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Enantioselective Total Synthesis and Absolute Configuration Assignment of (+)-Tronocarpine Enabled by an Asymmetric Michael/Aldol Reaction

Dong-Xing Tan,[a,b] Jie Zhou,[a,c] Chao-You Liu,[a] and Fu-She Han,[a,b]*

Abstract: *We present the first asymmetric total synthesis and absolute configuration determination of (+)-tronocarpine. The [6.5.7.6.6]-pentacyclic core was constructed at early stage by using a sequential cyclization strategy via a newly developed catalytic asymmetric Michael/aldol cascade to build the aza[3.3.1]-bridged cycle and a tandem reduction/hemiamidation procedure to assemble the seven-membered lactam. The side-chain functionalities were incorporated at a late stage by several appropriately orchestrated manipulations under mild conditions. The synthesis of enantiopure (+)-tronocarpine was achieved within a 20-step longest linear sequence from tryptamine.*

The plants of the genus Tabernaemontana have yielded a group of structurally novel chippiine-dippinine-type post-iboga indole alkaloids[1] (Figure 1, **1**–**6**). The members of this subfamily possess a strained [6.5.7.6.6]-pentacyclic core fused around a hemiaminal-containing aza[3.3.1]-bridged cycle, which represents an unique skeletal class in indole alkaloids. The unique ring skeletal class together with the existence of multiple stereocenters with one being an all-carbon quaternary stereocenter at C_{16} bridgehead and one labile hemiaminal at C_3 composes the synthetic challenges. Therefore, these molecules are ideal targets for the development of new synthetic strategies and methodologies. Biologically, this type of natural products display appreciable cytotoxicity against either vincristine-sensitive or resistant KB cells.[1b] Notably, the latter property is appealing because reversing multidrug resistance constitutes a major hurdle in cancer therapy.

Although the chippiine-dippinine-type alkaloids have garnered much attention since their structures have been exposed to synthetic community for over 30 years, a total synthesis has not been reported except for many racemic synthetic efforts toward the construction of the fused polycyclic skeleton[2] and one semisynthesis of *ent*-dippinine B from the naturally available (+)-catharanthine[3] (Figure 1, **7**). With our constant interest in the synthetic study of indole natural products,[4] we set this type of alkaloids as our target for synthesis. Among the members, tronocarpine[1c] (**1**) is a skeletal variant in the subfamily whose major structural difference from other siblings is, unlike the N_4–C_{21} connection in **2**–**6**, the linkage of the seven-membered lactam to the bridgehead quaternary carbon C_{16}. In addition, its absolute configuration has not yet been determined due to the paucity of natural sources, which can only be addressed by chemical synthesis. Thus, we chose (+)-tronocarpine **1** as our first target for synthesis.

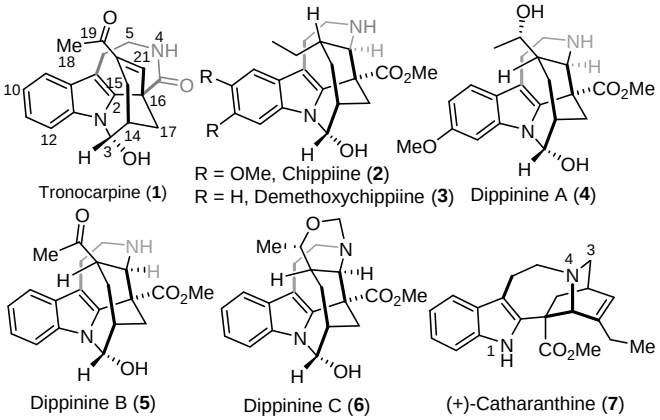

Figure 1. Selected structures of chippiine-dippinine alkaloids.

