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The total synthesis of (–)-strempeliopine *via* palladium-catalyzed decarboxylative asymmetric allylic alkylation †

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In the work reported herein, the concise and enantioselective total synthesis of the *Schizozygine* alkaloid (–)-strempeliopine was developed. This synthetic strategy featured the palladium-catalyzed decarboxylative asymmetric allylic alkylation of *N*-benzoyl lactam to set up the absolute configuration at the C20 position, a highly diastereoselective one-pot Bischler–Napieralski/lactamization and iminium reduction sequence for the construction of the pentacyclic core structure, and the late-stage dearomative addition of indole, leading to the otherwise difficult-to-achieve hexacyclic indoline framework with complete control of four neighbouring stereocenters.

Schizozygine alkaloids[1] (*e.g.*, **1**–**5**, Fig. 1), isolated almost exclusively from the twigs of the East Africa monotypic shrub *Schizozygia coffaeoides*, are family members of eburnamine–vincamine alkaloids[2] and display useful biological properties such as antifungal, antimicrobial, and antiplasmodial properties as well as other pharmacological properties.[3,4] The *Schizozygia coffaeoides* (Boj.) Baill[5] (Apocynaceae) is one of the plants used in Kenyan traditional medicine for treatment of skin and ectoparasitic diseases. (–)-Strempeliopine (**4**) and (–)-vallesamidine (**5**) isolated from the Cuban species *Strempeliopsis strempelioides* K. Schum[6] are exceptional members of the *Schizozygine* alkaloid group, having absolute configurations opposite to those of *Schizozygine* alkaloids (**1**–**3**). Structurally, (–)-strempeliopine (**4**)[7] embodies a unique class having a hexacyclic framework {hexahydro-ethanoindolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine ring system} with the consecutive 7*R*, 2*S*, 21*R*, and 20*R* stereocenters.

Owing to their striking molecular architecture and potent biological activities as well as low natural abundance, these *Schizozygine* alkaloids have attracted substantial attention from the synthetic community.[8] Significant efforts have been directed towards their synthesis. These endeavors include (see ESI†) (i) Le Men's semi-synthesis of (+)-**5** *via* the elegant reductive rearrangement from (–)-tabersonine,[8a] (ii) Trojánek's biomimetic synthesis of (–)-**4** from (+)-18-methylene-vincadifformine using Le Men's strategy,[8b] (iii) Heathcock's eight-step synthesis of (±)-**5** from 2-ethylcyclopentanone featuring the NBS-mediated cyclization of amino lactam,[8c] (iv) Padwa's racemic synthesis of (±)-**4** using an intramolecular 1,4-dipolar cycloaddition and Heathcock's NBS-induced cyclization as the key steps,[8d] (v) Okada's asymmetric synthesis of (–)-**5** from the chiral lactone using reductive radical cyclization as the key reaction,[8e] (vi) Qin's photocatalytic radical-based cascade approach toward (–)-**4** and (–)-**5**,[8fg] (vii) Anderson's asymmetric synthesis of (+)-**3** and (+)-**5** involving a [1,4]-hydride transfer/Mannich type cyclization,[8h] and (viii) Boger's recent asymmetric synthesis of (–)-**4** *via* a powerful $SmI_2/BF_3{\cdot}OEt_2$-induced dearomative transannular radical cyclization to forge the crucial

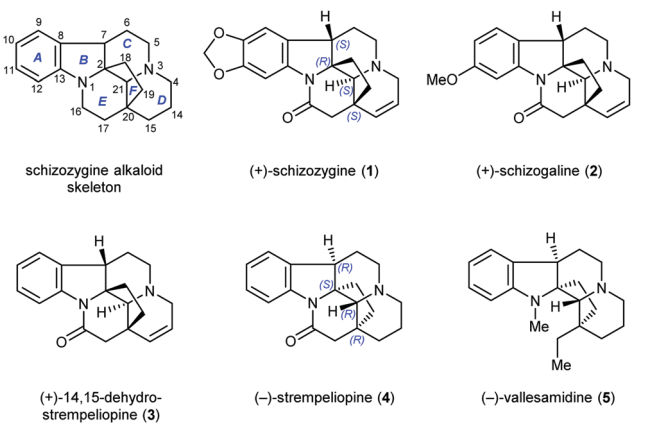

Fig. 1 Representative *Schizozygine* alkaloids (**1**–**5**).

