HETEROCYCLES, Vol. 99, No. 1, 2019, pp. 614 - 624. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 17th May, 2018, Accepted, 28th May, 2018, Published online, 4th June, 2018
DOI: 10.3987/COM-18-S(F)7

TOTAL SYNTHESIS OF HAPLACUTINES B AND C

Noriki Kutsumura,[1,2]* Keisuke Numata,[2] Shiho Mosaki,[2] and Takao Saito[2]*

[1] International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan. [2] Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan.
E-mail: kutsumura.noriki.gn@u.tsukuba.ac.jp, tsaito@rs.kagu.tus.ac.jp

Abstract – The total synthesis of 4-quinolone alkaloids, haplacutines B and C, has been achieved. The synthetic highlights are chemoselective construction of a 2-alkyl-4-quinolone skeleton *via* intramolecular base-promoted cyclocondensation of *ortho*-alkylamidoacetophenone and stereoselective elongation of the dienol side chain *via* the Stille coupling.

Haplacutines A (**1**)–F (**6**) are 4-quinolone alkaloids which were isolated from a crude ethyl acetate extract of the aerial parts of *Haplophyllum acutifolium* collected at a location 40 km west of Mashhad, Iran (Figure 1).[1] In general, *Haplophyllum* species are distributed from the Mediterranean region of Europe and Africa to the Eastern parts of Siberia. The extracts containing these compounds are often used as traditional medicines as analgesics, antispasmodics, diuretics, sedatives, and topical agents against skin diseases, in some areas.[1,2] Haplacutine E (**5**) and the known 4-quinolone alkaloid acutine (**7**),[2,3] which has identified from the same extract along with the other haplacutines, showed moderate anti-plasmodium activity with IC_{50} values of 2.17 ± 0.22 μM and 3.79 ± 0.24 μM, respectively,[1] although no significant biological activity of the other haplacutines has been reported so far.

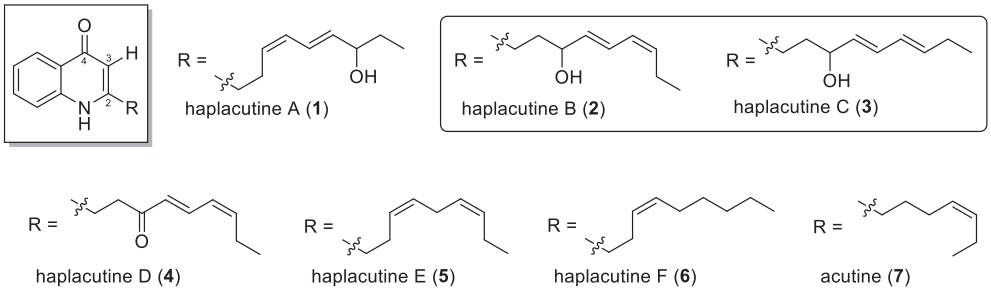


Figure 1. Structures of haplacutines A (**1**)–F (**6**) and acutine (**7**)

Therefore, we began a synthetic study of haplacutines to identify the structures proposed by Staerk *et al.*[1] and to supply sufficient quantities of synthetic haplacutines for biological activity tests. In this paper, we disclose the first total synthesis of haplacutines B (**2**) and C (**3**)[4] in detail.

Haplacutines **1**–**7** have the common structure of a 4-quinolone framework with an unsaturated alkyl side chain (R) at the 2-position and a hydrogen at the 3-position (Figure 1). We planned a simple and conventional synthetic method: (i) construction of a 2-substituted 4-quinolone framework, followed by (ii) transformation of the side chain at the 2-position. First, we prepared a 4-quinolone segment from substituted *ortho*-amidoacetophenones *via* cyclocondensation (Figure 2). Surprisingly, however, there are very few successful methods for synthesis of 4-quinolones bearing an alkyl group (CH_2R') at the 2-position, particularly *via* classical cyclocondensation reactions,[5,6] although there have been many examples of synthesis of 2-aryl-4-quinolones under similar conditions.[5] The substrates with two accessible carbonyl-α-protons could lead to the formation of a mixture of 2- and 4-quinolones (Figure 2). Thus, we undertook the challenge to search for selective, base-promoted cyclocondensation reaction for construction of 2-alkyl-4-quinolones **9** from *ortho*-alkylamidoacetophenone **8** toward the total synthesis of haplacutines B (**2**) and C (**3**) (Table 1). First, the reaction of **8** under the conditions of using three equivalents of sodium hydroxide in 1,4-dioxane reported by Buchwald *et al*.[5c] was attempted which provided desired 4-quinolone **9** (38%) and undesired 2-quinolone **10** (55%) (Table 1, entry 1). Change of the solvent significantly decreased the yields (10–16%) of the 4-quinolone **9** (entries 2–5), except for toluene (49%) (entry 6). Then, we examined the reactions using other bases in toluene (entries 7–11). Although no reaction occurred with amine bases in toluene (entries 7–10), potassium *tert*-butoxide gave the best results to afford 4-quinolone **9** in 66% yield together with 2-quinolone **10** in 30% yield (entry 11).[4] Interestingly, the reaction with lithium diisopropylamide (LDA) in THF proceeded slower than expected to afford 4-quinolone **9** (31%) as the sole product (entry 12). In contrast, the reaction with sodium hydroxide in *tert*-butyl alcohol under microwave (MW) irradiation gave 2-quinolone **10** (66%) as the sole product along with recovered **8** (33%) (entry 13).

