Total Synthesis Hot Paper

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Asymmetric Total Synthesis of Sarpagine and Koumine Alkaloids

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Abstract: *We report here a concise, collective, and asymmetric total synthesis of sarpagine alkaloids and biogenetically related koumine alkaloids, which structurally feature a rigid cage scaffold, with* L*-tryptophan as the starting material. Two key bridged skeleton-forming reactions, namely tandem sequential oxidative cyclopropanol ring-opening cyclization and ketone α-allenylation, ensure concurrent assembly of the caged sarpagine scaffold and installation of requisite derivative handles. With a common caged intermediate as the branch point, by taking advantage of ketone and allene groups therein, total synthesis of five sarpagine alkaloids (affinisine, normacusine B, trinervine, N_a-methyl-16-epipericyclivine, and vellosimine) with various substituents and three koumine alkaloids (koumine, koumimine, and N-demethylkoumine) with more complex cage scaffolds has been accomplished.*

Introduction

Sarpagine alkaloids belong to the monoterpene indole alkaloid family, and more than 100 members have been isolated, mainly from the Apocynaceae (e.g. *Alstonia* and *Rauvolfia* genera) and Gelsemiaceae (e.g. *Gelsemium* genus) plant families (some representative members are shown in Figure 1 A).[1] Structurally, sarpagine alkaloids feature a diversely substituted, cage-shaped scaffold, which can be disassembled into two bridged substructures, namely indole-fused azabicyclo[3.3.1]nonane and azabicyclo[2.2.2]octane (Figure 1 B). Ajmaline (trade name Gilurytmal), which is a prominent congener of sarpagine alkaloids, has been used as a diagnostic drug to induce arrhythmic contractions in patients suspected of having Brugada syndrome (Figure 1 C).[2] Koumine alkaloids, which are biogenetically derived from sarpagine alkaloids,[3] have more complex cage scaffolds and show a broad spectrum of biological properties, such as antitumor, antiinflammatory, analgesic, and immunomodulatory effects (Figure 1 C).[4] However, the potential biological activities of sarpagine alkaloids have not been widely or thoroughly evaluated, probably because of their natural paucity.[1]

The intriguingly diverse, structurally complex architectures and the biological profiles of above-mentioned alkaloids inspired our interest. With the objective of developing a new and efficient strategy that enable collective total synthesis of both sarpagine[5,6] and koumine[6h,7] alkaloids, ideally from a common late-stage intermediate, we embarked on a synthetic program toward these two natural product families. Our synthetic strategy (Scheme 1) involved the synthesis of sarpagine alkaloids with various substituents, for example, ester, aldehyde, or alcohol, on C16 together with vinyllidene or oxygenated ethyl substituents on C20. This could be achieved using an advanced cage intermediate **1** with versatile ketone and allene groups at the corresponding positions. Meanwhile, with intermediate **1** as the branchpoint, the scaffold of koumine alkaloids could be built by a π-Lewis acid-catalyzed biomimetic indolyl addition to the allene unit after a C3−N bond breakage.[8] We envisioned that the cage scaffold of **1** could be assembled by two critical bridged skeleton-forming steps: 1) ketone α-allenylation to form the bicyclo[2.2.2]octane moiety, and 2) intramolecular oxidative cyclopropanol cyclization to form the bicyclo[3.3.1]nonane moiety. The bicyclo[2.2.2]octane moiety is most commonly constructed by α-vinylation of a ketone via a palladium-catalyzed coupling process.[5,6] Instead of a vinyl group introduction at C20 via this known method, our proposed strategy installs a more versatile allene group. This would increase the potential for late-stage structural diversifications.[9] To access the azabicyclo[3.3.1]nonane motif, seminal and effective methods such as Dieckmann cyclization,[5] olefin metathesis,[6a,b] indolyl Friedel–Crafts reaction,[6c,d] and [5+2]-cycloaddition/ring enlargement,[6e,f] have been developed. We envisioned that a tandem amine oxidation and cyclopropanol ring-opening cyclization of substrate **5a** would allow rapid assemble of the azabicyclo[3.3.1]nonane skeleton and introduction of a versatile ketone group.[10] Enantiopure **5a** with a dictating chiral carbon center can be directly synthesized via Kulinkovich cyclopropanation of a carboxyl ester,[11] which can be easily derived from the cheap chiral starting material L-tryptophan.[12]

