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General Approach for the Synthesis of Sarpagine/Ajmaline Indole Alkaloids. Stereospecific Total Synthesis of the Sarpagine Alkaloid (+)-Vellosimine

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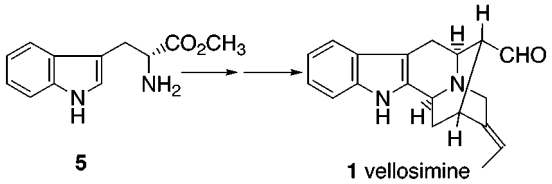
ABSTRACT



(+)-Vellosimine has been synthesized enantiospecifically in 27% overall yield from commercially available D-(+)-tryptophan methyl ester via the asymmetric Pictet–Spengler reaction and a stereocontrolled intramolecular palladium-coupling reaction as key steps.

The sarpagine alkaloid (+)-vellosimine **1** was first isolated from the tree *Geissospermum vellosii* in 1958 by Rapoport et al.[1,2] Amorphous extracts of this bark, known as *pao pereira*, have long enjoyed a reputation as a febrifuge[3] in Brazilian folk medicine and have also been reported to have curare-like activity.[4] During the following years, (+)-vellosimine has also been isolated from various species of *Rauwolfia* which are broadly distributed throughout Asia and Africa.[5−12] These plants are widely employed in traditional Chinese medicine for the treatment of neuralgia, migrain,[12] and hypertension.[8,10,13]

The structure of (+)-vellosimine **1** was elucidated on the basis of NMR spectroscopy as well as a comparison with the data from other indole alkaloids[2] and confirmed by analysis of its 2D NMR spectrum.[11] Common structural features of the sarpagine indole alkaloids include the asymmetric centers at C-3(*S*), C-5(*R*), C-15(*R*), and C-16(*R*) as well as the ethylidene double bond at C-19 and C-20 with the *E* configuration. No enantiospecific total synthesis of members of this class has appeared, to date. Sakai[14] earlier reported the partial synthesis (from ajmaline) of (−)-koumidine, which has a similar skeleton to that of (+)-vellosimine; however, the double bond is present in the *Z*-configuration and the chirality at C-16 is *S* rather than *R*. Establishment of the C(19)−C(20) double bond by Sakai by an elimination process yielded the *Z*-configuration

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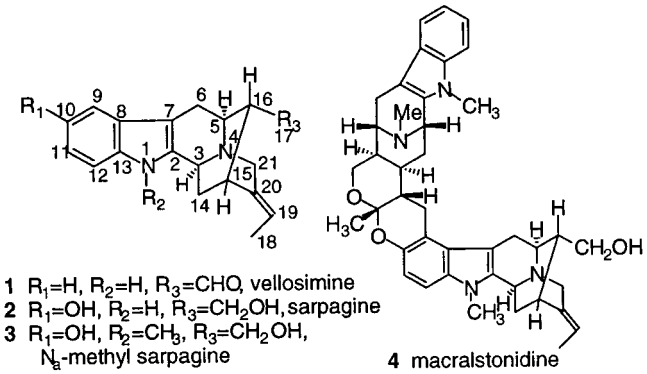
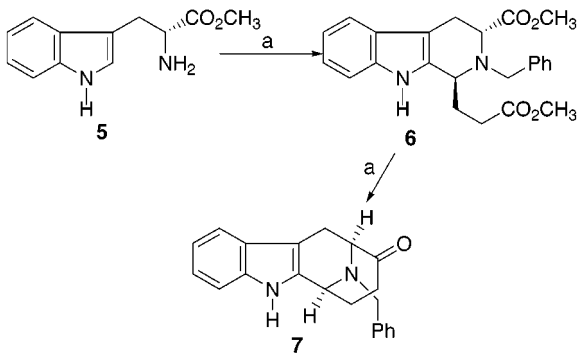
required for koumidine in a 5:1 ratio. Magnus[15] reported the total synthesis of the enantiomer of (−)-koumidine (from D-tryptophan); however, establishment of the double bond (*Z*:*E* = 1:5.7) was still not stereospecific. Several other groups have encountered a similar problem during the enantiospecific synthesis of the C(19)−C(20) related alkaloid geissoschizine; the ratio of *E* to *Z* was very good but not reported as stereospecific.[16,17] Recently, Martin reported the total synthesis of geissoschizine with stereoselective establishment of the double bond by an elimination process.[18] Furthermore Rawal and Bosch reported the total synthesis of *Strychnos* alkaloids with stereocontrolled establishment of the double bond by a Heck coupling reaction.[19,20]



