

Enantioselective Total Synthesis
of (+)-Reserpine

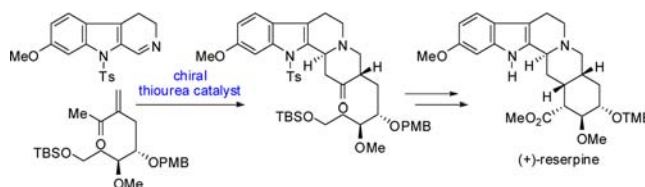
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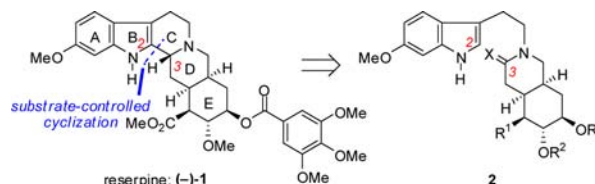
ABSTRACT



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

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



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

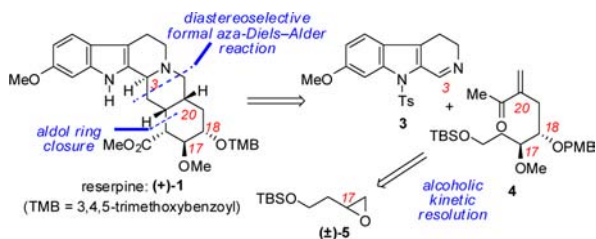
This approach is generally complicated by preferential formation of the C3 center with the undesired, thermodynamically favored relative stereochemistry.⁴ This limitation was overcome in a notable and most elegant manner in the Stork synthesis, wherein the desired C3 configuration

- (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.

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

Scheme 2. Retrosynthetic Analysis of (+)-Reserpine

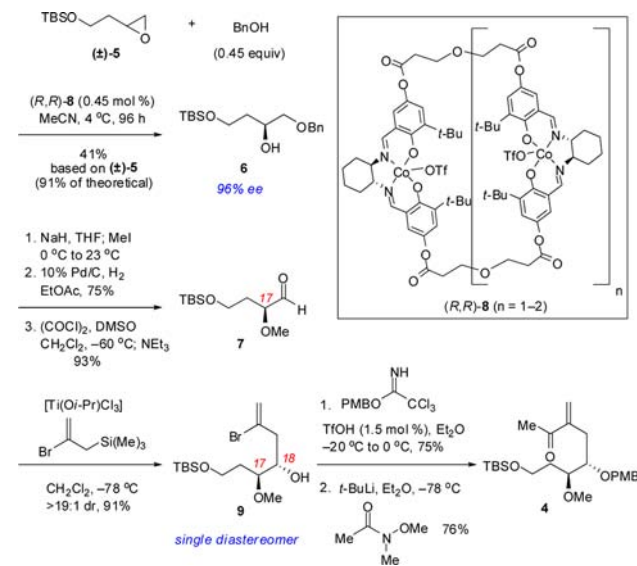


We envisioned an alternative approach to the reserpine framework focused on specifically targeting control over the C3 stereogenic center by means of a stereoselective formal aza-Diels–Alder (FADA) reaction between two fragments of comparable size (**3** and **4**, Scheme 2).⁶ Although high levels of 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 % aminothiurea **10**,⁷ providing the desired diastereomer **11** in 76% isolated yield. Notably, the enantiomeric primary aminothiurea *ent*-**10** induced a reversal of diastereoselectivity in the FADA reaction to afford ketone **12** selectively (entry 3).

(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.

(5) A related cyclization of an amino-nitrile intermediate was recently employed in the syntheses of C3-epimeric natural products venenatine and alstonine: 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) (\pm)-Deserpidine: Szántay, C.; Blaskó, G.; Honty, K.; Baitz-Gács, E.; Tamás, J.; Tóke, L. *Leibigs Ann. Chem.* **1983**, *8*, 1292. (b) (\pm)-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.

