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Stereodivergent Total Syntheses of Precoccinelline, Hippodamine, Coccinelline, and Convergine†

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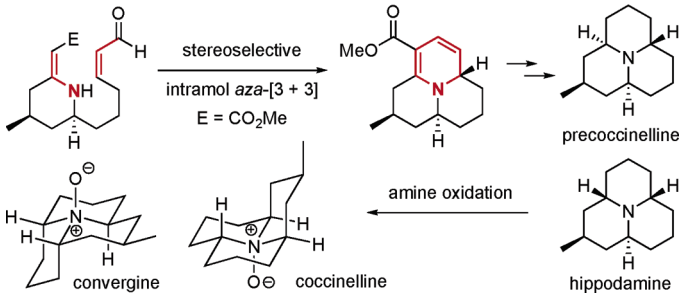
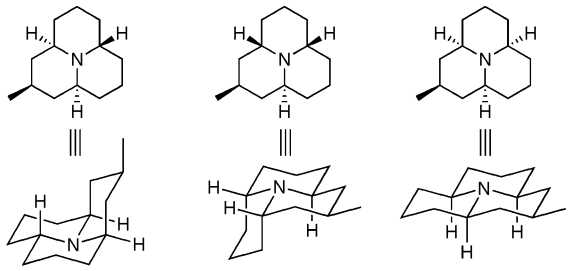
ABSTRACT



A stereodivergent approach toward total syntheses of *Coccinellidae* defensive alkaloids is described. These syntheses feature a highly diastereoselective intramolecular aza-[3 + 3] annulation strategy, which represents a *de novo* approach to this family of natural products.

Ladybird beetles (*Coccinellidae*) play an important role in controlling populations of agricultural pests such as aphids, mealy bugs, and scale insects, and to protect themselves from their natural predators such as ants and quails, they utilize a *reflex bleeding* mechanism.[1] When scarred or disturbed, they release an orange fluid from their joints that contains a mixture of defensive alkaloids.[2] In 1971, Tursch and co-workers[3a] first isolated precoccinelline **1** from this fluid along with a crystalline substance, which was confirmed as the *N*-oxide of **1** or as coccinelline **2** by X-ray analysis.[3b] Isolations of hippodamine[3c,d] **3**, its *N*-oxide convergine[3c,d] **4**, and the thermodynamically most stable all *syn* isomer myrrhine[3e] **5** were reported later. Alkaloids **1** and **3** represent the two other possible stereoisomers of the 2-methyl-perhydro-9b-azaphenalene system with the methyl group being equatorial. Interestingly, *N*-oxide of myrrhine **5** does not occur naturally.



Their unique structural feature has attracted a lot of attention[4−6] in the last 30 years, commencing with Ayer's first total syntheses of all these alkaloids in 1976[4a,5a] and some elegant constructions of **1** and **2** by Mueller,[5b,c] who also synthesized **3**−**5**,[5c] and by Stevens in 1979.[5d] Interestingly, most of these syntheses intercept a key intermediate

† Dedicated to Professor Jeffrey D. Winkler on the occasion of his 50th birthday.

(1) Happ, G. M.; Eisner, T. *Science* **1961**, *134*, 329.
(2) For reviews, see: (a) King, A. G.; Meinwald, J. *Chem. Rev.* **1996**, *96*, 1105. (b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.
(3) (a) Tursch, B.; Daloze, D.; Dupont, M.; Pasteels, J. M.; Tricot, M.-C. *Experientia* **1971**, *27*, 1380. (b) Karlsson, R.; Losman, D. *J. Chem. Soc., Chem. Commun.* **1972**, 626. (c) Tursch, B.; Daloze, D.; Pasteels, J. M.; Cravador, A.; Braekman, J. C.; Hootele, C.; Zimmermann, D. *Bull. Soc. Chim. Belg.* **1972**, *81*, 649. (d) Tursch, B.; Daloze, D.; Braekman, J. C.; Hootele, C.; Cravador, A.; Losman, D.; Karlsson, R. *Tetrahedron Lett.* **1974**, 409. (e) Tursch, B.; Daloze, D.; Braekman, J. C.; Hootele, C.; Pasteels, J. M. *Tetrahedron* **1975**, *31*, 1541.

