Photochemistry

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Complex Carbocyclic Skeletons from Aryl Ketones through a Three-Photon Cascade Reaction

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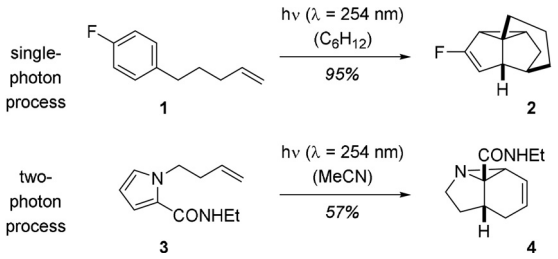
Abstract: *Starting from readily available 7-substituted 1-indanones, products with a tetracyclo[5.3.1.0^{1,7}0^{4,11}]undec-2-ene skeleton were obtained upon irradiation at $\lambda = 350$ nm (eight examples, 49–67 % yield). The assembly of the structurally complex carbon framework proceeds in a three-photon process comprising an ortho photocycloaddition, a disrotatory [4π] photocyclization, and a di-π-methane rearrangement. The flat aromatic core of the starting material is converted into a functionalized polycyclic hydrocarbon with exit vectors in three dimensions. Ring opening reactions at the central cyclopropane ring were explored, which enable the preparation of tricyclo[5.3.1.0^{4,11}]undec-2-enes and of tricyclo[6.2.1.0^{1,5}]-undecanes.*

There is an increasing demand in pharmaceutical research for molecules with spatially distinct functional groups (exit vectors) at defined locations.[1] While flat, often heterocyclic, skeletons have previously been dominant structural features of synthetic drugs,[2] it has been recognized in more recent years that chemical space needs to be explored in three dimensions in order to find molecules that match biological receptors.[3] This need can be nicely met by organic photochemistry, which provides a toolbox of reactions for the creation of molecular complexity in a few steps.[4] The most appealing transformations in this context enable the conversion of readily accessible molecules with a planar structure into complex alicyclic or heterocyclic scaffolds. The high energy content of the excited state paves the way for the construction of strained molecules, frequently through concomitant cleavage of strong bonds. Single-photon processes of this type include the celebrated *meta* photocycloaddition,[5,6] in which an arene core is converted into a polycyclic hydrocarbon (Scheme 1).

The transformation **1**→**2**[7] represents an intramolecular reaction of this type that proceeds with a high degree of regioselectivity. Cascade reactions in which an initial photochemical step is followed by a second photochemical transformation can be similarly efficient in creating molecular complexity. A notable two-photon process reported by Booker-Milburn and co-workers[8] enabled the formation of strained aziridines from pyrroles (e.g. **3**→**4**) in a sequence of [2+2] photocycloaddition and photochemical rearrangement.



Scheme 1. Examples of previously reported[7,8] photochemical transformations of arene substrates into complex polycyclic products.

In an ongoing project[9] on photochemical cascade reactions[10] initiated by an *ortho* photocycloaddition,[6,11] we have now found a facile entry into a yet unexplored class of hydrocarbons with a tetracyclo[5.3.1.0^{1,7}0^{4,11}]undec-2-ene core (**I**, Figure 1). Ring opening of the cyclopropane ring at positions **a** or **b** provides access to tricyclo[5.3.1.0^{4,11}]undec-2-enes (**II**) or tricyclo[6.2.1.0^{1,5}]undecanes (**III**), respectively. Both skeletons have high relevance to the synthesis of natural products.[12] It was found that the cascade reaction, which starts from simple aromatic ketones as precursors, is a three-photon process,[13] and we report herein our preliminary results on this topic.

