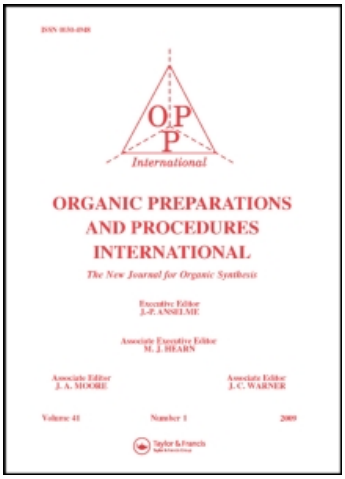

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AN UNUSUAL EPIMERIZATION IN THE OXIDATION OF A 4C-(HYDROXYMETHYL)-2,3,4-TRIDEOXY-2-HEXENOPYRANOSIDE USING FETIZON'S REAGENT

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AN UNUSUAL EPIMERIZATION IN THE OXIDATION OF A 4C-(HYDROXYMETHYL)-2,3,4-TRIDEOXY-2-HEXENOPYRANOSIDE USING FETIZON'S REAGENT

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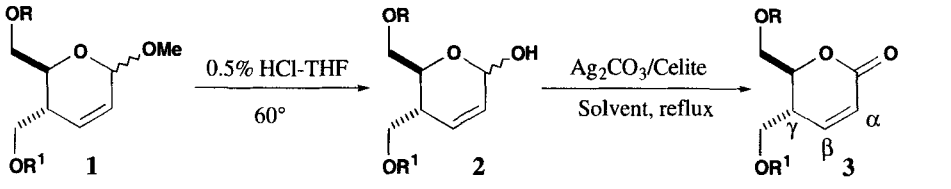
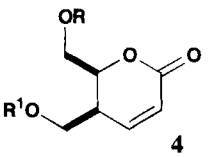
Fetizon's reagent[1] (Ag_2CO_3 on Celite) is a widely used and versatile oxidant for the oxidation of alcohols to the corresponding aldehydes or ketones.[2] The mild and essentially neutral reaction conditions means that a variety of groups (including protecting groups) are tolerated. Since the oxidation is a heterogenous reaction, the product is easily separated from the solid oxidant by simple filtration and evaporation of the solvent. The oxidant is especially useful for effecting selective oxidation in polyhydroxylated systems and, therefore, has found much use in the carbohydrate area.[3] Thus, allylic type alcohols[4] and lactols[5] are selectively oxidized in the presence of other hydroxyl groups. It has also been noted that the type of solvent used has a strong influence on the course of the oxidation. For example, the use of benzene as the solvent in the oxidation of aldoses leads to good yields of lactones, whereas the use of polar, hydroxylic solvents, such as methanol, resulted in oxidative cleavage between the C-1/C-2 position of the aldoses.[6] We report here an unexpected epimerization of the 4C-hydroxymethyl moiety in the enelactol **2a** under Fetizon oxidation reaction conditions. Such epimerization involving a substituent γ to the newly formed carbonyl function under the oxidation conditions has not been documented previously.[7]

The enelactol **2a** was prepared (Scheme I) by acid-catalysed hydrolysis of the known



R = $SiPh_2Bu$-*t* a) R^1 = H b) R^1 = $MeOC(O)CH_2C(O)$



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compound **1a**.[8] It was found that the best yield of **2a** was obtained when the reaction was performed in a mixture of 0.5% aqueous HCl with THF. The use of other acidic conditions led either to lower yields (e.g., 4:1 v/v THF–5% or 10% aq. HCl) or resulted in the decomposition (3:2:1 v/v AcOH–1,4 dioxane–H_2O) of **2a**.

