A Concise Synthesis of (*S*)-γ-Fluoroleucine Ethyl Ester

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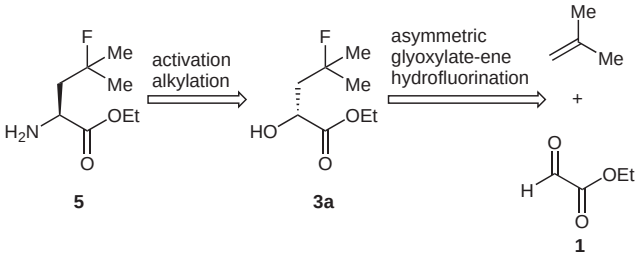
Abstract: We report herein a six-step, chromatography-free, through-process for the asymmetric synthesis of (*S*)-γ-fluoroleucine ethyl ester sulfate salt (**6**) that proceeds in 25% overall yield from inexpensive ethyl glyoxylate. This approach features a Ti/Zn-catalyzed glyoxylate-ene reaction–olefin hydrofluorination–amine alkylation as key steps.

Key words: (*S*)-γ-fluoroleucine ethyl ester, asymmetric synthesis, enantioselective glyoxylate-ene reaction, olefin hydrofluorination, amine alkylation

Fluorine-substituted molecules are extensively used in the preparation of biologically active agents.[1] The unique properties of fluorine induce profound changes in the physical properties of organic molecules. For example, fluorine substitution is commonly used in medicinal chemistry to increase lipophilic character and metabolic stability of drug candidates.[1d,e,h] Incorporation of fluorine into molecules frequently involves fluorinated amino acids as key intermediates.[2] Although a number of syntheses of fluorinated amino acids have been reported, the efficient preparation of γ-fluorinated α-amino acids remains a challenge. These amino acids have been prepared via Claisen rearrangement[3] or alkylation of *N*-diphenylmethylene glycine ester with fluoroalkanes electrophiles.[4] Similar alkylation strategies featuring the use of chiral auxiliaries successfully generated enantioenriched analogues.[5]

As part of a drug development program, we were required to prepare multi-gram quantities of (*S*)-γ-fluoroleucine ethyl ester sulfate salt (**6**). The synthesis of fluoroleucine **5** has been previously reported for the preparation of cyclosporine A derivatives.[6] Schöllkopf's bis-lactim ether alkylation methodology was used as a key step towards the synthesis of these immunosuppressive analogues. This approach suffered from low-yielding alkylation–hydrolysis step and required distillative separation from the expensive valine chiral auxiliary. Our research laboratories recently reported two synthetic approaches towards fluoroleucine **5**. One approach featured an enzyme-catalyzed dynamic kinetic ring-opening of an azalactone that efficiently generated fluoroleucine.[7] The second route involved the multi-step transformation of an L-aspartic acid derivative into fluoroleucine that featured a DAST-mediated fluorination of a tertiary alcohol.[8] Our objective was to develop a short, chromatography-free, catalytic asymmetric synthesis that would allow us to efficiently prepare fluoroleucine **5** (Scheme 1).



Scheme 1 Retrosynthetic analysis of (*S*)-γ-fluoroleucine ethyl ester **5**.

We envisioned that fluoroleucine **5** could be prepared via the displacement of activated γ-fluoroleucic acid ethyl ester (**3a**) by a nucleophilic nitrogen source. Hydroxy ester **3a** could be derived from an asymmetric glyoxylate-ene reaction between ethyl glyoxylate (**1**) and isobutylene followed by a hydrofluorination reaction of the *gem*-disubstituted olefin.

Bis(oxazoline)copper-catalyzed glyoxylate-ene reactions have been reported for the highly enantioselective preparation of α-hydroxyester **2**.[9] A drawback associated with the Cu-based ene reaction is that it requires the use of expensive and not readily available bis(oxazoline) chiral ligands. Consequently, we decided to investigate the Ti-catalyzed glyoxylate-ene reaction which uses readily available and inexpensive BINOL as chiral ligand.[10]

As illustrated in Table 1, the Ti-catalyzed reaction requires distillative depolymerization of ethyl glyoxylate (**1**) immediately prior to the reaction (Table 1, entries 1 and 2).[10c] This can be problematic for large scale applications since distilled ethyl glyoxylate was found to repolymerize at a rate of approximately 10%/h at room temperature (40% after 4 h) as determined by ^{1}H NMR spectroscopy. Therefore, we sought a way to promote the depolymerization of glyoxylate in situ without mediating a racemic glyoxylate-ene reaction. We investigated the depolymerization of ethyl glyoxylate using Lewis acid co-catalysts and found that $CuSO_4$ and $Zn(OTf)_2$ promoted the depolymerization of **1** but also catalyzed the ene reaction (Table 1, entries 3 and 4). After an extensive

