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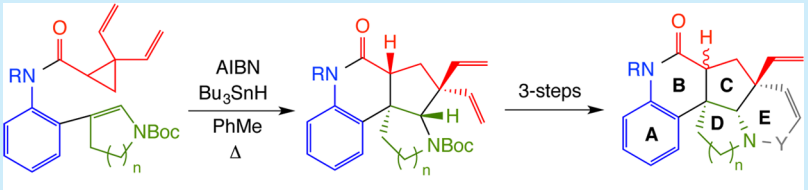
Radical [3 + 2]-Annulation of Divinylcyclopropanes: Rapid Synthesis of Complex Meloscine Analogs

Hanmo Zhang, Kyu Ok Jeon, E. Ben Hay, Steven J. Geib, Dennis P. Curran,* and Matthew G. LaPorte*

Department of Chemistry and Center for Chemical Methodology and Library Development, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

Supporting Information



ABSTRACT: A radical [3 + 2]-divinylcyclopropane annulation cascade has been extended to encompass five D-ring variants of the meloscine/epimeloscine core structure. Representative ABCD tetracyclic intermediates were further elaborated with novel substituted E-rings through subsequent transformations of advanced intermediates that provided opportunities for late-stage variation of the B-ring (lactam) *N*-substituents which were also developed.

The fascinating structures and powerful biological activities of natural products continue to inspire synthetic and medicinal chemists.[1] Recent cheminformatic analyses of natural products reveal increased structural diversity compared to typical commercial sample collections largely because the natural product samples contain more sp^3-hybridized carbon atoms.[2a−c] Accordingly, the construction of natural products and derivatives or natural product inspired libraries is an important goal.[2d]

It can be challenging to make core analogs of natural products like the members of the meloscine family shown in Figure 1.[3] To be suitable for analog preparation, syntheses of

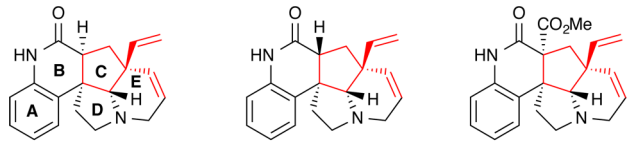
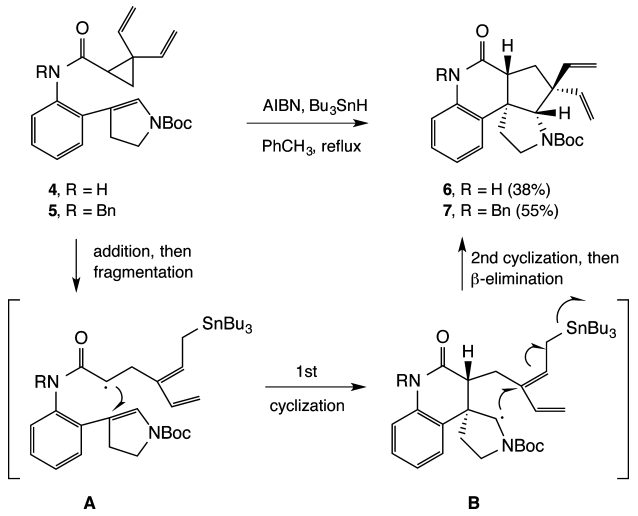


Figure 1. Structures of meloscine **1a**, epimeloscine **2s**, and scandine **3**.

such complex molecules need to be both short and flexible. The four interlocking B−E-rings with the central hexasubstituted cyclopentane C-ring poses a significant challenge. Methods to make complex cyclopentanes are often based on [3 + 2] cycloadditions to alkenes. These can involve 1,3-zwitterions or diradicals, or their equivalents.[4] Both transition-metal-catalyzed[5−11] and radical-mediated reactions of vinylcyclopropanes (VCPs) are also important.[12,13]

We have recently reported a short total synthesis of the pentacyclic alkaloid meloscine **1a** that featured a tandem [3 + 2] radical annulation reaction of a divinylcyclopropane (DVCP) to assemble the C-ring and the adjacent bonds (represented in red in Figure 1).[14−17] The two examples reported in that synthesis are shown in Scheme 1.[15] Radical cyclization of *sec*-amide **4** provided lactam **6** (R = H) in 38% yield while *tert*-amide **5** gave the corresponding lactam **7** (R = Bn) in 55% yield. Both products have the epimeloscine configuration at the BC-ring fusion.

