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Total Synthesis of (±)-Cylindricine C

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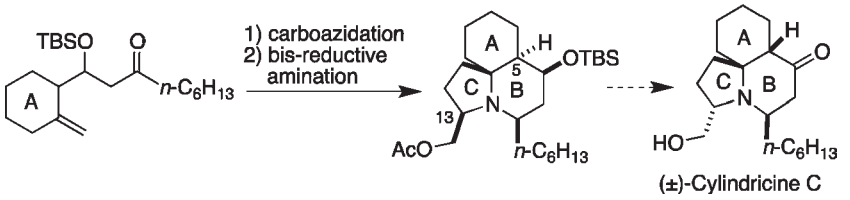
ABSTRACT



A concise synthesis of (±)-cylindricine C and its C(13)-epimer is described. Starting from 1-octyne, cylindricine C and 13-epi-cylindricine C were prepared in 11% and 15% yields, respectively. The synthesis involves the preparation of the central tricyclic moiety via a radical α-iodoketone carboazidation/bis-reductive amination sequence. Inversion of the stereochemistry at C(13) and C(5) was efficiently achieved on late stage intermediates.

Cylindricines (Figure 1) were isolated from the marine ascidian *Clavelina cylindrica* by Blackman et al. between 1993 and 1995.[1] These structurally related compounds all exhibited bioactivity against brine shrimp larvae in a bioassay. The tricyclic ring system of cylindricine C is closely related to the one found in lepadiformine A,[2,3] differing only in the *cis*/*trans* junction of the perhydroquinoline ring and the ketone at C(4).

Several total syntheses of cylindricine C are reported.[4] The introduction of the azaspirocenter represents one of the main challenges in the preparation of the key pyrrolo-[1,2,*j*]quinoline ring system. For this purpose, different strategies were developed: an intramoleular Michael addition,[5] an iminium ion/diene cyclization protocol,[6] an

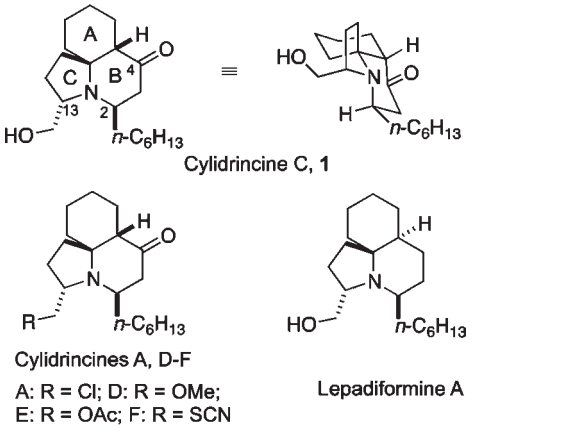


Figure 1. Structures of the cylindricines and lepadifromine A.

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

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(3) For some recent syntheses, see: (a) Mei, S.-L.; Zhao, G. *Eur. J. Org. Chem.* **2010**, *9*, 1660–1668. (b) Fujitani, M.; Tsuchiya, M.; Okano, K.; Takasu, K.; Ihara, M.; Tokuyama, H. *Synlett* **2010**, *5*, 822–826. (c) Lygo, B.; Kirton, E. H. M.; Lumley, C. *Org. Biomol. Chem.* **2008**, *6*, 3085–3090.

(4) For reviews, see: (a) Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531–2549. (b) Schär, P.; Cren, S.; Renaud, P. *Chimia* **2006**, *60*, 131–141.

(5) (a) Molander, G. A.; Rönn, M. *J. Org. Chem.* **1999**, *64*, 5183–5187. (b) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 4599–4602.

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(7) (a) Ciufolini, M. A.; Canesi, S.; Ousmer, M.; Braun, N. A. *Tetrahedron* **2006**, *62*, 5318–5337. (b) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336–4338.

