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An Efficient Chemoenzymatic Approach to (*S*)-γ-Fluoroleucine Ethyl Ester

John Limanto,* Ali Shafiee,* Paul N. Devine, Veena Upadhyay, Richard A. Desmond, Bruce R. Foster, Donald R. Gauthier, Jr., Robert A. Reamer, and R. P. Volante

Department of Process Research, Merck Research Laboratories, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065

john_limanto@merck.com; ali_shafiee@merck.com

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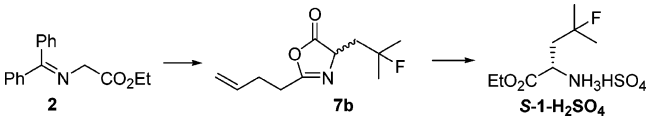
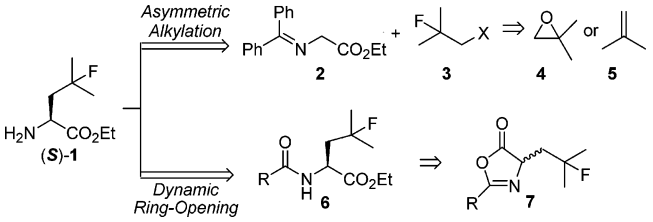


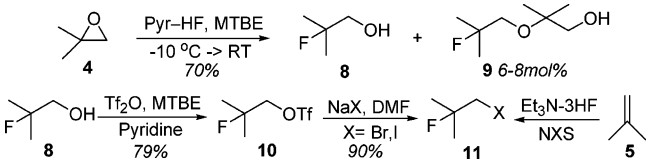
An asymmetric synthesis of (*S*)-γ-fluoroleucine ethyl ester **1** is described. The key transformation involves a lipase-catalyzed dynamic ring-opening of 2-(3-butenyl)azlactone **7b** with EtOH to give amide ester (*S*)-**6b** in 84% enantiomeric excess. Removal of the *N*-pentenoyl group with *N*,*N*′-dibromodimethylhydantoin in the presence of trifluoroacetic acid afforded the titled compound, which was isolated as its hydrogen sulfate salt in 75% yield and >97% ee.

Fluorinated amino acids and their derived peptides have been widely employed as potential pharmaceutical agents due to their broad biological properties, including enzyme inhibitors, receptor antagonists, and lipophilicity enhancing agents.[1] While much development has focused on the preparation of various fluorinated analogues of natural and nonproteinogenic amino acids,[2] asymmetric syntheses of γ-fluoro-α−amino acids still remain a challenge.[3] In this regard, stereoselective incorporations of the γ-F-containing side chain have been mostly executed by either a chiral auxiliary-directed diastereoselective alkylation[4] or a chiral phase transfer-catalyzed alkylation[3c] of *N*-protected precursors; albeit, only modest stereoselectivities (<40% de or ee) were usually obtained in the latter cases.

SCHEME 1. Possible Approaches to (*S*)-γ-Fluoroleucine Ethyl Ester



SCHEME 2. Preparation of Fluorine-Containing Electrophiles



We recently required an asymmetric route to γ-fluoroleucine ethyl ester **1**, which has been previously employed to prepare a cyclosporin A derivative for probing the immunosuppressive activity of the drug.[4b] While the previous approach to **1**, which relies on Schöllkopf's bis-lactim ether methodology, allows access to the molecule, the high cost of this bis-lactim ether precursor and the low-yielding diastereoselective alkylation step prompted us to develop a more practical and efficient route.[4b]

Establishment of the stereochemistry in the product was initially envisioned via an asymmetric alkylation of *N*-diphenylmethylene glycine ethyl ester **2** with fluorine-containing electrophiles **3** (X = OTf, Br, I), which could in turn be prepared by a regioselective hydrofluorination[5] of isobutylene oxide **4** or a halofluorination[6] of isobutylene **5** (Scheme 1). Hence, subjection of **4** to Olah's reagent (Pyr·9HF) in MTBE at −10 °C → rt afforded fluoro alcohol **8**[4b] in 75% assay yield as a single regioisomer, along with 6−8% of dimer alcohol **9** (Scheme 2).[7] Formation of the dimeric side product increased dramatically at much higher concentrations of substrate and/or HF, which is consistent with previously reported observations.[5a] Subsequent triflation was carried out under standard conditions (Tf_2O, MTBE, −10 °C, 1 h) to yield **10** in 79% yield. The corresponding halides **11** were prepared by

