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Domino Michael/Mannich/*N*-Alkylation Route to the Tetrahydrocarbazole Framework of Aspidosperma Alkaloids: Concise Total Syntheses of (−)-Aspidospermidine, (−)-Tabersonine, and (−)-Vincadifformine

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Supporting Information

ABSTRACT: We report a novel, asymmetric domino Michael/Mannich/*N*-alkylation sequence for the rapid assembly of the tetrahydrocarbazole framework of *Aspidosperma* alkaloids. This method was utilized in the concise total syntheses of classical targets (−)-aspidospermidine, (−)-tabersonine, and (−)-vincadifformine in 10 or 11 steps. Additional key steps include ring-closing metathesis to prepare the D-ring and Bosch−Rubiralta spirocyclization to prepare the C-ring.

Monoterpene indole alkaloids of the *Aspidosperma* class, which include over 250 unique members, are fascinating natural products endowed with an irresistible combination of architectural complexity and pharmacological activity.[1] Moreover, these intriguing molecules have greatly benefited both organic chemistry and medicine. The structures of four classical members of the *Aspidosperma* family, namely (−)-aspidospermine (**1a**),[2] (−)-aspidospermidine (**1b**),[3] (−)-tabersonine (**2**),[4] and (−)-vincadifformine (**3**),[5] are shown in Figure 1. Of these,

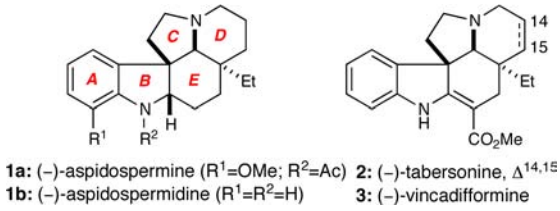
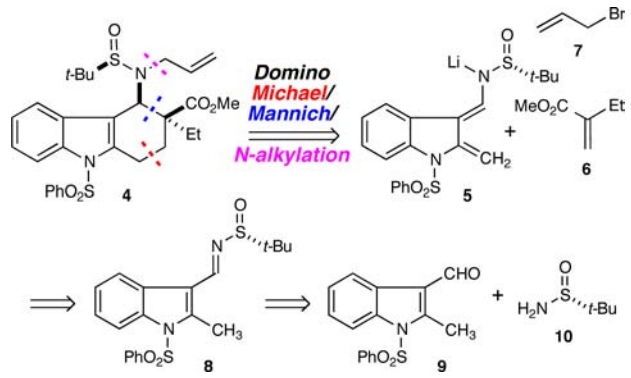


Figure 1. Structures of (−)-aspidospermine (**1a**), (−)-aspidospermidine (**1b**), (−)-tabersonine (**2**), and (−)-vincadifformine (**3**).

aspidospermidine (**1b**) is the most representative insofar as it possesses the hallmark ABCDE pentacyclic framework and common structural denominator among the *Aspidosperma* alkaloids. Accordingly, targets **1**−**4** have stimulated considerable interest in the synthetic community dating back to Stork's elegant, stereoselective total synthesis of **1a** in 1963 and continues unabated to this day.[2a]

Although we have been engaged in the total synthesis of complex indole alkaloids of the *Strychnos* class[6] and most recently rearranged *Aspidosperma* alkaloids,[7] our methods were ill suited for preparing targets such as **1**−**4**. We were, nonetheless, intrigued by two disparate bodies of work whose merger, if successful, would offer facile, concise access to appropriately functionalized ABE tetrahydrocarbazole cores of **1**−**4** with satisfactory control over relative and absolute stereochemistry. Specifically, we were inspired by Magnus's elegant and step-efficient indole-2,3-quinodimethane approach to *Aspidosperma* and *Kospia* alkaloids[3h,8] and Ellman's clever use of metalloenamines derived from *tert*-butanesulfinylimines as asymmetric nucleophiles.[9] Retrosynthetically, we reasoned that tetrahydrocarbazole **4** could be obtained in one operation by means of a domino Michael/Mannich sequence (Scheme 1)

Scheme 1. Retrosynthetic Analysis of Tetrahydrocarbazole 4 via Novel Domino Michael/Mannich/*N*-Alkylation Route



from the reaction of *N*-sulfinyl metallodienamine **5** and methyl ethacrylate (**6**).[10] The efficiency of the operation could be enhanced in the forward sense by productive trapping the *N*-sulfinylanion intermediate with allyl bromide (**7**). Metallodienamine **5** would in turn be derived from *N*-sulfinylimine **8**, which was readily accessible from commercial **9** and (*R*)-*N*-*tert*-butanesulfinamide (**10**).[9]

