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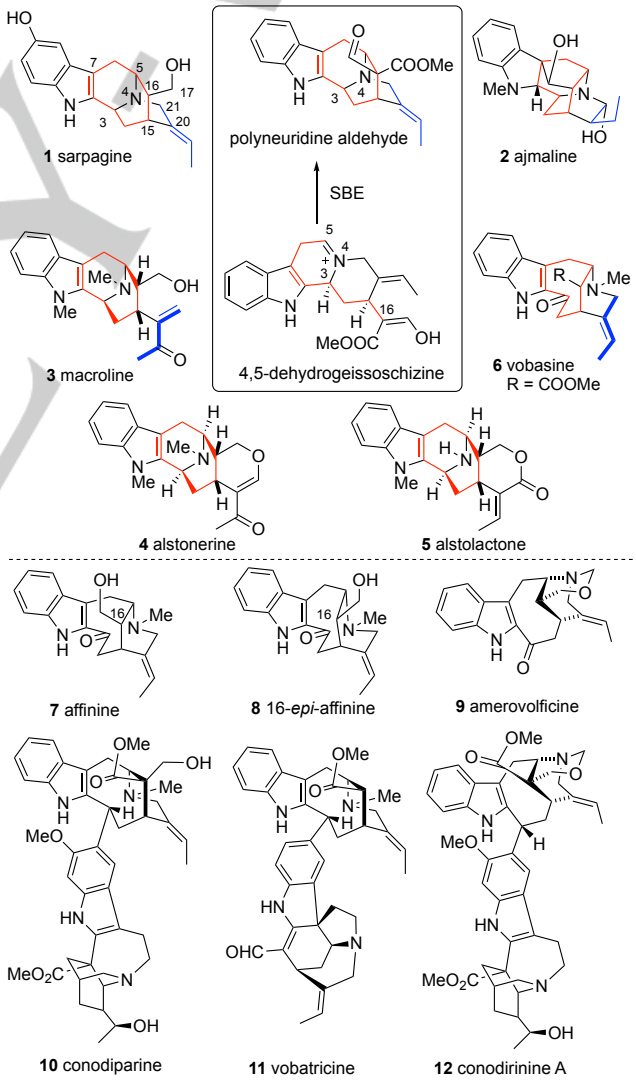
Towards Sarpagine-Ajmaline-Macroline Family Indole Alkaloids: Enantioselective Synthesis of *N*-Demethyl Alstolactone Diastereomer

Dylan Dagoneau, Qian Wang and Jieping Zhu*

Abstract: *We report herein our strategy aiming at using the functionalized tetrahydro-6H-cycloocta[b]indol-6-one as a key intermediate for the synthesis of sarpagine-ajmaline-macroline family of monoterpene indole alkaloids. The desired tricycle was synthesized via following key steps: a) Evans' syn-selective aldolization; b) Liebeskind-Srogl cross-coupling using phenylthiol ester of 3-chloropropanoic acid as a surrogate of acrylic thioester for the synthesis of 2,3-disubstituted indoles; c) ring-closing metathesis (RCM) for the formation of the 8-membered ring. An N-allylation followed by intramolecular 1,4-addition was planned for the synthesis of vobasine class of natural products. However, cyclization under a diverse set of conditions involving anionic, radical and organopalladium/organonickel species failed to produce the bridged ring system. On the other hand, esterification of the pendent primary alcohol with acetoacetic acid followed by intramolecular Michael addition afforded the desired tetracycle with an excellent diastereoselectivity. Subsequent functional group manipulation and transannular cyclization of the amino alcohol afforded the N(1)-demethyl-3,5-diepi-alstolactone. We believe that the same synthetic route would afford the alstolactone should the amino alcohol with appropriate stereochemistry be used as a starting material.*

Introduction

The sarpagine-ajmaline-macroline family of monoterpene indole alkaloids comprises more than 300 members, including over 80 bisindoles. [1] Several of these natural products exhibit cytotoxicity against various cancer cell lines and are capable of reversing the multi-drug resistance.[2] Biosynthetically, sarpagine (**1**) is produced by a reduction and decarboxylation sequence from polyneuridine aldehyde which is in turn generated from 4,5-dehydrogeissoschizine via an intramolecular Mannich reaction (C5-C16 bond formation).[3] Ajmaline (**2**), a class Ia antiarrthythmic agent widely used in the acute treatment of atrial or ventricular tachycardia, is formed from polyneuridine aldehyde via a key intramolecular aldol reaction. Sarpagine itself is in turn a biogenetic precursor of a number of other natural products. Thus, macroline (**3**) is proposed to be biosynthesized from sarpagine derivative via a sequence of *N*-methylation/oxidation/retro-Michael addition. Although it has not been isolated from plants, macroline is believed to be a precursor of numerous other alkaloids such as alstonerine (**4**) [4] and alstolactone (**5**).[5] Alternatively, cleavage of the C3-N4 bond of sarpagan alkaloids affords another sub-family of natural products represented by vobasine (**6**),[6] affinine (**7**), 16-*epi*-affinine (**8**) [7] and amerovolficine (**9**).[8] The presence of a carbonyl or a hydroxy group at C3 in vobasine (**6**) and its congeners renders this carbon intrinsically electrophilic, prone to react with electron-rich aromatic ring of other indole alkaloids. Indeed, vobasine (**6**) and its relatives are main constituents of many dimeric indole alkaloids as



Scheme 1. The sarpagine-ajmaline-macroline family of indole alkaloids: representative examples and biosynthesis.

