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NOVEL SYNTHESIS OF (-)-SECOLOGANIN AGLUCON-O-SILYL ETHER FROM (+)-GENIPIN VIA OXIDATIVE FRAGMENTATION OF γ-HYDROXYALKYLSTANNANE

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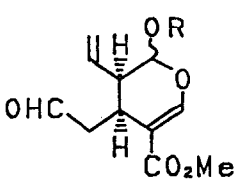
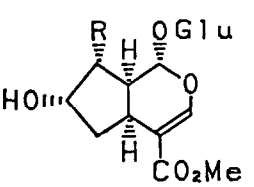
Summary: The synthesis of (-)-Secologanin aglucone-O-silyl ether was achieved via the oxidative fragmentation of γ-hydroxyalkylstannane which was obtained by 1,4-addition of tributyltin to cisoid enone derived from (+)- genipin.

Secologanin (1) is a key compound not only as a biogenetic precursor of various alkaloids and secoiridoids, but also as a building block for the synthesis of pharmacologically interesting compounds.[1] Among synthetic efforts of secologanin aglucone 2, [1,2] the representative one is the synthesis employing Grob type fragmentation of the **trans** isomer of hydroxyloganin aglucone-O-methyl ether monotosylate.[3] In the biogenetic route of secologanin (1), hydroxyloganin (3) was first suggested as an intermediate from loganin (4), and later it has been concluded that loganin directly generates secologanin via an oxidative radical or ionic process.[1] None of the valuable methods, however, adopting an oxidative radical process to O-protected loganin aglucone has been reported for the synthesis of O-protected secologanin aglucone.[4] Now we describe the novel synthesis of (-)-secologanin aglucone-O-silyl ether 5 from (+)- genipin (6, R=Glu) by the method applying oxidative fragmentation reaction of γ-hydroxyalkylstannane 17 with lead tetraacetate[5] (Scheme 1).

