Natural Product Synthesis

International Edition: DOI: 10.1002/anie.201511638
German Edition: DOI: 10.1002/ange.201511638

Total Synthesis of (±)-Strictamine

*Weiwu Ren, Qian Wang, and Jieping Zhu**

Abstract: *The total synthesis of strictamine has been achieved in nine steps from a known enol triflate. Characteristic features of our approach included: a) creation of a C7 all-carbon quaternary stereocenter at an early synthetic stage; b) use of an N,N-dimethyl tertiary amine as a surrogate of the primary amine for the rapid build-up of a functionalized 2-azabicyclo-[3,3,1]nonan-9-one skeleton (achieved by using a reaction sequence of α-bromination of the ketone, followed by a stereoconvergent intramolecular nucleophilic substitution reaction); and c) a late-stage construction of the indolenine unit.*

Akuammiline alkaloids, known since the 1870s, display a wide variety of biological properties, including antibacterial, anticancer, anti-inflammatory, antitussive, and antimalarial activities.[1] Over 30 members of this family with different ring connectivities have been isolated to date. The characteristic structural feature of this class of monoterpene indole alkaloids is the presence of a C7–C16 bond that creates a rigid and cage-like framework.[2] Their complex molecular architectures have for years presented significant challenges for synthetic chemists. Indeed, only relatively recently have the total syntheses of four congeners, namely, vincorine (**1**),[3] aspidophylline A (**2**),[4] picrinine (**3**),[5] and scholarisine A[6] (**4**; Figure 1) been accomplished.

Strictamine (**5**; Figure 1), isolated in 1965 from the flowers of *Alstonis scholaris*, has been used in folk medicine for its potent antitumor, anti-inflammatory, and antibiosis activities.[7] The absolute configuration of strictamine was determined by X-ray crystallographic analysis in 1977.[7c] Biosynthetically, the compound is formed by an intramolecular oxidative coupling between the C7 and C16 atoms of geissoschizine (**6**) followed by deformylation.[8] The formation of the C7–C16 bond led to a compact octahydro-2*H*-2,8-methanoquinolizine skeleton **A**, which was difficult to access as a result of the presence of two parallel 1,3-bridged [3,3,1]bicycles built from the central cyclohexane core. The synthesis of strictamine has attracted the attention of synthetic chemists ever since its structural identification.[7c] Additionally, the recently discovered potent in vitro inhibitory activities of **5** against nuclear factor-κB[9] had drawn increasing attention towards this 50-year-old unanswered synthetic challenge. Late-stage cyclization with concurrent

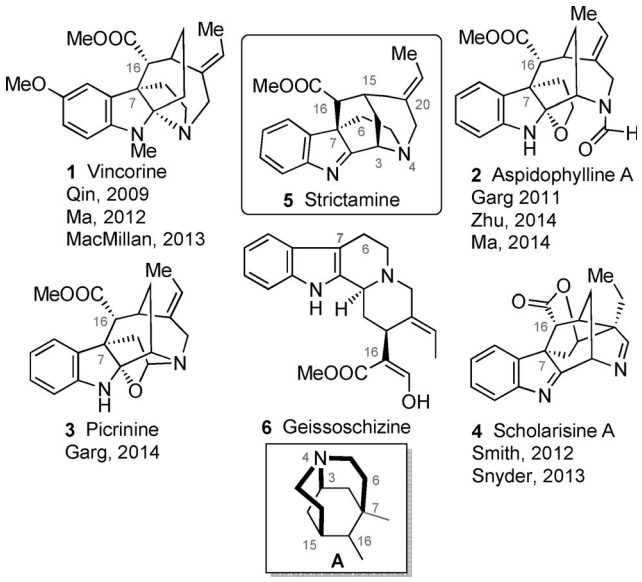

Figure 1. Representative akuammiline alkaloids.

creation of a quaternary carbon center (C7) through the formation of C7–C16[10] or C7–C6[11] bonds are among the most investigated routes.[12] However, none of these methods, including the biomimetic C7–C16 bond-forming approach, has been successful. The peculiar structure of this rigid polycycle has rendered many otherwise powerful bond-forming processes inefficient.