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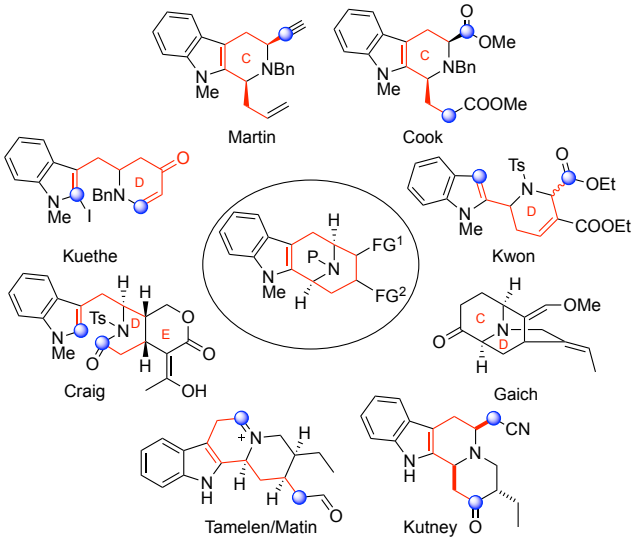
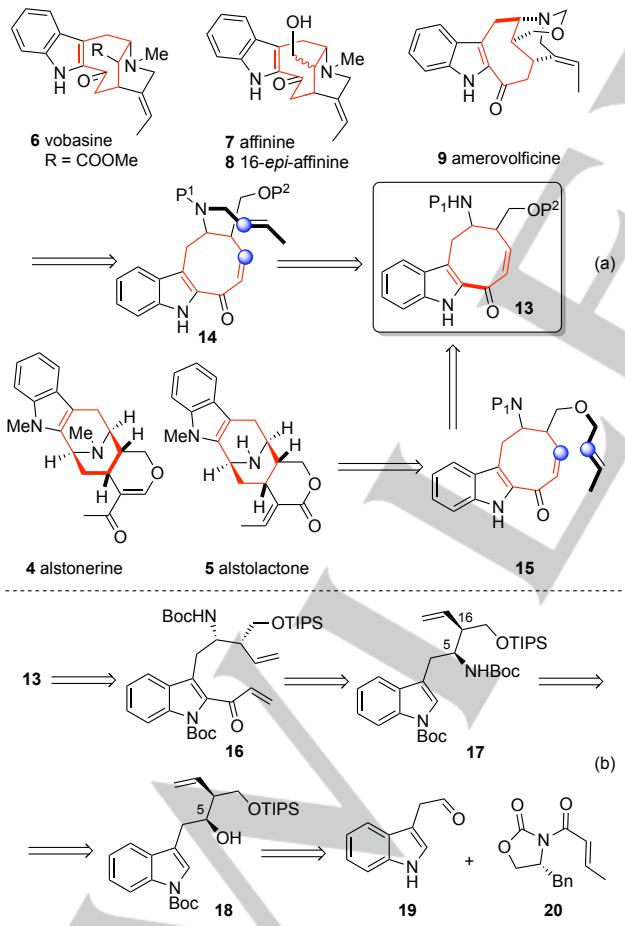


Scheme 2. The sarpagine-ajmaline-macroline family of alkaloids: representative synthetic strategies: Formation of 6-membered ring via C-C bond formation between two blue color coded carbons for the construction of [3,3,1]bicycle.



Scheme 3. Proposed synthetic approach to sarpagine-ajmaline-macroline family alkaloids.

exemplified by conodiparine (**10**),[9] vobatricine (**11**),[10] and conodirinine A (**12**) (Scheme 1).[11]

The common structural feature of this family of indole alkaloids is the presence of an 8-membered ring, either in its native form or embedded in a bridged [3,3,1]bicyclic structure (Scheme 2, highlighted in red). Total synthesis of this class of natural products has attracted attention of synthetic chemists for many years.[12] The representative approaches developed by Tamelen,[13] Kutney,[14] Cook,[15] Martin,[16] Kuethe,[17] Kwon,[18] Craig[19] and Gaich[20] are depicted in Scheme 2. As it is seen, all these successful routes involved the stepwise construction of C and D ring to reach the [3,3,1]bicyclic ring system.

