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Natural Products

Total Synthesis of (−)-Arborisidine

*Feng-Yuan Wang and Lei Jiao**

Abstract: *An asymmetric total synthesis of cage-like indole alkaloid arborisidine is presented. The new synthetic strategy features a catalytic parallel kinetic resolution based on ambident nucleophilicity (C3/N) of indole to set the absolute configurations of the two quaternary chiral centers, and a 5-exo-trig radical cyclization to form the bridged nitrogen-containing five-membered ring.*

Indole alkaloids constitute a major category of natural products with unique chemical structures and promising biological activities,[1] which have been constantly stimulating the development of new chemical transformations and synthetic strategies.[2] Over the past years, a group of indole alkaloids including arborisidine (**1**),[3] subincanadine A (**2**)[4] and taberdivamine B (**3**)[5] (Figure 1 a) have posed challenges to synthetic chemists due to their diverse polycyclic skeletons bearing an unusual aza-quaternary chiral center. Among these molecules, arborsidine (**1**) featuring a novel bridged pentacyclic structure with two quaternary stereocenters caught our attention. It was found to inhibit gastric cancer in vivo in combination with pimelautide,[6] yet with an extremely low natural abundance.[3] The unique structural feature and promising biological activity, together with its scarcity, highlighted the value of its chemical synthesis.

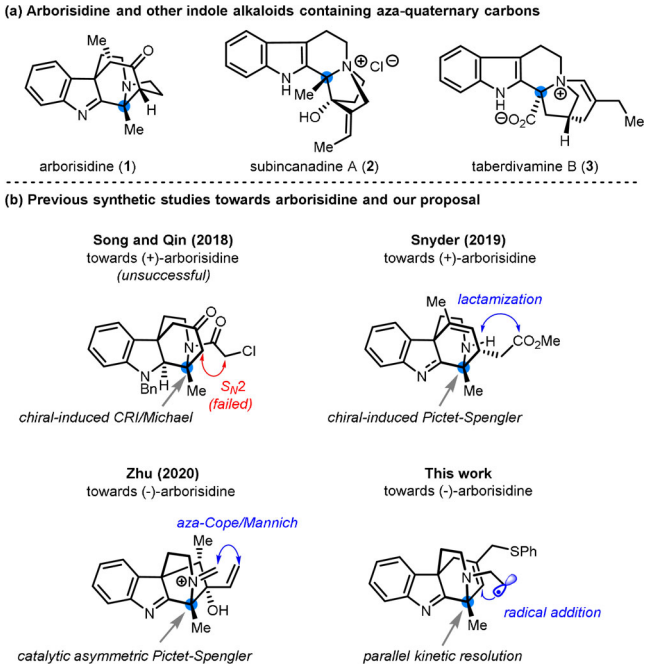

Figure 1. Representative indole alkaloids (a) and synthetic studies towards arborisidine (b). CRI = cyclopropanation/ring-opening/iminium cyclization.

Although arborisidine has been the target of several research groups, only until very recently two successful total syntheses were reported by the research groups of Snyder[7] and Zhu,[8] respectively. One of the synthetic challenges is to build the bridged nitrogen-containing five-membered ring (Figure 1 b). A straightforward approach is an intramolecular S_N2 reaction between the ketone enolate and an alkyl electrophile to build the C14-C15 bond. However, in this case a *retro*-Michael reaction overrides the anticipated S_N2 pathway, as revealed by Song, Qin and co-workers[9] as well as Snyder,[7] probably due to the generation of an anion with the lone pair of electrons approximately coplanar to the σ* orbital of the C–N bond. To avoid this problem, Snyder and co-workers used an elegant intramolecular lactam formation reaction, and the Zhu group invoked an aza-Cope/Mannich cascade.

