Synthetic Studies on Haplophytine: Protective-Group-Controlled Rearrangement

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Received 8 October 2007

Abstract: The characteristic tetracyclic structure of haplophytine containing a bridged ketone, aminal, and γ-lactam was constructed by oxidative rearrangement of a tetrahydro-β-carboline derivative.

Key words: haplophytine, aspidophytine, alkaloids, oxidations, rearrangements

Haplophytine (**1**, Figure 1) is the major alkaloid isolated from the leaves of the Mexican 'cockroach plant', *Haplophyton cimicidum* (Apocynaceae).[1] After the pioneering work of Snyder and co-workers,[2] the structure of haplophytine (**1**) was reported by Cava and Yates in 1973[3] and was unambiguously confirmed by X-ray crystallography in 1976.[4] The compound is composed of two subunits, which are connected by forming a quaternary carbon center. The left-hand segment is a hitherto-unknown tetracyclic structure including bridged ketone and aminal functionalities. The right-half constituent, aspidophytine (**2**), is a member of the aspidosperma class of alkaloids, which was obtained by acid-mediated chemical degradation of **1**.[3,5] Because of its structural complexity, compound **1** has attracted considerable attention as a challenging synthetic target. While no total synthesis of **1** has been reported to date,[6,7] four groups have accomplished the total synthesis[8–11] of the right-hand segment, aspidophytine, including Corey's first total synthesis[8] and one by our laboratory.[9] After completion of the total synthesis of the right-hand segment, we continued extensive research toward the total synthesis of haplophytine (**1**) and carried out model studies for the construction of the characteristic left-hand segment. Recent publication of a similar approach by Nicolaou and co-workers[7] has prompted us to disclose our own independent effort. We herein report an efficient construction of the left-hand segment via an oxidative skeletal rearrangement.[12]

For construction of the left-hand segment, we planned to apply the inherent skeletal rearrangement of haplophytine (**1**) that was observed during its structural determination (Scheme 1). Yates and Cava found that treatment of haplophytine (**1**) with HBr promoted a skeletal rearrangement as depicted in Scheme 1 to provide a tetrahydro-β-carboline derivative **3**.[5c,13] In addition, the rearranged isomer **3** was converted back into the natural form **1** under basic conditions.

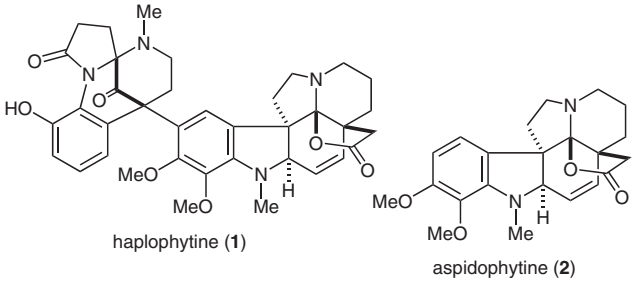
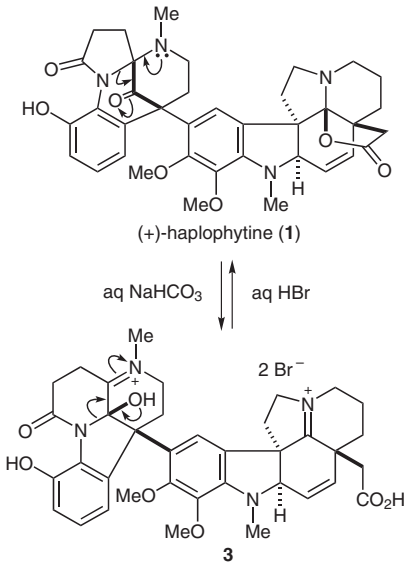


Figure 1



Scheme 1 Skeletal rearrangement of haplophytine (**1**)

Based on these observations, we postulated that the characteristic left-hand segment could be formed from a diamino epoxide, such as **5**, through an epoxide opening by electron-pushing from one of the nitrogens to give an iminium ion species **4** and subsequent 1,2-shift of the C–N bond (Scheme 2). The diamino epoxide **5** would be obtained by oxidation of the 1,2-diaminoethene derivative **6**. The key intermediate **6** would be prepared via introduction of the aspidophytine segment to the tetrahydro-β-carboline derivative **8** and lactam formation.

