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New route to 15-hydroxydehydroabietic acid derivatives: application to the first synthesis of some bioactive abietane and nor-abietane type terpenoids

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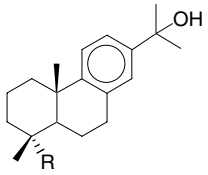
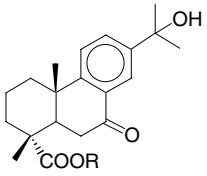
Abstract—A new route to 15-hydroxydehydroabietic acid derivatives from abietic acid (**11**), via abieta-8,13(15)-dien-18-oic acid (**12**), is reported. Utilizing this, the first synthesis of bioactive terpenes **3**, **6**, **9** and **10**, as well as natural diol **4** and lactones **7**–**8** was achieved.

Abietane-type diterpenes constitute a group of secondary metabolites that are widespread in the vegetable kingdom. Recent years have seen growing interest in this class of substances after the isolation of a large variety of compounds, mainly oxidized derivatives that present various biological activities, for example, antitumour,[1] antibiotic,[2] antiviral,[3] anti-inflammatory,[4] immunosuppressive,[5] antioxidant[6] and antiparasitic,[7] among others. Moreover, many abietane terpenoids have long been applied in various fields.[8] Recently, some dehydroabietic acid derivatives have been described as a novel scaffold for large-conductance calcium-activated K^+ channels.[9]

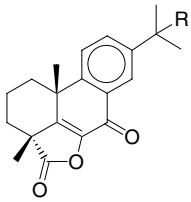
Continuing our research on the synthesis of bioactive terpenoids,[10] we have focused on the preparation of 15-hydroxydehydroabietic acid derivatives. Compounds **3**, **6** and **8** are representative examples, due to their biological activity or structural features. Diol **3**[11] and keto-ester **6**[12] show potent inhibitory effects on Epstein-Barr virus early antigen (EBV-EA) activation induced by the tumour promoter 12-*O*-tetradecanoylphorbol 13-acetate. Picealactone B (**8**), a recently isolated diterpene, contains a rare 5-dehydro-18,6-olide functionality.[13] These 15-hydroxydehydroabietic acid derivatives are also suitable intermediates to synthesize the corresponding



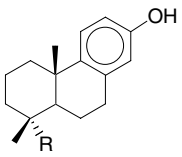
1 R: COOH
2 R: COOMe
3 R: CH_2OH
4 R: OH



5 R: H
6 R: Me



7 R: H
8 R: OH



9 R: COOH
10 R: Me

Keywords: Abietane diterpenes; Enantiospecific synthesis; Bioactive compounds; Oxidation; Selenium dioxide.
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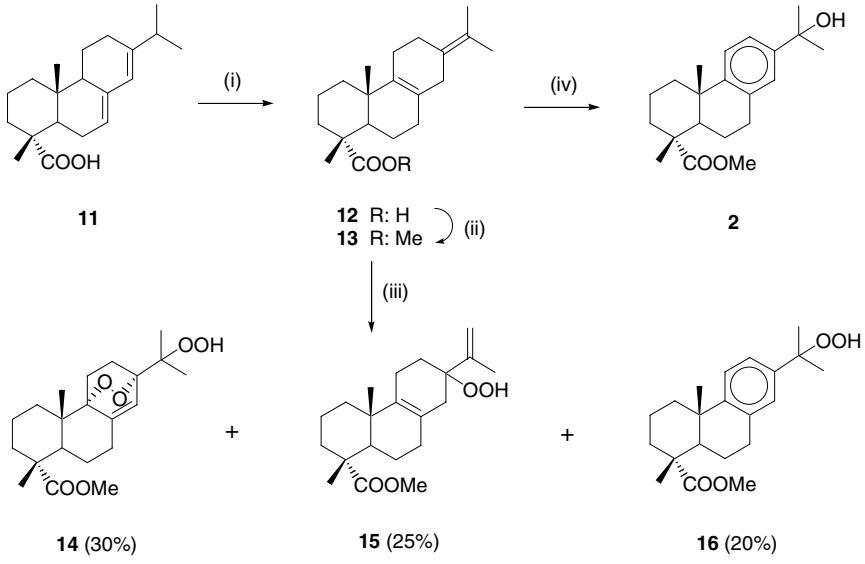
13-hydroxy-8,11,13-podocarpatriene derivatives, such as **9**, a highly fungistatic nor-abietane type terpenoid,[14] and **10**, an antioxidant metabolite isolated from *Taiwania cryptomerioides*.[15]

