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Preparation of cyclobutene acetals and tricyclic oxetanes via photochemical tandem and cascade reactions

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Abstract: We describe a photochemical reaction paradigm using two starting materials, a cyclopent-2-enone and an alkene, which are transformed in a controlled manner via the initial [2+2]-photocycloaddition adducts into cyclobutene aldehydes (conveniently trapped as stable acetals) or unprecedented angular tricyclic 4:4:4 oxetane-containing skeletons. These compounds are formed via tandem or triple cascade photochemical reaction processes, respectively. Small libraries of each compound class have been prepared, suggesting that this photochemistry paradigm opens new opportunities for fine synthesis design and for widening molecular diversity.

Photochemical reactions constitute a powerful toolkit for modern synthetic chemistry.[1] The selective activation of molecules through the acquisition of a considerable amount of energy by the absorption of light can provide access to complex molecular structures which are difficult to obtain otherwise, via transformations which have no parallel in ground-state chemical reactivity. Such processes are attractive in the context of sustainable development, since the explicit reagent is a simple photon. Significant recent advances have been collated in the areas of catalyst-free photochemical synthesis,[2] visible-light photocatalysis,[3] enantioselective catalysis,[4] photochirogenesis[5] and the use of flow processes,[6] testifying to the potential of organic photochemistry for selective synthesis.

In the context of tandem or cascade reactions, photochemical transformations play an active role.[7] A photochemical step can be conveniently combined with other categories of synthetic transformations, notably those employing transition-metal catalysis[8] or featuring radical cyclizations.[9] Much less common are cascade reactions in which two (or more) discreet photochemical processes are implicated consecutively.[10]

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The [2+2]-photocycloaddition of an enone and an alkene provides a versatile access to functionalized cyclobutanes and, in particular, the use of cyclopent-2-enone derivatives leads to bicyclo[3.2.0]heptan-2-one adducts (Figure 1).[11] Some reports describe the photochemical transformation of bicyclo[3.2.0]heptan-2-one derivatives, via a Norrish-Type-I cleavage followed by γ-hydrogen (γ-H) transfer, to provide cyclobutenylpropanals (Figure 1).[12] It appeared logical to us that it should be possible to combine a cyclopent-2-enone and an alkene in a tandem photochemical reaction involving a [2+2]-cycloaddition followed by a Norrish-I/γ-H transfer. Indeed, careful inspection of the literature revealed a few isolated reports on the formation of cyclobutenylpropanal derivatives via such a process;[13] however, these compounds were formed in low yields and considered as side-products (Figure 1). To the best of our knowledge, no general photochemical procedure allowing the direct and selective preparation of such structures has been described to date.

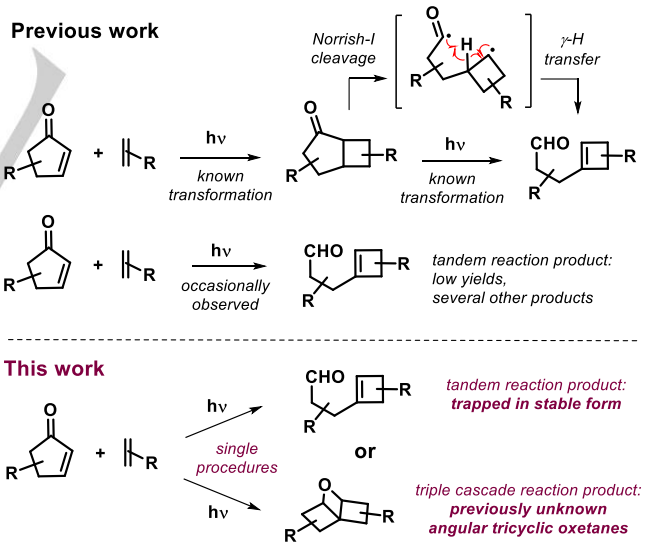

Figure 1. Background for this study.

