ChemComm

COMMUNICATION



Cite this: Chem. Commun., 2016, 52, 11363

Received 25th July 2016, Accepted 16th August 2016 Formal total synthesis of (\pm) -strictamine – the [2,3]-Stevens rearrangement for construction of octahydro-2*H*-2,8-methanoquinolizines[†]

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DOI: 10.1039/c6cc06125g

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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 Picralima nitida (family: *Apocinaceae*, synonyms: *Picalima klaineana*, *Picralima 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- κ B (NF- κ B),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

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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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crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cc06125g

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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 methanoguinolizidine **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 K₂CO₃ in dimethylformamide at 90 °C to generate the quarternary 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 1 Mechanism of Stevens rearrangement-II.





tertiary α -stereocenter at the pyrrolidine ring proceeded *via* Stevens rearrangement-I with silver(1) 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 Fmoccarbamate **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_N 2-reaction with NaSePh afforded vinylcompound **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.



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 Fmocdeprotection 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 nitrone 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**).

Financial support was granted by the Fonds der Chemischen Industrie *via* a Liebigstipendium.

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