Results and Discussion

Bicyclo[3.3.1]nonane Skeleton Construction

First, We explored the feasibility of constructing the bicyclo[3.3.1]nonane motif via the proposed tandem amine oxidation and cyclopropanol ring-opening cyclization (Ta-

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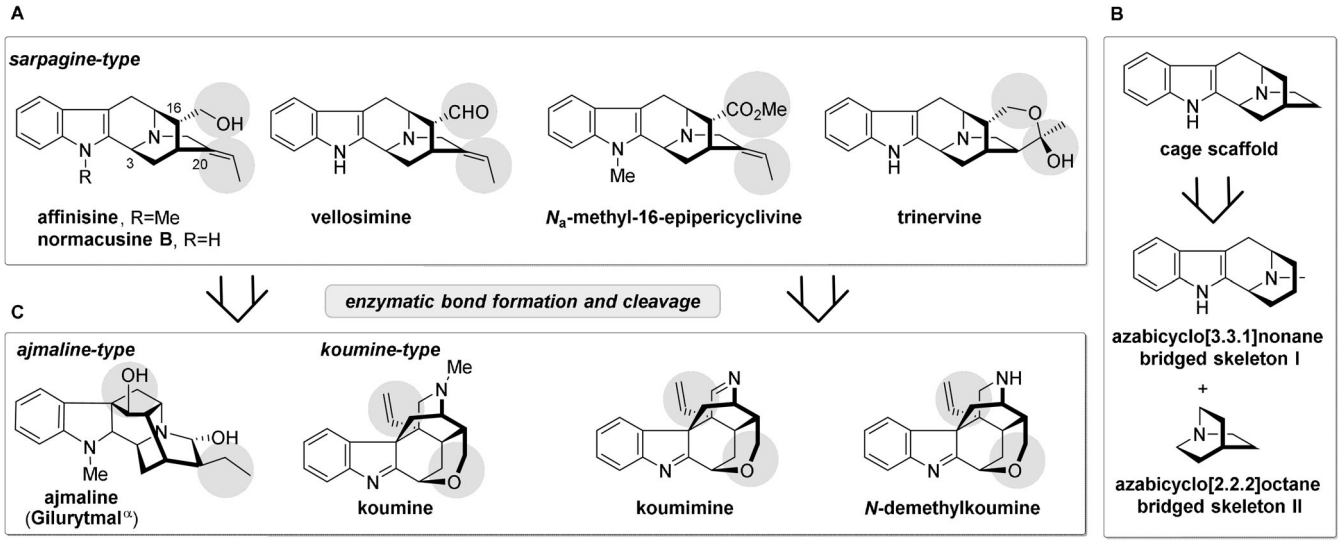
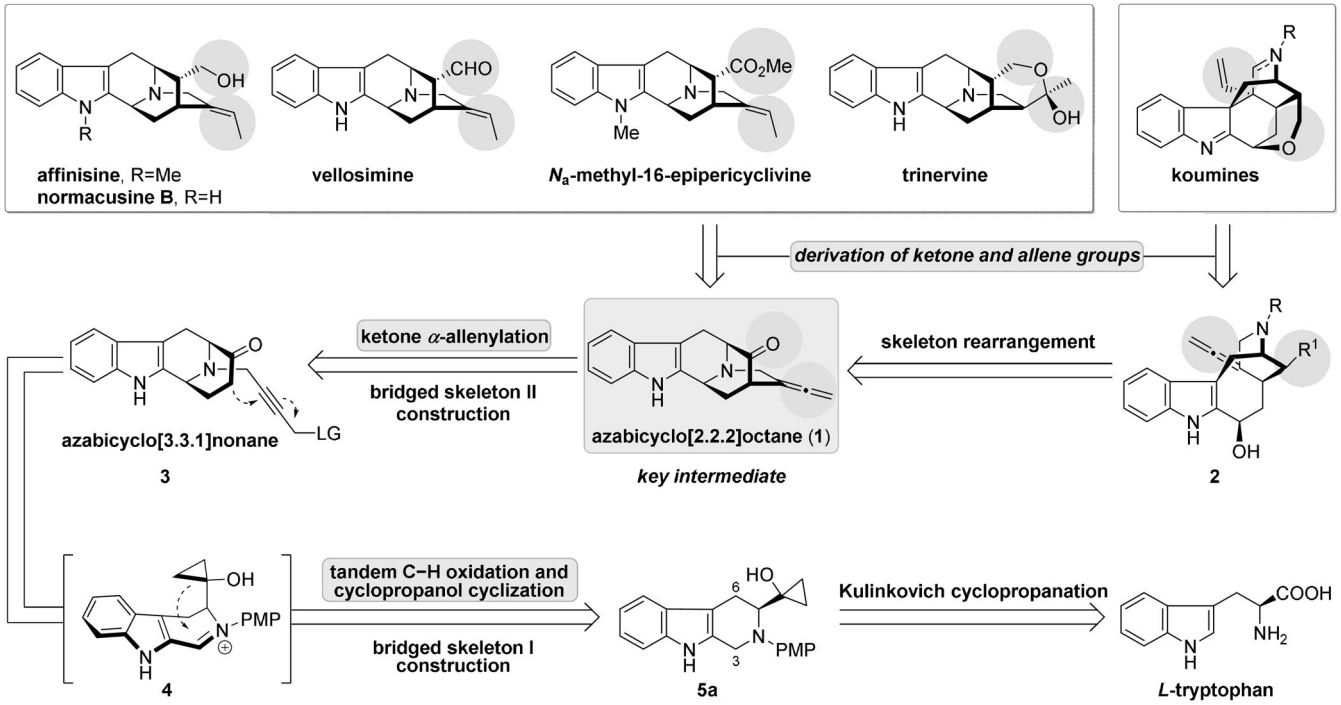


