How to cite: *Angew. Chem. Int. Ed.* **2023,** *62,* e202301517
International Edition: doi.org/10.1002/anie.202301517
German Edition: doi.org/10.1002/ange.202301517

*Indole Alkaloids*

# Divergent Asymmetric Total Synthesis of (−)-Voacafricines A and B

*Rémi Andres, Qian Wang, and Jieping Zhu**

**Abstract:** A divergent asymmetric total synthesis of voacafricines A and B, hexacyclic monoterpene indole alkaloids, has been accomplished featuring the following key steps: a) a catalyst-controlled asymmetric Pictet–Spengler reaction of 6-methoxytryptamine with a chiral α-ketoester affording a 1,1-disubstituted tetrahydro-β-carboline in excellent yield and diastereoselectivity; b) oxidative cleavage of a 3,5-disubstituted cyclopentene furnishing a dialdehyde intermediate, which was effectively differentiated through spontaneous cyclization with the neighboring hydroxy and secondary amine functions; c) intramolecular nucleophilic addition of a tertiary amino nitrogen atom to the in situ generated oxonium species generating stereoselectively an unprecedented 8-alkyl octahydro-2*H*-5,8-methanofuro[2,3-*b*]azepin-8-ium motif bearing five contiguous stereocenters. The synthesis confirmed the absolute configuration of these two natural products.

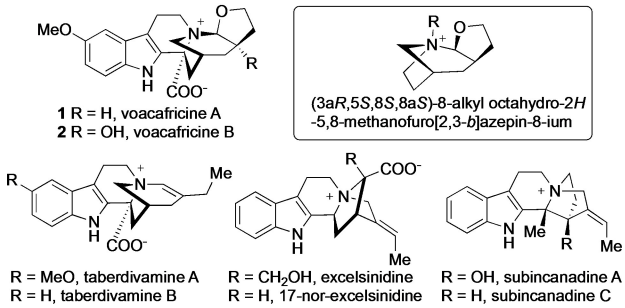


***Figure 1.*** Voacafricines A (**1**), B (**2**) and related monoterpene indole alkaloids containing a bridged bicyclic ammonium moiety.

**V**oacafricines A (**1**, R = H) and B (**2**, R = OH) were isolated from the fruits of *Voacanga Africana* (Apocyanaceae) by Luo and co-workers (Figure 1).[1] The extracts of this tree, native to tropical Africa, have been used to treat bacterial infections. In line with its success as a traditional medicine, in vitro assays indicated that both **1** and **2** displayed inhibitory activities against *Staphylococcus aureus* and *Salmonella typhi* higher than berberine and fibrauretine, two antibacterial drugs. 19-*epi*-Voacristine, an iboga-type indole alkaloid co-isolated from the same tree, was suggested to be a plausible biogenetic precursor. However, the energy barriers for the proposed skeleton reorganization steps were found to be too high to be kinetically feasible on the basis of recent DFT calculations.[2]

Structurally, voacafricines A (**1**) and B (**2**) are hexacyclic compounds containing an unprecedented 8-alkyl octahydro-2*H*-5,8-methanofuro[2,3-*b*]azepin-8-ium motif with five contiguous stereocenters. Different from other alkaloids bearing a bridged bicyclic ammonium moiety, such as taberdivamines A, B,[3] excelsinidine,[4] nor-excelsinidine[5] and subincanadines A and C (Figure 1),[6] one of the quaternary $N^+$–C bonds in voacafricines A (**1**) and B (**2**) is part of an aminal functionality. This unique structural feature implies that a new synthetic strategy needs to be developed at a late stage of the synthesis to build this sensitive functionality. The stereoselective construction of the 1,1-disubstituted tetrahydro-β-carboline unit constitutes yet another synthetic challenge.[7–13] Indeed, solutions to this daunting task started to appear only recently.[13] No total synthesis of **1** or **2** has been reported to date.

