Tetrahedron Letters,Vol.29,No.10,pp 1173-1176,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

HIGHLY EFFICIENT TOTAL SYNTHESIS OF MANOALIDE AND SECO-MANOALIDE VIA Pd(0) CATALYZED COUPLING OF ALLYLHALIDE WITH CO AND 2-SILYL-4-STANNYLFURAN†

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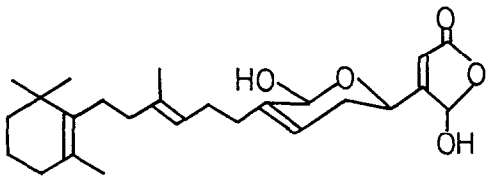
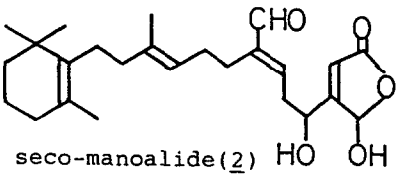
Summary: Total synthesis of manoalide and seco-manoalide from an allylchlolide derivative was achieved by 6 steps in 56.4% overall yield by Pd(0) catalyzed coupling with CO and 2- trimethylsilyl-4-tributylstannylfuran followed by chemoselective oxidation of 2-trimethylsilylfuran with $^1O_2$.

Manoalide(1) and seco-manoalide(2) isolated from the marine sponge Luffariella variabilis[1] have been paid much attention because of their quite interesting biological activities. Manoalide significantly reduces chemically induced inflammation in vivo and irreversively inhibits phospholipase A_2(IC_{50} 1.7μM)[2] directly which is an enzyme found in several neurotoxic venoms and is also a rate limiting enzyme important in phospholipid metabolisms.[3] Seco-manoalide inhibits the enzyme aldose reductase(IC_{50} 1.0μM) whose unusual action causes diabetic cataracts resulting from abnormal accumulation of sorbitol by reduction of glucose.[4]



manoalide(1)



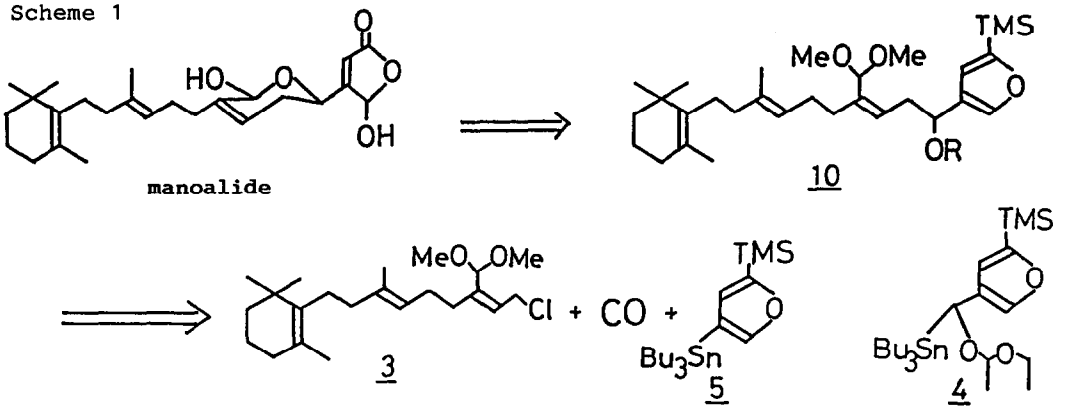
seco-manoalide(2)

For the synthesis of these unique pentaprenoids, the crucial problem was synthesis of γ-hydroxybutenolide moiety. We have already established the general and regiospecific synthesis of γ-hydroxybutenolide possessing various olefins in the side chain by chemoselective oxidation of α-silylfuran derivatives with singlet oxygen.[5] Therefore, the efficient synthesis of the key intermediate 10 was required at the next stage. In our previous and the first synyhesis of manoalide, 10 was synthesized from allylchlolide 3 and 2-trimethylsilyl-4-alkoxytributylstannylmethylfuran 4 according to Still's procedure.[6] In the reaction of 3 and 4, however, a 1,3-diene derivative resulting from unexpected 1,4-elimination of chlorine and methoxy groupe of 3

was obtained as major by-product depending on the reaction conditions.[7]

