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Enantiospecific Total Synthesis of the Important Biogenetic Intermediates along the Ajmaline Pathway, (+)-Polyneuridine and (+)-Polyneuridine Aldehyde, as well as 16-Epivellosimine and Macusine A

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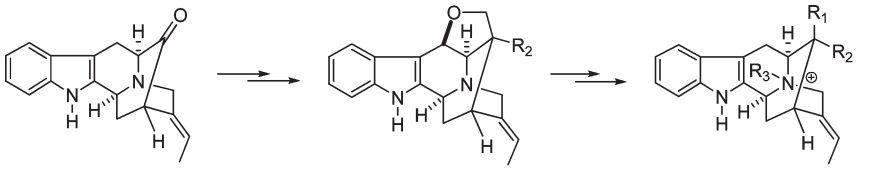

6 R_1 = CHO, R_2 = CO_2CH_3, R_3 = :
7 R_1 = CHO, R_2 = H, R_3 = :
8 R_1 = CH_2OH, R_2 = CO_2CH_3, R_3 = :
9 R_1 = CH_2OH, R_2 = CO_2CH_3, R_3 = CH_3

The first stereospecific synthesis of polyneuridine aldehyde (**6**), 16-epivellosimine (**7**), (+)-polyneuridine (**8**), and (+)-macusine A (**9**) has been accomplished from commercially available D-(+)-tryptophan methyl ester. D-(+)-Tryptophan has served here both as the chiral auxiliary and the starting material for the synthesis of the common intermediate, (+)-vellosimine (**13**). This alkaloid was available in enantiospecific fashion in seven reaction vessels in 27% overall yield from D-(+)-trytophan methyl ester (**14**) via a combination of the asymmetric Pictet−Spengler reaction, Dieckmann cyclization, and a stereocontrolled intramolecular enolate-driven palladium-mediated cross-coupling reaction. A new process for this stereocontrolled intramolecular cross-coupling has been developed via a copper-mediated process. The initial results of this investigation indicated that an enolate-driven palladium-mediated cross-coupling reaction can be accomplished by a copper-mediated process which is less expensive and much easier to work up. An enantiospecific total synthesis of (+)-polyneuridine aldehyde (**6**), which has been proposed as an important biogenetic intermediate in the biosynthesis of quebrachidine (**2**), was then accomplished in an overall yield of 14.1% in 13 reaction vessels from D-(+)-tryptophan methyl ester (**14**). Aldehyde **13** was protected as the N_a-Boc aldehyde **32** and then converted into the prochiral C(16)-quaternary diol **12** via the practical Tollens' reaction and deprotection. The DDQ-mediated oxidative cyclization and TFA/Et_3SiH reductive cleavage served as protection/deprotection steps to provide a versatile entry into the three alkaloids polyneuridine aldehyde (**6**), polyneuridine (**8**), and macusine A (**9**) from the quarternary diol **12**. The oxidation of the 16-hydroxymethyl group present in the axial position was achieved with the Corey−Kim reagent to provide the desired β-axial aldehydes, polyneuridine aldehyde (**6**), and 16-epivellosimine (**7**) with 100% diastereoselectivity.

Introduction

Indole alkaloids have long held a prominent position in the history of natural products chemistry because of their structural similarity to the essential amino acid tryptophan and related metabolites, such as the neurotransmitter serotonin. New alkaloids have been isolated from a variety of sources with increasing frequency and characterized via the latest spectroscopic techniques; moreover, thousands of alkaloids have been obtained from plant sources worldwide.[1−6] Bisindole alkaloids are the dimeric forms of these natural products, and they have been

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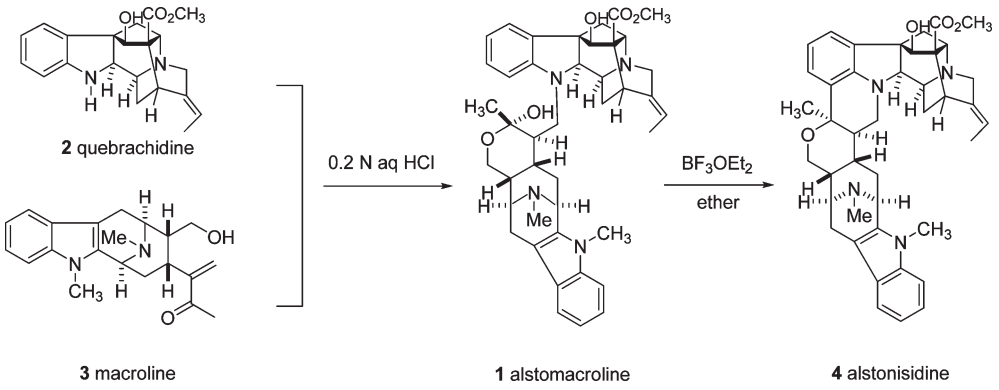

FIGURE 1. Partial synthesis of alstomacroline (**1**).

isolated from various species of plants accompanied by their monomeric progenitors.[7] (+)-Alstomacroline (**1**), a bisindole alkaloid, was isolated from the root bark of *A. macrophylla* collected in Thailand and exhibited activity against malaria parasites (IC_{50} of 1.12 μM against the *Plasmodia falciparum* K1 strain).[8,9] A partial synthesis of **1** was reported by Le Quesne et al.[10] via a biomimetic coupling process of the two components, (+)-quebrachidine (**2**) and macroline (**3**) (Figure 1).

(+)-Ajmaline (**5**) was isolated from the roots of *Rauwolfia serpentina* in 1931 by Siddiqui.[11] It is a clinically important cardiovascular indole alkaloid[12−17] with historical significance[7] and has been extensively used in Europe to treat arrhythmias. Although (+)-ajmaline (**5**) itself represents a class of monoterpene alkaloids, it is also related to the sarpagine bases,[18−20] which contain one or two functional groups at C-16.

The investigation of the biogenetic link between the sarpagine- and ajmaline-related alkaloids derives from the isolation of important biogenetic intermediates and specific enzymes from the biosynthesis of ajmaline, which is known as the ajmaline pathway by Stoeckigt.[21−24] All the major reactions which have occurred in cell suspension cultures of *Rauwolfia* have been established at the enzymatic level. Tryptamine and secologanin are converted into polyneuridine aldehyde (**6**) by the reactions catalyzed by strictosidine synthase (SS), strictosidine synthase (SG), and sarpagine bridge enzyme (SBE), respectively. In addition, the enzyme (PNAE) has been shown to catalyze the central reaction which transforms polyneuridine aldehyde (**6**) into 16-epivellosimine (**7**).[21−23] This latter alkaloid has been identified as the immediate precursor for the biosynthesis of the ajmaline monoterpenoid alkaloids. Four major special enzymes (vinorine synthase, vinorine hydroxylase, vomilenine reductase, and norajmaline *N*-methyltransferase) are involved in this biosynthetic pathway, which eventually provides ajmaline (**5**) from epi-vellosimine (**7**).[21−24]

The unique and complex architecture of the above-mentioned indole alkaloids depicted in Figures 1 and 2, coupled with their largely unexplored potential in medicine or as tools for biological studies, make these compounds attractive targets for total synthesis. (−)-Vincamajinine and its ring-A-substituted analogue, (−)-11-methoxy-17-epi-vincamajine, have been recently synthesized by Yu et al.[25,26] In addition, an approach to the synthesis of (−)-**2** has also been reported by Martin.[27] However, no total synthesis of polyneuridine (**8**), polyneuridine aldehyde (**6**), or 16-epivellosimine (**7**) (Figure 2) has been reported. Herein, the initial goal was to develop an efficient enantiospecific and stereocontrolled route for these specific ajmaline-related indole alkaloids, which contain a methoxycarbonyl group at C-16. The major challenges to the synthesis of this group of indole alkaloids related to (+)-quebrachidine (**2**) include generation of the C-16 quaternary carbon center, complete control of the stereochemistry at C-2 and C-17, formation of the C(19)−C(20) olefinic bond in the *E*-configuration, and development of an efficient route for the preparation of the rigid hexacyclic system which contains a C-16 carbomethoxy group. Inspired by the biogenetic connection between the sarpagine- and ajmaline-related alkaloids