From the retrosynthetic perspective, there are two most obvious ways to form the quaternary ammonium salt of voacafricines A (**1**) and B (**2**). Disconnection *a* implies the generation of azabicyclic ring through intramolecular $S_N2$ displacement of the primary alkyl (pseudo)halide by the internal amine nitrogen atom, whereas disconnection *b* entails intramolecular addition of the tertiary amine to the oxonium intermediate generated in situ (Scheme 1). The first strategy has been largely developed for the synthesis of quaternary ammonium salts and has been successfully applied to the total synthesis of 17-*nor*-excelsinidine[14] and subincanadines,[6] while the second one remains, to the best of our knowledge, unexploited in natural product total synthesis. We decided to explore the second option not only for its originality, but also for its complexity-generating power. Indeed, this disconnection would allow us, in a forward sense, to build not only the bridged ring system, but also the quaternary ammonium cation imbedded in an aminal functional group in one operation from lactol **3**. Furthermore, compound **3** (R = H) could in principle be converted into **4** (R = OH) through a

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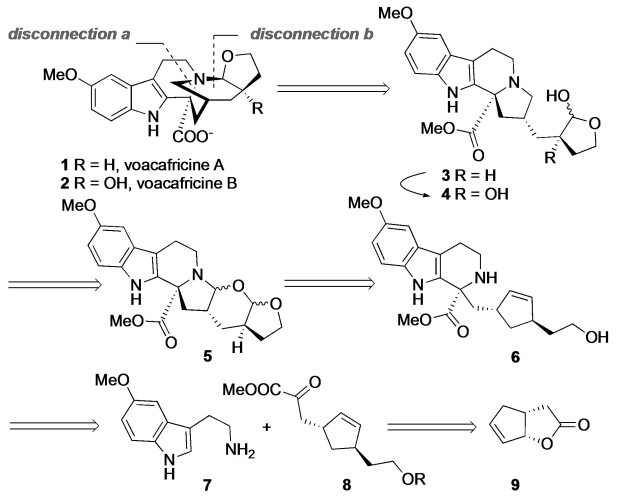
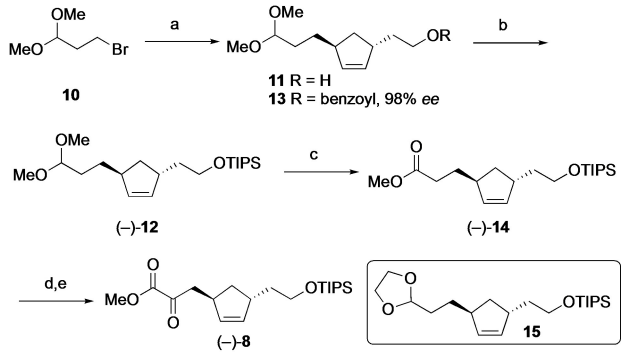



