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An *N*-Acyliminium Cyclization Approach to a Total Synthesis of (+)-Cylindricine C

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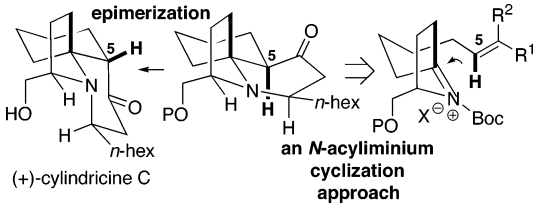

Details of problems and solutions encountered during the development of an enantioselective total synthesis of (+)-cylindricine C are described here. The total synthesis itself was accomplished in 8 steps, featuring an *N*-acyliminium cyclization strategy, the seldom-used Wharton rearrangement, and a key epimerization at C5.

Introduction

(−)-Cylindricines A−K were isolated from the marine ascidian *Clavelina cylindrica* collected in Tasmania[1] with the picrate salts of A [**1a**] and B [**1b**] assigned by X-ray structures [Figure 1].[1a] Their unique structural motif has attracted an impressive array of synthetic efforts.[2−5] We became interested in cylindricine alkaloids because of an intriguing observation that the powerful *N*-acyliminium cyclization approach[6] has been exclusively employed in total syntheses of the related alkaloid (−)-lepadiformine [**5**][7−13] and never for any of the cylindricine family members.[2−5]

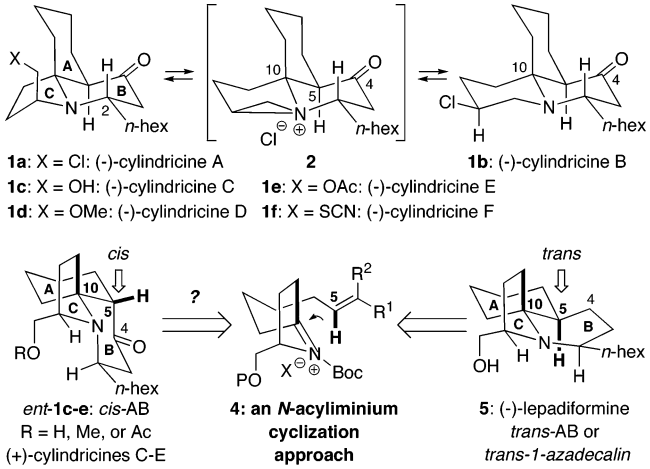

FIGURE 1.

Specifically, Kibayashi[11] and Weinreb[12] constructed the C5−10 bond in the *aza*-spirocyclic AC-ring of (−)-lepadiformine **5** via an *N*-acyliminium cyclization of **4**. It appears that this strategy is feasible for the synthesis of

(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) For a detailed account on efforts involving the cylindricine synthesis, see: Liu, J.; Hsung, R. P. *ChemTracts* **2005**, *18*, in press.

(3) 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.

(4) 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.

(5) For recent syntheses 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. (c) See ref 17.

(6) For reviews, see: (a) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev*. **2004**, *104*, 2311. (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221. (c) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (d) Scholz, U.; Winterfeldt, E. *Nat. Prod. Rep*. **2000**, *17*, 349. (e) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed*. **1998**, *37*, 1044. (f) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(7) For isolation of lepadiformine, see: Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett*. **1994**, *35*, 2691.

(8) (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.

(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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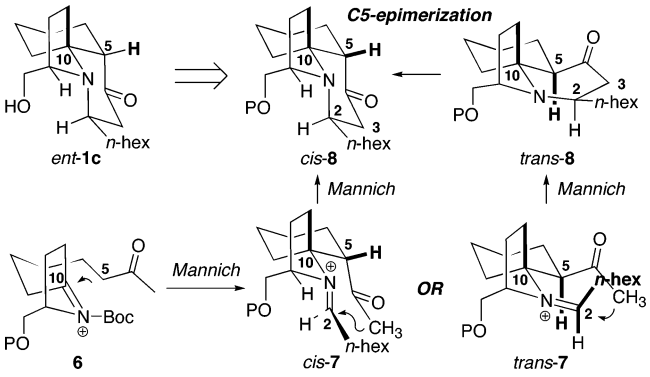
SCHEME 1



