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Preparation of 3-alkylpyridines. Formal total synthesis of Haliclamines A and B

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Abstract

The formal total synthesis of two sponge alkaloids Haliclamines A and B is achieved through the preparation of 3-alkylpyridines **3**, **4** and **5** via an advanced common intermediate **6**.

Keywords: sponge; pyridines; alkaloids; Haliclamines.

3-Alkylpyridine is a motif commonly found in sponge derived natural products.[1] It has been suggested that 3-alkylpyridines are plausible biosynthetic precursors for the complex manzamine and related alkaloids.[2] Recently this principle has been demonstrated by the biomimetic synthesis of sponge alkaloid keramaphidin B.[3,4] One subclass of these 3-alkylpyridine containing natural products is the bispyridine macrocycles, exemplified by the cyclostellettamines[5] (in pyridinium form) and Haliclamines[6] (in tetrahydropyridine form).

Haliclamines A **1** and B **2** are two macrocyclic alkaloids isolated from the sponge of the genus *Haliclona* by Fusetani et al.[6] These compounds inhibit cell division of fertilized sea urchin and the growth L1210 and P338 leukaemia cells. The total synthesis of Haliclamines A **1** and B **2** was reported by Morimoto et al.[7,8] In Morimoto's synthesis, Haliclamine A **1** was obtained from precursors **3** and **4**. Similarly, union of precursors **3** and **5** gave Haliclamine B **2**. Our continued interest in 3-alkylpyridine derived sponge natural products[9,10] prompted us to investigate an alternative synthesis of compounds **3**, **4** and **5**. We envisaged the use of an advanced intermediate **6** for the preparation of all three compounds and kept the use of protecting groups to a minimum (Scheme 1).

Our synthesis began with the esterification[11] of *trans*-β-hydromuconic acid **7** to give diester **8** in 90% yield. Reduction of diester **8** to diol **9** was effected in 78% yield with lithium aluminium hydride. Selective monoprotection of diol **9** with *tert*-butyldiphenylsilyl chloride using McDougal's protocol[12] delivered alcohol **10** in 55% yield. Iodination of **10** by Corey's method[13,14] furnished iodide **6**, the common advanced intermediate, in 97% yield (Scheme 2).

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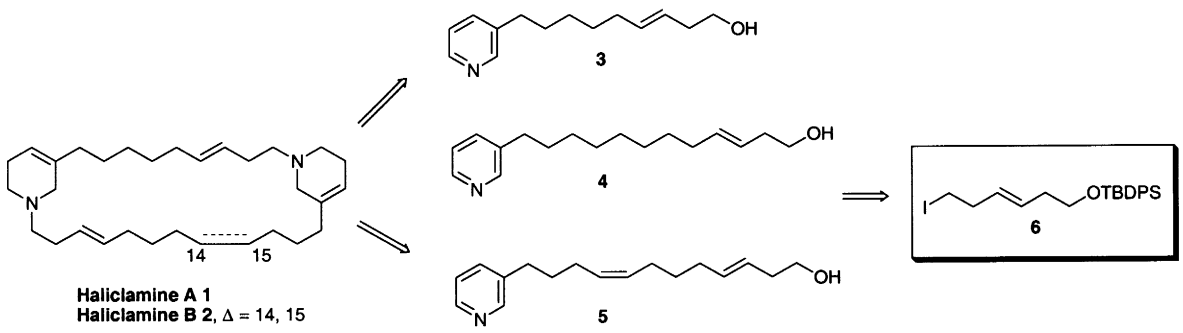
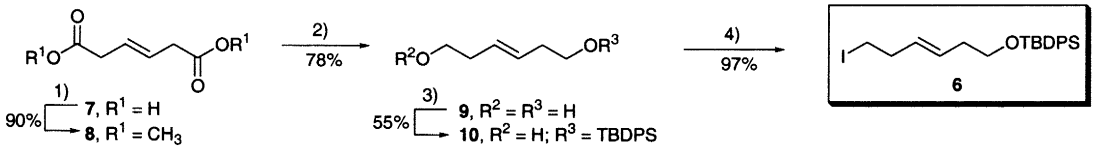
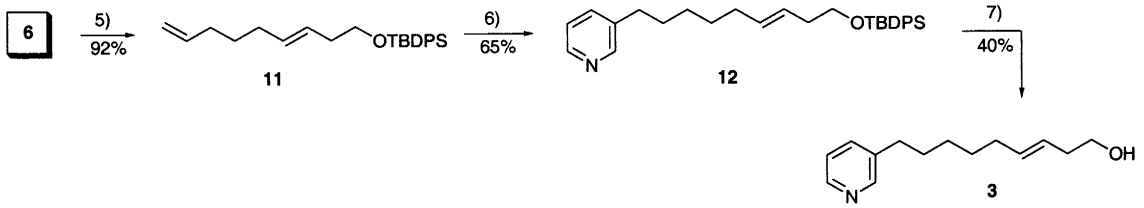


Scheme 1.



