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Synthesis of pyrinodemins A and B. Assignment of the double bond position of pyrinodemin A

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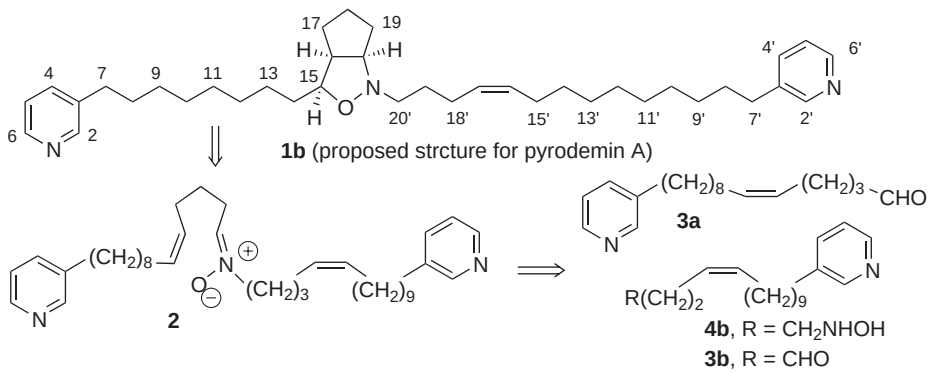
Abstract—Condensation of aldehyde **3a** with hydroxylamine **4b** afforded nitrone **2**, which underwent an intramolecular cycloaddition to give **1b**, the proposed structure of pyrinodemin A. A similar condensation of aldehyde **3a** and hydroxylamine **4a** provided pyrinodemin A (**1a**), which has the double bond one carbon further away from the isoxazolidine. An analogous sequence gave pyrinodemin B (**21**). © 2001 Elsevier Science Ltd. All rights reserved.

Kobayashi and co-workers reported the isolation of the novel bis 3-alkylpyridine substituted *cis*-cyclopent[*c*]isoxazolidine alkaloid pyrinodemin A (**1b**) from the marine sponge *Amphimedon* sp. that shows potent cytoxicity to murine leukemia L1210 (IC_{50} 0.058 μg/mL) and KB epidermoid carcinoma cells (IC_{50} 0.5 μg/mL) in vitro.[1,2] The structure of pyrinodemin A was assigned by analysis of the ^{1}H, ^{13}C, and 2D NMR and mass spectra. The position of the double bond was tentatively assigned based on the fragmentation pattern in the mass spectrum.



Retrosynthetically, and presumably biosynthetically as well, **1b** can be prepared by the well-known intramolecular [3+2] dipolar cycloaddition of **2**.[3] Nitrone **2** can be prepared by condensation of aldehyde **3a** and hydroxylamine **4b**, which can be formed from aldehyde **3b**, not **3a**. It seemed unlikely that both aldehydes **3a** and **3b** are intermediates in the biosynthesis of pyrinodemin A. This analysis suggested that the double bond of pyrinodemin A is not between carbons 16′ and 17′ as in **1b**, but rather between carbons 15′ and 16′ as in **1a**. Retrosynthetically, and biosynthetically, **1a** is a dimer that can be prepared by the condensation of aldehyde **3a** and hydroxylamine **4a**, which can be formed from **3a**. Analysis of the chemical shifts of the allylic carbons provides further support for this analysis. Both allylic carbons of pyrinodemin A absorb at δ 27.1,[1] as expected for **1a**. Analysis of the expected substituent effects suggests that the γ-nitrogen should shield C-18′ of **1b**, which should therefore absorb at δ 25. The potent cytotoxicity of pyrinodemin A prompted us to undertake the syntheses of both **1a** and **1b** to provide material for further biological evaluation and to determine the double bond position unambiguously.

