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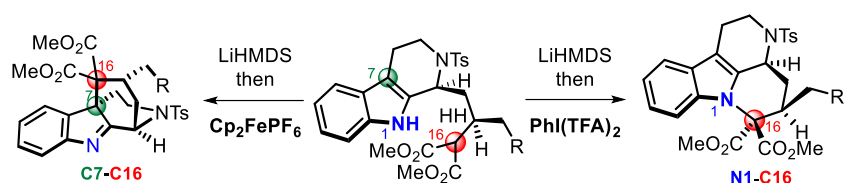
Bioinspired Early Divergent Oxidative Cyclization Towards Pleiocarpamine, Talbotine and Strictamine

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Supporting Information Placeholder

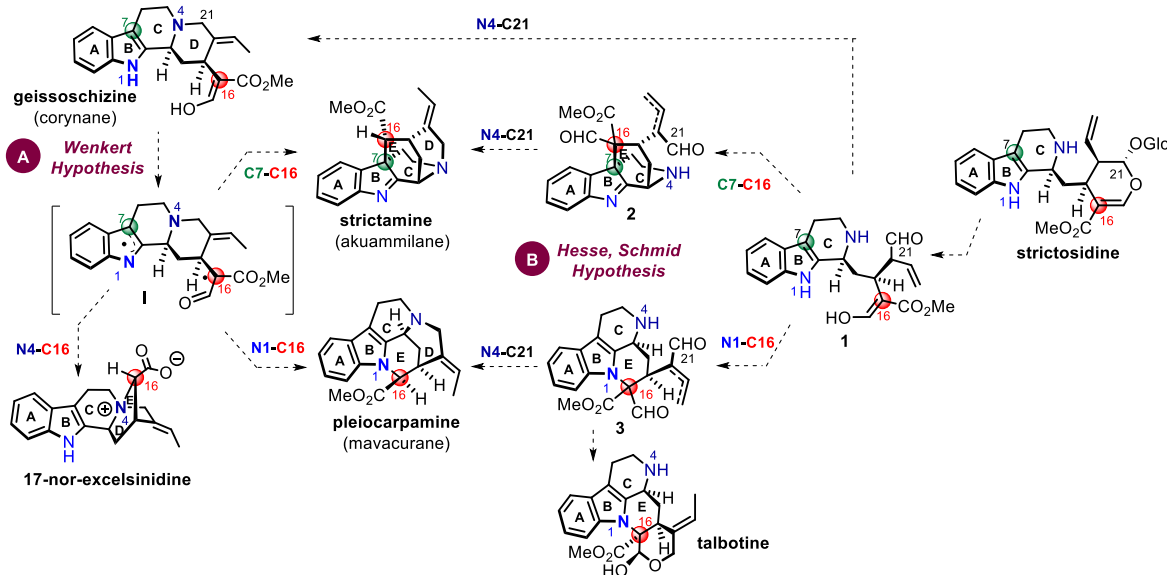


ABSTRACT: Towards the mavaurane and akuammilane monoterpene indole alkaloids, we developed divergent oxidative couplings between the indole nucleus (at N1 or C7) and the C16-malonate of a common tricyclic model related to strictosidine according to a biosynthetic hypothesis postulated by Hesse and Schmid. These oxidative cyclizations lead selectively to the formation of the N1-C16 bond of pleiocarpamine or to the C7-C16 bond of strictamine. We were then able to obtain the scaffold of talbotine.

Pleiocarpamine,¹ strictamine² and 17-nor-excelsinidine³ are representative members of respectively the mavaurane, akuammilane and excelsinidine sub-families of monoterpene indole alkaloids⁴ which are popular targets for total synthesis.^{5,6} These pentacyclic compounds are constituted of cyclized

geissoschizine skeletons via unsolved formal oxidative couplings between the C16-formyl ester and either the C7-indolic carbon for strictamine or the N1-indolic nitrogen for pleiocarpamine or the N4-quinolizidinic nitrogen for 17-nor-excelsinidine (Scheme 1).

