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SYNTHESIS OF CONSTRAINED BICYCLIC DIPEPTIDE MIMETICS

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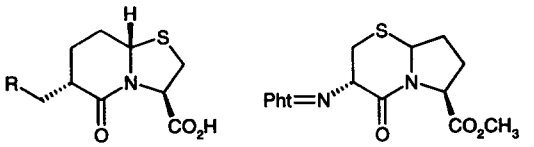
Abstract: An efficient synthesis of constrained bicyclic peptidomimetics of (R)-Phe-Pro dipeptide is described. Such mimetics may provide an opportunity to develop inhibitors of thrombin possessing the desired pharmacological features. © 1997 Elsevier Science Ltd.

There has been a considerable interest in conformationally constrained peptidomimetics.[1] The obvious advantage of such peptidomimetics may lie in enhanced binding to receptors or enzymes, metabolic stability, and/or oral bioavailability. Early examples of lactam based dipeptide mimetics demonstrated their facile synthetic accessibility and utility.[2-4] Recently, a number of papers have appeared in the literature describing the synthesis of lactam based bicyclic peptidomimetics.[5-6]

Thrombotic vascular disease is a major cause of morbidity and mortality in the industrialized world. Thrombin, a trypsin-like serine protease and a key enzyme in the blood coagulation cascade, plays a major role in the development of the disease state.[7] To combat the disease, considerable efforts have been placed on the direct inhibition of thrombin. Several inhibitors of thrombin are designed based on the tripeptide motif (R)-Phe-Pro-Arg.[8] As a part of the program to develop low molecular weight thrombin inhibitors, we rationalized that the dipeptide sequence (R)-Phe-Pro can be conveniently replaced by the mimetics **1** and **2** (**Figure**).



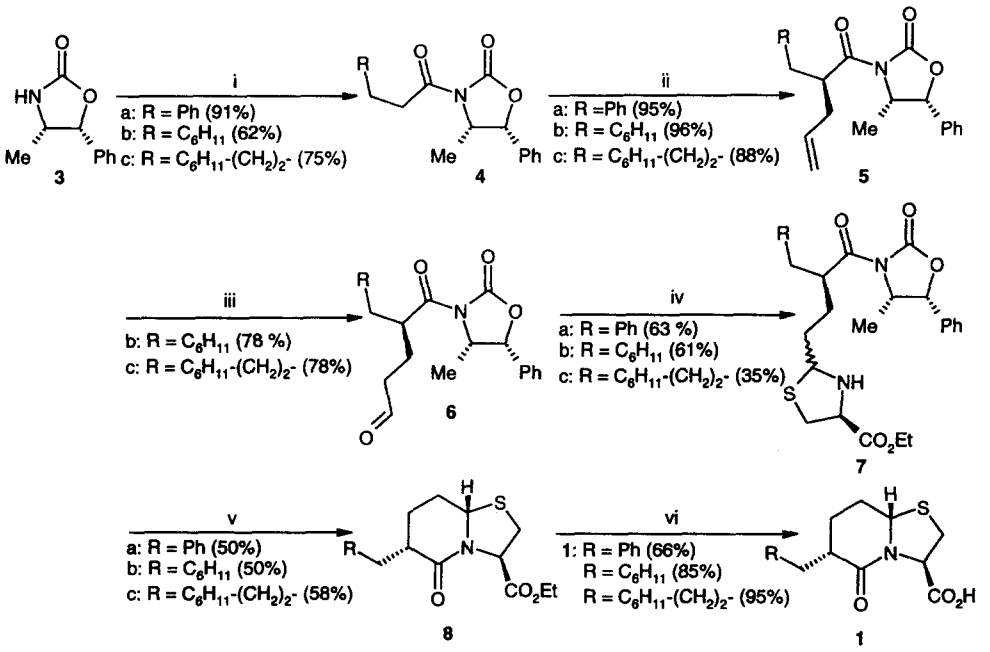
1 **2**

R = Ph, C_6H_{11}, C_6H_{11}-$(CH_2)_2$-

Figure

In this letter we describe the synthesis of peptidomimetics **1** and **2**. Synthesis of peptidomimetic **1** is based on Evans asymmetric alkylation methodology[9] (**Scheme 1**). Following a general procedure, the auxiliary

