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A stereocontrolled synthesis of 2*R*-benzyl-5*S*-*tert*-butoxycarbonylamino-4*R*-(*tert*-butyldimethylsilanyloxy)-6-phenyl-hexanoic acid (Phe–Phe hydroxyethylene dipeptide isostere)

Alan Nadin,* José M. Sánchez López, Joseph G. Neduvelil and Steven R. Thomas

Department of Medicinal Chemistry, Merck Sharp and Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Harlow, Essex CM20 2QR, UK

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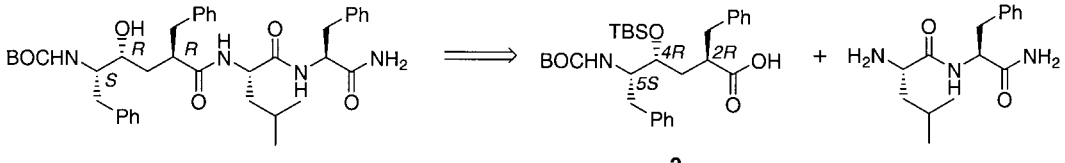
Abstract—2*R*-Benzyl-5*S*-*tert*-butoxycarbonylamino-4*R*-(*tert*-butyldimethylsilanyloxy)-6-phenyl-hexanoic acid, a hydroxyethylene dipeptide isostere corresponding to Phe–Phe, has been synthesized in a practical, stereocontrolled fashion from (L)-phenylalanine.

1. Introduction

We recently reported that compounds based on structure **1** (L-685,458) are potent inhibitors of γ-secretase, and thus of potential therapeutic benefit in the treatment of Alzheimer's disease and other neurological disorders.[1] Compound **1** is easily divided retrosynthetically into two domains, an N-terminal hydroxyethylene dipeptide isostere (**2**) and a C-terminal dipeptide moiety (**3**) (Scheme 1). Although there are many efficient syntheses of hydroxyethylene dipeptide isosteres,[2] the 2*R*,4*R*,5*S* stereochemical pattern found in **2** (and essential for the biological activity of **1**) is not well-described—the existing syntheses[3] produce **2** in small amounts as mixtures with other stereoisomers. Herein we report a flexible, stereocontrolled synthesis of **2**, capable of delivering large quantities of **1** and related analogs.

2. Results and discussion

Our synthesis of **2** began with epoxide **4** (Scheme 2). There are a number of published syntheses of **4**,[2] but the one we found most convenient was the Barrish–Polniaszek[4] modification of the Kowalski homologation[5] of *N*-acyl-α -amino acid esters. Treatment of epoxide **4** with the sodium salt of diethyl malonate gave, after aqueous work-up, the lactone **5** as a mixture of stereoisomers.[3c] Without further purification, **5** was subjected to hydrolysis and decarboxylation to give **6** as a crystalline solid in 81% yield. The alkylation of lactone **6** with a variety of electrophiles, including benzyl bromide, is known[6] to provide the undesired 2*S* stereoisomer with very high stereoselectivity, and thus was not suitable for our purposes. Alternatively, lactone **5** can be alkylated with benzyl bromide, and the resulting compound hydrolyzed and decarboxylated, but this leads to a mixture of isomers of **8**, which cannot be easily separated.[3c] Accordingly, we introduced the C-2 stereocenter by an aldol–elimination–hydrogenation sequence[7] as shown in Scheme 2. Thus, treatment of the lithium enolate of **6** with benzaldehyde gave the corresponding β-hydroxy-lactones in quantitative yield as a complex mixture of stereoisomers. This mixture was dehydrated with acetic anhydride-triethylamine at elevated



1 (L-685,458) **2** **3**

Scheme 1.

