Synthesis and structural characterisation of ring B oxidised derivatives of dehydroabietic acid

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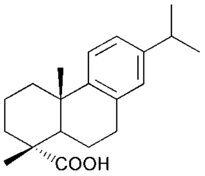
The synthesis and structural characterisation of some new derivatives of dehydroabietic acid, oxidised in the 6 and 7 positions of ring B, are described. Other known derivatives were exhaustively characterised for the first time and the previous NMR assignments for three compounds are corrected.

Dehydroabietic acid (**1a**) can be easily obtained by catalytic dehydrogenation of abietic type resin acids, which are very abundant in pine resin.[1] This acid has been considered as an interesting starting material for the synthesis of new compounds with interesting biological properties.[2] In particular, some oxygenated derivatives of dehydroabietic acid have demonstrated promising antifungal[3] and tumour-inhibitory[4] properties.



1a

Pursuing our studies in the chemical transformation of dehydroabietic acid,[5,6] we have been looking at the possibility of preparing new compounds from **1b** through the cleavage or functionalisation of ring B. Oxidative cleavage of the C_6–C_7 bond of **1** can be a way to prepare the aldehyde or carboxylic acid derivatives (**7** and **8**) that could then be used in the synthesis of other compounds with potential biological interest. During the synthetic studies of oxidative cleavage of the C_6–C_7 bond, several new dehydroabietic acid derivatives (**7**–**10**) were prepared and fully characterised by MS and NMR techniques. Various known compounds were also obtained; in some cases (**11** and **12**) they were fully characterised by MS and NMR for the first time; for others (**2**–**4**) the published ^{1}H NMR assignments were corrected and the ^{13}C NMR data reported for the first time.

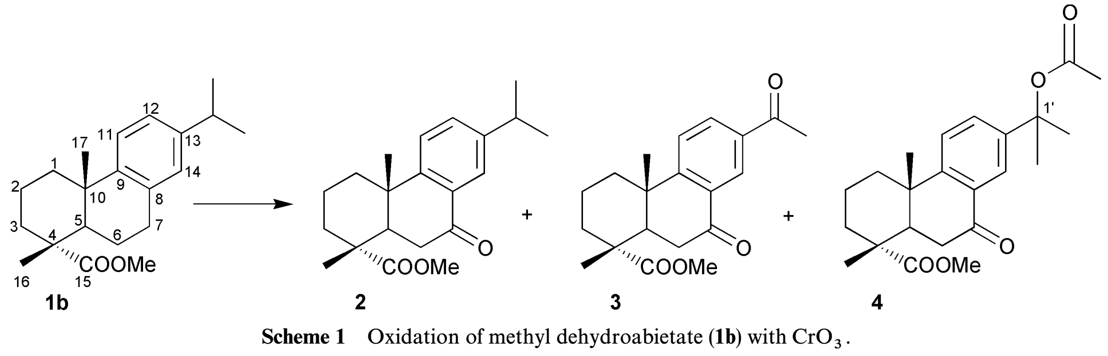
Results and discussion

Synthesis

Methyl dehydroabietate (**1b**) was prepared as described in the literature;[1] it was then treated with chromium trioxide to give compound **2** in 67% yield, as well as minor amounts of methyl 13-acetyl-7-oxopodocarpe-8,11,13-trien-15-oate, **3**, and methyl 13-(1-acetoxy-1-methylethyl)-7-oxopodocarpe-8,11,13-trien-15-oate, **4** (Scheme 1). These three compounds are known from the literature,[7,8] however, they have not been characterised by ^{13}C NMR, and some of their reported ^{1}H NMR assignments were considered to be incorrect. The ^{13}C NMR data, and the new ^{1}H NMR assignments are reported below.

The ketone **2** was then reduced with sodium borohydride in methanol to obtain a diastereomeric mixture of two alcohols **5** (Scheme 2). This mixture could not be separated by preparative TLC; however the NMR analysis allowed us to conclude that it was composed of a 1 : 10 ratio of these two alcohols. The mixture was then treated with mesyl chloride in dry triethylamine[9] to yield **6**, a compound that has already been prepared from **1b** following a different synthetic route.[10]

Our target compound, methyl 2-formyl-3-(2-formyl-4-isopropylphenyl)-1,3-dimethylcyclohexanecarboxylate, **7**, was then prepared by treating compound **6** with sodium periodate in the presence of catalytic amounts of osmium tetroxide.[11] In addition to **7**, other oxidised derivatives **8**–**11**, and the lactone **12**, were also isolated (Scheme 3). Compound **8** is probably the oxidation product of the 2-CHO group of compound **7**, while compounds **9**–**11** represent different degrees of oxidation of compound **6** with an uncleaved C_6–C_7 bond. The forma-



Scheme 1 Oxidation of methyl dehydroabietate (**1b**) with CrO_3.

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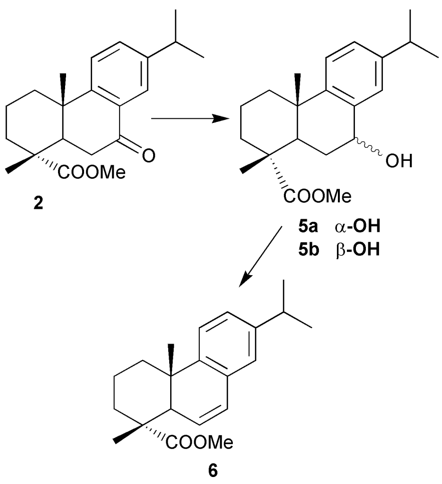


Scheme 2 Synthesis of methyl 13-isopropylpodocarpe-6,8,11,13-tetraen-15-oate, **6**.

tion of the lactone **12** can result from the oxidation of compound **9** to form a 6,7-dione derivative; the enolic form of this dione might lactonise spontaneously to yield **12**. Alternatively, the former enol might also result from the hydroxylation of the β,γ-unsaturated ester **11**, catalysed by osmium tetroxide.[12] Compounds **7–10** are reported for the first time, while compounds **11** and **12** have already been described[13] without considering any spectroscopic characterisation.

Structural characterisation

The general features of the ^{1}H and ^{13}C NMR of methyl dehydroabietate and some derivatives are well described in the literature,[6] allowing us to directly assign several resonances of the synthesised compounds.

Analysis of the NMR spectra (^{1}H, ^{13}C HETCOR, COSY and selective INEPT) of compounds **2–4** allowed us to conclude that the literature assignments[8] of the resonances of H-5 and H-6 were incorrect.

