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Acid-Catalyzed Autoxidation of 12-Hydroxyeudesman-3,6-dione to 6,12-Epoxyeudesma-4,6-dien-3-one

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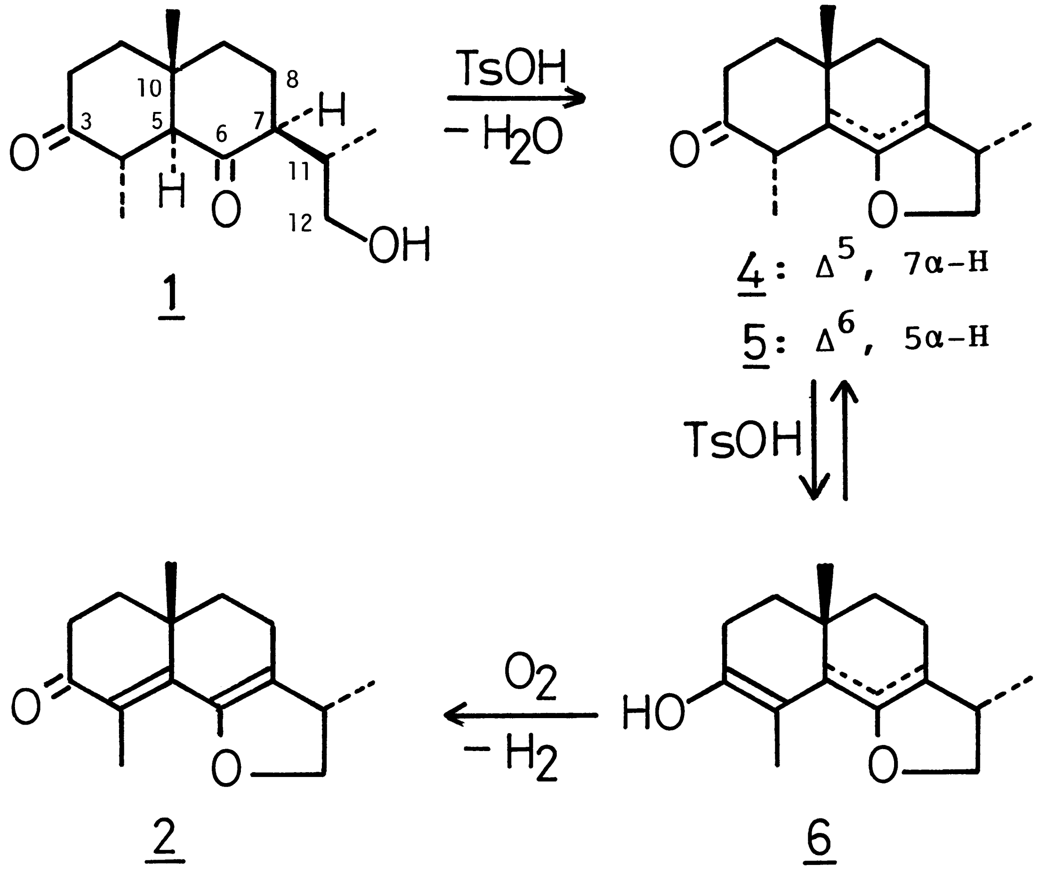
Treatment of a benzene solution of 12-hydroxyeudesman-3,6-dione with p-toluenesulfonic acid in air gave 6,12-epoxyeudesma-4,6-dien-3-one (2) in 57% yield. Dienone 2 was further oxidized to give 7-hydroxyeudesmanes.

Autoxidation of electron rich dienes, such as the oxygenation of enamines of α,β-unsaturated ketones to γ-keto products,[1)] has been well investigated. Base-catalyzed autoxidation of cyclic 1,4-diketones to enediones (e.g.,cholestane-3,6-dione to 4-cholestene-3,6-dione) proceeds via intermediately formed dienolate ions.[2)] However, acid-catalyzed autoxidation of 1,4-diketones to enediones proceeding via dienols or their equivalents has not been reported. We now describe the acid-catalyzed autoxidation of 12-hydroxyeudesman-3,6-dione (1), a cyclic 1,4-diketone, assisted by the neighboring hydroxyl group[3)] to give 6,12-epoxyeudesma-4,6-dien-3-one (2).

