Natural Product Synthesis

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Enantioselective, Protecting-Group-Free Total Synthesis of Sarpagine Alkaloids—A Generalized Approach**

*Sebastian Krüger and Tanja Gaich**

Dedicated to Professor Johann Mulzer on the occasion of his 70th birthday

Abstract: *A generalized synthetic access to sarpagine alkaloids through a joint synthetic sequence has been accomplished. Its applicability is showcased by the enantioselective total syntheses of vellosimine (**1**), N-methylvellosimine (**3**), and 10-methoxyvellosimine (**8**). The synthetic sequence is concise (eight steps) from known compound **13**, and requires no protecting groups. The indole heterocycle was introduced in the last step. This strategy allows access to sarpagine alkaloids through a shared synthetic route leading to precursor **10**, which we term "privileged intermediate". Starting from this intermediate, all sarpagine alkaloids can be synthesized using phenylhydrazines with different substitution patterns (**15**–**17**). Our approach brings about the advantage, that synthesis optimization only needs to be performed once for many natural products. The key features of the synthesis are a [5+2]-cycloaddition and a ring enlargement.*

Sarpagine alkaloids belong to the group of monoterpenoid indole alkaloids. Their family consists of more than 90 congeners, which were mainly isolated from the plant family *Apocynaceae* (specifically from the genus *Rauvolfia*).[1] Cook et al. accomplished very elegant total syntheses of some sarpagines using Pictet–Spengler type chemistry (early introduction of the indole core).[2] With regard to the biosynthesis of these complex molecular architectures, primary as well as secondary cyclizations are well investigated by Stöckigt et al.[3] Yet, the biological potential of these beautiful architectures, especially when it comes to the investigation of synthetic analogues, is by far underexplored. Substructures of sarpagines were synthesized by Waldmann et al. for library design, and revealed potent tyrosine kinase inhibitors.[4] Unfortunately the scarcity of the natural products themselves, and the lack of synthetic analogues of comparable complexity have so far hampered further biological investigations.

When we launched our synthetic program on sarpagine alkaloids (**1**–**9**), we not only aimed at solving the problem of material supply for a single family congener, but at accomplishing a joint synthetic sequence that enables access to a large number of sarpagines through a shared late-stage synthetic intermediate, which we term "privileged intermediate". At the outset we had to define the molecular structure of this intermediate. Therefore, the individual congeners were analyzed for common structure patterns as well as differences in stereochemistry and oxidation states.

Important structural variations such as: 1) additional rings [gardnutine (**6**), Figure 1], 2) variability of the absolute configuration at C16 [biosynthetic numbering; highlighted in green in Figure 1], and 3) hydroxylation pattern of the indole core (highlighted in red in Figure 1) were identified. Furthermore, we assessed an octahydro-1*H*-2,6-methanoquinolizine system as common structural motif of all sarpagines (highlighted in blue in Figure 1 for vellosimine (**1**)).

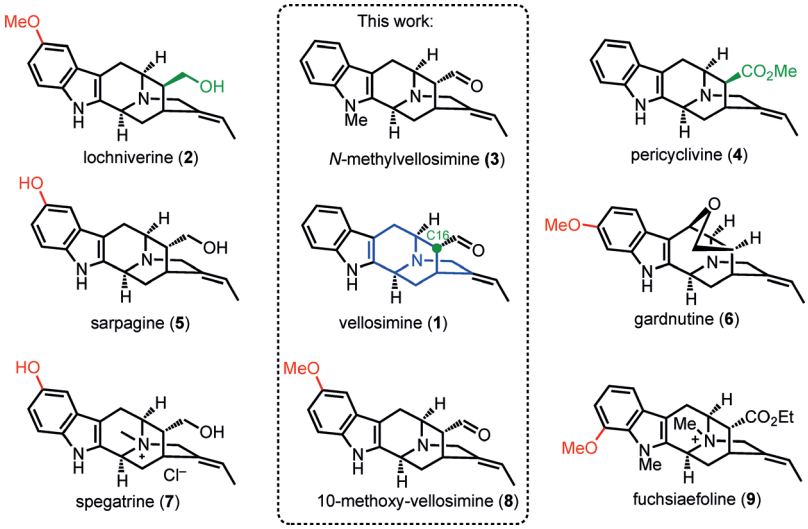

Figure 1. Selected family members of sarpagine alkaloids.

