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Investigation into the absolute stereochemistry of the marine sponge alkaloid pyrinodemin A

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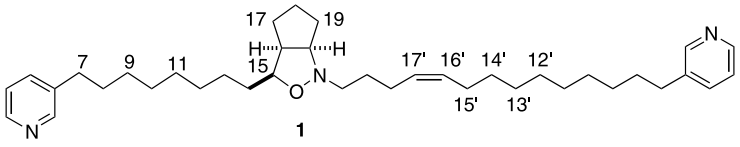
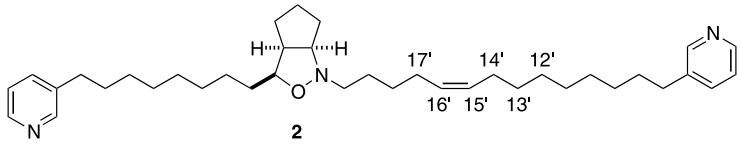
Abstract—The absolute configuration of the marine sponge alkaloid pyrinodemin A is established by organic synthesis.

Pyrinodemin A is a bis-3-alkylpyridine alkaloid isolated from the Okinawan marine sponge *Amphimedon* sp. by Kobayashi et al.[1] The compound is chiral ($[\alpha]_D^{25} = -9$) and cytotoxic towards murine leukaemia L1210 and KB epidermoid carcinoma cells. The structure and relative stereochemistry of pyrinodemin A was proposed as **1** based on a combination of NMR spectroscopy and electron impact mass spectrometry studies. The interesting structure of pyrinodemin A has attracted the attention of two research groups. Both our group and the Snider group have achieved the synthesis of racemic **1** and discovered that the spectroscopic data of synthetic **1** did not correspond to pyrinodemin A.[2,3] In the ^{13}C NMR spectrum of synthetic **1** the olefinic carbons (C16′ and C17′) were observed as two clearly resolved signals ($\Delta\delta = 1.1$ ppm) whereas in the natural product only one signal was attributed to the olefinic carbons. In an attempt to clarify the actual structure of pyrinodemin A, both groups have separately suggested and synthesised the C15′–C16′ double bond isomer **2** as an alternative structure of the natural product. It was observed by both groups that the spectroscopic data of racemic **2** was also not consistent with the published data of natural pyrinodemin A. Hence we concluded that **2** was not the real structure of pyrinodemin A.[2] In contrast the Snider group advocated that **2** was probably the correct structure of pyrinodemin A.[3]

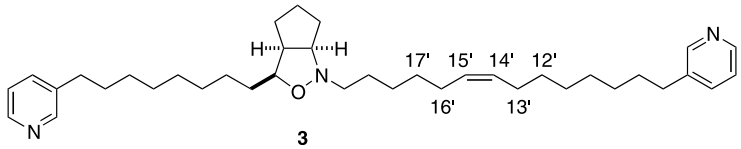


1

(Kobayashi's structure)



2



3

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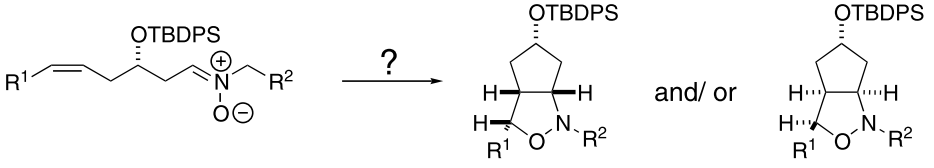
We subsequently prepared the corresponding C14′–C15′ double bond isomer **3** in racemic form and found the ^{1}H and ^{13}C NMR data matched the published results ($\Delta\delta = 0.02$ ppm).[4] However the lack of an authentic sample for comparison made it difficult to solve this problem solely by organic synthesis. Therefore we considered **3** as a possible candidate for the true structure of pyrinodemin A.

