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Synthesis of a Constrained Enkephalin Analog to Illustrate a Novel Route to the Piperazinone Ring Structure

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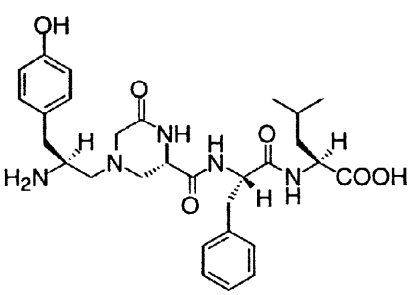
Abstract: **The synthesis of a constrained, piperazinone analog of Leu-enkephalin is presented. A key step in this synthesis was the use of the secondary amine, Boc-Tyr(O*t*Bu)Ψ[CH_2NH]Gly-OMe, to ring open the β-lactone of Z-protected L-serine (the Vederas lactone). The resulting free acid was then coupled to H-Phe-Leu-O*t*Bu in a one-pot fashion using standard carbodiimide coupling conditions. This linear precursor cyclized upon hydrogenolysis of the Z group to form the N^4-substituted, 6-carboxy-derived piperazinone (5). Deprotection of compound 5 using 1:1 TFA:CH_2Cl_2 yielded the target compound 1.** © 1997 Elsevier Science Ltd. All rights reserved.

The synthesis of peptidomimetic ring structures is an area of active interest. Such ring structures provide a template by which pharmacophores of a biologically active peptide can be arranged to yield a congener with altered selectivity or potency. The piperazinone ring structure has been developed as a conformational constraint for peptides[1] and has been incorporated into ligands for the neurokinin-2,[2] cholecystokinin,[3] and opioid receptors.[4] As part of our effort to design scaffold-containing enkephalin analogs, we have discovered a novel synthetic route to the piperazinone (2-oxopiperazine) ring structure and applied it to the synthesis (Scheme 1) of a constrained analog of Leu-enkephalin (**1**).



(1)

A variety of syntheses in solution of the piperazinone ring structure are known.[5] Some of the earliest syntheses of this ring structure rely on a two point condensation of ethylenediamine derivatives with derivatives of α-haloacetic acids.[6] Other examples are based on ring closure of a linear precursor to form the piperazinone amine[1b-d,7] or amide[8] bond. More recently, solid phase methods have been developed that attach a linear precursor to a resin. Cyclization followed by cleavage then yields a carboxylic acid bearing piperazinone.[9]

The synthesis of the target compound **1** begins with Boc-Tyr(O*t*Bu)Ψ[CH_2N]Gly-OMe (**4**). Using the methodology of Fehrentz and Castro,[10] Boc-Tyr(O*t*Bu)-$NCH_3(OCH_3)$ (**2**) was prepared from Boc-Tyr(O*t*Bu)-OH and *N, O*-dimethylhydroxylamine using BOP in CH_2Cl_2. Upon treatment with an excess of $LiAlH_4$ in Et_2O, this amide was converted to the aldehyde **3** and used immediately in the next reaction. The secondary amine **4** was prepared from compound **3** under reductive amination conditions using $NaCNBH_3$ and an excess of H-Gly-OMe·HCl (3 equiv.) in 1% AcOH/MeOH.

