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

Enrique Alvarez-Manzaneda,[a,*] Rachid Chahboun,[a] Eduardo Cabrera,[a] Esteban Alvarez,[a] Ramón Alvarez-Manzaneda,[b] Mohammed Lachkar[c] and Ibtissam Messouri[c]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Instituto de Biotecnología, Universidad de Granada, 18071 Granada, Spain*
[b]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Almería, 04120 Almería, Spain*
[c]*Laboratoire d'Ingenierie des Materiaux Organometalliques et Moleculaires, Faculté des Sciences, Université Sidi Mohammed Ben Abdellah, BP 1786 (Atlas), 30000 Fès, Morocco*

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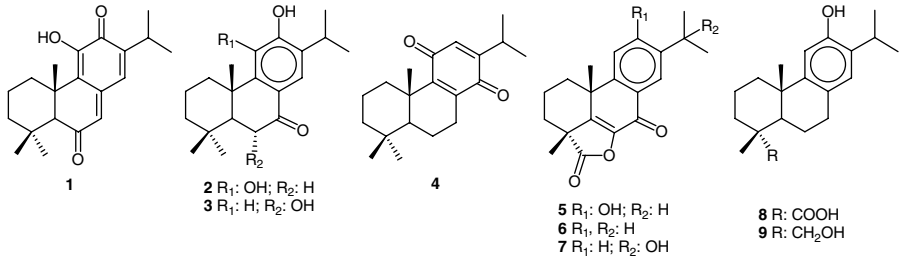
**Abstract**—A new route to 12-hydroxyabietic acid (**10**) and related compounds from abietic acid (**12**), via acetoxyalcohol **15**, is reported. Utilizing this, the first synthesis of picealactone C (**5**) was achieved. The synthesis of natural 12-hydroxydehydroabietic acid (**8**), 18-hydroxyferruginol (**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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* Corresponding author. Tel./fax: +34 958 24 80 89; e-mail: eamr@ugr.es

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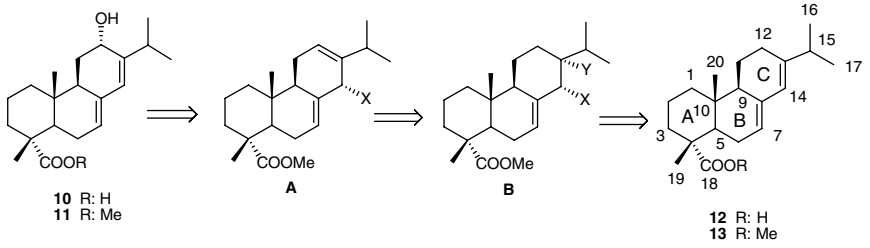
which will enable the synthesis of bioactive compounds such as **1**–**3** and related abietic acid derivatives, including picealactone C (**5**)[7] and 12-hydroxydehydroabietic acid (**8**), recently described as a new natural product.[8] Only two procedures to synthesize 12-hydroxyabietic acid derivatives 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).

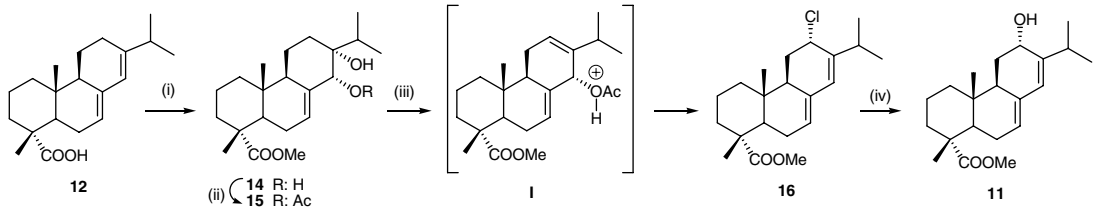
When monoacetate **15** was treated with thionyl chloride and triethylamine in dichloromethane at −78 °C, and the reaction was quenched by adding aqueous sodium bicarbonate, methyl 12α-chloroabietate (**16**) was obtained in a high yield. This compound could be formed via intermediate **I** through an $S_N2'$ 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]

