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Cyclization of terpenoid polyalkenes via photo-induced electron transfer—versatile single-step syntheses of mono- and polycycles

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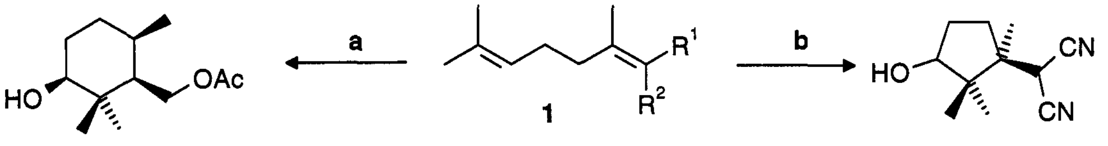
Abstract: Light-induced radical cationic cyclizations of suitably functionalized polyalkenes, readily available from geraniol, all-*trans*-farnesol and all-*trans*-geranylgeraniol, establish a powerful access to mono- and polycyclic compounds. Within these highly stereo- and chemoselective transformations, the cyclization mode, optionally yielding five- and six-membered rings, is efficiently controlled by the substitution pattern of the polyalkenes (acetate *vs.* α,β-unsaturated ester and dicyano groups). In all examples, protic solvents add highly stereoselectively to the ω-alkene site of the isoprenoid starting materials in *anti-Markovnikov* sense suggesting that radical cation intermediates are intercepted. Notably, these transformations achieved upon light-induced electron transfer mimic *in vivo* processes of non-oxidative cationic terpene cyclizations.

A major objective of our work has been the exploration of light-induced radical cationic cyclizations of isoprenoid polyalkenes, thus mimicking biosynthetic non-oxidative terpene cyclizations which are traditionally assumed to be purely caused by (enzyme-mediated) protonation and hydroxylation of the isoprenoids (1). In our earlier studies (2) we have shown that the acetates of geraniol **1a**, all-*trans*-farnesol **4a** and all-*trans*- geranylgeraniol **9a** undergo 6-*endo*-trig cyclizations to yield exclusively six-membered and *trans*-fused products **2**, **5**, **6** and **10a** upon photo-induced electron transfer (PET) (3) using 1,4-dicyanobenzene together with phenanthrene as the electron acceptor couple. These reactions proceeded in microheterogeneous media only, suggesting that the anionic surfactant (sodium dodecyl sulfate) either ensured folding of the polyalkene prior to cyclization and/or suppressed back electron transfer by enhanced separation of the radical ions.



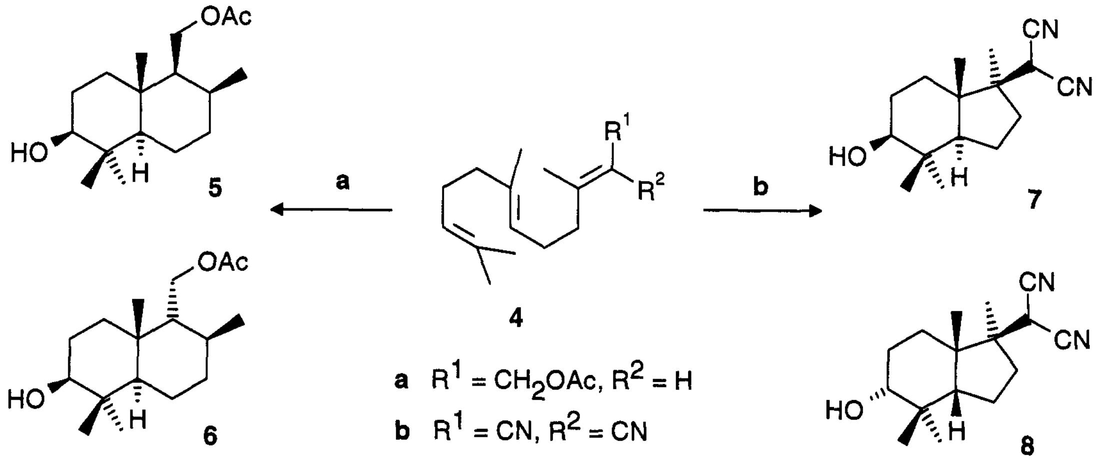
2
major isomer

1

a $R^1 = CH_2OAc$, $R^2 = H$
b $R^1 = CN$, $R^2 = CN$

3

However, our recent findings (4) revealed, that such transformations can efficiently be achieved also in homogeneous media. Catalytic amounts (0.1-0.2 mol-equivalents) of 1,4-dicyano-2,3,5,6-tetramethyl benzene (TMDCB) (5) in combination with biphenyl are sufficient to achieve cyclizations in acetonitrile/water or acetonitrile/methanol (4:1) in yields of at least 15-30% yields, avoiding the earlier laborious work-up procedures. 6-*endo*-trig cyclizations, leading to the *trans*-fused products **5** and **6** from **4a**, are again accompanied by highly stereoselective addition of the protic solvent to the ω-alkene site in *anti-Markovnikov* sense suggesting that radical cations (6) are intercepted (7).