The methinic C-5 and the methylenic C-6 carbons were unambiguously assigned, respectively at δ 43.3–43.6 and 37.7–38.0 using DEPT experiments. The assignments of the H-5 and H-6 resonances were made by an analysis of the HETCOR spectra. The resonances of the two H-6 protons appear at δ 2.28–2.40 (overlapped with the resonance of H-1) and at δ 2.71–2.74 (overlapped with the resonance of H-5), these assignments were confirmed with the COSY spectrum. On the other hand, coupling was also observed between the resonance at δ 2.28–2.40, assigned to one H-1 proton and that at δ 1.61–1.82; this in conjugation with the correlation of these two proton resonances and the carbon resonance at δ 37.0–38.0 confirmed their assignments to H-1 and C-1.

The assignment of the quaternary carbons C-8, C-9 and C-13 was performed using a one-dimensional selective INEPT experiment carried out with compound **2**. Table 1 shows the connectivities found and the corresponding ^{13}C resonance assignments upon irradiation of H-11 (δ 7.30) and 13-C*H*(CH$_3$)$_2$ (δ 2.90). No signal enhancement was observed for the resonance at δ 152.9, which was then assigned to C-9. The resonances of such quaternary carbons in compounds **3** and **4** were assigned by comparison with data obtained for compound **2**.

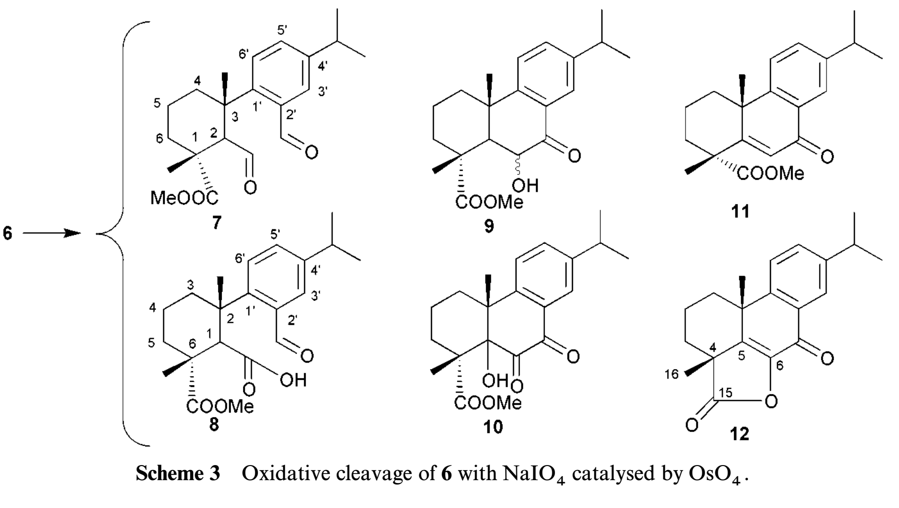
In the ^{1}H NMR spectrum of compound **5** two signals in a 1 : 10 ratio, at δ 4.72 and 4.85, can be detected; these chemical shifts are characteristic of benzilic protons with a geminal hydroxyl group, and were therefore attributed to H-7. The major signal appears as a doublet of doublets and has been assigned to the H-7α proton, while the minor signal appears as a triplet and was assigned as H-7β; these data indicate that alcohol **5b** was formed predominantly rather than its stereoisomer **5a**.

Compound **6** was characterised by NMR and MS, and the obtained spectroscopic results are in agreement with the literature data.[10]

Formation of compounds **7** and **8** resulted from the oxidative cleavage of the ring B of **6**, so they are structurally different from the other derivatives characterised so far in this paper, therefore some differences in the NMR profiles were observed. For compound **7**, the 1-CO$_2$CH$_3$ proton resonance appears at δ 3.00; this shift to lower δ values, as well as the shift to higher δ values of H-2 (δ 3.90), when compared to those of the preceding compounds, is probably due to the anisotropic shielding effect of the carbonylic group in position 2. The resonances at δ 10.77 and 9.98 are characteristic of CHO protons: the signal at δ 10.77 was assigned to 2-CHO, since it appears as a doublet (*J* 4.2 Hz) by coupling with H-2; the resonance at δ 9.98 was then assigned to 2′-CHO. Assignment of the quaternary carbons C-1′, C-2′ and C-4′ of compound **7** was performed by using HMBC experiments (Fig. 1): correlations were observed between the H-6′ resonance (δ 7.42) and the carbon resonances at δ 135.8 and 147.4, assigned to C-2′ and C-4′, respectively. Assignment of C-2′ was further confirmed since correlation was observed with the proton resonance at δ 9.98 (2′-CHO). The C-1′ resonance was assigned

Table 1 Signal enhancements observed by irradiation of the H-11 and 13-C*H*(CH$_3$)$_2$ resonances of compound **2**

^{1}H irradiation (δ)	^{13}C signal enhancements (δ)
13-C*H*(CH$_3$)$_2$ (2.90)	C-13 (146.8); C-12 (132.5); C-14 (124.9); 13-CH(C*H*$_3$)$_2$ (23.7 and 23.6)
H-11 (7.30)	C-13 (146.8); C-8 (130.5)



Scheme 3 Oxidative cleavage of **6** with NaIO$_4$ catalysed by OsO$_4$.

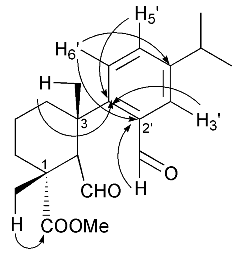
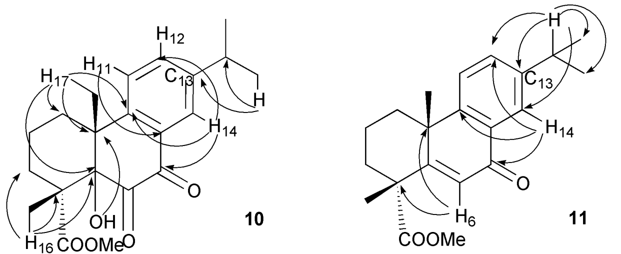


Fig. 1 Connectivities found in the HMBC spectrum of **7**.



10 **11**

Fig. 2 Connectivities found in the HMBC spectra of **10** and **11**.

at δ 144.7 since correlations with the proton resonances of H-5', H-3' and 3-CH_3 (δ 7.36, 7.82 and 1.14, respectively) were observed. Assignments of the resonances of 1-CH_3 and 3-CH_3 (δ 1.48 and 1.14, respectively) were also confirmed through the correlations observed in the HMBC spectrum.

Assignment of most of the ^1H and ^{13}C resonances of compound **8** was made by comparison with the results obtained for compound **7**. The resonance of the carbonylic proton 2-CHO observed in compound **7** was not found for **8**. On the other hand, in the mass spectrum of compound **8** it has been possible to observe a molecular ion at *m*/*z* 360, and two intense fragments at *m*/*z* 147 and 213, resulting from cleavage of the molecule at the C_2–$C_{1'}$ bond, giving a fragment at *m*/*z* 213 corresponding to the aliphatic part of the molecule, and a fragment at *m*/*z* 147 corresponding to the aromatic part. The fragment with *m*/*z* 147 is also observed in the mass spectrum of compound **7**, suggesting that no structural modifications occurred in the aromatic part of **8**. Instead of the fragment at *m*/*z* 213 observed for **8** compound **7** shows a fragment at *m*/*z* 197; suggesting that compound **8** has one more oxygen atom in the aliphatic part. These observations are consistent with the replacement of the 2-CHO group of compound **7** by a carboxylic group in compound **8**.

