## Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

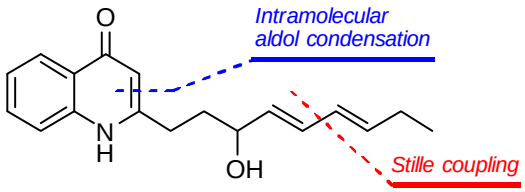
**First total synthesis of haplacutine C**

Leave this area blank for abstract info.

Noriki Kutsumura,[a,b,*] Keisuke Numata,[b] and Takao Saito[b,*]

[a]*International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, 1-1-1 Tennnodai, Tsukuba, Ibaraki 305-8575, Japan*

[b]*Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan*




Haplacutine C

Tetrahedron Letters
journal homepage: www.elsevier.com

# First total synthesis of haplacutine C

Noriki Kutsumura[a,b,*], Keisuke Numata[b] and Takao Saito[b,*]

[a] *International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan*
[b] *Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan*

ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
Total synthesis
Haplacutine C
Natural product
Quinolinone alkaloid
Stille coupling

ABSTRACT

A total synthesis of haplacutine C has been achieved. The synthetic key features were the intramolecular aldol condensation for construction of the 4-quinolinone skeleton and the Stille coupling for elongation of the dienol side chain. In addition, the 4-*O*-protected-quinolines were also utilized as the synthetic equivalents of 4-quinolinone at the stage of side chain transformation.



In 2009, Staerk et al. identified the novel quinolinone alkaloids haplacutines A–F (Figure 1)[1] together with several known related compounds from a crude extract of *Haplophyllum acutifolium* by their original method, viz., direct hyphenation of analytical-scale high-performance liquid chromatography, photo-diode array detection, mass spectrometry, solid-phase extraction and nuclear magnetic resonance spectroscopy (HPLC–PDA–MS–SPE–NMR). *H. actifolium* is distributed from the Mediterranean parts of Europe and Africa to Eastern parts of Siberia, and in general, known as a rich source of quinolinone alkaloids. The extracts are widely used in traditional medicine because of their estrogenic, antifungal, antibacterial, and antiparasitic activity.[2] In fact, the extract including the haplacutines also showed antiplasmodial activity with $IC_{50}$ < 12 μg/mL *in vitro* (chloroquine-sensitive *Plasmodium falciparum* 3D7 strain).[1] We therefore initiated the synthesis of the series of haplacutines A–F, with the exception of the isolated haplacutine E, because of our interest in the bioactivity of each of the quinolinone alkaloids. We describe herein the synthesis of haplacutine C (**1**) (Figure 1).

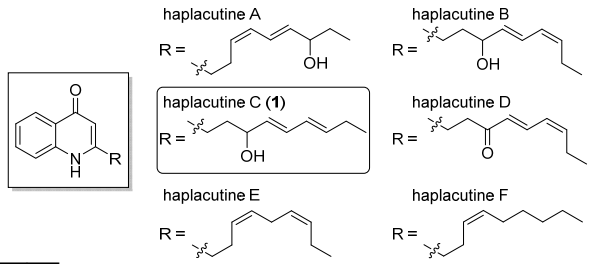
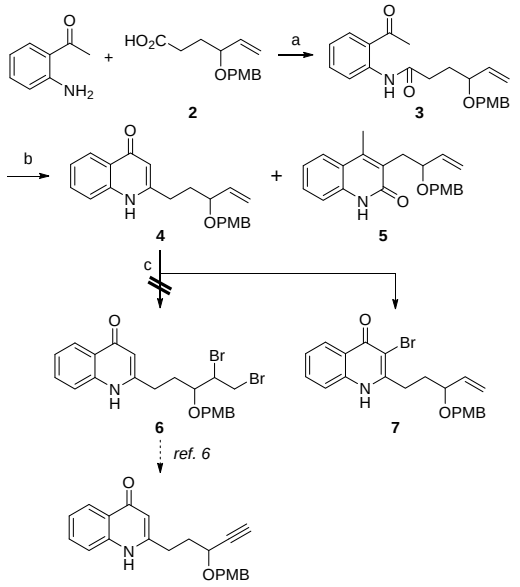



