Fragmentation of 4. A solution of distilled aluminum isopropoxide (2.57 g, 12.6 mmol) in 15 mL of dry toluene was added slowly by syringe to a solution of **4**[5] (0.504 g, 2.5 mmol) in 15 mL of dry toluene. This mixture was stirred and refluxed under N_2 for 71 h and worked up as described above. The product (**5**) was a pale yellow oil (0.409 g, 81%, one spot on TLC), which slowly began depositing crystalline material, assisted by ether trituration.

Crop 1: mp 106-107 °C (recrystallized from Et_2O); 0.110 g; positive Baeyer and CrO_3 tests. Anal. Calcd for $C_{13}H_{16}O_2 \cdot 0.1H_2O$: C, 75.80; H, 7.87. Found: C, 75.48; H, 7.89. IR (mull) 3200, 1600, 751, 723, 692 cm^{-1}; ^1H NMR δ 7.35 (5 H, aromatic), 6.12 (1 H, br s, olefinic H), 3.70 (3 H, complex, HCO), 2.60 (5 H, complex) (the complex pattern at 3.70 ppm was nearly identical with that found at the same chemical shift in the NMR spectra of model 1,2 glycols);[11] ^{13}C NMR δ 35.8, 35.9, 40.6 (alkane), 65.6, 76.0 (CO), 124.3, 136.3 (alkene), 125.5, 127.0, 128.3, 141.7 (aromatic); UV λ_{max} 246 nm (ϵ 17 500) (styrene chromophore).[12]

Crop 2: mp 82-84 °C (recrystallized from Et_2O); 0.052 g; positive Baeyer test. Anal. Calcd for $C_{13}H_{16}O_2 \cdot 0.1H_2O$: C, 75.80; H, 7.87. Found: C, 75.98; H, 7.92. IR (mull) 3348, 1600, 761, 723, 694 cm^{-1}; UV λ_{max} 247 nm; ^1H NMR δ 7.35 (5 H, aromatic), 6.12 (1 H, br s, olefinic H), 3.65 (3 H, complex, HCO), 2.60 (5 H, complex); ^{13}C NMR δ 35.7, 35.9, 40.6 (alkane), 65.7, 75.9 (CO), 124.9, 136.2 (alkene), 125.5, 127.0, 128.3, 141.2 (aromatic).

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Reaction of β-Hydroxy α-Amino Acid Derivatives with (Diethylamino)sulfur Trifluoride (DAST). Synthesis of β-Fluoro α-Amino Acids

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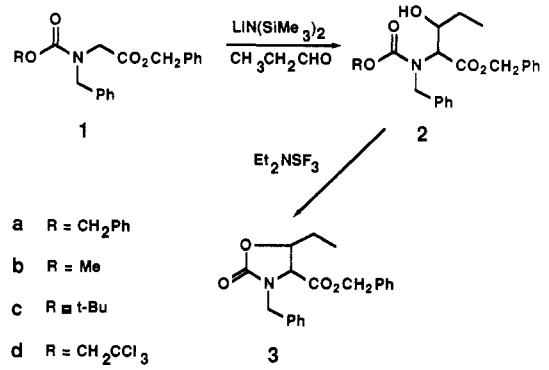
Amino acids that bear fluorine at a β-carbon can act as mechanism-based irreversible inactivators of certain enzymes and can block important metabolic pathways.[1] For example, alanine racemase, an enzyme which provides D-alanine for bacterial cell wall formation, is inactivated by β-fluoroalanine and its analogues.[2] Such chemotherapeutic potential has encouraged development of methods for synthesis of α-amino acids bearing the β-fluorine directly on the parent side chain. Previous approaches include the following: ammonolysis of 2-bromo-3-fluoro carboxylic acids;[3] reaction of azirines,[4] aziridines[5] or glycidonitriles[5b,6] with hydrogen fluoride in pyridine; fluorodehydroxylation or -desulfurization of β-hydroxy or β-thiol amino acids with sulfur tetrafluoride in liquid hydrogen fluoride;[7,8] reductive amination of fluoropyruvic acids;[5c,9] and fluoroalkylation of glycinate anions.[10] Although generally applicable, these procedures often require special precautions due to the toxicity of the reagents. The present work describes the use of the mild fluorinating agent, (diethylamino)sulfur trifluoride (DAST),[11] for synthesis of aliphatic β-fluoro amino acids.

Scheme I



As a mild reagent for substitution of hydroxyl groups by fluorine, DAST has been employed extensively in the synthesis of fluorinated carbohydrates[12] but has not been utilized on a general basis in the preparation of free β-fluoro α-amino acids from corresponding β-hydroxy derivatives.[13] Previous studies on the reaction of DAST with N-protected β-hydroxy amino acid esters have usually yielded[13] the corresponding dehydro compounds[14] or the rearranged α-fluoro β-amino acids.[15] However, since the dehydration occurred in the presence of pyridine and the rearrangement required a nucleophilic amino group, we decided to investigate the reaction in the absence of amines.

Initially the enolate of benzyl [*N*-benzyl-*N*-(benzyloxycarbonyl)glycinate (**1a**) was generated ($LiN(SiMe_3)_2$, THF, -78 °C) and condensed with propionaldehyde to afford **2a**

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Table I. Yields of Condensations 4 → 5, Fluorination-Dehydration 5 → 6 and/or 8, and Deprotection 6 → 7[a]

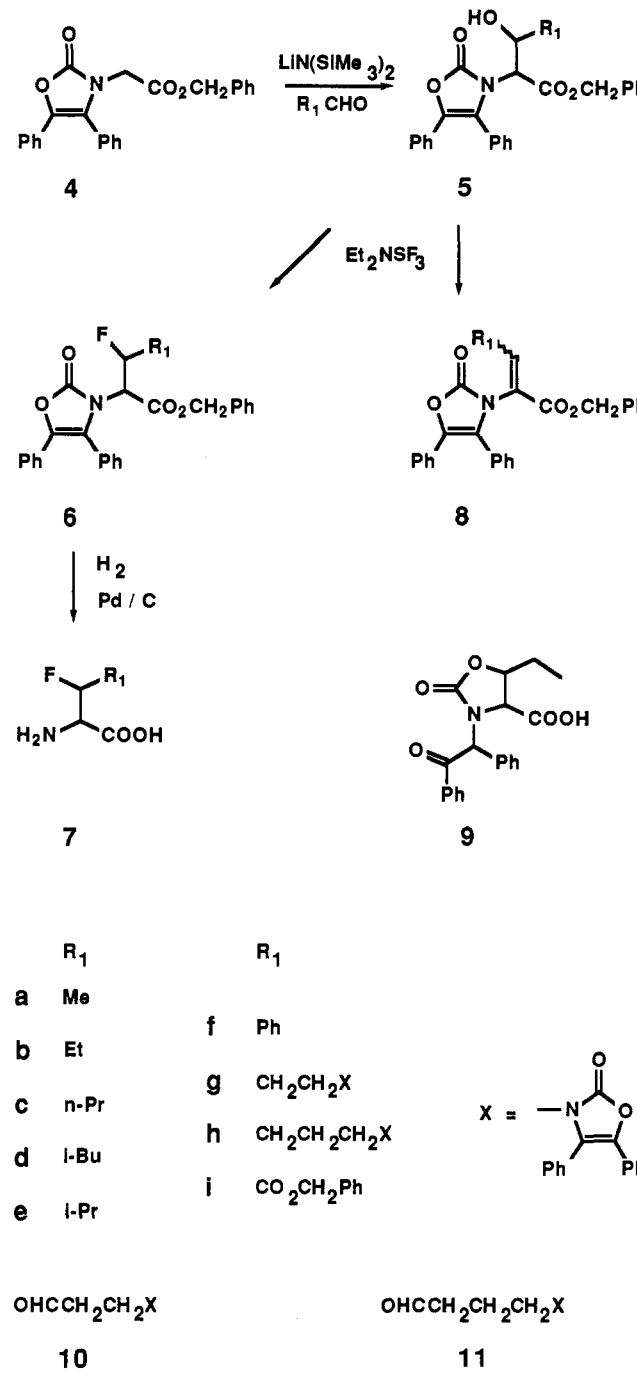
entry	R_1	yields, % 5	6	7	8
a	Me	90	45	99	24
b	Et	84	48	88	17
c	*n*-Pr	80	65	89	14
d	*i*-Bu	70	64	91	12
e	*i*-Pr	81			75
f	Ph	79			
g	CH_2CH_2X[b]	60[c]			46
h	$CH_2CH_2CH_2X$[b]	55[c]			73
i	CO_2CH_2Ph	61[c]			76[d]

[a] See Scheme II, yields of isolated products. [b] X is 4,5-diphenyl-2-oxo-4-oxazolin-3-yl group. [c] Reaction at −78 °C. [d] Reaction of DAST only with major diastereomer.

as a mixture of diastereomers (Scheme I).[16] Reaction of this β-hydroxy amino acid ester derivative with DAST in dichloromethane at −78 °C gave only the oxazolidinone **3** as a diastereomeric mixture (75% yield). This results from intramolecular attack of the carbamate oxygen on the activated β-carbon followed by loss of the benzyl group. Since the latter can in principle proceed either by S_N2 attack of fluoride on the benzylic carbon or by an S_N1 process involving a benzylic cation, it seemed that appropriate choice of an alkyl group in the carbamate could suppress either of these processes. Replacement of the benzyl group with methyl, *tert*-butyl, or trichloroethyl did not significantly affect formation of the β-hydroxy compounds **2b–d** from **1b–d**. Unfortunately, in each case the DAST reaction again produced **3** (54–91%) rather than the desired β-fluoro products.

