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Stereocontrolled Total Synthesis of (−)-Vincamajinine and (−)-11-Methoxy-17-epivincamajine

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Indole alkaloid natural products are an important source of biologically active compounds that includes the potential for development of novel antiprotozoal drugs.[1] (+)-Alstomacroline (**1**), a bisindole alkaloid, was isolated from the root bark of *A. macrophylla* collected in Thailand and exhibited activity against malaria parasites.[2] A partial synthesis of **1** was reported by Le Quesne et al.[3] via a biomimetic coupling process. Bisindole alkaloid (−)-11-methoxy-10-(11′-vincorinyl)-17-epivincamajine (**2**) was isolated in 1992 from the leaves of *Tonduzia pettieri* (*Alstonia pettieri*),[4a] accompanied by the monomeric base (−)-11-methoxy-17-epivincamajine (**6**).[4] The latter two alkaloids have not been evaluated for antimalarial activity to date. (+)-Quebrachidine (**3**) and (−)-vincamajine (**4**) were initially isolated in 1963 and have since been obtained from many species of *Alstonia*.[5] (−)-Vincamajinine (**5**, 17-epivincamajine) has only been isolated from the aerial parts of *Vinca major*.[6] Indole alkaloids **3**−**6** belong to the ajmaline family of bases, but specifically from the series that contain a carbomethoxy group at C(16). The constitution and relative configuration of (+)-**3**, (−)-**4**, and (−)-**6** were established on the basis of NMR studies and chemical correlation,[4,5] whereas (−)-**5** was confirmed by chemical conversion and spectral data.[6] They have in common a unique rigid, caged hexacyclic carbon skeleton that contains seven stereogenic centers (carbons 2, 3, 5, 7, and 15−17) as well as the olefinic bond at C(19)−C(20) in the *E* configuration. However, the configuration of the C(17) hydroxyl group in (+)-**3** and (−)-**4** [17(*S*)] is different from that in (−)-**5** and (−)-**6** [17(*R*)]. An approach to the synthesis of (−)-**3** has been reported by Martin;[7] however, no total synthesis of **1**−**6** has yet been reported. Herein is described the first stereocontrolled total synthesis of both (−)-**5** and the 11-methoxy analogue (−)-**6**.

The major challenges to the synthesis of **5** and **6** include generation of the C(16) quaternary carbon center, complete control of the stereochemistry at C(2) and C(17), as well as development of an efficient route for the preparation of the rigid hexacyclic system that contains a C(16) carbomethoxy group. A biogenetic Scheme for the formation of the ajmaline-type indole alkaloids has been reviewed by Lounasmaa et al.,[8] which includes the proposals of Bartlett, Taylor,[9] and van Tamelen,[10] amenable perhaps to formation of the C(7)−C(17) bond. As a means to construct the strained hexacyclic ring framework, this biomimetic intramolecular cyclization was attractive as a potential route as long as a stereospecific means to introduce the C(17) hydroxyl group could be developed. It was felt that experimental conditions could be found to take advantage of the vicinal location of the nucleophilic *β*-position of the indole nucleus and the electrophilic aldehyde following the work of Bartlett, Taylor, and van Tamelen.[9,10]

