Diastereoselective (Ethoxycarbonyl)difluoromethylation of Chiral Imide Enolates Mediated by Triethylborane

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Triethylborane-mediated reactions of lithium enolates derived from chiral *N*-acyloxazolidinones with ethyl difluoroiodoacetate allows easy access to α-(ethoxycarbonyl)difluoromethylated carboximides with good diastereomeric excess (86—>98% de). The stereochemistry of the (ethoxycarbonyl)difluoromethylated carboximides indicates that the (ethoxycarbonyl)difluoromethyl radical generated from ethyl difluoroiodoacetate and triethylborane reacts preferentially on the *si* face of the lithium enolates.

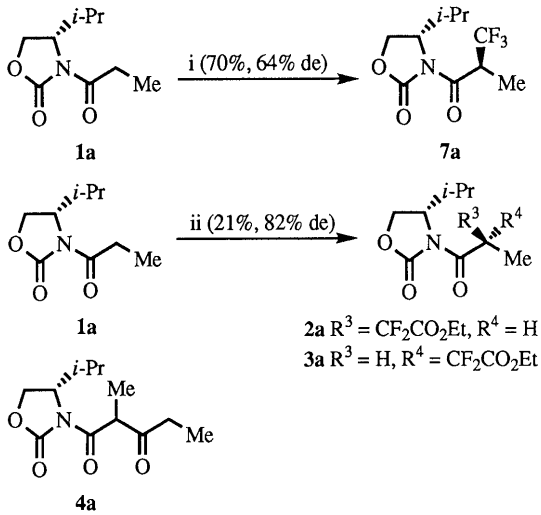
Key words (ethoxycarbonyl)difluoromethylation; asymmetric synthesis; chiral fluorinated compound; triethylborane; ethyl difluoroiodoacetate; *N*-acyloxazolidinone

The synthesis of selectively fluorinated chiral compounds is an important aspect of organofluorine chemistry in connection with analytical, biological and medicinal chemistry and opto-electric substances such as liquid crystals.[1] In the case of fluorine-containing molecules with unexpected and generally unusual reactivity, methodologies for synthesizing nonfluorinated chiral compounds are frequently inapplicable, the results giving rise to the term, "flustrates" by Seebach.[2] Thus, homochiral fluorinated compounds have been prepared so far mainly by chemical or biocatalytic resolutions of racemates, selective fluorination of chiral nonfluorinated substances and enzymatic or biological methods. However, much attention has been directed to the asymmetric synthesis of such chiral molecules for some years.[3] We previously described diastereoselective reactions of the trifluoromethyl radical with the lithium enolates generated from chiral *N*-acyloxazolidinones.[4] Here we present the diastereoselective introduction of an (ethoxycarbonyl)difluoromethyl group into lithium enolates of chiral *N*-acyloxazolidinones with ethyl difluoroiodoacetate mediated by triethylborane.[5]

Results and Discussion

Several imides (**1b—f**) were synthesized according to the literature.[6] Trifluoromethylation was achieved in the previous study by the addition of iodotrifluoromethane and triethylborane to a solution of the lithium enolates derived from *N*-acyloxazolidinones **1** in tetrahydrofuran (THF) at −78 °C, followed by stirring the reaction system at −78 °C for 10 min and at −20 °C for 2 h.[4] The present (ethoxycarbonyl)difluoromethylation was conducted using ethyl difluoroiodoacetate in place of iodotrifluoromethane. Ethyl difluoroiodoacetate (1.3 eq) was added to the lithium enolate solution of **1a** at −78 °C followed by triethylborane (1.0 eq) over a period of 1 min and the reaction mixture was then stirred at −78 °C for 1 h and at 0 °C for 30 min prior to quenching with saturated aqueous ammonium chloride (NH_4Cl). α-(Ethoxylcarbonyl)difluoromethyl carboximides, **2a** and **3a**, were obtained with good diastereoselectivity (82% de), but in only modest yield (21%). Variation in conditions such as reaction temperature and time, and in quantities of reagents failed to improve the product yield. Stirring at −20 °C and below afforded (ethoxycarbonyl)difluoromethylated products only in trace amounts. Reaction at 0 °C and above gave the by-product **4a** (Chart 1) in large amounts.