In order to examine the strategy for the construction of the left-hand segment, we chose 2,3-dimethoxy-*N*,*N*-dimeth-

SYNLETT 2007, No. 20, pp 3137–3140
Advanced online publication: 21.11.2007
DOI: 10.1055/s-2007-990911; Art ID: U09707ST
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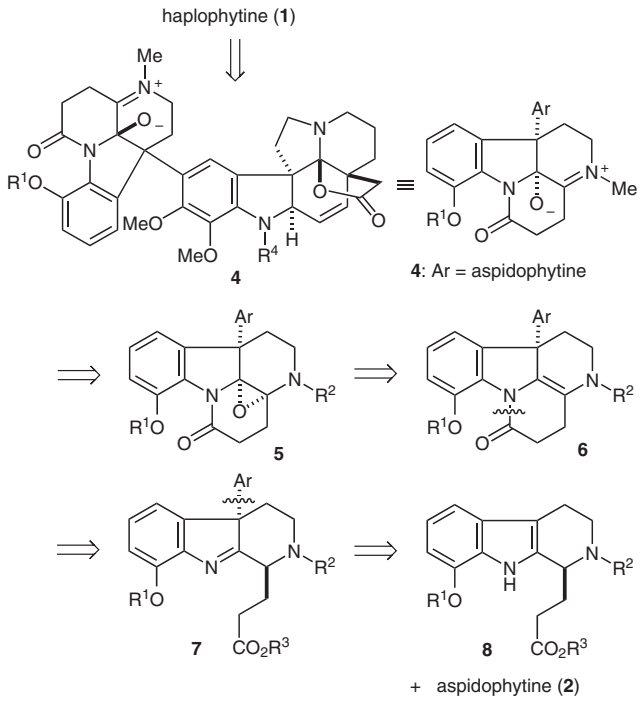
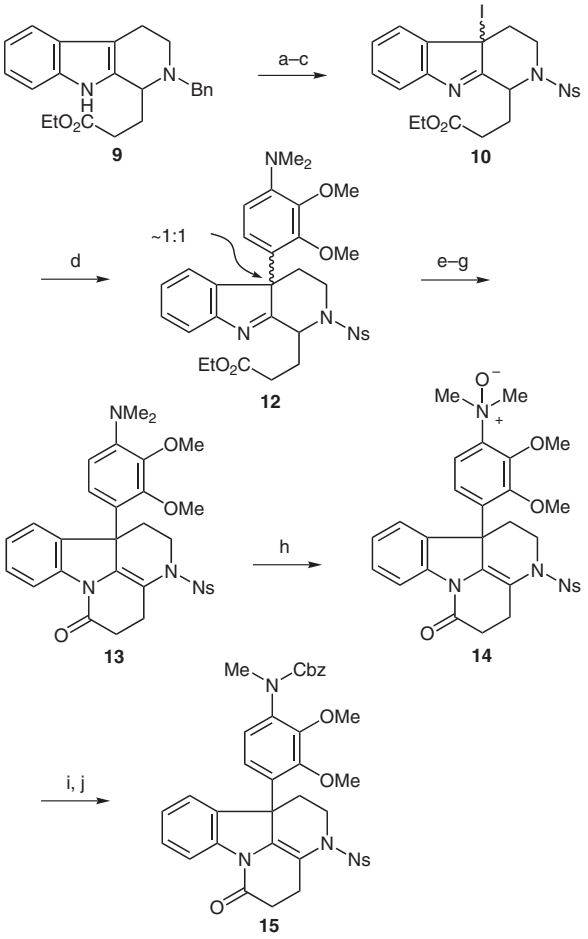


Scheme 2 Retrosynthetic analysis of haplophytine

ylaniline (**11**) as a model compound of the aspidophytine unit and prepared the tetrahydro-β-carboline derivative **15** as a substrate for the oxidative rearrangement reaction (Scheme 3).

