

Biomimetic radical polycyclizations of isoprenoid polyalkenes initiated by photoinduced electron transfer

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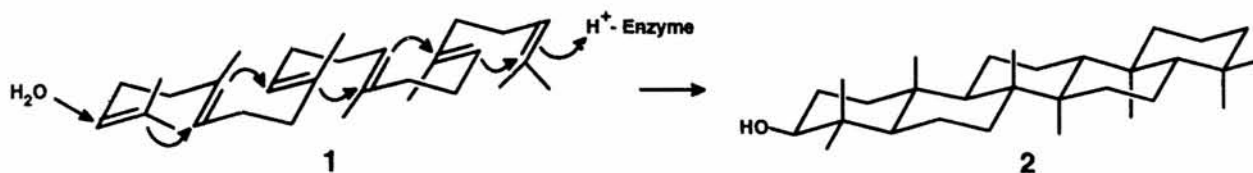
Isoprenoid polyalkene radicals, formed by anti-Markovnikov addition of a nucleophile to their parent radical cations, which are readily accessible via photoinduced electron transfer, undergo cascade cyclizations. The regioselectivity is efficiently controlled by the substitution pattern, i.e., the generally observed 6-*endo*-trig mode is replaced by 5-*exo*-trig, if electron-deficient double bonds (e.g. 1,1-dicyanovinyl groups) are involved. Moreover, remarkably high asymmetric inductions have been achieved by the use of chiral spirocyclic dioxinones, derived from the chiral auxiliary (-)-menthone, notably remotely located from the initiation site of the cyclizations. These asymmetric photoinduced cyclizations constitute strong evidence of spontaneous coiling/folding of the terpenoid polyalkene chain and give ready access to the enantiomerically pure tricyclic terpenoids of complementary chiralities by means of the single chiral auxiliary (-)-menthone.

Many eucaryotes produce steroids and triterpenoids via cationic cyclizations of (3*S*)-2,3-oxidosqualene¹. In some bacteria and protozoans, squalene **1** is cyclized to pentacyclic 3-deoxytriterpenes, such as tetrahymanol **2** in a non-oxidative cyclization process^{1,2} (Scheme I). Thus, stimulated by the original concepts³, numerous biomimetic approaches utilizing cationic⁴ cyclization strategies have been published. Alternative radical-type pathways, also considered as possibly relevant biological cyclization modes⁵, were likewise mimicked⁶.

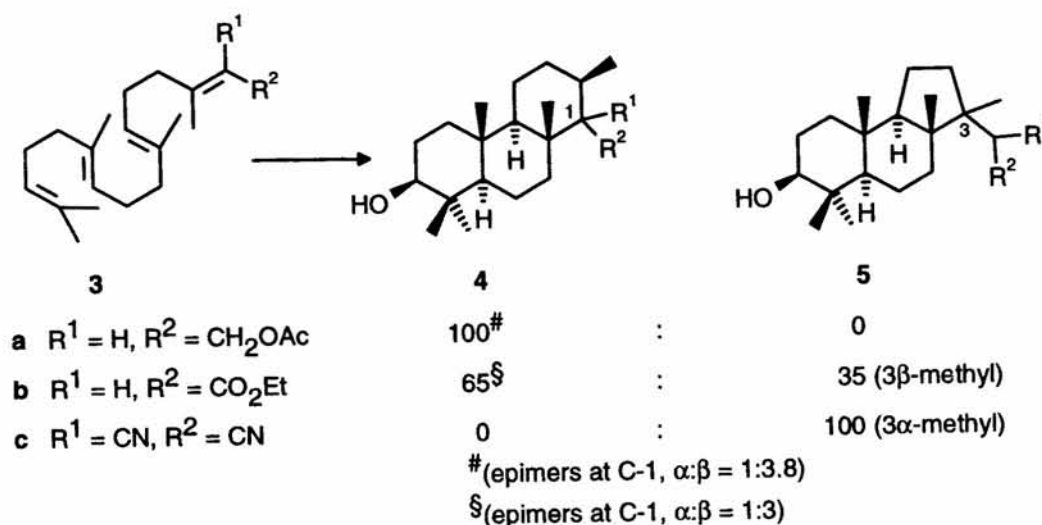
Our biomimetic approach utilizes the photoinduced electron transfer to initiate the cyclization of readily available polyalkenes, such as the isoprenoid acetate **3a**, the α,β -unsaturated ester **3b** and the 1,1-dicarbonitrile **3c** (Scheme II; for transformations of analogues, see refs. 7 and 8). In the course of these

reactions, carried out in acetonitrile-water, electron transfer to an excited electron acceptor (e.g. 1,4-dicyanotetramethylbenzene) regioselectively brings about oxidation of the polyalkene at the ω -site. The radical cations thus obtained are most likely trapped by *anti*-Markovnikov addition of water prior to cyclization⁹ (lifetime of the intermediates ≈ 10 -100 ps¹⁰ under the preparative reaction conditions). The cyclization event has therefore to be regarded as a radical, rather than a radical cationic mechanism. Within these cascade cyclizations, intramolecular addition of a tertiary radical centre to an alkene proceeds exclusively in 6-*endo*-trig fashion (cf. also ref. 11). Consequently, the acetate **3a** leads to six-membered and *trans*-fused cyclization products **4a** only.

