Concise Syntheses of γ-Oxo-β,β-difluorinated Amino Acids via Chelated [3,3]-Rearrangement of Difluoroallylic Alcohols

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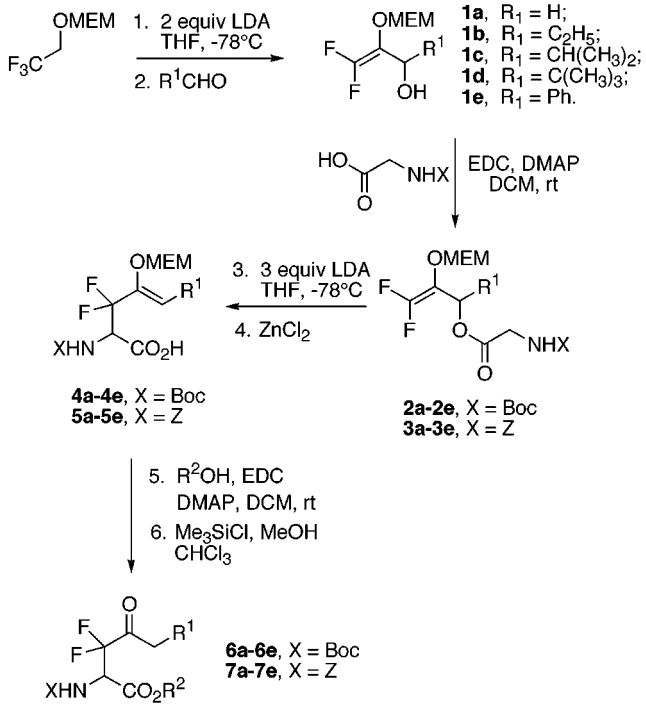
Nonproteinogenic amino acids continue to attract the attention of synthetic chemists, not the least from those within the organofluorine community.[1] Inspired by the work of Kazmaier[2] (and subsequent approaches to the morphine skeleton by the Hudlicky group)[3] and consistent with our interest in sigmatropic rearrangements[4] of trifluoroethanol-derived fluorinated building blocks,[5] we decided to investigate the possibility of generating γ-oxo-β,β-difluorinated amino acids by a chelated [3,3]-rearrangement of protected glycinate esters of readily available difluoroallylic alcohols. Release of the masked carbonyl group would afford amino acid products in which the side chain contained a ketonic carbonyl group flanked by a CF_2 center (Scheme 1). The unusual hydration properties of this array are well known;[6] indeed, they have found a number of applications in the area of protease inhibition. Though the array is usually located as a backbone modification in short peptides,[7] C-terminal modifications are also well tried.[8] The title compounds containing modified side chains are novel and may have interesting properties; herein we wish to report a short route to the title compounds from trifluoroethanol (Scheme 1).

Difluoroallylic alcohols **1a**−**f** were synthesized according to our published procedure.[9] Glycinate esters **2a**−**e** and **3a**−**e** were prepared from the alcohols **1a**−**e** and commercial Boc- or Z-glycine in excellent yield according to standard procedures (EDC, DMAP, DCM, 0 °C, 18 h).

Scheme 1



Exposure of the glycinate esters to modified Kazmaier conditions (3.0 equiv of LDA, THF, −78 °C and then $ZnCl_2$, THF) followed by acidic workup afforded acids **4a**−**e** and **5a**−**e** (Table 1). Analysis by both ^{19}F and ^{1}H NMR spectroscopy revealed that the rearranged acid was the only product of the reaction in each case, with yields of up to 99%. Whereas Kazmaier used the less reactive lithium hexamethyldisilazide to form the chelated enolates, we found that LDA was quite suitable for forming the chelated lithium enolates.

Attempted release of the masked ketone at the acid stage resulted in complete decomposition of the crude

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(2) For recent examples, see: (a) Kazmaier, U. *J. Org. Chem.* **1996**, *61*, 3694. (b) Kazmaier, U. *Synlett* **1995**, 1138.

(3) Gonzalez, D.; Schapiro, V.; Seoane, G.; Hudlicky, T.; Abboud, K. *J. Org. Chem.* **1997**, *62*, 1194. For a more general description of chelation-controlled [3,3]-rearrangements, see: Frauenrath, H. In *Stereoselective Synthesis*; Helmchen, G.; Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1996; E21, *D.1.6*, 3420. For a recent review of chelated [3,3]-rearrangements, see: Kazmaier, U. *Liebigs. Ann./Recl.* **1997**, 285.

