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An Unexpected Selective Formation of a δ-Lactone in the Ozonolysis of a Santonin Derivative: Neighboring Participation of a Methoxycarbonyl Group

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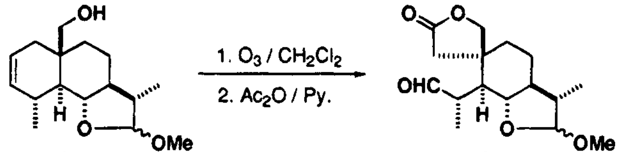
Ozonolysis is a convenient method for oxidative cleavage of an olefinic double bond to give a carboxylic acids, ketones, aldehydes, and alcohols, depending on subsequent exposure to the intermediate ozonide to oxidative or reductive conditions.[1] It is known, however that this useful reaction sometimes follows an abnormal course to afford unexpected products. In order to minimize such products, it is sometimes desirable to execute ozonolysis in the presence of an alcohol. Often the intermediate zwitterion plays an important role in determining ozonization products. For example, ozonization of certain enol ethers and (silyloxy)alkenes gives unexpected oxidation products, and α-alkoxy hydroperoxides generated by ozonolysis afford acetates and esters accompanied by aldehyde or acetals, depending on the treatment of the intermediate peroxide.[2−4]

Santonin derivatives with functionalized angular substituents have been frequently employed as key intermediates for the synthesis of natural products.[5] During the course of our investigation of oxidative double-bond cleavage of santonin derivative **1**, we found that ozonolysis in the absence of methanol followed by treatment with acetic anhydride and pyridine gave spiro-γ-lactone **2** in fair yield. Its formation was accounted for by the intramolecular addition of the angular hyroxymethyl group to the molozonide or ozonide initially formed.[3,4] Herein we report that, on ozonolysis in the presence of methanol followed by reductive treatment, the ester **3a**[6] related to **1** gave the unexpected, thermodynamically unstable δ-lactone **4**.



1 **2**

As noted above, ozonolysis of cycloalkenes in the presence of alcohols gives α-alkoxy hydroperoxides, which upon being treated with acid or acetic anhydride give acyclic products which retain differentiated terminal functionality.[3] It is also reported that certain double bonds on ozonolysis in the presence of an alcohol give esters or lactones by Criegee rearrangement upon treatment with acetic anhydride and an amine.[7] Recently, it was reported that ozonolysis of a variety of alkenes in methanolic sodium hydroxide leads directly to methyl esters.[8]

When the ester **3a** was submitted to ozonolysis in a mixture of dichloromethane and methanol at −78 °C and the resulting product was treated with sodium borohydride, lactone **4** was isolated in 95% yield (Figure 1). Ozonization of the methyl analogue **3b** followed by reduction with sodium borohydride gave the γ-lactone diol **6b** in fair yield,[9] but **3a** gave neither diol **6a** nor hydroxy bis-γ-lactone **5**. Hydrolysis of bis-δ-lactone **4** with sodium hydroxide in aqueous methanol and successive careful treatment with cold 10% hydrochloric acid provided bis-γ-lactone **5** as a sole product in 91% yield. The structure of lactones **4** and **5** were supported by spectral data, in particular by infrared absorptions at 1770 and 1730, and 1770 cm^{-1}, respectively. Translactonization of **4** to **5** was also examined under acidic and basic conditions. When 10% HCl or camphorsulfonic acid in methanol was employed, the reaction was sluggish at room temperature, and heating at reflux was necessary in order to complete the reaction. On the other hand, bis-γ-lactone **5** was produced smoothly in over 86% yield within 1 h at room temperature when potassium *tert*-butoxide, sodium methoxide, or sodium hydride was used. An attempt to isolate **6a** by treatment with sodium methoxide also gave **5**. Moreover, **5** was recovered unchanged on hydrolysis with base followed by careful acidification with cooling in an ice bath.[10] From the above results, it is obvious that **4** is the kinetic product, while **5** is the thermodynamically stable one. It is doubtful that diol **6a**, if produced under the ozonolysis−reduction conditions, would lactonize to **4** exclusively *prior to* formation of **5**. The formation of a γ-lactone is usually faster than that of a δ-lactone. For example, 2-hydroxyglutaric acid derived from glutamic acid gives only the γ-lactone derivative.[11]

A reasonable mechanistic hypothesis leading to the δ-lactone **4** is shown in Figure 2. Cleavage of the

