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# An asymmetric induction principle and biomimetics with photons *via* electron transfer

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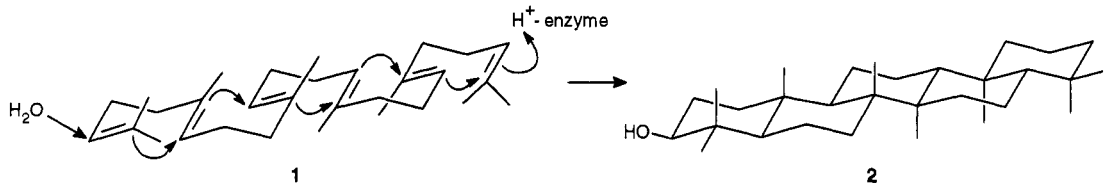
***Abstract***: Isoprenoid polyalkene radicals, formed upon *anti-Markovnikov* addition of a nucleophile to their parent radical cations, which are readily accessible *via* photo-induced electron transfer, undergo cascade cyclizations. The regioselectivity is efficiently controlled by the substitution pattern, *i.e.* the generally observed 6-*endo*-trig mode is replaced by 5-*exo*-trig, if electron-deficient double bonds are involved. Mechanistic studies revealed that these synthetically useful transformations, initiated by polyalkene radical cations being trapped by water, are propagated in a plain radical fashion and terminated upon either protonation of carbanions or hydrogen transfer. Cyclization products were used for a natural product total synthesis, *i.e* of stypoldione. Moreover, high asymmetric inductions in such transformations have been achieved by the use of chiral spirocyclic dioxinones, derived from the auxiliary (-)-menthone, remotely located from the initiation site of the cyclizations. These asymmetric photoinduced cyclizations are further examples of a more general enantiodivergent induction principle giving access to enantiomerically pure polycyclic terpenoids of complementary chiralities by means of the single chiral auxiliary (-)-menthone. Finally, the efficient application of solar radiation for photochemical purpose is demonstrated by the use of flat collectors which in contrast to concentrating technologies not only employ direct, but also diffuse radiation (the latter amounts to about 40% of the global radiation at central European latitude).

## INTRODUCTION

For more than five decades, chemists have aimed at mimicking *in vivo* cyclizations (1,2) of squalene (**1**) to polycyclic terpenoids. The non-oxidative pathways of these enzyme-catalyzed processes, such as the formation of tetrahymanol (**2**), have so far never been successfully accomplished *in vitro*. While the majority of publications followed the original concepts (3,4), *i.e.* a cationic cyclization strategy mimicking the oxidative paths (5), our approach (6-14) focusses on the parent non-oxidative transformations. The only attempts in the latter field have so far been undertaken with radical-type reactions (15,16). Interestingly, radical processes have been considered as a biologically relevant (17).




Scheme 1. Non-oxidative *in vivo* cyclization of squalene (**1**) to tetrahymanol (**2**).

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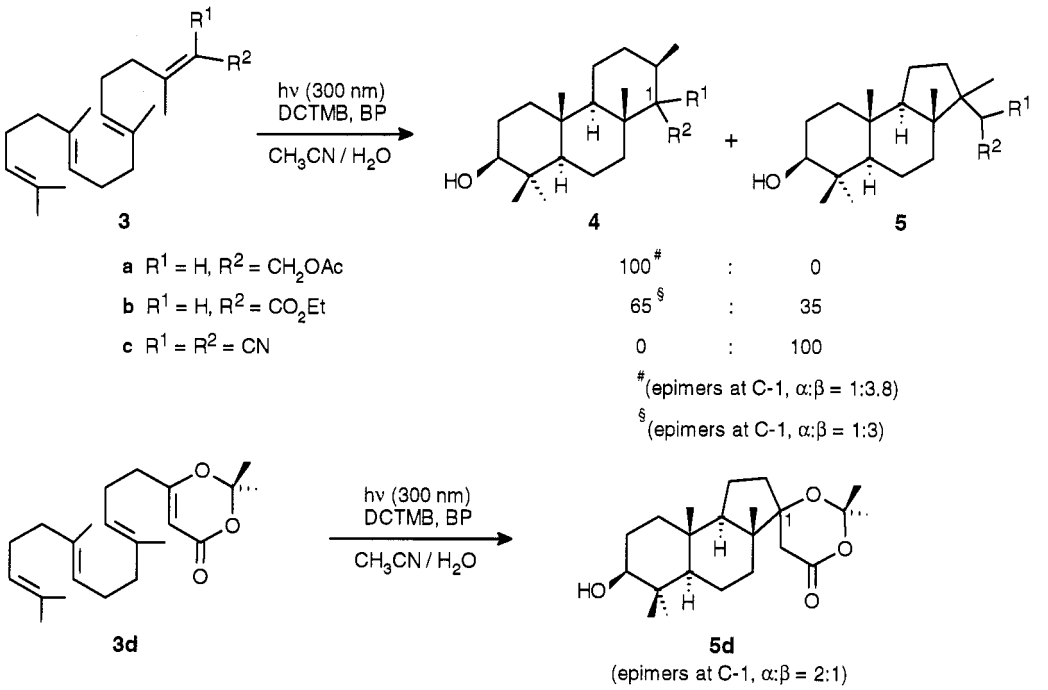
## BASIC IDEA AND SCOPE OF THE CYCLIZATIONS

