Synthesis of L-4,4-Difluoroglutamic Acid via Nucleophilic Addition to a Chiral Aldehyde

Yun Ding, Jianqiang Wang,† Khalil A. Abboud, Yuelian Xu,‡ William R. Dolbier, Jr., and Nigel G. J. Richards*

Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200

richards@qtp.ufl.edu

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Fluorine-containing derivatives of amino acids are assuming increasing importance as probes of biological function and enzyme mechanism. We now report a new, flexible route to enantiomerically pure L-4,4-difluoroglutamic acid that exploits the addition of difluorinated nucleophiles to configurationally stable α-aminoaldehydes. Conversion of the difluorinated adducts to L-4,4-difluoroglutamic acid can be accomplished in three steps by Barton−McCombie dehydroxylation and acid hydrolysis.

Introduction

Fluorinated derivatives of amino acids are assuming increasing importance as probes of biological function and enzyme mechanism,[1] particularly because the electron-withdrawing effects of fluorine substituents[2] often have profound effects on reactivity and conformational preferences.[3,4] For example, fluorinated analogues of glutamic acid possess antitumor activity[5] and are modulators of folate poly-γ-glutamate biosynthesis.[6] Our interest in fluorinated amino acids has been stimulated by our recent efforts to characterize the structure and mechanism of asparagine synthetase (AS),[7] a glutamine-dependent amidotransferase[8] that appears to be intimately linked with progression through the cell cycle[9] and cellular responses to amino acid starvation.[10] Specifically, we required L-4,4-difluoroglutamine **1** to investigate whether AS could employ this nonnatural amino acid as a nitrogen source in place of L-glutamine as part of ongoing efforts to trap and structurally characterize specific intermediates formed during the kinetic mechanism.[7c] Since DL-4,4-difluoroglutamic acid had been converted to a racemic mixture of the fluorinated substrate analogue **1** in three steps,[11] we wished to prepare optically pure L-4,4-difluoroglutamate **2** from cheap starting materials via a route that might be easily modified to yield functionalized derivatives of 4,4-difluoroglutamine. In this regard, the elegant synthesis of L-4,4-difluoroglutamate **2**,[12] reported during our studies, seems to be less suitable for our purposes than the route

* To whom correspondence should be addressed. Phone: (352) 392-3601. Fax: (352) 846-2095. Portions of the work described in this paper were presented at the 218th National Meeting of the American Chemical Society in New Orleans, August 1999 (MEDI-244).

† Present address: Triad Therapeutics, Inc., 5820 Nancy Ridge Drive, #200, San Diego, CA 92121.

‡ Present address: Clariant LSM (Florida), Gainesville, FL 32609.

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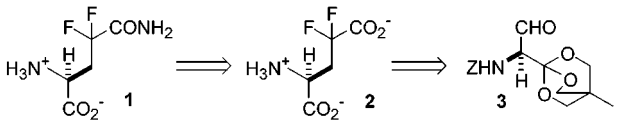
Scheme 1

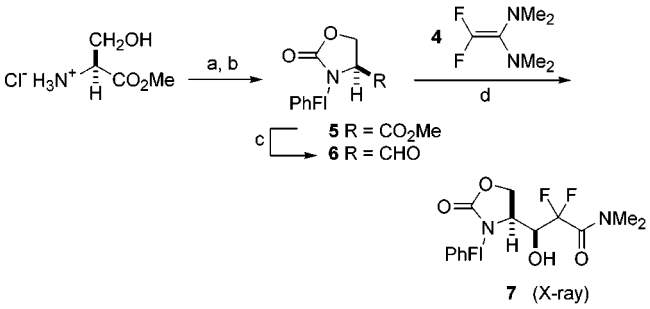


we describe here. We note that the only other synthesis of L-4,4-difluoroglutamic acid **2** in enantiomerically pure form requires the use of an expensive precursor, that is not readily available,[13] and other practical routes for the large-scale synthesis of 4,4-difluoroglutamic acid[14] and related compounds[15,16] either give the target fluorinated amino acids as racemic mixtures or require tedious resolution procedures.[17] We now report the successful preparation of **2** by a strategy in which the difluorinated side chain is constructed by nucleophilic addition to the configurationally stable aldehyde **3** (Scheme 1).[18]

Results and Discussion

The introduction of difluoromethylene groups into amino acids has been accomplished using a variety of reagents,[19] including DAST,[20] *N*-fluorobenzenesulfonimide (NFSi),[12,21] and difluorobromoacetate esters.[22] In our initial experiments, we investigated whether 1,1-bis(dimethylamino)-2,2-difluoroethene **4**, a novel reagent for building difluoromethylene centers into molecules,[23] would undergo clean addition to a suitably protected chiral aldehyde (Scheme 2).

Scheme 2[a]



[a] PhFl = 9-phenylfluoren-9-yl. Key: (a) 9-bromo-9-phenylfluorene, Et_3N; (b) $COCl_2$, Et_3N, CH_2Cl_2; (c) $LiAlH_4$, THF, −78 °C; (d) **4**, dry THF, rt.

Although difluoroolefin **4** is a powerful nucleophile that undergoes facile addition to aromatic aldehydes and conjugated carbonyl compounds,[23] its reaction with aldehydes that possess α-hydrogens yields only *N*,*N*-dimethyldifluoroacetamide, presumably due to proton abstraction by the highly basic double bond.[23] Our first efforts to prepare **2** therefore involved reaction of **4** with the configurationally stable aldehyde **6**[24] as the electrophilic component. Molecular modeling studies[25] indicated that the PhFl protecting group shields the C-2 proton preventing its abstraction by **4**, and it is well established that racemization of the chiral center in **6** is very slow under a wide variety of conditions.[26] Although synthesis of **2** by this route ultimately requires D-serine as a starting material, we elected to use **6** in these early experiments in order to establish the feasibility of this synthetic approach. Hence, the commercially available methyl ester of L-serine was converted to the chiral ester **5** following literature procedures.[24,26] After some experimentation, we discovered that aldehyde **6** could be prepared in good yield (and without any significant loss in enantiopurity) by treatment of **5** with $LiAlH_4$ at −78 °C.[27] As anticipated, the difluoroolefin **4** underwent smooth addition to aldehyde **6** in THF at room temperature, giving an alcohol **7** as a single adduct in a purified yield of 58% (based on **6**) (Scheme 2). We assigned the

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(27) Efforts to obtain the aldehyde **6** by direct reduction of **5** were reported to yield only the alcohol,[24] although **6** could be obtained by treatment of an acylisoxazolide moiety in place of the ethyl ester in **5**.[24] We note, however, that $LiAlH_4$ reduction was carried out at temperatures exceeding 0 °C in these studies. The molecular basis for the clean reduction of ester **5** to aldehyde **6** at very low temperature under our conditions remains to be established, although a series of model studies have suggested that the presence of the *β*-oxygen substituents may control reactivity by stabilization of the initial intermediate (Ding, unpublished results). We note that esters are reduced to aldehydes at RT by $LiAlH_4$ in the presence of diethylamine: Cha, J.; Kwon, S. S. *J. Org. Chem.* **1987**, *52*, 5486-5487.

