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Asymmetric Total Synthesis of *Apocynaceae* Hydrocarbazole Alkaloids (+)-Deethylibophyllidine and (+)-Limaspermidine

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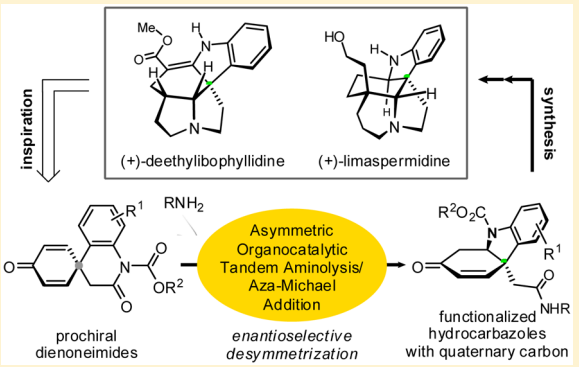
Supporting Information

ABSTRACT: An unprecedented asymmetric catalytic tandem aminolysis/aza-Michael addition reaction of spirocyclic *para*-dienoneimides has been designed and developed through organocatalytic enantioselective desymmetrization. A unified strategy based on this key tandem methodology has been divergently explored for the asymmetric total synthesis of two natural *Apocynaceae* alkaloids, (+)-deethylibophyllidine and (+)-limaspermidine. The present studies not only enrich the tandem reaction design concerning the asymmetric catalytic assembly of a chiral all-carbon quaternary stereocenter contained in the densely functionalized hydrocarbazole synthons but also manifest the potential for the application of the asymmetric catalysis based on the *para*-dienone chemistry in asymmetric synthesis of natural products.



INTRODUCTION

The alkaloids with a densely functionalized hydrocarbazole scaffold (Figure 1), which are widely present in many natural

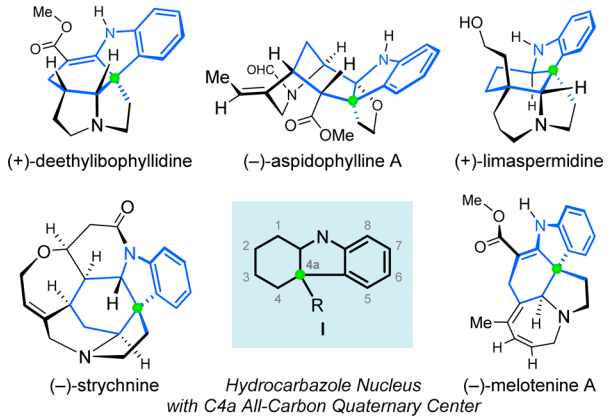


Figure 1. Selected members of hydrocarbazole alkaloids.

sources, constitute one structurally unique class of plant-derived nitrogen containing natural products.[1] Because of their high structural diversity and various biological properties,[2] some of these alkaloids have become attractive targets for synthetic chemists to develop the methodologies and strategies in synthesis design over the past half century.[3] Chemically, from a synthetic point of view, how to expeditiously establish such a privileged functionalized hydrocarbazole nucleus **I** with the crucial C4a all-carbon quaternary stereocenter (Figure 1) would be one of the key issues in the asymmetric synthesis of structurally related hydrocarbazole alkaloids.

Importantly, the catalytic asymmetric construction of a chiral all-carbon quaternary stereocenter, especially embedded in the synthetically interesting, multifunctionalized building blocks, is one of the most challenging and dynamic research areas in modern organic synthesis.[4] Recently, by focusing on the enantioselective assembly of the hydrocarbazole-containing subunits **I** (Scheme 1), several asymmetric catalytic methods have been elegantly developed on the basis of Heck cyclization,[5a−d] [4 + 2] cycloaddition,[5e−g] formal [4 + 2] cycloaddition,[5j,k] formal [3 + 3] cycloaddition,[5h,i] and Fischer indolization,[5l] tactically showing the direct approach for the simultaneous formation of a C−C bond centered on the chiral quaternary carbon atom. To our knowledge, however, the strategy of enantioselective desymmetrization[6] has still not been explored in the installation of functionalized hydrocarbazoles **I**, wherein the indirect approach for accessing such a stereogenic center from the prochiral quaternary carbon atom would be involved. To address this point, particularly associated with potential for use in the synthesis of hydrocarbazole alkaloids (Figure 1), a highly functionalized new hydrocarbazole synthon **A** (Scheme 1) is conceived in terms of the general model **I**. Stimulated by accessing such an intriguing tricyclic building block **A** as well as recent progress in *para*-dienone chemistry,[7−10] an unprecedented asymmetric catalytic tandem aminolysis/aza-Michael addition[11] (Scheme 1) could

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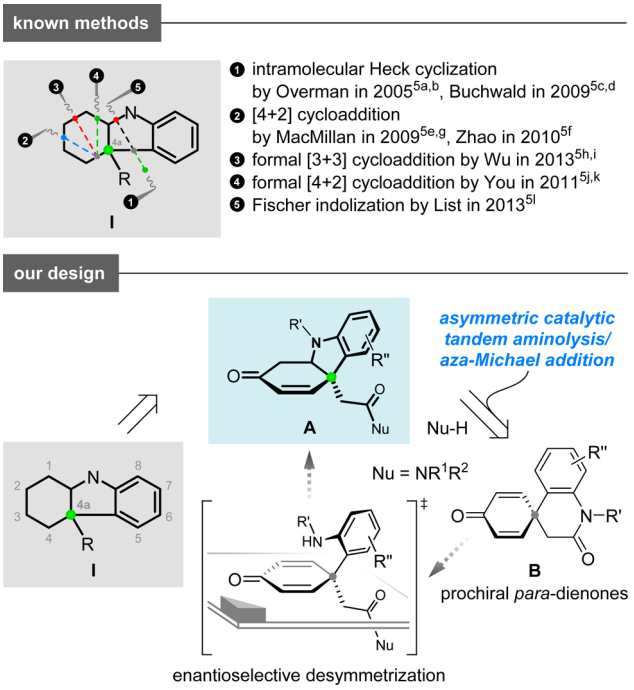
Scheme 1. Design for the Asymmetric Synthesis of Functionalized Hydrocarbazole Units with All-Carbon Quaternary Stereocenter