In connection with our research program dealing with the indole alkaloids synthesis,[21] we became interested in the sarpagine-ajmaline-macroline family of natural products. Keeping in mind the literature precedents, we decided to explore a completely different strategy aimed at using 6/5/8 fused tricycle **13** as a springboard to these alkaloids (Scheme 3a). Specifically, *N*-alkylation of **13** by a suitably functionalized four carbon synthon would afford **14** which, upon intramolecular Michael addition or related transformations and functional group manipulation, would afford vobasine (**6**), affinine (**7**) or *epi*-affinine (**8**) and amerovolficine (**9**). On the other hand, *O*-alkylation followed by cyclization of the resulting ether **15** would provide macroline-type alkaloids such as alstonerine (**4**) [22] and alstolactone (**5**). Tricycle **13** would be accessible by intramolecular ring closing metathesis of the corresponding diene **16** which could in turn be synthesized by C-2 acylation of indole **17** (Scheme 3b). The latter was thought to be synthesized from **18** by functional group interconversion including a double S_N2 reaction of the secondary alcohol in order to obtain the desired relative stereochemistry between C5 and C16 (monoterpene indole alkaloid numbering). The Evans' aldolization between aldehyde **19** and imide **20** followed by reduction was planned to reach **18**. We report herein the synthesis of the tricycle **13** and its subsequent conversion to a stereoisomer of alstolactone. As it will be detailed below, should the correct relative stereochemistry of the amino alcohol be secured, the same strategy would lead us to the alstolactone **5**.

Results and Discussion

Synthesis of 6/5/8 fused tricycle. Reaction of aldehyde **19**, freshly prepared by reduction of the corresponding Weinreb amide with DIBAL,[23] with imide **20** (*ee* 99%)[24] under the standard conditions developed by Evans[25] gave aldol **21** in 74% yield with excellent *syn*-diastereoselectivity (Scheme 4). Reduction of **21** with lithium borohydride[26] followed by treatment of the resulting crude reaction mixture with TIPSCl afforded chemoselectively the monoprotected silyl ether **22** in 84% overall yield together with the recovered chiral oxazolidinone (78%). *N*-Boc protection of **22** afforded **18** in 91% yield.

To reach amerovolficine (**9**), 1,3-amino alcohol **17** was needed and a double S_N2 process involving a sequence of halogenation of the secondary alcohol **18** followed by displacement of the resulting alkyl halide with azide was initially pursued to convert **21** to **17**. Unfortunately, halogenation of the secondary alcohol **22** turned out to be problematic. Under a variety of conditions, either decomposition of the substrate

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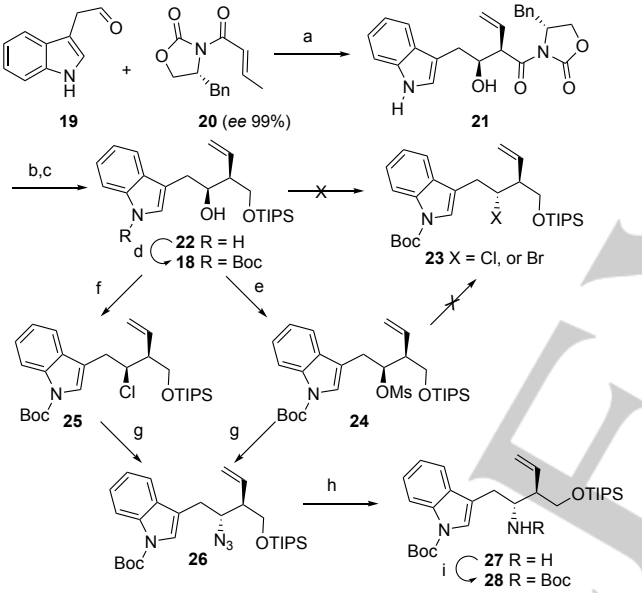
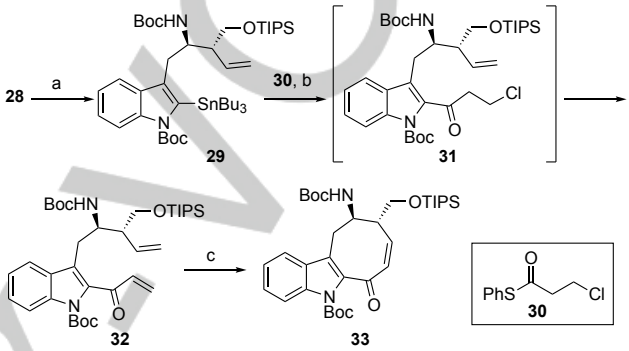
(PBr_3/DIPEA, $POCl_3$/pyridine or PCl_3/pyridine) or unwanted elimination processes (CCl_4 or CBr_4/PPh_3, Br_2 or I_2/PPh_3/imidazole) were observed and the desired product **23** was never isolated (Scheme 4).[27] Similarly, only decomposition occurred applying these conditions to the *N*-unprotected indole **22**. Alternatively, mesylation of **18** (MsCl, Et_3N) furnished the mesylate **24** in excellent yield. Attempt to perform an S_N2 reaction of **24** with different sources of halides (TBAC, TBAB, LiCl or LiBr) [28] failed to afford the substitution product **23**. A complex mixture containing the elimination products was instead obtained. Finally, chlorination of **18** with thionyl chloride in the presence of pyridine or 2,6-lutidine afforded **25** in high yields (89%). However, the reaction occurred with retention of configuration instead of the desired inversion process.[29] This was confirmed by converting both the chloride **25** and mesylate **24** to the same alkyl azide **26**. We note that the reaction between tetrabutylammonium azide and mesylate **24** proceeded much cleaner than that involving alkyl chloride **25**. Staudinger reduction of the crude azide **26** resulting from mesylate **24** afforded **27** in 65% overall yield from alcohol **18**.