(−)-lepadiformine **5** because it provides the desired trans relative stereochemistry at C5−10. On the other hand, the AB-ring is cis-fused at C5−10 in cylindricines, thereby implying that an *N*-acyliminium cyclization approach may not be suitable. However, we wanted to examine the validity of this speculation because we intended to pursue a tandem Mannich approach[6] en route to cylindricines. As shown in Scheme 1, *ent*-**1c**−**e** could be envisioned from a tandem Mannich strategy starting from the *N*-acyliminium intermediate **6** [**6** → **7** → **8**, counteranion omitted for clarity]. This seldom used tandem strategy is attractive in alkaloid synthesis[14,15] and can lead to the formation of two σ-bonds [C5−10 and then C2−3] in a stereoselective manner.

The critical issues in this approach are (1) the feasibility of such a tandem process for the synthesis of cylindricines and (2) the stereochemical outcome for the *N*-acyliminium cyclization in the first Mannich addition for constructing the C5−10 bond. While *cis*-**7** cannot be readily precluded as a result of the Mannich-type *N*-acyliminium addition, if *trans*-**7** indeed predominates as suggested from Kibayashi[11] and Weinreb's[12] syntheses, an epimerization of C-5 would then be needed. We recently communicated the success in using *trans*-**8** as a common intermediate en route to both (−)-lepadiformine and (+)-cylindricines C−E.[16,17] We disclose here full details of our failures that ultimately led to the success in executing an *N*-acyliminium cyclization approach toward an enantioselective total synthesis of (+)-cylindricine C.

SCHEME 2

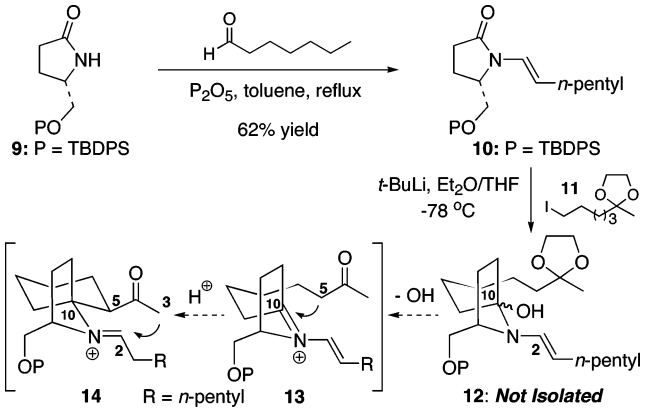
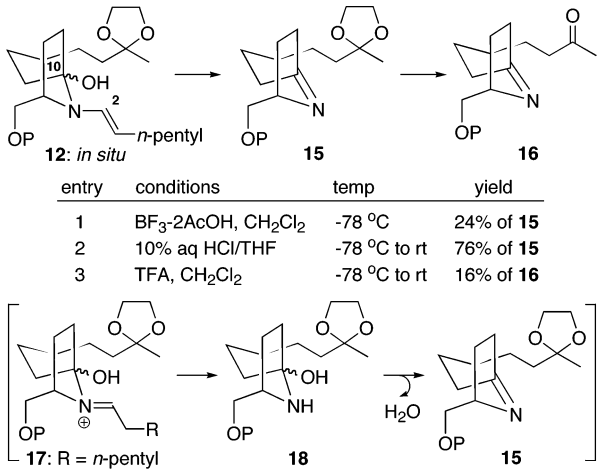


TABLE 1



entry	conditions	temp	yield
1	BF_3-2AcOH, CH_2Cl_2	-78 °C	24% of **15**
2	10% aq HCl/THF	-78 °C to rt	76% of **15**
3	TFA, CH_2Cl_2	-78 °C to rt	16% of **16**

Results and Discussion

To pursue the tandem Mannich concept, we prepared enamide **10** from lactam **9**[18] in 62% yield [Scheme 2]. Formation of hemiaminal **12** was accomplished in situ via addition of lithiated **11** to enamide **10**. Hemiaminal **12** should be suitable in generating the two iminium intermediates required for the tandem Mannich additions: in the direction toward C10 via eliminating the hydroxyl group [**12** → **13**, counteranion omitted for clarity] and toward C2 via protonation of the enamide [**13** → **14**].

