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Total synthesis of pyrano[3,2-*e*]indole alkaloid fontanesine B by a double cyclization strategy†

Tomoki Itoh, Yuusuke Chiba, Shunsuke Kawaguchi, Yuki Koitaya, Yuuma Yoneta, Koji Yamada and Takumi Abe *

The regioselective synthesis of pyrano[3,2-*e*]indole alkaloid fontanesine B by two different cyclizations is described. The complete regioselectivity is controlled by the C4 Pictet–Spengler cyclization, in which an iminium ion acts as a transient directing (TDG) group. Furthermore, carbolines were constructed by a new Bischler–Napieralski-type cyclization, in which an unprecedented trichloromethyl carbamate serves as a reactive group.

Fontanesines A (1), B (2), and C (3) were isolated from the stem bark and leaf fractions of *Conchocarpus fontanesianus* by Queiroz and co-workers in 2016 (Fig. 1).¹ These compounds have a characteristic pyrano[3,2-*e*]indole moiety fused with quinazolinone. A crucial challenge in the synthesis of fontanesines is the regioselective formation of the pyrano[3,2-*e*]indole core. Although the structures were unique and unprecedented, there are no reports on their partial preparation or total synthesis.

The importance of a pyrano[3,2-*e*]indole framework in medicinal chemistry had encouraged Macor,² Pandit,³ May,⁴ and Conforti⁵ to develop efficient methods for the regioselective construction of this framework. The majority of these methods relied on the thermal Claisen rearrangement,^{2–4} and Pt-mediated cyclization.⁵ To keep the pyran intact from earlier stage of total synthesis is difficult due to its instability.⁶

In our continuing efforts in the synthesis of indole alkaloids,⁷ we developed a novel strategy for the synthesis of

azepinoindoles by C4 Pictet–Spengler reaction of serotonin⁸ or 5-hydroxytryptophans⁹ and aldehydes. This approach proved useful in the one-pot regioselective synthesis of pyrano[3,2-*e*]indoles.¹⁰ We considered the above facts and envisioned that the synthesis of pyrano[3,2-*e*]indoles by C4 Pictet–Spengler reaction would allow a rapid and regioselective formation of fontanesines, keeping the pyran intact. Herein, we report the results of our efforts to synthesize 2.

The retrosynthetic analysis of fontanesine B (2) is shown in Scheme 1. The quinazolinone moiety in 2 might be forged by

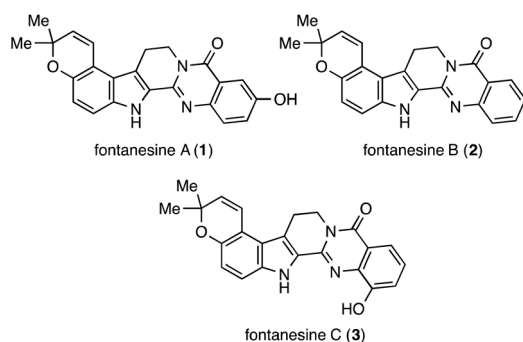
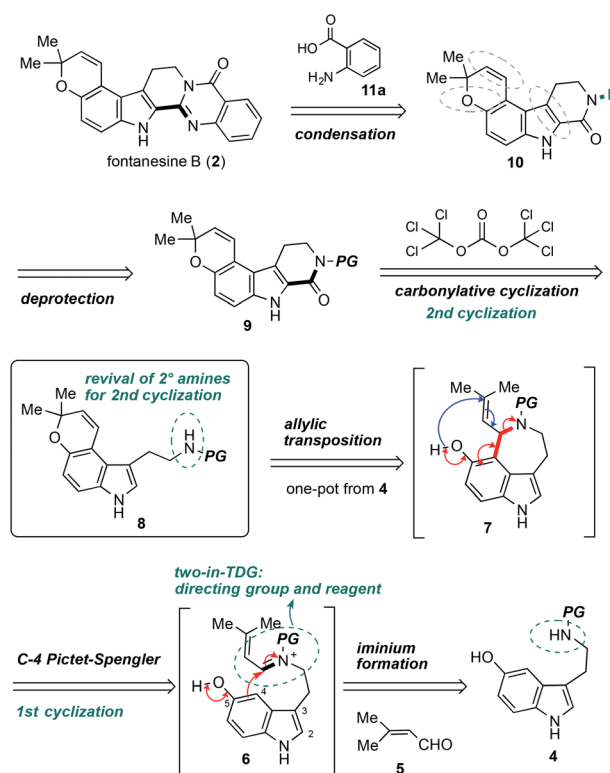


Fig. 1 Fontanesines A (1), B (2), and C (3).