Scheme 1. Divinylcyclopropane Cascade Cyclization with Likely Intermediates



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This transformation is believed to occur through addition of the tributyltin radical to one of the vinyl groups of **4** or **5**, followed by fragmentation of the cyclopropane ring to give radical **A**. A subsequent 6-*exo*-*trig*-cyclization gives tricyclic intermediate **B**, which in turn undergoes an *exo*-*trig* cyclization. Elimination of the starting tin radical then gives the final product **6** or **7**. The better yield afforded by **5** compared to **4** probably reflects amide rotamer differences.[15] Intermediate **6** is then converted to epimeloscine **2a** in only three steps followed by an epimerization to give meloscine **1a**.

We hypothesized that this synthesis anchored by the DVCP annulation would be short and flexible enough for opportunities to diversify the meloscine core at the B,D- and E-rings. The plan for making the desired analogs incorporates the four fragments **8**–**11** in Figure 2.

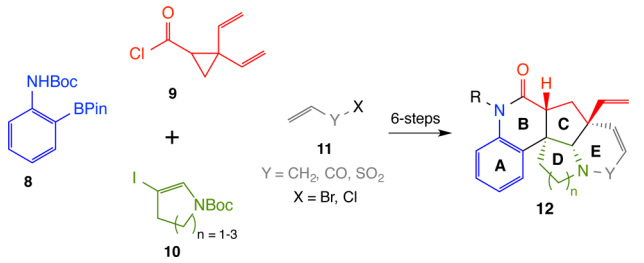


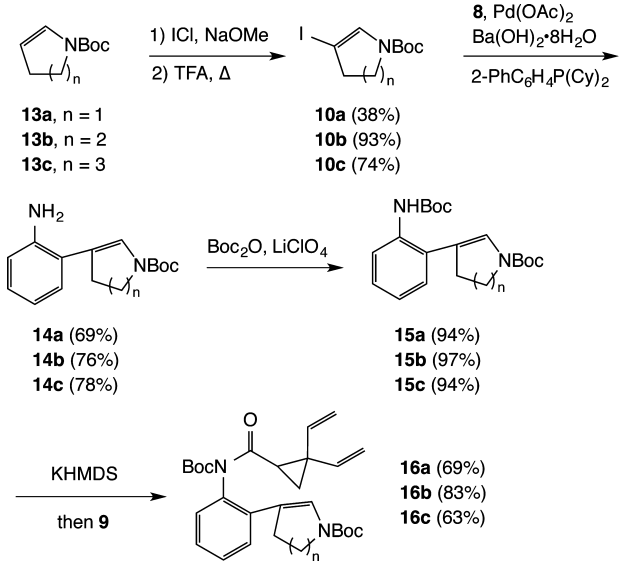
Figure 2. Fragments in the design of the pentacyclic analogs.

The variable fragments are alkenyl iodides **10** and late-stage electrophiles **11**, which provide access to various sized D-rings and differently functionalized E-rings, respectively. The invariant fragment **9** is the core of the DVCP annulation. The aniline fragment **8** is also constant with the selection of a *N*-Boc substituent to favor radical cyclization (due to amide conformation[15]) and to facilitate simultaneous protecting group removal of advanced intermediate **17**. In this manner, no additional steps are required for analog preparation and the *N*-substituent R on the B-ring of the final pentacycle **12** is conveniently varied through alkylations. Finally, if the radical annulation remains stereoselective providing the less-stable BC-fusion isomer, then the number of final analogs can potentially be doubled simply by adding end-game epimerizations.

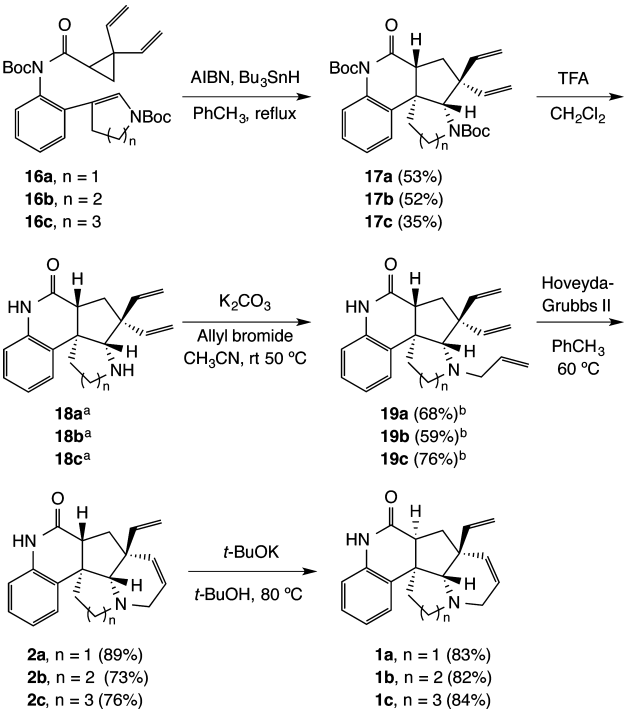
Scheme 2 shows the synthesis of annulation precursors **16a**–**c** with three different sized D-rings. To make the five-membered precursor **16a**, *N*-Boc-2,3-dihydro-1*H*-pyrrole **13a** was converted to vinyl iodide **10a** by reaction with ICl/NaOMe followed by exposure to TFA.[18] Palladium-catalyzed coupling of **10a** with boronic ester **8** provided aniline **14a** in 69% yield. Exposure of this aniline to Boc-anhydride gave *bis*-carbamate **15a** in 94% yield. Finally, acylation with acid chloride **9** provided the annulation precursor **16a**. The six- and seven-membered precursors **16b** and **16c** were assembled by similar reaction sequences in comparable yields.

