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Utilization of a Michael Addition: Dipolar Cycloaddition Cascade for the Synthesis of (±)-Cylindricine C

Andrew C. Flick, Maria José Arevalo Caballero, and Albert Padwa*

Department of Chemistry, Emory University, Atlanta, Georgia 30322

chemap@emory.edu

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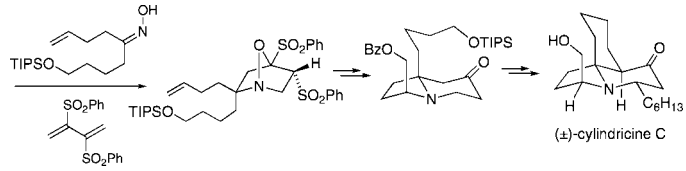
ABSTRACT



A new approach to the marine alkaloid (±)-cylindricine C has been devised. The key element of the synthesis consists of a Michael addition/dipolar cycloaddition cascade between 2,3-bis(phenylsulfonyl)-1,3-butadiene and 9-triisopropylsilanyloxy-non-1-en-5-one oxime. The resulting cycloadduct was converted into (±)-cylindricine C by a sequence of reactions including a reductive cyclization, intramolecular enolate alkylation, and conjugate addition to introduce the *n*-hexyl side chain.

The cylindricines A−K represent a family of alkaloids that were isolated by Blackman and co-workers from the ascidian *Clavelina cylindrica* found in Tasmania in the early 1990s.[1] Members of this family possess either the pyrrolo or pyrido[2,1-*j*]quinoline tricyclic framework and are readily interconverted via an aziridinium ion intermediate.[2] Among this class of alkaloids, cylindricine C (**1**) represents an intriguing target.[3] This natural product is closely related to the marine tricyclic alkaloid lepadiformine (**2**) differing only in the *cis*/*trans* stereorelationship of the perhydroquinoline ring system and the functionality at C_4 (Figure 1).[4] Given the unique structural motif, cylindricine C (**1**) and the related lepadiformine (**2**) have already attracted an impressive array of synthetic efforts.[5,6] The Molander[5a] and Trost groups[5b] utilized a double Michael addition to create the tricyclic skeleton from a monocyclic substrate. Independent work by Kibayashi[5c,d] and Hsung[5e] made use of a pivotal *N*-acyliminium ion/diene cyclization protocol. An oxidative spirocyclization of a phenolic primary amine was the key strategy used by Ciufolini[5i] and co-workers in their asymmetric synthesis of (−)-cylindricine C. Despite these earlier efforts, new and efficient approaches toward the tricyclic core of the cylindricines are still important as they would allow not only the synthesis of other members of this family of natural products but also related non-natural analogues possessing biological activity. In this communication, we report a concise stereocontrolled synthesis of (±)-cylindricine C (**1**) where an efficient tandem Michael addition/dipolar cycloaddition sequence developed in our laboratory plays a crucial role.[7]

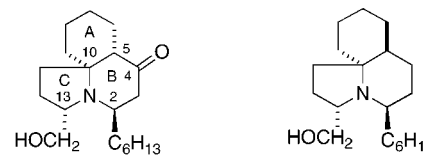


Figure 1. Marine tricyclic alkaloid framework.

(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.* **1995**, *48*, 955.

(2) (a) For a recent review, see: Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531. (b) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686.

(3) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1994**, *47*, 1355.

