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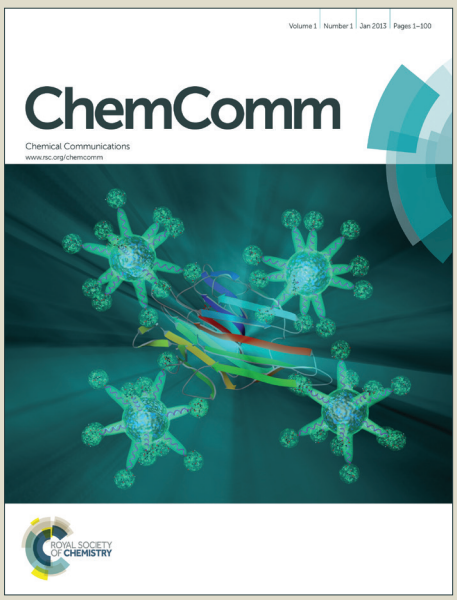

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Total synthesis of (+)-Cylindradine A†

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Cylindradines A and B, members of the polycyclic pyrrole-imidazole alkaloids (PIAs) are the only congeners bearing a 3-carbamoylpyrrole unit among the PIAs. In this communication, we described a total synthesis of (+)-cylindradine A based upon intramolecular Friedel-Crafts type cyclization of pyrrole-aldehyde and oxidative cyclization of tricyclic pyrrolopyrrolidine-guanidine with hypervalent iodine to construct the cyclic guanidine structure including the *N,N'*-aminal moiety.

Polycyclic pyrrole-imidazole alkaloids (PIAs) are oroidin-derived marine natural products[1] with diverse and complex architectures. They include monomeric oroidins as shown in Figure 1, and dimeric and tetrameric oroidins as exemplified by palau'amine, massadine, axinellamine (dimeric), and stylissadine A (tetrameric).[2] Most of these alkaloids show multiple biological activities, including antitumor and immunosuppressive activities, and adrenoceptor-agonistic activity. Consequently, there has been considerable synthetic interest,[3] and total syntheses of several monomeric and dimeric PIAs have been reported.[4]

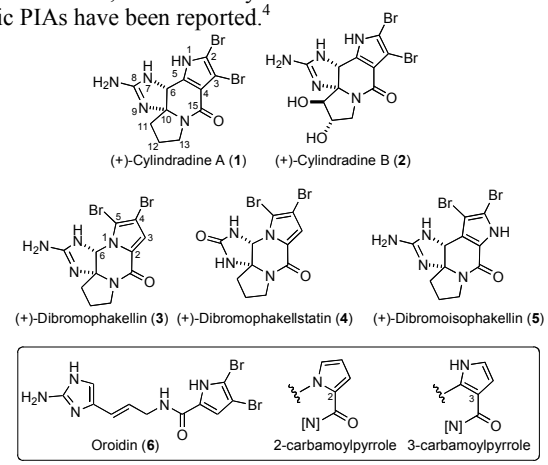
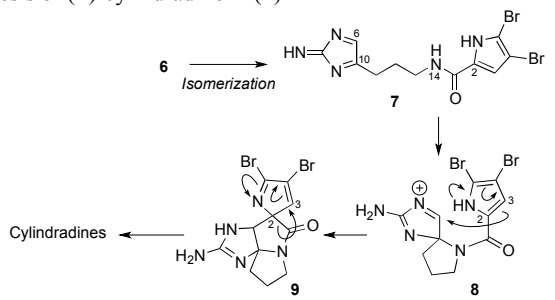


Figure 1 Structures of oroidin-derived tetracyclic pyrrole-imidazole alkaloids (PIAs).

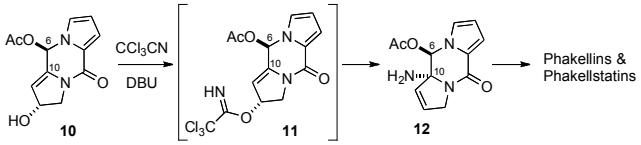
Recently, Kuramoto and co-workers isolated the (+)- and (–)-enantiomers of cylindradines A (**1**) and B (**2**), which are PIAs of a structurally novel type, from marine sponge *Axinella cylindratus*.[5] All previously reported PIAs contain a 2-carbamoylpyrrole unit, but cylindradines **1** and **2** possess an unusual 3-carbamoylpyrrole unit (4-carbamoylpyrrole based upon the numbering of cylindradines), formation of which cannot be explained in terms of the usual biosynthetic pathways of PIAs from oroidin.[6] Kuramoto and co-workers thus proposed a unique biosynthetic pathway for cylindradines involving "ipso" rearrangement process from **9** via **8** (Scheme 1).[5,6] We already had a synthetic interest in PIA-related alkaloids,[7] and we were fascinated by the extraordinary structure of cylindradines. We therefore designed a synthetic strategy for these compounds, and in this communication, we describe the first total synthesis of (+)-cylindradine A (**1**)



