Regioselective Preparation of 1,6- and 1,8-Dihydroxy-9,10-anthraquinones from the Common Intermediates: Synthesis of Aloesaponarin I and K1115A

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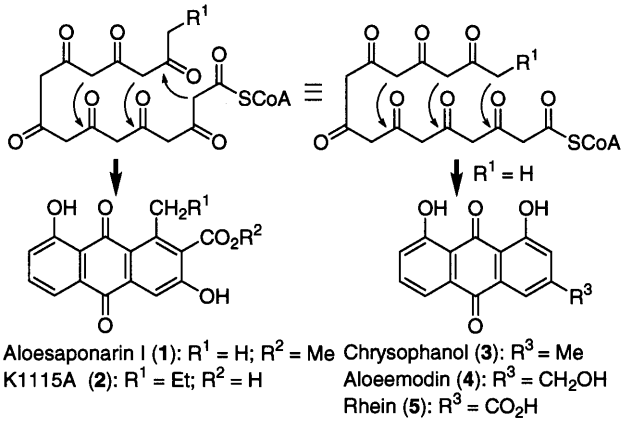
(Received June 12, 2000; CL-000565)

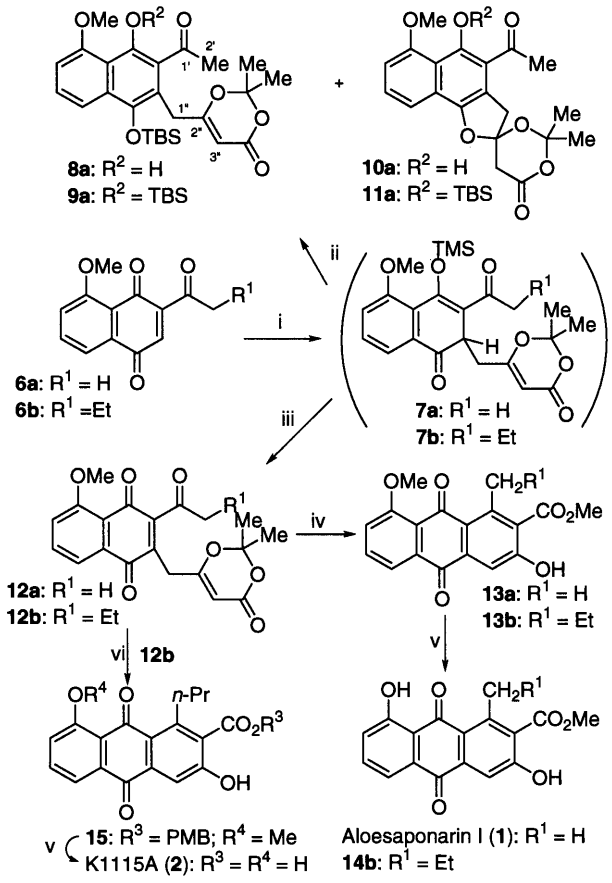
Treatment of 3-acyl-2-[(2,2-dimethyl-6-oxo-1,3-dioxin-4-yl)methyl]-5-methoxy-1,4-naphthoquinones with K_2CO_3 in an alcohol brought about the intramolecular condensation to give 1-alkyl-3-hydroxy-8-methoxy-9,10-anthraquinone-2-carboxylates in good yields, while the same naphthoquinone gave 1-hydroxy-8-methoxy-9,10-anthraquinone-3-acetic acid in good yield by treatment with KHMDS.

