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A Tandem Prins/Schmidt Reaction Approach to Marine Alkaloids: Formal and Total Syntheses of Lepadiformines A and C

Angelica M. Meyer, Christopher E. Katz, Sze-Wan Li, David Vander Velde, and Jeffrey Aubé*

Department of Medicinal Chemistry, University of Kansas, Structural Biology Center, 2121 Simons Drive, West Campus, Lawrence, Kansas 66047

jaube@ku.edu

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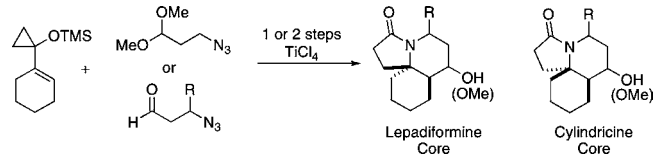
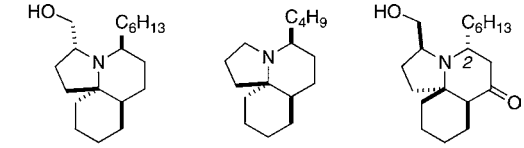
ABSTRACT



The tricyclic core of the cylindricine or lepadiformine families of alkaloid natural products was assembled via a Prins addition/intramolecular Schmidt rearrangement under Lewis acid conditions. Both single-pot and two-stage variations of this process were examined, with particular attention to the stereochemical outcome of the processes. This technology has been applied to a formal total synthesis of lepadiformine A and a total synthesis of lepadiformine C.

The ocean is a fertile source of natural products, many of which are valuable due to their biological properties. The genus *Clavelina* has proven no exception, yielding a number of alkaloids that have attracted substantial synthetic interest over the past decade. Two such families are the lepadiformines and the cylindrines (Figure 1). The cyclindricines are a large family of tricyclic compounds that were isolated by the Blackman group from *Clavelina cylindrica* found off of the coast of Tasmania.[1] At about the same time, the structurally related lepadiformines were isolated from several different species by Biard and co-workers.[2] Despite only a few reports of biological activity (e.g., lepadiformines A and B are inwardly rectifiying K^+ channel blockers[2,3] and some of the cyclindricines have modest cytotoxicity[1]), the members of both families have attracted a great deal of attention due to their intricate tricyclic structures.[4] In this paper, we describe a synthetic method that allows rapid access to the tricyclic ring systems embodied by these alkaloids, a formal total synthesis of lepadiformine A,[5] and the first total synthesis of lepadiformine C.[3]



Lepadiformine A (**1**) Lepadiformine C (**2**) Cylindricine C (**3**)

Figure 1. Representative structures from the genus *Clavelina*.

One retrosynthetic analysis of cyclindricine C would entail the late-stage installation of the hydroxymethyl substituent

(1) (a) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645–8656. (b) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1994**, *47*, 1355–1361. (c) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1995**, *48*, 955–965.

(2) Juge, M.; Grimaud, N.; Biard, J.-F.; Sauviat, M.-P.; Nabil, M.; Verbist, J.-F.; Petit, J.-Y. *Toxicon* **2001**, *39*, 1231–1237.

(3) Sauviat, M.-P.; Vercauteren, J.; Grimaud, N.; Juge, M.; Nabil, M.; Petit, J.-Y.; Biard, J.-F. *J. Nat. Prod.* **2006**, *69*, 558–562.

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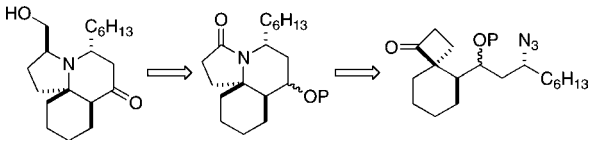
via a lactam intermediate, a maneuver that had been utilized by the Renaud group's total synthesis of lepadiformine A (Scheme 1).[6] Going further, one could gain access to this lactam via an intramolecular Schmidt reaction on a [5.3]spirocyclic ketone such as that shown. Although the lepadiformines lack the oxygenation associated with cyclindricine C (Figure 1), incorporating an appropriately protected alcohol at this stage of the synthesis would enable, in principle, access to analogues of both classes by deoxygenation or oxidation as appropriate. However, the preparation of the necessary [5.3]spirocyclic keto azide precursor still constitutes a considerable synthetic challenge.