To overcome the problem caused by this change in mechanism, the nitrogen was protected as a 4,5-diphenyl-4-oxazolin-2-one moiety, a protecting group which had been reported to be stable to acidic or basic conditions but readily cleaved by hydrogenolysis.[17] Benzyl glycinate *p*-toluenesulfonate salt[18] was converted to **4** by using a modification of the literature procedure.[17] Condensation of **4** with propionaldehyde using $LiN(SiMe_3)_2$ in THF at −78 °C gave the expected product **5b** (~70%) and by-product **9** (~30%), each as a diastereomeric mixture (Scheme II). Compound **9** arises from intramolecular reaction of the initially formed β-alkoxide with the carbonyl of the oxazolinone protecting group and subsequent ring opening. Although change in the reaction quench conditions (H_2O, HCl, or AcOH) at low temperature did not significantly alter the amount of **9**, warming the reaction mixture to room temperature before quenching gave exclusively **9** and no **5b**. When the reaction was done at −130 °C in dimethyl ether/THF, the yield of **5b** rose to 84% and **9** could not be detected. These conditions were generally applicable to the reaction of **4** with a variety of

Scheme II



aldehydes to form the β-hydroxy compounds **5a–i** with a diastereomeric ratio of approximately 5:1 in each case (Table I).[19] The N-protected amino aldehydes **10** and **11**, which were required for the preparation of **5g** and **5h**, respectively, were easily obtained from 3-aminopropanol (N-protection followed by oxidation) and 4-aminobutyraldehyde diethyl acetal (N-protection followed by hydrolysis).

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(19) The relative stereochemistry and isomeric ratios of **5a–i** could be determined from the chemical shifts of the C-2 hydrogens in the ^1H NMR spectra. Thus threonine (2*S*,3*R*) and allothreonine (2*S*,3*S*) were converted to their 4,5-diphenyl-2-oxo-4-oxazolin-3-yl benzyl esters. The C-2 hydrogen of the threonine derivative appeared at δ 4.04 while that of the allothreonine derivative was seen at δ 3.88, thereby showing that the major diastereomer of **5a** obtained by condensation of **4** with acetaldehyde had the allothreonine relative stereochemistry. All condensation products **5** (except **5e**) showed similar behavior and diastereomeric ratios.

Fluorodehydroxylation of **5a–i** with DAST was examined under a variety of conditions. Treatment of a solution of **5b** (5:1 diastereomeric mixture) with DAST (1.1 equiv, CH_2Cl_2, −78 → 20 °C) followed by aqueous workup produced the β-fluoro compound **6b** in ~50% yield as a 1:1 mixture of diastereomers[20] along with 17% of the elimination product **8b**. All attempts to improve this reaction using a variety of conditions and reagents including bis(diethylamino)sulfur difluoride (reported to reduce elimination/rearrangement)[11] failed. However, hydrogenolysis (Pd/C, EtOH/HCl) of **6b** to β-fluoronorvaline (**7b**) proceeded readily in high yield (88%) without any cleavage of the carbon–fluorine bond. This sequence was easily applied to form other aliphatic β-fluoro α-amino acids **7a–d** (Table I). In contrast, treatment of functionalized or sterically crowded hydroxy derivatives **5e–i** with DAST gave none of the desired β-fluoro compounds **6e–i**. Instead, the corresponding elimination products **8e–i** (*E*/*Z* mixture) were isolated, in some cases (**5g** and **5h**) together with recovered starting material. Attempts to reduce carbocationic character at the β-carbon by decreasing the solvent polarity (e.g., $CFCl_3$)[11] had no effect. Since the desired fluorination requires attack by fluoride ion at the β-carbon, tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[21] was added at −78 °C after addition of DAST to **5e**. Unfortunately this only increased the yield of elimination product **8e**, presumably because fluoride can act as a base to remove the α-hydrogen.

In summary, a method has been developed to synthesize aliphatic β-fluoro-α-amino acids using (diethylamino)sulfur trifluoride (DAST), an easily handled fluorinating reagent. Condensation of readily available glycinate **4** with aldehydes affords good yields (55–90%) of β-hydroxy α-amino acid derivatives **5**. Although conversion of these to the corresponding β-fluoro derivatives **6** is limited to cases having unfunctionalized side chains (e.g., **6a–d**), the free β-fluoro α-amino acids **7** are available in high yield (≥88%) by single-step hydrogenolytic deprotection. Previous investigations have shown that deprotection of amino acid derivatives having β-fluorine on the parent side chain is usually problematic.[5c,10] The present method offers an attractive alternative.

Experimental Section

The general procedures and instrumentation which were employed have been described previously.[22] In the present work Bruker WM360 and AM300 NMR spectrometers were also used.

Benzyl *N*-Benzylglycinate. This ester was required for preparation of **1a–d**. A suspension of benzyl glycinate *p*-toluenesulfonate salt[18] (6.4 g, 20 mmol), benzaldehyde (2.0 mL, 20 mmol), and triethylamine (5.0 mL, 40 mmol) in 10 mL of anhydrous methanol was stirred at room temperature for 1 h to produce a clear solution. This was treated with $NaBH_4$ (1.5 g, 40 mmol) in small portions and stirred at 20 °C for 2.5 h. The mixture was poured into 5% $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give an oil, which was dissolved in a minimum amount of CH_2Cl_2. Ether was added, the suspension was filtered, and the filtrate was concentrated in vacuo to give 4.96 g of an oil. Flash chromatography[23] (CH_2Cl_2/10% EtOAc) of a portion (1.60 g) gave 0.90 g (74%) of benzyl *N*-benzylglycinate: IR ($CHCl_3$ cast) 3063, 3031, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.4 (m, 10 H, Ar *H*), 5.3 (s, 2 H, $ArCH_2O$), 3.8 (s, 2 H, $ArCH_2N$), 3.5 (s, 2 H, CH_2N), 1.9 (br s, 1 H, N*H*); exact mass 255.1256 (255.1259 calcd for $C_{16}H_{17}NO_2$).

Benzyl *N*-Benzyl-*N*-(benzyloxycarbonyl)glycinate (1a). A solution of benzyl *N*-benzylglycinate (0.45 g, 1.8 mmol) in CH_2Cl_2 (8 mL) was cooled to 0 °C, and Et_3N (0.28 mL, 2.0 mmol) was added. To this was added benzyl chloroformate (0.29 mL, 2.0 mmol). The mixture was stirred at 0 °C for 1.5 h and at 20 °C for 0.5 h and was then washed with H_2O (5 mL) and 0.5 N HCl (5 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give an oil (0.77 g), which was purified by flash chromatography[23] (CH_2Cl_2) to furnish 0.54 g (69%) of **1a**: IR ($CHCl_3$ cast) 1749, 1706 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.3 (m, 15 H, Ar *H*), 5.2 (4 H, m, $COOCH_2Ph$), 4.6 (s, 2 H, NCH_2CO), 4.0 (br d, 2 H, $ArCH_2N$); exact mass 389.1632 (389.1627 calcd for $C_{24}H_{23}NO_4$). Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.03; H, 5.91; N, 3.59. Found: C, 74.28; H, 5.72; N, 3.81.

Benzyl *N*-Benzyl-*N*-(methoxycarbonyl)glycinate (1b). Reaction of benzyl *N*-benzylglycinate (0.96 g, 3.8 mmol), triethylamine (0.6 mL, 4.0 mmol), and methyl chloroformate (0.30 mL, 4.0 mmol) as described above for **1a** gave **1b** (1.05 g, 89%): IR ($CHCl_3$ cast) 1750, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.25–7.37 (m, 10 H, Ar *H*), 5.15 (s, 2 H, OCH_2Ph), 4.60 (s, 2 H, NCH_2CO), 3.95 (br d, 2 H, NCH_2Ph), 3.75 (br d, 3 H, CH_3); exact mass 313.1314 (313.1314 calcd for $C_{18}H_{19}NO_4$). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.46. Found: C, 69.01; H, 6.00; N, 4.47.

Benzyl *N*-Benzyl-*N*-(*tert*-butoxycarbonyl)glycinate (1c). Reaction of benzyl *N*-benzylglycinate (0.37 g, 1.4 mmol), triethylamine (0.2 mL, 1.5 mmol), and *tert*-butyl pyrocarbonate (0.33 g, 1.5 mmol) as above gave **1c** (0.47 g, 92%): IR ($CHCl_3$ cast) 1751, 1701 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.25–7.50 (m, 10 H, Ar *H*), 5.15 (s, 2 H, OCH_2Ph), 4.52 (s, 2 H, NCH_2CO), 3.9 (br d, 2 H, NCH_2Ph), 1.45 (br s, 9 H, $C(CH_3)_3$); exact mass 355.1789 (355.1783 calcd for $C_{21}H_{25}NO_4$); MS (CI, NH_3), *m*/*z* 373 ($M{\cdot}NH_4^+$, 100%). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.08; N, 3.94. Found: C, 71.24; H, 7.19; N, 3.90.

