ORGANIC LETTERS

2003
Vol. 5, No. 15
2611−2614

Total Synthesis and Assignment of the Double-Bond Position and Absolute Configuration of (−)-Pyrinodemin A

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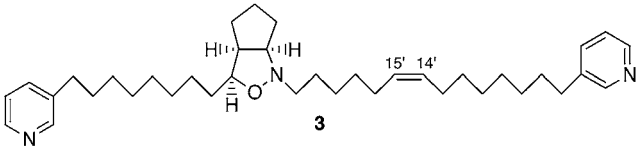
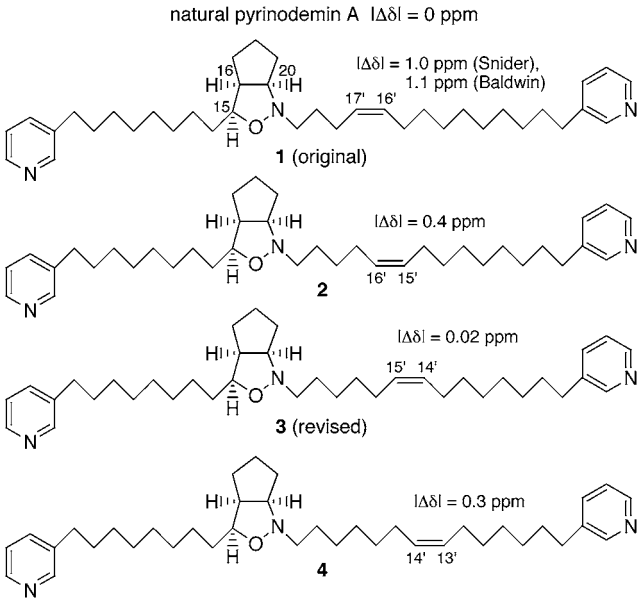
Received April 28, 2003

ABSTRACT



The first asymmetric total synthesis of a structurally novel *cis*-cyclopent[*c*]isoxazolidine alkaloid, (−)-pyrinodemin A (3), which exhibits potent cytotoxicity, has been accomplished through a highly diastereoselective intramolecular nitrone−olefin cycloaddition reaction as the key step. Thus, it has been found that the hitherto unknown absolute configuration of pyrinodemin A is as indicated in the structural formula 3.

Recently, an increasing number of structurally and bioactively unique 3-alkylpyridine alkaloids have been isolated from marine sponges of several genera.[1] In 1999, Kobayashi and co-workers reported the isolation of a structurally novel *cis*-cyclopent[*c*]isoxazolidine alkaloid, pyrinodemin A, from the marine sponge *Amphimedon* sp. collected off Nakijin, Okinawa.[2] Pyrinodemin A shows potent cytotoxicity against murine leukemia L1210 (IC_{50} = 0.058 μg/mL) and KB epidermoid carcinoma cells (IC_{50} = 0.5 μg/mL) in vitro and has relatively weak antifungal activity.[3] The plane structure and relative configuration of pyrinodemin A were primarily proposed as **1** on the basis of analysis of the ^{1}H and ^{13}C NMR and mass spectra. Although Kobayashi et al. also reported a family of compounds similar to pyrinodemin A obtained from the same sponge, pyrinodemins B−D, which possessed prominent cytotoxicity and the *cis*-cyclopent[*c*]-isoxazolidine ring system characteristic of pyrinodemin A,[3] the absolute configuration of pyrinodemins has not yet been determined.



The novel structure of pyrinodemin A coupled with its bioactive and biogenetic interests prompted synthetic organic

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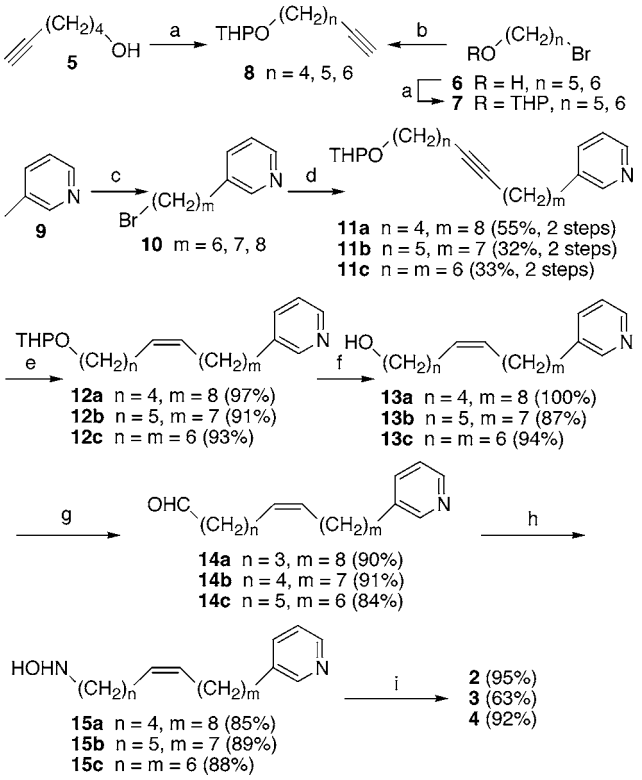
10.1021/ol034700v CCC: $25.00
Published on Web 07/02/2003

