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A Desymmetrization-Based Total Synthesis of Reserpine

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Dedicated to Professor E. J. Corey on the occasion of his 90th birthday

Abstract: *Reported herein is a desymmetrization-based synthetic approach to the fused polycyclic indole alkaloid reserpine. The centerpiece of the developed strategy features an internal desymmetrization process that enabled the use of a readily accessible and nonstereogenic reserpine E-ring precursor, in contrast to the synthesis-intensive and stereodefined E-ring intermediates employed in all past reserpine syntheses. Utilization of inexpensive reagents through an orchestrated sequence of carefully selected chemical transformations further highlight the overall effectiveness of the developed pathway.*

More than sixty years on since Woodward's total synthesis of reserpine (**1**; Figure 1),[1] this landmark achievement stood the test of time as one of the most powerful lessons in conformational control and stereoselective organic synthesis.[2] From a synthetic viewpoint, the pentacyclic core structure of **1**, characterized by its array of functional groups and stereocenters, poses numerous "problem centers", with the most challenging of all being the densely-substituted cyclohexyl "E" ring. Indeed, the stereocontrolled preparation of the reserpine E-ring precursors was rigorously investigated in each of the past synthetic studies,[1] and collectively showcased the richness of ingenious solutions ranging from cycloaddition [Woodward (4+2, intermolecular),[1b–d] Pearlman (2+2, intramolecular),[1e] Martin (4+2, intramolecular),[1h,i] Stork (4+2/double-Michael, intermolecular),[1j,r] Liao (4+2, intramolecular),[1m] Shea (4+2, intramolecular),[1p,q] and Mehta (4+2, intermolecular)],[1o] radical cyclization (Fraser-Reid, intramolecular),[1k,l] Cope rearrangement (Wender),[1f,g] and chiron approach (Hanessian).[1n] While appreciating the valuable lessons from these historical achievements, we pondered if a simplified synthon could be utilized as the precursor for the reserpine E ring. In particular, as part of our continued investigations in desymmetrization-based target-oriented synthesis,[3] we hypothesized the symmetrical cyclohexanone **3** (monocyclic or bridged-bicyclic) to be a viable synthetic intermediate as illustrated in Scheme 1. Upon installation of a tryptamine subunit, the newly generated C3 stereocenter in the tetrahydro-β-carboline **4** renders C16 and C20 diastereotopic and therefore could be differentiated (locally desymmetrized) either externally (reagent control) or internally (substrate control). Further-

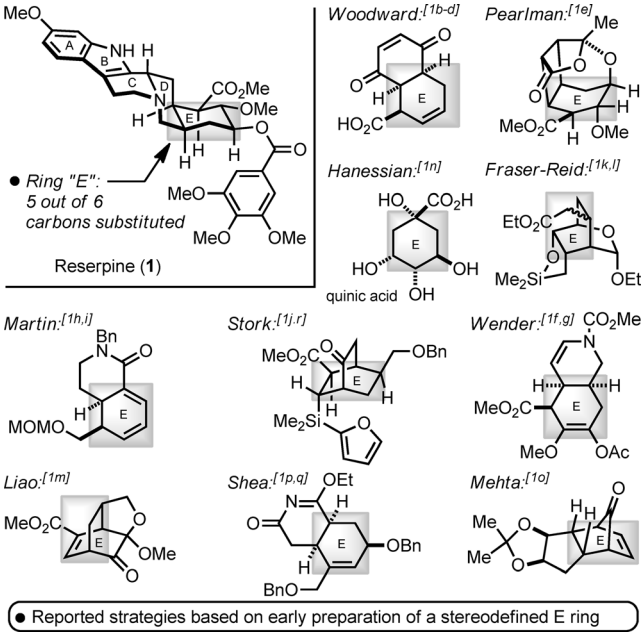
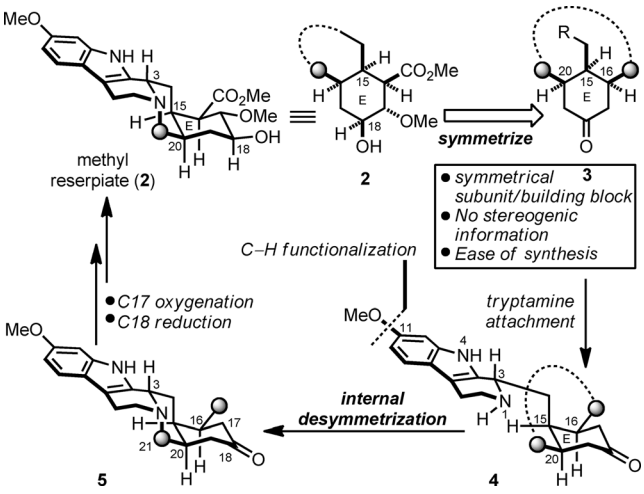


Figure 1. Chemical structure of reserpine (**1**) and reported synthetic approaches to reserpine based on the preparation of a stereodefined reserpine E-ring precursor. Ac = acetyl, Bn = benzyl, MOM = methoxymethyl.