We have been working on the development of a general strategy towards the synthesis of diverse structures of the akuammiline family of alkaloids. Two strategic considerations guided our synthetic design: a) to start the synthesis by formation of the C7 quaternary carbon and b) to form the indolenine unit at a late synthetic stage. For this purpose, we identified compound **7** as a possible platform to obtain skeletal diversity (Scheme 1) and we successfully converted cyclohexanone **7a** (X = OH) into aspidophylline A (**2**) via intermediate **8**.[4b] As a continuation of this research program, we reasoned that compound **7b** ($X = NMe_2$) could be an appropriate starting material for the synthesis of strictamine (**5**). If **7b** could be successfully converted into [3,3,1]azabicycle **9**, then a concise synthesis of **5** could be developed.

After some unsuccessful trials and detours, our strategy leading to the successful synthesis of (±)-strictamine (**5**) is depicted retrosynthetically in Scheme 2. We envisioned to access strictamine (**5**) from vinyl iodide **11** through formation of the C15–C20 bond by way of an intramolecular Michael addition or related transformations. Compound **11** could be traced back to **12**, which could in turn be synthesized from **13** through a sequence of *N*-demethylation and indolenine

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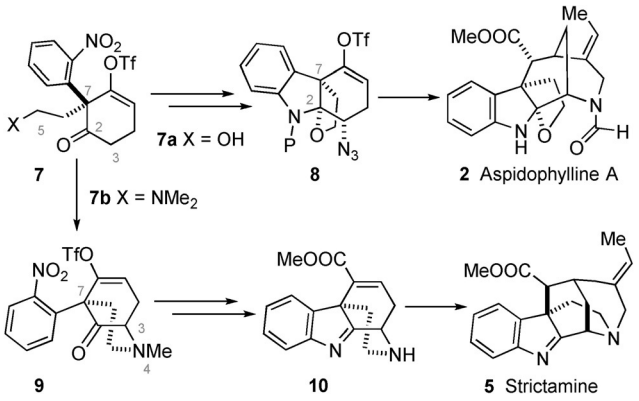
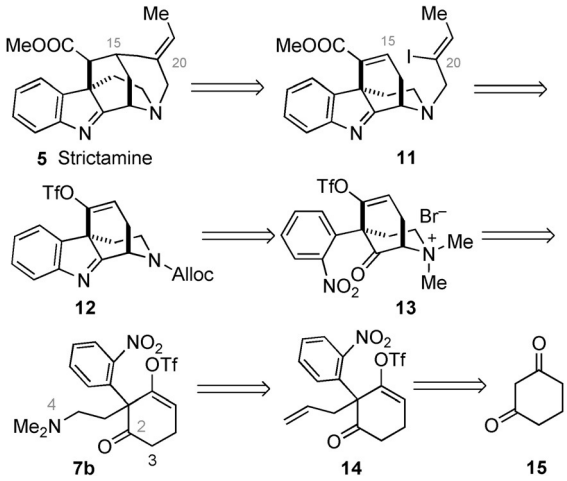
Supporting information for this article can be found under http://dx.doi.org/10.1002/anie.201511638.



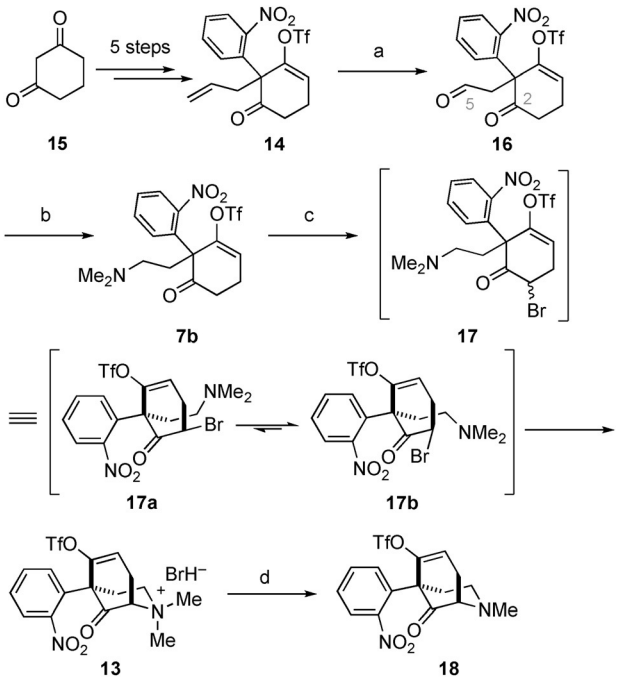
Scheme 1. Synthetic strategy for the preparation of akuammiline alkaloids.



