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# Two-Component Method to Enantiopure Quinolizidinones and Indolizidinones. Total Synthesis of (–)-Lasubine II

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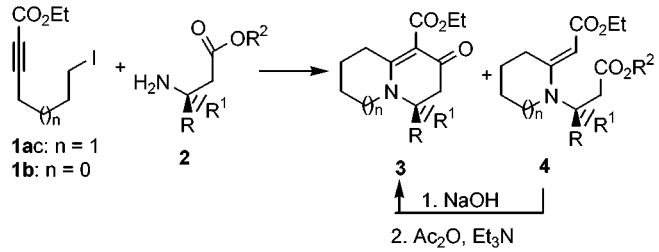
## ABSTRACT

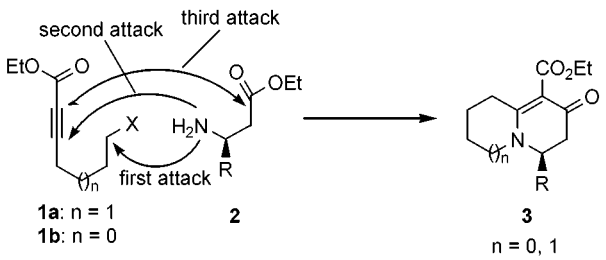



**The reaction of iodides 1 and enantiopure β-amino esters 2 mediated by potassium carbonate in acetonitrile at 65 °C provides quinolizidinones or indolizidinones 3, together with piperidines or pyrrolidines 4. Hydrolysis of 4 to the corresponding carboxylic acids followed by treatment of acetic anhydride/triethylamine gives 3 in high yields. Using 3a as a key intermediate, (–)-lasubine II is synthesized in four steps.**

Quinolizidine and indolizidine skeletons exist widely in many biologically important natural products or artificial molecules. The stereoselective formation of these skeletons has therefore become an important objective for synthetic chemists in the past decades.[1,2] One of the powerful methods for producing these skeletons is through the reduction of quinolizidinones or indolizidinones. In addition, some alkaloids bearing the quinolizidinone moiety such as myrtine[3] have been found in Nature. As a continuing effort on the synthesis from enantiopure β-amino esters,[4] we were interested in building enantiopure quinolizidinones and indolizidinones using the method shown in Scheme 1. The amino group of enantiopure β-amino ester **2**[5] first attacks the terminal carbon of methyl 7-halo-2-heptynoate **1a**[6] or methyl 7-halo-2-hexynoate **1b**[6] to form a secondary amine, which attacks the electron-deficient triple bond to provide a heterocyclic intermediate. The vinylogous anion generated in a Michael addition step may attack the carbonyl group of **2** to give the bicyclic product **3**.

We noticed that the reaction sequence was crucial for this strategy. If the amino group attacked the triple bond first,

**Scheme 1**




(1) For reviews, see: (a) Michael, J. P. *Nat. Prod. Rep.* **1993**, 51. (b) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862. (c) Michael, J. P. *Nat. Prod. Rep.* **1997**, 605.

(2) For recent reports, see: (a) Comins, D. L.; Brooks, C. A.; Ingalls, C. L. *J. Org. Chem.* **2001**, *66*, 2181. (b) Peroche, S.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron Lett.* **2001**, *42*, 4617. (c) Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2000**, *41*, 275. (d) Michel, P.; Rassat, A.; Daly, J. W.; Spande, T. F. *J. Org. Chem.* **2000**, *65*, 8908. (e) Enders, D.; Thiebes, C. *Synlett* **2000**, 1745. (f) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098.

(3) Slosse, P.; Hootele, C. *Tetrahedron Lett.* **1978**, 397.

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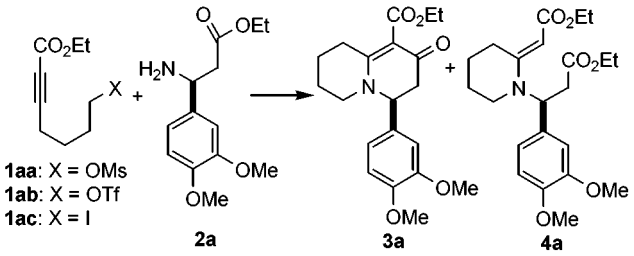
the enamine intermediate generated would not be sufficiently reactive to displace the primary halide. Accordingly, the reactions of several halides **1a** were tested with the $\beta$-amino ester **2a** under various conditions. As indicated in Table 1,

