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# Application of a Raney-Cobalt-Mediated Tandem Reductive Cyclization Protocol to Total Syntheses of the *Aspidosperma* Alkaloids (±)-Limaspermidine and (±)-1-Acetylaspidoalbidine

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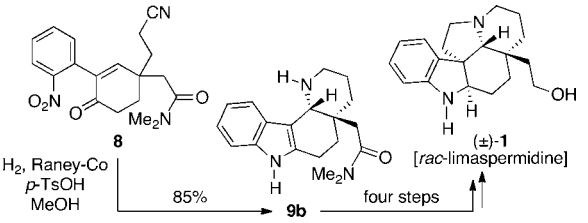
## ABSTRACT




**The racemic modification of the *Aspidosperma* alkaloid limaspermidine (1) has been prepared in ten steps including one involving a Raney-cobalt-mediated tandem reductive cyclization of nitrile 8 to give the tetracyclic system 9b. Compound (±)-1 has been converted over two steps into (±)-1-acetylaspidoalbidine [(±)-13].**

The natural product limaspermidine (**1**, Figure 1) was isolated from the trunk bark of the small tree *A. rhombeosignatum* MARKGRAF found growing in the Venezuelan Amazonas[1] and shown to be the C21-hydroxylated derivative of the more well-known alkaloid aspidospermidine.[2] The racemic modification of compound **1** was first described by Ban et al. in the mid-1970s[3] and served as an advanced intermediate in that group's landmark synthesis of (±)-fendleridine (**2**).[3,4] It also served as an advanced intermediate in Overman's 1991 synthesis of compound **2**.[5]

Our own interest in compound **1** and certain related systems stems from their potential to serve as precursors to a range of alkaloids including those of the aspidofractinine, kopsine, and vincadifformine series.[6] Accordingly, we now report a novel synthesis of it wherein the B- and D-rings are formed in a tandem reductive cyclization process that is mediated, in a remarkably chemo- and stereoselective fashion, by hydrogen in the presence of Raney-cobalt.[7]

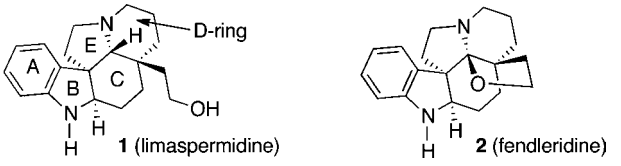



**Figure 1.** Structures of limaspermidine and fendleridine.

(1) Medina, J. D.; Di Genova, L. *Planta Med.* **1979**, *37*, 165.
(2) For details of the most recent synthesis of this alkaloid as well as useful background material, see: Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183.
(3) Honma, Y.; Ohnuma, T.; Ban, Y. *Heterocycles* **1976**, *5*, 47.
(4) For the second and enantioselective synthesis of this alkaloid, see: Campbell, E. L.; Zuhl, A. M.; Liu, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3009.
(5) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598.
(6) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 50, p 343.
(7) For previous applications of Raney-cobalt to the selective reduction of nitriles, see: (a) White, L. V.; Schwartz, B. D.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2011**, *76*, 6250 and references therein. (b) Kukula, P.; Studer, M.; Blaser, H.-U. *Adv. Synth. Catal.* **2004**, *346*, 1487.

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This work emphasizes the particularly effective manner in which this activated alloy can selectively bring about the reduction of nitrogen-containing functionalities, especially nitro and nitrile units, in the presence of other potentially reactive groups, especially ketones, alkenes, and enamines.

