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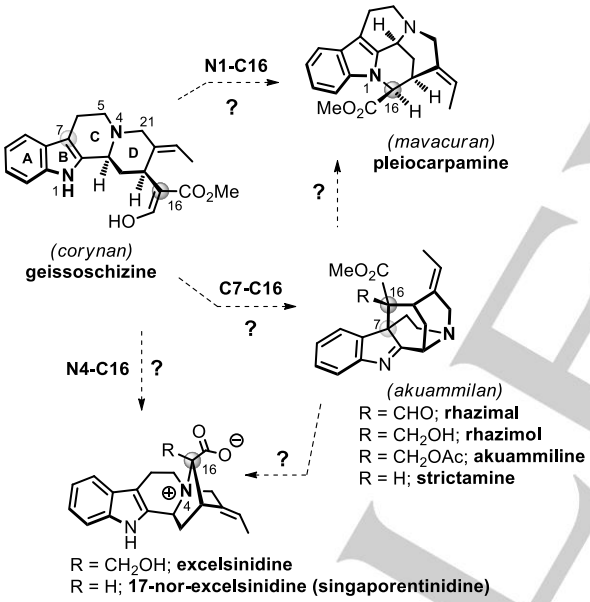
Bioinspired Oxidative Cyclization of the Geissoschizine Skeleton for the Total Synthesis of (–)-17-nor-Excelsinidine

Maxime Jarret, [‡,a] Aurélien Tap, [‡,a] Cyrille Kouklovsky,[a] Erwan Poupon,[b] Laurent Evanno*[b] and Guillaume Vincent*[a]

Abstract: We report the first total synthesis of (–)-17-nor-excelsinidine, a zwitterionic monoterpene indole alkaloid, which displays an unusual N4-C16 connection. Inspired by the postulated biosynthesis, we explored an oxidative coupling approach from the geissoschizine framework to forge the key ammonium-acetate connection. Two strategies allowed us to achieve this goal: an intramolecular nucleophilic substitution of the N4-nitrogen on a 16-chlorolactam or a direct I_2-mediated N4-C16 oxidative coupling from the enolate of geissoschizine.

Geissoschizine seems, intuitively, to be at the common biosynthetic origin of several families of monoterpene indole alkaloids[1] *via* unsolved oxidative cyclizations.



Scheme 1. Postulated biosynthesis of the mavacurans, akuammilans and excelsinidines.

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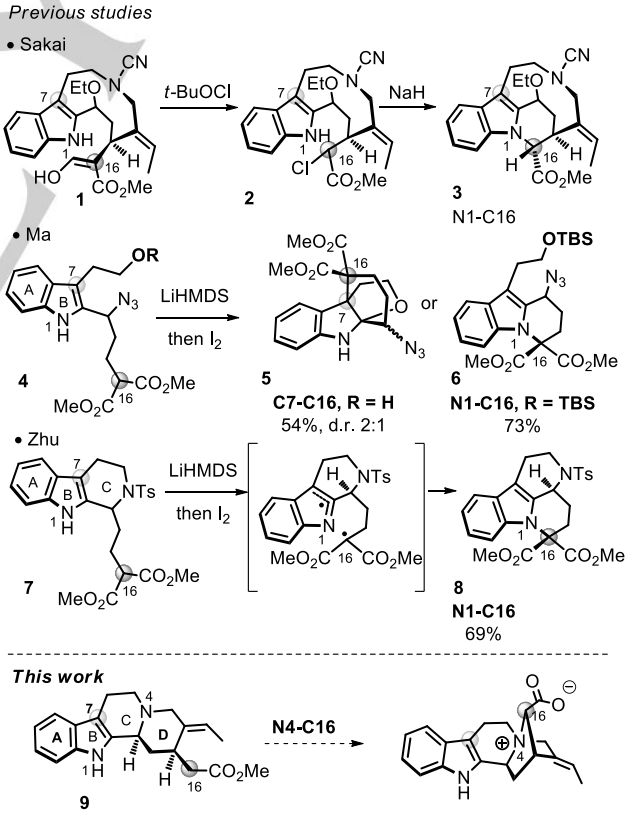
These umpolungs involve the C16 carbon of the formyl methyl ester[2] and respectively the N1-nitrogen for mavacuran alkaloids (e. g. pleiocarpamine), the C7-carbon for akuammilan alkaloids (e. g. rhazimal, rhazimol, akuammiline and strictamine) or the N4-nitrogen for the recently discovered zwitterionic excelsinidine and 17-nor-excelsinidine, also known as singaporentinidine as its protonated form (Scheme 1).[3]

All the interconnections and mechanisms between these families of alkaloids are not completely understood or proven. While divergent direct oxidative couplings between C16 and N1 or C7 or N4 are possible,[2a] it has also been postulated that the akuammilan skeleton could be the biogenetic precursor of both the mavacuran[2c] and the excelsinidine frameworks.[3d] The akuammilans have been the subject of very intense synthetic efforts and several members of this family have succumbed to total synthesis in the last decade.[4,5] The synthesis of mavacurans have also been well studied over the years.[6]



Scheme 2. Divergent oxidative couplings for the formation of the N1-C16, C7-C16 or N4-C16 bonds.

