ELSEVIER

Journal of Fluorine Chemistry 73 (1995) 221–224

JOURNAL OF FLUORINE CHEMISTRY

Highly efficient synthesis of 2(*S*)-3(*R*,*S*)-2-amino-4,4-difluoro-1,6-diphenyl-3-hydroxyhexane — the key intermediate for a series of potent HIV proteinase inhibitors

Hing L. Sham *, David A. Betebenner, Norman E. Wideburg, Dale J. Kempf, Jacob J. Plattner, Daniel W. Norbeck

Abbott Laboratories, Pharmaceutical Discovery Division, Department 47D, Building AP9A, Abbott Park, IL 60064-3500, USA

Received 12 August 1994; accepted 21 November 1994

Abstract

Many α,α-difluoroketones such as 2S-(N-benzyloxycarbonyl-valinyl)amino-3-oxo-4,4-difluoro-1,6-diphenyl-hexane (**1**), with the strongly electronegative fluorines next to the carbonyl group, are usually fully hydrated. As a result of the hydration of the carbonyl group, the difluoroketones can act as transition-state analog inhibitors of certain proteinases. Reformatsky reaction of aldehyde *N*-t-butyloxycarbonyl L-phenylalaninal (**3**), with bromodifluoromethylphenyl acetylene provided the key intermediate for the synthesis of a series of potent HIV proteinase inhibitors exemplified by **1**.

Keywords: Synthesis; Aminodifluorodiphenylhydroxyhexane; HIV proteinase inhibitors; NMR spectroscopy; Mass spectrometry

1. Introduction

During the hydrolytic steps for the production of mature proteins needed for the production of infectious viral particles, the HIV proteinase cleaves specific amide bonds by the generation of a high-energy, tetrahedral intermediate (see Fig. 1) from a low-energy trigonal amide. α,α-Difluoroketones, due to their strongly electronegative fluorines next to the carbonyl group, are usually fully hydrated [1]. As a result of this hydration, the *gem*-diol produced is a very good transition-state mimic of the diol produced in the high-energy tetrahedral intermediate [2]. Following this logic, a series of highly potent HIV proteinase inhibitors exemplified by 2S-(N-benzyloxycarbonyl-valinyl)amino-3-oxo-4,4-difluoro-1,6-diphenyl-hexane (**1**), which contains a difluoroketone as its core unit has been synthesized. The efficient synthesis of the key intermediate **6a,b** via Reformatsky reaction of bromodifluoromethylphenyl acetylene with **3** is described.

2. Results and discussion

As shown in Scheme 1, oxidation of Boc-L-phenylalaninol by the Swern method [3] provided the corresponding aldehyde **3** in 95% yield. The Reformatsky reaction of the aldehyde **3** with bromodifluoromethylphenyl acetylene [4] under sonication [5] at room temperature provided a mixture of α- and β-hydroxy diastereomers **4a** and **4b** in a ratio of