Compound 1[4)] was prepared in 6 steps (65% overall yield) from the known keto lactone 3[5)] [reagents: (i) ethylene glycol, p-toluenesulfonic acid(TsOH), (ii) $LiAlH_4$, (iii) acetic anhydride, pyridine (mono acetylation), (iv) H_3O^+, (v) Jones oxidation, and (vi) OH^-]. Treatment of a benzene solution of compound 1 with an excess of TsOH at room temperature in air for 15 h gave 2 in 57% yield. The UV [$\lambda_{max.}^{MeOH}$ 336 nm (ε 12000), 252 (ε 5300) and 210 nm (ε 3500)], IR [$\nu_{max.}$ 1665, 1633, and 1583 cm^{-1}], and ^{13}C NMR [$\delta(CDCl_3)$ 199.76(C-3), 149.52 (C-5), 146.93 (C-6), 128.36(C-4), and 125.41(C-7)] spectra[6)] indicated the presence of a conjugated dienone moiety in 2. The two-dimensional ^1H-^1H shift-correlation spectrum (COSY)



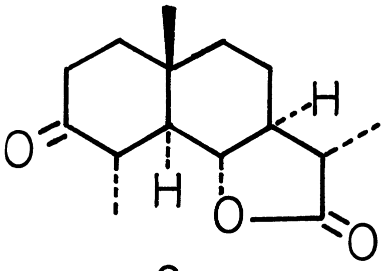
1

4: Δ^5, 7α-H

5: Δ^6, 5α-H

6

2



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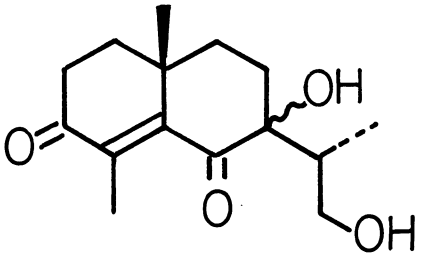
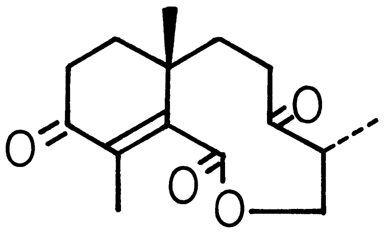


7: 7α-OH

8: 7β-OH



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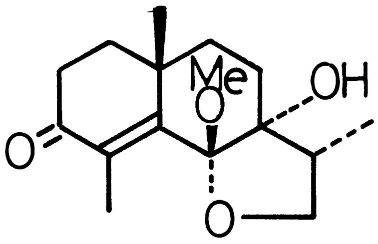

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further showed the presence of partial structures, $-O-CH_2CH(CH_3)-$ and $-CH_2CH_2C(CH_3)CH_2CH_2-$, in 2.

When 1 was treated with TsOH in benzene under nitrogen, an inseparable mixture of enol ethers, 4 and 5 (4 : 5 = 1 : 2),[7)] was afforded. The mixture was further transformed to 2 in the presence of TsOH in air. The dehydrogenation reaction, however, did not proceed without TsOH; this indicates that the reaction proceeds via the acid catalyzed enolization of C-3 carbonyl group of 4 and/or 5. The intermediately formed electron rich diene(s) 6 may be oxygenated with molecular oxygen.[1,2)]

Dienone 2 was further oxygenated to give 7-hydroxy derivatives, 7 (30%) and 8 (15%),[8)] upon standing in air. These hydroxy ketones may be yielded via the epoxidation of the γ,δ-double bond with molecular oxygen.[9)] Treatment of dienone 2 with m-chloroperbenzoic acid (MCPBA) in aqueous tetrahydrofuran gave stereoselectively 7 in 54% yield along with lactone 9 (10%).[10)] Oxidation of 2 with MCPBA in methanol gave 10[11)] in 51% yield.[12)] The down-field shift of 8α-H signal [δ 1.10 to 3.04 (ddd, J=14.0, 4.3, and 2.5 Hz); assigned based on the COSY spectra measured in C_6D_6] by addition of trichloroacetyl isocyanate and the nuclear Overhauser enhancement of OMe signal on irradiation of 10β-Me revealed the stereochemistry of 10 and consequently the stereochemistry of 7 and 8.

Autoxidation of 8-hydroxyoctane-2,5-dione,[13)] an acyclic 1,4-diketone, in the similar conditions did not proceed. Base-catalyzed autoxidation of acyclic 1,4-diketone to enedione has not been reported. Under acidic conditions as well only cyclic 1,4-diketones may be autoxidized to enediones.

Examination of the generality of the acid-catalyzed autoxidation and further transformation of 7, 8, and 10 to 7- and 8-hydroxyeudesmanolides are under way.

References

1) S. K. Malhotra, J. J. Hostynek, and A. F. Lundin, J. Am. Chem. Soc., 90, 6565 (1968).

2) W. G. Dauben, G. A. Boswell, and W. Templeton, J. Org. Chem., 25, 1853 (1960).

