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Ether-Directed, Stereoselective Aza-Claisen Rearrangements: Synthesis of the Piperidine Alkaloid, α-Conhydrine

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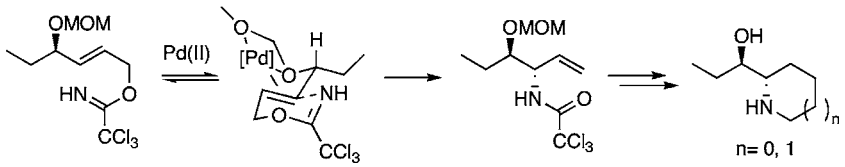
ABSTRACT



A new approach for the stereoselective synthesis of the piperidine alkaloid (+)-α-conhydrine and its pyrrolidine derivative has been developed using a palladium(II)-catalyzed, MOM-ether-directed aza-Claisen rearrangement and ring-closing metathesis to effect the key steps.

Biologically active alkaloids containing a 2-(1-hydroxyalkyl)-piperidine unit are abundant in nature and have attracted much attention due to their antiviral and antitumor properties.[1,2] This class of compound includes (+)-α-conhydrine **1** which was first isolated from the seeds and leaves of the poisonous plant, *Conium maculatum* L, in 1856.[3]

Following elucidation of its structure in 1933,[4] the synthesis of (+)-α-conhydrine **1** and its stereoisomers has been the subject of intense study.[5] Different approaches for the synthesis of this piperidine alkaloid include a racemic synthesis by Beak and co-workers involving the α-lithiation and electrophilic substitution of Boc-piperidines.[5a] Comins and co-workers have prepared (+)-α-conhydrine using an iodocyclocarbamation of tetrahydropyridines to effect the key step,[5d] and the research group of Kumar has reported the synthesis of (+)-α-conhydrine using a diastereoselective addition of an organomagnesium reagent to an amino aldehyde.[5j] A number of these elegant approaches give (+)-α-conhydrine **1** in good overall yield and enantiopurity but are limited by access to structural analogues (Figure 1).

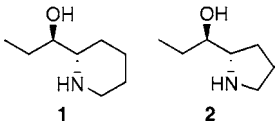


Figure 1. (+)-α-Conhydrine and its pyrrolidine analogue.

We recently began a program to study how the aza-Claisen rearrangement of allylic trichloroacetimidates (the Overman reaction)[6] can be influenced by stereogenic centers within the molecule. This work led to the development of a MOM-ether-directed, palladium(II)-catalyzed reaction which allows the formation of *erthyro*-products in diastereomeric ratios of up to 15:1.[7] Further investigation of this process using a number of structural analogues has shown that both oxygen atoms of the MOM group are utilized in directing the Pd(II)

(1) Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677−1716.
(2) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 619−636 and references therein.
(3) Wertheim, T. *Liebigs. Ann. Chem.* **1856**, *100*, 328−330.
(4) Späth, E.; Adler, E. *Monatsh. Chem.* **1933**, *63*, 127−140.
(5) For recent examples, see: (a) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109−1117. (b) Hoye, T. R.; Renner, M. K.; Vos-DiNardo, T. J. *J. Org. Chem.* **1997**, *62*, 4168−4170. (c) Guerreiro, P.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Chirality* **2000**, *12*, 408−410. (d) Comins, D. L.; Williams, A. L. *Tetrahedron Lett.* **2000**, *41*, 2839−2842. (e) Agami, C.; Couty, F.; Rabacco, N. *Tetrahedron* **2001**, *57*, 5393−5401. (f) Lysenko, I. L.; Bekish, A. V.; Kulinkovich, O. G. *Russ. J. Org. Chem.* **2002**, *38*, 875−879. (g) Enders, D.; Nolte, B.; Raabe, G.; Runsink, J. *Tetrahedron: Asymmetry* **2002**, *13*, 285−291. (h) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957−1958. (i) Kandula, S. V.; Kumar, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3268−3274. (j) Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 4091−4093. (k) Chang, M.-Y.; Kung, Y.-H.; Chen, S.-T. *Tetrahedron* **2006**, *62*, 10843−10848.

