ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Enantioselective Total Synthesis of (+)-Reserpine

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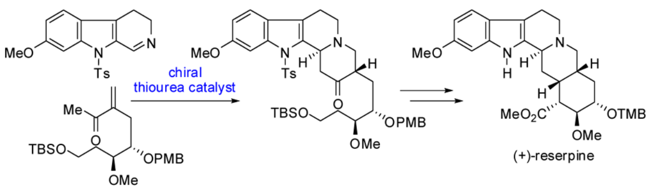
Received January 8, 2013

ABSTRACT

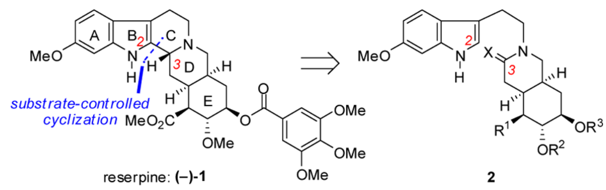


A catalytic, enantioselective synthesis of (+)-reserpine is reported. The route features a highly diastereoselective, chiral catalyst-controlled formal aza-Diels–Alder reaction between a 6-methoxytryptamine-derived dihydro-β-carboline and an enantioenriched α-substituted enone to form a key tetracyclic intermediate. This approach addresses the challenge of setting the C3 stereogenic center by using catalyst control. Elaboration of the tetracycle to (+)-reserpine includes an intramolecular aldol cyclization and a highly diastereoselective hydrogenation of a sterically hindered enoate.

Reserpine (**1**) has represented an iconic target for organic synthesis since its isolation six decades ago.[1] The stereochemically complex pentacyclic structure of this indole alkaloid continues to serve as a forum for exploring the frontiers of stereoselective synthesis and has inspired some of the most important work in the history of the field.[2] Despite the scope of this effort, each of the successful approaches to this molecule has relied on the same fundamental strategy, namely, a late-stage generation of the C-ring and its embedded C3 stereocenter from a 2,3-*seco*-derivative (**2**, Scheme 1).[3]

This approach is generally complicated by preferential formation of the C3 center with the undesired, thermodynamically favored relative stereochemistry.[4] This limitation was overcome in a notable and most elegant manner in the Stork synthesis, wherein the desired C3 configuration

Scheme 1. Synthetic Strategy Common to All Previous Successful Approaches to Reserpine



(1) Müller, J.; Schlittler, E.; Bein, H. *Experientia* **1952**, *8*, 338.

(2) (a) For a review of synthetic efforts directed toward reserpine, see: Chen, F.-E.; Huang, J. *Chem. Rev.* **2005**, *105*, 4671. For more recent approaches, see: (b) Barcan, A. G.; Patel, A.; Houk, K. N.; Kwon, O. *Org. Lett.* **2012**, *14*, 5388. (c) Yar, M.; Arshad, M.; Akhtar, M. N.; Shahzad, S. A.; Khan, I. U.; Khan, Z. A.; Ullah, N.; Ninomiya, I. *Eur. J. Org. Chem.* **2012**, *3*, 26. (d) Huang, J.; Chen, F.-E. *Helv. Chim. Acta* **2007**, *90*, 1366.

(3) (a) Woodward, R. B.; Bader, F. E.; Bickel, H.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1. (b) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2023. (c) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2657. (d) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6398. (e) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157. (f) Wender, P. A.; Schaus, J. M.; White, A. W. *Heterocycles* **1987**, *25*, 263. (g) Martin, S. F.; Grzejszczak, S.; Rueger, H.; Williamson, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 4072. (h) Martin, S. F.; Rueger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124. (i) Stork, G. *Pure Appl. Chem.* **1989**, *61*, 439. (j) Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 4048. (k) Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 3859. (l) Chu, C.-S.; Liao, C.-C.; Rao, P. D. *Chem. Commun.* **1996**, 1537. (m) Hanessian, S.; Pan, J. W.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997**, *62*, 465. (n) Mehta, G.; Reddy, D. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1399. (o) Sparks, S. M.; Shea, K. J. *Org. Lett.* **2001**, *3*, 2265. (p) Sparks, S. M.; Gutierrez, A. J.; Shea, K. J. *J. Org. Chem.* **2003**, *68*, 5274. (q) Stork, G.; Tang, P. C.; Casey, M.; Goodman, B.; Toyota, M. *J. Am. Chem. Soc.* **2005**, *127*, 16255.

(4) (a) Zhang, L.-H.; Gupta, A. K.; Cook, J. M. *J. Org. Chem.* **1989**, *54*, 4708. (b) Lounasmaa, M.; Berner, M.; Tolvanen, A. *Heterocycles* **1998**, *48*, 1275.

