Cooperative Catalysis

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Enantioselective Syntheses of Heteroyohimbine Natural Products: A Unified Approach through Cooperative Catalysis**

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Abstract: *Alstonine and serpentine are pentacyclic indoloquinolizidine alkaloids (referred to as "anhydronium bases") containing three contiguous stereocenters. Each possesses interesting biological activity, with alstonine being the major component of a plant-based remedy to treat psychosis and other nervous system disorders. This work describes the enantioselective total syntheses of these natural products with a cooperative hydrogen bonding/enamine-catalyzed Michael addition as the key step.*

Alstonine (**1**) and serpentine (**2**) are pentacyclic alkaloids proposed to contain a zwitterionic indolo[2,3-a]quinolizidine, referred to as an anhydronium base[1] (Figure 1 A). This structural motif is rare among natural products[2] and is especially unusual in total synthesis, with the only examples being strychnoxanthine (**3**) and melinonine-E (**4**).[3] Alstonine has recently been identified as the major component of a plant-based treatment used in Nigeria by traditional healers to treat psychotic disorders.[4] However, the scarcity and lack of purity from natural sources, as well as the uncertainty regarding its exact mechanism of action, illustrates the need for an asymmetric synthesis to enable further study. The related *trans* diastereomer, serpentine, exhibits anticancer[5] and antimalarial[6] properties and there have been limited efforts at elucidating its mechanism of action.[7]

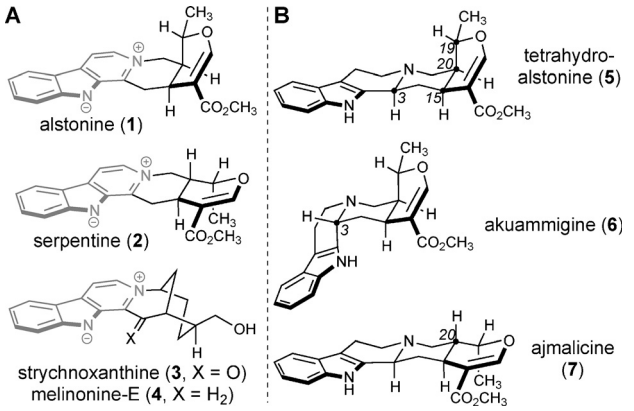

Figure 1. A) Examples of known anhydronium base natural products; B) structurally related heteroyohimbine alkaloids.

The closely related heteroyohimbine family of alkaloids (Figure 1 B) has elicited the interest of numerous synthetic groups for multiple decades,[8] with representative alkaloids of this family including tetrahydroalstonine (**5**), akuammigine (**6**), and ajmalicine (**7**). These natural products are structurally similar to alstonine and serpentine, only differing in ring saturation and relative stereochemistry at C3 and C20 (Figure 1 B). Though 80 years have passed since the first isolations of alstonine (from *Alstonia constricta*[9]) and serpentine (from *Rauvolfia serpentina*[10]), surprisingly, no total syntheses of these specific compounds have been reported to date. Herein, we disclose enantioselective syntheses of these indole alkaloids and their natural product progenitors (**5** and **7**), from a common intermediate employing a cooperative catalysis strategy necessitated by the intrinsic lack of reactivity of a common acyclic substrate.

Our approach toward alstonine and serpentine focused on the corresponding heteroyohimbine alkaloids tetrahydroalstonine (**5**) and ajmalicine (**7**), respectively. Both of these intermediates can be derived in principle from the corresponding bicyclic dihydropyrans through successive *N*-functionalization (reductive amination and oxidative iminium ion cyclization[8d,11] (**8**→**9**→**10**, Figure 2).

These dihydropyran stereoisomers (**11** and **12**) could be obtained through a known "acyl–lactone rearrangement" from the corresponding lactones (**13** and **14**), a reaction first disclosed by Korte.[12] Both diastereomers of the bicyclic lactone can be derived from the same *trans*-substituted piperidine (**15**), which we sought to assemble through what at first seemed to be a straightforward enamine-catalyzed intramolecular Michael reaction. Asymmetric enamine catalysis is a field that has seen tremendous innovation in the past 15 years.[13] The large majority of publications utilizing enamine-catalyzed Michael additions have involved the use of electron-deficient Michael acceptors such as alkylidene malonates, nitro-olefins, and vinyl ketones.[14] For more challenging transformations, additives such as Brønsted acids,[15] H-bond donors,[16] and Lewis acids,[17] which generally facilitate conversion by activation of the electrophile,[18] are employed. Given all of this innovation, it is surprising that asymmetric intramolecular Michael additions[19] into simple unsaturated esters still remain underexplored, with reported