After a trial-and-error examination, acceptable yields were obtained by the addition of the lithium enolate to ethyl difluoroiodoacetate and triethylborane solution in THF. The chiral imide enolate, generated at −78 °C in THF by treatment of 2.0 mmol of **1** with 1.1 eq of lithium diisopropylamide (LDA) for 60 min, was added to a solution of 1.3 eq of ethyl difluoroiodoacetate and 1.0 eq of triethylborane in THF with a cannula at 5 °C over a period of 12 min.[7] The reaction mixture was stirred at 5 °C for 3 to 45 min prior to quenching with saturated aqueous NH_4Cl. α-(Ethoxycarbonyl)difluoromethyl carboximides **2** and their minor diastereomers **3** were isolated by flash chromatography. Diasteromeric excess was determined by capillary GLC. The results are summarized



(i) (a) LDA (1.3 equiv) in THF, -78°C, 60 min; (b) CF_3I (5 equiv), Et_3B (1.0 equiv), -78°C, 10 min, -20°C, 2 h; (ii) (a) LDA (1.1 equiv) in THF, -78°C, 60 min; (b) ICF_2CO_2Et (1.3 equiv), Et_3B (1.0 equiv), -78°C, 60 min, 0°C, 30 min

Chart 1

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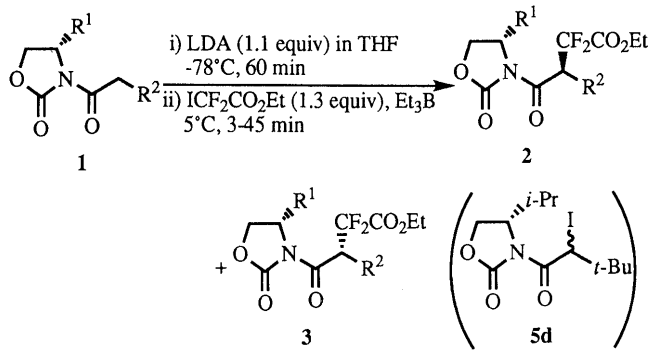
Table 1. Diastereoselective (Ethoxycarbonyl)difluoromethylation of Imide **1**



Entry	Imide **1**			Reaction time (min)	Et_3B (eq)	Yield[a] (%)	de[b] (%)
	R^1	R^2					
1	iso-Pr	Me	(**1a**)	3	1.0	74 (84)	88 (*S*)[c]
2	iso-Pr	Bn	(**1b**)	3	1.0	61 (75)	86
3	iso-Pr	*n*-Bu	(**1c**)	3	1.0	64 (76)	88
4	iso-Pr	*tert*-Bu	(**1d**)	45	1.0	19 (22)	>98
5	Bn	Me	(**1e**)	30	1.0	70 (84)	87
6	iso-Pr	Me	(**1a**)	30	0.0	0	—
7	iso-Pr	Me	(**1a**)	3	0.2	20 (57)	93 (*S*)[c]
8[d]	iso-Pr	Me	(**1a**)	3	1.0	7 (49)	90 (*S*)[c]

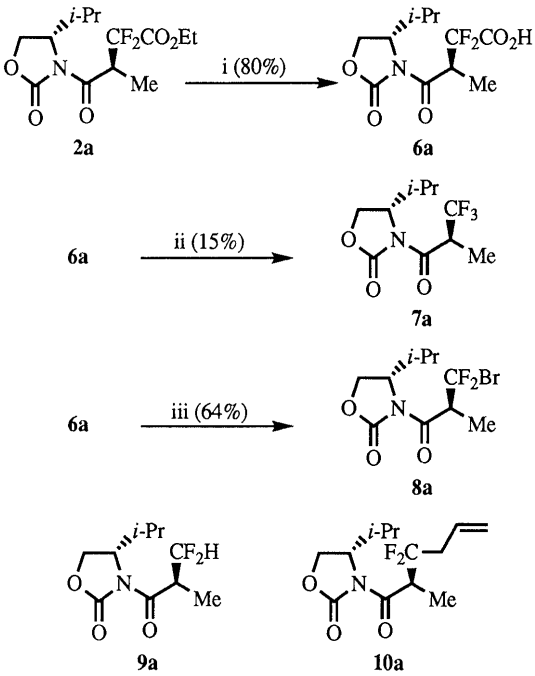
a) All yields are those of isolated compounds. Values in parentheses indicate conversion yields. *b*) de values were determined by capillary GLC. *c*) Configuration of the new asymmetric center of the major isomer. *d*) The reaction was carried out in the presence of 1.0 eq of galvinoxyl.

in Table 1.

