Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 5469–5471

# The first total synthesis of SB87-Cl and pestalone, novel bioactive benzophenone natural products

Daisuke Iijima, Daisuke Tanaka, Motoko Hamada, Takahisa Ogamino, Yuichi Ishikawa and Shigeru Nishiyama*

*Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223-8522, Japan*

Received 15 April 2004; revised 6 May 2004; accepted 7 May 2004

**Abstract**—SB87-Cl **1**, an inhibitor of testosterone-5α-reductase, and pestalone **2** exhibiting effective antimicrobial activity against MRSA (MIC = 37 ng/mL) and VRE (MIC = 78 ng/mL), were novel bioactive benzophenone natural products. Total synthesis of **1** and **2** has been successfully accomplished. The common synthetic precursor **18** of **1** and **2**, was successfully obtained by the coupling of **8** with **12**.


In connection with the male-disorder caused by 5α-dihydrotestosterone, which is reductively produced from testosterone, some inhibitors of testosterone-5α-reductase have been reported. However, their steroidal or related structures exhibited undesired hormone actions. In this context, SB87-Cl **1**,[1] isolated from the genus *Chrysosporium* as an inhibitor of the reductase, has a different structural feature from other inhibitors, which would be expected for safe use of an active ingredient of hair growth stimulants. On the other hand, pestalone **2**,[2] obtained from the mixed fermentation broth of *Pestalotia* sp. CNL-365 and CNJ-328, exhibited highly potent antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (MIC = 37 ng/mL) and vancomycin-resistant *Enterococcus faecium* (VRE) (MIC = 78 ng/mL). Accordingly, **2** would be a new lead against such drug-resistant strains.

In spite of their closely similar structures, **1** and **2** exhibited entirely different bioactivities. Although synthesis of deformyl analogues of **2** has been reported by Schmalz and Kaiser,[3] **2** itself, as well as **1** has not been synthesized to date. To understand their diverse mode of action, we initiated total synthesis of **1** and **2**, which would enable their extensive chemical and biological investigation. We describe herein our investigation process.

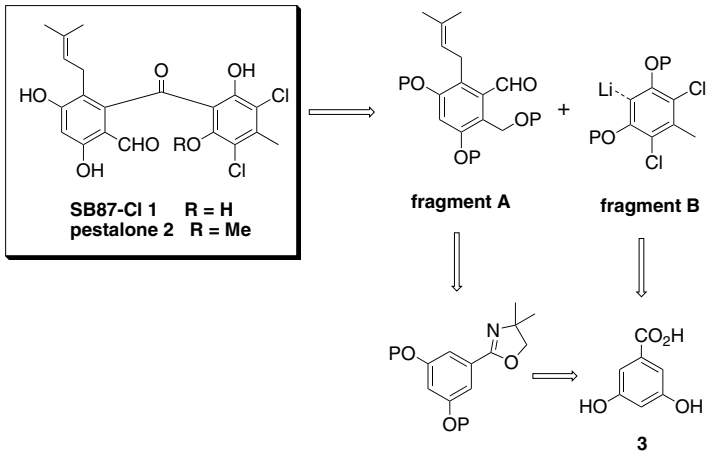
Retrosynthetically, the common highly functionalized benzophenone framework of **1** and **2** would be divided into two aromatic derivatives, **A** and **B** (Scheme 1). The prenyl side chain and formyl group of fragment **A** might be introduced by *ortho*-lithiation of the oxazoline derivative, produced from 3,5-dihydroxybenzoic acid **3**, which might also be a precursor of **B**. The Schmalz group employed closely similar strategy, and they reported the difficulty of introduction of the formyl group at the final stage.[3]

Synthesis of fragment **A** (**8**) was initiated from oxazoline **4**,[4] produced from 3,5-dihydroxybenzoic acid **3** (Scheme 2). The process involving methoxycarbonylation, reduction, TBS protection, and subsequent prenylation was unsuccessful, probably owing to steric hindrance. Therefore, the order of functionalization was switched; **4** was prenylated first, and then a methoxycarbonyl group was successfully introduced to **5**, leading to ester **6** in 62% yield. After reduction, the corresponding alcohol was protected as a TBDPS ether. Reductive deprotection[4,5] of oxazoline **7** afforded the desired aryl aldehyde **8**.