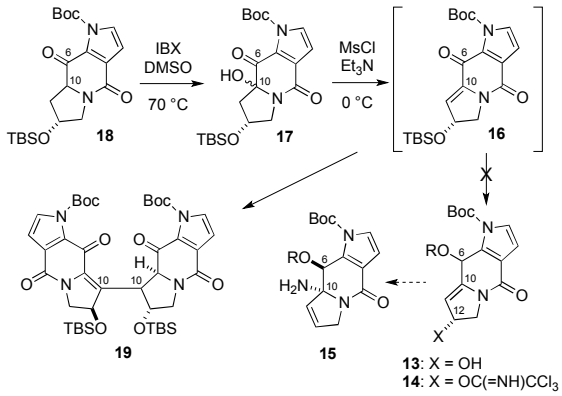
Scheme 1 Proposed biosynthetic pathway to cylindradines via "ipso" rearrangement.

Cylindradine A (**1**) possesses a characteristic *N,N'*-aminal moiety in the cyclic guanidine structure, like other members of monomeric PIA families, such as phakellins and phakellstatins, and construction of this aminal structure in an enantioselective manner is one of the challenging issues[4d,4e,7] to be addressed for the synthesis of cylindradines. In our previous synthetic work on phakellins and phakellstatins, we adopted an enamide-type Overman rearrangement reaction[7,8] to construct the *N,N'*-aminal moiety at C10 in optically active form (**10** to **12** in Scheme 2). Thus, we aimed to apply a similar approach for the synthesis of cylindradine A (**1**) (Scheme 3). We planned to use an enamide-type Overman rearrangement reaction of **14** to construct the *N,N'*-aminal structure at C10 by

transferring the chirality at C12 in **14**, which would lead to the stereoselective construction of the cyclic guanidine moiety in cylindradine A (**1**). However, when we examined the Overman rearrangement process (**14** to **15**), we could not even obtain the necessary precursor **16** (Scheme 3). Thus, we examined installation of the double bond using the aminal **17**, which was obtained by IBX oxidation of **18**.[9] In this reaction, however, unexpected dimerization reaction took place, and dimer **19** was obtained in 58% yield as a single stereoisomer. This reaction was considered to proceed via a homocoupling reaction between the enamine and enone moieties in **16**, which was generated in situ from **17** by treatment with methanesulfonyl chloride and triethylamine. Unfortunately, we could not isolate either enone **16** or allylic alcohol **13** because of their instability.

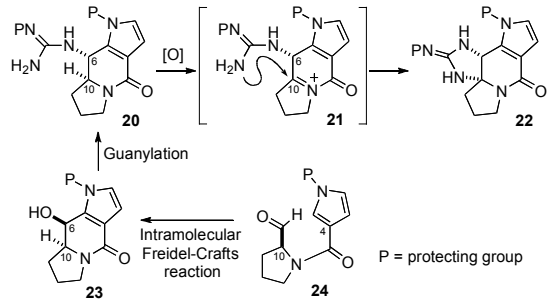


Scheme 2 Synthesis of phakellins and phakellstatin by enamide-type Overman rearrangement.[7]



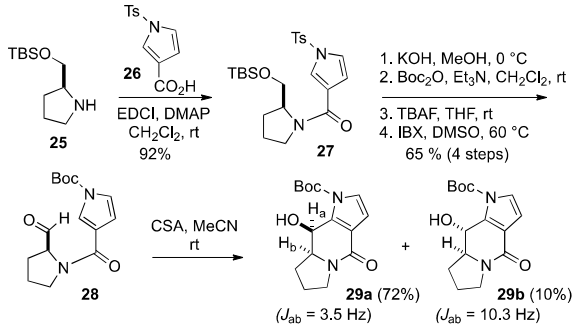
Scheme 3 Synthetic approach to **15** via enamide-type Overman rearrangement.

Next, we developed an alternative strategy to construct the cyclic guanidine **22** from **20** under oxidative conditions via iminium cation **21**, as originally demonstrated by Wang and Romo in their synthesis of (+)-dibromophakellin (**3**) (Scheme 4).[4e] To obtain the precursor **20** for the oxidative cyclization, we planned to use intramolecular Friedel-Crafts type reaction of **24** bearing aldehyde and 4-carbamoylpyrrole functional groups.