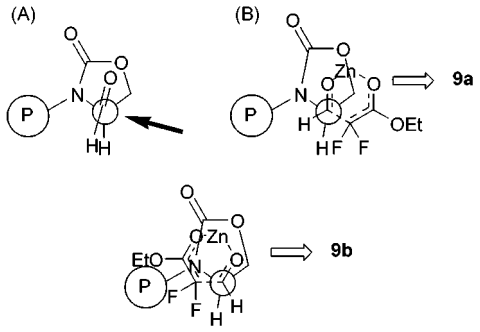


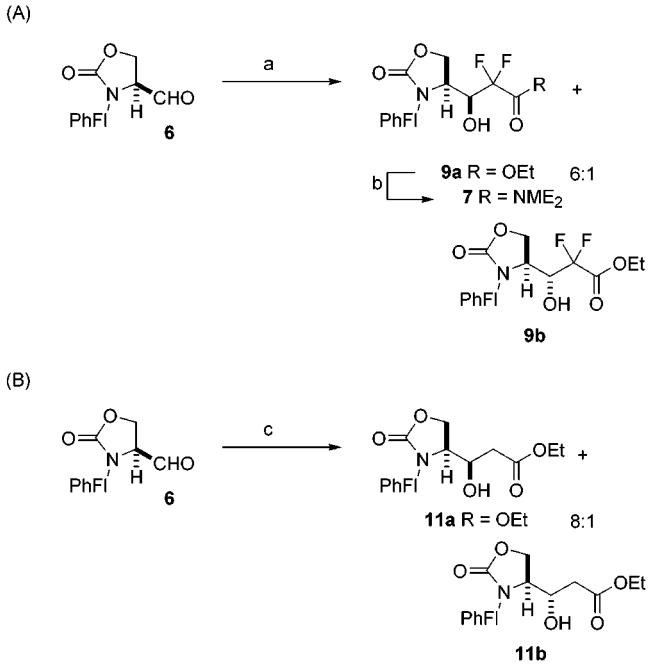
Figure 1. (A) Felkin−Anh model for the addition reaction between difluoroolefin **4** and aldehyde **6**. (B) Models for the metal-directed addition of Reformatsky reagent **8** and aldehyde **6** leading to major and minor products **9a** and **9b**, respectively.

relative and absolute stereochemistry of **7** on the basis of X-ray crystallography,[28] assuming that no racemization had taken place at C-2 under the conditions.[26] The stereochemical preference for attack on **6** is consistent with that reported previously and can be rationalized on the basis of the Felkin−Anh model in which the bulky protecting group completely hinders the *si*-face of the carbonyl group (Figure 1A).[29]

Although this result confirmed the hypothesis that reaction of **4** and **6** proceeded with a very high level of diastereoselection and that the presence of the bulky N-protecting group suppressed deprotonation at C-2, a number of technical difficulties precluded the routine use of difluoroolefin **4** for large-scale preparations of intermediate **7**, including the need for its in situ preparation from 1,1-bis(dimethylamino)-2,2,2-trifluoroethane[30] using *n*-butyllithium. We therefore investigated whether addition of the Reformatsky reagent **8** to the chiral aldehyde **6** would proceed with equally high diastereoselectivity. Dropwise addition of ethyl bromodifluoroacetate to a solution of zinc and **6** was required for clean reaction and gave the diastereoisomeric adducts **9a** and **9b** as a 6:1 mixture in 85% total yield after purification (Scheme 3A). Stereochemical assignments for these compounds were based on the observation that treatment of the major isomer **9a** with lithium dimethylamide **10** gave a single product with physical and spectroscopic properties that were identical to those of amide **7**. The loss in stereochemical control is probably associated with stabilization of the transition state leading to the minor isomer due to chelation of zinc by the oxygen in the oxazolidine ring (Figure 1B).[31]

Any influence of electronic effects, associated with the fluorine substituents, on product stereochemistry was ruled out by the observation that the cognate Reformatsky reagent formed from ethyl bromoacetate reacted with **6** to give a 8:1 ratio of the diastereoisomeric adducts **11a** and **11b** (Scheme 3B). The major isomer **11a** was

Scheme 3[a]



[a] PhFl = 9-phenylfluoren-9-yl. Key: (a) $ZnCF_2CO_2Et$ **8**, THF, rt; (b) $LiNMe_2$ **10**, THF, rt; (c) Zn, $BrCH_2CO_2Et$, THF, rt.

assigned on the basis of the $^1H-^1H$ coupling constant (J = 6.6 Hz) for the protons attached to C-4 and C-3′, which is similar in magnitude to the dipolar coupling observed between the cognate protons in **7** (for which the relative stereochemistry was unequivocally established). The stereochemical outcome is also consistent with the results of previous investigations into the reactions of nucleophiles with aldehyde **6**.[24,26]

Having devised conditions for the preparation of the difluorinated secondary alcohols **7** and **9a**, we next investigated conditions for removing the hydroxyl group so as to complete the synthesis of the side chain.

Methods for accomplishing this synthetic transformation at carbon atoms adjacent to CF_2 groups, especially in highly functionalized derivatives such as **7** and **9a**, do not seem to have been investigated in detail.[32] Given the inductive effects of the fluorine substituents, we envisaged that this reduction might be best accomplished using radical-based methods, such as the Barton−McCombie reaction.[33] The difluoroamide **7** was therefore converted to the *O*-pentafluorophenylthioate **12** by reaction with pentafluorophenylthiochloroformate (Scheme 4). Relatively strong conditions were required for the

(28) Data for **7**: $C_{27}H_{26}F_2N_2O_5$, M_r = 478.17 g mol^{-1}, orthorhombic, space group $P2(1)2(1)2(1)$, a = 8.5056(5) Å, b = 11.6903(7) Å, c = 23.913(2) Å, $\alpha = \beta = \gamma = 90°$, $T = 173 \pm 1$ K. Crystallographic data for **7** (excluding structure factors) are included in the Supporting Information for this paper.

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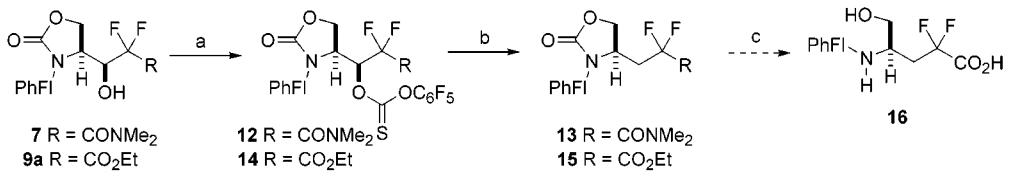
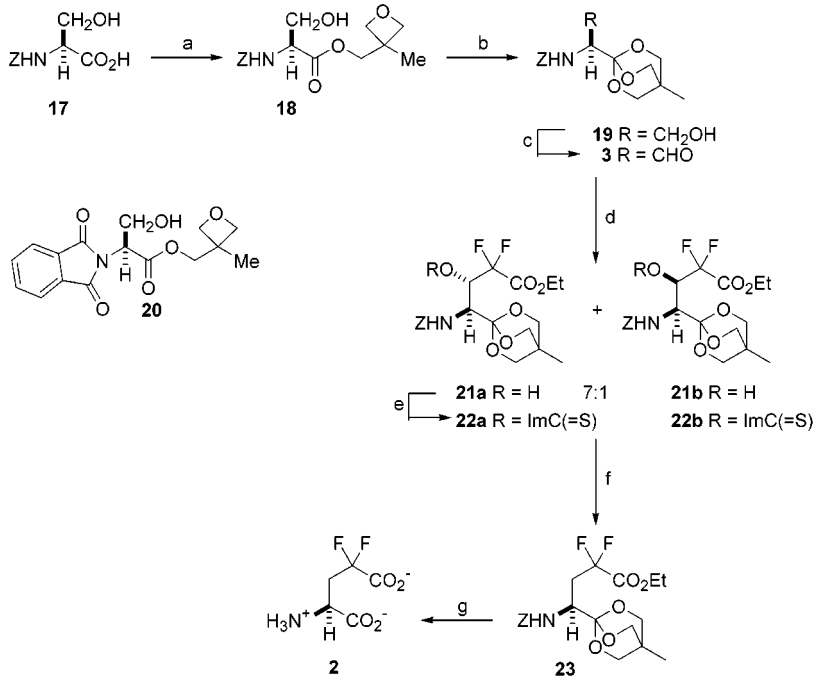
Scheme 4[a]



[a] PhFl = 9-phenylfluoren-9-yl. Key: (a) $C_6F_5OC(=O)Cl$, DMAP, *N*-hydroxysuccinimide, toluene, 90 °C; (b) $(n\text{-}Bu)_3SnH$, AIBN, toluene, reflux; (c) KOH, EtOH or 6 N HCl.

