Organic LETTERS

Letter

pubs.acs.org/OrgLett

# Short and Scalable Total Synthesis of Myrioneuron Alkaloids (±)-α,β-Myrifabral A and B

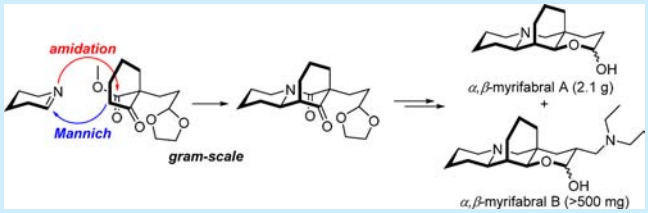
Dengpeng Song,[†] Zhengshen Wang,[†] Ruoming Mei,[†] Weiwei Zhang,[†] Donghui Ma,[†] Dengyu Xu,[†] Xingang Xie,[†] and Xuegong She*[,†,‡]

[†]State Key Laboratory of Applied Organic Chemistry, Department of Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China

[‡]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, People's Republic of China

Supporting Information

**ABSTRACT:** The first total synthesis of the *Myrioneuron* alkaloids (±)-α,β-myrifabral A and B has been accomplished in only four steps from conveniently available starting materials. This short synthesis relied on the use of a key tandem Mannich/amidation reaction to rapidly construct the core framework and two carbon stereocenters. The synthetic route allows for large scale preparation of these promising natural products against the hepatitis C virus (HCV).




The *Myrioneuron* alkaloids (Figure 1) are a small but growing group of plant metabolites that have a common

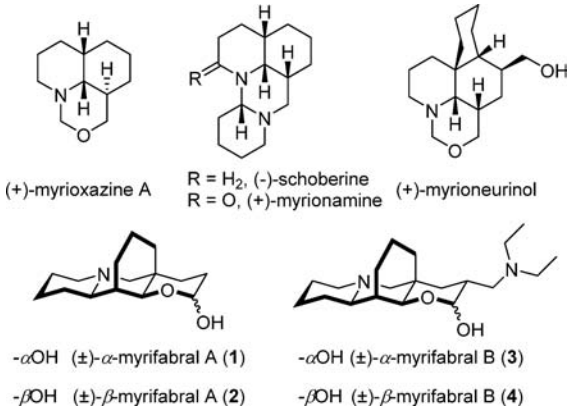



**Figure 1.** Representative *Myrioneuron* alkaloids.

biosynthesis originating from lysine.[1] Structurally, these alkaloids share a *cis*-decahydroquinoline system that often incorporates 1,3-oxazine and/or 1,3-diazine rings. In 2014, two clusters including four new *Myrioneuron* alkaloids (±)-α,β-myrifabral A (**1** and **2**) and B (**3** and **4**) were isolated by Hao and co-workers from *Myrioneuron faberi*, which is a unique plant mainly distributed in China.[2] Unlike all previously known *Myrioneuron* alkaloids, the four new members possess a novel cyclohexane-fused octahydroquinolizine skeleton together with a six-membered cyclic hemiacetal. Additionally, these natural compounds contain four continuous chiral centers including a quaternary stereocenter embedded in the bridgehead. Preliminary bioactivity test indicated that, even obtained as racemic mixtures, both clusters and some derivatives presented promising anti-HCV activity ($IC_{50}$ 0.9 to 4.7 μM) with cytotoxicity lower than that of telaprevir, a commercial pharmaceutical drug for the treatment of hepatitis C. In consideration of their appealing architecture and significant bioactive potential as lead compounds for the discovery of new drugs, it is necessary to develop a short and scalable synthetic route to (±)-α,β-myrifabral A and B for a further and detailed structure−activity relationship (SAR) study. However, relatively little study on the synthesis of the *Myrioneuron* alkaloids has been accomplished at the present.[3] Herein, we describe a tandem Mannich/amidation reaction to efficiently establish all of the carbons and molecule framework, and a concise total synthesis of the targeted alkaloids in only four steps from known iodide **9**.