The key bioinspired oxidative couplings have been achieved synthetically in few occasions (Scheme 2). Sakai, in its pioneering

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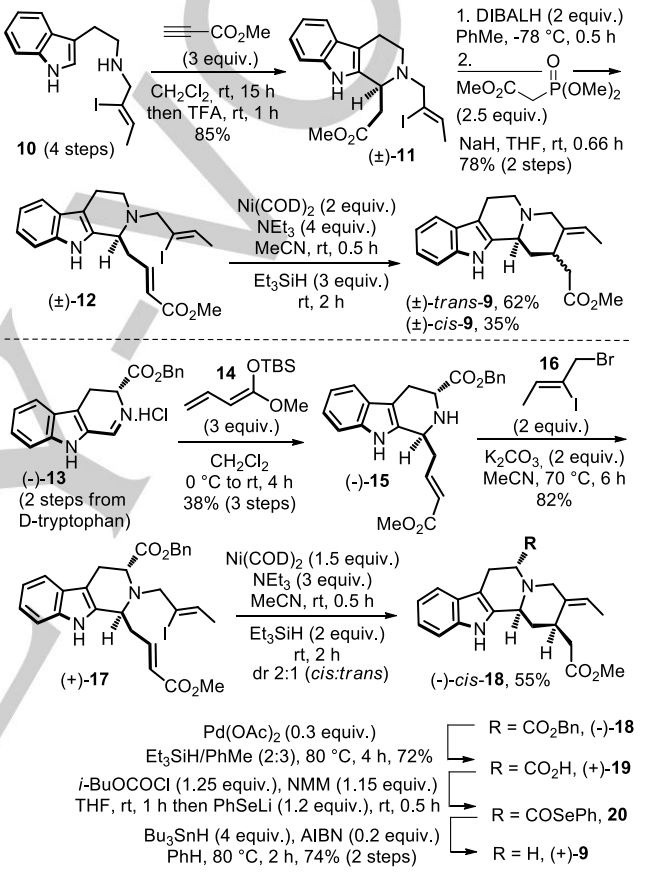
work, adopted a two-stage approach to form the N1-C16 bond of **3**.[6a,b] Oxidative chlorination of the C16 carbon of **1**, followed by a nucleophilic substitution of **2** was performed on a substrate lacking the CD-ring junction in order to have more flexibility. More recently, Ma developed a direct strategy *via* deprotonation of both a malonate and the NH of the indole of **4** followed by an oxidation of the resulting dianion with I_2 into a biomimetic *bis*-radical intermediate.[5] Importantly, to favor the C7-C16 oxidative coupling (e.g. **5** from **4** with R = H), a free alcohol is required to form a chelated-anion at C7.[5b] Otherwise, the N1-C16 bond is formed (e.g. **6** from **4** with R = TBS and **8** from **7**).[5b,6d] In contrast, no synthetic work has been reported towards the excelsinidines, which contain a bridged bicyclic ammonium moiety. Therefore, in line with our interest in the chemistry of monoterpene indole alkaloids,[7] we would like to report our endeavors towards the total synthesis of these natural products with an emphasis on the formation of the key N4-C16 bond over the N1-C16 and C7-C16 bonds. We sought to study the intrinsic selectivity of the intramolecular oxidative coupling between C16 and N1 or N4 or C7 directly from complete geissoschizine skeleton **9** (Scheme 2) since Sakai, Ma and Zhu have achieved oxidative cyclizations on C3-N4 *seco* or C13-N14 *seco* or acyclic unconstrained substrates.[8]