The stereocontrolled synthesis of (−)-**5** began with the readily available pentacyclic aldehyde **7** obtained from D-(+)-tryptophan methyl ester in stereospecific fashion in seven reaction vessels in 39% overall yield. This had been previously achieved via a combination of the asymmetric Pictet−Spengler reaction, Dieckmann cyclization, and a stereocontrolled intramolecular enolate-driven palladium-mediated cross-coupling reaction.[11] After numerous attempts, it was found the aldehydic group at C(16) in synthetic N_a-methylvellosimine **7** could be elaborated to diol **8** in 85% yield via the Tollens reaction by using 37% aqueous formaldehyde and KOH in methanol, as shown in Scheme 1. This important transformation established the prochiral hydroxymethyl groups at C(16) without the need for chiral reagents or asymmetric induction. Selective conditions for the oxidation of the 16-hydroxymethyl group contained in the axial position in contrast to the equatorial hydroxymethyl group was achieved with TPAP to provide the desired aldehyde **9** with >10:1 diastereoselectivity in 78% yield. When aldehyde **9** was dissolved in a mixture of TFA/Ac_2O, the conjugate acid of the aldehyde was sufficiently electrophilic to cyclize to the indoleninium salt **10**, which was trapped as the diacetate **11** by Ac_2O.[12] This cyclization stereospecifically provided the 17(*R*) stereochemistry in **11** in 84% yield. The use of trifluoroacetic acid was key to the stereoselectivity in this process. This provided the kinetic product, while cyclization of **9** with Ac_2O/HCl(g) gave the thermodynamic 17(*S*) isomer, although the ds was not 100%. Acid-assisted reduction of the carbinolamine function in **11** with Et_3SiH[13] furnished the C2(α)-H stereochemistry in indolinine **12** from the bottom face as the sole product in 90% yield. The required rigid hexacyclic ring system that contained the 17(*R*) hydroxyl function and the C2(α)-H was efficiently built in three steps. Hydrolysis of diacetate **12** under basic conditions gave diol **13** in 87% yield. Diol **13** was labile to some conditions of oxidation that ultimately resulted in cleavage of the C(7)−C(17) bond. However, careful treatment of diol **13** with Dess−Martin periodinane[14] furnished the ketone **14** with the C(16) primary alcohol moiety intact. After isolation of **14**, further oxidation of ketone **14** with Dess−Martin periodinane provided the desired aldehydoketone **15** (78% for two steps).[15] To this end, the aldehydic group of **17** was converted into the methyl ester **16** upon treatment with KOH/I_2 in 92% yield by the procedure of Yamada and Yamamoto et al.[16] The stereochemical issue of the C(17) hydroxyl group that

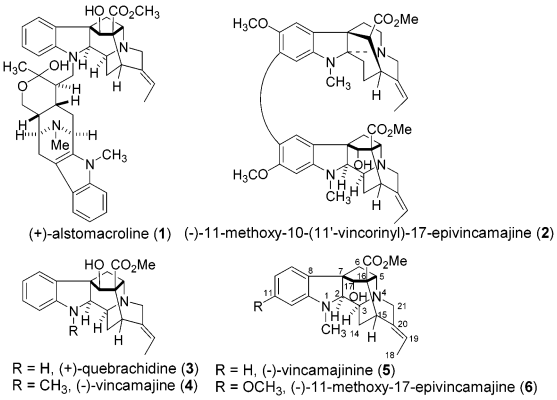

Figure 1. Representative structures of vincamajine-related alkaloids.

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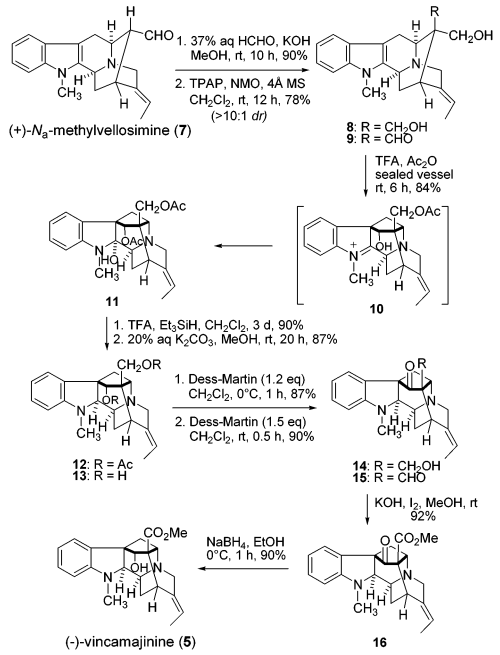
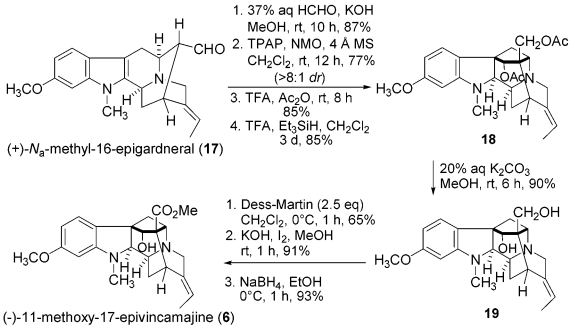
Scheme 1. Stereocontrolled Total Synthesis of (−)-Vincamajinine (**5**)



