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A divergent approach to the synthesis of the yohimbinoid alkaloids venenatine and alstovenine

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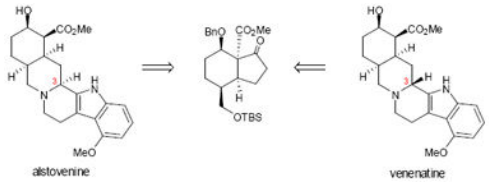
Abstract



The yohimbinoid alkaloids have received considerable attention from the synthetic community due to their interesting chemical structures and varied biological activity. Although there have been several elegant syntheses of certain members of this group of alkaloids, a truly unified approach has yet to be developed. In short, general approaches to this compound class have been hampered by a lack of complete control in setting the C(3) stereocenter at a late stage. Herein, we report that a functionalized hydrindanone enables a divergent strategy that builds on precedent from Stork, which addresses this long standing challenge. Utilizing an aminonitrile intermediate, the stereochemistry at C(3) of the yohimbinoid skeleton can be effectively controlled in a Pictet-Spengler reaction. This approach has been applied to the first total syntheses of the C(3) epimeric natural products venenatine and alstovenine.

The yohimbine indole alkaloids are among the most studied natural products, primarily owing to their potent and multifarious bioactivity.[1,2,3,4,5,6,7,8] While there have been many elegant syntheses to arrive at specific members of this class,[9,10,11,12,13,14,15,16,17,18,19,20] especially the archetypal member, reserpine (**2**, Figure 1), a unified approach to these molecules remains an unsolved problem.[21] In the realm of complex molecule assembly, the total synthesis of **2** by R. B. Woodward and co-workers is well recognized as a milestone

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Author contributions

T.P.L, J.L.W, and R.S. conceived and designed the synthetic experiments. T.P.L., J.L.W. and J.D. carried out the synthetic work. M.W.L. and D.J.T. carried out the computational work. T.P.L., J.L.W. and R.S. co-wrote the manuscript. All authors discussed the results and commented on the mansuscript.

event.[9,10,11] In many ways, reserpine presented a perfect forum to illustrate the power of stereoelectronic considerations in the preparation of the E-ring of this natural product and ultimately arrive at cyclization precursor **1**. Unfortunately, in the Woodward synthesis of reserpine, cyclization of amide **1** to forge the C ring of **2** led to the undesired C(3) epimer. As a result, a lactonization and acid-catalyzed epimerization sequence was required to invert the stereochemistry at C(3) to match the natural product (i.e., **2**).

Following Woodward's pioneering synthesis of reserpine (**2**), subsequent syntheses of **2** and related yohimbinoid natural products have appeared in the literature. However, because many of these syntheses adopted a strategy that is similar to the Woodward approach, they were also plagued with a stereoselectivity problem (or in some cases, a regioselectivity issue)[1] in installing the C(3) center, which had to be corrected to obtain the desired diastereomer. In 1989, Stork reported an inventive solution to the reserpine C(3) problem, that took advantage of the ionization of an intermediate aminonitrile (i.e., **3**, Figure 1).[12,13] The subtleties in stereocontrol in the Pictet-Spengler reaction afforded by aminonitriles allowed Stork to selectively access the undesired as well as the desired C(3) epimer necessary for the total synthesis of reserpine. While the Stork approach sets the foundation to address the C(3) problem, it remained unclear whether this tactic could be extended to the synthesis of other yohimbinoid natural products given the significant influence of the indole nucleophile on the diastereoselectivity of the Pictet-Spengler ring closure from an aminonitrile as discovered in our own work (*vide infra*). A general solution to this problem would yield a strategy for the preparation of the yohimbinoid alkaloids, given that structures in this class vary in the substitution about the indole moiety (see **4-13**, Figure 1), and include several members that are epimeric at C(3).[22,23,24,25,26,27] Herein, we disclose our efforts toward a general synthesis of the D/E cis-fused members of the yohimbinoid alkaloid family (i.e., **8-13**, Figure 1). This approach is showcased in the first total syntheses of the C(3) epimeric natural products venenatine (**9**) and alstovenine (**12**) in racemic form.[28,29,30,31,32,33]