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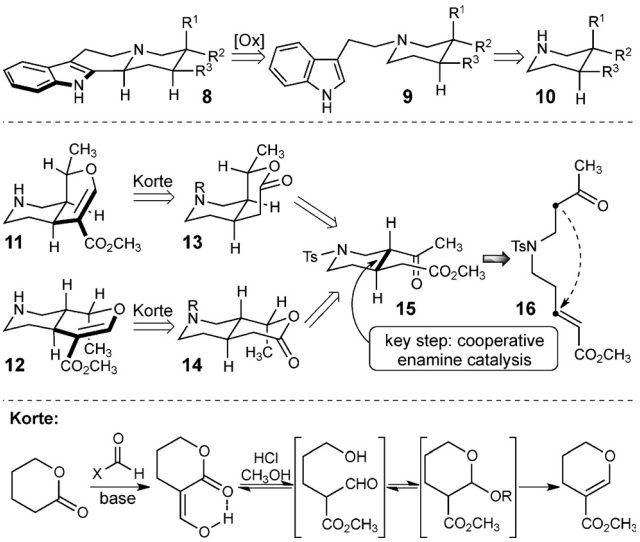


Figure 2. Retrosynthetic approach for alstonine and serpentine via **15**.

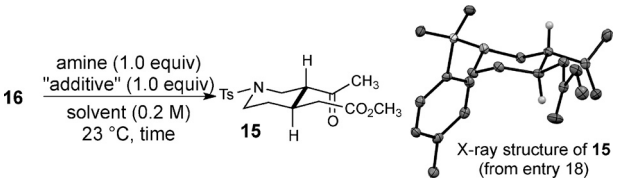
examples typically involving stoichiometric amine and extended reaction times (3–4 weeks).[20] In our studies to form *trans*-piperidine **15**, we first used stoichiometric pyrrolidine (Table 1, entry 1) with linear precursor **16** (obtained in 41% yield over four steps from 3-amino-1-propanol; see the Supporting Information, SI) to obtain (±)-**15**.

Known chiral secondary amines (entries 2–4) were evaluated, but these sterically congested amines surprisingly did not afford any desired product in a reasonable time (< 120 h). Trace amounts of product were observed after 120 h when using stoichiometric α-methylbenzylamine (**E**, entry 5), which has been utilized previously in similar systems,[20] but again, we desired much more rapid conversion with high levels of selectivity. To this end, we sought to utilize an additive to activate the unreactive enoate electrophile and drive conversion.

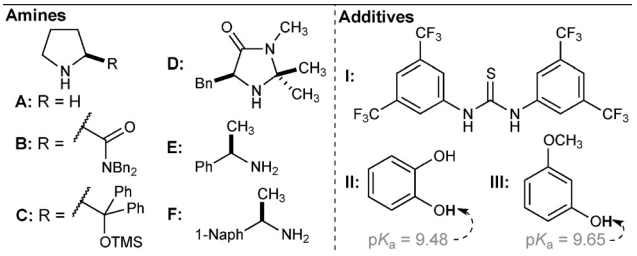
In our initial additive screen, we found that Brønsted acids (entries 6–8) had no effect on conversion; however, the addition of a stoichiometric amount of Schriener's thiourea[21] (**I**, entry 9) promoted the full consumption of **16** within our desired timeframe. Unfortunately, this reaction was plagued by the formation of several undesired side products, though the product could be isolated in modest yield and good enantioselectivity. This result suggested that the ideal approach would need to involve an H-bond donor[22] to activate the previously unreactive ester. By switching to the more sterically demanding primary amine **F** (entry 10), we could increase the enantioselectivity. Then, switching the H-bond donor to catechol (**II**, entry 12) and increasing the temperature to 40 °C, complete consumption of **16** was observed in only 96 h, but yield and selectivity were diminished slightly. We ultimately desired to achieve catalysis with the amine and found that increasing the concentration facilitated this goal (entries 13–15). Finally, we observed that changing the solvent had drastic effects on conversion and selectivity, with cyclopentyl methyl ether[23] (CPME) being the optimal solvent (entry 18), providing **15** in good yield and excellent enantioselectivity in just 48 h. Gratifyingly, the optimized catalysis conditions could be scaled up to provide multigram quantities of enantioenriched piperidine **15** (absolute stereochemistry determined by X-ray crystallographic analysis). Finally, because catechol is an unconventional H-bond donor,[24] we assessed its role in activating the substrate. To this end, catechol was substituted with a monophenol (**III**) with a nearly identical pK_a (entry 20), but observed no reaction after 120 h, supporting that it is acting beyond a simple Brønsted acid.