(4) For chelated [3,3]-rearrangements of difluoroallylic alkoxyacetates, see: Broadhurst, M. J.; Percy, J. M.; Prime, M. E. *Tetrahedron Lett.* **1997**, *38*, 5903. [2,3]-Wittig rearrangements have also been described Patel, S. T.; Percy, J. M.; Wilkes, R. D. *J. Org. Chem.* **1996**, *61*, 166.

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(6) Neder, K. M.; French, S. A.; Miller, S. P. F. *Tetrahedron* **1994**, *50*, 9847.

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(8) (a) 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. (b) Angelastro, M. R.; Burkhart, J. P.; Bey, P.; Peet, N. P. *Tetrahedron Lett.* **1992**, *33*, 3265. (c) Angelastro, M. R.; Baugh, L. E.; Bey, P.; Burkhart, J. P.; Chen, T. M.; Durham, S. L.; Hare, C. M.; Huber, E. W.; Janusz, M. J.; Koehl, J. R.; Marquart, A. L.; Mehdi, S.; Peet, N. P. *J. Med. Chem.* **1994**, *37*, 4538. (d) Janusz, M. J.; Durham, S. L.; Hare, C. M.; Geary, J. L.; Mandagere, A. K.; Poole, J. C.; Thompson, T. N.; Xu, D.; Angelastro, M. R.; Burkhart, J. P.; Chen, T. M.; Marquart, A. L.; Peet, N. P.; Hwang, K. K. *J. Pharmacol. Exp. Ther.* **1995**, *275*, 1233. (e) Hornsperger, J. M.; Collard, J. N.; Heydt, J. G.; Giacobini, E.; Funes, S.; Dow, J.; Schirlin, D. *Biochem. Soc. Trans.* **1994**, *22*, 758.

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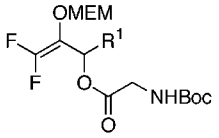
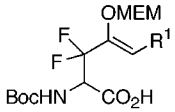
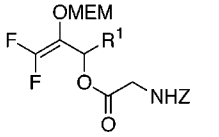
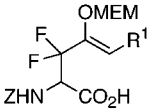
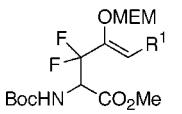
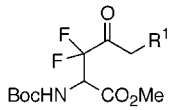
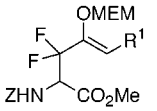
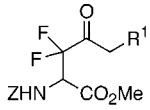
Table 1. Preparation and [3,3]-Rearrangements of Difluoroallylic Glycinates

Entry	Substrate			Yield/%[a]	Product			Yield/%[b]
1		**2a**	R_1 = H	85		**4a**	R_1 = H	80[c]
2		**2b**	R_1 = C_2H_5	95		**4b**	R_1 = C_2H_5	86
3		**2c**	R_1 = $CH(CH_3)_2$	89		**4c**	R_1 = $CH(CH_3)_2$	95
4		**2d**	R_1 = $C(CH_3)_3$	88		**4d**	R_1 = $C(CH_3)_3$	99
5		**2e**	R_1 = Ph	86		**4e**	R_1 = Ph	92
6		**3a**	R_1 = H	80		**5a**	R_1 = H	75[c]
7		**3b**	R_1 = C_2H_5	79		**5b**	R_1 = C_2H_5	82[c]
8		**3d**	R_1 = $C(CH_3)_3$	86		**5d**	R_1 = $C(CH_3)_3$	95[c]
9		**3e**	R_1 = Ph	75		**5e**	R_1 = Ph	89[c]

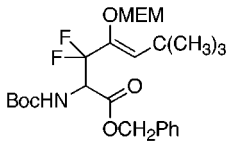
[a]Isolated yields after purification. [b]Crude yields (>95% purity by $^{19}F/^1H$ NMR). [c]The acids were taken on directly to the corresponding esters without characterisation or purification.

Table 2. Esterification and Deprotection of [3,3]-Rearrangement Products

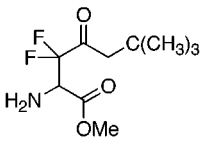
Entry	Substrate	Ester			Yield/%[a]	Ketoester			Yield/%[b]
1	**4a**		**6a**	R_1 = H	80		**8c**	R_1 = $CH(CH_3)_2$	65
2	**4b**		**6b**	R_1 = C_2H_5	85				
3	**4c**		**6c**	R_1 = $CH(CH_3)_2$	79[c]				
4	**4d**		**6d**	R_1 = $C(CH_3)_3$	88				
5	**4e**		**6e**	R_1 = Ph	83				
6	**5a**		**7a**	R_1 = H	72		**9b**	R_1 = C_2H_5	66
7	**5b**		**7b**	R_1 = C_2H_5	74[c]		**9d**	R_1 = $C(CH_3)_3$	60
8	**5d**		**7d**	R_1 = $C(CH_3)_3$	79[c]		**9e**	R_1 = Ph	72
9	**5e**		**7e**	R_1 = Ph	70[c]				

[a]Unoptimised isolated crude yields (>95% purity by $^{19}F/^1H$ NMR). [b]Unoptimised isolated yields after purification. [c]Taken on directly to the corresponding ketoester without characterisation or purification.