***Scheme 1.*** Divergent synthesis of voacafricines A (**1**), B (**2**): Retrosynthetic analysis.

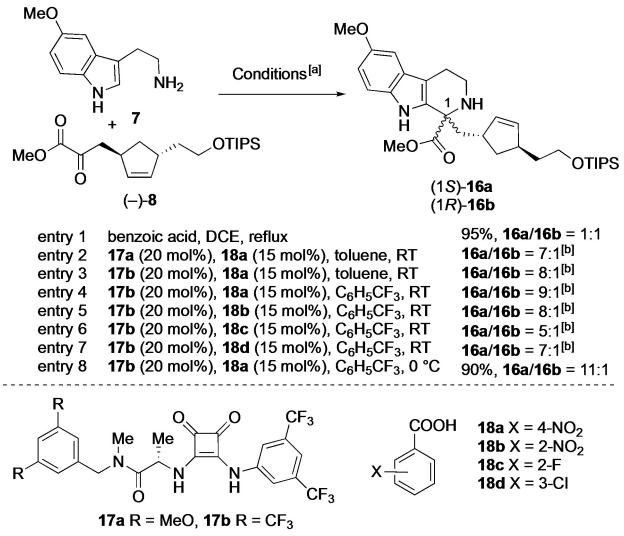



***Scheme 2.*** Synthesis of 3,5-disubstituted cyclopent-1-ene (−)-**8**. Reagents and conditions: a) **10** (1.0 equiv), Mg (1.1 equiv), $I_2$ (cat.), THF, room temperature, then $CuBr \cdot Me_2S$ (1.2 equiv), **9** (1.0 equiv), THF, −20 °C, then LAH (3.0 equiv), −20 °C→RT; b) TIPSCl (1.2 equiv), imidazole (2.5 equiv), DCM, room temperature, 92% over 2 steps. c) $P(OEt)_3$ (3.0 equiv), TESOTf (2.0 equiv), THF, 0 °C, then $NEt_3$ (3.0 equiv), LHMDS (3.0 equiv), −78 °C, then $O_2$, −78 °C, 81%; d) KHMDS (1.2 equiv), Davis oxaziridine (1.2 equiv), THF, −78 °C. e) DMP (2.5 equiv), DCM, 0 °C→RT, 58% over 2 steps. TIPS = triisopropylsilyl, TESOTf = triethylsilyl trifluoromethanesulfonate, LHMDS = lithium bis(trimethylsilyl)amide, KHMDS = potassium bis(trimethylsilyl)amide, Davis oxaziridine = 2-(benzenesulfonyl)-3-phenyloxaziridine, DMP = Dess–Martin periodinane, DCM = dichloromethane.

sequence of dehydration and dihydroxylation, thus allowing late-stage diversification to access both **1** and **2** from the same advanced intermediate. Compound **3** could be obtained by chemoselective reduction of aminal **5**, in turn derived from the oxidative cleavage of the cyclopentene in **6** followed by an aminal–acetal-forming cascade of the resulting dialdehyde.[15] The 1,1-disubstituted tetrahydro-β-carboline **6** was expected to be prepared from 6-methoxytryptamine **7** and chiral 3,5-disubstituted cyclopent-1-ene **8** through either a substrate-controlled or a catalyst-controlled asymmetric Pictet–Spengler reaction.[16] Compound **8** could be traced back to the known enantiomerically enriched bicyclic lactone **9**.[17] We report herein the development of a concise and divergent synthesis of voacafricines A (**1**) and B (**2**) based on this strategy.

The bicyclic lactone **9** was synthesized following a previously reported route on a multigram scale.[17] Its conversion into 3,5-disubstituted cyclopent-1-ene **8** is depicted in Scheme 2. The reaction of the Grignard reagent, freshly prepared from 3-bromo-1,1-dimethoxypropane (**10**), with **9** in the presence of $Me_2S \cdot CuBr$ afforded, after in situ reduction of the resulting carboxylic acid, alcohol **11**, which was, without purification, converted into triisopropylsilyl ether **12** in 92% overall yield from **9**. The ring opening of the allylic lactone proceeded with an excellent $S_N2'$ *anti* selectivity in agreement with the studies of Curran et al.[18] The *ee* value of **11** was determined to be 98% by its conversion into its UV-active benzoate **13**. Following the procedure of Fujioka and co-workers,[19] the dimethyl acetal in **12** was converted in one step into methyl ester (−)-**14**, which was isolated in 81% yield. We initially synthesized cyclopentene **15** (Scheme 2, inset) using the corresponding commercially available Grignard reagent; however, oxidation of the dioxolane to an ester turned out to be much less efficient under identical conditions. A classic pathway for conversion of **12** into **14** would involve the hydrolysis of the dimethyl acetal to an aldehyde, followed by oxidation and esterification. However, a facile intramolecular Prins reaction occurred when **12** was treated under diverse acidic conditions. Deprotonation of **14** followed by oxidation of the resulting enolate with the Davis oxaziridine[20] furnished the α-hydroxy ester as a mixture of two diastereomers, which were, without purification, oxidized with DMP[21] to afford α-ketoester **8** in 58% overall yield.