Although the starting imides (**1a—e**) were partially recovered to the extent of 12—18%, (ethoxycarbonyl)-difluoromethylated imides **2** and **3**, except **2d** and **3d** (R^1 = iso-Pr, R^2 = *tert*-Bu), were produced in synthetically useful yields (61—74%). For all imides including **1d**, significant diastereoselectivity was observed at 86 to >98% de (entries 1—5). Diastereomeric excess (>98% de) was greatest for **1d** but the product yield was poor (19%), though that of the α-iodocarboximide **5d** was considerable (53%). The ratio of stereoisomers of **5d** was determined to be 56:44 by ^{1}H-NMR.

The (ethoxycarbonyl)difluoromethylation was inhibited not only by lack of triethylborane (entry 6), but also by the radical scavenger galvinoxyl (entry 8). It is noteworthy that 0.2 eq of triethylborane, based on **1a**, mediated (ethoxycarbonyl)difluoromethylation in only modest yield (20%) with recovery of **1a** (65%), since trifluoromethylation with the same quantity of triethylborane proceeded in 86% yield (entry 7).[4]

Hydrolysis of the major diastereomer **2a** with sodium bicarbonate ($NaHCO_3$) in aqueous methanol (MeOH) gave the corresponding carboxylic acid **6a** in 80% yield. Treatment of **6a** with xenon difluoride (XeF_2) in dichloromethane (CH_2Cl_2) afforded the α-trifluoromethyl carboximide **7a** in 15% yield.[8] The stereochemistry of **7a** was confirmed by comparison with an authentic sample prepared according to the literature.[4] Treatment of **6a** with XeF_2 and bromine (Br_2) in CH_2Cl_2 at room temperature provided α-bromodifluoromethyl carboximide **8a** in 64% yield. The bromide **8a** can be converted



(i) $NaHCO_3$ in methanol-H_2O, room temperature;
(ii) XeF_2 in CH_2Cl_2, room temperature;
(iii) XeF_2, Br_2, NaF in CH_2Cl_2, room temperature

Chart 2

to the α-difluoromethyl carboximide **9a** by reduction with tributyltin hydride and to the α-allyldifluoromethyl carboximide **10a** by allylation with allyltributyltin, in the presence of 2,2′-azobis(isobutyronitrile) under reflux with benzene.[9]

The present (ethoxycarbonyl)difluoromethylation is considered to occur through the radical chain mechanism shown in Chart 3. An ethyl radical, generated by autoxidation of triethylborane with a catalytic amount of oxygen in argon,[10] is attacked by ethyl difluoroiodoacetate with consequent displacement of an (ethoxycarbonyl)difluoromethyl radical.[11] Attack by the (ethoxycarbonyl)difluoromethyl radical on the Li-chelated *Z* enolate **11** may possibly proceed with C(α)-*si*-face preference in order to avoid steric crowding on the face shielded by the bulky group R^1 to give the radical anion intermediate **12**. Substitution of **12** with ethyl difluoroiodoacetate yields the α-(ethoxycarbonyl)difluoromethyl carboximide **2** and regenerates the (ethoxycarbonyl)-difluoromethyl radical. In the case of the reaction of **1a** mediated by 20 mol% triethylborane (Table 1, entry 7), the last step of these free-radical chain reactions may possibly be suppressed to some extent.[12] With the imide **1d** bearing a bulky group (R^2 = *tert*-Bu), considerable α-iodocarboximide **5d** may be produced *via* an ionic mechanism.

In conclusion, the introduction of an (ethoxycarbonyl)-difluoromethyl group into the chiral imide enolates of **1** with ethyl difluoroiodoacetate mediated by triethylborane proceeds with good diastereoselectivity. The present results are being applied to the synthesis of useful chiral fluoroorganic compounds.