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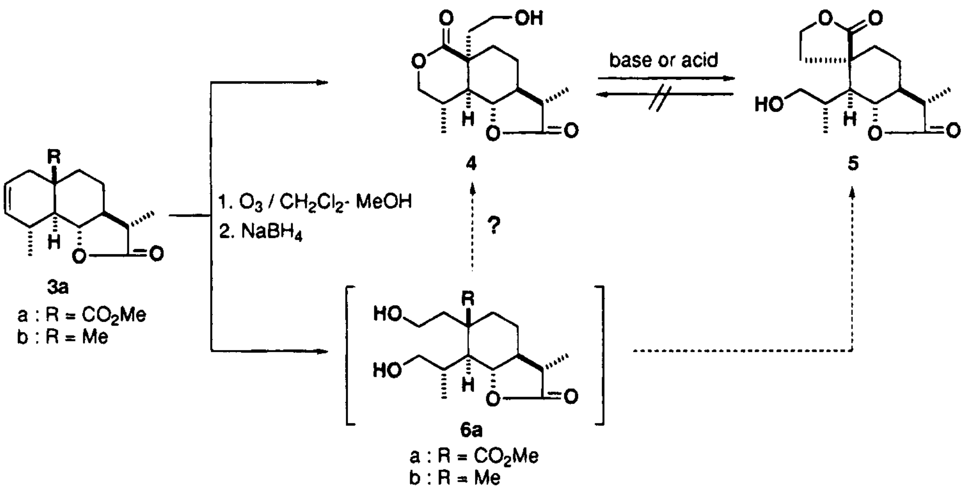

Figure 1.

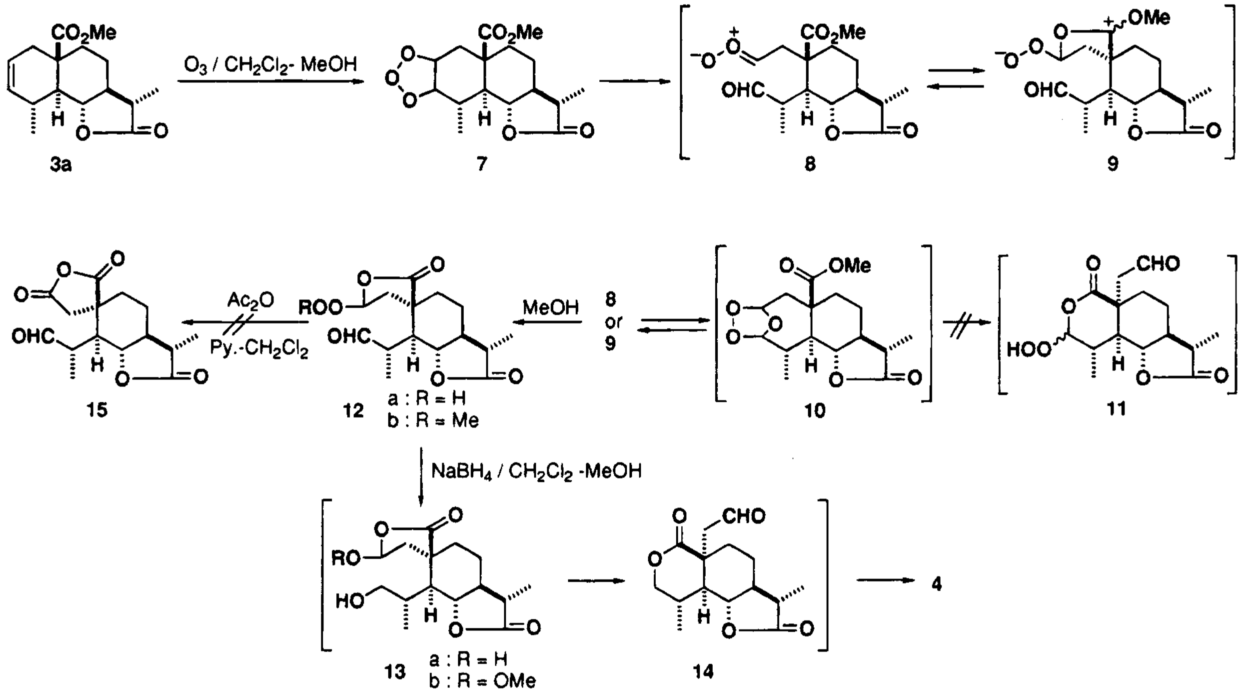

Figure 2.

molozonide **7** initially formed on ozonolysis gives zwitterion **8** or **9** with participation of the angular methoxycarbonyl group.[12] Once **8** or **9** is formed, it could revert to the ozonide **10** reversibly or it could proceed to γ-lactonic peroxide **12**.[13] The aldehyde and hydroperoxide moiety of **12** is reduced with sodium borohydride to give hydroxy γ-lactone acetal **13**. Translactonization gives δ-lactonic aldehyde **14**. Finally, **14** is reduced with sodium borohydride to afford **4**.