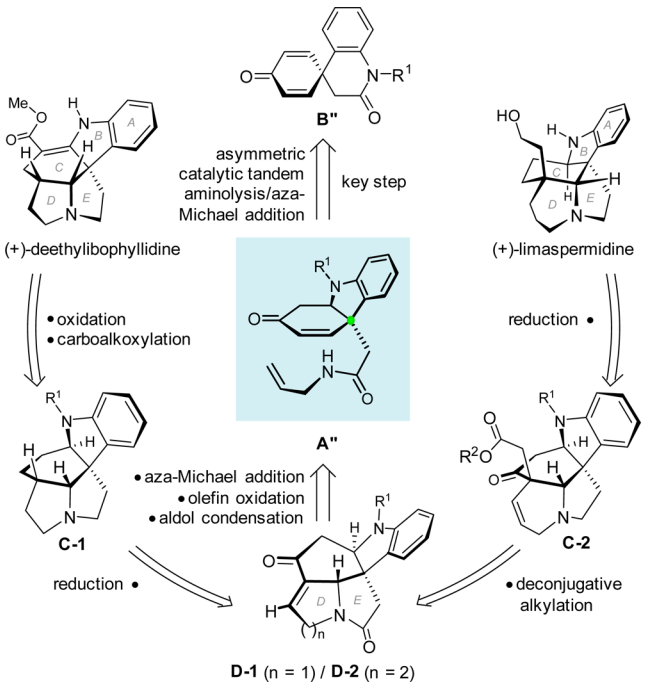


be designed in connection with our previous exploration of tandem alcoholysis/oxa-Michael addition in the formal synthesis of morphine.[9f] Strategically, this methodology design could provide a new synthetic consideration for the multifunctionalized hydrocarbazole synthon **A** with the crucial C4a all-carbon quaternary stereocenter.

RESULTS AND DISCUSSION

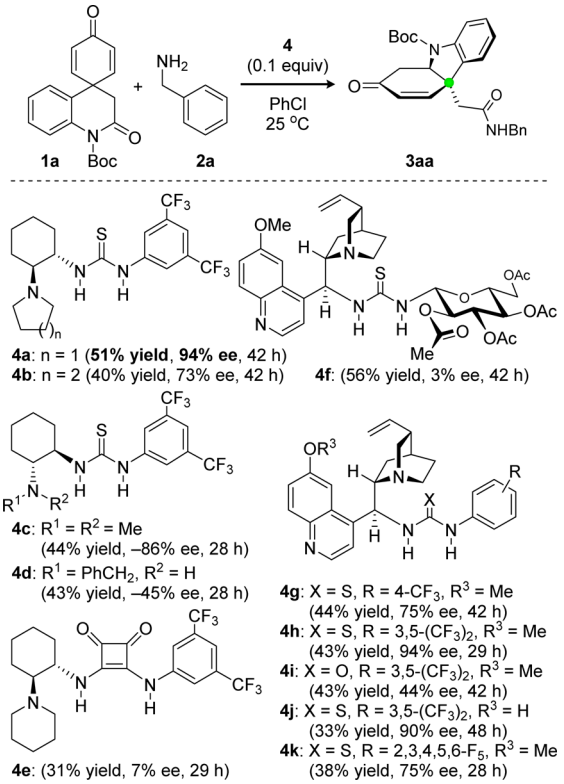
To explore such topics driven by natural product synthesis, two representative *Apocynaceae* hydrocarbazole alkaloids, (+)-deethylibophyllidine[1c,12] (also known as desethylibophyllidine) and (+)-limaspermidine,[1c,13] are selected as targets in this case. Considering the occurrence of the common hydrocarbazole core, a unified retrosynthetic analysis could be evolved to show the divergent strategy (Scheme 2). For (+)-deethylibophyllidine, the unsaturated ester moiety in its ring C could be stepwise introduced by chemoselective imine-forming oxidation of arylamine unit and subsequent carboalkoxylation from the synthon **C-1**, which could be accessed by the reduction of synthon **D-1**. For (+)-limaspermidine, the 2-hydroxyethyl group in its fused ring C/D system could arise from the reduction of synthon **C-2**, which could be installed by a deconjugative alkylation of enone moiety of synthon **D-2**. Retrosynthetically, the structurally unified synthons **D-1** and **D-2** could be generally elaborated from the common tricyclic hydrocarbazole synthon **A″** by using stereoselective intramolecular aza-Michael addition for the formation of ring E and regioselective olefin oxidation/intramolecular aldol condensation for the forging of ring D. Followed by this methodology design (Scheme 1), a key asymmetric catalytic tandem aminolysis/aza-Michael addition of spirocyclic *para*-dienone synthon **B″** could be strategically envisioned for the enantioselective construction of crucial functionalized hydrocarbazole building block **A″**.

