VIP Natural Product Synthesis

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Total Synthesis of (+)-Haplophytine**

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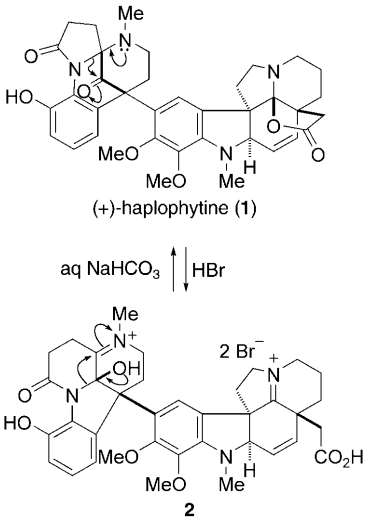
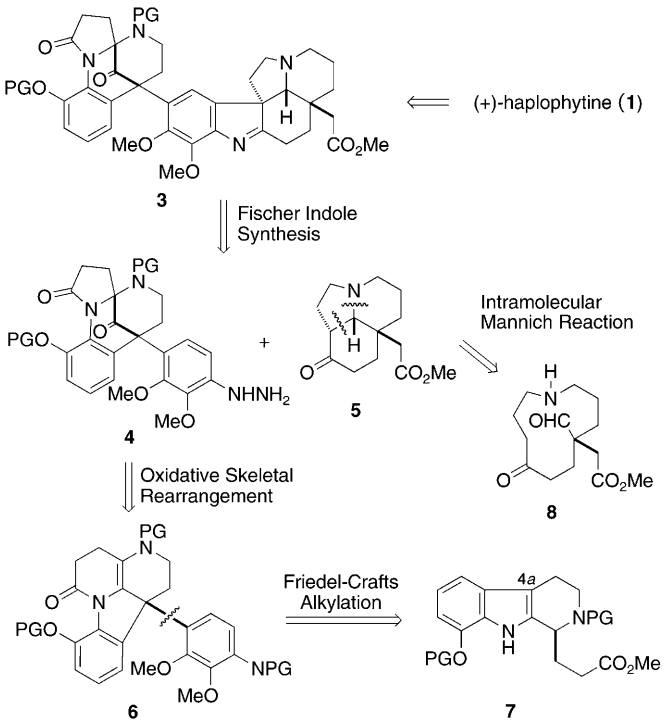
Haplophytine (**1**) is the major indole alkaloid found in the dried leaves of the Mexican plant *Haplophyton cimicidum* and was first isolated by Snyder and co-workers in 1952.[1,2] Two decades after its isolation, Yates, Cava, and co-workers determined its structure by X-ray crystallography.[3] Haplophytine (**1**) is composed of two segments that are connected by the formation of a quaternary carbon center (Scheme 1). The left-half segment has an exceptionally unique structure, which possesses a bicyclo[3.3.1]skeleton that includes bridged ketone and aminal functionalities. The right-half segment is a hexacyclic aspidosperma class of alkaloid, named aspidophytine, which is obtained by the acidic degradation of (+)-haplophytine.[3] Although five total syntheses of (−)-aspidophytine[4–8] have been reported to date, a total synthesis of haplophytine has so far not been achieved owing to its unique structural complexity.[9] Herein, we report the first total synthesis of (+)-haplophytine through a convergent route.



Scheme 1. Structure of (+)-haplophytine (**1**) and its rearrangement.

Our synthetic strategy is outlined in Scheme 2. We planned to construct the dimeric structure **3**, a possible precursor of (+)-haplophytine, by Fischer indole synthesis[10,11] between the fully elaborated left-hand segment **4** (having a phenylhydrazine moiety) and the tricyclic ketone **5**. We envisaged that the key left-hand segment would be formed by taking advantage of the intrinsic skeletal rearrangement of (+)-haplophytine, which was observed by Yates, Cava, and co-workers during the structural determination of **1**.[3] Thus, treatment of **1** with HBr would afford the iminium ion **2** through 1,2-migration of the C–N bond. On the other hand, the iminium ion **2** can be converted into the natural compound under basic conditions (Scheme 1) by a semipinacol-type rearrangement.[12] We have demonstrated the utility of the rearrangement for construction of the left-hand segment.[13] Nicolaou, Chen, and co-workers[14] independently reported the synthesis of a model compound of haplophytine by a similar rearrangement reaction. The rearrangement precursor **6** would be accessible by Friedel–Crafts alkylation at the 4*a* position of a tetrahydro-β-carbo-



Scheme 2. Retrosynthetic analysis of (+)-haplophytine (**1**). PG = protecting group.