Synthesis of compound **15** was started by esterification of the known tetrahydro-β-carboline derivative **9**, which was readily prepared by modified Pictet–Spengler reaction.[14] After switching the benzyl group to the 2-nitrobenzenesulfonyl (Ns) group,[15] the resultant Ns-amide was treated with *N*-iodosuccinimide to give the iodoindolenine derivative **10**. At this stage, introduction of 2,3-dimethoxy-*N*,*N*-dimethylaniline (**11**) was investigated. We found that a Friedel–Crafts-type alkylation proceeds when iodoindolenine **10** was activated with silver triflate in the presence of aniline derivative **11** to furnish the desired coupling product **12** as a ca. 1:1 mixture of diastereomers in moderate yield. A lactam ring was then formed by saponification, conversion of the resultant carboxylic acid into the acid chloride, and cyclization with Hünig's base. In an attempt to oxidize the 1,2-diamino olefin moiety of compound **13** with dimethyldioxirane, we instead observed oxidation of the *N*,*N*-dimethylaniline moiety to form the corresponding *N*-oxide **14**. Thus, one of the methyl groups was switched to a Cbz group by demethylation via a Polonovsky-type elimination and protection of the resultant *N*-methylaniline derivative with a Cbz group.

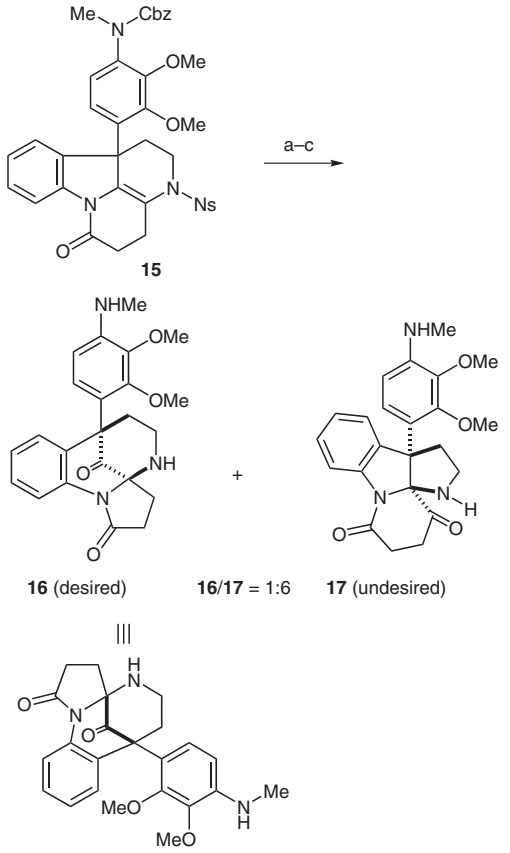
Having synthesized the desired key intermediate **15**, we then subjected it to oxidation conditions to examine the expected oxidation of the double bond followed by skeletal rearrangement (Scheme 4). Unexpectedly, treatment of the 1,2-diaminoethene derivative **15** with MCPBA provided a mixture of two products in a ratio of 6:1, which were separated after deprotection of Ns and Cbz groups.



