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Total synthesis of (+)-cylindricine C

Toshiharu Arai, Hideki Abe, Sakae Aoyagi and Chihiro Kibayashi*

School of Pharmacy, Tokyo University of Pharmacy and Life Science, Horinouchi, Hachioji, Tokyo 192-0392, Japan

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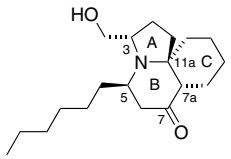
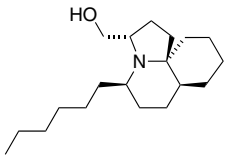
Abstract—A stereoselective total synthesis of (+)-cylindricine C has been achieved starting with (*S*)-*N*-Boc-2-pyrrolidinone. The key elements of this synthesis involve the sequence of reactions including BF_3-mediated addition of the allyl Grignard reagent to the cyclic imine, spirocyclization via enamine formation, and intramolecular Michael addition to form the tricyclic core.

Tunicates (ascidians) have been proven to be a particularly rich source of a variety of structurally fascinating and bioactive nitrogen compounds.[1] Since the first members were reported by Blackman and co-workers in 1993, 11 cylindricines A–K[2] have been identified from the Tasmanian ascidians, *Clavelina cylindrica*, as new marine alkaloids with an unusual azatricyclic skeleton. Among this class of alkaloids, cylindricine C (**1**),[2b] possessing the perhydropyrrolo[2,1-*j*]quinoline framework, is intimately related to the marine tricyclic alkaloid lepadiformine (**2**)[3] isolated from *Claverina lepadiformis*, differing structurally only in the *cis*/*trans* stereorelationship of the perhydroquinoline ring system and the functionality at C7. While the synthesis of both enantiomers of cylindricine C (*ent*-**1** and **1**) has been achieved,[4] the absolute configuration of natural cylindricine C remains unassigned since the optical rotation of the natural product has not been determined and no sample remains of the isolated cylindricine C. Recently, we have reported the enantioselective synthesis of (−)-lepadiformine,[5] which allowed us to establish the absolute configuration of naturally occurring lepadiformine as shown in structure **2**. Biogenetically, it can be envisaged that both tunicate alkaloids **1** and **2** presumably arise from an amino acid-derived azaspirocyclic compound, corresponding to the A/C ring of these alkaloids, by closure of the B ring (bond formed C7–C7a). Consequently, we assumed that the correct absolute stereochemistry for natural cylindricine C is defined by **1**, which is epimeric with the natural lepadiformine (**2**) at C7a.

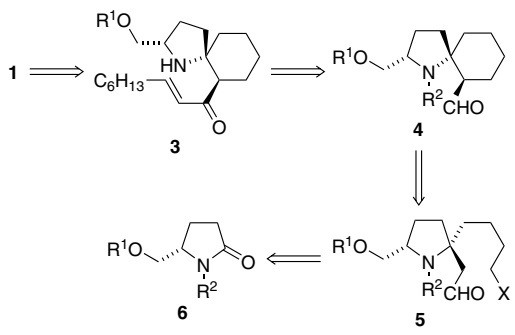


Cylindricine C (**1**)



Lepadiformine (**2**)

In this paper, we describe the stereocontrolled total synthesis of (+)-cylindricine C (**1**). Our synthetic strategy for **1** was based on the approach outlined in Scheme 1, which involves cyclization to assemble the azatricyclic core of **1** by an intramolecular Michael reaction[6] of the spirocyclic enone **3** which corresponds to a potential biosynthetic precursor to **1** as described above. The



Scheme 1. Retrosynthetic analysis of cylindricine C (**1**).

