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Iminium Ion Cascade Reaction in the Total Synthesis of (+)-Vincadifformine

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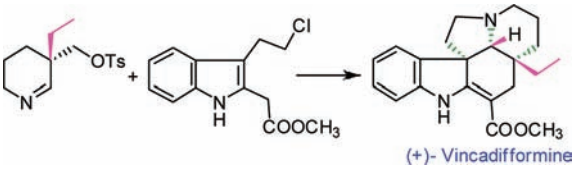
ABSTRACT



An iminium ion triggered cascade reaction is described in the total synthesis of (+)-vincadifformine by the coupling of 3,3-substituted tetrahydropyridine and indole derivative. The strategy allows simultaneous construction of two new rings, three new sigma bonds, and two new stereogenic centers in one pot with complete stereochemical control.

Asymmetric synthesis of biologically active complex natural products involving cascade reactions with the formation of multiple bonds or multiple rings has been the subject of intense research in recent years.[1] The design of cascades to obtain specific biologically active structurally complex natural products poses a significant intellectual challenge and can be one of the most impressive activities in natural product synthesis.

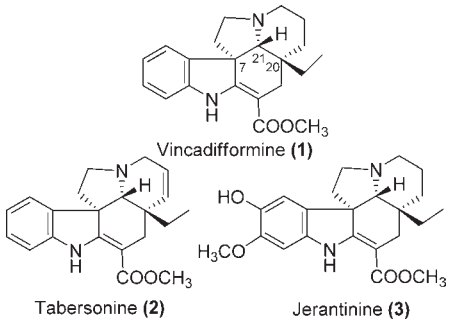


Figure 1. Representatives of *Aspidosperma* alkaloids.

In continuation with our interest in the synthesis of alkaloids,[2] we became interested in developing a new and nonbiogenetic route for the synthesis of *Aspidosperma* alkaloids. Vincadifformine (**1**), tabersonine (**2**) and jerantinine (**3**) belonging to this class have caught the attention of synthetic chemists over the past several years due to their unique structural features and cytotoxic activities against human cancer cell lines (Figure 1).[3] In particular, **1** has significant value because it is a valuable precursor for pharmaceutically important vincamine, vincamone and Cavinton.[4] In addition, it is also suggested to be a possible biogenetic and synthetic precursor for the cytotoxic leucophyllidine and rhazinilam alkaloids, respectively.[5]

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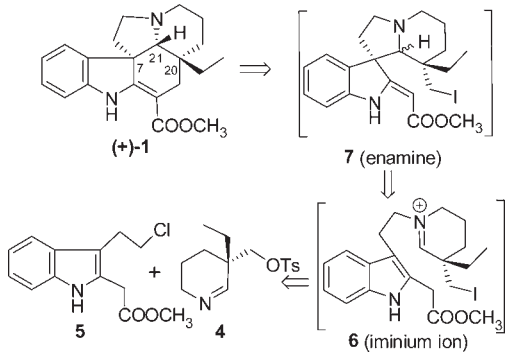
This alkaloid displays a complex pentacyclic conformationally rigid skeleton due to the *cis*-relationship of the three contiguous stereocenters in the cyclohexyl ring at C-7, C-21 and C-20. Owing to the challenge associated with the construction of these structural frame works including a quaternary carbon center, extensive synthetic efforts have been made to obtain **1** both in racemic[6] as well as in optically pure form.[7] Majority of these approaches have relied on intramolecular Diels–Alder (DA) type cycloaddition reaction of a biogenetically postulated secodine intermediate.[8] However, auxiliary controlled or chiral substrate controlled cycloaddition of secodine intermediate have generally led to the formation of mixture of diastereomers.[7b]

