First Total Synthesis of Neoantimycin

Hikaru Ogawa, Hideo Iio, Yoshinosuke Usuki

First Total Synthesis of Neoantimycin

Hikaru Ogawa, Hideo Iio, and Yoshinosuke Usuki*
Division of Molecular Materials Science, Graduate School of Science, Osaka City University, 3-3-138 Sugimoto, Sumiyoshi-ku, Osaka 558-8585

(E-mail: usuki@sci.osaka-cu.ac.jp)

The first total synthesis of neoantimycin (**1**), an unusual ring-extended antibiotic of the antimycin class, has been achieved, wherein intramolecular transesterification was utilized for construction of the 15-membered tetralactone core.

Neoantimycin (**1**) is a rare and unusual ring-extended member of the antimycin class. First isolated in 1967 from a South American soil isolate of *Streptomyces orinoci*,[1] the partial configuration of **1** was assigned in 1969 by preparative-scale degradation that yielded methyl (*S*)-2-hydroxyisovalerate and methyl (2*S*,3*S*)-2-hydroxy-3-methylvalerate.[2] At that time, an L-Thr configuration was also asserted but not proven. A subsequent study using NOE experiments, reported by Takeda in 1998, attributed a 3*S*,4*S* configuration to the 3,4-dihydroxy-2,2-dimethyl-5-phenylvaleric acid residue in neoantimycin.[3] Literature references to **1** were thus limited, but the recent discovery of prunustatin A (**2**) as a selective GRP78 molecular chaperone down-regulator,[4] which could lead to the development of new approaches toward combatting cancer, highlights the potential of this class as research probes (Figure 1). As an extension of our synthetic studies on prunustatin A (**2**),[5] we have been engaged in studies directed toward the synthesis and structure determination of **1**. During our pursuit of a total synthesis, Capon reported all configurational assignments of **1** based on spectroscopic analysis and micro-scale degradation, and its inhibitory activity toward K-Ras.[6] We then focused on a synthetic confirmation on the stereochemical structure of **1**. Herein, we report the first total synthesis of neoantimycin (**1**).

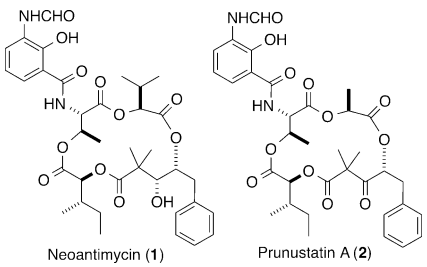
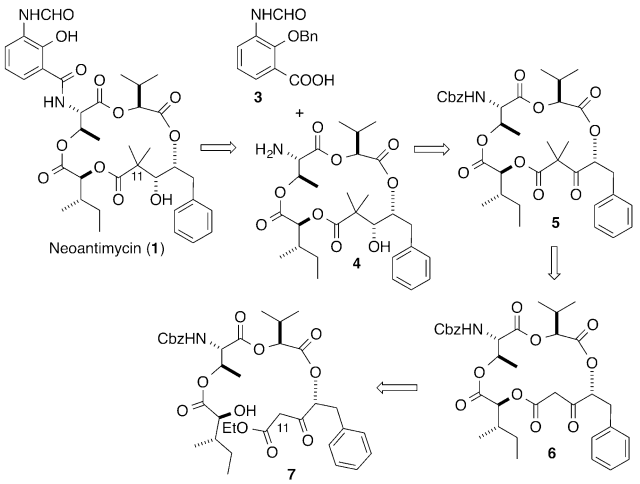


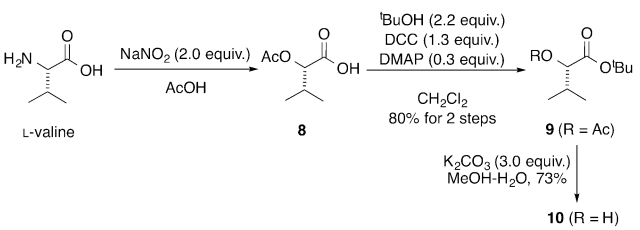
Figure 1. Structures of neoantimycin (**1**) and prunustatin A (**2**).

Preliminary molecular mechanics calculations suggest that the ring-closing precursors prefer a liner, extended conformation due to the *gem*-dimethyl groups at C11. Therefore we adopted synthetic strategy for **1** that involves cyclization via transesterification of β-keto ester **7** followed by the late-stage introduction of the *gem*-dimethyl groups at C11 (Scheme 1). Transesterification of β-keto ester mediated with metal salt would proceed under mild conditions, which minimize the epimerization at other stereogenic centers.



