

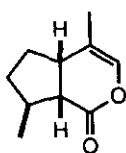
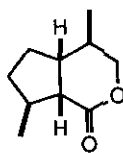
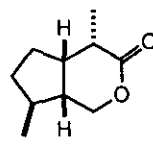
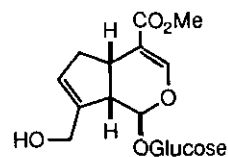
## SYNTHESIS OF IRIDOLACTONES ISOLATED FROM *SILVER VINE*

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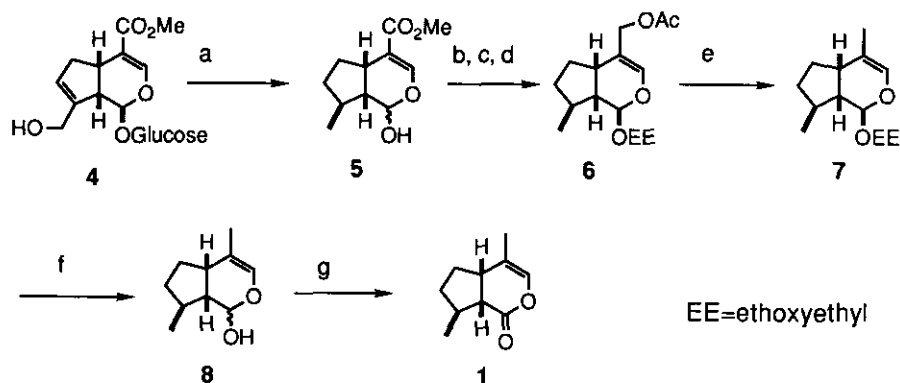
**Abstract**----The naturally occurring iridolactones, nepetalactone, isodihydronepetalactone, and iridomyrmecin are synthesized in optically active forms starting from natural glycoside geniposide. The stereogenic centers were introduced with highly stereoselective hydrogenations.

Fruits of *silver vine* is known to contain several iridoids, in which (+)-nepetalactone (**1**), (+)-isodihydronepetalactone (**2**), and (+)-iridomyrmecin (**3**) are classified as iridolactones because of their structural characters.<sup>1,2</sup> Interestingly, in spite of their small molecular size, they have contiguous chiral centers on their ring systems. Being interested in these stereostructural features, we have pursued studies on the synthesis of these iridolactones possessing natural absolute configurations. In this paper, we describe the stereoselective synthesis of nepetalactone (**1**), isodihydronepetalactone (**2**) and iridomyrmecin (**3**) from geniposide (**4**), which is readily available chiral source.

**1****2****3****4**

The synthesis started with stereoselective reduction of allylic alcohol moiety of geniposide to the  $\beta$ -oriented methyl group which is common to the three iridolactones. The straightforward catalytic reduction and subsequent acidic hydrolysis of glucoside gave single aglycon (**5**)<sup>3</sup> in 40% in the desired sense (scheme 1). The fact that hydrogenation occurred exclusively from concave side is in good accord with previously known results,<sup>4</sup> and we presume this selectivity is caused by the  $\beta$ -oriented bulky sugar moiety of glucoside.

scheme 1



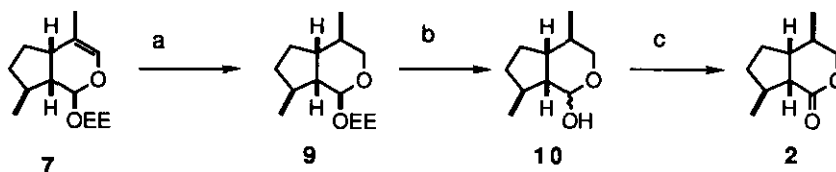
a) Pd-C/H<sub>2</sub>, acetone-H<sub>2</sub>O (1:1); 2N-HCl, 80°C (40%); b) ethyl vinyl ether, PPTS, CH<sub>2</sub>Cl<sub>2</sub> (90%); c) DIBAH, -50°C, THF d) Ac<sub>2</sub>O, py, DMAP, CH<sub>2</sub>Cl<sub>2</sub> (80%); e) Pd-C/H<sub>2</sub>, AcOEt-py (2eq) (93%); f) 2N-HCl, THF (82%); g) PDC, MS-4A, CH<sub>2</sub>Cl<sub>2</sub> (33%)

