

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

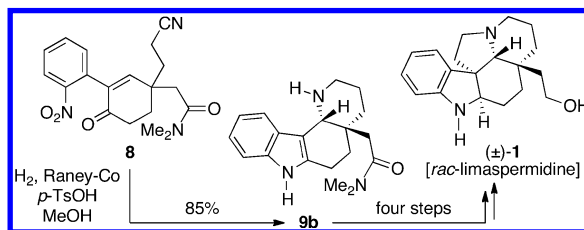
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ABSTRACT



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-acetylaspidobalbidine [(±)-**13**].

The natural product limaspermidine (**1**, Figure 1) was isolated from the trunk bark of the small tree *A. rhombosignatum* MARKGRAF found growing in the Venezuelan Amazonas¹ 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-1970s³ 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,

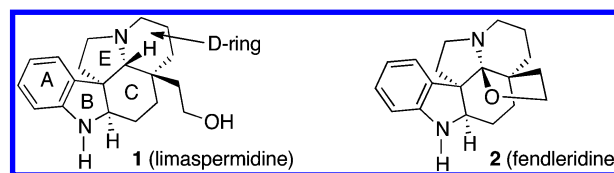


Figure 1. Structures of limaspermidine and fendleridine.

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

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(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.

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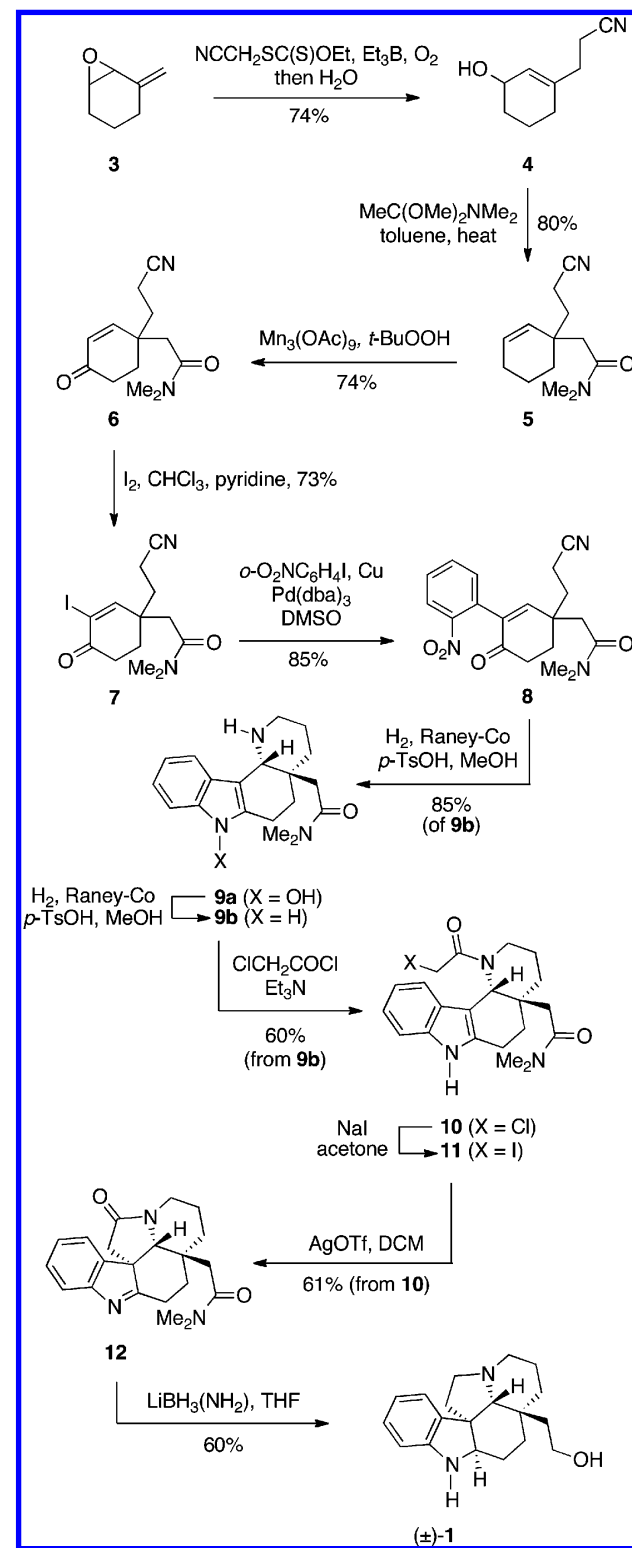
This work emphasizes the particularly effective manner in which this activated alloy can selectively bring about the reduction of nitrogen-containing functionalities, especially nitro and nitrile units, in the presence of other potentially reactive groups, especially ketones, alkenes, and enamines.