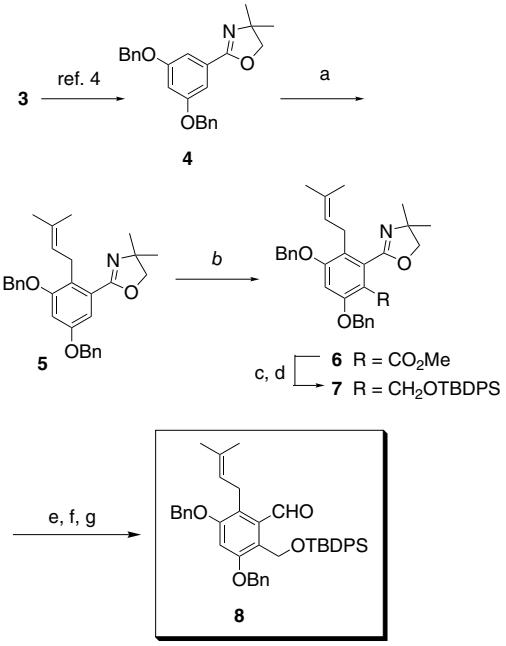
Fragment **B** (**12**) was also synthesized from **3** (Scheme 3); after exhaustive protection by benzyl groups, the

*Keywords*: SB87-Cl; Testosterone-5α-reductase; *Chrysosporium*; Pestalone; *Pestalotia*; MRSA; VRE.
* Corresponding author. Tel./fax: +81-45-566-1717; e-mail: nisiyama@chem.keio.ac.jp

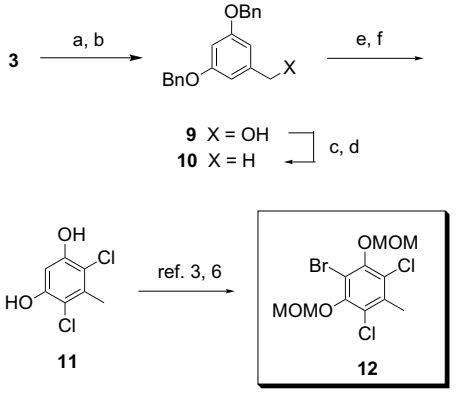
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.063




**Scheme 1.** Structures and retrosynthesis of SB87-Cl **1** and pestalone **2**.




**Scheme 2.** Synthesis of fragment **A**. Reagents and conditions: (a) *n*-BuLi, −78 °C; prenyl bromide, DME, 0 °C, 78%; (b) *n*-BuLi, −78 °C; $ClCO_2Me$, DME, 0 °C, 62%; (c) $LiAlH_4$, THF, 86%; (d) TBDPSCl, Imid., DMF, 99%; (e) MeI, 40 °C; (f) $NaBH_4$, MeOH, THF; (g) 60% AcOH, THF, 69% in three steps.



