Polyene Cyclizations Related to Oxidosqualene Cyclization. A Model for the Anti-Markovnikov Closure of Ring C

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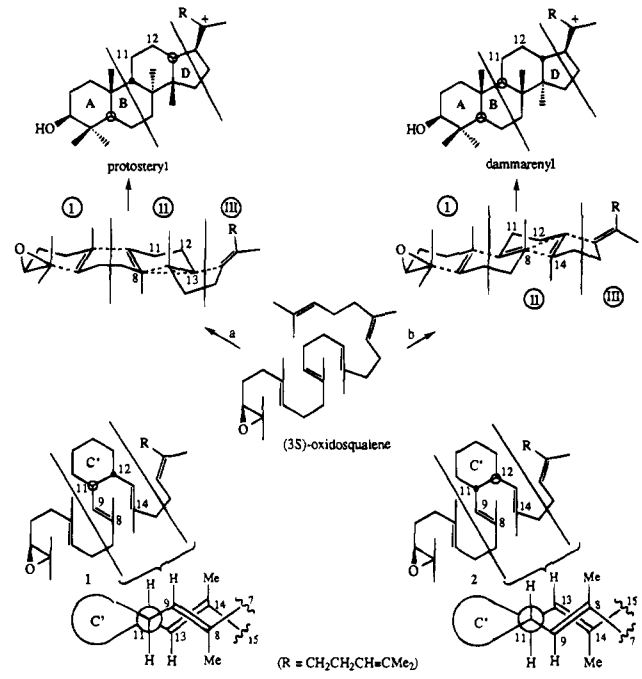
The polycyclization of (3*S*)-2,3-oxidosqualene to the tetracyclic protosteryl cation, one of the several steps involved in the biosynthesis of steroids, still remains a unique transformation (Scheme 1). The resulting stereochemistry is in accord with a cyclization with the polyene folded in a prechair−preboat−prechair conformation (pathway a). The analogous cyclization leading to pentacyclic triterpenes via the dammarenyl cation would proceed through the corresponding prechair−prechair−prechair geometry (pathway b).[1] Following the 1955 Stork−Eschenmoser postulate,[2] systematic studies, in particular in the laboratories of Johnson[3] and of van Tamelen,[4] have confirmed that cation-induced concerted polyene cyclizations do occur via antiparallel addition, hence with conservation of the π-stereochemistry, in a process whereby the resulting six-membered rings normally adopt chair conformations, and where the regioselectivity issue is invariably regulated by the stability of the resulting carbocations in compliance with Markovnikov's rule.[5] The quest of uncovering the exact role of the enzyme in the biogenetic cyclization has initiated decades of bioorganic studies in which the enzymatic cyclization of a variety of oxidosqualene analogues was investigated.[1] These have led to a detailed understanding of the substrate structural requirements and of the specificity and stereochemistry of the cyclization.[6,7] Whereas most aspects of the biocyclization have been successfully reproduced under nonenzymic conditions, the non-Markovnikov ring C closure remains exceptional; indeed, upon acid treatment of oxidosqualene there have been isolated, besides a bicyclic product with rearranged backbone (20−25% yield), two tricyclic products (25−30% yield) with a five-membered C-ring in accord with the formation of the thermodynamically favored

Scheme 1



tertiary cation.[8] In this context we report now on the Lewis acid catalyzed cyclization of the simple polyene aldehyde **3**, designed so as to enforce ring closure to the "natural" CD-ring system.

The present study is part of a project in which we wish to study the possibility that the full course of the oxidosqualene cyclization would be determined by one specific localized torsion at bond 11−12 in the acyclic precursor polyene.[9] The following observations are at the basis of this hypothesis (Scheme 1). Of the three regions I−III that one may distinguish within the cyclization process, the central region II is the most critical: (i) its orientation relative to the (*S*)-epoxide moiety determines, at least in a concerted pathway, if the protosteryl or dammarenyl cation is formed; (ii) it incorporates the chemically unchallenged anti-Markovnikov closure of ring C; and (iii) it may also be involved in the final construction of the side chain, in particular the stereospecific obtention of C-20. The enantiomeric relation of this particular region in both series and the presence of a pseudo-C_2 axis through bond 11−12 within region II suggest that the sense of chirality of the torsion at 11−12 could eventually determine the outcome of the process. In addition, the magnitude of the torsion could be responsible for induction of anti-Markovnikov C-ring closure (*vide infra*). In this context the study of the ring closure of epoxides such as **1** and **2** should allow for eventual confirmation. The role of the six-membered C′-ring at 11−12 consists of enforcing the relative orientation of the two polyene chains in one or the other chiral sense as illustrated by the Newman projections, hence determining the cyclization pathway that is followed. Moreover, due to the presence of this extraneous ring, ring C upon concerted cyclization becomes connected to two other rings (i.e., the B- and C′-rings) via *trans*-fusions at 11−12 and at 8−9. The resulting strain is expected to be better accommodated by a six-membered than a smaller five-membered ring size, hence possibly favoring ring closure toward the anti-Markovnikov product.[10] Finally, due to the presence of the C′-ring the