Keywords: Cylindricine; Cyclic imine; Grignard reaction; Azaspirocyclization; Intramolecular Michael addition.
* Corresponding author. Tel.: +81-426-76-3275; fax: +81-426-76-4475; e-mail: kibayasi@ps.toyaku.ac.jp

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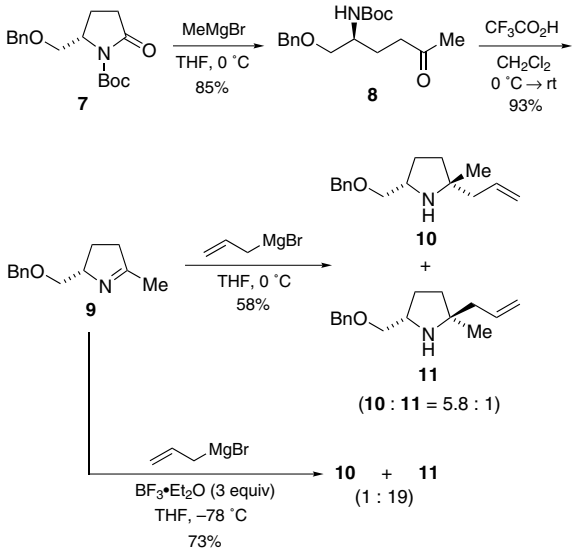
enone **3** should be formed from the spirocyclic aldehyde **4**, which should be conveniently accessible from the trisubstituted pyrrolidine **5** available using the (*S*)-pyrrolidinone **6** as the starting material.

Following this approach, we initially examined the stereoselective preparation of the trisubstituted pyrrolidine starting with (*S*)-*N*-Boc-2-pyrrolidinone **7**[7] in preliminary experiments (Scheme 2). Thus, upon treatment with methylmagnesium bromide, **7** underwent a selective attack on the endocyclic (ring) carbonyl group[8] to yield the *N*-Boc-amino ketone **8**. *N*-Boc deprotection with trifluoroacetic acid followed by basic treatment (3 M NaOH) led to the cyclic imine **9**. Reaction of **9** with allylmagnesium bromide in THF at 0 °C produced the trisubstituted pyrrolidine as a separable mixture of **10** and **11** (58% total yield) in a ratio of 5.8:1 favoring the α-allylated isomer **10**.[10] When **9** was treated with $BF_3{\cdot}Et_2O$ (3 equiv) prior to the addition of allylmagnesium bromide, the imine addition reaction proceeded smoothly at −78 °C and reversal of the selectivity in favor of β-allylated isomer **11** was observed, giving a ratio of 19:1 for **11** and **10** (73% total yield).

The stereochemical models which provide explanation of the observed diastereoselectivity are shown in Figure 1. The addition reaction of allylmagnesium bromide to the imine **9** in the absence of a Lewis acid might proceed via a chelated transition state **A**, where Mg is coordinated by the nitrogen and oxygen atoms of the imine **9** and the internal delivery of the allyl group might occur on the α-face leading to **10**. In the case of the Grignard allylation mediated by the presence of $BF_3{\cdot}Et_2O$, on the other hand, BF_3 blocks chelation with Mg and the reaction might proceed via an open-chain transition state **B**. Addition of the allyl Grignard reagent from the less hindered β-face then gives rise to the observed product **11**.



Scheme 2.

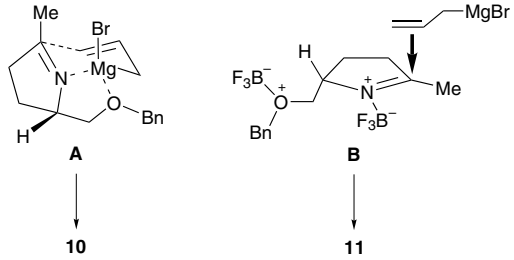
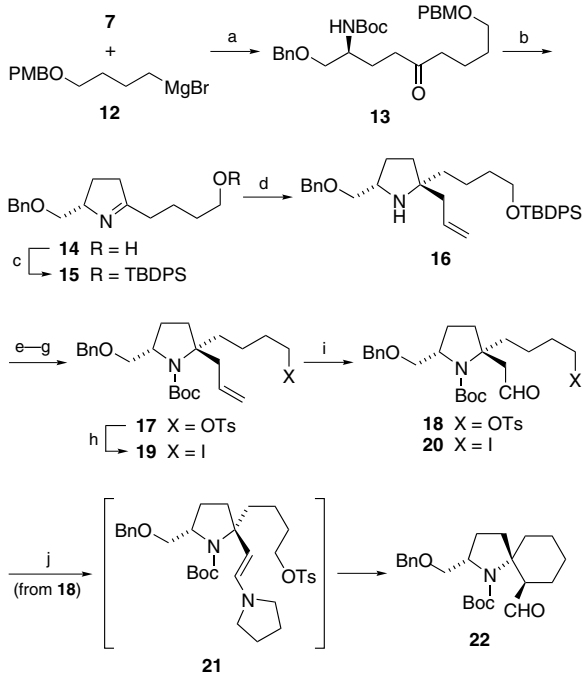


