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Asymmetric Total Synthesis of Vincadifformine Enabled by Thiourea-Phosphonium Salts Catalyzed Mannich-type Reaction

Lu Pan, Chang-Wu Zheng, Guo-Sheng Fang, Hao-Ran Hong, Jun Liu, Long-Hui Yu, Gang Zhao*

Abstract: A novel asymmetric total synthesis of Vincadifformine is described. The limited tactics with Chiral cation-directed catalysis in total synthesis inspired the development of our strategy for accessing this alkaloid in enantionrich form. The route features Thiourea-Phosphonium Salts catalyzed Mannich-type reaction, Phosphine promoted Aza-Morita-Barrie-Hillman reaction and TFA promoted deprotection/ amidation cascade process.

Structurally complex monoterpenoid indole alkaloids from the species of the genus Aspidosperma comprise over 250 unique members and show a considerable structural diversity. [1] The structures of these compounds are striking in that they contain a cage-like [*6.5.6.6.6*] fused pentacyclic skeleton. It bears three contiguous *cis*-stereogenic centers, two of which are all carbon quaternary centers. (Figure 1a) Vincadifformine, one of its representative members, is originally isolated from Vincadifformis in 1962 by Djerassi and Janot et al.[2] Both Vincadifformine and its analogues display remarkable cytotoxicity *in vitro* against a total of 60 human tumor cell lines derived from nine cancer types.[3] Given its fascinating structure and distinguished pharmacological activities, many synthetic chemists have devoted great efforts toward its syntheses. [4]

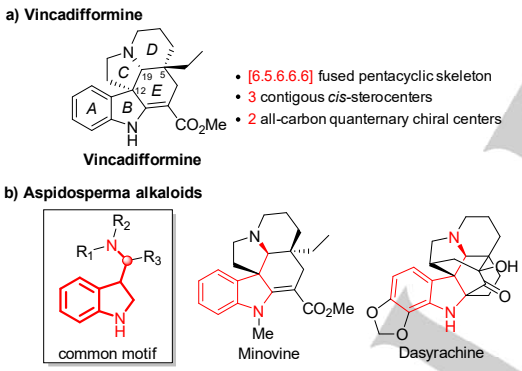

Figure 1. Representatives of Aspidosperma alkaloids and their analogues.

Since the isolation and structure elucidation of Vincadifformine, four splendid syntheses in asymmetric versions have been achieved. [5] Each has its own feature in assembling the three-contiguous *cis*-stereocenters in E ring. In 2011, Pandey et al demonstrated a cascade strategy to simultaneously construct C/E rings as well as the C12/C19 stereogenic centers in one pot. More recently, Andrew reported an elegant approach to introduce the enantioenriched E ring and C19/C5 stereogenic centers by the domino Micheal/Mannich/*N*-alkylation reactions. Chiral auxiliaries play indispensable roles in controlling the stereoselectivity in both previous works. In 2017, Jiang and co-workers established a divergent and practical synthesis toward Vincadifformine and related alkaloids through Fischer indolization reaction. In his work, a chiral pool based intermolecular [4+2] cycloaddition was utilized to forge C12/C19 stereogenic centers. Besides the strategy with chiral auxiliary and chiral pool, MacMillan et al successfully completed a series of monoterpene indole alkaloids synthesis based on an impressive organocatalytic cascade method. Despite the numerous successful syntheses of Vincadifformine, the asymmetric synthesis of Vincadifformine utilizing Chiral cation-directed catalysis still remains desirable as scarce examples of this catalytic strategy have been applied to total syntheses.

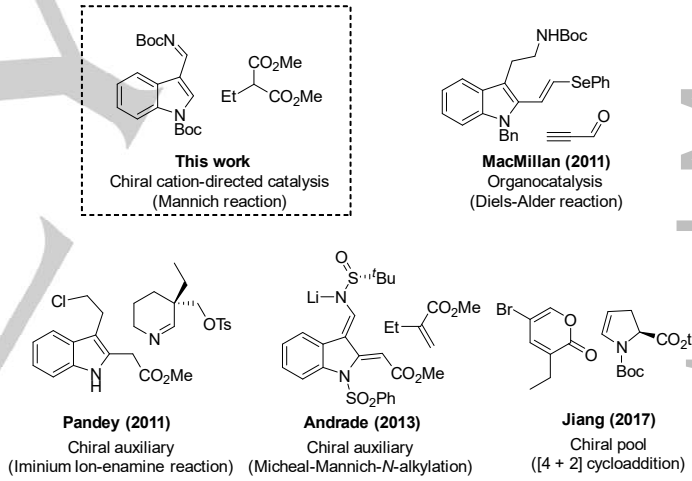

Figure 2. Asymmetric synthetic strategies leading to Vincadifformine and our unique approach.