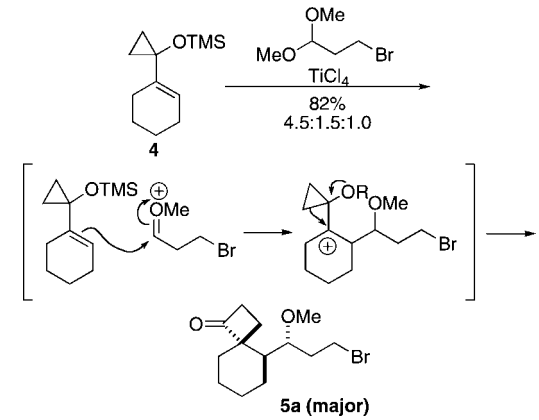
Scheme 1. Retrosynthetic Analysis of Cylindricine C



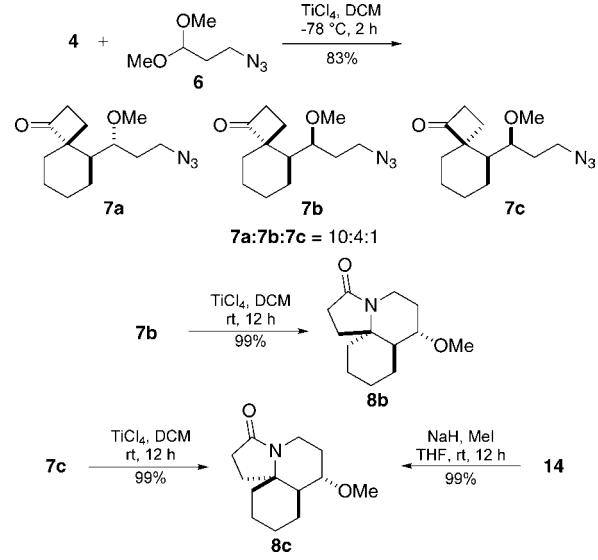
One attractive solution would be to employ the Prins-like reactivity of 1-silyloxy-1-alkylcyclopropanes introduced by Trost[7] and later exploited by Cha's group[8] as shown in Scheme 2. In this chemistry, cyclopropane **4**[8,9] was treated with an acetal in the presence of Lewis acid. Conversion of the acetal to a reactive oxonium ion and attachment of **4** yields a cyclopropyl cation that undergoes ring expansion to afford a mixture of three spirocyclobutanone diastereomers, of which **5a** was predominant. Not only would this approach afford a concise entry into the appropriately functionalized ring system, but the use of Lewis acid in the key step suggested that incorporation of an azide into the starting acetal (or its equivalent) might lead directly into a subsequent Schmidt-styled ring expansion of the cyclobutanone adduct to achieve the 5,6,6-tricyclic lactam.[10,11]

The concept was initially tested by treating **4** with azide-containing acetal **6**, which yielded three spirocyclobutanone diastereomers **7a**, **7b**, and **7c** in high combined yield (Scheme 3). The structure of the major product **7a** was based on the structure of **5a** as determined by Cha and via X-ray crystallography.[8b] The structures of the minor products **7b** and **7c** were determined by subsequent conversion of the ketones to the corresponding lactams via intramolecular Schmidt rearrangement. Thus, treatment of **7b** with $TiCl_4$

Scheme 2. Prins Precedent[8b]



Scheme 3. Two-Step Prins/Schmidt Reaction Sequence



(4) For recent reviews on cylindricine and lepadiformine syntheses, see: (a) Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531–2549. (b) Liu, J.; Hsung, R. P. *Chemtracts* **2005**, *18*, 321–330. (c) Kibayashi, C. *Chem. Pharm. Bull.* **2005**, *53*, 1375–1386. For recent approaches and syntheses of these molecules not covered in the reviews, see: (d) Vital, P.; Hosseini, M.; Shanmugham, M. S.; Gotfredsen, C. H.; Harris, P.; Tanner, D. *Chem. Commun.* **2009**, 1888–1890. (e) Zhang, X.-M.; Wang, M.; Tu, Y.-Q.; Fan, C.-A.; Jiang, Y.-J.; Zhang, S.-Y.; Zhang, F.-M. *Synlett* **2008**, 2831–2835. (f) Flick, A. C.; Caballero, M. J. A.; Padwa, A. *Org. Lett.* **2008**, *10*, 1871–1874. (g) Lygo, B.; Kirton, E. H. M.; Lumley, C. *Org. Biomol. Chem.* **2008**, *6*, 3085–3090. (h) Caldwell, J. J.; Craig, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2631–2634.

