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Singular Features of Hydrolysis of Partially Blocked β,δ-Dihydroxy Enol Ether from Pantolactone

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Abstract—Enol ether from pantolactone, 5-hydroxy-4,4-dimethyl-1-methoxy-3-methoxymethyloxy-1-pentene in hydrolysis reactions catalyzed by ions H+ and Hg++ afforded the corresponding products of methoxymethanol elimination.

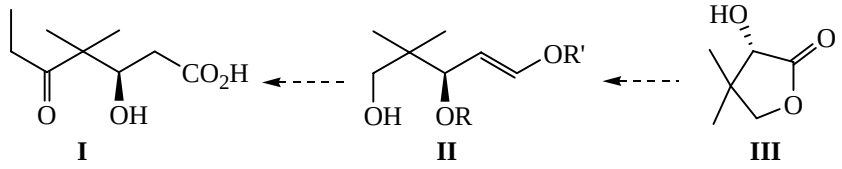
Among methods of aldehyde homologization by one carbon atom Wittig reaction with alkoxymethylidenephenyl phosphoranes is of interest as a practical procedure converting the aldehydes into the corresponding enol ethers with subsequent acid hydrolysis [1, 2]. Enol ethers containing a hydroxy or another leaving group in the allyl position under conditions of the "hard" acid hydrolysis commonly afford α,β-unsaturated aldehydes. However it is necessary often to generate the aldehyde function in the molecules of the mentioned β-oxy enol ethers with retention of the hydroxy group. Note that the configurationally uniform β-oxycarbonyl fragments are present in the structures of many naturally occurring substances; for instance, an important block in the synthesis of epothilones [3–5] is β-hydroxyacid **I**. We planned to perform synthesis of acid **I** from pantolactone (**III**) via enol ether **II**.

Following this scheme the main task formally consisted in insertion of a double bond into position *1*(*2*) of pantolactone along the above discussed enol ether procedure.

The model experiments were carried out with the racemic pantolactone. First a methoxymethyl ether (MOM) of pantolactone (**IV**) was prepared which was reduced with *i*-Bu_2AlH into lactol **V**. The latter cleanly reacted with phosphorane reagent **VI** [6] to afford the isomer mixture of enol ethers **VII** (*Z*:*E*, ~1:4, ^1H NMR) in a 62% yield.

Under standard conditions of the mild acid hydrolysis of acetals (water solution HCl–MeOH or *p*-TsOH–

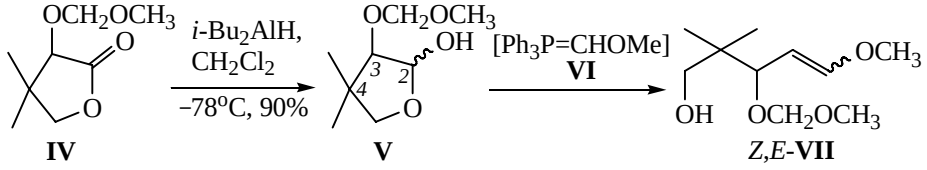
Scheme 1.



I **II** **III**

R, R' are protecting groups

Scheme 2.



IV **V** *Z*,*E*-**VII**

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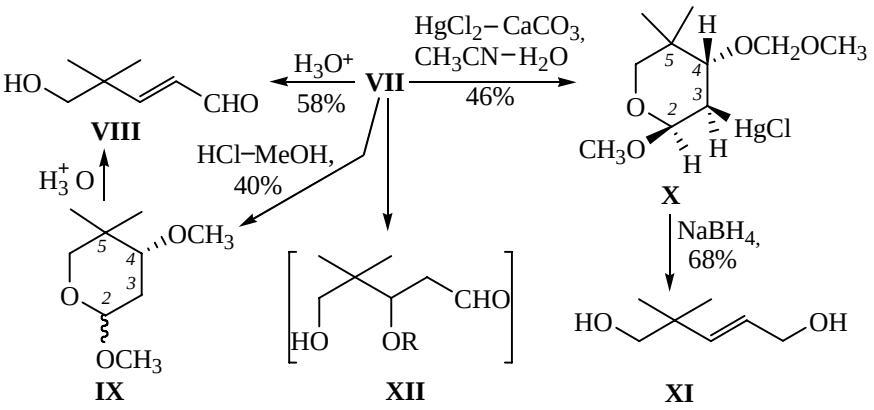
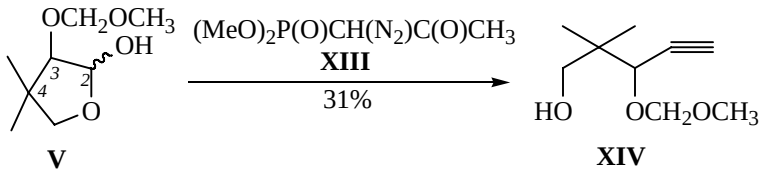
Scheme 3.



