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Audrey Mauger, Maxime Jarret, Aurélien Tap, Rémi Perrin, Régis Guillot,, et al.. Collective Total Synthesis of Mavacuran Alkaloids via an Intermo-lecular 1,4-Addition Approach. *Angewandte Chemie International Edition*, 2023, 62, 10.1002/anie.202302461 . hal-04274088

HAL Id: hal-04274088

<https://hal.science/hal-04274088v1>

Submitted on 7 Nov 2023

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Indole Alkaloids

Collective Total Synthesis of Mavacuran Alkaloids through Intermolecular 1,4-Addition of an Organolithium Reagent**

Audrey Mauger, Maxime Jarret, Aurélien Tap, Rémi Perrin, Régis Guillot, Cyrille Kouklovsky, Vincent Gandon,* and Guillaume Vincent*

How to cite: *Angew. Chem. Int. Ed.* **2023**, *62*, e202302461

International Edition: doi.org/10.1002/anie.202302461

German Edition: doi.org/10.1002/ange.202302461

Abstract: We report a synthetic endeavor towards the highly strained pentacyclic caged framework of the mavacuran alkaloids which culminated with the concise total synthesis of *C*-fluorocurine, *C*-profluorocurine, *C*-mavacurine, normavacurine, 16-*epi*-pleiocarpamine and taberdivarine H. We designed a strategy involving late-stage construction of the D ring by Michael addition of a vinylic nucleophile to a 2-indolyl acrylate moiety. While the intramolecular Michael addition did not succeed, we were able to perform a diastereoselective unusual intermolecular 1,4-addition of a functionalized vinyl lithium reagent to a readily accessible Michael acceptor with the assistance of the piperidine nitrogen atom through the formation of a complex as suggested by DFT computations. Final cyclization was achieved by nucleophilic substitution to form an ammonium intermediate. The first total syntheses of *C*-profluorocurine and *C*-fluorocurine were finalized by the dihydroxylation of *C*-mavacurine and a pinacol rearrangement, respectively.

Introduction

The mavacuran alkaloids^[1] belongs to the large family of monoterpene indole alkaloids.^[2] The pentacyclic mavacuran skeleton is characterized by a C–N bond between the N1 indole nitrogen atom and the C16 carbon atom of the

geissoschizine framework (Figure 1).^[1] *C*-Mavacurine (1) and pleiocarpamine (2) are the two representative members of this family.^[1,3] *C*-Mavacurine (1)^[3a–d] is the name-giver of this subfamily, and pleiocarpamine (2)^[3a,e,f] is a constitutive unit of several complex indole alkaloids, including bis-indole alkaloids.^[1]

We have recently performed the hemisynthesis of voacalgine and bipleiophylline from natural pleiocarpamine.^[4] Therefore, access to the mavacuran alkaloids became of high interest for us. Normavacurine (3),^[3a,g,h] taberdivarine H (4)^[3i] and 16-*epi*-pleiocarpamine (5)^[3a,j] are also closely related, only differing by the presence of an N4-methyl ammonium group, the nature of the oxygenated function connected to the C16 carbon center and the stereochemistry of the latter. *C*-Profluorocurine (6, previously known as *C*-alkaloid Y)^[3a,k,l] and 2,7-dihydroxypleiocarpamine (7)^[3m] are oxidized natural analogues of *C*-mavacurine and pleiocarpamine, respectively, in which the

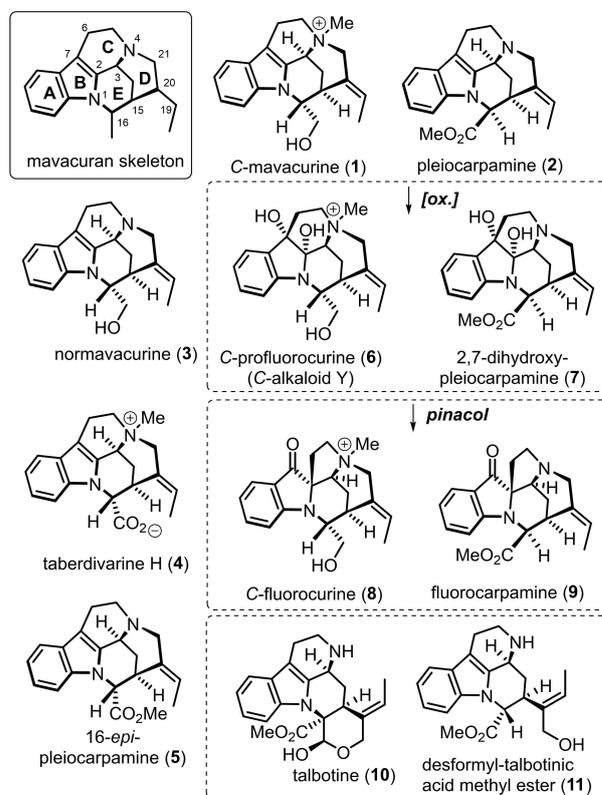


Figure 1. Mavacuran alkaloids.