Due to our interest in the synthesis of indole alkaloids,[10] we were also attracted by this interesting molecule. As our early attempts on intramolecular S_N2 cyclization of **4** was unsuccessful (Scheme 1 a) and the same strategy was later proved infeasible by Song and Qin,[9] we intended to develop an alternative strategy. In the retrosynthetic analysis (Scheme 1 a), we hypothesized that radical addition might be a suitable method to forge the C14-C15 linkage, which avoids the formation of a carbanion neighboring the C–N bond. According to this design, arborisidine is derived from intermediate **5**, which is the expected 5-*exo-trig* radical cyclization product of allylic thioether **6**.[11] We anticipated that, an intramolecular dearomative allylic alkylation of substrate **8**, followed by a regioselective functionalization of the exocyclic alkene in intermediate **7** could afford intermediate **6**. The Barbier-type addition of bromide **10**[12] to harmalane (**9**)[13] is an ideal choice for the preparation of **8**. To assess the feasibility of the radical cyclization, DFT calculation was performed (Scheme 1 b). The anticipated 5-*exo-trig* cyclization (**TS-1**) is favored over other possible competing pathways, such as 5-*exo-trig* cyclization with the imine (**TS-3**) or 1,5-hydrogen atom transfer from the methyl group (**TS-4**).

With the encouraging DFT result in hand, we commenced our synthetic study towards arborisidine. The crucial point for asymmetric synthesis is to set the absolute configuration of the aza-quaternary chiral center. In the reported syntheses, either a chiral-induced or an organocatalyzed asymmetric

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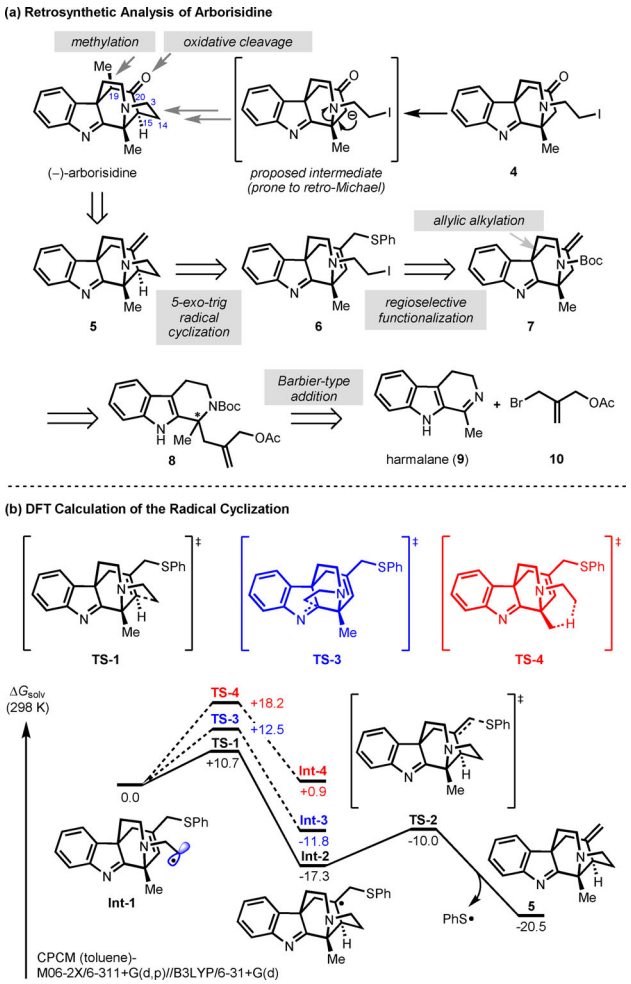
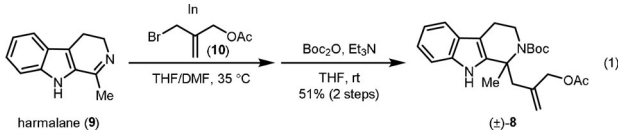


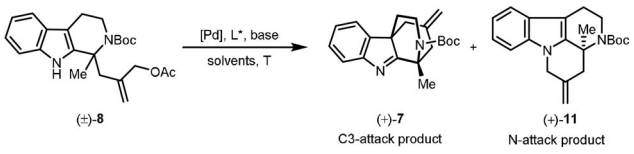
Scheme 1. Retrosynthetic analysis of arborisidine (a) and DFT calculation on the designed radical cyclization (b).