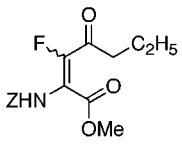
products.[10] Attempts to prepare methyl esters on a small scale using diazomethane in diethyl ether led to complete decomposition of the crude acids. Instead, the crude acids were converted to the methyl esters (EDC, excess MeOH, DMAP, DCM, 0 °C, 18 h) **6a**−**e** and **7a**−**e** without purification. Other alcohols could be used; for example, **4d** coupled with benzyl alcohol in a satisfactory (58%) yield to afford **10d**. Coupling procedures using DCC (1.1



10d



11d



12b

equiv DMAP, DCM) gave unsatisfactory results (typically ≪50% yield). Upon exposure of methyl esters **6c** and **7b**−**e** to thionyl chloride in a mixture of chloroform and methanol (9:1), methanolysis of the enol acetal group occurred and the latent ketone functionality was revealed, affording **8c** and **9b**−**e** in good yields (Table 2).

Given the acid lability of the Boc protecting group, we were not too surprised to isolate **11d** as a side product in one instance; however, the Z-protected amino acids were stable under the methanolysis conditions. In one case, we also detected the presence of an unstable dehydrofluorination product which displayed spectra consistent with structure **12b**.

In conclusion, a facile route to γ-oxo-β,β-difluorinated amino acids has been established using chelated rearrangement technology and smooth deprotection chemistry. Given the potential for asymmetric [3,3]-rearrangement in the presence of optically pure N,O-ligands,[11] we believe this may be a promising route to enantiomerically enriched or pure, novel, difluorinated materials.[12]

Experimental Section

General Methods. All difluoroallylic alcohols were prepared according to our published procedure.[9] Boc- and Z-glycine are available commercially and were used without further purification. All rearrangements were performed in THF dried over and freshly distilled from sodium and benzophenone and collected by syringe as required. All esterifications were performed in DCM which had been distilled from calcium hydride. NMR

(10) We described previously (ref 4a) a mild enol acetal hydrolysis, that occurred during an attempted esterification following a recent protocol: Hosangadi, B. D.; Dave, R. H. *Tetrahedron Lett.* **1996**, *37*, 6375. Lewis acid-mediated cleavage of MEM acetals is a considerably more widely used procedure; see: (a) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912. (b) Herbert, J. M.; Knight, J. G.; Sexton, B. *Tetrahedron* **1996**, *52*, 15257. The only example, to our knowledge, of a MEM enol acetal cleavage was reported by Magnus and co-workers; see: Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544.

(11) Kazmaier, U.; Krebs, A. *Tetrahedron Lett.* **1996**, *37*, 7945.

(12) For a recent asymmetric synthesis of β-difluorinated amino acids from L-isoascorbic acid, see: Li, K.; Leriche, C.; Liu, H.-W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1097.

spectra were obtained at 75 (^{13}C), 282 (^{19}F), or 300 (^{1}H) MHz in $CDCl_3$ using residual $CHCl_3$ as internal reference.

General Procedure for the Preparation of Boc- or Z-Glycinates. EDC (11 mmol), was added in one portion to a cooled solution of difluoroallylic alcohol **1** (10 mmol), Boc- or Z-glycine (11 mmol) and DMAP (4 mmol) in DCM (50 mL) at 0 °C. After 5 min of stirring at 0 °C, the reaction mixture was concentrated in vacuo and the residue was taken up in ethyl acetate and washed consecutively with HCl (1 M, 15 mL), water (15 mL), saturated sodium bicarbonate (15 mL), and brine (15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the glycinates **2** or **3** as oils. Purification was achieved by flash column chromatography.

