Biomimetic Cascade Cyclizations of Terpenoid Polyalkenes *via* Photoinduced Electron Transfer. Long-Distance Asymmetric Induction by a Chiral Auxiliary

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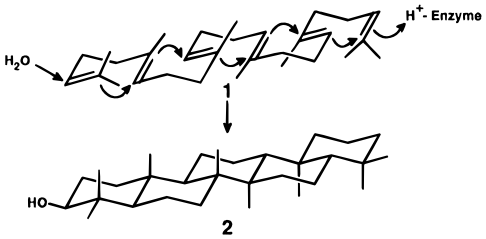
Reported herein are the first examples of highly diastereoselective cascade cyclizations of terpenoid polyalkenes *via* photoinduced electron transfer (PET)[1] by means of the chiral auxiliary (−)-menthone, which is remotely located from the initiation site of the reactions. These transformations give ready access to functionalized and enantiomerically pure cyclic terpenoids.

In addition to the biosynthesis of polycyclic triterpenoids *via* cationic cyclizations of (3*S*)-2,3-oxidosqualene, some bacteria and protozoans produce pentacyclic 3-deoxytriterpenes, such as tetrahymanol (**2**), *via* a nonoxidative cyclization mode of squalene (**1**).[2] It is generally accepted that in these processes the folding of squalene in an all-prechair conformation prior to the cyclization is supported by a cyclase (Scheme 1).[2,3]

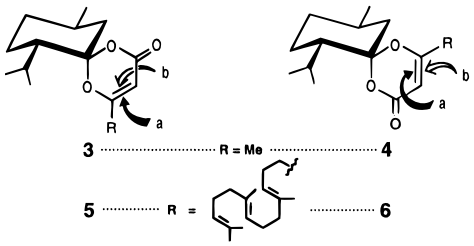
Such biosynthetic transformations have been mimicked by cationic as well as radical-type cyclizations. The former class is based on the pioneering work of Eschenmoser, Ruzicka, Jeger, and Arigoni[4] and of Stork and Burgstahler[5] and has been well documented in the literature.[6] Biomimetic processes triggered by radicals were first investigated by Breslow.[7] In this context we have demonstrated[8] the potential of photoinduced radical cations[9,10] for triggering cascade cyclizations[11] of terpenoid polyalkenes to mimic nonoxidative biosynthetic transformations. A further goal, the subject of this paper, was to efficiently induce asymmetry in such cyclizations.

In radical[11a,12] and cationic cyclizations,[13] in the course of which high asymmetric inductions have been achieved, the chiral information is in close spatial proximity to the centers which transform into the initially formed stereogenic carbon atoms. When such prerequisites are not fulfilled, low diastereoselection is generally encountered.[6b,14]

Scheme 1



Scheme 2



Surprisingly, asymmetric induction in PET-triggered cyclizations of **5** and **6** (Scheme 2) proved highly successful, although the chiral auxiliary (−)-menthone is very remotely located from the initiation site of the cyclizations (i.e., the radical cation of the ω-alkene (Scheme 3)). Thus, compound **5** afforded the photoproducts **7** and **9** in a 20:1 ratio upon irradiation (Rayonet reactor, $\lambda_{max} = 300$ nm) with 1,4-dicyano-2,3,5,6-tetramethylbenzene and biphenyl as an electron-acceptor couple in MeCN/H_2O[15] 10:1 at −25 °C. The combined yield after chromatography on silica gel was 21%. Conversion of **6** to **11** and **13**, under the same reaction conditions, exhibited an appreciable but lower selectivity (1:3 ratio, 23% yield).[16] In these processes, water adds in *anti-Markovnikov* sense to the radical cation site of the polyalkenes[9] and the cyclization cascades are typically terminated by 5-*exo*-trig ring closures. The latter feature is in agreement with earlier findings concerning cyclizations of substrates which contain an electron deficient alkene.[8b,c] Formation of further fully cyclized diastereomeric products in more than 3% of **7** and **13** can be ruled out by NMR spectroscopy. The starting materials (i.e., the terpenoid polyalkenes **5** and **6**) were prepared by coupling (*E*,*E*)-farnesyl bromide with the 1,3-dioxin-4-ones **3** and **4**, both of which are readily available by reaction of (−)-menthone and diketene in the presence of *p*-toluenesulfonic acid.[17] Removal of the chiral auxiliary (−)-menthone from **7** and **9** with NaOH in MeOH/H_2O followed by treatment with TMSCl (trimethylsilyl chloride) in MeOH afforded the enantiomerically pure[18] tricyclic esters **8** and **10** in 86 and 90% yield, respectively. For **11** and **13**, it was possible to cleave the dioxanone moiety with NaOMe in MeOH

