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First Total Synthesis of Hinckdentine A

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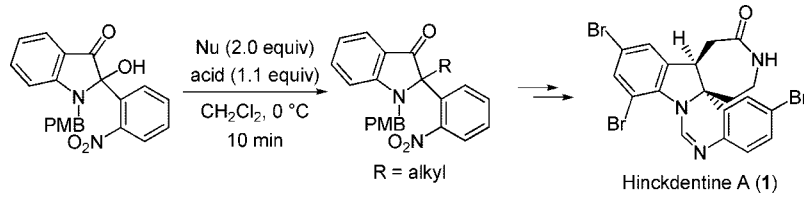
ABSTRACT



We have accomplished the first total synthesis of (±)-hinckdentine A (1). The key steps are *m*-CPBA oxidation of 2-arylindole followed by acid-mediated Mannich-type C−C bond formation of 2-hydroxyindolin-3-one, seven-membered ring closure, and regioselective tribromination.

Hinckdentine A (**1**) was isolated from the bryozoans *Hincksinoflustra denticulata* living in the eastern coast of Tasmania.[1] Its structure and absolute configuration were determined by single-crystal X-ray analysis. Hinckdentine A (**1**) has a unique architecture containing a seven-membered lactam ring fused to the tribromoindolo[1,2-c]quinazoline with a quaternary carbon center.

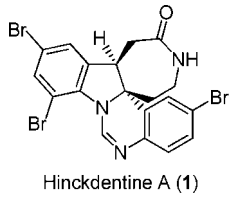


Figure 1. Structure of Hinckdentine A.

The framework of **1** consists of biologically important dihydrotryptamine and dihydropyrimidine units together with a cataleptically active indolo[1,2-*c*]quinazoline core,[2] although the biological activity of **1** has not yet appeared in the literature. Structural and biological interests have attracted several organic chemists to attempt the synthesis of **1**.[3] Although several synthetic applications were reported, the total synthesis of **1** has not yet been realized. Recently, McWhorter has achieved the synthesis of the 8-desbromo derivative of hinckdentine A (**1**).[4] Here, we report the first total synthesis of (±)-hinckdentine A (**1**).

Our synthetic plan for **1** is shown in Scheme 1. Bromination of the indolo[1,2-*c*]quinazoline core holding the *N*-bulky substituent in **2** was expected to provide the desired tribromide, thus enabling the total synthesis of **1**. Furthermore, we envisioned that the hexahydroazepino[4′,5′:2,3]indolo[1,2-*c*]tetrahydroquinazoline skeleton in **2**, the central part of this alkaloid, would be constructed by the cyclization of aminonitrile **3**, derived by pyrimidine-ring formation of 2,2-disubstituted indolin-3-one **4** followed by olefination. We anticipated that the quaternary carbon center in **4** would be formed from indole **6** via novel oxidation and following Mannich-type addition of a carbon-nucleophile to the α-ketoiminium intermediate generated from **5**.

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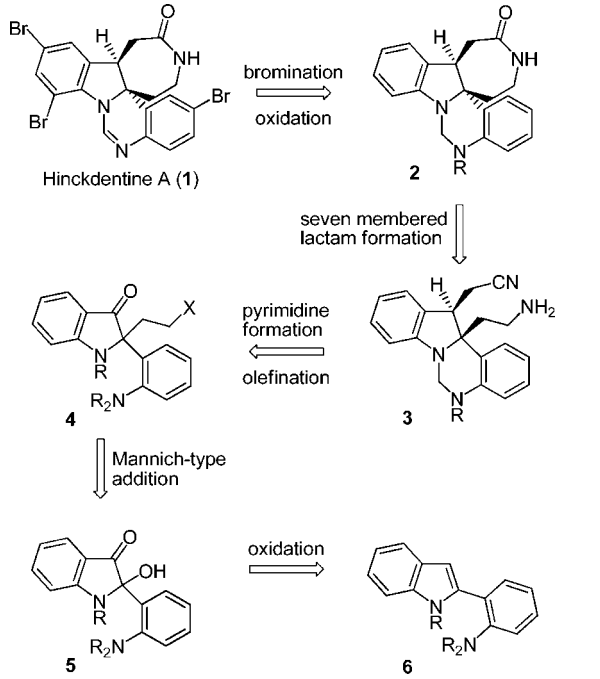
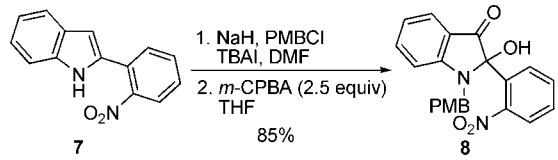
Scheme 1. Retrosynthetic Analysis for Hinckdentine A (**1**)