Pictet-Spengler (P-S) reaction was utilized.[7,8] However, the construction of this aza-quaternary chiral center remained a challenge, as the chiral-induced P-S reaction exhibited a moderate diastereoselectivity and required removal of the auxiliary group, and the efficiency of the organocatalytic P-S reaction of ketone substrate was barely satisfactory. Consequently, we hope to search for another approach towards this challenging chiral center. Although the reaction between harmalane (**9**) and allyl bromide **10** afforded (±)-**8** in a decent yield through an indium-mediated addition/Boc-protection sequence [Eq. (1)], its asymmetric variant was not simply accessible. We envisaged to use an asymmetric Barbier-type addition by applying a chiral indium reagent,[14] or a copper-catalyzed enantioselective allylation employing allylboron reagents.[15] Unfortunately, extensive attempts failed to give a satisfactory result.

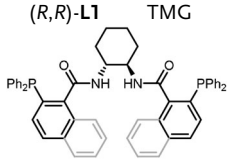


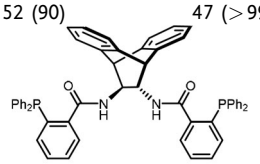
Given that intramolecular dearomative asymmetric allylic alkylation (AAA) of indole could be highly stereoselective,[10,16] we then considered to attempt a kinetic resolution (KR) on (±)-**8** using the catalytic AAA protocol.[17] To the best of our knowledge, although examples of intermolecular KR through Pd-catalyzed AAA were reported,[18] there was no precedent on an intramolecular version. The key challenge for the proposed intramolecular KR is the difficulty in controlling the reaction progress, because adjusting the equivalent of the reagent is not possible. Despite this, the KR of (±)-**8** was still attempted (Table 1). With $Pd_2(dba)_3$ as the palladium source and K_2CO_3 as the base, several ligands reported to be efficient for Pd-catalyzed AAA reaction of indole were tested, including the diaminocyclohexane (DACH)-phenyl Trost ligand (*R*,*R*)-**L1**, the DACH-naphthyl Trost ligand (*R*,*R*)-**L2**, and the dihydro-9,10-ethanoanthracene (ANDEN)-phenyl Trost ligand (*S*,*S*)-**L3** (entries 1–4). It was found that the reaction proceeded smoothly with **L1** and **L3**, but the conversion of the reaction was indeed difficult to control and the enantioselectivities of product (+)-**7** were poor even under a low conversion, implying an unsuccessful KR. However, we noticed that the performance of **L1** was better than that of **L3**, and the N-attack product **11** was also detected (entry 1). This prompted us to imagine a scenario that takes the advantage of the C3/N ambident nucleophilicity

Table 1: Optimization of the kinetic resolution conditions.



Entry	Ligand	Base	(+)-**7** Yield (*ee*) [%][b]	(+)-**11** Yield (*ee*) [%][b]
1[a]	(*R*,*R*)-**L1**	K_2CO_3	15 (45)	< 5 (–[c])
2[a]	(*R*,*R*)-**L2**	K_2CO_3	0	0
3[a,d]	(*S*,*S*)-**L3**	K_2CO_3	75 (–[c])	0
4[a,e]	(*S*,*S*)-**L3**	K_2CO_3	5 (39)	0
5[a]	(*R*,*R*)-**L1**	DIPEA	54 (53)	29 (99)
6[a]	(*R*,*R*)-**L1**	TMG	49 (66)	24 (> 99)
7[a,f]	(*R*,*R*)-**L1**	TMG	41 (68)	24 (> 99)
8[g]	(*R*,*R*)-**L1**	TMG	52 (90)	47 (> 99)


(*R*,*R*)-**L1** DACH-phenyl Trost ligand
(*R*,*R*)-**L2** DACH-naphthyl Trost ligand