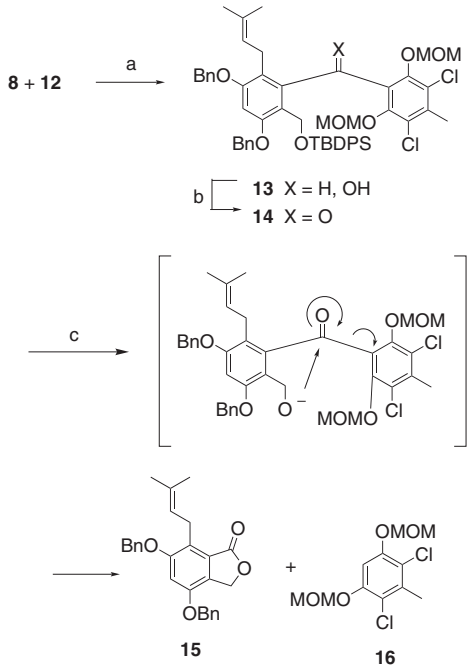

**Scheme 3.** Synthesis of fragment **B**. Reagents and conditions: (a) BnBr, $K_2CO_3$, DMF; (b) $LiAlH_4$, THF, 91% in two steps; (c) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C; (d) $LiAlH_4$, THF, 60 °C, 74% in two steps; (e) $SO_2Cl_2$, $CHCl_3$, 0 °C, 88%; (f) $H_2$, 10% Pd–C, EtOAc, 90%.

corresponding benzyl ester was reduced to give alcohol **9**. Mesylation, followed by reduction provided **10**. After dichlorination and removal of the benzyl groups, **11** was converted by the reported procedure[3,6] into bromide **12**.

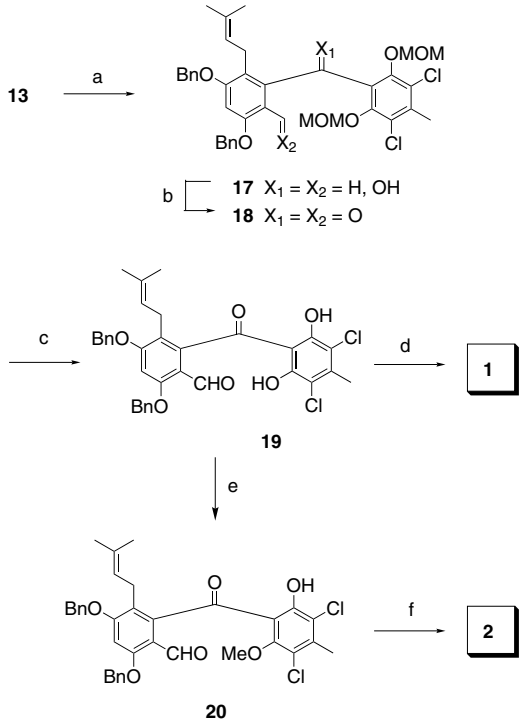
With both fragments in hand, our attention was focused on the critical coupling reaction of **8** with **12** (Scheme 4). The bromine–lithium exchange reaction of **12**, followed by coupling with **8** gave the desired product **13**[7] in quantitative yield. Subsequent IBX oxidation afforded the nona-substituted benzophenone **14**. Unexpectedly, removal of the TBDPS group under TBAF conditions caused benzophenone cleavage, leading to **15** and **16**, probably by the intramolecular nucleophilic attack of the benzyloxy anion. Among several attempts, relatively acidic conditions, such as HF–Py, caused decomposition of **14**.

Accordingly, the TBDPS group of **13** was removed in advance (Scheme 5). Subsequent IBX-oxidation of **17** provided the desired benzophenone **18** in 53% yield, without undesired cleavage. Removal of the MOM groups under acidic conditions gave **19**. Whereas the hydrogen transfer method provided a complex mixture, the Lewis acid conditions employing $BBr_3$ gave SB87-Cl **1** successfully. In the next stage, we attempted synthesis of pestalone **2**, carrying the asymmetric property at the chlorinated aromatic residue, derived from fragment **B**. Monomethylation of **19** led to the desired compound **20**, which on deprotection with $BBr_3$ afforded **2**. The spectroscopic data of the synthetic **1** and **2**, was identical with the reported data.[1,2]

In conclusion, the first total synthesis of SB87-Cl **1** and pestalone **2** has been accomplished, employing the common synthetic precursor. These results will contribute to investigation of the structure–activity relationship and creation of biologically more potent substances.