Several preparative methods for 2,2-disubstituted indolin-3-ones are well-known, for example, rearrangement of 2,3-dihydroxyindolines,[5] rearrangement of 2,3-disubstituted indolin-3-ols,[6] alkylation of 2-arylindolin-3-ones,[7] oxidative rearrangement of 2,3-disubstituted indoles,[8] cyclization of *o*-azidophenyl alkylketones,[9] and so on.[10] Recently, Kobayashi's group has disclosed the acid-mediated substitution of 2-alcohoxyindolin-3-one with aromatic, organosilicon, and organoboron compounds as carbon-nucleophiles.[11] This is a fascinating methodology as a direct preparative tool of 2,2-disubstituted indolin-3-one.

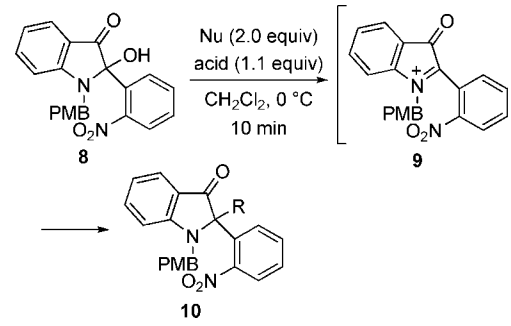
At the beginning of the synthesis of **1**, we studied the Mannich-type reaction of 2-hydroxyindolin-3-one **8** with several carbon-nucleophiles via an indoleninium intermediate. Initially, preparation of **8** was carried out by PMB protection of 2-(2-nitirophenyl)indole **7**[12] and *m*-CPBA oxidation in 85% yield (Scheme 2).

Scheme 2. Oxidation of 2-Arylindole



We explored the reaction of 2-hydroxyindolin-3-one **8** with various carbon-nucleophiles under acidic conditions (Table 1). When **8** was treated with allyltrimethylsilane and $TiCl_4$ in CH_2Cl_2 at 0 °C, the desired reaction proceeded successfully to afford 2-aryl-2-allylindolin-3-one **10a** in 98% yield (entry 1). In addition, a modified Petasis−boronic acid−Mannich reaction[13] with allylboronic ester gave **10a** in 98% yield (entry 2). Alkylation with silylketenacetal and silylenolates also furnished carbonyl compounds **10b**, **10c**, and **10d**, respectively (entries 3−5). The addition of *N*-methyl indole also worked efficiently with camphorsulfonic acid to provide **10e** in 98% yield (entry 6).

Table 1. Mannich-Type Reaction of **8**



entry	Nu	acid	R	yield (%)
1	TMS	$TiCl_4$		**10a** 98
2		$TiCl_4$		**10a** 98
3	OTMS, OMe	$TiCl_4$	OMe	**10b** 93
4	OTMS, Ph	$TiCl_4$	Ph	**10c** 98
5	OTMS, H	$TiCl_4$	H	**10d** 37
6	OTMS, H	CSA	H	**10d** 56[a]
7	N, Me	CSA	N, Me	**10e** 98

[a] **8** was recovered in 41% yield.

With 2,2-disubstituted indolin-3-one **10d** in hand, we then constructed the pyrimidine ring and introduced the side chain at the **3** position of **10d** to convert into **15** (Scheme 3).

