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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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Abstract

The first stereoselective synthesis of epimeloscine is accomplished in a longest linear sequence of 10 steps and with 13 total 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 RCM 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] In nature, **1** and its less stable epimer epimeloscine **2** are thought to 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 that features 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,b** 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 that constructs the B and C rings of an ABCD-ring product 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** or 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 *ortho*-alkenyl

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Supporting Information Available: Contains 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.

anilides[6] and the early studies by several groups of radical annulations of monovinylcyclopropanes[7,8] supported the feasibility of this retrosynthetic analysis.

Divinylcyclopropane carboxylate **9** was readily prepared in five steps, as summarized in Scheme 1. Rhodium (II) catalyzed cyclopropanation of *bis*-benzyl 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 a dialdehyde **12** in 86% yield. Double Wittig reaction of **12** followed by hydrolysis of the crude product produced acid **9** in 60% yield over 2 steps.

The completion of the synthesis is shown in Scheme 2. Initially we pursued a traditional strategy with a protecting group on the anilide nitrogen. Aniline **13b** (R = H) is a known compound that was prepared in three steps[9] (see Supporting Information), then benzylated under standard conditions to provide **13a** (R = Bn) in 73% yield. The acid chloride **14** was prepared in situ from **9** with Ghosez reagent ($Me_2C{=}C(Cl)NMe_2$),[10] then aniline **13a** was added to provide **15a** in 83% yield. Importantly, this key precursor is expected to exist predominately as shown in the E rotamer,[11] and is therefore predisposed 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 followed on cue by removal of the N-Boc group with TFA and N-allylation to provide **17a**, then RCM with the second-generation Grubbs-Hoveyda catalyst. As expected based on 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 not successful.

Faced with the apparent choice of scaling up to make more **18a** for renewed tries of debenzylation or with 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 cuts two steps from the synthesis, but there is uncertainty because anilide **15b** has a Z ground state geometry[11] so its derived radical is not predisposed for cyclization.[12] We elected this option since it was easy to prepare **15b**.

Indeed, acylation of acid **9** and aniline **13b** with Ghosez's reagent as before provided **15b** in 77% yield. Now, 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. Then RCM as above directly provided the natural product (±)-epimeloscine **2** in 89% yield.1a,c Overman produced epimeloscine in his classic synthesis,[3] but 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 about 6% overall yield. (±)-Meloscine **1** is readily produced from **2** by epimerization. The core part of the synthesis (Scheme 2)—coupling of two simple precursors (**13b** and **9**) and rapid formation of rings C and D (in tandem) then ring E—takes just five steps and proceeds in almost 20% overall yield. There is room for improvement because yield of the radical cyclization (38%) is 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 C and D rings paves the way for immediate construction of ring E to complete the synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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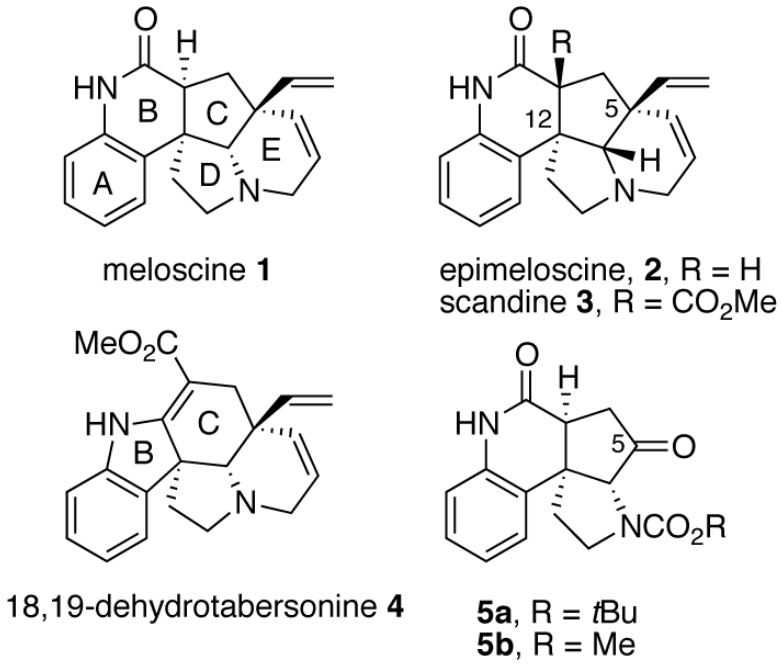


