Natural Products Synthesis

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Biomimetic Synthesis: Discovery of Xanthanolide Dimers**

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Dedicated to Professor K. C. Nicolaou

Abstract: *Starting from xanthatin, the biomimetic synthesis of 4β,5β-epoxyxanthatin-1α,4α-endoperoxide, a novel monomeric xanthanolide, has been achieved. Moreover, four unprecedented xanthanolide dimers were synthesized by three different dimerizations of xanthatin, either in a head-to-head or head-to-tail fashion. Notably, these dimeric compounds were firstly identified as artifacts in the laboratory, and two of them, mogolides A and B, proved to be natural products present in the Xanthium mogolium Kitag plant.*

Xanthanolides are a growing family of sesquiterpenoids with over one hundred members having been identified to date.[1] Structurally, most of the xanthanolides feature a five/seven bicyclic system with a butyrolactone *trans* or *cis* fused to a seven-membered carbocycle, as represented by xanthatin (**1**)[2] and 8-*epi*-xanthatin (**2**; Figure 1 a).[3] Additionally, some structurally more complex congeners, such as 4β,5β-epoxyxanthatin-1α,4α-endoperoxide (**3**; Figure 1 a)[2d] and pungiolides A–C (**4**–**6**)[3b,c,4a] and E (**7**; Figure 1 b),[4b] are also found in nature. Not surprisingly, the intriguing chemical structures of xanthanolides, combined with their diverse biological profiles, attract extensive interest from synthetic community.[5]

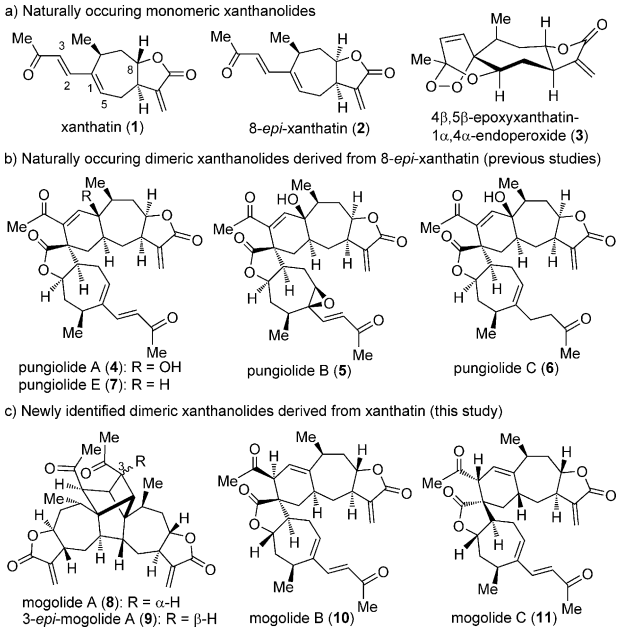

Figure 1. Representative monomeric and dimeric xanthanolides.

Recently, we achieved the collective synthesis of various monomeric xanthanolides with a dyotropic rearrangement of the 3,4-*cis*-β-lactone as a key step.[6] The chemistry paves the way for the synthesis of some more challenging targets such as **3**–**7**. The polycyclic skeletons of **3**–**7** differ from those of other xanthanolides, thus posing challenging synthetic targets which have not yet been achieved. Moreover, **3**–**7** bear interesting biosynthetic origins. As illustrated in Scheme 1 a, **3**[2d] was assumed to be derived from **1** by sequential double-bond isomerization, 6π electronic cyclization, and singlet-oxygen-mediated [4+2] cycloaddition,[7] and **4**–**7**[3b,c,4] might arise from **2** through a Diels–Alder dimerization[8] followed by additional functionality elaborations (Scheme 1 b). Notably, such hypotheses have never been implemented in practice. Herein, we report the first total synthesis of **3** based upon the above biosynthetic proposal. Moreover, four unprecedented xanthanolide dimers (**8**–**11**; Figure 1 c) were synthesized from **1** by three different dimerizations. Interestingly, although **8**–**11** were serendipitously identified as artifacts in the laboratory, two of them, mogolides A (**8**) and B (**10**), proved to be