**Figure 1.** Structure of haplacutines A–F from *H. acutifolium*.

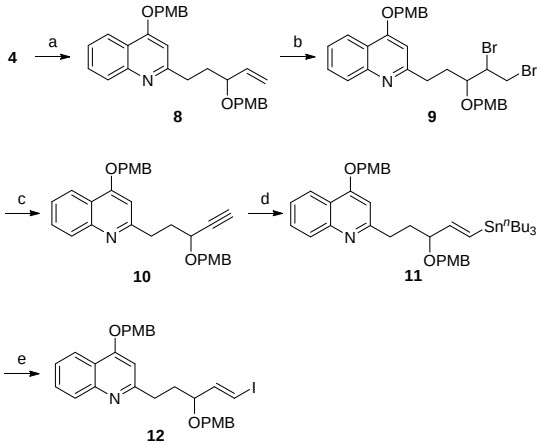
First, we prepared the aldol cyclization precursor **3** by amidation of 2'-aminoacetophenone with the known carboxylic acid (±)-**2**[3] using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI•HCl) (Scheme 1). Then, the intramolecular aldol condensation of **3** in the presence of *t*-BuOK[4] under optimized conditions[5] gave the desired 4-quinolinone derivative **4** in 66% yield together with the undesired 2-quinolinone derivative **5** in 30% yield. After separation of both isomers by column chromatography on silica gel, we attempted a bromine addition of the terminal double bond of the side-chain in **4** to transform a prerequisite terminal triple bond at the following step by utilizing the method of double HBr-elimination.[6] Unfortunately, this approach under any conditions was unsuccessful, resulting in the formation of an undesired 3-bromo-4-quinolinone derivative **7** in quantitative yield.

* Corresponding author. Tel./fax: +81-29-853-6568; e-mail: kutsumura.noriki.gn@u.tsukuba.ac.jp (N. K.), tsaito@rs.kagu.tus.ac.jp (T. S.)



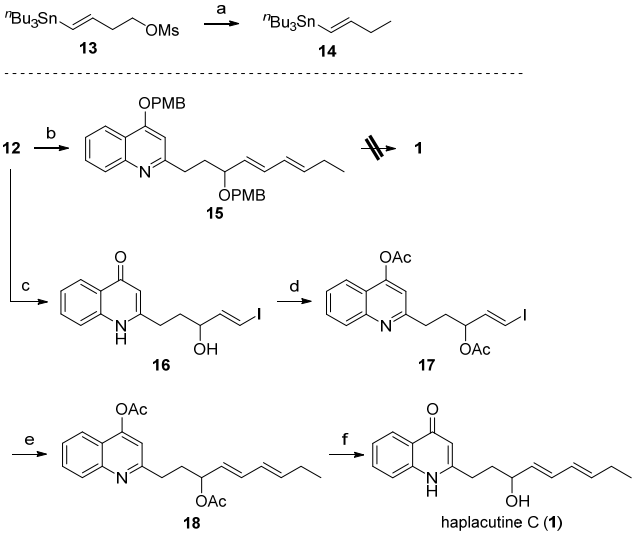
**Scheme 1.** Reagents and conditions: (a) EDCI•HCl (2.0 equiv), *N*,*N*-dimethyl-4-aminopyridine (2.0 equiv), $CH_2Cl_2$, rt, 5.0 d (65%); (b) *t*-BuOK (3.0 equiv), toluene, reflux, 8 h (**4**: 66%, **5**: 30%); (c) Pyr.-$HBr_3$ (1.1 equiv), DMF, rt, 30 min (100%).

