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New Methyl Dehydroabietate Derivatives: Synthesis and Structural Characterization

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Summary. The synthesis of some new chalcone and pyrazole type derivatives of methyl dehydroabietate is described. All compounds were exhaustively characterized using NMR and MS techniques. In order to confirm the information obtained by those techniques, the X-ray single crystal structures of methyl 12-acetyldehydroabietate and methyl 12-(4-methoxycinnamoyl)-dehydroabietate were determined. Molecular mechanics calculations were performed in order to evaluate the steric influence of the bulk of the C-12 substituent on the conformational preference of the isopropyl group in these derivatives. The energy barriers of 52.3 and 53.6 kJ/mol found for the two compounds indicated that the C-12 substituent hinders the free rotation of the isopropyl group in both cases.

Keywords. Chemical transformation; Methyl dehydroabietate; Chalcones; Pyrazoles; Pyrazolines.

Neue Methyldehydroabietatderivative: Synthese und strukturelle Charakterisierung

Zusammenfassung. Die Synthese einiger neuer Derivate des Dehydroabietinsäuremethylesters vom Typ der Chalkone und Pyrazole wird beschrieben. Alle Verbindungen wurden mit Hilfe von NMR- und MS-Techniken charakterisiert. Um die Ergebnisse dieser Techniken zu sichern, wurden Röntgen-Einkristallstrukturanalysen des 12-Acetyldehydroabietinsäuremethylesters und des entsprechenden (12-(4-Methoxycinnamoyl)-Derivates durchgeführt. Mittels molekülmechanischer Berechnungen wurde der Einfluß der Raumerfüllung des Substituenten in Position 12 auf die Konformation der Isopropylgruppe in diesen Derivaten studiert. Energiebarrieren von 52.3 und 53.6 kJ/mol für diese beiden Verbindungen weisen darauf hin, daß die freie Rotation der Isopropylgruppe in beiden Fällen sterisch gehindert ist.

Introduction

Pine resin is a very abundant renewable source mainly composed by diterpenic resin acids of the general formula $C_{19}H_{29}COOH$. This raw material has a wide range of industrial uses and is also a source of fine chemicals [1].

Among resin acid, those of the abietic acid (**1**) type are the most abundant; they are also the most versatile for chemical synthesis due to the presence of a conjugated double bond system.

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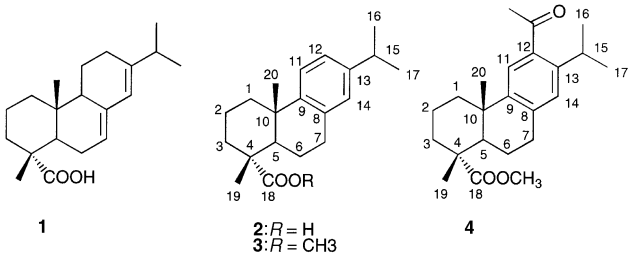


Fig. 1

Dehydroabietic acid (**2**) can be easily obtained by catalytic dehydrogenation of abietic type resin acids. A considerable interest has been devoted to this easily available compound as a starting material, either as free acid or ester, for the synthesis of other important natural and/or bioactive compounds mainly through transformations that involve the benzylic or aromatic positions of the molecule. In this way, oxygenated derivatives of methyl dehydroabietate (**3**) can be obtained by various methods [2–6] and are well known for their antifungal properties [7]; also, reactions of the aromatic moiety, involving various substitution reactions [8–13] and ozonolysis [14, 15] have been used in the synthesis of several other bioactive products [16–18].

It is well known that many natural compounds, or certain synthetic analogues, might have important applications as agrochemicals, pharmaceutical drugs, food additives, *etc*. Flavonoids and pyrazoles are included in such types of compounds; therefore, studies on the synthesis of new molecular entities of such types can give access to other potentially important compounds.

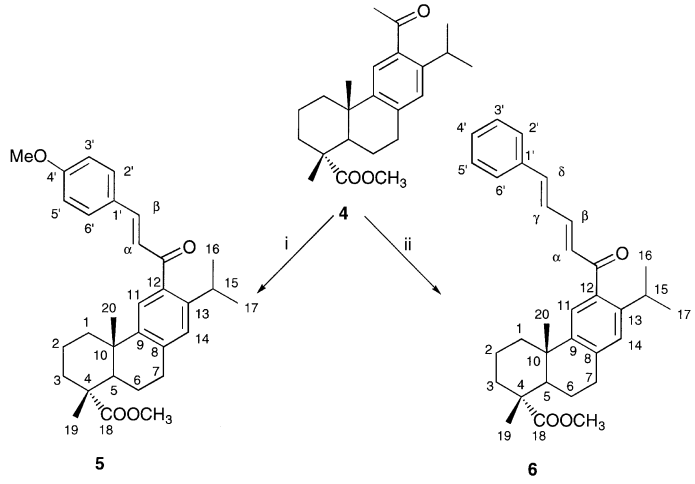
In the present case, a programme was started a few years ago aiming at the synthesis of new value added compounds from chemical transformations of raw materials easily available from vegetal sources [4, 19, 20]. Considering, at the same time, our previous experience on the synthesis of chalcone and pyrazole derivatives [21, 22], synthetic studies have been undertaken to obtain new chalcone, cinnamylideneacetophenone, β-diketone, and pyrazole derivatives from methyl 12-acetyldehydroabietate (**4**), a reagent easily available by *Friedel-Crafts* acylation of **3** [9].

Results and Discussion

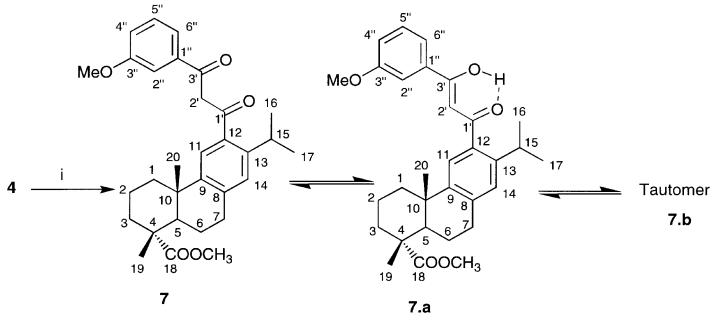
Syntheses

The chalcone-type compound methyl 12-(*p*-methoxycinnamoyl)dehydroabietate (**5**) and the cinnamylideneacetophenone derivative methyl 12-cinnamalacetyldehydroabietate (**6**) were obtained in good yields by base (NaH) catalyzed aldol condensation of methyl 12-acetyldehydroabietate (**4**) with *p*-methoxybenzaldehyde and cinnamaldehyde at room temperature in dry *THF* (Scheme 1).

