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Synthesis studies on the *Melodinus* alkaloid meloscine

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ABSTRACT

The pentacyclic *Melodinus* alkaloid (±) meloscine was synthesized in 19 chemical steps from 2 bromobenzaldehyde through a route featuring an allenyl azide cyclization cascade to deliver the core azabicyclo[3.3.0]octane substructure. Peripheral functionalization of this core included a Tollens type aldol condensation to set the quaternary center at C(20) and a diastereoselective ring closing metath esis to forge the tetrahydropyridine ring.

1. Introduction

The *Melodinus* alkaloids comprise a small class of plant derived pentacyclic compounds isolated from either Apocynaceae or Kopsia species.[1] Among the 14 members of this family, three related iso lates all extend from the melodan skeleton, Fig. 1. The complex and compact framework of scandine (**3**) has been hypothesized to emerge from rearrangement of the more common tabersonine species.[1,2] Scandine then can serve as the direct precursor to both meloscine (**1**) and epimeloscine (**2**) via decarboxymethylation. Permissive evidence for this biosynthesis proposal was garnered by Palmisano et al., who documented a high yield (72%) pinacol type shift in a system related to **4**→**3**.[3a] Alternatively, Hugel and Lévy have described a high temperature rearrangement process that passes through an aziridine intermediate en route to the melodan skeleton from a tabersonine derivative.[3b,5a]

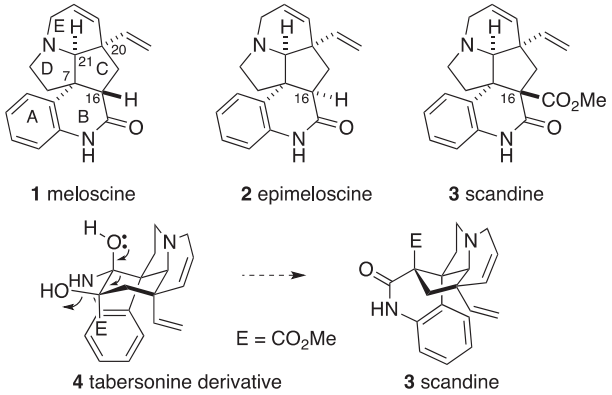

Fig. 1. Alkaloids with the melodan skeleton from Apocynaceae *Melodinus*; a bio-synthetic hypothesis for the formation of the melodan structure from a tabersonine precursor.

The melodan alkaloids have remained an enduring challenge for chemical synthesis, with reports spanning the last three decades that describe either approaches to,[3,4] or syntheses of,[5] one or more members of this family. The melodan alkaloids' congested bicyclic core, featuring four contiguous stereogenic carbon atoms about a cyclopentane ring, two of which are all carbon quaternary cen ters, poses a formidable test for stereoselective synthesis. Not sur prisingly, this challenge has been addressed through widely differing synthesis strategies, and four total syntheses have been recorded prior to our work, Scheme 1. The initial success in this area was reported by Overman et al.,[5b] who relied on an aza Cope–Mannich sequence (**5**→**6**) for the elaboration of the racemic meloscine core. This work stood as the only total synthesis of meloscine for almost 20 years, when in 2008 Bach et al. described a synthesis of natural (+) meloscine through an enantioselective [2π+2π] photocycloaddition of **7** and methyl 2 (trimethylsiloxy) acrylate to furnish the cyclobutyl containing species **8**.[5c,d] Neither the Overman work nor the Bach work delivered the core cyclo pentyl C ring directly; in the former case, a Wolff reaction mediated ring contraction was utilized to formulate this ring, whereas in the latter case, a pinacol like ring expansion served the same strategic function. More recently, Mukai et al. have completed a synthesis of (±) meloscine through Pauson–Khand cyclization of

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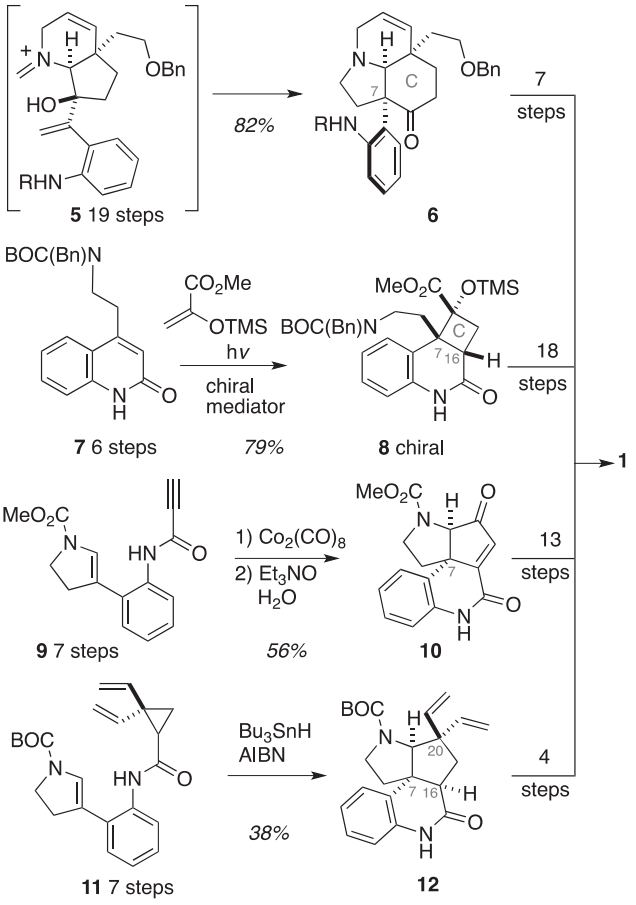
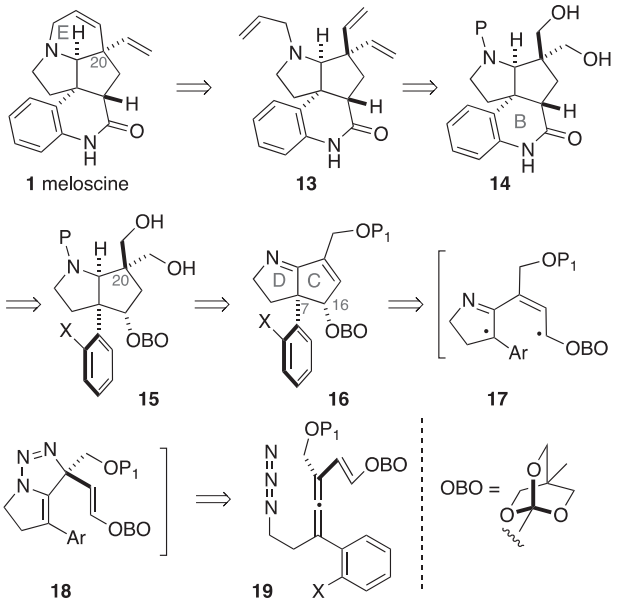


