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DESIGN AND SYNTHESIS OF A PROTOTYPICAL NON-PEPTIDIC INHIBITOR MODEL FOR THE ENZYME RENIN

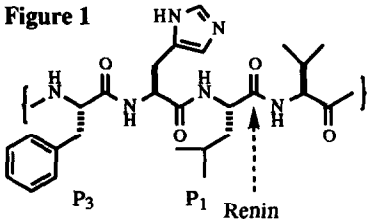
Stephen Hanessian* and Sadagopan Raghavan
Department of Chemistry, Université de Montréal
P.O. Box 6128, Succ. Centre-ville, Montréal, P.Q., Canada, H3C 3J7

Abstract: The synthesis of non-peptidic acyclic and conformationally constrained compounds is described with the intention of designing models and chemical intermediates, for an inhibitor of the enzyme renin.

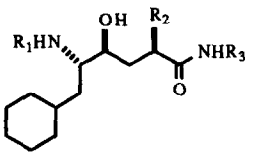
The release of the proteolytic enzyme renin in the blood stream is regarded as a primary step in the cascade of molecular events in the renin-angiotensin system, that leads to an increase in arterial blood pressure causing hypertension.[1] This important process is associated with the rate-limiting cleavage of a specific peptidic bond, at the Leu-Val site in angiotensinogen which leads to angiotensin I. Further enzyme-mediated cleavages produce angiotensins II and III, whose pharmacological effects are reflected in a variety of hemodynamic conditions.[2]

In view of the specificity of its action, and the importance of the disease, renin has been the target of intense research activity in the quest of finding an inhibitor substance that effectively mimics the natural peptide substrate. Remarkable success has been achieved toward this end, with the discovery of potent *in vitro* and *in vivo* inhibitors through the aegis of synthesis.[3] Much of this effort has been directed at structures in which the surrogate scissile Leu-Val bond is of a non-peptidic nature or consisting of an unnatural peptide.[4] The incorporation of a so-called "hydroxyethylene" isostere[5] in two general substructures shown as Type I and II (Figure 1), and the replacement of the Leu side-chain by a cyclohexylmethyl group,[6] have been the basis of a great deal of analog syntheses.[3,7,8]

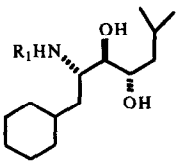
Figure 1



- - - Phe - His - Leu - Val - - -



Type I



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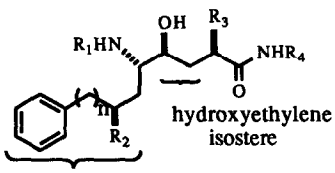
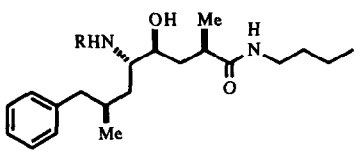