Scheme 4. Synthesis of 1,3-amino alcohol involving the Evans aldolization as a key step. Reagents and conditions: [a] *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, -78 to 0 °C, 74%; [b] $LiBH_4$, MeOH, THF, 0 °C; [c] TIPSCl, imidazole, CH_2Cl_2, RT, 84% in two steps; [d] Boc_2O, DMAP, CH_2Cl_2, RT, 91%; [e] MsCl, Et_3N, CH_2Cl_2, RT; [f] $SOCl_2$, 2,6-lutidine, 1,2-DCE, RT; [g] *n*-Bu_4NN_3, MeCN, 65 °C from **24** or DMF, 85 °C from **25**; [h] PPh_3, THF/H_2O, 40 °C, 65% from **18** via **24**; 38% from **18** via **25**; [i] Boc_2O, CH_2Cl_2, 0 °C, 93%.

Since the relative and absolute configuration of compound **28** matches with that of the enantiomer of affinine (**7**),[30] we decided to move forward our synthesis with **28** in order to test the feasibility of our strategy. The deprotonation of the C-2 position of indole **28** with LiTMP followed by trapping of the resulting lithiated intermediate with electrophiles, such as acryloyl and crotonyl chloride and their corresponding Weinreb amides provided a complex reaction mixture. A two-step sequence was subsequently developed for the C-2 acylation of **28** (Scheme 5). Treatment of indole **28** with LiTMP followed by adding tributyltin chloride afforded C-2 stannylated indole **29**. The palladium-catalyzed Liebeskind-Srogl coupling[31] between **29** and the thioester **30** under our recently optimized conditions[32] provided the desired coupling adduct **31** which underwent β-elimination during the flash column chromatography (eluent containing Et_3N) to furnish directly the desired diene **32** in 90% yield on a multigram scale. It is interesting to note that coupling of **29** with *S*-phenyl prop-2-enethioate gave **32** in rather poor and unreproducible yield due to the easy polymerization of this conjugated thioester. Diene **32** was then submitted to several ring-closing metathesis (RCM) conditions.[33,34] Gratefully, the desired tricycle **33** was obtained in 85% yield when the reaction was performed in DCE at 80 °C in the presence of Grubbs 2nd generation catalyst. It was important to add the catalyst in 4 portions over a period of 30 h in order to reach a complete and clean conversion, particularly on large scale.



Scheme 5. Synthesis of 6/5/8 fused tricycle. Reagents and conditions: [a] LiTMP, then *n*-Bu_3SnCl, THF, -78 °C, 95%; [b] $Pd_2(dba)_3$ (10 mol%), $AsPh_3$ (10 mol%), CuDPP, hexane/THF, RT, 90%; [c] Grubbs II (4 x 5 mol%), 1,2-DCE, 80 °C, 85%.

Approach towards the affinine skeleton. A sequence of *N*-allylation of **33** followed by intramolecular 1,4-addition was envisaged to reach the affinine (**7**). Selective deprotection of the C5-NHBoc without touching the indolyl *N*-Boc of **33** was accomplished using modified Ohfune conditions (Scheme 6).[35] Thus, stirring a CH_2Cl_2 solution of **33** with TBDMSOTf/lutidine afforded the corresponding *tert*-butyldimethylsilyl carbamate which, upon treatment with a solution of HCl in Et_2O at 0 °C for 30 min, furnished the desired primary amine **34**. *N*-Allylation of the crude amine **34** with allyl bromide **35** in the presence of cesium carbonate afforded the desired *N*-allyl amine **36** together with the allyl carbamate **37**. The latter appeared to be formed by carbonylation of the amine with CO_2 generated *in situ* from the partial neutralization of Cs_2CO_3.[36] To avoid this side reaction, other bases, particularly organic bases, were screened and DIPEA was found to give the cleanest reaction leading to vinyl iodide **36** in 69% overall yield from **33**.