**Table 1.** Reaction of **1a** with $\beta$-Amino Ester **2a**[a]



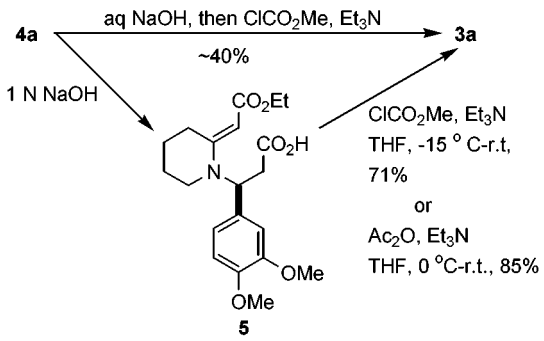

| | | | | | yield (%)[b] | |
|---|---|---|---|---|---|---|
| entry | X | solvent | temp (°C) | time (h) | **3a** | **4a** |
| 1 | OMs | DMF | 25 | 24 | *c* | |
| 2 | OTf | $CH_2Cl_2$ | −15 to 0 | 12 | 5 | 65 |
| 3 | I | DMF | 40−50 | 12 | 16 | 30 |
| 4 | I | DMF | 40−50 | 12 | 30 | 32 |
| 5 | I | DMF | 25 | 24 | 25 | 39 |
| 6 | I | DMF | 70 | 2 | 33 | 26 |
| 7 | I | EtOH | 25 | 10 | *d* | |
| 8 | I | DMSO | 25 | 12 | 21 | 26 |
| 9 | I | $C_6H_6$ | 25 | 12 | *e* | |
| 10 | I | MeCN | 65 | 36 | 44 | 45 |
| 11 | I | MeCN | 80 | 24 | 48 | 31 |

[a] Reaction condition: iodide (0.22 mmol), $\beta$-amino ester (0.22 mmol), 4 Å MS (50 mg) in 4 mL of solvent, $Cs_2CO_3$ (0.22 mmol) for entries 1 and 3, 2,6-lutidine (0.22 mmol) for entry 2, or $K_2CO_3$ (0.22 mmol) for entries 4−11. [b] Isolated yield. [c] 79% Michael product was isolated. [d] Complex mixture was determined by TLC. [e] No reaction occurred.

reaction of mesylate **1aa** with **2a** in DMF under the action of $Cs_2CO_3$ provided the Michael addition product exclusively (entry 1). However, when the more reactive triflate **1ab** was used as a substrate, the reaction in methylene chloride mediated by 2,6-lutidine gave the desired quinolizidinone **3a** in 5% yield, together with piperidine **4a** in 65% yield (entry 2). This result prompted us to try another more reactive substrate, iodide **1ac**. It was found that reaction of **1ac** with **2a** in DMF under the action of $Cs_2CO_3$ produced **3a** in 16% yield and **4a** in 30% yield (entry 3). Switching the base from $Cs_2CO_3$ to $K_2CO_3$ gave a better result (compare entries 3 and 4). Among the solvents tested, acetonitrile was best, providing **3a** and **4a** in excellent yields (entry 10). Ethanol and benzene were not suitable solvents because a complex mixture was produced, or no reaction occurred in these cases (entries 7 and 9). A higher reaction temperature was favored for producing **3a** but gave slightly lower total yields (compare entries 4, 5 and 6, 10 and 11).

To make the present method more useful for the preparation of enantiopure quinolizidinones, we sought a method to convert **4a** to **3a**. Initially, Michael's procedure was tested.[7] Thus, **4a** was hydrolyzed selectively with 1 equiv of NaOH and the resultant sodium salt was treated with methyl chloroformate. It was found that **3a** was produced but the yield was only about 40%. After some investigations, we found that a stepwise method provided **3a** in much better yield (Scheme 2). Accordingly, hydrolysis of **4a** followed

**Scheme 2**




by workup gave acid **5**, which was converted into **3a** in 71% yield by treatment with methyl chloroformate/triethylamine, or even higher yield by treatment with acetic anhydride/triethylamine.[8] This success implied that the present method provided the quinolizidinone **3a** in 82% total yield from **1ac** and **2a**.

