Communications

Total Synthesis of Clavepictines A and B. Cross-Coupling of an Acylenamino Triflate and Cyclization of a δ-Aminoallene

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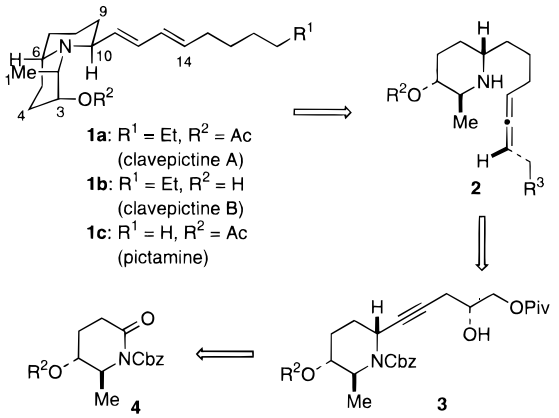
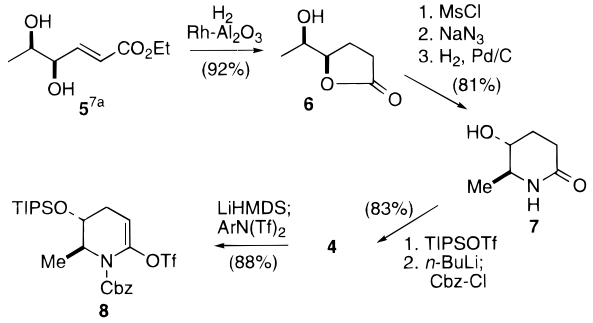
Three new quinolizidine alkaloids, clavepictines A and B (**1a**,**b**) and pictamine (**1c**), which showed antimicrobial, antifungal, and antitumor activity, were recently isolated from the tunicate *Clavelina picta*.[1,2] The structures of these alkaloidal homologs were determined on the basis of spectroscopic data and X-ray diffraction analysis, while their absolute configuration remained undefined. Key structural characteristics include a rare *cis*-ring-fused quinolizidine nucleus with axially disposed methyl and acetoxy (or hydroxy) groups (presumably to avoid the otherwise severe 1,3-diaxial interaction) and an (*E*,*E*)-deca- or octa-1,3-diene side chain. Recently, Momose and co-workers disclosed the first enantioselective total synthesis of clavepictines A and B (**1a** and **1b**).[3,4] Herein, we report our own synthesis of **1a** and **1b**.



Subsequent to several unsuccessful approaches, we ultimately chose the electrophilic cyclization of the δ-allenic amine **2** for the stereoselective construction of the requisite quinolizidine system.[5] In contrast to the oxygen-containing heterocycles, the intramolecular cyclization of ω-aminoallenes has been limited to a handful of monocyclic ring formations; to our knowledge, only a single application was reported for the stereocontrolled synthesis of nitrogen-containing bicyclic rings.[6] The requisite allene **2** could be prepared diastereoselectively by elaboration of alcohol **3**. Finally, our plan called for the stereoselective installation of the 2,6-*trans* side chain onto the monocyclic lactam **4**.

Scheme 1



The 5,6-disubstituted lactam **4** was readily prepared starting from the known and enantiopure diol **5** (Scheme 1).[7,8] Hydrogenation afforded (92% yield) γ-lactone **6**, which allowed the regioselective introduction of the amino group at C-2 (clavepictine numbering system).[1] By means of the azide intermediate, lactam **7** was prepared in 81% overall yield.

Reductive alkylation of lactams, thiolactams, or imino ethers to amines with concomitant attachment of the alkyl side chain was previously achieved by Eschenmoser sulfide contraction[9] or by addition of organometallic reagents.[10] Unfortunately, most of the known methods proved unsuitable for the subsequent introduction of the allene functionality. We were thus prompted to develop cross coupling of vinyl triflates derived from lactams with a suitable nucleophile under mild conditions.[11] Toward

(1) Raub, M. F.; Cardellina, J. H., II; Choudhary, M. I.; Ni, C.-Z.; Clardy, J.; Alley, M. C. *J. Am. Chem. Soc.* **1991**, *113*, 3178.

(2) Kong, F.; Faulkner, D. J. *Tetrahedron Lett.* **1991**, *32*, 3667.

(3) Toyooka, N.; Yotsui, Y.; Yoshida, Y.; Momose, T. *J. Org. Chem.* **1996**, *61*, 4882.

