Preparation of α,α-Difluoro-β-hydroxy Esters via a Modified Reformatsky Reaction

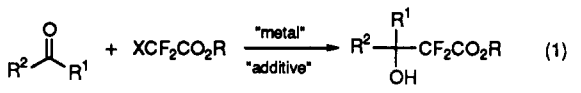
Timothy T. Curran

Marion Merrell Dow Research Institute, 2110 E. Galbraith Road, Cincinnati, Ohio 45215

Received June 14, 1993[•]

A modified Reformatsky reaction has been developed which allows for the reproducible preparation of α,α-difluoro-β-hydroxy- and γ-amino-α,α-difluoro-β-hydroxy esters in good yield from the corresponding aldehyde, ketone, or α-*N*-carbamoyl aldehyde.

The Reformatsky reaction of ethyl bromodifluoroacetate was first reported by Fried et al.,[1] and several examples of its application toward the preparation of fluorinated biologically active compounds have appeared.[2] Since Fried's initial report, he and others have published modifications for this reaction using either chloro-, bromo-, or iododifluoroacetate with various additives,[3] eq 1. In conjunction with our program to prepare transition-state-mimicking enzyme inhibitors, it was necessary to investigate the Reformatsky reaction between a halodifluoroacetate and an *N*-protected-α-amino aldehyde. Although several examples have been published utilizing these substrates, many report the use of sonicating conditions to achieve good yields,[2d-f,3b] while others report the use of thermal conditions and obtain low or variable yields.[2b,c,g]



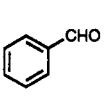
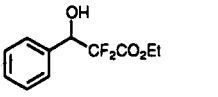
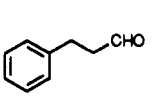
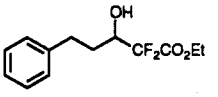
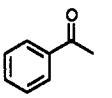
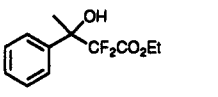
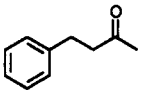
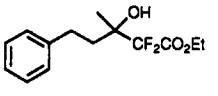
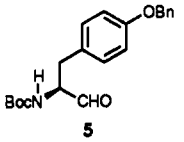
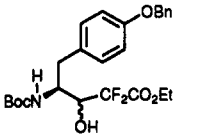
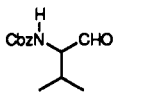
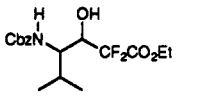
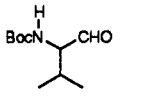
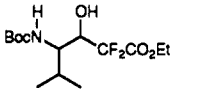
R^1, R^2 = Alkyl, Aryl, or H; X = I, Br, Cl; R = Alkyl

We would like to report our experimental details on the reaction of ethyl bromodifluoroacetate with aliphatic or aromatic ketones, aldehydes, and *N*-protected-α-amino aldehydes. This method allows the preparation of α,α-difluoro-β-hydroxy esters at 0 °C to rt and without sonication in good, reproducible yield.

Results and Discussion

We found that when $BrCF_2CO_2Et$ (2 equiv) was treated with Zn (2 equiv), AgOAc (0.3 equiv), and Et_2AlCl (1.1–2 equiv) to generate a nucleophilic species,[3a,4] in the presence of an aldehyde or ketone at 0 °C to rt, we obtained the α,α-difluoro-β-hydroxy esters consistently in 51–69% yield. As shown in Table I, this reaction proved to be general. Aliphatic and aromatic aldehydes or ketones (entries 1–4, Table I) provided good yields of the α,α-difluoro-β-hydroxy esters.[1,3c] More importantly, reaction of *N*-carbamoyl-α-amino aldehydes[5] with $BrCF_2CO_2Et$ under the Et_2AlCl–AgOAc conditions provided yields of the γ-*N*-carbamoyl-α,α-difluoro-β-hydroxy esters which are superior to those previously published on similar substrates utilizing thermal conditions[2] (entries 5–7, Table I).

