VIP Natural Products Synthesis

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Total Synthesis of (−)-Conophylline and (−)-Conophyllidine**

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(−)-Conophylline (**1**), isolated from *Tabernaemontana divaricata* in 1992,[1] is a bis(indole) alkaloid consisting of two pentacyclic aspidosperma skeletons (Figure 1). This compound acts as a potent inhibitor of the *ras* function[2] and, furthermore, has been found to induce beta-cell differentiation in rat pancreatic acinar carcinoma cells and in cultured fetal rat pancreatic tissue.[3] Thus, this compound has the potential to be a lead compound in the development of novel drugs for cancer chemotherapy as well as for regeneration therapy used for the treatment of diabetes mellitus type 1. As a result of the important biological activity as well as the complex structure possessing a unique connectivity between its two segments, conophylline has attracted considerable attention from the synthetic community as a challenging target.[4] Herein, we report the first total synthesis of (−)-conophylline (**1**) and its congener, (−)-conophyllidine (**2**),[1b] in a convergent route utilizing the Polonovski–Potier-type coupling reaction.

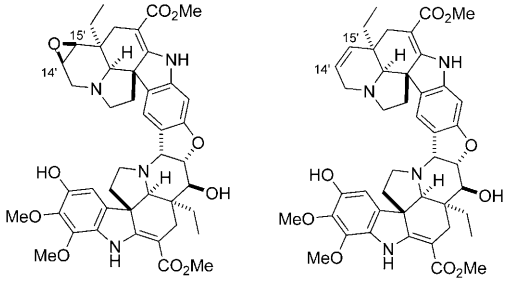
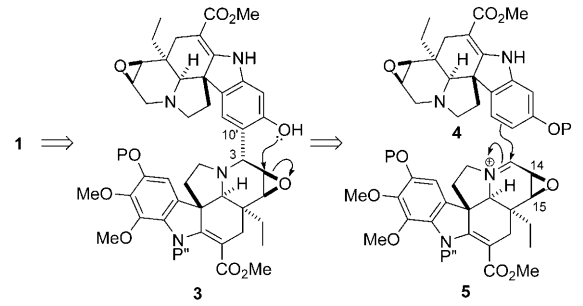
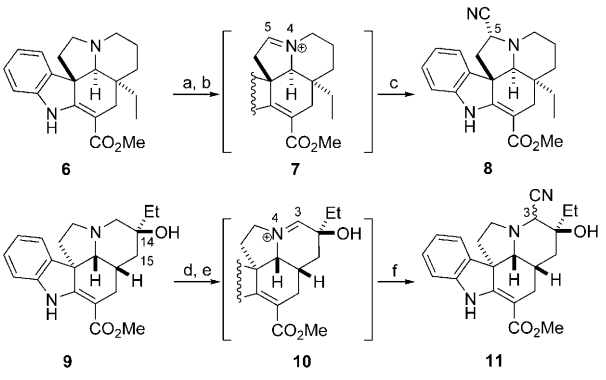


Figure 1. Structures of (−)-conophylline (**1**) and (−)-conophyllidine (**2**).

A convergent and potentially biomimetic synthesis of **1** should consist of the construction of the central dihydrobenzofuran ring at the final stage of the synthesis. Scheme 1 represents our synthetic strategy for the construction of the dihydrofuran moiety. We envisioned that if we could generate an iminium ion regioselectively in the lower-half (segment **5**), the electron-rich aromatic ring of the upper-half (segment **4**) would attack the iminium ion to form the C3–C10′ linkage with a subsequent intramolecular epoxide opening to furnish the dihydrofuran structure with the requisite stereochemistry. Husson, Lounasmaa, and co-workers reported their seminal work on the regiochemical issue of the Polonovski–Potier reaction[5] in which vincadifformine (**6**) gave the 5α-cyano compound **8** via the iminium ion at C5–N4, whereas the reaction of epipandoline (**9**) bearing a hydroxy group at C14 provided the 3-cyano compound **11** via an iminium ion at C3–N4 (Scheme 2).[6] On the basis of these observations as well as the potential cyclopropane-like role of the epoxide in stabilizing the adjacent carbocation, we hoped that a substrate having an epoxide at C14–C15 might also generate the C3–N4



Scheme 1. Synthetic strategy for the central part of (−)-conophylline (**1**).