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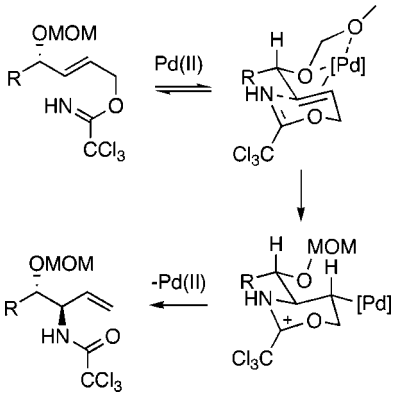
Scheme 1. Stereoselective MOM-ether-Directed Aza-Claisen Rearrangement

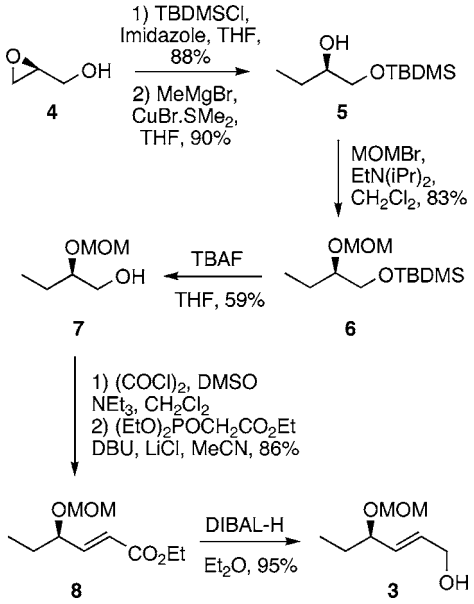


catalyst to one face of the allylic trichloroacetimidate, resulting in a highly diastereoselective reaction (Scheme 1).[8] This process has subsequently been used for the stereoselective synthesis of β- and γ-hydroxy-α-amino acids.[9]

With a good understanding of the ether-directed aza-Claisen rearrangement, we were interested in using this process for the efficient synthesis of cyclic natural products containing *erthyro*-hydroxyl and -amino functional groups. We now report a new approach for the stereoselective synthesis of (+)-α-conhydrine **1** as well as its pyrrolidine analogue **2**,[10] a known inhibitor of a proline-specific endopeptidase using our ether-directed aza-Claisen rearrangement and ring-closing metathesis (RCM) reactions to effect the key steps.

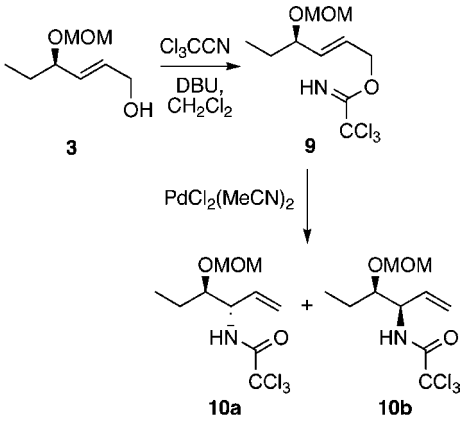
The first stage of the synthesis of (+)-α-conhydrine **1** involved the preparation of allylic alcohol **3** required for the first key step (Scheme 2). Thus, (*S*)-glycidol **4** was protected as the *tert*-butyldimethylsilyl ether followed by regioselective ring opening of the epoxide using a copper-catalyzed Grignard reaction to give **5** in excellent yield.[11] Formation of the MOM-ether **6** using Hünig's base and bromomethyl methyl ether and then removal of the silyl-ether using TBAF gave alcohol **7**. A one-pot Swern oxidation/Horner−Wadsworth−Emmons (HWE) reaction gave *E*-α,β-unsaturated ester **8** in excellent overall yield.[12] Although a number of different reaction conditions can be used to carry out the HWE step, we have found that the Masamune−Roush procedure for this one-pot process is the most efficient, giving exclusively the *E*-alkene.[13] Reduction of the ester using DIBAL-H gave the required *E*-allylic alcohol **3** in 95% yield.

Scheme 2. Synthesis of *E*-Allylic Alcohol **3**



The allylic trichloroacetimidate **9** was prepared using a catalytic amount of DBU and trichloroacetonitrile (Scheme 3).[14] Aza-Claisen rearrangement of **9** in THF using bis-(acetonitrile)palladium(II) chloride (10 mol %) as the catalyst gave the *erthyro*- and *threo*-allylic trichloroamides **10a** and **10b** in 52% yield over the two steps in a 12:1 ratio. We recently reported that the stereochemical outcome of this directed rearrangement can be optimized using noncoordinating solvents, and so, the reaction was repeated using toluene.[7b] This gave **10a** and **10b** in 55% yield and in an excellent 16:1 ratio. The desired major isomer **10a** was then easily separated from **10b** using flash column chromatography. As previously observed,[7b] these results clearly demonstrate that by switching to a noncoordinating solvent the

Scheme 3. MOM-ether-Directed Rearrangement of **9**



solvent	yield (%)	ratio
THF	52%	12 : 1
toluene	55%	16 : 1

(6) Overman, L. E.; Carpenter, N. E. *Org. React.* **2005**, *66*, 1−107 and references therein.

(7) (a) Jamieson, A. G.; Sutherland, A. *Org. Biomol. Chem.* **2005**, *3*, 735−736. (b) Jamieson, A. G.; Sutherland, A. *Org. Biomol. Chem.* **2006**, *4*, 2932−2937.