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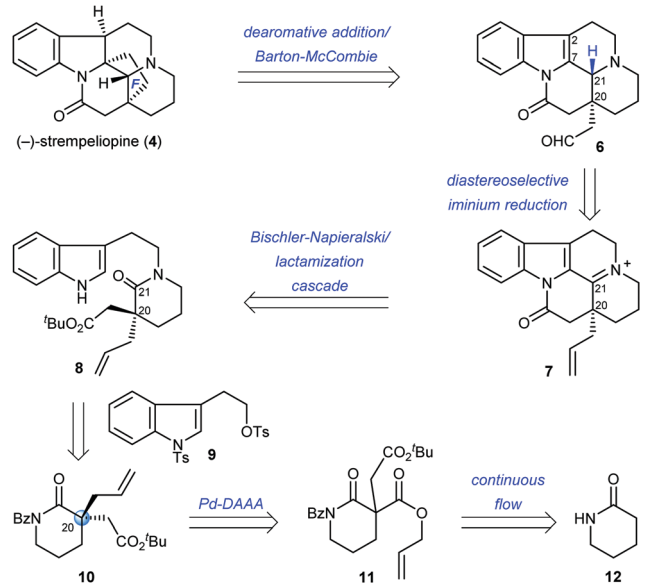


Scheme 1 Retrosynthetic analysis of (–)-strempeliopine (**4**).

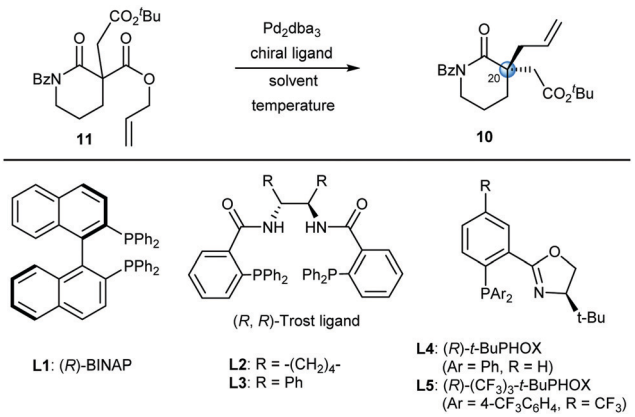
C2–C21 bond.[8i] Despite these examples of progress, efficient access to *Schizozygine* alkaloids with high stereochemical control still remains an important and formidable challenge. Considering that subtle structural differences have tremendous impacts on the biological activities within this family of natural products, we embraced the development of a *de novo* asymmetric total synthesis of *Schizozygine* alkaloid (–)-**4** that would provide the opportunity for flexible and deep-seated structural modifications inaccessible when carrying out a ready-made semi-synthesis or a total synthesis. Herein, we report our efforts leading to a general, efficient and conceptually new strategy for the catalytic enantioselective total synthesis of (–)-strempeliopine (**4**).

Our retrosynthetic analysis of the target natural product (–)-strempeliopine (**4**) is depicted in Scheme 1. We envisioned that **4** would be obtained from pentacyclic aldehyde **6** *via* a transannular dearomative addition followed by a Barton–McCombie reaction. This known protocol would be used to construct the hexacyclic scaffold with the consecutive C2, C7, C21 and C20 stereocenters, and provide a platform for synthesizing *Schizozygine* alkaloids. A Bischler–Napieralski/lactamization cascade of *N*-ethylindole-β-amidoester **8** could furnish the pentacyclic iminium **7** and the ensuing hydride reduction would occur from the less hindered *Si*-face to give the *trans*-fused octahydroquinoline subunit in **6**. Tricyclic compound **8** could be accessed *via* a union of known tryptophol tosylate **9** and enantiomerically pure *N*-benzoyl-β-amidoester **10**. The palladium-catalyzed decarboxylative asymmetric allylic alkylation (Pd-DAAA) of lactams has proven to be a powerful tool for accessing otherwise difficult-to-obtain enantioenriched quaternary-stereocenter-containing N-heterocycles,[9] and is expected to be used as the key step of a general method to stereoselectively synthesize a variety of *Schizozygine* alkaloids. Based on this consideration, the pivotal **10**, in turn, would arise from racemic amidodiester **11** *via* a Pd-DAAA to build the all-carbon quaternary center at the C20 position. The diester **11** could be readily prepared from the commercially available piperidin-2-one **12** by a series of routine functional group transformations in continuous flow.