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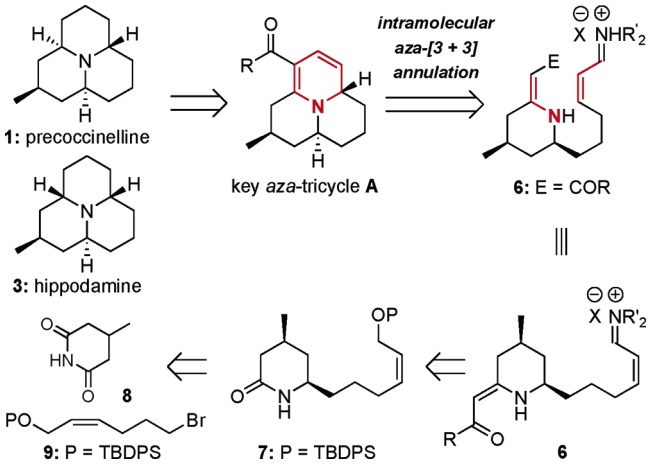
Scheme 1. Retrosynthetic Analysis

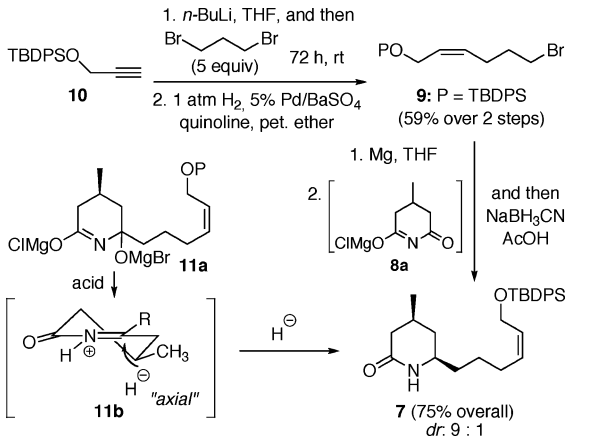


in Ayer's syntheses,[5a] and in all syntheses of these alkaloids except for one,[4a] the equatorial methyl group is being introduced in the latter steps of the sequence. Herein, we report a *de novo* approach to precoccinelline **1** and hippodamine **3** and their respective *N*-oxides **2** and **4**, featuring a highly stereoselective intramolecular aza-[3 + 3] annulation.[7−10]

Retrosynthetically, as shown in Scheme 1, we envisioned that both **1** and **3** could be derived from the same aza-tricyclic intermediate **A** upon hydrogenation of the double bonds and removal of the carboxymethyl group. The key tricycle **A** can be prepared via an intramolecular aza-[3 + 3] annulation of vinylogous urethane **6**,[7,10] which should be accessible in several steps from *cis*-1,3-disubstituted lactam **7** with bromide **9** and glutarimide **8** as the essential starting points.

Our synthesis commenced with alkylation of TBDPS-protected propargyl alcohol **10**[11,12] employing excess 1,3-dibromopropane followed by Lindlar hydrogenation that led to bromide **9** in 59% overall yield (Scheme 2). Lactam **7**

Scheme 2. Synthesis of Lactam **7**



was prepared via reductive alkylation[13] of 4-methyl glutarimide **8**.[14] The Grignard reagent generated from bromide **9** was added to the Mg salt **8a** formed *in situ* from glutarimide **8** and 1.0 equiv of CH_3MgCl, and after stirring overnight at room temperature, $NaBH_3CN$ and AcOH were added to reduce the intermediate hemi-aminal (see **11a**). The reduction proceeded stereoselectively and afforded lactam **7** in 75% overall yield exclusively as the 1,3-*syn* isomer. This is likely a result of an *axial* approach of hydride to the conformation shown for *N*-acyliminium ion **11b**.

