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C–H functionalization of 2-alkyl tryptamines: direct assembly of azepino[4,5-*b*]indoles and total synthesis of ngouniensines†

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The Pictet–Spengler type condensation of tryptamine derivatives and aldehydes or ketones is a classic reaction, and has been previously applied to assemble indole-annulated 5-, 6- and 8-membered heterocyclic rings. In this work, we further expand the synthetic scope of this reaction to the 7-membered azepino[4,5-*b*]indole skeleton through the direct C–H functionalization of 2-alkyl tryptamines, in which the non-activated methylene group participates in a 7-membered ring formation with aldehydes. By combining this unprecedented ring-forming process with a second C–H olefination at the same carbon, the concise total synthesis of natural products ngouniensines is achieved, demonstrating the synthetic potential of the developed chemistry in simplifying retrosynthetic disconnections.

Introduction

The Pictet–Spengler type condensation of tryptamine derivatives and aldehydes or ketones is a classic reaction, and represents a direct and convergent strategy for the synthesis of indole-annulated heterocyclic structures.[1–4] Depending on whether there is a substituent at the C2-position, two types of cyclization occurring at C2 or C3 have been well known, leading to the formation of 6-membered tetrahydro-*b*-carboline (**I**) and 5-membered spiroindolenine (**II**) skeletons, respectively (Fig. 1). In addition, with a 2-vinyl substituent, the vinylogous Pictet–Spengler type cyclization is also feasible, affording the 8-membered tetrahydroazocinoindole (**III**) ring system.[5] The wide presence of these skeletons (**I**, **II**, **III**) in natural products and biologically important molecules has prompted the growth of this class of reactions in popularity. The further development of novel reaction modes for the Pictet–Spengler type condensation would be highly desirable to expand the synthetic scope of this class of reactions.

The 7-membered azepino[4,5-*b*]indole skeleton (**IV**, Fig. 1) is characteristic of a variety of indole alkaloids, as exemplified by the structures of ngouniensines (**1a**, **1b**), ibogaine and many others.[6–16] The significance of the azepino[4,5-*b*]indole skeleton as an essential therapeutic pharmacophore has been recently highlighted by the structural simplification of ibogaine, leading to the development of tabernanthalog (Fig. 1) as a safer and non-hallucinogenic psychedelic analog with therapeutic potential.[17] In contrast to the structural and biological importance of the azepino[4,5-*b*]indole skeleton (**IV**), relatively few synthetic methods have been developed for its synthesis, which mainly have relied on the inherent reactivity of functional groups toward ring forming processes.[18–31] While a variety of azepino[4,5-*b*]indoles with varied substitution patterns could be thus generated, the resulting structural diversity could not fully meet the demand for the synthesis of natural products and diversified synthetic analogs. Herein, we report an unprecedented approach for the synthesis of the azepino[4,5-*b*]indole skeleton by the direct C–H functionalization of 2-alkyl tryptamines, and showcase the synthetic utility in the concise total synthesis of ngouniensines.

The application of C–H functionalization logic in chemical synthesis has become a vibrant research area due to the admirable ability in simplifying retrosynthetic disconnections by avoiding the preinstallation of requisite functional groups.[32] The indole alkaloids ngouniensines (**1a**, **1b**)[33,34] structurally feature the azepino[4,5-*b*]indole core and an exocyclic conjugated alkene, which were both constructed by the manipulation of preinstalled functional groups in the previous synthesis.[6] We surmised to develop a C–H functionalization based approach, not only to offer a concise entry to ngouniensines, but also to