However, under a range of conditions, we did not observe any Mannich-related products that could be derived from **13** or **14**. Instead, the cyclic imine **15** was found in most cases [Table 1]. Lewis acid conditions such as BF_3−2AcOH [entry 1] or protic conditions such as aq HCl [entry 2] led to **15** as the only discernible product along with recovered starting enamide **10**. The use of TFA [entry 3] led to **16** in which the ketal was hydrolyzed to ketone. The formation of **15** suggests that the enamine was being hydrolyzed likely via intermediates **17** and **18** under these reaction conditions. Attempts to isolate hemiaminal **12** via neutral aqueous conditions also failed and gave only **15**.

With this information in hand, we abandoned the enamide approach and directly pursued the synthesis of

(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. (d) See ref 17.

(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: Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511.

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

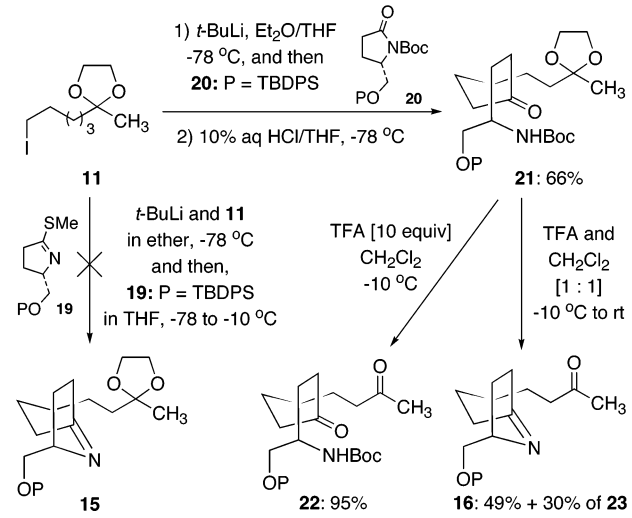
(15) For some examples of natural product synthesis that employ tandem Mannich strategy, see: (a) Corey, E. J.; Balanson, R. D. *J. Am. Chem. Soc.* **1974**, *96*, 6516. (b) Rykman, D. M.; Stevens, R. V. *J. Am. Chem. Soc.* **1987**, *109*, 4940. (c) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. 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.

(16) Liu, J.; Hsung, R. P.; Peters, S. D. *Org. Lett.* **2004**, *6*, 3989.

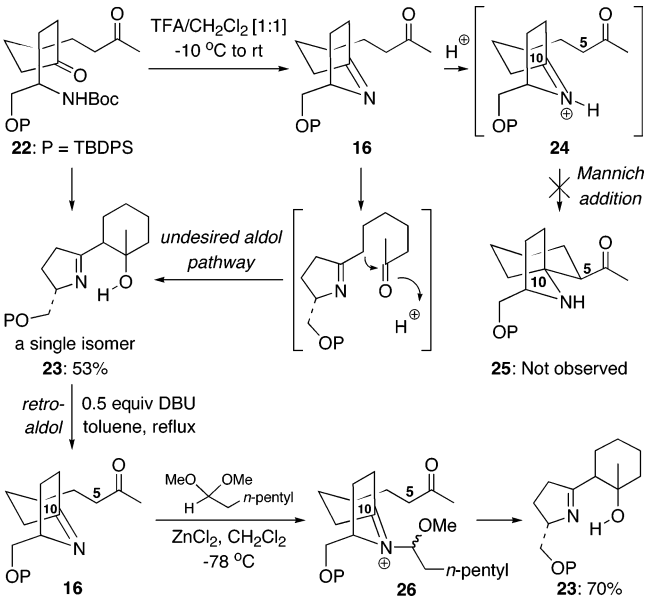
(17) For a recent account employing a similar concept of achieving total syntheses of both (−)-lepadiformine and (+)-cylindricines C−E via a *aza*-spirocyclic common intermediate, see: Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473.

(18) Woo, K.; Jones, K. *Tetrahedron Lett.* **1991**, *32*, 6949.

