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Skeletal Rearrangements of Polycyclic α-Ketols

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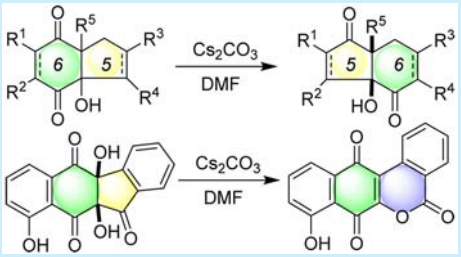
Supporting Information

ABSTRACT: It has been proposed that prekinamycin and kinobscurinone may biogenetically isomerize to isoprekinamycin and prefluostatin, respectively, through the corresponding bridgehead α-ketol intermediates. In this transformation, the 6−5 ring system is converted into a 5−6 ring system via an α-ketol rearrangement. In this report, the skeletal rearrangement of polycyclic α-ketols inspired by this hypothetical biosynthetic transformation is reported. In addition, an unexpected rearrangement from dibenzo[*b*]fluorene to benzo[*g*]chromene is also reported.



Prekinamycin (**1**)[1] and isoprekinamycin (**2**)[2] (Figure 1) were isolated from *Streptomyces murayamaensis*. Prekinamycin

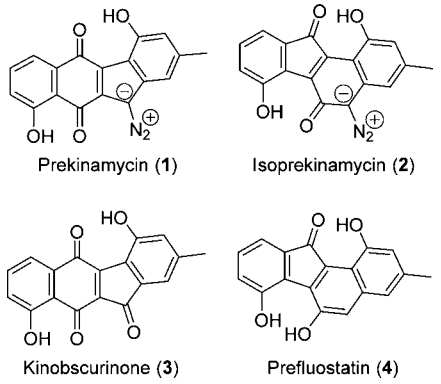
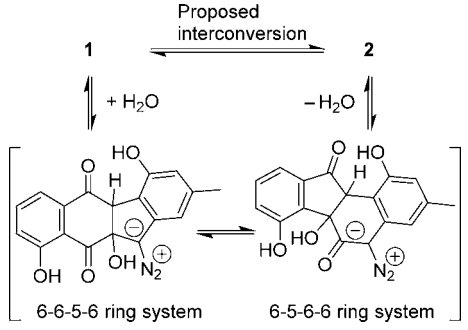


Figure 1. Structures of prekinamycin (**1**), isoprekinamycin (**2**), kinobscurinone (**3**), and prefluostatin (**4**).

(**1**) contains a dibenzo[*b*]fluorene moiety and, thus, has a fused 6−6−5−6 carbon skeleton. Isoprekinamycin (**2**) has a dibenzo[*a*]fluorene skeleton and is made up of a 6−5−6−6 ring system. It has been proposed that **2** could be biogenetically derived from **1** because these natural products were isolated from the same *Streptomyces* species.[2−4] A reversible interconversion between **1** and **2** is proposed in their biosynthetic pathways (Scheme 1).[2] Hydration of **1**, skeletal rearrangement of the resultant bridgehead α-ketol, and dehydration may afford **2**. Calculations using the restricted Hartree−Fock (RHF) method with the 6-31G basis set predict that **1** is more stable than **2** by 2.4 kcal/mol, suggesting the existence of an equilibrium between **1** and **2**.[2] This interconversion is also supported by the isotopic labeling patterns of **1** and **2** obtained from *S. murayamaensis* fed with

Scheme 1. Proposed Interconversion between 1 and 2



sodium [1,2-$^{13}C_2$]acetate.[2,5] A similar skeletal rearrangement is proposed for the biogenetic conversion of kinobscurinone (**3**)[6] to prefluostatin (**4**).[7,8] However, the α-ketol rearrangements related to these biotransformations have not been fully examined.[5,9] Although the hypothetical interconversion between diazobenzo[*a*]fluorenes and diazobenzo[*b*]fluorenes is considered as an enzyme-catalyzed reaction rather than a spontaneous chemical transformation,[5,9] no enzymes and genes associated with this transformation have been identified. The interesting rearrangement pattern motivated us to investigate the details of the skeletal rearrangement in these compounds. In this paper, the α-ketol rearrangement from the 6−5 ring system to the 5−6 ring system is reported. In addition, a dynamic skeletal rearrangement from dibenzo[*b*]fluorene to benzo[*g*]chromene is also reported.

