Natural Products Synthesis

International Edition: DOI: 10.1002/anie.201609285
German Edition: DOI: 10.1002/ange.201609285

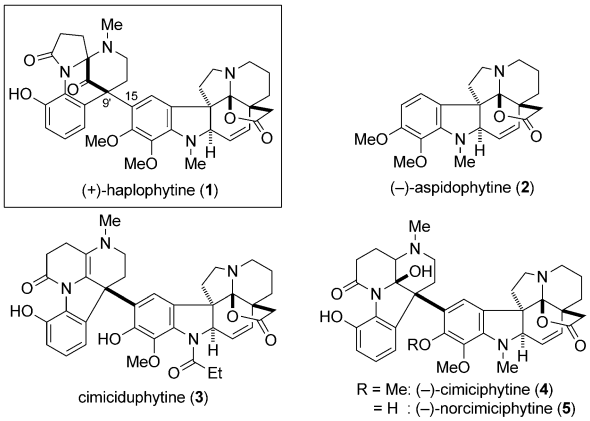
Bioinspired Total Synthesis of the Dimeric Indole Alkaloid (+)-Haplophytine by Direct Coupling and Late-Stage Oxidative Rearrangement

*Hitoshi Satoh, Ken-ichi Ojima, Hirofumi Ueda, and Hidetoshi Tokuyama**

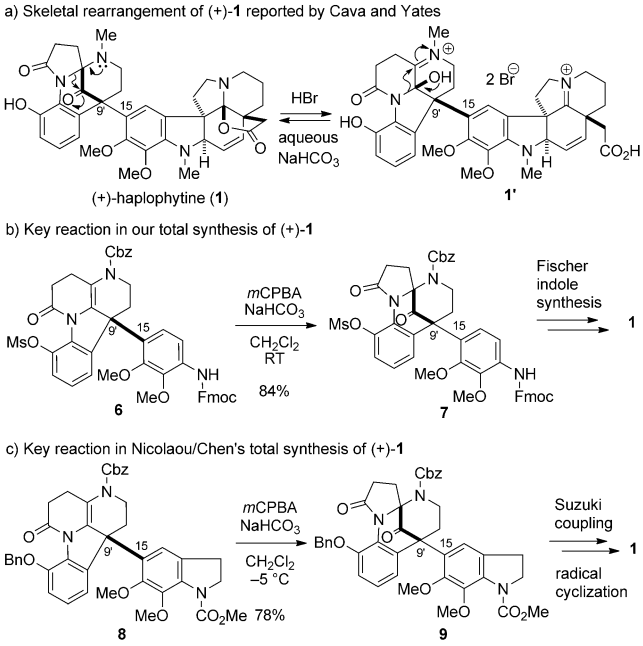
Abstract: *A bioinspired convergent total synthesis of (+)-haplophytine, a dimeric indole alkaloid with diazabicyclo-[3.3.1]nonane and hexacyclic aspidosperma segments, is described. This synthesis involves the direct coupling of the two segments in a $AgNTf_2$-mediated Friedel–Crafts reaction and construction of the diazabicyclo[3.3.1]nonane skeleton through late-stage chemoselective aerobic oxidation of the 1,2-diaminoethene moiety and a sequential semipinacol-type rearrangement.*

(+)-Haplophytine (**1**) is a dimeric indole alkaloid[1] isolated from the shrub *Haplophyton cimicidum*, which is native to Central America;[2] its dried leaves have been used as an insecticide since Aztec times. Alam and co-workers found that several compounds isolated from this plant showed inhibitory activity against acetylcholinesterase.[3] Structurally, **1** has a characteristic diazabicyclo[3.3.1]nonane skeleton in the left segment; the right segment possesses an aspidosperma skeleton: specifically, the structure of (−)-aspidophytine (**2**; Scheme 1). This intriguing structure has inspired a number of synthetic studies.[4] Following the landmark total synthesis of (−)-aspidophytine (**2**) by Corey and co-workers,[5a] a number of research groups established a route to **2**.[5] Recently, we completed the first total synthesis of (+)-haplophytine (**1**)[6a] after more than a half century since its isolation; this synthesis was immediately followed by a further synthesis by the Nicolaou/Chen group.[6b]

