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Total Synthesis of Mavacuran Alkaloids with Bioinspired and non-Bioinspired Strategies

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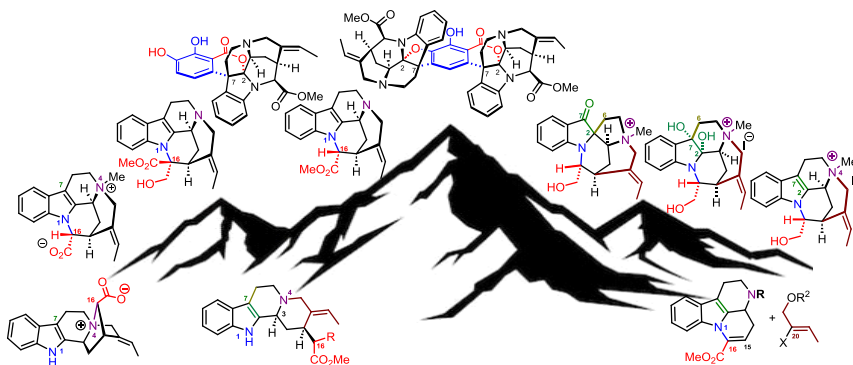
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Abstract In this account, we report our endeavors towards the total synthesis of the mavacuran alkaloids and some of their highly natural complex bis-indoles. This study started with the hemisynthesis of voacalgine A and bipleiophylline, made an excursion to a related family of monoterpene indole alkaloids (total synthesis of 17-nor-excelsinidine) and ended with the total synthesis of several mavacuran alkaloids (16-epi-pleiocarpamine, 16-hydroxymethylpleiocarpamine, taberdivarine H, normavacurine, C-mavacurine, C-proflurocurine, and C-fluorocurine) via a combination of bioinspired and non-bioinspired synthetic routes.

1 Introduction

2 Bioinspired hemisynthesis of voacalgine A and bipleiophylline

3 Total synthesis of the mavacuran alkaloids

4 Bioinspired oxidative cyclization of a geissoschizine ammonium derivative to form the N1-C16 bond and E ring

5 Non-bioinspired Michael addition to form the C15-C20 bond and the E ring

6 Conclusion

Key words monoterpene indole alkaloids, bipleiophylline, pleiocarpamine, C-mavacurine, taberdivarine H, C-fluorocurine, biomimetic, oxidative coupling

Introduction

In the frame of this cluster on biomimetic synthesis,¹ the objective of the present account towards the synthesis of the mavacuran alkaloids² is to tell the story of the joint efforts of our two research teams at the Faculty of Pharmacy (BioCIS: Biomolécules, Conception, Isolement, Synthèse) and at the Faculty of Science (ICMMO: Institut de Chimie Moléculaire et des Matériaux d'Orsay) of Université Paris-Saclay (formerly Université Paris-Sud). This project started with the ambition to accomplish the total synthesis of bipleiophylline (**1**),³ which is a quite complex bis-indole alkaloid containing two units of pleiocarpamine (**2**),⁴ an emblematic mavacuran alkaloid,

connected with a 2,3-bis(hydroxy)benzoic acid (**3**)-derived aromatic spacer (Figure 1).

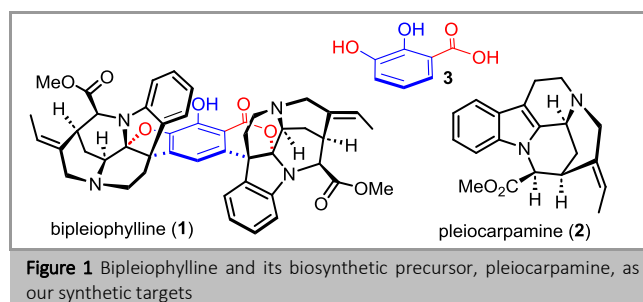


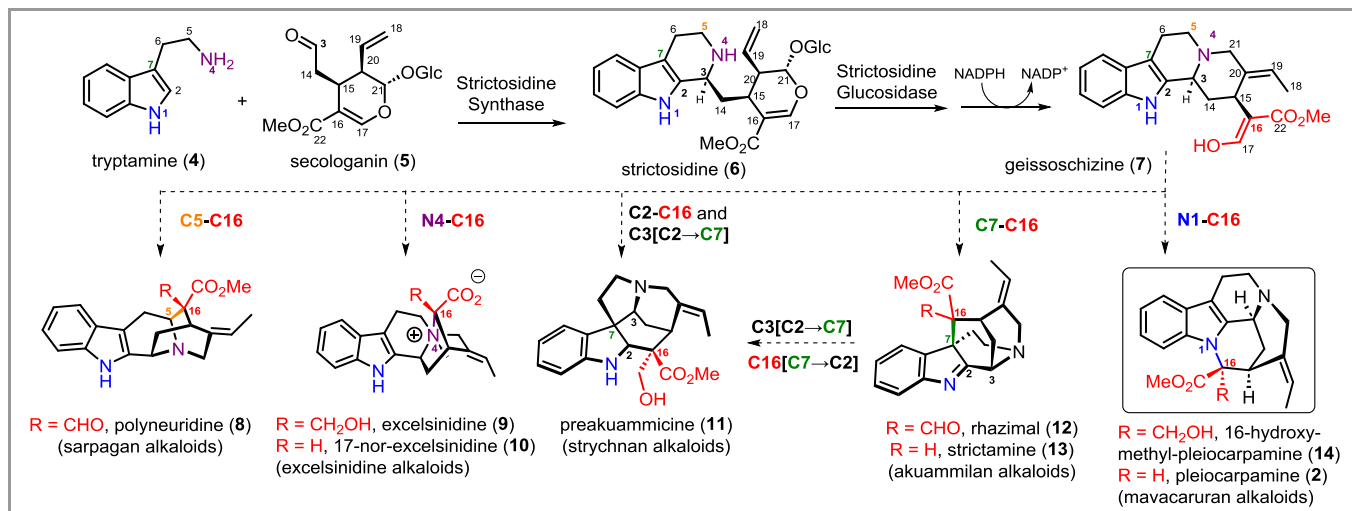
Figure 1 Bipleiophylline and its biosynthetic precursor, pleiocarpamine, as our synthetic targets