Scheme 1. Proposed synthetic strategy in this work based on the symmetrical reserpine E-ring precursor **3** and an internal desymmetrization (**4**→**5**).

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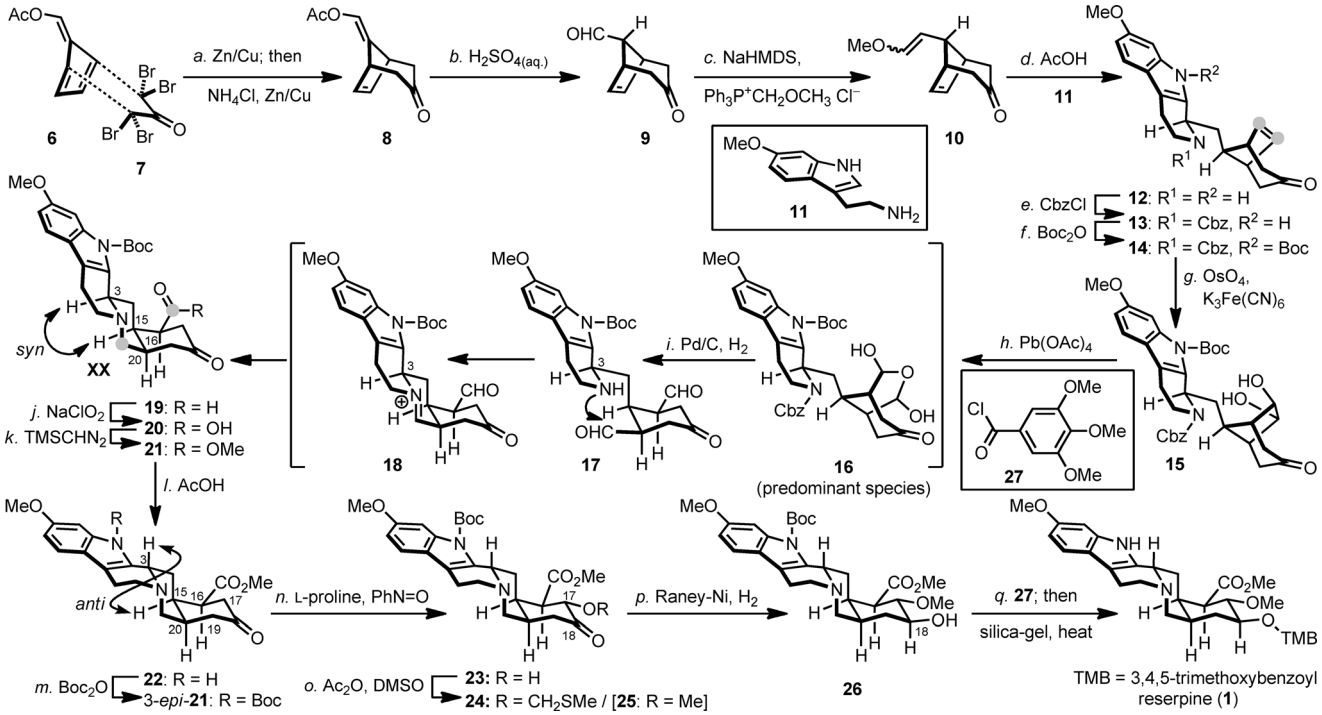