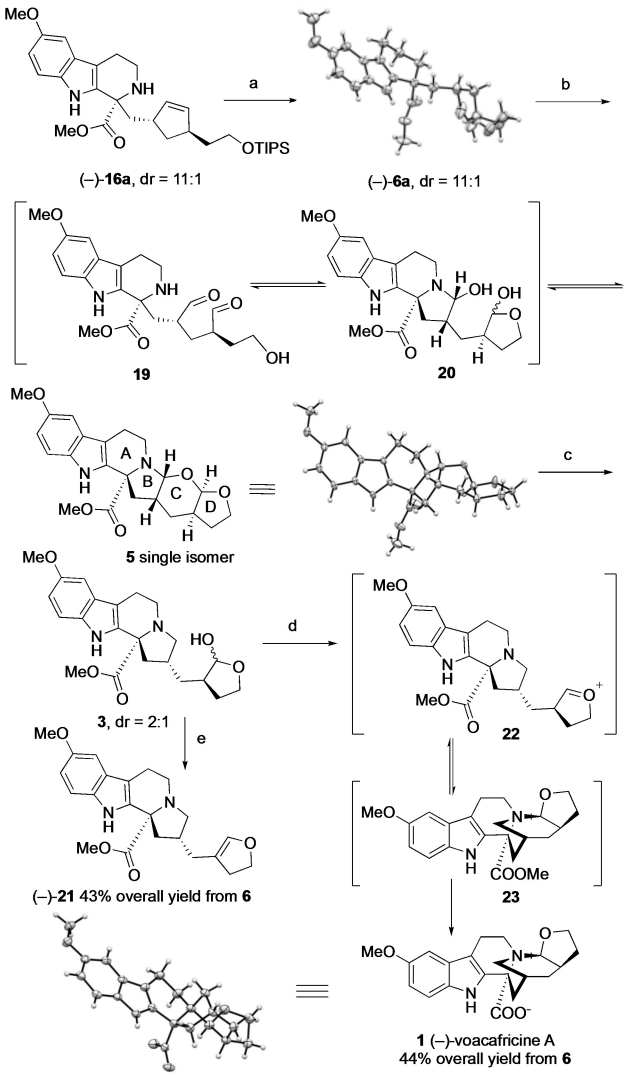
The Pictet–Spengler reaction between 6-methoxytryptamine (**7**) and chiral 3,5-disubstituted cyclopent-1-ene **8** in the presence of benzoic acid afforded 1,1-disubstituted tetrahydro-β-carboline **16** as a mixture of two diastereomers (dr 1:1) in 95% yield (entry 1, Scheme 3). The lack of diastereoselectivity was in fact not unexpected in light of the structure of the cyclopentene. We therefore turned our attention to the catalyst-controlled process. Squaramides **17a** and **17b**[13c] stood out in our catalyst screening (see the Supporting Information, Table S2), affording the products **16a** and **16b** in a ratio of 7:1 (entry 2) and 8:1 (entry 3), respectively. Further fine-tuning of the reaction conditions by varying the solvent (entry 4), the structure of acid co-catalysts (entries 4–7) and the temperature (entry 8) allowed us to conclude that the reaction is best performed in trifluorotoluene in the presence of **17b**, 4-nitrobenzoic acid (**18a**) and 5 Å molecular sieves at 0 °C. Under these conditions, compound **16** was isolated in 90% yield with a diastereomeric ratio (dr) of 11:1 in favour of (1*S*)-**16a**. The reaction was performed on a gram scale without erosion of yield and diastereoselectivity. The 1*S* configuration of the major diastereomer (1*S*)-




***Scheme 3.*** Pictet–Spengler reaction of 6-methoxytryptamine (**7**) with ketoester **8**. [a] Standard conditions for the chiral-squaramide-catalyzed reaction: **7** (0.05 mmol), **8** (0.06 mmol, 1.2 equiv), catalyst **17** (20 mol%), substituted benzoic acid **18** (15 mol%), 5 Å molecular sieves (21 mg), solvent (*c* 0.04 M). [b] Yield was not determined.