(5) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691–2694.

(6) Schar, P.; Renaud, P. *Org. Lett.* **2006**, *8*, 1569–1571.

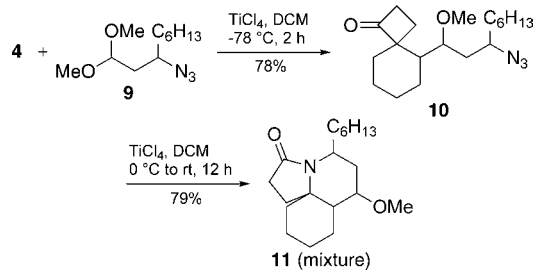
(7) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556–6558. Trost, B. M.; Chen, D. W. C. *J. Am. Chem. Soc.* **1996**, *118*, 12541–12554.

(8) (a) Ethirajan, M.; Oh, H.-S.; Cha, J. K. *Org. Lett.* **2007**, *9*, 2693–2696. (b) Lysenko, I. L.; Oh, H.-S.; Cha, J. K. *J. Org. Chem.* **2007**, *72*, 7903–7908. (c) Oh, H.-S.; Lee, H. I.; Cha, J. K. *Org. Lett.* **2002**, *4*, 3707–3709.

(9) Girard, C.; Amice, P.; Barnier, J. P.; Conia, J. M. *Tetrahedron Lett.* **1974**, *37*, 3329–3332.

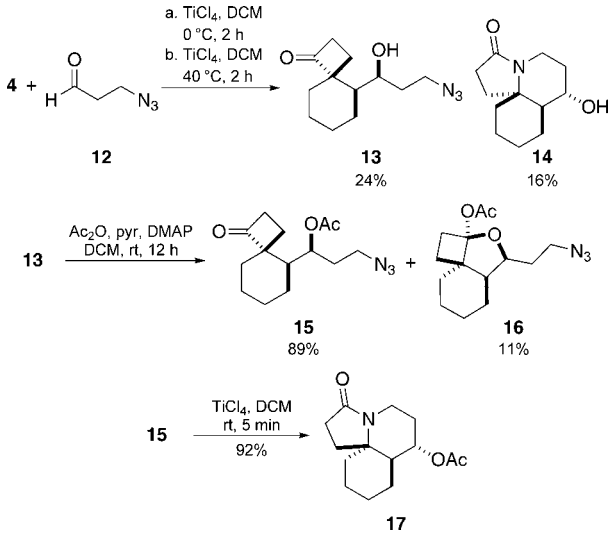
(10) For a recent review of the intramolecular Schmidt reaction, see: (a) Grecian, S.; Aubé, J. In *Organic Azides: Syntheses and Applications*; Bräse, S., Banert, K., Eds.; John Wiley and Sons: Chichester, UK, 2009; pp 191−237. For selected examples of domino reactions involving alkyl azides and Lewis acids, see: (b) Reddy, D. S.; Judd, W. R.; Aube, J. *Org. Lett.* **2003**, *5*, 3899–3902. (c) Zeng, Y.; Reddy, D. S.; Hirt, E.; Aube, J. *Org. Lett.* **2004**, *6*, 4993–4995. (d) Golden, J. E.; Aube, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316–4318. (e) Reddy, P. G.; Varghese, B.; Baskaran, S. *Org. Lett.* **2003**, *5*, 583–585. (f) Reddy, P. G.; Baskaran, S. *J. Org. Chem.* **2004**, *69*, 3093–3101. (g) Song, D.; Rostami, A.; West, F. G. *J. Am. Chem. Soc.* **2007**, *129*, 12019–12022. (h) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aube, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018–6024. (i) Huh, C. W.; Somal, G. K.; Katz, C. E.; Pei, H.; Zeng, Y.; Douglas, J. T.; Aubé, J. *J. Org. Chem.* **2009**, *74*7618−7626.

