Simple Synthesis and Physiological Activities of Acerogenins

([1]*Graduate School of Systems Engineering, Kindai University*, [2]*Faculty of Engineering, Kindai University*) ○Ikumi Ohata,[1] Mina Nagarede,[2] Yoshiharu Okada,[2]

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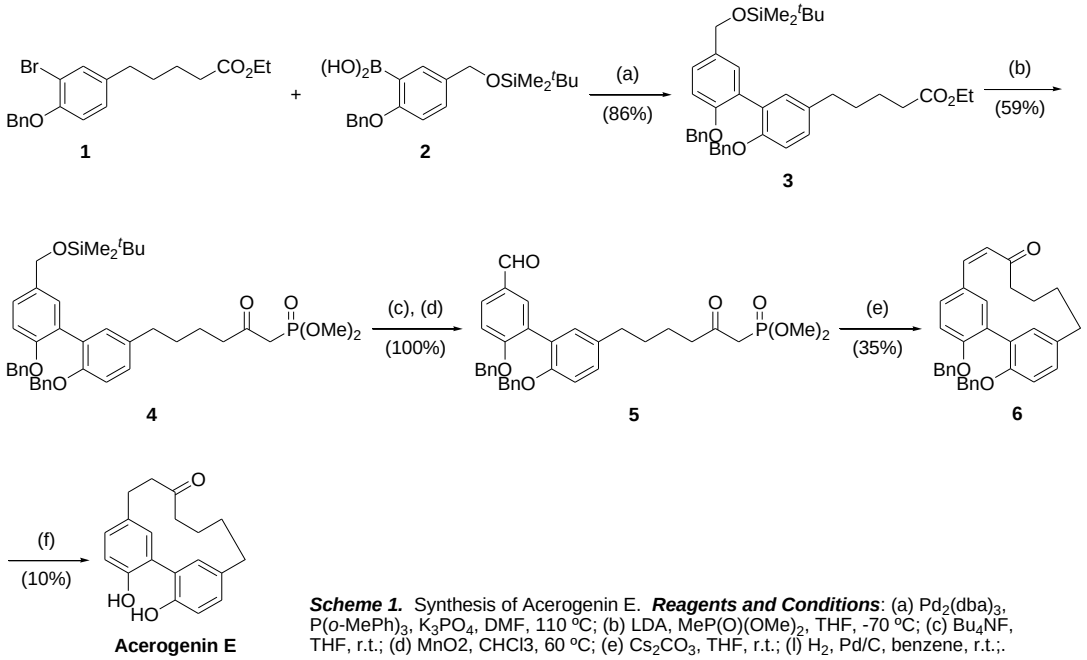
Acerogenins bearing 4-(4-hydroxyphenyl)-2-butanol moieties were isolated from bark of *Acer nikoense* M., a maple indigenous in Japan, and assigned chemical structures. It is known that acerogenins have interesting physiological activities such as anti-inflammatory effect, anti-tumor promoting effect, nitric oxide production inhibition activity. In addition, acerogenins have melanogenesis inhibitory activity (whitening effect). We have interested in these natural occurring compounds and investigated the activity of their analogues. So, we report here the simple synthesis of acerogenins and their physiological activities.

Ethyl 5-(4-benzyloxy-3-bromophenyl)pentanoate **1** was prepared from 4-benzyloxy-3-bromobenzaldehyde in five steps. 2-Benzyloxy-5-(*tert*-butyldimethylsiloxymethyl)phenyl-boronic acid **2** was prepared from similar benzaldehyde in three steps. Suzuki-Miyaura cross-coupling reaction of **1** with **2** gave biphenyl derivative **3** in 86% yield. Reaction of **3** with dimethyl methylphosphonate in the presence of LDA gave β-keto phosphonate **4** in 59% yield. Deprotection of **4** with TBAF and subsequent oxidation with MnO_2 gave aldehyde **5** in quantitative yield. Intramolecular Horner-Wadsworth-Emmons reaction of **5** in the presence of Cs_2CO_3 was succeeded to give acerogenin E precursor **6** in 35% yield. Hydrogenation and hydrogenolysis of **6** in the presence of Pd/C catalyst gave acerogenin E in 10% yield.



Scheme 1. Synthesis of Acerogenin E. ***Reagents and Conditions***: (a) $Pd_2(dba)_3$, P(*o*-MePh)$_3$, K_3PO_4, DMF, 110 ºC; (b) LDA, MeP(O)(OMe)$_2$, THF, -70 ºC; (c) Bu_4NF, THF, r.t.; (d) MnO2, CHCl3, 60 ºC; (e) Cs_2CO_3, THF, r.t.; (l) H_2, Pd/C, benzene, r.t.;.