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Mild alkaline hydrolysis of some 7-*O*-flavone glycosides. Application to a novel access to rutinose heptaacetate

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Abstract—Alkaline hydrolysis of some 7-*O*-flavone glycosides was performed through the 6,8-dibromo derivative. When the sugar linked to the aglycon has a 2-hydroxy group *trans* to the sugar–aglycon bond as in β-D-glucosides or rutinosides, hydrolysis occurred at room temperature under very mild conditions. Application to a novel preparation of rutinose heptaacetate by hydrolysis of a diosmin derivative is described.

1. Introduction

In a previous publication,[1] we reported a regioselective 6-iodination of 5,7-dioxygenated flavones by benzyltrimethylammonium dichloroiodate (BTMA·ICl_2). This reagent allowed the 6-iodination of several natural 7-*O*-glycosylflavones such as diosmin **1** (7-*O*-rutinosyldiosmetin), linarin **2** (7-*O*-rutinosylacacetin) and rhoifolin **3** (7-*O*-neohesperidosylapigenin).[1,2] As iodination by BTMA·ICl_2 requires at least one free phenol and is carried out in CH_2Cl_2–MeOH as solvent, reactions were performed with **4**, **8** and **9**, the respective 5-hydroxyperacetylated derivatives of **1**, **2** and **3**,[3] according to the Kajigaeshi procedure.[4] Replacing BTMA·ICl_2 with *N*-bromosuccinimide (NBS) did not display any 6-regioselective bromination, but the subsequent saponification step led to the discovery of a new mild alkaline cleavage of the sugar–aglycon bond in the flavonoid field. This letter relates to the study of this bromination–saponification sequence applied to some 7-*O*-glycosylflavones.

2. Bromination–saponification of 5-hydroxyheptaacetyldiosmin 4

Reaction of **4** with 1 equiv of NBS (in CH_2Cl_2 or CH_2Cl_2–MeOH 2:1, 3 h, rt) provided, according to TLC, at least three compounds including the starting flavone. A second equivalent of NBS simplified the mixture, which led quantitatively to the 6,8-dibromoderivative **5**. By saponification under very mild conditions (THF–NaOH 0.5 N 1:1, 3.5 h, rt), **5** gave 6,8-dibromodiosmetin **6** (95%) instead of expected 6,8-dibromodiosmin **7**, and rutinose [6-*O*-(α-L-rhamnopyranosyl)-D-glucopyranose] as the main constituent of the recovered sugar moiety. Rutinose was purified and identified as rutinose heptaacetate (50% from **5**).[5] Under similar saponification conditions, diosmin **1** was entirely recovered from **4**.

3. Bromination–saponification of other 5-hydroxyperacetylglycosyloxyflavones

Rutinose, neohesperidose [2-*O*-(α-L-rhamnopyranosyl)-D-glucopyranose] and β-D-glucose are three of the most frequent sugar moieties in the flavonoids. Therefore, the bromination–saponification sequence was then studied with 7-*O*-neohesperidosyl and 7-*O*-β-D-glucosyl flavones. Bromination of 5-hydroxyheptaacetylrhoifolin **9** and 5-hydroxypentaacetyldiosmetin-7-*O*-β-D-glucoside **10** afforded, respectively, the 6,8-dibromo derivatives

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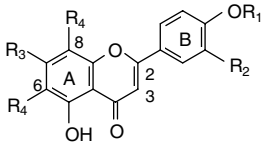
11 and **12** in a quantitative yield. Saponification of **12** allowed recovery of **6** from **5**, while the sugar–aglycon bond of **11** proved to be completely resistant (no trace of 6,8-dibromoapigenin even after 48 h).