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[**] A previous version of this manuscript has been deposited on a preprint server (<https://doi.org/10.26434/chemrxiv-2022-4nvqq>).

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indole ring has been dihydroxylated. A pinacol rearrangement of this 1,2-dihydroxy functionality delivers the pseudoindoxyl moiety of *C*-fluorocurine (**8**)^[3a,c,d,n] and fluorocarpamine (**9**).^[3m,o,p] Of note, talbotine (**10**) and desformyl talbotinic acid (**11**) are closely related to the mavacurans but lack the N4–C21 bond and the D ring.^[3q,l]

In contrast to the related akuammilan alkaloids^[5] or other families of monoterpene indole alkaloids, very few synthetic studies have been reported towards the mavacuran alkaloids.

Indeed, due to the particularly strained nature of its caged-fused-pentacyclic nature, the construction of the mavacuran skeleton is highly challenging. The choice of the last ring and bond to form is key to the success of such endeavor (Scheme 1).^[1]

For instance, inspired by the postulated biosynthesis of the mavacurans,^[1,6] final formations of the N1–C16 bond and the E ring have been targeted for several decades from tetracyclic ABCD derivatives (geissoschizine-type).^[1] In 1972, Boekelheide was able to form the pseudoindoxyl skeleton of unnatural 19–20-dihydro-norfluorocurine by the opening of a C16-epoxide by the indolic nitrogen atom (N1). Subsequently, reduction of the carbonyl and acid-mediated expansion of the C ring through a 1,2-shift of the C6 carbon atom from the C2 to the C7 positions led to unnatural 19–20-dihydronormavacurine.^[7] In 1976, Sakai and Shinma reported the hemisynthesis of 16-*epi*-pleiocarpamine (**5**) from geissoschizine through cleavage of the C3–N4 bond linking the C/D rings, then the key N1–C16 bond and E ring were formed by nucleophilic substitution on an α -chloro ester at C16, and eventually the C3–C4 bond and C/D ring junction had to be reformed.^[8] In 1981, Harley-Mason and co-workers employed a related strategy in their total

syntheses of 16-*epi*-pleiocarpamine (**5**) and *C*-mavacurine (**1**).^[9] In recent related approaches, both Takayama and co-workers^[10] and our group^[11] were able to form the pentacyclic framework by late-stage E ring formation, through a C16-carbenoid insertion into the N1–H bond or intramolecular N1–C16 oxidative coupling,^[12] respectively, leading to the synthesis of 16-*epi*-pleiocarpamine (**5**), pleiocarpamine (**2**), normavacurine (**3**), *C*-mavacurine (**1**), 16-hydroxymethyl-pleiocarpamine and taberdivarine H (**4**). Alternatively, during the Bosch synthesis of 2,7-dihydro-pleiocarpamine in 1993, the pentacyclic core was accessed by a Wiktop cyclization to forge the C6–C7 bond and the C ring.^[13]

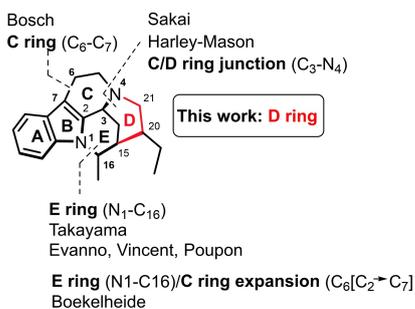
Results and Discussion

With the aim of devising a concise route to the mavacurans, we designed a retrosynthesis which involves a different disconnection to previous reported approaches (Scheme 1). We planned to construct the D ring and the C15–C20 bond as the last event through intramolecular 1,4-addition of the vinyl iodide in **12** to the α,β -unsaturated 2-indolyl-methylacrylate constitutive of the E ring. Performing the 1,4-addition in an intramolecular manner should ensure complete diastereoselectivity. Precursor **12** would arise from a Pictet–Spengler reaction between allylated tryptamine **13** and aldehyde **14** containing an α -ketoester, which would be spontaneously condensed with the nitrogen of the indole inspired by earlier reports.^[14]