Some chemical procedures to achieve 15-hydroxydehydroabietic acid derivatives have been reported previously. The direct oxidation of dehydroabietic acid involves the simultaneous reaction on C-7 and C-15, affording the corresponding 15-hydroxy-7-oxodehydroabietic acid (**5**) derivatives.[16] 15-hydroxydehydroabietic acid (**1**) was obtained in only 10% by hydroperoxidation of dehydroabietic acid and further reduction.[17] Methyl 15-hydroxydehydroabietate (**2**) was synthesized from methyl dehydroabietate in a two-step sequence involving the oxymercuration–demercuration of the corresponding dehydroisopropyl derivative; the main drawback of this procedure is the low yield besides the obtention of significative amounts of Δ^6-derivatives, which complicate the purification.[18] Some examples of biotransformations have also been reported for hydroxylation on the C-15 of dehydroabietic acid, even though the yields achieved are always very low.[19]

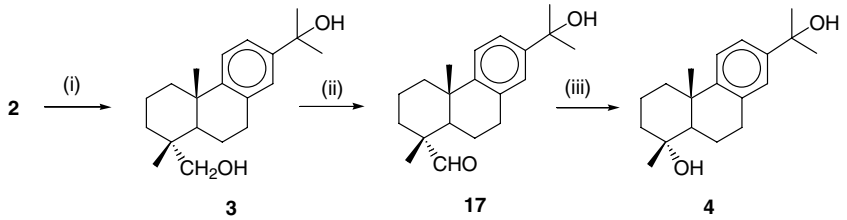
Abieta-8,13(15)-dien-18-oic acid (**12**), which is easily prepared from abietic acid (**11**),[20] could be a suitable intermediate to synthesize 15-hydroxyderivatives of abietane-type diterpenes. That is why we have studied the behaviour of methyl ester **13** under different oxidation conditions. In most cases, the simultaneous oxidation on C-7 and C-15 took place; only two oxidant reagents among those essayed prevented the C-7 oxidation. Photooxidation of **13** led to a complex mixture of hydroperoxides (**14**,[21,24] **15**[24] and **16**). Methyl 15-hydroxydehydroabietate (**2**)[24] was smoothly obtained in quantitative yield when **13** was refluxed with selenium dioxide in dioxane (Scheme 1).

Scheme 2 shows the first synthesis of bioactive diol **3**[11] and abietanediol **4**[22] from the 15-hydroxyderivative **2**. Compound **4** was obtained by saponification of the formate, which results from the Baeyer–Villiger oxidation of aldehyde **17**.[23]

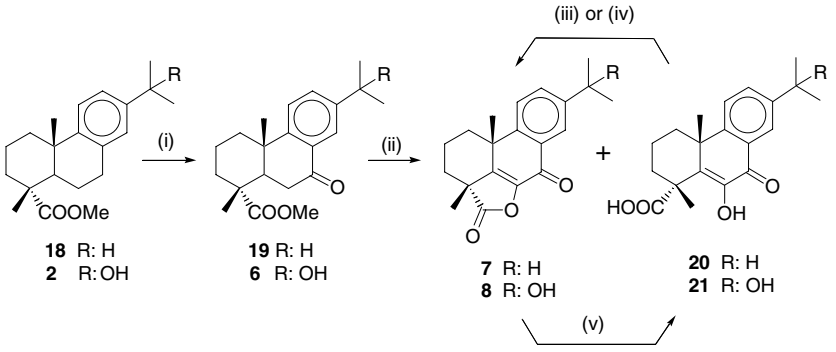
Bioactive ketoester **6** and picealactone B (**8**), an abietane-type diterpene recently isolated from *Picea morrisonicola*,[13] have also been prepared from **2** (Scheme 3). The elaboration of enol-lactone **8** was previously investigated on methyl dehydroabietate (**18**). When an oxygen stream was bubbled through a solution of 7-oxoderivative **19** in *tert*-butanol, in the presence of potassium *tert*-butoxide, a 1:2 mixture of lactone **7** and diosphenol **20**[24] was obtained. Compound **7**, which was easily separated from **20** after column chromatography, has the same spectroscopic properties reported for picealactone A, also isolated from *P. morrisonicola*.[13]



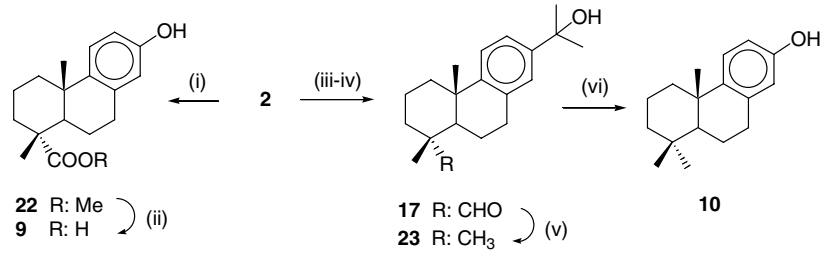
Scheme 1. Reagents and conditions: (i) Ref. 20, four steps, 59%; (ii) MeI, acetone, reflux, 12 h (95%); (iii) O_2, MeOH, *hv* (200 W), 0 °C, 3 h; (iv) SeO_2, dioxane, reflux, 30 min (quant.).