With vinyl iodide **36** in hand, cyclization to the bridged ring system of affinine was examined (Scheme 7). Attempts to generate *in situ* the vinyllithium species by lithium/halogen exchange (*t*-BuLi, THF, HMPA, TMSCl) [37] followed by intramolecular 1,4-addition led to the decomposition of the starting materials. Vinyl radical generated using AIBN/Bu_3SnH[38] or BEt_3[39] as initiators also failed to cyclize leading to the deiodinated compound **38** as an only isolable product. Transition metal-catalyzed reactions also failed to produce the desired product, although interesting polycycles were isolated. Thus, Ni(0)-catalyzed cyclization afforded polycycle **39** in 42% yield[40] while Pd(0)-catalyzed reductive Heck reaction under a variety of

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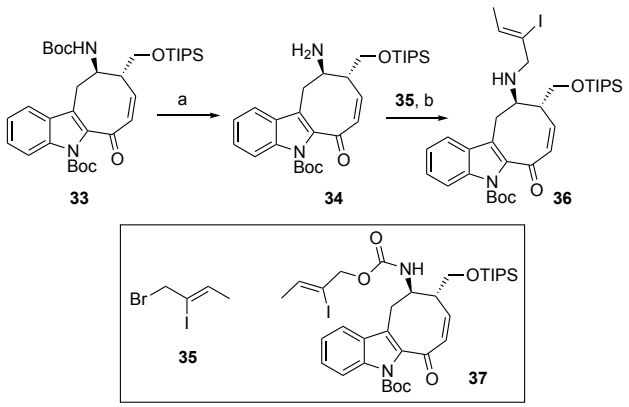
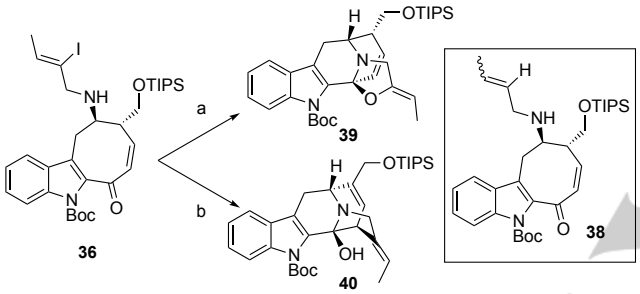
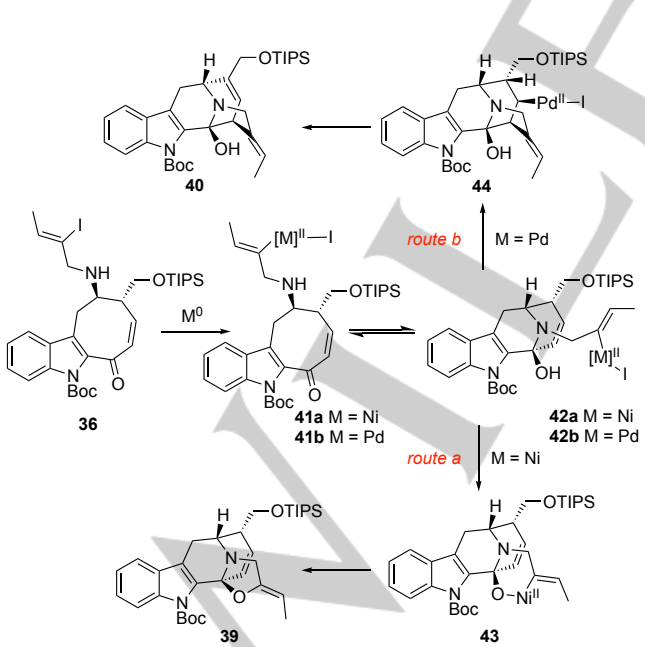
conditions[41] afforded the Heck product **40** in up to 63% yield together with **38** (see Table 1 in the Supporting Information)



Scheme 6. Reagents and conditions: [a] TBDMSOTf, 2,6-lutidine, CH_2Cl_2, RT, then 1 M HCl in Et_2O, 0 °C; [b] DIPEA, DMF, RT, 69% from **33**.



Scheme 7. Reagents and conditions: [a] $Ni(COD)_2$, Et_3N, MeCN, RT, then Et_3SiH, 42%; [b] $Pd(OAc)_2$, PPh_3, HCOONa, DMF, 60 °C, 63%.



Scheme 8. Postulated reaction pathways leading to **39** and **40**.

Possible reaction pathways leading to **39** and **40** are depicted in Scheme 8. Oxidative addition of vinyl iodide to low valent metal complex LnM(0) would generate the vinylM(II)X species **41** which may undergo transannular cyclization to hemiaminal **42**. In the case of Ni catalyst, intermediate Ni(II) species **42a** might undergo ligand exchange with the neighbouring hydroxy group to provide **43** which, upon reductive elimination, provided **39**. With Pd catalyst, the intermediate **42b** would undergo the intramolecular Heck reaction to afford **40** via the $C(sp^3)$-Pd species **44**.