Interestingly, the seemingly subtle difference in the stereochemistry of **9** and **12** (epimers at C(3)) results in a complete reversal of their effects on the central nervous system (CNS). Alstovenine (**12**) behaves as a CNS stimulant in mice (1 mg/kg) and significantly enhances the analgesic effects of morphine, whereas venenatine (**9**) displays activity analogous to reserpine (50 mg/kg in mice) and inhibits the analgesic effects of morphine.[34] Because the yohimbinoid "family at large" displays such interesting and contrasting activity, a concise and high-yielding synthesis of yohimbine congeners (which include the berbanes, see **14**, Figure 1)[35,36,37] would facilitate more detailed studies regarding the mode of action of these molecules.

Results and discussion

Our synthetic strategy (Figure 2), inspired by Stork's elegant synthesis of reserpine, targets a variety of yohimbinoid alkaloid natural products from the elaboration of pentacycles related to **15**, which vary only in the indole moiety. Pentacycle **15** could in turn arise from aminonitrile **16**, where careful tuning of the reaction conditions would enable cyclization to either series of C(3) epimeric natural products. The aminonitriles related to **16** would arise

from a condensation/Strecker sequence with a common intermediate aldehyde (**17**) and the requisite amine derivative. Aldehyde **17** was expected to arise from oxidative cleavage of hydrindanone **18**,[38,39,40] which could be constructed from a Diels-Alder reaction between diene **19** and enone ester **20**. This cycloaddition would set four contiguous stereocenters, leaving only the C(3) stereocenter to be set at a later stage.

Our synthetic studies commenced with readily available diene **19**[40] (Figure 2) and enone ester **20**.[41] Heating the mixture of these two compounds in toluene at 100 °C afforded hydrindanone **18** in 89% yield as a >10:1 ratio of the *endo:exo* diastereomers (*endo* assignment is in reference to the more electron withdrawing ketone moiety), which were readily separated by column chromatography. Of note, the enantiomers of the *endo* adducts can be readily separated on a preparatory scale using supercritical fluid chromatography and a chiral ODH column (for further details, see the Supporting Information). While access to **18** sets the stage for preparing the natural products in enantioenriched form, the syntheses reported herein were carried out in racemic form. Hydrogenation of **18**, silyl ether cleavage and sulfonation of the resulting primary alcohol group yielded benzenesulfonate **21** in 82% yield over three steps. At this juncture, α-hydroxylation followed by oxidative cleavage with lead tetraacetate unveiled aldehyde **17** in 70% yield. Treatment of aldehyde **17** with potassium cyanide in the presence of various tryptamine derivatives then furnished the desired aminonitriles (**16a-c**) as single diastereomers and in excellent overall yields. The relative stereochemistry of the 4-OMe tryptamine aminonitrile was unambiguously established by X-ray crystallographic analysis (see ORTEP **16b**, Figure 2; some hydrogen atoms removed for clarity).[42]

Substrates **16a-c** were subjected to Pictet-Spengler cyclization conditions (Table 1), with special attention paid to the role arene nucleophilicity[43,44] plays in both the rate and stereoselectivity of the pentacycle formation.[45,46,47] Consistent with the elegant studies of the Stork group, treatment of aminonitriles **16a-c** with hydrochloric acid (0.1 M in THF) at 23 °C resulted in exclusive formation of the β-diastereomer (i.e., **23a-c**; see entries 1-3) for all substrates. The relative stereochemistry was unambiguously assigned for substrate **23b** by X-ray crystallographic analysis (see ORTEP, Table 1; some hydrogen atoms removed for clarity).