Scheme 2. Retrosynthetic Analysis



According to these retrosynthetic considerations (Scheme 2), the target-oriented model using spirocyclic *para*-dienoneimide **1a** as substrate and benzylamine **2a** as nucleophilic initiator was then set up for our synthetic studies (Scheme 3). On the basis of the bifunctional catalysis mode involving Brønsted acid and base,[14] a series of amine thiourea catalysts (**4a**–**4d**, **4f**–**4h**, and **4j**–**4k**) as well as its analogues (**4e** and **4i**) were evaluated for

Scheme 3. Model of the Key Asymmetric Tandem Reaction



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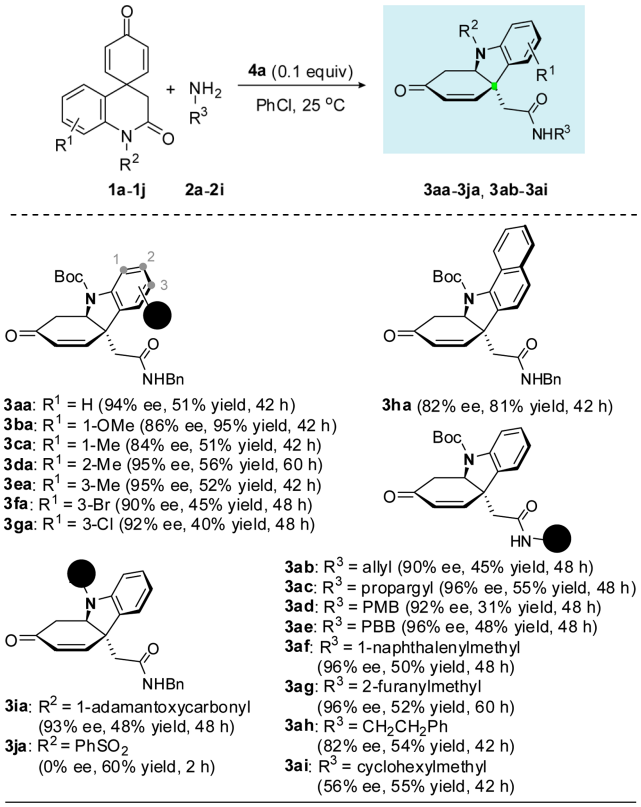
this asymmetric tandem reaction at 25 °C in the optimized solvent of PhCl.[15] In terms of the enantioselectivity and reactivity of the current model, the chiral tertiary amine thiourea **4a**,[16] which was derived from the structural combination of a rigid chiral cyclohexanediamine framework bearing a pyrrolidine moiety with an achiral *N*-thiourea substituent, gave the optimum results for the formation of the desired hydrocarbazole **3aa**[17−19] with 94% ee in 51% yield.

Encouraged by the positive result obtained, we then focused our preliminary efforts on the exploration of the generality of substrate scope in this key tandem aminolysis/aza-Michael addition (Table 1). First, to probe the structure influences of

Table 1. Generality of Enantioselective Tandem Aminolysis/Aza-Michael Addition[a,b]



[a]Performed with **1a−1j** (0.05 mmol) and **2a−2i** (0.25 mmol) in the presence of catalyst **4a** (0.005 mmol) in PhCl (1.0 mL) at 25 °C. The yields refer to the isolated products, and the ee's were determined by chiral high-performance liquid chromatography (HPLC) analysis. [b]The absolute configuration of **3ab** was established by X-ray crystallographic analysis of a later-stage pentacyclic intermediate **9** (Scheme 5), and accordingly the reaction enantioselectivity in other cases was assigned by analogy. PMB = 4-methoxybenzyl, PBB = 4-bromobenzyl.

para-dienoneimides, a variety of *N*-Boc-protected substrates **1a−1h** having different substituents (R^2 = Boc, R^1 = H, OMe, Me, Cl, Br, and 1,3-butadiene-1,4-diyl) on the phenyl ring were examined by using benzylamine **2a** (R^3 = $PhCH_2$) as nucleophile under the optimized conditions, leading to the desired hydrocarbazole products **3aa−3ha** in moderate to good yields with good to high enantioselectivities of up to 95% ee. Compared with these *N*-Boc-protected cases (R^2 = Boc) in *para*-dienoneimides, two additional examples **1i−1j** having different *N*-substituted groups (R^1 = H, R^2 = 1-adamantoxycarbonyl and phenylsulfonyl) were also investigated. Analogously, the tandem reaction of **1i** (R^1 = H, R^2 = 1-adamantoxycarbonyl) with benzylamine **2a** (R^3 = $PhCH_2$) under the standard conditions could deliver the product **3ia** in 48% yield with 93% ee. Interestingly, while employing **1j** (R^1 = H, R^2 = phenylsulfonyl) as substrate in the presence of benzylamine **2a** (R^3 = $PhCH_2$) under the optimized conditions, an enhanced reactivity for the formation of hydrocarbazole product **3ja** in 60% yield was observed with a significantly shortened reaction time of 2 h. To our surprise, however, no enantiodiscrimination in this case was achieved,[20] clearly indicating the fact that the increased chemical stability of achiral *N*-aryl sulfonamide anion, generated in situ from the initial aminolysis of tandem reaction, resulted in an unexpectedly negative impact to the enantiocontrol in the subsequent intramolecular aza-Michael addition.

In addition to the evaluation of *para*-dienoneimides as substrates, various nucleophilic amines were also investigated. Compared with benzylamine **2a** (R^3 = $PhCH_2$), it was found that a series of benzylamine analogues **2b−2g** (R^3 = allyl, propargyl, 4-methoxybenzyl, 4-bromobenzyl, 1-naphthalenylmethyl, and 2-furanylmethyl) also could be effective in the current enantioselective tandem aminolysis/aza-Michael addition, affording the expected products **3ab−3ag** in reasonable yields with high enantioselectivities of up to 96% ee.[19] Notably, while using homobenzylamine **2h** (R^3 = $PhCH_2CH_2$) as a one-carbon homologue of **2a** (R^3 = benzyl) in this reaction, a decreased enantioselectivity was observed in the formation of product **3ah** (82% ee). When the aliphatic amine **2i** (R^3 = cyclohexylmethyl) as a fully hydrogenated analogue of **2a** (R^3 = benzyl) was subjected to the present tandem reaction, a lower level of enantiocontrol for **3ai** (56% ee) was detected analogously.

