Synthesis of Antitumor Triterpenoid Derivatives Modified in Positions 2 and 3.

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Introduction.

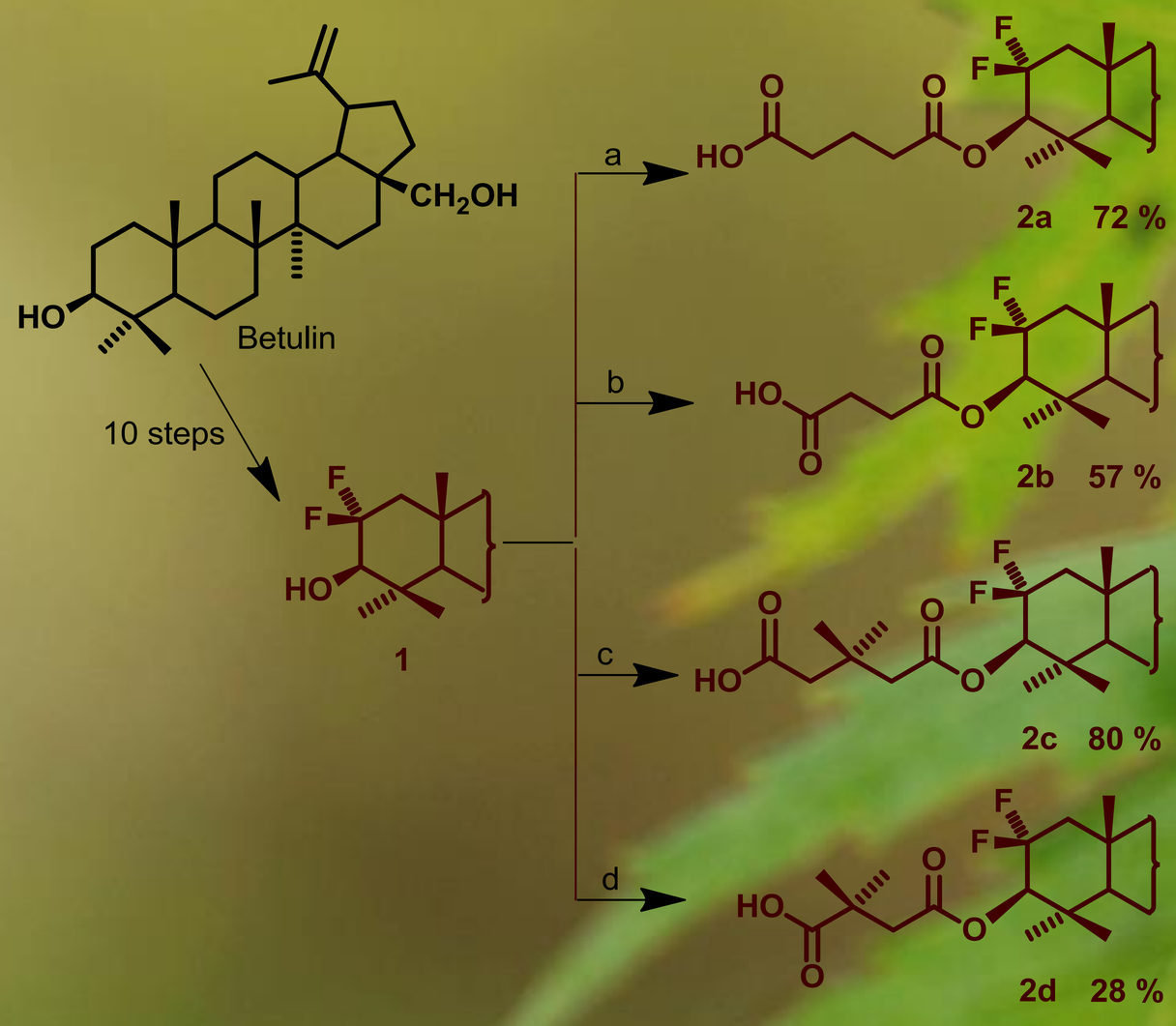
Triterpenes are natural compounds that often show a variety of biological activities (e.g. anti-inflammatory and anti-HIV). Therefore they became promising candidates for new drug development.[1,2,3] The main interest is currently oriented towards screening of the activities of lupane and oleanane derivatives.[2,3] In our group, we study the influence of modifications of lupane triterpenes on their cytotoxicity and recently we found significant anti-cancer effects in many of them.[4]

Triterpenoids with substituents on C-2.