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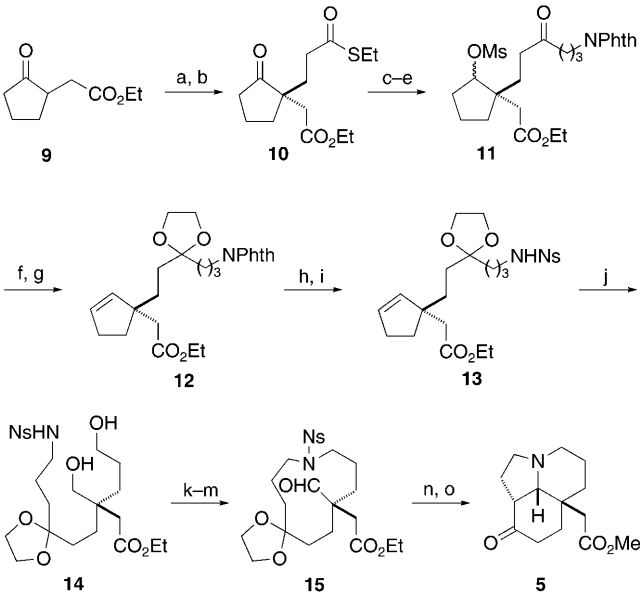
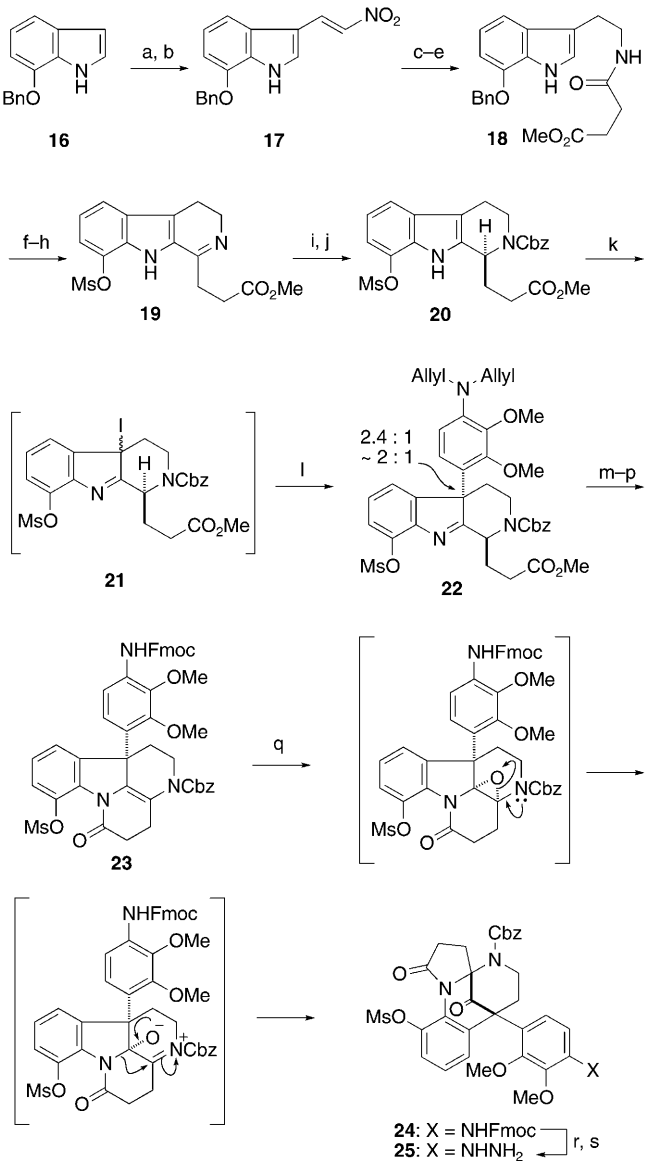
line derivative **7**.[13] For a synthesis of optically active tricyclic ketone **5**,[11] we planned to develop a facile assembly through a stereoselective intramolecular Mannich reaction.[15]