With enantioenriched **15** in hand, the next phase was to elaborate this structure to the desired bicyclic lactones for both alstonine and serpentine. First, ketone reduction of **15** provided alcohol **17** in excellent yield as a single diastereomer (Scheme 1). The *trans*-lactone (**18**) required for serpentine was obtained in acceptable yield (68%) by lactonization of **17** with TsOH.

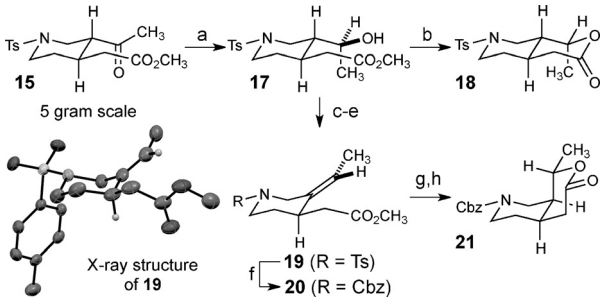
Table 1: Optimization of enamine catalyzed Michael addition.



Entry	Amine	Additive	Solvent	*t* [h]	Yield [%][a]	e.r.[b]
1	**A**	–	THF	36	99	N/A
2	**B**	–	THF	96	51	80:20
3	**C**	–	THF	120	no reaction	–
4	**D**	–	THF	120	no reaction	–
5	**E**	–	THF	120	trace	–
6	**E**	TsOH	THF	120	no reaction	–
7	**E**	HCl	THF	120	no reaction	–
8	**E**	TFA	THF	120	no reaction	–
9	**E**	**I**	THF	120	45	91:9
10	**F**	**I**	THF	120	45	96:4
11[c]	**F**	**I**	THF	144	39	88:12
12[c]	**F**	**II**	THF	96	43	93:7
13[c]	**F**[d]	**II**	THF	120	trace	–
14[c]	**F**[d]	**II**	THF[e]	120	low conversion[g]	–
15[c]	**F**[d]	**II**	THF[f]	120	51	91:9
16[c]	**F**[d]	**II**	toluene[f]	48	73	82:18
17[c]	**F**[d]	**II**	Et_2O[f]	70	59	99:1
18[c]	**F**[d]	**II**	**CPME**[f]	**48**	**79**	**99:1**
19[c]	**F**[d]	(*R*)-BINOL	CPME[f]	120	65	99:1
20[c]	F[d]	**III**	CPME[f]	120	no reaction	–



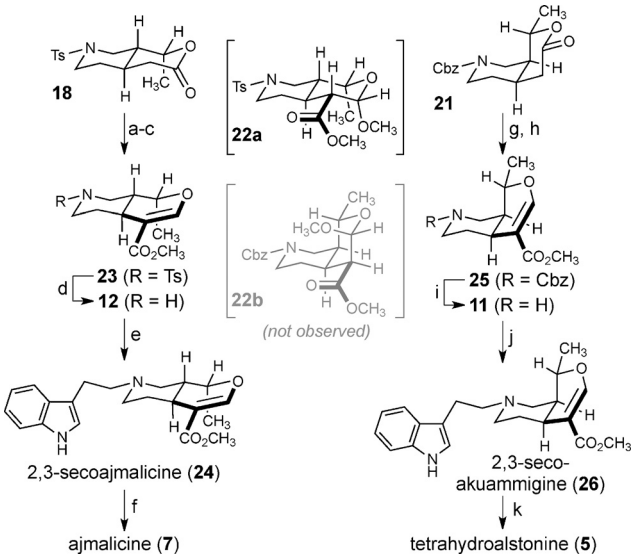
[a] Yield of isolated product. [b] Determined by HPLC analysis. [c] Reaction conducted at 40 °C. [d] 30 mol% amine used. [e] Reaction carried out at 0.5 M. [f] Reaction carried out at 1.0 M. [g] < 50% consumption of **16** observed by NMR spectroscopy after 120 h, product not isolated. N/A = not applicable, TFA = trifluoroacetic acid.



