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Efficient Construction of Novel Quaternary Lactam Dipeptide Surrogates

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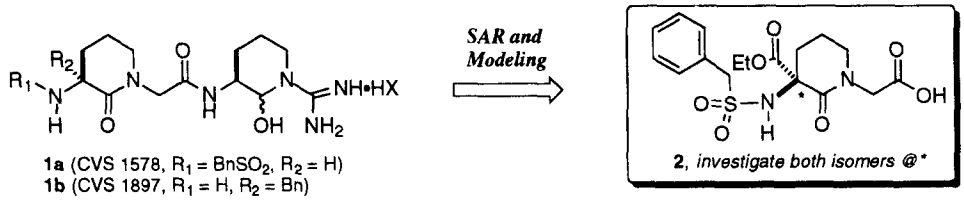
Abstract: Concise, facile synthetic routes to the hindered quaternary α-aminolactam intermediates **2**, **10** and **12** were developed. These functionalized intermediates ultimately serve as novel types of Phe/nor-Asp-Pro dipeptide surrogates which in turn are useful as enzyme active site probes.

Design and synthesis of novel drug candidates incorporating lactam,[1] pyridone,[2] and related heterobicyclic[3] scaffolds is currently an area of intensive investigation in the field of medicinal chemistry. The backbone structures of these interesting 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 and incorporate critical hydrogen bond donor and acceptor β-sheet elements such as amide NH and carbonyl groups.

The novel lactam sulfonamide derivative **1a** (CVS 1578[1a,b]) and the quaternary amino variant **1b** (CVS 1897[1b,4a]) were recently identified in our laboratories as potent (Ki ~ 1 nM) transition-state thrombin inhibitors. Such lactam systems serve as novel types of d-Phe-Pro dipeptide mimics. Employing X-ray structural information[1a] along with various topological considerations, the new peptidomimetic key intermediate **2** was designed which features a quaternary lactam moiety[4] containing both α-benzylsulfonamido and α-ester residues. (Figure 1). This novel template may be regarded as a hybrid type of Phe/nor-Asp-Pro dipeptide mimic. Judicious substitution on the lactam ring positions with hydrophilic and/or hydrophobic groups, which can now be considered as rigidified amino acid sidechain residues, provides additional handles for probing a biological target site. Such motifs may therefore possess a range of useful structural features that help stabilize interactions in a receptor or active site of a targeted enzyme. Synthetic approaches to the key quaternary lactam intermediates **2**, **10**, and **12** will be presented herein.



1a (CVS 1578, R_1 = $BnSO_2$, R_2 = H)
1b (CVS 1897, R_1 = H, R_2 = Bn)

Figure 1: Design of quaternary lactam advanced intermediate **2**.

Our foray towards the preparation of an attractive α-nitro quaternary lactam intermediate **5** was thwarted by some unexpected chemistry as outlined in Scheme 1.[5] We envisioned that generation of intermediate **4** would be followed by a rapid in situ cyclization process to deliver lactam **5**. A Michael-type addition reaction to produce

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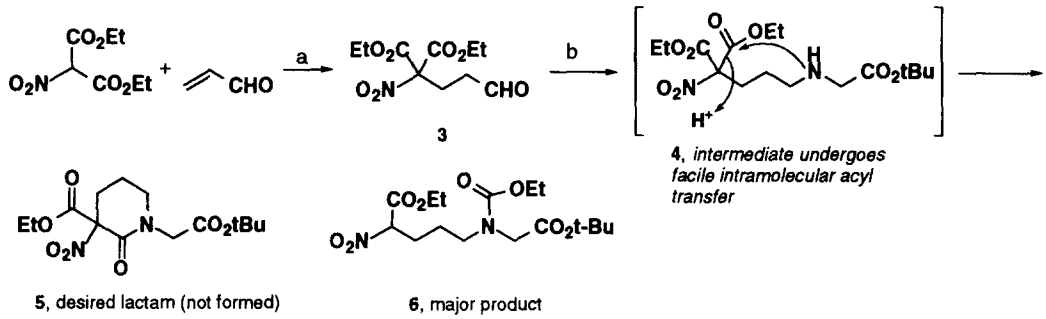
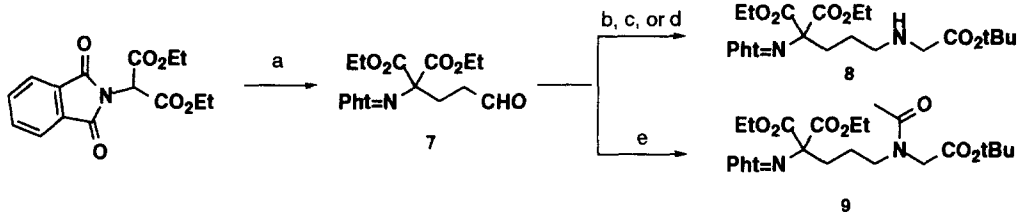
3 proceeded smoothly. However, reductive amination protocols with **3**, glycine t-butyl ester and $Na(OAc)_3BH$[6] or $NaBH_4$ generated the presumed intermediate **4**, which apparently underwent a facile intramolecular acyl group transfer to deliver **6** as the major isolable product. No trace of **5** was observed under these conditions.