While radical cyclization approaches often suffer from tedious synthesis of the precursors of the radical intermediates for cyclization, we sought for a way to generate the reactive intermediates directly from readily available isoprenoid polyalkenes, such as the acetate **3a**, the α,β-unsaturated ester **3b**, the 1,1-dicarbonitrile **3c** and the 1,3-dioxin-4-one **3d** (Scheme 2). Oxidation of a trisubstituted alkene, *e.g.* by photoinduced electron transfer (PET), could serve as a viable trigger to mimick a non-oxidative cyclization process in that the intermediate radical cation is trapped *anti-Markovnikov*-wise by a nucleophile (water) liberating a free radical site which can ultimately initiate bond formation (→ cyclizations).

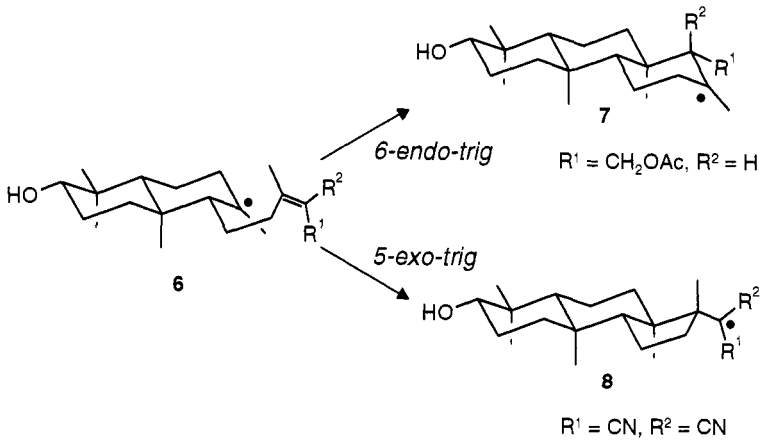
Generally, irradiations on a preparative scale are performed in a *Rayonet* reactor ($\lambda_{max}$ = 300 nm) in acetonitrile/water using 1,4-dicyano-2,3,5,6-tetramethylbenzene (DCTMB) as an acceptor and 1,1'-biphenyl (BP) as a cosensitizer (18). In the course of these reactions, PET to the excited acceptor from BP gives rise to a $DCTMB^{\bullet-}$ / $BP^{\bullet+}$ pair. Subsequent electron transfer from the polyalkenes to $BP^{\bullet+}$ regioselectively oxidizes the ω-alkene of the polyalkene and restores the uncharged cosensitizer. As anticipated, the polyalkene radical cations thus obtained are trapped by *anti-Markovnikov* addition of water (19) and the resulting β–distonic radical cations are expected to undergo rapid deprotonation (20) delivering neutral β–hydroxy radicals which in turn could initiate the cyclizations. As will be shown in the next chapter this hypothesis regarding the timing of the mechanistic events has been confirmed.




Scheme 2. PET triggered tricyclizations of isoprenoid polyalkenes.