Treatment of **4** under basic or acidic conditions gave only **5** as shown in Figure 1. The route from **8** or **9** to **12** is preferable to that from **8** or **9** to **11** *via* **10** due to the greater stability of a five-membered lactone.[11] We attempted to form anhydride aldehyde **15** by ozonolysis in dichloromethane followed by acetic anhydride.[4] Unfortunately neither **15** nor the derived methyl ester could be isolated.[14] Moreover, all attempts to isolate the intermediate hydroperoxides or peroxides were unsuccessful. Finally, we examined the stability of **4** in the presence of sodium borohydride used in the reductive procedure after ozonization. Upon treatment of **4** with sodium borohydride in methanolic solution, no relactonization from **4** to **5** could be detected by thin layer chromatography.

An application of these findings to the synthesis of natural products is currently in progress.

Experimental Section

General. ^{1}H NMR (300 MHz) spectra were recorded with TMS as an internal standard. Anhydrous $MgSO_4$ was used for drying extracts. Kieselgel GF_{254} was employed for silica gel preparative TLC; solvents for elution are shown in parentheses.

(3*S*,3a*S*,5a*R*,9*R*,9a*S*,9b*S*)-3,9-Dimethyl-5a-(2-hydroxyethyl)octahydrofuro[2,3-e]-2-benzopyran-2(3*H*),6-dione (4). Ozone was bubbled through a solution of **3a** (1.10 g, 4.32 mmol) in a mixture of CH_2Cl_2 (20 mL) and methanol (10 mL) at −78 °C until the solution turned slightly blue. After excess ozone was purged with argon gas, $NaBH_4$ (160 mg, 4.2 mmol) was added in one portion. The solution was stirred for 1.5 h at rt,

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[12] Bunnelle, W. H.; Schlenmper, E. O. *J. Am. Chem. Soc.* **1987**, *109*, 612 and references cited therein.

after which water (10 mL) was added. After removal of the organic solvents, a large amount of water was added to precipitate the product, which was collected by filtration and washed successively with water and then a small amount of cold ethyl acetate to give **4** (1.06 g, 95%) as crystals,[15] mp 187.5–189 °C (recrystallized from ethyl acetate/THF): IR (KBr) 1770, 1730 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 0.78 (d, 3H, J = 7 Hz), 1.15 (d, 3H, J = 7 Hz), 3.39–3.51 (m, 2H), 3.39–3.51 (m, 2H), 4.13 (t, 1H, J = 11); ^{13}C NMR (75 MHz DMSO-d_6) δ 11.7, 12.3, 24.6, 33.5, 33.6, 41.2, 47.1, 47.9, 50.5, 51.5, 57.2, 66.5, 80.3, 175.1, 176.9. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.53; H, 8.09.

Spiro[(3*S*,3a*S*,6*R*,7*S*,7a*S*)-7-[(*S*)-2-hydroxy-1-methylethyl]-3-methylhexahydrobenzofuran-2(3*H*)-one-6,3′-4′,5′-dihydrofuran]-2′(3*H*)-one (5). Hydrolysis followed by Lactonization. A solution of **4** (282 mg, 1.0 mmol), KOH (240 mg, 6 mmol), water (2 mL), and methanol (7 mL) was refluxed for 1 h. The solution was then carefully acidified with 10% HCl with ice bath cooling. After removal of most of the methanol, the residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried. Removal of the ethyl acetate afforded **5** (257 mg, 91%) as crystals, mp 118–119.5 °C (recrystallized from ethyl acetate/hexane): IR (KBr) 1770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, 3H, J = 7 Hz), 1.23 (d, 3H, J = 7 Hz), 3.57–3.62 (m, 2H), 4.33 (d, 1H J = 8.0 Hz), 4.36 (d, 1H J = 7.3 Hz), 4.70 (t, 1H, J = 11 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 12.4, 23.0, 34.8, 35.1, 37.2, 40.5, 46.5 46.7, 51.5, 66.1, 67.7, 79.5, 179.4, 179.6. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 8.10. Found: C, 63.43; H, 8.10.

Translactonization by Treatment with 10% Hydrochloric Acid. A solution of **4** (80 mg, 0.28 mmol), 10% HCl (0.5 mL), and methanol (3 mL) was refluxed for 2 h. The reaction mixture was diluted with brine and then extracted with ethyl acetate. After the organic layer was dried, the solvent was removed to give a crude oil. The crude oil was purified by TLC (ethyl acetate) to afford crystals (60 mg, 75%), which were identified as **5** by comparison of IR, NMR, and mp with those of the authentic sample.