Among all substitution types of dihydroxyanthraquinones, 1,6- and 1,8-dihydroxyanthraquinone skeletons have been commonly found in naturally occurring quinones.[1] Considerable efforts have been focused on elucidation of the precise biosynthetic pathways by using biotechnology.[2] These quinones such as aloesaponarin I (**1**)[3] and chrysophanol (**3**) are believed to be synthesized from the common octaketides via the different biosynthetic pathways and a key step forming the skeletons is the aldol-type reaction (Scheme 1).[4] Contrary to the biosynthesis, most successful syntheses of these quinones involve the Diels–Alder or Friedel–Crafts reaction as a key step in the construction of the quinone skeletons,[5] although some biomimetic syntheses of naturally occurring quinones from polyketide precursors have been reported by Krohn's, Yamaguchi's, Harris' and one of authors' groups.[6] We thought that both types of quinones could be separately prepared via biomimetic pathways from an appropriate precursor by a simple choice of conditions, if the precursor had the carbonyl groups in appropriate positions. In this communication, we would like to report differentiation of quinone syntheses from a common pentaketo precursor by the choice of conditions and the total synthesis of aloesaponarin I (**1**)[3] and K1115A (**2**),[7] latter of which is reported to show an inhibitory activity towards activation protein I (AP-I).



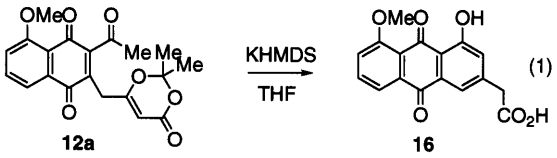
Scheme 1. Biosynthesis of 1,6- and 1,8-dihydroxy-9,10-anthraquinones.

Construction of the key octaketide intermediates was examined by connection of hexaketide and diketide units. We chose acyljuglones **6**[8] and 2,2-dimethyl-6-methylene-4-trimethylsilyloxy-1,3-dioxin[9] as the starting parts. Acyljuglone **6a** and the dioxin reagent reacted smoothly even in the absence of a catalyst at –78 ˚C to give adducts **7a**[10] (Scheme 2).[11] The adduct **7a** was too unstable to isolate and was treated with TBSCl and imidazole to afford mono-silyl ether **8a** (46%), disilyl ether **9a** (20%) and spiro compounds (**10a** and **11a**; 10%). As the spiro compounds could be converted to the key intermediates by oxidation, the mixtures from the reaction of **6a** and **6b** with the dioxin reagent were oxidized by CAN after treatment with TMSCl and Et_3N. The key masked pentaketo compounds **12a** and **12b** were obtained in 84% and 76% yields, respectively.



Scheme 2. Reagents and conditions: i) The dioxin reagent, CH_2Cl_2/MeOH, -78 ˚C. ii) TBSCl, imidazole, rt. iii) TMSCl, Et_3N, -78 ˚C → rt; CAN, aq-MeCN, rt. iv) K_2CO_3, MeOH, rt. v) BBr_3, CH_2Cl_2, -78 ˚C. vi) 4-$MeOC_6H_4CH_2OH$, K_2CO_3, rt.

When the key quinone compound **12a** was treated with K_2CO_3 in methanol, an intramolecular condensation between the acyl and masked β-keto ester moieties was triggered by nucleophilic attack of methanol to give only the aimed 3-hydroxy-8-methoxy-9,10-anthraquinone-2-carboxylate **13a** in 70% yield. Deprotection of the methyl ether of **13a** with BBr_3 gave aloesaponarin I (**1**) in 69% yield. The physical and spectroscopic data were identical with those of reported ones.[3] The butyroyl intermediate **12b** was also converted to K1115A methyl ester **14b**. Since saponification of the methyl ester **14b** to K1115A failed, the nucleophile was changed to *p*-methoxybenzyl alcohol (PMB alcohol) and the PMB ester **15** was obtained in 72% yield. Simultaneous deprotection of the methyl ether and PMB ester of **15** was achieved by the treatment with BBr_3 at –78 ˚C to provide K1115A (**2**) in 59% yield. Identity of the synthetic and authentic K1115A was confirmed by NMR experiments of the mixed sample. On the other hand, when the key intermediate **12a** was treated with a strong base such as KHMDS, a clean intramolecular Michael-type reaction between the acyl and β-alkoxy α,β-unsaturated ester moieties occurred to give only 1-hydroxy-8-methoxy-9,10-anthraquinone-3-acetic acid (**16**) in 62% yield (eq 1).



