ORGANIC LETTERS

2001
Vol. 3, No. 19
2961−2963

A Concise Synthesis of Turneforcidine via a Metalloiminium Ion Cyclization Terminated by the 2-(Methylthio)-3-(trimethylsilyl)-1-propenyl Moiety

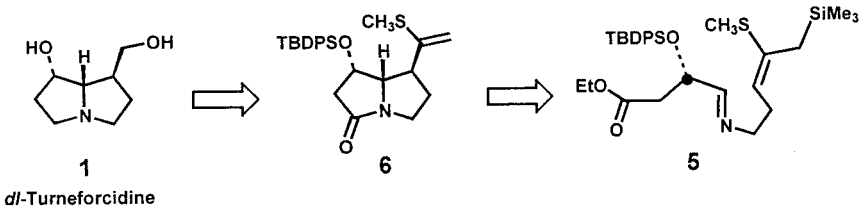
Duk Keun An, David Duncan, Tom Livinghouse,* and Paul Reid

Department of Chemistry and Biochemistry, Montana State University, Bozeman, Montana 59717

livinghouse@chemistry.montana.edu

Received June 4, 2001

ABSTRACT



A concise synthetic route to racemic turneforcidine (1) is described that relies on the stereocontrolled cyclization of the 2-(methylthio)-3-(trimethylsilyl)-1-propenyl bearing imine 5 in the presence of $TiCl_4$.

The pyrrolizidine alkaloids constitute a large and structurally diverse class of azabicyclo[3.3.0]-based natural products that possess a noteworthy range of biological activities.[1] Although the structural and stereochemical complexity of these alkaloids is comparatively modest by contemporary standards, these compounds remain popular targets for total synthesis and the demonstration of new synthetic methodology.[2] We recently reported that imines tethered to the 2-(methylthio)-3-(trimethylsilyl)-1-propenyl terminator could be induced to undergo highly stereoselective cyclizations,[3a] in close analogy with our previous results involving 2-propylidine-1,3-bis-(silane) terminated heteroannulations.[3b,4] In this Letter, we show the efficacy of this protocol in a stereocontrolled total synthesis of the pyrrolizidine alkaloid turneforcidine (**1**). Turneforcidine was envisaged to arise from the bicyclic pyrrolizidone **7** by global reduction. Pyrrolizidone **7**, in turn, was anticipated to be available by oxidation of **6**, which should derive from the $TiCl_4$-mediated bicyclization of imine

(1) (a) Culvenor, C. C. J.; Bull, L.; Dick, A. T. *The Pyrrolizidine Alkaloids*; North-Holland Publishing Co.: Amsterdam, 1968. (b) Mattocks, A. R. *Chemistry and Toxicology of the Pyrrolizidine Alkaloids*; Academic Press: San Diego, 1986.

(2) (a) For a particularly intriguing and general synthetic strategy to the pyrrolizidine alkaloids, see: Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125; *J. Org. Chem.* **1994**, *59*, 5672 and references therein. (b) Simple allylsilanes have been used as terminators in cyclizations involving acyliminium ions to provide the pyrrolizidine nucleus: Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014. (c) For the use of allylstannanes as terminators in a related context, see: Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54*, 4345.

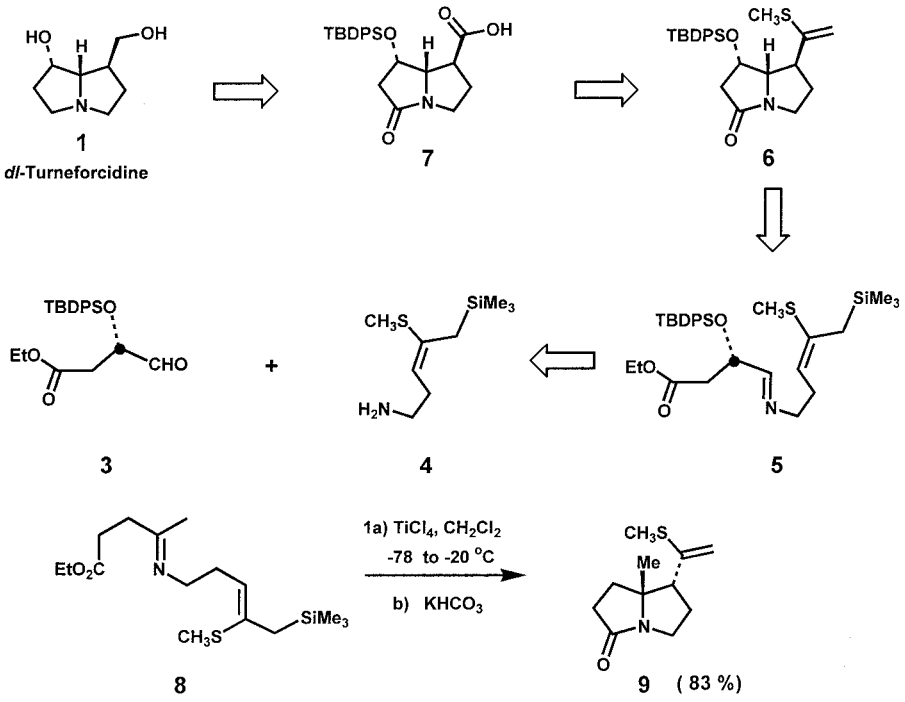
(3) (a) Duncan, D.; Livinghouse, T. *J. Org. Chem.* **2001**, *66*, 5237. (b) The *intermolecular* addition of 2-(methylthio)-3-(trimethylsilyl)-1-propene to simple imines has previously been described: Narasaka, K.; Shibata, T.; Hayashi, Y. *Bull. Soc. Chem. Jpn.* **1992**, *65*, 1392.

