Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3997–4000

Synthesis of bhimamycin B based on oxidative rearrangement of 4-acetylnaphtho[1,2-*b*]furan-5-ol to naphtho[2,3-*c*]furan-4,9-dione

Hidemitsu Uno,* Seiya Murakami, Akiko Fujimoto and Youtarou Yamaoka

Division of Synthesis and Analysis, Department of Molecular Science, Integrated Center for Sciences, 2-5 Bunkyo-cho, Matsuyama 790-8577, Japan

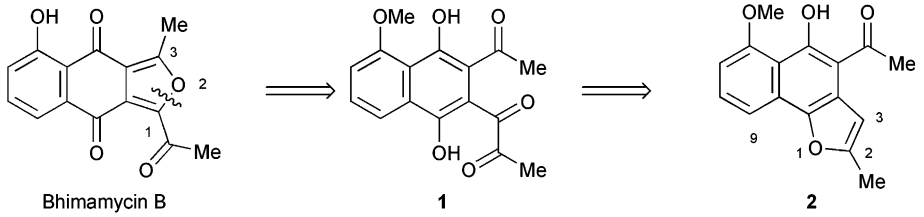
Received 3 March 2005; revised 9 April 2005; accepted 11 April 2005

Abstract—The first total synthesis of bhimamycin B, a novel member of naphtho[2,3-*c*]furan quinone antibiotics, was achieved by oxidative skeletal rearrangement of 4-acetylnaphtho[1,2-*b*]furan-5-ol.

A naphtho[*c*]furan skeleton, furan fused with naphthalene at β,β-positions, is not common in a various kind of naturally occurring furanonaphthoquinones and a few compounds have been reported so far.[1] Recently, Fotso et al. isolated an interesting new member of antibacterial naphtho[1,2-*c*]furan quinones, namely bhimamycins, from *Streptomyces* sp. GW32/698 together with dihydroxyanthraquinones such as chrysophanol and aloesaponarins.[2] We already reported our successful approach to the dihydroxyanthraquinones based on biomimetic intramolecular condensation of octaketide-mimicking compounds.[3] If our route would be close to the natural metabolic pathways to such dihydroanthraquinones, bhimamycins could be also synthesized from our key intermediates by a proper choice of reagents. This is proven by using naphtho[1,2-*b*]furan **2**[3] as the key compound. In this communication, we would like to show the first synthesis of bhimamycin B based on the oxidative skeletal rearrangement of naphtho[1,2-*b*]furan to naphtho[2,3-*c*]furan.

Retro-synthetic analysis of bhimamycin B is shown in Scheme 1. The furan ring of bhimamycin B is cleaved between C1 and oxygen to give hydrojuglone derivative **1** with acetyl and pyruvic units, which may be in turn obtained by oxidative cleavage of naphtho[1,2-*b*]furan **2**.

Preparation of naphtho[1,2-*b*]furan **2** was achieved by the Lewis acid-promoted reaction of acetyljuglone derivative **3**[4] with 2-(trimethylsiloxy)propene followed by treatment with Ac_2O/pyridine and saponification with aq-NaOH (Scheme 2). First, we tried to introduce a bromine atom at the 3-position of **2**. Treatment of **2** with NBS in dichloromethane, however, gave a 9-bromo derivative of **2** in quantitative yield. This result is easily rationalized by HOMO coefficients of the unsubstituted



