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Synthesis of actiketal, a glutarimide antibiotic

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Abstract

The first synthesis of actiketal (RK-441S), an antibiotic from *Streptomyces pulveraceus* subsp. *epiderstagenes*, was achieved from 5,7-dimethylbenzofuran and dimethyl glutaconate via palladium-assisted coupling reaction as a key step.

Keywords: acetals; antibiotics; glutarimides; polyketides.

Actiketal (RK-441S, **1**) was isolated from the culture extracts of *Streptomyces pulveraceus* subsp. *epiderstagenes* as a new acetal-type glutarimide antibiotic.[1] This compound inhibited the EGF-induced DNA formation in murine epithelial cell (100% at 1 μM) and the Con A-induced blast formation in spleen cell (100% at 20 nM).[2] It also showed the inhibitory activity towards the incorporation of [^{3}H]thymidine into epidermal growth factor-stimulated Balb/MK cells (IC_{50} 14.5 μM).[1] Although these activities are much weaker than those of cycloheximide (**2**), **1** is expected to be a new anti-cancer agent and an immnosuppressant because of its low cytotoxicity.[1,2] To provide **1** in a sufficient quantity for further biological studies, we began the synthetic study and achieved the first total synthesis (Fig. 1).

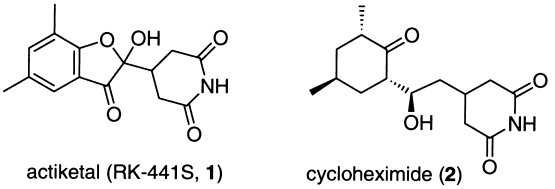

Figure 1.

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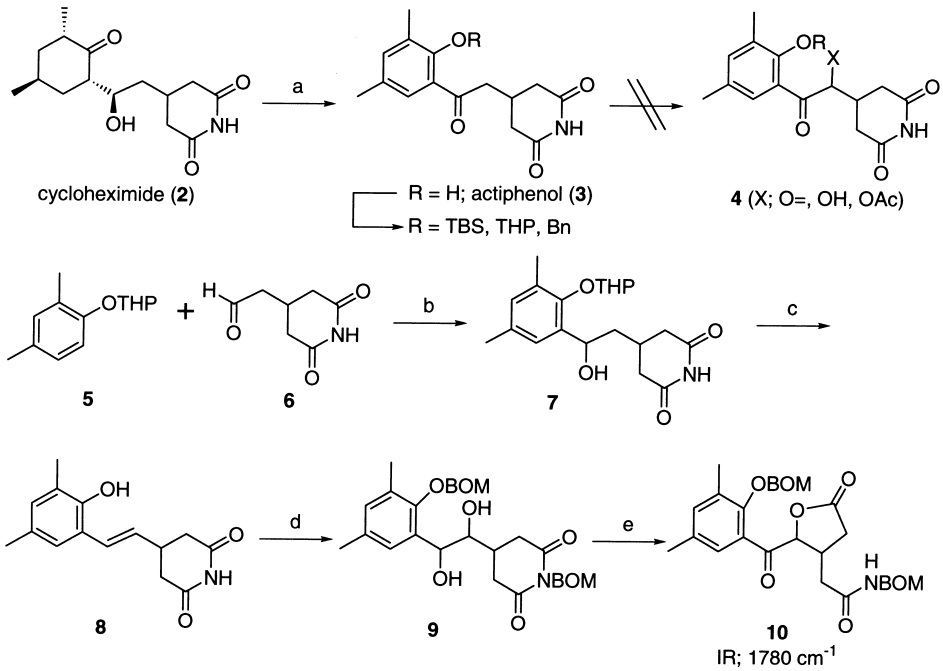
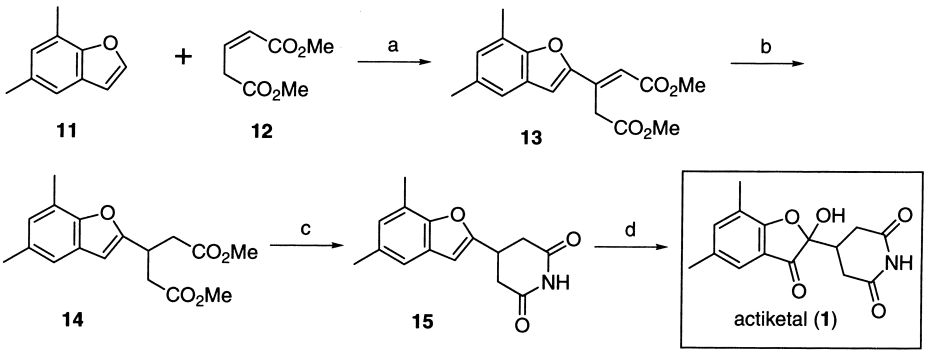
The natural actiketal (**1**) was reported to be optically inactive $\{[\alpha]_D^{26} \pm 0^\circ$ (c 0.1, MeOH)$\}$[2] and the asymmetric center of **1** is made up of a hemiacetal carbon. It could therefore be presumed that **1** occurs in the racemic form, so we started the synthetic study for the racemate. Firstly, we tried semi-synthesis of **1** from cycloheximide (**2**), which is well-known as a protein synthesis inhibitor and commercially available. As shown in Scheme 1, cycloheximide (**2**) was converted to actiphenol (**3**)[3] according to Highet's procedure.[3] However, the desired compound **4** could not be obtained: oxygenation of the α-position to keto carbonyl function failed in various conditions in the protected form of the phenolic hydroxy group. Next we examined the total synthesis. 2,4-Dimethylphenol THP ether (**5**) was coupled with glutarimide acetaldehyde (**6**)[4] to give **7**. Dehydration of **7** with acidic conditions afforded **8**. Once the OH and NH groups of **8** had been protected with the BOM group, the double-bond was oxidized to give diol **9**. This diol was unstable and the formation of undesired γ-lactone **10** predominated during the next oxidation step.