**16a** was assigned based on our previous results[13c] and was subsequently confirmed by X-ray structural analysis of its downstream products.

The endgame of the total synthesis of voacafricine A (**1**) is detailed in Scheme 4. Removal of the TIPS protecting group from (−)-**16a** under mild acidic conditions afforded compound (−)-**6a** (80 %), whose absolute and relative configuration was determined by X-ray crystallographic analysis.[22] Selective cleavage of a cyclopentene double bond in the presence of an indole has been documented. However, in most of the reported cases, the indole nitrogen atom needs to be protected by either an electron-withdrawing functionality (tosyl, acyl)[23] or a bulky TBS group.[24] We set out to examine the selective cleavage of cyclopentene without prior N-protection and found that Lemieux–Johnson conditions[25] worked well to directly convert **6** into fused hexacyclic compound **5** as a single diastereomer, presumably via intermediates **19** and **20**. The minor diastereomer (1*R*)-**6b** might decompose during this domino transformation. As shown by the X-ray crystal structure of **5**,[22] the chiral centers α to the two aldehyde functions were preserved, and the four heterocycles (A, B, C, D ring) are all *cis*-fused, leading to a ladderlike structure to minimize steric interactions. The lone pair of the nitrogen atom in this conformation is in a synclinal relationship with the C–O bond of the C ring, which would not be particularly conducive to the subsequent chemoselective reduction of the aminal functionality. We were therefore pleased to observe that reduction of **5** with a slight excess of sodium cyanoborohydride in a buffered solution (pH 6) was highly chemoselective, affording **3** as a mixture of two diastereomers at the hemiacetal carbon atom. Neither **3** nor **5** was stable enough to be purified by flash column chromatography

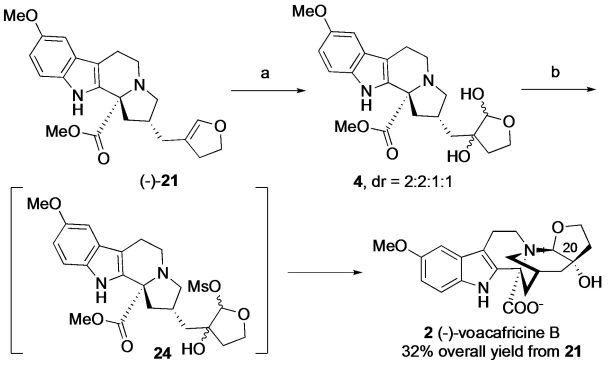



***Scheme 4.*** Total synthesis of voacafricine A (**1**). Reagents and conditions: a) 4 N aqueous HCl/MeOH (v/v = 1 : 1), room temperature, 80 %; b) $K_2OsO_4 \cdot 2H_2O$ (4 mol%), $NaIO_4$ (2.1 equiv), dioxane/$H_2O$ (v/v = 1 : 1), room temperature; c) $NaBH_3CN$ (1.5 equiv), pH 6 buffer/dioxane (1 : 1), room temperature; d) MsCl (2.0 equiv), $NEt_3$ (3.0 equiv), DCM, room temperature, then workup with saturated aqueous $Na_2CO_3$, 44 % over 3 steps from **6**; e) MsCl (2.0 equiv), DIPEA (3.0 equiv), DCM, 50 °C, 43 % over 3 steps from **6**. DIPEA = diisopropylethylamine, Ms = methanesulfonyl.