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(2) For a recent review, see: Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189−2206.

(3) Caspi, E. *Acc. Chem. Res.* **1980**, *13*, 97−104.

(4) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890−1904.

(5) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068−5077.

(6) For recent reviews on cationic polyene cyclizations, see: (a) Johnson, W. S. *Tetrahedron* **1991**, *47*, xi−xlix. (b) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 341−377.

(7) (a) Breslow, R.; Barrett. E.; Mohacsi, E. *Tetrahedron Lett.* **1962**, 1207−1211. (b) Breslow, R.; Olin, S. S.; Groves, J. T. *Tetrahedron Lett.* **1968**, 1837−1840.

(8) (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*. In press.

(9) Such cyclization cascades, triggered by radical cations, are rather of radical-type since the initial radical cation is likely trapped by water prior to the cyclization event. (X. Xing, Ph.D. Thesis, Max-Planck-Institut für Strahlenchemie/Universität-GH Essen, in preparation.)

(10) Roth, H. D. *Top. Curr. Chem.* **1992**, *163*, 131−245.

(11) For other recent references to cascade cyclizations *via* radical intermediates, see: (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339−363. (b) Batsanov, A.; Chen, L.; Gill, G. B.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 45−55. (c) Zoretic, P. A.; Zhang, Y.; Ribeiro, A. A. *Tetrahedron Lett.* **1996**, *37*, 1751−1754.

(12) See, *inter alia*: (a) Porter, N. A.; Lacher, B.; Chang, V. H.-T.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, *111*, 8309−8310. (b) Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtake, Y.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc.* **1994**, *116*, 6455−6456.

(13) For some examples, see: (a) Johnson, W. S.; DuBois, G. E. *J. Am. Chem. Soc.* **1976**, *98*, 1038−1039. (b) Macco, A. A.; Buck, H. M. *J. Org. Chem.* **1981**, *46*, 2655−2660. (c) Fish, P. V.; Johnson, W. S.; Jones, G. S.; Tham, F. S.; Kullnig, R. K. *J. Org. Chem.* **1994**, *59*, 6150−6152.

(14) Kato, T.; Kumazawa, S.; Kitahara, Y. *Synthesis* **1972**, 573−574.