To confirm this hypothesis, a small amount of compound **8** was treated with diazomethane. The ^1H NMR of the resulting product revealed the presence of an additional singlet at δ 3.77, characteristic of a methyl ester proton resonance, confirming the presence of an extra carboxylic group in compound **8**.

The NMR characterisation of **9** was achieved by comparison with the spectroscopic data of the previously characterised compounds and also with HETCOR experiments. The H-5 resonance appears as a doublet at δ 2.91 due to coupling with H-6, which appears as a doublet of doublets at δ 4.47 due to coupling with H-5 and 6-OH, this last proton resonance appears as a doublet at δ 3.47. It was also possible to observe a shift to higher δ values in the resonance of H-16 and H-17 to δ 1.53 and 1.40, respectively, relative to the previously characterised compounds. The assignment of quaternary carbons C-9 and C-13 was performed using a one-dimensional selective INEPT experiment, by irradiation of H-12 and H-14. Upon irradiation, enhancements were found in the signal at δ 153.1, which was therefore assigned to C-9. The resonance of C-13 was then assigned at δ 147.4.

The ^1H and ^{13}C resonances of compound **10** were assigned by taking into account the characterisation of compound **9**. The assignment of the resonances of protonated carbons was confirmed through DEPT and HETCOR experiments, which also allowed the assignment of the H-1 (δ 2.14 and 2.38), H-2 (δ 1.88) and H-3 (δ 1.64) resonances. The resonances of quaternary carbons and the 5-OH proton were assigned through an HMBC experiment. The main connectivities observed are shown in Fig. 2.

Compound **11** has already been described in the literature,[13] however its characterisation by NMR and MS has not yet been reported. The molecular ion at *m*/*z* 326, two mass units less than that of compound **2**, as well as the disappearance of the resonances corresponding to H-5 and H-6 and the appearance of a new signal at δ 6.14, suggested that compound **11** differs from **2** by the presence of a double bond between carbon centres C-5 and C-6. The resonances of 13-$CH(CH_3)_2$, as well as those of 13-$CH(CH_3)_2$, appear at δ values different from the usual ones. According to previously published work[6] this might be due to steric hindrance caused by substituents in positions 12 or 14; however, taking into consideration the above-mentioned molecular ion no aromatic substituents were expected. In addition, in the aromatic region of the ^1H spectrum three signals were detected; H-14 appears as a singlet at δ 7.98 while H-11,12 appear as an AB system at δ 7.44 and 7.45.

Assignment of all proton and carbon resonances was made by considering 2D-NMR (HETCOR and HMBC) and DEPT experiments. Based on the connectivities found in the HMBC spectrum (Fig. 2) and starting from the 13-$CH(CH_3)_2$ resonance, 13-$CH(CH_3)_2$, C-14, C-12 and C-13 resonances were assigned. The HETCOR spectrum allowed the assignment of H-14 and H-12 resonances, and also the confirmation of those of 13-$CH(CH_3)_2$. Starting from H-14, the connectivities found in the HMBC spectrum allowed us to identify the resonances of C-9, C-12 and C-7. The connectivities with the resonance of H-6 (δ 6.14) allowed us to unambiguously assign the resonances of C-10 and C-4. The assignment of the quaternary C-5 resonance at δ 167.4 was further confirmed by its absence in the DEPT spectrum. Finally, the resonances of H-11 and H-12 have very close chemical shifts, and it has not been possible to differentiate them based on the HETCOR spectrum.

Compound **12** is known from the literature, although it has not yet been fully characterised.[13] The ^1H spectrum of compound **12** confirmed that H-5 and vinylic H-6 protons are not present. This indicates that, in addition to the C_5–C_6 double bond, another group replaces H-6. The disappearance of the C-6 resonance, as observed for compound **11**, and the appearance of a new carbon resonance at δ 142.4 strongly suggested that C-6 exists in an enolic form. Finally, no proton resonance for a $COOCH_3$ group was observed, and the mass spectrum for this compound showed a mass fragment of *m*/*z* 310. All this information coupled with a single crystal X-ray diffraction analysis allowed the identification of the molecular structure of this compound as the lactone shown in **12**.

The molecular structure found by X-ray diffraction for compound **12** is shown in Fig. 3, together with the atomic labelling scheme adopted. The distance between the carbon atom C6 and the oxygen atom O152 is 1.403(5) Å, indicating definitively the formation of a five-membered lactone ring. The molecule has a planar central core constituted of the aromatic and lactone rings and the intervening six-membered ring. In fact, the maximum deviation from the least-squares plane determined by the thirteen atoms that compose this central core is 0.140(4) Å for carbon atom C5. Despite this planarity, the bonds C5–C6 [1.321(6) Å] and C7–O71 [1.241(6) Å] both have double bond character, indicating that they are not involved in π electronic delocalisation. Furthermore the distances C7–C8 [1.491(6) Å], C7–C6 [1.457(7) Å] and C6–O152 [1.403(5) Å] are typical of single bond lengths. The distance C15–O151 [1.403(5) Å] is shorter than the distance C7–O71

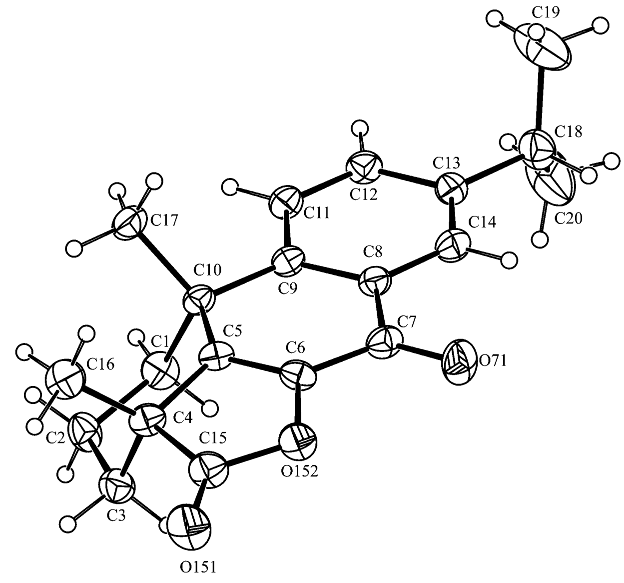


Fig. 3 ORTEP view of **12** with thermal ellipsoids drawn at 30% probability level. Selected bond distances (Å) and angles (°): C7–O71 1.241(6), C7–C8 1.491(6), C6–C7 1.457(7), C5–C6 1.321(6), C6–O152 1.403(5), O152–C15, 1.380(6), C15–O151, 1.200(6), C15–C4 1.526(6), C4–C5 1.520(6); C5–C6–O152 114.0(4), O152–C15–C4 110.3(4), C4–C5–C6 108.6(3), C5–C4–C15 100.3(4), C15–O152–C6 106.6(3).

by *ca.* 0.04 Å, suggesting that the carbonyl bond of the ester group also retains some double bond character. So the unique π electronic delocalisation present is this compound is due to the aromatic stabilisation of the benzene ring.