Figure 1. Stereochemical models to explain diastereoselective formation of the 2,2,5-trisubstituted pyrrolidines **10** and **11**.

Having established effective conditions for the highly selective β-allylation of the imine **9**, we next applied this protocol to the diastereoselective synthesis of the trisubstituted pyrrolidine **16**. Thus, following the identical sequence as described for **9**, the (*S*)-*N*-Boc-pyrrolidinone **7** was treated with 4-(*p*-methoxybenzyl)oxybutylmagnesium bromide (**12**) to give the *N*-Boc-amino ketone **13**, which was converted to the (*S*)-pyrroline **15** via treatment with trifluoroacetic acid followed by TBDPS protection of the primary alcohol (Scheme 3). Addition of allylmagnesium bromide to the BF_3 pretreated imine **15** in THF at −78 °C produced the β-allylated pyrrolidine **16** in 74% yield as a single isomer (based on ^1H NMR). After N-protection of **16** with the Boc group, deprotection of the TBDPS ether (Bu_4NF) followed by tosylation of the resulting primary alcohol gave the tosylate **17**, which underwent the sequential oxidative cleavage of the olefin moiety using OsO_4–



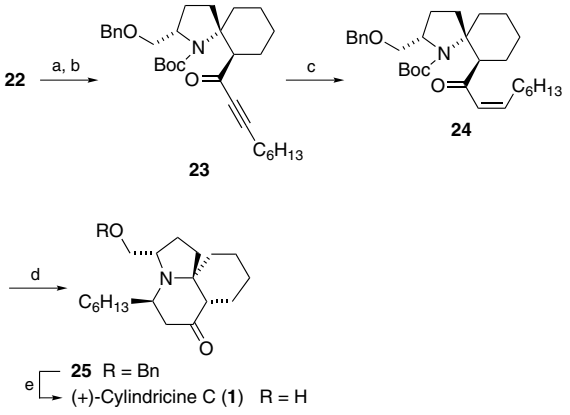
Scheme 3. Reaction conditions: (a) THF, 0 °C, 85%; (b) TFA, CH_2Cl_2, 0 °C → rt, then 3 M NaOH, 0 °C, 87%; (c) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, 79%; (d) allylmagnesium bromide (3 equiv), BF_3Et_2O (3 equiv), THF, −78 °C, 74%; (e) Boc_2O, aqueous Na_2CO_3, benzene, rt, 90%; (f) Bu_4NF, THF, rt, 96%; (g) TsCl, pyridine, rt, 93%; (h) NaI, acetone, reflux, 97%; (i) OsO_4, $NaIO_4$, THF/H_2O, rt, 85% for **18** and 88% for **20**; (j) pyrrolidine, MS 4 A, toluene, reflux, then 50% AcOH, rt, 60%.

$NaIO_4$ to afford the aldehyde **18**. The iodide **19** derived from the tosylate **17** (NaI, acetone) was also converted to the aldehyde **20** by the oxidative cleavage of the olefin.

With the tosylate **18** having the desired configurations at the C2 and C5 positions of the pyrrolidine in hand, we next tried cyclization to construct the azaspirodecane ring system **22** by means of intramolecular enolate alkylation. However, all attempts to cyclize under basic conditions failed resulting in no reaction at low temperature, or, under more forcing conditions, to production of a complex mixture. With the iodide **20** similar results were obtained under the same reaction conditions. These failures of **18** and **20** to undergo cyclization were possibly due to the low stability of the enolates formed from **18** and **20**, and their propensity to undergo retro-Michael reaction[9] under these reaction conditions.