Scheme 1. a) $NaBH_4$, CH_3OH/THF, −20 °C, 97%; b) TsOH, benzene, 80 °C, 68%; c) MsCl, pyridine, 89%; d) NaI, acetone, 60 °C, e) DBU, benzene, 80 °C, 78% (over two steps); f) Mg°, CH_3OH, then CbzCl, K_2CO_3, EtOAc, 70%; g) 9-BBN, THF, 60 °C, then CH_3OH, NaOH, H_2O_2, 0 °C, h) TsOH, benzene, 51% (over two steps). 9-BBN = 9-borabicyclo[3.3.1]nonane, Cbz = carboxybenzyl, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, Ms = methanesulfonyl, Ts = *para*-toluenesulfonyl.

To craft the *cis*-lactone necessary for the synthesis of alstonine, alcohol **17** was carried through a three-step inversion and elimination sequence to obtain Z-alkene **19** in very good yield (olefin geometry confirmed by X-ray crystallographic analysis). This particular olefin geometry was required so that *si*-face hydroboration/oxidation would provide the proper relative stereochemistry for the alstonine scaffold. However, we found this substrate to be unreactive to various borane sources even under forcing conditions, possibly due to the electron-withdrawing allylic sulfonamide limiting the capacity for electrophilic substitution by boron. By removing the tosylate[25] and reprotecting with the less electron-withdrawing benzyl carbamate (Cbz), we were able to obtain *cis*-lactone **21** through the desired hydroboration-oxidation and lactonization sequence in moderate yield. Interestingly, when attempting to use a *N*-Cbz derivative of **16** in our cooperative catalysis reaction (not shown), we found this substrate to be substantially less reactive. We surmise that the higher Lewis basicity of the carbamate relative to the sulfonamide or methyl ester limits the desired H-bond activation.[26]

The acylation of lactones **18** and **21** with methyl formate[8l] provided the requisite α-formyl lactones (not shown) for the Korte rearrangement (Scheme 2). In the case of acyl lactone derived from **18**, exposure to methanolic HCl did not provide the desired dihydropyran. Instead, acetal **22a** was observed as the major product, which is the intermediate directly preceding the elimination in the reported mechanism of this rearrangement. Although prolonged exposure to methanolic HCl did not facilitate the desired elimination, the use of catalytic polyphoshoric acid with this intermediate acetal provided dihydropyran **23** in good yield (67%) over the three-step sequence from **18**. In the case of *cis*-lactone **21**, the acetal corresponding to the interrupted Korte rearrangement (**22b**) was not observed, with the expected dihydropran **25** being isolated as the major product in good (56%) yield after exposure to methanolic HCl.[27] A possible cause for this difference in reactivity is the conformation of the C19 methyl group, which is axial in *trans*-fused system as opposed to equatorial in the *cis*-fused system. The axial methyl group in acetal **22a** could hinder the necessary anti-periplanar elimi-