Table I. Preparation of α,α-Difluoro-β-hydroxy Esters

entry	carbonyl compound	product (*syn*/*anti*)[8]	yield, %
1	 1	 8	69
2	 2	 9	64
3	 3	 10	62
4	 4	 11	51
5	 5	 12 (2:3)	64
6	 6	 13 (1:1)	55
7	 7	 14 (1:1.4)	54

(5) Amino aldehydes were prepared by reduction of the Weinreb amide with LAH and purified by column chromatography on SiO_2 (6 and 7 are racemized) or recrystallized (5). (a) Castro, B.; Fehrentz, J.-A. *Synthesis* 1983, 676. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* 1981, 22, 3815.

• Abstract published in *Advance ACS Abstracts*, October 1, 1993.

(1) Hallinan, E. A.; Fried, J. *Tetrahedron Lett.* 1984, 25, 2301.

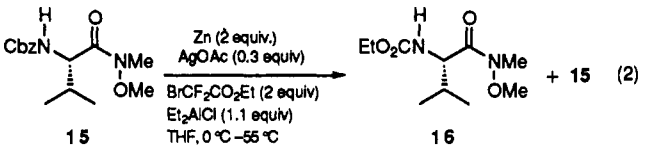
(2) (a) Welch, J. T. *Tetrahedron* 1987, 43, 3123. (b) Doherty, A. M.; Sicar, I.; Kornberg, B. E.; Quin, J.; Winters, R. T.; Kaltenbronn, J. S.; Taylor, M. D.; Batley, B. L.; Rapundalo, S. R.; Ryan, M. J.; Painchaud, C. A. *J. Med. Chem.* 1992, 35, 2. (c) Schirlin, D.; Baltzer, S.; Altenburger, J. M. *Tetrahedron Lett.* 1988, 29, 3687. (d) Schirlin, D.; Altenburger, J. M. *Tetrahedron Lett.* 1991, 32, 7255. (e) Robinson, R. P.; Donahue, K. M. *J. Org. Chem.* 1992, 57, 7309. (f) Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomasco, L. M.; Watt, W. *J. Med. Chem.* 1986, 29, 2080. (g) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* 1990, 33, 394. (h) Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Tustin, J. M. *J. Org. Chem.* 1988, 53, 2406. (i) Witkowski, S.; Rao, Y. K.; Premchandran, R. H.; Halushka, P. V.; Fried, J. *J. Am. Chem. Soc.* 1992, 114, 8464.

(3) (a) Kuroboshi, M.; Ishihara, T. *Tetrahedron Lett.* 1987, 28, 6481. (b) Lang, R. W.; Schaub, B. *Tetrahedron Lett.* 1988, 29, 2943. (c) Kobayashi, Y.; Taguchi, T.; Kitagawa, O. *Tetrahedron Lett.* 1988, 29, 1803. (d) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* 1991, 32, 7017. (e) Furstner, A. *Synthesis* 1989, 571 and refs cited therein.

(4) Yamamoto, H.; Nozaki, H.; Maruoka.; Hashimoto, S.; Kitagawa, Y. *J. Am. Chem. Soc.* 1977, 99, 7705.

0022-3263/93/1958-6360$04.00/0

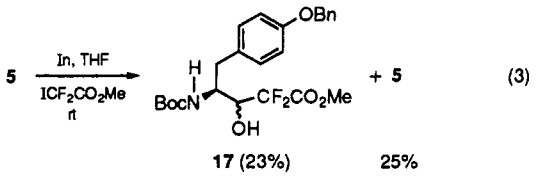
Attempts to couple Weinreb amide **15**[5] under the Et_2AlCl–AgOAc conditions described above failed; **15** was recovered in 93%. Increasing the reaction temperature to 55 °C for 14 h provided the ethyl carbamate **16** in a 27% yield along with recovered **15** (63%), eq 2.