An insight into the reported unsuccessful efforts[2] suggests that a feasible route should be such one that could build the strained polycyclic skeleton at the early stage, but leaving the incorporation of labile and/or reactive functionalities such as hemiaminal and acetyl groups at the late stage under the conditions as mild as possible. Such a strategy takes the advantage of diminishing the possible side-reactions arising from the excessively strained ring tension and the lability of side-chain functional groups. Accordingly, we designed a retrosynthetic strategy as shown in Figure 2A. The hemiaminal and acetyl groups in **1** were to be introduced at the final stage through the manipulation of indole lactam and alkynyl group in the advanced intermediate **A**. The alkynyl functionality in **A** could be incorporated via Sonogashira coupling from enone **B**, which might be synthesized through Saegusa-type oxidation of ketone **C**. We planed to construct the seven-membered lactam in **C** by adopting a reduction/amidation cascade of a cyano and amino group from the aza[3.3.1]-bridged cycle **D**. Scission of **D** led to nitrile **E**, whose asymmetric Michael/aldol cascade with acrolein would furnish **D**. Finally, **E** might be derived from the commercially available tryptamine.

In the devised strategy, the asymmetric Michael/aldol cascade reaction for constructing chiral aza[3.3.1]-bridged cycle **D** is crucial. If successful, it would promote the development of enantioselective syntheses of other related natural products. However, to our knowledge, such reaction has not been investigated for the indole-based substrates although a few examples using the cyclic 1,3-dicarbonyl substrates possessing sufficiently high reactivity as well as well-differentiated Michael and aldol reaction sites have been reported.[5] The key challenges for the indole substrate **E** to be investigated herein would arise from: (i) the base-mediated regioselective generation of carbon anion with the existence of a similarly weak acidic proton at C_{14}; and (ii) the following regioselective Michael addition at the sterically more hindered tertiary C_{16} vs. secondary C_{14}; (iii) the influence of the amino group at N_4 and base sensitive indoyl lactam at N_1[6] under basic conditions; (iv) finally, the efficient discrimination of enantioface due to the nearly planar conformation of the substrates.

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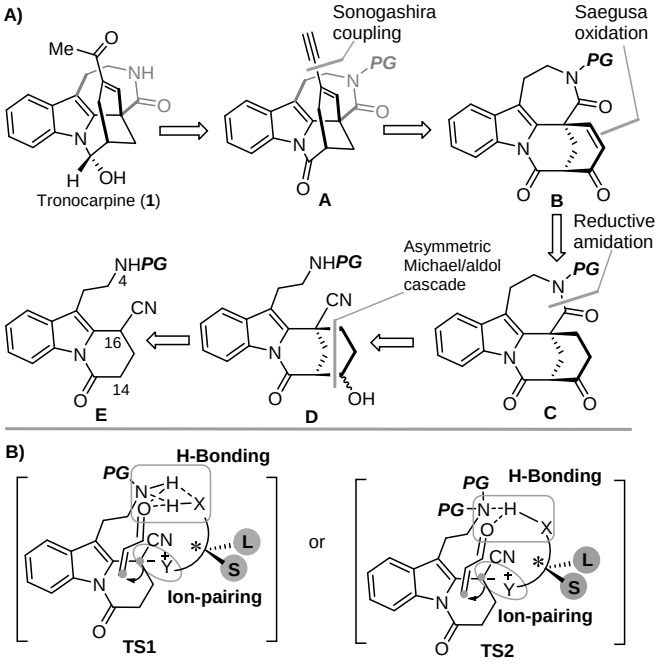
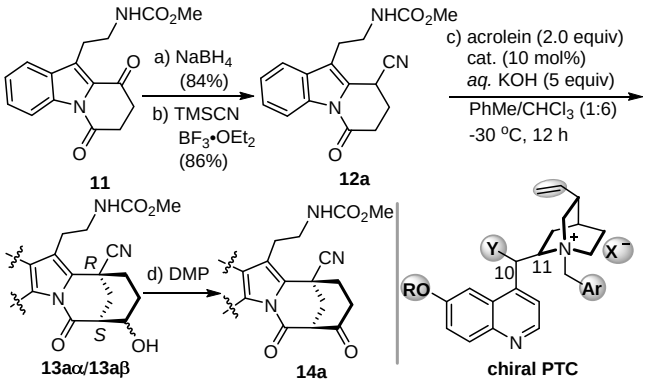


Figure 2. Retrosynthetic analysis of tronocarpine (**A**), and the proposed enantioselectivity model for asymmetric Michael/Aldol cascade reaction (**B**). PG stands for protecting group.

