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A New Approach toward Azabicyclic Frameworks Using Gold(I)-catalyzed Cycloisomerization of Mixed *N,O*-acetals of Homopropargylic Amines†

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Piperidine is one of the most common building blocks of alkaloids.[1] For this reason, there have been great efforts to develop new synthetic methods for piperidine structures.[2] Recently, we developed a unique approach to highly substituted piperidin-4-ones, using gold(I)-catalyzed cycloisomerization of mixed *N,O*-acetals derived from homopropargylic amines.[3] In progress of applying this method to total synthesis of natural alkaloids, special attention was given to the bicyclic indolizidine and quinolizidine structures, which are frequently found in various bioactive alkaloids.[4] For examples, swainsonine and homopumiliotoxin 223G are well known natural products that contain either indolizidine or quinolizidine core structures. As a consequence, we anticipated that the development of general synthetic routes for the construction of these core structures would assist the total synthesis of natural products bearing azabicyclic systems.

As illustrated in Scheme 1, we expected that the indolizidine (n = 1) and quinolizidine (n = 2) bicyclic framework **1** could be easily synthesized from the cyclic enol ether **2**, which could be accessed by the gold(I)-catalyzed cycloisomerization of mixed *N,O*-acetal precursor **3**. We intended to prepare the precursor **3** from readily available **4**.

As depicted in Scheme 2, our initial efforts focused on the preparation of mixed *N,O*-acetal substrate **8** for the gold(I)-catalyzed cycloisomerization. Epoxidation of PMB ether **5** with *m*-CPBA followed by the addition of TMS-acetylide and the subsequent desilylation generated homopropargylic alcohol **6** in 36~45% yield over three steps. Transformation of this compound into the homopropargylic amine **7** went uneventfully using a three-step sequence shown in Scheme 2. Preparation of the key substrate **8** was accomplished by the Cbz protection of the amino group followed by the introduc-

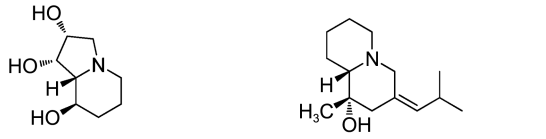
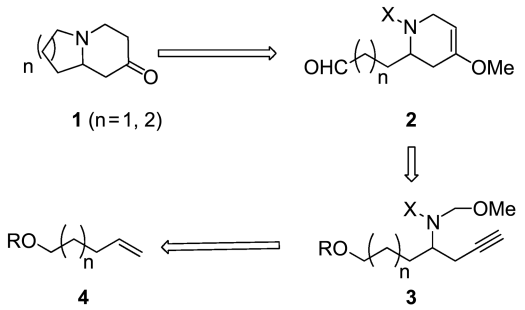
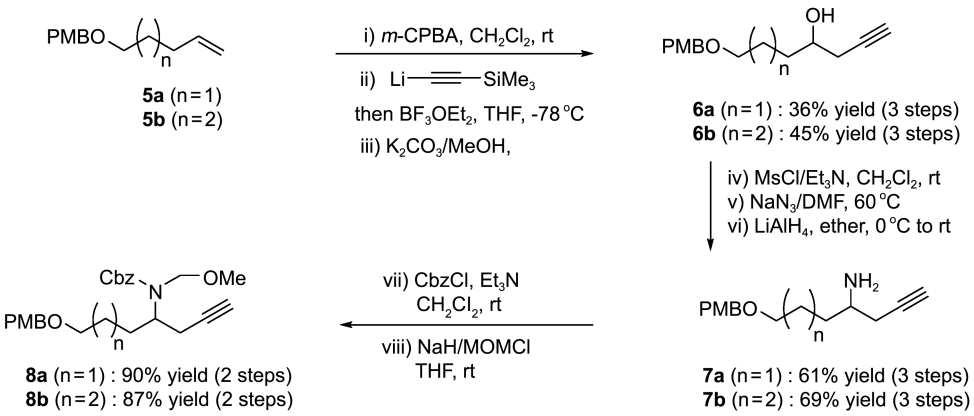


Figure 1. Examples of indolizidine and quinolizidine alkaloids.

