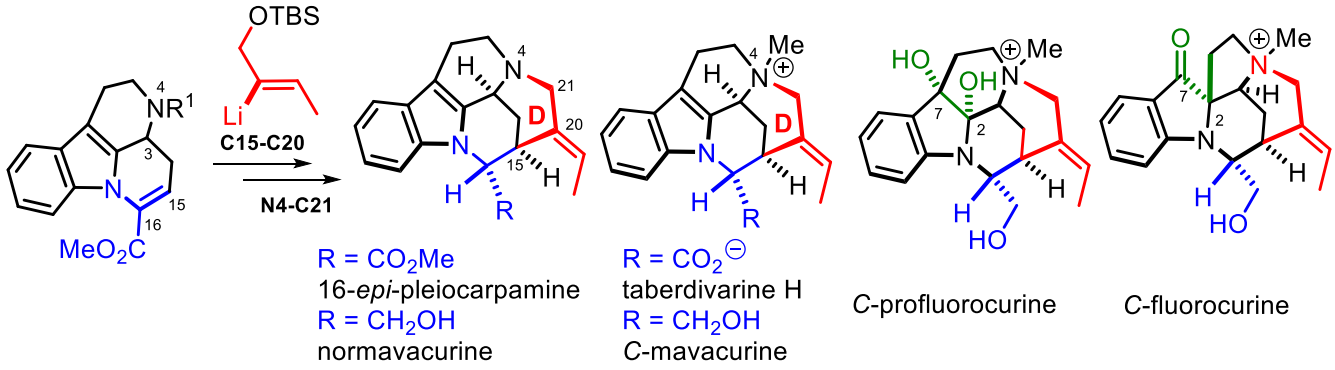
Collective Total Synthesis of Mavacuran Alkaloids via an Intermolecular 1,4-Addition Approach.

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

Institut de Chimie Moléculaire et des Matériaux d'Orsay, Université Paris-Saclay, CNRS, 91405 Orsay, France.

* guillaume.vincent@universite-paris-saclay.fr

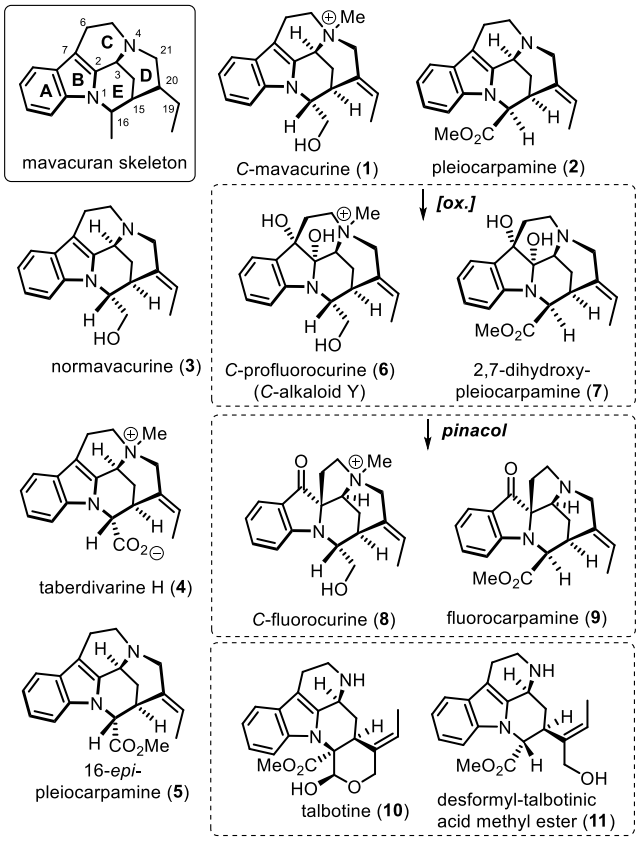
Abstract: We report a synthetic endeavor towards the highly strained pentacyclic caged framework of the mavacuran alkaloids which culminated with the concise total synthesis of *C*-fluorocurine, *C*-profluorocurine, *C*-mavacurine, normavacurine, 16-*epi*-pleiocarpamine and taberdivarine H. We designed an original strategy which involves a late stage construction of the D ring via a 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 onto a readily accessible Michael acceptor. Final cyclization was achieved via nucleophilic substitution into an ammonium intermediate. The first total syntheses of *C*-profluorocurine and *C*-fluorocurine were finalized via respectively the dihydroxylation of *C*-mavacurine and a pinacol rearrangement.



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 and the C16 carbon 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 sub-family and pleiocarpamine (**2**)[3a,e,f] is a constitutive unit of several complex indole alkaloids including bis-indole alkaloids.[1]

Figure 1. Mavacuran Alkaloids



We have recently performed the hemisynthesis of voacalgine and bipleiophylline from natural pleiocarpamine.[4] Therefore the 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 a *N*4-methyl ammonium, the nature of the oxygenated function born by the C-16 carbon 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 analog of respectively *C*-mavacurine and pleiocarpamine in which the indole ring has been dihydroxylated. A pinacol rearrangement of this 1,2-dihydroxyl function 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.

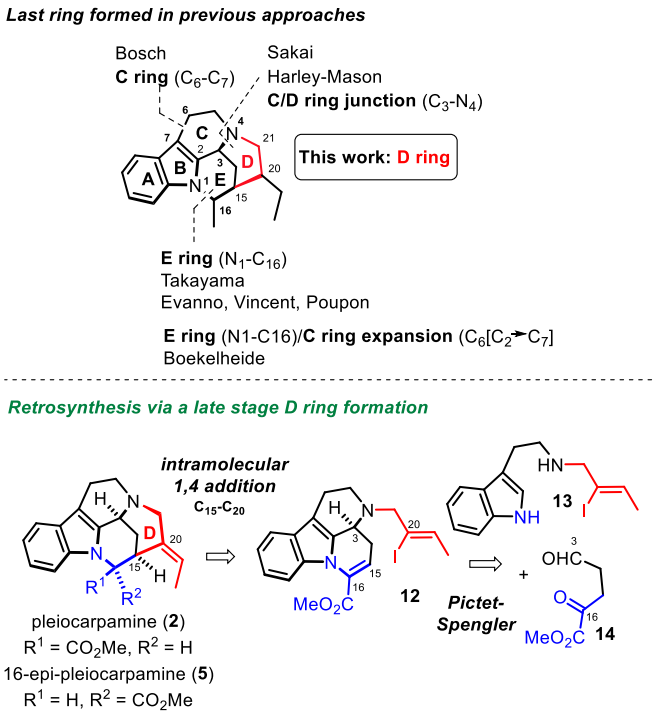
Indeed, due to the particularly strained nature of its caged-fused-pentacyclic nature, the construction of the mavacuran skeleton is highly challenging. The choice of the last ring and bond to form is key to the success of such endeavor (Scheme 1).[1]