To achieve the asymmetric reaction with high efficiency, we proposed an ion-pairing/H-bonding bifunctional catalysis model (Figure 2B, **TS1** or **TS2**) which has been frequently adopted for designing asymmetric reactions.[7] Expectedly, a chiral catalyst with an appropriate ion-pairing and H-bonding functionalities as scaffolding elements may form with the substrates a more rigid transition state conformation through properly positioning of the interaction sites, and thereby inducing a better regio- and enantioselectivity than the catalyst possessing a single interaction site. Accordingly, a few tartrate-derived chiral guanidine catalysts[8] were examined using **12a** (Figure 3) as model compound which could be readily prepared over 10 g scales from the known compound **11**[4e,9] through reduction followed by substitution with TMSCN.[10] Disappointedly, the desired reaction did not proceed with the starting material remained intact under various conditions presumably due to the weak basicity of guanidines.

We were then drawn to the chiral phase-transfer catalysts (PTCs) derived from cinchona bases because of the ease of preparation and tuning the basicity of aqueous phase.[5] Delightedly, an extensive screening of the conditions enabled us to establish a set of preliminary conditions affording a couple of separable products **13aα** and **13aβ** in 70% total yield with *ca.* 1:1 diastereomeric ratio (dr) and 35% ee using **C-1** as catalyst[11] (Figure 3). Interestingly, both diastereoisomers exhibited similar enantioselectivity after being oxidized to ketone **14a**, respectively. Thus, the ee values given in the following screening were deduced from the two diastereoisomers.

Next, we carried out a thorough evaluation of an array of chiral PTCs[11] by varying the patterns of Ar (**C-1** to **C-13**), counterion X^- (**C-14** to **C-17**), olefin moiety (**C-18**), chirality and functional groups at C_{10} and C_{11} (**C-19** to **C-23**), and substituents on quinolinyl ring (**C-24** and **C-25**) (Figure 3). This survey led us to identify that **C-6** with a strong electron-withdrawing *p*-NO_2 group in phenyl ring was the most promising candidate providing **13a** (*ca.* 1:1 mixture of **13aα** and **13aβ**) in 42% yield and 82% ee.[12] More importantly, in good agreement with our assumption (Figure 2B), the observation of a remarkable effect of the nature of counterion (**C-6** and **C-14** to **C-16** vs **C-17**) and H-bond donor (i.e, **C-6** vs **C-19** to **C-23** and **C-24** vs **C-25**) on the asymmetric reaction suggests that appropriate bifunctional ion-paring/H-bonding interaction is essentially important for the desired reaction. Stimulated by these outcomes, we attempted to improve the reaction efficiency by varying the *N*-protecting group tethered at C_3 position on the substrates **12** aiming at tuning the nature of H-bonding. Eventually, this variation associated with a minor change of the general parameters screened out in Figure 3 enabled us to establish a set of conditions (see Figure 4 and Table S1 for details) that could achieve the asymmetric Michael/aldol cascade reaction in good yield and excellent ee. Namely, with the use of Phth as protecting group, **14b** was obtained in 56% yield over two steps with 94% ee. Most importantly, the reaction could be reliably performed on multigram scale without compromising the yield and ee (*vide infra*).



