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Epoxide Opening-Induced Tandem 8-Azabicyclo[3.2.1]octane to 6-Azabicyclo[3.2.1]octane Rearrangement−Iminium Allylation: Synthesis of (±)-Peduncularine

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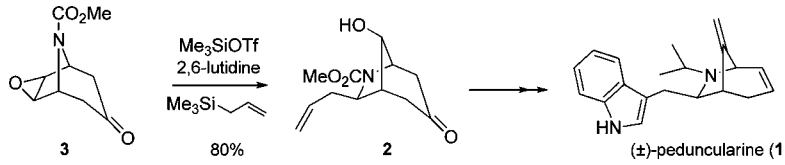
ABSTRACT



An efficient Lewis acid induced nitrogen-driven rearrangement iminium-trapping cascade from an epoxytropinone 3 gives a 7-allylated 6-azabicyclo[3.2.1]octan-3-one 2, which is converted into the alkaloid (±)-peduncularine (1).

(−)-Peduncularine (**1**) (Scheme 1), the first *Aristotelia* alkaloid isolated, was originally obtained from the Tasmanian shrub *A. peduncularis* and assigned by Bick and co-workers as an indole-pyrrolizidine in 1971;[1] degradative and more detailed spectroscopic studies led them to propose the correct structure in 1979.[2] Although its biosynthetic precursors are, in common with many indole alkaloids, considered to be tryptamine and a terpenoid unit,[3] peduncularine exhibits an unusual 6-azabicyclo[3.2.1]oct-3-ene core with a 7-*exo*-(indol-3-yl)methylene substituent and has proved a popular target for synthetic studies. Klaver, Hiemstra, and Speckamp reported the first synthesis of (−)-peduncularine in 1989, which unambiguously confirmed the structural reassignment;[4] however, stereochemistry at C-7 was not controlled. Four formal syntheses have subsequently appeared targeting intermediates in this route[5] with one, reported by Roberson and Woerpel, being later extended to a racemic total synthesis and which introduced the C-7 stereocenter will full control.[6] Kitamura and co-workers have recently reported another total synthesis of (±)-peduncularine.[7] A variety of strategies have been used in the above studies to form the bicyclic core of

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(2) Ros, H.-P.; Kyburz, R.; Preston, N. W.; Gallagher, R. T.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta* **1979**, *62*, 481–487.
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(4) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588–2595.
(5) (a) Rigby, J. H.; Meyer, J. H. *Synlett* **1999**, *S1*, 860–862. (b) Roberson, C. W.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 621–623. (c) Lin, X.; Stien, D.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 2333–2337. (d) Washburn, D. G.; Heidebrecht, R. W., Jr.; Martin, S. F. *Org. Lett.* **2003**, *5*, 3523–3525.
(6) Roberson, C. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 11342–11348.
(7) Kitamura, M.; Ihara, Y.; Uera, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1552–1560.

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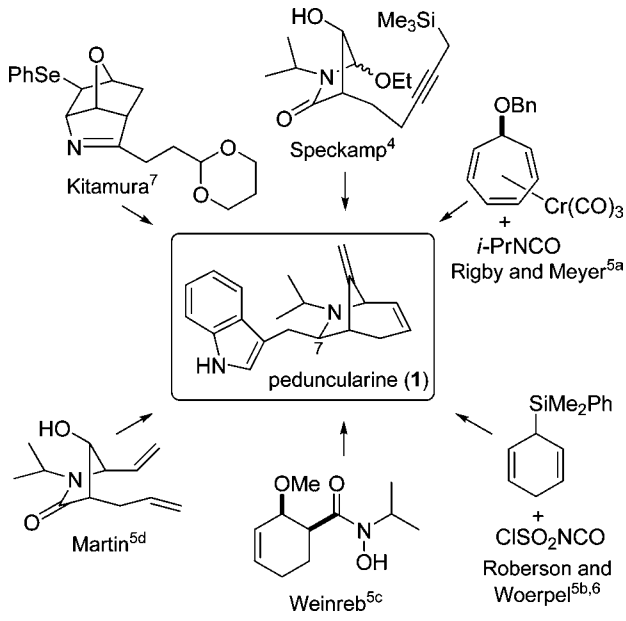
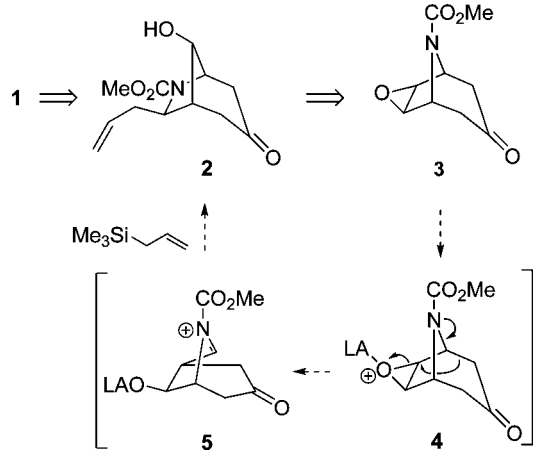
Scheme 1. Previous Approaches to Peduncularine (**1**)



