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Total Syntheses of (+)-Cylindricines C–E and (–)-Lepadiformine through a Common Intermediate Derived from an *aza*-Prins Cyclization and Wharton's Rearrangement

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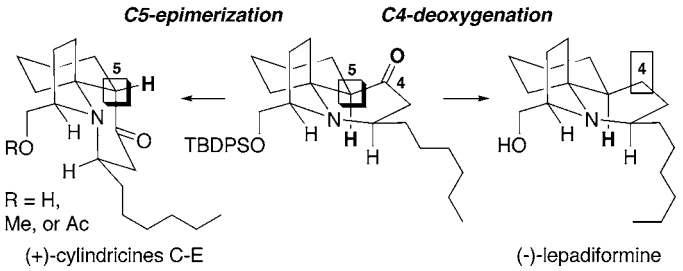
ABSTRACT



Enantioselective total syntheses of (+)-cylindricines C–E and (–)-lepadiformine through a common tricyclic intermediate are described here. These syntheses are concise and feature an *aza*-Prins cyclization and a seldom-used Wharton rearrangement en route to the common intermediate.

Blackman reported the isolation of (−)-cylindricines A−K from the marine ascidian *Clavelina cylindrica* collected in Tasmania.[1] Cylindricines A [**1a**] and B [**1b**] were assigned by X-ray structures of the corresponding picrates that exist as a 3:2 equilibrium mixture via the aziridinium intermediate **2** [Figure 1].[1a] Fasicularin **3** and lepadiformine **4**, two structurally related alkaloids, were isolated from the marine ascidian *Nephteis fasicularis*[2] and ascidian *Clavelina lepadiformis*,[3] respectively. Given their unique structural motif and biological activity [**3** shows cytotoxicity to Vero cells, and **4** is cytotoxic toward KB, HT29, and P388 cell lines],[2,3] the cylindricines,[4−6] fasicularin,[7] and lepadiformine[8−13] have already attracted an impressive array of synthetic efforts.

During our pursuit of these alkaloids employing the *aza*-[3 + 3] formal cycloaddition strategy,[14−16] we recognized

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

(2) Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. *Tetrahedron Lett*. **1997**, *38*, 363.

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

(4) For the first two total syntheses of (±)-cylindricines, see: (a) Snider, B. B.; Liu, T. *J. Org. Chem*. **1997**, *62*, 5630. (b) Liu, J. F.; Heathcock, C. H. *J. Org. Chem*. **1999**, *64*, 8263.

(5) For the total synthesis of (−)-cylindricines, see: (a) Molander, G. A.; Ronn, M. *J. Org. Chem*. **1999**, *64*, 5183. (b) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int Ed*. **2004**, *43*, 4336.

(6) For a recent synthesis of (+)-cylindricines, see: (a) Trost, B. M.; Rudd, M. T. *Org. Lett*. **2003**, *5*, 4599. (b) Arai, T.; Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett*. **2004**, *45*, 5921−5924.

(7) For two elegant syntheses of fasicularin, see: (a) Maeng, J.-H, Funk, R. L. *Org. Lett*. **2002**, *4*, 331. (b) Fenster, M. D. B.; Dake, G. R. *Org. Lett*. **2003**, *5*, 4313.

(8) For a detailed account on efforts involving the lepadiformine synthesis, see: Weinreb, S. M. *Acc. Chem. Res*. **2003**, *36*, 59.

(9) (a) Werner, K. M.; De Los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem*. **1999**, *64*, 686. (b) Werner, K. M.; De Los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem*. **1999**, *64*, 4865.

(10) (a) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett*. **1997**, *38*, 3369. (b) Pearson, W. H.; Ren, Y. *J. Org. Chem*. **1999**, *64*, 688.

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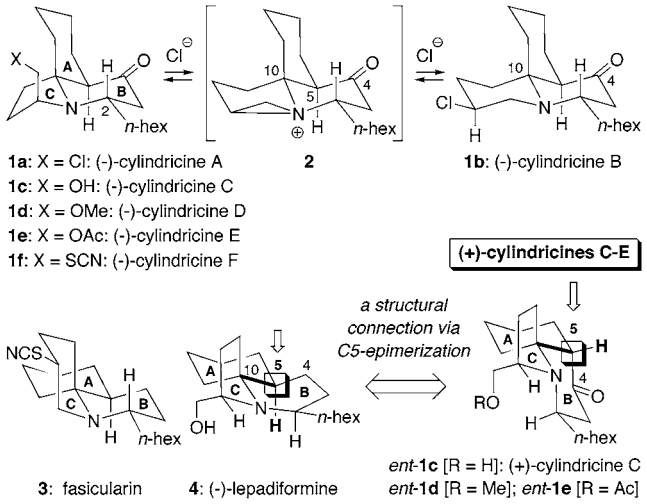