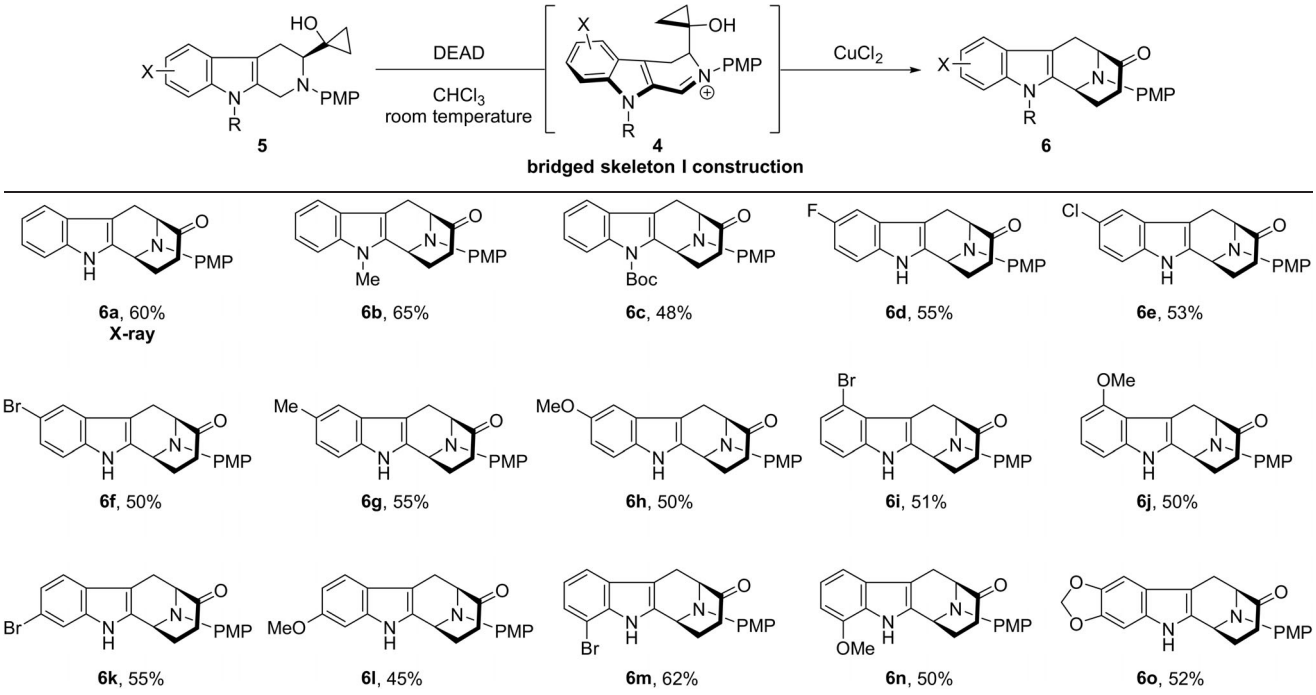
Figure 1. A) Selected sarpagine alkaloids with ester, aldehyde, or alcohol substituents at C16 and vinyllidene or oxygenated ethyl substituents at C20. B) Caged core framework of sarpagine alkaloids. C) Selected ajmaline and koumine alkaloids.



