Tetrahedron Letters,Vol.23,No.20,pp 2063-2066,1982 0040-4039/82/202063-04$03.00/0
Printed in Great Britain

STEREOSPECIFIC CYCLOPROPANE RING-OPENING OF PETROSTEROL. A POSSIBLE BIOMIMETIC PROCESS.

Robert W. Lang and Carl Djerassi*

Department of Chemistry, Stanford University, Stanford, California 94305

Abstract: Acid-catalyzed isomerization of the petrosterol side chain (1) proceeds stereospecifically to yield the naturally occurring 26-dehydro-25-epiaplysterol side chain (2); in addition, a 1.5-hydride shift leading to 22-dehydro-25-epiaplysteryl acetate (3) has also been observed.

Our postulate[1] that biosynthetic C-alkylation may also occur by isomerization of a cyclopropane intermediate together with our recent progress[2] on the acid-catalyzed ring-opening of steroidal cyclopropanes prompted us to examine both the stereo- and the regio-specificity of this process with a naturally occurring cyclopropane. For this purpose, we selected the acetate 1 of the sponge sterol petrosterol[3] (isolated from Petrosia ficiformis[3a]), since one of the possible products of acid-catalyzed[2] ring-opening should be the recently isolated[4] "26-dehydroaplysterol" (cf. 2) of unknown configuration at C-25. Elucidation of its C-25 stereochemistry is important in order to demonstrate a conceivable biosynthetic relation between 1 and 2. We now report a successful resolution of both problems, which increases the likelihood that the postulated[1,5] biosynthetic intermediacy of cyclopropanes operates in nature.

Petrosteryl acetate (1; m.p. 109-110°C (MeOH); m/z 394.3596, 100, M-HOAc)[6] was treated in the usual manner[2] with gaseous HCl in acetic acid for 150 min at room temperature. The complex reaction mixture was separated by reverse-phase HPLC (two Altex-Ultrasphere columns in series with absolute MeOH (3 mL/min) as the mobile phase) and 11 fractions, yielding together over 80%, were collected and each analyzed by mass spectrometry. All short retention time fractions (< 135 min) show acetoxylated or chlorinated side chain fragments in their mass spectra which are due to molecules generated by nucleophilic ring-opening of the initially protonated steroidal cyclopropane.[2] The two "true" isomers 2 and 3, having both retention times >150 min on HPLC, were isolated in 23% yield. The ^{1}H-NMR spectrum (see Table) of the main component (m/z 394.3587, 100, M-HOAc)[6] showed it to be the anticipated isomerization product 2 which was identical with "26-dehydroaplysterol" isolated[4] from the sponge Petrosia ficiformis. The constitution of the side chain of the minor component 3 (m/z 394.3599, 100, M-HOAc)[6] was established initially by comparison of its ^{1}H-NMR spectrum (see Table) with that of crinosteryl acetate (4)[2] which differs

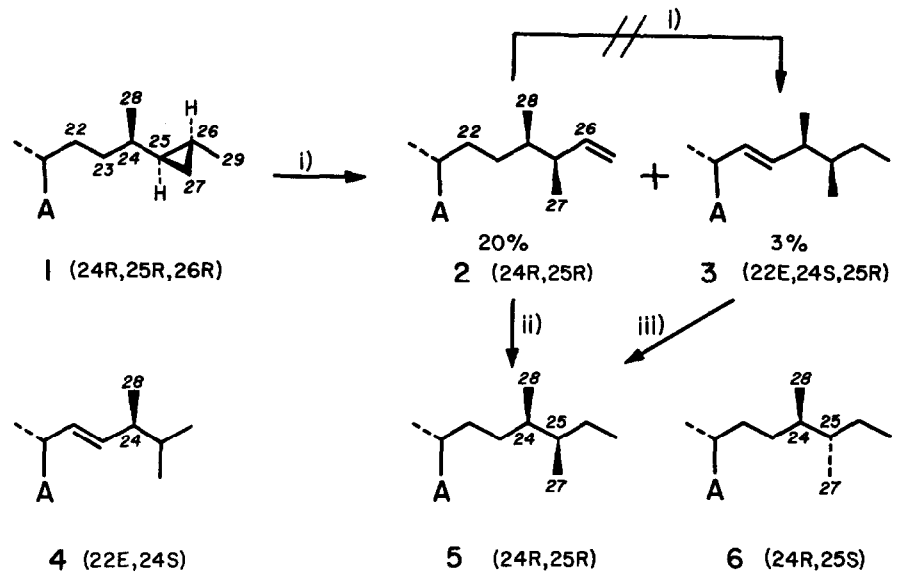
Table Methyl Group Region ^{1}H-NMR (360 MHz) Chemical Shifts[a]