MODEL INHIBITOR PROTOTYPE



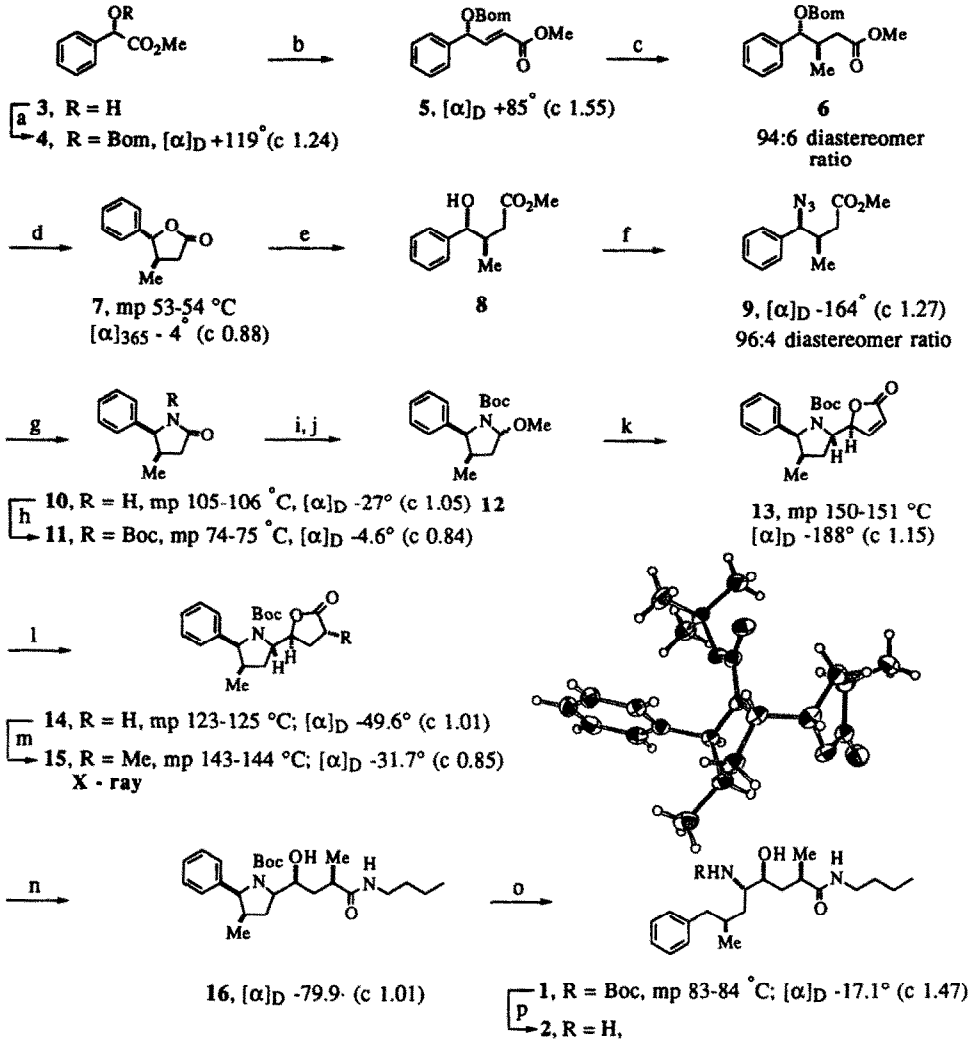
1, R = Boc; **2**, R = H

The need for increased oral bioavailability and longer duration of action have been added challenges in the quest for a marketable antihypertensive drug based on the inhibition of this enzyme. An important design element has taken advantage of increasingly available information from structure-activity relationships,[3] from molecular modeling[9] and NMR spectroscopy, and from X-ray analysis.[10] Clearly, one of the major challenges in the synthesis of such structures, is the control of absolute and relative stereochemistry of a minimum of three stereogenic centers bearing different functional groups.

Based on extensive SAR and molecular modeling studies carried out at Ciba,[11] we became interested in developing methodology for the synthesis of chemical intermediates to be used as rudimentary inhibitor prototype models (Figure 1). The prototype molecule shown in expression **1**, embodies functional and spatial features considered essential for minimal activity of a Type I substructure.[11] The amino alcohol subunit with an L-*threo*, configuration is a prominent feature, and the hydrophobic portion corresponding to the Leu side-chain of the natural substrate is simulated by a methyl and a benzyl group. This corresponds to an "extension" of the isobutyl side-chain of the Leu residue in the P_1 hydrophobic site towards the P_3 site, thus probing the spatial requirements of the extended S_1 and S_3 binding pockets. A conceptually similar strategy has been independently recently reported by the Parke-Davis group in relation to a Type II structure,[12] based on previous observations.[13]