(*S*,*S*)-**L3**
ANDEN-phenyl Trost ligand

[a] Reaction conditions: **8** (0.05 mmol), $Pd_2(dba)_3$ (1.5 mol%), ligand (4.5 mol%), base (1 equiv) in anhydrous toluene (0.5 mL, 0.1 M), 50 °C for 6 h. [b] Yields of products isolated after flash column chromatography and enantiomeric excess (*ee*) determined by chiral-phase HPLC were reported. [c] Not determined. [d] 25 °C for 12 h. [e] $Pd_2(dba)_3$ (0.5 mol%), ligand (1.2 mol%), 25 °C for 8 h. [f] $[Pd(allyl)Cl]_2$ instead of $Pd_2(dba)_3$. [g] Optimal condition: **8** (0.54 mmol), $[Pd(allyl)Cl]_2$ (0.5 mol%), (*R*,*R*)-**L1** (1.5 mol%), TMG (1 equiv), 3 Å MS (330 mg) in anhydrous mesitylene (21.6 mL, 0.025 M), 15 °C for 23 h. dba = dibenzylideneacetone, DIPEA = *N*,*N*-Diisopropylethylamine, TMG = 1,1,3,3-tetramethylguanidine.

of indole, in which one enantiomer of the substrate undergoes C3-allylation while the other undergoes *N*-allylation in a comparable rate in the presence of a chiral Pd catalyst. This hypothesis fits into the concept of parallel kinetic resolution (PKR).[19]

In further reaction condition optimization, we found that organic bases could enhance the performance of the Pd/**L1** catalytic system and allowed for the formation of significant amount of N-attack product (entries 5 and 6). Switching the Pd source to $[Pd(allyl)Cl]_2$ was slightly beneficial (entry 7). Systematic optimizations (Table S1) revealed that a diluted mesitylene solution, addition of molecular sieves, and a low reaction temperature were the key to success (entry 8): the reaction could be performed with only 1 mol% of Pd and 1.5 mol% of **L1** to afford (+)-**7** and (+)-**11** in high enantioselectivities and nearly equal yields. The absolute configuration of (+)-**7** was determined after having accomplished the synthesis of arborisidine and later confirmed by single crystal X-ray diffraction (XRD) analysis, while that of (+)-**11** was also identified by XRD analysis (vide infra). Since both (*R*,*R*)- and (*S*,*S*)-**L1** are commercially available, we reasoned that (−)-**7** could be prepared following the same way leading to the natural (+)-arborisidine.

We believed that this reaction represents a regiodivergent PKR of (±)-**8**, as supported by the following evidences (Figure 2): (1) The absolute configurations of (+)-**7** and

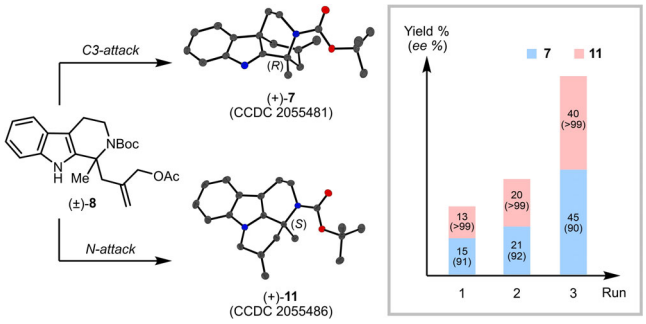
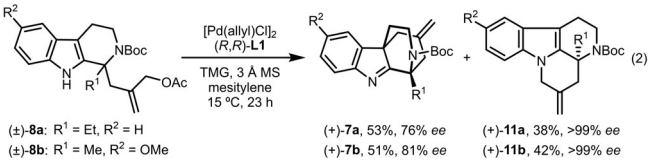


Figure 2. Experimental evidence for PKR. Deposition Number(s) 2055481 (for (+)-**7**) and 2055486 (for (+)-**11**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

