

Total Synthesis of (\pm)-Meloscine

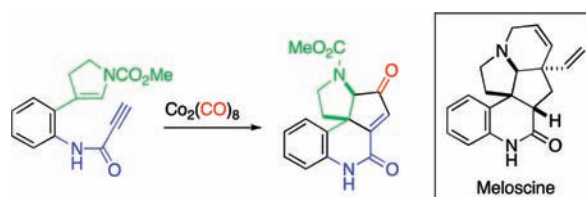
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Received February 1, 2011

ABSTRACT



The total synthesis of (\pm)-meloscine was completed in a highly stereoselective manner starting from the known 4-(2-aminophenyl)-2,3-dihydro-*N*-methoxycarbonylpyrrole. The crucial step in this total synthesis involves the efficient construction of the tetracyclic framework of the target natural product by the intramolecular Pauson–Khand reaction.

Meloscine (**1**) is a representative of the *Melodinus* alkaloids, which have been isolated from *Apocynacea* species, such as *Melodinus scandens* Forst.¹ The *Melodinus* alkaloids, otherwise known as meloquinolines, having a unique pentacyclic carbon framework, represent a group of monoterpenoid indole alkaloids and are believed to biosynthetically arise from the *Aspidosperma* alkaloid,² 18,19-dehydrotabersonine, through its oxidative skeletal rearrangement (Figure 1). The structural elucidation of meloscine was completed by the end of the 1960s.³ The first total synthesis of meloscine was completed in a racemic form by Overman⁴ using the Aza-Cope rearrangement–Mannich cyclization reaction, and recently, Bach⁵ reported the first enantioselective total synthesis of (+)-meloscine based on a template-controlled [2 + 2] photocycloaddition reaction.

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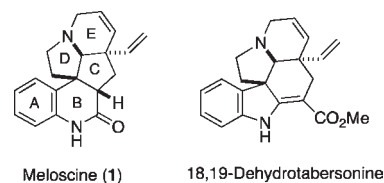


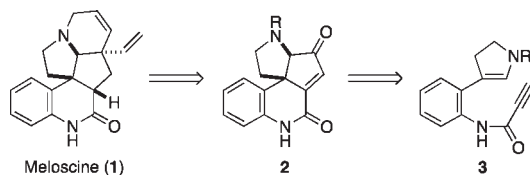
Figure 1. Meloscine and dehydrotabersonine.

We now report the short total synthesis of (\pm)-meloscine by taking advantage of the intramolecular carbonylative [2 + 2 + 1] cycloaddition reaction.^{6,7} As described in Scheme 1, our simple retrosynthetic analysis of the target natural product revealed that the dihydropyrrole-propionamide derivative **3** must be the proper substrate for the Pauson–Khand reaction,^{6,7} which would result in the

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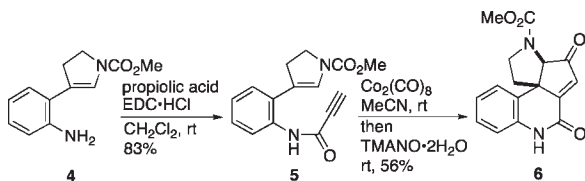
Scheme 1. Retrosynthesis of Meloscine



direct formation of four rings (A, B, C, and D rings) in one operation. The following chemical manipulation of the thus formed α -aminocyclopentenone moiety of **2** would lead to meloscine.

The known dihydropyrrole-aniline derivative **4**,⁸ easily available from (2-nitrophenyl)acetonitrile, was condensed with propiolic acid to afford the propiolamide **5** in 83% yield. After screening several Pauson–Khand conditions,^{6,7} the following procedure was found to be effective for the preparation of the tetracyclic skeleton. Thus, the treatment of **5** with dicobalt octacarbonyl in acetonitrile at room temperature furnished the corresponding dicobalt hexacarbonyl complex of **5**, which was subsequently exposed to trimethylamine *N*-oxide^{7b,c,9} at room temperature for 12 h, leading to the production of the desired tetracyclic derivative **6** in 56% yield (Scheme 2).

Scheme 2. Construction of A, B, C, and D Rings



The construction of the E ring was the next task for completion of the total synthesis. Bach⁵ reported the preparation of the *tert*-butoxycarbonyl analogue of **7** and its transformation into the target natural product via the Wittig reaction. We independently attempted an alternative method for the conversion of **7** into the target molecule. Hydrogenation of the double bond on the C ring of **6** was first performed in the presence of 10% Pd–C in methanol to provide the cyclopentanone derivative **7**. The subsequent removal of the methoxycarbonyl group of **7** with trimethylsilyl iodide was followed by allylation under conventional conditions to give **8** in a 73% overall yield as a mixture of two diastereoisomers in the ratio of 7 to 2, in which the major isomer¹⁰ has the required

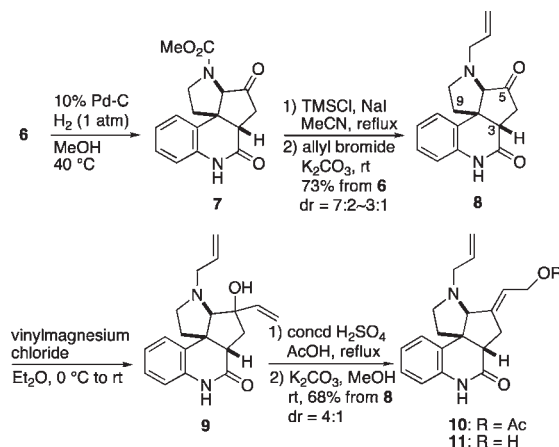
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(10) The stereochemistry of the major product of **8** was determined by the NOESY spectrum. In particular correlation between H-3 and H-9 was unambiguously detected.