Preparation of tricyclic ketone **5** commenced with stereoselective construction of the quaternary carbon center by an asymmetric Michael addition developed by d'Angelo et al. (Scheme 3).[16] We used thioacrylate[17] as a Michael accepter, and it allowed us to elongate the side chain by palladium-catalyzed coupling with a functionalized zinc reagent.[18] The optically active cyclopentanone **10** thus obtained was reduced and converted into its mesylate derivative as a mixture of diastereomers. Chemoselective coupling of the thioester with an alkylzinc reagent bearing a phthalimide group[19] proceeded smoothly and gave ketoimide **11**. Ketalization by using the protocol developed by Noyori and co-workers[20] and elimination of the mesylate group afforded cyclopentene **12**. After conversion of phthalimide **12** into the Ns-amide **13**, the cyclopentene ring was cleaved by ozonolysis and reductive treatment with $NaBH_4$ gave diol **14**. Regioselective sulfonylation of the sterically less-hindered alcohol, oxidation



Scheme 3. Synthesis of tricyclic ketone **5**. Reagents and conditions: a) (*S*)-1-phenylethylamine, benzene, reflux; b) ethyl thioacrylate, THF, 0 °C; then AcOH, EtOH/H_2O (5:3), RT, 74% (2 steps), 97.8% *ee*; c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, −78 °C; d) MsCl, Et_3N, $Me_3N{\cdot}HCl$, toluene, 0 °C to RT, (2 cycles), 90% (2 steps); e) $IZn(CH_2)_3NPhth$, $[PdCl_2(PPh_3)_2]$ (10 mol%), toluene/THF (5:6), RT to 43 °C, 83%; f) $TMSO(CH_2)_2OTMS$, TMSOTf, CH_2Cl_2, −78 °C to RT; g) LiCl, Li_2CO_3, M.S. (4 Å), DMPU/HMPA (4:1), 70 °C, 67% (2 steps); h) $MeNHNH_2$, EtOH, reflux; i) NsCl, Et_3N, CH_2Cl_2, 0 °C to RT, quant. (2 steps); j) O_3, CH_2Cl_2/EtOH (4:3), −78 °C; then $NaBH_4$, pH 6.5 buffer, −78 °C to RT, 87%; k) $MesSO_2Cl$, CH_2Cl_2/pyridine (1:1), 0 °C; l) PCC, Celite, CH_2Cl_2, RT, 79% (2 steps); m) Cs_2CO_3, M.S. (3 Å), MeCN, 70 °C, 87%; n) 1 M HCl, THF, 50 °C; o) PhSH, Cs_2CO_3, MeCN, RT to 50 °C; then evaporation; then silica gel, CH_2Cl_2, reflux; then $TMSCHN_2$, NH_4Cl, MeOH, RT, 83% (4 steps). DMPU = *N*,*N*′-dimethylpropyleneurea, HMPA = hexamethylphosphorous triamide, Mes = 2,4,6-trimethylphenyl, Ms = methanesulfonyl, M.S. = molecular sieves, Ns = 2-nitrobenzenesulfonyl, PCC = pyridinium chlorochromate, Phth = phthaloyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TMS = trimethylsilyl.



