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Enantioselective Synthesis of (–)-Vallesine: Late-stage C17-Oxidation via Complex Indole Boronation

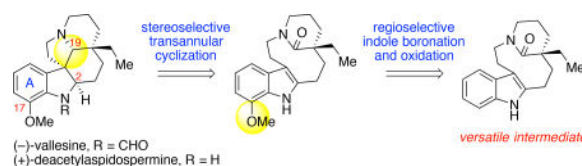
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Abstract

The first enantioselective total synthesis of (–)-vallesine via a strategy that features a late-stage regioselective C17-oxidation, followed by a highly stereoselective transannular cyclization is reported. The versatility of this approach is highlighted by divergent synthesis of the archetypal alkaloid of this family, (+)-aspidospermidine, and an A-ring oxygenated derivative (+)-deacetylaspidospermidine, the precursor to (–)-vallesine, from a common intermediate.

Graphical abstract



The aspidosperma alkaloids, a family containing over 250 structurally diverse members, have been a subject of significant interest over several decades due to their structural complexity and diverse biological activity.^{1,2} The development of a unified strategy to access this diverse family of natural products is critical to enabling access to a multitude of these alkaloids for comprehensive chemical and biological studies. Our group has pursued a unified strategy to allow diversification of complex intermediates, en route to various members of this alkaloids family.³ One intriguing subset of the aspidosperma alkaloids is those which contain C17-oxidation, including the antiplasmodial alkaloid (–)-vallesine (**1**, Figure 1),⁴ (–)-aspidospermidine (**2**),⁵ and (+)-deacetylaspidospermidine (**3**).⁶ Related compounds include the C21-oxygenated variants (+)-haplocidine (**5**)⁷ and (–)-cylindrocarpidine (**6**).⁸ Recently, we reported the first total synthesis of (+)-haplocidine (**5**) through a strategy that employs highly stereoselective cyclization events and regioselective late-stage A-ring functionalization.^{3e} This strategy relies on the in situ masking of the C9-amine via opening of the C19-hemiaminal to form an iminium ion, which is subject to directed, palladium-catalyzed *ortho*-C–H-acetoxylation of the aspidosperma indoline core.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectroscopic data, and NMR spectra (PDF).

The authors declare no competing financial interest.

While this strategy provided direct access to oxidized members of the fendleridine subfamily, it is not a viable approach for (–)-vallesine (**1**) and related alkaloids without C21-oxidation. We therefore sought a strategy toward these alkaloids as part of our interest in biogenetically inspired late-stage arene oxidation of aspidosperma alkaloids. Herein, we describe the first total synthesis of (–)-vallesine (**1**) based on a late-stage regioselective complex indole boronation strategy. This strategy provides access to both (+)-deacetylaspidospermine (**3**) and (+)-aspidospermidine (**4**) from a common advanced intermediate.

While aspidospermine (**2**)^{9,10} has served as an archetypal target for C17-oxidized aspidosperma alkaloids, most current synthetic routes rely on a late-stage Fischer indole synthesis utilizing 2-methoxyphenylhydrazine.^{9a} Recent advances include the synthesis of (–)-aspidospermine (**2**) through an intramolecular cycloaddition cascade strategy,^{10b} and the palladium-catalyzed decarboxylative asymmetric allylation approach toward (+)-aspidospermine (**2**).^{10c} The reliance on introducing C17-oxidation from commercial materials is a shared concept in all prior approaches to aspidospermine (**2**). We identified an opportunity to apply a strategy for regioselective indole boronation^{11,12} to offer a new opportunity for diversification of key intermediates en route to aspidosperma alkaloids.

Our retrosynthetic analysis of the C17-oxidized aspidosperma alkaloids is illustrated in Scheme 1, wherein we envisioned (–)-vallesine (**1**) to arise from N1-formylation of (+)-deacetylaspidospermine (**3**). Informed by our studies of transannular cyclization via amide activation^{3c,d} and key prior contributions,¹³ we envisioned (+)-deacetylaspidospermine (**3**) to arise from lactam **7**. The necessary oxidation state at C17 would be introduced via regioselective boronation of indole **10**, a compound related to intermediates that we have employed in syntheses of other aspidosperma alkaloids without A-ring oxygenation.^{3c}

Consistent with our interest in functionalization of complex indole-derived compounds and inspired by advances in Ir-catalyzed boronation of various arenes,¹² our group has reported a direct and scalable method for the one-pot conversion of C3-alkylindoles, including tryptophans and tryptamines, to the corresponding C7-boronated compounds (Scheme 2A).¹¹ Central to this strategy was a diboronation/protodeboronation sequence that took advantage of the increased nucleophilicity and basicity of the C2 position of the C3-substituted indoles. Related advances include the regioselective C6-boronation of tryptophan derivatives, wherein a triisopropylsilyl blocking group influences the regiochemical outcome.¹⁴ In our planned boronation strategy to C17-oxygenated aspidosperma alkaloids, the synthetic intermediate **10** contains a disubstituted indole,^{3c,e-f} possibly allowing a direct regioselective C17-boronation (Scheme 2B).^{12c,e-f}