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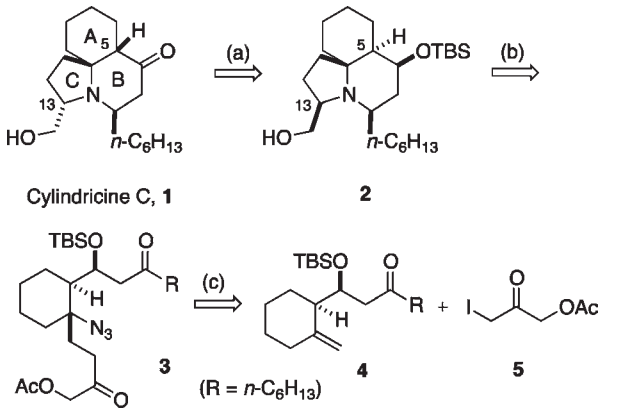
oxidative spirocyclization,[7] an aza [3 + 3] annulation,[8] and a Mannich reaction.[9] All of these approaches rely upon the simultaneous formation of both the azaspirocenter and the pyrrolidine C ring, and in these cases, the piperidine B ring is formed last. A less common disconnection involves the formation of the aza spirocenter prior to the formation of the pyrrolidine ring.[10] Two syntheses based on a nucleophilic addition onto pyridinium salt[11] and a conjugate addition/dipolar cycloaddition[12] use this strategy. In these few examples, the piperidine B ring serves as a template to build the complete tricyclic core. While this disconnection offers the possibility to make different late-stage derivatives of the skeleton, it was accompanied by the tedious installment of both the A and C rings along with selectivity issues during the introduction of the C(2) and C(13) side chains.

We report here a different approach based on a powerful strategy starting from ring A where the key azaspirocenter is introduced first. Both ring B and C will be constructed subsequently in a single intramolecular bis-reductive amination step (Scheme 1).[13] The retrosynthetic analysis is depicted in Scheme 1. Cylindricine C (**1**) could be derived from the azatricycle **2** (Scheme 1a), which in turn would emerge from the azide reduction/*bis*-reductive amination of the azidodiketone **3** (Scheme 1b). The *bis*-reductive amination should afford the C(5) and C(13) centers with opposite relative configurations to those found in cylindricine C, and therefore their epimerization should be addressed at the final stage of the synthesis (Scheme 1a).[14] The *trans* tertiary azide **3** could be prepared by the α-iodoketone radical carboazidation reaction we have recently described[15] departing from alkene **4** and α-iodoketone **5** (Scheme 1c).

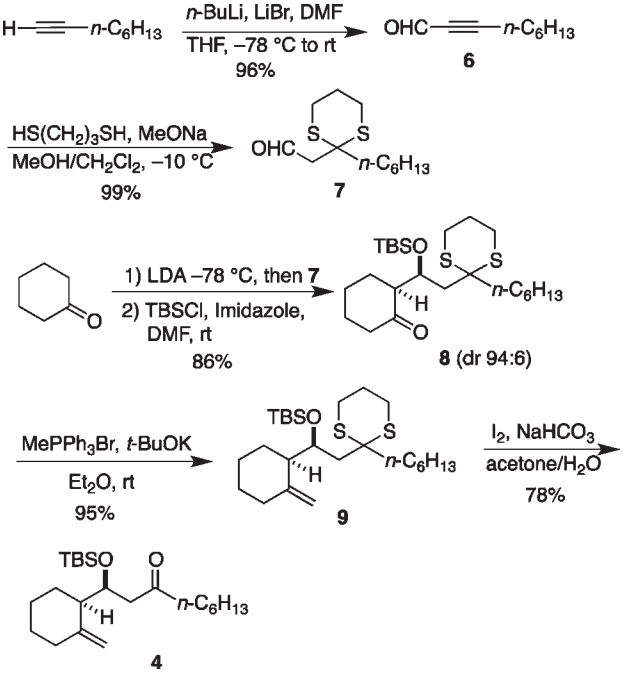
The synthesis starts with the preparation of the 2-substituted methylenecyclohexane **4**, the key substrate for the carboazidation step (Scheme 2). Addition of the alkynyl lithium to DMF afforded aldehyde **6**,[16] which was converted into the monoprotected ketoaldehyde **7** through *bis*-

Scheme 1



conjugate addition of 1,3-propanedithiol.[17] Subsequent aldol reaction between the lithium enolate of cyclohexanone and aldehyde **7** followed by concomitant protection of the alcohol as a silyl ether generated **8** in favor of the *anti* product. The ketone was then transformed into the *exo* methylene olefin **9** by Wittig olefination. Finally, removal of the dithiane moiety via an iodine-based oxidation process[18] afforded alkene **4**. The carboazidation precursor **4** was obtained in 57% overall yield starting from 1-octyne.