Within these cascade cyclizations, intramolecular addition of a tertiary radical center to an alkene proceeds in 6-*endo*-trig fashion (21) when reacting **3a** to form the *trans*-fused product **4a** exclusively. A mechanistically remarkable and synthetically very useful change in the cyclization mode is observed for polyalkenes bearing electron withdrawing substituents at the α-terminal site, such as **3b,c,d**. For the 1,1-dicarbonitrile **3c** and the dioxinone **3d,** enhanced stability of the terminal radical, *e.g.* **8**, is most likely responsible for exclusive 5-*exo*-trig cyclization in the terminal step leading exclusively to **5c** and **5d** contrasts the sequence **3a** → **6** → **7** → **4a** (Scheme 2, 3). Less efficient stabilization is obviously effective in the case of **3b** → **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

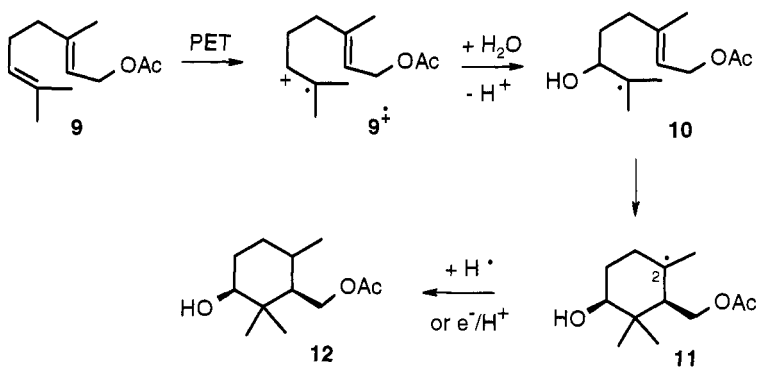
methyl group in **5c**, suggesting least steric interaction between these substituents as compared to the alternative methyl-methyl interaction in the transition state, which would lead to the epimer at C-3 of **5c**.




Scheme 3. 6-*endo*- vs. 5-*exo*-trig radical cyclizations controlled by the substituent pattern.

## INITIATION AND TERMINATION OF THE CYCLIZATION CASCADES

Mechanistic studies were conducted using geranyl acetate (**9**) as a model compound (22). Experiments including the irradiation of **9** in the presence of an excess of $CuCl_2$ supplied evidence for the proposed mechanism as depicted in Scheme 4, *i.e.* nucleophilic addition of $H_2O$ to the radical cation $\mathbf{9}^{\bullet+}$, formed by PET, generates radical **10** prior to the cyclization which leads to the cyclic radical intermediate **11**. Most notably, the cyclization event itself has therefore to be regarded as a radical, rather than radical cationic mechanism.




Scheme 4. Mechanism of the formation of the cyclic product **12** from **9** by PET.
A = 1,4-dicyano-2,3,5,6-tetramethylbenzene (DCTMB)

While the termination step in the case of **3c** unambiguously involves electron transfer from the acceptor radical anion $A^{\bullet-}$ (A = DCTMB) to the dicyano-substituted tertiary radical formed in the final ring closure, followed by protonation of the carbanion thus generated (7,10,28), this process is open to debate in the case of the polyalkene acetates. Diverging data are reported for the reduction potential of tertiary alkyl radicals (23-26). Two mechanisms are conceivable: a) reduction of **11** by $A^{\bullet-}$ followed by protonation *en route* to **12** or b) hydrogen atom transfer from $AH^{\bullet}$ (the conjugate acid of $A^{\bullet-}$) to **11**. The first mode would seem unlikely in view of the rather high reduction potentials for tertiary alkyl radicals earlier reported [$E_{1/2}^{red}$ for *tert*-butyl radical: -2.19 to -2.54 V *vs* SCE (23)], as compared to the oxidation potential of $A^{\bullet-}$ [$E_{1/2}^{ox}$ ($A^{\bullet-}$ / A) = $E_{1/2}^{red}$ (A / $A^{\bullet-}$) = -1.90 V *vs* SCE (27) and -2.14 V *vs* 0.01M $AgNO_3$ (28), resp.]. Furthermore,

*Vieira et al.* showed that the *tert*-butyl radical cannot be converted into its anion by electrolyses in DMF at a potential (−2.0 V) comparable to the reduction potential of A (24). Recent electrochemical studies (25,26), on the other hand, which place the standard reduction potential of the *tert*-butyl radical in the range of −1.48 to -1.77 V *vs* SCE, would eventually render the reduction of **11** to the carbanion still possible, if an additional activation energy for solvation and geometry changes of less than the proposed value of 0.5 eV, refered to as *intrinsic barrier* in ref. (25), would be realistic for homogeneous electron transfer. Alternatively, pathway b) could be conceived as a reasonable mechanistic variant if similar transient reactivities for 1-cyanonaphthalene (29) and DCTMB, used in the present work, are assumed.

