

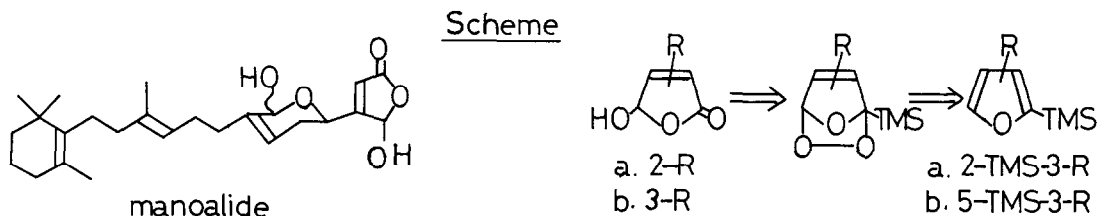
REGIOSPECIFIC SYNTHESIS OF γ -HYDROXYBUTENOLIDE.
PHOTOSENSITIZED OXYGENATION OF SUBSTITUTED 2-TRIMETHYLSILYLFURAN

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Summary: Regiospecific synthesis of substituted γ -hydroxybutenolide was accomplished by photosensitized oxygenation of 2-trimethylsilylfuran derivatives, and chemoselective oxidation of furan ring having tri- and tetra-substituted olefins in the side chain was also achieved.

γ -Hydroxybutenolide moiety is present in various biologically active natural products, such as strigol¹ and manoalide². 2-Methyl-4-hydroxybutenolide in strigol has been prepared by the addition of singlet oxygen to 3-methyl-2-furoic acid followed by reduction³, and other effort to synthesize 2-methyl derivative has been reported⁴. However the simple and efficient synthetic method of γ -hydroxybutenolide possessing various substituents, such as tri- and tetra-substituted olefins has not been established yet.



In the course of our synthetic study of antibiotic sesterterpenoid, manoalide, it was necessary to develop the efficient synthetic method of β -substituted- γ -hydroxybutenolide. The most likely method appears singlet oxygenation of 3-substituted-2-trimethylsilylfuran because of the following reasons. 1. The regiospecific generation of the carbonyl of γ -hydroxybutenolide would be achieved by the very fast intramolecular silyl migration of the intermediary endoperoxide of 2-trimethylsilylfuran⁵. 2. 2-Trimethylsilylfuran having various substituents will be readily prepared with the

regioselective manner.^{6,7} 3. 2-Trimethylsilyl substituent might accelerate the rate of 1,4-addition of singlet oxygen to furan resulting chemoselective oxidation of furan ring rather than ene reaction of the olefin moiety in the side chain with singlet oxygen (Scheme).

The requisite 2- and 5-trimethylsilyl-3-alkylfuran 1 and 2 were prepared from furan-3-methanol by similar procedure as Goldsmith's⁶. Compound 6 was prepared through compound 3 from β -cyclocitryl phenyl sulfone⁸ by the alkylation with 2-trimethylsilyl-3-chloromethylfuran⁷ (n-BuLi/-78°C/1h/0°C/2h), followed by reduction (Na-Hg/EtOH/reflux/1h).

The results of their oxygenation are listed in the Table. In entries 1, 2, and 3, the excellent results were obtained under the condition A: 0.08M solution of the silylfuran in CH₂Cl₂ was irradiated with iodo-halogen lamp (300W) under bubbling oxygen (15ml/min) for 5 minutes in the presence of catalytic amount of tetraphenylporphin at -78°C. Especially in the case of 3, furan ring was oxygenated highly chemoselectively because the tetrasubstituted double bond of compound 3 was hindered with phenylsulphone and trimethylsilyl-furan substituents. On the other hand, compound 4⁷ which had trisubstituted olefins afforded the objective γ -hydroxybutenolide (46%) and further oxidized products (21%) under the same condition. It has been known⁹ that the difference of the reaction rate between 1,4-addition to furan and ene reaction of trisubstituted olefin with singlet oxygen is enough large to control the reactions of these two types, and that the 2-methyl group of furan accelerates the reaction rate¹⁰. After studying the reaction condition in detail, flow rate of oxygen and concentration of substrates were found to be important factors for the selective oxygenation. Under the controlled condition (B), compounds 4, 6, and 7 which was the important intermediate for the synthesis of manoalide provided the corresponding γ -hydroxybutenolides in excellent yield chemoselectively. Condition B: 0.08M solution of the silylfuran in methanol was irradiated with the same lamp under bubbling oxygen (2.5ml/min) in the presence of catalytic amount of rose Bengal through aqueous sodium nitrite filter at -78°C. When dendrolasin (5)¹¹ was oxygenated under the condition B, a mixture of the regioisomers (1:1 by nmr) of γ -hydroxybutenolide were obtained in 48% yield. The time consumed the starting material was three times longer than that of 2-trimethylsilyl derivative 4. Therefore, 2-trimethylsilyl substituent of furan serves not only to the regiospecific formation of substituted γ -hydroxybutenolide but also to the clean fission of the intermediary peroxide and to the acceleration of the reaction rate of singlet oxygen to furan.

The above results demonstrate that photosensitized oxygenation of 2-trimethylsilylfuran derivatives is a useful synthetic method of substituted γ -hydroxybutenolide. Consequently, this method is also useful for the

Table. Oxygenation of 2-Trimethylsilylylfurans.^a

Entry	Substrate	Product	yield(%) ^b
1	 <u>1</u> R=Si≡		94
2	 <u>2</u>		91
3	 <u>3</u> R=SO ₂ Ph		93
4	 <u>4</u> R=TMS <u>5</u> R=H		93
		mixture(1:1) of regioisomers	48
5	 <u>6</u>		93
6	 <u>7</u> R= R'=		89

a. All products were characterized by ir, nmr, and mass or elemental analyses. b. Yields of entry 1 and 2 were based on nmr, and yields of others were isolated one.

synthesis of 2(5H)-furanon having substituted olefins in the side chain,^{12,13} because it can be derived from γ -hydroxybutenolide easily¹⁴. The application of this methodology to the synthesis of manoalide, iso-manoalide, and neo-manoalide will be described in forthcoming publication.

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