Benzyl *N*-Benzyl-*N*-[(2,2,2-trichloroethoxy)carbonyl]glycinate (1d). Reaction of benzyl *N*-benzylglycinate (0.37 g, 1.4 mmol), triethylamine (0.2 mL, 1.5 mmol), and trichloroethyl chloroformate (0.2 mL, 0.3 g, 1.5 mmol) as above gave **1d** (0.55 g, 88%): IR ($CHCl_3$ cast) 1751, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.25–7.50 (m, 10 H, Ar *H*), 5.18 (s, 2 H, $COOCH_2Ph$), 4.85 (d, 2 H, NCH_2CO), 4.67 (s, 2 H, CH_2CCl_3), 4.05 (d, 2 H, NCH_2Ph); MS (CI, NH_3), *m*/*z* 449 ($M{\cdot}NH_4^+$ 100%). Anal. Calcd for $C_{19}H_{18}NO_4Cl_3$: C, 52.98; H, 4.21; N, 3.25; Cl, 24.69. Found: C, 52.76; H, 4.13; N, 3.19; Cl, 24.75.

Benzyl 2-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-3-hydroxypentanoate (2a). A solution of **1a** (0.39 g, 1.0 mmol) in THF (4 mL) was added dropwise to a cooled (−78 °C) solution of lithium hexamethyldisilazide (from $HN(Si(Me)_3)_2$ (0.25 mL, 1.2 mmol), BuLi (1.56 M, 0.77 mL, 1.2 mmol), THF (4 mL), 0 °C). The solution was stirred at −78 °C for 45 min, and a solution of propionaldehyde (0.12 mL, 1.7 mmol) in THF (2 mL) was added over 5 min. The resultant colorless solution was stirred at −78 °C for 2.5 h. Water (10 mL) was added, and the mixture was acidified (pH ~5) with 1 N HCl. The aqueous phase was saturated with NaCl and extracted with ether (10 mL) and chloroform (3 × 10 mL). The combined extracts were dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography[23] (CH_2Cl_2/10% hexane then $CHCl_3$) to give 0.28 g (62%) of **2a** as a mixture of diastereomers: IR ($CHCl_3$ cast) 3500 (br), 1737, 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.1–7.4 (m, 15 H, Ar *H*), 3.8–5.3 (m, 9 H), 1.1–1.8 (m, 2 H, CH_2CH_3), 0.9 (m, 3 H, CH_3); MS (CI, NH_3), *m*/*z* 448 ($M{\cdot}H^+$, 100%), 465 ($M{\cdot}NH_4^+$, 15%). Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.12. Found: C, 72.39; H, 6.51; N, 3.14.

Benzyl 2-[*N*-Benzyl-*N*-(methoxycarbonyl)amino]-3-hydroxypentanoate (2b). Reaction of **1b** (0.31 g, 1.0 mmol), $LiN(SiMe_3)_2$ (1.2 mmol), and propionaldehyde (0.14 mL, 2.0 mmol) as described for preparation of **2a** gave 0.23 g (62%) of **2b** (mixture of diastereomers): IR ($CHCl_3$ cast) 3400, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.25–7.50 (m, 10 H, Ar *H*), 5.05 (s, 2 H, $COOCH_2Ph$), 3.5–4.75 (m, 9 H, *CHOH*), NCH_2Ph, $COOCH_2Ph$, $NCOOCH_3$), 1.25–1.75 (m, 2 H, CH_2CH_3), 0.9 (br t, 3 H, CH_3);

(20) The diastereomeric ratio was determined by ^{19}F NMR spectroscopy. The DAST reaction has previously been reported to afford isomeric mixtures: see citations in ref 5c and 10.

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exact mass 371.1737 (371.1733 calcd for $C_{21}H_{25}NO_5$); MS (CI, NH_3), m/z 372 ($M{\cdot}H^+$, 100%). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.88; H, 6.79; N, 3.77.

Benzyl 2-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]-3-hydroxypentanoate (2c). Reaction of **1c** (0.33 g, 0.90 mmol), $LiN(SiMe_3)_2$ (1.0 mmol), and propionaldehyde (0.09 mL, 1.2 mmol) by the above procedure gave 0.20 g (55%) of **2c** (diastereomeric mixture): IR ($CHCl_3$ cast) 3450 (br), 1697 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.0–7.5 (m, 10 H, Ar *H*), 5.0 (s, 2 H, $COOCH_2Ph$), 3.5–4.5 (br m, 5 H, $CHOH$, NCH_2Ph, NCH), 1.38 (br s, 9 H, $C(CH_3)_3$), 1–1.75 (m, 2 H, CH_2CH_3), 0.88 (br t, 3 H, CH_3); MS (CI, NH_3), m/z 414 ($M{\cdot}H^+$, 100%). Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.55; N, 3.38. Found: C, 69.60; H, 7.57; N, 3.38.

Benzyl 2-[*N*-Benzyl-*N*-((2,2,2-trichloroethoxy)carbonyl)amino]-3-hydroxypentanoate (2d). Reaction of **1d** (0.30 g, 0.75 mmol), $LiN(SiMe_3)_2$ (0.9 mmol), and propionaldehyde (0.07 mL, 1.0 mmol) by the above procedure gave 0.2 g (46%) of **2d** (diastereomeric mixture): IR ($CHCl_3$ cast) 3500 (br), 1720 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.25–7.5 (m, 10 H, Ar *H*), 3.75–5.05 (m, 9 H, CH_2CCl_3, $CHOH$, NCH_2Ph, $NCHCOOCH_2Ph$), 1.25–1.75 (m, 2 H, CH_2CH_3), 0.92 (br t, 3 H, CH_3); exact mass 487.0739 (487.0720 calcd for $C_{22}H_{24}NO_5{}^{35}Cl_3$), 489.0719 (489.0690 calcd for $C_{22}H_{24}NO_5{}^{37}Cl^{35}Cl_2$); MS (CI, NH_3) 505 ($M{\cdot}NH_4^+$).

***N*-Benzyl-4-carbobenzoxy-5-ethyloxazolidin-2-one (3).** A solution of DAST (0.03 mL, 0.25 mmol) in anhydrous CH_2Cl_2 (3 mL) at −78 °C was treated with a solution of **2a** (0.10 g, 0.22 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at −78 °C for 15 min and gradually brought to room temperature over 1 h at which point 5% $NaHCO_3$ (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography[23] (CH_2Cl_2/10% hexane) to afford 0.058 g (75%) of **3** as an oil (mixture of diastereomers): IR ($CHCl_3$ cast) 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) [major diastereomer] δ 7.1–7.4 (m, 10 H, Ar *H*), 5.15 (s, 2 H, CH_2Ph), 4.9 (d, 1 H, J = 15 Hz, NCH_2Ph), 4.35–4.4 (m, 1 H, $CHCH_2CH_3$), 4.1 (d, 1 H, J = 15 Hz, NCH_2Ph), 3.7 (d, 1 H, J = 5 Hz, $NCHCOOCH_2$), 1.6–1.7 (m, 2 H, CH_2CH_3), 0.9 (t, 3 H, J = 7.5 Hz, CH_3), [minor diastereomer] δ 7.1–7.4 (m, 10 H, Ar *H*), 5.2 (AB, 2 H, J = 12 Hz, $COOCH_2Ph$), 4.9 (d, 1 H, J = 15 Hz, NCH_2Ph), 4.4–4.5 (m, 1 H, $CHCH_2CH_3$), 4.1 (d, 1 H, J = 15 Hz, NCH_2Ph), 4.05 (d, 1 H, J = 8.5 Hz, NCHCOO), 1.45–1.55 (m, 2 H, CH_2CH_3), 0.96 (t, 3 H, J = 7 Hz, CH_3); exact mass 339.1479 (339.1470 calcd for $C_{20}H_{21}NO_4$); MS (CI, NH_3), m/z 357 ($M{\cdot}NH_4^+$, 100%). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.77; H, 6.23; N, 4.12. Found: C, 70.51; H, 6.38; N, 4.06.

Similar reaction of compounds **2b–d**, furnished **3** in yields of 58%, 91%, and 54%, respectively.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)ethanoate (4). A modification of the literature procedure[17] was used. A solution of benzyl glycinate *p*-toluenesulfonate salt[18] (1.9 g, 5.9 mmol), 4,5-diphenyl-1,3-dioxol-2-one (1.4 g, 5.9 mmol), DMF (20 mL), and triethylamine (1.0 mL, 7.2 mmol) was stirred 12 h at 20 °C. Ethyl acetate (75 mL) was added, and the solution was washed with water (3 × 30 mL). The aqueous phase was extracted with ethyl acetate (20 mL). Combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give an oil, which was dissolved in trifluoroacetic acid (10 mL) and stirred at 20 °C for 2 h. The trifluoroacetic acid was removed in vacuo. The residue was dissolved in CH_2Cl_2 (60 mL), washed with water (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography[23] (25% EtOAc/hexane) furnished 1.8 g (81%) of **4**: mp. 91–93 °C; IR ($CHCl_3$ cast) 1762 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7–7.5 (m, 15 H, Ar *H*), 5.15 (s, 2 H, $COOCH_2Ph$), 4.25 (s, 2 H, NCH_2COO); exact mass 385.1315 (385.1314 calcd for $C_{24}H_{19}NO_4$). Anal. Calcd for $C_{24}H_{19}NO_4$: C, 74.80; H, 4.93; N, 3.63. Found: C, 74.46; H, 4.97; N, 3.61.