Cyclic aryl ketones in which the carbonyl group is embedded in a five-membered ring (1-indanones) can be prepared from phenol and γ-chlorobutyryl chlorides in a two-step procedure.[14] Subsequent alkylation of the free phenolic hydroxy group with ω-alkenyl halides delivered potential starting materials **5** (Scheme 2) for an intramolecular *ortho* photocycloaddition (see the Supporting Information for more details). Although reactions of this type have been explored for acyclic aromatic ketones,[15] we are not aware of any studies with 1-indanones prior to our own work. Initial experiments were performed with ketone **5a** at an irradiation

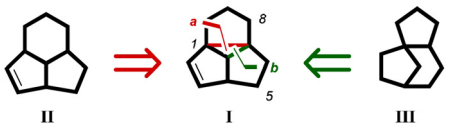


Figure 1. The tetracyclo[5.3.1.0^{1,7}0^{4,11}]undec-2-ene skeleton (**I**) as precursor for tricyclo[5.3.1.0^{4,11}]undec-2-enes (**II**) through cleavage of bond **a** and for tricyclo[6.2.1.0^{1,5}]undecanes (**III**) through cleavage of bond **b**.

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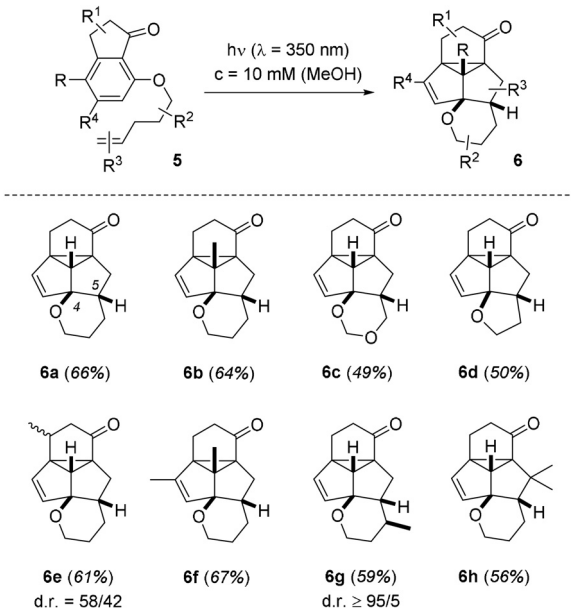
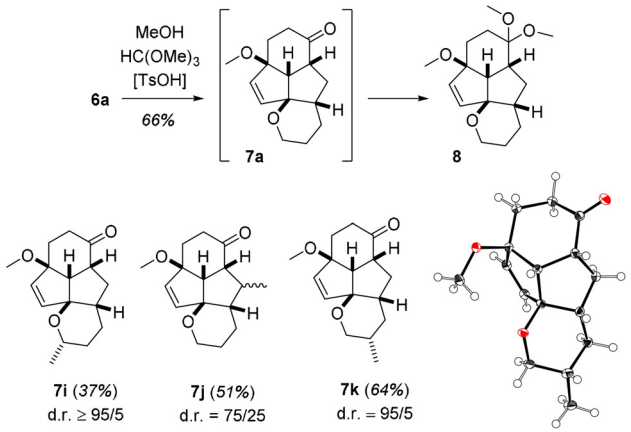


Scheme 2. Synthesis of pentacyclic ketones **6** from aryl ketones **5** through a photochemical reaction cascade.

wavelength of $\lambda = 350$ nm (fluorescent lamps) in methanol as the solvent. Unexpectedly, the product of the reaction (irradiation time 17 h) did not exhibit the structure of previously reported *ortho* photocycloaddition cascade products[9] but turned out to be the pentacyclic ketone **6a**. The initial structure assignment for compound **6a** was based on one- and two-dimensional NMR experiments and was later confirmed by X-ray crystallographic data (see below). In subsequent reactions, we probed the influence of methyl substituents at various positions (R-R^4) of the substrate. In all cases, we were able to isolate a defined product with a tetracyclo[5.3.1.$0^{1,7}0^{4,11}$]undec-2-ene core. A heterocyclic six-membered ring is attached to positions C4 and C5 by a four-atom bridge that originally linked the arene and the olefin in the substrate. This linker can contain two oxygen atoms (product **6c**) making it amenable to easy ring opening or it can contain a stereogenic center which, as seen for product **6g**, induces high facial diastereoselctivity. The facial diastereoselectivity achieved with a chiral ketone that exhibits a stereogenic center in β-position to the carbonyl group was less pronounced (product **6e**).

