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Total synthesis of dehydroaltenusin

Shunya Takahashi,[a,*] Shinji Kamisuki,[b] Yoshiyuki Mizushina,[c] Kengo Sakaguchi,[b] Fumio Sugawara[b] and Tadashi Nakata[a]

[a]*RIKEN (The Institute of Physical and Chemical Research), Wako-shi, Saitama, 351-0198, Japan*
[b]*Department of Applied Biological Science, Tokyo University of Science, Noda, Chiba 278-8510, Japan*
[c]*Laboratory of Food and Nutritional Sciences, Department of Nutritional Science, Kobe-Gakuin University, Nishi-ku, Kobe, Hyogo 651-2180, Japan*

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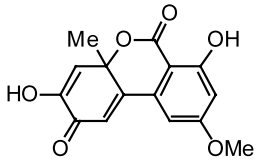
Abstract—First total synthesis of dehydroaltenusin, a natural enzyme inhibitor, is described. The key step involves Suzuki-couplig reaction of aryl triflate prepared from 2,4,6-trihydroxy benzoic acid with a catechol-derived boronic acid. The synthetic sample was evaluated as a potent inhibitor against an eukaryotic DNA polymerase α.

Dehydroaltenusin was first discovered from mycelium extracts of *Alternaria tennuis* and *A. kikuchiana* by Rosett et al. in 1957.[1] Since then, this compound has been found from a variety of fungi.[2,3] The structure was initially suggested to be a γ-lactone derivative of β-resorcylic acid monomethylether based on the chemical and spectroscopic data[2] and later revised to **1** possesing a δ-lactone ring by the X-ray crystallographic analyses (Fig. 1).[4] In 1995, **1** was reported to inhibit the calmodulin-dependent activity of myosin light chain kinase (MLCK) with IC_{50} value of 0.69 μM.[5] Recently, we have also isolated (–)-**1** from *Acremonium* sp. 98H02B04-1 (**2**) and shown it to be a powerful mammalian DNA polymerase α inhibitor.[6] These results suggest that **1** might be a promising biological tool. However its low producibility has prevented such utilization. Furthermore, no total synthesis of **1** or (–)-**1** has been reported so far, and the absolute configuration of (–)-**1** has still remained unsolved. In connection with our studies directed towards total synthesis of (–)-**1**, we report herein the first synthesis of **1** and its inhibitory activity against a couple of DNA polymerases.



Dehydroaltenusin (**1**)

Figure 1.

Our synthetic efforts toward **1** involved Suzuki-coupling[7] reaction of an aryl triflate **2** with an aryl boronic acid **3** as a key step. Synthesis of the aryltriflate **2** started from 2,4,6-trihydroxybenzoic acid **4**.[8] According to Danishefsky's method,[9] the carboxylic acid **4** was transformed into 1,3-benzodioxin **5** in 43% yield (Scheme 1). Regioselective methylation of **5** was performed by Mitsunobu conditions[10] with diisopropyl azodicarboxylate-triphenyl phosphine in the presence of methanol to afford monomethyl ether **6**[11] in 89% yield. Treatment of **6** with triflic anhydride-pyridine gave the corresponding triflate **2** in 94% yield. On the other hand, a 4-bromocatechol **8**[12] prepared from 4-methylcatechol (**7**) [8] was subjected to methoxymethylation (NaH, MOMCl), giving bis-MOM ether **9** in 90% yield. Halogen–lithium exchange (*n*-BuLi, THF, −78 to −40°C) of **9** followed by trapping with triisoproyl borate (Et_2O, −78°C–rt) afforded an aryl boronic acid **3** in 95% yield. This compound was, without purification, employed to the next coupling reaction, because of its instability.

Introduction of a catechol moiety into **2** was best realized by using 1.5 equiv. of **3** in the presence of tetrakis(triphenylphospine)palladium (0.05 mol equiv.), K_3PO_4 (1.5 equiv.) and KBr (1.0 equiv.) in dioxane[13] at 100°C to produce a coupled product **10** in 93% yield.[14] Alkaline hydrolysis of **10** and subsequent acid treatment provided artenusin **11** in 64% yield. This com-

