Dramatic Effect of the Gas Atmosphere on the Deprotection of (*Z*)-γ-Hydroxy-α,β-unsaturated Esters

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Abstract-The deprotection of *O*-protected (*Z*)-α-methyl-γ-hydroxy-α,β-unsaturated ester **1** furnishes dimer **2** when the reaction is performed under a nitrogen atmosphere, while compound **3** forms when the reaction is performed under an oxygen atmosphere.

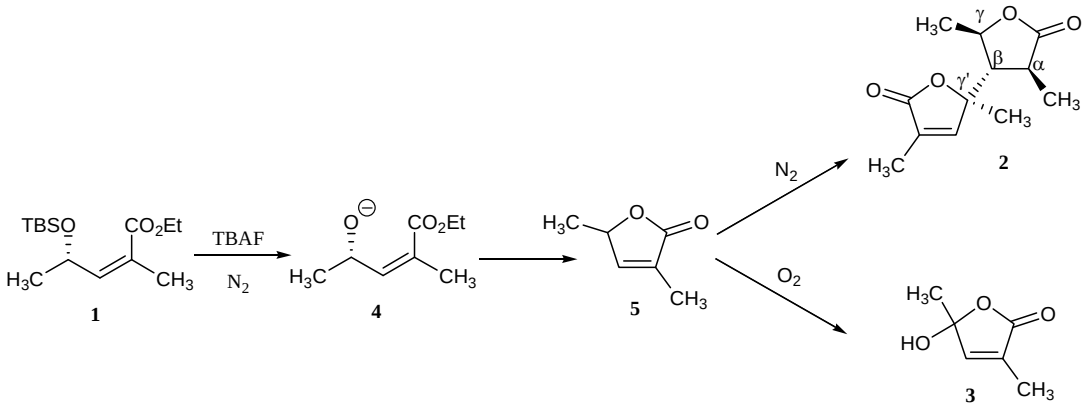
Keywords: butenolides, dimerization, γ-hydroxybutenolides

1. Introduction

Butenolides are interesting building blocks in organic synthesis [1], and their dimerization offers an attractive approach for the synthesis of natural products [2]. The formation of □□□′ dimers from butenolides under basic conditions has been reported [3,1b], and the □-hydroxybutenolide derivatives are known antimicrobial compounds and are often used as anticancer or anti-inflammatory agents [4]. Thus, the development of facile methods for synthesizing this class of structures is important [5,2d]. Herein, we report that both types of compounds (□□□′ dimers and □-hydroxybutenolides) can be obtained from the same butenolide, depending upon the reaction conditions. Under an inert atmosphere, the □□□′□dimer is formed, but under an oxygen atmosphere the □-hydroxybutenolide is obtained.

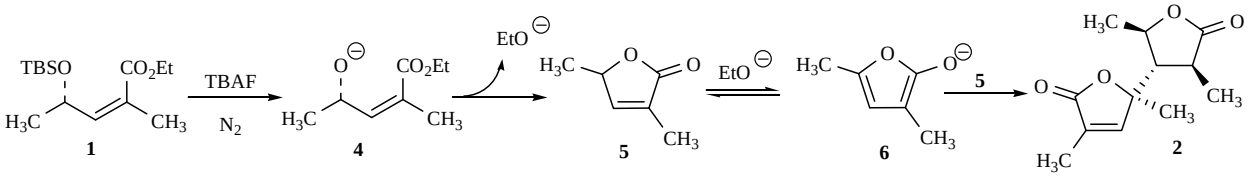
2. Results

In the course of our work on the epoxidation of □-hydroxy-□□□-unsaturated esters [6], we easily prepared *O*-protected (*Z*)-□-methyl-□-hydroxy-□□□-unsaturated ester **1** from (*S*)-lactaldehyde [7]. During the deprotection of (*Z*) enoate **1**, we observed the formation of dimer **2**. Serendipitously, when the deprotection reaction was carried out in the open air, compound **3** was obtained. Presumably, deprotection of compound **1** gave rise to □-hydroxy enoate **4**, which, upon cyclization, furnished butenolide **5**. Butenolide **5** would subsequently be converted into dimer **2** or, if the oxidative process takes place promoted by an oxygen atmosphere, compound **3** (Scheme 1).