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-norfluorocorine via the opening of a C16-epoxide by the N1 indolic nitrogen. Subsequently, reduction of the carbonyl and acid-mediated expansion of the C ring via a 1,2-shift of the C6-carbon from the C2 to the C7 positions led to unnatural 19-20-dihydronormavacurine.[7] In 1976, Sakai reported a hemisynthesis of 16-*epi*-pleiocarpamine (**5**) from geissoschizine via cleavage of the C3-N4 bond linking the C/D rings, then the key N1-C16 bond and E ring were formed by a nucleophilic substitution on a □-chloro ester at C16 and eventually, the C3-C4 bond and C/D ring junction had to be reformed.[8] In 1981, Harley-Mason employed a related strategy in its total syntheses of 16-*epi*-pleiocarpamine (**5**) and *C*-mavacurine (**1**).[9] In recent related approaches, both Takayama[10] and our group[11] were able to form the pentacyclic framework via a late stage E ring formation via respectively a C16-carbenoid insertion into the N1-H bond or an intramolecular N1-C16 oxidative coupling[12] 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 access via a Wiktop cyclization to forge the C6-C7 bond and the C ring.[13]

In the aim to devise a concise access towards the mavacurans, we designed a retrosynthesis which involves a different disconnection than the previous published approaches (Scheme 1).

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



We plan to construct the D ring and the C15-C20 bond as the last event via an intramolecular 1,4-addition of a vinyl iodide into an α,β–unsaturated 2-indolyl-methylacrylate **12** constitutive of the E ring. Performing the 1,4-addition in an intramolecular manner should ensure a total diastereoselectivity. Precursor **12** would arise from a Pictet-Spengler reaction between allylated tryptamine **13** and aldehyde **14** containing a α-keto-ester which would be spontaneously condensed with the nitrogen of the indole inspired by early work from Hannart.[14]

Results and Discussion

Indeed, related intramolecular 1,4-additions of a vinyl iodide into 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 via lithium halogen-exchange or reductive Heck-reaction with $Ni(cod)_2$ during the total syntheses of aspidophylline A and strictamine.[12c,15a,b] It should be noted that just after the completion of the present work, the group of Tokuyama reported during the total synthesis of vinoxine, a related radical-mediated cyclisation on 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.

Vinyl iodide-containing tryptamine **13** was prepared according to a known method (Scheme 2).[14b] Crotonaldehyde **15** was first iodinated and reduced to afford allylic alcohol **16**, which, after mesylation, provided **13** in presence of excess tryptamine **17**. Aldehyde **14** was also obtained by adjusting a known method.[11b,17] In presence of dimethyl oxalate **19**, the Grignard reagent derived from 4-bromo-1-butene **18** yielded alkene **20**, which was ozonolyzed to **14**. With these two compounds in hands, the Pictet-Spengler cyclization in presence of a catalytic amount of diphenyl phosphate allowed the formation of the C-ring with, as expected, spontaneous D-ring closure *via* condensation of the nitrogen atom of the indole onto the ketone[14b] leading to hemiaminal (±)-**21** as a single diastereoisomer. The latter was then smoothly dehydrated with TFAA in presence of 2,6-lutidine to give α,β–unsaturated ester (±)-**12**.

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 (±)-**22**. [12c,15b-e,] Others radical cyclization conditions did not help the reaction outcome since the use of Bu_3SnH/AIBN[15a] afforded mainly (±)-**22**. Attempted palladium-catalyzed reductive Heck coupling of (±)-**12** also failed to deliver the desired cyclization product under various conditions such as $Pd(PPh_3)_4/HCO_2H$, which led to deiodination. Moving to cobalt-catalyzed conditions or Zn/CuI-mediated conditions resulted in the formation of dehalognated compound (±)-**22** as the major product.

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 (±)-**22** was the main product obtained. Switching *t*-BuLi to *n*-BuLi in THF,

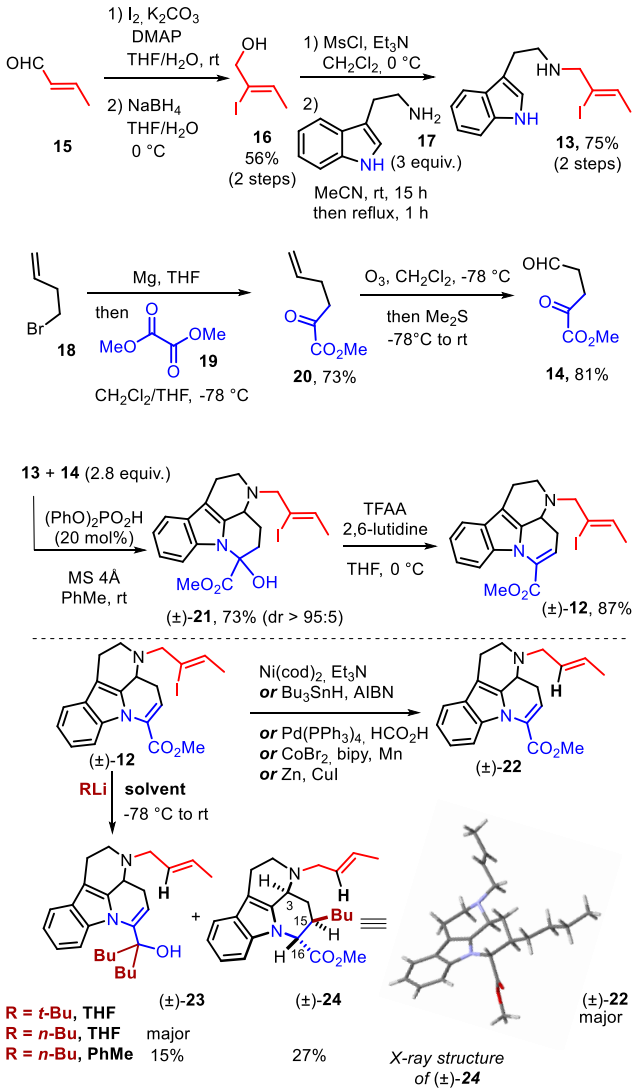
gave a double 1,2-addition of *n*-BuLi onto the ester and concomitant deiodination of the vinyliodide to afford (±)-**23**. Interestingly, replacing THF by toluene as solvent led to the formation of (±)-**24** which results from the intermolecular 1,4-addition of *n*-BuLi to the 2-indolyl acrylate in 27% along with double 1,2-addition product (±)-**23** (see SI for details).