* Corresponding author. Fax: +81-48-462-4666; e-mail: shunyat@riken.go.jp

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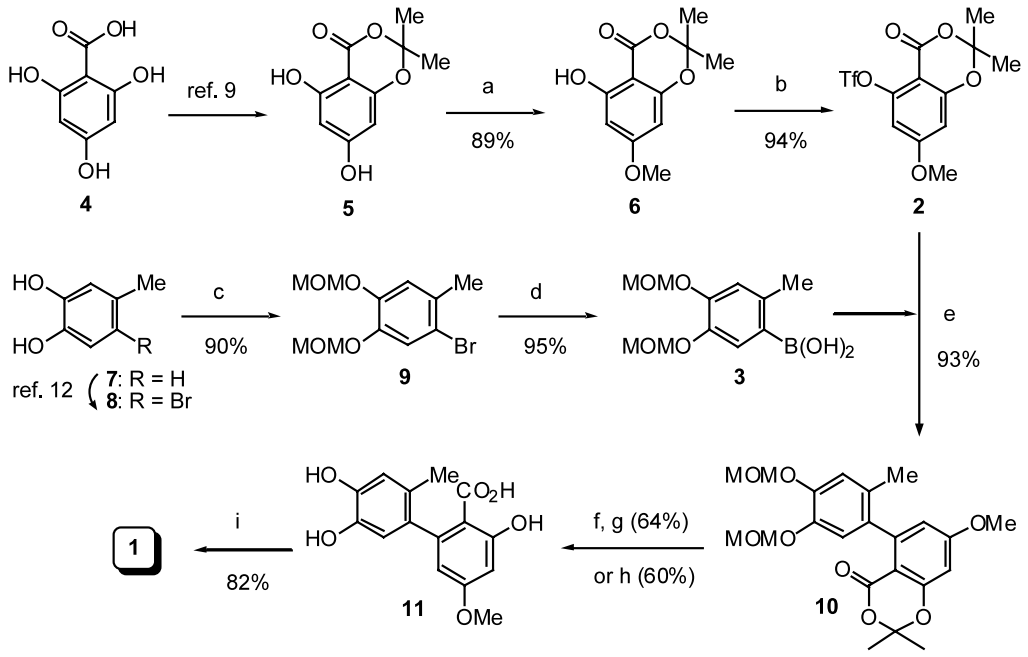

Scheme 1. *Reagents and conditions*: (a) DIAD (1.05 equiv.), Ph_3P (1.05 equiv.), MeOH (1.05 equiv.), THF, rt; (b) Tf_2O (1.1 equiv.), pyridine, 0°C; (c) MOMCl (2.5 equiv.), NaH (2.5 equiv.), DMF, 0°C; (d) *n*-BuLi (1.1 equiv.), THF, −78 to −40°C, then $(i\text{-PrO})_3B$ (1.1 equiv.), Et_2O, −78°C–rt; (e) $(Ph_3P)_4Pd$ (0.05 equiv.), K_3PO_4 (1.50 equiv.), KBr (1.0 equiv.), dioxane, 100°C; (f) 2N KOH, EtOH, 60°C; (g) 10% HCl–MeOH, CH_2Cl_2, rt; (h) BCl_3 (10 equiv.), CH_2Cl_2, 0°C–rt; (i) $FeCl_3$, aq. EtOH, rt.

pound was also obtained by the action of BCl_3 in CH_2Cl_2 from **10** in a single step (60%). Finally, $FeCl_3$-promoted oxidation[1] of **11** afforded dehydroaltenusin (**1**)[15] in 82% yield. The spectral and physical properties of **1** were identical with those of natural **1**.

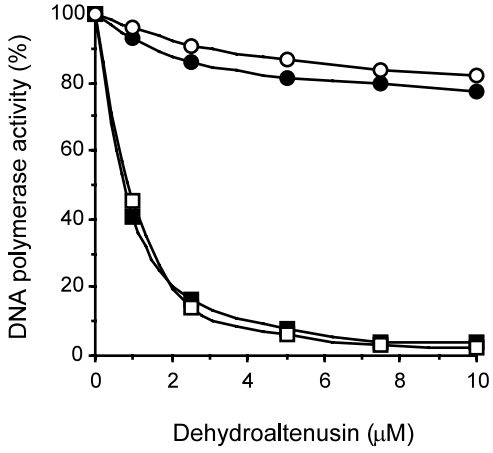

Figure 2. Inhibition of eukaryotic DNA polymerase α and β. The synthetic **1** and natural (−)-**1** are depicted as open and closed symbols, respectively. Inhibition activity against DNA polymerase α and β are shown as square and circle symbols, respectively. DNA polymerase activity in the absence of compound was taken as 100%.

DNA polymerase inhibition assay was performed as described previously.[16,17] The calf DNA polymerase α (0.05 units) and rat DNA polymerase β (0.05 units) inhibitory activity of the synthetic compound **1** were examined and compared with those of natural (−)-**1**. As illustrated in Figure 2, the IC_{50} values of **1** and (−)-**1** for DNA polymerase α were 0.8 and 0.7 μM, respectively. Therefore, the inhibitory activity of the two compounds was not distinguishable.

In summary, the first synthesis of dehydroaltenusin (**1**) has been accomplished in 7 steps with an 18% overall yield from a commercially available carboxylic acid **4**. This synthetic process would be quite useful for preparation of many analogs of **1** suitable for clinical usage. Now asymmetric synthesis of (−)-**1** and determination of the absolute configuration are underway.

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