The central cyclopropane ring of products **6** lends itself to subsequent ring-opening reactions. Given the potential of the ketone to act as an enol leaving group in acidic medium,[16] ring opening of bond **a** (see Figure 1) at the allylic position by a nucleophile is facile. Compound **6a** readily produced the corresponding methyl ether **7a** upon treatment with catalytic quantities of *para*-toluenesulfonic acid (TsOH) but formation of ketal **8** was also observed. Addition of trimethylorthoformate enabled isolation of the latter product as a single isomer in 66% yield (Scheme 3). For other photoproducts, ring opening occurred already during irradiation, presumably due to the increased ring strain exerted by substituents R^2 and R^3.

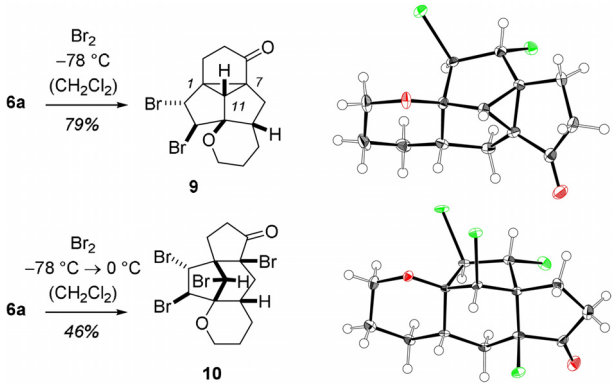
Product **7i** was isolated as a single diastereoisomer, which gives testimony to the high facial diastereoselectivity of the



Scheme 3. Cleavage of cyclopropane bond **a** (Figure 1) in intermediates **6** by MeOH: Direct formation of products **7** from aromatic ketones **5**.

cascade reaction. The same observation was made for product **7k** derived from substrate **5k**, which displayed a stereogenic center at the central carbon atom of the propyloxy linker. The constitution and relative configuration of product **7k** was established by single-crystal X-ray analysis. Product **7j** was obtained as a mixture of products from the respective *E*-configured hex-5-enyloxy substituted ketone **5j**. The relative configuration of the olefin is not retained in the product and the reaction is not stereospecific.

The more challenging ring opening of the tetracyclo[5.3.1.$0^{1,7}0^{4,11}$]undec-2-ene at bond **b** was accidentally discovered when we attempted to prove the constitution of parent product **6a** (Scheme 4). The compound was converted into the crystalline dibromide **9** by treatment with bromine in dichloromethane. Stereospecific *anti* addition to the double bond occurred at −78 °C leaving the carbon skeleton of the molecule untouched. Upon treatment with an excess of bromine at higher temperature (0 °C) the cyclopropane was opened selectively and tetrabromide **10** with an alicyclic tricyclo[6.2.1.$0^{1,5}$]undecane core was isolated. The ring opening occurs with retention at carbon atom C7 and with inversion at carbon atom C11 of the tetracyclo[5.3.1.$0^{1,7}0^{4,11}$]undecane core. The result is in line with

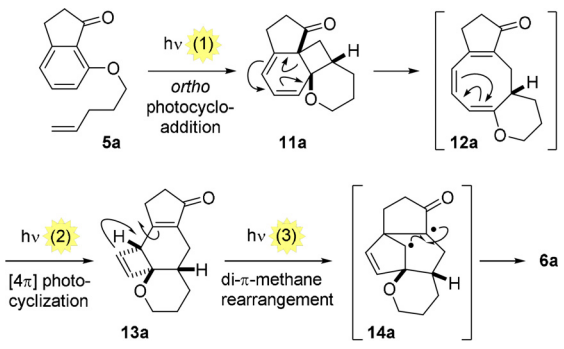


Scheme 4. Structural evidence for compound **6a**: bromination and cleavage of cyclopropane bond **b** (Figure 1) to product **10**.

initial formation of a tetracyclic bromonium intermediate followed by nucleophilic attack by a bromide ion.[17]