## SPECTROSCOPICALLY DETECTABLE INTERMEDIATES

Laser flash photolysis ($\lambda_{exc}$ = 308 nm) of DCTMB and BP in argon-saturated acetonitrile in the presence and absence of the polyalkenes using time-resolved UV-VIS spectroscopy provide more detailed information on the mechanism of these photocyclizations (10,14,28). Initial electron transfer (ET) between the excited acceptor and the cosensitizer is indicated by linear Stern-Volmer plots obtained for the quenching of DCMB fluorescence by BP with a rate constant of $k = 1.3 \times 10^{10}$ $M^{-1}$ $s^{-1}$ and moreover confirmed with the observation of two transients, namely the absorption of the acceptor radical anion $DCTMB^{\bullet-}$ ($\lambda_{max}$= 360 nm) and the cosensitizer radical cation $BP^{\bullet+}$ ($\lambda_{max}$ = 660 nm) with typical half-live times of 6 and 4 μs in the presence of 10 M $H_2O$, respectively. The oxidation of the polyalkenes by $BP^{\bullet+}$ in a subsequent ET step, although not documented with the appearance of new transients, is clearly derived from the dependency of the decay kinetics of $DCTMB^{\bullet-}$ and $BP^{\bullet+}$ upon addition of the polyalkenes. The lifetime of the cosensitizer radical cation is strongly reduced, *e.g.* a half-live value of 0.1 μs was found in the presence of **3c** (Figure 1).

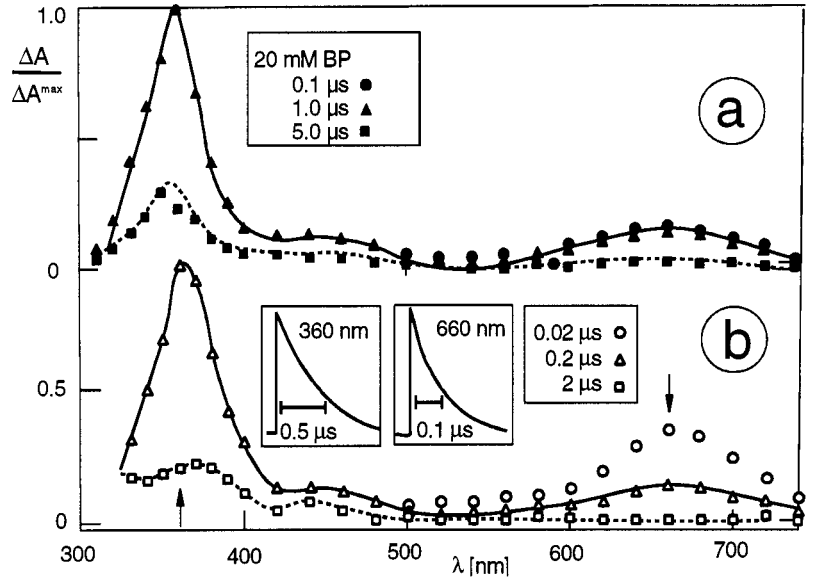
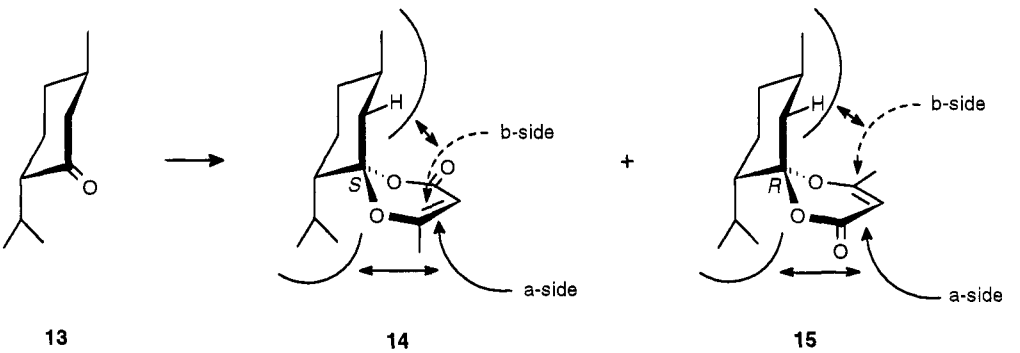



Figure 1. Transient absorption spectra of DCTMB (0.5 mM) and BP (20 mM) in the absence **a** and presence **b** of the polyalkene-1,1-dicarbonitrile **3c** (2 mM).

