THE PRACTICAL METHOD FOR THE PREPARATION OF IRIDOID AGLYCONS FROM THEIR GLYCOSIDES

Masahide Tanaka, Masaharu Kigawa, Hiroshi Mitsuhashi,
and Takeshi Wakamatsu*
Tsumura Research Institute for Biology and Chemistry (TRIBIC)
3586 Yoshiwara, Ami-machi, Inashiki-gun
Ibaraki 300-11, Japan

Abstract——The liberation of iridoid aglycons from their glycosides is achieved by the successive treatment with sodium metaperiodate, sodium borohydride, and hydrochloric acid in one pot operation. This simple and efficient method has advantages over the enzymatic hydrolysis from the preparative point of view.

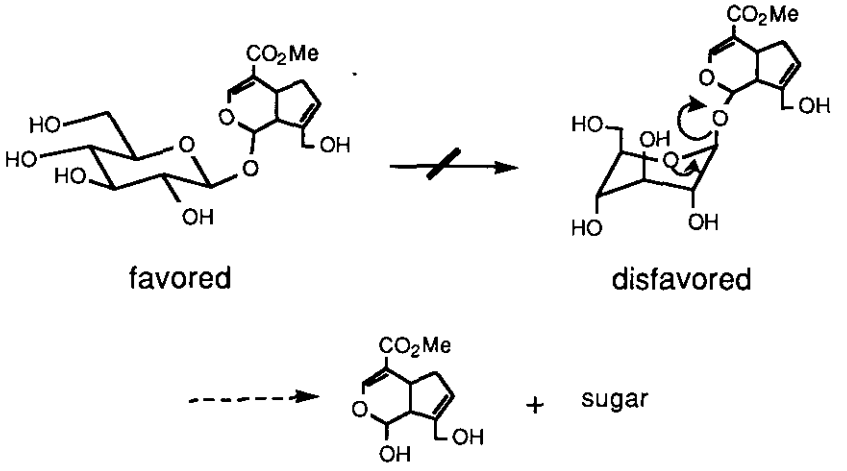
In nature, a large number of iridoids are found, and often, they exist as glycosides by making acetal linkage between hydroxyl group of iridoids and anomeric carbon of the sugars.[1] The removal of their sugar moiety to liberate aglycon is the essential operation in the course of the structure elucidation of those glycosides, and usually the enzymatic hydrolysis is the choice for that purpose.[2,3]

In the course of our study on the iridoid glycosides, we were urged to obtain their aglycons in quantities. But, soon, we realized the neccessity of the more practical method because the enzymatic hydrolysis is far from our satisfaction from the preparetive point of view for its expensiveness.[2]

Now we report the simple and efficient method for the liberation of the iridoid aglycons from their glycosides.[3,4] As a first attempt, we tried an acid catalyzed hydrolysis. Although the sturcturally simple glycoside (**4a**) gave aglycon (**4b**) upon treatment with hydrochloric acid at 80°C in the yield of 80 %, geniposide (**1**) gave only trace amount of genipin (**2**) forming untractable mixture under the identical conditions.[4] The milder reaction conditions at lower temperature to prevent

undesired side reactions were fruitless resulting in no hydrolysis. The stereoelectronic consideration suggested that the conformation of the sugar moiety with all substituents axial is neccessary for the acidic hydrolysis (Scheme 1).[5] But the results mentioned above showed that, in the hydrolysis of geniposide (**1**), the required condition for this conformation change was too harsh for genipin (**2**) to survive.

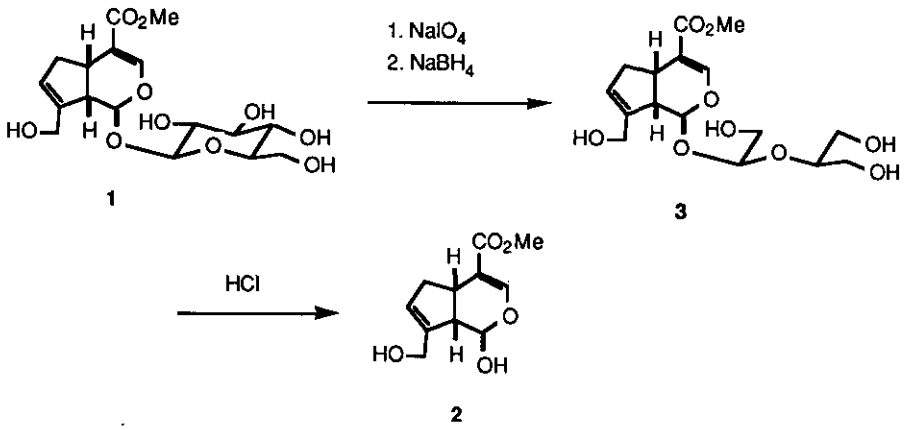
Scheme 1



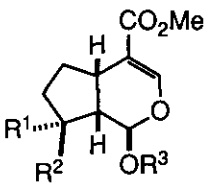
To avoid this problem, we turned our attention to the degradative deglycosidation.[6] As shown in the Scheme 2, the conformationally rigid sugar ring was cleaved by successive treatment with sodium periodate and sodium borohydride to give **3**. Now, as the sugar moiety is not conformationally rigid any more, the acid catalyzed hydrolysis of **3** proceeded readily under the mild conditions to give **2** in the yield of 74 % from **1**. The same operation was applied to the several iridoid glycosides including loganin (**4a-8a**),[7~9] and in all cases, the aglycons (**4b-8b**) were obtained in good yields.

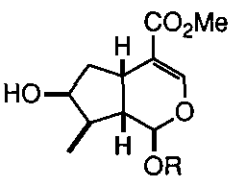
The method now established is superior to the enzymatic method, because this highly efficient method can be conducted in one pot operation in molar scale using unexpensive reagents instead of expensive enzyme. The typical experimental procedure was shown below.

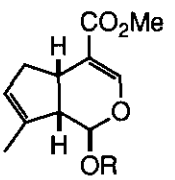
Scheme 2



Sodium metaperiodate (115 g, 0.54 mol) was added to the solution of geniposide (100 g, 0.26 mol) in water (650 ml) and the mixture was stirred at room temperature for 2 h. After the reaction mixture was cooled to 0°C, sodium borohydride (41 g, 1.1 mol) was added to the mixture and the whole was stirred at room temperature for 2 h, and then 6 N hydrochloric acid (317 ml, 1.9 mol) and ether (1 l) were added. After the whole mixture was stirred at room temperature for 4 h, sodium chloride (50 g) and sodium bisulfite (50 g) were added, the ether layer was separated, water layer was extracted with ether (1 l x 3), and the combined ether layer was dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was recrystallized from methanol-ether to afford genipin as colorless needles (43.1 g, 74 %) of mp 122-123 °C.







4a: R^1=H, R^2=CH_3, R^3=Glucose[7]
4b: R^1=H, R^2=CH_3, R^3=H (81%)
5a: R^1=H, R^2=CH_2OH, R^3=Glucose[8]
5b: R^1=H, R^2=CH_2OH, R^3=H (68%)
6a: R^1, R^2=CH_2, R^3=Glucose[9]
6b: R^1, R^2=CH_2, R^3=H (76%)

7a: R=Glucose
7b: R=H (74%)

8a: R=Glucose[7]
8b: R=H (57%)

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Received, 20th May, 1991