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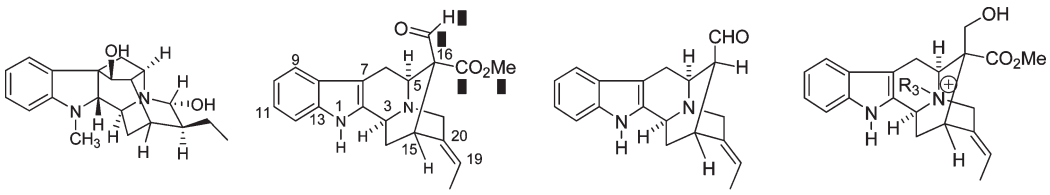
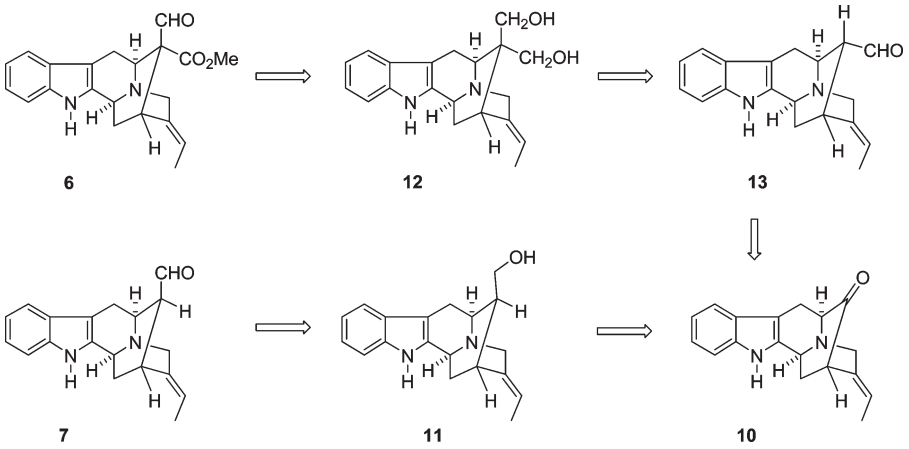


FIGURE 2. Important biogenetic intermediates and synthetic targets.

SCHEME 1

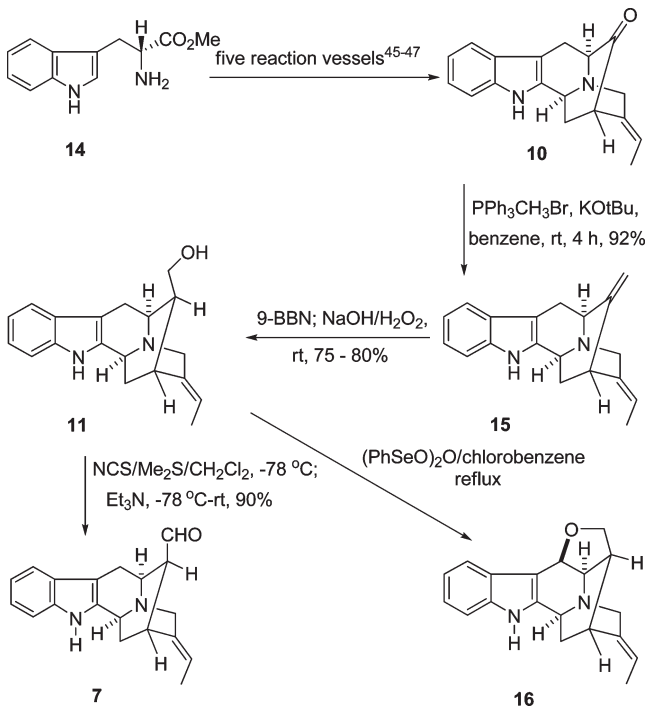


proposed previously,[28,29] Stoeckigt has reported a biosynthetic route via polyneuridine aldehyde (**6**) which contains the unique C-16 axial aldehyde function located in the middle of the ajmaline biosynthetic pathway.[30] A related process is the transformation of aldehyde **6** to the previously unknown biogenetic intermediate,[21] 16-epivellosimine (**7**), and provides a direct precursor for the biosynthesis of the ajmaline skeleton.[21−23,30]

As illustrated in Scheme 1, in a retrosynthetic sense, both polyneuridine aldehyde (**6**) and 16-epivellosimine (**7**) might be available via a common intermediate, the (*E*)-ethylidene ketone **10**. This ketone **10** could then be converted into (*E*)-16-epinormacusine B (**11**),[31] which could be employed as an intermediate in the total synthesis of **7**. The synthesis of the axial aldehyde function of **6** could be approached by selective oxidation of the N_a-H diol **12**. The latter intermediate, which contained a quaternary center at C-16, might be obtained from vellosimine (**13**) via the Tollens reaction in one step. The diol **12** which results might be further oxidized selectively to provide entry into polyneuridine aldehyde **6** in a stereoselective fashion.

In this regard, the (*E*)-ethylidene ketone **10**[32] had been synthesized in enantiospecific fashion in five steps from D-(+)-tryptophan methyl ester **14** (Scheme 2) via the asymmetric Pictect−Spengler reaction, Dieckmann cyclization, and palladium-mediated cross coupling previously.[32−34]

SCHEME 2



In addition, two other palladium-mediated enolate driven cross-coupling processes have been employed to provide ketone **10**, as well as a copper-mediated method to generate related ketones (see Scheme 5). This synthetic strategy was an efficient way to provide pentacyclic ketone **10** on gram scale. With the advantage of this method, attention turned to the

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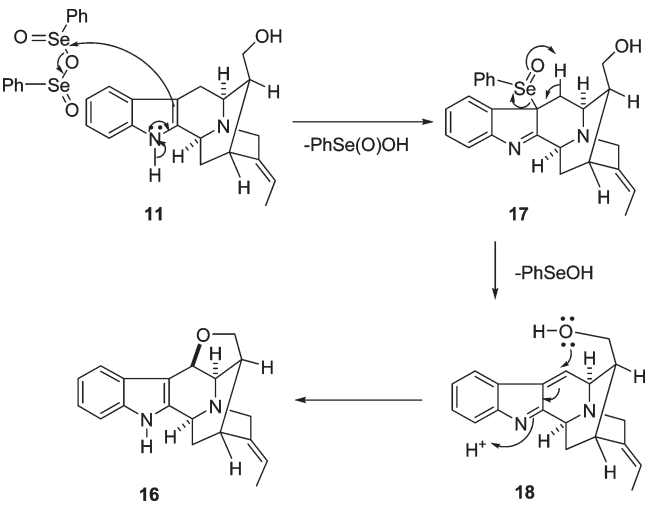
synthesis of the N_a-H axial aldehyde at C-16 in order to construct the two desired aldehydes **6** and **7** in an enantiospecific fashion.

Results and Discussion

Synthesis of 16-Epivellosimine (6) and Strategy for the Construction of the Axial Aldehyde at C-16. The synthesis of 16-epivellosimine (**6**) began with the pentacyclic ketone **10**,[35−37] as mentioned. The (*E*)-16-epinormacusine B (**11**) was obtained from **10** via a Wittig reaction coupled with a hydroboration/oxidation following the published procedure.[31] When the two double bonds in the diene **15** were compared, it was felt the less hindered double bond at C(16)−C(17), relative to the ethylidene at C(19)−C(20), would be more readily attacked by the hindered hydroborating reagent. This was in agreement with the previous work of Magnus.[38,39] Treatment of diene **15** with 9-BBN was followed by oxidative workup to provide the alcohol **11** as the only detectable diastereomer in 80% yield (Scheme 2). When the workup was altered to the procedure ($NaBO_3$) of Kabalka, the yield was 90%.

Once the β-axial alcohol **11** was in hand, the axial aldehyde **7** could, presumably, be obtained via selective oxidation under mild conditions if epimerization to the thermodynamically more stable α-equatorial aldehyde could be avoided. Recently, during the total synthesis of ajmaline[40] and the vincamajinine-related alkaloids[25] entry into the 16-N_a-methyl axial aldehyde was achieved,[25] as well as evidence for the close synthetic relationship to the indolenine group. In the previous approach to the related N_a-methyl diol,[25] the TPAP selective oxidation of the β-axial alcohol on the Boc-protected 16-functionalized quaternary diol as well as the N_a-methyl diol was employed to provide a 16-β-axial aldehyde (dr $>$8:1);[26,41] however, the synthesis of aldehydes in the N_a-H series was more difficult. This was, presumably, due to the acidic nature of the indole N_a-H function, as well as the lability of the N_a-H 2,3-indole system in the presence of oxidative reagents. Moreover, it was well-known the aldehyde function at C-16 preferred the α-equatorial stereochemistry.[42] The axial aldehyde function of **7** could be easily epimerized into the sarpagine series of alkaloids,[30] even on silica gel chromatography. Previously, the difficulty in isolation and preparation of N_a-H axial aldehydes at C-16 had prevented use of this biogenetic-type strategy for the synthesis of ajmaline/quebrachidine-like alkaloids. Consequently, the strategy here rested on the use of the proper mild oxidative reagents to provide the desired 16-epivellosimine (**7**) without epimerization at C-16. Moreover, polyneuridine aldehyde could be synthesized by extension of this approach to the C-16-quaternary N_a-H diol **12**.