3-[(*N*-*tert*-Butyloxycarbonyl)glycinoyl]-1,1-difluoro-2-[(methoxyethoxy)methoxy]-4-methylpent-1-ene: $R_f = 0.57$ (50:50 diethyl ether/hexanes); ^{1}H NMR δ 0.88 (d, J = 6.62 Hz, 3H), 0.92 (d, J = 6.62 Hz, 3H), 1.40 (s, 9H), 2.06−2.20 (m, 1H), 3.35 (s, 3H), 3.50−3.58 (m, 2H), 3.76−3.80 (m, 2H), 3.87−3.92 (m, 2H), 4.85 (d, J = 6.25 Hz, 1H), 4.98 (d, J = 6.25 Hz, 1H), 5.03−5.11 (m, 1H), 5.20−5.30 (m, 1H); ^{19}F NMR δ −97.4 (d, J = 55.9 Hz, 1F), −105.7 (d, J = 55.9 Hz, 1F); ^{13}C NMR δ 18.2, 18.8, 28.3, 29.0, 42.5, 58.9, 68.4, 71.6, 75.9, 79.8, 97.1, 112.4 (dd, J = 14.7 Hz), 113.0 (d, J = 14.7 Hz) 155.8 (t, J = 296.1 Hz), 169.6; HRMS calcd for $C_{17}H_{29}NO_7F_2Na$ 420.180979, found 420.181458.

3-[(*N*-Benzyloxycarbonyl)glycinoyl]-1,1-difluoro-4,4-dimethyl-2-([methoxyethoxy)methoxy]pent-1-ene: $R_f = 0.45$ (50:50 diethyl ether/hexanes); ^{1}H NMR δ 1.00 (s, 9H), 3.35 (s, 3H), 3.51−3.58 (m, 2H), 3.67−3.90 (m, 2H), 4.00 (d, J = 5.52 Hz, 2H), 4.81 (d, J = 6.25 Hz, 1H), 4.96 (d, J = 6.25 Hz, 1H), 5.00−5.22 (m, 3H), 5.66 (t, J = 5.52 Hz, 1H), 7.35 (s, 5H); ^{19}F NMR δ −97.8 (d, J = 55.9 Hz, 1F), −100.5 (d, J = 55.9 Hz, 1F); ^{13}C NMR δ 26.1, 35.1, 42.8, 58.8, 66.9, 68.6, 71.6, 76.6, 97.8, 112.9 (d, J = 14.6 Hz), 113.0 (d, J = 14.6 Hz), 128.0, 128.4, 136.2, 156.4 (t, J = 288.8 Hz, 1C); HRMS calcd for $C_{21}H_{30}NO_7F_2$ 446.199034, found 446.199397.

General Procedure for the Chelated Rearrangements. Boc- or Z-glycinate **2** or **3** (1 mmol) was added to a cold (−78 °C) stirred solution of freshly prepared LDA generated by the slow addition of butyllithium (3 mmol of a 1.7 M solution in hexanes) to diisopropylamine (3.3 mmol) in THF (20 mL) at −78 °C. Approximately 5 min after the addition of the glycinate was complete, zinc(II) chloride (1.2 mmol) in THF (2 mL) was added in one portion and the reaction mixture was allowed to warm to room temperature with stirring over 1 h. Dilute HCl (1 M, 10 mL) was added to the orange colored solution and the mixture was extracted with diethyl ether (3 × 20 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude amino acid as an orange oil. The rearrangement products were used without further purification.

General Procedure for the Esterification of the Rearrangement Products. EDC (5.5 mmol) was added in one portion to a cooled solution of N-protected amino acid **4** or **5** (5 mmol), methanol (50 mmol) and DMAP (2 mmol) in DCM at 0 °C. After 5 min of stirring at 0 °C, the reaction mixture was warmed to room temperature and stirred overnight. The resulting reaction mixture was concentrated in vacuo, and the residue was taken up in ethyl acetate and washed consecutively with HCl (1 M, 15 mL), water (15 mL), saturated sodium bicarbonate (15 mL), and brine (15 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to yield the methyl ester **6** or **7** as an oil.

Methyl-2-[*N*-*tert*-butyloxycarbonyl]amino-3,3-difluoro-4-([methoxyethoxy]methoxy)-(*Z*)-non-4-enoate (6d): R_f = 0.40 (40:60 diethyl ether/hexanes); ^{1}H NMR δ 1.15 (s, 9H), 1.43 (s, 9H), 3.38 (s, 3H), 3.55−3.62 (m, 2H), 3.76 (s, 3H), 3.82−3.93 (m, 2H), 4.92−5.13 (m, 3H), 5.38 (d, J = 10.3 Hz, 1H), 5.44 (s, 1H); ^{19}F NMR δ −106.6 (dd, J = 247.9 Hz, J = 14.0 Hz, 1F), −107.5 (dd, J = 247.9 Hz, J = 11.4 Hz, 1F); ^{13}C NMR δ 28.2, 30.2, 31.9, 52.6, 56.4 (t, J = 28.4 Hz), 58.9, 68.9, 71.5, 80.3, 117.1 (t, J = 252.9 Hz), 130.3, 142.4 (t, J = 24.3 Hz), 154.6, 167.8. Anal. Calcd for $C_{19}H_{33}O_7NF_2$: C, 53.64; H, 7.82; N, 3.29. Found: C, 53.83; H, 7.82; N, 3.11.

