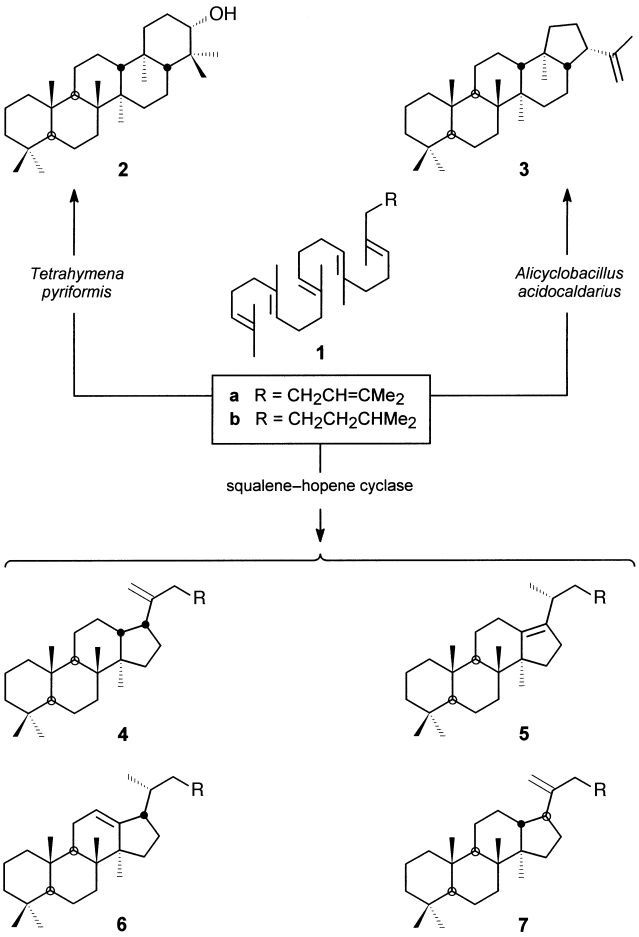
[7] T. J. Boyle, N. W. Eilerts, J. A. Hepert, F. Tagusagawa, *Organometallics* **1994**, *13*, 2218 – 2229.
[8] M. Terada, Y. Matsumoto, Y. Nakamura, K. Mikami, *Inorg. Chim. Acta.* **1999**, *296*, 267 – 272.
[9] E. P. Kyba, G. W. Gokel, F. de Jong, K. Koga, L. R. Sousa, M. G. Siegel, L. Kaplan, G. D. Y. Sogah, D. J. Cram, *J. Org. Chem.* **1977**, *42*, 4173 – 4184.
[10] M. Asakakawa, H. M. Janssen, E. W. Meijer, D. Pasini, J. F. Stoddart, *Eur. J. Org. Chem.* **1998**, 983 – 986.
[11] L. Pu, *Chem. Rev.* **1998**, *98*, 2405 – 2494.
[12] F. Toda, K. Tanaka, M. C. Wong, T. C. W. Mak, *Chem. Lett.* **1987**, 2069 – 2072.
[13] M. Ye, S. Logaraj, L. M. Jackman, K. Hillegas, K. A. Hirsch, A. M. Bollinger, A. L. Grosz, V. Mani, *Tetrahedron* **1994**, *50*, 6109 – 6116.
[14] H. C. Aspinall, J. L. M. Dwyer, N. Greeves, A. Steiner, *Organometallics* **1999**, *18*, 1366 – 1368.
[15] K. Mori, Y. Masuda, S. Kashino, *Acta Crystallogr. Sect. C* **1993**, *49*, 1224 – 1227.
[16] F. Toda, K. Tanaka, H. Myamoto, H. Koshima, I. Miyakara, K. Hirotsu, *J. Chem. Soc. Perkin Trans. 2* **1997**, 1877 – 1885.
[17] R. E. Mulvey, *Chem. Soc. Rev.* **1991**, *20*, 167 – 209.
[18] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-139116 – 139118. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

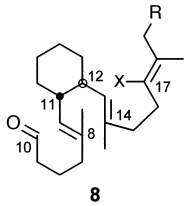
A Model for the Nonenzymatic BCD Cyclization of Squalene**

