Short Biomimetic Synthesis of a Steroid by Photoinduced Electron Transfer and Remote Asymmetric Induction

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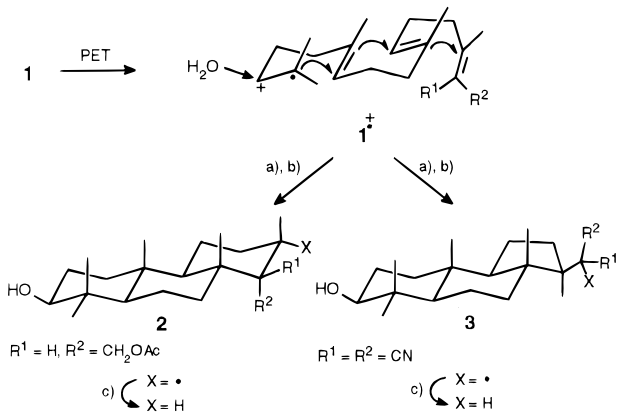
Received November 23, 1998

Photoinduced electron transfer (PET)[1] has in our hands turned out to be a viable tool for the synthesis of mono- and polycyclic terpenoid skeletons[2] which are assembled via regioselective oxidation of terpenoid polyalkenes at the omega alkene sites. Such oxidations, generating the parent radical cations, give rise to (a) trapping of the radical cations by a nucleophile, such as water, (b) radical-type cyclization(s), and (c) termination of such processes either by reduction/protonation at the resulting tertiary radical center of the cyclization products or by trapping of this center by a hydrogen atom (Scheme 1).[3] Depending on the electron-withdrawing properties of the substituent(s) $R^{1/2}$ of the polyalkene chain, 6-*endo* (→ **2**) vs 5-*exo*-trig (→ **3**) ring closures terminate the cyclization of **1**.

Such PET-triggered cascade cyclizations were found to mimic the parent nonoxidative enzymatic processes[4] which in turn have originally been proposed to proceed via cationic intermediates, generated upon enzymatic protonation and anti-Markovnikov addition of water. A representative example of such transformations is that of squalene to tetrahymanol.[4b] However, the latter proposal has so far not been validated in vitro. The present principle, based on the intermediacy of radical cations, which are generated photochemically from readily accessible terpenoid polyalkenes, provides nature-like cascade cyclizations, including the requisite anti-Markovnikov addition of a nucleophile, such as methanol or water.

(*E,E,E)*-Geranylgeranylmethyl dioxinones **4** and **7**[5] were irradiated (Rayonet reactor, $\lambda_{max} = 300$ nm) in the presence of 1,4-dicyanotetramethylbenzene (DCTMB) and biphenyl (BP) as electron-acceptor couple in MeCN/H_2O 10:1 at −25 °C,[6] adopting conditions[7] which have already been successfully employed in earlier work concerning the biomimetic PET cyclization of shorter terpenoid polyalkene chains.[8,9] This electron-acceptor combination can be used in homogeneous solution rather than in micellar media which we employed in our earlier efforts and which posed difficulties with respect to the handling and workup.[2a] Furthermore, catalytic amounts of DCTMB and BP are sufficient to drive the reactions to completion since the electron acceptors are chemically stable.

Scheme 1



The spirocyclic dioxinone moieties of **4** and **7** were chosen as asymmetric inducers, adopting an enantiodivergent induction principle applied earlier in [2 + 2] photocycloadditions[10] and more recently in PET-induced cyclizations of shorter polyalkenes.[9] This method, although using a single chiral auxiliary such as (−)-menthone, generates products of complementary chiralities, provided that the reactions involving the dioxinone moieties are sufficiently face-selective. The major photoproducts of **4** were identified as a diastereomeric mixture of **5** and **6** in a 7:1 ratio (Scheme 2).[11−13] Analogously, **7** (diastereomer of **4**) when subjected to the above PET conditions, afforded **8** and **9** in a 2:1 ratio. The absolute configurations of all compounds have been secured via stereochemical correlation and NOE/NOESY spectroscopy. Both cyclizations are highly regio- and stereoselective in that anti-Markovnikov and equatorial addition of a nucleophile (water) are observed, furnishing tetracyclic products (**5**/**6** and **8**/**9**) with all-trans ring fusions.

(1) For general references to PET, see: (a) *Photoinduced Electron Transfer*; Fox, M. A., Chandon, M., Eds.; Elsevier: New York, 1988; Parts A−C. (b) Kavarnos, G. *Fundamentals of Photoinduced Electron Transfer*, Wiley-VCH: New York, 1993. (c) Hintz, S.; Heidbreder, A.; Mattay, J. *Top. Curr. Chem.* **1996**, *177*, 77−124.