The association of our two teams to reach this goal was evident and highly complementary due to our respective expertises in bioinspired synthesis of indole alkaloids⁵ and in synthetic methodologies towards the benzofuroindoline unit⁶ presents in bipleiophylline. We were thrilled to be funded by the French Research National Agency (ANR) to tackle this ambitious target with a collaborative grant that we named “Mount Indole” in reference to the front cover of an authoritative book by Hanessian and co-workers “design and strategy in organic synthesis” that represented bipleiophylline at the top of a mountain.⁷

The mavacuran alkaloids sub-family² belongs to the monoterpene indole alkaloids which are originated from strictosidine, the product of an enzymatic Pictet-Spengler reaction between tryptamine (**4**), the indolic part and secologanin (**5**), the monoterpene part (Scheme 1).⁸ Among various biosynthetic pathways, the deglycosylation of strictosidine (**7**) and the following reductive amination is a very important biosynthetic transformation that lead to the tetracyclic corynanthe skeleton of geissoschizine. It is a pivotal

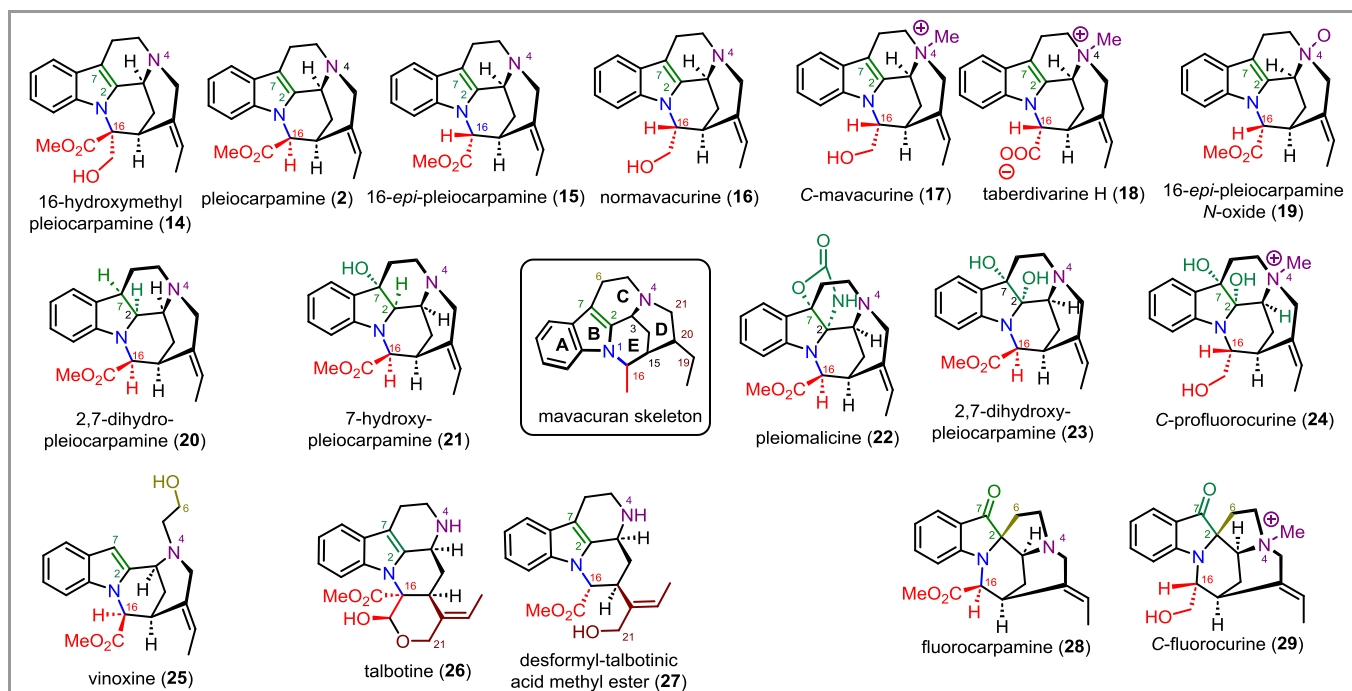
intermediate for several others sub-families of monoterpene indole alkaloids via for instance divergent oxidative cyclizations involving the C16-formyl ester leading to diverse pentacyclic structures. On one hand, the coupling of the C16-formyl ester with the piperidinic C-ring delivers either the sarpagan alkaloids (**8**, C5-C16 coupling)⁹ or the excelsinidine alkaloids (**9**, **10**, N4-C16 coupling).¹⁰ On the other hand, oxidative coupling of C16 with different positions of the indole part is also observed.¹¹ The strychnan alkaloids are the formal

products of a C2-C16 coupling and migration of the C3 carbon from the C2 to the C7 positions.¹² Alternatively, C7-C16 coupling yields the akuammilan alkaloids (**12**, **13**)¹¹ which have been postulated to be the biosynthetic precursors of the strychnan alkaloids via concomitant migrations of the C3 carbon from C2 to C7 and of the C16 carbon from C7 to C2.¹¹ Finally, the indolic nitrogen (N1) could also be involved in an oxidative cyclization yielding to the mavacuran alkaloids (**2**, **14**, N1-C16 coupling) which are of interest to us.^{11,13}



Overall the N1-C16 bond is characteristic of the pentacyclic mavacuran skeleton which encompass more than 20 natural products and some of them are represented in Figure 2. It is interesting to note that this family of natural products was named after the isolation of one of this congener, *C*-mavacurine (**17**), from a curare called mavacure used in Venezuela for the preparation of arrow poisons.^{4a,14}