chemists to investigate its synthesis. The groups of Snider[4] and Baldwin[5] have recently synthesized in a racemic form the originally proposed structure **1** for pyrinodemin A and positional isomer **2** of the double bond; further, Baldwin's group[6] has also reported the racemic synthesis of positional isomer **3** of the double bond. Both groups concluded that the position of the double bond in the natural product was incorrectly assigned between C16′−C17′, mainly on the basis of critical carbon chemical shift differences ($\Delta\delta$) observed between the olefinic carbons, $|\Delta\delta| = 1.0$ ppm (Snider), 1.1 ppm (Baldwin) in **1**; $|\Delta\delta| = 0$ ppm in natural pyrinodemin A. In light of the difference $|\Delta\delta| = 0.4$ ppm in **2**, Baldwin's group reported that **2** does not correspond to the natural product as well. In contrast, Snider's group concluded that **2** is probably the correct structure of pyrinodemin A, albeit $|\Delta\delta| = 0.4$ ppm in **2**. On the other hand, Baldwin's group suggested the C14′−C15′ double-bond positional isomer **3** as a possible structure of pyrinodemin A because $|\Delta\delta| = 0.02$ ppm in **3** is nearer to the natural $|\Delta\delta| = 0$ ppm. Thus, there has been inconsistency with the correct structure of natural pyrinodemin A between both groups. In this paper, we report the racemic synthesis of possible structures **2**−**4** for pyrinodemin A and support the C14′−C15′ double-bond positional isomer **3**, which Baldwin's group proposed, as the correct structure. Furthermore, we report the first enantioselective total synthesis of (−)-pyrinodemin A (**3**) through a highly diastereoselective intramolecular 1,3-dipolar cycloaddition reaction as the key step and the determination of its absolute configuration.

In comparison of the synthetic compounds **1**−**3** with the natural product, the most critically discriminating point is $\Delta\delta$ between the olefinic carbons. The farther the position of the double bond is from the isoxazolidine ring, the nearer the value of $\Delta\delta$ is to zero in natural pyrinodemin A. Therefore, we were interested in the $\Delta\delta$ of compound **4**, which has the double bond one carbon farther from the isoxazolidine ring than **3**. Thus, we first embarked on the synthesis of **4** as an alternative possible structure for pyrinodemin A.

The preparation of hydroxylamine **15c** required for the synthesis of **4** began with THP protection of 6-bromo-1-hexanol (**6**) (Scheme 1). Alkylation of the lithium acetylide ethylenediamine complex with bromide **7** ($n = 6$)[7] in DMSO containing NaI[4] afforded terminal alkyne **8** ($n = 6$) in 82% yield. Coupling of the lithium acetylide of **8** ($n = 6$) with bromide **10** ($m = 6$),[8] prepared by alkylating a lithio derivative of 3-picoline (**9**)[9] with 1,5-dibromopentane, provided alkyne **11c**, hydrogenation of which over Lindlar catalyst yielded *cis*-alkene **12c**. Deprotection of the THP ether in **12c** and Swern oxidation[10] of the resulting alcohol **13c** gave aldehyde **14c**, which was converted into the desired hydroxylamine **15c** by reductive amination with hydroxylamine and sodium cyanoborohydride in good yields. Dehydration condensation of the hydroxylamine **15c** and aldehyde **14a**, prepared from 5-hexyn-1-ol (**5**) by a similar sequence of reactions, generated a nitrone intermediate, an intramolecular 1,3-dipolar cycloaddition[11] of which in situ proceeded in refluxing toluene to diastereoselectively produce the fourth double-bond positional isomer **4** in 92% yield.[4−6,12] The synthesis of other possible double-bond positional isomers

Scheme 1[a]



[a] Reagents and conditions: (a) 3,4-dihydro-2*H*-pyran, 10-camphorsulfonic acid, CH_2Cl_2, 0 °C, 2 h, 100%; (b) $LiC{\equiv}CH{\cdot}H_2N(CH_2)_2NH_2$, NaI, DMSO, rt, 4 h, 82%; (c) **9**, LDA, THF, −78 °C, 30 min, then $Br(CH_2)_{m-1}Br$ ($m = 6, 7, 8$), −78 °C to room temperature, 12 h; (d) lithium acetylide of **8**, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone/THF (1:1), −15 °C to room temperature, 16 h; (e) H_2, 5% Pd−$CaCO_3$, EtOAc, rt, 18 h; (f) *p*-TsOH·H_2O, EtOH, rt, 45 min; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to room temperature, 1 h; (h) $NH_2OH{\cdot}HCl$, KOH, MeOH, rt, 30 min, then HCl (pH 3), $NaBH_3CN$, rt, 2 h; (i) **14a**, toluene, rt, 40 min, then reflux, 13 h.

