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Synthesis of bidesmosidic lupane saponins – comparison of batch and continuous-flow methodologies

Anna Korda, Zbigniew Pakulski*, Piotr Cmoch, Katarzyna Gwardiak, Romuald Karczewski

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

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ABSTRACT

Synthesis of lupane bidesmosides was optimized. The title compounds were obtained by glycosylation of 3-*O*- or 28-*O*-substituted betulin monodesmosides with Schmidt donors catalyzed by TMSOTf. Classical batch procedure and microreactor technique were used and compared in the above synthesis. Experimental results clearly showed that both methods are comparable, although any particular outcome strongly depends on the structure of the reagents. Undesired allobetulin derivatives formed by the Wagner-Meerwein rearrangement were usually isolated in minute amounts. In the case of batch reaction, shorter reaction time significantly decreased formation of side-products.

1. Introduction

Betulin and betulinic acid – pentacyclic triterpenoids belonging to the lupane family and easily accessible from bark of *Betula* species – are regarded as interesting bioactive natural compounds and valuable starting materials in synthesis [1,2]. Nevertheless, their pharmacological use is often limited due to the poor solubility in water. These problems can be addressed by introduction of polar moieties at the C-3 and/or C-28 positions, e.g. by glycosylation to form saponins. Saponins, owing to their broad range of medicinal and biological properties, attract attention of numerous research groups and their chemical synthesis has been recently reviewed [3–6]. Monodesmosidic saponins of betulin were synthesized and their structure-activity relationship studies were reported [7–10]. In contrast, the betulin bidesmosides persist as a difficult to prepare target (Fig. 1). When the hydroxyl group at the C-28 position in lupane skeleton is targeted during glycosylation process, the Wagner-Meerwein rearrangement (Scheme 1) leading to allobetulin derivatives usually predominates [11–15], although some exceptions are known [16,17]. Since the bidesmosidic saponins are considered to be less haemolytic than monodesmosidic congeners, it is worthwhile to develop a general and efficient method of their synthesis [18,19].

Glycosylation reaction, although universally performed for over a century, continues to be a synthetic challenge due to the fact that numerous factors affect the outcome of the process (stereoelectronic effects, conformation and stereochemistry of reagents, concentration, temperature, reaction time, to name a few). Recently, flow reactors became available in laboratory environment and they can offer advantage over traditional batch reactors, due to the differences in reagent contact time, mixing characteristics and heat transport [20,21]. In the recent example of oligosaccharide synthesis, flow reactor proved to be superior over traditional flask methodology because better control of the contact of the reagents minimized side reaction [22–28].

As stated earlier, synthesis of lupane saponins by glycosylation of the 28-OH group of betulin derivatives **1** is often accompanied by the Wagner-Meerwein rearrangement, promoted by the Lewis acids, leading to allobetulin derivatives **2** (Scheme 1) [29]. In the case of betulin glycosylated at the 28-*O*-position (**3**), the recently observed sugar migration induced by the Wagner-Meerwein rearrangement leading to 3-*O*-glycosylated allobetulin **4** derivatives must also be considered as potentially high-yielding side-reaction (Scheme 2) [30].

Herein, we report on the synthesis of bidesmosidic betulin saponins by the glycosylation of monodesmosides and side-by-side comparison of the batch and flow methodologies. Two approaches to the bidesmosides were proposed, differing in order of attaching sugar moieties to the betulin core. In the first approach, monodesmoside **5** [30] substituted at the 28-*O* position was glycosylated at the 3-OH position in reaction with the trichloroacetimidate sugar donors under Schmidt's procedure [31,32].

* Corresponding author.
E-mail address: zbigniew.pakulski@icho.edu.pl (Z. Pakulski).

