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Simple structural modifications confer cytotoxicity to allobetulin

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ABSTRACT

A variety of allobetulin derivatives was synthesized from allobetulin or allobetulone. These compounds were screened for their cytotoxic activity using a photometric SRB assay employing six different human tumor cell lines. In summary, opening of ring A of allobetulin in general lowers the cytotoxicity, but the 2,3-*seco* diethyl ester was highly cytotoxic and remarkable selective for A549 lung carcinoma cells while being significantly less cytotoxic for non-malignant mouse fibroblasts. The introduction of an amino group at position C-3 in the allobetulin skeleton enhances cytotoxicity and furnishes highly cytotoxic compounds. Their selectivity to distinguish between cancer cell and non-malignant cell depends on the configuration at position C-3.

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1. Introduction

Plant derived secondary metabolites have been exploited by humankind for thousands of years to combat diseases. Over the last decade, these natural products were subject to many biological studies, and—in order to improve their biological activities—miscellaneous chemical transformations have been performed, and numerous new derivatives were obtained and screened for their activity.[1]

Natural triterpenoids[2] have been used in traditional medicine for their anticancer, antiviral/virostatic, anti-inflammatory and hepatoprotective activity.[3–11] These triterpenes are important for the survival of the plant, and they form a wide family of compounds. They are biosynthesized by numerous higher plants and some higher fungi from 2,3-epoxy-squalene by a cyclization reaction; by this way, most abundant betulin (Fig. 1) is formed. A re-arrangement reaction, however, transforms betulin to allobetulin (**1**).

While betulin was first accessed as early as 1788[12] from the sublimation of birch bark, and its oxidized product betulinic acid (Fig. 1) was first described[13] in 1902—albeit of uncertain structure—the structure of a 're-arranged' betulin remained unclear until 1922 when Schulze and Pieroh[14] treated betulin with formic acid, and allobetulin (**1**), a (3β,18α,19β) 19,28-epoxy-18-olean-3-ol was formed. The correct molecular formula was determined by Dischendorfer,[15] but it took almost another century to obtain a single crystal X-ray structure.[16]

The cytotoxic activity of betulin and betulinic acid has been investigated,[17] and numerous derivatives have been prepared and screened. Interestingly enough, only a few reports have been published concerning the biological activity of **1** and derivatives thereof.[18] Thus, allobetulin as well as some acetylated and phosphorylated analogs and some oxime-derived compounds have been shown to exhibit moderate antiviral activity.[18–20] In addition, for several derivatives a moderate antiulcer activity[21,22] was determined, and the cytotoxicity of some quinoxaline, pyrazine, azoles or 2-hydroxymethylene derivatives of **1** was significantly lower than those of the corresponding betulin derived analogs.[23–25] Quite recently, a moderate activity was reported for an allobetulin derived ozonide.[26]

The diminished cytotoxicity of allobetulin derivatives as compared to their parent betulin analog is not unexpected at all. The presence of a carbonyl or carboxyl group at C-28 of the betulin skeleton seems mandatory for obtaining good cytotoxicity, although there some exceptions to this rule of thumb.[27] As previously shown for several pentacyclic triterpenoids, the presence of an amino group at position C-3 seems favorable and enhances cytotoxicity.[28–30] Hence, we decided to investigate allobetulin and derivatives thereof in more detail.

2. Results and discussion

2.1. Chemistry

Allobetulin (**1**) can be obtained (Scheme 1) from betulin by a Wagner–Meerwein re-arrangement, and many different conditions have been applied including formic acid, sulfuric acid, hydrochloric acid, or solid supported reagents as well as ferric chloride hydrate, trifluoroacetic acid, orthophosphoric acid, bismuth triflate or *p*-toluenesulfonic acid.[18] In our hands, the reaction of betulin with

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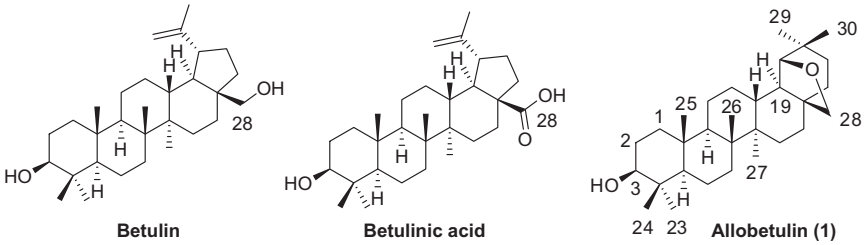
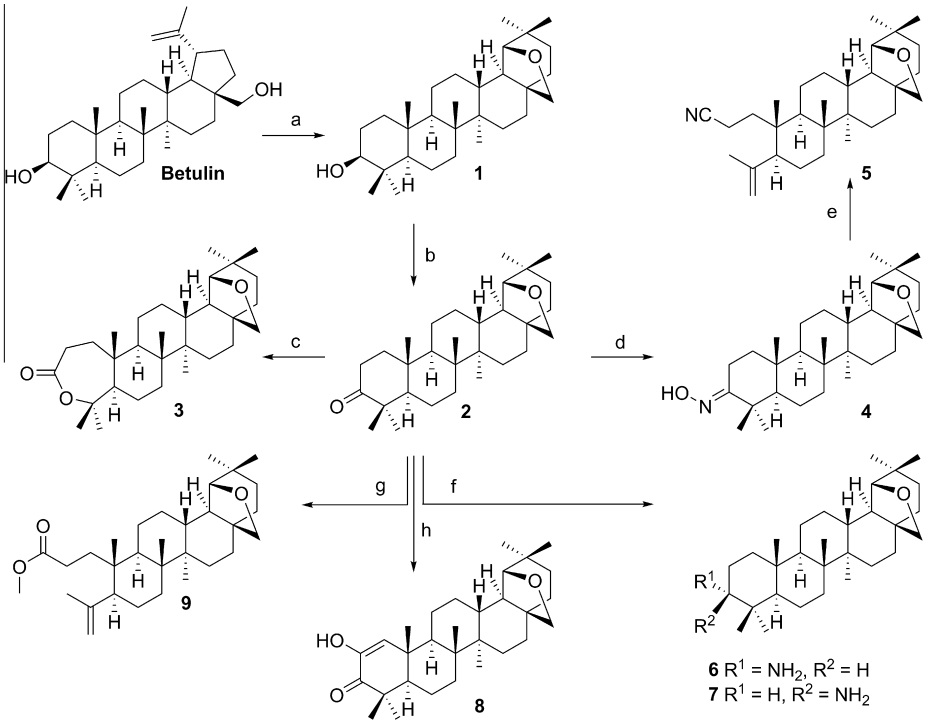


