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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 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

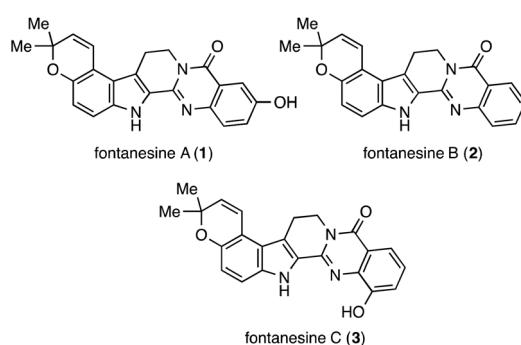
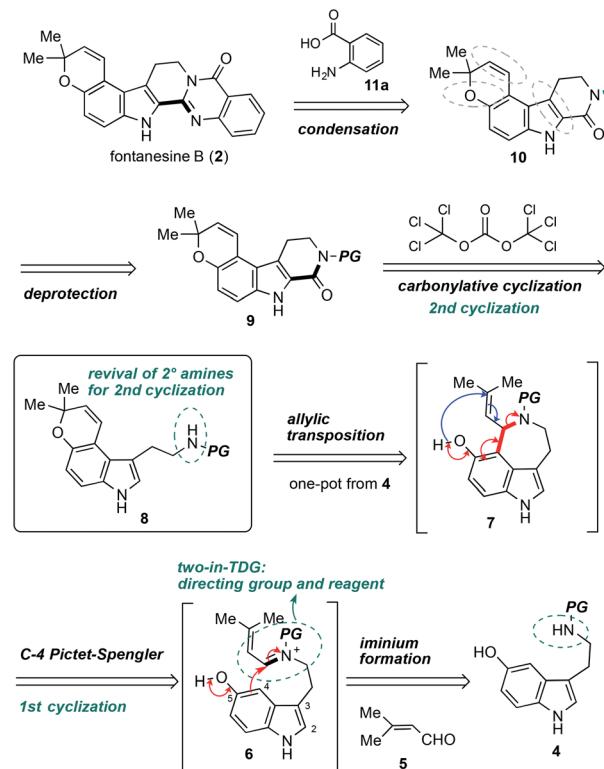


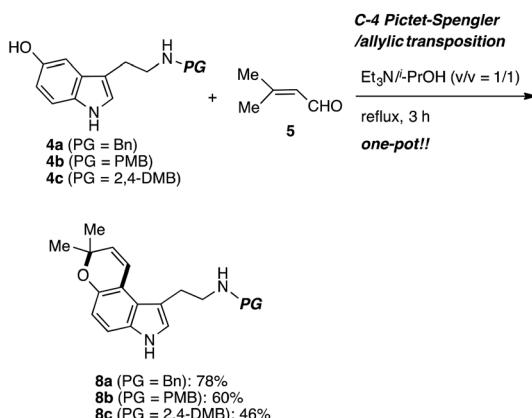
Fig. 1 Fontanesines A (1), B (2), and C (3).

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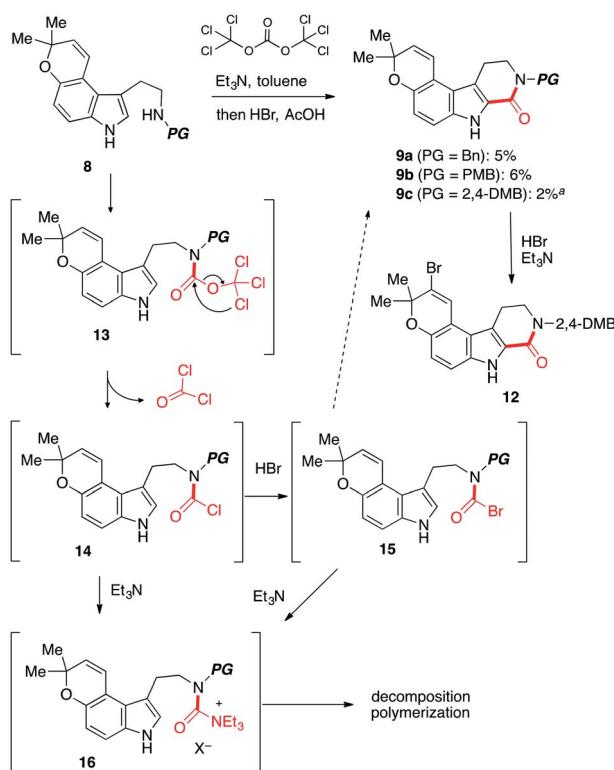
† Electronic supplementary information (ESI) available: Detailed experimental procedures and spectra data for all compounds, including scanned images of ¹H and ¹³C NMR spectra. See DOI: 10.1039/c9ra02321f