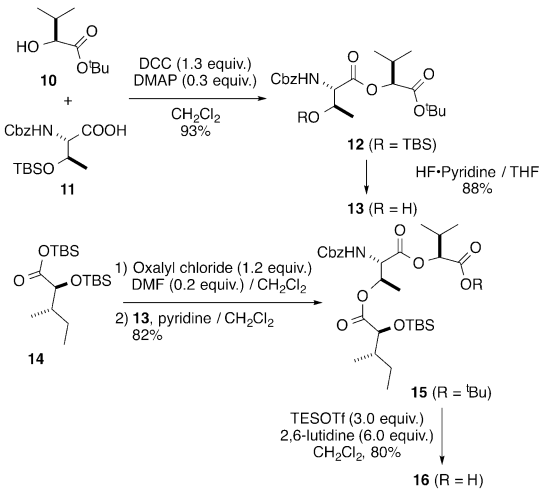
Scheme 1. Retrosynthetic analysis of neoantimycin (**1**).

Our total synthesis of **1** commenced with L-valine (Scheme 2). Treatment of L-valine with $NaNO_2$ in acetic acid provided acetate **8**,[7] which was converted to *tert*-butyl ester **9**. Hydrolysis of the acetyl group with K_2CO_3 in aq MeOH resulted in the formation of **10** in 73% yield.



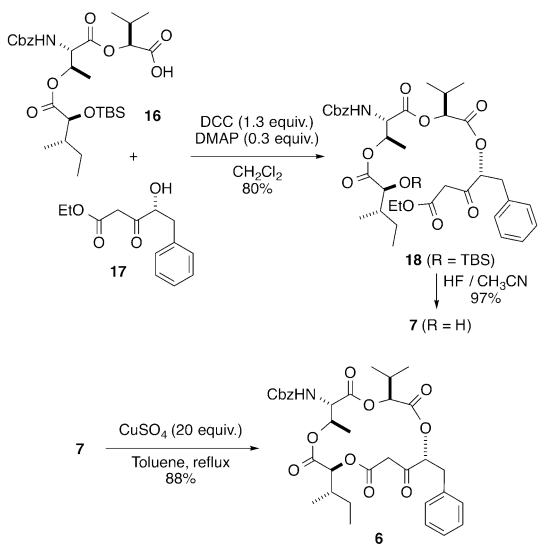
Scheme 2. Preparation of *tert*-butyl (*S*)-2-hydroxy-3-methylbutyrate **10**.

Condensation of **10** with *O*-TBS-protected *N*-Cbz-L-threonine **11**[8] in the presence of DCC and DMAP provided **12** in 93% yield (Scheme 3). Removal of the TBS group was achieved with HF-pyridine to afford **13** in 88% yield. Treatment of bis-*O*-TBS-protected L-isoleucine derivative **14** with oxalyl chloride in the presence of a catalytic amount of DMF afforded the corresponding acid chloride,[9] which was esterified with **13** to provide **15** in 82% yield. The *tert*-butyl group was removed with TESOTf and 2,6-lutidine to give **16** in 80% yield.[10]



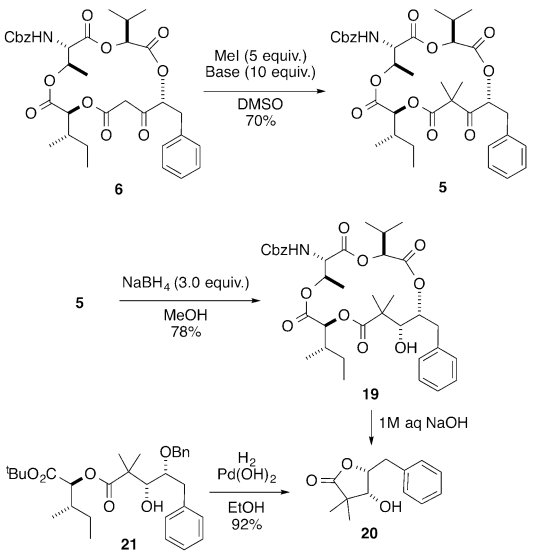
Scheme 3. Preparation of acid **16**.

The ring-closure precursor **7** was obtained by condensation of **16** with **17**[5b] in the presence of DCC and DMAP and subsequent removal of the TBS group with HF in CH_3CN (Scheme 4). A mixture of **7** and anhydrous $CuSO_4$ (20 equiv.) in toluene was heated under reflux. The desired transesterification proceeded smoothly to provide the 15-membered tetralactone **6** in 88% yield.[11]



Scheme 4. Preparation and transesterification of **7**.