Experimental

Melting points were determined on a Yanaco MP-500D hot stage

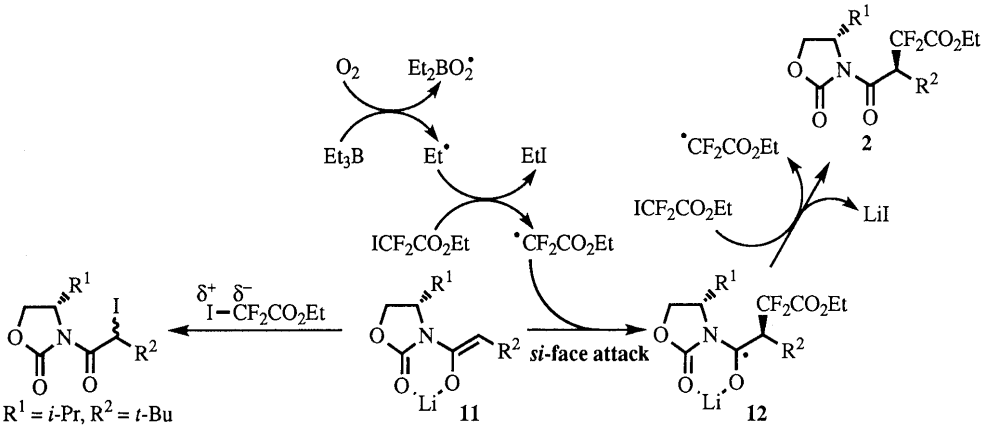


Chart 3

microscope without correction. Optical rotations were measured in a 1.0 dm cell with a JASCO DIP-370 polarimeter. IR spectra were obtained on a Perkin Elmer 1600 Fourier transform (FT)-IR. ^{1}H-NMR and ^{19}F-NMR spectra were recorded at 200 and 188 MHz, respectively, on a Varian Gemini-200 instrument. ^{1}H-NMR data are given in parts per million (ppm) downfield from tetramethylsilane (TMS) as the internal standard. The ^{19}F-NMR data are given in ppm upfield from CCl_3F as the internal standard. The abbreviations used are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (J values) are given in hertz (Hz). Low- and high-resolution MS analysis was conducted using a Kratos CONCEPT-1H double-focusing magnetic sector spectrometer. Elemental analysis was done at Toray Research Center, Inc., Tokyo. GLC analysis was carried out on a Shimadzu GC-17A instrument using a Shimadzu CBPI (25 m × 0.32 mm) capillary column with a film thickness of 0.5 μm. Kieselgel 60 (Merck, 230—400 mesh) was used for column chromatography. Thin-layer chromatography (TLC) was carried out with pre-coated Kieselgel 60F_{254} plates (Merck). All reactions were carried out under an argon atmosphere with magnetic stirring in oven-dried glassware.

Materials (*S*)-4-Isopropyl-3-propionyl-2-oxazolidinone (**1a**) was purchased from Aldrich. (*S*)-4-Isopropyl-3-(3-phenylpropionyl)-2-oxazolidinone (**1b**), (*S*)-3-hexanoyl-4-isopropyl-2-oxazolidinone (**1c**), (*S*)-3-(3,3-dimethylbutanoyl)-4-isopropyl-2-oxazolidinone (**1d**) and (*S*)-4-benzyl-3-propionyl-2-oxazolidinone (**1e**) were prepared according to the literature.[6] Ethyl difluoroiodoacetate was prepared from ethyl bromodifluoroacetate according to Yang and Burton.[7]