Benzene and toluene[2,4] are commonly employed as solvents in oxidations using Fetizon's reagent.[9] Therefore, the oxidation of the enelactol **2a** was first carried out in refluxing benzene to effect selective oxidation of the allylic hemiacetal hydroxyl group. The reaction was closely monitored by t.l.c and was judged to be complete when the enelactol **2a** had disappeared. Interestingly, two products, identified as the desired enelactone **3a** and its epimer **4a** based on NMR data (*vide infra*), were obtained in a 1.1:1.0 ratio (73%). Oxidation using reagent that was further dried by azeotropic distillation with benzene also gave similar results. When the oxidation was performed in refluxing toluene, enelactones **3a** and **4a** were obtained in a ratio of 1.3:1.0 (81%). It has been reported[9] that allylic alcohols are efficiently oxidized with Fetizon's reagent when conducted in refluxing acetone. Thus, the enelactol **2a** was oxidized under the prescribed conditions[9] and, to our surprise, the enelactone **3a** was obtained in 80% yield. The epimer **4a** was not detected. Furthermore, brief exposure of **3a** to Fetizon's reagent in refluxing benzene resulted in the formation of **4a** (**3a**:**4a**= 2:1).

This prompted further studies in the oxidation of the malonate ester derivative **2b**, which was obtained from the acid hydrolysis of **1b**. Oxidation in refluxing acetone gave the enelactone **3b** in excellent yield (96%). In contrast, the oxidation of **2b** in refluxing benzene resulted in unidentified decomposition products, and no starting material was recovered.[10]

The structures for the enelactones **3a** and **4a** were readily assigned based on their ^{1}H NMR and ^{13}C NMR and including COSY experiments. The salient feature in the ^{1}H NMR spectra of **3a** and **4a** is the resonance due to H-3, which resonated as a double doublet in both compounds. In **3a**, the signal is centered at δ 6.97 whereas in **4a** it is centered at δ 6.76. The vicinal coupling constant between H-3 and H-4 is diagnostic in that for **3a**, $J_{3,4}$= 3.3 Hz and in **4a**, $J_{3,4}$= 4.2 Hz. In the ^{13}C NMR spectra, the C-4 resonance in **3a** appeared at slightly higher field at δ 36.80 whereas in **4a** it is observed at δ 37.89. For the enelactone **3b**, H-3 resonated as a double doublet centered at δ 6.72 with a vicinal coupling constant $J_{3,4}$= 3.8 Hz. In the ^{13}C NMR spectrum, the C-4 resonance was observed at δ 34.39.

In summary, we have demonstrated that epimerization of the allylic 4C-hydroxymethyl group occurred when the oxidation of the enelactol **2a** with Fetizon's reagent was conducted in non-polar solvents. However, epimerization was inhibited when oxidation was conducted in a polar solvent, such as acetone. Although the mechanism of the epimerization remains unclear,[11] the process described here provides access to both D-*erythro*- and D-*threo*- 4C-hydroxymethyl-2-hexenopyrano-1,5-δ-lactones from the enelactol **2a**.

EXPERIMENTAL SECTION

Infrared spectra were recorded using a Perkin-Elmer 1600FT infrared spectrophotometer. N.M.R. spectra were obtained on a Bruker AC200 QNP; chemical shifts are reported in parts per million (δ)

relative to the appropriate reference signals. ^{1}H N.M.R. (200 MHz) were recorded in deuteriochloroform ($CDCl_3$) using tetramethylsilane (δ_H 0.0) or residual chloroform (δ_H 7.24) as reference, and coupling constants are given in Hertz. Proton assignments were based on homonuclear decoupling experiments and, where appropriate, supported by homonuclear 2D-COSY experiments. ^{13}C N.M.R. and ^{13}C N.M.R DEPT (50.32 MHz) were recorded in $CDCl_3$ using the $CDCl_3$ signal at δ 77.0 as reference. The ^{13}C DEPT-135 pulse sequence[12] inverted only the CH_2s (designated -); the CHs and CH_3s remained upright. Quaternary carbons are not seen. Microanalyses were performed at the Microanalytical Department, University of Alberta and at the University of Regina, Canada. Reaction progress was monitored by thin-layer chromatography (TLC) on Merck silica gel 60_{F254} precoated (0.25 mm) on aluminum backed sheets. TLC plates were stained using an 7% ethanolic solution of phosphomolybdic acid. Chromatographic purification means flash chromatography[13] performed on Merck silica gel 60 (230-400 mesh). Dichloromethane, benzene and toluene were dried by distillation from calcium hydride. Fetizon's reagent was prepared as described in the literature.[9]

