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

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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 Conforti[5] 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 serotonins[8] or 5-hydroxytryptophans[9] 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

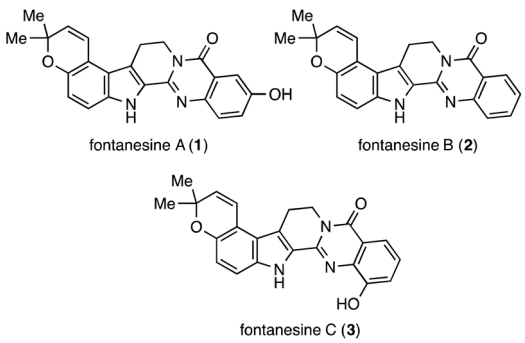
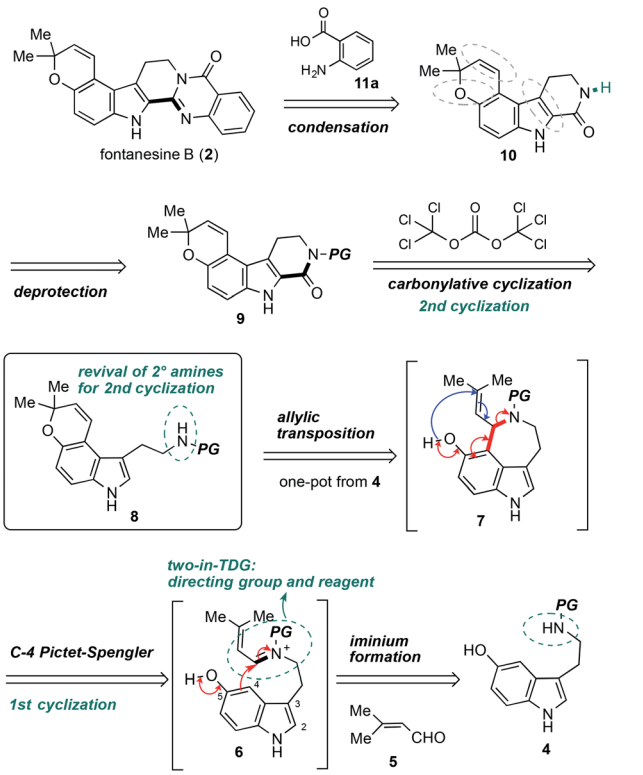


Fig. 1 Fontanesines A (**1**), B (**2**), and C (**3**).



Scheme 1 Retrosynthetic analysis of fontanesine B (**2**).

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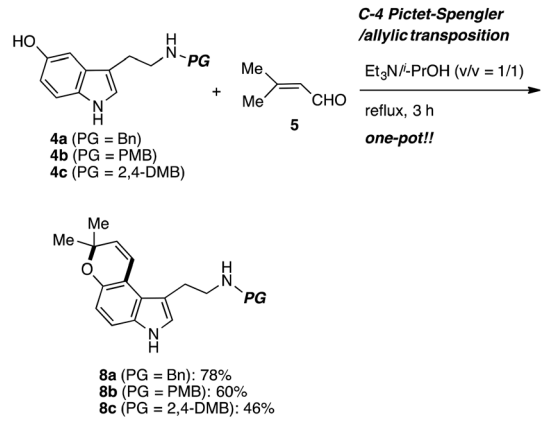
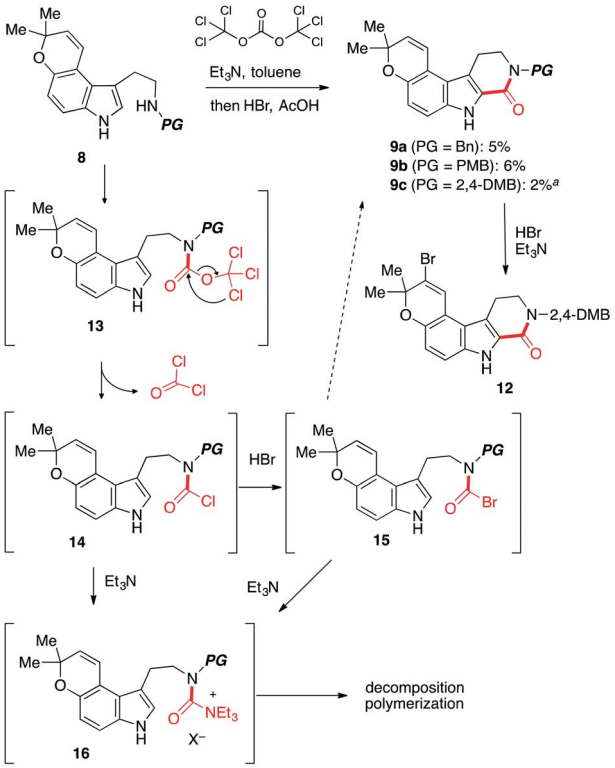
† Electronic supplementary information (ESI) available: Detailed experimental procedures and spectra data for all compounds, including scanned images of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c9ra02321f