We have previously demonstrated the synthesis of lactam (+)-**8** in >99% ee via an asymmetric alkylation strategy^{3c} utilizing the synthetic (+)-(1*R*,2*R*)-pseudoephedrine chiral auxiliary, prepared in four steps from commercial materials.¹⁵ For the purposes of this study, we required lactam (–)-**8**, which we chose to synthesize through a parallel strategy utilizing the commercially available (+)-(1*S*,2*S*)-pseudoephedrine chiral auxiliary^{3a} to provide lactam (–)-**8** in 80% ee.¹⁶ In order to access the indole substrate for the planned boronation, we conducted removal of the N1-*para*-methoxybenzyl group from lactam (–)-**8**

under Birch reductive conditions using sodium metal in liquid ammonia to afford lactam **9** in 91% yield (Scheme 3), followed by hydrogenation to afford indole **10** in 99% yield. Importantly, complete and regioselective boronation of indole **10** was accomplished using $[\text{Ir}(\text{cod})\text{OMe}]_2$ and pinacolborane to provide boronic ester **11**, which was then subjected to oxidation using a solution of aqueous hydroxylamine to provide phenol **12** in 31% yield over two steps (Scheme 3).

Next, we required optimal conditions for transannular cyclization to secure the pentacyclic aspidosperma core of (–)-vallesine (**1**). While we have previously promoted transannular cyclization of lactam (–)-**8** through an electrophilic amide activation strategy to enable access to the corresponding C19-iminium ion for further derivatization,³ we envisioned a partial reduction strategy would be more effective in conversion of intermediate **12** to alkaloid (–)-**1**. Inspired by seminal reports¹³ using lithium aluminum hydride for the partial reduction of related lactams, we chose the milder diisobutylaluminum hydride to enable direct, efficient formation of imine **13** from lactam **10** as a model substrate for the projected cyclization en route to (–)-vallesine (**1**). The intermediate imine **13** was reduced using lithium aluminum hydride to afford (+)-aspidospermidine (**4**)^{2,3c} in 77% yield over two steps from lactam **10** (Scheme 4).

With the optimized conditions for reductive transannular cyclization in hand, we evaluated their application to the requisite C17-oxygenated aspidosperma intermediate. Methylation of phenol **12** with iodomethane in the presence of cesium carbonate afforded C17-methyl ether **7** in 98% yield as the optimal substrate for transannular cyclization (Scheme 5). In the event, exposure of lactam **7** to diisobutylaluminum hydride led to transannular cyclization, and the resultant imine was reduced using lithium aluminum hydride to afford (+)-deacetylaspidospermine (**3**) in 55% yield over two steps. All spectroscopic data for (+)-deacetylaspidospermine (**3**) were consistent with the literature reports.^{6,10d} The optical rotation data for alkaloid (+)-**3** (observed $[\alpha]_{\text{D}}^{24} = +25$ ($c = 0.83$, CHCl_3); lit. $[\alpha]_{\text{D}} = +3$ (CHCl_3)^{6c} and $[\alpha]_{\text{D}} = +8$ (MeOH)^{6f} and $[\alpha]_{\text{D}}^{25} = +4.7$ ($c = 1.0$ CHCl_3)^{10d}) indicated the correct sign with an increased magnitude as compared to the literature reports.¹⁶ Furthermore, completion of the first total synthesis of (–)-vallesine (**1**) was achieved via formylation of (+)-deacetylaspidospermine (**3**) using acetic anhydride in formic acid to afford alkaloid (–)-**1** in 87% yield. All spectroscopic data, as well as the optical rotation data, for (–)-vallesine (**1**, observed $[\alpha]_{\text{D}}^{24} = -71$ ($c = 0.71$, CHCl_3); lit. $[\alpha]_{\text{D}} = -91$ ($c = 1$, CHCl_3)^{4b}) were consistent with the literature reports.^{4,6f,16}

We describe the first total synthesis of (–)-vallesine (**1**) based on a strategy involving late-stage regioselective complex indole boronation, followed by transannular cyclization. This strategy uniquely offers access to both (+)-deacetylaspidospermine (**3**) and (+)-aspidospermidine (**4**), representing A-ring oxidized and nonoxidized aspidosperma alkaloids, respectively, from a common intermediate. This approach not only removes the need for reliance on starting material to introduce the C17-oxidation found in a subset of aspidosperma alkaloids, but it also serves as the first example of boronation chemistry to secure the C17-oxygenation in these alkaloids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

