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Formal total synthesis of (±)-strictamine – the [2,3]-Stevens rearrangement for construction of octahydro-2H-2,8-methanoquinolizines†

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For decades, akuammiline alkaloids have attracted synthetic chemists due to their intriguing molecular architecture. Among the different structural elements embedded in their carboskeleton, the methanoquinolizidine system constitutes the signature structural element of this alkaloid family. Herein, we describe a novel synthetic access to this system which relies on a [2,3]-Stevens rearrangement and results in the formal synthesis of strictamine.

Akuammiline alkaloids belong to the group of monoterpenoid indole alkaloids. Akuamma, one of the native names of the tree *Picalima nitida* (family: *Apocinaceae*, synonyms: *Picalima klaineana*, *Picalima macrocarpa*), is a rainforest tree occurring in the African forest region from the Ivory Coast to Uganda. The plant is used for the treatment of a variety of diseases in traditional medicine in these regions of Africa.¹ Extracts from its seeds, fruit rind and stem bark demonstrated antimalarial activity² as well as antimicrobial³ and anti-inflammatory effects.^{3b,4}

Its alcoholic extracts contain 3.5–4.8% of alkaloids.⁵ Early on, these alkaloids were studied as potential sources of pharmaceutical compounds. Henry and Sharp characterized four different alkaloids from the akuamma seeds in 1927^{1a} and named the first structure they elucidated akuammine (1). From these seeds, the second indole alkaloid akuammiline⁵ (2) served as an eponym of a whole natural product family – the akuammiline alkaloids (Fig. 1).

In 1966, strictamine (3) was isolated from the plant *Rhazya stricta* (family: *Apocinaceae*).⁶ It shows inhibitory effects of the nuclear factor-κB (NF-κB),⁷ which plays an important role in the regulation of gene expression in immune and inflammatory responses.

The unique challenging chemical structure of akuammiline alkaloids together with their biological activity has sparked the interest of the synthetic community during the last decades.⁸ Among them, strictamine (3) has succumbed only recently to total

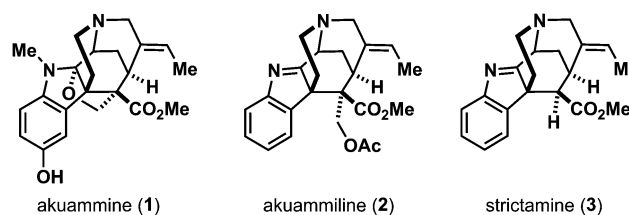


Fig. 1 Prominent members of the akuammiline alkaloids.

synthesis by the groups of Garg (enantioselective),⁹ Zhu (racemic),¹⁰ and Ohno (formal synthesis).¹¹

The architecture of strictamine (3) is characterized by the presence of methanoquinolizidine system 4 (highlighted in red, Fig. 2).^{1b} This structure element represents a tricyclic system containing the C–D–E rings of strictamine (3). The methanoquinolizidine is assembled by the C7–C16 carbon carbon bond (biosynthetic numbering). This bond is crucial, since it accounts for the dearomatized indolenine system bearing a quaternary carbon center at C7. This leads to a very compact, cage like structure comparable to adamantane (5) (see Fig. 2).

Our retrosynthetic analysis commences with the removal of the indolenine core – a very sensitive structure element. Intramolecular 1,4-addition disassembles the methanoquinolizidine motif, leading to ketone 6. This compound constitutes the product of [2,3]-Stevens rearrangement-II,¹² obtained from bicycle 7 and iodide 8. In this rearrangement, the C–D ring system of 6 – an 2-azabicyclo[3.3.1]nonane – is assembled (Fig. 3).

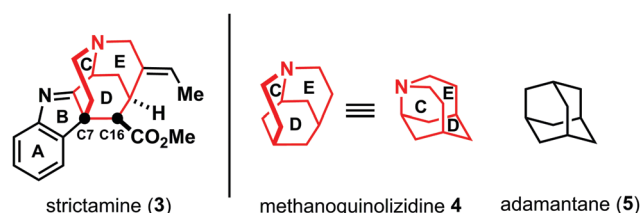


Fig. 2 Cage-like methanoquinolizidine structure 4 of the akuammiline alkaloids.