Considering the quite interesting biological activities of manoalide, we decided to investigate more efficient and convenient route for the synthesis of manoalide. In this paper, we describe the improved and highly efficient synthesis of manoalide and seco-manoalide by sequences of Pd(0) catalyzed coupling of the allylchlolide derivative 3, carbon monoxyde, and 2-trimethylsilyl-4-tributylstannylfuran 5 followed by chemoselective oxidation of α-trimethylsilylfuran 10 with singlet oxygen (Scheme 1).

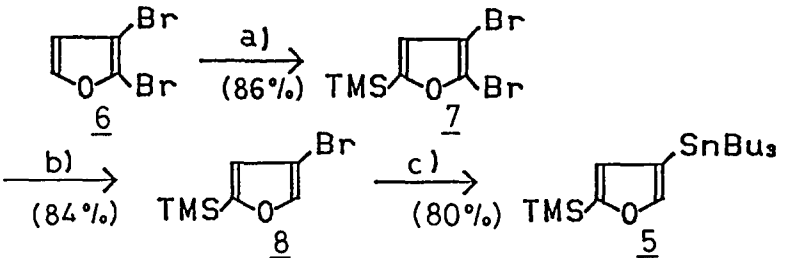
Scheme 1



2-Trimethylsilyl-4-tributylstannylfuran 5 was prepared from readily obtainable 2,3- dibromofuran(6)[8] by regioselective lithiation as follows (Scheme 2). Treatment of 6 with lithium diisopropylamide[9] and then trimethylsilyl chloride (THF/-78°C-room temperature) gave 2,3-dibromo-5-trimethylsilylfuran(7) (86% yield) which was treated with n-butyllithium for 3 minutes (ether/-78°C)[10] followed by addition of water yielding 2-trimethylsilyl-4-bromofuran(8) in 84% yield. Successively, treatment of 8 with sec-butyllitium for 30 minutes (ether/-78°C) followed by trapping the generated anion with tributylstannyl chloride (room temperature/ 1hr) afforded the desired 2-silyl-4-stannylfuran 5 in 80% yield. This new furan derivative 5 may be useful for synthesis of various natural products having butenolide or furan function.[11] Synthesis of another segment 3 has already been confirmed from methyl trans-7,8-dihydro-β-ionyliden acetate in four steps (58.5% overall yield).[6] Connection of the above two segments with carbon monoxide was achieved by a Pd(0) catalyzed coupling reaction developed by J.K.Stille.[11] The allylchloride 3 and 2-silyl-4-stannylfuran 5 were stirred under 3 atmospheric pressure of CO in the presence of palladium dibenzylideneacetone (10M %) and triphenylphosphine (20M %) at 50°C for 36 hours. The desired coupling product 9 was obtained as a mixture of Z- and E-isomer of C-6,7 double bond in 94 % yield. The obtained ketone 9, whose C-6,7 double bond was isomerized easily to the conjugated position of the carbonyl by acid or base, was immediately reduced with lithium aluminum hydride yielding an alcohol[12] which was protected by ethoxyethyl group to afford 10 . Synthesis of manoalide was established through seco-manoalide by

