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Total Synthesis of (±)-Nocardione A and (±)-Nocardione B, Two Cdc25B Tyrosine Phosphatase Inhibitors

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Abstract: Two new naphthoquinones, nocardione A and B isolated from strain P-A0248, were synthesized from naphtho[1,2-b]furan **1**. The furan **1** was prepared from 5-methoxyl-1-naphthol.

Keywords: Synthesis, nocardione A, nocardione B.

Quinones are biologically important compounds, especially because of their cytotoxic and pharmacological action. The antitumor activities of the quinones, including naphthoquinones[1], were revealed more than two decades ago when the National Cancer Institute published a report in which 1500 synthetic and nature quinones were screened. Some natural naphthoquinones were under development for antitumor agents[2].

The protein tyrosine phosphatases (PTPase) and dual phosphatases (DSPase) are key enzymes for many cellular processes. Cdc 25 was DSPase involved in cell cycle regulation and response to the stimulation of growth factors. Cdc 25A has a peak expression in the G1 phase throughout the cell cycle in some cancer cells, and Cdc 25B has a peak expression in both G1/S and G2 phase. Therefore inhibiting the function of Cdc 25 may become potential chemotherapeutic method in the tumor treatment[3].

Recently, two new naphthoquinone compounds, nocardione A and nocardione B (**Figure 1**), were first isolated from strain P-A0248 by Japanese scientists[4]. The structure of nocardione A was elucidated as 2,3-dihydro-6-hydroxy-2-methyl-naphtho-[1,2-b]-furan-4,5-dione, and nocardione B as 2,3-dihydro-6-methoxy-2-methyl- naphtho-[1,2-b]-furan-4,5-dione, the absolute configuration of the nocardiones was unknown. The nocardiones inhibited the activity of Cdc 25B at a concentration of 10 μm and possessed antifungal and cytotoxic activities. In our program for developing Cdc 25 inhibitors, we have performed the synthesis of (±)-nocardiones A and B.

The nocardiones were synthesized from 5-methoxy-1-naphthol **2**[5]. Firstly the

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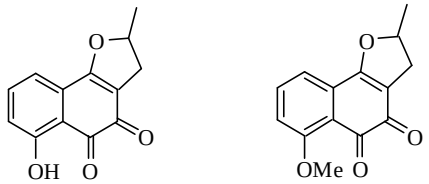
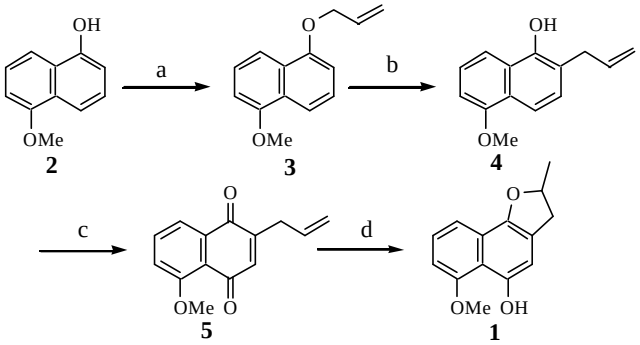
naphthol **2** was reacted with allyl bromide in acetone to yield the allyl ether **3** (**Scheme 1**). Claisen rearrangement of **3** under reflux in $PhN(Et)_2$ afford the naphthol **4** in high yield[6]. The construction of the 1, 4-naphthoquinone subunit of **5** was achieved by treating **4** with Fremy salt[7], but the quinone **5** was only in 35% yield. Alternatively, using [bis(trifluroacetoxy)iodo]benzene as oxidant, the quinone **5** was obtained in 77% yield[8]. Subsequently, reduction the quinone **5** with $SnCl_2$ in acetic acid, then treatment with HBr gave the cyclized naphthofuran **1** in 52% yield as a shallow-yellow precipitate[5b].

Figure 1



nocardione A nocardione B

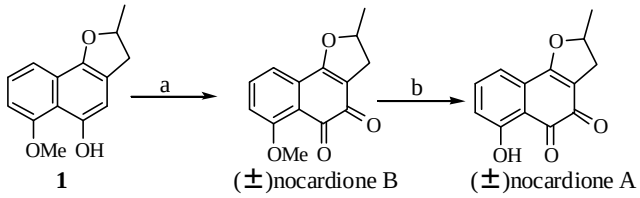
Scheme 1



Reagents and conditions: a) C_3H_5Br/K_2CO_3, 90%.
b) $PhN(Et)_2$, reflux, 98%.
c) $PhI(OCF_3CO)_2$, CH_3CN, 77%.
d) $SnCl_2$, HOAc, HBr, reflux, 52%.

Oxidation of **1** with $AgNO_3$ in ethyl alcohol afforded nocardione B quickly in 87% yield[9]. Demethylation of nocardione B was performed very difficultly, after several unsuccessful experiments, at last nocardione B was refluxed in DMF with EtSNa under N_2 to gave nocardione A in 34% yield[10] **(Scheme 2)**.

Scheme 2



Reagents and conditions: a): $AgNO_3$, EtOH, reflux 20 min, 87%.
b): EtSNa, DMF, reflux 3 h, 34%.

The spectral data of the synthetic nocardiones showed in agreement with the reported data of the natural products[4,11]. Now the asymmetric synthesis is proceeding in our research group.

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11. Data of nocardione A: Reddish brown power, mp 116-119°C; IR (KBr, cm^{-1}) 3400, 1645, 1614, 1589, 1496, 1446, 1309, 1213, 1026, 923, 769; ^{1}HNMR ($CDCl_3$, 300MHz, δ ppm) 1.58 (d, 3H, J=6.3Hz), 2.75 (dd, 1H, J=15.4,7.1Hz), 3.28 (dd, 1H, J=15.4, 9.6Hz), 5.25 (m, 1H), 7.13 (d, 1H, J=8.5Hz), 7.20 (d, 1H, J=7.1Hz), 7.55 (dd, 1H, J=7.4,8.5Hz), 11.95 (s, 1H); EIMS (*m/z*): 230(M^+), 202, 131, 92, 63; HREIMS (*m/z*): 230.0583 (calcd for $C_{13}H_{10}O_4$, 230.0579).
Data of nocardione B: Reddish brown power, mp 79-80°C; IR (KBr, cm^{-1}) 3450, 1647, 1622, 1578, 1644, 1300, 1271, 1058, 1032, 791; ^{1}HNMR ($CDCl_3$, 400MHz, δ ppm) 1.55 (d, 3H,

J=6.2Hz), 2.70 (dd, 1H, J=15.4, 7.3Hz), 3.24 (dd, 1H, J=15.4, 9.5Hz), 3.98 (s, 3H), 5.21 (m, 1H), 7.16 (d, 1H, J=8.4Hz), 7.26 (d, 1H, 8.2Hz), 7.58 (dd, 1H, 8.4, 7.8Hz); EIMS (*m/z*): 244(M^+), 216, 187, 173, 115, 75; Annal. Calcd for $C_{14}H_{12}O_4$: C 68.85, H 4.95, O 26.20; Found: C 68.50, H 5.25,O 26.35.

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