(2) (a) Hoffmann, U.; Gao, Y.; Pandey, B.; Klinge, S.; Warzecha, K.-D.; Krüger, C.; Roth, H. D.; Demuth, M. *J. Am. Chem. Soc.* **1993**, *115*, 10358−10359. (b) Warzecha, K.-D.; Xing, X.; Demuth, M.; Goddard, R.; Kessler, M.; Krüger, C. *Helv. Chim. Acta* **1995**, *78*, 2065−2076. (c) Warzecha, K.-D.; Xing, X.; Demuth, M. *Pure Appl. Chem.* **1997**, *69*, 109−112. (d) Heinemann, C.; Xing, X.; Warzecha, K.-D.; Ritterskamp, P.; Görner, H.; Demuth, M. *Pure Appl. Chem.* **1998**, *70*, 2167−2176.

(3) Xing, X. Ph.D. Thesis, Max-Planck-Institut für Strahlenchemie/University of Essen, 1998.

(4) For reviews, see: (a) Caspi, E. *Acc. Chem. Res.* **1980**, *13*, 97−104. (b) Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189−2206.

(5) Preparation of **4** and **7**: The (*E,E,E)*-geranylgeranylmethyl dioxinones **4** and **7** were prepared from (*E,E,E)*-geranylgeranyl bromide and the chiral spirocyclic dioxinone moieties in one step. Details can be found in the Supporting Information; see also ref 6.

(6) Heinemann, C. Ph.D. Thesis, Max-Planck-Institut für Strahlenchemie/University of Essen, 1998.

(7) Cyclization of dioxinone **7**: an argon flushed solution (CH_3CN/H_2O 10:1, 330 mL) of **7** (1.9 g, 3.7 mmol), biphenyl (0.45 g, 2.9 mmol) and 1,4-dicyanotetramethyl-benzene (0.22 g, 1.2 mmol) (for preparation, see: (a) Suzuki, H.; Nakamura, K.; Goto, R. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 128−131. (b) Suzuki, H.; Hanafusa, T. *Synthesis* **1974**, 53−55) in a Pyrex vessel was irradiated at −25 °C in a Rayonet reactor with $\lambda_{max} = 300$ nm for 15 h. Afterwards, the clear yellowish solution was concentrated at reduced pressure to give a pale yellow solid, from which biphenyl and 1,4-dicyanotetramethylbenzene were removed by flash chromatography (silica gel 0.063−0.02 mm, 20:1 → 1:10 pentane/Et_2O). ^{13}C NMR analysis of the mixture indicated a 2:1 ratio of the two diastereomeric products **8** and **9**. The mixture was chromatographed on silica gel (5:1 → 2:1 pentane/Et_2O). Further chromatographical purification on silica gel (30:1 → 15:1 CH_2Cl_2/EtOAc) and HPLC separation (Nucleosil-7-100, cyclohexane/2-propanol 100:1) gave 163 mg (0.31 mmol, 8%) of **8** and 74 mg (0.14 mmol, 4%) of **9**, each as a white solid and >95% pure by NMR. The structures of **8** and **9** were secured, besides IR, EI MS, and elemental analysis, by NOE and NOESY spectroscopy (see Supporting Information and ref 6).

(8) Heinemann, C.; Warzecha, K.-D.; Xing, X.; Demuth, M. *Ind. J. Chem.* **1997**, *36*, 494−497.

(9) Heinemann, C.; Demuth, M. *J. Am. Chem. Soc.* **1997**, *119*, 1129−1130.

(10) For the synthesis, availability, applications and patents of the dioxinone moieties as well as the facial selectivity in [2 + 2]-cycloadditions, see: (a) Demuth, M.; Palomer, A.; Sluma, H.-D.; Dey, A. K.; Krüger, C.; Tsay, Y.-H. *Angew. Chem.* **1986**, *98*, 1093−1095; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1117−1119. (b) Demuth, M. *Pure Appl. Chem.* **1986**, *58*, 1233−1238. (c) Demuth, M. In *Photochemical Key Steps in Organic Synthesis*; Mattay, J., Griesbeck, A. G., Eds.; VCH: Weinheim, 1994; pp 92−96. (d) Preparation and use are patented: Demuth, M.; Schaffner, K. EPPS 0254239; U.S. Patents 5,026,877, 5,142,054, and 4,864,037.