Scheme 1. Hypotheses for the biosynthesis of strictamine, pleiocarpamine, talbotine and 17-nor-excelsinidine.



The most accepted biosynthetic hypothesis involves that these oxidative cyclizations take place directly from tetracyclic

geissoschizine itself (Scheme 1, A). In 1965, Wenkert proposed that divergent radical cyclizations from an intermediate similar

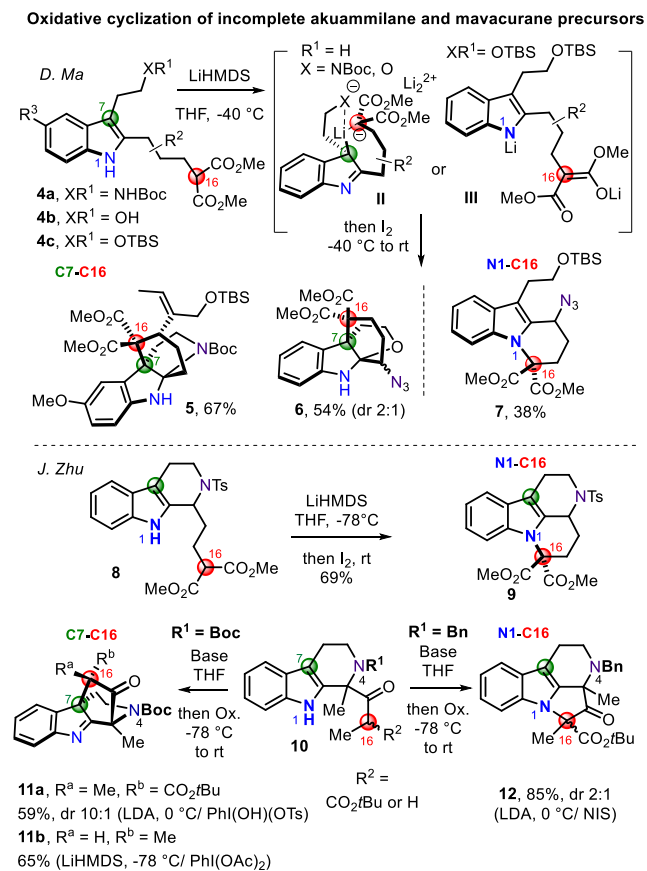
to **I** would forge the E rings and the C7-C16 bond of strictamine or the N1-C16 bond of pleiocarpamine.^{7,8} Oxidative cyclization of **I** could also lead to the N4-C16 bond of the recently discovered 17-nor-excelsinidine.^{3,8}

An alternative biosynthetic hypothesis has been proposed by Hesse and Schmid in which the divergent oxidative cyclizations leading to strictamine and pleiocarpamine would take place at an earlier stage (Scheme 1, B).⁹ This postulate was inspired by the isolation of the monoterpene indole alkaloid talbotine which displays the characteristic E-ring and N1-C16 bond of pleiocarpamine but lacks the D ring and N4-C21 bond of the geissoschizine template.⁹ It was suggested that the formation of the E rings and the C7-C16 bond of strictamine or the N1-C16 bond of pleiocarpamine and talbotine would be formed by divergent oxidative cyclizations on deglycosylated strictosidine leading to tetracyclic compounds **2** and **3**. A reductive amination would then deliver the D-ring and the N4-C21 bond of both strictamine and pleiocarpamine.

