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Interconversion of the Pallambins through Photoinduced Rearrangement

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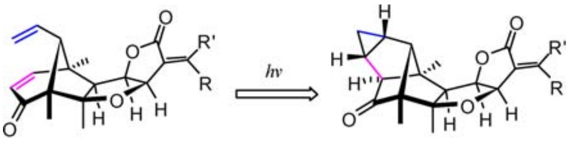
ABSTRACT



3 (R = H, R' = Me)
4 (R = Me, R' = H)

1 (R = H, R' = Me)
2 (R = Me, R' = H)

A new photoinduced interconversion of four naturally occurring 19-*nor*-7,8-secolabdane diterpenoids was discovered and analyzed. The photochemical mechanism, intramolecular diradical rearrangement reaction, was investigated by time-lapse monitoring of the end product formations with HPLC and UV, as well as detailed theoretical calculations.

The metabolic pathways are dependent on plant genomes or enzymes, eventually leading to the formation of structurally diverse secondary metabolites which are mainly derived from a small number of primary molecules.[1] In recent years, however, there is a growing recognition of the importance of both biotic and abiotic stresses on the diversity of natural products.[2] Among these stimuli, UV/vis irradiation is very significant, especially for compounds containing strong chromophores which easily undergo photoinduced reactions.[2b,3]

Recently, we disclosed two unprecedented 19-*nor*-7,8-secolabdane diterpenoids with tetracyclo[4.4.0^{3,5}.0^{2,8}] decane skeletons, pallambins A and B (**1** and **2**), and a pair of structurally related isomers, pallambins C and D (**3** and **4**), from the Chinese liverwort *Pallavicinia ambigua*.[4] The plausible biosynthesis pathway postulated that the formation of **1** and **2** was derived from a cascade of diradical reactions from the precursors **3** and **4**. In order to verify the UV/vis light role on the formation, we carried out the photochemical reaction and found that compounds **3** and **4** (with a 5-vinylcyclohex-2-enone structure) can be converted to **1** and **2** (having a tricyclic bicyclo[2.2.1]-heptanone with an anullated cyclopropane ring) in the presence of UV light at room temperature. This photochemical strategy unequivocally confirmed the above-mentioned unique intramolecular diradical-based transformation (Scheme 1). In response to UV irradiation (λ = 254 nm), compounds **3** and **4** go through a series of reactive diradical intermediates to produce the final compounds **1** and **2**. Attention was also devoted to determining *cis*/*trans* isomerism in the process. This phenomenon was extensively investigated and confirmed by a combined experimental approach utilizing high-performance liquid chromatography (HPLC), UV absorption, and transient absorption measurement, as well as theoretical calculations.

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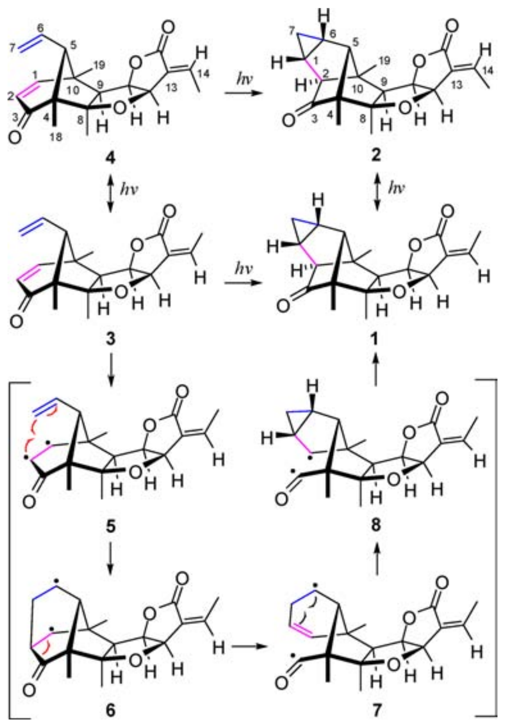
Therefore, our finding is more likely to represent an example of a nature-inspired method that can be used in the synthesis of complex natural products.

Scheme 1. UV Light-Induced Conversion of **3** or **4** to **1** and **2**, and Proposed Mechanism for the Conversion **3** to **1** through a Sequential Diradical Reaction