**Scheme 4.** Coupling reaction of fragment **A** with **B**. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 99% based on **8**; (b) IBX, DMSO, toluene, 69%; (c) TBAF, THF, 40%.




**Scheme 5.** Synthesis of SB87-Cl **1** and pestalone **2**. Reagents and conditions: (a) TBAF, THF, quant; (b) IBX, DMSO, toluene, 53%; (c) 6 M HCl, THF, quant; (d) $BBr_3$, $CH_2Cl_2$, −78 °C, 73%; (e) MeI, $K_2CO_3$, acetone, 40 °C, quant; (f) $BBr_3$, $CH_2Cl_2$, −78 °C, 56%.

## Acknowledgements

This work was supported by Grant-in-Aid for the 21st Century COE program 'Keio Life Conjugate Chemistry', as well as Scientific Research C from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

## References and notes

1. Wachi, Y.; Yamashita, T.; Komatsu, K.; Yoshida, S. JP Patent JKXXAF JP 07061950 A2 19950307, 1995.
2. Cueto, M.; Jensen, P. R.; Kauffman, C.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Nat. Prod.* **2001**, *64*, 1444–1446.
3. Kaiser, F.; Schmalz, H.-G. *Tetrahedron* **2003**, *59*, 7345–7355.
4. Kennedy, M.; Moody, C. J.; Rees, C. W.; Vaquero, J. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, *6*, 1395–1398.
5. Frey, L. F.; Tillyer, R. D.; Caille, A.-S.; Tschaen, D. M.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 3120–3124.
6. Katoh, T.; Ohmori, O.; Iwasaki, K.; Inoue, M. *Tetrahedron* **2002**, *58*, 1289–1299.
7. *The coupling procedure*: To a solution of **12** (0.14 g, 0.38 mmol) in dry THF (2.5 mL) was added *n*-BuLi in hexane (1.6 M, 0.19 mL, 0.30 mmol) at −78 °C. After 15 min, a solution of **8** (50 mg, 76 μmol) in dry THF (0.7 mL) was added to the resulting white suspension at −78 °C. The mixture was allowed to warm up to 0 °C for 3 h. Usual work-up gave **13** (71 mg, 99%, based on **8**) as a colorless oil; IR (film) 3388, 1587 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.97 (9H, s), 1.45 (3H, s), 1.52 (3H, s), 2.47 (3H, s), 3.24 (2H, br), 3.43 (6H, s), 4.45–4.47 (3H, complex), 4.52 (1H, d, $J = 12.0$ Hz), 4.63 (1H, d, $J = 12.0$ Hz), 4.84 (1H, d, $J = 4.4$ Hz), 4.95 (1H, d, $J = 12.6$ Hz), 4.99 (1H, d, $J = 12.6$ Hz), 5.22 (1H, d, $J = 11.4$ Hz), 5.29 (1H, d, $J = 11.4$ Hz), 5.73 (1H, d, $J = 2.4$ Hz), 6.32 (1H, s), 6.75 (1H, d, $J = 2.4$ Hz), 6.91–6.94 (2H, complex), 7.16–7.36 (14H, complex), 7.50–7.52 (2H, complex), 7.62–7.65 (2H, complex); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 17.9, 18.6, 19.2, 25.3, 25.4, 26.8, 57.7, 58.3, 69.3, 69.9, 70.2, 96.9, 99.7, 119.5, 121.9, 123.2, 125.6, 127.0, 127.0, 127.1, 127.4, 127.5, 127.6, 128.2, 128.3, 129.3, 129.4, 130.6, 132.0, 133.0, 133.4, 135.6, 135.6, 135.7, 136.9, 137.1, 143.2, 150.4, 155.7, 156.8; HRFABMS calcd for $C_{54}H_{60}O_8Cl_2SiNa$ ($[M+Na]^+$) 957.3332, found 957.3348.