Scheme 1. Prior art in the total synthesis of meloscine.



Scheme 2. Retrosynthetic analysis of meloscine via allenyl azide cascade cyclization chemistry.

the propynoylamide **9** to furnish the tetracyclic core of meloscine **10**.[5e] Soon thereafter, Curran et al. detailed the most efficient construction of meloscine to date through a radical mediated [3 atom+2 atom] addition within divinyl cyclopropane **11** to afford tetracycle **12**.[5f] Both the Mukai and the Curran approaches do deliver the central cyclopentanoid C ring directly and with the correct stereochemistry for meloscine at C(7) and C(21). The Curran cyclization chemistry furnishes the product tetracycle with the correct stereochemistry at C(16) for epimeloscine but not meloscine. However, the ready epimerization of the epimeloscine skeleton to meloscine is not problematic per the earlier observations of Bernauer et al.[1a] Thus, Curran's synthesis delivers not only epimeloscine but meloscine as well.

A different conceptualization of the meloscine problem can be envisioned, Scheme 2. Advances in allenyl azide cascade cyclization chemistry[6] has enabled the development of a synthesis strategy for meloscine that features efficient formation of the C/D ring azabicyclo[3.3.0]octane core with complete relative stereochemical control at C(7) and C(16). In this strategy, allenyl azide **19** plays a pivotal role; thermolysis of this species is expected to proceed through a reaction sequence involving first [3+2] cycloaddition to deliver an unisolable triazoline **18** whose subsequent fragmentation is driven by release of strain.[6d,g] Loss of N_2 from **18** should furnish the singlet diyl **17**, which is poised for formal electrocyclization through a conrotatory pathway to provide the C/D ring bicyclic product **16** as the diastereomer shown.[6d,g] Two further operations are required in order to convert **16** into the target meloscine; (1) union of the aryl ring with a carboxylic acid derivative, which would be revealed by deprotecting the OBO function, to deliver lactam ring B, and (2) construction of tetrahydropyridine ring E from the extant C(20) and nitrogen substituents. At the outset of this work, it was not obvious, which of these two operations should be executed first, so maintaining flexibility to pursue both options via appropriate choice of P and P_1 was built into the plan. In addition, formation of the C(20) quaternary center (**16**→**15**) was anticipated to be a difficult transformation, given the steric hindrance in the local environment of the C ring, and so several different options were envisioned. Finally, the ultimate operation of the synthesis route was anticipated to be a diastereoselective ring closing metathesis between the *N* allyl fragment and the β face vinyl appendage of **13**. At the initial planning stages, the expectation for diastereoselectivity in this transformation was undergirded by nothing more than density functional calculations on **1** and its C(20) epimer. While this work was in progress, both the Mukai and the Curran syntheses of meloscine were published; each utilized this same metathesis based ring closure, and no evidence for a C(20) epimer was reported. A preliminary account of this work has been published;[7] this report elaborates on that disclosure and details the detours, derailments, and dead ends encountered along the way to meloscine.

2. Results and discussion

Three issues were paramount at the outset of the meloscine synthesis effort as delineated in Scheme 2: (1) Would the ring closing metathesis to form the E ring proceed with satisfactory diastereoselectivity? (remembering that neither the Mukai nor the Curran precedents were reported yet) (2) What X group at the *ortho* position of the aryl ring would be tolerated during the chemistry used to prepare an advanced intermediate B ring precursor? (3) Should the E ring or the B ring be closed first? Either option has the potential to rigidify the resultant molecular skeleton and thereby influence the facility of the second choice ring closure.

The first issue (metathesis diastereoselectivity) was addressed with a model system that explicitly tested the metathesis based closure of the E ring but avoided any issues associated with the nature of the 'X' substituent or its use in lactam ring closure, Scheme 3. In this model system, the simple unfunctionalized benzoyl derivative **20**[8] served as the launch point. Acetylide addition to **20** and acetylation of the resulting alcohol delivered the activated