF (150 mL) was refluxed for 16 h. The crude reaction mixture was found to consist of a 12:88 mixture of *E* and *Z* isomers. Recrystallization from $CHCl_3$–hexane gave the pure *Z* isomer (18.91 g, 71% yield) as colorless powder. The pure *E* isomer (**8-E**) was obtained as a white solid from the mother liquor of the recrystallization by chromatographic separation on a silica gel column using $CHCl_3$–hexane as the eluent.

8-Z: mp 101–101.5 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 2.42 (qt, J = 10.4, 7.7 Hz, 2 H), 2.95 (q, J = 7.7 Hz, 2 H), 6.61 (t, J = 7.7 Hz, 1 H), 7.52 (m, 2 H), 7.62 (m, 1 H), 8.10 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −66.0 (t, J = 10.4 Hz); IR (KBr disk) 1800 (νC=O), 1680 (νC=C) cm^{-1}; MS (*m*/*e*) 269 (20, M^+), 105 (100). Anal. Calcd for $C_{13}H_{10}NO_2$: C, 58.00; H, 3.74; N, 5.20. Found: C, 58.03; H, 3.85; N, 5.24.

8-E: mp 110–111 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 2.37 (qt, J = 10.4, 7.5 Hz, 2 H), 3.11 (dt, J = 8.2, 7.5 Hz, 2 H), 6.76 (t, J = 8.2 Hz, 1 H), 7.50 (m, 2 H), 7.60 (m, 1 H), 8.04 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −65.9 (t, J = 10.4 Hz); IR (KBr disk) 1790 (νC=O), 1660 (νC=C) cm^{-1}. Anal. Calcd for $C_{13}H_{10}F_3NO_2$: C, 58.00; H, 3.74; N, 5.20. Found: C, 58.27; H, 4.08; N, 5.08.

Methyl (*Z*)-2-Benzamido-4-(trifluoromethyl)-2-pentenoate (*N*-Benzoyldehydrotrifluoroleucine Methyl Ester) (9a). A

solution of **7-Z** (7.79 g, 29 mmol) and triethylamine (0.5 mL) in methanol (150 mL) was refluxed for 2 h. After evaporation of the solvent, the residue was extracted by ethyl acetate, washed with water, and dried over anhydrous $MgSO_4$. Evaporation of the solvent and recrystallization of the crude product from $CHCl_3$–hexane gave **9a-Z** (6.86 g, 79% yield) as a colorless powder.

9a-Z: mp 93–94 °C; ^1H NMR ($CDCl_3$/TMS) δ 1.36 (d, J = 6.9 Hz, 3 H), 3.47 (m, 1 H), 3.84 (s, 3 H), 6.56 (d, J = 10 Hz, 1 H), 7.48 (m, 2 H), 7.57 (m, 1 H), 7.85 (bs, 1 H), 7.86 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −71.5 (d, J = 8.4 Hz); IR (KBr disk) 3300 (νNH), 1730 (νC=O), 1670 (νC=O), 1635 (νC=O), 1505 (δNH) cm^{-1}. Anal. Calcd for $C_{14}H_{14}F_3NO_3$: C, 55.82; H, 4.68; N, 4.65. Found: C, 55.86; H, 4.70; N, 4.65.

The E isomer (**9a-E**) was obtained by chromatographic separation of the E,Z mixture of **9a** on a silica gel column using $CHCl_3$–hexane as the eluent. The E,Z mixture of **9a** was obtained by the methanolysis of **7** (E/Z = 13/87, vide supra) in the same manner as described for **9a-E**.

9a-E: mp 79–80 °C; ^1H NMR ($CDCl_3$/TMS) δ 1.33 (d, J = 6.9 Hz, 3 H), 3.93 (s, 3 H), 4.16 (m, 1 H), 7.37 (d, J = 10.5 Hz, 1 H), 7.47 (m, 2 H), 7.55 (m, 1 H), 7.82 (m, 2 H), 8.34 (bs, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −72.1 (d, J = 8.1 Hz); IR (KBr disk) 3280 (νNH), 1728 (νC=O), 1662 (νC=C), 1640 (νC=O), 1515 (δNH) cm^{-1}. Anal. Calcd for $C_{14}H_{14}F_3NO_3$: C, 55.82; H, 4.68; N, 4.65. Found: C, 55.91; H, 4.71; N, 4.72.

Methyl (*Z*)-2-Benzamido-5-(trifluoromethyl)-2-pentenoate (*N*-Benzoyldehydrotrifluoronorleucine Methyl Ester) (10a). In a similar manner, a methanol solution of **8-Z** (7.79 g, 30 mmol) and triethylamine (0.5 mL) in methanol (150 mL) was refluxed for 2 h to give the crude product. Recrystallization from $CHCl_3$–hexane gave **10a-Z** (6.32 g, 73% yield) as a white solid. The E isomer (**10a-E**) was obtained through the methanolysis of **8** (E/Z = 12/88, vide supra) followed by chromatographic separation on a silica gel column using benzene–CH_2Cl_2.

10a-Z: mp 120–120.3 °C; ^1H NMR ($CDCl_3$/TMS) δ 2.32 (qt, J = 10.1, 7.7 Hz, 2 H), 2.50 (td, J = 7.7, 7.3 Hz, 2 H), 3.80 (s, 3 H), 6.70 (t, J = 7.3 Hz, 1 H), 7.46 (m, 2 H), 7.55 (m, 1 H), 7.78 (bs, 1 H), 7.86 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −66.0 (t, J = 10.1 Hz); IR (KBr disk) 3275 (νNH), 1725 (νC=O), 1660 (νC=C), 1637 (νC=O), 1509 (δNH) cm^{-1}. Anal. Calcd for $C_{14}H_{14}F_3NO_3$: C, 55.82; H, 4.68; N, 4.65. Found: C, 55.71; H, 4.51; N, 4.53.

10a-E: mp 100.5–101.9 °C; ^1H NMR ($CDCl_3$/TMS) δ 2.31 (qt, J = 11.0, 8.0 Hz, 2 H), 2.89 (td, J = 8.0, 7.9 Hz, 2 H), 3.92 (s, 3 H), 7.42 (t, J = 7.9 Hz, 1 H), 7.47 (m, 2 H), 7.55 (m, 1 H), 7.81 (m, 2 H), 8.30 (bs, 1 H); ^{19}F NMR (acetone-d_6/TMS) δ −66.0 (t, J = 11.0 Hz); IR (KBr disk) 3270 (νNH), 1728 (νC=O), 1660 (νC=C), 1636 (νC=O) 1524 (δNH) cm^{-1}. Anal. Calcd for $C_{14}H_{14}F_3NO_3$: C, 55.82; H, 4.68; N, 4.65. Found: C, 56.06; H, 4.55; N, 4.64.

Ethyl (*Z*)-2-Benzamido-4-(trifluoromethyl)-2-pentenoate (*N*-Benzoyldehydrotrifluoroleucine Ethyl Ester) (9b-Z). In a similar manner, a solution of **7-Z** (734 mg, 2.73 mmol) and sodium ethoxide (5 mg) in ethanol (30 mL) was refluxed for 6 h. Recrystallization of the crude product gave **9b-Z** (602 mg, 70% yield as a white solid.

9b-Z: mp 97–98 °C; ^1H NMR ($CDCl_3$/TMS) δ 1.35 (t, J = 7.1 Hz, 3 H), 1.38 (d, J = 6.9 Hz, 3 H), 3.48 (m, 1 H), 4.30 (m, J = 7.1 Hz, 2 H), 6.54 (d, J = 10 Hz, 1 H), 7.49–7.58 (m, 3 H), 7.81 (bs, 1 H), 7.87 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −71.5 (d, J = 8.5 Hz); IR (KBr disk) 3250 (νNH), 1730 (νC=O), 1670 (νC=C), 1645 (νC=O), 1520 (δNH) cm^{-1}; MS (m/e) 315 (2, M^+), 105 (100). Anal. Calcd for $C_{15}H_{16}F_3NO_3$: C, 57.14; H, 5.12; N, 4.44. Found: C, 56.96; H, 5.04; N, 4.39.

Ethyl (*Z*)-2-Benzamido-5-(trifluoromethyl)-2-pentenoate (*N*-Benzoyldehydrotrifluoronorleucine Ethyl Ester) (10b-Z). In a similar manner, a solution of **8-Z** (646 mg, 2.40 mmol) and sodium ethoxide (5 mg) in ethanol (30 mL) was refluxed for 2 h. Recrystallization of the crude product gave **10b-Z** (434 mg, 57% yield) as a colorless powder.

10b-Z: mp 112–112.5 °C; ^1H NMR ($CDCl_3$/TMS) δ 1.32 (t, J = 7.1 Hz, 3 H), 2.37 (qt, J = 9.8, 7.7 Hz, 2 H), 2.51 (td, J = 7.7, 7.2 Hz, 2 H), 4.27 (q, J = 7.1 Hz, 2 H), 6.69 (t, J = 7.2 Hz, 1 H), 7.48 (m, 2 H), 7.56 (m, 1 H), 7.75 (bs, 1 H), 7.86 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −66.0 (t, J = 9.8 Hz); IR (KBr disk) 3265 (νNH), 1720 (νC=O), 1665 (νC=C), 1638 (νC=O), 1510 (δNH) cm^{-1}; MS (m/e) 315 (3, M^+), 105 (100). Anal. Calcd for $C_{15}H_{16}F_3NO_3$: C, 57.14; H, 5.12; N, 4.44. Found: C, 57.36; H, 4.98; N, 4.57.