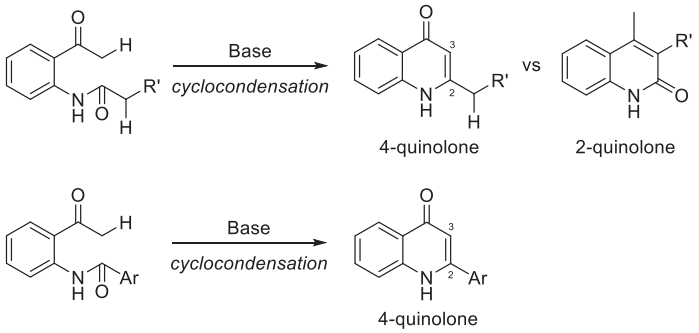
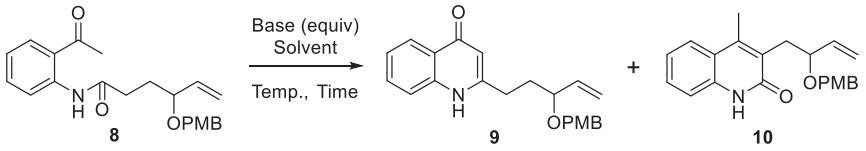


Figure 2. Base-promoted cyclocondensation to 2-substituted-4-quinolones

Table 1. Base-promoted cyclocondensation of **8** to produce 4-quinolone **9**

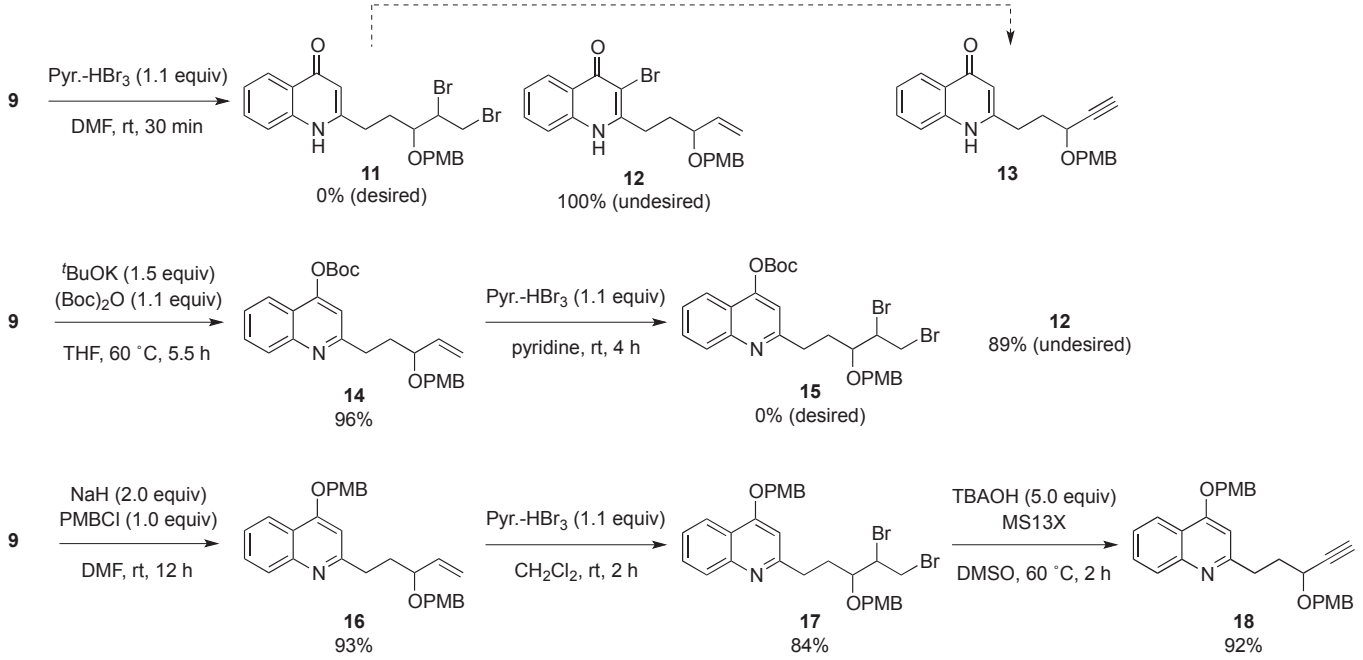


8 9 10

Entry	Base (equiv)	Solvent	Temp. (°C)	Time (h)	Yield (%)		
					9	**10**	**8** (recov.)
1	NaOH (3)	1,4-dioxane	reflux	3	38	55	0
2	NaOH (3)	DMF	80	8	10	67	5
3	NaOH (3)	DMSO	80	8	16	64	5
4	NaOH (3)	^{t}BuOH	reflux	2	16	67	0
5	NaOH (3)	$(CH_2Cl)_2$	reflux	14	11	50	39
6	NaOH (3)	toluene	reflux	3	49	46	0
7	^{i}Pr$_2$NEt (3)	toluene	reflux	8		NR	96
8	DBU (3)	toluene	reflux	12		NR	99
9	DABCO (3)	toluene	reflux	12		NR	99
10	$(TMS)_3N$ (3)	toluene	reflux	9		NR	98
11	^{t}BuOK (3)	toluene	reflux	8	66	30	0
12	LDA (3)	THF	rt[a] to reflux	3.5 to 2	31	0	45
13	NaOH (5)	^{t}BuOH	120 (MW[b])	10 min	0	66	33

[a] Room temperature. [b] Under microwave (MW) irradiation.