Scheme 1. Retrosynthetic analysis of sarpagine and koumine alkaloids.

ble 1). We recently developed an oxidative cyclopropanol ring-opening cyclization cascade of tetrahydroisoquinoline-type substrates for generation of bridged bicyclo-[3.3.1]nonanes.[13] Although similar in principle, methods that involve tetrahydroisoquinolines are not usually applicable to the homologous tetrahydro-β-carbolines, particularly if that selective oxidation of C3-H is involved (see **5a** in Scheme 1 for carbon numbering).[14] Inherent issues arising from the electron-rich indole motif, such as selectivity for C3-H over C6-H and proneness to aromatization by over-oxidation, need to be addressed.[15] Additionally, ring-opening addition of cyclopropanol to iminium ions or imines is underexplored, although cyclopropanol is widely used as a nucleophilic C3 synthon.[11] Appropriate oxidants and catalysts are key to the success for the tetrahydro-β-carbolines. Chiral cyclopropanol **5a** was prepared in three steps from L-tryptophan (Scheme 2A) and then evaluated under the original conditions for the tetrahydroisoquinolines ($CuCl_2$/air).[13] Although the desired bridged product **6a** was indeed observed in the messy reaction mixture, however, the isolated yield was low (<20%) and inconsistent.[16] After extensive screening of oxidants and other reaction parameters,[16] a one-pot tandem

Table 1: Applicable substrate scope for the tandem sequential amine oxidation and cyclopropanol ring-opening cyclization.

