Light-Induced Polyene Cyclizations *via* Radical Cations in Micellar Medium†

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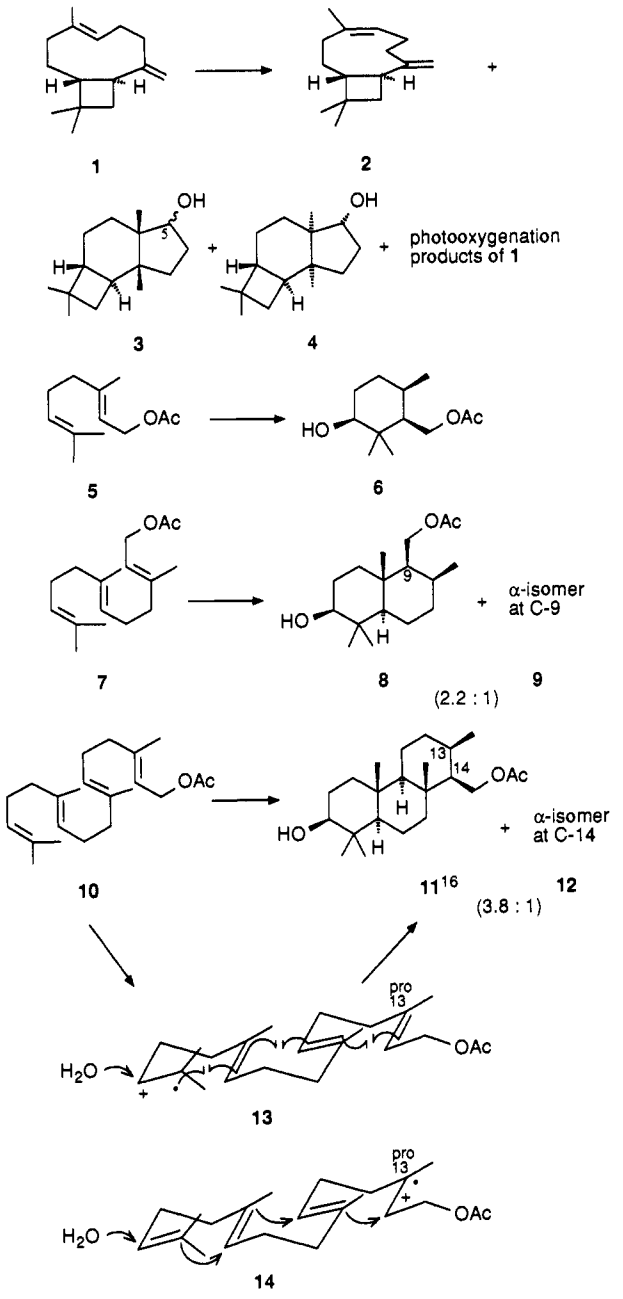
With a series of isoprenoid polyenes such as *trans*-caryophyllene (**1**) and the acetates of *trans*-geraniol (**5**), *all-trans*-farnesol (**7**), and *all-trans*-geranylgeraniol (**10**), we have been studying[1,2] light-induced cyclizations (Scheme I) in microheterogeneous medium with an emphasis on consecutive bond-forming reaction cascades triggered by single electron transfer (SET).[3] We now report that such transformations constitute a synthetically powerful method for the rapid buildup of arrays of stereogenic centers. Furthermore, we propose that radical cationic intermediates—such as the ones produced in this work photochemically[4]—could potentially play a role in the biogenesis of natural products in addition to the cationic intermediates invoked in classical concepts[5,6] and especially in nonoxidative cyclization processes for terpene biosynthesis.[7]

Whereas irradiation of *trans*-caryophyllene (**1**) in homogeneous solution (CH_3CN/water 20/1) in the presence of an electron acceptor such as 1-cyanonaphthalene (1-CN) or 1,4-dicyanobenzene (1,4-DCB) causes merely (*E*)/(*Z*) isomerization (**1** ⇄ **2**), competing transannular cyclization, affording **3**[8,9] and **4**,[8,9] is observed on irradiation in argon-flushed anionic micellar medium [sodium dodecyl sulfate (SDS)].[10] Seemingly, these products result from scavenging[11] of radical cationic intermediates by water[12] in an *anti-Markovnikov*[11] sense. This mode of interception of radical cations by nucleophiles is typical of SET processes. In addition to the tricyclic stereoisomers **3** and **4**, photooxygenation products of **1** are formed (note that it is difficult to remove oxygen entirely from a micellar solution).[1,2]

Scheme I



† Dedicated to Professor G. O. Schenck (Mülheim) on the occasion of his 80th birthday.

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§ The X-ray analyses reported herein were performed by the crystallographic service group directed by C.K., Max-Planck-Institut für Kohlenforschung, D-45413 Mülheim an der Ruhr.

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(1) Hoffmann, U. Ph.D. Thesis, Max-Planck-Institut für Strahlenchemie/University of Essen, 1989.