Scheme 1 Retrosynthetic analysis of fontanesine B (2).

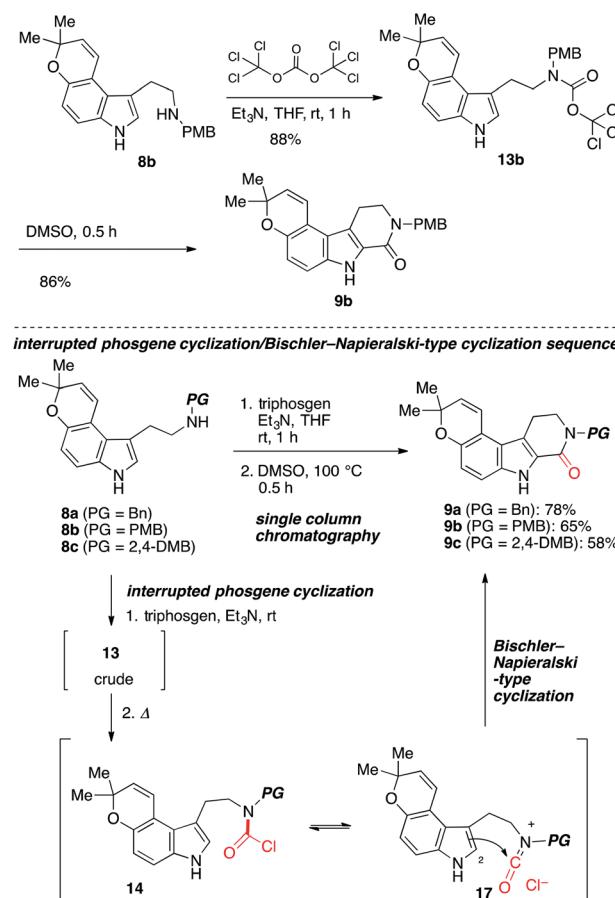


Scheme 2 Synthesis of substrates 8.

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**.

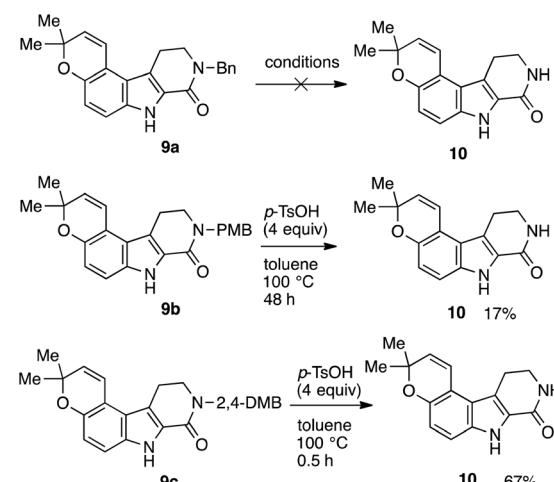
Before synthetic studies, we could predict the difficulty of removing the protecting group on the nitrogen atom at the late stage. Therefore, we decided to prepare the several tryptamines **4** with different protecting groups. The synthesis was started from the benzyl protected 5-hydroxytryptamine **4**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



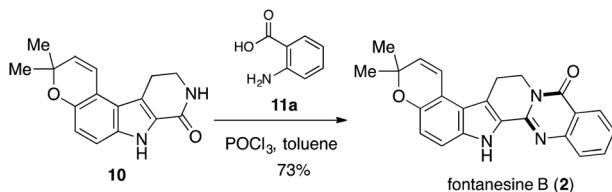
Scheme 4 Improved synthesis of β-carbolines 9 from 8 via interrupted phosgene cyclization and Bischler-Napieralski-type cyclization.