Our synthetic journey commenced with the preparation of *N*-benzoyl-β-amido-diester **11** from the commercially available piperidin-2-one **12** in continuous flow[10] (see Table S1 in ESI,† and the associated scheme for details). Initially, we examined the synthesis of lactam **13** by carrying out a continuous flow *N*-acylation reaction of benzoyl chloride with piperidin-2-one **12**. When an equimolar ratio of **12** and benzoyl chloride was streamed through a T-shaped mixer to a PTFE coil 1 (1 mL, 0.8 mm i.d.) at 25 °C with 10 minutes residence time and 5 bar back-pressure, only 80% conversion of **12** was achieved. When the amount of benzoyl chloride used was increased to 1.2 equiv., a 93% isolated yield of lactam **13** was obtained with full conversion of **12**. Next, a substantial effort was made to acylate the C3 position in **13** under continuous flow, but achieving this acylation proved quite challenging. A THF solution of lactam **13** combined with LiHMDS was pumped through a T-shaped mixer into a PTFE coil 2 (2 mL, 0.8 mm i.d.). Then the mixture was combined with a THF solution of acrylic ester **14** through another T-mixer and streamed to a PTFE coil 3 (2 mL, 0.8 mm i.d.) at −80 °C with a 16 minutes residence time and 5-bar back-pressure. This reaction worked out smoothly, but there was little corresponding acylation at the C3 position in **12** and the acylation that did occur showed poor regioselectivity (**17**/**18** = 3 : 4, inseparable products, entry 1, Table S1, ESI†). To improve the regioselectivity of the acylation reaction, two other acylation reagents were investigated. When the acylation reagent **14** was replaced with allyl 1*H*-imidazole-1-carboxylate **15**, no *O*-acylation by-product **18** was detected using LC–MS, and the desired monoester **17** was generated under flow conditions (1.2 equiv. LDA/THF at −80 °C in 16 minutes) in 32% yield (entry 2). To our delight, the use of allyl cyanoformate **16** as an acylation reagent provided the monoester **17** in 50% isolated yield under the same reaction conditions with no by-product **18** (entry 3). Ultimately, we optimized the temperature for the acylation of **13** and **16**, and this optimization afforded the expected acylation product **17** in 76% yield. Of note, the regioselectivity of this reaction was maintained (entry 4). Finally, an MF-200 fixed bed reactor was chosen (Shen-zhen E-Zheng tech Co., Ltd) with K_2CO_3 as filling material due to K_2CO_3 slightly dissolving in DMF. To start with, a DMF solution of monoester **17** and *t*-butyl bromoacetate was blended using a T-mixer, and then the mixture was injected into the MF-200 fixed bed reactor (7 mL internal volume) at 25 °C and 5-bar back-pressure with a residence time of 10 minutes. Here, the desired diester **11** was obtained in 87% yield. Notably, this time-economical, three-step continuous flow synthesis allowed us to efficiently prepare enough substrate **11** in the least possible time.