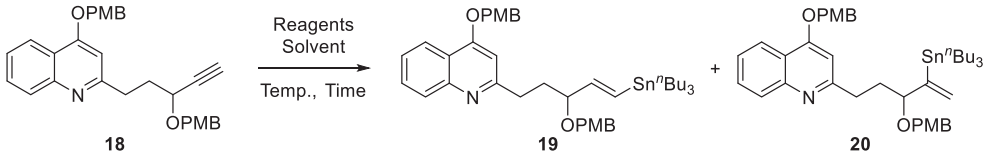
With 4-quinolone **9** in hand, we next elaborated transformation of the side chain in **9** for total synthesis of both haplacutines B (**2**) and C (**3**). Firstly, in order to obtain the intermediate target compound **13** from dibromide **11** *via* double HBr elimination,[7] bromine addition to the terminal double bond in **9** was attempted (Scheme 1). Unfortunately, the reactions of **9** with pyridine hydrobromide perbromide under any conditions[8,9] gave undesired 3-bromo-4-quinolone **12** predominantly, not the desired dibromide **11**. We then transformed 4-quinolone **9** into 4-(*tert*-butoxycarbonyloxy)quinoline **14** (96%) and 4-(4-methoxybenzyloxy)quinoline **16** (93%), respectively. The bromine addition of **16** succeeded without cleavage of the PMB group to afford PMB-protected dibromide **17** in 84% yield, whereas the reaction of **14** afforded not **15** but undesired **12** in 89% yield again with deprotection of the Boc group. Finally, alkynylated 4-quinolone **18** was obtained from **17** in 92% yield utilizing the double HBr-elimination by tetrabutylammonium hydroxide (TBAOH).[7]



Scheme 1. Synthesis of the intermediate **18**

To prepare the Stille coupling substrate, the transformation reaction of the obtained alkyne **18** into (*E*)-1-tributylstannyl-1-alkene **19** was examined (Table 2). The reaction of **18** with tributyltin hydride in the presence of a radical initiator, azobisisobutyronitrile (AIBN) afforded a complex mixture (entry 1). In contrast, all the palladium-catalyzed reactions gave desired stannyl alkene **19** (entries 2–4). Peculiarly, the use of the bulkier ligands such as Cy_3P and $^tBu_3P$ dramatically improved the yield of **19** and the regioselectivity of Pd-catalyzed hydrostannation (entries 3 and 4).[10]

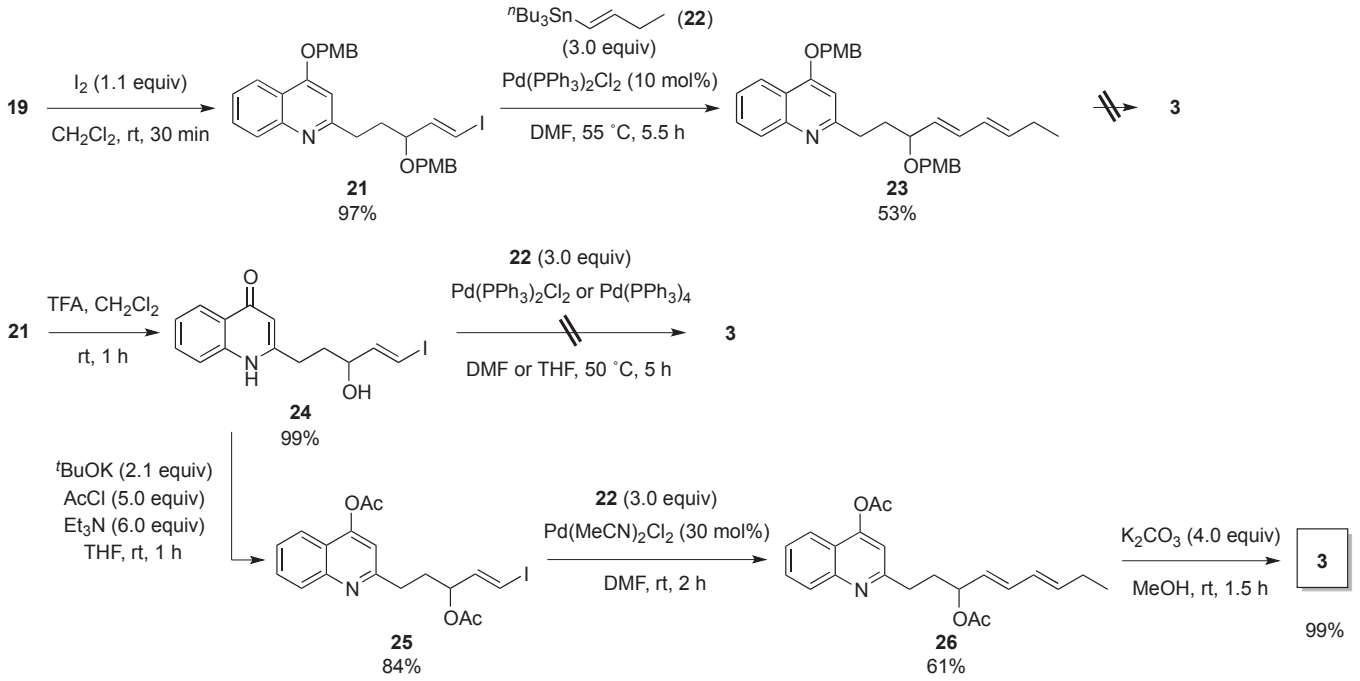
Table 2. Synthesis of the intermediate **19**