Scheme 2. Regiochemistry of Polonovski–Potier reaction reported by Husson, Lounasmaa, and co-workers.[6] Reagents and conditions: a) *p*-O_2N-$C_6H_4CO_3H$, $CHCl_3$, 0 °C; b) TFAA, CH_2Cl_2, 0 °C→RT; c) KCN, CH_2Cl_2/H_2O (4:1), TFA/CH_3CO_2K, pH 4, RT, 50% (3 steps); d) aq H_2O_2, EtOH/CH_2Cl_2 (1:1), 60 °C; e) TFAA, CH_2Cl_2, 0 °C→RT; f) KCN, CH_2Cl_2/H_2O (4:1), TFA/CH_3CO_2K, pH 4, RT, 30% (3 steps). TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride.

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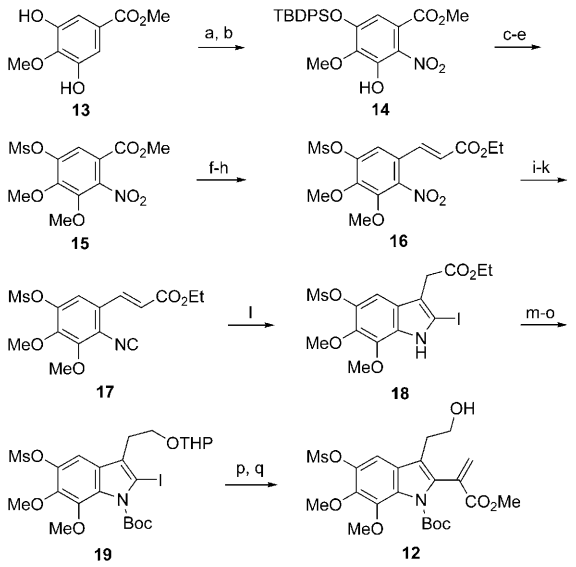
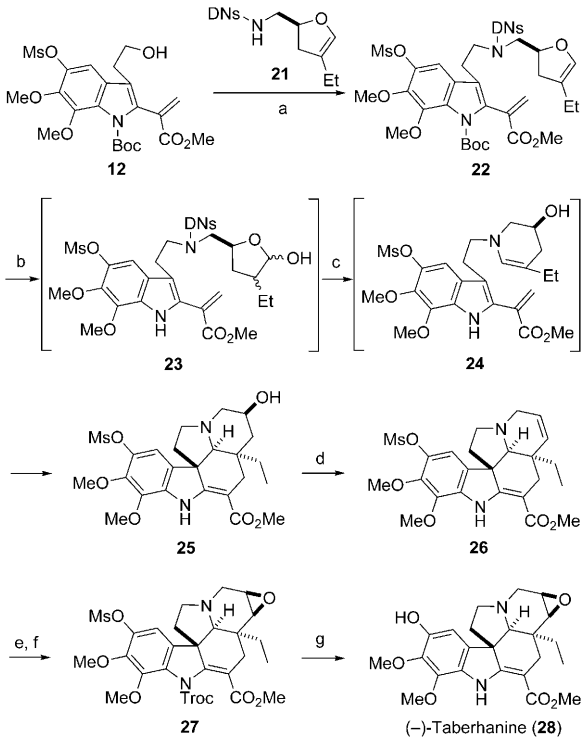
iminium ion **5**. For the synthesis of both the upper and lower aspidosperma indole segments, we planned to modify our previously established route to (−)-tabersonine[7] utilizing a combination of the tin-mediated indole synthesis[8] and the biomimetic cascade reaction for the formation of an aspidosperma skeleton.[7,9]