(1) (a) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. In *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier Biomedical Press: Amsterdam, The Netherlands, 1993. (b) Welch, J. T.; Eswarakrishan, S. In *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (c) Gelb, M. H.; Lin, Y.; Pickard, M. A.; Song, Y.; Vederas, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4932−4942. (d) Kollonitsch, J. In *Biomedical Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Elsevier Biomedical Press: Amsterdam, The Netherlands, 1982. (e) Bey, P., J. In *Enzyme-Activated Irreversible Inhibitors*; Seiler, N., Jung, M. J., Koch-Weser J., Eds.; Elsevier/North-Holland Biomedical Press: Amsterdam, The Netherlands, 1978.

(2) For representative examples, see: (a) Tsushima, T.; Kawada, K.; Ishihara, S.; Uchida, N. *Tetrahedron Lett.* **1988**, *44*, 5375−5387. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123 and references therein. (c) O'Donnel, M. J.; Barney, C. L.; McCarthy, J. R. *Tetrahedron Lett.* **1985**, *26*, 3067−3070. (d) Bey, P.; Ducep, J. B.; Schirlin, D. *Tetrahedron Lett.* **1984**, *25*, 5657−5660.

(3) For a few previously reported syntheses, see: (a) Haufe, G.; Laue, K. W.; Triller, M. U. *Tetrahedron* **1998**, *54*, 5929−5938. (b) Kröger, S.; Haufe, G. *Amino Acids* **1997**, *12*, 363−372. (c) Haufe, G.; Kröger, S. *Amino Acids* **1996**, *11*, 409−424. (d) Kukhar, V. P.; Soloshonok, V. A. In *Fluorine-containing Amino Acids—Synthesis and Properties*; Wiley: Chichester, UK, 1995. For a recent review on syntheses of fluorinated amino acids, see: Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711−6745.

(4) (a) Kröger, S.; Haufe, G. *Liebigs Ann.* **1997**, 1201−1206. (b) Papageorgiou, C.; Borer, X.; French, R. R. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 267−272.

(5) For examples, see: (a) Umezawa, J.; Takahashi, O.; Furuhashi, K.; Nohira, H. *Tetrahedron*: *Asymmetry* **1993**, *4*, 2053−2060. (b) Ammadi, F.; Chaabouni, M. M.; Amri, H.; Baklouti A. *Synth. Commun.* **1993**, *23*, 2389−2395. (c) Suga, H.; Hamatani, T.; Schlosser, M. *Tetrahedron* **1990**, *46*, 4247−4254. (d) Hamatani, T.; Matsubara, S.; Matsuda, H.; Schlosser, M. *Tetrahedron* **1988**, *44*, 2875−2881.

(6) See for example: (a) Haufe, G.; Alvernhe, G.; Andre, L.; Emet, T.; Goj, O.; Kröger, S.; Sattler, A. *Org. Synth.* **1999**, *76*, 159−168. (b) Barluenga, J.; Campos, P. J.; González, J. M.; Suárez, J. L. *J. Org. Chem.* **1991**, *56*, 2234−2237.

(7) While the alcohol can be purified by a vacuum distillation, a facile HF elimination to give isobutyraldehyde has been observed upon storage in Pyrex glassware at rt. It is, however, stable upon storage in a Teflon flask or in glassware at temperatures <−20 °C.