Introduction of *gem*-dimethyl groups at C11 was achieved by treatment of **6** with iodomethane (5 equiv.) and K_2CO_3 (10 equiv.) in DMSO at 40 ºC for 4 h (Scheme 5). The desired product **5** was obtained in 70% yield. Reduction of **5** with $NaBH_4$ proceeded smoothly to provide the corresponding alcohol **19** in 78% yield as a single diastereomer. Subsequent treatment of **19** with 1M aq NaOH resulted in formation of the five-membered lactone **20**, which was alternatively provided by reductive removal of the benzyl group in **21**[12]; the configuration at C10 was thus confirmed.



Scheme 5. Introduction of the *gem*-dimethyl groups and reduction with $NaBH_4$.

Molecular mechanics calculations on **5** were conducted using the MMFF94 force field.[13] A possible conformation, as shown in Figure 2, clearly explains the high stereoselectivity observed in the reduction of **5**: one of the gem-dimethyl groups hinders the approach of hydride to the alpha face of the carbonyl moiety.

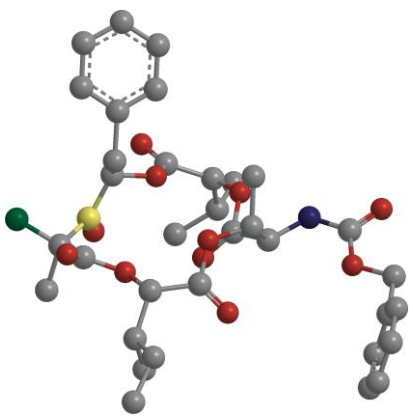
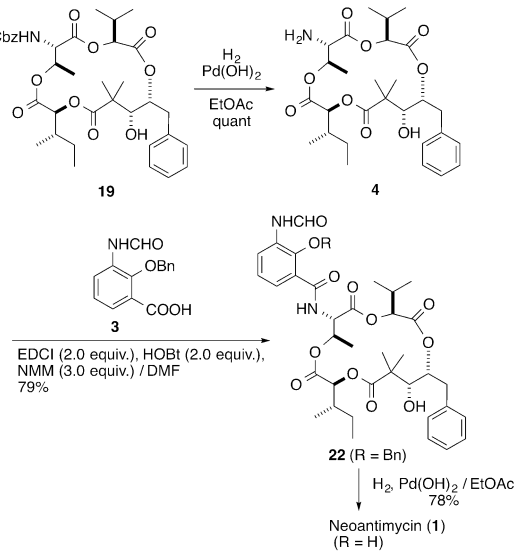


Figure 2. A possible conformation of **5** calculated with the MMFF94 force field. Green: one of the gem-dimethyl group, Yellow: carbonyl carbon.

To complete the synthesis of **1**, the Cbz group of **19** was removed by hydrogenolysis with $Pd(OH)_2$ in EtOAc to afford **4**. The subsequent condensation of **4** and **3**[14] was achieved using EDCI, HOBt, and NMM in DMF to provide the corresponding **22**[15] in 79% yield. Removal of the benzyl ether protecting group using $Pd(OH)_2$ in EtOAc afforded neoantimycin (**1**) in 78% yield (Scheme 6). The spectral data of synthetic **1** were identical to those reported for a natural sample.[15,16] The optical rotation of synthetic **1** ($[\alpha]_D$ +24.8, c 0.11, $CHCl_3$) was consistent with that of the natural product ($[\alpha]_D$ +21.2, c 0.01, $CHCl_3$).[2]



Scheme 6. Endgame towards Neoantimycine (**1**)

In summary, the first total synthesis of neoantimycin (**1**) has been achieved. Comparison of our spectroscopic data with those reported for natural verified the structure of the natural product. Further studies are now in progress, and the results will be reported in due course.

References and Notes

1 G. Cassinelli, A. Grein, P. Orezzi, P. Pennella, A. Sanfilippo, *Arch. Mikrobiol.* **1967**, *55*, 358.

2 L. Caglioti, D. Misiti, R. Mondelli, A. Selva, F. Arcamone, G. Cassinelli, *Tetrahedron* **1969**, *25*, 2193.

3 Y. Takeda, T. Masuda, T. Matsumoto, Y. Takechi, T. Shingu, H. G. Floss, *J. Nat. Prod.* **1998**, *61*, 978.

4 a) Y. Umeda, S. Chijiwa, K. Furihata, K. Furihata, S. Sakuda, H. Nagasawa, H. Watanabe, K. Shin-ya, *J. Antibiot.* **2005**, *58*, 206; b) Y. Umeda, K. Furihata, S. Sakuda, H. Nagasawa, K. Ishigami, H. Watanabe, M. Izumikawa, M. Takagi, T. Doi, Y. Nakao, K. Shin-ya, *Org. Lett.* **2007**, *9*, 4239.