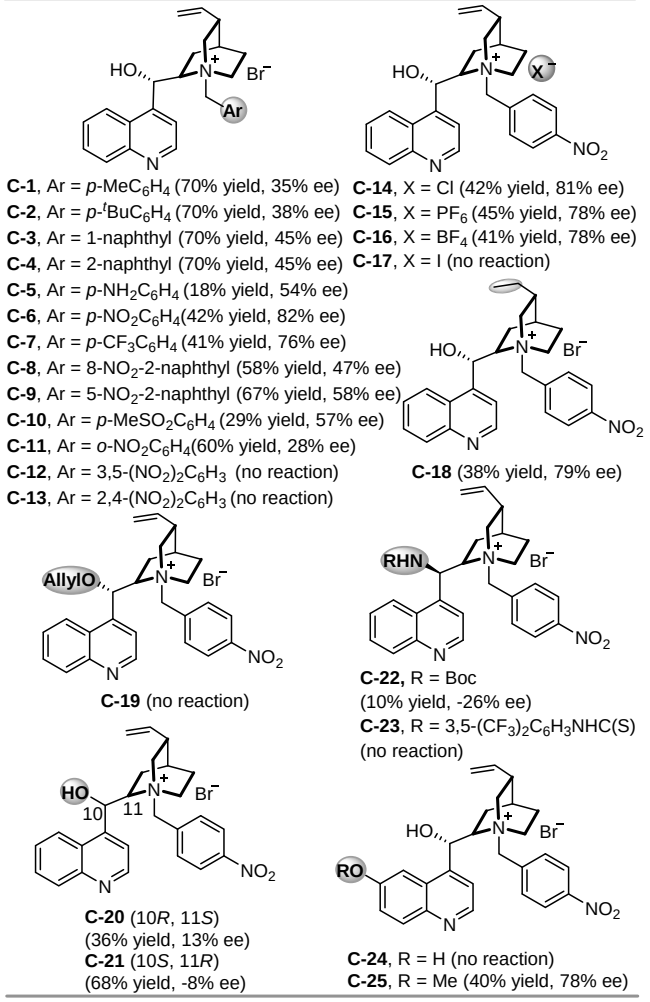


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Figure 3. Screening of Chiral Catalysts. [a] General conditions: **12a** (100 mg, 0.32 mmol), acrolein (2.0 equiv), PTC (10 mol %), and *aq.* KOH (50%, 5 equiv) in mixed PhMe/$CHCl_3$ (v/v = 1:6, 16 mmol/L) at -30 °C for 12 h; the yield was the total yield of **13aα** and **13aβ**; the ee % was determined by chiral HPLC.

With the optimized conditions in hand, we examined the substrate scope of the method[13] (Figure 4). Both electron-donating (**14c** and **14d**) and electron-withdrawing (**14e**–**14g**) substituents at different positions of indole ring periphery were compatible. In addition, the reaction was also tolerant of various substituents on Phth protecting group (**14h**–**14k**) albeit a slightly diminished yield and ee was observed for *meta*-substitution (**14h**). Finally, a variation of acrolein substrates revealed that the α-substituted acroleins were also viable substrates to afford α-face R^4 products (**14l**–**14n**) as a single diastereoisomer as confirmed by X-ray single crystal diffraction of **14m**. For a β-substituted acrolein, the yield and ee were a bit of diminished (**14o**). The absolute configuration of the products was (14*S*, 16*R*) for **14a**–**14n** and (14*S*, 16*S*) for **14o** as deduced from the X-ray structure of compound **18** in Scheme 1 (*vide infra*).

