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# TOTAL SYNTHESIS OF MANOALIDE AND SECO-MANOALIDE

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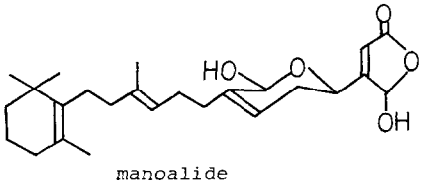
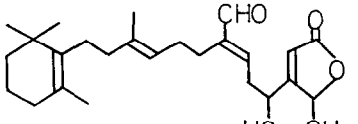
Summary: The first synthesis of manoalide and seco-manoalide from methyl 7,8-dihydro-β-ionylidene acetate was achieved in high yield by the new method utilizing regiospecific singlet oxygen oxidation of 3-alkenyl-5-trimethylsilylfuran to β-alkenyl-γ-hydroxybutenolide.

Manoalide was isolated from the sponge Luffariella variabilis and was characterized by Scheuer et al in 1980. They have reported that this sesterterpenoid has showed significant in vitro activity against Gram positive bacteria.[1] Most recently Jacobs et al has reported the following quite interesting biological activities of manoalide. Manoalide, a non-steroidal anti-inflammatory agent, inactivates directly phospholipase $A_2$ which is an enzyme found in several neurotoxic venoms, and is also a rate limiting enzyme important in phospholipid metabolisms and prostaglandin synthesis in man. Besides manoalide, seco-manoalide, E- and Z-neomanoalide have been isolated from the same sponge, and seco-manoalide has been transformed into manoalide by photoirradiation.[3] Because of the above interesting biological activities and the novel structure of manoalide, total synthesis of this highly oxidized pentaprenoid is quite attractive. We now describe the first and efficient synthesis of manoalide and seco-manoalide.




manoalide

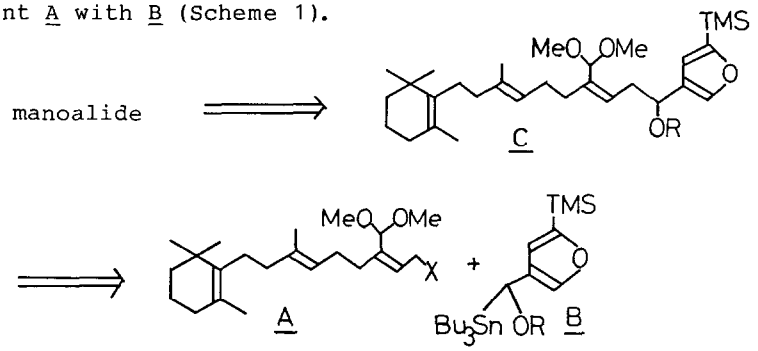



seco-manoalide

For the synthesis of manoalide, the construction of γ-hydroxybutenolide

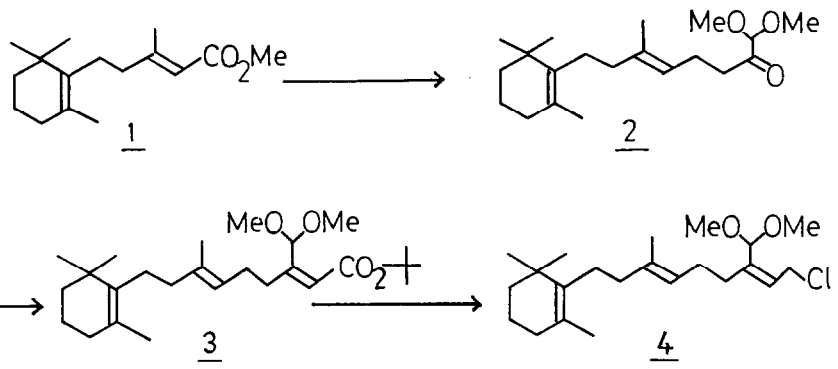
moiety is the main problem. Although singlet oxygen oxidation of furan derivative appears to be most likely for preparing γ-hydroxybutenolide,[4] the efficient synthetic method of γ-hydroxybutenolide possessing various substituents had not yet been established. In the preceding paper, we reported the general synthetic method of γ-hydroxybutenolide having various substituents by photosensitized oxygenation of substituted α-trimethylsilylfuran, and chemoselective oxidation of furan ring having tri- and tetra-substituted olefins in the side chain was achieved.[5] Now for the synthesis of manoalide, we need 3-substituted-5-trimethylsilylfuran derivative C, which is synthesized by connecting segment A with B (Scheme 1).