The polyalkene radical cations and their successors *en route* to the cyclization products could not be monitored directly, both the molar absorption coefficients and lifetimes of these species are too low to be detected with the spectroscopical techniques applied. Close inspection of the transient absorptions and decay kinetics of the radical ions of DCTMB and BP has nevertheless provided a consistent mechanistic scheme (9,14).

## ENANTIODIVERGENT ASYMMETRIC INDUCTION PRINCIPLE

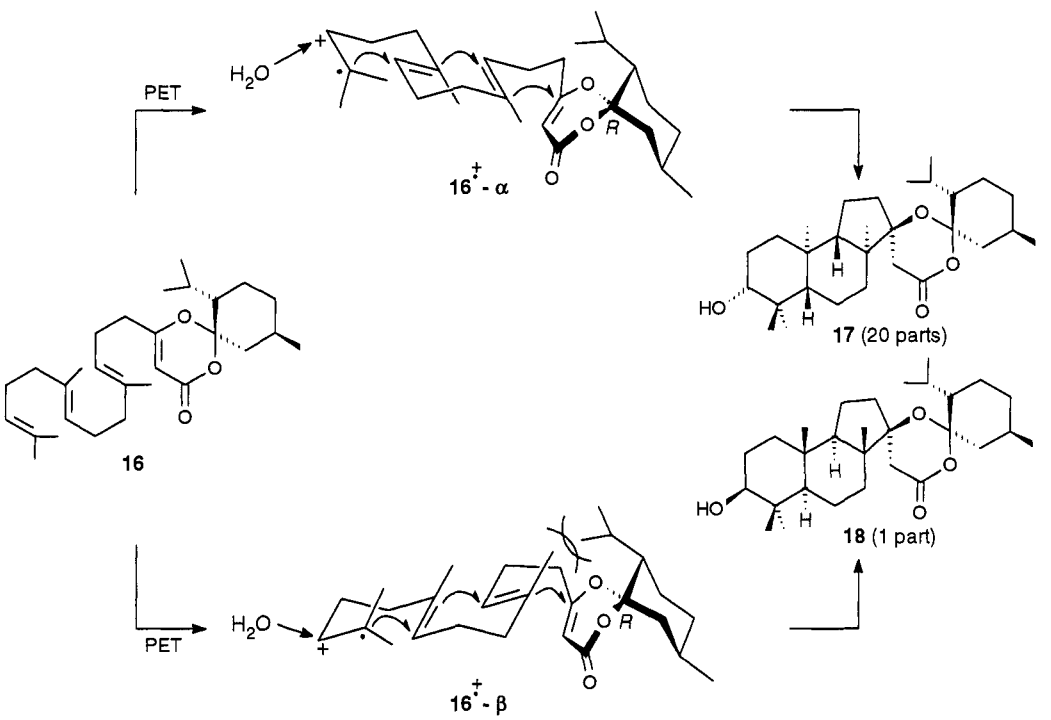
In order to induce asymmetry in the above discussed PET-triggered cyclizations, the enantiomerically pure spirocyclic dioxinones **14** and **15** (30-33) (Scheme 5) are attached to terpenoid mono-, bi-, tri- and tetraalkenes (11-13,34). The dioxinones **14** and **15** are readily available by reaction of (-)-menthone (**13**) and diketene in the presence of PTSA and have been shown in earlier studies to be pivots of a novel enantiodivergent induction principle (30-33). These earlier investigations revealed the advantageous use of **14** and **15** in [2+2] photocycloadditions ultimately leading to enantiomerically pure natural products.




**13** **14** **15**

Scheme 5. Synthesis of the enantiomerically pure dioxinones **14** and **15** from (-)-menthone (**13**).