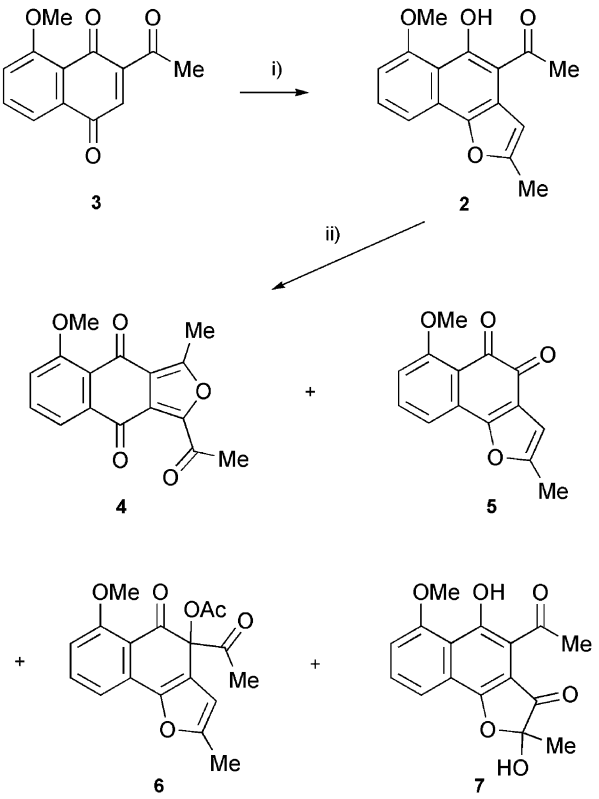
Scheme 1. Retro-synthesis of bhimamycin B.

Keywords: Bhimamycin B; Iodosobenzene diacetate; Naphtho[2,3-*c*]furan.
* Corresponding author. Tel.: +81 89 927 9660; fax: +81 89 927 9670; e-mail: uno@dpc.ehime-u.ac.jpc

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.04.037

positions of **2** calculated by MOPAC.[5] The calculation also revealed that the C3 carbon had the largest negative electron density (0.325) among the unsubstituted carbon atoms. Therefore, we examined the oxidation reaction of **2** under various conditions[6] and the results are summarized in Table 1.

Treatment of **2** with 2.2-molar equivalents of ceric(IV) ammonium nitrate (CAN)[7] gave single product (run 1), which was proven to be 5-*O*-methylbhimamycin B (**4**) by spectroscopic data† and finally by X-ray crystallographic analysis (Fig. 1).‡ However, the yield was quite low (18%) due to resinous material formation. This could not be improved by change of the equivalent of CAN. Oxidation of **2** with a 2.0-molar ratio of $Pb(OAc)_4$[8] gave a mixture of two compounds (run 2), which were assigned to be orthoquinone **5** (10%) and acetoxylated compound **6** (33%) by spectroscopic† and X-ray data (Fig. 1).‡ These yields were both improved by increasing molar ratio of $Pb(OAc)_4$ (run 3). The acetoxylated compound **6** was rather unstable and partially decomposed during the recrystallization from ethanol. From the mother liquid, presence of orthoquinone **5** was detected. Oxidation of $PhI(OAc)_2$[9] gave completely different results (runs 4–7). Treatment of $PhI(OAc)_2$ (2.0-molar ratio) gave a mixture of **4** (14%) and **7** (17%) as well as recovery of the starting material. The best result was obtained by using a 6.0-molar ratio of $PhI(OAc)_2$ and 5-*O*-methylbhimamycin B (**4**) was obtained in 57% yield. As treatment of **7** with acetic acid did not give **4**, compound **7** is a shunt product. Oxidations using other oxidants such as OsO_4 and Dess–Martin periodinane resulted in the formation of orthoquinone **5** in low yields (3% and 8%, respectively). Oxidation of 3-acetyl-2-(2-oxopropyl)-5-methoxy-1,4-naphthoquinone (**8**) with $PhI(OAc)_2$ also gave 5-*O*-methylbhimamycin B (**4**), but the yield was low (20%). Demethylation of 5-*O*-methylbhimamycin B (**4**) with $AlCl_3$ in CH_2Cl_2 at room temperature gave bhimamycin B in 56% yield. Spectroscopic and physical data of the synthetic bhimamycin B is completely identical with the natural ones.



Scheme 2. Reagents, conditions and yields: (i) 2-(trimethylsiloxy)-propene, $SnCl_4$, CH_2Cl_2, −78 °C; Ac_2O, pyridine, rt; 1.0 M NaOH, MeOH/THF; 65%. (ii) See in Table 1.

