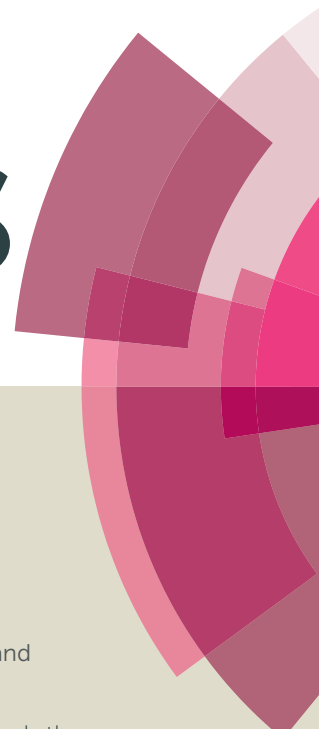


RSC Advances



This article can be cited before page numbers have been issued, to do this please use: H. Li, Z. Wang and L. Zu, *RSC Adv.*, 2015, DOI: 10.1039/C5RA11904A.



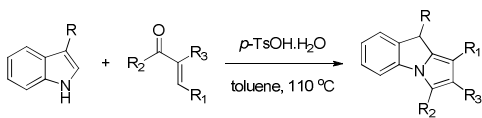
This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

The efficient assembly of densely substituted, highly functionalized pyrrolo[1,2-*a*]indoles by the direct annulation of indoles and α , β -unsaturated ketones is reported.



Journal Name

COMMUNICATION

[3+2] Annulations between Indoles and α , β -Unsaturated Ketones: Access to Pyrrolo[1,2-*a*]indoles and Model Reactions Toward the Originally Assigned Structure of Yuremamine

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

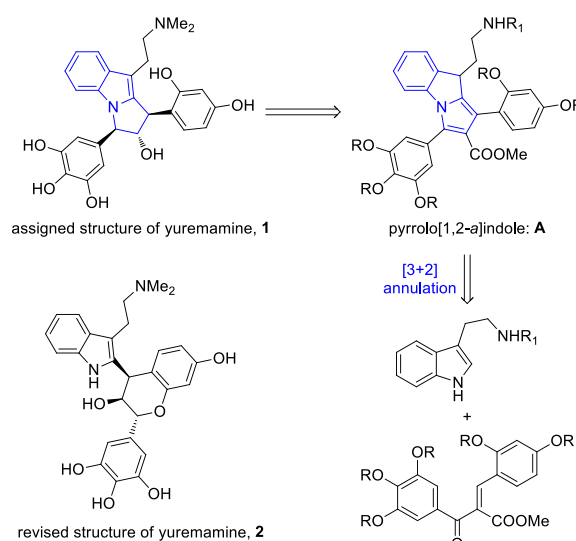
Haokun Li,^a Zhonglei Wang^a and Liansuo Zu^a

www.rsc.org/

A direct [3+2] annulation reaction between indoles and α , β -unsaturated ketones is reported, which allows the efficient assembly of densely substituted, highly functionalized pyrrolo[1,2-*a*]indoles. Model reactions toward the originally assigned structure of yuremamine were also described, leading to the successful construction of the core with required functionality.

The efficient transformations of simple starting materials into complex structures that resemble the core of natural products and medicinally important molecules are of great significance in organic synthesis. Pyrrolo[1,2-*a*]indole tricyclic ring system¹ is a basic nucleus of a number of complex natural products and biologically important molecules. For example, mitomycins and mitosenes containing the pyrrolo[1,2-*a*]indole core have received considerable attention of synthetic chemists and medicinal chemists because of their intricate structures and potent biological activities.² Yuremamine, a new member of pyrroloindole alkaloids, was isolated from the stem bark of *Mimosa hostiles* in 2005 by Callaway and co-workers and shown to have hallucinogenic and psychoactive effects.³ The originally assigned structure of yuremamine (**1**) features a densely decorated pyrrolo[1,2-*a*]indole core, three contiguous stereogenic centers and the polyphenolic rings. Since its isolation, several synthetic strategies toward the core structure have been developed by Kerr, Shi, Dethe, Chen, France and You.⁴ While these approaches are significant and have led to the successful construction of the pyrroloindole core, none of them could allow for the complete incorporation of all substituents/functionality in a single step that are positioned for the eventual chemical synthesis of **1**. Very recently, Sperry and co-workers reported a concise biomimetic total synthesis of yuremamine, leading to its structural revision from the pyrroloindole (**1**) to the flavonoidal indole (**2**), which was initially hypothesized as a biosynthetic intermediate (Scheme 1).⁵