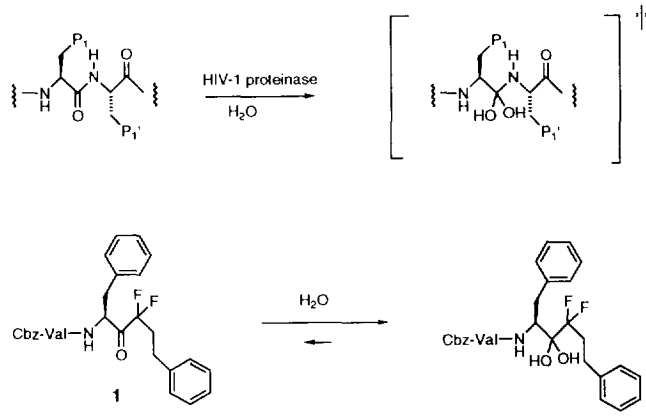
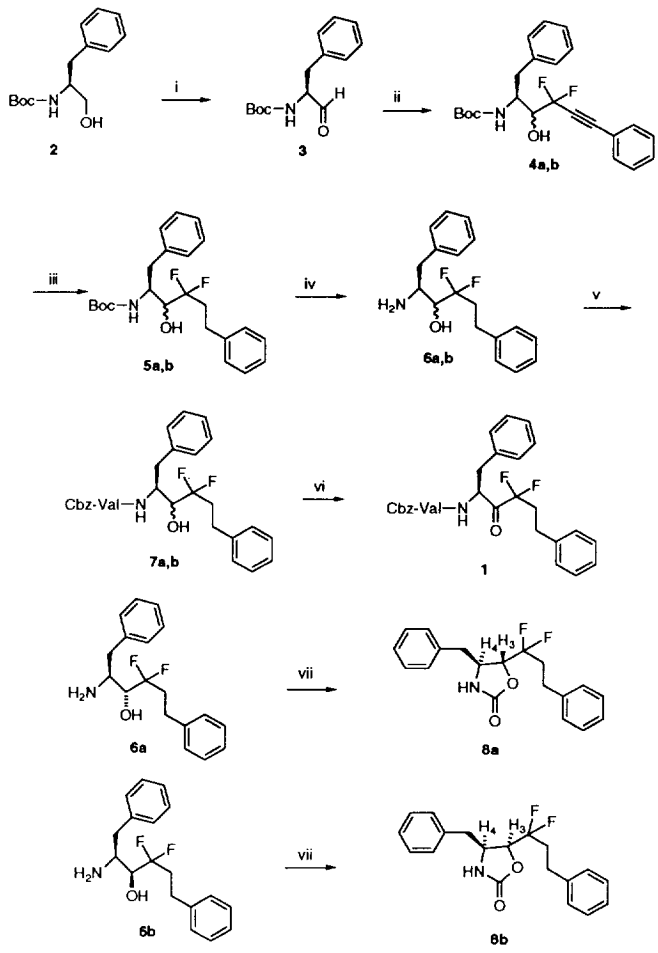


Fig. 1.

* Corresponding author.

SSDI 0022-1139(94)03223-8



Scheme 1. Reagents: (i) $(COCl)_2$–dimethyl sulfoxide; (ii) Zn/bromodifluoromethylphenyl acetylene; (iii) H_2/Pd/C; (iv) 4 N HCl; (v) Cbz-Val-OH/DCC; (vi) $Na_2Cr_2O_7$/AcOH; (vii) phosgene.

3:2. Since the hydroxy group will eventually be oxidized to the carbonyl group in the final product, the fact that the Reformatsky reaction is not diastereospecific is of no consequence. Saturation of the triple bond by hydrogenation of **4a,b** separately, using palladium on carbon as the catalyst, provided the diastereomers **5a,b** in quantitative yield. The diastereomers **4a** and **4b** can be easily separated by preparative HPLC, or they can be used as a mixture in the subsequent steps to the final difluoroketone **1**. The absolute stereochemistry of the hydroxy group in compounds **5a** and **5b** can be established as follows: separate deprotection of the Boc-protecting group in **5a** and **5b** and cyclization with phosgene gave the corresponding oxazolidinones **8a** and **8b**. The 300 MHz ^{1}H NMR spectrum ($CDCl_3$) of **8a** [δ 4.34 ($J_{2,3}$ = 5.4 Hz, H-3) ppm] and **8b** [δ 4.71 ($J_{2,3}$ = 8.7 Hz, H-3) ppm] compared well with the reported data [6] for the oxazolidinones of (3*S*,4*S*)-statine [δ 4.50 ($J_{3,4}$ = 5.0 Hz, H-3) ppm] and (3*R*,4*S*)-statine [δ 5.10 ($J_{3,4}$ = 8.8 Hz, H-3) ppm]. The ^{19}F NMR spectrum (observed at 282 MHz using C_6F_6 as internal standard in $CDCl_3$) of **5a** [δ 51.19 (d, J = 248.5 Hz); 52.64 (d, J = 248.5 Hz)] and **5b** [δ 49.95 (d, J = 249.4 Hz); 54.42 (d, J = 249.4 Hz)] showed each compound as a single diastereomer, with essentially no racemization during the Reformatsky reaction.