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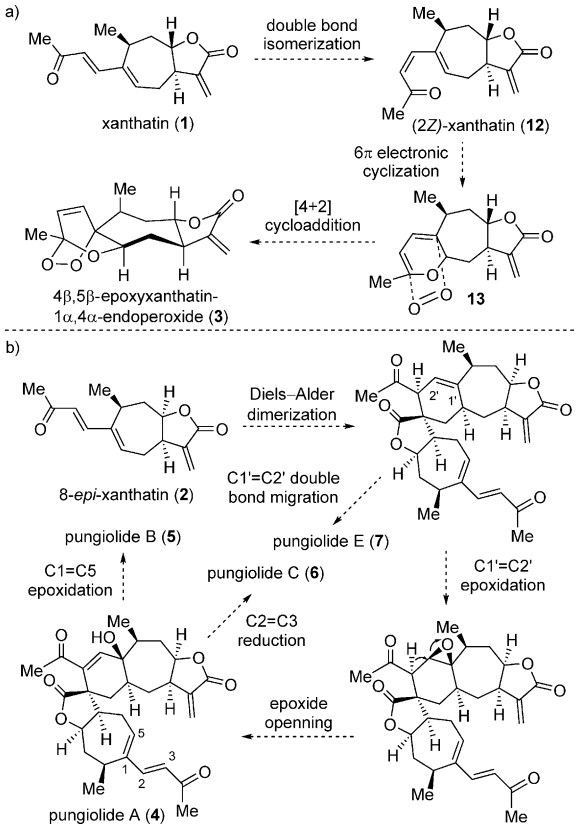
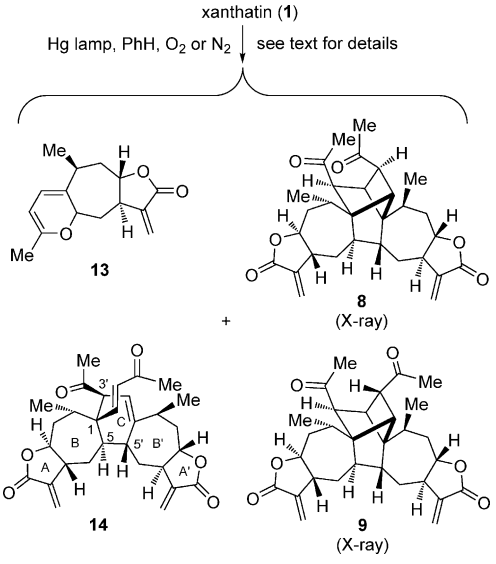


Scheme 1. Plausible biosynthetic pathways for **3**–**7**.

authentic natural products, thus making our work a showcase of biomimetic synthesis guided discovery of new natural products.[9]

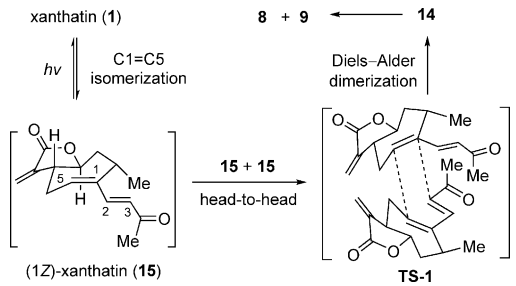
At the outset, we attempted to achieve the proposed transformations leading to **3** in one-pot manner by irradiating **1**[10] under an oxygen atmosphere (Scheme 2; conditions 1 used, as indicated in Scheme S1-2 in the Supporting Information).[7a,b] However, trace amounts of **3** could not be detected. Instead, a small amount of the pyran derivative **13** was obtained along with three other products. The LC-MS analysis showed that all three compounds have a molecular weight of 492, thus suggesting that they might be derived from **1** by dimerization. Fortunately, two of them were amenable to the crystallographic studies,[11] thus unambiguously confirming their structures as that of **8** (m.p. 125–126 °C, ethyl acetate/hexanes) and **9** (m.p. 156–157 °C, ethyl acetate/hexanes). We also found that the third product could be converted into **8** and **9** upon irradiation, and together with the spectroscopic evidence established its structure as that of **14**. The identification of **8**, **9**, and **14** were notable since they are derived from **1** by head-to-head dimerization (referred to as type I dimerization hereafter), which is distinct from the dimerization leading to the pungiolides **4**–**7**.



Scheme 2. Type I dimerization of **1**.

