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FULL PAPER

Bioinspired divergent oxidative cyclizations of geissoschizine: total synthesis of (–)-17-nor-excelsinidine, (+)-16-*epi*-pleiocarpamine, (+)-16-hydroxymethyl-pleiocarpamine and (+)-taberdivarine H

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In memory of Robert M. Williams

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Abstract: We report a full account of our efforts towards bioinspired oxidative cyclizations of geissochizine and analogues to mimic the biosynthesis of the *mavacuran*, *akuammilan* and *excelsinidine* groups of monoterpene indole alkaloids. The construction of the A,B,C,D ring system of geissoschizine was first achieved by merging two known syntheses of this alkaloid. Modified Ma's oxidative conditions (KHMDS/I_2) applied directly to geissoschizine induced formation of the N4-C16 bond encountered in the excelsinidines core. Identical conditions applied to C16-dimethylmalonate-containing N4-quaternized substrates ended to the formation of the *mavacurans* core (N1-C16 bond). With this unified oxidative cyclization strategy: (–)-17-*nor*-excelsinidine, (+)-16-*epi*-pleiococarpamine, (+)-16-hydroxymethyl-pleiocarpamine, 16-formyl-pleiocarpamine and (+)-taberdivarine H were synthetized. We also report a shortened total synthesis of 16-*epi*-pleiocarpamine compared to our preliminary communication from a C16-monoester analog. Alternatively, 17-*nor*-excelsinidine was synthetized *via* an intramolecular nucleophilic substitution of a 7-membered ring α-chlorolactame prepared from 16-desformyl-geissoschizine.

Introduction

Monoterpene indole alkaloids are a structurally diverse family of more than 3000 known molecules, originating from strictosidine (**1**) as the single biosynthetic precursor (Scheme 1).[1] At a very early stage of the biosynthetic route, a deglucosylation of **1** release a reactive C-21 aldehyde. Then, condensation with the N4-secondary amine and the isomerization of the terminal C18=C19 double bond lead to the *corynanthe*-type skeleton [4,21-dehydrogeissoschizine (**2**) and geissoschizine (**3**)]. The tetracyclic *corynanthe* skeleton plays a pivotal biosynthetic role as divergent biosynthetic routes from **2** or **3** lead to a large diversity of pentacyclic frameworks (Scheme 1).[1] On one hand from **2**, cyclization between the C17-aldehyde and the unsaturated iminium (or the corresponding dienamine) furnishes the *heteroyohimban* (ajmalicine) and *yohimban* (yohimbine **4**, reserpine) alkaloids.[2] On the other hand, reduction of the N4=C21 iminium of **2** delivers geissoschizine (**3**) which is central to generate structural diversity *via* divergent oxidative cyclizations. The C16-formyl ester moiety is pivotal in these oxidative couplings. The formation of the C5-C16 bond yields the *sarpagan* alkaloids such as polyneuridine aldehyde (**5**) *via* an oxidation of the N4-quinolizidine into a N4=C5 iminium.[3] Alternatively, oxidation of this N4-tertiary amine could also forge the N4-C16 bond and lead to the recently discovered excelsinidines (**6**, **7**).[4]

Oxidative cyclizations between the C16 formyl ester and two different positions of the indole nucleus, leading either to a C-C or a C-N bond formation are also possible. [5,6] The coupling with the C7-indolic position delivers the *akuammilan* alkaloids (rhazimal **8**, rhazimol **9**, akuammiline **10**, strictamine **11**) which are currently popular synthetic targets.[7] Importantly, the *strychnan* framework (akuammicine **12**) is postulated to arise from a skeletal rearrangement of the *akuammilan* scaffold,[8] thus constituting the main biosynthetic continuum of the monoterpene indole alkaloids.[1] Coupling of C16 with the N1-indolic position results in the formation of the *mavacuran* skeleton.[9,10] After the formation of the N1-C16 bond and postulated biosynthetic intermediate **13**, reduction of the aldehyde and desformylation would furnished 16-hydroxymethyl-pleiocarpamine (**14**) and pleiocarpamine (**15**). The indolyl-ester stereocenter of the latter could be epimerized into 16-*epi*-pleiocarpamine (**16**). Some members of the mavacurans such as *C*-mavacurine (**17**) and taberdivarine H (**18**) display a N4-methyl ammonium.

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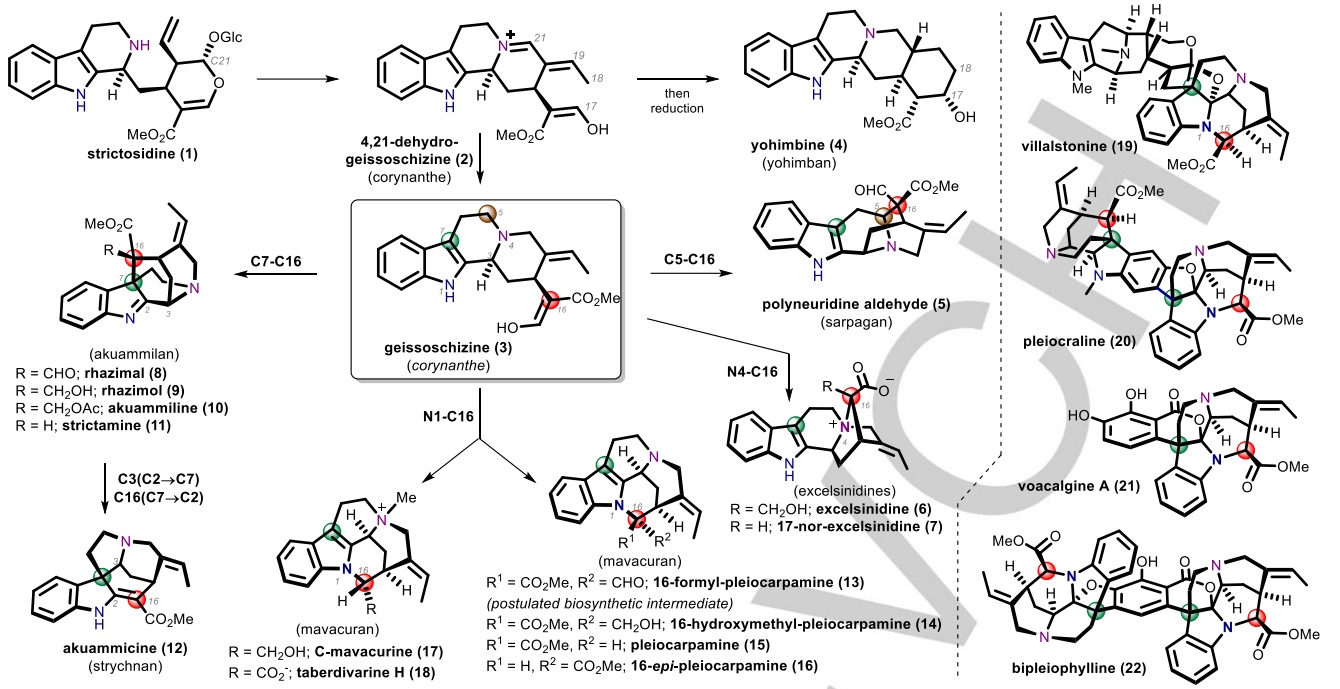
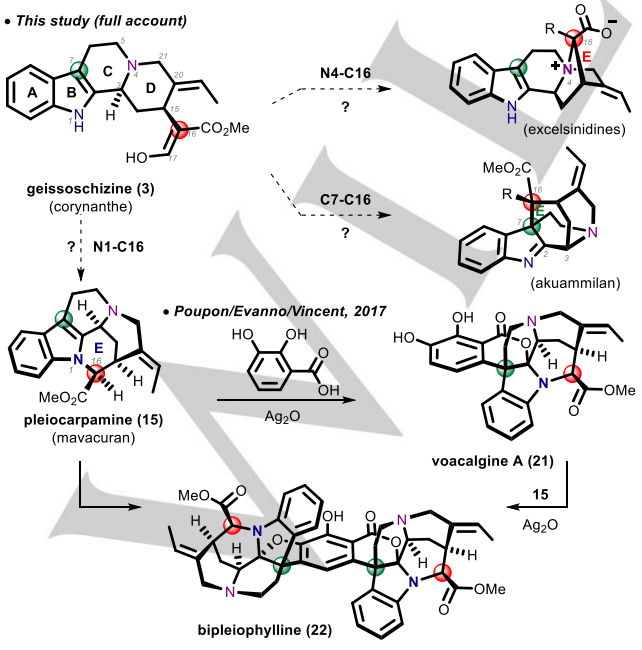


Scheme 1. Pivotal role of geissoschizine in the biosynthesis of several families of monoterpene indole alkaloids

Among those compounds, pleiocarpamine (**15**) is a particularly appealing synthetic target since it is found as a subunit of several of multimeric indole alkaloids (*eg* villalstonine **19**, pleiocraline **20**, voacalgine A **21** or bipleiophylline **22**).[11]

Actually, in 2017 we accomplished the bioinspired hemisyntheses of voacalgine A (**21**) and bipleiophylline (**22**) from pleiocarpamine (**15**) isolated from natural sources (Scheme 2).[12] In order to accomplish a full total synthesis of bipleiophylline which is a particularly intricate bis-indole alkaloid, we embarked in the total synthesis of pleiocarpamine (**15**).[13] Following an approach inspired by its biosynthesis, we sought to study the oxidative cyclization of the complete geissoschizine scaffold.[14]



Scheme 2. Our synthetic approach based on bioinspired oxidative cyclizations of geissoschizine.