Procedure for Condensation of Aldehydes with 4. Preparation of Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxypentanoate (5b). Lithium hexamethyldisilazide was prepared in dimethyl ether (5 mL) at −78 °C, from hexamethyldisilazane (0.25 mL, 1.2 mmol) and BuLi (1.56 M, 0.77 mL, 1.2 mmol) over 30 min. To this was added a solution of **4** (0.39 g, 1.0 mmol) in THF (4 mL) over 5 min. The resulting solution was stirred at −78 °C for 45 min and cooled to −130 °C, and a solution of propionaldehyde (0.14 mL, 2.0 mmol) in THF (2 mL) was added over 5 min. The mixture was stirred at −130 °C for 1.5 h, and a solution of glacial acetic acid (0.07 mL, 1.2 mmol) in THF (1 mL) was added. The mixture was warmed to 20 °C and H_2O (10 mL) was added. The aqueous phase was saturated with NaCl and extracted with ether (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give 0.47 g of an oil. Purification by column chromatography (silica, hexane/10% EtOAc) gave 0.37 g (84%) of **5a** as a ca. 5:1 mixture of diastereomers:[19] IR ($CHCl_3$ cast) 3400 (br), 1756, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) [major diastereomer] δ 7.2–7.6 (m, 15 H, Ar *H*), 5.28 (s, 2 H, CH_2Ph), 4.5 (br d, 1 H, O*H*), 4.3–4.4 (m, 1 H, $CHEt$), 4.0 (d, 1 H, J = 5 Hz, $NCHCOO$), 1.5–1.7 (m, 2 H, CH_2CH_3), 0.94 (t, 3 H, CH_3), [minor diastereomer] δ 7.2–7.6 (m, 15 H, Ar *H*), 5.2–5.4 (AB, 2 H, J = 12 Hz, CH_2Ph), 5.16 (d, 1 H, J = 5 Hz, O*H*), 4.15–4.22 (m, 1 H, $CHEt$), 4.08 (d, 1 H, J = 4 Hz, $NCHCOO$), 1.5–1.8 (m, 2 H, CH_2CH_3), 0.94 (t, 3 H, CH_3); exact mass 443.1737 (443.1733 calcd for $C_{27}H_{25}NO_5$). Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.15. Found: C, 73.07; H, 5.47; N, 3.18.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxybutanoate (5a). Reaction of **4** (0.39 g, 1.0 mmol), $LiN(SiMe_3)_2$ (1.2 mmol), and acetaldehyde (0.79 g, 18 mmol) as above gave 0.39 g (90%) of **5a** as a mixture of diastereomers:[19] IR ($CHCl_3$ cast) 3450 (br), 1758, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) [major diastereomer] δ 7.1–7.6 (m, 15 H, Ar *H*), 5.2–5.32 (AB, 2 H, J = 12 Hz, $COOCH_2Ph$), 4.7–4.8 (m, 1 H, $CHOH$), 4.32 (br d, 1 H, O*H*), 3.88 (d, 1 H, J = 5.5 Hz, N-CH-COO), 1.25 (d, 3 H, J = 6.5 Hz, CH_3), [minor diastereomer] δ 7.1–7.6 (m, 15 H, Ar *H*), 5.2–5.32 (AB, 2 H, $COOCH_2Ph$), 5.14–5.18 (d, 1 H, J = 7 Hz, O*H*), 4.46–4.54 (m, 1 H, $CHOH$), 4.04 (d, 1 H, J = 5 Hz, $NCHCOO$), 1.3–1.34 (d, 3 H, J = 6.25 Hz, CH_3); exact mass 429.1582 (429.1576 calcd for $C_{26}H_{23}NO_5$). Anal. Calcd for $C_{26}H_{23}NO_5$: C, 72.72; H, 5.36; N, 3.26. Found: C, 72.73; H, 5.50; N, 3.22.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxyhexanoate (5c). Reaction of **4** (0.39 g, 1.0 mmol), $LiN(SiMe_3)_2$ (1.2 mmol), and butyraldehyde (0.10 g, 1.5 mmol) as above gave 0.37 g (80%) of **5c** as a mixture of diastereomers:[19] IR ($CHCl_3$ cast) 3400 (br), 1757, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) [major diastereomer] δ 7.1–7.6 (m, 15 H, Ar *H*), 5.24 (AB, 2 H, $COOCH_2Ph$), 4.38–4.46 (m, 1 H, $CHOH$), 4.43 (br s, 1 H, O*H*), 3.9 (d, 1 H, J = 4.4 Hz, $NCHCOO$), 1.2–1.6 (m, 4 H, $CH_2CH_2CH_3$),0.8–0.96 (t, 3 H, CH_3), [minor diastereomer] δ 7.1–7.6 (m, 15 H, Ar *H*), 5.24 (AB, 2 H, $COOCH_2Ph$), 5.1 (d, 1 H, J = 2 Hz, O*H*), 4.2–4.3 (m, 1 H, $CHOH$), 4.03 (d, 1 H, J = 4.8 Hz, $NCHCOO$), 1.2–1.6 (m, 4 H, $CH_2CH_2CH_3$), 0.8–0.96 (t, 3 H, CH_3); exact mass 457.1892 (457.1889 calcd for $C_{28}H_{27}NO_5$). Anal. Calcd for $C_{28}H_{27}NO_5$: C, 73.52; H, 5.90; N, 3.06. Found: C, 73.63; H, 5.90; N, 3.06.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxy-5-methylhexanoate (5d). Reaction of **4** (0.39 g, 1.0 mmol), $LiN(SiMe_3)_2$ (1.2 mmol), and isovaleraldehyde (0.17 g, 2.0 mmol) as above gave 0.33 (70%) of **5d** as a viscous oil:[19] IR ($CHCl_3$ cast) 3500 (br), 1758, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.1–7.5 (m, 15 H, Ar *H*), 5.2–5.3 (AB, 2 H, J = 14 Hz, $COOCH_2Ph$), 4.4 (br d, 1 H, O*H*), 4.15 (m, 1 H, $CHOH$), 3.9 (d, 1 H, J = 5 Hz, $NCHCOO$), 1.7–1.85 (m, 1 H, $CH(CH_3)_2$), 1.5–1.6 (m, 1 H, CH_2), 1.15–1.30 (m, 1 H, CH_2), 0.85–0.95 (d, 6 H, J = 7 Hz, CH_3), [visible signals of minor diastereomer] δ 5.1–5.3 (AB, 2 H, J = 12 Hz, $COOCH_2Ph$), 4.0 (d, 1 H, J = 5 Hz, $NCHCOO$); exact mass 471.2052 (471.2046 calcd for $C_{29}H_{29}NO_5$); MS (CI, NH_3), m/z 472 ($M{\cdot}H^+$). Anal. Calcd for $C_{29}H_{29}NO_5$: C, 73.88; H, 6.15; N, 2.97. Found: C, 73.68; H, 6.16; N, 2.92.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxy-4-methylpentanoate (5e). Reaction of **4** (0.39 g, 1.0 mmol), $LiN(SiMe_3)_2$ (1.2 mmol), and isobutyraldehyde (0.14 g, 2.0 mmol) as above gave 0.37 g (81%) of **5e**:[19] IR ($CHCl_3$ cast) 3400 (br), 1757, 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) [major diastereomer] δ 7.2–7.6 (m, 15 H, Ar *H*), 5.25 (AB, 2 H, J = 12 Hz, $COOCH_2Ph$), 4.5 (d, 1 H, J = 3 Hz, O*H*), 4.25 (d, 1 H, J = 4.5 Hz, $NCHCOO$), 4.0 (m, 1 H, $CHOH$), 1.9–2.0 (m, 1 H, $CH(CH_3)_2$), 0.8 (br t, 6 H, $(CH_3)_2$), [minor diastereomer] δ 7.2–7.6 (m, 15 H, Ar *H*), 5.1–5.4 (AB, 2 H, J = 12 Hz, $COOCH_2Ph$), 5.3 (br d, 1 H, O*H*), 4.15 (d, 1 H, J = 4.5 Hz, $NCHCOO$), 3.7–3.8 (m, 1 H, $CHOH$), 1.8–1.9 (m, 1 H, $CH(CH_3)_2$), 1.1 (d, 3 H, J = 6.5 Hz, CH_3), 0.7 (d, 3 H, J = 6.5 Hz, CH_3); exact mass 457.1893 (457.1889 calcd for $C_{28}H_{27}NO_5$).