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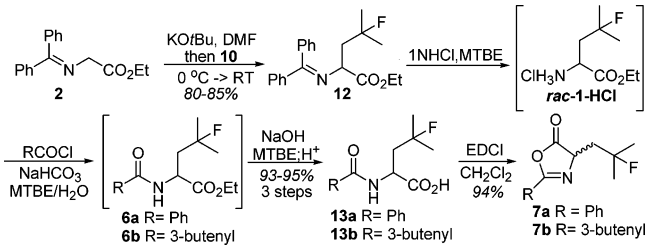
SCHEME 3. Synthesis of Azlactone 7

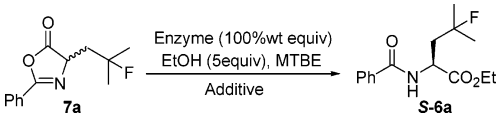


either a Finkelstein displacement of the triflate using NaX (X = Br, I) in DMF or a halofluorination of **5** using $Et_3N{\cdot}3HF$ and NXS (X = Br, I). Unfortunately, alkylations of **2** (or its *tert*-butyl ester analogue) under chiral phase-transfer catalysis were unsuccessful. Only hydrolysis of triflate **10** was observed under heterogeneous conditions (toluene, 50%KOH/H_2O) using *cinchona* alkaloid-derived catalysts[8] or Maruoka's C_2-symmetric quaternary ammonium salts,[9] and no reaction was observed under homogeneous conditions (CH_2Cl_2, phosphazane bases, *cinchona*-derived catalysts)[10] or when fluorohalides **11** were employed in the reactions.

Concurrently, a dynamic kinetic resolution[11] ring opening (deracemization) of 5(4*H*)-oxazolones (i.e., azlactones) was investigated as an alternative way for introducing the stereochemistry in the molecule. We envisioned that an enzymatic[12] or nonenzymatic[13] ring-opening of azlactone **7** with EtOH would furnish enantiomerically enriched *N*-protected γ-fluoroleucine ethyl ester **6**. In this regard, the requisite azlactones (**7a**: R = Ph, **7b**: R = 3-butenyl) were prepared according to Scheme 3. The fluorine-containing side chain was incorporated via deprotonation of **2** with KO^{t}Bu in DMF[3a] at 0 °C followed by alkylation with fluoro-triflate **10**, affording racemic product **12** in 81% yield. Subsequent transformations to the desired amide acid **13** were accomplished in 95% overall yield in a 3-step, one-pot process, involving imine hydrolysis with 1 N HCl/MTBE (**12** → *rac*-**1**·HCl), amide formation under Schotten−Baumman conditions (RCOCl, $NaHCO_3$, MTBE/H_2O, *rac*-**1**·HCl → **6**), and saponification with aqueous NaOH/THF-MTBE (**6** → **13**). Cyclodehydration[14] of **13** was then performed using EDCI in CH_2Cl_2 to give the desired azlactone **7** in 94% isolated yield.

Considering that a higher degree of asymmetry has been generally observed under enzymatic conditions,[12,13] our initial studies focused on screening a library of hydrolytic enzymes that would catalyze the ring-opening of **7a**. Applying the protocol developed by Sih and co-workers,[12b] a solution of azlactone **7a** in MTBE was exposed to commercial hydrolytic enzymes in the presence of 5 equiv of EtOH at 50 °C. As expected, no significant background alcoholysis (<2%) was observed in the absence of any enzyme even after 2 days (entry 1, Table 1). On the other hand, the ring-opening ethanolysis was complete in the presence of the screened enzymes after 24 h, affording the desired product in 0−89% enantiomeric excess. For further optimization, we selected an immobilized form of lipase B (Novozyme-435) from *C. Antarctica*, which affected the transformation in good enantioselectivity (70% ee, Table 1) during the initial screening. While running the reaction at lower temperature (25−37 °C) increased the reaction time, only

TABLE 1. Ring Opening of Azlactone 7a with Immobilized Lipase B (Novozyme-435)



				results	
enzymes[a]	additive	temp (°C)	time (h)	ee (%)[b]	yield (%)[c]
none	none	50	48		<2
immobilized lipase B	none	50	12	70	
(Novozyme-435)	none	37	16	84	
	Et_3N (50 mol %)	37	4	94	73
	Et_3N (50 mol %)	**25**	**4**	**95**	**80**

[a] Equal weight of enzyme was used during investigation. [b] Analyzed by chiral HPLC (chiralcel OD-H). [c] Isolated yields, not determined if blank.