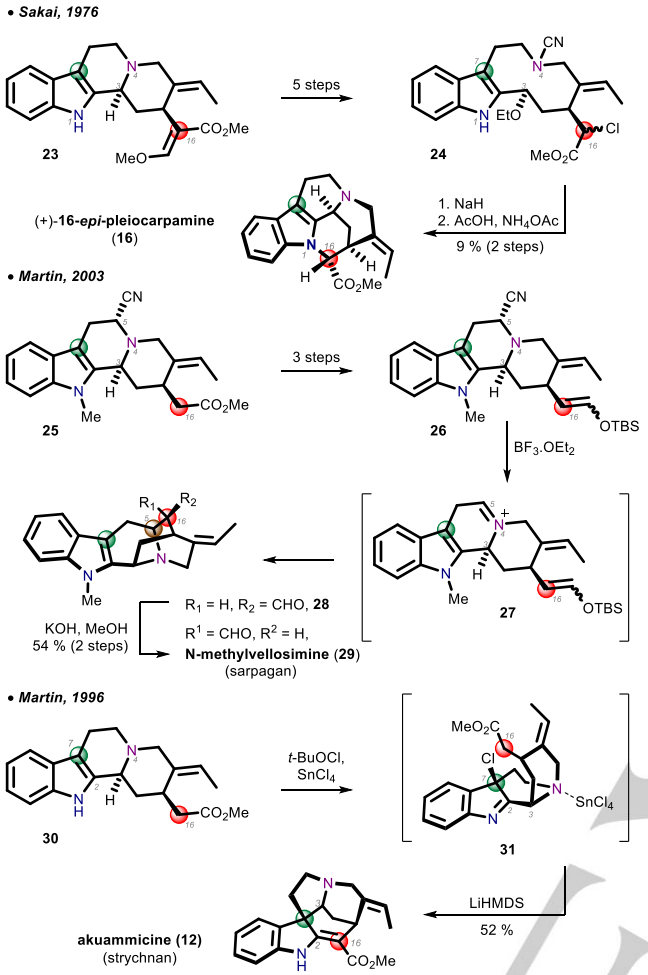
In relation with our interest in the bioinspired synthesis of monoterpene indole alkaloids,[8a,15] we would like to describe here, a full account of our efforts towards this goal. Our collaborative work recently led to the total synthesis of (–)-17-nor-excelsinidine (**7**),[16] (+)-16-*epi*-pleiocarpamine (**16**), (+)-16-hydroxy-methyl-pleiocarpamine (**14**) and (+)-taberdivarine H (**18**).[17]

Several synthetic studies mimicking the key oxidative couplings of the biosynthesis presented in scheme 1 were reported but on incomplete scaffolds.[18,19] A rare number of approaches were performed on the complete geissoschizine skeleton (Scheme 3). During the hemisynthesis of 16-*epi*-pleiocarpamine (**16**), Sakai and Shinma had to cleave the C3-N4 bond of **23** before effecting a nucleophilic substitution of 16-chloroester **24** by the indolic N1-nitrogen, and then reconstructed the C3-N4 bond.[13c,d] Harley-Mason used a similar strategy a few years later.[13e]

The *sarpagan* skeleton was accessed by van Tamelen and Martin *via* a biomimetic addition of an aldehyde or its corresponding enol ether onto a N4=C5 iminium (**27**).[20] However, the latter was not generated by selective oxidation of geissoschizine but from the α-amino-acid moiety of tryptophan (van Tamelen)[20b] or the corresponding α-aminonitrile **26** (Martin) [20a] leading to (+)-*N*-methylvellosimine (**29**).

Martin effected the first straightforward oxidative cyclization of the geissoschizine scaffold which resulted in the selective formation of akuammicine [(**12**), *strychan* skeleton].[21] Electrophilic chlorination of 16-desformyl-geissoschizine (**30**) in the presence of $SnCl_4$, was followed by the deprotonation of the C16-ester to induce the addition of the generated enolate onto 7-chloroindolenine **31**. It is debatable, whether the enolate adds

directly to the C2 imine or to the C7-chloride accompanied with a skeletal reorganisation.

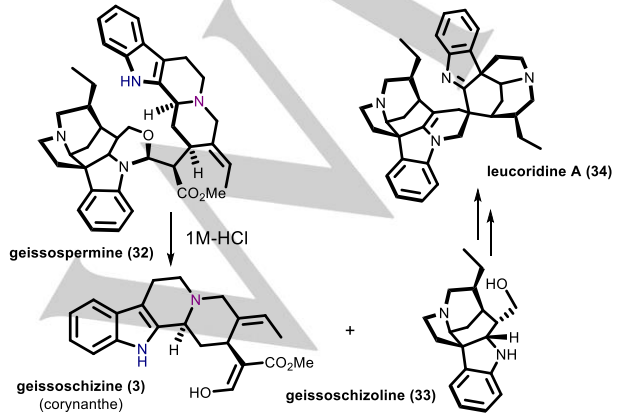


Scheme 3. Previous approaches to the oxidative cyclizations of the geissoschizine framework.

Results and Discussion

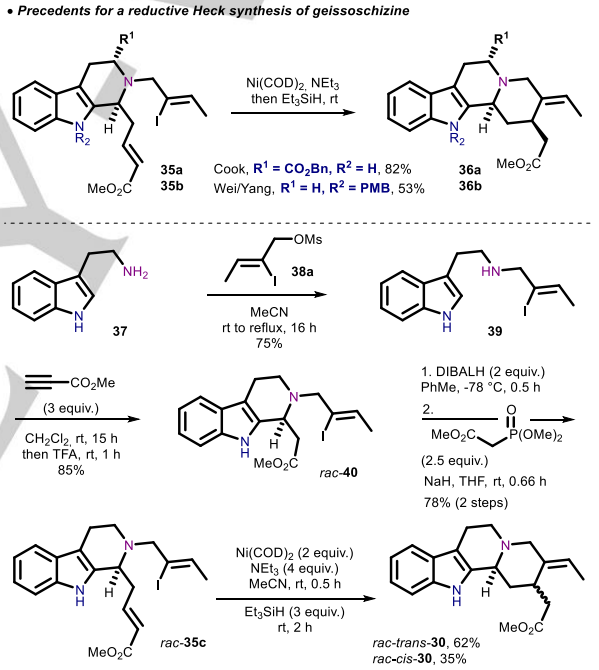
Access to the geissoschizine scaffold

In order to evaluate our oxidative cyclization strategies, we first needed to have geissoschizine in hands. A first batch of about 100 mg of geissoschizine (**3**) itself was produced by the hydrolysis of the natural product geissospermine (**32,** Scheme 4).[22] Geissoschizoline (**33**), the second subunit released was valorized for the biomimetic assembly of leucoridine A (**34**).[23]



Scheme 4. Hydrolysis of geissospermine (**32**).

However, due to a limited stock of the latter, the supply line of geissoschizine (**3**) was secured by synthesis. Several efficient total syntheses of enantioenriched geissoschizine (**3**) are indeed known.[24] The nickel-mediated reductive Heck reaction from vinyl iodide **35a**[25] employed by Cook is an attractive feature to introduce stereoselectively the *E*-ethylidene in **36a** (Scheme 5).[24d] To bypass the use of tryptophan as starting material and the necessity to remove its carboxylate after the key reaction, we used tryptamine **37** as starting material (Scheme 5). After coupling with allylmesylate **38a**,[26] allylated tryptamine **39** was added to methylpropiolate in a 1,4-fashion.[27] Then, addition of TFA induced a Pictet-Spengler type reaction *via* an iminium to generate β-tetrahydrocarboline *rac*-**40** in a racemic form. It is reasonable to think that an enantioselective Pictet-Spengler reaction could be implemented.[28] The ester of *rac*-**40** was then converted to a α,β-unsaturated ester *via* reduction of the aldehyde followed by a Horner-Wadsworth-Emmons olefination.

