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Formal total synthesis of (±)-strictamine *via* [2,3]-sigmatropic Stevens rearrangements

Ruben Eckermann,[a,b] Michael Breunig,[a] and Tanja Gaich*[a]

Abstract: To date, more than 100 congeners of the akuammiline alkaloid family have been isolated. Their signature structural element is a methanoquinolizidine moiety, a cage-like scaffold structurally related to adamantane. The structural variations of the family members originate from oxidative processes that mostly trigger rearrangements of the methanoquinolizidine motif. The family of the akuammiline alkaloids is best represented by strictamine. It bears the least functionalized carbon skeleton of all family members without lacking the signature structural motifs. Herein, we report the formal synthesis of stictamine *via* a Stevens [2,3]-sigmatropic rearrangement as a key step and the synthetic pitfalls related with its synthesis.

Introduction

Over the past decades, akuammline alkaoids have attracted the synthetic community due to their unique chemical structure and biological activity.[1-17] Especially strictamine (**1**) has first been synthesized in 2015 and 2016, respectively, by the groups of Neil K. Garg (enantioselective),[18] Jieping Zhu (racemic),[19] Hiroaki Ohno (formal),[20] and ours (formal).[21] Biosynthetically, strictamine (**1**) belongs to the group of monoterpenoid indole alkaloids, which are derived from (*E*)-geissoschizine (**4**).[22-29] In contrast to other monoterpenoid indole alkaloids, the akuammiline alkaloids are defined by one C–C bond between carbon atoms C-7 and C-16, leading to a very compact cage-like structure (methanoquinolizidine **2**) reminiscent of adamantane (**3**). In contrast to adamantane (**3**), which harbors four six-membered rings in a chair conformation, the methanoquinolizidine system **2** consists of two six-membered rings in a boat conformation and only one in a chair conformation. The different connectivity of the rings leads to an additional eight-membered ring (Figure 1).[30-31] Strictamine (**1**) was first isolated in 1966[32] from the plant *Rhazya stricta* (family: *Apocinaceae*) and shows inhibitory effects of the nuclear factor-κB (NF-κB), which is involved in the regulation of gene expression in immune and inflammatory responses.[33]

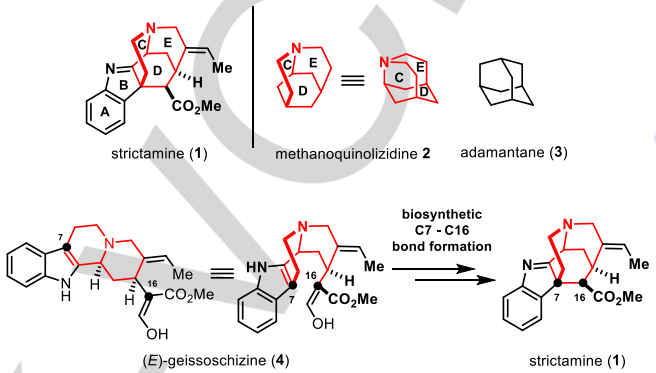

Figure 1. The akuammiline alkaloid strictamine (**1**), biosynthesis and structural characteristics.

Retrosynthetic analysis

The strategy of our synthesis of strictamine (**1**) is outlined in Figure 2. The retrosynthetic analysis starts with formation of the indolenine unit as a very sensitive structure motif. The indolenine is introduced by reduction of the nitro-group to aniline followed by intramolecular condensation with the ketone of compound **5**. The methanoquinolizidine system **2** is built up by two consecutive steps: intramolecular 1,4-addition of vinyl iodide **5** to the α,β-unsaturated ester and [2,3]-sigmatropic Stevens rearrangement[34-36] of ylide **6**.

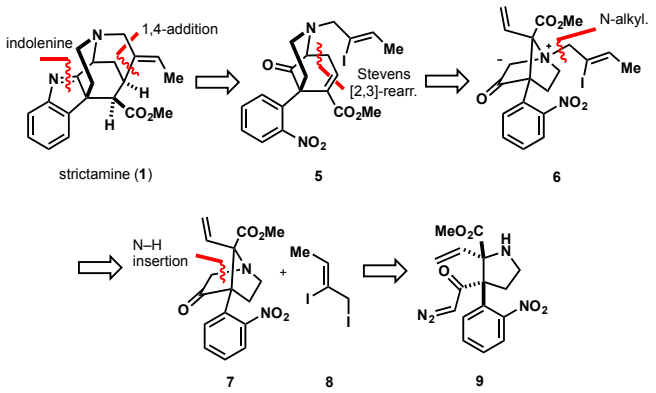

Figure 2. Retrosynthetic analysis of strictamine (**1**).

Ylide **6** is established by deprotonation of the ammonium salt resulting from *N*-alkylation of tertiary amine **7** and iodide **8**. Tertiary amine **7** is assembled by intramolecular N–H insertion

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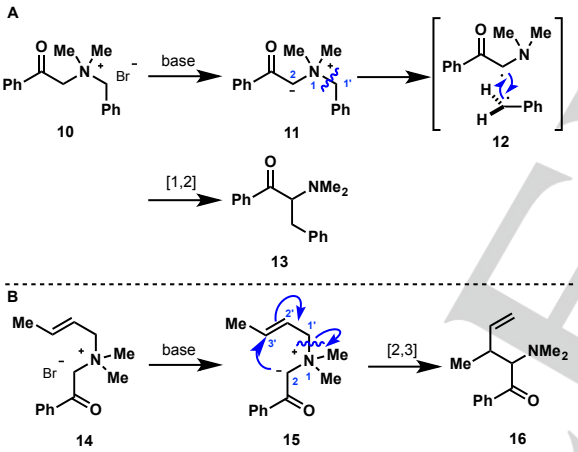
of the α-diazo carbonyl group of pyrrolidine **9**. The key transformation of the synthesis is the Stevens [2,3]-sigmatropic rearrangement (**6** to **5**).

