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First Enantiospecific Total Synthesis of the Important Biogenetic Intermediates, (+)-Polyneuridine and (+)-Polyneuridine Aldehyde, as Well as 16-Epi-vellosimine and Macusine A

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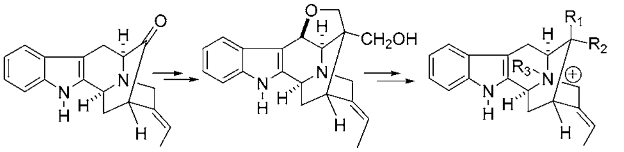
ABSTRACT

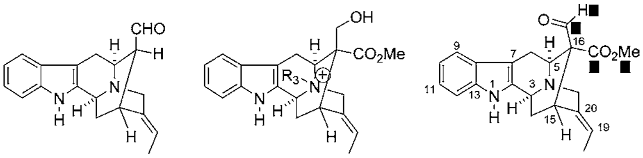


1 R_1 = CHO, R_2 = H, R_3 = H
2 R_1 = CH_2OH, R_2 = CO_2CH_3, R_3 = H
3 R_1 = CHO, R_2 = CO_2CH_3, R_3 = H
4 R_1 = CH_2OH, R_2 = CO_2CH_3, R_3 = CH_3

The first enantiospecific total synthesis of the alkaloids 16-epi-vellosimine (1), (+)-polyneuridine (2), (+)-polyneuridine aldehyde (3), and macusine A (4) is reported. The key oxidation was accomplished with the Corey–Kim reagent to provide the important biogenetic intermediates, 16-epi-vellosimine (1) and polyneuridine aldehyde (3), the latter of which is required for the conversion of the sarpagan skeleton into the ajmalan system in the biosynthesis of quebrachidine.

The indole alkaloids are an important source of biologically active compounds.[1,2] More than 84 sarpagine-related ajmaline/quebrachidine/vincamajine indole alkaloids have been isolated during the past few decades.[3] Interest in this group of indole alkaloids derives from both the structural diversity and the complexity of its members and the important medicinal properties of some of these natural bases.[3] The investigation of the biogenetic link between the sarpagine- and ajmaline-related alkaloids[4] has stimulated interest in the synthesis of **1**−**4** (Figure 1).

In 1983, Stöckigt reported the isolation of 16-epi-vellosimine (**1**)[5] from characterization of polyneuridine aldehyde esterase (PNA-esterase).[6] Analysis by proton NMR spectroscopy clearly identified the enzymatic product as **1** (aldehydic signal at δ 9.16).[6] Polyneuridine (**2**)[7] and poly-



1 16-epi-vellosimine
2 R_3 = H, (+)-polyneuridine
4 R_3 = CH_3, macusine A
3 (+)-polyneuridine aldehyde

Figure 1. Four synthetic targets.

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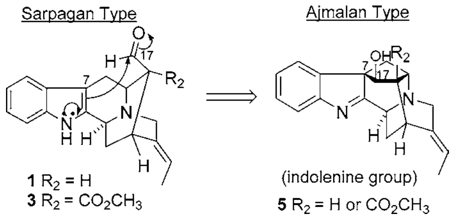
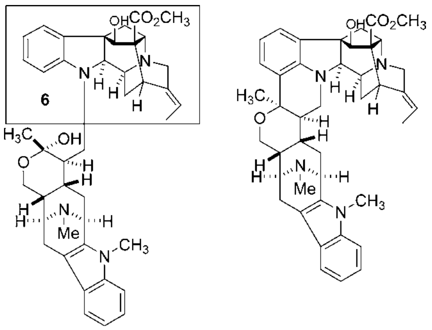
neuridine aldehyde (**3**)[8] were first isolated in the early 1960s from *Aspidosperma polyneuron* and *Aspidosperma dasycarpon*. The structure of polyneuridine (**2**) was elucidated on the basis of ^{1}H and ^{13}C spectroscopic studies,[9] in agreement with earlier studies by mass spectrometry.[7] As illustrated in Figure **1**, these two sarpagine bases and the related macusine A (**4**)[7,10] represented a series of polyneuridine alkaloids, which contained a different exo functional group at C-16 (*S*) with the β-axial stereochemistry and an equatorial carbomethoxy group. Polyneuridine aldehyde (**3**) contains the unique C-16 axial aldehyde function and is located in the middle of the ajmaline biosynthetic pathway.[11] A related process is the transformation of **3** to the previously unknown biogenetic intermediate, the important alkaloid 16-epi-vellosimine (**1**),[12] and provides a precursor for the biosynthesis of the ajmaline skeleton.[4,11] The biogenetic connection between the sarpagine- and ajmaline-related alkaloids proposed earlier[13,14] has been detailed by Stöckigt et al.[4,11,12] As illustrated in Figure 2,[4] 16-epi-vellosimine (**1**) and polyneuridine aldehyde (**3**) are proposed important biogenetic intermediates in the formation of the unique cage-related quebrachidine alkaloids including (+)-quebrachidine (**6**),[15] (+)-alstonisidine (**7**),[16] and the antimalarial bisindole, (+)-alstomacroline (**8**) (Figure 3).[17] The complex architecture of these alkaloids, as well as their largely unexplored potential in medicine or as tools for biological studies, stimulated interest in such systems. On the basis of the above discussion, cyclization of **1** or **3** at C-7−C-17 would provide the correct configuration at C-7 of all quebrachidine-related alkaloids.