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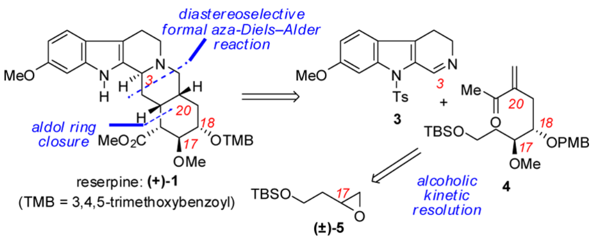
was installed through a kinetically controlled cyclization of an amino-nitrile 2,3-*seco*-derivative.[3i,q,5]

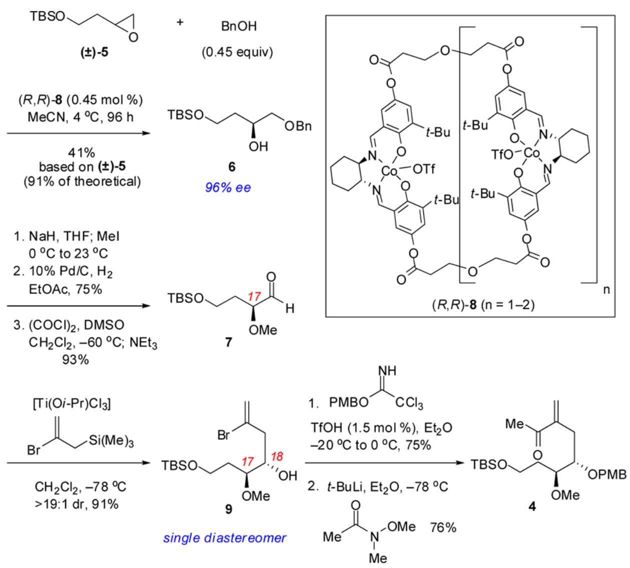
Scheme 2. Retrosynthetic Analysis of (+)-Reserpine



We envisioned an alternative approach to the reserpine framework focused on specifically targeting control over the C3 stereogenic center by means of a stereoselective formal aza-Diels−Alder (FADA) reaction between two fragments of comparable size (**3** and **4**, Scheme 2).[6] Although high levels of substrate-induced stereocontrol were deemed unlikely in such a coupling reaction, we were encouraged by the prospect of selectively introducing the key C3 stereocenter through the use of the chiral catalyst-controlled formal FADA reaction discovered recently in our laboratories.[7] Herein, we describe the successful application of the asymmetric FADA methodology to a catalytic enantioselective total synthesis of (+)-reserpine.[8]

The synthetic efforts toward the requisite enone component **4** began with a highly selective alcoholic kinetic resolution of racemic terminal epoxide **5**. The differentially protected 4-carbon triol **6** was obtained in 96% ee through the use of oligomeric cobalt salen catalyst **8**,[9] employing benzyl alcohol as the nucleophile (Scheme 3). This procedure proved more efficient and reliable in our hands than routes originating from malic acid,[10] particularly when applied on multigram scale. Elaboration of protected alcohol **6** to aldehyde **7** was accomplished in a three-step sequence consisting of methylation of the secondary alcohol, subsequent hydrogenolysis of the benzyl ether, and Swern oxidation of the resulting primary alcohol. The α-methoxy group of aldehyde **7** then served to direct a chelation-controlled diastereoselective allylation, thereby installing the adjacent C18 stereogenic center and providing vinyl bromide **9** as a single diastereomer.[11] Finally, elaboration to enone **4** was accomplished via protection of the C18 alcohol, followed by lithium−halogen exchange and subsequent addition into *N*-methoxy-*N*-methylacetamide.

Scheme 3. Stereoselective Synthesis of Enone **4**



The key coupling of enone **4** and 6-methoxytryptamine-derived dihydro-*β*-carboline **3**[7] to generate tetracyclic ketone **11** was then examined under a series of conditions (Scheme 4). The FADA reaction could be carried out with a small excess of enone **4** (1.2 equiv) relative to imine **3** only with primary amine catalysts, consistent with previous observations employing simple, hindered enone derivatives.[12] The degree of intrinsic substrate-induced diastereocontrol was evaluated using achiral amine promoters. With stoichiometric *n*-hexylamine,[13] ketones **11** and **12**, which contain a trans-relationship between the newly formed C3 and C20 stereocenters, were generated in a 1:1 diastereomeric ratio (dr) (entry 1). In contrast, high levels of chiral catalyst-controlled diastereoselectivity were observed in the presence of 20 mol % aminothiourea **10**,[7] providing the desired diastereomer **11** in 76% isolated yield. Notably, the enantiomeric primary aminothiourea *ent*-**10** induced a reversal of diastereoselectivity in the FADA reaction to afford ketone **12** selectively (entry 3).