Preparation of Enelactones 3a and 4a.

a) Acid Hydrolysis of Compound 1a.- Compound **1a**[8] (179.8 mg, 0.436 mmol) was dissolved in a mixture of THF-aq. 0.5% HCl (4:1 v/v, 15.5 mL), under Ar, and then heated at 60°. After 25 min., the reaction mixture was cooled to 0° and quenched with excess solid $NaHCO_3$. EtOAc (12 mL) was added and the mixture was concentrated, and the remaining traces of water were removed by azeotropic distillation using toluene (25 mL). The residue was then dissolved in EtOAc (12 mL), dried (Na_2SO_4), filtered and concentrated. Enelactol **2a** (ratio of α:β anomers; 1.5: 1.0) was obtained as a pale yellow oil after chromatography (acetone-dichloromethane, 1:6 v/v). IR υ_{max}(neat): 3540–3020, 1589 cm^{-1} . ^{1}H NMR: (The resonances for the minor β-anomer are in parentheses): δ 1.08 (s, 9H, Bu-t), [2.21–2.40, 0.4H] and 2.40–2.60 (0.6H) (m, H-4), 2.64–2.94 (br s, 1H, OH), 3.30–3.99 (m, 6H, H-5, H-6, H-7, OH), 5.14–5.36 (m, 1H, H-1), 5.84 (br s, 1H, H-2), [5.73–5.93, 0.4H] and 5.93–6.14 (0.6H) (m, H-3), 7.30–7.53 (m, 6H, PhH), 7.56–7.71 (m, 4H, PhH). ^{13}C NMR: (The signals for the minor anomer are in parentheses): δ 19.17, 26.80, 36.82, [39.99], 59.81, [63.32], 65.41, [66.05], 71.66, [73.48], 88.52, 127.46, 127.75, [127.81], [128.25], 129.58, 129.82, [129.92], [130.49], 132.94, 135.46, [135.60].

a) Oxidation of Compound 2a in Refluxing Dry Benzene.– Compound **2a** (200 mg, 0.503 mmol) was dissolved in dry benzene (50 mL) and to this solution was added Fetizon's reagent (2.07 g, 7.538 mmol), under Ar. The mixture was refluxed for 40 min; during this time, it turned black. The reaction mixture was cooled to rt, filtered and benzene was evaporated. The residual oil was chromatographed (acetone-CH_2Cl_2, 4:100 v/v) to afford the enelactones **3a** (76.3 mg) and **4a** (68.2 mg) in a combined yield of 73 %. Enelactone **3a**: $[\alpha]_D^{23.5}$ - 54.4 (c, 1.01, $CHCl_3$). IR υ_{max} (neat): 3558–3250, 1726, 1589, 1500 cm^{-1}. ^{1}H NMR: δ 1.08, (s, 9H, t-Bu), 2.50–2.65 (br s, 1H, OH), 2.65–2.80 (m, 1H, H-4), 3.57–3.80 (m, 3H, H-5, H-6), 4.22 (dd, 2H, J= 11.1, 7.7 Hz, H-7), 6.02 (dd, 1H, J= 9.7, 2.3 Hz, H-2), 6.97 (dd, 1H, J= 9.7, 3.2 Hz, H-3), 7.30–7.53 (m, 6H, PhH), 7.56–7.71(m, 4H, PhH). ^{13}C NMR: δ 19.19, 26.85, 36.80, 65.27(-), 68.08(-), 71.07, 121.44, 127.95, 130.12, 135.46, 147.22, 161.90.