The group of Ma discovered an intramolecular dearomative oxidative coupling between indoles and carbanions stabilized by two electron-withdrawing groups¹⁰ and recognized that this process could mimic the biosynthetic formation of the C7-C16 bond of the akuammilanes.¹¹ Therefore, the dearomative oxidative cyclization of tryptamine derivative **4a** bearing a dimethyl malonate on the C2-substituent delivered pyrroloindoline **5**.^{11a} In a similar manner, the same process applied to tryptophol derivative **4b** yielded furanoindoline **6**.^{11b} The formation of the C7-C16 bond was explained by chelation of the lithium at the C7 position via tridentate intermediate **II**. When the primary alcohol was protected as TBS ether **4c**, such stabilization is not possible, and a different outcome of the oxidative cyclization was observed resulting in coupling of enolate **III** with the N1 indole nitrogen instead of the C7 indole carbon leading to compound **7** related to the mavacuranes. In fact, the formation of the N1-C16 bond with the Ma's oxidative coupling conditions was first reported by the group of Zhu with the formation of tetracyclic compound **9** from β -tetrahydrocarboline **8** during synthetic studies towards strictamine.¹² Very recently, Zhu reported a remarkably short synthesis of (-)-arborisidine via an oxidative cyclization of β -tetrahydroisoquinoline **10** into **11b**.¹³ Intriguingly, the selectivity of the oxidative coupling is dependent of the N4-nitrogen protecting group. A Boc group led to the C7-C16 bond of **11**, while a benzyl group yielded the N1-C16 bond of **12**. Nevertheless, the oxidative couplings of substrates **10** delivers five membered-rings with an intracyclic carbonyl and a quaternary carbon at the C3 position which differ from the requirements to access strictamine, pleiocarpamine or talbotine.

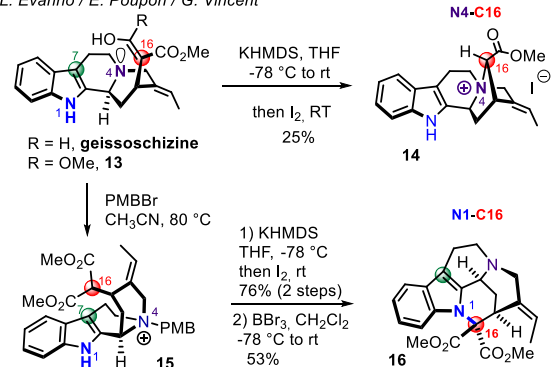
After achieving the hemisyntheses of voacalgine A and bipleiophylline via divergent oxidative couplings from natural pleiocarpamine,¹⁴ we were eager to achieve the total synthesis of pleiocarpamine. In line with our interest in bioinspired oxidative couplings^{15,16} and based on the Wenkert biosynthetic hypothesis,⁷ we decided to apply modified Ma's oxidative condition directly to geissoschizine and we observed the formation of the N4-C16 bond of **14** which was then converted to 17-nor-excelsinidine.¹⁷ This result could be explained by the high reactivity of the N4 tertiary amine and the *trans*-conformation of geissoschizine in which the formyl ester at C16 is closer to the N4-quinolizidinic nitrogen than the indole nucleus.¹⁸ To overcome these issues, we transformed the N4-tertiary amine into a PMB ammonium¹⁹ and we were then able to selectively obtain the pentacyclic framework **16** of the mavacuranes.²⁰

Scheme 2. Previous bioinspired divergent intramolecular oxidative coupling between an indole and an enolate.



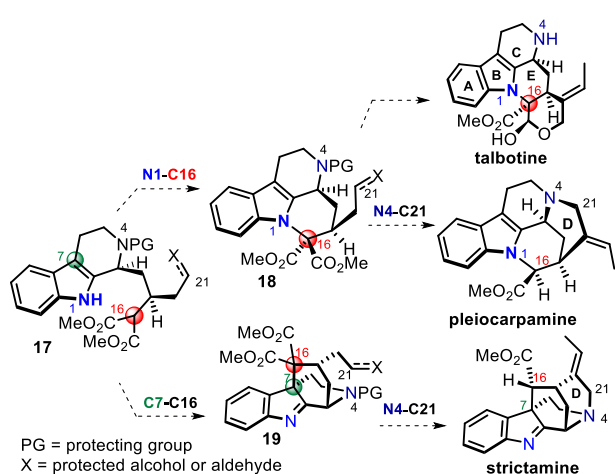
Oxidative cyclization of the full geissoschizine skeleton