Removal of the Boc-protecting group in **5a** by acidolysis with trifluoroacetic acid in methylene chloride provided the amine **6a**, which upon coupling to Cbz-L-valine using 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride, provided compound **7a**. Oxidation of **7a** using chromium trioxide in acetic acid [7] provided the final difluoroketone **1** which is a potent inhibitor of the HIV-1 proteinase with an $IC_{50} = 5 \times 10^{-9}$ M. The final difluoroketone **1** can be synthesized from **5b** using an identical sequence of reactions as described for **5a**.

In summary, we have described a highly efficient synthesis (six steps) of an α,α-difluoroketone which is a potent inhibitor of the HIV-1 proteinase.

3. Experimental details

Melting points were obtained on a Fischer–Johns melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a General Electric QE 300 spectrometer (300 MHz) in $CDCl_3$ with chemical shifts reported in ppm downfield from tetramethylsilane as internal standard. ^{19}F NMR spectra were recorded on a QE 300 spectrometer in $CDCl_3$ with chemical shifts reported in ppm downfield from hexafluorobenzene as internal standard. Reformatsky reactions were performed in a Bransonic model 2200 sonicator. Thin layer chromatography was performed on Merck 60 F254 silica gel plates (0.25 mm thickness). Flash column chromatography was performed with EM Science silica gel (230–400 mesh). Preparative HPLC was done on a Waters Prep-500 model.

3.1. Synthesis of compound 3

To a solution of 1.8 ml of dimethyl sulfoxide in 20 ml of dichloromethane, cooled to −78 °C (Dry Ice/acetone), was added slowly 1.65 ml of oxalyl chloride. The solution was stirred for 10 min at −78 °C and a solution consisting of 3.6 g (0.012 mol) of Boc-protected L-phenylalaninol in 45 ml of dichloromethane added slowly. After 15 min, 7.6 ml of triethylamine was added over 10 min. After stirring for 25 min, 20 ml of cold 10% citric acid solution was added. After warming to 0 °C, 200 ml of ether and 55 ml of cold 10% citric acid was added. The organic layer was separated and washed repeatedly (5×60 ml) with water and finally with brine solution. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give compound **3** as a white solid. ^{1}H NMR ($CDCl_3$) δ: 3.15 (2H, d, J = 9 Hz); 4.52 (m, 1H); 5.10 (s, 2H); 5.28 (br d, 1H); 7.10–7.35 (m, 5H); 9.15 (s, 1H) ppm. Mass spectrum: $(M+NH_4)^+ = 301$. Analysis: Calc. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62%. Found: C, 67.70; H, 7.50; N, 5.60%.

3.2. Synthesis of compounds 4a and 4b

A solution consisting of 9.8 g of compound **3** (aldehyde) in 120 ml of dry THF was sonicated at room temperature under argon with zinc dust (7.9 g) and mercuric chloride (1.65 g). A solution consisting of 18.35 g of bromodifluoromethylphenylacetylene in 40 ml of THF was added dropwise via a syringe pump over 1.5 h. After an additional 0.5 h of sonication, the mixture was vacuum filtered through a pad of Celite and the filtrate concentrated in vacuo. The resulting oil was partitioned between EtOAc (200 ml) and 10% $KHSO_4$ (100 ml), the aqueous phase was extracted with EtOAc (2×100 ml). The combined organic layer was washed with water (2×150 ml) and saturated brine solution (150 ml), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a mixture of **4a** and **4b**. The mixture was separated by preparative HPLC (5%–10% EtOAc/CH_2Cl_2) to give 5.07 g (32%) of **4a** and 3.31 g (21%) of **4b**.

Compound **4a**: ^{1}H NMR ($CDCl_3$) δ: 1.34 (s, 9H); 2.91–3.23 (m, 2H); 3.85–3.97 (m, 2H); 4.06–4.18 (m, 1H); 5.05 (br d, 1H); 7.20–7.55 (m, 10H) ppm. Analysis: Calc. for $C_{23}H_{25}F_2NO_3$: C, 68.81; H, 6.28; N, 3.49%. Found: C, 68.89; H, 6.34; N, 3.39%. M.p. 98–99 °C; R_f=0.39 (30% EtOAc/hexane).