Indeed, it is very well admitted that organolithium reagents selectively add in a 1,2-fashion to carbonyl-containing Michael acceptors, even though, there are precedents for the regioselective 1,4-additions in special cases.[19]

Therefore, the present Michael addition of an organolithium reagent is quite remarkable and was unexpected. The reversal of selectivity from 1,2 to 1,4-addition by switching from THF to toluene as solvent may be explained by the nature of the organolithium aggregate in a THF or toluene solution.[20]

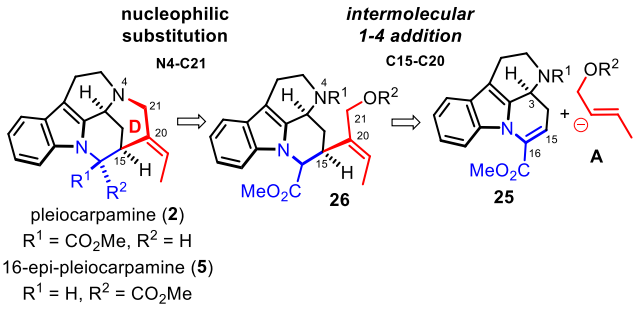
The relative configuration of (±)-**24** was determined through X-ray crystallography which indicated a *trans* relationship between the 15 and 16 positions and more interestingly a *cis* relationship between the 3 and 15 position which is the one required to access the mavacurane framework.

Scheme 2. Synthesis of tetracyclic indolyl acrylate 12 and attempts towards the intramolecular 1,4-addition.



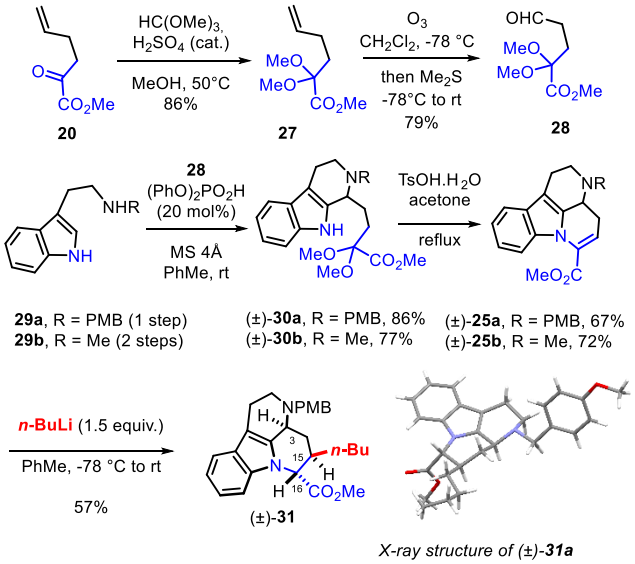
If the planned intramolecular 1,4-addition failed probably due to an unfavorable conformation, the non-anticipated observation of an intermolecular addition with the relative stereochemistry of the mavacuran framework opens the way to a revised retrosynthesis. It would involve the intermolecular 1,4-addition of a vinylic nucleophilic synthon **A** into the 2-indolylacrylate moiety embedded in the E ring of **25** to form the C15-C21 bond of **26** followed by an intramolecular nucleophilic substitution to form the N4-C21 bond and the D ring of the mavacurans (Scheme 3).

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



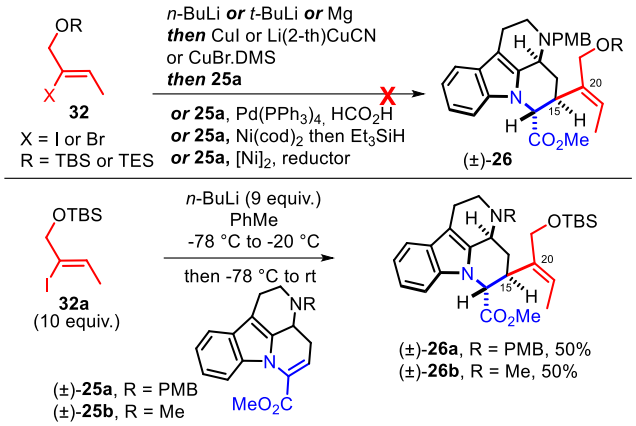
We decided to start from N^b-PMB tryptamine **29a** and N^b-Me tryptamine **29b** since in one hand the PMB group could be removed latter in the synthesis and in the other hand, several mavacurane alkaloids display a methyl group at N4 (Scheme 4). We were not able to isolate the Pictet-Spengler product of **29a** and aldehyde **14** due to decomposition. Reasoning that the keto-ester moiety might be problematic, we protected the latter as dimethyl acetal **28** prepared from **20** via **27**.[11b,17b] The Pictet-Spengler reaction of the latter with tryptamines **29a,b** furnished successfully tetrahydroisoquinolines (±)-**30a,b**.[11b,14a] Hydrolysis of the dimethyl acetal in acidic condition at 80 °C was followed by the spontaneous condensation of the thus liberated ketoester with the indole nitrogen to form the desired 1-indolyl acrylate of (±)-**25a,b**.[14a] The stage was set to test the 1,4-addition into this Michael acceptor (Scheme 4). Inspired, by the serendipitous discovery on substrate (±)-**12**, *n*-BuLi could be chemo and diastereoselectively added in a 1,4-fashion into N-PMB derivative (±)-**25a** to yield (±)-**31** in 57% yield for which the relative configurations of the newly created stereocenters were determined through noesy experiments and X-ray analysis and proved to be similar to (±)-**24** with a C15-C16-*trans* and C3-C15-*cis* relationships.

Scheme 4. Diastereoselective intermolecular 1,4 additions to tetracyclic indolyl acrylates 25a,b.



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 via the generation of a Grignard or organocopper reagent from vinyl iodide or bromide derivatives **32**. Reductive Heck-reaction with Nickel or Palladium catalysts were also unsuccessful as well as radical-mediated reactions.

Scheme 5. Diastereoselective synthesis of 26a,b via intermolecular 1,4 additions of functionalized vinyl lithium intermediate.



