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Total synthesis of cytotoxic sponge alkaloids hachijodines F and G

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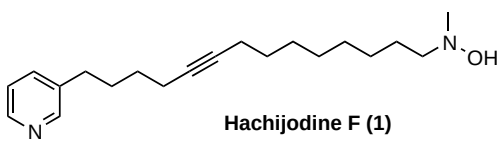
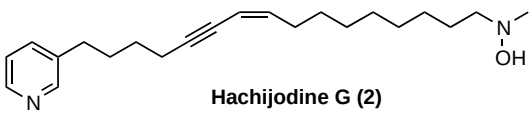
Abstract—The total synthesis of two cytotoxic sponge alkaloids hachijodines F (**1**) and G (**2**) via a common intermediate **3** is described.

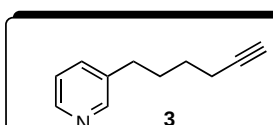
Hachijodines F (**1**) and G (**2**) are 3-alkylpyridine alkaloids recently isolated among other alkaloids from the marine sponge of the genera *Amphimedon*.[1] Both **1** and **2** were found to be cytotoxic towards P388 murine leukaemia cells with IC_{50} at 1 μg/mL. The structures of **1** and **2** were established via NMR spectroscopy and mass spectrometry. The relatively low abundance of **1** and **2** from the natural source (10.2×10^{-4}% and 30.2×10^{-4}% yield, respectively) and their interesting biological property prompt us to investigate their synthesis. Herein we describe the successful total synthesis of **1** and **2**.



Hachijodine F (1)



Hachijodine G (2)



3

Common intermediate

The synthesis of **1** and **2** makes use of compound **3** as a common intermediate. The preparation of **3** is shown in Scheme 1. 5-Bromo-1-pentene **4** was treated with an excess of lithiated 3-picoline[2–5] (prepared from 3-picoline and LDA) in THF and DMPU to give **5**[6] in 70% yield. Compound **5** was then subjected to the Lemieux–Johnson oxidation[7] to deliver aldehyde **6** in 73% yield. Conversion of **6** to acetylene **3** was effected in 79% yield with dimethyl(1-diazo-2-oxopropyl)phosphonate in the presence of potassium carbonate and methanol[8] (Scheme 1).

The synthesis of hachijodine F (**1**) commenced with the selective monobromination[9] of octane-1,8-diol **7** to give 8-bromooctan-1-ol **8** in 95% yield. Compound **8** was converted to its *tert*-butyldiphenylsilyl ether **9** in 89% yield with *tert*-butyldiphenylsilyl chloride and imidazole.[10] Iodide **10** was obtained in 95% yield from **9** via a Finkelstein reaction.[11] Compound **10** was reacted with the acetylide anion generated from **3** (**3**+^{n}BuLi in THF/DMPU) to deliver **11** in 48% yield.[12] Deprotection of **11** was effected with ammonium fluoride in methanol[13] to afford alcohol **12** in 90% yield. Reaction of **12** with *p*-toluenesulphonyl chloride and triethylamine[14,15] gave tosylate **13** in 67% yield. Compound **13** was subjected to nucleophilic displacement with *N*-methylhydroxylamine under the modified Mukaiyama conditions[16] to give hachijodine F (**1**) in 61% yield (Scheme 2).

The synthesis of hachijodine G (**2**) began with the selective protection of nonane-1,9-diol **14** with *tert*-butyldiphenylsilyl chloride with Hunig's base in *N*,*N*-

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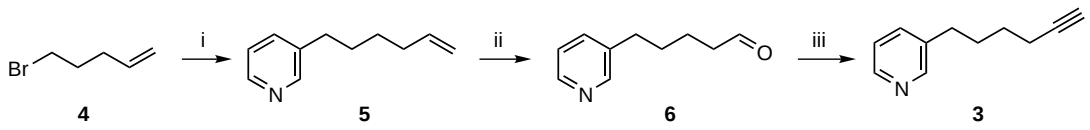
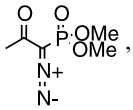
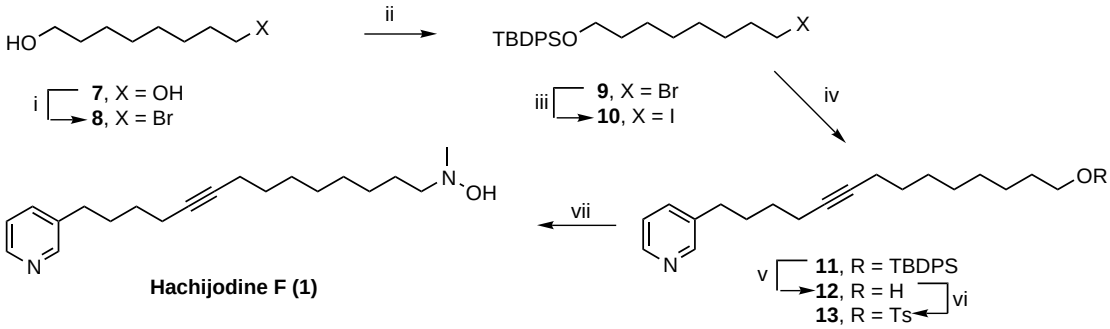