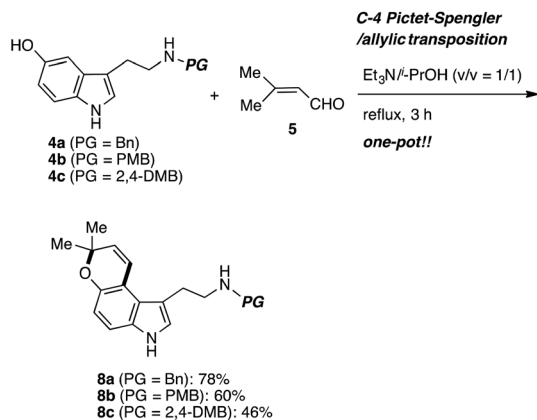
Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-tobetsu, Hokkaido 0610293, Japan. E-mail: abe-t@hoku-iryo-u.ac.jp

† Electronic supplementary information (ESI) available: Detailed experimental procedures and spectra data for all compounds, including scanned images of ¹H and ¹³C NMR spectra. See DOI: 10.1039/c9ra02321f

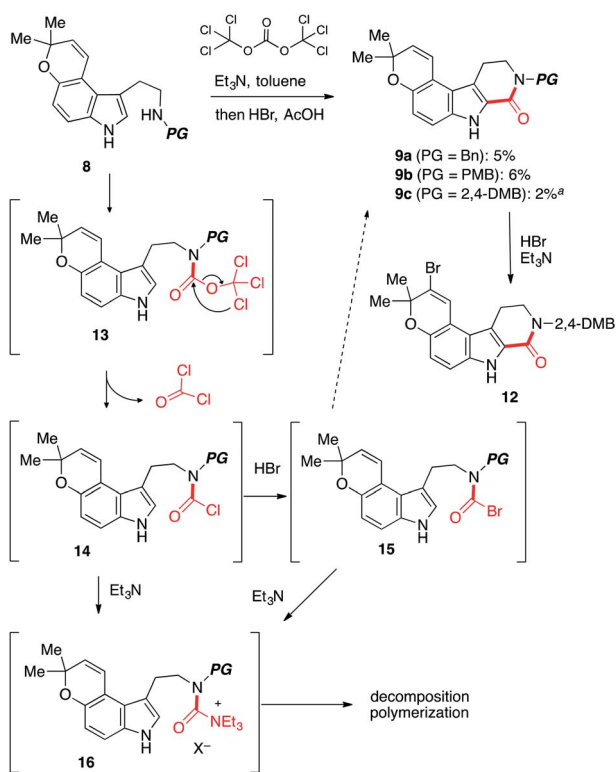


Scheme 1 Retrosynthetic analysis of fontanesine B (2).



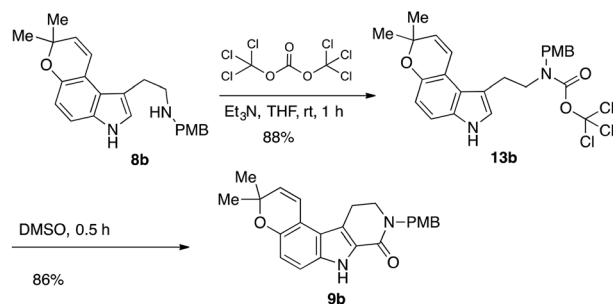
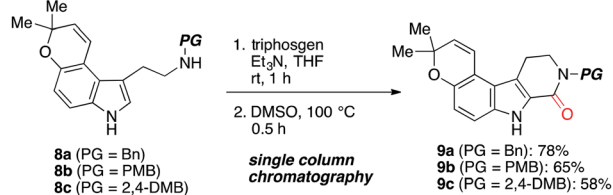
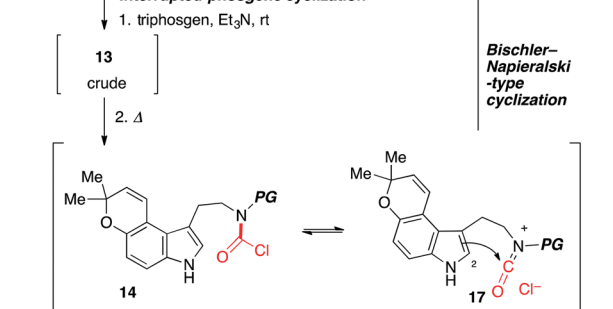


Scheme 2 Synthesis of substrates 8.

Scheme 3 Attempted synthesis of 9. ^a12 was obtained in 14% yield.