Scheme 4.



dioxane, 20°C) enol ether **VII** was totally converted into α,β-unsaturated aldehyde **VIII**. The keeping of enol ether **VII** in an anhydrous 3% HCl solution in MeOH afforded methoxyacetal **IX**. In this case the protected hydroxy function was not eliminated, and only transetherification occurred (MOM group was replaced by Me). The subsequent water-acid hydrolysis of acetal **IX** also resulted in uncontrolled formation of enal **VIII**. At an attempt to hydrolyze enol ether **VII** by a mild system $HgCl_2$– $CaCO_3$–MeCN–H_2O recommended for use with such compounds [7, 8] we isolated only pure diastereomer of organomercury compound **X**. The structure of compound **X** follows from its spectral data. Its ^1H NMR spectrum contains doublet signals from H^2 and H^4, and H^3 gives rise to a doublet of doublets, *J* 3.08 and 11.7 Hz. These data indicate the *trans*-diaxial position of protons attached to C^3 and C^4, and the H^2 proton has an equatorial orientation in the pyran ring existing in the *chair* conformation with an axially located methoxy group (anomeric effect). The reductive removal of Hg from compound **X** effected by $NaBH_4$ provided exclusively unsaturated diol **XI** (Scheme 3) whose formation mechanism was not understood.

The difficulties arising in preparation of β-oxyaldehydes **XII** at hydrolysis of enol ethers **VII** we attribute to its structural features. Apparently the hydrolysis products **VIII** and **XI** form through an intermediate aldehyde **XII** which readily eliminates the methoxymethanol CH_3OCH_2OH (the compound is sterically loaded, and the primary OH group renders assistance to the elimination of ROH).

The alternative method of building up the carbon skeleton of **VII** applying phosphonate **XIII** [9] via acetylene alcohol **XIV** that might be converted into aldehyde **XII** by hydroboration-oxidation procedure is also unattractive due to the low yield of compound **XIV**.

EXPERIMENTAL

IR spectra were recorded on spectrophotometers UR-20 and Specord-80 from samples as thin films or as mulls in mineral oil. ^1H and ^{13}C NMR spectra were registered on spectrometer Bruker AM-300 at operating frequencies 300.13 and 75.47 MHz respectively, internal reference TMS.

2-Hydroxy-4,4-dimethyl-3-methoxymethoxytetrahydrofuran (V). To a stirred solution of 0.5 g (2.87 mmol) of compound **IV** in 10 ml of anhydrous CH_2Cl_2 at –78°C under inert atmosphere was added dropwise 1.9 ml of 60% *i*-Bu_2AlH solution in hexane. On complete consumption of initial ketone (TLC monitoring) the reaction mixture was treated with a saturated NH_4Cl solution and extracted with CH_2Cl_2 (3×10 ml), the combined extracts were washed in succession with cold

water and a saturated NaCl solution, dried over $MgSO_4$, and evaporated to obtain 2.57 g (90%) of alcohol **V** as a colorless oily substance that was brought into the next stage of the synthesis without purification. IR spectrum, cm^{-1}: 3000–3400, 1390, 1310, 1290, 1130, 940, 840. **Prevailing diastereomer.** ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.04 s and 1.07 s (6H, *gem*-CH_3), 3.38 s (3H, OCH_3), 3.52 m (1H, OH), 3.62 s (2H, OCH_2), 3.8 d (1H, OC^3H, *J* 8.4 Hz), 4.71 s (2H, OCH_2O), 5.28 d (1H, OC^2H, *J* 3.1 Hz). **Minor diastereomer**. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.07 s and 1.1 s (6H, *gem*-CH_3), 3.41 s (3H, OCH_3), 3.52 m (1H, OH), 3.61 s (2H, OCH_2), 3.72 d (1H, OC^3H, *J* 8.1 Hz), 4.65 d (1H, *J* 6.6 Hz) and 4.76 d (1H, OCH_2O, *J* 6.6 Hz), 5.43 d (1H, OC^2H, *J* 4.2 Hz).