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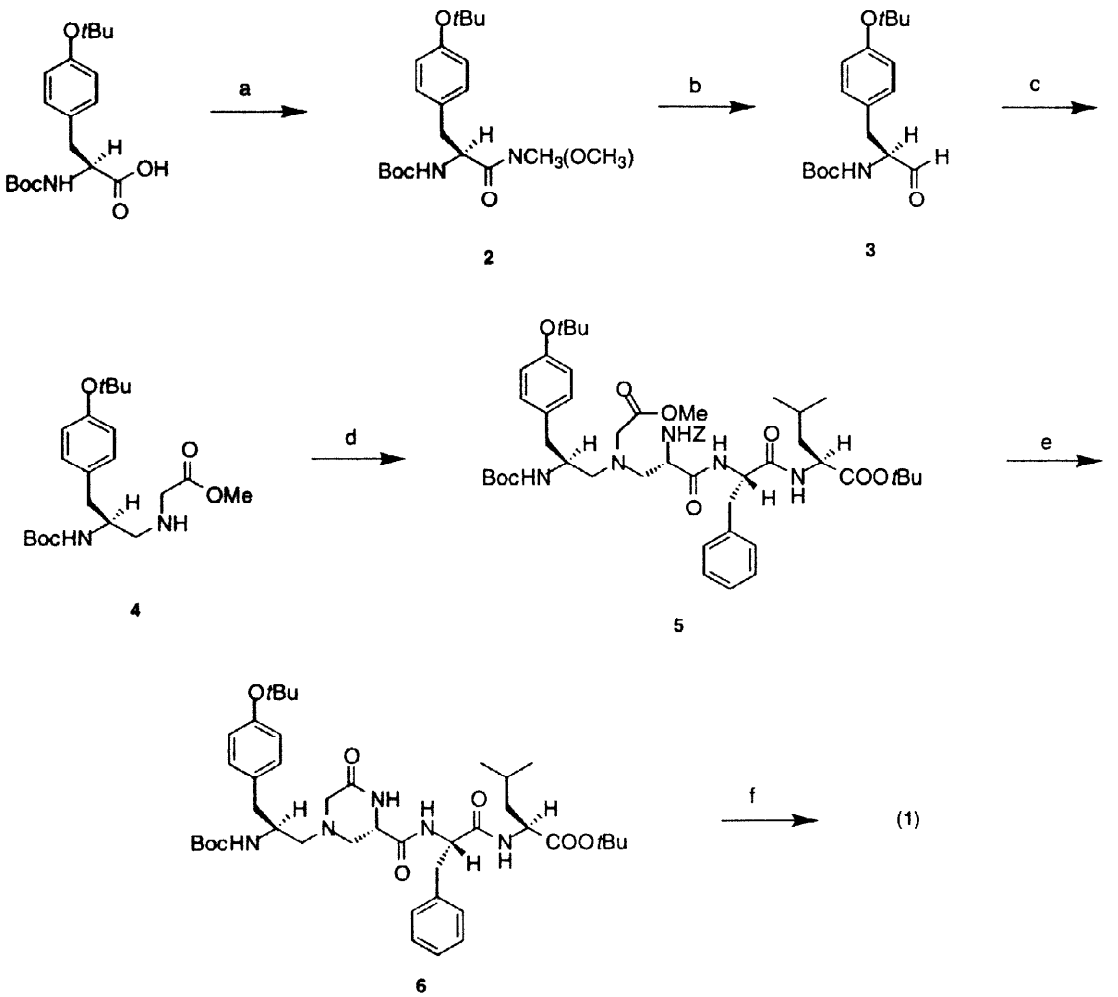
Extension of the backbone of compound **1** resulted from the key reaction of compound **4** with benzyloxycarbonyl (Z)-L-serine-β-lactone (the Vederas lactone).[11] When compound **4** was heated with this lactone in CH_3CN, a new compound resulted that stained bright yellow when treated with the TLC spray reagent bromocresol blue. This result is consistent with the formation of a species containing a free carboxylic acid. This acid results, presumably, from CH_2-O ring opening of the β-lactone in a S_N2 fashion. Because this intermediate proved difficult to isolate, it was coupled in a one-pot fashion to H-Phe-Leu-O*t*Bu using standard carbodiimide coupling conditions. The resulting linear precursor **5** was then readily isolated using silica gel chromatography in 55% yield from the secondary amine **4**.



Scheme 1: (a) $NH(OCH_3)CH_3$·HCl, DIEA, BOP, DCM, 0° C then 23° C overnight; 74% (b) $LiAlH_4$ (5 equiv.), Et_20, 0° C, 45 min. (c) H-Gly-OMe·HCl (3 equiv.), $NaCNBH_3$, 1% AcOH/MeOH, 23° C, 24 h, 35% from **2** (d) [**4**] = 300 mM, Z-L-Ser-β-lactone (1.2 equiv.), CH_3CN, 65° C then H-Phe-Leu-O*t*Bu, EDC, NHS, DMF, 23° C, 24 h, 55% from **4** (e) H_2 (1 atm), 10% Pd/C, EtOH, 23° C, 14 h, 92% (f) 1:1 TFA/CH_2Cl_2, 23° C, 6 h, quant.

Ring closure was achieved during deprotection of the Z group. Catalytic hydrogenolysis of **5** in an atmosphere of H_2 using 10% Pd on carbon gave the N^4-substituted, 6-carboxy substituted piperazinone derivative **6** in an isolated yield of 92% after silica gel column chromatography. Deprotection of compound **6** using 1:1 TFA:CH_2Cl_2 yielded the target compound **1**, which was purified using reverse phase HPLC. The structure was confirmed using high resolution FAB mass spectometry and two-dimensional TOCSY, COSY, ROESY ^1H NMR spectroscopies.[12] The target compound **1** exhibits modest affinity for both the μ and δ receptors.

The use of serine derived β-lactones in the synthesis of piperazinones offers a new route to this peptidomimetic structure. Advantages of this synthesis include the ready incorporation of amino acid or peptide building blocks and the mild conditions utilized for ring closure which are compatible with acid labile protecting groups. The general route presented here will be applicable to the incorporation of this heterocycle into a wide variety of constrained peptide analogs. By analogy, simple amines can also be incorporated into the synthetic scheme making this a useful method to design non-peptidic piperazinones as well.