Anal. Calcd for $C_{28}H_{27}NO_5$: C, 73.52; H, 5.90; N, 3.06. Found: C, 73.64; N, 5.98; N, 2.90.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxy-3-phenylpropanoate (5f). Reaction of **4** (0.39 g, 1.0 mmol), $LiN(SiMe_3)_2$ (1.2 mmol), and benzaldehyde (0.16 g, 1.5 mmol) as above gave 0.33 g (79%) of **5f**:[19] IR ($CHCl_3$ cast) 3500 (br), 1767 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) [major diastereomer] δ ~7.0–7.5 (m, 20 H, Ar *H*), 5.7 (dd, 1 H, C*H*OH), 5.2–5.4 (AB, 2 H, COOCH_2Ph), 4.3 (d, 1 H, O*H*), 4.0 (d, 1 H, NC*H*COO), [minor diastereomer] δ 6.6–6.9 (br m, 20 H, Ar *H*), 6.28 (d, 1 H, O*H*), 5.56 (dd, 1 H, C*H*OH), 5.25 (s, 2 H, COOCH_2Ph), 4.34 (d, 1 H, NC*H*COO); exact mass 491.1741 (491.1733 calcd for $C_{31}H_{25}NO_5$). Anal. Calcd for $C_{31}H_{25}NO_5$: C, 75.74; H, 5.09; N, 2.85. Found: C, 75.37; H, 5.45; N, 2.76.

Benzyl 2,5-Bis(4,5-diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxypentanoate (5g). Reaction of **4** (0.19 g, 0.5 mmol), $LiN(SiMe_3)_2$ (0.6 mmol), and aldehyde **10** (0.15 g, 0.5 mmol) at −78° C as above gave 0.20 g (60%) of **5g**:[19] IR ($CHCl_3$ cast) 3500 (br), 1755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) [major diastereomer] δ 7.1–7.5 (m, 25 H, Ar *H*), 5.1–5.25 (AB, 2 H, *J* = 12 Hz, COOCH_2Ph), 4.4 (br s, 1 H, O*H*), 4.2–4.3 (m, 1 H, C*H*OH), 3.94 (d, 1 H, *J* = 4.5 Hz, NC*H*COO), 3.62 (t, 2 H, *J* = 7 Hz, CH_2N), 1.7–1.9 (m, 2 H, CH_2), [minor diastereomer] δ 7.1–7.5 (m, 25 H, Ar *H*), 5.1–5.25 (AB, 2 H, COOCH_2Ph), 5.0 (d, 1 H, O*H*), 4.16–4.24 (m, 1 H, C*H*OH), 4.02 (d, 1 H, *J* = 6.5 Hz, NC*H*COO), 3.62 (br t, 2 H, CH_2N), 0.8–1.4 (m, 2 H, CH_2); FAB MS, *m/z* 679.46 (M·H^+, 50.5%). Anal. Calcd for $C_{42}H_{34}N_2O_7$: C, 74.33; H, 5.01; N, 4.12. Found: C, 73.94; H, 5.22; N, 3.99.

Benzyl 2,6-Bis(4,5-diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxyhexanoate (5h). Reaction of **4** (0.19 g, 0.5 mmol), $LiN(SiMe_3)_2$ (0.6 mmol), and aldehyde **11** (0.15 g, 0.5 mmol) at −78 °C as above gave 0.19 g (55%) of **5h**:[19] IR ($CHCl_3$ cast) 3500 (br), 1754 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) [major diastereomer] δ 7–7.6 (m, 25 H, Ar *H*), 5.22 (AB, 2 H, *J* = 12.5 Hz, COOCH_2Ph), 4.38 (br s, 1 H, O*H*), 4.22–4.32 (m, 1 H, C*H*OH), 3.87 (d, 1 H, *J* = 5 Hz, NC*H*COO), 3.4–3.64 (m, 2 H, CH_2N), 1.36–1.8 (m, 4 H, CH_2) [minor diastereomer] δ 7–7.6 (m, 25 H, Ar *H*), 5.22 (AB, 2 H, *J* = 12.5 Hz, COOCH_2Ph), 5.06 (d, 1 H, O*H*), 4.1–4.2 (m, 1 H, C*H*OH), 4.0 (d, 1 H, *J* = 5 Hz, NC*H*COO), 3.4–3.64 (m, 2 H, CH_2N), 1.36–1.8 (m, 4 H, CH_2); FAB MS, *m/z* 693.73 (M·H^+, 100%). Anal. Calcd for $C_{43}H_{36}N_2O_7$: C, 74.56; H, 5.20; N, 4.04. Found: 74.35; H, 5.30; N, 4.10.

Dibenzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxybutanedioate (5i). Reaction of **4** (0.39 g, 1.0 mmol), $LiN(SiMe_3)_2$ (1.2 mmol), and benzyl glyoxylate[24] (0.24 g, 1.5 mmol) at −78 °C gave 0.30 g (55%) of diastereomers, which were separable by flash chromatography.

Major diastereomer (61%): IR ($CHCl_3$ cast) 3200–3450 (br), 1758, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.9–7.5 (m, 20 H, Ar *H*), 6.22 (d, 1 H, *J* = 12 Hz, O*H*), 5.16–5.3 (2 × AB, 4 H, *J* = 12 Hz each, COOCH_2Ph), 4.98 (dd, 1 H, *J* = 12, 5 Hz, C*H*OH), 4.7 (d, 1 H, *J* = 5 Hz, NC*H*COO); exact mass 549.1784 (549.1788 calcd for $C_{33}H_{27}NO_7$); MS (CI, NH_3) 550 (M·H^+, 100%). Anal. Calcd for $C_{33}H_{27}NO_7$: C, 72.13; H, 4.91; N, 2.55. Found: C, 71.91; H, 4.98; N, 2.40.

Minor diastereomer (39%): IR ($CHCl_3$ cast) 3200–3450 (br), 1761, 1756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.1–7.6 (m, 20 H, Ar *H*), 5.0–5.2 (2 × AB, 4 H, *J* = 12.5, 12 Hz, COOCH_2Ph), 5.04 (d, 1 H, *J* = 4 Hz, O*H*), 4.92 (t, 1 H, *J* = 3.5 Hz, C*H*OH), 4.78 (d, 1 H, *J* = 3 Hz, NC*H*COO): exact mass 549.1773 (549.1788 calcd for $C_{33}H_{27}NO_7$). Anal. Calcd for $C_{33}H_{27}NO_7$: C, 72.13; H, 4.91; N, 2.55. Found: C, 71.95; H, 5.18; N, 2.61.

Procedure for Fluorination of Protected β-Hydroxy α-Amino Acid Esters 5a–d with DAST. Preparation of Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-fluoropentanoate (6b). A solution of DAST (0.11 mL, 0.15 g, 0.9 mmol) in CH_2Cl_2 (12 mL) was cooled to −78 °C, and a solution of **5b** (0.37 g, 0.80 mmol) in CH_2Cl_2 (12 mL) was added dropwise. The mixture was stirred at −78 °C for 2 h and at −45 °C for 2 h and was then gradually brought to 20 °C. Water (10 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (5 mL). The organic phases were dried (Na_2SO_4) and concentrated to give 0.34 g of an oil, which was purified by chromatography (SiO_2, hexane/8% EtOAc) to give 0.22 g (48%) of **6b** and 0.06 g (17%) of **8b**. For **6b** (mixture of diastereomers): IR ($CHCl_3$ cast) 1765 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) [major isomer] δ 7.2–7.6 (m, 15 H, Ar *H*), 5.2 (AB, 2 H, *J* = 6 Hz, CH_2Ph), 5.1–5.4 (m, 1 H, FCH), 4.26 (br t, 1 H, *J* = 8.8 Hz, NC*H*COO), 1.5–1.68 (m, 2 H, CH_2CH$_3$), 0.92 (t, 3 H, *J* = 8.1 Hz, CH$_3$), [minor isomer] δ 7.2–7.6 (m, 15 H, Ar *H*), 5.24 (AB, 2 H, *J* = 6.2 Hz, CH_2Ph), 5.1–5.4 (m, 1 H, FC*H*), 4.2 (dd, 1 H, *J* = 13.6, 6.8 Hz, NC*H*COO), 1.7–2.05 (m, 2 H, CH_2CH$_3$), 0.98 (t, 3 H, *J* = 7.2 Hz, CH$_3$); exact mass 445.1686 (445.1689 calcd for $C_{27}H_{24}NO_4F$); MS (CI, NH_3) 463 (M·NH_4^+, 100%); ^{19}F NMR ($CDCl_3$, 376 MHz, $CFCl_3$ standard) δ −187.1 to −187.4 (m), −189.5 to −189.8 (m). The compound was light sensitive and a satisfactory analysis could not be obtained. Anal. Calcd for $C_{27}H_{24}NO_4F$: C, 72.79; H, 5.43; N, 3.14. Found: C, 72.09; H, 5.52; N, 2.92.

