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Synthesis of Asperuloside Aglucon Silyl Ether and Garjasmine from (+)-Genipin via Gardenoside Aglucon Disilyl Ether as a Common Intermediate

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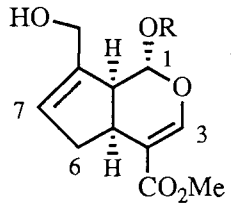
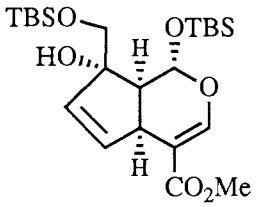
Synthesis of asperuloside aglucon silyl ether (**4**) and garjasmine from (+)-genipin was accomplished by utilizing the gardenoside aglucon disilyl ether (**3**) as a common intermediate. During the transformation of **3** into **4** the acid catalyzed transposition reaction of hydroxy group was found to proceed from more hindered concave side.

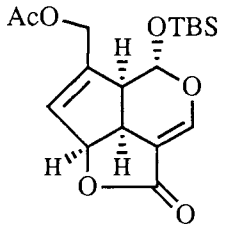
We have been investigating the transformation of (+)-genipin (**2**), which can be supplied from industry in hundreds gram scale,[1] into more valuable polyfunctionalized iridoids such as secologanin,[2] plumericin[3] and marine natural products petiodial[4] and udoteatrial.[5] We, herein, would like to report that the gardenoside aglucon disilyl ether (**3**) obtained by functionalization at C6 position of **2** was realized to be a key and common intermediate for the synthesis of asperuloside aglucon silyl ether (**4**)[6] and garjasmine (**5**)[7] recently isolated from *Gardenia jasminoides Ellis*.



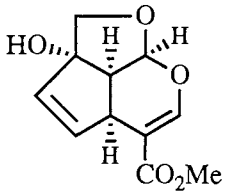
R = Glu geniposide **1**
R = H genipin **2**



gardenoside aglucon disilylether **3**

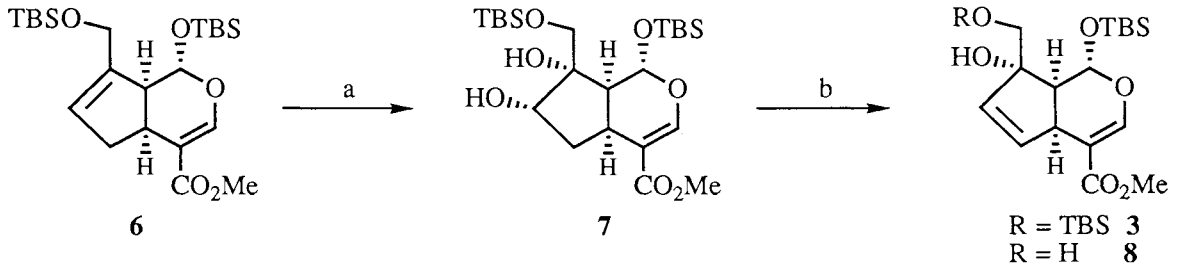


asperuloside aglucon silylether **4**



garjasmine **5**

Although the enzymatic allylic oxidation of geniposide (**1**) has been shown to be a key step in the biosynthesis of C6 functionalized iridoids,[8] such a chemical transformation was found not to be easy to accomplish in simple operations. After numerous experimentations dehydration of the secondary alcohol in the diol (**7**) was found to give the $\Delta^{6,7}$-compound. (Scheme 1) Thus, dihydroxylation of the (+)-genipin disilyl ether (**6**) with catalytic amount of OsO_4 in the presence of N-Me-morpholine-N-oxide (NMO) smoothly proceeded to give the diol (**7**). The stereochemistry of **7** was assigned by assuming that osmium reagent approached from the less hindered side of the double bond and was later confirmed by its successful conversion into **5**. The dehydration of the secondary alcohol in **7** was effected by treatment with trifluoromethanesulfonic



