Bioinspired Oxidative Cyclization of the Geissoschizine Skeleton for the Enantioselective Total Synthesis of Mavacuran Alkaloids

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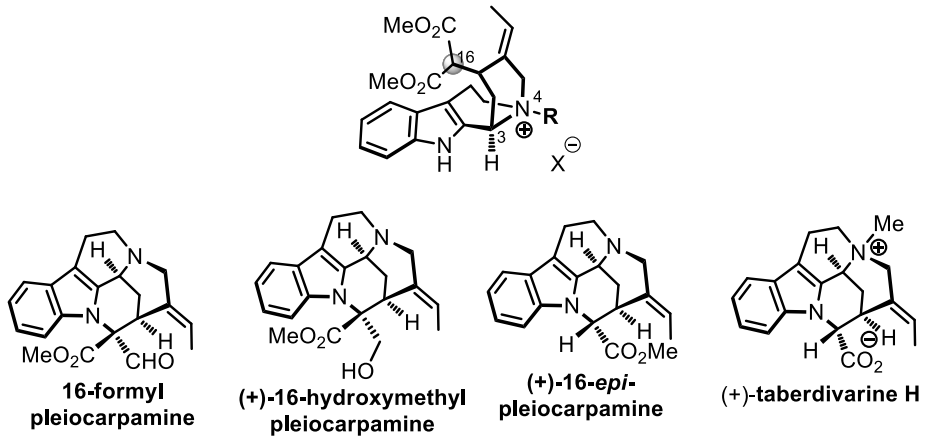
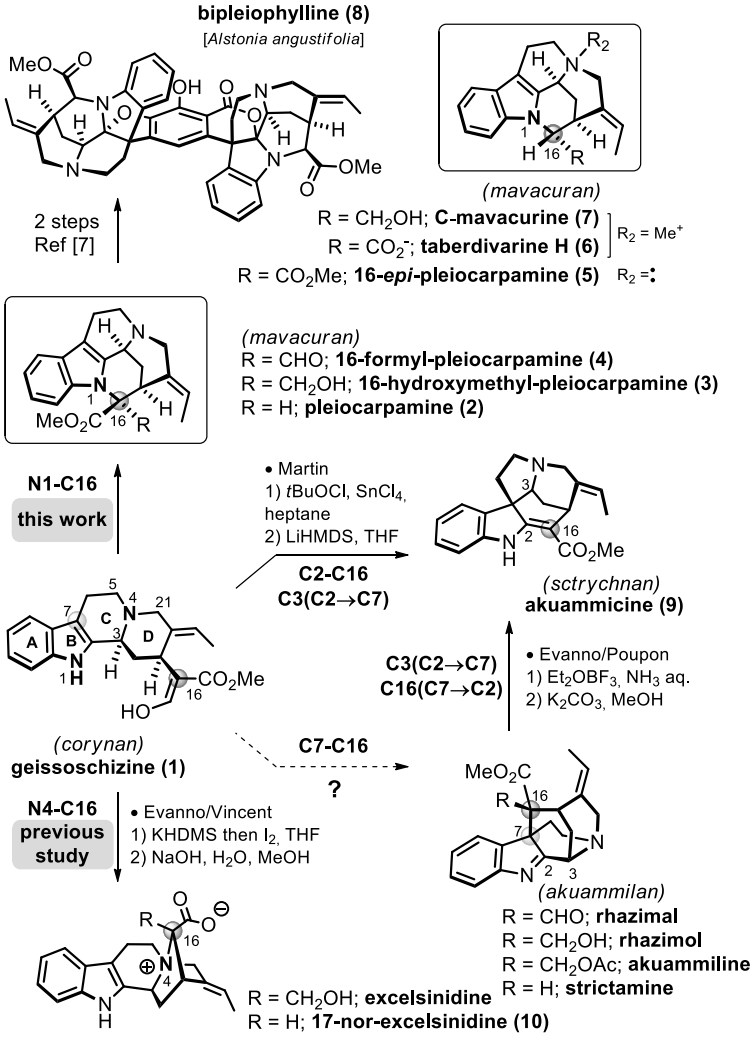
Abstract: We report the enantioselective total syntheses of mavacurans alkaloids, (+)-taberdivarine H, (+)-16-hydoxymethyl-pleiocarpamine, (+)-16-epi-pleiocarpamine, and their postulated biosynthetic precursor 16-formyl-pleiocarpamine. This family of monoterpene indole alkaloids is a target of choice since some of its members are subunits of intricate bisindole alkaloids such as bipleiophylline. Inspired by the biosynthetic hypothesis, we explored an oxidative coupling approach from the geissoschizine framework to form the N1-C16 bond. Quaternization of the aliphatic nitrogen was key to achieve the oxidative coupling induced by KHMDS/I_2 since it hides the nucleophilicity of the aliphatic nitrogen and locks the required cis conformation.