Figure 1.

that one issue involving these alkaloids has remained unexplored. The *aza*-tricyclic motif in **1**, **3**, and **4** can be accessed through a tandem Mannich strategy that has not been employed in the synthesis of the cylindricines, although Kibayashi[11] and Weinreb[12] constructed the C5−10 bond in the *aza*-spirocyclic AC-ring of (−)-lepadiformine **4** via a Mannich-type addition.

These strategies[11,12] appear to selectively provide a relative C5−10 stereochemistry suitable only for the synthesis of the *trans*-fused AB-ring in lepadiformine **4**, whereas cylindricines possess the *cis*-fused 1-*aza*-decalinic AB-ring. However, this implies that the cylindricine family, specifically (+)-cylindricines [*ent*-**1c**−**e**], and (−)-lepadiformine [**4**] can be related structurally through an epimerization at C5 of a suitable common intermediate. We report here total syntheses of (+)-cylindricines C−E and (−)-lepadiformine via a common intermediate derived from an *aza*-Prins cyclization and Wharton's rearrangement.

(11) (a) Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1205. (b) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583. For (−)-lepadiformine, see: (c) Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3017.

(12) For a recent total synthesis of (−)-lepadiformine, see: (a) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337. (b) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507.

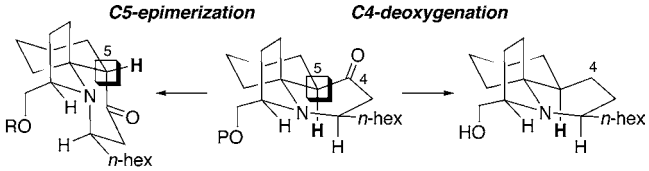
(13) For a recent total synthesis of (±)-lepadiformine, see: (c) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511.

(14) For intermolecular formal *aza*-[3 + 3] cycloadditions, see: (a) Sydorenko, N.; Hsung R. P.; Darwish, O. S.; Hahn, J. M.; Liu, J. *J. Org. Chem.* **2004**, *69*, ASAP (DOI: 10.1021/jo001219z). (b) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.-L.; Gerasyuto, A. I.; Brennessel, W. W. *J. Am. Chem. Soc.* **2002**, *124*, 10435. (c) Sklenicka, H. M.; Hsung, R. P.; Wei, L.-L.; McLaughlin, M. J.; Gerasyuto, A. I.; Degen, S. J.; Mulder, J. A. *Org. Lett.* **2000**, *2*, 1161. (d) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509.

(15) For intramolecular formal *aza*-[3 + 3] cycloaddition, see: Wei, L.-L.; Sklenicka, H. M.; Gerasyuto, A. I.; Hsung, R. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1516.

(16) For applications in natural product syntheses, see: (a) Luo, S.; Zificsak, C. Z.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709. (b) McLaughlin, M. J.; Hsung, R. P.; Cole, K. C.; Hahn, J. M.; Wang, J. *Org. Lett.* **2002**, *4*, 2017.

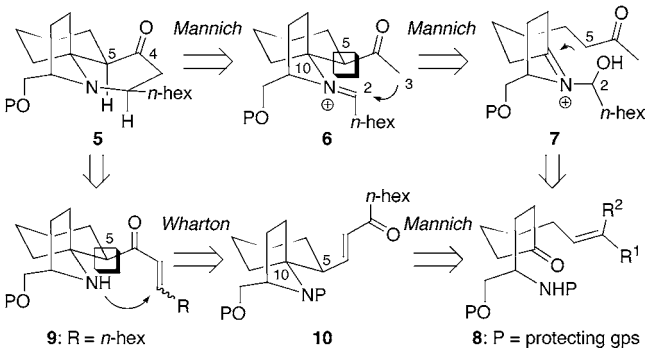
Scheme 1



The common intermediate, the *aza*-tricycle **5**, that would link together pathways toward (+)-cylindricines [*ent*-**1c**−**e**] and (−)-lepadiformine [**4**], is shown in Scheme 1. A C4-deoxygenation of **5** would lead to (−)-lepadiformine [**4**], whereas an appropriate epimerization at C5 would lead to the *ent*-cylindricines.