Eventually, we relied on the unorthodox regio and setereoselective 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 **32a** and addition of the latter in toluene to (±)-**25a,b** allowed to form stereoselectively the C15-C20 bond of N4-PMB and N4-Me derivatives (±)-**26a,b** of the natural product desformyl talbotinic acid. The relative stereochemistry was determined by noesy experiments. Fine-tuning of the reaction conditions was necessary: 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.

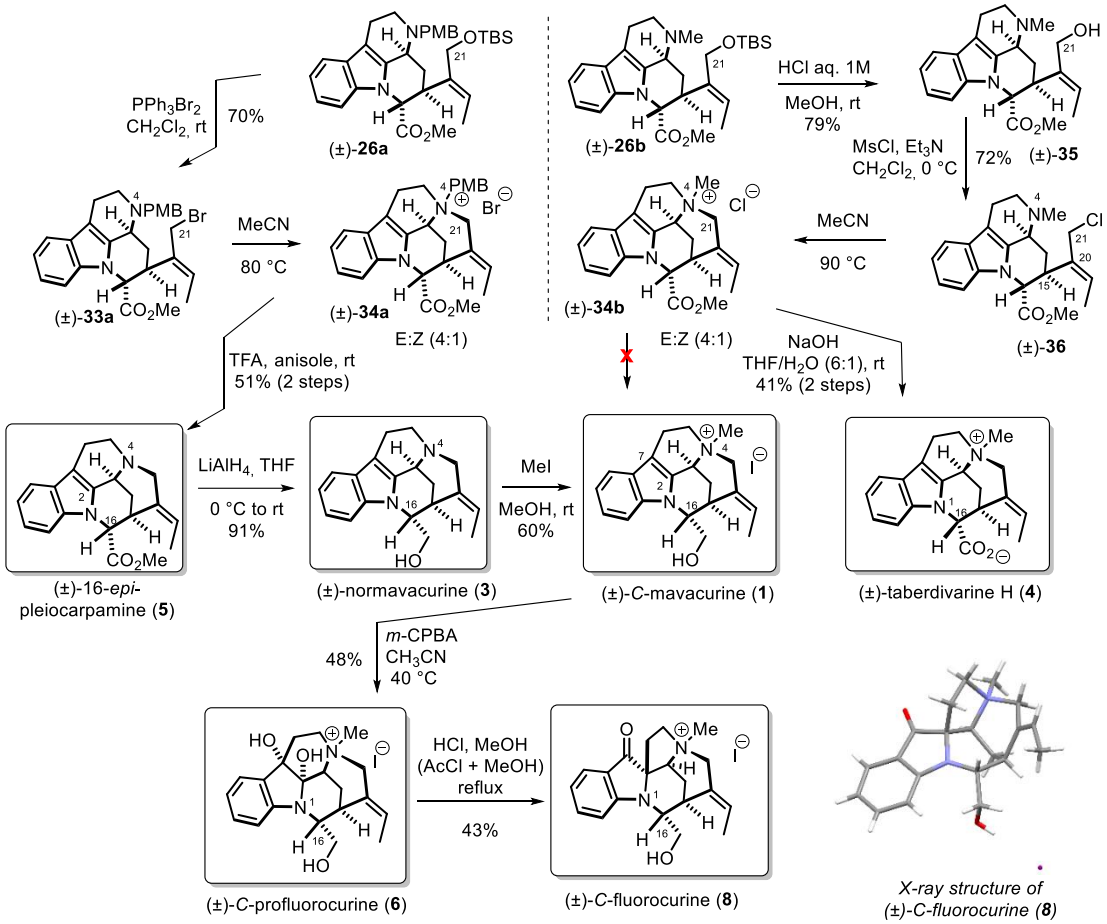
Having successfully achieved the first key step of our strategy, we then focused on the closing of the D ring via an intramolecular nucleophilic substitution (Scheme 6). The silyl ether of N-PMB intermediate (±)-**26a** was converted in one step into allyl bromide (±)-**33a** which was then subjected to cyclization by heating at reflux of acetonitrile. Formation of the N4-C21 bond delivered the pentacyclic mavacuran skeleton in the form of ammonium (±)-**34a**. It should be noted that a minor *E* to *Z* isomerisation of the ethylidene was observed at this stage. Removal of the PMB from the N4-nitrogen was effected by treatment in TFA in presence of anisole[21] leading efficiently to (±)-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 $LiAlH_4$ delivers (±)-normavacurine (**3**) and subsequent methylation of the latter with methyl iodide furnished (±)-*C*-mavacurine (**1**) iodide.[9a,10] To access the latter, N4-methylated 1,4-addtion product **26b** seemed more convenient than the N-PMB analog (±)-**26a** to avoid dequaternization and requaternization of the N4-nitrogen. Direct conversion of TBS ether of (±)-**26b** into allyl bromide (±)-**33b** failed. Therefore, a two-step sequence was deployed to access a corresponding allyl halide. In order to avoid lactonisation, treatment of (±)-**26b** in mild acidic conditions liberated smoothly the allyl alcohol of N-methyl desformyl-talbotinic acid (±)-**35**. Its reaction with mesyl chloride, spontaneously delivered allyl chloride (±)-**36** which cyclization into the pentacyclic N-methyl ammonium (±)-**34b** was performed upon heating in acetonitrile. Saponification of the methyl ester allowed to complete the synthesis of (±)-taberdivarine H (**4**).[11] However, N-methyl ammonium (±)-**34b** proved to be too sensitive towards reductants for the conversion of its ester into the alcohol of (±)-*C*-mavacurine (**1**).

The next challenge was directed toward the dihydroxylation of the indole nucleus and the subsequent ring contraction of the mavacuran skeleton into the fluorocuran one[3k,9c,22] via dihydroxylation of the indole and pinacol rearrangement into the pseudoindoxyl moiety.[23,24]

The dihydroxylation[3m,9c,22,23] of *C*-mavacurine (**1**) with *m*-CPBA was achieved in acetonitrile for solubility issues and (±)-*C*-profluorocurine (**6**, *C*-alkaloid Y) iodide was synthesized.[25] Finally, we completed our synthetic endeavor by performing, the pinacol rearrangement of the diol motif of (±)-*C*-profluorocurine (**6**) into the desired pseudoindoxyl.[3m,9c,22,23a-e,24] It was promoted by a solution of hydrogen chloride in methanol[9c,22] which was prepared in-situ by adding acetyl chloride to methanol to yield (±)-*C*-fluorocurine (**8**) iodide which structure was secured through X-ray analysis for the first time. It represents the first total synthesis of this monoterpene indole alkaloid.