Cyclobutene derivatives are attractive intermediates in synthesis,[14] and the presence of an aldehyde function further enhances the value of such compounds. The opportunity for developing an expedient access to cyclobutenylpropanals from simple cyclopent-2-enone and alkene substrates seemed to us to have been overlooked or at least underexploited. We therefore decided to study this tandem photochemical reaction, with the aim of developing an efficient and viable synthetic procedure. During

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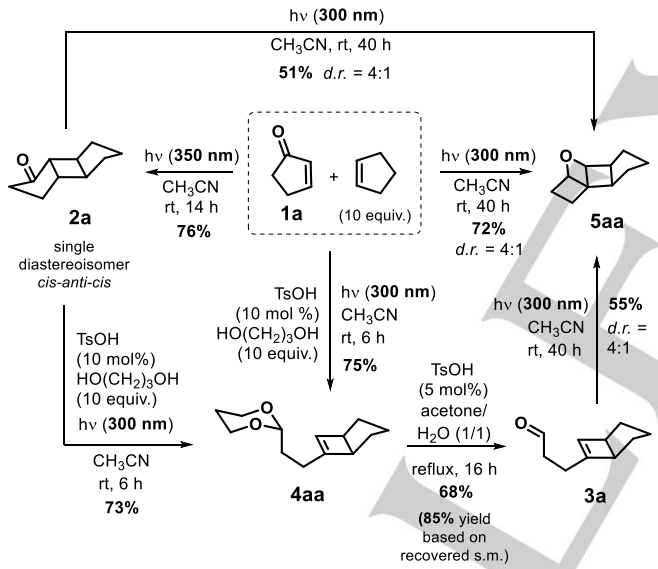
the course of this study we discovered a triple photochemical cascade reaction which leads to unprecedented angular tricyclic structures (Figure 1).

We first searched for experimental conditions which would allow a simple and practical preparation of cyclobutenylpropanals via a tandem photochemical [2+2]-cycloaddition – Norrish-I/γ-H transfer process. Cyclopent-2-enone **1a** and cyclopentene (in a 10-fold excess) were selected as the model substrates, and an initial screening was performed by irradiating solutions of these two compounds in different solvents (acetone, acetonitrile, cyclohexane, benzene, toluene, methanol, dichloromethane) using polychromatic light (Hg lamp, Pyrex filter). After 6 h irradiation time, the reaction mixture was examined by ^{1}H NMR spectroscopy and in each case (with the exception of acetone, in which the main product was **2a**), the target cyclobutenylpropanal **3a** was formed along with a number of other photoproducts. Retaining acetonitrile as a convenient solvent, we irradiated a solution of the model substrates using fluorescent lamps (RPR-3500 Å) with an emission maximum at λ = 350 nm for 14 h, which gave selectively the [2+2]-cycloaddition adduct **2a** in 76% isolated yield as a single *cis-anti-cis* diastereoisomer (*d.r.* > 95:5, as determined by ^{1}H NMR analysis) (Scheme 1).



Scheme 1. Single, tandem, or triple cascade photoreactions between cyclopent-2-enone and cyclopentene. The intermediacy of the [2+2]-cycloaddition adduct in the formation of the cyclobutene aldehyde (and thus its acetal) as well as the intermediacy of both of these compounds in the formation of the tricyclic oxetane is supported by the independent transformations.

When the model substrates were irradiated in acetonitrile solution with higher energy light using fluorescent lamps (RPR-3000 Å) with an emission maximum at λ = 300 nm, the main photoproduct observed after 6 h was the target cyclobutene aldehyde **3a**. Unsurprisingly, this compound was rather volatile and easily degraded, making its isolation difficult. Furthermore we noticed the formation of another unidentified photoproduct, to which we will return later. At best, **3a** could be isolated in a moderate 40% yield. To resolve the problems of product isolation, we envisaged trapping the aldehyde product as an acetal during the photochemical reaction. We screened a variety of acid catalysts and alcohols (see Table S1 in Supporting Information), and found that the most efficient procedure was to irradiate the standard mixture (λ = 300 nm) for 6 h in the presence of 10 equivalents of 1,3-propanediol and 10 mol% *p*-toluenesulfonic acid. Under these conditions, the stable acetal **4aa** could be isolated easily in 75% yield (Scheme 1).

To confirm the role of the tricyclic ketone **2a** as an intermediate in the tandem process, this compound was converted into cyclobutene acetal **4aa** in 73% yield by irradiation under the standard conditions (Scheme 1). It was noteworthy that there was no apparent depletion of the chemical yield when the more convenient tandem reaction protocol was used instead of the sequential route.