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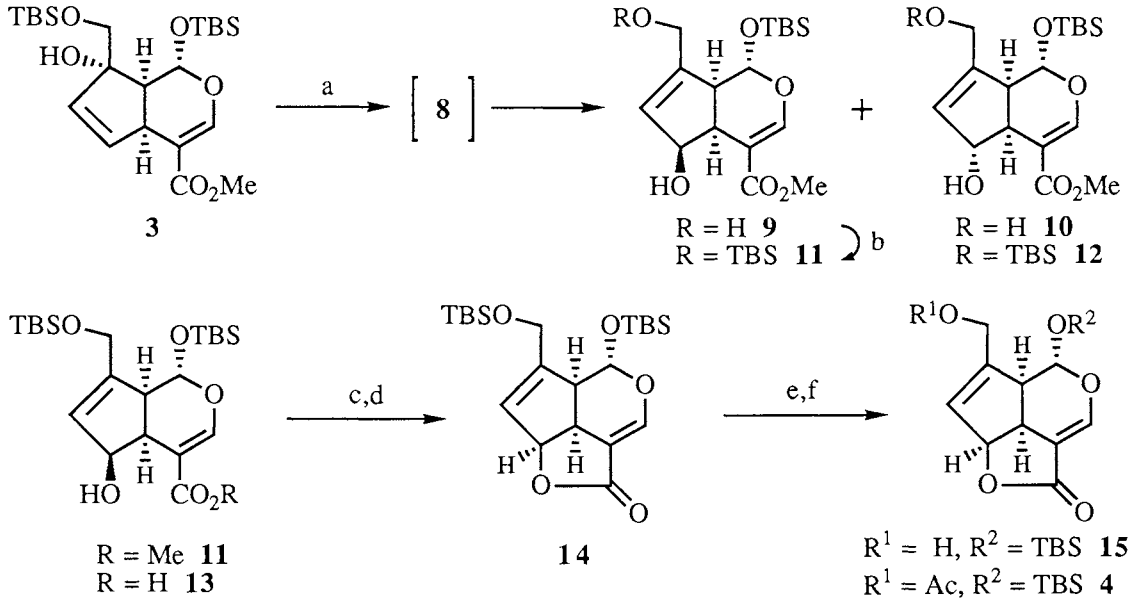
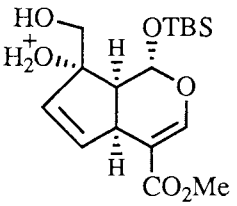
Scheme 1. Conditions: a) cat. OsO_4, NMO, t-BuOH:acetone:H_2O=10:3:1, 85%, b) Tf_2O (1.5 equiv.), DMAP (3 equiv.), CH_2Cl_2 then DBU (3.6 equiv.), 70%.

anhydride (Tf_2O) with 4-dimethylaminopyridine (DMAP) followed by DBU[9] to afford **3** in good yield.

With the $\Delta^{6,7}$-compound in hand we then focused our attention on the introduction of oxygen functionality at C6 aiming at the synthesis of asperuloside derivatives. Upon treatment of **3** with PPTS in aqueous acetone the silyl group attached at the primary alcohol was first hydrolyzed to give gardenoside aglucon silyl ether (**8**). The prolonging the reaction time, however, further caused hydroxy group transposition of **8** to afford the desired C6



Scheme 2.
Conditions: a) PPTS, acetone:H_2O=2:1, reflux, **9** 43%, **10** 12%, b) TBSCl, imidazole, DMF, 93%, c) KH, THF, 0 °C, d) DCC, CH_2Cl_2, 85% (2 steps), e) PPTS, acetone:H_2O=3:1, reflux, f) Ac_2O, Py, DMAP, 54% (2 steps).