stereochemistry at the C-3 position as depicted in Scheme 3. The fact that the production ratio between **8** and its C₃-epimer varied in a range of 7:2 to 3:1 indicates that the partial epimerization at the C-3 position must occur during these three steps. The construction of the quaternary carbon center at the C-5 position was achieved via the following sequence. The reaction of **8** with vinylmagnesium chloride provided the adduct **9**, the treatment of which with concentrated sulfuric acid in acetic acid¹¹ under reflux effected the migration of the double bond to afford the allyl acetate derivative **10**. Basic methanolysis of the acetate **10** furnished the allyl alcohol **11** in a 68% overall yield from **8**. It was obvious from the spectral evidence that compound **11** consisted of two diastereoisomers in the ratio of 4 to 1 due to the C-3 position, and both isomers have the (*E*)-hydroxyethylidene functional unit (Scheme 3). According to Bach's procedure,⁵ **11** was exposed to the Johnson–Claisen rearrangement with methyl orthoacetate at 130 °C for 22 h to furnish the corresponding methyl acetate derivative **12** in 65% yield as a mixture of two diastereoisomers (3:1) due to the C-5 position. Compound **12** was more efficiently and conveniently obtained in 73% yield when the Johnson–

Scheme 3. Synthesis of Hydroxyethylidene Derivative 11

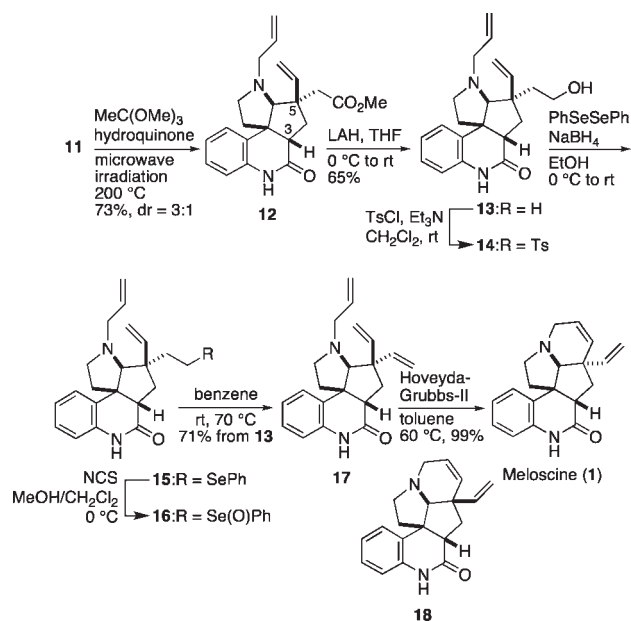


Claisen rearrangement was performed with the aid of microwave irradiation at 200 °C for 3 h. It should be mentioned that the two diastereoisomers of **11** completely converged to compound **12**, possessing the required stereochemistry at the C-3 position during this transformation. The transformation of the methoxycarbonylmethyl moiety at the C-5 position into a vinyl group was accomplished in reasonable yields as follows. The selective reduction of **12** with lithium aluminum hydride gave the hydroxyethyl derivative **13** in 65% yield. The tosylate **14**, derived from **13**, was reacted with sodium phenylselenide¹² to furnish the

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Scheme 4. Completion of Total Synthesis of (±)-Meloscine (**1**)



corresponding phenylselenol derivative **15**, which was subsequently oxidized by *N*-chlorosuccinimide in methanol.¹³ The resulting selenoxide **16** was susceptible to a thermal

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elimination reaction to produce the bis(vinyl) derivative **17** in a 71% overall yield from **13**. Upon exposure of compound **17** to the Hoveyda–Grubbs-II catalyst¹⁴ in toluene at $60\text{ }^\circ\text{C}$, ring-closing metathesis between the *N*-allyl moiety and the upper-oriented vinyl group exclusively occurred¹⁵ to produce (±)-meloscine (**1**) in 99% yield (Scheme 4). The *C*₅-epimeloscine **18**, which should be derived by the reaction with the down-oriented vinyl group, could not be obtained.

In conclusion, we have completed the highly stereoselective short total synthesis of (±)-meloscine (**1**) from the known 4-(2-aminophenyl)-2,3-dihydro-*N*-methoxycarbonylpyrrole (**4**). The most significant tactical feature of this synthesis involves the intramolecular Pauson–Khand reaction between the alkyne and *N*-protected-dihydropyrrole functional groups, which enabled us to construct the tetracyclic compound **6** with suitable functional groups in one operation. Furthermore, all of the undesired stereoisomers produced during this protocol could be ultimately converged into the target natural product.

Acknowledgment. This work was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, for which we are thankful.

Supporting Information Available. Full experimental details, compound characterization data, ¹H and ¹³C NMR spectra for all new compounds described. This material is available free of charge via the Internet at <http://pubs.acs.org>.