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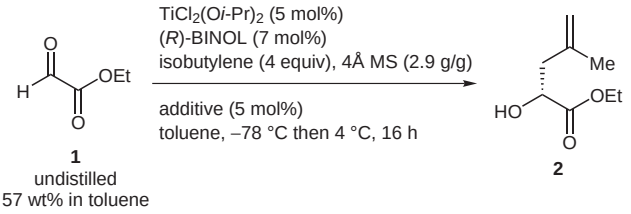
investigation we were pleased to find that addition of $MgCl_2$ led to depolymerization of ethyl glyoxylate without adverse effects on the ene reaction (Table 1, entry 5). Ultimately, we identified $ZnCl_2$ as the additive of choice (Table 1, entry 6). Addition of 5 mol% $ZnCl_2$ proved to be the optimal amount. These conditions afforded the best yield (60%) and enantioselectivity (>95% ee). By comparison, addition of 1 mol% $ZnCl_2$ led to lower yield (55%) and addition of 10 mol% $ZnCl_2$ led to erosion of enantioselectivity (92%ee).

Table 1 Enantioselective Ti-Catalyzed Glyoxylate-Ene Reaction

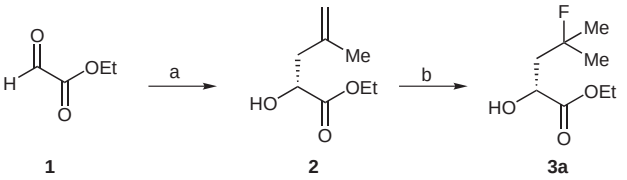


Entry	Additive	Yield (%)[a]	ee (%)[b]
1	None	27	Nd
2[c]	None	67	>95
3	$CuSO_4$[d]	43	90
4	$Zn(OTf)_2$[d]	59	86
5	$MgCl_2$	47	>95
6	$ZnCl_2$	60	>95

[a] Determined by HPLC analysis.
[b] Determined by chiral GC analysis (Cyclodex-B column).
[c] Freshly distilled ethyl glyoxylate was used.
[d] 1 mol% of additive was used.

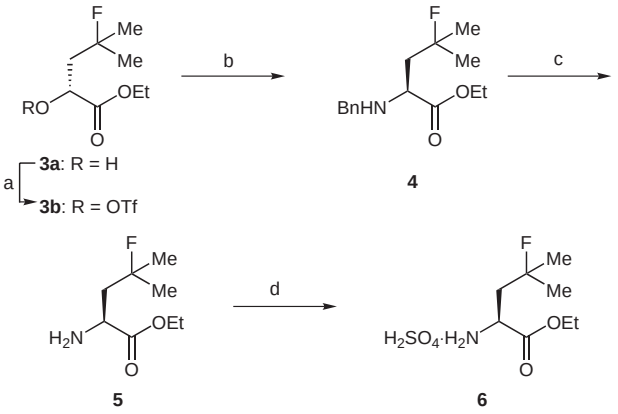
The desired hydroxy ester **2** was readily isolated by precipitation of the titanium salts by controlled addition of heptane in the presence of Darco KB-B activated carbon (Scheme 2). Alternatively, the crude hydroxy ester could be distilled under high vacuum to yield the desired product **2** in 52% yield. The purification of the hydroxy ester was critical in order to reach complete conversion in the following hydrofluorination step.

We found that hydrofluorination of hydroxy ester **2** proceeded smoothly using HF·pyridine at 0 °C in heptane as solvent to afford (*R*)-γ-fluoroleucic acid ethyl ester (**3a**) in 71% yield.[11] Heptane was superior to a broad variety of solvents in terms of yield and impurity generation. HF·pyridine also afforded the best conversion and yield among several HF sources.[12] We observed that longer reaction time (≥2.5 h) led to decreased yields of **3a** and significant impurity generation. Work up involved neutralization of excess HF·pyridine with a pH 7 Na_2HPO_4/NaH_2PO_4 aqueous buffer solution directly in the reaction vessel. This procedure obviated the use of a Teflon-lined separatory funnel for subsequent extractions. We used the crude isolated (*R*)-γ-fluoroleucic acid ethyl ester **3a** directly without purification.