Sheng-Ze Zhou, Mario Sey, Pierre J. De Clercq,* Marco Milanesio, and Davide Viterbo

The enzymatic polycyclization of squalene (**1a**) and 2,3-oxidosqualene (epoxysqualene) is a fascinating biogenetic process.[1] Whereas oxidosqualene cyclases produce sterols and plant triterpenes, the squalene cyclases (SC) of the protozoan *Tetrahymena pyriformis* and of the thermoacidophilic bacterium *Alicyclobacillus acidocaldarius* convert squalene (**1a**) into tetrahymanol (**2**) and hop-22(29)-ene (**3**, diploptene), respectively.[2, 3] Interestingly, a few years ago it was reported that squalene – hopene cyclase converts non-natural 2,3-dihydrosqualene (**1b**) in high yield into a mixture of the tetracyclic triterpenes (20*R*)-dammar-13(17)-ene (**5b**) and (20*R*)-dammar-12-ene (**6b**) (Scheme 1).[4] More surprising even is the recent report about the isolation, next to the classical hopanoids, of the tetracyclic derivatives **4a**, **5a**, **6a**, and **7a**, each representing less than 2% relative to **3**, when the natural substrate squalene (**1a**) is treated with purified squalene – hopene cyclase.[5] This result raises the intriguing possibility that this enzyme has been "prepared" for performing the seemingly more complex transformation that bears analogy with the formation of lanosterol.[6] In this evolutionary context, however, one fundamental question remains unanswered: what is the nonenzymatic course of the poly-(tetra, penta)cyclization of squalene (and epoxysqualene)? Here we report on the results of the Lewis acid catalyzed cyclization of aldehydes **8a** – **c** that can provide an answer to the above question.



Scheme 1. Triterpenoids originating from cyclization of squalene (**1a**) and 2,3-dihydrosqualene (**1b**) catalyzed by bacterial squalene cyclases.



8

a X = H ; R = $CH_2CH{=}CMe_2$
b X = H ; R = $CH_2CH_2CHMe_2$
c X = D ; R = $CH_2CH_2CHMe_2$

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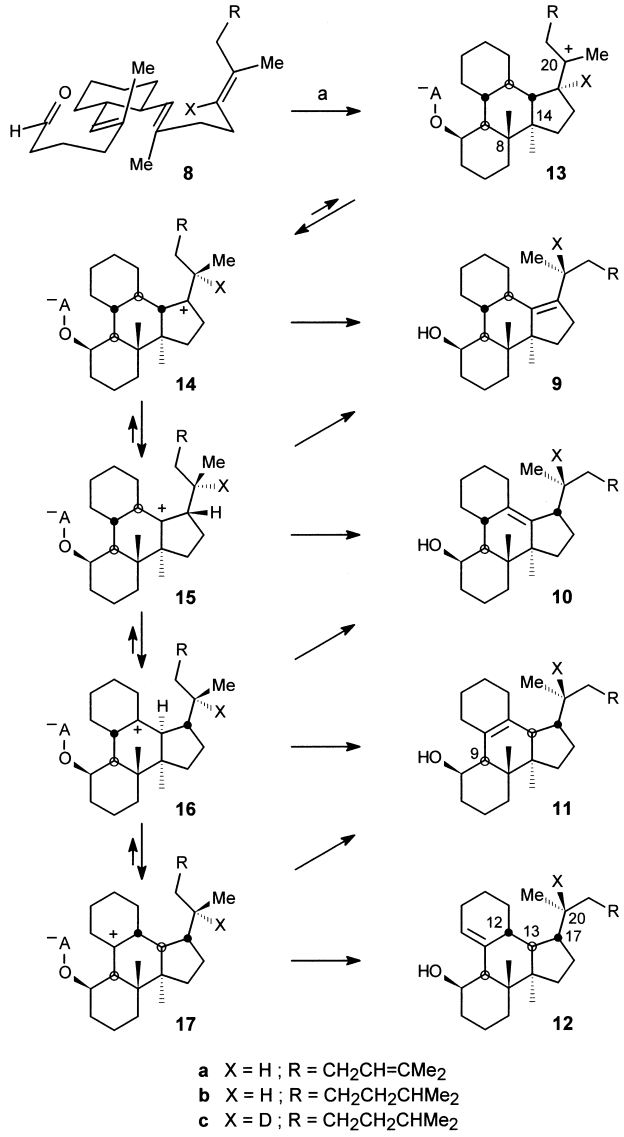
[**] This research was supported by FWO-Vlaanderen. We thank Dr. Davide Proserpio (Università di Milano) and Dr. Annalisa Guerri (Università di Firenze) for the allowance to use the CCD diffractometers.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