1 $R_2 = H$
3 $R_2 = CO_2CH_3$
5 R_2 = H or CO_2CH_3

Figure 2. Biogenetic connection between two indole types.[4]



6 quebrachidine
8 alstomacroline
7 alstonisidine

Figure 3. Quebrachidine related bisindole alkaloids.

Recently, the total synthesis of ajmaline[18] and the vincamajinine-related alkaloids[19] provided direct proof for the close synthetic relationship of 16-N$_a$-methyl axial aldehydes to the indolenine group.[4] However, it was well-known that the aldehyde function at C-16 preferred the α-equatorial stereochemistry.[20] The axial aldehyde function of **1** can be easily epimerized into the sarpagine series of alkaloids.[11] Previously, the difficulty in isolation and preparation of N$_a$−H axial aldehydes at C-16 has prevented use of this biogenetic-type strategy for the synthesis of ajmaline/quebrachidine-like alkaloids. To the best of our knowledge, these two crucial intermediates, 16-epi-aldehydes **1** and **3**, have not previously been synthesized. Facile entry into these systems and related alkaloids **2** and **4** provided much of the impetus for this letter. In addition, functions that could be readily radio-labeled for biogenetic studies are shown in **3** with a box (Figure 1), in regard to their potential biosynthetic use.

As illustrated in Scheme 1, in a retrosynthetic sense, both 16-epi-vellosimine (**1**) and polyneuridine aldehyde (**3**) might be available via a common intermediate, the *E*-ethylidene ketone (**9**). The synthesis of the axial aldehyde function of **3** could be approached by selective oxidation of the N$_a$−H diol **10**, analogous to the previous (TPAP) approach on the related N$_a$-methyl diol.[19] Although the TPAP-selective oxidation of the β-axial alcohol on the Boc-protected 16-quaternary diol was used to provide a 16-β-axial aldehyde (dr > 8:1),[21,22] synthesis of aldehydes in the N$_a$−H series was more difficult.

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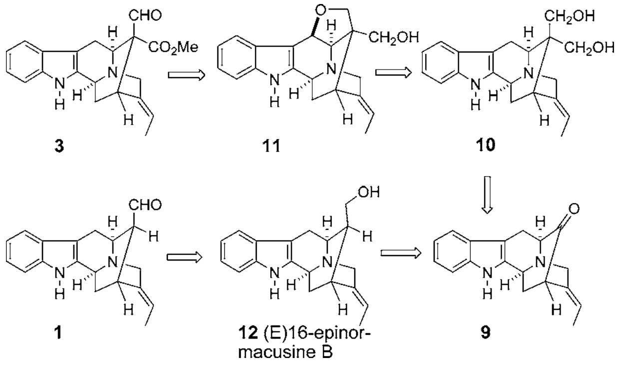
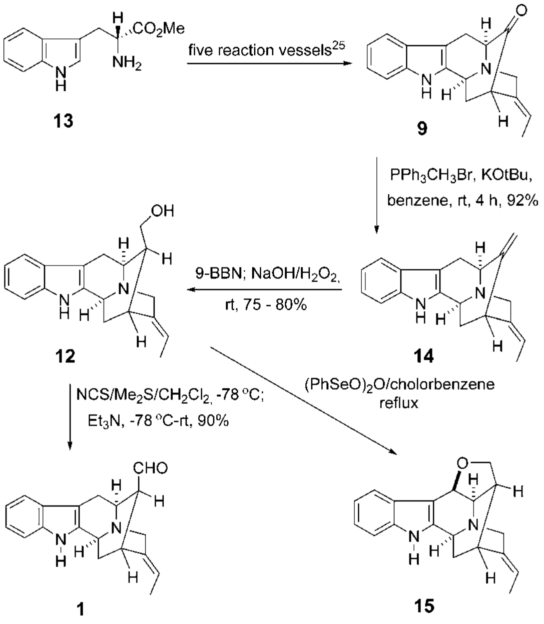
Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of 16-(+)-Epi-vellosimine