Scheme 1: *Reagents and Conditions:* (a)1. NaOEt (cat.), EtOH, rt; 2. HOAc, 71%, 9 g scale; (b) HCl•GlyO-tBu, $Na(OAc)_3BH$, DCE, Et_3N, HOAc, rt, 61% *or* HCl•GlyO-tBu, $NaBH_4$, Et_3N, MeOH, rt to 50° C,18 hr, ~85%.

A second approach to the related quaternary α-amino lactam intermediate **12** is outlined in Schemes 2 and 3. A convenient Michael addition process produced intermediate **7** in multi-gram quantities. Various reductive amination reactions were investigated (Scheme 2) and we determined that the $Na(OAc)_3BH$ protocol was the safest and most convenient route to amine **8**. Prolonged reaction times led to the N-acetyl byproduct **9**. Thermal cyclization of sterically encumbered intermediate **8** to the desired quaternary lactam intermediate **10** was investigated under a wide variety of conditions (Scheme 3, Table 1). This proved to be a difficult, slow reaction and of the 20 variations investigated, we found 2-propanol or t-butanol solvents in the presence of 10 equiv. anhydrous sodium acetate[4c], optionally in the presence of catalytic acetic acid in a sealed tube at 120-175°, to be the optimal conditions for providing modest yields of product **10**. The phthalimido ring-opened byproducts **11** were

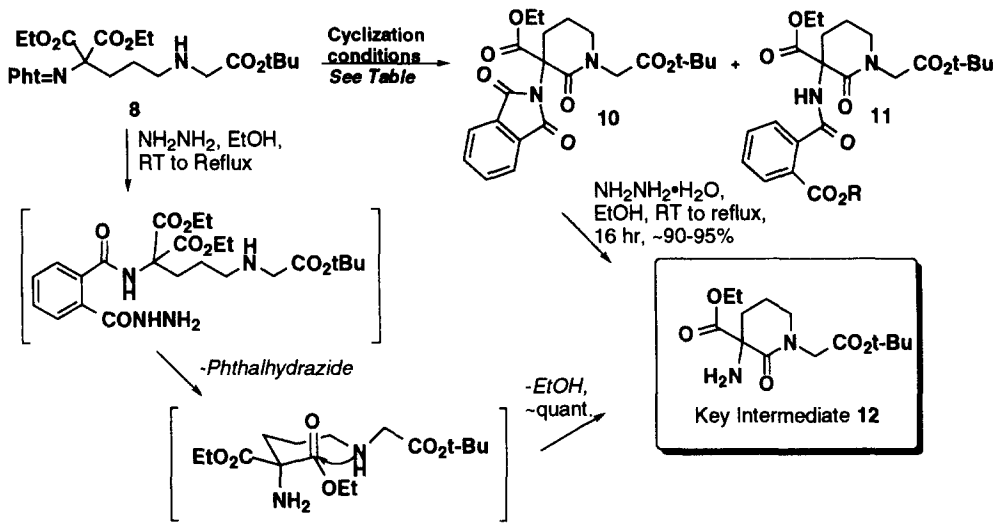


Scheme 2: *Reagents and Conditions:* (a) 1. Acrolein, DIPEA, EtOH, 0° C to rt, 3 d; 2. HOAc, 72 %, 20-25 g scale *or* 1. NaOEt (cat.), EtOH, 0° C to rt, 1 d; 2. HOAc, 38%, 5-10 g scale; (b)1. HCl• GlyO-tBu, Et_3N, EtOH, rt; 2. H_2, Pd/C, 1 atm, ~27-40%; (c) HCl•GlyO-tBu, $NaCNBH_3$, EtOH, rt, 79 %; (d) HCl•GlyO-tBu, $Na(OAc)_3BH$, DCE, Et_3N, rt, 65-68%, 9-15 g scale; (e) HCl•GlyO-tBu, $Na(OAc)_3BH$, DCE, Et_3N, rt to 50° C to reflux, 7 d, 44%.

identified as the major byproducts. Hydrazinolysis of **10** under standard conditions delivered the desired key intermediate **12** in high yield.