At this moment, it is difficult to figure out the oxidation mechanism. Taking the characteristic reaction feature of $Pb(OAc)_4$ and $PhI(OAc)_2$ into account,[6,10] however, the possible reaction mechanism is shown in Scheme 3. First, ligand exchange between the naphthoxyl and acetoxyl groups would occur in both reagents. In the case of $Pb(OAc)_4$, the intermediate **9** [R-X = $(AcO)_2Pb$] would decompose via radical process[6] to transfer one acetoxyl group at the *ortho* position (C4) and the observed compound **6** was obtained. Then, hydrolysis and further oxidative deacetylation would give the orthoquinone **5**. On the other hand, the ionic process would be favoured in the case of $PhI(OAc)_2$.[10] Therefore, the less hindered C9b would be attacked by an acetoxy anion to afford **10**. Hydrolysis of **10** would give **11**, which then decomposed to give **8**. The acetonylnaphthoquinone **8** would be acetoxylated and then hydrolyzed to give **13**. The

† *Spectroscopic data for* **4**: δ_H ($CDCl_3$) 7.96 (1H, d, J = 7.6 Hz), 7.73 (1H, dd, J = 8.6 and 7.6 Hz), 7.36 (1H, d, J = 8.6 Hz), 4.05 (3H, s), 2.84 (3H, s) and 2.83 (3H, s); δ_C ($CDCl_3$) 187.2, 180.0, 179.1, 161.4, 160.8, 147.8, 138.2, 135.1, 123.0, 122.3, 120.6, 119.9, 118.2, 56.6, 29.2 and 14.2; ν_{max} (KBr) 1682 and 1656 cm^{-1}. Compound **5**: δ_H ($CDCl_3$) 7.56 (1H, d, J = 7.6 Hz), 7.30 (1H, dd, J = 8.6 and 7.6 Hz), 7.02 (1H, d, J = 8.6 Hz), 6.43 (1H, s), 3.99 (3H, s), 22.41 (3H, s); δ_C ($CDCl_3$) 179.5, 174.2, 162.6, 159.2, 155.7, 136.5, 130.3, 122.1, 115.2, 114.5, 114.2, 104.3, 56.24 and 13.6; ν_{max} (KBr) 1674 and 1562 cm^{-1}. Compound **6**: δ_H ($CDCl_3$) 7.54 (1H, t, J = 8.1 Hz), 7.25 (1H, d, J = 8.1 Hz), 6.85 (1H, d, J = 8.1 Hz), 5.99 (1H, s), 3.92 (3H, s), 2.36 (3H, s) 2.30 (3H, s) and 2.18 (3H, s); δ_C ($CDCl_3$) 198.7, 198.3, 168.6, 161.3, 154.8, 147.1, 136.3, 132.6, 120.0, 114.5, 112.8, 111.1, 105.2, 56.1, 25.9, 20.9 and 14.0; ν_{max} (KBr) 1755, 1697, 1227 and 1007 cm^{-1}. Compound **7**: δ_H ($CDCl_3$) 14.05 (1H, s changeable with D_2O), 7.83 (1H, d, J = 8.1 Hz), 7.65 (1H, t, J = 8.1 Hz), 7.23 (1H, d, J = 8.1 Hz), 4.07 (3H, s), 3.89 (1H, s, changeable with D_2O), 2.72 (3H, s) and 1.73 (3H, s); δ_C ($CDCl_3$) 202.6, 196.7, 165.4, 158.9, 158.7, 131.0, 126.2, 120.1, 115.5, 112.7, 198.7, 103.7, 56.5, 31.3, 22.1 and one carbon is not found due to overlap; δ_C (DMSO-d_6) 200.5, 197.1, 163.2, 157.3, 147.8, 129.7, 123.6, 119.1, 114.8, 114.2, 112.0, 109.5, 105.0, 56.7, 31.5 and 22.0; ν_{max} (KBr) 3425 and 1712 cm^{-1}.