The synthesis of indole **12**, the intermediate to the lower segment, commenced with the nitration of the commercially available phenol **13** and the silylation of the sterically less-hindered phenolic hydroxy group to give **14**, which was then converted into mesylate **15** by a three-step sequence (Scheme 3). The ester was then elongated by reduction to the aldehyde and subsequent Wittig reaction to give cinnamate **16**. Next, the nitro group was transformed into an isocyano group by a conventional three-step sequence. The isocyanide **17** thus obtained was subjected to the tin-mediated radical cyclization[8] to produce 2-stannylindole, which was then converted into 2-iodoindole **18** by in situ treatment with iodine.[10] Then, reduction of the ester, protection of the resultant alcohol as THP ether, and Boc protection of the indole nitrogen atom gave **19**. Finally, introduction of the substituent at the 2 position by Stille coupling[11] with the 2-stannylacrylate derivative **20**[12] and removal of the THP group furnished the indole intermediate **12**.

We then constructed the aspidosperma skeleton by the intramolecular Michael addition/Mannich reaction cascade. Dinitrobenzenesulfonamide **21**, which was prepared by our previously reported route,[9] was coupled with alcohol **12** by using a Mitsunobu protocol (Scheme 4).[13] Next, both



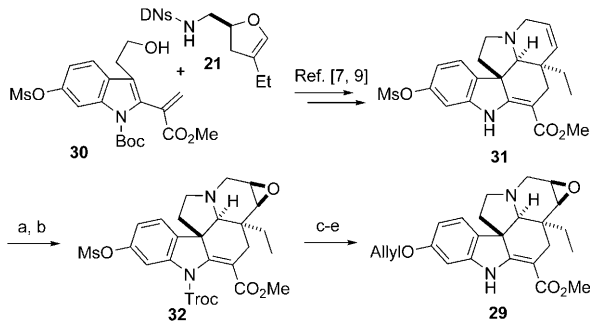
Scheme 3. Synthesis of the indole segment **12**. Reagents and conditions: a) HNO_3, AcOH, RT; b) TBDPSCl, 2,6-lutidine, THF/DMF (4:1), 0°C→RT, 42% (2 steps); c) *t*BuOK, Me_2SO_4, THF/DMF (3:1), 0°C→RT, 96%; d) TBAF, THF, RT; e) MsCl, Et_3N, CH_2Cl_2, 0°C→RT, 60% (2 steps); f) DIBAL-H, CH_2Cl_2, −78°C; g) TPAP, NMO, 4 Å M.S., CH_2Cl_2, RT; h) $Ph_3P{=}CHCO_2Et$, toluene, RT, 61% (3 steps); i) Zn, AcOH, CH_2Cl_2, 0°C→RT; j) HCO_2H, Ac_2O, CH_2Cl_2, 0°C; k) $POCl_3$, Py, CH_2Cl_2, 0°C, 64% (3 steps); l) *n*Bu_3SnH, AIBN, CH_3CN, reflux; I_2, RT 81% (2 steps); m) DIBAL-H, CH_2Cl_2, −78→0°C; n) DHP, CSA, CH_2Cl_2, RT; o) Boc_2O, DMAP, CH_3CN, 0°C→RT, 94% (3 steps); p) [BnPd(PPh_3)$_2$Cl], CuI, (2-furyl)$_3$P, methyl 2-(tributylstannyl)acrylate (**20**), DMF/HMPA (2:1), 80°C, 63%; q) CSA, MeOH, RT, 98%. AIBN = azobisisobutyronitrile, Boc = *tert*-butoxycarbonyl, CSA = 10-camphorsulfonic acid, DHP = 3,4-dihydro-2*H*-pyrane, DIBAL-H = diisobutylaluminum hydride, DMAP = *N*,*N*-dimethyl-4-aminopyridine, DMF = *N*,*N*-dimethylformamide HMPA = hexamethylphosphoric triamide, Ms = methanesulfonyl, M.S. = molecular sieves, NMO = *N*-methylmorpholine-*N*-oxide, TBDPS = *tert*-butyldiphenylsilyl, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran, TPAP = tetrapropylammonium perruthenate.