To identify the photochemical reaction of **3** or **4** in nitrogen-saturated acetonitrile, HPLC was used to detect the compounds by comparing their retention times with those of pure isolates (Figures 1 and S2).[5] The HPLC chromatograms ($\lambda_{\text{detection}}$ = 210 nm) as a function of irradiation time clearly depicted compound modification in terms of integration area, indicating that compounds **1** and **2** were accumulating in the solution at different rates while **3** decreased accordingly. After reaction completion, HPLC showed an equilibrium consisting of **1** and **2** with a ratio of integrated peaks at 4:5. This amplified reaction (12.4 mg for **3**) was subjected to semipreparative HPLC providing **1** (3.25 mg) in 26% yield and **2** (3.70 mg) in 30% yield (Figures S14–S17). Specifically, compound **4** was found to be formed in the initial 30 min as an intermediate in the interconversion reaction with the decrease of **3**. The amount of **1** increased first to attain a maximal concentration after about 30 min before decreasing to the level of equilibrium including **1** and **2**. The detailed analysis above implied that the *cis*/*trans* isomerizations at $\Delta^{13(14)}$ occurred during the entire process. These results are in accordance with the proposed diradical reaction shown in Scheme 1. This conversion is further supported by monitoring the UV absorption of **3** (Figure 2). The lack of an isosbestic point for the photochemical reaction of **3** suggested that more than one species were involved in the process.[6] In addition, the decreased absorbance at 210 nm and the hypsochromic shift at different irradiation time intervals indicated that there was a reduced conjugated system involved in the photoreaction, thereby supporting the conversion of **3** to **1**.[7] The similar transformation from **4** to **2** was also observed (Figure S2). Furthermore, the constituents of liverwort *Pallavicinia ambigua* were also analyzed to determine the presence of compounds **1**–**4** in nature (Figures S1 and S2).

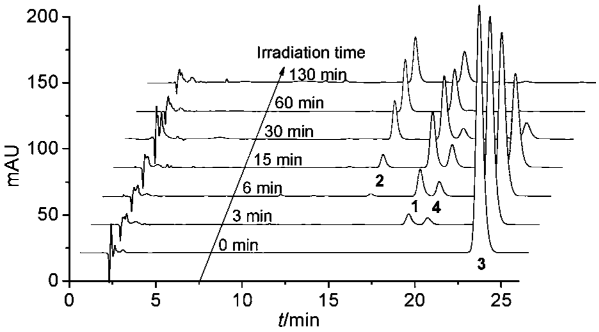


Figure 1. HPLC chromatograms ($\lambda_{\text{detection}}$ = 210 nm) obtained for the irradiation of compound **3** in N_2-saturated CH_3CN solution ($\lambda_{\text{excitation}}$ = 254 nm) at different time intervals.

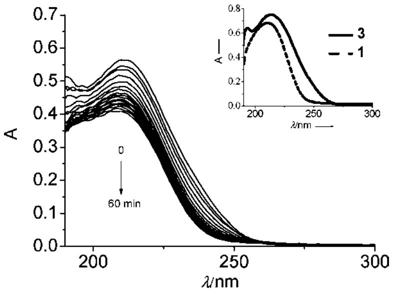


Figure 2. Changes in the UV absorption spectra of N_2-saturated CH_3CN solution for compound **3** (2.8×10^{-2} mmol/L) irradiated by 254 nm light. The internal plot: the comparison of UV spectra between compounds **3** and **1**.

To gain better insight into the mechanism of this light-induced diradical rearrangement reaction, a computational analysis of the reaction coordinate and the transition states (TSs) was performed using density functional theory (DFT) at the UB3LYP/6-31G* level. It is now generally accepted that the photoexcitation of an enone first forms a

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singlet excited state. Based on the literature, the singlet excited state is typically very short-lived and will undergo rapid intersystem crossing to form the triplet state.[8] Thus, it is expected that the reactive excited state of the reaction will be the enone triplet state, as in other reactions reported previously.[9] Our calculation indicated that the photoexcitation of **3** preferentially occurred on the cyclic enone, affording triplet diradical intermediate **5**. Once **5** was formed, a series of subsequent diradical reactions occurred via triplet states to generate compound **1** (Scheme 1, and Figures 3 and S9), which was confirmed partly by the laser flash photolysis (LFP) studies (Figures S7 and S8).

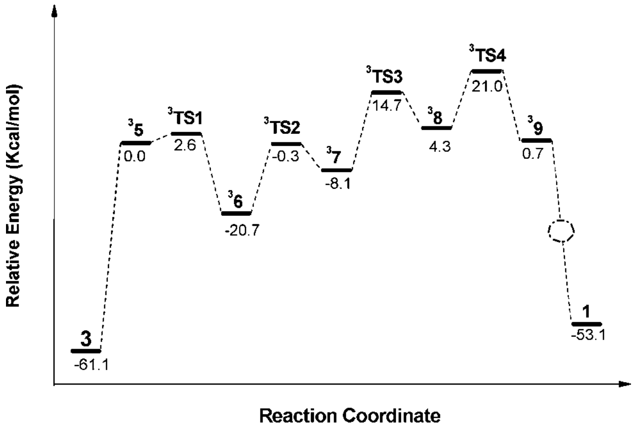

Figure 3. Potential energy profile of the triplet diradical reaction pathway of compound **3** to produce the compound **1**, where the circle means an intercrossing system between the triplet–singlet surfaces.