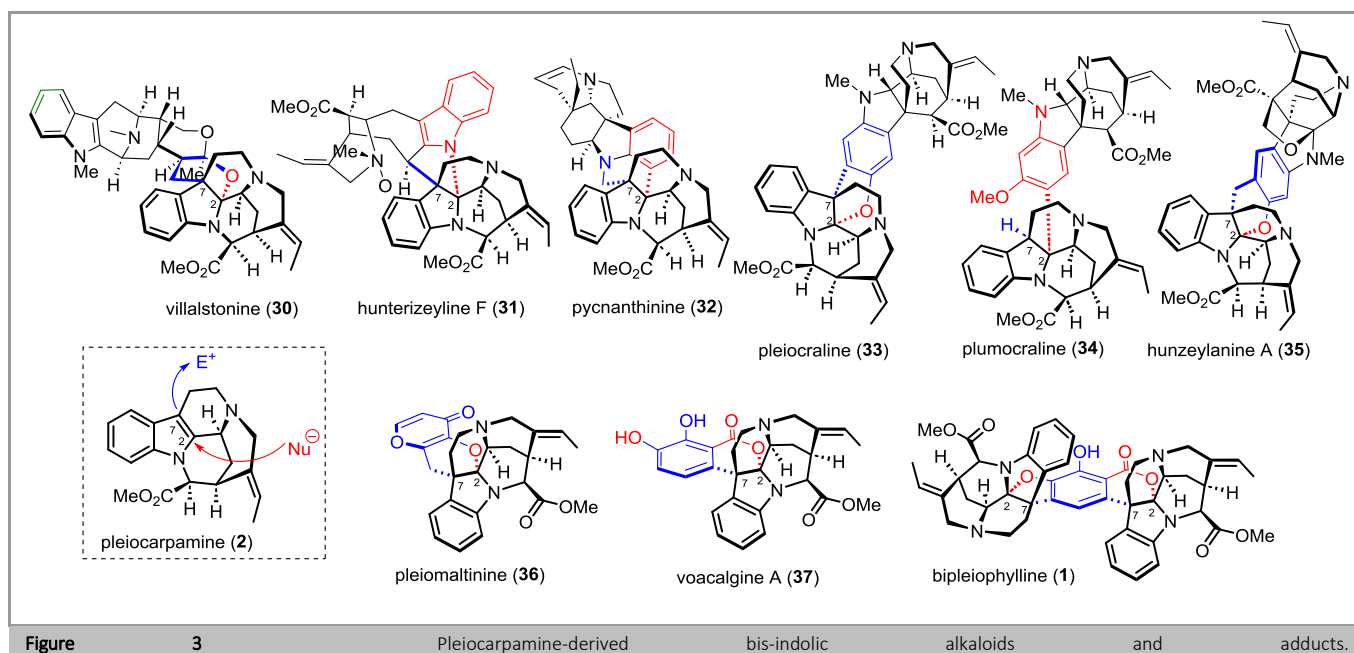
The diversity of structure is found mainly in the stereochemistry and nature of the oxygenated functional group borne by the C16 carbon [ester/carboxylate (**2**, **15**, **18-23**)] or primary alcohol (**16**, **17**, **24**) or both (**14**), the N4-nitrogen [tertiary amine (**14-16**, **20-23**) or *N*-methyl ammonium (**17**, **18**, **24**) or *N*-oxide (**19**)] or the substitution of the C2-C7 indolic bond [indoles (**2**, **14-19**), reduced indoline (**20**) or oxidized indoline (**21-24**)].^{2,4a,15}



Fluorocarpamine (**28**) and *C*-fluorocurine (**29**) display a rearranged skeleton with a pseudo-indoxyl motif as the A/B rings and the ring contraction of the C ring with the migration of the C6 carbon from C7 to C2 via a pinacol rearrangement of the 2,7-dihydroxyindoline of respectively 2,7-dihydroxypleiocarpamine (**23**) and *C*-profluorocurine (**24**).^{2,4a}

The pentacyclic mavacuran caged-skeleton is highly strain which makes the C7-carbon of the indolic nucleus particularly reactive towards electrophiles and the resulting iminium at C2 could then be trapped by a nucleophile resulting in a difunctionalization of the indole nucleus (Figure 3). For this reason, pleiocarpamine (**2**) has a propensity to add to other monterpene indole alkaloids leading to bis-indole alkaloids

such as villalstonine (**30**), hunterizeyline F (**31**), pycnanthine (**32**), pleiocraline (**33**), plumocraline (**34**) or hunzylanine A (**35**).² Pleiocarpamine (**2**) could also react in nature with non indolic electrophiles such as a pyrone-derived *ortho*-quinomethide to deliver pleiomaltinine (**36**) or an *ortho*-quinone leading to voacalgine A (**37**) and ultimately to bipleiophylline (**1**).²