This is 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. It was anticipated that selective protection of the axial hydroxymethyl group in N$_a$−H diol **10** to give **11**, which could serve as a key intermediate for further oxidation−deprotection−oxidation transformations[23] to provide the target compound **3**, would be required. In addition, Yu et al. had reported the enantiospecific total synthesis of *E*-16-epinormacusine B (**12**),[24] which could be employed as an intermediate in the total synthesis of **1**. The strategy here rested on the use of the proper oxidative reagents to provide the desired 16-epivellosimine (**1**) from the monol (**12**). Moreover, polyneuridine aldehyde (**3**) could be synthesized by extension of this approach to 16-quaternary N$_a$−H diol **10**. With the prior success in the construction of quebrachidine diol,[21] synthesis of **3** should provide an efficient route for the future synthesis of quebrachidine (**6**).

The synthesis began with the *E*-ethylidene ketone (**9**) (Scheme 2),[25] available in enantiospecific fashion in five steps from D-(+)-tryptophan methyl ester (**13**). Consequently, *E*-16-epinormacusine B (**12**) was obtained from **9** via a Wittig reaction coupled with a hydroboration/oxidation following the published procedure.[24] Once the β-axial alcohol (**12**) was obtained, various oxidative conditions were attempted to furnish the less stable axial aldehyde (**1**).

Most of these efforts resulted in the decomposition of the starting material or equatorial aldehyde. It is noteworthy that the hydroxymethyl group of **12** was converted into the ether (**15**) by oxidative cyclization when it was treated with benzeneselenic anhydride. The ether, dehydro-16-epinormacusine B, had been previously prepared by DDQ-mediated oxidative cyclization.[24] However, the Corey−Kim reagent[26,27] reacted readily with **12** in the presence of Et$_3$N to give 16-epi-vellosimine (**1**) in high yield (Scheme 2). The spectroscopic properties of synthetic **1** were similar to the pattern reported for (+)-vellosimine;[28] however, examination of the proton NMR spectrum indicated that the aldehydic peak had shifted from δ 9.65 to 9.16. This is typical for the hindered axial aldehyde. Herein, (+)-16-epi-vellosimine (**1**) has been prepared in a short synthetic sequence from D-(+)-tryptophan methyl ester (**13**) in nine reaction vessels in 23% overall yield. This material was epimerized into (+)-16-vellosimine on simple stirring with base or exposure to silica gel during chromatography.

As illustrated in Scheme 3, the synthesis of **3** began from D-(+)-tryptophan methyl ester (**13**), which was converted into (+)-vellosimine (**16**) in enantiospecific fashion in seven reaction vessels in 27% overall yield.[25,29] Aldehyde **16** was protected as the N$_a$-Boc intermediate in the presence of DMAP to afford **17** in 85% yield. This was necessary to prohibit reaction of formaldehyde with the indole N$_a$−H moiety of **16**. The N$_a$-Boc-protected vellosimine **17** was then converted into the prochiral C-16 quaternary diol **18** via the Tollens-like reaction,[21] and this was followed by deprotection under acidic conditions. Following the process employed earlier in this laboratory,[23] the DDQ-mediated oxidation permitted the selective protection of the axial hydroxymethyl group to give **11**, which permitted further modification of the equatorial hydroxymethyl group to the methyl ester via the two steps detailed below. Various oxidative reagents (i.e., TPAP,[30] Dess−Martin periodinate,[31] and benzeneselenic anhydride[32]) were employed to furnish the equatorial aldehyde **19**; however, most of these efforts resulted in the

