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Reductive PET-fragmentation–cyclization processes of bicyclo[*n*.3.0]alkanones: synthesis of angular quasi-triquinane and propellane systems

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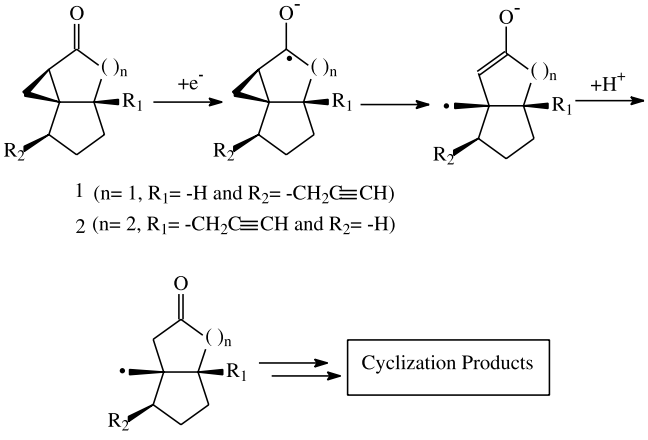
Abstract—Bicyclo[3.3.0]octanone and bicyclo[4.3.0]nonanone derivatives with a cyclopropane unit in the α-position and an unsaturated side chain in the γ-position of the carbonyl group undergo fragmentation–cyclization processes leading to quasi-triquinane systems upon reductive photoinduced electron transfer (PET). For example, the new angular triquinane derivative **6** and the new propellane derivative **12** were synthesized in one step from these starting materials in moderate to good yields.

Triquinanes and propellanes with specifically condensed or bridged five-membered carbocyclic rings represent a class of natural products and belong to the polyquinane family.[1] They are still the object of ongoing research including the development of various synthetic methods for the construction of natural and artificial polyquinane systems.[2]

Among these methods photochemical ring closure reactions such as intramolecular [2+2]-photocycloaddition[3] and reductive photoinduced electron transfer (PET)[4,5] were used. For example, the natural sesquiterpenes isocomene[6] and periplanone[7] were synthesized via an intramolecular [2+2]-photocycloaddition as key step. We and others made use of the cleavage of α-cyclopropyl ketones by reductive PET leading to γ-keto radicals which may undergo further cyclizations if suitable unsaturated side chains are present[4,5] (Scheme 1).

There are several requirements to be followed when using this methodology for the construction of polyquinane systems: (i) both the cyclopropyl group and the unsaturated substituent units be *cis* to each other and (ii) the length of the side chain has to be adjusted to the ring size of the desired product. In this communication we present our results concerning the synthesis of quasi-triquinane systems of both angular and propellane type.

Following our strategy we started from bicyclo-[3.3.0]octenones (Scheme 2: **5a**) and bicyclo-[4.3.0]nonenones (Scheme 5: **9**) with alkynyl side chains generally in the γ-position of the carbonyl group. These bicycloenones were synthesized following well-known procedures.[3–5,8,9] The details of the first example are shown in Scheme 2.



Scheme 1. Formation of γ-ketoradicals by photoinduced electron transfer (PET) and ring closure reactions to triquinane systems.

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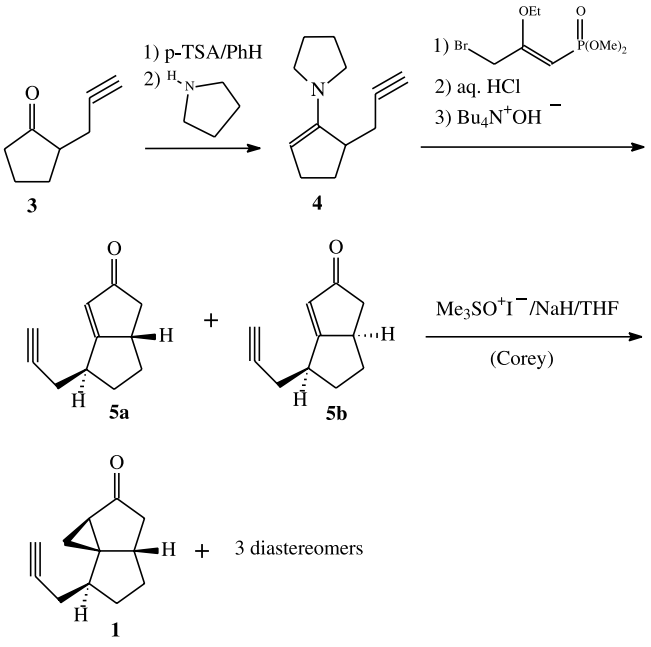
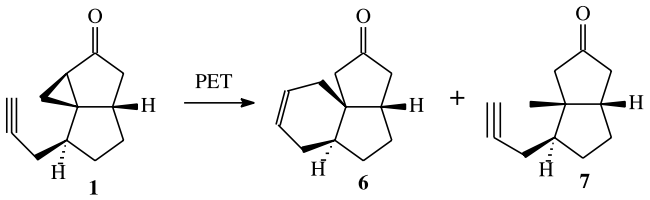
For the synthesis of the bicycloenones **5a**/**5b** and **9** we used α-propynylcyclopentanone **3** as starting material generated in 75% isolated yield by alkylation of cyclopentanone with propargyl bromide (~80% in toluene) via the enamine method.[10,11] **3** was transformed into its enamine **4** (75% isolated yield) followed by alkylation and subsequent intramolecular cyclization of the Horner–Wadsworth–Emmons type.[12] The diastereomeric bicyclooctenones **5a** and **5b** were obtained in a 94:6 ratio in 16% overall yield starting from **3** (Scheme 2).