The absolute configuration of an organic compound cannot always be obtained directly and unequivocally from an X-ray structure determination, even if an appropriate X-ray radiation source is used. The X-ray data for compound **12** were collected with molybdenum radiation and therefore its absolute stereochemistry was not determined. However, the *R* configuration of the two chiral centres C10 and C4 is known from the precursor compound **1b** and the molecular diagram shown in Fig. 3 corresponds to the correct structure. Thus, the methyl groups attached to the carbon atoms C4 and C10 are above the least-squares plane mentioned above by 1.169(6) (C17) and 0.932(2) Å (C16) while the carbon atoms C1 and C3 are below it by 1.371(6) and 1.520(6) Å, respectively. The hexane ring adopts an approximate chair conformation with the following puckering parameters: Q 0.550(5) Å, θ 7.9(5)°, ϕ 91(4)°.[14]

Finally, in the crystal structure the molecules of **12** are self-assembled only by crystal packing forces. No hydrogen bonds were found and no relevant structural order is apparent from the crystal packing.

Having the X-ray structural proof in hand, it was possible to complete the NMR analysis. Assignment of the resonances of quaternary carbons C-5, C-7, C-8, C-9, C-13 and C-15 was made by considering the connectivities found in the HMBC spectrum (Fig. 4); the resonance at δ 142.4 was assigned by default to C-6.

A general interpretation of the electron impact (EI) mass spectra of all synthesised compounds can be based on the characteristic fragmentations of methyl dehydroabietate **1b**,[15] and of the functional groups present. Fragments such as $M^{\cdot+}$, $[M-CH_3]^+$, $[M-COOCH_3]^+$ and $[M-(CH_3+HCO_2CH_3)]^+$, which are typical for **1b**, can be found in the mass spectra of compounds **2**, **3**, **4**, **6** and **9** as the most relevant fragments (Table 2). The main fragments observed the in mass spectra of compounds **7** and **8** result from cleavage of the C_3–$C_{1'}$ and C_2–$C_{1'}$ bonds, respectively. The mass spectrum of compound **9** was characterised by a cluster of peaks in a small range of m/z values; this kind of spectrum indicates that extensive fragmentation of compound **9** occurred under EI conditions. For compound **10** the molecular ion is not observed in the EI mass spectrum; however, the fragment $[M+H]^{\cdot+}$ can be observed under FAB$^+$ conditions. In the EI–MS spectrum of compound **10**, the highest mass observed was at m/z 330, corresponding to the fragment $[M-CO]^{\cdot+}$, the most relevant fragments correspond to the loss, from the previous fragment, of 10-CH_3 (m/z 315) followed by the loss of HCO_2CH_3 (m/z 255) and the loss of CO_2CH_3 (m/z 271). The main fragments observed in MS spectra of **12** result from the cleavage of the lactone ring. These fragments corresponded to $[M-44]^{\cdot+}$ [loss of C(O)O], $[M-28]^{\cdot+}$ (loss of CO) and $[M-59]^+$ [loss of C(O)O and CH_3].

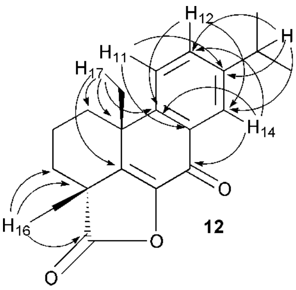


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Fig. 4 Connectivities found in the HMBC spectrum of **12**.

In conclusion, it can be stated that the present work is related to a valorisation procedure of resin acids; it describes the syntheses and characterisation of several new dehydroabietic acid derivatives, which arise from the cleavage or functionalisation of ring B of such a resin acid.

Experimental

General

NMR spectra were acquired on a Bruker AMX 300 spectrometer (300.13 and 75.47 MHz, for ^1H and ^{13}C, respectively) using $CDCl_3$ as solvent, TMS as internal reference; chemical shifts (δ) in ppm and coupling constants (J) in Hz. ^1H–^1H coupling constants are reported as calculated from spectra and, as a result, slight differences between J_{ab} and J_{ba} were occasionally obtained. Unequivocal ^1H and ^{13}C assignments were made with the aid of 2D-HETCOR ($^1H/^{13}C$) experiments, one-dimensional selective INEPT[16] (long-range C/H coupling constants optimised to 7 Hz) and HMBC (the low-pass J-filter portion of the experiment was optimised for an average of one-bond heteronuclear coupling of 145 Hz. The delay for evolution of long-range couplings was optimised for 7 Hz). Electron impact (EI, 70 eV), fast atomic bombardment (FAB)$^+$ using 3-nitrobenzyl alcohol as matrix, and high resolution (HRMS) mass spectra were obtained with VG Autospec Q and M mass spectrometers. Preparative thin-layer chromatography was done using Riedel silica gel 60 DGF_{254}. Column chromatography used Merck silica gel 60, 70–230 mesh. All chemicals and solvents were obtained from commercial sources and used as received or dried according to standard procedures.

Table 2 Relative intensity (%) of fragments found in the mass spectra of compounds **2**–**4**, **6** and **9**

Fragment	2	3	4	6	9
$[M]^{\cdot+}$	78	83	31	68	93
$[M-CH_3]^+$	19	44	[a]	13	32
$[M-CO_2CH_3]^+$	36	47	22	22	90
$[M-CO_2CH_3+CH_3]^{\cdot+}$	100	100	100	100	71

[a] Not observed.

Syntheses

Methyl 13-isopropylpodocarpe-8,11,13-trien-15-oate (methyl dehydroabietate), 1b. Methyl dehydroabietate was obtained by catalytic dehydrogenation of methylated resin according to known methods.[1]

Oxidation of methyl dehydroabietate 1b. A solution of CrO_3 (165 mg, 1.65 mmol) in 9 ml of acetic anhydride–acetic acid (2 : 1) was added dropwise to a solution of methyl dehydroabietate **1** (500 mg, 1.56 mmol) in acetic acid. The mixture was stirred at room temperature for 15 min, heated at 50 °C with magnetic stirring for 12 h. The mixture was then poured into water and ice, extracted with chloroform (3 × 100 ml), the combined organic layers dried over anhydrous sodium sulfate, and the solvent evaporated. The residue was dissolved in dichloromethane (5 ml) and purified by thin layer chromatography using light petroleum–ethyl acetate (4 : 1) as eluent. After elution three spots were isolated; the higher one was identified as compound **2** (343 mg, 67%), the middle one as compound **4** (36 mg, 6%) and the lower one as compound **3** (20 mg, 4%).