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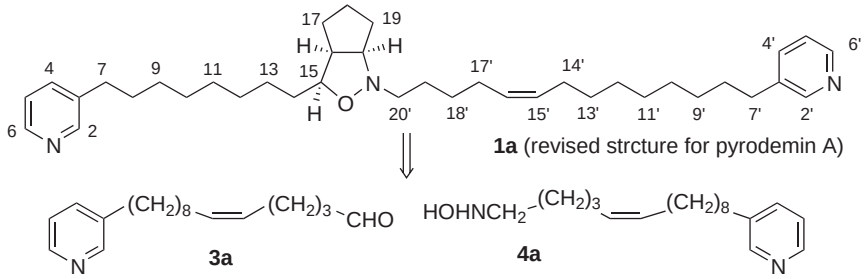
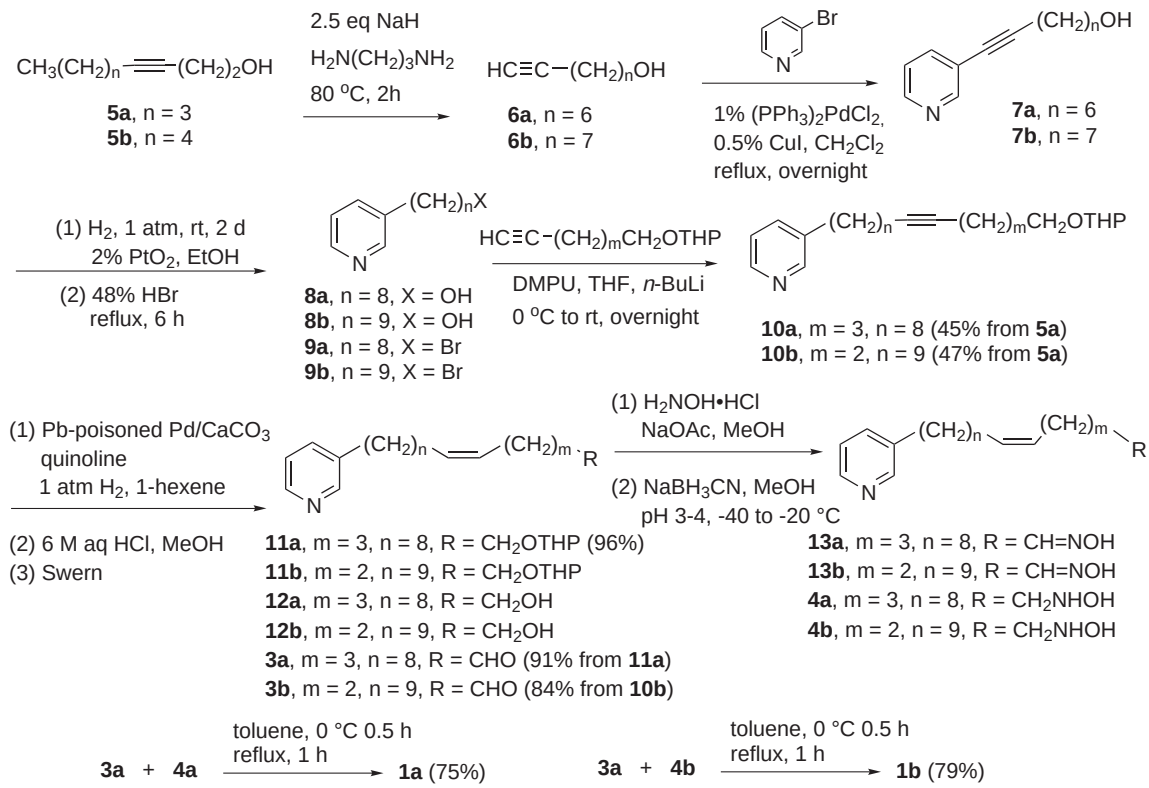