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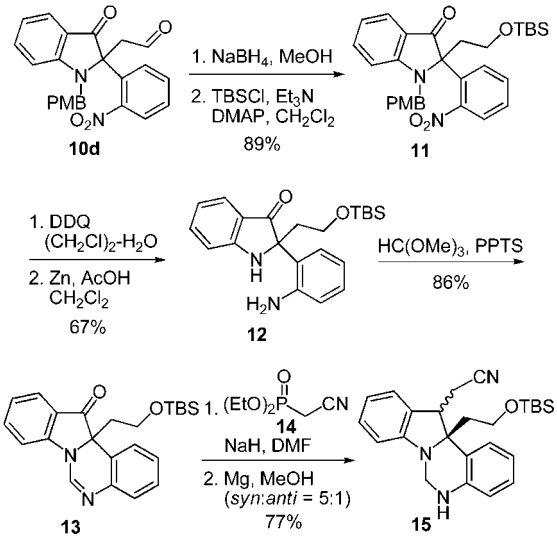
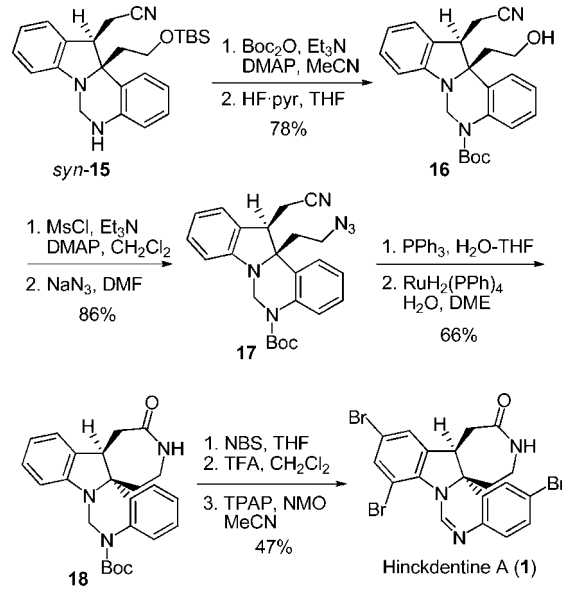
Scheme 3. Synthesis of **15**



Initially, $NaBH_4$ reduction of aldehyde **10c** followed by TBS protection of alcohol provided **11** (89%). After the removal of the PMB group with DDQ, the nitro group was reduced with zinc in AcOH−CH_2Cl_2 to afford aniline **12** in 67% two-step yield. The formation of the dihydropyrimidine ring within **13** was achieved by the treatment of **12** with trimethylorthoformate in the presence of PPTS in 86% yield.[14] Horner−Wadsworth−Emmons olefination of **13** with phosphonate **14** in the presence of NaH followed by magnesium reduction of olefin and imine moieties gave **15** in 77% yield. The stereochemistry of **15** was confirmed by NOE experiments.[15]

We performed transformation of **15** to hinckdentine A (**1**) through lactamization to build the core of **1** and regioselective tribromination by the following procedure (Scheme 4). The secondary amino group in **15** was protected by a Boc group, and then the silylether was deprotected by HF·pyridine to furnish alcohol **16**. The conversion of **16** to mesylate followed by substitution with NaN_3 provided azide **17** in 86% yield. The reduction of azide **17** using the Staudinger protocol and the subsequent ruthenium-catalyzed lactamization of aminonitrile[16] afforded lactam **18** in 66% yield. Finally, bromination on both aromatic rings of **18** was accomplished by treatment with NBS to produce the desired tribromide. Because of the bulkiness of Boc group on the quinazoline nitrogen, a fourth bromination did not take place. Deprotection of the *N*-Boc group followed by TPAP oxidation of tetrahydropyrimidine gave hinckdentine A (**1**). The spectroscopic data of synthetic **1** were consistent with those of the natural product.[1]

Scheme 4. Total Synthesis of Hinckdentine A (**1**)



In conclusion, we have accomplished the first total synthesis of (±)-hinckdentine A (**1**). As a key step for the construction of a quaternary carbon center, Mannich-type C−C bond formation to 2-hydroxyindolin-3-one under acidic conditions was successfully achieved. Further application of this methodology to the synthesis of other alkaloids and the enantioselective preparation of 2,2-disubstituted indolin-3-one are now under investigation in our laboratory.

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Supporting Information Available: Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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