Scheme 1. *Reagents and conditions*: (i) LDA, DMPU, 3-picoline, THF, 70%; (ii) OsO_4, $NaIO_4$, ^tBuOH, H_2O, 73%; (iii) K_2CO_3, MeOH,  , 79%.



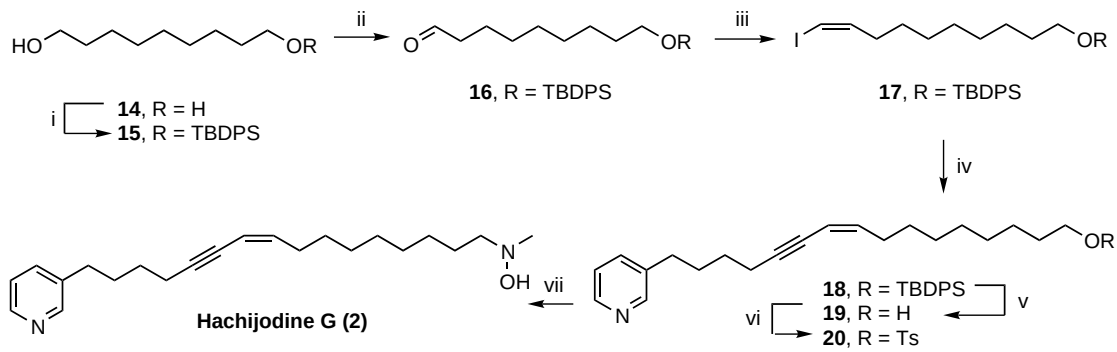
Scheme 2. *Reagents and conditions*: (i) $HBr_{(aq.)}$, toluene, reflux, 95%; (ii) TBDPSCl, imidazole, THF, 89%; (iii) NaI, acetone, reflux, 95%; (iv) **3**, ^nBuLi, DMPU, 48%; (v) NH_4F, MeOH, 90%; (vi) TsCl, Et_3N, CH_2Cl_2, 67%; (vii) Et_4NI, Et_3N, MeNHOH·HCl, DMPU, 61%.

dimethylformamide[17] to give monoprotected diol **15** in 55% yield. Alcohol **15** was oxidised with 2-iodoxybenzoic acid (IBX)[18–20] to aldehyde **16** in 83% yield. Compound **16** was converted into *cis*-vinyl iodide **17** in 65% using the Stork and Zhao olefination protocol.[21,22] Compound **17** was coupled to **3** using Alami's modified Sonogashira reaction[23] to deliver **18** in 87% yield. Compound **18** was deprotected with ammonium fluoride in methanol[13] to deliver alcohol **19** in 92% yield. Compound **19** was converted to its tosylate **20** in 81% yield with *p*-toluenesulphonyl chloride and triethylamine.[14,15] Compound **20** was treated with *N*-methylhydroxylamine[16] to give hachijodine G (**2**) in 46% yield (Scheme 3).

The ^1H NMR data of hachijodines F (**1**) and G (**2**) (in $CDCl_3$ with traces of trifluoroacetic acid added) are consistent with the literature data. In conclusion, we have developed efficient routes to both hachijodines F (**1**) and G (**2**) using **3** as a common intermediate.

Acknowledgements

We thank Professor Nobuhiro Fusetani for providing us with the spectra of hachijodines F (**1**) and G (**2**).



Scheme 3. *Reagents and conditions*: (i) $^iPr_2NEt$, DMF, TBDPSCl, 55%; (ii) IBX, DMSO, THF, 83%; (iii) $NaN(TMS)_2$, $[Ph_3PCH_2I]^+I^-$, THF, DMPU, 65%; (iv) $Pd(PPh_3)_4$, pyrrolidine, CuI, **3**, 87%; (v) NH_4F, MeOH, 92%; (vi) TsCl, Et_3N, DCM, 81%; (vii) Et_4NI, Et_3N, MeNHOH·HCl, DMPU, 46%.

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