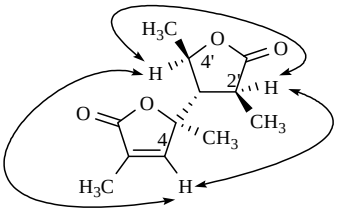
Scheme1.

The formation of dimer **2** can be easily explained by the basic enolization of butenolide **5**, giving rise to enolate **6** which, upon conjugate addition with **5,** furnishes dimer **2** (Scheme 2). Compound **2** was formed in a highly stereoselective fashion (d.r. 19:1) giving rise to the *endo*-product. It is noteworthy that 4 stereocenters were formed in one pot with stereoselectivity. Although Michael dimerizations of □-substituted butenolides [3] have been previously reported, we report here a stereoselective Michael dimerization of a□□□□-disubstituted butenolide. Thus, Michael dimerization is more selective toward □□□-disubstituted butenolides than toward □-substituted butenolides.



Scheme 2.

Stereochemical assignment in compound **2** was performed by NOE experiments. Dimer **2** gave NOE between H-4′ and H-2′ and between H-4′ and H-4, while H-2′ also gave NOE with H-4 (Scheme 3).



Scheme 3.

The X-ray crystal structure of **2** definitively confirmed the stereochemistry (Figure 1). Compound **2** crystallizes in the centrosymmetric C2/c space group. Figure 1a shows the molecular structure of the corresponding enantiomers related by a crystallographic inversion center. The structure of **2** comprises two linked five-membered lactones. Both rings are almost coplanar (interplanar angle below 10 º) and their relative orientation is linear with respect to the long axis of the 5-membered ring crossing at the C linking both lactones.

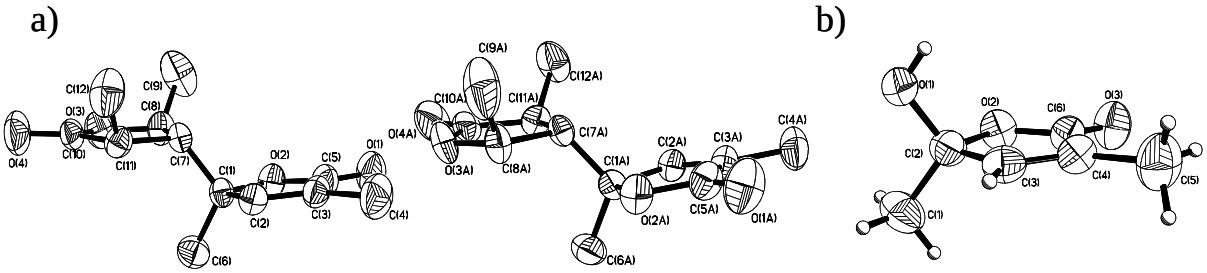
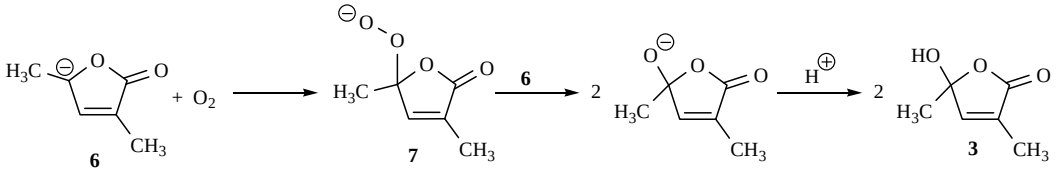


Fig. (1).