Scheme 5[a]



[a] Z = $PhCH_2OCO$; Im = $C_3H_3N_2$. Key: (a) Cs_2CO_3, then C_5H_9BrO, DMF, rt; (b) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, then Et_3N; (c) DMSO, $(COCl)_2$, −78 °C; (d) $ZnCF_2CO_2Et$ **8**, THF, rt; (e) $(C_3H_3N_2)C{=}S$, dry THF, rt; (f) Et_3SiH, $(PhCO_2)_2$, C_6H_6, reflux; (g) 6 N HCl, reflux, then anion-exchange chromatography.

synthesis of the activated *O*-pentafluorophenylthioate **12**, presumably due to steric hindrance of the secondary alcohol by the bulky N-protecting group. In addition, the complete conversion of starting alcohol **7** was difficult to achieve, even after the addition of additional amounts of pentafluorophenylthiochloroformate. Radical-mediated dehydroxylation from **12** also proved to be more difficult than anticipated. Although the desired difluorinated amide could be obtained using Bu_3SnH, with AIBN as a radical initiator, a complicated mixture of products was formed from which **13** was isolated in a disappointing 30% yield. It is possible that the secondary radical resulting from breakdown of the *O*-pentafluorophenylthioate moiety undergoes reaction with the electron-rich phenylfluorenyl-protecting group, although this remains to be established. Efforts to optimize the yield by changing the leaving group to a xanthate or thioimidazolide gave compounds that either did not react with Bu_3SnH, or gave complex product mixtures, under a variety of deoxygenation conditions (Ding and Richards, unpublished results). Similar results were obtained for the *O*-pentafluorophenylthioate **14** that could be prepared from alcohol **9a**. The reasons for these difficulties in using Bu_3SnH for deoxygenation remain unclear, especially in light of experiments outlined below. Having established conditions for removal of the hydroxyl group from the pentafluorophenyl derivatives **12** and **14**, albeit in low yield, we next confronted the problem of hydrolyzing the oxazolidinone ring. All attempts to prepare the acyclic material **16** by hydrolysis of either **13** or **15** under acidic or basic conditions, as previously reported,[24] gave only complex product mixtures. ^{19}F NMR analysis supports the hypothesis that these technical problems are likely associated with dehydrofluorination taking place at a rate similar to heterocyclic ring opening.

Although we had demonstrated that addition of Reformatsky reagent **8** to configurationally stable α-aminoaldehydes proceeds smoothly, these unexpected difficulties in radical-mediated deoxygenation and hydrolysis of the heterocyclic ring in either **13** or **15** caused us to reexamine our choice of starting aldehyde. In particular, we sought to avoid the use of potentially reactive nitrogen protecting groups that might participate in transformations leading to the desired difluorinated side chain. We therefore investigated reaction of the difluorinated reagent **8** with the 4-methyl-2,6,7-trioxabicyclo[2.2.2] ortho ester (OBO) derivative **3** (Scheme 5).

Thus, the N-protected derivative of L-serine **17** was converted to optically pure aldehyde **3** in three steps, according to literature procedures.[34] After esterification with 3-methyl-3-(hydroxymethyl)oxetane to give the ester **18**, the OBO ester **19** was formed by BF_3-catalyzed

rearrangement.[35] Swern oxidation then gave the target aldehyde **3** in excellent yield. The optical purity of this compound was verified by ^{1}H NMR analysis of resonance associated with the aldehyde proton in the presence of Eu(hfc)$_3$.[18c] We note that rearrangement of the cognate *N*-phthaloyl derivative **20** under these conditions was found to proceed in very poor yield.[36] Reaction of **3** with the difluorinated Reformatsky reagent **8** again proceeded smoothly to give the enantiomerically pure alcohol **21** as a 7:1 mixture of diastereoisomers that could not be separated by column chromatography. The relative stereochemistry of the major isomer was assigned as **21a** by analogy to the major product obtained by reaction of **3** and the cognate, nonfluorinated Reformatsky reagent derived from ethyl bromoacetate.[18c] As reported previously, examination of the ^{1}H and ^{19}F NMR spectra revealed that there was no dipolar coupling between the protons at C-2 and C-3. Reaction of **8** with **3** therefore proceeds via a simple Felkin−Anh model in which the nucleophile attacks the less hindered *si*-face of the aldehyde moiety. Again the diastereoselectivity of the addition of the difluorinated reagent **8** is significantly reduced relative to that reported in other experiments employing aldehyde **3** as an electrophilic component. This may reflect stabilization of the transition state leading to **21b** through zinc chelation or equilibration of the initial adduct under the reaction conditions. The mixture of diastereoisomers **21** was then refluxed with thiocarbonyl bis-imidazolide in THF overnight to give the oxythiocarbonylimidazole derivatives **22**. In an attempt to avoid using Bu_3SnH to deoxygenate the secondary alcohol adjacent to the difluoromethylene moiety, we investigated the use of Et_3SiH in the presence of benzoyl peroxide at 90 °C.[32] We note that because BzOOBz also acts as a trap for triethylsilyl radicals produced during the reaction,[37] relatively high amounts of the peroxide (1−1.2 equiv) were needed to drive the reaction to completion. The protected difluoroester **23** was obtained in 44% overall yield (for three steps), however, from aldehyde **3**. Conversion of **23** to L-4,4-difluoroglutamate **2** could be accomplished by heating in 6 N HCl for 2 h, with purification using anion-exchange chromatography. Comparison of the optical and spectroscopic properties for this material with those reported previously[12,13] confirmed our observations that the synthesis had proceeded with little loss of stereochemical integrity at the chiral center. We note that this synthesis is amenable to use on large scale and, therefore, represents a practical approach to the enantiospecific preparation of this difluorinated amino acid.

Experimental Section

Melting points were recorded using a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were measured using a Polyscience model SR-6 polarimeter. ^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained at 300, 75.4, and 282 MHz, respectively, using Varian VXR-300, Gemini-300, and Mercury-300 spectrometers. For ^{1}H and ^{13}C, chemical shifts are reported in ppm (δ) downfield of tetramethylsilane as an internal reference (δ 0.0). In the case of ^{19}F, $CFCl_3$ was used as an internal standard (δ 0.0). Splitting patterns are abbreviated as follows: s, singlet, d, doublet, t, triplet, q, quartet and m, multiplet. EI, CI and FAB mass spectra were recorded on a Finnegan MAT 25Q (high resolution) spectrometer. Methane was generally employed in obtaining CI mass spectra. Analytical thin-layer chromatography (TLC) was performed on silica gel 60F-254 plates. Flash chromatography was performed using standard procedures[38] on Kieselgel (230−400 mesh). All reagents were purchased from Aldrich or Fisher Scientific, and were used without further purification except for chromatography solvents, which were distilled before use. Moisture-sensitive reactions were carried out under an argon atmosphere in glassware that was flame-dried with an inert gas sweep. THF and benzene were freshly distilled before use from sodium benzophenone ketyl.

