ELECTROPHILIC OLEFIN HETEROCYCLIZATION IN ORGANIC SYNTHESIS.[1] STEREOSELECTIVE INTRAMOLECULAR AMIDOMERCURATION OF γ-HYDROXY-δ,ε-UNSATURATED URETHANES

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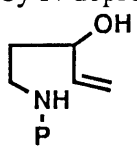
Mercuric acetate driven cyclization of γ-hydroxy-δ,ε–unsaturated urethanes ***1a,b*** *proceeded regio- and stereoselectively to afford cis-2-acetoxymercurymethyl-3-hydroxypyrrolidines* ***2a,b,*** *respectively. These were transformed into the key intermediates for several biologically active compounds.*

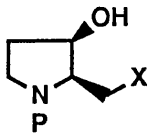
KEYWORDS electrophilic olefin heterocyclization; amidomercuration; γ-hydroxy-δ,ε-unsaturated urethane; pyrrolidine; 1,2-relative asymmetric induction; detoxinine; slaframine; 3-hydroxyglutamic acid

Diastereoselective electrophilic heterocyclization reactions *via* asymmetric induction are commonly used to control the stereochemistry in cyclic compounds.[2] A reaction that is especially well-suited for this kind of asymmetry transfer is the formation of 5-membered rings by electrophilic activation of an allylic alcohol moiety.[3] However, most of these works are confined to the cyclization by oxygen nucleophiles.[4] In spite of the high potentiality as a strategy for the synthesis of the stereochemically defined nitrogen heterocycles, the hydroxyl-directed intramolecular amination of unsaturated hydroxy amines has been less studied.[5] In connection with our interests in the development of electrophilic olefin heterocyclization,[1] we describe the stereoselective intramolecular amidomercuration of γ-hydroxy-δ,ε-unsaturated urethanes, and subsequent elaboration leading to the biologically interesting compounds.

Mercuric acetate [$Hg(OAc)_2$]-promoted cyclization of γ-hydroxy-δ,ε-unsaturated urethanes **1a,b**, which were readily obtained by treating lithioacetonitrile with acrolein followed by reduction with lithium aluminum hydride and N-protection, was performed with high regioselectivity and 1,2-relative asymmetric induction. Intramolecular amidomercuration[6] of **1a,b** with $Hg(OAc)_2$ in tetrahydrofuran (THF) at room temperature proceeded to give *cis*-2-acetoxymercurimethyl-3-hydroxypyrrolidines **2a,b**, which, without isolation due to instability, were converted with potassium bromide in the presence of $NaHCO_3$ to the corresponding mercury bromides **3a,b** in good yields (74% and 87%, respectively), with no isolation of *trans*-isomers. Reductive oxygenation (O_2-$NaBH_4$-DMF)[7] of **3a,b** was carried out to give *cis*-2-hydroxymethyl-3-hydroxypyrrolidines **4a,b** in 65% and 36% yields together with 2-methyl-3-hydroxypyrrolidines **5a,b** in 7% and 15% yields, respectively. The *cis* stereochemistry between the C-2 substituent and C-3 hydroxyl in these pyrrolidines was determined by ^{13}C NMR[8] of the hydrochloride salt of **6** prepared by N-deprotection of **4a,b** with hydrochloric acid.

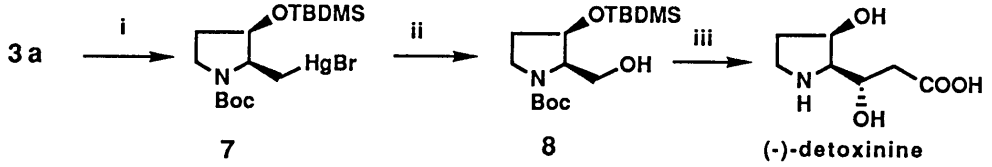


1a,b a: P=Boc ($COOBu^t$) b: P=Z ($COOCH_2Ph$)