Converting **7** to the corresponding thiolactam using Lawesson's reagent[15] followed by alkylation with α-bromo methyl acetate gave thiol ether **12** in 90% yield over two steps (Scheme 3). Eschenmoser sulfide contraction[16] of **12** proceeded smoothly and led to the protected *Z*-vinylogous

(4) For syntheses of hippodamine, convergine, and myrrhine, see: (a) Ayer, W. A.; Dawe, R.; Eisner, R. A.; Furuichi, K. *Can. J. Chem.* **1976**, *54*, 473. (b) Adams, D. R.; Carruthers, W.; Crowley, P. J. *J. Chem. Soc., Chem. Commun*. **1991**, 1261. (c) Rejzek, M.; Stockman, R. A.; Hughes, D. L. *Org. Biomol. Chem.* **2005**, *3*, 73.

(5) For syntheses of precoccinelline and coccinelline, see: (a) Ayer, W. A.; Furuichi, K. *Can. J. Chem.* **1976**, *54*, 1494. (b) Mueller, R. H.; Thompson, M. E. *Tetrahedron Lett.* **1979**, 1991. (c) Mueller, R. H.; Thompson, M. E.; DiPardo, R. M. *J. Org. Chem.* **1984**, *49*, 2271. (d) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032. (e) Yue, C.; Nicolay, J.-F.; Royer, J.; Husson, H.-P. *Tetrahedron* **1994**, *50*, 3139. (f) Takahata, H.; Ouchi, H.; Ichinose, M.; Nemoto, H. *Org. Lett.* **2002**, *4*, 3459.

(6) For an elegant total synthesis of related alkaloid (−)-205B, see: Smith, A. B., III.; Kim, D. S. *Org. Lett.* **2005**, *7*, 3247.

(7) For reviews, see: (a) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1349. (b) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23. (c) Coverdale, H. A.; Hsung, R. P. *ChemTracts* **2003**, *16*, 238.

(8) For a review on vinylogous amide chemistry, see: Kucklander, U. Enaminones as Synthons. In *The Chemistry of Functional Groups: The Chemistry of Enamines Part I*. Rappoport, Z., Ed. John Wiley & Sons: New York, 1994; p 523.

(9) For recent studies in this area, see: (a) Pattenden, L. C.; Wybrow, R. A. J.; Smith, S. A.; Harrity, J. P. A. *Org. Lett.* **2006**, *8*, 3089. (b) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 6330. (c) Halliday, J. I.; Chebib, M.; Turner, P.; McLeod, M. D. *Org. Lett.* **2006**, *8*, 3399. (d) Bose, D. S.; Kumar, R. K. *Heterocycles* **2006**, *68*, 549. (e) Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2005**, *7*, 2993. (f) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 207. (g) Agami, C.; Dechoux, L.; Hebbe, S.; Ménard, C. *Tetrahedron* **2004**, *60*, 5433. (h) Ji, S.-J.; Jiang, Z.-Q.; Lu, J.; Loh, T.-P. *Synlett* **2004**, 831. (i) Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286.

(10) For intramolecular aza-[3 + 3] annulation, see: (a) Swidorski, J. J.; Wang, J.; Hsung, R. P. *Org. Lett.* **2006**, *8*, 777. (b) Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. W. *J. Org. Chem.* **2005**, *70*, 4248. (c) Sydorenko, N.; Zificsak, C. A.; Gerasyuto, A. I.; Hsung, R. P. *Org. Biomol. Chem.* **2005**, *3*, 2140. (d) Luo, S.; Zificsak, C. Z.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709. (e) Wei, L.-L.; Sklenicka, H. M.; Gerasyuto, A. I.; Hsung, R. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1516. For references on intermolecular aza-[3 + 3] annulation, see: (f) Sydorenko, N.; Hsung, R. P.; Vera, E. L. *Org. Lett.* **2006**, *8*, 2611. (g) Sydorenko, N.; Hsung, R. P.; Darwish, O. S.; Hahn, J. M.; Liu, J. *J. Org. Chem.* **2004**, *69*, 6732. (h) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.-L.; Gerasyuto, A. I.; Brennessel, W. W. *J. Am. Chem. Soc.* **2002**, *124*, 10435.