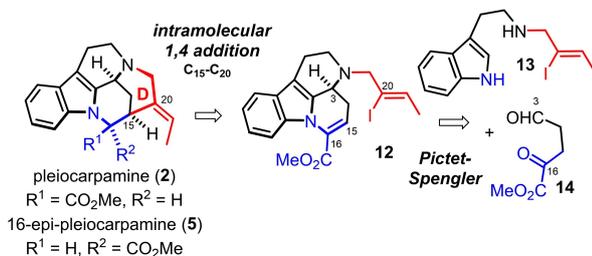
Indeed, related intramolecular 1,4-additions of a vinyl iodide to an α,β -unsaturated ester have been employed during the total synthesis of various monoterpene indole alkaloids.^[12c,15] This is particularly true in the cases of the akuammilan alkaloids, as showcased by Zhu and Ma through lithium–halogen exchange or reductive Heck reaction with Ni(cod)₂ during the total syntheses of aspidophylline A and strictamine.^[12c,15a,b] Just after the completion of the present work, the group of Tokuyama reported in the context of the total synthesis of vinoxetine, a related radical-mediated cyclization of a tricyclic substrate lacking the C ring and the C6–C7 bond hampered by isomerization of the C20 ethylidene in a 1:1 ratio.^[16] Nevertheless, the present desired cyclization of tetracyclic vinyl iodide **12** is more challenging, since it would lead to a particularly strained pentacyclic substrate.

After the synthesis of **12** from allyl tryptamine **13**^[14b] and aldehyde **14**^[11b,17] according to the retrosynthesis in Scheme 1 (see the Supporting Information for details), the stage was set to study the key intramolecular 1,4-addition (Scheme 2). The Ni(cod)₂-mediated cyclization conditions led only to formation of the deiodinated compound (\pm)-**15**.^[12c,15b–e] Other radical cyclization conditions did not help the reaction outcome since the use of Bu₃SnH/AIBN^[15a] afforded mainly (\pm)-**15**. Attempted palladium-catalyzed reductive Heck coupling of (\pm)-**12** also failed to deliver the desired cyclization product under various conditions, such as Pd(PPh₃)₄/HCO₂H, which led to deiodination. Moving to cobalt-catalyzed conditions or Zn/CuI-mediated conditions

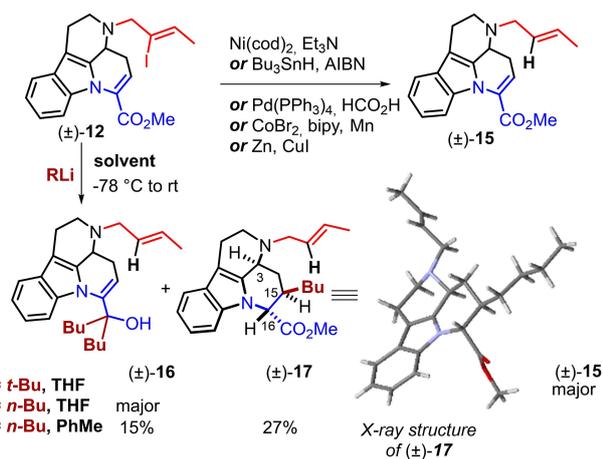
Last ring formed in previous approaches



Retrosynthesis via a late stage D ring formation



Scheme 1. Previous approaches and retrosynthesis through late-stage D-ring construction towards the mavacurans.



Scheme 2. Attempts towards D-ring formation from indolyl acrylate **12** and unexpected observation of the intermolecular 1,4-addition of *n*-butyllithium ($\text{Ni}(\text{cod})_2 = \text{bis}(\text{cyclooctadiene})\text{nickel}(0)$, AIBN = azobisisobutyronitrile, bipy = 2,2'-bipyridine).

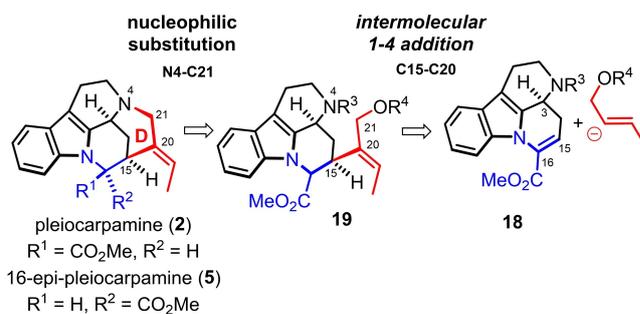
resulted in the formation of dehalogenated compound (±)-**15** as the major product (see the Supporting Information for details).

We then turned our attention towards the halogen–lithium exchange approach.^[15a,18] The use of *t*-BuLi allowed the exchange to take place, but unfortunately no cyclization occurred since (±)-**15** was the main product obtained. Switching *t*-BuLi to *n*-BuLi in THF led to double 1,2-addition of *n*-BuLi to the ester and concomitant deiodination of the vinyl iodide to afford (±)-**16**. Interestingly, replacing THF with toluene as the solvent led to the formation of (±)-**17**, which results from the intermolecular 1,4-addition of *n*-BuLi to the 2-indolyl acrylate, in 27% yield along with double 1,2-addition product (±)-**16** (see the Supporting Information for details).