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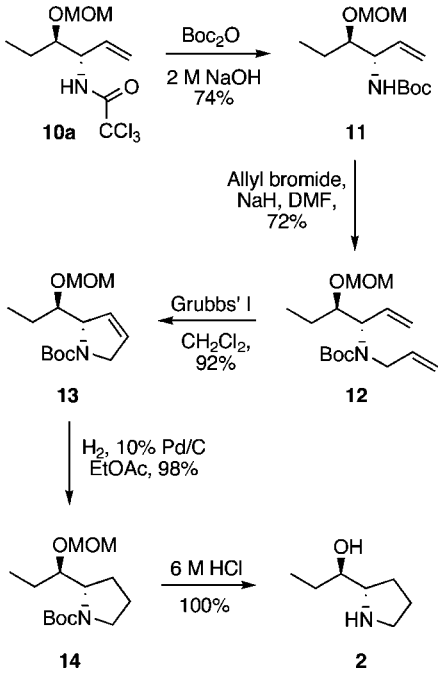
Pd(II) catalyst can now bind more effectively to the MOM group, leading to a significant enhancement in diastereoselectivity.

Having achieved the first key step, the next stage of our synthesis of (+)-α-conhydrine **1** was reprotection of the amine with a more suitable protecting group followed by alkylation to form a diene which could undergo RCM to give the piperidine ring. A change of protecting group was necessary at this stage as early attempts to alkylate **10a** gave only starting material. Amide hydrolysis of **10a** and reprotection of the resulting amine with the Boc group were easily achieved giving **11** in good overall yield (Scheme 4).

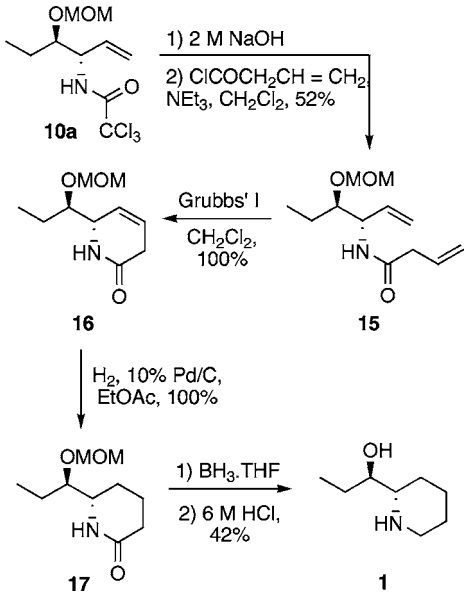
Scheme 4. Synthesis of Pyrrolidone **2**



Attempted alkylation of **11** using sodium hydride and either 4-bromobutene or the triflate derivative of 3-buten-1-ol returned only starting material. However, using a procedure developed by Hartley and co-workers and the more reactive allyl bromide as an alkylating agent gave diene **12** in good yield.[15] Ring-closing metathesis of **12** using Grubbs' first-generation catalyst, $Cl_2Ru(=CHPh)(PCy_3)_2$ (5 mol %), in refluxing dichloromethane proceeded smoothly to give the dihydropyrrole **13** in 92% yield.[16] Hydrogenation of the resulting alkene and acid-mediated removal of the protecting groups gave the endopeptidase inhibitor[10] (2*S*,1′*R*)-2-(1′-hydroxypropyl)pyrrolidine **2** in nearly quantitative yield over the two steps.

In an effort to produce a substrate which on RCM would give the piperidine analogue, an acylation strategy was proposed. Thus, hydrolysis of **10a** followed by acylation with 3-butenoyl chloride gave **15** in good yield over the two steps (Scheme 5). Ring-closing metathesis again proceeded smoothly

Scheme 5. Synthesis of (+)-α-Conhydrine **1**



using Grubbs' first-generation catalyst to give the unsaturated δ-lactam **16** in quantitative yield. Finally, hydrogenation of the alkene, reduction of the lactam with borane-THF, and deprotection of the hydroxyl group under acidic conditions gave (+)-α-conhydrine **1** in 42% yield over the three steps.

In conclusion, we have developed a simple and direct route for the synthesis of (+)-α-conhydrine **1** and its pyrrolidine analogue **2** using a MOM-ether-directed, palladium-catalyzed aza-Claisen rearrangement to establish the second stereogenic center followed by RCM to form the piperidine and pyrrolidine rings, respectively. Although only two compounds have been made during this study, we believe that a range of analogues with varying ring sizes can be easily accessed using this approach. Work is currently underway to achieve this goal as well as the stereoselective functionalization of alkenes such as **13** and **16** for the preparation of polyhydroxylated derivatives.

Acknowledgment. Financial support from EPSRC (DTA award) and the University of Glasgow is gratefully acknowledged.

Supporting Information Available: Full experimental procedures, spectroscopic data, and NMR spectra for compounds **1**−**3**, **6**, **8**, and **10a**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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