Scheme 2. (1) $MeOH/H_2SO_4$; (2) $LiAlH_4$/THF; (3) (a) NaH/THF, (b) TBDPSCl; (4) PPh_3/I_2/imidazole/Et_2O/CH_3CN

Iodide **6** was coupled with allyl magnesium chloride catalysed by lithium tetrachlorocuprate(II)[15] to give diene **11** in 92% yield. Selective hydroboration[16] of diene **11** with 9-BBN under ultrasound irradiation[17,18] followed by Suzuki coupling of the resultant alkylborane with 3-bromopyridine[19,20] furnished compound **12** in 65% yield. Deprotection of **12** with ammonium fluoride in methanol[21] gave compound **3** in 40% yield (Scheme 3).

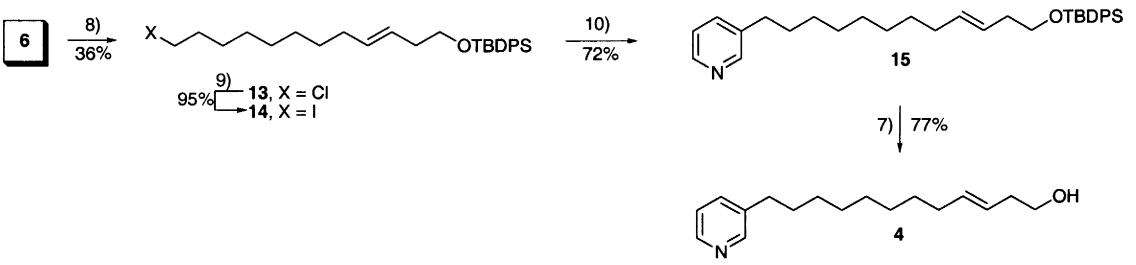


Scheme 3. (5) Allylmagnesium chloride/Li_2CuCl_4/THF; (6) (a) 9-BBN/THF/ultrasound, (b) 3-bromopyridine/$Pd(PPh_3)_4/K_3PO_{4(aq.)}$/THF; (7) NH_4F/MeOH

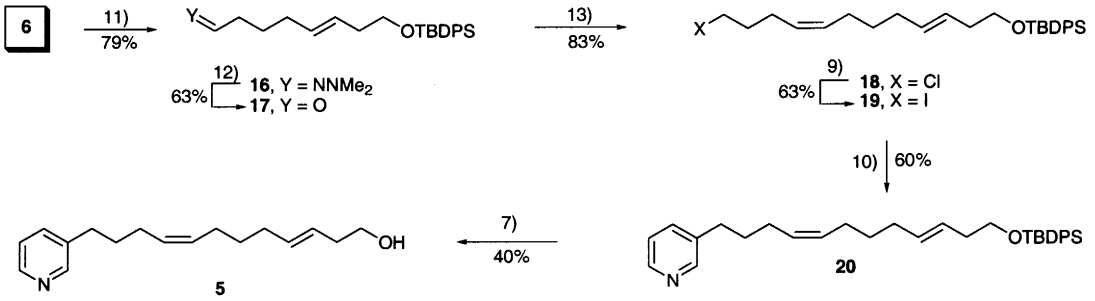
To synthesise compound **4**, intermediate **6** was coupled with 6-chlorohexylmagnesium iodide[22] mediated by lithium tetrachlorocuprate(II) to give chloride **13** in 36% yield. Finkelstein reaction of **13** with sodium iodide provided iodide **14** in 95% yield. Transmetallation of iodide **14** with *tert*-butyllithium followed by the addition of 9-methoxy-9-borabicyclo[3.3.1]nonane generated the corresponding boronate in situ.[23] Suzuki coupling of this boronate with 3-bromopyridine delivered **15** in 72% yield. Deprotection of **15** gave **4** in 77% yield (Scheme 4).

The synthesis of compound **5** commenced with the reaction of **6** with lithiated acetaldehyde dimethylhydrazone[24] to give dimethylhydrazone **16** in 79% yield. Deprotection of **16** with buffered periodic acid[25] at pH 4 provided aldehyde **17** in 63% yield. Wittig reaction of aldehyde **17** with ylide generated from (4-chlorobutyl)triphenylphosphonium iodide[26–30] furnished chloride **18** in 83% yield. Iodide **19** was obtained in 63% yield from **18** via a Finkelstein reaction. Suzuki coupling of **19** with 3-bromopyridine delivered **20** in 60% yield. Compound **20** was deprotected to give **5** in 40% yield (Scheme 5).

We have completed the synthesis of compounds **3**, **4** and **5** using a series of σ-bond forming reactions



Scheme 4. (8) $Cl(CH_2)_6MgI/Li_2CuCl_4$/THF; (9) NaI/acetone/reflux; (10) (a) ^{t}BuLi, Et_2O, (b) 9-BBN-OMe, (c) 3-bromopyridine/$PdCl_2$(dppf)/$K_3PO_{4(aq.)}$/THF; (7) NH_4F/MeOH



Scheme 5. (11) LDA/$CH_3CHNNMe_2$/THF; (12) H_5IO_6/HOAc/NaOAc/H_2O/THF; (13) $[Cl(CH_2)_4PPh_3]^+I^-$/KHMDS/THF; (9) NaI/acetone/reflux; (10) (a) ^{t}BuLi/Et_2O; (b) 9-BBN-OMe, (c) $PdCl_2$(dppf)/3-bromopyridine/$K_3PO_{4(aq.)}$/THF; (7) NH_4F/MeOH

and a minimal protection strategy. As compounds **3**–**5** were previously converted into Haliclamines, our work constitutes a formal total synthesis of Haliclamines A **1** and B **2**.

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