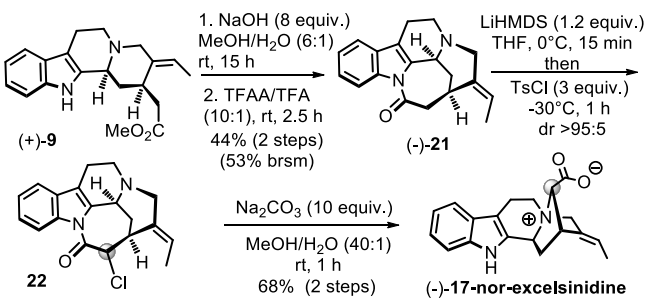
In order to rapidly access 16-desformyl-geissoschizine **9**,[8a,9] as a platform for our study, we evaluated the nickel-mediated 1,4-intramolecular addition of vinyl iodide (±)-**12** onto its α,β–unsaturated methyl ester (Scheme 3).[9d,f] The latter was obtained by a Pictet-Spengler-like reaction from tryptamine derivative **10** and methyl propiolate[10] followed by DIBAL-H reduction and olefination of ester (±)-**11**. Unfortunately, the high yielding intramolecular radical 1,4-addition of (±)-**12** produced the undesired (±)-*trans*-**9** compound as the major diastereoisomer in a 1.8:1 ratio.

To overcome this issue, we decided to perform this key cyclization with a C5-benzyloxycarbonyl substituent, which will control the stereoselectivity of the nickel-mediated 1,4-addition as demonstrated by Cook.[9d,11] Therefore, starting from enantiopure D-tryptophan instead of tryptamine will allow us to perform a diasteroselective synthesis leading to an enantiopure final product.[11] The Mannich addition, developed by Martin, of vinyl ketene acetal **14** onto dihydro-β-carboline (–)-**13** delivered stereoselectively *trans*-tetrahydro-β-carboline (–)-**15**.[9c,12] The 2-iodoprop-2-ene moiety was then introduced *via* a nucleophilic N4-substitution with allyl bromide **16**. In presence of $Ni(COD)_2$, the radical cyclization of (+)-**17** occurred, with a 2:1 diastereoselectivity in favor of the desired diastereoisomer (–)-*cis*-**18** which could be isolated in 55% yield.[9d,11]] The benzyl ester was then removed in a classical sequence:[9c,d] debenzylation into acid (+)-**19**, formation of a phenylselenoester **20** and decarboxylation in reductive radical conditions to yield the expected enantiopure (+)-16-desformyl-geissoschizine (**9**) in 8 steps in the longest linear sequence.

Having the required scaffold in hands, the stage was set to explore the key oxidative cyclization. Several attempts to achieve this transformation directly from (+)-**9** were unsuccessful.[13] At this point, we believed that accessing a rigid framework would bring closer the potential reactive centers, which should allow us to perform the expected intramolecular coupling with selectivity (Scheme 4). Therefore, the indole nitrogen and the carbonyl of the ester were connected by forming 7-membered-lactam (–)-**21**.[9a] The oxidative process was effected in two stages. First, the C16-carbon was subjected to umpolung by a highly diastereoselective chlorination, leading to α-chlorolactam **22**.[14,15] Then, addition of sodium carbonate, in wet methanol, induced the nucleophilic substitution of the chlorine by the quinolizidinic nitrogen[16] and the cleavage of the lactam to form selectively the expected N4-C16 bond of the bridged-ammonium bicycle, delivering enantiopure (–)-17-nor-excelsinidine in 68% yield in two steps.



Scheme 3. Synthesis of (±) and (+)-16-desformyl-geissoschizine (**9**).



Scheme 4. Completion of the total synthesis of (–)-17-nor-excelsinidine.

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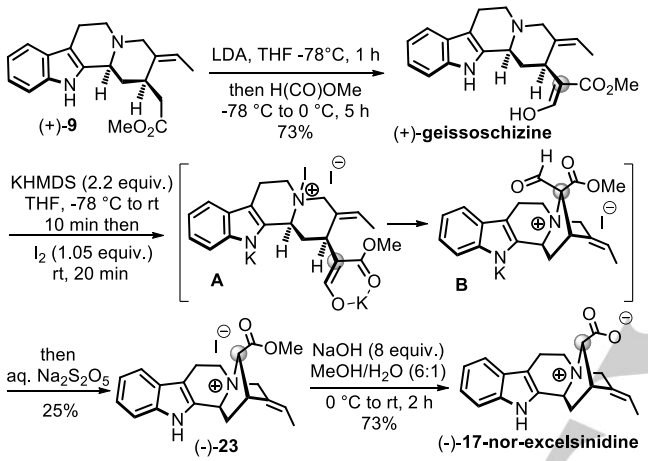
Very pleased to have achieved the first synthesis of 17-nor-excelsinidine with a selective two steps N4-C16 coupling, we wondered if a direct oxidative cyclization from geissoschizine would be possible.[17] Unfortunately, this approach failed from desformyl-geissoschizine (+)-**9**, however we reasoned that the presence of the formylester function of geissoschizine itself should be more reactive (Scheme 5). Therefore, geissoschizine was prepared from (+)-**9** by a known formylation step.[9]