Indeed, it is well recognized that organolithium reagents selectively add in a 1,2-fashion to carbonyl-containing Michael acceptors, even though there is precedent for regioselective intermolecular 1,4-addition in special cases.^[19] Therefore, the present Michael addition of an organolithium reagent is quite remarkable and was unexpected.

The relative configuration of (±)-**17** was determined through X-ray crystallography, which indicated a *trans* relationship between the C15 and C16 positions and more interestingly a *cis* relationship between the C3 and C15 position, which is the required arrangement to access the mava-curans framework.^[20]

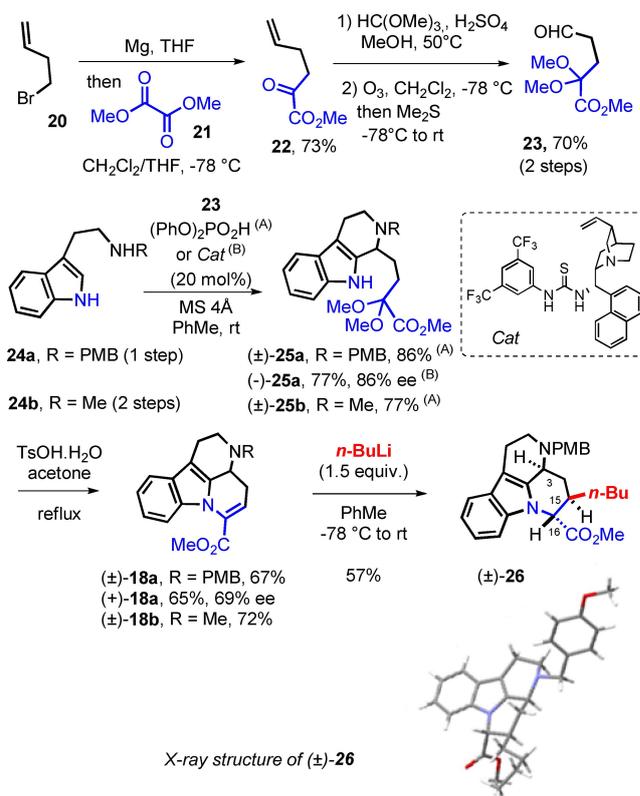
Although the planned intramolecular 1,4-addition failed, probably owing to an unfavorable conformation, the non-anticipated observation of an intermolecular addition with the relative configuration of the mava-curans framework opened the way to a revised retrosynthesis. The new strategy would involve the intermolecular 1,4-addition of a vinylic nucleophilic synthon to the 2-indolyl acrylate moiety embedded in the E ring of **18** to form the C15–C21 bond of **19**, followed by intramolecular nucleophilic substitution to form the N4–C21 bond and the D ring of the mava-curans (Scheme 3).



Scheme 3. Revised retrosynthesis: Intermolecular 1,4-addition and intramolecular nucleophilic substitution for late-stage D ring formation.

We decided to start from N^b -PMB tryptamine **24a** and N^b -Me tryptamine **24b**, since on one hand the PMB group could be removed later in the synthesis and on the other hand, several mava-curans alkaloids display a methyl group at N4 (Scheme 4).

We were not able to isolate the Pictet–Spengler product of **24a** and aldehyde **14** owing to decomposition (not shown). Reasoning that the ketoester moiety might be problematic, we prepared the corresponding dimethyl acetal **23**. In the presence of dimethyl oxalate **21**, the Grignard reagent derived from 4-bromo-1-butene **20** yielded ketoester



Scheme 4. Diastereoselective intermolecular 1,4-addition to tetracyclic indolyl acrylates **18a,b** (MS = molecular sieves, TsOH = *para*-toluenesulfonic acid, PMB = *para*-methoxybenzyl).