With this analysis we directly deduced the retrosynthesis leading us to ketone **10**, as the "privileged intermediate" (Figure 2 A). From this last synthetic intermediate all sarpagines can be synthesized in one step, introducing the different hydroxylation patterns of the respective natural products by

[*] M. Sc. S. Krüger, Dr. T. Gaich
Institute of Organic Chemistry, Leibniz University of Hannover
Schneiderberg 1b, 30167 Hannover (Germany)
E-mail: tanja.gaich@oci.uni-hannover.de

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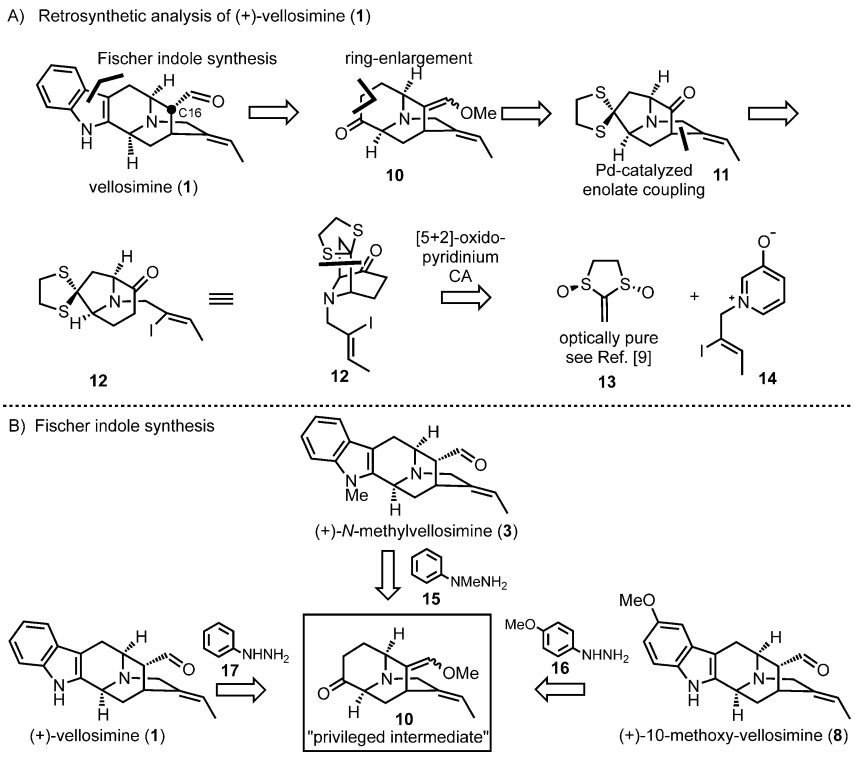


Figure 2. Retrosynthetic analysis for a generalized synthesis of sarpagines **1**, **3**, and **8**.

using the corresponding phenylhydrazines (**15**–**17**) in a Fischer indole synthesis (Figure 2B).[5] The absolute configuration of C16 (Figure 2A) can be adjusted to give the α-isomer, which is thermodynamically favored.[6] Ketone **10** itself was obtained through ring enlargement from compound **11**.[7] The tricyclic system of **11** was formed through a palladium-catalyzed enolate coupling[8] starting from bicyclic compound **12**. This compound **12** represents the product of a [5+2]-cycloaddition between oxidopyridinium ion **14** and Aggarwal's chiral ketene equivalent **13** (prepared in four steps).[9] Similar pyridinium ions are known to undergo intermolecular [5+2] cycloadditions with regioselectivities around 2:1, typically yielding the desired regioisomer **12** as a major product.[10] When we performed the cycloaddition of **13** and **14**, we obtained our desired cycloadduct **19** in a 2:1 ratio (77% combined yield) in favor of the desired regioisomer and 93% *ee* (Scheme 1). Luckily the stability of the vinyliodide moiety in **14** allowed the direct assembly of compound **19** without the need of protecting groups.

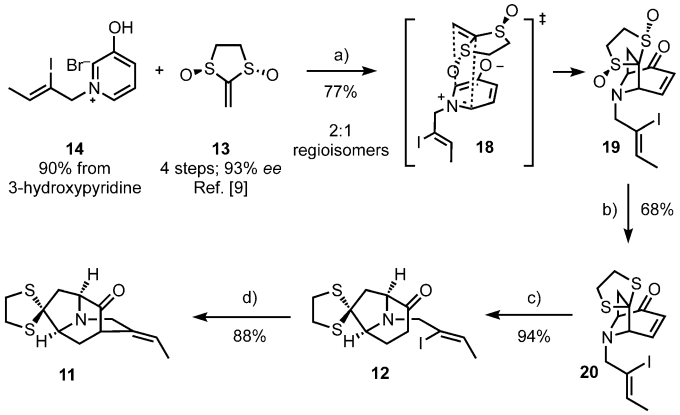
Reductive removal of the bis(sulfoxide) after the [5+2] cycloaddition was affected by treatment of **19** with trifluoroacetic anhydride and sodium iodide affording dithiolane **20** in 68% yield.[10] The next task was the formation of tricycle **11** through an intramolecular palladium-catalyzed enolate coupling. This was achieved in a sequential manner by treating **20** with L-selectride to form ketone **12**, which was reacted with palladium (tetrakis)triphenylphosphine to yield tricyclic ketone **11** in 88% yield (Scheme 1).[7] This two-step process was also performed in one pot, but then the yields dropped significantly to about 50%.