Having primarily developed this unprecedented key tandem methodology proposed in the retrosynthetic analysis (Scheme 2), we then focused our attention to probe such target-oriented synthesis, which could be strategically based on the unique multifunctionalized hydrocarbazole **3ab**[19] (Table 1) that resulted from our asymmetric organocatalytic tandem aminolysis/aza-Michael addition reaction. To access the structurally unified synthons **D-1** and **D-2** (Scheme 2), as shown in Scheme 4, a divergent approach to the pentacyclic building blocks **7a** and **7b** was therefore developed. Commenced with the tricyclic carbazole **3ab** (90% ee), the base-promoted intramolecular aza-Michael addition could smoothly deliver the versatile tetracyclic precursor **5** in 85% yield in a diastereomerically defined manner. Divergently, the aldehydes **6a** and **6b** could be selectively obtained from **5** by ozonolysis and palladium-catalyzed anti-Markovnikov oxidation,[21] respectively. Particularly, it should be noted that the transformation of **5** to **6b** under the hydroboration/oxidation conditions (BH_3·THF/H_2O_2) only gave a complicated reaction mixture. Subsequently, the assembly of enone moiety by intramolecular aldol condensation of **6a** and **6b** afforded the pentacyclic intermediates **7a** and **7b**, respectively, which could be further elaborated for the asymmetric synthesis of (+)-deethylibophyllidine and (+)-limaspermidine.

As a member of the *Apocynaceae* alkaloids, (+)-deethylibophyllidine was originally isolated from the bark of *Tabernaemontana albiflora* and *Anacampta disticha* in 1980,[12] and its biogenetic pathway has been illuminated from tryptamine and secologanin.[22] Over the past three decades, since the pioneering synthetic study by Kuehne in 1981, the chemical

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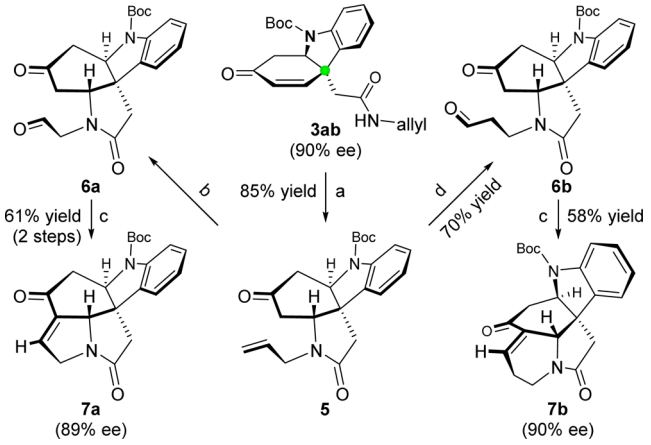
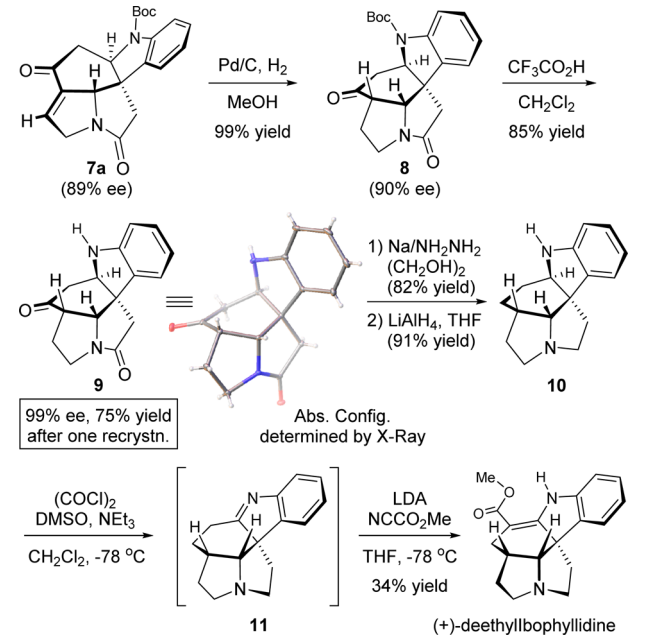
Scheme 4. Divergent Synthesis of Pentacyclic Building Blocks 7a and 7b[a]



[a]Conditions: (a) NaOH (aq.), THF; (b) O_3, CH_2Cl_2, then Me_2S; (c) *p*-TsOH, PhH; (d) $Pd(MeCN)_2Cl_2$, CuCl, O_2, HMPA, $(CH_2Cl)_2$.