Scheme 6. Completion of the total synthesis of 16-*epi*-pleiocarpamine (5), normavacurine (3), *C*-mavacurine (1), taberdivarine H (4), *C*-profluorocurine (6) and *C*-fluorocurine (8).



Conclusion

We devised a very concise access to the highly strained mavacuran scaffold of the monoterpene indole alkaloids via 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 task. Final cyclization via an intramolecular allylic nucleophilic substitution allowed to complete the very concise total synthesis of six mavacuran alkaloids. 16-*epi*-Pleiocarpamine, taberdivarine H, normavacurine, C-mavacurine, C-profluorocurine and C-fluorocurine were respectively obtained in only 9 to 13 steps in the longest linear sequence which compared very favorably with previous known total synthesis for the former four natural products,[9a-b,10,11] while it is the first total synthesis of the two latter alkaloids. Due to the occurrence of the mavacuran 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.

* guillaume.vincent@universite-paris-saclay.fr

Acknowledgments

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 mavacuran 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.

References

(1) Mauger, A.; Jarret, M.; Kouklovsky, C.; Poupon, E.; Evanno, L.; Vincent, G. The Chemistry of Mavacurane Alkaloids: A Rich Source of Bis-Indole Alkaloids. *Nat. Prod. Rep.* **2021**, *38* (10), 1852–1886. https://doi.org/10.1039/D0NP00088D.

(2) (a) O'Connor, S. E.; Maresh, J. J. Chemistry and Biology of Monoterpene Indole Alkaloid Biosynthesis. *Nat. Prod. Rep.* **2006**, *23* (4), 532–547. https://doi.org/10.1039/B512615K; (b) Szabó, L. F. Rigorous Biogenetic Network for a Group of Indole Alkaloids Derived from Strictosidine. *Molecules* **2008**, *13* (8), 1875–1896. https://doi.org/10.3390/molecules13081875.

(3) Assignment of the structures of *C*-mavacurine, pleiocarpamine, *C*-fluorocurine, *C*-profluorocurine (*C*-alkaloid Y), normavacurine and 16-*epi*-pleiocarpamine: (a) Hesse, M.; Philipsborn, W. V.; Schumann, D.; Spiteller, G.; Spiteller-Friedmann, M.; Taylor, W. I.; Schmid, H.; Karrer, P. Die Strukturen von C-Fluorocurin, C-Mavacurin und Pleiocarpamin. 57. Mitteilung über Curare-Alkaloide. *Helv. Chim. Acta* **1964**, *47* (3), 878–911. https://doi.org/10.1002/hlca.19640470325; isolation of *C*-mavacurine: (b) Wieland, T.; Merz, H. Über die Alkaloide aus Cale-bassen-Curare, VI. Mitteilung. *Chem. Ber.* **1952**, *85* (7–8), 731–743; (c) Tits, M.; Franz, M.; Tavernier, D.; Angenot, L. Les Alcaloïdes Quaternaires Majoritaires Du Strychnos Variabilis Du Zaïre. *Planta Med* **1981**, *42* (08), 371–374 https://doi.org/10.1002/cber.19520850709; (d) Coune, C.; Tits, M.; Angenot, L. RMN C13 des alcaloïdes des Strychnos : les dérivés de l'usambarine, de la sarpagine et de la mavacurine. *J. Pharm. Belg.* **1982**, *37* (3), 189–194; isolation of pleiocarpamine: (e) Kump, W. G.; Schmid, H. Über die Alkaloide von Pleiocarpa mutica BENTH. *Helv. Chim. Acta* **1961**, *44* (6), 1503–1516. https://doi.org/10.1002/hlca.19610440608; (f) Bartlett, M. F.; Sklar, R.; Smith, A. F.; Taylor, W. I. The Alkaloids of Hunteria Eburnea Pichon. III.1 The Tertiary Bases. *J. Org. Chem.* **1963**, *28* (9), 2197–2199. https://doi.org/10.1021/jo01044a011; isolation of normavacurine: (g) Massiot, G.; Thépenier, P.; Jacquier, M.-J.; Le Men-Olivier, L.; Delaude, C. Normavacurine and Minfiensine, Two New Alkaloids with C19H22N2O Formula from Strychnos Species. *Heterocycles* **1989**, *29* (8), 1435. https://doi.org/10.3987/COM-89-4987; (h) Massiot, G.; Thepenier, P.; Jacquier, M.-J.; Le Men-Olivier, L.; Delaude, C. Alkaloids from Roots of Strychnos Potatorum. *Phytochemistry* **1992**, *31* (8), 2873–2876. https://doi.org/10.1016/0031-9422(92)83650-N; isolation of taberdivarine H : (i) Zhang, B.-J.; Teng, X.-F.; Bao, M.-F.; Zhong, X.-H.; Ni, L.; Cai, X.-H. Cytotoxic Indole Alkaloids from Tabernaemontana Officinalis. *Phytochemistry* **2015**, *120*, 46–52. https://doi.org/10.1016/j.phytochem.2014.12.025; isolation of 16-*epi*-pleiocarpamine: (j) Langlois, N.; Diatta, L.; Andriamialisoa, R. Z. Alcaloïdes Mono-Indoliques de Catharanthus Ovalis. *Phytochemistry* **1979**, *18* (3), 467–471. https://doi.org/10.1016/S0031-9422(00)81889-0; isolation of profluorocurine (alkaloid Y) : (k) Asmis, H.; Bächli, E.; Giesbrecht, E.; Kebrle, J.; Schmid, H.; Karrer, P. Über weitere aus Calebassen isolierte quartäre Alkaloide. 11 Mitteilung über Curare-Alkaloide aus Calebassen. *Helv. Chim. Acta* **1954**, *37* (7), 1968–1973. https://doi.org/10.1002/hlca.19540370708; (l) Penelle, J.; Tits, M.; Christen, P.; Molgo, J.; Brandt, V.; Frédérich, M.; Angenot, L. Quaternary Indole Alkaloids from the Stem Bark of Strychnos Guianensis. *Phytochemistry* **2000**, *53* (8), 1057–1066. https://doi.org/10.1016/S0031-9422(00)00033-9; isolation of 2,7-dihydroxypleiocarpamine: (m) Jacquier, M. J.; Vercauteren, J.; Massiot, G.; Le Men-Olivier, L.; Pussett, J.; Sevenet, T. Alkaloids of Alstonia Plumosa. *Phytochemistry* **1982**, *21* (12), 2973–2977; https://doi.org/10.1016/0031-9422(80)85080-1; isolation of *C*-fluorocurine: (n) Schmid, H.; Karrer, P. Über Curare-Alkaloide Aus Calebassen. *Helv. Chim. Acta* **1947**, *30* (7), 2081–2091. https://doi.org/10.1002/hlca.19470300721 and ref 3c,d; isolation of fluorocarpamine: (o) Kaschnitz, R.; Spiteller, G. Anwendungen der Massenspektrometrie zur Strukturaufklärung von Alkaloiden, 7. Mitt.: Neue Alkaloide aus Gonioma Kamassi E. Mey. *Monatsh. Chem.* **1965**, *96* (3), 909–921. https://doi.org/10.1007/BF00919164; (p) Atta-Ur-Rahman; Pervin, A.; Muzaffar, A.; De Silva, K. T. D.; Silva, W. S. J. Alkaloids of Petchia Ceylanica. *Phytochemistry* **1989**, *28* (11), 3221–3225. https://doi.org/10.1016/0031-9422(89)80311-5 and ref 3m; isolation of talbotine and desformyl talbotinic acid: (q) Pinar, M.; Hanaoka, M.; Hesse, M.; Schmid, H. Über Die Struktur Eines Neuartigen Indolalkaloids, Des Talbotins. 141. Mitteilung Über Alkaloide [1]. *Helv. Chim. Acta* **1971**, *54* (1), 15–43. https://doi.org/10.1002/hlca.19710540104; (l) Pinar, M.; Hesse, M.; Schmid, H. Die Isolierung Weiterer Alkaloide Aus Pleiocarba Talbotii WERNHAM. 150. Mitteilung Über Alkaloide. *Helv. Chim. Acta* **1973**, *56* (8), 2719–2722. https://doi.org/10.1002/hlca.19730560807.

