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OXIDATION OF 2-TRIMETHYLSILYLOXY-1,3-DIENES WITH TRIPHENYL PHOSPHITE OZONIDE. A REGIOSELECTIVE α'-HYDROXYLATION OF α,β-UNSATURATED KETONES

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Summary: The present work deals with a novel method for the introduction of hydroxyl group to the α'-carbon of α,β-unsaturated ketones using triphenyl phosphite ozonide.

Regioselective introduction of oxgenated functionality to the α'-carbon of α,β-unsaturated ketones is one of very important subjects in synthetic organic chemistry, since some α,β-unsaturated ketones with hydroxyl group at the α'-position have been serving as potential intermediates for various natural products syntheses: e.g., acorenone-B,[1] pyroangolensolide,[2] prostaglandin analogues,[3] cytochalasin C,[4] and phytoalexins.[5] Intense searches for regioselective oxygenation to α,β-unsaturated ketones have led to development of several admirable methods, including acetoxylation of the enones with metal acetates,[6] oxidation of the enolates with a molybdenum peroxide reagent,[7] and oxidation of the silyl enol ethers with MCPBA[8] or with tert-butyl hydroperoxide.[9] In the course of our synthetic studies on spirovetivane-type phytoalexins,[10] we have been forced to overcome a crucial step, stereoselective and regioselective hydroxylation of an α,β-unsaturated ketone intermediate. As the known oxidation methods were found to be inefficient for the present purpose, a search has been made for an another useful oxidation method. In this communication we wish to present a novel method for regioselective and stereoselective hydroxylation of α,β-unsaturated ketones by treatment of their silyl enol ethers with triphenyl phosphite ozonide (TPPO).[11]

Several α,β-unsaturated ketones (**1**) were selected as substrates for the present work and their derivation to the trimethylsilyl enol ethers (**2**) was successfully accomplished according to the known procedure.[8b] TPPO, which is a representative of organic trioxides and is a well-known chemical source for singlet oxygen,[11] was found to react smoothly with the enol ethers (**2**) even at

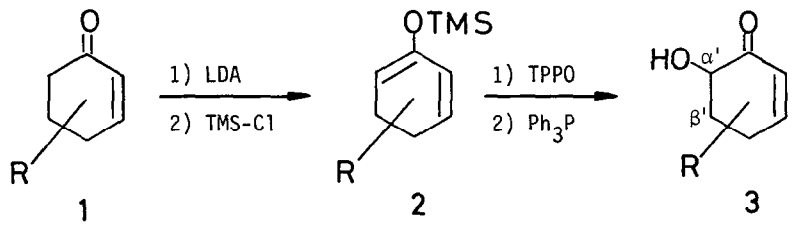
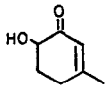
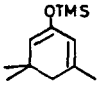
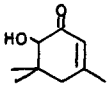
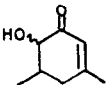
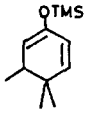
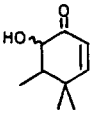
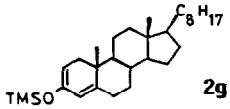
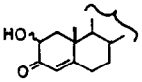


Table. α'-Hydroxylation of α,β-Unsaturated Ketones via the Silyl Enol Ethers with TPPO

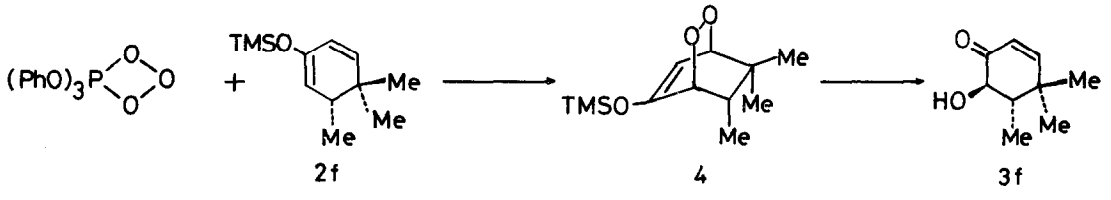
Entry	Substrate (2)	Conditions[a] TPPO (eq.)	Temp. (°C)	Product (3)	Yield (%)[b,c]	Ratio of trans/cis[f]
1	 **2a**	1.1	-78	 **3a**	58 (56)[d]	—
2	 **2b**	1.1	-78	 **3b**	69	—
3	 **2c**	1.1	-78	 **3c**	79 (66)[d]	—
4	 **2d**	1.1	-78	 **3d**	61 (65)[e]	2/1 (2/3)[e]
5	 **2e**	1.1	-78	 **3e**	65 (74)[d]	2/1 (2/3)[d]
6	 **2f**	1.5	-50	 **3f**	61 (70)	8/1 (3/4)
7	 **2g**	1.5	-50	 **3g**	59 (80)[d]	2.2/1 (2/3)[d]

