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The Syntheses and Absolute Configurations of Nellionol and 5-Dehydronellionol

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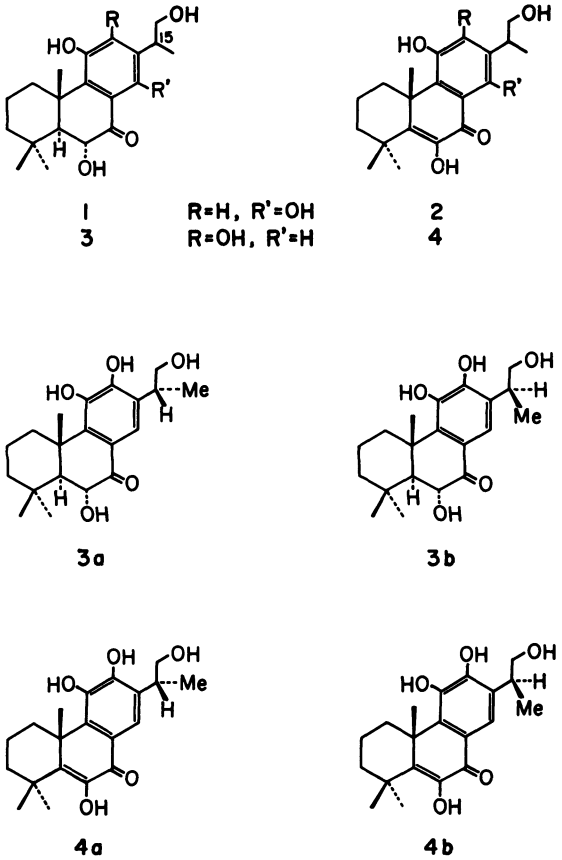
To determine the absolute configurations of C-15 in natural nellionol and 5-dehydronellionol, (15*R*)-8,11,13-abietatriene-12,16-diol was converted into (15*R*)-6α,11,12,16-tetrahydroxy-8,11,13-abietatrien-7-one (**3a**) and (15*R*)-6,11,12,16-tetrahydroxy-5,8,11,13-abietatetraen-7-one (**4a**), which were identical with natural products. For direct comparisons with **3a** and **4a**, (15*S*)-6α,11,12,16-tetrahydroxy-8,11,13-abietatrien-7-one (**3b**) and (15*S*)-6,11,12,16-tetrahydroxy-5,8,11,13-abietatetraen-7-one (**4b**) were also synthesized from (15*S*)-8,11,13-abietatriene-12,16-diol. The synthetic **3b** and **4b** were not identical with the natural products. From the present study, the absolute configurations of nellionol and 5-dehydronellionol were conclusively assigned as 5*S*,6*R*,10*S*,15*R* (**3a**) and 10*R*,15*R* (**4a**), respectively.

Nellionol and 5-dehydronellionol have been isolated from the root bark of *Premna latifolia* Roxb. by Rao *et al.*[1] On the basis of chemical and spectroscopic studies they deduced the structures of nellionol and 5-dehydronellionol to be 6α,11,14,16-tetrahydroxy-8,11,13-abietatrien-7-one (**1**) and 6,11,14,16-tetrahydroxy-5,8,11,13-abietatetraen-7-one (**2**), respectively. However, our examination on the published ^{1}H NMR spectral data[1] suggested alternate structures, 6α,11,12,16-tetrahydroxy-8,11,13-abietatrien-7-one (**3**) and 6,11,-12,16-tetrahydroxy-5,8,11,13-abietatetraen-7-one (**4**), for nellionol and 5-dehydronellionol respectively. The correctness of these revised structures was supported by the syntheses of C-15 epimeric mixtures of **3** and **4**,[2] whereas the precise stereochemistry of C-15 in these natural products could not be determined. Burnell *et al.*[3] also reported independently the same revised structures, **3** and **4**, for nellionol and 5-dehydronellionol, but the stereochemistry of C-15 still remained unsettled. In order to determine the absolute configurations of C-15 in these natural products we have now attempted the syntheses of (15*R*)-6α,11,-12,16-tetrahydroxy-8,11,13-abietatrien-7-one (**3a**), (15*R*)-6,11,12,16-tetrahydroxy-5,8,11,13-abietatetraen-7-one (**4a**), and their (15*S*)-epimers (**3b** and **4b**). For this purpose, (15*R*)-8,11,13-abietatriene-12,16-diol (16-hydroxyferruginol) (**5a**) and its (15*S*)-isomer (**5b**) were chosen as convenient relay intermediates, because these compounds have recently been synthesized in our laboratory by an unambiguous method starting from (*R*)-(−)-α-cyclocitral.[4]

In the present study, however, new preparations of **5a** and **5b** using natural dehydroabietic acid (**6**) were carried out as follows. Dehydration of 12-methoxy-8,11,13-abietatrien-15-ol (**7**)[2] prepared from **6**, with refluxing acetic anhydride, followed by hydroboration-oxidation of the resulting tetraene (**8**),[2] afforded a mixture of the C-15 epimeric alcohols. The mixture was separated by repeated column chromatography on silica gel to give (15*R*)-12-methoxy-8,11,13-abietatrien-16-ol (**9a**) and its (15*S*)-epimer (**9b**). The alcohols, **9a** and **9b**, were demethylated respectively with anhydrous aluminium chloride, sodium iodide, and