Synthesis of the β-diketone **7** from condensation of **4** with *m*-methoxybenzoyl chloride or with the corresponding methyl or ethyl esters under the same conditions as mentioned for compounds **5** and **6** was not successful. However, β-diketone **7**



Scheme 1. i, dry *THF*, NaH, *p*-methoxybenzaldehyde, r.t., ii, dry *THF*, NaH, cinnamaldehyde, r.t.

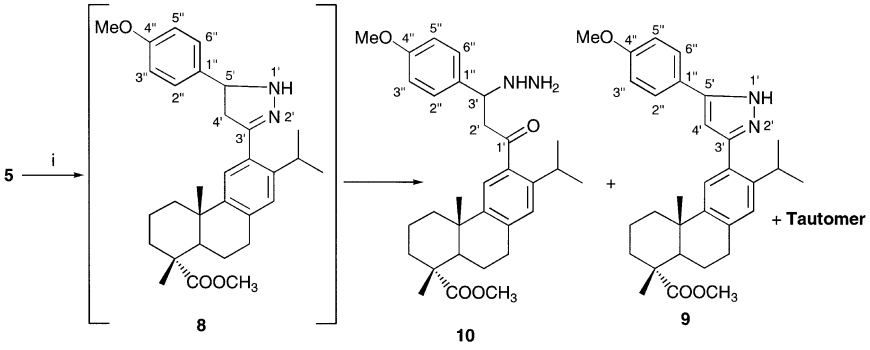


Scheme 2. i, dry *THF*, butyl lithium, *m*-methoxybenzoyl chloride, −78°C

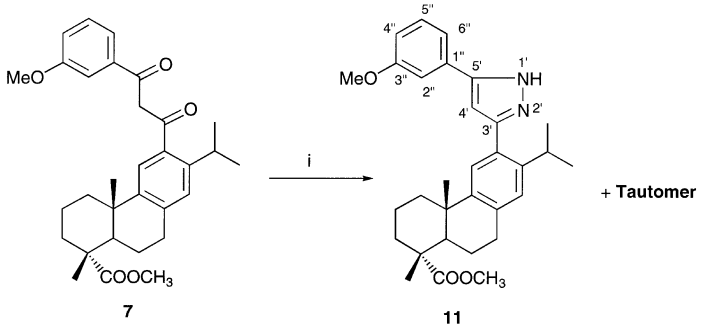
was obtained by condensation of **4** with *m*-methoxybenzoyl chloride in presence of butyl lithium at low temperatures (Scheme 2).

Compounds **5**, **6**, and **7** were tested as precursors in the synthesis of pyrazole derivatives by reaction with hydrazine hydrate in refluxing methanol. The reaction between **5** and hydrazine hydrate was monitored by TLC; after 5 hours, all starting material was consumed with the formation of only one reaction product which, however, decomposed immediately when the solvent was removed, forming a complex mixture of products from which pyrazole **9** and compound **10** were isolated (Scheme 3).

This unstable compound was expected to be the pyrazoline **8** since it is well known that such type of compounds are frequently very unstable intermediates in the syntheses of pyrazoles [23, 24], and this was confirmed by NMR and MS analysis of a reaction carried out in CD_3OD. Attempts were made to improve the yield of **9** through the addition of an oxidizing agent (aqueous $KMnO_4$) to the reaction media (using *THF* as solvent); however, no significant changes in the yield of the pyrazole **9** were found.



Scheme 3. i, methanol, hydrazine hydrate, reflux



Scheme 4. i, methanol, hydrazine hydrate, reflux

Attempts to prepare pyrazole derivatives from compound **6** were unsuccessful, yielding very complex mixtures. When the β-diketone **7** was treated with hydrazine hydrate, the desired pyrazole **11** was obtained in 64% yield (Scheme 4).

Structural characterization

The ^{1}H and ^{13}C NMR spectra of methyl dehydroabietate (**3**) can be found in the literature [25–28] and were the basis for the assignments of the NMR resonances of the new compounds. The ^{1}H and ^{13}C NMR spectra of the diterpenic part of molecules **4**–**11** have many similarities with those of compound **3**, and therefore most protons and carbons could be immediately assigned; in some cases, these assignments were further confirmed by using COSY (^{1}H, ^{1}H) and HETCOR (^{1}H, ^{13}C) experiments. The quaternary carbons C-8, 9, 12, and 13 could not be assigned directly.

The assignment of the quaternary carbons of methyl 12-acetyldehydroabietate (**4**) was performed using a one-dimensional selective INEPT experiment [29]. In the case of compound **4**, H-11 ($\delta = 7.40$ ppm) and H-15 ($\delta = 3.47$ ppm) were irradiated; the connectivities found in each case and the corresponding ^{13}C resonance assignments are shown in Table 1. The results of this experiment are in agreement with our previous assignments of the resonances of C-10, 14, 16, 17, and 12-CO. No signal enhancement was observed for the resonance at $\delta = 146.5$ ppm which was then assigned to C-9.

Table 1. Signal enhancements observed by irradiation of the resonances of H-11 and H-15 in compound **4**

^{1}H irradiation (δ, ppm)	^{13}C signal enhancements (δ, ppm)
7.40 (H-11)	36.8 (C-10), 138.7 (C-8), 144.9 (C-13), 203.3 (12-CO)
3.47 (H-15)	24.0 and 24.2 (C-16, 17), 126.5 (C-14), 136.3 (C-12), 144.9 (C-13)

The NMR data for compound **4** show that the methyl groups 16 and 17 are no longer equivalent, appearing with distinct ^{1}H ($\delta = 1.19$ and 1.21 ppm) and ^{13}C ($\delta = 24.0$ and 24.2 ppm) resonances. This behaviour is common to compounds **4**–**11**. In order to understand this fact, a NOE experiment has been carried out. Upon irradiation of the 12-$COCH_3$ resonance ($\delta = 2.55$ ppm), NOE effects were observed at H-11 ($\delta = 7.40$ ppm), but not on the isopropyl group. This result indicates that the 12-$COCH_3$ protons are closer to H-11 than to H-16,17.

An X-ray single crystal diffraction analysis was undertaken for **4** in order to establish its overall molecular stereochemistry. The molecular structure including the labelling scheme is shown in Fig. 2. As expected for diterpenic compounds [30], rings A and B show a *trans* ring junction with two methyl groups in axial positions of the six membered rings. Selected torsion angles[1] show a classical chair conformation and a half-chair conformation for rings A and B, respectively.