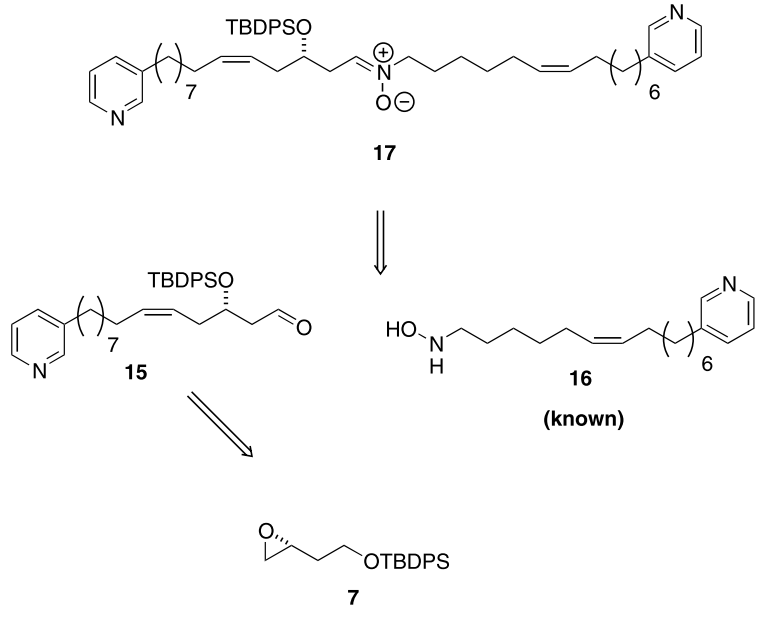
Herein we report the asymmetric synthesis of **3** thus establishing the absolute stereochemistry of pyrinodemin A. Although the precise location of the double bond in pyrinodemin A is not known, we are confident that the sign and the magnitude of the specific rotation of this natural product is primarily due to the asymmetric central core and the exact position of the double bond in the side chain of the molecule does not have any significant effect on its specific rotation.

We envisaged that an asymmetric synthesis of pyrinodemin A could be achieved by introducing a stereodirecting group in the nitrone precursor. We chose a secondary alcohol as the chiral inducing group because it could also act as a reference point for establishing the absolute configuration of the cycloaddition (Scheme 1). We were optimistic that even if the cycloaddition generated a mixture of diastereoisomers, separation of these compounds would still enable us to execute our plan. Based on this analysis, nitrone **17** could be derived from aldehyde **15** which in turn could be synthesised from chiral epoxide **7** (Scheme 2).

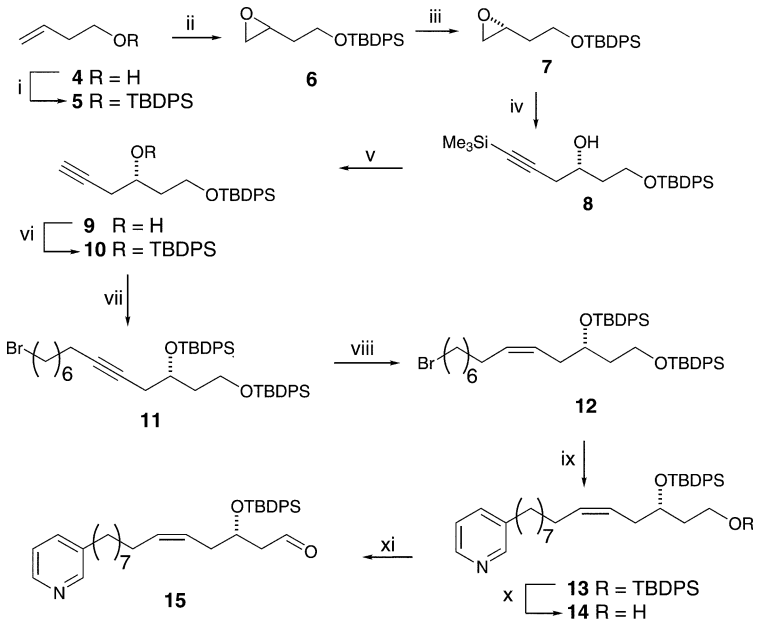
The commercially available but-3-en-1-ol **4** was protected as it *tert*-butyldiphenylsilyl ether **5** in 99% yield.[5] The double bond in **5** was oxidised with MCPBA to give epoxide **6** in 98% yield.[6] Epoxide **6** was subjected to Jacobsen's hydrolytic kinetic resolution to give stereochemically pure (ee>95%) epoxide **7** in 47% yield.[7,8] The choice of this particular enantiomer is purely arbitrary. Reaction of **7** with lithium trimethylsilylacetylide in the presence of boron trifluoride–THF complex[9] afforded a 94% yield of secondary alcohol **8**. The terminal trimethylsilyl group was removed by potassium carbonate in methanol[10] to deliver acetylene **9** in 89% yield. Alcohol **9** was converted into bis-silyl ether **10** in 98% yield with *tert*-butyldiphenylsilyl triflate and 2,6-lutidine.[11] The terminal acetylene **10** was treated with *n*-butyllithium followed by the addition of 1,7-dibromoheptane in the presence of DMPU to furnish compound **11** in 81% yield. Semi-hydrogenation of **11** with Lindlar catalyst in the presence of quinoline gave alkene **12** in 99% yield.[12] Reaction of **12** with lithiated 3-picoline delivered compound **13** in 76% yield.[13] Selective deprotection of the primary silyl ether in **13** was effected with HF·pyridine[14] to afford alcohol **14** in 85% yield. Alcohol **14** was oxidised with IBX[15–17] to aldehyde **15** in 88% yield (Scheme 3).