General Procedure for Ethoxycarbonyldifluoromethylation with Lithium Enolates 1. Ethyl (4′*S*)-2,2-Difluoro-4-(4′-isopropyl-2′-oxo-3′-oxazolidinyl)-3-methyl-4-oxobutanoate (2a, 3a) An (*S*)-4-isopropyl-3-propionyl-2-oxazolidinone (**1a**, 370 mg, 2.0 mmol) in THF (6 ml) was added at −78 °C to a solution of LDA, prepared from diisopropylamine (308 μl, 2.2 mmol) and BuLi (2.39 M in hexane, 920 μl, 2.2 mmol) in THF (4 ml) at 0 °C. After 60 min at the same temperature, the enolate solution was added to a solution of ethyl difluoroiodoacetate (340 μl, 2.6 mmol) and triethylborane (1 M in hexane, 2.0 ml, 2.0 mmol) in THF (4 ml) at 4 to 5 °C with a cannula over 12 min. The mixture was stirred at the same temperature for 3 min, then the reaction was quenched with saturated aqueous NH_4Cl and the whole system was extracted with Et_2O. The combined ethereal extracts were washed with brine, dried over anhydrous $MgSO_4$ and filtered. Diastereomeric excess was determined to be 88% by capillary GLC analysis. After evaporation of the solvent, chromatography of the residue with CH_2Cl_2–hexane (4 : 1, v/v) and hexane–EtOAc (5 : 1, v/v) gave the starting material **1a** (43 mg, 12%) and 3-(3′-ethoxycarbonyl-3′,3′-difluoro-2′-methylpropionyl)-4-isopropyl-2-oxazolidinone (**2a** and **3a**, 455 mg, 74%) as a mixture of stereoisomers. The isomers were separated by HPLC with hexane–EtOAc (7 : 1, v/v) as the eluent. Ethyl (3*S*,4′*S*)-2,2-difluoro-4-(4′-isopropyl-2′-oxo-3′-oxazolidinyl)-3-methyl-4-oxobutanoate (major isomer, **2a**): colorless oil, $[\alpha]_D^{24}$ +45.1° (c = 1.02, $CHCl_3$). IR (neat): 1779, 1704, 1391, 1206, 1123 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, d, J = 6.9 Hz), 0.91 (3H, d, J = 7.1 Hz), 1.35 (3H, t, J = 7.1 Hz), 1.41 (3H, d, J = 7.0 Hz), 2.37 (1H, qqd, J = 7.1, 6.9, 3.7 Hz), 4.20—4.46 (5H, m), 4.72 (2H, ddq, J = 14.4, 11.9, 7.0 Hz). ^{19}F-NMR ($CDCl_3$) δ: 106.71 (1F, dd, J = 270.0, 11.9 Hz), 110.85 (1F, dd, J = 270.0, 14.4 Hz). MS m/z: 307 (M^+), 179, 151. HRMS Calcd for $C_{13}H_{19}F_2NO_5$ (M^+): 307.123. Found: 307.122. Ethyl (3*R*,4′*S*)-2,2-difluoro-4-(4′-isopropyl-2′-oxo-3′-oxazolidinyl)-3-methyl-4-oxobutanoate (minor isomer, **3a**): colorless oil, $[\alpha]_D^{25}$ +71.7° (c = 0.70, $CHCl_3$). IR (neat): 1783, 1704, 1390, 1207, 1122 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, d, J = 7.0 Hz), 0.91 (3H, d, J = 7.0 Hz), 1.35 (3H, t, J = 7.2 Hz), 1.50 (3H, d, J = 7.2 Hz), 2.32 (1H, qqd, J = 7.0, 7.0, 4.1 Hz), 4.20—4.51 (5H, m), 4.62 (2H, ddq, J = 15.6, 10.5, 7.2 Hz). ^{19}F-NMR ($CDCl_3$) δ: 106.15 (1F, dd, J = 272.9, 10.5 Hz), 112.63 (1F, dd, J = 272.9, 15.6 Hz). MS m/z: 307 (M^+), 179, 151. HRMS Calcd for $C_{13}H_{19}F_2NO_5$ (M^+): 307.123. Found: 307.122.

