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First synthesis of picealactone C. A new route toward taxodione-related terpenoids from abietic acid

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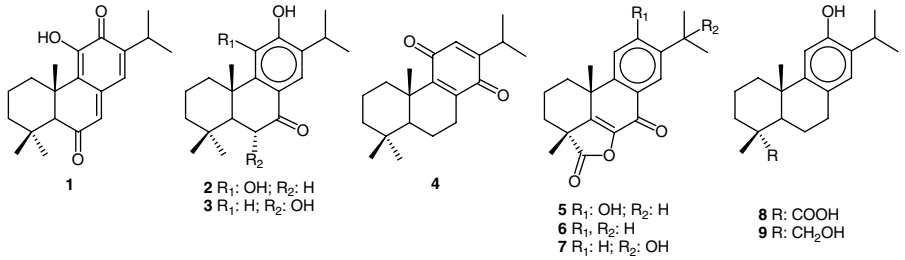
Abstract—A new route to 12-hydroxyabietic acid (**10**) and related compounds from abietic acid (**12**), via acetoxyalcohol **15**, is reported. Utilizing this, the first synthesis of picealactone C (**5**) was achieved. The synthesis of natural 12-hydroxydehydroabietic acid (**8**), 18-hydroxyferruginol (**9**) and methyl 12α-hydroxyabietate (**11**) is also reported.

Abietane diterpenes constitute an important group of secondary metabolites that are widely found in nature. Continuing research into the isolation of such compounds reveals their considerable structural diversity; moreover, many of them present interesting biological activities. Among these a number of variously oxidized compounds bearing oxygenated functions on the C ring should be emphasized. Representative examples of the latter are taxodione (**1**)[1] and salvinolone (**2**),[2] which are active against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), two bacteria that are increasingly found in hospitals worldwide. Other significant oxidized abietane diterpenes are 6α-hydroxysugiol (**3**), which strongly inhibits various human tumors and oncogen transformed cells,[3] and the antileishmanial 12-deoxyroyleanone (**4**).[4]

In previous papers, we reported new procedures to introduce the oxygenated function on the abietane skeleton C-14, which we utilized to prepare **4** from abietic acid (**12**)[5] and on C-15, which allowed us to synthesize some bioactive terpenoids and lactones **6**–**7**.[6]

Continuing our studies on the abietane C ring functionalization, we are now interested in investigating new methods to place the oxygenated function on C-12,



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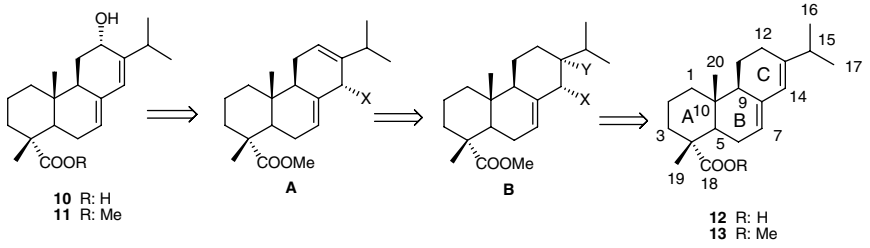
which will enable the synthesis of bioactive compounds such as **1**–**3** and related abietic acid derivatives, including picealactone C (**5**)[7] and 12-hydroxydehydroabietic acid (**8**), recently described as a new natural product.[8] Only two procedures to synthesize 12-hydroxyabietic acid derivatives from abietic acid (**12**), based on the preparation of an iron complex[9] and on the electrochemical oxidation of the corresponding methyl ester,[10] have been reported. Other process, based on the solvolysis of the products resulting from the treatment of methyl abietate with *N*-bromosuccinimide, affords the target compound in a very low yield.[11] 12-Hydroxydehydroabietic acid (**8**) derivatives have been synthesized by electrophilic substitution via the Baeyer–Villiger oxidation of the corresponding 12-acetylderivative obtained after Friedel–Crafts acylation, which takes place in a moderate yield.[12,13]

We planned a strategy to prepare methyl 12α-hydroxyabietate (**11**) based on the allylic displacement of a suitable X leaving group in an intermediate **A**, which results from the regioselective HY elimination of 13,14-adduct **B** (Scheme 1).