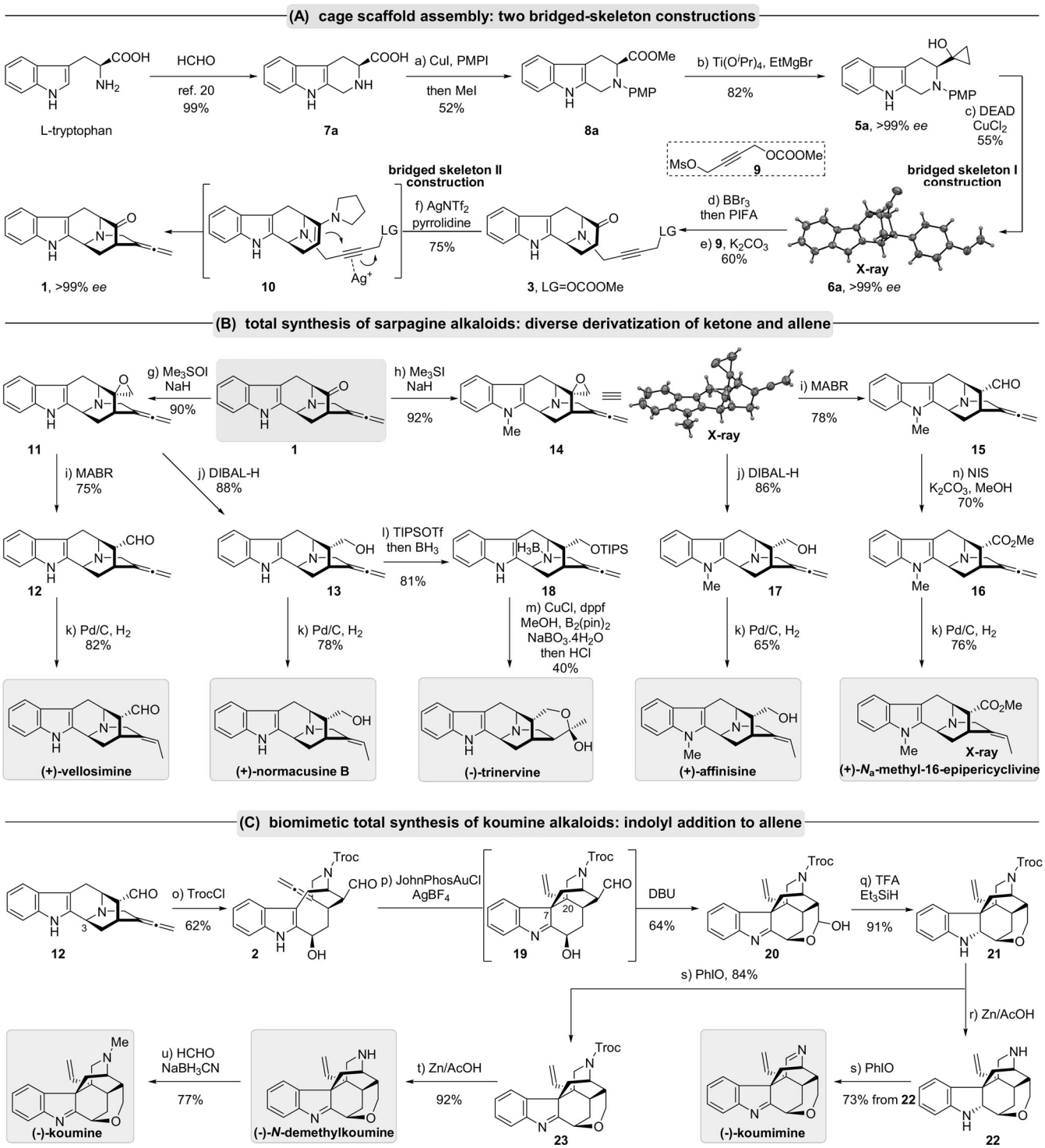


Reaction conditions: **5** (0.1 mmol), DEAD (0.11 mmol), $CHCl_3$ (2 mL), rt, 3 h, followed by addition of $CuCl_2$ (0.02 mmol), 3–8 h.

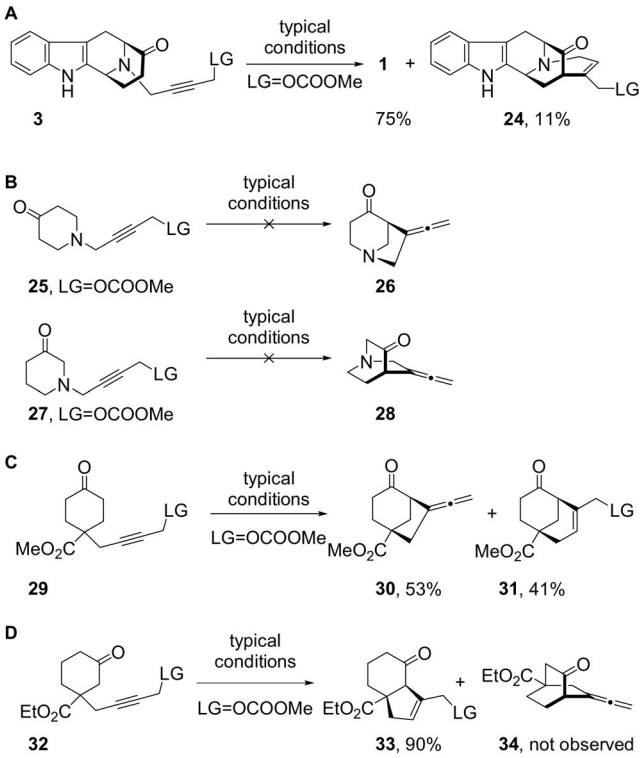
sequential process[17] with diethyl azodicarboxylate (DEAD)[18] as the oxidant and $CuCl_2$ as the catalyst was identified as the best choice; **6a** was obtained in 60% yield.[19] Because sarpagine alkaloids have alkoxyl groups at various indole-ring positions, and to obtain bridged products with more handles for analogue synthesis, cyclopropanols **5** with various substituents on the indole ring were prepared in 10–78% yields over 2–5 steps and tested in this tandem sequential process. Table 1 shows that substrates with electronically different substituents at the 5-position of the indole ring, for example, F, Cl, Br, Me, and MeO, readily participated in this tandem sequential oxidative cyclization (**6d**–**6h**). Notably, cyclopropanols with a bromine atom or methoxy group at the problematic 4-position of the indole ring were viable substrates (**6i** and **6j**). Bromine atoms and methoxy groups at the 6- and 7-positions of the indole ring were well tolerated (**6k**–**6n**). A substrate with a methylenedioxy substituent on the indole ring gave **6o** in a comparable yield.