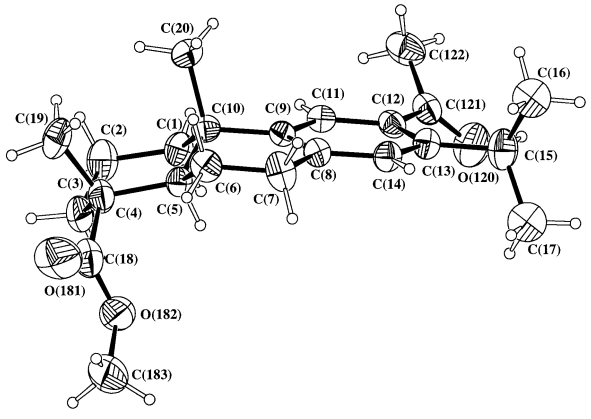


Fig. 2. Molecular structure of compound **4** with labelling scheme (30% thermal ellipsoids); disordered methyl groups are shown in one position only for clarity reasons

[1] Additional material to the structure determination, comprising atomic coordinates, thermal parameters, all bond lengths, angles, and selected endocyclic torsion angles may be ordered from Fachinformationszetrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Federal Republic of Germany, referring to the deposition number CSD-59457, the names of the authors, and the citation of the present paper.

The proximity of H-11 to 12-$COCH_3$ as suggested by the NMR data is also observed in the solid state: the intramolecular distance between H-11 and one of the protons of 12-$COCH_3$ (H(11)$\cdots$(H(111) = 2.35 Å) is comparable to the sum of the *van der Waals* radii for two hydrogen atoms. On the other hand, in spite of the disorder found for the methyl groups of the isopropyl group, its protons are too far from the 12-$COCH_3$ protons for any NOE effect to be observed.

The assignments of the ^1H and ^{13}C resonances of compounds **5** were made by comparing its spectra with the spectroscopic data obtained for compounds **3** and **4**, and also using a HETCOR experiment; the latter allowed the assignment of C-11, C-14, C-α, and C-1′. In this compound, H-α and H-β resonances appear as doublets ($J = 16.0$ Hz) at $\delta = 9.94$ and 7.35 ppm, respectively, indicating a *trans* stereochemistry of this double bond. In order to evaluate the spatial orientation of the side chain at position 12, a NOESY has been recorded. In this spectrum, only a very weak NOE cross peak was observed between H-α and H-11, and no NOE cross peaks were observed between H-α and the isopropyl protons.

A single crystal X-ray structure determination for **5** was carried out. The molecular structure and atom numbering scheme is shown in Fig 3. The overall geometry of **5** is comparable to that found for **4**, apart from small details: in compound **5**, the carbon atoms C(10), C(7), and C(121) deviate by −0.14(1), 0.16(1), and −0.28(1) Å from the best least squares plane defined by the carbon atoms of the aromatic ring of the dehydroabietic skeleton. The pronounced deviation exhibited by C(121) is probably the result of the minimization of the steric interactions between the bulky aromatic side chain and the isopropyl group. In compound **4**, these atoms are co-planar with the carbon atoms of the aromatic ring. The analysis of intramolecular distances for compound **5** reveals that H-11, H-α, and the isopropyl protons are too far from each other to establish any type of

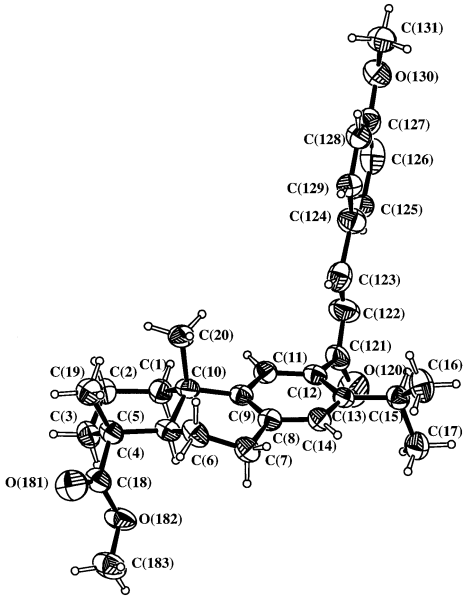


Fig. 3. Molecular structure of compound **5** with labelling scheme (30% thermal ellipsoids)

interaction in the solid state. This observation is therefore consistent with the NOESY results.

The above observation that the methyl groups 16 and 17 of compounds **4–11** show different ^{1}H and ^{13}C chemical shifts due to steric hindrance caused by the substituent at C-12 prompted us to perform molecular mechanics calculations on compounds **4** and **5** in order to evaluate the steric influence of the C-12 substituent on the conformational preference of the isopropyl group. Steric energy profiles were obtained for the rotation of isopropyl groups around of the bond C-13-C15 changing the torsion angle C-14-C-13-C-15-C-16 (see Experimental for further details). The profiles obtained for both compounds are very alike showing two rotational barriers with similar energies. The energy minima are flat. However, the X-ray torsion angle C-14-C-13-C-15-C-16 of 80.5(8)° for compound **4** is located in one of the broad minima. The disorder found for the methyl groups in compound **4** leads to two different values of 60.1(10)° and 98.6(12)° for that torsion angle.

The rotational barriers of 52.3 and 53.6 kJ/mol for **4** and **5** indicate that in both compounds rotation of the isopropyl group is hindered by the C-12 substituent. The similarity of these two values suggests that steric hindrance is independent of the bulk of the C-12 substituents in compounds **4** and **5**. As discussed above for compound **5**, C(121) is significantly bent out of the plane of the aromatic ring of the dehydroabietic skeleton; this fact can contribute to the reduction of energy barrier of compound **5**.

The assignment of the proton resonances of the side chain of compound **6** was based on a 2D COSY experiment. Starting from the resonance of H-α ($\delta = 6.61$ ppm) we have assigned the other resonances of the $\alpha,\beta,\gamma,\delta$-unsaturated system at 7.18, 6.90, and 6.98 ppm to the resonances of H-β, H-γ, and H-δ. The coupling constants ($J_{\alpha,\beta} = 15.2$ Hz and $J_{\gamma,\delta} = 15.4$ Hz) indicate a *trans-trans* stereochemistry of this unsaturated system. This stereochemistry was also confirmed by a NOE experiment: upon irradiation of the resonance of H-α ($\delta = 6.61$ ppm), NOE effects were observed on the proton resonances of H-γ ($\delta = 6.98$ ppm) and H-11 ($\delta = 7.20$ ppm). These results show that the stereochemistry of the double bond is as shown in Scheme 1. The NOE effect confirms the closer proximity of the side chain to H-11 rather than to the isopropyl group.