Ethyl (4′*S*)-3-Benzyl-2,2-difluoro-4-(4′-isopropyl-2′-oxo-3′-oxazolidinyl)-4-oxobutanoate (2b, 3b) The general procedure was followed, using 523 mg (2.0 mmol) of (*S*)-4-isopropyl-3-(3-phenylpropionyl)-2-oxazolidinone (**1b**). Diastereomeric excess was determined to be 86% by capillary GLC analysis. Chromatography of the residue with CH_2Cl_2–hexane (2 : 1, v/v) gave the major isomer (435 mg, 57%) and a mixture of the starting material **1b** and a minor isomer (132 mg). The mixture was separated by HPLC with hexane–iso-PrOH (20 : 1, v/v) as the eluent to give the minor isomer (33 mg, 4.3%) and **1b** (96 mg, 18%). Major isomer: colorless needles (hexane–Et_2O), mp 76.6—77.6 °C, $[\alpha]_D^{24}$ +117.4° (c = 1.62, $CHCl_3$). IR (KBr): 1769, 1755, 1705, 1388, 1220, 1100, 705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, d, J = 6.8 Hz), 0.86 (3H, d, J = 7.0 Hz), 1.36 (3H, t, J = 7.1 Hz), 2.30 (1H, qqd, J = 7.0, 6.8, 3.8 Hz), 3.09—3.28 (2H, m), 3.74 (1H, dd, J = 10.8, 8.2 Hz), 4.00—4.13 (2H, m), 4.32 (2H, q, J = 7.1 Hz), 5.21—5.42 (1H, m), 7.17—7.34 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: 106.40 (1F, dd, J = 268.5, 13.1 Hz), 107.21 (1F, dd, J = 268.5, 12.9 Hz). MS m/z: 383 (M^+), 260, 131, 91. HRMS Calcd for $C_{19}H_{23}F_2NO_5$ (M^+): 383.154. Found: 383.153. *Anal.* Calcd for $C_{19}H_{23}F_2NO_5$: C, 59.5; H, 6.0; N, 3.7. Found: C, 59.6; H, 6.0; N, 3.7. Minor isomer: colorless oil, $[\alpha]_D^{25}$ +11.0° (c = 0.49, $CHCl_3$). IR (neat): 1780, 1705, 1387, 1205, 1106, 702 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.30 (3H, d, J = 7.0 Hz), 0.75 (3H, d, J = 7.1 Hz), 1.37 (3H, t, J = 7.2 Hz), 1.97 (1H, qqd, J = 7.1, 7.0, 3.8 Hz), 3.14—3.33 (2H, m), 4.04—4.45 (5H, m), 5.28—5.49 (1H, m), 7.13—7.33 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: 106.98 (1F, dd, J = 266.0, 13.0 Hz), 107.13 (1F, dd, J = 266.0, 13.3 Hz). MS m/z: 383 (M^+), 260, 131, 91. HRMS Calcd for $C_{19}H_{23}F_2NO_5$ (M^+): 383.154. Found: 383.154.

Ethyl (4′*S*)-3-Butyl-2,2-difluoro-4-(4′-isopropyl-2′-oxo-3′-oxazolidinyl)-4-oxobutanoate (2c, 3c) The general procedure was followed, using 454 mg (2.0 mmol) of (*S*)-3-hexanoyl-4-isopropyl-2-oxazolidinone (**1c**). Diastereomeric excess was determined to be 88% by capillary GLC analysis. Chromatography of the residue with CH_2Cl_2–hexane (1 : 1—2 : 1, v/v) gave the starting material **1c** (74 mg, 16%), the major isomer (418 mg, 60%) and a minor isomer (28 mg, 3.9%). Major isomer: colorless oil, $[\alpha]_D^{25}$ +53.8° (c = 1.83, $CHCl_3$). IR (neat): 1782, 1704, 1388, 1203 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84—0.96 (3H, m), 0.91 (3H, d, J = 6.8 Hz), 0.92 (3H, t, J = 7.0 Hz), 1.18—1.43 (4H, m), 1.36 (3H, t, J = 7.1 Hz), 1.67—2.02 (2H, m), 2.40 (1H, qqd, J = 7.0, 6.8, 3.6 Hz), 4.20—4.52 (5H, m), 4.81—5.01 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: 106.30 (1F, dd, J = 265.1, 13.6 Hz), 106.80 (1F, dd, J = 265.1, 12.7 Hz). MS m/z: 349 (M^+), 293, 221, 193. HRMS Calcd for $C_{16}H_{25}F_2NO_5$ (M^+): 349.170. Found: 349.169. Minor isomer: colorless oil, $[\alpha]_D^{25}$ +51.7° (c = 0.80, $CHCl_3$). IR (neat): 1782, 1704, 1388, 1203 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85—0.96 (9H, m), 1.18—1.48 (4H, m), 1.35 (3H, t, J = 7.1 Hz), 1.78—2.07 (2H, m), 2.35 (1H, qqd, J = 7.0, 6.9, 3.8 Hz), 4.17—4.55 (5H, m), 4.76—4.97 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: 105.29 (1F, dd, J = 268.0,

12.6 Hz), 108.35 (1F, dd, J=268.0, 14.4 Hz). MS m/z: 349 (M^+), 293, 221, 193. HRMS Calcd for $C_{16}H_{25}F_2NO_5$ (M^+): 349.170. Found: 349.169.

