First Total Synthesis of Neoantimycin

Hikaru Ogawa, Hideo Iio, Yoshinosuke Usuki

<table>
<thead>
<tr>
<th>Citation</th>
<th>Chemistry Letters, 44 (9): 1214-1216</th>
</tr>
</thead>
<tbody>
<tr>
<td>Issue Date</td>
<td>2015</td>
</tr>
<tr>
<td>Type</td>
<td>Journal article</td>
</tr>
<tr>
<td>Text version</td>
<td>author</td>
</tr>
<tr>
<td>Rights</td>
<td>© 2015 The Chemical Society of Japan. This article may be downloaded for personal use only. Any other use requires prior permission of The Chemical Society of Japan. The following article has been submitted to ‘Chemistry Letters’. After it is published, it will be found at <a href="https://doi.org/10.1246/cl.150509">https://doi.org/10.1246/cl.150509</a></td>
</tr>
<tr>
<td>DOI</td>
<td>10.1246/cl.150509</td>
</tr>
</tbody>
</table>

Self-Archiving by Author(s)

Placed on: Osaka City University
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 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 tetractone 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 (2S,3S)-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 3S,4S 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) with metal salt would proceed under mild conditions, which minimize the epimerization at other stereogenic centers.

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

Our total synthesis of 1 commenced with L-valine (Scheme 2). Treatment of L-valine with NaNO2 in acetic acid provided acetate 8,7 which was converted to tert-butyl ester 9. Hydrolysis of the acetyl group with K2CO3 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-Chz-L-threonine 118 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
The ring-closure precursor 7 was obtained by condensation of 16 with 17 in the presence of DCC and DMAP and subsequent removal of the TBS group with HF in CH₂CN (Scheme 4). A mixture of 7 and anhydrous CuSO₄ (20 equiv.) in toluene was heated under reflux. The desired transesterification proceeded smoothly to provide the 15-membered tetralactone 6 in 88% yield.

Introduction of gem-dimethyl groups at C11 was achieved by treatment of 6 with iodomethane (5 equiv.) and K₂CO₃ (10 equiv.) in DMSO at 40 °C for 4 h (Scheme 5). The desired product 5 was obtained in 70% yield. Reduction of 5 with NaBH₄ 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; the configuration at C10 was thus confirmed.

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 was achieved using EDCI, HOBt, and NMM in DMF to provide the corresponding 22 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. The optical rotation of synthetic 1 ([α]D +24.8, c 0.11, CHCl₃) was consistent with that of the natural product ([α]D +21.2, c 0.01, CHCl₃).
In summary, the first total synthesis of neoantimycin (1) has been achieved. Comparison of our spectroscopic data with those reported for the natural product further studies are now in progress, and the results will be reported in due course.

References and Notes

15. The 'H and 13C NMR spectra indicated that it existed as a ca. 9:1 mixture of two rotamers.
16. I: m.p. 120-121°C, natural: m.p. 121-122°C; [α]D = +53.3 (c 0.30, CHCl3), natural: [α]D = +58.3 (c 1, CHCl3). 1H NMR (600 MHz, CDCl3): δ 12.63 (1H, s), 8.56 (1H, d, J = 8.1 Hz), 8.60 (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); 13C NMR (150 MHz, CDCl3): δ 176.90, 170.20, 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 C19H17N2O2: 699.3224; found 699.3224 [M+H]+.
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 the 15-membered tetralactone core of 1. Comparison of our spectroscopic data with those reported for 1 verified the structure of the natural product.