(4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-carboxaldehyde (6). The N-protected methyl ester **5** (2.51 g, 6.5 mmol) was dissolved in dry THF (50 mL) under an argon atmosphere. After the reaction mixture was cooled to −78 °C, $LiAlH_4$ (7.8 mL of a 1 M solution in THF, 7.8 mmol) was added dropwise so that the reaction temperature did not exceed −75 °C. After the mixture was further stirred for 2 h at this temperature, TLC showed complete consumption of the starting ester and the reaction was quenched by the addition of a solution of $KHSO_4$ (3 g) in H_2O (60 mL). The mixture was then allowed to warm to rt before being extracted with EtOAc (3 × 80 mL). The combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$) before removal of the solvent under reduced pressure. The oily residue was purified using flash chromatography (eluant: 2:1 hexane/EtOAc) to give the target aldehyde **6** as a white foam: 1.96 g, 85%; $[\alpha]^{20}_D$ = −313.3° (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.95 (1 H, m), 4.12 (1 H, dd, *J* = 9.3, 5.5 Hz), 4.34 (1 H, t, *J* = 9.3 Hz), 7.27−7.80 (13 H, m), 9.03 (1 H, d, *J* = 3.6 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 61.88 (d), 63.75 (t), 72.71 (s), 120.50 (d), 124.79 (d), 125.34 (d), 126.43 (d), 127.10 (d), 127.68 (d), 128.56 (d), 128.66 (d), 128.86 (d), 129.94 (d), 130.11 (d), 139.61 (s), 139.74 (s), 140.11 (s), 145.09 (s), 146.98 (s), 157.56 (s), 196.02 (d); MS (CI, CH_4) 356 (MH^+, 4), 355 (M^+, 3), 269 (6), 241 (100).

***N*,*N*-Dimethyl (4*S*,3′*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)-oxazolidine-4-(2′,2′-difluoro-3′-hydroxy)propionamide (7).** A solution of 1,1-bis(dimethylamino)-2,2-difluoroethene **4** (11.5 mL of a 0.47 M solution in THF, 5.4 mmol) was added to the aldehyde **6** (1.3 g, 3.6 mmol) in dry THF (10 mL), and the reaction mixture was stirred at rt overnight. The reaction was quenched by the addition of a few drops of H_2O, and the organic solvent was removed under reduced pressure after drying ($MgSO_4$). The oily residue was then purified using flash chromatography (eluant:1:1 EtOAc/hexane) to yield the adduct **7** as a white solid. A portion was recrystallized (EtOAc/hexane) to give **7** as colorless plates: 998 mg, 58%; mp 244.7−245.2 °C; $[\alpha]^{20}_D$ = −464° (*c* = 1.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.80 (1 H, d, *J* = 3.5 Hz), 2.85 (3 H, s), 2.94 (3 H, dd, $^5J_{HF}$ = 2.4, 1.5 Hz), 3.46 (1 H, dt, $^3J_{HF}$ = 26.1 Hz, *J* = 3.4 Hz), 4.38 (2 H, m), 4.59 (1 H, dt, *J* = 8.3, 1.5 Hz), 7.21−7.54 (10 H, m), 7.66 (1 H, d, *J* = 7.5 Hz), 7.74 (1 H, d, *J* = 7.5 Hz), 8.20 (1 H, d, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 36.54 (q), 36.68 (q), 55.76 (d), 62.36 (t), 68.56 (ddd, $^2J_{CF}$ = 28.7, 21.2 Hz), 71.62 (s), 115.56 (dd, $^1J_{CF}$ = 268.0, 261.0 Hz), 120.09 (d), 120.54 (d), 124.69 (d), 126.05 (d), 127.19 (d), 128.00 (d), 128.12 (d), 128.37 (d), 129.04 (d), 129.51 (d), 139.12 (s), 139.61 (s), 141.65 (s), 145.01 (s), 148.04 (s), 157.92 (s), 161.92 (t, $^2J_{CF}$ = 27.5 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) −108.22 (1 F, d, $^2J_{FF}$ = 290.1 Hz), −119.56 (1 F, dd, $^2J_{FF}$ = 290.1 Hz, $^3J_{HF}$ = 25.5 Hz); MS (CI, CH_4) 479 (MH^+, 4), 478 (M^+, 11), 242 (19), 241 (100); exact mass calcd for M^+ $C_{27}H_{24}F_2N_2O_4$ requires 478.1704, found 478.1687 (CI).

Ethyl (4*S*,3′*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-(2′,2′-difluoro-3′-hydroxy)propanoate (9a) and Eth-

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(35) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571−5574.

(36) The reaction appears to be complicated by the formation of products in which ring-opening of the *N*-phthaloyl substituent has taken place. Complicated mixtures of products were obtained under a variety of conditions for conversion of the oxetane into the ortho ester moiety (Ding, Y.; Richards, N. G. J. Unpublished results).

(37) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1991**, *32*, 7187−7190.

(38) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2935.

yl (4*S*,3′*R*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-(2′,2′-difluoro-3′-hydroxy)propanoate (9b). Ethyl bromodifluoroacetate (658 mg, 3.25 mmol) was added slowly to a stirred mixture of aldehyde **6** (464 mg, 1.3 mmol) dissolved in dry THF (10 mL) and acid-washed zinc powder (316 mg, 4.87 mmol) at rt under a N_2 atmosphere. The reaction mixture was stirred vigorously for 2 h until TLC analysis showed complete consumption of the aldehyde. After the addition of NH_4Cl (3 mL) and saturated NaCl (3 mL), the mixture was filtered through Celite. The precipitate was washed well with EtOAc (3 × 10 mL) and the organic phase separated. After extraction of the aqueous phase with EtOAc (2 × 10 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oily residue. This material was purified by flash chromatography (eluant: 3:1 hexane/EtOAc) to yield the desired adduct as a mixture of diastereoisomers **9a** and **9b** (529 mg, 85%), in a 6:1 ratio by ^{19}F NMR. This mixture was sufficiently pure for use in subsequent transformations. Careful column chromatography yielded a small amount of pure difluoro alcohol **9a**, a portion of which was recrystallized (EtOAc/hexane) to give colorless plates: mp 169−172 °C; $[\alpha]^{20}_D = -506°$ ($c = 1.06$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (3 H, t, $J = 7.2$ Hz), 1.61 (1 H, d, $J = 6.6$ Hz), 3.41 (1 H, dt, $^3J_{HF} = 20.1$ Hz, $J = 6.6$ Hz), 4.13 (2 H, m), 4.34 (1 H, dd, $J = 8.4$, 1.2 Hz), 4.43 (1 H, t, $J = 8.4$ Hz), 4.53 (1 H, ddd, $J = 9.0$, 2.4, 1.2 Hz), 7.44 (10 H, m), 7.74 (2 H, m), 8.21 (1 H, m); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.74 (q), 56.18 (d), 62.14 (dt, $^4J_{CF} = 6.9$ Hz), 63.19 (t), 68.45 (dd, $^2J_{CF} = 28.0$, 21.0 Hz), 71.70 (s), 113.56 (dd, $^1J_{CF} = 261.0$, 254.0 Hz), 120.32 (d), 120.68 (d), 124.66 (d), 126.19 (d), 127.47 (d), 127.63 (d), 128.54 (d), 129.27 (d), 129.45 (d), 129.83 (d), 138.82 (s), 140.08 (s), 141.17 (s), 144.77 (s), 148.38 (s), 157.82 (s), 161.09 (t, $^2J_{CF} = 31.0$ Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) −112.35 (1 F, dd, $^2J_{FF} = 269.0$ Hz, $^3J_{HF} = 6.2$ Hz), −124.21 (1 F, dd, $^2J_{FF} = 269.0$ Hz, $^3J_{HF} = 19.2$ Hz); MS (CI, CH_4) 480 (MH^+, 4), 479 (M^+, 11), 242 (19), 241 (100); exact mass calcd for M^+ $C_{27}H_{24}F_2NO_5$ requires 480.1622, found 480.1623 (CI).