Geissochizine (**1**) is considered as a common biosynthetic precursor of several frameworks (akuammilan, mavacuran, strychnan) encountered in the family of monoterpene indole alkaloids.[1] Despite the recent identification of some enzyme systems,[2] most of the interconnections and mechanisms from geissoschizine (**1**) remain partially understood and proven (Scheme 1). According to the different hypotheses, divergent oxidative couplings between the C16 carbon and the N1 nitrogen, the N4 nitrogen or the C7 carbon would lead respectively to excelsinidines, mavacurans and akuammilans.[3] Mavacurans[4] sparked our interest since its emblematic representative, pleiocarpamine (**2**) is a subunit encountered in several indole and bisindole alkaloids of particularly complex structure.[5-6] We already accomplished the synthesis of bipleophylline (**8**) *via* oxidative couplings between pyrocatechic acid and pleiocarpamine isolated from plant material.[7] Motivated by the complexity of these

frameworks, we sought to develop a synthesis of pleiocarpamine (**2**) as a benchmark to the total synthesis of other multimeric bisindoles.

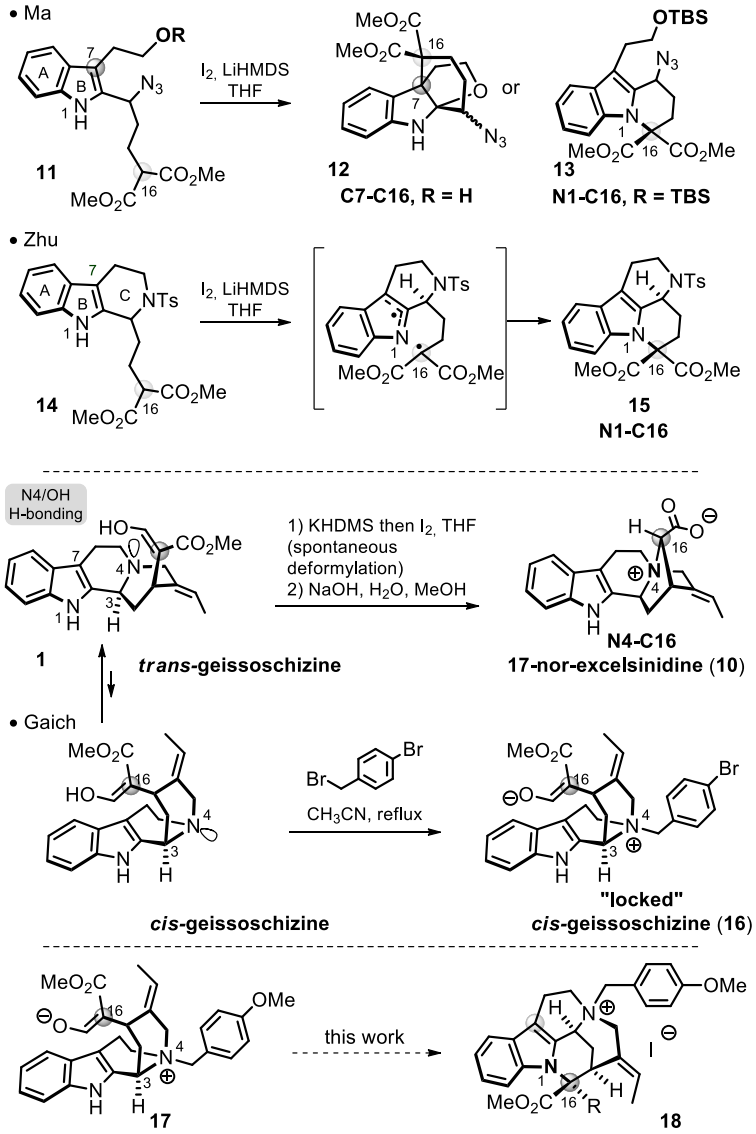
Akuammilans,[8] strychnans[9] and mavacurans[10] have been the subject of very intense synthetic efforts but, a late stage bioinspired oxidative cyclisation of a geissoschizine type structure was performed only in few occasions.[11-13] In a seminal study, Martin reported the direct cyclization of 16-deformyl-geissoschizine leading directly to akuammicine (**9**).[12] An oxidative chlorination in the presence of $SnCl_4$ gave a chloroindolenine that underwent skeletal reorganization in basic conditions. A transient formation of an akuammilan structure was postulated, and similar correlation between the akuammilans and the stychnans was evidenced by us in buffered conditions.[14] To date, for the synthesis of akuammilans, C7-C16 oxidative couplings were only performed on simplified structures.[15]



