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A Short Total Synthesis of (±)-Epimeloscine and (±)-Meloscine Enabled by a Cascade Radical Annulation of a Divinylcyclopropane

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Supporting Information

ABSTRACT: The first stereoselective synthesis of epimeloscine has been accomplished in 13 total steps with a longest linear sequence of 10 steps. The core of the synthesis takes only five steps, the key ones being acylation, stereoselective tandem radical cyclization of a divinylcyclopropane to make two rings, and group-selective ring-closing metathesis of the resulting divinylcyclopentane to make the last ring.

Meloscine (**1**) is the parent of a small but important group of *Melodinus* alkaloids (Figure 1).[1] It is thought that in nature, **1** and its less stable epimer epimeloscine (**2**) arise from scandine (**3**) by hydrolysis and decarboxylation. In turn, scandine arises from 18,19-dehydrotabersonine (**4**) by expansion of the B ring and contraction of the C ring.[2]

The highly functionalized C ring of meloscine with its four stereocenters (two of which are quaternary) presents a significant synthetic challenge. Overman met this challenge in 1989 with a 22-step synthesis featuring a classic example of the aza-Cope Mannich reaction.[3] Appealing syntheses of meloscine have been reported by Bach in 2008[4] and very recently by Mukai.[5] Bach made (+)-meloscine through key intermediate **5a**, which was made by [2 + 2] cycloaddition and ring expansion to construct rings B and C. Mukai made intermediate **5b** by a Pauson−Khand cyclization. Both Bach and Mukai ultimately made the E ring of meloscine by a ring-closing metathesis (RCM) reaction, but the sequences from **5a** and **5b** to the natural product took 10−11 steps.

The elegant syntheses of Bach and Mukai illustrate the challenge of late introduction of the E ring with its C5 quaternary stereocenter. Herein we report an exceptionally short synthesis of the meloscines in which the B and C rings of an ABCD-ring product are constructed in a single step by a cascade radical annulation of a divinylcyclopropane. The subsequent synthesis of the E ring is then expedited by the presence of the two vinyl groups that are essential for the radical cascade. As a bonus, the sequence produces exclusively (±)-epimeloscine, which is readily epimerized to (±)-meloscine.[1a]

Figure 2 shows our retrosynthetic analysis. Meloscine (**1**) and epimeloscine (**2**) should be readily available from **6** by an RCM end game à la Bach and Mukai but in just a few short steps (removal of the protecting group, N-allylation, RCM). Divinylcyclopentane **6** is the direct product of the cascade radical annulation of divinylcyclopropane **7**. In turn, **7** is formed by acylation of aniline **8** by acid **9**. Our recent work on radical cyclizations and *o*-alkenyl anilides[6] and the early studies of radical annulations of monovinylcyclopropanes by several groups[7,8] supported the feasibility of this retrosynthetic analysis.

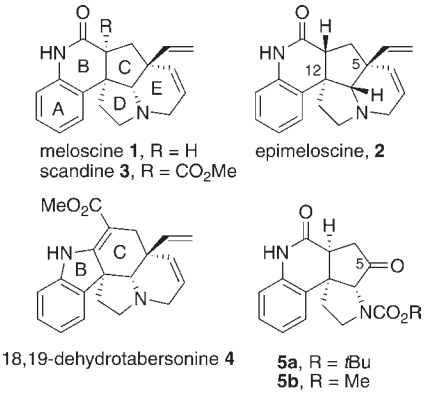

Figure 1. Structures of meloscine alkaloids and key synthetic intermediates of Bach and Mukai.

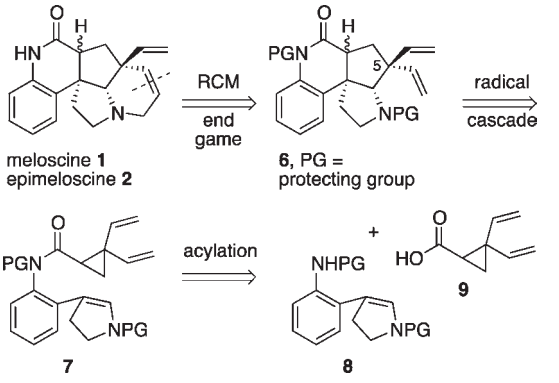

Figure 2. Retrosynthetic analysis of meloscines based on RCM, a radical cascade, and acylation.

Divinylcyclopropanecarboxylic acid **9** was readily prepared in five steps, as summarized in Scheme 1. Rhodium(II)-catalyzed cyclopropanation of bisbenzyl ether **10** provided trisubstituted cyclopropane **11** in 66% yield. Hydrogenation of **11** with Pearlman's catalyst followed by TEMPO oxidation of the resulting crude diol afforded dialdehyde **12** in 86% yield. Double Wittig reaction of **12** followed by hydrolysis of the crude product produced acid **9** in 60% yield over two steps.

