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SUCCESSIVE METHYL MIGRATIONS OCCURRING IN THE ACID TREATMENT OF 1-EPOXYETHYL-1,2,2-TRIMETHYL-CYCLOPENTANE DERIVATIVE

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Summary: Acid treatment of (1R,3S,1'S)-1-(1',2'-Epoxyethyl)-1,2,2-trimethyl-3-acetoxymethyl-cyclopentane (6) has been shown to yield three products (8, 9, 10), among which 8 and 9 are 1-oxa-bicyclo[3.3.0]octane derivatives formed via successive methyl migrations followed by an oxorane ring closure.

During the course of our synthetic study on naturally occurring bioactive compounds starting from *d*-camphor(1),[1)] we have found that BF_3-etherate treatment of an epoxide (6) furnishes three products (8, 9, 10) among which 8 and 9 are 1-oxa-bicyclo[3.3.0]octane derivatives formed through successive migrations of methyl residues (cf. i) and an oxorane ring formation. This paper provides supporting evidence for this interesting finding.

The epoxide (6) was synthesized from *d*-camphoric acid (2)[2)] which was prepared by nitric acid oxidation of 1. Methylation followed by $LiAlH_4$ reduction of 2 gave a diol (3),[3)] which, on treatment with Ac_2O-AcONa, furnished a monoacetate (4), oil, $C_{12}H_{22}O_3$,[4)] $[\alpha]_D$ +39° ($CHCl_3$), IR (film) cm^{-1}: 3440, 1737, ^1H-NMR (CCl_4) δ: 0.81, 0.95, 1.00, 2.00 (all 3H, s), 3.37, 3.50(2H, ABq, J= 9, $-\overset{|}{\underset{|}{C}}-C\underline{H}_2OH$), 3.8-4.1 (2H, AB in ABX, $-\overset{|}{C}H-C\underline{H}_2OAc$). Pyridinium chlorochromate (PCC) oxidation[5)] of 4 gave an unstable aldehyde which was immeidately subjected to methylenation to furnish a vinyl-acetate (5), oil, $C_{13}H_{22}O_2$, IR (film): 1747, 1645, 910, δ (CCl_4): 3.98 (2H, d, J= 6), 4.8-5.9 (3H, ABC, vinyl). *m*-Chloroperbenzoic acid oxidation of 5 gave two epoxides, 6 (70%), oil, $C_{13}H_{22}O_3$, $[\alpha]_D$ +44° ($CHCl_3$), IR (film): 1744, 870, 814, δ (CCl_4): 0.87, 0.90, 1.00, 1.94 (all 3H, s), 2.1-2.8 (3H, ABC, $-\overset{O}{\overbrace{C\underline{H}-C\underline{H}_2}}$), 3.7-4.2 (2H, AB in ABX, $-\overset{|}{C}H-C\underline{H}_2OAc$), and 7 (19%), oil, $C_{13}H_{22}O_3$, $[\alpha]_D$ +43° ($CHCl_3$), IR (film): 1741, 850, 805, δ (CCl_4): 0.86, 0.92, 1.02, 1.96 (all 3H, s), 2.4-2.9 (3H, ABC), 3.8-4.3 (2H, AB in ABX).

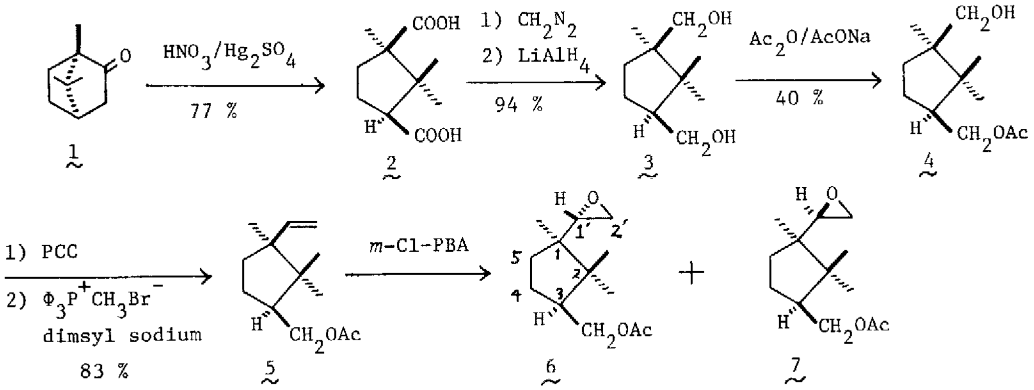
The C-1' configurations of both epoxides (S for **6**, R for **7**) were elucidated by application of the Horeau's method[6] for respective diol-monoacetates (**6b**, **7b**), which were prepared from epoxides (**6**, **7**) by $LiAlH_4$ reduction (giving **6a**, **7a**) followed by partial acetylation: **6b**, δ ($CDCl_3$): 1.14 (3H, d, J= 6), 3.76 (1H, q, J= 6)($-C\underline{H}(OH)-C\underline{H}_3$), 3.8-4.3 (2H, AB in ABX, $-\overset{|}{C}H-C\underline{H}_2-OAc$); **7b**, δ ($CDCl_3$): 1.08 (3H, d, J= 6), 3.7-4.2 (3H, m); recovered α-phenylbutyric acid: $[\alpha]_D$ +4.8° (c= 1.59, benzene) in preparation of **6c** and -0.9° (c= 2.19) for **7c**.