SCHEME 3



Various oxidative conditions were then attempted to convert monol **11** into aldehyde **7** to furnish the less stable axial aldehyde. These previous efforts (Swern oxidation,[43] Dess−Martin periodinate,[44] and IBX[45]) resulted in the decomposition of the starting material or the isolation of the equatorial aldehyde. Analogous to the previous work of Sakai et al.,[46] it was found that the Corey−Kim reagent[47] reacted readily with the alcohol **11** in the presence of Et_3N at −78 °C to give 16-epivellosimine (**7**) in high yield when this was allowed to warm to room temperature. The spectroscopic properties of synthetic **7** were similar to the pattern reported for (+)-vellosimine;[48] however, examination of the proton NMR spectrum indicated the aldehydic peak had shifted from δ 9.65 to 9.16 (Table 1, Supporting Information). This was the typical chemical shift reported for the hindered axial aldehyde.[49] Herein, (+)-16-epivellosimine (**7**) had been prepared in a short synthetic sequence from D-(+)-tryptophan methyl ester (**14**) in nine reaction vessels in 23% overall yield. This material was epimerized into (+)-vellosimine on stirring with base or exposure to silica gel during chromatography for comparison to natural (+)-vellosimine. In addition, it was noteworthy that the hydroxymethyl group of **11** was converted into the ether **16** by oxidative cyclization when it was treated with benzeneselenic anhydride.[50] The ether, dehydro-16-epinormacusine B (**16**), had been previously prepared by DDQ-mediated oxidative cyclization.[31] A potential mechanism of oxidation of indole **11** to provide ether **16** is illustrated in Scheme 3.

The Corey−Kim oxidation can be employed for a wide variety of primary and secondary alcohols with the exception of allylic and benzylic alcohols. The polar solvent CH_2Cl_2 was chosen in this approach. In this oxidation, a side reaction may occur in which the alcohol formed the corresponding

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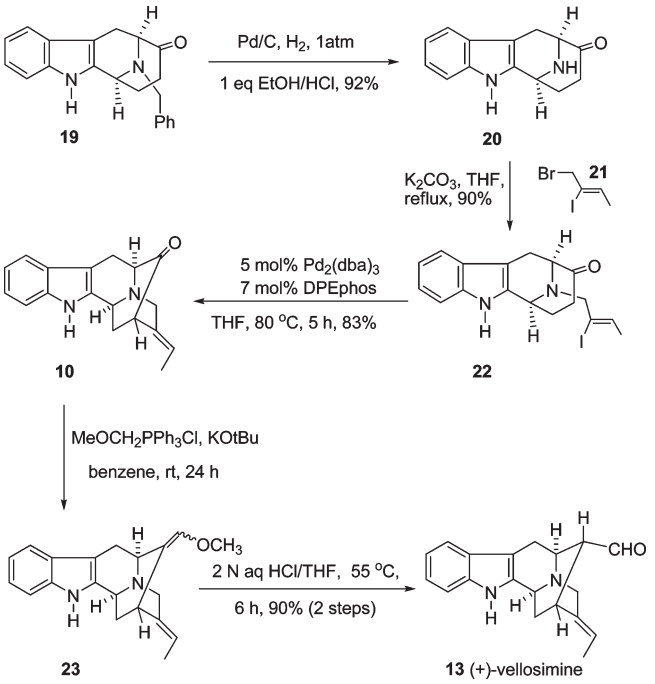
SCHEME 4



methylthiomethyl ether ($ROCH_2SCH_3$) by deprotonation. This side product was observed in the case of the preparation of polyneuridine aldehyde (**6**); however, in the analogous approach to 16-epivellosimine (**7**), a clean and pure aldehyde was obtained in 90% yield. The reaction conditions for the Corey−Kim oxidation are mild and tolerate most functional and protecting groups. Therefore, it was employed in the next sequence for the total synthesis of polyneuridine related alkaloids.

The key intermediate, (+)-vellosimine (**13**), was prepared from the common intermediate, (*E*)-ethylidene ketone **10**, which was synthesized via the asymmetric Pictect−Spengler reaction, Dieckmann cyclization, and palladium mediated cross coupling in high overall yield.[35−37] As illustrated in Scheme 4, the route began with the readily available (−)-N_a-H tetracyclic ketone **19**, which was subjected to the conditions of catalytic hydrogenolysis to remove the benzyl function in 92% yield. This base **20** was reacted with the (*Z*)-1-bromo-2-iodo-2-butene **21** in the presence of K_2CO_3 in THF at reflux to provide the N_b-alkylated ketone **22** in 90% yield. The ketone **22** was initially converted into the desired ketone **10** in 80% yield via an intramolecular palladium (enolate mediated) cross-coupling reaction (see the Supporting Information for experimental details)[51,52] analogous to the process developed by Wang et al.[32,53,54] Further development of this palladium-mediated cross-coupling reaction was achieved when ketone **22** was stirred in combination with 5.0 mol % of $Pd_2(dba)_3$, 7.0 mol % of DPEphos, and 1.5 equiv of NaO*t*Bu in THF at 80 °C for 8 h. The desired ketone **10** was obtained in 83% yield which was superior to the previously reported results (Scheme 6). In addition, another process was also carried out with ketone **22** in combination with 6.0 mol % of $Pd(PPh_3)_4$ and the base PhOK[52] (which was generated previously in the reaction vessel from 2.0 equiv of PhOH and 1.5 equiv of KO*t*Bu). The desired ketone **10** was obtained in 80% yield, which was the same as reported in previous processes [improvements and previous results are summarized in Table 1 (Supporting Information)], but less of the vinyl acetylene byproduct was observed. Ketone **10** was then subjected to the Wittig reaction with (methoxymethyl)triphenylphosphonium chloride and anhydrous potassium *tert*-butoxide to provide a mixture of two stereoisomeric enol ethers represented by olefin **23**. After a short wash column, the mixture of enol ethers **23** was hydrolyzed under acidic conditions to provide vellosimine **13** in 90% yield (overall yield for two steps). Since the aldehyde at C(16) obtained from **23** preferred the more stable α-configuration because of a *syn* pentane interaction with the indole methylene bridge, the mixture was simply stirred until all of the *β*-epimer was converted into the more stable, natural α-epimer present in (+)-vellosimine **13**. Because of the cost of palladium, an alternative, viable, and cheaper route was investigated in regard to the cross-coupling to provide ketone **10**. The recent report[55] on the copper-mediated preparation of vinyl sulfides encouraged use of the same catalytic system (CuI in combination with 1,2-*cis*-cyclohexanediol) for this cross-coupling reaction to obtain ketone **10** from vinyl iodide **22**. The treatment of **24** in combination with 50 mol % of CuI and 50 mol % of 1,2-*cis*-cyclohexanediol as a ligand and 2.0 equiv of Cs_2CO_3 as a base in DMF at 140 °C for 15 h provided pentacyclic ketone **25** in 75% yield (Scheme 5). This was the best yield in this copper-mediated strategy obtained to date, and it was much easier to work up this reaction than the corresponding palladium-mediated process (Scheme 4). A series of ligands in combination with CuI were screened and optimized (see the Supporting Information, Scheme 2); however, this process has not worked as well in the N_a-H series of interest here (see the Supporting Information for details). Further work is underway to maximize the yields in both the N_a-methyl case **25** and the N_a-H case **10**.

