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COMMUNICATION

Flexible synthesis of montanine-like alkaloids: revisiting the structure of montabuphine†

Yifu Guan, Hongbin Zhang,* Chengxue Pan, Jia Wang, Rong Huang and Qilin Li

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An efficient and stereocontrolled synthetic strategy towards the synthesis of montanine-like alkaloids was developed. Our results suggest that the structure elucidation for natural montabuphine needs further elaboration.

In the *Amaryllidaceae* alkaloids, there is a small family of natural products, namely the montanine-type alkaloids, bearing a unique pentacyclic 5,11-methanomorphanthridine skeleton (Fig. 1).[1] These alkaloids encompass anxiolytic, anti-depressive, anti-convulsive and weak hypotensive activities.[2] The unique structural features and important biological activities associated with these alkaloids have attracted considerable synthetic efforts.[3] Recently, Banwell reported an elegant strategy towards the synthesis of montanine-type alkaloids.[4a] Although they successfully synthesized the assigned structure for montabuphine[4b] (**5**, Fig. 1), unfortunately the physical and spectral data of this compound do not match those recorded for the natural product. Their result established that the structure of montabuphine needs to be revised.[5] Based on Banwell's work, we deduced that the two structures, with a *trans* spatial arrangement for the C4a-H and the aromatic ring, as highlighted in Fig. 1 (**6** and **7**) might be the alternative possibility for montabuphine. Although most of the montanine-type alkaloids have been synthesized, few efforts have been directed towards the synthesis of montanine-like diastereoisomers with a C4a-H orientated *trans* to the aromatic ring. Herein, we report the stereocontrolled synthesis of these structures (**6** and **7**).

Our flexible approach towards the synthesis of the 5,11-methanomorphanthridine alkaloids is outlined in Scheme 1. Developing a regioselective and stereocontrolled palladium-catalyzed cross coupling of vinyl epoxides (**11** and **12**) with organoboronic acid **13** is the key issue[6] for the synthesis of montabuphine structure (**6** or **7**) proposed in Fig. 1.

Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming, Yunnan 650091, P. R. China. E-mail: zhanghb@ynu.edu.cn, zhang_hongbin@hotmail.com

†Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR spectra of new products and experimental details. CCDC 867573 (**11**), 867574 (**12**), 867575 (**14b**), 871431 (**14c**) and 867576 (**15b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc11949d

Our research was initiated with preparation of tosylamide **10**. Treatment of 2-(4-hydroxyphenyl)ethylamine (**8**, Scheme 2) with *p*-toluenesulfonyl chloride afforded **8a**, which, after oxidative dearomatization with iodobenzene diacetate (IBD)[7] and subsequent aza Michael addition,[8] afforded compound **9a** in 48% yield in 3 steps. Dehydration of **9a** with phosphorus oxychloride in pyridine provided enone **10** in 69% yield.