(2)

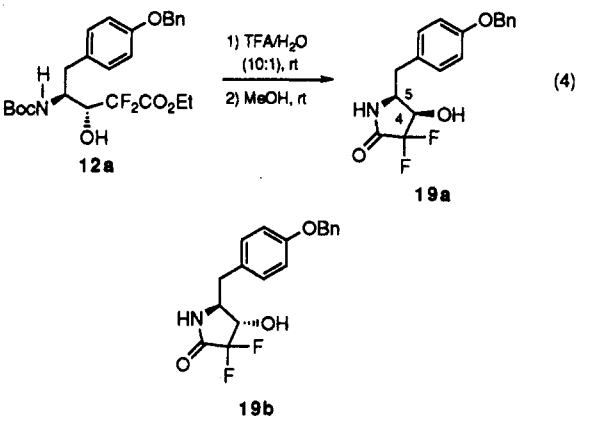
Alternatively, we found that we also could use a modified two-step procedure[1,2d] and obtain good yields of the *N*-Boc-γ-amino-α,α-difluoro-β-hydroxy ester **12**. This procedure was as follows: (1) generate the Reformatsky reagent using $BrCF_2CO_2Et$ (2 equiv) and Zn (2 equiv) in THF at 55–78 °C for 15 min; (2) allow the reaction mixture to cool to about 45 °C; (3) add aldehyde **5** as a THF solution; and (4) add a Lewis acid (BF_3·OEt_2 or $ZnCl_2$, 1 equiv) followed by stirring at ambient temperature for 6 h. This method provided α,α-difluoro-β-hydroxy ester **12** in 58–64% as a 1:1 diastereomeric mixture. At ambient temperature and without a Lewis acid, the desired product **12** is not observed (^1H and ^{19}F NMR). Poor yields of **12** resulted when the Reformatsky reagent was generated at elevated temperatures for longer periods of time (>20 min).[6] Rapid cooling was problematic on scale-up; and therefore, this method was less attractive for our purposes.

Using thermal Reformatsky conditions to promote the reaction of $BrCF_2CO_2Et$ with α-amino aldehyde **5** in THF provided low and variable yields of **12** (20–38%). Use of CuCl to catalyze the Reformatsky reaction of $BrCF_2CO_2Et$ with **5** in THF or DMF also gave poor yields (10–30%). Attempts to react the less expensive ethyl chlorodifluoroacetate with aldehyde **5** under either the Et_2AlCl–AgOAc conditions, the above-mentioned Lewis acid-catalyzed conditions (BF_3·OEt_2 or $ZnCl_2$, 1 equiv), or Zn–CuCl[3a] in THF, or DMF between rt and 70 °C[3b] failed to provide good yields of **12**; 30% or less yields were obtained with no recovered starting aldehyde **5**. Attempts to react methyl iododifluoroacetate with aldehyde **5** using Zn in CH_3CN with or without TESCl, as reported by Kobayashi,[3c] failed to provide the Reformatsky product. Interestingly, the reaction of methyl iododifluoroacetate with aldehyde **5** using indium[3d] did provide some of the desired Reformatsky product **17** in 23% yield (eq 3); however, we were unable to force the reaction to completion and aldehyde **5** was recovered (25%).



(3)

The stereoselectivity for the Et_2AlCl–AgOAc promoted Reformatsky reaction with the *N*-carbamoyl-α-amino aldehydes of entries 5–7 was judged to be poor by ^1H and ^{19}F NMR (1:1 to 2:3).[7] The stereochemistry of Reformatsky product **12** was determined by the chromatographic separation of the two diastereomers **12a** and **12b** and their independent conversion to cyclic derivatives, followed by NOE assignment of stereochemistry for their respective derivatives. Treatment of minor diastereomer **12a** with CF_3CO_2H/H_2O (10:1) at rt, followed by stirring the resulting crude γ-amino ester in MeOH, promoted cyclization[2e] to provide **19a** in 37% yield, eq 4. The major diastereomer **12b** was cyclized in a similar fashion. NOESY and 1D-NOE spectra of **19a** showed a strong through-space interaction between C4-H and C5-H indicating that these hydrogens have a *cis* relationship in the pyrrolidinone ring. No such interaction was observed in the NOESY or 1D-NOE spectra for **19b**, indicating that the C4-H and C5-H have a *trans* relationship in **19b**. It



