ORGANIC LETTERS

2004
Vol. 6, No. 18
3095−3097

# Synthetic Studies on (+)-Naphthyridinomycin: Stereoselective Synthesis of the Tetracyclic Core Framework

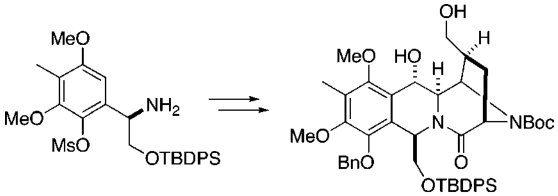
**Kazuki Mori, Kentaro Rikimaru, Toshiyuki Kan, and Tohru Fukuyama***

*Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo,
Bunkyo-ku, Tokyo, Japan*

*fukuyama@mol.f.u-tokyo.ac.jp*

**Received June 16, 2004**

## ABSTRACT



10

21

**The stereoselective synthesis of the tetracyclic intermediate 21 for (+)-naphthyridinomycin (1) has been accomplished. The convergent synthesis used the Ugi 4CC reaction with the amine derivative 10. The key features of the stereoselective synthesis of 21 were the intramolecular Mizoroki–Heck reaction, an aromatic–aldehyde cyclization, and a stereoselective hydroboration.**

Naphthyridinomycin (**1**), an antitumor antibiotic alkaloid isolated from *Streptomyces lusitanus* by Kluepfel et al. in 1974,[1] has shown potent activity against both Gram-negative and Gram-positive bacteria.[2] In addition, it has displayed activity against a penicillin-sensitive, resistant *Staphylococcus aureus* but showed lethal toxicity against laboratory mice. This remarkable biological activity, coupled with its highly complex structure, has made naphthyridinomycin an attractive target for total synthesis, and several synthetic studies on this family of compounds have been published.[2] However, only two total syntheses, by Evans[3] and by our[4] group in the 1980s, of a stable derivative **2**, that is readily converted to **1**, have been reported to date. One of the crucial steps in the total synthesis of **1** is the construction of the highly strained 3,8-diazabicyclo[3.2.1]octane framework in the complex ring system of **1**. During the course of our total synthesis of ecteinascidin 743 (Et 743),[5] we established an efficient synthetic strategy for tetrahydroisoquinoline alkaloids via the Ugi four-component condensation (4-CC) and the intramolecular Mizoroki−Heck reaction. We thought that this protocol could be applied to the synthesis of related natural products. Herein, we report a stereocontrolled synthesis of the tetracyclic intermediate **21** for the total synthesis of **1**.

The heart of our synthetic plan is illustrated in Scheme 1. Since the hemiaminal and the quinone moiety of **1** would be highly labile to many reaction conditions, they must be formed in the latter stages of any total synthesis. Thus, the tetracyclic diol **3**, from which the oxazolidine ring could be

---

(1) (a) Kluepfel, D.; Baker, H. A.; Piattoni, G.; Sehgal, S. N.; Sidorowicz, A,; Singh, K.; Vezina, C. *J. Antibiot*. **1975**, *28*, 497. (b)Sygusch, J.; Brisse, F.; Hanessian, S. *Tetrahedron Lett*. **1974**, *15*, 4021. (c) erratum: Sygusch, J.; Brisse, F.; Hanessian, S. *Tetrahedron Lett*. **1975**, *16*, 170. (c) Hanessian, S.; Kluepfel, D. *Acta Crystallogr*. **1976**, *B32*, 1139.

(2) For a recent review of tetrahydroisoquinoline alkaloids, see: Scott, J. D.; Williams, R. M. *Chem. Rev*. **2002**, *102*, 1669.