(4) (a) Kercher, T.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 4200. (b) For cyclizations involving the intramolecular coupling of *C*-acylnitrilium ions with 2- propylidene-1,3-bis(silane)s, see: Kercher, T.; Livinghouse, T. *J. Org. Chem.* **1997**, *62*, 805.

(5) (a) It should be noted that the stereochemical outcome of cyclizations involving aldimines is, in the cases studied thus far, generally *opposite* that observed for ketimines, with aldimines leading to *trans*-2, 3-disubstituted pyrrolidines.[3a,4] (b) As part of a related study, we have found that 2-propylidene-1,3-bis(silane) containing imines bearing a comparatively more coordinating α-benzyloxy moiety are prone to undergo competitive protodesilylation in the presence of $TiCl_4$.

10.1021/ol010122b CCC: $20.00
Published on Web 08/30/2001

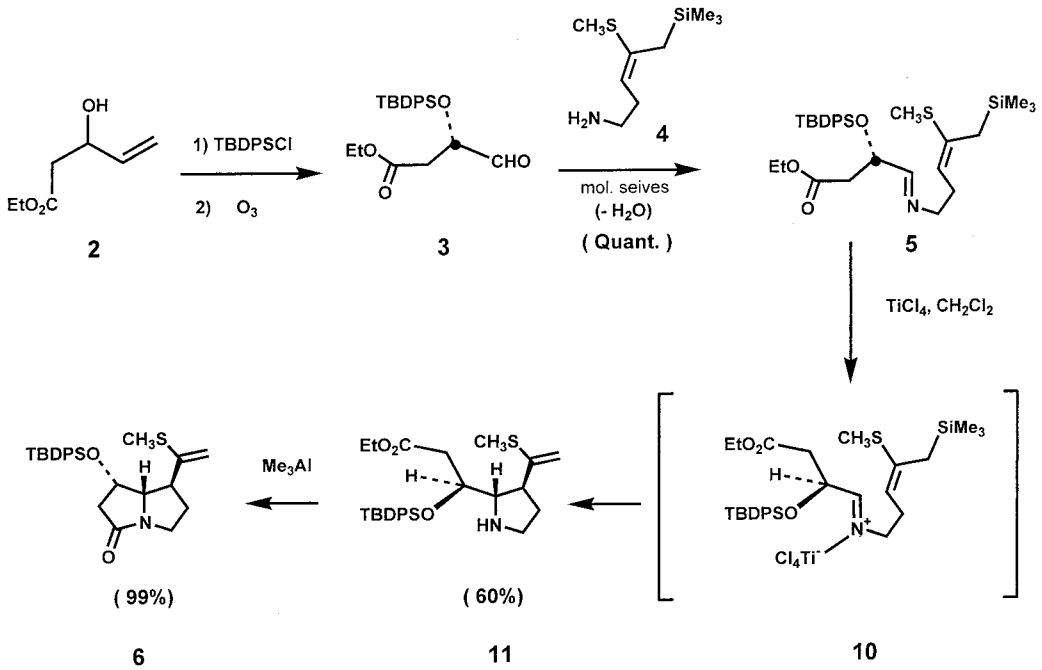
Scheme 1



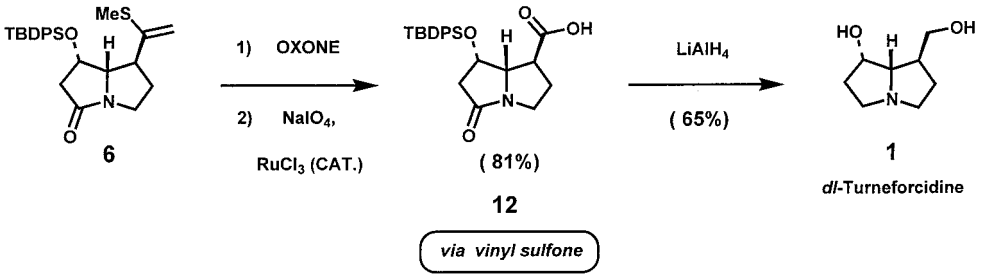
5, in close analogy with the bicyclization of imine **8** to pyrrolizidone **9** reported previously by us.[3,5] Simplification of imine **5** reveals the immediate precursors **3** and **4** (Scheme 1).

Synthesis of Turneforcidine. We commenced the present synthesis of turneforcidine (**1**) with the preparation of the 4-oxoester **3**, which was easily prepared in 84% overall yield by sequential silylation [(*t*-Bu(Ph)$_2$SiCl, imidazole, DMF] and ozonolysis [(a) O_3, (b) Me_2S] of the readily available 3-hydroxyester **2**.[6] Condensation of **3** with amine **4**[3] (4 Å molecular sieves, CH_2Cl_2) furnished the precyclization imine **5** in quantitive yield, which was immediately subjected to $TiCl_4$-mediated cyclization without further purification. In contrast to expectations based on our previous studies,[3,4]

Scheme 2



Scheme 3



exposure of **5** to 1.0 equiv of $TiCl_4$ (CH_2Cl_2, −78 → −20 °C) gave rise to a highly stereoselective *monocyclization* to afford pyrrolidine **11** in 60% yield. Presumably, pyrrolidine **11** is less predisposed to undergo spontaneous lactamization since it does not benefit from Thorp−Ingold conformational acceleration, which is operative in the bicyclization of the pyrrolidine corresponding to pyrrolizidone **9**. The stereochemical outcome observed for the conversion of **5** to **11** can be rationalized by preferred *si*-attack of the nucleophilic terminator on the conformationally biased metalloiminium acceptor **10** (Scheme 2).[5a] Subsequent lactamization of **11** was readily accomplished by simple treatment with Me_3Al to provide the desired pyrrolizidone **6** in 99% purified yield.