After optimizing the reaction, we tested the reaction scope by varying the $\beta$-amino esters and the iodide. As summarized in Table 2, alkyl-substituted $\beta$-amino esters also worked well to provide the corresponding quinolizidinones and piperidines in good yields. The ratios for **4** and **3** were from 1.25 to 2.27, and all piperidines **4** were converted into the corresponding quinolizidinones in good yields under the conditions noted in Scheme 2 (entries 1−5). Moreover, when ethyl 6-iodohexynoate was employed as the electrophilic reagent, indolizidinones and pyrrolidizines were obtained. The ratios for these two types of compounds were from 1/2.6 to 1/3 (entries 6−8). Hydrolysis of **4g**, **4h**, or **4i** followed by treatment with acetic anhydride/triethylamine afforded the

(4) (a) Ma, D.; Xia, C. *Org. Lett*. **2001**, *3*, 2583. (b) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. *Org. Lett*. **2001**, *3*, 2189. (c) Wang, Y.; Ma, D. *Tetrahedron: Asymmetry* **2001**, *12*, 725. (d) Ma, D.; Sun, H. *J. Org. Chem.* **2000**, *65*, 6009. (e) Ma, D.; Sun, H. *Org. Lett*. **2000**, *2*, 2503. (f) Ma, D.; Sun, H. *Tetrahedron Lett*. **2000**, *41*, 1947. (g) Ma, D.; Sun, H. *Tetrahedron Lett*. **1999**, *40*, 3609. (h) Ma, D.; Zhang, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1703. (i) Ma, D.; Zhang, J. *Tetrahedron Lett*. **1998**, *39*, 9067. (j) Ma, D.; Jiang, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1137. (k) Ma, D.; Jiang, J. *Tetrahedron: Asymmetry* **1998**, *9*, 575.

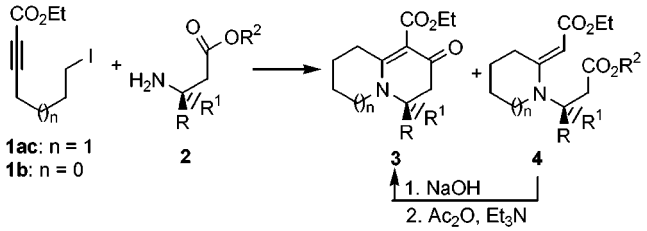
(5) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183.

(6) Kita, Y.; Okunaka, R.; Honda, T.; Shindo, M.; Taniguchi, M.; Kondo, M.; Sasho, M. *J. Org. Chem*. **1991**, *56*, 119.

(7) (a) Howard, A. S.; Gerrans, G. C.; Michael, J. P. *J. Org. Chem*. **1980**, *45*, 1713. (b) Michael, J. P.; Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem*. **1999**, *71*, 979.

(8) **Typical procedure:** A solution of **4a** (0.25 mmol), NaOH (1 mmol) in 2 mL of ethanol and 1 mL of water was stirred at room temperature for 4 h before it was acidified to pH = 4. Methylene chloride extractive workup followed by solvent evaporation afforded the crude acid, which was dissolved in 3 mL of THF. To this solution were added $Et_3N$ (1 mmol) and a solution of $Ac_2O$ (0.5 mmol) in 1 mL of THF dropwise at 0 °C. The resultant solution was stirred at room temperature for 12 h. Methylene chloride extractive workup followed by chromatography provided **3a**.

**Table 2.** Synthesis of Enantiopure Quinolizidinones and Indolizidinones[a,9]



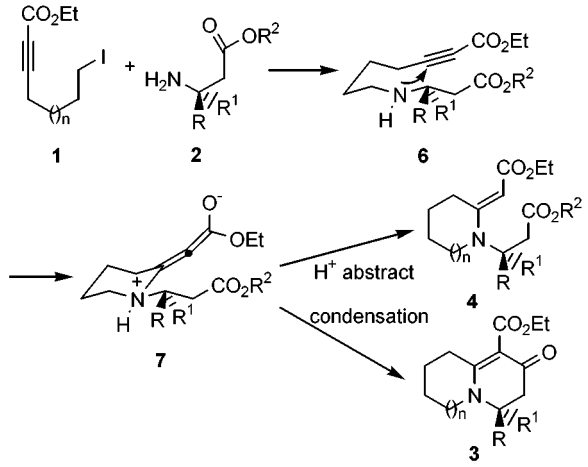

| | | | | | product (yield (%))[b] | | |
|---|---|---|---|---|---|---|---|
| entry | *n* | R | $R^1$ | $R^2$ | **3** | **4** | **4** to **3** |
| 1 | 1 | *n*-Pr | H | Me | **3b** (34) | **4b** (42) | 84 |
| 2 | 1 | *c*-hexyl | H | Et | **3c** (24) | **4c** (55) | 73 |
| 3 | 1 | H | *n*-hexyl | Et | **3d** (31) | **4d** (51) | 85 |
| 4 | 1 | H | *i*-Pr | Me | **3e** (28) | **4e** (55) | 79 |
| 5 | 1 | Ar[c] | H | Me | **3a** (43) | **4f** (39) | 89 |
| 6 | 0 | *n*-Pr | H | Me | **3g** (22) | **4g** (66) | 77 |
| 7 | 0 | H | Ar[c] | Et | **3h** (24) | **4h** (63) | 72 |
| 8 | 0 | H | *i*-Pr | Me | **3i** (24) | **4i** (62) | 80 |