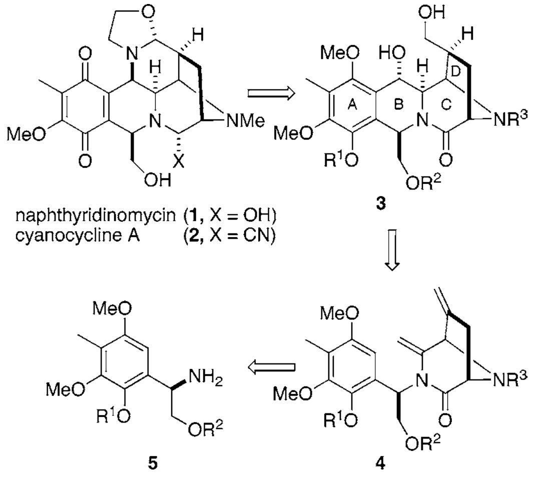
(3) (a) Evans, D. A.; Biller, S. A. *Tetrahedron Lett*. **1985**, *26*, 1907. (b) Evans, D. A.; Biller, S. A. *Tetrahedron Lett*. **1985**, *26*, 1911. (c) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc*. **1986**, *108*, 2478.

(4) (a) Fukuyama, T.; Laird, A. A. *Tetrahedron Lett*. **1986**, *27*, 6173. (b) Fukuyama, T.; Li, L.; Laird, A. A.; Frank, R. K. *J. Am. Chem. Soc*. **1987**, *109*, 1587. (c) Fukuyama, T. *Adv. Heterocycl. Nat. Prod. Synth*. **1992**, *2*, 189.

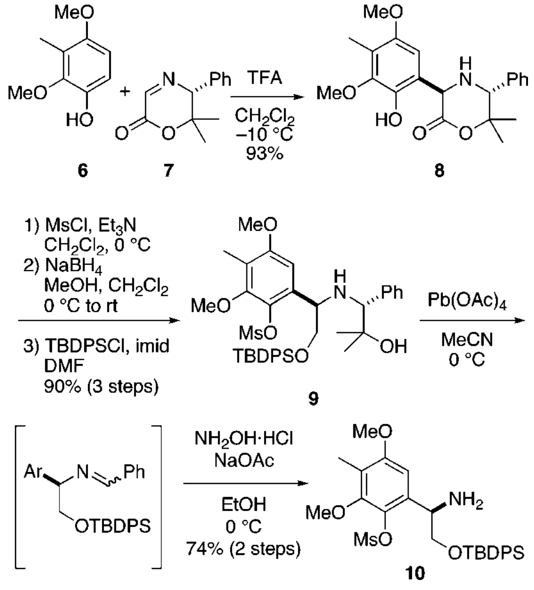
(5) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc*. **2002**, *124*, 6552.

10.1021/ol048857e CCC: $27.50

**Scheme 1.** Structure and Synthetic Strategy of **1**



**Scheme 2.** Synthesis of the Left-Hand Segment **10**



readily prepared, was designed as the key intermediate in our total synthesis of **1**. The primary alcohol of **3** was expected to be constructed by a stereoselective hydroboration of the *exo*-olefin of the tetracyclic intermediate after construction of the B-ring from **4**. According to our Et 743 synthesis,[5] the bicyclo[3.2.1]octane ring of the enamide **4** could be formed by the intramolecular Mizoroki−Heck reaction. We anticipated that the cyclization precursor would be prepared by the Ugi 4-CC reaction through a diketopiperazine intermediate.

Synthesis of the highly functionalized (*R*)-arylglycinol **10** was accomplished via the Mannich-type reaction of the phenol **6**[6] with the chiral template **7**, developed in our laboratories[7] (Scheme 2). Thus, coupling of the phenol **6** with the chiral iminolactone **7** proceeded smoothly in high regio- and stereoselectivity under acidic conditions to provide the desired adduct **8** as a single product.[8] Protection of the phenol of **8** with the mesyl group, reductive ring opening of the lactone, and selective silylation of the resulting primary alcohol provided **9**. Oxidative cleavage of the 1,2-amino alcohol moiety was effected with $Pb(OAc)_4$, and subsequent treatment with $NH_2OH$ converted the imine to the desired arylglycinol **10**.