The *aza*-tricycle **5** was envisioned originally from a tandem Mannich strategy[17−19] starting from amino ketone **8** [**8**→**7**→**6**→**5**] as outlined in Scheme 2. Although this strategy

Scheme 2



is attractive in alkaloid synthesis[18,19] and can allow formation of two bonds [C5−10 and then C2−3] in a stereoselective manner, in this specific application, we experienced many difficulties.

To demonstrate the concept of using **5** as a common intermediate to access both (+)-cylindricines and (−)-lepadiformine, we ultimately prepared **5** from **8** through an *aza*-Prins cyclization[20] followed by Wharton's rearrangement.[21,22]

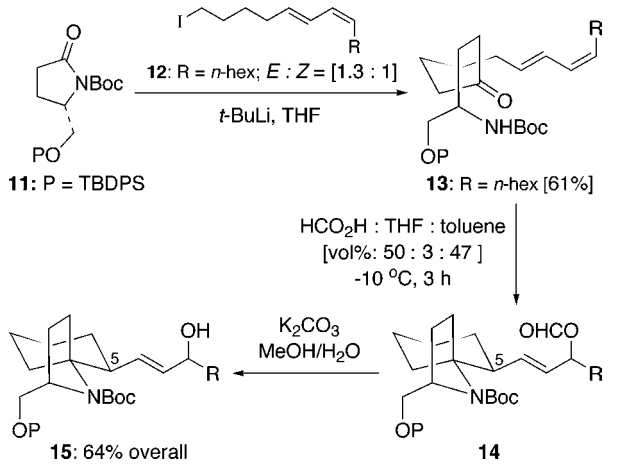
Our synthesis commenced with butyrolactam **11**[23] as shown in Scheme 3. Addition of the alkyllithium gen-

(17) Robinson, R. *J. Chem. Soc.* **1917**, 762.

(18) For recent reviews, see: (a) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (c) Scholz, U.; Winterfeldt, E. *Nat. Prod. Rep.* **2000**, *17*, 349. (d) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (e) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(19) For some examples of natural product synthesis that employ a tandem Mannich strategy, see: (a) Corey, E. J.; Balanson, R. D. *J. Am. Chem. Soc.* **1974**, *96*, 6516. (b) Rykman, D. M.; Stevens, R. V. *J. Am. Chem. Soc.* **1987**, *109*, 4940. (c) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164. (d) Takahashi, I.; Tsuzuki, M.; Yokota, H.; Kitajima, H. *Heterocycles* **1994**, *37*, 933. (e) Takahashi, I.; Tsuzuki, M.; Yokota, H.; Morita, T.; Kitajima, H. *Heterocycles* **1996**, *43*, 71. (f) Scott, R. W.; Epperson, J.; Heathcock, C. H. *J. Org. Chem.* **1998**, *63*, 5001.

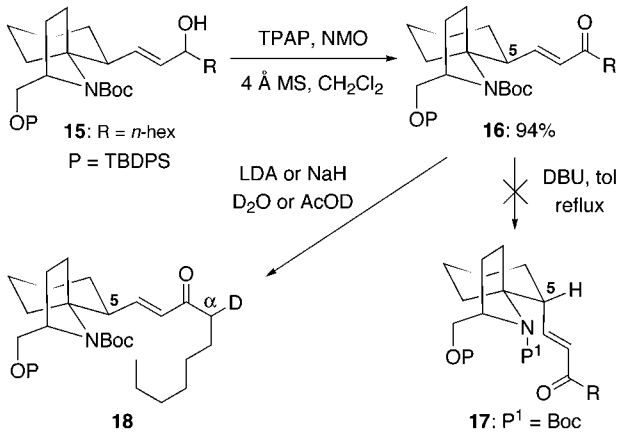
Scheme 3



erated from iodide **12** to **11** led to the ring-opened Boc-protected amino ketone **13**.[11c,24] A subsequent formic acid-promoted[11c,18,20] *aza*-Prins cyclization led to *aza*-spirocycle **14** in which the allyl cation intermediate has been trapped by the formate anion. Removal of the formyl group using K_2CO_3 and MeOH led to allyl alcohol **15** in 64% overall yield.