The NMR spectroscopic characterization of the β-diketone **7** was achieved by comparison with data from previous compounds and based on HETCOR experiments. The resonance at 6.42 ppm is characteristic of α-enolic protons (attributed to H-2′), and the broad resonance at 16.60 ppm is characteristic of hydrogen bonded OH groups and indicates that compound **7** exists mainly in the enol form.

The assignment of ^{1}H and ^{13}C resonances of compound **10** was performed by comparing its spectroscopic characteristics with those from other compounds (in particular, **5**). H-2′ and H-3′ resonances appear as multiplets at 3.26 and 5.26 ppm; the assignment of the corresponding ^{13}C resonances was possible *via* the HETCOR spectra. The resonance of H-15 appears as a heptet of doublets due to coupling with H-16,17 ($J = 6.1$ Hz) and to long distance coupling with H-11 ($J = 1.2$ Hz). The assignment of H-11 was based on a NOESY spectrum: NOE cross-peaks were observed between the signal at 7.30 ppm and the signals at 1.17 ppm (H-20) and 3.26 ppm (H-2′), therefore confirming the assignment of the former resonance to H-11; on the other hand, NOE cross-peaks were also found between the signal at

$\delta = 7.05$ ppm and the resonances of H-7 and H-16,17, confirming the assignment of H-14.

The resonances of quaternary carbons of compound **10** were assigned from an INEPT experiment: upon irradiation of H-3″, 5″ ($\delta = 6.91$ ppm), enhancements were observed at the signals at 159.0 and 135.2 ppm which were therefore assigned to C-4″ and C-1″. Less intense signal enhancements were also observed at 146.7 and 137.7 ppm, which were then attributed to C-9 and C-12. These last signal enhancements were due to the simultaneous irradiation of H-14.

The assignments of the ^{1}H NMR resonances of the pyrazoles **9** and **11** were made taking into account the spectra of their precursors **5** and **7**. The resonance of H-4′ was assigned at 6.53 and 6.60 ppm for **9** and **11**. ^{13}C NMR resonances were also assigned by comparison with those of previous compounds and based on a HETCOR experiment. The resonances of the quaternary carbons C-8 ($\delta =$ 136.2 ppm) and C-9 ($\delta = 147.1$ ppm) were assigned through an INEPT experiment by irradiation of the H-7 resonance ($\delta = 2.94$ ppm). This experiment also confirmed the previous assignments of C-5, 6, and 14 at 44.7, 21.6, and 126.3 ppm, respectively. As expected, the resonances of C-3′,5′ were not detected due to the existence of tautomeric forms [31].

The unstable pyrazoline **8** was identified by ^{1}H NMR through the assignment of the resonances of H-4′ and H-5′. The resonances of H-4′ protons were assigned based on a COSY experiment and appear at 3.36–3.49 ppm (overlapped with H-15 resonance) and at 1.20 ppm. H-5′ resonates at 4.84 ppm overlapped with the water signal.

The interpretation of the mass spectra of the synthesized compounds can be based on the characteristic fragmentations of methyl dehydroabietate **3** [25, 32–35] and of the substituent groups present in position 12 of the other synthesized derivatives.

Fragments such as those at $m/z = 91$ $(C_7H_7)^+$ and $m/z = 121$ $(C_9H_{13})^+$, which are typical of **3**, can be found in the mass spectra of the new compounds; however, the most relevant fragments correspond to the loss of 10-CH_3 ($M^{+\cdot} - 15$) followed by the loss of HCO_2CH_3 ($M^{+\cdot} - 75$). These fragments occur with retention of the 12-substituent, and by comparing the m/z values of the fragments with those of the corresponding fragments of **3**, one can confirm the mass of such substituents. Characteristic fragmentations of the carbonylic side chains of compounds **4**–**7** involve mainly the cleavage of C–C bonds around the 12-CO group [36].

Apart from the fragmentation of the diterpenic moiety of the molecule, the mass spectra of the isomeric compounds **9** and **11** also show the characteristic fragmentations of pyrazole compounds. The intense molecular ion observed in both cases is common with this type of compounds, as well as the fragments at $m/z = 240$ and 354 resulting from the cleavage of the pyrazole ring [37].

The molecular ion for compound **10** is not observed in its mass spectrum; however, an intense fragment at $m/z = 474$ can be observed which results from the loss of H_2NNH_2. The molecular ion is so unstable that it could not be detected even when FAB^+ ionization was used. Under those conditions, the highest mass observed was at $m/z = 475$, corresponding to the same fragment detected by EI ionization. Finally, the identity of the pyrazoline **8** was also confirmed since its molecular ion can easily be detected at $m/z = 488$.

Experimental

Melting points are uncorrected and were determined on a Reichert Thermovar apparatus fitted with a microscope. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ solutions (not degassed), except when another solvent is specified, on a Bruker AMX 300 spectrometer at 300.13 and 75.47 MHz (*TMS* as internal reference). 2D experiments were obtained using Bruker standard microprograms. 2D COSY spectra were collected in a 1024× 256 matrix. In the 2D heteronuclear shift correlation (HETCOR) the initial matrix of 2048×512 was zero filled to 2048×1024; the relaxation delay was 2 s. The phase sensitive NOESY spectra were acquired in a 2048×512 matrix with a mixing time and a relaxation delay of 1 s each and then processed in a 2048×1024 matrix. One-dimensional selective INEPT experiments (INAPT sequence) were acquired using a 2 s relaxation delay; $\Delta 1$ and $\Delta 2$ of the pulse sequence were optimized for a 7 Hz long-range $J_{(C,H)}$ coupling constant. Low (MS) and high resolution (HRMS) mass spectra were obtained at 70 eV electron impact ionisation using a VG Autospec Q mass spectrometer. Elemental analyses were performed on a Carlo Erba-Strumentazione, Elemental Analiser-Mod. 1106.

Preparative thin layer chromatography (TLC) was carried out on silica gel plates (Riedel silica gel 60 DGF_{254}). Column chromatography was also performed on silica gel (Merck silica gel 60, 70–230 mesh). All other chemicals and solvent used herein were obtained from commercial sources and used as received or dried using standard procedures. Light petroleum was the fraction of b.p. 40–60°C. Elemental analysis of novel compounds were found to be in agreement with the calculated values.