Scheme 1.



Scheme 2.

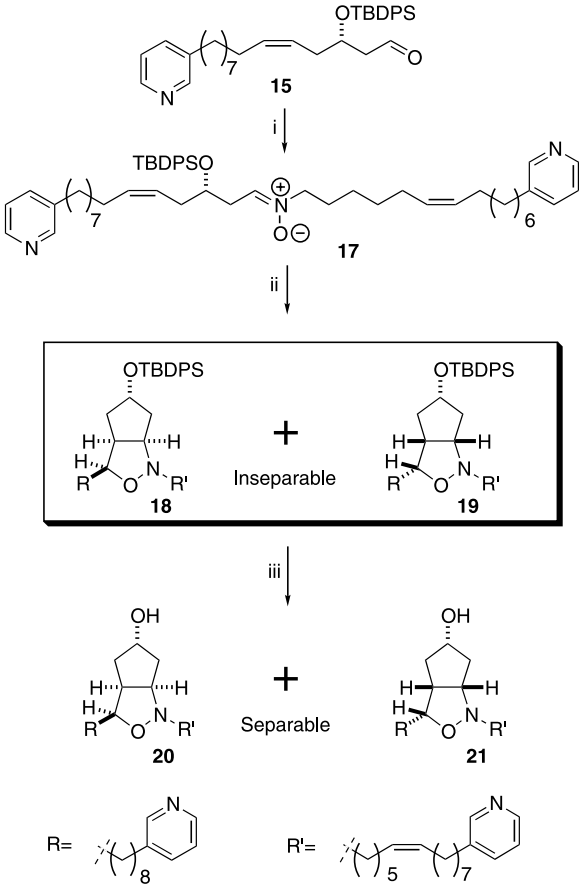


Scheme 3. *Reagents and conditions*: (i) TBDPSCl, imidazole, THF, 99%; (ii) MCPBA, DCM, 98%; (iii) (*R*,*R*)-(salen)Co(III)·OAc, THF, H_2O (0.55 equiv.), 47%; (iv) trimethylsilylacetylene, *n*-BuLi, BF_3·THF, 94%; (v) K_2CO_3, MeOH, 89%; (vi) TBDPSOTf, 2,6-lutidine, 98%; (vii) *n*-BuLi, DMPU, $Br(CH_2)_7Br$, THF, 81%; (viii) Lindlar catalyst, H_2, quinoline, benzene, 99%; (ix) 3-picoline, LDA, DMPU, THF, 76%; (x) HF·pyridine, THF, 85%; (xi) IBX, DMSO, THF, 88%.

Aldehyde **15** was condensed with known hydroxylamine **16**[2] to afford nitrone **17** in 62% yield. Thermal cyclisation of nitrone **17** in benzene under reflux delivered an inseparable mixture of **18** and **19** in a combined yield of 82%. The mixture of **18** and **19** was deprotected with ammonium fluoride in methanol[18] to give alcohols **20** (59% yield) and **21** (30% yield) which could be separated by flash chromatography (Scheme 4).

The relative configurations of **20** and **21** were determined by 1D DPFGSE-NOESY studies[19] using H-18 as the reference point. For the major diastereoisomer **20**, a significant NOE enhancement for H-17β was observed when H-18 was irradiated while the signal enhancement for H-17α was relatively small. This implied that H-17α is on the opposite face of the ring with respect to H-18. Irradiation of H-16 led to NOE enhancement for H-17α and H-20. The signal for H-16 was enhanced when H-15 was irradiated. The results demonstrated that H-15, H-16, H-17α, H-20 are on the same face of the molecule. Hence the absolute stereochemistry of **20** is (15*S*,16*S*,18*S*,20*R*). In the minor product **21**, irradiation of H-18 led to NOE enhancement for H-16 and H-20. The signal for H-16 was also enhanced when either H-20 or H-15 was irradiated. NOE enhancement was observed for H-20 and H-18 when H-19β was irradiated. Hence all these protons are located on the same face of the molecule and the absolute stereochemistry of **21** is assigned as (15*R*,16*R*,18*S*,20*S*) (Fig. 1).