Rapid syntheses of the six target pentacycles (**1**/**2a**–**c**) from **16a**–**c** are summarized in Scheme 3. Again illustrating with the five-membered D-ring series, slow addition of Bu_3SnH to **16a** in refluxing toluene provided **17a** in 53% yield. The *trans* BC-ring fusion was confirmed by removal of the two Boc groups with TFA to give **18a**, which is an intermediate in the prior meloscine synthesis.[15] Conversion of crude **18a** to allyl amine **19a** followed by RCM provided epimeloscine **2a** which was then epimerized to meloscine **1a** using *t*-BuOK.

Scheme 2. Synthesis of Annulation Precursors 16a–c



Scheme 3. Completion of the D-Ring Analog Synthesis



[a] crude product used directly in the next step. [b] Two-step yield.

Radical annulations of higher homologues **16b**,**c** also gave single isomers **17b**,**c** in 52% and 35% isolated yields.[19] Removal of the Boc groups, allylation (59% and 76% over two steps), and RCM (73% and 76%) provided the ring-expanded epimeloscines **2b**,**c**. Finally, epimerization of these two samples provided ring-expanded meloscines **1b**,**c** in 82% and 84% yield.

Assignment of the *trans* configurations of the products in the ring-expanded series followed from similarities in the NMR spectra of **18a**–**c**. (Spectra of **17a**–**c** have broadened resonances due to the Boc groups and were not instructive.) The *trans* BC fusion of **18b** was ultimately confirmed by X-ray crystallography (Figure 3).

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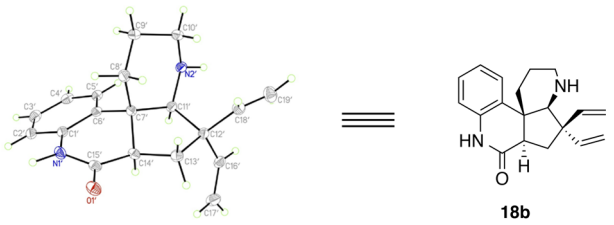
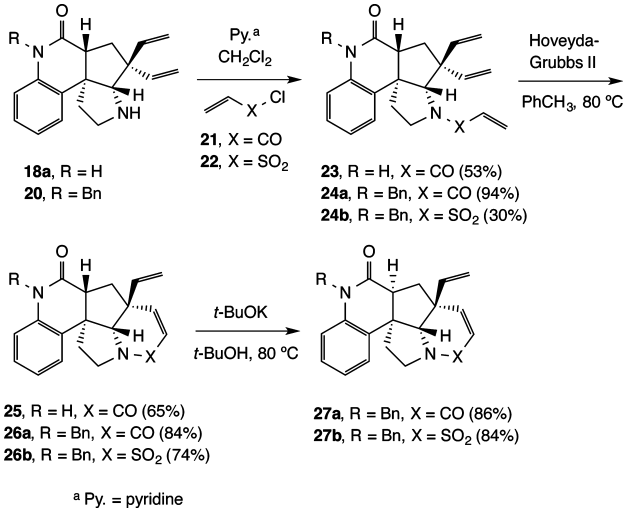


Figure 3. ORTEP structure of amine **18b**.

Overall, the short synthetic sequence to the pentacycles **1**/**2a**–**c** (4–5 steps from *N*-Boc DVCP intermediates **16a**–**c**) is reliable with comparable yields across the three series. The radical cyclizations were all selective for the epi-configuration, and epimerization of epimeloscine **2a** and its fused piperidine and homopiperidine D-ring congeners **2b**–**c** gave the corresponding meloscines **1a**–**c**.