[a] Reaction condition: iodide (0.22 mmol), $\beta$-amino ester (0.22 mmol), $K_2CO_3$ (0.22 mmol), 4 Å MS (50 mg) in 4 mL of MeCN, stirred at 65 °C for 36 h. [b] Isolated yield. [c] Ar = 3,4-dimethoxyphenyl.

corresponding indolizidinones in 72% to 80% yields. When these results are taken together, it is obvious that the present method provides an efficient protocol for preparing enantiopure quinolizidinones and indolizidinones.

On the basis of Harris's and Henin's report,[10] we proposed a possible mechanism for the formation of **3** and **4** as illustrated in Scheme 3. After the $S_N2$ reaction of **1** and **2**

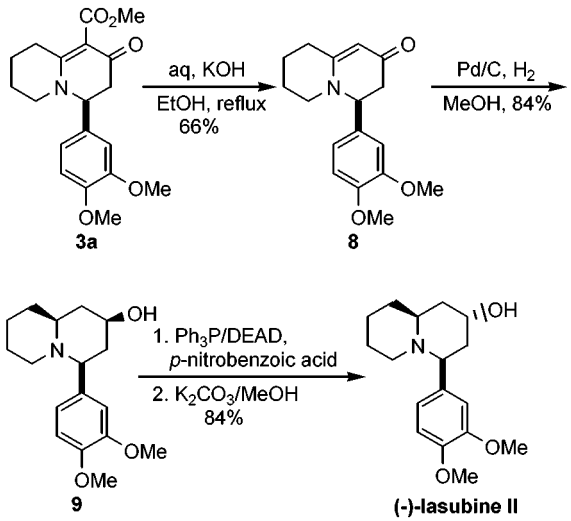
**Scheme 3**




took place to form the secondary amine **6**, intramolecular Michael addition occurred to provide the intermediate **7**. There were two possibilities for **7** to process the further conversion. One was intramolecular condensation to afford the thermodynamically controlled product **3**, another one was performing inter- or intramolecular proton abstraction to give the dynamically controlled product **4**. This hypothesis was supported by our observation that only **4** was isolated when the reaction was run in wet acetonitrile.

With quinolizidinone **3a** in hand, we developed a facile route to (−)-lasubine II[11] as outlined in Scheme 4. Hydrolysis

**Scheme 4**




of **3a** with aqueous potassium hydroxide followed by decarboxylation provided the enone **8** in 66% yield. Hydrogenation of **8** afforded the alcohol **9**, which was subjected to Mitsunobu conversion to give (−)-lasubine II. Its optical rotation value ($[\alpha]_D^{20}$ −46 (*c* 2.1, MeOH)) was close to that reported ($[\alpha]_D^{20}$ −41 (*c* 2.7, MeOH)).[11c] The overall yield for this total synthesis from the $\beta$-amino ester **2a** was about 36%.

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**Supporting Information Available:** Experimental procedures and characterizations for compounds **3**, **4**, **8**, and **9** This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) **Typical procedure:** To a mixture of 4 Å MS (50 mg), anhydrous $K_2CO_3$ (0.22 mmol), and $\beta$-amino ester (0.22 mmol) in 4 mL of $CH_3CN$ was added iodide **1** (0.22 mmol). The suspension was heated at 65 °C for 32 h before it was subjected to ether workup. Chromatography of the crude products afforded **3** and **4**.

(10) (a) Walter, P.; Harris, T. W. *J. Org. Chem.* **1978**, *43*, 4250. (b) Henin, J.; Vercauteren, J.; Mangenot, C.; Henin, B.; Nuzillard, J. M.; Guilhem, J. *Tetrahedron* **1999**, *55*, 9817.

(11) Isolation: (a) Fuji, K.; Yamada, T.; Fujita, E.; Murata, H. *Chem. Pharm. Bull.* **1978**, *26*, 2515. Racemic synthesis: (b) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717, and references therein. Enantioselective synthesis: (c) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361. (d) Ukaji, Y.; Ima, M.; Yamada, T.; Inomata, K. *Heterocycles* **2000**, *52*, 563. (e) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623.