(11) Parts of these results have been communicated at the 17th IUPAC Symposium on Photochemistry, Sitges, Spain, 1998.

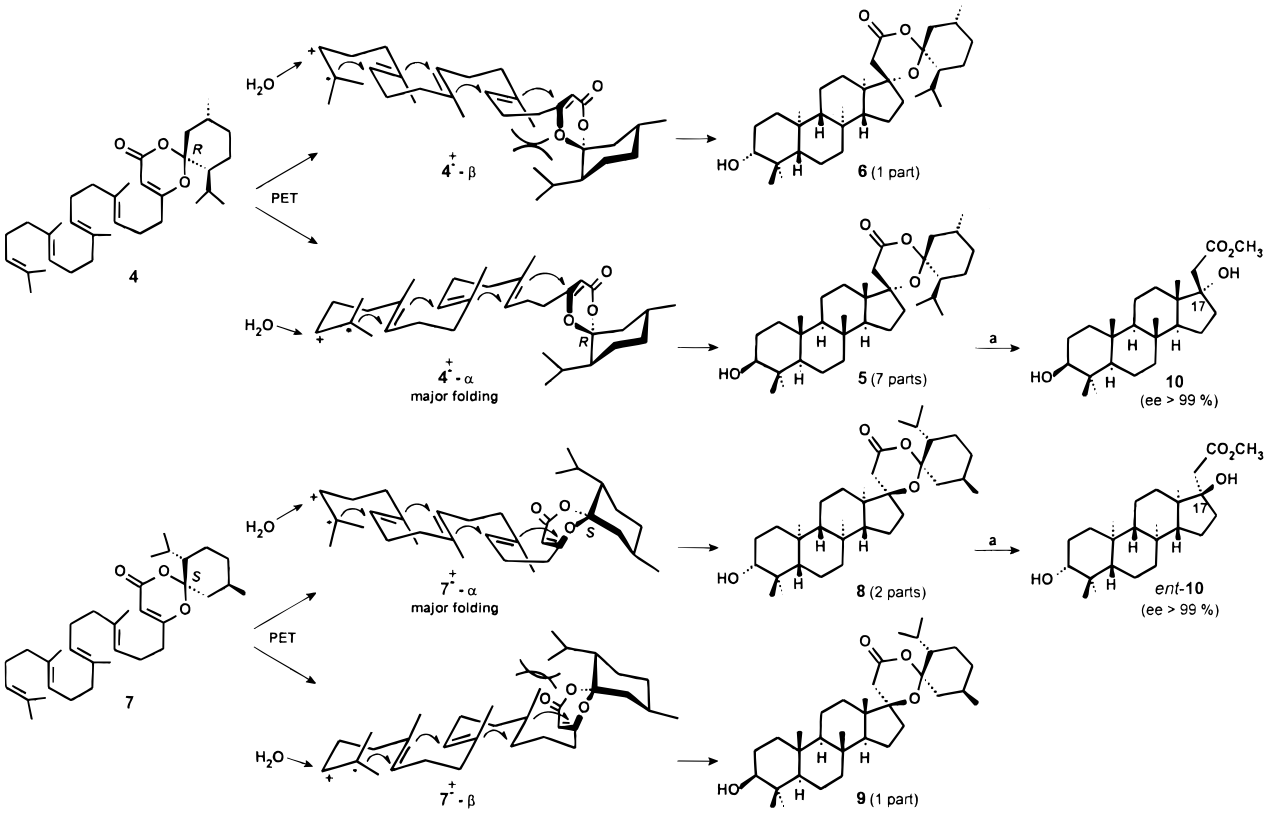
(12) The ratio of the cyclization products was determined by ^{13}C NMR analysis, and is about the same for the isolated pure products.

(13) Further products identified in a related study stem from disproportionation, dimerization, and hydroxylation of the polyalkene, cf. ref 3.

(14) For precoiling in cationic cyclization processes, see: (a) Johnson, W. S. *Angew. Chem.* **1976**, *88*, 33−66; *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9. (b) Macco, A. A.; Buck, H. M. *J. Org. Chem.* **1981**, *46*, 2655−2660. (c) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, pp 341−409.

10.1021/ja984035z CCC: $18.00
Published on Web 05/07/1999

Scheme 2[a]



[a] Reagents and conditions: (PET) biphenyl, 1,4-dicyanotetramethylbenzene, *hν* (300 nm), MeCN/H_2O 10:1, −25 °C, 10% (**5** and **6**), 12% (**8** and **9**); (a) NaOMe, MeOH, 25 °C, 91% (**10**), 95% (*ent*-**10**).