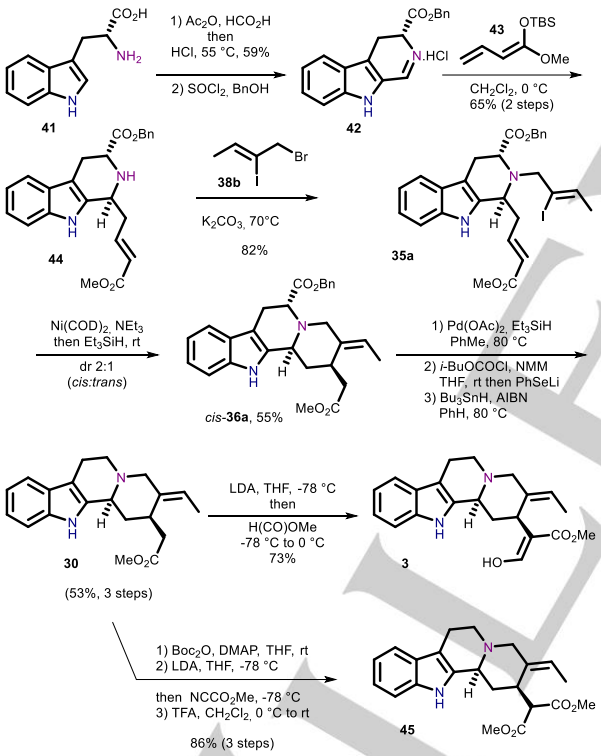


Scheme 5. Initial attempts for the synthesis of geissoschizine.

Disappointingly, the nickel-mediated intramolecular 1,4-addition of the vinyl iodide of *rac*-**35c** to the α,β-unsaturated ester led to a 1.8:1 mixture of diastereoisomers of *rac*-**30** with the undesired *trans* product as the major compound. Evidently, it seems that the carboxylate in **35a** from tryptophan controls the diastereoselectivity of the reductive Heck reaction. From the work of Wei and Yang, the presence of a PMB group on the indolic nitrogen of **35b** could also direct the *cis*-selectivity (Scheme 5), however introduction and removal of the PMB group would lengthen the synthetic sequence.[24f]

With this information in mind, we thus decided to reproduce the nickel-mediated reaction of Cook on D-tryptophan-derived vinyl iodide **35a**. To improve the access of the latter, we reproduced

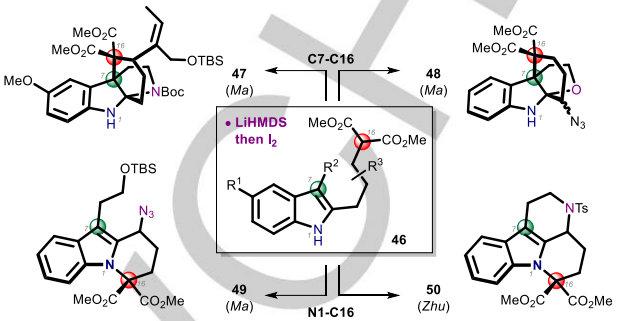
the Martin's *trans*-selective vinylogous Mannich addition of silyl ketene acetal **43** onto dihydro-β-carboline **42** derived from D-tryptophan (**41**, Scheme 6).[24c] Nucleophilic substitution of allyl bromide **38b** with the N4-secondary amine allowed to intercept Cook's intermediate **35a**. Indeed, the reductive Heck reaction allowed to isolate the desired *cis*-isomer **36a** as the major product in a useful yield of 55%. Nevertheless, it should be noted that the diastereoselectivity is moderate with a *cis*/*trans* ratio of 2:1. Removal of the carboxylate was achieved as previously described in three steps: a reductive debenzylation and formation of a selenoester were followed by a tributyltin hydride-mediated decarboxylation. Useful quantities of pivotal 16-desformyl-geissoschizine **30** were thus secured in an efficient manner in several batches, building on the previous Martin's and Cook's works. Geissoschizine (**3**) itself was accessed by a known direct formylation of the ester at C16 in presence of LDA. We also wanted to get a hand on malonate analog **45** of geissoschizine. In this case, the direct carboxylation resulted in the formation of the additional unwanted indolic methyl carbamate. Therefore, the indole ring was protected with a Boc group, before the formation of the C16-malonate with methyl cyanoformate and LDA and, finally deprotected with TFA to yield **45**.



Scheme 6. Synthesis of the geissoschizine scaffold based on Martin's and Cook's work.

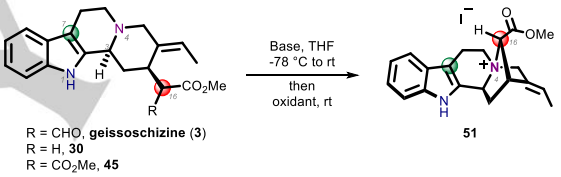
Direct oxidative cyclization of geissoschizine: total synthesis of (–)-17-nor-excelsinidine

With geissoschizine in hand, the stage was set to study its bioinspired oxidative cyclization. It seemed logical to try the process first described by Ma to form the C7-C16 bond of the *akuammilan* alkaloids on simplified substrates **46** leading to **47** or **48** (Scheme 7).[18] This oxidative coupling proceeds *via* the double deprotonation of a C16-malonate and of the NH indole with LiHMDS, followed by addition of I_2 as oxidant to presumably form a bis-radical intermediate. This oxidative coupling is substrate dependent since in the cases of **49** and **50**, coupling of the C16-malonate with the N1 indolic nitrogen was observed respectively by Ma[18b] and Zhu.[19a]



Scheme 7. Ma's indole-malonate intramolecular oxidative coupling.

Table 1. Oxidative cyclization of geissoschizine into 17-*nor*-excelsinidine methyl ester **51**.



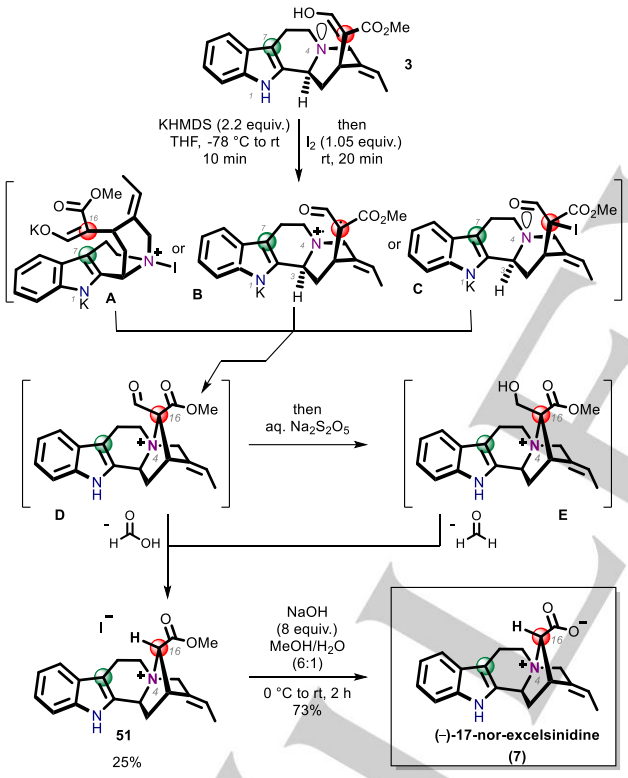
Entry	Substrate	Base then Oxidant	Yield **51**[a]
1	**3**	KHMDS (2.2 equiv.) then I_2 (1.05 equiv.)	25%
2	**3**	KHMDS (1.1 equiv.) then I_2 (1.05 equiv.)	23%
3	**3**	LiHMDS (2.4 equiv.) then I_2 (1 equiv.)	not detected
4	**3**	No base I_2 (1 equiv.)	not detected
5	**3**	KHMDS (2.2 equiv.) then PIFA (1.05 equiv.)	not detected
6	**30**	KHMDS (2.2 equiv.) then I_2 (1.05 equiv.)	not detected
7	**45**	KHMDS or LiHMDS (2.2 equiv.) then I_2 (1.05 equiv.)	not detected

[a] Isolated yield.