Scheme 1. Synthetic study of actiketal from cycloheximide. (a) NBS, CCl_4, reflux (10%). (b) *n*-BuLi, TMEDA, DME, THF, HMPA, –78 to 0°C (32%). (c) TsOH, toluene (85%). (d) i. BOMCl, *i*-Pr_2NEt. ii. OsO_4, NMO, *t*-BuOH (61%). (e) Dess–Martin periodinane

Consequently, the vicinal oxygen function must be introduced in the final step to prevent the γ-lactone formation. We thought that the corresponding benzofuran derivative would be a good precursor, so we chose 5,7-dimethylbenzofuran[5] (**11**) and dimethyl glutaconate (**12**) as the starting materials, which would be coupled together by the key palladium-assisted reaction. As shown in Scheme 2, the oxidative coupling reaction[6] of **11** and **12** mediated by 1 equiv. of $Pd(OAc)_2$ in AcOH proceeded successfully to give **13** in 57% yield. An attempt of the catalytic method [0.01 equiv. of $Pd(OAc)_2$ and 1 equiv. of $PhCO_2t$-Bu][7] resulted in the formation of a bibenzofuran derivative as the major product. The double-bond conjugated with



Scheme 2. Synthesis of actiketal (**1**). (a) **12** (1.4 equiv.), $Pd(OAc)_2$ (1 equiv.), AcOH, 60°C (57%). (b) H_2, Pd powder, EtOAc (98%). (c) i. KOH, MeOH. ii. Ac_2O, heat. iii. NH_3 gas, Et_2O. iv. NaOAc, Ac_2O, heat (62%). (d) OsO_4 (1.3 equiv.), Py, Et_2O, 20°C, then aq. $NaHSO_3$ 60°C (33%)

methoxycarbonyl group was selectively hydrogenated over Pd powder to afford **14** in 98% yield. Formation of glutarimide function was performed in the conventional manner, similar to that of Matsuda et al.[8] to give the desired precursor **15**. Finally, oxidation of the electron rich double bond with OsO_4,[9] followed by hydrolysis of the resulting osmate with aq. $NaHSO_3$ at 60°C gave over-oxidated product,[10] actiketal (**1**). [11] The total yield was 11.4% in six steps. ^1H and ^{13}C NMR data[12] were in good accordance with those reported.[1]

In conclusion, the first synthesis of actiketal (RK-441S), an antibiotic from *Streptomyces pulveraceus* subsp. *epiderstagenes*, was achieved.

Acknowledgements

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10. According to Ref. 9, hydrolysis of the osmate derived from a benzofuran with aq. $NaHSO_3$ gave the diol, while that with aq. Na_2SO_3 gave the ketol. In our case, treatment with aq. Na_2SO_3 failed in decomposition of the product.
11. **1**; amorphous powder, mp 79.5–80.5°C (Ref. 1 96–100°C). The mixed melting point could not be measured because the natural sample was absent. However, the value of the synthetic product is reliable for its smaller melting range (Δ 1°C).

12. ^{1}H-NMR (500 MHz, $CDCl_3$, all protons and carbons were assigned according to Ref. 1) δ: 2.27 (s, 3H, 12-Me), 2.33 (s, 3H, 4-Me), 2.55 (dd, 1H, $J = 17$, 10 Hz, 14-H), 2.66 (dd, 1H, $J = 17$, 4 Hz, 14-H), 2.65–2.71 (m, 1H, 9-H), 2.75 (dd, 1H, $J = 17$, 10 Hz, 10-H), 2.91 (dd, 1H, $J = 17$, 4 Hz, 10-H), 4.42 (br, s, 1H, OH), 7.22 (s, 1H, 5-H), 7.33 (s, 1H, 3-H), 8.03 (s, 1H, NH). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.1 (2-Me), 20.6 (4-Me), 30.9 (C-10), 31.5 (C-14), 35.7 (C-9), 103.2 (C-8), 118.2 (C-6), 121.6 (C-5), 123.1 (C-2), 132.7 (C-4), 142.0 (C-3), 167.5 (C-1), 171.3 (C-11), 171.6 (C-13), 198.6 (C-7). HR-FABMS (glycerol-PEG) m/z calcd for $C_{15}H_{16}NO_5$, 290.1029; found, 290.1029.