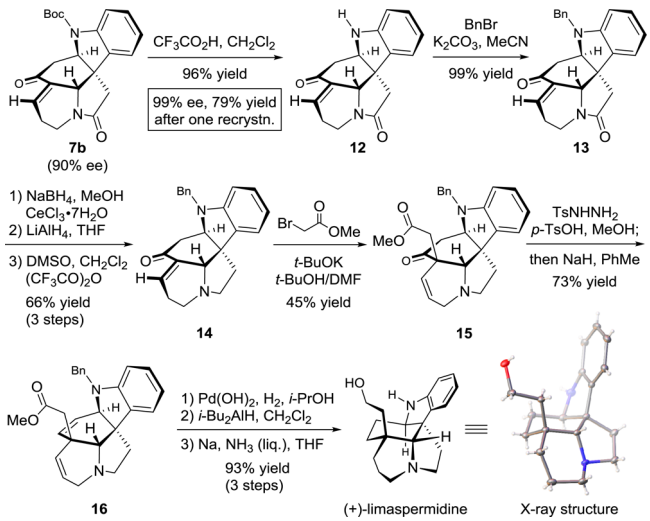
routes for the racemic synthesis of deethylibophyllidine have been mainly developed on the basis of [4 + 2] cycloaddition,[23a,b,g] [3 + 2] cycloaddition,[23h] crisscross annulation,[23d,f] and Fischer indolization/Pummerer rearrangement.[23c,e] However, it should be noted that there is still no report on its asymmetric synthesis. Our chiral synthesis of (+)-deethylibophyllidine, as shown in Scheme 5, began with a highly stereoselective hydrogenation of pentacyclic building block **7a**, giving the functionalized ketone **8** in almost quantitative yield. The subsequent acidic deprotection of the *N*-Boc group afforded the amine **9** (90% ee) in 85% yield, and pleasingly its enantiopurity could be further enhanced through a homochiral crystallization to provide an optically pure amine **9** (99% ee, 75% yield), thereby leading to a definite assignment of absolute stereochemistry of its hydrocarbazole skeleton by X-ray crystallography.[24] The Wolff–Kishner ketone reduction of **9**, followed by $LiAlH_4$-mediated amide reduction, furnished the reductive product **10** in 75% yield over two steps. The chemoselective Swern oxidation of secondary arylamine motif in **10** resulted in the formation of imine intermediate **11**, which sequentially underwent the further methoxycarbonylation/enamine tautomerization in the presence of lithium diisopropyl amide (LDA) and Mander's reagent, giving the final desired (+)-deethylibophyllidine in 34% yield over two steps. The NMR spectroscopic data are identical to those from previous racemic syntheses,[12,23e] and the specific rotation of our synthetic (+)-deethylibophyllidine ($[\alpha]_D^{20}$ = +413 (*c* = 1.0, MeOH)) was consistent with the reported value.[12] Importantly, the absolute configuration of (+)-deethylibophyllidine was unambiguously confirmed by our first enantioselective total synthesis.

Scheme 5. Asymmetric Synthesis of (+)-Deethylibophyllidine



To further explore the synthetic diversity of tandem methodology, we then pursued our current studies in an effort toward the asymmetric synthesis of another member of the *Apocynaceae* alkaloids, (+)-limaspermidine, which was initially isolated from the trunk bark of a small Venezuelan tree *A. rhombeosignatum MARKGRAF* in 1979.[13] Biologically, its synthetic pathway is also associated with tryptamine and secologanin.[22] Regarding its chemical synthesis in racemic form, efforts have been devoted to the strategies featured by Ban's *N*-acyliminium cyclization/aldol condensation,[25a−c] Overman's aza-Cope rearrangement/Mannich cyclization,[25d] Banwell's Raney-cobalt-mediated tandem reductive cyclization,[25f] and Qiu's Diels–Alder cycloaddition.[25g] Recently, the chiral synthesis of its non-natural enantiomer was revealed by Shao on the basis of asymmetric palladium-catalyzed decarboxylative allylation.[26] Our enantioselective synthesis of (+)-limaspermidine, as outlined in Scheme 6, commenced with the acidic removal of the *N*-Boc group of the structurally unified synthon **7b**, readily producing arylamine **12** (90% ee) in 96% yield. To further enhance its optical purity, amine **12** (90% ee) was readily recrystallized to yield an enantiomerically enriched amine **12** (99% ee, 79% yield). After the *N*-benzylation of **12** with $BnBr/K_2CO_3$ in 99% yield, amide **13** was subjected to a three-step protocol involving sequential enone/amide reduction and Swern oxidation, giving the tertiary amine **14** in 66% yield over three steps. Unfortunately, the attempts for direct chemoselective reduction of the amide

Scheme 6. Asymmetric Synthesis of (+)-Limaspermidine



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group in the presence of the enone moiety failed.[27] With the enone intermediate **14** in hand, a deconjugative C-alkylation with methyl bromoacetate in the presence of *t*-BuOK/*t*-BuOH straightforwardly released the advanced precursor **16** in 45% yield, in which an additional all-carbon quaternary stereocenter was stereospecifically assembled on the rigid pentacyclic framework. Then, the smooth transformation of ketone **15** to olefin **16** was implemented in 73% yield by Bamford−Stevens reaction. Notably, the resulting alkene units in **16** allow for the possibility of future application in the synthesis of some other structurally related *Aspidosperma* and *Strychnos* alkaloids and analogues. Following a three-step sequence involving olefin hydrogenation, ester reduction, and reductive debenzylation, the asymmetric synthesis of (+)-limaspermidine could be accomplished in 93% yield from intermediate **16**. The absolute configuration of our synthetic (+)-limaspermidine ($[\alpha]_D^{20}$ = +32 (c = 0.5, $CHCl_3$)) was also confirmed by single-crystal X-ray crystallography,[24] and the NMR spectroscopic characteristics were in accord with those reported in the literature.[25d,f,g,26]