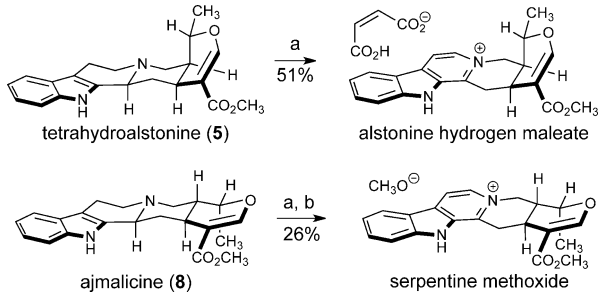


Scheme 2. a) *t*BuOK, methyl formate, THF; b) AcCl, CH_3OH, 60 °C; c) polyphosphoric acid, benzene, 80 °C, 67% (over three steps); d) Mg°, CH_3OH, 75%; e) indole-3-acetaldehyde, $NaBH(OAc)_3$, CH_2Cl_2, 67%; f) $Hg(OAc)_2$, EDTA disodium salt, AcOH/H_2O, 80 to 100 °C, then $NaBH_4$, CH_3OH, 0 °C, 45%; g) NaH, methyl formate, THF; h) AcCl, CH_3OH, 60 °C, 56% (over two steps); i) 10% Pd/C, H_2 (balloon), EtOH, 99%, j) indole-3-acetaldehyde, $NaBH(OAc)_3$, CH_2Cl_2, 66%; k) $Hg(OAc)_2$, EDTA disodium salt, AcOH/H_2O, 80 °C, then $NaBH_4$, CH_3OH, 0 °C, 41%. EDTA = ethylenediaminetetraacetic acid.

nation of the methoxy substituent through 1,3-diaxial strain, which would be absent in the corresponding *cis*-fused system **22b**. Subsequent deprotection of purified bicyclic dihydropyrans **23** and **25** followed by reductive amination with indole-3-acetaldehyde[28] provided 2,3-secoajmalicine (**24**) and 2,3-secoakuammigine (**26**), respectively.

At this juncture, we actively pursued a biomimetic cyclization approach because the biosynthetic pathways for many indole alkaloids are presumed to involve monoamine oxidase triggered C–C bond cyclizations.[29] While the N-oxides of **24** and **26** could be accessed through smooth oxidation with DMDO (not shown) the exposure of either compound to a host of acylation species and conditions unfortunately provided very low yields of any desired products (i.e., **5** and **7**). We also pursued the combination of indole-3-acetaldehyde and a free amine (i.e., **11** and **12**) to promote a compelling redox-neutral iminium ion formation, isomerization, and Pictet–Spengler reaction based on inspiring reports by Seidel (not shown).[30] However, these systems did not behave productively under numerous conditions surveying solvent, acid additives, and dehydrating agents. Ultimately, the desired oxidative iminium ion cyclization was accomplished based on prior precedent involving mercuric acetate/EDTA[8g] to afford the natural products ajmalicine (**7**) and tetrahydroalstonine (**5**) in modest yield in line with previous reports. Given the potential importance of these substances in central nervous system research, new methods to induce these cyclizations are under investigation.

As the last key transformation, the aromatization of the β-carboline subunits of ajmalicine and tetrahydroalstonine was necessary to produce the requisite, final anhydronium base



Scheme 3. a) Pd black, maleic acid, H_2O, 100°C; b) NaOH, CH_3OH/H_2O.

functionality. This final transformation was accomplished through a palladium black mediated dehydrogenation[3,31] to obtain the corresponding β-carbolinium salts (Scheme 3).

As for the reported zwitterionic functionality of **1** and **2**, pH-dependent UV/Vis and NMR spectroscopic studies of other anhydronium base natural products have shown the indole nitrogen is only deprotonated at elevated pH (>10).[31,32] Of note for alstonine, the initial isolation paper noted high instability for the neat free base form of the natural product.[9] We observed decomposition of the β-carbolinium salts upon exposure to dilute aqueous NaOH; however, an analytical sample of serpentine was recovered. Interestingly, ^{1}H and ^{13}C NMR signals for this recovered sample matched both the pre-basified mixture as well as an authentic sample of a commercial sample of serpentine hydrogen tartrate salt (SI). This is in line with reports that these compounds exist as salts in protic solvents.[31] Data for the hydrogen maleate salt form of alstonine matches the authentic sample as well. While ambiguity exists in the literature regarding exact counterion associated with the natural products at isolations and testing, the reported UV/Vis and NMR data suggests the natural products predominately have the indole N–H present (versus the zwitterionic form commonly drawn). Importantly, the successful routes outlined herein are fueling further needed investigations on this topic.

In conclusion, the first total syntheses of alstonine and serpentine were accomplished with a novel cooperative H-bond donor/enamine catalysis reaction as the key step. These scalable routes highlight the need for continued catalysis research in the context of total synthesis and lay the foundation for further study of the biological activity of these unique alkaloids, particularly in the realm of neurotherapeutics. Lastly, the enabling cooperative catalysis utilized here merging enamine activation with H-bond donors will be explored for additional applications to other challenging asymmetric Michael additions.

Keywords: cooperative catalysis · enamine catalysis · enantioselectivity · schizophrenia · total synthesis

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