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A Concise Total Synthesis of (–)-Cylindricine C through a Stereoselective Intramolecular *Aza*-[3 + 3] Annulation Strategy

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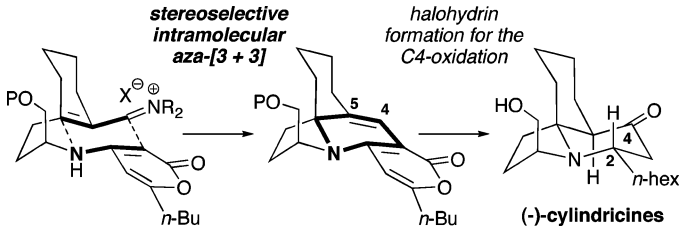
ABSTRACT



An enantioselective total synthesis of (–)-cylindricine C is described, featuring a diastereoselective intramolecular aza-[3 + 3] annulation strategy and an interesting halohydrin formation of the C4–5 olefin for construction of C4-ketone. This work provides a unique approach to this family of natural products.

Isolations of cylindricines A−K, from the marine ascidian *Clavelina cylindrica* collected in Tasmania, were first reported by Blackman in 1993.[1] Cylindricines A (**1**) and cylindricine B (**7**) exist as a 3:2 equilibrium mixture presumably via the aziridinium intermediate **6**.[1a] Two related marine alkaloids, lepadiformine **8b** and fasicularin **9**, were isolated from the marine ascidian *Clavelina lepadiformis*[2] and the Micronesian ascidian *Nephteis fasicularis*,[3] respectively. While **8b** possesses moderate cytotoxicity toward tumor cell lines in vitro,[2] **9** shows cytotoxicity to Vero cells with IC_{50} of 14μg/mL.[3] The correct structure of lepadiformine was established to be **8b** independently by Weinreb,[4] Pearson,[5] and Kibayashi.[6] Given their unique tricyclic structural motif, biological activity, and low natural abundance, lepadiformine **8b**,[4−7] fasicularin **9**,[8] and the cylindricines[9−11]

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

(3) 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.

(4) (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. (c) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507.For their recent total syntheses of (−)-lepadiformine, see: (d) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337.

(5) (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.

(6) (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. (c) For a synthesis of (−)-lepadiformine, see: Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3017. (d) For a recent account on total syntheses of both (−)-lepadiformine and (+)-cylindricines C−E via an aza-spirocyclic common intermediate, see: Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473.

(7) (a) For a detailed account on efforts involving the lepadiformine synthesis, see: (a) Weinreb, S. M. *Acc. Chem. Res.* **2003**, *36*, 59. (b) Also see: Kibayashi, C.; Aoyagi, S.; Abe, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2059. For another synthesis of (±)-lepadiformine, see: Sun Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511.

(8) For total syntheses of fasicularin, see: (a) Maeng, J.-H, Funk, R. L. *Org. Lett.* **2002**, *4*, 331. (b) Fenster, M. D. B.; Dake, Gregory R. *Chem.−Eur. J.* **2005**, *11*, 639. (c) Fenster, M. D. B.; Dake, Gregory R. *Org. Lett.* **2003**, *5*, 4313.

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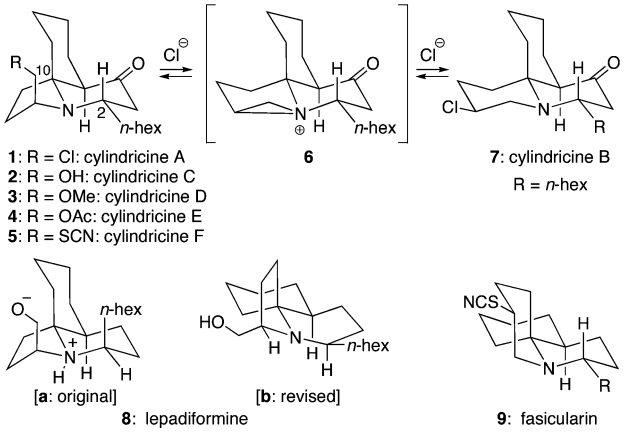
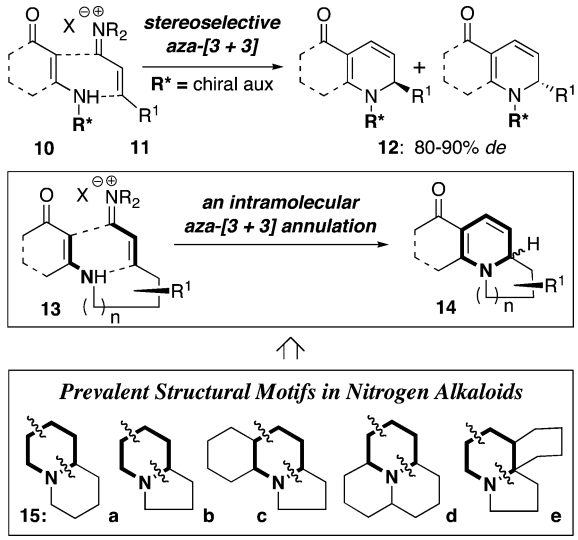
have attracted much effort from many synthetic groups.