(11) Toshima, K.; Ohta, K.; Ohashi, A.; Nakamura, T.; Nakata, M.; Tatsuta, K.; Matsumura, S. *J. Am. Chem. Soc.* **1995**, *117*, 4822.

(12) See Supporting Information.

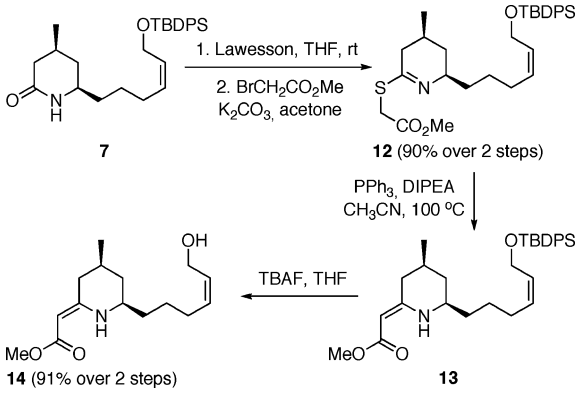
(13) (a) Karstens, W. F. J.; Stol, M.; Rutjes, F. P. J. T.; Kooijman, H.; Spek, A. L.; Hiemstra, H. *J. Organomet. Chem.* **2002**, *624*, 244. (b) Esch, P. M.; Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Heterocycles* **1987**, *26*, 75. (c) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695.

(14) Handley, G. J.; Nelson, E. R.; Somers, T. C. *Aust. J. Chem.* **1960**, *13*, 129.

(15) For a recent review, see: Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, 1929.

(16) (a) Roth, M.; Dubs, P.; Götchi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1995**, *54*, 710. (b) Shiosaki, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, p 865.

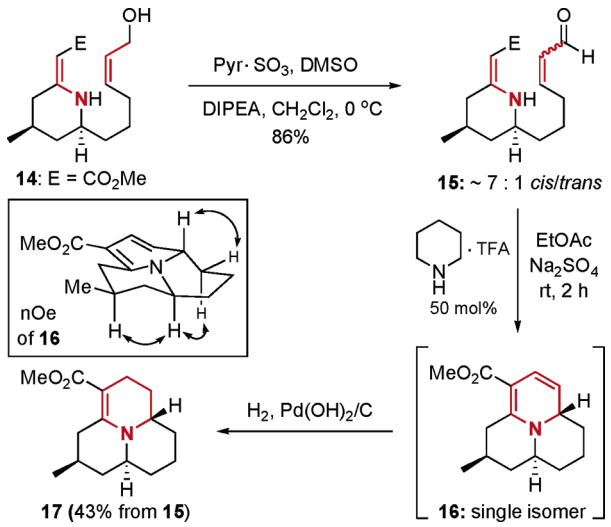
Scheme 3. Synthesis of Allyl Alcohol **14**



urethane **13**. Subsequent deprotection of the TBDPS group with TBAF furnished allyl alcohol **14**. It is noteworthy that the described sequence was suitable for multigram scale synthesis of alcohol **14** with an 82% overall yield starting from lactam **7**.

Pyr·SO_3 oxidation[17] of allyl alcohol **14** led to the corresponding enal **15** as a 7:1 *cis/trans* isomeric mixture (Scheme 4). Enal **15** was subjected to the aza-[3 + 3] annulation

Scheme 4. Key Intramolecular Aza-[3 + 3] Annulation



conditions employing piperidinium trifluoro acetate in EtOAc. The desired cycloadduct **16** was obtained as a single diastereomer in 51% yield, and its *anti* relative stereochemistry at the ring junction was established using nOe's (see the box in Scheme 4) and by X-ray of a later intermediate. The observed stereoselectivity is in good agreement with our previous experience.[10b]

Because of the precarious nature of **16**, we found it more convenient to hydrogenate the reaction mixture over $Pd(OH)_2$

(17) (a) Chen, L.; Lee, S.; Renner, M.; Tian, Q.; Nayyar, N. *Org. Proc. Res. Dev.* **2006**, *10*, 163. (b) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

a.

b.