A plausible Buchwald−Hartwig catalytic cycle for the enolate-driven, palladium-catalyzed α-vinylation reaction is illustrated in Scheme 6. It was felt the active $Pd(0)L_2$ species was generated primarily by reduction of $Pd(OAc)_2$ with triphenylphosphine in this phosphine-assisted catalytic cycle.[56,57] The active $Pd(0)L_2$ species could then undergo oxidative addition on the vinyl iodide to form a vinylpalladium(II) iodide complex. Ligation to the oxygen and rearrangement to the carbon atom at C(15) can then occur. Finally, reductive elimination of the carbon-bound Pd(II) intermediate would furnish the desired (*E*)-olefin **10** while regenerating the active $Pd(0)L_2$ species. A key to the success of this Pd-mediated cross-coupling reaction rested on the enolate concentration. This must be high enough to permit ligand substitution to occur.[36] It was well-known that vinyl iodides would be quite reactive in the oxidative-addition step. If nucleophilic substitution of the iodide by the nucleophilic enolate

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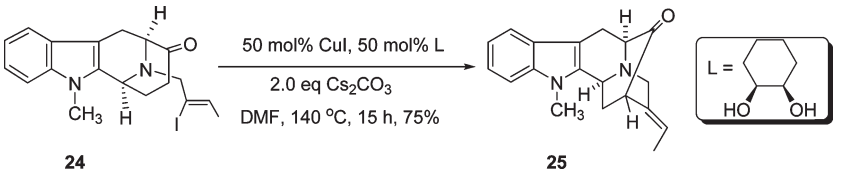
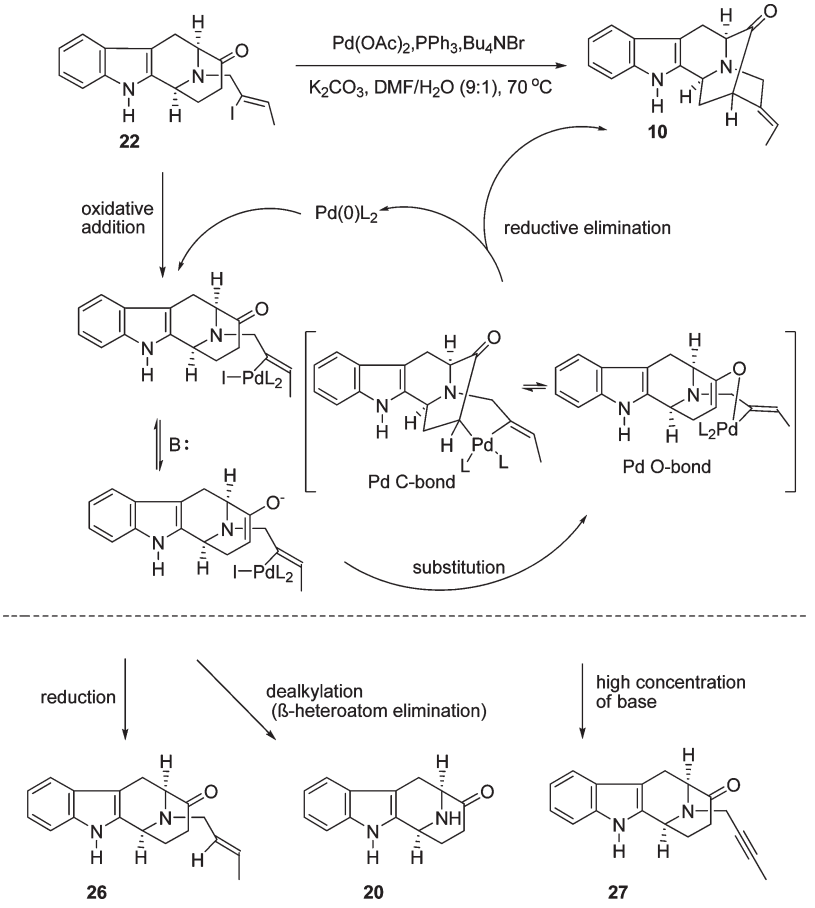
(57) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

SCHEME 5



SCHEME 6



in the coupling process was comparably slow, the rate of byproduct formation would be significant. Eventually, a highly reproducible yield could be obtained by employing an excess of the phosphine ligand.[32] In the case of different substrates, sometimes it was necessary to carry out the reaction with a 10:1 ratio of PPh_3 (30 mol %) to $Pd(OAc)_2$ (3 mol %). The process then took 3 days to go to completion in comparison to the 5 h required under the original conditions, but the amount of byproducts (Scheme 6) was decreased. The yield of the sequence in this series was 81%. Furthermore, the best solvent system to date was DMF/H_2O (9/1); alternation to CH_3CN, pure DMF, or DMF/H_2O (4/1) resulted in no reaction or low yields.[58] Because the conditions employed for the enolate-driven, palladium-coupling process were different from the recent Buchwald–Hartwig arylation reactions,[32] efforts were directed toward intramolecular α-vinylation under the conditions of the arylation process.[32] This might permit lower catalyst loading[32,51] and be effective for both (*E*)- and (*Z*)-ethylidenes. The homogeneous reaction conditions might permit a faster rate and thereby facilitate scaleup. In fact, Liao first reported a Pd(0)-catalyzed α-vinylation process in which the cheaper DPEphos was employed in the case of a (*Z*)-ethylidene[59] for the synthesis of (−)-koumidine.[60] Moreover, utilization of this ligand for the synthesis of the (*E*)-ethylidene **10** was also executed by Liao et al. in 80% yield.[59] However, a related approach has also been effective based on a palladium-catalyzed coupling of amino-tethered vinyl halides with ketones reported by Solé, Bonjoch, et al.[51,52] In this regard, ketone **22** was heated to 70−75 °C in the presence of a palladium(0) triphenylphosphine catalyst and potassium phenoxide. The intramolecular cyclization took place to afford ketone **10** in 80% yield, again in stereospecific fashion (see the Supporting Information, Scheme 1). The use of the weaker potassium phenolate base limited the presence of any acetylene byproduct formed from loss of HI from halide **22**.

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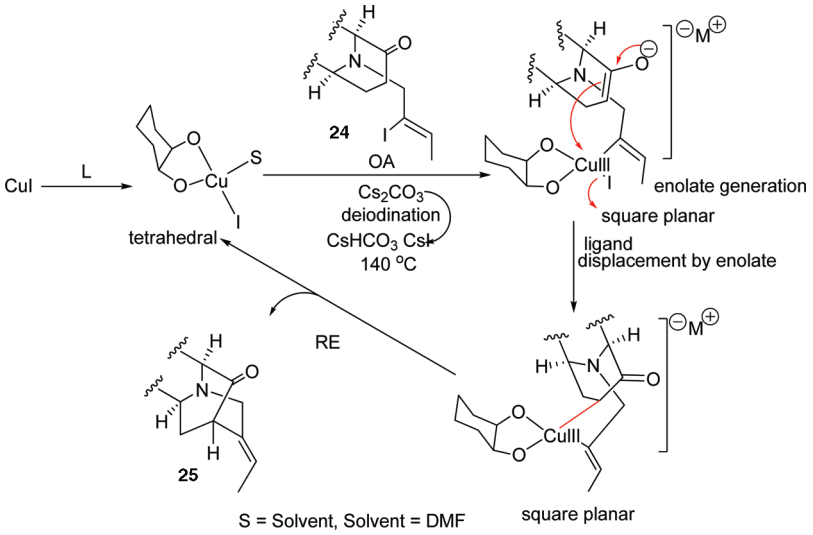
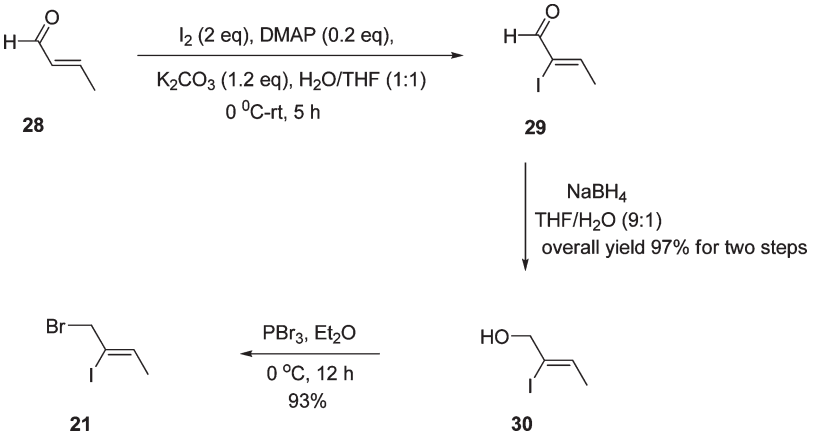
(60) Cao, H.; Yu, J.; Wearing, X.; Zhang, C.; Liu, X.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 8013.