Scheme 2. Total synthesis of reserpine (**1**). Reagents and conditions: a) **6** (1.0 equiv), **7** (2.0 equiv), Zn/Cu (3.0 equiv), dibromomethane (cat.), MeCN, 23 °C, 1 h; then Zn/Cu (3.0 equiv), NH_4Cl (sat. in MeOH), 23 °C, 35 min, 27%; b) H_2SO_4 (10% aq.), 1,4-dioxane, 100 °C, 4 h, 50%; c) NaHMDS (1.0 M in THF, 1.3 equiv), $Ph_3P^+CH_2OCH_3Cl^-$ (1.1 equiv), THF, 0 °C, 1.5 h, 60%; d) **11** (1.1 equiv), AcOH, 125 °C, 1.5 h; e) CbzCl (1.2 equiv), CH_2Cl_2/$NaHCO_3$(aq.) (1:1), 23 °C, 1 h, 61% for two steps; f) Boc_2O (3.0 equiv), DMAP (0.1 equiv), MeCN, 23 °C, 2 h, 90%; g) K_2CO_3 (3.0 equiv), $MeSO_2NH_2$ (1.0 equiv), $K_3Fe(CN)_6$ (3.0 equiv), OsO_4 (4% wt/wt, 10 mol%), *t*BuOH/H_2O (1:1), 23 °C, 11 h, 65%; h) Na_2CO_3 (1.5 equiv), $Pb(OAc)_4$ (1.5 equiv), CH_2Cl_2, 23 °C, 30 min; i) Pd/C (10% wt/wt, 10 mol%), H_2 (1 atm), EtOAc, 13 h, 23% for two steps; j) 2-methyl-2-butene (4.7 equiv), NaH_2PO_4 (4.3 equiv), $NaClO_2$ (4.3 equiv), *t*BuOH/H_2O/acetone (1:1:0.6), 23 °C, 1.5 h; k) $TMSCHN_2$ (20 equiv), MeOH/toluene (1:3), 0 to 23 °C, 20 min, 43% for two steps; l) AcOH, 125 °C, 3 h; m) Boc_2O (3.0 equiv), DMAP (0.1 equiv), MeCN, 23 °C, 2 h, 3-*epi*-**21**:31% for two steps and recovered **21**:65%; n) L-proline (50 mol%), nitrosobenzene (2.0 equiv), DMF, 23 °C, 12 h; then re-subject: L-proline (50 mol%), nitrosobenzene (2.0 equiv), DMF, 23 °C, 35 h, 60%; o) AcOH/Ac_2O/DMSO (1:6:10), 23 °C, 10 h, 64%; p) Raney Ni®, H_2 (1 atm), EtOH, 23 °C, 1 h, 65%; q) **27** (3.5 equiv), Et_3N (4.5 equiv), DMAP (1.0 equiv), 23 °C, 9 h; then silica gel, toluene, 120 °C, 2.5 h, 61% for two steps. Ac_2O = acetic anhydride, AcOH = acetic acid, Boc_2O = di-*tert*-butyl dicarbonate, Boc = *tert*-butyloxycarbonyl, Cbz = carboxybenzyl, CbzCl = benzyl chloroformate, DMAP = *N*,*N*′-(dimethylamino)pyridine, DMF = *N*,*N*′-dimethylformamide, DMSO = dimethylsulfoxide, EtOAc = ethyl acetate, NaHMDS = sodium bis(trimethylsilyl)amide, TMS = trimethylsilyl.

more, internal differentiation of C16/C20 by engaging the secondary aliphatic nitrogen center (N1) in **4** could provide a direct entry to the entire reserpine pentacyclic core structure (e.g. **5**). Finally, a late-stage regioselective (and countra-steric) C17 oxygenation and a stereoselective C18 ketone reduction would need to be addressed to complete the total synthesis.

