

## The Double [3 + 2] Photocycloaddition Reaction

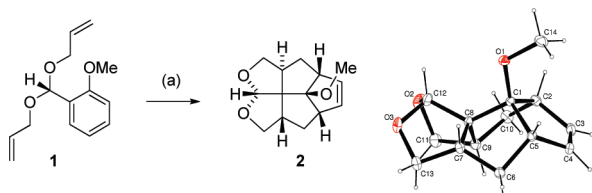
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A common challenge confronting synthetic organic chemists is the atom-efficient creation of molecular complexity.<sup>1</sup> The meta photocycloaddition reaction<sup>2</sup> is useful in this context, as three new  $\sigma$  bonds, three new rings, and up to six new stereocenters are formed in a single step. More complexity can be added by tethering the two reacting partners together,<sup>3,4</sup> and the elegant work of Wender<sup>2c–j</sup> pioneered the reaction's application in natural product synthesis. While investigating the photochemistry of aromatic acetal **1**, we discovered a unique double [3 + 2] photocycloaddition reaction that resulted in the formation of the fenestrane<sup>5</sup> derivative **2**<sup>6</sup> (Scheme 1). This dramatic transformation represents the creation of five new rings, four new carbon–carbon  $\sigma$  bonds, and seven new stereocenters in a one-pot process.

**Scheme 1.** The Double [3 + 2] Photocycloaddition Reaction To Form Fenestrane **2**<sup>6 a</sup>

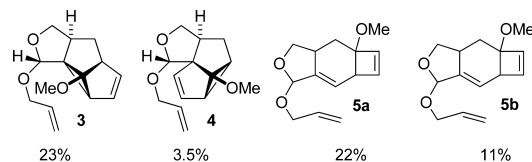


<sup>a</sup> Conditions: (a)  $h\nu$  (254 nm), cyclohexane, 18 h, 8%.

Although the synthetic utility of fenestrane-type structures has yet to be fully explored, a recent synthesis of the insecticide (–)-penifulvin A<sup>5d</sup> might suggest an untapped potential. Theoretical interest in fenestrans remains high because of the distortion of the central quaternary carbon away from the standard tetrahedral bond angle of 109.5°. In the case of compound **2**, the transverse bond angle (C7–C8–C9) is 120.2° and the longitudinal bond angle (C12–C8–C1) is 128.5°.

Compound **1** was prepared in 98% yield using Noyori's acetal-forming procedure<sup>7</sup> by the reaction of allyloxytrimethylsilane with *o*-anisaldehyde in the presence of trimethylsilyl triflate. Irradiation of **1** in cyclohexane using 254 nm UV light for 18 h led to the formation of a multitude of products, including the pentacycle **2** in 8% yield (Scheme 1). In a separate experiment, **1** was irradiated to the point of its total consumption (4 h) to yield four major components: linear meta photocycloadduct **3**, angular meta photocycloadduct **4**, and two ortho-derived cycloadducts<sup>3d,8</sup> **5a** and **5b** whose relative configuration could not be determined (Figure 1). The absence of any fenestrane adduct **2** formation under these conditions led us to conclude that it must have been generated sequentially from one of the monocyclized compounds shown in Figure 1.

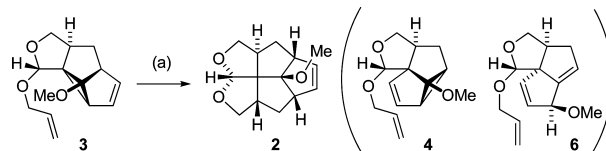
To investigate this, a solution containing only the major meta photoadduct **3** in cyclohexane was irradiated using 254 nm UV light for 16 h; this resulted in the formation of fenestrane **2** in 38% yield (Scheme 2). We also discovered that small amounts of the angular meta photoadduct **4** and a rearranged photoproduct **6** were



**Figure 1.** The four principal photoadducts formed by irradiation of aromatic acetal **1** in cyclohexane for 4 h using 254 nm UV light.

also formed during this secondary irradiation process. It should be noted that compound **6** was difficult to obtain free of other contaminants because of coelution with **3**.

**Scheme 2.** Conversion of Linear Meta Photoadduct **3** into Fenestrane **2**<sup>a</sup>

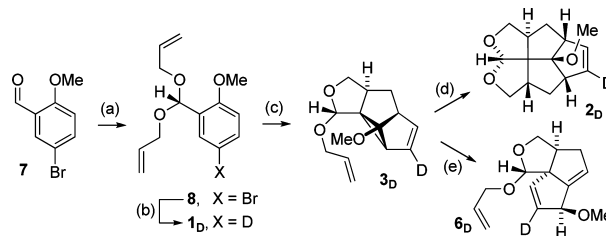


<sup>a</sup> Conditions: (a)  $h\nu$  (254 nm), cyclohexane, 16 h, 38%.

The minor meta photoadduct **4** could also be converted into **2** under the same photolytic conditions, although it primarily led to the formation of photoproduct **6**.

To aid in obtaining a mechanistic understanding of these transformations and interpreting the NMR spectra, we prepared **1<sub>D</sub>**, a deuterated version of the aromatic starting material, from 5-bromo-2-anisaldehyde (**7**) (Scheme 3).

**Scheme 3.** Formation and Photolysis of Deuterated Substrate **1<sub>D</sub>**<sup>a</sup>



<sup>a</sup> Conditions: (a) 2.5 equiv of  $\text{Me}_3\text{SiOCH}_2\text{CH}=\text{CH}_2$ , 0.01 equiv of  $\text{Me}_3\text{SiOTf}$ ,  $-84^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ , 87%; (b)  $n\text{-BuLi}$ ,  $-78^\circ\text{C}$ , THF then MeOD, 78%; (c)  $h\nu$  (254 nm), cyclohexane, 18 h, 14%; (d)  $h\nu$  (254 nm), cyclohexane, 2 days, 11%; (e)  $h\nu$  ("old lamp"), cyclohexane, 7 days, 16%.

