Asymmetric Synthesis of Double Bond Isomers of the Structure Proposed for Pyrinodemin A and Indication of Its Structural Revision

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Abstract: Asymmetric synthesis of double bond isomers (+)-2 (Δ15',16') and (+)-3 (Δ14',15') of the structure (1) (Δ16',17') proposed for pyrinodemin A, a cytotoxic bis-pyridine alkaloid with a unique cis-cyclopent[c]isoxazolidine moiety from a marine sponge, has been accomplished. Pyrinodemin A was indicated to be a 1:1 racemic mixture of 2 from comparison of C18 and chiral HPLC analysis for pyrinodemin A and the synthetic compounds as well as ESIMS data of oxidative degradation products of pyrinodemin A.

Keywords: Pyrinodemin A, Amphimedon sp., asymmetric synthesis, structural revision

Pyrinodemin A, a cytotoxic bis-pyridine alkaloid with a unique cis-cyclopent[c]isoxazolidine moiety, has been isolated from a marine sponge Amphimedon sp., and its relative stereostructure was proposed as 1 (Δ16',17') on the basis of spectral data [1]. The unique structure of pyrinodemin A has prompted synthetic chemists to its total synthesis of 1 as well as syntheses of the double bond isomers 2 (Δ15',16') and 3 (Δ14',15')[2-4] followed by different proposals of the structural revision of pyrinodemin A to be 2 [2] or 3 [3,4].

In order to examine the correct structure of pyrinodemin A, we have synthesized (+)-2 and (+)-3, the double bond isomers of 1, as an optically active form, and compared HPLC profiles of the synthetic compounds and pyrinodemin A. In addition, oxidative degradation experiments were performed for a remaining small amount of pyrinodemin A to determine the position of a double bond. In this paper, we describe asymmetric synthesis of (+)-2 and (+)-3, and indication of the structure of pyrinodemin A to be (±)-2.
The Δ15',16' double bond isomer (+)-2 was synthesized as follows (Scheme 1). The synthesis of hydroxylamine 6a commenced with known pivaloate 5a [5]. Oxidation of alcohol 5a with 2-iodobenzoic acid (IBX) [6] in DMSO and THF afforded its aldehyde. Treatment of the aldehyde with NH2OH·HCl and NaOAc in MeOH provided oxime which was reduced with NaBH3CN in MeOH to afford hydroxylamine 6a [7,8]. Condensation of 6a and optically active aldehyde 7 [8] in CHCl3 containing Na2SO4 at r.t. gave the nitrone 8a, which was followed by heating to afford cis-cyclopent[c]isoxazolidine [9] 9a in 58% yield.

Scheme 1.

Reagents and conditions: (a) IBX, DMSO, THF (69%); (b) H2NOH·HCl, AcONa, MeOH (96%); (c) NaBH3CN, MeOH, pH 3, 0 °C; (d) Na2SO4, 6, CHCl3, r.t.-reflux (58% for 2 steps); (e) 3N HCl, dioxane (80%); (f) NaIO4, MeCN, H2O, 0 °C; (g) Br[Ph3P(CH2)7CH2OH], n-BuLi, THF, 0 °C (51% for 2 steps); (h) TIPSCI, imidazole, CH2Cl2 (75%); (i) H2, Pd-C, MeOH (93%); (j) DIBAL, CH2Cl2, -78 °C (75%); (k) IBX, DMSO (80%); (l) Br[Ph3P(CH2)7CH2OH], n-BuLi, THF, 0 °C (81%); (m) 46% HF, MeCN (55%); (n) CBr4, Ph3P (80%); (o) 3-methylpyridine, LDA, DMPU, -40 °C (64%)

Treatment of 9a with 3N HCl in dioxane gave diol, which was converted into its aldehyde by treatment with NaIO4 and then into alcohol 10a by Wittig reaction [10]. Protection of alcohol 10a as its TIPS ether followed by reduction with Pd-C gave its saturated TIPS ether, which was converted
into alcohol $11a$ with DIBAL. IBX oxidation of $11a$ followed by Wittig reaction [10] afforded its unsaturated alcohol, which was subjected to deprotection with HF to give diol $12a$ in 55%. Treatment of diol $12a$ with CBr$_4$ and PPh$_3$ provided its dibromide, which was coupled with 3-methypyridine using LDA and DMPU [11] in THF to furnish optically active compound (+)-$2$. This is the first synthesis of optical active form of $2$, although its racemic form ((±)-$2$) has been synthesized [2-4]. The $\Delta^{14',15'}$ double bond isomer (+)-$3$ was prepared from pivaloate $5b$ by almost same procedure as described for synthesis of (+)-$2$ (Scheme 1).