Scheme 2. Retrosynthetic analysis of (±)-strictamine (**5**).

formation under reductive conditions. We planned to prepare the key 2-azabicyclo[3,3,1]non-6-en-9-one **13** from amino ketone **7b**, accessible from 1,3-cyclohexanedione (**15**) via enol triflate **14**.

Our total synthesis began with the elaboration of **14**, which could be prepared on a multigram scale from 1,3-cyclohexanedione (**15**; Scheme 3).[4b,13] OsO_4-catalyzed dihydroxylation of the terminal olefin in **14** followed by cleavage of the resulting diol afforded the corresponding aldehyde **16**,[14] which, without purification, was employed directly in the next step. Chemoselective reductive amination of the ketoaldehyde **16** with dimethylamine ($NaBH(OAc)_3$, DCE, RT) provided tertiary amine **7b** in 60% overall yield from **14**.[15] The use of a secondary amine as an amination agent is of utmost importance for streamlining our synthetic sequence. In fact, if a primary amine were used, its cyclocondensation with both the C2 and C5 carbonyl groups of ketoaldehyde **16** would afford a hexahydroindole, a reaction that has been elegantly exploited by Bonjoch, Bosch, and co-workers for the synthesis of *Strychnos*-type alkaloids.[16] To construct the [3.3.1]-azabicycle **13** from **7b**, a sequence involving the α-bromination of the ketone followed by intramolecular *N*-



Scheme 3. Synthesis of [3,3,1]-azabicycle **18**. a) OsO_4 (4 mol%), NMO, THF/H_2O (v/v = 25:1), 0°C to RT, 12 h, $NaIO_4$, 40°C, 6 h; b) Me_2NH, $NaBH(OAc)_3$, DCE, RT, 1 h, 60% from **14**; c) $PTSA{\cdot}H_2O$, NBS, CH_2Cl_2 (DCM), RT, 48 h, then workup and evaporation; d) NaI (2.0 equiv), DMSO, 140°C, 1 h, 40% overall yield from **7b**. NMO = *N*-methylmorpholine-*N*-oxide; DCE = 1,2-dichloroethane.

alkylation of the tertiary amine was investigated.[17] After much experimentation, an efficient and reliable procedure was found. Treatment of **7b** with *p*-toluenesulfonic acid monohydrate ($PTSA{\cdot}H_2O$) and *N*-bromosuccinimide (NBS) gave α-bromo ketone **17** as a mixture of two diastereomers. After a basic aqueous work-up, evaporation of the ethereal extracts of the crude bromination product **17** afforded directly compound **13** as a brown precipitate in quantitative yield. It is reasonable to assume that the intramolecular *N*-alkylation proceeded through an S_N2 mechanism, which implied that one of the diastereomers of **17a** might undergo epimerization via the enolate intermediate to **17b** before the cyclization occurred. The process was apparently autocatalytic as no external base was needed to promote the desired cyclization. We stress that the vinyl triflate was stable under these reaction conditions.

