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ANODIC AMIDE OXIDATIONS: A NOVEL SYNTHESIS OF THE ANGIOTENSIN-CONVERTING ENZYME INHIBITOR A58365A

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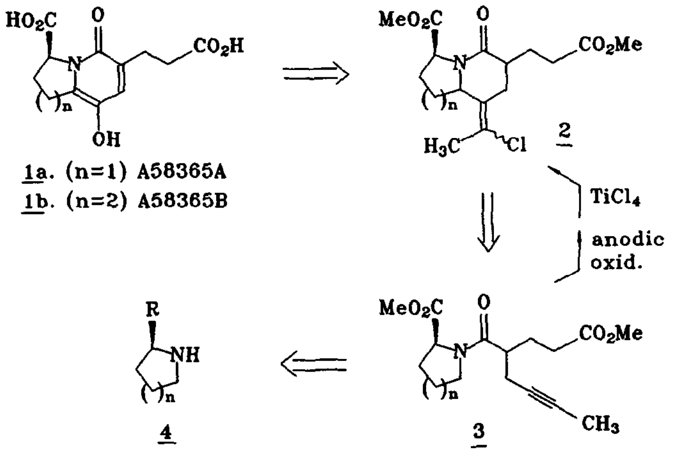
Abstract: An anodic amide oxidation based annulation procedure for fusing lactam rings onto amines has been used to construct the angiotensin-converting enzyme inhibitor A58365A.

In principle, the anodic amide oxidation reaction[1] holds great promise as a tool for constructing the lactam rings often found in medicinally active enzyme inhibitors and conformationally restricted peptide mimetics.[2] The potential of this reaction centers around the ability of electrochemistry to selectively functionalize amino acid derivatives, and the possibility that anodic amide oxidations can lead to a general procedure for annulating rings onto amines and amides.[3] For example, the potent angiotensin-converting enzyme inhibitors A58365A (**1a**) and A58365B (**1b**) can both be viewed as arising from the net annulation of a lactam ring onto an amino acid derivative (Scheme 1).[4,5] In this scenario, the key bicyclic ring skeleton would be constructed from amide precursor 3 *via* a sequential anodic amide oxidation-Lewis acid catalyzed cyclization sequence. A synthetic route of this nature would be ideal because it could lead to the synthesis of both A58365A and A58365B by simply altering the size of the ring in the starting amine.

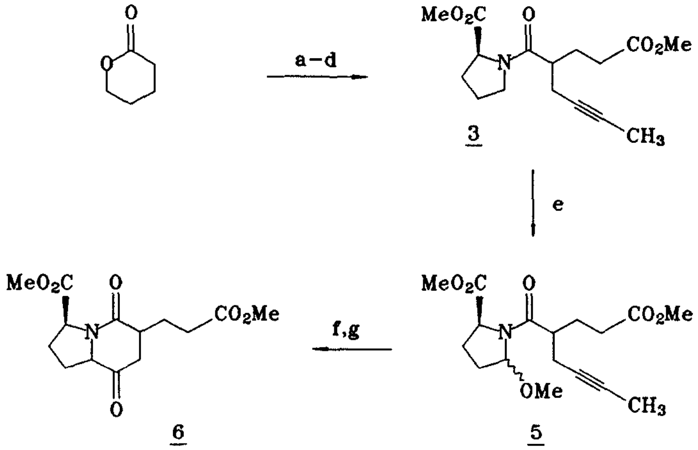
Scheme 1



In spite of this potential, anodic amide oxidations have not been extensively studied as a method for constructing either lactam based enzyme inhibitors or rigid peptide analogs.[6] With this in mind, we initiated a program aimed at determining the feasibility of an anodic amide oxidation based route for synthesizing both A58365A and A58365B. We report here a convenient asymmetric synthesis of A58365A.

The synthesis of oxidation substrate **3a** (n = 1) was accomplished by alkylation of δ-valerolactone with 1-bromo-2-butyne, conversion of the lactone to an amide by treatment with (S)-(+)-pyrrolidinemethanol and trimethylaluminum in refluxing toluene,[7] oxidation of the resulting diol using Jones conditions, and treatment of the diacid with *N,N*-dimethylformamide dimethyl acetal (Scheme 2). The use of L-proline methyl ester in place of the pyrrolidinemethanol led to epimerization of the stereogenic atom on proline during the trimethylaluminum step.