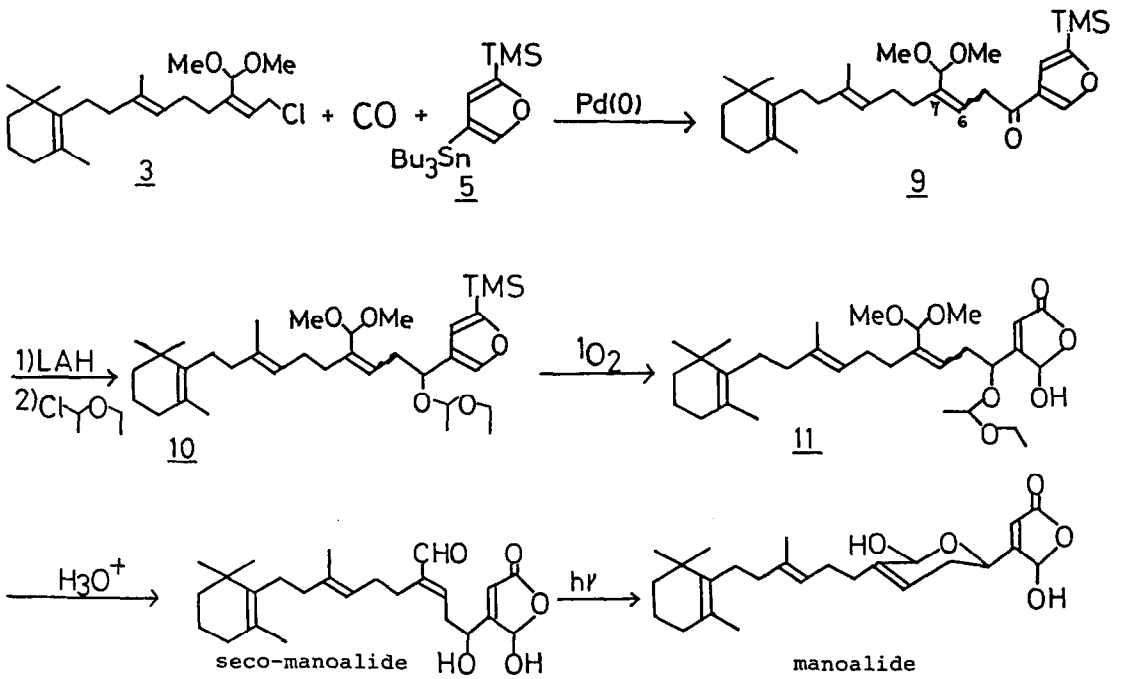
following three sequences from 10. Photosensityzed oxygenation of 10 under the condition established previously[5] proceeded chemoselectively yielding γ-hydroxybutenolide 11 cleanly which was followed by acid treatment (2N HCl/THF-H_2O) to afford seco-manoalide (60% yield from 9). Manoalide was obtained quantitatively by photoirradiation of seco- manoalide as reported by Scheuer[1] (high pressure Hg lamp/ benzene/0°C) (Scheme 3).

Scheme 2



a) LDA/TMSCl/THF b) n-BuLi/ether,-78°C, 3min./H_2O
c) sec-BuLi/ether,-78°C, 30min./Bu_3SnCl

Scheme 3



Thus, manoalide was synthesized from the allylchloride 3 through seco-manoalide by 6 steps in 56.4 % overall yield. Our synthesis of these unique sesterterpenoids may promise not only to supply enough amount of these biologically important pentaprenoids but also to make possible the synthesis of various analogs of manoalide. Additionally, we have found that seco-manoalide inhibits both phospholipase A_2 and aldose reductase more strongly than manoalide in vitro.

Acknowledgement: We are grateful to Professor P.J.Scheuer (University of Hawaii) for providing us with the copies of spectral charts of natural manoalide and seco-manoalide, and to Drs. M.Nakagawa and M.Ishihama (Suntory Institute for Biomedical Research) for their test of aldose reductase inhibition assey. We also thank Kuraray Co., Ltd. for the supply of β-ionone. This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (No 62607005) from Japanese Ministry of Education, Science, and Culture.

References and Notes

†) Dedicated to Emeritus Professor Takeo Sakan of Osaka City University on the occasion of his 77th birthday.

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7. It was found that such elimination reaction proceeded very smoothly by treatment of 3 with tributylstannyllithium. The details of this elimination reaction will be reported elsewhere.
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12. Treatment of 9 with DIBAL gave monomethoxyl derivative resulting from hydrogenolysis of dimethylacetal function in excellent yield.

(Received in Japan 15 December 1987)