Translactonization by Treatment with Camphorsulfonic Acid. A mixture of **4** (80 mg, 0.28 mmol) and camphorsulfonic acid (20 mg, 0.09 mmol) in methanol (5 mL) was refluxed overnight, and then most of the methanol was removed. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated. The obtained crude oil was purified by TLC (ethyl acetate) to afford **5** (66 mg, 82%) as crystals.

Translactonization by Treatment with Potassium *tert*-Butoxide. To a stirred suspension of **4** (80 mg, 0.28 mmol) in a dry THF (5 mL) was added potassium *tert*-butoxide (50 mg, 0.42 mmol) with ice bath cooling. The reaction mixture was stirred at room temperature for 1 h, and then the reaction was quenched with 10% HCl. The residue obtained after removal of the organic solvent was extracted with ethyl acetate. The organic layer was washed with brine, dried, and then concentrated to give a crude oil, which was purified by TLC (ethyl acetate) to afford **5** (69 mg, 86%) as crystals.

Translactonization by Treatment with NaH. To a stirred suspension of **4** (282 mg, 1.0 mmol) in a dry THF (10 mL) was added sodium hydride (36 mg, 1.5 mmol) with ice bath cooling. The reaction mixture was stirred for 1 h, the reaction was quenched with methanol, and then the mixture was diluted with aqueous NH_4Cl. The solution was extracted with ethyl acetate. The organic layer was washed with brine, dried, and then concentrated to give a crude oil, which was purified by TLC (ethyl acetate) to give **5** (257 mg, 91%) as crystals.

Attempted Isolation of 6a. To a stirred suspension of **4** (282 mg, 1.0 mmol) in dry methanol (10 mL) was added sodium (58 mg, 2.5 mmol) with ice bath cooling. The reaction mixture was stirred for 1 h at rt and then refluxed for 1 h, and the reaction was quenched with 10% HCl with ice bath cooling. After dilution with brine, the solution was extracted with a mixture of ether and CH_2Cl_2 (3:1). The organic layer was washed with brine, dried, and then concentrated to give a crude oil, which was purified by TLC (ethyl acetate) to afford **5** (262 mg, 93%) as crystals.

Attempted Isolation of (3*S*,3a*S*,6*R*,7*S*,7a*S*)-3-Methyloctahydrobenzofuran-2(3*H*)-one 6,6-Acetic, Formic Anhydride (15) or Its Dimethyl Ester.[14] Ozone was bubbled through a solution of **3** (0.55 g, 2.16 mmol) in dichloromethane (15 mL) at −78 °C until the solution turned slightly blue. After excess ozone was purged with argon gas, the solution was passed through a short pad of anhydrous $MgSO_4$. To the solution were added acetic anhydride (0.3 mL) and pyridine (0.5 mL). After the mixture was stirred overnight, monitoring of an aliquot by TLC showed multiple products. Finally, the reaction was quenched with dry methanol (2 mL), and the reaction mixture was diluted with water, acidified carefully with 10% HCl, and then extracted with ethyl acetate. The organic layer was washed with 10% hydrochloric acid and brine, dried, and then concentrated. The obtained oil was dissolved in ether and treated with diazomethane to give gummy products, from which the desired methyl ester of **15** could not be isolated.

Treatment of 4 with Methanolic Sodium Borohydride. To a solution of **4** (10 mg, 0.035 mmol) in methanol (5 mL) was added $NaBH_4$ (13 mg, 0.34 mmol) dissolved with methanol (1 mL) with ice bath cooling. The solution was stirred for 3 h at rt, at which time no **5** was identified by TLC.

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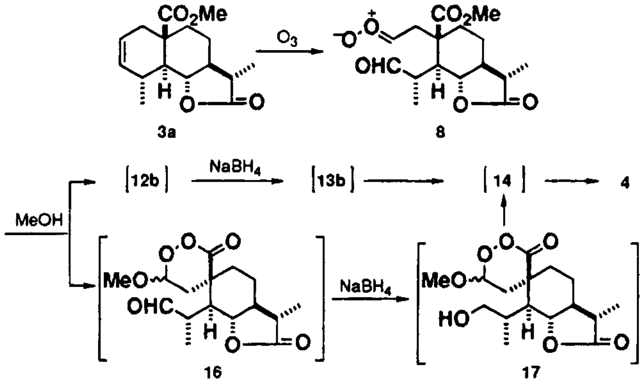
(13) One of referees proposed another pathway from **8** to **14** as shown below. As we unfortunately failed to isolate the intermediate hydroperoxides or peroxides, both pathways shown in Figure 2 and below may be plausible.



(14) As the anhydride **14** could possibly be hydrolyzed on workup, we attempted to isolate it as the dimethyl ester, but without success.

(15) The crude product is sufficiently pure for use in the next reaction.