a slight increase in enantioselectivity was observed. Subjection of the product to the reaction conditions exhibited no erosion in the entity and enantioselectivity, suggesting that the stereochemistry of the product was established selectively during the ring-opening process. Further investigations revealed that faster reaction time and higher enantioselectivity were obtained when an organic base was employed during the reaction.[15] The best results were obtained with 20 mol % of Et_3N and 5 equiv of EtOH at rt for 4 h, affording the ethyl ester product in 95% ee and 80% isolated yield. Due to the inherent presence of water in the enzyme, less than 10% of acid **13a** was typically observed during the transformation. While attempts to dry the enzyme or perform the reaction in the presence of molecular sieves inhibited the enzyme reactivity, the use of excess EtOH (>10 equiv) resulted in a lower enantioselectivity.

Despite the effective enzymatic ring-opening process, removal of the benzoyl protecting group proved to be problematic. Subjection of (*S*)-**6a** to EtOH in the presence

(8) See for example: (a) Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403−2409 and references therein. (b) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347−5350. (c) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507−4518.

(9) (a) Ooi, T.; Uematsu, Y.; Maruoka, K. *Tetrahedron Lett.* **2004**, *45*, 1675−1678. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228−5229.

(10) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775−8778.

(11) For reviews, see: (a) Stecher, H.; Faber, K. *Synthesis* **1997**, 1−16. (b) Ward, R. S. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1475−1490. (c) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−56.

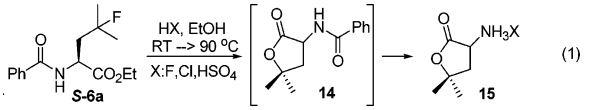
(12) (a) Turner, N. J.; Winterman, J. R.; McCague, R.; Parratt, J. S.; Taylor, S. J. C. *Tetrahedron Lett.* **1995**, *36*, 1113−1116. (b) Crich, J. Z.; Brieva, R.; Marquart, P.; Gu, R. L.; Flemming, S.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 3252−3258. (c) Bevinakatti, H. S.; Banerji, A. A.; Newadkar, R. V.; Mokashi, A. A. *Tetrahedron*: *Asymmetry* **1992**, *3*, 1505−1508. (d) Gu, R. L.; Lee, I. S.; Sih, C. J. *Tetrahedron Lett.* **1992**, *33*, 1953−1956.

(13) (a) Gottwald, K.; Seebach, D. *Tetrahedron* **1999**, *55*, 723−738. (b) Xie, L.; Hua, W.; Chan, A. S. C.; Leung, Y. C. *Tetrahedron*: *Asymmetry* **1999**, *10*, 4715−4728. (c) Xie, L. J.; Hua, W. T. *Chinese Chem. Lett.* **1998**, *9*, 605−606. (d) Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154−3155.

(14) See for examples: (a) Tripathy, P. K.; Mukerjee, A. K. *Synthesis* **1984**, 418−422. (b) Hoyng, C. F.; McKenna, M. G.; Walters, D. L. *Synthesis* **1982**, 191−193. (c) Chen, F. M. F.; Kuroda, K.; Benoiton, N. L. *Synthesis* **1979**, 230−232.

(15) Although the role of the base is unclear at this moment, the same effects on a similar enzymatic transformation have been previously observed: see ref 12a.

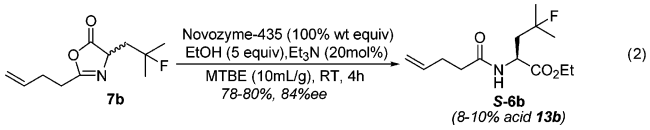
of H_2SO_4, HCl, or Pyr·9HF[16] resulted only in a defluorolactonization, giving initially lactone **14**, which underwent subsequent hydrolysis to aminolactone **15** as observed by ^{1}HNMR spectroscopy (eq 1). Alternative



(1)

hydrolysis conditions using triflic anhydride/pyridine[17] or Meerwein's salt[18] also gave des-fluorinated products. This undesired lactonization prompted us to investigate 4-pentenoyl as the nitrogen protecting group, which has been previously shown to undergo oxidative cleavage under mild conditions.[19] The requisite azlactone **7b** was then prepared similarly according to Scheme 3.