Since at that time, we did not have LiHMDS in hand, we used KHMDS as base instead which was decisive to observe any oxidative cyclization (Table 1, entry 1). Deprotonation of geissoschizine (**3**) with 2.2 equivalents of KHMDS, followed by addition of 1.05 equivalent of I_2 did not lead to pleiocarpamine or strictamine as planned but to the methyl ester of 17-nor-excelsnidine (**51**) *via* an N4-C16 unexpected bond formation and desformylation at C16.[29] While this result was not what we have

expected, it was still a useful discovery since the excelsinidine skeleton was accessed for the first time. The indole moiety being not involved in this oxidative coupling, the deprotonation of this heterocycle may probably not be needed. Indeed, with only 1.1 equivalent of KHMDS, a similar yield of 23% was obtained (entry 2). Curiously, when we switched from KHMDS to LiHMDS, the base of the original Ma's condition, no oxidative coupling was observed (entry 3). The absence of base did not allow the oxidative cyclization to proceed either (entry 4). Replacing I_2 as oxidant by PIFA did not lead to a favorable outcome (entry 5).[19] Intriguingly, the oxidative cyclization is specific to geissoschizine itself: 16-desformylgeissoschizine (**30**) and malonate analog **45** in presence of LiHMDS or KHMDS and I_2 as oxidant could not lead to any pentacyclic scaffold (Table 1, entries 6, 7).

Retrospectively, the formation of the N4-C16 bond is not surprising. NMR conformation studies have demonstrated that geissoschizine adopts a C3-N4 *trans* conformation in which the C16-formyl ester or the N4 nitrogen are in proximity.[30] More importantly, the N4-tertiary amine of **3** is more reactive than in previous substrates **46** in which the lone pair of the nitrogen is sequestered.



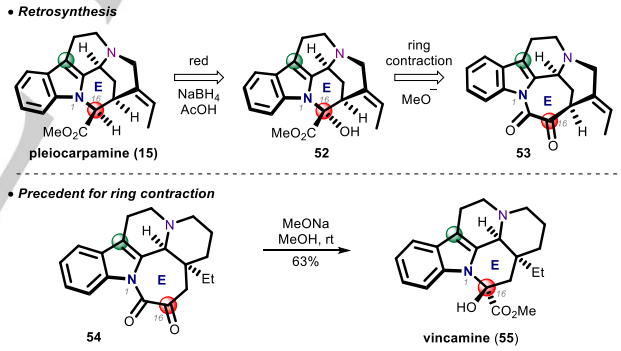
Scheme 8. Total synthesis of (–)-17-*nor*-excelsinidine by oxidative cyclization of geissoschizine.

We could postulate than reaction of tertiary amine with I_2 would lead to *N*-iodoamonium **A** which could succumb to the addition of the C16-potassium enolate to complete the cyclization into **D** (Scheme 8).[31] It is also possible to envision that the N4-amine and the C16-enolate could be oxidized into respectively a radical cation and a free radical (intermediate **B**) that would associate to form the N4-C16 bond. Alternatively, the C16-enolate could react with I_2 to form 16-iodoformylester **C** which can then be engaged in a nucleophilic substitution by the nucleophilic N4-tertiary amine. This last hypothesis is less likely based on the observation of Zhu.[19] We believe that the spontaneous and biomimetic desformylation of intermediate **D** occurs during the aqueous workup with sodium metabisulfite used to reduce the excess of I_2. Addition of water to the aldehyde of **D** would generate formic acid. Otherwise, reduction of the aldehyde of **D** into primary alcohol **E** with sodium metabisulfite would be associated with release of formaldehyde.

Finally, methyl ester **51** was saponified to complete the first total synthesis of zwitterionic (–)-17-nor-excelsinidine (**7**) in 11 steps from **41** (Scheme 8).

Rearrangement of a seven-membered ring lactam: total synthesis of (–)-17-nor-excelsinidine

The direct oxidation of geissoschizine does not lead to the *mavacurans* for, among hypothetical reasons, conformational considerations. We consequently planned to overcome this issue by bringing the N1 indolic nitrogen and the C16-carbon in close proximity to favor their coupling (Scheme 9). We were inspired by the synthesis of vincamine (**55**) for which the 6-membered **E** ring was formed by the ring contraction of the 7-membered-ring α-ketolactam **54** under the action of sodium methoxide.[32] Accordingly, our retrosynthesis to obtain pleiocarpamine, implied protonation of the hydroxyl group of **52** and stereoselective addition of a hydride into the more accessible face of the resulting carbocation. 16-Hydroxy-pleiocarpamine **52** would, indeed, arise from the ring contraction of keto-lactam **53**.



Scheme 9. Ring contraction approach towards pleiocarpamine from α-ketolactam **53**.

The first task to study this ring contraction approach consisted in the synthesis of α-ketolactam **53**. Two routes were envisioned to access this target (Scheme 10). Cyclization of tetracyclic ketoester **56** seemed to be a reasonable approach. The latter was sought to be accessed either *via* a palladium-catalyzed intramolecular α-vinylation of the tricyclic keto-ester **57** with a iodopropenyl moiety[33] or a 6-exo-*dig* cyclization of enol ether **58** onto the propynyl functionality (Conia-ene-type reaction) with a cationic gold catalyst[34] to ensure the stereoselective formation of the *E*-ethylidene *via* intermediate **F**. As an alternative, lactamization of 16-desformyl-geissoschizine **30** into **59** could be followed by α-oxidation into ketolactam **53**.

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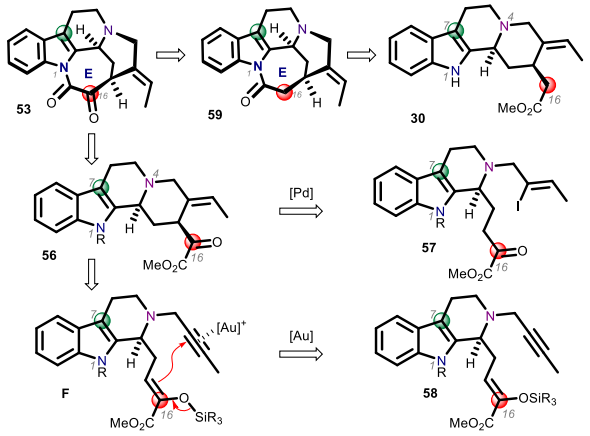
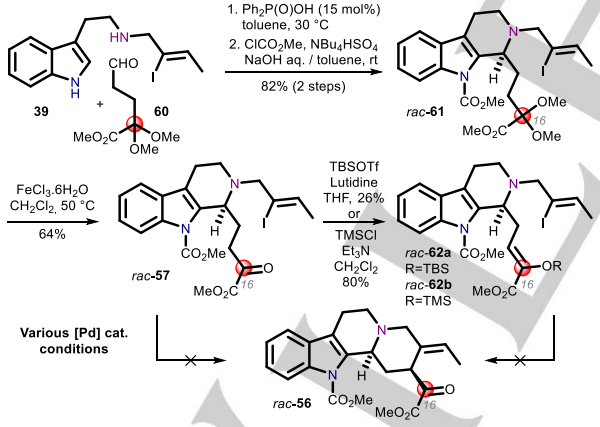


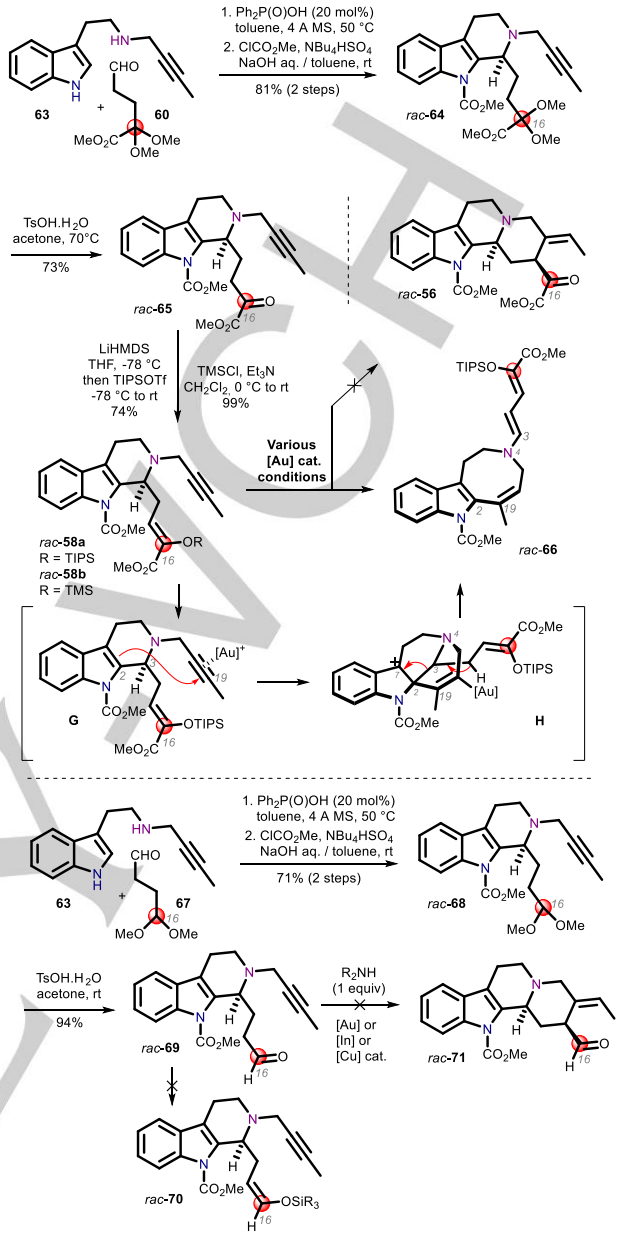
Scheme 10. Retrosynthesis to access 7-membered ring ketolactam **53**.