12a **16**

The similar transformation to 1,6- and 1,8-dihydroxyanthraquinones was also achieved by employing the TBS ether **8a** as a substrate. Treatment of **8a** with K_2CO_3 in MeOH and with KHMDS in THF brought about the similar ring closures followed by air oxidation to give the quinone **13a** and **16** in 55% and 56% yields, respectively. Very facile ring closures observed in the reactions of **8** and **12** would be understood by the spatial proximity between the two intramolecular reacting carbons. From the X-ray analysis of **8a** (Figure 1),[12] intramolecular hydrogen bonding of the phenolic hydrogen is not observed with the acetyl oxygen but with the peri-positional oxygen, and the aromatic ring and the acetyl group are not coplanar (52.4˚) probably due to the sterical congestion of the substituents. Both distances of C1'–C3" and C2'–C2" are quite short (3.97 and 3.27 Å, respectively). This conformation would be kept in solution, because the phenolic proton signal of **8a** was observed 4.22-ppm higher than that of 2-acetyl-4,8-dimethoxy-1-naphthol,[8] where intramolecular hydrogen bonding with the acetyl group would be expected (9.60 ppm for **8a** and 13.82 ppm for the latter).

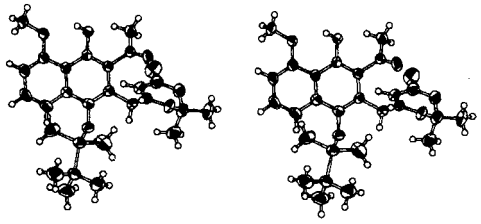


Figure 1. Stereo view (Ortep) of **8a**.

In conclusion, we succeeded in constructing the 1,6- and 1,8-dihydroxy-9,10-anthraquinone skeletons from the common pentaketo precursors via biomimetic routes. To our knowledge, this is the first example of complete differentiation of biomimetic pathways by the simple modification of reaction conditions. Aloesaponarin I and K1115A were prepared in good yields.

This work was partially supported by a Grant-in-Aid for Scientific Research (No 12640521) from the Ministry of Education, Science, Sports and Culture. We greatly thank Dr. Masaki Goto (Tsukuba Lab., Eisai Co.) for the gift of authentic K1115A.

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10 ^{1}H NMR Data for **7a**: δ ($CDCl_3$) 0.22 (9H, s), 1.39 (3H, s), 1.59 (3H, s), 1.91 (1H, dd, *J* = 13.9 and 12.0 Hz), 2.25 (1H, dd, *J* = 13.9 and 5.6 Hz), 2.34 (3H, s), 3.93 (4H, m), 4.12 (1H, s), 7.20 (1H, br d, *J* = 8.3 Hz), 7.42 (1H, br d, *J* = 7.3 Hz), and 7.51 (1H, dd, *J* = 8.3 and 7.3 Hz).
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12 Crystallographic summary for **8a**: $C_{26}H_{34}O_7Si$, FW = 486.64, yellow crystal, 0.5 × 0.1 × 0.1 mm, orthorhonbic, $P2_12_12_1$ (#19), *Z* = 4, *a* = 13.131(1) Å, *b* = 26.173(2) Å, *c* = 7.621(1) Å, *V* = 2619.2(5) Å^3, ρ_{calc} = 1.23 g·cm^{-3}, Cu Kα, *F*(000) = 1040.0, 2375 unique reflections. The final *R* = 0.075, R_w = 0.126, R_1 = 0.049 (1974 reflns), goodness-of-fit = 1.36 for 309 parameters refined on F^2. The absolute conformation was determined by the anomarous dispersion method and the probability was over 99.5% by the Hamilton limitation based on the *R*-factor ratio.[13]
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