Despite these achievements, both synthetic routes remain unsatisfactory in terms of convergency, and no synthesis based on the biomimetic direct coupling of the two segments, as proposed by Corey,[4c] has been described so far. Thus, each total synthesis constructed the C15−C9′ linkage at the C9′ position through a coupling reaction of the precursor of the left segment and a partial structure of the right segment (Scheme 2 b,c). The characteristic diazabicyclo[3.3.1]nonane skeleton was then constructed by an oxidative skeletal rearrangement on the basis of the semipinacol-type rearrangement of **1** reported by Cava, Yates, et al. (Scheme 2 a).[2f] For completion of the synthesis of **1**, a further lengthy sequence was necessary to construct the right segment and manipulate the functional groups.



Scheme 1. (+)-Haplophytine and related compounds.



Scheme 2. Rearrangement reaction of (+)-**1** and its application to total synthesis. Cbz = benzyloxycarbonyl, Ms = methanesulfonyl, Fmoc = 9-fluorenylmethoxycarbonyl, *m*CPBA = *m*-chloroperbenzoic acid, Bn = benzyl.

On the basis of a careful inspection of the structures of the congeners of (+)-haplophytine (**1**) isolated from the same plant,[2] including cimiciduphytine (**3**),[2h] (−)-cimiciphytine

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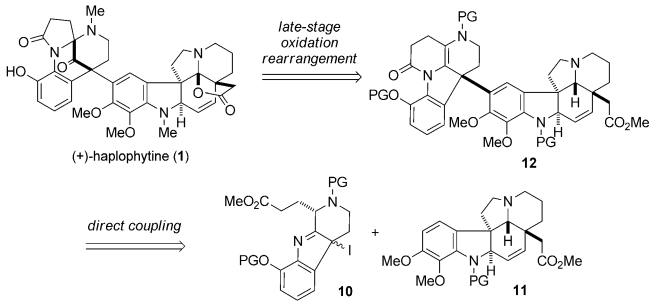
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201609285.

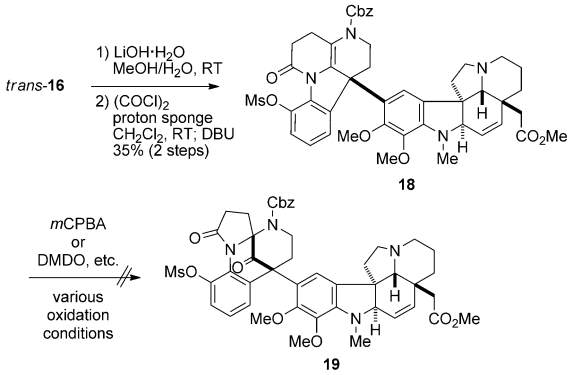
(**4**), and (−)-norcimiciphytine (**5**),[2g] we hypothesized that **1** could be biosynthesized via related intermediates through oxidation and subsequent skeletal rearrangement, as shown in Scheme 2a. With this proposed biosynthesis in mind, we designed a convergent route to **1** through the direct coupling of advanced precursors of the left and the right segments and a late-stage oxidation and rearrangement cascade (Scheme 3). Thus, the coupling of **10** and **11**[6a] should give the fully elaborated compound **12** after formation of the lactam ring, and **12** could be readily converted into haplophytine (**1**) through the challenging late-stage chemoselective oxidation of the 1,2-diaminoethene moiety and a semipinacol-type rearrangement.