Scheme 4. Synthesis of the left-segment **25**. Reagents and conditions: a) $POCl_3$, DMF, 0 °C to RT; then 1 M KOH, 0 °C to reflux; b) $MeNO_2$, NH_4OAc, reflux, 88% (2 steps); c) $LiAlH_4$, THF, 0 °C to reflux; d) succinic anhydride, CH_2Cl_2, RT; e) $SOCl_2$, MeOH, 0 °C to RT, 71% (3 steps); f) H_2, Pd/C, CH_2Cl_2/MeOH (1:1), RT; g) MsCl, Et_3N, CH_2Cl_2, 0 °C, 86% (2 steps); h) $POCl_3$, CH_2Cl_2, reflux; i) (*R*,*R*)-TsDPEN-Ru^{II} complex, HCO_2H/Et_3N (5:2), DMF, 0 °C; j) CbzCl, iPr_2NEt, CH_2Cl_2, 0 °C, 67% (3 steps), 96.6% *ee*; k) NIS, CH_2Cl_2, RT; l) *N*,*N*-diallyl-2,3-dimethoxyaniline, AgOTf, CH_2Cl_2, −10 °C, 61% (2 steps; *trans*/*cis* 2.4:1–2:1); m) $LiOH{\cdot}H_2O$, MeOH/H_2O (3:1), RT; n) $SOCl_2$, DMF, CH_2Cl_2, RT; then iPr_2NEt, RT, 59% (2 steps); o) $[Pd(PPh_3)_4]$, *N*,*N*-dimethylbarbituric acid, CH_2Cl_2, reflux, 94%; p) FmocCl, $NaHCO_3$, 1,4-dioxane/H_2O (10:1), RT, 97%; q) *m*CPBA, $NaHCO_3$, CH_2Cl_2, RT, 84%; r) piperidine, DMF, RT, 96%; s) *i*AmONO, 6 M HCl/MeOH/MeCN (3:2:2), 0 °C; then $SnCl_2$, conc. HCl, −10 °C to 0 °C, 77%. Bn = benzyl, Cbz = benzyloxycarbonyl, DMF = *N*,*N*-dimethylformamide, DPEN = 1,2-diphenylethylenediamine, Fmoc = 9-fluorenylmethoxycarbonyl, *m*CPBA = *m*-chloroperbenzoic acid, NIS = *N*-iodosuccinimide, Ts = 4-toluenesulfonyl.

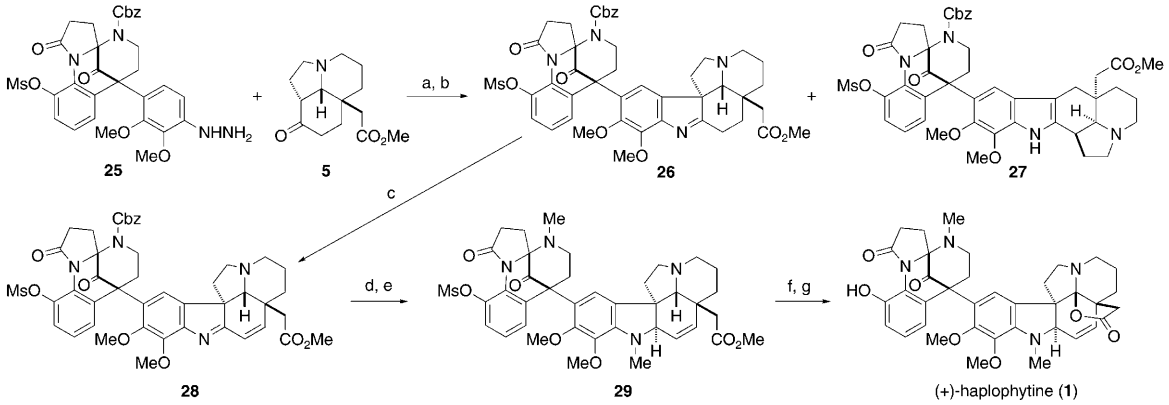
of the remaining alcohol, and intramolecular N-alkylation of the Ns-amide gave the 11-membered cyclic secondary amine derivative **15**.[21] At this stage, we extensively studied the crucial intramolecular Mannich reaction. After acidic hydrolysis of the ketal and ester groups, the Ns group was removed under standard reaction conditions.[22] We found that the expected Mannich-type cyclization took place quite smoothly by treatment of the crude amine with silica gel. The desired tricyclic ketone **5** was obtained as a single isomer in 83% yield after esterification with trimethylsilyldiazomethane. Notably, this three-step sequence was carried out in a one-pot operation.

With the key tricyclic ketone **5** in hand, we then turned our attention to the synthesis of the left-hand segment. After formylation of 7-benzyloxyindole **16**[23] under the Vilsmeier–Haack conditions, the resultant aldehyde was condensed with nitromethane and afforded nitroalkene **17** (Scheme 4). Reduction of the nitroalkene unit and subsequent acylation with succinic anhydride gave the tryptamide derivative, which was converted into amide **18**. After replacing the phenolic benzyl ether group with a mesylate group, Bischler–Napieralski cyclization was executed and provided dihydro-β-carboline **19**,[14,24] which was then subjected to the Noyori asymmetric reduction[24,25] and subsequent protection of the resultant secondary amine with CbzCl led to tetrahydro-β-carboline **20** in 96.6% *ee*.