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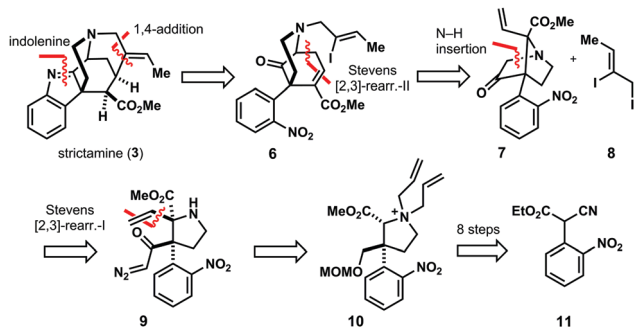


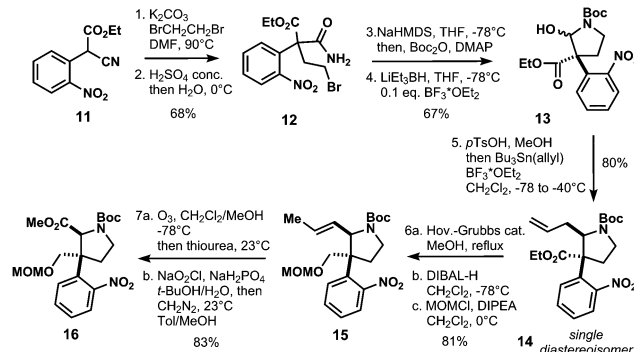
Fig. 3 Retrosynthetic analysis of strictamine (3).

Therefore, this Stevens rearrangement-II represents the key transformation of our synthesis. Its mechanism is outlined in Scheme 1 detailing the assembly of the C–D bicyclic system of methanoquinolizidine 4.

The bridged bicyclic core of rearrangement precursor 7 is generated *via* N–H insertion of diazoketone 9 (Fig. 3). This highly substituted pyrrolidine harbors two vicinal stereocenters, the β -center constituting a quaternary carbon center rendering its synthesis a formidable synthetic challenge. The α -stereocenter of 9 is introduced by [2,3]-Stevens rearrangement-I of ammonium salt 10 with complete control of diastereoselectivity. Pyrrolidine 10 is obtained in eight isolated steps from known nitrobenzene 11.¹³

Our synthesis started with α -cyanoacetate 11,¹³ which was alkylated with dibromoethane and K_2CO_3 in dimethylformamide at 90 °C to generate the quaternary carbon center of 12 after hydrolysis of the nitrile group with concentrated sulfuric acid to afford carboxylic amide 12 in 68% overall yield (Scheme 2). Lactam formation was affected with sodium hexamethyldisilazane at –78 °C, which was subsequently protected as *tert*-butyl carbamate to give hemiaminal 13 in 67% yield upon reduction with superhydride in the presence of catalytic amounts of boron trifluoroetherate.

Conversion of 13 to the methoxy aminal with *p*-toluenesulfonic acid and concomitant allylation *via* *N*-acyl iminium ion chemistry afforded compound 14 as a single diastereoisomer in 80% yield. The allyl-group in 14 was isomerized with Hoveyda–Grubbs II catalyst, then reduction of the ester with DIBAL-H and subsequent protection with chloromethyl methyl ether (MOMCl) gave 15 in 81% yield (Scheme 2). The isomerized double bond of 15 was thus converted to the methyl ester by ozonolysis, Pinnick oxidation and methylation with diazomethane to furnish 16 in 83% yield. Deprotection of the Boc-group with trifluoroacetic acid in dichloromethane followed by *N*-alkylation with allyl bromide gave access to allyl amine 17 (Scheme 3). Introduction of the

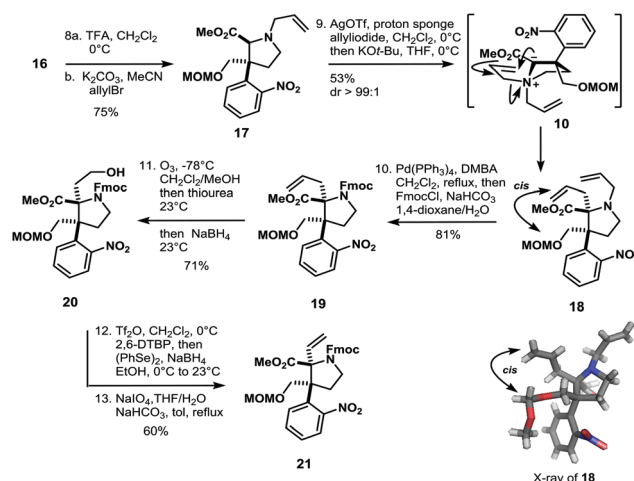
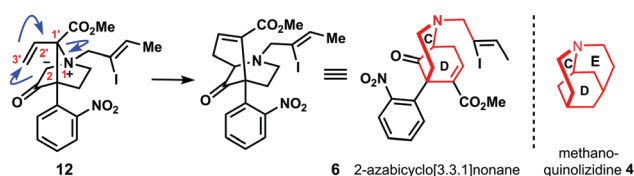


Scheme 2 Establishment of quaternary carbon center in 12.