Methyl-2-[*N*-benzyloxycarbonyl]amino-3,3-difluoro-4-([methoxyethoxy]methoxy)pent-4-enoate (7a): R_f = 0.50 (40:60 diethyl ether/hexanes); ^{1}H NMR δ 3.38 (s, 3H), 3.49−3.55 (m, 2H), 3.62−3.80 (m, 5H), 4.78 (s, 2H), 4.96−5.21 (m, 5H), 5.60 (d, J = 9.56 Hz, 1H), 7.31−7.40 (m, 5H); ^{19}F NMR δ −110.1 (dd, J = 252.7 Hz, J = 11.00 Hz, 1F), −110.8 (dd, J = 252.7 Hz, J = 13.2 Hz, 1F); ^{13}C NMR δ 53.0, 56.4 (t, J = 168.5 Hz), 59.0, 67.5, 68.1, 71.4, 90.5, 93.8, 115.5 (t, J = 251.0 Hz), 128.2, 128.4, 128.6, 128.8, 135.9, 151.0 (t, J = 29.4 Hz), 155.3, 167.2; HRMS calcd for $C_{18}H_{24}NO_7F_2$ 404.152084, found 404.152005.

General Procedure for the Enol Acetal Hydrolysis of the Methyl Esters. Thionyl chloride (2.2 mmol) was added dropwise to a cooled solution of the methyl ester **6** or **7** (2 mmol) in a 9:1 chloroform/methanol mixture (15 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight, after which time the reaction was stopped by the addition of water (10 mL) the mixture was extracted with DCM (3 × 20 mL), and the organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to yield the ketoester **8** or **9** as an oil. Purification of these ketoesters was achieved by flash column chromatography.

Methyl-2-[*N*-*tert*-butyloxycarbonyl]amino-3,3-difluoro-4-oxooct-4-enoate (8c): R_f = 0.76 (50:50 diethyl ether/hexanes); ^{1}H NMR δ 0.92 (d, J = 6.62 Hz, 6H), 1.41 (s, 9H), 2.08−2.23 (m, 1H), 2.55 (d, J = 6.61 Hz, 2H), 3.70 (s, 3H), 5.01−5.18 (m, 1H), 5.35 (d, J = 9.93 Hz, 1H); ^{19}F NMR δ −111.0 (dd, J = 273.4 Hz, J = 10.2 Hz, 1F), −115.8 (dd, J = 273.4 Hz, J = 14.0 Hz, 1F); ^{13}C NMR δ 22.1, 23.2, 27.9, 45.2, 52.9, 55.1 (t, J = 24.87 Hz), 80.9, 113.7 (t, J = 260.5 Hz), 154.7, 166.8, 198.6 (t, J = 29.4 Hz). Anal. Calcd for $C_{14}H_{23}NO_5F_2$: C, 52.01; H, 7.17; N, 4.33. Found: C, 52.06; H, 7.26; N, 4.25.

Methyl-2-[*N*-benzyloxycarbonyl]amino-3,3-difluoro-4-oxo-5-phenylpent-4-enoate (9e): R_f = 0.51 (30:70 diethyl ether/hexanes); ^{1}H NMR δ 3.70 (s, 3H), 4.10 (s, 2H), 5.15−5.27 (m, 1H), 5.72 (d, J = 9.56 Hz, 1H), 7.37 (m, 10H); ^{19}F NMR δ −108.5 (dd, J = 274.1 Hz, J = 9.31 Hz, 1F), −115.9 (dd, J = 274.1 Hz, J = 15.8 Hz, 1F); ^{13}C NMR δ 43.5, 53.4, 56.5 (t, J = 26.1 Hz), 67.9, 114.4 (t, J = 261.0 Hz), 127.5, 128.2, 128.4, 128.6, 128.7, 129.1, 129.9, 131.4, 135.7, 155.9, 166.8, 196.8 (t, J = 28.6 Hz); HRMS calcd for $C_{20}H_{20}NO_5F_2$ 392.130955, found 392.130641.

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Supporting Information Available: ^{13}C, ^{1}H, and ^{19}F NMR data and mass spectra (43 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.

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