In contrast, compound **3** was obtained when the deprotection reaction was performed under an oxygen atmosphere. The □-substituted □-hydroxybutenolides are known to form through photooxidation of furans [8]. However, formation of compound **3** takes place without any photosensitizer, so singlet oxygen is not generated. In a

mechanism similar to the autoxidation of benzylic carbanions [9], carbanion **6** combines with molecular oxygen, furnishing intermediate **7** which, upon reaction with another molecule of starting enolate **6,** gives hemiketal **3**. The molecular structure of compound **3** has also been unambiguously determined by single-crystal X-ray methods (see Figure 1 b).



Scheme 4.

3. Conclusions

In summary, we have shown that the deprotection of enoate **1** furnishes □□□´ dimer **2** in a highly stereoselective fashion if the reaction is performed under a nitrogen atmosphere whilst deprotection of enoate **1** under an oxygen atmosphere furnishes □-hydroxybutenolide **3**.

4. Experimental Section

General Experimental Methods. All solvents used in reactions were freshly distilled from appropriate drying agents before use. ^{1}H NMR spectra and ^{13}C NMR spectra were measured in $CDCl_3$ (^{1}H, 7.24 ppm; ^{13}C 77.0 ppm) solution at 30 °C on a 300 MHz Mercury Varian or a 500 MHz Innova Varian NMR spectrometer at the Serveis Centrals d'Instrumentació Científica de la Universitat Jaume I. Mass spectra were measured in a QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface (Micromass, Manchester, UK). IR spectra were recorded as oily films on NaCl plates on a Perkin-Elmer 2000 FT-IR spectrometer. EM Science Silica Gel 60 was used for column chromatography while TLC was performed with E. Merck precoated plates (Kieselgel 60, F_{254}, 0.25 mm). Unless otherwise specified, all reactions were carried out under argon atmosphere with magnetic stirring. About the X-ray crystallographic study, the crystals are air stable and were mounted on the tip of a glass fiber with the use of epoxi cement. X-ray diffraction experiment was carried out on a Bruker SMART CCD diffractometer using Mo-Kα radiation (λ = 0.71073 Å) at room temperature. The data were collected with a frame width of 0.3 º in ω and a counting time of 30 and 60 s per frame for compounds **2** and **3** at a crystal to detector distance of 4 cm. The diffraction frames were integrated using the SAINT package and corrected for absorption with SADABS [10]. The structures were solved by direct methods and refined by the full-matrix method based on F^2 using the SHELXTL software package [11]. All non hydrogen atoms were refined anisotropically. Hydrogen atoms were generated geometrically, assigned isotropic thermal parameters and allowed to ride on their respective parent carbon atoms.

(*Z*)-Ethyl 4-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-pent-2-enoate 1. To an ice-bath cold suspension of sodium hydride (60% in mineral oil) (2.39 g, 59.75 mmol) in THF (59 mL) was added triethyl 2-phosphonopropionate (13 mL, 59.42 mmol). The resulting mixture was stirred at room temperature for 1h and then was cooled with an ice-bath and a solution of *O-tert*-butyldimethylsilyl lactaldehyde [12] (10.21 g, 54.30 mmol) in THF (40 mL) was added. The resulting mixture was stirred at room temperature for 7h and then was quenched with brine and extracted with Et_2O (3 x 30 mL), the organic layers were washed (brine), dried (Na_2SO_4) and concentrated. The crude oil was purified by silica gel chromatography, eluted with hexanes/Et_2O (99:1) to afford 5.85 g of compound **1** and 6.8g of *E* isomer (86%). [□$_D^{20}$]= -5.3 (c= 1.3, $CHCl_3$).