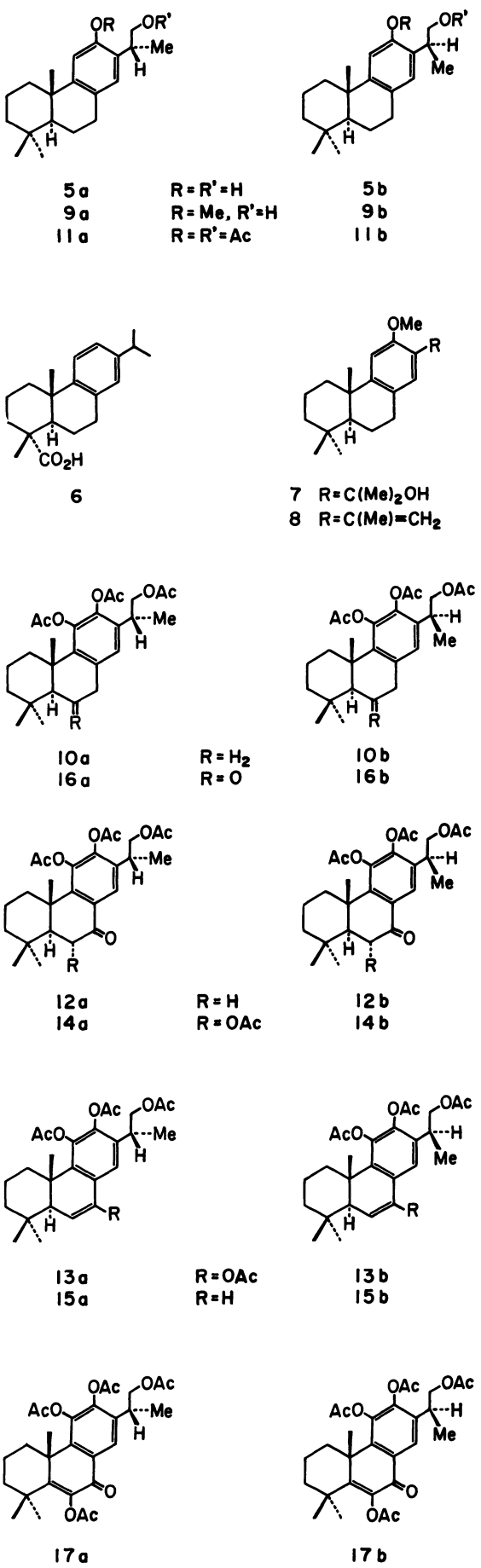


acetonitrile in dichloromethane[5] at 35—40 °C under a stream of nitrogen to give the crystalline diols, which were shown to be identical with authentic **5a** and **5b**[4] by physical and spectral comparisons. Oxidation of the diol **5a** with benzoyl peroxide in refluxing chloroform, followed by reduction with lithium aluminium hydride in ether and subsequent acetylation with acetic anhydride in pyridine, afforded (15*R*)-11,12,16-triacetoxy-8,11,13-abietatriene (**10a**: 49.5%) along with (15*R*)-12,16-diacetoxy-8,11,13-abietatriene[4] (**11a**: 26.7%). Similar treatment of the diol **5b** also produced the corresponding (15*S*)-triacetate (**10b**: 47.0%) and (15*S*)-diacetate[4] (**11b**: 29.8%). The triacetates, **10a** and **10b**, were oxidized respectively with chromium trioxide in acetic acid at room temperature to give (15*R*)-11,12,16-

triacetoxy-8,11,13-abietatrien-7-one (**12a**: 73.2%) and its (15*S*)-isomer (**12b**: 76.1%). The 7-oxo compound **12a** was refluxed with isopropenyl acetate in the presence of *p*-toluenesulfonic acid to give an enol acetate (**13a**: 95.0%). This was converted into (15*R*)-6α,11,-12,16-tetraacetoxy-8,11,13-abietatrien-7-one (**14a**: 91.3%), mp 185—187°C, by oxidation with *m*-chloroperbenzoic acid in dichloromethane and subsequent acetylation with acetic anhydride in pyridine. Hydrolysis of **14a** with dilute hydrochloric acid in refluxing ethanol gave **3a** (77.3%), mp 222—224°C. The synthetic **3a** and **14a** were identical with natural nellionol (mp 226—227°C) and its tetraacetate (mp 185—186°C). Subsequently the 7-oxo compound **12a** was reduced with sodium borohydride in methanol to give a mixture of C-7 epimeric alcohols, which was immediately converted into (15*R*)-11,12,16-triacetoxy-6,8,11,13-abietatetraene (**15a**: 75.5%) by refluxing with *p*-toluenesulfonic acid in dry benzene. The tetraene **15a** was further converted into (15*R*)-11,12,16-triacetoxy-8,11,13-abietatrien-6-one (**16a**: 85.5%) by a series of reactions: oxidation with *m*-chloroperbenzoic acid in dichloromethane at room temperature, refluxing with dilute hydrochloric acid in methanol, and acetylation with acetic anhydride in pyridine. Oxidation of **16a** with Jones reagent, followed by refluxing with sodium acetate in acetic anhydride, afforded (15*R*)-6,11,12,16-tetraacetoxy-5,8,11,13-abietatetraen-7-one (**17a**: 68.7%), mp 149—153°C. Hydrolysis of **17a** with dilute hydrochloric acid in refluxing methanol afforded **4a** (82.3%), mp 211—213°C. The synthetic **4a** and **17a** were identical with natural 5-dehydronellionol (mp 210—212 °C) and its tetraacetate (mp 141—142°C). The specific rotation of **3a**, **14a**, and **17a** showed positive values, which were also in the same direction as those of the corresponding natural products.