Having synthesized the desired optically active β-carboline derivative **20**, we examined coupling of **20** with 2,3-dimethoxy-*N*,*N*-diallylaniline (Scheme 4). Iodoindolenine **21**, which was generated by treatment of a solution of **20** in CH_2Cl_2 with NIS, was activated with silver triflate in the presence of 2,3-dimethoxy-*N*,*N*-diallylaniline. The Friedel–Crafts alkylation reaction proceeded smoothly and furnished the desired coupling product **22** as the major isomer in approximately a 2.4:1–2:1 diastereoselectivity. Judicious choice of solvent was crucial for this coupling reaction. Thus, polar solvents such as MeCN or DMF, resulted in only recovery of the starting carboline **20**. After separation of the diastereomers, the lactam ring was formed by saponification and cyclization via a ketene intermediate. The desired rearrangement precursor **23** was obtained by replacing the two *N*-allyl groups to an Fmoc group. As expected, the key oxidative skeletal rearrangement,[13] which was initiated by *m*CPBA oxidation of the 1,2-diaminoethene moiety from the convex face, took place and furnished the desired product **24**—which has a bicyclo[3.3.1]skeleton—in 84% yield. Finally, removal of the Fmoc group and conversion of the aniline into a hydrazine gave **25** as the key precursor of the Fischer indole synthesis.

The pivotal construction of the right-hand segment by Fischer indole synthesis and the end game sequence are illustrated in Scheme 5. Condensation of hydrazine **25** and ketone **5** with 50% sulfuric acid gave the corresponding hydrazone. First, we examined the crucial Fischer indole synthesis in acetic acid at reflux, according to the protocol developed by Stork and Dolfini for the total synthesis of aspidospermine.[11a] To our disappointment, only a small amount of the expected indolenine **26** and indole byproduct **27** were obtained (ca. 20% combined yield). After extensive optimization, we eventually found that careful control of the reaction temperature and the appropriate choice of acid and solvent were essential to preferentially obtain the desired indolenine **26** over the indole **27** in reasonable yield.[25] Thus, treatment with *p*TsOH in *t*BuOH at 80 °C gave indolenine **26** in 47% yield along with indole **27** in 29% yield. After conversion of imine **26** into the conjugated imine **28** [5b,26] the Cbz group was removed by BBr_3 in the presence of pentamethylbenzene, which acted as a cation scavenger.[27] One-pot 1,2-reduction of the imine and reductive methylation of two secondary amino groups led to **29**. Finally, basic hydrolysis of the ester and the phenolic mesylate groups and subsequent formation of the lactone ring with potassium ferricyanide[4] furnished (+)-haplophytine (**1**). The spectroscopic data of the synthetic material were identical to those of natural (+)-haplophytine (**1**).[2,3]

In conclusion, we have accomplished the first total synthesis of (+)-haplophytine (**1**) featuring the facile assembly of tricyclic ketone **5** by the intramolecular Mannich reaction, construction of the quaternary carbon by the Friedel–Crafts alkylation, formation of the left-hand segment



Scheme 5. Completion of the total synthesis of (+)-haplophytine (**1**). Reagents and conditions: a) 50% aq H_2SO_4, 1,4-dioxane, 0 °C, 80%; b) *p*TsOH, *t*BuOH, 80 °C, 47% of **26** and 29% of **27**; c) benzeneseleninic anhydride, THF, reflux, 61%; d) BBr_3, pentamethylbenzene, CH_2Cl_2, −78 °C to −25 °C, 67%; e) HCHO (37%), $NaBH_3CN$, AcOH, CH_2Cl_2/MeOH (1:1), −78 °C to RT, 55%; f) 1 M NaOH, MeOH, 60 °C; g) $K_3[Fe(CN)_6]$, $NaHCO_3$, *t*BuOH/H_2O (1:2), 0 °C to RT, 70% (2 steps).

possessing the aminal structure by oxidative rearrangement, and the Fischer indole synthesis of the fully elaborated hydrazine derivative.

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