After we had converted the 4-quinolinone derivative **4** into the 4-(4-methoxybenzyloxy)quinoline **8** to avoid the generation of the undesired **7**, the alkene **8** was successfully transformed into the desired alkyne **10** by way of the double HBr-elimination from vicinal dibromide **9** (Scheme 2).[6] Hydrostannation of **10** using 2 mol% of $Pd_2(dba)_3$ with 8 mol% of *t*-$Bu_3P$ gave (*E*)-1-tributylstannyl-1-alkene **11** with high regioselectivity (>95/5).[7] Finally, the important intermediate (*E*)-alkenyl iodide **12** was obtained in quantitative yield from **11**.[8]



**Scheme 2.** Reagents and conditions: (a) NaH (2.0 equiv), PMBCl (1.0 equiv), DMF, rt, 12 h (93%); (b) Pyr.-$HBr_3$ (1.1 equiv), $CH_2Cl_2$, rt, 2 h (84%); (c) tetrabutylammonium hydroxide (10% in MeOH, 5.0 equiv), molecular sieves 13X (10 times the mass of **9**), DMSO, 60 °C, 2 h (92%); (d) *n*-$Bu_3SnH$ (1.5 equiv), $Pd_2(dba)_3$ (2 mol%), *t*-$Bu_3P$ (8 mol%), toluene, rt, 30 min (80%); (e) $I_2$ (1.1 equiv), $CH_2Cl_2$, rt, 30 min (97%).

At the final synthetic stage, we first prepared (*E*)-but-1-enyltributylstannane (**14**)[9] from the known **13**,[10] then attempted the Stille coupling of **12** with **14**, followed by the deprotection of both PMB groups to achieve the first synthesis of **1** (Scheme 3). However, the expected PMB-deprotection step of the coupling product **15** gave complex mixtures under any reaction conditions (TFA[11], CAN, 1 M HCl aq., or DDQ), though the carbon elongation proceeded smoothly. This outcome is probably because of the rapid decomposition of the diene moiety of **15** under the PMB cleavage conditions. Therefore, the PMB groups of **12** were replaced with acetyl groups by TFA hydrolysis[11] and subsequent acetylation. Finally, the Stille coupling[12] of **17** with **14** gave diene **18** with high stereoselectivity (*E*-form, >99/1) albeit in moderate yield, and then the deprotection of both acetyl groups under mild basic condition succeeded to give haplacutine C (**1**) in quantitative yield, which was identical spectroscopically to that reported by Staerk et al.[1,13]



**Scheme 3.** Reagents and conditions: (a) $LiAlH_4$ (2.5 equiv), THF, rt, 2 h (98%); (b) **14** (3.0 equiv), $PdCl_2(PPh_3)_2$ (10 mol%), DMF, 55 °C, 5.5 h (53%); (c) TFA–$CH_2Cl_2$, rt, 1 h (99%); (d) *t*-BuOK (2.1 equiv), AcCl (5.0 equiv), $Et_3N$ (6.0 equiv), THF, rt, 1 h (84%); (e) **14** (3.0 equiv), $Pd(CH_3CN)_2Cl_2$ (30 mol%), DMF, rt, 2 h (61%); (f) $K_2CO_3$ (4.0 equiv), MeOH, rt, 1.5 h (99%).

In conclusion, we achieved the total synthesis of haplacutine C (**1**) for the first time, by a method that ensured the structure **1**, which was proposed previously.[1] In our synthesis, the intramolecular aldol condensation was used for the formation of 4-quinolinone skeleton and the Stille coupling was used for the carbon side-chain elongation. This synthetic method can be utilized for other haplacutines and related compounds. Further investigation is in progress.

## Acknowledgments

This work was partly supported by the Sasakawa Scientific Research Grant from the Japan Science Society and the Tokyo Ohka Foundation for The Promotion of Science and Technology.

## References and notes

1. Staerk, D.; Kesting, J. R.; Sairafianpour, M.; Witt, M.; Asili, J.; Emami, S. A.; Jaroszewski, J. W. *Phytochemistry* **2009**, *70*, 1055–1061.
2. Nazrullaev, S. S.; Bessonova, I. A.; Akhmedkhodzhaeva, Kh. S. *Chem. Nat. Compd.* **2001**, *37*, 551–555.
3. (a) Jana, N.; Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2622–2628; (b) Giri, A. G.; Mondal, M. A.; Puranik, V. G.; Ramana, C. V. *Org. Biomol. Chem.* **2010**, *8*, 398–406; (c) Wadavrao, S. B.; Ghogare, R. S.; Narsaiah, A. V. *Synthesis* **2015**, *47*, 2129–2137.
4. (a) Hadjeri, M.; Mariotte, A.-M.; Boumendjel, A. *Chem. Pharm. Bull.* **2001**, *49*, 1352–1355; (b) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968–7973; (c) Marques, E. F.; Bueno, M. A.; Duarte, P. D.; Silva, L. R. S. P.; Martinelli, A.