We report an efficient, enantiospecific total synthesis of (+)-vellosimine **1** with the stereospecific establishment of the double bond by a key palladium (enolate-mediated) carbon−carbon bond forming process.[21] This approach should provide a route to other sarpagine indole alkaloids including N_a-methylsarpagine **3** (10-hydroxy-N_a-methyl-vellosimine) required for the total synthesis of the bisindole alkaloid macralstonidine **4** synthesized in biomimetic fashion by LeQuesne et al.[22]

The chirality at C-3 and C-5 was established by the asymmetric Pictet−Spengler reaction and Dieckmann reaction in a two-pot process as reported previously[23] and

Scheme 1



[a] See reference 23 for details.

illustrated briefly in Scheme 1. Benzylation of the N_b-amino moiety of D-tryptophan methyl ester **5** provided N_a-H, N_b-benzyl D-tryptophan methyl ester, which was easily converted (without isolation and purification) into the *trans* diastereomer **6** with 100% diastereoselectivity under the improved conditions of the Pictet−Spengler reaction (83% yield for the complete process on 400 g scale). The *trans* diester **6** was subjected to a Dieckmann cyclization on scales above the 100 g level to provide the *β*-ketoester which (without isolation) was hydrolyzed to furnish the (−)-N_a-H, N_b-benzyl tetracyclic ketone **7** in >98% ee (80% yield for this process).[23]

Incorporation of the *E*-ethylidene function into the sarpagine skeleton required the *Z*-1-bromo-2-iodo-2-butene **9** employed earlier by Bosch,[20] Rawal,[19,24] and Kuehne.[25] The ketone **7** was subjected to the conditions of catalytic hydrogenation to provide the N_a-H, N_b-H ketone **8** in 80% yield which underwent alkylation with *Z*-1-bromo-2-iodo-2-butene **9** to provide N_b-*Z*-2′-iodo-2′-butenyl ketone **10** in 87% yield. Ketone **10** was then successfully converted into α,*β*-unsaturated aldehyde **11** in high yield, according to the procedure earlier reported from our laboratory in a different system.[23]

Several attempts to convert **11** into (+)-**1** by Michael reactions were unsuccessful; however, treatment of **11** with Bu_3SnH/AIBN/Δ/benzene did provide (+)-vellosimine **1**, accompanied by the undesired *Z*-olefinic isomer **12** (**1**:**12** = 1:3), as illustrated in Scheme 2. The radical-mediated coupling had taken place with loss of stereochemistry as expected, but did provide (+)-vellosimine for characterization.

Attempts to couple the α,*β*-unsaturated aldehyde **11** with a Pd^0 catalyst under basic conditions furnished the interesting insertion product **13** (Scheme 3) presumably via the enolate **11***. A similar insertion reaction has been observed in other systems by Miura et al.[26] However, this result led to a solution to the problem of the stereochemistry of the C(19)−C(20) *E* ethylidene function.