Despite the failure to access **3**, the identification of small amounts of **13** shed light on the proposed biomimetic strategy. Thus, we attempted to improve the reaction by using the photosensitizer rose bengal[12] (conditions 2, Scheme S1-2) or conducting the reaction under highly dilute condition (conditions 3, Scheme S1-2). However, in both cases similar distributions of products were observed. Of note, when we conducted the reaction under a nitrogen atmosphere, a mixture of **8** and **9** (4:3 ratio) was obtained and they were the major products present in a 74% combined yield (conditions 4, Scheme S1-2).

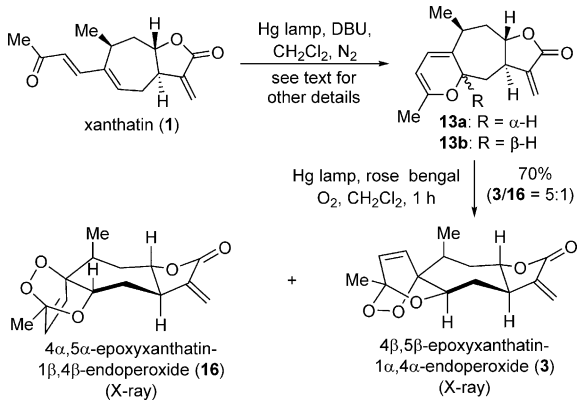
Mechanistically, the dimerization leading to **8** and **9** takes place by tandem [4+2]/[2+2] cycloadditions. However, the [4+2] reaction appears unusual. First, the direct dimerization of **1** through a Diels–Alder reaction could be excluded, since it cannot account for the observed stereochemical outcomes of **14** (*trans*-fused B-C rings and *trans* relationship of H-5′ and H-3′; Scheme 2). While a stepwise [4+2] cycloaddition via a radical intermediate could explain the stereochemical outcomes, it is not consistent with the fact that such dimerization proceeded smoothly in the presence of the radical scavenger TEMPO (see Scheme S1-3). Taken together, a mechanism involving C1–C5 double-bond isomerization and a subsequent Diels–Alder reaction is postulated. As depicted in Scheme 3, **1** first undergoes photoinduced C1–C5 double-bond isomerization to afford the *trans*-cycloheptene **15**, which is highly reactive and rapidly undergoes Diels–Alder dimerization via the transition state **TS-1** to yield **14**. The speculation of a *trans*-cycloheptene intermediate seems



Scheme 3. Proposed mechanism of type I dimerization of **1**.

to be daunting; however, it is substantiated by the pioneering work from the groups of Eaton and Corey,[13] together with that of the groups of Rawal and Davies.[14] In our scenario, the intermediacy of **15** was further proven by its capture with 1,3-cyclopentadiene (see Scheme S1-4). Apparently, although both the C1–C5 and C2–C3 double bonds of **1** could undergo isomerization, the high tendency of **15** to homodimerize drives the reaction to form **14** as the major product.

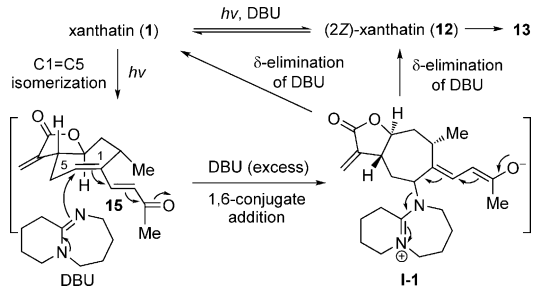
Keeping the above considerations in mind, we realized that achieving the crucial proposed transformations leading to **13** relied on whether we could regioselectively effect the C2–C3 instead of C1–C5 double-bond isomerization. Notably, an interesting photochemical/Et_3N-promoted tandem double-bond isomerization/6π electronic cyclization was reported by Carroll and co-workers.[15] Thus, we attempted this protocol (conditions 1, see Scheme S1-5) in our case. However, it still led to **8** and **9** as major products (69% yield, 1.2:1 ratio). Serendipitously, we found that the use of DBU (conditions 2, Scheme S1-5) in the reaction could largely inhibit the dimerization. As a result, a mixture of the desired product **13a** and its epimer **13b** (4:1 ratio) were obtained in a 25% combined yield (Scheme 4). More appealingly, increasing the



Scheme 4. Biomimetic synthesis of **3**.