(4)

should be noted that the major stereoisomer (**12b**, *anti*[8]) that we obtained using the Et_2AlCl–AgOAc conditions was opposite to the major stereoisomer (**12a**, syn) reported by others[2b-f] for the reaction of *N*-carbamoyl-α-amino aldehydes with ethyl bromodifluoroacetate under thermal or sonicating Reformatsky reaction conditions.

We feel that the Et_2AlCl–AgOAc procedure is an attractive extension to the existing methods for the preparation of α,α-difluoro-β-hydroxy esters. This is especially true for the preparation of γ-*N*-carbamoyl-α,α-difluoro-β-hydroxy esters. One potential disadvantage may be that this method is virtually nonstereoselective.[9]

Experimental Section

General Information. Tetrahydrofuran (THF) was purchased from the Aldrich Chemical Co., Inc. in Sure/Seal bottles. All reactions were run under anhydrous conditions (N_2 or Ar). Starting aldehydes and ketones 1–4 were purchased from the Aldrich Chemical Co., Inc. and used without purification. Aldehydes 5–7 were prepared as described in ref 5. Products

(6) In these cases, $HCF_2(HO)C(CF_2CO_2Et)_2$ was detected (^{19}F NMR, MS) and no aldehyde was recovered. Presumably this above side product is formed by generation of the Refomatsky reagent and bis-addition to $BrCF_2CO_2Et$ followed by anion formation and protonation. Comments on the thermal stability of the organozinc species generated from $BrCF_2CO_2Et$ can be found in ref 3b.

(7) Under thermal or sonication Reformatsky reaction conditions the *syn* product predominates due to chelation and approach of the nucleophile from the least hindered face.[2f] Using Et_2AlCl–AgOAc reaction conditions the nucleophile is presumably the Al enolate.[4] The formation of the nucleophilic agent was monitored by ^{19}F NMR by cooling Zn and AgOAc in THF-d_8 to 0 °C and treating with $BrCF_2CO_2Et$. After 30 min the ^{19}F NMR (282 MHz) showed $BrCF_2CO_2Et$ (s, δ –60.3) and presumably the Reformatsky reagent (s, δ –119.3). Et_2AlCl was added (0 °C) and after 2 h ^{19}F NMR showed another peak (s, δ –167.3). The structure of this compound is unknown, but if the Al enolate is formed one would expect the fluorines to be nonequivalent, and only a singlet was observed. Although this does not rule out that the Al enolate is the nucleophilic species, the author is reluctant to propose a model for the lack or change in diastereoselectivity.

(8) *Syn* and *anti* are used as described by Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 557.

(9) It was brought to our attention by an editor that using Me_2AlCl vs Et_2AlCl could increase the selectivity of this reaction. See: Dener, J. M.; Zhang, L.-H.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 1159.

were purified by flash column chromatography on SiO_2 230–400 mesh. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Mattson Galaxy Series 5000 FTIR. NMR spectra were recorded on a Varian XL-300 or Gemini 300 at 300 MHz (^1H) and chemical shifts are reported in ppm relative to TMS standard, or at 282 MHz (^{19}F) relative to $CFCl_3$. Mass spectra were obtained on a Finnigan MAT4600 spectrometer.

