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Reaction of Lithiated 2-Trimethylsilyl-1,3-dithiane with (±)-Pantolactone

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Abstract—Pantolactone methoxymethyl ether reacted with lithiated 2-trimethylsilyl-1,3-dithiane to give the corresponding ketene dithioacetal and formal monoaddition product of silicon-free 2-lithio-1,3-dithiane at a ratio of 2:1. Possible ways of formation of the latter are discussed.

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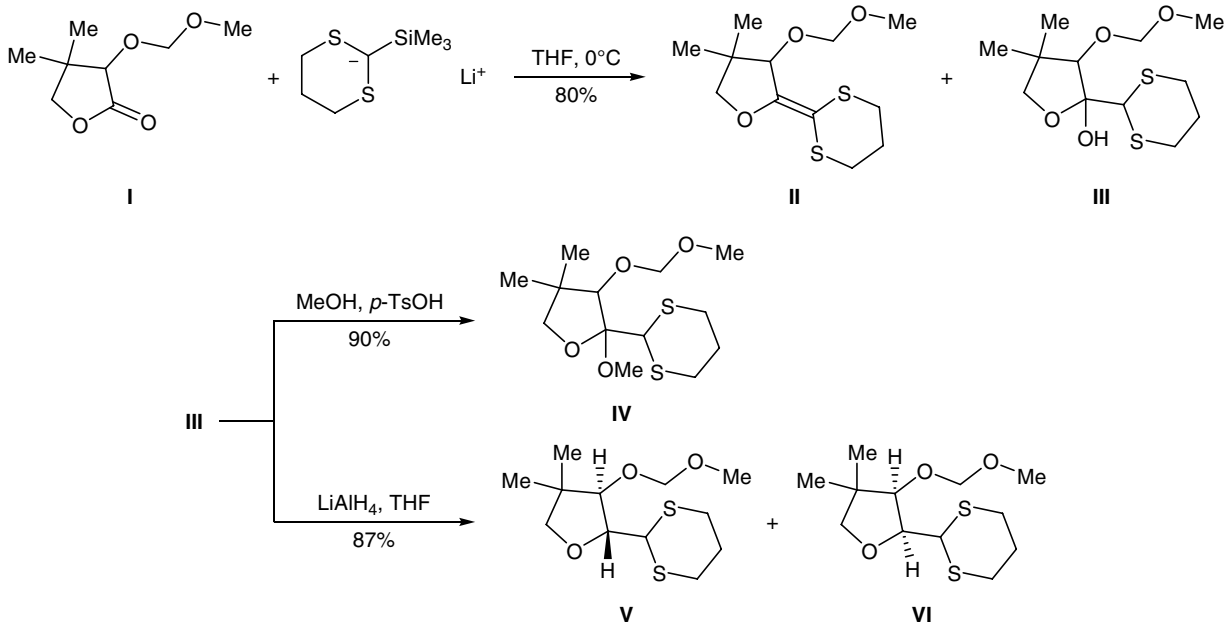
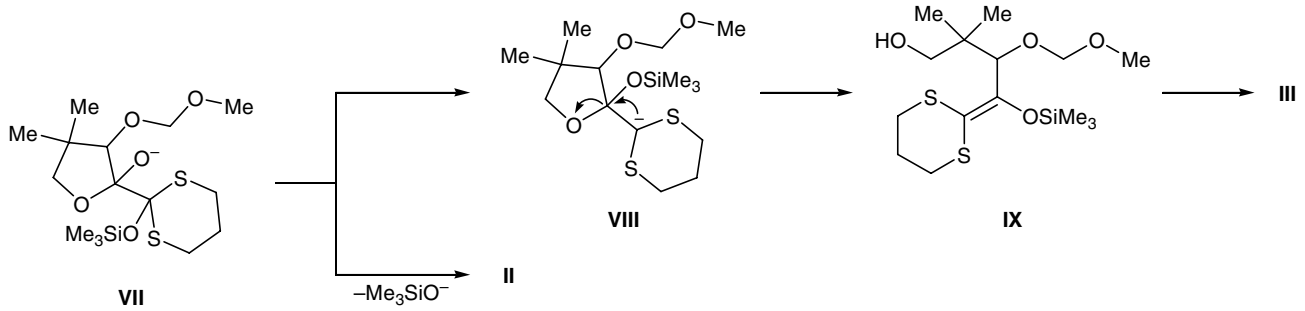
With the goal of obtaining functional derivatives of pantolactone at the C^1 atom we examined the reaction of its methoxymethyl ether **I** with 2-trimethylsilyl-1,3-dithiane lithium salt [1, 2]. It is known that the latter is used as reagent in the Peterson olefination of aldehydes and ketones [3] to obtain the corresponding ketene dithioacetals [4]. In our experiments, the reaction of equimolar amounts of compound **I** and 2-trimethylsilyl-1,3-dithiane lithium salt in THF at 0°C led to the formation of a mixture of two products, ketene dithioacetal **II** and hydroxy derivative **III**, at a ratio of 2:1 (Scheme 1). Compounds **II** and **III** were separated by column chromatography on silica gel and were subjected to reduction and acetalization. The reaction of **III** with methanol in the presence of *p*-toluenesulfonic acid gave methoxy derivative **IV** in quantitative yield. Although we failed to reduce the double bond in molecule **II** with $LiAlH_4$ in THF at 65°C, compound **III** under analogous conditions was smoothly converted into a mixture of epimeric substituted tetrahydrofurans **V** and **VI** which can be separated by chromatography on silica gel. Signals from the C^2, C^3, and $C^{2'}$ atoms in