Scheme 2



The radical carboazidation[15] between alkene **4** and the α-iodoketone **5**[19] is shown in Scheme 3. Azide **3** is obtained

(8) Swidorski, J. J.; Wang, J.; Hsung, R. P. *Org. Lett.* **2006**, *8*, 777–780.

(9) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Sakubara, S.; Ohshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4634–4637.

(10) Syntheses of cylindricine A using this type of disconnection: (a) Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8263–8266. (b) Snider, B. B.; Liu, T. *J. Org. Chem.* **1997**, *62*, 5630–5633.

(11) Donohoe, T. J.; Brina, P. M.; Hargaden, G. C.; O'Riordan, T. J. C. *Tetrahedron* **2010**, *66*, 6411–6420.

(12) (a) Flick, A. C.; Caballero, M. J. A.; Padwa, A. *Tetrahedron* **2010**, *66*, 3643–3650. (b) Flick, A. C.; Caballero, M. J. A.; Padwa, A. *Org. Lett.* **2008**, *10*, 1871–1874.

(13) A related strategy involving a reductive amination–lactamization process to construct rings B and C was used in our recent syntheses of Lepadiformine A and C: (a) Schär, P.; Renaud, P. *Org. Lett.* **2006**, *8*, 1569–1571. (b) Weidner, K.; Giroult, A.; Panchaud, P.; Renaud, P. *J. Am. Chem. Soc.* **2010**, *132*, 17511–17515.

(14) For an example of the C(5) epimerization, see ref 6c. The C(13) epimerization has been achieved in lepadiformine A: Caldwell, J. J.; Craig, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2631–2634.

(15) Lapointe, G.; Schenk, K.; Renaud, P. *Chem.—Eur. J.* **2011**, *17*, 3207–3212.

(16) Prakesch, M.; Grée, D.; Grée, R. *Tetrahedron* **2003**, *59*, 8833–8841.

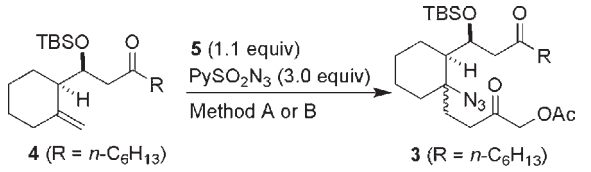
(17) Sneddon, H. F.; van der Heuvel, A.; Hirsch, A. K. H.; Booth, R. A.; Shaw, D. M.; Gaunt, M. J.; Ley, S. V. *J. Org. Chem.* **2006**, *71*, 2715–2725.

(18) Other reagents known for dithiane deprotection such as MeI, NBS, and $PhI(OC(O)CF_3)_2$ afforded a complex mixture of products.

(19) Clark, E. R.; Howes, J. G. B. *J. Chem. Soc.* **1956**, 1152–1158.

in 75% yield using the $(Bu_3Sn)_2$ mediated reaction. The triethylborane-mediated carboazidation procedure affords the same product in 59% yield. As expected from previous studies,[20] the radical carboazidation involving 2-substituted methylenecyclohexanes affords predominantly the *trans* azide (trans/cis 7:3). The two diastereomers are separated by flash column chromatography.

Scheme 3



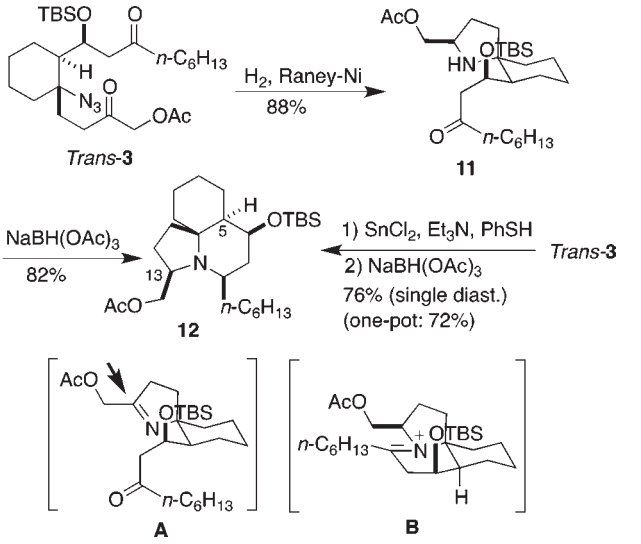
Method A: $(Bu_3Sn)_2$ (1.2 equiv), *t*-BuON=NO*t*-Bu (0.1 equiv), 75% (*trans*/*cis* 7:3)