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

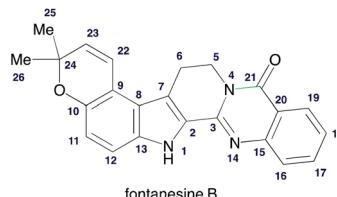


Scheme 5 Removal of benzyl substituents on the nitrogen atoms in 9.



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 pyrano[3,2-*e*]indole afforded troublesome,

Table 1 Comparison of ¹H and ¹³C NMR data of synthetic compound 2 and natural fontanesine B¹H 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, <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)

¹³C 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 16b) 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.^{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 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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Notes and references

- R. S. Cabral, P.-M. Allard, L. Marcourt, M. C. M. Young, E. F. Queiroz and J.-L. Wolfender, *J. Nat. Prod.*, 2016, **79**, 2270.
- (a) J. E. Macor, C. B. Fox, C. J. Johnson, B. K. Koe, L. A. Lebel and S. H. Zorn, *J. Med. Chem.*, 1992, **35**, 3625; (b) J. E. Macor, K. Ryan and M. E. Newman, *Tetrahedron*, 1992, **48**, 1039; (c) J. E. Macor, D. H. Blank and R. J. Post, *Tetrahedron Lett.*, 1994, **35**, 45; (d) J. E. Macor, *Tetrahedron Lett.*, 1995, **36**, 7019; (e) J. E. Macor, O. D. Langer, J. Z. Gougoutas, M. F. Malley and L. A. M. Cornelius, *Tetrahedron Lett.*, 2000, **41**, 3541.
- J. P. M. Plung, G.-J. Koomen and U. K. Pandit, *Tetrahedron Lett.*, 1992, **33**, 2179.
- J. A. May, H.-H. Chen, A. Rusinko, V. M. Lynch, N. A. Sharif and M. A. McLaughlin, *J. Med. Chem.*, 2003, **46**, 4188.
- M. S. Sinicropi, A. Caruso, F. Conforti, M. Marrelli, H. EI Kashef, J.-C. Lancelot, S. Rault, G. A. Statti and F. Menichini, *J. Enzyme Inhib. Med. Chem.*, 2009, **24**, 1148.
- In alkaloids synthesis, pyran formation had been conducted at a late stage. For reviews, see: (a) H.-J. Knölker and K. R. Reddy, *Chem. Rev.*, 2002, **112**, 3193; (b) M. Ishikura, K. Yamada and T. Abe, *Nat. Prod. Rep.*, 2010, **27**, 1630; (c) A. W. Schmidt, K. R. Reddy and H.-J. Knölker, *Chem. Rev.*, 2012, **102**, 4303; (d) M. Ishikura, T. Abe, T. Choshi and S. Hibino, *Nat. Prod. Rep.*, 2013, **30**, 694; (e) M. Ishikura, T. Abe, T. Choshi and S. Hibino, *Nat. Prod. Rep.*, 2015, **32**, 1389.
- (a) T. Abe, T. Ikeda, R. Yanada and M. Ishikura, *Org. Lett.*, 2011, **13**, 3356; (b) T. Abe, T. Ikeda, R. Yanada and M. Ishikura, *Org. Lett.*, 2013, **15**, 3622; (c) T. Abe, T. Itoh, S. Hibino, T. Choshi and M. Ishikura, *Tetrahedron Lett.*, 2014, **55**, 5268; (d) T. Itoh, T. Abe, S. Nakamura and M. Ishikura, *Heterocycles*, 2015, **91**, 1423; (e) T. Itoh, T. Abe, T. Choshi, T. Nishiyama and M. Ishikura, *Heterocycles*, 2016, **92**, 1132; (f) T. Abe and K. Yamada, *Org. Lett.*, 2016, **18**, 6504; (g) T. Abe, K. Kida and K. Yamada, *Chem. Commun.*, 2017, **53**, 4362; (h) T. Itoh, T. Abe, T. Choshi, T. Nishiyama and M. Ishikura, *Heterocycles*, 2017, **95**, 507; (i) T. Abe, T. Suzuki, M. Anada, S. Matsunaga and K. Yamada, *Org. Lett.*, 2017, **19**, 4275; (j) T. Abe and K. Yamada, *Org. Lett.*, 2018, **20**, 1469; (k) T. Abe and M. Terasaki, *Helv. Chim. Acta*, 2018, **101**, e1700284; (l) T. Abe, *Heterocycles*, 2018, **96**, 490.
- (a) K. Yamada, Y. Namerikawa, T. Abe and M. Ishikura, *Heterocycles*, 2009, **77**, 825; (b) K. Yamada, Y. Namerikawa, T. Haruyama, Y. Miwa, R. Yanada and M. Ishikura, *Eur. J. Org. Chem.*, 2009, 5752.
- (a) T. Abe and K. Yamada, *J. Nat. Prod.*, 2017, **80**, 241; (b) T. Abe, T. Haruyama and K. Yamada, *Synthesis*, 2017, **49**, 4141.
- K. Yamada, S. Yamaguchi, N. Hatae, T. Abe, T. Iwamura and M. Ishikura, *Heterocycles*, 2011, **83**, 815.
- Phosgene cyclization of N-substituted tryptamines has not been reported. For examples of phosgene cyclization of primary tryptamines *via* isocyanates, see: (a) F. Bracher and D. Hilderband, *Liebigs Ann. Chem.*, 1992, 1315; (b)