(+)-**11** determined by XRD analysis [*R* for (+)-**7** and *S* for (+)-**11** at the aza-quaternary center]; (2) Parallel generation of the two products repeatedly observed at different conversions; and (3) Fitness of the *ee* values and yields of the two products to the equation $ee_x \cdot [x] = ee_y \cdot [y]$.[20] Since proposed in 1997 by Vedejs, PKR has been recognized as a rare type of resolution with strict kinetic requirements, and its application in natural product synthesis was extremely rare.[21] The present reaction is the first example of PKR using the Pd-catalyzed AAA reaction, which set the absolute configurations of two quaternary chiral centers in a single step and overcame the shortcomings of traditional KR in the intramolecular AAA. Gratifyingly, we found that the optimal reaction conditions were applicable to the PKR of more substrates, though perturbation on substrate structure affected the resolution result to some extent [Eq. (2)]. Ethyl as the R^1 group in place of methyl (substrate **8a**) and tuning of the electronic property of the indole core by methoxy substitution (substrate **8b**) still rendered the reaction under the regime of PKR, albeit the resolution deviated from perfect parallelity. This implies subtle matches among certain reaction components to be the key to an ideal PKR.



In order to gain mechanistic insights into this intriguing PKR, DFT calculation was performed. We noticed that a number of computational studies on Pd-catalyzed AAA reactions have been reported,[22] but only a few of them focused on the Pd/**L1** catalytic system.[23] In modeling the AAA transition states (TSs) in this reaction, we adopted the established Lloyd-Jones/Norrby model[23a] while taking the effect of TMG into consideration due to the observed base effect (Table 1). Surprisingly, our initial calculation on a cationic mechanism involving [(*R*,*R*)-**L1**-Pd(allyl)]$^+$ intermediates failed to reproduce the observed selectivity (see the Supporting Information for details). Given that this PKR proceeded in a nonpolar solvent, we reasoned that a tight ion-pair mechanism[24] may operate instead of a cationic mechanism. Therefore, a mechanism involving neutral [(*R*,*R*)-**L1**-Pd(allyl)]$^+$·OAc$^-$ intermediates was modeled, in which various possible TSs with different geometries and anion binding modes were surveyed (Figure 3).

Among them, **TS-(*R*)-C**/**TS-(*R*)-N** and **TS-(*S*)-C**/**TS-(*S*)-N** were the most favorable C-/N-attack TSs for (*R*)- and (*S*)-substrates, where AcO^- binds to the amide N-H by hydrogen bonding and TMG abstracts the indole N-H to assist the reaction. For the (*R*)-substrate, **TS-(*R*)-C** is 4.8 kcal mol^{-1} favorable than **TS-(*R*)-N**; for the (*S*)-substrate, **TS-(*S*)-N** is 2.0 kcal mol^{-1} favorable than **TS-(*S*)-C**. This is in good agreement with the observation that the PKR favors C3-attack for (*R*)-**8** and N-attack for (*S*)-**8**, as well as the high *ee* of product (*S*)-**11** owing to the highly selective C-attack in the (*R*)-pathway. The unfavorable N-attack in the (*R*)-pathway is likely caused by the repulsion of the cyclohexane ring in **L1** with the methylene group adjacent to the π-allyl unit and the Boc group in **TS-(*R*)-N**; on the other hand, in **TS-(*S*)-C**, the repulsion of the Boc group and the indole core with the phenyl rings in **L1** might be responsible for the unfavorable C-attack in the (*S*)-pathway (see the double-headed red arrows in Figure 3).

Successful preparation of (+)-**7** paved the way towards (−)-arborisidine (Scheme 2). Treatment of (+)-**7** with benzenesulfenyl chloride[25] led to the crude chloride **12** as diastereomeric mixture (dr = 1.2:1). The following elimination reaction was highly dependent on the base used, and the *n*-Bu_4NCl/2,4,6-collidine system[26] was the optimal choice to

