First Total Synthesis of Hinckdentine A

Kazuhiro Higuchi, Yukihiro Sato, Mei Tsuchimochi, Kenta Sugiura, Masatoshi Hatori, and Tomomi Kawasaki*

Meiji Pharmaceutical University, 2-522-1 Noshio Kiyose, Tokyo 204-8588, Japan

10 min

kawasaki@my-pharm.ac.jp

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ABSTRACT

We have accomplished the first total synthesis of (\pm) -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.

R = alky

Hinckdentine A (1) was isolated from the bryozoans *Hincksi-noflustra 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.



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 (\pm) -hinckdentine A (1).

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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Several preparative methods for 2,2-disubstituted indolin-3-ones are well-known, for example, rearrangement of 2,3dihydroxyindolines,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 2,2disubstituted 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).





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 TiCl₄ in CH₂Cl₂ 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 reaction¹³ 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).





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, NaBH₄ 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–CH₂Cl₂ to afford aniline **12** in 67% twostep 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 NaN₃ provided azide **17** in 86% yield. The reduction of azide **17** using the Staudinger protocol and the subsequent ruthenium-catalyzed lactamization of

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aminonitrile¹⁶ 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





In conclusion, we have accomplished the first total synthesis of (\pm) -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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