A Palladium-Catalyzed Vinylcyclopropane (3 + 2) Cycloaddition Approach to the Melodinus Alkaloids

Alexander F. G. Goldberg and Brian M. Stoltz*
The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 East California Boulevard, MC 101-20, Pasadena, CA 91125, USA

Abstract

A palladium-catalyzed (3 + 2) cycloaddition of a vinylcyclopropane and a β-nitrostyrene are employed to rapidly assemble the cyclopentane core of the Melodinus alkaloids. The ABCD ring system of the natural product family is prepared in six steps from commercially available materials.

The Melodinus alkaloids are a family of dihydroquinolinone natural products originally isolated over 40 years ago from Melodinus scandens Forst. This family of natural products is structurally related to the Aspidosperma alkaloids by means of an oxidative rearrangement of 18,19-dehydrotabersonine (1) (Scheme 1). Although no biological activity has been directly attributed to any member of this class to date, some species of the Melodinus genus are used in Chinese folk medicine to treat meningitis in children and rheumatic heart disease.2,3

Despite the apparent lack of biological activity, we were nonetheless interested in the prospects of preparing non-natural derivatives for biological evaluation, and we were intrigued by their structural complexity (Figure 1). The Melodinus alkaloids feature a congested cyclopentane core, bearing four contiguous stereocenters; in the case of (+)-scandine (2),1 (+)-meloscandonine (3),4 and others,5 three of these are all-carbon quaternary stereocenters. Indeed, construction of this highly substituted C ring constitutes a formidable challenge, and the only members of the family to have been synthesized to date are derivatives meloscine (4) and its C(16) epimer, epimeloscine (5).6,7,8
The parent of the natural product family, (+)-scandine (2), is believed to be the biosynthetic precursor to the 13 other known members of this family of natural products, and, unlike meloscine (4), features a quaternary stereocenter at C(16). In the interest of a general route to the Melodinus alkaloids, we sought a strategy for the rapid assembly of the core of the natural product family, including the C(16) quaternary stereocenter. Thus, we targeted tetracycle 6 as a suitable model for evaluating this strategy.

Retrosynthetically, we envisioned that the D and B rings of 6 could be formed by ring-closing metathesis and lactamization respectively from vinylcyclopentane 7 (Scheme 2). This intermediate could arise, in turn, from nitrocyclopentane (8), the product of a palladium-catalyzed, intermolecular (3 + 2) cycloaddition between a trans-β-nitrostyrene (9) and vinylcyclopropane 10. Our approach relied on the conservation of the trans relationship between the aryl and nitro substituents of nitrostyrene through the course of the cycloaddition. The necessary stereochemistry at C(16) could be then effected by a cis selective lactamization to build the B–C ring junction.

To examine the viability of our route, known vinyl cyclopropane 10 was prepared according to literature methods. Reaction of this cyclopropane with commercially available β,2-dinitrostyrene (11) under conditions similar to those developed by Tsuji resulted in the formation of vinylcyclopentane 12 in 60% yield as a mixture of two inseparable diastereomers, (Scheme 3). Upon zinc reduction of the diastereomeric mixture and in situ lactamization, two separable dihydroquinolinone products, 13a and 13b were obtained in 79% yield. Gratifyingly, the relative stereochemistry of these diastereomers was unambiguously determined by single crystal X-ray analysis, revealing that they are epimeric only at C(20). The observed stereochemistry confirmed our hypothesis that the trans relationship from the nitrostyrene would be conserved in the (3 + 2) cycloaddition. Furthermore, the aniline lactamization was completely selective for the 6,5 cis ring junction. Of note, the low diastereomeric ratio at C(20) is inconsequential with regard to the application of this strategy to total synthesis, as the installation of a second vinyl group at C(20) would negate stereochemical information at this stage.

Following construction of the ABC ring system of the Melodinus alkaloids, we turned our attention to the installation of the D ring of our model by ring-closing metathesis (Scheme 4). Monoalkylation of the primary amine (13a) proved non-trivial, yielding mixtures including bisalkylated products when reacted with allylic electrophiles or under standard reductive amination conditions. Fortunately, preforming the cinnamaldimine, followed by dilution and reduction with sodium borohydride yielded secondary cinnamyl amine exclusively. This product was then acylated with acetic anhydride, providing a potential functional handle for further elaboration toward the final E ring. Finally, upon treatment of the crude product with the Grubbs 2nd generation catalyst (16), the desired tetracycle (6) was obtained in 84% yield over two steps. Conveniently, these final two steps could be accomplished without need for chromatographic purification, as the bisamides precipitated from their respective reaction mixtures with >95% purity.

