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REDUCTIVE ROUTES TO RIGID PEPTIDE BUILDING BLOCKS: THE DEPENDENCE OF A REGIOSELECTIVE IMIDE REDUCTION ON THE NATURE OF AN α-ALKOXY SUBSTITUENT

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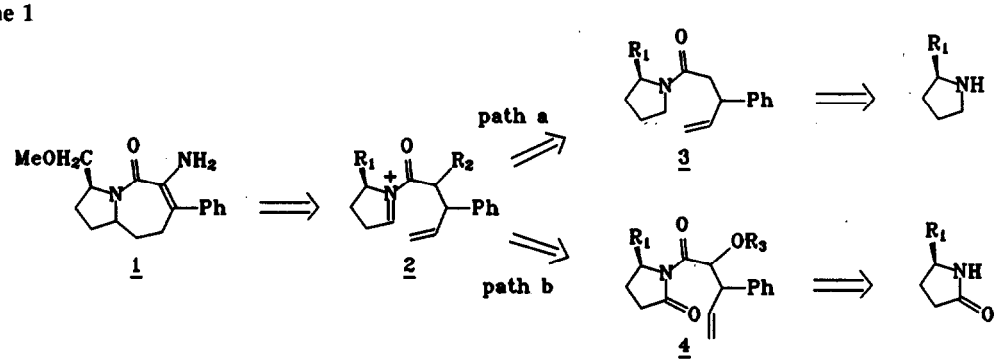
Abstract: The reduction of several *N*-acylpyrrolidinones has been studied. The regioselectivity of the reductions was found to depend on the nature of the *N*-acyl group. In one example, the use of a sterically bulky triisopropylsiloxy substituent alpha to the *N*-acyl carbonyl led to exclusive reduction of the pyrrolidinone carbonyl and the formation of a product that could be used in the synthesis of the 1-azabicyclo[5.3.0]decane ring skeleton found in a key bicyclic Pro-Phe building block.

In conjunction with our efforts to synthesize a series of conformationally restricted thyroliberin (TRH) analogs,[1] we recently reported the use of an anodic amide oxidation based annulation procedure for constructing the key bicyclic Pro-Phe building block 1 (Scheme 1, path a).[2]

Scheme 1



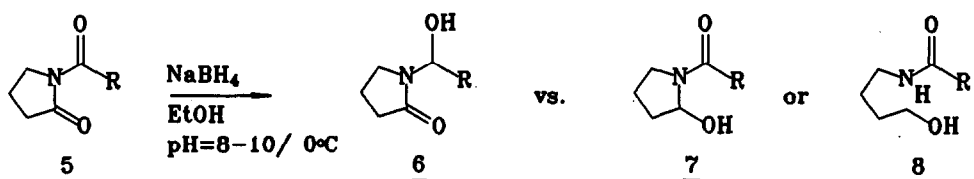
Although this oxidation based route proved very successful for the synthesis of 1 and looks to be applicable to a number of Pro-X building blocks, its generality with respect to building blocks with oxidation sensitive functionality is the cause of some concern. In particular, the use of an amide oxidation based strategy precludes the incorporation of histidine, tryptophane, or cysteine amino acid units into the conformationally restricted building blocks. Clearly, a complimentary reductive pathway to the bicyclic lactam ring systems would be desirable for occasions where incorporation of these amino acid units into restricted peptide building blocks is essential.

One potentially attractive reductive pathway is outlined in Scheme 1 (path b). This pathway would

involve the annulation of a seven-membered ring lactam onto a pyroglutamate based starting material. In this scenario, both reductive and oxidative pathways would originate from simple amino acid derivatives. However, the reductive pathway outlined would require the regioselective reduction of an *N*-acylpyrrolidinone.[3] To date, such a regioselective reduction has not been reported. Most studies concerning the regioselective reduction of unsymmetrical imides have been restricted to cyclic imides. In these examples, the regioselectivity of the reductions was dramatically influenced by neighboring substituents.[4] For example, geminal substituents at C_3 of succinimide led to reduction of the proximal imide carbonyl at C_2,[5] whereas geminal substituents at C_3 of glutarimide led to reduction of the distal imide carbonyl at C_6.[6] In addition, neighboring alkoxy groups have been shown to lead to selective reduction of the proximal imide carbonyl;[7] an observation that would predict reduction of the wrong carbonyl in the synthetic scheme suggested above. In 1986, the regioselective reduction of several related *N*-alkoxycarbonyl lactams (R = OR' in **5**) was reported, however, attempts to effect the regioselective reduction of the corresponding *N*-acyl lactams were not successful.[8]

We report herein that *N*-acylpyrrolidines can be reduced in a regioselective fashion and describe the factors that govern the regioselectivity of these reactions. The results of this initial study are summarized in Table 1.