SCHEME 3



SCHEME 4

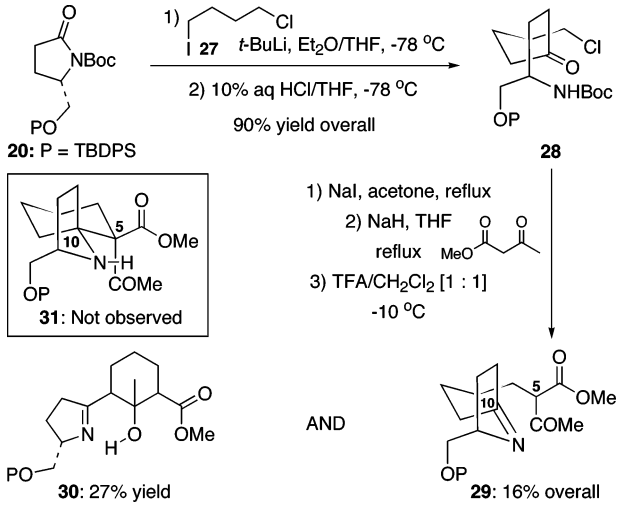


15 and/or **16**. As shown in Scheme 3, while the addition of lithiated **11** to thiol-imidate **19** failed to give **15**, the addition to lactam **20** led to ketone **21** [the initial hemiaminal intermediate evidently had ring-opened] in 66% yield. Treatment of **21** with 10 equiv of TFA afforded diketone **22** in 95% yield, whereas the cyclic imine **16** was obtained in 49% yield along with an unknown isolated in 30% yield that was later assigned as alcohol **23** [see Scheme 4] when TFA was used as cosolvent.

However, diketone **22** failed to provide the desired *aza*-spirocycle **25** that could be derived from a single Mannich addition involving iminium ion **24** [Scheme 4]. Instead surprisingly, alcohol **23** was obtained in 53% yield as a single diastereomer via an intramolecular aldol of cyclic imine **16**. Interestingly, retro-aldol occurred to regenerate **16** when alcohol **23** was refluxed with 0.5 equiv of DBU in toluene, but **16** did not proceed further to give any Mannich addition product under these conditions.

While being stymied by this undesired aldol pathway, attempts to use the cyclic imine **16** in achieving the tandem Mannich concept were pursued but also met with

SCHEME 5



similar difficulties. For an example, the use of Lewis acids such as $ZnCl_2$ to mediate the aminal formation with an acetal to generate the iminium intermediate **26**, which is capable of two Mannich additions, gave again only alcohol **23** in good yield.

To discourage this undesired aldol pathway, chloride **28** was prepared from the addition of lithiated **27** to lactam **20** in 90% yield [Scheme 5]. Ketoester **29** was generated from **28** in three steps with an overall yield of 16% along with, interestingly, alcohol **30** as the other isolable product in 27% yield via the related undesired aldol pathway, thereby implying that we were going down the wrong aldol pathway again. In hindsight, this design suffers from having to construct two adjacent quaternary centers shown at C5 and C10 in **31** [see the box in Scheme 5].

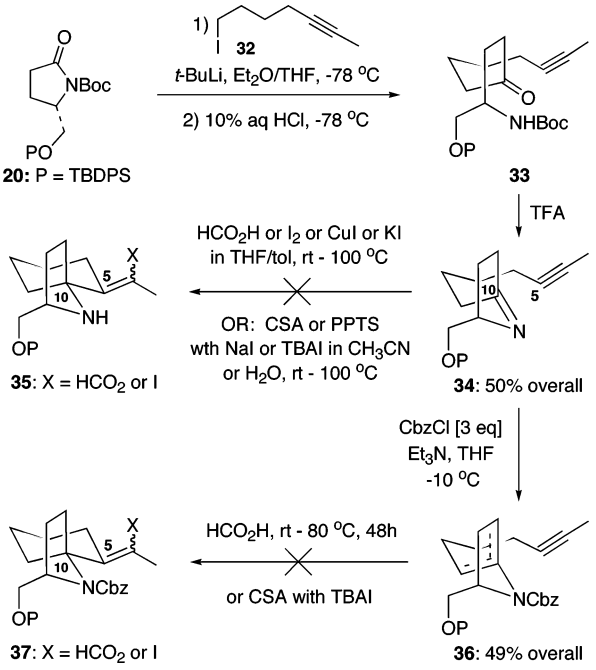
These failures suggest that not only significant modifications of our precursors are needed, but also more importantly, the Mannich-type *N*-acyliminium addition may not be the best approach. Thus, we turned our attention to *aza*-Prins-type *N*-acyliminium addition.[6,19] Toward this goal, we prepared alkyne **34** from the addition of lithiated **32** to lactam **20** [Scheme 6]. However, no desired *aza*-Prins cyclization product **35** was found by using a variety of initiation methods. Attempted *aza*-Prins cyclization with enamide **36**, prepared from **34**, was also unsuccessful.[20,21]