General Procedure. A solution of ketone or aldehyde (1 mmol), Zn (20 mesh, 2.1 mmol, activated[10]), and AgOAc (0.3 mmol) in THF (3.8 mL) was cooled to 0 °C and treated sequentially with $BrCF_2CO_2Et$ (2 mmol) and then dropwise with Et_2AlCl (1.8 M in PhMe, 1.1–2.0 mmol). The reaction mixture was stirred for 2 h at 0 °C and then allowed to warm to rt and stirred for 4–15 h. The reaction mixture was treated sequentially with EtOH (1 mL) and aqueous NH_4Cl (saturated, 5 mL). After effervescence ceased, the reaction mixture was treated sequentially with aqueous sodium potassium tartrate (1 M, 5 mL) and EtOAc (10 mL) and then filtered. Phases were separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The organic phases were combined and dried ($MgSO_4$), the drying agent was filtered, and filtrate was concentrated *in vacuo*. The crude material was chromatographed using 10 or 20% EtOAc/hexane on SiO_2 to provide the Reformatsky products.

Ethyl 2,2-Difluoro-3-hydroxy-3-phenylpropionate (8). Aldehyde 1 (0.1 mL, 0.98 mmol) afforded 161 mg of 8 (69%) as a yellow oil. For 8: R_f = 0.14, 10% EtOAc/hexane; ^1H NMR ($CDCl_3$) 7.40 (m, 5H), 5.15 (ddd, 1H, J = 5.2, 8, 15.5 Hz), 4.29 (q, 2H, J = 7.1 Hz), 2.78 (d, 1H, J = 5.2 Hz), 1.28 (t, 3H, J = 7.1 Hz); ^{19}F NMR ($CDCl_3$) −114.5 (dd, J = 8, 262 Hz), −120.8 (dd, J = 15.5, 262 Hz); IR (neat) ν_{max} 3493, 2987, 1759, 1496, 1456, 1375, 1319, 1194, 1097, 1072, 1028 cm^{-1}; CIMS (CH_4) m/e (rel inten) 230 (M^+, 20), 213 (M + H^+ − H_2O, 58), 185 (M + H^+ − EtOH, base); FABHRMS m/e (MNBA) 231.0823 ($C_{11}H_{13}F_2O_3$ requires 231.0833).

Ethyl 2,2-Difluoro-3-hydroxy-5-phenylpentanoate (9). Aldehyde 2 (0.13 mL, 0.98 mmol) afforded 170 mg of 9 (64%) as a yellow oil. For 9: R_f = 0.15, 10% EtOAc/hexane; ^1H NMR ($CDCl_3$) 7.28 (m, 5H), 4.34 (q, 2H, J = 7.1 Hz), 4.03 (m, 1H), 2.92 (ddd, 1H, J = 5.2, 8.8, 14 Hz), 2.75 (d app t, 1H, J = 8.2, 14 Hz), 2.09 (m, 1H), 1.91 (m, 2H), 1.34 (t, 3H, J = 7.1 Hz); ^{19}F NMR ($CDCl_3$) −115.2 (dd, J = 7.8, 266 Hz), −122.3 (dd, J = 14.6, 266 Hz); IR (neat) ν_{max} 3487, 3028, 2986, 2962, 2939, 1759, 1496, 1456, 1398, 1375, 1315, 1219, 1172, 1093, 1072 cm^{-1}; CIMS (CH_4) m/e (rel inten) 259 (M + H^+, 22), 241 (M + H^+ − H_2O, 50), 119 (base). Anal. Calcd for $C_{13}H_{16}F_2O_3$: C, 60.46; H, 6.24. Found: C, 60.69; H, 6.25.