Compound **4b**: ^{1}H NMR ($CDCl_3$) δ: 1.34 (s, 9H); 2.92–3.04 (m, 1H); 3.17 (m, 1H); 3.87 (d, 1H, J=5.4 Hz); 4.08–4.28 (m, 2H); 4.77 (br d, 1H); 7.19–7.46 (m, 8H); 7.53–7.59 (m, 2H) ppm. Analysis: Calc. for $C_{23}H_{25}F_2NO_3$: C, 68.81; H, 6.28; N, 3.49%. Found: C, 68.98; H, 6.30; N, 3.42%. M.p. 144–145 °C; R_f=0.32 (30% EtOAc/hexane).

3.3. Synthesis of compounds 5a and 5b

A solution consisting of 3.3 g of **4a** in 115 ml of absolute ethanol was added to a suspension of 10% Pd/C (0.33 g) in 10 ml of ethanol. The mixture was stirred vigorously under an atmosphere of hydrogen for 1 h. The catalyst was removed by filtration and the filtrate concentrated in vacuo. Purification by silica gel column chromatography (10% EtOAc/CH_2Cl_2) provided 3.2 g of product **5a** (96%). ^{1}H NMR ($CDCl_3$) δ: 1.37 (s, 9H); 2.09–2.39 (m, 2H); 2.70 (m, 2H); 2.88–3.12 (m, 2H); 3.48 (br s, 1H); 3.70 (m, 1H); 4.00 (m, 1H); 4.94 (br d, 1H); 7.13–7.35 (m, 10H) ppm. ^{19}F NMR ($CDCl_3$) δ: 51.19 (d, J=248.5 Hz, 1F); 52.64 (d, J=248.5 Hz, 1F) ppm. Analysis: Calc. for $C_{23}H_{29}F_2NO_3$: C, 68.13; H, 7.21; N, 3.46%. Found: C, 68.05; H, 7.20; N, 3.38%. M.p. 127–128 °C.

Similarly, 10 g of **4b** was hydrogenated to give 0.94 g of product **5b**. ^{1}H NMR ($CDCl_3$) δ: 1.38 (s, 9H); 2.18–2.51 (m, 2H); 2.86 (t, J=9.0 Hz, 2H); 2.95 (m, 2H); 3.39 (br s, 1H); 3.95 (m, 1H); 4.10 (m, 1H); 4.78 (br d, 1H); 7.15–7.35 (m, 10H) ppm. ^{19}F NMR ($CDCl_3$) δ: 49.95 (d, J=249.4 Hz, 1F); 54.42 (d, J=249.4 Hz, 1F) ppm. Analysis: Calc. for $C_{23}H_{29}F_2NO_3$: C, 68.13; H, 7.21; N, 3.46%. Found: C, 67.98; H, 7.21; N, 3.48%. M.p. 156–157 °C.

3.4. Synthesis of compound 6a

To 2.0 g of **5a** was added 20 ml of 1:1 (v/v) of trifluoroacetic acid/dichloromethane. The solution was stirred at room temperature for 0.5 h. The solvent was removed in vacuo and the residue dissolved in 250 ml of EtOAc and washed with saturated $NaHCO_3$ solution (50 ml). The organic layer was washed with saturated brine solution (50 ml), dried over Na_2SO_4 and concentrated to provide 1.5 g of product **6a** (quantitative). ^{1}H NMR ($CDCl_3$) δ: 1.53 (br s, 2H); 2.10–2.48 (m, 2H); 2.67 (dd, J=9.6, 13.2 Hz, 1H); 2.85 ppm (9m, 3H); 3.46 (dd, J=3.6, 24 Hz, 1H); 3.67 (dd, J=54, 9.3 Hz, 1H); 7.15–7.42 (m, 10H) ppm. Analysis: Calc. for $C_{18}H_{21}F_2NO$: C, 70.80; H, 6.93; N, 4.59%. Found: C, 70.75; H, 6.97; N, 4.54%. M.p. 103–105 °C.

Similarly, using 0.84 g of **5b** provided 0.63 g of product **6b** (quantitative). ^{1}H NMR ($CDCl_3$) δ: 2.22–2.58 (m, 5H); 2.65 (m, 1H); 2.85 (m, 2H); 3.15 (br s, 1H); 3.28 (m, 1H); 3.76 (m, 1H); 7.18–7.37 (m, 10H) ppm. Analysis: Calc. for $C_{18}H_{21}F_2NO$: C, 70.80; H, 6.93; N, 4.59%. Found: C, 70.65; H, 6.85; N, 4.60%. M.p. 95–96 °C.