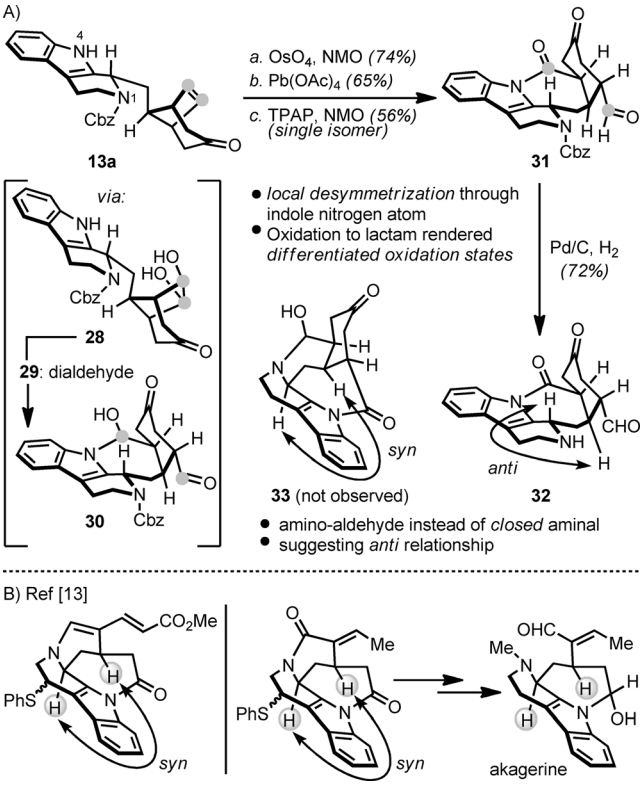
As shown in Scheme 2, our synthetic studies began with the preparation of the bicyclic ketoaldehyde **9**. Reductive [4+3] cycloaddition[4] between the acetoxyfulvene **6**[5] and tetrabromoacetone **7**[6] afforded the bicyclic enol acetate **8**, which was subjected to enol acetate hydrolysis with concomitant aldehyde epimerization to afford **9** in 14:1 d.r.[7] One-carbon homologation of **9** was carefully performed by engaging solely its aldehyde functionality ($Ph_3P^+CH_2OCH_3Cl^-$, NaHMDS), furnishing the methyl enol ether **10** as an inconsequential mixture of geometrical isomers. In this manner, our proposed symmetrical reserpine E-ring precursor **10** was readily prepared and ready for the attachment of the tryptamine domain. In contrast to the conventional Pictet–Spengler protocol that usually required an aldehyde reacting partner, **10** proved equally competent[8] in the reaction with the tryptamine **11** to deliver the tetrahydro-β-carboline **14** after sequential Cbz and Boc protection of the intermediate **12**. At this juncture, the stage was set for the rupture of the [3.2.1]-bicyclic domain of **14** and examination of the feasibility of the proposed internal desymmetrization. In this context, **14** was first subjected to OsO_4-catalyzed alkene dihydroxylation in the presence of $K_3Fe(CN)_6$[9] as the co-oxidant to afford the diol **15**. In contrast, dihydroxylation of **14** under the Upjohn conditions (NMO)[10] led to an intractable mixture of over-oxidized products, presumably because of the electron-rich nature of the methoxy-substituted tetrahydro-β-carboline (see below). Treatment of **15** with $Pb(OAc)_4$ led to a mixture diol-cleavage products containing predominantly the bis-hemiacetal **16** instead of its parent dialdehyde. Subjecting this mixture of compounds under Pd/C-mediated hydrogenation conditions in EtOAc[11] cleanly delivered the ketoaldehyde **19** as the only detectable constituent in the crude reaction mixture (by ^{1}H NMR analysis). The formation of **19** most likely proceeded through the initial hydrogenolysis with removal of the Cbz

protecting group, followed by intramolecular iminium formation (**18**) and in situ hydrogenation. More importantly, the exclusive formation of **19** as a single stereoisomer suggested the iminium formation took place by selectively engaging one of the two diastereotopic aldehydes in **17**. In doing so, our proposed internal desymmetrization had been realized as the result of the conformational bias imposed by the C3 stereocenter, which led to selective iminium formation followed by an irreversible reduction. This process can also be considered as an unconventional form of remote stereoinduction originating from the C3 stereocenter, and faithfully transmitted stereochemical information to three stereocenters at C15, C16, and C20. The ketoaldehyde **19** was converted into the ketoester **21** through $NaClO_2$ oxidation and methylation of the carboxylic acid intermediate (**20**) with trimethylsilyl diazomethane.

The stereochemical assignment of **21** was established based on extensive NMR experiments and spectral correlation studies, and found to possess the C3/C15-*syn*, C15/C16-*syn*, and C16/C20-*syn* relative stereochemistry. Gratifyingly, **21** could be conveniently converted into the ketoester **22** with the C3/C15-*anti* stereochemical relationship (and C15/C16-*syn*, C16/C20-*syn*), required for **1**, under AcOH-mediated equilibration conditions with near quantitative mass recovery, and **22** and 3-*epi*-**22** (and Boc-carbamates, **21** and 3-*epi*-**21**) could be effortlessly separated by standard silica gel chromatography ($\Delta R_f > 0.5$, EtOAc) to permit recycling.