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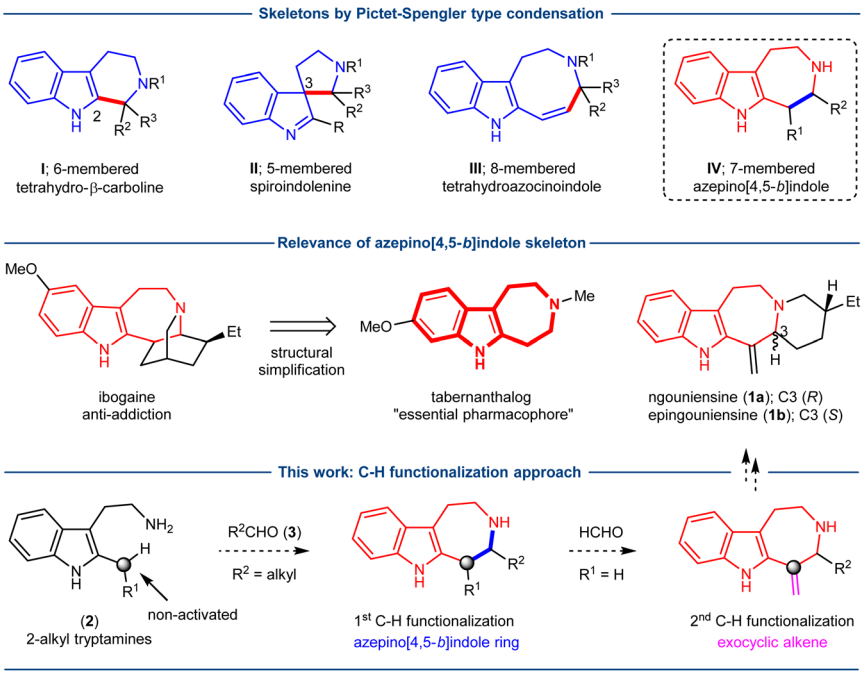


Fig. 1 Azepino[4,5-*b*]indole skeleton and the proposed C–H functionalization based strategy.

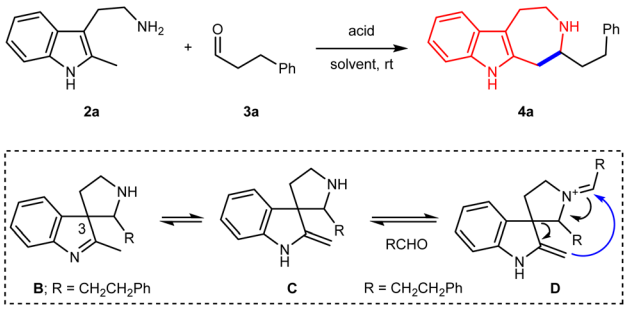
facilitate the preparation of azepino[4,5-*b*]indole containing molecules in general. Specifically, as depicted in Fig. 1, we envisioned to construct the azepino[4,5-*b*]indole skeleton by the direct C–H functionalization of 2-alkyl tryptamines **2**, in which the non-activated methylene at C2 would participate in a 7-membered ring formation with aldehydes **3**. The direct coupling of **2** and **3** could be regarded as a homologated Pictet–Spengler condensation, which, if realized, would further expand the synthetic scope of this classic reaction beyond the indole-annulated 5-, 6- and 8-membered heterocyclic skeletons (**I–III**, Fig. 1). The exocyclic conjugated alkene in ngouniensines could be introduced by a second C–H functionalization of the same carbon with formaldehyde (R^1 = H). Based on the above hypothesis, the chemical synthesis of ngouniensines could be attempted with unconventional bond disconnection tactics.

Results and discussion

Synthesis of azepino[4,5-*b*]indoles

In continuation with our interest in developing skeletal rearrangements within the indole system,[35–40] we became interested in the possible fate of certain spiroindolenine intermediates toward subsequent transformations. As depicted in the model reaction of **2a** and **3a** (Table 1), we envisioned that the tautomerization of spiroindolenine **B** (generated by the Pictet–Spengler reaction) to the exocyclic enamine **C** would set the basis for the C–H functionalization of the non-activated methyl group, and the 7-membered azepino[4,5-*b*]indole skeleton would be subsequently formed *via* the intermediate **D** through either the concerted [3,3]-sigmatropic rearrangement or stepwise Mannich/retro Mannich pathway. Based on such a proposal, different Brønsted acids were screened with this model reaction. Using AcOH as the acid in chloroform, we were pleased to observe the formation of the desired azepino[4,5-*b*]indole **4a**, albeit in only 11% yield (Table 1, entry 1). The