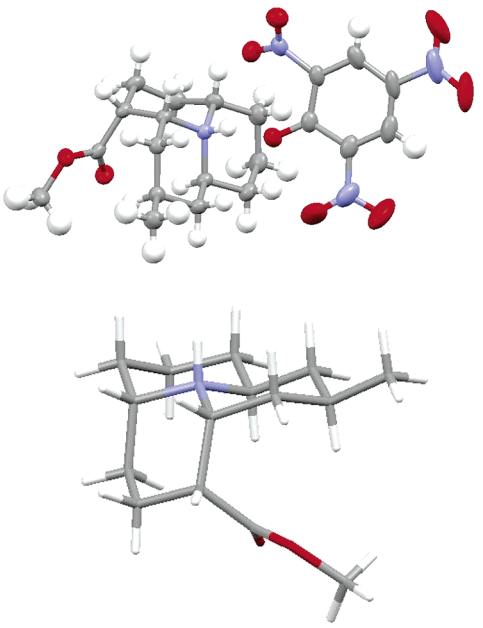
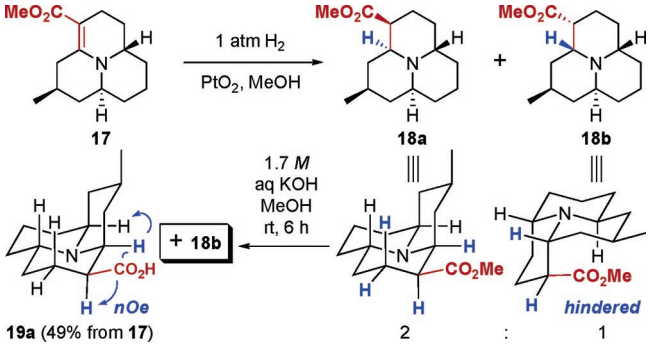


Figure 1. X-ray structure of the picrate salt of **18b**. (a) Structure with picrate. (b) Structure with picrate removed for clarity.

after the annulation.[10e] The one-pot protocol allowed us to access the more stable aza-tricycle **17** with a consistent 43% overall yield from **15**. It is noteworthy that aza-tricycle **17** contains three of the four stereogenic centers required for precoccinelline **1** and hippodamine **3**.

With aza-tricycle **17** in hand, we hydrogenated the internal double bond employing Adam's catalyst[18] (Scheme 5).

Scheme 5. Stereodivergent Hydrogenation of **17**



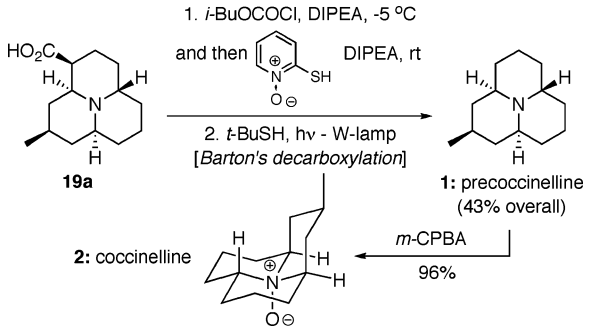
Hydrogenation occurred in a stereodivergent manner, leading to both isomers **18a** and **18b** with a ratio of 2:1. Major isomer **18a** resembles the aza-tricyclic manifold in precoccinelline **1**, whereas **18b** has the framework of hippodamine **3**.

(18) (a) Akhrem, A. A.; Lakhvich, F. A.; Lis, L. G.; Pshenichnyi, V. N.; Arsen'ev, A. S. *Zh. Org. Khim.* **1980**, *16*, 1290. (b) Akhrem, A. A.; Lakhvich, F. A.; Lis, L. G.; Kuz'mitskii, B. B.; Mizulo, N. A.; Gorbacheva, I. A. *Zh. Org. Khim.* **1985**, *21*, 1348.