The *N*-demethylation of the quaternary ammonium salt **13** was next investigated. Reductive C–N bond cleavage using lithium triethylborohydride as the reducing agent led to the decomposition of ammonium salt **13**.[18] Various nucleophiles including 1,4-diazobicyclo[2.2.2]octane (DABCO),[19] metal thiolates,[20] and iodides[21] were examined (see the Supporting Information). Among them, sodium iodide was found to be the most effective reagent and afforded, under optimized conditions (NaI (2.0 equiv), DMSO, 140°C, 1 h), tertiary amine **18** in 40% overall yield from **7b**. The structure of [3.3.1]-azabicycle **18** was confirmed by X-ray structural analysis (Figure 2).[22]

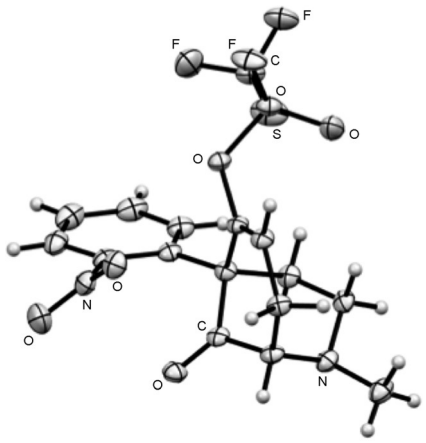
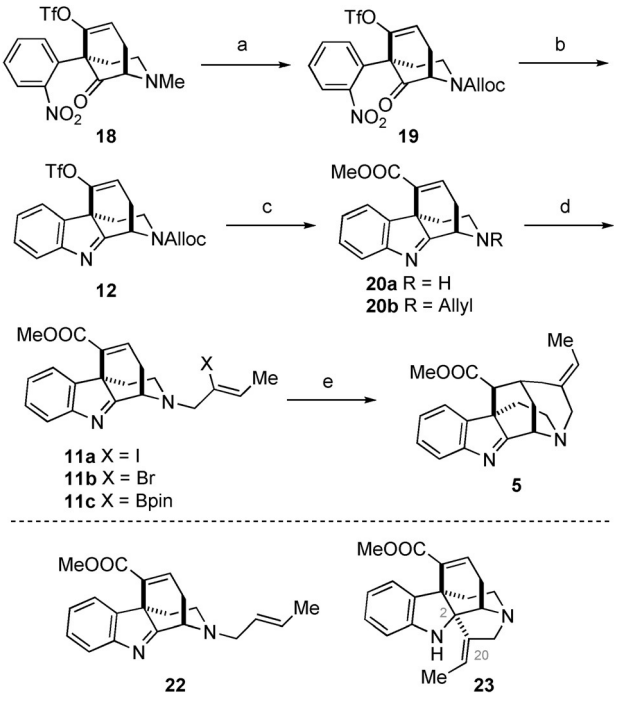


Figure 2. ORTEP representation of [3,3,1]-azabicycle **18**.

The final section of our total synthesis is depicted in Scheme 4. A modified von Braun *N*-demethylative acylation of tertiary amine **18** was realized with allyl chloroformate to give *N*-Alloc derivative **19** in 68% yield (Alloc = allyloxy carbonyl). $TiCl_3$-mediated reductive cyclization of **19** produced indolenine **12** without over-reduction to indoline.[23] We next set out to carry out a one-pot methoxycarbonylation of the vinyl triflate with concurrent removal of the *N*-Alloc functional group from **12**. Treatment of **12** with $[Pd(PPh_3)_4]$ under an atmosphere of carbon monoxide at 50 °C for 1 h followed by addition of 1,3-dimethylbarbituric acid as the allyl scavenger afforded secondary amine **20a**, with a suitable structure for the next transformation step. Careful monitoring of the reaction mixture indicated that the *N*-allyl derivative **20b** was formed at the initial stage, which was subsequently converted into **20a** upon addition of an external nucleophile. This observation indicated that the oxidative addition of vinyl triflate and *N*-Alloc took place concurrently. In the absence of an external nucleophile, the *N*-Alloc group was partially converted into an *N*-allyl derivative that was subsequently *N*-deallylated upon addition of 1,3-dimethylbarbituric acid. Reaction of **20a** with (*Z*)-1-bromo-2-iodobut-2-ene (**21**) under standard conditions provided **11a** in 73% yield.