Table 1 Optimized reaction conditions[a]



Entry	Acid	Solvent	Yield[b] (%)
1	AcOH (2.0 equiv.)	$CHCl_3$	11
2	CSA (2.0 equiv.)	$CHCl_3$	Trace
3	*p*-TsOH (2.0 equiv.)	$CHCl_3$	Trace
4	$(PhO)_2POOH$ (2.0 equiv.)	$CHCl_3$	Trace
5	TFA (2.0 equiv.)	$CHCl_3$	52
6	TFA (1.0 equiv.)	$CHCl_3$	Trace
7	TFA (4.0 equiv.)	$CHCl_3$	85
8	TFA (6.0 equiv.)	$CHCl_3$	60
9	TFA (4.0 equiv.)	CH_2Cl_2	80
10	TFA (4.0 equiv.)	Toluene	56

[a] A mixture of **2a** (0.2 mmol) and **3a** (0.4 mmol) in the specified solvent (0.2 M) was stirred at rt in the presence of the specified acid. [b] Isolated yield. rt = room temperature. TFA = trifluoroacetic acid. CSA = camphorsulfonic acid. *p*-TsOH = *p*-toluenesulfonic acid.

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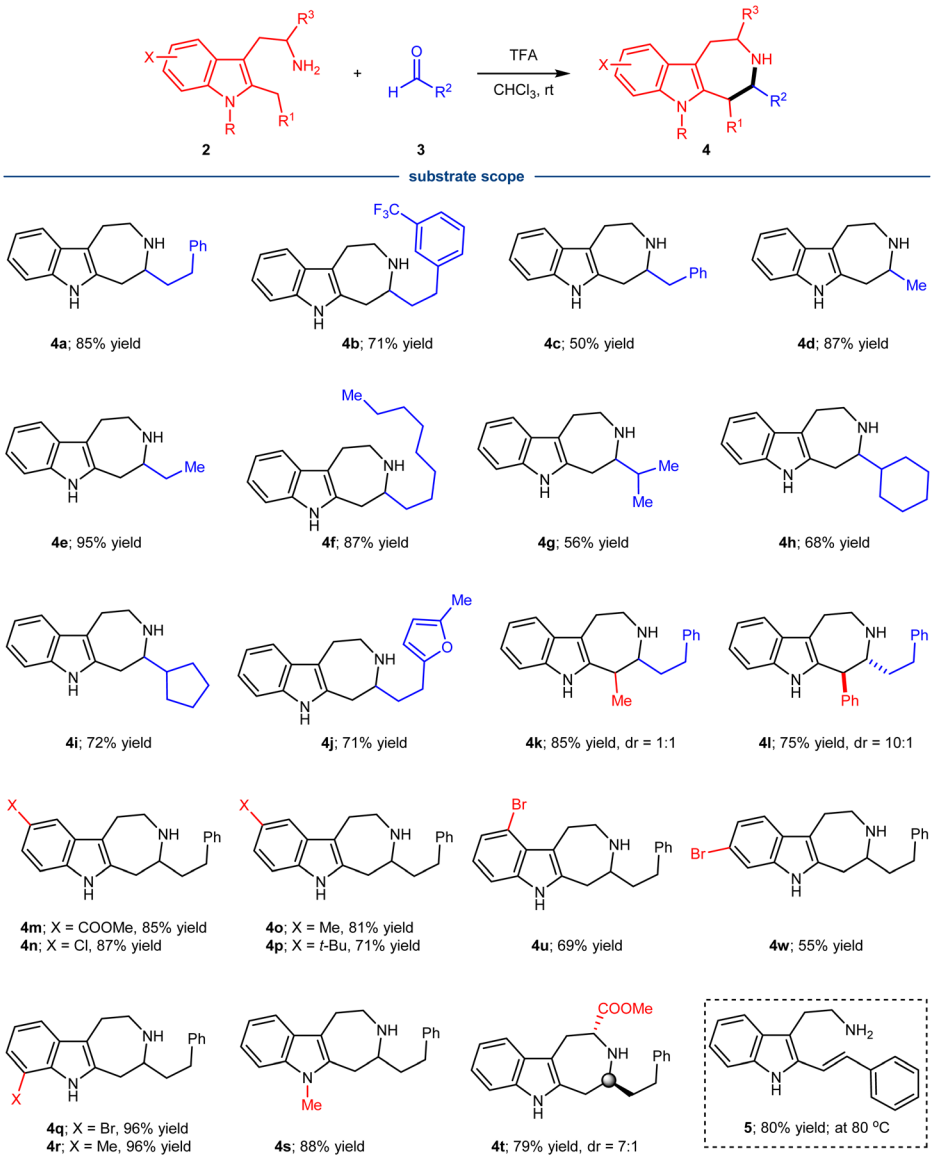
structure of **4a** was unambiguously confirmed by single crystal X-ray diffraction. Camphorsulfonic acid (CSA, entry 2), *p*-toluene sulfonic acid (*p*-TsOH, entry 3) and diphenyl phosphate (entry 4) were not successful promotors for the formation of **4a**. A promising result was obtained using trifluoroacetic acid (TFA), delivering **4a** in 52% yield (entry 5). The equivalent of TFA was then found to be a key factor (entries 6–8). With 4.0 equivalent of TFA as the acid, **4a** could be isolated in 85% yield (entry 7). The reaction also proceeded in other solvents: similar yield using CH_2Cl_2, albeit with lower yield using toluene.