Ethyl 2,2-Difluoro-3-hydroxy-3-methyl-3-phenylpropionate (10). Ketone 3 (0.12 mL, 1.0 mmol) afforded 157 mg of 10 (62%) as a reddish oil. For 10: R_f = 0.17, 10% EtOAc/hexane; ^1H NMR ($CDCl_3$) 7.53 (m, 2H), 7.37 (m, 3H), 4.16 (q, 2H, J = 7.1 Hz), 3.09 (s, 1H), 1.75 (s, 3H), 1.12 (t, 3H, J = 7.1 Hz); ^{19}F NMR ($CDCl_3$) −115.9 (s), −116.0 (s); IR (neat) ν_{max} 3512, 2989, 2877, 1450, 1375, 1311, 1176, 1132, 1066, 1037 cm^{-1}; EIMS (CH_4) m/e (rel inten) 244 (M^+, 22), 121 (base). Anal. Calcd for $C_{12}H_{14}F_2O_3$: C, 59.01; H, 5.78. Found; C, 58.88; H, 5.96.

Ethyl 2,2-Difluoro-3-hydroxy-3-methyl-5-phenylpentanoate (11). Ketone 4 (0.15 mL, 0.99 mmol) provided 138 mg of 11 (51%) as a yellow oil. For 11: R_f = 0.31, 20% EtOAc/hexane; ^1H NMR ($CDCl_3$) 7.28 (m, 2H), 7.21 (m, 3H), 4.36 (q, 2H, J = 7.1 Hz), 2.76 (m, 2H), 1.95 (m, 2H), 1.41 (s, 3H), 1.36 (t, 3H, J = 7.1 Hz); ^{19}F NMR ($CDCl_3$) −117.4 (d, J = 259 Hz), −118.2 (d, J = 259 Hz); IR (neat) ν_{max} 3504, 3028, 2987, 2943, 1759, 1496, 1456, 1373, 1311, 1199, 1174, 1120, 1068 cm^{-1}; CIMS (CH_4) m/e (rel inten) 273 (M + H^+, 58), 255 (M + H^+ − H_2O, base). Anal. Calcd for $C_{14}H_{18}F_2O_3$: C, 61.76; H, 6.66. Found: C, 61.82; H, 6.97.

(3*R*,4*S*)- and (3*S*,4*S*)-Ethyl 4-[(*tert*-butyloxycarbonyl)amino]-2,2-difluoro-3-hydroxy-5-[4-(benzyloxy)phenyl]pentanoate (12).[11] (*S*)-*N*-Boc-α-Amino aldehyde 5 (200 mg, 0.56 mmol) provided 173 mg of 12 (64%, a 2:3 *syn/anti* mixture) as a yellowish solid. For 12: R_f = 0.18 and 0.14, 20% EtOAc/hexane; ^1H NMR ($CDCl_3$) 7.40 (m, 5H), 7.23 (m, 2H), 6.95 (m, 2H), 4.89 and 4.69 (d, 1H, J = 7.5 and 7.0 Hz), 4.31 (m, 3H), 3.95 (m, 1H), 2.93 (m, 2H), 1.46 (m, 3H), 1.33 (s, 9H); ^{19}F NMR ($CDCl_3$) −112.8 (dd, J = 6.0, 262.5 Hz), −113.8 (dd, J = 5.3, 267 Hz), −120.5 (dd, J = 15.1, 267 Hz), −122.1 (dd, J = 17.4, 262.5 Hz); IR ($CHCl_3$) ν_{max} 3605, 3445, 3032, 3011, 2982, 1764, 1707,1510, 1454, 1392, 1369, 1298, 1244, 1105 cm^{-1}; CIMS (CH_4) m/e (rel inten) 480 (M + H^+, 10), 479 (M^+, 10), 424 (M + H^+ − C_4H_8, 90), 380 (M + H^+ − Boc, 100). Anal. Calcd for $C_{25}H_{31}F_2NO_6$: C, 62.62; H, 6.52; N, 2.92. Found: C, 62.77; H, 6.45; N, 2.92.

Portions of 12a and 12b were separated using flash chromatography on SiO_2 as described above.

