Note

A Concise Synthesis of Monoterpene Pyridine Alkaloid Aucubinine B†

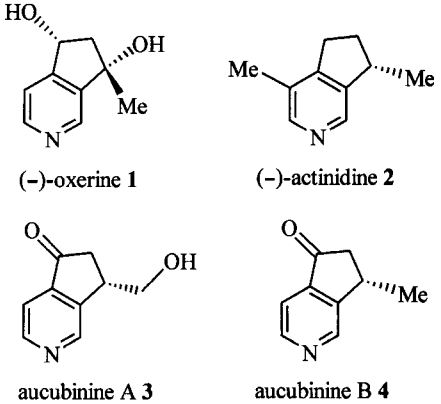
YANG, Xiao-Xia[a](杨晓霞) ZHAO, Jing-Rui[a,b](赵景瑞) JIA, Xue-Shun[b](贾学顺)
YANG, Li-Wei[a,c](杨力维) ZHAI, Hong-Bin*[,a](翟宏斌)
[a] *Laboratory of Modern Synthetic Organic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*
[b] *Department of Chemistry, Shanghai University, Shanghai 200436, China*
[c] *College of Life Sciences, Shanghai University, Shanghai 200436, China*

Aucubinine B (4), a monoterpene alkaloid obtained from the metabolites of aucubin in the presence of human intestinal bacteria, has been synthesized from 3-bromo-4-pyridinecarboxaldehyde (5) in four steps with 39% overall yield. The construction of the cyclopenta[*c*]pyridine intermediate (7) was realized by an intramolecular Heck reaction.

Keywords aucubinine B, monoterpene alkaloid, intramolecular Heck reaction

A number of monoterpene alkaloids possessing the cyclopenta[*c*]pyridine ring system has been proved to be biologically significant, as exemplified by (−)-oxerine[1] (**1**) and (−)-actinidine[2] (**2**) (Chart 1). (*R*)-Aucubinine A (**3**) and (−)-aucubinine B (**4**), representing another two pyridine alkaloids containing this framework, were first obtained from the metabolites of aucubin in the presence of human intestinal bacteria.[3] Aucubinine B can also be obtained by either metabolic or chemical conversion of harpagide, harpagoside and 8-*O*-*p*-coumaroylharpagide.[4] The unique structural characteristics and significant biological activities of cyclopenta[*c*]pyridine alkaloid family of natural products have stimulated considerable interest for their syntheses.[1,2] Herein we wish to disclose our total synthesis of (±)-aucubinine B via cyclopenta[*c*]pyridine intermediate (**7**) formed by an intramolecular Heck reaction (Scheme 1).

Chart 1



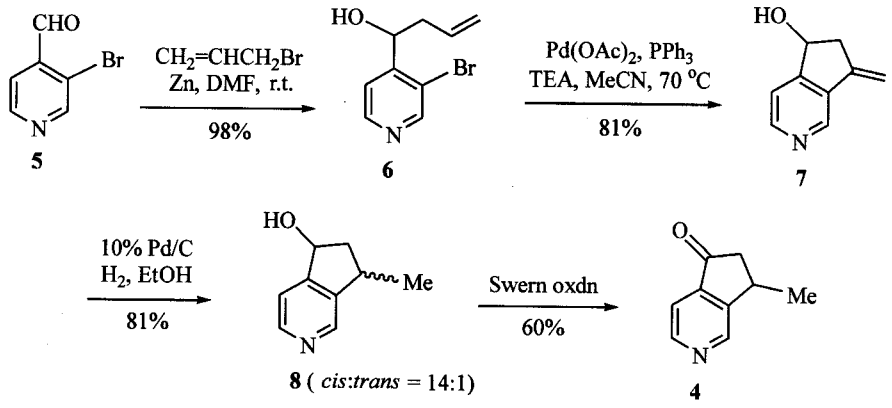
(−)-oxerine **1** (−)-actinidine **2**

aucubinine A **3** aucubinine B **4**

The cyclopenta[*c*]pyridine ring system was previously built by either a free radical cyclization[1c,1d] or an intramolecular oxazole-olefin Diels-Alder reaction.[1e] The former approach involves the use of a radical initiator such as tributyltin hydride, while the latter requires the synthesis of a suitable oxazole precursor. We envisioned that the framework could be efficiently constructed by an intramolecular Heck reaction. To explore the feasibility of this novel strategy, an appropriate precursor **6** should be prepared first. This intermediate was reportedly[1c,1d] synthesized in 73% yield by Barbier reaction of 3-bromo-4-pyridinecarboxaldehyde[5] (**5**) with allyl bromide and activated zinc in THF for 2 h. In our case, allylation of aldehyde **5** with allyl bromide and unactivated zinc in DMF for 30 min afforded homoallylic alcohol **6** in excellent yield (98%). With alcohol **6** in hand, its intramolecular Heck reaction was then investigated. Gratifyingly, under the typical Heck conditions[7] (5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 300 mol% Et_3N, CH_3CN, 70 ℃, 3.5 h), the cyclization of **6** was effected to give the desired cyclopenta[*c*]pyridine intermediate (**7**) (81%) along with a small amount of **4**, produced presumably as a result of the rearrangement of the initially formed **7**. The observed direct formation of **4** from **6** (though in low yield) led us to examine the possibilities of (i) modifying the standard Heck conditions to favor the rearrangement product **4**, and (ii) realizing a one-step conversion of **7** to **4** via base or precious metal-promoted rearrangement. The fact that the above efforts turned out to be unfruitful prompted us to resort to a circuitous but practical strategy to obtain the target

* E-mail: zhaih@mail.sioc.ac.cn
Received March 3, 2003; revised April 18, 2003; accepted May 12, 2003.
Project supported by Chinese Academy of Sciences Hundreds of Talent Program, Science & Technology Commission of Shanghai Municipality Venus Program (No. 02QB14058) and National Natural Science Foundation of China (No. 20102008).
†Dedicated to Professor ZHOU Wei-Shan on the occasion of his 80th birthday.