The synthesis began with the condensation of *N*-benezensulfonyl-2-methylindole-3-carboxaldehyde (**9**), sulfinamide **10**, and $Ti(OEt)_4$ to afford *N*-sulfinylimine **8** in 97% yield (Scheme 2). Treatment of **8** with 1.2−2.2 equiv of LHMDS in THF at −78 °C generated *N*-sulfinyl metallodienamine **5** via deprotonation of the acidic 2-methyl group. Addition of methyl ethacrylate (**6**)[11] triggered a Michael reaction whose enolate

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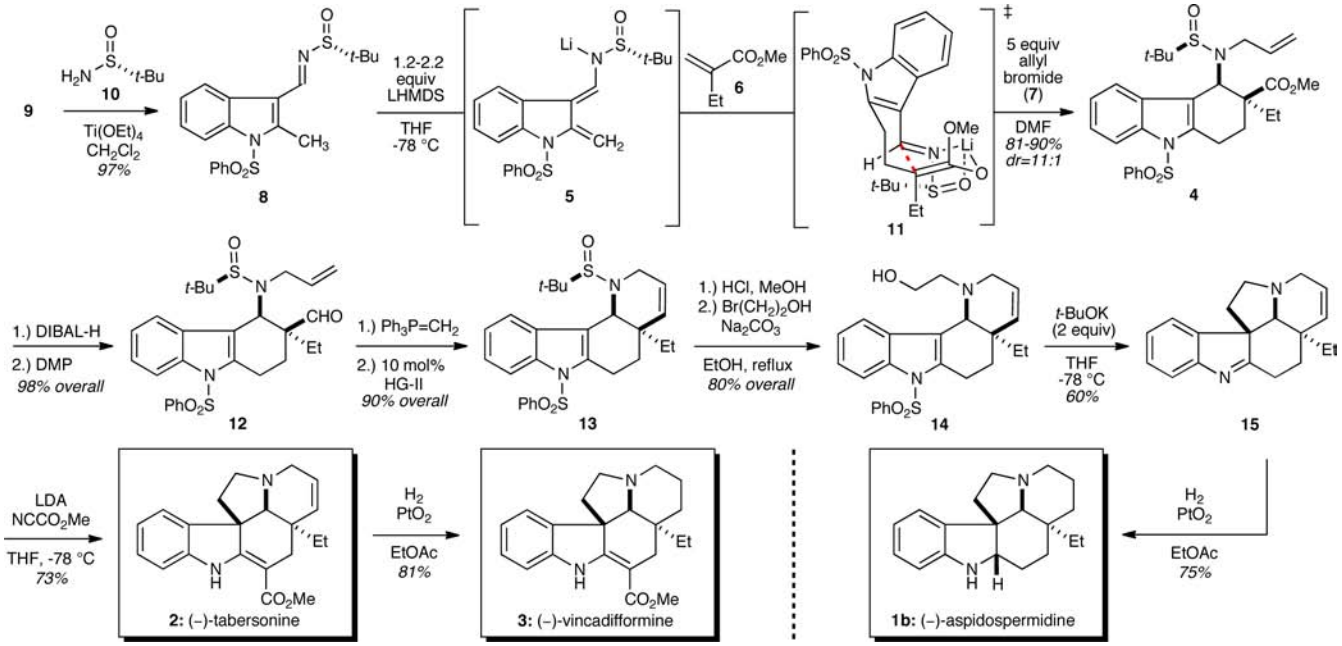
Scheme 2. Total Syntheses of (−)-Aspidospermidine (1b), (−)-Tabersonine (2), and (−)-Vincadifformine (3)



stereoselectively cyclized onto the regenerated *N*-sulfinylimine moiety in a Mannich fashion; trapping the resulting anion with 5 equiv of allyl bromide in DMF furnished tetrahydrocarbazole **4** in 81−90% yield (dr = 11:1).[12] We rationalized the relative and absolute stereocontrol in the domino Michael/Mannich sequence by means of transition state **11**, which is consistent with those posited by Ellman[13] and Davis.[14] To the best of our knowledge, this method represents the first use of a vinylogue of an *N*-sulfinyl metalloenamine, domino process wherein the *in situ*-generated nucleophile cyclizes onto an *N*-sulfinylimine, and intramolecular process wherein *β*-amino esters (i.e., Mannich bases) bearing *α*-quaternary stereocenters are prepared in both high yield and diastereoselectivity.