(*Z*)-2-Benzamido-4-(trifluoromethyl)-2-pentenoic Acid (*N*-Benzoyldehydrotrifluoroleucine) (9c-Z). An aqueous solution (50 mL) of **7-Z** (698 mg, 2.59 mmol) and sodium hydroxide (120 mg) was refluxed for 3 h. The reaction mixture was concentrated and acidified with 1 N hydrochloric acid to yield a white precipitate. The precipitate was collected on a glass filter and dried in vacuo to give **9c-Z** (561 mg, 76% yield) as a white solid.

9c-Z: mp 170–172 °C; ^1H NMR (CD_3OD/TMS) δ 1.30 (d, J = 7.0 Hz, 3 H), 3.45 (m, 1 H), 6.69 (d, J = 9.9 Hz, 1 H), 7.49 (m, 2 H), 7.58 (m, 1 H), 7.92 (m, 2 H); ^{19}F NMR (CD_3OD/$CFCl_3$) δ −71.9 (d, J = 10.4 Hz); IR (KBr disk) 3600–2400 (νOH), 3250 (νNH), 1710 (νC=O), 1660 (νC=C), 1650 (νC=O), 1510 (δNH) cm^{-1}; MS (m/e) 287 (1, M^+), 105 (100). Anal. Calcd for $C_{13}H_{12}F_3NO_3$: C, 54.36; H, 4.21; N, 4.88. Found: C, 54.09; H, 4.16; N, 4.79.

***N*-Benzoyl-5,5,5-trifluoroleucine Methyl Ester (11a).** A methanol (15 mL) solution of **9a-Z** (305 mg, 1.01 mmol) was charged in a standard hydrogenation apparatus containing 300 mg of 5% palladium/carbon and stirred for 48 h at room temperature. After the catalyst was separated from the reaction mixture by filtration, the solvent was removed in vacuo to give **11a** (306 mg, 100% yield) as a white solid. The ^1H and ^{19}F NMR analyses showed that the obtained **11a** was a mixture of two diastereomers: (S^*,S^*)/(R^*,S^*) = 67/33. The stereochemistry of the two diastereomers was assigned on the basis of the reported ^1H NMR data for enantiomerically pure (R)- and (S)-trifluoroleucine (**5**)[16] after hydrolysis with 6 N hydrochloric acid (vide infra).

11a (a 67:33 mixture of diastereomers): mp 79–82 °C; ^1H NMR ($CDCl_3$/TMS) (S^*,S^*) δ 1.27 (d, J = 6.8 Hz, 3 H), 2.01 (m, 2 H), 2.30 (m, 1 H), 3.80 (s, 3 H), 4.97 (m, 1 H), 6.82 (bd, J = 8.5 Hz, 1 H), 7.43–7.54 (m, 3 H), 7.79–7.83 (m, 2 H) (R^*,S^*) δ 1.23 (d, J = 6.9 Hz, 3 H), 1.83 (m, 2 H), 2.40 (m, 1 H), 3.81 (s, 3 H), 4.88 (m, 1 H), 6.89 (bd, J = 6.9 Hz, 1 H), 7.43–7.54 (m, 3 H), 7.79–7.83 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −72.7 (d, J = 6.1 Hz) (R^*,S^*); δ −72.9 (d, J = 9.6 Hz) (S^*,S^*); IR (KBr disk) 3320 (νNH), 1750 (νC=O), 1640 (νC=O), 1535 (δNH) cm^{-1}. Anal. Calcd for $C_{14}H_{16}F_3NO_3$: C, 55.45; H, 5.32; N, 4.62. Found: C, 55.25; H, 5.26; N, 4.52.

***N*-Benzoyl-5,5,5-trifluoroleucine Ethyl Ester (11b).** In a similar manner, **9b-Z** (315 mg, 1.00 mmol) was hydrogenated over 10% Pd/carbon (297 mg) in ethanol at room temperature for 31 h to give **11b** (317 mg, 100% yield) as a white solid: (S^*,S^*)/(R^*,S^*) = 84/16.

11b (a 84:16 mixture of two diastereomers); mp 54–57 °C; ^1H NMR ($CDCl_3$/TMS) (S^*,S^*) δ 1.29 (d, J = 6.6 Hz, 3 H), 1.31 (t, J = 7.1 Hz, 3 H), 2.00 (m, 2 H), 2.31 (m, 1 H), 4.25 (q, J = 7.1 Hz, 2 H), 4.95 (m, 1 H), 6.82 (d, J = 8.2 Hz, 1 H), 7.44–7.53 (m, 3 H), 7.82–7.90 (m, 2 H); (R^*,S^*) δ 1.23 (d, J = 6.9 Hz, 3 H), 1.32 (t, J = 7.1 Hz, 3 H), 1.81 (m, 2 H), 2.44 (m, 1 H), 4.27 (q, J = 7.1 Hz, 2 H), 4.84 (m, 1 H), 6.89 (d, J = 7.5 Hz, 1 H), 7.44–7.53 (m, 3 H), 7.82–7.90 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −72.7 (d, J = 8.5 Hz) (R^*,S^*); δ −73.0 (d, J = 8.5 Hz) (S^*,S^*); IR (KBr disk) 3280 (νNH), 1745 (νC=O), 1640 (νC=O), 1545 (δNH) cm^{-1}; MS (m/e) 317 (0.5, M^+), 105 (100). Anal. Calcd for $C_{15}H_{18}F_3NO_3$: C, 56.78; H, 5.72; N, 4.41. Found: C, 56.65; H, 5.66; N, 4.36.

In the same manner, the reaction was carried out in THF to give **11b**, in which the (S^*,S^*)/(R^*,S^*) ratio was 90/10. This diastereomer mixture (3.0 g) was submitted to medium pressure liquid chromatography on silica gel using hexane/EtOAc (5/1) as the eluent to give the pure S^*,S^* isomer (2.37 g) as colorless needles.

(S^*,S^*)-11b: mp 63.5–64 °C; ^1H NMR ($CDCl_3$/TMS) δ 1.27 (d, J = 6.9 Hz, 3 H), 1.31 (t, J = 7.1 Hz, 3 H), 1.95 (ddd, J = 14.0, 10.3, 3.9 Hz, 1 H), 2.05 (ddd, J = 14.0, 10.6, 3.5 Hz, 1 H), 2.32 (m, 1 H), 4.24 (q, J = 7.1 Hz, 2 H), 4.95 (ddd, J = 10.6, 8.6, 3.9 Hz, 1 H), 6.85 (d, J = 8.6 Hz, 1 H), 7.43 (m, 2 H), 7.52 (m, 1 H), 7.80 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −72.9 (d, J = 8.5 Hz).

***N*-Benzoyl-5,5,5-trifluoroleucine (11c).** In a similar manner, **9c-Z** (134 mg, 0.47 mmol) was hydrogenated over 10% palladium/carbon (100 mg) in ethanol (10 mL) at room temperature for 14 h to give **11c** (135 mg, 100% yield) as a white solid: (S^*,S^*)/(R^*,S^*) = 82/18.

11c (a 82:18 mixture of two diastereomers): mp 173–178 °C dec; ^{1}H NMR (CD_3OD/TMS) (*S**,*S**) δ 1.21 (d, *J* = 6.9 Hz, 3 H), 2.01 (m, 1 H), 2.17–2.60 (m, 2 H), 4.79 (dd, *J* = 11.7, 3.8 Hz, 1 H), 7.46 (m, 2 H), 7.52 (m, 1 H), 7.87 (m, 2 H); (*R**,*S**) δ 1.22 (d, *J* = 6.9 Hz, 3 H), 1.84 (m, 1 H), 2.17–2.60 (m, 2 H), 4.71 (t, *J* = 7.4 Hz, 1 H), 7.46 (m, 2 H), 7.52 (m, 1 H), 7.87 (m, 2 H); ^{19}F NMR ($CD_3OD/CFCl_3$) δ −73.1 (d, *J* = 8.7 Hz) (*R**,*S**); δ −73.4 (d, *J* = 6.7 Hz) (*S**,*S**); IR (KBr disk) 3290 (νNH), 3600–2300 (νOH), 1730 (νC=O), 1625 (νC=O), 1545 (δNH) cm^{-1}; MS (*m*/*e*) 289 (1, M$^+$), 105 (100). Anal. Calcd for $C_{13}H_{14}F_3NO_3$: C, 53.98; H, 4.88; N, 4.84. Found: C, 53.82; H, 4.86; N, 4.81.

***N*-Benzoyl-6,6,6-trifluoronorleucine Methyl Ester (12a).** In a similar manner, **10a-Z** (3.39 g, 11.3 mmol) was hydrogenated over 5% palladium/carbon (300 mg) in methanol (25 mL) at room temperature for 48 h to give **12a** (3.38 g, 99% yield) as a colorless powder.