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* Corresponding author; e-mail: alan_nadin@merck.com

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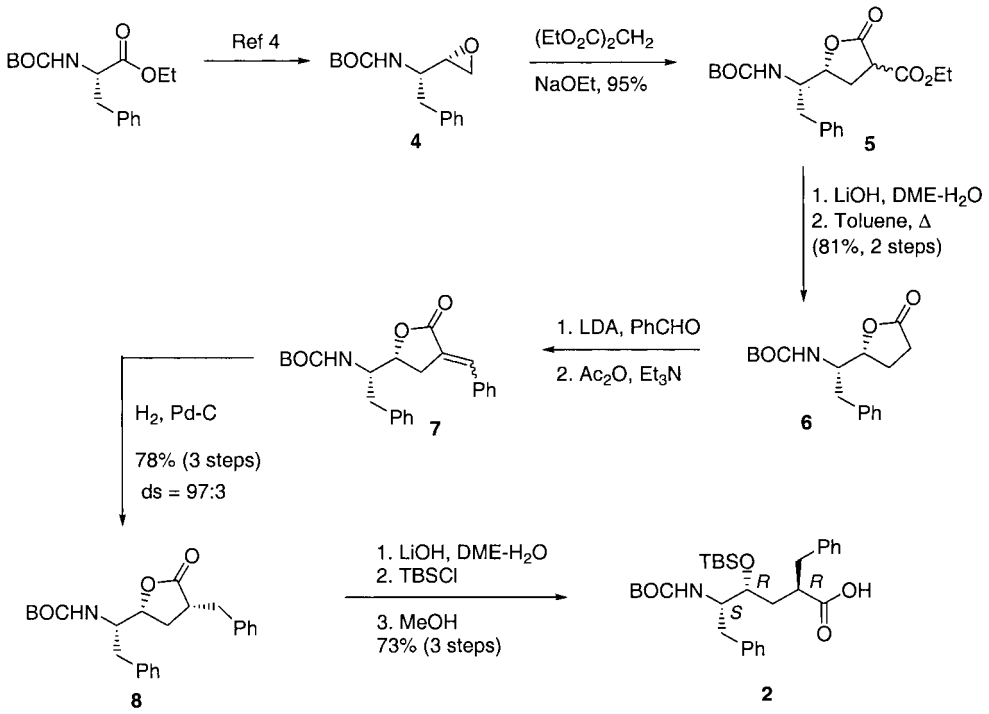


Scheme 2.

temperature (or methanesulfonyl chloride-DBU at room temperature) to give the α,β-unsaturated lactone **7**. Without further purification, **7** was hydrogenated (50 psi) with Pd–C catalyst to give **8** as a mixture of diastereomers (ratio=97:3 by reverse phase HPLC analysis). The stereochemistry of the newly formed chiral center was readily confirmed by observation of an NOE between H2 and H4 of **8** (Scheme 1 numbering), whereas the minor 2*S* diastereomer exhibited an NOE between H5 and H2. This three-step process can be conveniently performed on a multi-gram scale and requires no chromatography.

Hydrolysis of lactone **8** with lithium hydroxide, per-silylation of the resulting hydroxy acid and selective desilylation of the acylsiloxy moiety[3c] gave **2** in excellent yield and high purity, following chromatography.

By the substitution of other amino acids for the (L)-phenylalanine starting material, and replacement of benzaldehyde with other aldehydes and ketones, a variety of hydroxyethylene dipeptide isosteres should be accessible by the same methodology.

Compound **1** (L-685,458) is readily prepared from **2** and Leu-Phe-NH_2 by a simple peptide coupling reaction and deprotection of the resulting silyl ether with TBAF (Scheme 3).

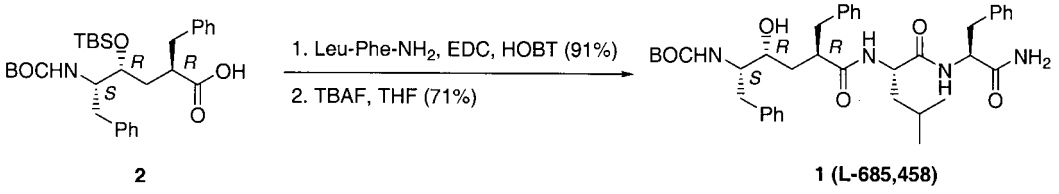
3. Conclusions

A practical, stereocontrolled synthesis of 2*R*-benzyl-5*S*-*tert*-butoxycarbonylamino-4*R*-(*tert*-butyldimethylsilanyloxy)-6-phenyl-hexanoic acid has been achieved, starting from (L)-phenylalanine. The entire sequence can be performed on a multi-gram scale, requires little chromatography and is applicable to the preparation of other dipeptide isosteres containing this stereochemical pattern.