Method B: Et_3B (4.0 equiv), air, rt, 59%, (*trans*/*cis* 7:3)

The *trans* isomer of **3** was used for the next step. hydrogenation of *trans*-**3** using Raney-nickel afforded the spirobicyclic amine **11**. Under these conditions, the second reductive amination did not take place but conversion of **11** to the pyrrolo[1,2,*j*]quinoline ring system could be achieved by treatment of **11** with $NaBH(OAc)_3$. A more convenient way to convert *trans*-**3** to **12** was developed. Reduction of the azide *trans*-**3** with stannous chloride[21] in the presence of triethylamine and thiophenol afforded the corresponding primary amine that was used without purification for the next step.[22] The *bis*-reductive amination was achieved by treatment of the intermediate crude amine with $NaBH(OAc)_3$. The tricyclic product **12** was obtained as a single diastereomer in 76% overall yield from the azide **3**. Ultimately, it was found that isolation of the crude amine was not necessary and a one-pot process was developed to convert azide **3** into **12** in 72% yield.

The relative stereochemistry of the tricyclic amine **12** was established by single crystal X-ray analysis (Figure 2).[23] This structure confirms our prediction that the bis-reductive amination affords a product that differs from cyclindricine C by its relative configuration at C(5) and C(13). The observation that both reductive aminations are highly diastereoselective is best rationalized by the formation of the pyrrolidine ring prior to the piperidine ring. This hypothesis is supported by the observation that Raney-nickel hydrogenation of *trans*-**3** afforded exclusively the spirocyclic pyrrolidine **11**. Reduction of the dihydropyrrole **A** (Scheme 4) by $NaBH(OAc)_3$ occurs from the less

Scheme 4



hindered face to afford **11**. The second reductive amination involves the iminium ion **B** (Scheme 4) and takes place opposite to the C(13) silyloxymethyl side chain.

Compound **12**, with the "non-natural" stereochemistry at C(13), represents a straightforward entry to the unknown 13-epicylindricine C. The synthesis of this epimer is

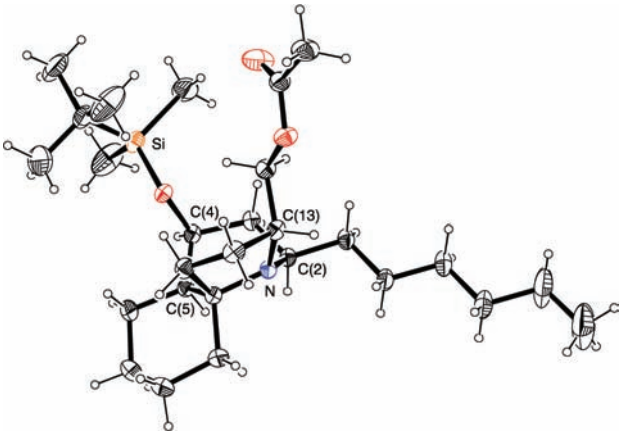


Figure 2. X-ray crystal structure of **12**.

shown in Scheme 5. Desilylation of **12** was attempted under various conditions. Unpredictably, **12** proved to be very resistant to desilylation under all standard deprotection conditions. However, removal of the acetate first afforded the free alcohol **13** that could be easily desilylated with TBAF in THF. The intermediate diol was monosilylated at the primary alcohol postition to give **14** in 83% yield.

(20) Cren, S.; Schär, P.; Renaud, P.; Schenk, K. *J. Org. Chem.* **2009**, *74*, 2942–2946.