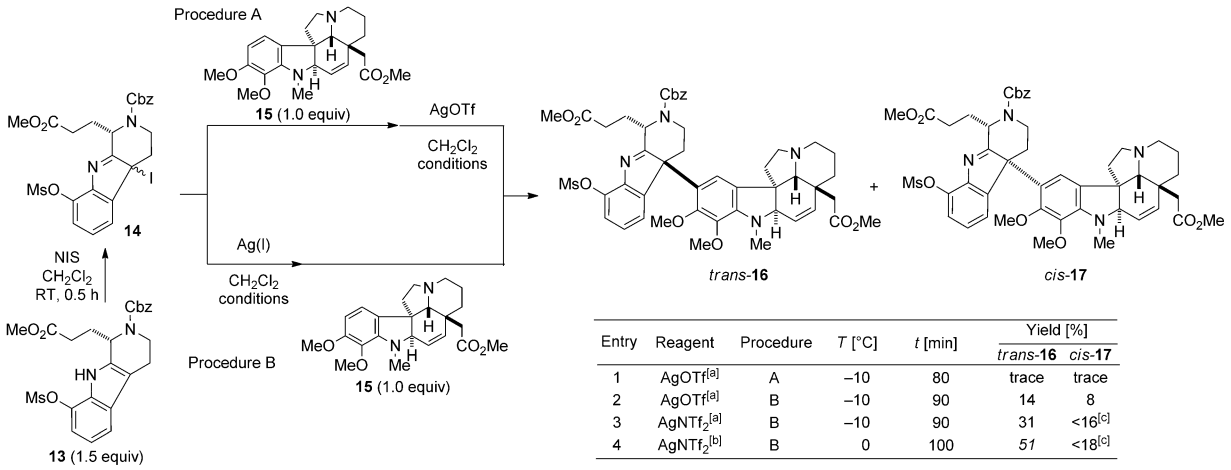
Scheme 3. Retrosynthesis of **1** featuring a late-stage oxidation/rearrangement cascade and direct coupling of the two segments. PG = protecting group.

At the outset, the direct coupling of the left and right segments was investigated by the use of tetrahydro-β-carboline **13**[6a] and the aspidosperma segment **15**[5h] as the substrates (Scheme 4). Thus, after the conversion of **13** into the corresponding iodoindolenine **14**, a silver-mediated Friedel–Crafts alkylation with the right aspidosperma segment **15** was examined by modification of the previously established conditions.[6a] First, AgOTf was added to a mixture of iodoindolenine **14** and indoline **15** at −10 °C (procedure A, entry 1). However, the reaction resulted in the recovery of the β-carboline derivative **13**, and the desired coupling product *trans*-**16** was not obtained at all. After extensive investigation, we found that the order of mixing of the substrates was crucial for successful coupling. Thus, iodoindolenine **14** was initially treated with AgOTf at −10 °C, and then **15** was added to the reaction mixture (procedure B) to provide the coupling product *trans*-**16** in 14% yield along with *cis*-**17** (entry 2). We also observed that the choice of the silver salt was important for reproducibility and a high-yielding reaction. Extensive studies with various silver salts revealed that $AgNTf_2$[7] significantly improved the reaction, and the reaction in CH_2Cl_2 at 0 °C furnished the desired coupling product in approximately 69% combined yield (*trans*-**16**/*cis*-**17** 2.8:1), whereas $AgBF_4$, $AgPF_6$, and $AgSbF_6$ gave only a trace amount of **16**.

We then converted the coupling product **16** into lactam **18** and examined the late-stage oxidative skeletal rearrangement to construct the characteristic diazabicyclo[3.3.1]nonane skeleton (Scheme 5). After chromatographic separation of



Scheme 5. Attempted oxidative skeletal rearrangement of the fully elaborated 1,2-diaminoethene **18**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMDO = dimethyldioxirane.

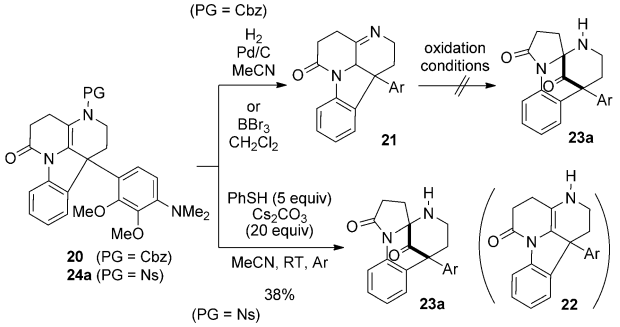


Entry	Reagent	Procedure	*T* [°C]	*t* [min]	Yield [%]	
					trans-**16**	*cis*-**17**
1	$AgOTf^{[a]}$	A	−10	80	trace	trace
2	$AgOTf^{[a]}$	B	−10	90	14	8
3	$AgNTf_2^{[a]}$	B	−10	90	31	<16[c]
4	$AgNTf_2^{[b]}$	B	0	100	*51*	<18[c]