Although the central tricyclo[3.3.0.0^{2,8}]oct-3-ene skeleton of products **6** is reminiscent of reaction products obtained from a *meta* photocycloaddition (cf. product **2** in Scheme 1), neither the stereoelectronic properties of the substrates nor the exact constitution of the products fit to this transformation. Rather it seems likely that the 1-indanones undergo a three-photon process (Scheme 5) that initially follows a known reaction pathway.[9] For substrate **5a**, *ortho* photocycloaddition is suggested to lead to cyclobutane **11a**, which undergoes a thermally allowed pericyclic ring opening to cyclooctatriene **12a**. A second photon induces a disrotatory [4π] cyclization to cyclobutene **13a**. Unlike the ketone that bears an α,α-disubstitution[9b] and unlike the respective ester derivatives,[9a] this compound appears to undergo a successive di-π-methane rearrangement.[18,19] Rearrangements of this type are known to occur mostly on the triplet hypersurface and are conceived as a 1,2-migration followed by cyclopropane ring closure. Accordingly, 1,3-diradical **14a** is postulated as an intermediate which upon ISC and ring closure delivers product **6a**. The relative configuration of product **6a** (see Scheme 4) is in line with the suggested 1,2-shift, which is directed by the stereogenic center in the α-position to the ether oxygen atom and by conformational restrictions within the tetracyclic skeleton. Support for the intermediacy of cyclobutenes **13** stems from the fact that it was possible to isolate the respective compound **13b** from the reaction mixture of the reaction **5b**→**6b** in 27% yield if the irradiation was stopped after 2.5 hours. Continued irradiation of cyclobutene **13b** at $\lambda = 350$ nm in MeOH for another five hours gave product **6b** in 72% yield.

Given the high ISC rate of aromatic ketones[20] it is likely that the initial formation of cyclobutanes **11** occurs via the indanone triplet.[21] The addition step is indeed not stereospecific (product **7j**) but it is decisive for the configuration of the stereogenic center within the tetrahydropyran ring which is retained throughout the sequence (products **6g**, **7i**, **7k**). If a 6-heptenyloxy substituent was linked to the 7-position of the 1-indanone but not a 4-pentenyloxy group, product **15** was observed in which the alkenyl chain was dehydrogenated and the ketone group was reduced (Figure 2). The formation of this product can be explained by an intramolecular hydrogen abstraction at the α-position to the oxygen atom by the



Scheme 5. Suggested mechanism of the three-photon cascade illustrated for the reaction **5a**→**6a**.

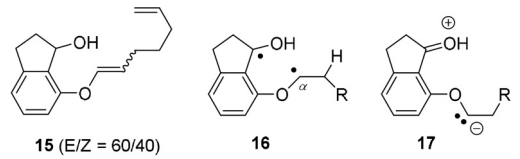


Figure 2. Intramolecular redox reaction of substrate **5l** to product **15** and proposed intermediates **16** and **17** formed by intramolecular hydrogen abstraction.

indanone nπ* triplet.[22] Subsequent hydrogen atom transfer within radical **16** (R = $CH_2CH_2CH_2CH{=}CH_2$) to product **15** is preferred over the Norrish–Yang cyclization.[23]

If the reaction **5a**→**6a** was performed in MeOD but not in MeOH, we observed deuterium incorporation in α-position to the oxygen atom in the product. After a shorter reaction time, (30 min) recovered starting material **5a** showed the same degree (ca. 20%) of deuteration. Irradiation of product **6a** in MeOD did not lead to any deuterium incorporation. Likewise, no deuterium incorporation was found to occur in CD_3OH. A potential explanation for the observations could be a deuteration of putative intermediate **17** (R = $CH_2CH{=}CH_2$) derived from intramolecular hydrogen abstraction.

In conclusion, we have discovered an unprecedented cascade reaction that converts a readily available starting material into a pentacyclic molecule with a complex carbon skeleton. The reaction holds promise for applications in the concise synthesis of natural products, and two consecutive reactions have already been found that illustrate its potential use.

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Conflict of interest

The authors declare no conflict of interest.

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