Methyl 13-isopropyl-7-oxopodocarpe-8,11,13-trien-15-oate, 2. Yellow oil; δ_H (300.13 MHz; $CDCl_3$; Me_4Si) 1.25 [6 H, d, *J* 7.2, 13-CH(CH_3)$_2$], 1.26 (3 H, s, H-17), 1.34 (3 H, s, H-16), 1.61–1.82 (5 H, m, H-1,2,3), 2.28–2.40 (2 H, m, H-1,6), 2.71–2.74 (2 H, m, H-5,6), 2.90 [1 H, heptet, *J* 6.9, 13-C*H*(CH_3)$_2$], 3.64 (3 H, s, 15-OCH_3), 7.30 (1 H, d, *J* 8.1, H-11), 7.41 (1 H, dd, *J* 8.4 and 2.2, H-12), 7.87 (1 H, d, *J* 2.4, H-14); δ_C (75.47 MHz; $CDCl_3$; Me_4Si) 16.2 (C-16), 18.0 (C-2), 23.6 [13-CH(CH_3)$_2$], 23.7 (C-17), 33.5 [13-*C*H(CH_3)$_2$], 36.9 (C-3), 37.0 (C-1), 37.2 (C-10), 37.7 (C-6), 43.6 (C-5), 46.5 (C-4), 52.1 (15-OCH_3), 123.4 (C-11), 124.9 (C-14), 130.5 (C-8), 132.5 (C-12), 146.8 (C-13), 152.9 (C-9), 177.7 (C-15), 198.4 (C-7); *m/z* (EI) 328 ($M^{\cdot+}$, 78%), 312 (19), 296 (16), 269 (36), 253 (100), 237 (13), 227 (12), 213 (29), 199 (20), 187 (37), 171 (15), 159 (19), 145 (15), 128 (20), 115 (23), 91 (16), 83 (18), 77 (13), 69 (15), 59 (41), 55 (23), 53 (13).

Methyl 13-acetyl-7-oxopodocarpe-8,11,13-trien-15-oate, 3. Yellow oil; δ_H (300.13 MHz; $CDCl_3$; Me_4Si) 1.29 (3 H, s, H-17), 1.36 (3 H, s, H-16), 1.76–1.85 (5 H, m, H-1,2,3), 2.39–2.44 (2 H, m, H-1,6), 2.64 (3 H, s, 13-$COCH_3$), 2.74–2.78 (2 H, m, H-5,6), 3.68 (3 H, s, 15-OCH_3), 7.51 (1 H, d, *J* 8.4, H-11), 8.16 (1 H, dd, *J* 1.8 and 8.4, H-12), 8.55 (1 H, d, *J* 2.1, H-14); δ_C (75.47 MHz; $CDCl_3$; Me_4Si) 16.4 (C-16), 18.0 (C-2), 23.4 (C-17), 26.7 (13-CO*C*H_3), 36.4 (C-3), 36.8 (C-1), 37.6 (C-10), 38.0 (C-6), 43.3 (C-5), 46.6 (C-4), 52.3 (15-OCH_3), 124.2 (C-11), 128.1 (C-14), 130.8 (C-8), 133.0 (C-12), 135.3 (C-13), 159.8 (C-9), 177.6 (C-15), 197.3 and 197.5 (C-7 and 13-*C*OCH_3); *m/z* (EI) 328 ($M^{\cdot+}$, 83%), 313 (44), 296 (25), 268 (48), 253 (100), 239 (11), 225 (15), 213 (47), 202 (32), 199 (33), 187 (66), 171 (16), 165 (13), 157 (12), 152 (11), 141 (18), 128 (30), 115 (31), 101 (14), 95 (19), 91 (13), 77 (13), 69 (18), 59 (25), 55 (22).

Methyl 13-(1-acetoxy-1-methylethyl)-7-oxopodocarpe-8,11,13-trien-15-oate, 4. Yellow oil; δ_H (300.13 MHz; $CDCl_3$; Me_4Si) 1.26 (3 H, s, H-17), 1.34 (3 H, s, H-16), 1.76–1.82 (5 H, m, H-1,2,3), 1.76 [6 H, s, 1′-(CH_3)$_2$], 2.04 (3 H, s, 1′-OCOC*H*$_3$), 2.33–2.36 (2 H, m, H-1,6), 2.70–2.74 (2 H, m, H-5,6), 3.66 (3 H, s, 15-OCH_3), 7.34 (1 H, d, *J* 8.4, H-11), 7.53 (1 H, dd, *J* 2.4 and 8.4, H-12), 7.98 (1 H, d, *J* 2.1, H-14); δ_C (75.47 MHz; $CDCl_3$; Me_4Si) 16.4 (C-16), 18.1 (C-2), 22.3 (1′-OCO*C*H_3), 23.6 (C-17), 28.5 [1′-(CH_3)$_2$], 36.4 (C-3), 37.0 (C-1), 37.3 (C-10), 37.8 (C-6), 43.5 (C-5), 46.6 (C-4), 52.2 (15-OCH_3), 81.0 (C-1′), 123.2 (C-14), 123.6 (C-11), 130.1 (C-12), 130.6 (C-8), 144.1 (C-13), 153.8 (C-9), 168.8 (1′-O*C*OCH_3), 177.8 (C-15), 198.2 (C-7); *m/z* (EI) 386 ($M^{\cdot+}$, 31%), 343 (68), 327 (100), 311 (50), 267 (19), 251 (66), 245 (20), 211 (16), 199 (15), 185 (16), 159 (19), 55 (11).