  1433-7851/00/3916-2861 $ 17.50+.50/0

The enzymatic conversion of both squalene and epoxysqualene produces a variety of cyclization products depending on the cyclase used. This diversity arises through different folding patterns that are adopted by the polyene in either the early (AB-ring formation) or the late (D- and E-ring formation) stages of the process.[7] On the other hand, all tetra- and pentacyclizations have in common an anti-Markovnikov like closure of the six-membered C-ring. From the mere chemical point of view this third ring closure constitutes a formidable challenge. Not surprisingly, the (Lewis) acid-catalyzed cyclizations of squalene and epoxysqualene afford tricyclic products whose structures, and in particular the resulting five-membered C-ring, are determined by Markovnikov's rule.[8, 9] Considering the C-ring region as the crucial one in the polycyclization, substrates **8**[10] were designed to 1) initiate the cyclization at pro-C10, hence skipping the early stage of the cyclization, and to 2) enforce the anti-Markovnikov six-membered C-ring formation through the incorporation of an extraneous cyclohexane ring at pro-C(11),C(12).[11] The role of the latter consists not only in inducing the prechair geometry of the chain in the 11,12-region through the *trans*-diequatorial substitution and in enforcing the proximity of C8 and C14, which should ease the entropic burden of the polycyclization, but also and foremost in preventing the Markovnikov five-membered C-ring formation; indeed, concerted cyclization should lead to a C-ring that is connected to two six-membered rings by *trans*-fusions at 11,12 and at 8,9—a situation that is better accomodated by a six- than by a smaller five-membered ring.[12] Thus, surmounting the activation energy that is involved with the C-ring formation should enable us to take a view on the nonenzymatic course of the polycyclization beyond the C-ring.

Treatment of aldehyde **8a** under standard conditions (see Scheme 2; saturated $NaHCO_3$ workup) led to an apolar fraction (19%), to a second fraction (48%) consisting of a complex mixture of pentacyclic derivatives (as judged from the absence of the characteristic resonances of the olefinic protons of the polyene chain), and to the two tetracyclic alcohols **9a** (13%) and **12a** (4%).[13] The structure of the latter cyclization product was solved by X-ray diffraction,[14] which revealed, next to a genuine BCD-skeleton containing the two quaternary centers at C8 and C14, a most interesting stereochemical pattern at C12, C13, C17, and C20. Indeed, the latter pattern indicates that **12a** is formed in two steps (Scheme 2): a) the cyclization of **8a** involving a polyene chain folding with least steric interactions, which affords the dammarane-type cation **13**, followed by b) a series of four consecutive antiparallel 1,2-hydride migrations which led to carbocation **17**. The sequence is then terminated by proton elimination. At this point it is evident that any of the intermediate cations encountered en route to **17**, such as **14**–**16**, could be subject to proton elimination leading to the cyclization derivatives **9**–**11**, whose isolation would further confirm the above pathway. Indeed, the spectroscopic data of the second isolated product were in full accord with structure **9a**, in particular the ^{1}H NMR (i.e., low-field resonance $\delta =$ 3.06 for H20) and ^{13}C NMR/DEPT data.[13] The full configurational assignment was established by X-ray diffraction on the related compound **9c** (vide infra).



Scheme 2. Stereochemical course of the Lewis acid catalyzed cyclization of **8a**–**c**. a) 0.03 M in dichloromethane, 0.5 equiv tin(IV) chloride (A), room temperature, 15 min.