Following the Pd-DAAA of lactam established by Stoltz and co-workers,[11] the stage was set for the key transformation to construct the critical lactam **10** from **11**. A series of chiral ligands incorporating Pd_2dba_3 in dioxane at 80 °C were

Table 1 Exploratory and optimization studies for the synthesis of the enantioenriched α-quaternary lactam **10**[a]

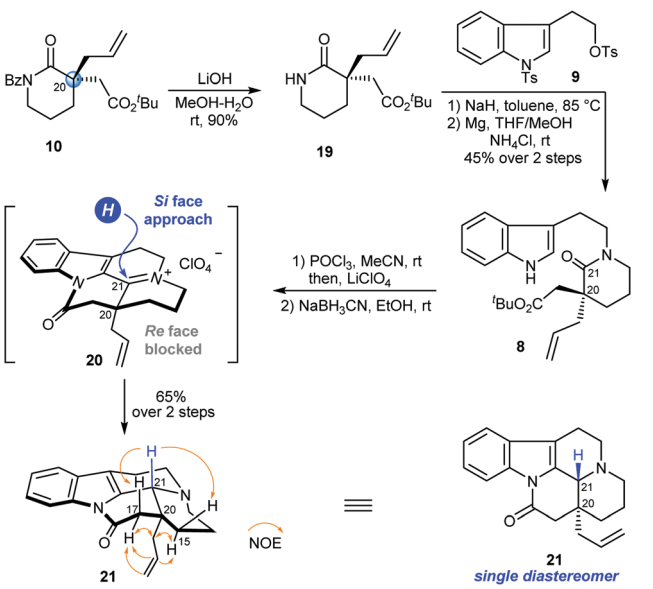


Entry	Lig.	Sol.	Temp. (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**L1**	Dioxane	80	4	92	5
2	**L2**	Dioxane	80	120	<10	10
3	**L3**	Dioxane	80	120	<10	15
4	**L4**	Dioxane	80	6	94	51
5	**L5**	Dioxane	80	6	92	88
6	**L5**	Dioxane	60	10	90	91
7	**L5**	Dioxane	45	15	90	92
8	**L5**	THF	45	15	90	94
9	**L5**	MTBE	45	15	89	99
10	**L5**	Toluene	45	15	92	99
11[d]	**L5**	Toluene	45	25	90	99

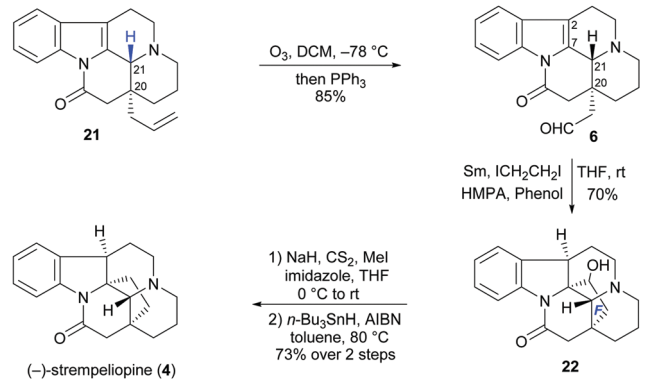
[a] Unless noted otherwise, the reactions were run using 0.1 mmol of **11**, 5 mol% Pd_2dba_3, and 12.5 mol% ligand in 4 mL of solvent. [b] Isolated yields. [c] Determined from chiral HPLC analysis. [d] 1.2 g scale.

investigated.[12] The chiral bisphosphine ligand (*R*)-BINAP **L1**[13a] was observed to be inefficient at yielding the desired enantioselectivity outcome, despite delivering a high yield (92%, 5% ee, entry 1, Table 1). The Trost group successfully accomplished the Pd-DAAA of δ-valerolactams by using their labelled (*R*,*R*)-ANDEN-phenyl Trost ligand, but the use of the 2-diphenylphosphinobenzoate chiral ligands **L2** and **L3** proved to be futile.[13b] In our case, the (*R*,*R*)-Trost ligands **L2** and **L3** were also not workable for the transformation of **11** (entries 2 and 3). We were pleased to observe that the reaction of **10** using the Pfaltz ligand (*R*)-*t*-BuPHOX **L4**[13c] smoothly afforded the desired lactam **10** in 94% yield and an encouraging 51% ee level of enantioinduction (entry 4). And switching to (*R*)-$(CF_3)_3$-*t*-BuPHOX **L5**[13d] resulted in a drastic improvement in the enantioselectivity of the reaction (92%, 88% ee, entry 5). Inspired by this result, we then continued optimizing the conditions of the experiments with **L5**. Performing the reaction in dioxane at 60 °C instead of 80 °C led to a 90% yield of the allylated product with a 91% ee (entry 6). Decreasing the temperature further to 45 °C gave a similar yield and a slightly higher enantioselectivity (90%, 92% ee, entry 7). In a solvent screening, the use of THF gave a further increase in enantioinduction, specifically to 94% ee, with a similar level of conversion to dioxane (entry 8)—while the transformations in MTBE or toluene both smoothly afforded the desired lactams with excellent enantioselectivity levels of up to 99% ee, and retained comparable yields (entries 9 and 10). Of note, this transformation was effected efficiently and with excellent enantioselectivity on the gram scale (entry 11), and provided enough supplies of materials for the subsequent synthetic investigations.