More surprising, however, was that the inherent diastereoselectivity of the thermal Pictet-Spengler cyclization (heating to 160 °C in acetonitrile; Method B in Table 1) of the substrates was greatly influenced by the nature of the indole fragment (see entries 4-6). Tryptamine-derived aminonitrile **16a** cyclized upon heating in acetonitrile to afford a 1:3 (β:α) mixture of diastereomers, whereas 4-methoxytryptamine substrate **16b** and 6-methoxytryptamine substrate **16c** cyclized to give a 1:1.8 (β:α) and 1:8 (β:α) mixture of diastereomers, respectively. Of note, the latter observation is in line with the observed diastereoselectivity for the thermal cyclization of aminonitrile **3** in refluxing acetonitrile reported by Stork.[12,13]

Because several yohimbinoid natural products possess the indole substitution pattern present in **16a** and **16b**, the stereoselectivities for these cyclizations needed to be improved if a versatile approach to the yohimbinoid natural products was to be realized. As such, we

embarked upon a campaign to optimize the diastereoselectivity of the Pictet-Spengler cyclization under thermal conditions (i.e., Method B) and chose to focus on substrate **16b** as it represented the most challenging selectivity scenario. Stork has previously proposed the formation of a tight ion pair between the departing cyanide and forming iminium ion under thermal Pictet-Spengler conditions for aminonitriles, which leads to attack of the arene nucleophile from the β-face (see **26→24b**, Figure 3).[12,13] On the basis of this analysis, we reasoned that a solvent with a lower static permittivity (dielectric constant)[48] would lead to tighter ion pairing and further enhance the diastereoselectivity of the cyclization. In an initial investigation of solvent effects (entries 3-7, Table 2), only acetonitrile and isopropanol, among solvents of similar polarity, provided the desired diastereomer (**24b**) as the major product, suggesting a more participatory role of the solvent. Several mechanistic possibilities that may exist are shown in Figure 3.

In one scenario, an acetonitrile solvent molecule could engage iminium ion **26'** to form a different electrophilic species (see **27** or **28**, Figure 3) that could then be displaced by the indole moiety in a direct intramolecular S_N2-like process. As a probe for this mechanistic possibility, nucleophilic additives such as DMAP and imidazole were investigated. Gratifyingly, heating aminonitrile **16b** to 160 °C in the presence of DMAP in toluene led to reversal of the stereoselectivity (from a 1.8:1.0 d.r. (β:α) for the thermal cyclization without additives in toluene; entry 7, Table 2) to favor the α diastereomer (1:2 d.r., (β:α); entry 9, Table 2). Furthermore, in acetonitrile, the diastereoselectivity was enhanced (1:4 d.r. (β:α); entry 10, Table 2) relative to cyclization in the absence of additives (1:1.8 d.r. (β:α); entry 3, Table 2). Upon addition of a stronger nucleophile (in the form of NaI; entry 11, Table 2), a greater than 1:10 d.r. (β:α) in favor of the α-diastereomer at C(3) was obtained.

Although the mechanism of the thermal Pictet-Spengler cyclization and the role of the iodide additive is still unclear, it may be that rapid exchange of the cyanide for the iodide occurs to produce a reactive iodo species (analogous to **16b**, Figure 3). At this juncture, iminium ion **27** could begin to form with the much larger iodide serving as an intimate counteranion and effectively blocking the α-face and leading, overwhelmingly, to the α-diastereomer (**24b**) as the major product. Computational studies are currently underway to provide insight on the observed diastereoselectivities of the Pictet-Spengler reaction as well as the role of additives such as NaI.

