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Stereoselective total synthesis of (±)-homochelidonine

Makoto Yoshida, Toshiko Watanabe and Tsutomu Ishikawa*

Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi, Inage, Chiba 263-8522, Japan

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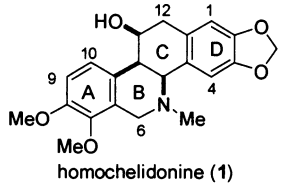
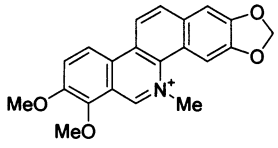
Abstract—(±)-Homochelidonine, a B/C-*cis*-11-hydroxyhexahydrobenzo[*c*]phenanthridine alkaloid, was stereoselectively synthesized from arnottin II, a non-alkaloidal spirolactonyl tetralone which had been structurally correlated to chelerythrine, a fully aromatized-type alkaloid, by the common use of a 2-benzofuranyl-1-tetralone as a synthetic key intermediate. Thus, a valuable synthetic method accessible to benzo[*c*]phenanthridine alkaloids with different oxidation stages of the basic skeleton could be proposed. © 2002 Elsevier Science Ltd. All rights reserved.

Benzo[*c*]phenanthridine alkaloids[1] showing interesting biological activities can be classified into two main categories of a B/C-*cis*-11-hydroxyhexahydro-type (a partially hydrogenated-type) and a fully aromatized-type alkaloid based on the oxidation stage of a basic skeleton;[2] e.g. homochelidonine (**1**) as the former and chelerythrine (**2**) as the latter. Various types of synthetic methods have been reported for the construction of the benzo[*c*]phenanthridine skeleton;[2] however, only limited approaches have appeared on a partially hydrogenated-type.[3] We had already succeeded in establishing a general and practical synthetic method[4] for the fully aromatized-type alkaloids including **2**[5] through 2-aryl-1-tetralones as key intermediates in the process of the examination of structure–activity relationship against tumor cells. On the other hand, for the structural determination of a naturally-occurring non-alkaloidal arnottin II (**3**) coexisting with benzo[*c*]-phenanthridine alkaloids, its synthesis had been also achieved using 2-benzofuranyl-1-tetralone (**4**) as a key synthetic intermediate of **2**.[6] The presence of a unique 2-spirolactonyl-3,4-dehydro-1-tetralone moiety in arnottin II (**3**) prompted us to undertake synthesis of homochelidonine (**1**) by the chemical conversion of **3**. In this paper we present the stereoselective total synthesis of (±)-homochelidonine (**1**) from arnottin II (**3**), leading to synthetic correlation between partially hydrogenated-type and fully aromatized-type benzo[*c*]-phenanthridine alkaloids.

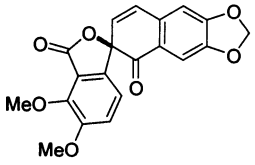
The retrosynthetic analysis is shown in Scheme 1, in which a hexahydrobenzo[*c*]phenanthridine skeleton **5** with all *cis* relation of the hetero atom functions on the C ring and an 1,2,3,4-tetrahydro-1-naphthylamine derivative **6** with a spirolactone moiety are planned to be key intermediates.



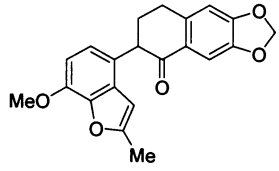
homochelidonine (**1**)



chelerythrine (**2**)

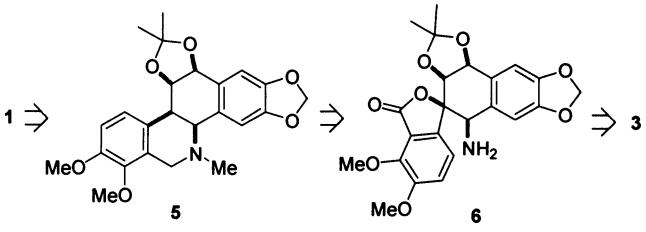


arnottin II (**3**)



4

Oxidation of **3** with a stoichiometric amount of OsO_4[7] afforded a *cis*-diol **7** due to approach of the reagent from the less hindered site. Introduction of a nitrogen function at the 1 position of **7** was carried out by treatment with hydroxylamine after protection of the glycol function as an acetonide to give an oxime **9**.



Scheme 1.