3.5. Synthesis of compound 1

Coupling of 1.0 g of **6a** with Cbz-Val-OH using the standard DCC/HOBt peptide coupling procedure provided 1.52 g of product (88%) which was oxidized to the difluoroketone **1** using the procedure of Gallina and Giordano [7]. The difluoroketone was obtained in 60% yield (0.92 g). ^{1}H NMR ($CDCl_3$) δ: 0.82 (d, J=4.5 Hz, 3H); 0.90 (d, J=4.5 Hz, 3H); 2.05 (m, 1H); 2.35 (m, 2H); 2.80 (t, J=6.0 Hz, 2H); 2.90 (m, 1H); 3.30 (m, 1H); 3.90 (m, 1H); 5.08 (s, 2H); 5.28 (m, 1H); 6.12 (d, J=6 Hz, 1H); 7.10–7.35 (m, 15H) ppm. Analysis: Calc. for $C_{31}H_{34}F_2N_2O_4$: C, 69.12; H, 6.36; N, 5.20%. Found: C, 69.20; H, 6.32; N, 5.25%.

3.6. Synthesis of oxazolidinone 8a

To a solution consisting of 0.5 g of compound **6a** in 10 ml of dichloromethane was added 1.05 equiv. of triethylamine and 1.0 equiv. of triphosgene. After 1 h at room temperature, the solvent was removed in vacuo and purification of the crude product by silica gel column chromatography (5% EtOAc/CH_2Cl_2) provided 0.46 g of product **8a** (85%). ^{1}H NMR ($CDCl_3$) δ: 2.11–2.48 (m, 2H); 2.85 (m, 3H); 2.99 (dd, J=4.2, 14.1 Hz, 1H); 4.20 (m, 1H); 4.34 (ddd, J=3.3, 5.4, 18.3 Hz, 1H); 5.50 (s, 1H); 7.17–7.40 (m, 10H) ppm. Analysis: Calc. for $C_{19}H_{19}F_2NO_2$: C, 68.87; H, 5.78; N, 4.23%. Found: C, 69.05; H, 5.89; N, 4.24%. ^{19}F NMR ($CDCl_3$) δ: 45.37 (d, J=256.7 Hz, 1F); 48.83 (d, J=256.7 Hz, 1F) ppm. M.p. 111–112 °C.

Similarly, oxazolidinone **8b** was synthesized in 81% yield starting with compound **6b**. ^{1}H NMR ($CDCl_3$) δ: 2.18–2.61 (m, 2H); 2.80–3.08 (m, 3H); 3.25 (m, 1H); 4.25 (m, 1H); 4.71 (dd, J=8.7, 23.7 Hz, 1H); 4.79 (s, 1H); 7.18–7.40 (m, 10H) ppm. Analysis: Calc. for $C_{19}H_{19}F_2NO_2$: C, 68.87; H, 5.78; N, 4.23%. Found: C, 68.83; H, 5.85; N, 4.22%. ^{19}F

NMR ($CDCl_3$) δ: 50.33 (d $J=256.9$ Hz, 1F); 52.98 (d, $J=256.9$ Hz, 1F) ppm.

References

[1] M.H. Gelb, J.P. Svaren and R.H. Abeles, *Biochemistry, 27* (1985) 1813.
[2] D.W. Norbeck and D.J. Kempf, *Rep. Med. Chem., 26* (1991) 141.
[3] K. Omura and D. Swern, *Tetrahedron, 34* (1978) 1651.
[4] I. Rico, D. Cantacuzene and C. Wakselman, *J. Chem. Soc., Perkin Trans. 1,* (1982) 1063.
[5] S. Thaisrivong, D.T. Pals, W.M. Kati, S.K. Turner, L.M. Thomasco and W. Watt, *J. Med. Chem., 29* (1986) 2080.
[6] D.H. Rich and E.T. Sun, *J. Med. Chem., 23* (1980) 27.
[7] C. Gallina and C. Giordano, *Synthesis,* (1989) 466.