Scheme 1.



Scheme 2.



the ^{13}C NMR spectra of sterically hindered *cis* stereoisomer **VI** appeared in a stronger field relative to the corresponding signals of isomer **V**. In the ^{1}H NMR spectra of **V** and **VI**, characteristic were signals from the 2-H and 3-H protons with coupling constants $J_{2,3}$ of 9.62 Hz for *cis* isomer **VI** and 2.86 Hz for *trans* isomer **V**.

Scheme 2 shows possible ways of formation of compounds **II** and **III**. The key intermediate is likely to be tetrahedral 1,2-adduct **VII** which undergoes Peterson olefination with elimination of Me_3SiOLi to give product **II**. Another part of adduct **VII** is converted into carbanion **VIII** via [1,3]-Brook rearrangement [5], and β-elimination in **VIII** (with ring opening) yields compound **III** through silyl enol ether **IX**.

The reduction of **III** gives no expected diol (only compounds **V** and **VI** were detected in the alkaline reaction mixture). Therefore, a possible way of formation of substituted tetrahydrofurans **V** and **VI** is that involving ionic hydrogenation where $LiAlH_4$ acts as Lewis acid (which abstracts hydroxide ion) and a source of hydride ion.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer from samples prepared as thin films or dispersed in Nujol. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer at 300 and 75.47 MHz, respectively, using $CDCl_3$ as solvent. Thin-layer chromatography was performed on Silufol plates.

2-(1,3-Dithian-2-ylidene)-3-methoxymethyloxy-4,4-dimethyltetrahydrofuran (II) and 2-(1,3-dithian-2-yl)-3-methoxymethyloxy-4,4-dimethyltetrahydrofuran-2-ol (III). A solution of 1.1 g (5.7 mmol) of 2-trimethylsilyl-1,3-dithiane in 10 ml of anhydrous THF was cooled to 0°C, and 2.85 ml (5.7 mmol) of a 2 N solution of *n*-butyllithium in hexane was added over a period of 5 min under argon. The mixture was stirred for 15 min at 0°C and was added dropwise over a period of 5 min to a solution of 1.0 g (5.7 mmol) of compound **I** [6] in 5 ml of anhydrous THF, maintaining the temperature at 0°C. The mixture was stirred for 10 h and treated with 10 ml of a saturated solution of ammonium chloride, the aqueous phase was extracted with ethyl acetate (3×20 ml), the extract was dried over Na_2SO_4 and evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel to isolate 0.84 g (53%) of ketene dithioacetal **II** and 0.46 g (27%) of compound **III** as oily liquids.