With the common intermediate (**5**) to **1-3** in hand, we next carried out the modification of dihydropyrane ring of **5** to complete the synthesis of **1**. After protection of hemiacetal as ethoxyethyl ether,<sup>5</sup> treatment of the resulted product with diisobutylaluminum hydride (DIBAH) followed by acetylation produced **6** in 80%. Hydrogenolysis of **6** over Pd-C in ethyl acetate containing pyridine afforded deoxygenated product (**7**) in 92%.<sup>6</sup> Acidic hydrolysis of ethoxyethyl ether (78%), and subsequent oxidation of the resulted nepetalactol (**8**) gave nepetalactone (**1**) in 33%. The physical data (<sup>1</sup>H-NMR, IR, MS, and optical rotation value) of synthetic **1** were identical with those reported.<sup>7</sup>

Next, the synthesis of isodihydronepetalactone (**2**) was achieved. It is well known that the reduction of **1** gives the stereoselectively hydrogenated nepetalactone with 4 $\alpha$ -methyl group.<sup>8</sup> So, to obtain the product with C-4 $\beta$  methyl group, we utilized the intermediate (**7**) having  $\beta$ -oriented bulky substituent at C-1 position. The hydrogenation of **7** over Pd-C afforded the saturated product (**9**) with C-4 $\beta$ -methyl group. This reverse

observation in the stereoselectivity was presumably caused by the introduction of the bulky C-1 substituent, and this fact supports our presumption about the stereoselectivity observed in the hydrogenation of geniposide (**4**) (vide supra). The removal of ethoxyethyl group of **9** to isodihydronepetalactol (**10**) (85%)<sup>9</sup> and following oxidation afforded **2**, and physical data (<sup>1</sup>H-NMR, IR, MS, and optical rotation value) were identical with reported ones<sup>10</sup> (scheme 2).

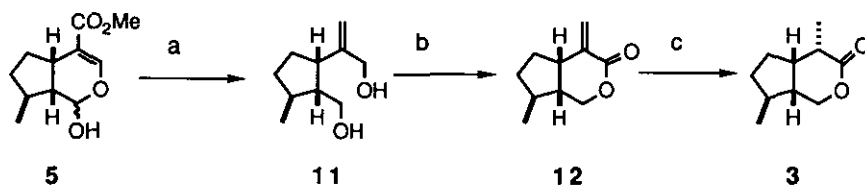
scheme 2



a) Pd-C/H<sub>2</sub>, AcOEt (quant); b) 2N-HCl, THF (78%); c) PDC, MS-4A, CH<sub>2</sub>Cl<sub>2</sub> (35%)

Finally, iridomyrmecin (**3**) having the C-4 $\alpha$ -methyl group was synthesized under the usually expected hydrogenation from convex face of the molecule. The reductive ring opening of **5** with DIBAH gave allylic diol (**11**),<sup>11</sup> which in turn was converted into  $\alpha$ -methylene lactone (**12**) with manganese dioxide mediated oxidation in 58% yield in 2 steps. The hydrogenation of **12** over Pd-C gave **3** with complete stereoselectivity as expected (scheme 3). The structure of the synthetic iridomyrmecin including the configuration at C-4 was conformed by the comparison of the physical data (<sup>1</sup>H-NMR, IR, MS, and optical rotation value) of synthetic material with reported ones.<sup>12</sup>

scheme 3



a) DIBAH, THF, 0°C (70%); b) MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 50°C (83%); c) Pd-C/H<sub>2</sub>, MeOH (quant)

In conclusion, it was demonstrated that the efficient synthesis of several iridolactones in naturally occurring forms from iridoid glycoside geniposide was achieved in highly stereoselective manner.

#### Reference and Notes

† Dedicated to Emeritus Professor Yoshio Ban on the occasion of his 70th birthday.

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6. Without pyridine, the hydrogenolytic removal of ethoxyethoxy group at C-1 position was observed.
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