Our retrosynthetic analysis is shown in Scheme 1. α,β-Myrifabral B could be derived from α,β-myrifabral A, which was assumed to be constructed from tricyclic intermediate **5** via several simple chemical transformations (reduction, deacetalization, and hemiacetalization). Considering the biosynthesis of these alkaloids from lysine, we reasoned that pivotal tricyclic intermediate **5** could be obtained through a tandem Mannich/amidation sequence from lysine derivative **6** and compound **7**, which was readily accessible from commercial available compound **8** and known iodide **9** (Scheme 1).

As shown in Scheme 2, our synthesis commenced with the known iodide **9**, which was easily prepared in one step from acrolein using Gil's conditions.[4] Then it was coupled with commercial compound **8** to provide the required alkylative product **7**.[5] The other required segment imine **6** was also readily prepared from piperidine.[6]

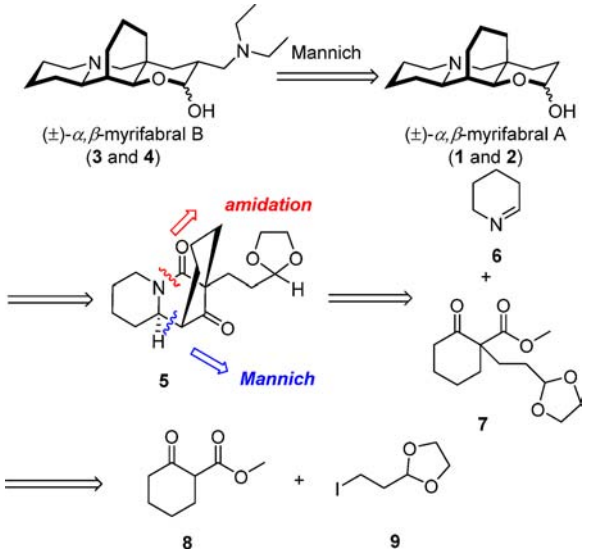
**Received:** January 2, 2016
**Published:** February 5, 2016



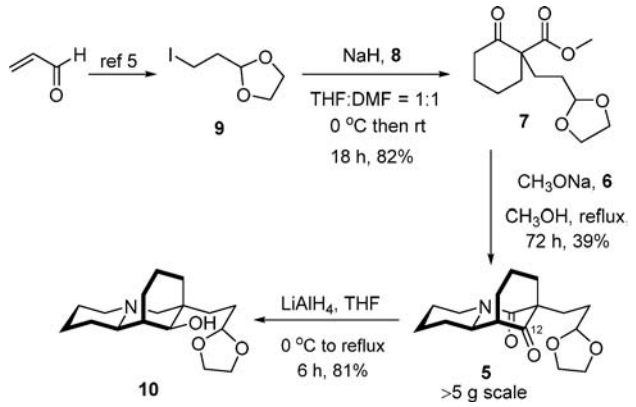


DOI: 10.1021/acs.orglett.6b00005
*Org. Lett.* 2016, 18, 669−671

**Scheme 1. Retrosynthetic Analysis for (±)-α,β-Myrifabral A and B**



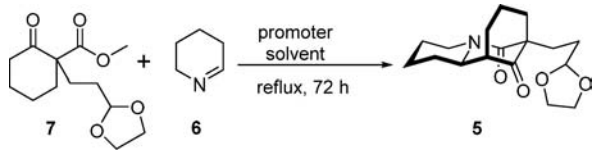

**Scheme 2. Preparation of Key Intermediate 10**




With segments **6** and **7** in hand, we subsequently investigated the feasibility of the key tandem Mannich/amidation reaction. As shown in Table 1, under organocatalyst or weak acid−base pairs condition only provided a few unidentified compounds (Table 1, entries 1−2). Brønsted acid was also ineffective with only starting material recovered (Table 1, entry 6). To our delight, the desired tricyclic **5** was obtained with 46% yield in the presence of MeONa in MeOH under reflux for 72 h (Table 1, entry 3). Moreover, more hindered base and alcohols proved to be invalid (Table 1, entries 4, 5, and 7). It is worth mentioning that this procedure could be carried out on a large scale (up to 5 g of **5** prepared per batch) with slightly reduced yield (Table 1, entry 8) from relatively inexpensive staring materials and the requisite piperidine ring together with two new stereogenic centers were efficiently assembled in this one-step operation.

