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TOTAL SYNTHESIS OF E-NEOMANOALIDE VIA Pd(0) CATALYZED COUPLING OF ALLYLHALIDE AND α-STANNYLFURAN FOLLOWED BY CHEMOSELECTIVE OXYGENATION OF α-SILYLFURAN†

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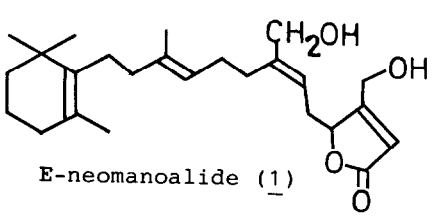
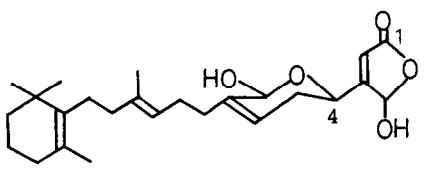
Summary: The first synthesis of E-neomanoalide (1) from an allylchloride 3 was achieved in short steps by Pd(0) catalyzed coupling with a α-stannylfuran derivative 5 followed by chemoselective oxygenation of a α-silylfuran derivative 2 and reduction. The essential part causing the biological activities of manoalide is suggested.

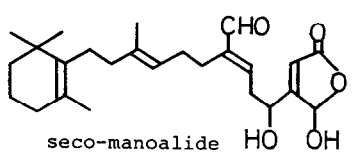
E- and Z-neomanoalide[1] were isolated from the sponge Lufferiella variabilis together with manoalide[2] and seco-manoalide,[1] and it was reported that their in vitro activity against gram positive bacteria was similar to that of manoalide and seco-manoalide. Most recently, it has been further reported that manoalide is an anti-inflammatory agent and it inhibits the neurotoxic action of β- bungarotoxin and phospholipase A_2[3],in addition that seco-manoalide inhibits aldose reductase.[4] The structural relationship between manoalides and neo-manoalides is that the hydroxy group at C-4 of manoalides cyclizes to the carbonyl group at C-1 and the resulting two aldehyde groups are reduced to give neo-manoalides. The similarity of both the structures and the anti-bacterial activity of manoalides and neo-manoalides described above prompted us to synthesize neo-manoalides and their derivatives, and to test their various biological activities.



E-neomanoalide (1)



manoalide

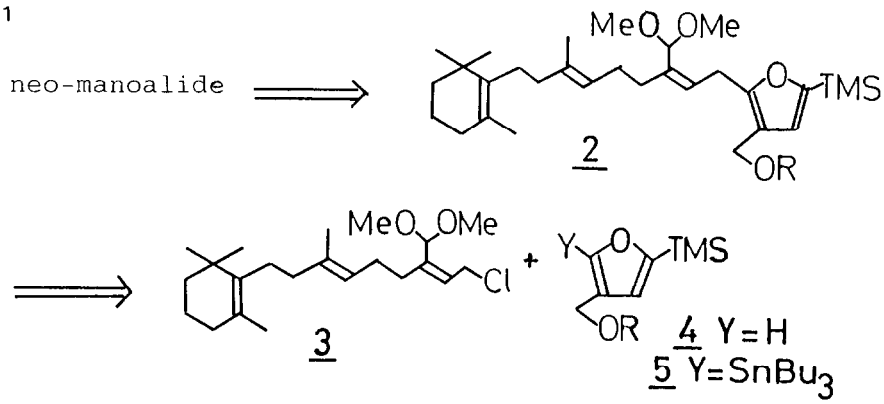


seco-manoalide

In the course of our study to synthesize biologically active terpenoids, we have previously reported the first total synthesis of manoalide and seco-manoalide.[5] In this paper, we describe the first and the efficient total synthesis of E- neomanoalide (1) by the sequences of the Pd(0) catalyzed coupling of a α-stannylfuran derivative and an allylhalide followed by chemoselective oxygenation of a α-silylfuran derivative, and reduction.