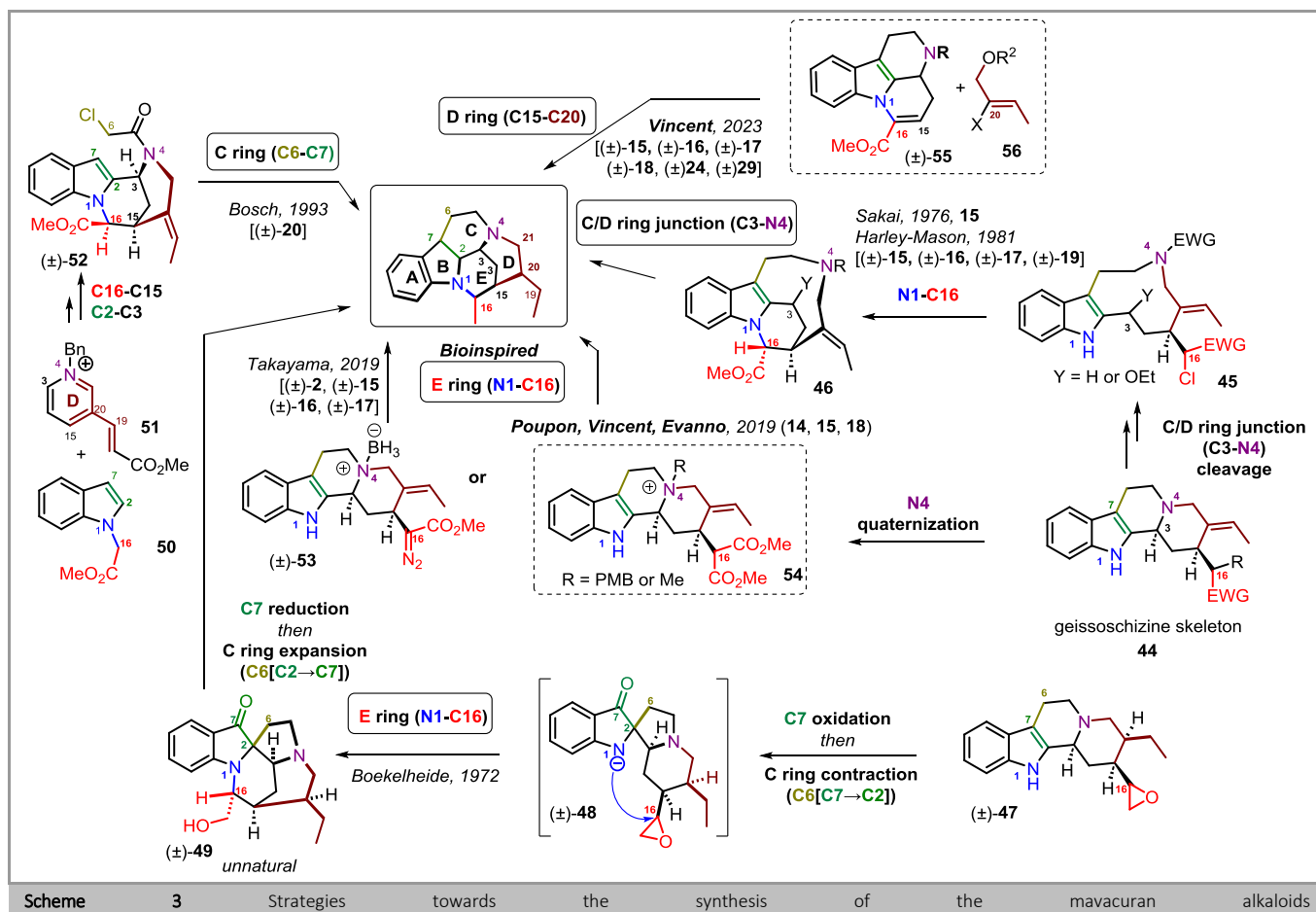


Bioinspired hemisynthesis of voacalgine A and bipleiophylline

We tackled our endeavor to reach, bipleiophylline, our synthetic summit by the final ascent: starting from pleiocarpamine up to bipleiophylline via voacalgine A. The reason was that the total synthesis of the strained mavacuran skeleton and in particular pleiocarpamine is a more difficult climb that it may seem. Fortunately, we were able to isolate almost 100 mg of pleiocarpamine as its formic salt from the bark of *Alstonia balansae* with an isolation yield below 0.2%. It should be noted that the biomimetic hemisynthesis of bis-indole natural products villalstonine (**30**), macrocarpamine and plumocraline (**34**) as well as pyrone-adduct pleiomaltinine (**36**) from natural pleiocarpamine (**2**) have already been reported.¹⁶

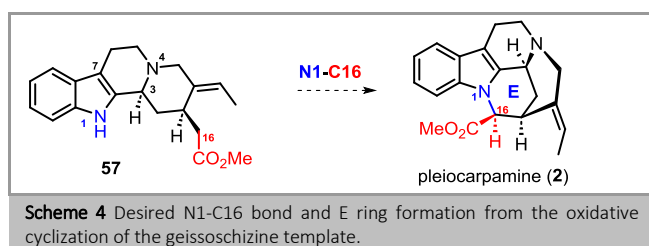
While we developed several synthetic methods towards the synthesis of the benzofuroindoline part of bipleiophylline (**1**) and voacalgine A (**37**), none of them could be applied to the synthesis of these natural products.⁶ We therefore design a new oxidative coupling between indoles and 2,3-bishydroxybenzoic acid **3** or its methyl ester **39** to yield respectively the isochromenoindoline **38** and benzofuroindoline **40** parts of bipleiophylline.^{17,18} Application

of this method to pleiocarpamine and 2,3-bishydroxybenzoic acid **3** led successively to the hemisynthesis of voacalgine A (**37**) and bipleiophylline (**1**).¹⁷ This method proceeds via the oxidation of the catechol of **3** with silver oxide to generate the corresponding *ortho*-quinone **41** onto which the nucleophilic indole of **2** (as its formate salt) could add to form a C-C bond and the iminium of **42** is then intercepted by the carboxylate to yield the isochromenoindoline of voacalgine A (**37**). Of note, before our synthesis of voacalgine, its structure was thought to contain a benzofuroindoline motif ("the other half" of bipleiophylline)¹⁹ and our work allowed to revised its structure to **37** via the chemoselectivity observed during the oxidative coupling and via 2D NMR. In the case of voacalgine A (**37**) and isochromenoindolines **38**, HMBC correlations are observed between the same hydrogen of the aromatic platform and both the carbonyl and the C7 carbon. In contrast, these two carbons are correlated with two different hydrogens of the aromatic platform for benzofuroindolines **40**. In a second step, further oxidation with silver oxide in presence of pleiocarpamine (**2** as its formate salt), leads to addition of the latter to *ortho*-quinone **43**. After the formation of a new C-C bond, the iminium **44** cyclized with the oxygen of the catechol to complete the formation of the benzofuroindoline of



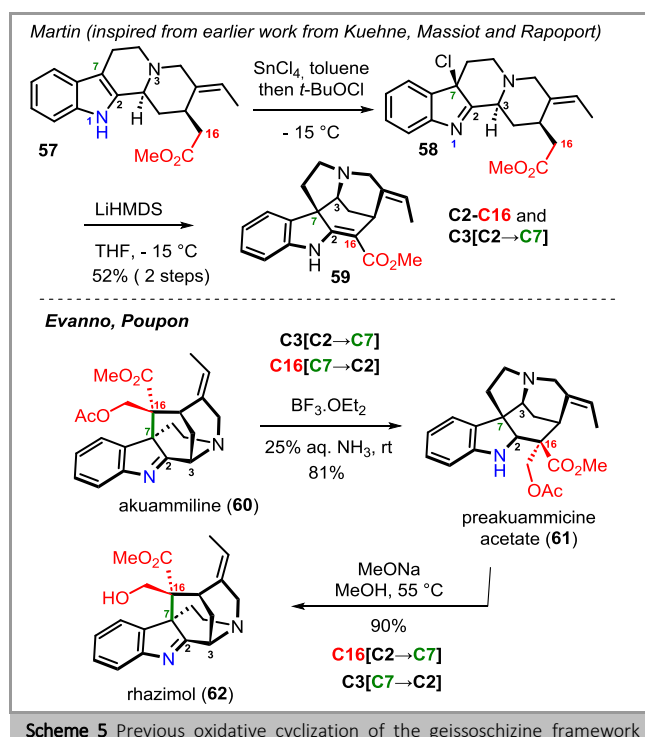
Bioinspired oxidative cyclization of a geissoschizine ammonium derivative to form the N1-C16 bond and E ring

The objective of our approach towards the mavacuran alkaloids relies on the postulated last step of the biosynthesis, i.e. the oxidative cyclization of geissoschizine to form the N1-C16 bond (Scheme 4).