SCHEME 7



SCHEME 8



In the case of the copper-mediated process for the above-mentioned cross-coupling (Scheme 5), a working mechanistic hypothesis is illustrated in Scheme 7. It is believed that 1,2-*cis*-cyclohexanediol ligated with CuI and solvent in a tetrahedral fashion. The deiodination of the iodide ligand by a base and a subsequent oxidative addition to vinyl iodide **24** with copper may lead to Cu(III) with a negative charge on the overall complex. Enolate generation and subsequent ligand displacement by the enolate would furnish the square planar complex (Scheme 7). It is believed that the final step involved reductive elimination to provide the desired ketone **25** in the usual fashion. It is important to point out that neither 1,2-*trans*-cyclohexanediol (see the Supporting Information) nor ethylene glycol worked as well as the 1,2-*cis*-cyclohexanediol in this procedure.

Initially, the vinyl iodide **21** required for this route was synthesized according to a literature procedure.[61] However, the free-radical hydrostannation of the propargyl alcohol was difficult, and the desired iodide was extremely hard to purify. Importantly, as illustrated in Scheme 8, an improved method was recently developed[62] to prepare **21** via α-iodination of an α,*β*-unsaturated aldehyde **28** under the conditions of Krafft,[63] which provided only the *Z*-isomer of **29**. After workup without further purification of **29**, the subsequent reduction[61] of **29** provided the desired alcohol **30** in 97% overall yield. This alcohol **30** was treated with PBr_3 in dry ether at 0 °C for 12 h to provide the desired bromide **21** in 93% yield (see the Experimental Section for details). The sequence was scaled up to the 200 g level starting from crotonaldehyde **28**. Overall, vellosimine **13** was synthesized in gram quantities; moreover, some optimized reaction conditions have been updated in this report to provide the best synthesis of **13**, to date.

With gram quantities of vellosimine **13** in hand, attention turned to the enantiospecific preparation of the two biogenetic intermediates polyneuridine (**8**) and polyneuridine aldehyde (**6**). This route began with the N_a-H diol **12** (Scheme 1) and could, presumably, be employed for the synthesis of quebrachidine (**2**). Instead of the early-stage TPAP-mediated regioselective oxidation of the C-16 axial hydroxymethyl function employed by Yu,[25] in the total synthesis of vincamajinine, it was felt selective protection of the axial hydroxymethyl group in diol **12** would

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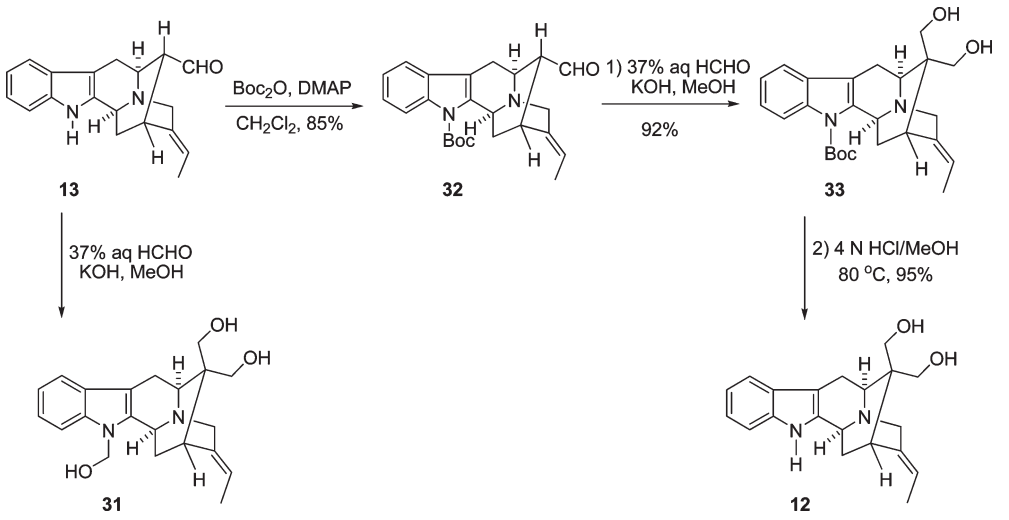
(62) Yang, J.; Rallapalli, S. K.; Cook, J. M. *Tetrahedron Lett.* **2010**, *51*, 815.
(63) Krafft, M. E.; Cran, J. W. *Synlett* **2005**, *8*, 1263.

SCHEME 9

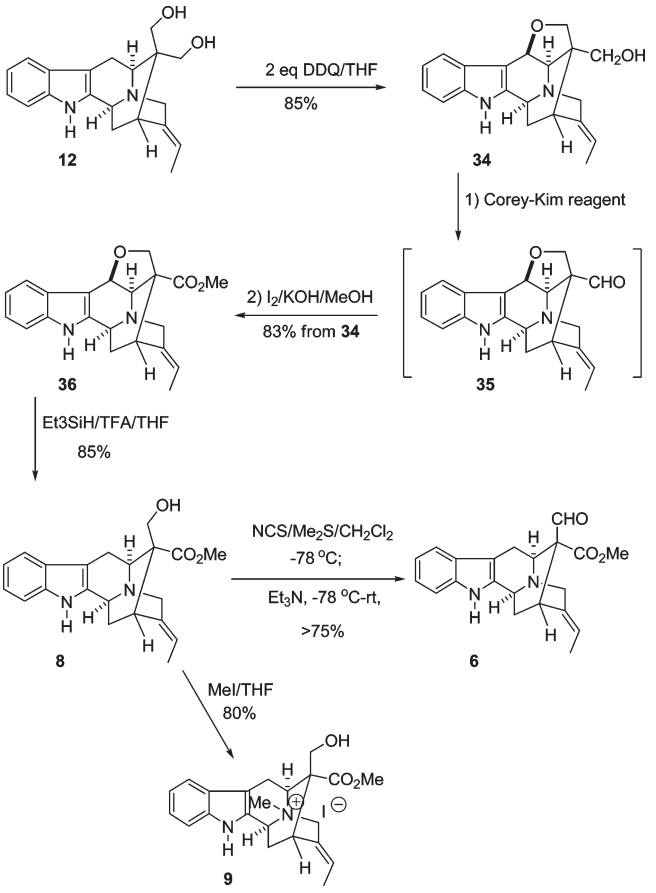


differentiate between the two hydroxymethyl groups to provide polyneuridine (**8**). Analogous to the synthesis of 16-epi-vellosimine (**7**) developed here, the Corey−Kim oxidation would be employed to alter the oxidation state of the C-16 axial hydroxymethyl group in ester **8** to provide polyneuridine aldehyde (**6**).

In order to construct the quaternary carbon center at C-16, numerous efforts (aldolizations, alkylations, and acylations) were originally carried out, but they were not successful.[64−67] Gratifyingly, it was found that the aldehydic group at C-16 in N_a-methylvellosimine could be converted into its related diol after 60 h in 88% yield via the Tollens reaction by using 37% aqueous formaldehyde (5 equiv) and KOH (10 equiv) in methanol.[26] However, this was not as easy in the N_a-H system of vellosimine (**13**). As illustrated in Scheme 9, the undesired triol **31** formed in 83% yield when **13** was treated with formaldehyde and base. Attempts to readily remove the N_a-H-substituted hydroxymethyl function were not successful. Therefore, it was necessary to prohibit reaction of formaldehyde with the indole N_a-H moiety of vellosimine (**13**). Consequently, aldehyde **13** was protected as the N_a-Boc intermediate with Boc_2O in the presence of DMAP to afford **32** in 85% yield. It was then converted into the Boc-protected prochiral C-16-quaternary diol **33** via the Tollens-like reaction (crossed Cannizzaro process), and this was followed by deprotection under acidic conditions. The prochiral quaternary carbon center at C-16 that contained the structurally hindered diol of **12** was constructed in two steps within one reaction vessel in this process. More importantly, because of the symmetry of the two diol moieties at C-16, generation of a new chiral center was avoided. However, the two hydroxymethyl groups are prochiral, which was useful, as planned.