Scheme 4. Direct coupling of the two segments by $AgNTf_2$-mediated Friedel–Crafts alkylation. [a] The reaction was carried out with 2 equivalents of the silver salt relative to **14**. [b] The reaction was carried out with 1.5 equivalents of the silver salt relative to **14**. [c] Including a small amount of an inseparable side product. NIS = *N*-iodosuccinimide, Tf = trifluoromethanesulfonyl.

trans-**16**, saponification of the sterically less hindered methyl ester and lactamization via the acid chloride provided **18**. To our disappointment, however, all oxidative conditions tested generated a complex mixture instead of the expected oxidative rearrangement product **19**, possibly as result of the undesired oxidation of sensitive functional groups, such as the tertiary amines, the electron-rich aromatic ring, and the alkene.

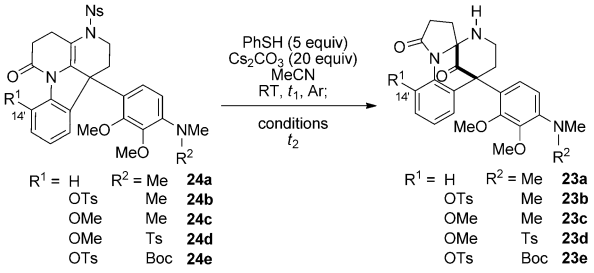
In order to realize the formidable chemoselective oxidation of the fully elaborated dimeric substrate, which has several oxidation-sensitive functionalities, we tried to enhance the reactivity of the 1,2-diaminoethene moiety by removing the Cbz protecting group. We examined this idea by using a model substrate (Scheme 6). First, the Cbz group of **20**[8] was cleaved by hydrogenolysis or treatment with BBr_3. However, hydrogenolysis provided imine **21** instead of the corresponding 1,2-diaminoethene **22**. The expected oxidation of imine **21** under various conditions did not proceed at all. We next tested the Ns-protected substrate **24a**.[4d] Surprisingly, upon removal of the Ns group of **24a** under the standard conditions with a combination of thiophenol and cesium carbonate,[9] the diazabicyclo[3.3.1]nonane product **23a** was obtained in 38% yield along with a trace amount of imine **21**, thus indicating that oxidation followed by skeletal rearrangement somehow proceeded after removal of the Ns group.



Scheme 6. Oxidation after cleavage of the protecting group on the nitrogen. Ns = 2-nitrobenzenesulfonyl.

This unexpected result prompted us to optimize the reaction conditions as well as the structure of the substrate (Table 1). Initially, the argon atmosphere was replaced with oxygen after the removal of the Ns group; however, the yield of **23a** decreased to 19% (Table 1, entry 2).[10] Conversely, the yield of **23a** was improved to 46% upon the replacement of the argon atmosphere with air (entry 3). We observed substantial effects of substituents on the two benzene rings. The reaction of substrate **24c** bearing an electron-donating methoxy group at the C14′ position provided the desired product **23c** in higher yield (50%) than that observed with the tosyloxy substrate **24b** (Table 1, entries 4 and 5). These results can be explained by the influence of the C14′ substituents on the electron density of the 1,2-diaminoethene moiety. We discovered that the substituent on the aniline nitrogen atom was also important. Substrate **24d**, which has a tosyl group instead of one of the two methyl groups on the nitrogen atom, provided the product **23d** in higher yield (73%, entry 6)

Table 1: Optimization of the cascade reaction.