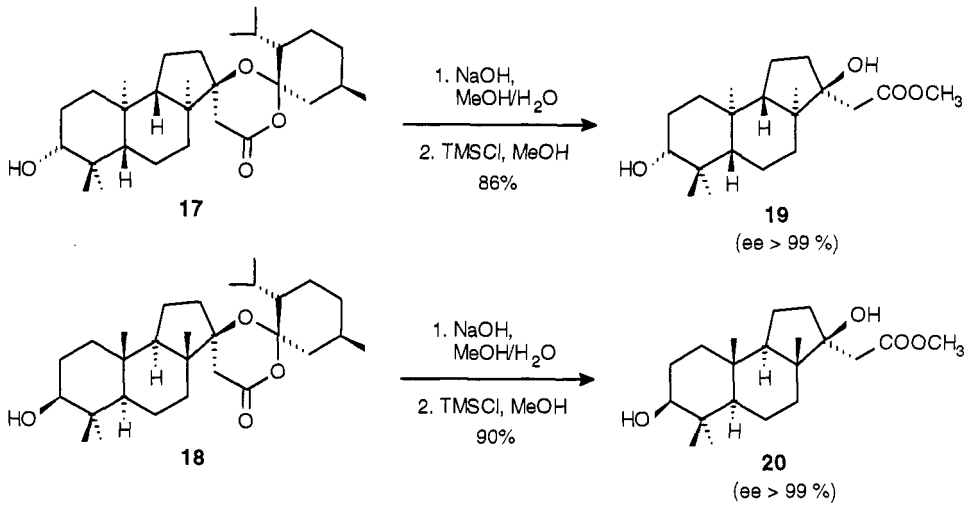
In [2+2] photocycloadditions with various alkenes, the enantiomerically pure dioxinones **14** and **15** are attacked preferentially from the a-side (30-34). Even exclusive attack from the a-side was observed in PET cyclizations of mono- and polyalkenyl dioxinones such as **16** and **21** (11-13,34) (Scheme 6,7). This diastereofacial selectivity is controlled conformationally (Scheme 5) and rules out any effective shielding of the a-side by the isopropyl group (11,30,34).




Scheme 6. Asymmetric PET cyclization of enantiomerically pure (*E*,*E*)-farnesylmethyl dioxinone **16** to the photoproducts **17** and **18**.

For example, (*E*,*E*)-farnesylmethyl dioxinone **16** affords the photoproducts **17** and **18** in a 20 : 1 ratio upon irradiation (*Rayonet* reactor, $\lambda_{max}$ = 300 nm) with DCTMB and biphenyl as an electron-acceptor couple in MeCN/$H_2O$ 10:1 at -25 °C (11-13,34) (Scheme 6). The combined yield after chromatography on silica gel is 21 %. In these processes, water adds in *anti-Markovnikov* sense to the radical cation site of the polyalkenes and the cyclization cascades are typically terminated by 5-*exo*-trig ring closures.

Removal of the chiral auxiliary (-)-menthone from **17** and **18** with NaOH in MeOH/$H_2O$, followed by treatment with TMSCl in MeOH affords the enantiomerically pure tricyclic esters **19** and **20** in 86 and 90 % yield, respectively (Scheme 7). The relative and absolute stereochemistries of all dioxinone derivatives were assigned *via* a combination of X-ray single-crystal analysis, NOE/NOESY spectroscopy and chemical correlation.

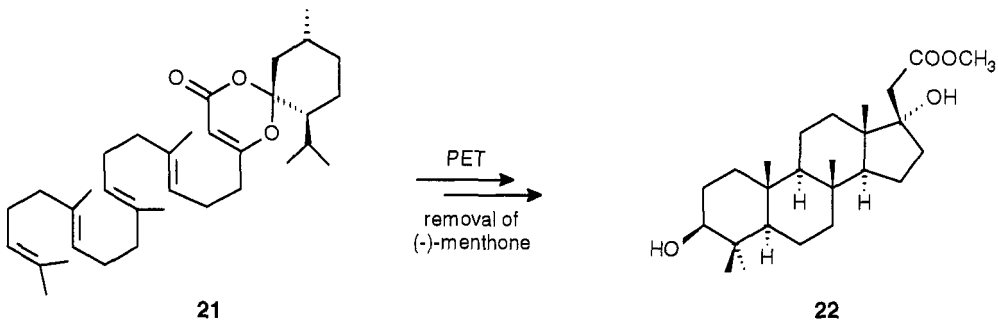



**17** **19** (ee > 99 %)

**18** **20** (ee > 99 %)

Scheme 7. Removal of the chiral auxiliary (-)-menthone from **17** and **18**.

PET cyclization of **21** affords, after splitting off the auxiliary, the enantiomerically pure steroid skeleton **22** (34) (Scheme 8).