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12. compound **1**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.83 (3H, d, -CH_3, J = 6.2 Hz), 0.88 (3H, d, -CH_3, J = 6.4 Hz), 1.53 (2H, m, Leu-H_β), 1.61 (1H, m, Leu-H_γ), 2.25 (1H, dd, TyrΨ[CH_2NH], J = 13.2Hz, 4.4 Hz), 2.34 (1H, b, C_{pip}^5-H), 2.38 (1H, m, TyrΨ[CH_2NH]), 2.61 (1H, dd, TyrΨ[CH_2NH]-H_β, J = 13.5 Hz, 7.1Hz), 2.67 (1H, dd, C_{pip}^5-H, J = 12.0 Hz, 3.4 Hz), 2.77 (1H, dd, Phe-H_β, J = 14.2 Hz, 5.6 Hz), 2.78 (1H, dd, TyrΨ[CH_2NH]-H_β, J = 13.5 Hz, 8.6 Hz), 2.90 (1H, d, C_{pip}^3-H, J = 15.7 Hz), 2.99 (1H, d, C_{pip}^3-H, J = 15.7 Hz), 3.05 (1H, dd, Phe-H_β, J = 13.9 Hz,4.1 Hz), 3.90 (1H, b, C_{pip}^6-H), 4.21 (1H, q, Leu-H_α, J = 7.2 Hz), 4.58 (1H, q, Phe-H_α, J = 7.1 Hz), 6.73 (2H, d, TyrΨ[CH_2NH]-$H_{3,5}$, J = 8.2 Hz), 7.03 (2H, d, TyrΨ[CH_2NH]-$H_{2,6}$, J = 8.2 Hz), 7.08 (1H, m, Phe-H_4), 7.14 (2H, m, Phe-$H_{2,6}$), 7.19 (2H, m, Phe-$H_{3,5}$), 7.62 (3H, b, TyrΨ[CH_2NH]-NH_3), 7.90 (1H, b, N_{pip}^1-H), 7.92 (1H, d, Phe-NH, J = 8.1 Hz), 8.23 (1H, b, Leu-NH), 9.34 (1H, s,TyrΨ[CH_2NH]-OH); HRMS (FAB+) [M + H]$^+$ calcd for $C_{29}H_{40}N5O_6$: 544.2979, found: 544.2959.

compound **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (9H, s), 1.38 (9H, s), 2.90 (2H, m), 3.14 (2H, s), 3.60 (2H, s), 4.92 (1H, b), 5.15 (1H, b), 6.90 (2H, d, J = 2.7 Hz), 7.07 (2H, d, J = 2.7 Hz); MS (FAB$^+$) 325, 381, 403 (M + Na$^+$); HRMS (FAB+) [M + H]$^+$ calcd for $C_{20}H_{33}N_2O_5$: 381.2389, found: 381.2377.

compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (9H, s), 1.41 (9H, s), 2.63 (2H, d), 2.73 (2H, m), 3.35 (1H, d, J = 17.5 Hz), 3.45 (1H, d, J = 17.5 Hz), 3.71 (3H, s), 3.86 (1H, b), 4.79 (1H, b), 6.90 (2H, d, J = 8.3 Hz), 7.08 (2H, d, J = 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8, 28.2, 37.7, 50.1, 51.0, 77.6, 78.4, 123.5, 129.1, 132.3, 153.1, 155.0, 172.3; MS (FAB$^+$) 295, 339, 395, 417 (M + Na$^+$); HRMS (FAB+) [M + H]$^+$ calcd for $C_{21}H_{35}N_2O_5$: 395.2546, found: 395.2557.

compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (6H, d, J = 5.4 Hz), 1.34 (9H, s), 1.38 (9H, s), 1.44 (9H, s), 1.55 (2H, m), 2.6-2.9 (6H, m), 3.14 (2H, m), 3.42 (2H, s), 3.68 (s + b, 4H), 4.00 (1H, b), 4.42 (1H, m), 4.57 (1H, m), 5.07 (3H, s + b), 6.23 (1H, b), 6.57 (1H, b), 6.90 (2H, d, J = 8.1 Hz), 7.05 (2H, d, J = 8.1 Hz), 7.1-7.4 (10H, m), 7.80 (1H, b); MS (FAB$^+$) 1064 (M + Cs$^+$); HRMS (FAB+) [M + Cs]$^+$ calcd for $C_{51}H_{73}CsN_5O_{11}$: 1064.4361, found: 1064.4409.

compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (6H, m), 1.31 (9H, s), 1.35 (9H, s), 1.38 (9H, s), 1.52 (2H, m), 2.27 (2H, m), 2.7-3.3 (10H, m), 3.81 (1H, b), 3.94 (1H, m), 4.32 (1H, m), 7.78 (1H, m), 6.32 (1H, d, J = 7.5 Hz), 6.90 (2H, d, J = 8.3 Hz), 7.06 (2H, d, J = 8.3 Hz), 7.1-7.3 (10H, m), 7.45 (1H, b), 7.90 (1H, d, J = 7.8 Hz); MS (FAB$^+$) 610, 660, 766, 788 (M + Na$^+$); HRMS (FAB+) [M + H]$^+$ calcd for $C_{42}H_{64}N_5O_8$: 766.4755, found: 766.4781.