We first tried to access tetracyclic α-ketoester *rac*-**56** *via* palladium-catalyzed cyclization of vinyliodide *rac*-**57** (Scheme 11). The latter was obtained in a racemic manner using a Pictet-Spengler reaction between *N*-functionalized tryptamine **39**[33a] and aldehyde **60**[35] which contains an α,α-dimethoxyester. After protection of the indolic nitrogen, the acetal was hydrolyzed with iron(III) chloride hexahydrate. Unfortunately, all our attempts to effect the intramolecular α-vinylation of ketoester *rac*-**57** or of the corresponding enol ethers *rac*-**62a/b** failed (see SI for details). Most of the times, Claisen-type dimerization of *rac*-**57** or deallylation of the N4-amine were observed. It is in stark contrast with the reported successful α-vinylation of a very similar substrate bearing a C16-methylketone instead of the ketoester.[33a]



Scheme 11. Attempts towards the synthesis of tetracyclic *rac*-**56** via Pd-catalyzed intramolecular α-vinylation of ketoester *rac*-**57**.

We thus turned to our second option to access *rac*-**56** using a Conia-ene-type reaction (Scheme 12). Pictet-Spengler reaction between propargylated tryptamine **63** and aldehyde **60** yielded acetal *rac*-**64**. Then, hydrolysis catalyzed by *para*-toluene sulfonic acid in acetone, released α-ketoester *rac*-**65**. The corresponding silylenol ethers *rac*-**58a/b** were then formed in order to test the 6-*exo*-*dig* cyclization leading to *rac*-**56**.



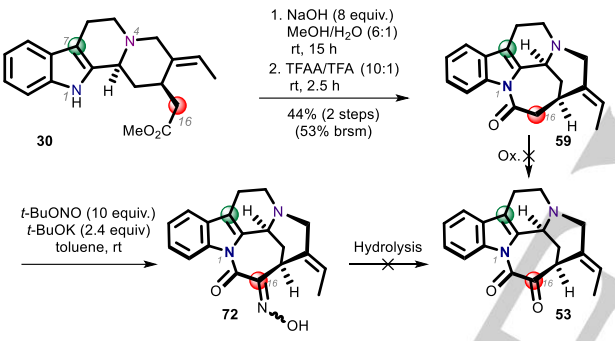
Scheme 12. Attempts towards the synthesis of tetracyclic *rac*-**56** via Au-catalyzed cyclization of propynyl-containing enolethers *rac*-**58**.

Unfortunately, various cationic gold catalysts were evaluated without success (see SI for details).[34a-c] The enol ether moiety derived from the α-ketoester is not nucleophilic enough to add to the gold-activated alkyne and instead, we unexpectedly obtained the 8-membered ring-containing indole *rac*-**66**. Despite the presence of an electron-withdrawing group on the nitrogen, the indole added to the alkyne (**G**) leading to carbocation **H**. Rearomatization was possible, inducing cleavage of the C2-C3 bond and, leading to the dienamine part of *rac*-**66**. Such a transformation has rarely been observed.[36]

Since the silyl enol ethers of *rac*-**58a/b** are not reactive enough to intramolecularly add to the alkyne, we envisioned to replace it by the aldehyde-derived silyl enol ethers *rac*-**70**. Aldehyde *rac*-**69** was prepared via the Pictet-Spengler reaction between **63** and

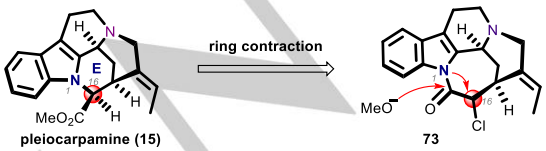
mono-protected dialdehyde **67**[37] and hydrolysis of dimethyl acetal *rac*-**68**. Despite several attempts, we were unable to convert the aldehyde into its silyl enol ethers *rac*-**70**. We also unsuccessfully, turned our attention towards the generation of an enamine intermediate with a secondary amine to induce the gold-catalyzed direct α-addition of the aldehyde to the alkyne.[34d] Only dimerization was observed *via* aldolization/crotonisation (see SI for details). The use of an indium or copper catalyst gave similar results. [34e,f]

Facing the impossibility to obtain ketoester **56**, we believed that α-ketolactam **53** could be obtained by α-oxidation of lactam **59** (Scheme 13). The latter was indeed obtained by cyclization of 16-desformylgeissoschizine **30**. Saponification of the latter was followed by the formation of an activated mixed anhydride in presence of trifluoroacetic anhydride (TFAA) to promote lactamization into **59**. Due to the poor solubility of the carboxylic acid resulting from **30** in pure TFAA, addition of trifluoroacetic acid was required to ensure reproducibility of the cyclization. We were unable to obtain **53** by direct oxidation of **59**,[38] we therefore turned towards a two-step procedure previously used in the synthesis of vincamine.[32a] Oxidation of lactam **59** with *t*-butyl nitrite delivered crude α-ketoxime ester **72**.[39] Despite several attempts, hydrolysis of the latter into **53** did not meet with success.



Scheme 13. Attempts to form ketolactam **53** from 16-desformylgeissoschizine (**30**).

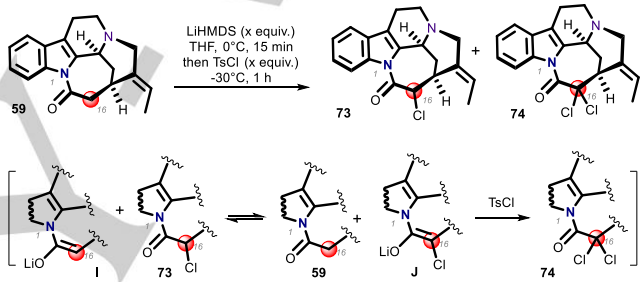
Having failed to produce α-ketolactam **53**, another revision of our strategy was needed which involved a formal *aza*-Favorskii-type rearrangement.[40] It became apparent to us that performing the ring contraction on α-chlorolactam **73** could be advantageous over the ketoester strategy by saving few steps (Scheme 14). Oxidation of **59** into α-chlorolactam **73** should require a single step and the ring contraction of **73** should deliver directly pleiocarpamine as we would not have to reduce 16-hydroxyl-pleiocarpamine **52** (see Scheme 9).



Scheme 14. Ring contraction approach towards pleiocarpamine from α-chlorolactam **73**.

α-Chloration of lactam **59** was first undertaken *via* the formation of an enolate with LiHMDS and trapping with TsCl which was previously developed for the α-chlorination of ketones (Table 2).[41] A 2:1 mixture of the targeted α-chlorolactam **73** with its dichloro analogue **74** was obtained with 1.2 equivalent of TsCl (entry 1). Counterintuitively, a large excess of TsCl (3 equivalents, entries 2,3) allowed to dramatically improve the selectivity in favor of the monochloro compound **73**. It could be explained by the fact that if the trapping of enolate **I** with the chlorinating reagent is too slow, persistent enolate **I** could deprotonate the formed monochlorolactam **73** to generate α-chloro enolate **J** which could react with TsCl and lead to dichlorolactam **74**. Fast addition of an excess of the electrophilic chlorine reagent allows to rapidly trap the totality of enolate **I** before the latter could transform **73** into **J**. A single but undetermined C16-diastereoisomer of **73** was formed. Therefore, it seems logical to assume that an α-chlorination on the convex face of the pentacyclic framework occurred.

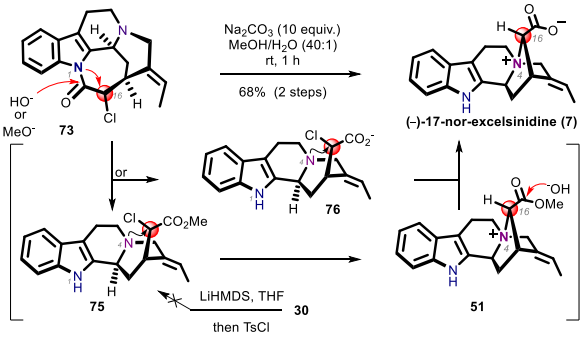
Table 2. α-chloration of lactam **59**.



Entry	LiHMDS	TsCl	Yield **73**+**74**[a]	ratio **73**/**74**
1	1.2 equiv.	1.2 equiv.	73%	2:1
2	1.0 equiv.	3.0 equiv.	54%	> 95:5
3	1.2 equiv.	3.0 equiv.	69%	> 95:5

[a] Isolated yield based on **59**.