22, which was protected as a dimethyl acetal, and the ozonolysis of the alkene furnished aldehyde **23**.^[11b,17b] The Pictet–Spengler reaction of the latter with tryptamines **24a,b** furnished successfully tetrahydro- β -carbolines (\pm)-**25a,b**.^[11b,14a] Hydrolysis of the dimethyl acetal under acidic conditions at 80 °C was followed by the spontaneous condensation of the thus liberated ketoester with the indole nitrogen atom to form the desired 1-indolyl acrylate of (\pm)-**18a,b**.^[14a] An enantioselective approach to this compound was also sought. After evaluation of some chiral catalysts, such as phosphoric acids, thioureas and squaramides (see the Supporting Information for details), we found out that a cinchonidine-derived thiourea catalyst was able to promote the enantioselective Pictet–Spengler reaction to form (–)-**25a** with 86 % *ee*.^[21] Upon hydrolysis of the dimethyl acetal of the ketoester moiety, (+)-**18a** was obtained with erosion of the *ee* value to 69 % in the same vein as the observation by Hiemstra and co-workers.^[14b]

Nevertheless, the stage was set to test the 1,4-addition to this Michael acceptor (Scheme 4). Inspired by the serendipitous discovery with substrate (\pm)-**12**, *n*-BuLi could be chemo- and diastereoselectively added in a 1,4-fashion to *N*-PMB derivative (\pm)-**18a** to yield (\pm)-**26** in 57 % yield, for which the relative configuration of the newly created stereocenters was determined through NOESY experiments and X-ray crystal-structure analysis and proved to be similar to that in (\pm)-**17**, with a C15–C16-*trans* and C3–C15-*cis* relationship.^[20]

We then aimed to understand this exquisite diastereoselective 1,4-addition of an organolithium species to the indolyl acrylate of **18**. Indeed, the reversal of selectivity from 1,2- to 1,4-addition by switching from THF to toluene as the solvent (see Scheme 2) may be explained by the nature of the organolithium aggregate in a THF or toluene solution.^[22] We postulated that in a non-coordinating solvent, such as toluene, the nitrogen atom of the tertiary amine (N4) could form a complex with an aggregate of *n*-BuLi to direct the addition of *n*-BuLi, whereas such complexation would be precluded with a coordinating solvent, such as THF. To evaluate this hypothesis and to rationalize the chemo- and diastereoselectivities observed during the synthesis of (\pm)-**26**, DFT computations were carried out (Figure 2).^[23] The Gaussian 16 set of programs, the PBE0 functional and the 6–31+G(d,p) basis set were used. Solvation correction for toluene was obtained using the PCM model. The calculated energies are Gibbs free energies at 298.15 K. Compound (\pm)-**18a** was optimized from its X-ray structural coordinates.^[20] Although the major aggregate of *n*-BuLi in toluene is probably the hexamer,^[22] we used a tetramer, which may be formed in presence of a chelating tertiary amine^[22b] (and also to avoid a memory overflow at the chosen level of theory with the hexamer). A monomeric *n*-BuLi was also used to activate the ester functionality towards the 1,4-addition of one butyl group belonging to the tetramer (Figure 2).

Starting with the (BuLi)₄ aggregate on the *N*-PMB side of (\pm)-**18a**, geometry optimization led to the N–Li coordinated complex **A** (2.18 Å). One face of the Li₄ tetrahedron is oriented toward the heterocycle and is no longer available

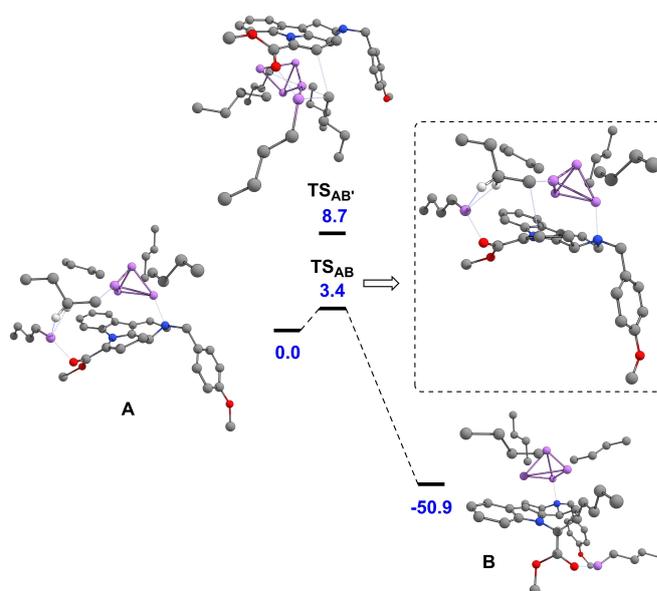


Figure 2. Computed free energy profile related to the stereoselective 1,4-addition of *n*-BuLi to (\pm)-**18a** to form (\pm)-**26** (ΔG_{298} , kcal mol⁻¹; hydrogen atoms have been omitted for clarity).