Entry	Reagents	Solvent	Temp. (°C)	Time (h)	Yield (%)	
					19	**20**
1	$^nBu_3SnH$ (1.2 equiv), AIBN (4 mol%)	benzene	80	10	Not detected	
2	$^nBu_3SnH$ (1.5 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol%)	THF	rt[a]	3	34	11
3	$^nBu_3SnH$ (1.5 equiv), $Pd_2(dba)_3$ (2 mol%) Cy_3P (4 mol%)	toluene	rt	3	76	8
4	$^nBu_3SnH$ (1.5 equiv), $Pd_2(dba)_3$ (2 mol%) $^tBu_3P$ (8 mol%)	toluene	rt	0.5	80	0

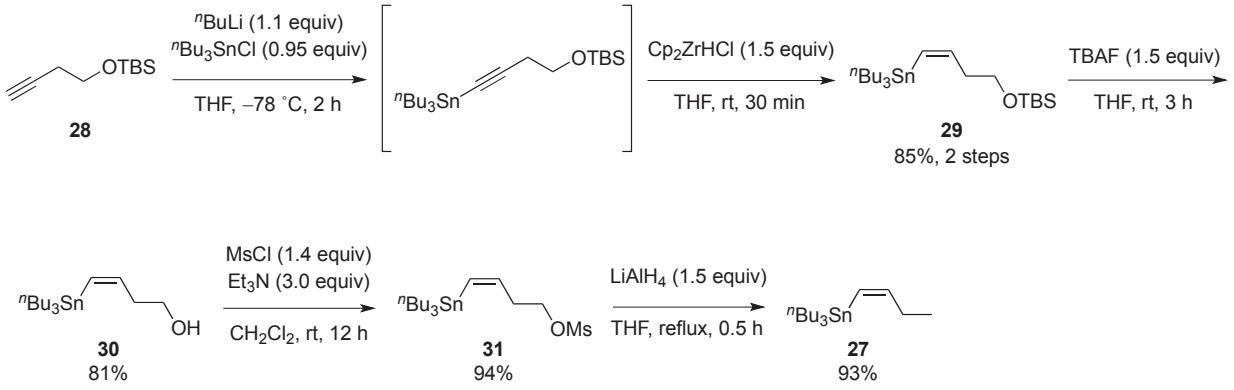
[a] Room temperature.

At the final stage, the (*E*)-stannyl alkene **19** was transformed into the (*E*)-alkenyl iodide **21** in 97% yield (Scheme 2). The Stille coupling between **21** and (*E*)-but-1-enyltributylstannane (**22**)[4] afforded PMB-protected diene **23** in moderate yield (53%) together with a mixture of byproducts including a dimeric (*E*,*Z*)-diene generated from **21**.[11] Disappointingly, any PMB-deprotection method (TFA, CAN, 1 M HCl aq, or DDQ) for (*E*)-**23** that we attempted afforded complex mixtures. This result was probably due to the presence of the conjugated diene moiety. Therefore, the PMB groups in **21** were initially deprotected, and subsequent Stille coupling of the obtained **24** with stannane (*E*)-**22** was attempted. However, all the alternative efforts were unsuccessful. Finally, after the acetylation of **24**, the Stille coupling of Ac-protected (*E*)-alkenyl iodide **25** with (*E*)-**22** and the subsequent deacetylation of **26** produced haplacutine C (**3**) in good yield.[4]



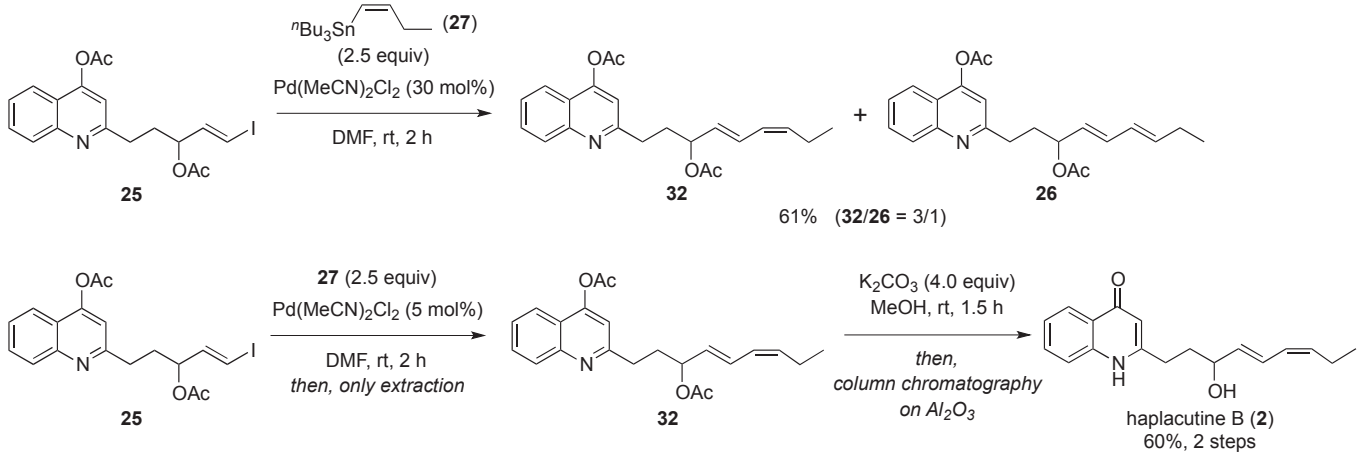
Scheme 2. Total synthesis of haplacutine C (**3**)