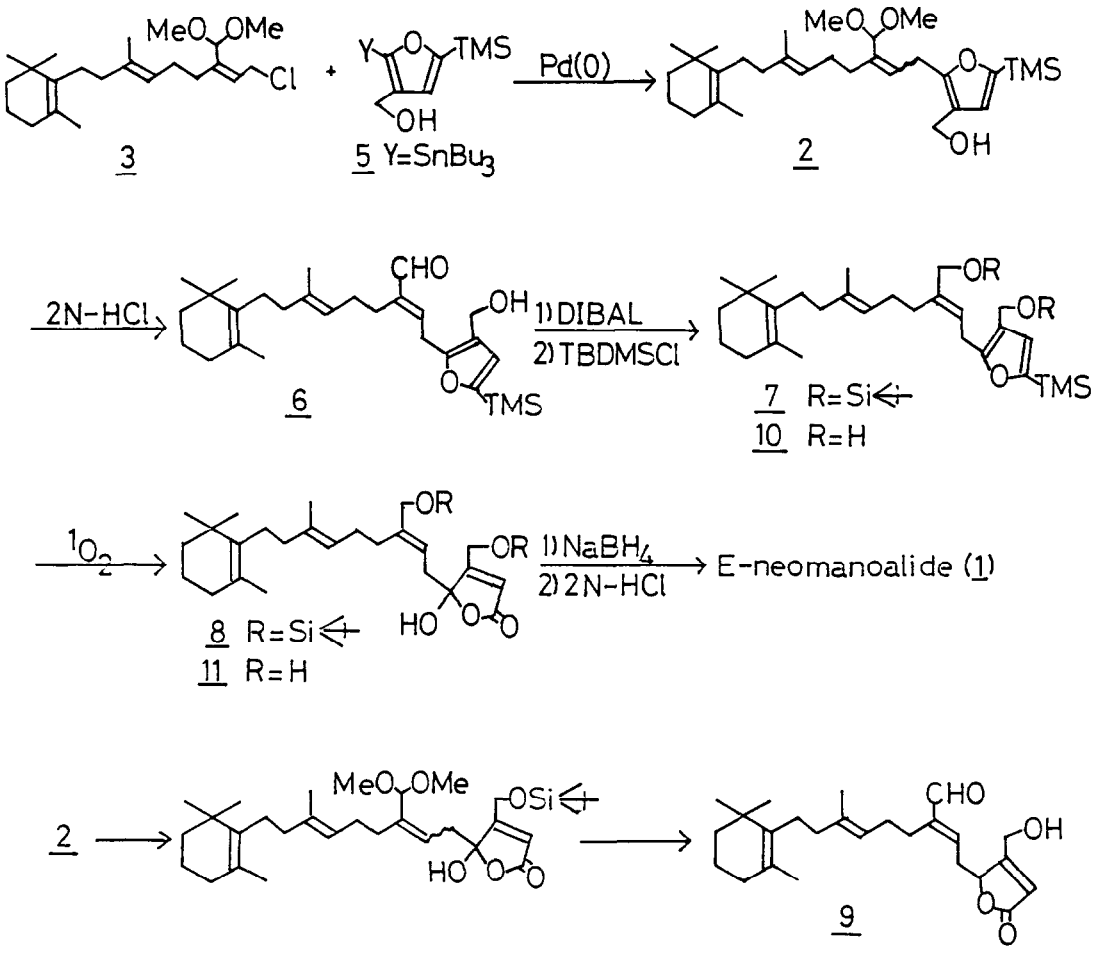
Our synthetic plan is shown in scheme 1. We have already realized the chemoselective oxidation of α-trimethylsilylfuran with singlet oxygen rather than tri- and tetra-substituted olefines in the same molecule.[6] This synthetic method of regiospecific formation of γ- hydroxybutenolide is also applicable to the synthesis of β- and γ- substituted butenolide existing in the neo-manoalide molecule by the combination with reduction. Upon the above consideration, we chose a α-trimethylsilylfuran derivative 2 which could be derived from an allylchlolide 3 and a α-stannylfuran derivative 5 as a key intermediate for the synthesis of neo-manoalide.

Scheme 1



The first trial to obtain 2 is the alkylation of the lithium anion generated regioselectively from 4 with the allyl chloride 3.[5] Unfortunately objective 2 was obtained only in less than 5 % yield after trials under the various reaction conditions, although furan without oxygen function at 3-position gave the alkylation product at 2-position in excellent yield under the same reaction condition.[7] Therefore, we turned the method to prepare 2 to the one using Pd(0) catalyzed coupling reaction developed by Stille recently.[8] The required segment, 2-trimethylsilyl-4-hydroxymethyl-5-tributyl-stannylfuran(5), was prepared as an unstable oil from 4 by stannylation (n-BuLi/Bu_3SnCl /THF/-78°C, 91 % yield). The desired coupling product 2 was obtained as the 1:1 mixture of the stereoisomers in 66 % yield (79 % of the conversion yield) by a reaction of 3 with 2 equivalent of 5 in the presence of palladium dibenzylidenacetone and triphenylphosphine (50°C, 12 hours). Acid treatment of 2 (2N HCl/THF/0° C/2 hours) afforded unsaturated aldehyde 6 with E geometry,[5] in which trimethylsilyl group in the furan ring remained. Reduction of 6 with DIBAL followed by protection of the resulting two hydroxy

groups gave 7 in 77% yield from 2. Singlet oxygen oxidation of 7 under the same condition as before[6] yielded quantitatively the expected γ-hydroxybutenolide 8 without any oxidation of tri- and tetra-substituted olefins in the side chain. The synthesis of E-neomanoalide (1) was achieved by reduction of 8 with $NaBH_4$ (0°C, EtOH) followed by acidification (10 % H_3PO_4, pH2) and then removing the silyl groups (2N HCl/THF/0°C/2.5 hours) in 74 % yield. The synthesized compound was identical with the natural one by ^1H and ^{13}C nmr (400 MHz). We also synthesized aldehyde 9 in 55.1 % yield from 2 by another reaction sequences, that is, protection of the hydroxy group, singlet oxygen oxidation, reduction-acidification, and deprotection. The chemical shifts of nmr (400 MHz) of this synthesized aldehyde 9 was also identical with those reported for the aldehyde which was derived from natural product by Scheuer et al.[1]



The synthetic method of neo-manoalide using Pd(0) catalyzed coupling of highly oxidized systems developed above would be applicable to the synthesis of manoalides. Further study along this plan is now under investigation.

Finally, we describe the results of the test toward aldose reductase inhibition in vitro. All of the compounds, 1, 9, 10, and 11 showed weak activity (MIC_{50}, $2x10^{-4}M$: 41%; 68%; 35%; 25% respectively) comparing to the strong activity of seco-manoalide (MIC_{50}, $2x10^{-6}M$: 82%).[3] This suggests that β-substituted -γ-hydroxybutenolide function is the essential part causing the interesting biological activities of manoalides.

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