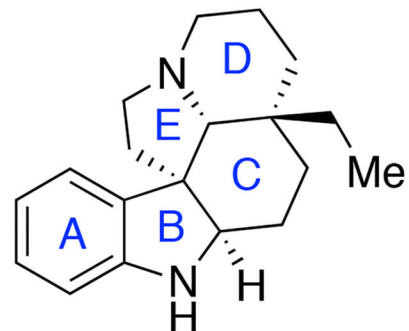
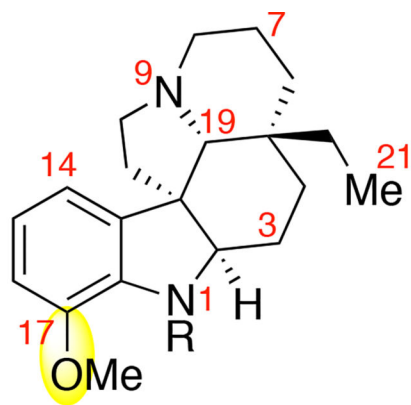
Acknowledgments

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References

1. (a) Saxton, JE. Alkaloids of the Aspidospermine Group. The Alkaloids, Chemistry and Biology. Cordell, GA., editor. Vol. 51. Academic Press; San Diego: 1998. p. 1-197.(b) O'Connor, SE. Alkaloids. In: Mander, L., Liu, H-W., editors. Comprehensive Natural Products II. Vol. 1. Elsevier; Amsterdam: 2010. p. 977-1007.
2. For a review of aspidosperma alkaloids synthesis, see: Lopchuk JM. Prog. Heterocycl. Chem. 2011; 23:1. For selected total syntheses of aspidosperma alkaloids, see: Harley-Mason J, Kaplan M. Chem. Commun. 1967; 18:915. Kutney JP, Abdurahman N, Gletsos C, Le Quesne P, Piers E, Vlattas I. J. Am. Chem. Soc. 1970; 92:1727. [PubMed: 5418453] Ban Y, Yoshida K, Goto J, Oishi T. J. Am. Chem. Soc. 1981; 103:6990. Gallagher T, Magnus P, Huffman J. J. Am. Chem. Soc. 1982; 104:1140. Ban Y, Yoshida K, Goto J, Oishi T, Takeda E. Tetrahedron. 1983; 39:3657. Node M, Nagasawa H, Fuji K. J. Am. Chem. Soc. 1987; 109:7901. Node M, Nagasawa H, Fuji K. J. Org. Chem. 1990; 55:517. Kozmin SA, Iwama T, Huang Y, Rawal VH. J. Am. Chem. Soc. 2002; 124:4628. [PubMed: 11971711] Jones SB, Simmons B, Mastracchio A, MacMillan DWC. Nature. 2011; 475:183. [PubMed: 21753848] Zhao S, Andrade RB. J. Am. Chem. Soc. 2013; 135:13334. [PubMed: 23971538] Wagnières O, Xu Z, Wang Q, Zhu J. J. Am. Chem. Soc. 2014; 136:15102. [PubMed: 25270053]
3. (a) Medley JW, Movassaghi M. Angew. Chem. Int. Ed. 2012; 51:4572.(b) Medley JW, Movassaghi M. Org. Lett. 2013; 15:3614. [PubMed: 23829389] (c) Mewald M, Medley JW, Movassaghi M. Angew. Chem. Int. Ed. 2014; 53:11634.(d) White KL, Mewald M, Movassaghi M. J. Org. Chem. 2015; 80:7403. [PubMed: 26166404] (e) White KL, Movassaghi M. J. Am. Chem. Soc. 2016; 138:11383. [PubMed: 27510728] (f) Kang T, White KL, Mann TJ, Hoveyda AH, Movassaghi M. Angew. Chem. Int. Ed. 2017; 56:13857.
4. (a) Holker JSE, Cais M, Hochstein FA, Djerassi C. J. Org. Chem. 1959; 24:314.(b) Zèches M, Mesbah K, Richard B, Moretti C, Nuzillard JM, Le Men-Olivier L. Planta Med. 1995; 61:89. [PubMed: 17238065] (c) Mitaine-Offer AC, Sauvain M, Valentin A, Callapa J, Mallié M, Zèches-Hanrot M. Phytomedicine. 2002; 9:142. [PubMed: 11995947]
5. (a) Mills JFD, Nyburg SC. Tetrahedron Lett. 1959; 11:1.(b) Conroy H, Brook PR, Amiel Y. Tetrahedron Lett. 1959; 11:4.(c) Lyon RL, Fong HHS, Farnsworth NR, Svoboda GH. J. Pharm. Sci. 1973; 62:218. [PubMed: 4686392] (d) Craveiro AA, Matos FJA, Serur LM. Phytochemistry. 1983; 22:1526.(e) Deutsch HF, Evenson MA, Drescher P, Sparwasser C, Madsen PO. J. Pharm. Biomed. Anal. 1994; 12:1283. [PubMed: 7841224]
6. (a) Ewins AJ. J. Chem. Soc. Trans. 1914; 105:2738.(b) Biemann K, Spiteller-Friedmann M, Spiteller G. J. Am. Chem. Soc. 1963; 85:631.(c) McLean S. Can. J. Chem. 1964; 42:191.(d) Walser A, Djerassi C. Helv. Chim. Acta. 1965; 48:391.(e) Klyne W, Swan RJ, Bycroft BW, Schumann D, Schmid H. Helv. Chim. Acta. 1965; 48:443.(f) Laguna A, Dolejs L, Novotny L. Coll. Czech. Chem. Commun. 1980; 45:1419.(g) Erra-Balsells R. Phytochem. 1988; 27:3945.
7. (a) Cava MP, Talapatra SK, Nomura K, Weisbach JA, Douglas B, Shoop EC. Chem. Ind. 1963:1242. (b) Cava MP, Nomura K, Talapatra SK. Tetrahedron. 1964; 20:581.(c) Dastoor NJ, Gorman AA, Schmid H. Helv. Chim. Acta. 1967; 50:213. [PubMed: 5593208]
8. (a) Saxton JE, Smith AJ, Lawton G. Tetrahedron Lett. 1975; 16:4161.(b) Lawton G, Saxton JE, Smith AJ. Tetrahedron. 1977; 33:1641.