To the best of our knowledge, oxidative cyclization of the full geissoschizine template has been only reported by Martin and co-workers via the diastereoselective formation of chloroindolenine **58** from desformylgeissoschizine **57** with *t*-butyl hypochlorite in presence of tin chloride in 52% yield which is quite impressive considering the complexity of this skeletal reorganization (Scheme 5).²⁸ Deprotonation of the ester of **58** induced the cyclization into the strychnan skeleton of **59** via formally the formation of the C2-C16 bond and migration of the C3 bond from C2 to C7 according to precedents from Kuehne then Massiot and then Rapoport.²⁹

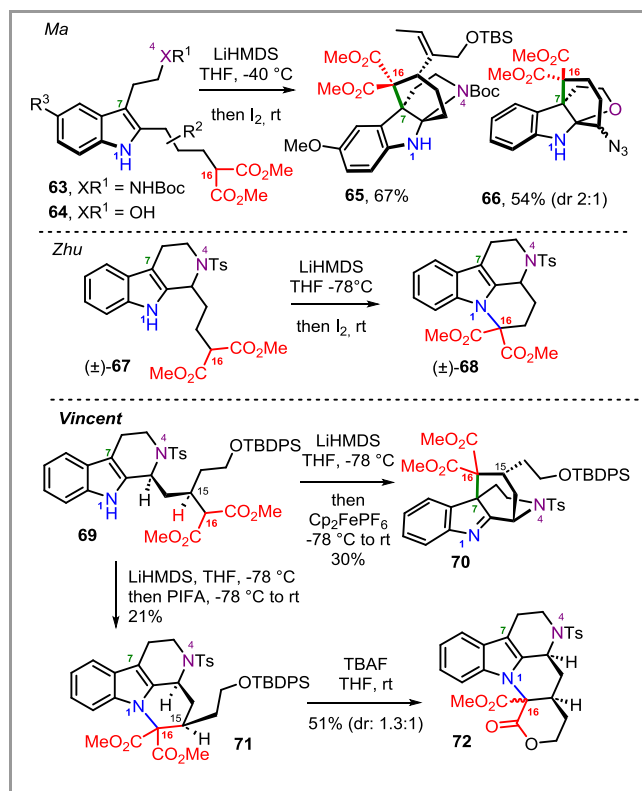
The C7-C16 bond of the akuammilan could also be formed first before a skeletal reorganization leading to **59**. This route is postulated among others as a biosynthetic pathway (see Scheme 1).



into the strychnan skeleton and skeletal interconversion between the akuammilan and strychnan frameworks.

This hypothesis could be supported by the fact that the rearrangement of akuammiline (**60**, akuammilan skeleton) to preakuammicine acetate (**61**, strychnan skeleton) involving the interconversion of the C3 and C16 carbons from the C2 to C7 position³⁰ has been observed in presence of boron trifluoride by one of our two research groups,^{30a} and similar transformation were also observed previously with a strong base.^{30b-d} Interestingly, the reverse bond migrations are also possible after saponification of preakuammicine acetate delivering rhazimol (**62**). While this skeletal reorganization is possible in a laboratory, it does not mean that the biosynthesis of the strychnan alkaloids follow this pathway via the akuammilan template.

Nevertheless, an oxidative cyclization method has been developed by the group of Ma in the context of the total synthesis of the akuammilan alkaloids on simplified geissoschizine structures that are missing two rings such as in **63** and **64** that led respectively to **65** and **66**.³¹ The reaction proceeds via the deprotonation of both the NH indole (N1) and the malonate (C16) followed by the addition of iodine as oxidant which lead to the formation of the C7-C16 bond. It turned out that this reaction could be substrate dependent since the group of Zhu reported that tricyclic β -tetrahydrocarboline (\pm)-**67** lead in a chemodivergent manner to N1-C16 bond formation (\pm)-**68**.³² In certain cases, this chemoselectivity could be controlled by the choice of the oxidant as we demonstrated with β -tetrahydrocarboline **69** which possess an additional substituent in comparison to **67**.³³ After formation of the bis-anion with LiHMDS, the use of ferrocenium hexafluorophosphate led to the C7-C16 bond formation and **70**, while phenyliodine(III)bis(trifluoroacetate) delivered the N1-C16 product **71** which could then be converted with TBAF to talbotine analog **72** as a mixture of diastereoisomers.



Scheme 6 Indole-malonate oxidative cyclizations related to the akuammilan and mavacurans alkaloids.

In this context, our ambition was to apply the Ma's oxidative conditions to geissoschizine itself in order to promote the N1-C16 bond formation and to obtain pleiocarpamine (**2**). In order to ensure a scalable and robust access to geissoschizine we identified that the combination of two known total synthesis of geissoschizine would be optimal.³⁴ According to Martin and co-workers, diastereoselective Mannich reaction between silyl dienol ether **74** and chiral tryptophan-derived imine **73** yielded β -tetrahydrocarboline **75**.³⁵ The only undescribed step of our synthesis is the allylation of **75** with iodoalkenyl-containing bromide **76** to intercept intermediate **77** of the Cook's synthesis.³⁶ Intramolecular reductive Heck reaction delivered with a 2:1 diastereoselectivity the tetracyclic geissoschizine framework from which removal of the benzyl ester yielded 16-desformylgeissoschizine **57** and then (+)-geissoschizine (**7**) itself via a formylation reaction.

