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Highly functionalized donor–acceptor cyclopropanes applied toward the synthesis of the *Melodinus* alkaloids

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Dedicated to Professor Harry H. Wasserman (1920–2013); a dear friend and mentor

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ABSTRACT

A series of highly substituted vinylcyclopropanes were prepared and examined as reaction partners in a palladium-catalyzed (3+2) cycloaddition with nitrostyrenes. Described herein are our efforts to synthesize an elusive 1,1-divinylcyclopropane by several distinct approaches, and to apply surrogates of this fragment toward the synthesis of the *Melodinus* alkaloids.

The *Melodinus* alkaloids are a class of dihydroquinolinone natural products related to the *Aspidosperma* alkaloids through an oxidative rearrangement of dehydrotabersonine (**1**, Scheme 1).[1,2] Despite their lack of known biological activity,[3,4] the structural complexity of the *Melodinus* alkaloids and the prospects of preparing non-natural derivatives for biological evaluation were both extremely appealing to our lab.

In the case of (+)-scandine (**3**),[1] (+)-meloscandonine (**4**),[5] and others,[6] three of the four contiguous stereocenters on the characteristic central cyclopentane ring are quaternary. To date, the only members of the family to have been synthesized are meloscine (**5**) and epimeloscine (**6**), both of which possess only two quaternary stereocenters on the central C ring.[7–9] It is hypothesized that (+)-scandine (**3**) is the biosynthetic precursor to the other *Melodinus* alkaloids.[2] Thus, we began to pursue the synthesis of scandine (**3**), which could allow access to the related dihydroquinolinone natural products.

In planning a concise synthesis, we chose to exploit elements of symmetry found within the target natural product. In particular, the quaternary stereocenter at C(20) bears two olefinic substituents, and C(16) bears two carbon substituents in the carboxylic acid oxidation state. Accordingly, after disconnection of the E ring via benzylic C–H insertion, we envisioned that the D and B rings of **7** could be formed by substrate-controlled diastereoselective ring-closing metathesis and lactamization steps of divinylcyclopentane **8** (Scheme 2). This intermediate could arise, in turn, from nitrocyclopentane **9**, the product of a transition metal catalyzed, intermolecular formal (3+2) cycloaddition between a *trans*-β-nitrostyrene (**10**) and divinylcyclopropane **11**.[10]

At the outset of our synthetic efforts, we examined several possible approaches toward the synthesis of the desired divinylcyclopropane (**11**, Scheme 3). The geminal vinyl groups could potentially be installed through substitution of 1,1-dihalocyclopropane **12**,[11] itself generated from a dihalocarbene **13** and methylidene dimethylmalonate (**14**).[12] Alternatively, the two vinyl groups could be formed by elimination from cyclopropane **15**, derived from the reaction of olefin **17** with a malonate-derived carbenoid (**16**). Finally, we envisioned utilizing an S_N2' displacement of alkylidene cyclopropane **18** with a vinyl nucleophile. This cyclopropane could be synthesized from allene **19**.

We first examined the use of a 1,1-dihalocyclopropane (e.g., **12**) toward divinylcyclopropane **11** (Pathway A, Scheme 3). The synthesis and reactions of these building blocks have been extensively researched.[12] 1,1-Dihalocyclopropanes are known to react with dialkyl cuprates,[13] trialkyl zincates,[14] manganates,[15] or magnesates[16] to yield alkylated cyclopropyl metals, which can react with