With the success in the synthesis of the diol **12**, selective protection of the C-16 axial hydroxymethyl group in preference to the equatorial hydroxymethyl group was achieved with dichlorodicyanobenzoquinone (DDQ)-mediated oxidation. As illustrated in Scheme 10, following a process

SCHEME 10



developed previously in this laboratory,[68] the diol **12** was treated with DDQ in anhydrous THF to give the ether **34**, which permitted further modification of the equatorial hydroxymethyl group. The hydroxymethyl group which remained was converted into the methyl ester **36** via the two steps detailed below. Various oxidative reagents (i.e., TPAP,[69] Dess−Martin

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(67) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.
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(69) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

periodinate,[44] and benzeneselenic anhydride[50]) were employed to furnish the equatorial aldehyde **35**; however, most of these efforts resulted in the decomposition of the starting material or cleavage of the C(6)−C(17)−oxygen bridge. Again, the conditions of the Corey−Kim oxidation could be employed successfully in this system; the monol **34** was converted into the equatorial aldehyde **35** in 90% yield. The aldehyde function of intermediate **35** was then oxidized to the methyl ester **36** with I_2 and KOH in MeOH, following the work of Yamamoto et al.[33,68,70] This illustrated atom economy at its best. After oxidative formation of the α-methyl ester **36** at C-16, the ether bond was reductively cleaved with TFA/Et_3SiH[68] in 85% yield to provide polyneuridine (**8**) [FTIR 3267 cm^{-1} (OH), 1736 cm^{-1} (CO_2-Me)] (Figure 1, Supporting Information). As illustrated in Table 2 (Supporting Information), the spectral data of polyneuridine were in excellent agreement with the natural product.[71,72] Furthermore, the important biogenetic intermediate, polyneuridine aldehyde (**6**) [FTIR 1731 cm^{-1} (CO_2Me), 1707 cm^{-1} (CHO)] was then obtained by a second Corey−Kim oxidation (Figure 2, Supporting Information). Consequently, aldehyde **6** could be prepared from D-(+)-tryptophan methyl ester (**14**) in 13 reaction vessels in 14.1% overall yield. Reduction of polyneuridine aldehyde **6** with sodium borohydride returned polyneuridine **8**, which confirmed the presence of the aldehyde moiety in **6**. Finally, quarternization of the N_b nitrogen function in polyneuridine (**8**) with MeI provided the N_b-methiodide salt, macusine A (**9**), in 80% yield. This was the first total synthesis of these three alkaloids and was accomplished in stereospecific fashion.

It is important to note the Corey−Kim oxidation provided an extremely mild method to complete the key oxidation of the C-16-hydroxymethyl group of the indole alkaloids, 16-epivellosimine (**7**), and polyneuridine aldehyde (**6**) in the N_a-H series in the absence of epimerization to the more stable C-16 equatorial aldehyde as in **13**. Treatment of alcohols **11** and **8** with 5 equiv of the Corey−Kim reagent in CH_2Cl_2 at −78 °C for 2 h was followed by the standard workup[46] to provide the respective aldehydes in high yield. The DDQ oxidation of diol **12** to provide ether **34** was not simple. The oxidation was run at a lower temperature in a dry ice bath under argon, and approximately 50% of the desired ether **34** appeared on TLC in 5 min. This was after the addition of 1 equiv of DDQ. Since no further change occurred after 0.5 h, another 1 equiv of DDQ was added to the mixture, and no obvious change was observed over a 2 h period at this temperature. The reaction mixture was allowed to warm to rt at which time the process went to completion. Analysis by TLC indicated that only one component (Scheme 10) was present under these conditions, and that was ether **34**.

Conclusion

The first stereospecific total synthesis of 16-epivellosimine (**7**), (+)-polyneuridine (**8**), (+)-polyneuridine aldehyde (**6**), and macusine A (**9**) has been accomplished from commercially available D-(+)-tryptophan methyl ester (**14**). The asymmetric Pictet−Spengler reaction and palladium-mediated enolate cross-coupling process were key steps to construct the sapargine skeleton. An alternative palladium-mediated enolate cross-coupling was developed (Scheme 4 and see the Experimental Section) and the use of a milder base PhOK generated in situ may minimize the formation of the acetylene byproduct (see the Supporting Information, Scheme 1). In addition, the application of the copper-mediated cross-coupling process in the case of the N_a-Me iodo ketone has been realized with comparable results. The Pd to Cu switch has permitted extension of this process to one that is cheaper and much easier to workup.

A stereocontrolled formation of the C-16 quaternery carbon center was accomplished by a very practical Tollens' (crossed Cannizzaro) reaction. This important transformation established the prochiral hydroxymethyl groups at C-16 without the need for chiral reagents or asymmetric induction. Presumably, this robust reaction could be scaled up to kilogram scale in this series. The DDQ-mediated oxidative cyclization and TFA/Et_3SiH reductive cleavage served as protection/deprotection steps in order to provide a versatile entry into these alkaloids. The chemospecific and regiospecific oxidations with the Corey−Kim reagent were key steps in these syntheses to provide the desired aldehydes. This constituted the first stereospecific synthetic solutions to the axial aldehydes in 16-epivellosimine (**7**) and polyneuridine aldehyde (**6**) and should also provide access to the ajmaline/quebrachidine alkaloids.

Experimental Section

Conversion of N_a-H-17-Hydroxysarpagan-16-methanol (12) into N_a-H-17-Hydroxysarpagan-16-methyl-6-cyclic Ether (34). The recrystallized (from CH_2Cl_2) DDQ (253 mg, 1.111 mmol) was added to a solution of diol **12** (180 mg, 0.556 mmol) in dry THF (10 mL) at −78 °C (dry ice bath). The black-blue colored mixture which resulted was stirred at this temperature and gradually allowed to warm to rt. The reaction was completed in 20 min to 0.5 h until analysis by TLC indicated the absence of starting material. The mixture was then diluted with CH_2Cl_2 (90 mL), washed with a saturated solution of aq $NaHCO_3$ (10 mL × 2), and then concentrated under reduced pressure. The residue was again dissolved in a mixture of CH_2Cl_2 (90 mL) and MeOH (10 mL), after which it was washed with a solution of 20% aq NH_4OH (30 mL × 2) and brine (2 × 10 mL). It was dried over K_2CO_3. The organic layer was then removed under reduced pressure, and the residue which resulted was flash chromatographed (silica gel, CH_2Cl_2/MeOH = 20:1) to provide the cyclic ether **34** (161 mg, 90%): FTIR (NaCl) 3745, 1698, 1450, 744, 464 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.61 (d, J = 4.5 Hz, 3H), 1.78 (m, 1H), 1.90 (m, 1H), 2.80 (d, J = 6 Hz, 1H), 2.95 (s, 1H), 3.15 (m, 1H), 3.22 (m, 1H), 3.40 (s, 1H), 3.58 (d, J = 10.5 Hz, 1H), 3.68 (d, J = 3 Hz, 1H), 3.92 (dd, 1H), 4.68 (t, 1H), 5.34 (m, 1H), 5.42 (d, J = 3 Hz, 1H), 6.98 (t, 1H), 7.04 (t, 1H), 7.31 (d, J = 5.1 Hz, 1H) 7.46 (d, J = 6 Hz, 1H), 10.98 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 29.1, 30.2, 32.0, 46.4, 48.8, 55.4, 63.6, 66.2, 66.7, 103.5, 112.1, 115.3, 118.9, 119.7, 121.4, 127.0, 136.5, 138.6, 144.2; EIMS (70 eV) (*m*/*e* relative intensity) 322 (M^+, 100), 305 (26), 291 (16), 182 (41), 169 (85); HRMS calcd for $C_{20}H_{22}N_2O_2$ 322.1681, found 322.1670. This material was used directly in the next step.