CONCLUSION

In conclusion, driven by the asymmetric synthesis of hydrocarbazole alkaloids, an unprecedented enantioselective catalytic tandem aminolysis/aza-Michael addition of spirocyclic *para*-dienoneimides has been designed and developed under bifunctional catalysis on the basis of enantioselective desymmetrization, providing a new method for the expeditious assembly of multifunctionalized hydrocarbazole building blocks bearing the crucial all-carbon quaternary stereocenter. On the basis of this key asymmetric tandem methodology, the chiral total synthesis of two *Apocynaceae* alkaloids, (+)-deethylibophyllidine and (+)-limaspermidine, has been preliminarily explored, manifesting the potential in the first enantioselective synthesis of such natural products. The present studies not only chemically enrich the tandem reaction design concerning the asymmetric catalytic construction of a chiral all-carbon quaternary stereocenter embedded in the synthetically useful functionalized hydrocarbazole building blocks but also strategically illustrate a potential of asymmetric catalysis based on *para*-dienone chemistry in the asymmetric synthesis of architecturally related hydrocarbazole alkaloids.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. X-ray data for compound **9** and the synthetic (+)-limaspermidine (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. *50*, Chapter 9. (b) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. *51*, Chapter 1. (c) *Dictionary of Alkaloids*, 2nd ed.; Buckingham, J., Baggaley, K. H., Roberts, A. D., Szabó, L. F., Eds.; CRC Press: Boca Raton, FL, 2010. (d) O'Connor, S. E. In *Comprehensive Natural Products II*; Mander, L., Liu, H.-W., Eds.; Elsevier: Amsterdam, 2010; Vol. *1*, p 977.

(2) (a) Ramirez, A.; Garcia-Rubio, S. *Curr. Med. Chem.* **2003**, *10*, 1891. (b) Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *4*, 253.

(3) For selected reviews on the synthetic studies of the related alkaloids, see: (a) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. (b) Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455. (c) Hájíček, J. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1681. (d) Mori, M. *Heterocycles* **2010**, *81*, 259. (e) Cannon, J. S.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 4288. (f) Shibasaki, M.; Ohshima, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 2007; Vol. *64*, Chapter 3. (g) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447. (h) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 400.

(4) For selected reviews on the catalytic asymmetric construction of all-carbon quaternary centers, see: (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (d) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (e) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (f) Christoffers, J. *Chem.—Eur. J.* **2003**, *9*, 4862. (g) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533. (h) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (i) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (j) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (k) Trost, B. M.; Jiang, C. *Synthesis* **2006**, *38*, 369. (l) Mohr, J. T.; Stoltz, B. M. *Chem.—Asian J.* **2007**, *2*, 1476. (m) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (n) Alexakis, A.; Vuagnoux-d'Augustin, M.; Martin, D.; Kehrli, S.; Palais, L.; Hénon, H.; Hawner, C. *Chimia* **2008**, *62*, 461. (o) Bella, M.; Gasperi, T. *Synthesis* **2009**, *41*, 1583. (p) Jautze, S.; Peters, R. *Synthesis* **2010**, *42*, 365. (q) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295. (r) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593. (s) Wang, B.; Tu, Y. Q. *Acc. Chem. Res.* **2011**, *44*, 1207. (t) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247. (u) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745. (v) Repka, L. M.; Reisman, S. E. *J. Org. Chem.* **2013**, *78*, 12314.

(5) For asymmetric catalytic synthesis of such hydrocarbazole-containing subunits by using intramolecular Heck cyclization, see: (a) Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186. (b) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368. (c) Hyde, A. M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *47*, 177. (d) García-Fortanet, J.; Kessler, F.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6676. By using [4 + 2] cycloaddition, see: (e) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606. (f) Zheng, C.; Lu, Y.; Zhang, J.; Chen, X.; Chai, Z.; Ma, W.; Zhao, G. *Chem.—Eur. J.* **2010**, *16*, 5853. (g) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. By using formal [3 + 3] cycloaddition, see: (h) Huang, J.; Zhao, L.; Liu, Y.; Cao, W.; Wu, X. *Org. Lett.* **2013**, *15*, 4338. (i) Wu, X.; Huang, J.; Guo, B.; Zhao, L.; Liu, Y.; Chen, J.; Cao, W. *Adv. Synth. Catal.* **2014**, *356*, 3377. By using formal [4 + 2] cycloaddition, see: (j) Cai, Q.; Zheng, C.; Zhang, J.-W.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8665. (k) Cai, Q.; You, S.-L. *Org. Lett.* **2012**, *14*, 3040. By using Fischer indolization, see: (l) Martínez, A.; Webber, M. J.; Müller, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 9486.

(6) For selected general reviews on enantioselective desymmetrization, see: (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. (b) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313. (c) Studer, A.; Schleth, F. *Synlett* **2005**, 3033. (d) Rovis, T. In

DOI: 10.1021/jacs.5b01926
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

New Frontiers in Asymmetric Catalysis; Mikamiand, K., Lautens, M., Eds.; Wiley: Hoboken, NJ, 2007; pp 275−309. (e) Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683. (f) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2011**, *111*, PR110.

(7) For using *para*-dienones (*p*-dienones) as a terminology for this type of 4,4-disubstituted cyclohexa-2,5-dienones, see: (a) Burling, E. D.; Jefferson, A.; Scheinmann, F. *Tetrahedron* **1965**, *21*, 2653. (b) Regel, W.; von Philipsborn, W. *Helv. Chim. Acta* **1969**, *52*, 1354. (c) Barton, D. H. R.; Magnus, P. D.; Pearson, M. J. *Chem. Commun.* **1969**, 550.

(8) For recent reviews on asymmetric transformations of *para*-dienones, see: (a) Maertens, G.; Ménard, M.-A.; Canesi, S. *Synthesis* **2014**, *46*, 1573. (b) Kalstabakken, K. A.; Harned, A. M. *Tetrahedron* **2014**, *70*, 9571. (c) Yang, X.; Wang, J.; Li, P. *Org. Biomol. Chem.* **2014**, *12*, 2499.