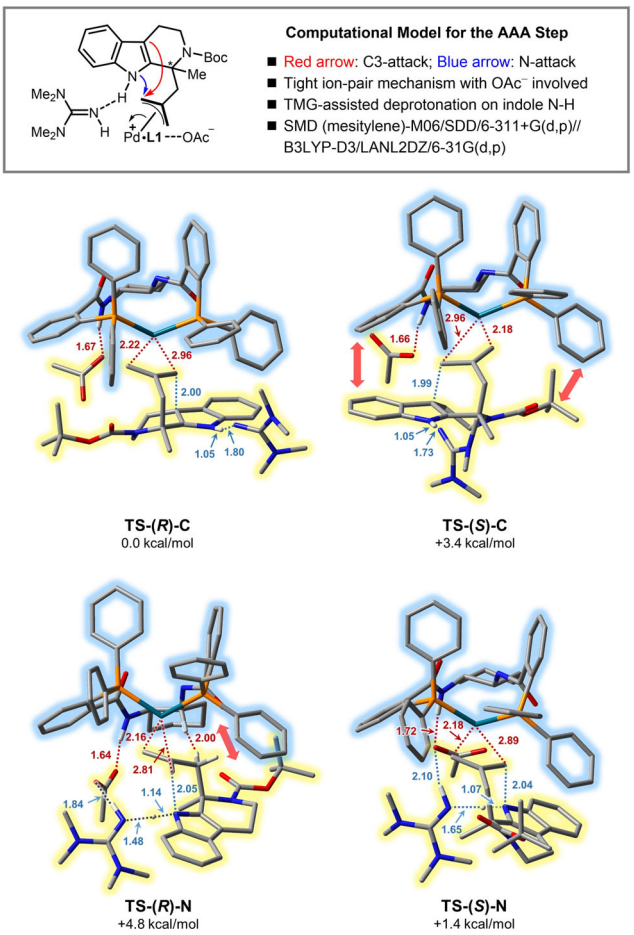
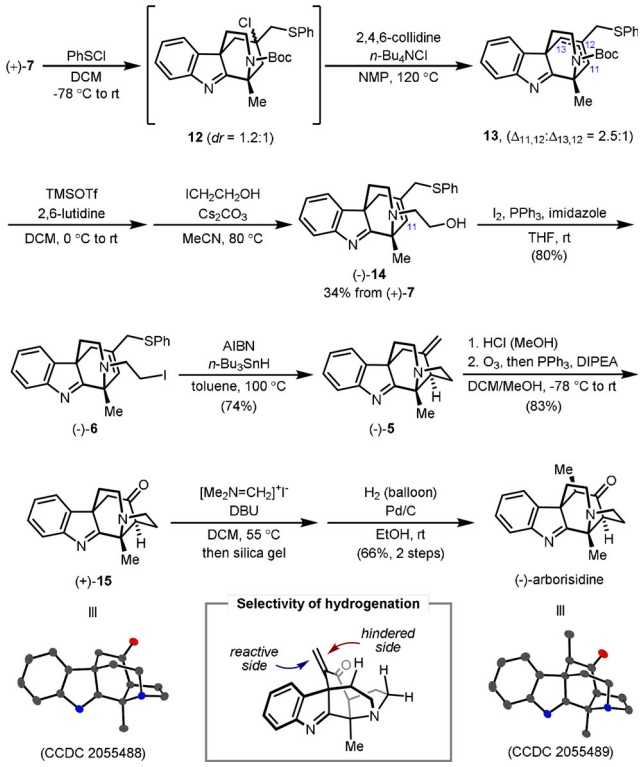


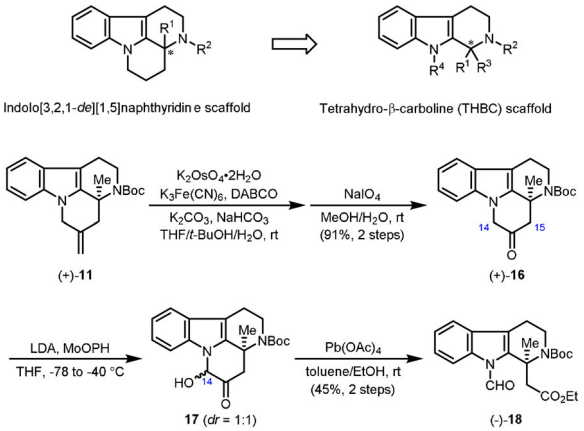
Figure 3. DFT calculation on the AAA step. Key distances (in unit of Å) were marked in the transition structures.