With optimized cyclization conditions leading to either C(3) epimer in hand, all that remained to complete the synthesis of venenatine (**9**) and alstovenine (**12**) was removal of the allyl ester by deallylation/decarboxylation and cleavage of the benzyl ether in **23b** and **24b** (Figure 4). Toward this end, we have found that treatment of ester **23b** with a Pd(II) precatalyst under neutral conditions and elevated temperature facilitates conversion to the desired monoester (**29**) along with some elimination of the benzyloxy group to give an enoate (**30**). Hydrogenolysis of the benzyl ether in **29** to give venenatine (**9**) was fraught with its own challenges. Initial attempts utilizing palladium on carbon and H_2 (1 atm) were unfruitful. Neither increasing the H_2 pressure (up to 200 psi) nor using acid additives resulted in the desired benzyl ether cleavage. However, treatment of **29** with BBr_3 at low temperature selectively cleaved the benzyl ether, leaving both the methyl ester and methyl ether intact, to afford venenatine (**9**) in 60% yield. The stereochemical assignment of the

methyl ester group was determined by NOESY studies (for further details, see Supporting Information). Interestingly, in the case of alstovenine the use of the deallylation/ decarboxylation conditions employed for venenatine pentacycle **23b** led only to recovered starting material and the product of β-hydroxy elimination. This undesirable outcome could be circumvented through the use of a more homogenous catalyst system (Pd_2dba_3, pyrrolidine) to afford **31**. Lastly, BBr_3 promoted cleavage of the benzyl ether yielded alstovenine (**12**).

While the spectroscopic data for synthetic and natural alstovenine were in reasonable agreement, we were surprised to observe some large inconsistencies (> 4.8 ppm) when the ^{13}C data for synthetic venenatine was compared with that reported for the isolated natural product, especially given the support for our assignment by X-ray and NOESY analysis of key intermediates. In an effort to identify the origin of these discrepancies, computational predictions for the ^{13}C NMR chemical shifts[49] of **9** were undertaken since all attempts to obtain an authentic sample for comparison failed. In general, the computed predictions for the ^{13}C NMR chemical shifts (Calculated at the SMD(chloroform)-mPW1PW91/6-311+G(2d,p)//B3LYP/6-31+G(d,p) level with linear scaling; for complete computational details see the Supporting Information) were found to be in better agreement with our synthetic data (mean absolute deviation (MAD) of 1.37 ppm) than with the isolation data (MAD of 1.85 ppm). Furthermore, the computational predictions identified two ^{13}C resonances (at 104.3 ppm and 31.0 ppm) from the isolation data as outliers; both deviating by 5.0 ppm or more from the computational data (A complete line listing comparison can be found in the Supporting Information). Importantly, the outlier at 104.3 ppm reported in the ^{13}C data for isolated venenatine, which was one of the resonances that differed markedly from our synthetic ^{13}C data, also varies significantly from the corresponding ^{13}C resonances reported for closely related congeners including alstovenine, 16-*epi*-alstovenine, 16-*epi*-venenatine, and 9-methoxy-3-epi-α-yohimbine, which are all in line with our synthetic data. While no conclusive statement can be made regarding the origin of this discrepancy, it is possible that the reported data for isolated venenatine may have been mistabulated.