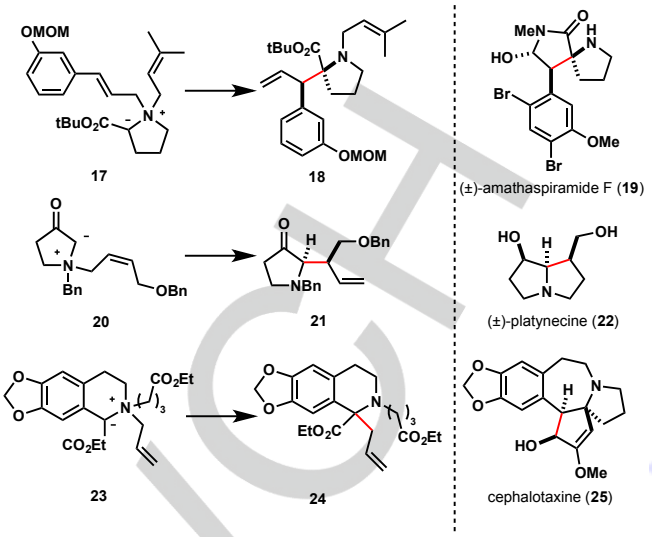
Stevens rearrangement of ammonium ylides

In general, ammonium ylides can react in two different manners depending on the substitution pattern. The first possibility is a [1,2]-shift of an ammonium ylide **11** to the corresponding tertiary amine **13**.[37] This type of rearrangement is called Stevens [1,2]-rearrangement and is predicted to proceed *via* a radical pair mechanism.[38-39] This mechanism involves homolytic cleavage of the carbon nitrogen bond to the most stable carbon centered radical **12**, followed by recombination of the radicals to the shifted product **13** (Scheme 1A). If the nitrogen atom of the ammonium ylide harbors one or more allylic substituents (see **15**), a [2,3]-sigmatropic rearrangement becomes feasible resulting in tertiary amine **16**.[40] This type of rearrangement is called Stevens [2,3]-rearrangement (Scheme 1B). The [2,3]-sigmatropic rearrangement is a symmetry allowed reaction and therefore proceeds *via* a concerted mechanism with lower activation energies compared to the [1,2]-reaction pathway.[41-43]



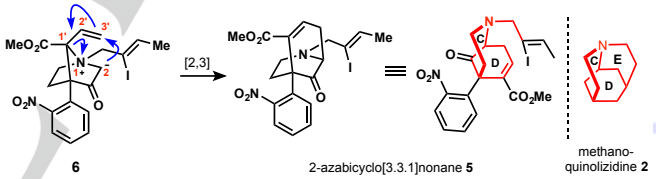
Scheme 1. Stevens [1,2]-rearrangement and Stevens [2,3]-rearrangement in comparison.

Although the Stevens [2,3]-rearrangement is a very powerful transformation, only a few applications in natural product synthesis are reported to date.[44-48] Three examples are summarized in Scheme 2. Soheili and Tambar achieved the total synthesis of (±)-amathaspiramide F (**19**) *via* a Stevens [2,3]-rearrangement as key step.[44] Ammonium ylide **17** rearranges to pyrrolidine **18** under formation of two new stereocenters. Zhou et al. used the [2,3]-sigmatropic reaction to install two stereocenters of (±)-platynecine (**22**).[45] For this, ammonium ylide **20** rearranges at 50 °C to compound **21**. Cephalotaxine (**25**) was synthesized by Li and Wang in 2003 by rearrangement of ammonium ylide **23** to tertiary amine **24**.[46]



Scheme 2. Application of the Stevens [2,3]-rearrangement in natural product synthesis.

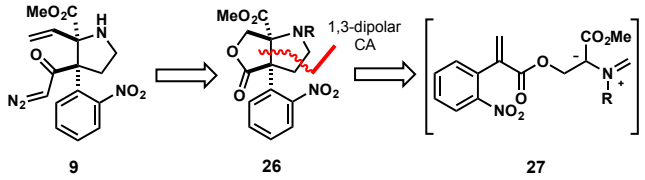
In our synthesis of strictamine (**1**), the Stevens [2,3]-sigmatropic rearrangement is used to install the second ring (**D**) of the methanoquinolizidine system **2**. Therefore, ammonium ylide **6** rearranges in a [2,3]-sigmatropic fashion to bridged bicycle **5** – a very strained 2-azabicyclo[3.3.1]nonane system (Scheme 3).



Scheme 3. Application of the Stevens [2,3]-rearrangement for the synthesis of bicycle **5** – an 2-azabicyclo[3.3.1]nonane system.

Results and Discussion

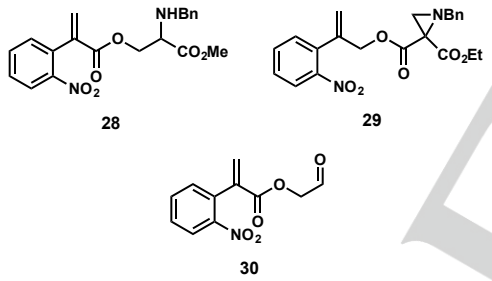
To examine the Stevens [2,3]-sigmatropic rearrangement of ylide **6**, densely functionalized pyrrolidine **9** had to be synthesized. This highly substituted pyrrolidine harbors two vicinal stereocenters, the β-center constituting a quaternary carbon center rendering its synthesis a formidable synthetic challenge. Intramolecular 1,3-dipolar cycloaddition of an azomethine ylide to a double bond gives straightforward access to highly substituted pyrrolidines under complete control of the newly defined stereocenters.[49] The central pyrrolidine **9** can be established by standard functional group interconversions starting from lactone **26**. The latter can be generated by intramolecular 1,3-dipolar cycloaddition starting from azomethine ylides like intermediate **27**. The appropriate dipol precursors can be synthesized starting from the corresponding acrylic acid (Figure 3).