We then applied these conditions to prepare a wide range of cyclobutenylpropanal acetals **4aa**-**jc** (Table 1). Cyclopent-2-enone **1a** and a number of 2- or 4-substituted derivatives **1b-j** were examined in combination with three representative alkenes: ethylene, tetramethylethylene and cyclopentene. While the yields were not universally high, this procedure harnessed for the first time the tandem photochemical process by trapping cyclobutenylpropanals as stable acetals, making the protocol easy to apply with a satisfactory substrate scope. Moreover, synthetically useful functional groups such as a nitrile (**4ca**), and a protected (**4ga**, **4hb**, **4hc**) or a free (**4da**, **4dc**, **4fa**, **4fb**) hydroxyl group were tolerated under the reaction conditions. For substrate **1e**, bearing a benzyl chromophore, a longer reaction time was required (48 h), but compounds **4ea** and **4ec** were obtained in satisfactory yields.

To confirm the availability of cyclobutene aldehydes by deprotection of the corresponding acetals, **4aa** was refluxed with 5 mol% *p*-toluenesulfonic acid in aqueous acetone, which furnished **3a** in 68% yield (85% yield based on recovered starting material) (Scheme 1). Significantly, this procedure gave **3a** as a much cleaner sample than that obtained via additive-free irradiation of cyclopent-2-enone **1a** and cyclopentene.

As mentioned above, the model reaction of cyclopent-2-enone **1a** with cyclopentene (where acetal trapping was not applied) led to the formation of a second photoadduct along with **3a**. We followed the appearance of this new adduct using ^{1}H NMR spectroscopy, and found that irradiation (λ = 300 nm) of the model compounds in acetonitrile for 40 h furnished the new adduct as the only major compound, with no **3a** remaining. The new compound was isolated and its molecular structure was determined by extensive NMR spectroscopic analysis. It had the tetracyclic structure **5aa** which featured an unprecedented angular 4:4:4 fused ring architecture incorporating an oxygen atom at the apex. The compound was formed as a mixture of two diastereoisomers (*d.r.* = 4:1) and the major isomer was found to have a *cis-syn-cis* geometry of the linear 4:4:5 ring sequence (Scheme 1).

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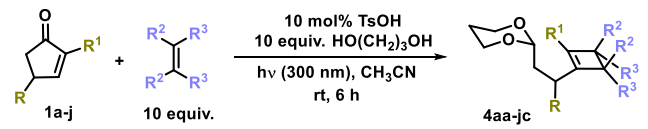
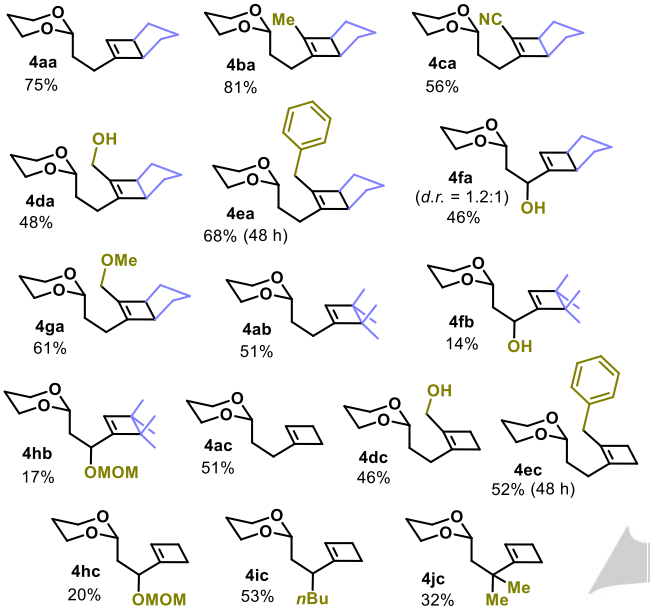
Table 1. Preparation of cyclobutene acetals via the tandem photochemical process.[a]