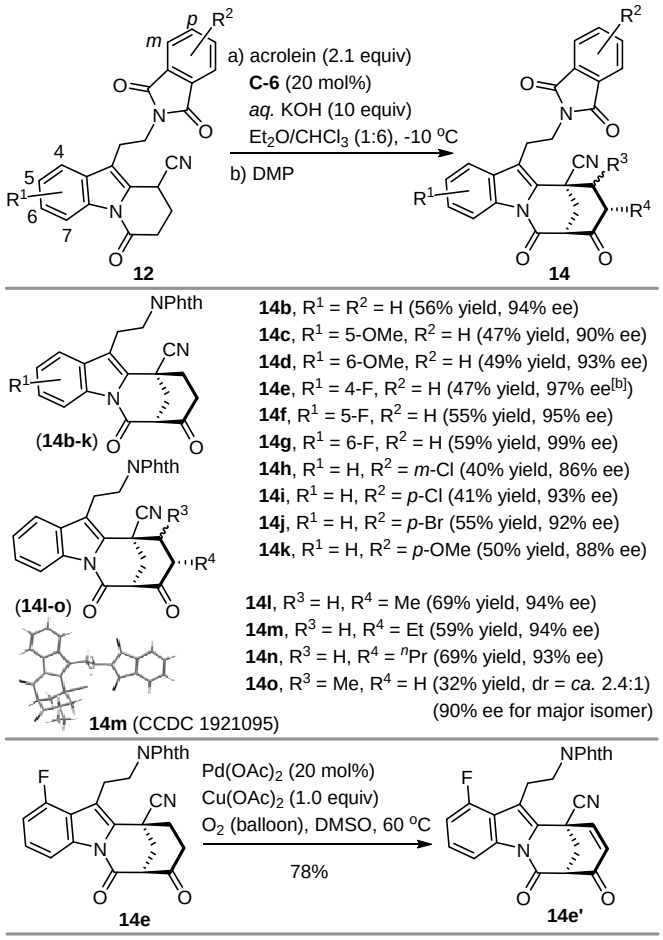

Figure 4. The Evaluation of Substrate Scope. [a] Genaral conditions: **12** (100 mg), acrolein (2.1 equiv), **C-6** (20 mol %), and *aq*. KOH (10–30%, 10 equiv) in mixed $Et_2O/CHCl_3$ (v/v = 1:6, 16 mmol/L) at -10 °C until the starting materials had disappeared as monitored by TLC; the yield was the isolated yield of **14** for two-steps; the ee % was determined by chiral HPLC. [b] The ee% of **14e** was determined from its corresponding enone **14e'**.

Having developed a robust and general method for the asymmetric construction of aza-[3.3.1]-bridged cycle, we then moved forward to the asymmetric total synthesis of (+)-tronocarpine (**1**) (Scheme 1). Asymmetric Michael/aldol reaction of **12b** (see SI for the details of preparation of **12b**) was performed on 1.5 g scale to give **13b** in 67% yield with 93% ee. By crystallization from a slowly evaporating CH_2Cl_2/EtOAc solution, the enantiomeric purity of **13b** in mother liquid might be improved easily to >98% ee. Removal of the Phth group followed by protecting the amino group with methoxycarbonyl and oxidation of hydroxy group afforded **14a** in 50% yield and 98.5% ee over three steps. The conversion of cyano group into aldehyde or ester group toward constructing the seven-membered lactam was rather problematic owing to the disruption of ketone and N_1-lactam functionalities under various reductive conditions. However, we found that the reaction could proceed effectively via a tandem procedure involving reduction of cyano group with Raney-Ni followed by a concomitant intramolecular hemiamidation with the carbamate functionality, furnishing the seven-membered hemiaminal **15**. To compare with the reported conditions,[14] replacing the acetic acid with TFA and avoiding the use of NaH_2PO_2 were pivotal to suppress the side-reaction resulting from the cleavage of C_{14}–C_{15} bond in **14a** possibly *via retro*-aldol-type reaction. Oxidation of **15** delivered lactim **16** in 53% yield over two steps from **14a**.

Having established an efficient route for the construction of the [6.5.7.6.6]-pentacyclic core, our attention was shifted to the incorporation of the side-chain functionalities. Stimulated by a few recent methodological studies on $Pd^{(II)}$-catalyzed direct α,β-dehydrogenation of carbonyl compounds,[15] we explored the direct oxidative dehydrogenation of **16** for the synthesis of enone **17** and found that the reaction proceeded smoothly in high yield by modifying the conditions reported by Stahl.[15a] Iodination of **17** provided the α-iodinated enone **18** with 99.2% ee whose absolute configuration was (14*S*, 16*S*) as confirmed by single crystal X-ray analysis. Sonogashira cross-coupling of **18** with ethynyltrimethylsilane **19** proceeded smoothly to give alkyne **20**. The removal of CO_2Me tether to N_4 was unexpectedly challenging. Significant decomposition of starting material was observed under an array of reported conditions[9,16] presumably due to the excessively strained ring tension as well as the existence of various reactive functonalities such as ketone, alkynyl and lactam groups. Thus, we conceived of a Lewis acid-activated nucleophilic deprotection through an assumed complex **21**. As expected, we found that a combination of $CeCl_3$ and *i*PrOH could efficiently cleave the protecting group to give lactam **22** in 91% yield whose structure was verified by single X-ray crystallographic diffraction. Of note is that while other Lewis acids such as $Sc(OTf)_3$ were also effective, the use of $CeCl_3$ offered an advantage of merging the deprotection and the following Luche reduction into a one-pot operation, affording **23** in 75% yield.