Scheme 2 *Reagents and conditions*: (a) $TiCl_2(Oi\text{-}Pr)_2$ (5 mol%, 0.3 M toluene), (*R*)-BINOL (7 mol%), isobutylene (4 equiv), 4 Å MS (2.9 g/g), $ZnCl_2$ (5 mol%), toluene, –78 °C then 4 °C, 16 h. Darco KB-B (1 g/g), heptane, 57%, >95% ee; (b) HF·pyridine (20 equiv), heptane, 0 °C, 2 h, 71%, >95% ee.

We converted hydroxy ester **3a** to triflate **3b** by reaction with Tf_2O and 2,6-lutidine in heptane (≥99% conversion by GC analysis, Scheme 3). The crude triflate **3b** was used without purification in the subsequent nucleophilic displacement reaction. We also prepared the corresponding tosylate, brosylate and nosylate but these electrophiles afforded lower conversion or generated more impurities in the following nucleophilic displacement.



Scheme 3 *Reagents and conditions*: (a) Tf_2O (1.5 equiv), 2,6-lutidine (2.0 equiv), heptane, 0 °C, 1 h, ≥99% conv.; (b) $BnNH_2$ (1.2 equiv), K_2CO_3 (2.0 equiv), MeCN, 0 °C, 1.5 h, 80% (two steps), >95% ee; (c) H_2 (54 psi), $Pd(OH)_2/C$ (4 wt%, 20 wt% on C), EtOH, r.t., 18 h, 95%, 95% ee; (d) H_2SO_4 (1.1 equiv), *i*-PrOAc, 0 °C, 1 h, 83%, 96% ee.

We performed the subsequent alkylation of benzylamine with triflate **3b** by using MeCN as solvent and powdered K_2CO_3 as base (Scheme 3).[13] A slight excess of benzylamine was used and the reaction afforded complete conversion after 1.5 hours at 0 °C to afford *N*-benzyl fluoroleucine **4** in 83% yield over two steps. We also investigated solutions of ammonia (in MeOH, *i*-PrOH, dioxane) and hexamethyldisilazane as nitrogen sources but we observed lower conversions as well as significant amounts (20–40%) of dialkylation at nitrogen. Acid/base work-up led to significant removal of color and complete rejection of BINOL-related impurities that were carried through from the glyoxylate-ene step. We observed less than 1% epimerization at the reacting triflate chiral center as determined by chiral HPLC analysis. Unfortunately, this material behaved erratically in the subsequent hydrogenolysis step, presumably because of residual amine-in-

duced catalyst poisoning. We ultimately found that a $CuSO_4$ wash (10% aqueous) of the organic layer was required in order to obtain reproducible conversion in the following hydrogenolysis step.

We proceeded to the hydrogenolysis of *N*-benzyl fluoroleucine **4** in EtOH with Pearlman's catalyst under 54 psi of H_2 at room temperature and obtained γ-fluoroleucine ethyl ester **5** in 95% yield.[14] The use of lower pressure of H_2 led to incomplete conversion (0–50%). After filtration to remove the catalyst and concentration, crude fluoroleucine **5** (95% ee HPLC) was isolated as its sulfate salt according to published procedure.[7,16] (*S*)-γ-Fluoroleucine ethyl ester sulfate salt (**6**) was obtained in 83% yield and 96% ee according to chiral HPLC analysis.

In conclusion, we have reported a chromatography-free, through-process for the multigram synthesis of (*S*)-γ-fluoroleucine ethyl ester sulfate salt that proceeds in 6 steps and 25% overall yield from inexpensive ethyl glyoxylate. This approach features an unprecedented Ti/Zn-catalyzed asymmetric glyoxylate-ene reaction.

General Methods

All reactions were conducted under N_2 atmosphere. Commercial reagents and solvents were used without further purification. Concentration under vacuum refers to removal of the solvents using a rotary evaporator at reduced pressure (10–20 torr). ^{1}H NMR and ^{13}C NMR spectra were measured on either a 400 MHz or 500 MHz Bruker instrument and the chemical shifts were measured relative to solvent residual peak ($CHCl_3$ or DMSO). ^{19}F NMR spectra were measured on a 400 MHz Bruker instrument and the chemical shifts were measured relative to α,α,α-trifluorotoluene as an internal reference (δ = –62.7 ppm). Infrared spectra were reported in wave numbers and measured on a Nexus 470 FT-IR spectrometer or an ASI React IR instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Melting points were measured on a Büchi B-540 instrument and are uncorrected. High-resolution mass spectrometry (HRMS) measurements were performed at Merck Research Laboratories, Rahway, NJ.