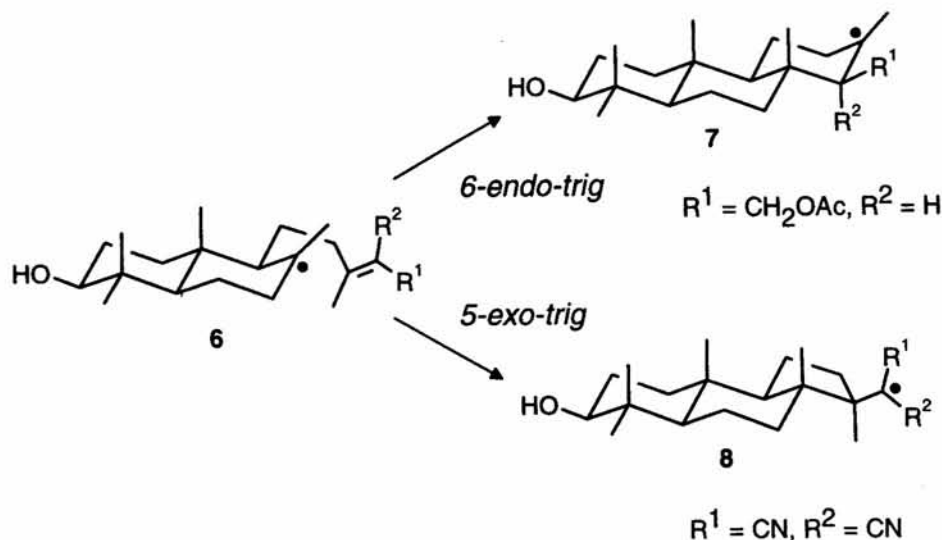
A mechanistically remarkable and synthetically very useful change in the cyclization mode is ob-