Scheme 4. Total synthesis of strictamine (**5**). a) K_2CO_3, NaI, $ClCOOCH_2CH{=}CH_2$, DCE, reflux, 9 h, 68%; b) $TiCl_3$, NH_4OAc, acetone/H_2O (1:1 v/v), RT, 20 min, 74%; c) $[Pd(PPh_3)_4]$, Et_3N, CO (1 atm), MeOH/DMF(2:1 v/v), 50 °C, 1 h, then 1,3-dimethylbarbituric acid, RT, 2 h, 55%; d) For **11a**: (*Z*)-1-bromo-2-iodobut-2-ene (**21**), Cs_2CO_3, 4 Å molecular sieves (MS), DMF, RT, 36 h, 73%; e) $[Ni(cod)_2]$ (2.0 equiv), Et_3N (4.0 equiv), CH_3CN, RT, 20 min, then Et_3SiH (2.0 equiv), 1 h, RT, 5–10% yield from **11a**. cod = 1,5-cyclooctadiene.

The cyclization of **11a** to strictamine (**5**) turned out to be a difficult task.[24] Intramolecular Michael addition of vinyllithium generated in situ by lithium–halogen exchange led only to formation of the de-iodinated compound **22** as the only isolable product (8%). A Pd-catalyzed reductive Heck reaction gave a complex reaction mixture under a variety of conditions, including $[Pd(OAc)_2]$/HCOONa/K_2CO_3/Bu_4NCl,[25] $[Pd(OAc)_2]$/PPh_3/Et_3N,[26] and $[Pd(PPh_3)_4]$/HCOOH/piperidine.[27] Radical cyclization conditions (Bu_3SnH/AIBN,[28] Bu_3SnH/Et_3B[29]) produced **22** as a mixture of *E*/*Z* isomers. The complex $[CoBr_2(2,2'\text{-bipyridine})]$ also failed to catalyze the desired intramolecular Michael addition process.[30] Finally, stirring an acetonitrile solution of **11a** at room temperature in the presence of an excess of $[Ni(cod)_2]$ (2.0 equiv) and Et_3N (4.0 equiv) for 20 min followed by addition of Et_3SiH[4c,31] afforded strictamine (**5**; 5–10% yield), with physical and spectroscopic data identical in all respects to those of the natural product. Compound **23** (7% yield) resulting from the formation of the C2–C20 bond, was also isolated. Systematic variation of the nature of the nickel complexes, the bases, the solvents, the temperature, and the reducing agents did not allow us to improve the reaction outcome. The cyclization of vinyl bromide **11b** and vinylboronate **11c** was also investigated under various reaction conditions without success.

In summary, the first total synthesis of strictamine (**5**) has been achieved. The method involves: a) the creation of a C7 all-carbon quaternary stereocenter at an early synthetic stage; b) the use of an *N*,*N*-dimethyl tertiary amine as a surrogate of the primary amine for the rapid build-up of the functionalized 2-azabicyclo[3,3,1]nonan-9-one skeleton through a reaction sequence of α-bromination of the ketone followed by a stereoconvergent intramolecular nucleophilic substitution reaction; c) the late-stage construction of the indolenine unit. Although the yield of the final cyclization step is low, the synthesis is straightforward with a minimum number of nonconstructive steps. Indeed, strictamine was obtained in only 9 steps from the known enol triflate **14** (or in 14 steps from the commercially available compound 1,3-cyclohexanedione). This method can thus be considered as highly step efficient in view of the synthetic challenges associated with this complex natural product.[32]

Acknowledgements

Financial supports from the EPFL (Switzerland), the Swiss National Science Foundation (SNSF), and the Swiss National Centres of Competence in Research (NCCR-Chem Biol) are gratefully acknowledged. We are grateful to Dr. Rosario Scopelliti for performing X-ray structural analysis. We thank Prof X.-D. Luo of Kunming Institute of Botany, China, for the authentic sample of strictamine.

Keywords: alkaloids · cyclization · heterocycles · natural products · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 3500–3503
Angew. Chem. **2016**, *128*, 3561–3564

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Received: December 15, 2015
Published online: February 4, 2016