In summary, we have identified, an effective, general path to the syntheses of a subset of yohimbinoid alkaloids that are epimeric at C(3). This work, which has resulted in the first total syntheses of the alkaloids venenatine and alstovenine in racemic form, builds on important observations by Stork pertaining to aminonitrile Pictet-Spengler cyclizations. Key to the success of our synthetic studies was the identification of conditions to effectively control the diastereoselectivity of a late-stage Pictet-Spengler cyclization employing a variety of indole nucleophiles. Highlights from this study include: 1) the use of a hydrindanone intermediate **18**, which allows rapid, stereoselective synthesis of the yohimbinoid skeleton, 2) the discovery that nucleophilicity of the indole moiety plays a significant role in the inherent diastereoselectivity of the Pictet-Spengler cyclization, and 3) the addition of an exogenous nucleophile (NaI) that leads to the complete reversal of the diastereoselectivity in the installation of the C(3) center.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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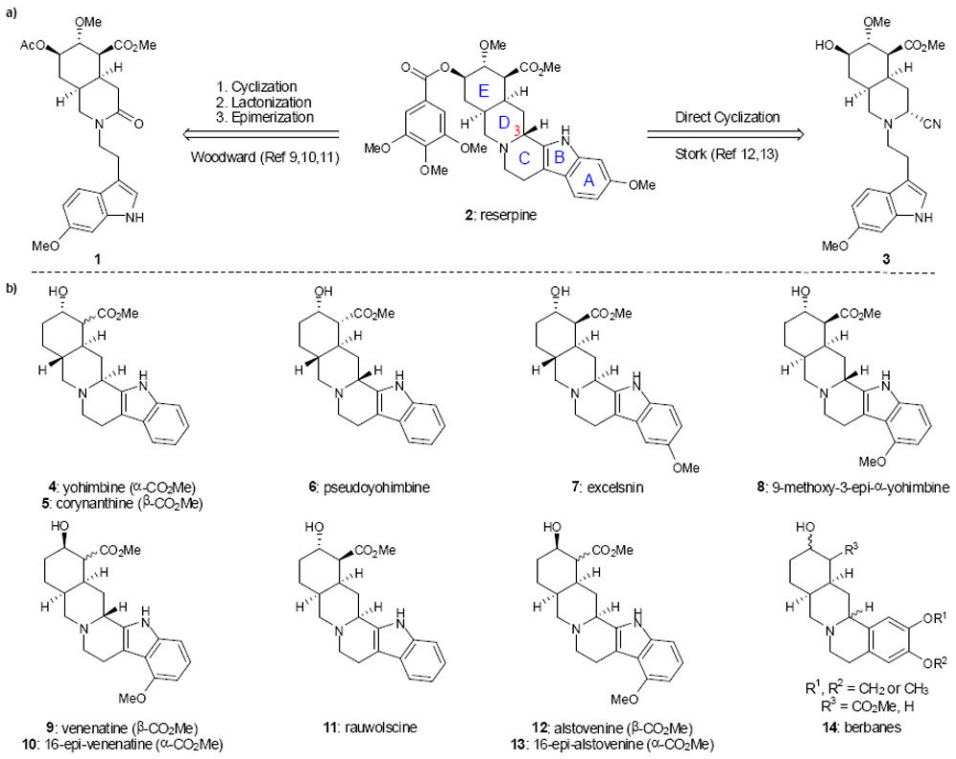


Figure 1.

Classic approaches to reserpine and selected yohimbine and berbane alkaloids. **a)** Classic approaches to closure of the C-ring and setting of the C-3 stereocenter of reserpine. **b)** Selected yohimbinoid natural products that vary in the substitution pattern of the indole ring. The ability to access a variety of yohimbine natural products from a common precursor would allow for a unified approach to this group of alkaloids. Me, methyl; Ac, acetyl