Scheme 1. *Postulated biosynthesis and bioinspired synthetic approaches of the mavacurans, akuammilans, strychnans and excelsinidines.*

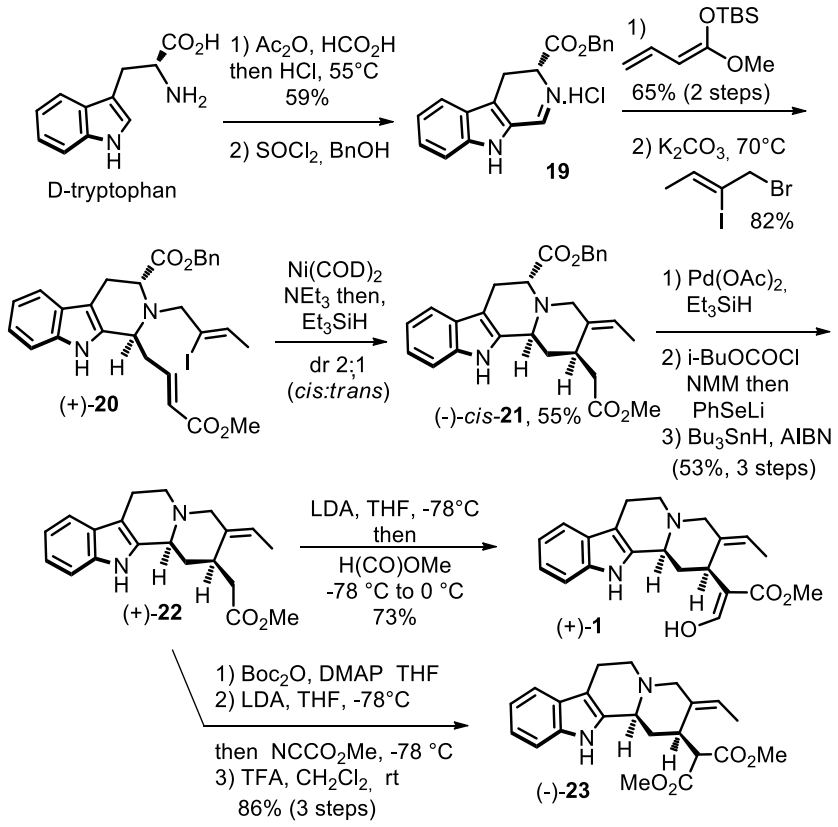
Toward mavacurans synthetic approaches are even more limited.[10] Notably, Sakai[10b,c] and then Harley-Mason[10d] used a sequence of oxidative chlorination of the C16 carbon, followed by a nucleophilic substitution by N1 nitrogen performed on a substrate lacking the CD-ring junction in order to benefit from more flexibility. During the preparation of the present manuscript, Takayama reported a racemic synthesis of mavacuran alkaloids using a metal carbenoid cyclization of a 16-deformyl-geissoschizine-type structure bearing a carbenoid at C16.[16] The key cyclization delivered (±)-16-epi-pleiocarpamine (**5**) as the major product and (±)-pleiocarpamine (**2**) as a minor product. In a previous communication, we reported a N4-C16 biomimetic oxidative cyclization of geissoschizine (**1**) induced by KHMDS/I_2 leading to zwitterionic 17-nor-excelsinidine (**10**).[13] We present herein further