number of equivalents of DBU used (conditions 3, Scheme S1-5) improved the yield (60%) and diastereoselectivity (5:1) of the reactions. The mixture of **13a** and **13b** was submitted to the standard reaction conditions for the singlet-oxygen-promoted Diels–Alder reaction. To our delight, the reaction worked smoothly to yield a mixture of **3** and its diastereoisomer, **16** (5:1 ratio), in a 70% combined yield. The structures of **3** (m.p. 167–168 °C, ethyl acetate/hexanes) and **16** (m.p. 137–138 °C, ethyl acetate/hexanes) were unambiguously confirmed by X-ray crystallographic studies.[11]

To understand the mechanism of the above transformations, a control reaction was carried out without irradiation (**1**, CH_2Cl_2, DBU, N_2, 25 to 50 °C, 3 h). It was found that trace amounts of **13a/b** could not be identified. Thus, a photochemical mechanism involving DBU was postulated. As shown in Scheme 5, upon irradiation, **1** could first convert into (1*Z*)-xanthatin (**15**), which, in the presence of excess DBU, undergoes 1,6-conjugate addition to afford the zwitterionic intermediate **I-1**. After elimination of DBU, **I-1** diverts into

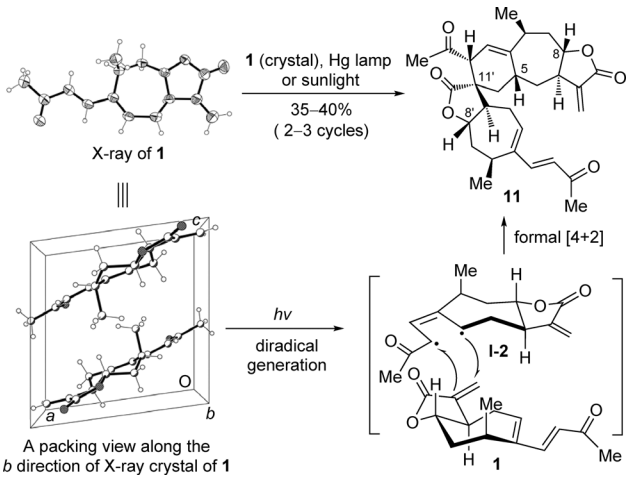


Scheme 5. Proposed mechanism of photochemical/DBU-promoted double-bond isomerization.

1 and **12**, and the latter undergoes 6π electronic cyclization to yield **13**. Notably, this mechanism is supported by the seminal studies of Noyori and co-workers,[16] who showed that the *trans*-cycloheptenone intermediate could be readily trapped by O- or N-centered nucleophiles by 1,4-conjugate addition.

With the synthesis of **3** completed, we then turned our attention to the dimeric xanthanolides **4**–**7**. As mentioned above, **4**–**7** were assumed to be derived from **2** by head-to-tail dimerization, which differs from the one leading to **8** and **9**. Thus, we wondered if we could achieve such a dimerization with **1**? Although dimeric xanthanolides originating from **1** have not been identified in nature, such chemistry, if it works, would serve an ideal model study for the total synthesis of **4**–**7**.

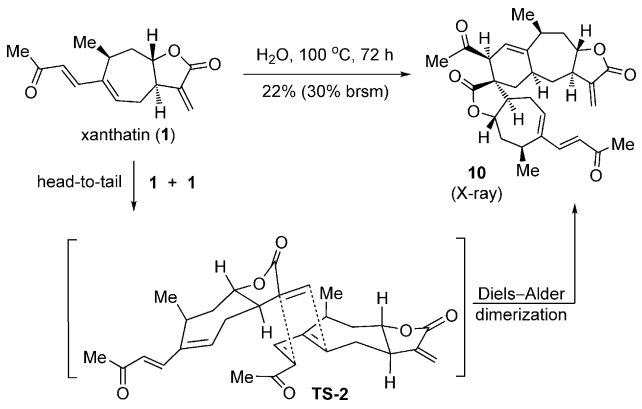
It is known that the photoreactions in the solid state sometimes show different behavior compared to their solution counterparts.[17] We also attempted this protocol in our case by irradiating a crystal of **1** with a Hg lamp. Gratefully, although substantial amounts of **1** remained unchanged after several hours, a new product was obtained, and was confirmed to be **11** (Scheme 6). Interestingly, a similar result was obtained by directly exposing **1** in the solid state to the sunlight for long time (3 days), and the overall yield could be improved to 35–40% by recycling the recovered starting material two to three times. In contrast with **8** and **9**, **11** represents a new dimer derived from **1** by head-to-tail dimerization. While a full elucidation of the differences