Scheme 1



compound. Catalytic hydrogenation[8] of **7** with 10% Pd/C in ethanol at room temperature for 8 h gave **8** as a mixture of two inseparable stereomers[1d,9] in a combined yield of 81%. The diastereomeric ratio of 14:1 favoring the *cis*-isomer was deduced from the line integrals of ^{1}H NMR spectrum. Each isomer displays its distinct NMR spectral characteristics.[1d] This is a case where the haptophilicity consideration is not the predominate factor to determine the stereoselectivity. Finally, upon Swern oxidation,[10] **8** was converted to (±)-aucubinine B (**4**)[11] in a moderate yield of 60% (unoptimized). The material obtained from this sequence gave ^{1}H NMR and ^{13}C NMR spectral data in accord with those reported previously.[3,4]

In summary, (±)-aucubinine B (**4**) has been synthesized from 3-bromo-4-pyridinecarboxaldehyde (**5**) in four steps with 39% overall yield. The construction of the cyclopenta[*c*]pyridine intermediate (**7**), realized by an intramolecular Heck reaction, is the core of our current work and should be adaptable for the synthesis of oxerine,[1] which is ongoing in our laboratory and will be reported in due course.

References and notes

1 (a) Benkrief, R.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M.; Pusset, J. *Planta Med*. **1991**, *57*, 79.
(b) Aoyagi, Y.; Inariyama, T.; Arai, Y.; Tsuchida, S.; Matuda, Y.; Kobayashi, H.; Ohta, A.; Kurihara, T.; Fujihira, S. *Tetrahedron* **1994**, *50*, 13575.
(c) Jones, K.; Fiumana, A. *Tetrahedron Lett*. **1996**, *37*, 8049.
(d) Jones, K.; Fiumana, A.; Escudero-Hernandez, M. L. *Tetrahedron* **2000**, *56*, 397.
(e) Ohba, M.; Izuta, R.; Shimizu, E. *Tetrahedron Lett*. **2000**, *41*, 10251.

2 Sakan, T.; Fujino, A.; Murai, F.; Butsugan, Y.; Suzui, A. *Bull. Chem. Soc. Jpn*. **1959**, *32*, 315.

3 Hattori, M.; Kawata, Y.; Inoue, K.; Shu, Y.-Z.; Che, Q.-M.; Namba, T.; Kobashi, K. *Phytother. Res*. **1990**, *4*, 66.

4 (a) Baghdikian, B.; Ollivier, E. Faure, R.; Debrauwer, L.; Rathelot, P.; Balansard, G. *J. Nat. Prod*. **1999**, *62*, 211.
(b) Baghdikian, B.; Guiraud-Dauriac, H.; Ollivier, E.; N' Guyen, A.; Dumenil, G.; Balansard, G. *Planta Med*. **1999**, *65*, 164.

5 Aldehyde **5** was prepared from 3-bormopyridine by ortho lithiation (LDA) followed by formylation (DMF), according to a reported precedure.[6]

6 Corey, E. J.; Pyne, S. G.; Schafer, A. I. *Tetrahedron Lett*. **1983**, *24*, 3291.

7 (a) Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun*. **1984**, 1073.
(b) Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44*, 2033.

8 Blaser, A.; Reymond, J.-L. *Helv. Chim. Acta* **1999**, *82*, 760.

9 **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.30 (d, J = 6.9 Hz, 0.2H), 1.40 (d, J = 6.9 Hz, 2.8H), 1.49—1.60 (m, 1H), 2.75—2.84 (m, 1H), 3.15 (dd, J = 13.3, 6.6 Hz, 1H), 3.50 (br, 1H), 5.20 (t, J = 7.8 Hz, 0.93H), 5.28—5.35 (m, 0.07H), 7.35 (dd, J = 3.8, 0.6 Hz, 1H), 8.43 (s, 1H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 19.28, 34.62, 45.34, 75.56, 118.94, 142.49, 144.35, 146.94, 155.29; MS (EI) m/z (%): 149 (M^+). Anal. cacld for $C_9H_{11}NO$: C 72.46, H 7.43, N 9.39; found C 72.27, H 7.58, N 9.32.

10 Anthory, J. M.; Debra, S. B.; Daniel, S. *J. Org. Chem*. **1979**, *44*, 4148.

11 **4**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.49 (d, J = 7.2 Hz, 3H), 2.30—2.38 (m, 1H), 2.96—3.06 (m, 1H), 3.56—3.62 (m, 1H), 7.54—7.57 (m, 1H), 8.72 (dd, J = 4.6, 2.2 Hz, 1H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.08, 31.40, 45.06, 115.97, 142.11, 148.29, 149.03, 152.39, 205.95. Anal. calcd for C_9H_9NO: C 73.45, H 6.16, N 9.52; found C 73.06, H 6.59, N 9.12.

(E0207081 LU, Y. J.; LU, Z. S.)