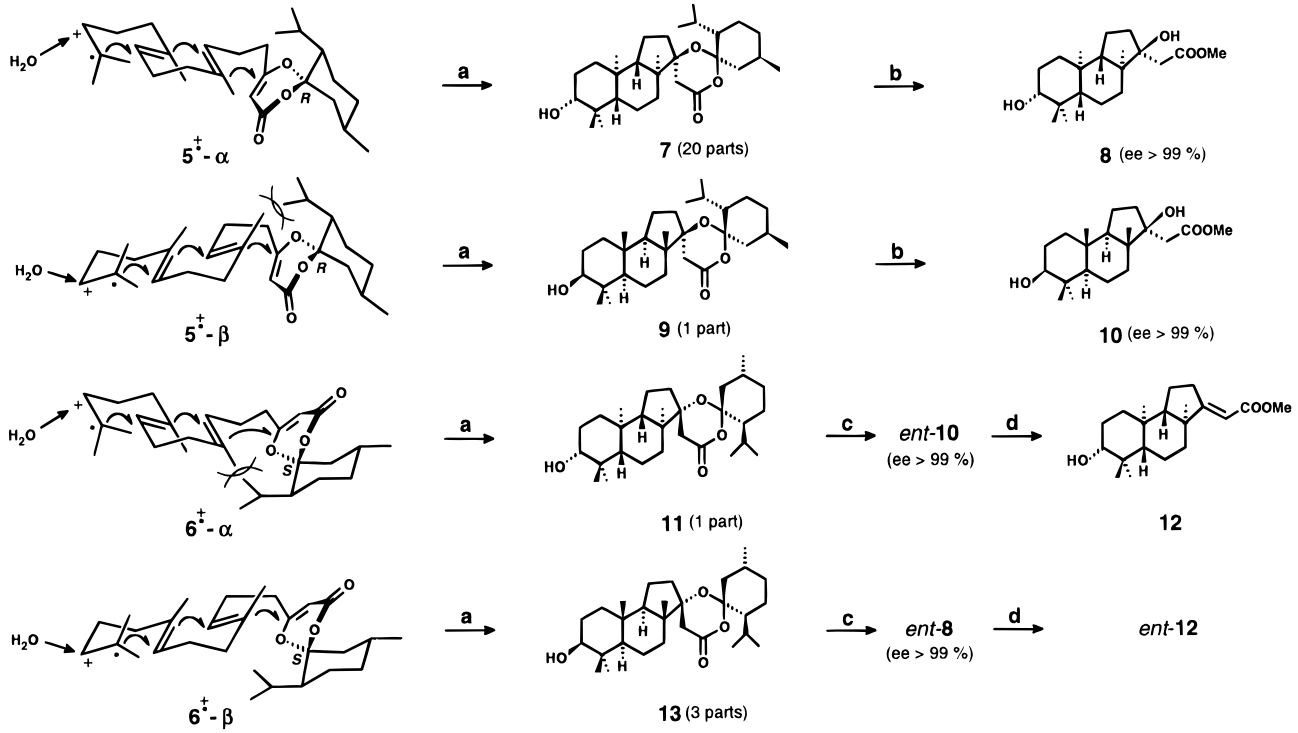
(15) MeCN is, in view of its ϵ value, a routine solvent for PET reactions (ref 1, 10). H_2O acts as nucleophile; in other cases MeOH has also been used successfully instead (ref 8b).

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

(17) For the synthesis, availability, applications, and patents of **3** and **4** 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) Compounds **3** and **4** are available from Merck. (e) The preparation and use of **3** and **4** are patented: Demuth, M.; Schaffner, K. EPPS 0254239 B1 (1992); USP 5026877, 5142054, and 4864037 (1991).

S0002-7863(96)02479-1 CCC: $14.00

Scheme 3[a]



[a] Reagents and conditions: (a) biphenyl, 1,4-dicyano-2,3,5,6-tetramethylbenzene, *hν* (300 nm), MeCN/H_2O 10:1, −25 °C, 21% (**7** and **9**), 23% (**11** and **13**); (b) 1. NaOH, MeOH/H_2O, 25 °C; 2. TMSCl, MeOH, 25 °C, 86% (**8**), 90% (**10**); (c) NaOMe, MeOH, 25 °C, 97/98%; (d) $SOCl_2$, pyridine, 0 °C, 40% (**12**), 34% (*ent*-**12**).

quantitatively, giving the enantiomeric tricyclic esters *ent*-**8** and *ent*-**10**, respectively.[18,19] The absolute configurations of all compounds reported have been elucidated in the following way. The structures of **8** and *ent*-**8**[19] were secured by an X-ray single-crystal analysis of **7**. Elimination of water from *ent*-**8** afforded *ent*-**12** which in turn allowed the assignment[19] of the structures of **10**, *ent*-**10**, **12**, and *ent*-**12**.