We then explored the incorporation of additional diversity elements by synthesis of lactam and sultam E-ring analogs (Scheme 4). The pyrrolidine intermediates **18a** and **20** were

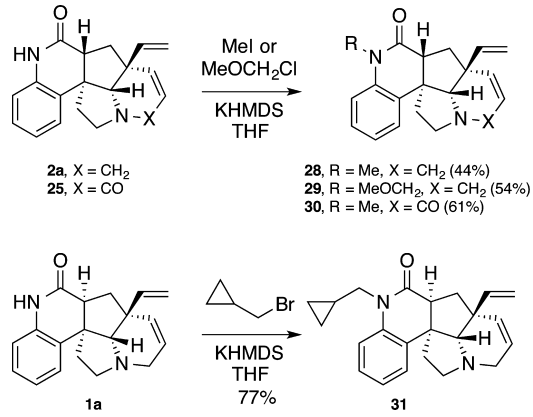
Scheme 4. Synthesis of E-Ring Analogs



acylated with **21** under standard conditions to give amides **23** and **24a** in 53% and 94% yields. Attempts to sulfonylate *sec*-amide **18a** with **22** were not successful, but the *N*-benzyl amide **20** gave the desired sulfonamide **24b** in 30% yield. Subsequent RCM reactions of these three precursors with the Hoveyda–Grubbs catalyst generated the E-ring lactams **25** and **26a** in 65% and 84% yield, while the E-ring sultam[20] **26b** was isolated in 74% yield. The *N*-benzyl epimeloscine analogs **26a,b** were epimerized to the new melsocine analogs **27a** and **27b** in 86% and 84% yield.

Although the primary focus of this work involved synthetic methodology scope, we were mindful that these alkaloid-like products are prime targets for biological screens as molecular probes or in other settings.[21] In this respect, meloscine is an attractive complex core because its molecular weight (292.4 g M^{-1}) and calculated log *P* (clog *P*, 2.2) are both relatively low.[22] Thus, the structure of meloscine can be varied significantly without high molecular weight or high lipophilicity limitations. The described methodology to both of the meloscine epimers provided further diversification opportunities via small alkyl B-ring lactam substitutions that would augment the overall lipophilicities (Table S1 in the Supporting Information shows selected calculated properties for all of the final products described herein). The treatment of lactams **1a**, **2a**, and **25** with potassium hexamethyldisilazane followed by the corresponding alkyl halides provided the *N*-alkylated derivatives **28**–**31** in moderate to good yields (Scheme 5).

Scheme 5. Synthesis of Substituted B-Ring Analogs



The molecular weights for the analogs range upward from 292.4 to 432.5 g M^{-1}, though most remain below 400 g M^{-1}. Calculated log P values span about 2 orders of magnitude from 2.2 to 4.2. These values are squarely within accepted ranges for biological screening.[22]

In summary, the recent synthesis of meloscine and epimeloscine[15] was expanded to include new ring sizes, ring types, and ring substituents. The radical [3 + 2]-annulation of various DVCP precursors provided the A–D tetracycles with various sized D-rings. This key reaction was reliably stereoselective and tolerant of several different *N*-substituents (H, Bn, Boc) that allowed for additional B-ring functionalizations of epimeloscine and meloscine. New lactam- and sultam-containing E-rings were made by straightforward conversions of common advanced intermediates. Products with the epimeloscine configuration were conveniently epimerized to the analogous meloscines. The work shows that the DVCP approach to the melsocines meets the brevity and flexibility requirements for making diverse analogs of meloscine.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: curran@pitt.edu.
*E-mail: mgl12@pitt.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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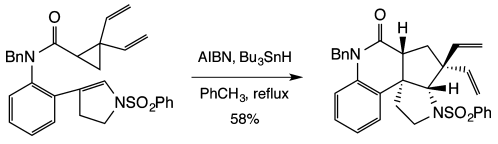
(19) The related *N*-benzyl-containing DVCP intermediate **C** with the pendant *N*-sulfonyl-dihydropyrrolidine also cyclizes in 58% yield. Although the *N*-sulfonyl group on **D** is difficult to remove, the result further shows the generality of the DVCP radical cascade.



C D

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(21) Samples of all the final products have been deposited in the UPitt CMLD Center library. For synthetic and biological probe aims of Chemical Methodology and Library Development Centers (CMLDs), see: http://www.nigms.nih.gov/Research/FeaturedPrograms/CMLD/.

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