5-Hydroxy-4,4-dimethyl-1-methoxy-3-methoxymethyloxy-1-pentene (VII). To ylide prepared from 3.04 g (8.57 mmol) of phosphonium salt **VI** and 1.92 g (17.14 mmol) of *t*-BuOK in 20 ml of anhydrous benzene was added dropwise under argon at stirring a solution of 0.5 g (2.86 mmol) of compound **V**. The reaction mixture was stirred for 10 h at room temperature, then it was treated with a saturated NH_4Cl solution and diluted with $CHCl_3$. The organic layer was separated, and the products from the water layer were extracted into $CHCl_3$ (3×20 ml). The combined organic solutions were washed with a NaCl solution, dried over $MgSO_4$, evaporated, and the residue was subjected to chromatography on SiO_2 (eluent EtOAc–petroleum ether, 3:1) to obtain 0.36 g (62%) of oily compound **VII** as a mixture of *trans*- and *cis*-isomers in a ratio ~4:1 (^1H NMR). IR spectrum, cm^{-1}: 3358, 1690, 1654, 1438, 1390, 1168, 1120, 1042, 724. Found, %: C 57.90; H 9.70. $C_{10}H_{20}O_4$. Calculated, %: C 58.82; H 9.87. ***trans*-Isomer.** ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.74 s and 0.77 s (6H, *gem*-CH_3), 2.84 br.s (1H, OH), 3.24 s (3H, OCH_3), 3.43 s (3H, OCH_3), 3.19 d (1H, *J* 10.4 Hz) and 3.44 d (1H, OC^5H_2, *J* 10.6 Hz), 3.67 d (1H, OC^3H, *J* 9.8 Hz), 4.31 d (1H, *J* 6.6 Hz) and 4.60 d (1H, OCH_2O, *J* 6.4 Hz), 4.49 d.d (1H, *J* 2.8 and 12.7 Hz) and 6.31 d (1H, HC=CH, *J* 12.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 19.87 and 22.44 (*gem*-CH_3), 39.85 (C^4), 55.64 and 56.17 (OCH_3), 70.30 (C^5), 80.65 (C^3), 92.71 (OCH_2O), 96.32 (C^2), 152.14 (C^1). ***cis*-Isomer.** ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.71 s and 0.79 s (6H, *gem*-CH_3), 2.84 br.s (1H, OH), 3.26 s (3H, OCH_3), 3.47 s (3H, OCH_3), 3.21 d (1H, *J* 10.4 Hz) and 3.44 d (1H, OC^5H_2, *J* 10.6 Hz), 3.71 d (1H, OC^3H, *J* 9.9 Hz), 4.36 d (1H, *J* 6.3 Hz) and 4.55 d (1H, OCH_2O, *J* 6.4 Hz), 4.21 d.d (1H, *J* 3.7 and 6.3 Hz) and 6.02 d (1H, HC=CH, *J* 6.4 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.13 and 21.10 (*gem*-CH_3), 39.03 (C^4), 55.81 and 59.91 (OCH_3), 70.50 (C^5), 75.29 (C^3), 94.05 (OCH_2O), 96.13 (C^2), 149.89 (C^1).

5-Hydroxy-4,4-dimethyl-2-pentenal (VIII). A mixture of 0.1 g (0.5 mmol) of compound **VII** and 1 mg of *p*-TsOH was dissolved in a system dioxane–H_2O, 1:1, and then stirred for 30 min at 50°C. On cooling the mixture was neutralized by adding crystalline $NaHCO_3$, dioxane was distilled off, and the products were extracted from water into $CHCl_3$, the extract was dried over $MgSO_4$, evaporated, and the residue was subjected to chromatography on SiO_2 (eluent EtOAc–petroleum ether, 3:1) to obtain 0.05 g (58%) of colorless oily compound **VIII**. IR spectrum, cm^{-1}: 3400, 2356, 1714, 1696, 1654, 1468, 1366, 1306, 1180, 1048, 1000, 982. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.11 s (6H, *gem*-CH_3), 2.38 br.s (1H, OH), 3.47 s (2H, C^5H_2), 6.09 d.d (1H, C^2H, *J* 7.7 and 16.0 Hz), 6.86 d (1H, C^3H, *J* 16.0 Hz), 9.48 d (1H, CHO, *J* 7.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.56 (*gem*-CH_3), 34.25 (C^4), 65.17 (C^5), 125.10 (C^2), 159.50 (C^3), 188.98 (CHO).