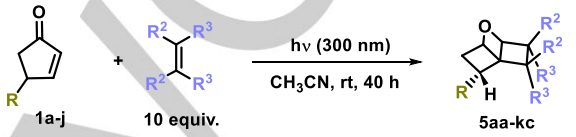


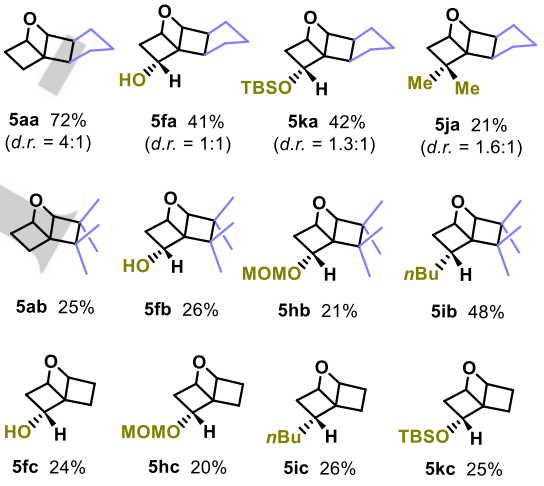
[a] Reactions were performed with **1** (1.5 mmol), alkene (10 equiv. or saturated (for ethylene)), 1,3-propanediol (10 equiv.) and TsOH (10 mol%) in acetonitrile (50 mL) in a sealed quartz tube at room temperature; irradiation was performed using a 300 nm light source for a period of 6 h (48 h for **4ea** and **4ec**); yields are given for isolated products; *d.r.* was determined by ^{1}H NMR analysis of the crude reaction mixture.

A plausible mechanism for the formation of **5aa** is a triple photochemical cascade, starting with the [2+2]-photocycloaddition to give **2a** which evolves via the Norrish-I/γ-H transfer reaction to give **3a**, which is then converted into **5aa** via an intramolecular Paternò-Büchi reaction.[15] This hypothesis was supported by the fact that a sample of **3a** (isolated from its acetal as described above) could be transformed into **5aa** in 55% yield when irradiated (λ = 300 nm) for 40 h in acetonitrile (Scheme 1). Likewise, the tricyclic [2+2]-photoadduct **2a** provided **5aa** in 51% yield in the same conditions (Scheme 1). It was particularly gratifying to note that the yield of **5aa** from cyclopent-2-enone **1a** and cyclopentene obtained directly via the cascade reaction was significantly higher than that using any combination of sequential operations which implicate isolated samples of **2a** and/or **3a**. Intramolecular Paternò-Büchi reactions have occasionally been used to construct 4:4 fused ring systems[16] or to elaborate more complex polycyclic skeletons containing an oxetane core,[17] but to our knowledge the formation of the angular 4:4:4 fused ring system of **5aa** is unprecedented, and would be difficult to access by any other synthetic pathway.

The unique architecture of **5aa** prompted efforts to prepare other complex polycyclic oxetanes using the same photochemical procedure. Although 2-substituted cyclopentenones did not lead to the formation of the desired products, we were pleased to find that irradiation (λ = 300 nm) of alkenes and selected 4-substituted derivatives for 40 h in acetonitrile provided a panel of new compounds **5aa**-**kc** (Table 2). Despite their inherent ring strain, these compounds displayed remarkable stability and could be isolated by column chromatography on silica gel. Moreover, the presence of a free alcohol group in such structures (**5fa**, **5fb**, **5fc**) was fully tolerated by the reaction conditions.

Table 2. Preparation of angular tricyclic oxetanes via the triple photochemical cascade process.[a]





[a] Reactions were performed with **1** (1.5 mmol) and alkene (10 equiv. or saturated (for ethylene)), in acetonitrile (50 mL) in a sealed quartz tube at room temperature; irradiation was performed using a 300 nm light source for a period of 40 h; yields are given for isolated products; *d.r.* was determined by ^{1}H NMR analysis of the crude reaction mixture.

Among these compounds, **5fb** alone was a solid product, and we obtained a single crystal which was suitable for X-ray diffraction (Figure 2).[18] As expected, the oxetane ring was planar, but both cyclobutanes were unusually flattened with ring puckering not exceeding 8°. Striking structural features were the sterically challenging torsion angles of 9.9° and 9.4° for the vicinal methyl group pairs and the 134.4° C-C-C bond angle connecting the three rings.