(21) Barta, M.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron* **1990**, *46*, 587–594.

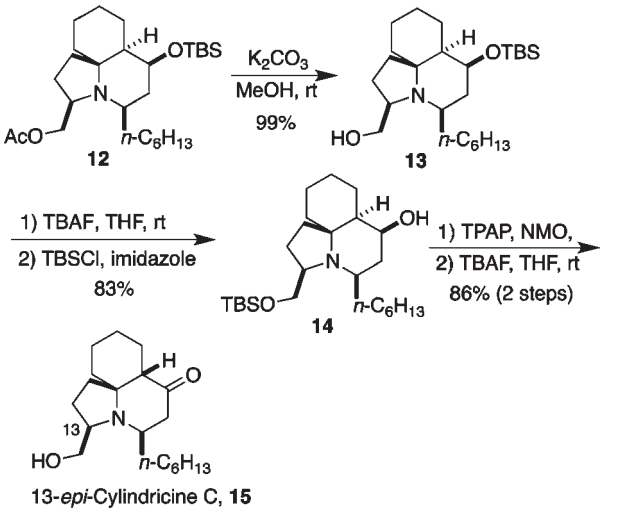
(22) The primary amine was not characterized. Its complex ^1H NMR spectra indicate that it exists in equilibrium with imine/hemiaminal forms.

(23) The crystal structure of **12** has been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 831535.

(24) Ley, S.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.

TPAP-oxidation[24] of the secondary alcohol followed by TBAF deprotection afforded 13-epi-cylindricine C in 86% yield. As expected, epimerization at C(5) occurred during the converstion of **14** to **15**.[25]

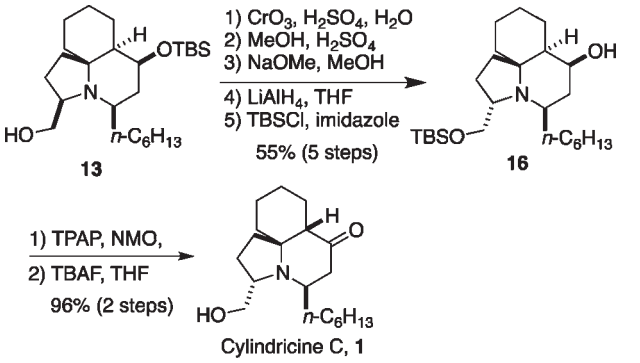
Scheme 5



The synthesis of the natural isomer of cylindricine C is highlighted in Scheme 6. Inversion of the relative configuration at C(13) was achieved first. For this purpose, the primary alcohol **13** was oxidized under Jones conditions (CrO_3, H_2SO_4, H_2O) to the corresponding carboxylic acid. Esterification (MeOH, H_2SO_4) followed by base-mediated epimerization (MeONa in MeOH), reduction of the epimerized ester to the primary alcohol, and silylation gave **16** as a single diastereomer. Fortuitously, the silyl protecting group at the C(4) hydroxy group was cleaved during the esterification step. It is also noteworthy to mention that the epimerization, besides being significantly slower than the one reported in the lepadiformine A synthesis,[14] afforded only the product with the desired inverted configuration. The synthesis was completed through selective silylation of the primary alcohol, TPAP-oxidation of the secondary alcohol, and desilylation/epimerization at C(5) using TBAF.

(25) In analogy to cylindricine C, no interaction between the C(2) and C(5) hydrogen atoms was found in the NOESY NMR spectra of **15**. This strongly suggests that epimerization at C(5) had taken place.

Scheme 6



In conclusion, the syntheses of 13-epi-cylindricine C and cylindricine C were achieved from 1-octyne in 15% and 11% yields, respectively. The strategy involves the preparation of the tricyclic skeleton via a radical α-iodoketone carboazidation/bis-reductive amination sequence. Inversion of the stereochemistry at C(13) and C(5) is efficiently achieved on late stage intermediates. Further work to improve the diastereoselectivity of the carboazidation step and to prepare enantiomerically pure cylindricines is currently underway.

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra of all new compounds. X-ray crystallographic data for compounds **12** (cif file). This material is available free of charge via the Internet at http://pubs.acs.org.