The stage was set to test the key oxidative cyclization. After few experiments, we found out that upon double deprotonation with LiHMDS and addition of I₂ as oxidant, an oxidative cyclization occurred. However, it did not lead to pleiocarpamine (**2**) or even stricatmine (**13**) as we have hoped via the coupling of the C16-formyl ester and one of the position of the indole nucleus. Instead, the C16-formylester reacted with the N4-tertiary amine with spontaneous desformylation leading to the excelsinidine skeleton **78** which could be saponified into the zwitterionic natural product (–)-17-nor-excelsinidine (**10**) which was synthesized for the first time.³⁴

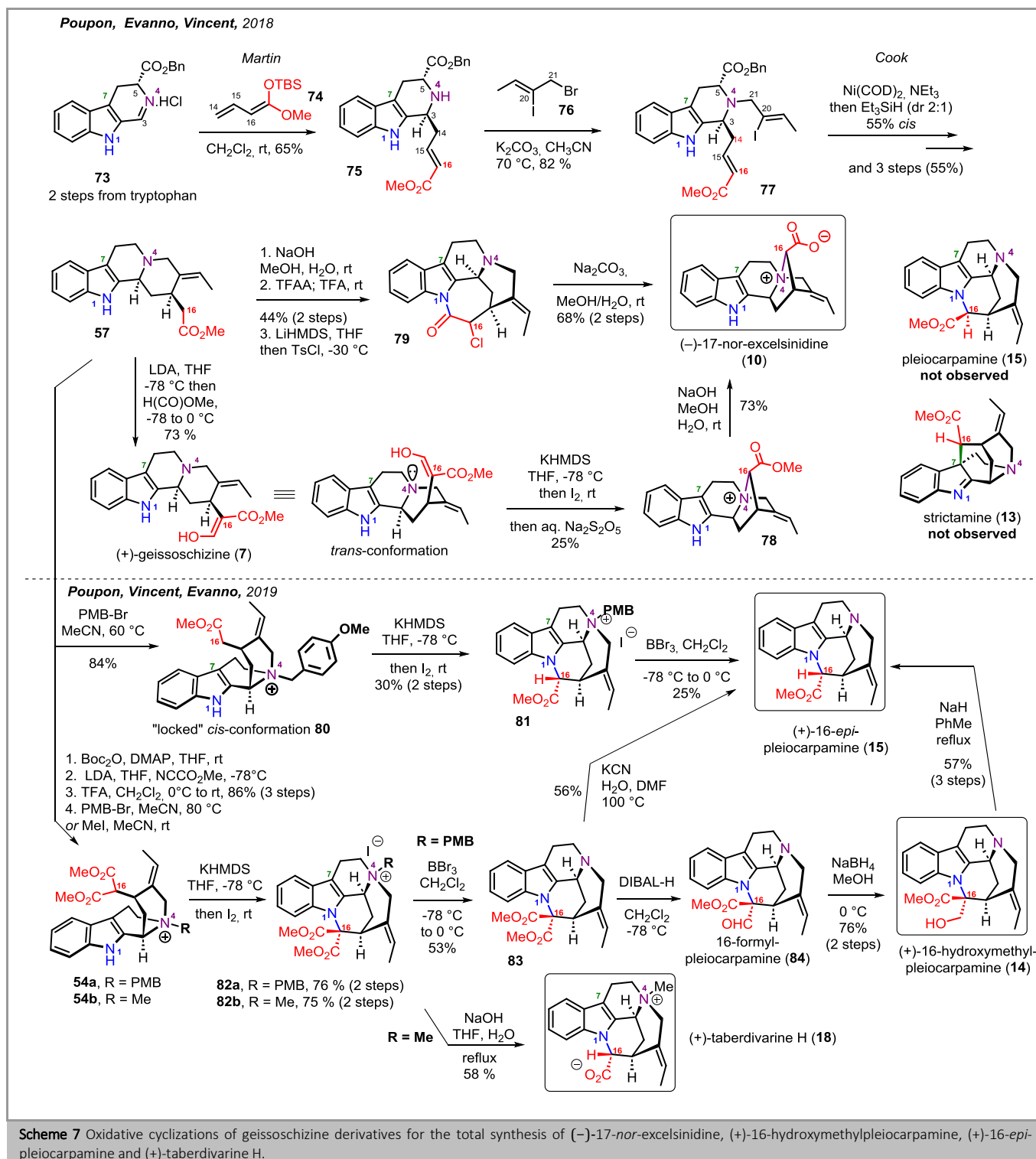
At this stage, we reasoned that formation of the N1-C16 bond of pleiocarpamine could be facilitated by bringing in close proximity the indolic nitrogen N1 and the C16 carbon. Therefore, a ring contraction of chlorolactam **79** derived from 16-desformylgeissoschizine **57** was sought. Once again, (–)-

17-*nor*-excelsinidine (**10**) was obtained upon treatment of **79** in basic condition via concomitant nucleophilic substitution of the C16-chlorolactam by the N4-tertiary amine and opening of the lactam.³⁴

We realised that the lone pair of the N4-tertiary amine was more reactive than the indole nucleus. Moreover, based on earlier conformational study from Sakai and co-workers, geissoschizine (**7**) adopts a *trans*-conformation in which the N4 tertiary amine and the C16-formyl ester are in close proximity which probably facilitate their oxidative coupling.³⁷ Taking all these considerations together, we acknowledged that in order to access the mavacuran skeleton, we needed to sequester the

too reactive lone pair of the N4-tertiary amine and to push the conformation of geissoschizine into the *cis*-conformation in which the C16-carbon and the indole would be spatially able to interact. It appeared to us that transforming the N4-tertiary amine into an ammonium would fulfil both objectives since the team of Gaich proved that the *N*-(4-bromo)benzylammonium of geissoschizine adopts a *cis*-conformation according to X-ray analysis.³⁸

However, we were aware with fear, that performing a double deprotonation on an already positively charged intermediate may end-up in decomposition. Nevertheless, we decided to pursue this strategy.



Scheme 7 Oxidative cyclizations of geissoschizine derivatives for the total synthesis of (-)-17-nor-excelsinidine, (+)-16-hydroxymethylpleiocarpamine, (+)-16-epi-pleiocarpamine and (+)-taberdivarine H.