5 **6** **4** **7** **8**

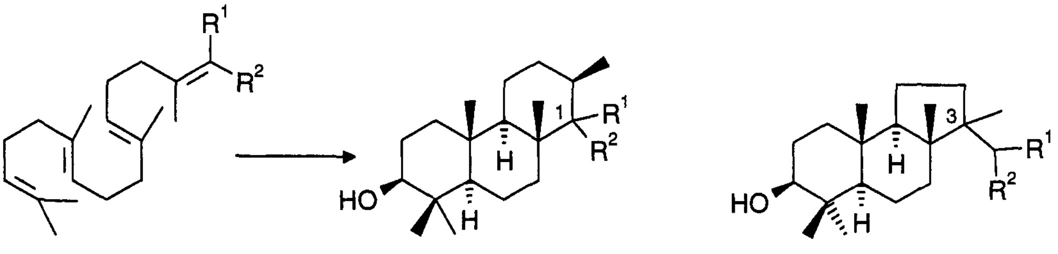
a $R^1 = CH_2OAc$, $R^2 = H$

b $R^1 = CN$, $R^2 = CN$

5 : **6** = 2.2 : 1

7 : **8** = 1 :1

In order to evaluate the synthetic scope of such transformations, experiments were extended to polyalkene starting materials which contain α,β-unsaturated nitrile and ester groups. Irradiation of the α,β-unsaturated 1,1-dicarbonitriles **1b**, **4b** and **9c** revealed an intriguing change of the mode of cyclization. While the polyalkene acetates led exclusively to six-membered cyclization products (**2**, **5**, **6** and **10a**), **1b**, **4b** and **9c** afforded characteristically products containing a five-membered ring, such as **3** (55% yield) **7**, **8** (25-30% yield) and **11c** (25% yield).

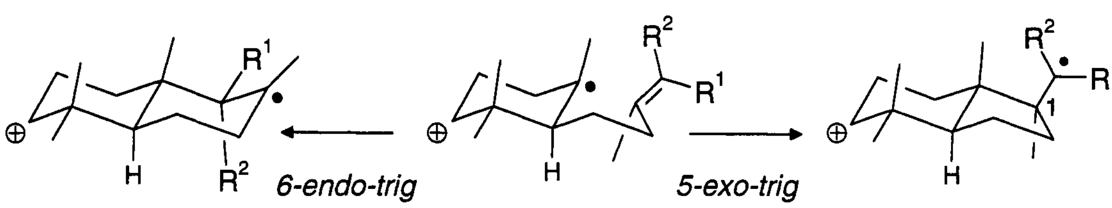


	9	**10**		**11**
a	$R^1 = H$, $R^2 = CH_2OAc$	$100^{\#}$	:	0
b	$R^1 = H$, $R^2 = CO_2Et$	$65^{\S}$	:	35 (3β-methyl)
c	$R^1 = CN$, $R^2 = CN$	0	:	100 (3α-methyl)

[#](epimers at C-1, α:β = 1:3.8)

[§](epimers at C-1, α:β = 1:3)

This synthetically most intriguing general variant of the cyclization mode, *viz* .6-*endo*-trig *vs*. 5-*exo*-trig as exemplified for **4** → **5** and **7** *via* **13** and **14** respectively, is depicted in figure 1. The second ring forming step can be rationalized in terms of altered radical stabilization. The intramolecular addition of the tertiary radical to the allylic acetate moiety (**12** → **13**) strongly resembles the cyclization of the 2,6-dimethylhept-6-en-2-yl radical (8), both leading exclusively to six-membered cyclic products.



13 $R^1 = CH_2OAc$, $R^2 = H$ **12** $R^1 = CN$, $R^2 = CN$ **14**

Figure 1: 6-*endo*- vs. 5-*exo*-trig radical cyclizations steered by the R^1/R^2 substitutent pattern

In case of the α,β-unsaturated dinitriles exclusive formation of one five-membered cycle (**12** → **14**) was found. The malonodinitrile radical intermediate **14** should be stabilized by about 8.5 kcal·mol^{-1} (9) as compared to the alternative trialkyl-substituted radical exemplified for **13**. Notably, the stereochemical outcome of these transformations with regard to the malonodinitrile group (R^1=R^2=CN) is consistently β-selective , i.e. *syn* to the respective vicinal angular methyl group (→ **7**, **8** and **11c**), suggesting least steric interaction between these substituents as compared to the alternative methyl-methyl interaction in the transition state, which would lead to the epimer at C-1 of **14**.

