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ASYMMETRIC SYNTHESIS OF NOVEL QUATERNARY α-HYDROXY-δ-LACTAM DIPEPTIDE SURROGATES[1]

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Abstract: Application of the Sharpless AD protocol to a series of α-(*E*)-benzylidene-δ-lactam precursors followed by selective deoxygenation provided efficient synthetic routes to the chiral quaternary α-hydroxy-γ-lactam derivatives **4** and **5**. These functionalized intermediates and the diol precursors **3** are regarded as novel types of D-Phe-Pro dipeptide surrogates that are useful as enzyme active site probes.

Serving as attractive scaffolds for drug design and conferring more "drug-like" characteristics into numerous structural motifs, lactam,[2] pyridone,[3] and related heterobicyclic[4] systems are finding increasing applications in organic and medicinal chemistry. The backbone structures of these rigidified peptidomimetics maintain or restrict biologically relevant dihedral angle, conformational, and stereochemical information derived from a parent peptide array. Furthermore, they can effectively mimic the i + 1 and i + 2 residues of type II' β-turn conformations while incorporating critical hydrogen bond donor and acceptor β-sheet elements such as amide NH and carbonyl groups. Judicious choice of backbone appendages permits the presentation of cationic, anionic, polar, or hydrophobic functionality for probing the specificity pockets of either a protease active site or receptor binding site. Potentially enhanced binding affinity would result in inhibitors with increased potency and selectivity profiles.

Recently, lactam sulfonamide **1a** (CVS 1578[2c]), quaternary amino variant **1b** (CVS 1897[5a]) and ester **1c** (CVS 1832[5b,c]) were identified in our laboratories as potent (K_i ~ 1 nM) transition-state thrombin inhibitors. The P_2-P_4 moieties in **1a–c** are regarded as novel types of D-Phe-L-Pro dipeptide surrogates. Critical hydrogen bond β-sheet elements between the lactam α-NH and carbonyl groups with the Gly216 active site residue were evident in the X-ray crystal structure of the **1a**-thrombin complex.[2,6] Combining these observations with the topology of **1b,c**, a novel series of lactam targets **2** were designed wherein the lactam α-amino group is replaced with quaternary α-(*R*)-hydroxy- or α-(*R*),β'-(*S*)-diol moieties (Figure 1). Modeling and in vitro SAR suggested that the former α-(*R*)-hydroxyl may effectively mimic the lactam α-NH by hydrogen bonding with Gly 216, while the

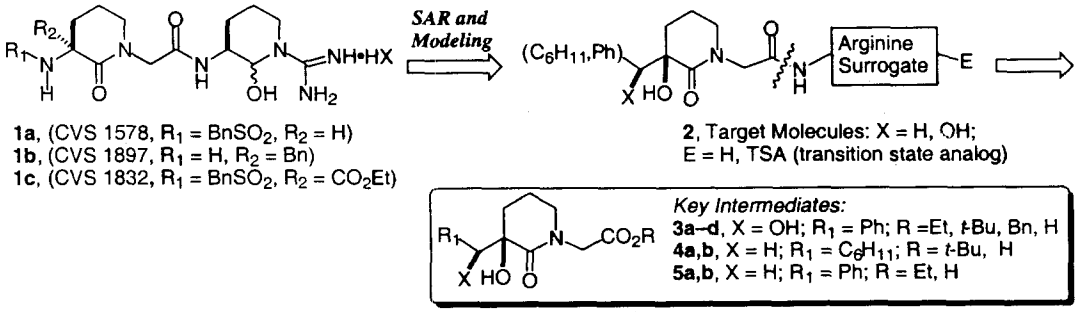

Figure 1: Design of second generation quaternary α-hydroxylactam intermediates **3–5**.

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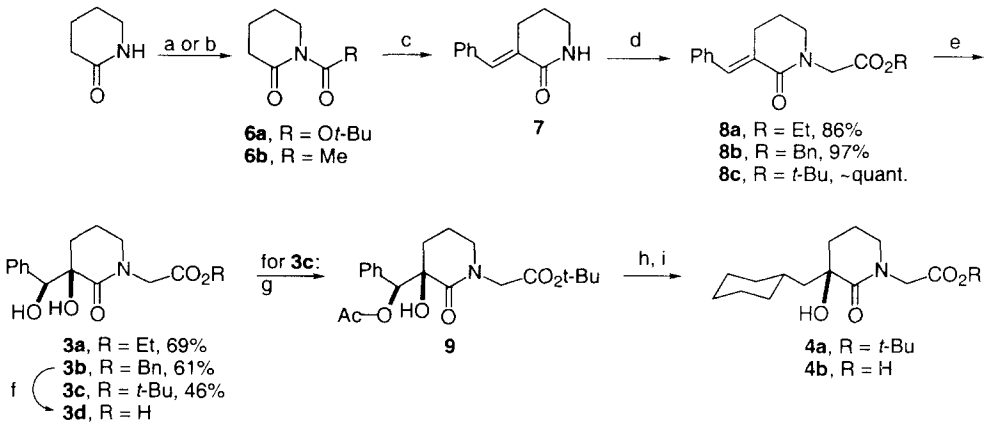
latter α-(*R*),β'-(*S*)-diol has the additional potential of mimicking a water molecule at S3 in the enzyme active site. The synthesis of the chiral quaternary α,β'-diol intermediates **3a–d** and α-hydroxy intermediates **4a,b** and **5a,b**, necessary for the construction of these antithrombotic targets, will be presented in this letter.