For direct comparisons with **3a** and **4a**, the syntheses of (15*S*)-isomers (**3b** and **4b**) were also carried out starting from **12b** in the same manner to that described for the preparation of **3a** and **4a**. The synthetic **3b** (mp 216—217°C) and **4b** (mp 187—189°C) were not identical with natural nellionol and 5-dehydronellionol.

From the present study, the absolute configurations of nellionol and 5-dehydronellionol were conclusively assigned as 5*S*, 6*R*, 10*S*, 15*R* (**3a**) and 10*R*, 15*R* (**4a**), respectively.



Experimental

All melting points are uncorrected. The IR spectra and optical rotations were measured in chloroform, and the ^1H NMR spectra in deuteriochloroform at 90 MHz, with tetramethylsilane as an internal standard, unless otherwise stated; s: singlet, bs: broad singlet, d: doublet, dd: double doublet, m: multiplet. The column chromatography was performed using Merck silica gel (0.063 mm).

12-Methoxy-8,11,13,15-abietatetraene (8). A solution of 12-methoxy-8,11,13-abietatrien-15-ol (**7**)[2] (18.6 g) in acetic anhydride (80 ml) was refluxed for 1 h. After removal of the

acetic anhydride *in vacuo*, the residue was chromatographed on silica gel (250 g), using hexane–benzene (7:3) as the eluent, to give **8** (16.0 g: 91.4%). The IR and ^{1}H NMR spectra of **8** were identical with those of the authentic sample.[2]

*(15R)-12-Methoxy-8,11,13-abietatrien-16-ol (**9a**) and Its (15S)-Epimer (**9b**).* A solution of borane–tetrahydrofuran complex (1 mol dm^{-3}: 18.1 ml) was added to a stirred solution of **8** (6.748 g) in dry tetrahydrofuran (67 ml) at −10 °C for 10 min under a stream of nitrogen. After the mixture had been stirred at −10—0 °C for 25 min and at 0—5 °C for 3 h, there were added successively aqueous tetrahydrofuran (50%: 7.8 ml), aqueous sodium hydroxide (12%: 7.8 ml), and hydrogen peroxide (30%: 7.8 ml) at −10—−4 °C. The mixture was stirred at −5—0 °C for 30 min and then at room temperature for 1 h, diluted with water, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (250 g), using ether–benzene (1:99 and then 8.5:91.5) as the eluent, to give a mixture of C-15 epimers (**9a** and **9b**)[2] (6.873 g: 96.1%). The mixture was carefully separated by repeated column chromatography on silica gel to give **9a** and **9b**, by monitoring of doublet signal due to C-15 methyl group in the ^{1}H NMR spectra (60 MHz: δ in CCl_4, 1.17 for **9a** and 1.16 for **9b**)[2] of fractions.

*(15R)-8,11,13-Abietatriene-12,16-diol (**5a**) and Its (15S)-Epimer (**5b**).* *a)*: Anhydrous aluminium chloride (2.237 g), sodium iodide (2.514 g), and a solution of **9a** (265 mg, containing a small amount of **9b**) in dichloromethane (5.5 ml) were added in this order to acetonitrile (11.0 ml) with stirring at −5—5 °C under a stream of nitrogen over a 20 min period. The mixture was stirred at this temperature for 10 min and then at 35—40 °C for 5 h, poured into water, and extracted with ether. The ether extract was washed successively with aqueous sodium thiosulfate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (15 g), using ether–benzene (3:97) as the eluent, to give the demethylated diol (242 mg: 95.6%). This was recrystallized from ether–hexane to give **5a**, mp 139—140 °C, $[\alpha]_D$ +64.5° (*c* 2.79), whose IR and ^{1}H NMR spectra were identical with those of the authentic sample.[2] Found: C, 79.29; H, 10.27%. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%.

b): Anhydrous aluminium chloride (1.073 g), sodium iodide (1.206 g), and a solution of **9b** (127 mg, containing a small amount of **9a**) in dichloromethane (4.0 ml) were added in this order to acetonitrile (8.0 ml) with stirring at −5—5 °C under a stream of nitrogen over a 16 min period. The mixture was stirred at this temperature for 15 min and then at 35—40 °C for 5 h. After the work-up as described in *a)*, the crude product was chromatographed on silica gel (8.0 g), using ether–benzene (3:97) as the eluent, to give the demethylated diol (87 mg: 71.2%). This was recrystallized from ether–hexane to give **5b**, mp 178—179 °C, $[\alpha]_D$ +45.5° (*c* 2.18), whose IR and ^{1}H NMR spectra were identical with those of the authentic sample.[2] Found: C, 79.25; H, 10.13%. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%.

*(15R)-11,12,16-Triacetoxy-8,11,13-abietatriene (**10a**) and Its (15S)-Epimer (**10b**).* *a)*: A solution of **5a** (215 mg) and benzoyl peroxide (269 mg) in chloroform (6.0 ml) was refluxed for 5 h, cooled, and diluted with ether (9.0 ml). After addition of acetic acid (1.26 ml) and aqueous potassium iodide (20%: 6.3 ml), the mixture was stirred at room temperature for 2 h and then washed successively with water, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and brine. The dried solution was evaporated *in vacuo* to give the crude product, which was used, without purification, in the next reaction.