Scheme 2. Completion of the total synthesis of (−)-arborisidine. DIPEA = *N*,*N*-Diisopropylethylamine, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene. Deposition Number(s) 2055488 (for (+)-**15**) and 2055489 (for (−)-arborisidine) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

afford allylic phenyl sulfide **13** (Table S2). The inseparable regiomeric mixture of **13** was carried forward into further transformations directly. After *N*-Boc group deprotection by TMSOTf/2,6-lutidine and the subsequent *N*-alkylation with 2-iodoethanol, alcohol (−)-**14** could be separated as a single regioisomer in 34% overall yield from (+)-**7** (4 steps), which was converted to iodide (−)-**6** under I_2/PPh_3/imidazole conditions. At this stage the substrate for testing the designed radical cyclization reaction was ready. To our delight, the classical radical cyclization protocol (AIBN/*n*-Bu_3SnH) was competent for promoting the anticipated 5-*exo*-*trig* radical cyclization of (−)-**6** to produce (−)-**5** in a good yield, which verified the feasibility of the designed synthetic strategy. Ozonolysis of (−)-**5** and subsequent reductive work-up afforded demethylarborisidine (+)-**15**. To install the 19-methyl group, a Mannich reaction was first performed with Eschenmoser's salt under basic conditions. The Mannich product underwent elimination on silica gel to form an α-methylenated ketone intermediate. Finally, Pd/C-catalyzed hydrogenation of the exocyclic C=C bond led to addition of hydrogen on the less hindered side of the molecule, affording (−)-arborisidine in a good yield and excellent diastereoselectivity. The structure and absolute configuration of both demethylarborisidine (**15**) and (−)-arborisidine were confirmed by XRD analysis.

Finally, the usefulness of the *N*-allylation product (+)-**11** in target-oriented synthesis was explored (Scheme 3). We noticed that (+)-**11** itself contains the bioactive indolo[3,2,1-*de*][1,5]naphthyridine skeleton.[27] The exocyclic methylene group in **11** provides a handle for further chemical derivatization towards the bioactive tetrahydro-β-carboline (THBC) scaffold.[28] The dihydroxylation/oxidative cleavage produced ketone (+)-**16** in a high yield, and regioselective α-hydrox-



Scheme 3. Chemical derivatization of the *N*-allylation product (+)-**11**.

ylation by LDA/MoOPH[29] afforded hydroxyketone **17** as a 1:1 diastereomeric mixture. Cleavage of the hydroxyketone functionality gave (−)-**18** with the THBC skeleton.

In summary, asymmetric total synthesis of (−)-arborisidine was accomplished by employing a distinctive strategy, which features a serendipitous regiodivergent catalytic PKR to rapidly construct the tetracyclic core structure with two quaternary chiral centers, and a non-intuitive 5-*exo-trig* radical cyclization drawing a lesson from unsuccessful yet intuitive S_N2 attempts. We hope that this synthesis could inspire and benefit the synthesis of other alkaloids with complexed ring systems, as well as the exploration of novel possibilities in the Pd-catalyzed AAA reaction.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: arborisidine · palladium catalysis · parallel kinetic resolution · radical cyclization · total synthesis

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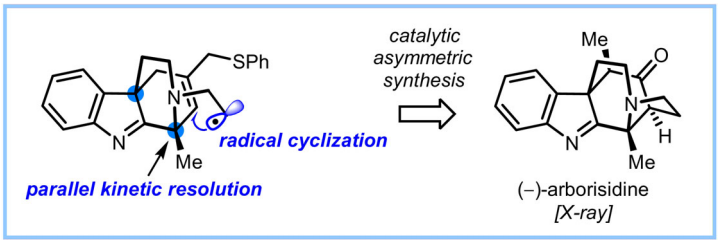
Communications

Natural Products

F.-Y. Wang, L. Jiao* _____ ■■■■–■■■■

Total Synthesis of (−)-Arborisidine



A serendipitous regiodivergent parallel kinetic resolution via dearomative asymmetric allylic alkylation, together with a 5-*exo-trig* radical cyclization, realized a novel approach to (−)-arborisidine.