5 a) T. Inaoka, Y. Tei, Y. Usuki, H. Iio, *Abstracts of Papers*, 457, 52nd Symposium on the Chemistry of Natural Products, Shizuoka, **2010**; b) Y. Usuki, H. Ogawa, K.-I. Yoshida, T. Inaoka, H. Iio, *Asian J. Org. Chem.* in press.

6 A. A. Salim, K.-J. Cho, L. Tan, M. Quezada, E. Lacey, J. F. Hancock, R. J. Capon, *Org. Lett.* **2014**, *16*, 5036.

7 A. B. Hughes, M. M. Sleebs, *J. Org. Chem.* **2005**, *70*, 3079.

8 T. Sengoku, Y. Nagae, Y. Ujihara, M. Takahashi, H. Yoda, *J. Org. Chem.* **2010**, *77*, 4391.

9 A. Murai, Y. Amino, T. Ando, *J. Antibiot.* **1985**, *58*, 1610.

10 M. Oikawa, T. Ueno, H. Oikawa, A. Ichihara, *J. Org. Chem.* **1995**, *60*, 5048.

11 B. P. Bandgar, V. S. Sadavarte, L. S. Uppala, *Synth. Commun.* **2001**, *31*, 2063.

12 S. Yamakoshi, E. Kawanishi, *Tetrahedron Lett*. **2014**, *55*, 1175.

13 T. A. Halgren, *J. Comput. Chem.* **1996**, *17*, 490.

14 G. R. Pettit, T. H. Smith, S. Feng, J. C. Knight, R. Tan, R. K. Pettit, P. A. Hinrichs, *J. Nat. Prod.* **2007**, *70*, 1073.

15 The ^{1}H and ^{13}C NMR spectra indicated that it existed as a ca. 9:1 mixture of two rotamers.

16 **1**: m.p. 120-121ºC, natural[2]: m.p. 121-122 ºC; $[\alpha]_D$ = +53.3 (c 0.30, $CHCl_3$), natural[2]: $[\alpha]_D$ = +58.3 (c 1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.63 (1H, s), 8.56 (1H, d, *J* = 8.1 Hz), 8.50 (1H, d, *J* = 1.7 Hz), 7.92 (1H, s), 7.32 (1H, dd, *J* = 8.1, 1.5 Hz), 7.29–7.19 (5H, m), 7.14 (1H, d, *J* = 8.7 Hz), 6.94 (1H, t, *J* = 8.1 Hz), 5.73 (1H, qd, *J* = 6.5, 2.6 Hz), 5.52 (1H, dd, J = 9.6, 5.8 Hz), 5.44 (1H, d, *J* = 3.5 Hz), 5.12 (1H, dd, *J* = 8.7, 2.6 Hz), 4.66 (1H, d, *J* = 8.3 Hz), 3.54 (1H, d, *J* = 12.4 Hz), 3.18 (1H, d, *J* = 12.4 Hz), 3.16 (1H, dd, *J* = 14.0, 9.6 Hz), 2.94 (1H, dd, *J* = 14.0, 5.8 Hz), 1.99–1.93 (1H, m), 1.83–1.78 (1H, m), 1.55–1.48 (1H, m), 1.41 (3H, s), 1.33 (1H, d, *J* = 6.5 Hz), 1.30 (3H, s), 1.25–1.16 (1H, m), 0.89 (3H, d, *J* = 6.9 Hz), 0.88 (3H, t, *J* = 7.5 Hz), 0.81 (3H, d, *J* = 6.9 Hz), 0.45 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.90, 170.20, 168.27, 168.27, 168.10, 158.93, 150.53, 136.74, 129.20, 128.62, 127.34, 126.85, 124.73, 120.25, 118.96, 112.85, 79.05, 77.00, 76.70, 75.10, 72.38, 71.79, 55.16, 45.39, 40.26, 35.97, 30.68, 26.89, 24.73, 21.87, 18.70, 16.27, 16.09, 14.30, 10.52; HR-ESI-MS: calcd. For $C_{36}H_{47}N_2O_{12}$: 699.3124; found 699.3224 $[M+H]^+$.

Graphical Abstract

Textual Information

A brief abstract	First total synthesis of neoantimycin (**1**), a rare and unusual ring-extended member of the antimycin class, has been achieved. The key step involved an intramolecular transesterification for the construction of 15-membered tetralactone core of **1**. Comparison of our spectroscopic data with those reported for **1** verified the structure of the natural product.
Title	First Total Synthesis of Neoantimycin
Authors' Names	Hikaru Ogawa, Hideo Iio, and Yoshinosuke Usuki*

Graphical Information