2a,b X=HgOAc
3a,b X=HgBr
4a,b X=OH
5a,b X=H
6 X=OH, P=H

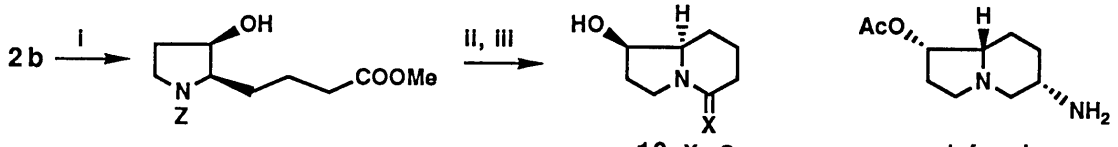
Since the *cis* configuration of the C-2 substituent with respect to the C-3 hydroxyl in the pyrrolidines such as **3a,b** is ubiquitously observed in many interesting alkaloids (detoxinine,[10] slaframine,[11] retronecin,[12] anisomycin,[13] *etc*), we turned our attention to the transformation of **3a,b** into several biologically active compounds. We first examined the conversion of **3a** into the key intermediate **8** for the synthesis of (-)-detoxinine. *tert*-Butyldimethylsilylation of **3a** afforded **7**, and subsequent reductive oxygenation of the latter gave **8** in 71% yield from **3a**, of which the spectral data (^{1}H NMR and IR) were identical with those of an authentic sample.[10]



7 8 (-)-detoxinine

i TBDMSCl/imidazole/DMF; ii O_2/$NaBH_4$/DMF; iii ref. 10)

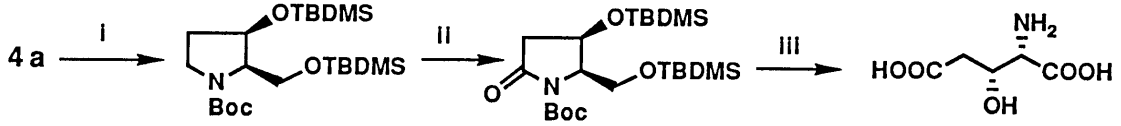
The carbon-carbon bond formation reaction employing radical addition to alkenes is one of the most promising methodologies in organic synthesis.[14] Since alkylmercury compounds were frequently used as radical precursors, radical propagation of **2b**[15] with methyl acrylate was carried out. Reaction of **2b** with sodium trimethoxyborohydride[16] in CH_2Cl_2 in the presence of excess methyl acrylate provided **9** in 58 % yield. Hydrogenolysis of **9** with palladium hydroxide under a hydrogen atmosphere in methanol brought about spontaneous ring closure to give the indolizidinone **10** in a quantative yield, of which the reduction with $LiAlH_4$ afforded *cis*-1-hydroxyindolizidine (**11**)[17] (93% yield) as the racemate of a key precursor in the biosynthesis[19] of the toxic indolizidine alkaloid slaframine.



9 10 X=O 11 X=H_2 slaframine

i CH_2=CHCOOMe/$NaBH(OMe)_3$/CH_2Cl_2; ii $Pd(OH)_2$/H_2; iii $LiAlH_4$

γ-Lactams are regarded as the precursors of γ-amino acids with pharmacological interests.[20] Oxidation of **12**, prepared by di-*tert*-butyldimethylsilylation of **4a**, with RuO_4 (RuO_2-$NaIO_4$-MeCOOEt-H_2O)[21] readily gave the γ-lactam **13** in 76% yield. The γ-lactam **13** has been transformed *via* ring-opening into (2R*,3S*)-3-hydroxyglutamic acid among unusual γ-amino acids having 1,2-amino alcohol functions (statine,[22] 3-hydroxyglutamic acid,[23] *etc*) by us.[1d]



12 13 (2R*,3S*)-3-hydroxyglutamic acid

i TBDMSCl/Imidazole/DMF; ii RuO_2/$NaIO_4$; iii ref. 1d)

In summary, this intramolecular amidomercuration of γ-hydroxy-δ,ε-unsaturated urethanes proceeds regioselctively to give pyrrolidines, which are predominantly of the *cis* arrangement of the hydroxyl and the

substituent on the newly formed stereogenic center due to the directing effect of the allylic hydroxyl group.[3,4a] The present method provides a new and promising access to functionalized pyrrolidines, which should be convertible to related biologically active compounds such as alkaloids and amino acids, and some examples are actually demonstrated. Encouraged by these results, further investigations using optically active forms along this line are in progress in our laboratory.

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8) ^{13}C NMR of hydrochloride salt of **6**: (D_2O) δ 33.398, 43.982, 58.390, 66.062, 70.546. *Trans* isomer:[9] (D_2O) δ 32.695, 44.585, 59.189, 67.918, 71.652. Dioxane was used as an internal reference.
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15) Although we first examined a similar reaction using **3b**, **9** was not obtained. Surprisingly, the reaction produced the ring-opened compound **1b**.
16) The use of sodium borohydride in place of sodium trimethoxyborohydride resulted in a low yield (less than 10 %).
17) The picrate of **11** had mp 178-181 °C (lit., [18], mp 178-180 °C).
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