The next stage of the synthesis called for ring-closing metathesis (RCM) of the D-ring, a strategy employed by Rawal in the *Aspidosperma* series.[3ag,4j] To this end, we converted the methyl ester in **12** to a requisite terminal olefin via the intermediary aldehyde. This goal was best accomplished by sequential reduction to the alcohol with DIBAL-H and oxidation with the Dess−Martin periodinane (DMP) in 98% overall yield.[15] Wittig methylenation of **12** and ring-closing metathesis under the agency of 10 mol% Hoveyda−Grubbs second generation catalyst (HG-II)[16] delivered ABDE tetracycle **13** in 90% overall yield.

We envisioned installing the C-ring with a step-efficient process discovered by Bosch and Rubiralta wherein an *N*-benzenesulfonyl protecting group on indole is transferred to an appropriately positioned primary hydroxyl group by the action of *t*-BuOK; spirocyclization of the ensuing indolyl anion at C3 with the benzenesulfonate ester establishes the C-ring.[17,18] Accordingly, removal of the *N*-sulfinyl group in **13** with HCl in MeOH and *N*-alkylation with 2-bromoethanol, Na_2CO_3 in refluxing EtOH gave substrate **14** in 80% overall yield. Addition of 2 equiv of *t*-BuOK in THF at 0 °C effected the Bosch−Rubiralta spirocyclization to afford ABCDE pentacycle **15** in 60% yield.

Endgame for **1b**, **3**, and **4** commenced with indolenine **15**. Whereas previous reports had employed a two-step protocol (i.e., hydride reduction of the imine and metal-catalyzed hydrogenation of the D-ring olefin), we found hydrogenation of **15** over Adams's catalyst in EtOAc at room temperature delivered (−)-aspidospermidine (**1b**) in a single step (75% yield). The synthesis of **2** featured tactics first employed in Overman's elegant synthesis of classical *Strychnos* alkaloid akuammicine.[19] Specifically, treatment of **15** with LDA at −78 °C and quenching the intermediary metalloenamine with Mander's reagent[20] furnished (−)-tabersonine (**2**) in 73% yield. Hydrogenation of **2** over Adams's catalyst in EtOAc afforded (−)-vincadifformine (**3**) in 81% yield. Spectral data for **1b**, **2**, and **3** (e.g., ^1H and ^{13}C NMR, IR, optical rotation) were in complete agreement with those reported in the literature.[3−5]

In summary, we have completed concise, asymmetric total syntheses of classical *Aspidosperma* alkaloids (−)-aspidospermidine (**1b**, 10 steps, 27% overall yield), (−)-tabersonine (**2**, 10 steps, 26% overall yield), and (−)-vincadifformine (**3**, 11 steps, 22% overall yield) from commercial starting materials. Key steps include a novel domino Michael/Mannich/*N*-alkylation sequence to access the tetrahydrocarbazole framework of the *Aspidosperma* alkaloids, ring-closing metathesis to prepare the D-ring, and the Bosch−Rubiralta spirocyclization to prepare the C-ring. We are currently exploring the scope of this novel process and applying it toward the total synthesis of other complex, bioactive alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectra. 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) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. *51*, Chapter 1.

(2) For racemic syntheses of **1a**, see: (a) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872−2873. (b) Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, *6*, 2261−2268. (c) Kuehne, M. E.; Bayha, C. *Tetrahedron Lett.* **1966**, *7*, 1311−1315. (d) Stevens, R. V.; Fitzpatrick, J. M.; Kaplan, M.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1971**, 857−858. (e) Martin, S. F.; Desai, S. R.; Phillips, G. W.; Miller, A. C. *J. Am. Chem. Soc.* **1980**, *102*, 3294−3296. (f) Pearson, A. J.; Rees, D. C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2467−2476. (g) Wu, P. L.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1988**, *53*, 963−972. For asymmetric syntheses of **1a** see: (h) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673−4676. (i) Fukuda, Y.; Shindo, M.; Shishido, K. *Org. Lett.* **2003**, *5*, 749−751. (j) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 6159−6162. (k) Lajiness, J. P.; Jiang, W.; Boger, D. L. *Org. Lett.* **2012**, *14*, 2078−2081.