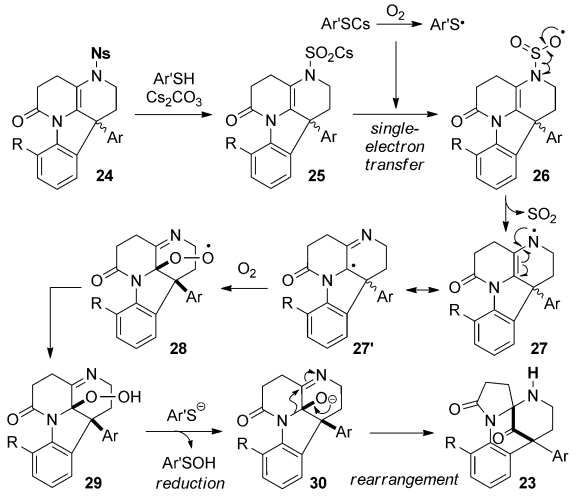
Entry	Substrate	R^1	R^2	Atmosphere	t_1 [h]	t_2 [h]	Yield[a] [%]
1	**24a**	H	Me	Ar	6		38
2	**24a**	H	Me	O_2	0.5	23.5	19
3	**24a**	H	Me	air	0.5	23.5	46
4	**24b**	OTs	Me	air	2.0	22.0	25
5	**24c**	OMe	Me	air	1.5	22.5	50
6	**24d**	OMe	Ts	air	1.5	22.5	73
7	**24e**	OTs	Boc	air	0.5	23.5	57

[a] Yield of the isolated product. Boc = *tert*-butoxycarbonyl, Ts = *p*-toluenesulfonyl.

possibly owing to suppression of the undesired oxidation of the electron-rich benzene ring. Finally, the synthetically more useful substrate **24e** bearing readily removable TsO and Boc groups gave the product in acceptable yield (Table 1, entry 7).

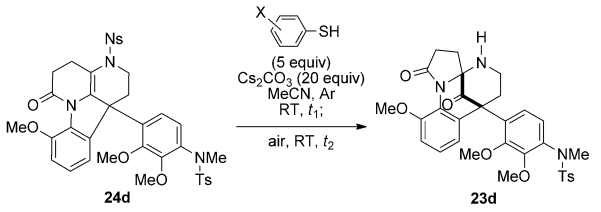
We propose that this cascade reaction is initiated by nucleophilic addition of a thiolate anion to the Ns group to give the amidosulfurous acid anion **25** via a Meisenheimer complex (Scheme 7).[9] At this point, **25** would be oxidized in a single-electron-transfer (SET) process to a thiyl radical generated from the thiolate anion through aerobic oxidation[11] to afford the radical species **26**. Extrusion of SO_2 should provide the aminyl radical **27**, which would be trapped by molecular oxygen. Then, hydroperoxide **29** would be reduced by the thiolate anion,[12] and subsequent semipinacol-type rearrangement should furnish **23**, which has a diazabicyclo[3.3.1]nonane skeleton.

Considering the possibility that the thiolate anion and/or thiyl radical species participate in the oxidation/reduction



Scheme 7. Plausible mechanism of the cascade reaction.

Table 2: Effect of thiophenol substituents on the cascade reaction.