9. For syntheses of (\pm)-aspidospermine, see: Stork G, Dolfini JE. *J. Am. Chem. Soc.* 1963; 85:2872. Ban Y, Sato Y, Inoue I, Nagai M, Oishi T, Terashima M, Yonemitsu O, Kanaoka Y. *Tetrahedron Lett.* 1965; 27:2261. Kuehne ME, Bayha C. *Tetrahedron Lett.* 1966; 12:1311. Pearson AJ. *Tetrahedron Lett.* 1981; 22:4033. Coldham I, Burrell AJM, White LE, Adams H, Oram N. *Angew. Chem. Int. Ed.* 2007; 46:6159.
10. For syntheses of enantioenriched aspidospermine, see: Fukuda Y, Shindo M, Shishido K. *Org. Lett.* 2003; 5:749. [PubMed: 12605506] Lajiness JP, Jiang W, Boger DL. *Org. Lett.* 2012; 14:2078. [PubMed: 22480368] Shen X-L, Zhao R-R, Mo M-J, Peng F-Z, Zhang H-B, Shao Z-H. *J. Org. Chem.* 2014; 79:2473. [PubMed: 24559389] Wang N, Du S, Li D, Jiang X. *Org. Lett.* 2017; 19:3167. [PubMed: 28570070]
11. (a) Loach RP, Fenton OS, Amaike K, Siegel DS, Ozkal E, Movassaghi M. *J. Org. Chem.* 2014; 79:11254. [PubMed: 25343326] (b) Amaike K, Loach RP, Movassaghi M. *Org. Synth.* 2015; 92:373. [PubMed: 26839440]
12. (a) Takagi J, Sato K, Hartwig JF, Ishiyama T, Miyaura N. *Tetrahedron Lett.* 2002; 43:5649. (b) Ishiyama T, Takagi J, Yonekawa Y, Hartwig JF, Miyaura N. *Adv. Synth. Catal.* 2003; 345:1103. (c) Paul S, Chotana GA, Holmes D, Reichle RC, Maleczka RE Jr, Smith MR III. *J. Am. Chem. Soc.* 2006; 128:15552. [PubMed: 17147340] (d) Kallepalli VA, Shi F, Paul S, Onyeozili EN, Maleczka RE Jr, Smith MR III. *J. Org. Chem.* 2009; 74:9199. [PubMed: 19894699] (e) Robbins DW, Boebel TA, Hartwig JF. *J. Am. Chem. Soc.* 2010; 132:4068. [PubMed: 20199022] (f) Meyer FM, Liras S, Guzman-Perez A, Perreault C, Bian J, James K. *Org. Lett.* 2010; 12:3870. [PubMed: 20695449] (g) Liskey CW, Hartwig JF. *Synthesis.* 2013; 45:1837. (h) Zhou S, Jia Y. *Org. Lett.* 2014; 16:3416. [PubMed: 24885528] (i) Sadler SA, Tajuddin H, Mkhaliid IAI, Batsanov AS, Blakemore DC, Lin Z, Marder TB, Steel PG. *Org. Biomol. Chem.* 2014; 12:7318. [PubMed: 25116330] (j) Homer JA, Sperry J. *Tetrahedron Lett.* 2014; 55:5798. (k) Eastbrook AS, Wang C, Davison EK, Sperry J. *J. Org. Chem.* 2015; 80:1006. [PubMed: 25525818]
13. (a) Kutney JP, Piers E, Brown RT. *J. Am. Chem. Soc.* 1970; 92:1700. [PubMed: 5418449] (b) Ban Y, Yoshida K, Goto J, Oishi T. *J. Am. Chem. Soc.* 1981; 103:6990. (c) Yoshida K, Sakuma Y, Ban Y. *Heterocycles.* 1987; 25:47.
14. Feng Y, Holte D, Zoller J, Umemiya S, Simke LR, Baran PS. *J. Am. Chem. Soc.* 2015; 137:10160. [PubMed: 26256033]
15. Morales MR, Mellem KT, Myers AG. *Angew. Chem. Int. Ed.* 2012; 51:4568.
16. Please see the Supporting Information for further details.