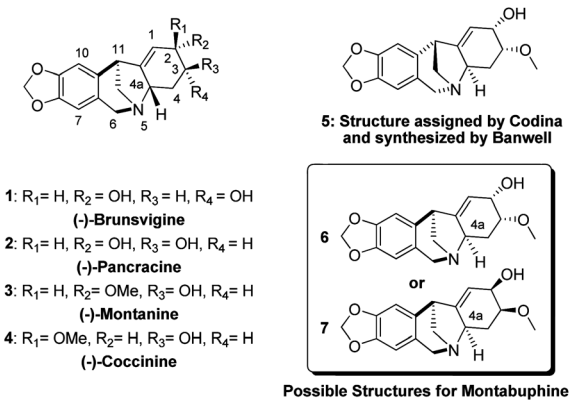
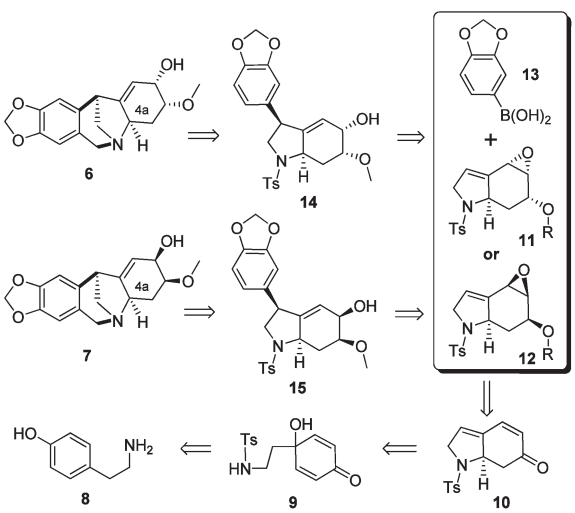
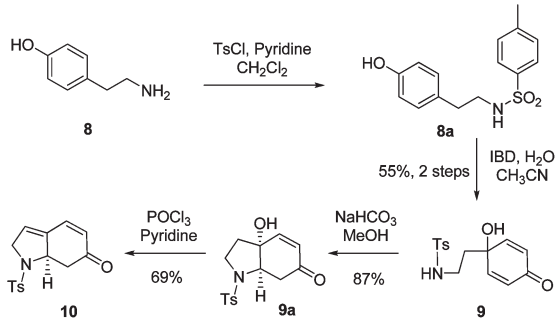


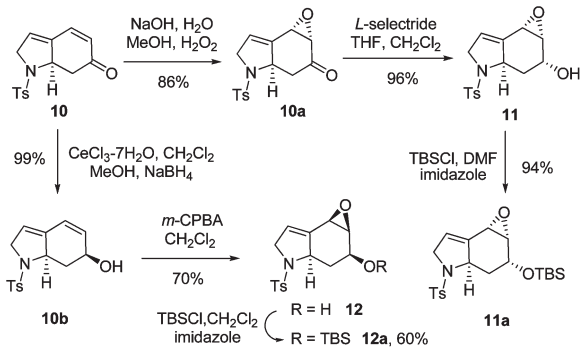
Fig. 1 Speculation for the structure of montabuphine.



Scheme 1 Retrosynthetic analysis of compound **6** and **7**.



Scheme 2 Synthesis of enone **10**.

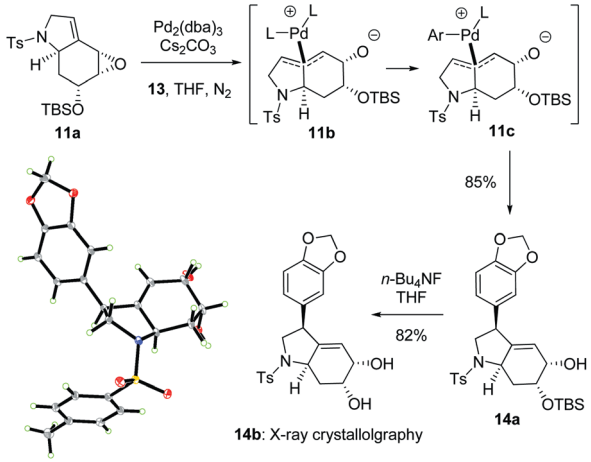


Scheme 3 Stereoselective synthesis of epoxides **11** and **12**.