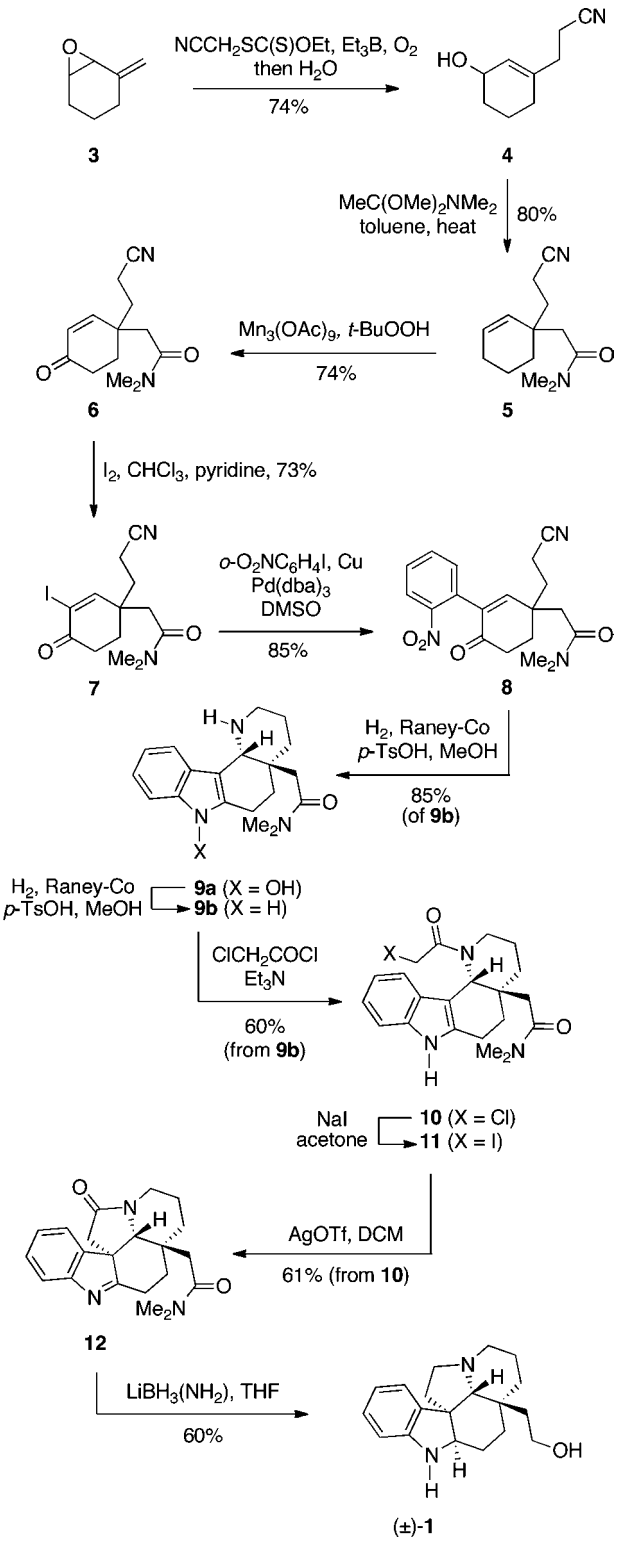
The reaction sequence leading to (±)-limaspermidine [(±)-**1**] is shown in Scheme 1 and starts with the alkenyl oxirane **3**, a compound that is easily prepared from 2-cyclohexenone via nucleophilic epoxidation and methylenation of the 7-oxabicyclo[4.1.0]heptan-2-one so-formed.[8] Treatment of substrate **3** with the readily available xanthate $NCCH_2SC(S)OEt$ in the presence of triethylborane and oxygen led, via a free-radical addition process,[9] to the 2-cyclohexen-1-ol **4** (74%) that engaged in an Eschenmoser–Claisen rearrangement[10] on treatment with the dimethylacetal of *N*,*N*-dimethylacetamide in refluxing toluene. The product cyclohexene-amide **5** (80%), now incorporating a quaternary carbon center, was subjected to allylic oxidation with manganese triacetate/*tert*-butylhydroperoxide under conditions reported by Shing et al.[11] The product 2-cyclohexen-1-one **6** (74%) was subjected to Johnson-type iodination,[12] and the resulting iodide **7** (73%) engaged in a Pd[0]-catalyzed Ullmann cross-coupling reaction[13] with *o*-nitroiodobenzene, thus providing the α-arylated cyclohexenone **8** (85%), the substrate required for the Raney-cobalt-mediated tandem reductive cyclization reaction.

In the pivotal step, compound **8** was exposed to a large excess of freshly prepared Raney-cobalt in MeOH with 5 mol equiv of *p*-TsOH at 40 °C. A chromatographically separable mixture of indole **9b** (85%) and its *N*-hydroxy counterpart **9a** (variable yields) was thereby obtained, and the structures of both of these products were established by single-crystal X-ray analyses.[14] The ORTEP derived from the latter analysis is shown in Figure 2. Resubjection of the compound **9a** to the reductive cyclization conditions resulted in the generation of additional quantities of congener **9b**, while running the original process at higher temperatures and/or for extended reaction times resulted in the exclusive formation of the former product (**9b**) in 85% yield.

There are several rather interesting features to the conversion **8** → **9b**. In particular, the exclusive formation of the *cis*-ring fused product **9b** over its (presumably) more stable *trans*-configured counterpart suggests that the cyclization event leading to D-ring formation is a kinetically controlled process. Furthermore, it appears that the cyclization process leading to B-ring formation proceeds, at least to some degree, through the hydroxylamine derived from reduction of the nitro group in substrate **8**.

With amide **9b** in hand the completion of the synthesis of (±)-limaspermidine (**1**) proved relatively straightforward. Thus, the former compound served as the substrate for an

**Scheme 1.** Total Synthesis of Limaspermidine [(±)-**1**]




(8) Welker, M.; Woodward, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 576.
(9) Charrier, N.; Gravestock, D.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 6520.
(10) Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162 and references therein.
(11) Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149.
(12) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1992**, *33*, 917.
(13) Banwell, M. G.; Jones, M. T.; Reekie, T. A. *Chemistry in New Zealand* **2011**, *75*, 122.
(14) CCDC 894937–894939 contain the crystallographic data for **1**, **9b**, and **9a**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

