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

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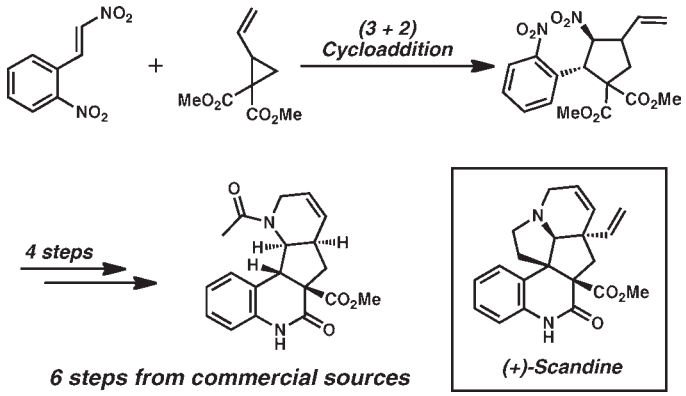
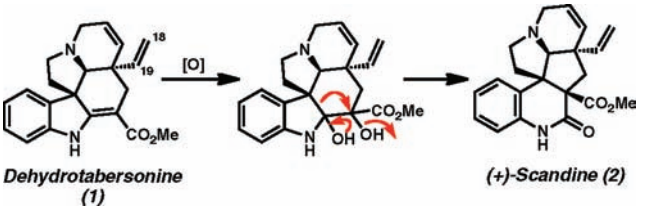
ABSTRACT



A palladium-catalyzed (3 + 2) cycloaddition of a vinylcyclopropane and a β-nitrostyrene is 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).[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]

Scheme 1. Biosynthesis of the *Melodinus* Alkaloids



Despite the apparent lack of biological activity, we were nonetheless interested in the prospects of preparing non-natural derivatives for biological evalution, and we were intrigued by their structural complexity (Figure 1). The

(1) (a) Bernauer, K.; Englert, G.; Vetter, W. *Experientia* **1965**, *21*, 374–375. (b) Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. *Helv. Chim. Acta* **1969**, *52*, 1886–1905. (c) Cannon, J. R.; Croft, K. D.; Matsuki, Y.; Patrick, V. A.; Toia, R. F.; White, A. H. *Aust. J. Chem.* **1982**, *35*, 1655–1664.

(2) Guo, L.-W.; Zhou, Y.-L. *Phytochemistry* **1993**, *34*, 563–566.

(3) Bach and co-workers 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.

(4) (a) Plat, M.; Hachem-Mehri, M.; Koch, M.; Scheidegger, U.; Potier, P. *Tetrahedron Lett.* **1970**, *11*, 3395–3398. (b) Rodier, N.; Mauguen, Y.; Hachem-Mehri, M.; Plat, M. *Acta. Crystallogr., Sect. B: Struct. Sci.* **1978**, *34*, 232–237.

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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 succumbed to total synthesis are derivatives meloscine (**4**) and its C(16) epimer, epimeloscine (**5**).[6−8]

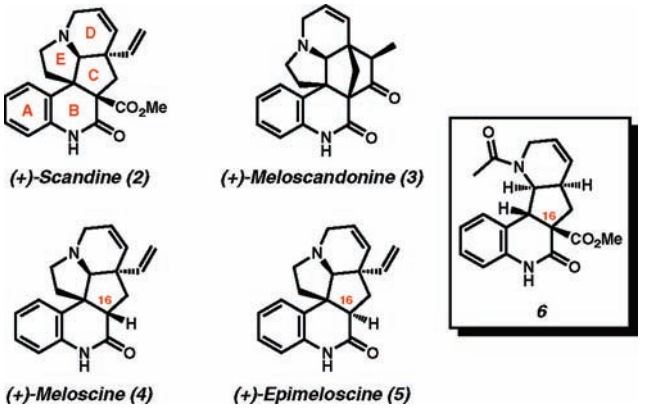
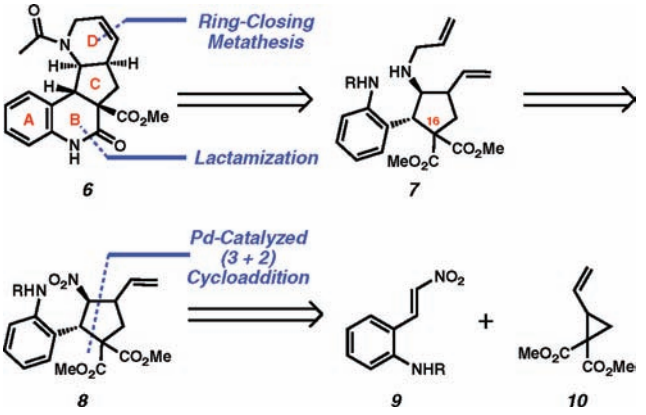


Figure 1. Representative examples of the *Melodinus* alkaloids.

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).[9] 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**.[10−12] Our approach relied on the conservation of the trans relationship between the aryl and nitro substituents of nitrostyrene **9** 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.