A stirred suspension of the above crude product and lithium aluminium hydride (130 mg) in dry ether (20 ml) was refluxed for 80 min. The mixture was cooled, poured into ice–dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was acetylated with acetic anhydride (2.0 ml) in pyridine (2.0 ml) at 75—80 °C for 2 h. After the usual work-up, the crude product was chromatographed on silica gel (20 g), using ether–benzene (1:99) as the eluent, to give a diacetate (**11a**) (73 mg: 26.7%), $[\alpha]_D$ +56.9° (*c* 3.59). The IR and ^{1}H NMR spectra of **11a** were identical with those of (15*R*)-12, 16-diacetoxy-8,11,13-abietatriene.[2] Found: C, 74.84; H, 9.01%. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87%.

Further elution with ether–benzene (1:9) gave **10a** (157 mg: 49.5%), $[\alpha]_D$ +61.3° (*c* 2.76); IR: 1765, 1730 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4): δ=0.95 (6H, bs, $-\underset{|}{C}(CH_3)_2$), 1.19 (3H, d, *J*= 7 Hz, C_{15}–CH_3), 1.21 (3H, s, C_{10}–CH_3), 1.94 (3H, s, C_{16}–$OCOCH_3$), 2.21 (6H, s, C_{11}–$OCOCH_3$ and C_{12}–$OCOCH_3$), 3.92 (2H, d, *J*=7 Hz, $-C\underline{H_2}OAc$), 6.77 (1H, s, C_{14}–H).

b): A solution of **5b** (204 mg) and benzoyl peroxide (255 mg) in chloroform (6.0 ml) was refluxed for 5 h. The crude product was reduced with lithium aluminium hydride (130 mg) in dry ether (20 ml) and then acetylated with acetic anhydride (2.0 ml) in pyridine (2.0 ml) as described in *a)*. The product was purified by column chromatography on silica gel (20 g), using ether–benzene (1:99) as the eluent, to give a diacetate (**11b**) (78 mg: 29.8%), $[\alpha]_D$ +33.7° (*c* 3.29). The IR and ^{1}H NMR spectra of **11b** were identical with those of (15*S*)-12,16-diacetoxy-8,11,13-abietatriene.[2] Found: C, 74.79; H, 9.17%. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87%.

Further elution with ether–benzene (1:9) gave **10b** (141 mg: 47.0%), $[\alpha]_D$ +43.9° (*c* 4.00); IR: 1768, 1733 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4): δ=0.95 (6H, bs, $-\underset{|}{C}(CH_3)_2$), 1.17 (3H, d, *J*= 7 Hz, C_{15}–CH_3), 1.22 (3H, s, C_{10}–CH_3), 1.95 (3H, s, C_{16}–$OCOCH_3$), 2.22 (6H, s, C_{11}–$OCOCH_3$ and C_{12}–$OCOCH_3$), 3.98 (2H, d, *J*=7.5 Hz, $-C\underline{H_2}OAc$), 6.78 (1H, s, C_{14}–H). Found: C, 70.45; H, 8.42%. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16%.

*(15R)-11,12,16-Triacetoxy-8,11,13-abietatrien-7-one (**12a**) and Its (15S)-Epimer (**12b**).* *a)*: A mixture of **10a** (965 mg) and chromium trioxide (413 mg) in acetic acid (20 ml) was stirred at room temperature for 23.5 h. The mixture was diluted with water and extracted with ether. The ether extract was washed successively with water, aqueous sodium hydrogencarbonate, and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (50 g), using ether–benzene (5:95) as the eluent, to give the starting **10a** (88 mg). Further elution with ether–benzene (5:95 and then 15:85) afforded **12a** (729 mg: 73.2%), $[\alpha]_D$ +66.8° (*c* 4.40); IR: 1775, 1734, 1687, 1608 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4): δ=0.98 (6H, s, $-\underset{|}{C}(CH_3)_2$), 1.29 (3H, s, C_{15}–CH_3), 1.32 (3H, s, C_{10}–CH_3), 1.94 (3H, s, C_{16}–$OCOCH_3$), 2.25 (6H, s, C_{11}–$OCOCH_3$ and C_{12}–$OCOCH_3$), 3.95 (2H, d, *J*=7 Hz, $-C\underline{H_2}OAc$), 7.93 (1H, s, C_{14}–H). Found: C, 68.09; H, 7.51%. Calcd for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47%.

b): A solution of **10b** (957 mg) in acetic acid (21 ml) was oxidized with chromium trioxide (409 mg) at room temperature for 22 h as described in *a)*. The crude product was

chromatographed on silica gel (50 g), using ether–benzene (5:95) as the eluent, to give **10b** (162 mg) and **12b** (667 mg: 67.6%), $[\alpha]_D$ +8.6° (*c* 14.35); IR: 1776, 1732, 1686, 1608 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ=1.00 (6H, s, $-C(CH_3)_2$), 1.27 (3H, d, *J*=7 Hz, C_{15}–CH_3), 1.34 (3H, s, C_{10}–CH_3), 1.96 (3H, s, C_{16}–$OCOCH_3$), 2.27 (6H, s, C_{11}–$OCOCH_3$ and C_{12}–$OCOCH_3$), 4.02 (2H, d, *J*=7 Hz, $-CH_2OAc$), 7.93 (1H, s, C_{14}–H). Oxidation of the recovered **10b** (162 mg) with chromium trioxide (69 mg) in acetic acid (3.5 ml) was then carried out as described above. The crude product was purified by column chromatography on silica gel (10 g) to give some additional **12b** (84 mg: 8.5%).