peduncularine:[8] four approaches used ring closure onto an existing ring (Speckamp, Roberson and Woerpel, Weinreb, and Martin) (Scheme 1), whereas Rigby and Meyer utilized a [6 + 2] cycloaddition,[5a] and Kitamura formed and then fragmented a tricyclic intermediate.[7] In the present paper, we communicate a cascade rearrangement process to access a 7-allylated 6-azabicyclo[3.2.1]octan-3-one, which is subsequently converted to peduncularine.

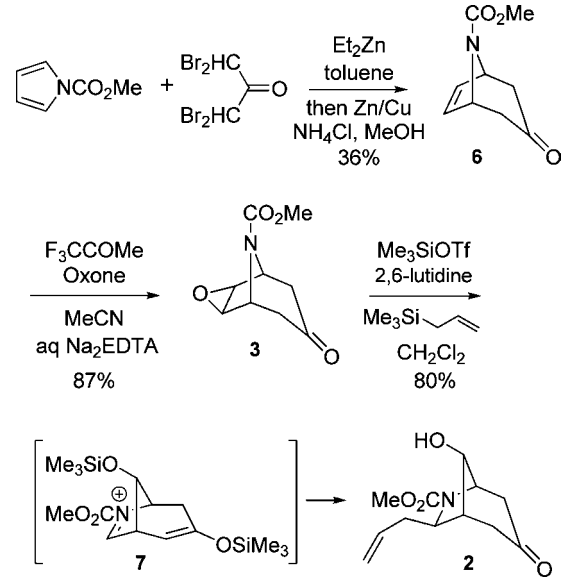
With the electrophile-induced rearrangement of 8-azabicyclo[3.2.1]octa-2,6-dienes to 6-azabicyclo[3.2.1]oct-2-enes reported by Davies and Cao in mind,[9] we envisaged that readily accessible epoxytropinone **3**[10] (Scheme 2) could undergo a Lewis acid assisted, nitrogen-driven (formal) 1,2-shift (shown in **4**) to generate intermediate iminium **5**. By analogy to the trapping of a related iminium in Roberson and Woerpel's total synthesis,[6] intermediate iminium **5** should be capable of interception by allyltrimethylsilane[11] to generate the 7-allylated 6-azabicyclo[3.2.1]octan-3-one **2**, possessing potentially suitable functionality for conversion to peduncularine.

Scheme 2. Strategy to Peduncularine



So as to examine the above strategy, epoxytropinone **3** was prepared following the procedure of Mann and de Almeida Barbosa[10] with slight modifications.[12] This chemistry involves [4 + 3] cycloaddition between commercially available *N*-methoxycarbonyl pyrrole[13] and 1,1,3,3-tetrabromoacetone[14] to provide 8-azabicyclo[3.2.1]oct-6-en-3-one **6** (36%), which was subsequently epoxidized with methyl(trifluoromethyl)dioxirane to give *exo*-epoxytropinone **3** (87%, Scheme 3). Pleasingly, we found that epoxytropinone **3**