Wittig reaction of **11** and deprotection of the dithiolane moiety with Meerwein's salt afforded ketone **21** (Scheme 2).[11] This set the stage for the ring enlargement reaction to give ketone **10** in 80% yield. The ring enlargement proceeded smoothly and regioselectively, resulting in the exclusive insertion of the methylene group on the sterically less hindered side.[12]

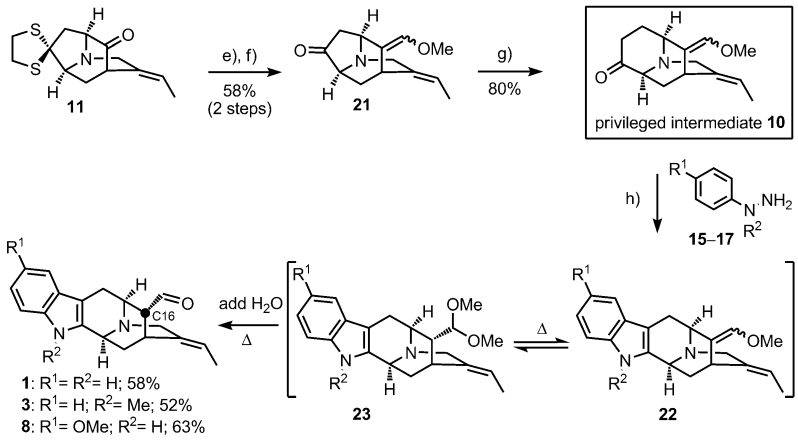
With ketone **10** in hands we carried out the Fischer indole synthesis with phenylhydrazines **15**–**17**.[13] In the course of this reaction, enol ether **22** was converted to dimethylacetal **23**, which we observed by ^{1}H NMR spectroscopy on the crude sample. **23** was hydrolyzed in situ affording (+)-vellosimine (**1**) (+)-*N*-methylvellosimine (**3**), and (+)-10-methoxyvellosimine (**8**) in 52–63% yield. As anticipated, the desired absolute configuration at C-16 was exclusively obtained under these reaction conditions in all three natural products **1**, **3**, and **8**.[14]

An important feature of this synthesis is the strategy to pursue a "privileged intermediate", which paves the synthetic road to most of the sarpagine alkaloids in a single last transformation—in our case the Fischer indole synthesis. This avoids synthetic inconveniences normally observed when substituents have to be varied at the starting point of a synthesis, which at worst can cause (partial) redesign of the route.

In conclusion we have accomplished a generalized, enantioselective access to the sarpagine alkaloid family in a very concise manner. (+)-Vellosimine (**1**), (+)-*N*-methylvellosimine (**3**), and (+)-10-methoxyvellosimine (**8**) were synthesized in eight steps starting from known compounds



Scheme 1. The [5+2] cycloaddition reaction for the construction of the core structure. Reagents and conditions: a) N*i*Pr$_2$Et, CH_2Cl_2, 12 h, 77%; b) TFAA, NaI, MeCN, 0°C, 68%; c) L-selectride, THF, −78°C, 94%; d) KO*t*Bu, PhOH, [Pd(PPh$_3$)$_4$], THF, reflux, 88%.



Scheme 2. Synthesis of intermediate **10**, and total syntheses of (+)-vellosimine (**1**), (+)-*N*-methylvellosimine (**3**), and (+)-10-methoxyvellosimine (**8**).Reagents and conditions: e) $MeOCH{=}PPh_3$; f) TFA, CH_2Cl_2, Me_3OBF_4, 58% (2 steps); g) $TMSCH_2N_2$, *n*BuLi, THF, then MeOH; then silica, 80%; h) AcCl, MeOH, Δ, then water.

14 and **13** (12 steps from commercial materials) in 10–13% overall yields. The joint synthetic sequence requires no protecting groups, and can be carried out on multigram scale. Therefore the lack of synthetic analogues and the limited amount of material, currently hampering detailed biological testing, is no longer an issue. Our synthetic route will enable the production of almost every family member on demand. The syntheses of further sarpagine congeners are currently performed in our laboratories.

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[14] NOESY analysis for the configuration of C16 is provided in the Supporting Information.