*(15R)-7,11,12,16-Tetraacetoxy-6,8,11,13-abietatetraene (**13a**) and Its (15S)-Epimer (**13b**).* *a)*: A mixture of **12a** (220 mg) and *p*-toluenesulfonic acid (20 mg) in isopropenyl acetate (5.0 ml) was refluxed for 18 h. The mixture was cooled and diluted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (20 g), using ether–benzene (1:9) as the eluent, to give a mixture of **12a** and **13a** (61 mg). Further elution gave **13a** (176 mg: 73.3%), which was recrystallized from methanol, mp 140.5—141.5 °C, $[\alpha]_D$ +28.6° (*c* 3.40); IR: 1768, 1737sh, 1668, 1610 cm^{-1}; ^1H NMR: δ=0.94 (3H, s) and 1.02 (3H, s) ($-C(CH_3)_2$), 1.22 (3H, d, *J*=7 Hz, C_{15}–CH_3), 1.27 (3H, s, C_{10}–CH_3), 2.01 (3H, s, C_{16}–$OCOCH_3$), 2.25 (3H, s) and 2.28 (6H, s) (C_7–$OCOCH_3$, C_{11}–$OCOCH_3$, and C_{12}–$OCOCH_3$), 2.39 (1H, d, *J*=3 Hz, C_5–H), 3.15 (1H, m, C_{15}–H), 4.03 (2H, d, *J*=7 Hz, $-CH_2OAc$), 5.68 (1H, d, *J*=3 Hz, C_6–H), 7.01 (1H, s, C_{14}–H). Found: C, 67.05; H, 7.45%. Calcd for $C_{28}H_{36}O_8$: C, 67.18; H, 7.25%. The above mixture of **12a** and **13a** (61 mg) was then treated with *p*-toluenesulfonic acid (10 mg) in refluxing isopropenyl acetate (2.5 ml) for 15.5 h to give some additional **13a** (52 mg: 21.7%).

b): A mixture of **12b** (312 mg) and *p*-toluenesulfonic acid (30 mg) in isopropenyl acetate (7.0 ml) was refluxed for 18 h. After the work-up as described in *a)*, the crude product was chromatographed on silica gel (30 g), using ether–benzene (7:93) as the eluent, to give **13b** (285 mg, containing a small amount of **12b**: *ca.* 83.5%). This was recrystallized from methanol, mp 203—204 °C, $[\alpha]_D$ −7.8° (*c* 7.66); IR: 1765, 1738 sh, 1668, 1610 cm^{-1}; ^1H NMR (60 MHz): δ=0.93 (3H, s) and 1.01 (3H, s) ($-C(CH_3)_2$), 1.19 (3H, d, *J*=7 Hz, C_{15}–CH_3), 1.27 (3H, s, C_{10}–CH_3), 1.99 (3H, s, C_{16}–$OCOCH_3$), 2.25 (3H, s) and 2.29 (6H, s) (C_7–$OCOCH_3$, C_{11}–$OCOCH_3$, and C_{12}–$OCOCH_3$), 4.08 (2H, dd, *J*=7 and 3.5 Hz, $-CH_2OAc$), 5.65 (1H, d, *J*=3 Hz, C_6–H), 6.95 (1H, s, C_{14}–H). Found: C, 67.45; H, 7.34%. Calcd for $C_{28}H_{36}O_8$: C, 67.18; H, 7.25%.

*(15R)-6α,11,12,16-Tetraacetoxy-8,11,13-abietatrien-7-one (**14a**) and Its (15S)-Epimer (**14b**).* *a)*: A mixture of **13a** (67.0 mg) and *m*-chloroperbenzoic acid (80%: 40.4 mg) in dichloromethane (1.5 ml) was stirred at room temperature for 22.5 h. The mixture was diluted with ether and washed successively with aqueous potassium iodide, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and brine. The dried solution was evaporated *in vacuo* to give a mixture of 6α-acetoxy and 6α-hydroxy derivatives, which was immediately acetylated with acetic anhydride (0.7 ml) in pyridine (0.7 ml) at 75—80 °C for 2 h. After the usual work-up, the crude product was purified by column chromatography on silica gel (8.0 g), using ether–benzene (1:9) as the eluent, to give **14a** (63.1 mg: 91.3%). This was recrystallized from acetone–hexane, mp 185—187 °C, $[\alpha]_D$ +103.5° (*c* 2.54); IR: 1778, 1740, 1705, 1610 cm^{-1}; ^1H NMR: δ=1.05 (3H, s) and 1.14 (3H, s) ($-C(CH_3)_2$), 1.27 (3H, s, C_{15}–CH_3), 1.50 (3H, s, C_{10}–CH_3), 2.00 (3H, s, C_{16}–$OCOCH_3$), 2.24 (3H, s) and 2.30 (6H, s) ($C_{6\alpha}$–$OCOCH_3$, C_{11}–$OCOCH_3$, and C_{12}–$OCOCH_3$), 2.27 (1H, d, *J*=13 Hz, C_5–H), 3.20 (1H, m, C_{15}–H), 4.06 (2H, d, *J*=7 Hz, $-CH_2OAc$), 5.83 (1H, d, *J*=13 Hz, $C_{6\beta}$–H), 8.00 (1H, s, C_{14}–H). Found: C, 64.93; H, 7.04%. Calcd for $C_{28}H_{36}O_9$: C, 65.10; H, 7.03%. The synthetic **14a** was identical with natural nellionol tetraacetate (mp 185—186 °C).[1]