The direct oxidative degradation of the vinyl sulfide moiety present in **7** to the corresponding carboxylic acid, under a wide variety of reaction conditions, proved ineffective, with the observed formation of multiple products. Accordingly, **7** was first converted to the corresponding sulfone (OXONE, MeOH−H_2O, 23 °C, 5 h)[7] in 92% isolated yield. Subsequent oxidative degradation [$RuCl_3$ (cat.), $NaIO_4$, CCl_4−CH_3CN−H_2O, 23 °C, 12 h] then provided the desired acid **12** in 88% purified yield. Global reduction of **12**, with concomitant hydride-mediated *O*-desilylation, ($LiAlH_4$, THF, reflux, 12 h) ultimately delivered racemic turneforcidine (**1**) in 65% yield after chromatographic purification (Scheme 3).[8]

In conclusion, this study has demonstrated that a metalloiminium ion cyclization terminated by a 2-(methylthio)-3-(trimethylsilyl)-1-propenyl moiety serves as an effective means for the synthesis of a pyrrolidine that contains the essential stereochemical triad present in turneforcidine (**1**). In addition, an efficient method for the oxidative degradation of vinyl sulfide substituents that result from this method of cyclization has been developed. The utilization of this annulation strategy for the stereodefined synthesis of other bioactive substances and alternative methods for the synthetic modification of the postcyclization vinyl sulfide are under current investigation.

Acknowledgment. Generous financial support for this research by a grant from the National Institutes of Health is gratefully acknowledged.

Supporting Information Available: Experimental procedures and listings of spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010122B

(6) Ethyl 3-oxo-4-pentanoate (Nazarov's reagent). Zibuck, R.; Streiber, J. *Org. Synth.* **1993**, *71*, 236.

(7) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

(8) The spectroscopic characteristics of the synthetic turneforcidine prepared in this manner were identical to those reported in the literature.[9]

(9) Knight, D. W.; Share, A. C.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2089.