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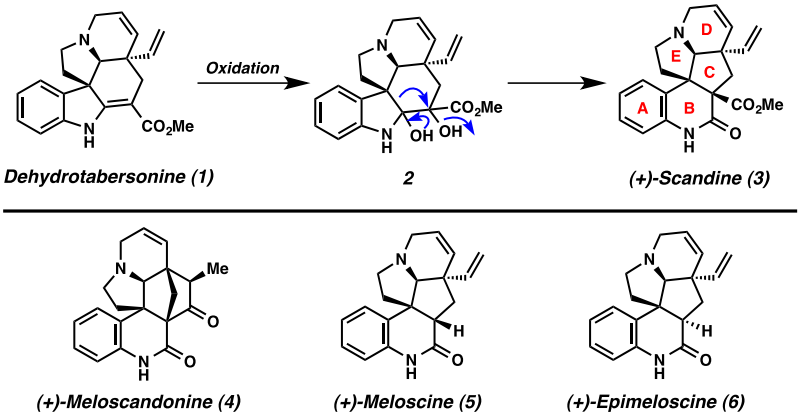
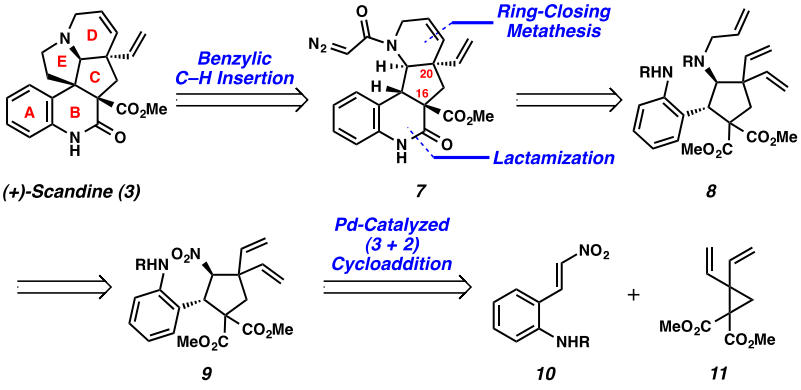
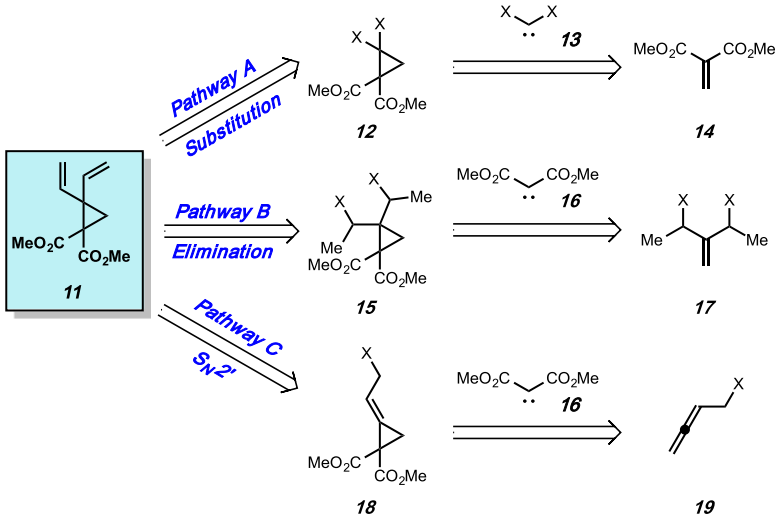


Scheme 1. Proposed biosynthesis of the *Melodinus* alkaloids.



Scheme 2. Retrosynthetic analysis of scandine (**3**).



Scheme 3. Retrosynthetic analyses of cyclopropane **11**.

an electrophile to deliver products with geminal substitution. Furthermore, the cyclopropyl metal intermediates can be used in metal-catalyzed cross-coupling reactions with vinyl halides to deliver vinylcyclopropanes.[15]

Due to the highly reactive nature of methylidene dimethylmalonate (**14**),[17] we sought to first examine the vinylation of *gem*-dihalocyclopropanes using a reduced substrate. Accordingly, acrylate derivative **20** was prepared by a known procedure and protected as a silyl ether (**21**, Scheme 4).[18] Olefin **21** was then cyclopropanated using phase-transfer catalysis to afford *gem*-dibromocyclopropane **22**.

Unfortunately, efforts to directly vinylate cyclopropane **22** failed (Scheme 5). A Stille coupling with tetravinyltin was unsuccessful, as was the palladium-catalyzed cross coupling of the in situ-generated organomanganate with vinyl bromide.[15b] An attempt at a bis-alkynylation using Sonogashira coupling was also