Synthesis and photoinitiated radical cyclization of allyl- and propynyloxymethyl substituted cyclopentanones to tetrahydrocyclopenta[c]furanols

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Abstract—Bicyclic cyclopentafuranols were formed by photoinitiated radical cyclization of allyl- and propinyloxymethyl substituted cyclopentanones with high regioselectivity. The irradiations were carried out at a wavelength of 300 nm in aprotic solvents such as benzene and acetonitrile. We could also show that reductive photoinduced electron transfer (PET) of the propynyloxymethyl substituted cyclopentanone 5 does not lead to any cyclization. The starting materials were synthesized in good yields following known procedures.
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Bicyclic cyclopentanols and cyclopentafuranols are important structural units in a wide range of unusual and biologically interesting natural products such as cyclopentanoid monoterpenes (diquinane) and sesquiterpenes.[1] Furthermore, the cyclopentafuranols can be used as key intermediates for the synthesis of promising building blocks for artificial oligonucleotides and other complex molecules (e.g., hybrids with different pharmacophoric units).[2]

Intramolecular radical reactions have been proven to be synthetically useful for the construction of five-membered fused carbocyclic and heterocyclic structures.[3] In agreement with Baldwin's rules[4] and the literature data,[5] formation of the cyclopentane ring via 5-exo cyclization mode is highly favored. Accordingly, substituted bicyclooctanols and α-hydroxy bicyclooctanones have been synthesized using various methods such as electrochemistry[6] or chemical reduction, for example, naphthalene sodium[7] and samarium(II)iodide[8] (SmI$_2$). An alternative procedure which combines fragmentation with intramolecular 1,5-hydrogen atom abstraction is initiated by tributyltin hydride and led to the formation of bicyclic tertiary cycloalkanols.[9] Similarly, the same

compounds can be prepared from δ,ε-unsaturated ketones in good yields, initiated by photoinduced electron transfer (PET) from triethylamine (TEA) in acetonitrile or by photoionization in pure hexamethylphosphoric triamide (HMPA).[10] This methodology has also been successfully applied for the synthesis of natural products[11] and biologically active N-heterocyclics such as (±)-isooxyskyanthine.[12] The aim of this paper is to report simple photochemical cyclization reaction of α-allyl- and α-propynyloxymethyl substituted cyclopentanones leading to bicyclic tertiary cyclopentafuranols.[13]

The general concept is illustrated in Scheme 1 showing that a δ-hydrogen atom abstraction by an electronically excited carbonyl function is the key step. Here this hydrogen abstraction from a δ-position rather than from the generally more favored γ-position (cf. Norrish-Type II reaction) is the exclusive process due to the special features of the reactants: the γ-position is
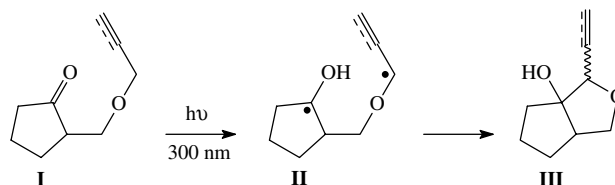
Scheme 1. Possible pathway for the synthesis of bicyclic cyclopentafuranols.
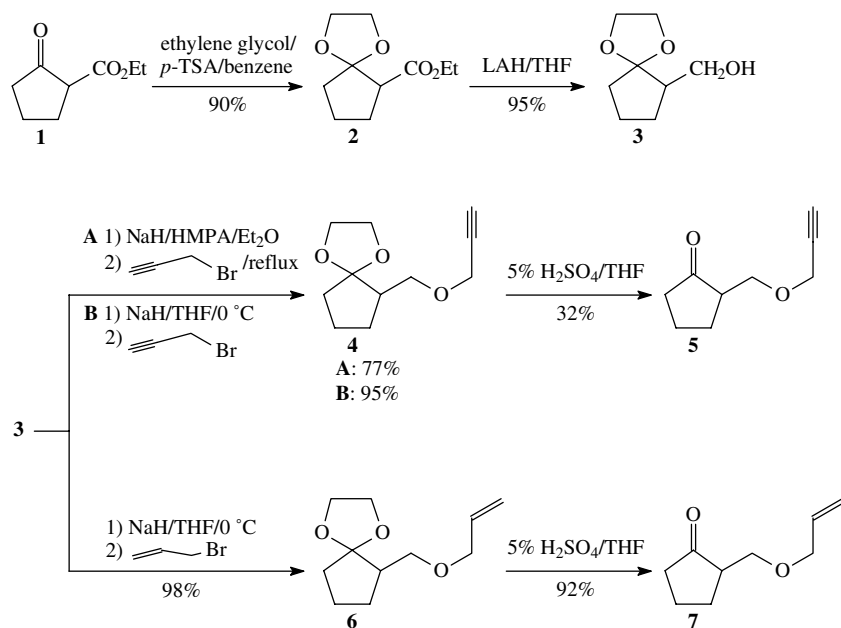
**Scheme 2.** Synthesis of α-monosubstituted cyclopentanones **5** and **7**.

blocked by O-substitution and the δ-position is highly reactive because of its allylic character. Other groups have also made use of these special features.[14]

Accordingly, by irradiation at an appropriate wavelength the alkyloxymethyl substituted cyclopentanone **I** gives the 1,5-biradical **II**, which cyclizes to the tertiary bicyclic cyclopentafuranol **III** (Scheme 1).