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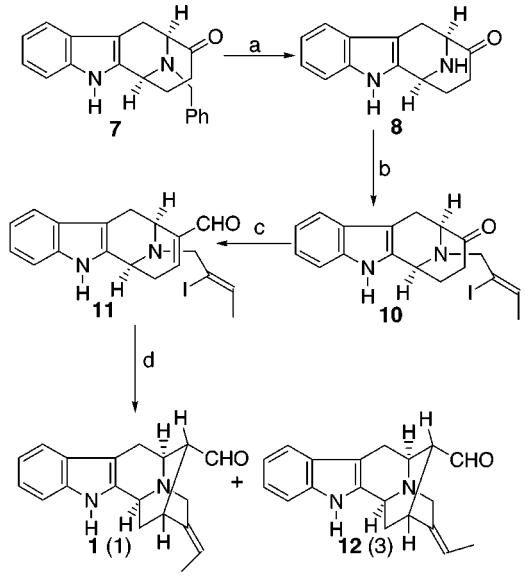
Scheme 2[a]

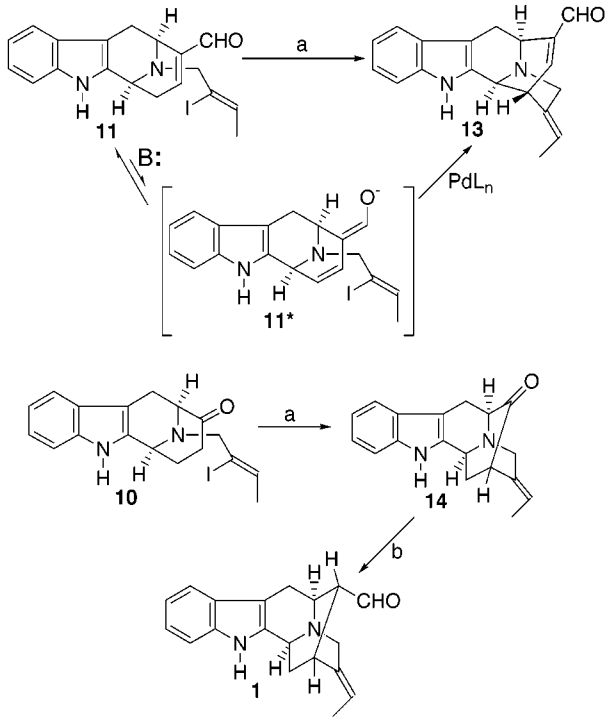


[a] (a) Pd/C, H_2, 5% HCl−ethanol, rt, 12 h, 80%. (b) *Z*-1-Bromo-2-iodo-2-butene **9**, THF, K_2CO_3, rt, 24 h, 87%. (c) $PhSOCH_2Cl$/LDA/THF, −78 °C, KOH(aq), 12 h, rt; $LiClO_4$/dioxane, reflux, 24 h, 87%. (d) Bu_3SnH, AIBN, benzene, 80 °C, syringe pump, 40%.

When the ketone **10** was subjected to the same conditions as **11**, (Pd^0, base)[19−21,24,26] the intramolecular palladium (enolate-mediated) coupling reaction took place stereospecifically in 80% yield. Ketone **14** was then converted into vellosimine **1** via a Wittig reaction, followed by hydrolysis. The latter process was possible since it was known that the sarpagine stereochemistry at C(16) was favored thermodynamically from other work in our laboratory.[23c,d]

In summary, the first stereospecific total synthesis of the N_a-H substituted indole alkaloid (+)-vellosimine **1** has been accomplished from commercially available D-(+)-tryptophan methyl ester **5** in seven reaction vessels in 27% overall yield via the asymmetric Pictet−Spengler reaction and a stereocontrolled intramolecular palladium (enolate-mediated) coupling reaction.

Scheme 3[a]



[a] (a) $Pd(OAc)_2$, PPh_3, Bu_4NBr, K_2CO_3, DMF−H_2O (9:1), 70 °C, 5 h, 71% (**13**); 80% (**14**). (b) $H_3COCH_2PPh_3$, KOt-Bu, PhH, rt, 24 h; HCl (2 N, aq), △, 6 h, 73%.

This approach provides the first stereospecific solution to the problem of the stereochemistry of the C(19)−C(20) *E*-ethylidene function in the sarpagine alkaloids. This route should also provide easy access to other sarpagine alkaloids including that of N_a-methyl sarpagine **3** required for the synthesis of the bisindole macralstonidine **4**.

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