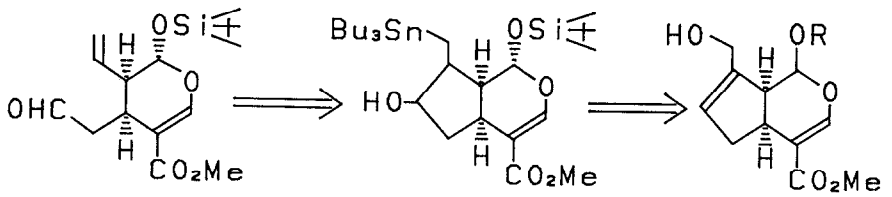


1 R=Glu
2 R=H



3 R=CH2OH
4 R=CH3

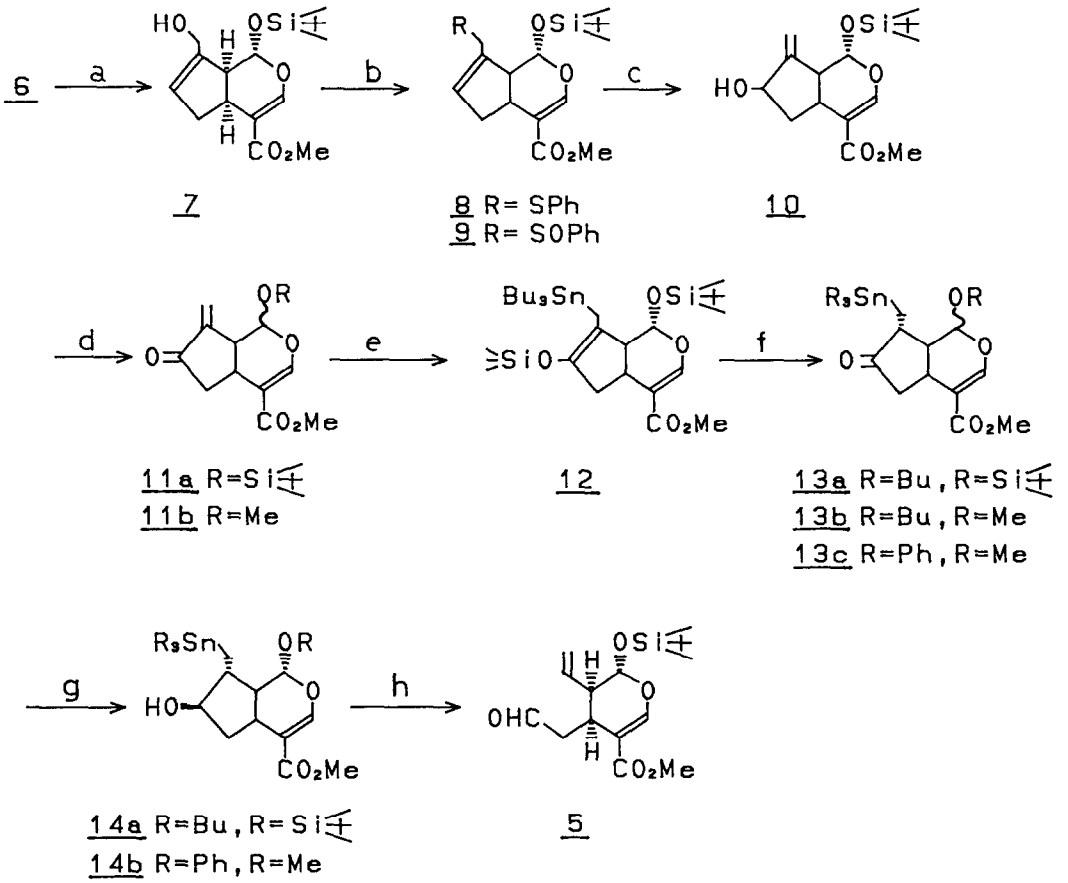
Scheme 1



5 14a 6

In the course of our synthetic study of optically active iridoids,[6] (+)-genipin (6, R=H), which was obtained easily by enzymatic hydrolysis (Cellulosin AC_{40}) of geniposide (6, R=Glu) isolated from Gardenia jasminoides in large quantity, was employed as a starting material. Genipin monosilyl ether 7 was obtained from 6 (R=H) by silylation (t-butyldimethylsilyl chloride/ $AgNO_3$/ DMF) followed by selective desilylation (cat. PPTS/ EtOH/ reflux) in 98% yield. This simple procedure was very useful for both regioselective and stereoselective protection of hydroxyl group of hemiacetal in genipin. Allylic rearrangement of free hydroxyl group of 7 was achieved by Evans rearrangement.[7] Thus, 7 was converted to thioether 8 (PhSSPh/ n-Bu_3P/ benzene, 94% yield) which was oxidized to give sulfoxide 9 (m-CPBA / -78°C, 89% yield). Thermal rearrangement of 9 proceeded smoothly to give alcohol 10 [$(MeO)_3P$/ MeOH/ reflux, 94% yield] which was subjected to oxidation yielding enone 11a ($BaMnO_4$/ CH_2Cl_2, 85% yield). It is well known that trialkyltin lithium normally adds to α,β-unsaturated ketone to give formal 1,4-adduct in excellent yield.[8] Unexpectedly, treatment of 11b prepared from genipin-O-methyl ether (6, R=Me) with tri**butyl**tin lithium gave desired 1,4-adduct 13b in only 23% yield along with dimeric products which might be formed by Michael type addition of α-anion of 11b to the starting enone. On the other hand, tri**phenyl**tin lithium gave normal 1,4-adduct 13c in 70 % yield. After reduction of 13c ($NaBH_4$/ MeOH), treatment of the resulting alcohol 14b with lead tetraacetate under the previous reaction condition[5] did not afford any secologanin aglucone-O-methyl ether(2). Then, it was necessary to find effective reagent which give 1,4-adduct of tributyltin to cisoid enone like 11. Attempt to use ate complexes, ($PhSCuSnBu_3$-n)$^-Li^+$ and n-$Bu_3SnCu \cdot Me_2S$-LiBr,[9] also gave the desired enone 13a in low yield. The dimeric products of the different type from the ones produced by the reaction with tributyltin lithium were isolated.[10] These dimeric products might result from one electron transfer from the reagent to enone 11a. Fortunately, it was found that (trimethylsilyl)tributylstannane was an excellent reagent for 1,4- addition of tributyltin group to cisoid enone 11 catalyzed by naked CN anion.[11] Thus, enone 11a reacted cleanly with the above reagent in the presence of both catalytic amount of KCN and 18-crown-6 (THF/ -20°C/ 1h) to

afford desired silylenol ether 12 which was subjected to selective removal of trimethylsilyl group with $Bu_4NF \cdot 3H_2O$ in the presence of acetic acid (2 equivalent/ THF/ -20°C). Tributylstannyl ketone 13a was obtained in 70% yield from 11a.[12] Finally, synthesis of (-)-secologanin aglucone-O-silyl ether 5, $[\alpha]_D^{21}$ -63.22° (c=0.52, MeOH), was achieved by reduction of 13a ($NaBH_4$/ EtOH, 91% yield) followed by the oxidative fragmentation with lead tetraacetate ($CaCO_3$/ benzene/ reflux / 15 minutes)[5] in 82% yield. It should be noted that this oxidative fragmentation proceeded from both cis and trans isomers in the relation to hydroxyl and tributylstannylmethyl group of 14a in contrast to Grob type fragmentation.[3,5]



(a)TBDMSCl/$AgNO_3$/DMF; PPTS/EtOH (b)$(PhS)_2$/n-Bu_3P; m-CPBA/CH_2Cl_2 (c)$(MeO)_3P$/ MeOH reflux (d)$BaMnO_4/CH_2Cl_2$ (e)TMS-$SnBu_3$/KCN/18-Crown-6 (f)$Bu_4NF \cdot 3H_2O$/ 2eq.AcOH (g)$NaBH_4$/MeOH (h)$Pb(OAc)_4$/benzene reflux

In conclusion, optically active secologanin aglucone-O-silyl ether 5 was synthesized from (+)-genipin(6, R=H), $[\alpha]_D^{29}$ +114.1° (c=1.0, MeOH), by the similar oxidation process to its biogenesis in 34% overall yield. In addition, it is noteworthy that protection of hydroxyl group of hemiacetal with easily removable silyl ether makes possible to synthesize various seco-iridoids without migration of double bond from 5. Works on this line are in progress.

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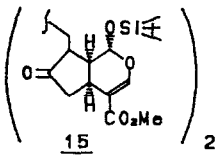
9. E.Piers, J.M.Chong, B.A.Keay, Tetrahedron Lett., 26, 6265 (1985) and references cited therein.
10. The structure of these dimeric products was presumed as a mixture of stereoisomers of 15 by ir, nmr, and mass spectra.



15 2

11. B.L.Chenard, E.D.Laganis, F.Davidson, T.V. RajanBabu, J.Org.Chem., 50, 3666 (1985).
12. Two isomers were observed (10:1 by nmr). The stereochemistry of stannyl-methyl group in the major component was tentatively assigned α.

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