12a: mp 72.5–73.5 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.55–1.80 (m, 2 H), 1.80–2.25 (m, 4 H), 3.79 (s, 3 H), 4.84 (td, *J* = 7.5, 5.7 Hz, 1 H), 6.87 (bd, *J* = 5.7 Hz, 1 H), 7.44 (m, 2 H), 7.52 (m, 1 H), 7.81 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −65.8 (t, *J* = 10.9 Hz); IR (KBr disk) 3345 (νNH), 1750 (νC=O), 1642 (νC=O), 1532 (δNH) cm^{-1}. Anal. Calcd for $C_{14}H_{16}F_3NO_3$: C, 55.45; H, 5.32; N, 4.62. Found: C, 55.67; H, 5.23; N, 4.91.

***N*-Benzoyl-6,6,6-trifluoroleucine Ethyl Ester (12b).** In a similar manner, **10b-Z** (490 mg, 1.55 mmol) was hydrogenated over 10% palladium/carbon (460 mg) in ethanol (18 mL) at room temperature for 2 h to give **12b** (492 mg, 100% yield) as a white solid.

12b: mp 77.5–78 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.30 (t, *J* = 7.2 Hz, 3 H), 1.66 (m, 2 H), 1.79–2.20 (m, 4 H), 4.24 (m, *J* = 7.2 Hz, 2 H), 4.81 (td, *J* = 7.3, 5.6 Hz, 1 H), 6.99 (bd, *J* = 5.6 Hz, 1 H), 7.43 (m, 2 H), 7.51 (m, 1 H), 7.81 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −65.8 (t, *J* = 11.2 Hz); IR (KBr disk) 3320 (νNH), 1735 (νC=O), 1635 (νC=O), 1520 (δNH) cm^{-1}; MS (*m*/*e*) 317 (1, M$^+$), 105 (100). Anal. Calcd for $C_{15}H_{18}F_3NO_3$: C, 56.78; H, 5.72; N, 4.41. Found: C, 56.38; H, 5.75; N, 4.43.

5,5,5-Trifluoroleucine (5). A mixture of **11a** (501 mg, 1.65 mmol) and 6 N hydrochloric acid (5 mL) was refluxed for 24 h. The reaction mixture was washed with ether and concentrated to dryness. Water (4 mL) was added to the residue and the resulting solution was neutralized with aqueous ammonia to cause precipitation. The resulting precipitate (colorless leaves) was collected on a glass filter and dried in vacuo to give **5** (222 mg, 73% yield). ^{19}F NMR analysis showed that **5** thus obtained was a 67:33 mixture of two diastereomers: The major isomer was found to be the *S**,*S** isomer as described below.

5 (a 67:33 mixture of two diastereomers): mp 245 °C dec [lit.[16] mp 245 °C]; ^{1}H NMR (D_2O/TSP) δ 1.21 (d, *J* = 6.9 Hz, 3 H), 1.77–2.30 (m, 2 H), 2.54 (m, 1 H), 3.81 (m, 1 H); ^{19}F NMR (D_2O/CF_3COOH) δ 2.17 (d, *J* = 8.3 Hz) (minor) (−74.83 from $CFCl_3$); 2.38 (d, *J* = 9.1 Hz) (major) (−74.62 from $CFCl_3$); IR (KBr disk) 3400–2000 (νNH), 1615 (δNH), 1585 (νC=O), 1505 (δNH) cm^{-1}. Anal. Calcd for $C_6H_{10}F_3NO_2$: C, 38.92; H, 5.44; N, 7.57. Found: C, 39.23; H, 5.70; N, 7.52.

In the same manner, diastereomerically pure **11a** (vide supra) was hydrolyzed to give diastereomerically pure **5**, which was unambiguously assigned to the *S**,*S** isomer on the basis of the reported ^{1}H NMR data of enantiomerically and diastereomerically pure 5,5,5-trifluoroleucines.[16] Therefore, the major isomer, obtained in the diastereomer mixture described above, was also assigned as the *S**,*S** isomer.

(*S,*S**)-5**: mp 245 °C dec [lit.[16] mp 245 C dec]; ^{1}H NMR (D_2O/TSP) δ 1.21 (d, *J* = 6.9 Hz, 3 H), 1.97 (ddd, *J* = 14.8, 9.5, 5.1 Hz, 1 H), 2.15 (ddd, *J* = 14.8, 9.2, 4.4 Hz, 1 H), 2.54 (m, 1 H), 3.80 (dd, *J* = 9.2, 5.1 Hz, 1 H); ^{19}F NMR (D_2O/CF_3COOH) 2.38 (d, *J* = 9.1 Hz) (−74.62 from $CFCl_3$).

Direct formation of **5** from **7-Z** is as follows. A mixture of **7-Z** (536 mg, 2.00 mmol), acetic anhydride (2.5 mL), 50% hydriodic acid (2.5 mL), and red phosphorus (400 mg, 12.9 mmol) was refluxed for 4 h. The reaction mixture was filtered to remove insoluble materials, which were washed with acetic acid (20 mL × 2). The filtrate was concentrated and water (5 mL) was added to the residue. The resulting aqueous solution was washed with ether several times, treated with Norit, and concentrated to dryness in vacuo to give a crude product. Recrystallization of the crude product from aqueous ethanol gave **5** (282 mg, 76% yield) as a 1:1 diastereomer mixture.

(*Z*)-2-Phenyl-4-[2-(pentafluorophenyl)propylidene]-5-oxazolone (13-Z). A mixture of 2-PFPPA (1.12 g, 5.0 mmol), hippuric acid (895 mg, 5.0 mmol), lead(II) acetate trihydrate (948 mg, 2.5 mmol), and acetic anhydride (1.53 g, 15 mmol) in THF (10 mL) was refluxed for 3 h. The reaction mixture was concentrated and water (50 mL) was added. The resulting aqueous solution was extracted with ethyl acetate and the extract solution was washed with water. After being dried over anhydrous $MgSO_4$, the solvent was evaporated to give a crude product. NMR analysis (^{1}H and ^{19}F) of the crude product showed that the *E*:*Z* ratio was 18:82. Recrystallization of the crude product from hexane gave pure *Z* isomer (**13-Z**) (771 mg, 42% yield) as a colorless powder.

13-Z: mp 85–86.5 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.61 (d, *J* = 7.2 Hz, 3 H), 4.89 (m, 1 H), 6.86 (dt, *J* = 9.3, 1.8 Hz, 1 H), 7.51 (m, 2 H), 7.62 (m, 1 H), 8.07 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −142.7 (bdd, *J* = 21.5, 7.6 Hz, 2 F), −158.0 (t, *J* = 20.4 Hz, 1 F), −163.4 (ddd, *J* = 21.5, 20.4, 7.6 Hz, 2 F); IR (KBr disk) 1800 (νC=O), 1662 (νC=C) cm^{-1}. Anal. Calcd for $C_{18}H_{10}F_5NO_2$: C, 58.87; H, 2.74; N, 3.81. Found: C, 58.78; H, 2.67; N, 3.80.

Methyl (*Z*)-2-Benzamido-4-(pentafluorophenyl)-2-pentenoate (*N*-Benzoyl-4-(pentafluorophenyl)dehydronorvaline Methyl Ester) (14-Z). A methanol (15 mL) solution of **13-Z** (734 mg, 2.0 mmol) and triethylamine (50 mL) was refluxed for 2 h. After removal of solvent, the residue was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated to give a crude product. Recrystallization of the crude product from hexane–$CHCl_3$ gave **14-Z** (646 mg, 81% yield) as colorless needles.

14-Z: mp 149–150 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.53 (d, *J* = 7.1 Hz, 3 H), 3.81 (s, 3 H), 4.34 (dq, *J* = 9.3, 7.1 Hz, 1 H), 7.01 (dt, *J* = 9.3, 2.2 Hz, 1 H), 7.47 (m, 2 H), 7.53–7.56 (m, 2 H), 7.81 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −142.4 (bdd, *J* = 21.9, 7.3 Hz, 2 F), −158.8 (t, *J* = 20.4 Hz, 1 F), −163.7 (m, 2 F); IR (KBr disk) 3280 (νNH), 1737 (νC=O), 1660 (νC=C), 1645 (νC=O), 1520 (δNH) cm^{-1}. Anal. Calcd for $C_{19}H_{14}F_5NO_3$: C, 57.15; H, 3.53; N, 3.51. Found: C, 57.18; H, 3.66; N, 3.50.

***N*-Benzoyl-4-(pentafluorophenyl)norvaline Methyl Ester (15).** In a manner similar to that for the hydrogenation of **9**, an ethanol (10 mL) solution of **14-Z** (40 mg, 0.10 mmol) was hydrogenated over 5% palladium/carbon (40 mg) at 0 °C for 48 h to give **15** (40 mg, 99.5%) as white powder. ^{19}F NMR analysis showed that **15** thus obtained was a 93:7 mixture of two diastereomers. On the basis of the fact that the two isomers show unique coupling patterns in their ^{1}H NMR spectra at the chiral methine protons with close similarity to those of **11a**, the major isomer can most probably be assigned to (*S**,*S**)-**15** and the minor, (*R**,*S**)-**15**. Accordingly, the observed mode of diastereoface differentiation is the same as that for **11a**.