Our initial studies revealed that subjection of **7b** to the optimized enzymatic conditions (Novozyme-435, 5 equiv of EtOH, 50 mol % of Et_3N, MTBE, rt) afforded the desired amide ester (*S*)-**6b** after 4 h in 84% ee and 78−80% yield, along with 8−10% of acid **13b** (eq 2).



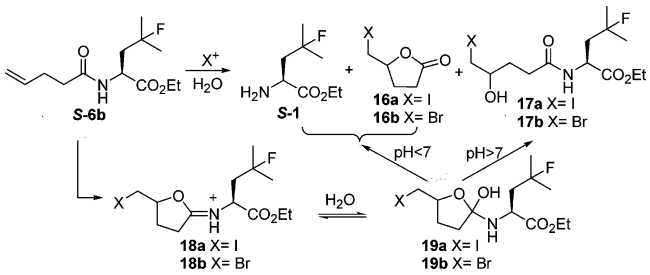
(2)

Variation in the reaction parameters (i.e., solvent, base additive or alcohol, temperature) showed virtually no improvement in enantioselectivity. For example, while MTBE proved to be the best solvent among others screened (MeCN, toluene, THF, CH_2Cl_2, iPAc), Et_3N was superior to other amines (DBU, 2,6-lutidine, DABCO). Furthermore, ring-opening with MeOH gave substantially a much lower enantioselectivity (<60%), while the conversion rate was relatively poor using ^{n}BuOH even after 3 days at 50 °C (<40%). A much lower conversion and enantioselectivity (80%, 70% ee, respectively) were also observed when the enzyme loading was reduced to about 75% weight equivalent.

Further experiments revealed that addition of 1 mol equiv of H_2O resulted in an increase of enantioselectivity (95% ee), albeit a lower yield was obtained (58% assay). Under these reaction conditions, the corresponding acid **13b** was obtained as the major side product in 30% assay yield and 67% ee. To understand the formation of the acid, the product **6b** was re-subjected to the enzyme in the presence of 10 equiv of H_2O and Et_3N. After 3 days at 50 °C, no decomposition or hydrolysis of the product was observed. Although slightly lower enantioselectivity (84% vs 95% ee) was observed without additional H_2O, higher yields (79% vs 58%) were reproducibly obtained under "anhydrous" conditions, making it the preferred method for the transformation.

With *N*-pentenamide fluoroleucine in hand, liberation of the free amino acid ester was initially carried out employing the protocol developed by Fraser-Reid and coworkers.[20] Hence, subjection of (*S*)-**6b** to 3 equiv of I_2 in a 1:1 mixture of THF:H_2O for 30 min at rt gave the free amine **1**, which was isolated as its HCl salt in 60% yield, as well as 20% side products derived from iodohydrins **17a**[21] (Scheme 4). Variations of reaction temperature, solvent, and water concentration showed virtually no

SCHEME 4. Deprotection of the *N*-Pentenamide Group



improvement in the reaction yields. The necessary use of a large excess amount of I_2 and the significant formation of iodohydrins byproducts prompted us to seek alternative deprotection methods.

Oxidative removal of the pentenoyl group was subsequently investigated using commercially inexpensive *N,N′*-dibromodimethylhydantoin (DBDMH). Hence, treatment of **6b** with 0.6 equiv of DBDMH in 5%H_2O/MeCN at rt gave after 3 h a 1:1 mixture of bromohydrins **17b** and the free amine. Considering that the formation of free amine (*S*)-**1** and bromolactone **16b** would be favored under acidic conditions (Scheme 4), the effect of acid additives on hydrolysis of the imidate ester **18b** was investigated.[22] To ascertain that the transformation did proceed through such an intermediate, amide (*S*)-**6b** (84% ee) was subjected to DBMDH and 2 equiv of trifluoroacetic acid (TFA) in MeCN. After 1 h at rt, exclusive formation of a 1:1 mixture of the diastereomeric cyclic imidate esters **18b** was observed by ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy. Addition of H_2O (3 equiv) to the reaction mixture, followed by aging for 12 h, gave a 9:1 molar ratio of the free amine and bromohydrins **17b**. The desired amino acid ester was isolated from IPAc or MTBE as its hydrogen sulfate salt in 60% yield and 97% ee, demonstrating a 13% enantiopurity upgrade from the starting material. Further investigation led to the optimum reaction conditions in which subjection of a 0.2 M solution of

(16) Jagers, E.; Gehrmann, K.; Koll, H. P. Verfahren zur Herstellung von Aminosäureestern, European Patent 0244711A1, Nov 11, 1987.