9b: ^{19}F NMR ($CDCl_3$, 282 MHz) −112.98 (1 F, dd, $^2J_{FF} = 269.0$ Hz, $^3J_{HF} = 8.5$ Hz), −122.96 (1 F, dd, $^2J_{FF} = 269.0$ Hz, $^3J_{HF} = 19.2$ Hz).

***N*,*N*-Dimethyl (4*S*,3′*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)-oxazolidine-4-(2′,2′-difluoro-3′-hydroxy)propionamide (7) (from 9a).** *n*-BuLi (0.08 mL of a 2.5 M solution in THF, 0.2 mmol) was added to a solution of dimethylamine (0.1 mL of a 2 M solution in THF, 0.2 mmol) at −78 °C. The reaction mixture was warmed to 0 °C and stirred for 30 min, before a solution of **9a** (76 mg, 0.16 mmol) in THF (0.5 mL) was added. The mixture was warmed to rt and stirred for a further 1.5 h, to ensure complete consumption of starting ester, before being poured into ice (2 g). The aqueous solution was then extracted with EtOAc (3 × 2 mL). The organic extracts were washed with saturated brine (2 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oily residue. Purification by flash chromatography (eluant: 1:1 EtOAc/hexane) gave a white solid that had spectroscopic properties identical to those of an authentic sample of **7**: 75 mg, 98%.

Ethyl (4*S*,3′*R*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-(3′-hydroxy)propanoate (11a) and Ethyl (4*S*,3′*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-(3′-hydroxy)-propanoate (11b). Ethyl bromoacetate (1.14 mL, 10 mmol) was added slowly to a mixture of aldehyde **6** (2.29 g, 6 mmol) and acid-washed zinc dust (0.78 g, 12 mmol) in dry THF (40 mL) at rt under a N_2 atmosphere. The reaction mixture was stirred vigorously for 2 h before the addition of aqueous NH_4-Cl (20 mL) and brine (20 mL). After filtration through Celite, the precipitate was washed well with EtOAc (4 × 10 mL) and the organic phase separated. After extraction of the aqueous phase with EtOAc (4 × 10 mL), the combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give an oily residue. This material was purified by flash chromatography (eluant: 4:1 hexane/EtOAc). The major diastereoisomer **11a** was eluted as the first material from the column, followed by **11b**. Both compounds were obtained as colorless oils.

11a: 1.92 g, 72%; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11 (3 H, t, $J = 7.2$ Hz), 1.50 (1 H, d, $J = 4.4$ Hz), 1.71 (1 H, dd, $J = 15.6$, 4.8 Hz), 2.05 (1 H, dd, $J = 15.6$, 8.9 Hz), 3.28 (1 H, m), 3.90 (3 H, m), 4.27 (1 H, dd, $J = 8.8$, 2.7 Hz), 4.34 (1 H, t, $J = 8.6$ Hz), 7.18−7.42 (9 H, m), 7.51 (1 H, dt, $J = 7.6$, 0.6 Hz), 7.69 (1 H, d, $J = 7.6$ Hz), 7.77 (1 H, d, $J = 7.6$ Hz), 8.20 (1 H, d, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.88 (q), 37.06 (t), 60.06 (d), 60.63 (d), 61.86 (t), 65.88 (t), 71.52 (s), 120.31 (d), 120.52 (d), 124.63 (d), 124.73 (d), 125.98 (d), 127.21 (d), 127.32 (d), 128.03 (d), 128.37 (d), 129.08 (d), 129.68 (d), 139.04 (s), 140.01 (s), 141.46 (s), 145.01 (s), 148.22 (s), 157.73 (s), 169.93 (s); MS (CI, CH_4) 443 (M^+, 16), 241 (100); exact mass calcd for MH^+ $C_{27}H_{26}NO_5$ requires 444.1811, found 444.1812 (CI).

11b: 512 mg, 23%; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (3 H, t, $J = 7.2$ Hz), 1.42 (1 H, d, $J = 4.6$ Hz), 1.75 (1 H, dd, $J = 15.4$, 5.0 Hz), 2.15 (1 H, dd, $J = 15.4$, 8.4 Hz), 3.28 (1 H, m), 3.90 (1 H, ddd, $J = 8.4$, 2.4, 1.5 Hz), 4.11 (2 H, q, $J = 7.2$ Hz), 4.29 (1 H, dd, $J = 8.7$, 2.7 Hz), 4.37 (1 H, t, $J = 8.7$ Hz), 7.20−7.42 (9 H, m), 7.52 (1 H, m), 7.70 (1 H, m), 7.79 (1 H, m), 8.21 (1 H, m); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.15 (q), 36.88 (t), 51.84 (d), 60.08 (d), 61.88 (t), 65.95 (t), 71.66 (s), 120.44 (d), 120.68 (d), 124.71 (d), 124.79 (d), 126.07 (d), 127.35 (d), 127.38 (d), 128.09 (d), 128.49 (d), 129.17 (d), 129.83 (d), 139.20 (s), 140.12 (s), 141.46 (s), 145.14 (s), 148.34 (s), 157.75 (s), 170.39 (s); MS (CI, CH_4) 443 (M^+, 12), 241 (100).