First, the reaction conditions for the α-ketol rearrangement were examined using **5a**[10] as a substrate (Table 1). When **5a** was treated with Cs_2CO_3 in DMF, the desired rearrangement

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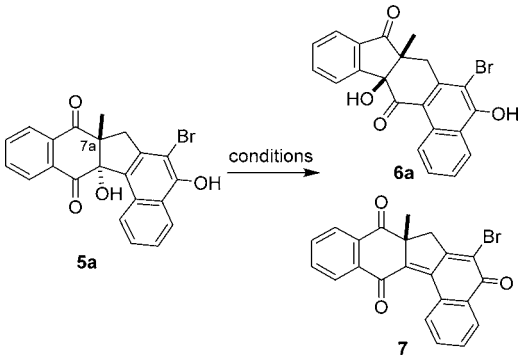
Table 1. Reaction Optimization[a]



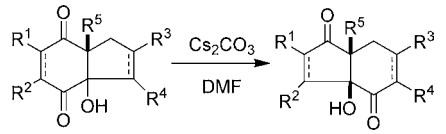
entry	conditions	product	yield[b] (%)
1	Cs_2CO_3 (1.0 equiv), DMF	**6a**	74
2	K_2CO_3 (1.0 equiv), DMF	**6a**	53
3	TsOH·H_2O (0.1 equiv), DMF	7	86

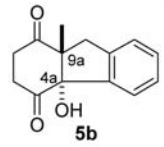
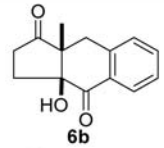
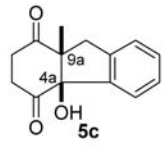
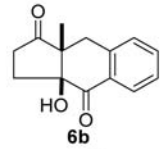
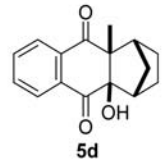
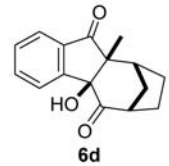
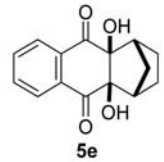
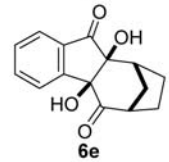
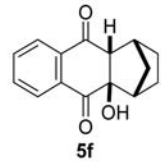
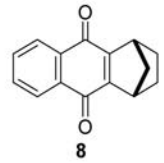
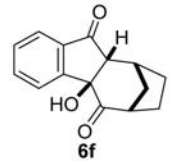
[a]The reactions were carried out at 0 °C. [b]Yields of the isolated product.

proceeded to afford **6a**[11] in 74% yield (entry 1). When **6a** was treated with Cs_2CO_3, **5a** was not obtained, and **6a** was recovered from the reaction mixture. These results indicate that **6a** is thermodynamically more stable than **5a**. Indeed, density functional theory (DFT) calculations at the B3LYP/6-31G (d,p) level of theory indicate that the lowest energy conformation of **6a** is more stable than that of **5a** by 10.6 kcal/mol (Table S1 in the Supporting Information). Using K_2CO_3 as a base slightly reduced the yield of **6a** (entry 2). In contrast, when **5a** was treated with a catalytic amount of TsOH·H_2O, the dehydration of **5a** occurred preferentially to give **7** in 86% yield (entry 3). The structure of **7** was confirmed by X-ray crystallography (see the Supporting Information). The results summarized in Table 1 indicate that the α-ketol rearrangement is initiated by deprotonation of the hydroxyl group at the ring juncture by a base, followed by a 1,2-shift of C-7a.[12]

Next, the scope of this skeletal rearrangement was investigated using **5b**–**f**[10] as substrates (Table 2). Isomerization of 4a,9a-*trans*-isomer **5b** and 4a,9a-*cis*-isomer **5c** proceeded to afford the same *cis*-fused product **6b**[13] in 78% and 79% yields, respectively (entries 1 and 2). Compounds **5d** and **5e** isomerized to **6d** and **6e** in 56% and quantitative yields, respectively (entries 3 and 4).[13] However, compound **5f** failed to undergo isomerization (entry 5). Compound **8**[14] was obtained in 98% yield, and the desired **6f** was not obtained (entry 5). Although several attempts to isomerize **5f** under basic and acidic conditions were made, the desired isomerization did not occur; instead, dehydration occurred to give 1,4-napthoquinone (**8**). Entries 3–5 in Table 2 indicate the importance of the substituent at the ring junction (R^5) for the rearrangement. When R^5 was a methyl or hydroxyl group, the skeletal rearrangement occurred to provide the thermodynamic product. In contrast, when R^5 was hydrogen, dehydration was preferred. In other words, substituent R^5 prevents the dehydration and induces the skeletal rearrangement. When products **6b**, **6d**, and **6e** were treated under basic or acidic conditions, the corresponding substrates **5b**–**e** were not obtained. DFT calculations at the B3LYP/6-31G (d,p) level indicate that products **6b**, **6d**, and **6e** are more stable than the corresponding substrates **5b**–**e** (Table S1 in the Supporting Information). Thus, these results indicate that rearrangement occurs to give the most thermodynamically stable product, similar to the typical α-ketol rearrangement.[12]

Table 2. Substrate Scope[a]



entry	substrate	product	yield (%)[b]
1			78
2[c]			79
3[d]			56
4			100
5			98
			—[e]

[a]Unless otherwise noted, the reactions were carried out at 0 °C. [b]Yield of the isolated product. [c]The reaction was carried out at 70 °C. [d]The reaction was carried out at 80 °C. [e]**6f** was not detected.