(9) For examples on tandem reaction starting from *para*-dienones via enantioselective desymmetrization, see: (a) Rubush, D. M.; Morges, M. A.; Rose, B. J.; Thamm, D. H.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 13554. (b) Tello-Aburto, R.; Kalstabakken, K. A.; Harned, A. M. *Org. Biomol. Chem.* **2013**, *11*, 5596. (c) He, Z.-T.; Tian, B.; Fukui, Y.; Tong, X.; Tian, P.; Lin, G.-Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 5314. (d) Keilitz, J.; Newman, S. G.; Lautens, M. *Org. Lett.* **2013**, *15*, 1148. (e) Liu, P.; Fukui, Y.; Tian, P.; He, Z.-T.; Sun, C.-Y.; Wu, N.-Y.; Lin, G.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 11700. (f) Li, J.; Liu, G.-L.; Zhao, X.-H.; Du, J.-Y.; Qu, H.; Chu, W.-D.; Ding, M.; Jin, C.-Y.; Wei, M.-X.; Fan, C.-A. *Chem.—Asian J.* **2013**, *8*, 1105. (g) Corbett, M. T.; Johnson, J. S. *Chem. Sci.* **2013**, *4*, 2828. (h) Rubush, D. M.; Rovis, T. *Synlett* **2014**, *25*, 713. For examples of one-pot reaction involving in situ formed *para*-dienones via enantioselective desymmetrization, see: (i) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404. (j) Ratnikov, M. O.; Farkas, L. E.; Doyle, M. P. *J. Org. Chem.* **2012**, *77*, 10294.

(10) For recent examples on nontandem reaction of *para*-dienones via enantioselective desymmetrization, see: (a) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Synthesis* **1993**, *1993*, 920. (b) Imbos, R.; Brilman, M. H. G.; Pineschi, M.; Feringa, B. L. *Org. Lett.* **1999**, *1*, 623. (c) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184. (d) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Dalton Trans.* **2003**, 2017. (e) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028. (f) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (g) Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056. (h) Leon, R.; Jawalekar, A.; Redert, T.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 1487. (i) Gu, Q.; You, S.-L. *Chem. Sci.* **2011**, *2*, 1519. (j) Gu, Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 5192. (k) Tello-Aburto, R.; Kalstabakken, K. A.; Volp, K. A.; Harned, A. M. *Org. Biomol. Chem.* **2011**, *9*, 7849. (l) Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Enders, D.; Sasai, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5423. (m) Jia, M.-Q.; You, S.-L. *Chem. Commun.* **2012**, *48*, 6363. (n) Jia, M.-Q.; Liu, C.; You, S.-L. *J. Org. Chem.* **2012**, *77*, 10996. (o) Wu, W.; Li, X.; Huang, H.; Yuan, X.; Lu, J.; Zhu, K.; Ye, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1743. (p) Liu, K.; Teng, H.-L.; Yao, L.; Tao, H.-Y.; Wang, C.-J. *Org. Lett.* **2013**, *15*, 2250.

(11) For recent reviews on asymmetric aza-Michael addition, see: (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (b) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633. (c) Vicario, J. L.; Badía, D.; Carrillo, L.; Etxebarria, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proced. Int.* **2005**, *37*, 513. (d) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065. (e) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* **2009**, *65*, 9657. (f) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058. (g) Reyes, E.; Fernandez, M.; Uria, U.; Vicario, J. L.; Badia, D.; Carrillo, L. *Curr. Org. Chem.* **2012**, *16*, 521. (h) Wang, J.; Li, P.; Choy, P. Y.; Chan, A. S. C.; Kwong, F. Y. *ChemCatChem* **2012**, *4*, 917. (i) Amara, Z.; Caron, J.; Joseph, D. *Nat. Prod. Rep.* **2013**, *30*, 1211. (j) Sánchez-Roselló, M.; Aceña, J. L.; Simón-Fuentes, A.; del Pozo, C. *Chem. Soc. Rev.* **2014**, *43*, 7430.

(12) Kan, C.; Husson, H.-P.; Jacquemin, H.; Kan, S.-K.; Lounasmaa, M. *Tetrahedron Lett.* **1980**, *21*, 55.

(13) Medina, J. D.; Genova, L. D. *Planta Med.* **1979**, *37*, 165.

(14) For selected reviews on organocatalysis based on bifunctional (thio)ureas and bifunctional squaramides, see: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (b) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (e) Connon, S. J. *Chem. Commun.* **2008**, 2499. (f) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (g) Kotke, M.; Schreiner, P. R. In *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; Wiley-VCH: Weinheim, Germany, 2009; pp 141−351. (h) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem.—Eur. J.* **2011**, *17*, 6890. (i) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330. (j) Jakab, G.; Schreiner, P. R. In *Comprehensive Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2013; pp 315−341. (k) Tsakos, M.; Kokotos, C. G. *Tetrahedron* **2013**, *69*, 10199. (l) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051. (m) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. *Eur. J. Org. Chem.* **2014**, 2633.

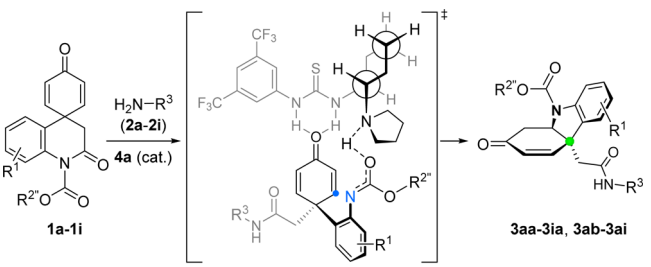
(15) For details on the condition optimization, see the Supporting Information.

(16) For recent examples on asymmetric catalysis using **4a**, see: (a) Li, L.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 12248. (b) Lu, R.-j.; Yan, Y.-y.; Wang, J.-j.; Du, Q.-s.; Nie, S.-z.; Yan, M. *J. Org. Chem.* **2011**, *76*, 6230. (c) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Jia, L.-N.; Tian, F.; He, G.-Y.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2012**, *77*, 2947. (d) Tripathi, C. B.; Mukherjee, S. *Org. Lett.* **2014**, *16*, 3368.