Scheme 3. Synthesis and Rearrangement-Allylation of Epoxytropinone **3**



cleanly underwent the desired rearrangement-allylation to give 6-azabicyclo[3.2.1]octan-3-one **2** (80%) following reaction with TMSOTf (3 equiv), allyltrimethylsilane (1.1 equiv), and 2,6-lutidine (1.1 equiv) in CH_2Cl_2 at rt for 16 h (Scheme 3). Attempts to use cat. TMSOTf resulted in no reaction, whereas other variations to the above conditions (Lewis acid, solvent, temperature, reaction time) were detrimental to the yield. The *exo*-disposition of the allyl group was established by X-ray crystallographic analysis of a diol derived from reduction of ketone **2**.[12] Despite the presence of the *syn* oxy substitutent on the one-carbon bridge of the putative iminium **7**,[15] *exo*-face allylation appeared to be the sole reaction

(8) For other strategies to 6-azabicyclo[3.2.1]oct-3-enes, see: (a) Holmes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *Chem. Commun.* **1990**, 1412–1414. (b) Magnus, P.; Ródriguez-López, J.; Mulholland, K.; Matthews, I. *Tetrahedron* **1993**, *49*, 8059–8072. (c) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310–6311.

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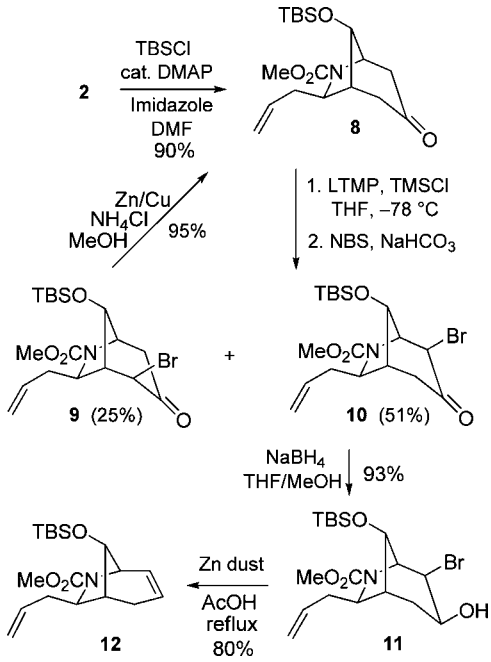
pathway; even on scale-up (using 8 g of epoxytropinone **3**) none of the *endo*-addition product was observed.

With the viability of the rearrangement-allylation of epoxytropinone **3** established, attention turned to the introduction of the endocyclic (C-3−C-4) double bond present in peduncularine. We considered that regioselective alkene installation in the desired sense should be possible using an enolization strategy with ketone **2**, due to a potential activating (acidifying) effect of the carbamate functionality. While several avenues based on this theme were investigated, the following sequence was developed to access endocyclic alkene **12** (Scheme 4). Bromination (NBS/$NaHCO_3$) of a

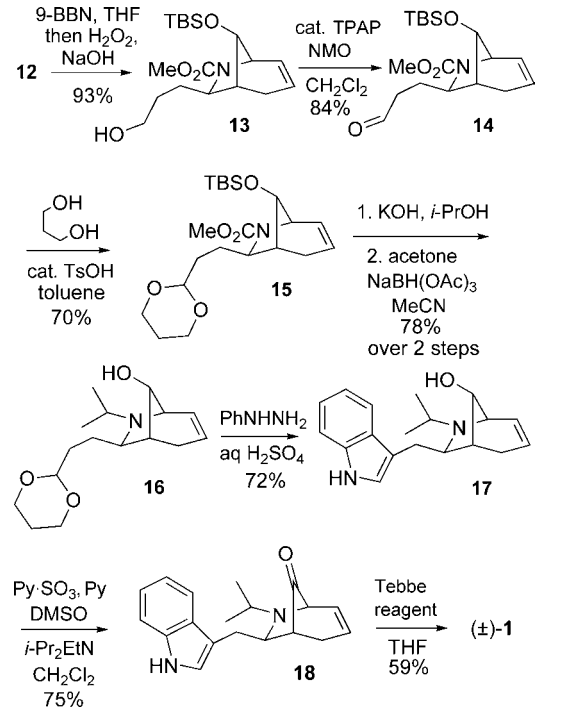
Scheme 4. Installation of the Endocyclic Alkene from Ketone **2**