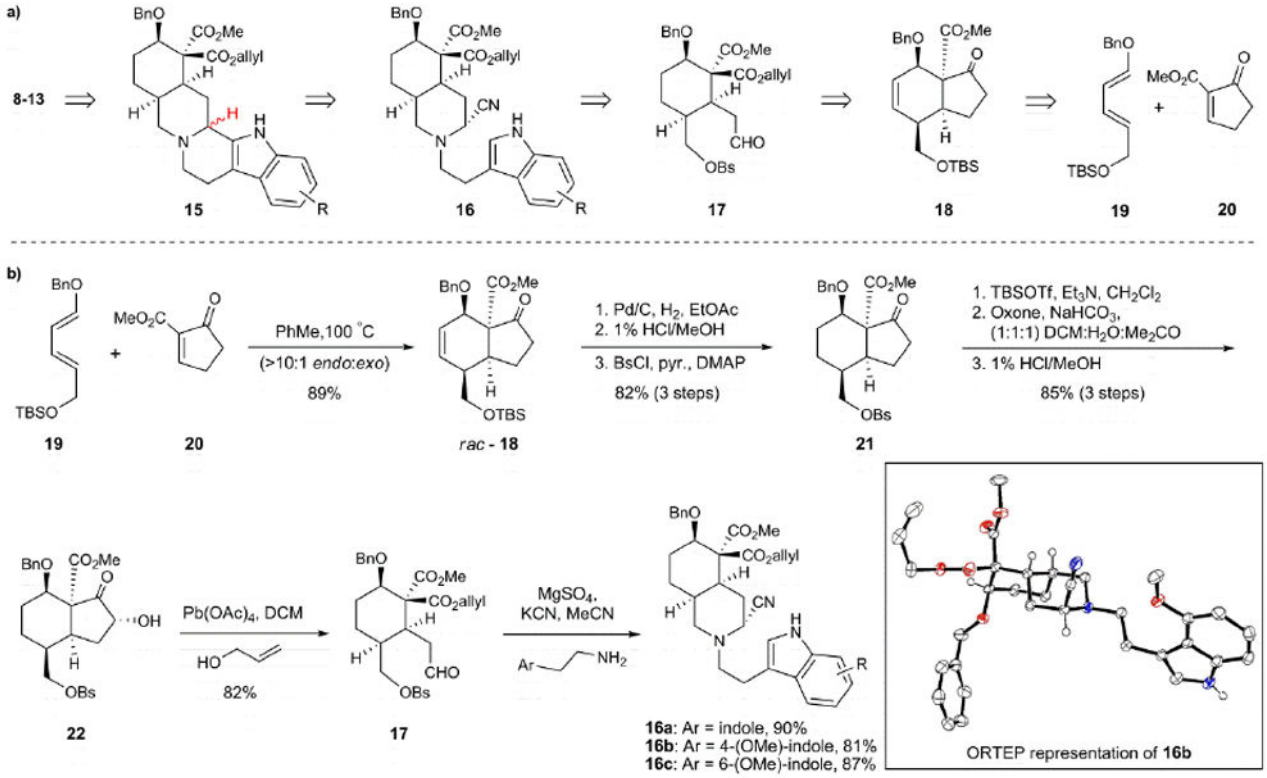


Figure 2.

Retrosynthetic plan and synthesis of the aminonitrile Pictet-Spengler substrates. **a)** A variety of yohimbinoid natural products can be accessed from common hydrindanone precursor **18.** **b)** The Diels-Alder cyclization between diene **19** and dienophile **20** provides hydrindanone **18** setting four contiguous stereocenters. Conversion of hydrindanone **18** into aldehyde **17** sets the stage for rapid formation of aminonitriles (**16a-c**) with varying substitution on the indole moiety. Bs, benzenesulfonyl; TBS, *tert*-butyldimethylsilyl; Bn, benzyl; PhMe, toluene; pyr, pyridine; DMAP, 4-dimethylaminopyridine; TBSOTf, *tert*-butyldimethylsilyl triflate; Oxone, potassium monopersulfate; DCM, dichloromethane.