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(5) Baldwin, J. E.; Romeril, S. P.; Lee, V.; Claridge, T. D. W. *Org. Lett.* **2001**, *3*, 1145−1148.
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(7) All new compounds reported here were satisfactorily characterized on the basis of their ^1H and ^{13}C NMR, IR, MS, and HRMS spectra. For selected characterization data, see Supporting Information.
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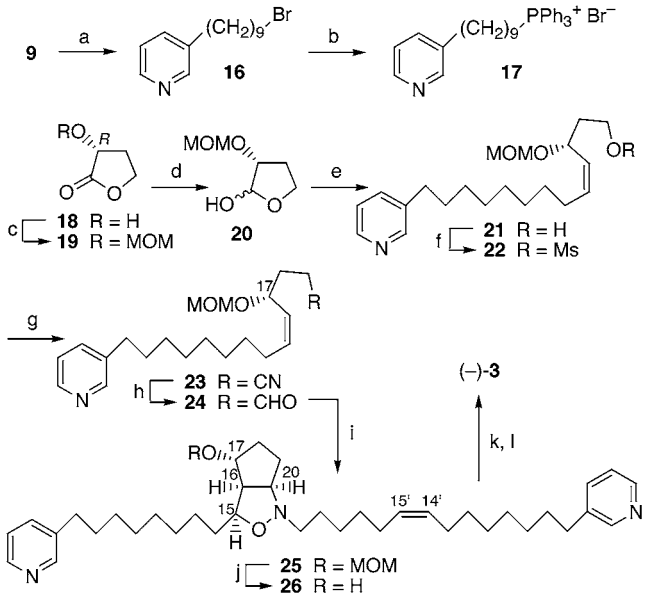
2 and **3** was also carried out by the same synthetic methodology as that of **4**.

The ^{13}C NMR spectral data and $|\Delta\delta| = 0.4$ ppm of our synthetic **2**[7] were identical to those of the authentic sample reported by Snider and Baldwin.[4,5] The $|\Delta\delta| = 0.02$ ppm of our synthetic **3** was also identical to Baldwin's $\Delta\delta$.[6] Surprisingly, it has been found that the $|\Delta\delta| = 0.3$ ppm of synthetic **4** becomes larger than that of **3**. Moreover, the ^{13}C NMR data of **3** were in better agreement with the literature data of natural product than either **2** or **4**.[7] Therefore, we conclude that the structure **3** with a C14′−C15′ double bond is the correct one of natural pyrinodemin A as proposed by Baldwin et al.

To solve the problem of the absolute configuration of pyrinodemin A, we next planned the enantioselective synthesis of the natural product employing chiral aldehyde **24** with an asymmetric center at the allylic C17 position instead of aldehyde **14a** (Scheme 2). Commercially available (*R*)-

Scheme 2[a]



[a] Reagents and conditions: (a) **9**, LDA, THF, −78 °C, 30 min, then $Br(CH_2)_8Br$, −78 °C to room temperature, 9 h, 65%; (b) HBr, PPh_3, CH_3CN, reflux, 29 h, 93%; (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to room temperature, 41 h, 88%; (d) DIBALH, toluene, −78 °C, 1 h, 89%; (e) **17**, KHMDS, THF, 0 °C, 1 h, then **20**, −78 °C to room temperature, 30 min, 91%; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C to room temperature, 1 h, 81%; (g) KCN, 18-crown-6, CH_3CN, 50 °C, 20 h, 90%; (h) DIBALH, toluene, −78 °C, 20 min, 81%; (i) **15b**, toluene, reflux, 13 h, 95%; (j) HCl, EtOH, 50 °C, 16 h, 95%; (k) PhOCSCl, DMAP, CH_3CN, rt, 41 h; (l) *n*-Bu_3SnH, AIBN, toluene, 100 °C, 10 min, 59% (two steps).