The propynyl- and allyloxymethyl substituted cyclopentanones **5** and **7** were synthesized starting from the ethyl 2-oxocyclopentanecarboxylate[15] **1** in a four-step reaction. The details for the synthesis of the starting materials are shown in Scheme 2.

During ketalization,[16] **2** was formed in high yield and further used without additional purification. The subsequent reduction of the ester group of **2** with LAH furnished **3**. Synthesis of **4** and **6** was carried out by alkylation of **3** with propargyl and allyl bromides, generally by using sodium hydride in dry THF (see method B in Scheme 2).[17a] To transform **3** into **4**, we also used sodium hydride in pure HMPA as an alternative method (see method A in Scheme 2).[17b] However, this procedure gives lower yield of **4** compared to the method B. Cleavage of the ketal group of **4** and **6** afforded the corresponding propynyl- and allyloxymethyl cyclopentanones **5** and **7** in good yields.

Irradiations of **5** and **7** were carried out at a wavelength of 300 nm in dry benzene as well as in a polar solvent such as acetonitrile (Scheme 3).[18] In all cases, we observed the same regioselectivity for the formation of the bicyclic cyclopentafuranols. At the same time the unsaturated ethynyl and vinyl function remain unchanged. The photoinduced reaction of **5** led to the formation of the diastereomeric bicyclic products **8a/ 8b** in 3:1 ratio and the one noncyclized minor product **9**. Starting from allyloxymethyl cyclopentanone **7**, mix-
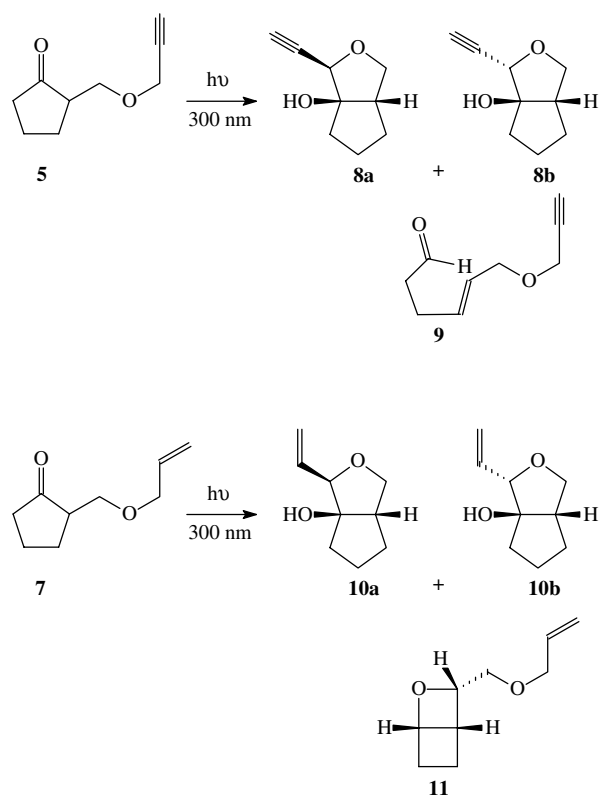
Scheme 3. Photoinduced reactions of **5** and **7**.

ture of the isomers **10a/10b** in 1:3 ratio and the oxetane **11** were obtained. Although the yields are not very high (Table 1). Analysis of the reaction mixtures could not reveal any reduction products such as alkyloxymethyl cyclopentanols. Interestingly, both cyclization reactions show diverse stereoselectivity. Whereas the alkynyl derivative **5** preferentially leads to the all-cis configured tetrahydrocyclopenta[*c*]furanol **8a**, **7** forms **10b** with the vinylsubstituent in the trans position as the major

**Table 1.** Product yields of photoinduced reactions of **5** and **7** depending on reaction conditions

Entry	Conditions	hυ (nm)	Time (h)	Conversion (%)	Product	Yield (%)
5	PhH (0.12 M)	300	20	100	**8a**	13
					8b	5
					9	3[a]
5	MeCN (0.12 M)	300	24	100	**8a**	14
					8b	4
					9	5
5	MeCN/5 equiv Et$_3$N/1 equiv LiClO$_4$	300	24	—	—	—
7	PhH (0.12 M)	300	53	100	**10a**	3[a]
					10b	16
					11	8[a]
7	MeCN (0.12 M)	300	28	89	**10a**	4[a]
					10b	12
					11	5

[a] The product yields were detected by GC from the combined isolated product fractions after purification by column chromatography.

product (substituent effect). To check the potential of an alternative PET-cyclization, we irradiated **5** at 300 nm in acetonitrile in presence of five equivalents of TEA and one equivalent of lithium perchlorate (LiClO$_4$). However, conversion of the starting material under these conditions was not detected. After purification **5** was recovered almost completely. Reduction of the carbonyl group or other side reactions, such as cleavage of the ether side chain and/or photodimerization,[19] was not detected. The results of the photoinduced reactions of **5** and **7** as well as the reaction conditions are shown in Scheme 3 and Table 1.