K. C. Nicolaou, J. L. Kiappes, W. Tian, V. B. Gondi and J. Becker, *Org. Lett.*, 2011, **13**, 3924; (c) J. Zhang, S. Da, X. Feng, X. Chen, J. Jiang and Y. Li, *Chin. J. Chem.*, 2013, **31**, 123.

12 For examples of triphosgene mediated halogenations, see: (a) C. E. Ayala, A. Villalpando, A. L. Nguyen, G. T. McCandless and R. Kartika, *Org. Lett.*, 2012, **14**, 3676; (b) A. Villalpando, C. E. Ayala, C. B. Watson and R. Kartika, *J. Org. Chem.*, 2013, **78**, 3989; (c) M. A. Saputra, L. Ngo and R. Kartika, *J. Org. Chem.*, 2015, **80**, 8815; (d) A. Villalpando, M. A. Saputra, T. H. Tugwell and R. Kartika, *Chem. Commun.*, 2015, **51**, 15075; (e) A. H. Cleveland, F. R. Fronczeck and R. Kartika, *J. Org. Chem.*, 2018, **83**, 3367.

13 For selected examples of coupling reactions using triphosgene, see: (a) A. Armstrong, I. D. Edmonds and M. E. Swarbrick, *Tetrahedron Lett.*, 2003, **44**, 5335; (b) O. P. Gulin, F. Rabanal and E. Giralt, *Org. Lett.*, 2006, **8**, 5385; (c) W. Su, S. J. Gray, R. Dondi and G. A. Burley, *Org. Lett.*, 2009, **11**, 3910; (d) S. T. Le Quement, T. Flagstad, R. J. T. Mikkelsen, M. R. Hansen, M. C. Givskov and T. E. Nielsen, *Org. Lett.*, 2012, **14**, 640; (e) Z. Wu, T. Hu, L. He and B. Gong, *Org. Lett.*, 2012, **14**, 2504; (f) L. Fang, G. Yao, Z. Pan, C. Wu, H.-S. Wang, G. A. Burley and W. Su, *Org. Lett.*, 2015, **17**, 158; (g) K. Leczycka-Wilk, K. Dabrowa, P. Cmoch and S. Jarosz, *Org. Lett.*, 2017, **19**, 4596; (h) S. E. Varjosaari, P. Suating and M. J. Adler, *Synthesis*, 2016, **48**, 43.