Although esters **18a**,**b** could be separated by a tedious alumina gel column, it was found that they could be readily resolved *via* a selective alkaline hydrolysis of the equatorial ester **18a** (Scheme 5). Upon treatment of the crude hydrogenation mixture with 1.7 M aq KOH, unreacted axial ester **18b** was recovered by simple extraction in 36% overall yield from **17**. Upon acidification of the aqueous phase, acid **19a** was isolated in 49% yield with its assigned relative stereochemistry being supported by nOe's.[12] The structure of **18b** was unambiguously assigned by X-ray analysis of its corresponding picrate salt (Figure 1).

To complete the total synthesis of precoccinelline **1**, acid **19a** was subjected to Barton's decarboxylation conditions[19] (Scheme 6). The desired alkaloid was isolated in 43% overall

Scheme 6. Completion of Total Syntheses of **1** and **2**

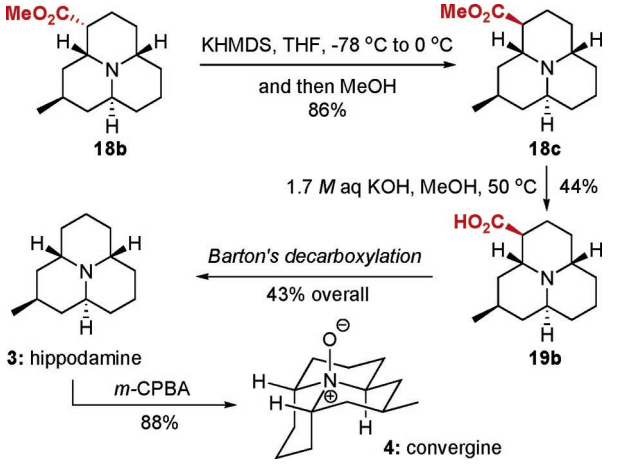


yield with all physical data matching the reported literature data.[5c,21] Subsequent oxidation of precoccinelline employing *m*-CPBA provided coccinelline **2** in excellent yield.

The synthesis of hippodamine **3** turned out to be more challenging, as all attempts to directly hydrolyze ester **18a** failed. This can be attributed to the inaccessibility of the hindered axial ester group in **18b**. We attempted to epimerize the axial ester to the more stable equatorial one using K_2CO_3/MeOH and DBU/toluene protocols, but neither condition was suitable with complete recovery of the starting material.

Ultimately, we found that treatment of ester **18b** with KHMDS[20] at −78 °C with subsequent quenching of the reaction mixture with MeOH at 0 °C led to the desired equatorial ester **18c** with 86% yield (Scheme 7). Hydrolysis

Scheme 7. Completion of Total Syntheses of **3** and **4**



of **18c** was successful using 1.7 M aq KOH at 50 °C, leading to carboxylic acid **19b** in 44% yield. Subsequently, hippodamine **3** was obtained in 43% overall yield after decarboxylation of **19b** under Barton's conditions.[19] Successive oxidation of **3** with *m*-CPBA afforded convergine **4** in 88% yield. Both natural products matched the literature spectroscopic data.[4c,21]

We have described here total syntheses of precoccinelline and hippodamine (overall yields from glutarimide are 4.8% and 1.3%, respectively) and their respective *N*-oxides coccinelline and convergine (overall yields from glutarimide are 4.6% and 1.2%, respectively), featuring a stereoselective intramolecular aza-[3 + 3] annulation strategy, an interesting Eschenmoser sulfide contraction, and a stereodivergent hydrogenation. This work provides a novel approach toward the 2-methyl-perhydro-9b-azaphenalene family of alkaloids.

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Supporting Information Available: Experimental and ^{1}H NMR spectral data and characterizations for all new compounds as well as X-ray structural data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) (a) Barton, D. H. R.; Bridon, D.; Fernandez-Picot, I.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 2733. (b) Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1987**, *44*, 5479.

(20) Klotz, P.; Mann, A. *Tetrahedron Lett.* **2003**, *44*, 1927.

(21) Lebrun, B.; Braekman, J. C.; Daloze, D. *Magn. Reson. Chem.* **1999**, *37*, 60.