(3*R,4*R**)- and (3*S**,4*R**)-Ethyl 4-[(benzyloxycarbonyl)amino]-2,2-difluoro-3-hydroxy-5-methylhexanoate (13).** (*R**)-*N*-Cbz-α-Amino aldehyde 6 (375 mg, 1.51 mmol) provided 298 mg (55%, a 1:1 *syn/anti* mixture) of 13 as a yellow oil. For 13: R_f = 0.2, 20% EtOAc/hexane; ^1H NMR ($CDCl_3$) 7.35 (m, 5H), 5.21 and 4.75 (d, 1H, J = 9.9 Hz), 5.10 (s, 2H), 4.28 (m, 2H), 3.91 (m, 1H), 3.65 (m, 1H), 3.28 (d, 1H, J = 7.6 Hz), 2.11 (m, 1H), 1.31 (t, 3H, J = 7.1 Hz), 0.96 (m, 6H); ^{19}F NMR ($CDCl_3$) −113.9 (dd, J = 7.8, 267 Hz), −114.4 (dd, J = 9, 265 Hz), −119 (dd, J = 15.3, 265 Hz), −120.6 (dd, J = 14.7, 267 Hz); IR (neat) ν_{max} 3389, 2967, 1759, 1701, 1520, 1310, 1222, 1078 cm^{-1}; CIMS (CH_4) m/e (rel inten) 360 (M + H^+, 65), 316 (M + H^+ − CO_2, base); FABHRMS (glycerol) m/e 360.1644 ($C_{17}H_{23}F_2NO_5$ requires 360.1623).

(3*R,4*R**)- and (3*S**,4*R**)-Ethyl 4-[(*tert*-butyloxycarbonyl)amino]-2,2-difluoro-3-hydroxy-5-methylhexanoate (14).** (*R**)-*N*-Boc-α-Amino aldehyde 7 (345 mg, 1.7 mmol) provided 297 mg (54%, a 1:1.4 *syn/anti* mixture) of 14 as a yellow oil. For 14: R_f = 0.28, 20% EtOAc/hexane; ^1H NMR ($CDCl_3$) 4.98 and 4.50 (d, 1H, J = 9.8 Hz), 4.35 (m, 2H), 4.22 and 4.08 (m, 1H), 3.81 and 3.50 (m, 1H), 3.61 (d, 1H, J = 8.2 Hz), 2.12 (m, 1H), 1.44 (s, 9H), 1.37 (t, 3H, J = 7.1 Hz), 0.98 (m, 6H); ^{19}F NMR ($CDCl_3$) −113.9 (dd, J = 6.8, 266 Hz), −114.2 (dd, J = 8.1, 265 Hz), −119.4 (dd, J = 15.8, 265 Hz), −121.4 (dd, J = 15.3, 266 Hz); IR (neat) ν_{max} 3439, 3393, 2970, 1774, 1761, 1695, 1392, 1369, 1309, 1170, 1078 cm^{-1}; CIMS (CH_4) m/e (rel inten) 326 (M + H^+, 10), 270 (M + H^+ − C_4H_8, base). Anal. Calcd for $C_{14}H_{25}F_2NO_5$: C, 51.68; H, 7.74; N, 4.31. Found: C, 51.58; H, 7.79; N, 4.24.