9 26 27

Figure 3. 1,3-Dipolar cycloaddition for construction of pyrrolidine **9**.

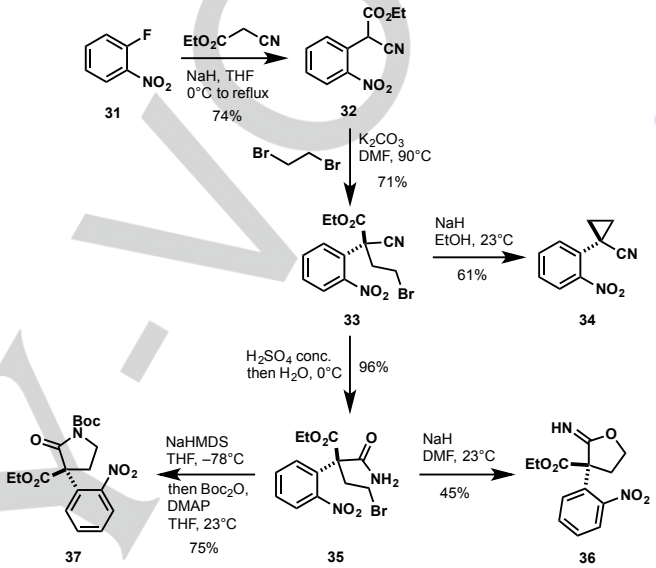
Different methodologies for the preparation of azomethine ylides are literature-known[49] and were examined by our group to synthesize pyrrolidines like compound **26**. In this publication, we will present three complementary strategies that have been investigated. Figure 4 shows three common precursors of azomethine ylides (for details about their syntheses see supporting information). Secondary amine **28** was subjected to formaldehyde under different reaction conditions in order to generate a 1,3-dipol.[50] Aziridine **29** was subjected to high temperatures or light, thus triggering decomposition to the corresponding azomethine ylide.[51-54] Aldehyde **30** was reacted with *tert*-butyl glycinate and different transition metals under basic conditions resulting in a 1,3-dipol, which could add to the acrylic acid double bond.[55-56] Unfortunately, only decomposition of starting material was observed in all three cases (see supporting information).



28 29 30

Figure 4. Three examined azomethine ylide precursors.

Due to these unexpected drawbacks, we decided to investigate a more linear sequence in order to synthesize pyrrolidine **9**. For this purpose, fluoronitrobenzene **31** was converted to α-cyanoacetate **32** *via* nucleophilic aromatic substitution.[57] Alkylation with 1,2-dibromoethane under basic conditions afforded the quaternary carbon center of compound **33** in 71% yield, and consecutive hydrolysis of the nitrile gave the corresponding amide. Usually, this transformation can be accomplished under basic conditions. Unfortunately, treatment of compound **33** with various nucleophiles like sodium ethanolate resulted in formation of cyclopropane **34**. This can be explained by nucleophilic attack at the ester group followed by decarboxylation and intramolecular alkylation with the primary bromide. Nevertheless, treatment of nitrile **33** with concentrated sulfuric acid followed by pouring on an ice/water mixture resulted in the formation of carboxylic amide **35**. The reaction can be stopped at the stage of the carboxylic amide by direct filtration of precipitating amide **35**. If this is reacted for a longer time under the acidic aqueous conditions, an increasing amount of complete hydrolysis to the carboxylic acid is observed. In order to cyclize carboxylic amide **35** to the corresponding five-membered lactam, the latter was treated with sodium hydride in dimethylformamide at 23 °C. Instead of the lactam formation, imido ester **36** was isolated in 45% yield, thus underscoring the ambident nucleophilicity of amides in general.[58] Only treatment of **35** with sodium hexamethyldisilazane in tetrahydrofuran at –78 °C resulted in lactam formation, which is followed by protection with di-*tert*-butyl dicarbonate (Boc_2O) to imide **37** (Scheme 4).



31 32 33 34 35 36 37

Scheme 4. Formation of pyrrolidinone **37**.

The next task was to install the functional groups and the correct relative stereochemistry at the second stereocenter of pyrrolidine **9** starting from **37** (Scheme 5). We tried different methods after reduction of imide **37** with superhydride and catalytic amounts of boron trifluoroetherate, which yielded Boc-protected hemiaminal **38**. Transformation of the corresponding aldehyde with Wittig reagent **39** resulted in the formation of compound **40** in 70% yield. This can be explained by fragmentation of Boc-protected hemiaminal **38** to formamide **41** under basic conditions. Formamide **41** was isolated after treatment of Boc-protected hemiaminal **38** with sodium hydride in tetrahydrofuran. This fragmentation reaction is also preferred as reaction pathway if no Lewis acid is added during the reduction of imide **37**. Nevertheless, treatment of compound **38** with *para*-toluenesulfonic acid in methanol resulted in the formation of the Boc-protected methoxy aminal, which was transferred to either cyanide **42** or allylic compound **43** *via* *N*-acyl iminium ion chemistry[59] in good yields (Scheme 5). Several attempts to functionalize cyanide **42** by alkylation or Aldol reaction were unsuccessful. Unfortunately, only starting material could be re-isolated and no reaction was observed (see supporting information). Also transformation of the nitrile group to another carbonyl group was ineffective due to selectivity problems with either the Boc-group or the ethyl ester.