Note on nomenclature

The names of compounds **4**–**11** in the experimental part were derived according to IUPAC rules [38], considering all compounds as derivatives of methyl dehydroabietate (**3**). However, for a clear discussion and presentation of experimental NMR spectroscopic data, the numbering of side chains presented in the schemes is not totally consistent with IUPAC rules.

Methyl dehydroabietate (**3**; $C_{21}H_{30}O_2$)

Methyl dehydroabietate was obtained by catalytic dehydrogenation of methylated resin according to known methods [1].

Methyl 12-acetyldehydroabietate (**4**; $C_{23}H_{32}O_3$)

Methyl 12-acetyldehydroabietate was obtained by *Friedel-Crafts* acylation of **3** according to known methods [9].

Yield: 3.26 g (41%); m.p.: 135.4–136.1°C (recrystallized from a mixture of light petroleum:dichloromethane (1:1); Ref. [9]: m.p.: 133.5–134.0°C); ^{1}H NMR (300 MHz, δ $CDCl_3$): 1.19 and 1.21 (6H, d, $J = 7.4$, H-16, 17), 1.21 (3H, s, H-20), 1.28 (3H, s, H-19), 1.40–1.57 (2H, m, H-1,6), 1.65–1.91 (5H, m, H-2,3,6), 2.22 (1H, dd, $J = 2.1$ and 12.5, H-5,), 2.32 (1H, d, $J = 12$, H-1), 2.55 (3H, s, 12-$COCH_3$), 2.90 (2H, m, H-7), 3.47 (1H, hept, $J = 6.8$, H-15), 3.67 (3H, s, 4-$COOCH_3$), 7.04 (1H, s, H-14), 7.40 (1H, s, H-11) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$): 16.4 (C-19), 18.4 (C-2), 21.4 (C-6), 24.0 and 24.2 (C-16,17), 25.1 (C-20), 28.6 (C-15), 29.9 (C-7), 30.5 (12-CO*C*H_3), 36.5 (C-3), 36.8 (C-10), 37.8 (C-1), 44.6 (C-5), 47.5 (C-4), 52.0 (4-COO*C*H_3), 124.3 (C-11), 127.0 (C-14), 136.3 (C-12), 138.7 (C-8), 144.9 (C-13), 146.5 (C-9), 178.9 (C-18), 203.3 (12-CO) ppm; MS: $m/z = 356$ ($M^{+\cdot}$, 40%), 341 (27), 297, (6), 281 (100), 239 (9), 227 (6), 215 (11), 197 (8), 153 (6), 128 (7), 115 (7), 59 (10).

Methyl 12-(p-methoxycinnamoyl)dehydroabietate (**5**; $C_{31}H_{38}O_4$)

15 mg NaH (0.62 mmol) was added to a solution of 108 mg **4** (0.303 mmol) in dry 15 ml *THF* under a N_2 atmosphere. After 15 min, 56 mg *p*-methoxybenzaldehyde (0.41 mmol) were added, and the mixture was stirred for 12 h. Then the mixture was poured into H_2O and extracted with CH_2Cl_2, the organic layer was dried over anhydrous Na_2SO_4, and the solution concentrated on a rotary evaporator. The residue was then purified by TLC eluting with light petroleum: CH_2Cl_2 (1:1) and crystallized from a mixture of light petroleum: CH_2Cl_2 (1:1).

Yield: 115 mg (80%); m.p.: 129.3–130.5°C; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 1.19 and 1.22 (6H, d, $J = 6.8$, H-16,17), 1.22 (3H, s, H-20), 1.28 (3H, s, H-19), 1.43–1.54 (2H, m, H-1,6), 1.66–1.79 (3H, m, H-2,3), 1.81–1.90 (2H, m, H-3,6), 2.24 (1H, dd, $J =$ 2.2 and 12.4, H-5), 2.27 (1H, d, $J =$ 12.7, H-1), 2.94 (2H, m, H-7), 3.19 (1H, hept, $J = 6.8$, H-15), 3.68 (3H, s, 4-$COOCH_3$), 3.85 (3H, s, 4′-OCH_3), 6.92 (2H, d, $J = 8.8$, H-3′, 5′), 6.94 (1H, d, $J = 16.1$, H-α), 7.05 (1H, s, H-14), 7.21 (1H, s, H-11), 7.35 (1H, d, $J = 16.1$, H-β), 7.49 (2H, d, $J = 8.8$, H-2′, 6′) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$): 16.5 (C-19), 18.4 (C-2), 21.5 (C-6), 24.1 and 24.3 (C-16,17), 25.0 (C-20), 29.3 (C-15), 30.0 (C-7), 36.6 (C-3), 36.9 (C-10), 37.8 (C-1), 44.8 (C-5), 47.6 (C-4), 52.0 (4-COO*C*H_3), 55.4 (4′-OCH_3), 114.4 (C-3′, 5′), 123.6 (C-11), 125.8 (C-α), 126.5 (C-14), 127.3 (C-1′), 130.1 (C-2′, 6′), 136.7 (C-12), 137.4 (C-8), 144.0 (C-13), 145.8 (C-β), 146.5 (C-9), 161.6 (C-4′), 179.0 (C-18), 198.2 (12-CO) ppm; MS: $m/z = 474$ ($M^{+\cdot}$, 100%), 459 (10), 431 (9), 399 (12), 353 (51), 341 (21), 277 (17), 265 (13), 237 (12), 261 (20), 133 (11), 121 (89), 91 (9).

Methyl 12-cinnamalacetyldehydroabietate (**6**; $C_{32}H_{38}O_3$)

14 mg NaH (0.57 mmol) was added to a solution of 102 mg **4** (0.287 mmol) in dry 15 ml *THF* under a N_2 atmosphere. After 15 min, 52 mg cinnamaldehyde (0.40 mol) were added and the mixture was stirred for 12 h. Then the mixture was poured into H_2O and extracted with CH_2Cl_2, the organic layer was dried over anhydrous Na_2SO_4 and the solution concentrated on a rotary evaporator. The residue was then purified by TLC eluting with light petroleum:ethyl acetate (1:1) and crystallized from a mixture of light petroleum:CH_2Cl_2 (1:1).