(4*R*,5*S*)-5-[4-(Benzyloxy)benzyl]-3,3-difluoro-4-hydroxypyrrolidin-2-one (19a). A solution of TFA/H_2O (2.4 mL/0.24 mL) was added to Reformatsky product 12a (235 mg, 0.5 mmol) and the resulting mixture stirred at rt for 2.5 h. Solvent was evaporated in vacuo and the reddish oil dissolved in EtOAc (25 mL). The organic phase was washed sequentially with $NaHCO_3$ (saturated, 2 × 25 mL), H_2O (25 mL), and brine (25 mL). The organic phase was dried ($MgSO_4$) and filtered and the filtrate concentrated *in vacuo*. The resulting red oil was dissolved in MeOH (5 mL) and stirred for 18 h at rt. Solvent was evaporated *in vacuo* and the oil purified by flash column chromatography (10 g of SiO_2, 13 × 1.5 cm, 50% EtOAc/hexane, 100 mL) to provide an orange solid. Recrystallization from CH_2Cl_2/hexane gave a pale orange solid 19a, 60 mg (37%, two steps): mp 176–180 °C; ^1H NMR (DMSO-d_6) 8.58 (s (broad), 1H), 7.43 (m, 5H), 7.15 (d, 2H, J = 8.7 Hz), 6.95 (d, 2H, J = 8.7 Hz), 6.31 (d, 2H, J = 5.7 Hz), 5.07 (s, 2H), 4.21 (m, 1H), 3.83 (m, 1H), 2.94 (dd, 1H, J = 6.5, 13.8 Hz), 2.48 (ddd, 1H, J = 1.2, 7.8, 13.8 Hz); ^{19}F NMR (DMSO-d_6) −118.0 (dd, J = 11.8, 266 Hz), −122.3 (d, J = 8.3, 266 Hz); IR (KBr) ν_{max} 3296, 3034, 2928, 1722, 1612, 1452, 1381, 1300, 1248, 1224 cm^{-1}; CIMS (CH_4) m/e (rel inten) 334 (M + H^+, 100). Anal. Calcd for $C_{18}H_{17}F_2NO_3$: C, 64.86; H, 5.14; N, 4.20. Found: C, 64.64; H, 5.12; N, 4.13. NOESY and 1D-NOE experiments show a strong through-space interaction between C4-H (δ 4.21) and C5-H (δ 3.83) which support the *cis* positioning of the two substituents on the pyrrolidinone ring.

(4*S*,5*S*)-5-[4-(Benzyloxy)benzyl]-3,3-difluoro-4-hydroxypyrrolidin-2-one (19b). Prepared in a similar fashion to 19a. Isolated 19b as a white solid: mp 148–151 °C; ^1H NMR (DMSO-d_6) 8.97 (s (broad), 1H), 7.38 (m, 5H), 7.17 (d, 2H, J = 8.6 Hz), 6.95 (d, 2H, J = 8.6), 6.22 (d, 1H, J = 6.2 Hz), 5.06 (s, 2H), 3.79

(10) Zinc (20 mesh) was swirled in 20% HCl (1 mL/g) for approximately 15–30 s, filtered, and washed sequentially with H_2O, acetone, and Et_2O.

(11) We believe that epimerization of the α-amino aldehyde is minor under the Et_2AlCl–AgOAc conditions. Coupling of *N*-protected homochiral amino acids to the amino terminus of amides derived from 12a or 12b provides only a single isomer by crude ^{19}F NMR. Similarly, coupling of homochiral amines to the the carboxy terminus of 12a,b provides only a pair of diastereomers by crude ^{19}F NMR and HPLC.

(m, 1H), 3.54 (m, 1H), 2.80 (m, 2H); ^{19}F NMR (DMSO-d_6) −117.3 (dd, J = 11, 274 Hz), −126.9 (dd, J = 8, 274 Hz); CIMS (CH_4) m/e (rel inten) 334 (M + H^+, 100). NOESY and 1D-NOE difference spectra show no through space interaction between the C5-H and C4-H due to the *trans* disposition of the two substituents on the pyrrolidinone ring.

Acknowledgment. The author would like to thank D. Janowick, Drs. R. Farr, R. Cregge (SWAT), D. Schirlin, V. Van Dorsselaer (Strasbourg), F. M. Laskovics, J. Martin, and M. Kolb (Chem. Dev.) for their comments, helpful suggestions, and encouragement. The author extends his gratitude to Dr. E. Huber and W. Magner for obtaining NOE spectra.

Supplementary Material Available: ^{1}H and ^{19}F NMR spectra for compounds **8–14**, **19a**,and **19b**, and NOESY spectra for **19a** and **19b** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.