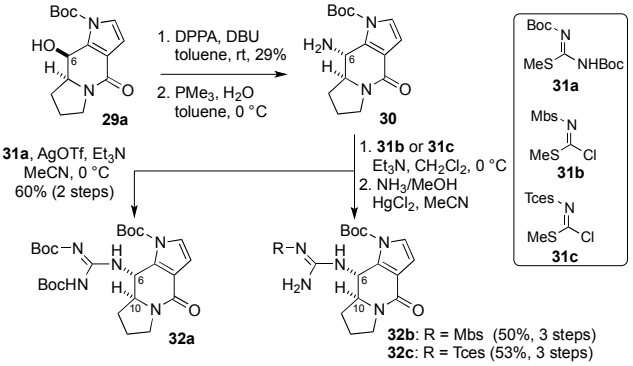
Scheme 4 Synthetic plan for tetracyclic guanidine **22** via oxidative cyclization of **20**.

Synthesis of tricyclic alcohol **29** via intramolecular Friedel-Crafts type reaction[10] is depicted in Scheme 5. Condensation reaction of L-prolinol **25** with *N*-Ts-protected pyrrole-3-carboxylic acid **26**[11] was carried out using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) in the presence of *N,N*-dimethyl-4-aminopyridine (DMAP) to give amide **27** (92% yield), whose *N*-Ts protective group was converted to *N*-Boc by deprotection with potassium hydroxide in methanol followed by reaction with $(Boc)_2O$ and triethylamine.[12] The *tert*-butyldimethylsilyl (TBS) ether was removed with *n*-tetrabutylammonium fluoride (TBAF), and the resulting alcohol was oxidized with IBX to give aldehyde **28** in 65% yield from **27** (4 steps). With the pyrrole-aldehyde **28** in hand, we investigated the construction of tricyclic alcohol **29** by acid-promoted intramolecular Friedel-Crafts type cyclization. After investigation of various acidic conditions, the Friedel-Crafts adduct **29** was obtained in 82% yield as a diastereomeric mixture in a ratio to *ca.* 7:1 (**29a** : **29b**) by treatment with 0.1 equivalent of camphorsulfonic acid (CSA).[13] The stereochemistry at C6 in **29** was confirmed by examination of the ^1H NMR signals, especially the coupling constants between H6 and H10 (i.e., H_a and H_b in **29a**). The diastereomers were easily separated by silica gel column chromatography.



Scheme 5 Synthesis of tricyclic structure by intramolecular Friedel-Crafts type cyclization.

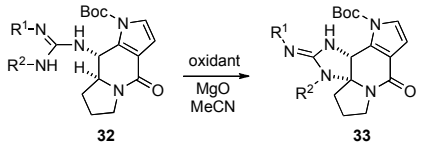
Next, guanidine bearing different protective groups was stereoselectively introduced at C6 in **29a** to give **32a-c** (Scheme 6). Thus, stereoselective azidation of **29a** with diphenylphosphoryl azide (DPPA) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (29% yield),[14] followed by reduction of resulting azide under Staudinger's conditions using trimethylphosphine, gave amine **30**. Then, guanidines **32a-c** were synthesized by reaction with bis-Boc-protected pseudo thiourea **31a**, *S*-methyl *N*-(4-methoxyphenylsulfonyl)carbonchloroimidothioate (**31b**),[15] and *S*-methyl *N*-(2,2,2-trichloroethoxysulfonyl)carbonchloroimidothioate (**31c**)[16] in 60, 50, and 53% yield, respectively.



Scheme 6 Synthesis of guanidines **32** for oxidative cyclization reaction.

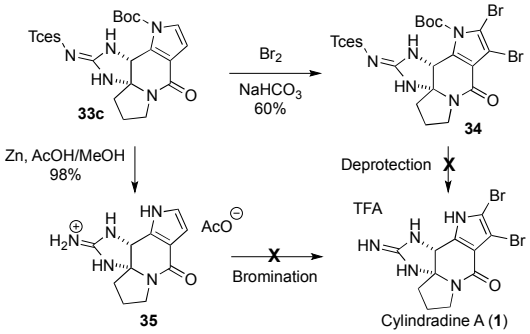
Next, oxidative cyclization reaction of **32a-c** to form tetracyclic compounds **33** was examined using hypervalent iodine reagents (Table 1). In the case of **32a** with two Boc protective group on guanidine, decomposition of the substrate was observed upon reaction with either PIDA (phenyliodine diacetate) or PIFA (phenyliodine bistrifluoroacetate) in the presence of magnesium oxide as a base (entries 1 and 2). Mono-Mbs-protected **32b** gave **33b** in 19% and 30% yield with PIDA and PIFA, respectively (entries 3 and 4). The best result was obtained with **32c**: tetracyclic guanidine **33c** was obtained in 60% yield by using PIDA in the presence of magnesium oxide at 65 °C in acetonitrile (entry 5). Unfortunately, lower yield or decomposition of the substrate was observed when more reactive PIFA and FPIFA (pentafluorophenyliodine bistrifluoroacetate),[17] respectively, were used (entries 6 and 7).