Compound **II**. IR spectrum, ν, cm^{-1}: 1050, 1625, 2910, 2955. ^{1}H NMR spectrum, δ, ppm: 1.03 s (3H, CH_3), 1.12 s (3H, CH_3), 2.10–2.20 m (2H, $SCH_2C\mathbf{H}_2$), 2.7–2.9 m (4H, SCH_2), 3.40 s (3H, OCH_3), 3.88 d (1H, CH_2O, J = 7.84 Hz), 4.12 d (1H, CH_2O, J = 7.84 Hz), 4.41 s (1H, OCH), 4.56 d (1H, OCH_2O, J = 6.73 Hz), 4.95 d (1H, OCH_2O, J = 6.73 Hz). ^{13}C NMR spectrum, δ_C, ppm: 17.83 (CH_3), 24.10 (CH_3), 25.84 ($SCH_2\mathbf{C}H_2$), 30.51 (SCH_2), 31.61 (SCH_2), 41.73 (C^4), 55.63 (OCH_3), 79.23 (C^3), 80.50 (C^5), 94.54 (OCH_2O), 97.67 ($C^{2'}$), 159.61 (C^2). Found, %: C 51.90; H 7.20; S 22.50. $C_{12}H_{20}O_3S_2$. Calculated, %: C 52.14; H 7.29; S 23.20.

Compound **III**. IR spectrum, ν, cm^{-1}: 1160, 1470, 2970, 3450. ^{1}H NMR spectrum, δ, ppm: 1.13 s (3H, CH_3), 1.14 s (CH_3), 2.00 m (2H, $SCH_2C\mathbf{H}_2$), 2.50–2.60 m (2H, SCH_2), 3.10–3.20 m (2H, SCH_2), 3.39 s (3H, OCH_3), 3.56 d (1H, CH_2O, J = 8.56 Hz), 3.73 d (1H, CH_2O, J = 8.56 Hz), 3.81 s (1H, OH), 4.15 s (1H, 2′-H), 4.41 s (1H, 3-H), 4.65 d (1H, OCH_2O, J = 6.70 Hz), 4.75 d (1H, OCH_2O, J = 6.70 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.88 (CH_3), 26.13 (CH_3), 25.04 ($SCH_2\mathbf{C}H_2$), 27.08 (SCH_2), 27.17 (SCH_2), 40.23 (C^4), 49.47 ($C^{2'}$), 56.06 (OCH_3), 77.76 (C^5), 85.22 (C^3), 97.49 (OCH_2O), 105.87 (C^2). Found, %: C 48.85; H 7.60; S 21.98. $C_{12}H_{22}O_4S_2$. Calculated, %: C 48.95; H 7.53; S 21.78.

2-(1,3-Dithian-2-yl)-2-methoxy-3-methoxymethyloxy-4,4-dimethyltetrahydrofuran (IV). *p*-Toluenesulfonic acid, 0.001 g, was added to a solution of 0.1 g (0.34 mmol) of compound **III** in 4 ml of anhydrous methanol, and the mixture was stirred for 4 h. The mixture was then treated with 0.01 g of $NaHCO_3$ and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel to isolate 0.104 g (99%) of compound **IV** as an oily substance. IR spectrum, ν, cm^{-1}: 1060, 1470, 2910. ^1H NMR spectrum, δ, ppm: 1.13 s (3H, CH_3), 1.16 s (CH_3), 1.80 m and 2.10 m (2H, SCH_2CH_2), 2.80–2.90 m (4H, SCH_2), 3.41 s (3H, OCH_3), 3.43 s (3H, OCH_3), 3.67 d (1H, CH_2O, J = 8.5 Hz), 3.73 d (1H, CH_2O, J = 8.5 Hz), 4.06 s (1H, 2′-H), 4.68 s (1H, 3-H), 4.71 d (1H, OCH_2O, J = 5.76 Hz), 4.75 d (1H, OCH_2O, J = 5.76 Hz). ^{13}C NMR spectrum, δ_C, ppm: 22.04 (CH_3), 26.97 (CH_3), 25.76 (SCH_2CH_2), 30.32 (SCH_2), 30.72 (SCH_2), 39.63 (C^4), 48.26 ($C^{2'}$), 51.32 (OCH_3), 56.17 (OCH_3), 79.33 (C^5), 86.62 (C^3), 98.12 (OCH_2O), 105.85 (C^2). Found, %: C 51.05; H 7.95; S 19.50. $C_{13}H_{24}O_4S_2$. Calculated, %: C 50.62; H 7.84; S 20.79.