5,5-Dimethyl-2,4-dimethoxytetrahydropyran (IX). In 10 ml of anhydrous 3% HCl solution in MeOH was dissolved 0.57 g (2.8 mmol)of compound **VII**, and the solution was stirred for 24 h at room temperature. On complete consumption of initial alcohol (TLC monitoring) the reaction mixture was neutralized by adding solid $NaHCO_3$ till pH 7, and MeOH was distilled off. The residue was dissolved in $CHCl_3$, washed with a saturated NaCl solution, dried over $MgSO_4$, evaporated, and the residue was subjected to chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1:3) to obtain 0.17 g (40%) of oily compound **IX** as a mixture of diastereomers in a ratio ~ 3:1 (^1H NMR). **Prevailing diastereomer.** ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.88 s and 0.93 s (6H, *gem*-CH_3), 1.59 m (1H) and 1.91–2.07 m (1H, C^3H_2), 3.03 d (1H, *J* 11.7 Hz) and 3.11 d (1H, CH_2O, *J* 11.2 Hz), 3.31 s (6H, OCH_3), 3.41 d (1H, OC^4H, *J* 11.7 Hz), 4.74 m (1H, C^2H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.50 and 23.48 (*gem*-CH_3), 30.96 (C^3H_2), 35.49 (C^5), 54.65 (OCH_3), 57.11 (OCH_3), 69.18 (C^6), 80.06 (C^4), 99.59 (C^2). **Minor diastereomer.** ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.22 s and 23.02 s (*gem*-CH_3), 31.74 (C^3H_2), 35.17 (C^5), 56.19 (OCH_3), 57.01 (OCH_3), 72.32 (C^6), 82.51 (C^4), 102.01 (C^2).

5,5-Dimethyl-2-methoxy-4-methoxymethyloxy-5,5-dimethyl-3-chloromercuriopyran (X). A mixture

of 0.1 g (4.9 mmol) of compound **VII**, 0.16 g (4.92 mmol) of $HgCl_2$, and 0.05 g (4.92 mmol) of $CaCO_3$ in 5 ml of a mixture MeCN–H_2O, 1:1, was stirred for 15 h at room temperature. The acetonitrile was distilled off, the residue was dissolved in $CHCl_3$ and filtered through a small zeolite bed. The organic layer was washed with a NaCl solution, dried over $MgSO_4$, evaporated, and the residue was subjected to chromatography on SiO_2 (eluent EtOAc–petroleum ether, 3:1) to obtain 0.093 g (46%) of colorless oily compound **X**. IR spectrum, cm^{-1}: 1576, 1450, 1378, 1336, 1150, 1108, 1036, 988, 922, 754, 700. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 s and 0.99 s (6H, *gem*-CH_3), 2.88 d.d (1H, H^3, *J* 3.5 and 11.7 Hz), 3.08 d (1H, *J* 11.3 Hz) and 3.5 d (1H, CH_2O, *J* 11.4 Hz), 3.38 s and 3.40 s (6H, OCH_3), 3.74 d (1H, H^4, *J* 11.7 Hz), 4.71 d.d (2H, OCH_2O, *J* 5.8 and 11.5 Hz), 4.77 d (1H, H^2, *J* 3.3 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.92 and 23.58 (*gem*-CH_3), 39.15 (C^5), 54.81 (C^3), 55.21 and 56.63 (OCH_3), 68.56 (C^6), 84.70 (C^4), 100.29 (OCH_2O), 101.46 (C^2). Found, %: C 27.74; H 4.64. $C_{10}H_{19}ClHgO_4$. Calculated, %: C 27.34; H 4.36.