Benzyl 2-(4,5-diphenyl-2-oxo-4-oxazolin-3-yl)-2-pentenoate (8b) (mixture of isomers): IR ($CHCl_3$ cast) 1768, 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) [major isomer] δ 7.2–7.4 (m, 15 H, Ar *H*), 7.1 (t, 1 H, C*H*CH$_2$), 5.1 (AB, 2 H, CH_2Ph), 2–2.4 (m, 2 H, CH_2CH$_3$), 1.0 (t, 3 H, CH$_3$), [minor isomer] δ 7.2–7.4 (m, 15 H, Ar *H*), 6.3 (t, 1 H, C*H*CH$_3$), 5.1 (AB, 2 H, CH_2Ph), 2.6 (m, 2 H, CH_2CH$_3$), 0.95 (t, 3 H, CH$_3$); exact mass 425.1623 (425.1627 calcd for $C_{27}H_{23}NO_4$); MS (CI, NH_3), *m/z* 443 (M·NH_4^+, 100%). Anal. Calcd for $C_{27}H_{23}NO_4$: C, 76.21; H, 5.44; N, 3.29. Found: C, 76.25; H, 5.40; N, 3.28.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-fluorobutanoate (6a). The procedure described above was used to convert **5a** (0.30 g, 0.7 mmol) with DAST (0.16 mL, 0.20 g, 1.3 mmol) to give 0.14 g (45%) of **6a** and 0.070 g (24%) of **8a**. For **6a** (mixture of diastereomers): IR ($CHCl_3$ cast) 1764 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) [major isomer] δ 7.18–7.58 (m, 15 H, Ar *H*), 5.38–5.46 (m, 1 H, C*H*F), 5.16–5.28 (AB, 2 H, *J* = 12 Hz, COOCH_2Ph), 4.18–4.26 (dd, 1 H, J_{H-F} = 14 Hz, J_{H-H} = 6.5 Hz, NC*H*COO), 1.4–1.54 (dd, 3 H, J_{H-F} = 12.5 Hz, J_{H-H} = 6 Hz, CH$_3$), [minor isomer] δ 7.18–7.58 (m, 15 H, Ar *H*), 5.5–5.6 (m, 1 H, C*H*F), 5.16–5.28 (AB, 2 H, COOCH_2Ph), 4.14–4.18 (br t, 1 H, *J* = 8.5 Hz, NC*H*COO), 1.4–1.54 (dd, 3 H, J_{H-F} = 13.5 Hz, J_{H-H} = 6 Hz, CH$_3$); exact mass 431.1530 (431.1533 calcd for $C_{26}H_{22}NO_2F$). Anal. Calcd for $C_{26}H_{22}NO_4F$: C, 72.38; H, 5.10; N, 3.25. Found: C, 72.14; H, 5.07; N, 3.28. ^{19}F NMR ($CDCl_3$, 376 MHz, $CFCl_3$ standard) δ −175.9 to −176.3 (m), −178.3 to −178.6 (m).

Benzyl 2-(4,5-diphenyl-2-oxo-4-oxazolin-3-yl)-2-butenoate (8a) (mixture of isomers): IR ($CHCl_3$ cast) 1768 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) [major isomer] δ 7.1–7.5 (m, 16 H, Ar *H* and C*H*CH$_3$), 5.1 (AB, 2 H, *J* = 12 Hz, COOCH_2Ph), 1.85–1.9 (d, 3 H, *J* = 7 Hz, CH$_3$); [minor isomer] 7.1–7.5 (m, Ar *H*), 6.5 (q, 1 H, *J* = 7 Hz, C*H*CH$_3$), 5.1 (s, 2 H, COOCH_2Ph), 2.1–2.15 (d, 3 H, *J* = 7 Hz, CH$_3$); exact mass 411.1466 (411.1466 calcd for $C_{26}H_{22}NO_4$). Anal. Calcd for $C_{26}H_{21}NO_4$: C, 75.88; H, 5.11; N, 3.40. Found: C, 75.76; H, 5.32; N, 3.39.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-fluorohexanoate (6c). Reaction of **5c** (0.3 g, 0.70 mmol) and DAST (0.1 mL, 0.13 g, 0.80 mmol) as above gave 0.22 g (65%) of **6c** (mixture of diastereomers): IR ($CHCl_3$ cast) 1764 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) [major isomer] δ 7.2–7.6 (m, 15 H, Ar *H*), 5.1–5.3 (m, 1 H, C*H*F), 5.2–5.3 (AB, 2 H, *J* = 11.5 Hz), 4.2–4.3 (dd, 1 H, J_{H-F} = 13 Hz, J_{H-H} = 6 Hz, NC*H*COO), 1.4–1.7 (m, 4 H, CH_2), 0.92–1.0 (t, 3 H, CH$_3$), [minor isomer] δ 7.2–7.6 (m, 15 H, Ar *H*), 5.4–5.5 (m, 1 H, C*H*F), 5.2–5.3 (AB, 2 H, COOCH_2Ph), 4.2–4.25 (br t, 1 H, *J* = 3 Hz, NC*H*COO), 1.7–2.0 (m, 4 H, CH_2), 0.85–0.92 (t, 3 H, CH$_3$); exact mass 459.1852 (459.1846 calcd for $C_{28}H_{26}NO_4F$). Anal. Calcd for $C_{28}H_{26}NO_4F$: C, 73.20; H, 5.66; N, 3.05. Found: C, 72.95; H, 5.76; N, 2.97. ^{19}F NMR ($CDCl_3$, 376 MHz, $CFCl_3$ standard) δ −186.3 to −186.6 (m), −188.5 to −188.8 (m).

Benzyl 2-(4,5-diphenyl-2-oxo-4-oxazolin-3-yl)-2-hexenoate (8c) was isolated from a similar reaction of **5c** (0.16 g, 0.4 mmol) and DAST (0.05 mL, 0.07 g, 0.4 mmol). The yield was 0.020 g (13%) (mixture of isomers): IR ($CHCl_3$ cast) 1767 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) [major isomer] δ 7.15–7.6 (m, 15 H, Ar *H*), 7.1–7.15 (t, 1 H, C*H*CH$_2$), 5.14 (s, 2 H, COOCH_2Ph), 2.0–2.4 (m, 2 H, CH_2), 1.2–1.6 (m, 2 H, CH_2), 0.85–1.0 (t, 3 H, CH$_3$), [minor isomer] δ 7.1–7.6 (m, Ar *H*), 6.3–6.4 (t, 1 H, C*H*CH$_2$), 5.2 (AB, 2 H, COOCH_2Ph), 2.4–2.7 (m, 2 H, CH_2), 1.2–1.6 (m, 2 H, CH_2), 0.8 (t, 3 H, CH$_3$); exact mass 439.1777 (439.1770 calcd for $C_{28}H_{25}NO_4$). Anal. Calcd for $C_{28}H_{25}NO_4$: C, 76.53; H, 5.69; N,

(24) Jung, M. E.; Shishido, K.; Davis, L. H. *J. Org. Chem.* **1982**, *47*, 891–892.

3.18. Found: C, 76.31; H, 5.77; N, 2.99.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-fluoro-5-methylhexanoate (6d). Reaction of **5d** (0.33 g, 0.7 mmol) and DAST (0.15 mL, 0.2 g, 1.7 mmol) as above gave 0.21 g (65%) of **6d** and 0.040 g (12%) of **8d**. **6d** (mixture of diastereomers): IR ($CHCl_3$ cast) 1765 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) [major isomer] δ 7.1–7.6 (m, 15 H, Ar *H*), 5.2–5.3 (m, 1 H, C*H*F), 4.2–4.28 (1 H, dd, J_{H-F} = 13 Hz, J_{H-H} = 9 Hz, NC*H*COO), 5.1–5.3 (AB, 2 H, J = 12 Hz, COOCH_2Ph), 1.4–1.8 (m, 3 H, CH_2C*H*), 0.9–1.0 (2 × d, 6 H, J = 6 Hz, CH_3), [minor isomer] δ 7.1–7.6 (m, 15 H, Ar *H*), 5.38–5.44 (m, 1 H, C*H*F), 5.18–5.22 (AB, 2 H, J = 12 Hz, COOCH_2Ph), 4.16–4.22 (t, 1 H, $J \simeq$ 8.5 Hz, NC*H*COO), 1.4–1.8 (m, 3 H, CH_2C*H*), 0.8–0.9 (t, 6 H, J = 6.5 Hz, CH_3); exact mass 473.1990 (473.2002 calcd for $C_{29}H_{28}NO_4F$). Anal. Calcd for $C_{29}H_{28}NO_4F$: C, 73.57; H, 5.91; N, 2.95. Found: C, 73.76; H, 5.97; N, 2.85. ^{19}F NMR ($CDCl_3$, 376 MHz, $CFCl_3$ standard) δ −184.8 to −185.1 (m), −186.7 to −187.0 (m).