Scheme 1. Synthetic strategy toward the originally assigned structure of yuremamine



Our synthetic strategy was inspired by the intricate molecular architecture of **1** without realizing that the structure of the natural product was mis-assigned when we started our study. Our approach to **1** is depicted in Scheme 1. We conceived that this pyrroloindole alkaloid (**1**) could be derived from pyrrolo[1,2-*a*]indole **A** involving functional group transformations and structural isomerization. The densely decorated pyrrolo[1,2-*a*]indole **A** could in turn be produced by the direct [3+2] annulation between a tryptamine derivative and the corresponding multi-substituted α , β -unsaturated ketone. One appealing feature of the synthetic design is that the pyrrolo[1,2-*a*]indole core (**A**), which bears useful substituents/functionality required by the structure of **1**, could be efficiently assembled from readily available starting materials in a single step operation.

While the reactions between indoles and α , β -unsaturated carbonyls to furnish the alkylated products at N1 or C2 or C3 via conjugate addition have been widely investigated,⁶ the annulation process to form a new ring is rare.⁷ Particularly, the related reactions of tryptamine derivatives with α , β -unsaturated ketone

^a Department of Pharmacology and Pharmaceutical Sciences, School of Medicine, Tsinghua University, Beijing, 100084 China.

Email: zuliansuo@biomed.tsinghua.edu.cn

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

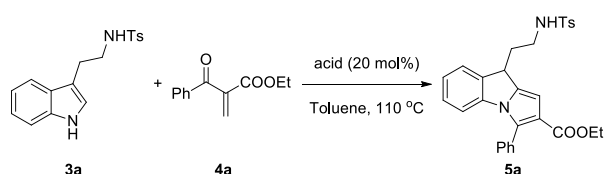
COMMUNICATION

Journal Name

as depicted in our synthetic design (Scheme 1), have been well studied for the preparation of fused indolines in the presence of organocatalysts and organometallic reagents.⁸ We envisioned that under suitable dehydrative conditions at elevated temperature, the thermodynamically more stable pyrrolo[1,2-*a*]indoles (**A**) could be formed, and thus the frame work of **1** could be assembled in a highly efficient manner.

A model reaction between **3a** and **4a** was carried out first to identify the optimized reaction conditions (Table 1). Gratifyingly, a variety of acids, both bronsted acids and Lewis acids, could be utilized to catalyze the transformation, producing **5a** with moderate to good yields. The best result (87% yield) was obtained using 20 mol% *p*-TsOH.H₂O as the catalyst and toluene as the reaction media. As expected, high reaction temperature was essential for the formation of **5a**, indicating that the pyrrolo[1,2-*a*]indole should be the thermodynamically more stable product.