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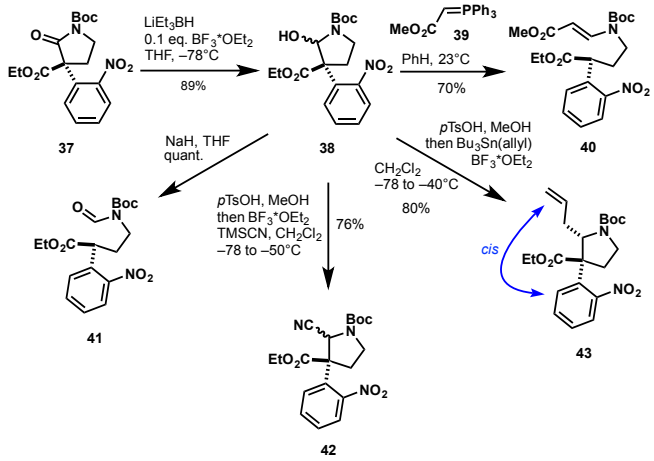
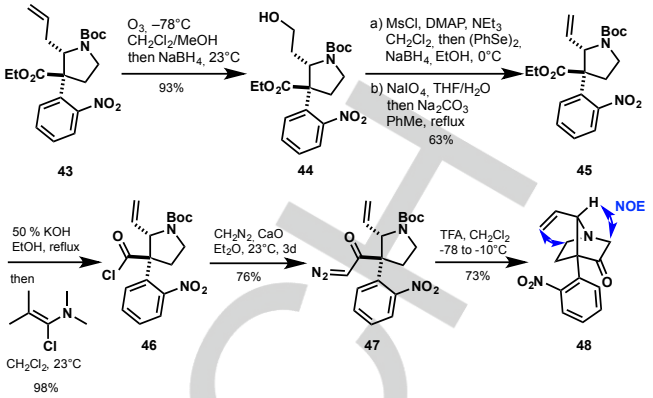


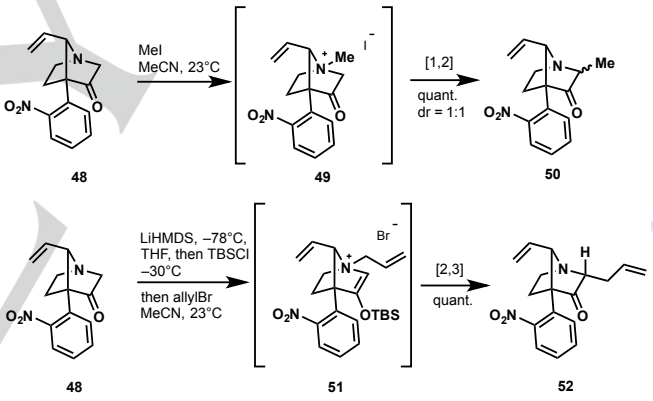
Scheme 5. Functionalization of Boc-protected hemiaminal **38**.

Due to these problems, we decided to continue the sequence with allylic compound **43**. The allyl substituent was introduced as a single diastereoisomer. The steric preference of the allyl group could not be determined by NOE-experiments and crystallization of compound **43** was not successful. A stereochemical prerequisite for the Stevens [2,3]-sigmatropic rearrangement to proceed is the *cis* orientation of the ketone and the vinyl group in **6.** This relationship is established in the course of the pyrrolidine synthesis and caused severe difficulties as described in Scheme 6. Transformation of the allyl group of **43** to the vinyl substituent could be achieved by ozonolysis and reductive workup yielding alcohol **44** in 93%. Mesylation followed by stepwise Grieco elimination[60] resulted in desired vinyl substrate **45**. Saponification of the ethyl ester was only possible under very harsh reaction conditions. The carboxylic acid was obtained by using 50% aqueous potassium hydroxide in refluxing ethanol and could be transformed to acid chloride **46** in 98% yield using 1-chloro-N,N,2-trimethyl-1-propenylamine (Ghosez's reagent)[61] under very mild conditions. Acyl chloride **46** was very unreactive and took three days at 23 °C in a sealed tube to convert to the corresponding α-diazo ketone **47** in 76% yield. Finally, cyclization to bridged tertiary amine **48** was initiated by treatment with trifluoroacetic acid at low temperatures (Scheme 6). The conformationally fixed bicycle **48** showed clear NOE-contacts unfortunately indicating the *cis* stereo relationship of the allyl substituent and the nitro-aryl group in **43** (Scheme 5). This experimental finding led to conclude that the allylation reaction (**38** to **43**) proceeded with complete diastereocontrol implementing the *cis* relationship of nitro-aryl and allyl group.



Scheme 6. Cyclization to bridged tertiary amine **48**.

Due to the undesired relative stereochemistry of **48**, the [2,3]-sigmatropic rearrangement for the construction of an 2-azabicyclo[3.3.1]nonane system could not be tested at this stage. Nevertheless, the reactivity of bicyclic amine **48** in alkylation processes was investigated. Thereby, treament of **48** with iodomethane in acetonitrile gave compound **50** in quantitative yields (Scheme 7).