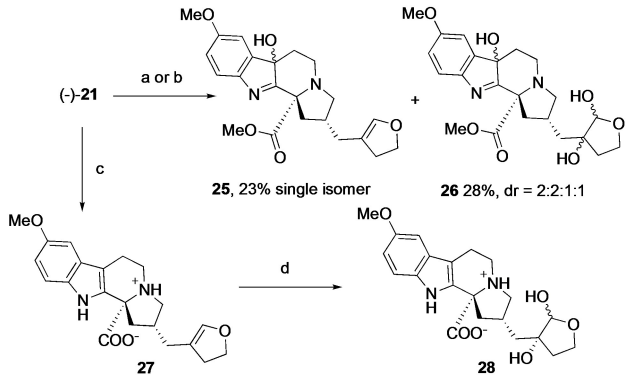
without partial decomposition; the crude product **3** was therefore directly used for the last cyclization step. After a survey of different activation methods (see Tables S1 and S5), the optimum conditions consisted of stirring a solution of **3**, mesyl chloride (2.0 equiv) and triethylamine (3.0 equiv) in dichloromethane at room temperature, followed by workup with saturated aqueous sodium carbonate solution. Under these conditions, (−)-voacafricine A (**1**) was isolated in 44 % yield over three steps from compound **6** together with dihydrofuran **21** in 10 % yield. Mesylation of the hydroxy group in **3**, elimination of mesylate to give oxonium **22** and intramolecular nucleophilic addition of the tertiary amine to

the oxonium moiety could account for the formation of **23**, which was subsequently hydrolyzed during workup to furnish the natural product (−)-**1** {$[\alpha]_D = -89.6$ (c 1.0, MeOH); $[\alpha]_D$[1] = −66.1 (c 3.98, MeOH)}. Although it was planned as a strategic transformation, we were still fascinated by the facile stereoselective formation of the 8-alkyl octahydro-2*H*-5,8-methanofuro[2,3-*b*]azepin-8-ium motif found in the natural product. The presence of an α-quaternary ammonium cation might in turn facilitate the saponification of the hindered methyl ester in **23**, presumably due to the proximity of the hydroxide ion pair. Indeed, the methyl ester of **21** remained untouched under these conditions. By synthesizing (±)-**1** following the same synthetic route, the *ee* value of synthetic (−)-voacafricine A (**1**) was determined to be higher than 99%. Since we have obtained the X-ray crystal structure of (−)-**1**,[22] the present synthesis confirmed the absolute stereostructure of (−)-voacafricine A (**1**) assigned by Luo and co-workers.[1]

Formation of dihydrofuran **21**, an ideal precursor for the synthesis (−)-voacafricine B (**2**), might result from the deprotonation of oxonium **22**. Therefore, conditions were optimized again to favor the production of **21** (see Table S5). Interestingly, simply performing the mesylation at 50 °C in the presence of diisopropylethylamine completely shut down the aminal-forming pathway, affording instead isomerization product **21** in 43% overall yield from **6** (Scheme 4). Conversion of **21** into (−)-voacafricine B (**2**) was next examined (Scheme 5). Chemoselective dihydroxylation of the dihydrofuran was realized under Upjohn conditions[26] to afford **4** as a mixture of four diols resulting from non-diastereoselective dihydroxylation and epimerization of the hemiacetal carbon. Under conditions developed for the synthesis of (−)-**1**, the above crude reaction mixture was converted into (−)-voacafricine B (**2**) {$[\alpha]_D = -110$ (*c* 0.4, MeOH); $[\alpha]_D$[1] = −99.3 (*c* 1.46, MeOH)} in 32% yield from **21**.[27] The reaction might be initiated by chemoselective monomesylation of the lactol at the expense of the tertiary alcohol. The resulting mesylate **24** would then undergo




***Scheme 5.*** Total synthesis of (−)-voacafricine B (**2**). Reagents and conditions: a) $K_2OsO_4 \cdot 2H_2O$ (4 mol%), NMO·$H_2O$ (2.5 equiv), THF/$H_2O$ (v/v = 1.5:1), room temperature; b) MsCl (2.0 equiv), $NEt_3$ (3.0 equiv), DCM, room temperature, then saturated aqueous $Na_2CO_3$, 32% yield over 2 steps.