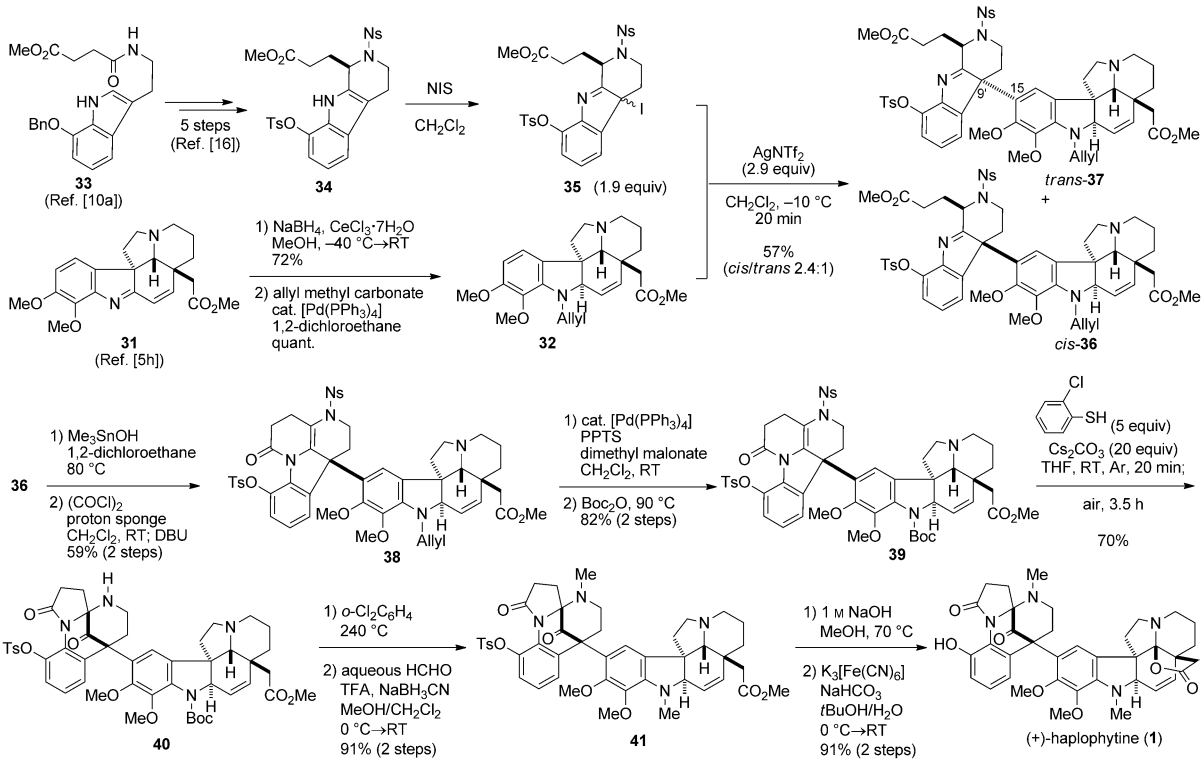
Entry	X	t_1 [h]	t_2 [h]	Yield[a] [%]
1	H	1.5	22.5	73
2	4-MeO	0.5	23.5	41
3	4-Cl	0.25	23.75	70
4	3-Cl	0.5	23.5	70
5	2-Cl	2.0	22.0	89

[a] Yield of the isolated product.

process,[13] we tested various thiophenols for the oxidation/rearrangement process (Table 2) and observed substantial substituent effects. Thus, 4-methoxythiophenol accelerated the removal of the Ns group; however, the oxidation/rearrangement step was considerably slower, which led to a decrease in the yield of **23d** (Table 2, entry 1 versus 2). Conversely, acceleration of the oxidation/rearrangement step was observed with 4-, 3-, and 2-chlorothiophenol (entry 1 versus 3–5). 2-Chlorothiophenol gave the desired product **23d** in the highest yield (89%). These results suggested that thiophenol, which has a higher redox potential,[14] accelerated the oxidation process.

Having successfully established a one-pot aerobic oxidation/skeletal rearrangement cascade for the formation of the diazabicyclo[3.3.1]nonane skeleton, we prepared the fully elaborated dimeric substrate protected with a Ns group and examined the feasibility of the cascade process (Scheme 8). The aspidosperma compound **31**[5h] was reduced under Luche conditions[15] to give a secondary amine, which was allylated to give **32**. Iodoindolenine **35**, the precursor of the left segment, was readily prepared from indole **33**[6a] by conversion into optically active tetrahydro-β-carboline **34**[16] and treatment with NIS. As expected, the direct coupling of **32** and **35** under the $AgNTf_2$-mediated Friedel–Crafts alkylation conditions proceeded quite smoothly to furnish the dimeric compounds *cis*-**36** and *trans*-**37** (ca. 2.4:1) in 57% combined yield. Notably, in contrast to the Cbz-protected substrate **14**, the Ns-protected substrate **35** preferentially provided *cis*-**36**.[17] After the separation of *cis*-**36**, the lactam ring was formed by selective hydrolysis with Me_3SnOH[18] and lactamization. For the problematic deallylation of **38**, we devised novel conditions involving the use of $[Pd(PPh_3)_4]$ in the presence of PPTS and dimethyl malonate. Finally, the secondary amine was protected with a Boc group to give **39**, ready for the key one-pot aerobic oxidation/skeletal rearrangement cascade. Gratifyingly, the expected cascade reaction proceeded smoothly to give the desired diazabicyclo-[3.3.1]nonane **40** with the oxidant-sensitive groups untouched.[19]

The total synthesis of (+)-haplophytine (**1**) was completed by the endgame sequence without event. Thus, after removal of the Boc group under thermal conditions, reductive methylation of the two secondary amino groups provided **41**. Finally, one-pot removal of the tosyl group, saponification of the methyl ester, and oxidative formation of the lactone ring[5a] afforded (+)-haplophytine (**1**).[20]



Scheme 8. Bioinspired total synthesis of (+)-haplophytine (**1**). PPTS = pyridinium *p*-toluenesulfonate, TFA = trifluoroacetic acid.