The failures here suggest that either we were not successful in executing the formation of the desired *N*-acyliminium ion from **34** or **36**, or the alkyne itself was not sufficiently reactive under these conditions to trap

(19) (a) For a related review, see: (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1988; Vol. 2, pp 271−339. For some 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.

(20) For examples of alkynes in *aza*-Prins-type cyclizations, see: (a) Schoemaker, H. E.; Boer-Terpstra, Tj.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 143. (b) Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron* **1982**, *38*, 3255. (c) Dijkink, J.; Speckamp, W. N. *Heterocycles* **1979**, *12*, 1147. (d) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, *21*, 1987. (e) Wijnberg, B. P.; Speckamp, W. N.; Oostveen, A. R. C. *Tetrahedron* **1982**, *38*, 209. (f) Hamersma, J. A. M.; Nossin, P. M. M.; Speckamp, W. N. *Tetrahedron* **1985**, *41*, 1999.

SCHEME 6

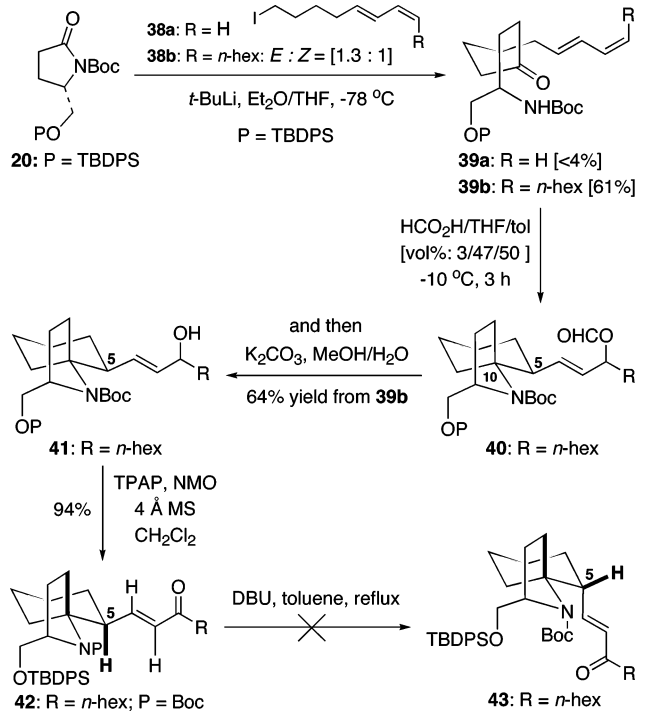


out the *N*-acyliminium intermediate. This particular *N*-acyliminium cyclization process presumably would generate a vinyl cation-like intermediate, which is energetically uphill, prior to being trapped by the X group. It is noteworthy that there are only a few examples with alkynes in *aza*-Prins-type *N*-acyliminium addition.[22]