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

(2) (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068−5077. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890−1904.

(3) (a) Johnson, W. S. *Tetrahedron* **1991**, *47* (41), xi−xxiv. (b) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 8341−8343.

(4) (a) van Tamelen, E. E. *Pure Appl. Chem.* **1981**, *53*, 1259−1270. (b) van Tamelen, E. E.; Hwu, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2490−2491.

(5) For recent reviews on polyene cyclizations, see: (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 341−409. (b) Taylor, S. K. *Org. Prep. Proced. Int.* **1992**, *24*, 245−284. (c) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York; 1991; Vol. 3, pp 341−377.

(6) For studies especially relevant to the formation of the C and D rings, see: (a) van Tamelen, E. E.; Leopold, E. J.; Merson, S. A.; Waespe, H. R. *J. Am. Chem. Soc.* **1982**, *104*, 6479−6480. (b) Krief, A.; Schauder, J.-R.; Guittet, E.; du Penhoat, C. H.; Lallemand, J.-Y. *J. Am. Chem. Soc.* **1987**, *109*, 7910−7911. (c) Corey, E. J.; Virgil, S. C.; Liu, D. R.; Sarshar, S. *J. Am. Chem. Soc.* **1992**, *114*, 1524−1525.

(7) For a seminal study relevant to the selective obtention of the (20*R*) stereochemistry, see: (a) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1991**, *113*, 4025−4026. (b) Corey, E. J.; Virgil, S. C.; Sarshar, S. *J. Am. Chem. Soc.* **1991**, *113*, 8171−8172.

(8) (a) van Tamelen, E. E.; Willet, J.; Schwartz, M.; Nadeau, A. *J. Am. Chem. Soc.* **1966**, *88*, 5937−5938. (b) Sharpless, K. B.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1969**, *91*, 1848−1849.

(9) The numbering used throughout the paper is consistent with the usual steroid numbering.

(10) Full details are provided in the supplementary material section.

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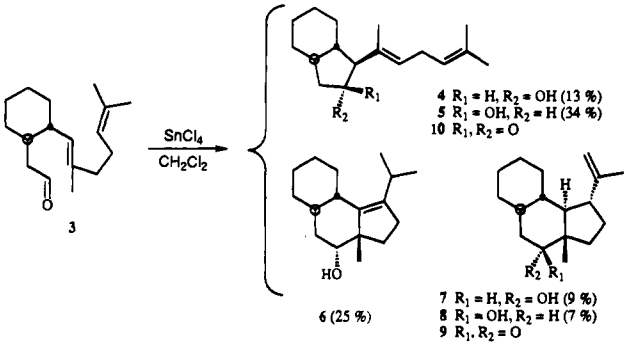
Scheme 2

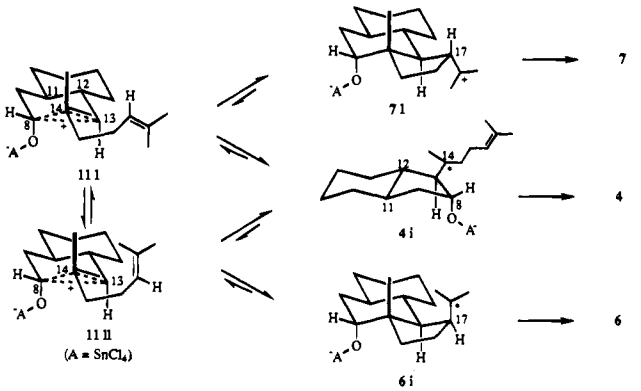


proximity of C-8 and C-14 is enforced. This should ease the entropic burden inherent in a polycyclization and help favor a concerted pathway beyond the second cyclization.[11] As a first and simple model in the investigation of the above hypothesis we report on the successful cyclization of aldehyde **3** with formation of anti-Markovnikov ring closed products.