Although the monoterpenoid indole alkaloids possess extraordinary structural diversity, when considered broadly. If certain elements of these molecules are considered in isolation, a common motif featuring a tertiary carbon stereogenic center adjacent to indoline and tertiary amine are frequently shared by these alkaloids (Figure 1b). [7] We hypothesize that this common motif could be introduced by the Mannich reaction between *N*-Boc indole aldimine **1** and a nucleophile reagent. Inspired by recent work of our groups (Scheme 1), in which the asymmetric Mannich reaction catalyzed by amino acids-derived chiral organocatalysts gave the related products in excellent yield and enantiopurity.[8] Herein we developed a novel method to construct this key structure **2**.

[a] L. Pan, C.-W. Zheng, G.-S. Fang, H.-R. Hong, J. Liu, L.-H. Yu, Prof. G. Zhao
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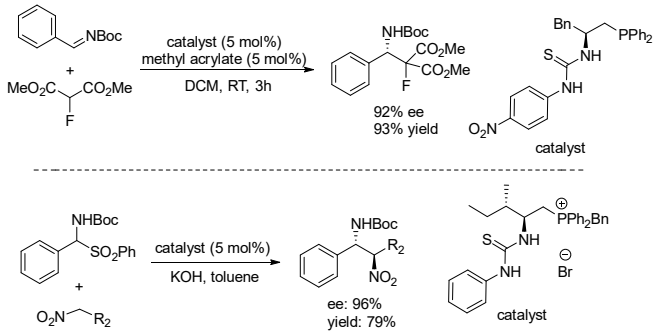
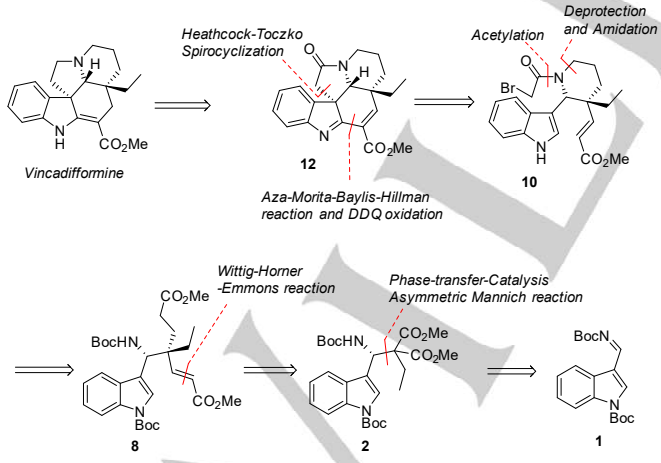


Scheme 1. Prior arts of asymmetric Mannich-type reaction in our group

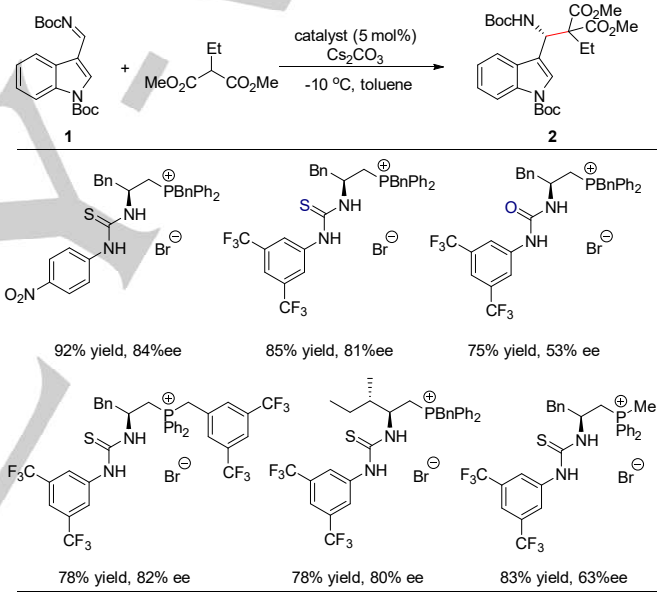
Based on this strategy, a retrosynthetic analysis is shown in Scheme 2. The quaternary stereocenter C12 and E rings could be introduced by alkylation at the 3-position of indole, followed by a trimethylphosphine promoted Aza-Morita-Baylis-Hillman reaction. Noteworthily, the conjugate addition between the nucleophilic phosphine and a sterically hindered activated alkene with a γ-quaternary carbon center is insurmountable. [9] Then the intermediate **10** could be easily obtained by deprotection/amidation in the presence of trifluoroacetic acid and *N*-acetylation from **8**. The prolonged carbon chains at C-5, which is required in the construction of E ring, could be extended by Horner-Wadsworth-Emmons olefination from the diesters. The C19 tertiary carbon stereogenic center in **2**, which is essential for controlling the stereoselectivity of following reactions, could be obtained through the asymmetric Mannich-type reaction between *N*-Boc indole aldimine **1** and dimethyl ethylmalonate by Chiral cation-directed catalysis.