The position of a double bond and the stereochemistry of pyrinodemin A were examined as follows. Compounds (±)-$1$ [2], (±)-$2$ [2], and (+)-$3$ were subjected to C$_{18}$ HPLC [Wako sil-II 5C18 RS, Wako Ind., Ltd., 4.6 x 250 mm; flow rate 1.0 mL/min: eluent; MeOH/H$_2$O (91:9); UV detection at 263 nm] and found to be separated ($1$, t$_R$ 21.6 min; $2$, t$_R$ 17.0 min; $3$, t$_R$ 15.8 min), while the retention time (t$_R$ 17.0 min) of pyrinodemin A was identical with that of $2$ under the same condition, indicating that the position of a double bond of pyrinodemin A corresponded to that ($\Delta^{15',16'}$) of $2$. To elucidate the stereochemistry of pyrinodemin A, compound (±)-$2$ was subjected to chiral HPLC [CHIRALCELL OD-H, Daicel Co., Ltd., 4.6 x 250 mm; flow rate 1.0 mL/min: eluent: hexanes/i-PrOH (95:5); UV detection at 263 nm] and found to be separated (t$_R$ 44 and 47 min), while the retention time of (+)-$2$ was 47 min (Figure 1). On the other hand, pyrinodemin A gave the two peaks corresponding to those of (±)-$2$ in a ratio of 1:1 under the same conditions, indicating that pyrinodemin A is a 1:1 racemic mixture of $2$. Furthermore, pyrinodemin A was treated with OsO$_4$ and then NaIO$_4$ to give degradation products, one of which showed an ESIMS fragment ion peak at $m/z$ 242 (M+Na)$^+$, corresponding to an aldehyde ($13$) of C-7′~C-15′ segment connected to a pyridine ring (Scheme 2). From the results described above, it was indicated that the olefin position of pyrinodemin A was C-15′ and C-16′ ($2$), as proposed by Snider’s group [2], and that pyrinodemin A was a 1:1 racemic mixture of $2$.

**Figure 1.** Chiral HPLC profiles of (a) synthetic compounds (±)-$2$, (b) (+)-$2$, and (c) pyrinodemin A.
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Experimental

General

Optical rotations were determined on a JASCO P-1030 polarimeter. Infrared spectra were obtained on a JASCO FT/IR-230 spectrometer. Proton and carbon NMR spectra were recorded on a Bruker 600 MHz spectrometer. Chemical shifts are reported in \(\delta\) values relative to chloroform (\(\delta\) 7.26 for proton and \(\delta\) 77.0 for carbon NMR. EI mass spectra were measured on a JEOL JMS-DX303 spectrometer.

**Synthetic Compound** \((\pm)-2\): \([\alpha]^{25}_{D} +5.5^\circ (c 0.6, CHCl_3); IR (neat) 1575 cm\(^{-1}\); \(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\) 1.25~1.50 (26H, m), 1.50~1.74 (9H, m), 1.75 (1H, m), 2.01 (4H, m), 2.60 (5H, m), 2.91 (2H, m), 3.50 (1H, m), 4.15 (1H, m), 5.33 (2H, m), 7.22 (2H, m), 7.51 (2H, m), 8.44 (4H, m); \(^{13}\)C-NMR (150 MHz, CDCl\(_3\)) \(\delta\) 26.3, 26.4, 27.0, 27.1, 27.2, 27.5, 27.8, 29.1, 29.3, 29.4, 29.7, 31.1, 33.0, 34.2, 49.9, 57.1, 72.6, 77.7, 123.2, 129.6, 130.0, 135.7, 137.9, 147.1, 149.9; HREIMS \(m/z\) 573.4643 [M\(^+\); calcd for C\(_{38}\)H\(_{59}\)N\(_3\)O\(_1\) 573.4658].

**Synthetic Compound** \((\pm)-3\): \([\alpha]^{25}_{D} +6.2^\circ (c 0.8, CHCl_3); IR (neat) 1575 cm\(^{-1}\); \(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\) 1.25~1.50 (26H, m), 1.50~1.74 (9H, m), 1.77 (1H, m), 2.00 (4H, m), 2.58 (5H, m), 2.82 (2H, m), 3.45 (1H, m), 4.04 (1H, m), 5.33 (2H, m), 7.18 (2H, m), 7.47 (2H, m), 8.43 (4H, m); \(^{13}\)C-NMR (150 MHz, CDCl\(_3\)) \(\delta\) 26.3, 26.4, 27.1, 28.0, 28.8, 29.1, 31.1, 33.0, 34.3, 49.9, 57.3, 77.7, 123.2, 129.8, 135.7, 137.9, 147.1, 149.9; HREIMS \(m/z\) 573.4661 [M\(^+\); calcd for C\(_{38}\)H\(_{59}\)N\(_3\)O\(_1\) 573.4658].

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Sample Availability: Available from the authors.

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