15 (a 93:7 diastereomer mixture): mp 63–65 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.40 (d, *J* = 7.1 Hz, 3 H), 2.23–2.34 (m, 1 H), 2.38–2.47 (m, 1 H), 3.40 (m, 1 H), 3.67 (s, 3 H), [4.67 (m) (*R**,*S**), 4.84 (m) (*S**,*S**)] (1 H), 6.74 (d, *J* = 6.8 Hz, 1 H), 7.43–7.48 (m, 2 H), 7.51–7.57 (m, 1 H), 7.78 (m, 2 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) (*S**,*S**) δ −142.5 (dd, *J* = 21.7, 7.3 Hz, 2 F), −159.3 (t, *J* = 20.3 Hz, 1 F), −164.0 (ddd, *J* = 21.7, 20.3, 7.3 Hz, 2 F); (*R**,*S**) δ −142.8 (dd, *J* = 21.7, 7.3 Hz, 2 F), −158.7 (t, *J* = 20.4 Hz, 1 F), −163.6 (ddd, *J* = 21.7, 20.4, 7.3 Hz, 2 F); IR (KBr disk) 3250 (νNH), 1740 (νC=O), 1635 (νC=O), 1540 (δNH) cm^{-1}. Anal. Calcd for $C_{19}H_{16}F_5NO_3$: C, 56.86; H, 4.02; N, 3.49. Found: C, 56.68; H, 4.21; N, 3.42.

4-(Pentafluorophenyl)norvaline (16). A mixture of **15** (412 mg, 1.03 mmol) and 6 N hydrochloric acid (5 mL) was refluxed for 24 h. The reaction mixture was washed with ether and concentrated. The residue was neutralized to pH 7 with aqueous ammonia and the resulting precipitate was collected on a glass filter. Recrystallization of the precipitate from water gave **16** (284 mg, 72% yield) as colorless powder.

(*S,*S**)-16**: mp 236–237 °C dec; ^{1}H NMR (CD_3OD/TMS) δ 1.40 (d, *J* = 7.0 Hz, 3 H), 2.15–2.38 (m, 2 H), 3.42 (m, 1 H), 3.56 (m, 1 H); ^{19}F NMR ($CD_3OD/CFCl_3$) δ −142.3 (dd, *J* = 19.9 Hz, 2 F), −159.0 (t, *J* = 20.0 Hz, 1 F), −163.8 (m, 2 F); IR (KBr disk) 3120 (νNH), 1620 (νC=O and δNH) cm^{-1}.

6,6,6-Trifluoronorleucine (6). In the same manner to that described for **5**, **12b** (354 mg, 1.17 mmol) was hydrolyzed with 6 N hydrochloric acid (5 mL) (reflux for 20 h) followed by the

usual workup to give **6** (153 mg, 71% yield) as a colorless powder.

6: mp 258–260 °C dec [lit.[12] mp 274 °C]; ^{1}H NMR (D_2O/TSP) δ 1.73 (m, 2 H), 2.03 (m, 2 H), 2.27 (m, 2 H), 4.09 (t, J = 6.3 Hz, 1 H); ^{19}F NMR (D_2O/CF_3COOH) δ 9.48 (t, J = 10.5 Hz) (−67.52 from $CFCl_3$); IR (KBr disk) 3500–2000 (^{r}NH), 1620 (^{s}NH), 1575 (^{r}C=O), 1505 (^{s}NH) cm^{-1}. Anal. Calcd for $C_6H_{10}F_3NO_2$: C, 38.92; H, 5.44; N, 7.57. Found: C, 39.22; H, 5.54; N, 7.56.

Direct formation of **6** from **8-Z** was also performed in the same manner as that described for **5**. The reaction gave **6** in 69% yield.

Stereochemistry of Dehydro Amino Acid Esters. It has been shown that the C-3 alkyl protons of the *Z* isomers of *N*-acetyl dehydro amino acid esters show the signals at 0.19–0.77 ppm higher field than those of the *E* isomers.[14,15] For the trifluoro analogues **9a** and **10a**, the same trend was observed, viz., **9a-Z** (methine), δ 3.47; **9a-E** (methine), δ 4.16; **10a-Z** (methylene), δ 2.50; **10a-E** (methylene), δ 2.89. It has also been shown that the olefin protons of the *Z* isomers appear at 0.14–0.68 ppm higher field than those of the *E* isomers, when the *N*-acyl moiety is benzoyl, acetyl, substituted acetyl, carbobenzoxyl (CBZ), or *tert*-butoxycarbonyl (t-BOC).[14,15] The same trend was observed for **9a** and **10a**, viz., **9a-Z**, δ 6.56; **9a-E**, δ 7.37; **10a-Z**, δ 6.70; **10a-E**, δ 7.42.

The irradiation of the methyl ester moiety of **9a-Z** and **9a-E** gave rise to +1.0% and +3.2% NOE, respectively, at the methyl group of trifluoroisopropyl moiety, and that of **10a-Z** and **10a-E** gave 0% and +11.6% NOE, respectively. These consistent results allow us to assign, unambiguously, the stereochemistry of the dehydroamino acid and esters (**9** and **10**) and the azlactones (**7** and **8**) as shown.

***N*-Acetyl-6,6,6-trifluoronorleucine (17).** To an aqueous solution of **6** (1.00 g, 5.4 mmol) and sodium hydroxide (262 mg, 6.1 mmol) was added acetic anhydride (717 mg, 6.6 mmol) slowly with stirring at 0 °C, and the mixture was kept stirring for another 30 min at room temperature. The reaction mixture was acidified to pH 2.5 with concentrated hydrochloric acid and extracted with ethyl acetate and the extract solution was dried over anhydrous $MgSO_4$. Removal of the solvent gave a crude product and recrystallization of the crude product from $CHCl_3$–hexane gave **17** (877 mg, 71% yield) as colorless prisms.

17: mp 99.5–100.5 °C; ^{1}H NMR (DMSO-d_6/TMS) δ 1.46–1.84 (m, 4 H), 1.85 (s, 3 H), 2.17–2.35 (m, 2 H), 4.20 (ddd, J = 8.5, 7.9, 5.1 Hz, 1 H), 8.17 (d, J = 7.9 Hz, 1 H); ^{19}F NMR (DMSO-d_6/$CFCl_3$) δ −64.9 (t, J = 11.5 Hz); IR (KBr disk) 3290 (^{r}NH), 3400–2500 (^{r}OH), 1710 (^{r}C=O), 1620 (^{r}C=O), 1520 (^{s}NH) cm^{-1}. Anal. Calcd for $C_8H_{12}F_3NO_3$: C, 42.30; H, 5.32; N, 6.17. Found: C, 42.43; H, 5.33; N, 6.21.

Optical Resolution of *N*-Acetyl-6,6,6-trifluoronorleucine (17) with an Acylase. In the same manner to that described for **4**, kinetic resolution of **17** (600 mg, 2.64 mmol) was performed by using porcine kidney acylase I (15 mg, 850 unit/mg) at pH 7.0 and 25 °C for 14 h to give (*S*)-**6** (148 mg, 30%): $[\alpha]_D$ +6.2° (*c* 0.5, H_2O). From the filtrate of the reaction mixture (see the procedure for (*R*)-**4**) was obtained (*R*)-**17** (221 mg, 37% recovery): $[\alpha]^{20}_D$ −8.82° (*c* 2.8, EtOAc). Hydrolysis of (*R*)-**17** (200 mg, 0.88 mmol) with 3 N hydrochloric acid gave (*R*)-**6** (114 mg, 70% yield)): $[\alpha]^{20}_D$ −6.0° (*c* 0.4, H_2O).

Determination of Optical Purity of 6. In the same manner to that described for (*S*)-**2** and (*R*)-**2**, the optical purities of (*S*)-**6** and (*R*)-**6** were determined by the Mosher's MTPA method,[11] viz., **6** was converted to its methyl ester hydrochloride followed by the coupling with (*R*)-(+)-MTPA to give the corresponding (*R*)-MTPA ester, which was submitted to ^{19}F NMR analysis. The ^{19}F NMR analyses showed that the enantiomeric purities of (*S*)-**6** and (*R*)-**6** were >99% and 98%, respectively.

6,6,6-Trifluoronorleucine methyl ester hydrochloride: mp 109.5–110.5 °C; ^{1}H NMR (CD_3OD/TMS) δ 1.60–1.82 (m, 2 H), 2.00 (m, 2 H), 2.17–2.40 (m, 2 H), 3.86 (s, 3 H), 4.11 (t, J = 5.9 Hz, 1 H); ^{19}F NMR (CD_3OD/$CFCl_3$) δ −66.1 (t, J = 10.8 Hz); IR (KBr disk) 3400–2500 (^{r}NH), 1730 (^{r}C=O), 1580 (^{s}NH) cm^{-1}.

(*R*)-MTPA-(*S*)-trifluoronorleucine methyl ester: ^{1}H NMR ($CDCl_3$/TMS) δ 1.50–2.20 (m, 6 H), 3.37 (q, J = 1.3 Hz, 3 H), 3.77 (s, 3 H), 4.66 (m, 1 H), 7.39–7.54 (m, 6 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −65.85 (t, J = 11.2 Hz, 3 F), −68.86 (bs, 3 F).