4. Experimental

4.1. Synthesis of [1*S*-(5-oxo-tetrahydrofuran-2-yl)-2*R*-phenylethyl]-carbamic acid, *tert*-butyl ester (6)[3b]

A solution of **5**[3c] (23 g, 0.061 mol) in 1,2-dimethoxyethane (200 ml) and LiOH (2.0 M in H_2O, 200 ml) was stirred at 50°C for 6 h. The reaction mixture was evaporated partially in vacuo and acidified to pH 3 with 2N HCl (aq). The aqueous phase was extracted with ethyl acetate (three times). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated in vacuo. The resulting thick oil was dissolved in toluene (200 ml) and refluxed under Dean–Stark conditions for 8 h. The reaction mixture was evaporated in vacuo and purified by flash column



Scheme 3.

chromatography (using 1:1 ethyl acetate–hexane as eluant) to give **6**[3b] as a white solid (15 g, 81%) mp 137–139°C (ethyl acetate–hexane). **6** can also be purified by trituration with ether. Anal. Calcd for $C_{17}H_{23}NO_4$ C 66.86, H 7.59, N 4.59. Found C 66.38, H 7.91, N 4.47. $[\alpha]_D=-33.3$ (*c* 1.00, $CHCl_3$).

4.2. Synthesis of [1*S*-(4*R*-benzyl-5-oxo-tetrahydrofuran-2-yl)-2*R*-phenylethyl]-carbamic acid, *tert*-butyl ester (8)

A solution of [1*S*-(5-oxo-tetrahydrofuran-2-yl)-2*R*-phenylethyl]-carbamic acid, *tert*-butyl ester **6** (9.5 g, 3.11 mmol) in THF (35 ml) was added to a solution of lithium diisopropylamide [made from *n*-butyllithium (27.4 ml of a 2.5 M solution in hexane) and diisopropylamine (9.7 ml)] in THF (150 ml) at −78°C. The reaction mixture was stirred for 40 min at −78°C, then treated with benzaldehyde (6.9 ml). After 30 min, the reaction mixture was quenched by the addition of aqueous NH_4Cl (15 ml) and water. The resulting mixture was extracted with ethyl acetate and the combined extracts were washed with aqueous citric acid, aqueous $NaHCO_3$ solution and brine. The combined extracts were dried ($MgSO_4$), filtered and evaporated in vacuo to give a thick oil. This crude reaction product was treated with acetic anhydride (15 ml), triethylamine (15 ml) and heated at 120°C for 1 h. The reaction mixture was cooled to room temperature, diluted with ether and washed with aqueous citric acid, aqueous $NaHCO_3$ solution and brine. The ethereal extracts were dried ($MgSO_4$) and evaporated in vacuo to give **7** as a crude solid, which was used without further purification. This crude reaction product was dissolved in ethyl acetate (100 ml) and methanol (25 ml), treated with 5% Pd/C catalyst (10% w/w) and hydrogenated at 50 psi for 2 h. The reaction mixture was filtered and evaporated in vacuo to give **8**[3b] as a white solid, which was purified by trituration with ether. Mp 123–125°C; $[\alpha]^{25}_D=-69.5$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) 7.38–7.15 (10H, m); 4.38–4.11 (2H, m), 3.90 (1H, brs); 3.27 (1H, dd, *J*=13.7, 4.0 Hz); 2.95–2.67 (4H, m), 2.28–2.17 (1H, m); 1.86–1.70 (1H, m); 1.34 (9H, s).