TPAP/NMO oxidation of allyl alcohol **15** gave enone **16** in 94% yield [Scheme 4], providing us with the first

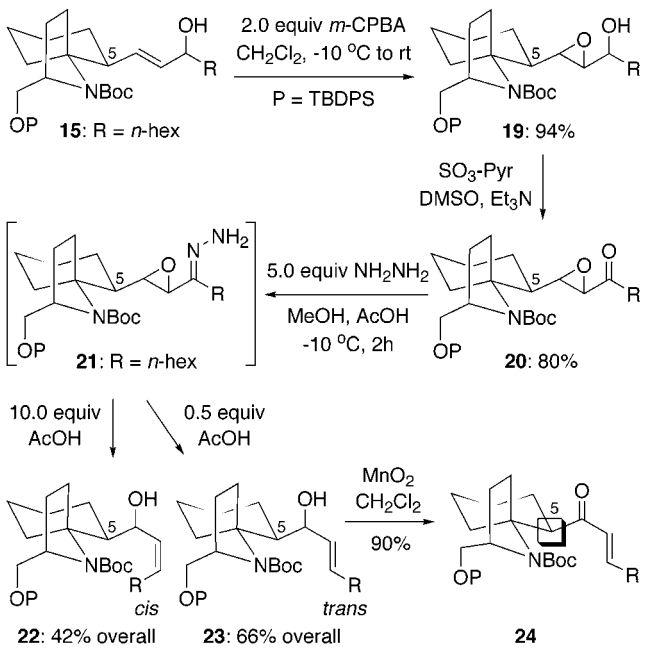
Scheme 4



opportunity to examine the possibility of epimerizing the C5 stereocenter. However, conditions such as refluxing DBU in toluene led to decomposition, while LDA or NaH only deprotonated the α-protons as evident by D_2O quenching.

With these failures, we nonetheless moved forward by first epoxidizing allyl alcohol **15** using *m*-CPBA, and a subsequent SO_3-Pyr/DMSO oxidation of epoxy alcohol **19** afforded epoxy ketone **20** [Scheme 5]. The ensuing Wharton's rearrangement using 5.0 equiv of hydrazine took place without the isolation of hydrazone **21** and gave the desired transposed allyl alcohol **23** in 66% yield. While we observed exclusively the *trans*-allyl alcohol **23** in most trials, we did find the *cis*-allyl alcohol **22** on one occasion in 42% yield. We are not certain at this point whether this is a phenomenon related to the equivalent of HOAc used or to the stereochemistry of the epoxide. We are currently examining this interesting observation from the Wharton's rearrangement.[21,22] MnO_2 oxidation of **23** provided enone **24** in 90% yield.

Scheme 5



Construction of the key common intermediate is shown in Scheme 6. Treatment of enone **24** with TFA in CH_2Cl_2 led to the desired tricycle **26**[25] in 72% yield with the *N*-1,4-addition taking place in situ through the free amine **25**.

We also isolated a second product on several occasions. After some careful examination,[25] we learned that the *aza*-tricycle **26** actually underwent rapid epimerization at C5 to give **27**, which is the second product, when exposed to silica gel [entry 1] or basic conditions [entries 2 and 3]. This

(20) (a) For a related review, see: Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Brossi, A., Ed.; Academic Press: San Diego, 1988; Vol. 2, pp 271−339. For some related examples, see: (b) Chao, W.; Waldman, J. H.; Weinreb, S. M. *Org. lett.* **2003**, *5*, 2915. (c) Dobbs, A.; Guesné, S. J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880. (d) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 951. (e) Evans, D. A.; Thomas, E. W. *Tetrahedron Lett.* **1979**, *20*, 411.

(21) (a) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615. (b) Wharton, P. S.; Dunny, S.; Krebs, L. S. *J. Org. Chem.* **1964**, *29*, 958.

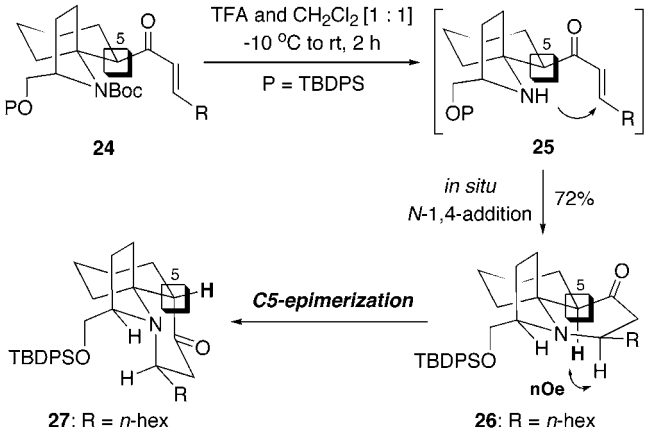
(22) Also see: (a) Stork, G., Williard, P. *J. Am. Chem. Soc.* **1977**, *99*, 7067. (b) Schult-Elte, K. H.; Rautenstrauch, V.; Ohloff, G. *Helv. Chim Acta* **1971**, *54*, 1805. (c) Ohloff, G.; Uhde, G. *Helv. Chim Act.* **1970**, *53*, 531.