Assuming that the hemiaminal intermediate **42** was responsible for the formation of **39** and **40**, it was decided to methylate the secondary amine since the final natural product affinine (**7**) contains the *N*-methyl group anyway. Reaction of **36** with an excess of formaldehyde in methanol in the presence of $NaBH_3CN$ at room temperature gave the desired tertiary amine **45** in 89% yield (Figure 1). Submitting the latter to lithium / halogen exchange (*t*-BuLi) led once again to decomposition. Unfortunately, the deiodination product was the only isolated product under a variety of radical-based or transition metal-based conditions. It should be noted that partial deallylation of the starting material was also observed when the reductive Heck reaction was performed in the presence of Et_3N at temperature higher than 80 °C.

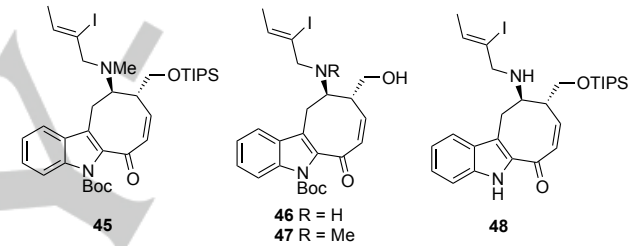
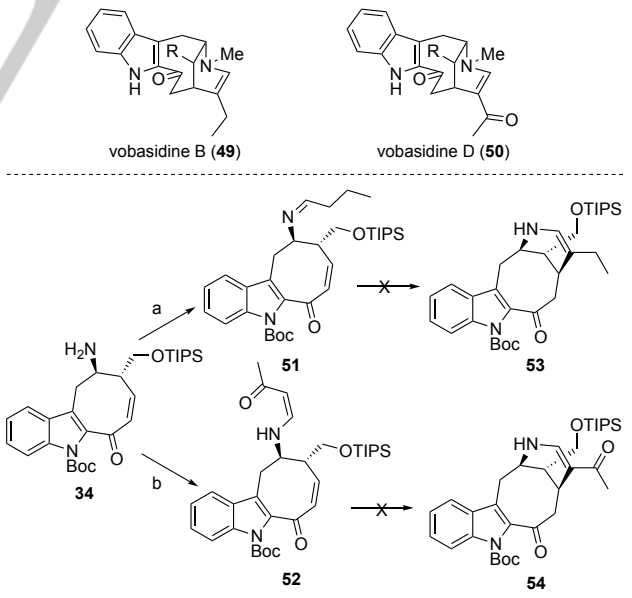


Figure 1. Other substrates investigated for the cyclization.

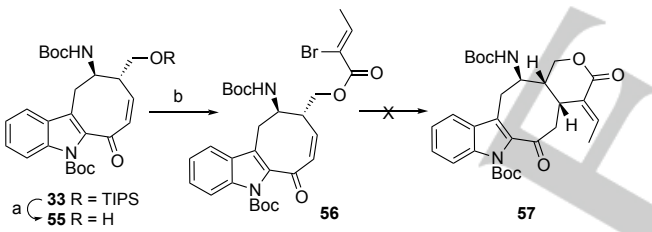


Scheme 9. Attempted cyclization of enamine and enaminone aimed at vobasidine B (**49**) and vobasidine D (**50**). Reagents and conditions: [a] *n*-C_3H_7CHO, 4 Å MS, 1,2-DCE, RT; [b] $MeCOCH{=}CHONa$, AcOH, 4 Å MS, 1,2-DCE, RT.

To determine the impact of the bulky TIPS group on the reaction outcome, compounds **46** and **47** were prepared from **36** and **45**, respectively (THF, TBAF, AcOH). However, neither of them underwent the desired cyclization under various conditions. Compound **48** with a free indolyl NH, prepared by removal of the *N*-Boc from **36** under acidic conditions (TFA), also failed to afford the bridged ring system of the affinine skeleton.

Knowing that the enamine and enaminone functions are found in natural products such as vobasidine B (**49**) and vobasidine D (**50**), imine **51** and enaminone **52** were prepared by condensation of primary amine **34** with butanal and *in situ* generated acetoacetaldehyde,[42] respectively (Scheme 9). The resulting crude mixture, after removal of molecular sieves by filtration and volatiles under vacuum, was submitted to intramolecular Michael addition. Unfortunately, neither **53** nor **54** were isolated under a variety of conditions varying the nature of Lewis acids, bases and temperature.[43]