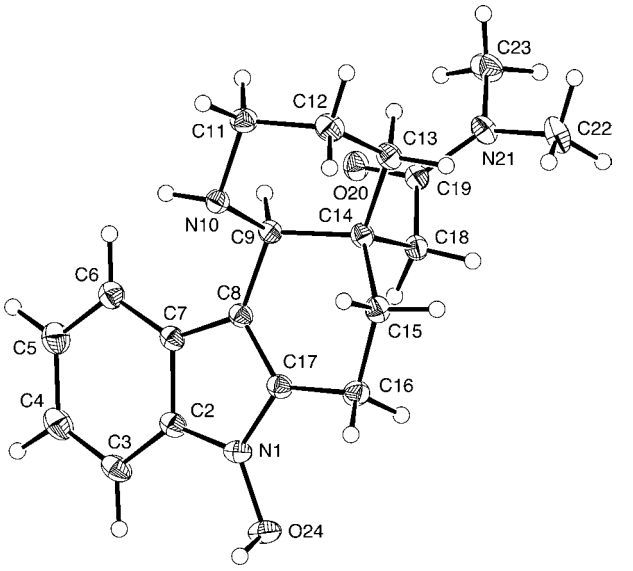
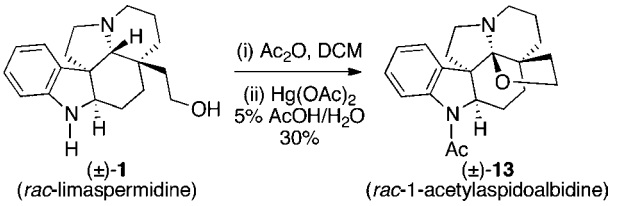



**Figure 2.** ORTEP derived from the single-crystal X-ray analysis of compound **9a** with labeling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

E-ring annulation protocol introduced by Toczko and Heathcock.[15] Specifically, amide **9b** was treated with α-chloroacetyl chloride in the presence of triethylamine, and the resulting acylated compound **10** (60%) was subjected to a Finkelstein reaction using sodium iodide in acetone, thus affording congener **11** that upon treatment with silver triflate in DCM produced the pentacyclic lactam **12** (61% from **10**). Finally, treatment of compound **12** with $LiBH_3(NH_2)$[16] in THF resulted in removal of the lactam carbonyl, reduction of the imine residue, and conversion of the amide into the corresponding primary alcohol to form (±)-limapermidine (**1**) in 60% yield. The $^1H$ and $^{13}C$ NMR spectral data obtained on this material matched those reported[5] by Overman et al., and its structure was secured by single-crystal X-ray analysis.[14]

Ban and co-workers have reported[3] that treatment of compound (±)-**1** with mercuric acetate in 5% acetic acid at 75 °C for 40−45 h provides (±)-fendleridine in an unspecified yield. Although we have been unable to reproduce this converison, when the readily derived 1-acetyllimaspermidine was treated under essentially the same conditions then the racemic modification, (±)-**13**, of the natural product 1-acetylaspidoalbidine (the *N*-acetyl derivative of fendleridine) was obtained in 30% yield (over two steps) (Scheme 2). The $^1H$ and $^{13}C$ NMR spectral data obtained on this material matched those reported by Boger et al.[4]

**Scheme 2.** Conversion of (±)-Limaspermidine [(±)-**1**] into (±)-1-Acetylaspidoalbidine [(±)-**13**]




The protocols reported here should be amenable to the enantioselective synthesis of either the (+)- or (−)-forms of the title alkaloids given the now ready availability of both (*S*,*S*)- and (*R*,*R*)-7-oxabicyclo[4.1.0]heptan-2-one[17] and the capacity of the Eschenmoser−Claisen reaction to faithfully convert, in a predictable manner, chiral nonracemic allylic alcohols into the corresponding γ,δ-unsaturated amides.[10]

Efforts are also underway to identify reaction conditions whereby compound **8** can be engaged in a reductive cyclization process that affords the *trans*-ring-fused isomer of compound **9b** since such a system could serve as a precursor to kopsihainananines A and B, two unusual alkaloids recently isolated from *Kopsia hainanensis*.[18] Details of the outcomes of such studies will be reported in due course.

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**Supporting Information Available.** Full experimental procedures; data derived from the single-crystal X-ray analyses of compounds **1**, **9a**, and **9b**; anisotropic displacement ellipsoid plots for compounds **1** and **9b**; and $^1H$ and $^{13}C$ NMR spectra of compounds (±)-**1** and **4**−(±)-**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(15) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642.
(16) Pasumansky, L; Goralski, C. T.; Singaram, B. *Org. Process Res. Dev.* **2006**, *10*, 959.
(17) See, for example: (a) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070. (b) Jiang, H.; Holub, N.; Jørgensen, K. A. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20630. (c) Lu, Y.; Zheng, C.; Yang, Y.; Zhao, G.; Zou, G. *Adv. Synth. Catal.* **2011**, *353*, 3129.
(18) Chen, J.; Chen, J.-J.; Yao, X.; Gao, K. *Org. Biomol. Chem.* **2011**, *9*, 5334.