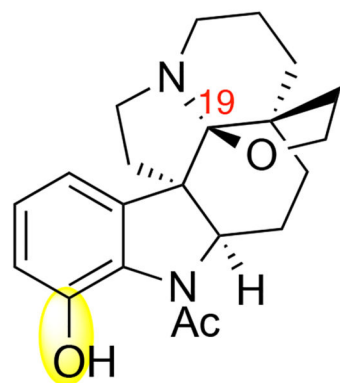


(-)-vallesine (**1**), R = CHO

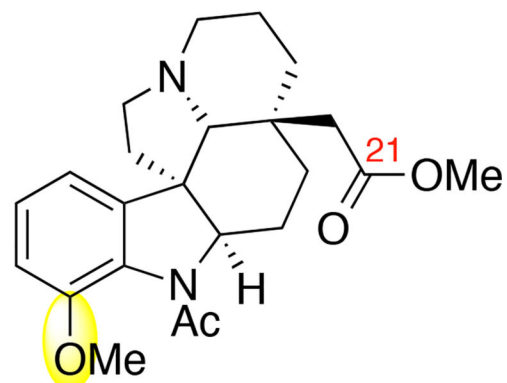
(-)-aspidospermine (**2**), R = Ac

(+)-deacetylaspidospermine (**3**), R = H

(+)-aspidospermidine (**4**)



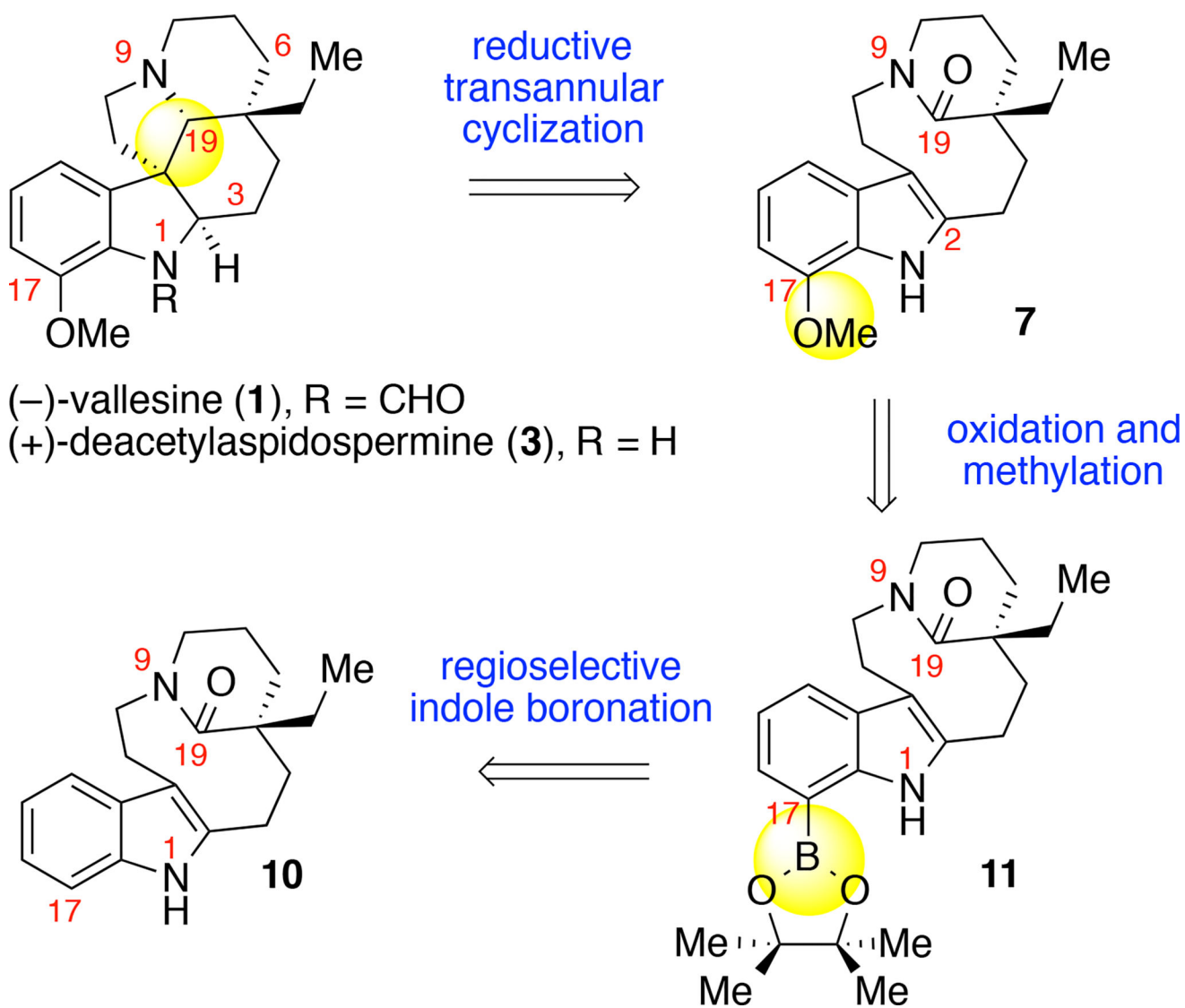
(+)-haplocidine (**5**)