(5) A related cyclization of an amino-nitrile intermediate was recently employed in the syntheses of C3-epimeric natural products venenatine and alstovenine: Lebold, T. P.; Wood, J. L.; Deitch, J.; Lodewyk, M. W.; Tantillo, D. J.; Sarpong, R. *Nat. Chem.* **2012**,10.1038/nchem.1528.

(6) Analogous fragment couplings have been applied in the synthesis of related alkaloids: (a) (±)-Deserpidine: Szántay, C.; Blaskó, G.; Honty, K.; Baitz-Gács, E.; Tamás, J.; Tőke, L. *Leibigs Ann. Chem.* **1983**, *8*, 1292. (b) (±)-Yohimbine congeners: Danishefsky, S.; Langer, M. E.; Vogel, C. *Tetrahedron Lett.* **1985**, *26*, 5983. (c) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1533. (d) Nagata, K.; Ishikawa, H.; Tanaka, A.; Miyazaki, M.; Kanemitsu, T.; Itoh, T. *Heterocycles* **2010**, *81*, 1791.

(7) Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, 10.1021/ja310718f.

(8) The three previous reported syntheses of (−)-reserpine have relied on either classical resolution or chiral pool approaches (refs 3i, 3j, and 3m).

(9) White, D. E.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **2003**, *14*, 3633.

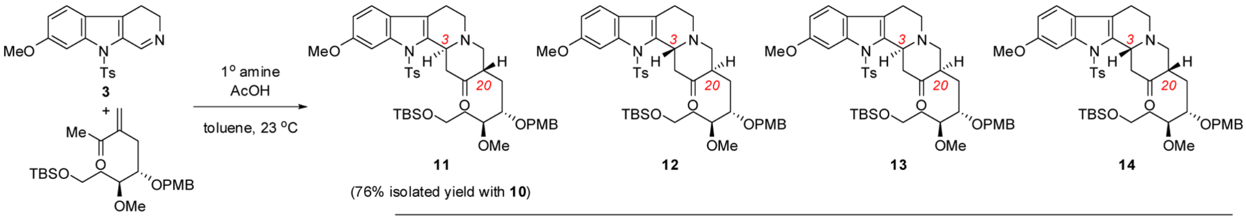
(10) Pattenden, G.; González, M. A.; Little, P. B.; Millan, D. S.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Org. Biomol. Chem.* **2003**, *1*, 4173.

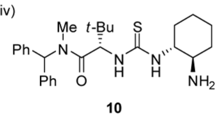
(11) The sequence of allylsilane addition and subsequent PMB protection was adapted from: Evans, D. A.; Rajapakse, H. A.; Stenkemp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4569.

(12) No catalysis was observed with proline or related secondary amine catalysts. The proline-catalyzed formal aza-Diels−Alder reaction between dihydro-*β*-carboline and enones has been shown to require a large excess of enone (30 equiv) relative to imine in those cases where catalysis is observed: See refs 6c and 6d.

(13) Very low conversions (< 10% after 6 d) were obtained using 20 mol % *n*-hexylamine and 20 mol % acetic acid.

Scheme 4. Diastereoselective Thiourea-Catalyzed Formal aza-Diels−Alder Reactions





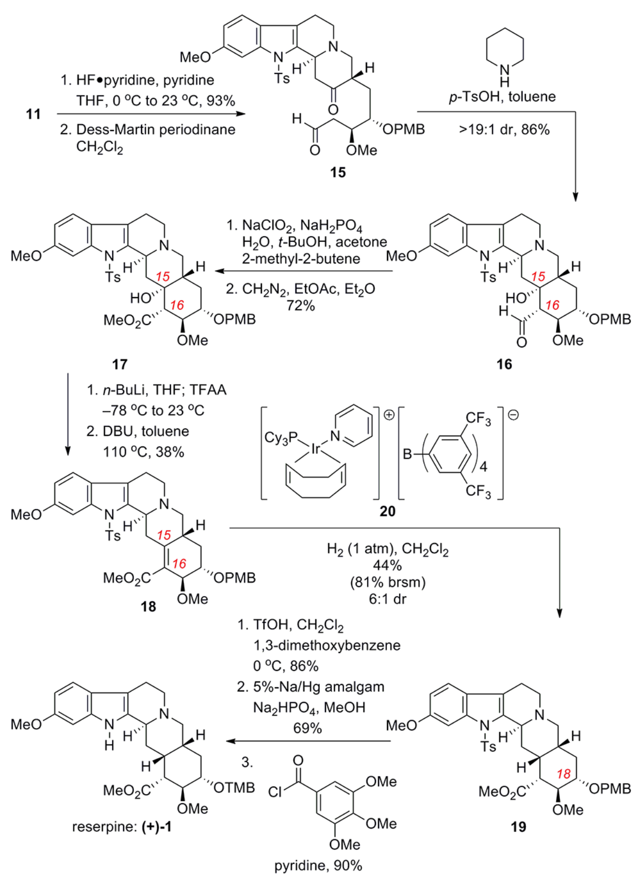
entry	amine (mol %)	AcOH (mol %)	time (d)	conv (%)	dr (**11**:**12**:**13**:**14**)
1	*n*-hexylamine (100)	100	9	90	1.0:1.0:0:0
2	**10** (20)	20	6	>99	11.5:1.0:1.8:0
3	*ent*-**10** (20)	20	6	>99	1.0:11.9:0:2.1