For the α,β-unsaturated ester **9b,** however, less selectivity is encountered and a mixture of all-6-*endo*-trig (**10b**) and 6-*endo*-6-*endo*-5-*exo*-trig (**11b**) products is the result. This can be readily understood by the radical stabilization argument, which should favour an ester group by about 3.5 kcal·mol^{-1} (9) as compared to a methyl substituent. Hence, the stereoselectivity of the terminal ring closure is expected to be less pronounced than with the acetate and malonodinitrile substrates.

Both, the preparative utilization of light-induced cascade cyclizations for organic synthesis as well as the mechanistic aspects are part of our investigations. In this connection, the fate of the tertiary radicals, as exemplified in figure 1 by **13** and **14** was examined. Potentially, three pathways are conceivable: a) disproportionation to afford olefinic products, b) hydrogen atom abstraction, possibly from allylic positions of unreacted starting material, or c) reduction by the acceptor radical anion prior to protonation. Irradiation of **1b** in CH_3CN/D_2O and CH_3CN/CH_3OD cleanly yielded deuteriated products, indicating that the terminal dicyano-substituted radical is reduced to the corresponding highly stabilized malonodinitrile anion followed by protonation or deuteriation. For the acetates as well as for the α,β-unsaturated esters, the termination step in homogeneous media is under further investigation.

Conclusion: With a sterically hindered electron acceptor such as 1,4-dicyano-2,3,5,6-tetramethyl benzene, in combination with biphenyl, light-induced polyalkene cascade cyclizations can be performed in homogeneous media. The cyclization is likely initated by single electron transfer from the ω-site of the polyalkene to the photoexcited acceptor couple (**A** in figure 2). During or prior to the cyclization which includes - depending on the substrate chain-length - several intramolecular annelations, a protic solvent (H_2O or MeOH) is added (**B**) in *anti-Markovnikov* sense. In case of the malonodinitriles, the cascade is terminated by reduction (**C**) and protonation/deuteriation (**D**).

These results represent a powerful and versatile tool for stereoselective single-step syntheses of mono- and polycyclic compounds from readily available starting materials. Further applications to organic synthesis as well as detailed mechanistic studies including time-resolved spectroscopy are currently under investigation.

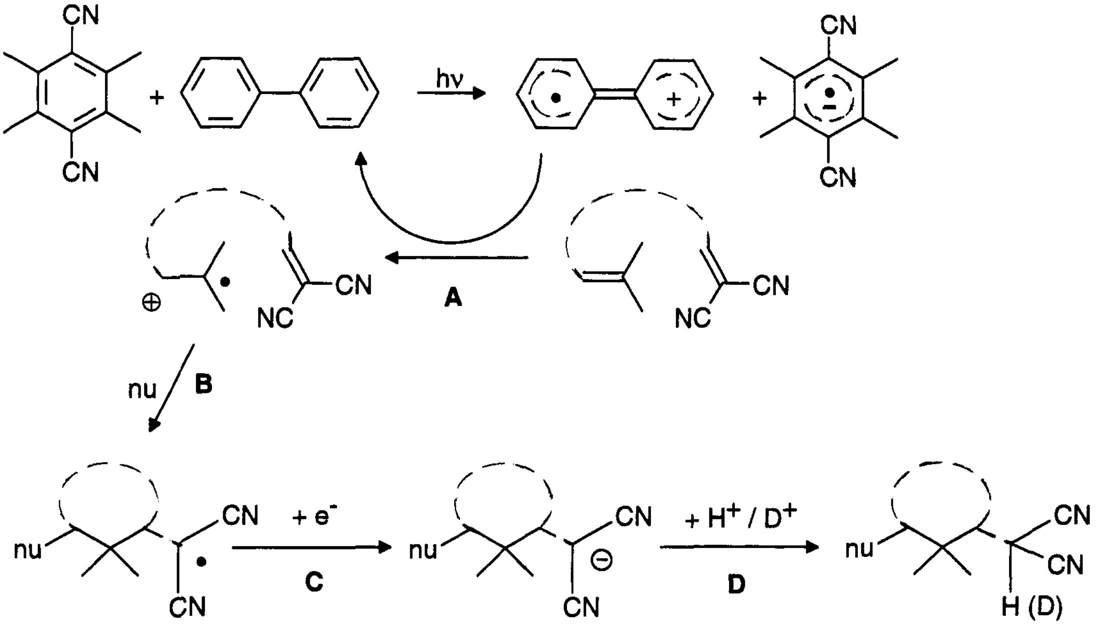


Figure 2: Schematic representation of the PET-triggered cyclization of α,β-unsaturated 1,1-dicarbonitrile polyalkenes

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