(4) Lachkar, D.; Denizot, N.; Bernadat, G.; Ahamada, K.; Beniddir, M. A.; Dumontet, V.; Gallard, J.-F.; Guillot, R.; Leblanc, K.; N'nang, E. O.; Turpin, V.; Kouklovsky, C.; Poupon, E.; Evanno, L.; Vincent, G. Unified Biomimetic Assembly of Voacalgine A and Bipleiophylline via Divergent Oxidative Couplings. *Nat. Chem.* **2017**, *9* (8), 793–798.

(5) For reviews: (a) Wang, C.; Zhang, S.; Wang, Y.; Huang, S.-H.; Hong, R. Total Synthesis of Strictamine: A Tutorial for Novel and Efficient Synthesis. *Org. Chem. Front.* **2018**, *5* (3), 447–452. https://doi.org/10.1039/C7QO00837F; (b) Adams, G. L.; Smith, A. B. Chapter Three - The Chemistry of the Akuammiline Alkaloids. In *The Alkaloids: Chemistry and Biology*; Knölker, H.-J., Ed.; Academic Press, 2016; Vol. 76, pp 171–257. https://doi.org/10.1016/bs.alkal.2015.08.001; (c) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. Cascade Reactions: A Driving Force in Akuammiline Alkaloid Total Synthesis. *Angew. Chem. Int. Ed.* **2015**, *54* (2), 400–412. https://doi.org/10.1002/anie.201406866; (d) Eckermann, R.; Gaich, T. The Akuammiline Alkaloids; Origin and Synthesis. *Synthesis* **2013**, *45* (20), 2813–2823. https://doi.org/10.1055/s-0033-1339711.

(6) Wenkert, E.; Wickberg, B. General Methods of Synthesis of Indole Alkaloids. IV. A Synthesis of Dl-Eburnamonine1,2. *J. Am. Chem. Soc.* **1965**, *87* (7), 1580–1589. https://doi.org/10.1021/ja01085a029.

(7) O'Rell, D. D.; Lee, F. G. H.; Boekelheide, V. Calabash Curare Alkaloids. Synthetic Study in the C-Fluorocurine-Mavacurine Series. *J. Am. Chem. Soc.* **1972**, *94* (9), 3205–3212. https://doi.org/10.1021/ja00764a05.

(8) (a) Sakai, S.; Shinma, N. The Partial Synthesis of 16-Epi-Pleiocarpamine. *Heterocycles* **1976**, *4* (5), 985–988. https://doi.org/10.3987/R-1976-05-0985; (b) Sakai, S.; Shinma, N. Transformation of Indole Alkaloids. V. Synthesis of C-Mavacurine Type Indole Alkaloid, 16-Epipleiocarpamine. *Yakugaku Zasshi* **1978**, *98* (7), 950–964. https://doi.org/10.1248/yakushi1947.98.7_950.

(9) (a) Calverley, M. J.; Banks, B. J.; Harley-Mason, J. The Total Synthesis of (±)-C-Mavacurine. *Tetrahedron Lett.* **1981**, *22* (17), 1635–1638. https://doi.org/10.1016/S0040-4039(01)90397-1; (b) Banks, B. J.; Calverley, M. J.; Edwards, P. D.; Harley-Mason, J. A New Synthesis of Indolo[2,3-α]Quinolizidine Derivatives: A Formal Total Synthesis of (±)-Geissoschizine. *Tetrahedron Lett.* **1981**, *22* (17), 1631–1634. https://doi.org/10.1016/S0040-4039(01)90396-X; (c) Calverley, M. J.; Harley-Mason, J.; Quarrie, S. A.; Edwards, P. D. On the Stereochemistry of the Solvolytic c/d Ring Cleavage of the 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a] Quinolizine System. *Tetrahedron* **1981**, *37* (8), 1547–1556. https://doi.org/10.1016/S0040-4020(01)92094-0.

(10) Sato, K.; Kogure, N.; Kitajima, M.; Takayama, H. Total Syntheses of Pleiocarpamine, Normavacurine, and C-Mavacurine. *Org. Lett.* **2019**, *21* (9), 3342–3345. https://doi.org/10.1021/acs.orglett.9b01084.