Scheme 4. Reaction of **4** and a β-Substituted Azido Acetal



cleanly afforded lactam **8b** in excellent yield, the stereochemistry of which was determined by NMR spectroscopy (see the Supporting Information for details of stereochemical assignments). The stereochemistry of **7c** was obtained by chemical correlation of **8c** with alcohol **14** as prepared below. We also sought conditions by which reaction of **4** and **6** would lead directly to **8** in a single pot, but the best overall yield obtained was considerably less than that of the two-step version (35% for **4** + **6** → **8** (mixture)) (Scheme 4).

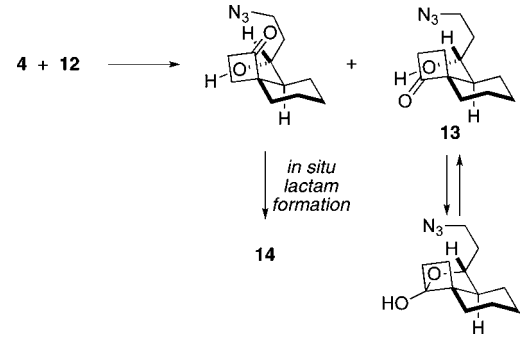
Scheme 5. Tandem Prins/Schmidt Reaction with 3-Azidopropanal



Although aldehydes were not previously reported as partners in this Prins reaction variant, we chose to examine them in the present instance, in part to avoid using a methyl ether as a protecting group.[12] Thus, reacting aldehyde **12** with **4** under optimized conditions for a one-pot sequence yielded two products, cyclobutanone **13** and lactam **14**, as single diastereomers (Scheme 5). Separate submission of **13** to a variety of Lewis acid conditions did not result in lactam formation. However, acetylation of the free hydroxyl group of **13** and subsequent treatment with $TiCl_4$ did generate the desired lactam **17** in high yield over the two steps. Compound **16** was also isolated from the acetylation procedure.

A crystal structure of **14** confirmed the relative stereochemistry shown, which maps onto that of the cylindricines (i.e., containing a *cis*-azadecalin ring system). The relative stereochemistry for **17** was determined by NMR and matched the core of the lepadiformines with a *trans*-azadecalin ring structure. It is interesting that the reaction pathways seem to diverge depending on the relative stereochemistry between the azide-containing side chain and the emerging cyclobutanone ring (Scheme 6). Thus, the intermediate in which the cyclobutanone carbonyl group is cis to the azide connector readily affords lactam **14** under these reaction conditions.

Scheme 6. Stereochemical Effect on Reaction Products from the Tandem Reaction of **4** and **12**



In contrast, the recovery of the ketone **13** from the reaction suggests that this isomeric species is unable to undergo an intramolecular Schmidt reaction in the presence of the free alcohol group (in contrast to the successful reaction with acetylated **15**). We suggest that in situ hemiketal formation, the likelihood of which is supported by the isolation of **16** from the acetylation reaction shown in Scheme 5, as one possible explanation for this divergent behavior.

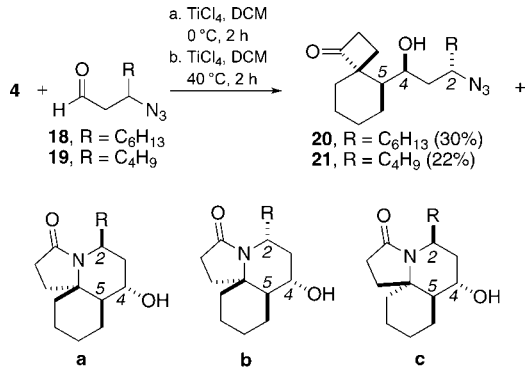
The reactions of β-substituted azidoaldehydes **18** and **19** behaved analogously to **12** (Scheme 7). Thus, these reactions afforded a single diastereomer of cyclobutanone (**20** or **21**) along with three diastereomers of lactams **22a**−**c** or **23a**−**c**, respectively (ratios estimated by ^{13}C NMR of the crude reaction mixture). In all isomers, the relative stereochemistry of the emerging alcohol from the Prins addition is syn (C-4 and C-5, cylindricine numbering imposed[1]). Interestingly, unexpectedly high 1,3-syn ratios were observed between C-2 and C-4 (ca. 11:1 for (**20** + **22a** + **22c**)/**22b** and 7:1 for (**21** + **23a** + **23c**)/**23b**)), suggesting a reasonable level of diastereofacial selectivity in additions to aldehydes **18** and **19**.