(+)-α-hydroxy-γ-butyrolactone (**18**) was chosen as a starting material. MOM protection of the hydroxy group in lactone **18** and subsequent DIBALH reduction of lactone **19** at −78 °C afforded lactol **20** in good overall yield. Phosphonium bromide **17**, requisite for Wittig reaction with the lactol **20**, was prepared from 3-picoline (**9**) by alkylation with 1,8-dibromooctane and subsequent substitution with triphenylphosphine.[13] Wittig olefination of the lactol **20** with a phosphorane generated by treating phosphonium bromide **17** with potassium hexamethyldisilazide (KHMDS) stereoselectively provided only (*Z*)-alkene **21** ($J = 10.9$ Hz between the olefinic protons) in 91% yield. One-carbon homologation of the alcohol **21** was performed by mesylation and substitution with KCN in the presence of 18-crown-6 to yield nitrile **23**, which was reduced to aldehyde **24** by DIBALH. An intramolecular asymmetric 1,3-dipolar cycloaddition reaction[14] of the alkenylnitrone derived from hydroxylamine **15b** and chiral aldehyde **24** proceeded smoothly to construct the desired *cis*-cyclopent[*c*]isoxazolidine ring system in 95% yield and excellent diastereoselectivity (>99:1).

The stereochemistry of the bicyclic ring system in **25** was unambiguously confirmed by the coupling constant $J_{16-17} = 2.6$ Hz and the presence of NOEs observed between the diagnostic protons[14b] as shown in Figure 1. The high

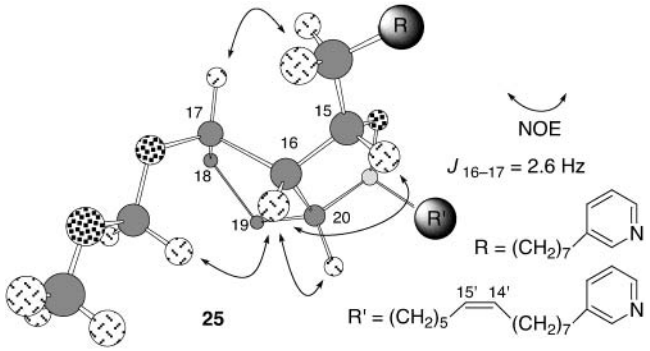


Figure 1. Diagnostic NOEs observed in **25**. Hydrogens on C18 and C19 have been omitted for clarity.

diastereoselectivity might be rationalized as follows. In the transition states **b** and **c** leading to another diastereomer, sterically encumbered $A^{1,3}$-strain[15] and 1,3-diaxial-like interaction[16] occur between respective substituents as shown in Figure 2. Therefore, because the transition state **a** without

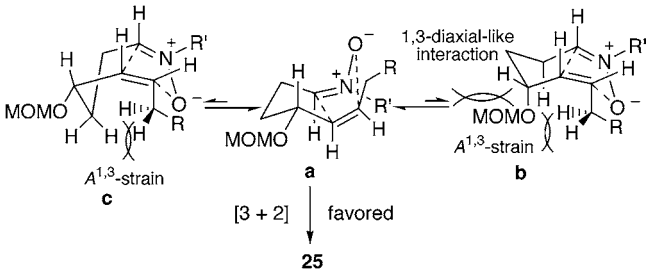


Figure 2. Plausible transition states leading to **25**. For R and R′, see Figure 1.

such a repulsive interaction becomes much more stable than **b** and **c**, **25** might exclusively be formed.[14]

Deprotection of the MOM ether in **25** under acidic conditions gave alcohol **26**, wherein deoxygenation of the secondary hydroxy group was effected by means of the following stepwise reactions: (1) thionocarbonate formation with phenyl chlorothionoformate and (2) reduction with *n*-Bu_3SnH in the presence of AIBN radical initiator.[17] The spectral characteristics (^1H and ^{13}C NMR and EI-MS) of synthetic **3**,[18] $[\alpha]^{26}_D$ −6.42 (*c* 0.94, $CHCl_3$) (lit.[2] $[\alpha]^{25}_D$ −9 (*c* 1.0, $CHCl_3$)), were identical to those reported for the natural product.[2] Thus, it has been found that the hitherto unknown absolute configuration of pyrinodemin A is as indicated in the structural formula **3**.

In conclusion, we have achieved the racemic synthesis of possible structures **2**−**4** for pyrinodemin A and assigned the C14′−C15′ position to the correct double-bond structure as had been proposed by Baldwin et al. We have also accomplished the first asymmetric total synthesis of (−)-pyrinodemin A (**3**), featuring a highly diastereoselective intramolecular nitrone−olefin cycloaddition, and determined the absolute configuration of (−)-**3**. These results may imply the unknown absolute configuration of pyrinodemins B−D related to (−)-**3** and will be essential for investigating their structure−activity relationships and biogenesis.

Acknowledgment. We thank Professors J. Kobayashi and M. Tsuda, Hokkaido University, for copies of the spectral data of natural pyrinodemin A. This research was partly supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science and the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and characterization data for **4** and (−)-**3**, characterization data for **2** and the natural product, and copies of ^1H and ^{13}C NMR and MS spectra of **2**, **4**, (−)-**3**, and the natural product. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Optical purity of synthetic **3** has been determined to be >99% ee by derivatization of alcohol **26** to a Mosher ester and integration of the signals in the ^1H NMR spectrum (Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549).