Isomerization of 3-octyn-1-ol (**5a**) with NaH in 1,3-diaminopropane at 80°C overnight[4] afforded 7-octyn-1-ol (**6a**),[5] which was coupled[6] with 3-bromopyridine using $(Ph_3P)_2PdCl_2$ and CuCl to give **7a**. Hydrogenation of **7a** over PtO_2 afforded saturated alcohol **8a**,[7] which was converted to bromide **9a**[8] in conc. hydrobromic acid at reflux. Alkylation of $LiC{\equiv}C(CH_2)_4OTHP$[9] with **9a** in DMPU[10] and THF provided **10a** in 45% overall yield from **5a**. Hydrogenation of **10a** over lead-poisoned Pd on $CaCO_3$ and quinoline in the presence of 1-hexene to prevent over reduction[11] afforded 96% of *cis* alkene **11a**, which was hydrolyzed with 6 M hydrochloric acid in MeOH to give **12a**. Swern oxidation afforded aldehyde **3a** in 91% yield from **11a**. Oxime **12a** was prepared by reaction with $NH_2OH{\cdot}HCl$ and NaOAc in MeOH.[12,13] Reduction of **12a** with $NaBH_3CN$ in MeOH at pH 3–4 at –40 to –20°C afforded hydroxylamine **4a**.[12,13] Condensation of **3a** and **4a** in toluene containing Na_2SO_4 at 0°C to form the nitrone and heating at reflux for 1 h to effect cycloaddition gave **1a**[14] in 75% yield from **3a** and **4a**. The stereochemistry of **1a** was confirmed by NOEs between H-15, H-16, and H-20. This sequence provides **1a** in 11 steps from 3-octyn-1-ol in 29% overall yield.

A similar five-step sequence starting with the conversion of 3-nonyn-1-ol (**5b**) to 8-nonyn-1-ol (**6b**)[15] and concluding with alkylation of $LiC{\equiv}C(CH_2)_3OTHP$[16] with **9b** in DMPU[10] and THF provided **10b** in 47% overall yield from **5b**. Hydrogenation, hydrolysis and Swern oxidation afforded 84% of **3b**, which was converted to hydroxylamine **4b** as described above for **4a**. Condensation of **3a** and **4b** in toluene containing Na_2SO_4 at 0°C to form the nitrone and heating at reflux for 1 h to effect cycloaddition gave **1b**[14] in 79% yield from **3a** and **4b**. This sequence provides **1b** in 11 steps from 3-octyn-1-ol and 3-nonyn-1-ol in 30% overall yield.

Spectral comparison indicates that pyrinodemin A is not **1b**, and is probably **1a**. The EI mass spectra of **1a** and **1b** are quite similar. Significant differences are: **1a** *m/z* 258 (4), 231 (15), 124 (17); **1b** *m/z* 258 (26), 231 (0), 124 (0). The EI mass spectrum of natural pyrinodemin A[17] is similar to that of **1a** with significant peaks at *m/z* 231 and 124, but not 258. The ^1H NMR spectra of **1a** and **1b** are again very similar except for the allylic methylene groups, which absorb at δ 2.07–1.96 (m, 4)



in **1a** and natural pyrinodemin A and at δ 2.17–2.04 (m, 2) and 2.01 (dt, 2, $J=6$, 6) in **1b**. The allylic carbons absorb at δ 27.1 and 27.2 in **1a**, while they both absorb at δ 27.1 in the natural product. In **1b**, they absorb at δ 27.0 for C-14′ and δ 24.9 for C-18′, as calculated, due to greater shielding by the γ-nitrogen than by a γ-carbon.

However, neither the ^{13}C NMR spectra of **1a** or **1b** match well with the published data for pyrinodemin A. For instance, the alkene carbons absorb at δ 129.6 and 129.9 in **1a**, at δ 129.3 and 130.3 in **1b**, and at δ 129.3 and 129.3 in the natural product. For **1a**, there are five absorptions between δ 27.0 and 28.5: C-13, 27.0; C-14′ and C-17′, 27.1 and 27.2; C-18′, 27.5; C-19′, 27.8. In the published data for pyrinodemin A there are only three absorptions in this region: δ 27.9, 27.1, and 27.1. However, examination[17] of the ^{13}C NMR spectrum of the natural product shows peaks in this region that are smaller than expected, but do correspond well to those of **1a**, suggesting that this is the structure of the natural product.