Ethyl (2*R*)-2-hydroxy-4-methylpent-4-enoate (2)

Powdered (*R*)-BINOL (6.01 g, 21.0 mmol) and 4 Å activated molecular sieves (88.80 g) were suspended in toluene (257 mL). $TiCl_2(O\textit{i}\text{-}Pr)_2$[10c,15] (50.0 mL of 0.3 M solution in toluene, 15.0 mmol) was added and the reaction mixture was stirred at r.t. for 1 h. Then, $ZnCl_2$ (2.04 g, 15.0 mmol) was added and the reaction mixture was cooled to –78 °C. Isobutylene was bubbled in the solution until a weight increase of 67.33 g (1.20 mol) was measured. Ethyl glyoxylate (53.73 g of 57 wt% in toluene by ^{1}H NMR, 30.63 g, 300.0 mmol) was added and the reaction was let stir at 4 °C for 16 h (GC analysis showed 90% conversion). The solution was filtered on Solka-Floc® and concentrated under vacuum. HPLC analysis showed 68.60 g of α-hydroxy-ester **2** at 41.5 wt% (28.47 g, 60% yield) isolated as a dark red oil. To a portion of hydroxy ester **2** (36.14 g at 41.5 wt%, 15.00 g, 94.8 mmol) was added Darco KB-B activated carbon (15.00 g) and heptane (150 mL) was added to the stirred mixture over 1 h. The resulting suspension was stirred for 16 h at r.t., filtered on Solka-Floc® and concentrated under vacuum to afford hydroxy ester **2** (20.36 g at 70.0 wt%, 14.25 g, 57% yield overall). $[\alpha]_D^{20}$ +8.8 (*c* 3.83, Et_2O) {lit.[9b] $[\alpha]_D^{20}$ +9.5 (*c* 5.3, Et_2O)}. IR (neat): ν = 3462 (br), 3080, 2984, 1733, 1648, 1447, 1374, 1200, 1096 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.88 (s, 1 H), 4.81 (s, 1 H), 4.31 (dd, *J* = 4.3, 8.2 Hz, 1 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 2.57 (br, 1 H), 2.52 (dd, *J* = 4.2, 14.2 Hz, 1 H), 2.36 (dd, *J* = 8.2, 14.2 Hz, 1 H), 1.78 (s, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 141.0, 114.0, 69.1, 61.7, 42.7, 22.5, 14.2. HRMS (ES): *m/z* calcd for $[C_8H_{14}O_3 + Na]^+$: 181.0841; found: 181.0838. Enantiomeric excess was determined by GC with a Cyclodex-B column (60 °C for 1 min, 20 °C/min to 100 °C, hold to 100 °C for 15 min, injector 180 °C, detector 250 °C, split 10:1, 13.5 psi helium); *R* enantiomer t_R = 10.9 min; *S* enantiomer t_R = 11.2 min; >95% ee. Conversion was determined by GC with a HP-1 column (50 °C for 1 min, 20 °C/min to 90 °C, 3 °C/min to 105 °C, 30 °C/min to 230 °C, injector 180 °C, detector 250 °C, split 5:1, 15.3 psi helium); ethyl glyoxylate t_R = 2.1 min; hydroxy ester **2** t_R = 5.5 min. Yield was determined by HPLC with a 4.6 mm × 25.0 cm Zorbax Rx-C8 column (0.1% H_3PO_4–MeCN 70:30 to 55:95 over 25 min, 2 mL/min, 220 nm, 35 °C); hydroxy ester **2** t_R = 4.01 min. The hydroxy ester **2** was directly used for the subsequent hydrofluorination reaction.

Ethyl (2*R*)-4-fluoro-2-hydroxy-4-methylpentanoate (3a)