L. Evanno / E. Poupon / G. Vincent



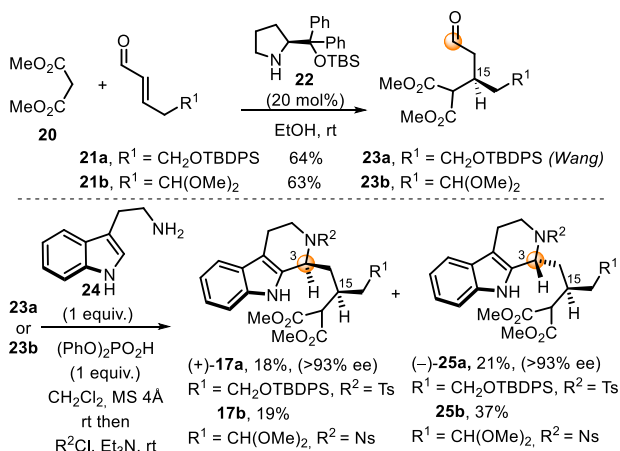
While we were developing the oxidative cyclization of the ammonium **15** of geissoschizine, we also pursued a strategy inspired by the Hesse-Schmid biosynthetic hypothesis. Accordingly, the synthesis of strictamine and pleiocarpamine would imply the formation of the D ring and the N4-C21 bond as the last event for both natural products from tetracyclic precursors **18** and **19** (Scheme 3). The latter would be obtained by divergent bioinspired oxidative cyclizations of β -tetrahydrocarboline **17**. Zhu demonstrated (see Scheme 2) that β -tetrahydrocarboline **8**, which is a simplified version of pivotal intermediate **17**, could lead selectively to the formation of the N1-C16 bond of pleiocarpamine and talbotine.¹² The purpose of the present work is to further extend this key result and find a divergent access to the pleiocarpamine/talbotine and strictamine ABCE tetracyclic compounds **18** and **19** from substrate **17** via divergent selective formation of the N1-C16 and C7-C16 bonds (Scheme 3).

Scheme 3. This work: divergent oxidative cyclization of functionalized β -tetrahydrocarboline 17.



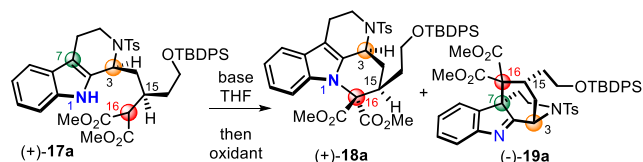
To undertake our study, we started to prepare compounds **17a/b** through a Pictet-Spengler reaction between tryptamine **24** and aldehydes **23a/b** which contain a malonate and a protected alcohol or aldehyde. The enantioselective synthesis of **23a** was already described by Wang and co-workers via iminium catalysis (Scheme 4).²¹ Slight modification of the Wang procedure allowed us to access aldehydes **23a/b** via Michael addition of dimethylmalonate **20** to enals **21a/b** in presence of L-proline-derived catalyst **22** to set the C15-stereocenter. Pictet-Spengler reaction of **23a/b** with tryptamine **24** was then effected in presence of diphenyl phosphoric acid. To prevent spontaneous lactamization between the N4 piperidinic amine and one of the ester of the malonate, protection of the secondary amine with an arylsulfonyl group was achieved at the end of the Pictet-Spengler reaction before the work-up to deliver diastereoisomers **17a/b** and **25a/b**. We did not try to improve the **17/25** ratio since we were curious to observe the effect of the relative stereochemistry on the oxidative cyclization. The enantiomeric excess of the Michael addition of **21a** to **20** was determined at this step on both diastereoisomers (+)-**17a** and (–)-**25a** and proved to be higher than 93%.²²

Scheme 4. Preparation of β -tetrahydrocarbolines 17 and 25.



We next started to study the oxidative cyclization on diastereoisomer (+)-**17a** which displays the relative stereochemistry between C3 and C15 of pleiocarpamine, talbotine and strictamine (Table 1).

Table 1. Optimization of the divergent oxidative cyclization of (+)-**17a** into (+)-**18a** and (–)-**19a**.



