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Short communication

Synthesis and biological evaluation of dehydroabietic acid derivatives

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ABSTRACT

A series of C18-oxygenated derivatives of dehydroabietic acid were synthesized from commercial abietic acid and evaluated for their cytotoxic, antimycotic, and antiviral activities.

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1. Introduction

Diterpene resin acids are important defense compounds of conifers against potential herbivores and pathogens [1]. The biological activity of natural abietane acids has been reviewed [2]. Antimicrobial, antiulcer and cardiovascular activities are the most representative for this class of diterpenoids. Dehydroabietic acid (DHA)(Fig. 1, R=COOH), a natural occurring diterpene resin acid, and its derivatives exhibit a broad spectrum of biological action. For example, they have shown antiulcer [3], antimicrobial [4], anxiolytic [5], antiviral [6], antitumor [7], and cytotoxic activities [8]. Recent studies have demonstrated that DHA and some derivatives are chemical modulators, particularly openers, of large-conductance calcium-activated K^+ channels (BK channels) [9]. This feature makes DHA a new scaffold in the treatment of acute stroke, epilepsy, asthma, hypertension, gastric hypermotility and psychoses. Also, DHA was reported to have properties of enhancing the inhibitory activity of anticancer drugs in cervical carcinoma cells, hepatocellular carcinoma cells, or breast cancer cells [10]. However, the cytotoxic activity of easily available derivatives of DHA have not yet been reported so far.

Continuing our research program on the synthesis of bioactive terpenoids, we were interested in confirming the results reported in a recent patent on the use of abietic acid **1** and derivatives as antitumor agents [11] (Scheme 1). As a result, we studied a series of abietic acid derivatives and found that methyl abietate **2** displayed the highest cytotoxicity against HeLa cancer cells (CC_{50} 11 μM), and showed good selectivity towards non-cancerous cells (selectivity index 13.7) [12]. Encouraged by these research results, DHA was chosen as the starting material in screening a series of derivatives for new potential bioactive compounds.

In this communication, we describe the syntheses of a number of derivatives of DHA from commercially available (−)-abietic acid (**1**) (Scheme 1) [13], and the results of preliminary evaluation of their cytotoxic, antimycotic and antiviral activities. In this study, an oxygenated moiety (such as methyl ester, alcohol, or aldehyde) was introduced into the lipophilic dehydroabietane skeleton. In this context, simple and sequential modifications were performed in the molecule of DHA (**4**). Compound **4** and nine derivatives with different functional groups at C7 and C18 were tested. All the compounds were easily obtained in good yield, by standard or reported chemical procedures. Some of the synthesized compounds have been isolated as natural products, in particular, dehydroabietinol (pomiferin A) (**5**) [14], dehydroabietinol acetate (**6**) [15], 7α-hydroxydehydroabietinol (**11**) [16] and 7-oxodehydroabietinol (**12**) [17], however, few reports have appeared on their biological activities.

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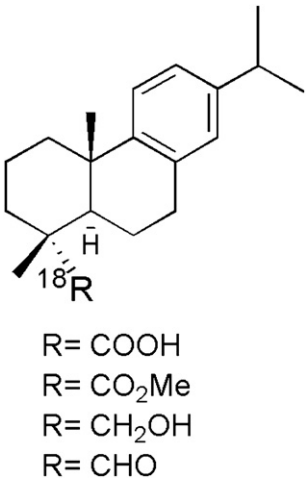


Fig. 1. Chemical structure of some tested dehydroabietanes.