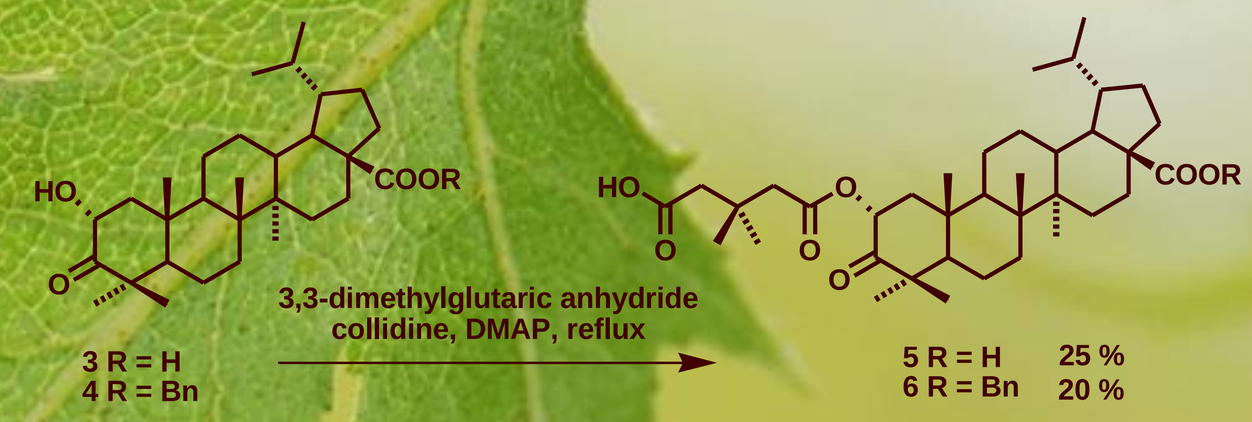
The main aim of this work was to synthesize a set of derivatives with various functional groups on C-2 because our previous research with 2-bromoderivatives (similar to **8**) indicated that the cytotoxicity of such compounds is higher than of those with unsubstituted C-2. First we synthesized 2,2-difluoroderivative **1** from betulin. Despite it's high *in vitro* cytotoxic activity we found that the solubility in water based media is rather limited. Then we synthesized 2-cyano, 2-azido, 2-hydroxy, and 2-amino derivatives and found the same solubility problems. Therefore we decided to prepare hemiesters that are known to improve the solubility and other pharmacological properties. A variety of hemiesters was investigated to find the optimum prodrug.

Synthesis of hemiesters.

The first serie of hemiesters was prepared from 2,2-difluorodihydrobetulinic acid (**1**) via acylation using the appropriate anhydride. 3,3-dimethylglutaric anhydride was found to be the best, however, interesting cytotoxic activity of IC_{50} between 4.2 and 8.3 μmol/L was observed among all of the prepared hemiesters **2a - 2d**, **5** and **6**.