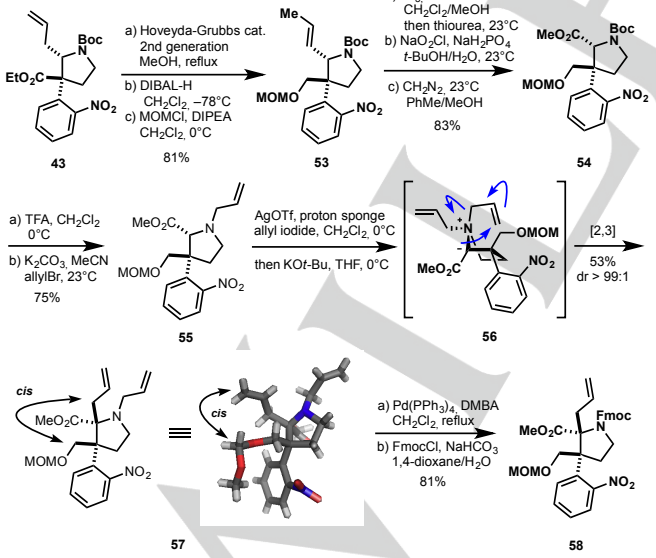


Scheme 7. Stevens [1,2]- and [2,3]-rearrangement of tertiary amine **48** after quarternization.

This experimental fact can be explained by a Stevens [1,2]-rearrangement of intermediate **49**, since **50** was formed even without the addition of base. The diastereomeric ratio of 1:1 reflects a radical mechanism of the [1,2]-shift. The [2,3]-sigmatropic rearrangement was observed after transformation of **48** to the TBS-enol ether and *N*-alkylation with allyl bromide. Ammonium salt **51** could also not be isolated and reacted directly to rearrangement product **52** in quantitative yields at 23 °C. The complete control of diastereoselectivity most probably hints towards a concerted mechanism of the [2,3]-rearrangement.

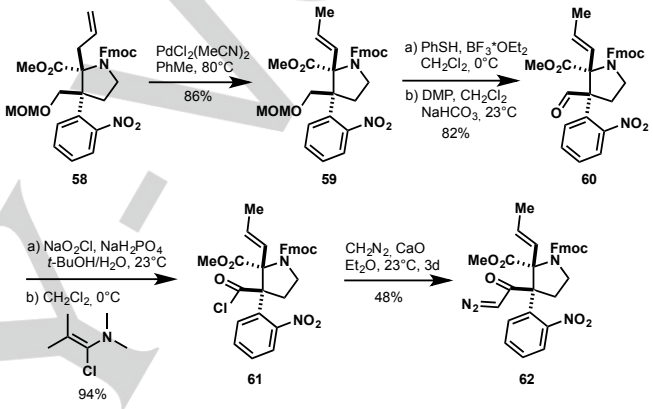
We thus turned our attention back to the completely stereoselective allylation from **38** to **43**, which gave the undesired *cis* diastereomer. This undesired selectivity could be turned into our advantage. Instead of converting the allyl group in **43** into the vinyl group, as has been described in Scheme 6**,** it

was converted into the methyl ester in **54** (Scheme 8). The allyl group of **9** was installed in the reaction sequence from **55** to **57**. For this purpose, the allyl substituent of compound **43** was first isomerized by Hoveyda–Grubbs catalyst, followed by reduction of the ethyl ester to the corresponding primary alcohol and subsequent protection with chloromethyl methyl ether (MOMCl) to yield **53** in 81% over three steps. Ozonolysis, Pinnick oxidation and esterification with diazomethane transformed olefin **53** into methyl ester **54**. Boc-deprotection with trifluoroacetic acid furnished the secondary amine, which was alkylated with allyl bromide to allylic amine **55** in 75% yield. Quarternization of tertiary amine **55** to the ammonium salt could only be achieved employing very reactive electrophiles, while allylation under Tsuji–Trost conditions[62] or with allyl bromide or allyl iodide even under refluxing conditions did not show any reaction. Only the addition of allyl iodide in combination with silver(I) triflate gave rise to the ammonium salt. By the addition of proton sponge to the reaction mixture, yields and reproducibility could be improved. Subsequent addition of potassium *tert*-butoxide in tetrahydrofuran at 0 °C converted the ammonium salt to ylide **56**, which directly undergoes a [2,3]-sigmatropic rearrangement yielding compound **57** in 53% (21% recovered starting material). The Stevens rearrangement proceeds under complete control of the stereochemistry, which was determined by X-ray analysis (Scheme 8). We surmise that this selectivity originates from steric hindrance exerted by the nitrophenyl group in the course of the rearrangement of **56**. Therefore, the stereocenter is established in a *cis* fashion with respect to the MOM-protected alcohol. Allyl amine **57** could be further converted to Fmoc-carbamate **58** by palladium-catalyzed deallylation with dimethylbarbituric acid (DMBA) as nucleophile followed by reaction of the secondary amine with Fmoc-Cl in an overall yield of 81%.



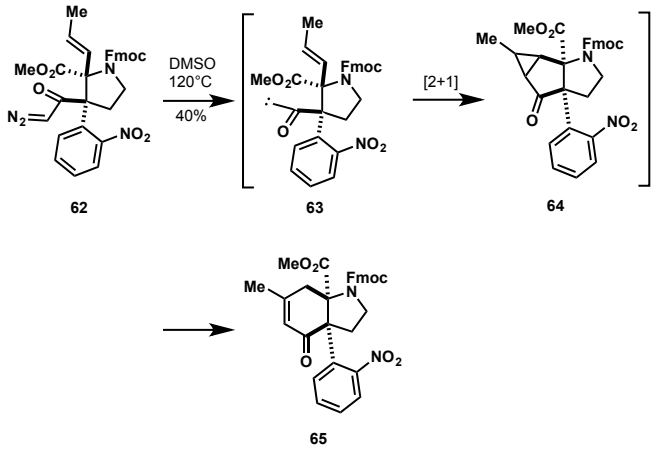
Scheme 8. Establishment of the second stereocenter by a Stevens [2,3]-rearrangement.