Next, for the total synthesis of haplacutine B (**2**), another coupling partner, (*Z*)-but-1-enyltributylstannane (**27**), was prepared in 60% total yield starting from TBS-protected 3-butyn-1-ol (**28**) (Scheme 3). (*Z*)-Vinylstannane **29** was synthesized in 85% yield in two steps from **28** *via* stannylation and the following stereoselective hydrozirconation[12] of the intermediary alkynylstannane.[13] Deprotection of the TBS group in **29** and the following mesylation of the hydroxy group in **30**[14] afforded (*Z*)-vinylstannane **31** in 94% yield. $LiAlH_4$-Reduction of **31** in refluxing toluene gave the desired (*Z*)-**27** in 93% yield with complete retention of the stereochemistry.[15]



Scheme 3. Synthesis of the coupling partner (*Z*)-**27**

At the final stage, the Stille coupling of Ac-protected (*E*)-alkenyl iodide **25** with (*Z*)-**27** under the same coupling reaction conditions as in Scheme 2 (for synthesis of **26**) was attempted, resulting in the formation of a 3:1 mixture of desired (*E*,*Z*)-diene **32** and undesired (*E*,*E*)-diene **26** (Scheme 4). The partial isomerization of **32** to **26** might be caused by the column chromatography purification process on silica gel. Finally, we succeeded in acquiring pure haplacutine B (**2**) as a sole product by use of alumina column chromatography for purification after deacetylation of **32**.[16]



Scheme 4. Total synthesis of haplacutine B (**2**)

In conclusion, we have achieved the total synthesis of haplacutines B and C to ensure the structures which were proposed by *Staerk et al.* using the HPLC-PDA-MS-SPE-NMR method.[1] The 2-alkyl-4-quinolone skeleton was constructed by the intramolecular cyclocondensation of the *ortho*-alkylamidoacetophenone **8** using potassium *tert*-butoxide in refluxing toluene and the dienol side chains were elongated by the Stille coupling reaction with (*E*)-but-1-enyltributylstannane or (*Z*)-but-1-enyltributylstannane. This synthetic method can be utilized for other haplacutines and related compounds. Further investigation is in progress.

EXPERIMENTAL

All melting points (MP) were determined on a Yanaco melting point apparatus and are uncorrected. Infrared spectra were recorded with a Horiba FT-710 model spectrophotometer. ^{1}H and ^{13}C NMR spectral data were obtained with a Bruker Avance 600, a JEOL JNM-LA 500, a JEOL JNM-AL 300, or Bruker BioSpin AV400M instruments. Chemical Shifts are quoted in ppm using tetramethylsilane (TMS, δ = 0 ppm) as the reference for ^{1}H NMR spectroscopy, and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. Mass spectra were measured with a Bruker Daltonics microTOF or a Hitachi double focusing M-80B spectrometer. Column chromatography was carried out on silica gel (Kanto Chemical Co. or Merck Co. Ltd) or on aluminium oxide 90 active neutral (Merck KGaA). The synthetic procedures and their analytical data of the compounds **8**, **9**, **10**, **16**, **17**, **18**, **19**, **21**, **24**, **25**, **26**, and, haplacutine C (**3**) were reported in our brief paper.[4] Also, the analytical data of the compounds **22**,[4,17] **29**,[18] and **30**[14] have been reported.

3-Bromo-2-(3-((4-methoxybenzyl)oxy)pent-4-en-1-yl)quinolin-4(1*H*)-one (12).

A mixture of **9** (0.016 g, 0.046 mmol) and Pyr.-HBr_3 (>85%, 0.019 g, 0.050 mmol) in DMF (2.5 mL) was stirred at room temperature for 30 min. After the addition of 5% $NaHSO_3$ aq. (5.0 mL) at 0 °C, the mixture was extracted with *tert*-butyl methyl ether (15 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1) to afford **12** (0.020 g, 100%) as a colorless crystal.