* Corresponding author. Tel./fax: +81-43-290-2910; e-mail: benti@p.chiba-u.ac.jp

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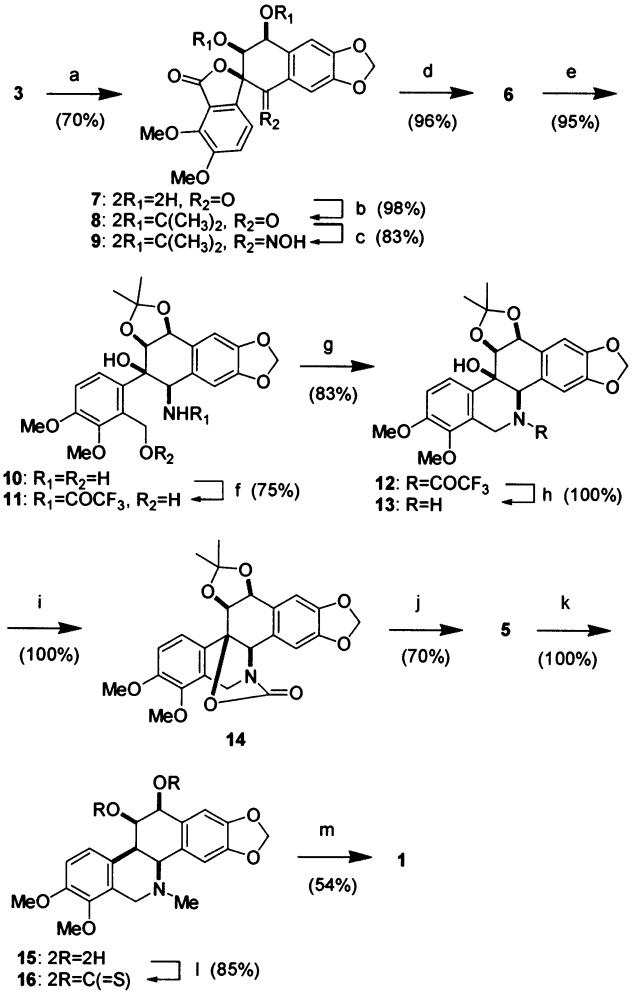
Reduction of **9** with $NaBH_3CN$ in the presence of $TiCl_3$[8] successfully provided an amine **6** as the desired single stereoisomer. Reductive cleavage of the spirolactone ring in **6** with $LiAlH_4$ followed by cyclization under the Mitsunobu reaction conditions after conversion of the reduction product **10** into a trifluoroacetamide derivative **11** gave a 10*b*,11,12-trioxygenated hexahydrobenzo[*c*]phenanthridine skeleton **12**. All *cis* relation among the hetero atom substituents on the C ring system of **12** was determined by NOE enhancements in NMR experiments.

Hydrolysis of the amide function of **12** followed by treatment with Boc_2O afforded an unexpected cyclic carbamate **14** quantitatively. This fact unambiguously indicated the *cis*-orientation between the 4*b*-amine function and the 10*b*-hydroxyl group. It was found that selective deoxygenation of the 10*b*-oxygen function and reductive *N*-methylation concomitantly occurred when the cyclic carbamate **14** was treated with 20% $Pd(OH)_2/C$ under hydrogen atmosphere in the presence of formaldehyde, to directly give an 11,12-dioxygenated hexahydro-*N*-methylbenzo[*c*]-phenanthridine skeleton **5** with all *cis*-oriented hydrogen atoms on the C ring. Interestingly, reductive inversion at the 10*b*-position by displacement of an oxygen function to a hydrogen atom was observed in this reduction, resulting in the formation of a product with the desired stereochemistry. After deprotection of the acetal function in **5** followed by thiocarbamation, treatment of the thiocarbamate **16** under radical conditions using Bu_3SnH[9] smoothly afforded the expected homochelidonine (**1**), which was identical with an authentic sample[3b] (Scheme 2). The overall yield of **1** from **3** was 11% in 15 steps.



Scheme 2. (a) (i) OsO_4, pyridine, rt, 1 h; (ii) $NaHSO_3$ aq., rt, 20 h; (b) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH·H_2O, DMF, 90°C, 1 h; (c) NH_2OH·HCl, pyridine, 100°C, 6 h; (d) $TiCl_3$ aq., $NaBH_3CN$, NH_4OAc, dioxane, rt, 5 h; (e) $LiAlH_4$, THF, rt, 1 h; (f) (i) $(CF_3CO)_2O$, pyridine, 0°C, 2 h; (ii) $NaHCO_3$ aq., MeOH, rt, 16 h; (g) DEAD, Ph_3P, THF, rt, 3 h; (h) NaOH aq., MeOH, rt, 24 h; (i) Boc_2O, DMAP, CH_3CN, 60°C, 2 h; (j) H_2, 20% $Pd(OH)_2/C$, HCHO aq., HCOOH, MeOH, rt, 24 h; (k) CF_3COOH, CH_2Cl_2, rt, 20 h; (l) thiocarbonyldiimidazole, $(CH_2Cl)_2$, reflux, 3 h; (m) Bu_3SnH, AlBN, toluene, reflux, 3 h.

In conclusion, (±)-homochelidonine (**1**) was stereoselectively synthesized from arnottin II (**3**) through three key steps of (i) the introduction of oxygen functions to the 11 and 12 positions, (ii) reduction of the oxime group, and (iii) hydrogenolysis of the 10*b*-hydroxyl group. It should be noted that synthetic correlation among homochelidonine (**1**) (a partially hydrogenated-type alkaloid), chelerythrine (**2**) (a fully aromatized-type alkaloid), and arnottin II (**3**) (a non-alkaloidal spirolactonyl tetralone) in the use of the 2-benzofuranyl-1-tetralone (**4**) as a common key intermediate could propose a valuable synthetic method accessible to both types of alkaloids. Presently, optimization of each step and trials for application to asymmetric synthesis are under investigation.

Acknowledgements

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