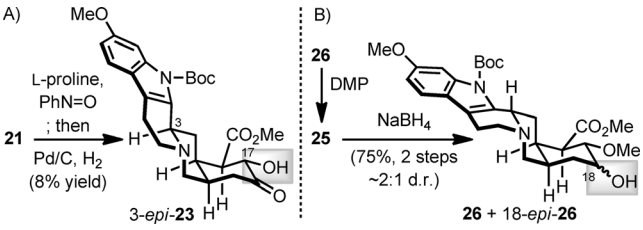
Besides the successful differentiation of the diastereotopic aldehydes in **17** through selective iminium formation (**18**), an alternative and complementary dialdehyde differentiation was also realized through the involvement of the indole nitrogen center (N4, Scheme 3 A). In this context, dihydroxylation of the tetrahydro-β-carboline **13a** could be successfully executed under OsO_4-NMO conditions, in stark contrast with the earlier observations for **14**. $Pb(OAc)_4$-mediated cleavage of the diol intermediate **28** led to the formation of the hemiaminal-aldehyde **30**, which underwent further oxidation (TPAP, NMO)[12] to afford the lactam **31** as a single stereoisomer. This finding once again suggested the internal desymmetrization of the dialdehyde intermediate (**29**), derived from oxidative cleavage of the diol **28**, was completely selective, and **31** with differentiated lactam and aldehyde oxidation states represents a versatile intermediate for further synthetic explorations. The relative stereochemical assignment of **31** was tentatively established upon hydrogenolysis removal of the Cbz carbamate to afford the aminoaldehyde **32**. We speculated **32** (hence lactam **31**) exhibited an *anti* relationship between the indicated hydrogen atoms since the corresponding *syn* isomer is likely to exist as its closed aminal (**33**) based on literature reports of related systems (Scheme 3 B).[13]

Advancing 3-*epi*-**21** next called for a regio- and stereoselective C17 oxygenation to complete the substitution pattern required for the E ring (Scheme 2). This easily stated objective underestimated several inherent challenges, most notably the "countra-steric" placement of an oxygen atom at C17 instead of the sterically less-demanding C19 position. While several enolate-oxygenation protocols[14] on simplified model systems provided mixed results, much to our surprise,



Scheme 3. A) Synthesis of the pentacyclic amino aldehyde **32** by formation of the hemi-aminal **30** through the indole nitrogen center. B) Reported literature examples of related polycyclic tetrahydro-β-carboline systems. TPAP = tetrapropylammonium perruthenate.

the L-proline/nitrosobenzene[15] combination smoothly delivered the α-hydroxyketone **23** as a single regio- and stereo isomer. In contrast, L-proline/nitrosobenzene-mediated α-oxygenation of the C3 epimeric ketoester **21** also afforded the desired C17 oxygenation but in significantly diminished yield (Scheme 4 A), hence the necessity to perform C3 isomerization on the pre-oxygenated intermediate **21**. Methylation of the newly installed C17 oxygen center also proved nontrivial, particularly considering the tendency of the tertiary amine in **23** to undergo undesired nitrogen quaternization under the conventional methylation conditions. After considerable experimentation, a two-step procedure involving thiomethylation of **23** under Pummerer-type conditions (DMSO, Ac_2O)[16] was implemented to afford an intermediate methylthiomethyl ether (**24**), which further underwent reductive desulfurization to achieve an overall oxygen methylation

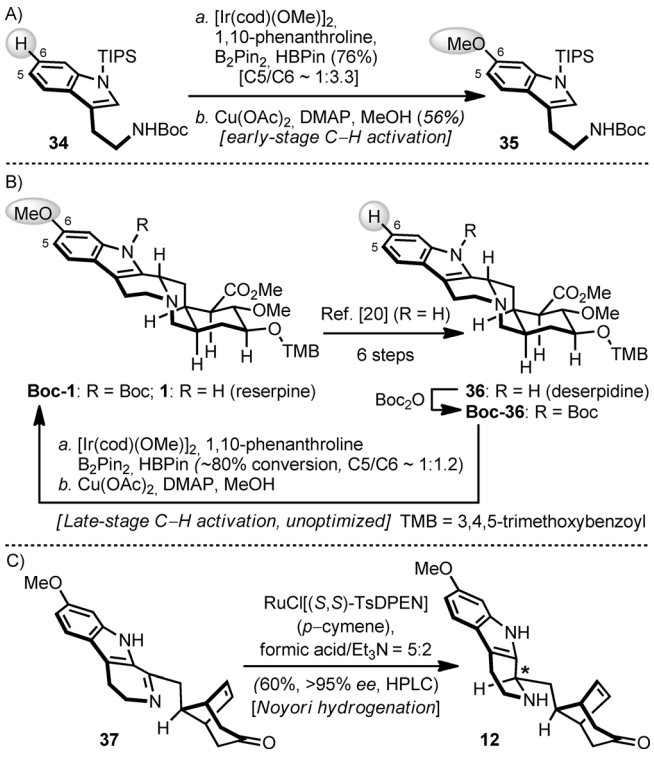


Scheme 4. A) L-proline/nitrosobenzene-mediated α-hydroxylation of **21**. B) $NaBH_4$-mediated reduction of ketone **25** leading to a mixture of C18 hydroxy stereoisomers. DMP = Dess–Martin periodinane.