In order to incorporate a benzyl group, and possibly secure stereochemical control over the "isolated" C-methyl branch in the hydrophobic domain of the intended target **1**, we devised a strategy that capitalizes partly on the Chiron approach where (*S*)-mandelic acid was used as a chiral template. It was our intention to use the inherent and resident chirality in (*S*)-mandelic acid for a systematic and stereocontrolled introduction of carbon, oxygen and nitrogen substituents by a sequence of reactions which were dependent on internal asymmetric induction. Scheme 1 illustrates the successful implementation of such a strategy which utilizes a stereocontrolled addition of 2-(trimethylsiloxy)-furan to a cyclic iminium ion intermediate.[14] Thus, the BOM ether derivative **4**, was extended via a two-step process to give the α,β-unsaturated ester **5**. The introduction of the C-methyl group in highly stereocontrolled manner was based on a conjugate addition of an organocuprate, recently published from our laboratories,[15] in which an *anti*-orientation was predominant. Compound **6** and its *syn*-isomer were obtained as a 94:6 mixture of diastereomers, contaminated with a small amount (~5% by NMR) of a deconjugated ester by product. Cleavage of the BOM group in the presence of TMSiBr[16] led to the crystalline lactone **7** in 72% overall yield (2 steps). Hydrolysis, careful acidification, esterification and introduction of the benzylic azido group using a Mitsunobu reaction[17] proceeded uneventfully to give **9**. Reduction of the azido group with 1,3-propanedithiol,[18] followed by formation of the N-Boc derivative gave the crystalline lactam **11**. Treatment with DIBAL-H and trapping the iminium ion with methanol under acid catalysis led to **12** as a mixture of anomers and rotamers. Lewis acid catalyzed condensation of **12** with 2-(trimethylsilyloxy)-furan[19] furnished the desired diastereomer **13** as a crystalline major product (6:1 threo/erythro). This stereochemical outcome[14,20] was in part predicated upon the intentional *syn*-disposition of the C-methyl and phenyl groups in **12**, thus assuring an *anti*-approach of the furan derivative and an (*S*)-configuration at the amine center (Figure 2). The crystallinity of the resulting major product, thus facilitating its isolation and purification, was an added bonus. With the butenolide moiety in place, the entire carbon framework of the intended target molecule had been efficiently assembled.Selective hydrogenation of the double bond led to the crystalline lactone **14**, which was subjected to C-methylation.[21] After extensive trials,[22] it was found that use of $(TMSi)_2NLi$ as base, gave the desired product **15** in acceptable yield, in addition