4,4-Dimethyl-2-pentene-1,5-diol (XI). To a dispersion of 0.09 g (2.35 mmol) of $NaBH_4$ in 10 ml of anhydrous EtOH at 0°C was added dropwise 0.2 g (0.47 mmol) of compound **X** in 3 ml of EtOH. The reaction mixture was stirred at room temperature for 15 h, the excess $NaBH_4$ was decomposed by a little of saturated NH_4Cl solution, the solution was decanted from the precipitated metallic mercury, EtOH was distilled off, and the reaction products were extracted from the residue into EtOAc (3×20 ml). The combined extracts were dried over $MgSO_4$, evaporated, and the residue was subjected to chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1:1). We obtained as the main product 0.06 g (68%) of colorless oily compound **XI**. IR spectrum, cm^{-1}: 3382, 3346, 1462, 1384, 1354, 1078, 1042, 970, 760. ^1H ($CDCl_3$), δ, ppm: 0.97 s (*gem*-CH_3), 1.48 br.s (1H, OH), 3.26 s (2H, OC^5H_2), 3.26–3.36 m (2H, OC^1H_2), 3.41 s (1H, OH), 4.06 d (1H, C^2H, *J* 1.4 Hz), 5.60 d (1H, C^3H, *J* 1.2 Hz). ^{13}C ($CDCl_3$), δ, ppm: 23.75 (*gem*-CH_3), 38.21 (C^4), 63.46 (C^5), 71.53 (C^1), 127.51 (C^2), 139.6 (C^3).

2,2-Dimethyl-3-methoxymethyloxy-5-hexyn-1-ol (XIV). To a stirred solution of 0.1 g (0.77 mmol) of lactol **V** and 0.42 g (3.08 mmol) of K_2CO_3 in 20 ml of anhydrous MeOH at room temperature under argon was added dropwise a solution of 0.26 g (1.35 mmol) of phosphonate **XIII** in 3 ml of MeOH. The reaction mixture was stirred for 14 h, then the solution was decanted from the precipitate, MeOH was distilled off, the residue was diluted with a saturated NaCl solution, the reaction products were extracted into $CHCl_3$ (3×10 ml), the extract was dried over $MgSO_4$, evaporated, and the residue was subjected to chromatography on SiO_2 (eluent petroleum ether–EtOAc, 1:3) to obtain 0.03 g (31%) of colorless oily compound **XIV**. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.01 s (3H) and 1.04 s (3H, *gem*-CH_3), 2.38 br.s (1H, OH), 2.45 d (1H, ≡CH, *J* 1.1 Hz), 3.39 s (3H, OCH_3), 3.42 m (1H) and 3.64 d (1H, OC^1H_2, *J* 11.1 Hz), 4.26 d (1H, OC^3H, *J* 1.1 Hz), 4.56 d (1H, *J* 6.7 Hz) and 5.60 d (1H, OCH_2O, *J* 6.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.07, 21.44 (*gem*-CH_3), 39.44 (C^2), 56.00 (OCH_3), 69.48 (C^1), 72.42 (C^5), 75.09 (C^4), 80.42 (C^3), 94.45 (OCH_2O).

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REFERENCES

1. Martin, S.F., *Synthesis*, 1979, p. 633.
2. Brewer, J.D. and Elix, J.A., *Aust. J. Chem*., 1972, vol. 25, p. 545.
3. Hofle, G., Bedorf, N., Steinmetz, H., Schomburg, D., Gerth, K., and Reichenbach, H., *Angew. Chem., Int. Ed.*, 1996, vol. 35, p. 1567.
4. Meng, D., Bertinato, P., Balog, A., Su, D., Kamenecka, T., Sorensen, E.J., and Danishefsky, S.J., *J. Am. Chem. Soc*., 1997, vol. 119, 10079.
5. Nicolaou, K., Vourloumis, D., He, Y., and Vallberg, H., *J. Am. Chem. Soc.*, 1997, vol. 119, p. 7960.
6. Marganoff, B.E. and Reitz, A.B., *Chem. Rev.*, 1989, p. 863.
7. Bommer, R., Kinzy, W., and Schmidt, R.R., *Lieb. Ann.*, 1991, p. 425.
8. Ireland, R.E. and Norbeck, D.W., *J. Am. Chem. Soc.*, 1985, vol. 107, p. 3279.
9. Thiery, J.-Ch., Frechon, C., and Demally, G., *Tetrahedron Lett.*, 2000, vol. 41, p. 6337.