Scheme 2. Retrosynthetic Analysis of Tetracycle (**6**)



To examine the viability of our route, known vinyl cyclopropane **10** was prepared according to literature methods.[13] 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).[10] 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).[14]

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.[15,16]

(5) Daudon, M.; Hachem Mehri, M.; Plat, M. M.; Hagaman, E. W.; Wenkert, E. *J. Org. Chem.* **1976**, *41*, 3275–3278 and references therein.

(6) Four syntheses, three racemic (a/b, c, and d) and one enantioselective (e/f), have been reported to date: (a) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Org. Chem.* **1989**, *54*, 1236–1238. (b) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610. (c) Hayashi, Y.; Inagaki, F.; Mukai, C. *Org. Lett.* **2011**, *13*, 1778–1780. (d) Zhang, H.; Curran, D. P. *J. Am. Chem. Soc.* **2011**, *133*, 10376–10378. (e) Selig, P.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5082–5084. (f) Selig, P.; Herdtweck, E.; Bach, T. *Chem.—Eur. J.* **2009**, *15*, 3509–3525.

(7) A biomimetic semisynthesis of (+)-scandine and (+)-meloscine from 18,19-dehydrotabersonine: Hugel, G.; Levy, J. *J. Org. Chem.* **1986**, *51*, 1594–1595.

(8) Efforts toward a total synthesis of (±)-scandine have been reported: Denmark, S. E.; Cottell, J. J. *Adv. Synth. Catal.* **2006**, *348*, 2397–2402.

(9) Szabó, L. F. *ARKIVOC* 2007, No. vii, 280−290.

(10) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3825–3828.

(11) An enantioselective variant of Tsuji's (3 + 2) cycloaddition was recently reported using alkylidene azlactones as a dipolarophile: Trost, B. M.; Morris, P. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 6167–6170.

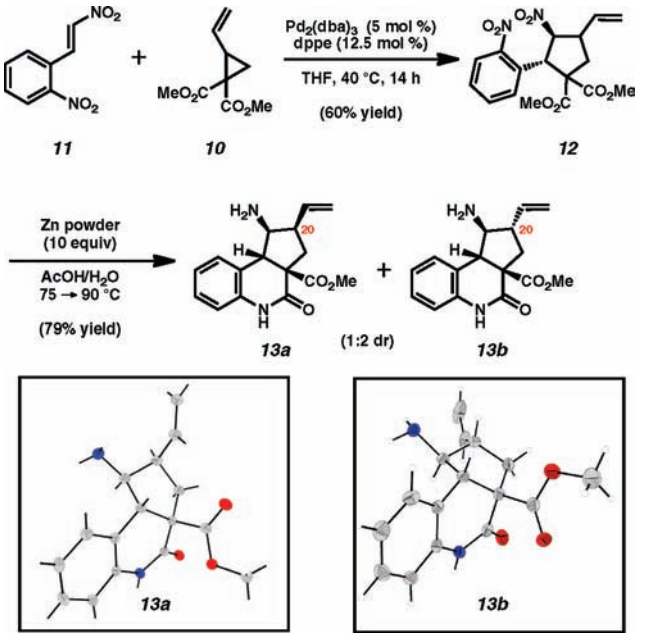
(12) A similar, intramolecular radical-based cycloaddition was employed in Curran's recent syntheses of (±)-epimeloscine and (±)-meloscine. See ref 6d.

(13) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541–2544.

(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 and 6d.

Scheme 3. Synthesis of the ABC Ring System

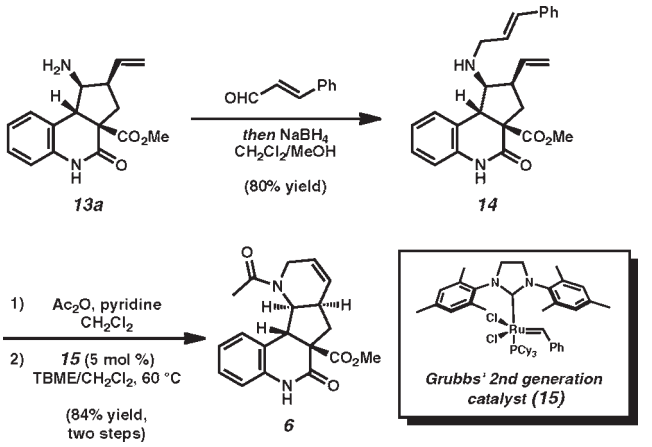


Following construction of the ABC ring system of the *Melodinus* alkaloids, we turned our attention to the installation of the D ring of our model by ring-closing metathesis (Scheme 4). Monoalkylation of the primary amine (**13a**) proved nontrivial, yielding mixtures including bisalkylated products 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 **14** 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 second 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.

(16) The major, trans diastereomer of **12**, corresponding to **13b**, appears to be more stable, based on semiempirical (AM1) ground-state calculations.

Scheme 4. Closure of D Ring



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Supporting Information Available. Experimental details and NMR spectra of all intermediates. These materials are available free of charge via the Internet at http://pubs.acs.org.