Scheme 1

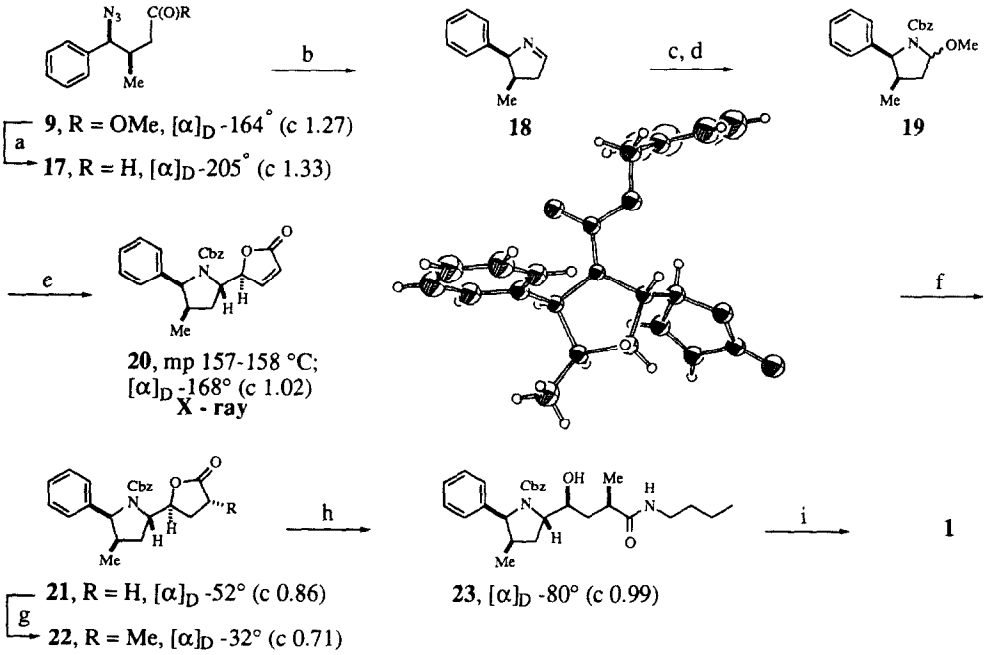


(a) $PhCH_2OCH_2Cl$, i-Pr_2EtN, CH_2Cl_2, rt, 100 h, 83%; (b) i. DIBAL-H, Toluene, -78 °C, 3 h 30 min; ii. MeOH, -78 °C, 30 min; iii. Methyltriphenylphosphoranylideneacetate, rt, 20min, 75%trans, 6%cis, (c) Me_2CuLi_2.3TMSCl, THF, -78 °C, 2 h; (d) TMSBr, CH_2Cl_2, -23 °C to rt, 16 h, 72% for 2 steps; (e) i. 0.5 N NaOH, MeOH, 0 °C to rt, 2 h; ii. 1N HCl; iii. CH_2N_2-Et_2O, EtOAc, 0 °C, 98%; (f) $(PhO)_2P(O)N_3$, DEAD, PPh_3, THF, 0 °C to rt 16 h, 89%; (g) 1,3-Propanedithiol, i-Pr_2EtN, MeOH, rt, 48 h, 86%; (h) $(Boc)_2O$, i-Pr_2EtN, DMAP, CH_2Cl_2, rt, 24 h, 99%; (i) i. DIBAL-H, Toluene, -78 °C, 4 h; ii. MeOH, -78 °C, 30 min, 72%; (j) CSA, MeOH, rt, 1 h, 100%; (k) 2-(trimethylsiloxy)-furan, $BF_3.Et_2O$, CH_2Cl_2, -78 °C, 1 h, (threo:erythro 6:1), 98%; (l) 10% Pd/C, H_2 (1atm), EtOAc, rt, 1 h, 93%; (m) i. $(TMS)_2NLi$, THF, -78 °C, 40 min; ii. MeI, -78 °C, 90 min, -50 °C, 1 h; iii. AcOH-THF, 67%; (n) $BuNHAlMe_2$, CH_2Cl_2, rt, 7 h, 76%; (o) 20% Pd $(OH)_2$, H_2 (56 psi), EtOH/EtOAc (2:3), rt, 48 h, 73%; p. aq. HCl, Dioxane, 0°C, 2h, quant.

to some (~15%) dimethylated product. Single crystal X-ray analysis of **15** confirmed its structure and stereochemistry unequivocably. Thus, the choice to bias the cyclic iminium ion intermediate from **12**, with the *syn*-orientated C-methyl and phenyl groups in anticipation of a stereocontrolled furan addition was justified. There now remained to open the lactone ring and to effect hydrogenolysis at the benzylic position to unveil the acyclic framework of the intended prototype model inhibitor. Treatment of **15** with dimethylaluminum butylamine[23] gave the pyrrolidine derivative **16**, which was subjected to hydrogenolysis in the presence of Pearlmans' catalyst[24] to give the target molecule **1** as a crystalline solid. Finally, treatment of **1** with aq. HCl in dioxane gave the amino analog **2**.