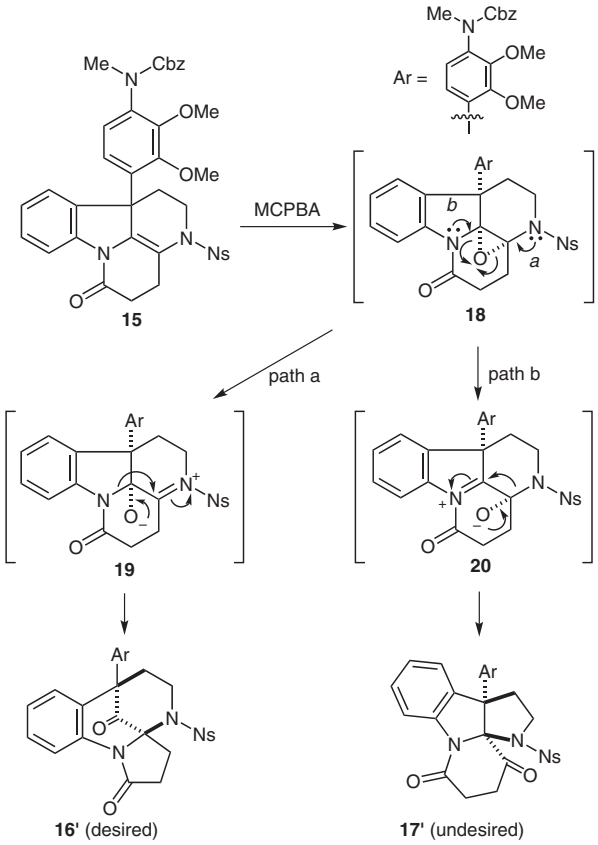
Scheme 3 *Reagents and conditions:* (a) H_2, Pd/C, AcOH–EtOH; (b) NsCl, Et_3N, CH_2Cl_2, 79% (2 steps); (c) NIS, CH_2Cl_2; (d) 2,3-dimethoxy-*N*,*N*-dimethylaniline (**11**), AgOTf, CH_2Cl_2, 0 °C to r.t., 38%; (e) KOH, EtOH, 88%; (f) $SOCl_2$, DMF (cat.); (g) *i*-Pr_2NEt, CH_2Cl_2, 32% (2 steps); (h) dimethyldioxirane, CH_2Cl_2–acetone; (i) Ac_2O, 2,6-lutidine, DCE; (j) CbzCl, NaH, THF–DMF, 47% (3 steps).

The structural determination of the two products by X-ray crystallographic analysis revealed that the structure of the minor product **16** was certainly the desired product, which had the bridged ketone and the aminal functionalities. The major product **17**,[16] however, was not the one we expected, but the tetracyclic compound possessing a pyrrolo[2,3-*b*]indole skeleton.

Plausible mechanistic details for the formation of compounds **16** and **17** are depicted in Scheme 5. The desired compound **16** (minor product) should be formed by epoxidation of the 1,2-diaminoethene moiety and subsequent ring opening of the epoxide due to electron-pushing from nitrogen of the Ns-amide (path a) to form **19**, followed by a 1,2-shift of the C–N bond. On the other hand, opening of the epoxide by the other nitrogen of the lactam ring (path b) and subsequent 1,2-shift of the C–N bond would lead to the undesired product **17** (major product). Thus, the low selectivity of the expected rearrangement pathway (path a) is attributed to competitive epoxide opening due to electron-pushing from nitrogen of the lactam ring (path b). Based on this observation, we speculated that the selectivity of the mode of oxidative rearrangements should



Scheme 4 *Reagents and conditions*: a) MCPBA, $NaHCO_3$, CH_2Cl_2, r.t., 60 h, 64%; b) PhSH, Cs_2CO_3, MeCN, 79%; c) H_2, Pd/C, EtOH, 94%.



Scheme 5 Two modes of the oxidative rearrangement

be controlled by tuning of electron density on the two nitrogens by switching the protective group.

With these considerations in mind, we prepared a substrate **25**[17] bearing a Cbz group instead of a Ns group on the nitrogen by an improved synthetic sequence and subjected it to the oxidation conditions with MCPBA (Scheme 6).[18] Interestingly, a dramatic rate acceleration of the oxidative rearrangement was observed and the substrate **25** gave the desired tetracyclic compound **26** exclusively. Finally, deprotection of the Cbz group under hydrogenation conditions and reductive methylation gave the model compound **27** of haplophytine (**1**).

In summary, we have developed a protocol to construct the left-half segment of haplophytine. The characteristic tetracyclic structure containing bridged ketone and aminal functionalities was selectively formed by the protective-group-controlled oxidative skeletal rearrangement. Synthetic studies toward haplophytine based on the strategy described in this paper are currently under investigation.

Acknowledgment

The authors thank Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan, PRESTO, the Japan Science and Technology Agency, and the Uehara memorial foundation.