Scheme I



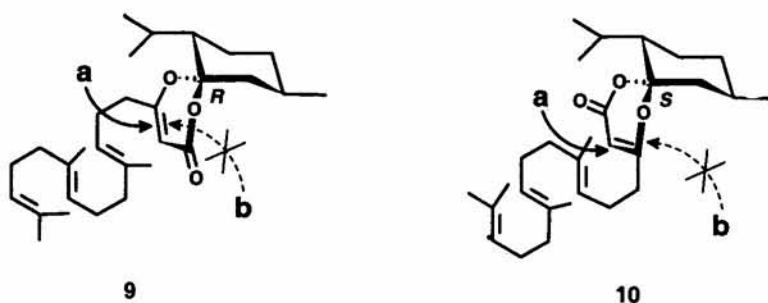
Scheme II



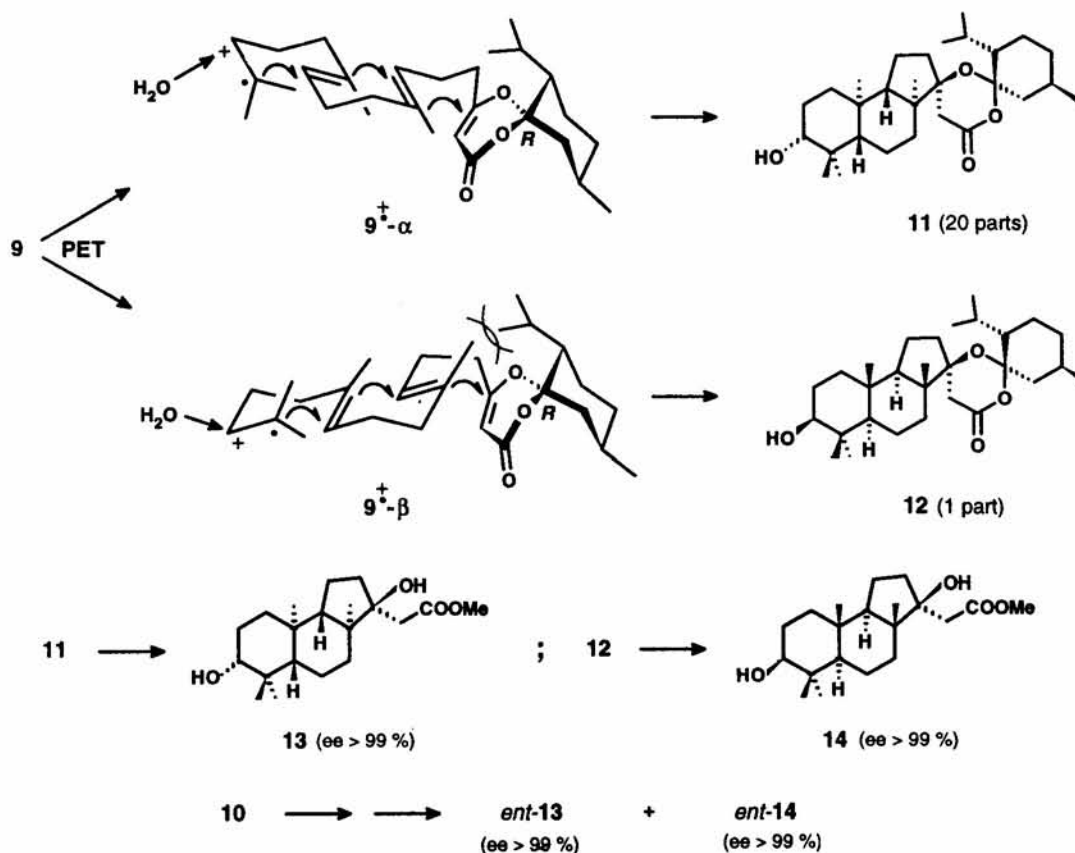
Scheme III

served for polyalkenes bearing electron-withdrawing substituents at the α -terminal site, such as **3b,c**. For the 1,1-dicarbonitrile **3c**, enhanced stability of the malonodinitrile radical, i.e. **8**, is most likely responsible for exclusive 5-*exo*-trig cyclization in the terminal step leading exclusively to **5c**. This contrasts the sequence **3a** $\rightarrow$ **6** $\rightarrow$ **7** $\rightarrow$ **4a** (Schemes II, III). Less efficient stabilization is obviously effective in the

case of **3b** $\rightarrow$ **4b** + **5b**. Notably, the stereochemical outcome of these transformations with regard to the dicyanomethyl group ($R^1=R^2=CN$) is consistently β -selective, i.e. *syn* to the respective vicinal angular methyl group in **5c**, 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-3 of **5c**.



Scheme 4



Scheme V

A further objective of our work was to explore effective asymmetric induction in these cyclizations. When chiral spirocyclic dioxinones¹², derived from the chiral auxiliary (-)- menthone, are attached to a terpenoid polyalkene (**9** and **10**; cf Scheme IV), high asymmetric inductions are observed for the cyclizations¹³.

Irradiation of compound **9** with 1,4-dicyanotetra-methylbenzene and biphenyl in MeCN-H₂O (10:1) at -25°C furnishes the cyclization products **11** and **12**

in 20 : 1 ratio and 21 % yield (Scheme V)¹³. The cyclization of **9** and **10** proceeds identically as that of compound **3c** solely terminated by 5-*exo*-trig ring closure. Removal of the chiral auxiliary (-)-menthone from **11** and **12** affords the enantiomerically pure tricyclic esters **13** and **14** with NaOH in MeOH-H₂O and subsequent treatment with TMSCl in MeOH¹³. Similarly, cyclization of **10** affords, after splitting off the auxiliary, the enantiomerically pure compounds *ent*-**13** and *ent*-**14**.

These highly selective cyclizations of **9** and **10** are likely based on: (a) an exclusive α -side diastereofacial differentiation of the dioxinone moieties (Scheme IV) and (b) long distance asymmetric induction from the chiral auxiliary at one end across the molecule to the other end of the polyalkene chain, which we assume to be the result of diastereoselective folding of the polyalkene chain (cf. proposed conformations **9- α** and **9- β**)¹³. Distinction of whether this folding occurs prior to or shortly after the photochemical oxidation of the ω -alkene cannot be made at this point. Notably, such highly face selective cyclizations allow to synthesize enantiomers by the use of only a single chiral auxiliary, (-)-menthone.

In conclusion, these results represent a versatile method for stereoselective synthesis of polycyclic compounds from the readily available starting materials. The efficient asymmetric induction by the chiral spirocyclic dioxinones enables a ready access to enantiomerically pure tricyclic terpenoids of complementary chiralities with the aid of only one chiral auxiliary, (-)-menthone. Spontaneous folding of the terpenoid polyalkene substantiates the idea of "minimal enzymatic assistance" in non-oxidative biosynthesis¹.

References and Notes

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