‡ *Crystallographical data for* **4**: $C_{16}H_{12}O_5$; FW = 284.26, orange prisms, 0.15 × 0.10 × 0.10 mm, monoclinic, P-1 (#2), Z = 2 in a cell of dimensions a = 7.716(2) Å, b = 9.803(2) Å, c = 10.166(2) Å, α = 109.43(2)°, β = 110.61(2)°, γ = 98.98(3)° V = 645.4(3) $Å^3$, D_{calcd} = 1.463 g cm^{-3}, Mo Kα, F(000) = 296.0, 2857 unique reflections, 1893 with $F^2 > 2\sigma(F^2)$. The final R_1 = 0.079, $R_w(all)$ = 0.168, goodness-of-fit = 1.16 for 191 parameters refined on F^2. CCDC 256976. Compound **5**: $C_{14}H_{10}O_4$; FW = 242.23, red rods, 0.60 × 0.15 × 0.15 mm, monoclinic, $P2_1/n$ (#14), Z = 4 in a cell of dimensions a = 7.620(4) Å, b = 11.236(4) Å, c = 13.321(4) Å, β = 91.13(4)°, V = 1140.2(8) $Å^3$, D_{calcd} = 1.411 g cm^{-3}, Mo Kα, F(000) = 504.0, 2611 unique reflections, 1338 with $F^2 > 2\sigma(F^2)$. The final R_1 = 0.064, $R_w(all)$ = 0.188, goodness-of-fit = 1.01 for 164 parameters refined on F^2. CCDC 256977.

Table 1. Oxidation of naphtho[1,2-*b*]furanol **2**

Run	Reagent (mol. ratio)	Solvent	Product/%[a]			
			4	**5**	**6**	**7**
1	CAN (2.2)	aq-MeCN	18	—	—	—
2	$Pb(OAc)_4$ (2.0)	EtOAc	—	10	33	—
3	$Pb(OAc)_4$ (4.0)	EtOAc	—	16	40	—
4	$PhI(OAc)_2$ (2.0)	MeCN	14	—	—	17
5	$PhI(OAc)_2$ (4.0)	MeCN	27	—	—	—
6	$PhI(OAc)_2$ (6.0)	MeCN	57	—	—	—
7	$PhI(OAc)_2$ (8.0)	MeCN	38	—	—	—

[a] Isolated yield.