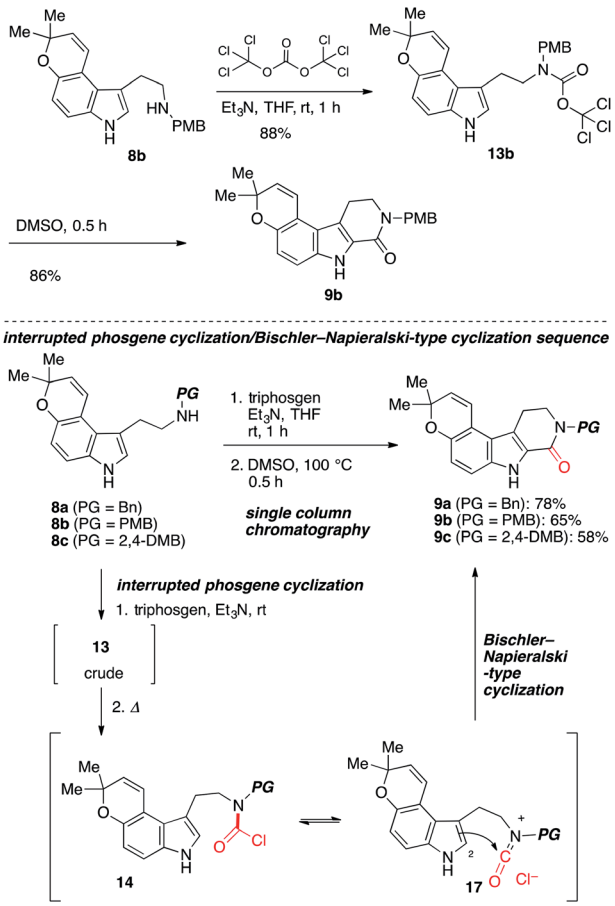
Scheme 2 Synthesis of substrates **8**.



Scheme 3 Attempted synthesis of **9**. [a]**12** 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**.

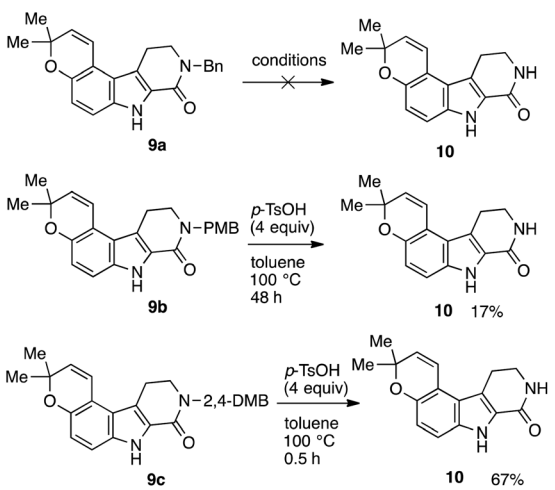
Before synthetic studies, we could predict the difficulty of removing the protecting group on the nitrogen atom at the late stage. Therefore, we decided to prepare the several tryptamines **4** with different protecting groups. The synthesis was started from the benzyl protected 5-hydroxytryptamine **4** (Scheme 2). It was reacted with 3-methyl-2-butenal (**5**) in 2-propanol/Et_3N



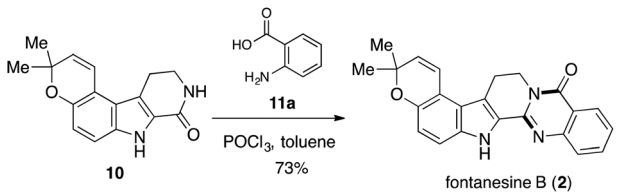
Scheme 4 Improved synthesis of β-carbolines **9** from **8** *via* interrupted phosgene cyclization and Bischler–Napieralski-type cyclization.

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



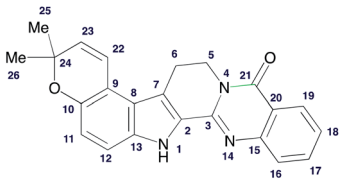
Scheme 5 Removal of benzyl substituents on the nitrogen atoms in **9**.



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 halogenation[13] of **8** over the carbonylative cyclization.[12] Upon exposure of **8c** to triphosgene in the presence of Et_3N 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 pyrano[3,2-*e*]indole afforded troublesome,

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



fontanesine B

^{1}H NMR (DMSO-d_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, J = 6.9 Hz, H-6)	3.06 (2H, t, J = 7.5 Hz, H-6)
4.43 (2H, t, J = 6.9 Hz, H-5)	4.38 (2H, t, J = 6.9 Hz, H-5)
5.77 (1H, d, J = 9.8 Hz, H-23)	5.81 (1H, d, J = 9.8 Hz, H-23)
6.77 (1H, d, J = 8.7 Hz, H-11)	6.53 (1H, d, J = 9.7 Hz, H-11)
6.88 (1H, d, J = 9.8 Hz, H-22)	6.93 (1H, s, H-22)
7.25 (1H, d, J = 8.7 Hz, H-12)	7.12 (1H, s, H-12)
7.47 (1H, ddd, J = 8.0, 7.1, 1.2 Hz, H-18)	7.43 (1H, td, J = 7.4, 1.2 Hz, H-18)
7.67 (1H, dd, J = 8.3, 1.2 Hz, H-16)	7.64 (1H, d, J = 8.1 Hz, H-16)
7.81 (1H, ddd, J = 8.3, 7.1, 1.5 Hz, H-17)	7.77 (1H, td, J = 6.5, 1.2 Hz, H-17)
8.16 (1H, dd, J = 8.0, 1.5 Hz, H-19)	8.12 (1H, d, J = 8.0 Hz, H-19)
11.72 (1H, s, H-1)	11.71 (1H, s, H-1)

^{13}H NMR (DMSO-d_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 Et_3N,[16] it was clear that the Et_3N[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 Et_3N at room temperature afforded a trichloromethyl carbamate intermediate **13b** in 88% yield (Scheme 4).[17] Then, after aqueous work-up to remove Et_3N 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.[11–17] 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 $POCl_3$ (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 strategy[24] to the syntheses of other indole alkaloids is ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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