With the reaction conditions identified, the substrate scope of the condensation of tryptamine derivatives **2** with different aliphatic aldehydes **3** was investigated (Scheme 1). It turned out that the reaction represented a general approach for the synthesis of azepino[4,5-*b*]indoles **4**, tolerating significant structural variations of both partners. A variety of linear aldehydes of different size were successful substrates, generating the corresponding products with good to excellent yield (**4a–f**). The steric more hindered branched aldehydes containing isopropyl-, cyclopentyl- and cyclohexyl-groups also proved to be efficient substrates (**4g–i**). Of note, the reaction could tolerate the presence of heterocyclic furan (**4j**), which is also a good nucleophile for the Pictet–Spengler type reaction and could potentially interact with the related active intermediates. When R^1 was a methyl (**4k**) or phenyl group (**4l**), both reactions proceeded well with good yields, but the diastereoselectivity was different. The poor diastereoselectivity of **4k** and excellent diastereoselectivity of **4l** indicated the importance of steric effect of R^1 in governing the stereochemistry. The relative stereochemistry of **4l** was determined by single crystal X-ray diffraction of a derivative. Substituents (X) on the benzenoid part of **2** were also well tolerated, including both electron donating and withdrawing groups at the varied positions (**4m–4r**, **4u**, **4w**). Finally, the substrate with a methyl group on indole-*N* also



Scheme 1 Synthesis of the 7-membered azepino[4,5-*b*]indoles.