Segments **10** and **11**[9] were incorporated into the diketopiperazine **13** by means of the powerful Ugi 4-CC reaction[10] (Scheme 3). A mixture of the amine **10**, the carboxylic acid **11**, *p*-methoxyphenyl isocyanide,[11] and acetaldehyde in MeOH afforded the dipeptide **12** in almost quantitative yield. Subsequent cleavage of the Boc group gave the primary amine, which cyclized to afford **13** upon reflux in toluene. Conversion of **13** into the cyclic enamide **14** was performed by a three-step sequence involving introduction of a Boc group onto the lactam nitrogen,[12] partial reduction of the ring carbonyl group with $NaBH_4$, and dehydration of the resulting hemiaminal derivative by treatment with CSA and quinoline. With the requisite enamide **14** in hand, we then focused our attention on the construction of the bicyclo[3.2.1]octane ring of **15**. Although the construction of the bicyclo[3.3.1] ring system in Et 743 was accomplished by common Mizoroki−Heck reaction conditions,[13] such as a combination of $Pd_2(dba)_3$, P(*o*-tol)$_3$, and $Et_3N$, unfortunately, the desired reaction of **14** did not proceed under these conditions. After an extensive search for alternative conditions, we found that the combination of the $Pd_2(dba)_3$ catalyst with $Et_3N$ in DMA without a phosphine ligand was suitable for the construction of the bicyclo[3.2.1] ring system of the enamide **15**. The next challenge in the synthesis was the production of the hydroxymethyl group of **17** with control of the stereochemistry at the C-13c position. According to the Et 743 synthesis,[5] the enamide of **15** was regioselectively oxidized with dimethyldioxirane[14] in MeOH−acetone to generate an acid-sensitive epoxide, which, without isolation, was immediately treated with CSA to afford the methoxy alcohol **16** as a single isomer. The subsequent acyliminium ion-mediated reduction under acidic conditions occurred from the less hindered *exo*-face of the molecule to afford the alcohol **17** as a single isomer with the correct stereochemistry.[15]

---

(6) Fukuyama, T.; Yang, L. *Tetrahedron Lett.* **1986**, *27*, 6299.

(7) (a) Tohma, S.; Endo, A.; Kan, T.; Fukuyama, T. *Synlett* **2001**, 1179. (b) Tohma, S.; Rikimaru, K.; Endo, A.; Shimamoto, K.; Kan, T.; Fukuyama, T. *Synthesis* **2004**, 1179.

(8) The confirmation of the stereochemistry of **8** was performed by X-ray analysis; see ref 7a,b.

(9) The allylglycine derivative **11** was synthesized by utilizing Oppolzer's camphorsultam chiral auxiliary, see: (a) Leanna, M. R.; Morton, H. E. *Tetrahedron Lett.* **1993**, *34*, 4485. (b) Lopez, A, Pleixats, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1967.

(10) For a recent review, see: Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.

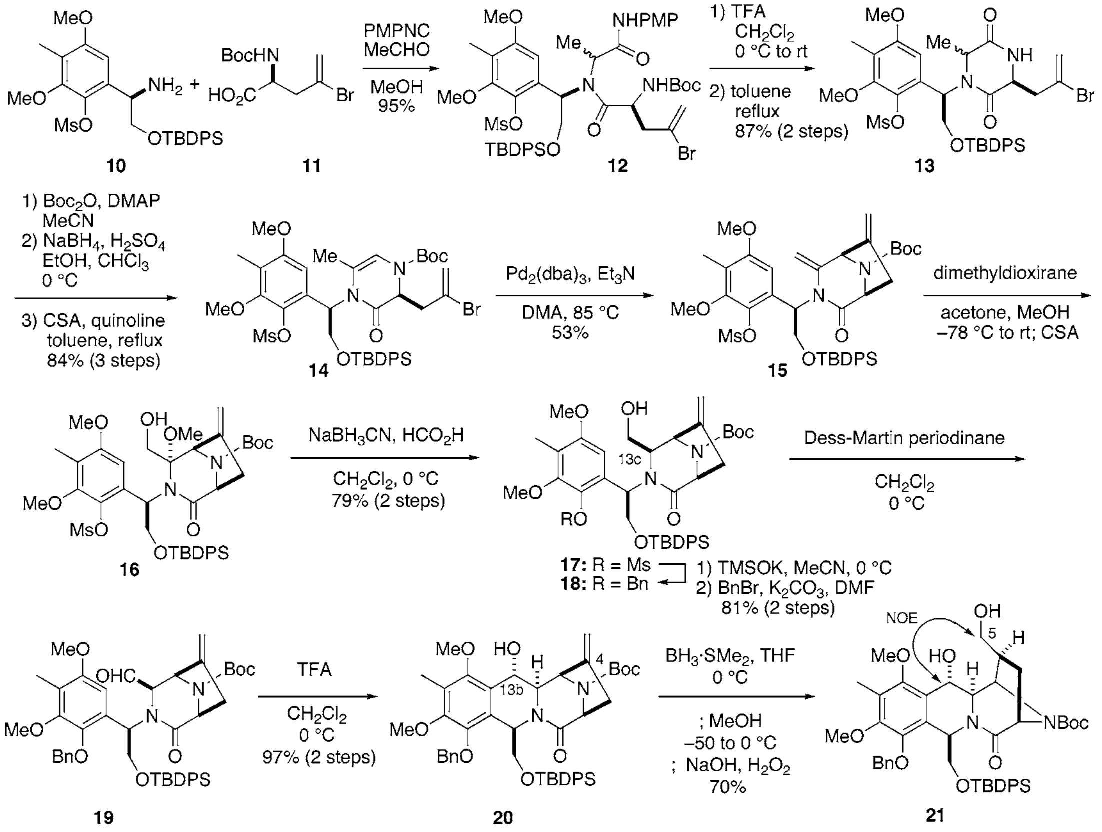
(11) Gokel, G. W.; Widera, R. P.; Weber, W. P. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 232.