After establishing the core framework of the targeted alkaloids, we then attempted to reduce the two carbonyl groups simultaneously. The carbonyl group at C12 of **5** was anticipated to be stereoselectively reduced due to the steric hindrance of the cyclohexane ring. As expected, we were pleased to discover that reduction of **5** with $LiAlH_4$ delivered a 6.75:1 mixture of two diastereomers and that the major product **10** could be reliably isolated in 81% yield.

**Table 1. Reaction Condition Survey for Tandem Mannich/Amidation Reaction[a]**

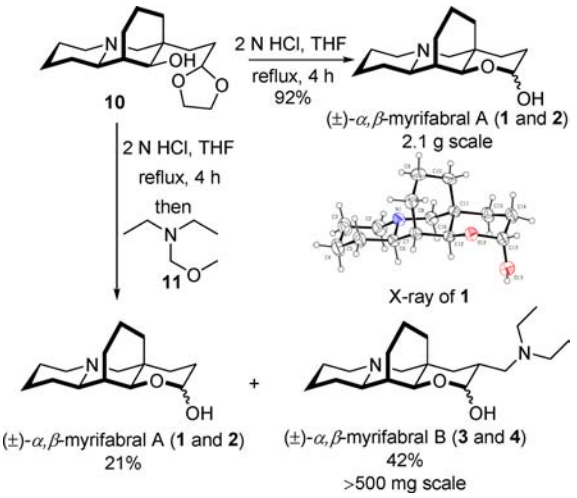



| entry | promoter | solvent | yield (%)[c] |
|---|---|---|---|
| 1 | proline | $CH_3CN$ | n.d. |
| 2 | LiCl/DBU | DMF[b] | n.d. |
| 3 | MeONa | MeOH | 46 |
| 4 | MeONa | EtOH | 17 |
| 5 | MeONa | *i*-PrOH | trace |
| 6 | *p*-TSA | MeOH | n.d. |
| 7 | *t*-BuOK | *t*-BuOH | n.d. |
| 8 | MeONa | MeOH | 39[d] |

[a]Unless otherwise specified, the reaction was carried out with **7** (1.0 mmol) and **6** (1.5 mmol) in the presence of promoter (2.0 mmol) and solvent (2.0 mL) under reflux for 72 h. [b]Reaction temperature is 100 °C. [c]Isolated yields. [d]Run on gram scale.

The completion of the total synthesis of (±)-α,β-myrifabral A and B is depicted in Scheme 3. Deprotection of **10** with 2 N

**Scheme 3. Synthesis of (±)-α,β-Myrifabral A and B**




HCl followed by spontaneous hemiacetalization smoothly delivered (±)-α,β-myrifabral A as a cluster in 92% overall yield, the synthesis was carried out on a multigram scale to provide 2.1 g of cluster A. Interestingly, (±)-α-myrifabral A (**1**) could be recrystallized from EtOAc solution of cluster A, and its X-ray diffraction experiment was confirmed against the structure information on (±)-α-myrifabral A (**1**) reported by Hao and co-workers.

At last stage, transformation of (±)-α,β-myrifabral A to (±)-α,β-myrifabral B was investigated, formaldehyde and diethylamine were added to the reaction mixture, but the expected mannich reaction did not occurr under various conditions such as numerous solvents (THF, MeOH, *i*-PrOH, and $H_2O$) and different acids (HCl, $H_2SO_4$, and $H_3PO_4$). We postulated that the failure was attributed to the difficulty of forming the requisite imine for the next Mannich reaction. To overcome this obstacle, a labile aza-acetal **11**[7] was used to in situ generate the required imine intermediate. Gratifyingly,



DOI: 10.1021/acs.orglett.6b00005
*Org. Lett.* 2016, 18, 669−671

treatment of **10** with 2 N HCl in THF under reflux for 4 h followed by slow addition of **11**, we successfully obtained (±)-α,β-myrifabral B and (±)-α,β-myrifabral A with 42% (>500 mg scale) and 21% yield in one pot, respectively. The spectroscopic data ($^1$H and $^{13}$C NMR spectra and HRMS) of synthetic clusters A and B were in good agreement with those of the natural products.