Scheme 6. Type II dimerization of **1**. Thermal ellipsoids shown at 30% probability.

between the reactions in solution and the solid state remains unattainable, the packing view of the crystal structure of **1**[11] (m.p. 113–114 °C, ethyl acetate/hexanes) provided some insight: the two neighboring monomers adopt a head-to-tail stacking pattern, thus upon irradiation one of the two monomers generates the diradical intermediate **I-2**, which then reacts with the other through a stepwise [4+2] cycloaddition to give **11** (referred as type II dimerization hereafter). The high diastereoselectivity of the reaction might be attributed to the restricted molecular motion and conformation in the solid state.

The realization of type II dimerization of **1** seemed to be encouraging; however, we noticed that **11** and **4**–**7** bear contrasting stereochemistries at the C5 and C11′ chiral centers (Scheme 6), thus implying that they might arise from the corresponding monomers through the same dimerization mode but different facial selectivity. Thus, we anticipated that there is another type of dimerization which has not yet been identified. To validate the hypothesis, various thermal and Lewis acid involved conditions were attempted to achieve the direct dimerization of **1** through a Diels–Alder reaction. However, most of the examined reaction conditions failed to yield promising results. After many failures, we attempted to use H_2O as the reaction solvent. The beneficial effect of H_2O on a Diels–Alder reaction has been well documented,[18] and mainly attributed to the combination of hydrophobic interactions and hydrogen-bonding effect. To our delight, when we carried out the reaction by stirring **1** in H_2O at 100 °C for 72 hours, the dimeric product **10** was obtained in 22% yield upon isolation (Scheme 7), and the



Scheme 7. Type III dimerization of **1**.

structure was confirmed by crystallography (m.p. 135–136 °C, MeOH).[11] As shown, **10** possesses the expected molecular architecture and stereochemistry, which should arise from **1** through Diels–Alder dimerization via the transition state **TS-2** (referred as type III dimerization hereafter).

With a systematic investigation on the dimerizations of **1** completed, another question arose: are the dimeric compounds **8**–**11** simply artifacts manufactured in the lab or naturally occurring substances yet to be discovered? Indeed, although xanthanolide dimers derived from 8-*epi*-xanthatin (**2**) are well documented,[3,4] the corresponding dimeric forms of xanthatin (**1**) have not been discovered before, neither as natural products nor as synthetic derivatives. Given that **1** is found to be one of the most abundant constituents of xanthanolides in nature and readily undergoes dimerizations in our studies, it is possible that **8**–**11** are natural products which have not yet been discovered. To verify this hypothesis, we initiated a program to search for these underlying xanthanolide dimers in nature. To our delight, after extensive studies (for details, see the Supporting Information), we finally identified two dimeric xanthanolides, mogolides A and B, from the *Xanthium mogolium* Kitag. (Compositae), a Chinese medicinal plant distributed in Northeast China. The spectroscopic data of mogolides A and B are identical to that of **8** and **10**, respectively, thus confirming their natural origins. Of note, although **9** and **11** (named 3-*epi*-mogolide A and mogolide C, respectively) could not be detected at this stage, the possibility of their natural existence cannot be excluded.

In conclusion, the biomimetic synthesis of several novel xanthanolides was accomplished, the highlights of which include: 1) the tandem photochemical/DBU double-bond isomerization/6π electronic cyclization was developed for the synthesis of 4β,5β-epoxyxanthatin-1α,4α-endoperoxide (**3**); 2) four unprecedented xanthanolide dimers (**8**–**11**) were synthesized from xanthatin by three different dimerizations; 3) the type I dimerization proceeded via a *trans*-cycloheptene intermediate which has been rarely utilized in natural product synthesis; 4) two of the synthetic dimers **8** and **10** were proven to be authentic natural products. Taken together, our work affords a proof-of-concept case of biomimetic synthesis guided discovery of low-abundance natural products. Efforts to synthesize the xanthanolide dimers **4**–**7** are underway.

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[10] Most of the xanthatin used in this study was made by total synthesis (for details, see the Supporting Information). In addition, some of the material was obtained from natural sources during the course of the identification of dimeric xanthanolides.

[11] CCDC 1008585 (**9**), 1008586 (**3**), 1008587 (**16**), 1008588 (**8**), 1008589 (**10**), and 1008590 (**1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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