Yield: 105 mg (78%); m.p.: 152.3–154.5 °C; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 1.19 and 1.21 (6H, d, $J = 6.9$, H-16,17), 1.22 (3H, s, H-20), 1.28 (3H, s, H-19), 1.43–1.55 (2H, m, H-1,6), 1.65–1.93 (5H, m, H-2,3,6), 2.24 (1H, dd, $J = 2.1$ and 12.5, H-5), 2.29 (1H, d, $J = 12.6$, H-1), 2.93 (2H, m, H-7), 3.20 (1H, hept, $J = 6.8$, H-15), 3.68 (3H, s, 4-$COOCH_3$), 6.61 (1H, d, $J = 15.2$, H-α), 6.90 (1H, d, $J = 15.4$, H-δ), 6.98 (1H, m, H-γ), 7.04 (1H, s, H-14), 7.18 (1H, dd, $J = 9.9$ and 15.2, H-β), 7.20 (1H, s, H-11), 7.35 (3H, m, H-3′, 4′, 5′), 7.48 (2H, dd, $J = 1.5$ and 8.0, H-2′, 6′) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$): 16.5 (C-19), 18.4 (C-2), 21.5 (C-6), 24.1 and 24.3 (C-16,17), 25.1 (C-20), 29.3 (C-15), 30.0 (C-7), 36.6 (C-3), 36.9 (C-10), 37.8 (C-1), 44.7 (C-5), 47.6 (C-4), 52.0 (4-COO*C*H_3), 123.6 (C-11), 126.5 (C-14), 126.8 (C-γ), 127.3 (C-2′, 6′), 128.8 (C-3′, 4′), 129.2 (C-5′), 131.2 (C-α), 136.0 (C-1′), 136.5 (C-12), 137.5 (C-8), 141.5 (C-δ), 144.1 (C-13), 145.8 (C-β), 146.5 (C-9), 179.0 (C-18), 198.0 (12-CO) ppm; MS: $m/z = 470$ ($M^{+\cdot}$, 100%), 455 (21), 427 (6), 401 (20), 395 (25), 366 (17), 353 (52), 351 (14), 341 (14), 329 (8), 391 (29), 273 (11), 265 (9), 237 (8), 197 (9), 157 (14), 129 (15), 128 (18), 117 (23), 115 (13), 91 (28).

Methyl 12-(3-(3-methoxyphenyl)-3-oxopropanoyl)dehydroabietate (**7**; $C_{31}H_{38}O_5$)

A solution of 100 mg methyl 12-acetyldehydroabietate **4** (0.280 mmol) in freshly dried 15 ml *THF* under a N_2 atmosphere was cooled to −78°C; then 40 µl butyl lithium (1.0 mmol) were added, and the solution was stirred for 25 min. After that time, 100 µl *m*-methoxybenzoyl chloride (0.712 mmol) were added and the mixture was stirred for 3 h. Then the mixture was poured into H_2O, acidified to *pH* 3 with 1 *M* HCl, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous

Na_2SO_4, the solution was concentrated on a rotary evaporator, and the residue was purified by TLC eluting with light petroleum:ethyl acetate (9:1); compound **7** was obtained as an oil.

Yield: 15.1 mg (11%); HRMS: found: 490.2692, $C_{31}H_{38}O_5$ requires 490.2719; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 1.23 (3H, s, H-20), 1.23 and 1.26 (6H, d, $J = 6.8$, H-16,17), 1.28 (3H, s, H-19), 1.36–1.58 (2H, m, H-1,6), 1.63–1.93 (5H, m, H-2,3,6), 2.23 (1H, dd, $J = 2.0$ and 12.5, H-5), 2.33 (1H, d, $J = 12.2$, H-1), 2.93 (2H, m, H-7), 3.44 (1H, hept, $J = 6.9$, H-15), 3.67 (3H, s, 4-$COOCH_3$), 3.87 (3H, s, 3″-OCH_3), 6.50 (1H, s, H-2′), 7.24 (2H, m, H-14,4″), 7.43 (1H, s, H-11), 7.50 (1H, m, H-5″), 7.63 (2H, m, H-2″,6″), 16.60 (broad, enolic OH) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$): 16.5 (C-19), 18.4 (C-2), 21.5 (C-6), 24.2 and 24.4 (C-16,17), 25.0 (C-20), 29.2 (C-15), 29.9 (C-7), 36.6 (C-3), 37.0 (C-10), 37.9 (C-1), 44.7 (C-5), 47.6 (C-4), 52.0 (4-$COOCH_3$), 55.4 (3″-OCH_3), 98.0 (C-2′), 111.9 and 119.5 (C-2″,6″), 118.5 (C-4″), 124.1 (C-11), 126.8 (C-14), 129.6 (C-5″), 134.1 (C-1″), 136.8 (C-12), 138.2 (C-8), 144.2 (C-13), 147.0 (C-9), 159.8 (C-3″), 179.0 (C-18), 184.4 and 191.7 (C-1′,3′) ppm; MS: $m/z = 490$ ($M^{+\bullet}$, 30%), 447 (33), 355(33), 341 (100), 338 (17), 313 (11), 283 (29), 265 (18), 143 (17), 135 (64), 107 (16), 85 (14), 83 (21), 77 (14), 55 (10).

Synthesis of methyl 12-(5-(3)-(4-methoxyphenyl)pyrazol-3(5)-yl)dehydroabietate (**9**)

40 µl Hydrazine hydrate (0.54 mmol) were added to a solution of 101.0 mg methyl 12-(4-methoxycinnamoyl)dehydroabietate (**5**, 0.213 mmol) in 70 ml methanol under a N_2 atmosphere; the mixture was stirred and refluxed for 12 h. The mixture was then poured into H_2O and extracted with $CHCl_3$; the organic layer was dried over anhydrous Na_2SO_4 and concentrated in the rotary evaporator. The mixture was then purified by TLC eluting with light petroleum:ethyl acetate (9:1). Two products were isolated: pyrazole **9** and hydrazine **10**. When the reaction was carried out in CD_3OD, the direct NMR analysis of the reaction mixture allowed the identification of pyrazoline **8**. Compounds **9** and **10** were obtained as pure oils.