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, THF, rt, 12 h (95%); (ii) PCC, CH_2Cl_2, rt, 45 min (75%); (iii) MCPBA, $NaHCO_3$, CH_2Cl_2, reflux, 3 h; KOH, MeOH, reflux, 1 h (90%).



Scheme 3. Reagents and conditions: (i) PCC, AcONa, CH_2Cl_2, reflux, 4 h (**19**, 73%; **6**, 65%); (ii) O_2, *t*-BuOK, *t*-BuOH, rt, 2 h (**7**, **20**, 96%; **8**, **21**, 98%); (iii) Amberlyst A-15, THF, 40 °C, 4 h (95%); (iv) DCC, THF, rt, 90 min (97%); (v) 2 N KOH–MeOH, rt, 3 h; 2 N HCl, 0 °C (81%).



Scheme 4. Reagents and conditions: (i) H_2O_2, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 45 min (95%); (ii) KOH, MeOH, reflux, 1 h (90%); (iii) $LiAlH_4$, THF, reflux, 12 h (95%); (iv) PCC, CH_2Cl_2, rt, 45 min (75%); (v) $N_2H_4{\cdot}H_2O$, triethylene glycol, reflux, 4 h (75%); (vi) H_2O_2, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 1 h (97%).

Under the same reaction conditions, the 15-hydroxy-derivative **6** afforded an unresolvable 1:1 mixture of lactone **8** and diosphenol **21**[24], which were characterized after chemical interconversion. Treatment of the mixture with amberlite A-15 or DCC in THF gave **8** as the only product; alternatively, the treatment of lactone **8** with KOH in MeOH and further acidification yielded **21**.

Methyl 15-hydroxydehydroabietate (**2**) has also been efficiently converted into the bioactive phenol **9**, by treating with hydrogen peroxide and boron trifluoride etherate in dichloromethane and subsequent saponification. In a similar way, the natural phenol **10** was synthesized from **2**, after reduction of the methoxycarbonyl group (Scheme 4).

In summary, a new route from abietic acid (**11**) to 15-hydroxydehydroabietic acid derivatives is reported. Utilizing this, the first synthesis of natural terpenoids **3**, **4**, **6**, **8**–**10** has been achieved, which allows to confirm the assigned structures for these compounds.[24]