***N*,*N*-Dimethyl (4*S*,3′*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)-oxazolidine-4-(2′,2′-difluoro-3′-oxythiocarbonylpentafluorophenyl)propionamide (12).** The difluorinated alcohol **7** (372 mg, 0.78 mmol) was dissolved in toluene together with DMAP (220 mg, 1.8 mmol) and *N*-hydroxysuccinimide (45 mg, 0.39 mmol). After the addition of pentafluorophenylthiochloroformate (408 mg, 1.5 mmol), the reaction was heated at 90 °C overnight. The solution was then filtered through Celite and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude product was purified using flash chromatography (eluant: 1:2 EtOAc/hexanes) to yield **12** as a yellowish foam: 296 mg, 54% (74% based on recovered **7**): ^1H NMR ($CDCl_3$, 300 MHz) δ 2.78 (6 H, s), 4.58 (1 H, m), 4.74 (2 H, m), 5.04 (1 H, m), 7.15−7.50 (10 H, m), 7.70 (2 H, m), 8.13 (1 H, d, $J = 7.6$ Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 37.19 (qt, $^4J_{CF} = 6.8$ Hz), 37.57 (q), 55.41 (dt, $^3J_{CF} = 5.0$ Hz), 63.19 (t), 72.11 (s), 80.27 (dt, $^2J_{CF} = 24.1$ Hz), 114.01 (dd, $^1J_{CF} = 268.0$, 261.0 Hz), 120.21 (d), 120.46 (d), 124.64 (d), 126.77 (d), 127.47 (d), 128.38 (d), 128.44 (d), 128.59 (d), 129.45 (d), 129.71 (d), 129.83 (d), 137.00 (m), 139.65 (s), 139.83 (s), 140.28 (m), 140.93 (m), 141.54 (s), 144.44 (s), 147.33 (s), 157.21 (s), 159.99 (t, $^2J_{CF} = 26.0$ Hz), 189.97 (s); ^{19}F NMR ($CDCl_3$, 282 MHz) −107.37 (2 F, d, $^3J_{HF} = 10.7$ Hz), −151.84 (2 F, d, $^3J_{FF} = 17.1$ Hz), −156.58 (1 F, t, $J = 21.3$ Hz), −162.16 (2 F, dt, $^3J_{FF} = 21.3$, 17.1 Hz); MS (CI, CH_4) 705 (MH^+, 5), 704 (M^+, 14), 242 (20), 241 (100); exact mass calcd for M^+ $C_{34}H_{23}F_7N_2O_5S$ requires 704.1216, found 704.1224 (CI).

Further elution gave unreacted alcohol **7**: 102 mg.

***N*,*N*-Dimethyl (4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-(2′,2′-difluoro)propionamide (13).** A solution of the difluorinated derivative **12** (295 mg, 0.42 mmol) dissolved in toluene (8 mL) was degassed for 15 min before being heated to reflux under an Ar atmosphere. A mixture of Bu_3-SnH (0.45 mL, 1.68 mmol) and AIBN (42 mg, 0.26 mmol) dissolved in toluene (4 mL) was then added dropwise to the hot solution. After being heated for an additional 15 min, the reaction mixture was cooled to rt and quenched by the addition of H_2O (0.1 mL). The solvent was then removed under reduced pressure, and the residue was purified using flash chromatography (eluant: 5:2 hexane/EtOAc) to yield the deoyxygenated amide **13** as a white foam. A portion was recrystallized from EtOAc/hexane: 76 mg, 39%; mp 211−211.5 °C; $[\alpha]^{20}_D = -638°$ ($c = 0.1$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.78 (3 H, s), 2.89 (3 H, t, $^5J_{HF} = 1.8$ Hz), 3.64 (1 H, ddd, $^3J_{HF} = 21.3$, 12.3 Hz, $J = 8.4$ Hz), 4.51 (1 H, dd, $J = 9.0$, 8.4 Hz), 4.61 (1 H, t, $J = 8.6$ Hz), 4.85 (1 H, dd, $J = 16.2$, 8.1 Hz), 6.58 (2 H, m), 6.70 (1 H, s), 6.84−7.04 (6 H, m), 7.18 (1 H, m), 7.39 (1 H, m), 7.52 (2 H, m), 7.76 (1 H, m); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 36.90 (q), 37.24 (q), 49.21 (t, $^2J_{CF} = 22.0$ Hz), 58.24 (d), 61.69

(t), 65.60 (s), 119.15 (t, $^1J_{CF}$ = 257.0 Hz), 125.42 (d), 126.01 (d), 126.08 (d), 127.28 (d), 127.59 (d), 128.15 (d), 128.79 (d), 129.09 (d), 130.39 (d), 130.58 (d), 133.37 (s), 136.42 (s), 138.21 (s), 139.85 (s), 141.43 (s), 158.29 (s), 162.10 (t, $^2J_{CF}$ = 26.0 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) −89.86 (1 F, dd, $^2J_{FF}$ = 281.4 Hz, $^3J_{HF}$ = 12.7 Hz), −93.43 (1 F, dd, $^2J_{FF}$ = 281.4 Hz, $^3J_{HF}$ = 21.4 Hz); MS (CI, CH_4) 463 (MH^+, 100), 462 (M^+, 18), 443 (72), 241 (10); exact mass calcd for MH^+ $C_{27}H_{25}F_2N_2O_3$ requires 463.1833, found 463.1828 (CI).

Ethyl (4*S*,3′*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-(2′,2′-difluoro-3′-oxythiocarbonylpentafluorophenyl)propanoate (14a) and Ethyl (4*S*,3′*R*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-(2′,2′-difluoro-3′-oxythiocarbonylpentafluorophenyl)propanoate (14b). The mixture of diastereoisomeric fluorinated alcohols **9** (1.66 g, 3.5 mmol) was dissolved in toluene (50 mL), together with DMAP (885 mg, 7 mmol) and *N*-hydroxysuccinimide (403 mg, 3.5 mmol). After the addition of pentafluorophenylchlorothioformate (408 mg, 1.5 mmol), the reaction mixture was heated to 90 °C and stirred overnight. The solution was then filtered through Celite and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude product was purified using flash chromatography (eluant: 1:6 EtOAc/hexane) to yield the desired pentafluorophenyl ester as a mixture of diastereoisomers **14a** and **14b**: 1.47 g, 60%; ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.60 (q), 55.09 (d), 63.07 (t), 64.07 (t), 72.21 (s), 79.76 (ddd, $^2J_{CF}$ = 21.7, 30.2 Hz), 111.09 (dd, $^1J_{CF}$ = 258.4, 261.7 Hz), 120.39 (d), 120.69 (d), 124.78 (d), 126.42 (d), 127.51 (d), 127.73 (d, $^1J_{CF}$ = 225.6 Hz), 128.21 (d), 128.41 (d), 128.57 (d), 129.56 (d), 129.70 (d), 129.74 (d), 137.96 (m), 139.61 (s), 139.87 (s), 140.18 (m), 141.02 (s), 144.32 (s), 146.94 (s), 149.40 (s), 157.12 (s), 160.84 (t, $^2J_{CF}$ = 29.7 Hz), 189.58 (s).

14a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (3 H, t, J = 7.2 Hz), 4.10 (2 H, m), 4.58 (3 H, m), 5.03 (1 H, dd, $^3J_{HF}$ = 15.9 Hz, J = 8.4 Hz), 7.20−7.48 (10 H, m), 7.71 (2 H, m), 8.07 (1 H, m); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −111.76 (1 F, dd, $^2J_{FF}$ = 264.7 Hz, $^3J_{HF}$ = 8.5 Hz), −116.83 (1 F, dd, $^2J_{FF}$ = 264.7 Hz, $^3J_{HF}$ = 16.9 Hz), −151.93 (2 F, d, J = 19.2 Hz), −156.38 (1 F, t, J = 21.5 Hz), −161.9 (2 F, dt, $^3J_{FF}$ = 21.5, 19.2 Hz); MS (CI, CH_4) 705 (M^+, 7), 704 (16), 241 (100).

14b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (3 H, t, J = 7.2 Hz), 4.10 (2 H, m), 4.58 (4 H, m), 7.20−7.48 (10 H, m), 7.71 (2 H, m), 8.07 (1 H, m); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −113.29 (1 F, dd, $^2J_{FF}$ = 266.7 Hz, $^3J_{HF}$ = 8.5 Hz), −118.72 (1 F, dd, $^2J_{FF}$ = 266.7 Hz, $^3J_{HF}$ = 15.0 Hz), −152.57 (2 F, d, J = 16.9 Hz), −156.75 (1 F, t, J = 21.5 Hz), −161.87 (2 F, dt, $^3J_{FF}$ = 21.5, 16.9 Hz).