Methyl 7-hydroxy-13-isopropylpodocarpe-8,11,13-trien-15-oate, 5. To a solution of **2** (240 mg, 0,74 mmol) in methanol (25 ml) under nitrogen at 0 °C, $NaBH_4$ (225 mg, 5.92 mmol) was slowly added. After stirring for 3 h, the solvent was removed by evaporation. The residue was dissolved in chloroform, poured into water and acidified with commercial hydrochloric acid (pH of resulting mixture adjusted to 2). The mixture was extracted with chloroform (3 × 50 ml), the combined organic layers were dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in dichloromethane (2 ml) and purified by thin layer chromatography using light petroleum–ethyl acetate (4 : 1) as eluent. Methyl 7-hydroxy-13-isopropylpodocarpe-8,11,13-trien-15-oate **5** (198 mg, 81%), was isolated as a mixture of diastereomers. Yellow oil; δ_H (300.13 MHz; $CDCl_3$; Me_4Si) 1.23 [6 H, d, *J* 6.9, 13-CH(C*H*$_3$)$_2$], 1.27 (3 H, s, H-17), 1.28 (3 H, s, H-16), 1.36–1.86 (6 H, m, H-1,2,3,6), 2.06 (1 H, d, *J* 7.2, H-5), 2.21–2.31 (2 H, m, H-1,6), 2.87 [1 H, heptet, *J* 6.9, 13-C*H*(CH_3)$_2$], 3.66 (s, 3 H, 15-OCH_3), 4.72 (0.1 H, t, *J* 4.6, H-7β) , 4.85 (1 H, dd, *J* 8.2 and 16.2, H-7α), 7.09 (1 H, dd, *J* 1.9 and 8.2, H-12), 7.16 (1 H, d, *J* 8.1, H-11), 7.38 (1 H, d, *J* 1.8, H-14); δ_C (75.47 MHz; $CDCl_3$; Me_4Si) 16.4 (C-16), 18.3 (C-2), 23.8 and 24.0 [13-CH(*C*H_3)$_2$], 25.4 (C-17), 32.7 [13-*C*H(CH_3)$_2$], 33.6 (C-3), 36.4 (C-1), 37.5 (C-10), 37.8 (C-6), 43.3 (C-5), 47.2 (C-4), 52.0 (15-OCH_3), 70.6 (C-7), 124.1 (C-11), 125.2 (C-14), 125.8 (C-12), 137.5 (C-8), 146.4 (C-13), 146.6 (C-9), 178.7 (C-15); *m/z* (EI) 330 ($M^{\cdot+}$, 31%), 312 (25), 287 (9), 255 (20), 237 (100), 195 (26), 162 (37).

Methyl 13-isopropylpodocarpe-6,8,11,13-tetraen-15-oate, 6. To a solution of the diastereomeric mixture of **5** (198 mg, 0.60 mmol) in chloroform (10 ml) under nitrogen and at 0 °C, dry triethylamine (330 µl, 2.40 mmol) and mesyl chloride (66 µl, 0.80 mmol) were added. After stirring for 3 h, the mixture was poured into water. This mixture was extracted with chloroform (3 × 30 ml), the combined organic layers were dried with anhydrous sodium sulfate, and the solvent was evaporated to dryness. The residue was dissolved in dichloromethane (2 ml) and purified by thin layer chromatography using light petroleum–ethyl acetate (9 : 1) as eluent to give compound **6** (168 mg, 90%). Yellow oil; δ_H (300.13 MHz; $CDCl_3$; Me_4Si) 1.07 (3 H, s, H-17), 1.23 [6 H, d, *J* 6.9, 13-CH(C*H*$_3$)$_2$], 1.39 (3 H, s, H-16), 1.60–1.84 (5 H, m, H-1,2,3), 2.17 [1 H, d, *J* 11.4, H-1], 2.85 [1 H, heptet, *J* 6.9, 13-C*H*(CH_3)$_2$], 2.92 (1 H, m, H-5), 3.64 (3 H, s, 15-OCH_3), 5.71 (1 H, dd, *J* 9.3 and 2.7, H-6), 6.51 (1 H, dd, *J* 9.45 and 3.15, H-7), 6.91 (1 H, d, *J* 1.2, H-14), 7.06 (1 H, dd, *J* 8.1 and 1.8, H-12), 7.09 (1 H, d, *J* 8.1, H-11); δ_C (75.47 MHz; $CDCl_3$; Me_4Si) 17.9 (C-16), 18.4 (C-2), 20.8 (C-17), 24.0 [13-CH(*C*H_3)$_2$], 33.5 [13-*C*H(CH_3)$_2$], 35.3 (C-1), 35.6 (C-3), 37.1 (C-10), 46.3 (C-5), 46.6 (C-4), 52.0 (15-OCH_3), 121.6 (C-11), 124.6 (C-14), 125.7 (C-12), 129.8 (C-6), 128.3 (C-7), 132.5 (C-13), 145.0 (C-9), 146.3 (C-8), 178.5 (C-15); *m/z* (EI) 312 ($M^{\cdot+}$, 68), 297 (13), 253 (22), 237 (100), 223 (11), 212 (16), 209 (23), 197 (53), 183 (24), 179 (26), 167 (31), 165 (30), 155 (31), 147 (11), 141 (29), 128 (11), 115 (11), 59 (11).

Oxidative cleavage of 6. To a solution of **6** (160 mg, 0.513 mmol) in THF (15 ml) at 0 °C, OsO_4 (1 mg) and pyridine (82 µl, 1.026 mmol) were added. The reaction mixture was stirred for 20 min and then an aqueous (10 ml) of solution $NaIO_4$ (549 mg, 2.565 mmol) was slowly added. After stirring for 23 h, the solution was poured into water. This mixture was extracted with chloroform (3 × 50 ml), the combined organic layers were dried over anhydrous sodium sulfate, and the solvent was evaporated to dryness. The residue was dissolved in dichloromethane (3 ml) and purified by thin layer chromatography using dichloromethane as eluent. After several elutions six spots were isolated; the higher one was identified as compound **10** (18 mg, 10%), the second as compound **7** (21 mg, 12%), the third as compound **12** (14 mg, 9%), the fourth as compound **11** (10 mg, 6%), the fifth as compound **9** (32 mg, 18%), and the lower one as compound **8** (4 mg, 2%).

Methyl 2-formyl-3-(2-formyl-4-isopropylphenyl)-1,3-dimethylcyclohexane carboxylate, 7. Yellow oil; δ_H (300.13 MHz; $CDCl_3$; Me_4Si) 1.14 (3 H, s, 1-CH_3), 1.26 [6 H, d, *J* 6.9, 4′-$CH(CH_3)_2$], 1.48 (3 H, s, 3-CH_3), 1.71–2.40 (6 H, m, H-4,5,6), 2.97 (1 H, heptet, *J* 6.9, 4′-CH), 3.00 (3 H, s, 1-CO_2CH_3), 3.90 (1 H, d, *J* 4.2, H-2), 7.36 (1 H, dd, *J* 2.1 and 8.4, H-5′), 7.42 (1 H, d, *J* 8.1, H-6′), 7.82 (1 H, d, *J* 2.1, H-3′), 9.98 (1 H, d, *J* 4.2, 2′-CHO), 10.77 (1 H, s, 2-CHO); δ_C (75.47 MHz; $CDCl_3$; Me_4Si) 19.7 (C-5), 23.5 and 23.7 [4′-$CH(CH_3)_2$], 25.1 (1-CH_3), 30.5 (3-CH_3), 31.7 (C-6), 33.3 (4′-CH), 35.9 (C-4), 40.5 (C-3), 43.2 (C-1), 51.2 (1-CO_2CH_3), 60.5 (C-2), 128.0 (C-6′), 131.1 (C-3′), 131.1 (C-5′), 135.9 (C-2′), 144.7 (C-1′), 147.4 (C-4′), 175.6 (1-CO_2CH_3), 192.4 (2′-CHO), 203.8 (2-CHO); *m/z* (EI) 346 ([M + 2H]$^{\cdot+}$, 27%), 328 (32), 314 (34), 311 (35), 310 (78), 299 (26), 283 (33), 282 (62), 269 (28), 268 (47), 267 (67), 266 (100), 256 (25), 255 (65), 254 (59), 253 (51), 252 (26), 251 (60), 240 (35), 239 (92), 238 (32), 237 (36), 228 (27), 223 (35), 215 (39), 214 (34), 213 (50), 211 (33), 209 (29), 201 (25), 199 (36), 197 (60), 195 (32), 189 (37), 188 (35), 187 (88), 185 (32), 183 (26), 181 (30), 179 (26), 173 (26), 171 (30), 167 (26), 165 (31), 155 (27), 153 (26), 147 (39), 145 (30), 143 (29), 141 (35), 131 (29), 129 (38), 128 (40), 117 (25), 115 (37), 91 (38), 85 (26), 83 (35), 69 (26); HRMS found [M + 2H]$^+$ 346.1176; $C_{21}H_{28}O_4 + 2$ H requires 346.1780.