(4) There also appeared a synthetic study toward clavepictine A: Hart, D. J.; Leroy, V. *Tetrahedron* **1995**, *51*, 5757.

(5) As also noted by the Momose group,[3] an intramolecular conjugate addition to the corresponding δ-amino α,β-unsaturated ester was found to afford predominantly the undesired C-10 epimer: Ha, J. D.; Cha, J. K. Unpublished results.

(6) For cyclization of allenes bearing an internal nitrogen nucleophile, see: (a) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4253. (b) Arseniyadis, S.; Gore, J. *Tetrahedron Lett.* **1983**, *24*, 3997. (c) Arseniyadis, S.; Sartoretti, J. *Tetrahedron Lett.* **1985**, *26*, 729. (d) Lathbury, D.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1986**, 114. (e) Kinsman, R.; Lathbury, D.; Vernon, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1987**, 243. (f) Shaw, R. W.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3549.

(7) (a) The Sharpless asymmetric dihydroxylation of ethyl sorbate was shown to give the diol **5** in excellent ee: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) For regioselective osmylation of dienoates, see also: Whang, K.; Cooke, R. J.; Okay, G.; Cha, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 8985.

(8) As the absolute configuration of these alkaloids was unknown at the outset, we arbitrarily chose $(DHQD)_2$−PHAL for asymmetric dihydroxylation.

(9) (a) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710. (b) Shiosaki, K. In *The Eschenmoser Coupling Reaction*; Trost, B. M., Fleming, I., Ed.; *Comprehensive Organic Synthesis*; Heathcock, C. H., Vol. Ed.; Pergamon: Oxford, 1991; Vol. 2, Chapter 3.7. (c) Gugelchuk, M. M.; Hart, D. J.; Tsai, Y.-M. *J. Org. Chem.* **1981**, *46*, 3671. (d) For a recent modification, see: Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30.

(10) See *inter alia*: (a) LaLonde, R. T.; Muhammad, N.; Wong, C. F.; Sturiale, E. R. *J. Org. Chem.* **1980**, *45*, 3664. (b) Hwang, Y. C.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 3885. (c) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 1719. (d) Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682. (e) Tominaga, Y.; Kohra, S.; Hosomi, A. *Tetrahedron Lett.* **1987**, *28*, 1529. (f) Takahata, H.; Takahashi, K.; Wang, E.-C.; Yamazaki, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1211. (g) Zezza, C. A.; Smith, M. B.; Ross, B. A.; Arhin, A.; Cronin, P. L. E. *J. Org. Chem.* **1984**, *49*, 4397.

(11) In marked contrast to the widely utilized vinyl triflates from ketone or ester enolates, the corresponding vinyl triflates of lactams have received surprisingly little attention. While our synthetic studies were in progress, Comins and Foti reported their preparation and reactions: (a) Foti, C. J.; Comins, D. L. *J. Org. Chem.* **1995**, *60*, 2656. For more recent examples, see also: (b) Okita, T.; Isobe, M. *Tetrahedron* **1995**, *51*, 3737. (c) Luker, T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1996**, *37*, 8257 and references cited therein. (d) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3592.

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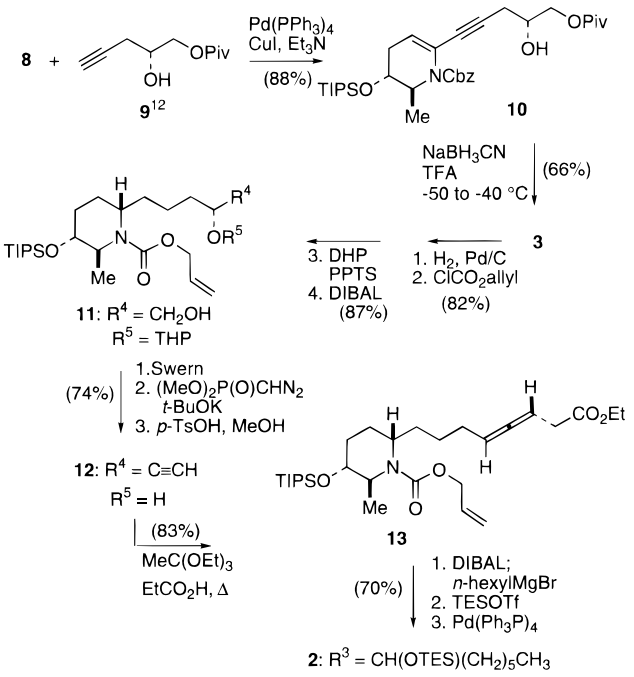
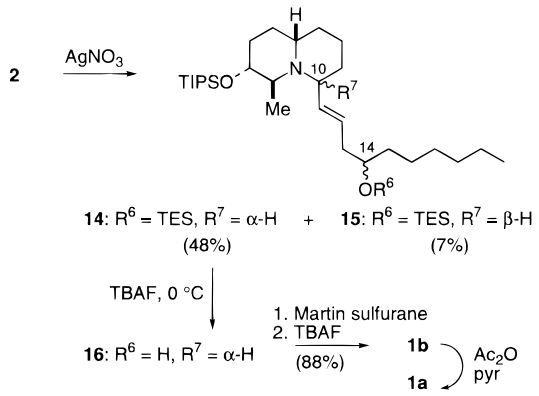
Scheme 2