Alternative Pd-Catalyzed Cyclization of (6*S*,10*S*)-(−)-9-Oxo-12-[(*Z*)-2′-iodo-2′-butenyl]-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (22) To Provide Pentacyclic Ketone (10). The N_b-*Z*-2′-iodo-butenyltetracyclic ketone **22** (1 g, 2.46 mmol) was dissolved in anhydrous THF (60 mL). To this solution were added NaO-*t*-Bu (0.354 g, 3.69 mmol), DPEphos (0.0927 g, 7.0 mol %), and $Pd_2(dba)_3$ (0.112 g, 5.0 mol %). This reaction mixture was degassed under argon and placed in a preheated oil

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(71) Antonaccio, L. D.; Pereira, N. A.; Gilbert, B.; Vorbrueggen, H.; Budzikiewicz, H.; Wilson, J. M.; Durham, L. J.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 2161.
(72) Jokela, R.; Lounasmaa, M. *Heterocycles* **1996**, *43*, 1015.

bath at 80 °C for 5 h. The reaction solution was then quenched with water and extracted with EtOAc (3 × 250 mL). The organic layer was separated and dried (Na_2SO_4). The EtOAc was then removed under reduced pressure, and residue was flash chromatographed with CH_2Cl_2/MeOH (4.5:0.5) to provide the coupling product **10** (0.569 g, 83% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (3H, d, J= 6.86 Hz), 2.15−2.20 (1H, m), 2.38 (1H, t, J = 9.87 Hz), 2.97 (1H, dd, J = 15.58, 6.20 Hz), 3.27 (1H, d, J = 14.43 Hz), 3.37 (1H, bs), 3.59 (1H, d, J = 5.70 Hz), 3.78 (2H, bs), 4.26 (1H, d, J = 9.11 Hz), 5.49 (1H, q, J = 6.85 Hz), 7.05−7.15 (2H, m), 7.25 (1H, d, J = 7.25 Hz), 7.47 (1H, d, J = 7.29 Hz), 7.92 (1H, bs); ^{13}CNMR (75.5 MHz, $CDCl_3$) δ 12.68, 22.39, 36.40, 44.55, 50.83, 55.24, 64.17,105.62, 110.89, 118.54, 119.69, 121.26, 122.00, 126.88, 131.88, 135.87, 136.34, 217.00; CIMS (*m*/*e*, relative intensity) 291 ($M^+ + 1$, 100); EIMS (*m*/*e*, relative intensity) 278 (M^+, 10), 250 (75), 249 (85), 182 (6), 169 (100), 168 (5); HRMS (*m*/*e*, relative intensity) required for $C_{18}H_{18}N_2O$ 278.1419, found 278.1437. The spectral data of this ketone were identical to the published values.[73]

Copper-Mediated Cyclization of (6*S*,10*S*)-5-Methyl-(−)-9-oxo-12-[(*Z*)-2′-iodo-2′-butenyl]-6,7,8,9,10,11-hexaydro-6,10-iminocyclooct[*b*]indole (24) To Provide 3-Ethylidine-12-methyl-1,3,4,7,12,12b-hexahydro-13-hydroxymethyl-2*H*,6*H*-2,6-methanoindolo[2,3-α]quinolizin-13-one (25). A mixture of tetracyclic ketone **24** (1.00 mmol), CuI (99.99%) (50 mol %), 1,2-*cis*-cyclohexanediol (50 mol %), and Cs_2CO_3 (2.0 mmol) was placed in dry DMF (Aldrich sure seal bottle), after which it was degassed (3 times) under reduced pressure at rt and refilled with argon (3 times). The reaction mixture was then placed on a preheated oil bath (140 °C) under argon and allowed to stir at 140 °C for 12 h. At this point, analysis by TLC (silica gel, EtOAc/hexane =1:1, double runs) indicated the absence of starting material **24**. The mixture was cooled to rt, diluted with EtOAc, and filtered through Celite. The reaction mixture was then washed with H_2O (5 × 100 mL) and brine (100 mL) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the oil which resulted was purified by chromatography on silica gel (EtOAc/hexane 1:1) to provide pure pentacyclic ketone **25**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (1H, t, J = 6.9 Hz), 1.85 (3H, s), 2.40 (1H, m), 2.74 (1H, d, J = 12.2 Hz), 2.95 (1H, m), 3.04 (1H,m), 3.30 (1H, m), 3.61 (3H, s), 3.92(1H, d, J = 5.4 Hz), 4.01 (1H, m), 4.43 (1H, d, J = 9.4 Hz), 5.40 (1H, q, J = 6.9 Hz), 7.11 (1H, t, J = 7.5 Hz), 7.22 (1H, t, J = 6.9 Hz) 7.28 (1H, d, J = 8.1 Hz), 7.51 (1H, d, J = 7.5 Hz); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.7, 22.3, 29.3, 35.5, 44.1, 49.7, 55.4, 64.1, 104.4, 108.8, 118.5, 119.1, 119.5, 121.5, 126.4, 132.1, 136.9, 137.4, 215.8. The spectral data for this material were identical to the published values.[32,59]

Preparation of 1-Bromo-2-iodobut-2-ene 21 from But-2-enal 28. Potassium carbonate (24 g, 172 mmol), I_2 (72.42 g, 286 mmol), and DMAP (3.48 g, 28.6 mmol) were successively added to a solution of crotonaldehyde **28** (10 g, 143 mmol) in a mixture of THF (350 mL) and water (350 mL). After being stirred for 4−5 h, the reaction mixture was diluted with EtOAc and washed with a solution of saturated aq $Na_2S_2O_3$. The organic layer was dried (Na_2SO_4), and the crude product **29** obtained after evaporation in vacuo was used in the next step without purification. The crude product **29** (143 mmol) was taken up in THF−H_2O (9:1) and cooled to 0 °C. The $NaBH_4$ (2.69 g, 71.5 mmol) was added slowly, and the reaction was stirred for 1 h. The reaction mixture was quenched with water and extracted with EtOAc (3×500 mL). The organic layer was concentrated and the residue purified by flash chromatography with silica gel in ethyl acetate/hexane (1:9) to obtain iodide **30** (27.40 g, 97% yield): ^{1}H NMR δ 5.98 (q, J = 6.3 Hz, 1H), 4.23 (s, 2H), 1.79 (d, J = 6.3 Hz, 3H). The spectral properties of this iodide were identical to the published values.[61]

(*Z*)-2-Bromo-2-buten-1-ol **30** (2 g, 10 mmol) was dissolved in anhydrous ethyl ether (20 mL). Phosphorus tribromide (0.380 mL, 4 mmol) was added dropwise to this solution at 0 °C. This reaction mixture which resulted was stirred for 12 h at rt. The reaction was quenched with a cold aq solution of K_2CO_3 and extracted with ethyl ether after which it was washed with brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give **21** (2.45 g, 93% yield) which was directly used in the next step:[74] ^{1}H NMR δ 6.08 (q, J = 6.4 Hz, 1H), 4.36 (s, 2H), 1.81 (d, J = 6.4 Hz, 3H). The spectral properties of this bromide were identical to the published values.[75]

Preparation of Aldehyde 35. To a stirred solution of *N*-chlorosuccinimide (400 mg, 3.0 mmol) in dry CH_2Cl_2 (15 mL) was added dimethyl sulfide (1.1 mL, 15 mmol) at 0 °C under argon. A white precipitate appeared immediately after addition of the sulfide. The mixture was cooled to −78 °C (EtOAc−dry ice bath), and stirring was continued for 1 h at −78 °C. The mixture of ether **34** (194 mg, 0.6 mmol) in dry CH_2Cl_2 (3 mL) was then added into the resulting white complex at −78 °C, and the stirring was continued for 2 h at −78 °C. A solution of triethylamine (1.4 mL, 10 mmol) in CH_2Cl_2 (0.5 mL) was added to the mixture. The stirring was continued for an additional 1 h. The cooling bath was then removed, and after 10 min, ether (20 mL) was added. The organic layer was diluted with a mixture of CH_2Cl_2 (45 mL) and MeOH (5 mL), after which it was washed with a solution of 1% aq hydrochloric acid (5 mL) and twice with water (2 × 15 mL). The organic layer was separated and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide the crude aldehyde **35** (180 mg, 93%). Analysis of the ^{1}H NMR spectrum indicated the presence of the desired aldehydic peak at δ 9.56 or occasionally at 9.60. This material was employed in a later step without further purification.