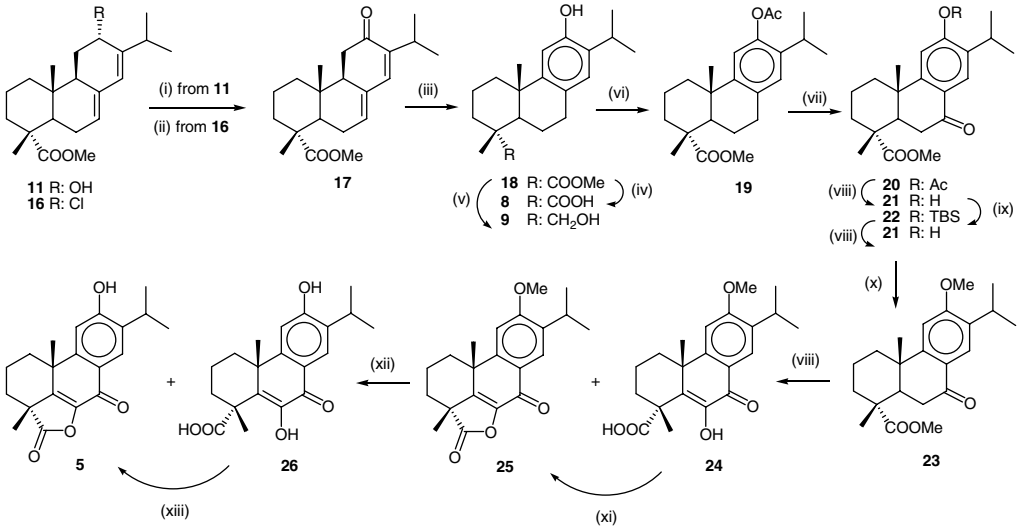
Next, the preparation of picealactone C (**5**), a new diterpene recently isolated from *Picea morrisonicola*,[7] was undertaken. After protecting the phenolic hydroxyl group of ester **18** as acetate, the 7-oxo group of the target molecule was introduced, obtaining ketoester **20**, and then the elaboration 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%).




**Scheme 3.** Reagents and conditions: (i) PDC, $CH_2Cl_2$, rt, 45 min (60%); (ii) $NaHCO_3$, DMSO, rt, 15 h (96%); (iii) $H_2SO_4$, AcOH, reflux, 12 h (85%); (iv) $K_2CO_3$, MeOH, reflux, 12 h (92%); (v) $LiAlH_4$, THF, rt, 12 h (93%); (vi) AcONa, $Ac_2O$, reflux, 2 h (91%); (vii) $Na_2CrO_4$ (2 equiv), AcONa, AcOH, benzene, reflux, 18 h (90%); (viii) $O_2$, *t*-BuOK, *t*-BuOH, rt, 2 h (95%); (ix) TBSCl, imidazole, DMF, rt, 12 h (90%); (x) MeI, $K_2CO_3$, acetone, reflux, 4 h (95%); (xi) DCC, THF, rt, 30 min (75% from **23**); (xii) HBr, AcOH, 40 °C, 1 h and (xiii) DCC, THF, rt, 30 min (71% from **25**).

only deacetylation, affording ketophenol **21**. This product also resulted when silylderivative **22** was subjected to the same reaction conditions. These results could be attributed to the electron attractive effect of the carbonyl group bearing C-7. Our objective was achieved by utilizing the corresponding methyl ether. Thus, the oxidation of compound **23** gave a 1:1 mixture of diosphenol **24** and lactone **25**, which after treatment with dicyclohexylcarbodiimide afforded lactone **25** as the only product. Finally, the treatment of a solution of methoxyderivative **25** in acetic acid with hydrobromic acid gave a 1:2 mixture of diosphenol **26** and picealactone (**5**), which was completely converted into the desired lactone **5**, by treating with DCC. The spectroscopic properties of compound **5**[19] were identical to those reported in the literature.[7]

In summary, a new route to 12-hydroxyabietic acid derivatives from abietic acid (**12**) is reported. The key step involves an $S_N2'$ process on the allylic acetate which results from the dehydration of acetoxyalcohol **15**. Utilizing this methodology, the first synthesis of picealactone C (**5**) has been accomplished.