We envisioned an asymmetric synthesis strategy for the construction of the key intermediates **3**, **4**, and **5**. Application of the Sharpless asymmetric dihydroxylation protocol[7] to an appropriate trisubstituted (*E*)-arylidene lactam substrate was deemed attractive for the stereocontrolled generation of the requisite α-(*R*),β'-(*S*)-diol intermediates **3a–d**. Selective aromatic reduction and/or hydrogenolysis of the benzylic hydroxyl residue would then deliver the α-(*R*)-lactam targets **4** and **5**. Our foray towards intermediates **4a,b** is outlined in Scheme 1.[8] Activation of δ-valerolactam as the N-Boc (**6a**)[9] or N-acetyl (**6b**)[10] derivatives followed by aldol condensation provided an improved route to the known (*E*)-benzylidene lactam **7**.[10a,c] The intermediates **8a–c** were prepared in multigram quantities and in high yields by alkylation of **7**. Lithium bis-trimethylsilylamide was the preferred base, and reactions with ethyl-, benzyl- or *t*-butyl bromoacetate proceeded smoothly.

Asymmetric dihydroxylation of the substrates **8a–c** with commercial AD-mix-α® (Aldrich) and methanesulfonamide under standard conditions[7a] proceeded slowly over the course of several days and provided the corresponding adducts **3a–c** in acceptable yield but with only modest enantioselectivity (crude products ca. 3:1 to 11:1 enantiomeric ratio).[11] However, increasing the potassium osmate catalyst loading to ca. 2% dramatically increased the reaction rate and selectivity, now delivering the desired adducts **3a–c** in satisfactory yield and with significantly improved enantiomeric ratios that ranged from 27:1 to ca 65:1 (crude product).[12] A single trituration or recrystallization (hexane, ether mixtures) afforded α-(*R*),β'-(*S*)-lactams **3a–c** of ≥99% e.e. in 49–69% isolated yield. To the best of our knowledge, this is the first example of the application of the AD process to (*E*)-arylidene lactam substrates.[12b,13] Catalytic hydrogenolysis of benzyl ester **3b** afforded the corresponding carboxylic acid **3d** quantitatively, which was subsequently shown to participate in typical amide bond forming reactions without prior protection of the diol moiety.

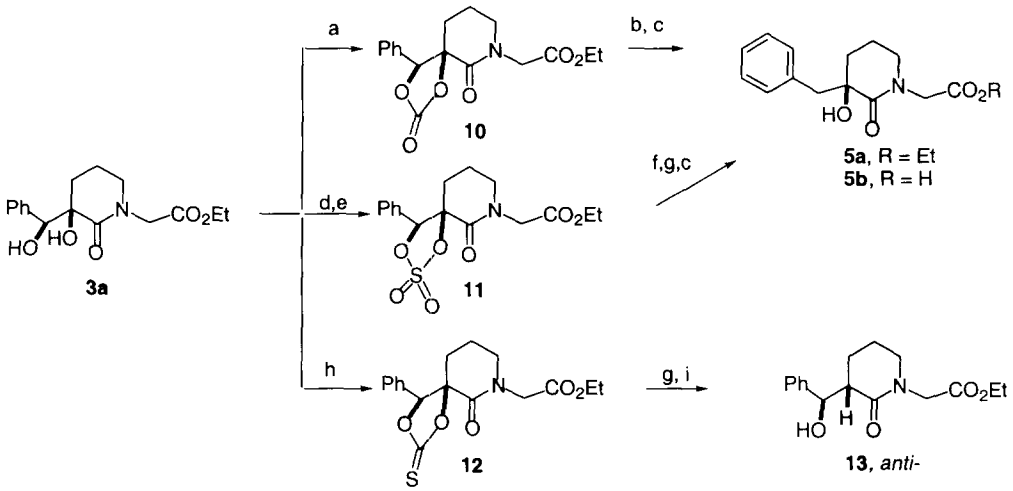


Scheme 1: *Reagents and Conditions:* (a) for **6a:** Boc_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 80%; (b) for **6b:** Ac_2O, NaOAc, reflux, 83%; (c) PhCHO, NaH, MeOH, THF, 5 °C to rt, HOAc, 33% from **6a**, 56% from **6b**, only (*E*)-isomer detected; (d) LiHMDS, THF, $BrCH_2CO_2R$, 0 °C to rt; (e) 2% K_2OsO_4, AD-mix alpha, *t*-BuOH, H_2O, $MeSO_2NH_2$, rt, 46-69% after recrystallization; (f) for **3b**: H_2, Pd/C, EtOH, 35 psi, ~quant.; (g) Ac_2O, pyridine, DMAP, THF, 0 °C to rt, 77%; (h) H_2, Pd/C, EtOH, HOAc, H_2O, 50 psi, 37%; (i) TFA, CH_2Cl_2, 0 °C to rt, ~quant.

