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Photochemical studies on ladderane formation from conjugated esters in solution or solid phase

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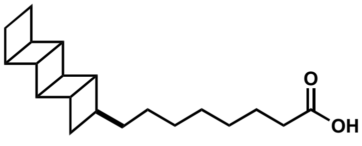
Abstract—This letter describes a combined photochemical and X-ray crystallographic study of routes for the synthesis of cyclobutane or ladderane structures by a [2+2]-cycloaddition pathway and leads to a clearer definition of the 3-D structural requirements for such processes in the solid state.

Recently, we reported the first enantioselective total synthesis[1] of the unusual microbial fatty acid pentacycloanammoxic acid **1**: a molecule that harbors a unique carbon framework composed of five cis-fused cyclobutane rings (referred to as a [5]-ladderane). In connection with this work, we conducted some exploratory studies to test the feasibility of constructing the complete [5]-ladderane unit of this molecule based on photoirradiation of easily accessible polyenes in solution and/or in the solid phase. This letter reports some of our preliminary results in this arena.

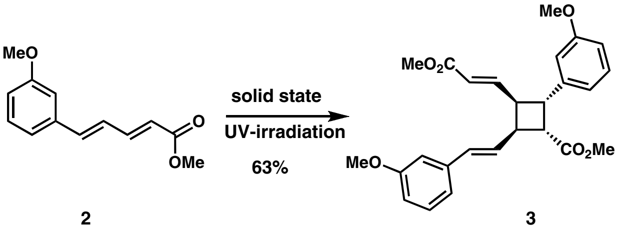


1
pentacycloanammoxic acid
(+)-enantiomer

The pioneering study of Schmidt over 50 years ago on the solid-state photodimerization of *trans*-cinnamic acid showed that when crystal packing placed double bonds of neighboring molecules in proximity, a [2+2]-photocycloaddition occurred upon irradiation.[2] Thus, in the crystalline α- and β-forms of the acid a solid-state photo[2+2]-cycloaddition occurs, involving face-to-face double bonds at a distance of 4.1 Å. However, in the γ-form no photodimerization occurs since the two adjacent double bonds are further away from each other (>4.7 Å) and are no longer properly aligned. Moreover, in solution only trans/cis isomerization occurs.

Following this initial report, the dimerization of cinnamic acid derivatives has been extensively studied and the concept of locking two olefinic systems in a special arrangement favoring a [2+2]-photocycloaddition has been extended to the synthesis of ladderane motifs (i.e., an assembly of cis-fused cyclobutane rings) starting from polyolefinic substrates. Recent work reported by Hopf,[3] who employed a polyunsaturated substrate rigidly held by a [2,2]-paracyclophane scaffold in solution, and by MacGillivray[4] with a polyene in the solid state are good examples.

We started our investigations by studying the UV-irradiation[5] of dienoate **2** (Scheme 1), easily synthesized in quantitative yield via Horner–Wadsworth–Emmons reaction between *m*-anisaldehyde and methyl-4-(dimethylphosphono)crotonate in THF at −50 °C using



Scheme 1.

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NaHMDS as a base. When a sample of **2** (mp = 62–64 °C, recrystallized from Et_2O–hexanes) was placed between two layers of Pyrex® glass and irradiated with ultraviolet light from a Hanovia medium-pressure Hg lamp, the reaction proceeded cleanly to produce the monocyclobutane head-to-tail derivative **3** (Scheme 1) in 63% isolated yield (80% conversion after 7 h).[6] The formation of **3** correlates with the X-ray crystal structure of **2** that is shown in Figure 1. The double bonds that react to form **3** are close to one another (C–C distances: 3.9 and 3.96 Å) and are arranged in a head-to-tail manner with only a slight offset. Encouraged by this result, we then investigated the solid-state UV-irradiation of trienoate **4** (mp = 114 °C, recrystallized from EtOAc/heptane[7] in the solid state). Unfortunately, the UV-irradiation of this adduct (Scheme 2) in the solid state, either as suspension in water or in dry form (finely ground crystals placed between two layers of Pyrex® glass), led solely to polymeric material as evidenced by ^1H NMR.

Although initially unexpected, these results were readily rationalized once we obtained the X-ray crystal structure of **4**. That structure (see Fig. 2) clearly indicated that the two closest neighbors in the lattice are not only too far away from each other (4.3 Å) to do a [2+2]-cycloaddition, but are also not properly oriented. This result emphasizes the importance of a face-to-face parallel stacking arrangement rather than a criss-cross orientation of double bonds for solid-state photoaddition. Consequently, we reasoned that the formation of a dienoate such as **5** (Fig. 3; mp = 102–104 °C, recrystallized from EtOAc–heptane) might favor the orientation of the two triene units in an arrangement where an intramolecular solid-state [2+2]-photocycloaddition could occur. Although **5** was readily synthesized, irradiation of the solid between two layers of Pyrex® glass for 10 h failed to produce any of the desired ladderane skeleton and only a chloroform insoluble material (presumably polymeric) could be recovered. The reason for this lack of intramolecular photocyclization was clarified once again by the X-ray crystal structure of **5**, which showed that the two triene units are too far away (4.7 Å) and are also not well aligned (Fig. 3).