3) H. Nagano, T. Iwadare, and M. Shiota, J. Chem. Soc., Chem. Commun., 1985, 656; J. Chem. Soc., Perkin Trans. 1, 1986, 2291.

4) 1: mp 95.0 - 96.0 °C; IR(KBr) 3420 and 1705 cm^{-1}; ^1H NMR($CDCl_3$) δ 0.94(d, J=6.8 Hz), 0.99(s, 10-Me), 0.99(d, J=6.4 Hz), 3.44(dd, J=10.7 and 6.7 Hz, 12-H),

and 3.55(dd, J=10.7 and 4.9 Hz, 12-H). Found: m/z 252.1741. Calcd for $C_{15}H_{24}O_3$: M, 252.1725.

5) K. Yamakawa, J. Org. Chem., 24, 897 (1959).

6) Purified by HPLC [RP-18 column; MeOH-H_2O (3:2)]. 2: an oil; $[\alpha]_D^{18}$ + 549° (c 0.72, $CHCl_3$); ^1H NMR($CDCl_3$) δ 1.13(s, 10-Me), 1.15(d, J=6.8, 11-Me), 2.06 (s, 4-Me), 3.85(t, J=8.7 Hz, 12-H), and 4.49(dd, J=9.8 and 8.7 Hz, 12-H). Found: m/z 232.1477. Calcd for $C_{15}H_{20}O_2$, M, 232.1463.

7) Mixture of 4 and 5: an oil; IR(neat) 1715 cm^{-1}; ^1H NMR($CDCl_3$)[4: δ 0.68 (d, J=6.3 Hz, 11-Me), 1.00(s, 10-Me), 1.55(d, J=7.3 Hz, 4-Me), 3.22(dd, J=10.4 and 8.2 Hz, 12-H), 3.73(q, J 7.3 Hz, 4-H), and 3.92(dd, J=8.2 and 7.7 Hz, 12-H). 5: δ 0.75 (s, 10-Me), 0.90(d, J=6.7 Hz, 11-Me), 1.50(d, J=6.6 Hz, 4-Me), 3.59 (t, J=8.5 Hz, 12-H), and 4.24(dd, J=9.3 and 8.5 Hz, 12-H)]. Found: m/z 234.1637. Calcd for $C_{15}H_{22}O_2$: M, 234.1620.

8) 7 (less polar diastereomer): an oil, IR(neat) 3480 and 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03(d, J=7.1 Hz, 11-Me), 1.15(s, 10-Me), 1.74(s, 4-Me), 3.72(dd, J=10.7 and 6.1 Hz, 12-H), and 4.11(dd, J=10.7 and 3.7 Hz, 12-H). Found: m/z 266.1517. Calcd for $C_{15}H_{22}O_4$: M, 266.1518. 8 (more polar diastereomer): an oil; IR(neat) 3400 and 1670 cm^{-1}; ^1H NMR($CDCl_3$) δ 0.89(d, J=7.0 Hz, 11-Me), 1.21(s, 10-Me), 1.83(s, 4-Me), 3.68(dd, J=11.0 and 3.5 Hz, 12-H), and 4.01 (dd, J=11.0 and 3.5 Hz, 12-H). Found: m/z 266.1514.

9) H. Hart and P. B. Lavrik, J. Org. Chem., 39, 1793 (1974).

10) Treatment of 2 with an excess of MCPBA in dichloromethane gave 9 in 56% yield. Satisfactory spectral data (IR, ^1H NMR, ^{13}C NMR, and high resolution MS) were obtained. I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, J. Org. Chem., 31, 3032 (1966).

11) 10: mp 179.0 - 179.5 °C; UV(MeOH) 244 nm (ε 9100); IR(KBr) 3400, 1665, and 1600 cm^{-1}; ^1H NMR(C_6D_6) δ 0.79(d, J=7.0 Hz, 11-Me), 1.09(s, 10-Me), 2.40 (s, 4-Me), 2.79(s, OMe), 3.13(t, J=8.3 Hz, 12-H), and 3.64(t, J=8.7 Hz, 12-H); Found: m/z 280.1655. Calcd for $C_{16}H_{24}O_4$: M, 280.1674.

12) A. A. Frimer, Synthesis, 1977, 578.

13) Prepared from γ-valerolactone as follows. (i) diisobutylaluminium hydride, (ii) CH_2=$CHCH_2CH_2MgBr$, (iii) Jones oxidation, (iv) ethylene glycol, TsOH, (v) O_3 then $NaBH_4$, and (vi) H_3O^+. I. F. Bel'skii and Z. K. Vol'nova, Izv. Akad. Nauk SSSR, Ser. Khim., 1967, 1383; Chem. Abstr., 68, 21757w (1968).

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