Heating compound **58** in toluene to 80 °C with catalytic amounts of bis(acetonitrile) dichloropalladium(II) afforded isomerization of the double bond to substrate **59** in 86% yield (Scheme 9). Several attempts to convert this olefin in a metathesis reaction to the terminal double bond with ethylene gas were not successful and resulted mostly in re-isolation of starting material (see supporting information). At this point, we decided to postpone this step and continued with the installation of α-diazo ketone **62**. Deprotection of the MOM-group of **59** under Lewis-acidic conditions and the addition of thiophenol furnished the primary alcohol, which was subsequently oxidized to the aldehyde by Dess–Martin periodinane (DMP) in a yield of 82%. Pinnick oxidation to the carboxylic acid followed by transformation to acid chloride **61** with Ghosez's reagent was performed smoothly. Acid chloride **61** was directly converted to α-diazo ketone **62** in a sealed tube at 23 °C over 3 days and an overall yield of 48% was obtained (Scheme 9).



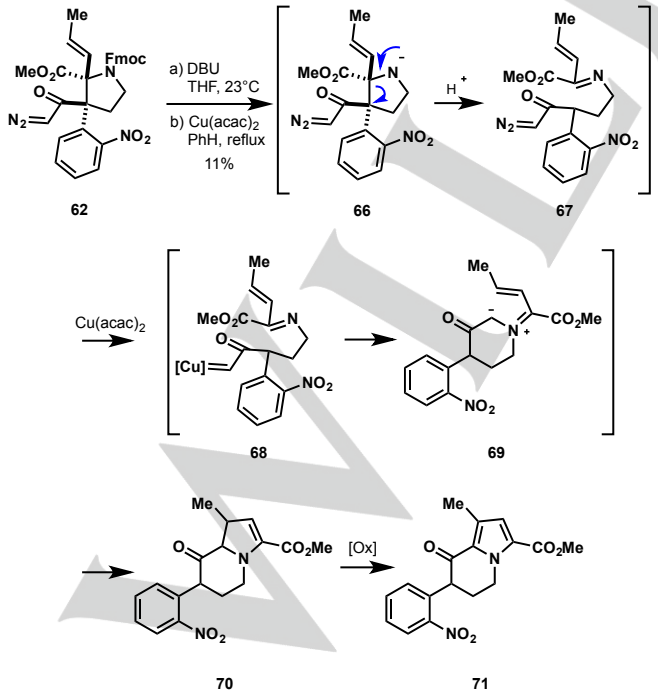
Scheme 9. Transformation to α-diazo ketone **62**.

With α-diazo ketone **62** in hands, conditions for the Fmoc-deprotection could be screened. In most cases, secondary amines are used to initiate deprotection by deprotonation and to trap the formed dibenzofulvene *in situ*.[63] For **62**, secondary amines are not feasible for deprotection due to the reactivity with the α-diazo ketone and only resulted in decomposition. Another option for Fmoc-deprotection is heating the substrate in dimethyl sulfoxide.[64] Unfortunately, under these conditions the Fmoc-group was stable and instead of the secondary amine, product **65** was isolated in 40% yield. Formation of this product can be explained *via* cyclopropane **64** as intermediate, which undergoes a ring opening reaction to α,β-unsaturated ketone **65**.[65] Cyclopropane **64** is formed after degradation of the diazo-group to carbene **63** and intramolecular cycloaddition with the double bond (Scheme 10).



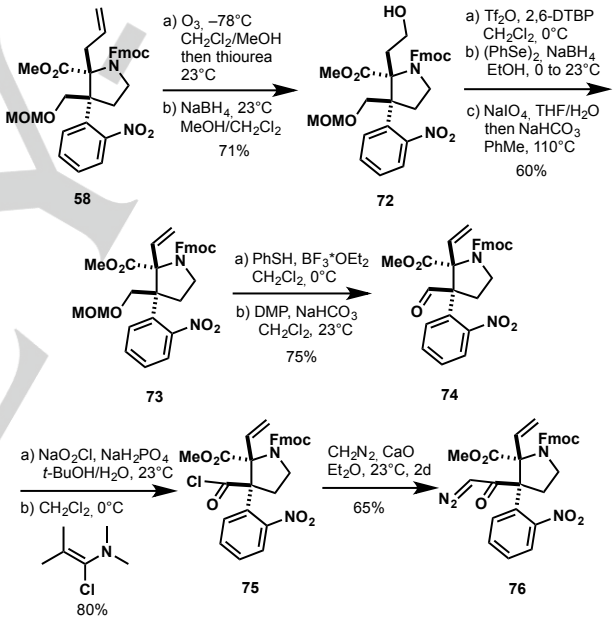
Scheme 10. Proposed mechanism to annulation product **65**.

We therefore required milder conditions for Fmoc-deprotection and applied DBU in tetrahydrofuran. After complete consumption of starting material, the crude reaction mixture was exposed to copper(II) acetylacetonate in refluxing benzene to perform the intramolecular N–H insertion. Interestingly, instead of the bridged tertiary amine, pyrrole **71** was observed in low yields (Scheme 11). The formation of pyrrole **71** can be explained *via* fragmentation product **67**, which could also be isolated. Fmoc-deprotection under aprotic conditions yields anion **66**, which tends to fragment to imine **67**. Formation of carbenoid **68** is followed by an intramolecular insertion into the imine lone pair[66] resulting in ylide **69**. This reacts in a Michael addition to dihydropyrrole **70**, which is oxidized to pyrrole **71** immediately. This reaction outcome proved the importance of a protic solvent during Fmoc-deprotection favoring protonation instead of fragmentation.



Scheme 11. Mechanistic considerations to the formation of pyrrole **71**.