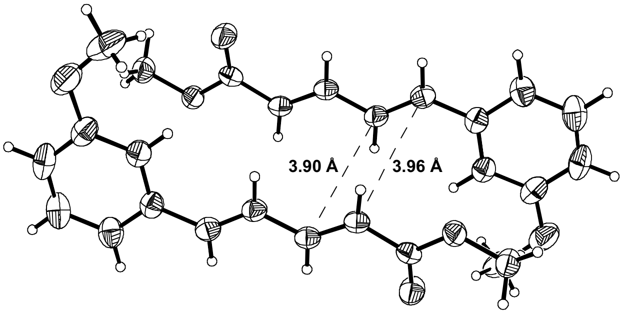
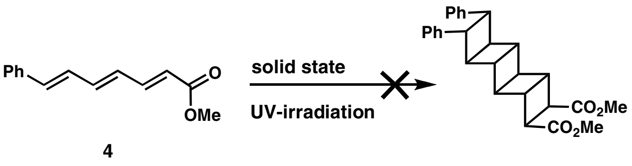


Figure 1. Arrangement of two closest neighbors in the crystal structure of **2**.



Scheme 2.

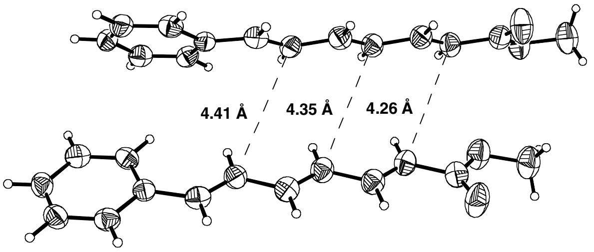


Figure 2. Arrangement of two closest neighbors in the crystal structure of **4**.

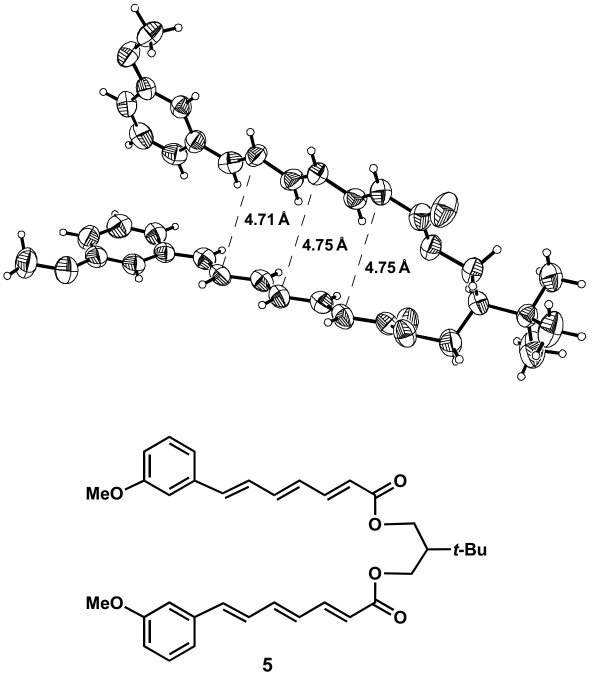
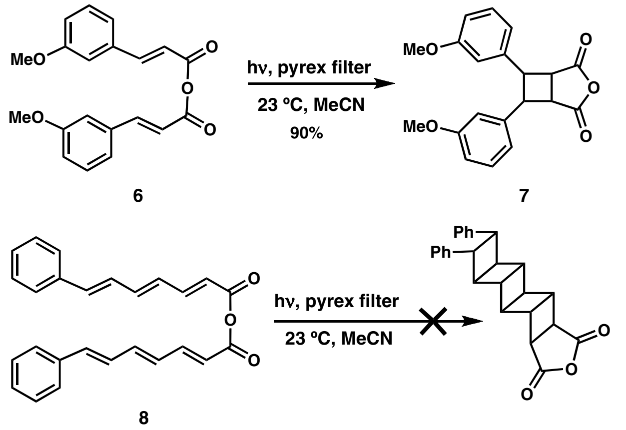