Kobayashi and co-workers recently reported the isolation of additional cytotoxic pyridine natural products from *Amphimedon* sp including oxime **13a**[18] and pyrinodemin B (**21**), which differs from pyrinodemin A (**1a**) by the absence of a double bond and a one-carbon shorter side chain. Coupling of aldehyde **3a** with hydroxylamine **20** should provide an expeditious route to pyrinodemin B (**21**). Alkylation[19] of the lithium acetylide ethylenediamine complex with 13-bromo-1-tridecanol (**14**) in DMSO containing NaI afforded **15**,[20] which underwent Pd-catalyzed coupling to give 48% of **16** from bromo alcohol **14**. Hydrogenation afforded 90% of saturated alcohol **17**, which was oxidized to aldehyde **18**. Reaction with $NH_2OH{\cdot}HCl$ and NaOAc provided 85% of oxime **19** from **17**. Low temperature reduction of **19** with $NaBH_3CN$ in MeOH at pH 3–4 gave 92% of hydroxylamine **20**, which was condensed with aldehyde **3a** in toluene at 0°C to reflux to give 81% of pyrinodemin B (**21**)[14] in 26% overall yield from **14**. The ^{1}H NMR spectrum of **21** is identical to that reported for the natural product. The ^{13}C NMR spectrum is similar, except for the presence of peaks at δ 27.0, 27.3, and 28.1 in synthetic **21**, but only δ 27.9 in the natural product as with synthetic and natural pyrinodemin A.

Pyrinodemins **1a** and **1b** are moderately toxic to DU 145 prostate cancer cells (IC_{50} 8 μM) and HT-29 colon cancer cells (IC_{50} 8 μM).[21]

In conclusion, we have developed efficient syntheses of pyrinodemins A (**1a**) and B (**21**) that proceed in 26–30% overall yield. Analysis of the spectral data indicates that pyrinodemin A is definitely not **1b** and is probably **1a**.

Acknowledgements

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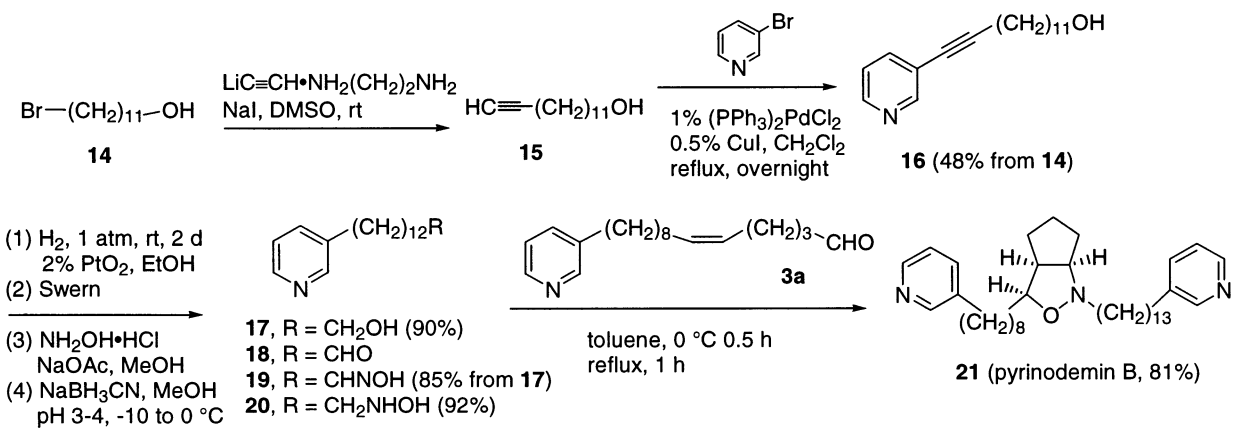