Anal. Calcd. for $C_{23}H_{28}O_4Si$: C, 69.65; H, 7.12. Found: C, 69.54; H, 7.19

Enelactone **4a**: $[\alpha]_D^{23.5}$ +45.8 (c, 0.818, $CHCl_3$). IR υ_{max} (neat): 3558–3250, 1730 (sh), 1707, 1589, 1575, 1500 cm^{-1}. ^1H NMR: δ 1.10 (s, 9H, t-Bu), 1.92–2.28 (br s, 1H, OH), 2.80–2.98 (m, 1H, H-4), 3.71 (dd, 2H, J= 9.6 Hz, H-7), 3.88 (dd, 2H, J= 17.8, 7.6 Hz, H-6), 4.43–4.56 (m, 1H, H-5), 6.01 (dd, 1H, J= 10.1, 2.5 Hz, H-2), 6.76 (dd, 1H, J= 10.1, 4.2 Hz, H-3), 7.30–7.50 (m, 6H, PhH), 7.55–7.75 (m, 4H, PhH). ^{13}C NMR: δ 19.23, 26.81, 37.89, 62.13(-), 64.01(-), 79.25, 121.43, 127.88, 130.00, 132.55, 132.78, 135.56, 135.62, 146.66, 163.37.

Anal. Calcd. for $C_{23}H_{28}O_4Si$: C, 69.65; H, 7.12. Found: C, 69.82; H, 7.17

The oxidation of **2a** (360 mg, 0.909 mmol) using Fetizon's reagent (5.40 g, 19.58 mmol) in refluxing dry toluene (80 mL) yielded **3a** (165.6 mg) and **4a** (126 mg) in a combined yield of 81.4%.

b) Oxidation of Enelactol 2a in Refluxing Dry Acetone.- Enelactol **2a** (160 mg, 0.39 mmol) was dissolved in dry acetone (25 mL) and Fetizon's reagent (1.8 g, 15 mole equivalent) was added under Ar. The mixture was refluxed for 1 hr and then cooled to rt, filtered, and the inorganic residue washed with acetone (2 x 10 mL). The filtrate was evaporated and the crude enelactone was chromatographed (acetone - CH_2Cl_2, 4 : 100 v/v) to give enelactone **3a**, which had identical NMR data to those reported above. Yield: 80%. $[\alpha]_D^{23.5}$ -54.5 (c 1.01, $CHCl_3$).

Treatment of Enelactone 3a with Ag_2CO_3 on Celite in Refluxing Dry Benzene.- Compound **3a** (24 mg, 0.0604 mmol) was dissolved in dry benzene (5 mL) under Ar, and Fetizon's reagent (250 mg, 0.9060 mmol) was added. The mixture was refluxed for 30 min and then cooled to rt. The mixture was filtered, the residue washed with ethyl acetate (3 x 5 mL) and the filtrate was evaporated *in vacuo* to leave an oil (100%). TLC analysis of the oil using authentic **3a** and **4a** as references and ^1H NMR analysis of the oil showed that it is comprised of **3a** and **4a**. The ratio of **3a**: **4a** is 2:1 and was based on the integration of the H-3 double doublet centred at δ 6.96 (**3a**) and 6.76 (**4a**).

Preparation of Enelactone 3b.