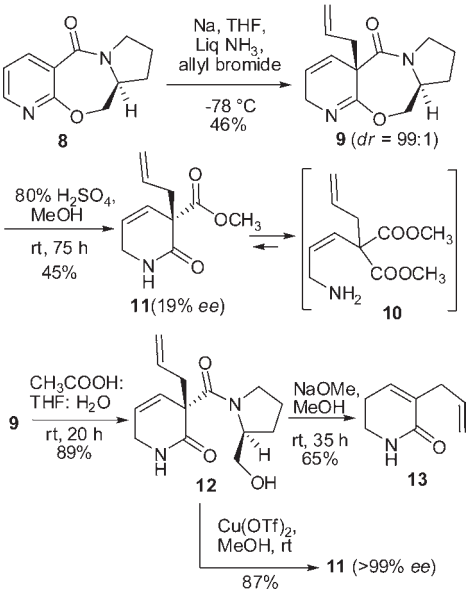
In an effort to develop a nonbiogenetic route to **1** in optically pure form, we looked at the problem entirely from a different angle and devised a cascade strategy as outlined retrosynthetically in Scheme 1. This strategy was envisioned to provide two new rings, two new stereogenic centers and three new sigma bonds in a single operation through the sequential involvement of reactive intermediates **6** and **7**. We are happy to disclose herein our successful endeavor of accomplishing the total synthesis of (+)-**1** in overall 4% yield and >99% *ee*.

Scheme 1. Retrosynthetic Analysis



The synthetic design of crucial precursor **4** was visualized through Birch reduction-alkylation of the chiral nicotinic acid derivative **8**. Although enantioselective construction of all carbon quaternary stereocenter in the cyclohexane ring employing Birch reduction-alkylation of benzoic acid derivatives[9] is known, to the best of our knowledge, no report is found for similar transformation for generating substituted piperidine system.

Scheme 2. Synthesis of **11**



On the simple premise that Birch reduction-alkylation of **8**, obtained by the reaction of 2-chloronicotininc acid and (*S*)-prolinol, followed by simple chemical transformation would give **4**, we subjected **8** to Birch reduction-alkylation at −78 °C using ethyl iodide, but to our utter surprise, it gave the expected product only in ∼6% yield. Therefore, we used more electrophillic allyl bromide for alkylation reaction and succeeded in getting **9** in 46% yield (*de* = 97.9%).[10a] Single crystallization in dichloromethane-*n*-pentane afforded **9** as (colorless crystals, mp 105–106 °C) a single diastereomer. The stereochemistry of **9** was confirmed unambiguously through X-ray crystallographic analysis.[10b] The excellent diastereoselectivity in the formation of **9**, presumably, results from the involvement of rigid molecular architecture of enolate intermediate where proline stereocenter directs the alkylation preferentially at β-face.

Our initial attempt to remove chiral auxiliary from **9** by stirring with a mixture of 80% H_2SO_4/MeOH (1:8) gave

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(7) (a) Kuehne, M. E.; Podhorez, D. E. *J. Org. Chem.* **1985**, *50*, 924. (b) Kuehne, M. E.; Bandarage, U. K.; Hammach, A.; Li, Y. L.; Wang, T. *J. Org. Chem.* **1998**, *63*, 2172. (c) Yuan, Z. Q.; Ishikawa, H.; Boger, D. L. *Org. Lett.* **2005**, *7*, 741.

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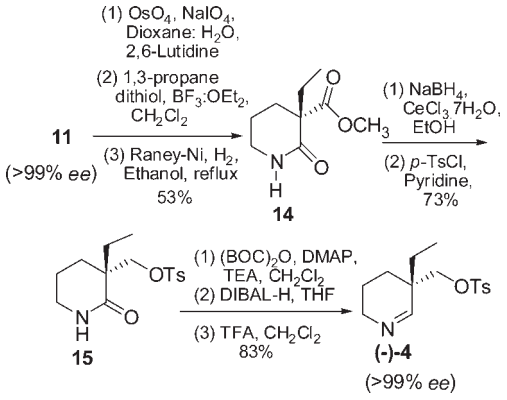
(9) (a) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828. (b) Donohoe, T. J.; McRiner, A. J.; Helliwell, M.; Sheldrake, P. *J. Chem. Soc., Perkin. Trans. 1* **2001**, 1435.