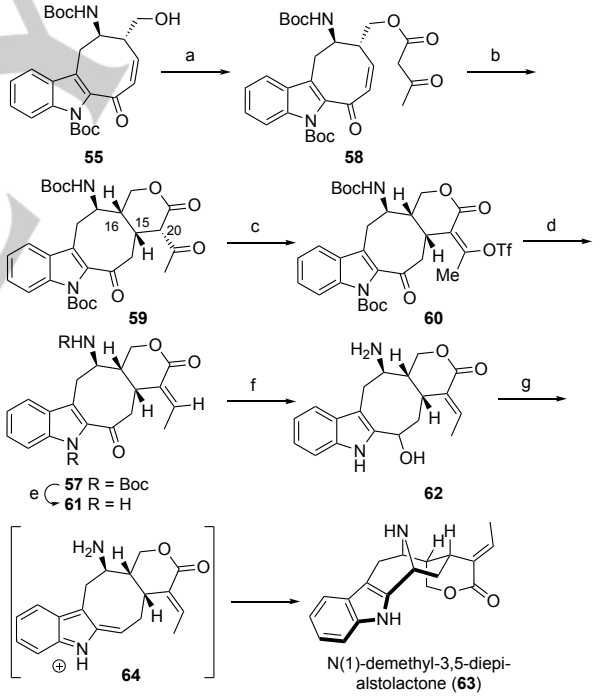
Approach towards the macroline skeleton. The difficulties encountered in forming the desired bridged ring system of the vobasine skeleton prompted us to investigate the macroline family and more specifically the synthesis of alstolactone (**5**). As we already had in hand the advanced tricyclic enone **33**, we decided to start our exploration from this intermediate although we were aware of the fact that the relative stereochemistry of **33** did not match the natural product and its cyclization would afford a diastereomer of the natural product (*cf* Scheme 11). To reach this goal, formation of a 8/6 *cis*-fused ring system and transannular cyclization leading to aza-bridged [3,3,1] bicycle would have to be accomplished.



Scheme 10. Attempted cyclization of enamine and enaminone aimed at vobasidine B (**49**) and vobasidine D (**50**). Reagents and conditions: [a] TBAF, AcOH, THF, RT; [b] (*Z*)-2-bromobut-2-enoic acid, EDCI, DMAP, DIPEA, RT, 87% from **33**.

The synthesis of the required vinyl bromide **56** was accomplished in a two-step sequence (Scheme 10). Removal of the silyl protecting group from **33** (TBAF buffered with acetic acid) followed by acylation of the resulting alcohol **55** with (*Z*)-2-bromobut-2-enoic acid, synthesized in 3 steps from methyl crotonate,[44] furnished the desired ester **56** in 87% yield over 2 steps. Unfortunately, submitting **56** to different cyclization conditions led only to the decomposition of the starting material.

Intramolecular Michael addition using 1,3-ketoester as an internal nucleophile turned out to be more rewarding which led to a successful synthesis of alstolactone skeleton as shown in Scheme 11. Esterification of alcohol **55** with acetoacetic acid, freshly prepared by hydrolysis of *tert*-butyl acetoacetate under acidic conditions (TFA),[45] furnished the ketoester **58**. After screening of various bases, it was found that heating to reflux an acetone solution of **58** in the presence of Cs_2CO_3 triggered the desired cyclization to afford tetracycle **59**. The reaction was highly diastereoselective leading to an 8/6 *cis*-fused ring system as a single diastereomer in 87% yield from **55**. The relative stereochemistry of the two newly formed stereocenters was confirmed by ROESY analysis which highlighted the correlations of H16/H15 and H16/H20. We note that the cyclization did not go to completion with Na_2CO_3 and K_2CO_3 as bases even after extended reaction time. Using stronger bases such as DBU, *t*-BuOK or NaH led only to decomposition of the substrate.[46] The 1,3-ketolactone moiety of **59** was then converted to the desired conjugated lactone **57** by triflation followed by Pd-catalyzed reduction of the resulting enol triflate **60**. The choice of the reductant proved to be critical for the final geometry of the double bond. For instance, triethylsilane[47] and methyl formate gave *E*/*Z* ratio of 2/1 and 2.5/1, respectively. More promising results for the generation of the desired (*E*)-isomer were obtained using triethylammonium formate.[48] With equimolar amount of formic acid and triethylamine, a 4/1 mixture (*E*/*Z*) was obtained but when an excess of formic acid was employed, the ratio decreased to 3/1. Finally, using an excess of triethylamine, an excellent *E*/*Z* ratio of 12/1 was obtained and the desired (*E*)-product **57** was isolated in 72% yield over 2 steps. Since the geometry of enol triflate was not determined, we hypothesized that in the presence of an excess of base, the vinylpalladium triflate intermediate might undergo the β-hydride elimination to afford an allene intermediate which then was reduced stereoselectively to the *E*-alkene **57**.