Bicyclo[2.2.2]octane Skeleton Construction

Another critical step in the assembly of the sarpagine cage scaffold is construction of the bicyclo[2.2.2]octane motif. As shown in Scheme 2A, gram quantities of **6a** were obtained by a sequence of reactions, namely Pictet-Spengler reaction of L)-tryptophan,[20] *N*-arylation and carboxylic acid esterification, Kulinkovich cyclopropanation of the carboxyl ester, and our one-pot tandem sequential amine oxidation/cyclopropanol ring-opening cyclization. Dearylation of **6a** and alkylation of the free amine with **9** afforded **3** in good yield. With **3** in hand, we explored the feasibility of constructing the bicyclo[2.2.2]octane skeleton via ketone α-allenylation. Generally, allenes have more versatile reactivities than alkenes, therefore installation of an allene unit on the core framework enables synthesis of more diverse natural products and their analogues.[9] Although great progress has been made in α-functionalization of ketones, methods for α-allenylation of ketones via a S_N2' propargyl substitution are less known.[21] Our initial efforts to achieve this reaction through a direct S_N2' reaction under basic conditions (e.g. LDA, ^{t}BuOK) were fruitless. We then turned our attention from a single-activation model to a multiple-activation one.[22–24] In Magnus' work, a secondary amine-catalyzed Michael addition of a ketone to an activated alkyne was used to build the bicyclo[2.2.2]octane skeleton.[7a,b] We envisioned that an appropriate amine could activate the ketone via formation of an enamine similarly, and a π-acidic metal could simultaneously activate the alkyne group via complexation with the triple bond, thus facilitating this bridged-skeleton forming reaction. Although gold has been used to promote the cyclization of preformed enol silyl ethers to alkynes, an alkene group, which was formed after protonation of the C–Au bond, was generated rather than an allene group.[9] We envisioned that with a suitable leaving group at the propargyl position and use of an appropriate metal, a formal S_N2' substitution would take place to afford an allene. Extensive screening of various leaving groups, metals, and amines, showed that treatment of **3** with pyrrolidine and $AgNTf_2$ was the best choice, and provided caged intermediate **1** in 75% yield along with the *7-endo-dig* cyclization byproduct **24** in 11% yield (Schemes 2A and 3A).[16] To test the application scope of this method, four representative substrates were prepared and subjected to the typical reaction conditions