Benzyl 2-(4,5-diphenyl-2-oxo-4-oxazolin-3-yl)-5-methyl-2-hexenoate (8d) (mixture of isomers): IR ($CHCl_3$ cast) 1765 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) [major isomer] δ 7.15–7.5 (m, 16 H, Ar *H* and C*H*CH_2), 5.1 (AB, 2 H, J = 13 Hz, COOCH_2Ph), 2.0–2.3 (m, 2 H, CH_2), 1.7–1.8 (m, 1 H, C*H*$(CH_3)_2$), 0.95 (d, 3 H, J = 6.5 Hz, CH_3), 0.85 (d, 3 H, J = 6.5 Hz, CH_3), [minor isomer] δ 7.15–7.5 (m, Ar *H*), 6.4 (t, 1 H, J = 8 Hz, C*H*CH_2), 5.1–5.2 (AB, 2 H, J = 11 Hz, COOCH_2Ph), 2.5 (dd, 2 H, $J \simeq$ 8 Hz, CH_2), 1.5–1.65 (m, 1 H, C*H*$(CH_3)_2$), 0.75 (d, 6 H, J = 6.5 Hz, CH_3); exact mass 453.1947 (453.1940 calcd for $C_{29}H_{27}NO_4$). Anal. Calcd for $C_{29}H_{27}NO_4$: C, 76.78; H, 6.00; N, 3.09. Found: C, 76.39; H, 5.89; N, 2.97.

Dehydration of Protected β-Hydroxy α-Amino Acid Esters 5e,g–i by DAST. Attempted fluorination of **5e,g–i** by the procedure described above for **5a-d** gave none of the desired fluoro compound but afforded **8e,g–i**, respectively, as the major products.

8e: obtained from the reaction of **5e** (0.11 g, 0.34 mmol) with DAST (0.05 mL, 0.07 g, 0.4 mmol) and TASF (0.24 g, 0.9 mmol); yield, 0.06 g (54%, 75% based on recovered starting material) of oil; IR ($CHCl_3$ cast) 1768, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.1–7.5 (m, 15 H, Ar *H*), 6.98 (d, 1 H, C*H*CH$(CH_3)_2$), 5.2 (s, 2 H, COOCH_2Ph), 2.65 (m, 1 H, C*H*$(CH_3)_2$), 1.16 (d, 3 H, CH_3), 0.82 (d, 3 H, CH_3); exact mass 439.1778 (439.1783 calcd for $C_{28}H_{25}NO_4$). Anal. Calcd for $C_{28}H_{25}NO_4$: C, 76.53; H, 5.69; N, 3.18. Found: C, 76.60; H, 5.84; N, 3.31.

8g: obtained from the reaction of **5g** (0.14 g, 0.2 mmol) and DAST (0.04 mL, 0.05 g, 0.3 mmol); yield, 0.034 g (25%, 46% based on recovered starting material); mixture of diastereomers; IR ($CHCl_3$ cast) 1765 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) [major isomer] δ 7.1–7.5 (m, 25 H, Ar *H*), 6.9 (t, 1 H, C*H*CH_2), 5.1 (AB, 2 H, COOCH_2Ph), 3.65 (m, 2 H, CH_2N), 2.5 (m, 2 H, CHCH_2), [minor isomer] δ 7.1–7.5 (m, Ar*H*), 6.35 (t, 1 H, C*H*CH_2), 5.04 (s, 2 H, COOCH_2Ph), 3.65 (m, 2 H, CH_2N), 2.5 (m, 2 H, CHCH_2); FAB MS, m/z 661 ($M{\cdot}H^+$, 100%), 660 (M^+, 40%). The compound was light sensitive, and satisfactory elemental analysis could not be obtained. Anal. Calcd for $C_{42}H_{32}N_2O_6$: C, 76.35; H, 4.89; N, 4.24. Found: C, 75.70; H, 4.92; N, 4.24.

8h: obtained from the reaction of **5g** (0.09 g, 0.14 mmol) and DAST (0.02 mL, 0.03 g, ~0.2 mmol); yield, 0.050 g (56%, 73% based on recovery of starting material); mixture of diastereomers; IR ($CHCl_3$ cast) 1763 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) [major isomer] δ 7.1–7.6 (m, 25 H, Ar *H*), 6.9 (t, 1 H, C*H*CH_2), 5.1 (AB, 2 H, COOCH_2Ph), 3.5 (t, 2 H, CH_2N), 1.9–2.3 (m, 2 H, C*H*CH_2), 1.4–1.7 (m, 2 H, C$H_2$$CH_2$N), [minor isomer] δ 7.1–7.6 (m, 25 H, Ar *H*), 6.15 (t, 1 H, C*H*CH_2), 5.04 (s, 2 H, COOCH_2Ph), 3.3–3.4 (t, 2 H, CH_2N), 1.9–2.3 (m, 2 H, C*H*CH_2), 1.2–1.4 (m, 2 H, C$H_2$$CH_2$N); exact mass 674.2409 (674.2416 calcd for $C_{43}H_{34}N_2O_6$). Anal. Calcd for $C_{43}H_{34}N_2O_6$: C, 76.55; H, 5.04; N, 4.15. Found: C, 76.63; H, 5.21; N, 4.07.

8i: obtained from **5i** (0.32 g, 0.6 mmol of pure major diastereomer) and DAST (0.12 mL, 0.16 g, 1.0 mmol); yield 0.2 g (76%); mixture of diastereomers; IR ($CHCl_3$ cast) 1773, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) [major isomer] δ 7.1–7.4 (m, 20 H, Ar *H*), 7.05 (s, 1 H, C*H*COO), 5.2 (s, 2 H, COOCH_2Ph), 5.05 (br d, 2 H, J = 6 Hz, COOCH_2Ph), [minor isomer] δ 7.1–7.4 (m, Ar *H*), 6.2 (s, 1 H, C*H*COO), 5.0 (s, 2 H, COOCH_2Ph), 4.8 (s, 2 H, COOCH_2Ph); exact mass 531.1669 (531.1682 calcd for $C_{33}H_{25}NO_6$). Anal. Calcd for $C_{33}H_{25}NO_6$: C, 74.57; H, 4.70; N, 2.63. Found: C, 74.52; H, 4.71; N, 2.65.

Deprotection of 6a–d to β-Fluoro α-Amino Acids 7a–d. Preparation of 2-Amino-3-fluoropentanoic Acid (β-Fluoronorvaline) (7b).[3] The literature procedure[17] was adapted. A mixture of 10% palladium on charcoal (0.10 g) and **6b** (0.27 g, 0.60 mmol) in 25 mL of ethanol was hydrogenated for 2 days in a low-pressure hydrogenation apparatus at 45 psi until no fluorescent material was seen by thin-layer chromatography. The mixture was filtered through Celite, the Celite was washed with ethanol, and the filtrate was concentrated in vacuo. The residue was treated with water (10 mL) and filtered. Concentration and lyophilization of the filtrate gave 0.12 g of solid, which was purified by ion-exchange chromatography (AG50, H^+) to give 0.070 g (88%) of **7b**, as a nearly equal mixture of diastereomers: mp 189–191 °C (lit.[3] mp 182 °C dec); IR (KBr) 2600–3200 (br), 1588 cm^{-1}; ^1H NMR (D_2O, 300 MHz) [major isomer] δ 4.9–5.05 (m, 1 H, FC*H*CH_2), 3.9 (dd, 1 H, J = 27, 4 Hz, H_2NC*H*COOH), 1.6– 1.9 (m, 2 H, C$H_2$$CH_3$), 1.0 (t, 3 H, J = 7 Hz, CH_3), [minor isomer] δ 4.9–5.05 (m, 1 H, FC*H*CH_2), ~4.1 (dd, 1 H, J = 19, 3 Hz, H_2NC*H*COOH), 1.5–1.6 (m, 2 H, C$H_2$$CH_3$), 1.0 (t, 3 H, J = 7 Hz, CH_3); FAB MS, m/z 136.07 ($M{\cdot}H^+$). Anal. Calcd for $C_5H_{10}NO_2F$: C, 44.44; H, 7.46; N, 10.36. Found: C, 44.32; H, 7.40; N, 10.08. ^{19}F NMR (D_2O, 376 MHz, $CFCl_3$ std) δ −187.3 to −187.6 (m), −189.7 to −190 (m).

2-Amino-3-fluorobutanoic Acid (7a).[3] Compound **6a** (0.10 g, 0.24 mmol) was hydrogenated as described above by using 10% Pd/C (0.6 g) to yield 29 mg (>99%) of **7a** as a 1:1 mixture of diastereomers: mp 188–190 °C dec (lit.[3] mp 204.5–205 °C dec); IR (KBr) 3374–3475 (br), 1648, 1623, 1589 cm^{-1}; ^1H NMR (D_2O, 400 MHz) [isomer A] δ 5.0–5.26 (m, 1 H, C*H*F), 4.0 (dd, 1 H, J_{H-F} = 16.5 Hz, J_{H-H} = 3.5 Hz, NC*H*), 1.45–1.55 (dd, 3 H, J_{H-F} = 25 Hz, J_{H-H} = 6.5 Hz, CH_3), [isomer B] δ 5.0–5.26 (m, 1 H, C*H*F), 3.74 (dd, 1 H, J_{H-F} = 25.5 Hz, J_{H-H} = 4 Hz), 1.35–1.45 (dd, 3 H, J_{H-F} = 25 Hz, J_{H-H} = 6.5 Hz, CH_3); FAB MS (glycerol/HCl), m/z 122.12 ($M{\cdot}H^+$, 100%), 243 ($2M{\cdot}H^+$); ^{19}F NMR (D_2O, 376 MHz, $CFCl_3$ std) (~1:1) δ −181.7 (m), −184 to −184.5 (m).