Ethyl (4′*S*)-3-*tert*-Butyl-2,2-difluoro-4-(4′-isopropyl-2′-oxo-3′-oxazolidinyl)-4-oxobutanoate (2d, 3d) The reaction was carried out using 454 mg (2.0 mmol) of (*S*)-3-(3,3-dimethylbutanoyl)-4-isopropyl-2-oxazolidinone (**1d**) according to the general procedure, but with the following modification: the reaction mixture was stirred for 45 min prior to quenching. Chromatography of the residue with hexane–EtOAc (8 : 1—6 : 1, v/v) and CH_2Cl_2–hexane (1 : 1—2 : 1, v/v) gave the starting material **1d** (62 mg, 14%), ethyl (4′*S*)-3-*tert*-butyl-2,2-difluoro-4-(4′-isopropyl-2′-oxo-3′-oxazolidinyl)-4-oxobutanoate (133 mg, 19%) and (4*S*)-3-(2′-iodo-3′,3′-dimethylbutanoyl)-4-isopropyl-2-oxazolidinone (**5d**, 373 mg, 53%). Ethyl (4′*S*)-3-*tert*-butyl-2,2-difluoro-4-(4′-isopropyl-2′-oxo-3′-oxazolidinyl)-4-oxobutanoate: colorless oil, $[\alpha]_D^{25}$ +55.1° (c=0.65, $CHCl_3$). IR (neat): 1778, 1704, 1386, 1204, 1103 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, d, J=7.0 Hz), 0.93 (3H, d, J=7.1 Hz), 1.13 (9H, s), 1.36 (3H, t, J=7.2 Hz), 2.43 (1H, qqd, J=7.1, 7.0, 3.3 Hz), 4.18—4.27 (2H, m), 4.31 (2H, q, J=7.2 Hz), 4.43—4.54 (1H, m), 5.14 (1H, dd, J=16.8, 15.0 Hz). ^{19}F-NMR ($CDCl_3$) δ: 101.34 (1F, dd, J=270.4, 15.0 Hz), 102.82 (1F, dd, J=270.4, 16.8 Hz). MS m/z: 349 (M^+), 293, 221. HRMS Calcd for $C_{16}H_{25}F_2NO_5$ (M^+): 349.170. Found: 349.169. **5d**: colorless solid. IR (KBr): 1771, 1702, 1366, 1256, 1216, 1191, 1111, 766, 710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (1.32H, d, J=6.9 Hz), 0.93 (3H, d, J=7.1 Hz), 0.98 (1.68H, d, J=7.0 Hz), 1.22 (9H, s), 2.28—2.49 (1H, m), 4.18—4.56 (3H, m), 5.96 (0.44H, s), 5.99 (0.56H, s). MS m/z: 353 (M^+), 226, 97. HRMS Calcd for $C_{12}H_{20}INO_3$ (M^+): 353.049. Found: 353.049. *Anal.* Calcd for $C_{12}H_{20}INO_3$: C, 40.8; H, 5.7; N, 4.0. Found: C, 40.9; H, 5.7; N, 4.0.

Ethyl (4′*S*)-4-(4′-Benzyl-2′-oxo-3′-oxazolidinyl)-2,2-difluoro-3-methyl-4-oxobutanoate (2e, 3e) The reaction was carried out using 466 mg (2.0 mmol) of (*S*)-4-benzyl-3-propionyl-2-oxazolidinone (**1e**) according to the general procedure modified as follows: the reaction mixture was stirred for 30 min prior to quenching. Diastereomeric excess was determined to be 87% by capillary GLC analysis. Chromatography of the residue with CH_2Cl_2–hexane (3 : 1—4 : 1, v/v) gave the starting material **1e** (60 mg, 13%) and a mixture of stereoisomers (**2e** and **3e**, 500 mg, 70%). Major isomer: colorless plates (hexane–Et_2O), mp 50.0—51.0 °C, $[\alpha]_D^{24}$ +35.8° (c=1.54, $CHCl_3$). IR (KBr): 1771, 1740, 1691, 1398, 1328, 1254, 1113, 994, 763, 706 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.2 Hz), 1.46 (3H, d, J=7.1 Hz), 2.75 (1H, dd, J=13.5, 9.7 Hz), 3.31 (1H, dd, J=13.5, 3.2 Hz), 4.17—4.27 (2H, m), 4.36 (2H, q, J=7.2 Hz), 4.58—4.82 (2H, m), 7.20—7.40 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: 106.42 (1F, dd, J=271.5, 10.8 Hz), 111.68 (1F, dd, J=271.5, 15.7 Hz). MS m/z: 355 (M^+), 179, 151, 91. HRMS Calcd for $C_{17}H_{19}F_2NO_5$ (M^+): 355.123. Found: 355.120. *Anal.* Calcd for $C_{17}H_{19}F_2NO_5$: C, 57.5; H, 5.4; N, 3.9. Found: C, 57.4; H, 5.5; N, 3.9.