Mp 180.7–181.6 °C; IR (KBr) 3263, 3016, 2931, 2399 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.99–2.13 (m, 2H), 3.09 (dt, *J* = 14.5, 7.3 Hz, 1H), 3.24 (dt, *J* = 14.5, 7.3 Hz, 1H), 3.78 (s, 3H), 3.88 (td, *J* = 12.1, 7.6 Hz, 1H), 4.26 (d, *J* = 10.7 Hz, 1H), 4.54 (d, *J* = 10.7 Hz, 1H), 5.20–5.25 (m, 2H), 5.71 (ddd, *J* = 17.3, 9.6, 7.6 Hz, 1H), 6.83 (d, *J* = 7.2 Hz, 2H), 7.00 (t, *J* = 8.9 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 1H), 7.43 (t, *J* = 8.9 Hz, 1H), 8.33 (d, *J* = 8.9 Hz, 1H), 11.77 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 31.4, 32.9, 55.3, 70.3, 80.2, 106.7, 114.0 (× 2), 118.0, 118.1, 123.2, 123.9, 126.0, 129.7 (× 2), 129.9, 131.6, 137.4, 138.8, 152.0, 159.4, 173.3; HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{22}H_{22}BrNO_3Na$: 450.0681, found: 450.0672.

tert-Butyl (2-(3-((4-methoxybenzyl)oxy)pent-4-en-1-yl)quinolin-4-yl) carbonate (14).

A mixture of **9** (0.16 g, 0.46 mmol) and potassium *tert*-butoxide (>98%, 0.080 g, 0.70 mmol) in THF (4.6 mL) was stirred at room temperature for 1 h and then, di-*tert*-butyl dicarbonate (0.12 mL, 0.52 mmol) was added. The reaction mixture was stirred at 60 °C for 5.5 h. After the addition of H_2O (5.0 mL) at 0 °C, the mixture was extracted with EtOAc (5.0 mL × 3). The organic layer was dried over $MgSO_4$ and

concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc) to afford **14** (0.20 g, 96%) as a brown oil.

IR (neat) 2978, 2931, 2360, 1766 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 1.59 (s, 9H), 2.03–2.19 (m, 2H), 2.99–3.14 (m, 2H), 3.79 (s, 3H), 3.84 (td, *J* = 12.2, 7.0 Hz, 1H), 4.30 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.4 Hz, 1H), 5.23–5.26 (m, 2H), 5.80 (ddd, *J* = 17.3, 9.2, 7.0 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 2H), 7.25–7.27 (m, 3H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 27.6 (× 3), 35.1, 35.2, 55.2, 69.8, 79.5, 84.5, 112.2, 113.7 (× 2), 117.3, 120.7, 121.0, 125.9, 128.8, 129.3 (× 2), 129.9, 130.8, 138.8, 149.5, 150.5, 154.3, 159.0, 163.3; HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{27}H_{31}NO_5Na$: 472.2100, found: 472.2091.

(*E*)-But-1-enyltributylstannane (22).[4,17]

IR (neat) 2954, 2923, 2869, 1596, 1457, 1373 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.82–0.93 (m, 15H), 1.00 (t, *J* = 7.4 Hz, 3H), 1.31 (tq, *J* = 7.3, 7.3 Hz, 6H), 1.41–1.58 (m, 6H), 2.14 (m, 2H), 5.86 (d, *J* = 18.9 Hz, 1H), 6.50 (dt, *J* = 18.9, 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 10.0 (× 3), 13.8 (× 3), 14.4, 28.5 (× 3), 29.8 (× 3), 31.2, 120.3, 151.8; HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{16}H_{34}SnNa$: 369.1580, found: 369.1579.

4-((4-Methoxybenzyl)oxy)-2-((4*E*,6*E*)-3-((4-methoxybenzyl)oxy)nona-4,6-dien-1-yl)quinoline (23).

A mixture of **21** (27 mg, 0.045 mmol), **22** (49 mg, 0.14 mmol), and $Pd(PPh_3)_2Cl_2$ (3.2 mg, 0.0045 mmol) in DMF (0.5 mL) was stirred at 55 °C for 5.5 h. After the addition of H_2O (5.0 mL) at 0 °C, the mixture was extracted with $CHCl_3$/MeOH (3/1, 5.0 mL × 5). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1 to EtOAc) to afford **23** (13 mg, 53%) as a pale-yellow oil.

IR (neat) 2954, 2931, 2838, 1727, 1596 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 1.03 (m, 3H), 1.97–2.27 (m, 4H), 2.88–3.14 (m, 2H), 3.78 (s, 3H), 3.83–3.90 (m, 1H), 3.84 (s, 3H), 4.28 (d, *J* = 11.2 Hz, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 5.13 (s, 2H), 5.54 (dd, *J* = 15.0, 8.1 Hz, 1H), 5.76 (dt, *J* = 15.0, 6.6 Hz, 1H), 6.07 (dd, *J* = 15.0, 10.5 Hz, 1H), 6.19 (dd, *J* = 15.0, 10.5 Hz, 1H), 6.71 (s, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.39–7.45 (m, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.65 (dd, *J* = 8.2, 8.2 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 13.4, 25.6, 29.7, 35.8, 55.2, 55.3, 69.7, 70.0, 79.2, 101.1, 113.7 (× 2), 114.1 (× 2), 120.1, 121.8, 124.8, 127.8, 128.0, 128.5, 129.31 (× 2), 129.34 (× 2), 129.8, 130.8, 131.2, 133.3, 137.0, 148.6, 159.0, 159.7, 161.5, 163.6; HRMS-ESI: *m*/*z* $[M+H]^+$ calcd for $C_{34}H_{38}NO_4$: 524.2801, found: 524.2795.