Scheme 4. Synthesis of the lower-segment **27**. Reagents and conditions: a) PPh_3, DEAD, benzene, 0C°→RT, 76%; b) TFA, Me_2S, CH_2Cl_2, RT; c) pyrrolidine, MeOH/CH_3CN (5:1), 0→60°C, 65% (2 steps); d) PPh_3, CCl_4, 2-methyl-2-butene, CH_3CN, 60°C, 35%; e) *t*BuOK, TrocCl, DMAP, THF, 0°C; f) *m*CPBA, aq $HClO_4$, MeOH, 0→50°C, 42% (2 steps); g) LDA, THF, −78→0°C, 60%. DEAD = diethyl azodicarboxylate, DNs = 2,4-dinitrobenzenesulfonyl, LDA = lithium diisopropylamide, *m*CPBA = *meta*-chloroperbenzoic acid, Troc = 2,2,2-trichloroethoxycarbonyl.

removal of the Boc group and hydration of the enol ether were effected by treatment with TFA to give lactol **23**. After removal of the DNs group,[14] the reaction mixture was stirred at 50°C to promote sequential reactions involving cyclic enamine formation, Michael addition of the enamine to α,β-unsaturated ester, and Mannich reaction of the indole to the resultant iminium ion to furnish the desired **25** as the sole isomer. Finally, regioselective dehydration and stereoselective epoxidation in the presence of perchloric acid[15] furnished the desired lower segment **27**. The structure of **27** was unambiguously confirmed by transformation into (−)-taberhanine (**28**)[16] in a one-pot removal of both the mesyl and Troc groups under conditions reported by Carreira and co-workers[17] in which excess LDA was used.

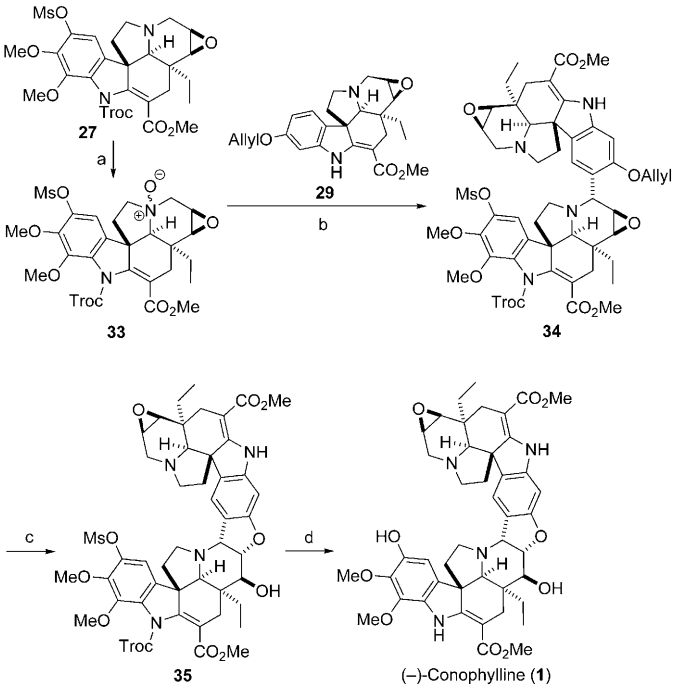
With the lower segment of (−)-conophylline (**1**) in hand, we then synthesized the upper segment **29** from 7-mesyloxytabersonine **31**, which was synthesized from indole derivative **30** and sulfonamide **21** in a similar manner as described in Scheme 4. After protection of enamine **31** with a Troc group, stereoselective epoxidation was carried out by treatment with *m*CPBA (Scheme 5).[15] Finally, removal of the Troc group and switching of the mesyl group to an allyl group afforded the upper segment **29**.