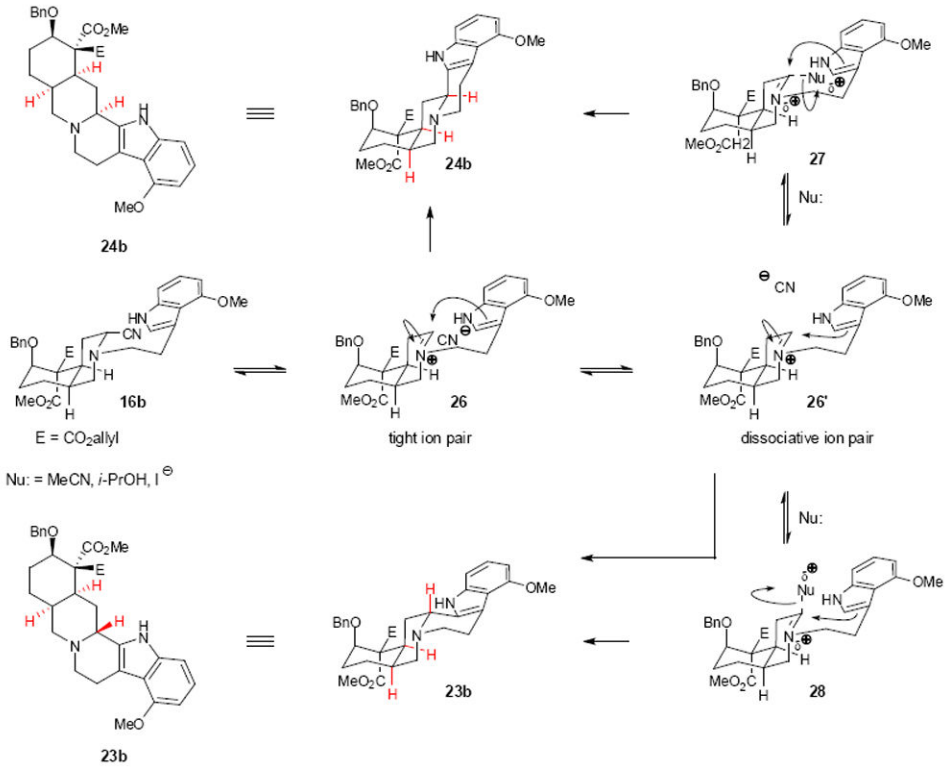


Figure 3.

Plausible reaction pathways for the thermal cyclization. Thermal cyclization of aminonitrile **16b** leads to a diastereomeric mixture of pentacycles **23b** and **24b**. The diastereomeric ratio is dependent on the reaction conditions employed with nucleophilic solvents and additives favouring formation of the α-diastereomer **23b**. Several mechanistic possibilities are presented. Nu, nucleophile; Bn, benzyl.

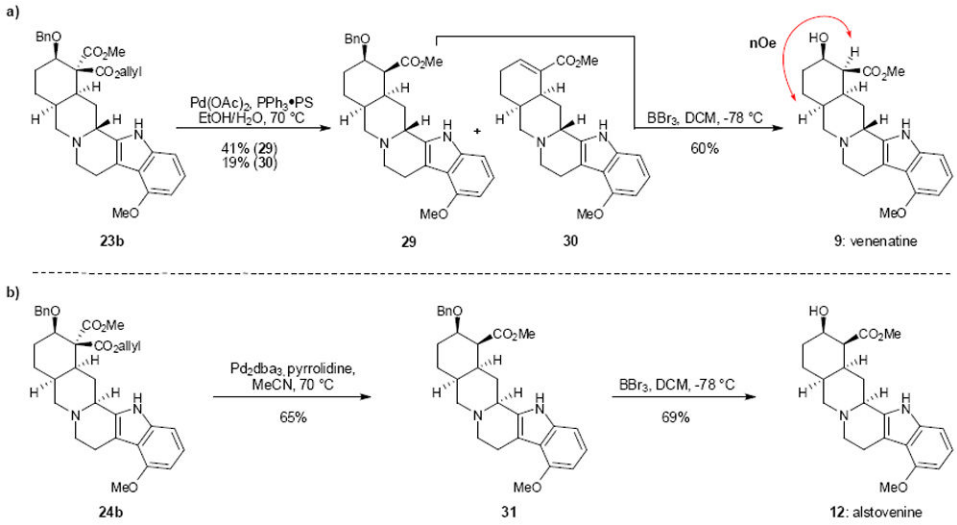
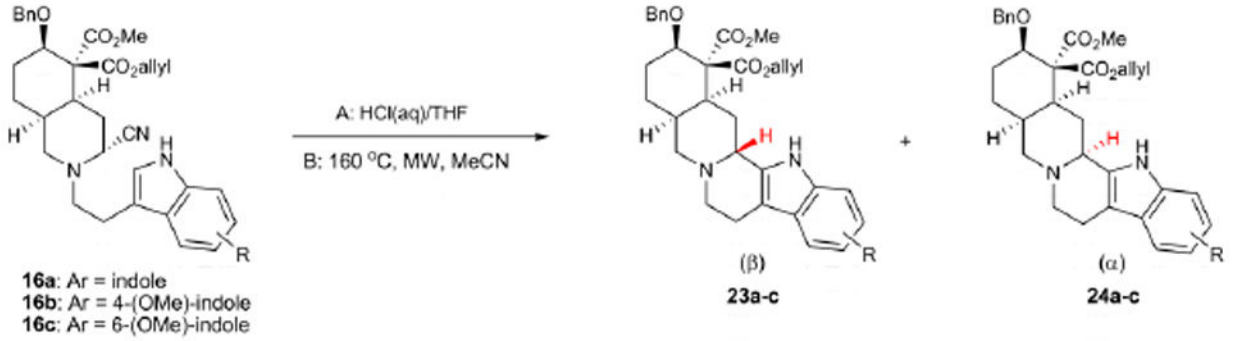


