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ANOMALOUS SOLVOLYSIS OF A POLYENOL ETHER OF GLYCEROL

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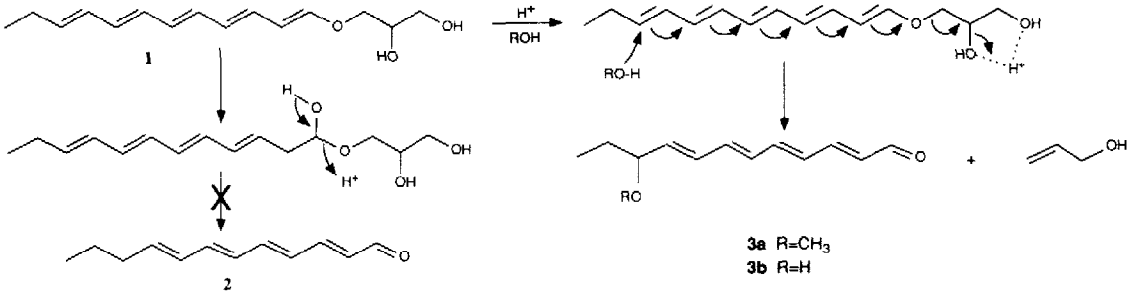
ABSTRACT. Fecapentaene-12 **1** displays an unexpected reactivity when treated with hydrochloric acid in aqueous solvents. Instead of forming the unsubstituted aldehyde 2,4,6,8-dodecatetraenal **2**, a completely different pathway is observed, resulting in the exclusive formation of 10-methoxy-2,4,6,8-dodecatetraenal **3a** (methanol/water) or 10-hydroxy-2,4,6,8-dodecatetraenal **3b** (tetrahydrofuran/water).

Fecapentaene-12 is a major representative of a group of structurally closely related strongly mutagenic compounds, isolated from human feces [1-8].

In a previous paper, we reported the unusual chemical reactivity of these polyunsaturated enol ethers under basic conditions. An unprecedented ring closure was observed, caused by base catalyzed addition of the 2'-hydroxyl group to the enol ether double bond. Also external nucleophiles could be added to the polyene under these conditions [9,10].

Recently we have discovered that also under mildly acidic conditions fecapentaene-12 reacts completely differently from the expected pattern. It was anticipated that upon acid-catalyzed solvolysis, protonation at the enol ether ß-carbon atom would be followed by addition of water to form the hemi-acetal, which would subsequently decompose to give the unsaturated aldehyde **2** [11]. Instead, a completely different pathway is followed, for which we propose the mechanism depicted in Scheme 1.



Scheme 1.

Protonation at the glyceryl side-chain is followed by loss of water, disruption of the carbon-oxygen bond (formation of a carbonyl group and allylic alcohol), a flow of the π-electrons towards the enol ether oxygen atom and addition of a nucleophile to the ω-carbon atom of the polyene. When using a methanol/water mixture as the solvent 10-methoxy-2,4,6,8-dodecatetraenal **3a** is formed exclusively; using a THF/water mixture as the solvent 10-hydroxy-2,4,6,8-dodecatetraenal **3b** is formed as the sole product.

This newly discovered reactivity has been applied in an analysis of fecapentaenes and their precursors in human feces which we have recently described [12].
Work is in progress to study the influence of several variables (length of the polyene system, structure of the hydroxylated side chain, polarity of the solvent) on this unique acid catalyzed solvolysis.

EXPERIMENTAL

All synthesis were carried out in the dark, in an oxygen-free atmosphere.

10-METHOXY-2,4,6,8-DODECATETRAENAL **3a**

In an atmosphere of dry argon, fecapentaene-12 (200 mg, 0.8 mmol) was dissolved in 125 ml methanol. Subsequently 125 ml water and 7 ml 36% aqueous HCl were added. After stirring for 4 hours, the reaction was quenched with water (200 ml). The methanol layer was separated and the water layer was extracted with ether (3 x 100 ml). The combined organic layers were washed with saturated brine (3 x 100 ml), dried with anhydrous potassium carbonate and evaporated *in vacuo*. The crude adduct was purified by flash column chromatography [petroleum ether 40-60°C/triethylamine (9/1)]. Evaporation *in vacuo* yielded pure 10-methoxy-2,4,6,8-dodecatetraenal; Yield: 65.9 mg (40%); Yellow solid.

uv: λmax (EtOH) 351 nm. ε= 35000 $lmol^{-1}cm^{-1}$.

ms: 207(14), 206(M^+, 100), 177(26), 149(14), 117(59), 91(44), 75(45), 51(47), 41(32). Exact mass: 206.1301 ($C_{13}H_{18}O_2$ requires 206.1307).