Methyl 12-(5-(3)-(4-methoxyphenyl)pyrazol-3(5)-yl)dehydroabietate (**9**; $C_{31}H_{38}N_2O_3$)

Yield: 19.8 mg (19.2%); HRMS: found 486.2862, $C_{31}H_{38}N_2O_3$ requires 486.2882; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 1.17 and 1.20 (6H, d, $J = 6.8$, H-16,17), 1.22 (3H, s, H-20), 1.28 (3H, s, H-19), 1.42–1.54 (2H, m, H-1,6), 1.63–1.93 (5H, m, H-2,3,6), 2.24 (1H, dd, $J = 2.1$ and 12.3, H-5), 2.28 (1H, m, H-1), 2.94 (2H, m, H-7), 3.20 (1H, hept, $J = 6.8$, H-15), 3.68 (3H, s, 4-$COOCH_3$), 3.85 (3H, s, 4′-OCH_3), 6.53 (1H, s, H-4′), 6.95 (2H, d, $J = 8.8$, H-3″, 5″), 7.06 (1H, s, H-14), 7.22 (1H, s, H-11), 7.73 (2H, d, $J = 8.8$, H-2″, 6″) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$): 16.5 (C-19), 18.5 (C-2), 21.6 (C-6), 24.2 and 24.4 (C-16,17), 25.1 (C-20), 29.2 (C-15), 29.8 (C-7), 36.6 (C-3), 36.9 (C-10), 37.9 (C-1), 44.7 (C-5), 47.6 (C-4), 52.0 (4-$COOCH_3$), 55.3 (4″-OCH_3), 102.7 (C-4′), 114.1 (C-3″, 6″), 125.3 (C-1″), 125.7 (C-11), 126.3 (C-14), 126.9 (C-2″, 6″), 136.2 (C-8,12), 144.4 (C-13), 147.1 (C-9), 179.1 (C-18) ppm; MS: $m/z = 487$ (36%), 486 ($M^{+\bullet}$, 100), 485 (20), 473 (30), 471 (13), 411 (25), 341 (29), 339 (16), 338 (43), 292 (15), 281 (18), 236 (16), 208 (23), 194 (15), 177 (30), 167 (26), 163 (16), 135 (15), 134 (16), 121 (34), 77 (15), 71 (22), 57 (25), 55 (18).

Methyl 12-(3-hydrazino-3-(4-methoxyphenyl)propanoyl)dehydroabietate (**10**; $C_{31}H_{42}N_2O_4$)

Yield: 12.1 mg (14%); HRMS (FAB^+): found 475.2929 ($M\text{-}H_2NNH_2 + H)^+$, $C_{31}H_{39}O_4$ requires 475.2848; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 1.17 (3H, s, H-20), 1.20 (6H, m, H-16,17), 1.27 (3H, s, H-19), 1.41–1.48 (2H, m, H-1,6), 1.61–1.92 (5H, m, H-2,3,6), 2.19 (1H, dd, $J = 2.0$ and 12.5, H-5), 2.23 (1H, m, H-1), 2.90 (2H, m, H-7), 3.26 (2H, m, H-2′), 3.41 (1H, hept d, $J = 1.2$ and 6.8, H-15), 3.67 (3H, s, 4-$COOCH_3$), 3.81 (3H, s, 4″-OCH_3), 5.26 (1H, m, H-3′), 6.91 (2H, d, $J = 8.7$, H-3″, 5″), 7.05 (1H, s, H-14), 7.30 (1H, d, $J = 1.2$, H-11), 7.35 (2H, d, $J = 8.7$, H-2″, 6″) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$): 16.4 (C-19), 18.3 (C-2), 21.3 (C-6), 24.1 and 24.3 (C-16,17), 25.0 (C-20), 28.7 (C-15), 29.9

(C-7), 36.5 (C-3), 36.9 (C-10), 37.8 (C-1) 44.6 (C-5), 47.5 (C-4), 50.7 (C-3′), 52.0 (4-$COOCH_3$), 55.3 (4″-OCH_3), 70.2 (C-2″), 113.9 (C-3″, 5″), 124.0, (C-11), 127.0 (C-2″, 6″), 127.2 (C-14), 135.2 (C-1″), 135.7 (C-12), 139.3 (C-8), 145.2 (C-13), 146.7 (C-9), 159.1 (C-4″), 178.9 (C-18), 205.6 (C-1′) ppm; MS: $m/z = 476$ (39%), 474 (64), 459 (11), 431 (7), 399 (5), 358 (16), 357 (35), 356 (70), 355 (35), 353 (23), 343 (18), 342 (30), 341 (71), 340 (53), 339 (24), 325 (20), 313 (7), 283 (45), 282 (52), 281 (100), 265 (23), 239 (18), 237 (20), 215 (18), 181 (15), 167 (16), 155 (18), 150 (25), 149 (16), 141 (18), 137 (26), 136 (51), 135 (68), 128 (16), 121 (50), 107 (17), 92 (16), 91 (15), 77 (38), 65 (15), 55 (20).

Methyl 12-(5-(4-methoxyphenyl)pyrazolin-3-yl)dehydroabietate (**8**; $C_{31}H_{40}N_2O_3$)

^{1}H NMR (300 MHz, δ, CD_3OD): 1.16 and 1.18 (6H, d, $J = 2.5$, H-16,17), 1.20 (1H, m, H-4′) 1.21 (3H, s, H-20), 1.28 (3H, s, H-19), 1.36–1.46 (2H, m, H-1,6), 1.62–1.93 (5H, m, H-2,3,6), 2.14 (1H, dd, $J = 2.0$ and 12.1, H-5), 2.34 (1H, d, $J = 13.3$, H-1), 2.87 (2H, m, H-7), 3.35–3.49 (2H, m, H-15,4′), 3.67 (3H, s, 4-$COOCH_3$), 3.79 (3H, s, 4″-OCH_3), 4.84 (1H, m, H-5′), 6.92 (2H, d, $J = 8.7$, H-3″, 5″), 7.03 (1H, s, H-14), 7.15 (1H, s, H-11), 7.34 (2H, d, $J = 8.7$, H-2″, 6″) ppm; MS: $m/z = 488$ ($M^{+\bullet}$, 66%), 381 (9), 341 (8), 339 (31), 338 (100), 278 (9), 263 (6), 223 (5), 165 (5), 157 (5), 150 (6), 149 (9), 136 (18), 135 (12), 134 (20), 121 (18), 91 (8), 77 (8), 65 (5), 59 (9), 57 (9), 55 (8), 44 (18), 43 (12), 41 (22), 40 (12), 39 (10), 38 (6), 36 (21), 35 (5), 32 (31).

Methyl 12-(5(3)-(3-methoxyphenyl)pyrazol-3(5)-yl)dehydroabietate (**11**; $C_{31}H_{38}N_2O_3$)

20 µl Hydrazine hydrate (0.41 mmol) were added to a solution of 80 mg methyl 12-(3-(3-methoxyphenyl)-3-oxopropanoyl)dehydroabietate (**7**, 0.160 mmol) in 70 ml methanol under a N_2 atmosphere, and the mixture was stirred and refluxed for 12 h. The mixture was then poured into H_2O, extracted with $CHCl_3$, and the organic layer was dried over anhydrous Na_2SO_4 and concentrated using the rotary evaporator. The mixture was then purified by TLC eluting with light petroleum:ethyl acetate (9:1); compound **11** was obtained as an oil.