The direct reduction of carbonyl group in **22** to methylene was troublesome due to the significant decomposition of substrate under various conventional and modified Wolff-Kishner-Huang conditions.[17] However, the deoxygenation of **23** was carried out efficiently through a two-step procedure involving the formation of xanthate followed by Barton-McCombie radical deoxygenation,[18] producing **24** in 60% yield over two steps. Subsequently, selective reduction of the indolyl δ-lactam in **24** delivered hemiaminal **25** as a single diastereoisomer. The stereochemistry for β-OH at C_3 was determined by NOESY correlation (see Figure S43). Desilylation of **25** was effected by TBAF to afford alkyne **26**. Finally, the Hg-catalyzed alkyne hydration[19] and acid-promoted concomitant inversion of β-OH to thermodynamically more stable α-OH furnished the asymmetric total synthesis of tronocarpine (**1**). The structure of **1** was unambiguously affirmed by NMR, HRMS, and X-ray single crystallographic analyses. The data of NMR and $[\alpha]_D^{20}$ {Synthetic: +280 (*c* 0.1, CH_2Cl_2); lit.: +231 (*c* 0.08, CH_2Cl_2)} of the synthesized product matched well with those reported.[1c] Accordingly, the absolute configuration of tronocarpine (**1**) could be assigned as (3*S*, 14*R*, 16*S*).

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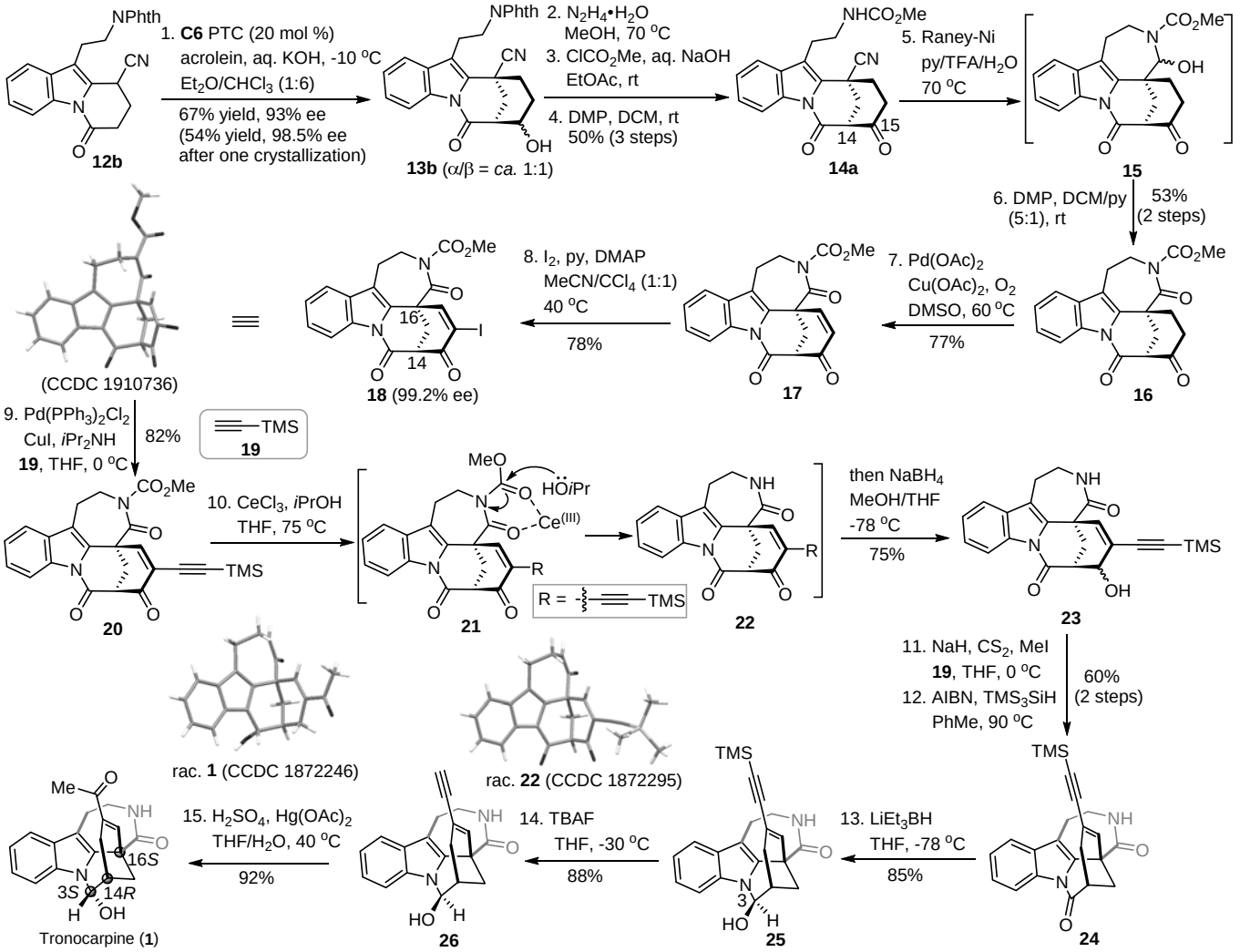