regioisomeric mixture of crude silyl enol ethers, formed from TBS-protected ketone **8** using LTMP/Me_3SiCl, gave a chromatographically separable mixture of bromoketones **9** (25%) and **10** (51%). The undesired 2-bromoketone **9** could be easily debrominated with Zn/Cu couple to retrieve starting ketone **2** (95%) for reuse. Reduction of the 4-bromoketone **10** using $NaBH_4$ in MeOH/THF (1:1) at −78 °C followed by careful quenching with 1 M aq HCl at 0 °C gave a single bromohydrin **11** (93%, assigned as the di-*exo*-isomer on the basis of NOE studies[12] and a related reduction in our synthesis of ibogamine[16]). Bromohydrin **11** underwent a Boord-like elimination[17] using Zn dust in AcOH at reflux to give the desired endocyclic alkene **12** (80%); rupture of the bicyclic system arising from elimination toward the carbamate was not observed.

Indole construction from alkene **12** (Scheme 5) employed several transformations similar to those found in the later stages of Roberson and Woerpel's peduncularine synthesis; their route proceeded through an intermediate differing from alkene **12** at the one-carbon bridge (by virtue of a directly attached (and epimeric) dimethylphenylsilyl group) and with trimethylsilylethoxycarbonyl protection at nitrogen.[6] Hydroboration/oxidation of the terminal alkene present in alkene **12** gave alcohol **13** (95%), and the derived aldehyde **14**, formed (84%) using cat. TPAP/NMO, was converted into the corresponding 1,3-dioxane **15** (70%), the latter for protection during the next two steps and to potentially improve reaction efficiency in the following Fischer indole reaction.[18] Carbamate deprotection with concomitant desilylation of 1,3-dioxane **15** was achieved using KOH in refluxing *i*-PrOH to provide a crude amino alcohol,[19] which underwent reductive amination[20] to install the *N*-*i*-Pr group giving alcohol **16** (78% yield from 1,3-dioxane **15**).

Scheme 5. Completion of (±)-Peducularine Synthesis



(10) Mann, J.; de Almeida Barbosa, L.-C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 787–790.

(11) For recent reviews on *N*-acyl iminium chemistry, see: (a) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339–368. (b) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513–541.

(12) See Supporting Information for details.

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(14) Kim, H.; Hoffman, H. M. R. *Eur. J. Org. Chem.* **2000**, 2195–2220.

(15) Silylenol ether formation from the ketone functionality in epoxytropinone **3** would be reasonably anticipated under the reaction conditions used, and is likely−though not certain (see: Murata, S.; Suzuki, M.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 247–254)−to precede the rearrangement.

(16) Hodgson, D. M.; Galano, J.-M. *Org. Lett.* **2005**, *7*, 2221–2224.

(17) (a) Swallen, L. C.; Boord, C. E. *J. Am. Chem. Soc.* **1930**, *52*, 651–660. (b) For a review, see: Schlosser, M. In *Houben-Weyl: Methoden der organischen Chemie*; Thieme Verlag: Stuttgart, 1972; Vol. V/lb, pp 204−219.

(18) Bidylo, T. I.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2008**, *44*, 379–418.

Fischer indole synthesis[18,21] from alcohol **16** furnished indole **17** in 72% yield (Scheme 5). Indole **17** (epimeric at the hydroxyl to an intermediate in Roberson and Woerpel's synthesis)[6] was oxidized under modified Parikh−Doering conditions,[22] to give ketone **18** in 75% yield, completing a formal synthesis. The final methylenation step was repeated using freshly prepared Tebbe reagent,[23] which provided (±)-peduncularine in 59% yield (lit.[6] 56%) and with data fully consistent with that previously reported.[12]

In summary, a synthesis of (±)-peduncularine has been completed in 15 steps from commercially available materials. The key transformation is an efficient Lewis acid induced nitrogen-driven rearrangement iminium-trapping cascade from an easily accessible epoxytropinone **3** to give the more unusual 6-azabicyclo[3.2.1]octane system present in the alkaloid **1**. Studies to render the approach asymmetric, by enantioselective desymmetrization of the achiral epoxytropinone **3**, are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures for the preparation of new compounds and characterization data, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Extraction using 10% *i*-PrOH in $CHCl_3$ (*The Synthetic Organic Chemist's Companion*; Pirrung, M. C., Ed.; John Wiley & Sons: New York, 2007; p 109) was found to be essential to ensure a good recovery of the crude polar amino alcohol.

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