16-Epivellosimine (**7**) was prepared from the alcohol **11** ((*E*)-16-epinormacusine B) following the analogous procedure employed for preparation of **35** above. **7**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.65 (d, J = 8.4 Hz, 3H), 1.75 (t, 1H), 2.02 (m, 1H), 2.26−2.32 (bs, 1H), 2.55−2.66 (m, 1H), 2.52−2.84 (m, 1H), 2.75 (bs, 1H), 3.51−3.69 (m, 2H), 3.76 (dt, 1H), 4.15 (d, J = 9 Hz, 1H), 5.30 (q, 1H), 7.106−7.14 (m, 2H), 7.24 (d, J = 6 Hz, 1H) 7.43 (d, J = 6 Hz, 1H), 8.18 (s, 1H), 9.16 (s, 1H); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.7, 23.8, 25.1, 26.5, 49.9, 50.1, 53.0, 55.8, 104.7, 110.9, 114.9, 118.0, 119.5, 121.8, 126.2, 136.6, 137.3, 138.2, 200.7. The spectra data were similar to those of the previous synthetic vellosimine **27**, except the aldehydic peak had shifted to 9.16 from 9.56 (Table 2, Supporting Information).

Oxidation of the Aldehyde 35 into Methyl Ester 36. The crude aldehyde **35** (87 mg, 0.272 mmol) which resulted from the Corey−Kim oxidation was triturated with hexane (6 × 5 mL) to remove impurities. The residue was dissolved in anhydrous MeOH (2 mL), and a solution of 85% KOH (148 mg, 2.21 mmol) and iodine (280 mg, 1.1 mmol) in anhydrous MeOH (4 mL) were successively added at 0 °C. After 6 h, the reaction mixture was diluted with CH_2Cl_2 (80 mL), washed with a 10% aq solution of $Na_2S_2O_3$ (20 mL), water (20 mL), and brine (20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue which resulted was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 20/1) to provide methyl ester **36** (98 mg, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (d, J = 6.9 Hz, 3H), 1.98−2.13 (m, 2H), 3.28 (t, J = 5.6 Hz, 1H), 3.51−3.80 (m, 3H), 3.72 (s, 3H), 3.95−3.98 (m, 2H), 4.52 (d, J = 8.0 Hz, 1H), 5.35 (q, J = 6.8 Hz, 1H), 5.77 (d, J = 7.9 Hz, 1H), 7.18 (m, 2H), 7.34 (d, J = 6.6 Hz, 1H) 7.68 (d, J = 5.6 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ

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12.8, 28.7, 29.7, 45.9, 48.7, 55.1, 62.8, 66.9, 68.4, 72.0, 104.2, 110.9, 116.2, 118.7, 120.2, 121.9, 126.4, 135.8, 136.3, 141.5, 162.2; EIMS *m*/*e* 350 (M^+ 100), 333 (12), 319 (25), 291 (20), 182 (34), 168 (86); HRMS calcd for $C_{21}H_{22}N_2O_3$ 350.1630, found 350.1629. This material was used directly in the next step.

Polyneuridine (8) (Sarpagan-16-carboxylic Acid, 17-Hydroxymethyl Ester, (16*R*)-9CI). The TFA (5 mL) and Et_3SiH (5 mL) were added to a solution of **36** (28 mg, 0.080 mmol) in CH_2Cl_2 (5 mL). The reaction mixture which resulted was stirred in a sealed vessel at rt for 12 h, after which the solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (80 mL), and a solution of 10% aq NH_4OH was added to bring the pH to 8. The organic layer was separated, washed with brine (2 × 20 mL), dried (Na_2SO_4), and removed under reduced pressure. The residue that resulted was purified by small column on silica gel (CH_2Cl_2/MeOH 20/1) to provide **8** (25 mg, 87%): $[\alpha]^{25}_D$ = 5.6 (*c* = 0.5, CH_2Cl_2) [lit.[71] $[\alpha]_D$ = +1 (chloroform)]; FTIR 3267 (OH), 2925, 2854, 1736 (CO_2Me), 1455, 1260, 1086, 799.5, 741 cm^{-1} (Figure 1, Supporting Information); ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, *J* = 6.8 Hz, 3H), 1.85 (ddd, 1H), 1.95(ddd, 1H), 3.01(br d, 1H), 3.12 (dd, *J* = 6.3 Hz, 1H), 3.18 (dd, 1H), 3.50 (m, 1H), 3.57 (m, 2H), 3.65 (d, *J* = 8.2 Hz, 1H), 3.73 (s, 3H), 4.18 (d, *J* = 9 Hz, 1H), 4.35 (d, *J* = 6.2 Hz, 1H), 5.23 (br q, *J* = 6.8 Hz, 1H), 7.10 (t, 1H), 7.16 (t, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 8.48 (s, 1H); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.6, 21.9, 28.6, 30.4, 48.8, 52.2, 53.3, 53.6, 55.1, 63.1, 105.6, 111.1, 116.7, 118.2, 119.4, 121.7, 126.1, 134.5, 135.8, 136.1, 175.7; EIMS *m*/*e* 352 (M^+ 45), 336 (20), 322 (100), 263 (39), 249 (47), 168 (100), 142 (82); HRMS calcd for $C_{21}H_{24}N_2O_3$ 352.1787, found 352.1768. The carbon NMR spectral data of **8** were in excellent agreement with those of the natural product **8** (Table 3, Supporting Information).

Polyneuridine aldehyde (**6**) was prepared from polyneuridine (**8**) in 75% yield following the procedure employed for the preparation of **35**. **6**: FTIR 2919, 2850, 1731 (CO_2Me), 1707 (CHO), 1456, 1257, 1107, 747 cm^{-1} (Figure 2, SI); EIMS *m*/*e* 350 (M^+ 48), 321 (16), 260 (19), 246 (100), 231 (20), 168 (25). This material was used directly in the next step to further prove the structure of **6**.

Reduction of Polyneuridine Aldehyde (6) to Polyneuridine (8). To a solution of the above polyneuridine aldehyde (**6**) (2 mg, 5.7×10^{-3} mmol) and glacial acetic acid (10 uL) in methanol (1 mL) was added sodium borohydride (8.6 mg, 0.23 mmol) in small portions at 0 °C. The mixture was stirred at this temperature for 2 h. Upon completion of the reaction, the mixture was poured into 2 mL of saturated aq sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with brine and dried, and the solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel and yield polyneuridine (**8**) with the same R_f as **8** prepared previously (1.2 mg, 60%): EIMS *m*/*e* 352 (M^+ 100), 249 (31), 219 (32), 168 (65), 142 (82); HRMS calcd for $C_{21}H_{24}N_2O_3$ 352.1785, found 352.1776.

Macusine A (9). Polyneuridine (**8**) (6 mg, 1.5×10^{-3}mmol) was dissolved in THF (1 mL) and cooled to 0 °C. The MeI (11 mg, 0.15 mmol) was added to the above solution dropwise. The reaction mixture was stirred at 0 °C for 8 h. The solvent was removed under reduced pressure, and the residue was purified by preparative TLC on silica gel (CH_2Cl_2/MeOH 10/1) to provide the iodomethylated salt 23 (6.8 mg, 81%): ^1H NMR (300 MHz, MeOH-d_4) δ 1.71 (d, *J* = 11 Hz, 3H), 2.15 (m, 1H), 2.47 (m, 1H), 3.26 (s, 3H), 3.31−3.36 (m, 2H, overlap with MeOH-d_4) 0.3.42 (m, 2H), 3.70 (m, 2H), 3.78 (s, 3H), 4.29 (d, *J* = 18 Hz, 1H), 4.48 (d, *J* = 20.3 Hz, 1H), 4.93 (br d, partial overlap with MeOH-d_4, 1H), 5.0385 (d, *J* = 5.91, 1H), 5.51 (q, 1H), 7,12 (t, 1H), 7.23 (t, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.99 (s, NH, 1H); ^{13}C NMR (75.7 MHz, MeOH-d_4) δ 11.3, 18.6, 28.6, 29.2, 29.9, 51.8, 55.1, 59.1, 62.4, 63.9, 64.6, 101.6, 111.1, 118.2, 119.3, 119.5, 122.5, 124.8, 127.2, 130.0, 137.1, 172.7; HRMS calcd for $C_{22}H_{27}N_2O_3$ 367.2022, found 367.2008. This salt was treated with AgCl to give the chloride salt. The spectral data are in good agreement with the literature.[76]

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Supporting Information Available: Alternate procedure for the synthesis of **10** and **25**; experimental data for **12**, **32**, and **33**; as well as ligand screening and optimization data for copper-mediated coupling process. ^1H NMR and ^{13}C NMR spectra for the intermediates and final products as well as FT-IR for polyneuridine (**8**) and polyneuridine aldehyde (**6**). This material is available free of charge via the Internet at http://pubs.acs.org.

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