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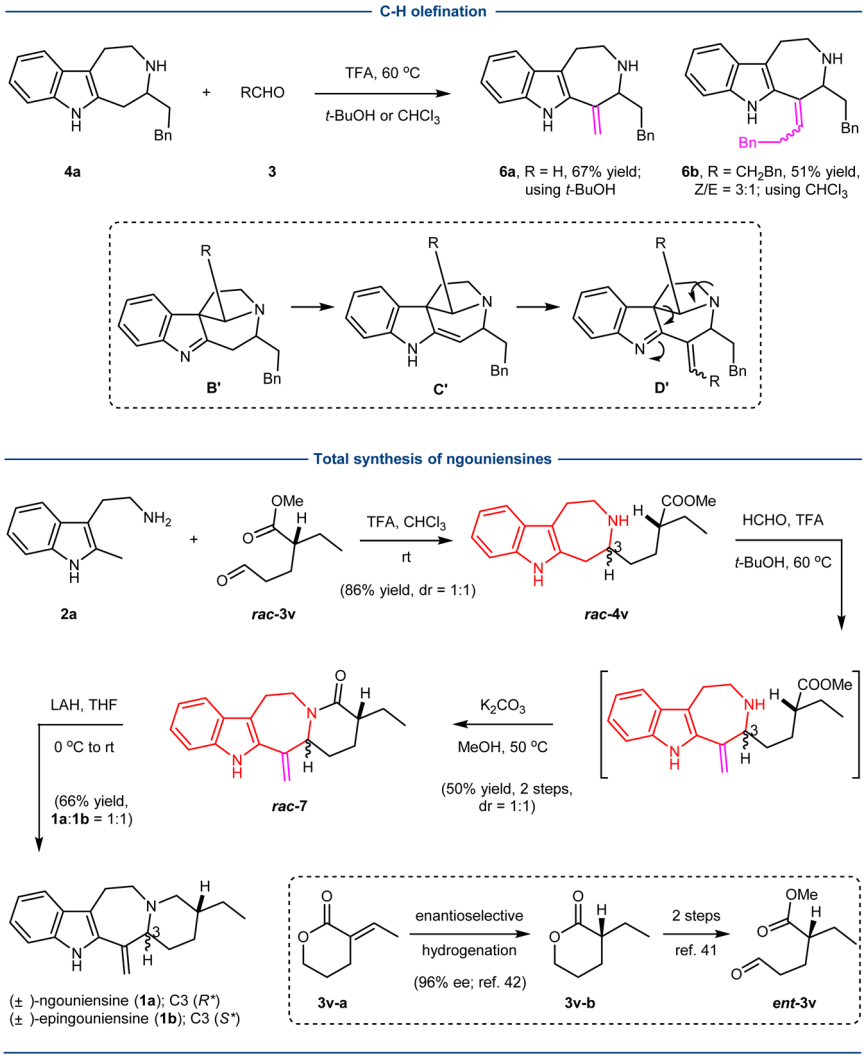
participated in the condensation process with good yield (**4s**). While attempts to make the process catalytically enantioselective using chiral Brønsted acids were not successful at this stage, the direct condensation for 7-membered ring formation could be rendered asymmetric by using a chiral tryptophan derivative, affording product **4t** with 7 : 1 diastereoselectivity. The relative stereochemistry of **4t** was determined by single crystal X-ray diffraction of a derivative. Of note, when aromatic benzaldehyde was allowed for the condensation with tryptamine derivatives **2a**, the reaction did not lead to the formation of the related 7-membered ring, instead the generation of alkene **5** was observed under slightly varied conditions.

Total synthesis of ngouniensines

Next, we examined the possibility of a second C–H functionalization to introduce the exocyclic alkene as shown in the natural products ngouniensines using **4a** as a model substrate (Scheme 2). We surmised that the further Pictet–Spengler cyclization of **4a** with aldehydes would furnish the spiroindolenine **B′**, which could undergo imine/enamine tautomerization to generate **C′**. The subsequent aldol condensation would afford alkene **D′**, which finally could lead to the product **6** with an exocyclic alkene through the retro-Mannich reaction and hydrolysis of the resulting imine. After extensive optimization of reaction conditions, we could realize the desired transformation using trifluoroacetic acid (TFA) as the acid in either *t*-BuOH (**6a**; 67% yield) or $CHCl_3$ (**6b**; 51% yield, *Z*/*E* = 3 : 1) at 60 °C.