***Scheme 6.*** Attempted diastereoselective dihydroxylation. Reagents and conditions: a) AD mix α (1.4 g mmol$^{-1}$), *t*BuOH/$H_2O$ (v/v = 1:1), room temperature, 23% for **25** and 28% for **26** (dr 2:2:1:1). b) AD mix β (1.4 g mmol$^{-1}$), *t*BuOH/$H_2O$ (v/v = 1:1), room temperature, 23% for **25** and 28% for **26** (dr 2:2:1:1). c) 2 M LiOH/dioxane (v/v = 1:1), room temperature. d) $K_2OsO_4 \cdot 2H_2O$ (4 mol%), NMO·$H_2O$ (2.5 equiv), THF/$H_2O$ (v/v = 1.5/1), room temperature.

the same domino sequence as is detailed for the formation of (−)-**1** (cf. Scheme 4). No other diastereomer of voacafricine B was isolated. We surmised that the stereoisomers with a C20 β-OH group might not be prone to aminal formation owing to the steric repulsion and decomposed instead.[28] The spectroscopic data of our synthetic voacafricine B match well with those reported for the natural product.

To increase the diastereoselectivity of the dihydroxylation step, AD mix β and AD mix α developed by Sharpless were tested (Scheme 6).[29] In both cases, the double bond of the pyrrole ring was dihydroxylated preferentially to afford **25** as a single stereoisomer (configuration was not determined). Compound **26** resulting from the dihydroxylation of both pyrrole and dihydrofuran was also isolated as a mixture of four diastereomers indicating the lack of both chemo- and stereocontrol with these two chiral reagents. We subsequently prepared zwitterion **27**, hoping that the carboxylate would be able to coordinate to the catalyst, hence directing the dihydroxylation step. Unfortunately, full decomposition occurred when Upjohn conditions were applied to compound **27**.

In summary, we have developed a divergent asymmetric total synthesis of voacafricines A (**1**) and B (**2**). Intramolecular nucleophilic addition of the tertiary amino nitrogen atom to the oxonium species generated in situ was developed for the stereoselective generation of the unprecedented 8-alkyl octahydro-2*H*-5,8-methanofuro[2,3-*b*]azepin-8-ium motif found in the natural products. The study also demonstrates the power of the chiral-squaramide-catalyzed Pictet–Spengler reaction in the construction of 1,1-disubstituted tetrahydro-β-carbolines.

## Acknowledgements

We thank EPFL (Switzerland) and Swiss National Science Foundation (SNSF 200020–169077) for financial support. We thank Dr. F. Fadaei-Tirani and Dr. R. Scopelliti for the X-ray structural analysis of compounds **1**, **5**, and **6**. Open Access funding provided by École Polytechnique Fédérale de Lausanne.

## 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 supplementary material of this article.

**Keywords:** Indole Alkaloids · Organocatalysis · Pictet–Spengler Reaction · Squaramides · α-Ketoesters

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or decomposition was observed in line with our failure to cyclize compound **3** under acidic conditions.

[28] The fact that (1*R*)-**6b** and the undesired diastereoisomer **4** were unproductive in the cascade cyclization would imply that there could well be stereochemical communication between the tetrasubstituted C1 stereocenter and the two other stereocenters residing in the cyclopentene unit. Assuming that the two stereocenters α to the two aldehyde functionalities in intermediate **19** could undergo epimerization via an enol/enamine intermediate, one could expect, in an ideal case, dynamic kinetic resolution of the diastereomers, hence a possibility to use (±)-**8**, instead of enantiomerically enriched **8**, for the synthesis of both (−)-voacafricine A and (−)-voacafricine B. We thank one of the referees for this insightful suggestion and would certainly like to explore this possibility in our future synthesis of related natural products.

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Manuscript received: January 31, 2023
Accepted manuscript online: February 24, 2023
Version of record online: March 13, 2023