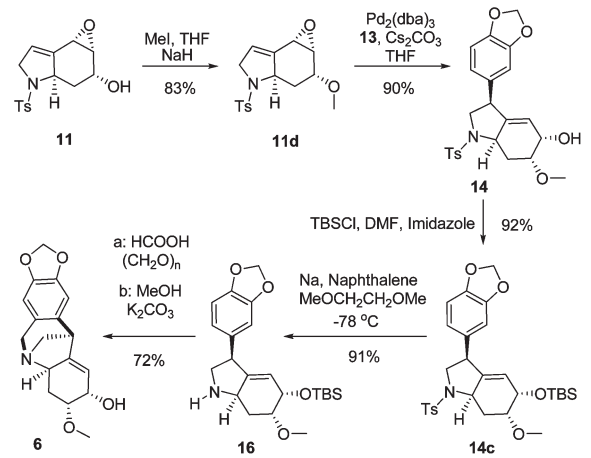
Having obtained enone **10**, we next set our goal as the stereocontrolled synthesis of epoxides **11** and **12** (Scheme 3). Treatment of compound **10** with hydrogen peroxide in methanol resulted in ketone **10a** stereoselectively. After reduction with L-selectride, epoxide **11** was isolated in 96% yield. Protection with *tert*-butyl dimethyl silyl chloride (TBSCl) afforded compound **11a** in 94% yield. Reduction of enone **10** under Luche condition followed by epoxidation of the resulting alcohol (**10b**) with *m*-chloroperbenzoic acid afforded epoxide **12** in 70% yield in two steps. The relative configurations for epoxides **11** and **12** were established by NMR and also confirmed by X-ray crystallography.[9]

Next we came to the key cross-coupling reaction of vinyl epoxide **11a** with organoboronic acid **13**. Utilization of Szabó's reaction condition, [$Pd_2(dba)_3$] as catalyst in THF–H_2O (10 : 1) in the presence of Cs_2CO_3, unfortunately gave only small amount (<3%) of desired coupling product.[6] After some experimentation, the optimal condition was found, treatment of compound **11a**, catalyst [$Pd_2(dba)_3$] and organoboronic acid **13** in the presence of Cs_2CO_3 in anhydrous THF at room temperature afforded the desired product **14a** in 85% yield. This reaction was presumed to form initially an (η3-allyl)-palladium(II) complex by opening of the epoxide ring.[6] After transmetalation of organoboronic acid, (Scheme 4, **11b** to **11c**) the aromatic group was added regioselectively and stereoselectively to the pyrrolidine ring. The relative stereochemistry was unambiguously established by X-ray crystallographic analysis of compound **14b**.

O-Methylation of epoxide **11** with methyl iodide in the presence of sodium hydride afforded ether **11d** (83%). The palladium(0) complex catalyzed cross coupling of epoxide **11d** with



Scheme 4 Stereoselective synthesis of the key intermediate.

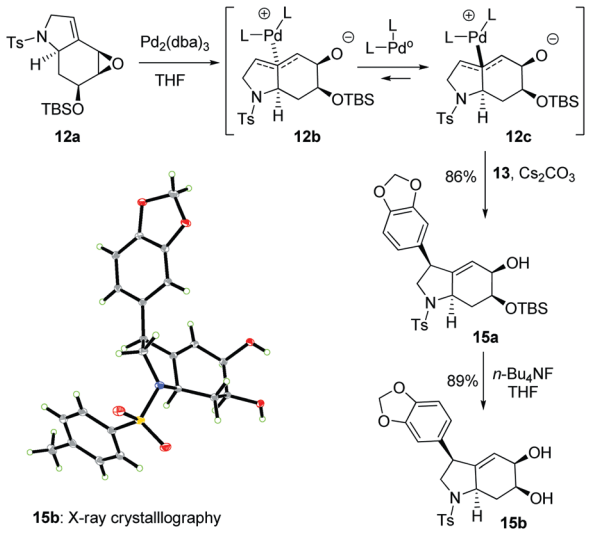


Scheme 5 Synthesis of the deduced structure, compound **6**.