Scheme 2. Retrosynthetic analysis of Vincadifformine

Although *N*-Boc indole aldimine **1** is shared in plenteous indole alkaloids and is also a promising building block for their syntheses, the aromatic electron-rich *N*-Boc indole aldimine **1** with relatively low electrophilicity, is a challenging Mannich addition acceptor. To the best of our knowledge, this synthon has only been used by Johnson group to synthesize enantioenriched β-amino-keto esters via dynamic kinetic resolution. [10] The application of *N*-Boc indole aldimine **1** in the catalytic asymmetric Mannich reaction remains unexplored.

Our synthesis is associated with the exploration of thiourea-phosphonium salts catalyzed asymmetric Mannich-type reaction, between *N*-Boc indole aldimine **1** and dimethyl ethylmalonate. After intensive modification of the catalyst structure and screening several reaction conditions, we found this asymmetric Mannich-type reaction could be accomplished under the condition of 5 mol% catalyst **G** in toluene, using 4Å molecular sieves as additive to give **2** in 92% yield and good enantiopurity (84% ee). the enantiopurity of the major diasomer could be elevated to 97% easily through recrystallization downstream at tert-butyldimethylsilylation stage. The reaction was readily adapted to the gram-scale without impacting its efficiency. (Scheme 3)



Scheme 3. Optimization of conditions and evaluation of chiral catalysts.

To inhibit the retro-Mannich reaction, the resulted **2** was reduced intermediately with DIBAL-H to give diol **3** (86% yield, 89% ee). It is worth noting that the reduced product would either be decomposed or partially racemized when other reductants such as $LiBH_4$, $NaBH_4$ or $LiAlH_4$ were used. We proposed that partial racemization occurred due to the retro-Mannich/Mannich reaction which is promoted by the reductants with Li^+ or Na^+ such as $LiBH_4$, $NaBH_4$ or $LiAlH_4$. Selective protecting one of the hydroxyl group in **3** with *tert*-butyldimethylsilyl chloride afforded a chromatographically separable diastereomeric mixtures **4** and **4'** (73% yield, 3 : 1 dr, 90% ee). The enantiopurity of the major diastereomer **4**, could be improved to 97% ee after a simple recrystallization in methanol. Its absolute configuration was fully secured by a crystallographic verification.