Figure 3 depicts the potential energy surface (PES) for the triplet photochemical reaction of **3**, which gives the stable compound **1** through four intermediates **5**–**8**. From triplet diradical **5**, attack of the C7 radical on the C2 atom of the olefin C1=C2 took place via a triplet transition state ^{3}**TS1** to give a triplet diradical intermediate ^{3}**6** with an activation free energy of 2.6 kcal/mol relative to **5**. Then, ^{3}**6** was converted to ^{3}**8** through homolytic cleavage of single bond C2–C3 and the formation of a cyclopropane ring via triplet transition states ^{3}**TS2**, ^{3}**TS3** and diradical intermediate ^{3}**7**. The free energy barrier for the cleavage of C2–C3 leading to ^{3}**7** is calculated to be 20.4 kcal/mol, which is 0.3 kcal/mol lower compared to **5**. ^{3}**6** is more stable than ^{3}**7** by 12.6 kcal/mol due to its highly rigid structure. The computed barrier for the succeeding formation of a cyclopropane ring to generate ^{3}**8** is 22.8 kcal/mol. ^{3}**8** is less favorable in energy by 4.3 kcal/mol than **5**. So it transformed readily into ^{3}**9** by forming the new C1–C3 bond via ^{3}**TS4** with a Gibbs energy barrier of 16.7 kcal/mol. ^{3}**9** must undergo intersystem crossing, with spin inversion, to give a singlet state before it evolves to compound **1**. The above-mentioned results suggest that the rate determining step of the overall reaction proceeds via transition state ^{3}**TS3** which lies ca. 14.7 kcal/mol above ^{3}**5**. So the titled photoinduced interconversion happens easily at room temperature once diradical intermediate **5** formed. **1** converted to **2** via a triplet excited state during the whole process, for the photoexcitation energy of the C13–C14 olefin was 53.8 kcal/mol as calculated. In addition, we also investigated an alternative mechanism which involved a nucleophilic attack of C7 on C1 of the olefin C1=C2, followed by homolytic cleavage of C1–C10 bond and the cyclopropane ring formation via triplet transition states ^{3}**TS2′**, ^{3}**TS3′** and diradical intermediate **7′**, to produce another diradical intermediate **8′**. We found that ^{3}**6′** can undergo intersystem crossing to singlet state ^{1}**6′**. The energies of the singlet species ^{1}**6′**, ^{1}**7′**, ^{1}**8′**, ^{1}**TS2′**, and ^{1}**TS3′** are much closer to those of the corresponding triplets species (Figures S10 and S11). However, our calculation indicated that ^{3}**TS2′** (or ^{1}**TS2′**) is less stable than ^{3}**TS2** (22.5 vs 20.4 kcal/mol), suggesting that this mechanism is slightly less favorable than that discussed above. We also explored the intramolecular [2 + 2] photocyclization mechanism, where a four-member ring was formed.[10] As mentioned previously, the triplet 1,4-diradical intermediate must evolve to the singlet 1,4-diradical to achieve the [2 + 2] photocyclization.[11] Our calculation showed that the triplet and singlet 1,4-diradical species ^{3}**6** and ^{1}**6** are very similar with each other in both geometry and energy (Figure S13), which indicated that these two species sit near the intersystem crossing region between the ground-state singlet and triplet energy surfaces of the system. Once formed via intersystem crossing, the singlet 1,4-diradical intermediate can evolve back to the initial reactants via transition state ^{1}**TS(R)** or give a cycloaddition adduct via ^{1}**TS(P)**. It was found that ^{1}**TS(R)** is more stable than ^{1}**TS(P)** by 2.8 kcal/mol, suggesting that the reversion of ^{1}**6** to reactants is more favorable than the ring closure leading to the cycloaddition product. Thus, it is a dead end along the [2 + 2] pathway. The fact that no [2 + 2] cycloaddition product was formed also supports the above-mentioned conclusion.

We have presented a photoinduced diradical reaction responsible for four natural product intertransformations. The mechanism, sequential radical reactions instead of a general [2 + 2] cycloaddition of cyclic α,*β*-enone with olefin, was investigated by theoretical calculations. We expect that this discovery could provide new and significant insights into the influence of UV/vis light on the naturally occurring metabolites. Moreover, when we discuss the art of total synthesis of natural products with

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unprecedented complex architectures, we often think in terms of how reactions can be efficiently achieved in fewer steps by reagents or other means, but frequently overlook the nature-inspired method of UV irradiation.

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Supporting Information Available. General experimental procedures, HPLC analysis, ^{1}H and ^{13}C NMR spectra of **1** and **2** isolated from the reaction, and theory and calculation details. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.