(17) Charette, A. B.; Chua, P. *Synlett* **1998**, 163−165 and references therein.

(18) Hanessian, S. *Tetrahedron Lett.* **1967**, *16*, 1549−1552.

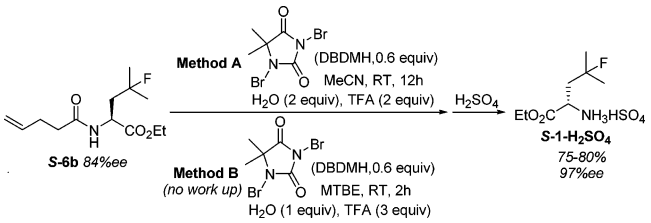
(19) *N*-4-Pentenamide derivatives have been shown to undergo efficient iodolactonization; see for examples: (a) Blot, V.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2004**, *69*, 1196−1201. (b) Rozners, E.; Liu, Y. *Org. Lett.* **2003**, *5*, 181−184. (c) Moon, H.; Eisenberg, S. W. E.; Wilson, M. E.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1994**, *59*, 6504−6505. (d) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079−1085.

(20) Various amino acid esters have been generated from their corresponding *N*-4-pentenamide esters, see: Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 7920−7926.

(21) Assigned by ^{1}H, ^{19}F, ^{13}C NMR, APT, and HMBC experiments. For exclusive formation of iodohydrin via iodoimidation−hydrolysis under basic conditions, see: (a) Maligres, P. E.; Weissman, S. A.; Upadhyay, V.; Cianciosi, S. J.; Reamer, R. A.; Purick, R. M.; Sager, J.; Rossen, K.; Eng, K. K.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron* **1996**, *52*, 3327−3338. (b) Maligres, P. E.; Upadhyay, V.; Rossen, K.; Cianciosi, S. J.; Purick, R. M.; Eng, K. K.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 2195−2198.

(22) For discussions on hydrolyses of cyclic imidate ester, see: (a) Deslongchamps, P.; Dubé, S.; Lebreux, C.; Patterson, D. R.; Taillefer, R. J. *Can. J. Chem.* **1975**, *53*, 2791−2807. (b) Pletcher, T. C.; Koehler, S.; Cordes, E. H. *J. Am. Chem. Soc.* **1968**, *90*, 7072−7076. (c) Kandel, M.; Cordes, E. H. *J. Org. Chem.* **1967**, *32*, 3061−3066. (d) Cunningham, B. A.; Schmir, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 551−558.

SCHEME 5. Optimized Conditions for Generation of γ-Fluoroleucine·H_2SO_4



(*S*)-**6b** in MeCN to DBDMH in the presence of H_2O (2 equiv) and TFA (2 equiv) at rt for 12 h, followed by treatment of the resulting free amine in MTBE or iPAc with H_2SO_4 (1 equiv) gave (*S*)-**1**·H_2SO_4 in 80% yield and 97% enantiopurity (Scheme 5). Alternatively, the reaction could be carried out in MTBE in the presence of H_2O (1 equiv) and TFA (3 equiv) at rt for 2 h, at which a complete hydrolysis of the ketoimidate ester **18b** was obtained. Addition of H_2SO_4 directly to the reaction mixture at rt, followed by cooling to 0 °C for 2 h, resulted in crystallization of the bisulfate salt, which was isolated in 75% yield and 97% enantiopurity (Scheme 5). The product isolated from the latter procedure, however, was typically contaminated with 6−8 wt % of dimethylhydantoin byproducts, which can be easily removed by a single recrystallization from MeCN to afford pure (*S*)-**1**·H_2SO_4 in 94% recovery (70% overall yield) and >99% enantiomeric excess.[23]