M.; dos Santos, C. Y.; Severino, R. P.; Brömme, D.; Vieira, P. C.; Corrêa, A. G. *Eur. J. Med. Chem.* **2012**, *54*, 10–21.
5. For example, NaOH-promoted cyclization in 1,4-dioxane (see ref. 4b) gave 38% of **4** and 55% of **5**.
6. (a) Kutsumura, N.; Kubokawa, K.; Saito, T. *Synlett* **2010**, 2717–2720; (b) Kutsumura, N.; Kubokawa, K.; Saito, T. *Synthesis* **2011**, 2377–2382; (c) Kutsumura, N.; Inagaki, M.; Kiriseko, A.; Saito, T. *Synthesis* **2015**, *47*, 1844–1850.
7. Darwish, A.; Lang, A.; Kim, T.; Chong, J. M. *Org. Lett.* **2008**, *10*, 861–864.
8. Matsuda, M.; Yamazaki, T.; Fuhshuku, K.; Sugai, T. *Tetrahedron* **2007**, *63*, 8752–8760.
9. (a) Jackson, S. K.; Banfield, S. C.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 1215–1218; (b) Kusakabe, T.; Kawai, Y.; Kato, K. *Org. Lett.* **2013**, *15*, 5102–5105; (c) Chandrasoma, N.; Brown, N.; Brassfield, A.; Nerurkar, A.; Suarez, S.; Buszek, K. R. *Tetrahedron Lett.* **2013**, *54*, 913–917.
10. Cerri, A.; Almirante, N.; Barassi, P.; Benicchio, A.; Fedrizzi, G.; Ferrari, P.; Micheletti, R.; Quadri, L.; Ragg, E.; Rossi, R.; Santagostino, M.; Schiavone, A.; Serra, F.; Zappavigna, M. P.; Melloni, P. *J. Med. Chem.* **2000**, *43*, 2332–2349.
11. Farhanullah, Kim, S. Y.; Yoon, E.-J.; Choi, E.-C.; Kim, S.; Kang, T.; Samrin, F.; Puri, S.; Lee, J. *Bioorg. Med. Chem.* **2006**, *14*, 7154–7159.
12. (a) Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508–524; (b) Paquette, L. A.; Barriault, L.; Pissarnitski, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2000**, *122*, 619–631; (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.
13. Synthetic sample's spectroscopic data: IR (neat) 3378, 3278, 2962, 2923, 2854, 1735, 1635, 1596, 1511 $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CD_3CN$) δ = 0.98 (t, *J* = 7.5 Hz, 3H), 1.87 (m, 2H), 2.08 (m, 2H), 2.68 (m, 2H), 3.25 (br s, 1H), 4.11 (m, 1H), 5.60 (dd, *J* = 15.1, 6.6 Hz, 1H), 5.73 (dt, *J* = 15.1, 6.6 Hz, 1H), 5.98 (s, 1H), 6.03 (dd, *J* = 15.1, 10.6 Hz, 1H), 6.18 (dd, *J* = 15.1, 10.6 Hz, 1H), 7.28 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.59 (dd, *J* = 8.4, 7.4 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 9.94 (br s, 1H); $^{13}C$ NMR (150 MHz, $CD_3CN$) δ = 13.8 ($CH_3$), 26.3 ($CH_2$), 30.8 ($CH_2$), 36.8 ($CH_2$), 71.6 (CH), 108.9 (CH), 118.6 (CH), 124.0 (CH), 125.9 (C), 126.0 (CH), 129.7 (CH), 131.3 (CH), 132.6 (CH) 134.8 (CH), 137.3 (CH), 141.3 (C), 154.8 (C), 178.9 (C); HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{18}H_{21}NO_2Na$, 306.1465, found: 306.1463.