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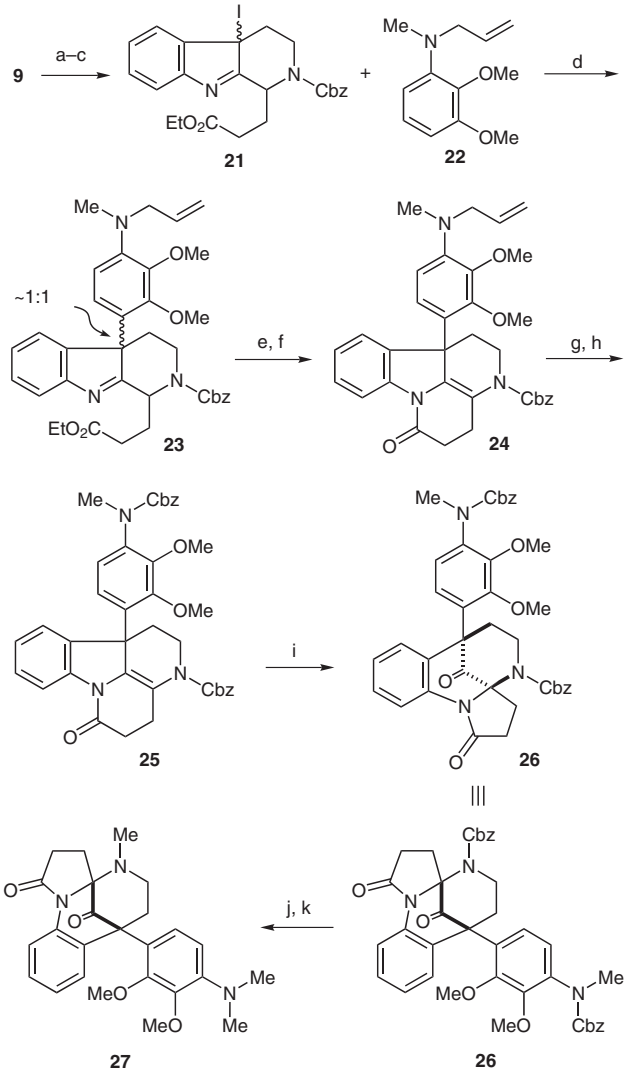

Scheme 6 *Reagents and conditions*: a) H_2, Pd/C, EtOH; b) CbzCl, $NaHCO_3$, dioxane–H_2O, 90% (2 steps); c) NIS, CH_2Cl_2; d) AgOTf, CH_2Cl_2, –10 °C, 32% (2 steps); e) KOH (1 M), EtOH; f) $SOCl_2$, DMF (cat.); *i*-Pr_2NEt, CH_2Cl_2, 56% (2 steps); g) $Pd(PPh_3)_4$, 1,3-dimethylbarbituric acid, CH_2Cl_2, 93%; h) CbzCl, $NaHCO_3$, dioxane, 93%; i) MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h, 82%; j) H_2, Pd/C, EtOH, 84%; k) aq HCHO, $NaBH_3CN$, AcOH, CH_2Cl_2–MeOH, 69%.

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(16) Major product **17**: mp 220–222 °C (dec.); IR (film): 3419, 3332, 2937, 1732, 1666, 1610, 1516, 1481, 1400, 912, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 8.4 Hz, 1 H), 7.20 (t, *J* = 8.4 Hz, 1 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 6.98 (t, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 7.6 Hz, 1 H), 6.38 (d, *J* = 8.0 Hz, 1 H), 3.59 (s, 3 H), 3.18–3.04 (m, 3 H), 2.84 (s, 6 H), 2.82–2.77 (m, 1 H), 2.69–2.60 (m, 2 H), 2.52–2.44 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.8, 169.1, 149.3, 143.0, 141.9, 139.9, 135.2, 127.9, 125.7, 124.4, 123.8, 121.3, 115.7, 104.7, 93.5, 64.0, 59.1, 58.4, 45.6, 42.1, 33.7, 31.3, 30.2. HRMS–FAB: *m/z* calcd for $C_{23}H_{25}N_3O_4$ $[M + H]^+$: 408.1923; found: 408.1918.