Scheme 1. Asymmetric Total Synthesis of Tronocarpine.

In summary, the first asymmetric total synthesis of tronocarpine (**1**) and the assignment of its absolute configuration have been achieved. In the synthetic route, the strategic use of a newly developed asymmetric Michael/aldol cascade reaction and an intramolecular reduction/hemiamidation cascade reaction enabled us to build efficiently the fused [6.5.7.6.6]-pentacyclic core at early stage. The late-stage synthesis was highlighted by a modified Pd-catalyzed direct dehydrogenation, a $CeCl_3$-promoted deprotection of methoxycarbonyl, and a Hg-catalyzed acid-promoted hydration of alkyne and a concomitant inversion of the stereochemistry of hemiaminal. We believe the synthetic strategy as well as the new methodologies established in this work would find broad applications for versatile synthesis of other unconquered members of the chippiine-dippinine subfamilies and related analogues. The synthetic study of the relevant natural products is currently underway.

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Conflict of interest

The authors declare no conflict of interest.

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[12] The ineffective reaction for the catalysts modified by two NO_2 (**C-12** and **C-13**) possibly resulted from their poor solubility.

[13] The ee% was determined by converting the diastereoisomeric mixtures of Michael/Aldol reaction products into the corresponding ketone **14**. The yields were given as the total yield for two steps from compounds **12**.

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Layout 2:

Natural Product Synthesis

Dong-Xing Tan, Jie Zhou, Chao-You Liu, , and Fu-She Han* _____

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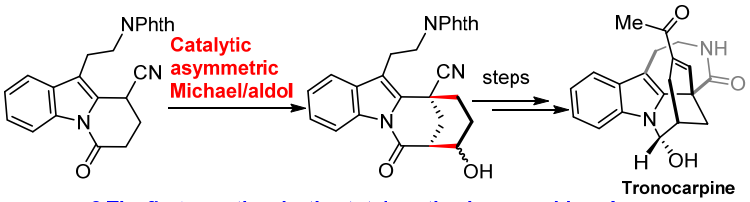
Enantioselective Total Synthesis and Absolute Configuration Assignment of Tronocarpine Enabled by an Asymmetric Michael/Aldol Reaction



- **The first enantioselective total synthesis was achieved**
- **The absolute stereochemistry was determined**

We present the first asymmetric total synthesis and absolute configuration determination of tronocarpine. The [6.5.7.6.6]-pentacyclic core was constructed at early stage by using a sequential cyclization strategy via a newly devised catalytic asymmetric Michael/aldol cascade to build the aza[3.3.1]-bridged cycle and a tandem reduction/hemiamidation procedure to assemble the seven-membered lactam. The side-chain functionalities were incorporated at the late stage by several appropriately orchestrated manipulations under mild conditions. The synthesis of enantiopure tronocarpine was achieved within a 20-step longest linear sequence from tryptamine.