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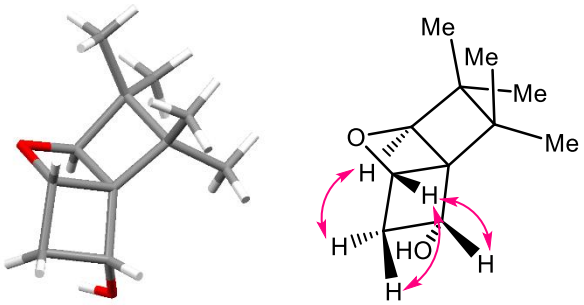

Figure 2. Structure of compound **5fb.** Left: the structure of the molecule in the single crystal, as determined by X-ray diffraction. Right: the diagnostic NOESY correlations observed in solution (20 mM in $CDCl_3$) for the *syn* relative configuration of the hydroxyl group with respect to the oxetane ring.

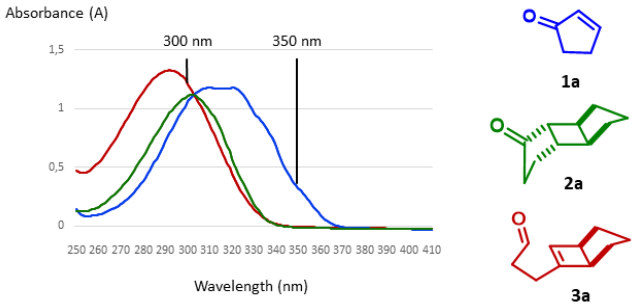

Figure 3. UV absorbance in the n→π* spectral region for compounds **1a** (blue), **2a** (green) and **3a** (red) (*c.* 40 mM solutions in acetonitrile).

NOESY NMR correlations observed for **5fb** in $CDCl_3$ solution were in complete agreement with the geometry indicated by the X-ray study, in particular the *syn* orientation of the hydroxyl group with regards to the fused oxetane (Figure 2). The same characteristic correlations were observed for each of the compounds **5** illustrated on Table 2, indicating that the intramolecular Paternò-Büchi step proceeds diastereoselectively, regardless of the identity of the substituent at the 4-position of the cyclopent-2-enone substrate. This is presumably the result of a preferred conformation of the cyclobutene aldehyde precursor which facilitates the intramolecular attack of the alkene by the excited state carbonyl oxygen atom in a diastereofacially selective fashion, although this hypothesis has not been investigated in detail.

Collectively, the above results provide an instructive demonstration of the controlled reorganization of atom connectivity starting from a simple "substrate package", whereby considerable molecular diversity is accessed from the same pair of substrates. Depending on the conditions employed, irradiation of a solution containing a cyclopent-2-enone and an alkene leads selectively to a bicyclic adduct, a cyclobutene aldehyde or a tricyclic angular oxetane, through a single, tandem, or triple photochemical process, respectively. The UV absorption spectra of **1a**, **2a** and **3a** reveal how the wavelength of the light is determinant for the reactivity profile: with a λ = 350 nm light source the [2+2]-cycloaddition can proceed but the bicyclo[3.2.0]heptan-2-one adduct does not react further, whereas with a λ = 300 nm light source the tandem or triple cascade reaction takes place efficiently (Figure 3). The importance of trapping the cyclobutene aldehyde in situ as an acetal is also underlined; without it, the triple reaction will ensue.

In conclusion, while some precedent had been observed for tandem photochemical transformations of cyclopent-2-enones and alkenes, this work outlines the first practical synthetic procedure applicable to a panel of derivatives: the key to success is to trap the products as stable acetals. Alternatively, a triple photochemical cascade process can be conducted, furnishing angular tricyclic oxetane cores in a highly stereoselective manner. These compounds seem likely to be of interest in drug discovery programs or for furthering molecular diversity.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: organic photochemistry • cascade reactions • oxetanes • cyclobutenes • cycloaddition

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[18] CCDC 1822925 contains the crystallographic data for compound **5fb**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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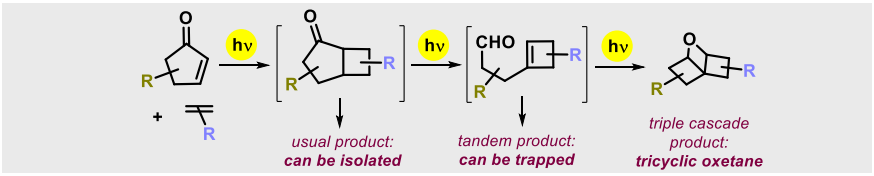

Juggling with atom connectivity. Single, tandem or triple cascade photochemical transformations of the atom set provided by a cyclopent-2-enone and an alkene can be carried out in a selective manner, providing high added-value products.

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