The closure of the E-ring to complete the carbon skeleton of reserpine was effected by an intramolecular aldol reaction of keto-aldehyde **15** (Scheme 5). Intermediate **15** was obtained in two steps from FADA adduct **11** through cleavage of the primary TBS ether with pyridine-buffered HF and oxidation of the resulting primary alcohol with the Dess−Martin periodinane. Treatment of crude aldehyde **15** with piperidine and catalytic TsOH resulted in an intramolecular enamine aldol reaction to afford C15 tertiary alcohol **16** as a single diastereomer. Pinnick oxidation of aldehyde **16** to the corresponding carboxylic acid followed by esterification with diazomethane provided methyl ester **17**.

Having efficiently accessed the pentacyclic framework of reserpine by means of the thiourea-catalyzed FADA reaction and a subsequent aldol cyclization, the key remaining challenge involved reduction of the hindered C15 alcohol of **17** with introduction of the desired cis-fusion at the D- and E-ring junction. While attempts to obtain the desired reduction product directly through radical deoxygenation were not fruitful, an elimination/reduction strategy proved successful. Regioselective elimination to α,β-unsaturated ester **18** was induced via trifluoroacetylation of alcohol **17** and subsequent elimination with DBU. After extensive evaluation of both homogeneous and heterogeneous catalytic systems under a range of conditions, cationic iridium complex **20**,[14] bearing the noncoordinating BArF counteranion, was identified as uniquely effective in the reduction of enoate **18**.[15] In addition, hydrogenation proceeded with a significant degree of facial selectivity (6:1 dr), ultimately affording the desired saturated ester **19** in 44% isolated yield (81% based on recovered olefin **18**). The stereochemical assignment of compound **19** was confirmed by X-ray crystallographic analysis.

With the fully elaborated pentacycle in hand, completion of the synthesis required only a global deprotection and installation of the trimethoxybenzoyl ester on the

Scheme 5. Completion of the Synthesis of (+)-Reserpine



E-ring. Thus, treatment of **19** sequentially with TfOH and sodium−mercury amalgam resulted in cleavage of the PMB ether and tosyl protective groups, respectively. The resulting C18 secondary alcohol was esterified using previously reported conditions to deliver reserpine ((+)-**1**).[3i]

The enantioselective total synthesis of reserpine was accomplished in 19 steps in the longest linear sequence from racemic epoxide **5**. The convergent approach relied on chiral catalysts to provide access to coupling component **4** and to address the historically problematic installation

(14) (a) Vazquez-Serrano, L. D.; Owens, B. T.; Buriak, J. M. *Inorg. Chim. Acta* **2006**, *359*, 2786. (b) Wüstenberg, B.; Pfaltz, A. *Adv. Synth. Catal.* **2008**, *350*, 174.
(15) Attempts to effect this transformation by means of conjugate reductions resulted instead in elimination of the C17 methoxy group.

of the C3 stereogenic center. Further application of the aminothiourea-catalyzed formal aza-Diels–Alder reaction in the synthesis of complex alkaloids of both natural and synthetic origin is anticipated.

Acknowledgment. This work was supported by the NIGMS (GM-43214, GM-59316, and GM-69721) and by predoctoral fellowship support to N.S.R. from Boehringer Ingelheim and to M.A.M. from Eli Lilly. We thank Dr. Shao-Liang Zheng at the Center for Crystallographic Studies at Harvard University for X-ray data collection and structure determination. We thank Dr. Yu-Sheng Chen at ChemMatCARS, APS, for his assistance with single-crystal data. ChemMatCARS Sector 15 is principally supported by the National Science Foundation/Department of Energy under Grant No. NSF/CHE 0822838. Use of the Advanced Photon Source was supported by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences, under Contract No. DE-AC02-06CH11357.

Supporting Information Available. Complete experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of all isolated intermediates, and crystallographic data for compound **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.