(-)-cylindrocarpidine (**6**)

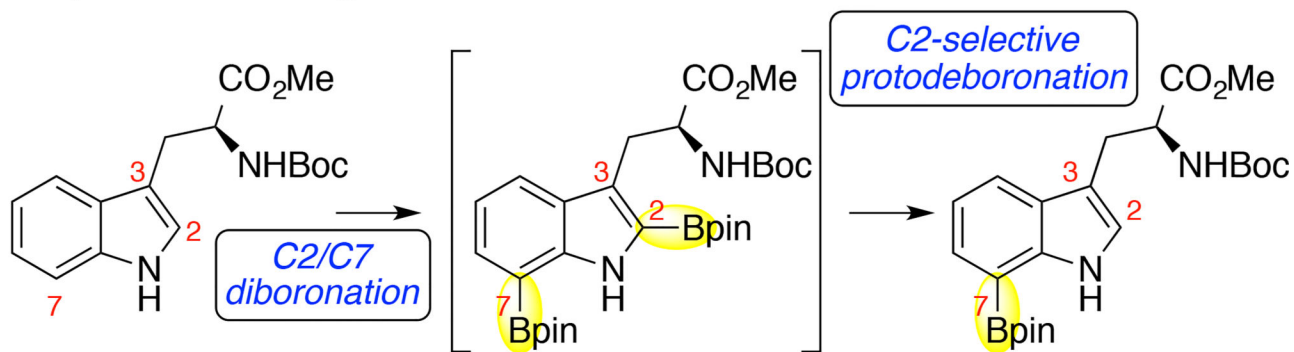
Figure 1.

Structure of (-)-vallesine (**1**) and related aspidosperma alkaloids.