In order to avoid the formation of the major pentacyclic fraction, the cyclization of aldehydes **8b** and **8c**, in which the double bond at pro-C(24),C(25) is missing, was studied. Furthermore, substrate **8c** was provided with a deuterium label at pro-C17 in order to ascertain that the cyclization products possessing a stereocenter at C20 originate from a direct 1,2-shift (and not from deprotonation–reprotonation sequences). Treatment of aldehyde **8b** under the standard conditions afforded, next to a major apolar fraction (78%), two tetracyclic alcohols, the expected **9b** (6%) and a novel cyclization product (7%) to which structure **10b** was tentatively assigned. We assume that the apolar fraction originates from the acid-catalyzed E1 elimination of the sterically congested axial hydroxy group. By careful exclusion of traces of water the formation of apolar derivatives could be reduced; under these improved conditions the cyclization of **8c** led to an apolar fraction (39%), and to the expected **9c** (20%) and **10c** (17%).

  1433-7851/00/3916-2862 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2000**, *39*, No. 16

That **9a**, **9b**, and **9c** belong to the same series was proven by partial hydrogenation of **9a** (Wilkinson's catalyst, toluene)[13] to **9b** (58% yield next to starting material), and by comparison of the relevant ^{1}H NMR spectral data of **9b** and **9c** which were identical except for the low-field resonance at $\delta = 3.03$ of H20 (absent in **9c**) and the doublet at $\delta = 0.93$ of the protons at C21 (singlet in **9c**). The final unambiguous identification of the structures in the **9**-series was established by the X-ray diffraction analysis of crystalline **9c**.[14]

Although full understanding of the process will necessitate further experiments to minimize the apolar fraction, the described cyclization of **8** is remarkable in that it constitutes a rare example of a nonenzymatic polycyclization that leads to anti-Markovnikov like cyclization products with a six-membered C-ring (**9**, **10** and **12**). The reactions are furthermore characterized by bond formation at vicinal quaternary centers.[15, 16] The "natural" pathway, which is now believed to involve a classical Markovnikov cyclization to a five-membered C-ring followed by ring expansion,[9] is considered in our case to be less likely,[12] although this alternative cannot be excluded at this stage.[17] The observed 20*R* configuration further confirms what one may have expected on the basis of chemical intuition: 1) the chain folding in the D-region is one that minimizes the steric interaction between C20 and the methyl group at C14, and 2) the C17 to C20 hydride shift which establishes the absolute configuration at C20 occurs faster than rotation at the C17–C20 bond. The analogy between structures **5b**/**6b** and **9b**/**10b**, respectively, is also striking. It may indicate that the cyclohexane ring at the 11,12 bond operates as a mimic of a rather tight binding of the central part of the natural substrate in the hydrophobic cleft of the enzyme.[18]

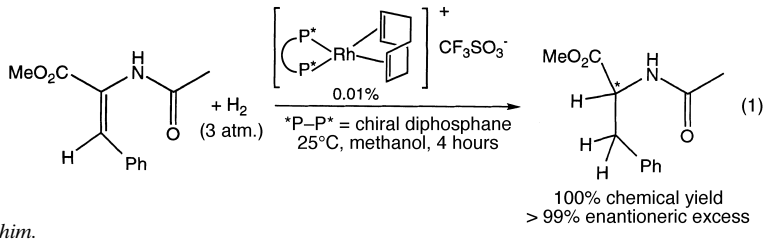
Received: February 9, 2000
Revised: May 11, 2000 [Z14677]