Table 1. Optimization of reaction conditions^a

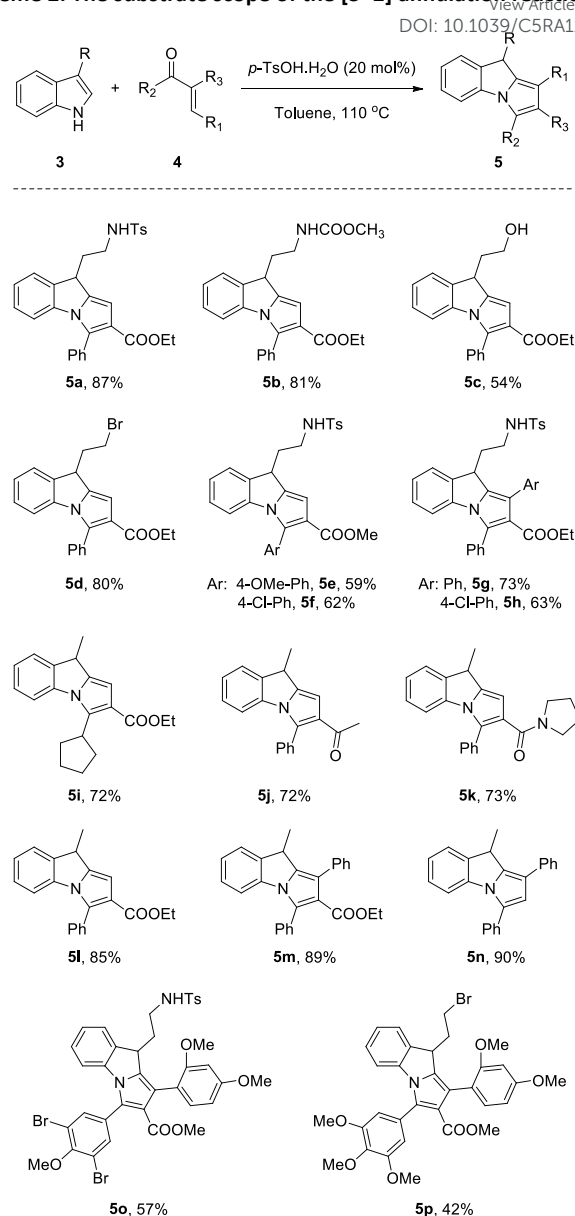


entry	acid	yield of 3a (%) ^b
1	none	0
2	Benzoic acid	47
3	AcOH	38
4	TFA	50
5	<i>p</i> -TsOH.H ₂ O	87
6	FeCl ₃	57
7	ZnCl ₂	50

^a Reaction conditions: To a solution of **3a** (62.8 mg, 0.2 mmol) and **4a** (49.0 mg, 0.24 mmol) in toluene was added the specified acid. The resulting mixture was heated to 110 °C for 2 h. ^b Isolated yield after silica gel chromatography.

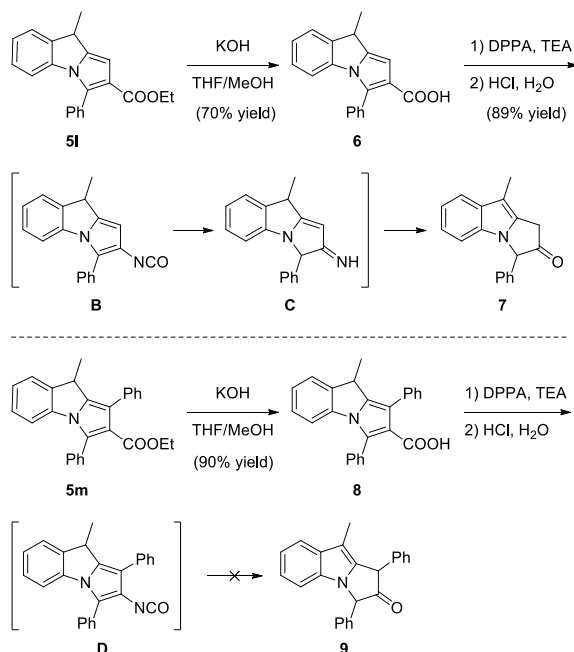
The substrate scope of the [3+2] annulations was next investigated (Scheme 2). Under optimized reaction conditions, a variety of 3-substituted indoles and α, β-unsaturated ketones proved to be suitable substrates, delivering the pyrrolo[1,2-*a*]indoles with good to excellent yields. Indoles with different tethered nucleophiles at 3-position as well as an alkyl bromide side chain were well tolerated, furnishing the desired products with different functionalized side chains (**5a-h**). A series of α, β-unsaturated ketones with different substitution patterns turned out to be efficient substrates, generating the pyrrolo[1,2-*a*]indoles bearing useful functionality. The electron withdrawing group R₃ could be varied (**5j**, **5k**), but is not required for the reaction to occur (**5n**). When R₂ is aliphatic, the annulation reaction also proceeded with high efficiency (**5i**). It should be noted that a variety of functional groups (protected amine, alcohol, alkyl bromide, ketone, ester, and amide) were compatible with the reaction conditions. Finally, two complex pyrrolo[1,2-*a*]indoles (**5o**, **5p**) that contain the substituents/functionality for the chemical synthesis of **1** were successfully constructed.