2-(1,3-Dithian-2-yl)-3-methoxymethyloxy-4,4-dimethyltetrahydrofurans V and VI. A solution of 0.100 g (0.34 mmol) of compound **III** in 2 ml of anhydrous THF was added to a suspension of 0.023 g (0.68 mmol) of $LiAlH_4$ in 4 ml of anhydrous THF, and the mixture was stirred for 1 h. Excess $LiAlH_4$ was quenched by treatment with 3 ml of a saturated solution of sodium chloride, the aqueous phase was extracted with chloroform (3×10 ml), the extracts were combined, dried over Na_2SO_4, and evaporated, and the residue was separated by column chromatography on silica gel to isolate 0.04 g (43%) of compound **V** and 0.041 g (44%) of stereoisomer **VI** as colorless oily substances.

trans Isomer **V**. IR spectrum, ν, cm^{-1}: 1050, 1440, 2950. ^1H NMR spectrum, δ, ppm: 1.00 s (3H, CH_3), 1.02 s (CH_3), 1.90 m and 2.10 m (2H, SCH_2CH_2), 2.80–3.00 m (4H, SCH_2), 3.48 s (3H, OCH_3), 3.42 d (1H, CH_2O, J = 11.3 Hz), 3.50 d (1H, CH_2O, J = 11.3 Hz), 3.60 d (1H, 2′-H, J = 7.0 Hz), 3.95 d.d (1H, 2-H, J = 7.0, 2.86 Hz), 4.45 d (1H, 3-H, J = 2.86 Hz), 4.75 d (1H, OCH_2O, J = 6.24 Hz), 4.87 d (1H, OCH_2O, J = 6.24 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.06 (CH_3), 22.27 (CH_3), 25.68 (SCH_2CH_2), 29.13 (SCH_2), 30.21 (SCH_2), 40.03 (C^4), 51.20 ($C^{2'}$), 56.50 (OCH_3), 69.65 (C^5), 75.14 (C^2), 85.16 (C^3), 99.71 (OCH_2O). Found, %: C 51.24; H 7.55; S 22.43. $C_{12}H_{22}O_3S_2$. Calculated, %: C 51.76; H 7.96; S 23.03.

cis Isomer **VI**. IR spectrum, ν, cm^{-1}: 1020, 1480, 2950. ^1H NMR spectrum, δ, ppm: 0.98 s (3H, CH_3), 0.99 s (CH_3), 2.10–2.30 m (2H, SCH_2CH_2), 2.7 m (2H, SCH_2), 2.9 m (2H, SCH_2), 3.40 s (3H, OCH_3), 3.31 d (1H, CH_2O, J = 11.61 Hz), 3.45 d (1H, CH_2O, J = 11.61 Hz), 3.84 s (1H, 2′-H), 3.96 d (1H, 2-H, J = 9.62 Hz), 4.06 d (1H, 3-H, J = 9.62 Hz), 4.72 d (1H, OCH_2O, J = 6.57 Hz), 4.80 d (1H, OCH_2O, J = 6.57 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.82 (CH_3), 23.51 (CH_3), 25.45 (SCH_2CH_2), 27.32 (SCH_2), 27.71 (SCH_2), 40.02 (C^4), 49.28 ($C^{2'}$), 56.37 (OCH_3), 67.94 (C^5), 68.86 (C^2), 83.08 (C^3), 99.45 (OCH_2O). Found, %: C 51.20; H 7.79; S 22.41. $C_{12}H_{22}O_3S_2$. Calculated, %: C 51.76; H 7.96; S 23.03.

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