Several of the compounds so prepared were used to gain entry into the alkaloids that inspired these studies in the first place, beginning with a formal synthesis of lepadiformine

(11) A related but stepwise spiroannulation/Schmidt sequence was reported previously: Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966. For a mechanistically related semipinacol arrangement coupled with an intramolecular Schmidt reaction, see: (b) Gu, P.; Zhao, Y.-M.; Tu, Y. Q.; Ma, Y.; Zhang, F. *Org. Lett.* **2006**, *8*, 5271–5273.

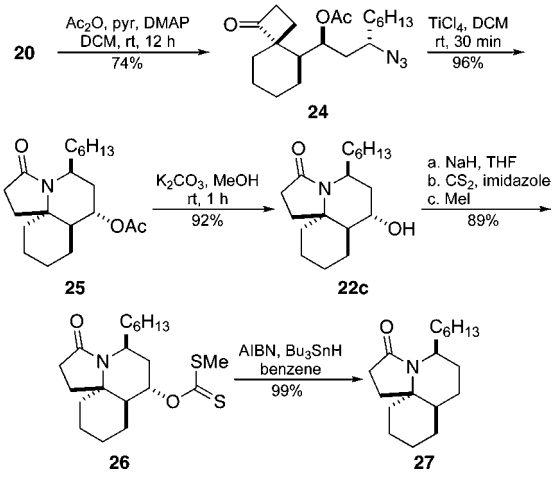
(12) Initial attempts to remove the methyl group on compounds like **8a** led to complex mixtures that included products arising from hydride shifts and elimination.

Scheme 7. Tandem Prins/Schmidt Reaction with β-Substituted Azidoaldehydes



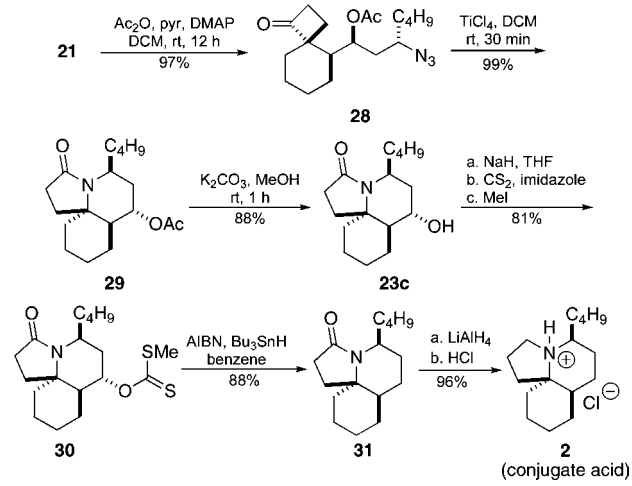
A. Thus, spirocyclobutanone **20** was acetylated and then treated with $TiCl_4$ to afford lactam **25** in excellent yield (Scheme 8). Deprotection of the hydroxyl group, xanthate formation, and Barton−McCombie dehydroxylation[13] furnished lactam **28**, which is a common intermediate to Renaud's synthesis of lepadiformine A.[6]

Scheme 8. Formal Synthesis of Lepadiformine A



Similarly, the total synthesis of lepadiormine C (**2**) was achieved from **21** as shown in Scheme 9. Analogous acetylation, intramolecular Schmidt reaction, and Barton−McCombie dehydroxylation followed by amide reduction and amine protonation yielded lepadiformine C, **2**.

Scheme 9. Total Synthesis of Lepadiformine C



In conclusion, we have developed a route to the tricyclic cores of the cylindricine and lepadiformine families using several variations of a tandem Prins/Schmidt sequence. Using this chemistry, we achieved a formal synthesis of lepadiformine A (corresponding to 12 steps and 8% overall yield) and the first total synthesis of lepadiformine C (9 total steps and 10% overall yield). Additional work on this and related domino reaction sequences involving the intramolecular Schmidt reaction is underway.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585.