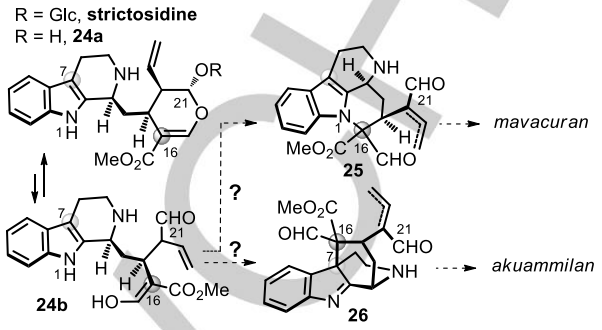
This latter was then deprotonated with KHMDS and the corresponding dianion was then submitted to oxidation with I_2 leading selectively, after aqueous work-up with sodium metabisulfite, to (–)-17-nor-excelsinidine methyl ester (**23**) (Scheme 5) in 25% yield.[18,19] Methyl ester (–)-**23** was then saponified to (–)-17-nor-excelsinidine in 73% yield.



Scheme 5. Direct oxidative cyclization of geissoschizine leading to (–)-17-nor-excelsinidine.

A plausible mechanistic hypothesis for this oxidative cyclization involves the oxidation of the aliphatic nitrogen into *N*-iodoammonium **A** which would be substituted by the C16-enolate.[20] While it is less likely to us, we cannot exclude that this cyclization proceeds by the heterocoupling of a N4,C16-*bis*-radical generated *via* two single electron transfers (SET), related to the original Ma's coupling[5,6d] or by a nucleophilic substitution of the aliphatic tertiary amine onto a 16-iodo ester.[6d]

The Zhu and Ma previous studies (Scheme 2) and this selective chemical transformation of geissoschizine into the excelsinidine skeleton over the akuammilan and mavacuran ones could raise questions about their respective biosynthesis from chemo-divergent oxidative annulations. Indeed, specific enzymes (oxidases) could induce selective couplings between C16 and N1 or N4 or C7 from geissoschizine as classically proposed.[2] However considering the constrained structure of the mavacurans and the akuammilans, it might also be postulated that the key N1-C16 and C7-C16 couplings could occur prior to the formation of the N4-C21 bond (Scheme 6). One can envision that these bond formations could arise from the open form **24b** of aglycon **24a** after deglycolysation of strictosidine, the common precursor of all monoterpene indole alkaloids, as previously proposed.[21] Subsequently, cyclization, *via* reductive amination, of compounds **25** and **26** would lead, respectively, to the mavacurans and the akuammilans. However, we should remain cautious on this hypothesis until proven by feeding experiments or identification of enzymes responsible for these oxidative couplings.[22,23]



Scheme 6. Alternative biosynthesis of the mavacurans and akuammilans.

In conclusion, we discovered two oxidative cyclization strategies of the complete geissoschizine skeleton, which led to the selective formation of the N4-C16 bond encountered in the excelsinidine alkaloids over the C7-C16 and N1-C16 bonds of the akuammilan and mavacuran alkaloids. The α-electrophilic chlorination of a 7-membered-ring lactam and its ring rearrangement *via* a nucleophilic substitution led to the first total synthesis of (–)-17-nor-excelsinidine. Alternatively, the cyclization of geissoschizine itself *via* a direct oxidative coupling delivered (–)-17-nor-excelsinidine methyl ester (**23**) which could be saponified into (–)-17-nor-excelsinidine

Acknowledgements

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Keywords: monoterpene indole alkaloids • oxidative coupling • excelsinidine • biosynthesis • geissoschizine

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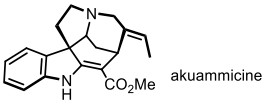

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[19] The spontaneous desformylation at C16 could occur, during the aqueous work-up, by attack of water on the aldehyde **B** leading to liberation of formic acid. Alternatively, reduction of the aldehyde **B** with sodium metabisulfite would lead to the corresponding alcohol, which would spontaneously release formadehyde.

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Bioinspired Oxidative Cyclization of the Geissoschizine Skeleton for the Total Synthesis of (–)-17-nor-Excelsinidine

Selectivity! Two unprecedented oxidative cyclization strategies from the complete geissoschizine skeleton allow to selectively achieve the first total synthesis of the monoterpene indole alkaloid 17-nor-excelsinidine over the mavacuran and akuammilan alkaloids.