(2) For preliminary communication of parts of this work, see proceedings of IUPAC Conference on Photochemistry: Hoffmann, U.; Klinge, S.; Demuth, M. Light-Induced Cyclisations via Radical Cations, Warwick, England, 1990, p P249; Third Belgian Org. Synth. Symposium: Hoffmann, U.; Klinge, S.; Demuth, M. Biomimetic Olefinic Cyclisations via Light-Induced Radical Cations, Leuven, 1990, p B39; First Int. Symp. Molecular Mech. of Electron Transfer—Basics of Solar Energy Storage: Hoffmann, U.; Klinge, S.; Demuth, M. Light-Induced Biomimetic Reactions via Radical Cations, Cairo, Egypt, 1991.

(3) For a survey on SET processes, see: *Photoinduced Electron Transfer*; Fox, M. A., Chandon, M., Eds.; Elsevier: New York 1988; Parts A–C.

(4) For a survey on the generation and reactions of radical cations, see: Roth, H.-D. *Top. Curr. Chem.* **1992**, *163*, 131–245.

(5) The concept invoking cationic intermediates was set forth independently by two groups: Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890–1904. Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068–5077. For a recent reference to cationic biomimetic polyene cyclizations, see: Johnson, W. S.; Chenera, B.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 493–497.

(6) Interestingly, a free-radical mechanism has also been proposed for the oxidative cyclization of squalene, albeit yet without experimental evidence: Breslow, R.; Barrett, E.; Mohacsi, E. *Tetrahedron Lett.* **1962**, 1207–1211.

(7) For a discussion of the biosynthesis of tetrahymanol and related compounds under anaerobic conditions, see: Caspi, E. *Acc. Chem. Res.* **1980**, *13*, 97–104.

(8) The structures were extensively characterized by IR (Bruker HFS-66), MS (Finnigan MAT 311A-DF), ^1H–^1H COSY, ^{13}C–^1H COSY, and NOESY (2D NMR spectra were recorded on a Bruker AM-400 instrument). For data, see supplementary material.

(9) GLC analysis after 91% conversion of 18 mmol of **1** in the presence of 26 mmol of 1-CN (20 h of irradiation): 10% 5β isomer of **3**, 11% 5α isomer of **3**, 6% **4**. Isolation of components by preparative GLC.

(10) Irradiations were conducted in a Rayonet reactor equipped with RPR 300-nm lamps. The concentration of SDS was above the critical micellar concentration in water.

(11) Maroulis, A. J.; Shigemitsu, Y.; Arnold, D. R. *J. Am. Chem. Soc.* **1978**, *100*, 535–541.

(12) Gassman, P. G.; Olson, K. D.; Walter, L.; Yamaguchi, R. *J. Am. Chem. Soc.* **1981**, *103*, 4977–4979.

(13) Structure determined by X-ray crystallographic analysis; details will be published in a full account. For a free-radical cyclization of geranyl acetate in very low yield, see: Kuehne, M. E.; Damon, R. E. *J. Org. Chem.* **1977**, *42*, 1825–1832.

(14) Yields refer to chromatographically isolated and >95% pure **6**, **8**, **8** + **9**, and **11** + **12**; **8** can be separated cleanly from **8** + **9** by careful chromatography. Repeated crystallizations of **11** + **12** from ethyl acetate afforded white crystalline **11** (mp 183–185 °C).[16]

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Similarly, irradiation of *trans*-geranyl acetate (**5**) in aqueous SDS solution (1–CN, λ_{irr} 300 nm) gives rise to formation of the six-membered cyclic product **6**[8,13] as the major component of the reaction mixture in 2–4% yield.[14] As in the previous example, cyclization occurs only in microheterogeneous and not in homogeneous media where (*E*)/(*Z*) isomerization is again the major event observed. The indispensibility of SDS for the cyclization processes can only be speculated upon at this stage of the investigation. It may be responsible for enhanced separation and hence longer lifetimes of the intermediate radical ion pairs as well as for the proper folding of the substrates. To test the reactivity of homologs of **6**, *all-trans*-farnesyl acetate (**7**) and *all-trans*-geranylgeranyl acetate (**10**)[15] were individually subjected to the same reaction conditions. Again, cyclizations took place only in the presence of SDS. **7** and **10** gave *trans* ring-fused products including the main components **8** and **11** (X-ray analysis)[16] plus their C-9α and C-14α isomers **9** and **12**, respectively (2–6% yields).[8,14] Despite the low yields, these results are remarkable since the regio- and stereoselective incorporation of water together with the formation of *trans* ring fusions mirror features characteristic of the biogenetic derivation of terpenes *via* cationic cyclizations and especially of those from nonoxidative processes.[7] Mechanistically, the products could either derive from free-radical-type (*via* **13**) or ionic (*via* **14**) *all*-chair cyclizations as exemplified for **10** → **11** (note that the corresponding chair/chair/boat folding would lead to **12**). An important question concerns scavenging of the free-radical site which develops at C-13 during such a sequential bond-forming cascade in any mechanistic event from **13** or **14**. Formally, three options for saturation at C-13 are conceivable, i.e., (a) reduction of the C-13 radical by 1-CN$^{\bullet-}$ to form a C-13 anion prior to protonation, (b) disproportionation, and (c) hydrogen abstraction by the C-13 radical, potentially from unreacted polyenes. The first option, albeit rather unlikely in view of the expected instability of an intermediate C-13 carbanion, can be ruled out since cyclization in D_2O/SDS does not lead to C-13 deuteriation; the second option does not apply to the given example since no olefinic cyclization products were detected.[17]