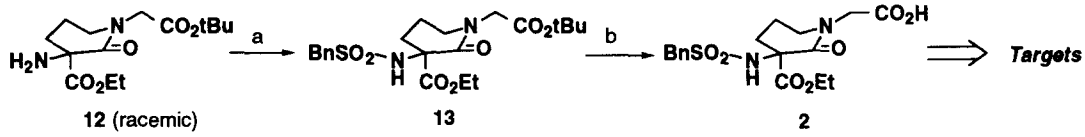
A third approach to the quaternary α-amino lactam intermediate **12** is outlined in Scheme 3. Cognizant that the difficulties of the thermal cyclization process to afford **10** were due to the sterically hindered nature of precursor **8**, we were intrigued by the possibility of removing the bulky phthalimido moiety first and determining the fate of the resulting amino intermediate. We were delighted to find that hydrazinolysis of **8** led via the

intermediates depicted in Scheme 3 directly to the key lactam **12** in essentially quantitative yield. The reaction proceeds under very mild conditions and gives >95% isolated yields of product on multigram scales.



Scheme 3: Cyclization studies to key intermediates **10** and **12**. See Table 1 and text.

Elaboration of the key intermediate α-aminolactam **12** is outlined in Scheme 4. Due to the sterically hindered nature of intermediate **12**, reaction with benzylsulfonyl chloride appeared to be a rather slow and capricious process, giving yields of **13** ranging from 45-62%. The conditions summarized below in the scheme were optimal for the formation of product **13**. Finally, treatment of **13** with TFA under standard conditions delivered the carboxylic acid derivative **2** which served as the key intermediate for the preparation of novel classes of protease inhibitors.[7]



Scheme 4: *Reagents and Conditions*: (a) $BnSO_2Cl$, Et_3N, DMAP, CH_3CN, 0° C to rt, 62%; (b) TFA, CH_2Cl_2, 0° C to rt, 82-85%

In conclusion, practical and efficient syntheses of **2**, **10**, and **12**, which serve as novel Phe/nor-Asp-Pro dipeptide surrogate precursors, were developed which feature cyclization of sterically hindered intermediates. Hydrazinolysis of **8** led directly to the key racemic intermediate **12** in essentially quantitative overall yield. Such densely functionalized quaternary lactam derivatives may find utility in the design and synthesis of new classes of drug targets. 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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Table 1. Thermal cyclization studies. Quaternary lactam **10** ring formation.

Expt.#	Conditions	%10	%11
	Sealed Tube Reactions @ [0.1M]: [a]		
1	MeOH, NaOAc, HOAc (cat); 105°, 8 h	none	70 (R= Me) + polar byproducts
2	EtOH, NaOAc, HOAc (cat); 105-110°, 6 h	11	63 (R = Et)
3	EtOH, NaOAc, *no* HOAc; 105-120°, 25 h	32	20 (R= Et)
4	EtOH, HOBt; 110°, 7 h	complex	mixture
5	i-PrOH, NaOAc, HOAc (cat.); 110°, 18 h	no	reaction
6	i-PrOH, NaOAc, HOAc (cat),120°, 63 h; 140°, 14 h	46	23 (R= i-Pr)
7	i-PrOH, NaOAc, HOAc (cat); 150°, 19 h	22	20 (R= i-Pr)
8	i-PrOH, NaOAc, *no* HOAc; 150°, 14 h	34	15 (R= i-Pr)
9	t-BuOH, NaOAc, HOAc (cat); 110-140°, 13 h	no	reaction
10	t-BuOH, NaOAc, *no* HOAc; 160°, 13 h; 175°, 68 h	40	N.D.
11	Toluene, DME, HOBt; 105-110°, 14 h	trace	minor byproducts
12	Toluene, DME, HOBt; 150°, 19 h	24	several byproducts
13	DCE, HOBt; 140°, 14 h	complex	mixture
	Other Reactions:		
14	Toluene [0.2M]; 110°, 26 h	no	reaction
15	Toluene [0.2M],1-2 eq. DBU; 110°, 22 h	no	reaction
16	Xylene [0.2 M], 1-3 eq. DBU; 140°, 1-15 h	decomposition	products
17	EtOH, HOBt; reflux, 21 h	trace	of product
18	EtOH, AcCl, pH~1; RT, 16 h	ring-opened	products
19	THF, NaH; RT to reflux, 14 h	polar	products
20	DMF; reflux, 3-17 h	complex	mixture

[a]All reactions with sodium acetate employed 10 equiv. of anhydrous reagent.

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