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14. **1a**: ^{1}H NMR 8.46–8.41 (m, 4), 7.48 (br d, 2, $J=7.9$), 7.20 (dd, 2, $J=7.9$, 4.9), 5.39–5.30 (m, 2), 4.05 (ddd, 1, $J=6$, 6, 6), 3.50–3.42 (br, 1), 2.89–2.78 (m, 2), 2.64–2.60 (m, 1), 2.60 (t, 4, $J=7.6$), 2.07–1.96 (m, 4), 1.82–1.72 (br, 1), 1.71–1.50 (m, 9), 1.50–1.36 (m, 6), 1.36–1.24 (m, 20); ^{13}C NMR 150.0 (2 C), 147.2 (2 C), 137.9 (2 C), 135.7 (2 C), 130.0, 129.6, 123.2 (2 C), 77.8 (br), 72.6 (br), 57.2 (br), 49.9, 34.2 (br), 33.0 (2 C), 31.1 (2 C), 29.7 (2 C), 29.4 (2 C), 29.33, 29.30, 29.2, 29.11, 29.08, 28.8, 27.8, 27.5, 27.18, 27.12, 27.0, 26.4, 26.3; IR (neat) 1574, 1464, 1422; MS m/z 575 (20), 574 (49), 365 (29), 355 (18), 327 (12), 301 (10), 299 (9), 289 (11), 288 (9), 287 (19), 286 (24), 285 (30), 270 (11), 258 (4), 244 (22), 231 (15), 220 (31), 204 (3), 190 (13), 176 (17), 162 (12), 148 (15), 146 (11), 136 (10), 134 (13), 124 (17), 120 (22), 106 (100), 93 (94); HRMS (DEI) calcd for $C_{38}H_{60}N_3O$ (MH^+) 574.4736; found 574.4753. **1b**: ^{1}H NMR 8.46–8.41 (m, 4), 7.49 (br d, 2, $J=7.9$), 7.20 (dd, 2, $J=7.9$, 4.9), 5.41–5.30 (m, 2), 4.05 (ddd, 1, $J=6$, 6, 6), 3.50–3.42 (br, 1), 2.89–2.79 (m, 2), 2.64–2.60 (m, 1), 2.60 (t, 4, $J=7.6$), 2.17–2.04 (m, 2), 2.01 (dt, 2, $J=6$, 6), 1.80–1.72 (br, 1), 1.71–1.52 (m, 10), 1.50–1.38 (m, 3), 1.36–1.24 (m, 22); ^{13}C NMR 149.9 (2 C), 147.1 (2 C), 137.91, 137.89, 135.7 (2 C), 130.3, 129.3, 123.2 (2 C), 77.8 (br), 72.6 (br), 56.8 (br), 49.9, 34.2 (br), 33.0 (2 C), 31.1 (2 C), 29.7 (2 C), 29.5 (2 C), 29.36, 29.35, 29.27, 29.24, 29.10, 29.06, 28.7, 28.0, 27.2, 27.0, 26.4, 26.3, 24.9; IR (neat) 1654, 1574, 1464, 1422;; MS m/z 575 (14), 574 (32), 365 (22), 355 (16), 327 (5), 301 (7), 299 (4), 289 (21), 288 (11), 287 (24), 286 (41), 285 (36), 270 (9), 258 (26), 244 (15), 231 (0), 220 (19), 204 (4), 190 (22), 176 (30), 162 (12), 148 (15), 146 (6), 136 (13), 134 (9), 124 (0), 120 (21), 106 (100), 93 (82); HRMS (DEI) calcd for $C_{38}H_{60}N_3O$ (MH^+) 574.4736; found 574.4761. **21**: ^{1}H NMR 8.46–8.41 (m, 4), 7.49 (br d, 2, $J=7.9$), 7.20 (dd, 2, $J=7.9$, 4.9), 4.06 (ddd, 1, $J=6$, 6, 6), 3.50–3.42 (br, 1), 2.88–2.79 (m, 2), 2.64–2.60 (m, 1), 2.59 (t, 4, $J=7.6$), 1.83–1.72 (br, 1), 1.71–1.38 (m, 13), 1.36–1.22 (m, 28); ^{13}C NMR 149.9 (2 C), 147.1 (2 C), 137.89, 137.85, 135.7 (2 C), 123.1 (2 C), 77.7 (br), 72.6 (br), 57.1 (br), 49.9, 34.2 (br), 32.9 (2 C), 31.1 (2 C), 29.7, 29.5–29.6 (5 C), 29.48, 29.35 (2 C), 29.27, 29.09, 29.05, 28.7, 28.1, 27.3, 27.0, 26.4, 26.3; HRMS (DEI) calcd for $C_{37}H_{59}N_3O$ (M^+) 561.4658; found 561.4645.
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21. We thank Dr. Bruce Littlefield, Eisai Research Institute for evaluating the cytotoxicity of **1a** and **1b**.