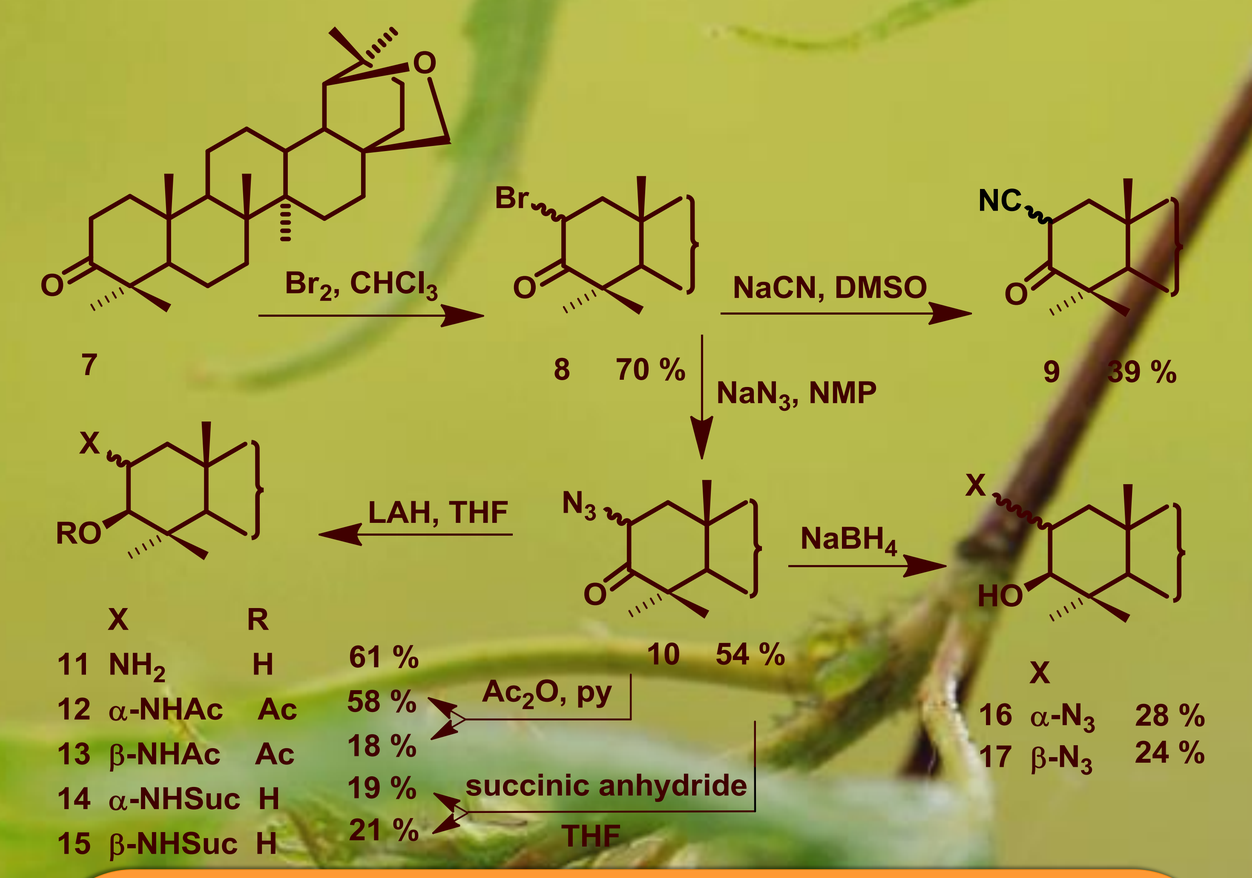


Reagents and conditions: a) glutaric anhydride; b) succinic anhydride; c) 3,3-dimethylglutaric anhydride; d) 2,2-dimethylsuccinic anhydride; all in collidine, DMAP, reflux.



Nucleophilic substitution.

2-Bromo-3-ketone **8** underwent nucleophilic substitution with sodium cyanide and sodium azide, which yielded cyano derivative **9** and azido derivative **10** respectively. 2-Amino-3-hydroxycompound **11**, it's derivatives **12 - 15**, and hydroxy azides **16** and **17** were obtained *via* reduction of azido ketones in presence of various reduction agents. Hemisuccinates were obtained by their reaction with succinic anhydride.



Conclusion.

Sixteen compounds were prepared and their structure was confirmed by spectral data: hemiesters **2a - 2d**, **5** and **6** and allobetulone derivatives **8 - 17**. Cyano derivative **9** is currently being tested for it's *in vitro* cytotoxic activity on T-lymphoblastic leukemia CEM cell line. In the area of nucleophilic substitution we are currently developing a method to prepare nitro compounds, sulfonic acids, sulfonamides and other oleanane and lupane derivatives.

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