(*R*)-MTPA-(*R*)-trifluoronorleucine methyl ester: ^{1}H NMR ($CDCl_3$/TMS) δ 1.40–2.20 (m, 6 H), 3.54 (q, J = 1.7 Hz, 3 H), 3.79 (s, 3 H), 4.69 (m, 1 H), 7.16 (d, J = 8.1 Hz, 1 H), 7.39–7.57 (m, 5 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −65.82 (t, J = 11.3 Hz, 3 F), −68.53 (bs, 3 F).

Asymmetric Hydrogenation of 10a-Z Catalyzed by Chiral Rhodium Complexes. Typically, an ethanol (10 mL) solution of **10a-Z** (293 mg, 0.973 mmol) and [(diPAMP)Rh(NBD)]ClO_4 (17.4 mg, 0.0237 mmol) was stirred under ambient pressure of hydrogen at 40 °C for 40 h. The reaction mixture was concentrated and passed through a silica gel column to remove the catalyst using $CHCl_3$ as the eluent, giving **12a** (294 mg, 100% yield): $[\alpha]^{20}_D$ −19.5° (*c* 0.99, EtOH); 89% optical purity (op) based on the maximum rotation of **12a**, $[\alpha]_D$ −22.0° (*c* 0.82, EtOH), which was obtained by recrystallization from ethanol. The absolute configuration of **12a** thus obtained was determined to be *S* on the basis of the following experiment. *N*-Benzoyltrifluoronorleucine methyl ester (**12a**; $[\alpha]^{20}_D$ −19.2°; 87% op) (150 mg, 0.495 mmol), which was obtained in another experiment, was hydrolyzed with 6 N hydrochloric acid under reflux for 24 h. Neutralization of the reaction mixture with aqueous ammonia gave (*S*)-**6** (62.6 mg, 68.3% yield): $[\alpha]^{20}_D$ +5.4° (*c* 0.5, H_2O); 87% op based on the specific rotation (+6.2°) of enantiomerically pure (*S*)-**6** obtained by enzymatic resolution (vide supra). The optical purity of this sample was further checked by the Mosher's MTPA method,[11] which showed that the diastereomeric purity of (*R*)-MTPA-(*S*)-**6** methyl ester was 87.2% de.

Results of the asymmetric hydrogenation catalyzed by other chiral rhodium complexes are listed in Table I.

1-Allyl-3-methyl-4,5,6,7-tetrafluoroindole (19a). A mixture of allylamine (2.25 ml, 30 mmol) and 2-PFPPA (4.48 g, 20 mmol) in chloroform was prepared at 0 °C and stirred at room temperature for 30 min. Then, anhydrous $MgSO_4$ (1 g) was added to the solution and the mixture was stirred for 10 min. Removal of drying reagent and evaporation of the solvent gave **18a** as a mixture of a Schiff base and enamine forms. A solution of 18a in THF (20 mL) was cooled to −78 °C and 1 M solution (20 mL) of LDA (20 mmol) in THF was added to it for the period of 25 min. Then, the cooling bath was taken out and the mixture was stirred at room temperature for 10 h. The reaction was quenched by addition of saturated aqueous ammonium chloride (20 mL) and water (50 mL). The reaction mixture was extracted with dichloromethane, dried over anhydrous $MgSO_4$, and concentrated to give a crude product. The crude product was purified on a silica gel column (eluent: hexane–benzene) to give **19a** (3.61 g, 74% yield) as colorless prisms.

19a: mp 31 °C; ^{1}H NMR ($CDCl_3$) δ 2.38 (d, J = 0.8 Hz, 3 H), 4.74 (ddd, J = 5.4, 1.4, 1.0 Hz, 2 H), 4.99 (ddt, J = 17.0, 1.4, 1.0 Hz, 1 H), 5.18 (ddt, J = 10.3, 1.4, 1.4 Hz, 1 H), 5.97 (ddt, J = 17.0, 10.3, 5.4 Hz, 1 H), 6.76 (s, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −155.2 (bdd, J = 19.1, 16.9 Hz, 1 F), −164.1 (ddd, J = 18.5, 16.9, 4.3 Hz, 1 F), −168.4 (ddd, J = 20.4, 18.5, 2.6 Hz, 1 F), −172.5 (ddd, J = 20.4, 19.1, 4.3 Hz, 1 F); IR (KBr disk) 3080, 2920, 1640, 1600, 1523, 1479, 1340, 1328, 1094, 1028, 980, 942, 910, 790 cm^{-1}; MS (*m/e*) 243 (48, M$^+$), 41 (100). Anal. Calcd for $C_{12}H_9F_4N$: C, 59.26; H, 3.73; N, 5.76. Found: C, 58.97; H, 3.48; N, 5.71.

1-Benzyl-3-methyl-4,5,6,7-tetrafluoroindole (19b). In a similar manner, the reaction of **2-PFPPA** (1.12 g, 5.0 mmol) and benzylamine (529 mg, 4.94 mmol) followed by the cyclization promoted by LDA gave **19b** (1.15 g, 79% yield) as a white solid.

19b: mp 86.9–87.3 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 2.38 (s, 3 H), 5.33 (s, 2 H), 6.81 (s, 1 H), 7.10 (m, 2 H), 7.30 (m, 3 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −155.0 (dd, J = 20.1, 16.1 Hz, 1 F), −163.1 (ddd, J = 19.6, 16.1, 4.3 Hz, 1 F), −168.1 (ddd, J = 19.6, 19.4, 2.5 Hz, 1 F), −172.3 (ddd, J = 20.1, 19.4, 4.3 Hz, 1 F); IR (KBr disk) 3060, 3020, 2970, 2940, 2920, 2885, 2860, 1605, 1522, 1478, 1328, 1094, 1028, 938, 790 cm^{-1}; MS (*m/e*) 293 (11, M$^+$), 91 (100). Anal. Calcd for $C_{16}H_{11}F_4N$: C, 65.53; H, 3.78; N, 4.78. Found: C, 64.44; H, 3.53; N, 4.65.

3-Methyl-4,5,6,7-tetrafluoroindole (20). A mixture of **19a** (8.97 g, 78.1 mmol) and $RhCl_3 \cdot 3H_2O$ (210 mg, 1.0 mol %) in ethanol (75 mL) was refluxed for 14 h followed by the addition of concentrated hydrochloric acid (25 mL). After the mixture was refluxed for another 20 min, the reaction mixture was concentrated to 40 mL and neutralized with 10% aqueous Na_2CO_3. The reaction mixture was then extracted with dichloromethane and the extract solution was dried over anhydrous $MgSO_4$ and concentrated to give a crude product. The crude product was purified on a silica gel column (eluent: hexane–benzene) to give

20 (15.29 g, 97% yield) as a colorless powder.

20: mp 98 °C [lit.[26] mp 96–97 °C]; ^{1}H NMR ($CDCl_3$/TMS) δ 2.40 (s, 3 H), 6.92 (s, 1 H), 8.05 (bs, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −155.4 (m, 1 F), −162.3 (m, 1 F), −168.8 (m, 1 F), −173.1 (m, 1 F); IR (KBr disk) 3480, 1536, 1488, 1336, 932, 808 cm^{-1}.

1-Acetyl-3-methyl-4,5,6,7-tetrafluoroindole (21a). A mixture of **20** (204.9 mg, 1.01 mmol), pyridine (1 mL), and acetic anhydride (1 mL) was refluxed for 1.5 h, and the solvent was evaporated. Recrystallization of the residue, thus obtained, from ether–hexane gave **21a** (231.4 mg, 94% yield) as colorless needles.

21a: mp 138 °C; ^{1}H NMR ($CDCl_3$/TMS) (a 1:1 mixture of two conformers) δ 2.380, 2.384 (d, J = 1.4 Hz, 3 H), 2.636, 2.641 (s, 3 H), 7.227, 7.229 (s, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −137.5 (bdd, J = 19.8, 16.2 Hz, 1 F), −154.2 (bdd, J = 20.1, 16.2 Hz, 1 F), −162.1 (bdd, J = 19.8, 19.7 Hz, 1 F), −165.6 (bdd, J = 20.1, 19.7 Hz, 1 F); IR (KBr disk) 1733 (ν C=O) cm^{-1}; MS (m/e) 245 (13, M$^+$), 202 (100). Anal. Calcd for $C_{11}H_7F_4NO$: C, 53.89; H, 2.88; N, 5.71. Found: C, 53.93, H, 2.75, N, 5.83.

1-Benzoyl-3-methyl-4,5,6,7-tetrafluoroindole (21b). A mixture of **20** (202.9 mg, 1.0 mmol), pyridine (1 mL), and benzoyl chloride (0.232 mL, 2.0 mmol) was stirred at 80 °C for 1 h. To the reaction mixture was added a mixture of water (0.1 mL) and benzene (5 mL) with stirring. The reaction mixture was dried over anhydrous $MgSO_4$, concentrated, and purified on a silica gel column (eluent: benzene) to give **21b** (297 mg, 97% yield) as a white solid.

21b: mp 138–139 °C, ^{1}H NMR ($CDCl_3$/TMS) δ 2.35 (s, 3 H), 7.03 (s, 1 H), 7.40–7.70 (m, 2 H), 7.70–7.90 (m, 2 H); ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ −140 (m, 1 F), −153 (m, 1 F), −161 (m, 1 F), −164 (m, 1 F); IR (KBr disk) 1717 (ν C=O) cm^{-1}; MS (m/e) 307 (6.5, M$^+$), 105 (100). Anal. Calcd for $C_{16}H_9F_4NO$: C, 62.55; H, 2.95; N, 4.56. Found: C, 62.73; H, 2.73; N, 4.38.