4. Bromination–saponification of 5-hydroxyheptaacetyl-hesperidin 14

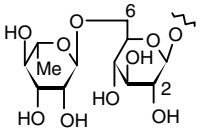
Compound **14** was prepared from hesperidin **13**, the flavanone precursor of diosmin, then was converted to its 6,8-dibromo derivative **15** (96%), which revealed a resistance of the sugar–aglycon bond to alkaline hydrolysis (only traces of rutinose after 48 h according to TLC).

the aglycon.[7–10] Comparative behaviour of dibromo derivatives **5**, **11** and **12** agrees with this mechanism: **5** and **12** with a potential *trans* 2-hydroxy group on the glucosyl moiety underwent the hydrolysis unlike **11** having the glucosyl C-2 involved in the interglycosidic link. Despite a rutinosyl structure, resistance to hydrolysis of **15** can be explained by its conversion in the alkaline medium to the open chalcone phenolate with a decreased electron-withdrawing character.

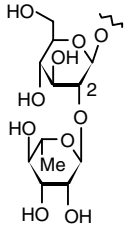
To the best of our knowledge, the cleavage of the sugar–aglycon bond in **5** and **12** is the first example of an alkaline hydrolysis of 7-*O*-flavone glycosides with recovery of the aglycon [in 1969, Litvinenko and Makarov



	R_1	R_2	R_3	R_4
1	Me	OH	rutinosyl	H
2	Me	H	rutinosyl	H
3	H	H	neohesperidosyl	H
4	Me	OAc	hexaacetylrutinosyl	H
8	Me	H	hexaacetylrutinosyl	H
9	Ac	H	hexaacetylneohesperidosyl	H
10	Me	OAc	tetraacetyl-β-D-glucosyl	H
13	2,3-dihydroderivative of **1**			
14	2,3-dihydroderivative of **4**			
5	Me	OAc	hexaacetylrutinosyl	Br
6	Me	OH	OH	Br
7	Me	OH	rutinosyl	Br
11	Ac	H	hexaacetylneohesperidosyl	Br
12	Me	OAc	tetraacetyl-β-D-glucosyl	Br
15	2,3-dihydroderivative of **5**			



rutinosyl



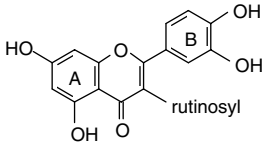
neohesperidosyl

5. Mechanism of the hydrolysis of the sugar–aglycon bond

Alkaline degradation of phenol glycosides is known to proceed well mainly by nucleophilic displacement of the aglycon. This displacement requires a sugar moiety with a neighbouring *trans* 2-hydroxy group to give a 1,2-anhydro sugar as the first intermediate,[6] and is facilitated by the presence of electron-withdrawing groups on

described the cleavage of 7-*O*-apigenin and luteolin rutinosides (0.5% aq KOH 100°, 30 min),[11] but in our hands no reaction occurred with diosmin **1** under these conditions]. Moreover, as bromine atoms can be easily removed by hydrogenolysis, this bromination–saponification sequence constitutes a new mild hydrolysis of some flavone glycosides besides the classic acid and enzyme methods. In other respects, in the special

case of the diosmin derivative **4**, our method is a novel chemical access to rutinose. As aforementioned,[6] the recovery of the intact sugar by alkaline hydrolysis was not expected. However, addition of THF as cosolvent in our procedure makes flavone **5** soluble at room temperature ; so the very mild conditions of saponification allow the recovery of rutinose in fair yield. Until now, almost all the chemical synthesis of rutinose from a flavonoid started from rutoside **16** (9–59% yields).[12–17]



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The best result was obtained by cleavage of the rutinosyl–aglycon bond with dihalomethyl methyl ethers, but this procedure was not at all selective with diosmin, which gave mainly a rhamnose derivative.[14] So, our method uses the readily available diosmin as a raw material for production of rutinose.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.04.085. General procedure of the bromination–saponification sequence; ^{1}H and ^{13}C NMR data of **4**–**6**, **9**, **11**, **12** and **15**.

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5. By comparison with an authentic sample from Extrasynthèse.
6. Reactivity of this intermediate depends on the structure of the sugar and experimental conditions: sugars with a free CH_2OH at C-6 give as final compound a 1,6-anhydro sugar by nucleophilic attack of the 1,2-epoxy system; in the absence of this free CH_2OH, the reaction leads to methyl glycoside in MeONa–MeOH by nucleophilic attack at C-1, and to tars in hot aqueous alkaline medium by degradation of the sugar. In any case, the intact sugar is not recovered at the end of the reaction.
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