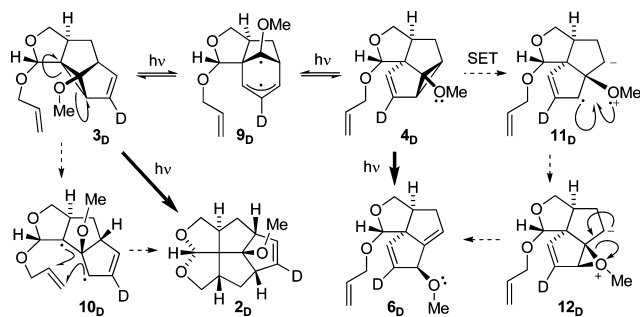
After conversion of **7** to bromoacetal **8** via the Noyori procedure<sup>7</sup> with allyloxytrimethylsilane, metal–halogen exchange was accomplished using *n*-butyllithium, and the resulting anion was quenched with MeOD to afford **1<sub>D</sub>** with >80% deuterium incorporation. The deuterated linear meta photoadduct **3<sub>D</sub>**<sup>9</sup> was obtained following an initial photolysis step, and this was then converted into the deuterated products **2<sub>D</sub>** and **6<sub>D</sub>** in secondary photolysis steps. We found this process to be lamp-dependent, as our initial attempt

to irradiate **3<sub>D</sub>** using an old 16 W low-pressure mercury vapor lamp resulted in the formation of **6<sub>D</sub>** as the principal product instead of **2<sub>D</sub>**. This extended irradiation period also caused the complete consumption of **3<sub>D</sub>**, which aided in the chromatographic isolation of **6<sub>D</sub>**.

The presence of various triplet sensitizers (acetone, acetophenone, and benzophenone) during the irradiation of compound **3** enhanced its conversion into the fenestrane product **2**. The efficiency of this process was sensitizer-dependent, with acetone forming significant quantities of **2** in a matter of hours, although it had the disadvantage of forming other impurities. Benzophenone appeared to inhibit the transformation, with comparatively little conversion of **3** to **2** even after several days of irradiation. Acetophenone presented a better compromise, although the subsequent purification process was hampered by coeluting impurities. During these sensitized reactions, a small amount of photoequilibration between **3** and **4** was observed, although the formation of the rearranged product **6** was completely suppressed. The addition of isoprene as a triplet quencher inhibited the formation of **2** from **3**, providing further evidence that a triplet state is involved in this process.

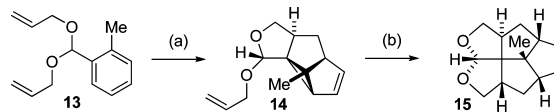
A plausible mechanistic rationale to account for the formation of **2<sub>D</sub>** and **6<sub>D</sub>** is presented in Scheme 4. Linear and angular meta photoadducts (**3<sub>D</sub>** and **4<sub>D</sub>**) are known to interconvert under photolytic conditions.<sup>10</sup> This could occur either by homolytic fission of the cyclopropyl ring (see **9<sub>D</sub>**) or by a [1,3]-sigmatropic rearrangement. Photoinduced homolytic fission of the external cyclopropyl ring bond of the linear meta photoadduct **3<sub>D</sub>** may afford diradical **10<sub>D</sub>**, which could cyclize onto the terminal alkene to create two new five-membered rings and hence **2<sub>D</sub>**. Photoexcitation of the angular meta photoadduct **4<sub>D</sub>** followed by single electron transfer (SET) from the methoxy group's lone pair of electrons to the external cyclopropyl ring bond would result in the fragmentation of the three-membered ring to afford **11<sub>D</sub>**. The allylic radical of **11<sub>D</sub>** could combine homolytically with the oxygen radical cation to form pseudo-methylated epoxide **12<sub>D</sub>**, which would fragment to give the doubly allylic ether **6<sub>D</sub>**.

**Scheme 4.** Mechanistic Proposal for the Formation of **2<sub>D</sub>** and **6<sub>D</sub>**



Wender, Dore, and deLong<sup>11</sup> prepared a similar fenestrane compound by reaction of the linear meta photocycloadduct **14** derived from the bisallyloxy acetal of *o*-tolualdehyde (**13**) with an acetonitrile radical. We found that **14** could be converted to fenestrane **15** after many days of irradiation, but it could not be isolated free of other contaminants (Scheme 5). Use of acetophenone as a sensitizer improved the rapidity of this process, although impurities again hindered purification.

**Scheme 5.** Photoconversion of *o*-Tolualdehyde-Derived Meta Photoadduct **14** into Fenestrane Adduct **15**<sup>a</sup>



<sup>a</sup> Conditions: (a)  $h\nu$  (254 nm), cyclohexane, 9.5 h, 24%; (b)  $h\nu$  (254 nm), cyclohexane, 8 days, <10%.

In conclusion, a remarkable double [3 + 2] photocycloaddition reaction resulting in the formation of fenestrane **2** from aromatic diene **1** has been reported. During this process, four carbon–carbon bonds, five new rings, and seven new stereocenters are created. The photoreaction occurred in a sequential manner from linear meta photocycloadduct **3**, while rearranged photoproduct **6** was derived from angular meta photocycloadduct **4**.

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**Supporting Information Available:** Experimental details, characterization data for all new compounds, and crystallographic data (CIF) for **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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