In summary, we have developed a novel route to (*S*)-γ-fluoroleucine ethyl ester **1** via a dynamic kinetic resolution of azlactone **7b** catalyzed by immobilized lipase B (Novozyme-435). Such transformation allows for the reaction to be performed in organic media and provides ease of product isolation. In this regard, we demonstrated that the lipase-catalyzed ring-opening of 3-butenylazlactone **7b** afforded the *N*-pentenamide ester **6b** in 80% yield and 84% ee. Considering the tendency of the molecule to undergo defluoro-lactonization under acidic conditions, the choice of the R group in **7** was determined such that the amide functionality in the ring-opened product **6** can be removed under mild conditions. Hence, subsequent treatment with DBMDH, TFA, and H_2O in MeCN or MTBE liberated the free amine, which was isolated as its hydrogen sulfate ((*S*)-**1**·H_2SO_4) in >97% ee and 75−80% yield.

Experimental Section

Enzymatic Dynamic Kinetic Ethanolysis of Azlactone 7b. To a solution of the azlactone **7b** (4 kg, 18.8 mol, 1 equiv) in MTBE (20 L, 5 mL/g) was added EtOH (5.5 L, 93.8 mol, 5 equiv), Et_3N (524 mL, 3.76 mol, 0.2 equiv), and immobilized lipase B (Novozyme-435) (4 kg, 100 wt % equiv). The resulting suspension was aged at rt for 4 h, at which a complete consumption of starting material was observed. The suspension was then heated to 35 °C for 0.5 h and then filtered. The enzyme was washed with MTBE until the filtrate turned colorless. The filtrate was then successively washed with 1 N aqueous HCl (10L), saturated aqueous $NaHCO_3$ (10 L), and brine, and then concentrated in vacuo to give crude ester, which can be deprotected directly without further purification (4 kg, 82%). If desired, the crude oil can be purified by SiO_2 gel chromatography (3:1 hexanes: MTBE) to give pure product as a white solid in 87% ee as analyzed by chiral HPLC spectroscopy (Chiralcel OD-H, 4% iPA/hexanes, 1 mL/min, 35 °C, 210 nm, retention time for (*S*)-*en*t 13.68 min, and (*R*)-*ent* 7.42 min). $[\alpha]^{25}_D$ −32.9 (*c* 0.56, EtOH). Mp: 35−37 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (1H, br), 5.82 (1H, ddt, *J* = 17.1, 10.3, 6.1 Hz), 5.07 (1H, dq, *J* = 17.1, 1.5 Hz), 5.00 (1H, dq, *J* = 10.3, 1.5 Hz), 4.19 (2H, mq, *J* = 7.2 Hz), 2.39 (2H, m), 2.32 (2H, m), 2.12 (1H, ddd, *J* = 25.2, 15.2, 5.2 Hz), 2.05 (1H, ddd, *J* = 19.2, 15.2, 8.4 Hz), 1.42 (3H, d, *J* = 21.6 Hz), 1.40 (3H, d, *J* = 21.5 Hz), 1.28 (3H, t, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 172.3, 137.1, 115.8, 95.6 (d, *J* = 165.6 Hz), 61.8, 50.1, 42.3 (d, *J* = 21.4 Hz), 35.8, 29.5, 27.8 (d, *J* = 24.3 Hz), 26.4 (d, *J* = 24.7 Hz), 14.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −136.6. IR (NaCl thin film): 3297, 3079, 2982, 2937, 1745, 1652, 1540, 1443, 1375, 1193, 1027, 915, 801, 665 cm^{-1}. HRMS (TOF) calcd for [$C_{13}H_{22}FNO_3$ + Na] 282.1482, found 282.1483.