In summary, we have completed the total synthesis of the dimeric indole alkaloid (+)-haplophytine (**1**) on the basis of a convergent strategy inspired by the presumed biosynthetic pathway. Our convergent route relies on two key reactions: 1) the highly effective $AgNTf_2$-mediated direct coupling of two polycyclic indole segments, and 2) a highly chemoselective late-stage aerobic oxidation/rearrangement cascade of the fully elaborated dimeric compound.

Acknowledgments

This research was supported by JSPS KAKENHI Grants JP16H01127 in Middle Molecular Strategy, JP16H00999 in Precisely Designed Catalysts with Customized Scaffolding, and JP10J06322, Grants-in-Aid for Scientific Research (A) (26253001) and Young Scientists (B) (26860004), the Emergency Fund of Astellas Foundation for Research on Metabolic Disorders, a Banyu Foundation Research Grant, the Shorai Foundation for Science and Technology, the Platform Project for Supporting in Drug Discovery and Life Science Research(Platform for Drug Discovery, Informatics, and Structural Life Science)from the MEXT and AMED. We thank Professor Tohru Fukuyama (Nagoya University) for valuable discussions.

Keywords: alkaloids · Friedel–Crafts reaction · oxidation · rearrangement · total synthesis

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[8] For the preparation of **20**, see the Supporting Information.

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[12] In contrast to results reported by Fukuyama and co-workers (Ref. [13b]), an additional reductant was not required, thus indicating that a thiol could function as a reductant of the peroxide intermediate.

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[16] For a preparation of **34**, see: Supporting Information.

[17] The stereoselectivity of this coupling reaction may be controlled by the steric repulsion between indoline **32** and the Ns group, whose aromatic ring covered the α-face of the substrate.

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[19] A substrate bearing a methoxy group at the C14′ position provided the corresponding product in 90% yield (for the preparation of the substrate and the key reaction, see the Supporting Information). However, the preparation of this substrate required deprotection, methylation, and demethylation reactions at the C14′ position, which decreased the efficiency of the total synthesis.

[20] The efficiency of the total synthesis (33 step longest linear sequence in 0.59% overall yield) is higher than that of our previous synthesis (29 step longest linear sequence in 0.11% overall yield). Notably, the efficiency of this synthesis after the coupling reaction is much higher (11.2% yield over 10 steps) than that of the previous synthesis (0.79% yield over 16 steps).

Received: September 22, 2016
Published online: ■■ ■■, ■■■■

Communications

Natural Products Synthesis

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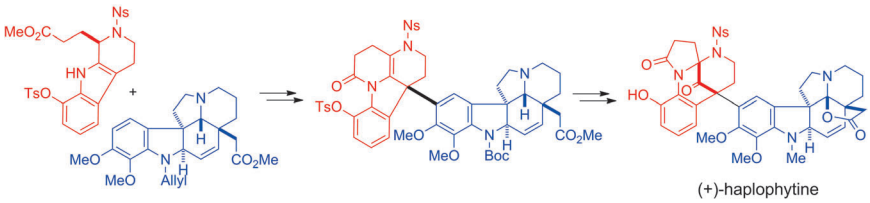
Bioinspired Total Synthesis of the Dimeric Indole Alkaloid (+)-Haplophytine by Direct Coupling and Late-Stage Oxidative Rearrangement



Direct and to the point: In a bioinspired convergent total synthesis of the dimeric indole alkaloid (+)-haplophytine, the two segments were coupled directly in a Friedel–Crafts reaction mediated by $AgNTf_2$. Another key step was the construction of the diazabicyclo[3.3.1]nonane skeleton by a highly chemoselective late-stage aerobic oxidation/skeletal rearrangement cascade (see scheme).