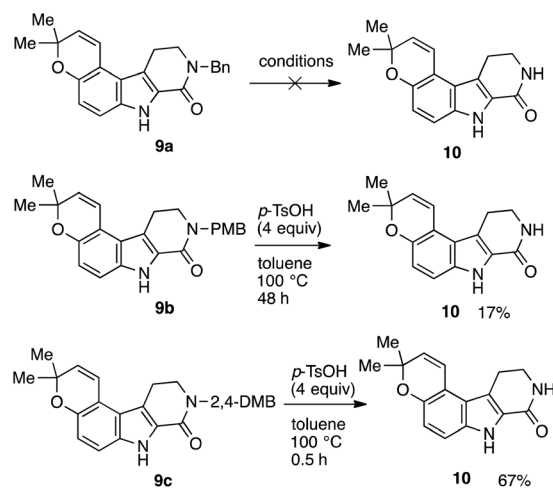
a deprotection followed by condensation of anthranilic acid (11a) with carboline 9. One of the key steps in the synthetic route involved the carbonylative cyclization of pyrano[3,2-*e*]indole 8 to afford carboline 9. The pyrano[3,2-*e*]indole 8 could be accessible from aldehyde 5 and benzyl protected 5-hydroxytryptamine 4 using our developed C4 Pictet-Spengler/allylic transposition *via* the iminium intermediate 6 and azepinoindole 7.

Before synthetic studies, we could predict the difficulty of removing the protecting group on the nitrogen atom at the late stage. Therefore, we decided to prepare the several tryptamines 4 with different protecting groups. The synthesis was started from the benzyl protected 5-hydroxytryptamine 4 (Scheme 2). It was reacted with 3-methyl-2-butenal (5) in 2-propanol/Et₃N

**interrupted phosgene cyclization/Bischler–Napieralski-type cyclization sequence****interrupted phosgene cyclization**Scheme 4 Improved synthesis of β-carbolines 9 from 8 *via* interrupted phosgene cyclization and Bischler–Napieralski-type cyclization.

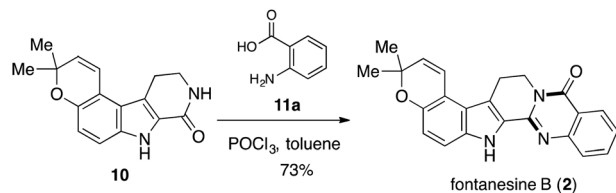
under reflux to produce the desired pyrano[3,2-*e*]indole 8 in a one-pot reaction. Normal Pictet–Spengler reaction occurs at the C2 position of the indole ring under the acidic conditions. All steps of this one-pot sequence take place under basic conditions, which is presumably key to its success.

To test the feasibility of our approach, we resorted to the carbonylative cyclization of 8. According to the previous report on



Scheme 5 Removal of benzyl substituents on the nitrogen atoms in 9.





Scheme 6 Completion of total synthesis of fontanesine B.

the reaction using triphosgene,^{11–13} which is a bench-stable solid and easy to handle,¹⁴ we investigated the conversion of **8** into **9** through intermediate **13** (ref. 15) (Scheme 3). Numerous attempts including screening of bases to achieve this have resulted in the polymerization and halogenation¹³ of **8** over the carbonylative cyclization.¹² Upon exposure of **8c** to triphosgene in the presence of Et₃N followed by addition of HBr,¹² the desired product **9c** was obtained in low yield along with unstable brominated product **12**. The acid lability of a pyran[3,2-*e*]indole afforded troublesome,

Table 1 Comparison of ¹H and ¹³C NMR data of synthetic compound 2 and natural fontanesine B