3 was acylated to give compound **4a-c**. Treatment of **4a-c** with LiHMDS and subsequent quenching of the resulting anion with allyl iodide or bromide afforded **5a-c** in high yields with diastereoselectivity greater than 95%, as determined by ^{1}H NMR. The allyl derivative **5b-c** was converted into corresponding aldehyde **6b-c** by sequential treatment with disiamylborane followed by PCC oxidation whereas aldehyde **6a** was obtained by treatment of **5a** with BH_3/m-CPBA and PCC oxidation.[10] Condensation of **6a-c** with L-cysteine ethyl ester in benzene or toluene using a catalytic amount of PTSA afforded thioaminal **7a-c** in a 1:1 mixture of two isomers. Initially, cylization of thioaminal **7a-c** to **8a-c** proved to be cumbersome. However, treatment of the thioaminal with three equivalents of trimethylaluminum provided the cyclized product as a single diastereoisomer.[11] The hydrolysis of **8a-c** with LiOH afforded corresponding acids **1**.



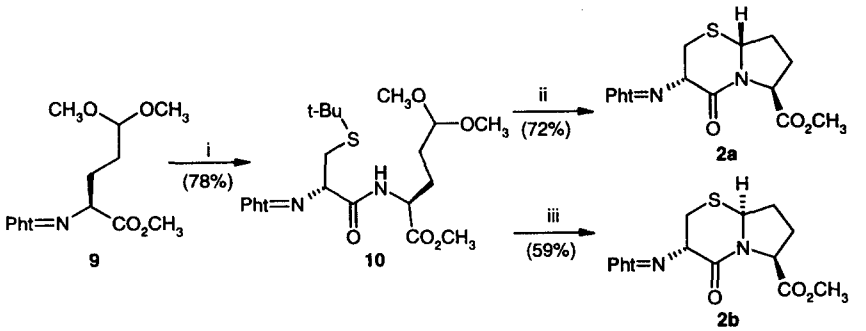
Scheme 1

Scheme 1. *Reagent and conditions.* i, a) n-BuLi/THF/-78°C, b) R-CH_2-COCl; ii, LiHMDS/THF/-78°C/Allyl iodide or bromide; iii, a) Disiamylborane/THF/0°C, b) PCC/DCM/reflux; iv, L-Cys-OEt/PhH/cat. PTSA; v, Me_3Al/DCM/0°C-RT; vi, LiOH/THF-H_2O/RT.

The mimetic **1** (R= C_6H_{11}-$(CH_2)_2$-) produced suitable crystals for X-ray crystallographic analysis to unambiguously confirm the structure as shown.[12]

Synthesis of peptidomimetic **2** was initiated by the coupling of glutamic ester analogue **9**[13] with protected cysteine to give dipeptide **10** (**Scheme 2**). Treatment of dipeptide **10** with neat TFA at ambient temperature

resulted in bicylic lactam **2a** in 72% yield and 6:1 diastereoselectivity, with the minor isomer being **2b**, as determined by ^{1}H NMR.[14] Interestingly, when dipeptide **10** was heated at 75°C in dichloroethane with a catalytic amount of TFA, isomer **2b** was a major product in 59% yield and 7:1 diastereoselectivity.[15] The cyclization of **10** to lactams **2a** or **2b** is believed to proceed via successive acyl iminium ion intermediates.[16] Predominance of one isomer over other, under two different reaction conditions, enabled us to obtain both diastereoisomers in moderate to good yield. We explored the possibility of converting isomer **2a** to **2b** or vice versa under the reaction conditions (TFA, r.t., 24h and cat. TFA, 75°C, DCE), however, with complete recovery of starting lactams. The X-ray crystal structure of the hydrocinnamoyl amide analogue of **2a** unambiguously confirmed the structure.[12]



Scheme 2

Scheme 2. *Reagent and conditions.* i, a) H_2N-NH_2/MeOH, b) Pht-cys(tBu)-OH, BOP, Et_3N/DMF; ii, TFA, r.t.; iii, TFA (cat), DCE, 75°C.

In summary, we have demonstrated that the constrained mimetics of (R)-Phe-Pro dipeptide can be synthesized in a concise manner. The scope of the described mimetics to design thrombin inhibitors will be published shortly.

