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A practical synthesis of betulinic acid

René Csuk,* Kianga Schmuck and Renate Schäfer

Institut f. Organ. Chemie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Str. 2, D-06120 Halle, Germany

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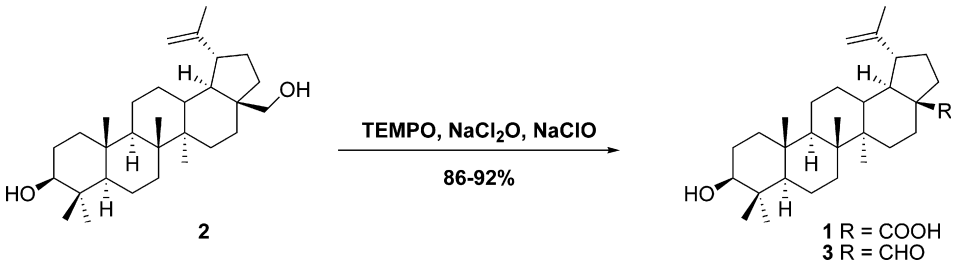
Abstract—A new synthetic route for the synthesis of betulinic acid from betulin has been developed. The main step of this procedure is the selective oxidation of the primary alcohol function of betulin without affecting the secondary hydroxyl group. Applying shorter reaction times and lower temperatures results in the exclusive formation of the corresponding aldehyde, betulinal.

1. Introduction

Betulinic acid (**1**), a pentacyclic triterpene, possesses several biological properties[1–5] such as antiviral, anticancer, anti-inflammatory, antiseptic, antimicrobial, antimalarial, antileishmanial, antihelmintic, antifeedent as well as spermicidal activities. In addition, it was shown that **1** possesses a high toxicity towards cancer cells and a weak toxicity to healthy cells thus allowing a selective destruction of melanoma cells[6] by apoptosis. Betulinic acid has been found in certain plants[7] but only in small amounts; it can be obtained by fractional extraction[8] and subsequent recrystallization at low[8,9] temperatures. In addition, this process requires the use of very large volumes of solvents making it less suitable for large scale industrial applications.

Betulin (**2**), a naturally occurring triterpene seems to be an ideal starting material for the synthesis of **1**. It can be isolated,[10] for example, from the outer layer of the bark of the white birch tree, *Betula alba*, containing **2** up to 25% of its weight. Thus, **2** has been converted into **1** using two different synthetic routes: The first approach utilized an oxidation of **2** to betulonic acid followed by a reduction to afford **1**. Although these two reactions gave good to moderate yields, the reduction step resulted in the formation of a mixture of epimers[11–13] that were difficult to separate. Thus, in a second synthetic route, the use of protecting groups has been suggested; this led to pure material albeit the whole sequence now involving five chemical reactions[14–16] thus lowering the overall yields significantly. Quite recently, a two-step route[17] utilizing solid-supported chromium oxide and potassium permanganate has been suggested and even more recently, a TEMPO-mediated electrochemical approach[18] has been devised. Both of these approaches, however, are small-scale preparations and the obtained yields only moderate. To circumvent all of these problems, we have developed a short one-step route to **1** from easily available, cheap compound **2**.



Scheme 1. The synthesis of betulinic acid and betulinal.

* Corresponding author. Tel.: +49 345 5525660; fax: +49 345 5527030; e-mail: rene.csuk@chemie.uni-halle.de

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Whereas the oxidation of **2** with TEMPO[19] (2,2,6,6-tetramethyl-piperidin-1-oxyl)/$NaClO_2$/NaOCl at 35 °C furnished 92% of the aldehyde betulinal (**3**),[20] the reaction of **2** with 4-acetamido-TEMPO/$NaClO_2$/NaOCl at 50 °C gave betulinic acid (**1**) in an 86% isolated yield.[21]

Preliminary work done in our laboratories indicates that this procedure for the synthesis of **1** can be scaled up to obtain larger amounts of **1** in a very convenient way. The main advantages of this approach include the use of inexpensive starting material and reagents as well as the simplicity of the route (Scheme 1).

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21. Synthesis of betulinal (**3**): To a 35 °C warm stirred mixture of dichloromethane (80 ml) and phosphate buffer (0.67 M, pH 6.8, 43 ml) containing betulin **2** (5.0 g, 11.3 mmol), TEMPO (125 mg, 0.8 mmol) and $Bu_4NBr{\cdot}H_2O$ (180 mg, 0.55 mmol) aq solutions of $NaClO_2$ (25%, 6.8 ml, 22.6 mmol) and NaOCl (12%, 115 µl, 0.25 mmol) were slowly added within 120 min. Additional aq NaOCl (17.8 ml, 34.6 mmol) and $Bu_4NBr{\cdot}H_2O$ (180 mg, 0.55 mmol) was then slowly added. After completion of the reaction (as monitored by tlc) and cooling to room temperature, water (85 ml) was added and the pH value adjusted to 8 by the addition of aq NaOH (2 N, 10.5 ml). The reaction mixture was poured in ice-cold water (60 ml), the aq phase was extracted (methyl-*tert*-butyl-ether, 60 ml) and the combined organic phases were washed (water, brine), dried (Na_2SO_4), and the solvents were evaporated in vacuo to afford the crude aldehyde that was subjected to recrystallization from methanol to afford pure **3** (4.58 g, 92%) as white crystals. Mp 189–191 °C, $[\alpha]_D$ +18.4 (*c*, 0.4, $CHCl_3$)[20] (Lit.: mp 183–187;[22] 192–193;[23] $[\alpha]_D$ +18 (*c*, 0.4, $CHCl_3$), $[\alpha]_D$ +19 ($CHCl_3$)[23]); ^1H and ^{13}C NMR data[24] as reported. Synthesis of betulinic acid (**1**): To a 50 °C warm mixture of butyl acetate (80 ml) and aq phosphate buffer (0.67 M, pH 7.6, 43 ml) containing **2** (5.0 g, 11.3 mmol), 4-acetamido-TEMPO[25] (171 mg, 0.8 mmol), $Bu_4NBr{\cdot}H_2O$ (180 mg, 0.55 mmol) aq solutions of $NaClO_2$ (25%, 6.76 ml, 22.6 mmol) and NaOCl (12%, 115 µl, 0.25 mmol) were slowly added within 120 min. Stirring at this temperature was continued and some additional NaOCl (12%, 10 ml, 19.44 mmol) was slowly added until tlc showed the reaction to be complete. After cooling to room temperature, water (85 ml) was added and the pH adjusted to 8 by the addition of aq NaOH (2 N, 0.5 ml). After extraction with butylacetate (300 ml), the phases were separated, the organic phase was washed (water, brine) and dried (Na_2SO_4). After evaporation of the solvents, crude 1 was recrystallized from methanol to afford pure **1** (4.43 g, 86%, >98% by HPLC). Mp 310–313 °C, $[\alpha]_D$ +9 (*c*, 0.36 $CHCl_3$ (Lit.: mp 316–318[26] $[\alpha]_D$ +5 ($CHCl_3$)[27]); ESI-MS: $m/z = 456$ $[M-H]^-$.
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