Scheme 2. Collective asymmetric total synthesis of sarpagine and koumine alkaloids. Reactions and conditions: a) CuI, PMPI, K_2CO_3, DMSO, 100 °C, 5 h, then MeI, 0 °C to rt, 20 min, 52%; b) $Ti(O^iPr)_4$, EtMgBr, THF, 8 h, 82%; c) DEAD, $CHCl_3$, 3 h, then $CuCl_2$, 6 h, 55%; d) BBr_3, CH_2Cl_2, −78 °C to 0 °C, 24 h, then PIFA, CH_3CN/H_2O, 0 °C, 1 min; e) **9**, K_2CO_3, CH_3CN, reflux, 60% (two steps); f) $AgNTf_2$, pyrrolidine, toluene, 90 °C, 30 min, 75%; g) Me_3SOI, NaH, DMSO, rt, 6 h, 90%; h) Me_3SI, NaH, DMSO/THF, 65 °C to 0 °C, then rt, 6 h, 92%; i) MABR, CH_2Cl_2, −78 °C, 1 h, 75% for **12**, 78% for **15**; j) DIBAL-H, THF, −30 °C, 2 h, 88% for **13**, 86% for **17**; k) Pd/C, H_2, MeOH, −40 °C, 3 h, $E/Z > 20:1$, 82% for vellosimine, 78% for normacusine B, 65% for affinisine, 76% for N_a-methyl-16-epipericyclivine; l) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, then BH_3·THF, THF, −78 °C, 20 min, 81%; m) CuCl, dppf, ^{t}BuONa, B_2pin_2, MeOH, THF, rt, 30 min; $NaBO_3 \cdot 4H_2O$; HCl (2 M), THF, 80 °C, 2 h, 40%; n) NIS, K_2CO_3, MeOH, 4 h, 70%; o) TrocCl, Na_2CO_3, TBAI, $H_2O/CHCl_3$, 8 h, 62%; p) JohnPhosAuCl, $AgBF_4$, CH_2Cl_2, rt, 1 h, then DBU, rt, 3 h, 64%; q) TFA, Et_3SiH, CH_2Cl_2, rt, 8 h, 91%; r) Zn, AcOH, THF/H_2O, 65 °C, 40 min; s) PhIO, CH_2Cl_2, rt, 40 min, 84% for **23**, 73% for koumimine; t) Zn, AcOH, THF/H_2O, 65 °C, 40 min, 92%; u) HCHO, $NaBH_3CN$, $MeOH/CH_2Cl_2$, rt, 40 min, 77%.



Scheme 3. Results of α-allenylation of various ketones. Typical conditions: $AgNTf_2$, pyrrolidine, toluene, 90 °C.

(Scheme 3).[16] Reaction of **25** or **27** only resulted in complex reaction mixtures without generation of azabicyclo-[3.2.1]octane **26** or azabicyclo[2.2.2]octane **28** (Scheme 3B). To our delight, **29** produced the expected allene **30** in 53% yield and *6-endo-dig* cyclization product **31** in 41% yield (Scheme 3C). Reaction of **32** provided only the *5-endo-dig* cyclization product **33** in 90% yield (Scheme 3D). A possible rationale for the successful preparation of **1** via ketone α-allenylation under the typical conditions is the specific and rigid architecture of precursor **3**.

Total Synthesis of Sarpagine Alkaloids

Having accessed the key intermediate **1** with ketone and allene groups on the cage skeleton, the stage was set for the diversified total synthesis of sarpagine alkaloids (Scheme 2B). Corey–Chaykovsky reaction of **1** with Me_3SOI as the ylide precursor afforded epoxide **11** as a single diastereomer in 90% yield. Treatment of **11** with methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) generated an epoxide-rearranged product, namely aldehyde **12**, whereas treatment with DIBAL-H led to the reductive epoxide-opening product, that is, alcohol **13**. Both **12** and **13** underwent partial allene hydrogenation to give the natural products vellosimine and normacusine B in good yields with $>20:1$ *E*/*Z* selectivities. Corey–Chaykovsky reaction of **1** with Me_3SI as the ylide precursor generated an epoxide unit with simultaneous introduction of a methyl group on the indole nitrogen atom, to furnish **14** with high efficiency. The stereochemistry of epoxide **14** was ascertained by X-ray crystallographic analysis, and the same configuration was analogously assigned to **11**.[19] Treatment of **14** with MABR and DIBAL-H provided **15** and **17**, respectively. Treatment of aldehyde **15** with NIS and K_2CO_3 in MeOH gave **16**. Partial hydrogenation of the allene unit of **16** and **17** enabled total synthesis of N_a-methyl-16-epipericyclivine[19] and affinisine as well. Unlike other sarpagine alkaloids, trinervine has a characteristic oxygenated ethyl group at C20, which can be readily installed by hydroboration/oxidation of the allene unit. After protection of the free hydroxyl group and bridge-head nitrogen atom of **13** as a borane-complexed silyl ether, hydroboration/oxidation of the allene group via Ma's protocol[25] and then deprotection of the silyl group and decomplexation of borane with HCl in one step furnished trinervine with good efficiency. In short, the concise total synthesis of five sarpagine alkaloids with different substituents at C16 and C20 was accomplished by simple manipulations of ketone and allene groups from intermediate **1**.