Ethyl (4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-(2′,2′-difluoro)propanoate (15). A solution of the difluorinated derivative **14** (490 mg, 0.695 mmol) dissolved in toluene (15 mL) was degassed for 15 min before being heated to reflux under an Ar atmosphere. A mixture of Bu_3SnH (0.56 mL, 2.09 mmol) and AIBN (30 mg, 0.15 mmol) dissolved in toluene (1 mL) was then added dropwise to the hot solution. After being heated for an additional 10 min, the reaction mixture was cooled to rt and quenched by the addition of H_2O (0.1 mL). The solvent was removed under reduced pressure, and the residue was purified using flash chromatography (eluant: 5:2 hexane/EtOAc) to yield the deoxygenated ester **15** as a white foam. A portion was recrystallized (EtOAc/hexane) to give **15** as white crystals: 119 mg, 37% (49% based on recovered **14**); mp 182.0−183.5 °C; $[\alpha]^{20}_D$ = −41.8° (c = 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (3 H, t, J = 7 Hz), 3.57 (2 H, ddd, $^3J_{HF}$ = 24.3, 12.9 Hz, J = 8.4 Hz), 3.87 (2 H, m), 4.69 (3 H, m), 6.54 (2 H, m), 6.71 (1 H, s), 6.87−7.01 (5 H, m), 7.13 (1 H, m), 7.33 (1 H, m), 7.54 (2 H, m), 7.73 (1 H, m); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.29 (q), 47.18 (tt, $^2J_{CF}$ = 18.0 Hz), 57.57 (d), 61.65 (t), 62.69 (t), 65.51 (s), 116.90 (dd, $^1J_{CF}$ = 254.0, 259.0 Hz), 125.27 (d), 126.11 (d), 127.61 (d), 127.85 (d), 128.40 (d), 128.93 (d), 129.18 (d), 130.01 (d), 130.59 (d), 131.61 (d), 131.75 (d), 133.42 (s), 136.36 (s), 138.11 (s), 139.60 (s), 141.68 (s), 158.13 (s), 161.50 (t, $^2J_{CF}$ = 32 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −89.47 (1 F, dd, $^2J_{FF}$ = 262.5 Hz, $^3J_{HF}$ = 13.0 Hz), −111.37 (1 F, dd, $^2J_{FF}$ = 262.5 Hz, $^3J_{HF}$ = 25.7 Hz); MS (CI, CH_4) 464 (MH^+, 100), 463 (M^+, 40), 254 (22), 241 (21); exact mass calcd for MH^+ $C_{27}H_{24}F_2NO_4$ requires 464.1673, found 464.1670 (CI).

Further elution gave the unreacted pentafluorophenyl derivative **14**: 116 mg.

1-[*N*-Benzyloxycarbonyl-(1*S*,2*R*)-1-amino-3,3-difluoro-3-ethoxycarbonyl-4-hydroxypropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (21a) and 1-[*N*-Benzyloxycarbonyl-(1*S*,2*S*)-1-amino-3,3-difluoro-3-ethoxycarbonyl-4-hydroxypropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane (21b). Ethyl bromodifluoroacetate (8 mL, 62.4 mmol) was slowly added to a well-stirred mixture of acid-washed zinc dust (6.08 g, 93.6 mmol) and aldehyde **3** (5 g, 15.6 mmol) dissolved in dry THF (150 mL) at rt, under an argon atmosphere. The reaction mixture was stirred for 2 h, after which time TLC analysis showed complete consumption of aldehyde. After the addition of 3% aqueous NH_4Cl (80 mL) and brine (80 mL), the mixture was filtered to remove solid materials. The solution was then extracted with EtOAc (3 × 150 mL) and washed with brine (150 mL), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent under reduced pressure and column chromatography (eluant: 2:3 EtOAc/hexane containing 1% Et_3N), the desired adduct was obtained as a 7:1 mixture of diastereoisomers **21a**:**21b**, based on ^{19}F NMR, as a white foam: 4.85 g, 70%; ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.10 (q), 14.41 (q), 30.95 (s), 52.11 (t), 63.39 (d), 67.17 (t), 68.84 (ddd, $^2J_{CF}$ = 31.0, 22.9 Hz), 73.08 (t), 108.74 (s), 113.97 (dd, $^1J_{CF}$ = 261.9, 250.9 Hz), 128.25 (d), 128.67 (d), 136.67 (s), 156.30 (s), 163.47 (dd, $^2J_{CF}$ = 32.7, 29.7 Hz); MS (FAB) 446 (MH^+, 58), 138 (64), 137 (100), 136 (85); exact mass calcd for MH^+ $C_{20}H_{26}F_2NO_8$ requires 446.1626, found 446.1614 (FAB).

21a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (3 H, s), 1.32 (3 H, t, J = 7.1 Hz), 3.24 (1 H, br. s), 3.92 (6 H, s), 4.26−4.35 (3 H, m), 4.66 (1 H, dd, $^3J_{HF}$ = 18.3, J = 5.4 Hz), 5.13 (2 H, m), 5.43 (1 H, d, J = 10.3 Hz), 7.32 (5 H, m); ^{19}F NMR ($CDCl_3$, 282 MHz) −112.69 (1 F, dd, $^2J_{FF}$ = 264.6 Hz, $^3J_{HF}$ = 6.4 Hz), −125.35 (1 F, dd, $^2J_{FF}$ = 264.6 Hz, $^3J_{HF}$ = 19.2 Hz).

21b: ^{19}F NMR ($CDCl_3$, 282 MHz) −112.33 (1 F, d, $^2J_{FF}$ = 262.5 Hz), −124.68 (1 F, dd, $^2J_{FF}$ = 264.6 Hz, $^3J_{HF}$ = 17.1 Hz).

1-[*N*-Benzyloxycarbonyl-(1*S*,2*R*)-1-amino-3,3-difluoro-3-ethoxycarbonyl-4-oxythiocarbonylimidazolepropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (22a) and 1-[*N*-Benzyloxycarbonyl-(1*S*,2*S*)-1-amino-3,3-difluoro-3-ethoxycarbonyl-4-oxythiocarbonylimidazolepropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (22b). Thiocarbonyldiimidazole (349 mg, 1.76 mmol) and the diastereoisomeric mixture of adducts **21a** and **21b** (491 mg, 1.1 mmol) were dissolved in dry THF (15 mL) and stirred at rt, under an argon atmosphere, for 10 h. The resulting reaction mixture was then washed with 5% aqueous NH_4Cl (15 mL), aqueous $NaHCO_3$ (15 mL), and brine (15 mL). After drying ($MgSO_4$), the solvent was removed to yield an oily residue that was purified by column chromatography (eluant: 1:3 EtOAc/hexane containing 1% Et_3N). The mixture of thioester derivatives **22a** and **22b** was obtained as a white foam: 465 mg, 76%; ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.63 (q), 14.00 (q), 30.72 (s), 52.11 (t), 63.60 (d), 67.34 (t), 72.82 (t), 75.51 (dt, $^2J_{CF}$ = 27.2 Hz), 107.12 (s), 111.75 (t, $^1J_{CF}$ = 258.9 Hz), 118.17 (d), 128.19 (d), 128.45 (d), 130.96 (d), 135.92 (s), 137.19 (d), 155.80 (s), 161.54 (dd, $^2J_{CF}$ = 31.2, 30.7 Hz), 182.63 (s); MS (FAB) 556 (MH^+, 33), 154 (70), 91 (100); exact mass calcd for MH^+ $C_{24}H_{28}F_2N_3O_8S$ requires 556.1565, found 556.1560 (FAB).