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

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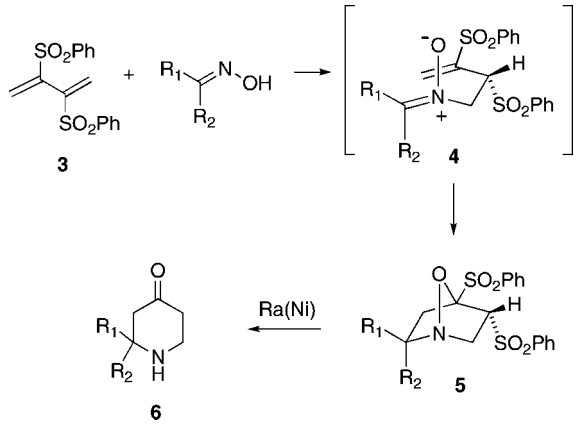
Our approach to cylindricine C was guided by a long-standing interest in the intramolecular [3 + 2]-cycloaddition of alkenyl nitrones for natural product synthesis.[8] In earlier work, we had described the formation of 7-oxa-1-azanorbornanes (i.e., **5**) from the reaction of oximes with 2,3-bis(phenylsulfonyl)-1,3-butadiene (**3**).[9] The formation of the bicyclic isoxazolidine **5** involves conjugate addition of the oxime with the activated diene **3** to give a transient nitrone **4** which then undergoes a further intramolecular 1,3-dipolar cycloaddition onto the adjacent vinyl sulfone (Scheme 1).

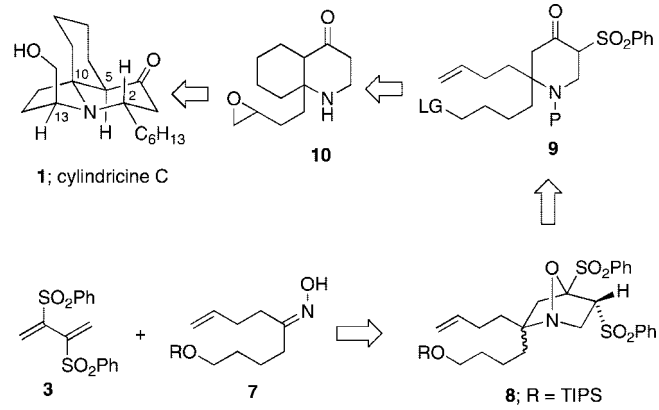
Scheme 1



Raney-Ni reduction of the 7-oxa-1-azanorbornane cycloadduct **5** results in sequential nitrogen−oxygen bond cleavage followed by desulfonylation to furnish a 2,2-disubstituted 4-piperidone of type **6**.

Our retrosynthetic analysis (Scheme 2) reveals a potentially convenient route to cylindricine C based on the above Michael addition/dipolar cycloaddition cascade. The cylindricine C core was envisioned to evolve from the easily accessible 4-piperidonyl B-ring precursor **9** which bears two

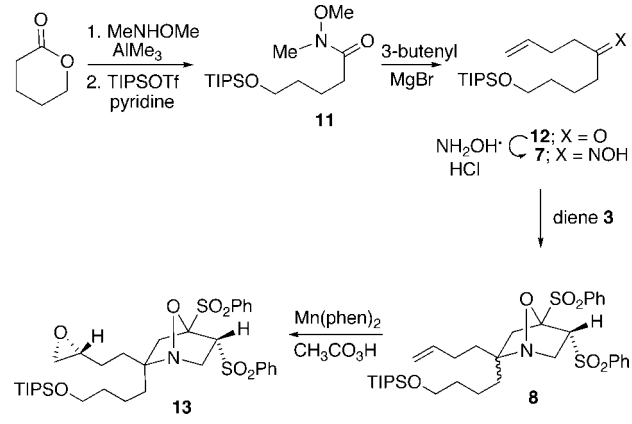
Scheme 2



distinguishable tethered groups at the congested C_2 stereogenic center. 2,3-Bis(phenylsulfonyl)diene **3** and oxime **7** (R = TIPS) were considered as the two building blocks for the construction of cycloadduct **8**. Challenges to overcome in this approach would include the construction of the remaining A- and C-rings around the 4-piperidone periphery. There would also be the need to leverage potential epimerization at the C_5 and C_{13} stereocenters within the azatricyclic core to geometries that would adopt the energetically preferred arrangement relative to the central tetrasubstituted C_{10} carbon prior to the late-stage *n*-hexyl group installation at the C_2 position.