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19. Spectroscopic properties of natural terpenoids (**5**, **8**, **9** and **11**) were identical to those reported in the literature. All

new compounds were fully characterized spectroscopically and had satisfactory high resolution mass spectroscopy data. Selected data:

Compound **11**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 0.74 (3H, s), 0.99 (3H, d, $J = 6.8$ Hz), 1.03 (3H, d, $J = 6.8$ Hz), 1.18 (3H, s), 2.25 (1H, br d, $J = 12.4$ Hz), 2.38 (1H, h, $J = 6.8$ Hz), 3.56 (3H, s), 4.20 (1H, t, $J = 2.9$ Hz), 5.45 (1H, m), 5.77 (1H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$: 38.1 (C-1), 18.1 (C-2), 37.2 (C-3), 46.6 (C-4), 45.1 (C-5), 25.9 (C-6), 124.3 (C-7), 134.5 (C-8), 43.6 (C-9), 34.1 (C-10), 26.0 (C-11), 66.4 (C-12), 144.1 (C-13), 125.6 (C-14), 32.6 (C-15), 21.7 (C-16), 22.4 (C-17), 178.9 (C-18), 16.9 (C-19), 14.4 (C-20), 51.9 (COO*CH*$_3$).

Compound **16**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 0.83 (3H, s), 1.04 (3H, d, $J = 6.8$ Hz), 1.12 (3H, d, $J = 6.8$ Hz), 1.25 (3H, s), 2.42 (1H, h, $J = 6.8$ Hz), 2.55 (1H, m), 3.66 (3H, s), 4.75 (1H, t, $J = 2.9$ Hz), 5.56 (1H, m), 5.90 (1H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$: 37.6 (C-1), 17.7 (C-2), 36.7 (C-3), 46.1 (C-4), 44.5 (C-5), 25.6 (C-6), 125.1 (C-7), 133.6 (C-8), 43.9 (C-9), 33.6 (C-10), 31.5 (C-11), 58.4 (C-12), 141.9 (C-13), 126.5 (C-14), 31.6 (C-15), 21.1 (C-16), 22.2 (C-17), 178.2 (C-18), 16.7 (C-19), 14.4 (C-20), 51.6 (COO*CH*$_3$).

Compound **18**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 1.19 (6H, d, $J = 5.1$ Hz), 1.22 (3H, s), 1.26 (3H, s), 2.17 (1H, br d, $J = 9.3$ Hz), 2.20 (1H, br d, $J = 8.1$ Hz), 2.80 (2H, m), 3.13 (1H, h, $J = 5.1$ Hz), 3.66 (3H, s), 6.63 (1H, s), 6.81 (1H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$: 36.7 (C-1), 18.6 (C-2), 38.1 (C-3), 47.7 (C-4), 44.9 (C-5), 21.9 (C-6), 29.3 (C-7), 126.8 (C-8), 147.8 (C-9), 37.0 (C-10), 110.8 (C-11), 151.1 (C-12), 132.0 (C-13), 126.7 (C-14), 26.8 (C-15), 22.6 (C-16), 22.8 (C-17), 179.4 (C-18), 25.1 (C-19), 16.5 (C-20), 51.9 (COO*CH*$_3$).

Compound **19**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 1.19 (6H, d, $J = 5.1$ Hz), 1.20 (3H, s), 1.26 (3H, s), 2.19 (1H, br d, $J = 9.3$ Hz), 2.30 (3H, s), 2.87 (2H, m), 2.88 (1H, h, $J = 5.1$ Hz), 3.66 (3H, s), 6.82 (1H, s), 6.93 (1H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$: 36.6 (C-1), 18.5 (C-2), 37.9 (C-3), 47.6 (C-4), 44.5 (C-5), 21.6 (C-6), 29.4 (C-7), 132.9 (C-8), 146.2 (C-9), 37.0 (C-10), 117.8 (C-11), 148.1 (C-12), 137.0 (C-13), 127.0 (C-14), 27.1 (C-15), 22.9 (C-16), 23.1 (C-17), 179.0 (C-18), 25.0 (C-19), 16.4 (C-20), 169.9 (O*CO*CH$_3$), 20.9 (OCO*CH*$_3$), 51.9 (COO*CH*$_3$).