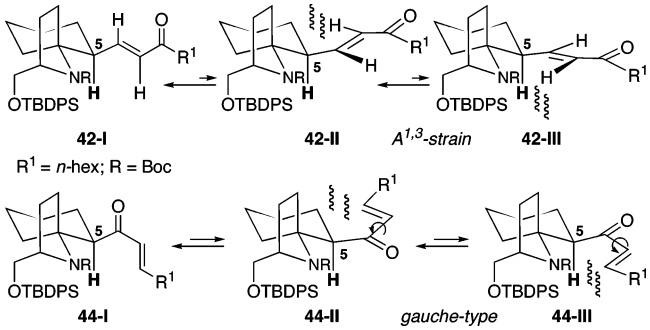
While we experimented some with more commonly used alkenes,[21,22] we focused our attention to *N*-acyliminium additions utilizing dienes.[6,19,11] As shown in Scheme 7, preparations of both ketones **39a** and **39b** from additions of lithiated **38a** and **38b**, respectively, to lactam **20** were pursued, but only **39b** was obtained in a synthetically useful manner. The *aza*-Prins cyclization of **39b**, promoted using formic acid, gave the desired *aza*-spirocycles **41** in 64% yield after removal of the formyl group using K_2CO_3 in MeOH. Enone **42** was obtained in 94% yield from **41** via TPAP/NMO oxidation, which provided access to the epimerization of the C5 stereocenter. However, various epimerization conditions, such as refluxing DBU in toluene, led to only decomposition.[23]

While this was a big set back, we speculated that the C5−H may not be as acidic as a normal γ-proton would have been because enone **42** should prefer conformation **I** and not conformation **II** or worse conformation **III** [Scheme 8] given the severe $A^{1,3}$-strain present in both latter conformations, although the C5−H is more aligned stereoelectronically and should be more acidic in both

SCHEME 7



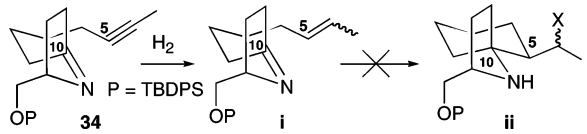
SCHEME 8



conformation **II** and **III**. Therefore, the acidity of the C5−H may be improved in enone **44** given that conformations **44-I**−**III** are more comparable in which both conformation **II** and **III** [likely a little less stable with more gauche-type interaction] could be suitable in allowing a successful deprotonation of C5−H.

While our conformation analysis might not have been completely accurate, it encouraged us to examine enone **44**. Toward this goal, we turned to the seldom-used Wharton's rearrangement[24,25] to transpose allyl alcohol **41**. As shown in Scheme 9, *m*-CPBA epoxidation of **41** followed by SO_3-Pyr/DMSO oxidation gave epoxy ketone **46**. Hydrazone formation occurred with 5.0 equiv of hydrazine in the presence of 0.5 equiv of HOAc, and without any isolation, hydrazone **47** rearranged exclusively to the trans allyl alcohol **48** with an overall yield of 66%.

(21) The use of alkenes for the *aza*-Prins-type *N*-acyliminium addition in this case also failed. Please refer to ref 6c for numerous examples of addition of alkenes to *N*-acyliminium intermediates.



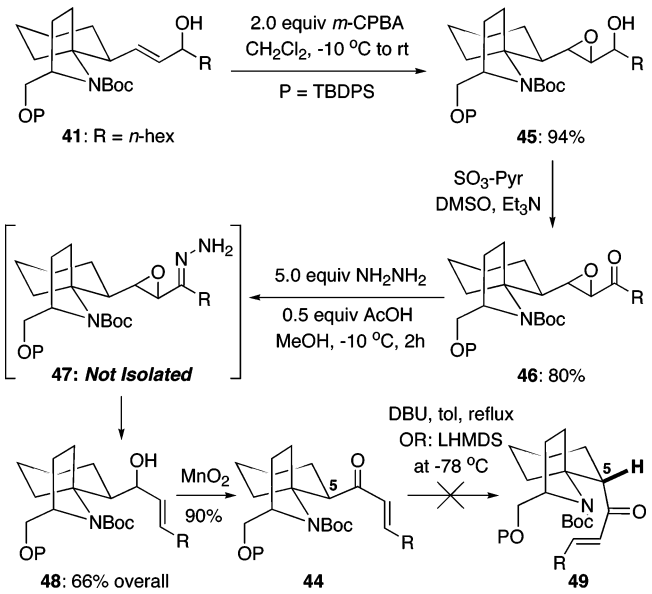
(22) Kibayashi also reported similar difficulties with alkenes and unsubstituted dienes: see ref 17.

(23) LDA or NaH only deprotonated the α-protons as is evident by D_2O quenching instead of the desired the γ-proton.