(10) (a) Diastereomeric excess of **9** was measured by HPLC analysis using Atlantis RP-18 column, CH_3CN/H_2O (40:60), λ = 224 nm. (b) CCDC 783953 contains the supplementary crystallographic data for **9**. (c) Enantiomeric purity of **11** was determined by HPLC using Chiralcel OD-H column; *i*-PrOH/petroleum ether (10:90) as eluent, λ = 220 nm.

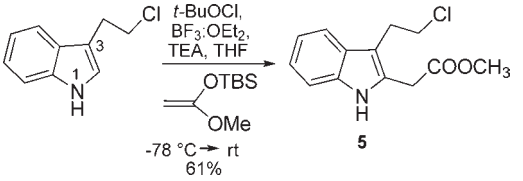
11 in low enantiopurity (19% *ee*)[10c] as well as yield (46%, Scheme 2). The loss of chirality results due to the involvement of intermediate **10**, formed by further methanolysis of **11** followed by recylization. Further, we also attempted a sequential approach of cleaving first the ether moiety of **9** (stirring with $CH_3COOH/H_2O/THF$ (1:1:8, rt)) to obtain **12** (89% yield), followed by methanolysis using sodium methoxide in methanol. However, this effort also gave undesired achiral **13**. Finally, we succeeded in transforming **12** to required **11** in excellent yield (87%) as well as high enantiopurity (>99% *ee*) by stirring with copper(II) triflate[11] in methanol.

Scheme 3. Synthesis of Imine (−)-**4**



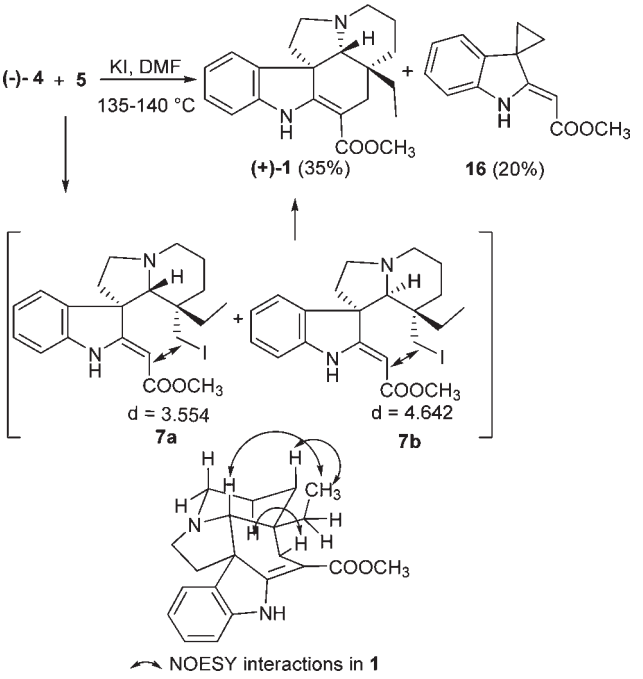
One carbon reductive degradation of terminal olefinic moiety of **11** by following the sequence of oxidative-cleavage ($OsO_4/NaIO_4$),[12] dithioacetalization of the resultant aldehyde followed by reductive desulfurization (Raney Nickel, H_2, EtOH, reflux) afforded **14** in 53% yield. Reduction of **14** under the Luche's condition[13] followed by tosylation of the primary alcohol moiety produced **15** in 73% yield. *N*-Boc protection followed by amide reduction using DIBAL-H resulted in the corresponding hemiaminal, which on treatment with trifluoroacetic acid in dichloromethane afforded chiral imine **4** in 83% yield (>99% *ee*, Scheme 3).[14,15] The required indole segment **5**, though reported in few steps,[16] was easily obtained in 61% yield starting from 3-(2-chloroethyl)-1H-indole in a single step operation (Scheme 4).[17]