2. Results and discussion

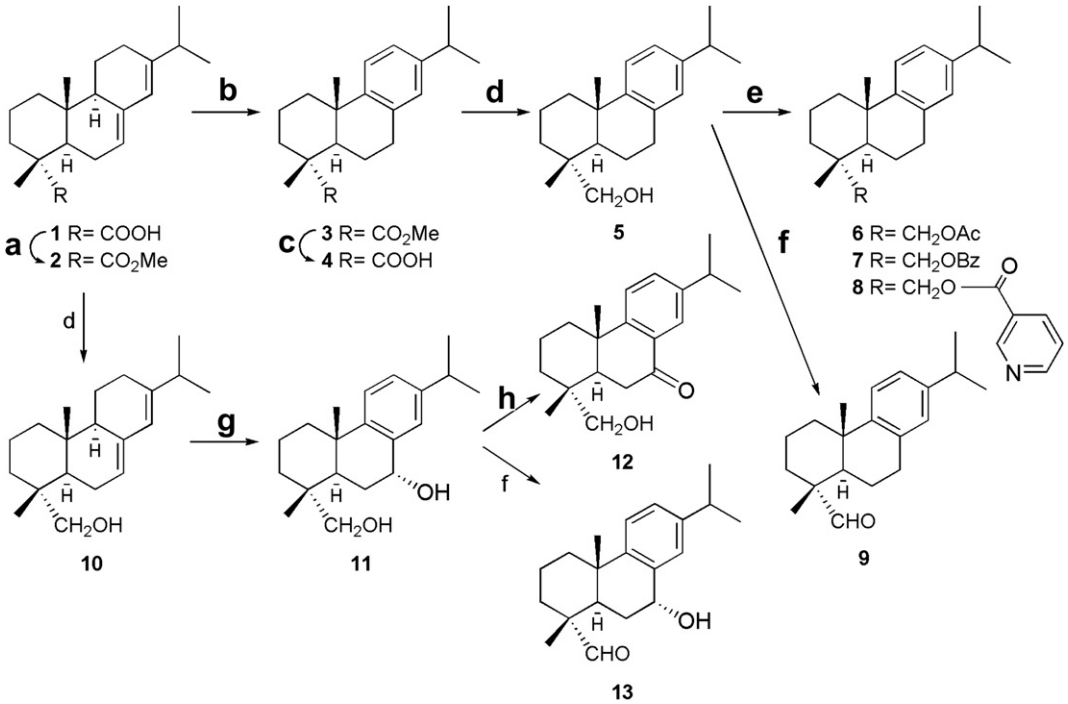
2.1. Chemistry

The synthesis of the C18-functionalized dehydroabietanes used in this work begins with the preparation of the required methyl ester **2** (methyl abietate) from commercial (−)-abietic acid, following a reported procedure (Scheme 1) [12]. Thus, abietic acid **1** was esterified by treatment with lithium hydroxide and methyl sulphate to give ester **2** in quantitative yield. With the ester **2** in hand, we carried out the reaction of aromatization to obtain the dehydroabietane skeleton (Scheme 1). The ester **2** was treated in a similar manner as pine rosin is treated to obtain disproportionated rosin [18]. Thus, neat ester **2** was heated at 250 °C in the presence of 5% Pd/C to give methyl dehydroabietate **3** in 85% yield. Then, we carried out the funtional group interconversions necessary to obtain six more derivatives. Thus, ester **3** was saponified with KOH in aqueous methanol to give dehydroabietic acid (**4**). Reduction of **3** with $LiAlH_4$ in dry tetrahydrofuran at reflux gave dehydroabietinol **5** in 90% yield. Esterification of **5** with acetyl chloride, benzoyl chloride and nicotinic chloride gave the corresponding esters **6**, **7**, and **8**, respectively. Finally, oxidation with Dess–Martin periodinane [19] of **5** afforded aldehyde **9** in 95% yield.

On the other hand, reduction of ester **2** with $LiAlH_4$ in dry tetrahydrofuran at reflux gave alcohol (abietinol) **10** in quantitative yield. Then, we reacted alcohol **10** with SeO_2 to produce the aromatization and simultaneous functionalization at C7 (Compound **11**) [20]. Finally, alcohol **11** was oxidized with MnO_2 and Dess–Martin periodinane to give the keto–alcohol **12** and the aldehyde **13**, respectively.

2.2. Biological evaluation

All compounds **1**–**13** (Scheme 1) were tested for antimycotic, cytotoxic and antiviral activity with the exception of compound **8** which was not soluble under the experimental conditions. Firstly, the compounds did not show antimycotic activity against *Candida parapsilosis, Candida krusei*, *Candida tropicalis and Candida albicans* in concentrations below 100 μg/mL (data not shown). MIC values for the two reference antifungal drugs, amphotericine B and itraconazole (Sigma, New Jersey, USA), used as positive controls, were within the established values for the AFST-EUCAST protocol. The reaction of aromatization of abietanes did not improve anti-*Candida* activity when we compare with the results of our previous report [12]. In contrast, the dehydroabietanes **4** and **11** showed anti-Aspergillus activity. The dehydroabietane **4** showed activity against *Aspergillus terreus* with MIC value of 39.7 μg/mL whereas compound **11** showed activity against *Aspergillus fumigates* and *Aspergillus niger* with MIC values of 50 and 63 μg/mL, respectively. Thus, the reaction of aromatization of abietanes improves anti-Aspergillus activity when we compare with the results of our previous report in which abietic acid **1** was not active.



Scheme 1. Reagents and conditions: a) LiOH, Me_2SO_4,DMF, 100%; b) 5% Pd/C, 250 °C, 85%; c) KOH, MeOH, H_2O, 75%; d) $LiAlH_4$, THF, 90%; e) AcCl, BzCl, nicotinic chloride, Et_3N, DCM, 75%, 70%, 80%, respectively; f) Dess–Martin periodinance, 90% for **9**,85% for **13**;g) SeO_2, TBHP, DCM, 65%; h) MnO_2, DCM, 60%.

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