The major alcohol **20** was converted into its thiocarbonate derivative **22** in 93% yield using phenyl chlorothionoformate[20] with 4-(1-pyrrolidino)pyridine.[21]



Scheme 4. *Reagents and conditions*: (i) **16**, Na_2SO_4, DCM, 62%; (ii) benzene, heat, 82% (**18**+**19**); (iii) NH_4F, MeOH, 70°C, chromatographic separation, 59% for **20**; 30% for **21**.

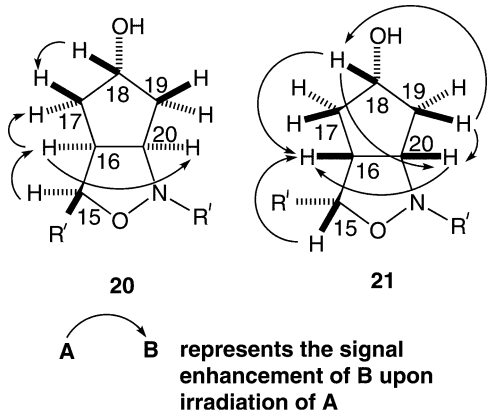
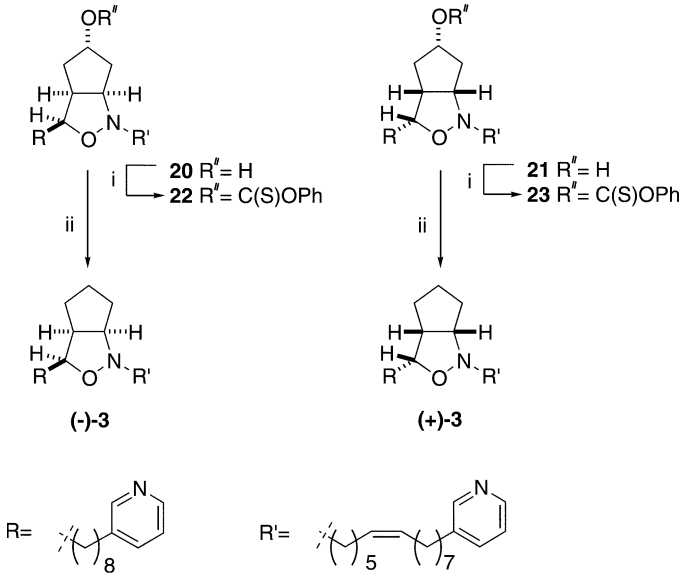


Figure 1.

Barton's deoxygenation of **22** with tris(trimethylsilyl)silane and AIBN afford (−)-**3** in 69% yield.[22] The ^{1}H and ^{13}C NMR data of (−)-**3** were consistent with racemic **3** we had previously prepared. Similarly the minor compound **21** was transformed into thiocarbonate **23** in 92% yield and reduced to (+)-**3** in 65% yield (Scheme 5).

The specific rotations of (−)-**3** and (+)-**3** are $[\alpha]_D^{24} = -5.1$ (*c* 1.0 $CHCl_3$) and $[\alpha]_D^{23} = +5.5$ (*c* 0.9 $CHCl_3$), respectively {cf. literature value of natural pyrinodemin A $[\alpha]_D^{25} = -9$ (*c* 1.0 $CHCl_3$)}. The enantiomeric excesses of (−)-**3** and (+)-**3** were determined to be 83% and 95% respectively by ^{1}H NMR analysis using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol as chiral shift reagent in C_6D_6.

Based on these findings we conclude that the absolute stereochemistry of natural pyrinodemin A corresponds to (−)-**3** and is (15*S*,16*S*,20*R*) (Fig. 2). A group of similar



Scheme 5. *Reagents and conditions*: (i) PhOC(S)Cl, 4-(1-pyrrolidino)pyridine, DCM, 93% for **22**, 92% for **23**; (ii) $(TMS)_3SiH$, AIBN, PhH, 69% for (−)-**3**, 65% for (+)-**3**.

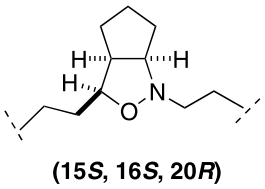


Figure 2. Absolute configuration of pyrinodemin A central core.

alkaloids, pyrinodemins B–D, have also been isolated from the same sponge extract.[23] Although their specific rotations have not been reported, it is likely that pyrinodemins B–D will have the same absolute stereochemistry as pyrinodemin A.

Acknowledgements

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