developments to control the N1-C16 bond formation and the application to the enantioselective total synthesis of mavacuran alkaloids: 16-hydroxymethyl-pleiocarpamine (**3**), 16-*epi*-pleiocarpamine (**5**) and taberdivarine H (**6**) as well as 16-formyl-pleiocarpamine (**4**), a postulated biosynthetic intermediate yet to be isolated from natural sources. In the context of alkaloids total syntheses, Ma and Zhu constructed, at early stages, either the C7-C16 bond[15a,b] or the N1-C16 bond[15b,17] bond using LiHMDS/I_2 oxidative conditions (Scheme 2). First, LiHMDS deprotonates both a malonate and the NH of an indole (**11**, 1**4**) followed by an oxidation of the resulting dianion with I_2. Ma and Zhu results suggested the applicability of the oxidative coupling to the synthesis of mavacurans but, in our hands, slightly modified conditions (KHMDS/I_2) applied to geissoschizine (**1**) led to the excelsinidines core (compound **10**).[13] Exclusive formation of the framework of **10** might be rationalized by the NMR conformational study of geissoschizine (**1**).[3f] In solution, the molecule adopts a C3-N4 *trans* configuration favorable to the formation of the excelsinidines core. As demonstrated by Eckermann and Gaich, a C3-N4 *cis* configuration is required to insure proximity between C16 carbon and the indole nucleus and can be locked by benzylation (Scheme 2).[3g,18] With all those considerations, we adopted a strategy consisting in the alkylation of the aliphatic nitrogen to inhibit its reactivity and favor the *cis* geissoschizine (**1**) configuration and then to use the KHMDS/I_2 oxidative conditions for the N1-C16 bond formation.



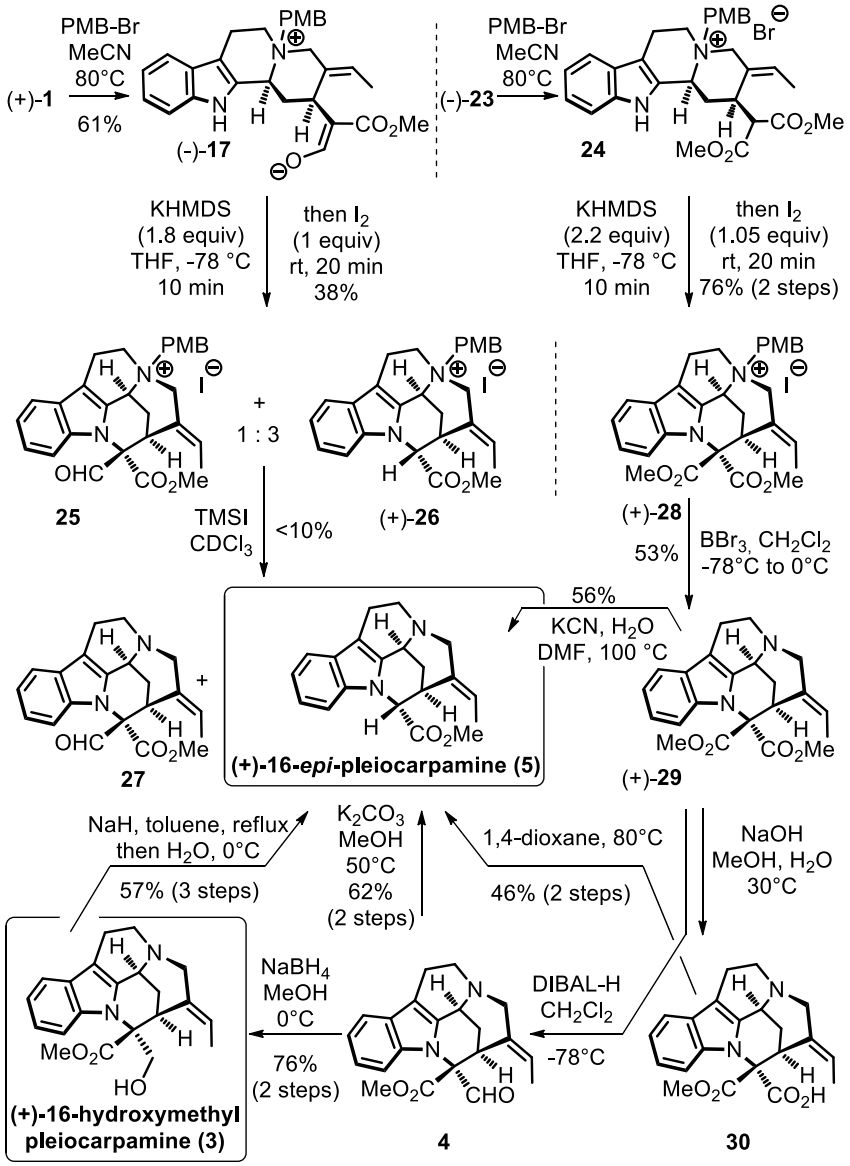
Scheme 2. *Divergent oxidative couplings for the formation of the N1-C16 or C7-C16 bonds and conformational studies of geissoschizine.*