ACKNOWLEDGMENT

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11. General procedure of cyclization: To a solution of **7a** (800 mg, 1.61 mmol) in anhydrous dichloromethane at 0°C was added slowly 2.0 M Me_3Al in hexane (2.4 mL, 4.8 mmol). The reaction was allowed to stir at ambient temprature for 16 h. The reaction mixture was carefully quenched with methanol, diluted with ethyl acetate and filtered through a short silica gel column. Removal of solvent from filtrate afforded a gummy material which was purified by flash column chromatography to give 50% (258 mg) of compound **8a**. ^1H NMR ($CDCl_3$) δ 1.28-1.31 (m, 3H), 1.72-1.81 (m, 3H), 2.11-2.13 (m, 1H), 2. 66 (dd, 1H, J = 13.6 and 11 Hz), 2.74-2.76 (m, 1H), 3.14 (dd, 1H, J= 11.5 and 6 Hz), 3.29-3.34 (m, 2H), 4.19-4.29 (m, 2H), 4.88 (dd, 1H, J= 8.8 and 4.6 Hz), 5.22 (dd, 1H, J= 8 and 6 Hz), 7.18-7.23 (m, 3H), 7.26-7.31(m, 2H).
12. Coordinates of mimetics **1** and **2** will be deposited at the Cambridge crystallographic data bank.
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14. Experimental procedure **2a**: Dipeptide **10** (1.07g, 2.2 mmol) in TFA (10 mL) was stirred at room temperature for 30 min. TFA was evaporated and the residue diluted with ethyl acetate (100mL), washed with aqueous sodium bicarbonate (5%, 2X25 mL), and dried over anhydrous magnesium sulfate. Removal of ethyl acetate resulted in a residue which was purified by silica gel flash chromatography (60% ethyl acetate in hexane) to give 576 mg of **2a**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (m, 2H), 7.74 (m, 2H), 5.27 (dd, J=7.0 Hz J=4.5 Hz,1H), 5.16 (dd, J=10.0 Hz J=7.0 Hz, 1H), 4.81 (dd, J=8.0 Hz J=4.0 Hz, 1H), 3.75-3.70 (m, 4H), 3.34 (dd, J=11.5 Hz J=7.0 Hz, 1H), 2.60-2.45 (m, 2H), 2.15-2.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.64, 167.57, 164.78, 134.24, 131.74, 123.53, 58.75, 57.45, 52.35, 49.64, 31.81, 27.39, 26.87. I.R. (n, film NaCl):3025, 1730, 1386, 1215, 784, 734, 669; M.S.(EI): 360 (M^+), 301 (M^+-$COOCH_3$); HRMS calculated: 360.0780 (M^+), experimental: 360.0778; $[\alpha]_D$-103 (c=1.02, $CHCl_3$).
15. Experimental procedure **2b**: To a solution of dipeptide **10** (95 mg, 0.18 mmol, 1.0 eq) in dichloroethane (7 mL) was added TFA (1.4 mL, 18 mmol, 0.1eq) and the reaction mixture stirred at 75°C for 2 days. TFA (0.5 mL) was added and the mixture stirred for additional 24 hours at 75°C. The solvent was evaporated to dryness yielding a residue which was purified by silica gel flash chromatography (1:1, ethyl acetate in hexane) to yield 41 mg of **2b**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.75 (m, 2H), 5.05 (m, 2H), 4.64 (d, J=9.0 Hz, 1H), 3.74 (s, 3H), 3.54 (dd, J=13.0 Hz J=12.0 Hz, 1H), 3.01 (dd, J=13.5 Hz J=6.5 Hz, 1H), 2.35-2.25 (m, 2H), 2.20-2.10 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.54, 166.45, 163.48, 133.33, 130.99, 122.64, 60.99, 58.57, 51.53, 49.06, 30.33, 28.97, 26.78; I.R. (n, film NaCl): 3025, 1728, 1385, 1210, 778; M.S. (EI): 360 (M^+), 301 (M^+-$COOCH_3$); HRMS: calculated: 360.0780 (M^+-$COOCH_3$) experimental: 360.0778; $[\alpha]_D$ -114 (c= 1.02, $CHCl_3$)
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