2-Amino-3-fluorohexanoic Acid (7c).[3] Compound **6c** (0.22 g, 0.48 mmol) was hydrogenated as described above by using 10% Pd/C (0.15 g) to yield 64 mg (89%) of **7c** as a 1:1 mixture of diastereomers: mp 185–190 °C dec (lit.[3] mp 180–181 °C dec); IR (KBr) 2600–3400 (br), 1655, 1651, 1628, 1609, 1587 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 4.9–5.2 (m, 1 H, C*H*F), 4.1–3.9 (2 × dd, 1 H, J_{H-F} = 18.5, 27 Hz, J_{H-H} = 3.5, 3.8 Hz, H_2NC*H*), 1.3–1.9 (m, 4 H, CH_2), 1.0–0.9 (2 × t, 3 H, CH_3); FAB MS (glycerol/HCl), m/z 150 ($M{\cdot}H^+$, 100%); ^{19}F NMR (D_2O, 376 MHz, $CFCl_3$ std) δ −210.7 to −210.9 (m), and −213.7 to −214.0 (m).

2-Amino-3-fluoro-5-methylhexanoic Acid (7d). Compound **6d** (0.18 g, 0.38 mmol) was hydrogenated as described above by using 10% Pd/C (0.1 g) to yield 56 mg (91%) of **7d** as a 1:1 mixture of diastereomers: mp 164–166 °C; IR (KBr) 3396–3456 (br), 2927, 2962, 1584, 1514, 1407, 1328 cm^{-1}; ^1H NMR (D_2O, 400 MHz) [isomer A] δ 5.36–5.58 (m, 1 H, C*H*F), 4.3–4.4 (dd, 1 H, J_{H-F} = 18 Hz, J_{H-H} = 3.4 Hz, H_2NC*H*); 1.85–2.0 (m, 2 H, CH_2), 1.48–1.85 (m, 1 H, C*H*$(Me)_2$), 1.05 (t, 6 H, J = 6.4 Hz, CH_3), [isomer B] δ 5.36–5.58 (m, 1 H, C*H*F), 4.02–4.14 (dd, 1 H, J_{H-F} = 27.3 Hz, J_{H-H} = 3.7 Hz, H_2N-C*H*-COOH), 1.01 (d, 3 H, J = 2.4 Hz, CH_3), 1.03 (d, 3 H, J = 2 Hz, CH_3); FAB MS (glycerol/HCl), m/z 164.00 ($M{\cdot}H^+$, 100%); ^{19}F NMR (D_2O, 376 MHz, $CFCl_3$ standard) δ −188.0 to −188.3 (m), −191.8 to −192.1 (m).

4,5-Diphenyl-3-(3-oxopropyl)-4-oxazolin-2-one (10). Condensation of 3-aminopropanol (0.442 g, 5.88 mmol) with 4,5-diphenyl-1,3-dioxol-2-one[17] (1.40 g) as described above for the preparation of **4** gave a mixture of the protected alcohol and its trifluoroacetate ester. Hydrolysis of this mixture (excess NaOH, aqueous THF, 25 °C, 1 h), gave after recrystallization (EtOAc/hexane) 1.22 g (70%) of 4,5-diphenyl-3-(3-hydroxypropyl)-4-oxazolin-2-one: mp 102–103 °C; IR ($CHCl_3$ cast) 3450 (br), 1754, 1739, 1381 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6–7.2 (m, 10 H, Ar *H*), 3.8–3.5 (m, 4 H, NCH_2, OCH_2), 2.8 (br t, 1 H, O*H*), 1.6 (m, 2 H, CH_2); exact mass 295.1205 (295.1209 calcd for $C_{18}H_{17}NO_3$). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.22; H, 5.76; N, 4.74. Found: 72.98; H, 5.64; N, 4.85.

This material was oxidized by using the Swern procedure.[25] A solution of oxalyl chloride (0.2 mL, 2.2 mmol) in anhydrous

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CH_2Cl_2 (4 mL) was cooled to −78 °C, and DMSO (0.30 mL, 4.4 mmol) in CH_2Cl_2 (1 mL) was added slowly. The mixture was stirred at −78 °C for 2 min, and a solution of the alcohol (0.53 g, 1.8 mmol) in CH_2Cl_2 (5 mL) was added rapidly. The resulting mixture was stirred at −78 °C for 30 min, and triethylamine (1.4 mL, 1.0 g 10 mmol) was added. The mixture was stirred at −78 °C for 5 min and brought to 20 °C. Water (10 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The organic phases were dried (Na_2SO_4) and concentrated to give 0.64 g of an oil, which was purified by flash chromatography[23] (CH_2Cl_2, 10% EtOAc) to afford 0.47 g (89%) of **10**: mp 102–103 °C; IR ($CHCl_3$ cast) 1775 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 9.13 (s, 1 H, C*H*O), 7.1–7.6 (m, 10 H, Ar *H*), 3.8 (t, 2 H, NCH_2CH_2), 2.77 (t, 2 H, CH_2CHO); exact mass 293.1051 (293.1052 calcd for $C_{18}H_{15}NO_3$). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.72; H, 5.12; N, 4.78. Found: C, 73.50; H, 4.98; N, 4.64.

4,5-Diphenyl-3-(4-oxobutyl)-4-oxazolin-2-one (11). This was prepared from commercially available 4-aminobutyraldehyde diethyl acetal (1.0 mL, 0.94 g, 5.9 mmol), 4,5-diphenyl-1,3-dioxol-2-one[17] (1.4 g, 5.9 mmol), and Et_3N (1.0 mL, 0.7 g, 7.2 mmol). The residue obtained after the CF_3COOH step[17] was dissolved in THF/H_2O (3:1 v/v, 20 mL). The solution was stirred 20 min at 20 °C, and the THF was removed in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with water and brine. Drying (Na_2SO_4) and concentration gave 2.30 g of an oil, which was recrystallized from EtOAc/hexane to give 1.17 g (65%) of **11**: IR ($CHCl_3$ cast) 1754 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 9.6 (s, 1 H, C*H*O), 7.0–8.0 (m, 10 H, Ar *H*), 3.55 (t, 2 H, CH_2N), 2.47 (t, 2 H, CH_2CHO), 1.53 (m, 2 H, $CH_2CH_2CH_2$); exact mass 307.1218 (307.1209 calcd for $C_{19}H_{17}NO_3$). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.26; H, 5.80; N, 4.56. Found: C, 73.99; H, 5.80; N, 4.40.

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Diethyl 3-Iodopropynephosphonate: An Alkylative β-Keto Phosphonate Equivalent

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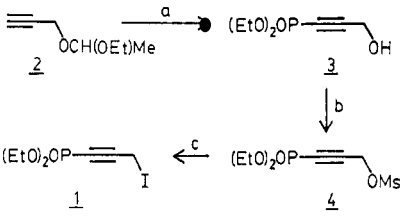
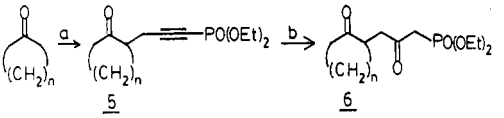
A wide range of natural products containing five-membered rings within their carbocyclic frameworks continue to be isolated and to challenge the imagination of synthetic chemists.[1] New strategies for their construction are constantly being developed; however, many of these methods require the establishment of a unique arrangement of functionalities in order to facilitate ring formation (i.e., vinylcyclopropane rearrangement,[2] Nazarov-type reactions,[3] α-alkynone cyclizations,[4] unsaturated diazoketone closures[5]). A straightforward approach to the introduction of a five-membered ring involves the alkylation of a ketone with an acetonyl equivalent, unmasking of the three-carbon appendage, and intramolecular cyclization. A variety of bromoacetone synthons have been developed for this purpose and utilized in the context of total synthesis.[6] For the most part, these reagents rely on an aldol reaction to close to the cyclopentenone ring. This process is often plagued with complications, such as base-catalyzed isomerization of initially formed products or anion exchange.[7] To improve the cyclization, the Wadsworth–Emmons reaction has become the method of choice, and two reagents have been developed for use in this manner: diethyl 3-bromo-2-ethoxypropenephosphonate[8] and bromoacetyl methylenetriphenylphosphorane.[9] Both reagents have

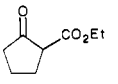
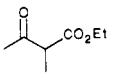
Scheme I[a]



[a] Reagents: (a) 1. *n*-BuLi/$ClPO(OEt)_2$, 2. 50% aqueous HOAc; (b) $MsCl/Et_3N$; (c) NaI.

Table I. Alkylation and Hydrolysis Results[a]



substrate	yield, % 5	6
n = 2	99	98
n = 3	99	97
n = 4	94	99
	98[b]	80
	96[b]	78

[a] Reagents: (a) $KN(SiMe_3)_2/BEt_3/1$; (b) $HgSO_4/10\%$ H_2SO_4/EtOH. [b] Alkylation conditions: NaH (1.1 equiv), substrate (1 M THF), 0 °C, 1 h, 1 (1 M THF), −78 °C, 30 min, room temperature 24 h.

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