b): Oxidation of **13b** (245 mg, containing a small amount of **12b**) with *m*-chloroperbenzoic acid (80%: 148 mg) in dichloromethane (5.0 ml), followed by acetylation with acetic anhydride (1.5 ml) in pyridine (1.5 ml), were carried out as described in *a)*. The crude product was chromatographed on silica gel (10 g), using ether–benzene (5:95) as the eluent, to give **14b** (203 mg: *ca.* 80.3%) (67.1% from **12b**). This was recrystallized from acetone–hexane, mp 142.5—143 °C, $[\alpha]_D$ +35.4° (*c* 0.91); IR: 1778, 1740, 1705, 1610 cm^{-1}; ^1H NMR: δ=1.06 (3H, s) and 1.13 (3H, s) ($-C(CH_3)_2$), 1.23 (3H, d, *J*=7 Hz, C_{15}–CH_3), 1.51 (3H, s, C_{10}–CH_3), 2.00 (3H, s, C_{16}–$OCOCH_3$), 2.23 (3H, s) and 2.30 (6H, s) ($C_{6\alpha}$–$OCOCH_3$, C_{11}–$OCOCH_3$, and C_{12}–$OCOCH_3$), 3.18 (1H, m, C_{15}–H), 4.07 (2H, d, *J*=7 Hz, $-CH_2OAc$), 5.83 (1H, d, *J*=13 Hz, $C_{6\beta}$–H), 7.98 (1H, s, C_{14}–H). Found: C, 64.86; H, 7.05%. Calcd for $C_{28}H_{36}O_9$: C, 65.10; H, 7.03%.

*(15R)-6α,11,12,16-Tetrahydroxy-8,11,13-abietatrien-7-one (Nellionol) (**3a**) and Its (15S)-Epimer (**3b**).* *a)*: A mixture of **14a** (60.0 mg) and dilute hydrochloric acid (15%: 0.5 ml) in ethanol (3.0 ml) was refluxed for 6 h. After removal of the ethanol *in vacuo*, the residue was extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (Mallinckrodt CC-4, 10 g), using hexane–chloroform (35:65) as the eluent, to give **3a** (31.3 mg: 77.3%). This was recrystallized from benzene, mp 222—224 °C, $[\alpha]_D$ +47.2° (*c* 0.36); IR (KBr): 3500, 3390, 1675, 1613 cm^{-1}; ^1H NMR (DMSO-d_6–D_2O): δ=1.13 (3H, s) and 1.16 (3H, s) ($-C(CH_3)_2$), 1.17 (3H, d, *J*=7 Hz, C_{15}–CH_3), 1.46 (3H, s, C_{10}–CH_3), 1.66 (1H, d, *J*=13 Hz, C_5–H), 3.0—3.4 (2H, m, $C_{1\beta}$–H and C_{15}–H), 3.53 (2H, d, *J*=6 Hz, $-CH_2OH$), 4.44 (1H, d, *J*=13 Hz, $C_{6\beta}$–H), 7.31 (1H, s, C_{14}–H). Found: C, 69.10; H, 8.20%. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10%. The synthetic **3a** was identical with natural nellionol (mp 226—227 °C).[1]

b): A mixture of **14b** (186.7 mg) and dilute hydrochloric acid (15%: 2.0 ml) in ethanol (10 ml) was refluxed for 6 h. After the work-up as described in *a)*, the crude product was chromatographed on silica gel (Mallinckrodt CC-4, 15 g), using hexane–chloroform (35:65) as the eluent, to give **3b** (79.4 mg: 63.1%). This was recrystallized from benzene, mp 216—217 °C, $[\alpha]_D$ +75.7° (*c* 0.52); IR (KBr): 3490, 3375, 3275, 1675, 1615 cm^{-1}; ^1H NMR (DMSO-d_6): δ=1.14 (3H, s) and 1.17 (3H, s) ($-C(CH_3)_2$), 1.18 (3H, d, *J*=7 Hz, C_{15}–CH_3), 1.48 (3H, s, C_{10}–CH_3), 1.68 (1H, d, *J*=13 Hz, C_5–H), 3.54 (2H, d, *J*=6 Hz, $-CH_2OH$), 4.47 (1H, d, *J*=13 Hz, $C_{6\beta}$–H), 7.32 (1H, s, C_{14}–H). Found: C, 69.13; H, 8.28%. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10%.

*(15R)-11,12,16-Triacetoxy-6,8,11,13-abietatetraene (**15a**) and Its (15S)-Epimer (**15b**).* *a)*: A mixture of **12a** (330 mg) and sodium borohydride (55 mg) in methanol (4.0 ml) was stirred at 0—5 °C for 30 min and then at room temperature for 1 h. The mixture was acidified with dilute hydrochloric acid and

extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residual oil was dissolved in dry benzene (3.5 ml) and then refluxed with *p*-toluenesulfonic acid (20 mg) for 1 h. The mixture was cooled, diluted with ether, and washed with brine. The dried solution was evaporated *in vacuo*. The residue was chromatographed on silica gel (18 g), using ether–benzene (5:95) as the eluent, to give **15a** (241 mg: 75.5%); IR: 1767, 1733 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ=0.97 (3H, s), 1.02 (3H, s), and 1.10 (3H, s) ($-\underset{|}{C}(CH_3)_2$ and C_{10}–CH_3), 1.22 (3H, d, J=7 Hz, C_{15}–CH_3), 1.93 (3H, s, C_{16}–$OCOCH_3$), 2.18 (3H, s) and 2.21 (3H, s) (C_{11}–$OCOCH_3$ and C_{12}–$OCOCH_3$), 3.92 (2H, d, J=7 Hz, $-\underline{CH_2}OAc$), 5.89 (1H, dd, J=9.5 and 3 Hz, C_6–H), 6.44 (1H, dd, J=9.5 and 3 Hz, C_7–H), 6.77 (1H, s, C_{14}–H).

