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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. © 2000 Elsevier Science Ltd. All rights reserved.

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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 μ M) 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 [³H]thymidine into epidermal growth factor-stimulated Balb/MK cells (IC₅₀ 14.5 μ M).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).

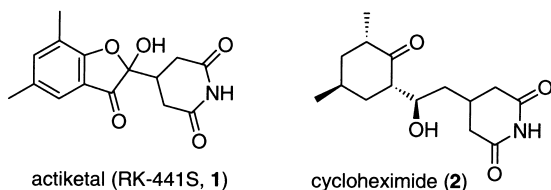
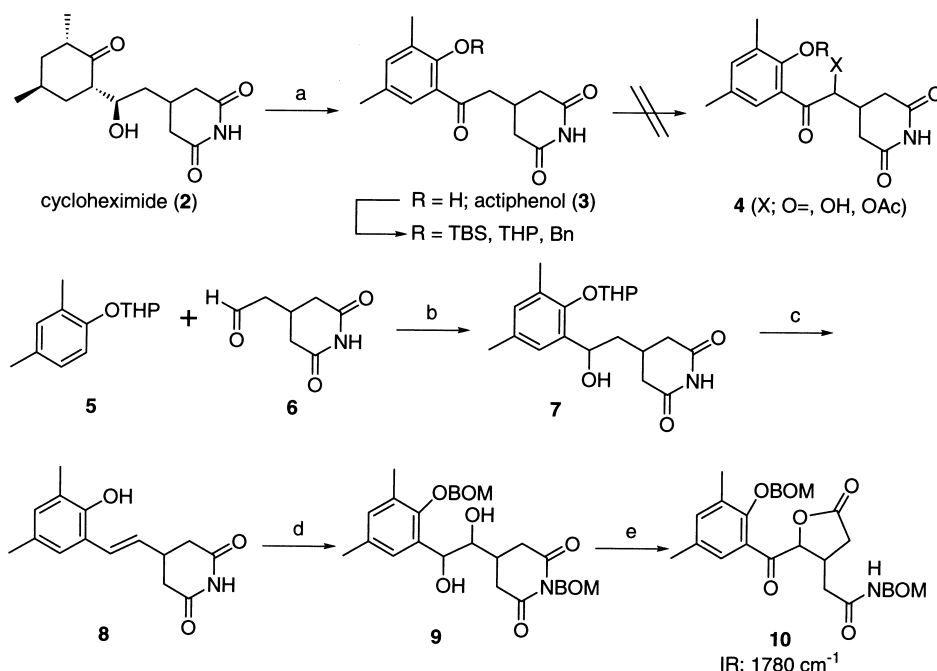


Figure 1.

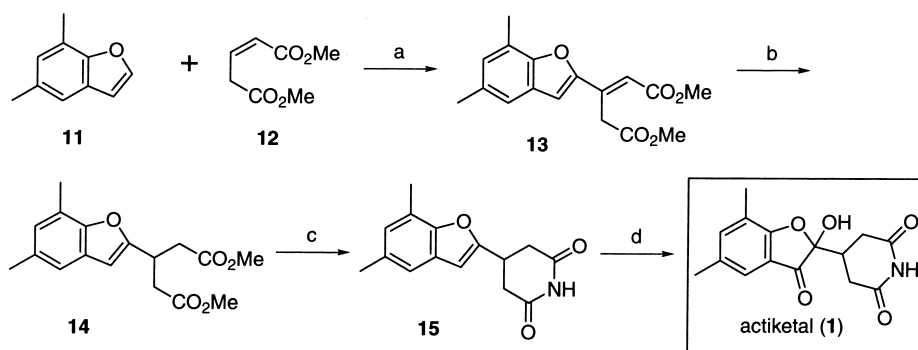
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The natural aktiketal (**1**) was reported to be optically inactive $\{[\alpha]_D^{26} \pm 0^\circ$ (c 0.1, MeOH) $\}^2$ and the asymmetric center of **1** is made up of a hemiacetal carbon. It could therefore be presumed that **1** occurs in the racemic 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 aktiketal from cycloheximide. (a) NBS, CCl_4 , reflux (10%). (b) $n\text{-BuLi}$, TMEDA, DME, THF, HMPA, -78 to 0°C (32%). (c) TsOH, toluene (85%). (d) i. BOMCl, $i\text{-Pr}_2\text{NEt}$. ii. OsO_4 , NMO, $t\text{-BuOH}$ (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-dimethylbenzofuran⁵ (**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 reaction⁶ of **11** and **12** mediated by 1 equiv. of $\text{Pd}(\text{OAc})_2$ in AcOH proceeded successfully to give **13** in 57% yield. An attempt of the catalytic method [0.01 equiv. of $\text{Pd}(\text{OAc})_2$ and 1 equiv. of $\text{PhCO}_2t\text{-Bu}$]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) H₂, Pd powder, EtOAc (98%). (c) i. KOH, MeOH. ii. Ac₂O, heat. iii. NH₃ gas, Et₂O. iv. NaOAc, Ac₂O, heat (62%). (d) OsO₄ (1.3 equiv.), Py, Et₂O, 20°C, then aq. NaHSO₃ 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 OsO₄,⁹ followed by hydrolysis of the resulting osmate with aq. NaHSO₃ at 60°C gave over-oxidated product,¹⁰ actiketal (**1**).¹¹ The total yield was 11.4% in six steps. ¹H and ¹³C NMR data¹² 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. NaHSO₃ gave the diol, while that with aq. Na₂SO₃ gave the ketol. In our case, treatment with aq. Na₂SO₃ 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. ^1H -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 $\text{C}_{15}\text{H}_{16}\text{NO}_5$, 290.1029; found, 290.1029.