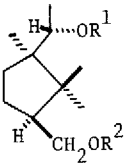
Treatment of **6** in benzene with BF_3-etherate at room temp. (20°) for 50 min. furnished three products: **8** (38%), **9** (13%), and **10** (42%): **8**, oil, $C_{13}H_{22}O_3$, $[\alpha]_D$ +12° ($CHCl_3$), IR (film) : 1738, δ (CCl_4): 0.90 (3H, d, J= 7), 0.96, 1.09, 1.93 (all 3H, s), 3.15 (1H, d.d, J= 8, 12, 2-H_A), 3.85 (1H, d.d, J= 8, 8, 2-H_B), 3.6-4.3 (2H, AB in ABX, $-\overset{|}{C}H-C\underline{H}_2OAc$); **9**, oil, $C_{13}H_{22}O_3$, $[\alpha]_D$ +37° ($CHCl_3$), IR (film): 1738, δ (CCl_4): 0.88 (3H, d, J= 7), 0.87, 1.02, 1.96 (all 3H, s), 3.27 (1H, d.d, J= 8, 9, 2-H_A), 3.83 (1H, d.d, J= 8, 6, 2-H_B), 3.6-4.2 (2H, AB in ABX).

Since **8** and **9** were respectively shown by ^1H-NMR to possess one sec. and two tert. methyls and two methylene protons attached to a carbon adjacent to an ether oxygen, they were presumed to be products formed from **6** *via* successive methyl migrations as shown in **i** (*via* a, c giving **8**, while *via* b, c giving **9**). The C-3R configurations of both **8** and **9** were presumed on the basis of CD analysis[7] of their lactone derivatives, **11** and **12**, prepared by RuO_4 oxidation[8] of **8** and **9**: **11**, $C_{13}H_{20}O_4$, mp 80-81° (transparent prism from *n*-hexane), $[\alpha]_D$ -42° ($CHCl_3$), IR (CCl_4): 1776, 1747, CD (MeOH): $[\theta]^{20}_{217}$ -6800 (neg. max.); **12**, oil, $C_{13}H_{20}O_4$, $[\alpha]_D$ +27° ($CHCl_3$), IR (CCl_4) : 1771, 1748, CD (dioxane): $[\theta]^{20}_{223}$ -2500 (neg. max.). Therefore, **8** and **9** were presumed to be isomeric at their angular configurations. Finally X-ray analysis of the lactone **11** was carried out to obtain a direct proof of the structure.

CRYSTAL DATA: $C_{13}H_{20}O_4$, M.W. = 240.30, monoclinic space group $P2_1$, a= 8.827(1), b= 7.467 (1), c= 10.713(1) Å, β= 112.52(1)°, z= 2, U= 652.2 Å^3, D_x= 1.21 g.cm^{-3}, D_o= 1.20 g.cm^{-3}. A total of 1043 non-zero independent reflections with $2\theta \leq 120°$ were measured on an automated diffractometer using 2θ-ω scan technique and Ni-filtered Cu Kα radiation. The structure was solved by direct method using "MULTAN" program.[9] Block-diagonal least-squares refinement with anisotropic nonhydrogen atoms and isotropic hydrogens reduced R to 0.071.[10] The figure is a computer generated ORTEP stereoview of the molecule (30% ellipsoids).