Figure 4.

Synthesis of venenatine and alstovenine. Pd catalyzed deallylation/decarboxylation allows for allyl ester removal in **23b** and **24b** under mild conditions, minimizing β-hydroxy elimination. Treatment of **29** and **31** with BBr_3 leads to selective removal of the benzyl protecting group and access to venenatine and alstovenine respectively. PS, polymer supported; nOe, nuclear Overhauser effect; dba, dibenzylideneacetone; Bn, benzyl; DCM, dichloromethane.

Table 1

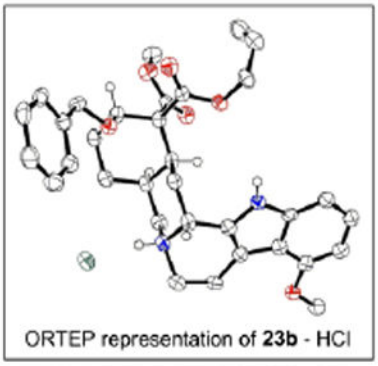
Role of the indole nucleophile in the stereoselectivity of the Pictet-Spengler cyclization.



16a: Ar = indole
16b: Ar = 4-(OMe)-indole
16c: Ar = 6-(OMe)-indole

Entry	Aryl Amine	Method[a]	Diastereomeric Ratio (β:α)[b]
1	**16a** (R = H)	A	1:0
2	**16b** (R = 4-OMe)	A	1:0
3	**16c** (R = 6-OMe)	A	1:0
4	**16a** (R = H)	B	1:3
5	**16b** (R = 4-OMe)	B	1:1.8
6	**16c** (R = 6-OMe)	B	1:8

[a] Method A: 1N HCl(aq)/THF, rt Method B: MeCN, 160 °C, μwave.
[b] Ratio determined by NMR analysis of the crude reaction mixture.



ORTEP representation of **23b** - HCl

Table 2

Solvent effects in the Pictet-Spengler cyclization.

Entry	Solvent	Temperature (°C)[a]	Additive[b]	Diastereomeric Ratio (β:α)[c]
1	THF	rt[d]	HCl	1:0
2	MeCN	82[e]	-	n/r
3	MeCN	160	-	1:1.8
4	acetone	160	-	2.5:1
5	*i*-PrOH	160	-	1:1.3
6	*i*-PrCN	160	-	1.4:1
7	PhMe	160	-	1.8:1
8	PhMe	160	Imidazole	1:1.6
9	PhMe	160	DMAP	1:2.0
10	MeCN	160	DMAP	1:4
11	MeCN	160	NaI	1:10

[a] Reaction carried out in microwave reactor in a sealed vial unless otherwise noted.

[b] 2.8 equivalents.

[c] Ratio determined by NMR analysis of the crude reaction mixture.

[d] Reaction carried out in a sealed vial under a N_2 atmosphere

[e] Reaction carried out in a sealed vial in an oil bath