compd	C-18	C-19	C-21	C-27	C-28	C-29
1 (24R,25R,26R)[b]	0.680	1.019	0.920 (6.51)	-	0.889 (6.70)	1.007 (6.21)
2 (24R,25R)[c]	0.674	1.017	0.902 (6.44)	0.930 (6.82)	0.793 (6.64)	-
3 (22E,24S,25R)[d]	0.690	1.020	1.002 (7.0)	0.794 (6.75)	0.882 (7.0)	0.848 (7.35)
4 (22E,24S)[e]	0.690	1.019	1.002 (6.68)	0.817 (6.63)	0.909 (6.78)	-
5 (24R,25R)[f]	0.662	0.921	1.031 (6.48)	0.836 (6.57)	0.848 (6.69)	0.910 (7.1)
6 (24R,25S)[f]	0.661	0.921	1.026 (6.26)	0.910 (7.0)	0.886 (6.84)	0.910 (7.0)

[a] Given as δ values; J values are given in parentheses in Hz. [b] $CDCl_3$; Cyclopropyl proton signals: 0.05-0.18 (m, 2H, C-26); 0.45 (m, 1H, C-27); 0.59 (m, 1H, C-25). [c] $CDCl_3$; 4.94 (ca. d, 2H, C-29); 5.74 (m, 1H, C-26). [d] $CDCl_3$; 5.171 (m, 2H, C-22/C-23). [e] See ref. 2; $CDCl_3$; 5.160 (m, 2H, C-22/C-23); 0.835 (d, 3H, C-26). [f] C_6D_6; C-27/C-28 assignments may be reversed.

from 3 only by a missing C-29 methyl group. In addition the diagnostic peak (m/z 337) from loss of the isopropyl radical in the mass spectrum[2] of crinosteryl acetate reflects itself in the spectrum of 3 by loss of a sec-butyl radical (m/z 337). Chemical proof was provided by catalytic hydrogenation of the two isomeric acetates 2 and 3 which yielded the same acetate 5 (^{1}H-NMR and high resolution mass spectroscopic evidence; GLC rrt 1.71 with cholesteryl acetate = 1.00). As is evident from their ^{1}H-NMR spectra (see Table), the chemical shifts of the C-27 and C-28 methyl groups in 5 and aplysteryl acetate 6 are quite different. This difference can only be due to epimeric substitution at C-25. Since the absolute configuration of aplysterol has been established[7] by X-ray analysis, the hydrogenation product 5 should be referred to as 25-epiaplysteryl acetate. This, in turn, leads to the trivial names 26-dehydro-25-epiaplysteryl acetate and 22-dehydro-25-epiaplysteryl acetate for 2 and 3 respectively. It could easily be proved by GLC-analysis (rrt 1.59 1; 1.66 2; 1.45 3 with cholesteryl acetate = 1.00) that 3 does not originate from an acid-catalyzed double bond migration in 2, or that it was a contaminant in naturally occurring petrosteryl acetate (1).

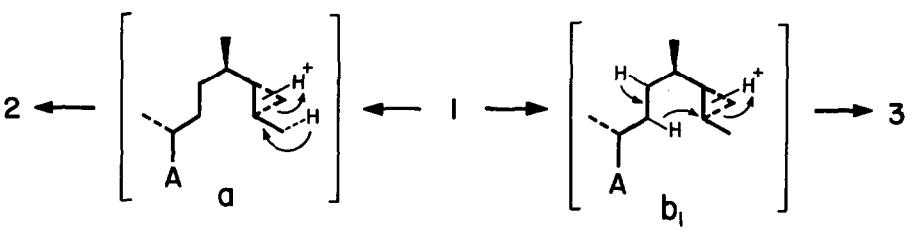
Based on our earlier mechanistic considerations,[2] the formation of 2 may best be explained through the intermediacy of a via a concerted C-C bond fission/hydrogen elimination. The acetate 3, which also originates from direct cyclopropane ring-opening and therefore contains the same C-24/C-25 methyl group configuration as the main isomer 2, appears to be the product of a 1.5-hydride migration (unprecedented for cyclopropanes) in the initially protonated cyclopropane b_1. On the assumption that intramolecular 1.5-hydride shifts generally proceed via a chairlike transition state,[8] the intermediate b_1 may be depicted more precisely as b_2 in which the quasi-equatorial methyl group at C-24 additionally stabilizes the six-membered ring conformation. Synthetic experiments with suitably labelled analogs are contemplated in order to provide unambiguous proof for such a hitherto unknown high-order hydride shift among protonated cyclopropanes.