A solution of hydroxy ester **2** (17.5 g at 70.0 wt%, 12.25 g, 77.4 mmol) in heptane (123 mL) was added to a solution of HF·pyridine (40.2 mL, 1.55 mol) in a Teflon-lined flask over 10 min while maintaining the temperature at 0–4 °C. The mixture was stirred at 0 °C for 2 h (GC analysis showed 93% conversion). Then, MTBE (123 mL) and an aq Na_2HPO_4/NaH_2PO_4 buffer solution (550 mL, 2 M, pH = 7) were added. Afterwards, aq 2 M NaOH (approximately 490 mL) was added until the aqueous layer reached pH = 7. The layers were separated and the aqueous layer was extracted with MTBE (123 mL). The combined organic layers were washed with aq 1 N HCl (123 mL), H_2O (123 mL), dried with $MgSO_4$, filtered and concentrated under vacuum to afford γ-fluoroleucic acid ethyl ester **3** as a yellow oil. GC analysis showed 17.71 g at 55.5 wt% (9.83 g, 71% yield) of desired product that was directly used for the next step. $[\alpha]_D^{20}$ +10.6 (*c* 1.43, EtOH). IR (neat): ν = 3474 (br), 2983, 1733, 1471, 1374, 1204, 1142, 1092 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.34 (ddd, *J* = 2.8, 5.3, 9.0 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.01 (d, *J* = 5.1 Hz, 1 H), 2.14 (ddd, *J* = 2.6, 14.8, 17.9 Hz, 1 H), 1.88 (ddd, *J* = 9.1, 14.7, 20.2 Hz, 1 H), 1.43 (d, *J* = 21.8 Hz, 3 H), 1.42 (d, *J* = 21.8 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 95.1 (d, *J* = 165.9 Hz), 67.7 (d, *J* = 5.5 Hz), 61.9, 45.1 (d, *J* = 22.6 Hz), 27.7 (d, *J* = 24.3 Hz), 26.9 (d, *J* = 24.5 Hz), 14.1. ^{19}F NMR (375 MHz, $CDCl_3$): δ = –136.1. HRMS (ES): *m/z* calcd for $[C_8H_{15}FO_3 + Na]^+$: 201.0903; found: 201.0896. Enantiomeric excess was determined by GC with a Cyclodex-B column (60 °C for 1 min, 20 °C/min to 100 °C, hold to 100 °C for 15 min, injector 180 °C, detector 250 °C, split 10:1, 13.5 psi helium); *R* enantiomer t_R = 12.4 min; *S* enantiomer t_R = 12.9 min; >95% ee. Conversion and yield were determined by GC with a HP-1 column (50 °C for 1 min, 20 °C/min to 90 °C, 3 °C/min to 105 °C, 30 °C/min to 230 °C, injector 180 °C, detector 250 °C, split 5:1, 15.3 psi helium); γ-fluoroleucic acid ethyl ester **3a** t_R = 5.6 min. γ-Fluoroleucic acid ethyl ester **3a** must be kept at –20 °C since it forms the corresponding lactone upon standing at r.t.

Ethyl 4-fluoro-4-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}pentanoate (3b)

(*R*)-γ-Fluoroleucic acid ethyl ester (**3b**, 11.44 g at 70.0 wt%, 8.01 g, 44.95 mmol) and 2,6-lutidine (10.46 mL, 89.90 mmol) were dissolved in heptane (80 mL) and cooled to 0–5 °C. Trifluoromethanesulfonic anhydride (11.34 mL, 67.43 mmol) was added dropwise over 10 min. The solution was let stir at 0–5 °C for 1 h and then diluted with heptane (80 mL) and H_2O (80 mL). The layers were separated and the organic layer was washed with 10% aq $CuSO_4$ (2 × 80 mL), H_2O (80 mL), brine (80 mL), dried with $MgSO_4$ filtered and concentrated at r.t. under vacuum to afford triflate **3b** that was directly used for the next step. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.31 (dd, *J* = 3.9, 7.4 Hz, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 2.41–

2.26 (m, 2 H), 1.47 (d, *J* = 21.3 Hz, 3 H), 1.46 (d, *J* = 21.2 Hz, 3 H), 1.33 (t, *J* = 7.1 Hz, 3 H). ^{19}F NMR (375 MHz, $CDCl_3$): δ = –74.8, –140.5. Conversion was determined by GC with a HP-1 column (50 °C for 1 min, 20 °C/min to 90 °C, 3 °C/min to 105 °C, 30 °C/min to 230 °C, injector 180 °C, detector 250 °C, split 5:1, 15.3 psi helium); triflate **3b** t_R = 8.0 min.