(12) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2425.

(13) For a recent review, see: (a) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1998; p 231.

(14) Murray, R. W.; Singh, M. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX, p 288.

**Scheme 3.** Synthesis of the Tetracyclic Key Intermediate **21**



Construction of the B-ring was accomplished by the coupling reaction between the aromatic ring and an aldehyde. Since the reactivity of the aromatic ring was dependent on its electron-donating nature, the protecting group of the phenol **17** was changed from the mesyl to the corresponding benzyl ether. After oxidation of the alcohol **18** with the Dess−Martin periodinane,[16] treatment of the resulting aldehyde **19** with TFA allowed the desired cyclization to proceed smoothly providing **20** as a single isomer. The secondary alcohol of **20** possessed the required oxidation state and stereochemistry at the C-13b position for the formation of the oxazolidine moiety. The construction of the hydroxymethyl group of **21** from the *exo*-methylene **20** was achieved by stereoselective hydroboration.[17] Treatment of **20** with 3 equiv of $BH_3$•$SMe_2$ at 0 °C produced the desired reaction with control of the stereochemistry at the C-4 position. The excess borane reagent was destroyed by treatment with MeOH at −50 °C. Oxidative treatment with NaOH and $H_2O_2$ gave the desired diol **21** without any loss of the lactam ring. The stereochemistry at C-13b and C-4 of **21** was confirmed by a strong NOE between the H-13b and $H_2$-5, as shown in Scheme 3.

In summary, we have accomplished the efficient synthesis of the tetracyclic backbone **21** of (+)-naphthyridinomycin (**1**) including the highly strained bicyclic[3.2.1]octane framework. The present synthesis features the powerful Ugi 4-CC reaction for a ready access to the diketopiperazine **13**, the Mizoroki−Heck reaction of the cyclic enamide **14** to give the highly strained tricycle **15**, and the completely stereoselective hydroboration of **20**. Further conversion of **21** to (+)-naphthyridinomycin (**1**) is currently under investigation in our laboratory.

**Acknowledgment.** This work was financially supported by CREST, JST, and a Grant-in-Aid from the Ministry of Education, Science, Sports, Culture and Technology, Japan.

**Supporting Information Available:** Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048857E

---

(15) Since the bicyclo[3.2.1] octane skeleton was more reactive than the related bicyclo[3.3.1] system of Et 743, the use of the weaker formic acid was required for the generation of the acyliminium ion from **16**.

(16) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 902. (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

(17) Presumably, the borane reagent attacked from the less hindered exo-face of the bicyclo[3.3.1] skeleton to afford the desired stereochemistry at the C-4 position. The selective-production of both stereochemistries at C-4 would be significant, since both stereochemistries were observed in this family of natural products. The endo-oriented compounds belong to the naphthyridinomycin family (naphthyridinomycin and dnacins), while the corresponding exo-oriented compounds belong to the quinocarcin family (quinocarcin, tetrazomine, and lemonomycin). See ref 2.