(3) For racemic syntheses of **1b** see: (a) Camerman, A.; Camerman, N.; Kutney, J. P.; Piers, E. *Tetrahedron Lett.* **1965**, 637−642. (b) Kutney, J. P.; Abdurahman, N.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1966**, *88*, 3656−3657. (c) Harley-Mason, J.; Kaplan, M. *Chem. Commun.* **1967**, 915−916. (d) Kutney, J. P.; Piers, E.; Brown, R. T. *J. Am. Chem. Soc.* **1970**, *92*, 1700−1704. (e) Kutney, J. P.; Abdurahman, N.; Gletsos, C.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1970**, *92*, 1727−1735. (f) Laronze, J. Y.; Laronze-Fontaine, J.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1974**, 491−494. (g) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990−6992. (h) Gallagher, T.; Magnus, P.; Huffman, J. *J. Am. Chem. Soc.* **1982**, *104*, 1140−1141. (i) Mandal, S. B.; Giri, V. S.; Sabeena, M. S.; Pakrashi, S. C. *J. Org. Chem.* **1988**, *53*, 4236−4241. (j) Le Menez, P.; Kunesch, N.; Liu, S.; Wenkert, E. *J. Org. Chem.* **1991**, *56*, 2915−2918. (k) Wenkert, E.; Liu, S. *J. Org. Chem.* **1994**, *59*, 7677−7682. (l) Forns, P.; Diez, A.; Rubiralta, M. *J. Org. Chem.* **1996**, *61*, 7882−7888. (m) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995−1002. (n) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642−2645. (o) Patro, B.; Murphy, J. A. *Org. Lett.* **2000**, *2*, 3599−3601. (p) Banwell, M. G.; Smith, J. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2613−2618. (q) Banwell, M. G.; Lupton, D. W.; Willis, A. C. *Aust. J. Chem.* **2005**, *58*, 722−737. (r) Sharp, L. A.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 831−834. (s) Callier-Dublanchet, A.-C.; Cassayre, J.; Gagosz, F.; Quiclet-Sire, B.; Sharp, L. A.; Zard, S. Z. *Tetrahedron* **2008**, *64*, 4803−4816. (t) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2009**, *74*, 2290−2300. (u) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941−2943. (v) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5767−5770. (w) Cho, H. K.; Tam, N. T.; Cho, C. G. *Bull. Kor. Chem. Soc.* **2010**, *31*, 3382−3384. (x) Guérard, K. C.; Sabot, C.; Beaulieu, M.-A.; Giroux, M.-A.; Canesi, S. *Tetrahedron* **2010**, *66*, 5893−5901. (y) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563−14572. (z) McMurray, L.; Beck, E. M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9288−9291. (aa) Kawano, M.; Kiuchi, T.; Negishi, S.; Tanaka, H.; Hoshikawa, T.; Matsuo, J.; Ishibashi, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 906−910. See also ref 2j. For asymmetric syntheses of **1b** see: (ab) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901−7903. (ac) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517−521. (ad) Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292−2303. (ae) Schultz, A. G.; Pettus, L. *J. Org. Chem.* **1997**, *62*, 6855−6861. (af) Iyengar, R.; Schildknegt, K.; Aubé, J. *Org. Lett.* **2000**, *2*, 1625−1627. (ag) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628−4641. (ah) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398−13399. (ai) Gnecco, D.; Vázquez, E.; Galindo, A.; Terán, J. L.; Orea, L.; Bernès, S.; Enríquez, R. G. *ARKIVOC* **2003**, 185−192. (aj) Iyengar, R.; Schildknegt, K.; Morton, M.; Aubé, J. *J. Org. Chem.* **2005**, *70*, 10645−10652. (ak) Ishikawa, T.; Kudo, K.; Kuroyabu, K.; Uchida, S.; Kudoh, T.; Saito, S. *J. Org. Chem.* **2008**, *73*, 7498−7508. (al) Suzuki, M.; Kawamoto, Y.; Sakai, T.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2009**, *11*, 653−655. (am) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D.W. C. *Nature* **2011**, *475*, 183−188. (an) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 4117−4121. (ao) Nidhiry, J. E.; Prasad, K. R. *Tetrahedron* **2013**, *69*, 5525−5536.