(23) Preparation of **11** was carried out according to: Woo, K.; Jones, K. *Tetrahedron Lett.* **1991**, *32*, 6949.

(24) All new compounds are characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and mass spectroscopy and $[\alpha]_D^{23}$.

(25) We note here that compound **26** actually has the identical characterizations as penultimate intermediate in Trost's synthesis [ref 6]. However, we are comfortable with our assignment of **26** on the basis of the fact that (1) a total synthesis of (−)-lepadiformine was achieved using **26** and (2) desilylation of **26** using TBAF directly gave (+)-cylindricine C concomitant with the C5 epimerization.

Scheme 6



entry	conditions	ratio
1	silica gel, rt	**27 : 26** = 1 : 1
2	K_2CO_3, MeOH, rt	**27 : 26** = 1 : 0
3	DBU, toluene, rt	**27 : 26** = 2 : 1

finding establishes one of the two necessary links to the cylindricines and lepadiformine.

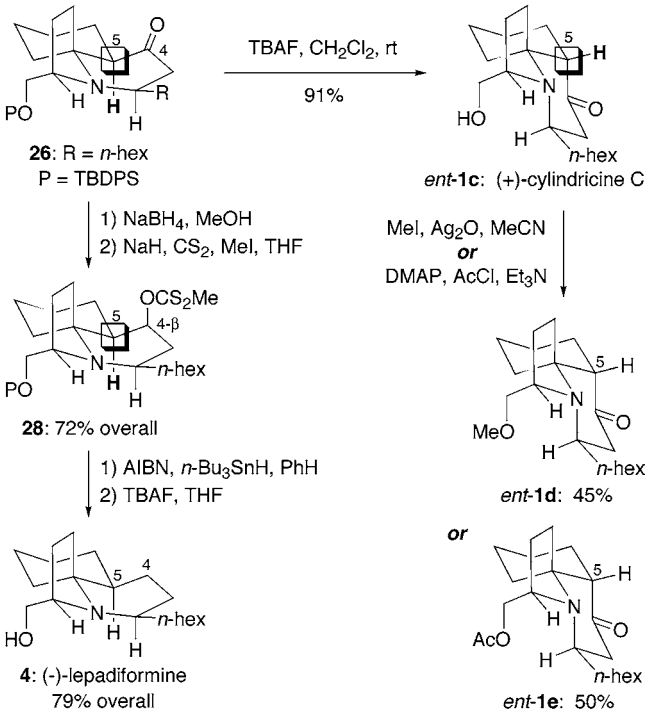
It turned out that (+)-cylindricine C [*ent*-**1c**] could be obtained in 79% yield directly from **26** via desilylation using TBAF, with the C5-epimeization occurring concomitantly[25] [Scheme 7]. Subsequent standard manipulations would lead to (+)-cylindricines D and E [*ent*-**1d** and **1e**].

To complete a total synthesis of (−)-lepadiformine **4**, we quantitatively reduced the C4-carbonyl using $NaBH_4$, which led to the C4−OH group being exclusively β [Scheme 7]. A variety of methods such as Burgess- or Chugaev-type elimination followed by hydrogenation were explored but failed to deoxygenate the C4−OH group.

Ultimately, xanthate **28** was prepared in 72% yield under standard conditions. Barton−McCombie deoxygenation protocol[26] was then employed, and subsequent desilylation led to (−)-lepadiformine **4** in a combined 79% yield. All four

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

Scheme 7



natural products prepared here spectroscopically matched those reported in the literature.[5,6,11,12]

We have described here enantioselective syntheses of both (+)-cylindricines C−E [11.1% overall yield in 9 steps from **11** for C] and (−)-lepadiformine [7.1% overall in 12 steps from **11**] through a common tricyclic intermediate. These syntheses are short and concise, featuring an *aza*-Prins cyclization and a seldom-used Wharton rearrangement.

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Supporting Information Available: Experimental procedures and selected ^1H and ^{13}C NMR spectra as well as characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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