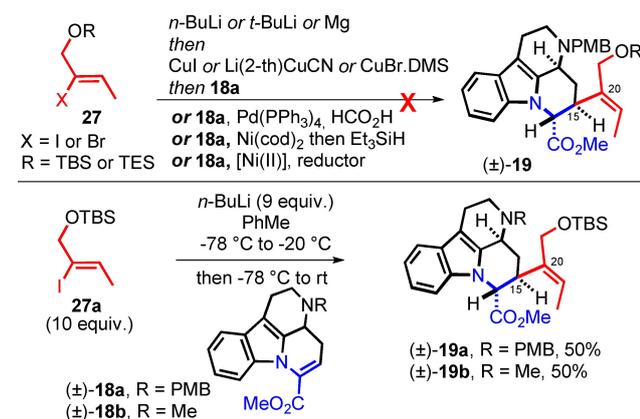
for a butyl anion. Thus, only three butyl chains are connected to Li₃ faces, while the fourth butyl group is monocoordinated to one Li in an apical manner. CH–Li interactions (2.21/2.01 Å) between the β carbon atom of this butyl chain and the Li on the ester group brings the fifth O-coordinated *n*-BuLi to the same side of the substrate as the *n*-BuLi tetramer. This bulk, as well as the long distance imposed by the N–Li coordination, seems to preclude 1,2-addition, which we could not model. On the other hand, the 1,4-addition can be readily computed using the apical butyl chain of the tetramer, which is only 3.43 Å away from the β carbon atom of the conjugated ester as a result of the aforementioned additional CH–Li interaction (**TS_{AB}**). The corresponding free energy of activation is only 3.4 kcal mol⁻¹. The resulting 1,4-addition complex **B** is obtained with the release of 50.9 kcal mol⁻¹ of free energy. Of note, **TS_{AB}** leads to the experimentally observed stereoisomer as far as the C3–C15-*cis* relationship is concerned. To explain this stereoselectivity, we modeled the 1,4-addition of *n*-BuLi to heterocycle (\pm)-**18a** without the N-directing effect. In such a scenario, the *n*-BuLi tetramer is irretrievably captured by the fifth BuLi fragment and partial disaggregation is observed. This brings more steric bulk around the β carbon atom of the conjugated ester as compared to the previous case and therefore a higher-lying transition state to reach the unobserved C3–C15-*trans* relationship, **TS_{AB'}** being 5.3 kcal mol⁻¹ less stable than **TS_{AB}**. Thus, in this proposal, the nitrogen atom (N4) of the piperidine ring (C ring) allows strong Li–Li interactions to be avoided between the butyl donor aggregate and the ester activator. In this case, only weak CH–Li interactions exist, limiting the steric hindrance at the receiving β carbon atom, yet shielding the α carbon atom.

In other words, this DFT study suggests that the tertiary amine (N4) acts as a directing group to control the chemo- and diastereoselective addition of *n*-BuLi to (\pm)-**18a**. The C15–C16-*trans* relationship will result from the protonation of the ester enolate during the quench of the reaction.^[24]

Having established the proof of concept of the stereoselective Michael addition with an unfunctionalized nucleophile, we then turned our attention to the incorporation of the ethylidene moiety required for the total synthesis of the mavacurans (Scheme 5). It proved to be quite challenging since we failed to add the desired nucleophile through the generation of a Grignard or organocopper reagent from vinyl iodide or bromide derivatives **27**. Reductive Heck reactions with nickel or palladium catalysts were also unsuccessful as well as radical-mediated reactions (see the Supporting Information for details).

Eventually, we relied on the unorthodox regio- and stereoselective Michael addition of an organolithium reagent in toluene that we just uncovered. Generation of the vinyl lithium species through lithium/halogen exchange from vinyl iodide **27a** and its addition in toluene to (\pm)-**18a,b** enabled stereoselective formation of the C15–C20 bond of N4–PMB and N4–Me derivatives (\pm)-**19a,b** of the natural product desformyl talbotinic acid. The relative configuration was determined by NOESY experiments. Fine-tuning of the reaction conditions was necessary (see the Supporting Information for details): Formation of the vinyl lithium intermediate needs to be performed from -78 to -20 °C to push to completion the iodine–lithium exchange but also to avoid decomposition of the vinyl lithium intermediate at a higher temperature. Presumably due to its steric hindrance, this vinyl lithium reagent needs to be used in excess. Unreacted (\pm)-**18a,b** was also observed. If all the *n*-BuLi is not consumed during the lithium–halogen exchange it would add preferentially to (\pm)-**18a,b** over the hindered vinyl lithium reagent.

Having successfully achieved the first key step of our strategy, we then focused on the closing of the D ring through intramolecular nucleophilic substitution (Scheme 6).



Scheme 5. Diastereoselective synthesis of **19a,b** by intermolecular 1,4 addition of a functionalized vinyl lithium intermediate (TBS = *t*-butyldimethylsilyl, TES = triethylsilyl, 2-th = 2-thienyl, DMS = dimethylsulfide).