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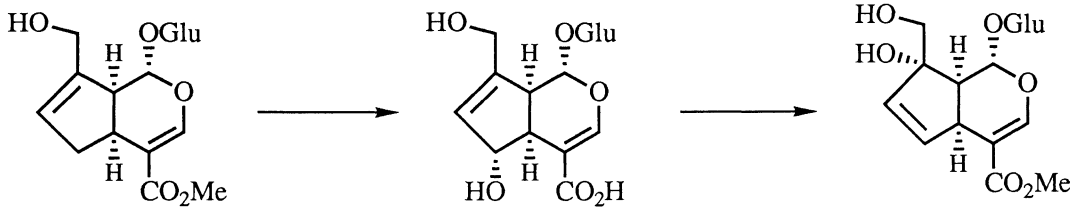
hydroxylated compounds as a mixture of stereoisomers (**9** and **10**) in about 3.6 to 1 ratio. The structure of each isomer was unambiguously assigned as shown in the Scheme 2 by the successful conversion of the major isomer (**9**) (Mp 130-131 °C, recrystalized from EtOAc-Hexane) into **4**.



1 **17** **18**

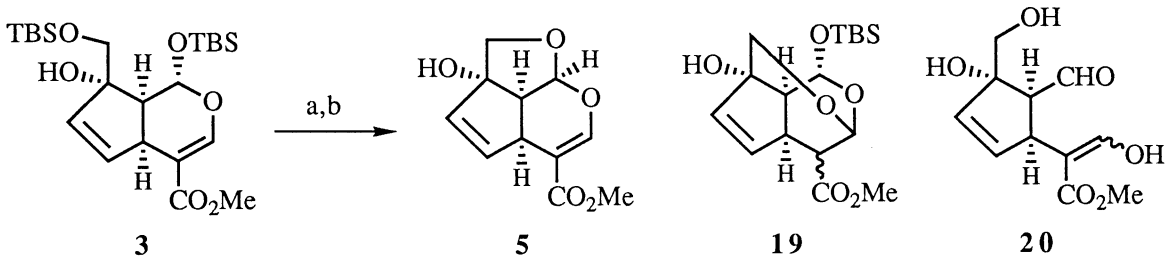
Scheme 3. Proposed biosynthesis of gardenoside (**18**) from geniposide (**1**).

The remaining task to convert **9** into **4** was the hydrolysis of the methyl ester and lactonization of the resulting hydroxy acid. Attempts to hydrolyze the methyl ester with an external nucleophile resulted in either recovery or decomposition of the starting material. In contrast hydrolysis by utilizing the neighboring alcohol as an internal nucleophile was found to be successful. Thus, treatment of the alcohol (**11**), obtained by silylation of the primary alcohol in **9**, with potassium hydride in THF cleanly afforded the hydroxy acid (**13**), which was then lactonized with DCC to give the desired lactone (**14**). Finally hydrolysis of the silyl group at primary alcohol followed by acetylation of the resulting alcohol accomplished the synthesis of **4**, whose structure was confirmed by its 400MHz ^{1}H-NMR spectrum.[10]

The introduction of hydroxy group from more hindered side of the cis fused bicyclo[4.3.0]nona-3,7-diene system could be accounted by concerted attack of water to the protonated compound **16**. **16** was apparently in an equilibration between an allylic cation to which nucleophilic attack of water obviously favoured from convex side to produce **10**. Since the direct formation of either **11** or **12** from **3** without hydrolysis of the TBS ether at primary alcohol was not detected on tlc analysis, the hydrolysis of silyl ether seemed to accelerate the transposition reaction of hydroxy group.