In an effort to probe the spatial and conformational relationship between the hydrophobic side-chain in **1** and the orientation of the amino group, we also considered the potential of a conformationally rigid analog such as the N-Boc pyrrolidine **16** and N-Cbz derivative **23** (Scheme 2). Application of the TMSi-furan condensation reaction in the N-Cbz series proceeded through the generation of the cyclic imine **18**, which was sequentially treated with benzyloxycarbonyl chloride, aq. acid and methanol in the presence of camphorsulfonic acid to give **19** as an anomeric and rotameric mixture. Treatment of **19** with TMSi-furan at -78°C in the presence of BF_3•Et_2O gave a

Scheme 2

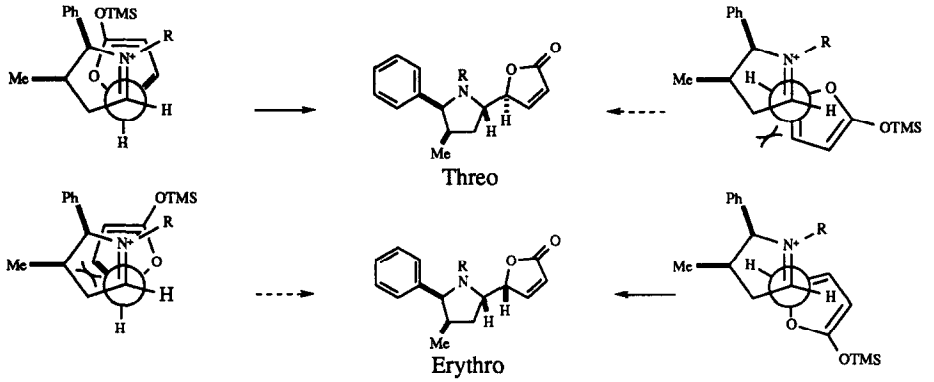


(a) i. DIBAL-H, Toluene, -78 °C, 1 h; ii. MeOH, -78 °C, 20 min, 77%; (b) PPh_3, Toluene, 16 h; (c) i. $PhCH_2C(O)Cl$, Toluene, -78 °C, 1 h; ii. 2N HCl, -78 °C to rt, 67%; (d) CSA, MeOH, rt, 1 h, 89%; (e) 2-(trimethylsiloxy)-furan, $BF_3.Et_2O$, CH_2Cl_2, -78 °C, 2 h, (threo:erythro 5:1) 78%; (f) 5% Pt/C, H_2 (1 atm), PhH, rt, 30 min, 90%; (g) i. $(TMS)_2NLi$, MeI, THF, -78 °C, 30 min; ii. satd. $NaHCO_3$, 57%; (h) $BuNHAlMe_2$, CH_2Cl_2, rt, 2 h, 52%; (i) $(Boc)_2O$, 20% $Pd(OH)_2$, H_2(60psi), MeOH/EtOAc (2·3), rt, 72 h, 46%.

mixture of *threo*- and *erythro* adducts in an isolated ratio of 5:1. An X-ray crystallographic analysis of the *threo*-isomer **20** confirmed its structure definitively. Reduction of the double bond and methylation of the enolate gave the C-methylated lactone **22** as the major product. Finally, opening of the lactone gave the desired amide **23**.

It is of interest that the TMSi-furan reaction proceeded smoothly with **12** and with **19** to give the corresponding *threo*-adducts as major isomers. Two plausible transition states can be envisaged to explain these results. However, as previously remarked,[14a,b] a clear distinction between the different orientations of the furan ring vis-a-vis the iminium ion that benefit from the best electronic and stereoelectronic features of the reacting partners, is difficult to ascertain (Figure 2).

Figure 2



The cyclic structures **16, 23** as well as the intended inhibitor model **1** showed no activity in the binding affinity assay (IC_{50} >100 μM). In contrast, the *amino* derivative **2** exhibited weak activity (IC_{50} 37μM).[25] It is possible therefore that further refinements in this simple prototype structure will lead to stronger inhibition of the enzyme, and eventually to a pharmacokinetic profile that is commensurate with the activity.[26,27]

Acknowledgments

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27. All new compounds were satisfactorily characterized by spectroscopic (^{1}H NMR, ^{13}C NMR), mass spectral (high resolution), and microanalytical methods. Melting points are uncorrected and optical rotations were recorded at 25°C.

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