Entry	Base	Oxidant	Yield ^a 18a	Yield ^a 19a
1	LiHMDS (2.2 equiv.), -78 °C	I ₂ (2 equiv.), -78 °C to rt	nd ^b	nd ^b
2	LiHMDS (2.2 equiv.), -78 °C to rt	I ₂ (2 equiv.), rt	nd ^b	nd ^b
3	LiHMDS (2.4 equiv.), -78 °C	PhI(OAc) ₂ (1.2 equiv.), -78 °C to rt	traces	nd ^b
4	LiHMDS (2.4 equiv.), -78 °C	PhI(TFA) ₂ (1.2 equiv.), -78 °C to rt	23%	nd ^b
5	LiHMDS (2.4 equiv.), HMPA, -78 °C	PhI(TFA) ₂ (1.2 equiv.), -78 °C to rt	19%	nd ^b
6	KHMDS (2.4 equiv.), -78 °C	PhI(TFA) ₂ (1.2 equiv.), -78 °C to rt	17%	28%
7	LiHMDS (2.4 equiv.), -78 °C	Cu(2-ethylhexanoate) ₂ (1.2 equiv.), -78 °C to rt	nd ^b	nd ^b
8	LiHMDS (2.4 equiv.), -78 °C	Cp ₂ FePF ₆ (1.2 equiv.), rt	nd ^b	30%

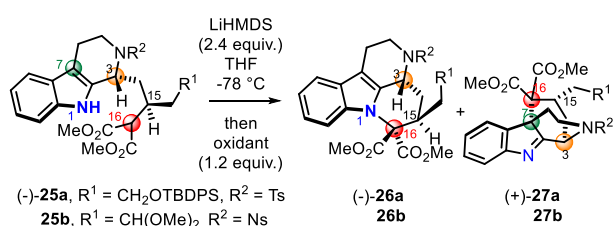
^aIsolated yield, ^bnot detected.

Double deprotonation of the malonate and the indole was effected with LiHMDS at -78 °C followed by addition of I₂ before warming up the reaction only led to recovery of 34% of the starting material and unknown products (entry 1). Zhu reported that formation of the N1-C16 bond from substrate **8** could only be achieved if iodine is added at room temperature after deprotonation at -78 °C. Unfortunately, in these conditions only a complex mixture was obtained from which the presence of the iodination product of the malonate of (+)-**17a** was detected (entry 2). The presence of the protected alcohol substituent at the β -position of the malonate has a dramatic impact on the oxidative cyclisation as it is apparent with the lack of reactivity of (+)-**17a** in comparison to **8**. Zhu also reported that the formation of **9** from **8** could be performed with hypervalent iodine reagents instead of I₂. While diacetate iodobenzene (PhI(OAc)₂, PIDA) was ineffective to achieve the cyclisation of (+)-**17a** (entry 3), the use of ditrifluoroacetate iodobenzene (PhI(TFA)₂, PIFA) gratifyingly allowed to forge the N1-C16 bond and afforded compound (+)-**18a** which is related to talbotine and pleiocarpamine in 23% (entry 4). The addition of HMPA did not improve the yield of (+)-**20a** as it was the case during the formation of **7** by Ma.^{11b} We then replaced LiHMDS by KHMDS as a base and we were surprised that in addition to 17% of (+)-**18a**, we also observed the formation of the C7-C16 bond and 28% of (–)-**19a** which is related to strictamine. We then continue to screen few other oxidants which are known to oxidize carbanions via single electron transfer (SET). Copper 2-ethylhexanoate was unsuccessful to induce any oxidative coupling after double deprotonation with LiHMDS (entry 7). In

contrast, Cp_2FePF_6 selectively afforded strictamine-like compound (–)-**19a** in 30% (entry 8)²³ and therefore allowed us to reach the objective of this study. In contrast to the work of Zhu and Ma, we were able to obtain selectively either the N1-C16 coupling or the C7-C16 coupling only by the choice of the oxidant. The reason for this divergence in selectivity is not yet clear. Nevertheless, we might postulate that the formation of the N1-C16 bond with $\text{PhI}(\text{TFA})_2$ could adopt an ionic pathway with the formation of electrophilic species on the indole or at C16, while the formation of the C7-C16 bond could proceed via the formation of a malonyl radical at C16 and/or an indolyl radical at C7.²³

After having identified divergent oxidative cyclisation conditions to produce selectively the talbotine/pleiocarpamine framework (+)-**18a** or the strictamine framework (–)-**19a**, we applied both conditions to diastereoisomers **25a/b** which do not possess the relative stereochemistry of pleiocarpamine, talbotine and strictamine (Table 2).