this end, **4** (R^2 = TIPS) was prepared in 83% yield by sequential protection. Subsequent treatment with LiHMDS, followed by Comins' reagent, furnished the aminovinyl triflate **8** in excellent (88%) yield. Sonogashira-type coupling with the enantiomerically pure acetylene **9**[12] afforded the cross-coupling product **10** in 88% yield (Scheme 2). Subsequent reduction with $NaBH_3CN$-TFA resulted in the stereoselective construction of the *trans*-2,6-disubstituted piperidine **3** in 52% yield, along with the corresponding desilylated diol in 17% yield.

Hydrogenation of the alkyne group, followed by straightforward functional group management in the carbamate and alcohol protecting groups, furnished the allyl carbamate **11**. In order to install the requisite allene functionality, the propargyl alcohol **12** was first prepared in three steps (74% overall yield): (1) Swern oxidation; (2) the Seyferth−Gilbert homologation;[13] (3) THP deprotection. Subsequent ortho ester-Claisen rearrangement afforded diastereoselectively the allenic ester **13** (83%). The remaining side chain was then introduced (86%) in a one-pot operation by sequential treatment with DIBAL and *n*-hexylmagnesium bromide.[14] Subsequent alcohol protection and removal of the allyl carbamate group by standard methods provided the *δ*-allenic amine **2** (70% overall).

Scheme 3



Silver nitrate-mediated cyclization of **2** produced (54%) a 7:1 mixture of the desired quinolizidine **14** (containing the correct C-10 stereochemistry and the *E*-double-bond geometry) and its C-10 epimer **15** (Scheme 3). It is noteworthy that a ca. 1:2 mixture of **14** and **15** was obtained from the otherwise identical cyclization of the 1:1 diastereomeric allenes in place of diastereomerically pure **2**. Finally, selective deprotection of the triethylsilyl group, followed by stepwise treatment with Martin sulfurane[15] and TBAF, afforded (+)-clavepictine B (**1b**). For additional characterization, (−)-clavepictine A (**1a**) was also prepared by acetylation.[16] The spectroscopic and physical properties of **1a** and **1b** were in excellent agreement with the literature data.

In summary, we have unequivocally established the absolute configuration of **1a** and **1b** by their stereocontrolled total synthesis. Key methods include cross-coupling of vinyl triflates **8** of *N*-acyllactams and diastereoselective cyclization of the *δ*-aminoallene **2**. Both transformations should be of general synthetic utility in the stereoselective synthesis of quinolizidines, indolizidines, and related aza-heterocylces. A more convergent, second-generation synthesis of **1a**,**b** is currently under way and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data (47 pages).

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(12) Prepared from (*S*)-(−)-glycidol in three steps: 1. *t*-BuCOCl, pyridine; 2. LiC≡CTMS, BF_3·OEt; 3. TBAF.

(13) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837. (c) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (d) Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. *J. Org. Chem.* **1996**, *61*, 2540.

(14) As expected, **2** was obtained as an inseparable 1:1 diastereomeric mixture at C-14. Since the C-14 stereocenter was destined to undergo dehydration, lack of stereocontrol was inconsequential.

(15) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604.

(16) Whereas (+)-clavepictine B (**1b**) is stable, (−)-clavepictine A (**1a**) is found to undergo slow decomposition in storage.