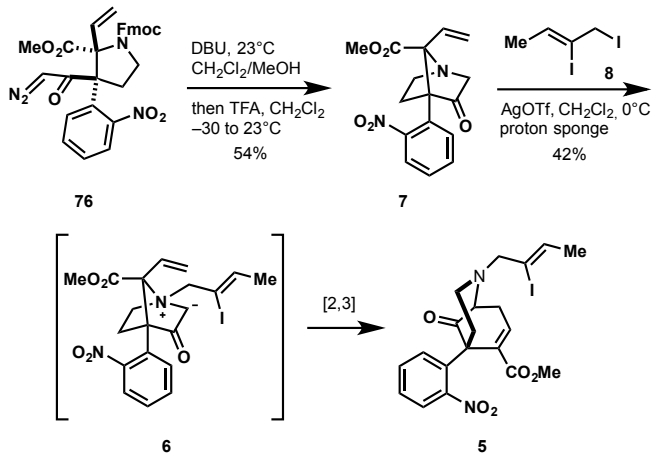
We thus went back to compound **58**, this time to first install the terminal vinyl group (**58** to **73**). This was accomplished by ozonolysis of **58** to the aldehyde followed by reduction to primary alcohol **72** in 71% yield. Direct reductive workup of the secondary ozonide with sodium borohydride resulted in decomposition. Next, transformation to the triflate was performed with trifluoromethanesulfonic anhydride and 2,6-di-*tert*-butylpyridine (2,6-DTBP), followed by substitution with NaSePh. Oxidation with sodium periodate yielded olefin **73** after heating to 110 °C. Deprotection of the MOM-group under Lewis-acidic conditions gave the corresponding primary alcohol, which was oxidized with DMP to aldehyde **74** in 75% yield. Pinnick oxidation resulted in formation of the carboxylic acid and treatment with Ghosez's reagent transformed the carboxylic acid into acid chloride **75**. This was reacted with diazomethane for two days in a sealed tube at 23 °C to yield desired α-diazo ketone **76** in 65% yield (Scheme 12).



Scheme 12. Transformation to α-diazo ketone **76**.

To prevent the undesired fragmentation reaction of Scheme 11, this time Fmoc-deprotection was performed with DBU under protic conditions (dichloromethane and methanol at 23 °C), affording secondary amine **9**. This amine is fairly unstable and immediately had to be cyclized to bridged tertiary amine **7** in the N–H insertion reaction. The cyclization was accomplished by the addition of trifluoroacetic acid at –30 °C and yielded tertiary amine **7** in 54% after warming to 23 °C. The Stevens [2,3]-sigmatropic rearrangement to the 2-azabicyclo[3.3.1]nonane system **5** was performed under the following conditions: freshly prepared iodide **8**[67] is mixed with silver(I) triflate in dichloromethane at 0 °C followed by the addition of a mixture of proton sponge and tertiary amine **7**. These reaction conditions

forced the formation of ylide **6**, which directly rearranges to the 2-azabicyclo[3.3.1]nonane system **5** in 42% yield (Scheme 13).



Scheme 13. Stevens [2,3]-sigmatropic rearrangement for the construction of the 2-azabicyclo[3.3.1]nonane system **5**.

An intramolecular 1,4-addition of the vinyl iodide to the α,β-unsaturated ester was examined, but mostly decomposition of starting material was observed (Table 1). First, 1,4-additions with bis(1,5-cyclooctadiene)nickel(0) according to literature known procedures on comparable compounds[68-70] were examined (Entries 1-3). By using up to 6 equivalents of the nickel(0) species, a reduction of the nitroarene should be facilitated *in situ*. Unfortunately, only decomposition of the starting material was observed. Also Heck cyclization under reductive conditions (Entries 4-6) according to literature-known procedures[71-74] only resulted in decomposition of starting material. Efforts to promote a radical cyclization of vinyl iodide **5** resulted in re-isolation of starting material in the case of triethylborane[75] (Entry 7) and decomposition of starting material in the case of azobisisobutyronitrile[76] (Entry 8). Surprisingly, lithium iodine exchange with *tert*-butyl lithium[77] also resulted in re-isolation of starting material (Entries 9-10).

Table 1. Condition screening for the intramolecular 1,4-addition of compound **5**.

Entry	Reagent ([eq])	Base ([eq])	Additive ([eq])	Solv.	T [°C]	t [h]	Prod.
1	$Ni(COD)_2$ (1.5)	NEt_3 (3)	Et_3SiH (3)	MeCN	23	18	-[a]
2	$Ni(COD)_2$ (6.6)	NEt_3 (3)	LiCN (10)	DMF	23	2	-[a]
3	$Ni(COD)_2$ (6)	NEt_3 (10)	BHT (2)	MeCN/ DMF	23	0.5	-[a]
4	$Pd(OAc)_2$ (0.01)	K_2CO_3 (5)	Bu_4NCl (2.5), NaO_2CH (1.2)	DMF	80	0.5	-[a]
5	$Pd(OAc)_2$ (1)	-	PPh_3 (2)	NEt_3	90	0.2	-[a]
6	$Pd(dppf)Cl_2$ (1)	NEt_3 (3)	Et_3SiH (5)	DMF	90	1	-[a]
7	BEt_3 (0.2)	-	Bu_3SnH (1.2)	PhMe	23	20	**5**
8	AIBN (0.1)	-	Bu_3SnH (2)	PhH	80	1	-[a]
9	*t*BuLi (2.5)	-	-	Et_2O	–78	1	**5**
10	*t*BuLi (2.5)	-	HMPA (3)	Et_2O	–78	1	**5**

[a] Decomposition of starting material.