Preparation of (*S*)-γ-Fluoroleucine Ethyl Ester·H_2SO_4: Method B (direct isolation). To a solution of the amide (31 g, 119.7 mmol, 1 equiv) in MTBE (620 mL, 20 mL/g) was added H_2O (2.2 mL, 119.7 mmol, 1 equiv), TFA (26.7 mL, 359.1 mmol, 3 equiv), and DBDMH (19 g, 71.8 mmol, 0.6 equiv) at rt. The resulting mixture was stirred at rt for 4 h, at which no more starting material nor imidate ester intermediate were observed. The reaction was then concentrated to half its volume (10 mL/g) and then treated with neat H_2SO_4 (1 equiv) at rt. The resulting suspension was then cooled to 0 °C, aged for 2 h, and filtered and the wet cake was washed with cold MTBE:iPAc (1:1) and dried in vacuo under a stream of N_2. The product was obtained in 75% corrected yield (91 wt %, 9 wt % dimethylhydantoin, 27.2 g) and 97% ee and, if desired, can be recrystallized from MeCN to afford pure compound in 94% recovery (70% overall yield and >99% ee). The enantiomeric excess value of the product was determined from its free base (liberated with K_2CO_3/H_2O and extracted with MTBE) using chiral GC spectroscopy [Restek Rt-βDEX sa column, 30 m × 0.32 mm i.d. × 0.25 μm df; Method: initial *T* = 100 °C (30 min), ramp at 20 °C/min to 230 °C (10 min), column pressure = 10.07 psi (1.7 mL/min), inlet *T* = 200 °C, inlet pressure = 10 psi, total flow = 46.4 mL/min; retention time for (*S*)-ent (desired) 28.86 min, for (*R*)-*ent* 30.38 min]. $[\alpha]^{25}_D$ +9.8 (*c* 0.52, EtOH). Mp: 105−106 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.63 (3H, br), 4.18 (2H, q, *J* = 7.1 Hz), 4.11 (1H, app t, *J* = 6.8 Hz), 2.20 (1H, ddd, *J* = 28.9, 14.9, 6.8 Hz), 2.12 (1H, ddd, *J* = 28.9, 14.9, 6.8 Hz), 1.39 (3H, d, *J* = 21.6 Hz), 1.38 (3H, d, *J* = 21.6 Hz), 1.23 (3H, t, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, d_6-DMSO): δ 169.4, 94.5 (d, *J* = 165.6 Hz), 61.9, 49.1, 41.0 (d, *J* = 21.8 Hz), 26.6 (d, *J* = 23.9 Hz), 26.2 (d, *J* = 23.7 Hz), 13.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ −137.0. IR (NaCl thin film): 2984 (br), 2937, 1748, 1598, 1520, 1377, 1290, 1205, 1173, 1045, 884 cm^{-1}.

(*S*)-γ-Fluoroleucine ethyl ester free base: $[\alpha]^{25}_D$ +15.9 (*c* 0.54, EtOH (lit.[4b] +9, *c* 0.5, EtOH)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (2H, q, *J* = 7.2 Hz), 3.62 (1H, dd, *J* = 7.9, 5.0 Hz), 2.09 (1H, ddd, *J* = 23.4, 14.6, 5.0 Hz), 1.80 (1H, ddd, *J* = 19.0, 14.6, 7.9 Hz), 1.57 (2H, br), 1.39 (3H, d, *J* = 21.6 Hz), 1.38 (3H, d, *J* = 21.5 Hz), 1.23 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 95.2 (d, *J* = 166.2 Hz), 61.1, 51.7 (d, *J* = 2.8 Hz), 45.8 (d, *J* = 21.6 Hz), 27.5 (d, *J* = 24.7 Hz), 27.0 (d, *J* = 24.6 Hz), 14.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −138.0. IR (NaCl thin film): 3382, 3315, 2982, 2939, 1732, 1467, 1375, 1282, 1186, 1032, 862 cm^{-1}.

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Supporting Information Available: Experimental procedures and characterization of the prepared substrates, including their NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) If desired, dimethylhydantoin byproduct can be removed by neutralizing the salt with aqueous K_2CO_3 or K_3PO_4 and the free base extracted with iPAc or MTBE and retreated with H_2SO_4. Alternatively, the salt can be recrystallized from MeCN to afford pure compound in a 94% recovery and >99% ee.