We accessed (+)-geissoschizine and its derivatives according to our recent synthesis which was inspired by the works of Martin and Cook (Scheme 3)[13] The diastereoselective Martin's vinylogous Mannich addition of a silyl ketene acetal onto β-dihydrocarboline **19** derived from (D)-tryptophan[19] was followed by *N*-allylation of the secondary amine with an allyl bromide. According to Cook, formation of the D-ring was promoted by $Ni(COD)_2$-mediated intramolecular addition of the vinyl iodide onto the unsaturated ester of (+)-**20** for which the diastereoselectivity was directed by the benzyl ester.[20] Removal of the latter was effected in 3 steps leading to (+)-16-deformyl-geissoschizine (**22**) and to (+)-geissoschizine (**1**) after a known formylation step. In addition, dimethyl malonate (–)-**23** was also obtained in 86% yield from (+)-**22**.



Scheme 3. *Synthesis of 16-deformyl-geissoschizine (**22**), geissoschizine (**1**) and geissoschizine malonate **23** according to our previous work.*

With a straightforward access to the geissoschizine framework, we were in position to evaluate our hypothesis of oxidative cyclization after quaternization of the aliphatic nitrogen N4. As demonstrated by Ma and then Zhu or us, the presence of a dicarbonyl functionality at C16 is essential to effect related oxidative couplings and geissoschizine itself seems to be a suitable candidate. Heating geissoschizine (**1**) with *p*-methoxybenzylbromide in acetonitrile led, as expected, to ammonium (–)-**17**. Deprotonation of the indolyl NH of **17** with KHMDS was followed by addition of I_2. For the first time, we observed the formation of the desired mavacuran skeleton *via* the long-expected formation of the N1-C16 bond as a mixture of **25** and deformyl counterpart **26**. This reaction reveals to be stereoselective but, careful NOESY analysis showed that the C16 stereochemistry for both compounds **25** and **26** corresponds to a 16-*epi*-pleiocarpamine-type stereochemistry rather than the pleiocarpamine one. We then reasoned that the use of a symmetric dicarbonyl at C16 (compound **24**) would allow us to fix the stereochemistry at C16 at a later stage and would also circumvent the problem of uncontrolled deformylation of **25**. Thus, the same sequence of quaternization of N4 and subsequent N1-C16 oxidative coupling applied to dimethyl malonate-containing **24** proceeded in 76% yield over 2 steps (compound (+)-**28**).



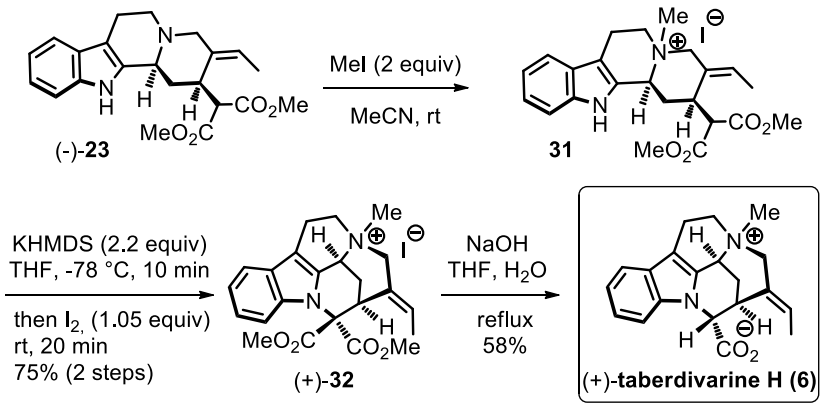
Scheme 4. *Total synthesis of 16-epi-pleiocarpamine and 16-hydroxymethyl pleiocarpamine via N1-C16 oxidative cyclization from N4-PMB-geissoschizinium derivatives.*