Figure 1.
Structures of meloscine alkaloids and a key synthetic intermediate of Bach and Mukai

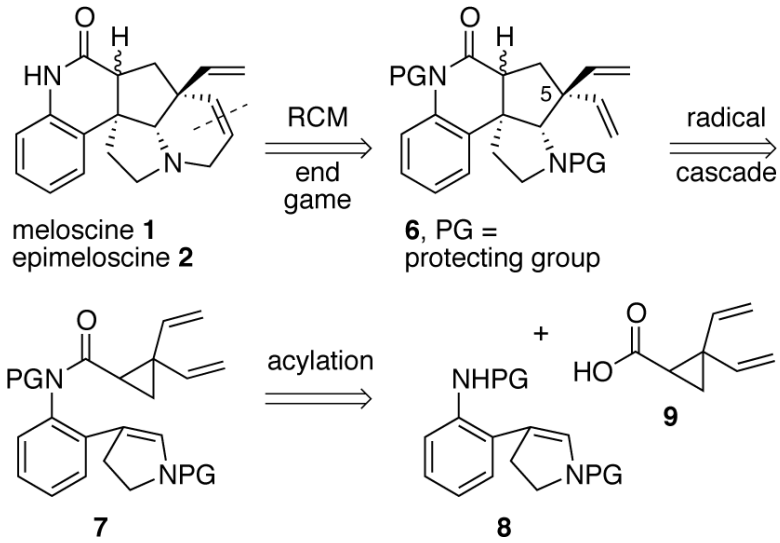
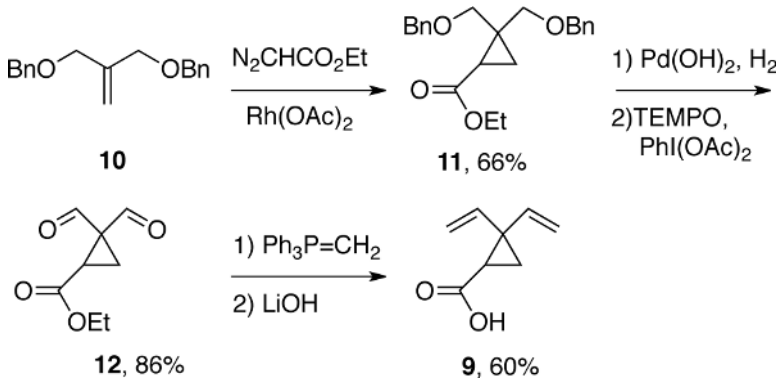
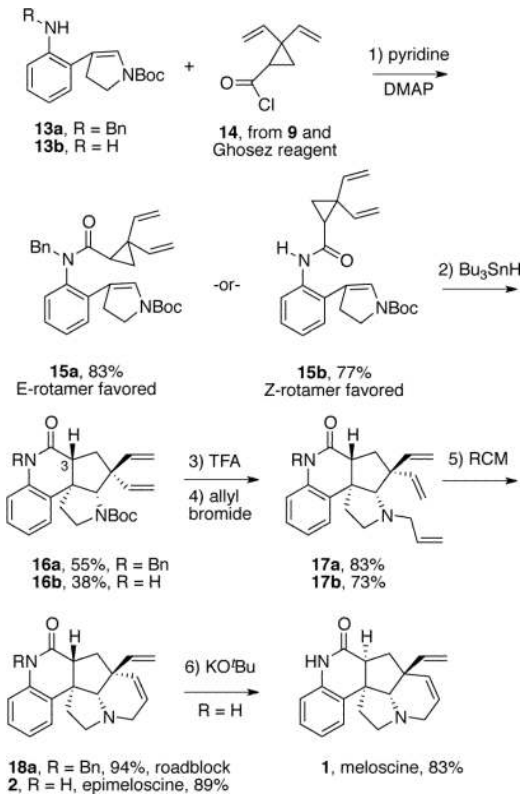


Figure 2.
Retrosynthetic analysis of meloscines based on RCM, a radical cascade and acylation



Scheme 1.
Five-step synthesis of divinylcyclopropane carboxylate **9**



Scheme 2.

Five- and six-step synthesis of (±)-epimeloscine and (±) meloscine from acid **9** and aniline **13b**