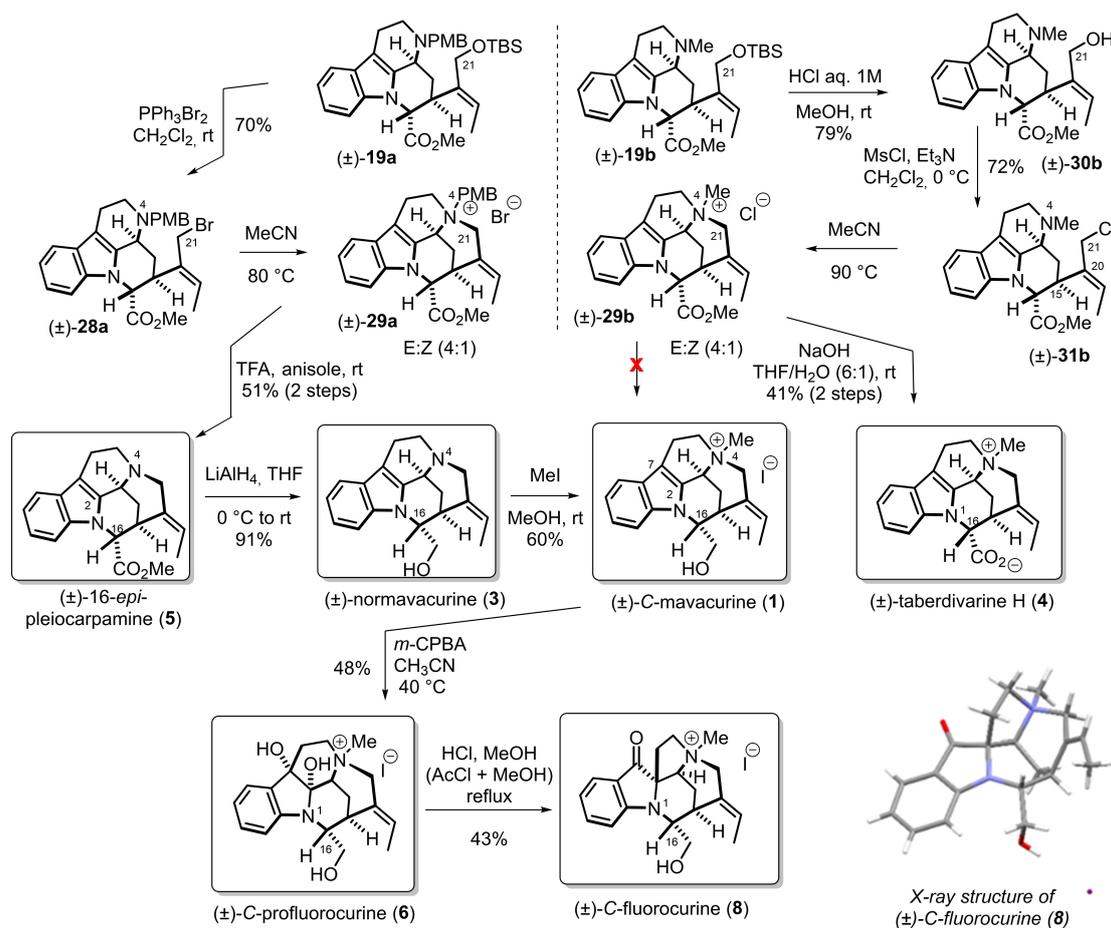
The silyl ether of *N*-PMB intermediate (\pm)-**19a** was converted in one step into allyl bromide (\pm)-**28a**, which was then subjected to cyclization by heating in acetonitrile at reflux. Formation of the N4–C21 bond delivered the pentacyclic mavacuran skeleton in the form of ammonium (\pm)-**29a**. A minor amount of *E* to *Z* isomerization of the ethylidene was observed at this stage. Removal of the PMB group from the N4-nitrogen was effected by treatment in TFA in presence of anisole,^[25] leading efficiently to (\pm)-16-*epi*-pleiocarpamine (**5**) in 51 % over two steps after separation from the minor *Z* isomer.