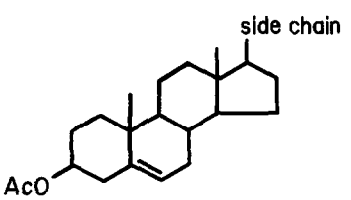


1 (24R,25R,26R) 2 (24R,25R) 3 (22E,24S,25R)

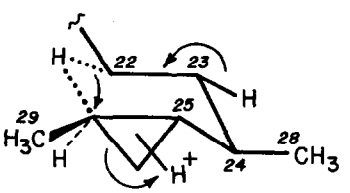
4 (22E,24S) 5 (24R,25R) 6 (24R,25S)

i) HCl(g)/HOAc, rt, 150 min; ii) $(Ph_3P)_3RhCl/H_2$, C_6H_6, rt, 15 h; iii) PtO_2/H_2, EtOAc, rt, 3 d.





A



b2

In summary, the above reported results offer support for the possible operation of an in vivo biomethylation process of the marine sterol side chain which involves isomerization of steroidal cyclopropane intermediates.[1,5] Furthermore our results represent independent chemical proof that petrosterol (cf. 1)[3a] and aplysterol (cf. 6)[7] possess opposite configurations at C-25.

Acknowledgments: Financial support was provided by NIH Grants No. GM-06840 and GM-28352. We are especially indebted to Prof. Dr. H.-J. Hansen (F. Hoffmann-La Roche & Co., Basle, Switzerland) for helpful discussions. We thank Dr. W.C.M.C. Kokke for assistance in the HPLC separation, Dr. Lois J. Durham for the NMR spectra and Ms. A. Wegmann for mass spectral determinations. Use of the NMR/MS center at the Stanford 360-MHz facility (NSF Grant No. GP-23633 and NIH Grant No. RR-0711) is gratefully acknowledged. R.W.L. thanks the Swiss National Science Foundation for a postdoctoral fellowship.

REFERENCES AND NOTES

1. C. Djerassi, Pure & Appl. Chem. 53, 873 (1981).
2. R.W. Lang and C. Djerassi, Helv. Chim. Acta 65, 0000 (1982).
3. a) C.A. Mattia, L. Mazzarella, R. Puliti, D. Sica and F. Zollo, Tetrahedron Lett. 1978, 3953; b) B.N. Ravi, W.C.M.C. Kokke, C. Delseth and C. Djerassi, Tetrahedron Lett. 1978, 4379.
4. M.W. Khalil, C. Djerassi and D. Sica, Steroids 35, 707 (1980).
5. C. Djerassi, N. Theobald, W.C.M.C. Kokke, C.S. Pak and R.M.K. Carlson, Pure & Appl. Chem. 51, 1815 (1979).
6. High resolution mass spectrum at 70 eV; calcd for $C_{29}H_{46}$ 394.35995.
7. P. De Luca, M. De Rosa, L. Minale, R. Puliti, G. Sodano, F. Giordano and L. Mazzarella, J. Chem. Soc., Chem. Commun. 1973, 825.
8. For a review see: J.L. Fry and G.J. Karabatsos in "Carbonium Ions", G.A. Olah and P.v.R. Schleyer, Eds., Vol. II, Wiley-Interscience, New York 1970 pp. 521; for recent publications see: M. Saunders and J.J. Stofko, Jr., J. Amer. Chem. Soc. 95, 252 (1973); H. Berner, G. Schulz and H. Schneider, Tetrahedron 36, 1807 (1980).

(Received in USA 26 January 1982)