(11) (a) Jarret, M.; Turpin, V.; Tap, A.; Gallard, J.-F.; Kouklovsky, C.; Poupon, E.; Vincent, G.; Evanno, L. Bioinspired Oxidative Cyclization of the Geissoschizine Skeleton for Enantioselective Total Synthesis of Mavacuran Alkaloids. *Angew. Chem. Int. Ed.* **2019**, *58* (29), 9861–9865. https://doi.org/10.1002/anie.201905227; (b) Jarret, M.; Tap, A.; Turpin, V.; Denizot, N.; Kouklovsky, C.; Poupon, E.; Evanno, L.; Vincent,

G. Bioinspired Divergent Oxidative Cyclizations of Geissoschizine: Total Synthesis of (–)-17-nor-Excelsinidine, (+)-16-Epi-Pleiocarpamine, (+)-16-Hydroxymethyl-Pleiocarpamine and (+)-Taberdivarine H. *Eur. J. Org. Chem.* **2020**, No. 40, 6340–6351. https://doi.org/10.1002/ejoc.202000962.

(12) (a) Jarret, M.; Abou-Hamdan, H.; Kouklovsky, C.; Poupon, E.; Evanno, L.; Vincent, G. Bioinspired Early Divergent Oxidative Cyclizations toward Pleiocarpamine, Talbotine, and Strictamine. *Org. Lett.* **2021**, *23* (4), 1355–1360. https://doi.org/10.1021/acs.orglett.1c00018; (b) Jarret, M.; Tap, A.; Kouklovsky, C.; Poupon, E.; Evanno, L.; Vincent, G. Bioinspired Oxidative Cyclization of the Geissoschizine Skeleton for the Total Synthesis of (−)-17-nor-Excelsinidine. *Angew. Chem. Int. Ed.* **2018**, *57* (38), 12294–12298. https://doi.org/10.1002/anie.201802610; (c) Teng, M.; Zi, W.; Ma, D. Total Synthesis of the Monoterpenoid Indole Alkaloid (±)-Aspidophylline A. *Angew. Chem. Int. Ed.* **2014**, *53* (7), 1814–1817. https://doi.org/10.1002/anie.201310928; (d) Ren, W.; Tappin, N.; Wang, Q.; Zhu, J. Synthetic Study towards Strictamine: The Oxidative Coupling Approach. *Synlett* **2013**, *24* (15), 1941–1944. https://doi.org/10.1055/s-0033-1339472.

(13) (a) Jiménez, J.-M.; Zulaica, E.; Bennasar, M.-L.; Bosch, J. A New Synthetic Entry to the Alkaloids of the Mavacurine Group. First Total Synthesis of (±)-2,7-Dihydropleiocarpamine. *J. Chem. Soc. Chem. Commun.* **1993**, No. 9, 732–733. https://doi.org/10.1039/C39930000732; (b) Bennasar, M. L.; Zulaica, E.; Jimenez, J. M.; Bosch, J. Studies on the Synthesis of Mavacurine-Type Indole Alkaloids. First Total Synthesis of (±)-2,7-Dihydropleiocarpamine. *J. Org. Chem.* **1993**, *58* (27), 7756–7767. https://doi.org/10.1021/jo00079a021.

(14) (a) Hannart, J. A. A. J. Indole Derivatives and Therapeutically Acting Drugs. US4200638A, April 29, 1980; see also: (b) Wanner, M. J.; Boots, R. N. A.; Eradus, B.; Gelder, R. de; van Maarseveen, J. H.; Hiemstra, H. Organocatalytic Enantioselective Total Synthesis of (−)-Arboricine. *Org. Lett.* **2009**, *11* (12), 2579–2581. https://doi.org/10.1021/ol900888e.

(15) (a) Ren, W.; Wang, Q.; Zhu, J. Total Synthesis of (±)-Aspidophylline A. *Angew. Chem. Int. Ed.* **2014**, *53* (7), 1818–1821. https://doi.org/10.1002/anie.201310929; (b) Ren, W.; Wang, Q.; Zhu, J. Total Synthesis of (±)-Strictamine. *Angew. Chem. Int. Ed.* **2016**, *55* (10), 3500–3503. https://doi.org/10.1002/anie.201511638; (c) Yu, S.; Berner, O. M.; Cook, J. M. General Approach for the Synthesis of Indole Alkaloids via the Asymmetric Pictet−Spengler Reaction: First Enantiospecific Total Synthesis of (−)-Corynantheidine as Well as the Enantiospecific Total Synthesis of (−)-Corynantheidol, (−)-Geissoschizol, and (+)-Geissoschizine. *J. Am. Chem. Soc.* **2000**, *122* (32), 7827–7828; (d) Ma, J.; Yin, W.; Zhou, H.; Liao, X.; Cook, J. M. General Approach to the Total Synthesis of 9-Methoxy-Substituted Indole Alkaloids: Synthesis of Mitragynine, as Well as 9-Methoxygeissoschizol and 9-Methoxy-Nb-Methylgeissoschizol. *J. Org. Chem.* **2009**, *74* (1), 264–273. https://doi.org/10.1021/jo801839t; (e) Yu, F.; Cheng, B.; Zhai, H. Fast and Protecting-Group-Free Synthesis of (±)-Subincanadine C. *Org. Lett.* **2011**, *13* (21), 5782–5783. https://doi.org/10.1021/ol202349g.

(16) Okada, K.; Ueda, H.; Tokuyama, H. Total Synthesis of (±)-Vinoxine: Construction of the Bridged Pyrido[1,2-a]Indole Skeleton via Tf2O-Mediated Bischler–Napieralski Reaction and Stereoselective Radical Cyclization. *Org. Biomol. Chem.* **2022**, *20* (30), 5943–5947. https://doi.org/10.1039/D2OB00274D.

(17) (a) Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. Total Synthesis of the Spirocyclic Oxindole Alkaloids Corynoxine, Corynoxine B, Corynoxeine, and Rhynchophylline. *Eur. J. Org. Chem.* **2013**, (6), 1100–1106. https://doi.org/10.1002/ejoc.201201505; (b) Guérard, C.; Demuynck, C.; Bolte, J. Enzymatic Synthesis of 3-Deoxy-D-Manno-2-Octulosonic Acid and Analogues: A New Approach by a Non Metabolic Pathway. *Tetrahedron Lett.* **1999**, *40* (22), 4181–4182. https://doi.org/10.1016/S0040-4039(99)00709-1.

(18) (a) Cooke, M. P.; Widener, R. K. Lithium-Halogen Exchange-Initiated Cyclization Reactions. 3. Intramolecular Conjugate Addition Reactions of Unsaturated Acylphosphoranes. *J. Org. Chem.* **1987**, *52* (8), 1381–1396. https://doi.org/10.1021/jo00384a001; (b) Piers, E.; Harrison, C. L.; Zetina-Rocha, C. Intramolecular Conjugate Addition of Alkenyl and Aryl Functions to Enones Initiated by Lithium−Iodine Exchange. *Org. Lett.* **2001**, *3* (21), 3245–3247. https://doi.org/10.1021/ol016288u.