Numerous attempts to selectively deoxygenate the benzylic hydroxyl of **3a–c** without prior conversion to a more active leaving group were unrewarding, returning only complex mixtures or poor yields of desired product. Attempted formation of mesylate, tosylate or epoxide derivatives were also unfruitful. However,

conversion of **3c** to acetate **9**, exhaustive hydrogenolysis to α-(*R*)-hydroxy-lactam **4a** and ester cleavage to target carboxylic acid **4b** proceeded in 29% overall yield.

Complimentary synthetic approaches to the α-(*R*)-hydroxy-α-benzyllactam targets **5a,b** are shown in Scheme 2. Quantitative conversion of **3a** to the cyclic carbonate **10**, followed by low-pressure hydrogenolysis, rapidly effected benzylic deoxygenation and produced **5a** in 52–62% yield. Extension of the reaction time beyond one hour resulted in complete hydrogenolysis to give racemic α-benzyllactam (not shown), suggesting that the putative quaternary carbonic ester intermediate is highly prone towards further reduction. We were surprised that such a sterically hindered moiety, α- to a carbonyl function, would suffer such facile deoxygenation. Base-catalyzed hydrolysis of **5a** delivered the target carboxylic acid **5b**. Our second approach to **5a** commenced with a two-step conversion of **3a** to the cyclic sulfate **11** using Sharpless conditions.[14] Ring opening of **11** with lithium bromide proceeded smoothly and was followed by radical dehalogenation using the Chatgilialoglu protocol[15] to afford **5a** in good overall yield.



Scheme 2: *Reagents and Conditions:* (a) CDI, THF, rt to reflux, ~quant.; (b) H_2, Pd/C,15 psi, EtOH, H_2O, <1 h, 52–62%; (c) NaOH, EtOH, H_2O, 0 °C to rt; H^+, 88%; (d) $SOCl_2$, Et_3N, THF, 0 °C to rt; (e) $NaIO_4$, $RuCl_3$, CH_3CN, CCl_4, H_2O, 0 °C to rt, 95%; (f) LiBr, THF, rt to reflux, 80%; (g) $(Me_3Si)_3SiH$, AIBN, toluene, 100 °C, 75%; (h) $Im_2C{=}S$, THF, reflux, 94%; (i) 3% HCl, Et_2O, 47%.

An interesting result was obtained when the cyclic thiocarbonate derivative **12** was subjected to thermal radical-generating conditions. Instead of the desired regioisomer **5a**, we isolated only the *anti*-β-hydroxy lactam derivative **13**, which was formed in an unoptimized yield of 47%. The ^{1}H-NMR spectrum showed the benzylic methine as a doublet at $\delta = 4.70$ ppm with $J = 9.5$ Hz, clearly in agreement with literature values for an *anti*-aldol product.[16] Mechanistically, radical-mediated fragmentation of **12** could proceed by two different pathways, ultimately producing either **5a** or **13**. It is unclear as to why **5a** was not produced, since, *a priori*, we predicted that a benzylic radical would be favored for this system. Based on the observed stereochemistry of **13**, hydrogen atom addition must occur at the most sterically accessible face of the presumed tertiary radical intermediate, a result consistent with recent literature reports on radical reductions with this bulky silane reagent.[17]

In conclusion, practical and efficient asymmetric syntheses of **3a–d**, **4a,b**, and **5a,b** were developed which serve as novel types of D-Phe-L-Pro dipeptide surrogates. Construction of the appropriate (*E*)-benzylidene lactam precursors, application of a modified Sharpless AD protocol, and selective reduction or deoxygenation steps led to these key intermediates in good overall yield and with high stereocontrol. The radical-initiated conversion of thiocarbonate **12** to *anti*-β-hydroxy lactam **13** is a novel process and may be of considerable utility

as an alternative to asymmetric directed aldol condensations. Furthermore, we envision that similar elaboration of the corresponding (*Z*)-trisubstituted olefin precursors would provide a convenient route to chiral *syn*-β-hydroxy lactams. This technology would in turn further enhance the utility of the Sharpless AD reaction. Such quaternary α-Hydroxylactam derivatives may find utility in the design and synthesis of new classes of drug targets especially protease inhibitors. The design, chiral synthesis, application, and evolution of related lactams is under active study in our laboratories, and the results of these investigations will be reported in due course.

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