Ethyl (2*S*)-2-(benzylamino)-4-fluoro-4-methylpentanoate (4)

Triflate **3b** (44.95 mmol) was dissolved in MeCN (80 mL). Then, K_2CO_3 (12.43 g, 89.90 mmol) was added and the slurry was cooled to 0–5 °C. Benzylamine (5.89 mL, 53.94 mmol) was added over 10 min and the slurry was stirred at 0–5 °C for 1.5 h (GC analysis showed complete conversion). The batch was diluted with MTBE (160 mL) and H_2O (80 mL). The layers were separated and the organic layer was washed with brine (80 mL). The organic layer was washed with aq 1 N HCl (2 × 80 mL). MTBE (80 mL) was added to the combined acidic aqueous layers which were neutralized with aq 2 M Na_2CO_3 (approximately 80 mL) until pH = 9. The layers were separated and the aqueous layer was extracted with MTBE (80 mL). The combined organic layers were washed with H_2O (80 mL), filtered on Solka-Floc®, concentrated under reduced pressure and flushed with toluene (80 mL). HPLC analysis showed 12.71 g of *N*-benzyl fluoroleucine ethyl ester **4** at 76.4 wt% (9.71 g, 81% yield) isolated as a pale yellow oil. A portion of crude *N*-benzyl fluoroleucine **4** (5.93 g at 76.4 wt%, 4.53 g, 16.96 mmol) was dissolved in MTBE (45 mL), 10% aq $CuSO_4$ (27 mL) was added and the biphasic mixture was stirred vigorously for 1 h at r.t. The layers were separated and the organic layer was washed with H_2O (2 × 27 mL), filtered on Solka-Floc® and concentrated under reduced pressure. HPLC analysis showed 5.80 g of *N*-benzyl fluoroleucine ethyl ester **4** at 76.7 wt% (4.45 g, 80% yield) isolated as a pale yellow oil. $[\alpha]_D^{20}$ –43.5 (*c* 1.24, EtOH). IR (neat): ν = 3330, 3030, 2984, 1733, 1459, 1374, 1185, 1026 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.34 (m, 4 H), 7.30–7.26 (m, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 3.83 (d, *J* = 12.8 Hz, 1 H), 3.67 (d, *J* = 12.8 Hz, 1 H), 3.49 (app t, *J* = 6.6 Hz, 1 H), 2.23 (br, 1 H), 2.10 (ddd, *J* = 6.4, 14.5, 17.9 Hz, 1 H), 1.95 (ddd, *J* = 6.8, 14.6, 23.0 Hz, 1 H), 1.44 (d, *J* = 21.5 Hz, 3 H), 1.40 (d, *J* = 21.6 Hz, 3 H), 1.32 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.0, 139.4, 128.4, 127.2, 94.9 (d, *J* = 165.6 Hz), 60.9, 57.5 (d, *J* = 3.7 Hz), 52.0, 44.5 (d, *J* = 22.4 Hz), 27.7 (d, *J* = 24.5 Hz), 26.5 (d, *J* = 24.7 Hz), 14.3. ^{19}F NMR (375 MHz, $CDCl_3$): δ = –135.7. HRMS (ES): *m/z* calcd for $[C_{15}H_{22}FNO_2 + H]^+$: 268.1713; found: 268.1711. Enantiomeric excess was determined by HPLC with a 4.6 mm × 25.0 cm Chiralcel OD column [1:1 *n*-PrOH/MeOH–hexane (0.8:99.2), hold 8 min, to 4:96 over 2 min, 1 mL/min, 224 nm, 25 °C]; *S* enantiomer t_R = 5.8 min; *R* enantiomer t_R = 6.3 min; >95% ee. Conversion was determined by GC with a HP-1 column (50 °C for 1 min, 20 °C/min to 90 °C, 3 °C/min to 120 °C, 20 °C/min to 250 °C, injector 180 °C, detector 250 °C, split 5:1, 15.3 psi helium); *N*-benzyl fluoroleucine ethyl ester **4** t_R = 17.8 min. Yield was determined by HPLC with a 4.6 mm × 25.0 cm Zorbax Rx-C8 column (0.1% H_3PO_4–MeCN 70:30 to 55:95 over 25 min, 2 mL/min, 220 nm, 35 °C); *N*-benzyl fluoroleucine ethyl ester **4** t_R = 2.72 min.