Following this approach, we prepared oxime **7** starting from *δ*-valerolactone by a tractable four-step sequence which proceeded in 62% overall yield. The known 5-hydroxy-*N*,*O*-dimethyl-pentanohydroxamic acid[10] derived from *δ*-valerolactone and *N*,*O*-dimethylhydroxylamine was converted to the corresponding TIPS protected alcohol in 79% yield for the two-step sequence (Scheme 3). Reaction of **11** with

Scheme 3



3-butenyl magnesium bromide gave ketone **12** in 98% yield which, in turn, was transformed into the corresponding oxime **7** (80%) when treated with $NH_2OH{\cdot}HCl$. Heating a sample

(5) (a) Molander, G. A.; Ronn, M. *J. Org. Chem.* **1999**, *64*, 5183. (b) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 4599. (c) Arai, T.; Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 5921. (d) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473. (e) Liu, J.; Hsung, R. P.; Peters, S. D. *Org. Lett.* **2004**, *6*, 3989. (f) Liu, J.; Swidorski, J. J.; Peters, S. D.; Hsung, R. P. *J. Org. Chem.* **2005**, *70*, 3898. (g) Wang, J.; Swidorski, J. J.; Sydorenko, N.; Hsung, R. P.; Coverdale, H. A.; Kuyava, J. M.; Liu, J. *Heterocycles* **2006**, *70*, 423. (h) Swidorski, J. J.; Wang, J.; Hsung, R. P. *Org. Lett.* **2006**, *8*, 777. (i) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336. (j) Mihara, H.; Shibuguchi, T.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Heterocycles* **2007**, *72*, 421. (k) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Sakuraba, S.; Takashi, O.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4635.

(6) (a) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688. (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. *J. Org. Chem.* **2002**, *67*, 4337. (d) Greshock, T. J.; Funk, R. L *Org. Lett.* **2001**, *3*, 3511. (e) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583. (f) Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew Chem., Int. Ed.* **2002**, *41*, 3017.

(7) (a) Padwa, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, *29*, 2417. (b) Norman, B. H.; Gareau, Y.; Padwa, A. *J. Org. Chem.* **1991**, *56*, 2154.

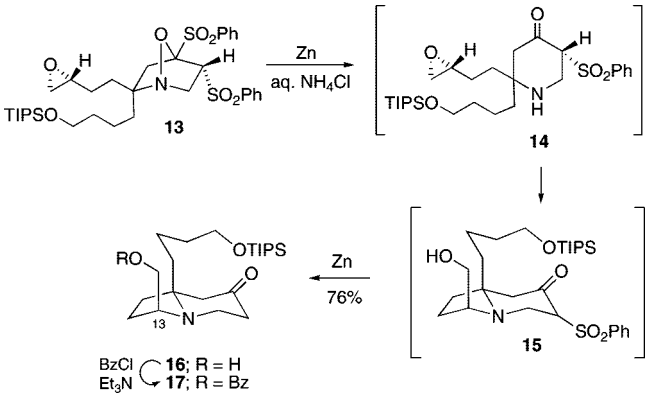
(8) (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, **1984**; Vol *2*, pp 83−168. (b) Jones, R. C. F.; Martin, J. N. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds; Wiley: New York, **2002**; Chapter 1.

(9) (a) Padwa, A.; Watterson, S. H.; Ni, Z. *Org. Synth.* **1997**, *74*, 147. (b) Jeganathan, S.; Okamura, W. H. *Tetrahedron Lett.* **1982**, *23*, 4763.

of oxime **7** and bis(phenylsulfonyl)diene **3** in $CHCl_3$ at 90 °C in a sealed tube for 12 h afforded the expected cycloadduct **8** as a 1:1 mixture of diastereomers in 75% yield. In a series of papers, Stack and co-workers showed that terminal olefins can be rapidly and efficiently epoxidized using manganese phenanthroline with commercially available peracetic acid in CH_3CN at room temperature.[11] Using these conditions, the alkenyl group present in cycloadduct **8** was epoxidized to give primarily **13** as a single diastereomer in 26% isolated yield.[12] The epoxidation of **7** proceeds with high *exo*-selectivity, and this is probably a result of different steric interactions in the transition state with the Mn^{II} complex for the two different diastereomers. In addition, complexation of the manganese catalyst with the N−O bond of the oxa-azanorbornene might also help to direct the facial selectivity of the epoxidation reaction.