Everything was in place to test the ring contraction step in methanol with sodium carbonate in presence of traces of water (Scheme 15). Unlike what we expected, the contraction of the 7-membered ring lactam into a 6-membered ring related to pleiocarpamine (**15**) did not take place despite the proximity of the N1 indolic nitrogen and the C16 carbon. Instead, we obtained directly (–)-17-nor-excelsinidine (**7**) and we, therefore, accomplished our second total synthesis of this natural product in 12 steps from **41**. We believe that a methoxide or a hydroxide adds on the carbonyl of the lactam to break the amide bond and form α-chloro ester **75** or α-chloro acid **76**. Nucleophilic substitution of the chloride by the N4-tertiary amine delivered either directly (–)-17-nor-excelsinidine (**7**) or its methyl ester **51** that is *in-situ* saponified into the natural product. While this synthesis necessitates one more step than the direct oxidation of geissoschizine, the overall yield from 16-desformygeissoschizine (**30**) is better (30% instead of 17%). It should be noted that in order to shortcut this overall sequence, we attempted, but failed, to directly chlorinate 16-desformylgeissoschizine **30** into **75**.

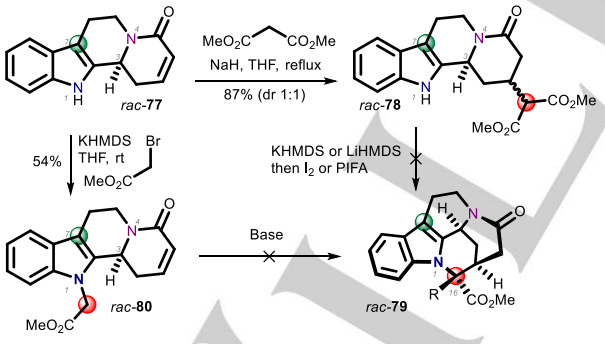


Scheme 15. Total synthesis of (–)-17-*nor*-excelsinidine (**7**) *via* rearrangement of α-chlorolactam **73**.

Oxidative cyclization of N4-geissoschizinium salts: total synthesis of (+)-16-hydroxymethyl-pleiocarpamine, (+)-16-*epi*-pleiocarpamine and (+)-taberdivarine H.

Considering the results of Ma and Zhu, we believed that the I_2/KHMDS-induced coupling of the C16 carbon with the indole nucleus of **3** was still possible.[18,19]

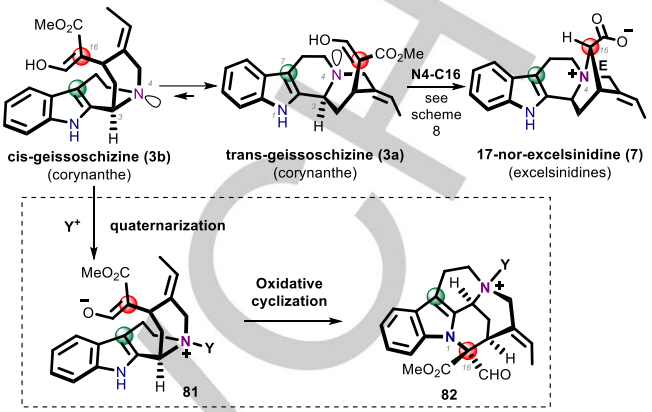
At first sight, sequestration of the lone pair of the N4-tertiary amine should avoid its reaction with the C16-formyl ester: switching from a tertiary amine to an amide functionality at N4 seemed appropriate. Therefore, we decided to attempt the oxidative cyclization on tetracyclic lactam *rac*-**78** which synthesis was described by Martin through the Michael addition of dimethyl malonate onto α,β-unsaturated lactam *rac*-**77** (Scheme 16).[42] Unfortunately, no oxidative cyclization to *rac*-**79** was observed in various conditions. Complementary to this approach, we also observed that *rac*-**79** couldn't be obtained *via* the intramolecular Michael addition from α-indolyester *rac*-**80** which aroused from the *N*-alkylation of rac-**77** with bromomethylacetate.[42]



Scheme 16. Attempts of cyclisation of tetracyclic lactams.

Obviously, masking the reactivity of the N4-tertiary amine is not the only hurdle to overcome to permit the formation of the key N1-C16 bond from a tetracyclic geissoschizine analog. It is also important to consider conformational parameters.

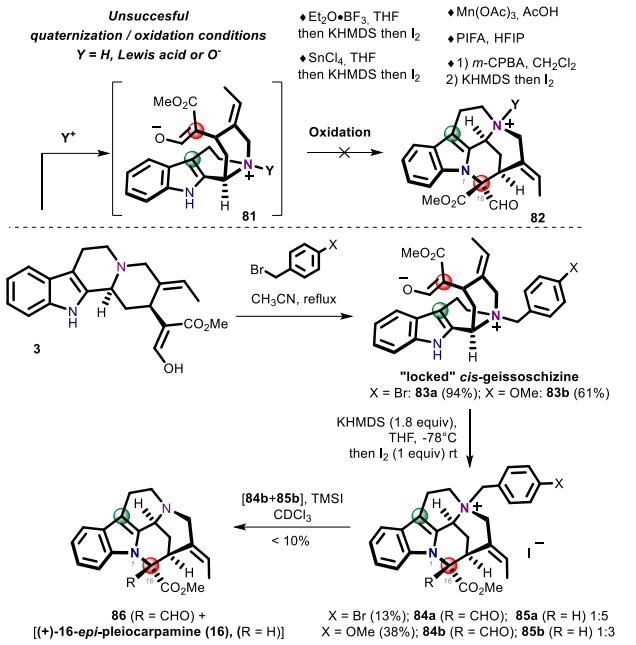
Geissochizine, as above mentioned, adopts in solution a C3-N4 *trans*-conformation **3a** suitable for the selective formation of the N4-C16 bond of the excelsinidines core.[30] However, a *cis*-conformation **3b** is needed to bring closer the C16-formyl ester and the indole nucleus to favor their oxidative coupling. We reasoned that quaternization of the aliphatic nitrogen N4 into **81** would inhibit its reactivity and more importantly would lock the required C3-N4 *cis*-conformation of geissochizine in order to access pentacycle **82** (Scheme 17).



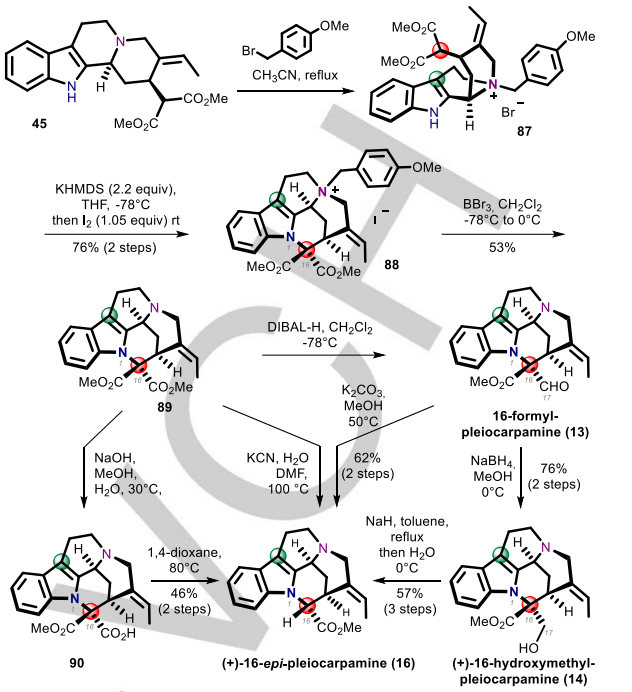
Scheme 17. Quaternization/oxidation strategy from geissoschizine

At first, we attempted to *in-situ* complex the N4 nitrogen of **3** with Lewis acids such as boron trifluoride etherate or tin tetrachloride (Scheme 18). Unfortunately, the oxidative coupling conditions resulted either in the recovery of the starting material or to the formation of 17-nor-excelsinidine methyl ester **51**. Protonation of the N4-tertiary amine was sought when we subjected geissoschizine to $Mn(OAc)_3$ in acetic acid but without success. Performing the oxidation with PIFA in HFIP which is able to induce hydrogen-bond interactions was also disappointing. Formation of geissoschizine *N*-oxide was then envisioned. Unprotected **3**, reacts cleanly with *m*-CPBA, but the reaction product could not be purified by flash chromatography.