In summary, we have accomplished the first total synthesis of the anti-HCV natural products (±)-α,β-myrifabral A and B in only four steps from conveniently available iodide **9**. The demonstrated short approach features a tandem Mannich/amidation reaction for the construction of the core framework, and a one pot deacetalization/Mannich reaction for the synthesis of cluster B. In addition, our strategy should allow asymmetric synthesis of these natural products, via an enantioselective Michael conjugate addition of **8** followed by selective protection of the aldehyde group according to the previously described method.[8] Notably, our route enables the synthesis of significant quantities and should be helpful for further SAR studies on natural *Myrioneuron* alkaloids and analogues.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00005.

X-ray data for compound **1** (CIF)

Detailed experimental procedures and full spectroscopic data for all new compounds (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: shexg@lzu.edu.cn. Fax: +86-931-8912582.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation of China (21125207, 21372103, 21472079, and 21572088), SRFDP (20130211110018), and IRT_15R28.

## ■ REFERENCES


(1) (a) Gravel, E.; Poupon, E. *Nat. Prod. Rep.* **2010**, *27*, 32. (b) Poupon, E.; Gravel, E. *Chem. - Eur. J.* **2015**, *21*, 10604.

(2) Cao, M.-M.; Zhang, Y.; Li, X.-H.; Peng, Z.-G.; Jiang, J.-D.; Gu, Y.-C.; Di, Y.-T.; Li, X.-N.; Chen, D.-Z.; Xia, C.-F.; He, H.-P.; Li, S.-L.; Hao, X.-J. *J. Org. Chem.* **2014**, *79*, 7945.

(3) (a) Pham, V. C.; Jossang, A.; Chiaroni, A.; Sévenet, T.; Bodo, B. *Tetrahedron Lett.* **2002**, *43*, 7565. (b) Pham, V. C.; Jossang, A.; Chiaroni, A.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *Org. Lett.* **2007**, *9*, 3531. (c) Pham, V. C.; Jossang, A.; Grellier, P.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *J. Org. Chem.* **2008**, *73*, 7565. (d) Burrell, A. J. M.; Coldham, I.; Oram, N. *Org. Lett.* **2009**, *11*, 1515. (e) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2009**, *74*, 2290. (f) Nocket, A. J.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 14162. (g) Nocket, A. J.; Feng, Y.; Weinreb, S. M. *J. Org. Chem.* **2015**, *80*, 1116.

(4) Gil, G. *Tetrahedron Lett.* **1984**, *25*, 3805.

(5) Ito, H.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 4380.

(6) (a) Rouchaud, A.; Braekman, J.-C. *Eur. J. Org. Chem.* **2009**, *2009*, 2666. (b) Darwich, C.; Elkhatib, M.; Steinhauser, G.; Delalu, H. *Helv. Chim. Acta* **2009**, *92*, 98. (c) Monaco, M. R.; Renzi, P.; Scarpino Schietroma, D. M.; Bella, M. *Org. Lett.* **2011**, *13*, 4546.

(7) (a) Stewart, T. D.; Aston, J. G. *J. Am. Chem. Soc.* **1926**, *48*, 1642. (b) Sakai, N.; Shimamura, K.; Ikeda, R.; Konakahara, T. *J. Org. Chem.* **2010**, *75*, 3923.

(8) (a) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796. (b) Wu, F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4301. (c) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628. (d) Quintard, A.; Constantieux, T.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12883.




DOI: 10.1021/acs.orglett.6b00005
*Org. Lett.* 2016, 18, 669–671