Acknowledgements

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24. Spectroscopic properties of natural terpenoids (**3**, **4**, **6**, **8**–**10**) 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 **2**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20 (s, 3H), 1.27 (s, 3H), 1.54 (s, 6H), 1.96 (br s, 1H), 2.22 (dd, $J = 12.5$, 2.2 Hz, 1H), 2.30 (br d, $J = 11.9$ Hz, 1H), 2.90 (m, 2H), 3.65 (s, 3H), 7.15 (br s, 1H), 7.20 (d, $J = 8.3$ Hz, 1H), 7.23 (d, $J = 8.3$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 179.1 (C-18), 147.9 (C-9), 146.1 (C-13), 134.7 (C-8), 124.9 (C-14), 124.1 (C-11), 122.0 (C-12), 72.2 (C-15), 51.9 ($COOCH_3$), 47.6 (C-4), 44.8 (C-5), 38.0 (C-3), 37.0 (C-10), 36.7 (C-1), 31.6 (C-16 and C-17), 24.8 (C-18), 21.7 (C-2), 18.6 (C-6), 30.1 (C-7), 16.5 (C-20).
Compound **3**: $[\alpha]_D^{25}$ −9.8 (*c* 1.1, $CHCl_3$) [lit.[11] $[\alpha]_D$ −12.0 (*c* 0.82, $CHCl_3$).
Compound **4**: $[\alpha]_D^{25}$ −11.2 (*c* 0.9, $CHCl_3$) [lit.[22] $[\alpha]_D^{26}$ −13.0 (*c* 0.32, $CHCl_3$).
Compound **6**: $[\alpha]_D^{25}$ +7.9 (*c* 1.0, $CHCl_3$) [not reported previously].
Compound **8**: $[\alpha]_D^{25}$ +19.8 (*c* 0.8, $CHCl_3$) [lit.[13] $[\alpha]_D^{19}$ +23.5 (*c* 0.25, $CHCl_3$).
Compound **9**: $[\alpha]_D^{25}$ +12.4 (*c* 0.9, $CHCl_3$) [not reported previously].
Compound **10**: $[\alpha]_D^{25}$ +18.1 (*c* 1.0, $CHCl_3$) [lit.[15] $[\alpha]_D^{21}$ +16.7 (*c* 0.43, $CHCl_3$).
Compound **14**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.07 (s, 3H), 1.16 (s, 3H), 1.26 (s, 6H), 2.09 (d, $J = 8.8$ Hz, 1H), 2.13 (d, $J = 8.8$ Hz, 1H), 2.38 (dd, $J = 12.0$, 7.2 Hz, 1H), 2.48 (m, 1H), 3.68 (s, 3H), 6.28 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.5 (C-18), 144.4 (C-8), 126.2 (C-14), 81.5 (C-13), 81.0 (C-9), 72.4 (C-15), 52.0 ($COOCH_3$), 51.6 (C-5), 46.7 (C-4),39.1 (C-10), 38.2 (C-3), 30.9 (C-1), 25.3 (C-16), 24.8 (C-17), 24.2 (C-7), 24.0 (C-12), 21.8 (C-11), 19.8 (C-6), 19.2 (C-19), 17.8 (C-20), 17.5 (C-2).
Compound **15**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.99 (s, 3H), 1.00 (s, 3H), 1.18 (s, 6H), 1.78 (br s, 3H), 1.79 (br s, 3H), 3.64 (s, 6H), 4.80 (t, $J = 1.6$ Hz, 1H), 4.83 (t, $J = 1.6$ Hz, 1H), 4.85 (br s, 1H), 5.01 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 179.3 (2 × C), 150.8 (C), 148.6 (C), 136.9 (C), 136.8 (C), 124.3 (C), 123.5 (C), 110.5 (CH_2), 109.3 (CH_2), 72.9 (C), 72.3 (C), 51.9 (2 × CH_3), 47.7 (2 × C), 46.3 (CH), 46.1 (CH), 42.9 (CH_2), 42.0 (CH_2), 37.3 (C), 37.2 (C), 36.7 (CH_2), 36.6 (CH_2), 36.0 (CH_2), 35.5 (CH_2), 32.8 (CH_2), 32.4 (CH_2), 31.7 (2 × CH_2), 21.5 (CH_2), 21.4 (CH_2), 21.1 (CH_2), 20.2 (CH_2), 20.1 (CH_3), 19.5 (CH_3), 18.8 (CH_3), 18.4 (CH_3), 18.2 (CH_2), 16.5 (2 × CH_3).
Compound **20**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (d, $J = 6.8$ Hz, 6H), 1.53 (s, 3H), 1.63 (s, 3H), 2.40 (br d, $J = 13.2$ Hz, 1H), 2.94 (h, $J = 6.8$ Hz, 1H), 6.91 (br s, 1H), 7.43 (d, $J = 7.4$ Hz, 1H), 7.45 (d, $J = 7.4$ Hz, 1H), 7.47 (s, 2H), 8.03 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.5 (C-18), 180.2 (C-7), 151.7 (C-9), 143.8 (C-5), 136.3 (C-13), 132.0 (C-12), 127.7 (C-8), 124.9 (C-11), 124.3 (C-14), 45.9 (C-4), 39.3 (C-10), 35.7 (C-20), 33.7 (C-15), 34.8 (C-1), 34.0 (C-3), 23.8 (C-16 and C-17), 22.0 (C-19), 17.6 (C-2).
Compound **21**: ^{1}H NMR (CD_3COCD_3, 400 MHz): δ 1.50–1.60 (m, 3H), 1.54 (m, 9H), 1.59 (s, 3H), 1.95 (m, 2H), 2.55 (m, 1H), 3.90 (br s, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.83 (dd, $J = 84$, 2.2 Hz, 1H), 8.24 (d, $J = 2.2$ Hz, 1H). ^{13}C NMR (CD_3COCD_3, 100 MHz): δ 180.6 (C-18), 177.8 (C-7), 152.7 (C-9), 149.6 (C-13), 145.1 (C-5), 137.6 (C-6), 130.7 (C-12), 128.5 (C-8), 125.6 (C-11), 122.7 (C-14), 71.8 (C-15), 46.3 (C-4), 40.0 (C-10), 36.6 (C-1), 36.0 (C-20), 35.6 (C-3), 32.0 (C-16 and C-17), 21.4 (CH_3), 18.2 (C-2).