[a] The oxidation was carried out in CH_2Cl_2 and followed by reduction with 1.1 eq. of Ph_3P. [b] Isolated yield from the parent enone (**1**). [c] Values in parenthes are the yields in the case of MCPBA oxidation. [d] Reference 8b. [e] Reference 4. [f] Footnote 13.

low temperature (-78°C), where TPPO is shown to be thermally stable,[11] and the α'-hydroxylated products (**3**) were obtained in moderate yields after treatment with triphenyl phosphine. The results were summarized in Table.

A typical procedure for oxidation of α,β-unsaturated ketones is shown in the case of isophorone (**1c**). A solution of the 2-trimethylsilyloxy-1,3-diene (**2c**; prepared from **1c** 97 mg according to the Rubottom's method[8b]) in dry CH_2Cl_2 1 ml was added dropwise to 1.1 equiv. of a stirred solution of TPPO[12] in dry CH_2Cl_2 (ca. 0.2 M; 3.9 ml) at -78°C under N_2. Stirring was continued at -78°C until the starting material had disappeared (3 hr). After a small amount of Et_3N was added to the reaction mixture to decompose the excess oxidant, a solution of Ph_3P (184 mg; 1.1 equiv.) in ether 3 ml was added and the resulting mixture was allowed to stand at r.t. for 1 hr. Removal of the solvent gave a crude product, which was chromatographed on SiO_2 in C_6H_6-AcOEt (9:1) to afford 85 mg (79%) of the hydroxylated enone (**3c**). ^{1}H-NMR δ(CCl_4) 0.77 (3H, s), 1.13 (3H, s), 1.90 (3H, s), 2.07 (1H, d, J=18), 2.44 (1H, d, J=18), 3.45 (1H, br s), 3.76 (1H, s), 5.80 (1H, s).

It is particularly noteworthy that stereoselectivity regarding the newly introduced hydroxyl group of the products (**3**) is remarkably different between the present work and the previously reported MCPBA method.[8b] For example, the silyl enol ether (**2e**) prepared from the dimethylcylohexenone (**1e**) had been reported to afford the α'-hydroxylated enone (**3e**) as a 3:2 mixture of cis- and trans-diastereoisomers[13] by MCPBA oxidation method. On the other hand, the TPPO oxidation of **2e** resulted in a predominant formation of the trans-isomer of **3e** along with a half amount of the cis-isomer. A excellent stereoselectivity was obtainable in the case of **1f**, which is structurally similar to spirovetivane compounds, and the ratio of trans/cis in the oxidation product (**3f**) has reached to 8/1. Such interesting stereoselectivity in the TPPO oxidation would lead to the speculation that the reaction chiefly proceeds via the endoperoxide intermediate (**4**).[14-16] Namely, a large factor governing stereochemistry of the intermediate (**4**) is expected to be steric hindrance around the cyclohexenone ring.



Thus, a novel oxidation of α,β-unsaturated ketones to α'-hydroxygenated derivatives with an interesting stereoselectivity has been developed by means of TPPO oxidation of their silyl enol ethers and in the foregoing paper we

wish to describe the fully stereoselective total synthesis of (±)-oxylubimin, a highly oxidized phytoalexin, using this stereoselective oxidation method.

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12. a) A solution of TPPO in CH_2Cl_2 was prepared according to the procedure described in the next literature; b) P.D. Bartlett and H.-K. Chu, J. Org. Chem., **45**, 3000 (1980).
13. In the present paper, the terms cis and trans mean the relative configuration of the newly introduced α'-hydroxyl group regarding the substituent attached at β'-position (or regarding the angular methyl group in the case of **3g**).
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15. A 1,3-diene was found to react with TPPO at higher temperature affording an endoperoxide product. See, ref. 11a.
16. On the other hand, in the case of MCPBA oxidation the initial C(α')-O bond formation step would determine the stereochemistry of the oxidation product via an axial attack with stereoelectronic preference and therefore noticable stereoselectivity is not obtained. cf. H.O. House, "Modern Synthetic Reactions," 2nd edition, W.A. Benjamin, Inc., California, 1972, pp. 468-471.

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