**21** **22** (ee > 99 %)

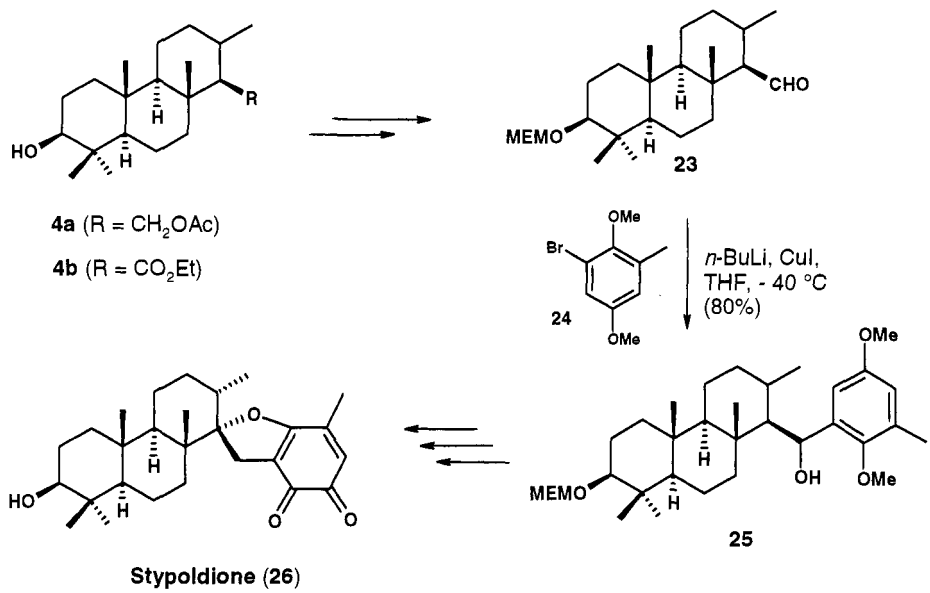
Scheme 8. Asymmetric PET cyclization of **21** and removal of the chiral auxiliary (-)-menthone.

In addition to the high chemo- and regioselectivities, the cyclizations are distinguished by exclusive a-side diastereofacial selectivity of the dioxinone moieties and efficient remote asymmetric induction from the chiral auxiliary at one end of the molecule to the other end of the polyalkene chain. The remote asymmetric induction most likely is the result of diastereoselective folding of the polyalkene chain prior to or shortly after the photochemical oxidation of the ω-alkene (cf. proposed conformations $\mathbf{16}^{\bullet+}$-α and $\mathbf{16}^{\bullet+}$-β,

Scheme 8). The uniform face selectivities and remote asymmetric inductions enable to synthesize both product enantiomers by the use of only a single chiral auxiliary, *i.e.* (-)-menthone (**13**).

These asymmetric biomimetic photochemical cyclizations offer short and efficient access to a variety of enantiomerically pure cyclic terpenoids possessing up to eight new asymmetric centers, the chirality of which can be controlled by the use of the dioxinones **14** and **15**, both of which are prepared from (-)-menthone (**13**).

## SYNTHETIC APPLICATION




Scheme 9. Total synthesis of stypoldione (**26**) starting from **4a** or **4b** both photoproducts of PET cyclizations.

The cyclic products **4a** and **4b** were successfully applied to a concise formal total synthesis of stypoldione (**26**) (22,35). A novel and efficient approach to **26** has been achieved *via* the key intermediate **25** which is obtained by the coupling of aldehyde **23** with the aryl bromide **24** (Scheme 9).

## THE USE OF SOLAR RADIATION FOR PHOTOCHEMICAL TRANSFORMATIONS

To date, photochemical reactions on an industrial scale, *e.g.* for the synthesis of pharmaceuticals and biological agents, have only been of minor interest industrially as they are considered uneconomical due to high acquisition costs for UV lamps, high and inefficient energy consumption of such light sources including cooling problems.

However, most photochemical processes have the advantage not to require any of the chemical auxiliary agents usually involved in conventional reactions, thus eliminating the need for the disposal of these substances. Under suitable technical conditions, it is thus advantageous to use photonic and thermal solar energy for chemical processes, especially in the production of fine chemicals.

Therefore, a suitable solar testing plant for chemical applications has been developed and probed with photo- and thermochemical processes (Figure 2). In order to achieve optimal harvesting of direct solar radiation, linearly focussing concentrators have been devised which track the course of the sun along a one- and two-axis system by means of photocells (36). They consist of parabolic collectors, typically 1×1 m in

dimension with a focal width of 1 to 5 cm, equipped with an aluminum coated teflon foil, and reaction tubes in the linear focus of these mirrors. By this means, direct solar irradiation is concentrated by a factor of 5 to 60. Usually, these reactors are operated with an average flow rate of the reactant solution of *ca.* 100 l/hour.