Scheme 11. Synthesis of alstolactone skeleton (**64**). Reagents and conditions: [a] $MeCOCH_2COOH$, EDCI, DMAP, DIPEA, RT; [b] Cs_2CO_3, 4 Å MS, acetone, 55 °C, 87% from **33**; [c] Cs_2CO_3, 4 Å MS, THF, RT then $PhNTf_2$; [d] $Pd(OAc)_2$ (20 mol%), PPh_3 (50 mol%), HCOOH (5.0 equiv), Et_3N (10 equiv), DMF, 60 °C, 72% over 2 steps; [e] $BF_3•Et_2O$, CH_2Cl_2, RT; [f] $NaBH_4$, $CeCl_3$, K_2CO_3, $MeOH/CHCl_3$, -40 °C, 77% over 2 steps; [g] TFE, 105 °C, 79%.

The double *N*-Boc deprotection by treating a dichloromethane solution of **57** with an excess of $BF_3•OEt_2$ afforded cleanly compound **61**. The chemoselective reduction of

the ketone in the presence of α,β-unsaturated lactone was attempted with sodium borohydride at low temperature (-40 °C).[49] However, the conversion was low and 1,4-reduction of the conjugated lactone moiety became competitive when the reaction was performed at higher temperature. Under the Luche conditions[50] at -40 °C, complete consumption of the starting material occurred after 4 h albeit with moderate yield due probably to the instability of the resulting benzylic alcohol. Fortunately, by adding a substoichiometric amount of potassium carbonate to buffer the reaction media, the desired secondary alcohol **62** was isolated in 77% yield. Although of no consequence, the reduction turned out to be highly diastereoselective providing **62** as a single diastereoisomer.

To accomplish the final transannular cyclization, an S_N1 mechanism via dehydration of the benzylic alcohol **62** followed by trapping the resulting azafulvenium species by the internal amine nucleophile was a reasonable pathway to pursue. To our surprise, this sequence has rarely been investigated although the reverse reaction involving the opening of azabicyclo[3.3.1]nonane system to the corresponding 8-membered ring is known.[51] Büchi and coworkers reported in 1964 that such cyclization could proceed by simple thermolysis of the substrate in refluxing xylene.[52] However, submitting our substrate **62** in refluxing xylene gave, after 12 h, a complex mixture from which the desired product is identified in about 10% yield. Lowering the reaction temperature by performing the reaction in refluxing toluene led to the recovery of the starting material. As strong acid could not assist the desired transformation due to the protonation of the amine nucleophile, fluorinated solvents (HFIP with pka of 9.3 and TFE with pka of 12.4), were evaluated as promoters.[53] The optimum conditions found consisted of heating a solution of **63** in TFE at 105 °C for 24 h. Under these conditions, the desired *N*(1)-demethyl-3,5-diepi-alstolactone (**63**) was isolated in 79% yield (Scheme 11).

Conclusion

In summary, we have developed an enantioselective synthesis of functionalized tetrahydro-6*H*-cycloocta[*b*]indol-6-one **33** via a key ring-closing metathesis for the formation of 8-membered ring. The tricycle **33** was designed as a key platform on the way to the sarpagine-ajmaline-macroline family of monoterpene indole alkaloids. An *N*-allylation followed by intramolecular 1,4-addition was planned for the synthesis of vobasine class of natural products. However, cyclization under a diverse set of conditions involving the anionic, radical and organopalladium/organonickel species failed to produce the bridged ring system. On the other hand, esterification of the pendent primary alcohol by acetoacetic acid followed by intramolecular Michael addition afforded the desired tetracycle **59** with an excellent diastereoselectivity. Subsequent functional group transformation and transannular cyclization of the amino alcohol **62** afforded the *N*(1)-demethyl-3,5-diepi-alstolactone (**63**). We believe that if the *syn*-amino alcohol **17**, instead of the *anti*-counterpart **28**, were used, the same synthetic route would afford the alstolactone (**5**).

Experimental Section

For details of the synthetic procedures, physical and spectroscopic data, copies of ^{1}H, ^{13}C NMR spectra of compounds, see the Supporting Information.

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Keywords: Indole alkaloid • sarpagine • ring closing metathesis (RCM) • transannular cyclization • asymmetric synthesis • homogeneous catalyst

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Layout 1:

Synthetic Methods

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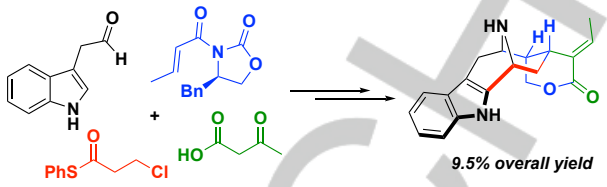
Towards Sarpagine-Ajmaline-Macroline family Indole Alkaloids: Enantioselective Synthesis of Alstolactone Diastereomer



Transannular cyclization *was a key step for the formation of azabicyclo[3.3.1]nonane, a common structural motif found in sarpagine-ajmaline-macroline family of natural products.*