Scheme 1

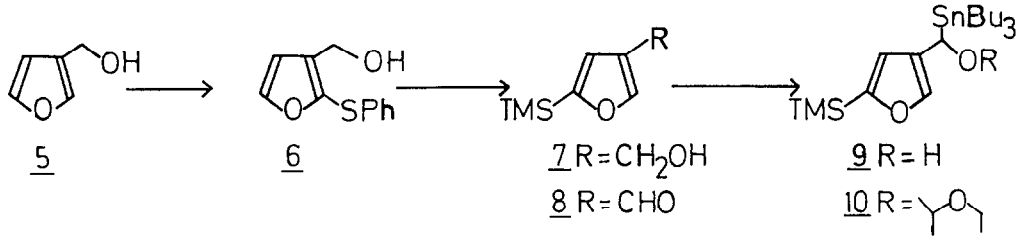



Segment A(4) was prepared starting from methyl trans-7,8-dihydro-β-ionyliden acetate(1)[6] according to the procedure of Larcheveque et al.[7] Reduction of ester 1 with lithium aluminum hydride followed by bromination ($PBr_3$/pyridine) afforded the corresponding bromide(86% yield) which was reacted with the lithium anion prepared from N,N-dimethylhydrazone of pyruvaldehyde dimethylacetal yielding α-ketodimethylacetal 2 in 72 % yield after acid treatment(2N HCl/0°C/3 min.). Compound 2 was reacted with the anion of t-butyl 2-trimethylsilyl acetate to give t-butylester 3 in 95% yield. The stereochemistry of the generated double bond was 95% trans by nmr. Reduction of ester 3 with diisobutylaluminum hydride in dichloromethane afforded the corresponding alcohol(95% yield) which was converted into chloride 4 (MsCl,LiCl, DMAP, $Et_3N/CH_2Cl_2$/0°C/30 min, DMF/0°C/3h) in 90% yield (Scheme 2). Segment B(10) was prepared regioselectively from 3-hydroxymethylfuran(5) by the following sequences.[5] Sulfenylation of the dilithio-derivative of 5 afforded sulfide 6 (91% yield).[8] A second dilithiation, silylation, acid treatment, and then desulfurization (n-BuLi/THF/-78°C/1h/0°C/2h, TMSCl/0°C/18h : 1%HCl/THF/0°C/5min. : Raney-Ni/EtOH/16h) yielded 5-trimethylsilyl-3-hydroxymethylfuran(7) which was oxidized with barium permanganate($CH_2Cl_2$/16h)[9] to give aldehyde 8 in 41% overall yield. Aldehyde 8 was converted into α-alkoxystannane 10 via α-hydroxystannane 9 by the reaction with tributylstannyllithium(THF/-78°C/1h) followed by treatment with α-chloroethy ethyl ether (diisopropyl ethylamine/$CH_2Cl_2$/0°C/1h) in 95% yield[10](Scheme 3). Segment A was connected with B as follows. The lithium anion derived from α-alkoxystannane

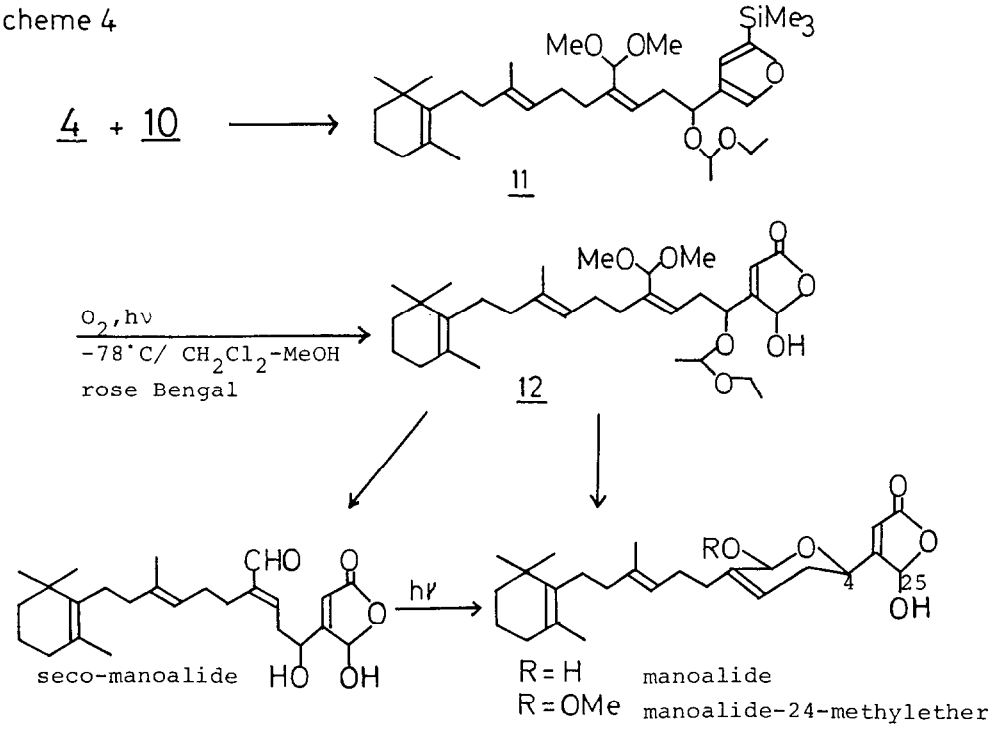
Scheme 2




Scheme 3




Scheme 4



10(n-BuLi/THF/-78°C/15 min.) was reacted with chloride 4 to afford the important intermediate 11 (THF/-78°C/1h) in 89% yield. Clean regiospecific formation of γ-hydroxybutenolide derivative 12 from α-silylfuran 11 was achieved by photosensitized oxygenation without any oxidation of the tri- and tetra-substituted olefins existing in the side chain (rose Bengal/-78°C/$CH_2Cl_2$-MeOH).[5] Finally, 12 was hydrolyzed to manoalide by treatment with 70% aqueous acetic acid in tetrahydrofuran (room temp./7h,55% yield),[11] while in methanol manoalide-24-methylether was obtained. On the other hand, treatment of 12 with 2N-hydrochloric acid in tetrahydrofuran afforded seco-manoalide quantitatively (room temp./2h) (Scheme 4). $^1H$ nmr of the synthesized manoalide and seco-manoalide were good agreement with those of natural compounds. $^{13}C$ nmr of the synthesized seco-manoalide was also good agreement with that of natural compound.[12]

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11. Seco-manoalide was produced togather with manoalide under this condition.
12. Although singlet oxygen could attack from the both face of the furan ring in compound 11, seco-manoalide was obtained as the single compound in $^{13}C$ nmr. The γ-hydroxybutenolide ring might be opened by the acid, and more stable isomer might be obtained. Further study on the relative stereochemistry at C-4 and C-25 is now under investigation.

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