To circumvent these problems, we then examined the cyclization exploiting an enamine for the synthesis of **22**. Thus, upon treatment of the tosylate **18** with pyrrolidine in refluxing toluene, the in situ generated enamine **21** underwent spontaneous cyclization under the neutral conditions, and subsequent treatment with 50% acetic acid provided the (6*S*)-azaspirocyclic aldehyde **22** as a single isomer (based on ^1H NMR)[11] in 60% yield from **18**. Octynyl Grignard addition to the aldehyde **22** and MnO_2 oxidation of the resulting carbinol (2:1 epimeric mixture) afforded the ynone **23** (80% from **22**), which was converted to the (*Z*)-enone **24** by Lindlar hydrogenation in toluene (Scheme 4). Removal of the Boc protecting group (TFA, 0 °C) and subsequent treatment of the resulting amine with a saturated $NaHCO_3$ solution at room temperature resulted in intramolecular Michael addition. This reaction proceeded presumably via an (*E*)-enone with complete equilibration to a thermodynamically favorable C7a epimer **25** of the tricyclic amine in 81% yield as a single diastereomer (within the detection limits of ^1H NMR).

Finally, the benzyl group of **25** was removed by hydrogenolysis using $Pd(OH)_2$ in MeOH to give (+)-cylindricine C (**1**), which has an optical rotation of $[\alpha]_D^{25}$ +61.8 (*c* 0.78, CH_2Cl_2) (lit.[4b] $[\alpha]_D^{25}$ +61 (*c* 0.4, CH_2Cl_2); for (−)-cylindricine C[4a] $[\alpha]_D^{25}$ −64 (*c* 0.2, CH_2Cl_2)). The synthetic material displayed spectroscopic data (^1H and ^{13}C NMR) identical to those reported[2b] for the natural product.



Scheme 4. Reaction conditions: (a) 1-octynylmagnesium bromide, THF, 0 °C, 88%; (b) MnO_2, CH_2Cl_2, rt, 91%; (c) H_2, Lindlar catalyst, toluene, rt, 99%; (d) TFA, CH_2Cl_2, rt, then saturated $NaHCO_3$, rt, 81%; (e) H_2, $Pd(OH)_2$–C, MeOH, rt, 83%.

In summary, a highly stereoselective method for the enantioselective synthesis of cylindricine C has thus been devised. This total synthesis consists of the key elements involving the sequence of reactions including BF_3-mediated addition of the allyl Grignard reagent to the cyclic imine, spirocyclization via enamine formation, and intramolecular Michael addition to form the tricyclic core.

References and notes

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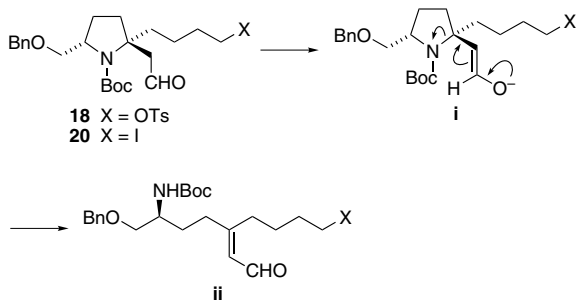
8. For the organometallic ring-opening reaction of *N*-alkoxycarbonyl lactams, see: Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228–234.
9. On basic treatment of **18** and **20**, ring opening is considered to take place via the following sequence involving retro-Michael addition generating the α,β-unsaturated aldehyde **ii**



10. The stereostructures of the allylated products **10** and **11** were assigned based on NOESY spectra which showed correlations between the C2-methyl protons and H5 for **10**, and the C5-allyl methylene protons and H5 for **11**.

11. The ^{1}H NMR spectrum of **22** showed a large vicinal coupling constant ($J = 12.1$ Hz) between H6 and $H7_{ax}$ at 3.80 ppm, indicating their *trans* diaxial relationship and, hence, the C6 formyl group existing in an equatorial position (β configuration) on the cyclohexane ring.