Upon treatment with *para*-methoxybenzyl bromide, 16-desformylgeissoschizine **57** delivered ammonium **80**, while the corresponding C16 malonate **54a** could also be obtained from **57** via temporary protection of the indole nitrogen.²⁵

To our delight and despite our fear, double deprotonation with KHMDS followed by the use of I₂ as oxidant allowed to selectively form the N1-C16 bond and the pentacyclic framework of the mavacuran alkaloids for the first time in our hands. A modest yield of 30% of cyclization product **81** was

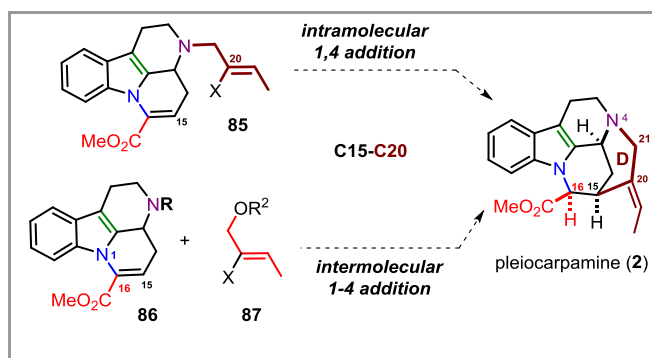
obtained from monoester **80** with the recovery of 52% of the starting material. The removal of the PMB group from **81** with BBr₃ restored the tertiary amine and delivered (+)-16-*epi*-pleiocarpamine (**15**) in 25% yield.^{25b} The oxidative coupling from the C16-malonate was more efficient since 76% of pentacyclic ammonium **82a** were obtained over the benzylation and oxidative coupling steps.^{25a} After removal of the PMB group with BBr₃, a Krapcho decarboxylation was performed which also delivered (+)-16-*epi*-pleiocarpamine (**15**). The *pseudo*-symmetry of the malonate could be broken

since the two esters were in different spatial environments induced by the shape of the mavacuran framework. Indeed, the ester lying on the convex face was more easily accessible than the one protected by the concave face. Therefore, selective reduction of the ester on the convex face by DIBAL-H gave 16-formyl-pleiocarpamine (**84**) which should likely be the biosynthetic precursor of 16-hydroxymethyl-pleiocarpamine (**14**) and pleiocarpamine (**2**). Further reduction of the aldehyde of **84** with NaBH₄ generated (+)-16-hydroxymethyl-pleiocarpamine (**14**). Then, deprotonation of the alcohol of **84** with NaH and heating resulted in a desformylation reaction and to the isolation of (+)-16-*epi*-pleiocarpamine. Unfortunately, we were never able to isolate pleiocarpamine itself (**2**). In each conditions, its more stable epimer 16-*epi*-pleiocarpamine (**15**) was isolated. All attempts to epimerize 16-*epi*-pleiocarpamine into the postulated kinetic product pleiocarpamine failed.

Having noticed that several mavacuran alkaloids display both a *N*-methyl ammonium and the stereochemistry of 16-*epi*-pleiocarpamine (**17**, **18**, **24**, **29**, see Figure 2), the quaternization was performed with methyl iodide to form *N*4-methyl ammonium **54b**. The oxidative cyclization smoothly delivered pentacyclic *N*-methyl ammonium **82b** and a double saponification and decarboxylation gave birth to zwitterionic (+)-taberdivarine H (**18**).²⁵

Non-biospired Michael addition to form the C15-C20 bond and the E ring

While the biospired oxidative cyclization of geissoschizine to complete the N1-C16 bond was the first approach that allowed us to access the mavacuran framework, it was not the first strategy that we investigated. Actually, our first thought was to perform an intramolecular 1,4-addition of a vinyl halide into an *N*-indolylacrylate **85** that failed (Scheme 8). Nevertheless, after the success of the biomimetic coupling, we went back to the Michael addition approach but in the intermolecular version with the addition of **87** to **86**.²⁷



Scheme 8 1,4-addition approaches of a vinylhalide into a *N*-indolylacrylate to form the C15-C20 bond and the D ring

The *N*-indolylacrylate function of **85** and **86** was prepared via the Pictet-Spengler reaction of *N*-substituted tryptamines **88a-c** with aldehydes **89a-b** containing respectively a keto-ester (**89a**) or a protected keto-ester (**89b,c**). The reaction of *N*4-allyltryptamine **88a** and aldehyde **89a** yielded hemiaminal (\pm)-**90** after the reaction of the indolic nitrogen and the carbonyl of the keto-ester. Dehydration with trifluoroacetic anhydride delivered the desired *N*-indolylacrylate (\pm)-**85**. The corresponding *N*4-Me and *N*4-PMB Michael acceptors **86a,b**

were obtained via the hydrolysis of the keto-ester acetal of Pictet-Spengler products (\pm)-**91a,b**. These two compounds and the synthetic route employed³⁹ are closely related to vinconate (OC-340, *N*4-ethyl analogue of **86**) that was in clinical trial for the treatment of cognitive disorder.⁴⁰

As already mentioned, the intramolecular addition of the vinyl iodide of (\pm)-**85** to the *N*-indolylacrylate moiety failed despite having precedents in the total synthesis of other families of monoterpene indole alkaloids.^{36,41,42} This failure is probably due to an unflavored conformation leading most of the time to the dehalogenated product (\pm)-**92** such as in reductive Heck or radical conditions. The generation of a vinyl lithium intermediate via iodide/lithium exchange with butyllithium was also not productive to induce the intramolecular Michael addition. Nevertheless, it was noted that in THF, excess of butyllithium added in a 1,2-fashion to the ester thus affording (\pm)-**93** which is indeed not surprising knowing the textbook reactivity of organolithium reagents. More interestingly, when we switched THF to toluene as solvent, we were very surprised to observe the 1,4-addition product (\pm)-**93** of butyllithium to the *N*-indolylacrylate moiety with a very high diastereoselectivity.⁴³ We postulated with the help of DFT studies that this selectivity in favor of the 1,4 addition in toluene is controlled by the formation of a complex involving the *N*4-tertiary amine and an aggregate of the organolithium reagent.⁴⁴ After few years focused on the successful biospired oxidative cyclization presented before, we desired to publish this intriguing observation on the intermolecular 1,4-addition of butyllithium on our tetracyclic Michael acceptor. During this publication process, we realized that we could take advantage of this unexpected reactivity to design a revised retrosynthesis via the corresponding intermolecular 1,4-addition strategy (cf Scheme 8).