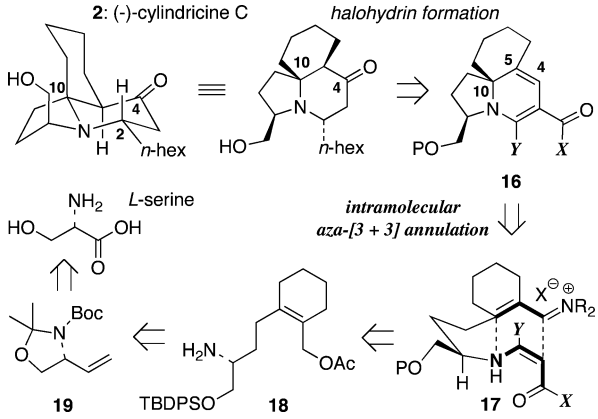
We envisioned an application of the aza-[3 + 3] annulation reaction[12−16] [vinylogous amides **10** + vinyl iminium ions **11** → **12** in Scheme 1] in the synthesis of cylindricines.

Scheme 1. Aza-[3 + 3] Annulation Strategy



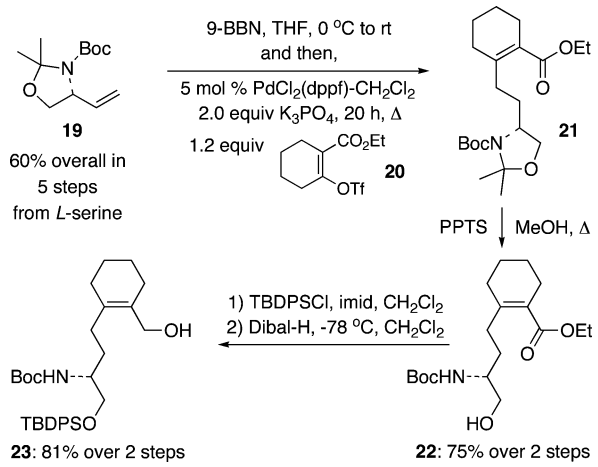
Specifically, we intended to utilize an intramolecular aza-[3 + 3] annulation[16] strategy (**13** → **14**) that could be suited for a wide range of nitrogen heterocycles **(15a−e)** including the motif found in lepadiformine or cylindricines **15e**. We report here the total synthesis of (−)-cylindricine C featuring a stereoselective intramolecular aza-[3 + 3] annulation strategy.

Scheme 2. Retrosynthetic Analysis



Our plan is outlined in Scheme 2.Tricycle **16**, a key versatile intermediate leading to the cylindricines, can be produced via an intramolecular aza-[3 + 3] formal cycloaddition of chiral vinylogous amides **17** that is tethered to the vinyl iminium ion. A range of vinylogous amides **17** could be prepared from chiral amine **18**, which can be prepared from the known vinyloxazoline **19**.[17] For the end game of the total synthesis, we intend to access the C4-carbonyl group via a sequence that would feature a halohydrin formation of the C4−5 olefin.

Scheme 3. Synthesis of the Protected Allyl Alcohol **23**



As shown in Scheme 3, our total synthesis commenced with hydroboration of vinyl oxazoline **19** (five steps from L-serine in 60% yield overall[17]) with 9-BBN followed by a Suzuki−Miyaura[18] coupling with vinyl triflate **20** to give ester **21**.[19] Subsequent removal of the acetonide group using

(9) For 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.