Under various conditions, selectivity problems with the aromatic nitro group were encountered, and therefore selective reduction of the nitro group and subsequent condensation to imine **79** was tested. Again under several reaction conditions, only decomposition of starting material was observed (Table 2). By using palladium on charcoal under a hydrogen atmosphere for one hour, partial hydration of the vinyl iodide besides starting material was observed (Entry 5). Nevertheless, selective reduction to the aniline was possible by using titanium(III) chloride[15, 78], but spontaneous cyclization to α,β-unsaturated lactam **77** was noticed due to acidic conditions (Entry 8, Scheme 14). If tin(II) chloride[79] was used as reducing agent, an incomplete reduction to nitrone **78** was observed in 61% yield (Entry 7, Scheme 14).

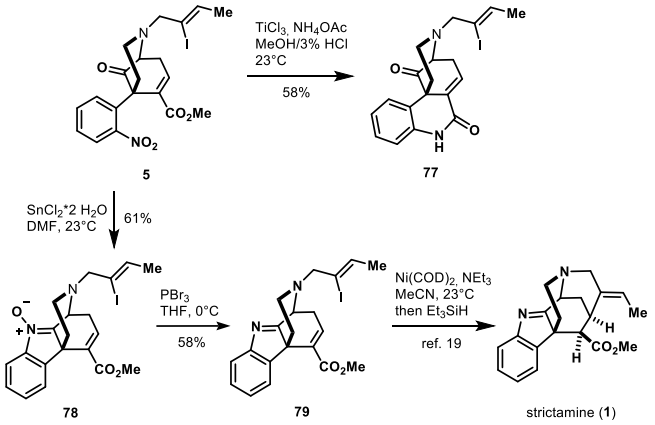
Table 2. Condition screening for the reduction of nitroarene **5**.

Entry	Reagent ([eq])	Additive ([eq])	Solvent	T [°C]	t [h]	Product
1	Zn (25)	-	HOAc	50	0.2	-[a]
2	Fe (5)	NH_4Cl (10)	EtOH/ H_2O	90	0.2	-[a]
3	Zn (70)	$CaCl_2$ (10)	MeOH	65	0.5	-[a]
4	PtO_2 (0.01)	H_2 (1 bar)	MeOH	23	1	-[a]
5	Pd/C (0.01)	H_2 (1 bar)	MeOH	23	1	**5**[b]
6	Ra/Ni (0.01)	-	MeOH	23	1	-[a]
7	$SnCl_2*2H_2O$ (10)	-	DMF	23	20	**78**
8	$TiCl_3$ (25)	HCl aq. (3%)	MeOH/ NH_4OAc (2.5 mol/L)	23	2.5	**77**

[a] Decomposition of starting material. [b] Partial hydration of vinyl iodide.

This nitrone was resistant to many further reductive conditions. Only after extensive experimentation, nitrone **78** could be

reduced to imine **79** in moderate yields under neutral conditions by using phosphorus tribromide[80] in dry tetrahydrofuran at 0 °C. In the last step, the vinyl iodide can be added in a 1,4-fashion to the α,β-unsaturated ester by using bis(1,5-cyclooctadiene)nickel(0) according to a literature-known procedure[19] (Scheme 14).



Scheme 14. Final transformations to strictamine (**1**).

Conclusions

We have accomplished a formal total synthesis of strictamine (**1**) based on 21 isolated steps (34 chemical transformations). The unexpected and undesired reactivities of some intermediates are illustrated by observed side reactions. Especially challenging was the suppression of fragmentation reactions under loss of the established quaternary carbon center. This reaction pathway was favored under many conditions and one of the major drawbacks during the development of this synthetic route to strictamine (**1**). We were able to show the versatility of a Stevens [2,3]-sigmatropic rearrangement for the construction of the 2-azabicyclo[3.3.1]nonane system **5**, which represents the key transformation in our synthesis of strictamine (**1**). Furthermore, a second Stevens [2,3]-sigmatropic rearrangement was demonstrated to be a powerful reaction to establish the correct relative stereochemistry of the highly substituted pyrrolidine **9**.

Experimental Section

Experimental and crystallographic details as well as compound characterization data and copies of ^{1}H and ^{13}C NMR spectra are available in the Supporting Information.

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Keywords: akuammiline alkaloids • monoterpenoid indole alkaloids • total synthesis • Stevens rearrangement • [2,3]-sigmatropic rearrangement

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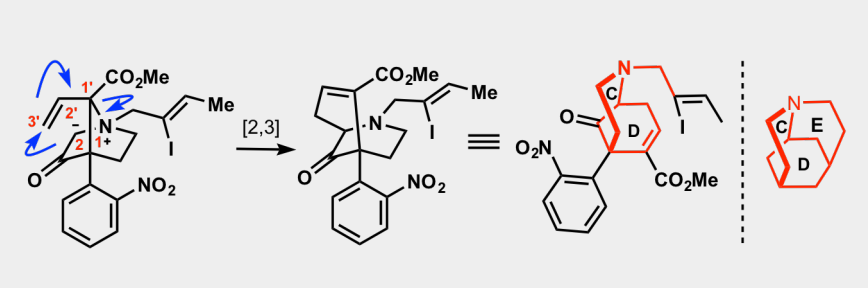

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Formal total synthesis of (±)-strictamine *via* [2,3]-sigmatropic Stevens rearrangements

To date, more than 100 congeners of the akuammiline alkaloid family have been isolated. Their signature structural element is a methanoquinolizidine moiety, a cage-like scaffold structurally related to adamantane. The structural variations of the family members originate from oxidative processes that mostly trigger rearrangements of the methanoquinolizidine motif. The family of the akuammiline alkaloids is best represented by strictamine. It bears the least functionalized carbon skeleton of all family members without lacking the signature structural motifs. Herein, we report the formal synthesis of stictamine *via* a Stevens [2,3]-sigmatropic rearrangement as a key step and the synthetic pitfalls related with its synthesis.