a) Acid Hydrolysis of Compound 1b.- Compound **1b** (170 mg) was dissolved in THF–0.5% aq. HCl (4:1 v/v) (12 mL). The mixture was heated, under Ar, at 60 ° for 4 hrs. The reaction mixture was processed in the same way as that described in the hydrolysis of **1a**. The crude product was chromatographed (ethyl acetate–pet. ether, 1:3 v/v) to give enelactol **2b** (140 mg, 87%) as an anomeric mixture. IR υ_{max} (neat): 3459, 1756 (sh), 1738, 1589 cm^{-1}. ^1H NMR: (Resonances for the minor anomer are in parentheses): δ 1.05 (s, 9H, Bu-t), 2.40–2.62 (m, 1H, H-4), 3.32 (s, 2H, $CH_2(CO)_2$), 3.47–3.57 (br hump, 1H, OH), 3.69 (s, 3H, OMe), 3.74–3.97 (m, 1H, H-5), 3.87 (br s, 2H, H-6), 4.02 (dd, 1H, J= 11.4, 6.2 Hz, H-7), 4.26 (dd, 1H, J= 11.4, 4.4 Hz, H-7'), [5.24, br d, 0.25H] and 5.30–5.50 (m, 0.75H) (H-1), [5.81, 0.5H] and 5.87 (1.5H) (br s, H-2, H-3), 7.30–7.50 (m, 6H, PhH), 7.59–7.76 (m, 4H, PhH). ^{13}C NMR: (The signals for the minor anomer are in parentheses): δ [19.03], 19.11, 26.69, [34.38] 35.48, [39.12], 40.97, 52.41, 64.63, 64.91, [65.14], [65.44], 66.39, [72.45], 88.28, [88.65], 126.45, 127.58, [129.19], 129.47, 129.59, [132.85], [133.09], 133.24, 135.46, 135.55, 166.03, [166.57], 166.88, [171.06].

b) Oxidation of Enelactol 2b in Refluxing Dry Acetone.– Enelactol **2b** (490 mg, 0.98 mmol) was oxidized using Fetizon's reagent (6.3 g, 23 mmol) in the same way as described above for **2a**. The

enelactone **3b** was obtained as a pale yellow oil (470 mg, 96%) after chromatographic purification (ethyl acetate–pet. ether, 1:1 v/v). $[\alpha]_D^{23.5}$ +56.2 (c 1.34, $CHCl_3$). IR υ_{max} (neat): 1746, 1731, 1714, 1589, 1500 cm^{-1}. ^1H NMR: δ 1.05 (s, 9H, Bu-t), 3.07–3.22 (m, 1H, H-4), 3.35 (s, 2H, $CH_2(CO)_2$), 3.70 (s, 3H, OMe), 3.83 (dd, 1H, J= 10.6, 4.2 Hz, H-6), 3.92 (dd, 1H, J= 10.6, 5.5 Hz, H-6'), 4.22 (dd, 1H, J= 11.9, 5.2 Hz, H-7), 4.31 (dd, 1H, J= 11.9, 5.9 Hz, H-7'), 4.47 (dt, 1H, J= 6.5, 4.5 Hz, H-5), 6.04 (dd, 1H, J= 9.9, 1.5 Hz, H-2), 6.72 (dd, 1H, J= 9.9, 3.8 Hz, H-3), 7.32–7.51 (m, 6H, PhH), 7.57–7.71 (m, 4H, PhH). ^{13}C NMR: δ 19.12, 26.69, 34.39, 40.89(-), 52.51, 63.32(-), 63.67(-), 78.59, 122.00, 127.81, 129.23, 132.34, 132.81, 135.42, 135.52, 144.40, 162.33, 165.99, 166.42.
Anal. Calcd. for $C_{27}H_{32}O_7Si$: C, 65.28; H, 6.50. Found: C, 65.22; H, 6.62

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7. Only in one isolated case has an epimerization reaction α to the newly formed carbonyl group been documented. (see Ref 5a).

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9. This reagent was prepared and dried according to the procedure described in M. Fieser and L. Fieser. *Reagents For Organic Synthesis*, Vol. 2, p. 363, Wiley Interscience, New York, NY 1969. The reagent was stored, under N2, in the dark.

10. A similar outcome was obtained when the acetate **2** (R^1 = Ac) was oxidized with Ag_2CO_3 on Celite in refluxing benzene.

11. No epimerization was observed when enelactone **3a** was treated with anhydrous Na_2CO_3 in either refluxing acetone or benzene for 1 hr. In the absence of additional information regarding this epimerization reaction, we reserve comment on its mechanism.

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