2-(2-Formyl-4-isopropylphenyl)-6-methoxycarbonyl-2,6-dimethylcyclohexane carboxylic acid 8. Yellow oil; δ_H (300.13 MHz; $CDCl_3$; Me_4Si) 1.16 (3 H, s, 6-CH_3), 1.25 [6 H, d, *J* 6.9, 4′-$CH(CH_3)_2$], 1.48, (3 H, s, 2-CH_3), 1.92 (6 H, m, H-3,4,5), 2.84 (3 H, s, 6-CO_2CH_3), 2.95 [1 H, heptet, *J* 6.9, 4′-$CH(CH_3)_2$], 4.12 (1 H, s, H-1), 7.32 (1 H, dd, *J* 2.3 and 8.3, H-5′), 7.42 (1 H, d, *J* 8.3, H-6′), 7.84 (1 H, d, *J* 2.3, H-3′), 10.75 (1 H, s, 2′-CHO); δ_C (75.47 MHz; $CDCl_3$; Me_4Si) 19.7 (C-4), 23.5 and 23.7 [4′-$CH(CH_3)_2$], 26.8 (6-CH_3), 28.5 (2-CH_3), 32.4 (C-5), 32.8 [4′-$CH(CH_3)_2$], 33.3 (C-3), 39.6 (C-2), 43.2 (C-6), 50.9 (6-CO_2CH_3), 55.5 (C-1), 128.4 (C-6′), 131.5 (C-3′,5′), 135.9 (C-2′), 144.5 (C-1′), 147.2 (C-4′), 175.3 (6-CO_2CH_3), 193.2 (2′-CHO); *m/z* (EI) 360 (M$^{\cdot+}$, 4%), 284 (28), 255 (25), 239 (46), 231 (28), 213 (100), 197 (39), 187 (50), 147 (66); *m/z* (FAB) 361 [(M + H)$^{\cdot+}$, 10%], 343 (37), 297 (13), 255 (14), 239 (13), 213 (12), 197 (10), 180 (11), 165 (15), 115 (18), 77 (51), 63 (25); HRMS found [M]$^+$ 360.1929; $C_{21}H_{28}O_5$ requires 360.1937.

Methyl 6-hydroxy-13-isopropyl-7-oxopodocarpe-8,11,13-trien-15-oate, 9. Yellow oil; δ_H (300.13 MHz; $CDCl_3$; Me_4Si) 1.20 [6 H, d, *J* 6.9, 13-$CH(CH_3)_2$], 1.40 (3 H, s, H-17), 1.53 (3 H, s, H-16), 1.61–1.78 (5 H, m, H-1,2,3), 2.35 (1 H, dd, *J* 12.9 and 3.0, H-1), 2.91 (1 H, d, *J* 13.2, H-5), 2.94 [1 H, heptet, *J* 6.9, 13-$CH(CH_3)_2$], 3.47 (1 H, d, *J* 2.7, 6-OH), 3.62 (3 H, s, 15-OCH_3), 4.47 (1 H, dd, *J* 13.5 and 2.7, H-6), 7.31 (1 H, d, *J* 8.1, H-11), 7.46 (1 H, dd, *J* 8.1 and 2.1, H-12), 7.91 (1 H, d, *J* 2.1, H-14); δ_C (75.47 MHz; $CDCl_3$; Me_4Si) 16.2 (C-16), 18.0 (C-2), 23.7 [13-$CH(CH_3)_2$], 24.1 (C-17), 33.5 [13-$CH(CH_3)_2$], 37.1 (C-3), 37.8 (C-1), 38.4 (C-10), 44.5 (C-4), 50.7 (C-5), 51.9 (15-OCH_3), 72.2 (C-6), 124.1 (C-11), 125.3 (C-14), 128.2 (C-8), 133.5 (C-12), 147.3 (C-13), 153.1 (C-9), 179.1 (C-15), 200.1 (C-7); *m/z* (EI) 345 ([M + H]$^{\cdot+}$, 28%), 344 (33), 326 (36), 311 (32), 299 (25), 298 (65), 285 (43), 284 (45), 267 (38), 266 (35), 256 (26), 255 (45), 251 (41), 241 (46), 239 (63), 238 (41), 237 (25), 228 (22), 226 (47), 223 (26), 216 (51), 215 (100), 213 (33), 209 (31), 199 (29), 197 (37), 195 (25), 187 (45), 181 (29), 155 (25), 145 (29), 141 (26), 129 (33), 128 (33), 115 (27), 91 (28), 85 (41), 83 (59), 69 (26), 59 (45); HRMS found (M)$^+$ 344.1986; $C_{21}H_{28}O_4$ requires 344.1988.