(10) For total syntheses 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. For a recent synthesis of (+)-cylindricines, see: (c) Trost, B. M.; Rudd, M. T. *Org. Lett*. **2003**, *5*, 4599. (d) Arai, T.; Abe, H.; Aoyagi, S. Kibayashi, C. *Tetrahedron Lett*. **2004**, *45*, 5921. (e) Also see 6d. (f) Taniguchi, T.; Tamura, O.; Uchiyama, M.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *Synlett* **2005**, 1179.

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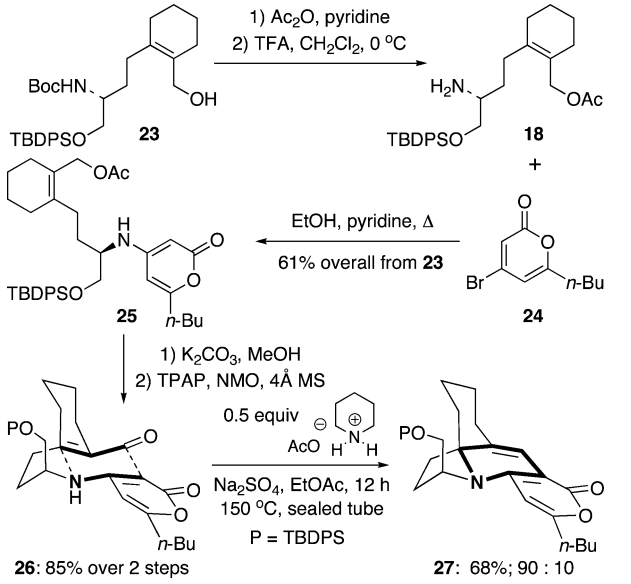
(12) For reviews, see: (a) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem*. **2005**, *3*, 1349. (b) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem*. **2005**, 23.

PPTS gave the Boc-protected amino alcohol **22** in 75% yield over two steps. The free primary alcohol **22** was capped with a TBDPS group followed by a Dibal-H reduction of the ester intermediate to afford allyl alcohol **23** in 81% yield over two steps.

Protection of **23** using Ac_2O followed by removal of the Boc group using TFA led to chiral amine **18** (Scheme 4).

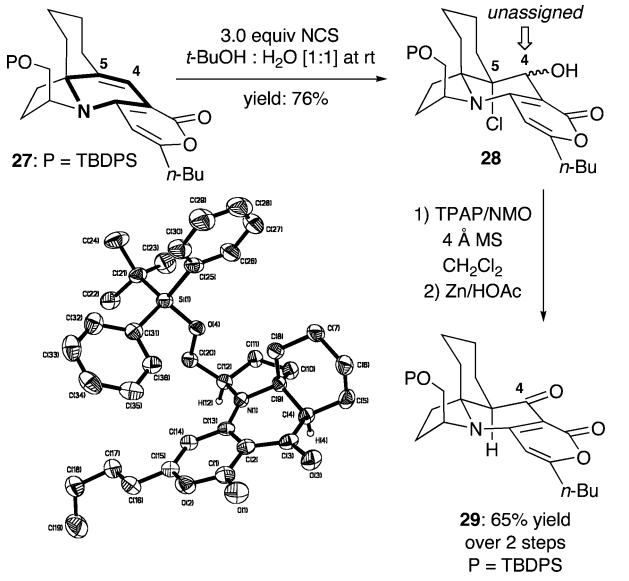
Scheme 4. Key Intramolecular Aza-[3 + 3] Annulation



The access to chiral amine **18** provides a significant flexibility in choosing an appropriate vinylogous amide (see **17** in Scheme 2). We elected to use bromopyrone **24** because we had already developed a protocol for reductive ring-opening of α-pyrones.[15c] Accordingly, condensation of amine **18** with 6-*n*-butyl-4-bromo-2-pyrone **24**[19] was pursued to give amino pyrone **25** in 61% yield. Deacylation and Ley−Griffith's oxidation[20] provided enal **26** in 85% yield over two steps.