In a typical cyclization experiment, aldehyde **3**[12] in CH_2Cl_2 (0.03 M) is treated with $SnCl_4$ (0.5 equiv) at room temperature (15 min; saturated $NaHCO_3$ workup; 75% yield). The relative concentrations of the cyclization products **4**–**8** (indicated within parentheses in Scheme 2) were determined separately by GC (three runs) and are representative for the cyclization experiment.[10] The unambiguous structural identification of the different derivatives rests on chemical, spectroscopic, and X-ray diffraction evidence.[10]

Especially the formation of **7** and **8** is noteworthy, since, to the best of our knowledge, this represents the first example of a nonenzymic polyene cyclization that leads to a *trans*-fused angular methyl substituted CD-ring system involving a true anti-Markovnikov closure.[13] A tentative rationale for the formation of the three different α-hydroxy isomers **4**, **6**, and **7** is shown in Scheme 3. Presumably **7** arises from **7i** via, if not a concerted pathway, at least one involving a conformationally rigid partially cyclized carbocationic intermediate such as **11i**.[14] A stepwise process, involving D-ring formation via equatorial attack on the secondary cyclohexyl cation, cannot be excluded at this stage but is regarded as less likely because elimination or rearrangement products from the intermediate cation were not isolated. It is tempting to assume that the elimination product **6** is formed through **11ii** and **6i**. The steric interaction between the angular methyl and the cationic side chain at C-17 in **6i** would then constitute the driving force for the subsequent hydride shift followed by elimination. Other pathways for the formation of

Scheme 3



6 such as a hydride shift–elimination sequence from **7i** or a stepwise process involving the intermediate formation of *cis*-fused derivatives cannot be excluded at this stage.

Obviously, the results obtained so far do not allow any extrapolation as to the possible role of the enzyme in enforcing a torsion at 11–12 as hypothesized above,[15] but certainly warrant further investigations on the cyclization of more elaborate polyenes based on the same 11,12-constrained model. Such studies are currently under way.[16]

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Supplementary Material Available: Synthetic scheme for **3** and spectroscopic data of relevant intermediates, the procedure for the cyclization of **3** and for the isolation and structural identification of the different cyclization products, the procedure for GC analysis of the cyclization mixture, crystallographic data of **6** and **9** including ORTEP figures and tables of positional and thermal parameters, spectroscopic data (^1H NMR, FTIR, MS) of **4**–**10** and of the *p*-nitrobenzoates derived from **4** to **5**, comparison table including experimental and calculated vicinal coupling constants of the *p*-nitrobenzoates of **4** and **5**, and conformational procedure for evaluation of the steric strain of the tetracyclic carbocations (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(11) Concertedness beyond the second ring formation is not likely; see ref 5a and experimental evidence in the following: Johnson, W. S.; Lindell, S. D.; Steele, J. *J. Am. Chem. Soc.* **1987**, *109*, 5852–5853.

(12) The synthesis of **3** involves a nine-step sequence starting from geraniol (see ref 10).

(13) For an electronically biased closure of a polyene including a fluoroalkene moiety, see: Fish, P. V.; Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett.* **1993**, *34*, 7849–7852.

(14) van Tamelen has suggested that the full polycyclization proceeds through a series of discrete conformationally rigid, partially cyclized carbocationic intermediates: van Tamelen, E. E. *J. Am. Chem. Soc.* **1982**, *104*, 6480–6481.

(15) The hypothesis stands in contrast with Johnson's recently proposed model based on transition state stabilization by adequately positioned negative point charges delivered by the enzyme and in which no particular conformational control is required by the enzyme; see ref 22 in the following: Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517–2518. On the other hand Corey's analysis suggests that proper folding is induced by key hydrophobic (methyl) groups of the cyclase; see ref 8 in ref 6c.

(16) A referee correctly pointed out that the true influence of the cyclohexyl ring on the outcome of the cyclization can only be assessed if the result of the acid-catalyzed cyclization of the corresponding acyclic substrate, i.e., (5*E*)-6,10-dimethyl-5,9-undecadienol, were known. This aspect will be studied and included in the full account of this work. On the basis of the result of the cyclization of a similar substrate, i.e., (5*E*)-8-*tert*-butyl-6,11-dimethyl-5,10-dodecadienol, the formation of only five-membered ring closed products is, however, expected; see: Missiaen, P.; De Clercq, P. J.; Van Meervelt, L.; King, G. S. D. *Bull. Soc. Chim. Belg.* **1988**, *97*, 993–1001.