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Synthesis of a possible structure of pyrinodemin A

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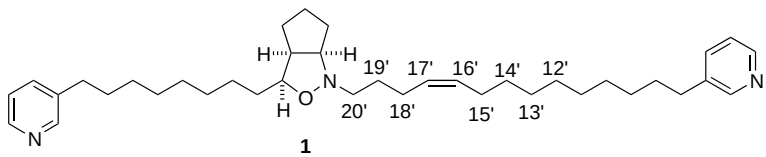
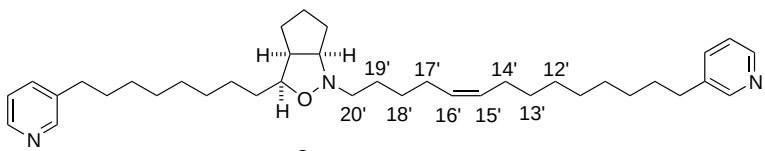
Abstract—An alternative possible structure of pyrinodemin A is synthesised. The ^{13}C NMR of the synthetic product **3** is in better agreement with the literature data.

Pyrinodemin A is a cytotoxic alkaloid isolated from the marine sponge *Amphimedon* sp. by Kobayashi et al.[1] The structure of pyrinodemin A was proposed as **1** based on NMR and mass spectrometry studies. Both we[2] and others[3] have recently synthesised structure **1** and concluded the position of the double bond in the natural product was incorrectly assigned between C16′–C17′. Both groups observed that in the ^{13}C NMR spectrum of synthetic **1**, the olefinic carbons appeared as two signals separated by 1 ppm. Both groups then prepared the C15′–C16′ double bond isomer **2**. The ^{13}C NMR of **2** also showed two separated signals for the olefinic carbons, albeit now 0.4 ppm apart. In light of the differences between the spectroscopic data of **2** and the literature data, we concluded that **2** does not correspond to natural pyrinodemin A.[2] In contrast, Snider et al. concluded **2** is probably the correct structure of pyrinodemin A.[3]

In this paper, we present the synthesis of a third structure, **3**, and show that the ^{13}C NMR data of **3** are in better agreement with the literature data than either **1** or **2**.



1



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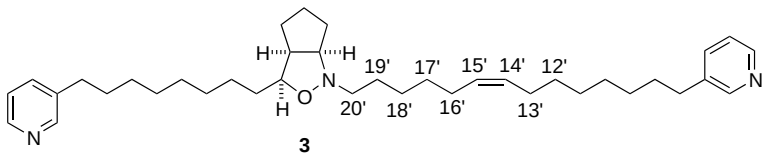

3

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The synthesis of **3** commenced with the selective monobromination[4] of pentane-1,5-diol **4** with hydrobromic acid and toluene to give 5-bromopentan-1-ol **5** in 60% yield. Compound **5** was protected as its *tert*-butyldiphenylsilyl ether **6** in 96% yield with *tert*-butyldiphenylsilyl chloride and imidazole in THF.[5] **6** was then subjected to S_N2 displacement with lithium acetylide ethylenediamine complex[6] in DMSO/THF to deliver terminal acetylene **7** in 84% yield. Deprotonation of acetylene **7** with *n*-butyllithium in THF/DMPU[7] followed by addition of 1-chloro-6-iodohexane gave **8** in 85% yield. Alkene **9** was obtained in 83% yield by semi-hydrogenation of **8** with Lindlar catalyst in benzene and quinoline.[8] Reaction of alkene **9** with lithiated 3-picoline in THF and DMPU gave **10** in 79% yield.[9] Deprotection of **10** was effected with ammonium fluoride in methanol to deliver alcohol **11** in 95% yield.[10] Alcohol **11** was oxidised with 2-iodoxybenzoic acid (IBX) in DMSO/THF to aldehyde **12** in 93% yield.[11–13] Aldehyde **12** was condensed with hydroxylamine hydrochloride in the presence of sodium acetate in methanol to give oxime **13** in 90% yield.[14] Reduction of **13** with sodium cyanoborohydride in methanol at pH 3 gave hydroxylamine **14** (Scheme 1).

14 was condensed with aldehyde **15**[2] to afford nitrone **16** in 79% yield over two steps. Thermal cyclisation of nitrone **16** at high dilution delivered **3** in 87% yield (Scheme 2).

In the 50.3 MHz ^{13}C NMR of **3**, the olefinic carbon resonances appeared as one signal. However, in the high field ^{13}C spectrum of **3** (125.73 MHz), the apparent olefinic singlet was resolved into two singlets at 129.91 and 129.93 ppm ($\Delta\delta$ 0.02, exponential line broadening 0.50 Hz, referenced to $CDCl_3$ at 77.16 ppm[15]). We also noticed that the signal distribution between 20 and 40 ppm appeared to be a better match with the literature spectrum than the two compounds that we had previously prepared.

We emphasise here that it would be hasty to conclude that **3** is the correct structure of natural pyrinodemin A. It is likely that the corresponding C13′–C14′ and C12′–C13′ double bond position isomers would have spectroscopic properties very similar to **3**. Hence, an unambiguous solution to the pyrinodemin A structural problem is not immediately available unless more intensive studies are conducted with the natural product. However, the work presented in this paper has set one end of the limit to where the double bond could reside in the natural product. In future if pyrinodemin A is isolated again from nature then the spectroscopic data of **3** can be used as a reference standard for natural product chemists. Another unresolved issue is the absolute configuration of natural pyrinodemin A. We are currently working on the asymmetric synthesis of structure **3** and hope to shed light on this matter.