In addition to the high chemo- and regioselectivities, the cyclizations of **5** and **6** are subject to exclusive a-side diastereofacial differentiation (Scheme 2) and asymmetric induction from the auxiliary at one end across the molecule to the other end of the polyalkene chain.[20] Interestingly, this a-side reaction selectivity of the dioxinone moieties, which is evident from the configurations of the newly formed spiro carbon atoms in **7**, **9**, **11**, and **13**, agrees with earlier observations concerning [2 + 2] photocycloadditions of **3** and **4**.[17] The a-side attack excludes effective shielding by the isopropyl group and is apparently determined conformationally.[17a] The face selectivities of the cyclizations are again the key to accessing enantiomers by the use of only a single chiral auxiliary (i.e., (−)-menthone).[17,21] The achiral analogue of **5** and **6** with geminal dimethyls replacing the (−)-menthylidene moiety afforded under identical reaction conditions two racemic photoproducts in 2:1 diastereoselection and 20% yield. Cleavage of the dioxanone ring of these photoproducts with NaOMe in MeOH gave *rac*-**8** and *rac*-**10** from the major and minor product, respectively (100% yield).[18] In view of comparable yields of the cyclizations of **5**, **6**, and the achiral analogue, such efficient long-distance asymmetric induction is most likely the result of highly selective folding of the polyalkene chain (cf., proposed conformations **5**-α/-*β* and **6**-α/-*β* or the radical cations thereof) prior to or shortly after the photochemical oxidation of the *ω*-alkene.[22] Spectroscopic investigations into this finding are currently in progress. Inspection of models reveals that the foldings as represented by $\mathbf{5}^{\bullet+}$-*β* and $\mathbf{6}^{\bullet+}$-α are sterically disfavored, when compared to the conformations $\mathbf{5}^{\bullet+}$-α and $\mathbf{6}^{\bullet+}$-*β*, by methyl interactions.

In summary, these photochemical cyclizations demonstrate an efficient method of generating enantiomerically pure *all-trans*-fused tricyclic terpenoids possessing six new asymmetric centers, the chirality of which can be controlled by the use of the dioxinones **3** and **4**, both of which are prepared from the single chiral auxiliary (−)-menthone. After removal of the auxiliary basic product skeletons, including *anti-Markovnikov* addition of water, are obtained which otherwise are typically derived from biosynthetic transformations. Additionally, these results constitute strong evidence of spontaneous folding of the terpenoid polyalkene chain supporting the idea of "minimal enzymatic assistance" in nonoxidative biosynthesis.[2,3]

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Supporting Information Available: Experimental procedures and characterization data for compounds **5**−**13** (12 pages). See any current masthead page for ordering and Internet access instructions.

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(18) The enantiomeric purity of **8**, **10**, *ent*-**8**, and *ent*-**10** follows from the diastereomeric purity of **7**, **9**, **11**, and **13**. Moreover, it was confirmed by ^{1}H NMR spectroscopy with the chiral shift reagent Eu(tfc)$_3$. Compounds *rac*-**8** und *rac*-**10**, prepared from 2,2,6-trimethyl-1,3-dioxin-4-one, an achiral analogue of **3** and **4**, served as racemic reference samples.

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

(20) Bicyclizations of the analogous optically pure geranyl derivatives furnished (*Z*)-fused 6,5-ring products, again demonstrating exclusive a-side diastereofacial differentiation, but at a low asymmetric induction through folding of the polyalkene chain. Similarly, cyclizations of the optically pure prenyl derivatives each afforded two diastereomeric 5-membered ring products, all resulting from an a-side attack (C. Heinemann and M. Demuth, unpublished results).

(21) For discussions concerning the face selectivity in various other applications of dioxinones, see: (a) Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 4763−4772. (b) Sato, M.; Uehara, F.; Kamaya, H.; Murakami, M.; Kaneko, C.; Furuya, T.; Kurihara, H. *J. Chem. Soc., Chem. Commun.* **1996**, 1063−1064 and references cited therein.

(22) For evidence of precoiling in cationic bicyclizations processes, see: (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, pp 341−409. (b) Reference 13b.