Helpfully, Eckermann and Gaich demonstrated that benzylation of geissoschizine (**3**) with 4-bromobenzyl bromide effectively lock the C3-N4 *cis*-conformation of **83a** and insure proximity between the C16 carbon and the indole nucleus.[43] We thus applied the oxidative conditions (KHMDS, then I_2) to ammonium **83a**. The *mavacuran* skeleton was selectively formed as a mixture of **84a** and deformyl counterpart **85a** *via* the expected N1-C16 bond formation. Unfortunately, the 4-bromobenzyl removal by methanolysis was inoperative, thus, we turned to quaternization of geissochizine (**3**) with a PMB group. The N1-C16 oxidative coupling performed on **83b**, resulted on similar results and a mixture of **84b** and **85b** was obtained. The reaction revealed to be stereoselective but, careful NMR analysis done on the mixture of products **84b** and **85b** indicated that both presents an 16-*epi*-pleiocarpamine-type stereochemistry rather than the pleiocarpamine one. The quaternary amine was then restored by the action of TMS iodide on the mixture of **84b** and deformyl **85b** which delivered 16-*epi*-pleiocarpamine (**16**) and 16-*epi*-16-formyl-pleiocarpamine (**86**). More efficient and convenient deprotection conditions were found latter during the improvement of the synthesis.



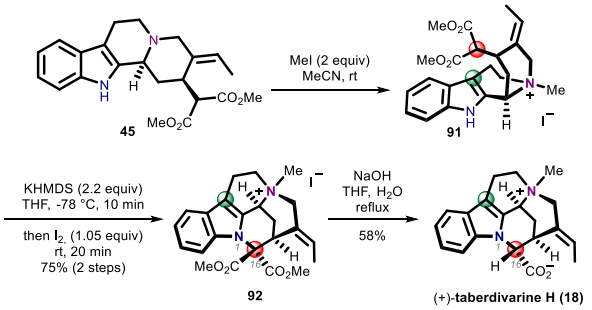
Scheme 18. Synthesis of 16-*epi*-pleiocarpamine (**16**) by oxidative cyclization of N-PMB geissoschizine.



Scheme 19. Total synthesis of 16-formyl-pleiocarpamine (**13**), (+)-16-hydroxymethyl-pleiocarpamine (**14**) and (+)-16-*epi*-pleiocarpamine (**16**).

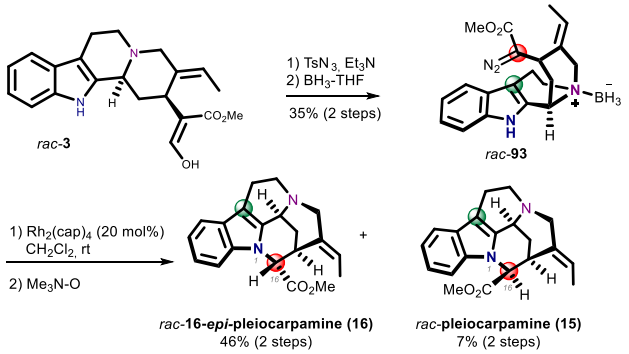
Despite the efficiency of the N1-C16 coupling step, the uncontrolled deformylation of **84b** eroded the reaction yield. To circumvent this, cyclization of symmetrical diester **45** was envisioned with also the aim to fix the C16 stereochemistry at a later stage (Scheme 19). The same N4-benzylation and N1-C16 cyclization sequence applied to malonate **45** afforded the *mavacuran*-type product **88** with a very satisfying 76% yield over 2 steps. The PMB removal was improved with the use of BBr_3, to give **89** with a 53% yield. To reach pleiocarpamine (**15**) our initial synthetic target, we reasoned that the lesser hindered α-ester of **89** could selectively be modified. At first, a diastereoselective decarboxylation strategy was envisioned. Krapcho decarboxylation of **89** with KCN delivered (+)-16-*epi*-pleiocarpamine (**16**) in 15 steps from **41**. We assumed that cyanide effectively reacts with the expected α-ester but, the transient enol formed during the decarboxylation is converted to the more thermodynamically stable epimer **16**. This hypothesis was confirmed when the α-ester of **89** was selectively saponified, into acid **90**. Again, decarboxylation of **90** ended to **16**. At this stage, the synthesis of 16-hydroxymethyl-pleiocarpamine (**14**) was targeted as Quirion claimed that its deformylation produced pleiocarpamine (**15**).[9c] Reduction of **89** by DIBAL-H selectively delivered 16-formyl-pleiocarpamine (**13**) which is postulated to be the direct product of oxidative cyclization of geissoschizine and the biosynthetic precursor of pleiocarpamine (**15**). In a second reduction step, aldehyde **13** was reduced with $NaBH_4$ into (+)-16-hydroxymethyl-pleiocarpamine (**14**) in 16 steps from **41**. Compounds **13** and **14** present a C16 stereochemistry matching with pleiocarpamine (**15**) and deformylation or retro-aldolization were performed on both compounds. Heating **13** in methanol in the presence of K_2CO_3 and heating **14** in toluene at reflux under the action of NaH both ended to (+)-16-*epi*-pleiocarpamine (**16**). Contrary to Quirion's report, release of the carbon C17 was accompanied with the isomerization of the transient enolate into **16**.

As the 16-*epi*-type stereochemistry and a N4-ammonium are encountered in the structure of taberdivarine H (**18**), its synthesis seemed well suited to our strategy (Scheme 20). This time, malonate **45** was strategically *N*-methylated and then the KHMDS/I_2 conditions were applied to **91** furnishing the cyclized product **92** with a 75% yield over two steps. Double saponification and decarboxylation of **92** by sodium hydroxide in a mixture of THF and water at reflux completed the total synthesis of (+)-taberdivarine H (**18**) in 14 steps from **41**.



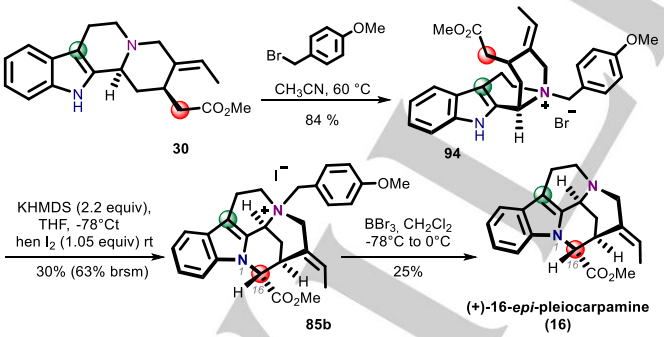
Scheme 20. Total synthesis of (+)-taberdivarine H (**18**).

Simultaneously to our work in 2019, Takayama reported the access to the *mavacurans via* a rhodium-catalyzed insertion of a carbenoid intermediate into the indolic N1-H bond (Scheme 21).[13a] Analogous to our strategy, blocking *the cis*-conformation *via* formation of aminoborane *rac*-**93** was key to the success of the cyclization. Oxidative cleavage of the aminoborane delivered *rac*-16-*epi*-pleiocarpamine (**16**) as the major compound and *rac*-pleiocarpamine (**15**) as the minor constituent as racemic mixtures.



Scheme 21. Total synthesis of *rac*-pleiocarpamine (**15**) and *rac*-16-epi-pleiocarpamine (**16**) by Takayama.

Finally, we aimed to shorten our access to the *mavacuran* skeleton. Accordingly, we recently wandered if the N1-C16 oxidative cyclization could be effected with a C16-monoester instead of a C16-malonate and what would be the outcome of the stereochemistry at C16 (Scheme 22). 16-Desformyl-geissoschizine **30** was thus transformed into ammonium **94** which was subjected to our optimized oxidative coupling conditions. Pleasantly, we were able to obtain a modest 30% yield of **85b**. This result is in contrast with the precedent from Ma or Zhu for which a soft dicarbonyl enolate is required. However, we were not able to obtain the pleiocarpamine stereochemistry at C16. Nevertheless, removal of the PMB group and restoration of the N4-tertiary amine yielded (+)-16-*epi*-pleiocarpamine (**16**) in 25%. This strategy allowed us to avoid 4 steps: 3 steps to transform 16-desformyl geissoschizine **30** into the corresponding malonate **45** and 1 step for the Krapcho decarboxylation of **89**. This approach shortens the longest linear sequence to 11 steps from **41** but was balanced by a lower overall yield.



Scheme 22. Shortened synthesis of (+)-16-*epi*-pleiocarpamine (**16**) from 16-desformyl-geissoschizine (**30**).