Compound **20**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 1.21 (3H, d, $J = 6.9$ Hz), 1.22 (3H, d, $J = 6.9$ Hz), 1.27 (3H, s), 1.34 (3H, s), 2.26 (1H, br d, $J = 9.1$ Hz), 2.33 (1H, m), 2.34 (3H, s), 2.72 (2H, m), 2.99 (1H, h, $J = 6.9$ Hz), 3.65 (3H, s), 6.99 (1H, s), 7.99 (1H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$: 37.0 (C-1), 18.1 (C-2), 37.7 (C-3), 46.7 (C-4), 43.6 (C-5), 36.4 (C-6), 197.4 (C-7), 138.7 (C-8), 152.7 (C-9), 37.4, (C-10), 117.6 (C-11), 154.3 (C-12), 128.9 (C-13), 126.6 (C-14), 27.3 (C-15), 22.7 (C-16), 22.8 (C-17), 177.7 (C-18), 23.6 (C-19), 16.4 (C-20), 169.1 (O*CO*CH$_3$) 21.0 (OCO*CH*$_3$), 52.2 (COO*CH*$_3$).

Compound **22**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 0.26 (3H, s), 0.28 (3h, 3H), 1.01 (9H, s), 1.19 (3H, d, $J = 6.9$ Hz), 1.20 (3H, d, $J = 6.9$ Hz), 1.24 (3H, s), 1.32 (3H, s), 2.19 (1H, br d, $J = 12.8$ Hz), 2.68 (2H, m), 3.15 (1H, h, $J = 6.9$ Hz), 3.64 (3H, s), 6.69 (1H, s), 7.88 (1H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$: 37.2 (C-1), 18.3 (C-2), 37.7 (C-3), 46.8 (C-4), 44.1 (C-5), 36.6 (C-6), 197.2 (C-7), 137.7 (C-8), 154.9 (C-9), 37.4 (C-10), 112.7 (C-11), 158.5 (C-12), 124.7 (C-13), 126.3 (C-14), 26.6 (C-15), 22.6 (C-16), 22.7 (C-17), 177.9 (C-18), 23.7 (C-19), 16.5 (C-20), −3.8 (3H, Me–Si), −4.0 (3H, Me–Si), 25.8 (Me, *t*-Bu), 29.8 (C, *t*-Bu) 52.2 (COO*CH*$_3$).

Compound **23**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 1.20 (6H, d, $J = 6.9$ Hz), 1.27 (3H, s), 1.34 (3H, s), 1.60–1.90 (5h, m), 2.33 (2H, m), 2.70 (2H, m), 3.25 (1H, h, $J = 6.9$ Hz), 3.64 (3H, s), 3.93 (3H, s), 6.75 (1H, s), 7.89 (1H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$: 37.1 (C-1), 18.3 (C-2), 37.7 (C-3), 46.8 (C-4), 44.1 (C-5), 36.5 (C-6), 197.1 (C-7), 135.6 (C-8), 155.6 (C-9), 37.8 (C-10), 104.3 (C-11), 161.8 (C-12), 124.1 (C-13), 125.8 (C-14), 26.6 (C-15), 22.4 (C-16), 22.6 (C-17), 177.8 (C-18), 23.6 (C-19), 16.5 (C-20), 55.5 (O*CH*$_3$), 52.2 (COO*CH*$_3$).

Compound **5**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 1.31 (6H, d, $J = 6.9$ Hz), 1.59 (3H, s), 1.62 (3H, s), 2.50 (1H, br d, $J = 13.2$ Hz), 3.29 (1H, h, $J = 6.9$ Hz), 3.96 (3H, s), 7.19 (1H, s), 7.98 (1H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$: 42.7 (C-1), 19.6 (C-2), 36.5 (C-3), 47.8 (C-4), 146.9 (C-5), 145.7 (C-6), 173.8 (C-7), 124.9 (C-8), 152.6 (C-9), 40.1 (C-10), 108.2 (C-11), 161.9 (C-12), 137.1 (C-13), 124.7 (C-14), 27.4 (C-15), 22.7 (C-16), 22.7 (C-17), 180.8 (C-18), 21.4 (C-19), 24.7 (C-20), 56.3 (O*CH*$_3$).