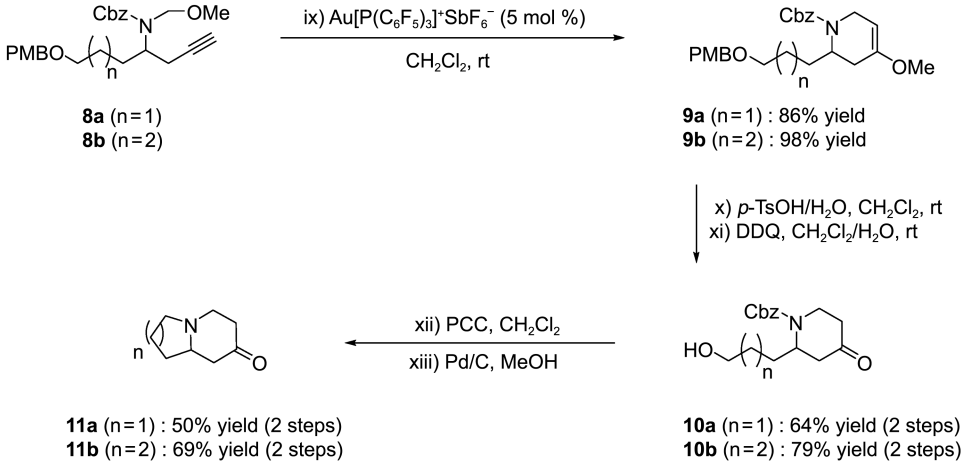


Scheme 1. Retrosynthetic analysis



Scheme 2. Synthesis of mixed *N,O*-acetal.

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.



Scheme 3. Synthesis of the bicyclic framework.

tion of MOM group under basic conditions in ~ 90% yield over 2 steps.

With mixed *N,O*-acetal **8** in hand, gold(I)-catalyzed cycloisomerization was successfully carried out to give the vinyl methyl ethers **9** with excellent 86~98% yield.[5] Hydration under acidic condition followed by the removal of PMB group generated the alcohol **10** in 64~79% yield (2 steps). The target piperidin-4-ones **11** were prepared using a two-step sequence involving PCC oxidation and the one-pot deprotection-intramolecular imine formation-reduction protocol in 50~69% yield (2 steps).[6,7,8,9]

In summary, we studied a new synthetic route to afford indolizidine and quinolizidine core structures by using gold (I)-catalyzed cycloisomerization of mixed *N,O*-acetals as the key strategy. Total synthesis of structurally complex natural products using this method is currently ongoing in our laboratory.

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5. (a) Spectral data of compound **9a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 7.23 (d, J = 7.8 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.13 (d, J = 1.4 Hz, 2H), 4.54-4.43 (br, 2H), 4.46-4.34 (br, 3H), 3.80 (s, 3H), 3.61-3.52 (br, 1H), 3.52 (s, 3H), 3.45-3.40 (br, 2H), 2.53 (d, J = 16.0 Hz, 1H), 1.88 (d, J = 16.0 Hz, 1H), 1.71-1.49 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 155.6, 137.1, 130.9, 129.4, 128.7, 128.19, 128.12, 114.0, 72.7, 69.8, 67.3, 57.5, 55.5, 54.4, 42.1, 38.7, 33.5, 31.9, 28.5, 26.8; IR (NaCl) ν 2937, 2837, 1699, 1248 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{32}NO_5$ (MH^+) 426.2280, found 426.2283. (b) spectral data of **9b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 7.23 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.13 (d, J = 1.5 Hz, 2H), 4.53-4.43 (br, 2H), 4.44-4.34 (br, 3H), 3.80 (s, 3H), 3.65-3.52 (br, 1H), 3.52 (s, 3H), 3.48-3.34 (br, 2H), 2.53 (d, J = 16.3 Hz, 1H), 1.87 (d, J = 16.3 Hz, 1H), 1.67-1.49 (m, 6H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 155.6, 137.1, 130.9, 129.4, 128.7, 128.12, 128.08, 113.9, 77.4, 72.7, 69.8, 67.2, 55.4, 54.4, 49.3, 38.7, 31.6, 29.9, 29.7, 23.2, 23.0; IR (NaCl) ν 2937, 2837, 1697, 1246 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{34}NO_5$ (MH^+) 440.2437, found 440.2439.
6. For selected examples on the synthesis of **11a**, see: *J. Org. Chem.* **2001**, 975. (a) Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *J. Comb. Chem.* **2000**, *2*, 337. (b) Harrison, J. R.; O'Brien, P.; Porter, D. W.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3623. (c) Pollet, O.; Cordonnier, G.; Bengourina, C.; Randria, C.; Silwa, H. *Heterocycles* **1996**, *43*, 1391. (d) King, F. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 447.
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8. Synthesis of **11a** represents a formal synthesis of racemic coniceine.
9. Spectral data of **11a** and **11b** are in accordance with those in the literature described in the references 6 and 7.