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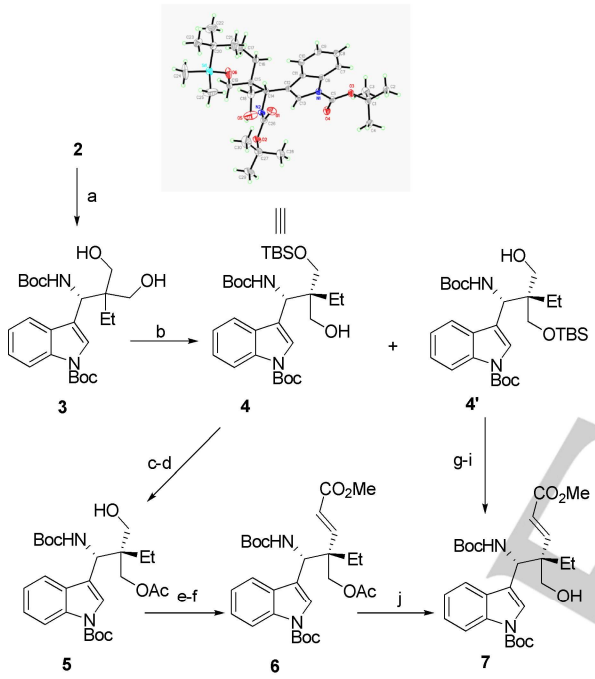
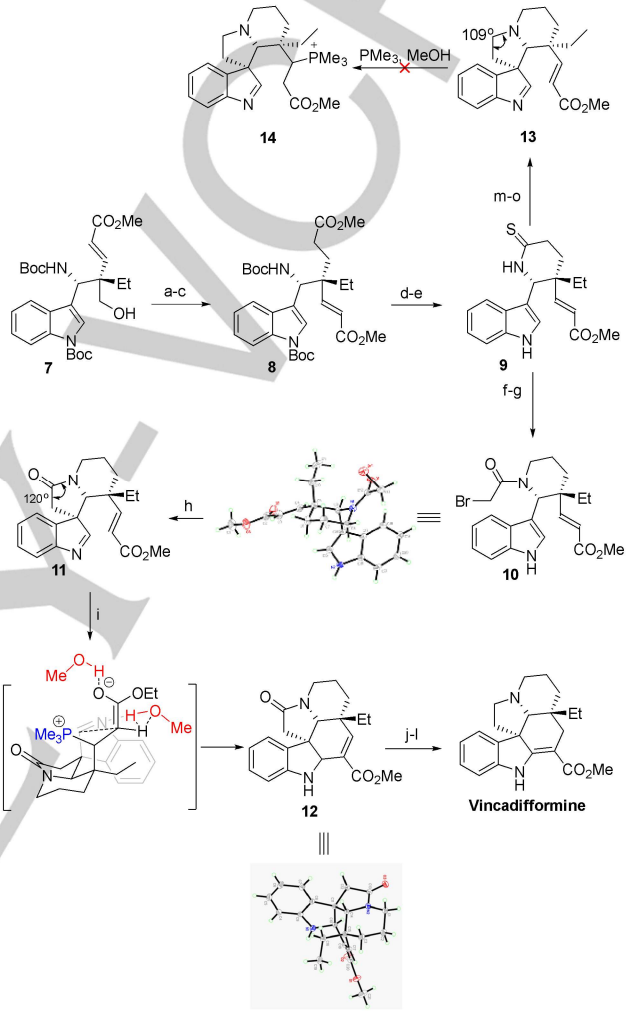
Both intermediates **4** and **4'** were used for assembling Vincadifformine. As demonstrated in Scheme **4**, acetylation of the remaining hydroxyl group in **4** followed by desilylation produced the intermediate **5** in 89% yield, which was then treated with Dess-Martin periodinane. The obtained aldehyde underwent the Horner-Wadsworth-Emmons olefination with trimethyl phosphonoacetate to afford **6**, which was deprotected of acetyl group under basic condition gave the α, β-unsaturated ester **7** in 90%yield.In a parallel procedure, oxidation of **4'** by Dess-Martin periodinane provided the corresponding aldehyde which was subjected to the Horner-Wadsworth-Emmons olefination with trimethyl phosphonoacetate and deprotection with tetrabutylammonium fluoride affording the same α, β-unsaturated ester **7** in 92% yield. (Scheme 4)



Scheme 4. a) DIBAl-H, CH_2Cl_2, 0 °C, 86%; b) TBSCl, NaH, THF 0 °C - rt, 73%; c) Ac_2O, Et_3N, DMAP, DCM, 92%; d) TBAF,THF,0 °C - rt, 89%; e) DMP,$NaHCO_3$,DCM, rt; f) trimethylpho- sphonoacetate, NaH, THF, 0 °C – rt; g) DMP, $NaHCO_3$, CH_2Cl_2, rt, 75%; h) Trimethyl phosphonoacetate, NaH, THF, 0°C - rt, 87%; i) TBAF,THF,0°C-rt, 93%; j) K_2CO_3, MeOH, rt, 90%. DIBAl-H = Diisobutylaluminium hydride; TBSCl = *tert*-Butyldimethylsilyl chloride; DMP = Dess-Martin periodinane; DMAP = 4-Dimethylaminopyridine; TBAF = Tetrab utylammonium fluoride; THF = Tetrahydrofuran. catalysts.

Having successfully established the key C19 stereogenic center and got the intermediate **7** (90% ee), several functional group transformations were performed to elaborate intermediate **7** into the desired cyclization precursor **10**. Pd/C-catalyzed hydrogenation of the α, β-unsaturated double bond with subsequent oxidation and Horner-Wadsworth-Emmons olefination delivered **8** in 74% yield over three steps. The construction of D ring was efficiently achieved via a TFA promoted deprotection/ amidation cascade process in high yields. To facilitate the selective reduction in further steps, the corresponding amide was converted to thioamide in the presence of Lawesson's reagent to give **9** in 90% yield. The intermediate **9** was treated with Raney-Ni to provide the cyclic amine. Without further column chromatography purification, the crude product was directly subjected to the reaction with bromoacetyl chloride to generate **10** in 90% yield. The absolute configuration of **10** was confirmed through X-ray analysis.