(Scheme 2). While this indirect two-step methylation may seem unattractive at the outset, reductive desulfurization of **24** under Raney-Ni/H_2 conditions proved particularly valuable and simultaneously reduced the C18 ketone to furnish the hydroxy methyl ether **26** as a single stereoisomer. In contrast, reduction of the ketone **25** (derived from DMP oxidation of hydroxy methyl ether **26**) under $NaBH_4$ conditions afforded an inseparable mixture of C18 diastereomeric alcohols (Scheme 4B). To complete the synthesis, **26** was acylated with 3,4,5-trimethoxybenzoyl chloride (**27**) followed by removal of the Boc-carbamate under thermal conditions in the presence of silica gel (Scheme 2). These two final operations could be streamlined as a one-pot process upon concentration of the acylation reaction mixture and direct Boc removal. The unique effectiveness of the developed Boc-removal conditions (silica-gel, toluene, reflux) also merits a short commentary, as a variety of conditions led to by-product formation including but not limited to isomerization and trimethoxybenzoate ester cleavage.[17]

Finally, in contrast to the reported syntheses of **1**, the 6-methoxytryptamine (**11**)[18] used in this work was made available through an iridium-catalyzed C–H activation/borylation sequence (Scheme 5A).[19a] Furthermore, complementary to the reported conversion of **1** into deserpidine (**36**),[20] a late-stage C–H activation based preparation of **1** from **36** has been demonstrated for the first time, and is potentially applicable to our developed total synthesis starting from unsubstituted and commercially available tryptamine (Scheme 5B).[19b] This developed synthetic entry to **1** was also rendered asymmetric through the optically active **12**, prepared from a Noyori transfer hydrogenation[21] of the imine **37** (Scheme 5C).

In conclusion, total synthesis of reserpine (**1**) has been accomplished through a rationally designed internal desymmetrization strategy, which permitted the use of a greatly simplified reserpine E-ring precursor compared to all of the past syntheses. In essence, the success of this developed strategy constitutes an unconventional form of remote stereoinduction, where the reserpine C3 stereocenter (introduced racemically or optically active) faithfully dictated the introduction of stereochemical information to the reserpine E ring. Late-stage functionalization of the reserpine E ring, including a countra-steric C17 oxygenation and a fortuitous stereoselective C18 ketone reduction, also played pivotal roles in completing the synthesis. Conceptually related internal desymmetrizations are currently being investigated in a variety of target-oriented synthesis projects in our laboratory.



Scheme 5. A) C–H activation based synthesis of 6-methoxytryptamine **35**. B) Reported conversion of reserpine (**1**) into deserpidine (**36**) and late-stage C–H functionalization based conversion of **36** into **1** in this work. C) Synthesis of the optically active tetrahydro-β-carboline **12** by Noyori asymmetric transfer hydrogenation of **37**.
B_2Pin_2 = bis(pinacolato)diboron, HBPin = pinacolborane, TIPS = triisopropylsilyl.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · C–H activation · desymmetrization · natural products · total synthesis

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Communications

Natural Products

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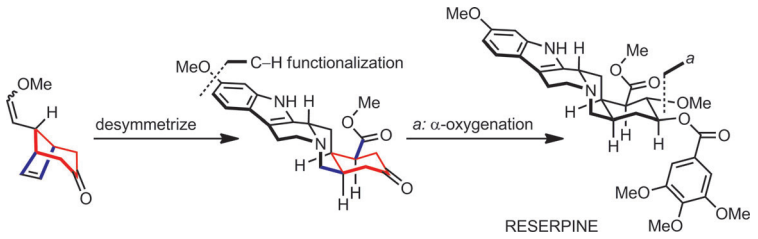
A Desymmetrization-Based Total Synthesis of Reserpine



Old target, new tricks: A total synthesis of the infamous polycyclic indole alkaloid reserpine has been accomplished. The synthetic strategy features a rationally designed internal-desymmetrization process, which renders the use of a greatly simplified reserpine E ring compared to all the past syntheses. A countra-steric late-stage oxygenation, C–H functionalization, and the use of inexpensive reagents further highlight the effectiveness of the developed synthetic pathway.