(17) The in situ formation of intermediate **3aa** has been previously proposed in a tandem protocol involving an uncontrollable aza-Michael addition. For details, see: Pereira, J.; Barlier, M.; Guillou, C. *Org. Lett.* **2007**, *9*, 3101.

(18) The constitutional structure arising from intramolecular aza-Michael addition of the carbamate moiety was assigned on the basis of the HMBC spectroscopy of **3aa**. For details, see page S77 of Supporting Information.

(19) The reaction enantioselectivity was assigned by analogy on the basis of a later assignment of the absolute configuration of **3ab**, which was unequivocally established by X-ray crystallographic analysis of a later-stage pentacyclic intermediate **9** (Scheme 5). Accordingly, a model for the observed enantioselectivity was also proposed as below.



front view, *Re* face attack

(20) In contrast to the positive results using substrates with bulky *N*-alkoxycarbonyl group (e.g., R^2 = Boc) in Table 1, the sulfonyl-protected secondary *aromatic* amino group generated in situ as nitrogen donor was not compatible for the enantioselectivity of our bifunctional catalyzed tandem reaction. Notably, the sulfonyl-protected secondary *aliphatic* amino group as nitrogen donor has been successfully described by Gu and You in the cinchonine derived thiourea-catalyzed asymmetric aza-Michael reaction (see ref 10i), but the corresponding *N*-Boc-protected aliphatic amino group could not act as an effective aza-Michael donor in that case.

(21) (a) Hosokawa, T.; Aoki, S.; Takano, M.; Nakahira, T.; Yoshida, Y.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1991**, *20*, 1559. (b) Weiner, B.; Baeza, A.; Jerphagnon, T.; Feringa, B. L. *J. Am. Chem. Soc.* **2009**, *131*, 9473. (c) Dong, J. J.; Harvey, E. C.; Fañanás-Mastral, M.; Browne, W. R.; Feringa, B. L. *J. Am. Chem. Soc.* **2014**, *136*, 17302. For a recent review, see: (d) Dong, J. J.; Browne, W. R.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2014**, *54*, 734.

(22) (a) Rahman, A.-u.; Basha, A. In *Biosynthesis of Indole Alkaloids*; Clarendon Press: Oxford, U.K., 1983. (b) Dewick, P. M. In *Medicinal*

DOI: 10.1021/jacs.5b01926
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Natural Products: A Biosynthetic Approach, 2nd ed.; Wiley: Chichester, U.K., 2002; p 350.

(23) For racemic (formal) synthesis of deethylibophyllidine, see: (a) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem.* **1981**, *46*, 2002. (b) Barsi, M.-C.; Das, B. C.; Fourrey, J.-L.; Sundaramoorthi, R. *J. Chem. Soc., Chem. Commun.* **1985**, *14*, 88. (c) Catena, J.; Valls, N.; Bosch, J.; Bonjoch, J. *Tetrahedron Lett.* **1994**, *35*, 4433. (d) Fernàndez, J.-C.; Valls, N.; Bosch, J.; Bonjoch, J. *J. Chem. Soc., Chem. Commun.* **1995**, *24*, 2317. (e) Bonjoch, J.; Catena, J.; Valls, N. *J. Org. Chem.* **1996**, *61*, 7106. (f) Bonjoch, J.; Fernàndez, J.-C.; Valls, N. *J. Org. Chem.* **1998**, *63*, 7338. (g) Tóth, F.; Kalaus, G.; Greiner, I.; Kajtár-Peredy, M.; Gömöry, Á.; Hazai, L.; Szántay, C. *Hetrocycles* **2006**, *68*, 2301. (h) Coldham, I.; Dobson, B. C.; Fletcher, S. R.; Franklin, A. I. *Eur. J. Org. Chem.* **2007**, 2676.

(24) The absolute configuration was determined by X-ray crystallographic analysis, and the intensity data were collected on an Agilent SuperNova diffractometer using graphite-monochromated Cu Kα radiation. CCDC 1049103 (**9**) and CCDC 1049104 (the synthetic (+)-limaspermidine) contain the crystallographic data for this paper. The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif.

(25) For racemic synthesis of limaspermidine, see: (a) Ban, Y.; Ohnuma, T.; Nagai, M.; Sendo, Y.; Oishi, T. *Tetrahedron Lett.* **1972**, *13*, 5023. (b) Ban, Y.; Ohnuma, T.; Seki, K.; Oishi, T. *Tetrahedron Lett.* **1975**, *16*, 727. (c) Honma, Y.; Ohnuma, T.; Ban, Y. *Heterocycles* **1976**, *5*, 47. (d) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598. (e) Guérard, K. C.; Guérinot, A.; Bouchard-Aubin, C.; Ménard, M.-A.; Lepage, M.; Beaulieu, M. A.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 2121. (f) Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A. *Org. Lett.* **2012**, *14*, 5621. (g) Jin, J.; Qiu, F. G. *Adv. Synth. Catal.* **2014**, *356*, 340.

(26) For asymmetric synthesis of non-natural limaspermidine, see: Zhang, S.-X.; Shen, X.-L.; Li, Z.-Q.; Zou, L.-W.; Wang, F.-Q.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* **2013**, *78*, 11444.

(27) (a) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 18. (b) Chen, Z.-H.; Zhang, Y.-Q.; Chen, Z.-M.; Tu, Y.-Q.; Zhang, F.-M. *Chem. Commun.* **2011**, *47*, 1836.

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J. Am. Chem. Soc. XXXX, XXX, XXX−XXX