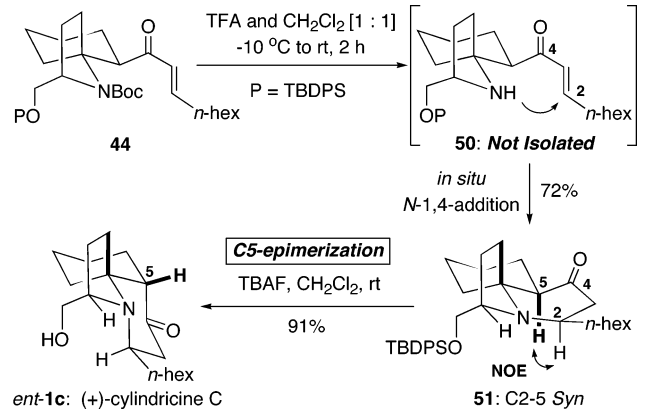
(24) (a) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615. (b) Wharton, P. S.; Dunny, S.; Krebs, L. S. *J. Org. Chem.* **1964**, *29*, 958.

(25) 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 Acta* **1970**, *53*, 531.

SCHEME 9



SCHEME 10



Subsequent MnO_2 oxidation of allyl alcohol **48** provided the desired enone **44** in 90% yield, allowing us to reexamine the C5-epimerization issue. However, it was quickly evident that standard epimerization conditions such as refluxing DBU and low-temperature LHMDS also could not epimerize the C5−H in **44**. This outcome prompted us to investigate the *aza*-tricycle preparation followed by epimerization of the C5−H.

Treatment of enone **44** with TFA in CH_2Cl_2 led to the desired *aza*-tricycle **51** in 72% yield with the *N*-1,4-addition taking place in situ through the free amine **50** [Scheme 10]. NOE experiment unambiguously established the relative stereochemistry at C2 and C5 to be syn. With *aza*-tricycle **51** in hand, we were able to successfully achieve an enantioselective total synthesis of (−)-lepadiformine **5** via a stepwise sequence that featured Barton's deoxygenation[26] to remove the C4-carbonyl of *aza*-tricycle **51**.[16] This also confirms our assignment of the relative stereochemistry at C2 and C5. However, to succeed in a total synthesis of cylindricine, we had to return to the C5-epimerization issue one last time.

Fortuitously, we observed a side product during the isolation and purification of *aza*-tricycle **51**. It turned out that the side product was a result of rapid epimerization at C5 when **51** was exposed to silica gel. There are two possible rationales for this rapid epimerization. First, the C5−H is perfectly aligned stereoelectronically in *aza*-tricycle **51**, thereby possessing the desired kinetic acidity for a rapid deprotonation. Second, there is an inherent preference for the cylindricine family of alkaloids to assume a cis-fusion for the 1-azadecalin AB-ring.[1] For related *aza*-tricycles, Kibayashi[17] reported that the *aza*-tricycle with a cis-fused 1-azadecalin AB-ring is about 5.5 kal mol^{-1} more stable than that of trans-fused.

Ultimately, we found that epimerization at the C5 position of *aza*-tricycle **51** occurred under the TBAF [2.0 equiv] conditions for removing the TBDPS group in **51**, leading directly to (+)-cylindricine C [*ent*-**1c**] in 91% yield [Scheme 10]. This finding establishes a unique and potentially biogenetic link between the cylindricines and lepadiformine, and that C5−H can be epimerized but likely only with an *aza*-tricyclic intermediate.

Conclusions

We have provided here details of problems and solutions encountered in an effort to achieve an enantioselective synthesis of (+)-cylindricine C via an *N*-acyliminium cyclization strategy. The total synthesis is accomplished in 8 steps with an overall yield of 11.1%, and in addition to the *aza*-Prins-type *N*-acyliminium cyclization, the synthesis features the seldom-used Wharton rearrangement and a key epimerization at C5 after the *aza*-tricycle formation.

Acknowledgment. Financial support from the Camille Dreyfus and the McKnight Foundations is greatly appreciated.

Supporting Information Available: Experimental procedures and ^1H NMR spectra and characterizations for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0501846

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