Conclusion

In the pursuit of the *mavacuran* framework encountered in pleiocarpamine, we adopted a biosinspired approach based on the oxidative cyclization of geissoschizine. The direct oxidation of the latter with KHMDS and I_2 afforded (–)-17-nor-excelsinidine via formation of the N4-C16 bond instead of the desired N1-C16 bond. In order to bring in close proximity, the indolic N1 nitrogen and the C16 carbon, a ring contraction strategy from a seven-membered ring α-chlorolactam, was therefore adopted and also resulted in the total synthesis of (–)-17-nor-excelsinidine. Realizing that the nucleophilicity of the N4-tertiary amine needed to be masked and that geissoschizine required to be blocked in its *cis*-conformation, alkylation of geissoschizine malonate was performed. The N4-ammonium obtained was then engaged in the oxidative cyclization with KHMDS and I_2 to successfully form the *mavacuran* skeleton. After diastereoselective reductions and/or decarboxylation, we completed the total synthesis of (+)-16-*epi*-pleiocarpamine, (+)-16-hydroxymethyl-pleiocarpamine and (+)-taberdivarine H. Performing the oxidative coupling with a C16-monoester instead of a C-16 malonate allowed to shorten the synthetic sequence towards (+)-16-*epi*-pleiocarpamine.

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Keywords: Indole • Oxidative coupling • Monoterpene Indole Alkaloids • Total synthesis • Biomimetic

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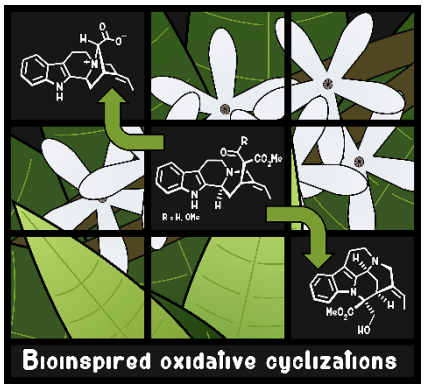
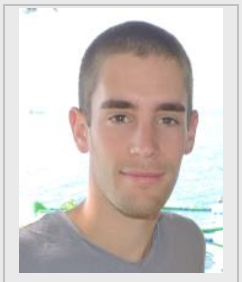


Total Synthesis

To synthetize excelsinidines and mavacurans alkaloids, bio-inspired oxidative cyclizations of (+)-geissochizine and analogues mediated by KHMDS/I_2 were studied. Applied to geissoschizine, the N4-C16 bond formation led to excelsinidines core. Quaternization of the aliphatic nitrogen was necessary to access the mavacurans core (N1-C16 bond). Alternatively, 17-*nor*-excelsinidine was synthetized *via* an intramolecular nucleophilic substitution of an α-chlorolactame.

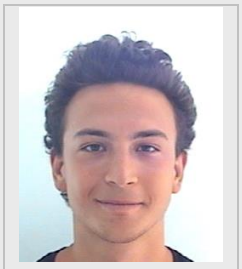
@MaximeJarret; @turpinvictor1; @erwan_poupon; @LaurentEvanno; @gvincentUPSUD

@BioCIS; #ICMMO



Maxime Jarret completed his Master degree in 2016 from Université de Nantes (France) with a one-year internship at GSK (Les Ulis, France) with Dr. Nicolas George. Then, he continued his education under the supervision of Dr. Guillaume Vincent at Université Paris-Saclay (France), focusing on the total synthesis of monoterpene indole alkaloids, and received his PhD in 2019. In 2020, he joined the group of Prof. Alois Fürstner, at the Max-Planck-Institut für Kohlenforschung (Mülheim/Ruhr, Germany), as a postdoctoral associate. His research interest include polyketide total synthesis.

Aurélien Tap is since 2017 a Research Chemist at Oncodesign (Villebon-sur-Yvette, France) designing kinase inhibitors. After a Bachelor degree in 2008 and a M. Sc degree in 2010 from Université Pierre et Marie Curie Paris-6 (France with internships at Sanofi, Rueil-Malmaison, France and with Dr. Sylvain Rolland, Institut Parisien de Chimie Moléculaire, France), he was awarded his PhD under the direction of Prof. Janick Ardisson at Université Paris-Descartes in 2013 on studies in total synthesis. He was then a postdoctoral researcher at the Max-Planck Institut für Kholenforschung (Germany) with Prof. Benjamin List from 2014 to 2016 in organocatalysis and at Institut de Chimie Moléculaire et des Matériaux d'Orsay of Université Paris-Saclay (France) with Dr. Guillaume Vincent in 2016-2017 in total synthesis.



Victor Turpin received his M.Sc. degree in Pharmaceutical Chemistry from Université Paris-Sud (France) in 2017 with a six-month internship at Sanofi with Dr. Baptiste Ronan and graduated in Pharmacy (Pharm.D degree) from Université Paris-Saclay (France) in 2019. He is now PhD student under the supervision of Prof. Erwan Poupon and Dr. Laurent Evanno at the Laboratoire BioCIS (Biomolécules: Conception, Isolement, Synthèse) of Université Paris-Saclay.

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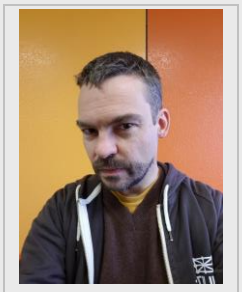
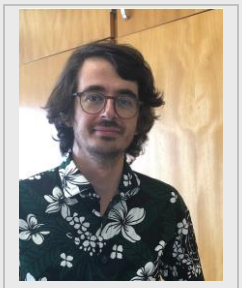
Natacha Denizot obtained her bachelor degree of chemistry from Université d'Avignon et Pays du Vaucluse (France) in 2009. She then was awarded her M.Sc. degree from Université Joseph Fourier, Grenoble (France) in 2012 with an internship at Givaudan (Switzerland) with Dr. Philip Kraft. In November 2015, she completed her PhD from Université Paris-Saclay in the group of Prof. Cyrille Kouklovsky and Dr. Guillaume Vincent on the synthesis of natural products. After a Master in project management from CESI (Lyon, France) in 2018, she is currently consulting project manager at Mi-GSO (Lyon, France).

Cyrille Kouklovsky was born in Paris, France, and educated at Université Paris-Sud, Orsay (France). He defended his PhD in 1989 under the supervision of Prof. Y. Langlois (CNRS, Gif-Sur-Yvette, France), working on the cationic asymmetric Diels-Alder reaction. Then he moved to a postdoctoral position in Prof. Steven V. Ley's research group (University of Cambridge, UK), working on the total synthesis of rapamycin. In 1995, he was appointed as a CNRS research fellow at Université Paris-Sud working on asymmetric dipolar cycloaddition reactions and their synthetic applications. He was promoted as Professor of Chemistry in 2003 and he is currently the MSMT team leader at the Institut de Chimie Moléculaire et des Matériaux d'Orsay of Université Paris-Saclay. His research interests are in the field of synthetic methodology, asymmetric synthesis and peptide synthesis. He was president of the Organic Chemistry Division of the French Chemical Society from 2015 to 2019.



Erwan Poupon is a full professor of Natural Product Chemistry at Université Paris-Saclay (France). He obtained his PharmD from the University of Rennes in 1996 and his PhD from Paris-Descartes University in 2000 under the guidance of Pr Henri-Philippe Husson and Dr. Nicole Kunesh. After a post-doctoral period in the group of Pr Emmanuel Theodorakis (University of California in San Diego, USA), he joined the faculty at Paris-Sud University. He is particularly interested in biomimetic strategies in total synthesis and in understanding the intimate mechanisms involved in the biosynthetic pathways of specialized metabolites. Other interests include the discovery of new natural products from plants, marine invertebrates and micro-organisms as well as natural product-based drug design.



Laurent Evanno received his PhD degree in 2007 from Université Pierre et Marie Curie, Paris (France), working on total synthesis under the supervision of Dr Bastien Nay at the 'Muséum National d'Histoire Naturelle'. He then undertook postdoctoral research with Professor Petri Pihko at Helsinki University of Technology – TKK (Finland) in 2008 and with Professor Janine Cossy at ESPCI – Paris Tech (France) in 2009. Since 2010, he has been an assistant professor at Paris-Saclay University (France) and his research interests encompass biomimetic synthesis.

Guillaume Vincent graduated from CPE Lyon (2002) with a one-year internship at Dupont Pharma (Wilmington, DE, USA) with Dr. Patrick Y. S. Lam. He obtained his Master (2002) and PhD (2005) degrees from Université Lyon-1 (France) with Prof. Marco A. Ciufolini. After two postdoctoral experiences with Prof. Robert M. Williams at Colorado State University (USA) and with Prof. Louis Fensterbank and Prof. Max Malacria at Université Pierre et Marie Curie Paris-6 (France), he was recruited as a CNRS researcher in 2007 ("Chargé de Recherche" and then "Directeur de Recherche" since 2019) at the Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO) of Université Paris-Sud which is now Université Paris-Saclay (France). He obtained in 2018, the Jean-Marie Lehn Prize (Advanced Researcher Prize) from the Organic Chemistry Division of the French Chemical Society.