now remained was resolved by reduction of ketone **16** with $NaBH_4$. Attack occurred from the least hindered side exclusively to provide (−)-vincamajinine (**5**) in 90% yield. Analysis of the proton NMR spectrum indicated that the characteristic singlet for the 17-H appeared at 3.98 ppm in (−)-**5**, in contrast to the 17(*S*) stereochemistry (δ 4.21) in (−)-vincamajine (**4**).[5] The structure of (−)-**5** was fully characterized by ^{1}H and ^{13}C NMR, NOESY, NOE, MS, and IR. This completed the first stereocontrolled total synthesis of (−)-**5** in 16 reaction vessels from D-(+)-tryptophan methyl ester in an overall yield of 11.8%.

Encouraged by the success in the total synthesis of (−)-**5**, the total synthesis of (−)-**6** was begun from (+)-**17**. This base (in brief) had been prepared from optically pure N_a-methyl-6-methoxy-(D)-tryptophan, available on 300 g scale from the Larock heteroannulation of a Schöllkopf chiral auxiliary developed in this laboratory (from L-valine), in six reaction vessels in 35% overall yield.[17] The heteroannulation, asymmetric Pictet−Spengler reaction, and enolate-driven palladium cross-coupling strategy was executed for **17** under analogous conditions for preparation of (+)-**7**. The Tollens reaction, TPAP oxidation (dr > 8:1), acid-assisted cyclization (TFA/Ac_2O), and stereospecific reduction with Et_3SiH were executed in high yield and provided the crucial diacetate intermediate **18** in 48% yield (overall for the four steps). Hydrolysis of diacetate **18** provided diol **19**, which contained all the required stereocenters. After oxidation of both the primary and secondary alcohol functions of **19** (see Scheme 2), the aldehyde thus formed was converted into the methyl ester identical to that developed in Scheme 1. The C(17) ketone that remained was stereospecifically reduced to furnish (−)-11-methoxy-17-epivincamajine (**6**). The spectroscopic properties and optical rotation ($[\alpha]_D$ −10.5; lit.[4b] −12.0) of synthetic (−)-**6** were in excellent agreement with those of natural (−)-11-methoxy-17-epivincamajine (**6**). This synthesis required 14 reaction vessels from N_a-methyl-6-methoxy-D-tryptophan ethyl ester and was completed in an overall yield of 8.4%.

Scheme 2. Stereocontrolled Total Synthesis of (−)-11-Methoxy-17-epivincamajine (**6**)



In summary, a stereocontrolled total synthesis of (−)-vincamajinine and (−)-11-methoxy-17-epivincamajine were accomplished through combination of the highly practical Tollens reaction, a stereospecific reduction, and an acid-assisted intramolecular cyclization that provided the required hexacyclic ring system in stereocontrolled fashion. This constitutes the first total synthesis of either alkaloid and provides the first regiospecific route to 11-alkoxy-substituted ajmaline-related alkaloids. Efforts toward the total synthesis of (+)-**1**, (−)-**2**, (+)-**3**, and (−)-**4** are currently underway in our laboratory and will be reported in due course.

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