With the annulation precursor enal **26** in hand, the key intramolecular *aza*-[3 + 3] annulation was found to proceed smoothly in toluene with 0.5 equiv of piperidinium acetate as the catalyst for vinyliminium ion formation. After the mixtre was heated at 150 °C for 12 h, tetracyclic annulation product **27** was obtained in 68% yield as two separable diastereomers in a ratio of 9:1 over several runs favoring of the desired isomer as shown. The relative stereochemistry of the major isomer was assigned rigorously using X-ray at a later stage (see Scheme 5).

Scheme 5. Installation of the C4-Carbonyl Group



Success in this key intramolecular aza-[3 + 3] annulation reaction provided us with an opportunity to complete our total synthesis of (−)-cylindricine C. The remaining goal is to install the desired ketone functionality at C4. However, this proved to be the most challenging facet of this endeavor. We ultimately were able to employ an interesting sequence that entails a halohydrin formation specifically using NCS in *t*-BuOH/H_2O (Scheme 5). This led to the chlorohydrin **28** in 76% yields as a single diastereomer.[21] TPAP-oxidation[20] followed by a reductive removal of the tertiary Cl

(13) For a review on vinylogous amide chemistry, see: Kucklander, U. Enaminones as Synthons. In *The Chemistry of Functional Groups: The Chemistry of Enamines*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1994; Part I, p 523.

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(15) For leading references on intermolecular aza-[3 + 3], see: (a) Sydorenko, N.; Hsung R. P.; Darwish, O. S.; Hahn, J. M.; Liu, J. *J. Org. Chem.* **2004**, *69*, 6732. (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) McLaughlin, M. J.; Hsung, R. P.; Cole, K. C.; Hahn, J. M.; Wang, J. *Org. Lett.* **2002**, *4*, 2017. (d) Wei, L.-L.; Hsung, R. P.; Xiong, H.; Mulder, J. A.; Nkansah, N. T. *Org. Lett.* **1999**, *1*, 2145.

(16) For intramolecular aza-[3 + 3], see: (a) Wei, L.-L.; Sklenicka, H. M.; Gerasyuto, A. I.; Hsung, R. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1516. (b) Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. W. *J. Org. Chem.* **2005**, *70*, 4248. For some simple applications, see: (c) Sydorenko, N.; Zificsak, C. A.; Gerasyuto, A. I.; Hsung, R. P. *Organic Biomol. Chem.* **2005**, *3*, 2140. (d) Luo, S.; Zificsak, C. Z.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709.

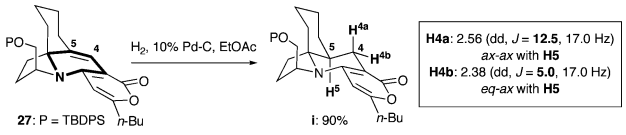
(17) (a) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707. (b) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. J. *Synthesis* **1994**, 31.

(18) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

(19) See the Supporting Information.

(20) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.

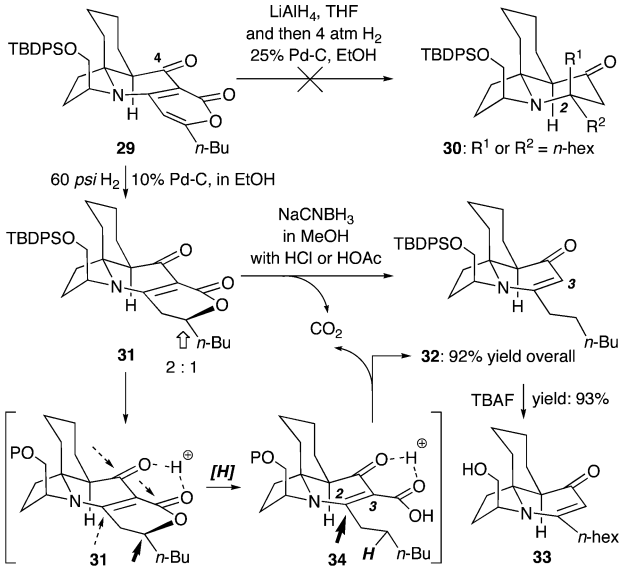
(21) Although we did not rigorously assign the relative stereochemistry at C4 and C5, we believed that NCS should have approached from the less hindered bottom face as observed in the hydrogenation of **27** that gave **i** in 90% yield as a single diastereomer. The relative stereochemistry C4 and C5 is unambiguous on the basis of coupling constants obtained for H4a and H4b.



group using Zn and HOAc afforded ketone **29** as a single diastereomer. NOE was suggestive, but an X-ray structure of **29** was obtained, thereby removing any doubts in the structural and stereochemical assignments.