Figure 1. Structure of betulin, betulinic acid and allobetulin (**1**).

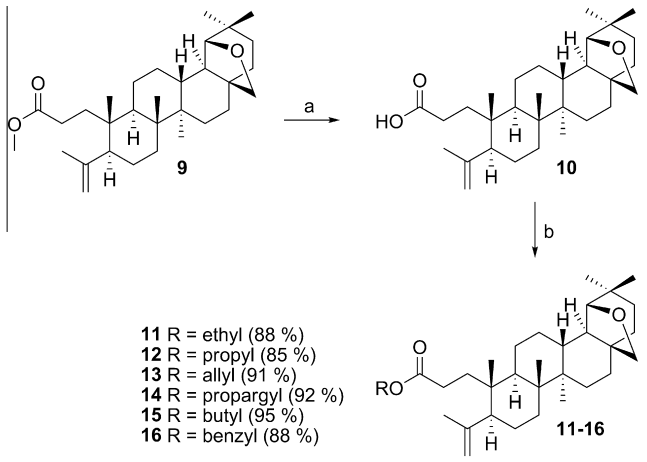


Scheme 1. Synthesis of allobetulin (**1**) and allobetulone (**2**) derived compounds **3**–**8**: (a) Montmorillonit K10, DCM, 3 h reflux, 5 days 25 °C, 79%; (b) CrO_3, H_2SO_4, acetone, 81%; (c) *m*-CPBA, $NaHCO_3$, DCM, 25 °C, 3 h, 85%; (d) $HONH_2{\cdot}HCl$, pyridine, 60 °C, 3 h, 91.5%; (e) $POCl_3$, pyridine, 25 °C, overnight, 46%; (f) $NH_4^+CH_3CO_2^-$, MeOH, $NaBH_3CN$, 25 °C, 24 h, 16% (of **6**) and 46% (of **7**); (g) Oxone®, MeOH, H_2SO_4, 25 °C, 7 days, 65%; (h) KO^{t}Bu, ^{t}BuOH, air, 40 °C, 1 h, 80%.

Montmorillonit K[31] worked quite nicely, and **1** was obtained in 79% yield. Jones oxidation of **1** gave 81% of allobetulone (**2**).[32] This compound is characterized in its IR spectrum by the presence of a signal at $\nu = 1702\ cm^{-1}$ being assigned to the C=O moiety. For this carbonyl group in the ^{13}C NMR spectrum a signal at $\delta = 218.2$ ppm was detected. Reaction of **2** with *m*-CPBA[33] in DCM in the presence of $NaHCO_3$ resulted in a Bayer–Villiger reaction, and lactone **3**[34–37] was obtained in 85% isolated yield.

From the reaction of **2** with hydroxylammonium chloride[38] in pyridine for 3 h at 60 °C oxime **4**[37,39,40] was obtained, whose treatment with $POCl_3$ gave *seco*-**5**. Reductive amination of **2** with ammonium acetate and sodium cyanoborohydride[41] gave a mixture of amines (3α)-**6** and (3β)-**7** that were easily separated by chromatography and their absolute configuration with respect to C-3 was established from their ^1H NMR spectra. From the reaction of **2** with potassium *tert*-butanolate in the presence of air compound **8** was obtained by the process of an abnormal Beckmann rearrangement.[42] A ring opening formation of an alkene occurred (as a consequence of a Bayer–Villiger rearrangement followed by an elimination reaction of the transient tertiary alcohol) also upon treatment of **2** with oxone®, and a yield of 65% of *seco*-**9** was obtained.

Treatment of **9** with potassium hydroxide in methanol (Scheme 2) furnished acid **10**. Esterification of **10** in DMF with



Scheme 2. Synthesis of *seco*-**10** and esters **9**, **11**–**16**: (a) MeOH, KOH, 25 °C, 7 d, 87%; (b) K_2CO_3, DMF, RX, 25 °C, 12 h.

different alkyl halides in the presence of potassium carbonate yielded esters **11**–**16**. Reaction of **1** with acetic acid and nitric acid (Scheme 3) as previously reported by Tolstikov et al.[43] gave 70% of

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