The completion of the synthesis is shown in Scheme 2. We initially pursued a traditional strategy with a protecting group on the anilide nitrogen. Aniline **13b** (R = H) is a known compound that

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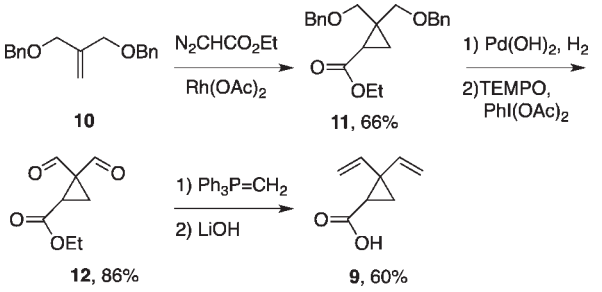
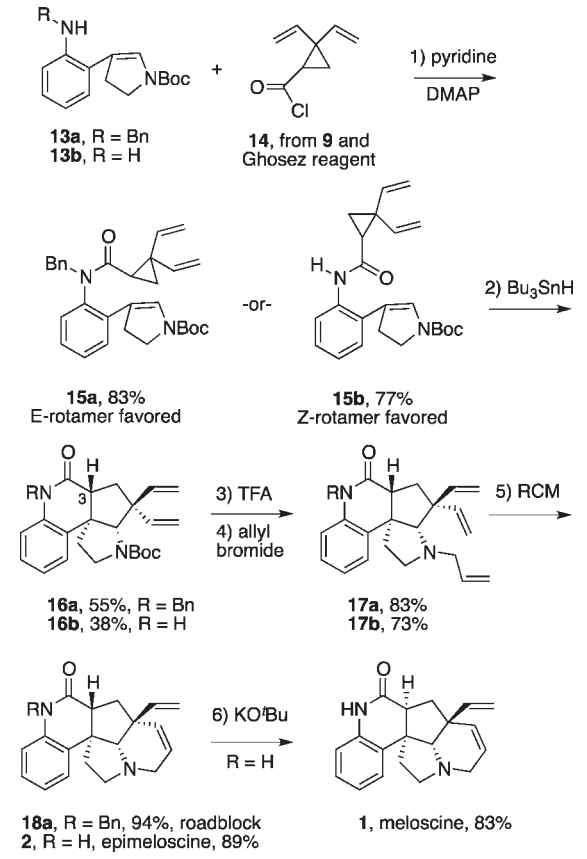
Scheme 1. Five-Step Synthesis of Divinylcyclopropanecarboxylic Acid 9



Scheme 2. Five- and Six-Step Syntheses of (±)-Epimeloscine and (±) Meloscine from Acid 9 and Aniline 13b



was prepared in three steps[9] (see the Supporting Information) and then benzylated under standard conditions to provide **13a** (R = Bn) in 73% yield. Acid chloride **14** was prepared in situ from **9** with Ghosez reagent [$Me_2C{=}C(Cl)NMe_2$],[10] after which aniline **13a** was added to provide **15a** in 83% yield. Importantly, this key precursor was expected to exist predominantly as the shown *E* rotamer,[11] predisposing it to undergo the first radical cyclization.[12]

Syringe pump addition of tributyltin hydride (2 equiv) and AIBN to a refluxing solution of **15a** in toluene provided **16a** in 55% yield after purification to remove the tin residues. This sole stereoisomer has the epimeloscine configuration at C3.

Construction of the E ring then followed on cue by removal of the N-Boc group with TFA, subsequent N-allylation to provide **17a**, and finally RCM with the second-generation Grubbs–Hoveyda catalyst. As expected on the basis of ring strain,[5] only one of the two diastereotopic vinyl groups was engaged to provide pentacycle **18a** in 94% yield. The synthesis then hit a minor roadblock when several pilot reactions to make epimeloscine by debenzylation of **18a** were unsuccessful.

Faced with the apparent choice of scaling up to make more **18a** for renewed tries of debenzylation or changing the N-protecting group to something easier to remove, we decided to do neither. Instead, we attempted to remove the N-protecting group entirely. This cut two steps from the synthesis, but there was uncertainty because anilide **15b** has a *Z* ground-state geometry,[11] so its derived radical would not be predisposed for cyclization.[12] We elected this option since it was easy to prepare **15b**.

Indeed, acylation of aniline **13b** using acid **9** and Ghosez's reagent as before provided **15b** in 77% yield. Syringe pump addition of tin hydride to **15b** under the conditions optimized for **15a** provided ABCD tetracycle **16b** in 38% yield after careful purification. Removal of the Boc group and N-allylation provided **17b** in 73% yield. RCM as described above then directly provided the natural product (±)-epimeloscine (**2**) in 89% yield.[1a,c] Overman produced epimeloscine in his classic synthesis,[3] but it came from a minor stereoisomer (<10%) of a mixture on the way to meloscine. Thus, this is the first stereoselective synthesis of epimeloscine. Epimerization of **2** with KO^{t}Bu provided (±)-meloscine (**1**) in 83% yield.

In summary, we have achieved the first stereoselective synthesis of (±)-epimeloscine (**2**) with a longest linear sequence of just 10 steps in ~6% overall yield. (±)-Meloscine (**1**) is readily produced from **2** by epimerization. The core part of the synthesis, which involves coupling of two simple precursors (**13b** and **9**) followed by rapid formation of rings B and C (in tandem) and then ring E (Scheme 2), takes just five steps and proceeds in almost 20% overall yield. There is room for improvement because the yield of the radical cyclization (38%) was unoptimized. This core sequence features no oxidations, no reductions, no functional-group transformations, and only one deprotection (removal of the N-Boc group). The use of a divinylcyclopropane in the cascade radical annulation to make the B and C rings paves the way for immediate construction of ring E to complete the synthesis.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental details and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ NOTE ADDED AFTER ASAP PUBLICATION

This article was published ASAP on June 16, 2011. Figure 1 was updated and a dedication was added to the Acknowledgment. The corrected version was posted on June 20, 2011.