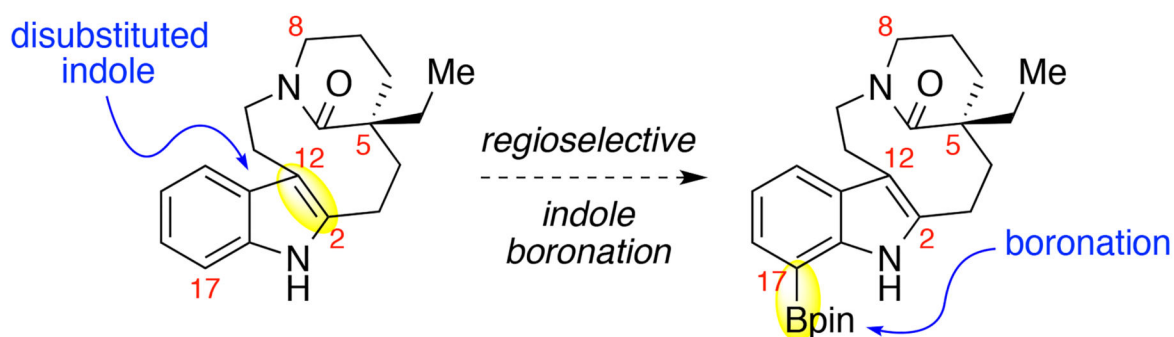


Scheme 1.
Retrosynthetic Analysis

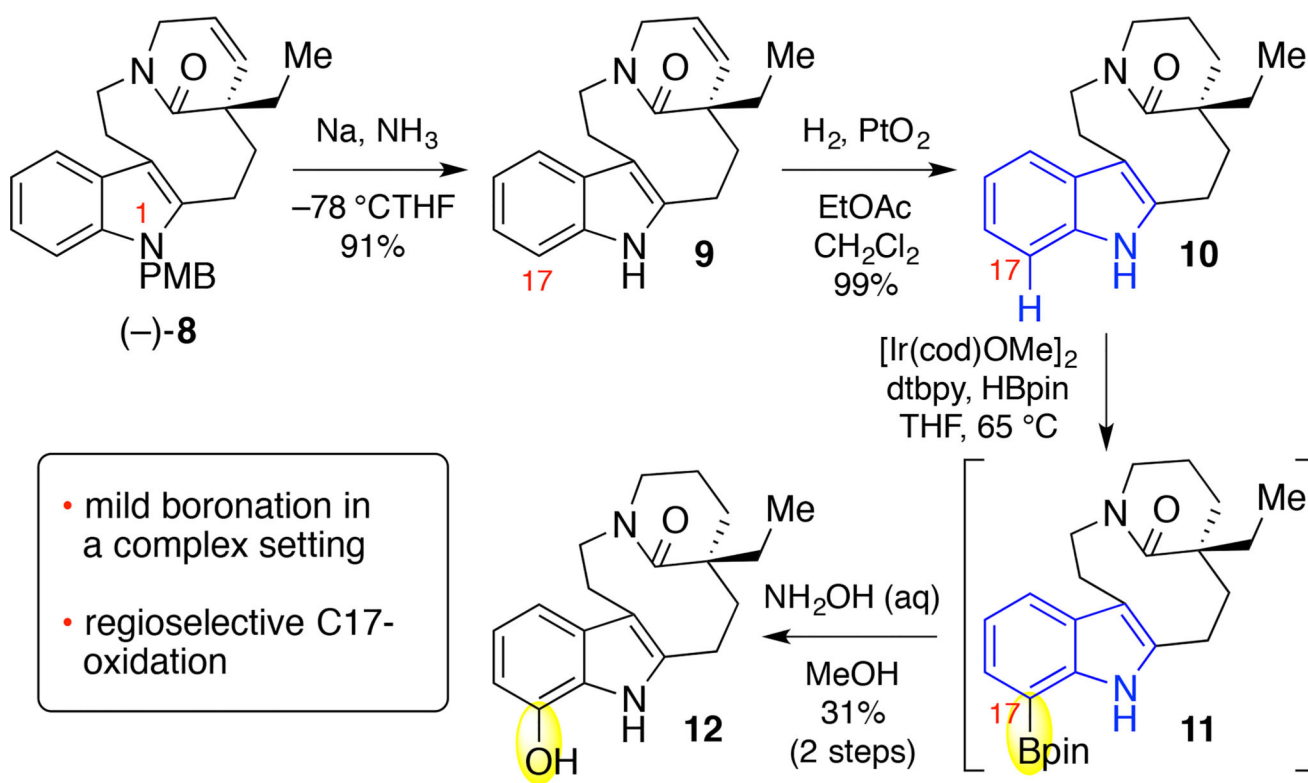
A. Representative Regioselective Indole Boronation



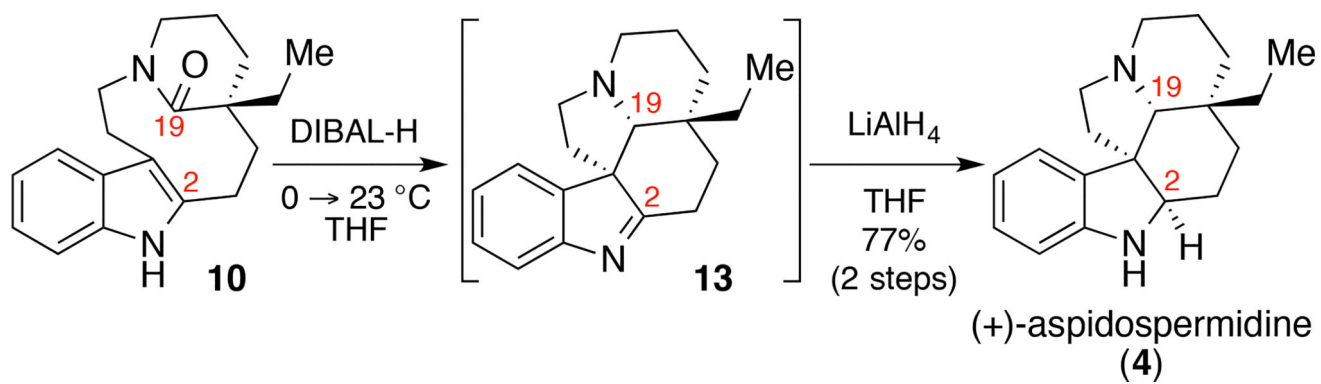
B. Planned Application to Aspidosperma Alkaloids