In order to obtain some of the mavacuran alkaloids, removal of the PMB was necessary to restore the tertiary amine at C4. It was at first effected with TMS iodide on the mixture of **25** and deformyl **26** which delivered (with a poor yield but enough to identify) a mixture of 16-*epi*-pleiocarpamine (**5**) and 16-*epi*-16-formyl-pleiocarpamine (**27**). It then turned to be more convenient to operate from malonate (+)-**28**. Indeed, deprotection of N4 was achieved with BBr_3 to give (+)-**29** in 53% yield. Subsequently, Krapcho decarboxylation with KCN delivered efficiently (+)-16-*epi*-pleiocarpamine (**5**).

In order to desymmetrize the diester at C16 of (+)-**29**, addition of DIBALH reduced selectively the more accessible ester into an aldehyde to yield 16-formyl-pleiocarpamine (**4**) which is believed to be the biosynthetic precursor of pleiocarpamine (**2**) as the direct product of oxidative cyclization of geissoschizine (**1**). The reaction delivered **4** with a complete control of C16 stereocenter and, at this stage, the configuration of the remaining ester was matching with pleiocarpamine (**2**). Deformylation by heating **4** in methanol under basic conditions delivered (+)-16-*epi*-pleiocarpamine (**5**). Further reduction of aldehyde **4** with $NaBH_4$ delivered (+)-16-hydroxymethyl-pleiocarpamine (**3**), the next biosynthetic intermediate *en route* to pleiocarpamine. The heating of **3** with NaH induced the release of formaldehyde to give again (+)-16-*epi*-pleiocarpamine (**5**) after an aqueous quench at 0°C.[21] The

desymmetrisation of malonate (+)-**29** was also possible *via* the selective saponification of the most accessible ester. Heating of the resulting carboxylic acid **30** resulted in a decarboxylation to, once again, form (+)-16-*epi*-pleiocarpamine (**5**). In all these attempts, the selective formation of (+)-16-*epi*-pleiocarpamine (**5**) over pleiocarpamine (**2**) is observed even though we started from substrates bearing the proper C16 pleiocarpamine-type stereochemistry (compounds **3**, **4** and **30**). It could be explained as in all cases an enolate or enol is formed at C16 which is converted to the more thermodynamically stable epimer **5**.

Indeed, performing the N1-C16 oxidative coupling on a substrate containing an ammonium at N4 seemed to be perfectly adapted to the total synthesis of (+)-taberdivarine H which contains an N4-methyl ammonium, like C-mavacurine (**7**). Malonate (–)-**23** was *N*-methylated with methyl iodide. Resulting ammonium **31** was then subjected to the preceding oxidative coupling conditions to form the N1-C16 bond of (+)-**32** in 75% yield over 2 steps. Finally, a double saponification accompanied by a decarboxylation furnished (+)-taberdivarine H (**6**) in 58% yield.



Scheme 5. *Total synthesis of taberdivarine H.*

In conclusion, we found a solution to the long-standing problem of the oxidative cyclization of the geissoschizine skeleton to forge the mavacuran scaffold *via* the formation of the key N1-C16 bond. The quaternization of the N4-quinolizidine nitrogen was decisive to achieve this endeavor. The formation of an N4 ammonium efficiently sequesters the superior nucleophilicity of N4 in comparison to the N1 indolic nitrogen and, moreover, favors the *cis* conformation of the geissoschizine framework which brings closer the indole nucleus and the C16 malonate. This strategy allowed us to achieve the total synthesis of (+)-16-*epi*-pleiocarpamine, (+)-16-hydroxymethyl-pleiocarpamine and (+)-taberdivarine H as well as 16-formyl-pleiocarpamine, a postulated biosynthetic intermediate.

Acknowledgements

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