With epoxide **13** in hand, treating a sample with excess zinc dust in an aqueous ammonium chloride−THF mixture[13] at 70 °C triggered a *reductive−cyclization* cascade whereby scission of the N−O bond was followed by the spontaneous ejection of phenyl sulfenic acid to furnish 4-piperidone **14** as a transient intermediate. Attack of the basic nitrogen atom of the 4-piperidone onto the epoxide ring proceeded rapidly and established the indolizidine ring system.[14] This was followed by a further reduction of the remaining phenylsulfonyl group in **15** to give **16** in 76% overall yield as a 9:1 mixture of diastereomers. The major isomer coincides with the hydroxymethylene geometry at the C_{13} position of the cylindricine C motif (Scheme 4). Esterification of alcohol

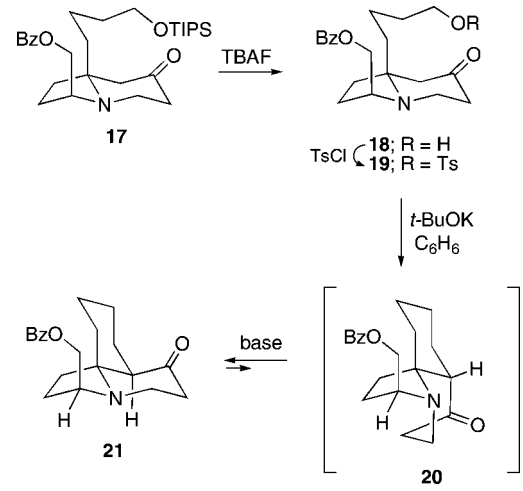
Scheme 4



16 with benzoyl chloride gave the corresponding ester **17**, and this allowed for the separation of the two diastereomers by column chromatography.

Desilylation of **17** with TBAF followed by tosylation of the resulting primary alcohol **18** furnished the expected tosylate **19** in 76% overall yield. We next carried out a base-induced cyclization of **19** so as to construct the core azadecalin ring system **21** by means of an intramolecular enolate alkylation reaction.[15] Thus, treatment of tosylate **19** with 2 equiv of *t*-BuOK in benzene followed by an aqueous workup afforded **21** in 69% yield (Scheme 5). This reaction

Scheme 5



presumably proceeds via the initially formed *trans*-1-azadecalin **20** which readily epimerizes to the thermodynamically more stable isomer **21**[4,5d,e] possessing the stereochemistry required for the structure of cylindricine C.

To complete the total synthesis of (±)-cylindricine C (**1**), oxidation of **21** to the corresponding 2*H*-piperidonyl enone **22** had to be affected to introduce the *n*-hexyl side chain. A variety of standard methods such as IBX, CAN, and PhSeCl/$NaIO_4$ were explored but failed to produce the required unsaturated enone. Ultimately, **22** was prepared in 95% yield by treating **21** with $Hg(OAc)_2$ in the presence of EDTA (Scheme 6).[16] Finally, the *n*-hexyl side chain was introduced by taking advantage of the tricyclic topography of **22** so as to influence the pseudoequatorial approach of the organometallic reagent. Thus, conjugate addition of the *n*-hexyl cuprate reagent to enone **22** using a modified Donohoe procedure[17] followed by alkaline saponification furnished a 3:1 mixture of cylindricine C (**1**) and 2-*epi*-cylindricine C

(10) Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265.