Table 1



5 **6** **7** **8**

Entry	Compound[a]	R	Yield 6[b]	Yield 7[b]	Yield 8[b]
1.	**5a.**	$-(CH_2)_8CH=CH_2$	36%	30%	--
2.	**5b.**	$-CH_2OCH_2Ph$	64%	--	--
3.	**5c.**	$-^tBu$	--[c]	68	--
4.	**5d.**	$-CH(OBz)CH(Ph)CH=CH_2$	56%	--	--
5.	**5e.**	$-CH(OSi^iPr_3)CH(Ph)CH=CH_2$	--	--	81%
6.	**5f.**	$-CH(OSiMe_2{}^iPr)CH(Ph)CH=CH_2$	15%[d]	--	34%

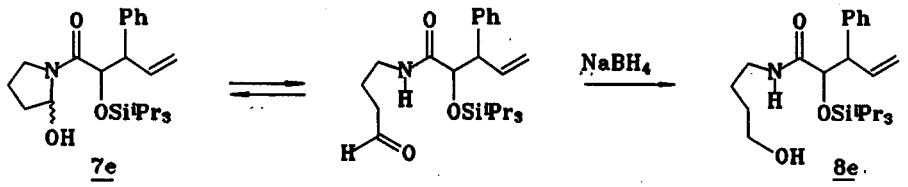
a. Imides **5a-f** were synthesized from pyrrolidinone and the corresponding acid chloride. *b.* The yields reported are unoptimized and indicate the amount of compound isolated after silica gel chromatography. *c.* An approximately 7% yield (by integration) of pyrrolidinone was observed in the ^1H NMR spectrum of the crude reaction mixture. *d.* By capillary column GC the crude reaction product was a 1:1 mixture of isomers. Some of **6f** was lost upon silica gel chromatography.

Compound **5a** was treated with $NaBH_4$ at a controlled pH of 8-10 in order to determine the inherent selectivity of the reductions. In this example, no preference was shown for the reduction of either carbonyl.[9] The reduction of compounds **5b** and **5c** quickly established that the regiochemistry of the reaction could be controlled in either direction by proper substitution of the carbon alpha to the imide carbonyl on the side chain. As in earlier imide reductions, an alkoxy group (**5b**) was shown to activate the proximal carbonyl for nucleophilic attack and led

to the reduction of the carbonyl on the side chain.[10] The placement of steric bulk at this position (**5c**) directed the reduction toward the carbonyl on the ring away from the steric hinderance.

Imides **5d-f** were examined in order to determine the selectivity of the reductions when sterics and α-alkoxy group activation were placed in direct competition. In case **5d**, the use of a benzyloxy group led to a 56% isolated yield of **6d** in spite of the steric bulk of the side chain. None of the desired reduction product **7d** was obtained. The use of bulkier reducing agents did not change the regioselectivity of the reduction. Fortunately, *exchange of the benzyl protecting group for a very bulky triisopropylsilyl protecting group led to clean reduction o the carbonyl on the ring.* In this example, the reduction of **5e** led to an 81% isolated yield of primary alcohol **8e**. Alcohol **8e** was derived from the opening of **7e** under the reaction conditions to form an aldehyde followed by a second reduction (Scheme 2). Product **7e** was never observed. When the reductions were cooled to -40°C

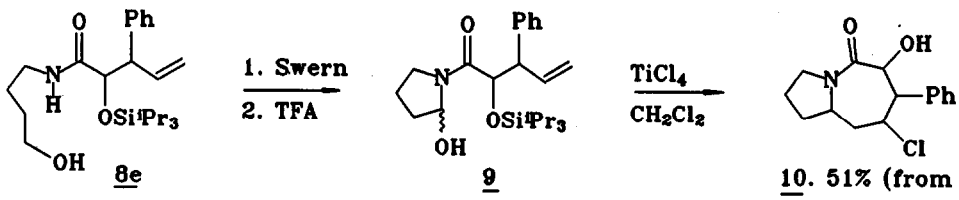
Scheme 2



and carried out to partial conversion, alcohol **8e**, a trace of aldehyde, and unreacted starting material were obtained. This result indicated that the opening and subsequent over reduction of **7e** proceeded faster than the initial reduction of **5e**. No product derived from initial reduction to form **6e** was obtained from any of the reductions of **5e**. The use of the less bulky dimethylisopropylsilane protecting group (**5f**) led to an *ca.* 1:1 mixture of products. Even with the use of the smaller protecting group, the reaction still led to the formation of over reduced product.

Alcohol **8e** was converted back to an *N*-α-hydroxyalkyl amide **9** with the use of a Swern oxidation followed by treatment with triflouroacetic acid (Scheme 3). The initially desired annulation procedure was completed by the cyclization of **9** with titanium tetrachloride in dichloromethane. The 1-azabicyclo[5.3.0]decan-2-one ring skeleton was obtained in a 51% isolated yield over the three steps.

Scheme 3



In conclusion, it was found that the regioselectivity of *N*-acylpyrrolidinones reductions can be controlled by a substituent alpha to the *N*-acyl carbonyl. The use of a triisopropylsiloxy group at this position led to the regioselective reduction of the pyrrolidinone carbonyl and allowed for the development of procedure to effect the net annulation of a seven membered ring lactam onto a pyrrolidinone. Studies aimed at determining the utility of this method for providing a reductive alternative to previously developed oxidation route to bicyclic

peptide building blocks like **1** are currently underway. The results of these studies will be reported in due course.

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