(17) Compound **25**: IR (film): 2944, 1706, 1681, 1601, 1390, 1336, 1158, 912, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 7.2 Hz, 1 H), 7.35–7.24 (m, 13 H), 7.08 (d, *J* = 8.4 Hz, 1 H), 7.03 (t, *J* = 8.4 Hz, 1 H), 5.11 (br s, 4 H), 3.65–3.55 (m, 2 H), 3.62 (br s, 3 H), 3.59 (br s, 3 H), 3.44–3.35 (m, 1 H), 3.27–3.20 (m, 1 H), 3.20 (s, 3 H), 2.99 (dt, *J* = 7.2, 15.6 Hz, 1 H), 2.76 (dd, *J* = 3.6, 15.6 Hz, 1 H), 2.46 (dt, *J* = 5.2, 15.6 Hz, 1 H), 1.82 (dt, *J* = 7.2, 14.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 155.9, 152.6, 150.2, 140.2, 137.1, 136.9, 136.4, 135.9, 133.2, 128.8, 128.7, 128.6, 128.5, 128.1, 124.6, 124.5, 123.2, 122.0, 115.9, 67.7, 67.4, 60.5, 60.1, 49.3, 41.9, 37.9, 33.4, 21.3, 14.5. HRMS–FAB: *m/z* calcd for $C_{39}H_{37}N_3O_7$: 659.2632; found: 659.2630.

(18) **Oxidative Rearrangement**
To a solution of **25** (100 mg, 0.152 mmol) in CH_2Cl_2 (1.5 mL) was added $NaHCO_3$ (38.2 mg, 0.455 mmol) and MCPBA (40.2 mg, 65% purity, 0.152 mmol) at 0 °C under an argon atmosphere. After stirring for 2 h at the same temperature, the reaction mixture was quenched with sat. Na_2SO_3 and stirred for 10 min. Then to the two-phase mixture was added CH_2Cl_2, and the organic layer was separated. The organic layer was washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4. Filtration and concentration on a rotary evaporator afforded a crude product. The crude product was purified by flash column chromatography on silica gel (neutral; 30–40% EtOAc in hexane, gradient elution) to give **26** (84.1 mg, 82%). IR (film): 2944, 1709, 1458, 1394, 1316, 1159, 912, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 8.29 (d, *J* = 8.4 Hz, 0.5 H), 8.08 (d, *J* = 8.0 Hz, 0.5 H), 7.36–6.95 (m, 14 H), 6.80 (dd, *J* = 7.2, 11.2 Hz, 1 H), 5.15 (br s, 2 H), 5.12 (s, 2 H), 3.83–3.76 (m, 0.5 H), 3.68–3.52 (m, 1.5 H), 3.68 (br s, 1.5 H), 3.61 (br s, 1.5 H), 3.41–3.29 (m, 1 H), 3.25 (s, 3 H), 2.99 (br s, 1 H), 2.88–2.76 (m, 1 H), 2.80 (br s, 3 H), 2.66–2.43 (m, 1.5 H), 2.25–2.05 (m, 1 H), 1.95–1.86 (m, 0.5 H). ^{13}C NMR (100 MHz, $CDCl_3$, doubling due to rotamers): δ = 195.2, 171.9, 168.0, 155.4, 154.6, 149.4, 149.2, 140.2, 136.3, 136.2, 135.3, 135.1, 134.8, 132.8, 130.5, 128.4, 128.3, 128.0, 127.8, 127.2, 125.3, 123.9, 122.9, 122.2, 121.8, 120.8, 120.5, 120.2, 115.7, 81.4, 67.7, 67.6, 66.9, 59.9, 58.1, 56.4, 52.3, 46.1, 40.4, 39.3, 37.4, 36.1, 30.6, 30.3, 30.1, 21.0. HRMS–FAB: *m/z* calcd for $C_{39}H_{37}N_3O_8$: 675.2581; found: 675.2578.

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