(4) For racemic syntheses of **2** see: (a) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1971**, *93*, 5930−5931. (b) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1973**, *95*, 7458−7464. (c) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1979**, *101*, 6414−6420. (d) Lévy, J.; Laronze, J.-Y.; Laronze, J.; Le Men, J. *Tetrahedron Lett.* **1978**, 1579−1580. (e) Kuehne, M. E.; Okuniewitcz, F. J.; Kirkemo, C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335−1343. (f) Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913−2927. (g) Kuehne, M. E.; Podhorez, D. E.; Mulamba, T.; Bornmann, W. G. *J. Org. Chem.* **1987**, *52*, 347−353. (h) Kalaus, G.; Greiner, I.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, C. *J. Org. Chem.* **1993**, *58*, 1434−1442. (i) Kuehne, M. E.; Wang, T.; Seaton, P. J. *J. Org. Chem.* **1996**, *61*, 6001−6008. (j) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523−13524. For asymmetric syntheses of **2** see: (k) Kuehne, M. E.; Podhorez, D. E. *J. Org. Chem.* **1985**, *50*, 924−929. (l) Kuehne, M. E.; Bandarage, U. K.; Hammach, A.; Li, Y.-L.; Wang, T. *J. Org. Chem.* **1998**, *63*, 2172−2183. (m) Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519−1522 See also ref 3ag..

(5) For racemic syntheses of **3** see: (a) Kutney, J. P.; Chan, K. K.; Failli, A.; Fromson, J. M.; Gletsos, C.; Nelson, V. R. *J. Am. Chem. Soc.* **1968**, *90*, 3891−3893. (b) Laronze, J.-Y.; Laronze-Fontaine, J.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1974**, *15*, 491−494. (c) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705−3710. (d) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Kikemo, C. L. *J. Org. Chem.* **1979**, *44*, 1063−1068. (e) Barsi, M. C.; Das, B. C.; Fourrey, J. L.; Sundaramoorthi, R. *J. Chem. Soc., Chem. Commun.* **1985**, 88−89. (f) Kalaus, G.; Greiner, I.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, C. *J. Org. Chem.* **1993**, *58*, 1434−1442. (g) Kuehne, M. E.; Wang, T.; Seaton, P. J. *J. Org. Chem.* **1996**, *61*, 6001−6008. (h) Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519−1522. For asymmetric syntheses of **3** see: (i) Pandey, G.; Kumara, P. C. *Org. Lett.* **2011**, *13*, 4672−4675 See also refs 4k, 4l, 3ag, and 3am..

(6) (a) Sirasani, G.; Andrade, R. B. *Org. Lett.* **2009**, *11*, 2085−2088. (b) Sirasani, G.; Paul, T.; Dougherty, W., Jr.; Kassel, S.; Andrade, R. B. *J. Org. Chem.* **2010**, *75*, 3529−3532. (c) Sirasani, G.; Andrade, R. B. *Org. Lett.* **2011**, *13*, 4736−4737. (d) Sirasani, G.; Andrade, R. B. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Academic Press: New York, 2013; Vol. *9*, pp 1−44.

(7) Zhao, S.; Sirasani, G.; Vaddypally, S.; Zdilla, M.; Andrade, R. B. *Angew. Chem., Int. Ed.* **2013**, *52*, 8309−8311.

(8) (a) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35−41. (b) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242−2248.

(9) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600−3740.

(10) For reviews of domino reactions in synthesis see: (a) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442−524. (b) Tietze, L. F.; Rackelmann, N.

Pure Appl. Chem. **2004**, *76*, 1967−1983. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136.
(11) Kuang, Y.-Y.; Chen, F.-E. *Org. Prep. Proced. Int.* **2005**, *37*, 184−188.
(12) The relative and absolute stereochemistry of tetrahydrocarbazole **4** was established by chemical correlation with **1b**, **2**, and **3**.
(13) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12−13.
(14) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993−9003.
(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(16) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.
(17) Rubiralta, M.; Diez, A.; Bosch, J.; Solans, S. *J. Org. Chem.* **1989**, *54*, 5591−5597.
(18) For a similar use of this tactic applied toward (±) pseudotabersonine see: Cheng, B.; Sunderhaus, J.; Martin, S. F. *Org. Lett.* **2010**, *12*, 3622−3625.
(19) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966−3976.
(20) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1991**, *70*, 256−264.