A preparative improvement[18] of the transformations of **5**, **7**, and **10** in aqueous SDS with 1,4-DCB can be achieved when phenanthrene is added to the reaction mixture as sensitizer[19] and the irradiation is conducted either at λ 350 nm (Rayonet reactor) or with a mercury medium-pressure lamp (Pyrex immersion well), i.e., conditions under which phenanthrene is excited predominantly. The product yields are improved to 8% for **6** and 20–25% for **8**/**9** and **11**/**12** with unchanged isomer ratios.[14]

These reactions, the yields of which are not yet optimized, constitute the first examples of photochemically triggered biomimetic-type terpene cyclizations *via* single electron transfer. The reactivity of further biogenetically relevant substrates, structural modifications to the substrates studied thus far, and variations of the reaction conditions to improve the preparative feasibility of such sequential cyclizations are under study.

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Supplementary Material Available: Listings of crystal data, atomic coordinates, bond distances and angles, and thermal parameters for **11**, and characterization data for compounds **6**, **8**, **8** + **9**, and **11** + **12** (10 pages); listings of observed and calculated structure factors for **11** (12 pages). Ordering information is given on any current masthead page.

(15) The literature procedure for the preparation of *all-trans*-geranylgeraniol (Coates, R. M.; Ley, D. A.; Cavender, P. L. *J. Org. Chem.* **1978**, *43*, 4915–4922) has been significantly improved (Klinge, S.; Demuth, M. *Synlett* **1993**, 783–784): (a) Wittig condensation on farnesyl acetone, performed with diisopropylethyl phosphonoacetate, affords geranyl geranate in 90% yield (*cis*/*trans* 1/10) and (b) reduction to geranylgeraniol, carried out with $LiAlH_4$ in the presence of $AlCl_3$, gives the isomerically pure product in 44% isolated overall yield from farnesyl acetone.

(16) X-ray crystal structure of **11** (see also supplementary material). A suitable crystal (0.35 × 0.32 × 0.11 mm) was mounted under argon in a glass capillary. Data ($\pm h+k+l$) were collected at room temperature on an Enraf-Nonius CAD-4 diffractometer with graphite monochromated Cu Kα radiation (λ = 1.541 78 Å). Cell constants and systematic absences correspond to space group No. 15 ($C2/c$) with cell dimensions a = 50.703(9) Å, b = 7.349(1) Å, c = 10.896(1) Å, β = 95.99(2)°, V = 4037.6 Å^3; Z = 8, calculated density = 1.15 g·cm^{-3}, $F(000)$ = 1552e, and μ = 5.46 cm^{-1} (no absorption correction applied). A total of 8228 reflections were collected, of which 4136 were unique (R_{av} = 0.03). 3213 observed reflections were used for the structure solution (direct methods, SHELXS-86) and subsequent full matrix least-squares refinement. R = 0.095, R_w = 0.120; final residual electron density = 0.27 eÅ^{-3}.

(17) NMR spectra of the crude reaction mixture do not reveal olefinic products in concentrations similar to those of **11**/**12**.

(18) Typical procedure: 2.2 mmol of polyene, 2.5 mmol of 1,4-dicyanobenzene, and 2.5 mmol of phenanthrene were added to 150 mL of Ar-flushed 0.5 M aqueous sodium dodecyl sulfate solution. After being stirred for 1 day, the transparent solution was irradiated either in a Rayonet RPR-100 photoreactor, equipped with RPR 350-nm lamps, or with a mercury medium-pressure lamp in a Pyrex immersion well. The reaction was monitored by GLC and brought to >95% conversion of polyene within 6–12 h. The reaction mixture was then cooled to 0 °C, and dichloromethane and calcium chloride solution were added. Both the precipitate, which is filtered off, and the aqueous layer were carefully washed with dichloromethane before the combined organic layers were dried over sodium sulfate. Evaporation gave a yellowish residue which was flash chromatographed on silica gel (Merck, silica 60, 150-fold, *n*-pentane/ethyl acetate 10:1 → 1:1), rendering fractions of **6**, **8**, **8** + **9**, and **11** + **12**, each in >95% purity as judged by GLC and ^{1}H NMR.

(19) For mechanistic considerations with regard to the 1,4-DCB/phenanthrene sensitizer couple, see: Arnold, D. R.; Snow, M. S. *Can. J. Chem.* **1988**, *66*, 3012–3026. At this stage of our investigation, we can only speculate about reasons for the observed improvement; possibly the relatively high energy content of the excited sensitizer couple may be of importance. Other combinations such as 1-CN or 1,4-DCB in conjunction with biphenyl as a cosensitizer were far less effective.