Scheme 2

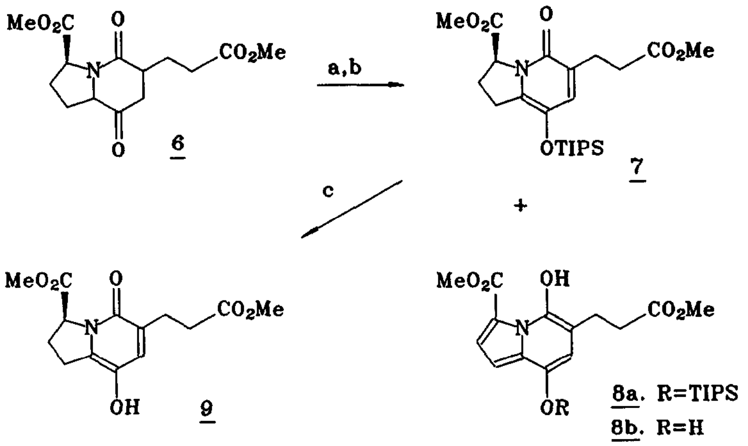


Reagents: a) i. LDA, -78°C, ii. 1-bromo-2-butyne, -78°C, 63%; b) (S)-(+)-pyrrolidinemethanol, $(CH_3)_3Al$, toluene, reflux, 90%; c) Jones oxidation; d) $(CH_3)_2NCH(OMe)_2$, benzene, reflux, 41% over two steps; e) Carbon anode, platinum cathode, 0.03 *N* Et_4NOTS in CH_3OH, undivided cell, constant current of 35.4 mA, 5.1 F, 79% (15% recovered sm); f) $TiCl_4$, CH_2Cl_2, -78°C to room temp.; g) i. O_3, CH_3OH, -78°C, ii. Zn, HOAc, -78°C to room temp., 72% over two steps.

The key anodic oxidation step was run in a 50 mL three neck round bottom flask using 3.18 g (10.3 mmol) of **3a**, a carbon anode, a platinum auxiliary electrode, and 20 mL of a 0.03 *M* Et_4NOTs in methanol electrolyte solution. A constant current of 35.4 mA was applied to the reaction until 5.1 faradays of charge had been passed.[8] A 79% isolated yield of the desired methoxylated amide **5** (formed from solvent trapping of the electrochemically generated *N*-acyliminium ion) was obtained along with 15% of the recovered starting material. Interestingly, the use of acetonitrile as a cosolvent for this oxidation did not lead to the improvement in current efficiency that we had observed in a number of earlier amide oxidation reactions.[3i,j,4] The annulation procedure was completed by treatment of the methoxylated amide **5** with titanium tetrachloride in dichloromethane followed by immediate ozonolysis of the resulting bicyclic vinyl chloride **2**. A 72% isolated yield of ketone **6** was obtained over the two steps. The intermediate vinyl chloride formed during the titanium tetrachloride cyclization step proved to be unstable.

Direct oxidation of ketone **6** with DDQ led to none of the desired six-membered ring oxidation product. Only the ten electron, fully aromatic product **8b** was obtained (Scheme 3).

Scheme 3



Reagents: a) (i-Pr)$_3$SiOTf, Et$_3$N, benzene, 76%; b) DDQ, p-dioxane, reflux, 51% of **7**, 15% of **8a**, 7% sm; c) 0.01 N HCl in 1:1 MeOH/ H_2O, 105°C, 49% (18% recovered sm).

This problem was circumvented by the introduction of an electron-rich double bond into the six-membered ring. This transformation was accomplished by treating ketone **6** with triisopropylsilyltriflate and triethylamine in order to form the triisopropylsilyl enol ether (76%). Only the tetrasubstituted enol ether regioisomer was obtained. Treatment of this enol ether with DDQ afforded the desired six-membered ring oxidation product **7** in a 51% isolated yield accompanied by a 15% isolated yield of the overoxidized compound **8a** and a 7% isolated yield of recovered starting enol ether.

The formal synthesis of A58365A was completed by hydrolysis of the silyl ether **7** with 0.01 N HCl in a 1:1 mixture of methanol in water to give the dimethyl ester **9**. Compound **9** had been previously converted to A58365A by Danishefsky and Fang.[6] An optical rotation of **9** ($[\alpha]_D^{21}$ -169.6° (CH_2Cl_2, c 1.5)) demonstrated that the stereogenic atom on the pyrrolidine ring was preserved throughout the synthesis (lit. value $[\alpha]_D^{25}$ -184.8 (CH_2Cl_2, c 1.5)).

In conclusion, an anodic amide oxidation based annulation procedure for fusing lactam rings onto amines was shown to provide a convenient method for preparing the angiotensin-converting enzyme inhibitor A58365A from (S)-(+)-pyrrolidinemethanol. This synthesis serves to highlight the utility of electrochemical oxidation reactions for constructing bicyclic lactam enzyme inhibitors. Efforts to utilize this route for the construction of A58365B, as well as a number of other rigid peptide mimetics are currently underway and will be reported in due course.

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Resolution NMR facility, partially supported by NIH 1S10R02004 and the Washington University Mass Spectrometry Resource Center, partially supported by NIH RR00954 for their assistance. We thank Professor Danishefsky for providing spectral data of compounds **9** and **1a**.

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