Haplacutine C (3).[4]

IR (neat) 3378, 3278, 2962, 2923, 2854, 1735, 1635, 1596, 1511 cm^{-1}; ^1H 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, 26.3, 30.8, 36.8, 71.6, 108.9, 118.6, 124.0, 125.9, 126.0, 129.7, 131.3, 132.6, 134.8, 137.3, 141.3, 154.8, 178.9; HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{18}H_{21}NO_2Na$: 306.1465, found: 306.1463.

(*Z*)-4-(Tributylstannyl)but-3-en-1-yl methanesulfonate (31).

A mixture of **30** (0.13 g, 0.36 mmol), triethylamine (0.15 mL, 1.1 mmol), and methanesulfonyl chloride (40 μL, 0.52 mmol) in CH_2Cl_2 (3.6 mL) was stirred at room temperature for 12 h. After the addition of H_2O (10 mL) at 0 °C, the mixture was extracted with $CHCl_3$ (10 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/$CHCl_3$ = 1/1) to afford **31** (0.15 g, 94%) as a colorless oil.

IR (neat) 2954, 2923, 2584, 1596, 1457, 1357 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.83–0.98 (m, 15H), 1.31 (tq, *J* = 7.2, 7.2 Hz, 6H), 1.44–1.57 (m, 6H), 2.49 (m, 2H), 3.00 (s, 3H), 4.24 (t, *J* = 6.9 Hz, 2H), 6.05 (dd, *J* = 12.6, 1.1 Hz, 1H), 6.46 (dt, *J* = 12.6, 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 10.9 (× 3), 14.3 (× 3), 27.9 (× 3), 29.8 (× 3), 37.0, 38.1, 69.7, 134.4, 142.4; HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{17}H_{36}O_3SSnNa$: 463.1305, found: 463.1296.

(*Z*)-But-1-enyltributylstannane (27).

A mixture of **31** (0.12 g, 0.28 mmol) and $LiAlH_4$ (1.0 M in THF, 0.42 mL, 0.42 mmol) in THF (2.7 mL) was stirred under reflux condition for 30 min. After the addition of excess amounts of Na_2SO_4•$10H_2O$ at 0 °C, the mixture was stirred at the same temperature for 30 min. The resulting insoluble solid was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane) to afford **27** (0.090 g, 93%) as a colorless liquid.

IR (neat) 2962, 2923, 2854, 1596, 1457, 1373 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.79–0.94 (m, 15H), 0.99 (t, *J* = 7.3 Hz, 3H), 1.31 (tq, *J* = 7.2, 7.2 Hz, 6H), 1.43–1.62 (m, 6H), 2.03 (dq, *J* = 7.3, 7.1 Hz, 2H), 5.74 (d, *J* = 12.3 Hz, 1H), 6.50 (dt, *J* = 12.3, 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 10.4 (× 3), 13.9 (× 3), 14.6, 27.5 (× 3), 29.4 (× 3), 30.5, 127.2, 150.9; HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{16}H_{34}SnNa$: 369.1580, found: 369.1578.

Haplacutine B (2).

A mixture of **25** (26.8 mg, 0.061 mmol), **27** (52.6 mg, 0.15 mmol), and $Pd(MeCN)_2Cl_2$ (0.9 mg, 0.0066 mmol) in DMF (0.6 mL) was stirred at room temperature for 2 h. After the addition of H_2O (3.0 mL), the mixture was extracted with hexane/EtOAc (2/1, 3.0 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in MeOH (0.6 mL). K_2CO_3 (33.1 mg, 0.24 mmol) was added to the solution and the mixture was stirred at room temperature for 1.5 h. After the solvent was removed by evaporator, the residue was purified by alumina column chromatography (EtOAc/MeOH = 15/1) to afford **2** (10.4 mg, 60%) as a colorless oil.

IR (neat) 3378, 2954, 2923, 2854, 1735, 1635, 1596, 1511 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ = 0.97 (t, *J* = 7.5 Hz, 3H), 1.83–1.98 (m, 2H), 2.11–2.23 (m, 2H), 2.59–2.78 (m, 2H), 3.18 (br s, 1H), 4.17 (dt, *J* = 6.5, 6.5 Hz, 1H), 5.44 (dt, *J* = 10.7, 7.6 Hz, 1H), 5.70 (dd, *J* = 15.3, 6.4 Hz, 1H), 5.95 (m, 1H), 5.98 (s, 1H), 6.53 (ddt, *J* = 15.1, 11.0, 1.2 Hz, 1H), 7.28 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.59 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 9.75 (br s, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ = 14.6, 21.7, 30.9, 36.8, 71.7, 109.0, 118.7, 124.1, 125.9, 126.05, 126.13, 128.4, 132.7, 134.9, 137.1, 141.4, 155.0, 179.0; HRMS-ESI: *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{22}NO_2$: 284.1651, found: 284.1642.