b): Reduction of **12b** (138 mg) with sodium borohydride (23 mg) in methanol (2.0 ml), followed by dehydration with *p*-toluenesulfonic acid (10 mg) in dry benzene (2.0 ml), were carried out as described in *a*). The crude product was chromatographed on silica gel (5.0 g) to give **15b** (112 mg: 84.0%); IR: 1766, 1735 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ=0.98 (3H, s), 1.03 (3H, s), and 1.12 (3H, s) ($-\underset{|}{C}(CH_3)_2$ and C_{10}–CH_3), 1.20 (3H, d, J=7 Hz, C_{15}–CH_3), 1.96 (3H, s, C_{16}–$OCOCH_3$), 2.20 (3H, s) and 2.23 (3H, s) (C_{11}–$OCOCH_3$ and C_{12}–$OCOCH_3$), 4.00 (2H, d, J=7 Hz, $-\underline{CH_2}OAc$), 5.91 (1H, dd, J=9.5 and 2.5 Hz, C_6–H), 6.45 (1H, dd, J=9.5 and 2.5 Hz, C_7–H), 6.78 (1H, s, C_{14}–H).

(15R)-11,12,16-Triacetoxy-8,11,13-abietatrien-6-one (16a) and Its (15S)-Epimer (16b). *a*): A mixture of **15a** (219 mg) and *m*-chloroperbenzoic acid (80%: 160 mg) in dichloromethane (4.0 ml) was stirred at 0—5 °C for 1 h and then at room temperature for 14.5 h. The mixture was diluted with ether and washed successively with aqueous potassium iodide, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and brine. The ether solution was dried over sodium sulfate and evaporated *in vacuo*. The residual oil was refluxed with dilute hydrochloric acid (15%: 0.5 ml) in methanol (4.0 ml) for 1 h. The mixture was evaporated *in vacuo*, diluted with water, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give an oil. This oil was acetylated with acetic anhydride (1.0 ml) in pyridine (1.0 ml) at 75—80 °C for 2 h. After the usual work-up, the crude product was chromatographed on silica gel (10 g), using ether–benzene (5:95) as the eluent, to give **16a** (194 mg: 85.5%), $[\alpha]_D$ +112.8° (*c* 3.13); IR: 1769, 1717 cm^{-1}; ^1H NMR (60 MHz): δ=1.03 (3H, s), 1.20 (3H, s), and 1.32 (3H, s) ($-\underset{|}{C}(CH_3)_2$ and C_{10}–CH_3), 1.22 (3H, d, J=7 Hz, C_{15}–CH_3), 2.00 (3H, s, C_{16}–$OCOCH_3$), 2.29 (6H, s, C_{11}–$OCOCH_3$ and C_{12}–$OCOCH_3$), 2.57 (1H, s, C_5–H), 3.20 (1H, m, C_{15}–H), 3:57 (2H, bs, $-CH_2CO-$), 4.02 (2H, d, J=7 Hz, $-\underline{CH_2}OAc$), 6.85 (1H, s, C_{14}–H).

b): Oxidation of **15b** (112 mg) with *m*-chloroperbenzoic acid (80%: 82 mg) in dichloromethane (2.5 ml), followed by treatment with dilute hydrochloric acid (15%: 0.25 ml) in methanol (2.5 ml) and subsequent acetylation with acetic anhydride (0.7 ml) in pyridine (0.7 ml), were carried out as described in *a*). The crude product was chromatographed on silica gel (5.0 g) to give **16b** (82 mg: 70.8%), $[\alpha]_D$ +39.5° (*c* 2.99); IR: 1770, 1725 cm^{-1}; ^1H NMR (60 MHz): δ=1.05 (3H, s), 1.22 (3H, s), and 1.33 (3H, s) ($-\underset{|}{C}(CH_3)_2$ and C_{10}–CH_3), 1.21 (3H, d, J=7 Hz, C_{15}–CH_3), 2.02 (3H, s, C_{16}–$OCOCH_3$), 2.32 (6H, s, C_{11}–$OCOCH_3$ and C_{12}–$OCOCH_3$), 2.58 (1H, s, C_5–H), 3.21 (1H, m, C_{15}–H), 3.60 (2H, bs, $-CH_2CO-$), 4.07 (2H, d, J=7 Hz, $-\underline{CH_2}OAc$), 6.90 (1H, s, C_{14}–H).