Scheme 2. The substrate scope of the [3+2] annulation reactions

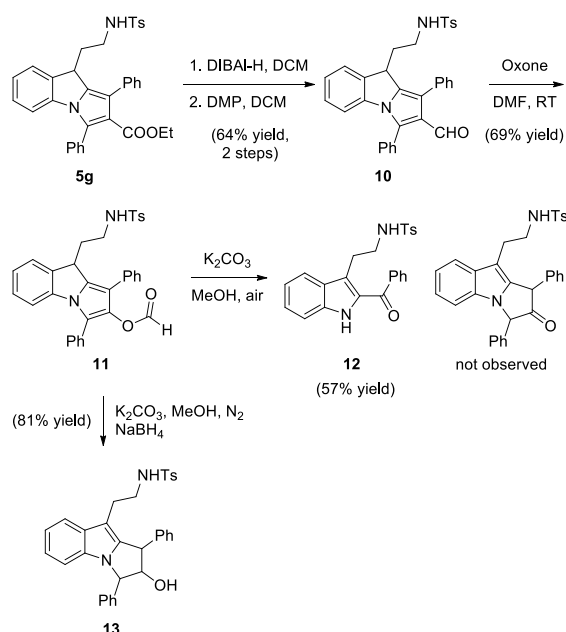


Next, we turned our attention to the construction of the core of **1**. Our first model reaction involved the Curtius rearrangement of the related carboxylic acid **6** with the hypothesis that the in situ generated isocyanate **B** could be hydrolyzed and isomerized to deliver ketone **7** (Scheme 3). The saponification of **5l** underwent well using potassium hydroxide, affording **6** with good yield. The Curtius rearrangement initiated cascade sequence presumably involving **B** and **C** as the intermediates proceeded smoothly, producing ketone **7** in 89% yield. Unfortunately, when the similar synthetic sequence was applied to a more advanced substrate **8**, the formation of ketone **9** was not observed. Under certain forcing reaction conditions, the generated isocyanate intermediate **D** was trapped by the nearby phenyl ring via Friedel-Crafts acylation reaction. Considering that the **1** contains more nucleophilic polyphenolic rings, which would attack the isocyanate intermediate more readily, we turned to an alternative approach as depicted in Scheme 4.

Scheme 3. Model reactions via Curtius rearrangement



Scheme 4. Model reactions via Baeyer-Villiger oxidation



The second model reaction for the synthesis of the core of **1** centered on the Baeyer-Villiger oxidation of aldehyde **10** and related structural isomerization (Scheme 4). Compound **10** was produced in good yield by a two step synthetic manipulation from **5g** involving DIBAL-H reduction of the ester followed by Dess-Martin oxidation of the resulted alcohol. The Baeyer-Villiger oxidation of **10** proceeded well in the presence of oxone, delivering **11** in 69% yield. Under basic conditions, the deprotection and structural isomerization of **11** did not occur to afford the desired ketone, but instead 2, 3-disubstituted indole **12** was isolated as the major product, presumably because that the electron rich system was further oxidized by molecular oxygen. A solution to this problem

was realized by carrying out the reaction under N₂ and adding sodium boron hydride to the reaction to reduce the in situ generated ketone. By doing this, alcohol **13** was generated in good yields as a mixture of three diastereomeric isomers. Although the diastereoselectivity of the reduction need to be further improved, the structure of **13** contains the side chain and correct substitution pattern, which resembles the key structural features of the originally assigned structure of yuremamine (**1**).

Conclusions

In conclusion, we have developed a direct annulation reaction between indoles and α , β -unsaturated ketones, which allows for the rapid assembly of densely substituted, highly functionalized pyrrolo[1,2-*a*]indoles in a single step. Model reactions toward the originally assigned structure of yuremamine were carried out leading to the successful construction of the core with required functionality and the discovery of several interesting synthetic transformations.