(11) (a) Terry, T. J.; Dubois, G.; Murphy, A.; Stack, T. D. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 945. (b) Murphy, A.; Stack, T. D. P. *J. Mol. Catal. A.* **2006**, *251*, 78. (c) Murphy, A.; Pace, A.; Stack, T. D. P. *Org. Lett.* **2004**, *6*, 3119. (d) Dubois, G.; Murphy, A.; Stack, T. D. P. *Org. Lett.* **2003**, *5*, 2469. (e) Murphy, A.; Dubois, G.; Stack, T. D. P. *J. Am. Chem. Soc.* **2003**, *125*, 5250.

(12) The low yield of **13** can be attributed to the recovery of a substantial amount of the *endo*-starting alkene **8** as well as some decomposition products derived from an *N*-oxide intermediate.

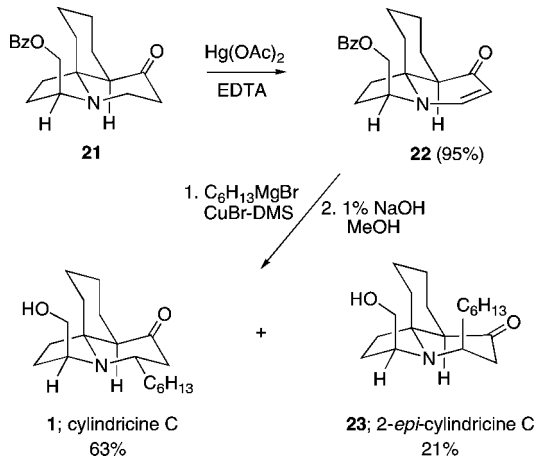
(13) White, J. D.; Hansen, J. D. *J. Org. Chem.* **2005**, *70*, 1963.

(14) Several examples of amplified nitrogen nucleophilicity under reductive conditions have been reported in the literature, particularly with substrates that bear a tethered electrophile. For some select cases, see:(a) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785. (b) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046. (c) Martin, S. F.; Chen, H. J.; Yang, C.-P. *J. Org. Chem.* **1993**, *58*, 2876. (d) Martin, S. F.; Chen, H. J.; Lynch, V. M. *J. Org. Chem.* **1995**, *60*, 276. (e) Smith, A. B.; Kim, D. S *Org. Lett.* **2004**, *6*, 1493. (f) Smith, A. B.; Kim, D. S. *Org. Lett.* **2005**, *7*, 3247. (g) Smith, A. B.; Kim, D. S. *J. Org. Chem.* **2006**, *71*, 2547.

(15) Also see: (a) Vite, G. D.; Spencer, T. A. *J. Org. Chem.* **1988**, *53*, 2555. (b) Conia, J. M.; Rouessac, F. *Tetrahedron* **1961**, *16*, 45.

(16) Möhrle, H.; Claas, M. *Pharmazie* **1988**, *43*, 749.

Scheme 6



(**23**) in 84% yield. The synthetic material displayed spectroscopic data identical to those reported for the natural product.[4]

In summary, a new approach to the marine alkaloid (±)-cylindricine C has been devised. The key element of the synthesis consists of a Michael addition/dipolar cycloaddition cascade of 2,3-bis(phenylsulfonyl)-1,3-butadiene with 9-triisopropylsilanyloxy-non-1-en-5-one oxime. The resulting cycloadduct was converted into cylindricine C by: (1) a reductive−cyclization cascade to set the BC-ring skeleton, (2) a base-induced cyclization to construct the tricyclic core, and (3) an oxidation-conjugate addition of the *n*-hexyl side chain. The applicability of the new methodology to other alkaloidal targets is currently under study and will be the subject of future reports.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Donohoe, T. J.; Johnson, D. J.; Mace, L. H.; Bamford, M. J.; Ichihara, O. *Org. Lett.* **2005**, *7*, 435.