As previously reported, reduction of 16-*epi*-pleiocarpamine with LiAlH₄ delivers (\pm)-normavacurine (**3**) and subsequent methylation of the latter with methyl iodide furnished (\pm)-*C*-mavacurine (**1**) iodide.^[9a,10] To access **1**, N4-methylated 1,4-addition product (\pm)-**19b** seemed more convenient than the *N*-PMB analogue (\pm)-**19a** to avoid dequaternization and requaternization of the piperidine nitrogen atom N4. Direct conversion of TBS ether of (\pm)-**19b** into allyl bromide (\pm)-**28b** failed. Therefore, a two-step sequence was deployed to access a corresponding allyl halide. To avoid lactonization, treatment of (\pm)-**19b** under mild acidic conditions liberated smoothly the allyl alcohol of *N*-methyl desformyl talbotinic acid (\pm)-**30b**. Its reaction with mesyl chloride spontaneously delivered allyl chloride (\pm)-**31b**, the cyclization of which to the pentacyclic *N*-methyl ammonium (\pm)-**29b** was performed upon heating in acetonitrile. Saponification of the methyl ester allowed completion of the synthesis of (\pm)-taberdivarine H (**4**).^[11] However, *N*-methyl ammonium (\pm)-**29b** proved to be too sensitive toward reductants for the conversion of its ester into the alcohol functionality of (\pm)-*C*-mavacurine (**1**).

The next challenge was the dihydroxylation of the indole nucleus and the subsequent ring contraction of the mavacuran skeleton into the pseudoindoxyl moiety of the fluorocuran skeleton^[3k,9c,26] through a pinacol rearrangement.^[27,28] The dihydroxylation^[3m,9c,26,27] of *C*-mavacurine (**1**) with *m*-CPBA was carried out in acetonitrile because of solubility issues to synthesize (\pm)-*C*-profluorocurine (**6**, *C*-alkaloid Y) iodide.^[29] Finally, we completed our synthetic endeavor by performing the pinacol rearrangement of the diol motif of (\pm)-*C*-profluorocurine (**6**) into the desired pseudoindoxyl.^[3m,9c,26,27a–e,28] The transformation was promoted by a solution of hydrogen chloride in methanol,^[9c,26] which was prepared in situ by adding acetyl chloride to methanol to yield (\pm)-*C*-fluorocurine (**8**) iodide, the structure of which was secured through X-ray crystallographic analysis for the first time.^[20] This represents the first total synthesis of this monoterpene indole alkaloid.

Conclusion

We devised a very concise synthetic route to the highly strained mavacuran scaffold of the monoterpene indole alkaloids by an original late-stage D-ring formation. A highly unconventional diastereoselective intermolecular Michael addition of an organolithium reagent to an indolyl acrylate moiety was the key to the success of this challenging



Scheme 6. Completion of the total synthesis of 16-*epi*-pleiocarpamine (**5**), normavacurine (**3**), C-mavacurine (**1**), taberdivarine H (**4**), C-proflurocurine (**6**) and C-fluorocurine (**8**; MsCl = methanesulfonylchloride, TFA = trifluoroacetic acid, *m*-CPBA = *meta*-chloroperbenzoic acid).

task. DFT computations suggest that the chemo- and diastereoselectivities observed for such reactions could be directed by the formation of a complex between the nitrogen (N4) of the piperidine ring and the aggregate of the organolithium reagent. Final cyclization through intramolecular allylic nucleophilic substitution allowed completion of the very concise total synthesis of six mava-curane alkaloids. 16-*epi*-Pleiocarpamine, taberdivarine H, normavacurine, C-mavacurine, C-proflurocurine and C-fluorocurine were obtained in only 9–13 steps in the longest linear sequence, which compared very favorably with previous known total syntheses for the former four natural products,^[9a–b,10,11] while it is the first total synthesis of the two latter alkaloids. Owing to the occurrence of the mava-curane template in a large number of bis-indolic monoterpene indole alkaloids,^[1,4] we believe that this approach will be of importance for the total synthesis of these highly complex indole alkaloids.

Acknowledgements

We thank Dr. Georges Massiot (Université de Reims and CNRS, France) for providing NMR spectra of natural normavacurine. Dr. Georges Massiot and Prof. Luc Angenot

(University of Liège, Belgium) are also acknowledged for insightful discussions concerning the isolation of the mava-curane alkaloids and their NMR analysis. We also thank Dr. Laurent Evanno and Prof. Erwan Poupon (BioCIS, Université Paris-Saclay, France) for helpful suggestions. The MESRI (ED 2MIB, Université Paris-Saclay) is gratefully acknowledged for the PhD fellowship of A.M. Financial support for this work was provided by the ANR (ANR-15-CE29-0001, “Mount Indole”), Université Paris-Saclay and the CNRS. This work was granted access to the HPC resources of CINES under the allocation 2020-A0070810977 made by GENCI.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Michael Addition · Monoterpene Indole Alkaloids · Organolithium Reagents · Pinacol Rearrangement · Total Synthesis

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Manuscript received: February 17, 2023

Accepted manuscript online: March 16, 2023

Version of record online: April 13, 2023