1-(*p*-Tolylsulfonyl)-3-methyl-4,5,6,7-tetrafluoroindole (21c). To a THF (5 mL) solution of NaH (50%) (56.3 mg, 1.17 mmol) and **20** (208 mg, 1.02 mmol) was added a THF (2 mL) solution of *p*-toluenesulfonyl chloride (230 mg, 1.21 mmol) at room temperature, and the mixture was stirred for 10 min. The reaction mixture was poured into water (10 mL) and extracted with dichloromethane. The extract solution was dried over anhydrous $MgSO_4$, concentrated, and submitted to purification on a silica gel column (eluent: hexane–CH_2Cl_2) to give **21c** (327 mg, 92% yield) as a white solid.

21c: mp 180–181 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 2.36 (t, J = 1.5 Hz, 3 H), 2.40 (s, 3 H), 7.24 (s, 1 H), 7.40 (d, J = 7.8 Hz, 2 H), 7.80 (d, J = 7.8 Hz, 2 H); ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ −149 (m, 1 F), −153 (m, 1 F), −161 (m, 1 F), −164 (m, 1 F); IR (KBr disk) 1521, 1491, 1377, 1193, 1181, 1091, 1031, 933, 665, 580 cm^{-1}; MS (m/e) 358 (5, M + 1), 357 (30, M$^+$), 202 (16), 91 (100). Anal. Calcd for $C_{16}H_{11}F_4NO_2S$: C, 53.78; H, 3.10; N, 3.92. Found: C, 54.08; H, 3.12; N, 3.91.

3-Formyl-4,5,6,7-tetrafluoroindole (22a). A mixture of selenium dioxide (7.77 g, 70 mmol) and **21a** (8.58 g, 35 mmol) in diglyme (35 mL) was heated at 160 °C (reflux) for 1.5 h. After the filtration of metallic selenium, the solvent was evaporated and the residue was submitted to purification on a silica gel column (eluent: EtOAc–CH_2Cl_2) to give **22a** (6.54 g, 86% yield) as colorless powder.

22a: mp 229–230 °C dec in a sealed tube [lit.[26] mp 228–229 °C); ^{1}H NMR (DMSO-d_6/TMS) δ 8.49 (s, 1 H), 9.96 (d, J = 4.2 Hz, 1 H), 13.31 (bs, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −141.2 (bdd, J = 18.2, 16.8 Hz, 1 F), −159.6 (ddd, J = 17.9, 16.8, 2.6 Hz, 1 F), −165.2 (dd, J = 21.1, 17.9 Hz, 1 F), −167.0 (ddd, J = 21.1, 18.2, 2.6 Hz, 1 F); IR (KBr disk) 3440 (ν NH), 1644 (ν C=O) cm^{-1}; MS (m/e) 217 (81, M$^+$), 216 (100).

In a similar manner, the reaction of **21b** (153 mg, 0.50 mmol) with selenium dioxide (109.3 mg, 0.99 mmol) was carried out in diglyme (1.00 mL) to give **22a** (79.5 mg) in 74% yield.

1-(*p*-Tolylsulfonyl)-3-formyl-4,5,6,7-tetrafluoroindole (22b). In a similar manner, the reaction of **21c** (145 mg, 0.404 mmol) with selenium dioxide (91.2 mg, 0.822 mmol) was carried out in diglyme (0.5 mL) at 160 °C for 3 h. Separation of metallic selenium and purification of the crude product on a silica gel column (eluent: hexane–$CHCl_3$) gave **22a** (121.1 mg, 81% yield) as pale yellow prisms.

22b: mp 180–181 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 2.44 (s, 3 H), 7.37 (d, J = 7.8 Hz, 2 H), 7.89 (d, J = 7.8 Hz, 2 H), 8.49 (s, 1 H), 10.20 (d, J = 3.3 Hz, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −138.2 (ddd, J = 21.0, 15.8, 3.3 Hz, 1 F), −147.6 (dd, J = 19.8, 15.8 Hz, 1 F), −159.7 (t, J = 19.8 Hz, 1 F), −161.6 (dd, J = 21.0, 19.8 Hz, 1 F); IR (KBr disk) 1708 (ν C=O) cm^{-1}. Anal. Calcd for $C_{16}H_9F_4NO_3S$: C, 51.76; H, 2.44; N, 3.77. Found: C, 51.41; H, 2.70; N, 3.63.

1-Acetyl-3-(acetoxymethyl)-4,5,6,7-tetrafluoroindole (23a). A mixture of acetic anhydride (0.2 mL), selenium dioxide (222 mg, 2 mmol), and **21a** (246.8 mg, 1.01 mmol) in diglyme (1.0 mL) was charged in a Pyrex ampule with a stirring bar. The sealed Pyrex ampule was heated at 160 °C for 1.5 h with stirring. After the filtration of selenium metal, the solvent was evaporated and residue was purified by column chromatography on silica gel (eluent: $CHCl_3$) to give **23a** (182.1 mg, 60% yield) as a pale yellow solid.

23a: mp 131–133 °C; ^{1}H NMR ($CDCl_3$/TMS) (a mixture of two conformers) δ 2.11 (s, 3 H), 2.682, 2.687 (s, 3 H), 5.27 (s, 2 H), 7.56 (s, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −137.3 (dd, J = 19.7, 16.0 Hz, 1 F), −152.0 (dd, J = 20.9, 16.0 Hz, 1 F), −161.3 (dd, J = 19.7, 19.5 Hz, 1 F), −164.7 (dd, J = 20.9, 19.5 Hz, 1 F); IR (KBr disk) 1734, 1725 (ν C=O) cm^{-1}; MS (m/e) 303 (8, M$^+$), 261 (30), 43 (100). Anal. Calcd for $C_{13}H_9F_4NO_3$: C, 51.50; H, 2.99; N, 4.62. Found: C, 51.73; H, 3.01; N, 4.71.

1-Benzoyl-3-(acetoxymethyl)-4,5,6,7-tetrafluoroindole (23b). In the same manner, the oxidation of **21b** (138 mg, 0.45 mmol) with selenium dioxide (101 mg, 0.91 mmol) was carried out. Chromatographic purification of crude product on a silica gel column (eluent: hexane–CH_2Cl_2) gave **23b** (82.1 mg, 50% yield) and unreacted **21b** (25.8 mg, 18.7% recovery).

23b: mp 113 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 2.07 (s, 3 H), 7.36 (s, 1 H), 7.40–7.90 (m, 5 H); ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ −125 (m, 1 F), −136 (m, 1 F), −144 (m, 1 H), −148 (m, 1 F); IR (KBr disk) 1734, 1730 (ν C=O) cm^{-1}; MS (m/e) 365 (4, M$^+$), 105 (100). Anal. Calcd for $C_{18}H_{11}F_4NO_3$: C, 59.19; H, 3.04; N, 3.83. Found: C, 58.87; H, 3.05; N, 3.88.

3-(Piperidinomethyl)-4,5,6,7-tetrafluoroindole (24). A mixture of piperidine (0.5 mL) and **23a** (29.4 mg, 0.097 mmol) was stirred at room temperature for 20 h. The excess amount of piperidine was evaporated and the residue was submitted to purification on a silica gel column (EtOAc/MeOH = 4/1) to give **24** (27 mg, 97% yield) as colorless leaves.

24: mp 166–168 °C [lit.[26] mp 168–169 °C]; ^{1}H NMR (CD_3OD/TMS) δ 1.40–1.70 (m, 6 H), 3.49 (m, 4 H), 3.76 ns, 2 H), 7.32 (s, 1 H); ^{19}F NMR (CD_3OD/$CFCl_3$) δ −152.1 (dd, J = 20.0, 16.2 Hz, 1 F), −162.6 (ddd, J = 18.9, 16.2, 4.4 Hz, 1 F), −169.0 (ddd, J = 18.9, 18.9, 2.0 Hz, 1 F), −172.3 (ddd, J = 20.0, 18.9, 4.4 Hz, 1 F); IR (KBr disk) 3120, 3030, 2995, 2935, 2850, 2820, 2800, 1530, 1478, 1340, 1290, 1082, 1063, 925, 790 cm^{-1}; MS (m/e) 286 (M$^+$, 26.5), 84 (100).

3-[(*N*-Methylpiperidiniumyl)methyl]-4,5,6,7-tetrafluoroindolyl Methyl Sulfate (26). A THF solution (0.2 mL) of dimethyl sulfate (296 mg, 2.35 mmol) was added dropwise to a THF solution (0.6 mL) of **24** (134.4 mg, 0.47 mmol) at 5 °C for a period of 30 min. Then, the reaction mixture was kept in the refrigerator overnight. The resulting precipitate was collected on a glass filter and dried to give **26** (138.7 mg, 72% yield) as colorless needles.