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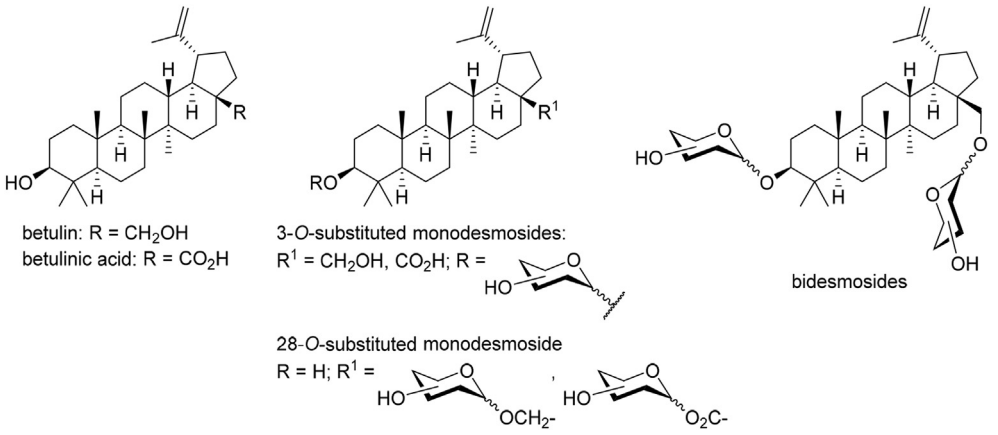
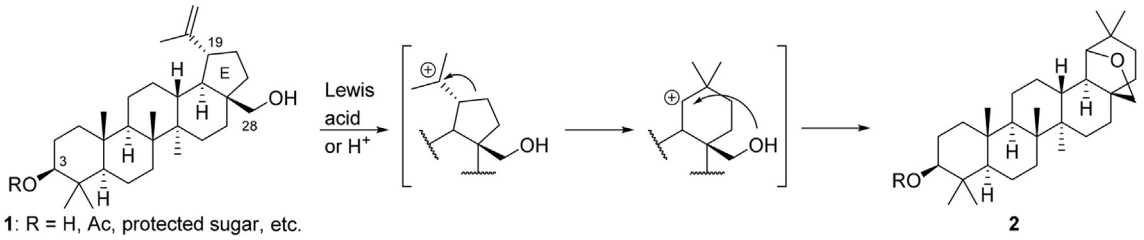
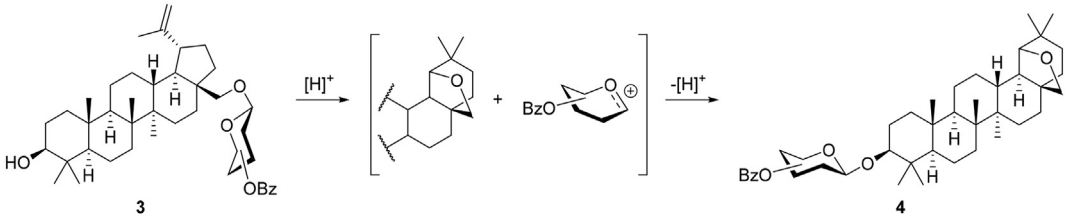


Fig. 1. Lupane type triterpenoids and saponins.



Scheme 1. The Wagner-Meerwein rearrangement of betulin derivatives.



Scheme 2. Sugar migration induced by the Wagner-Meerwein rearrangement.

In the second approach, compound **16** [11] substituted at the 3-*O* position was used as a starting material. Classical flask technique and microflow methodology were compared to identify the best conditions for the preparation of lupane bidesmosides.

2. Results and discussion

In the initial batch experiment, monodesmosidic saponin **5** glycosylated at the 28-*O* position was reacted with L-rhamnopyranosyl trichloroacetimidate **6** [33] under standard conditions (Scheme 3) [34]. Expected bidesmoside **10** [17] was obtained in 67% yield together with allobetulin glycoside **11** [30] which was isolated in 28% yield (Table 1, entry 1). Shorter reaction time inhibited formation of the rearranged product **11**, but at the cost of lower yield of desired product **10** (Table 1, entry 2, 46%).

Next, the microreactor was used to carry out the same reaction (Fig. 2). Flow experiments were performed in a coil reactor (PTFE microtube, OD × ID × L, 1/16" × 0.040" × 2 m) equipped with two Y-connectors and immersed in a cooling bath as described in previous paper [27]. Preliminary experiments allowed to determine the optimal residence time and concentration that resulted in a full conversion of the starting materials. The highest yield of bidesmoside **10** was observed for reaction performed at −40 °C (87%, Table 1, entry 4). In most cases, allobetulin glycoside **11** was also isolated in low to moderate yield (11–31%) as a by-product.

Reaction of **5** with D-mannopyranosyl trichloroacetimidate **7** [35] performed at −40 °C was selective and afforded required bidesmoside **12** as the only product (Table 1, entries 8, 10, and 12). Under flow conditions, even at 0 °C, rearrangement rate was low and allobetulinyl mannoside **13** [30] was obtained in 6–14% yield, only (Table 1, entries 9, 11). Under optimal conditions bidesmoside **12** was isolated in 78–80% yield (Table 1, entries 7 and 9).

Similarly, glycosylation of **5** with D-idopyranosyl trichloroacetimidate **8** [16] gave bidesmoside **14** in high yield (86–88%; Table 1, entries 13, 16, and 18). Allobetulinyl idopyranoside **15**, i.e. a by-product, was observed at a low yield (5–23%).

In the second step, monodesmosidic saponin **16**, with sugar moiety at the 3-*O* position was used as a starting material (Scheme 4, Table 2). Its reaction with L-rhamnopyranosyl donor **6** at −40 °C was highly selective towards bidesmosidic saponin **17** which was isolated in approx. 83% from batch experiments (Table 2, entries 1, 2), and in 95% from microflow reaction (Table 2, entry 4). At 0 °C moderate amount (18–20%) of allobetulin **21** [30] was also obtained (Table 2, entries 3, 5). Reaction with D-manno derivative **7**