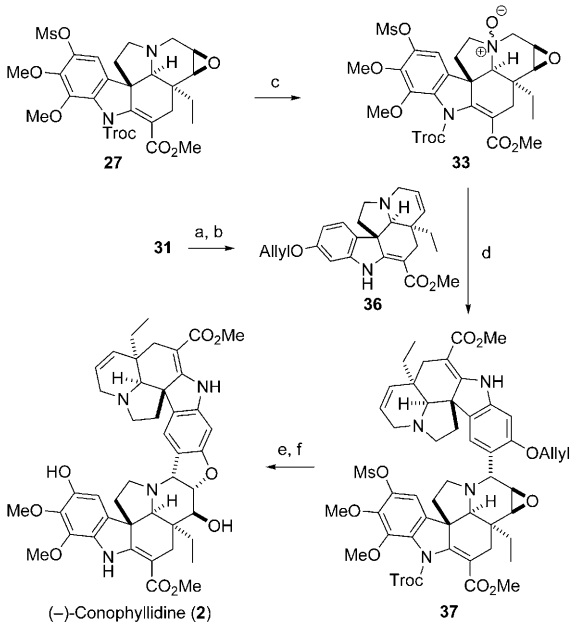
Scheme 5. Synthesis of the upper-segment **29**. Reagents and conditions: a) NaH, TrocCl, DMAP, THF/DMF (3:1), 0 °C; b) *m*CPBA, aq $HClO_4$, MeOH, 0→50 °C, 80% (2 steps); c) Zn, aq KH_2PO_4, THF, 60 °C; d) 1 M KOH, MeOH, 50 °C; e) AllylBr, K_2CO_3, DMF, 60 °C, 82% (3 steps).

Having synthesized the requisite upper and lower segments, we then turned our attention to the coupling reaction of the two segments (Scheme 6). For the crucial generation of the iminium ion, we examined the Polonovski–Potier-type reaction.[5] Thus, *m*CPBA oxidation of the lower-segment **27** provided the N-oxide **33** as a mixture of diastereomers, which was then treated with TFAA in the presence of the upper-segment **29**. Fortunately, the desired coupling product **34** was obtained as a single isomer in 50% yield based on **29**. Upon palladium-mediated removal of the allyl group, a spontaneous ring closure proceeded to furnish the dihydrofuran ring. This result unambiguously indicated that regioselective elimination of the O-acyl N-oxide proceeded to generate the iminium ion at C3–N4 and the subsequent nucleophilic attack of the upper-segment **29** occurred from the α face to give **34**. Finally, the Ms group on the phenolic hydroxy group and the Troc group were successfully removed using excess LDA[17] to furnish (−)-conophylline (**1**). All of the data regarding the synthetic conophylline were identical to those reported for the natural compound.[1]

Synthetic utility of the regio- and diastereoselective Polonovski–Potier-type reaction and the one-pot deallylation/cyclization cascade established for the synthesis of (−)-conophylline (**1**) proved to be applicable to the synthesis of conophyllidine (**2**; Scheme 7). Thus, the crude N-oxide **33** was subjected to the coupling reaction with the upper-segment **36**, which was prepared from **31** by switching the protective group from an Ms group to an allyl group, giving the desired coupling product **37** in 55% yield. Finally, the endgame sequence involving formation of the dihydrofuran ring initiated by the palladium-mediated deallylation and removal of both the Ms and Troc groups under Carreira's conditions[17] provided (−)-conophyllidine (**2**).[1b]



Scheme 6. Completion of the total synthesis of (−)-conophylline (**1**). Reagents and conditions: a) *m*CPBA, CH_2Cl_2, 0 °C; b) TFAA, CH_2Cl_2, 0 °C→RT, 50% (2 steps); c) $[Pd(PPh_3)_4]$, pyrrolidine, CH_2Cl_2, RT, 76%; d) LDA, THF, −78→0 °C, 72%.



Scheme 7. Completion of the total synthesis of (−)-conophyllidine (**2**). Reagents and conditions: a) 1 M KOH, MeOH, 50 °C; b) AllylBr, K_2CO_3, DMF, 60 °C, 82% (2 steps); c) *m*CPBA, CH_2Cl_2, 0 °C; d) TFAA, CH_2Cl_2, 0 °C→RT, 55% (2 steps); e) $[Pd(PPh_3)_4]$, pyrrolidine, CH_2Cl_2, RT, 72%; d) LDA, THF, −78→0 °C, 67%.

In conclusion, efficient total syntheses of (−)-conophylline (**1**) and (−)-conophyllidine (**2**) have been accomplished by using a newly developed coupling strategy of two aspidosperma indole segments through the regio- and diaste-

reoselective Polonovski–Potier reaction and the dihydrofuran ring formation.

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