This mixture was transformed into the corresponding cyclopropanes following Corey's method[8] from which the *cis*-isomer **1** was isolated by preparative HPLC in 40% yield.[13] Reductive PET cyclization of **1** in acetonitrile with triethylamine (TEA) or TEA/lithium perchlorate[4,5] as electron donor led to the formation of two products: the *endo*-cyclization-[4.2.2.0]-product **6** and the non-cyclized product **7** (Scheme 3).

Irradiation of **1** was carried out under various conditions (Table 1). For example, addition of lithium perchlorate reduces the reaction time by a factor 4 and, furthermore, irradiation at 254 nm in quartz tubes



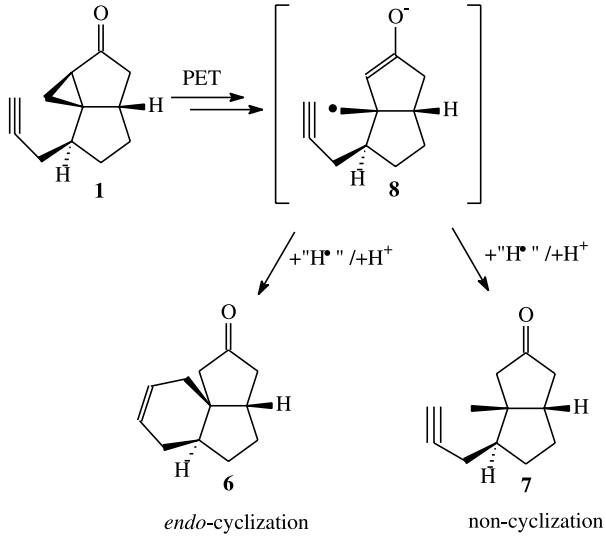
Scheme 2. Synthesis of propynylsubstituted α-cyclopropylbicyclo[3.3.0]octenone **1**.



Scheme 3. Reductive PET reactions of **1**.

increases the yield of the cylization product **6** up to 40%. We assume that under these conditions TEA is the light-absorbing species whereas at longer wavelengths the ketone **1** is electronically excited facilitating undesired side reactions. The accelerating effect of lithium perchlorate is probably due to the special salt effect.[4,5]

The mechanism of this reaction is shown in Scheme 4. The primarily formed ketyl radical anion of **1** spontaneously opens to the new distonic radical anion **8** which probably after protonation and tautomerization to the corresponding γ-keto radical cyclizes in a 6-*endo* fashion to **6**. Obviously this cyclization effectively competes with the simple H-saturation process leading to the non-cyclized product **7**. Whether the H-saturation proceeds in only one step or alternatively by single electron transfer followed by protonation is not yet known (Scheme 4).



Scheme 4. Mechanism of the reductive PET-fragmentation/cyclization process of **1**.

Table 1. Product yields of reductive PET reactions of **1** depending on reaction conditions

Entry	Conditions	Time (h)	*hv* (nm)	Product	Yield (%)
1	MeCN/5 equiv. Et_3N	21	300	**6**	29
				7	3
1	MeCN/5 equiv. Et_3N	5	300	**6**	29
	1 equiv. $LiClO_4$			**7**	3
1	MeCN/5 equiv. Et_3N	3	254	**6**	40
	1 equiv. $LiClO_4$			**7**	3

To search for possibilities of the formation of bridged quasi-triquinane systems containing a propellane structure by our strategy we chose the bicyclo[4.3.0]non-1-en-3-one derivative **9** with a propargyl substituent at the bridged carbon center 7 (Scheme 5). **9** Was synthesized from **3** in 35% overall yield following the Robinson annelation procedure.[14,15] Since Corey cyclopropanization method[8] failed[16] in this case we had to develop an alternative strategy involving additional steps, however, with higher selectivity.

First **9** was reduced using sodium boranate[17] to the mixture of diastereomeric alcohols **10a** and **10b** in a 93:7 ratio, which were separated by preparative HPLC in 33 and 2% yield, respectively.