With ketone **29** in hand, we were poised to execute a reductive ring opening of α-pyrones that we had developed using LAH and 4 atm of H_2 (Scheme 6).[15c] However, this

Scheme 6. Reductive Decarboxylation of the α-Prone Ring



was completely unsuccessful using ketone **29**. Alternatively, we carried out a stepwise sequence: (1) Hydrogenation with 60 psi *of* H_2 gave dihydropyrone **31**, which was not very stable, as a 2:1 isomeric mixture. (2) Without purification, an ensuing $NaCNBH_3$ reduction was carried out with HCl (or HOAc). This led to dihydro-4-pyridone **32** in 92% overall yield, and a subsequent desilylation gave alcohol **33** in 93% yield.[22]

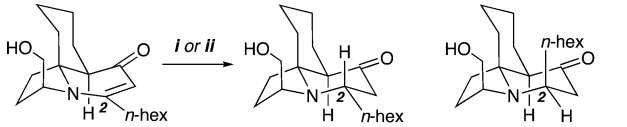
This reductive decarboxylation of the α-pyrone ring had likely proceeded through decarboxylation of intermediate **34** after a selective reduction ring opening of the lactone (solid arrow in **31** in the brackets) despite three other possibilities for reductions (dotted arrows).[23] Over-reduction did occur at C2 (solid arrow in **34**) when the reaction time was prolonged.

(22) The deprotection was carried out earlier than expected because we could not do anything with **33** in completing the total synthesis.

(23) There was a slight confusion initially as to if the decarboxylation had occurred. Attempted thermal "decarboxylation" of **32** led to no change in the proton NMR. For reasons unknown, the C3-H evidently was broadened in $CDCl_3$ and, thus, appeared to be missing. It shows up at 5.50 ppm in toluene-d_8.

To complete the total synthesis, a Stork−Crabtree-directed hydrogenation[24,25] of dihydro-4-pyridone **33** was carried out (entry *i* in Scheme 7). Instead of what we had hoped, we

Scheme 7. Completion of the Total Synthesis



entry	reagents and conditions	yields of **2**[a,b]	of **35**[a]
i	50 *psi* H_2, 10% Pd-C, EtOAc 1.0 equiv Ir[cod(PCy_3)py]PF_6, rt, 48 h	0	54
ii	$Na(OAc)_3BH$, cat. HOAc, $CDCl_3$, rt, 21 h, reflux, 40 min	83	0

a) Isolated yields. **b)** (-)-cylindricine C [**2**]: $[\alpha]_D^{25}$ = -66.7 (c 0.09, CH_2Cl_2); literature value [Molander: See reference 10a]: - 64.0 (c 0.2, CH_2Cl_2).

obtained (−)-2-*epi*-cylindricine C **35**[26] in 54% yield (**33** was recovered in 35% yield). On the other hand, a remote hydroxyl-directed reduction using $Na(OAc)BH_3$[10b] gave (−)-cylindricine **2** in 83% yield (entry *ii*). While **35** spectroscopically matched those reported by Weinreb[4b] and Ciufolini,[10b] (−)-cylindricine **2** matched Molander's report.[10a]

We have described here an enantioselective total synthesis of (−)-cylindricine C, featuring the first application of a stereoselective intramolecular aza-[3 + 3] annulation strategy with an overall yield of 7.4% in 17 steps (from **19**, or 4.5% overall yield in 22 steps from L-serine), and an interesting halohydrin formation for the construction of the C4-carbonyl group. This work provides a novel approach to this family of alkaloids.

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Supporting Information Available: Experimental and ^1H NMR spectral and characterizations for all new compounds as well as X-ray structrural data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) For some recent examples, see: (a) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515. (b) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.

(26) For (−)-2-*epi*-cylindricine C 35: $[\alpha]^{20}_D = -12.4$ (*c* 0.15, $CHCl_3$). Ciufolini's value is: $[\alpha]^{20}_D = -39.0$ (*c* 0.5, CH_2Cl_2) (see ref 10b).