Ethyl (2*S*)-2-amino-4-fluoro-4-methylpentanoate (5)

N-benzyl fluoroleucine ethyl ester **4** (5.80 g at 76.7 wt%, 4.45 g, 16.66 mmol) was dissolved in EtOH (42 mL) and $Pd(OH)_2$/C (890 mg at 20 wt%, 178 mg, 4 wt%) was added. The pressure bottle was filled, vented, and refilled 5 times with H_2 (54 psi). The suspension was then stirred at r.t. for 16 h under 54 psi of H_2. The suspension was then filtered on Solka-Floc® and the filtrate was concentrated under reduced pressure. HPLC analysis showed 3.79 g of fluoroleucine ethyl ester **5** at 74.0 wt% (2.81 g, 95% yield) isolated as a pale yellow oil. $[\alpha]_D^{20}$ +15.3 (*c* 0.56, EtOH) {lit.[7] $[\alpha]_D^{25}$ +15.9 (*c* 0.54, EtOH)}. IR (neat): ν = 3388, 3360, 2984, 1733, 1467, 1374, 1282, 1185, 1031, 861 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (q, *J* = 7.1 Hz, 2 H), 3.64 (dd, *J* = 5.0, 7.8 Hz, 1 H), 2.11 (ddd, *J* = 4.9, 14.6, 23.6 Hz, 1 H), 1.81 (ddd, *J* = 7.9, 14.6, 18.9 Hz, 1 H), 1.60 (br, 2 H), 1.41 (d, *J* = 21.5 Hz, 3 H), 1.39 (d, *J* = 21.5 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6, 95.1 (d, *J* = 165.7 Hz), 61.0, 51.5 (d, *J* = 2.7 Hz), 45.5 (d, *J* = 21.5 Hz), 27.4 (d, *J* = 24.7 Hz), 26.8 (d, *J* = 24.8 Hz), 14.1. ^{19}F NMR (375 MHz, $CDCl_3$): δ = –137.7. HRMS (ES): *m/z* calcd for $[C_8H_{16}FNO_2 + Na]^+$: 200.1063; found: 200.1065. Enantiomeric excess was determined by HPLC with a 4.6 mm × 15.0 cm Crownpack CR(+) column (0.3% $HClO_4$ in H_2O pH = 1.5–1.6, hold 20 min, 1 mL/min, 205 nm, 25 °C); *R* enantiomer t_R = 5.6 min; *S* enantiomer t_R = 7.6 min; 95% ee. Yield was determined by HPLC with a 3.0 mm × 15.0 cm Zorbax Extend-C18 column (14.4 mM NH_4Cl, pH = 9.0–MeCN 90:10 to 10:90 over 25 min, 0.75 mL/min, 205 nm, 25 °C); γ-fluoroleucine ethyl ester **5** t_R = 6.59 min.

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References and Notes

(1) For reviews, see: (a) Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 214. (b) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1. (c) Iseki, K. *Tetrahedron* **1998**, *54*, 13887. (d) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. In *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier Biomedical Press: Amsterdam, **1993**. (e) Welch, J. T.; Eswarakrishan, S. In *Fluorine in Bioorganic Chemistry*; Wiley: New York, **1991**. (f) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (g) Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381. (h) Kollonitsch, J. In *Biomedical Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y., Eds.; Elsevier Biomedical Press: Amsterdam, **1982**.

(2) (a) Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711. (b) Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **2000**, *17*, 621.

(3) (a) Tranel, F.; Fröhlich, R.; Haufe, G. *J. Fluorine Chem.* **2005**, *126*, 557. (b) For a review on γ-fluoro-α-amino acids synthesis see: Haufe, G.; Kröger, S. *Amino Acids* **1996**, *11*, 409.

(4) (a) Kröger, S.; Haufe, G. *Amino Acids* **1997**, *12*, 363. (b) Haufe, G.; Laue, K. W.; Triller, M. U. *Tetrahedron* **1998**, *54*, 5929.

(5) (a) Shendage, D. M.; Fröhlich, R.; Bergander, K.; Haufe, G. *Eur. J. Org. Chem.* **2005**, 719. (b) Laue, K. W.; Kröger, S.; Wegelius, E.; Haufe, G. *Eur. J. Org. Chem.* **2000**, 3737.

(6) Papageorgiou, C.; Borer, X.; French, R. R. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 267.

(7) Limanto, J.; Shafiee, A.; Devine, P. N.; Upadhyay, V.; Desmond, R. A.; Foster, B. R.; Gauthier, D. R.; Reamer, R. A.; Volante, R. P. *J. Org. Chem.* **2005**, *70*, 2372.

(8) Truong, V. L.; Gauthier, J. Y.; Boyd, M.; Roy, B.; Scheigetz, J. *Synlett* **2005**, 1279.

(9) For reviews on the ene reaction see: ref. 1c and: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. For Cu-catalyzed carbonyl-ene reaction see: (b) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936. (c) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879. (d) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824. (e) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541. (f) For a discussion on the Cu(II)-catalyzed carbonyl-ene reaction mechanism see: Morao, I.; McNamara, J. P.; Hillier, I. H. *J. Am. Chem. Soc.* **2003**, *125*, 628.