During the course of the investigation into the α-ketol rearrangement, an unexpected rearrangement of the dibenzo[*b*]fluorene skeleton to a benzo[*g*]chromene was observed (Scheme 2). When diazobenzo[*b*]fluorene **9**[15] was treated with $RuCl_3$ in the presence of $NaIO_4$, dihydroxylation occurred together with oxidation of the diazoalkane to give **10**. Treatment of **10** with Cs_2CO_3 in DMF gave benzo[*g*]chromene **11**. The proposed reaction mechanism for the transformation of **10** to **11** is depicted in Scheme 3.[16] The alkoxide generated by treatment of **10** with Cs_2CO_3 attacks the adjacent carbonyl carbon, and the resultant epoxyalkoxide rearranges to lactone **11**. Compound **9** possesses the core carbon skeleton of prekinamycin (**1**) and kinobscurinone (**3**), and compound **11** has the core skeleton of WS-5995A (**12**), which was isolated from *Streptomyces aurantiacolor*[17] (Figure 2). These results suggest that kinobscurinone (**3**) might be converted into WS-5995A (**12**) by dihydroxylation,

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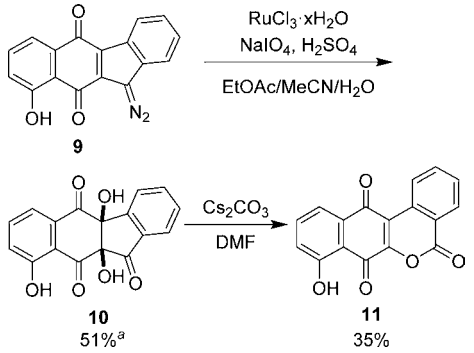
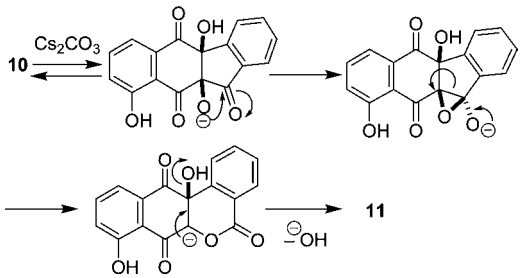
Scheme 2. Skeletal Rearrangement of Dibenzo[*b*]fluorene to Benzo[*g*]chromene



[a]Compound **9** was recovered in 39% yield.

Scheme 3. Proposed Mechanism for the Rearrangement of 10 to 11



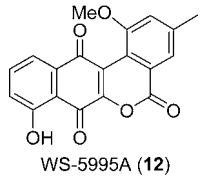


Figure 2. Structure of WS-5995A (**12**).

subsequent basic treatment, and *O*-methylation, both chemically and biogenetically.

In conclusion, we have demonstrated the skeletal rearrangement from the 6−5 ring system to the 5−6 ring system. This skeletal rearrangement is hypothesized to be involved in the biogenetic interconversions between prekinamycin and isoprekinamycin and between kinobscurinone and prefluostatin. Our results indicate that substituents at both ring junctions are necessary for the chemically induced rearrangement to occur. Furthermore, the dynamic skeletal change from dibenzo[*b*]fluorene to benzo[*g*]chromene was also demonstrated. The results reported in this paper provide new insights into the possible biosynthesis of this family of microbial metabolites. Further studies to experimentally corroborate the existence of these skeletal rearrangements in the biosynthesis of these natural products are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03541.

DFT calculations, crystal data for compounds **7** and **S3**, experimental procedures, spectroscopic data for new compounds, and copies of ^{1}H and ^{13}C NMR of new compounds (PDF)

Crystallographic data for compound **7** (CIF)

Crystallographic data for compound **S3** (CIF)

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Notes

The authors declare no competing financial interest.

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(10) For the preparation of substrates **5a**−**f**, and determination of the relative configurations of substrates **5a**, **5c**, **5d**, **5e**, and **5f**, see the Supporting Information.

(11) The relative configuration of **6a** was confirmed by X-ray crystallography of the structurally similar derivative **S3**; see Scheme S2 in the Supporting Information.

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(13) Determination of the relative configuration of products **6b**, **6d**, and **6e**; see Figure S1 in the Supporting Information.

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