4.3. Synthesis of 2*R*-benzyl-5*S*-*tert*-butoxycarbonylamino-4*R*-(*tert*-butyldimethylsilanyloxy)-6-phenyl-hexanoic acid (2)

A solution of **8** (3.5 g, 8.86 mmol) in 1,2-dimethoxyethane (60 ml) was treated with a solution of lithium hydroxide in water (1.0 M, 60 ml, 60 mmol) and stirred at room temperature for 5 h. The reaction mixture was carefully acidified to pH 4 with citric acid, and then extracted with ethyl acetate. The ethyl acetate extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated in vacuo. The crude hydroxyacid (3.6 g) was dissolved in DMF (50 ml) and treated with *tert*-butyldimethylsilyl chloride (13.3 g, 88 mmol) and imidazole (7.1 g, 0.10 mol) and stirred overnight. The reaction mixture was treated with methanol (30 ml) and stirred for 2 h, then evaporated in vacuo. The reaction mixture was partitioned between aqueous citric acid and ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated in vacuo. Purification by flash column chromatography (using 3% MeOH–CH_2Cl_2 as eluant) gave **2**[3a,c] (3.4 g, 73%) as a white foam.

Spectral data for **2**: $[\alpha]^{25}_D=-12.5$ (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO) 12.08 (1H, s); 7.25–7.04 (10H, m); 6.45 (1H, d, *J*=8.9 Hz);r 3.74–3.53 (2H, m); 2.76–2.50 (5H, m); 1.8–1.5 (2H, m); 1.22 (9H, s); 0.80 (9H, s); 0.07 (3H, s); 0.05 (3H, s). ^{13}C NMR (90.5 MHz, DMSO) 178.4, 157.4, 147.7, 141.7, 131.2, 131.0, 130.6, 130.3, 128.5, 128.1, 79.7, 74.0, 58.5, 45.5, 41.2, 39.8, 30.5, 28.2, 20.0, −2.25. Anal. Calcd for $C_{30}H_{45}NO_5Si$: C 68.27, H 8.59, N 2.65. Found C 68.36, H 8.53, N 2.69.

4.4. Synthesis of {1*S*-benzyl-4*R*-[1-(1*S*-carbamoyl-2-phenyl-ethylcarbamoyl)-3(1*S*)-methyl-butylcarbamoyl]-2*R*-hydroxy-5-phenyl-pentyl}-carbamic acid *tert*-butyl ester (1)

A solution of **2** (200 mg, 0.38 mmol), Leu-Phe-NH_2 (126 mg, 0.45 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (102 mg, 0.53 mmol) and 1-hydroxybenzotriazole (73 mg, 0.53 mmol) in DMF was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, and the organic phase was washed with aqueous citric acid, aqueous $NaHCO_3$, brine, dried ($MgSO_4$), filtered and evaporated in vacuo. Purification by flash column chromatography (using 5% MeOH–CH_2Cl_2 as eluant) gave the product (270 mg, 91%). This material was dissolved in a solution of tetrabutylammonium fluoride in THF (1.0 M, 2.5 ml) and stirred at room temperature overnight. The reaction mixture was diluted with citric acid and ether and the resulting precipitate was collected by filtration, washed, and dried in vacuo to give **1**. Further purification by flash column chromatography (using 6% MeOH–CH_2Cl_2 as eluant) gave **1** (163 mg, 64%) as a white solid. Mp 212–214°C; $[\alpha]^{25}_D=-27.9$ (*c* 0.50, $CHCl_3$).

Spectral data for **1**: ^{1}H NMR (400 MHz, DMSO) 7.88 (1H, d, *J*=7.8 Hz), 7.63 (1H, d, *J*=8.1 Hz), 7.28–7.06 (17H, m), 6.47 (1H, d, *J*=8.9 Hz), 4.71 (1H, brs), 4.39 (1H, m), 4.17 (1H, m), 3.41 (2H, m), 3.01–2.38 (7H, m), 1.70–1.45 (3H, m), 1.41–1.26 (2H, m), 1.24 (9H, s), 0.82 (3H, d, *J*=6.5 Hz), 0.75 (3H, d, *J*=6.5 Hz). ^{13}C NMR (90.5 MHz, DMSO) 175.2, 174.9, 174.0, 157.4, 142.3, 142.1, 140.0, 131.4, 131.2, 130.4, 130.3, 130.1, 128.5, 128.1, 127.8, 79.6, 73.5, 58.8, 55.7, 53.7, 46.7, 42.9, 39.8, 39.8, 38.0, 37.6, 30.5, 26.2, 25.3, 23.9. Anal. Calcd for $C_{39}H_{52}N_4O_6$ C 69.62, H 7.79, N 8.33. Found C 69.70, H 7.41, N 8.53.

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