(19) Hunt, D. A. Michael Addition of Organolithium Compounds. a Review. *Org. Prep. Proced. Int.* **1989**, *21* (6), 705–749. https://doi.org/10.1080/00304948909356219.

(20) Reich, H. J. Role of Organolithium Aggregates and Mixed Aggregates in Organolithium Mechanisms. *Chem. Rev.* **2013**, *113* (9), 7130–7178. https://doi.org/10.1021/cr400187u; For an example of the influence of a non-polar solvent on the formation of aggregates of organolithium reagents and their 1,4-addition: (b) Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Froment, F.; Corset, J. Effect of Aggregation of Nitrile Anions on the 1,2 versus 1,4 Regioselectivity towards Benzylideneacetone. *Tetrahedron Lett.* **1994**, *35* (23), 3935–3936. https://doi.org/10.1016/S0040-4039(00)76706-2.

(21) Moffat, D.; Nichols, C. J.; Riley, D. A.; Simpkins, N. S. The Synthesis of Bioactive Indolocarbazoles Related to K-252a. *Org. Biomol. Chem.* **2005**, *3* (16), 2953–2975. https://doi.org/10.1039/B506444A; BBr_3 in CH_2Cl_2 (see ref. 11b) delivered 16-*epi*-pleiocarpamine in only 25% yield over two steps, while CAN or DDQ were ineffective.

(22) The conversion of *C*-mavacurine into *C*-profluorocurine (alkaloid Y) with PtO_2 and O_2 and then to *C*-fluorocurine with HCl in methanol was reported in 1958. At that time, the structures of all these compounds were missassigned: Fritz, H.; Mitarbeit, T. W. U.; Besch, E. Über Die Alkaloide Aus Calebassen-Curare XII. Umwandlung Von C-Mavacurin In C-Fluorocurin Über Das C-Alkaloid-Y. *Justus Liebigs Ann. Chem.* **1958**, *611* (1), 268–276. https://doi.org/10.1002/jlac.19586110127.

(23) (a) Williams, R. M.; Glinka, Tomasz.; Kwast, Ewa. Facial Selectivity of the Intramolecular SN2' Cyclization: Stereocontrolled Total Synthesis of Brevianamide B. *J. Am. Chem. Soc.* **1988**, *110* (17), 5927–5929. https://doi.org/10.1021/ja00225a069; (b) Güller, R.; Borschberg, H.-J. Synthesis of Aristotelia-Type Alkaloids. Part XII. Total Synthesis of (−)-Tasmanine. Stereoelectronic Factors That Control the Rearrangement of 3H-Indol-3-Ol Derivatives to Oxindoles (= 1,3-Dihydro-2H-Indol-2-Ones) or to Pseudoindoxyls (=1,2-Dihydro-3H-Indol-3-Ones). *Helv. Chim. Acta* **1993**, *76* (5), 1847–1862. https://doi.org/10.1002/hlca.19930760505; (c) Mercado-Marin, E. V.; Garcia-Reynaga, P.; Romminger, S.; Pimenta, E. F.; Romney, D. K.; Lodewyk, M. W.; Williams, D. E.; Andersen, R. J.; Miller, S. J.; Tantillo, D. J.; Berlinck, R. G. S.; Sarpong, R. Total Synthesis and Isolation of Citrinalin and Cyclopiamine Congeners. *Nature* **2014**, *509* (7500), 318–324. https://doi.org/10.1038/nature13273; (d) Zhao, G.; Xie, X.; Sun, H.; Yuan, Z.; Zhong, Z.; Tang, S.; She, X. Bioinspired Collective Syntheses of Iboga-Type Indole Alkaloids. *Org. Lett.* **2016**, *18* (10), 2447–2450. https://doi.org/10.1021/acs.orglett.6b00989; (e) Godfrey, R. C.; Green, N. J.; Nichol, G. S.; Lawrence, A. L. Total Synthesis of Brevianamide A. *Nat. Chem.* **2020**, 1–5. https://doi.org/10.1038/s41557-020-0442-3; see also: (f); Dou, Y.; Kouklovsky, C.; Gandon, V.; Vincent, G. Enantioselective Total Synthesis of Cymoside through a Bioinspired Oxidative Cyclization of a Strictosidine Derivative. *Angew. Chem. Int. Ed.* **2020**, *59* (4), 1527–1531. https://doi.org/10.1002/anie.201912812; (g) Wu, J.; Guillot, R.; Kouklovsky, C.; Vincent, G. Electrochemical Dearomative Dihydroxylation and Hydroxycyclization of Indoles. *Adv. Synth. Catal.* **2020**, *362* (8), 1712–1719. https://doi.org/10.1002/adsc.202000158; (h) Xi, Y.-K.; Zhang, H.; Li, R.-X.; Kang, S.-Y.; Li, J.; Li, Y. Total Synthesis of Spirotryprostatins through Organomediated Intramolecular Umpolung Cyclization. *Chem. – Eur. J.* **2019**, *25* (12), 3005–3009. https://doi.org/10.1002/chem.201806411.

(24) (a) Schendera, E.; Lerch, S.; Drathen, T. von; Unkel, L.-N.; Brasholz, M. Phosphoric Acid Catalyzed 1,2-Rearrangements of 3-Hydroxyindolenines to Indoxyls and 2-Oxindoles: Reagent-Controlled Regioselectivity Enabled by Dual Activation. *Eur. J. Org. Chem.* **2017**, (22), 3134–3138. https://doi.org/10.1002/ejoc.201700085; for selected relevant reviews: (b) Dhote, P. S.; Patel, P.; Vanka, K.; Ramana, C. V.

Total Synthesis of the Pseudoindoxyl Class of Natural Products. *Org. Biomol. Chem.* **2021**, *19* (37), 7970–7994; (c) Delayre, B.; Wang, Q.; Zhu, J. Natural Product Synthesis Enabled by Domino Processes Incorporating a 1,2-Rearrangement Step. *ACS Cent. Sci.* **2021**, *7* (4), 559–569. https://doi.org/10.1021/acscentsci.1c00075.

(25) To the best of our knowledge, the ^{1}H or ^{13}C NMR of *C*-profluorocurine (*C*-alkaloid Y) was never reported despite the fact that it was isolated from natural source in few occasions: see ref 3k,l.