Yield: 49.7 mg (64%); HRMS: found: 486.2869, $C_{31}H_{38}N_2O_3$ requires 486.2882; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 1.18 and 1.21 (6H, d, $J = 6.9$, H-16,17), 1.23 (3H, s, H-20), 1.29 (3H, s, H-19), 1.44–1.56 (2H, m, H-1,6), 1.64–1.94 (5H, m, H-2,3,6), 2.25 (1H, dd, $J = 2.1$ and 12.4, H-5), 2.29 (1H, m, H-1), 2.94 (2H, m, H-7), 3.17 (1H, hept, $J = 6.8$, H-15), 3.68 (3H, s, 4-$COOCH_3$), 3.88 (3H, s, 3″-OCH_3), 6.60 (1H, s, H-4′), 6.90 (1H, m, H-4″), 7.07 (1H, s, H-14), 7.21 (1H, s, H-11), 7.34 (1H, m, H-5″), 7.40 (2H, m, H-2″, 6″) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$): 16.5 (C-19), 18.4(C-2), 21.6 (C-6), 24.2 and 24.4 (C-16,17), 25.1 (C-20), 29.2 (C-15), 29.8 (C-7), 36.6 (C-3), 36.9 (C-10), 37.9 (C-1), 44.7 (C-5), 47.6 (C-4), 52.0 (4-$COOCH_3$), 55.3 (3″-OCH_3), 103.3 (C-4′), 110.8 (C-2″), 113.9 (C-4″), 118.2 (C-6″), 125.6 (C-11), 126.4 (C-5″), 136.4 (C-8,12), 144.4 (C-13), 147.2 (C-9), 159.9 (C-3″), 179.0 (C-18) ppm; MS: $m/z = 487$ (35%), 486 ($M^{+\bullet}$, 100), 485 (22), 471 (15), 412 (15), 411 (45), 386 (12), 369 (10), 356 (11), 355 (11), 354 (14), 342 (18), 341 (65), 340 (13), 339 (27), 338 (68), 311 (14), 281 (36), 236 (39), 222 (12), 208 (62), 194 (32), 179 (15), 177 (80), 167 (11), 165 (15), 163 (26), 149 (33), 145 (28), 136 (24), 135 (23), 134 (22), 133 (19), 123 (37), 121 (32), 117 (20), 115 (11), 111 (11), 109 (12), 107 (15), 105 (20), 97 (15), 95 (15), 91 (21), 89 (26), 85 (15), 83 (20), 8 (19), 77 (31), 73 (16), 71 (24), 69 (33), 67 (17), 63 (17), 57 (42), 55 (46), 51 (25).

Single crystal diffraction analysis

Data collection and processing

The pertinent crystal data and refinement details for compounds **4** and **5** are given in Table 2. The crystal data for both compounds were collected with a MAR research image plate system using

Table 2. Crystal data and details of structure refinement for compounds **4** and **5**

Compound	**4**	**5**
Molecular Formula	$C_{23}H_{31}O_3$	$C_{31}H_{38}O_4$
M	355.48	474.61
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$
a (Å)	7.467(8)	6.222(9)
b (Å)	10.813(12)	8.153(9)
c (Å)	25.530(14)	26.35(2)
β (°)	(90.0)	94.21(1)
U (Å^3)	2061(3)	1333(3)
Z	4	2
D_c (g.cm^{-3})	1.145	1.182
μ (mm^{-1})	0.074	0.077
F (000)	772	512
θ range for data collection (°)	3.3−26.0	2.9−26.1
Index ranges	$0 \le h \le 8$, $-11 \le k \le 12$, $-30 \le l \le 30$	$0 \le h \le 7$, $-9 \le k \le 9$, $-32 \le l \le 32$
Measured reflections	1838	3764
Independent reflections (R_{int})	1542(0.0228)	3599(0.0464)
Data/parameters	1542/238	3599/323
a and b in weighting schemes	0.1457, 0.72	0.2000, 0.00
GOF on F^2	1.053	1.150
R and R_w ($I > 2\ \sigma\ (I)$)	0.0645, 0.1855	0.0880, 0.2672
R and R_w (all data)	0.0848, 0.2079	0.1369, 0.3051
Largest difference peak and hole (e · A^{-3})	0.183, −0.147	0.680, −0.313

graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å). The crystals were positioned at 75 mm from the image plate. An exposure time of 2 min was used per 2 for each of the 95 frames collected. Data analysis was carried out with the XDS program [39]. Intensities were not corrected for absorption effects.

Structure analysis and refinement

The structures were solved by direct methods. The earlier difference maps obtained for compound **4** revealed the two terminal carbons of one isopropyl group disordered over two positions in the crystal structure. Then, the coordinates of these two atoms were included in the refinement, occupying two alternate positions with occupancy factors of 0.5.

Anisotropic parameters were used for non hydrogen atoms, except for disordered carbon atoms of compound **4**, which were refined with individual isotropic temperature factors.

Hydrogen atoms were included in the refinement in geometric positions giving thermal parameters equivalents to 1.2 times those of the atom to which they were attached. The structures were refined by least-square methods on F^2 until convergence is achieved. A weighting scheme of the form $w = 1/(\sigma^2(F_o^2) + (aP)^2 + bP)$ with $P = (\max(F_o^2) + 2F_o^2)/3$ was used. The last difference *Fourier* maps calculated for both compounds showed no peaks with electronic density above 1 eÅ^{-3}.

All calculations were carried out with SHELXS and SHELXL within the SHELX97 package [40]. The molecular diagrams were drawn with ZORTEP [41].

Molecular mechanics calculations

Molecular mechanics calculations were carried out using the *Dreiding* force field within the CERIUS2 package software, release 3.0 [42]. Default values were used for all force field parameters except stated otherwise. The steric energy profiles of isopropyl group rotation presented for compounds **4** and **5** were calculated using the following procedure: X-ray structures of both compounds were taken as starting models for the corresponding molecular mechanics calculations. In both cases, the isopropyl group was rotated changing successively the torsion angle C(14)-C(13)-C(15)-C(16) of 10° intervals over range of −180° to 180°. A large force constant for a cosine-*Fourier* expansion torsion term was used in order to fix the torsion angle at a particular value. So 36 structures were minimized and an energy profile for the rotation of isopropyl group as a function of the exocyclic torsion angle was obtained. All structures were minimized employing a conjugate gradient until convergence. High convergence criteria with default parameters were used.

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