26: mp 152–155 °C [lit.[26] mp 151–153 °C]; ^{1}H NMR (CD_3OD/TMS) δ 1.50–2.00 (m, 6 H), 3.02 (s, 3 H), 3.41 (m, 4 H), 3.68 (s, 3 H), 4.75 (s, 2 H), 7.78 (s, 1 H); ^{19}F NMR (CD_3OD/$CFCl_3$) δ −151.4 (dd, J = 20.0, 16.2 Hz, 1 F), −160.6 (ddd, J = 18.8, 16.2, 3.2 Hz, 1 F), −166.5 (ddd, J = 19.1, 18.8, 12 Hz, 1 F), −169.1 (ddd, J = 20.0, 19.1, 3.2 Hz, 1 F); IR (KBr disk) 3150, 3100, 3020, 2980, 2940, 2890, 1535, 1485, 1245, 1200, 990, 740 cm^{-1}.

3-(Cyanomethyl)-4,5,6,7-tetrafluoroindole (27). A mixture of **26** (100 mg, 0.24 mmol), potassium cyanide (65 mg, 1.0 mmol), and water (0.5 mL) in DMF (1.3 mL) was refluxed for 2 h. The reaction mixture was poured into water (5 mL) and kept in a refrigerator overnight. The resulting precipitate was collected on a glass filter and dried to give **27** (53.3 mg, 96% yield) as colorless leaves.

27: mp 127–129 °C [lit.[25a] mp 129–130 °C]; ^{1}H NMR ($CDCl_3$/TMS) δ 3.95 (s, 2 H), 7.31 (s, 1 H), 8.46 (bs, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −154.0 (m, 1 F), −161.0 (m, 1 F), −167.1 (m, 1 F), −171.2 (m, 1 F); IR (KBr disk) 3280 (ν NH), 2260 (ν C≡N) cm^{-1}; MS (m/e) 228 (100, M$^+$).

4,5,6,7-Tetrafluoroindole-3-acetic Acid (28). A mixture of 20% aqueous KOH solution (1.3 mL) and **27** (49.6 mg, 0.218 mmol) was refluxed for 3 h. The reaction mixture was acidified with 6 N hydrochloric acid to pH 1. The resulting precipitate was collected on a glass filter and dried to give **28** (52.3 mg, 97% yield) as a white solid.

28: mp 207–209 °C [lit.[25a] mp 206–208 °C]; ^{1}H NMR (acetone-d_6/TMS) δ 3.86 (s, 2 H), 7.46 (s, 1 H), 11.06 (bs, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −154.0 (ddd, J = 20.0, 16.2, 2.4 Hz, 1 F), −162.0 (dddd, J = 19.0, 16.2, 4.5, 1.6 Hz, 1 F), −168.5 (dddd, J = 19.3, 19.0, 5.3, 2.4 Hz, 1 F), −172.5 (ddd, J = 20.0, 19.3, 4.5 Hz, 1 F); IR (KBr disk) 3320 (νNH), 3500–2500 (νOH), 1697 (νC=O) cm^{-1}.

3-(2-Nitroethenyl)-4,5,6,7-tetrafluoroindole (29). A mixture of nitromethane (2 mL), ammonium acetate (76 mg, 1.0 mmol), and **22a** (218 mg, 1.0 mmol) was stirred at 50 °C for 12 h. To the reaction mixture was added water (2 mL), and the solution was extracted with ether. The extract solution was dried over anhydrous $MgSO_4$, concentrated, and submitted to purification on a silica gel column (eluent: benzene–CH_2Cl_2) to give **29** (235 mg, 90% yield) as a yellow solid.

29: mp 213–217 °C dec; ^{1}H NMR ($CDCl_3$/TMS) δ 7.70 (s, 1 H), 7.77 (d, J = 13.6 Hz, 1 H), 8.24 (d, J = 13.6 Hz, 1 H), 9.02 (bs, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −147.5 (dd, J = 20.2, 15.9 Hz, 1 F), −159.5 (ddd, J = 19.4, 15.9, 2.8 Hz, 1 F), −164.9 (dd, J = 19.4, 1..3 Hz, 1 F), −167.5 (ddd, J = 20.2, 19.3, 2.8 Hz, 1 F); IR (KBr disk) 3230 (νNH), 1624 (νC=C), 1475 (νNO), 1320 (νNO) cm^{-1}; MS (m/e) 261 (10, M$^+$), 260 (100). Anal. Calcd for $C_{10}H_4F_4N_2O_2$: C, 46.17; H, 1.55; N, 10.77. Found: C, 45.99; H, 1.52; N, 10.53.

4,5,6,7-Tetrafluorotryptamine (30). A mixture of **29** (129 mg, 0.495 mmol) and lithium aluminum hydride (190 mg) in ether (5 mL) was refluxed for 3 h. Water (2 mL) and ether (10 mL) were added to the reaction mixture at ice-cooled temperature and the resulting solid was separated by filtration on a glass filter. The solid was washed with ether (10 mL × 3) and the combined ethereal solution was dried over anhydrous Na_2CO_3. The solvent was removed and residue was recrystallized from Et_2O–hexane to give **30** (105 mg, 92% yield) as a white solid.

30: mp 134–136 °C [lit.[25a] mp 136–138 °C]; ^{1}H NMR (acetone-d_6/TMS) δ 3.00 (bs, 2 H), 3.05 (t, J = 7.4 Hz, 2 H), 3.54 (t, J = 7.4 Hz, 2 H), 7.28 (s, 1 H), 11.18 (bs, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −153.9 (ddd, J = 20.3, 16.1, 2.5 Hz, 1 F), −162.1 (ddd, J = 19.2, 16.1, 4.7 Hz, 1 F), −169.0 (ddd, J = 19.3, 19.2, 2.5 Hz, 1 F), −172.9 (ddd, J = 20.3, 19.3, 4.7 Hz); IR (KBr disk) 3460, 3370, 3310 cm^{-1} (νNH); MS (m/e) 232 (3, M$^+$), 203 (27, M$^+$ − $CHNH_2$), 30 (100).

2-Phenyl-4-[(1-acetyl-4,5,6,7-tetrafluoroindolyl)-methylidene]-5-oxazolone (31). A mixture of **22** (1.00 g, 4.61 mmol), acetic anhydride (2 mL), sodium acetate (350 mg, 4.27 mmol), and hippuric acid (690 mg, 3.85 mmol) in THF (8 mL) was refluxed for 12 h. To the reaction mixture was added hexane (5 mL), and the resulting precipitate was collected on a glass filter and washed with dichloromethane to give **31** (1.47 g, 91% yield) as a yellow solid.

31: mp 235–236 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 2.86 (d, J = 1.1 Hz, 3 H), 7.56 (m, 2 H), 7.64 ns, 1 H), 7.65 (m, 1 H), 8.14 (m, 2 H), 8.97 (s, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −137.1 (dd, J = 19.9, 15.7 Hz, 1 F), −151.9 (dd, J = 21.1, 15.7 Hz, 1 F), −160.3 (dd, J = 19.9, 19.6 Hz, 1 F), −163.0 (dd, J = 21.1, 19.6 Hz, 1 F); IR (KBr disk) 1780, 1747 (νC=O), 1660, 1650 (νC=C, νC=N) cm^{-1}; MS (m/e) 402 (2, M$^+$), 105 (100). Anal. Calcd for $C_{20}H_{10}F_4N_2O_3$: C, 59.71; H, 2.51; N, 6.96. Found: C, 59.74; H, 2.37; N, 7.24.

Methyl (*Z*)-2-Benzamido-3-(4,5,6,7-tetrafluoroindolyl)-2-propenoate (32). A mixture of **31** (1.36 g, 3.37 mmol) and triethylamine (1 mL) in methanol (100 mL) was refluxed for 1 h. The solvent was evaporated from the reaction mixture and the residue was recrystallized from methanol–CH_2Cl_2–hexane to give **32** (1.20 g, 91% yield) as a white solid.

32: mp 243–245 °C; ^{1}H NMR (DMSO-d_6/TMS) δ 3.74 (s, 3 H), 7.50–7.70 (m, 3 H), 7.89 (s, 1 H), 7.95 (s, 1 H), 8.04 (m, 2 H), 9.78 (bs, 1 H), 12.80 (bs, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −153.2 (dd, J = 19.9, 16.1 Hz, 1 F), −160.5 (ddd, J = 19.3, 16.1, 3.4 Hz, 1 F), −166.6 (t, J = 19.3 Hz, 1 F), −169.3 (ddd, J = 19.9, 19.3, 3.4 Hz, 1 F); IR (KBr disk) 3247 (νNH), 1690 (νC=O), 1665 (νC=C), 1646 (νC=O), 1537 (δNH) cm^{-1}; MS (m/e) 392 (5, M$^+$), 105 (100). Anal. Calcd for $C_{19}H_{12}F_4N_2O_3$: C, 58.17; H, 3.08; N, 7.14. Found: C, 58.10; H, 3.15; N, 7.24.

***N*-Benzoyl-4,5,6,7-tetrafluorotryptophan Methyl Ester (33).** A mixture of **32** (1.00 g, 2.55 mmol), 5% palladium/carbon (250 mg), and methanol (10 mL) in a Pyrex reaction vessel was placed in a stainless steel autoclave and hydrogenation was carried out at 50 °C and 10 atm of hydrogen for 17 h. Separation of the catalyst from the reaction mixture by filtration with a fine glass filter and evaporation of the solvent gave **33** (951 mg, 95% yield) as a white solid.