Spectroscopic data for **1**: ^{1}H NMR (500MHz, $CDCl_3$) δ 5.91 (1H, dd, J= 8.0 and 1.5Hz), 5.15 (1H, dq, J= 7.0Hz), 4.19 (2H, m), 1.88 (3H, d, J= 1.5Hz), 1.30 (3H, t, J= 7.0Hz), 1.22 (3H, d, J= 6.5Hz), 0.87 (9H, s), -0.05 (3H, s), -0.06 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 148.1, 125.1, 66.7, 60.7, 26.2, 24.1, 20.5, 18.5, 14.6, -4.3, -4.4 ppm. IR (NaCl) δ 2957, 2930, 2858, 1719, 1591, 1473, 1374, 1255, 1126, 1078, 1005, 835, 776 cm^{-1}. HRMS *m/z* calcd. for $C_{14}H_{28}O_3SiNa$ [M+Na^+]: 295.1705, found: 295.1689.

(*R*)-5-((2*R*,3*S*,4*S*)-tetrahydro-2,4-dimethyl-5-oxofuran-3-yl)-3,5-dimethylfuran-2(5*H*)-one 2. To an ice cold solution of compound **1** (2.65 g, 9.74 mmol) in THF (28 mL) under a nitrogen atmosphere was added tetra-*n*-butylammonium fluoride (1.0 M in THF) (19 mL, 19 mmol). The resulting mixture was stirred under nitrogen and allowed to warm to room temperature over 16 h. The reaction then was quenched with brine and extracted with Et_2O (3 x 30 mL), and the organic layers were washed (brine), dried (Na_2SO_4) and concentrated. The crude oil was purified by silica gel chromatography, eluted with hexanes/EtOAc (1:1) and ethyl acetate, to afford 1.63 g (75%) of compound **2** as a white solid (m.p. 68-69ºC).

Spectroscopic data for **2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (1H, s), 4.22 (1H, dd, J= 6.6, 6.3Hz), 2.64 (1H, dd, J= 7.5, 8.4Hz), 2.10 (1H, dd, J= 7.2, 8.4Hz), 1.97 (3H, d, J= 1.8Hz), 1.52 (3H, s), 1.44 (3H, d, J= 5.7Hz), 1.42 (3H, d, J= 6.9Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 172.3, 150.2, 131.0, 85.1, 74.7, 57.1, 37.5, 23.0, 22.7, 18.1, 10.6 ppm. IR (NaCl) δ 2982, 1770, 1456, 1194, 893, 765, 713 cm^{-1}. HRMS *m/z* calcd. for $C_{12}H_{16}O_4Na$ [M+Na^+]: 247.0946, found:247.0958.

5-hydroxy-3,5-dimethylfuran-2(5H)-one 3. An oxygen-flushed mixture of compound **1** (1.5 g, 5.51 mmol) in THF (28 mL) was cooled with an ice bath. Then tetra-*n*-butylammonium fluoride (1.0 M in THF) (11 mL, 11 mmol) was added dropwise. The resulting mixture was stirred under oxygen atmosphere at room temperature for 3 h. The reaction was quenched with brine, the organic solvent was removed under vacuum and then extracted with Et_2O (3 x 30 mL). The organic layers were washed (brine), dried (Na_2SO_4), and concentrated. The crude oil was purified through chromatography (silica-gel, hexanes/EtOAc (6:4), (1:1) and ethyl acetate) to afford 494 mg (70%) of compound **3** as a white solid (m.p. 98-99ºC) (lit. 98-99ºC) [13].

Spectroscopic data for **3**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (2H, s), 1.88 (6H, d, J= 1.8Hz), 1.66 (6H, s). ^{13}C NMR (125MHz, $CDCl_3$) δ 172.3, 148.1, 131.5, 104.6, 24.7, 10.3 ppm. IR (NaCl) δ 3278, 2926, 1741, 1450, 1192, 1049, 929, 873, 713 cm^{-1}. HRMS *m/z* calcd. for $C_6H_8O_3Na$ [M+Na^+]: 151.0371, found: 151.0365.

5. Acknowledgments

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6. References and Footnotes

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