In summary, we have demonstrated the use of a palladium-catalyzed intermolecular (3 + 2) cycloaddition strategy to rapidly assemble the tetracyclic ABCD ring system of the Melodinus alkaloids (6). Importantly, this approach allows for the installation of the quaternary stereocenter at C(16), and is accomplished in six steps from commercial sources. The application of this strategy and an enantioselective approach toward this natural product family is currently underway, with particular focus on the closure of the E ring, and will be reported in due course.
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This publication is based on work supported by Award No. KUS-11-006-02, made by King Abdullah University of Science and Technology (KAUST). The authors wish to thank NIH-NIGMS (R01GM080269-01), Amgen, Abbott, Boehringer Ingelheim, and Caltech for financial support. A.G. gratefully acknowledges the Natural Sciences and Engineering Research Council (NSERC) of Canada for a PGS D scholarship. Christopher Henry, Hosea Nelson, Kristy Tran, Florian Vogt and Scott Virgil (Caltech) are thanked for helpful guidance. Lawrence Henling and Dr. Michael Day (Caltech) are gratefully acknowledged for X-ray crystallographic structural determination. The Bruker KAPPA APEXII X-ray diffractometer was purchased via an NSF CRIF:MU award to the California Institute of Technology, CHE-0639094. The Varian 400 MHz NMR spectrometer was purchased via an NIH grant (RR027690).

References


3. Bach and coworkers attribute the lack of biological activity “to the fact that the incorporated lactam moiety strongly impairs with the passage of melodan structures through biological membranes.” See ref. 6f.


11. An enantioselective variant of Tsuji’s (3+2) cycloaddition was recently reported using alkylidene azlactones as a dipolarophile: Trotz BM, Morris PJ. Angew. Chem., Int. Ed. 2011; 50:6167–6170.

12. A similar, intramolecular radical-based cycloaddition was employed in Curran’s recent syntheses of (±)-epimeloscine and (±)-meloscine. See ref. 6d.


14. Crystallographic data have been deposited at the CCDC and copies can be obtained on request, free of charge, by quoting the deposition number 820779 (13a) or 820778 (13b).

15. In both Mukai and Curran’s syntheses of meloscine, diastereoselective ring-closing metathesis was employed in the end-game to establish the necessary stereochemistry at C(20). See refs 6c, 6d.

16. The major, trans diastereomer of 12, corresponding to 13b, appears to be more stable, based on semi-empirical (AM1) ground-state calculations.
Figure 1.
Representative examples of the *Melodinus* alkaloids.
Scheme 1.
Biosynthesis of the *Melodinus* alkaloids
Scheme 2.
Retrosynthetic analysis of tetracycle (6)
Scheme 3.
Synthesis of the ABC ring system
Scheme 4.
Closure of D ring

13a

\[
\text{H}_2\text{N} \quad \begin{array}{c}
\text{H} \\
\text{H} \\
\text{C} \quad \text{O}_2\text{Me}
\end{array}
\]

\[
\text{OHC} \quad \begin{array}{c}
\text{Ph} \\
\text{then NaBH}_4 \\
\text{CH}_2\text{Cl}_2/\text{MeOH}
\end{array}
\]

\[
\text{CO}_2\text{Me}
\]

\[
\text{Ph}
\]

\[
\text{HN} \quad \begin{array}{c}
\text{H} \\
\text{H} \\
\text{C} \quad \text{O}_2\text{Me}
\end{array}
\]

\[
(80\% \text{ yield})
\]

14

13a

\[
\text{Ac}_2\text{O}, \text{pyridine} \\
\text{CH}_2\text{Cl}_2
\]

15 (5 mol %)

\[
\text{TBME/CH}_2\text{Cl}_2, 60 ^\circ \text{C}
\]

\[
(84\% \text{ yield,} \\
\text{two steps})
\]

6

\[
\text{Grubbs' 2nd generation} \\
\text{catalyst (15)}
\]