[1] I. Abe, M. Rohmer, G. D. Prestwich, *Chem. Rev.* **1993**, *93*, 2189–2206; see also: K. U. Wendt, G. E. Schulz, E. J. Corey, D. R. Liu, *Angew. Chem.* **2000**, *112*, 2930–2952; *Angew. Chem. Int. Ed.* **2000**, *39*, 2812–2833.
[2] E. Caspi, *Acc. Chem. Res.* **1980**, *13*, 97–104.
[3] G. Ourisson, M. Rohmer, *Acc. Chem. Res.* **1992**, *25*, 403–408.
[4] I. Abe, M. Rohmer, *J. Chem. Soc. Perkin Trans. 1* **1994**, 783–791.
[5] C. Pale-Grosdemange, C. Feil, M. Rohmer, K. Poralla, *Angew. Chem.* **1998**, *110*, 2355–2358; *Angew. Chem. Int. Ed.* **1998**, *37*, 2237–2240.
[6] M. Rohmer, P. Bouvier, G. Ourrison, *Proc. Natl. Acad. Sci. USA* **1979**, *76*, 847–851.
[7] a) A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta* **1955**, *38*, 1890–1904; b) G. Stork, A. W. Burgstahler, *J. Am. Chem. Soc.* **1955**, *77*, 5068–5077.
[8] a) K. B. Sharpless, E. E. van Tamelen, *J. Am. Chem. Soc.* **1969**, *91*, 1848–1849; b) P. F. Vlad, *Pure Appl. Chem.* **1993**, *65*, 1329–1336.
[9] For evidence that in the natural process the formation of the C-ring occurs by closing of a five-membered ring, followed by ring expansion, see: a) E. J. Corey, S. C. Virgil, H. Cheng, C. H. Baker, S. P. Matsuda, V. Singh, S. Sarshar, *J. Am. Chem. Soc.* **1995**, *117*, 11819–11820; b) C. Jenson, W. L. Jorgensen, *J. Am. Chem. Soc.* **1997**, *119*, 10846–10854; c) E. J. Corey, H. Cheng, C. H. Baker, S. P. T. Matsuda, D. Li, X. Song, *J. Am. Chem. Soc.* **1997**, *119*, 1289–1296; d) T. Hoshino, M. Kouda, T. Abe, S. Ohashi, *Biosci. Biotechnol. Biochem.* **1999**, *63*, 2038–41.
[10] The numbering used is consistent with the usual steroid numbering.
[11] For a previous model study, see: K. Berckmoes, P. J. De Clercq, D. Viterbo, *J. Am. Chem. Soc.* **1995**, *117*, 5857–5858.
[12] The simultaneous presence of the two *trans*-fusions at 8,9 and 11,12 in the cationic C-ring intermediate is calculated to generate about 35 kJ mol^{-1} more steric energy in the five-membered (Markovnikov) than in the six-membered (anti-Markovnikov) C-ring (see supplementary material to ref. [11]).
[13] Relevant procedures and spectroscopic data are given as Supporting Information.
[14] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-140162 (**9c**) and -140169 (**12a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[15] For reviews on polyene cyclizations, see: a) P. A. Bartlett in *Asymmetric Synthesis*, *Vol. 3* (Ed.: J. D. Morrison), Academic Press, New York, **1984**, pp. 341–409; b) S. K. Taylor, *Org. Prep. Proced. Int.* **1992**, *24*, 245–284.
[16] For an early example of six-membered C-ring formation involving quaternary centers at C8 and C14, but in which the D-ring is preformed, see: E. E. van Tamelen, R. G. Lees, A. Grieder, *J. Am. Chem. Soc.* **1974**, *96*, 2255–2256.
[17] M. Nishizawa, H. Takao, Y. Iwamoto, H. Yamada, H. Imagawa, *Synlett* **1998**, 76–80, and references therein.
[18] For the crystal structure of squalene–hopene cyclase from *A. acidocaldarius*, see: K. U. Wendt, A. Lenhart, G. E. Schulz, *J. Mol. Biol.* **1999**, *286*, 175–187.

A Simple Model for the Origin of Enantioselection and the Anti "Lock-and-Key" Motif in Asymmetric Hydrogenation of Enamides as Catalyzed by Chiral Diphosphine Complexes of Rh(I)**

Clark R. Landis* and Steven Feldgus

The historical and commercial significance of catalytic, enantiospecific enamide hydrogenation[1–4] has generated intense interest in the reaction mechanism [Eq. (1)].



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[**] This work was supported by the National Science Foundation (CHE-9618497) and by the National Center for Supercomputer Applications under MCA99S017N and used the CRAY ORIGIN 2000 computer system at the NCSA.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

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