The third product **10**, oil, $C_{13}H_{22}O_3$, $[\alpha]_D$ +9° ($CHCl_3$), IR (film), 3400, 1732, δ (CCl_4): 0.88, 1.11, 2.00 (all 3H, s), 1.07 (3H, d, J= 7), 3.1-3.6 (2H, AB in ABX), 4.07 (2H, m), 5.29



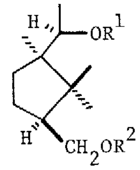


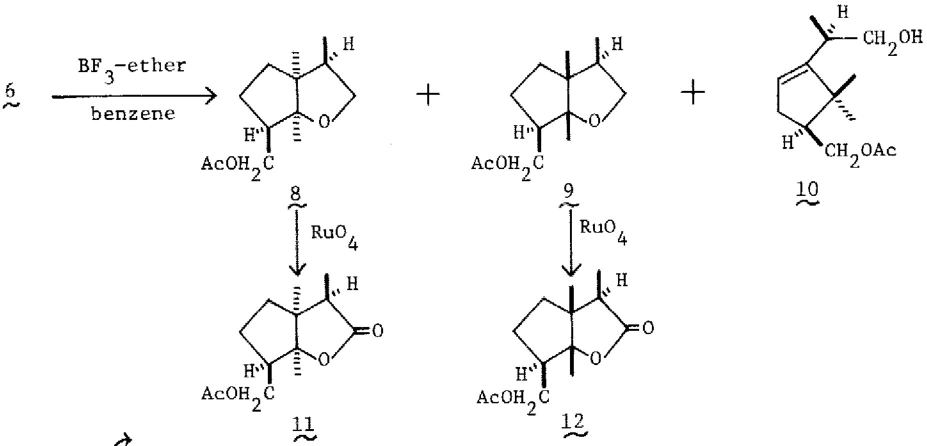
6a --- $R^1 = R^2 = H$ -------- 7a

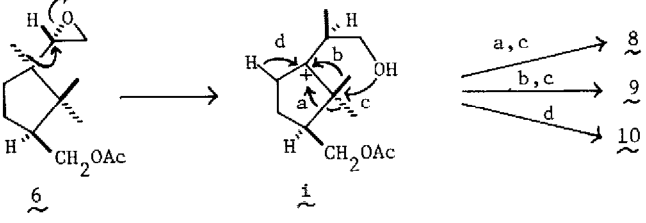
6b --- $R^1 = H$, $R^2 = Ac$ ----- 7b

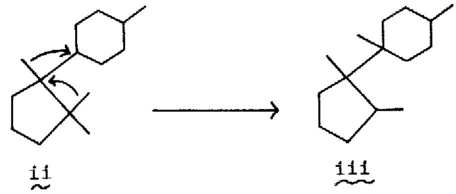
6c --- $R^1 = -\overset{O}{\overset{\|}{C}}-\underset{}{\overset{CH_2-CH_3}{\overset{|}{C}H}}-\Phi$ ---- 7c

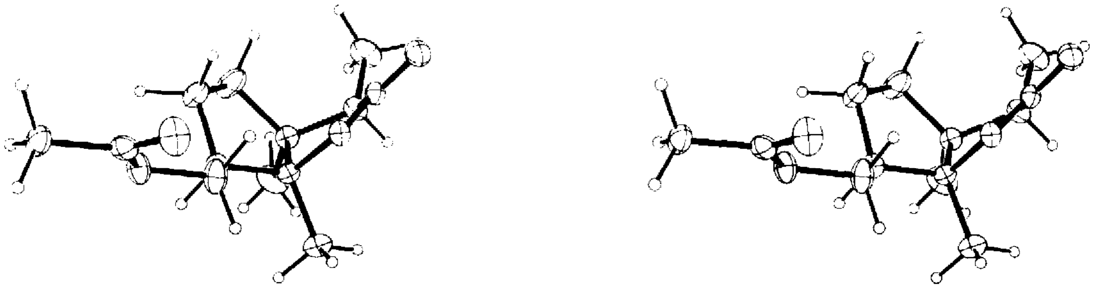
$R^2 = Ac$











Figure

(1H, narrow m, $W_{h/2}$= 5, $>C\underline{H}=C<$), was shown to possess one sec. and two tert. methyls and one olefinic proton and was presumed to be derived from i *via* deprotonation (route d). The structure 10 was further substantiated by a fact that BF_3-etherate treatment of 10 in benzene at room temp. for 24 hr gave 8 (51%) and 9 (9%) with recovery of 10 (33%).

The successive methyl migrations presented here are reminiscent of a biogenetic pathway from cuparane-type (ii) to trichothecane-type (iii) sesquiterpenes.[11] The behavior of minor epoxide (7) against acid is under investigation.

References and Footnotes

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