This observed hydroxy transposition reaction was significant in that the transposition of hydroxy group in the proposed biosynthetic pathway of gardenoside (**18**) from geniposide (**1**) proceeded to the opposite direction as shown in the Scheme 3 (from **17** to **18**).[8]

As mentioned above asperuloside derivative was successfully obtained from **3**, which was also found to be a key intermediate for the synthesis of garjasmine (**4**). Although the isolation of **4** was reported, its biological activity was remained uncertain. Since the acidic condition for hydrolysis of the silyl group in **3** could not be used to prevent hydroxy group transposition, the use of tetrabutylammonium fluoride (TBAF) was thus examined. Treatment of **3** with two equivalent of TBAF afforded a mixture of two stereoisomers of the cyclic acetal (**19**) resulted from the intramolecular Michael addition of alkoxide. Furthermore the silyl group at the hemiacetal oxygen was found to be inert even in the use of the theoretical amount of TBAF. After examining the condition of desilylation of **3** with TBAF, the use of a large excess amount of TBAF (5 equiv.) was found to be successful to give desilylated compound, which was, without isolation, acidified with p-toluenesulfonic acid (p-TsOH) to give **5** cleanly.[11] (Scheme 4) Since treatment of **19** with excess TBAF followed by p-TsOH did not afford **5**, it was apparent that the production of **19** was suppressed when **3** was treated with excess amount



3 5 19 20

Scheme 4. Conditions: a) TBAF (5 equiv.), THF, 2) p-TsOH (7 equiv.), THF, 53% (2steps).

of TBAF. Probably this is because that desilylation of both silyl ether with large excess amount of TBAF might produce the mono-cyclic trihydroxyaldehyde (**20**) of which unsaturated ester portion was less electrophilic than that of **3**. Upon acidification of **20** cyclic acetal formation became favorable to afford **5**.

The functionalization at C6 position in **2** can be achieved to give **3**, which was demonstrated to be a common intermediate for the synthesis of **4** as well as **5**. We believe those synthetic method reported here would widen the utility of (+)-genipin as a chiral source for a highly added-value materials. Study along this line will be reported in due course.

References

1) We express our appreciation to Glico Foods Corp for a kind gift of (+)-genipin.
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5) Y. Ge, S. Kondo, K. Nakatani, S. Katsumura, and S. Isoe, manuscript in preparation.
6) Asperuloside was the first isolated iridoid. see Ref. 8. structure: L.H. Briggs, B.F. Cain, P.W. Lequesen, and J.N. Shoolery, *Tetrahedron Lett.*, **1963**, 69.
7) The isolation of garjasmine was recently reported by Xu at Shanghi Institute of Materica Medica, Academia Sinica, Shanghai, China. The detail of the property of this compound was not appeared in the journal yet.
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10) ^{1}H-NMR of **4** ($CDCl_3$) δ= 0.11, 0.15 (sx2, each 3H, Si*Me*$_2$), 0.87 (s, 9H, Si^t*Bu*), 2.06 (s, 3H, -OCO*CH*$_3$), 3.10 (m, 1H, C9-H), 3.57 (dt, 1H, J=6.7, 2.4 Hz, C5-H), 4.62 (d, 1H, J=14.0 Hz, -*CH*OAc), 4.66 (dd, 1H, J=14.0, 1.2 Hz, -*CH*OAc), 5.46 (m, 1H, C1-H), 5.62 (d, 1H, J=1.8 Hz, C7-H), 5.07 (m, 1H, C6-H), 7.22 (d, 1H, J=1.8 Hz, C3-H)
11) **5**: Mp 135.0-135.5 °C (reported 132-133 °C, Ref. 8), ^{1}H-NMR ($CDCl_3$) δ= 2.06 (bs, 1H, -*OH*) 2.88 (dd, 1H, J=9.8, 6.1 Hz, C9-H), 3.73 (s, 3H, -O*CH*$_3$), 3.82 (m, 1H, C5-H), 3.92 (s, 2H, C10-H$_2$), 5.63 (d, 1H, J=6.1 Hz), 5.72 (dd, 1H, J=5.5, 2.4 Hz, C7-H), 5.99 (dd, 1H, J=5.5, 1.8 Hz, C6-H), 7.47 (s, 1H, C3-H) Anal. Found: C, 58.91; H, 5.40%. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39%.

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