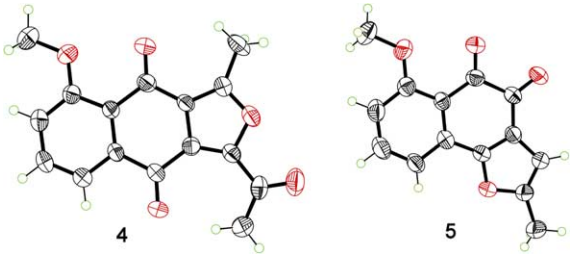


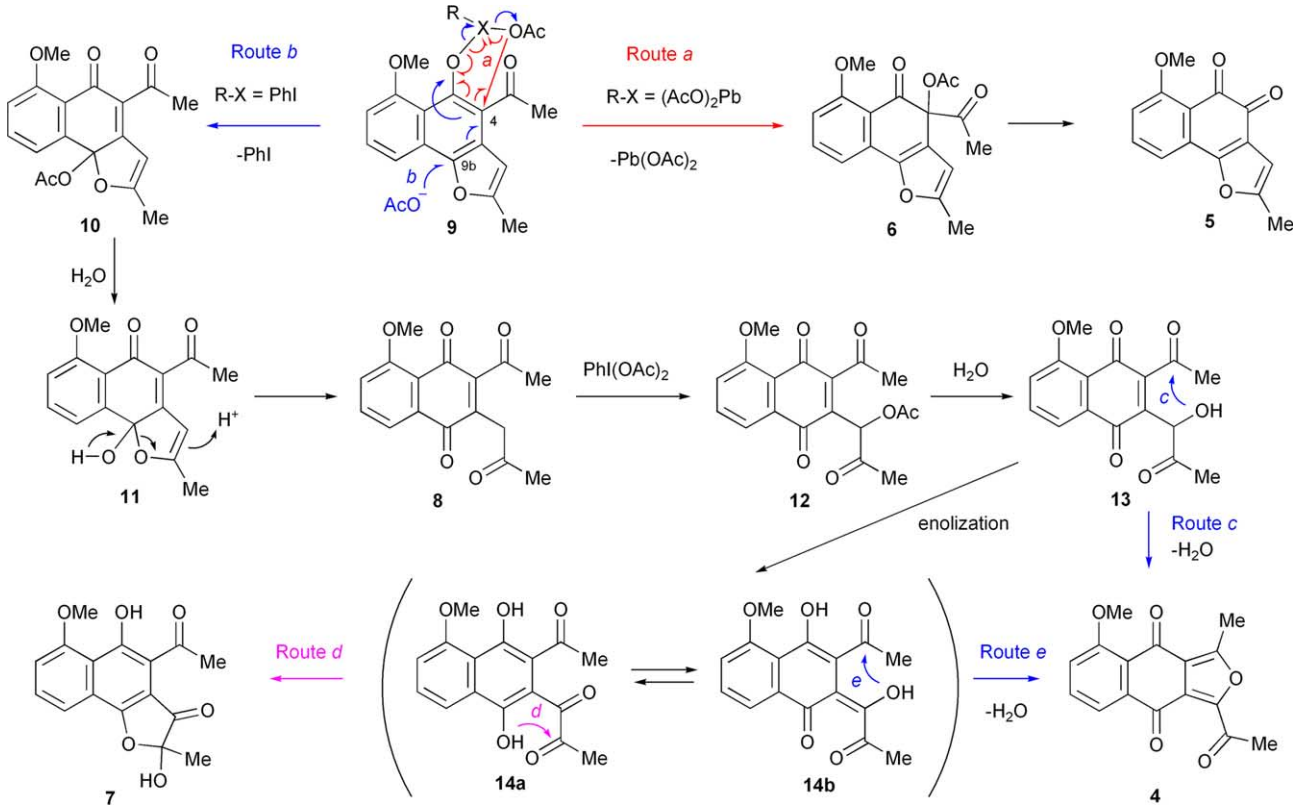
Figure 1. ORTEP drawing of **4** (left) and **5** (right) with 50% probability.

quinone **13** would directly undergo the dehydrative cyclization to give **4** (Route c), or enolized to the more stable form **14**, which would exist as a tautomeric mixture of **14a** and **14b**. Cyclization from tautomer **14b** followed by dehydration would also give 5-*O*-methylbhimamycin B (**4**), while cyclization from tautomer **14a** would afford **7**. From this scheme, the lower yield of **4** from **8** and no formation of compound **7** by increase of $PhI(OAc)_2$ could not be explained. Further mechanistic investigation is required.

In conclusion, we succeeded in the first synthesis of bhimamycin B based on the novel oxidative ring system transformation of naphtho[1,2-*b*]furan to naphtho[2,3-*c*]furan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.04.037.



Scheme 3. Tentative reaction mechanism.

References and notes

1. Thomson, R. H. *Naturally Occurring Quinones IV*; Blackie Academic & Professional: London, 1997.
2. Fotso, S.; Maskey, R. P.; Grün-Wollny, I.; Schulz, K.-P.; Munk, M.; Laatsch, H. *J. Antibiot.* **2003**, *56*, 931.
3. Uno, H.; Masumoto, A.; Honda, E.; Nagamachi, Y.; Yamaoka, Y.; Ono, N. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3189.
4. Uno, H. *J. Org. Chem.* **1986**, *51*, 350.
5. CambridgeSoft, MOPAC pro ver. 7.0.0.212.
6. Review for oxidation of phenols, see: Naruta, Y.; Maruyama, K. In *The Chemistry of Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1988; Vol. II; Akai, S.; Kita, Y. *Org. Prep. Proc.* **1998**, *30*, 603.
7. Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627.
8. Begley, M. J.; Gill, G. B.; Pattenden, G.; Stapleton, A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1677.
9. Tamura, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Kita, Y. *Synthesis* **1989**, 126.
10. Varvoglis, A. *Chem. Soc. Rev.* **1980**, 377.