Total Synthesis of Koumine Alkaloids

The reduction and oxidation of the allene unit, as described above, enabled diversified synthesis of five sarpagine alkaloids. Formation of a C20–C7 bond via a biomimetic indolyl addition to the allene unit after breakage of the C3–N bond would allow facile access to koumine alkaloids (Scheme 2C). Inspired by Sakai's work,[26] rupture of the C3–N bond was achieved by treating aldehyde **12** with TrocCl to provide **2** as a single diastereomer, presumably via a S_N2 reaction of water. Although there are a few precedents for dearomative addition of indole to an allene unit, to the best of our knowledge, use of this type of reaction in the synthesis of complex natural products is unknown.[9,27] Upon exposure of **2** to a cationic gold salt formed in situ, indolyl addition to the allene unit occurred and the C20–C7 bond was forged. Subsequent treatment of **19** with DBU enabled isomerization of the aldehyde group, and subsequent trapping by the newly generated hydroxyl group provided hemiacetal **20** as a single diastereomer. This completed assembly of the core framework of koumine alkaloids. Reaction of **20** with TFA/Et_3SiH reduced the hemiacetal and imine units. Removal of the Troc group of **21** and then oxidation of **22** installed two imine units and provided koumimine. Oxidation of **21** and subsequent removal of the Troc group of **23** generated *N*-demethylkoumine. Finally, reductive methylation of *N*-demethylkoumine with HCHO/$NaBH_3CN$ delivered koumine in good yield.

Conclusion

In conclusion, we have developed a tandem sequential oxidative cyclopropanol ring-opening cyclization and a cooperative organo/metal-assisted ketone α-allenylation for building the bicyclo[3.3.1]nonane and bicyclo[2.2.2]octane skeletons, respectively. These two methods enabled assembly of the caged core framework of sarpagine alkaloids and installation of two critical functional groups, that is, ketone

and allene. With a common late-stage intermediate as the branch point, and by diverse derivatization of the ketone and allene groups, concise and collective asymmetric total synthesis of five sarpagine alkaloids (affinisine, normacusine B, trinervine, N_a-methyl-16-epipericyclivine, and vellosimine) with various decorating groups was achieved from L-tryptophan. As a further extension of the synthetic value of the allene group, a biomimetic indolyl addition to allene unit after a skeleton rupture enabled rapid assembly of the koumine cage scaffold and thus a straightforward synthesis of three koumine alkaloids (koumine, koumimine, and *N*-demethylkoumine).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allene · cyclopropanol · koumine · sarpagine · total synthesis

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Research Articles

Total Synthesis

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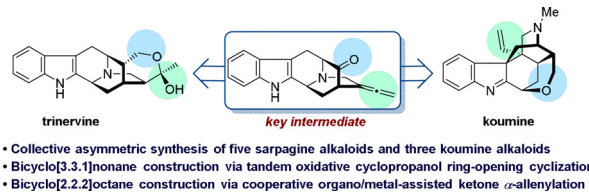
Asymmetric Total Synthesis of Sarpagine and Koumine Alkaloids



- Collective asymmetric synthesis of five sarpagine alkaloids and three koumine alkaloids
- Bicyclo[3.3.1]nonane construction via tandem oxidative cyclopropanol ring-opening cyclization
- Bicyclo[2.2.2]octane construction via cooperative organo/metal-assisted ketone α-allenylation

Two key bridged skeleton-forming reactions, namely tandem sequential oxidative cyclopropanol ring-opening cyclization and ketone α-allenylation, assembled the cage-shaped sarpagine scaffold. By late-stage diversifications of the ketone and allene groups, a concise, collective, and asymmetric total synthesis of two classes of indole alkaloids including five sarpagine alkaloids and three koumine alkaloids has been accomplished.