| ¹ H NMR (DMSO- <i>d</i> ₆ , 500 MHz, δ in ppm) | |
|--|---|
| Natural fontanesine B | Synthetic compound 2 |
| 1.40 (6H, s, CH ₃ -25, 26) | 1.34 (6H, s, CH ₃ -25, 26) |
| 3.33 (2H, t, <i>J</i> = 6.9 Hz, H-6) | 3.06 (2H, t, <i>J</i> = 7.5 Hz, H-6) |
| 4.43 (2H, t, <i>J</i> = 6.9 Hz, H-5) | 4.38 (2H, t, <i>J</i> = 6.9 Hz, H-5) |
| 5.77 (1H, d, <i>J</i> = 9.8 Hz, H-23) | 5.81 (1H, d, <i>J</i> = 9.8 Hz, H-23) |
| 6.77 (1H, d, <i>J</i> = 8.7 Hz, H-11) | 6.53 (1H, d, <i>J</i> = 9.7 Hz, H-11) |
| 6.88 (1H, d, <i>J</i> = 9.8 Hz, H-22) | 6.93 (1H, s, H-22) |
| 7.25 (1H, d, <i>J</i> = 8.7 Hz, H-12) | 7.12 (1H, s, H-12) |
| 7.47 (1H, ddd, <i>J</i> = 8.0, 7.1, 1.2 Hz, H-18) | 7.43 (1H, td, <i>J</i> = 7.4, 1.2 Hz, H-18) |
| 7.67 (1H, dd, <i>J</i> = 8.3, 1.2 Hz, H-16) | 7.64 (1H, d, <i>J</i> = 8.1 Hz, H-16) |
| 7.81 (1H, ddd, <i>J</i> = 8.3, 7.1, 1.5 Hz, H-17) | 7.77 (1H, td, <i>J</i> = 6.5, 1.2 Hz, H-17) |
| 8.16 (1H, dd, <i>J</i> = 8.0, 1.5 Hz, H-19) | 8.12 (1H, d, <i>J</i> = 8.0 Hz, H-19) |
| 11.72 (1H, s, H-1) | 11.71 (1H, s, H-1) |
| ¹³ C NMR (DMSO- <i>d</i> ₆ , 126 MHz, δ in ppm) | |
| Natural fontanesine B | Synthetic compound 2 |
| 20.7 (C-6) | 21.3 (C-6) |
| 27.0 (C-25, 26) | 27.5 (C-25, 26) |
| 40.6 (C-5) | 41.1 (C-5) |
| 75.0 (C-24) | 75.6 (C-24) |
| 112.6 (C-9) | 113.2 (C-9) |
| 112.7 (C-12) | 113.3 (C-12) |
| 115.6 (C-11) | 116.1 (C-11) |
| 116.5 (C-7) | 117.1 (C-7) |
| 119.2 (C-22) | 119.8 (C-22) |
| 120.6 (C-20) | 121.2 (C-20) |
| 120.9 (C-8) | 121.5 (C-8) |
| 125.9 (C-18) | 126.5 (C-18) |
| 126.4 (C-16) | 127.0 (C-16) |
| 126.5 (C-19) | 127.1 (C-19) |
| 127.9 (C-2) | 128.5 (C-2) |
| 130.1 (C-23) | 130.7 (C-23) |
| 134.3 (C-17) | 135.0 (C-17) |
| 134.4 (C-13) | 135.0 (C-13) |
| 145.2 (C-3) | 145.8 (C-3) |
| 146.2 (C-10) | 146.8 (C-10) |
| 147.4 (C-15) | 148.0 (C-15) |
| 160.5 (C-21) | 161.1 (C-21) |



with polymerized materials being the major spot observed. As this polymerization presumably arises from activated urea intermediate **16**, which was generated from less electrophilic acid chloride **14** (ref. 14 and 16*b*) or more electrophilic intermediate **15** by addition/elimination process by HBr and Et₃N,¹⁶ it was clear that the Et₃N^{14b} and HBr would require to be dismissed at the cyclization step in our synthetic route.

Because the product yield was not sufficient (up to 6% yield), further investigations were carried out. After intensive investigations, it was serendipity that we found that the treatment of **8** with triphosgene in the presence of Et₃N at room temperature afforded a trichloromethyl carbamate intermediate **13b** in 88% yield (Scheme 4).¹⁷ Then, after aqueous work-up to remove Et₃N in the reaction media, **13b** was heated in DMSO to afford **9b** in 86% yield. Furthermore, by employing a stepwise method, we obtained **9** from **8** in good yield through the carbamoyl ion **17** (ref. 18) using a single column chromatography. To the best of our knowledge, this is the first time that an unstable trichloromethyl carbamate intermediate has been applied to the C–C bond formations.^{14–17} In contrast to the mild Bischler–Napieralski-type cyclization developed by Saikawa and Nakata,¹⁹ and Clayden,²⁰ our protocol does not require additives to promote the cyclization.

Numerous attempts were made in case of benzyl-substituted lactam **9a**; however, all of them led to rapid decomposition (Scheme 5). On the other hand, treatment of **9b** with *p*-toluenesulfonic acid (*p*-TsOH)²¹ afforded the deprotected lactam **10** in 17% yield. As expected, lactam **9c** could also be deprotected under the same conditions to afford **10** in 67% yield. In general, 2,4-DMB group is more easily removed than PMB group.²¹

With the synthetic access to **9**, we were set to answer whether **9** could be deprotected keeping the alkene, pyran, and indole intact. Finally, the condensation of **10** and anthranilic acid (**11a**) in the presence of POCl₃ (ref. 22) generated the final product **2** (Scheme 6), whose structure was determined by spectroscopic experiments. All the physical data of synthetic **2** were in good agreement with those reported for the natural product (Table 1).¹

In conclusion, we have successfully accomplished the total synthesis of fontanesine B using C4 Pictet–Spengler/allylic transposition as the key step to construct the pyrano[3,2-*e*]indole core using the transient directing group (TDG). In this cyclization, the TDG played the dual important role of directing group and reagent.²³ In addition, the unprecedented carbamate intermediate produced in the carbonylative cyclization could be converted into pyrano[3,2-*e*]pyrido[3,4-*b*]indoles only by heating through the Bischler–Napieralski-type cyclization. Further investigations including application of the C2 and C4 cyclization strategy²⁴ to the syntheses of other indole alkaloids is ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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