Notes and references

- For selected 9H-pyrrolo[1,2-*a*]indoles synthesis: (a) A. Padwa, J. R. Gasdaska, *J. Am. Chem. Soc.* 1986, **108**, 1104; (b) S. Hwang, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* 2008, **130**, 16158; (c) S. J. Mahoney, E. Fillion, *Chem. Eur. J.* 2012, **18**, 68; (d) L. Hao, Y. Pan, T. Wang, M. Lin, L. Chen, Z. Zhan, *Adv. Synth. Catal.* 2010, **352**, 3215; (e) H. Liu, M. El-Salfiti, M. Lautens, *Angew. Chem. Int. Ed.* 2012, **51**, 9846; (f) H. Ren, P. Knochel, *Angew. Chem. Int. Ed.* 2006, **45**, 3462; (g) K. S. Feldman, M. R. Iyer, D. K. Hester, II, *Org. Lett.* 2006, **8**, 3113; (h) X. Huang, S. Zhu, R. Shen, *Adv. Synth. Catal.* 2009, **351**, 3118.
- For selected references about mitomycins and mitosenes: (a) H. Namiki, S. Chamberland, D. A. Gubler, R. M. Williams, *Org. Lett.* 2007, **9**, 5341; (b) A. L. Williams, J. M. Srinivasan, J. M. Johnston, *Org. Lett.* 2006, **8**, 6047; (c) R. S. Coleman, F.-X. Felpin, W. Chen, *J. Org. Chem.* 2004, **69**, 7309; (d) S. J. Danishefsky, J. M. Schkeryantz, *Synlett* 1995, 475; (e) T. Fukuyama, L. Yank, *J. Am. Chem. Soc.* 1989, **111**, 8303; (f) T. Fukuyama, F. Nakatsubo, A. J. Cocuzza, Y. Kishi, *Tetrahedron Lett.* 1977, 4295; (g) Z. Zheng, M. Touve, J. Barnes, N. Reich, L. Zhang, *Angew. Chem. Int. Ed.* 2014, **53**, 9302; (h) G. R., Jr. Allen, M. J. Weiss, *J. Org. Chem.* 1965, **30**, 2904; (i) J. C. Hodges, W. A. Remers, W. T. Bradner, *J. Med. Chem.* 1981, **24**, 1184; (j) R. M. Coates, P. A. MacManus, *J. Org. Chem.* 1982, **47**, 4822; (k) J. R. Luly, H. J. Rapoport, *Org. Chem.* 1984, **49**, 1671.
- J. J. Vepsäläinen, S. Auriola, M. Tukiainen, N. Ropponen, J. Callaway, *Planta Med.* 2005, **71**, 1053.
- (a) M. B. Johansen, M. A. Kerr, *Org. Lett.* 2008, **10**, 3497; (b) D. V. Patil, M. A. Cavitt, S. France, *Org. Lett.* 2011, **13**, 5820; (c) K. Chen, Z. Zhang, Y. Wei, M. Shi, *Chem. Commun.* 2012, **48**, 7696; (d) H.-L. Cui, X. Feng, J. Peng, J. Lei, K. Jiang, Y.-C. Chen, *Angew. Chem., Int. Ed.* 2009, **48**, 5737; (e) W. B. Liu, X. Zhang, L. X. Dai, S. L. You, *Angew. Chem. Int. Ed.* 2012, **51**, 5183; (f) D. H. Dethe, R. Boda, S. Das, *Chem. Commun.* 2013, **49**, 3260.
- M. B. Calvert, J. Sperry, *Chem. Commun.* 2015, **51**, 6202.
- (a) J. A. Joule, K. Mills, *Heterocyclic Chemistry*; 5th ed.; Blackwell: Oxford, 2009. (b) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, 2003.

COMMUNICATION

Journal Name

- 7 For indoline synthesis by direct annulation: Q. Cai, S. L. You, *Org. Lett.* 2012, **14**, 3040; For pyrroloindole synthesis by direct annulation employing rather specialized substrates: K. Wood, D. S. Black, N. Kumar, *Tetrahedron Lett.* 2009, **50**, 574.
- 8 (a) J. F. Austin, S. G. Kim, C. J. Sinz, W. J. Xiao, D. W. C. MacMillan, *Proc. Nat. Acad. Sci. USA*, 2004, **101**, 5482; (b) Z. Zhang, J. C. Antilla, *Angew. Chem. Int. Ed.* 2012, **51**, 11778; (c) Q. Cai, C. Liu, X. W. Liang, S. L. You, *Org. Lett.* 2012, **14**, 4588; (d) C. Liu, W. Zhang, L. X. Dai, S. L. You, *Org. Biomol. Chem.* 2012, **10**, 7177.

View Article Online
DOI: 10.1039/C5RA11904A

RSC Advances Accepted Manuscript