Methyl 5-hydroxy-13-isopropyl-6,7-dioxopodocarpe-8,11,13-trien-15-oate, 10. Yellow oil; δ_H (300.13 MHz; $CDCl_3$; Me_4Si) 1.27 [6 H, d, *J* 6.9, 13-$CH(CH_3)_2$], 1.34 (3 H, s, H-17), 1.61–1.68 (2 H, m, H-3), 1.71 (3 H, s, H-16), 1.82–1.96 (2 H, m, H-2), 2.09–2.18 (1 H, m, H-1), 2.38 (1 H, m, H-1), 2.96 [1 H, heptet, *J* 6.9, 13-$CH(CH_3)_2$], 3.77 (3 H, s, 15-OCH_3), 6.79 (1 H, s, 5-OH), 7.31 (1 H, d, *J* 8.1, H-11), 7.51 (1 H, dd, *J* 2.1 and 8.1, H-12), 7.96 (1 H, d, *J* 2.1, H-14); δ_C (75.47 MHz; $CDCl_3$; Me_4Si) 17.5 (C-2), 18.5 (C-16), 23.7 [13- $CH(CH_3)_2$],29.5 (C-17), 30.6 (C-1), 32.5 (C-3), 33.5 [13-$CH(CH_3)_2$], 44.9 (C-10), 46.4 (C-4), 53.1 (15-OCH_3), 81.8 (C-5), 123.8 (C-11), 126.3 (C-14) 130.7 (C-8), 134.3 (C-12), 147.4 (C-13), 151.4 (C-9), 180.9 (C-15), 183.9 (C-7), 191.9 (C-6); *m/z* (EI) 330 ([M$^{\cdot+}$ − CO], 11%), 315 (15), 271 (87), 255 (100), 211(11), 187 (17), 143 (11), 129 (16), 128 (16), 115 (15), 91 (16), 55 (14); *m/z* (FAB)$^+$ 359 ([M + H]$^+$, 100%); HRMS found (M)$^+$ 358.1783; $C_{21}H_{26}O_5$ requires 358.1780.

Methyl 13-isopropyl-7oxopodocarpe-5,8,11,13-tetraen-15-oate, 11. Yellow oil; δ_H (300.13 MHz; $CDCl_3$; Me_4Si) 1.27 and 1.28 [6 H, d, *J* 6.9, 13-$CH(CH_3)_2$], 1.53 (3 H, s, H-17), 1.65 (3 H,s, H-16), 1.72–2.08 (4 H, m, H-1,2,3), 2.17–2.27 (1 H, m, H-3), 2.51 [1 H, d, *J* 12.6, H-1], 2.98 (1 H, heptet, *J* 6.9, 13-$CH(CH_3)_2$), 3.72 (3 H, s, 15-OCH_3), 6.14 (1 H, s, H-6), 7.44 and 7.45 (2 H, AB, *J* 6.9, H-11,12), 7.98 (1 H, s, H-14); δ_C (75.47 MHz; $CDCl_3$; Me_4Si) 17.6 (C-2), 23.69 and 23.73 [13-$CH(CH_3)_2$], 25.0 (C-16), 33.6 [13-$CH(CH_3)_2$], 33.9 (C-17), 34.5 (C-3), 35.3 (C-1), 40.5 (C-10), 50.7 (C-4), 52.3 (15-OCH_3), 123.6 (C-14), 124.4 (C-11), 126.4 (C-6), 130.0 (C-8), 131.4 (C-12), 147.1 (C-13), 150.4 (C-9), 167.4 (C-5), 176.1 (C-15), 185.1 (C-7); *m/z* (EI) 326 (M$^{\cdot+}$, 93%), 311 (32), 268 (28), 267 (90), 266 (78), 252 (28), 251 (71), 239 (51), 238 (26), 237 (27), 227 (29), 226 (100), 225 (26), 223 (30), 213 (62), 212 (44), 211 (23), 209 (67), 197 (48), 195 (27), 183 (35), 181 (36), 179 (22), 178 (20), 167 (20), 166 (20), 165 (36), 59 (37).

13-Isopropyl-7-oxopodocarpe-5,8,11,13-tetraen-4,6-carbolactone, 12. White solid; M.p. 191–192 °C; δ_H (300.13 MHz; $CDCl_3$; Me_4Si) 1.29 [6 H, d, *J* 6.9, 13-$CH(CH_3)_2$], 1.36–1.42 (1 H, m, H-1), 1.61 (3 H, s, H-17), 1.65 (3 H, s, H-16), 1.83–1.90 (2 H, m, H-2), 2.05–2.18 (2 H, m, H-3), 2.37–2.44 (1 H, m, H-1), 3.01 [1 H, heptet, *J* 6.9, 13-$CH(CH_3)_2$], 7.46 (1 H, d, *J* 8.2, H-11), 7.52 (1 H, dd, *J* 8.2 and 2.0, H-12), 8.16 (1 H, d, *J* 1,9, H-14); δ_C (75.47 MHz; $CDCl_3$; Me_4Si) 18.9 (C-2), 21.0 (C-16), 23.7 and 23.8 [13-$CH(CH_3)_2$], 24.4 (C-17), 33.8 [13-$CH(CH_3)_2$], 35.9 (C-3), 38.9 (C-10), 42.3 (C-1), 47.1 (C-4), 124.6 (C-14), 125.8 (C-11), 130.7 (C-8), 131.6 (C-12), 142.4 (C-6), 145.6 (C-5), 148.0 (C-13), 148.4 (C-9), 174.0 (C-7), 179.6 (C-15); *m/z* (EI) 310 (M$^{\cdot+}$, 79%), 282 (55), 267 (54), 266 (100), 254 (43), 253 (23), 251 (52), 239 (47), 238 (22), 237 (25), 223 (20), 211 (21), 209 (21), 197 (27), 165 (24), 152 (20), 141 (22), 128 (21), 115 (22).

Crystallography

Single crystals of **12** suitable for a single crystal X-ray determination were obtained by slow evaporation from a light petroleum solution of this compound at room temperature. X-Ray data were measured using a Mar Research image plate system using graphite-monochromated Mo-Kα radiation ($\lambda = 0.710\,73$ Å) at $\approx$293 K. The selected crystal, mounted in a glass capillary under saturated solvent atmosphere, was positioned at 70 mm from the plate and 95 frames were taken at 2° intervals using a counting time adequate for the crystal diffraction pattern. Data analysis was performed with the XDS program.[17] Intensities of 5667 observations were collected, of which 3167 were independent reflections, giving a R_{int} of 0.0674. The structure was solved by direct methods using SHELXS[18] and refined by full-matrix least-squares refinement methods on F^2 using the SHELX97 software package.[19] Anisotropic displacements were refined for all non-hydrogen atoms. Hydrogen atoms bonded to carbon atoms were introduced in the refinement at idealised geometric positions with a $U_{\mathrm{iso}} = 1.2\ U_{\mathrm{eq}}$ of the parent carbon atom. The absolute stereochemistry of the structure was assigned from the known chirality of the substituents. The structure was refined on F^2 to convergence using SHELXL.[19] The final refinement of 214 parameters converged to $R_1 = 0.1163$ and $wR_2 = 0.2296$ for all unique *hkl* data and to $R_1 = 0.0828$ and $wR_2 = 0.2126$ for 2406 observed reflections with $I > 2\sigma(I)$.

Crystal data. $C_{20}H_{22}O_3$, $M = 310.38$, orthorombic, space group $P2_12_12_1$, $a = 8.776(11)$, $b = 10.233(16)$, $c = 18.853(24)$ Å, $U = 1693(4)$ Å^3, $Z = 4$, $\mu = 0.081$ mm^{-1}.

CCDC reference number 163568. See http://www.rsc.org/suppdata/nj/b1/b103737b/ for crystallographic data in CIF or other electronic format.

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