The products **8–11** were purified by column chromatography on silica gel and the resulting isomeric mixtures **8a/8b** and **10a/10b** were separated additionally by
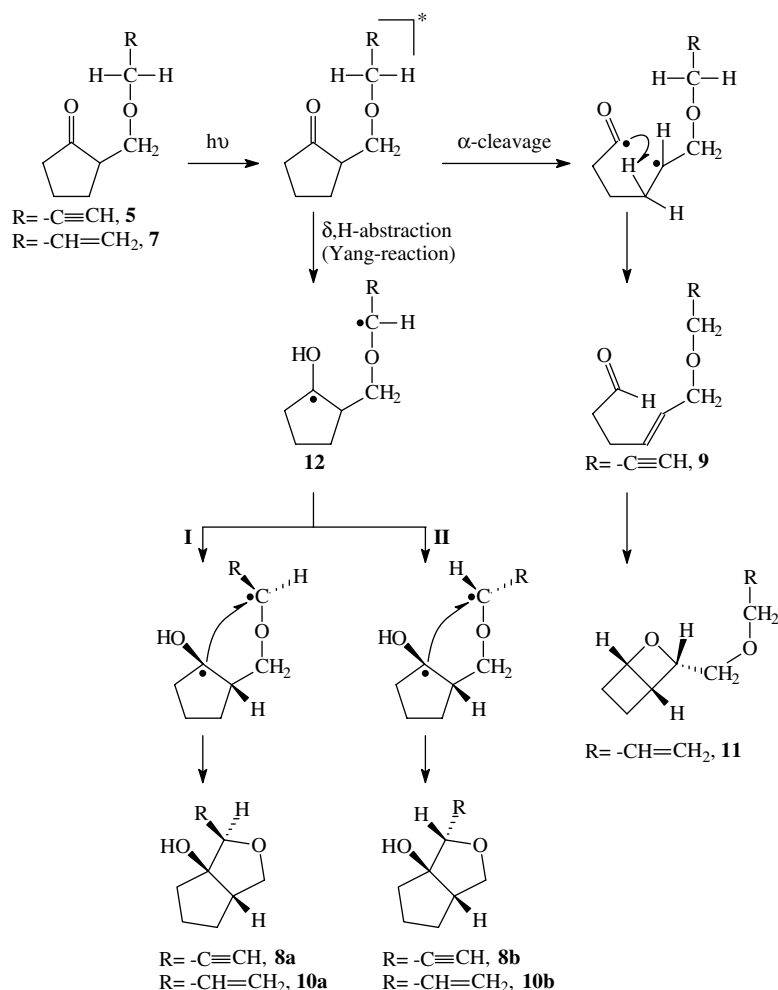
Scheme 4. Mechanism of the product formation for the photoreactions of **5** and **7**.

HPLC. The structural analysis was carried out by one- and two-dimensional NMR (COSY and HMQC: **8a/8b**, **10b**, and **11**) as well as mass spectroscopy, including HRMS. The stereochemistry of **8a/8b**, **10a/10b**, and **11** was assigned by qualitative NOESY in combination with ^{1}H NMR coupling constants. Additionally, the stereochemistry of **11** was detected by supported calculations using MMFF94 force field conformational analysis.[20]

Mechanistic details of the photoreaction of **5** and **7** are shown in Scheme 4.

The initial step is a n,π*-excitation of the carbonyl group followed either by an intramolecular δ-hydrogen atom abstraction to provide a 1,5-biradical **12** or by α-cleavage to form the acyclic product **9** and the oxetane **11**, which is probably formed via an intramolecular Paternó–Büchi reaction.[14,21] The intermediate **12** leads to the formation of the corresponding bicyclic cyclopentafuranols with the respective cis (pathway I: cyclization to **8a** and **10a**) and trans conformation (pathway II: cyclization to **8b** and **10b**). This 5-*exo* cyclization has to be considered as Yang type reaction,[14] also favorable according to Baldwin's rules.[4]

In summary, we have shown that the photoinitiated cyclization via 1,5-biradicals of propynyl- and allyl-oxymethyl substituted cyclopentanones **5** and **7** can be successfully used for the synthesis of ethynyl and vinyl substituted tertiary cyclopentafuranols.

Supplementary material

All synthetic procedures and analytical data of compounds **2**, **3**, **5**, and **7**–**11** are available from the authors on request.

Acknowledgements

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18. Photochemical reactions were performed in a Rayonet RPR-100 photochemical chamber reactor (Southern New England Ultraviolet Company, Brandford) fitted with 16 lamps RPR-3000 Å (emission maximum at 300 nm half band width, each lamp 21 W) and merry-go-round inset using duran tubes (12 mL vol, 1 cm diameter). Deoxygenated with argon solutions (0.12 M) of the respective propynyl- and allyloxymethyl cyclopentanones, **5** and **7**, were dissolved in dry benzene or acetonitrile and irradiated. The conversion of the starting material was monitored by GC and/or GC–MS.

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