ACKNOWLEDGEMENTS

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. D. Staerk, J. R. Kesting, M. Sairafianpour, M. Witt, J. Asili, S. A. Emami, and J. W. Jaroszewski, *Phytochemistry*, 2009, **70**, 1055.
2. S. S. Nazrullaev, I. A. Bessonova, and K. S. Akhmedkhodzhaeva, *Chem. Nat. Compd.*, 2001, **37**, 551.
3. D. M. Razzakova, I. A. Bessonova, and S. Y. Yunusov, *Chem. Nat. Compd.*, 1973, **9**, 199.
4. N. Kutsumura, K. Numata, and T. Saito, *Tetrahedron Lett.*, 2016, **57**, 5581.
5. Selected papers: (a) R. Camps, *Chem. Ber.*, 1899, **32**, 3228; (b) M. Hadjeri, E. Peiller, C. Beney, N. Deka, M. A. Lawson, C. Dumontet, and A. Boumendjel, *J. Med. Chem.*, 2004, **47**, 4964; (c) C. P. Jones, K. W. Anderson, and S. L. Buchwald, *J. Org. Chem.*, 2007, **72**, 7968; (d) A. I. S. Almeida, V. L. M. Silva, A. M. S. Silva, D. C. G. A. Pinto, and J. A. S. Cavaleiro, *Synlett*, 2008, 2593; (e) E. F. Marques, M. A. Bueno, P. D. Duarte, L. R. S. P. Silva, A. M. Martinelli, C. Y. dos Santos, R. P. Severino, D. Brömme, P. C. Vieira, and A. G. Corrêa, *Eur. J. Med. Chem.*, 2012, **54**, 10.
6. Reissig and co-workers reported that Et_3N in combination with TMSOTf can replace metal alkoxides

in the base-promoted cyclocondensation of *ortho*-amidoacetophenones leading to 4-quinolone derivatives. See: C. Eidamshaus, T. Triemer, and H. Reissig, *Synthesis*, 2011, 3261. However, this method could not be applied to our compound **8** having a PMB group, because the combination of reagents readily cleaved the PMB group to give directly the corresponding silyl ethers. See: T. Oriyama, K. Yatabe, Y. Kawada, and G. Koga, *Synlett*, 1995, 45.

7. (a) N. Kutsumura, T. Yokoyama, T. Ohgiya, and S. Nishiyama, *Tetrahedron Lett.*, 2006, **47**, 4133; (b) T. Yokoyama, N. Kutsumura, T. Ohgiya, and S. Nishiyama, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 578; (c) T. Ohgiya, N. Kutsumura, and S. Nishiyama, *Synlett*, 2008, 3091; (d) N. Kutsumura, K. Kubokawa, and T. Saito, *Synlett*, 2010, 2717; (e) N. Kutsumura, K. Kubokawa, and T. Saito, *Synthesis*, 2011, 2377; (f) N. Kutsumura, M. Inagaki, A. Kiriseko, and T. Saito, *Synthesis*, 2015, **47**, 1844.
8. The reaction of **9** with 1.1 equiv of Pyr.-HBr_3 in CH_2Cl_2 afforded a complex mixture even when the reaction was conducted at room temperature for only a few minutes. Based on the report of the selective bromination,[9] the addition of MS4A to the above reaction system also provided **12** in 31% yield together with many side-products after 15 min.
9. P. A. Risbood and D. M. Ruthven, *J. Am. Chem. Soc.*, 1978, **100**, 4919.
10. A. Darwish, A. Lang, T. Kim, and J. M. Chong, *Org. Lett.*, 2008, **10**, 861.
11. R. Munakata, H. Katakai, T. Ueki, J. Kurosaka, K. Takao, and K. Tadano, *J. Am. Chem. Soc.*, 2004, **126**, 11254.
12. B. H. Lipshutz, R. Keil, and J. C. Barton, *Tetrahedron Lett.*, 1992, **33**, 5861.
13. C. Bour and J. Suffert, *Org. Lett.*, 2005, **7**, 653.
14. Y. D. Wang, M. Dutia, M. B. Floyd, A. S. Prashad, D. Berger, and M. Lin, *Tetrahedron*, 2009, **65**, 57.
15. Interestingly, $LiAlH_4$-reduction of **31** in toluene at room temperature for 2 h gave a mixture of (*Z*)-**27** and (*E*)-**22** (71% yield, the ratio: 2/1). In addition, $LiAlH_4$-reduction in toluene at 0 °C for 11 h decreased the *Z*-selectivity (74% yield, the ratio: (*Z*)-**27**/(*E*)-**22** = 1/4).
16. Use of silica gel column chromatography for purification afforded a mixture of haplacutine B (**2**) and haplacutine C (**3**) in 55% yield (the ratio: **2**/**3** = 4/3).
17. (a) S. K. Jackson, S. C. Banfield, and M. A. Kerr, *Org. Lett.*, 2005, **7**, 1215; (b) N. Chandrasoma, N. Brown, A. Brassfield, A. Nerurkar, S. Suarez, and K. R. Buszek, *Tetrahedron Lett.*, 2013, **54**, 913; (c) T. Kusakabe, Y. Kawai, and K. Kato, *Org. Lett.*, 2013, **15**, 5102.
18. (a) M. D. Cliff and S. G. Pyne, *J. Org. Chem.*, 1995, **60**, 2378; (b) M. B. Rice, S. L. Whitehead, C. M. Horvath, J. A. Muchnij, and R. E. Maleczka, Jr., *Synthesis*, 2001, 1495.