After confirming the robustness of the Pd-DAAA reaction to access the pivotal enantioenriched lactam **10**, we then focused our attention on the completion of the synthesis of (–)-strempeliopine (**4**). After the removal of the benzoyl protecting group using LiOH in the mixed solvent MeOH/H_2O at room temperature, the requisite secondary amide **19** was furnished in 90% yield for the subsequent condensation reaction (Scheme 2). To this end, carrying out a treatment of **19** with tryptophol tosylate **9** in the presence of NaH in toluene at 85 °C, followed by removal of the Ts group attached to indole nitrogen atom, gave rise to the condensation product **8** in 45% isolated overall yield over the two steps.[14,15] With the cyclization precursor lactam **8** in hand, the stage was set for the key transformation to construct the critical pentacyclic core. Pleasingly, a Bischler–Napieralski/lactamization sequence using $POCl_3$ in MeCN successively on substrate **8** readily afforded a pentacyclic intermediate, which was directly treated with $LiClO_4$, thus providing the stable iminium intermediate **20**.[16] Following reduction of the C=N double bond in iminium **20** with $NaBH_3CN$ in EtOH, the desired amine **21**, with C20/C21 *trans* stereochemistry, was generated as a single diastereomer in 65% overall yield over two steps from **8**.[17] The relative stereochemistry of **21** was confirmed from the results of NOE experiments as shown in Scheme 2 (orange arrow). Thus, by using this two-step synthetic sequence, we were able to prepare the key pentacyclic scaffold with satisfactory stereochemical control. We proposed that the Re face would be blocked by the allyl group—and, thus, the reductive species would approach from the *Si* face, leading to the strong C20/C21 *trans* selectivity.



Scheme 2 The construction of the useful *trans*-fused pentacyclic lactam **21**.



Scheme 3 Completion of the synthesis of (–)-strempeliopine (**4**).

In accord with our synthetic plan, we turned our attention to the installment of the F-ring *via* a transannular dearomative addition. To convert the allyl group to the acetaldehyde moiety, compound **21** was subjected to ozonation (O_3, then PPh_3) to give aldehyde **6** in 85% yield (Scheme 3). Inspired by Qin's work,[8f] we turned our attention to constructing the F-ring by carrying out the alternative transannular dearomative cyclization: exposure of **6** to samarium powder and diiodoethane in the presence of HMPA and phenol furnished hexacyclic alcohol **22** in 70% yield.[18] Ultimately, a two-step Barton-McCombie radical deoxygenation[19] proceeded smoothly and afforded (–)-strempeliopine (**4**) in 73% overall yield, and the analytical data for this product were identical to those reported in the literature.[8f,i]

In summary, we have achieved the asymmetric total synthesis of the *Schizozygine* alkaloid (–)-strempeliopine (**4**) in 13 steps from the commercially available piperidin-2-one **12**. Our synthesis is marked by practical Pd-catalyzed decarboxylative asymmetric allylic alkylation (Pd-DAAA) to construct the generally difficult-to-synthesize all-carbon quaternary center at C20, with a remarkably efficient sequence including Bischler–Napieralski/lactamization/iminium reduction to forge the key pentacyclic core of **4** with high stereochemical control, and a late-stage modified transannular dearomative cyclization to establish the F-ring. The strategy and tactics we described are expected to provide guidance for the synthesis of other *Schizozygine* alkaloids that have different absolute configurations.

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Conflicts of interest

The authors declare no competing financial interests.

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