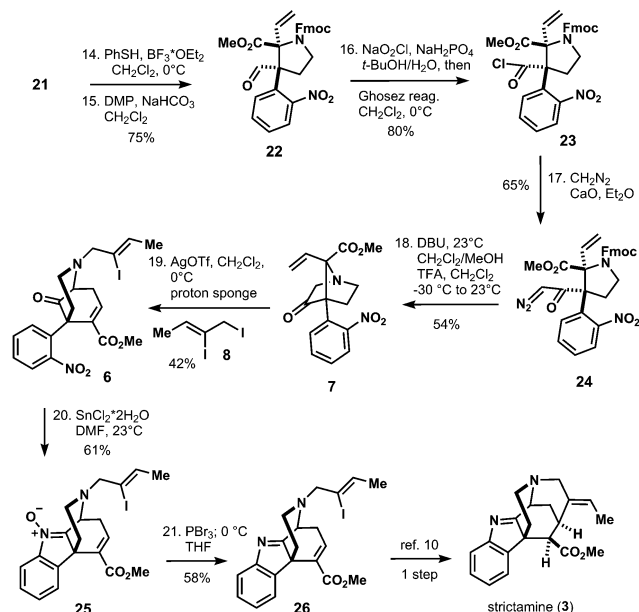
tertiary α -stereocenter at the pyrrolidine ring proceeded *via* Stevens rearrangement-I with silver(i) triflate to give product 18 with complete diastereoselectivity (99:1) in 53% yield (21% recovered starting material). The stereochemistry of 18 was determined by X-ray analysis. We surmise that this selectivity originates from steric hindrance exerted by the nitrophenyl group in the course of the rearrangement of 10. Therefore, the α -stereocenter is established in a *cis* fashion with respect to the MOM-protected alcohol (see 10 and 18 in Scheme 3).

The so obtained allyl amine 18 was converted to Fmoc-carbamate 19 in two transformations and 81% yield. In order to obtain envisioned Stevens rearrangement-II substrate 7, the next task was to transform the allylic side chain of 19 to the corresponding vinyl-chain (see compound 21 in Scheme 3). This was achieved by ozonolysis/reduction to furnish alcohol 20. Triflation of 20 and S_N2 -reaction with NaSePh afforded vinyl-compound 21 in 60% yield after oxidative workup with sodium periodate (Scheme 3). With the vinyl-chain established, the bridged bicyclic system of 7 was assembled in five isolated steps from 21 (Scheme 4).

Thus, deprotection of the MOM-ether of 21 and subsequent oxidation with Dess–Martin periodinane (DMP) afforded aldehyde 22. Pinnick oxidation to the corresponding carboxylic acid with concomitant acid chloride formation with Ghosez's reagent¹⁴

Scheme 3 Establishment of the α -stereocenter in 18.

Scheme 1 Mechanism of Stevens rearrangement-II.



Scheme 4 Endgame of the synthesis.

delivered **23**. The latter was reacted with diazomethane in a sealed tube to give desired α -diazo ketone **24**. With this compound in hands, bridged bicyclic system **7** was formed by Fmoc-deprotection of **24** and subsequent acid-triggered N–H insertion to yield Stevens rearrangement-II precursor **7** in 54% yield. N-Alkylation with iodide **8** and AgOTf in combination with proton sponge in dichloromethane provided the corresponding ylide, which directly underwent the envisioned [2,3]-sigmatropic Stevens rearrangement-II to give the crucial azabicyclo[3.3.1]-nonane skeleton **6** in 42% yield. With compound **6** in hands, reduction of the nitro group was attempted and resulted in decomposition under various conditions. However, treatment of **6** with tin(II)chloride dihydrate delivered 61% of incompletely reduced product **25** as a single product. After extensive experimentation we were able to reduce nitron **25** to imine **26** with phosphorus tribromide in tetrahydrofuran and 58% yield.¹⁵ Compound **26** can be converted to strictamine (**3**) in one more step according to Zhu's protocol.¹⁰

In conclusion, we have accomplished a formal total synthesis of strictamine (**3**) based on 21 isolated steps (34 chemical transformations). Our synthetic route is highly diastereoselective,

very robust and was performed on multigram-scale up to diazo-compound **24**. We were able to show the versatility of a [2,3]-Stevens rearrangement for the construction of the 2-azabicyclo[3.3.1]nonane system, which is a very challenging structure motif to synthesize and represents the key compound for the total synthesis of strictamine (**3**).

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