Scheme 5. a) Pd/C, H_2, THF, 95%; b) DMP,$NaHCO_3$,CH_2Cl_2, rt, 85%; c) Trimethyl phosphonoacetate, NaH, THF, 0°C - rt, 92%; d) TFA, CH_2Cl_2, 0 °C - rt, 80%; e) Lawesson's Reagent, THF, reflux, 90%; f) Raney-Ni, THF, H_2, 95%; g) bromoacetyl chloride, Et_3N, DCM, 90%; h) AgOTf, Et_3N, CH_2Cl_2, 95%; i) PMe_3, MeOH, 92%; j) Lawesson's Reagent, THF, rt, 95%; k) Raney-Ni, THF, H_2, 92%; l) DDQ, CH_2Cl_2, 75%; m) Raney-Ni, THF, H_2, 95%; n) ethylene oxide, MeOH, -10 °C, 90%; o) MsCl, Et_3N, CH_2Cl_2, 0 °C, 89%. THF = Tetrahydrofuran; DMP = Dess-Martin periodinane; TFA = Trifluoroacetic acid; DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; MsCl = Methanesulfonyl chloride.

The next stage of the synthesis involved an intramolecular alkylation, a strategy first employed by Heathcock and Toczko in the synthesis of Aspidospermidine.[11] Treatment of **10** with silver trifluoromethanesulfonate in a mixture of Et_3N and DCM successfully provided the spirocyclic indolenine **11** in 95% yield.

With the spirocyclic indolenine **11** in hand, we turned our attention to the formation of E ring. Inspired by kwon's elegant approach to ibophyllidine, similar strategy was investigated to close the E ring in our synthesis. [9d] When spirocyclic indolenine was exposed under the conditions (PMe_3, toluene /MeOH 14:1) as reported, to our disappointment, the reaction was rather sluggish and only trace amount of the desired product was detected by LC-MS. According to the crystallographic analysis of substrate **10,** We assumed that two reasons might be considered account for this. First, the ethyl group on the quaternary carbon is overlapping with the antibonding orbital of α, β-unsaturated ester, making the active alkene more obstructed for the attack by the phosphine. Second, compared to O-H in protic solvent, N-H on the product is a much weaker hydrogen bond donor which frustrated the reaction through the autocatalytic way. Consequently, both sterically undemanding phosphine and quantities of protic solvent was inevitable to accelerate the reaction. [12] After exhaustive study, the reaction was found to best perform in MeOH with trimethylphosphine as the nucleophile. The resulted pentacyclic skeleton was unambiguously confirmed by X-ray crystallography analysis.

It is rather remarkable that in our initial foray toward the pentacycle, Rulbita startegy was exploited to construct Spirocyclic indolnine giving substrate **13.** (as indicated in scheme **5**) Treating **13** under the optimal condition resulted in intermediate **14,** which was detected by LRMS, HRMS and HNMR with no observed formation of pentacycle. We proposed that a larger bonding angle (C-C=O-N: ~120°C) in C ring would push the α, β-unsaturated ester chain more close to indolenine, which facilitated the attacking of enolate to imine.

Completion of the synthesis would now require selective reduction of the lactam and migration of the double bond to deliver the requisite enamine. Amide **12** was then transformed to thioamide in the presence of Lawesson's reagent, subsequent reductive desulfurization with Raney-Ni and oxidation of the indoline unit with DDQ to afford Vincadifformine in 65% yield over three steps.

Notably, the ^1H and ^{13}C NMR data of the synthetic Vincadifformine were identical to that of natural Vincadifformine, which are different with those from Andrade's synthesis. We found that this problem could be solved by adding a trace amount of TFA during collecting NMR spectroscopic data. [13]

In summary, we have achieved asymmetric total syntheses of Vincadifformine. The key C19 stereogenic center capitalized on a chiral-cation-directed asymmetric Mannich reaction which catalyzed by our recently developed amino acids derived chiral bifunctional thiourea-phosphonium salts. Additional salient features of this synthesis including phosphine promoted Aza-Morita-Barrie-Hillman reaction for construction of the E ring and TFA promoted deprotection/amidation cascade process for construction of D ring. We anticipate that the novel transformation developed in this project will find further application in synthesis.

Acknowledgements

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Keywords: Chiral-cation directed catalysis, Asymmetric Mannich reaction, Alkaloids, Vincadifformine, Total synthesis.

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[14] CCDC 1897172 (**12**) and CCDC 1897173 (**10**) CCDC 1897174 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Asymmetric Total Synthesis of Vincadifformine Enabled by Thiourea-Phosphonium Salts Catalyzed Mannich-type Reaction

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