(3*S*,4′*S*)-2,2-Difluoro-4-(4′-isopropyl-2′-oxo-3′-oxazolidinyl)-3-methyl-4-oxobutanoic Acid (6a) A solution of **2a** (2.11 g, 6.89 mmol) in 5% aqueous $NaHCO_3$–MeOH (140 ml–90 ml) was stirred at room temperature for 21 h, then poured into water, and the whole system was extracted with Et_2O. The aqueous layer was acidified with hydrochloric acid and extracted with EtOAc. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$ and filtered. Evaporation of the solvent gave **6a** (1.53 g, 80%). **6a**: colorless plates (EtOAc–hexane), mp 133.7—135.9 °C, $[\alpha]_D^{25}$ +45.1° (c= 0.94, $CHCl_3$). IR (KBr): 3094, 1778, 1745, 1708, 1409, 1224, 1130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=6.8 Hz), 0.92 (3H, d, J=6.9 Hz), 1.45 (3H, d, J=7.1 Hz), 2.32—2.48 (1H, m), 4.22—4.50 (3H, m), 4.63—4.87 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: 106.36 (1F, dd, J=271.5, 10.9 Hz), 109.72 (1F, dd, J=271.5, 14.0 Hz). MS m/z: 279 (M^+), 151. HRMS Calcd for $C_{11}H_{15}F_2NO_5$ (M^+): 279.092. Found: 279.090. *Anal.* Calcd for $C_{11}H_{15}F_2NO_5$: C, 47.3; H, 5.4; N, 5.0. Found: C, 47.3; H, 5.5; N, 5.0.

(2′*S*,4*S*)-4-Isopropyl-3-(3′,3′,3′-trifluoro-2′-methylpropionyl)-2-oxazolidinone (7a) Xenon difluoride (33 mg, 0.20 mmol) was added to a solution of **6a** (55 mg, 0.20 mmol) in CH_2Cl_2 (3 ml) at room temperature. The mixture was stirred at room temperature for 18 h and the reaction was quenched with saturated aqueous $NaHCO_3$. The whole system was extracted with Et_2O. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$ and filtered. After evaporation of the solvent, chromatography of the residue with hexane–EtOAc (5 : 1, v/v) and hexane–CH_2Cl_2 (1 : 1, v/v) gave **7a** (7.2 mg, 15%), which was identical with an authentic sample prepared according to the literature.[4]

(2′*S*,4*S*)-3-(3′-Bromo-3′,3′-difluoro-2′-methylpropionyl)-4-isopropyl-2-oxazolidinone (8a) Xenon difluoride (93 mg, 0.55 mmol) was added to a solution of **6a** (154 mg, 0.55 mmol), bromine (0.28 ml, 5.5 mmol) and sodium fluoride (NaF, 231 mg, 5.5 mmol) in CH_2Cl_2 (9 ml) at room temperature. The mixture was stirred at room temperature for 2.5 h and the reaction was quenched with saturated aqueous $NaHCO_3$. The system was extracted with Et_2O. The combined extracts were washed with 5% aqueous $Na_2S_2O_3$ and brine, dried over anhydrous $MgSO_4$ and filtered. Following evaporation of the solvent, chromatography of the residue with hexane–EtOAc (2 : 1, v/v) gave **8a** (110 mg, 64%). **8a**: colorless oil, $[\alpha]_D^{25}$ +22.3° (c=1.05, $CHCl_3$). IR (neat): 1775, 1708, 1389, 1245, 1205, 1121 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, d, J=6.9 Hz), 0.94 (3H, d, J=7.1 Hz), 1.45 (3H, d, J=6.9 Hz), 2.30—2.53 (1H, m), 4.21—4.55 (3H, m), 4.98—5.20 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: 48.76 (1F, dd, J=159.8, 11.2 Hz), 49.22 (1F, dd, J=159.8, 10.8 Hz). MS m/z: 315 (M^+), 313 (M^+), 272, 270, 234, 190, 159, 157. HRMS Calcd for $C_{10}H_{14}BrF_2NO_3$ (M^+): 313.013. Found: 313.014.

References and Notes

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