The total synthesis of ngouniensines was then realized based on the developed sequential C–H functionalization (Scheme 2). The first C–H functionalization involving the coupling of **2a** and ***rac*-3v**[41] successfully built up the azepino[4,5-*b*]indole core, affording ***rac*-4v** in 86% yield with 1 : 1 dr. The second C–H functionalization of ***rac*-4v** with formaldehyde rapidly installed the exocyclic conjugated alkene, delivering ***rac*-7** upon subsequent amide formation with K_2CO_3. Finally, reduction of the amide group produced the natural products (±)-ngouniensines (**1a** : **1b** = 1 : 1). While the synthesis was carried out using ***rac*-3v**, the absolute chirality could be easily introduced by the known enantioselective hydrogenation (**3v–a** to **3v–b**).[42]



Scheme 2 Total synthesis of ngouniensines.

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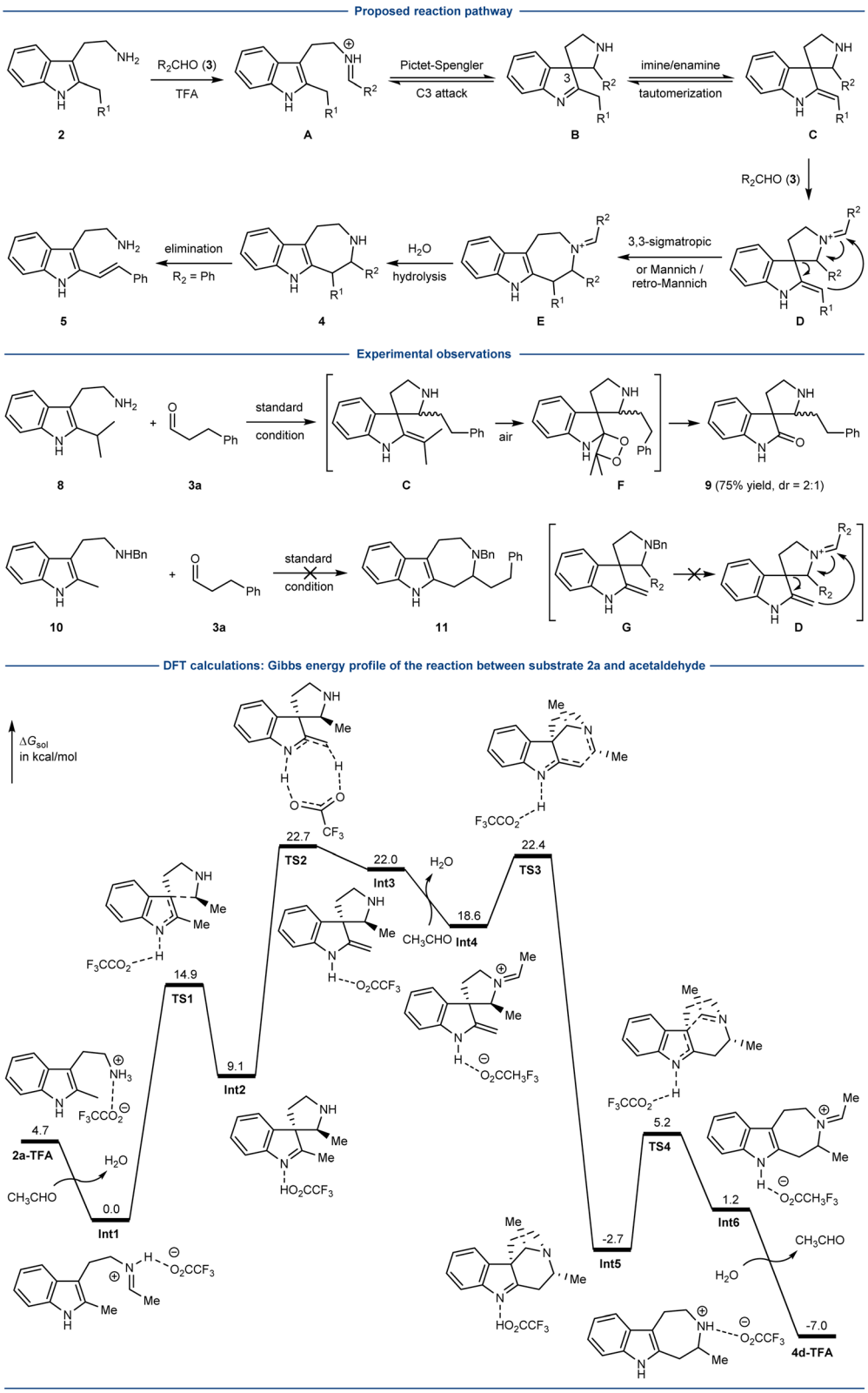

Scheme 3 Reaction mechanism.