Notably, the fourth ring closure occurs purely via a 5-*exo* mode, which is in agreement with earlier results concerning cyclizations of shorter polyalkene chains. The termination of such cascades depends on the electron-withdrawing capacity of the substituent(s) R[1/2] (cf. formation of **3**, Scheme 1).[2b] The dioxinone moiety, in the present case, directs the terminal ring closure exclusively toward a 5-*exo*-trig mode avoiding the 6-*endo* alternative.[11]

The degree of asymmetric induction associated with these cyclization cascades is quite remarkable. The chiral moiety is remote from the initiation site (radical cation), which suggests a diastereoselective folding of the polyalkene chain prior to or shortly after the initial PET oxidation step, i.e., **4** → **4**$^{+\bullet}$. The all-trans pre-chair folding pattern, as represented by **4**$^{+\bullet}$-α, should consequently be responsible for the formation of the major photoproduct **5**, and **4**$^{+\bullet}$-*β*, which exhibits considerable steric interactions at the bottom face (shown in Scheme 2) should lead to the minor component **6**.[14] Analogous considerations are applicable to explain the predominant formation of **8** vs **9** from **7** via **7**$^{+\bullet}$-α vs **7**$^{+\bullet}$-*β*, respectively. The finding that the major reaction paths proceed via α-folding of the polyalkene chain is in accord with earlier findings concerning the PET-triggered cyclizations of shorter terpenoid chains.[9]

Removal of the chiral auxiliary (−)-menthone, which can be recovered, from the major photoproducts **5** and **8** with NaOMe in MeOH renders in excellent yields (91 and 95%, respectively, of isolated materials) the steroidal products **10** and *ent*-**10**,[15] which demonstrates the viability of the induction principle (Scheme 2). These tetracyclic products exhibit uniformly all-trans ring fusions and a substituent pattern at C(17) which is appropriate for further functionalizations at this center, e.g., for chain elongations. The overall number of steps required for the assembly of these steroidal skeletons in >99% enantiomeric excess[16] is merely four, and the preparations start from readily available materials.

In conclusion it should be noted that in the cyclization cascades **4** → **5**/**6** and **7** → **8**/**9** *eight stereogenic centers are created in a single operational step and only 2 out of 256 possible isomers are formed* in 10−12% yield (isolated products)—a (photo)-synthetic achievement which can hardly be surpassed by stepwise techniques. In addition these transformations represent a *remarkably remote asymmetric induction*,[17] substantiating further the theory of "minimal enzymatic assistance"[4] in biosynthesis and ultimately giving access to the hitherto shortest biomimetic synthesis of steroidal skeletons in enantiomeric pure form.[18,19]

Acknowledgment. This paper is dedicated to Professor M. V. George of the Regional Research Laboratory, Trivandrum, India, on the occasion of his 70th birthday. We acknowledge continuous encouragement and support of this work by Professor Kurt Schaffner and generous financial support of our research by the Ministry of Research of the State North-Rhine Westfalia (support of projects related to the use of solar energy for photochemical synthesis).

Supporting Information Available: Experimental procedures and characterization data for compounds **4**−**10** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA984035Z

(15) ^{1}H NMR spectroscopy with Eu(tfc)$_3$ and measurement of optical rotations. Details can be found in the Supporting Information.

(16) The enantiomeric purity of **10** and *ent*-**10** follows from the diastereomeric purity of **5** and **8**. Moreover, it was confirmed by ^{1}H NMR spectroscopy with the chiral shift reagent Eu(tfc)$_3$.

(17) For some recent examples of remote asymmetric inductions, see: (a) Tanaka, K.; Ohta, Y.; Fuji, K. *J. Org. Chem.* **1995**, *60*, 8036−8043. (b) Stanway, S. J.; Thomas, E. J. *Synlett* **1995**, 214−216. (c) Stanway, S. J.; Thomas, E. J. *Tetrahedron Lett.* **1995**, *36*, 3417−3420. (d) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779−10780. (e) Linnane, P.; Magnus, N.; Magnus, P. *Nature* **1997**, *385*, 799−801. (f) Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265−1276. (g) ref 8.

(18) The shortest, albeit not asymmetric, synthesis of a steroid has in the past been performed in a one-pot multicomponent procedure: Posner, G. H.; Mallamo, J. P.; Black, A. Y. *Tetrahedron* **1981**, *37*, 3921−3926.

(19) The title expression *steroid* refers in the present case to steroidal skeletons embodying additional three methyls at C(4) and C(8) which derive from the readily available starting terpenoid polyalkene used for convenience.