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

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 aza-Diels–Alder (FADA) reaction discovered recently in our laboratories.⁷ Herein, we describe the successful

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Supporting Information Available Complete experimental procedures, characterization data, and ¹H and ¹³C 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>.

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 multi-gram scale. Elaboration of protected alcohol **6** to aldehyde **7** was accomplished in a 3-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.

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 equivalents) 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).

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Synthetic strategy common to all previous successful approaches to reserpine

Scheme 2.
Retrosynthetic analysis of (+)-reserpine

Scheme 3.
Stereoselective synthesis of enone 4

Scheme 4.
Diastereoselective thiourea-catalyzed formal aza-Diels–Alder reactions

Scheme 5.
Completion of the synthesis of (+)-reserpine