Scheme 4. Synthesis of Indole Fragment **5**



Since, the central feature of our proposed synthetic strategy for stereoselective formation of the aspidosperma skeleton rests on the iminium ion triggered cascade cyclizations by coupling of (−)-**4** and **5**, we proceeded to test our hypothesis by heating a mixture of **4** (0.4 mmol) and **5** (0.4 mmol) in the presence of NaI (2.8 mmol) in anhydrous acetonitrile at reflux. To our dismay, after 12 h, only a trace amount of product was noticed by TLC. Several experiments using other solvents such as HMPA, NMP along with additives like sodium bicarbonate, DMAP, TBAI etc. also failed to give satisfactory result. After several optimization studies, we found that the reaction proceeded in refluxing DMF in the presence of potassium iodide and produced **1** {$[\alpha]^{28}_D = +550$ (*c* 0.2, EtOH); lit[7a] {$[\alpha]^{28}_D = +542$ (*c* 0.04, EtOH)} in 35% yield (>99% *ee*).[18] All spectral data of **1** were found in good agreement with the literature report.[7b]

Scheme 5. Synthesis of (+)-Vincadifformine



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(13) Kim, S.; Ko, H.; Lee, T.; Kim, D. *J. Org. Chem.* **2005**, *70*, 5756.

(14) Enantiomeric excess of (−)-**4** was determined by HPLC analysis: Chiralcel OJ-H column, *i*-PrOH/petroleum ether (15:85), λ = 254 nm.

(15) Several protocols were evaluated to synthesize **4** in shorter steps, but poor enantiomeric excess even at key steps led us to proceed with this present approach. We continue to attempt to find an alternative route for its synthesis.

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(17) Parsons, R. L.; Berk, J. D.; Kuehne, M. E. *J. Org. Chem.* **1993**, *58*, 7482.

Presumably, the formation of **1** in this reaction involves a diastereomeric mixture of intermediate **7**. To provide support for the intermediacy of **7** in this cascade sequence, we carried out the reaction at a lower temperature (90 °C, 12 h) and observed the formation of diastereomeric mixture of **7a** and **7b** along with some amount of **1**, evidenced by HPLC and LC−MS analysis.[19] Since the formation of both diastereomers of **7** was always accompanied by some amount of **1**, we could not determine the exact ratio of **7a** and **7b**. Our attempt to isolate pure diastereomers through column chromatography (silica gel and neutral alumina) for characterization purposes was found unsuccessful due to their poor stability. Molecular models suggest that **7a**, in which the nucleophilic carbon center of enamine and electrophilic carbon center of iodomethylene group is in close proximity (Scheme 5), may get transformed to **1** faster compared to **7b**. The fate of presumed **7b** could not be ascertained as this could give **1** via **7a** through Curtin−Hammett equilibration or may decompose to some other compounds. The moderate yield of **1** through this cascade reaction may be due to the combined effect of parallel transformation of **5** to **16** (20%) and decomposition of (−)-**4** and **7b**.

In conclusion, the synthesis of pentacyclic *Aspidosperma* alkaloid (+)-vincadifformine is achieved with good enantiopurity (>99% *ee*) by a convergent route through an iminium−enamine cascade reaction. Further studies to synthesize some other alkaloids of this class and show optimization of the yield during a cascade sequence are in progress and will be revealed in due course.

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Supporting Information Available. Experimental details as well as characterization data and copies of the NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) The enantiomeric excess was measured and compared with racemic **1** by HPLC analysis using Chiralcel OD-H column (250 × 4.6 mm), ethanol/petroleum ether/TFA (15:85:0.1), λ = 220 nm.

(19) HPLC-Mass analysis of **7**: Kromasil RP-18 (150 × 4.6 mm) column, MeOH/H_2O (85:15), λ = 254 nm. See Supporting Information.