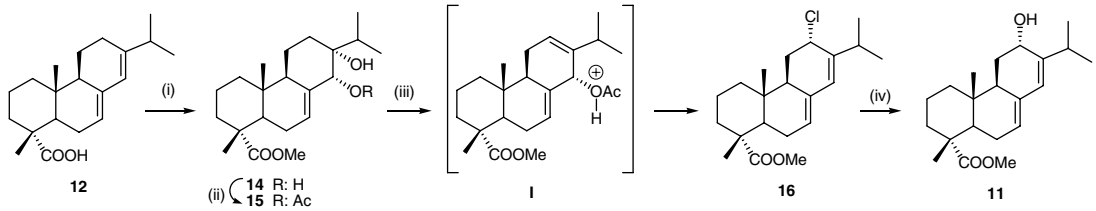
When monoacetate **15** was treated with thionyl chloride and triethylamine in dichloromethane at −78 °C, and the reaction was quenched by adding aqueous sodium bicarbonate, methyl 12α-chloroabietate (**16**) was obtained in a high yield. This compound could be formed via intermediate **I** through an S_N2' process. The chloride **16** was transformed into alcohol **11**, a natural diterpene found in some *Abies* and *Pine* species,[15] in a high yield by treating with sodium bicarbonate in water–dimethylsulfoxide. The C-12 configuration of compounds **16** and **11** was unequivocally established on the basis of the H-12 pattern in the ^{1}H NMR spectrum of these compounds; this proton appears as a triplet ($J = 2.9$ Hz) at 4.75 for chloride **16** and at 4.20 ppm for alcohol **11**. It should be noted that the ^{1}H NMR spectrum of the C12β-OH epimer of **11** showed a double doublet ($J = 10.0$, 4.7 Hz) at 4.41 ppm for H-12.[15] The transformation of **16** into **11** should take place through a S_N1 process; the retention of the configuration on C-12 can be attributed to the most favorable α-attack of nucleophile on the intermediate allyl cation, due to the presence of the β-axial methyl group on C-10 (Scheme 2).

The 12-hydroxydehydroabietic acid derivatives were then obtained via dienone **17**.[16] The oxidation of alcohol **11** to ketone **17** was not a trivial task; usual oxidizing reagents, such as pyridinium chlorochromate or benzeneseleninic anhydride, which have been successfully utilized with similar structures,[9] mainly gave the dehydration product. However, the treatment of alcohol **11** with pyridinium dichromate gave the desired compound **17** in an acceptable yield. Alternatively, dienone **17** was obtained in a high yield from chloride **16**, after reaction with sodium bicarbonate in freshly distilled dimethyl sulfoxide (Scheme 3). The isomerization of dienone **17** to phenol **18** was achieved by refluxing an acetic acid solution in the presence of sulfuric acid.[17] 12-Hydroxy-dehydroabietic acid (**8**), recently isolated from the stem bark of *Picea glehni*,[8] was obtained after saponification of ester **18**, which by reduction with lithium aluminum hydride gave the also natural 18-hydroxyferruginol (**9**), first isolated from *Torreya nucifera*.[18]

Next, the preparation of picealactone C (**5**), a new diterpene recently isolated from *Picea morrisonicola*,[7] was undertaken. After protecting the phenolic hydroxyl group of ester **18** as acetate, the 7-oxo group of the target molecule was introduced, obtaining ketoester **20**, and then the elaboration of the enol–lactone moiety of compound **5** was tackled. The same methodology previously reported by the present authors for synthesizing lactones **6** and **7** was essayed for this purpose.[6] However, the treatment of a solution of acetate **20** and potassium *tert*-butoxide in *tert*-butanol with oxygen produced



Scheme 1.



Scheme 2. Reagents and conditions: (i) Refs. 6 and 14; (ii) Ac_2O, pyridine, rt, 10 h (95%); (iii) $SOCl_2$, NEt_3, CH_2Cl_2, −78 °C, 20 min; aq $NaHCO_3$ (80%) and (iv) $NaHCO_3$, DMSO, H_2O, rt, 15 h (95%).