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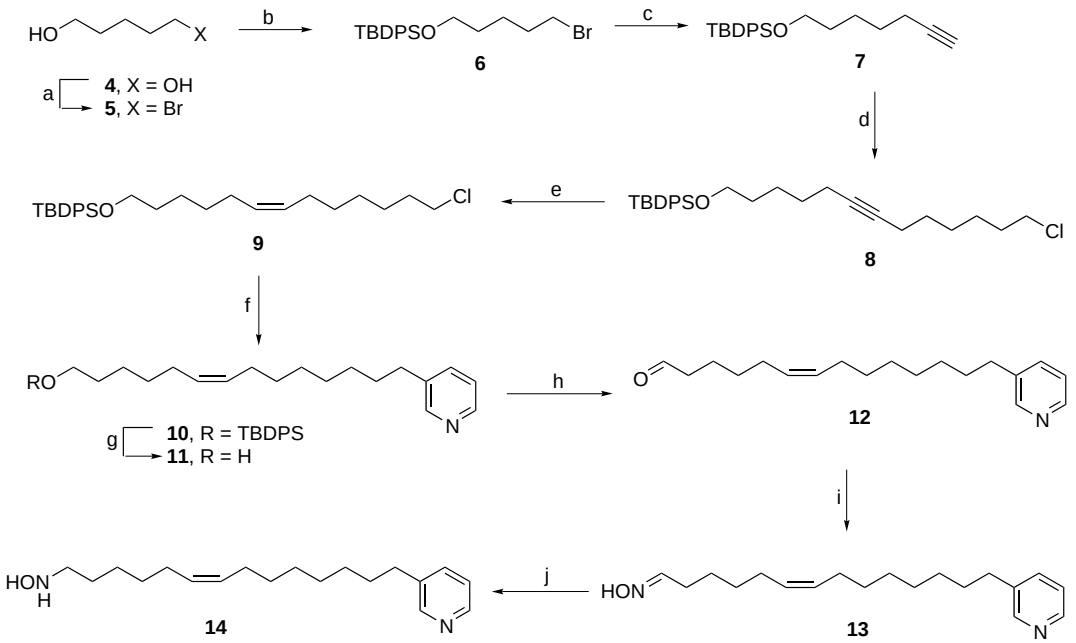
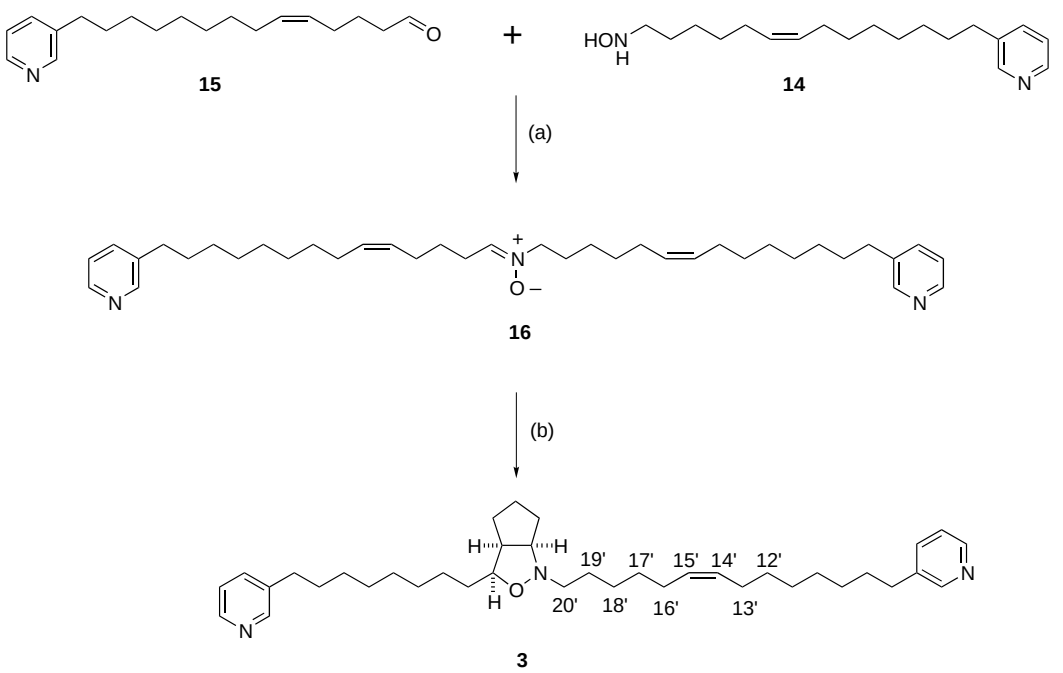


Scheme 1. (a) HBr (aq.), toluene, reflux, 60%; (b) TBDPSCl, imidazole, THF, 96%; (c) lithium acetylide ethylenediamine complex, DMSO, THF, 84%; (d) (1) ^nBuLi, THF, DMPU, (2) $Cl(CH_2)_6I$, 85%; (e) Lindlar catalyst, H_2, quinoline, benzene, 83%; (f) 3-picoline, LDA, DMPU, THF, 79%; (g) NH_4F, MeOH, 95%; (h) IBX, DMSO, THF, 93%; (i) $NH_2OH{\cdot}HCl$, MeOH, NaOAc, 90%; (j) $NaCNBH_3$, MeOH, pH 3.



Scheme 2. (a) Anhydrous Na_2SO_4, dichloromethane, 79%; (b) benzene, heat, 87%.

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