(10) (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940. (c) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. In *Organic Syntheses*, Vol. 71; Overman, L. E., Ed.; Wiley: New York, **1993**. (d) Brown, P. A.; Hans, H. Eur. Pat. Appl. EP 0816341, **1998**; *Chem. Abstr.* **1998**, *128*, 140701 . For reviews on the Ti-catalyzed carbonyl-ene reaction see ref. 1b and: (e) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639. (f) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255. For a discussion on the Ti-catalyzed carbonyl-ene reaction transition state see: (g) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W.; Goodman, S. N. *Tetrahedron Lett.* **1997**, *38*, 6513. For a discussion on the role of molecular sieves in the Ti-catalyzed carbonyl-ene reaction see: (h) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Inorg. Chim. Acta* **1999**, *296*, 267. (i) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *J. Mol. Catal. A: Chem.* **1998**, *132*, 165. (j) Mikami, K.; Terada, M.; Matsumoto, Y.; Tanaka, M.; Nakamura, Y. *Microporous Mesoporous Mater.* **1998**, *21*, 461. (k) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Chem. Commun.* **1997**, 281.

(11) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872.

(12) Poly-4-vinylpyridinium poly(hydrogen fluoride) (PVPHF), HF·melamine, Ishikawa's reagent, HF·NEt_3, HF·collidine, and HF·H_2O afforded lower conversion and yield. For references on the first five reagents see: (a) Olah, G. A.; Li, X.-Y. *Synthesis* **1990**, 267. (b) Yoneda, N.; Abe, T.; Fukuhara, T.; Suzuki, A. *Chem. Lett.* **1983**, 1135. (c) Watanabe, S.; Fujita, T.; Usui, Y.; Kimura, Y.; Kitazume, T. *J. Fluorine Chem.* **1986**, *31*, 135. (d) McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, 31. (e) Wozney, Y. V.; Kalicheva, I. S.; Galoyan, A. A. *Bioorg. Khim.* **1981**, *7*, 406.

(13) Effenberger, F.; Burkard, U.; Willfahrt, J. *Liebigs Ann. Chem.* **1986**, 314.

(14) (a) Pearlman, W. M. *Tetrahedron Lett.* **1967**, *17*, 1663. (b) Bernotas, R. C.; Cube, R. V. *Synth. Commun.* **1990**, *20*, 1209. (c) Yoshida, K.; Nakajima, S.; Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Heterocycles* **1988**, *27*, 1167.

(15) Dijkgraaf, C.; Rousseau, J. P. G. *Spectrochimica Acta, Part A* **1968**, *24*, 1213.

(16) Spectral data for compound **6**: $[\alpha]_D^{20}$ +9.9 (*c* 0.52, EtOH) {lit.[7]: $[\alpha]_D^{25}$ +9.8 (*c* 0.52, EtOH)}; mp 104–105 °C. IR (NaCl, thin film): ν = 3419 (br), 2986, 2942, 1742, 1520, 1377, 1291, 1204, 1171, 1050 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.34 (br, 3 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 4.17 (app t, *J* = 6.7 Hz, 1 H), 2.21 (ddd, *J* = 6.6, 15.0, 22.9 Hz, 1 H), 2.09 (ddd, *J* = 6.6, 15.0, 20.8 Hz, 1 H), 1.41 (d, *J* = 21.6 Hz, 3 H), 1.41 (d, *J* = 21.6 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.0, 95.1 (d, *J* = 165.5 Hz), 62.5, 49.5 (d, *J* = 1.1 Hz), 41.4 (d, *J* = 21.8 Hz), 26.9 (d, *J* = 23.6 Hz), 26.8 (d, *J* = 23.7 Hz), 14.3. ^{19}F NMR (375 MHz, DMSO-d_6): δ = –138.3. HRMS (ES): *m/z* calcd for $[C_8H_{16}FNO_2 + Na]^+$: 200.1063; found: 200.1067. Enantiomeric excess was determined by HPLC with a 4.6 mm × 15.0 cm Crownpack CR(+) column (0.3% $HClO_4$ in H_2O pH = 1.5–1.6, hold 20 min, 1 mL/min, 205 nm, 25 °C; *R* enantiomer t_R = 5.6 min; *S* enantiomer t_R = 7.6 min; 96% ee.