^1H nmr: δ 0.90 (3H, t, J=7.4, CH_3), 1.59 (2H, dq, J=7.4 and 6.2, $CH_3C\underline{H}_2$), 3.28 (3H, s, OCH_3), 3.56 (1H, dt, J=6.2 and 7.2, $C\underline{H}OCH_3$), 5.73 (1H, dd, J=7.2 and 15.5, $C\underline{H}CHCH_3$), 6.16 (1H, dd, J=8.0 and 15.2, $C\underline{H}CHO$), 6.29 (1H, dd, J=10.4 and 15.5, C8-H), 6.33 (1H, dd, J= 10.9 and 14.9, C6-H), 6.47 (1H, dd,

J=11.1 and 14.8, C4-H), 6.50 (1H, dd, J=14.9 and 10.4, C7-H), 6.71 (1H, dd, J=14.8 and 10.9, C5-H), 7.15 (1H, dd, J=15.2 and 11.1, C3-H), 9.57 (1H, d, J=8.0, CHO) ppm.

^{13}C nmr: δ 9.51 (C12), 27.67 (C11), 55.74 (C13), 82.13 (C10), 130.87, 130.43 (C2 and C4), 131.60, 131.74 (C6 and C8), 137.79, 137.96 (C7 and C9), 142.66 (C5), 152.50 (C3), 193.94 (C1) ppm.

10-HYDROXY-2,4,6,8-DODECATETRAENAL **3b**

In an atmosphere of dry argon, fecapentaene-12 (200 mg, 0.8 mmol) was dissolved in 125 ml THF. Subsequently 125 ml water and 7 ml 36% aqueous HCl were added. After stirring for 4 hours, the reaction was quenched with water (200 ml). The THF layer was separated and the water layer was extracted with ether (3 x 100 ml). The combined organic layers were washed with saturated brine (3 x 100 ml), dried with anhydrous potassium carbonate and evaporated *in vacuo*. The crude adduct was purified by flash column chromatography [ether/triethylamine (9/1)]. Evaporation *in vacuo* yielded pure 10-hydroxy-2,4,6,8-dodecatetraenal; Yield: 75.3 mg (49%); Yellow solid.

uv: λmax (EtOH) 351 nm. ε=37000 $lmol^{-1}cm^{-1}$.

ms: 193(15), 192(M^+, 100), 177(3), 174(45), 163(7), 138(3), 110(44). Exact mass: 192.1156 ($C_{12}H_{16}O_2$ requires 192.1150).

^{1}H nmr: δ 0.94 (3H, t, J=7.4, CH_3), 1.59 (2H, dq, J=7.4 and 6.4, $C\underline{H}_2CH_3$), 4.15 (1H, dt, J=6.4 (2x), C<u>H</u>OH), 5.89 (1H, dd, J=6.4 and 15.0, C<u>H</u>CHOH), 6.33 (1H, dd, J=15.0 and 10.7, C8-H), 6.49 (1H, dd, J=10.7 and 14.7, C7-H), 6.34 (1H, dd, J=14.7 and 10.8, C6-H), 6.70 (1H, dd, J=10.8 and 14.9, C5-H), 6.46 (1H, dd, J=15.2 and 8.0, C4-H), 7.14 (1H, dd, J=11.2 and 15.2, C3-H), 6.16 (1H, dd, J=15.2 and 8.0, C<u>H</u>CHO), 9.56 (1H, d, J=8.0, CHO) ppm.

^{13}C nmr: δ 9.61 (C12), 30.14 (C11), 73.64 (C10), 131.11, 129.79 (C2 and C4), 130.03, 131.55 (C6 and C8), 137.91, 139.90 (C7 and C9), 142.38 (C5), 151.66 (C3), 193.45 (C1) ppm.

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