To this end, lithium/halogen exchange from vinyl iodide **87** with BuLi was conducted under carefully controlled conditions and the resulting vinyl lithium reagent, used in large excess, could be added to Michael acceptors (\pm)-**86a,b** leading diastereoselectively to adducts (\pm)-**95a,b** and to unreacted Michael acceptors (Scheme 9).²⁷ The temperature of this process is key to both ensure an efficient lithium/halogen exchange and to avoid the decomposition of the thus generated vinyl lithium intermediate. The tetracyclic compounds (\pm)-**95a,b** could be cyclized into the pentacyclic framework of the mavacuran alkaloids as an ammonium salt via formation of an allyl halide and heating to achieve the intramolecular nucleophilic substitution. In the case of the *N*4-methyl substrate (\pm)-**95b**, a final saponification delivered (\pm)-taberdivarine H (**19**).

As for the *N*4-PMB substrate (\pm)-**95a**, removal of the *N*-PMB group to restore the tertiary amine was effected with TFA and anisole to yield (\pm)-16-*epi*-pleiocarpamine (**15**). Following steps described by Harley-Mason^{21a} and then Takayama,²⁶ the latter was converted to (\pm)-normavacurine (**16**) via reduction with LiAlH₄, and then to (\pm)-*C*-mavacurine (**17**) via treatment with methyl iodide. Note that we were not able to access this last natural product from the *N*-methylammonium arising from (\pm)-**95b**.

After this non-biomimetic approach to the mavacuran skeleton, the end-game to access the *C*-fluorocurine (**29**) was

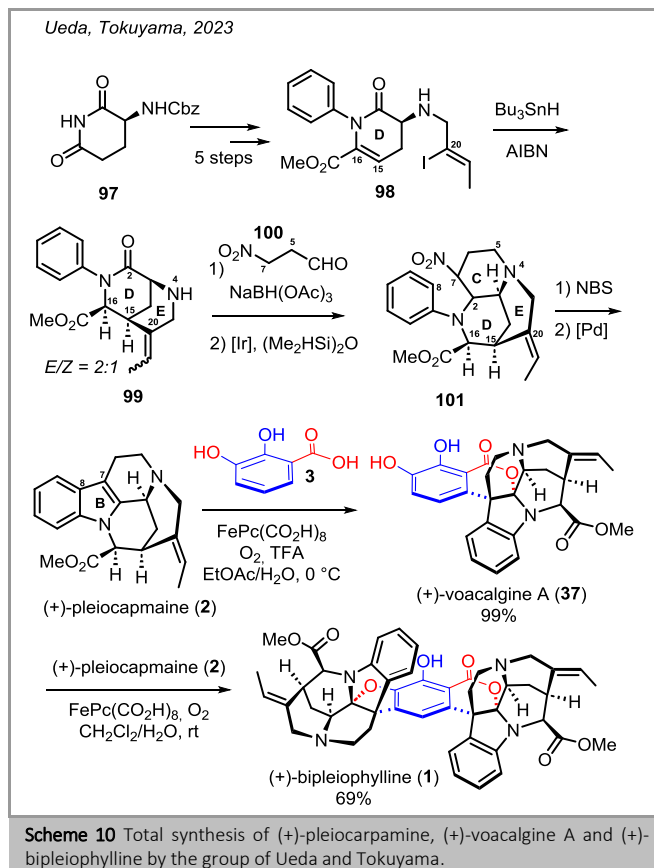
(**29**) were achieved in respectively 12 and 13 steps and 1.3% and 0.5% overall yields in the longest linear sequence.

Unfortunately, the epimerization at C16 is the last crevasse to cross to make the junction with the base camp: the total synthesis of pleiocarpamine. We are in the pursue of epimerization conditions allowing 1) the deprotonation of the hydrogen at C16 lying in the concave face which makes it difficult to reach and 2) a kinetic control during the reprotonation.

Epilogue

Few days after the submission of the first version of this personal account, the group of Ueda and Tokuyama published an enantioselective total synthesis of pleiocarpamine, voacalgine A and bipleiophylline.⁴⁷ The authors overcame the challenge of making the pleiocarpamine skeleton with the required stereochemistry at C16 which was the last problem that we were unable to solve.

In a very original manner, they built the indole and the B ring as the last event (Scheme10). N-Cbz glutamine-derived **97** was converted in 5 steps into Michael acceptor-containing vinyl iodide **98**. Related to their recent total synthesis of vinoxetine,⁴² the authors performed a radical-mediated intramolecular Michael addition of a vinyl radical onto the N-phenylamino-acrylate moiety to construct the C16-C20 bond and the E ring of **99**. The required relative *cis*-stereochemistry at C15 and C16 was fortunately obtained albeit significant isomerization of the alkylidene. The C ring of compound **101** was obtained via reductive amination with aldehyde **100** to form the N4-C6 bond, C2-lactam reduction and intramolecular *aza*-Henry reaction to form the C2-C7 bond. The B ring, the indole and the C7-C8 bond of (+)-pleiocarpamine (**2**) were constructed in a gram scale via a palladium-catalyzed reaction from the corresponding α -nitroalkane of **101**.



Related to our previous hemisyntheses, oxidative coupling of (+)-pleiocarpamine (**2**) with 2,3-bishydroxybenzoic acid **3** delivered (+)-voacalgine A (**37**) and then (+)-bipleiophylline (**1**) in impressive yields. Instead of our use of silver oxide (Ag_2O), the group of Ueda and Tokuyama performed the two successive oxidative biomimetic couplings by deploying iron octacarboxyphthalocyanine complex ($\text{FePc}(\text{CO}_2\text{H})_8$) as catalyst in presence of oxygen closely related to the catalytic system (iron phthalocyanine [FePc] and *t*-BuOOH) described by Chen and co-workers for the synthesis of isochromanoidolines.¹⁸

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Conflict of Interest

The authors declare no conflict of interest.

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