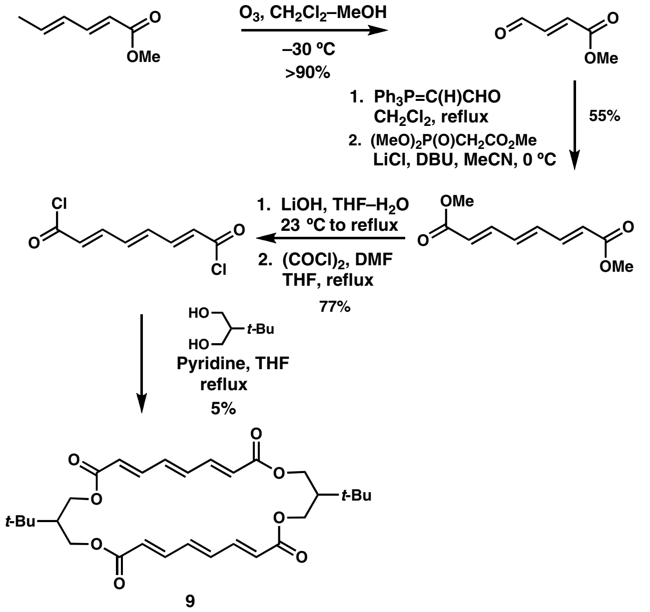
Figure 3. Arrangement of two triene units in the crystal structure of **5**.

In order to potentially reduce the intramolecular distance between the two triene units, we decided to investigate the feasibility of an intramolecular [2+2]-photocycloaddition of the olefinic anhydride **6** (Scheme 3). We were pleased to observe that when a dilute solution of **6** (this compound is an oil) in MeCN was irradiated with UV light at 23 °C for 20 h, a [2+2]-cycloaddition occurred to produce **7** in over 90% yield.[8] Unfortunately, UV-irradiation of the polyolefinic anhydride **8** (an oil) in MeCN led to only isomerization of the double bonds and formation of polymeric material.[8]

Another option for aligning the two triene units in a suitable arrangement for an intramolecular [2+2]-photocycloaddition was investigated using the 26-membered macrocyclic structure **9** (Scheme 4). This test substrate (**9**) was synthesized in six steps starting from methyl sorbate as summarized below. All the steps pro-



Scheme 3.



Scheme 4. Synthesis of macrocycle **9**.

ceeded in high yield except for the macrocyclization steps between the bis acid chloride and the diol, which produced the desired product **9** in 5% isolated yield. Although the last step was not optimized, the yield was sufficient to provide enough material to test the critical UV irradiation step, and **9** provided the bonus of being a solid. Unfortunately UV irradiation of **9**, either in solution or in the solid state, failed to produce the desired [5]-ladderane motif. Instead, in addition to the formation of some polymer material, we observed by ^{1}H NMR the formation of a complex mixture of polyolefinic products containing numerous olefinic proton peaks.

After extensive screening of different solvents, we found that **9** could be recrystallized from $CHCl_3$–heptane to produce single crystals suitable for X-ray diffraction analysis (mp not determined since at temperatures as high as 280 °C the solid shrank but did not melt). The X-ray crystal structure of **9** as the chloroform solvate is shown in Figure 4. In this case too, even though the two π-systems are somewhat parallel to each other they are unfortunately not well aligned and are too distant from one another (5.2 Å) for intramolecular photocyclization to occur without major disruption of crystal packing. Such disruption is likely very slow as compared to relaxation of the excited substrate to the ground state (likely to be very fast in the solid phase).

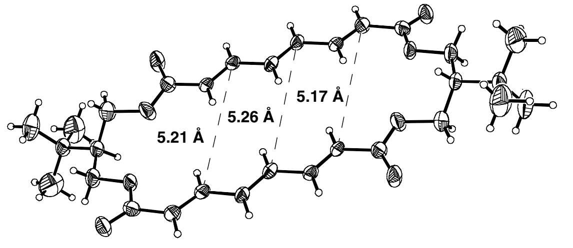


Figure 4. Arrangement of two triene units in the crystal structure of **9**.

The studies described herein provide useful guidelines on future approaches to the synthesis of ladderanes by a poly-[2+2]-cycloaddition pathway. It is clear that X-ray crystallographic analysis can serve as a useful screen for promising substrates in solid-state photoreactions. What is still required for the efficient application of this approach is a methodology for crystal engineering,[9,10] which in this context, means the prediction of crystal packing as a function of substrate structure. It is also apparent that photochemical [2+2]-cycloaddition strategies are only workable when the olefinic units of the substrate(s) are properly positioned relative to one another.[11]

References and notes

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5. All the UV irradiations reported in this letter were done using a Hanovia 450 W medium pressure Hg lamp equipped with a Pyrex® cooling jacket.
6. When **2** was suspended in water, the solid stayed in solution during the irradiation and we observed the clean formation of **3**. However, the reaction was slower (40% conversion after 7 h). Irradiation of **2** in hexanes led only to isomerization of the double bonds.
7. Compound **4** was synthesized in one step and 40% yield by a Horner Wadsworth Emmons reaction starting from *trans*-cinnamaldehyde and methyl-4-(dimethylphosphono)-crotonate.

8. As measured by NMR analysis of the total reaction product.
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11. The X-ray crystal structures of **2**, **4**, **5**, and **9** have been deposited with the Cambridge Crystallographic database.