Table 2. Divergent oxidative cyclization of **25** into **26** and **27**.



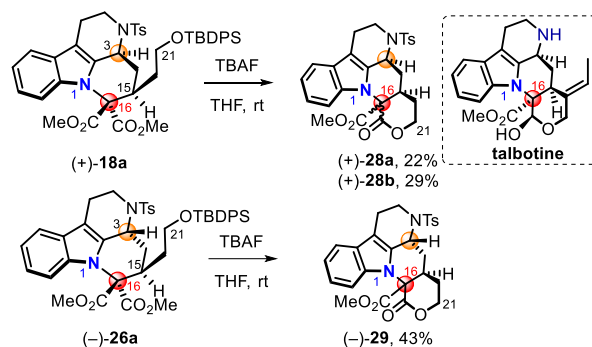
Entry	Substrate	Oxidant	Yield ^a 26a/b	Yield ^a 27a/b
1	25a	$\text{PhI}(\text{TFA})_2$, -78 °C to rt	38%	nd ^b
2	25b	$\text{PhI}(\text{TFA})_2$, -78 °C to rt	37%	nd ^b
3	25a	Cp_2FePF_6 , rt	nd ^b	45%
4	25b	Cp_2FePF_6 , rt	nd ^b	nd ^b

^aIsolated yield, ^bnot detected.

A similar trend of chemoselectivity was observed. With ditrifluoroacetate iodobenzene as oxidant, we were pleased to obtain as expected the formation of the N1-C16 bond of compound (–)-**26a** and **26b** (entries 1, 2). The C7-C16 oxidative cyclisation product (+)-**27a** was formed in 45% yield from **25a** with Cp_2FePF_6 (entry 3). It should be noted that the acetal of **25b** was too sensitive to the ferrocenium conditions (entry 4).

To get closer to the structure of talbotine, compound (+)-**18a**, which displays the necessary N1-C16 bond and the *cis* relationship between H3 and H15, was submitted to tetrabutylammonium fluoride to remove the TBDPS group (Scheme 5). The deprotection of the C21 primary alcohol was accompanied by a spontaneous lactonisation with one of the malonic methyl ester. The two diastereomeric pentacyclic lactones (+)-**28a** and (+)-**28b** were obtained in 22% and 29% yields. Interestingly when (–)-**26a** was subjected to the same deprotection conditions, the lactonisation event seemed to be diastereoselective since only one lactone (–)-**29** was observed in 43% yield.

Scheme 5. Synthesis of the talbotine scaffold.



Based on the Schmid, Hesse biosynthetic hypothesis, we investigated different oxidative coupling conditions to selectively achieve the early key divergent intramolecular couplings between a C16-malonate and the indole nucleus. After double deprotonation, the N1-C16 bond of pleiocarpamine and talbotine was forged with ditrifluoroacetate iodobenzene while the C7-C16 bond of strictamine could be constructed with Cp_2FePF_6 . The results obtained in this study by synthetic chemistry does not allow us to assume that the Hesse, Schmid's biosynthetic hypothesis is more accurate than the Wenkert's one since the involvement of enzymes is not considered. Nevertheless, it was a source of inspiration which allowed us to achieve the synthesis of the pleiocarpamine and strictamine scaffolds from the exact same precursor. A lactonisation of the N1-C16 coupling product also delivered the pentacyclic skeleton of talbotine.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectral and analytical data, copies of ¹H and ¹³C NMR spectra for new compounds (PDF).

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Author Contributions

All authors have given approval to the final version of the manuscript.

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