Reaction mechanism

A plausible mechanism was proposed for the coupling of 2-alkyl tryptamines **2** and aliphatic aldehydes **3** (Scheme 3). The imine (**A**) formation between **2** and aldehyde **3** could trigger the Pictet–Spengler type cyclization (C3) to afford the spiroindolenine **B**, which underwent imine/enamine tautomerization to furnish **C**. Iminium **D** could be then generated from **C** and an excess of **3**, and underwent either the concerted [3,3]-sigmatropic

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rearrangement or stepwise Mannich/retro Mannich pathway to furnish **E**. Finally, iminium hydrolysis would afford the 7-membered azepino[4,5-*b*]indoles **4**. The formation of alkene **5** could be explained by the elimination reaction from **4** (or **E**), presumably due to the high stability of the conjugated system when R^2 was an aromatic group.

While it was difficult to validate the proposed mechanism by the synthesis of a substrate resembling **B** or **C** due to its reversible transformation back to **A** under the acidic reaction conditions, some experimental observations supported the presence of intermediate **C** and the essential role of **D**. The reaction of bulky 2-*i*Pr tryptamine **8** with aldehyde **3a** afforded the oxindole **9** as the major product, presumably involving the oxidation of enamine **C** by oxygen (intermediate **F**).[43,44] In another control study, the Bn-protected 2-Me-tryptamine **10** failed to give the corresponding product **11**. According to the proposed reaction mechanism, this could be explained by the fact that the resulting **G** could not lead to the formation of intermediate **D** due to the presence of the Bn group.

To gain more insight, DFT calculations were carried out (Scheme 3). The reaction of substrate **2a** and acetaldehyde was chosen as the model reaction, and calculated at the SMD($CHCl_3$)/PBE0-D3BJ/6-311+G(d,p)//PBE0-D3BJ/6-31+G(d,p) level. One of the key steps, the tautomerization of the spiroindolenine (**Int2**) to enamine (**Int3**) has an activation free energy of 13.6 kcal mol^{-1} (*via* **TS2**). The key ring forming event probably undergoes a Mannich/retro-Mannich pathway with the activation free energy of 3.8 kcal mol^{-1} (**TS3**) and 7.9 kcal mol^{-1} (**TS4**), respectively. The Gibbs free energy profile involving the concerted [3,3]-sigmatropic rearrangement pathway could not be located. Of note, a similar retro-Mannich reaction was previously reported by the group of You, involving an intermediate resembling **Int5**.[25]

Conclusions

In summary, we have developed an unprecedented approach for the synthesis of the azepino[4,5-*b*]indole skeleton by the direct C–H functionalization of 2-alkyl tryptamines. The synthetic utility has been demonstrated by the concise total synthesis of natural products ngouniensines, in which 2-Me-tryptamine undergoes sequential C–H functionalization with different aldehydes to afford the azepino[4,5-*b*]indole core and an exocyclic conjugated alkene, respectively. The unprecedented reaction mode, the direct and convergent manner, the operational simplicity and broad substrate scope of the approach should find further applications in the synthesis of azepino[4,5-*b*]indole containing molecules.

Data availability

ESI† is available and includes the detailed synthetic procedure and characterization data of intermediates and final products. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers 2284681 (**4a**), 2284682 (**4l**) and 2284683 (**4t**).

Author contributions

K. X., Z. S., P. C., and H. D. performed experiments and analyzed experimental data. Z. Y. and L.Z. directed the investigations and prepared the manuscript with contributions from all authors; all authors contributed to discussions.

Conflicts of interest

There are no conflicts to declare.

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