Table 1 Oxidative cyclization of **32** into **33**.



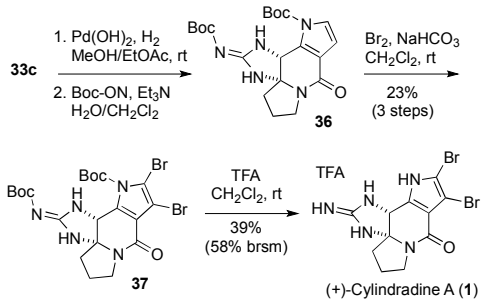
entry	substrate	R^1	R^2	oxidant	Temp (°C)	**33a-c** (yield %)
1	**32a**	Boc	Boc	PIDA	rt	decomp.
2	**32a**	Boc	Boc	PIFA	rt	decomp.
3	**32b**	Mbs	H	PIDA	65	19
4	**32b**	Mbs	H	PIFA	65	30
5	**32c**	Tces	H	PIDA	65	60
6	**32c**	Tces	H	PIFA	65	15
7	**32c**	Tces	H	FPIFA	65	decomp.

Completion of cylindradine A (**1**) synthesis from tetracyclic guanidine **33c** requires bromination at the C2 and C3 positions, and deprotection of the Tces and Boc groups. Bromination or deprotection of **33** took place to afford **34** or **35** in 60% and 98% yield, respectively, but deprotection and bromination of the resulting **34** or **35** (**34** to **1**, or **35** to **1**, Scheme 7) was unsuccessful. In particular, attempts to remove the Tces group from **34** resulted in debromination.



Scheme 7 Synthetic approaches to cylindradine A (**1**) from **33c**.

Thus, we decided to change the protective group in **33c** from Tces to a Boc group (Scheme 8). Reaction of **33c** with hydrogen in the presence of $Pd(OH)_2$ in a mixed solvent system of methanol-ethyl acetate followed by reaction with Boc-ON[18] and triethylamine gave bis-Boc-protected guanidine **36**. Then, bromination of the pyrrole in **36** was carried out with bromine and sodium bicarbonate to give bis-Boc cylindradine A (**37**). Finally, the two Boc groups were removed with TFA to afford (+)-cylindradine A (**1**) in 58% yield, based upon the recovered starting **37**.[19]



Scheme 8 Synthesis of (+)-cylindradine A (1) from **33c**.

In summary, we present the first synthesis of (+)-cylindradine A (**1**), a PIA that possesses an unusual 3-carbamoylpyrrole tetracyclic structure. Intramolecular Friedel-Crafts type cyclization of pyrrole-aldehyde **28** and oxidative cyclization of guanidine **32c** with hypervalent iodine proved effective for stereoselective construction of the cyclic guanidine structure in **1**.

Acknowledgments

We thank Prof. Dr. Makoto Kuramoto (Ehime University) for his helpful suggestions concerning purification of cylindraine A (**1**). We appreciate the reviewers for their valuable discussions about the biosynthetic pathway of cylindradines. This study was supported in part by a Grant-in-Aid for Challenging Exploratory Research from JSPS (No. 21655060) and a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details; ^{1}H and ^{13}C NMR spectra for all products. See DOI: 10.1039/b000000x/

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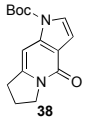
12 Electronic effects of the protective group in the pyrrole moiety affected the intramolecular Friedel-Crafts reaction, and an *N*-Boc group was mandatory.

13 Dehydration reaction of **29** proceeded further to generate **38** with equimolar or more CSA.



38

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19 Purification of **1** was very troublesome, since cylindraline A (**1**) is quite labile to acids. During the concentration process with rotary evaporator, the compound **1** was gradually decomposed even though a small amount of acids, which was observed on TLC and NMR. To avoid the decomposition of **1** during the concentration process, freeze-dry technique was essential. We deeply thank Prof. Makoto Kuramoto (Ehime University) for his very helpful suggestions for concentration and purification of cylindraine A (**1**).[20] Detail procedures for the purification of **1** were described in supporting information.

20 The ^{1}H and ^{13}C NMR data for the synthetic cylindraine A (**1**) contain small amounts of impurities because of its acid-labile nature.