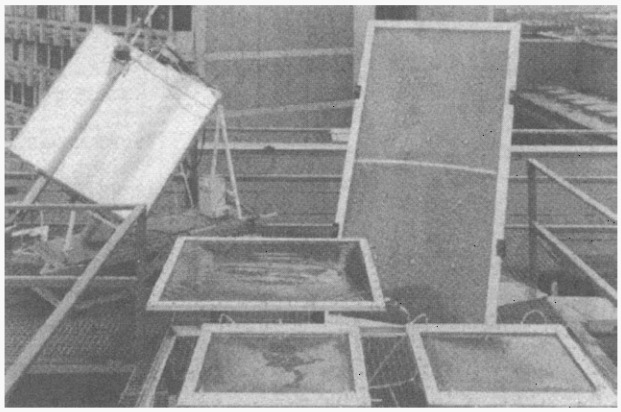
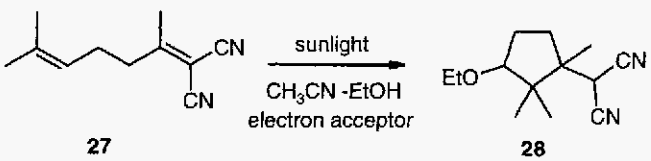


Figure 2. Solar testing plant on the roof of the *Max-Planck-Institut für Strahlenchemie* in *Mülheim* showing a linearly focussing concentrator and flat-bed reactors.

In the central European area, however, 40 % of the incident sunlight is of diffuse nature drastically limiting the use of solar concentrators. But even under these conditions, highly efficient solar photochemistry can be carried out at low cost using low-tech flat-bed reactors, developed recently (37) and lacking any complex mechanics or electronic control. Using the PET induced 5-*exo-trig* cyclization of the 1,1-dicarbonitrile **27** → **28** as a model (Scheme 10), it was shown that these setups allow very high turnover rates and are superior to the more sophisticated concentrators at central European latitude (Figure 3).




**27** **28**

Scheme 10. Cyclization of **27**.

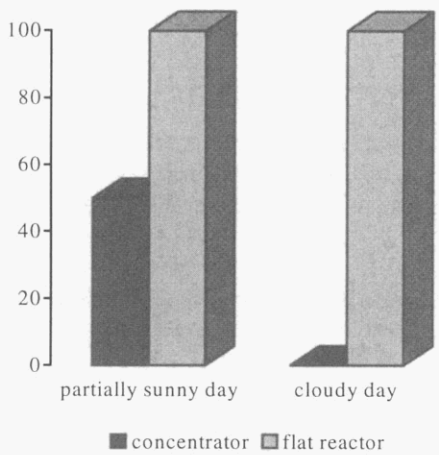



Figure 3. Comparison of concentrator *vs.* flat collector. Conversion of **27** in % after 3h (partially sunny day) and 6h (cloudy day) in Mülheim.

Similarly successful was the application of the flat-bed collector technique to singlet oxygen reactions, *i.e.* for the synthesis of fragrants such as rose oxide (37).

## CONCLUSION

Our results represent a versatile method for stereoselective syntheses of polycyclic compounds from readily available terpenoid polyalkenes *via* photochemically generated radical cations. The latter are trapped by water, the subsequent cyclizations propagated in a plain radical fashion and terminated upon either protonation of carbanions or hydrogen atom transfer. This general mechanistic scheme is fully supported by laser flash photolysis using time-resolved UV-VIS spectroscopy on the acceptor and cosensitizer radical anions as the main absorbing species. The efficient asymmetric induction by the chiral spirocyclic dioxinones enables ready access to enantiomerically pure tri- and tetracyclic terpenoids of complementary chiralities with the aid of a single chiral auxiliary, *i.e.* (-)-menthone. Evidence for spontaneous asymmetric folding of the terpenoid polyalkenes is likely to be the result of long distance asymmetric induction substantiating the idea of "minimal enzymatic assistance" in non-oxidative biosynthesis (1). Furthermore, it is shown that even at central European latitude solar radiation can efficiently be employed for photochemical transformations when using flat-bed collectors.

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