33: mp 142–143 °C; ^{1}H NMR (acetone-d_6/TMS) δ 3.35 (dd, J = 14.7, 9.4 Hz, 1 H), 3.52 (dd, J = 14.7, 5.2 Hz, 1 H), 3.71 (s, 3 H), 5.02 (dd, J = 9.4, 5.2 Hz, 1 H), 7.40–7.52 (m, 5 H), 7.82–8.00 (m, 3 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −153.5 (ddd, J = 20.0, 16.1, 2.2 Hz, 1 F), −161.8 (ddd, J = 19.3, 16.1, 4.4 Hz, 1 F), −168.4 (td, J = 19.3, 2.2 Hz, 1 F), −172.3 (ddd, J = 20.0, 19.3, 4.4 Hz, 1 F); IR (KBr disk) 3366 (νNH), 1738, 1644 (νC=O), 1543 (δNH) cm^{-1}; MS (m/e) 394 (2, M$^+$), 105 (100). Anal. Calcd for $C_{19}H_{14}F_4N_2O_3$: C, 57.87; H, 3.58; N, 7.10. Found: C, 57.89; H, 3.82; N, 6.97.

4,5,6,7-Tetrafluorotryptophan (25). A mixture of **33** (85.7 mg, 0.218 mmol) and concentrated hydrochloric acid (30 mL) was heated at 110 °C (reflux) for 10 h. The reaction mixture was cooled, washed with ether, and concentrated in vacuo. The residue was dissolved in a small amount of water and neutralized (pH 7.0) with aqueous ammonia. The resulting precipitate was collected on a glass filter and dried to give **23** (38.1 mg, 64% yield) as a white solid.

25: mp 257–259 °C dec [lit.[25b] mp 258–260 °C]; ^{1}H NMR (CD_3OD/TMS) δ 3.19 (dd, J = 15.2, 9.2 Hz, 1 H), 3.55 (dd, J = 15.2, 4.6 Hz, 1 H), 3.86 (dd, J = 9.2, 4.6 Hz, 1 H), 7.31 (s, 1 H); ^{19}F NMR (CD_3OD/$CFCl_3$) δ −153.3 (ddd, J = 19.4, 16.2, 1.7 Hz, 1 F), −162.3 (ddd, J = 18.5, 16.2, 4.2 Hz, 1 F), −168.5 (ddd, J = 19.0, 18.5, 1.7 Hz, 1 F), −172.3 (ddd, J = 19.4, 19.0, 4.2 Hz, 1 F); IR (KBr disk) 3465 (νNH), 3500–2700 (νNH), 1600 (νC=O), 1530 (δNH) cm^{-1}.

***N*,*O*-Bis(trimethylsilyl)-α-(trifluoromethyl)-β-alanine (34).** Hexamethyldisilazane (HMDS) (12.91 g, 40 mmol) was added to a solution of α-(trifluoromethyl)acrylic acid (α-TFMAA) (5.6 g, 20 mmol) in dry dichloromethane (56 mL) at 0 °C, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo to remove the solvent and any excess amount of HMDS, giving **34** (12.03 g, 100% yield) as a colorless liquid.

34: ^{1}H NMR ($CDCl_3$) δ 0.047 (s, 9 H), 0.31 (s, 9 H), 2.99–3.21 (m, 2 H), 3.25 (m, 1 H); ^{19}F NMR (acetone-d_6/$CFCl_3$) δ −66.3 (dd, J = 8.9, 3.1 Hz); IR (neat) 3360, 2940, 2845, 1730 (νC=O) cm^{-1}. Anal. Calcd for $C_{10}H_{22}F_3NO_2Si_2$: C, 39.84; H, 7.36; N, 4.65. Found: C, 39.68; H, 7.58; N, 4.51.

α-(Trifluoromethyl)-β-alanine (α-TFM-β-Ala). Methanol (20 mL) was added to **34** (4.00 g, 13.3 mmol) at 0 °C and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo to give α-TFM-β-Ala (1.98 g, 97% yield) as a colorless powder. Further purification was performed by recrystallization from MeOH/Et_2O for elemental analysis.

α-TFM-β-Ala: mp 125–126 °C dec; ^{1}H NMR (D_2O/TSP) δ 3.41–3.65 (m); ^{19}F NMR (D_2O/CF_3COOH) δ 8.70 (d, J = 8.9 Hz) (−68.30 from $CFCl_3$); IR (KBr disk) 3600–2500 (νNH), 1665 (δNH), 1610 (νC=O) cm^{-1}. Anal. Calcd for $C_4H_6NO_2F_3$: C, 30.58; H, 3.85; N, 8.92. Found: C, 30.30; H, 4.05; N, 8.66.

Direct Synthesis of α-TFM-β-Ala with Ammonia. A saturated solution of ammonia in dry dichloromethane (500 mL) was prepared by introducing ammonia gas to dry dichloromethane at 0–5 °C. To this solution was added a solution of α-TFMAA (8.0 g, 57.1 mmol) in dry dichloromethane (50 mL) with stirring. After the addition was complete, additional ammonia gas was introduced for another 10 min, and the mixture was stirred overnight. Then, the solvent was evaporated under reduced pressure and ether (100 mL) was added to the residue. The resulting precipitate was collected on a glass filter to give α-TFM-β-Ala (8.95 g, 100% yield) as a colorless powder.

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The Absolute Configuration of Jesromotetrol and Other *ent*-Rosenes

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The absolute configuration of jesromotetrol has been confirmed by the application of X-ray data published by other authors and the CD study of a derivative. The absolute configurations of three new products with rosene skeletons were established from spectral data, chemical transformations, and correlation with compounds with known absolute configurations.

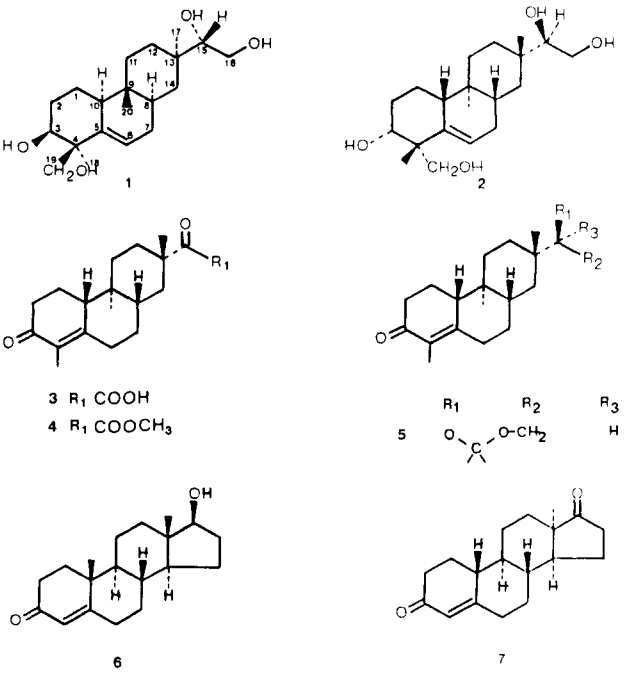
Introduction

Confusion abounds about diterpenes isolated from *Palafoxia*. For instance, Bohlmann et al.[1] first assigned a pimarane structure to some, later altering the identification to rosane,[2] and, later still, to *ent*-rosane,[3] arguing that the pimarane and rosane series can be clearly differentiated by their ^{13}C NMR data. They applied the same reasoning to other structures previously identified[4] as pimaranes. Elsewhere,[5,6] *ent*-isopimarene diterpenes have also been corrected to *ent*-rosenes.

In this paper a definitive sabsolute configuration is assigned to jesromotetrol[7,8] and related products isolated from various species of *Palafoxia*.

Earlier, the absolute configuration of jesromotetrol was given as **1**[7] although the X-ray diffraction data to support this assignment were not published at the time. The ^{13}C NMR data of jesromotetrol were analyzed[8] and were taken as confirming the structure. We ourselves reported[9] three new products that were correlated with **1**. However, the X-ray data for jesromotetrol, when published, only established its relative configurations.[10]

In view of the inconclusive nature of these data we decided to study jesromotetrol again in order to determine its absolute configuration. It was oxidized with Jones' reagent to yield a diketo acid **3**, from which methyl ester **4** was prepared, identified by its spectroscopic data (IR 3500–2880 cm^{-1}; UV 265 nm; no vinyl protons and a methyl on a conjugated double bond in ^1H NMR, 1.95 (d, J = 0.5, 3 H)). Compound **3** has an A, B, and C ring junction with an unsaturated α,β-ketone group in ring A, as do products **6** and **7**, earlier studied by circular dichroism[11-13] and which



were ideal for comparison purposes, with a negative Cotton effect at 340 nm and a positive one at around 250 nm, values similar to those shown by **3**. The absolute configuration of jesromotetrol was thus established as (3*R*,4*R*,8*S*,9*S*,10*R*,13*S*,15*R*)-3,15,16,18-tetrahydroxy-*ent*-ros-5-ene (**2**), enantiomeric to that previously assigned. All structures correlated with jesromotetrol[9] should be corrected accordingly.

Three products not previously reported were also isolated and were identified as 3-epijesromotetrol (**8**, (3*S*,4*R*,8*S*,9*S*,10*R*,13*S*,15*R*)-3,15,16,18-tetrahydroxy-*ent*-

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