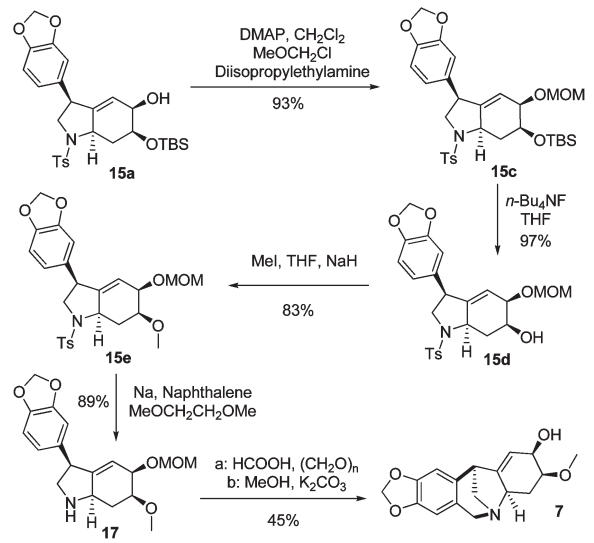
organoboronic acid **13** gave the key intermediate (**14**) in 90% yield. Protection of **14** with TBSCl afforded **14c** and the relative stereochemistry of **14c** was confirmed by X-ray crystallographic analysis. After detosylation of **14c** with sodium naphthalide,[3j] amine **16** was obtained in 83% yield in two steps (Scheme 5). Finally, treatment of amine **16** with formaldehyde in the presence of formic acid[4a] resulted in the desired product (**6**) in 72% yield.

To our disappointment, the spectroscopic data of compound **6** did not match these reported in the literature[4b] (see Table 1 in the ESI†). We next carried out the synthesis of structure **7**. To our delight, the palladium catalyzed reaction of vinyl epoxide **12a** with organoboronic acid **13** yielded the desired diastereoisomer (**15a**) as the sole product (Scheme 5, relative stereochemistry confirmed by X-ray crystallography).

This result could be explained by the mechanism of nucleophilic palladium(0) displacement of the (π-allyl)-palladium intermediate (**12b** to **12c** in Scheme 6) proposed by Bäckvall and Granberg.[10] Next, compound **15a** was converted to its methyl ether (**15e**) in three steps (45% overall yield) by manipulation of the C2 and C3 hydroxyl protecting groups. Detosylation of compound **15e** with sodium in naphthalene afforded amine **17** in 89% yield. Finally, utilization of Banwell's procedure furnished



Scheme 6 Synthesis of intermediate **15a**.



Scheme 7 Synthesis of the deduced structure, compound **7**.

the compound **7** in 45% yield. In comparison with data recorded in the literature,[4b] the ^{1}H and ^{13}C NMR spectra of compound **7** were unfortunately found to be different from that reported for montabuphine (Scheme 7).

In conclusion, we have developed an efficient and flexible strategy for the synthesis of montanine-like compounds. Although our results did not establish the true structure for montabuphine, this new approach, features a stereocontrolled palladium-catalyzed cross coupling of vinyl epoxides with organoboronic acids, provided a versatile route towards the synthesis of medicinally interesting montanine-type diastereoisomers. We are currently working on the issue of relative configuration for C2 and C3 in the hope that a true structure could be assigned to natural montabuphine in the near future.

Acknowledgements

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Notes and references

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5 There is an uncertainty about the C4a stereochemistry. In the original structure elucidation paper, Codina did not define the stereochemistry at C4a. Banwell synthesized the structure with the C4a hydrogen orientated *cis* to the aromatic ring. While in Pandey's paper, they draw the structure of montabuphine with the C4a hydrogen orientated *trans* to the aromatic moiety; see ref. 3*q*.

6 Recently Szabó published the first carbon–carbon cross coupling of vinyl epoxides with organoboronic acids catalyzed by palladium pincer complex. Only one example involving cyclic vinyl epoxide was reported, however with poor regioselectivity (2 : 1). See: J. Kjellgren, J. Aydin, O. A. Wallner, I. V. Saltanova and K. J. Szabó, *Chem.–Eur. J.*, 2005, **11**, 5260 and references cited therein.

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8 Recently, You's group reported an asymmetric synthesis of intermediate **9a**, see: Q. Gu and S.-L. You, *Chem. Sci.*, 2011, **2**, 1519.

9 CCDC 867573 (for **11**), CCDC 867574 (for **12**), CCDC 867575 (for **14b**), CCDC 871431 (for **14c**) and CCDC 867576 (for **15b**) contain the supplementary crystallographic data for this paper.

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