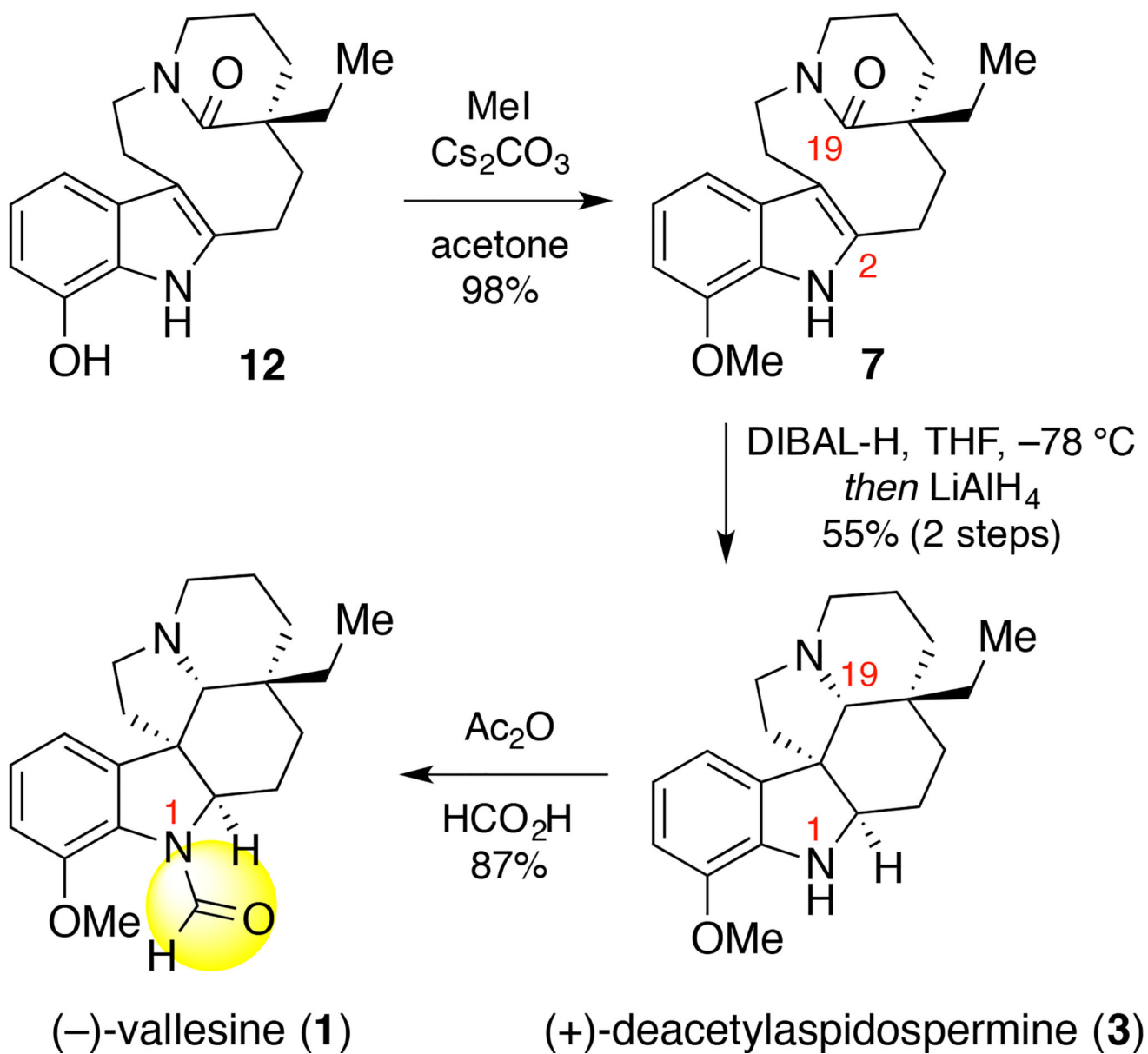
Scheme 2.
Indole Boronation Strategy



Scheme 3.
Synthesis of C17-Oxidized Intermediate Phenol 12



Scheme 4.
Synthesis of (+)-Aspidospermidine (4)



Scheme 5.
Synthesis of (+)-Deacetylaspidospermine (3) and (-)-Vallesine (1)