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 methylation of the 7-oxabicyclo[4.1.0]heptan-2-one so-formed.⁸ Treatment of substrate **3** with the readily available xanthate NCCH₂SC(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 rearrangement¹⁰ 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 reaction¹³ 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

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



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

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(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.

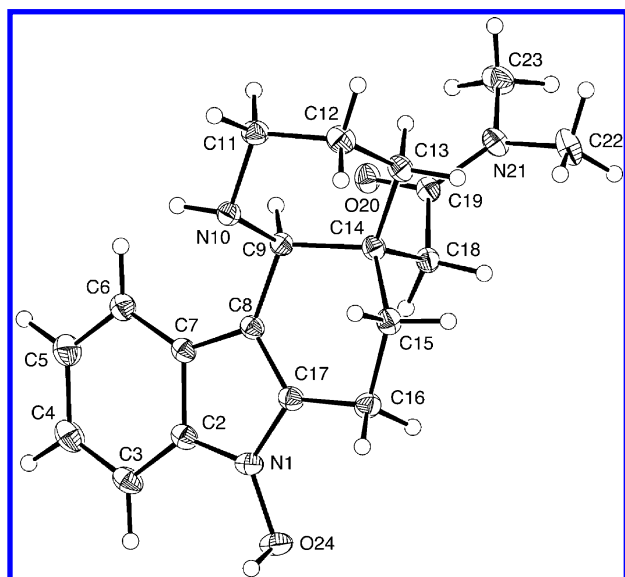
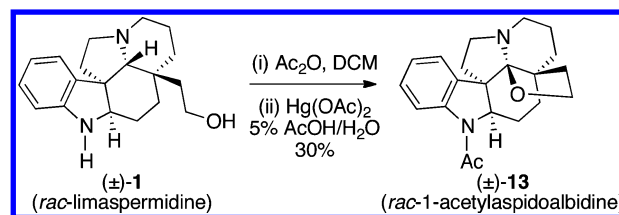


Figure 2. ORTEP derived from the single-crystal X-ray analysis of compound **9a** with labeling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

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 $\text{LiBH}_3(\text{NH}_2)$ 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 (\pm)-limapermidine (**1**) in 60% yield. The ^1H and ^{13}C NMR spectral data obtained on this material matched those reported⁵ by Overman et al., and its structure was secured by single-crystal X-ray analysis.¹⁴

Ban and co-workers have reported³ that treatment of compound (\pm)-**1** with mercuric acetate in 5% acetic acid at 75 °C for 40–45 h provides (\pm)-fendleridine in an

Scheme 2. Conversion of (\pm)-Limaspermidine [(\pm)-**1**] into (\pm)-1-Acetylaspidobaldine [(\pm)-**13**]



unspecified yield. Although we have been unable to reproduce this conversion, when the readily derived 1-acetyl-limaspermidine was treated under essentially the same conditions then the racemic modification, (\pm)-**13**, of the natural product 1-acetylaspidobaldine (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

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-one¹⁷ and the capacity of the Eschenmoser–Claisen reaction to faithfully convert, in a predictable manner, chiral non-racemic 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 kopsihainanines 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 (\pm)-**1** and **4**–(\pm)-**13**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

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