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Total Synthesis of (±)-Meloscine

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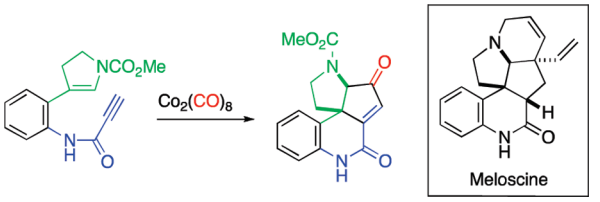
ABSTRACT



The total synthesis of (±)-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 melocine was completed in a racemic form by Overman[4] using the Aza-Cope rearrangement−Mannich cyclization reaction, and recently, Bach[5] reported the first enantioselctive total synthesis of (+)-meloscine based on a template-controlled [2 + 2] photocycloaddition reaction.

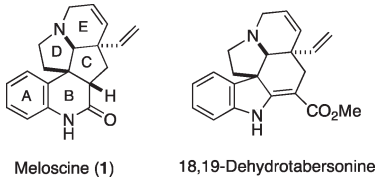


Figure 1. Meloscine and dehydrotabersonine.

We now report the short total synthesis of (±)-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-propiolamide derivative **3** must be the proper substrate for the Pauson−Khand reaction,[6,7] which would result in the

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(7) For total syntheses of natural products based on a Pauson−Khand reaction of enynes from our laboratory, see: (a) Mukai, C.; Kobayashi, M.; Kim., I. J.; Hanaoka, M. *Tetrahedron* **2002**, *58*, 5225–5230. (b) Nomura, I.; Mukai, C. *Org. Lett.* **2002**, *4*, 4301–4304. (c) Nomura, I.; Mukai, C. *J. Org. Chem.* **2004**, *69*, 1803–1812. (d) Kozaka, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem.* **2007**, *72*, 10147–10154. (e) Inagaki, F.; Kinebuchi, M.; Miyakoshi, N.; Mukai, C. *Org. Lett.* **2010**, *12*, 1800–1803. (f) Otsuka, Y.; Inagaki, F.; Mukai, C. *J. Org. Chem.* **2010**, *75*, 3420–3426.

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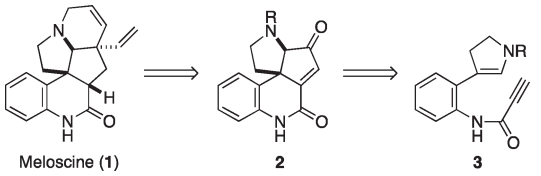
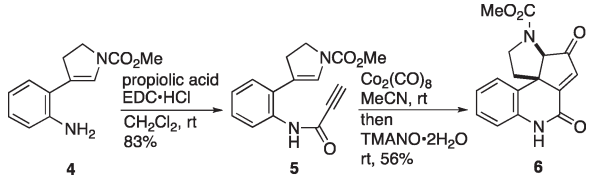
Scheme 1. Retrosynthesis of Meloscine



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.

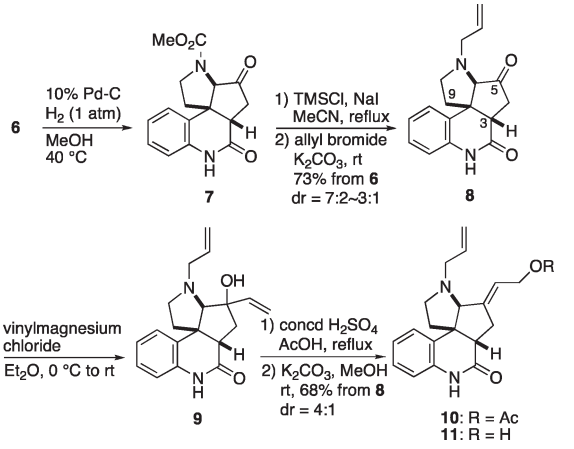
The known dihydropyrrole-aniline derivative **4**,[8] easily available from (2-nitrophenyl)acetonitrile, was condensed with propiolic acid to afford the propiolamide **5** in 83% yield. After screening several Pauson−Khand conditions,[6,7] the following procedure was found to be effective for the preparation 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. Bach[5] 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 isomer[10] has the required stereochemistry at the C-3 position as depicted in Scheme 3. The fact that the production ratio between **8** and its C_3-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 acid[11] under reflux effected the migration of the double bond to afford the allyl aetate 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 phenylselenide[12] to furnish the

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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.

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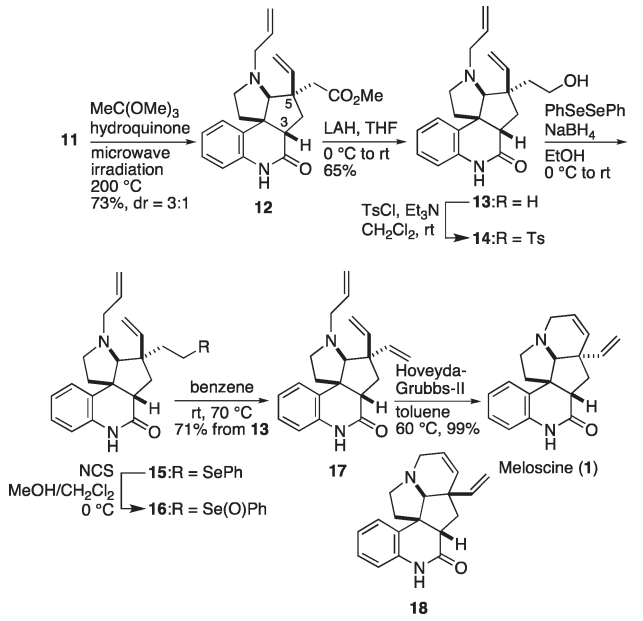
Scheme 4. Completion of Total Synthesis of (±)-Meloscine (**1**)



corresponding phenylselenol derivative **15**, which was subsequently oxidized by *N*-chlorosuccinimide in methanol.[13] The resulting selenoxide **16** was susceptible to a thermal 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 catalyst[14] in toluene at 60 °C, ring-closing metathesis between the *N*-allyl moiety and the upper-oriented vinyl group exclusively occurred[15] 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.

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

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