(15R)-6,11,12,16-Tetraacetoxy-5,8,11,13-abietatetraen-7-one (17a) and Its (15S)-Epimer (17b). *a*): A solution of **16a** (194 mg) in acetone (4.0 ml) was oxidized with Jones reagent (2.5 mol dm^{-3}: 0.26 ml) at 0—5 °C for 10 min and then at room temperature for 2 h. The mixture was diluted with water and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was refluxed with acetic anhydride (6.0 ml) in the presence of anhydrous sodium acetate (350 mg) for 2.5 h with stirring. The mixture was cooled and diluted with ether. The ether solution was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (10 g), using ether–benzene (1:9) as the eluent, to give **17a** (137 mg: 68.7%). This was recrystallized from hexane–benzene, mp 149—153 °C, $[\alpha]_D$ +88.0° (*c* 2.41); IR: 1778, 1730 sh, 1660, 1613 cm^{-1}; ^1H NMR: δ=1.29 (3H, d, J=7 Hz, C_{15}–CH_3), 1.40 (6H, s, $-\underset{|}{C}(CH_3)_2$), 1.64 (3H, s, C_{10}–CH_3), 2.00 (3H, s, C_{16}–$OCOCH_3$), 2.32 (3H, s) and 2.36 (6H, s) (C_6–$OCOCH_3$, C_{11}–$OCOCH_3$, and C_{12}–$OCOCH_3$), 3.25 (1H, m, C_{15}–H), 4.08 (2H, d, J=7 Hz, $-\underline{CH_2}OAc$), 8.12 (1H, s, C_{14}–H). Found: C, 65.53; H, 6.91%. Calcd for $C_{28}H_{34}O_9$: C, 65.36; H, 6.66%.

b): Oxidation of **16b** (130 mg) in acetone (3.0 ml) with Jones reagent (2.5 mol dm^{-3}: 0.18 ml), followed by treatment with anhydrous sodium acetate (210 mg) in acetic anhydride (4.0 ml), were carried out as described in *a*). The crude product was purified by column chromatography on silica gel (5.0 g) to give **17b** (100 mg: 68.8%). This was recrystallized from hexane–benzene, mp 249—252 °C, $[\alpha]_D$ +43.0° (*c* 0.54); IR: 1778, 1733 sh, 1660, 1613 cm^{-1}; ^1H NMR: δ=1.27 (3H, d, J=7 Hz, C_{15}–CH_3), 1.39 (6H, s, $-\underset{|}{C}(CH_3)_2$), 1.64 (3H, s, C_{10}–CH_3), 2.01 (3H, s, C_{16}–$OCOCH_3$), 2.32 (3H, s) and 2.36 (6H, s) (C_6–$OCOCH_3$, C_{11}–$OCOCH_3$, and C_{12}–$OCOCH_3$), 3.23 (1H, m, C_{15}–H), 4.10 (2H, d, J=7 Hz, $-\underline{CH_2}OAc$), 8.11 (1H, s, C_{14}–H). Found: C, 65.61; H, 6.82%. Calcd for $C_{28}H_{34}O_9$: C, 65.36; H, 6.66%.

(15R)-6,11,12,16-Tetrahydroxy-5,8,11,13-abietatetraen-7-one (5-Dehydronellionol) (4a) and Its (15S)-Epimer (4b). *a*): A mixture of **17a** (115.3 mg) and dilute hydrochloric acid (15%: 1.5 ml) in methanol (10 ml) was refluxed for 3 h. After removal of the methanol *in vacuo*, the residue was extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (Mallinckrodt CC-4, 10 g), using hexane–chloroform (35:65) as the eluent, to give **4a** (63.9 mg: 82.3%). This was recrystallized from hexane–benzene, mp 211—213 °C, $[\alpha]_D$ 0° (*c* 0.55); IR: 3600, 3500, 3370, 3150, 1633, 1597, 1565 cm^{-1}; ^1H NMR: δ=1.38 (3H, d, J=7 Hz, C_{15}–CH_3), 1.45 (6H, s, $-\underset{|}{C}(CH_3)_2$), 1.66 (3H, s, C_{10}–CH_3), 2.91 (1H, br, C_{16}–OH), 3.0—3.4 (2H, m, $C_{1\beta}$–H and C_{15}–H), 3.80 (1H, dd, J=8 and 10 Hz) and 4.08 (1H, dd, J=3 and 10 Hz) ($-\underline{CH_2}OH$), 7.58 (1H, s, C_{14}–H), 6.36 (1H, s), 7.08 (1H, s), and 9.56 (1H, br) (C_6–OH, C_{11}–OH, and C_{12}–OH). Found: C, 69.61; H, 7.67%. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57%. The synthetic **4a** was identical with natural 5-dehydronellionol (mp 210—212 °C).[1]

b): A solution of **17b** (143.0 mg) in methanol (16 ml) was hydrolyzed with dilute hydrochloric acid (15%: 2.5 ml) as described in *a*). The crude product was purified by column chromatography on silica gel (Mallinckrodt CC-4, 15 g) to

give **4b** (59.9 mg: 62.2%). This was recrystallized from hexane–benzene, mp 187—189 °C, $[\alpha]_D$ +52.4° (*c* 0.52); IR: 3610, 3500, 3375, 3150, 1633, 1598, 1565 cm^{-1}; ^1H NMR: δ=1.37 (3H, d, *J*=7 Hz, C_{15}-CH_3), 1.44 (6H, s, $-\underset{|}{C}(CH_3)_2$), 1.68 (3H, s, C_{10}-CH_3), 2.9—3.45 (3H, m, $C_{1\beta}$-H, C_{15}-H, and C_{16}-OH), 3.80 (1H, dd, *J*=8 and 10 Hz) and 4.07 (1H, dd, *J*=3 and 10 Hz) ($-C\underline{H}_2OH$), 7.58 (1H, s, C_{14}-H), 6.38 (1H, s), 7.07 (1H, s), and 9.60 (1H, br) (C_6-OH, C_{11}-OH, and C_{12}-OH). Found: C, 69.56; H, 7.64%. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57%.

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