22a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (3 H, s), 1.27 (3 H, t, J = 7.1 Hz), 3.77−3.86 (6 H, m), 4.24 (2 H, m), 4.62 (1 H, dd, J = 10.8, 1.0 Hz), 5.13−5.19 (3 H, m), 6.74 (1 H, m), 7.04 (1 H, m), 7.36 (5 H, m), 7.62 (1 H, m), 8.34 (1 H, m); ^{19}F NMR ($CDCl_3$, 282 MHz) −113.87 (1 F, dd, $^2J_{FF}$ = 269.0 Hz, $^3J_{HF}$ = 9.7 Hz), −115.19 (1 F, dd, $^2J_{FF}$ = 269.0 Hz, $^3J_{HF}$ = 11.7 Hz).

22b: ^{19}F NMR ($CDCl_3$, 282 MHz) −113.45 (1 F, dd, $^2J_{FF}$ = 270.0 Hz, $^3J_{HF}$ = 9.6 Hz), −115.78 (1 F, dd, $^2J_{FF}$ = 270.0 Hz, $^3J_{HF}$ = 11.8 Hz).

1-[*N*-Benzyloxycarbonyl-(1*S*)-1-amino-3,3-difluoro-3-ethoxycarbonylpropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane (23). The diastereoisomeric mixtures of thioester derivatives **22** (430 mg, 0.78 mmol) and Et_3SiH (6.2 mL, 39

mmol) were dissolved in freshly distilled benzene (10 mL). After the solution was degassed for 15 min using dry argon, the reaction mixture was heated to reflux prior to the careful addition of a solution of benzoyl peroxide (37.5 mg, 0.15 mmol) in dry benzene (0.2 mL). At 30 min intervals, additional portions of benzoyl peroxide were added to a total amount of 0.8 equiv. The reaction mixture was then refluxed for a further 30 min and then allowed to cool to rt. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (eluant: 4:1 hexane/EtOAc containing 1% Et_3N) to give the dehydroxylated OBO ester **23** as a white foam: 276 mg, 83%. A portion was recrystallized (EtOAc/hexane) to give **23** as colorless needles. mp 78.0−78.8 °C; $[\alpha]^{20}_D$ = −37.6° (*c* = 1, EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (3 H, s), 1.27 (3 H, t, *J* = 7.0 Hz), 2.17−2.36 (1 H, m), 2.58 (1 H, ddd, $^3J_{HF}$ = 29.8, 14.9 Hz, *J* = 2.3 Hz), 3.87 (6 H, s), 4.13−4.27 (3 H, m), 4.84 (1 H, d, *J* = 10.5 Hz), 5.11 (2 H, m), 7.29−7.34 (5 H, m); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.77 (q), 14.14 (q), 30.57 (s), 34.80 (ddt, $^2J_{CF}$ = 24.4, 23.3 Hz), 49.78 (t), 62.76 (d), 66.78 (t), 72.69 (t), 107.73 (s), 115.24 (dd, $^1J_{CF}$ = 252.1, 248.9 Hz), 127.99 (d), 128.03 (d), 128.37 (d), 136.34 (s), 155.76 (s), 163.90 (dd, $^2J_{CF}$ = 32.7, 32.2 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) −102.76 (1 F, ddd, $^2J_{FF}$ = 266.8 Hz, $^3J_{HF}$ = 14.9, 12.8 Hz), −106.29 (1 F, ddd, $^2J_{FF}$ = 266.7 Hz, $^3J_{HF}$ = 19.2, 14.9 Hz); MS (FAB) 430 (MH^+, 93), 307 (59), 136 (100), 107 (48); exact mass calcd for MH^+ $C_{20}H_{26}F_2NO_7$ requires 430.1677, found 430.1671 (FAB).

(2*S*)-4,4-Difluoroglutamic Acid (2). The N-protected OBO ester **23** (190 mg, 0.44 mmol) was dissolved in 6 N aqueous HCl (20 mL) and the solution heated at 90 °C for 2 h. The solvent was removed under vacuum to yield a viscous oil that was redissolved in doubly deionized (dd) H_2O. After the solution pH was adjusted to 7 using aqueous $NaHCO_3$, the solution was applied to an anion-exchange column (BioRad AG3-X4 resin) that had been equilibrated with ddH_2O. Elution was then carried out using ddH_2O and an increasing gradient of TFA up to a final concentration of 0.25 M. Ninhydrin positive fractions were then pooled and lyophilization yielded the crude product **2** as a solid. L-4,4-Difluoroglutamic acid **2** was then obtained by recrystallization from H_2O/^{i}PrOH as white needles: 35 mg, 37%; mp 174.5−176.5 °C dec (lit.[12] mp 173−176 °C dec); $[\alpha]^{20}_D$ = 6.5° (*c* = 1, ddH_2O) (lit.[13] $[\alpha]^{20}_D$ = 5.4° (*c* = 1.04, H_2O)); ^{1}H NMR (D_2O, 300 MHz) δ 2.55−2.92 (3 H, m), 4.32 (1 H, dd, *J* = 8.4, 3.8 Hz); ^{13}C NMR (D_2O, 75.4 MHz) δ 34.79 (tt, $^2J_{CF}$ = 24.7 Hz), 48.53 (d), 116.42 (dd, $^1J_{CF}$ = 251.8, 251.3 Hz), 169.00 (dd, $^2J_{CF}$ = 28.2, 27.7 Hz), 171.26 (s); ^{19}F NMR (D_2O, 282 MHz) −103.36 (1 F, ddd, $^2J_{FF}$ = 251.8 Hz, $^3J_{HF}$ = 21.3, 12.8 Hz), −104.45 (1 F, ddd, $^2J_{FF}$ = 251.8 Hz, $^3J_{HF}$ = 19.2, 14.9 Hz); MS (CI, CH_4) exact mass calcd for MH^+ $C_5H_8F_2NO_4$ requires 184.0421, found 184.0410.

X-ray Diffraction Structure Determination of *N*,*N*-Dimethyl (4*R*,3′*S*)-2-Oxo-3-(9-phenylfluorenyl-9-yl)oxazolidine-4-(2′,2′-difluoro-3′-hydroxy)propionamide (7). Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing Mo Kα radiation (λ = 0.710 73 Å). Cell parameters were refined using 5720 reflections. A hemisphere of data (1381 frames) was collected using the ω-scan method (0.3° frame width). The first 50 frames were remeasured at the end of data collection to monitor instrument and crystal stability (maximum correction on *I* was <1%). Absorption corrections by integration were applied based on measured indexed crystal faces. The structure was solved by direct methods in SHELXTL5[39] and refined using full-matrix least-squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms, except the O3′ hydroxyl and the water molecule protons which were obtained from a difference Fourier map and refined without any constraints. There is a water molecule of solvation present in the asymmetric unit. A total of 340 parameters were refined in the final cycle of refinement using 3880 reflections with $I > 2\sigma(I)$ to yield R_1 and wR_2 of 4.04% and 7.63%, respectively. Refinement was done using F^2.

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Supporting Information Available: ^{1}H, ^{13}C, and ^{19}F NMR spectra of **7**, **9a**, **13**, **15**, **21**, **23**, and **2**, together with ^{1}H and ^{13}C spectra for **11a**, an ORTEP plot of **7** and full information concerning the X-ray structure of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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