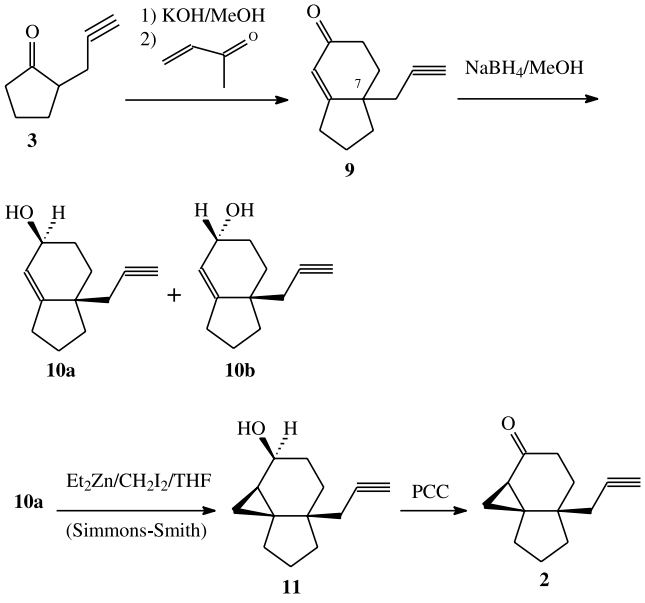
The major *cis*-isomer **10a** was cyclopropanized by the Simmons–Smith-method[9] quantitatively leading to the all-*cis*-stereomer **11**. Finally the ketone **2** was obtained as crystalline product in 30% isolated yield by oxidation with pyridinium perchlorochromate (PCC)[17c,18] (Scheme 5).

The proposed structure of **2** was proven by X-ray analysis.[19]

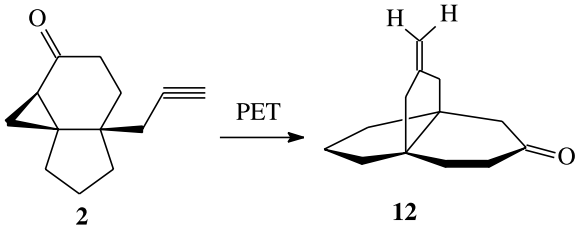
Reductive PET cyclization in acetonitrile and TEA/lithium perchlorate as electron donor led to only one product in yields up to 74% after purification by column chromatography. This product was assigned the propellane structure **12** by standards analytical methods (Scheme 6 and Table 2).

We assume an analogous mechanism of formation of **12** from **2** as shown for **1** (cf. Scheme 4).

If not otherwise stated, all products were isolated and purified by column chromatography using silica gel and



Scheme 5. Synthesis of the α-cyclopropyl-bicyclo[4.3.0]-octenone derivative **2**.



Scheme 6. Reductive PET cyclization of **2** to the propellane **12**.

Table 2. Yields of reductive PET cyclization of **2** to **12**

Entry	Conditions	Time (h)	*hv* (nm)	Yield (%)
2	MeCN/ 5 equiv. Et_3N 1 equiv. $LiClO_4$	2	254	74
2	MeCN/ 5 equiv. Et_3N 1 equiv. $LiClO_4$	15	300	46

cyclohexane/ethyl acetate mixtures as eluent. The structures were analyzed mainly by NMR spectroscopy (^1H, ^{13}C, DEPT), mass spectrometry including HRMS and IR spectroscopy. Especially compounds **1**, **2**, **4**–**7** and **9**–**11** were analyzed using 2D NMR techniques (HSQC, HMBC, COSY, and NOESY in combination with $^1H/^1H$ coupling constants for **1**, **5a**, **5b**, **10a**, **10b**, and **11**).

In summary, we have shown that α-cyclopropyl ketones of the bicyclo[3.3.0]octenone and bicyclo[4.3.0]-nonanone type can be successfully used for PET initiated fragmentation–cyclization processes leading to new quasi-triquinane systems. Studies aiming at further applications are in progress.

Supplementary material

All synthetic procedures and analytical data of compounds **1**–**7** and **9**–**12** are available from the authors on request.

Acknowledgements

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13. Corey cyclopropanation of the mixture of compounds **5a**/**5b** led to the formation of four diastereomeric products in a 80:10:6:4 ratio. This resulting mixture was purified by column chromatography in 75% combined isolated yield. The major *cis*-diastereomeric product **1** was separated from the mixtures by HPLC and correctly analyzed by NMR spectroscopy (1D, 2D and NOESY). The other three diastereomers are inseparable mixtures and analyzed only by GC/MS (EI, CI) and GC methods.
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16. Corey cyclopropanation of compound **9** led predominantly to the formation of two diastereomeric products in a 90:10 ratio, which were separated by preparative HPLC. The structure determination of the resulting *cis*- and *trans*-oxirane was accomplished by NMR (1D, 2D), IR spectroscopic and HRMS spectrometric techniques. We assume that in this case the configuration of the six-membered ring of the compound **9** causes a selective attack of the ylide reagent on the carbonyl group.
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19. Crystallographic data (excluding structure factors) for this cyclopropanation product **2** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 208441.