14 For reviews, see: (a) L. Cotarca, P. Delogu, A. Nardelli and V. Sunjic, *Synthesis*, 1995, 553; (b) L. Cotarca, T. Geller and J. Répasi, *Org. Process Res. Dev.*, 2017, **21**, 1439.

15 (a) J. Bermudez, S. Dabbs, K. A. Joiner and F. D. King, *J. Med. Chem.*, 1990, **33**, 1929; (b) P. A. Barsanti, Y. Xia, W. Wang, K. G. Mendenhall, L. M. Langniton, S. Ramurthy, M. C. Phillips, S. Subramanian, R. Boyce, N. M. Brammeier, R. Constantine, D. Duhl, A. O. Walter, T. J. Abrams and P. A. Renhowe, *US Pat. Appl. US 20070037853, CAN 146:251846*, 2007.

16 (a) L. Contarca and H. Eckert, *Phosgenations – A Handbook*, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2003; (b) L. Pasquato, G. Modena, L. Cotarca, P. Delouge and S. Mantovani, *J. Org. Chem.*, 2000, **65**, 8224; (c) V. K. Gumaste and A. R. A. S. Deshmukh, *Tetrahedron Lett.*, 2004, **45**, 6571.

17 Trichloromethyl carbamate easily decomposes to give the corresponding carbamic acid, see: A. C. Sosa, R. Conway, R. T. Williamson, J. P. Suchy, W. Edwards and T. Cleary, *Org. Process Res. Dev.*, 2011, **15**, 1458.

18 S. Hwang, D. Kim and S. Kim, *Chem.-Eur. J.*, 2012, **18**, 9977.

19 For the pioneering examples of Bischler–Napieralski-type cyclization using isopropyl carbamates and P_2O_5 , see: (a) S. Adachi, K. Watanabe, Y. Iwata, S. Kameda, Y. Miyaoka, M. Onozuka, R. Mitsui, Y. Saikawa and M. Nakata, *Angew. Chem., Int. Ed.*, 2013, **52**, 2087; (b) S. Adachi, M. Onozuka, Y. Yoshida, M. Ide, Y. Saikawa and M. Nakata, *Org. Lett.*, 2014, **16**, 358.

20 For an example of a mild Bishler–Napieralski-style cyclization using KI as a promoter, see: M. M. Amer, A. C. Carrasco, D. J. Leonard, J. W. Ward and J. Clayden, *Org. Lett.*, 2018, **20**, 7977.

21 C.-Y. Chern, Y.-P. Huang and W. M. Kan, *Tetrahedron Lett.*, 2003, **44**, 1039.

22 M. Decker, *Eur. J. Med. Chem.*, 2005, **40**, 305.

23 During the preparation of this manuscript, Zeng and Li reported a two-in-one strategy using a transient directing group (TDG) for palladium-catalyzed functionalization. See: H. Zheng, Z. Wang and C.-J. Li, *Angew. Chem., Int. Ed.*, 2019, **58**, 2859.

24 To the best of our knowledge, the synthetic approach involving both Pictet–Spengler and Bischler–Napieralski cyclization has not been explored. For reviews, see: (a) J. Stöckigt, A. P. Antonchick, F. Wu and H. Waldman, *Angew. Chem., Int. Ed.*, 2011, **50**, 8538; (b) M. Chrzanowska, A. Grajewska and M. D. Rozwadowska, *Chem. Rev.*, 2016, **116**, 12369.