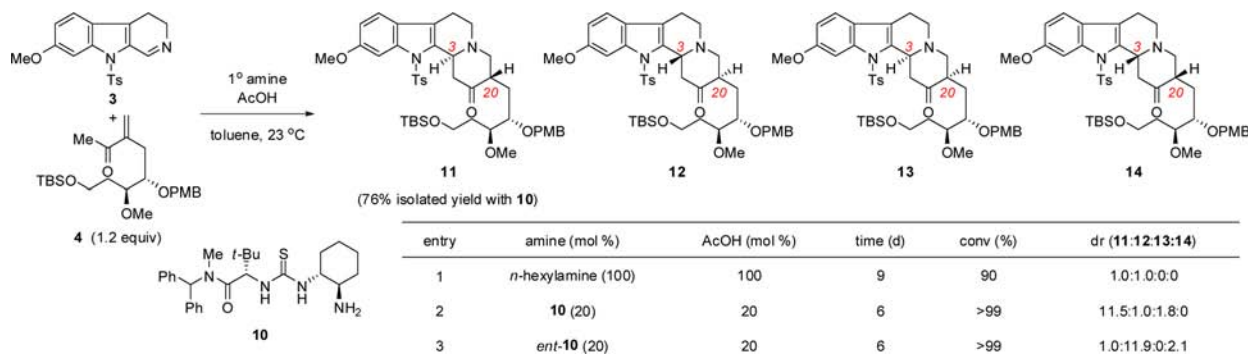
(7) Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 1021/ja310718f.

(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.

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

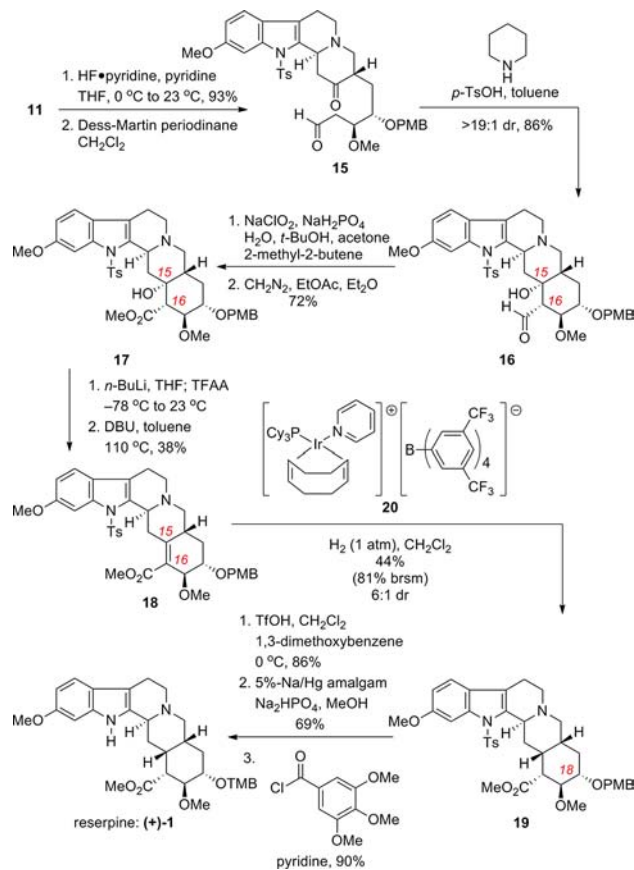


The closure of the E-ring to complete the carbon skeleton of reserpine was effected by an intramolecular aldol reaction of keto-aldehyde **15** (Scheme 5). Intermediate **15** was obtained in two steps from FADA adduct **11** through cleavage of the primary TBS ether with pyridine-buffered HF and oxidation 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**).³¹

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.

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Supporting Information Available. Complete experimental procedures, characterization data, ^1H 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.