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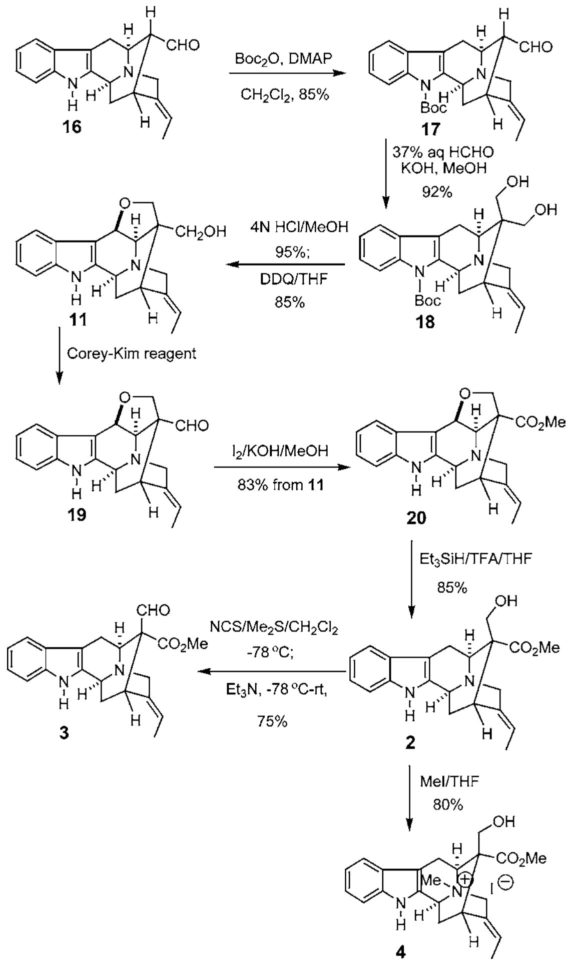
Scheme 3. Synthesis of Polyneuridine, Macusine A, and Polyneuridine Aldehyde



decomposition of the starting material or cleavage of the C(6)−C(17) oxygen bridge. Again, the Corey−Kim oxidative conditions could be employed successfully in this system; the monol **11** was converted into equatorial aldehyde **19** in 90% yield. The aldehyde function of intermediate **19** was then oxidized to the methyl ester **20** with I_2 and KOH in MeOH, following the work of Yamamoto et al.[21,23,33] After oxidative formation of the α-methyl ester **20** at C-16, the ether bond was reductively cleaved with TFA/Et_3SiH[23] in 85% yield to provide polyneuridine (**2**) [FTIR 3267 cm^{-1} (OH), 1736 cm^{-1} (CO_2Me)]. The spectral data of polyneuridine are in excellent agreement with the natural product.[7,9] Furthermore, the important biogenetic intermediate, polyneuridine aldehyde (**3**) [FTIR 1731 cm^{-1} (CO_2Me), 1707 cm^{-1} (CHO)] was then obtained by a second Corey−Kim oxidation. Consequently, **3** could be prepared from D-(+)-tryptophan methyl ester (**13**) in 13 reaction vessels in 14.1% overall yield. Reduction of **3** with sodium borohydride returned polyneuridine **2**, which confirmed the presence of the aldehyde moiety in **3**. Finally, quaternization of the N_b nitrogen function in polyneuridine (**2**) with MeI provided the N_b-methyl iodide salt, macusine A (**4**) in 80% yield.

It is important to note that, in the synthesis of 16-epi-vellosimine (**1**), the Corey−Kim oxidation provided an extremely mild method to complete the key oxidation of the C-16 hydroxymethyl group to provide indole alkaloids **1** and **3** in the N_a−H series in the absence of epimerization to the more stable C-16 equatorial aldehyde possible in **1**. Treatment of alcohols **12** and **2** with 5 equiv of the Corey−Kim reagent in CH_2Cl_2 at −78 °C for 2 h, followed by the standard workup,[27] resulted in the respective aldehydes in high yield.

In summary, the first stereospecific total synthesis of 16-epi-vellosimine (**1**), (+)-polyneuridine (**2**), (+)-polyneuridine aldehyde (**3**), and macusine A (**4**) has been accomplished from commercially available D-(+)-tryptophan methyl ester (**13**). The chemospecific and regiospecific oxidations with the Corey−Kim reagent were key steps in these syntheses. This approach provides the first stereospecific synthetic solutions to the axial aldehydes in 16-epi-vellosimine (**1**) and polyneuridine aldehyde (**3**) and should also provide access to ajmaline/quebrachidine skeletons.

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